Lec #1

CHEM 30B ORGANIC CHEMISTRY
REACTIVITY AND SYNTHESIS I

STUART CANTRILL

(I) WHO/WHEN/WHERE ?
(II) CALIFORNIA NANOSYSTEMS INSTITUTE (CNSI) - Seminars.
(III) EXTRA CREDIT !
(IV) ORGANIC SYNTHESIS
(V) RETROSYNTHETIC ANALYSIS
(VI) FUNCTIONAL GROUPS / REACTIONS

(I) TAs - CARI/ROB/AL

- ENGLISH ENGLISH ALUMINUM etc, Z
- QUESTIONS IN CLASS
- DISCUSSION SECTIONS - CONSISTENT
- HOMEWORK
- QUIZZES SHORT
- MIDTERMS + FINAL
- GRADES (COMPREHENSIVE)

(II) CNSI SEMINARS
CS50 Tuesdays 4:00pm
- LEARN SOMETHING NEW

(III) EXTRA CREDIT
1 WEEK, 250 WORD SYNOPSIS -
COUNTS FOR 1/2 QUIZ.
YOU CAN DO TWO OF THESE AND
HENCE GET CREDIT FOR A QUIZ

(EXTRA CREDIT PROBLEMS IF CAN'T ATTEND SEMINAR)

(IV) ORGANIC SYNTHESIS

WHY? → Medicines | Materials → Polymers

Crude oil → building blocks
→ larger, more complex molecules

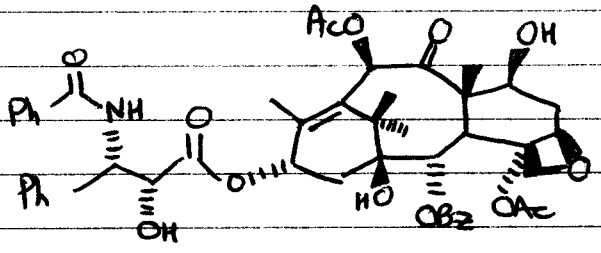
Some molecules → natural sources
Never Nature does the synthesis
- Might not be enough
- Structural analogs

SYNTHESIS - underpins most of Organic Chem
most of the time you need to
make a molecule before you can study it.

RULES - certain ways in which molecules
can be built ⇒ that's SYNTHESIS.

So, start with a SIMPLE MOLECULE - TAXOL

NOT IUPAC ⇒ STRUCTURE



MOST PROMISING ANTI-TUMOUR AGENT (3 DECADES)
SALES 1998 - $1.2 BILLION worldwide

BUT WHERE FROM? NOT LIKE IT GROWS ON TREES!

WELL- YES, IT DOES GROW ON TREES.

– PACIFIC YEW TREE BARK

Six trees (100yr old) to treat one patient (kills tree)

So, let's make it using CHEMICAL SYNTHESIS

HOW?

(V) RETROSYNTHETIC ANALYSIS

Let's say 26 steps to TAXOL

$$A \xrightarrow{rxn} B \xrightarrow{rxn} C \xrightarrow{rxn} D \rightarrow \rightarrow \rightarrow \rightarrow Y \rightarrow Z \rightarrow \text{TAXOL}$$

↑ commercially available small molecule (starting material)

Very difficult | IMPOSSIBLE to plan making TAXOL like this

RETROSYNTHESIS

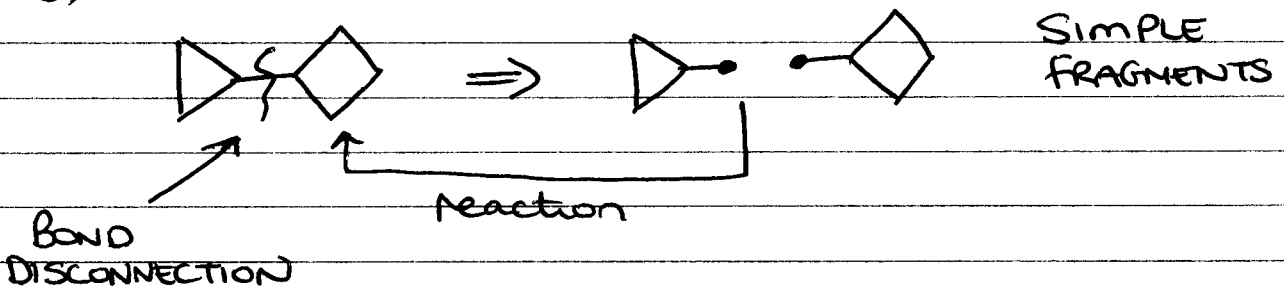
$$\text{Taxol} \Rightarrow Z \Rightarrow Y \Rightarrow X \Rightarrow W \Rightarrow\Rightarrow\Rightarrow B \Rightarrow A$$

↑ a slightly more simple structure that we can convert into TAXOL using a reaction we know

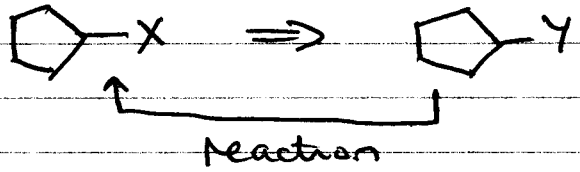
- Simplify STEP by STEP
- Must correspond to a real reaction in reverse.

$\Rightarrow$ RETROSYNTHETIC STEP (TWO TYPES)

(i) DISCONNECTION



(ii) FUNCTIONAL GROUP INTERCONVERSION (FGI)

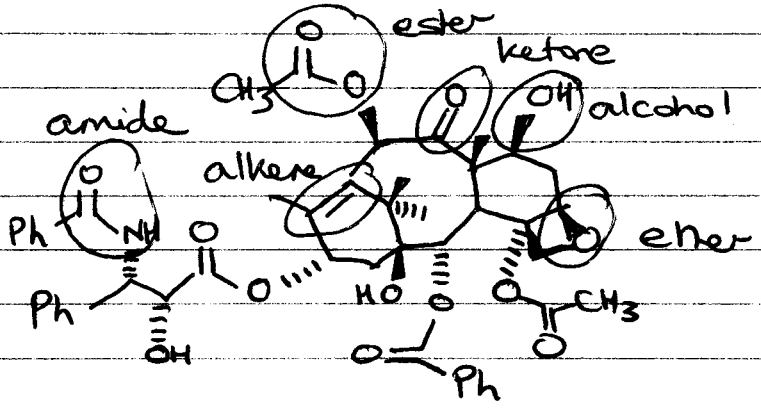


FOR a RETROSYNTHESIS TO WORK THERE MUST BE REAL CORRESPONDING FORWARD REACTIONS.

YOU NEED TO KNOW REACTIONS

IT'S THE ONLY WAY TO BE ABLE TO DO RETROSYNTHESIS

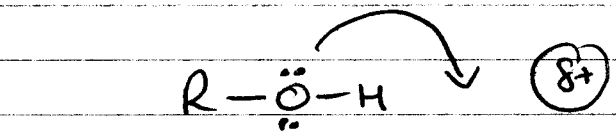
(VI) FUNCTIONAL GROUPS



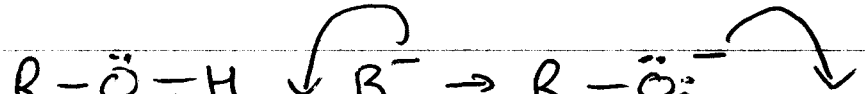
Label the REST

Overview from SYLLABUS

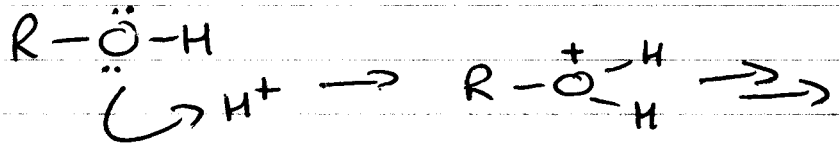
① Alcohols R–OH

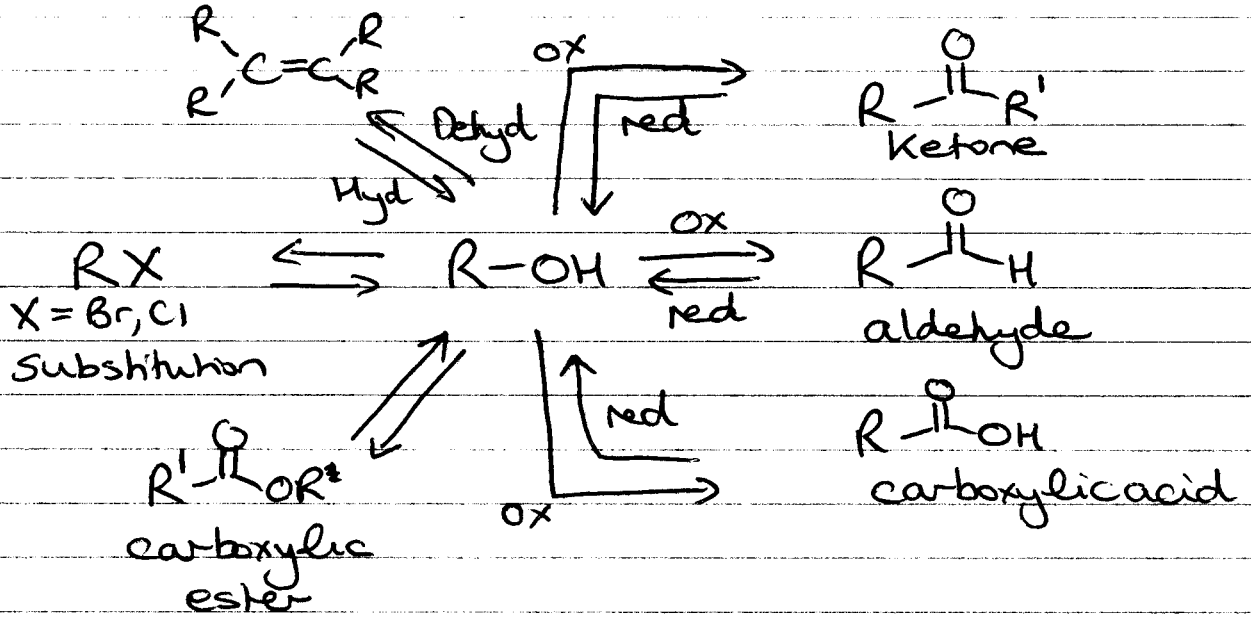


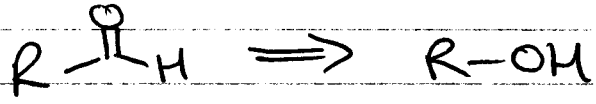
weak nucleophile



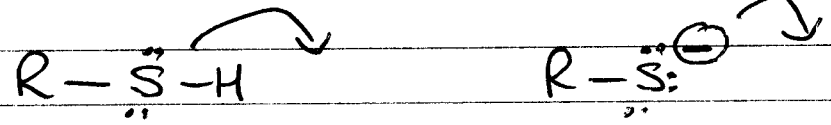
nucleophile





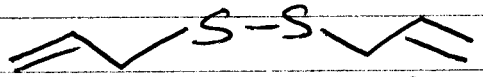


② Thiols

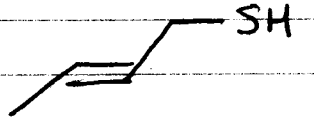


2 R–SH $\underset{\text{red}}{\overset{\text{oxid}}{\rightleftharpoons}}$ R–S–S–R disulfide

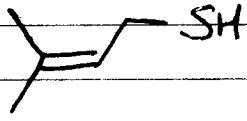
PROTEINS structure CYSTEINE Sect 26.6



diallyl disulfide — GARLIC

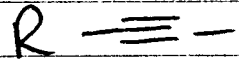


(E)-But-2-en-1-thiol — SKUNK

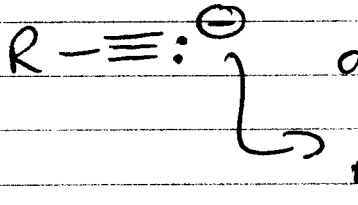


isopentenyl mercaptan — BEER! (<10 ng/l)

③ Alkynes



addition – like alkenes



deprotonate

nucleophile.

④ Organometallics

$M(\text{ligands})_n$ M–C bonds CATALYSIS

⑤ Ethers

R–O–R ⇒ relatively inert → solvents

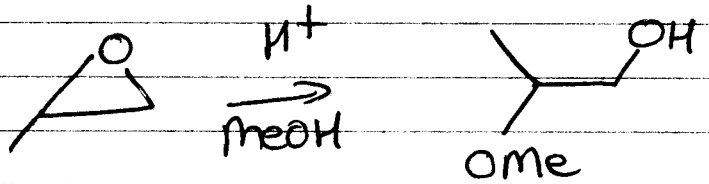
crown ethers 15C5 Na^+
18C6 K^+

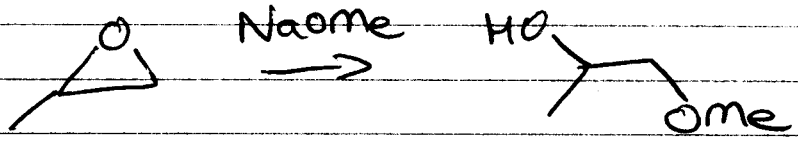
Cyclic ethers → same as linear ones

xcept  EPOXIDES

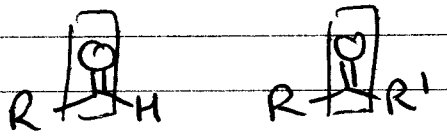
R=H Ethylene Oxide
4 million tons made each year in US.

Chemistry RING OPENING
(i) acid catalysed
(ii) nucleophilic

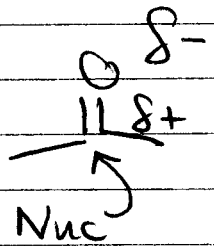




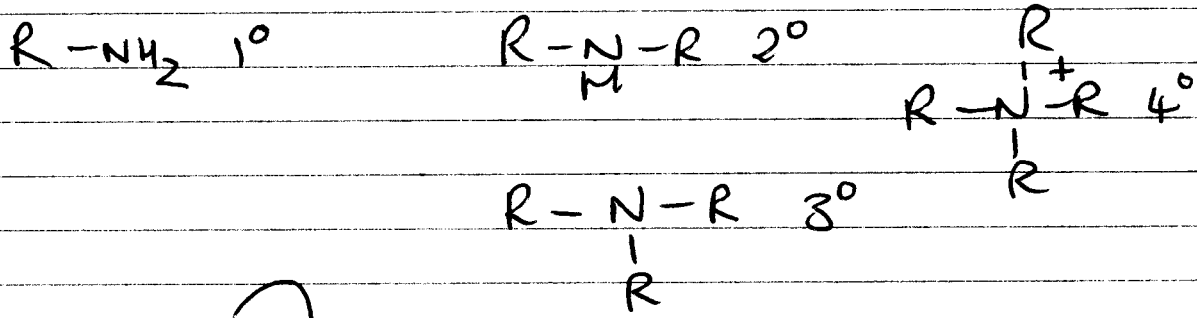
(6) CARBONYLS

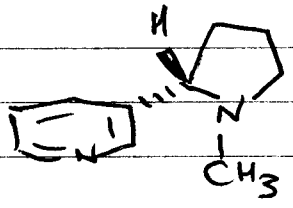


aldehyde Ketone carboxylic acid

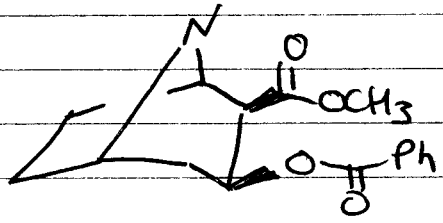


(7) AMINES





Nicotine



Cocaine.

Lec 2

Chem 30B

① Office Hours
Cari T, 8-10am / Rob T, 1-3pm / AL R, 10-12 noon
ALL in 3077F Young Hall
Me MW 1-2 pm 3077D Young Hall.

② Homework
9.1-9.7 Mix
9.14-9.24 Structure/Nomenclature/Phys Prop

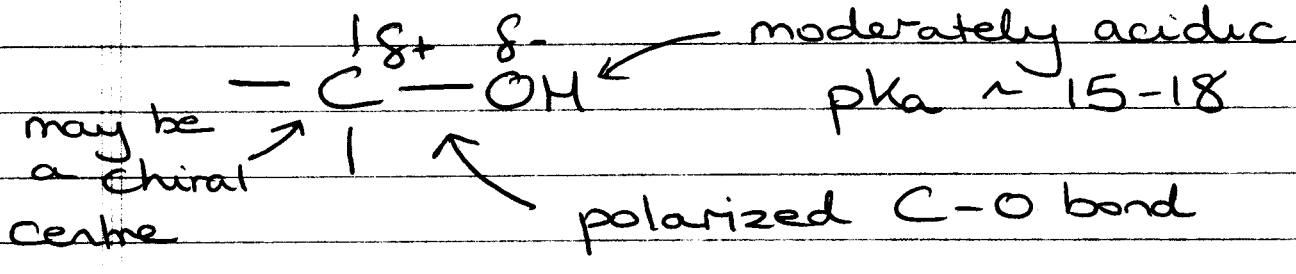
③ Friday's lecture PREVIEW
Quiz will be MWF of this week.

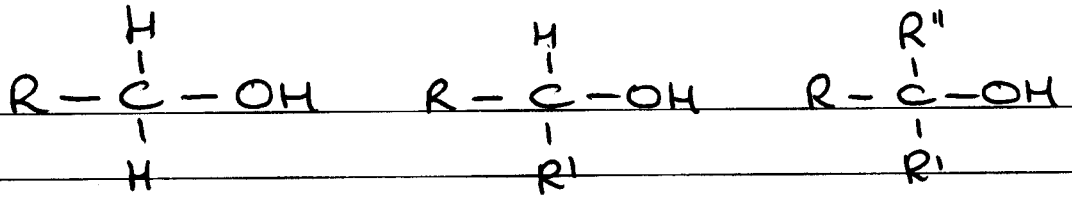
ALCOHOLS

(I) STRUCTURE
(II) NOMENCLATURE
(III) PHYSICAL PROPERTIES
(IV) ACIDITY / BASICITY
(V) 'ACTIVATION'

ALCOHOLS

(I) Functional Group $-OH$ hydroxyl

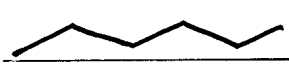




PRIMARY (1°) SECONDARY (2°) TERTIARY (3°)

(II) NOMENCLATURE

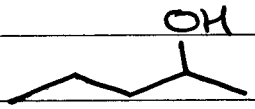
PENTANE



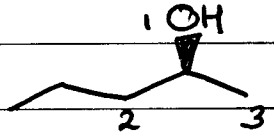
PENTANOL

Position of OH? either 5 or 1 ⇐

1-PENTANOL or PENTAN-1-OL

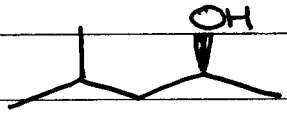


PENTAN-2-OL

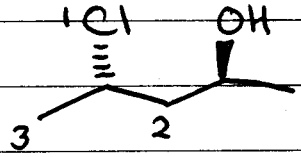


(S)-PENTAN-2-OL (Ch 3)

OH BEATS HALOGEN or ALKYL

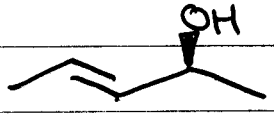


(S)-4-METHYL-PENTAN-2-OL



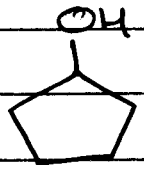
(2S,4S)-4-CHLORO-PENTAN-2-OL

ALSO BEATS C=C

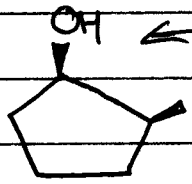


(E) or trans (S) 3-PENTEN-2-OL

CYCLIC



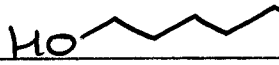
CYCLOPENTANOL



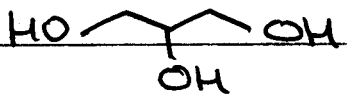
OH ← assumed #1

(1R,2S)-2-CHLOROCYCLOPENTANOL

DIOLS + TRIOLS



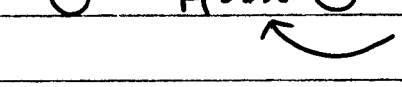
1,5-PENTANE DIOL



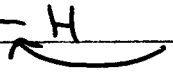
1,2,3-PROPANETRIOL
(Glycerol or Glycerine)

(iii) PHYSICAL PROPERTIES

HYDROGEN BONDING $\overset{\delta-}{X}-\overset{\delta+}{H}\cdots\overset{\delta-}{Y}$ X, Y electronegative

e.g. 

weak noncovalent bond
~ 5 kcal/mol



~120 Kcal/mol

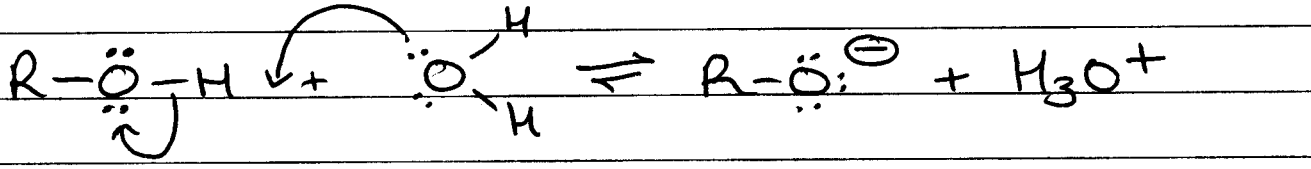
H-O-H bp 100°C
CH_3-O-H bp 65°C Infinite H_2O sol
CH_3-O-CH_3 bp -24°C 8g/100g

makes molecules stick together more

More OH, more sticky

1,4-butanediol	HO⌇⌇OH	bp 230°C
1-pentanol	HO⌇⌇	bp 138°C
hexane	⌇⌇	bp 69°C

(IV) ACIDITY / BASICITY



$$K_a = \frac{[R\text{-}O^{\ominus}][H_3O^+]}{[ROH]} \qquad [H_2O] = \text{constant}$$

$ROH = MeOH \quad K_a = 10^{-15.5}$

$pK_a = -\log_{10} K_a$

MeOH	15.5
H_2O	15.7
EtOH	15.9
>-OH	17
+OH	18

LESS ACIDIC

(Ch4)

Big R, $R\text{-}O^{\ominus}$ not solvated as well, so less stable

$$R-O-H \underset{}{\overset{\text{base}}{\rightleftharpoons}} R-O^- \quad \text{nucleophile}$$

Strong bases:

(i) $$NH_3 \overset{K_a}{\rightleftharpoons} NH_2^{\ominus} + H^+ \qquad K_a \sim 10^{-35}, \quad pK_a \sim 35$$

$NH_2^{\ominus}$ ↑ amide

$$R-O-H + {}^{\ominus}NH_2 \longrightarrow R-O^{\ominus} + NH_3 \uparrow$$
$$(NaNH_2) \qquad\qquad (Na^+)$$

(ii) $$H_2 \overset{K_a}{\rightleftharpoons} H^+ + H^- \qquad K_a \sim 10^{-35}, \quad pK_a \sim 35$$

H^- ← hydride

$$R-O-H + H^{\ominus} \longrightarrow R-O^{\ominus} + H_2 \uparrow$$
$$(NaH) \qquad\qquad (Na^+)$$

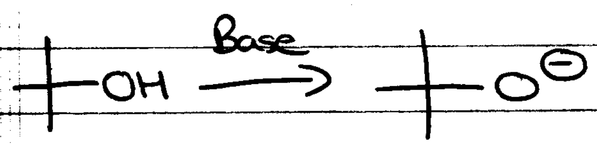
Active metals

$$R-O-H + Na \text{ (or Li, K)} \longrightarrow R-O^{\ominus}Na^+ + \tfrac{1}{2}H_2$$

$$Na^{\bullet} + H-OR \longrightarrow R-O^{\ominus}Na^+ + H^{\bullet}$$

$$H^{\bullet} + H^{\bullet} \longrightarrow H_2 \uparrow$$

ALKOXIDES AS NUCLEOPHILES / BASES



Act as base

HINDERED

MeOH $\xrightarrow{\text{base}}$ MeO^- base/nucleophile

$MeO^- + R-I \rightarrow MeO-R + I^-$

(V) 'ACTIVATION'

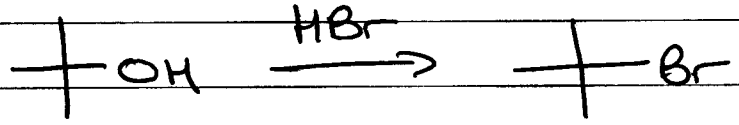
$R-OH + Nuc \rightarrow R-Nuc + OH^-$

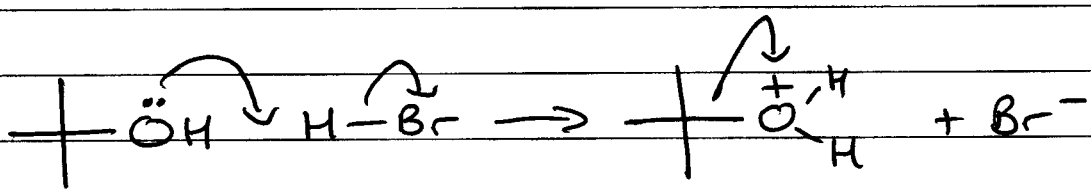
NOT GOOD LG

activate to leave:

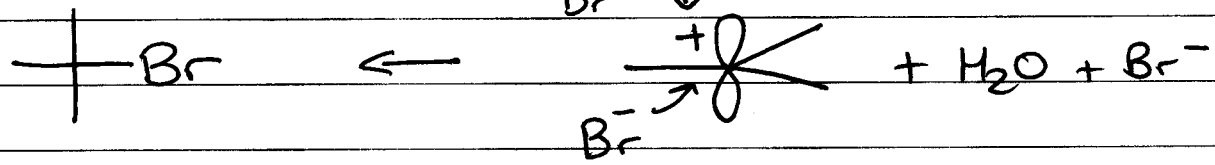
(i) ALKYL HALIDES (rxn HCl/HBr)

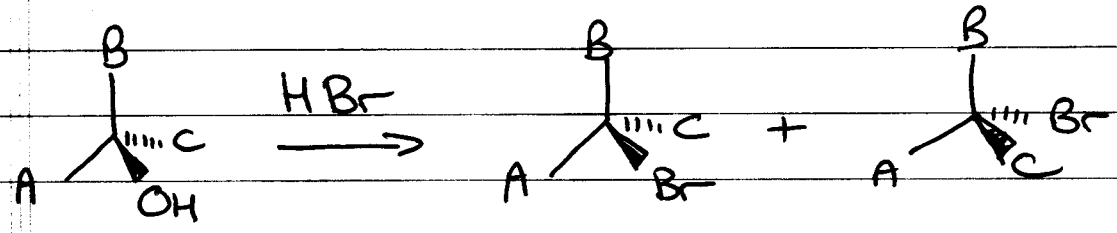
3° alcohols – RAPID at rt





↓ RDS (S_N1)

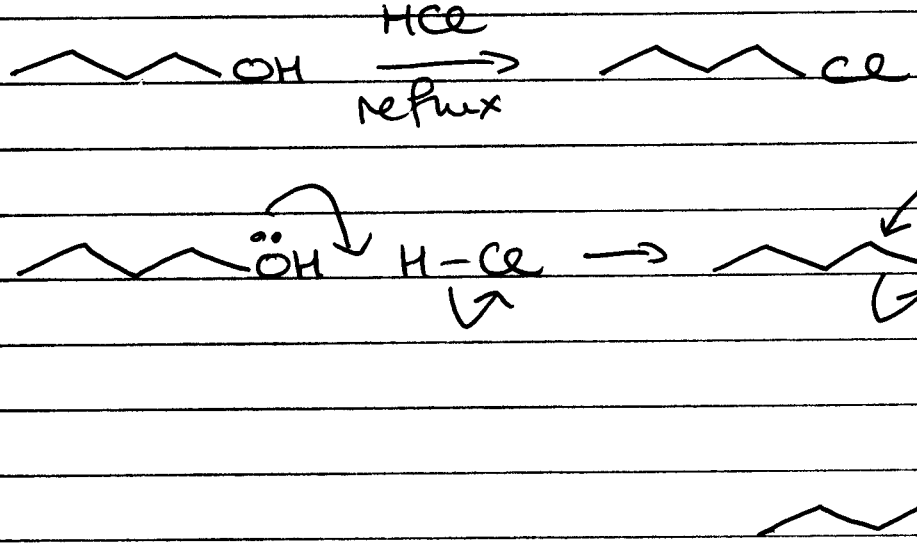




ENANTIOMERICALLY PURE

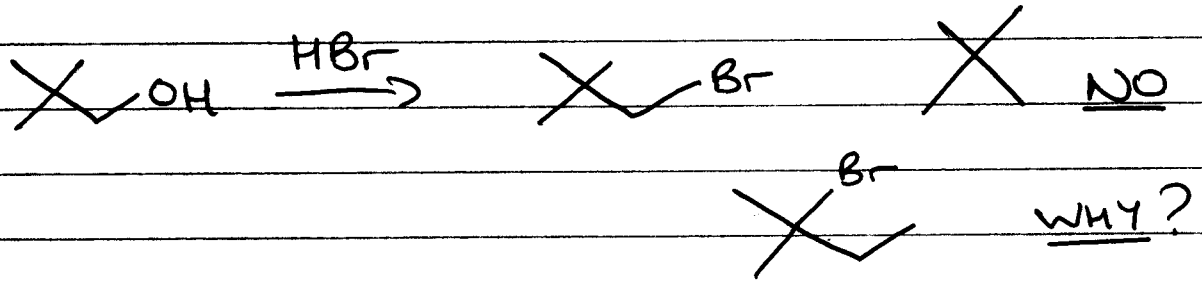
RACEMIC MIXTURE

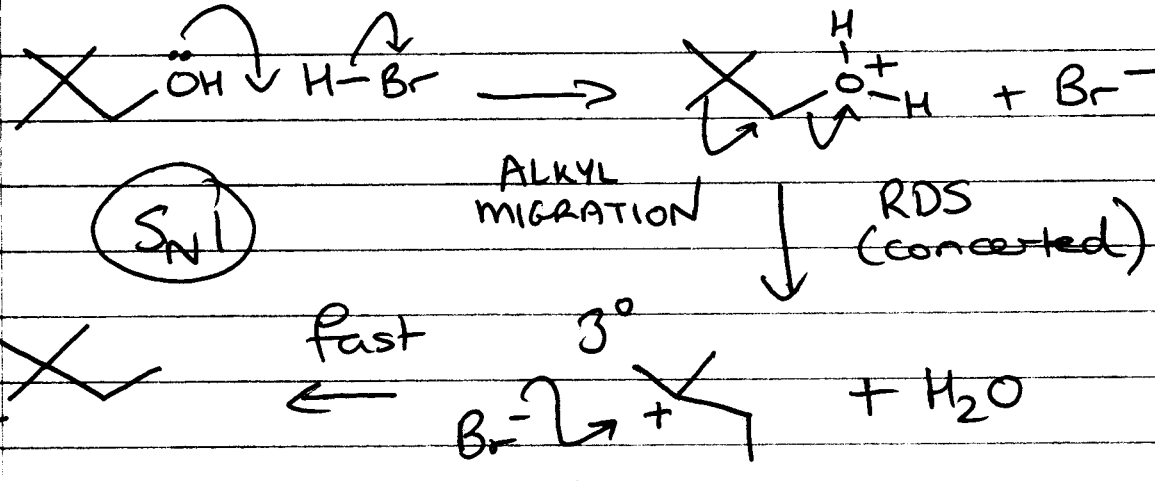
1° ALCOHOLS (UNBRANCHED)



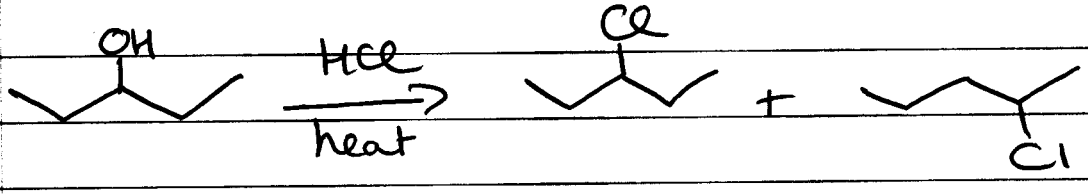
PRIMARY CARBOCATION NOT STABLE, AND PRIMARY –OH susceptible to nucleophilic attack, NOT SO HINDERED.

BRANCHED 1° ALCOHOL





2° ALCOHOLS (elimination?)

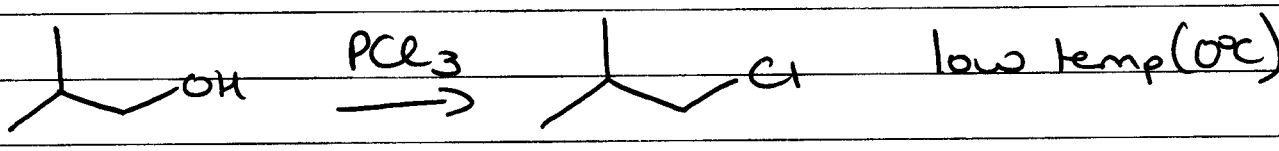


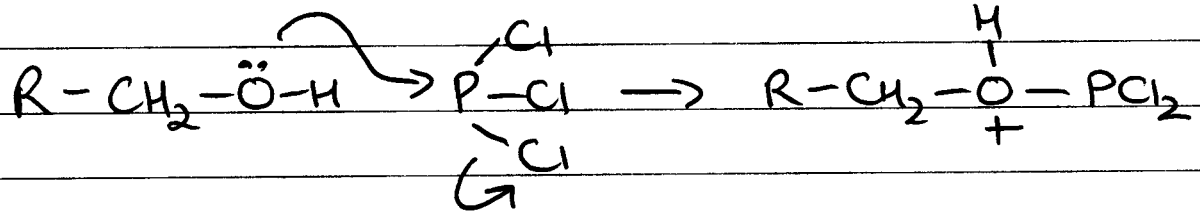
May be S_N1, S_N2 or both!
Some S_N1 → carbocation rearrangement.

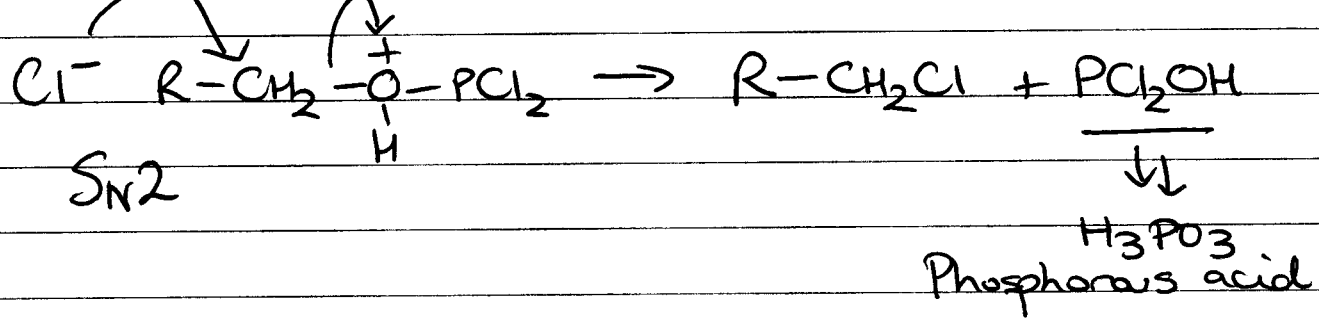
So HCl, HBr only really useful for 3° ROH and v. simple straight chain 1° ROH.

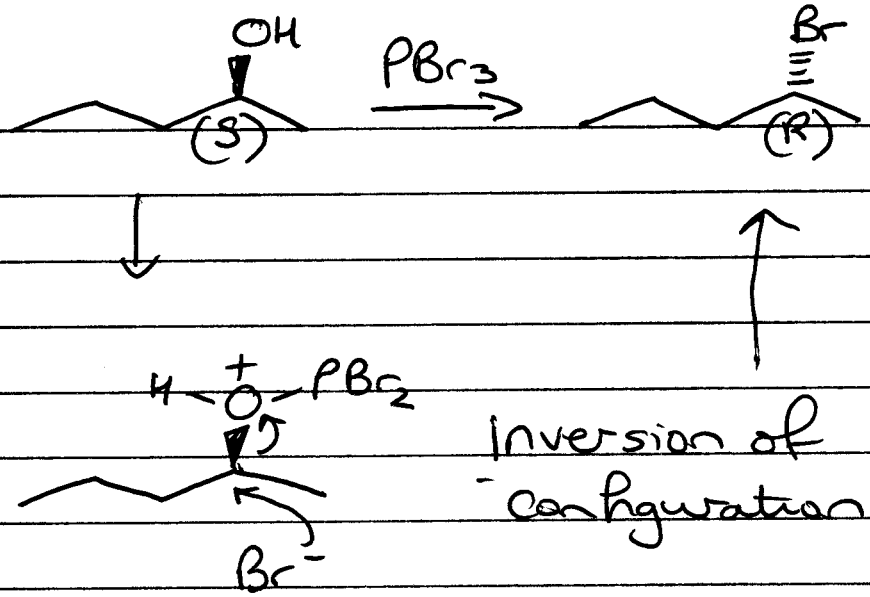
So, how do we deal with other 1° & 2°?

PX_3 X = Cl, Br (mild, less rearrangement)

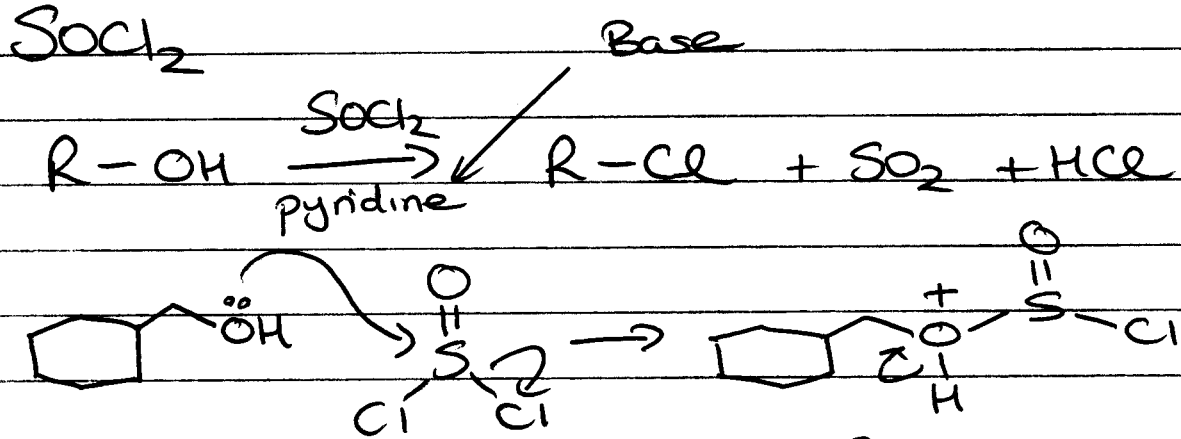


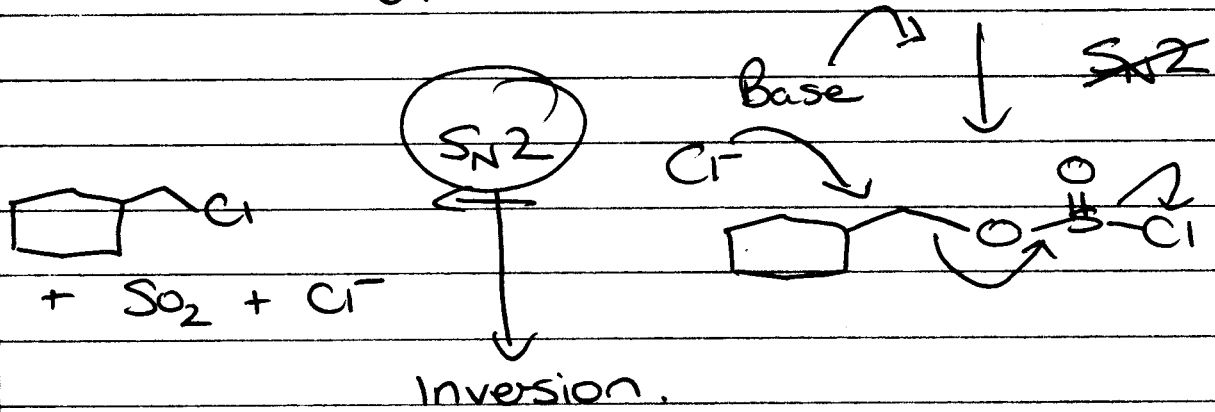




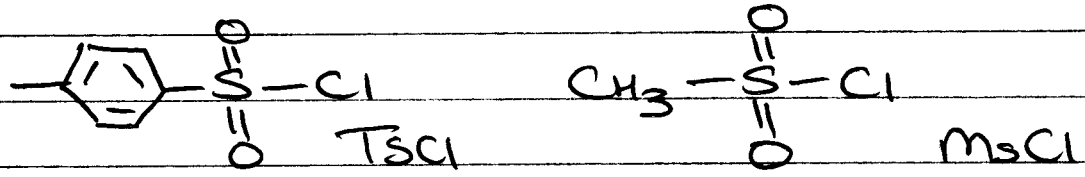


$SOCl_2$

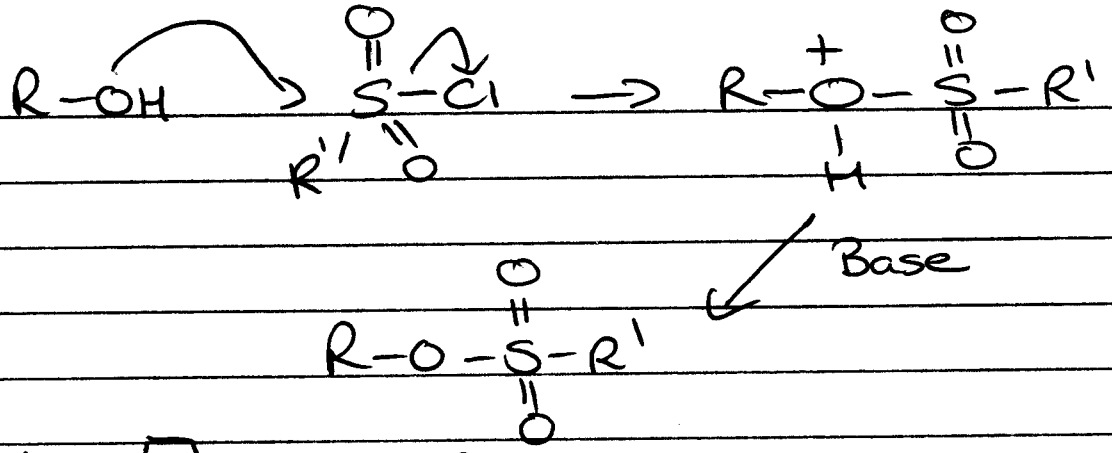




SULFONYL CHLORIDES



Tosyl chloride Mesyl chloride



$R-O-\overset{O}{\overset{\|}{S}}(=O)-R'$

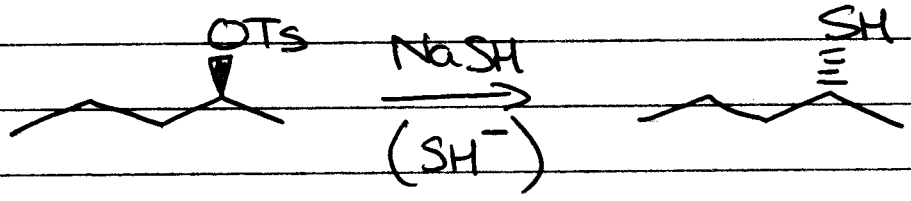
$R' = -C_6H_4-CH_3$ = ROTs → tosylate

$R' = -CH_3$ = ROMs → mesylate

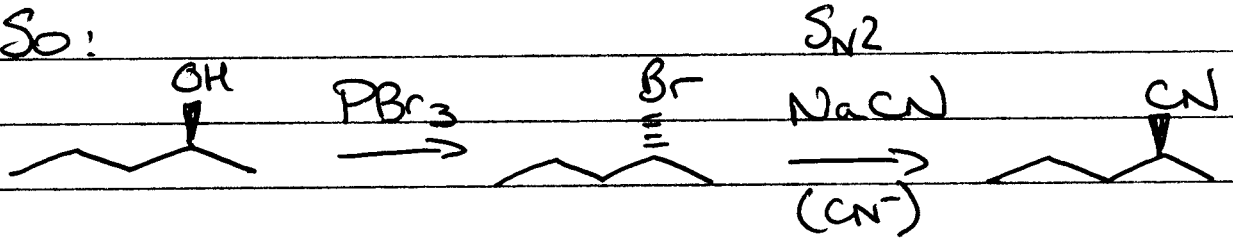
ALKYL SULFONATES

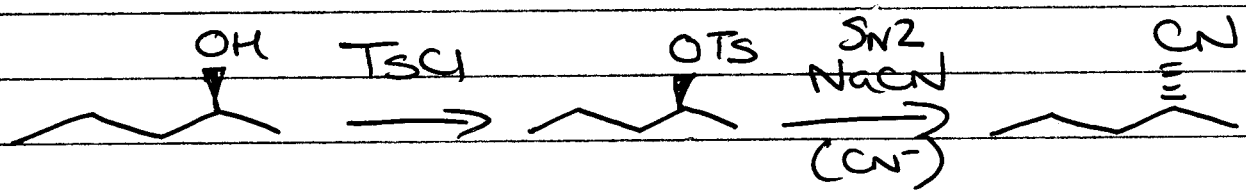
RETENTION OF CONFIGURATION

until....



So:





RETRO:

$R-CN \Longrightarrow R-Br$ or $R-OTs \Rightarrow R-OH$

NXT TIME: DEHYDRATION / OXIDATION / THIOLS

CHEM 30B — Lecture (3)

Announcements - Quiz next week Weds 8th
Homework 9.30 – 9.39

1. ALCOHOL ACTIVATION
   - HCl/HBr
   - PX_3 (X = Cl, Br)
   - $SOCl_2$
   - RSO_2Cl
2. ACID CATALYZED DEHYDRATION
3. PINACOL REARRANGEMENT
4. OXIDATION

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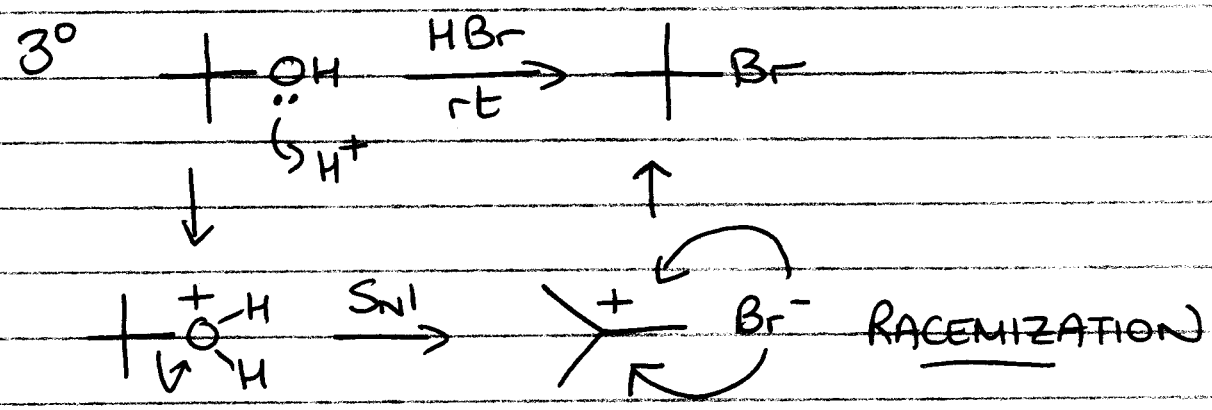
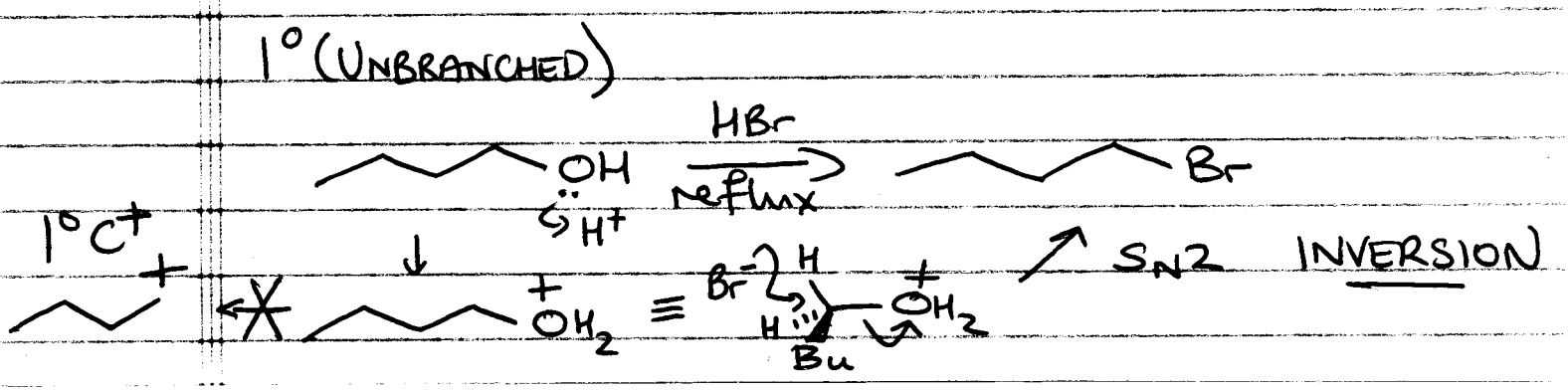
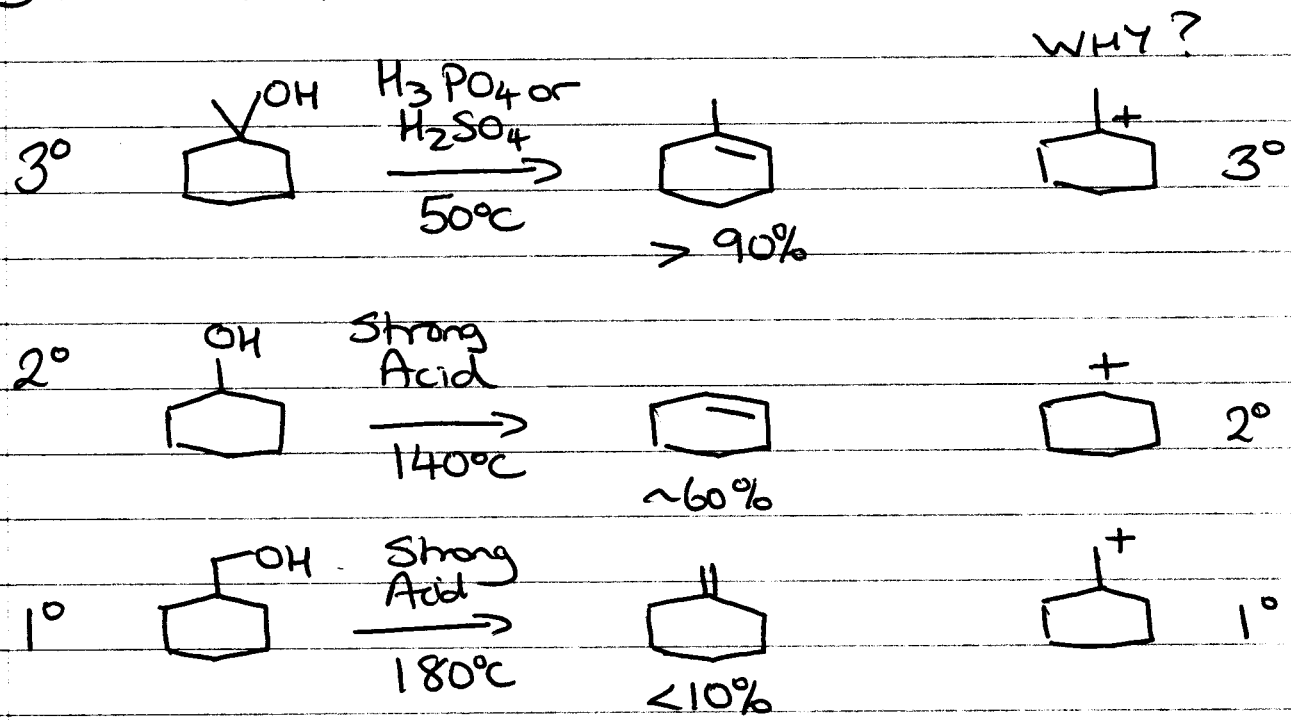
1. Quick Review (HBr/HCl)

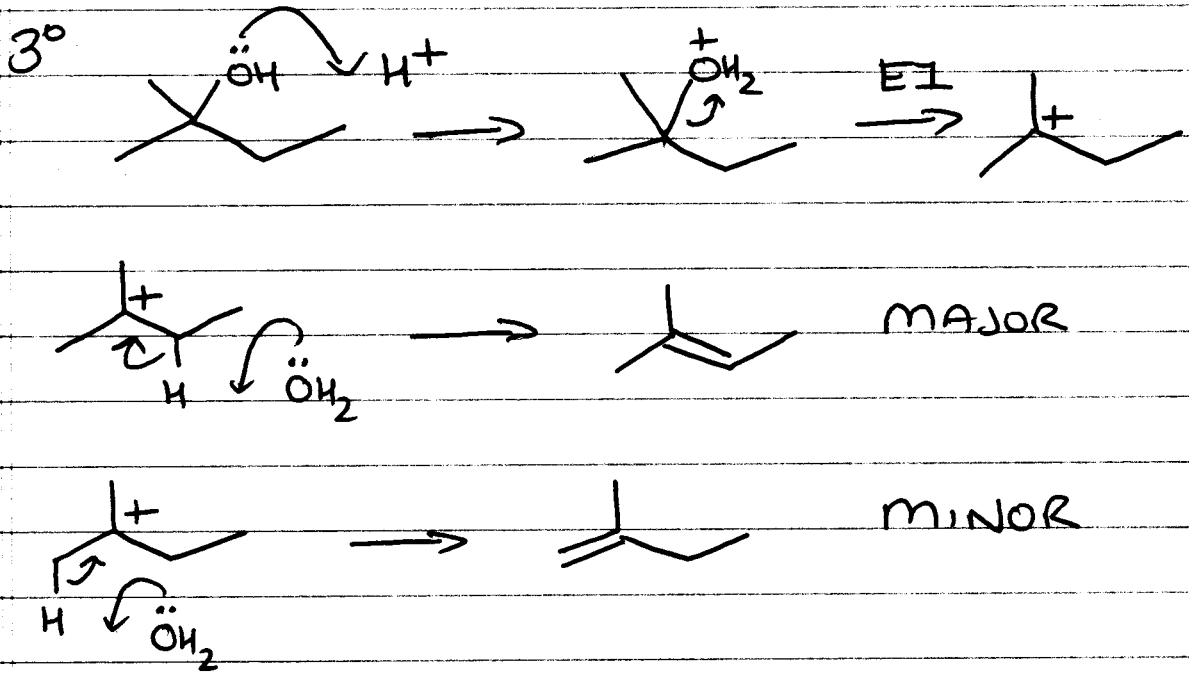




② ACID CATALYZED DEHYDRATION

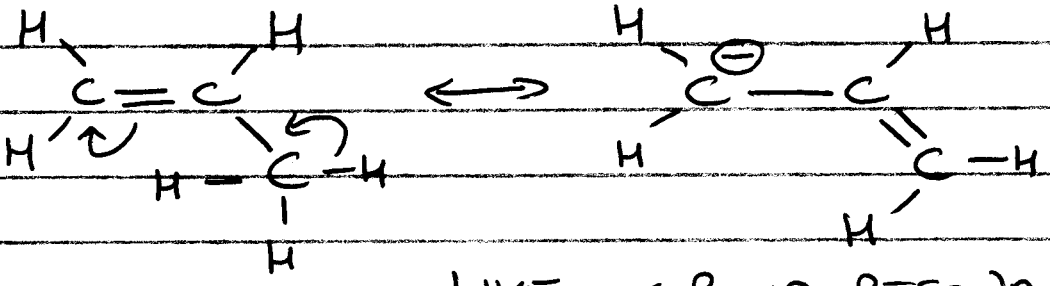


ONLY SYNTHETICALLY USEFUL FOR 3°

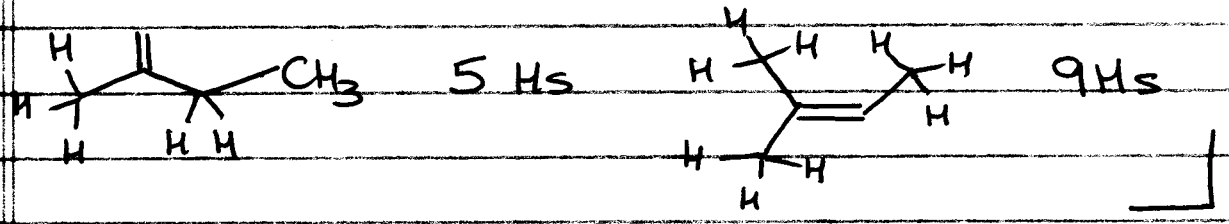


ZAITSEV RULE (more substituted alkene is formed more)

HYPERCONJUGATION

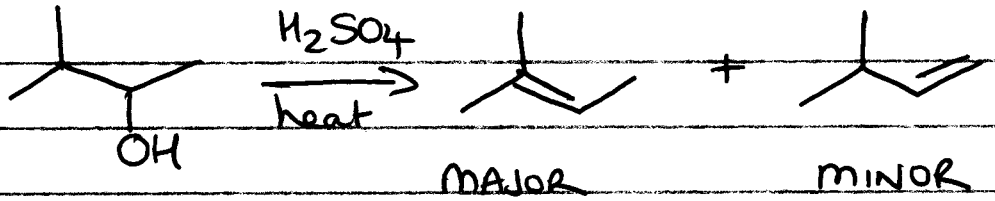


LIKE σ BOND RESONANCE

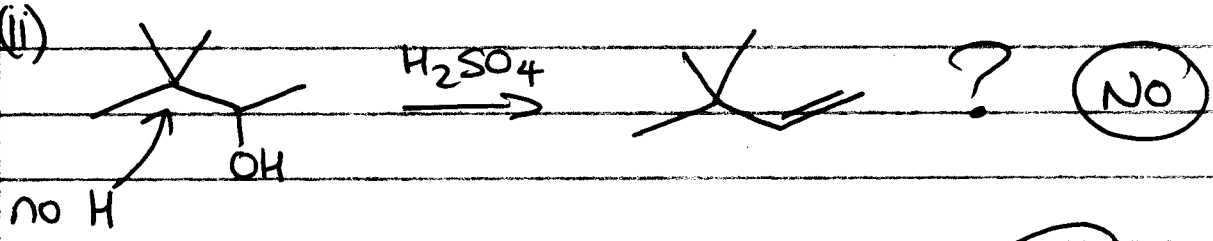


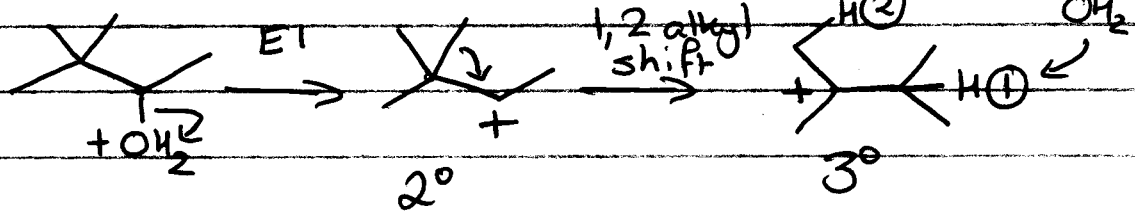
2° ALCOHOLS

(i)



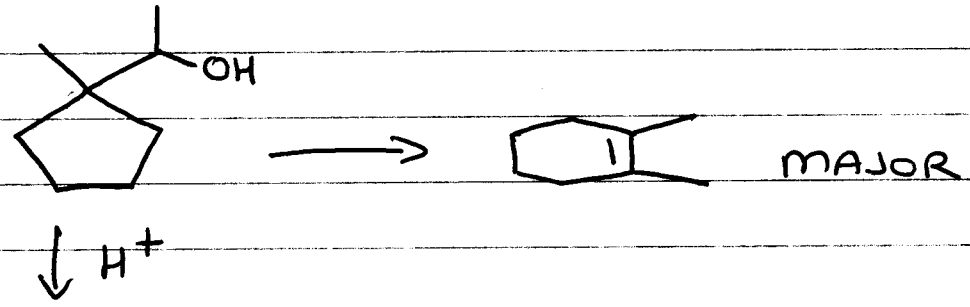
(ii)



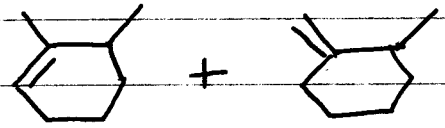


4 R groups 2 R groups

(iii)

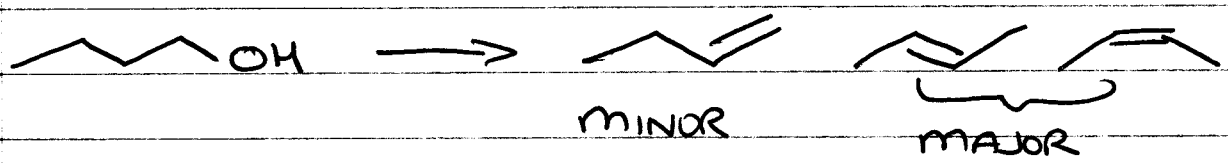


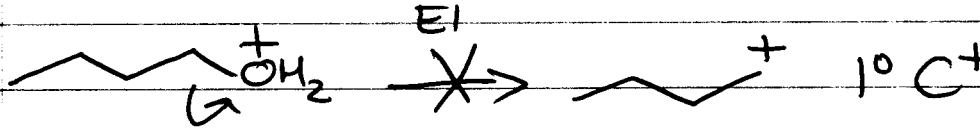
and

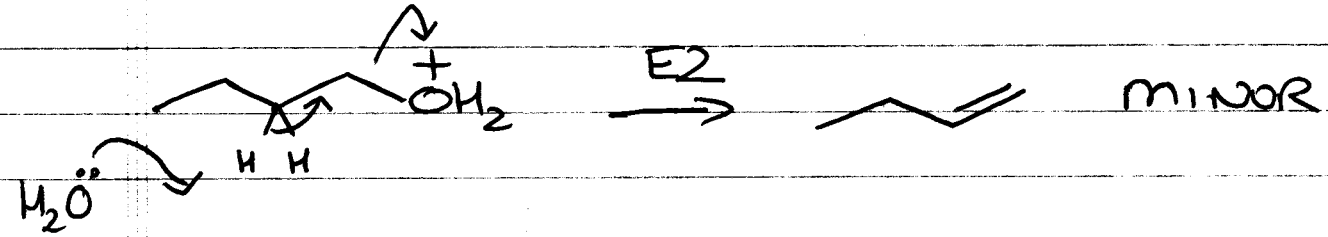


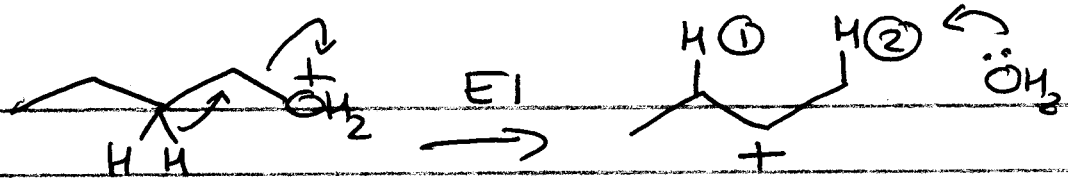
3R 2R

1° (REALLY FORCING CONDITIONS)







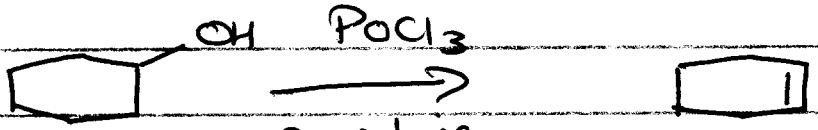


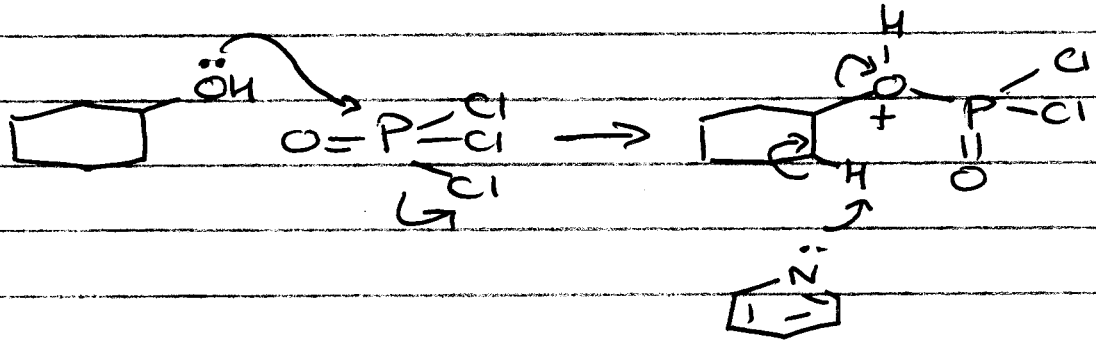
1,2 HYDRIDE SHIFT

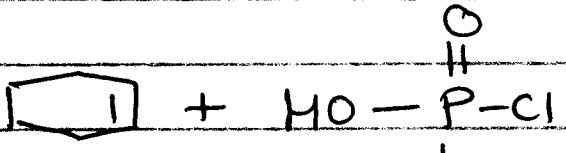
Cis / trans

MILDER METHOD ($POCl_3$)

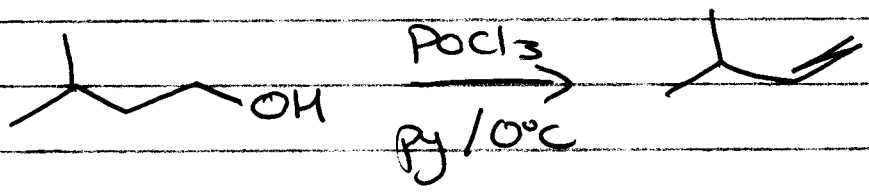
2°







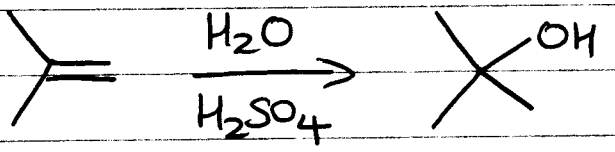
1°



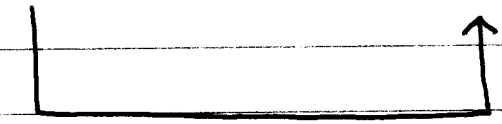
DEHYDRATE ALCOHOLS ⟶ ALKENES

HYDRATE ALKENES ⟶ ALCOHOLS

MUST KNOW THIS

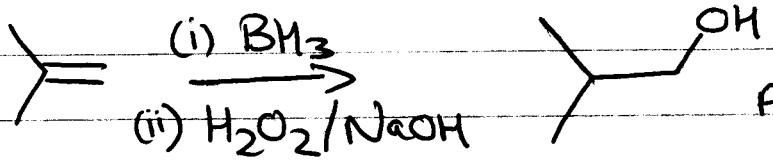


MARKOVNIKOV



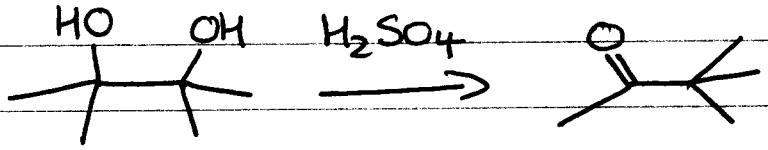
(i) $Hg(OAc)_2$ / H_2O (ii) $NaBH_4$

CHAPTER 6

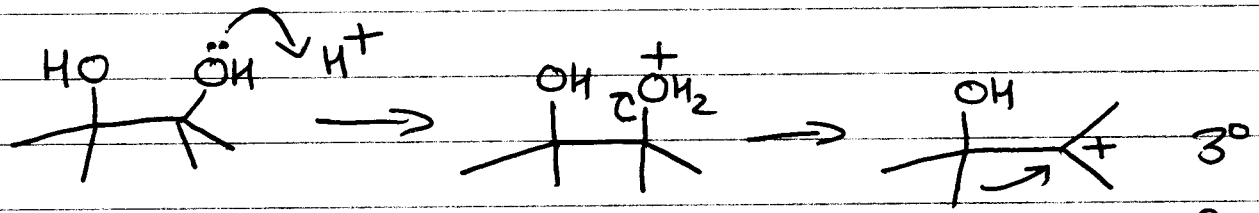


ANTI-MARKOVNIKOV

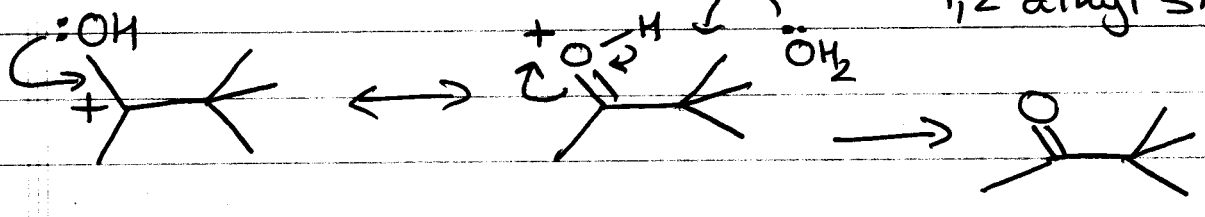
③ PINACOL REARRANGEMENT



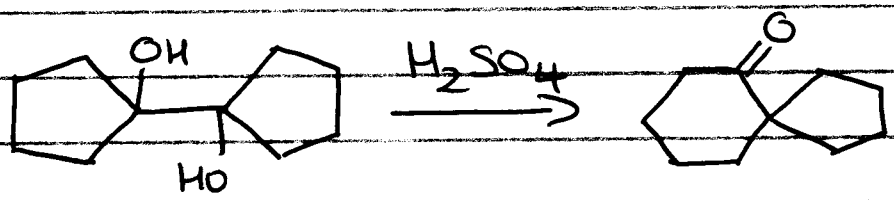
PINACOL



1,2 alkyl shift

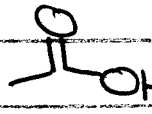


GENERAL FOR ALL 1,2 DIOLS

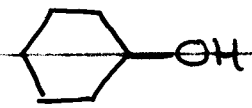


WORK OUT MECHANISM

(4) OXIDATION

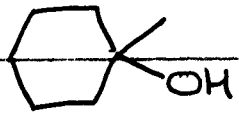
1° $RCH_2OH \xrightarrow{Ox}$  $\xrightarrow{Ox}$ 

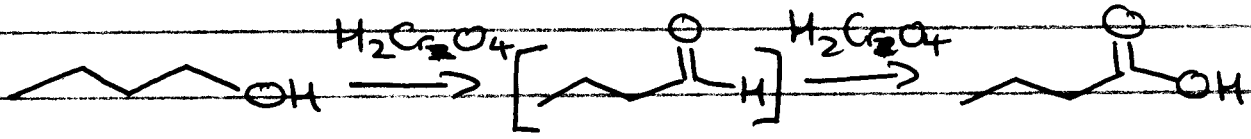
ALDEHYDE CARBOXYLIC ACID

2°  $\xrightarrow{Ox}$ 

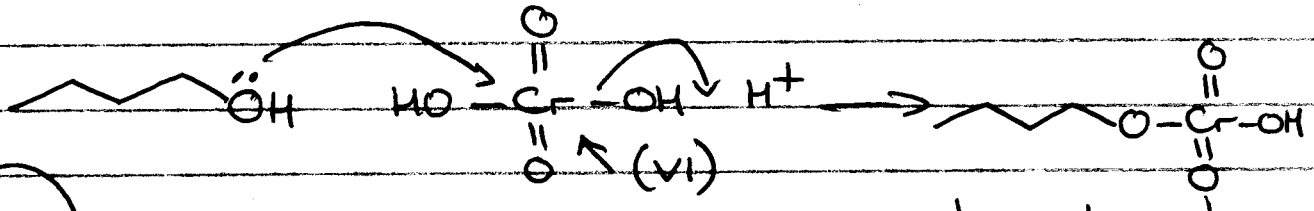
KETONE

STOPS HERE

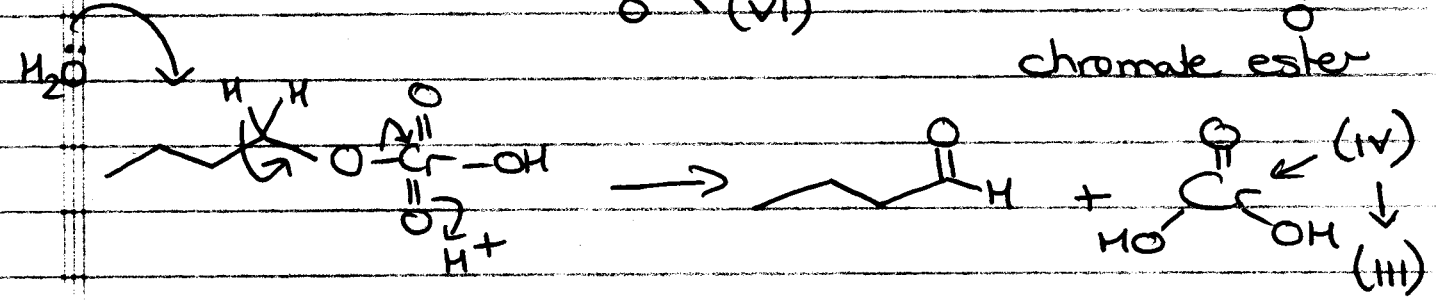
3°  $\xrightarrow{Ox}$ NO REACTION

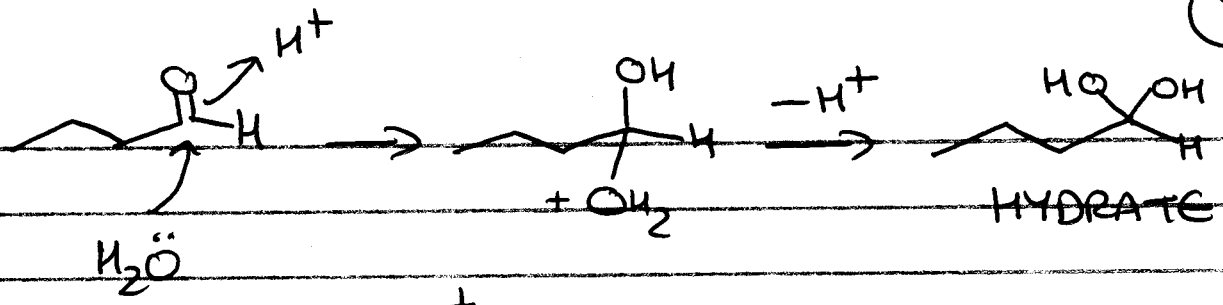


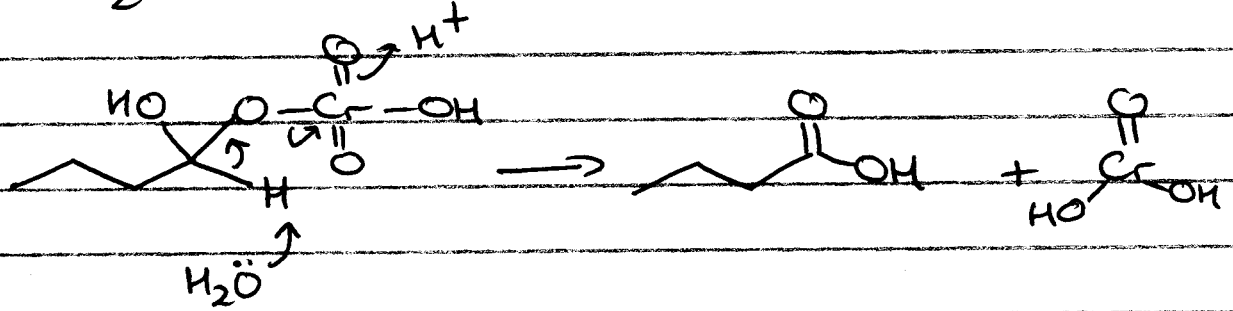
$CrO_3 + H_2SO_4 + H_2O \longrightarrow H_2CrO_4$

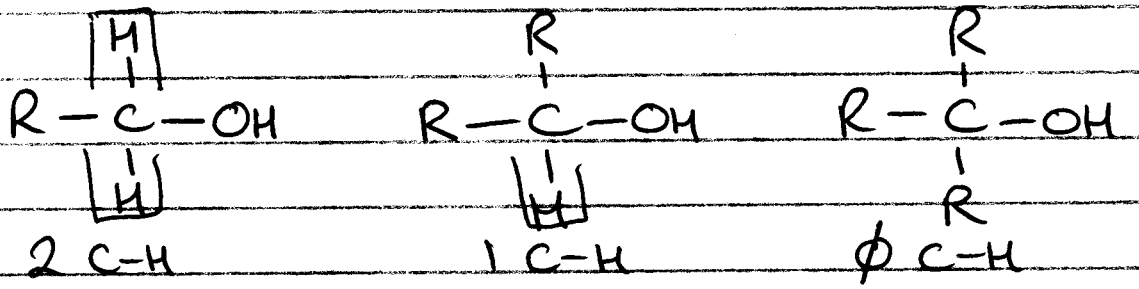


chromate ester





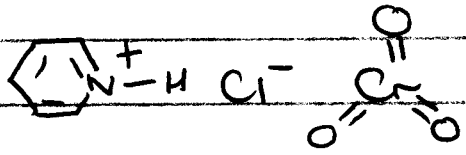


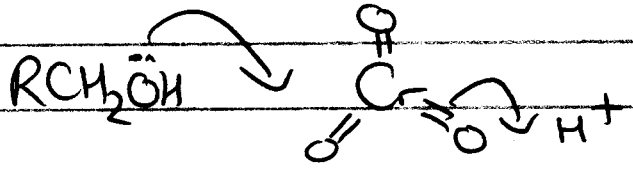


— $RCH_2OH \longrightarrow RCHO \leftarrow$ STOP HERE?

$CrO_3 + HCl +$  $\longrightarrow$ PCC

PYRIDINIUM CHLOROCHROMATE





$\Rightarrow$ chromate ester

↓

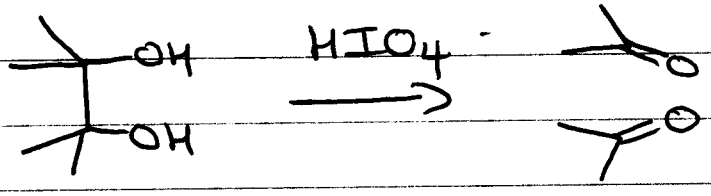
aldehyde

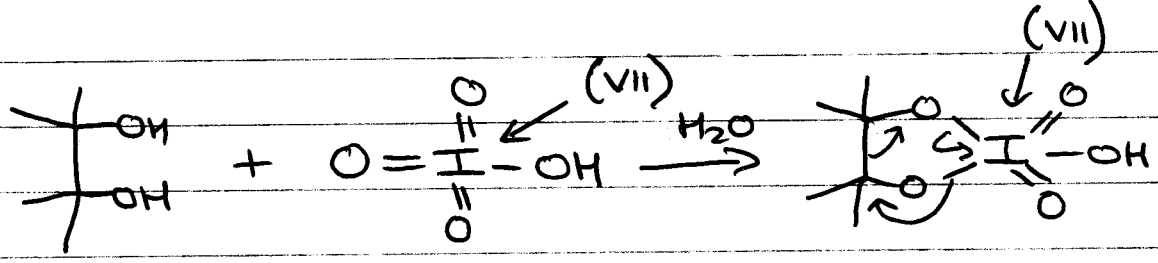
DOES NOT FORM HYDRATE — DONE IN ORGANIC SOLV (NO WATER)

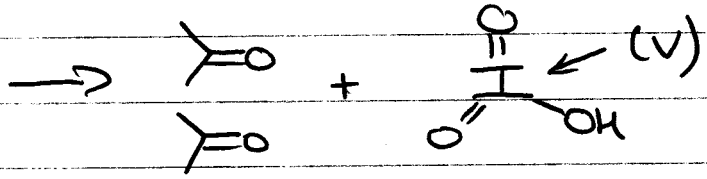
SELECTIVE / MILD — does 2° TOO

PERIODIC ACID

1,2 DIOLS (GLYCOLS)

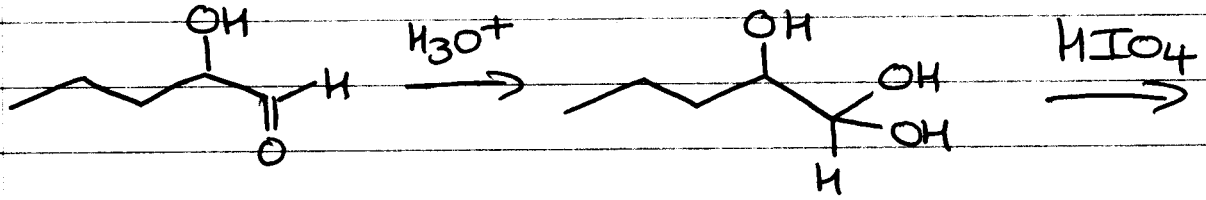




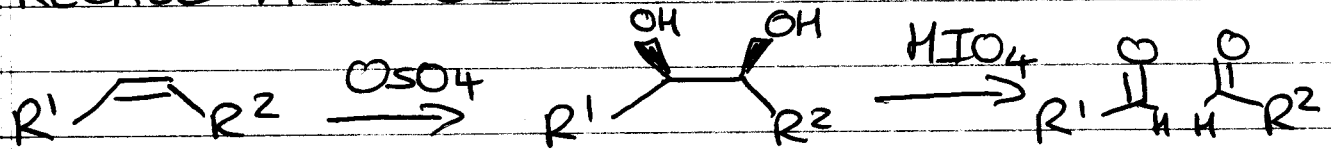


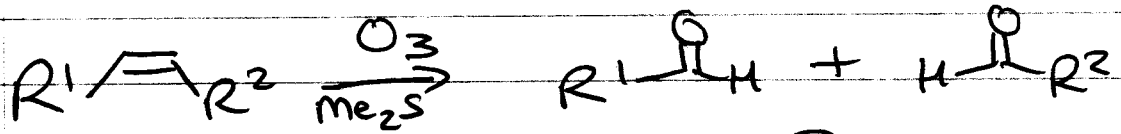
Iodic Acid

MUST BE ABLE TO FORM 5-MEM RING



RECALL ALKENES





THIOLS / ALCOHOL PROTECTION ?

CHEM 30B Lec 4

Homework 9.10-9.13, 9.30-9.32, 9.36-9.39, 9.41

1. SULFONYL CHLORIDES - RECAP
2. ALCOHOL DEHYDRATION
3. PINACOL REARRANGEMENT
4. OXIDATION
5. SULFUR ANALOGS

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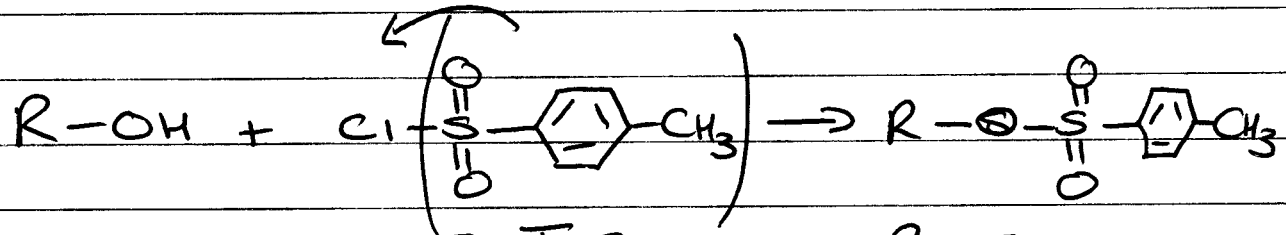
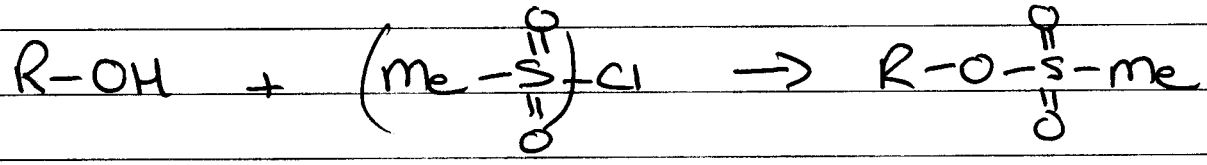
1. SULFONYL CHLORIDES



TsCl → ROTs

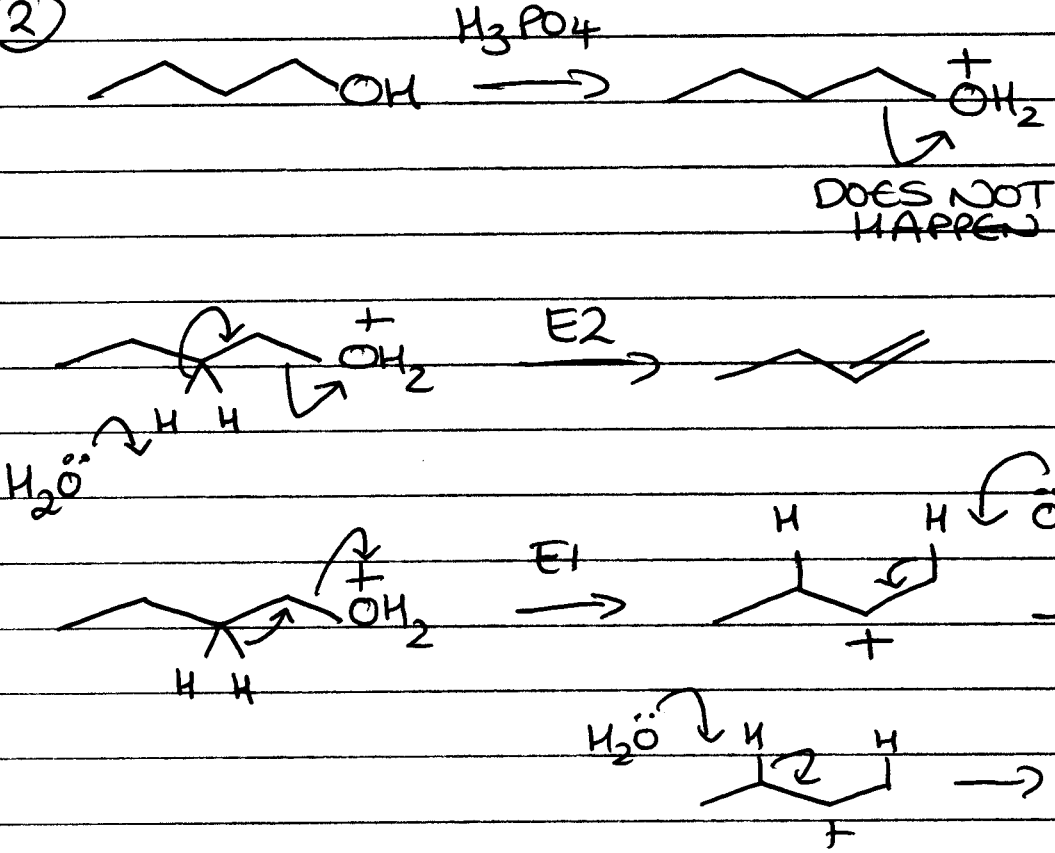
Tosyl chloride — Alkyl tosylate



MsCl → ROMs

Mesyl chloride — Alkyl mesylate

(2)



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(2) MILDER $POCl_3$

(3) PINACOL

(4) OXIDATION

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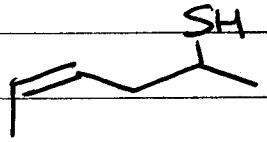
(5) SULFUR

(i) Thiols R-SH

CH_3SH methanethiol

CH_3CH_2SH ethanethiol



(Z)-4-hexene-2-thiol

(ii) Physical Properties

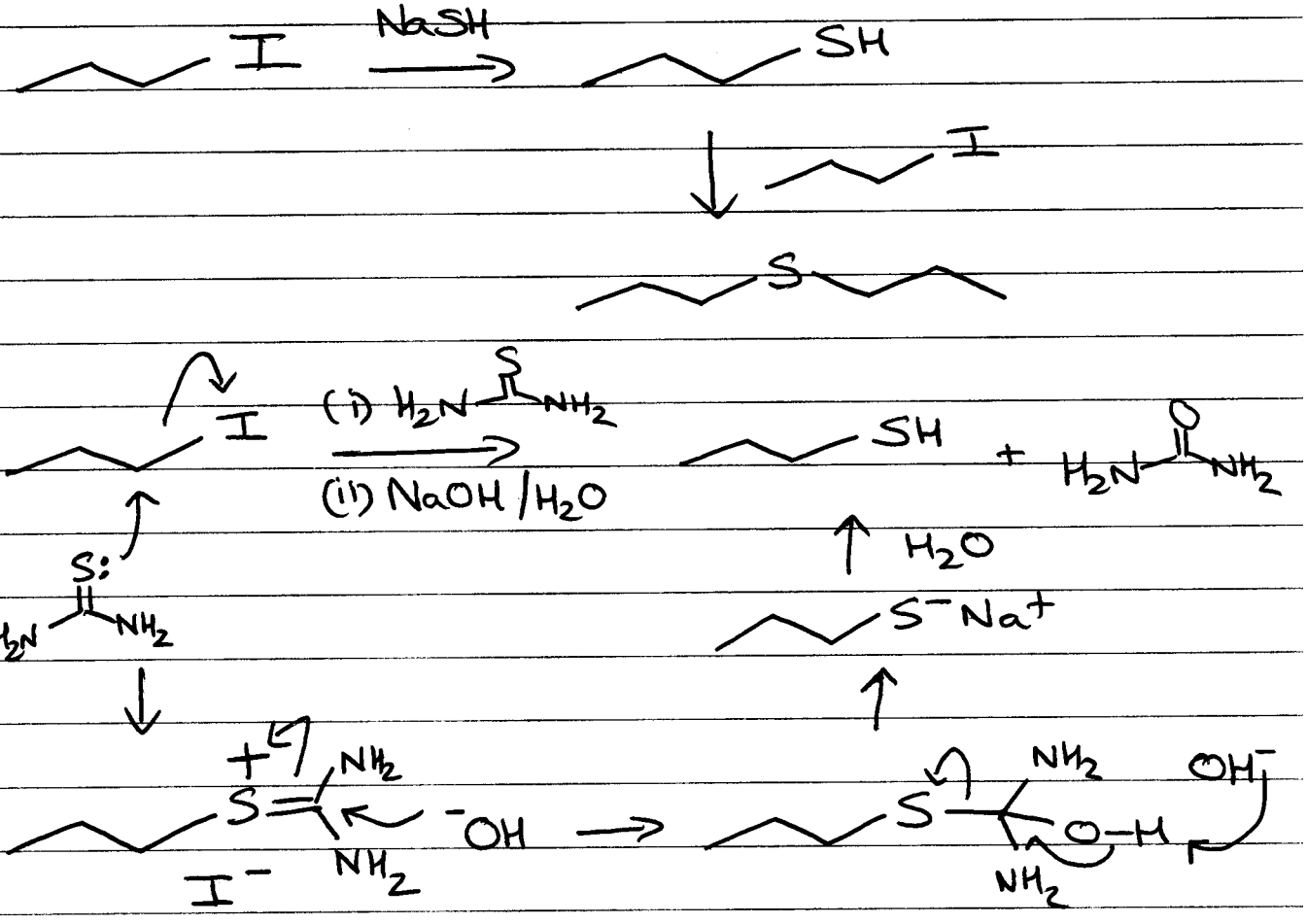
R – S – H
↑ low polarity

NO H-BONDING

CH_3CH_2SH bp 35°C
CH_3SCH_3 bp 37°C
} compare to oxygen analogs

DIMETHYL SULFIDE

(iii) Preparation



(iv) ACIDITY/BASICITY

$CH_3CH_2OH + H_2O \rightleftharpoons CH_3CH_2O^- + H_3O^+$ pka 15.9

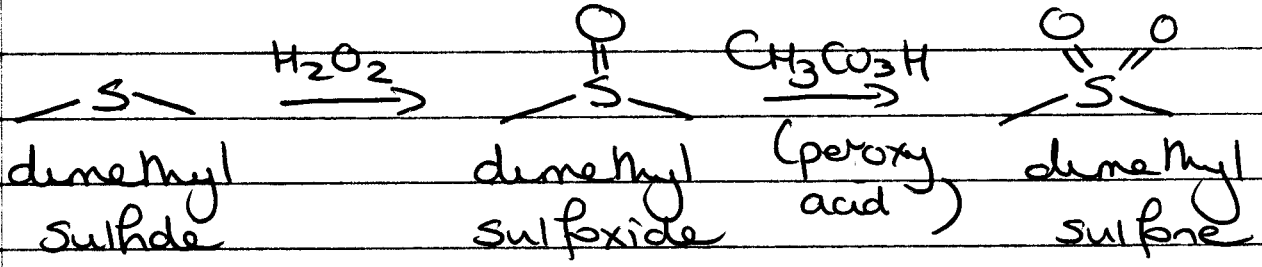
$CH_3CH_2SH + H_2O \rightleftharpoons CH_3CH_2S^- + H_3O^+$ pka 8.5

(v) OXIDATION

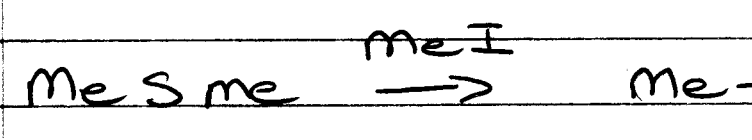
$$R\text{-}SH \xrightarrow{\ominus_2} R\text{-}S\text{-}S\text{-}R$$

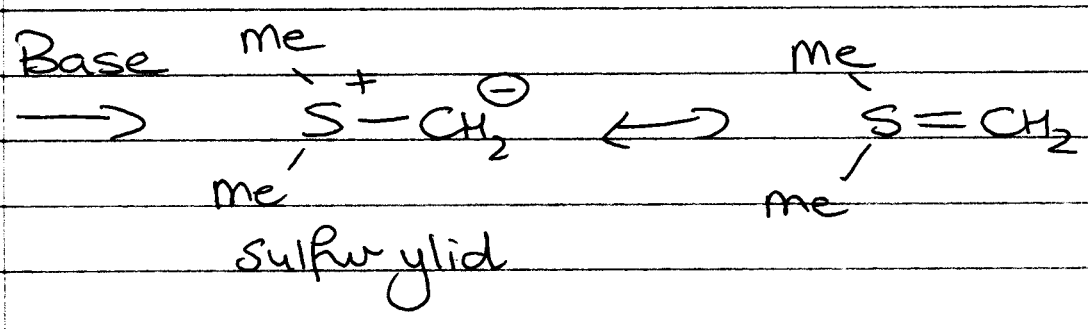
disulfide

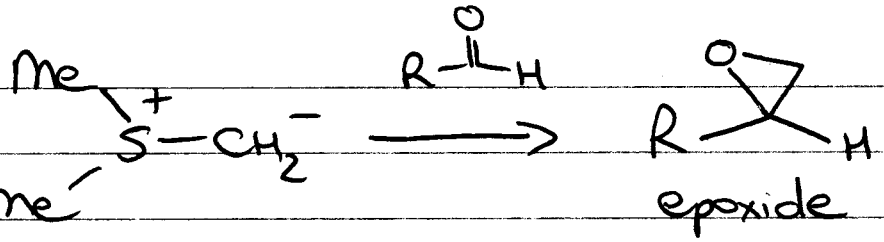
Important in tertiary structure of proteins

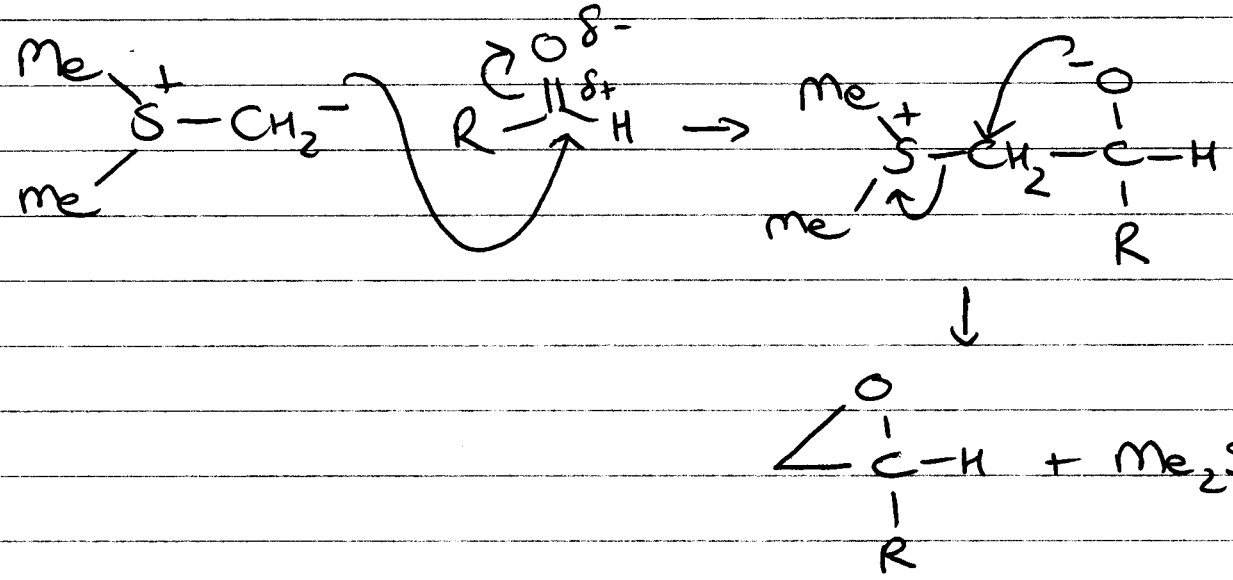


(VI) Reactions

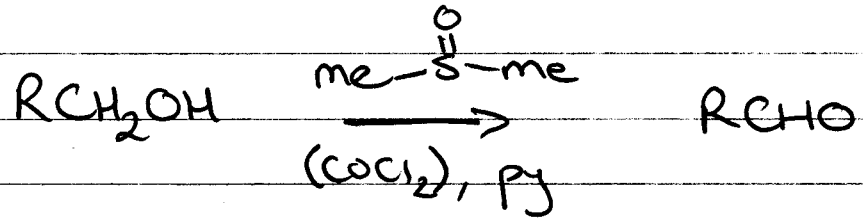


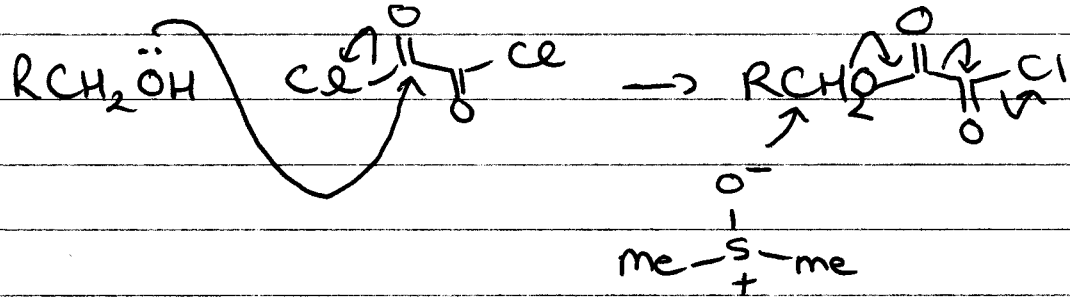


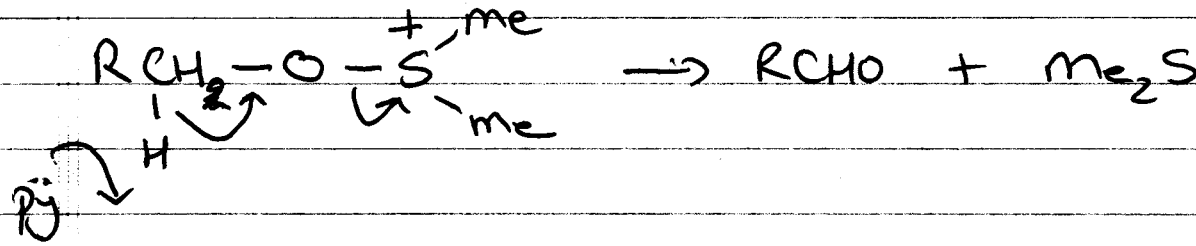




SWERN OXIDATION







CHEM 30B Lec (5)

ANNOUNCEMENTS
- Important Week
① CNSI Lecture 4pm CSSO Tuesday
'Single Molecule Nanoscale Rulers'
- Shimon Weiss
② Wednesday early morning
NOBEL PRIZE in CHEMISTRY
③ Wednesday morning QUIZ
④ Friday - LAST DAY TO DROP CLASS

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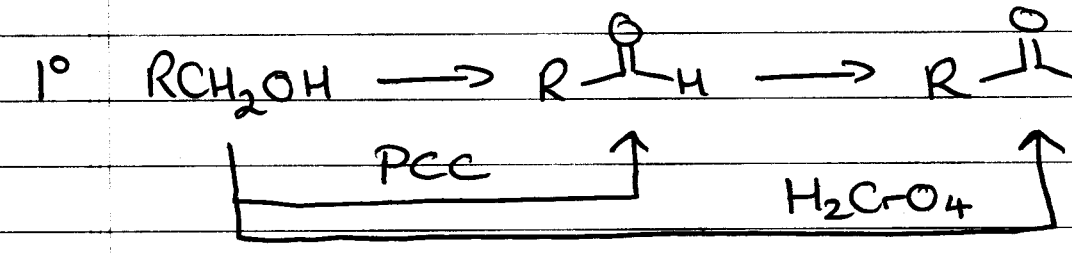
① OXIDATION SUMMARY (R-OH)
② THIOLS
③ ALKYNES (Ch 10)
Homework 9.13, 10.1, 10.3 - 10.18

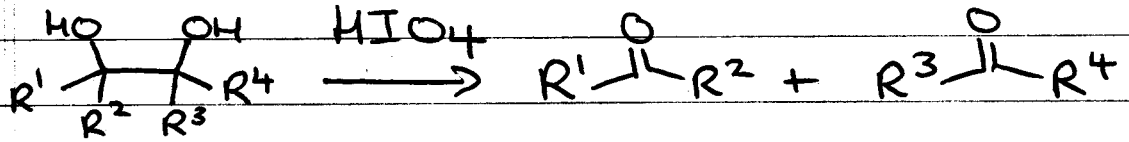
OXIDATION SUMMARY



2° $R_2CHOH \xrightarrow{PCC \text{ or } H_2CrO_4} R_2C{=}O$

3° $R_3C\text{-}OH \not\longrightarrow$ NO REACTION

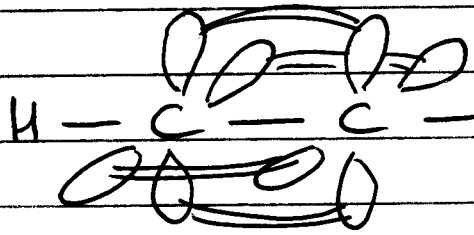
Diols



ALKYNES

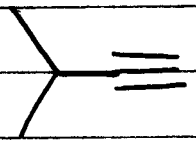
(I) H–C≡C–H acetylene (ethyne)

↑ sp hybridized

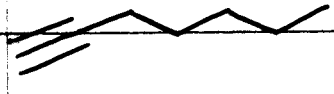


↑ π electron rich — ATTACKED by ELECTROPHILES

(II) NOMENCLATURE



3-METHYL-1-BUTYNE
(C≡C beats ALKYL)



5-HEXYN-1-OL
(OH beats C≡C)

PENT-1-EN-4-YNE
(C=C beats C≡C)

(III) ACIDITY
- MOST ACIDIC HYDROCARBONS

CH_3CH_2-H sp^3 pka > 50 $CH_2=CH-H$ sp^2 pka ~ 45 $CH\equiv C-H$ sp pka ~ 25

$C_{sp^3}-H$ $C_{sp^2}-H$ $C_{sp}-H$

25% 33% 50% → S character

S electrons held closer to nucleus

apparent C-atom electronegativity →

~~$HC\equiv C^-$~~

$CH_3CH_2^{\ominus}$ $CH_2=CH^{\ominus}$ $HC\equiv C^{\ominus}$

→

anion stability

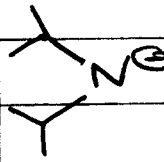
$H-C\equiv C-H + Na^+NH_2^- \rightleftharpoons HC\equiv C^{\ominus}Na^+ + NH_3$

pka ~25 $K_{eq} \sim 10^3$ pka ~38

Stronger acid Stronger base Weaker base Weaker acid

Other bases

NaH sodium hydride



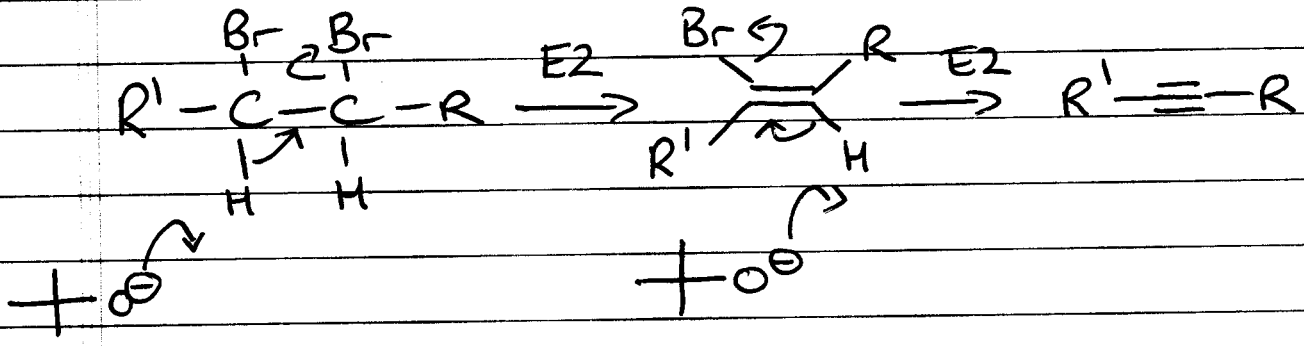
(LDA) lithium diisopropyl amide.

(IV) PREPARATION

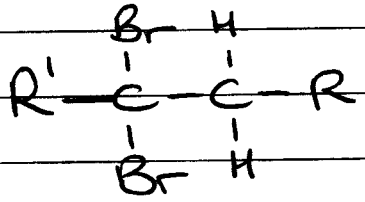
$R'CH=CHR \xrightarrow{Br_2} R'-\underset{H}{\overset{Br}{C}}-\underset{H}{\overset{Br}{C}}-R \longrightarrow R'-C\equiv C-R$

VICINAL DIBROMIDE

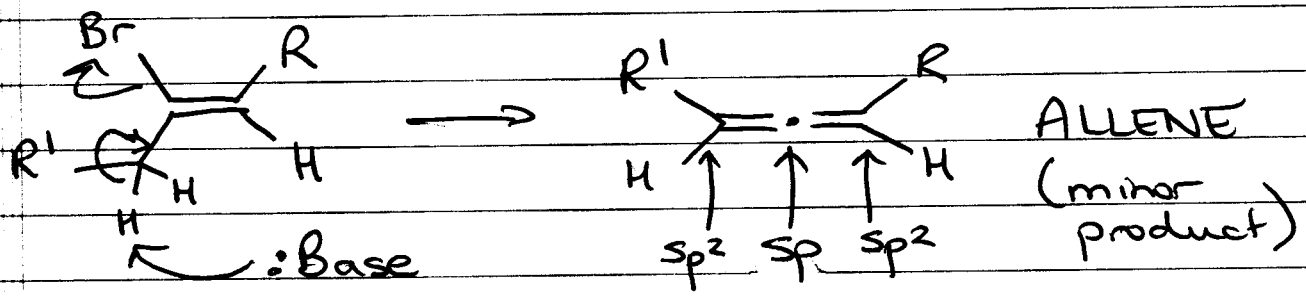
Dehydrohalogeration



Can also start from GEMINAL DIBROMIDE



SIDE REACTION

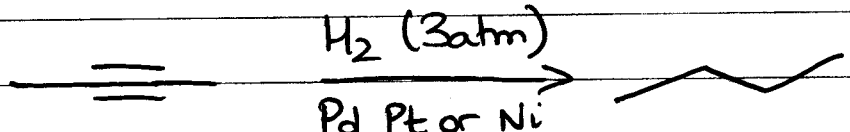


ALLENE (minor product)

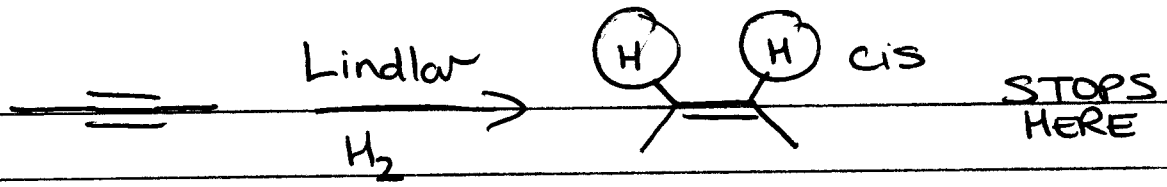
(V) REDUCTION (ADDITION OF H_2)

ALKYNE → [ALKENE] → ALKANE

(i) CATALYTIC HYDROGENATION

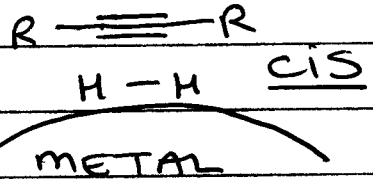


But-2-yne → Butane → NOT ISOLABLE

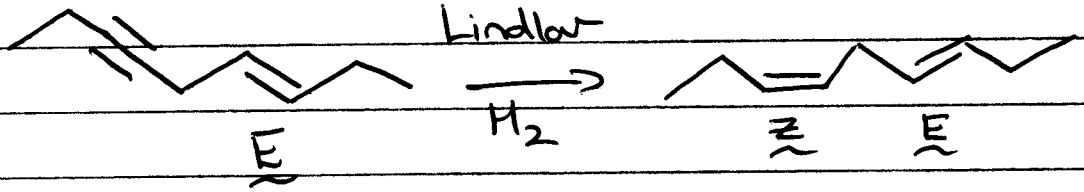


Lindlar catalyst ($Pd/CaCO_3/PbO$)

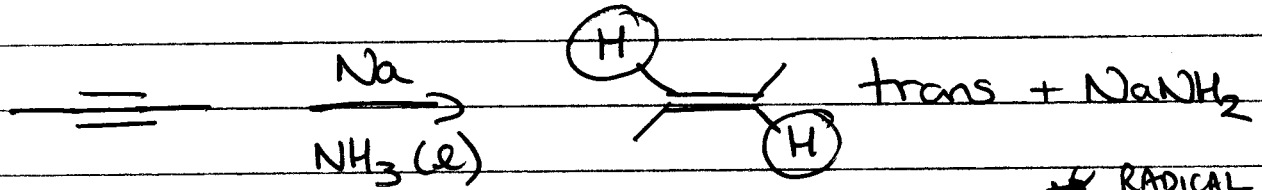
POISONED CATALYST

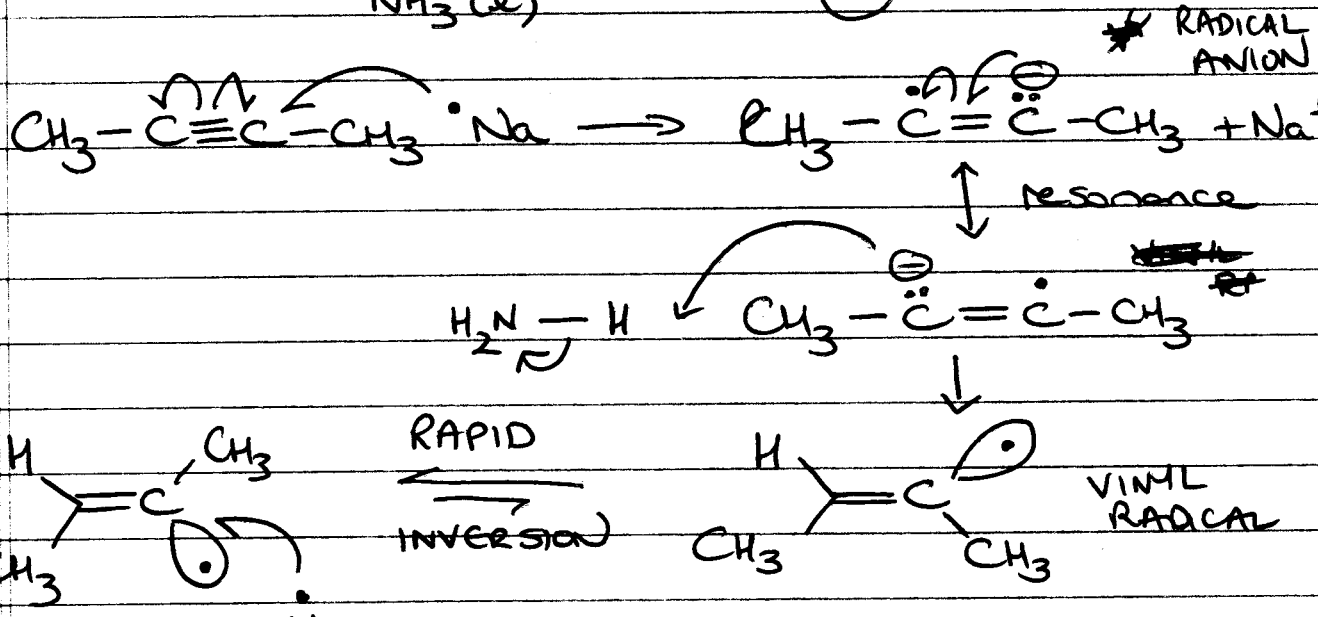


Selective reaction

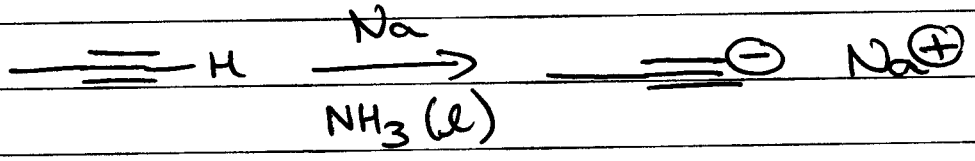


(ii) DISSOLVING- METAL REDUCTION

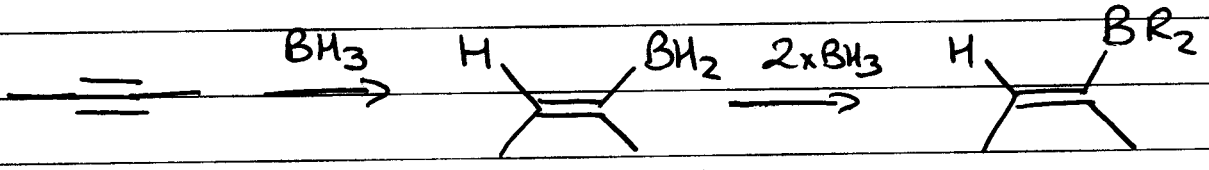


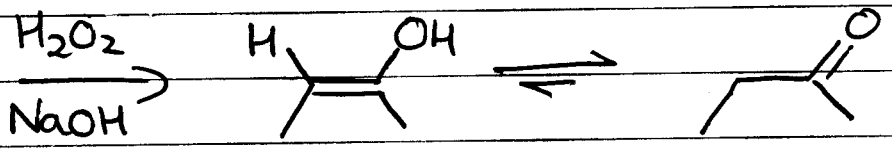


Does not work w/ terminal



(VI) HYDROBORATION (non terminal)





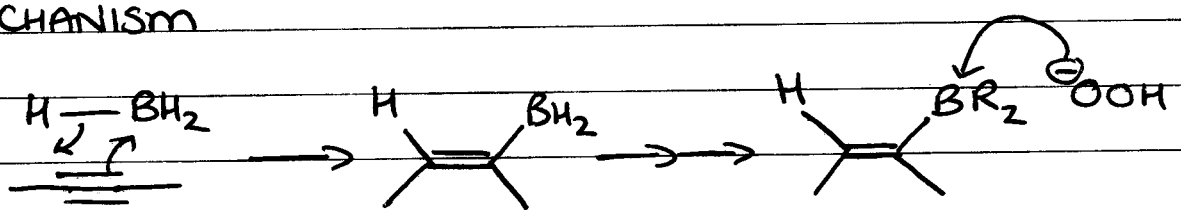
TAUTOMERS

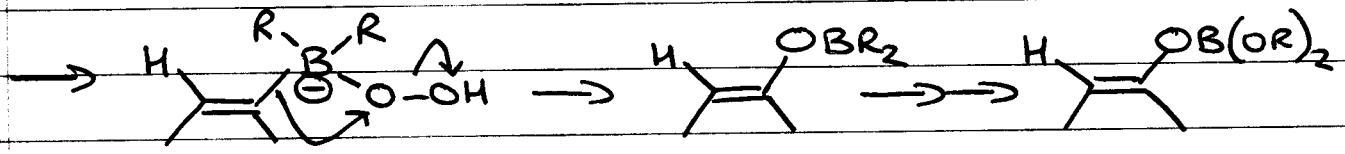
enol Keto

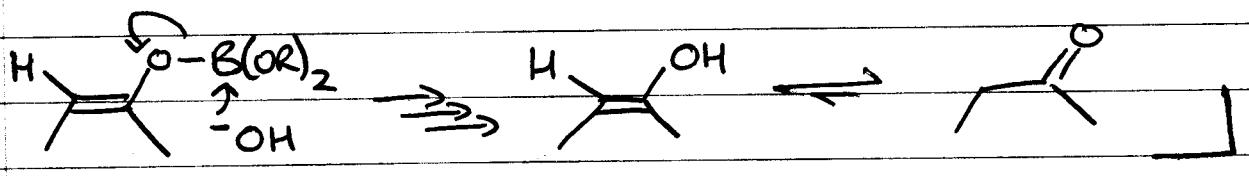
C=O stronger than C=C

SAME MECHANISM AS HYDROBORATION OF ALKENES

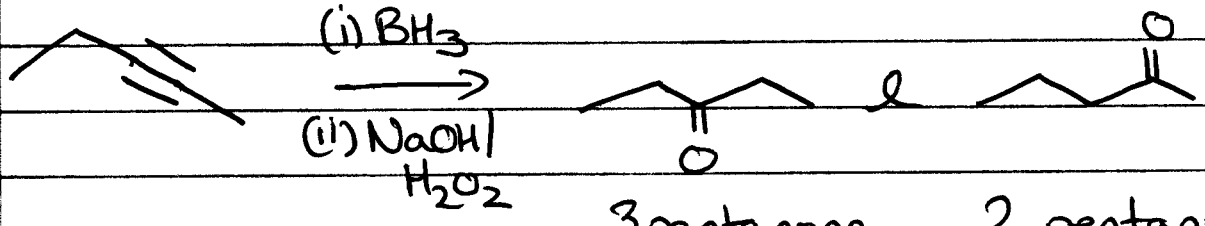
MECHANISM

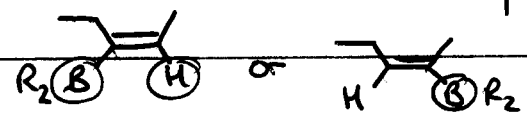


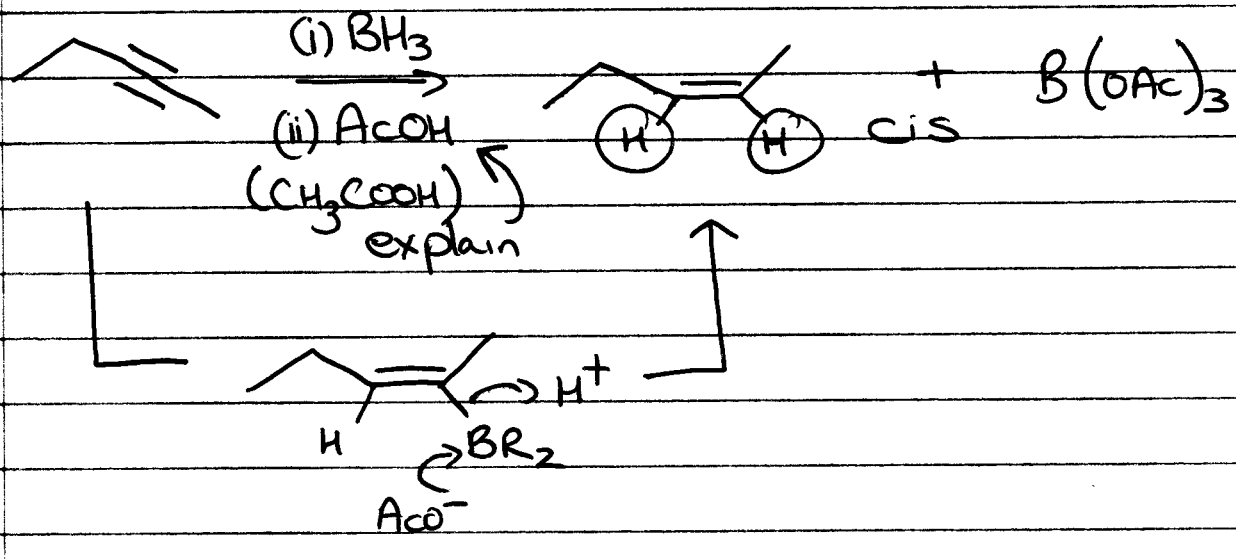




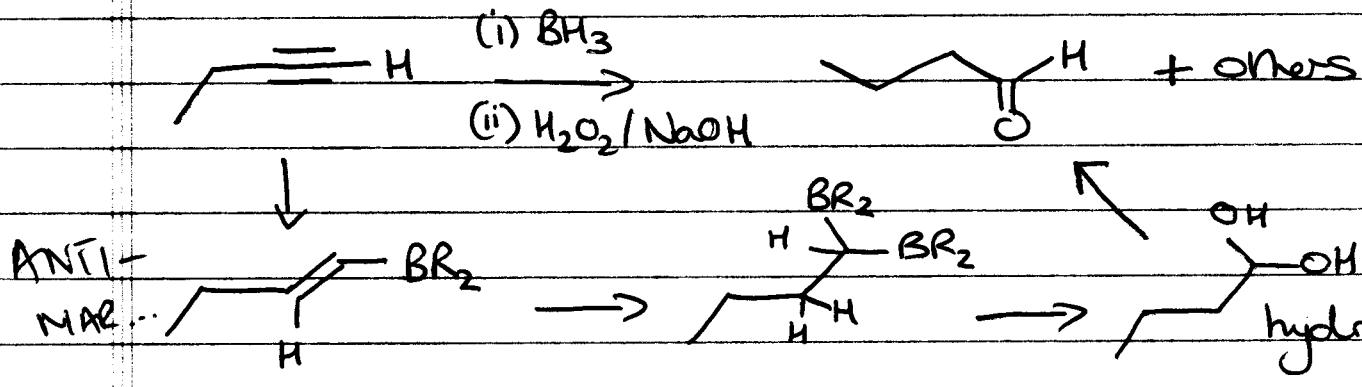
NO SELECTIVITY

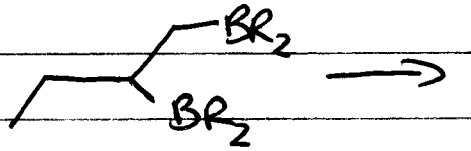


Via 



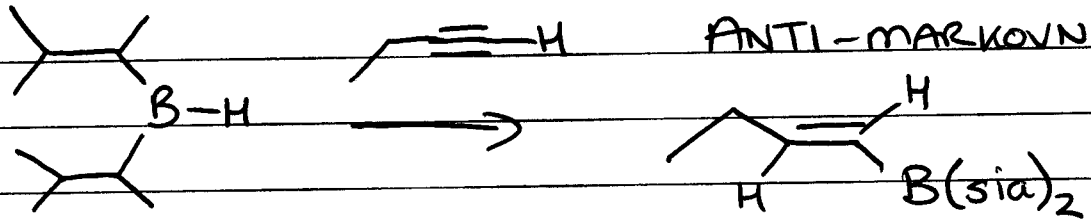
TERMINAL ALKYNES





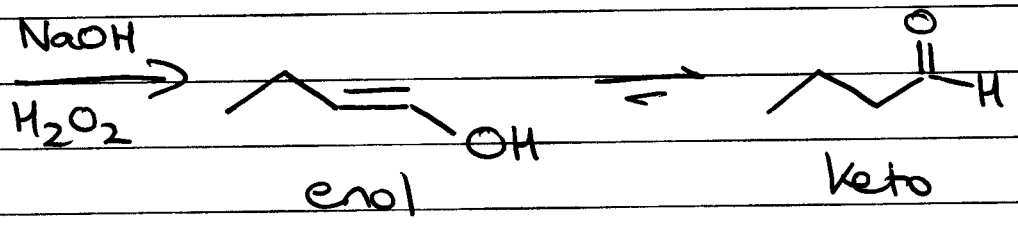
→ other products

[(ii) AcOH ↓ Alkane]

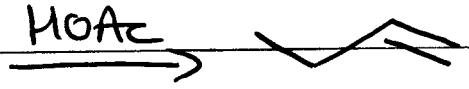


$(sia)_2BH$
DISIAMYLBORANE

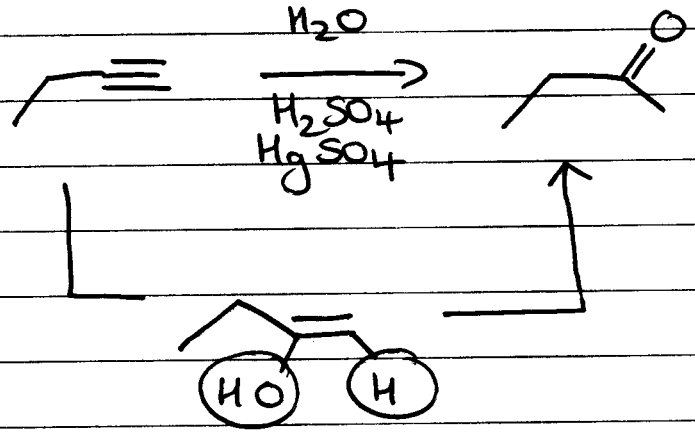
STOPS HERE - only one B–H addition



OR



(VII) HYDRATION



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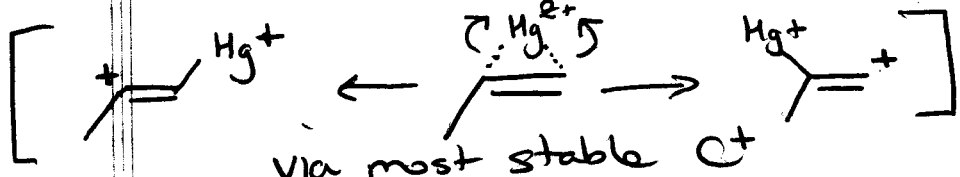
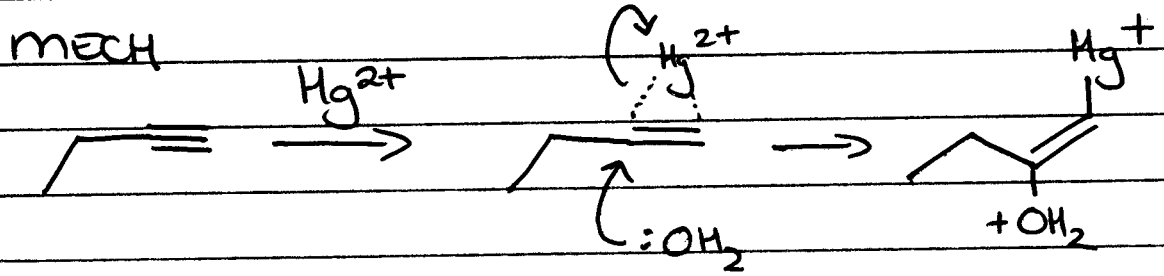
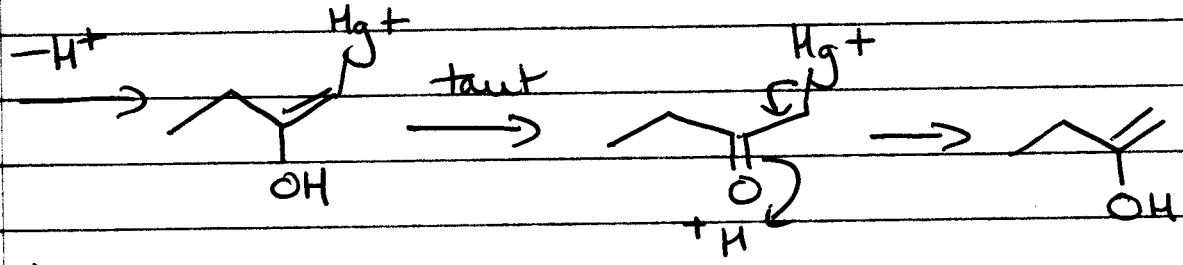
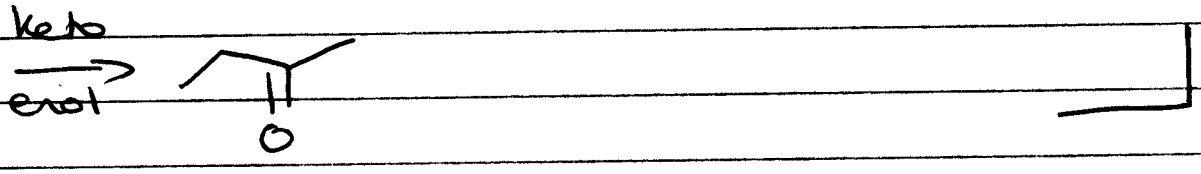
Mechanism v. similar to OXYMERCURATION of ALKENES.



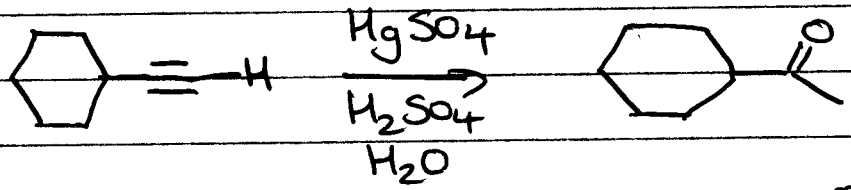
MECH







SUMMARY OF TERMINAL ALKYNES



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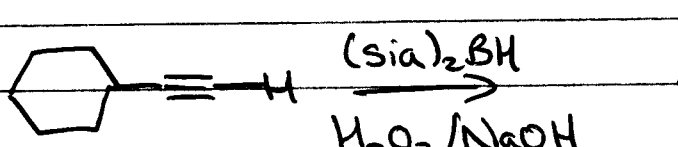
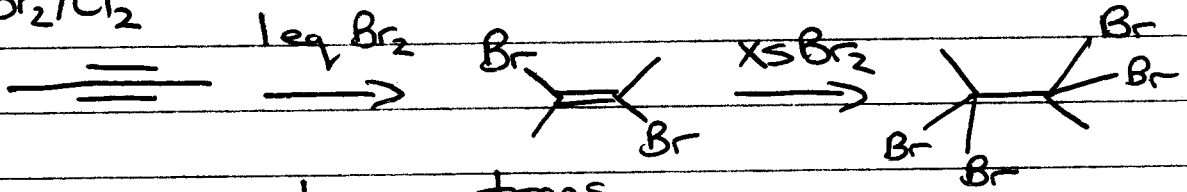
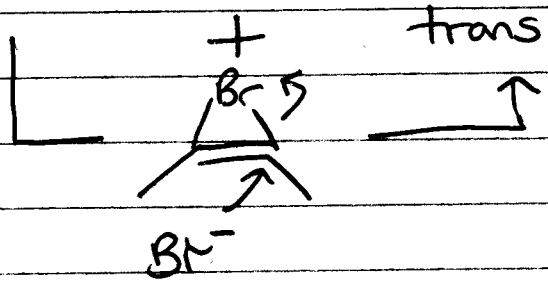


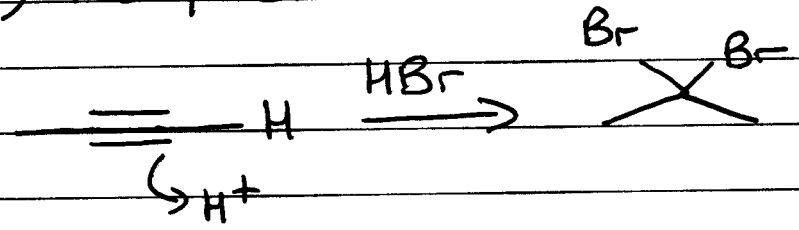
ANTI MARKOVNIKOV

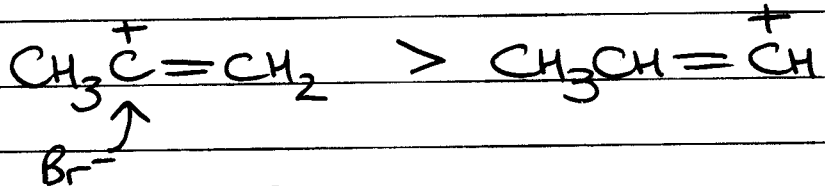
(VIII) Br_2/Cl_2

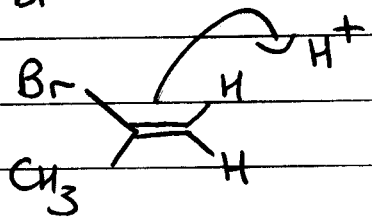


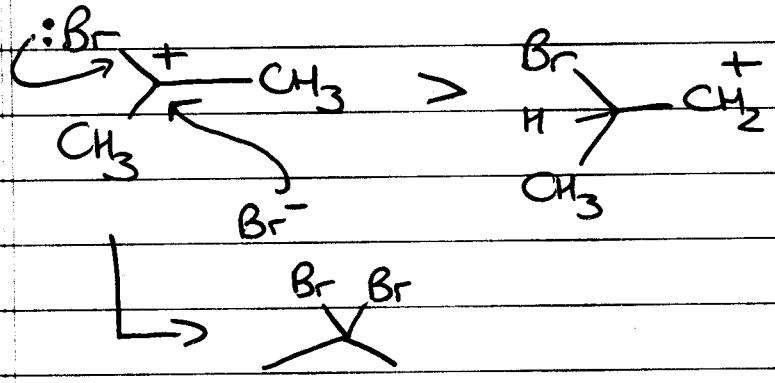


(IX) HCl / HBr

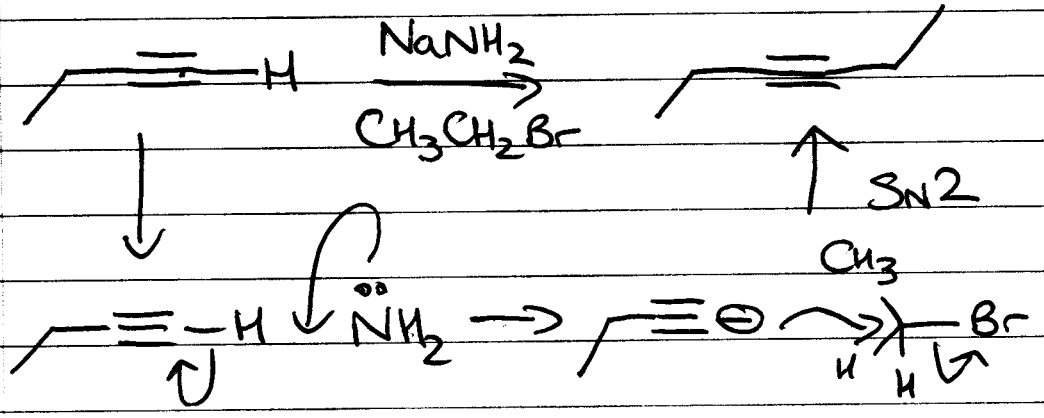






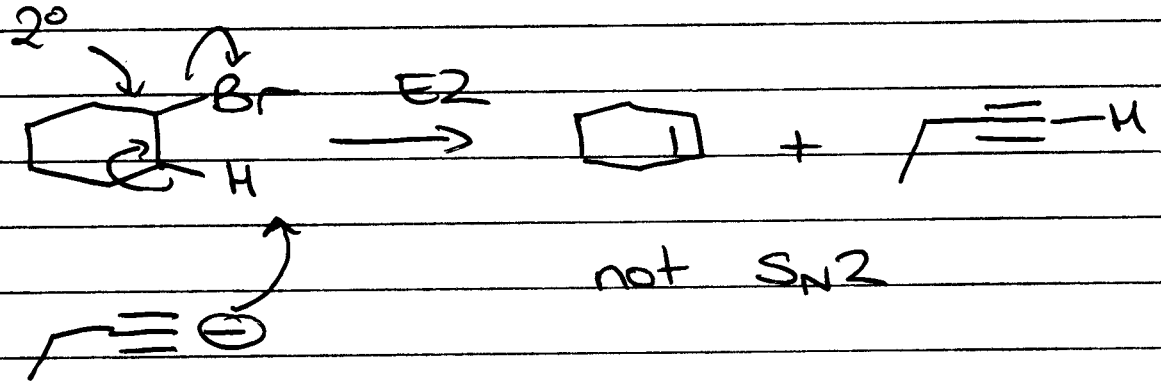


(X) R−≡⊖ as NUCLEOPHILE



GOOD FOR 1° HALIDES, OTS, OMS ONLY

GOOD BASE TOO



not S_N2

ALKYNES IN SYNTHESIS NEXT. (MAYBE)

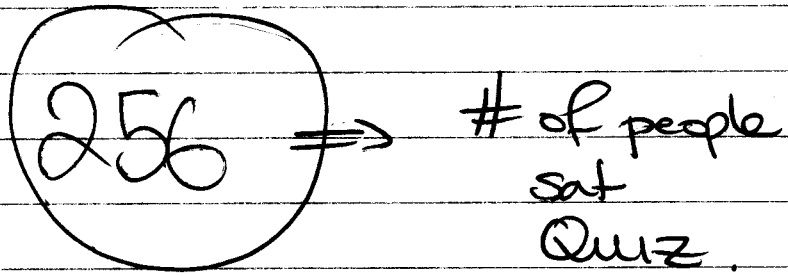
Lec (6)

(1) DO NOT OPEN! / ALTERNATE COVERS
(2) FILL OUT COVER PAGE
(3) PENCIL – NO REGRADES
(4) NO NEED TO ASK QUESTIONS
(5) PAGE 1 – 5 MINS PAGE 2 – 10 MINS
(5 MINS GONE, 1 MIN TO GO)
(6) NOTHING ON DESK BUT QUIZ + WRITING-STUFF
(7) CHECK 3 PAGES

MORE ON ALKYNES...

NO OFFICE HOURS TODAY
(FRIDAY AT 1pm)

HOMEWORK – THE QUIZ YOU DIDN'T DO.



LEC (7) CHEM 30B

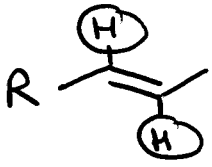
Announcements

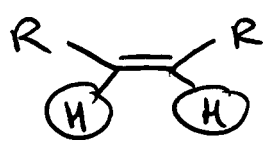
(1) All students on waitlist → enrolled
(2) Must drop by 5pm (IMPACTED COURSE)
(3) Quiz AVERAGE 22/36 HISTOGRAM ON VOH
(4) QUIZZES / ANSWERS POSTED ON WEB TODAY
(5) COLLECT FROM TAs AFTER CLASS (2 got 36)
— or in discussion sec
(6) NO MORE B_2H_6

(1) RED SUMMARY
(2) HYDROBORATION
(3) HYDRATION
(4) HALOGENATION
(5) NUCLEOPHILES
(6) SYNTHESIS

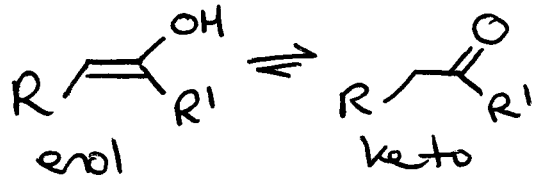
(1) ALKYNE REDUCTION SUMMARY

$R-\equiv-R' \xrightarrow[Pd]{H_2} R-CH_2CH_2-R'$

$R-\equiv-R' \xrightarrow[NH_3(l)]{Na}$  trans

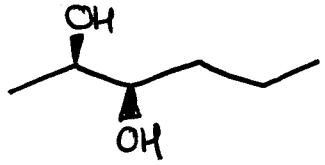
$R-\equiv-R' \xrightarrow[\text{LINDLAR}]{H_2}$  cis

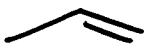
(2) HYDROBORATION (non-terminal)

$R-\equiv-R' \xrightarrow[(ii)\ H_2O_2/NaOH]{(i)\ BH_3}$ 

– continue w/ Lec 6

(6) SYNTHESIS



from  only C source

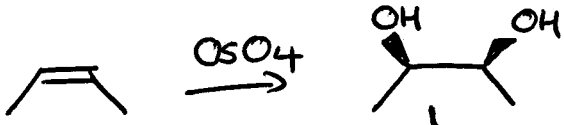
RETROSYNTHESIS

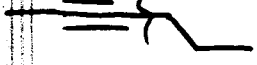
⇓ WHAT DOES A DIOL COME FROM

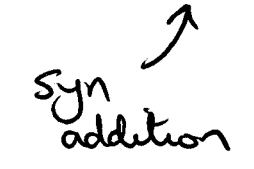
REMINDER:

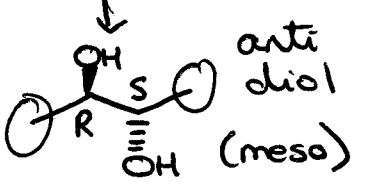
trans or E

⇓



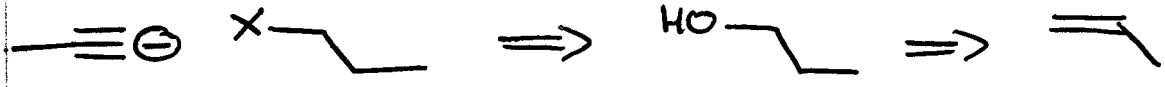






same SR is same

⇓



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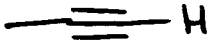

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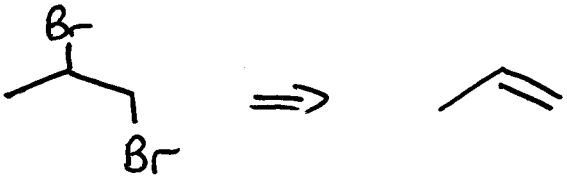
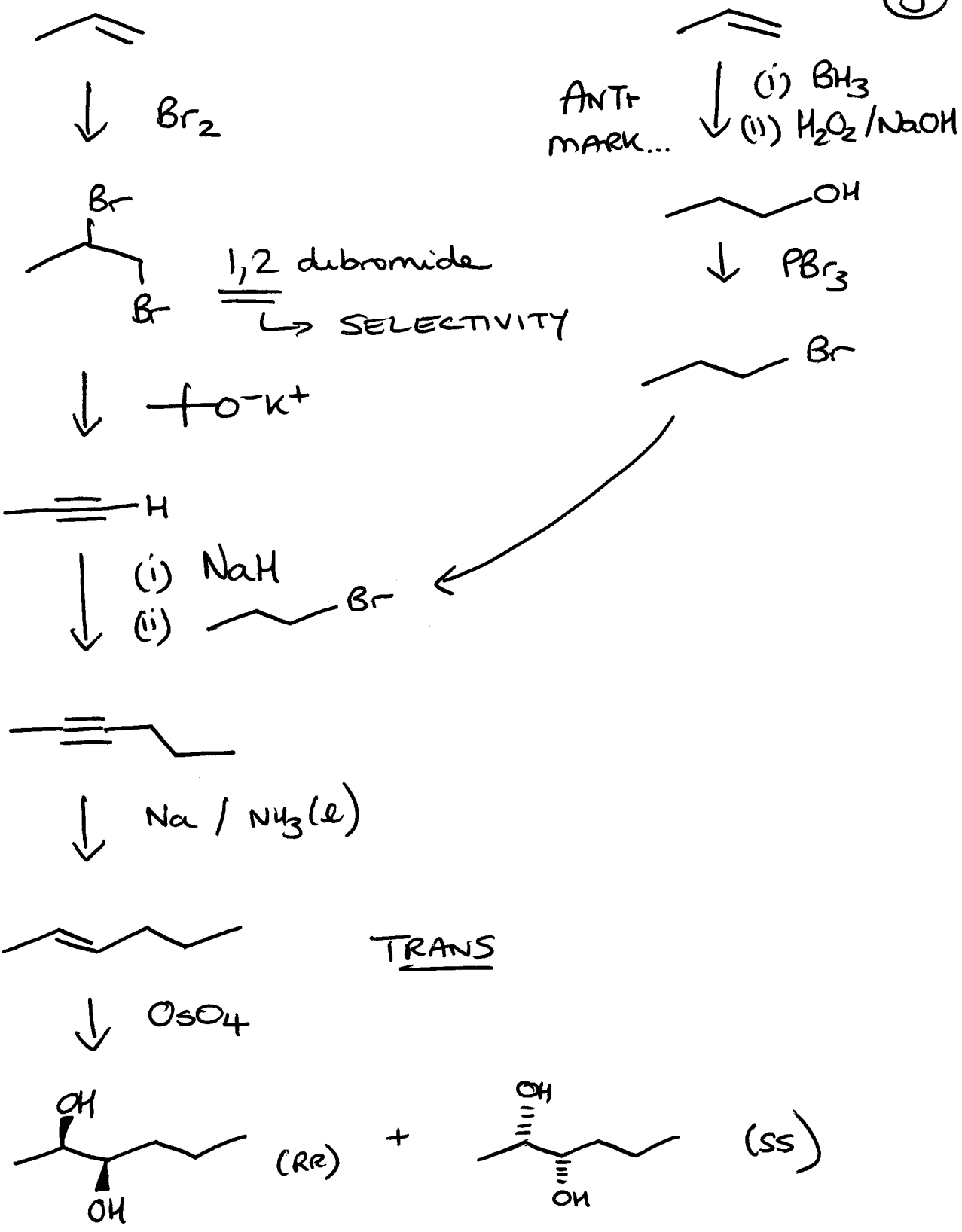


FORWARD SYNTHESIS



Chem 30B Lec (8)

Announcements

(1) Homework 11.2–11.9, 11.15–11.17

(2) Midterm Mon Oct 20th 10am

A – K CS 76

L – Z ROLFE 1200

(3) CNSI Lecture

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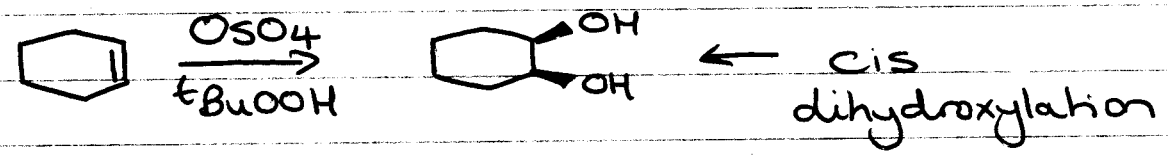
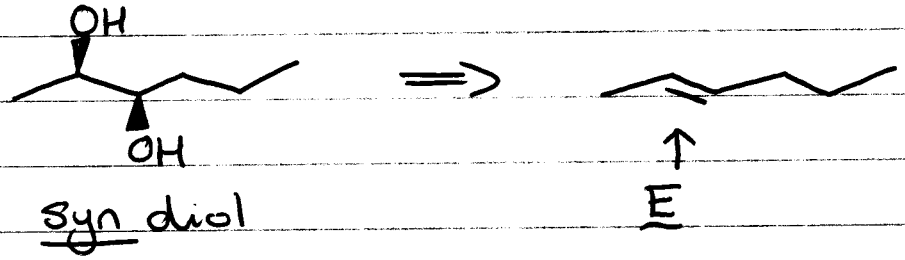
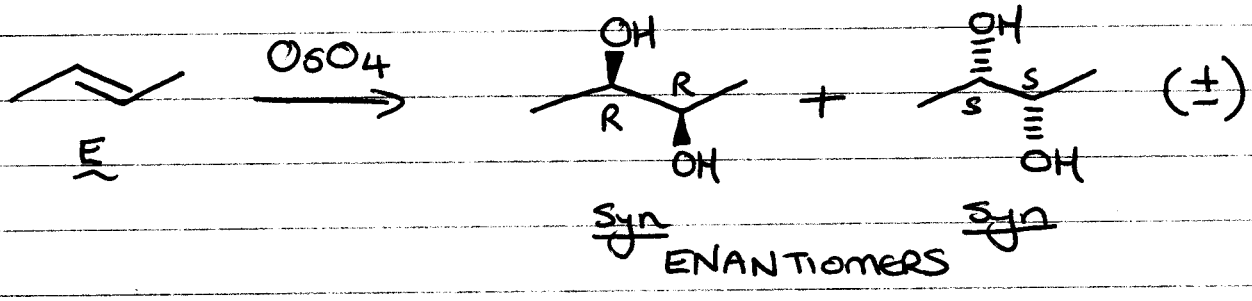
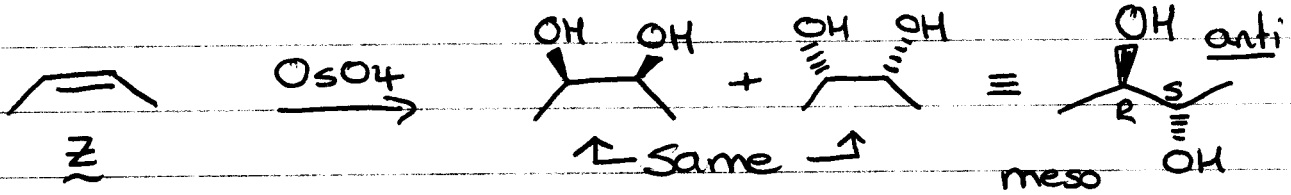
(1) RECAP – DIHYDROXYLATION (2) ETHERS

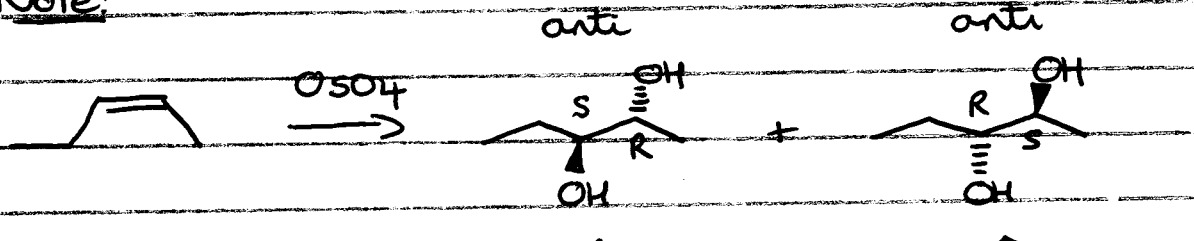








Note:



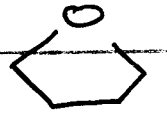
↑ ENANTIOMERS ↑

(2) ETHERS

$R-O-R'$

- ETHOXYETHANE
- DIETHYL ETHER
- ETHER

Cyclic Ethers


Ethylene Oxide — Tetrahydrofuran (THF) — 1,4 Dioxane

Special ↑

$\overset{\delta+}{CH_3}-\overset{\delta-}{O}-\overset{\delta+}{CH_3}$ weakly polar bp $-24°C$

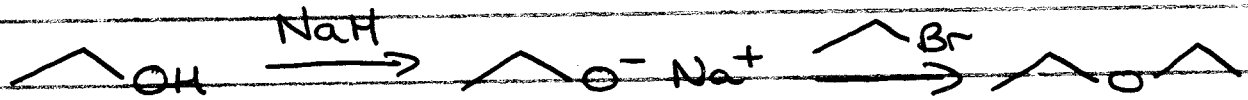
CH_3CH_2OH bp $78°C$

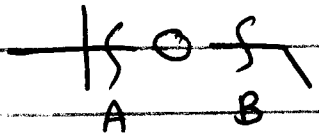
Generally CHEMICALLY INERT ⇒ GOOD SOLVENTS

Preparation

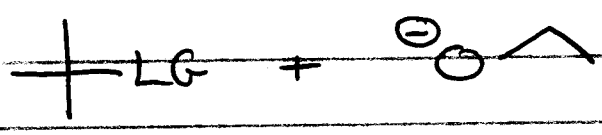
① WILLIAMSON ETHER SYNTHESIS

$$R-OH + R'-LG \xrightarrow{Base} R-O-R'$$

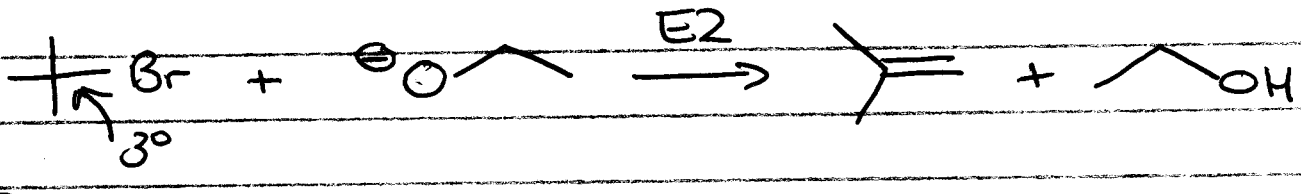




Ⓐ



III



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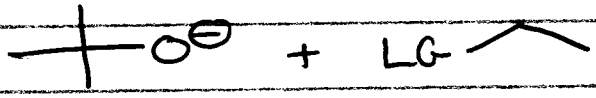
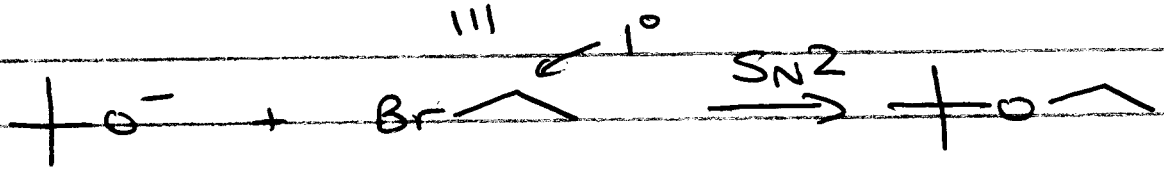
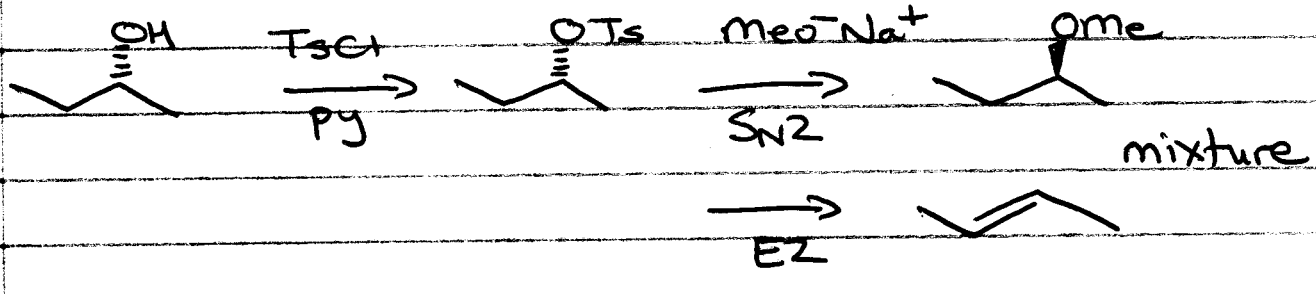


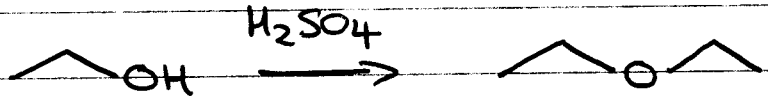
III



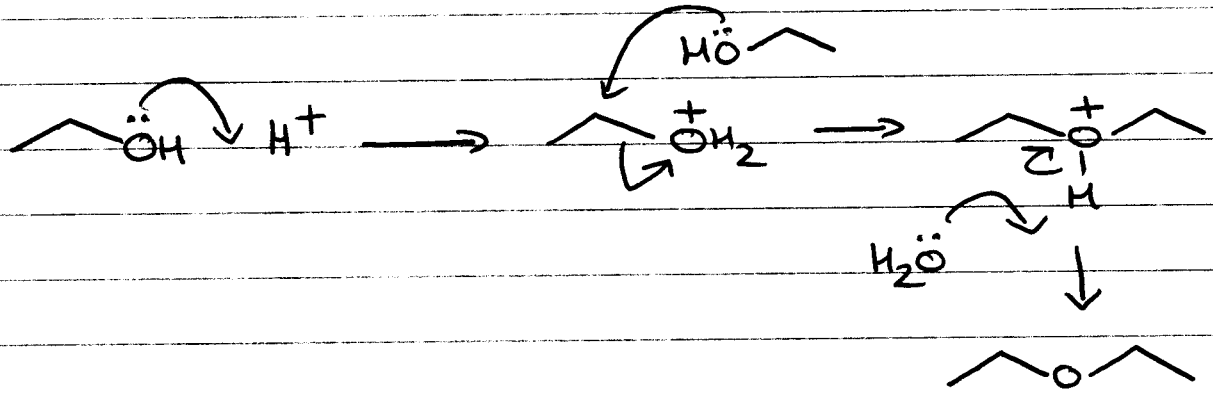
SECONDARY ALCOHOLS



(2) ACID CATALYZED DEHYDRATION ROH



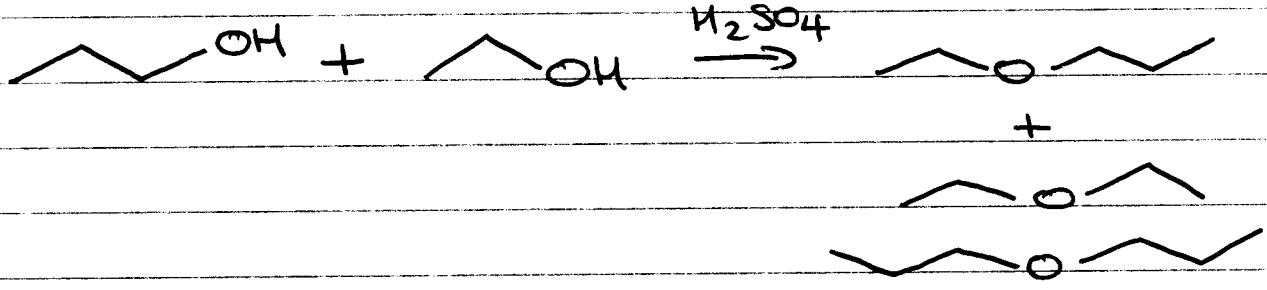
good for symmetrical unbranched ethers



2° R-OH ⟶ product mixture
ethers from substitution
alkenes from elimination

3° R-OH ⟶ alkenes from elimination

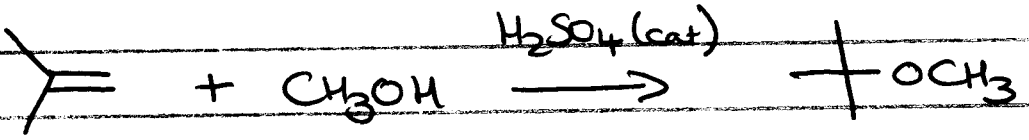
ONLY GOOD for 1° R-OH

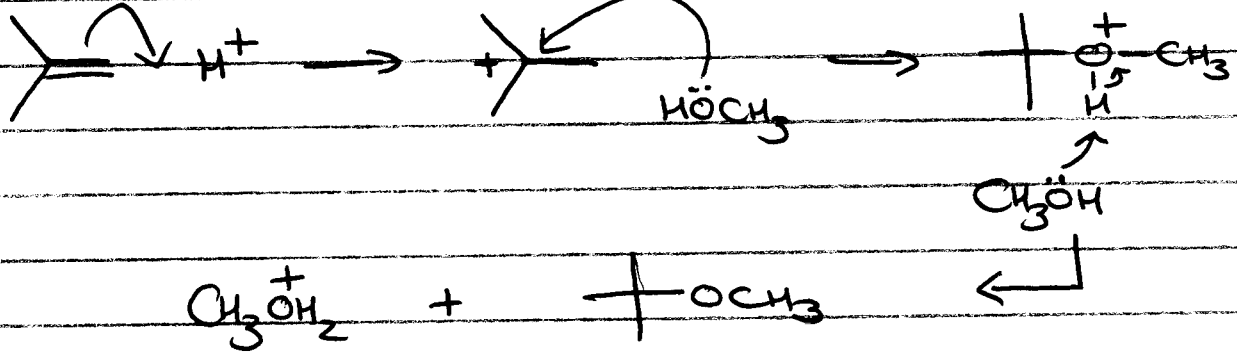


statistical
mixture

(3) ALKENE + ALCOHOL $\xrightarrow[\text{cat}]{\text{Acid}}$ ETHER

↑ be able to form stable C^+ ↑ not able to dehydrate



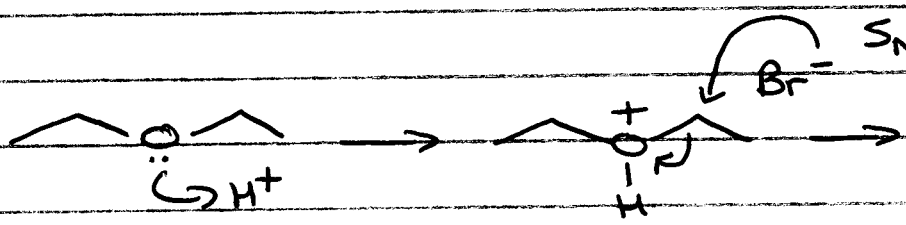


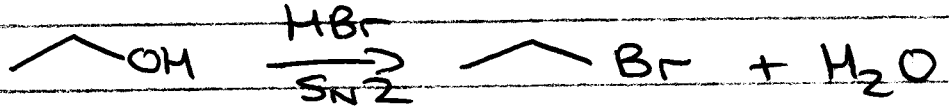
REACTIONS of ~~ALCOHOLS~~ ETHERS

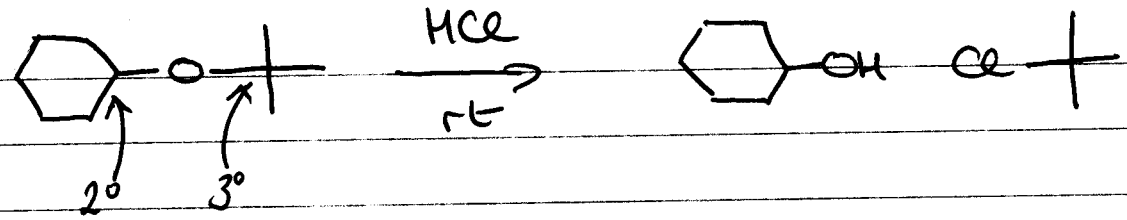
① Acid catalyzed cleavage

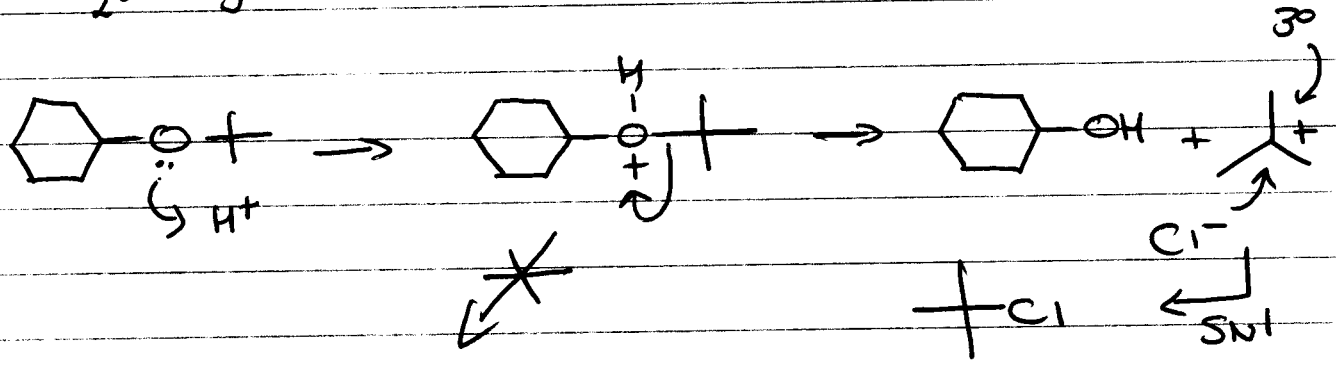
Cl^- not nucleophilic enough

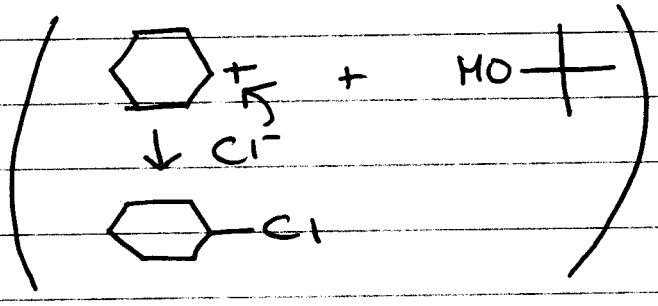
1°  $\xrightarrow[\text{HEAT}]{\text{xs HBr or HI (not HCl)}}$ 2 ×  + H_2O

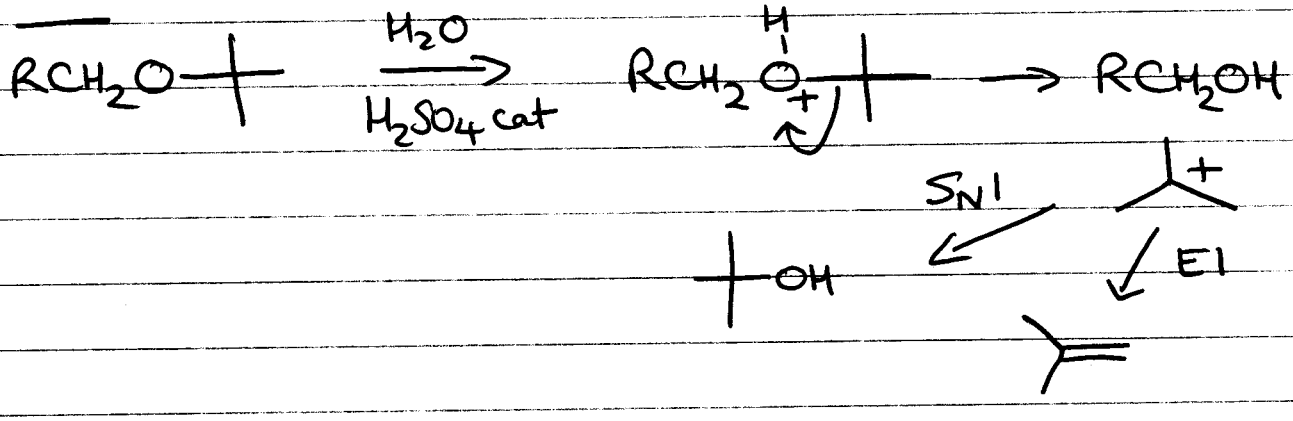




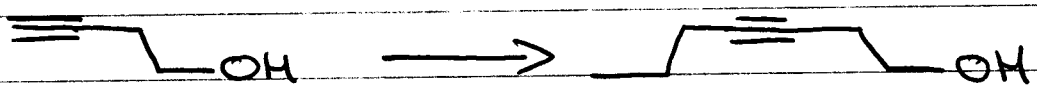


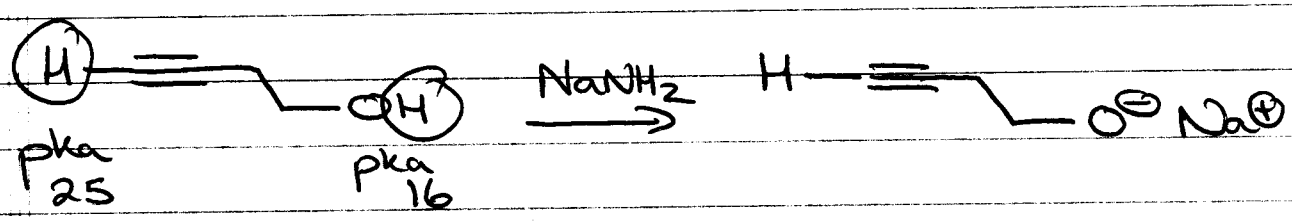


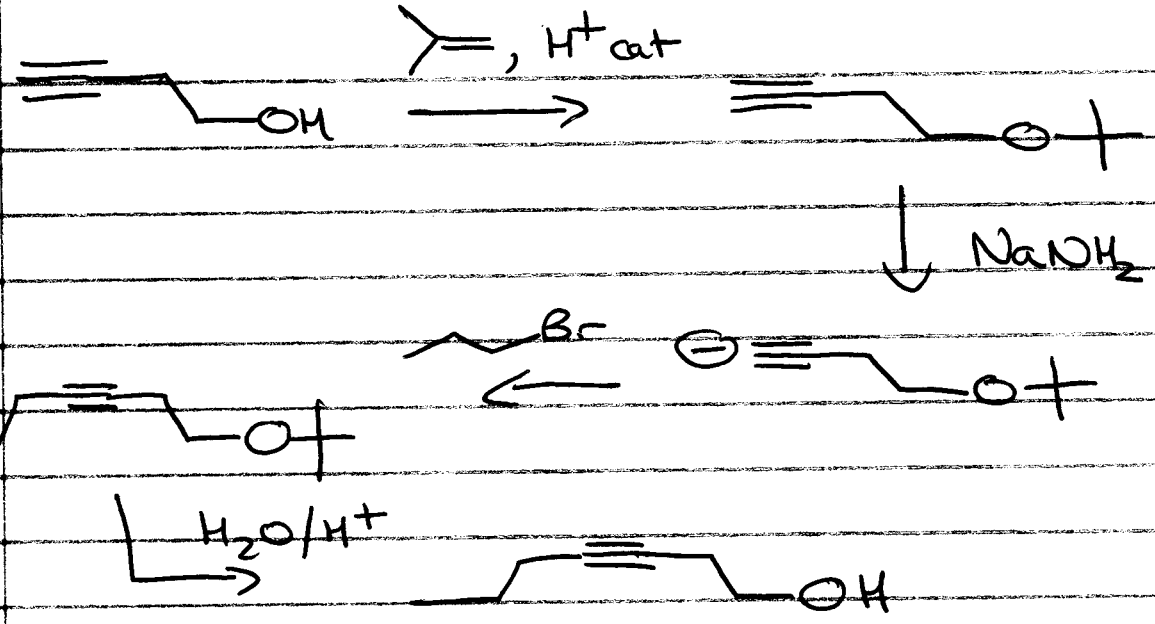




PROTECTING GROUPS







Other Protecting Groups

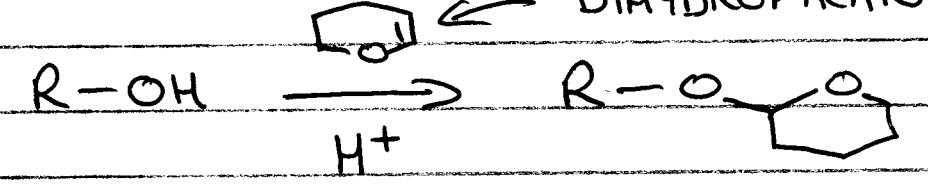
(1) Silyl Ethers

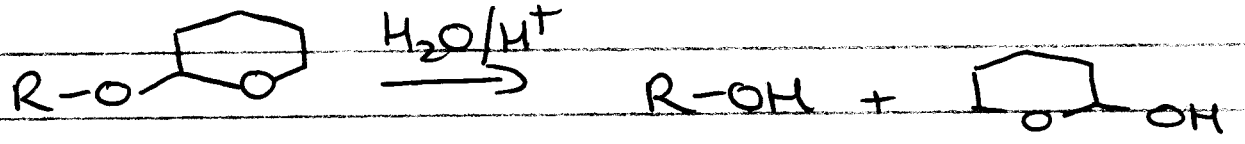
$RCH_2OH + Cl-\overset{|}{\underset{|}{Si}}- \xrightarrow{Py} RCH_2O-\overset{|}{\underset{|}{Si}}-$

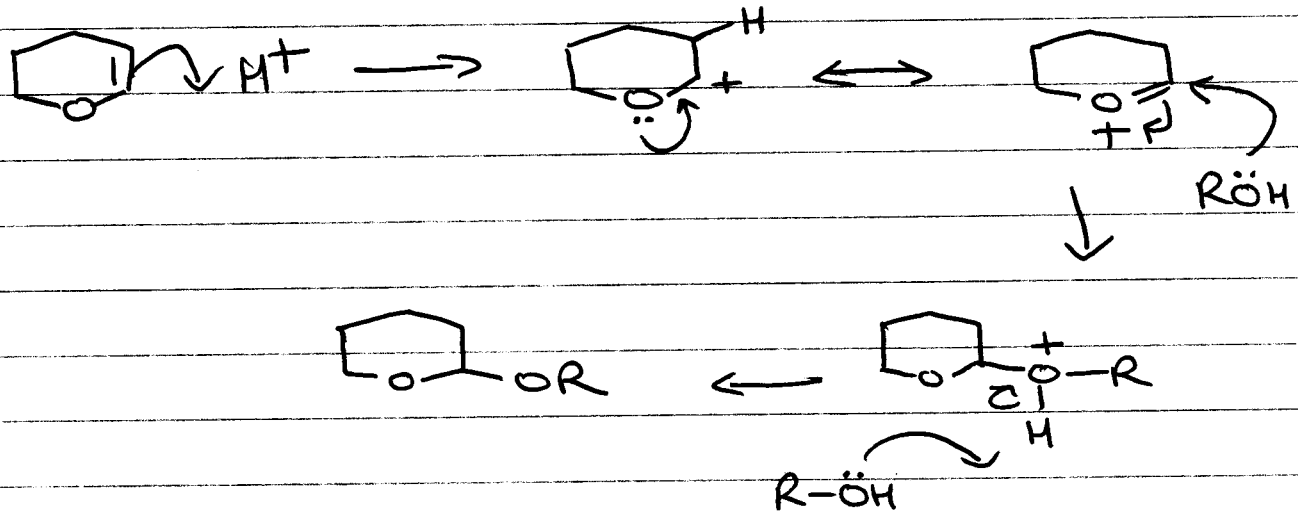
Tms–Cl — Tms ether (Silyl ether)

$RCH_2OTms \xrightarrow[\text{or } Bu_4N^+F^-]{H^+/H_2O} RCH_2OH$ (Si–OH) (Si–F)

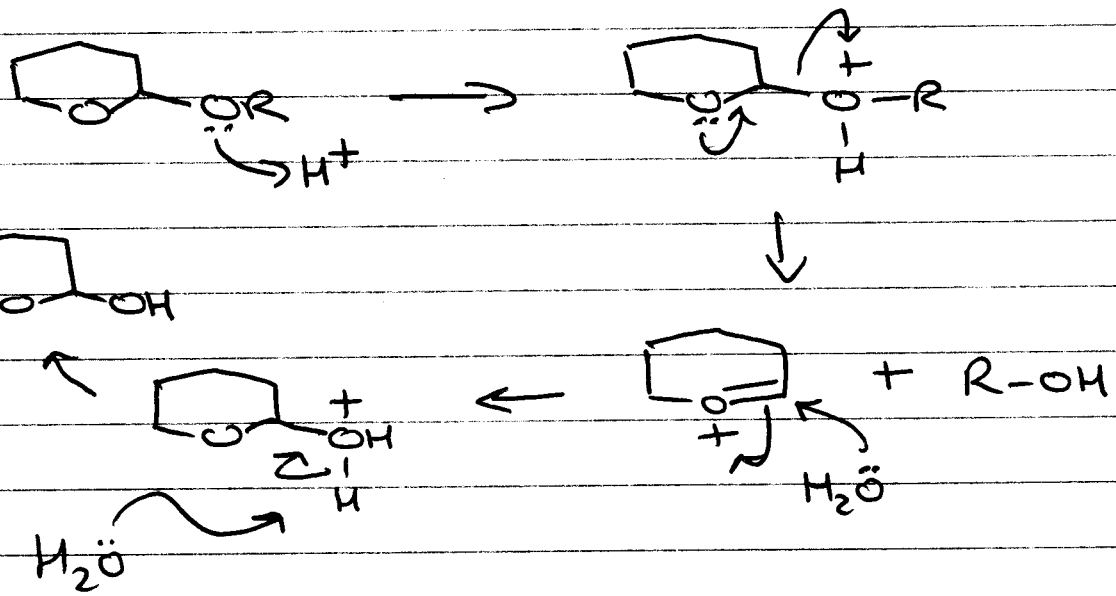
(2) THP Ethers



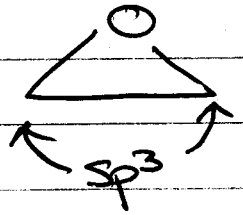




Deprotection:

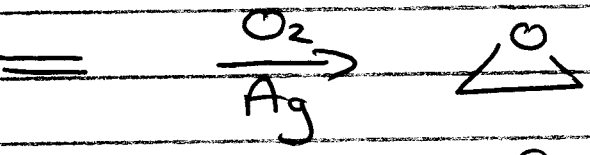


EPOXIDES



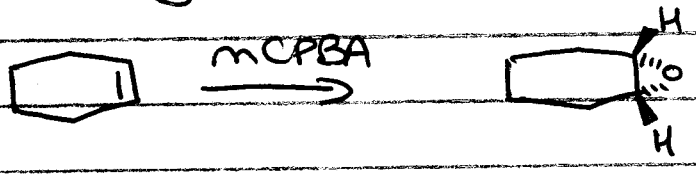
highly strained
↳ distorted bond angles

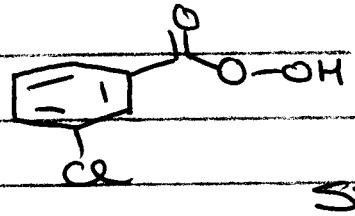
(A) Industrial Synthesis



~~test~~ doesn't work for other alkenes

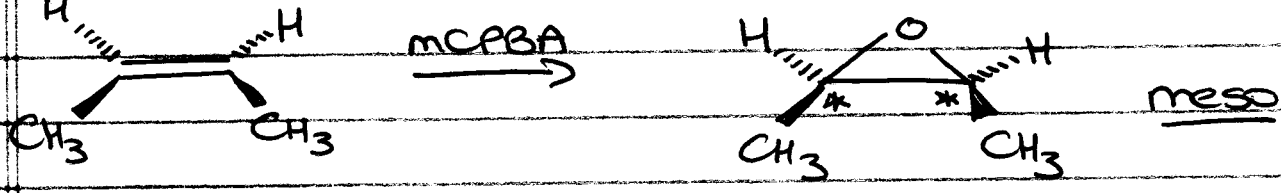
(B) Peroxyacids



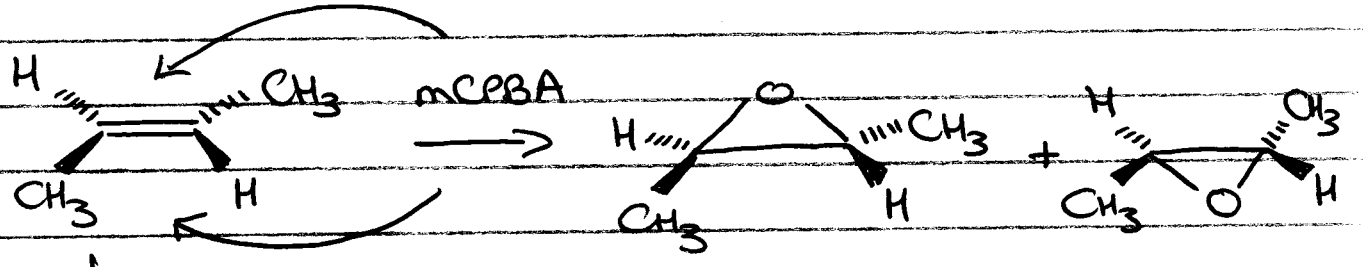


metachloroperoxybenzoic acid.

STEREOSPECIFIC



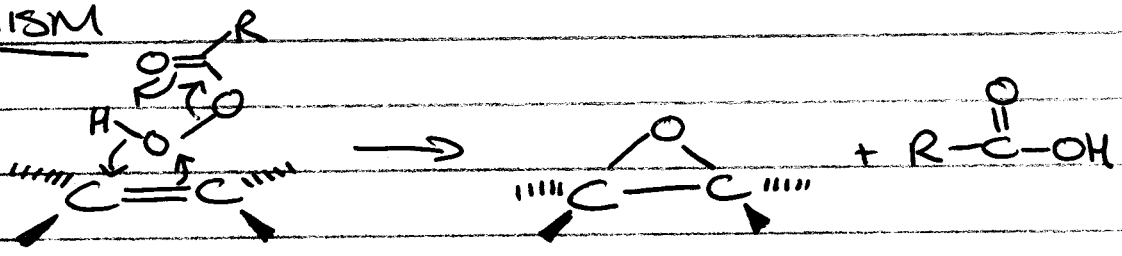
cis



trans

ENANTIOMERS

MECHANISM

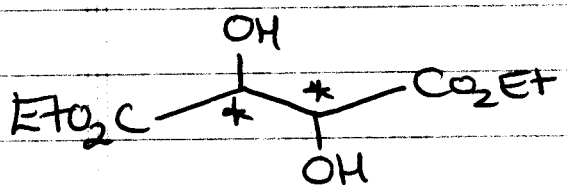


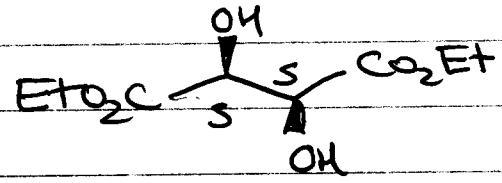
SHARPLESS ASYMMETRIC EPOXIDATION

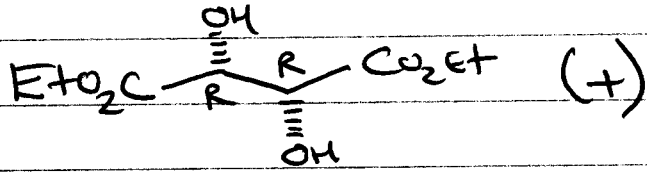
↑ NOBEL PRIZE CHEMISTRY 2001

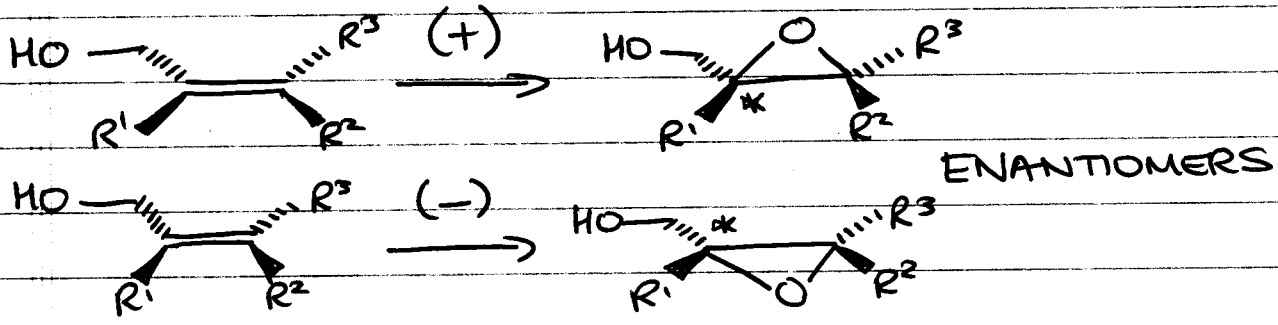
Epoxidation of allylic alcohols

DET = Diethyl Tartrate



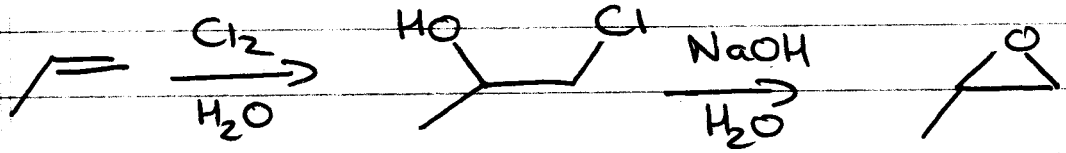


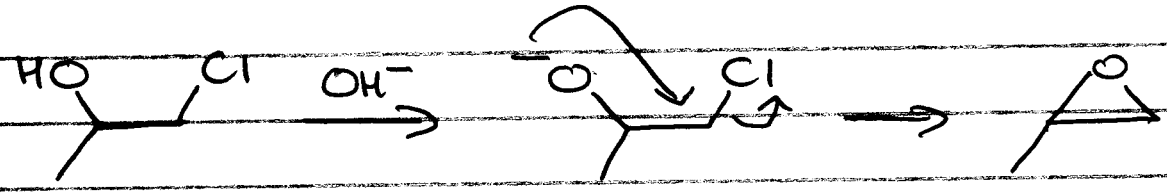




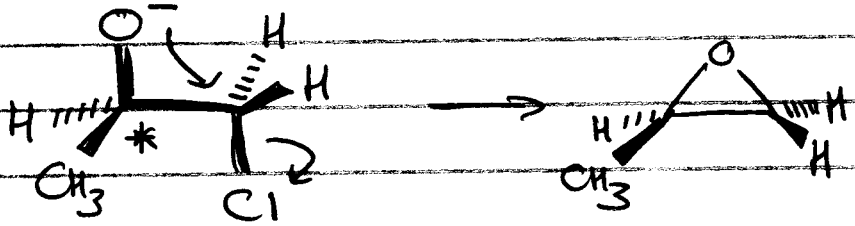
VIA HALOHYDRINS

Intramolecular S_N2

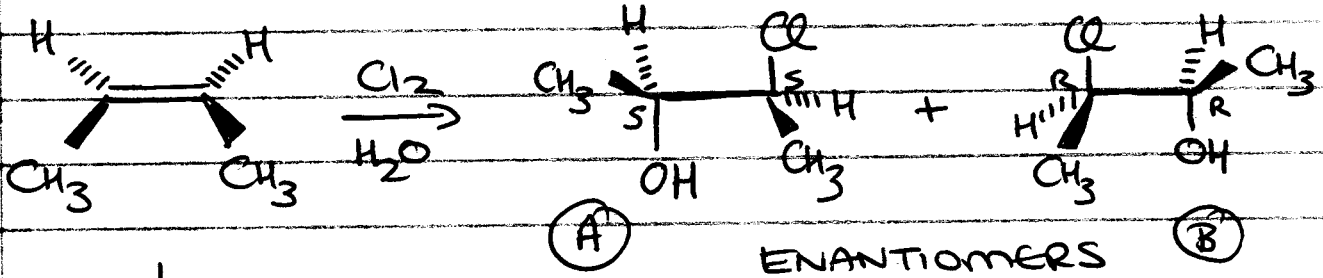




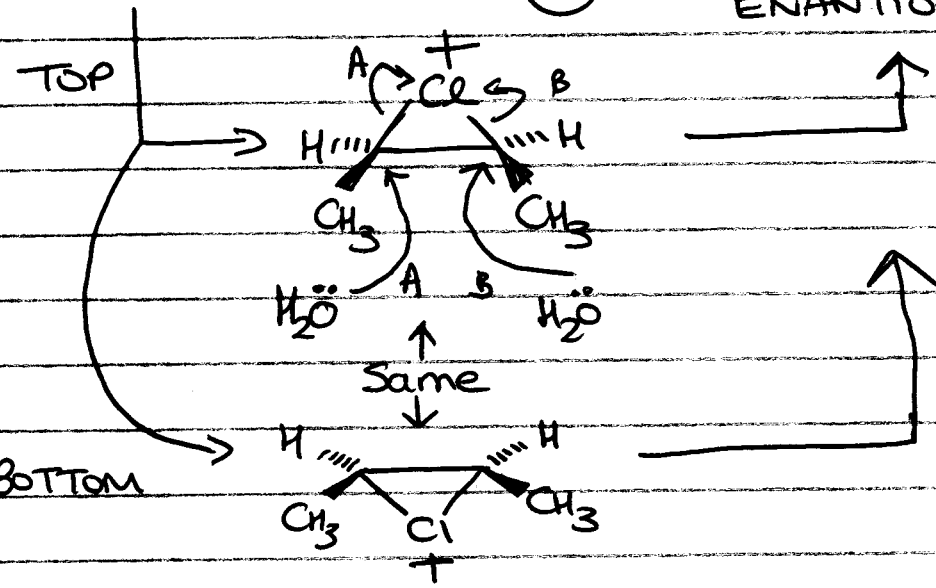
chlorohydrin

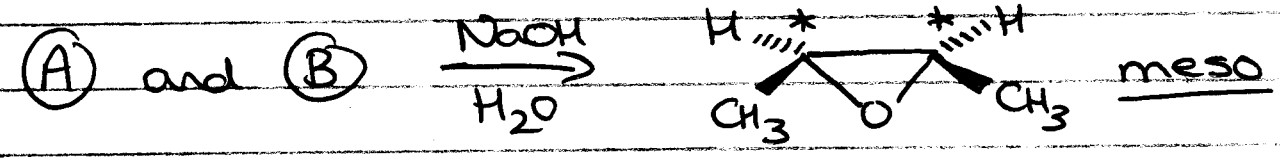


anti

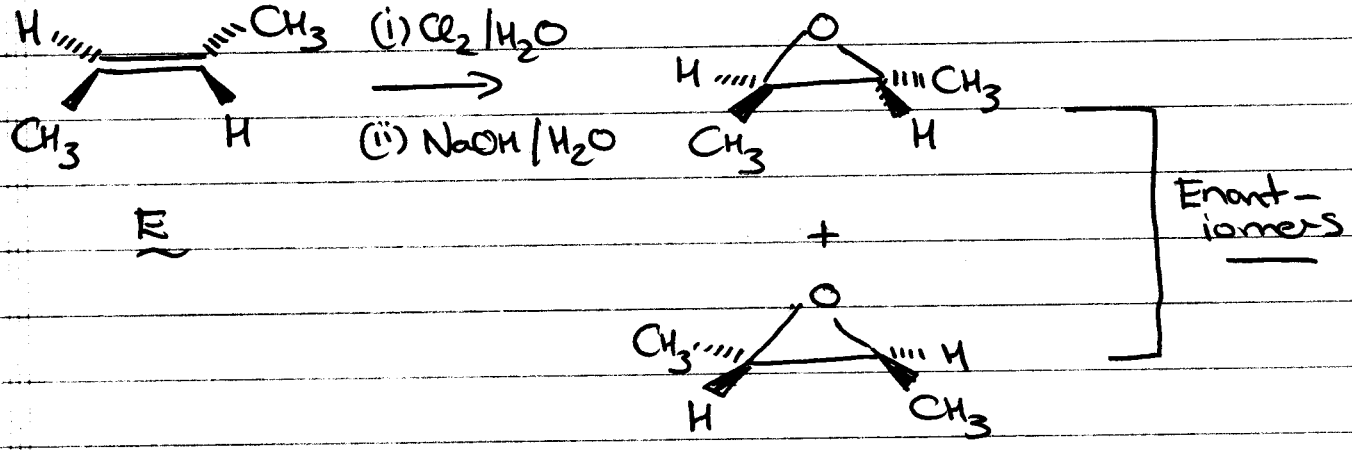


ENANTIOMERS

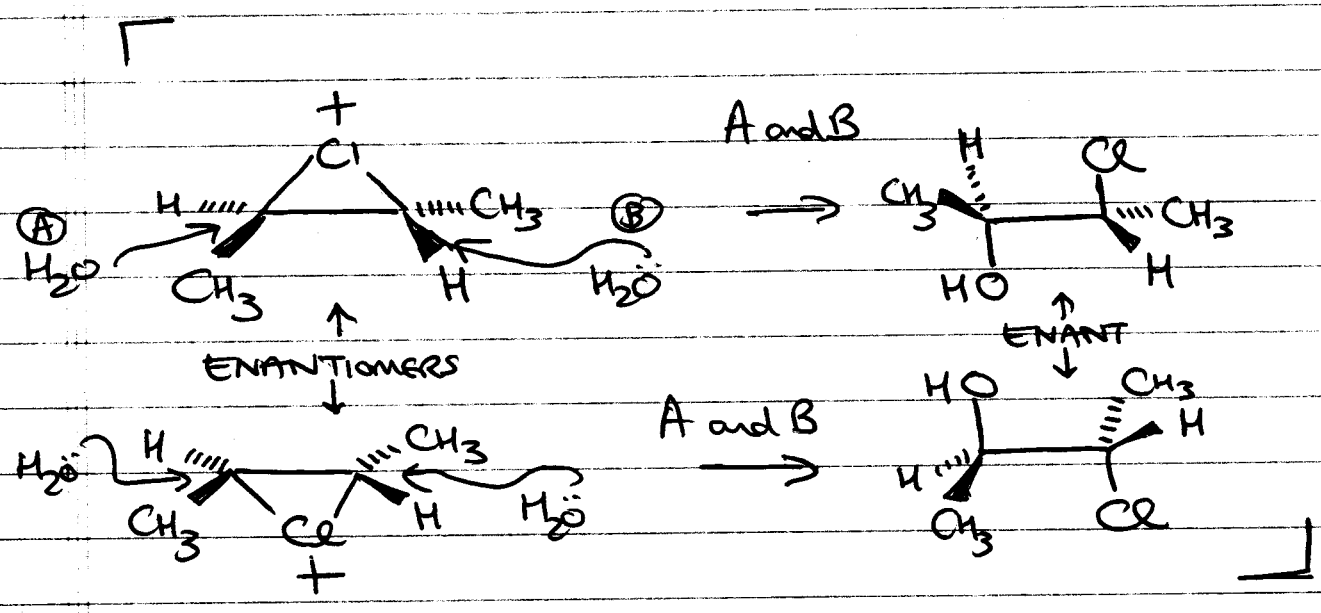




meso



GO THROUGH THIS AND KNOW WHY?



Next – reactions of epoxides

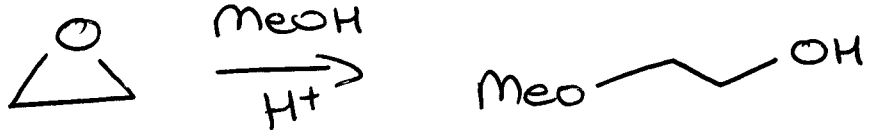
Chem 30B Lec (9)

(1) Midterm Monday 10am
- A-K CS76
- L-Z Rolfe 1200

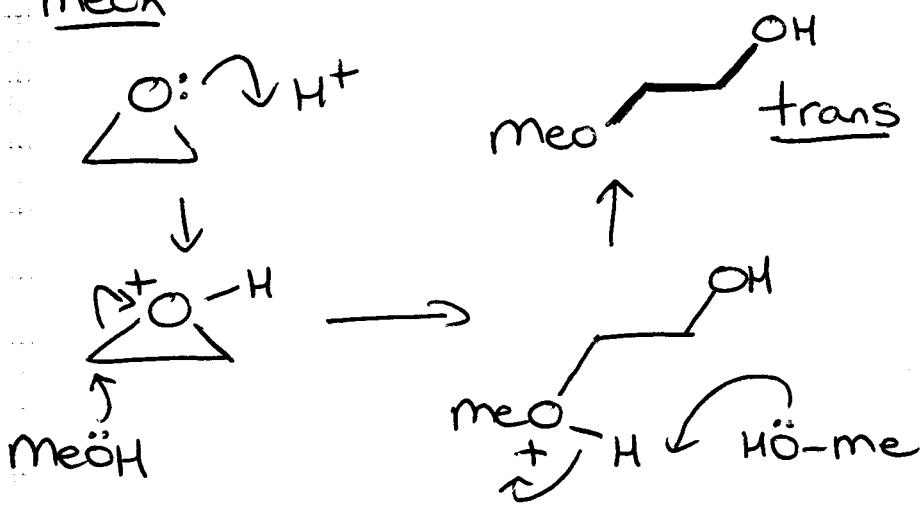
(2) Homework + Review Problems (today/Fri)
10.31, 11.19–11.40, 9.41, 9.46

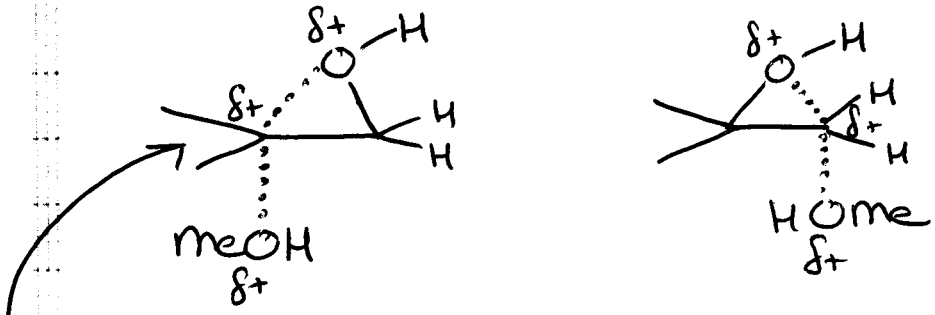
(1) Protecting Groups cont...
(2) Epoxides
- Preparation
- Reactions

(i) Acid-catalyzed ring opening



mech

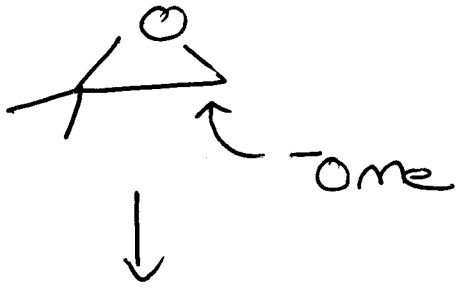




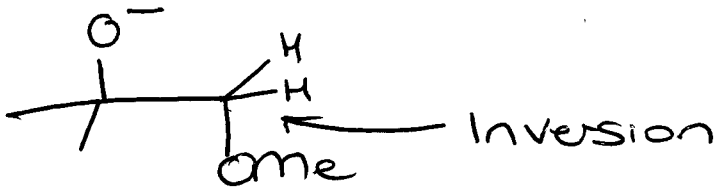
Open by more stable C+

Also get inversion S_N2

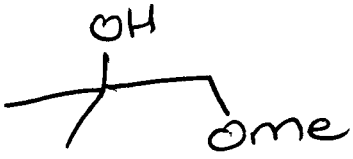
OMe ends up on most hindered C atom of epoxide.



attacks least hindered C atom of epoxide

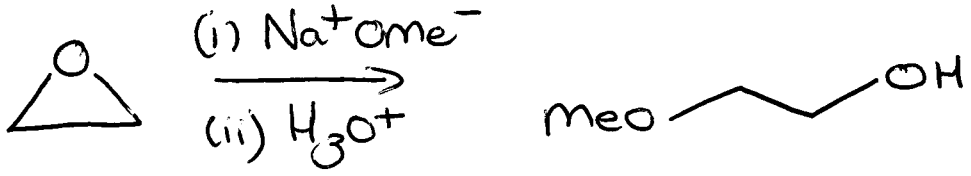


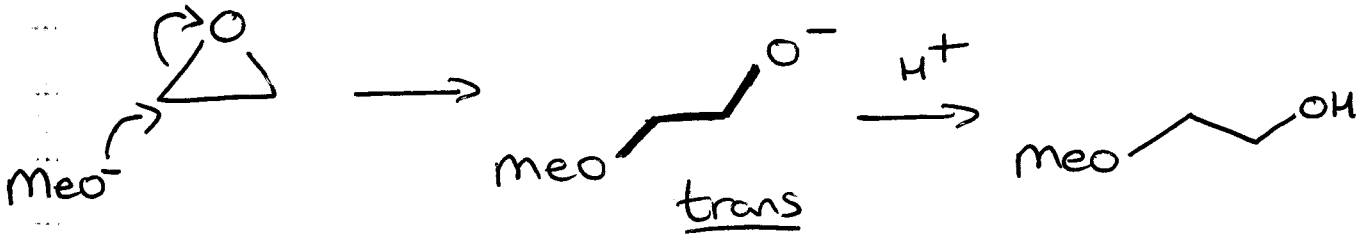
H_3O^+

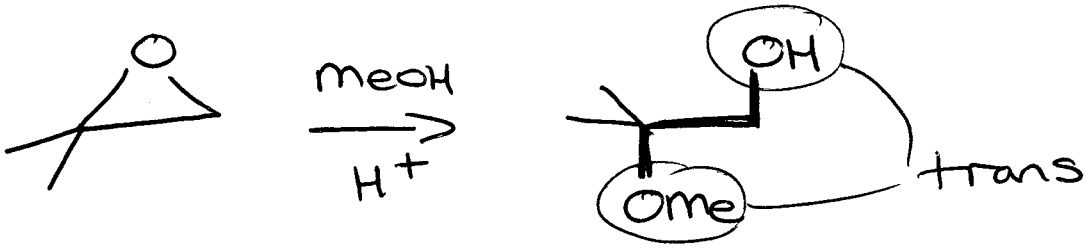


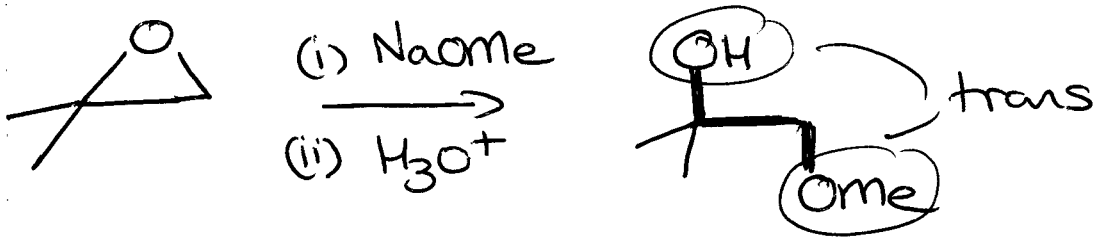
OMe ends up on least sub C atom of epoxide

(ii) NUCLEOPHILIC RING OPENING



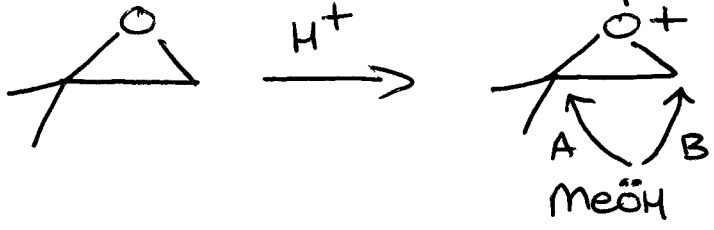






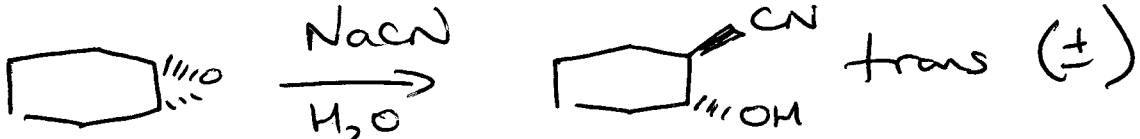
WHY?

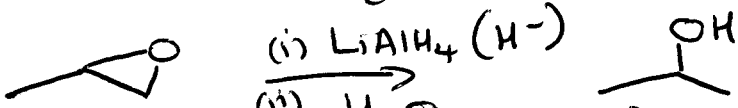
ACID



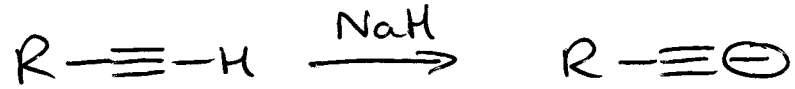
Concerted, but build up of +ve charge in TS on C that is attacked

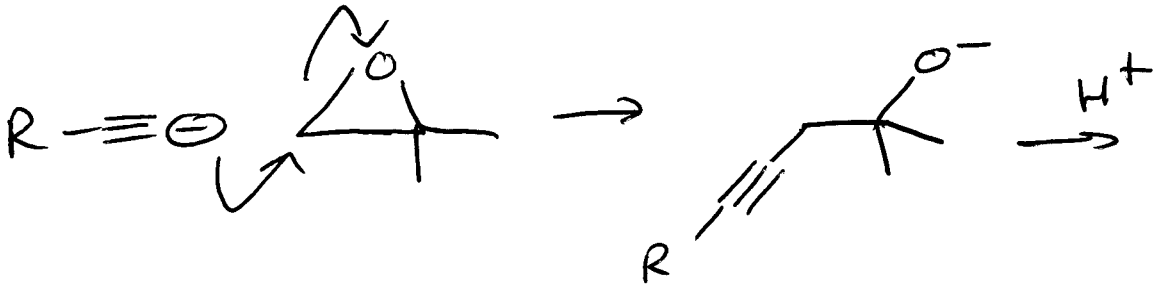
Open epoxide w/ other nucleophiles



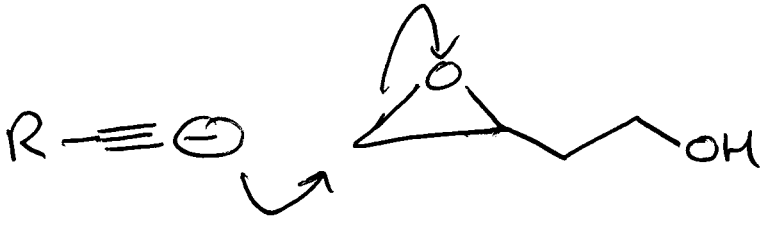


What about acetylide nucleophiles?

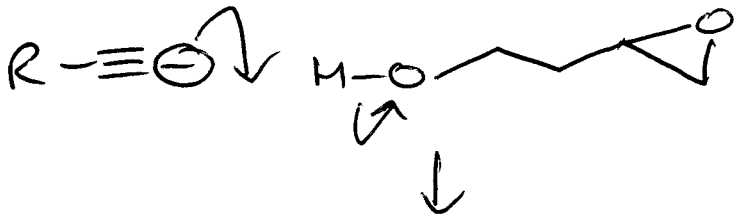




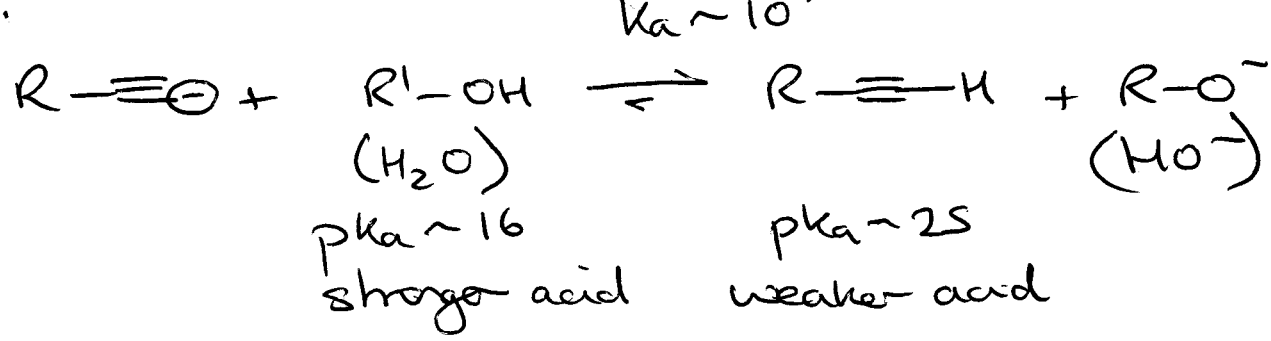
What about



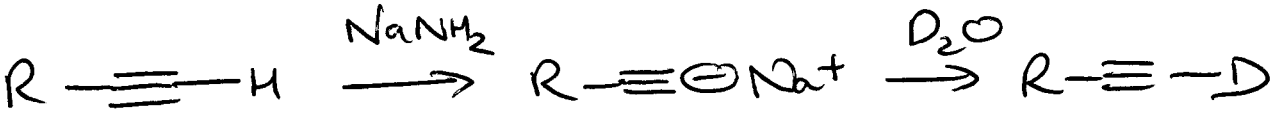
NO



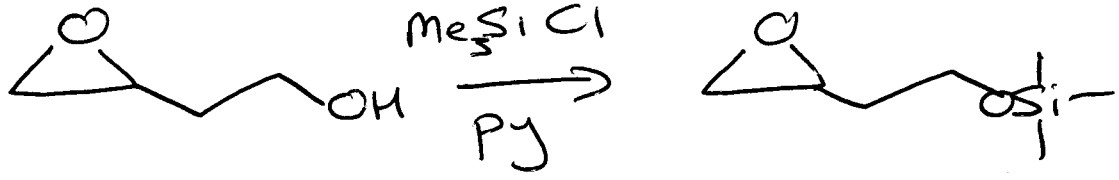
WHY?

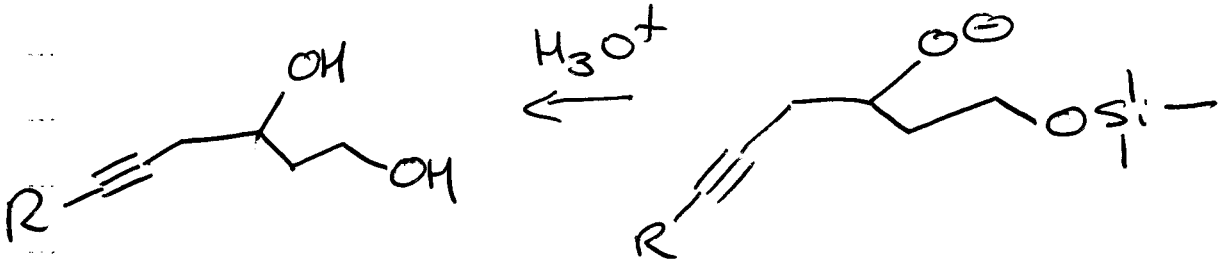


Useful:



Use PG Strategy





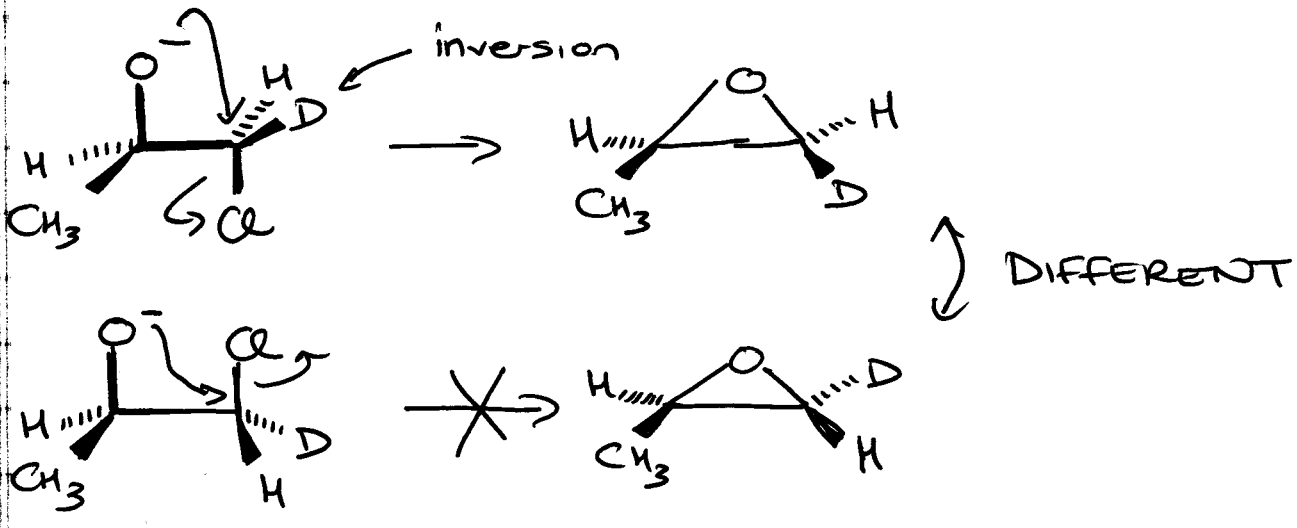
Chem 30B Lec (10)

1. MIDTERM MONDAY 10am
   A-K CS76 (what it covers)
   L-Z ROLFE 1200 (books)
2. LIST OF APPROPRIATE BOOK PROBLEMS ON VOH
3. ROB

---

1. HALOHYDRINS
2. OPENING EPOXIDES
3. THIOETHERS

HALOHYDRINS



Chem 30B Lec (11)

(1) MIDTERM: Average 45/100
Low 5 HIGH 100½
posted on web
→ do again for homework

Ch15 (NO HECK)

(2) Homework
15.1–15.4, 15.7, 15.9–15.15, 15.17, 15.24–15.26

(1) ORGANOMETALLICS OVERVIEW
(2) MAGNESIUM
(3) LITHIUM
(4) COPPER
(5) RUTHENIUM

(1) Compounds $M^{\delta+}-C^{\delta-}$ bond.

extreme resonance ⟷ $M^+ C^-$

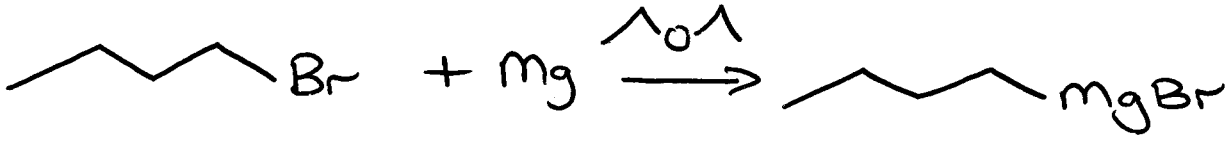
polar covalent (NOT SALTS)

V. important in synthesis (C–C BONDS)
(v. reactive — air moist sensitive)

(2) Organomagnesium compounds (GRIGNARD)

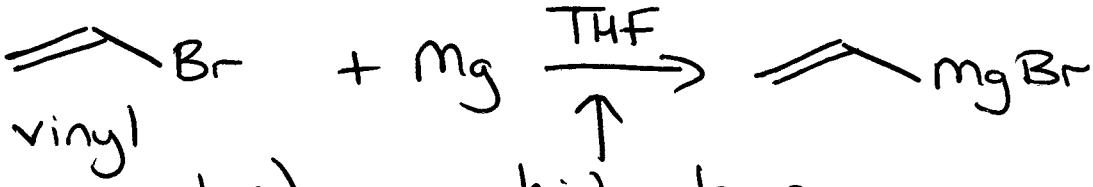
"$R-Mg-X$" ⟸ write like this, but actual structure is debatable
$\delta-\ \delta+$ (halogen) (Solvated / Clusters)

Preparation : add halide to Mg in ether



alkyl

aryl



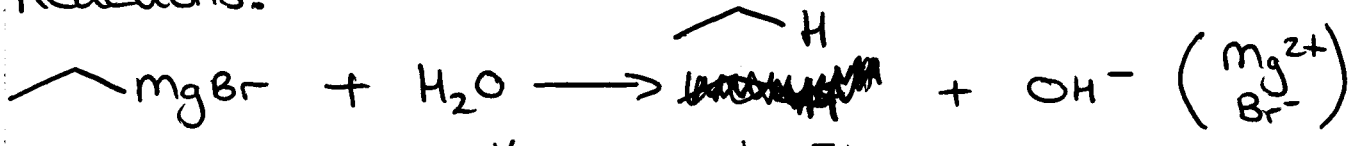
vinyl
(less reactive)

higher temp

Electrophilic C atom

Nucleophilic C atom (R^-)

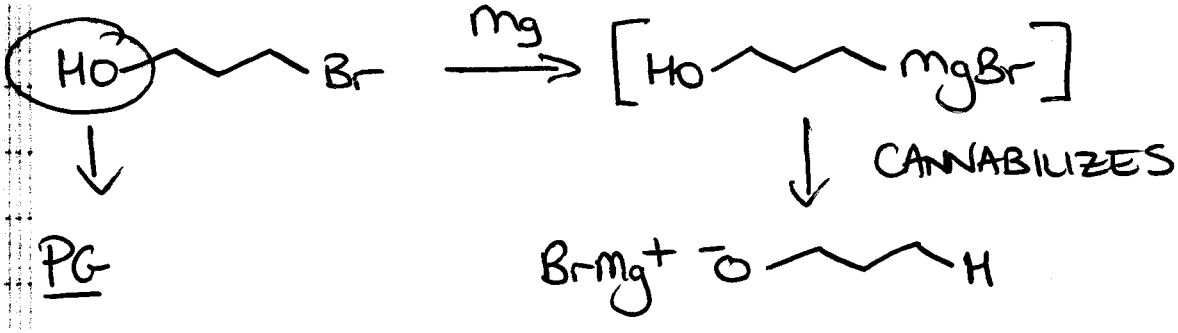
Reactions:



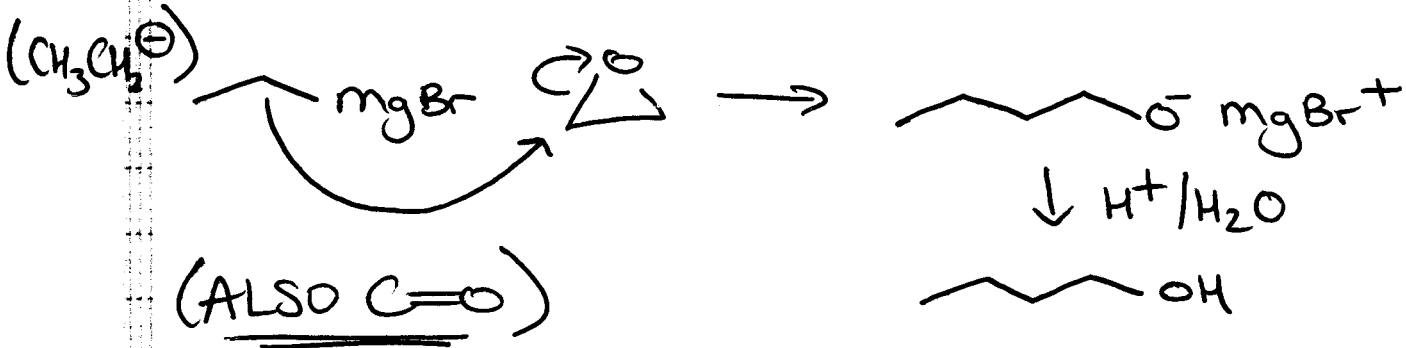
pka 16 pka 51

V. Strong base — will deprotonate

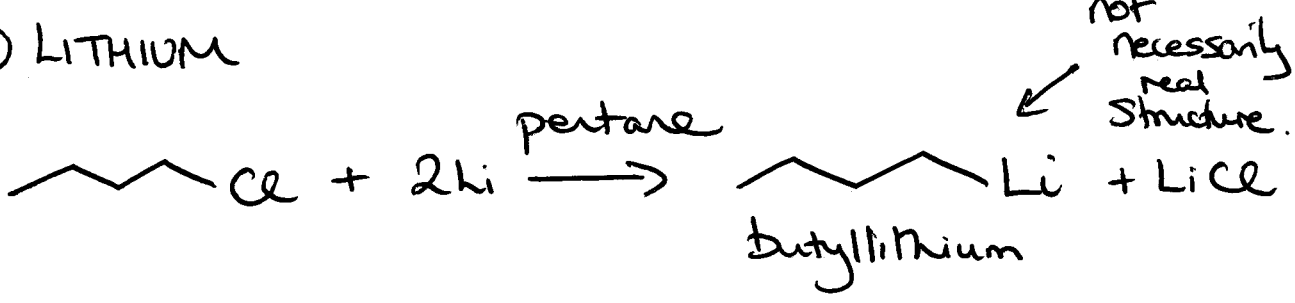
	RNH_3	$RC\equiv CH$	ROH	RSH	RCOOH
pka	~38	25	16	9	5



RXN w/ EPOXIDES



(3) LITHIUM



more nucleophilic than Grignards (R^-)
also v. powerful bases

One reaction of RMgX and RLi that does not work well is: with R–Hal

$$\begin{matrix} R\text{-}MgX \\ R\text{-}Li \end{matrix} \xrightarrow{R'\text{-}X} R\text{-}R' \quad \left(\begin{matrix} \text{Elimination} \\ \text{Side rxns} \\ \text{radicals} \end{matrix}\right)$$

(4) COPPER – GILMAN REAGENTS

$$2\ R\text{–}Li + CuI \xrightarrow[(THF)]{ether} R\text{–}Cu^{\ominus}\text{–}R\ (Li^{+}) + LiI$$

$$(R)_2CuLi \xrightarrow[ether]{R\text{–}Hal} R\text{–}R$$

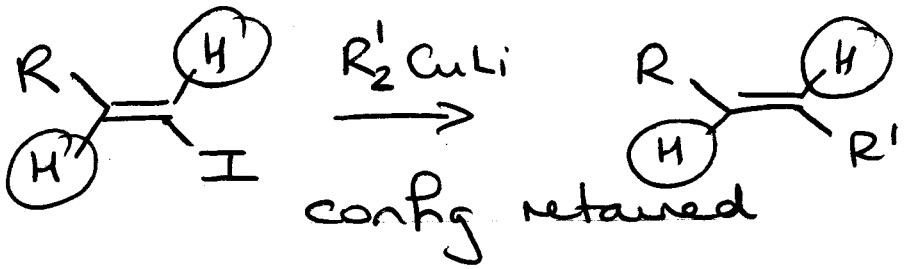
R–Hal = vinylic Br, RCH_2Br (1° alkyl), allylic Br, aryl Br

also reacts w/ epoxide

(see again in C=O chemistry)

$$I \xrightarrow[pentane]{Li} Li \xrightarrow{CuI} (\ )_2CuLi \xrightarrow{} \text{alkene}$$

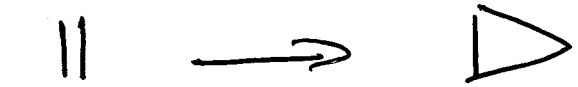
usually unreactive to Nu⁻ displacement



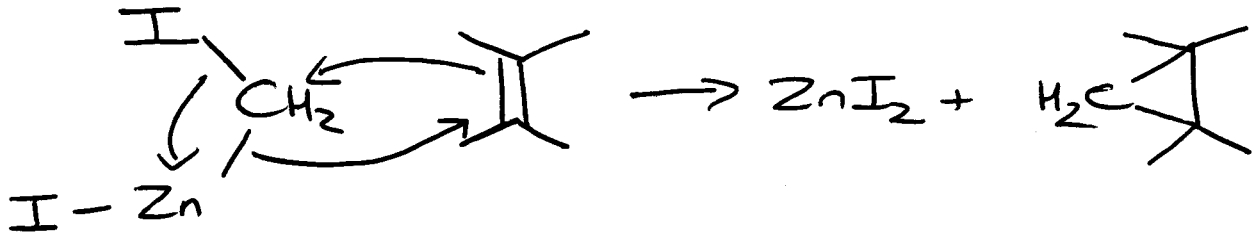
SIMMONS-SMITH RXN

small amt

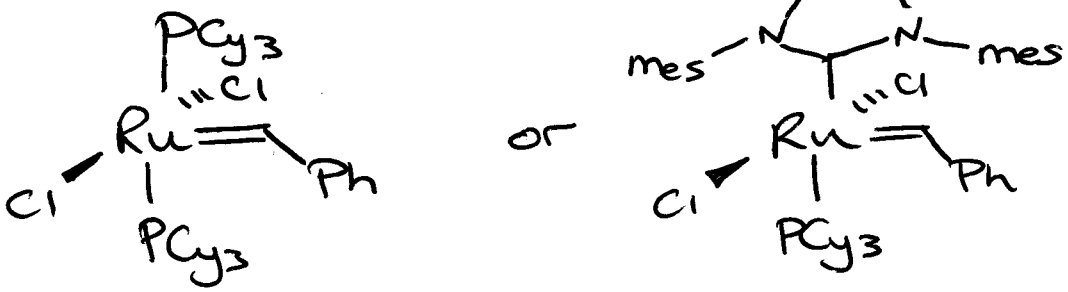
$CH_2I_2 + Zn/Cu \rightarrow ICH_2ZnI$



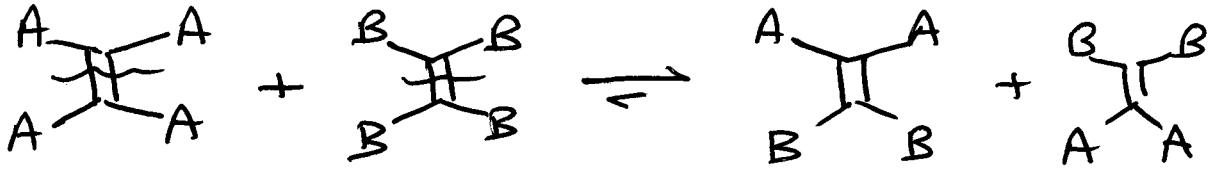
source of (CH_2)



(5) Ruthenium

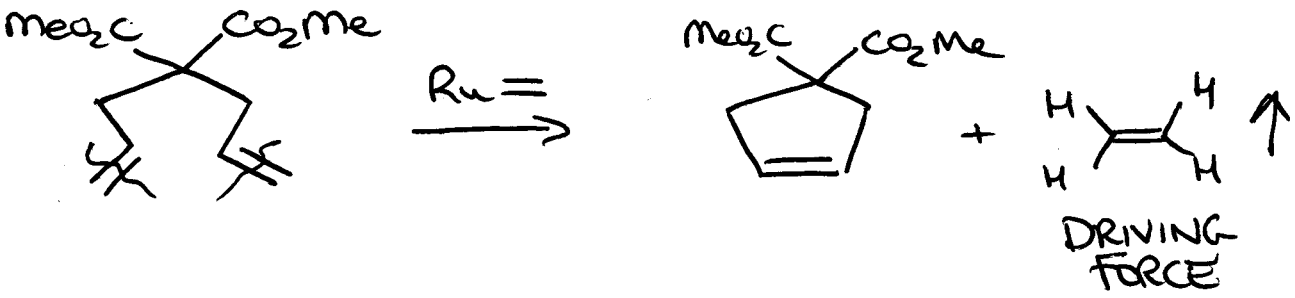


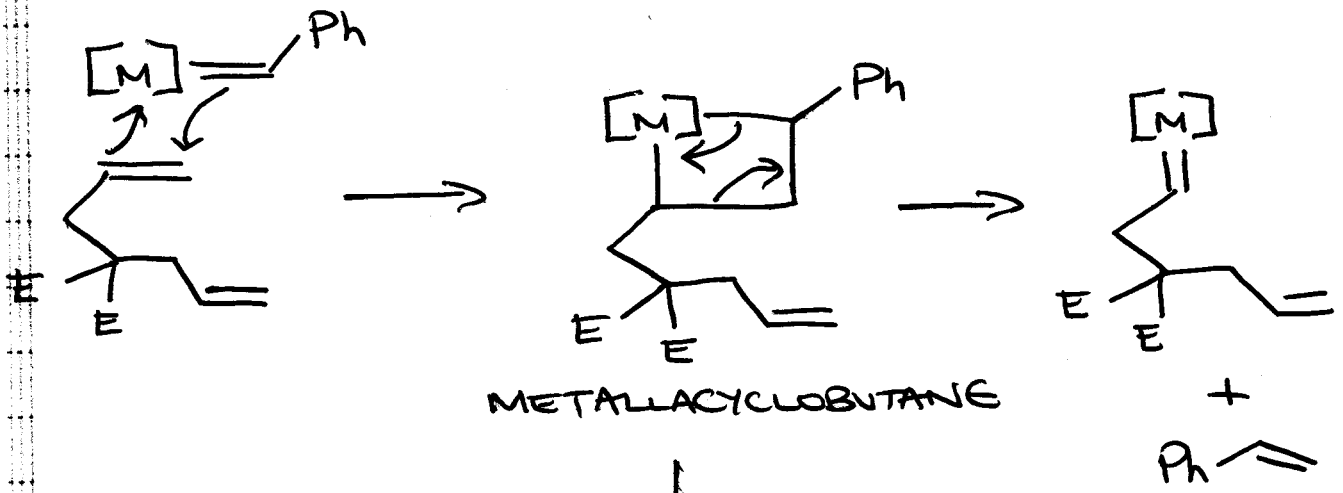
Alkene metathesis

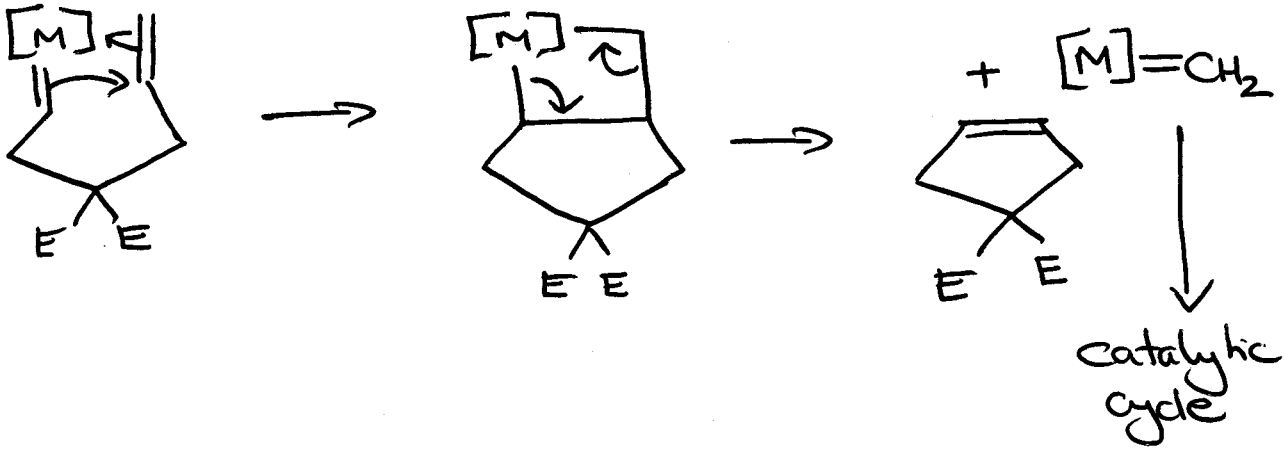


Interchange C atoms of C=C bonds

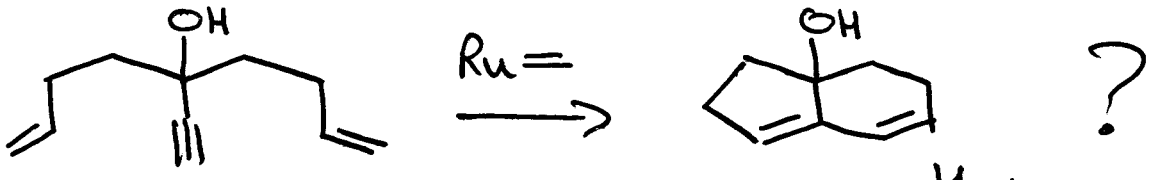
RING CLOSING METATHESIS



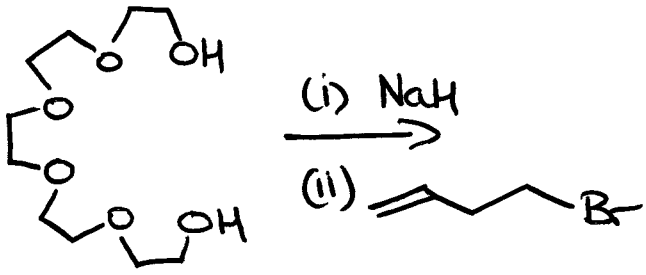




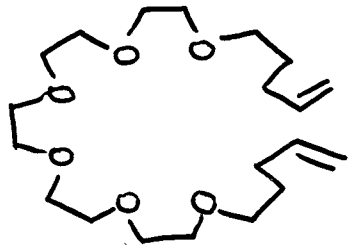
ALKYNE RELAY



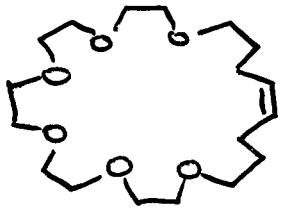
HMK



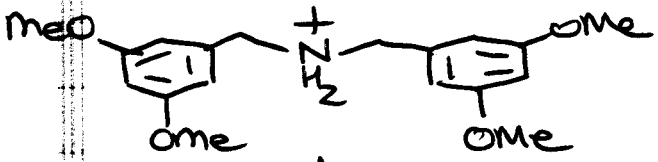
WILLIAMSON ETHER SYNTHESIS

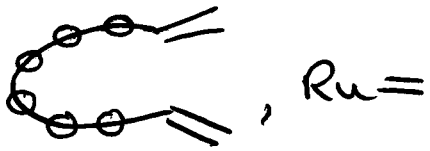


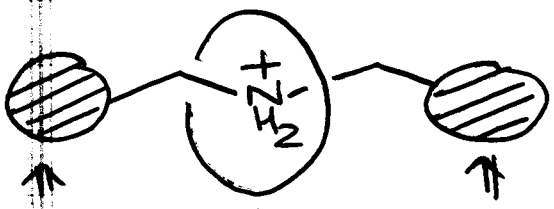
RCM



CROWN ETHER LIKE







TOO BIG

TOO BIG

CANNOT COME OFF

MECHANICALLY INTERLOCKED MOLECULE.

PUBLISHED IN 2003 in ANGEWANDTE CHEMIE

EXTRA CREDIT.

WHO AUTHORED THE PAPER (5 people)

CHEM 30B Lec (12)

(1) Homework
CARBONYL CHEM Ch 16
16.4, 16.5, 16.19 – 16.29

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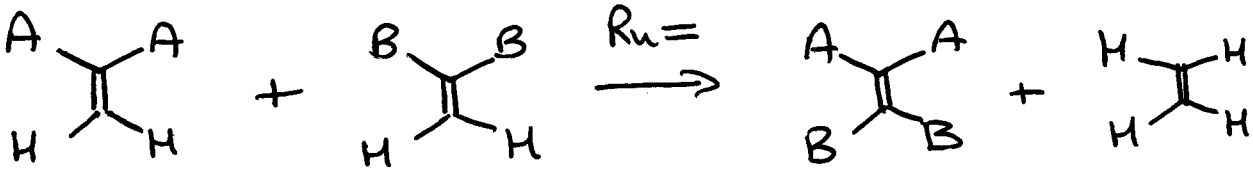
(1) EXTRA CREDIT PROBLEMS IN ORDER
(2) CARBONYL CHEM

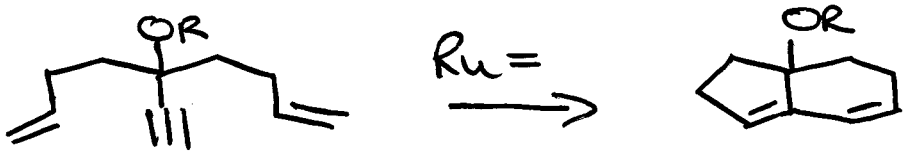
Pg 540 BROWN & FOOTE

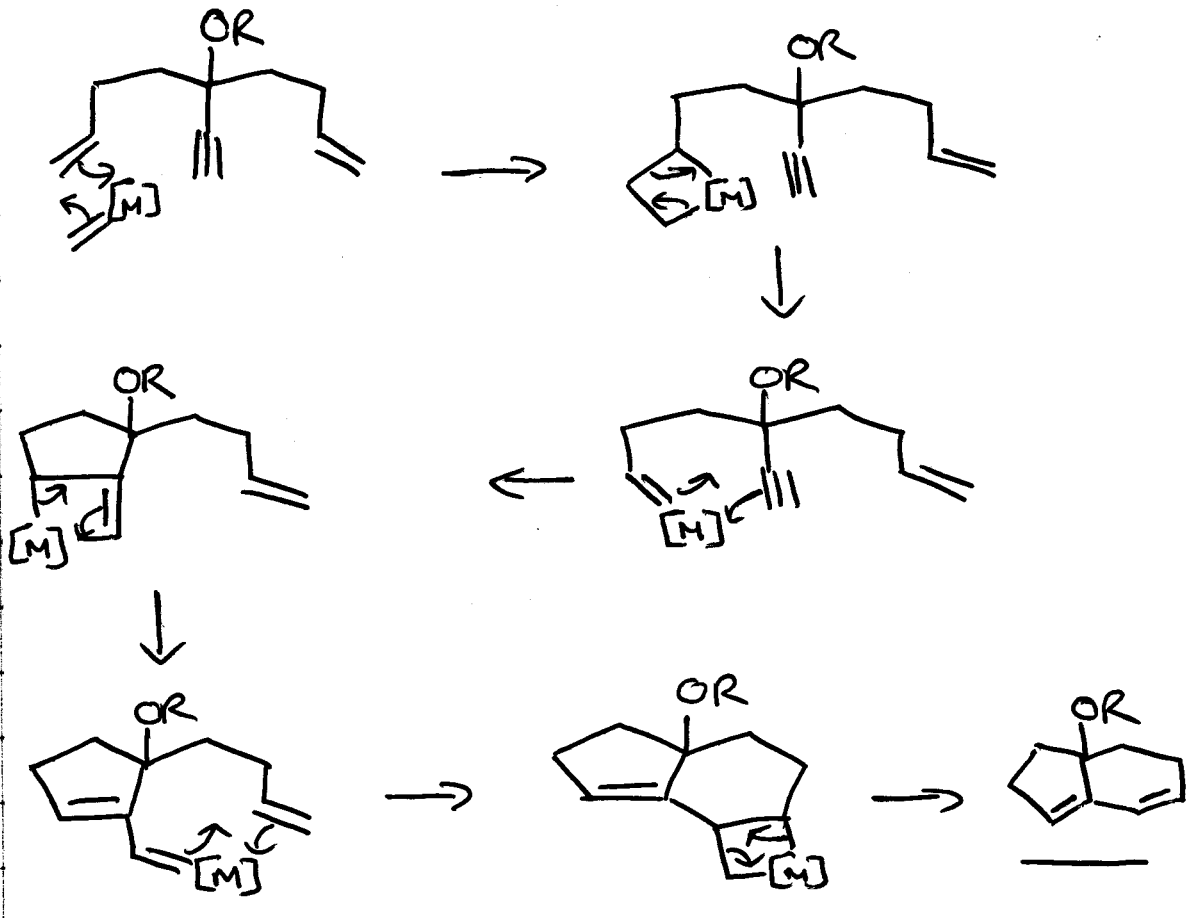


'SINGLE PRODUCT'

BUT, ALSO GET:

ALKYNE RELAY





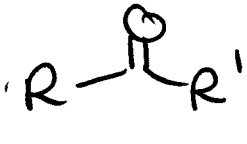
"MAGIC RING ROTAXANES BY OLEFIN METATHESIS"

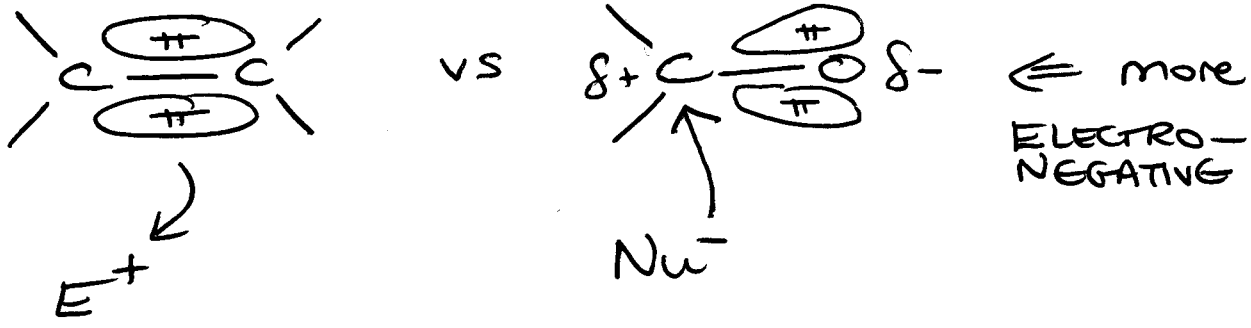
Kilbinger, Waltman, Day, Grubbs, Cantrill!

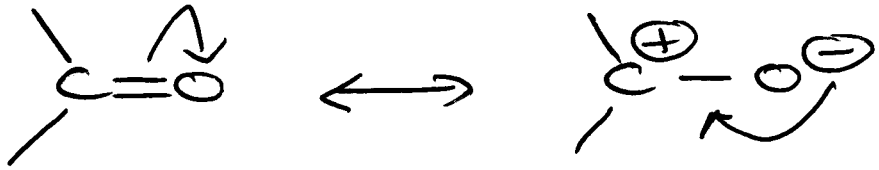
② CARBONYL CHEMISTRY

Aldehydes

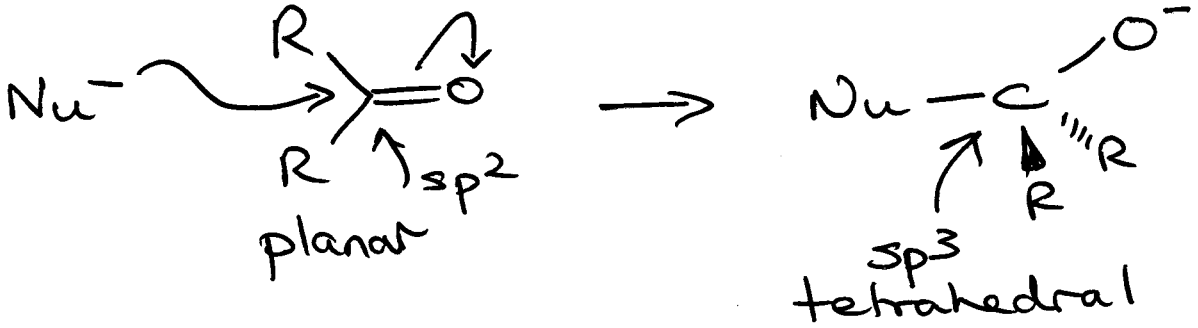
Ketones



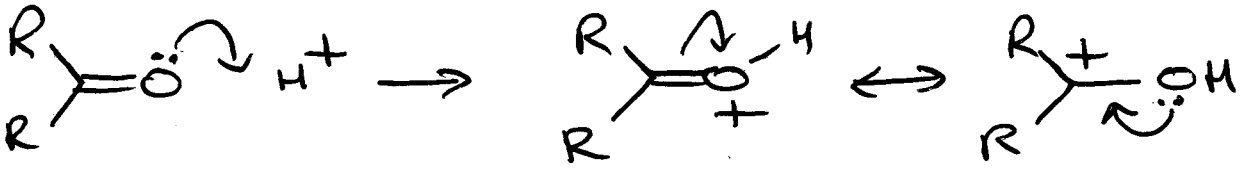




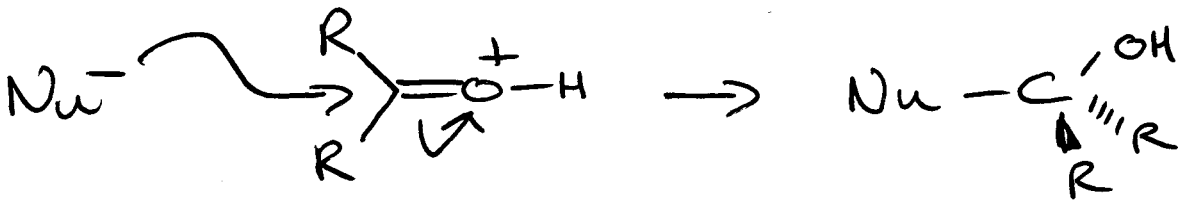
NUCLEOPHILIC ADDITION



ACTIVATION w/ H^+ or LEWIS ACID



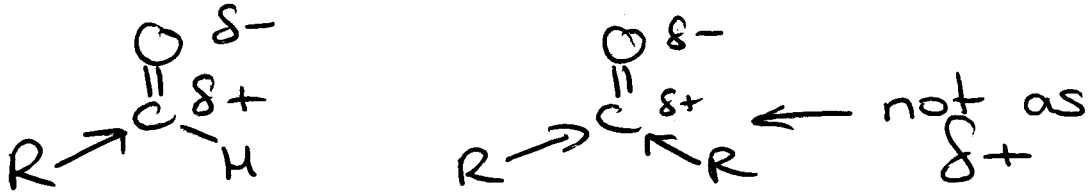
(4)



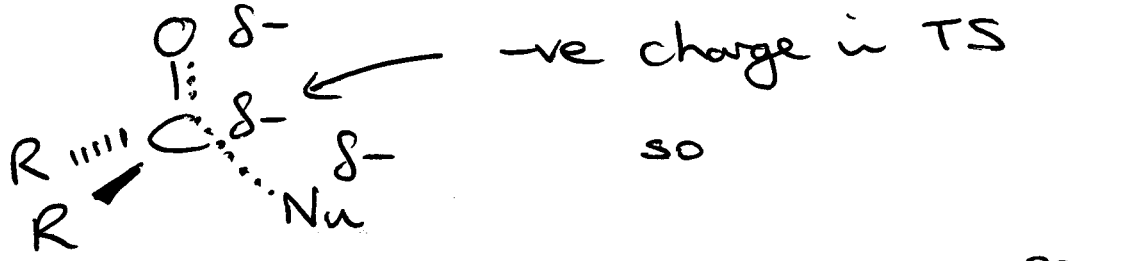
ALDEHYDES MORE REACTIVE KETONES

(1) LESS BULKY 1 R vs 2R

(2)



(3) TS



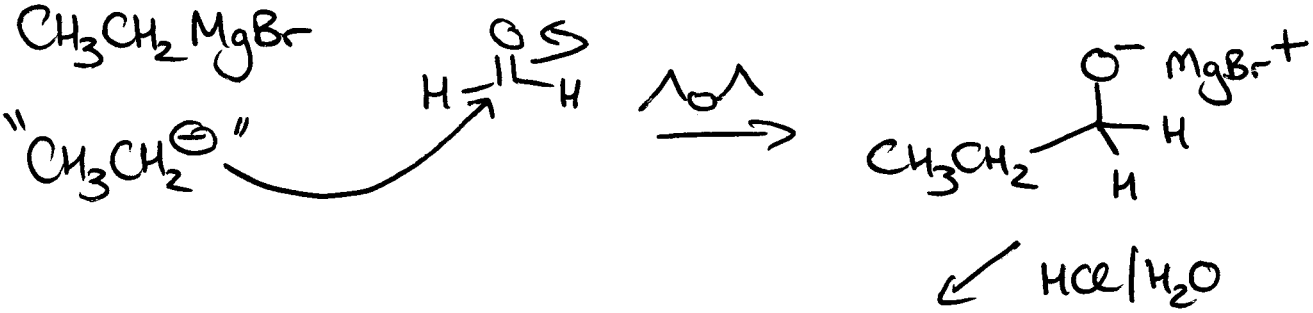
(A) CARBON NUCLEOPHILES

RMgX RLi $RC\equiv C^{\ominus}$ $\overset{\ominus}{C}N$

Important C–C bond formation

GRIGNARDS

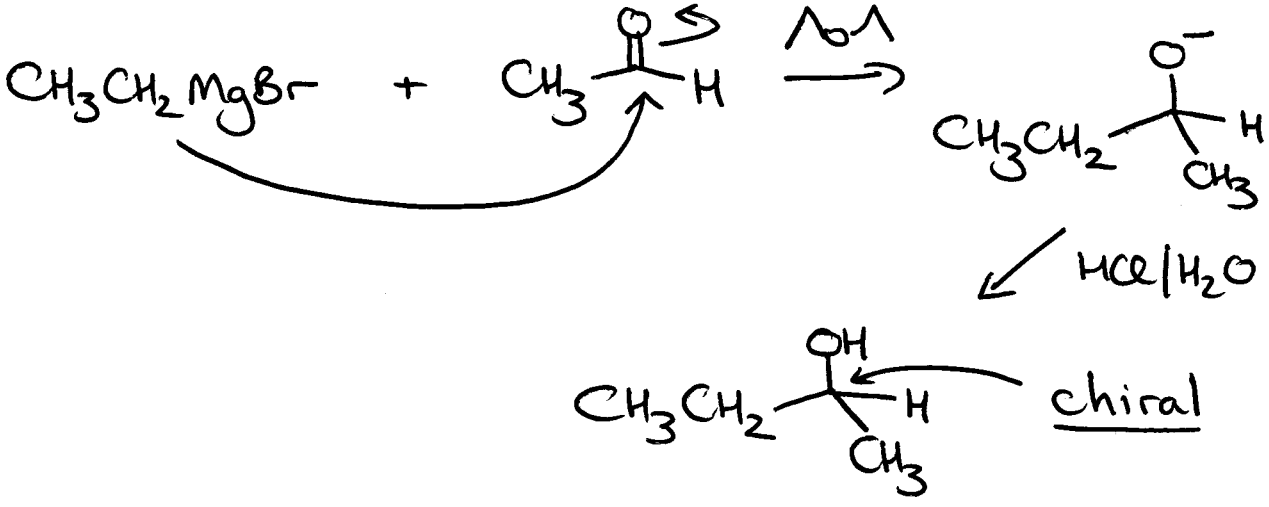
(i) FORMALDEHYDE



$CH_3CH_2CH_2OH$

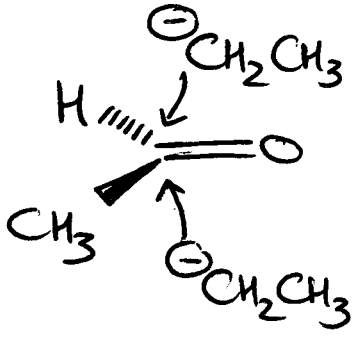
1° alcohol

(ii) ALDEHYDE, not $H_2C{=}O$



chiral

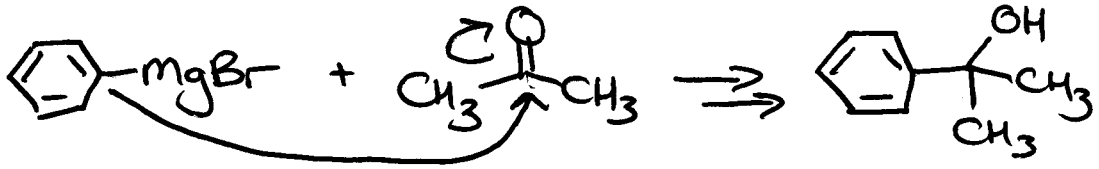
2° alcohol



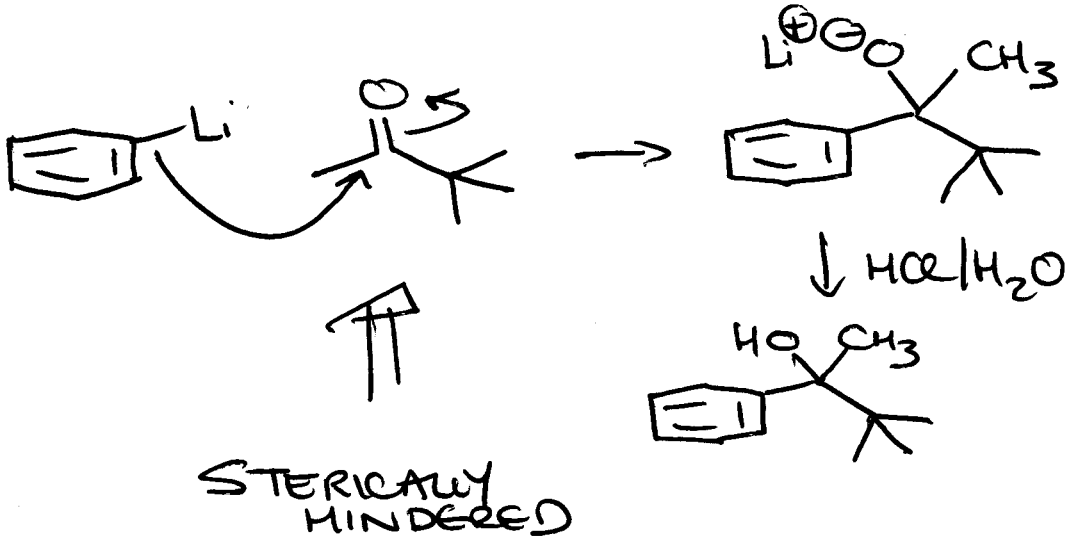
→ ENATIOMERS (draw them)

(iii) KETONES

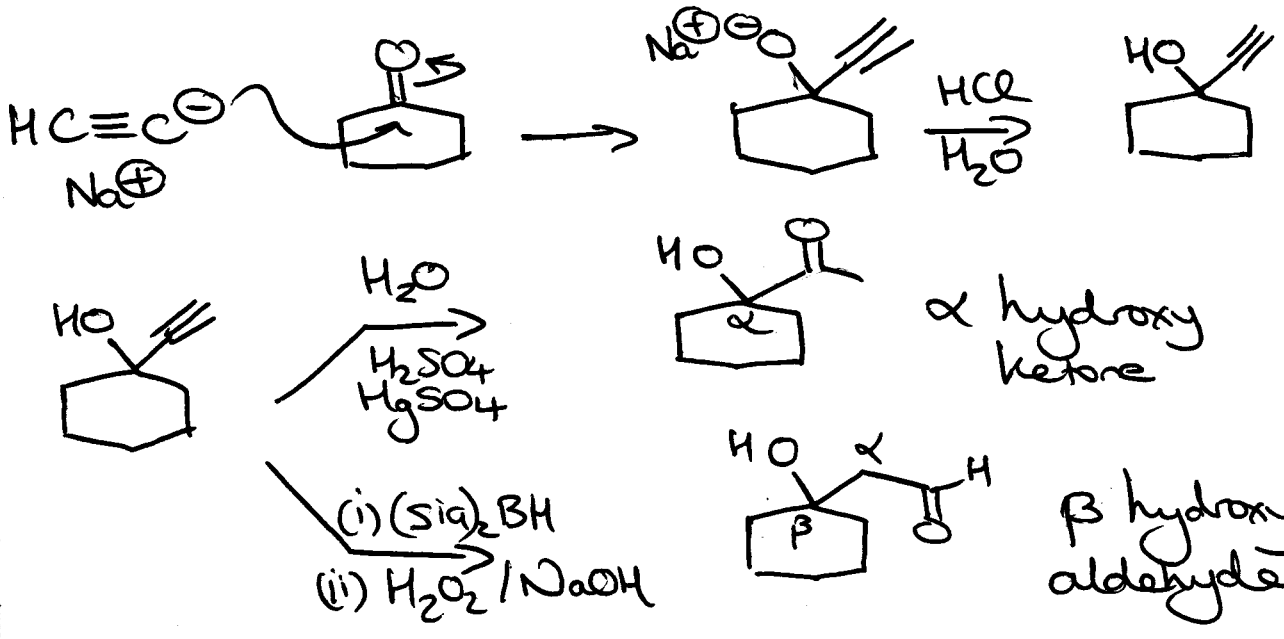
3° alcohol



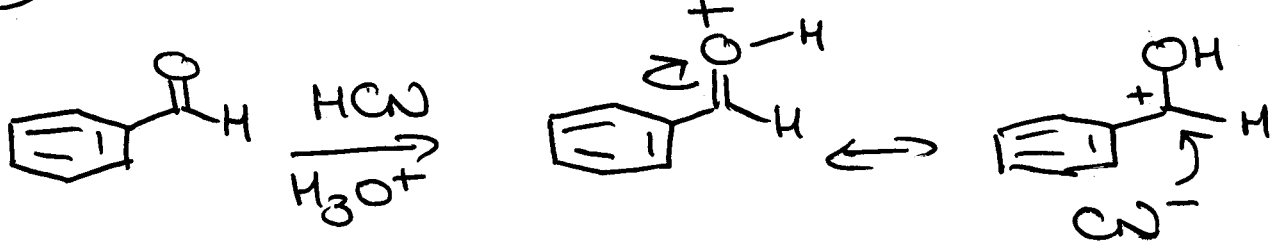
(B) ORGANOLITHIUMS
- more reactive (INERT ATMOS)

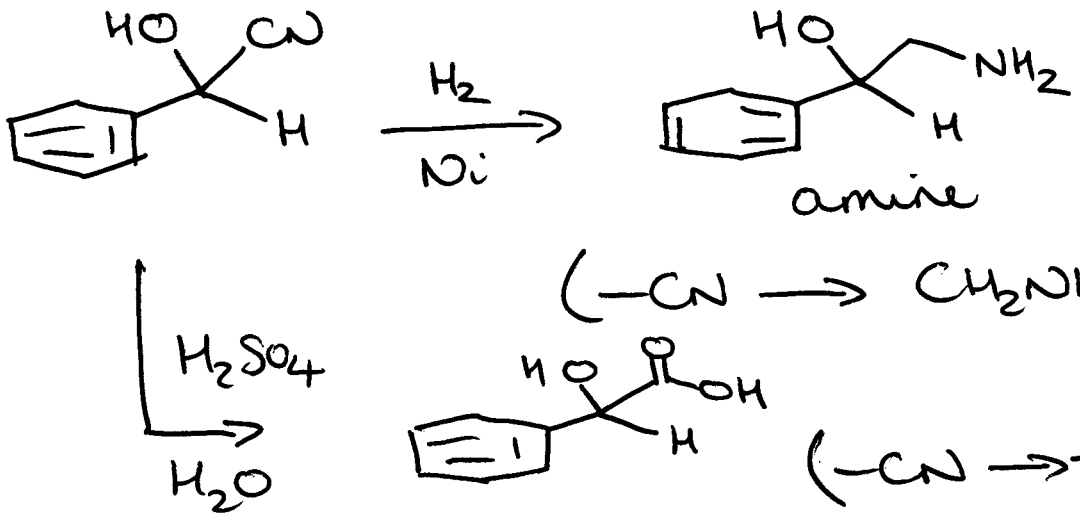


(C) ALKYNYL ANIONS $HC\equiv C^{\ominus}$



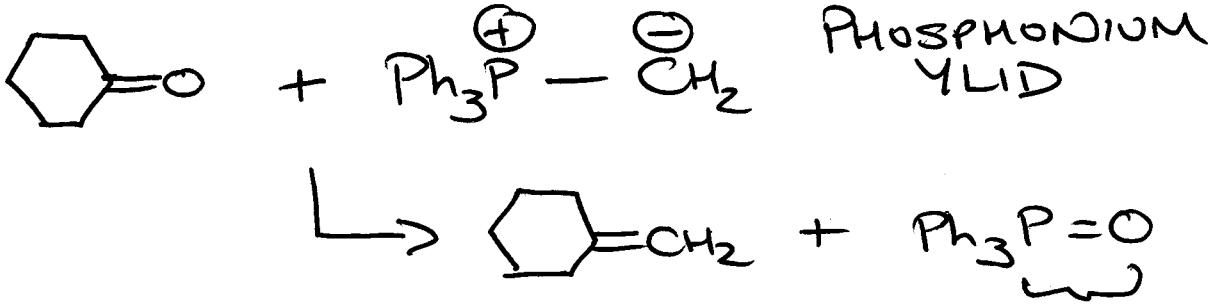
(D) CYANIDE CN^-



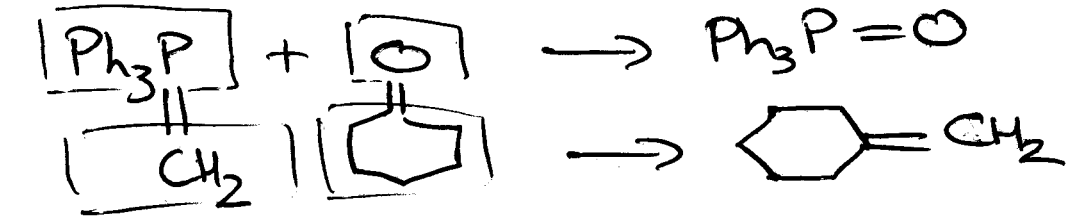


WITTIG REACTION (1979 NOBEL PRIZE)
w/ HC BROWN BH_3

$$C{=}O \longrightarrow C{=}C$$

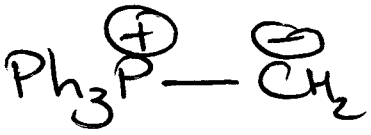


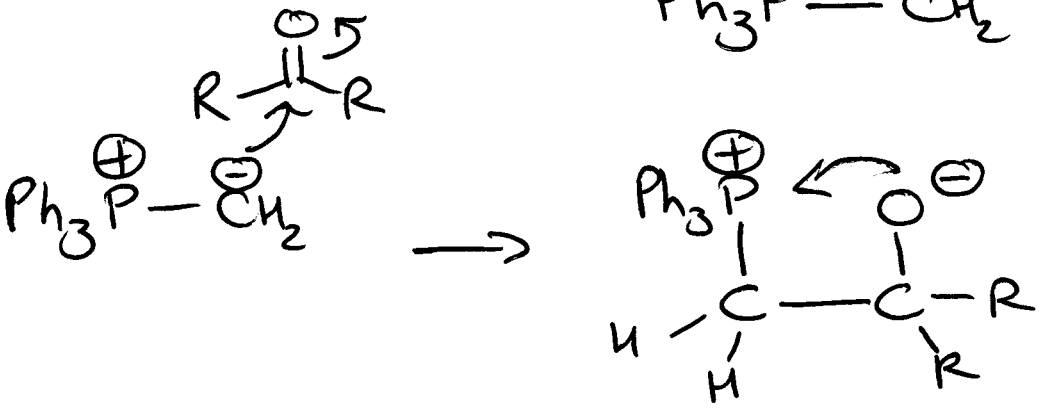
LIKE METATHESIS



THE YLID

↓ nBuLi / THF
or
NaOH2 / THF

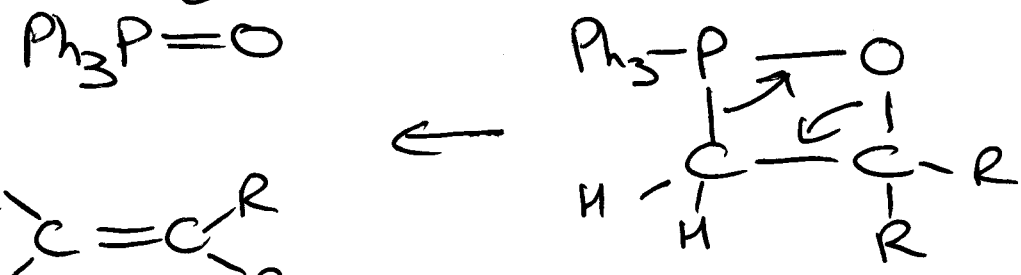


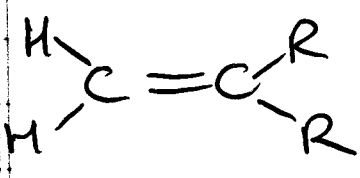


BETAINE

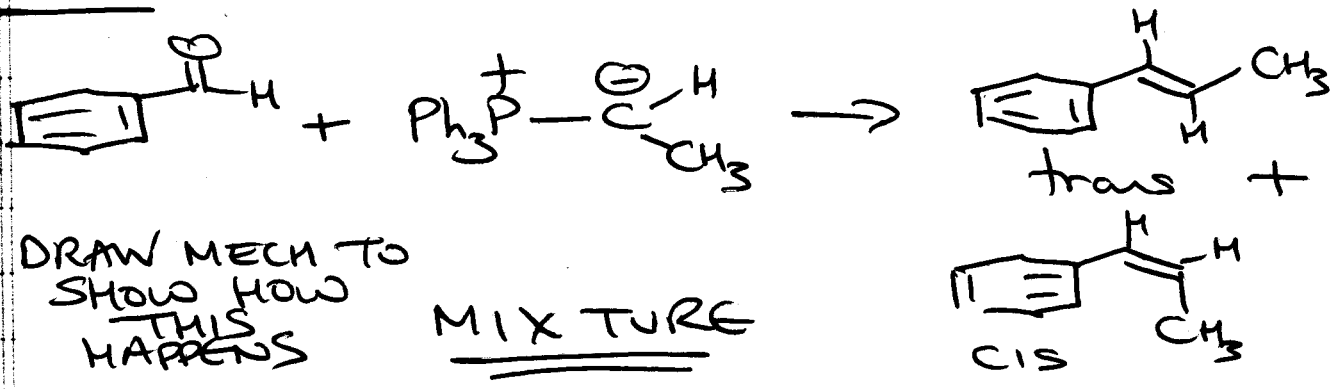
↓

STRONG BOND



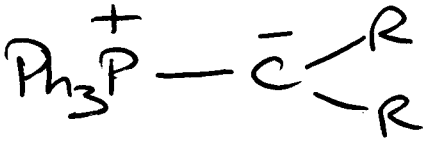


OXAPHOSPHETANE

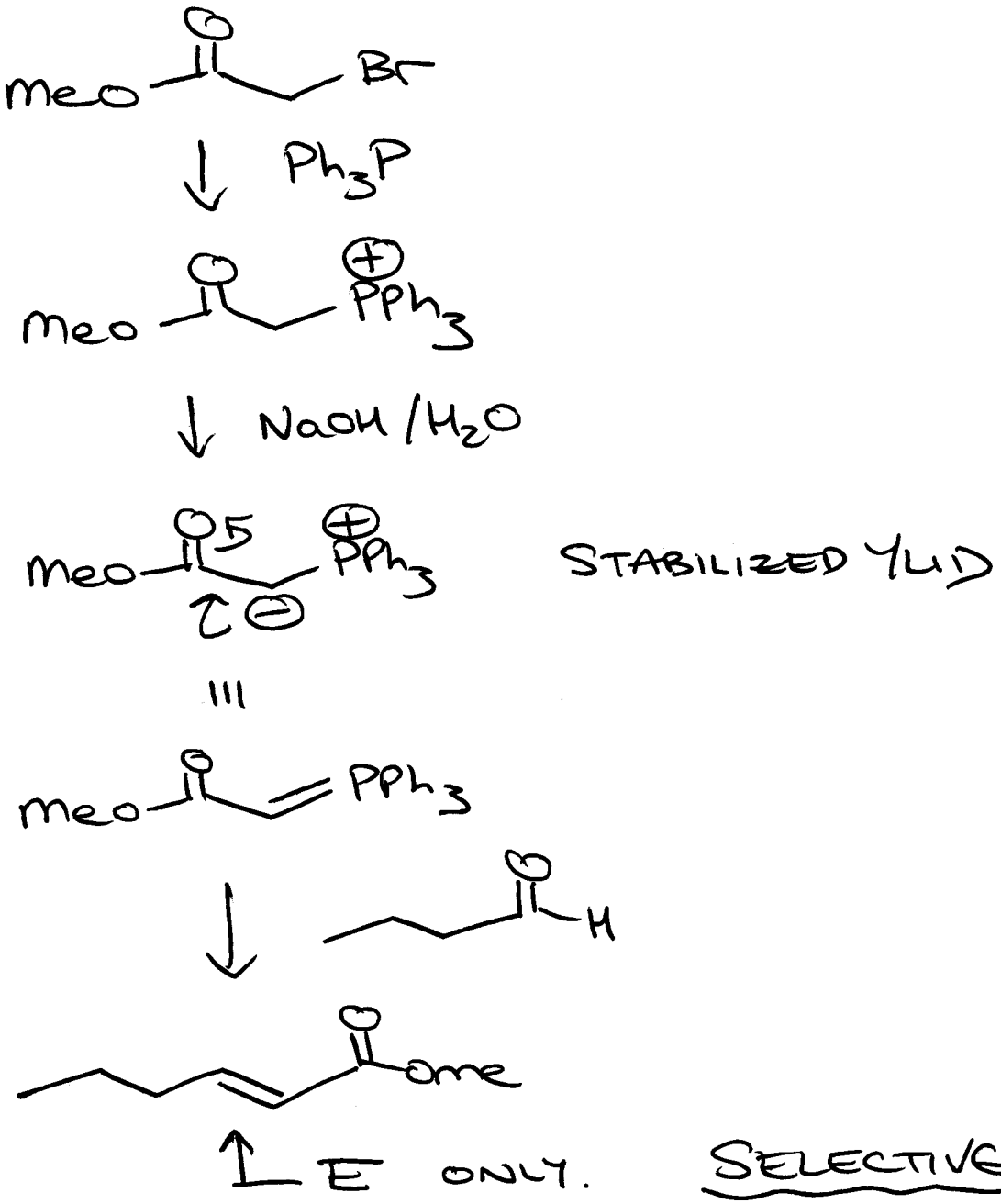


DRAW MECH TO SHOW HOW THIS HAPPENS

MIXTURE



Unstabilized YLID



E ONLY. SELECTIVE

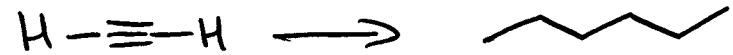
NEXT: Oxygen/Sulphur/Nitrogen $Nuc^{\ominus}$

Lec (13)

(1) Homework
16.6, 16.8, 16.9, 16.30-16.45

(2) CNSI Seminars
- Tues 4pm CS50
Ben Cravatt
"Chemical Strategies for Activity-Based Proteomics"
- Weds 4pm YH2033
Thomas Bjornholm
"Organic Molecules in Electronic Devices"

(3) Molecule of the Week



only C source

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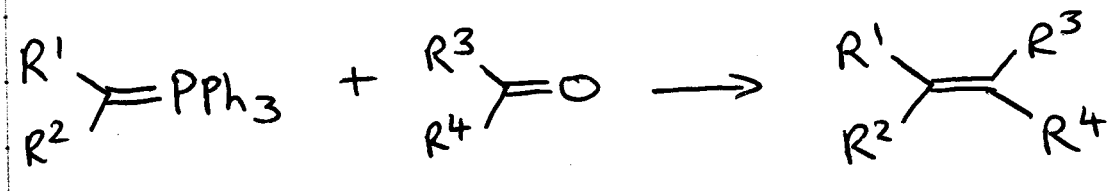
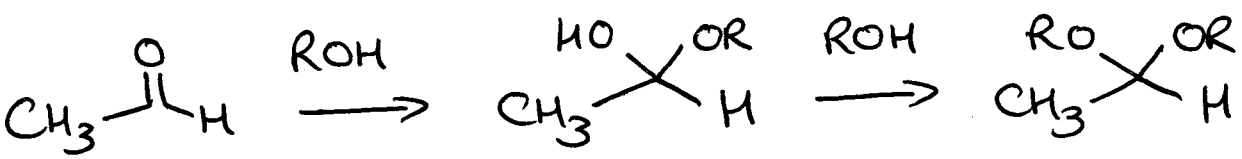
(1) WITTIG
(2) OXYGEN Nu^-
(3) SULFUR Nu^-
(4) NITROGEN Nu^-

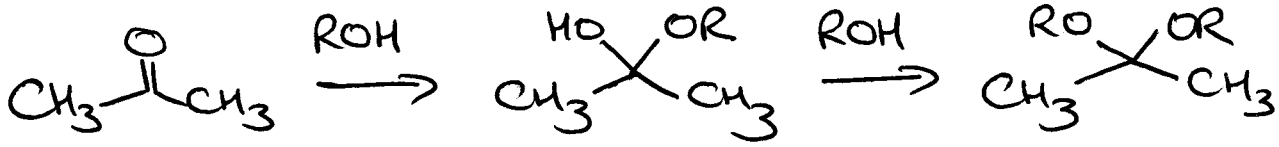
(1) WITTIG



(2) ROH nucleophiles

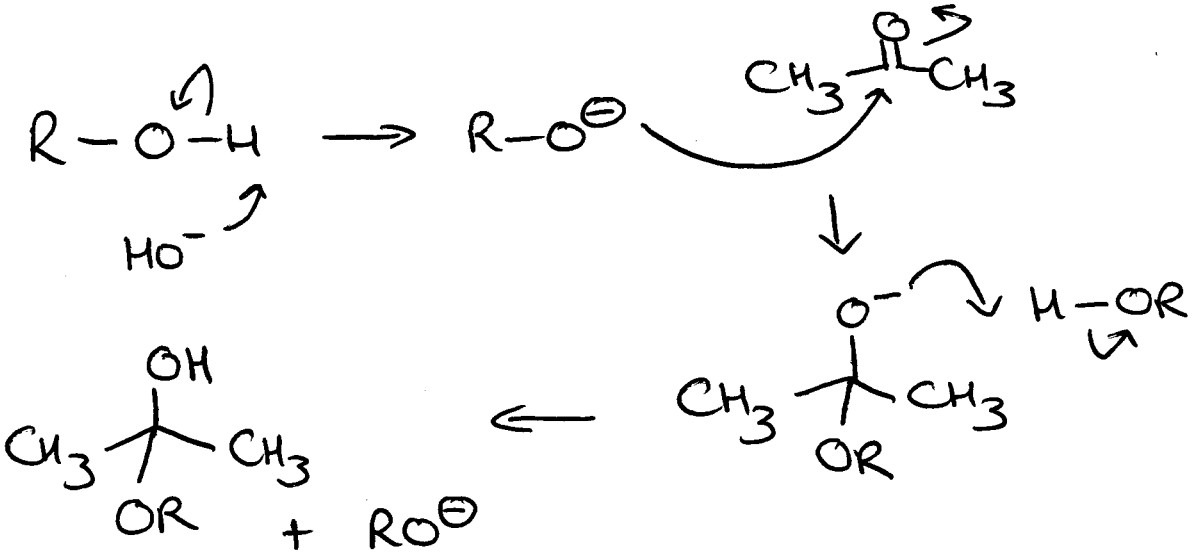


aldehyde hemiacetal acetal

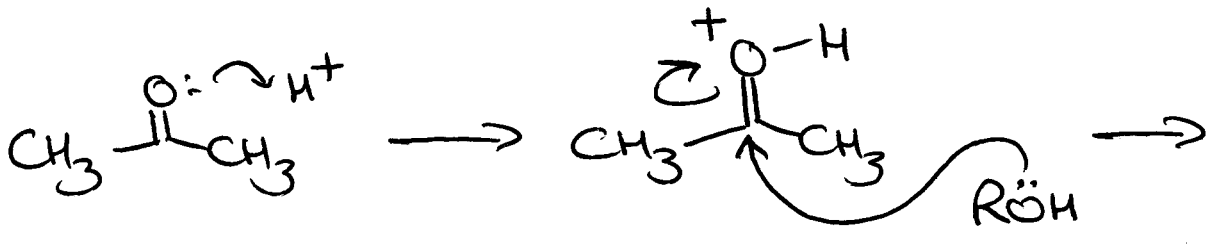


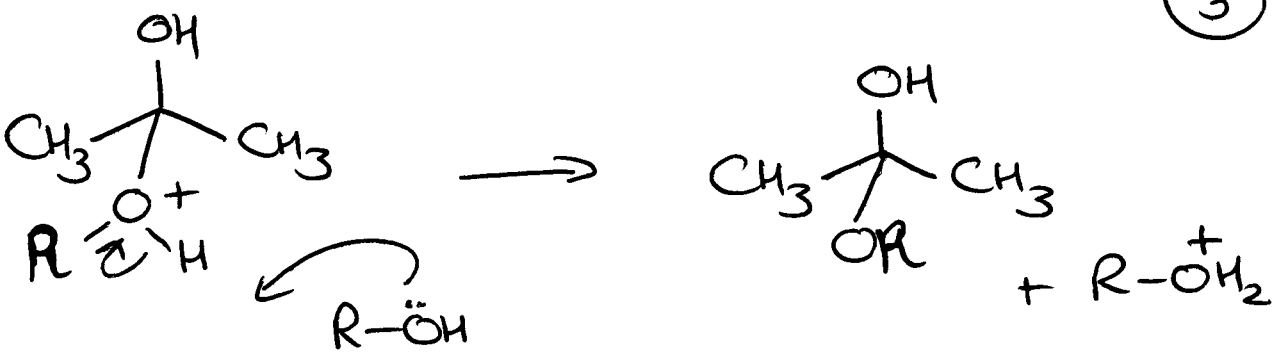
Ketone hemiketal ketal

HEMI (ACETALS/KETALS) – BASE CATALYZED

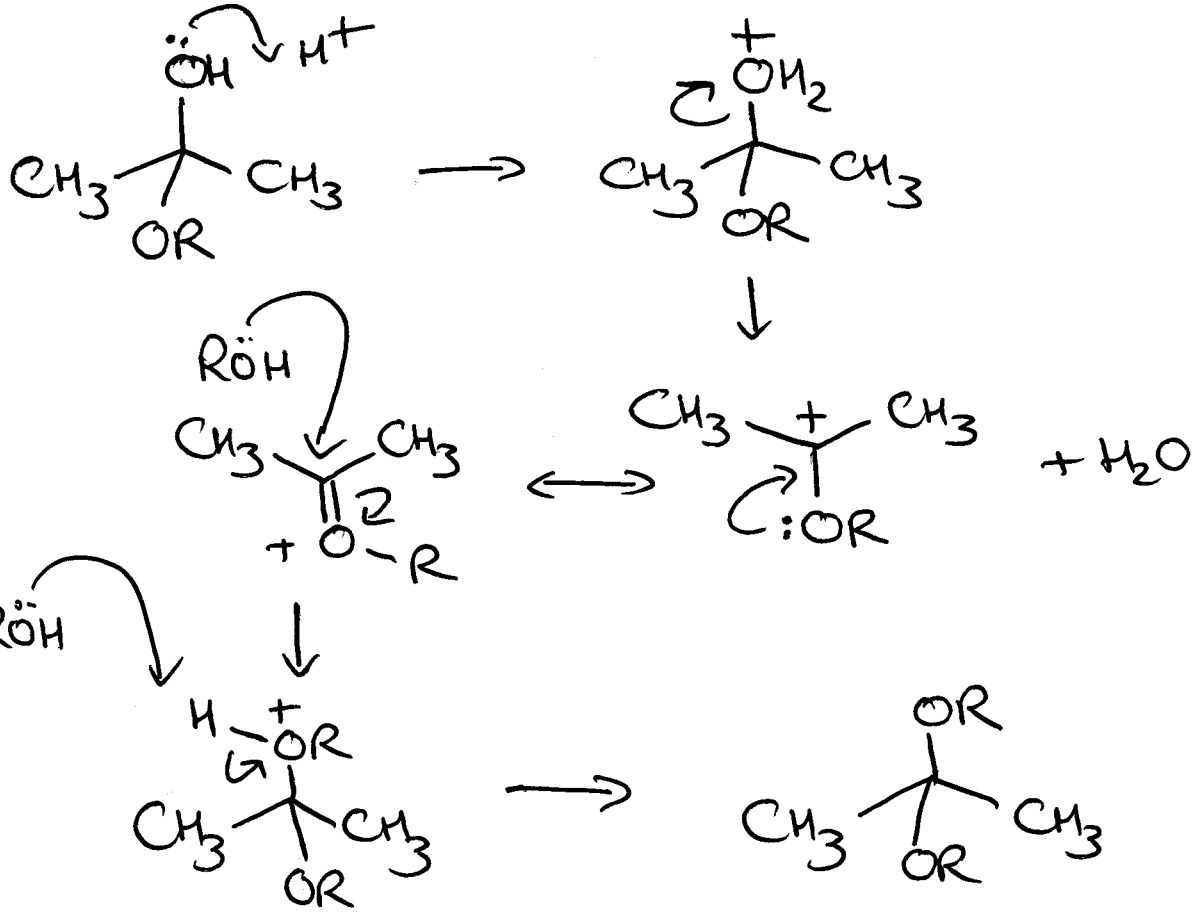


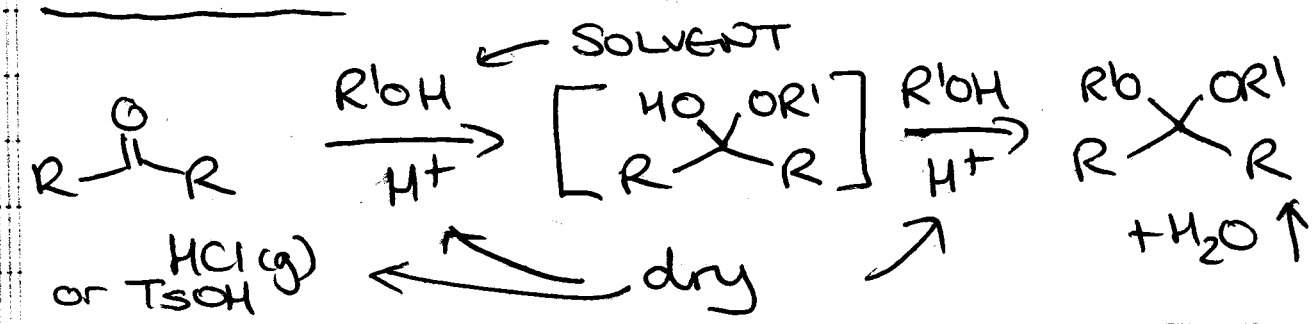
ACID-CATALYZED





HEMIACETAL ⟹ ACETAL ONLY H^+ catalyzed
HEMIKETAL ⟹ KETAL catalyzed

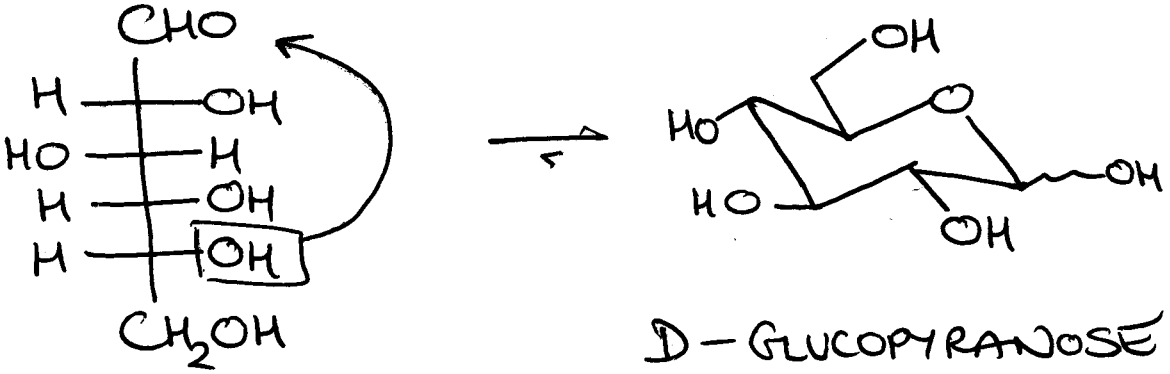




Hemiacetals/hemiketals ⇒ generally unstable

xcept for cyclic ones

IMPORTANT for 5/6 MEM RINGS

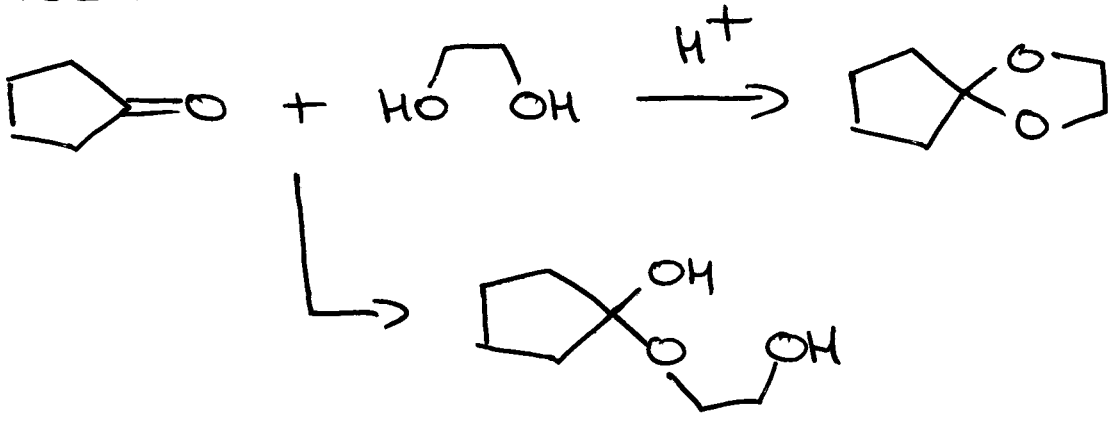


D-GLUCOSE
Straight Chain
(FISCHER)

D-GLUCOPYRANOSE

(SUGARS)

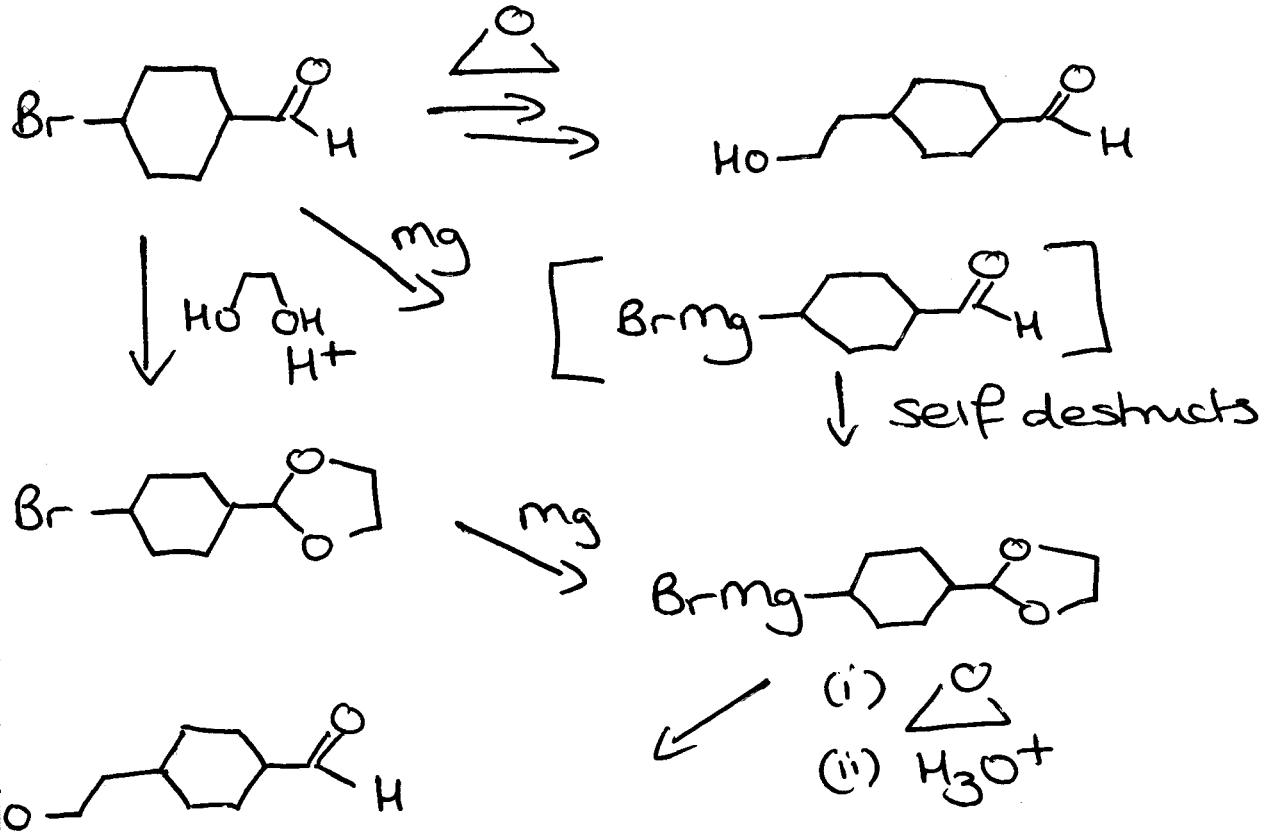
DIOLS



LIKE ETHERS, acetals / ketals stable to:
- bases
- organometallics (Grignard etc)
- non acidic oxidants
- reduction.

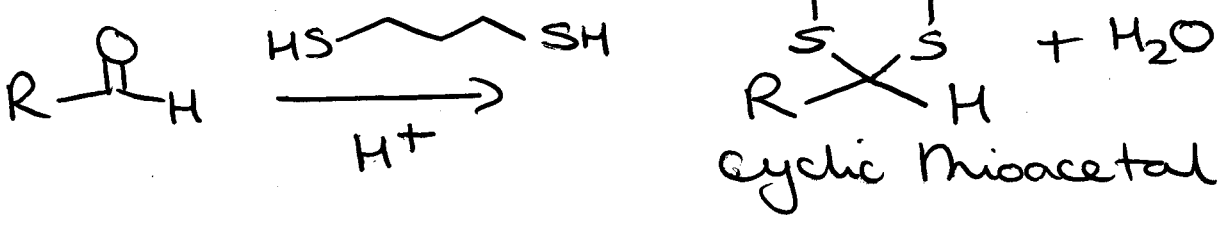
CLEAVED w/ AQUEOUS ACID

PROTECTING GROUPS

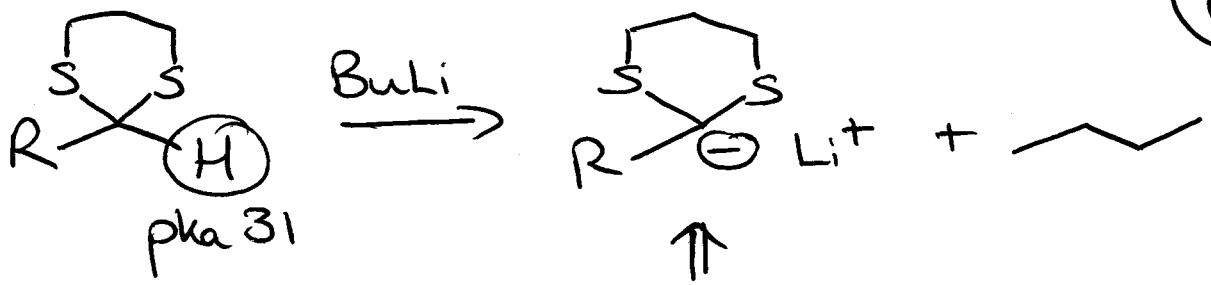


1,3 dithiane

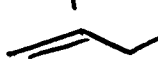
(3) SULFUR



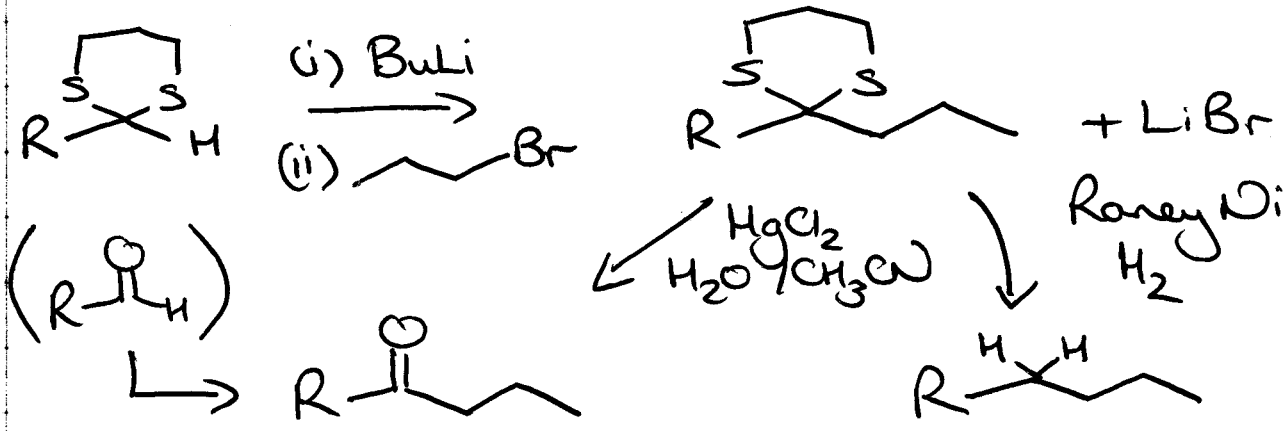
cyclic thioacetal

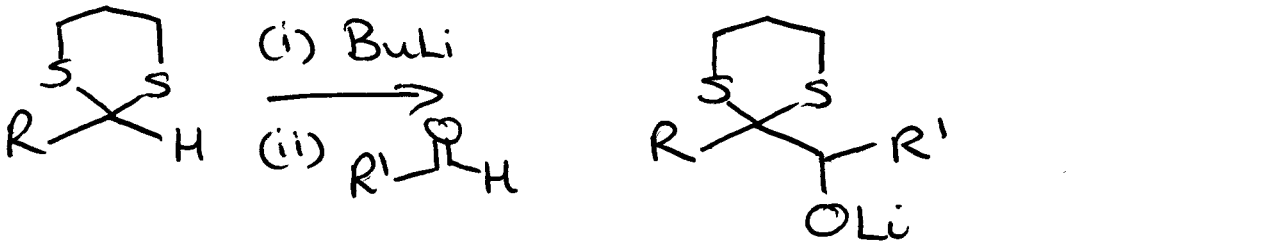


nucleophilic

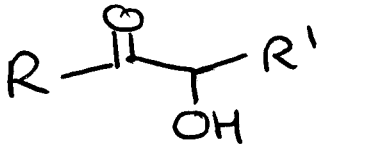
RCH_2Br,  S_N2

1° allyl



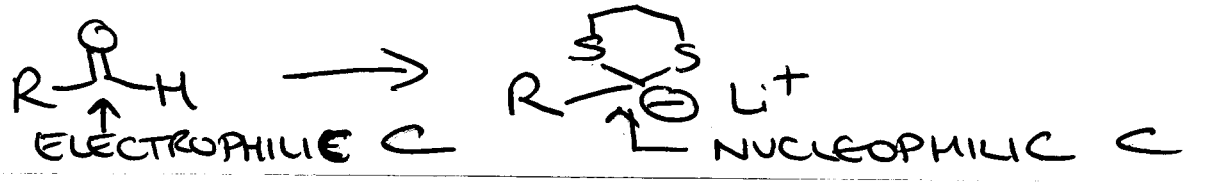


H_2O, $HgCl_2$, CH_3CN



α hydroxy ketone

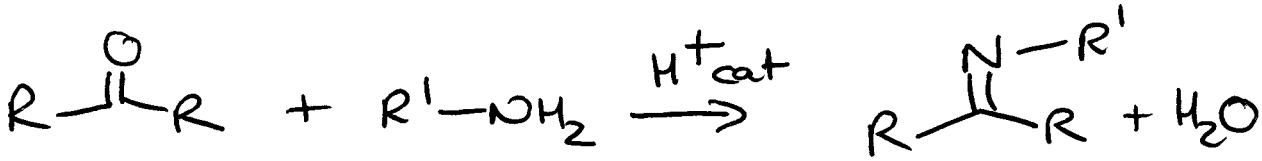
UMPOLUNG — POLE REVERSAL



(4) NITROGEN NUCLEOPHILES

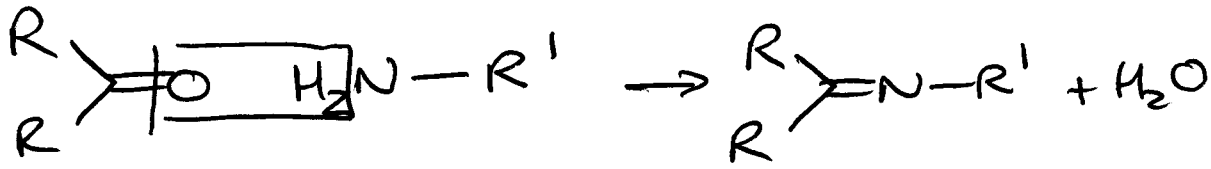
1° AMINES (NH_3, $R-NH_2$ R=aryl/alkyl)

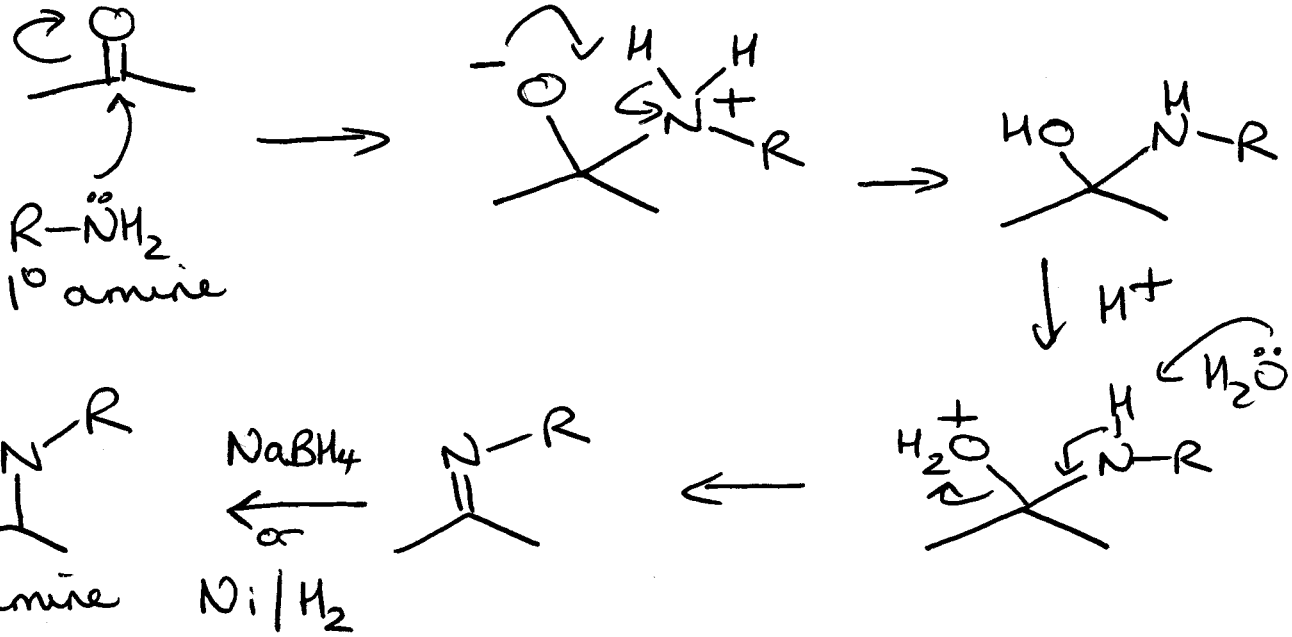
react w/ aldehydes/ketones



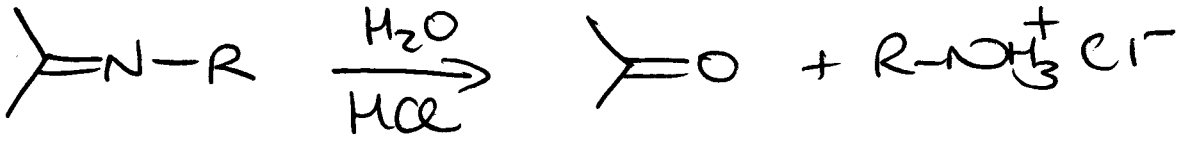
Imine / Schiff base

LASSO CHEM

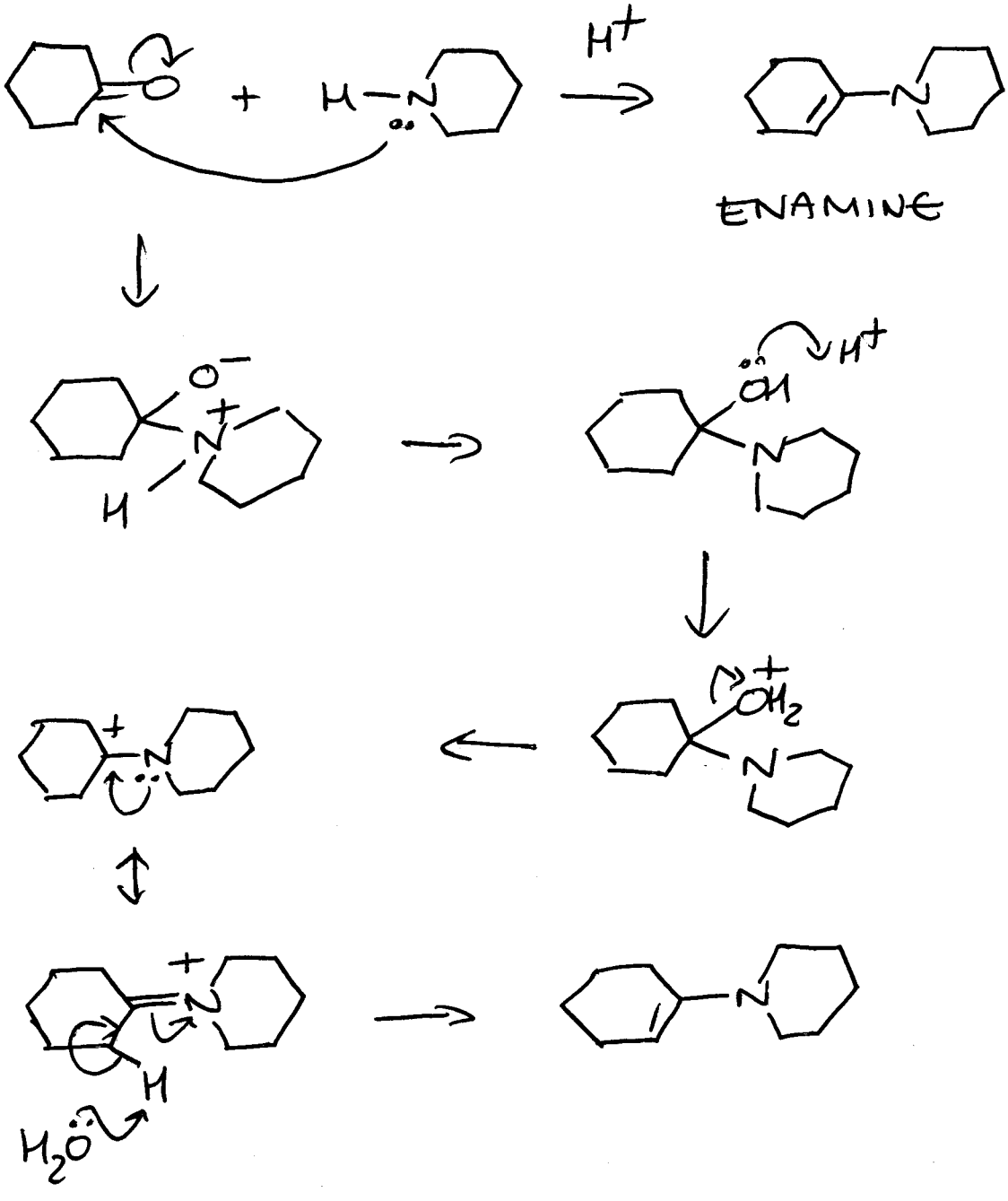




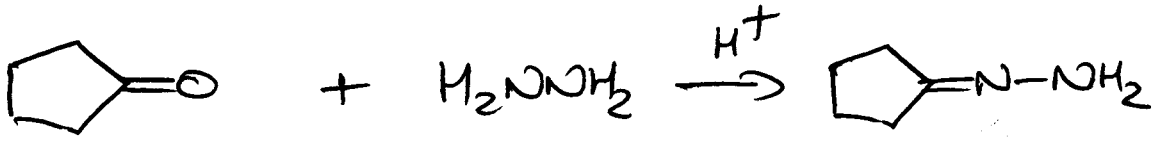
ACID CATALYZED HYDROLYSIS

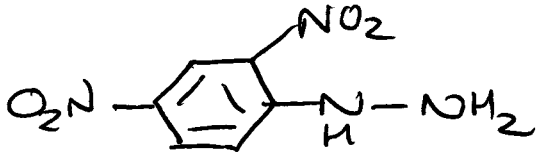


SECONDARY AMINES



HYDRAZINE





2,4 DINITROPHENYLHYDRAZINE
makes crystalline derivs of liquid aldehydes / ketones => mp.

NEXT : OXIDATION / REDUCTION and other STUFF.

Lec (14)

(1) Homework
16.12 – 16.14, 16.54, 16.55
(2) CNSI SEMINARS
Thomas Bjornholm 4pm YH2033
"Organic Molecules in Electronic Devices"
(3) Quiz on Monday
20 question multiple choice
MIDTERM => FRIDAY

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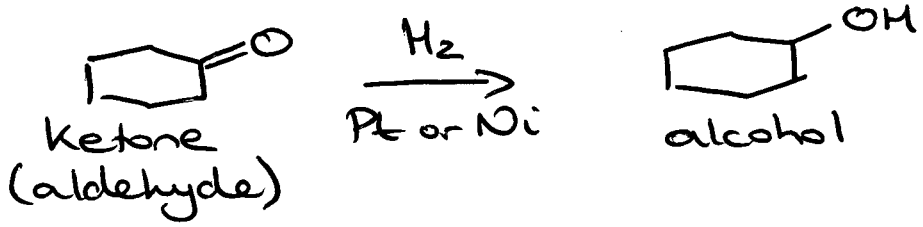
(1) SULFUR Nuc
(2) NITROGEN Nuc
(3) REDUCTION
(4) OXIDATION

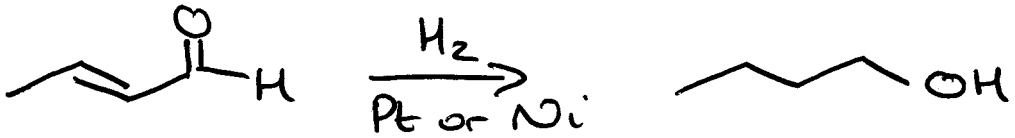
---

(3) REDUCTION (CATALYTIC HYDROGENATION)



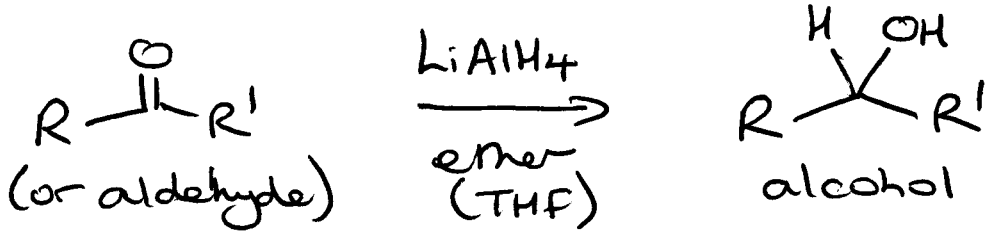
Ketone (aldehyde)

alcohol



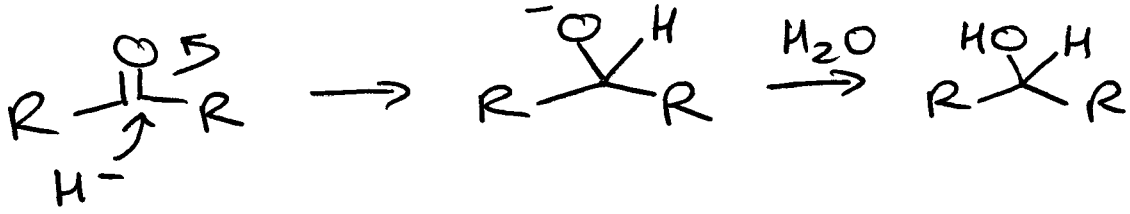
reduces C=C & C=O

METAL HYDRIDE

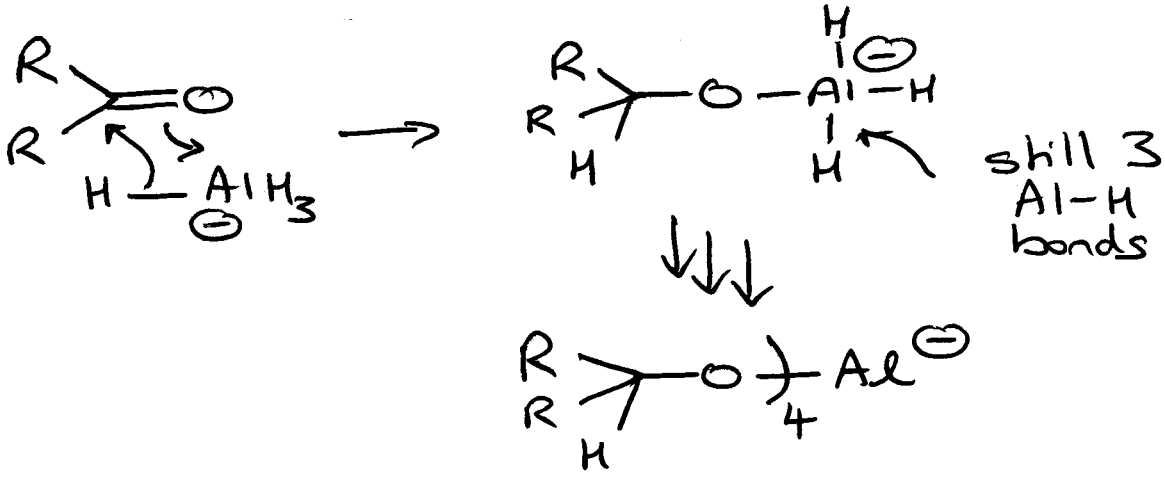


If $R \neq R'$, product is a racemic mixture

$LiAlH_4$ = "H^-"

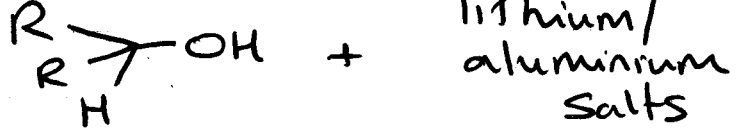


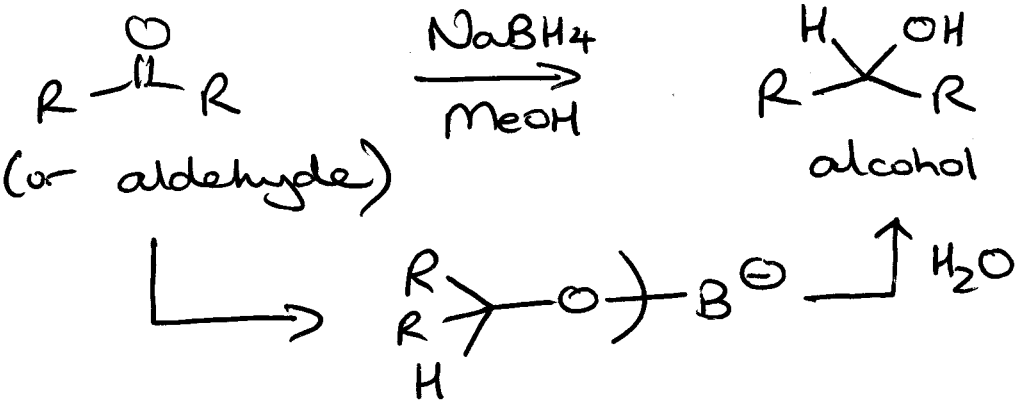
Not actually H^-, e.g. NaH is not REDUCING



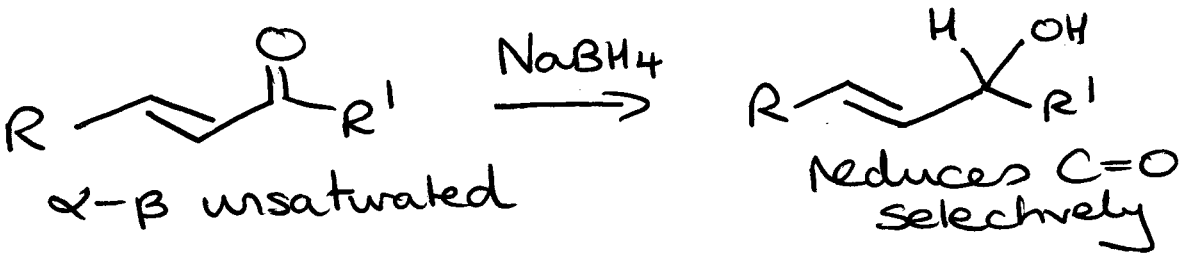
TETRAALKYL ALUMINATE

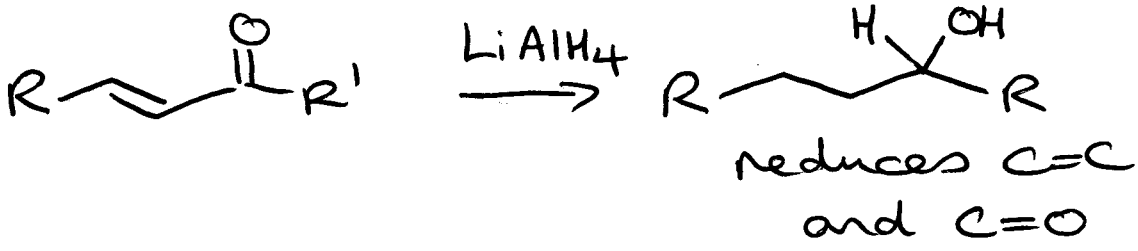
$\downarrow H_2O$



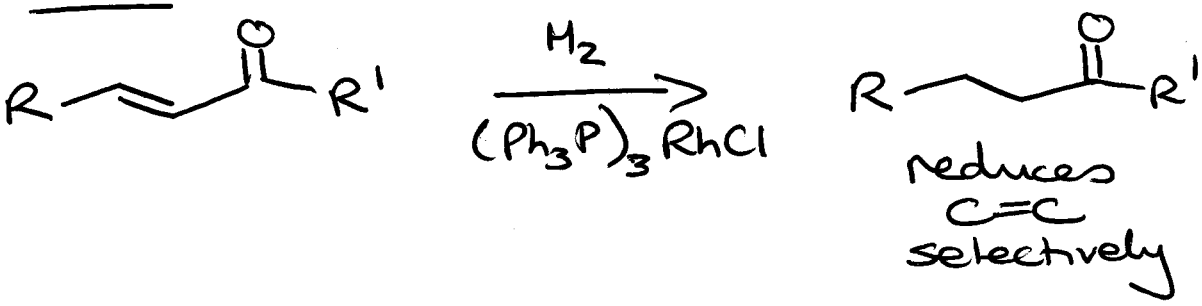


Write mechanism for homework.

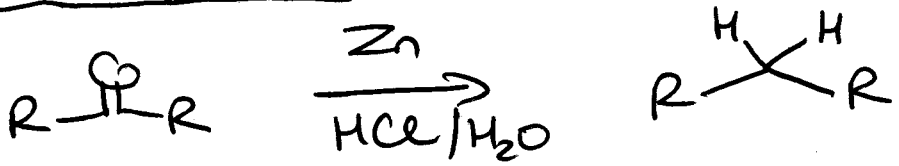


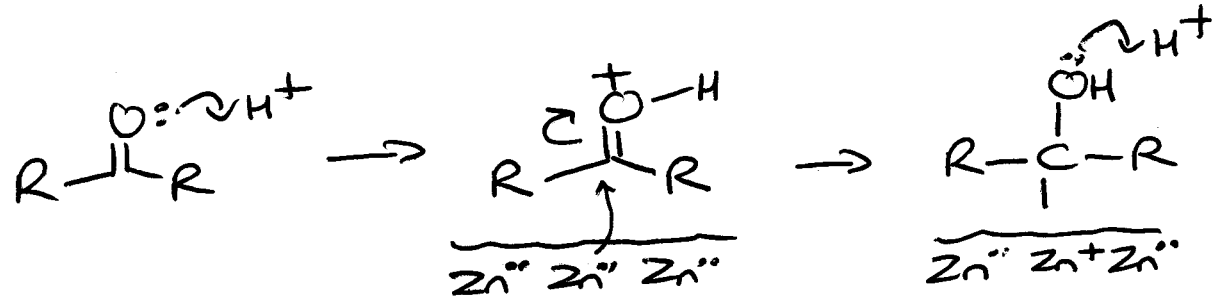


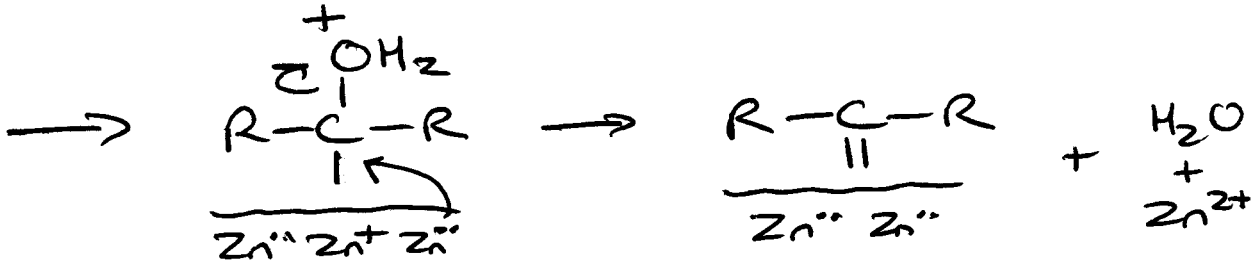
NOTE:



CLEMMENSEN





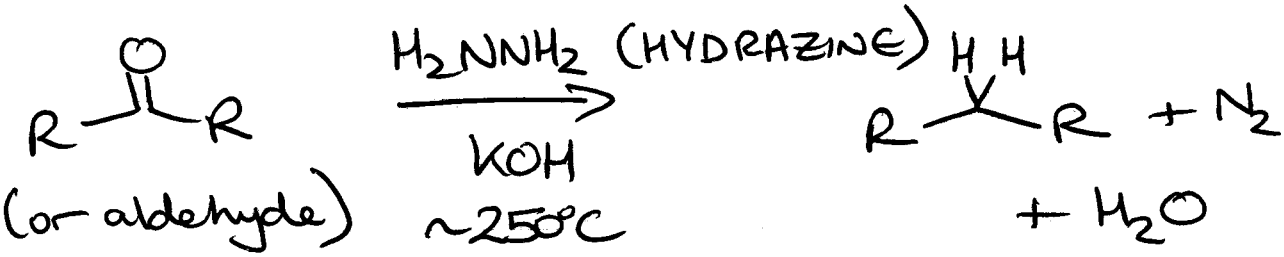


C=O REDUCED, Zn OXIDIZED

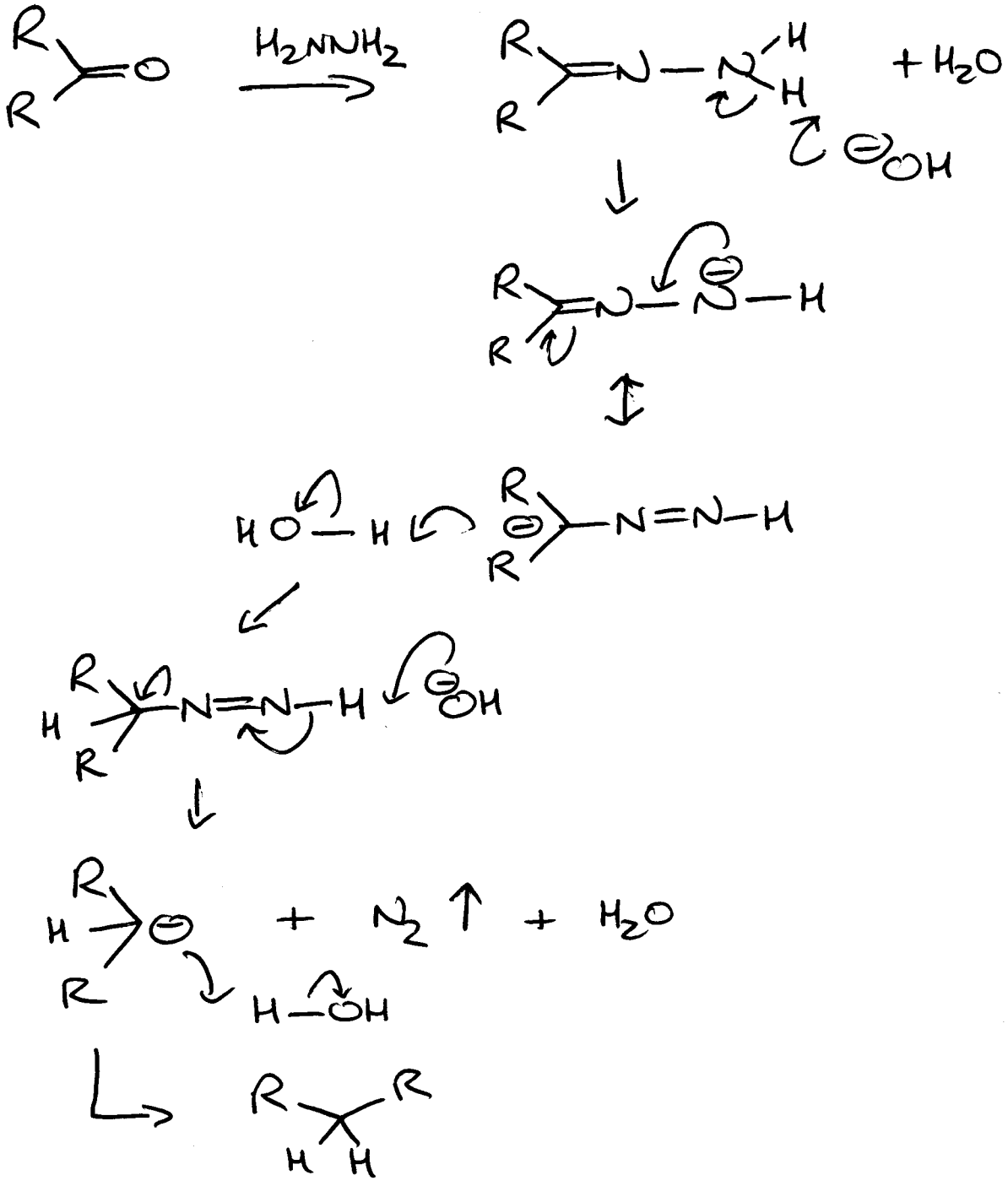
Cannot be used for ACID SENSITIVE CMPDS

WOLFF - KISHNER (complementary)

BASIC



(or aldehyde)



(milder conditions DMSO - solvent)

NH_2NH_2

$+O^-K^+$

OXIDATION

$$RCH_2OH \xrightarrow{ox} RCHO \xrightarrow{ox} RCO_2H$$

$$R\text{-}CHO \xrightarrow{H_2CrO_4} RCO_2H$$

$$R\text{-}CHO \xrightarrow[\text{or } H_2O_2]{O_2} RCO_2H$$

$$R\text{-}CHO \xrightarrow{Ag(I)} RCO_2H + Ag$$

EXPENSIVE

Ag ↑ METAL

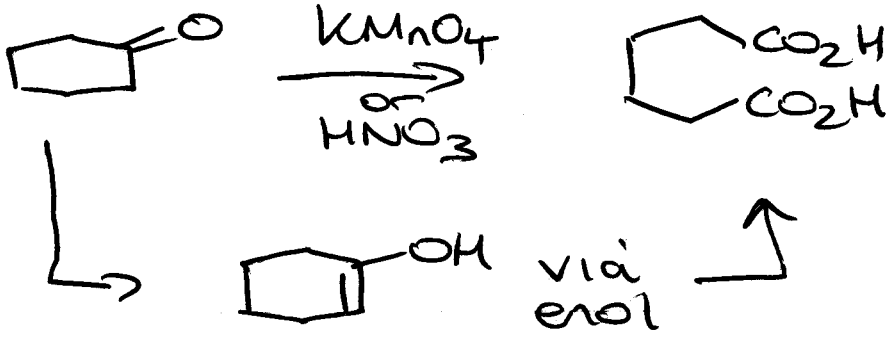
Ag_2O or $Ag(NH_3)_2^+ NO_3^-$

TOLLENS

OFTEN DONE FOR Ag as product

⇒ SILVERING GLASSWARE (MIRRORS)

KETONES (harsh conditions)



LEC 15

1. QUIZ MONDAY
2. REVIEW SESSION
   - HALLOWEEN HANGMAN

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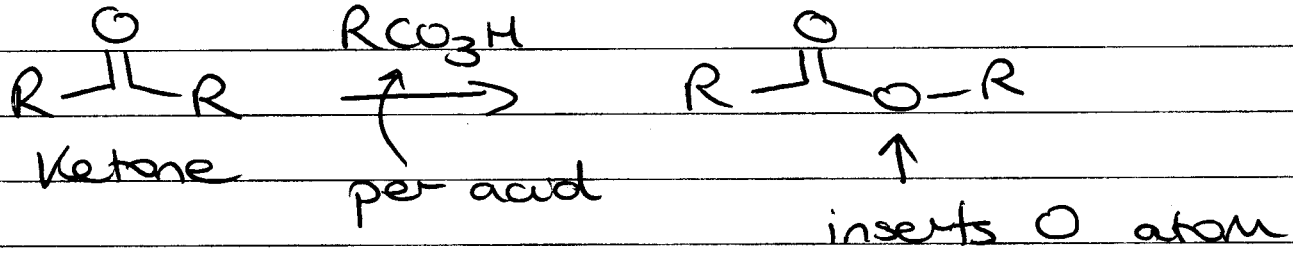
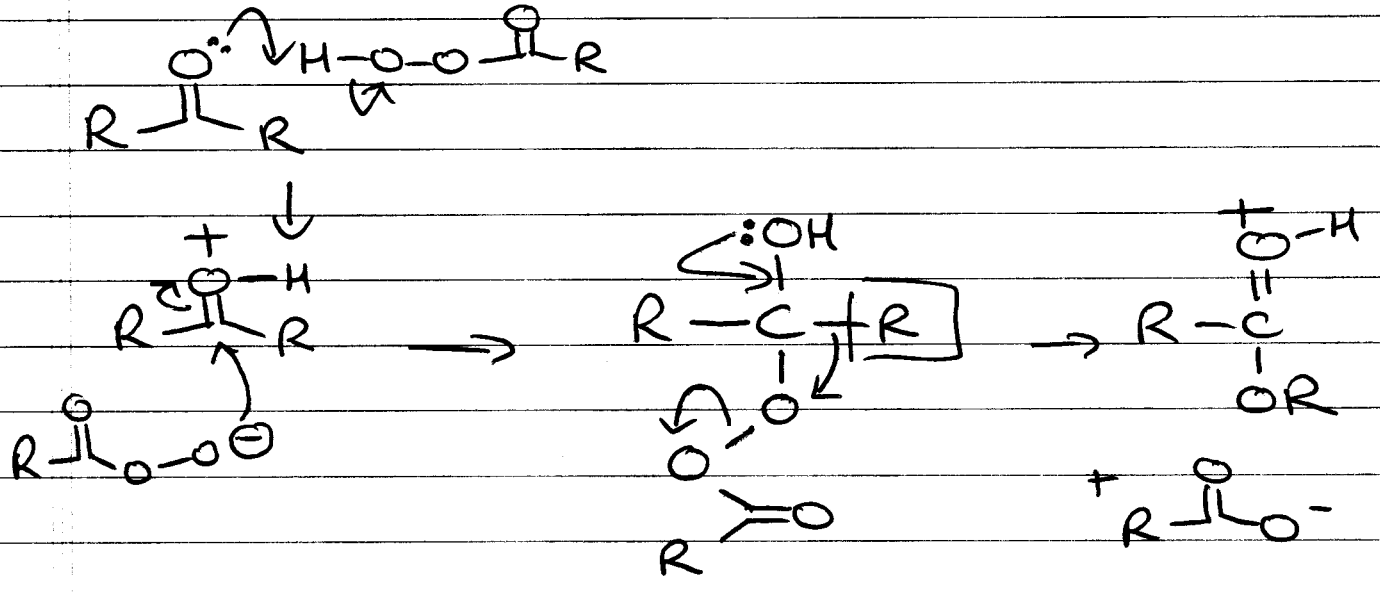
1. OXIDATION
2. REVIEW

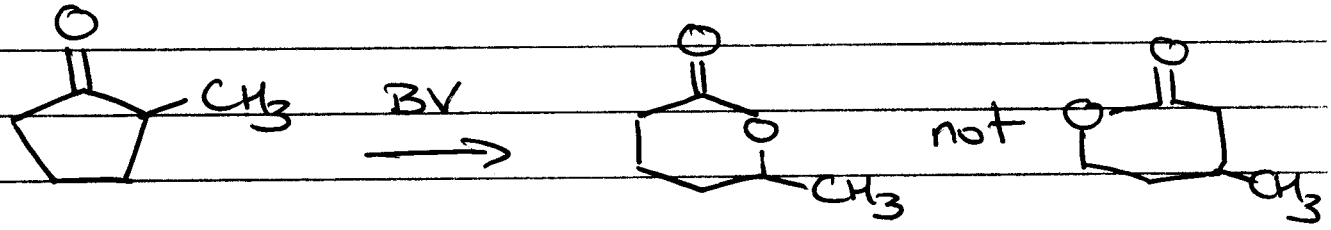
BAEYER–VILLIGER OXIDATION





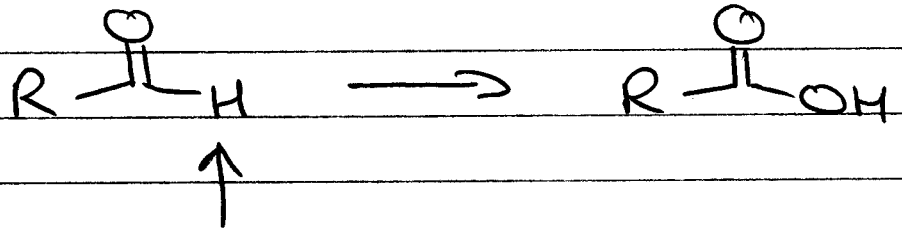
MIGRATION RATES

$3^\circ > 2^\circ \sim Ar > 1^\circ C > CH_3$



C^+ character in TS

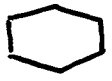
FOR ALDEHYDES



H MIGRATES

Lec (16)

(1) Quiz
(2) Hmk
Ch 16 SYNTHESIS 16.56 – 16.68
Ch 17: 17.2, 17.3, 17.15, 17.16, 17.18–31
(3) CNSI Seminar : KANG-WANG
NANOELECTRONICS – TODAY & BEYOND
(4) SYNTHESIS OF THE WEEK

 from H–C≡C–H and CH_3Br

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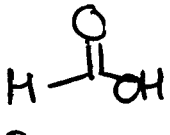
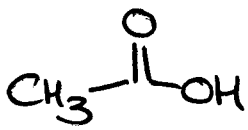
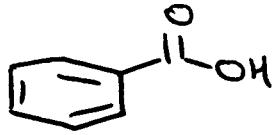
CARBOXYLIC ACIDS

(1) STRUCTURE
(2) PHYSICAL PROPERTIES
(3) PREPARATION
(4) REACTIONS

(1) $R-CO_2H$ / $R-COOH$ / 


formic acid

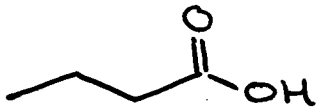

acetic acid (AcOH)


benzoic acid

$CH_3\overset{O}{\overset{\|}{C}}$ = acetyl group

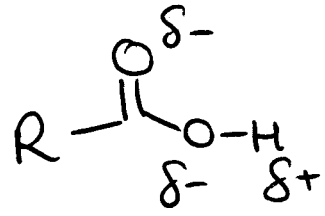
'COMEDY CHAPTER'

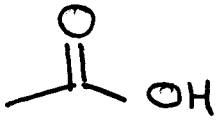
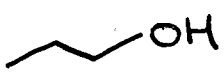
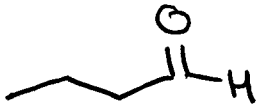
1670 formic acid obtained from "destructive distillation of ants"

 BUTANOIC ACID (C_4)

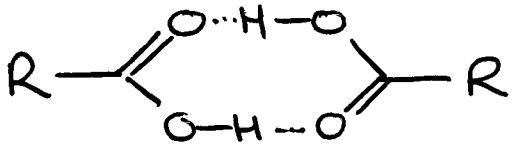
"Butanoic acid is found in stale perspiration and is a major component of "locker room odor". Pentanoic acid smells even worse, and goats, which secrete C_6, C_8, C_{10} acids are not famous for their pleasant odors."

② OTHER PHYSICAL PROPERTIES

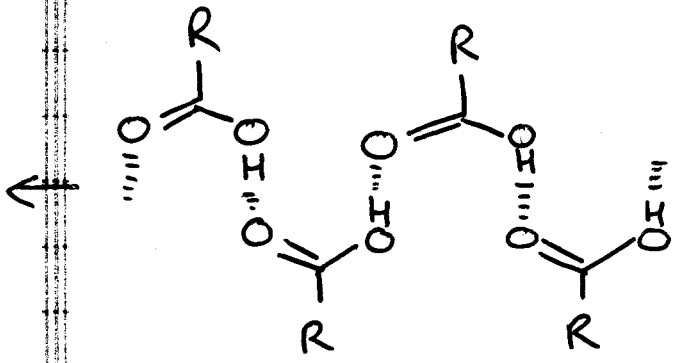
 V. polar

BPs  118°C  97°C  48°C

HYDROGEN BONDING



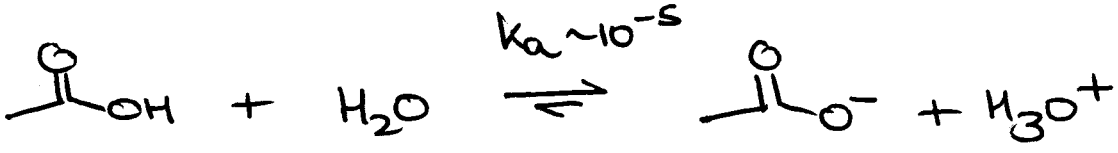
H-Bonded dimers



tapes

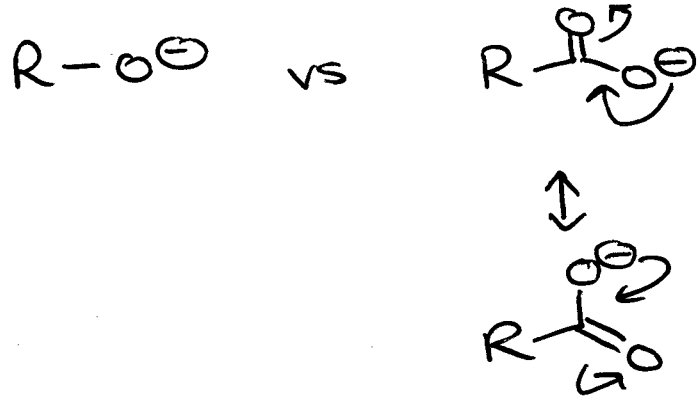
ACIDITY (CARBOXYLIC ACIDS)

Weak acids



$pK_a \sim 5$

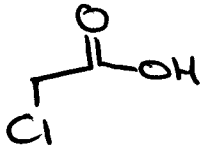
compare to alcohols ROH pK_a 16 ~ 18

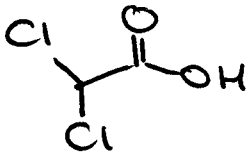


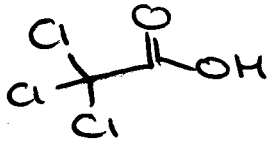
RESONANCE STABILIZED

Consider INDUCTIVE effects $\delta^- \leftarrow \delta^+$ $Cl-C$

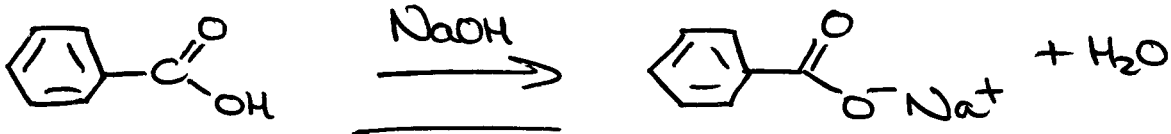

4.76


2.86


1.48


0.70

REACTION w/ BASES



slightly water soluble

USEFUL FOR SEPARATIONS

sodium benzoate (60g / 100 mL)

RCO_2H also react w/ amines & ammonia

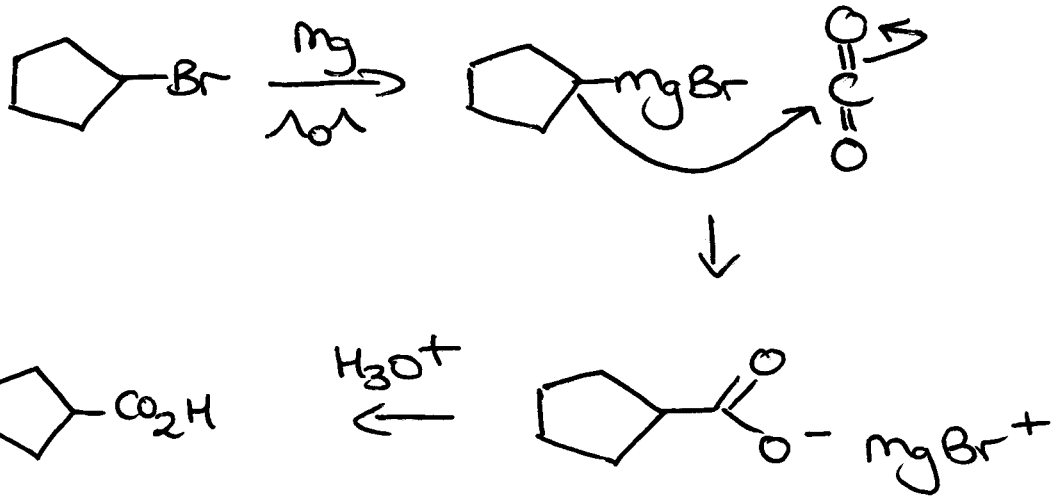
ammonium benzoate

(3) PREPARATION

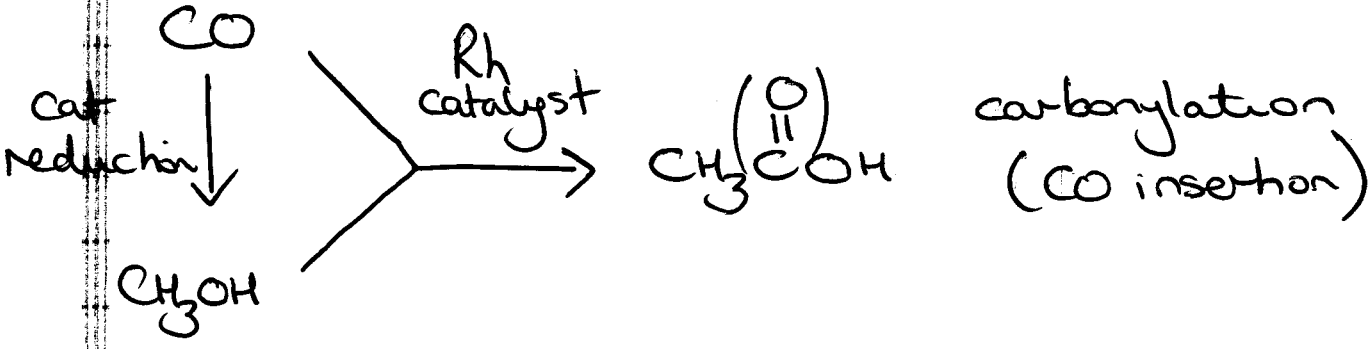
Oxidation of 1° alcohols / aldehydes

$RCH_2OH \longrightarrow RCHO \longrightarrow RCO_2H$

From Grignard rxns

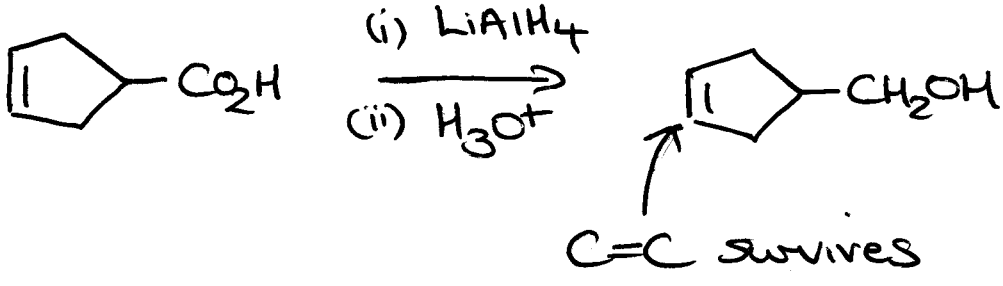


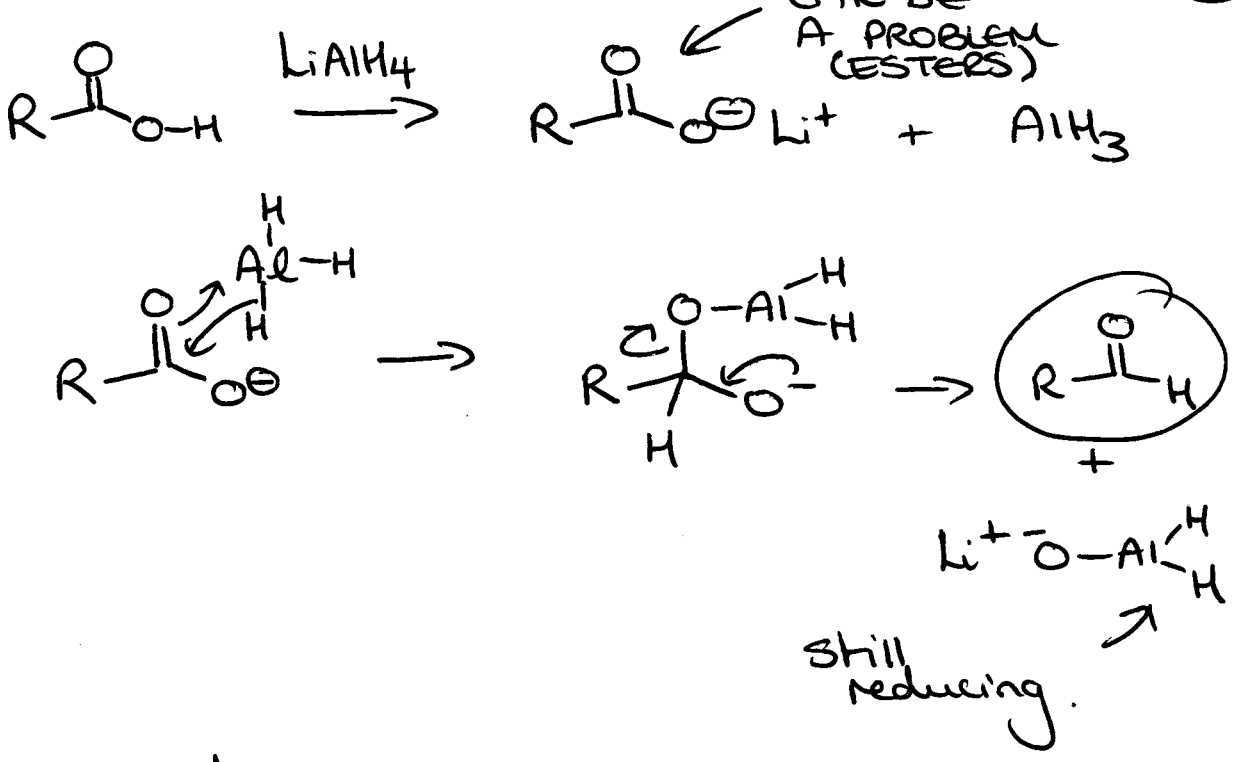
INDUSTRIAL PREP OF ACETIC ACID

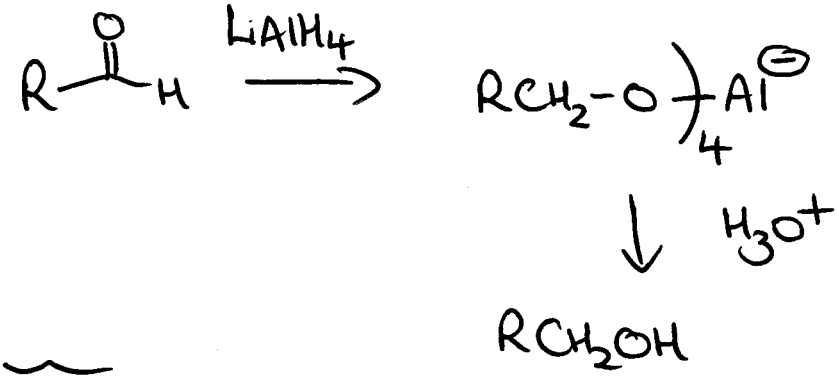


④ REACTIONS

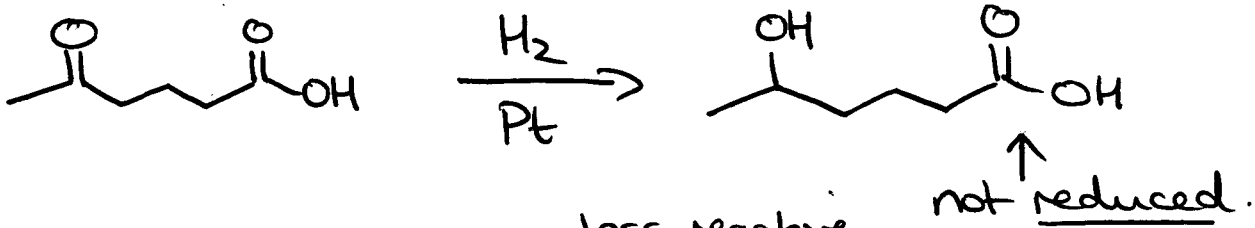
(i) REDUCTION of RCO_2H



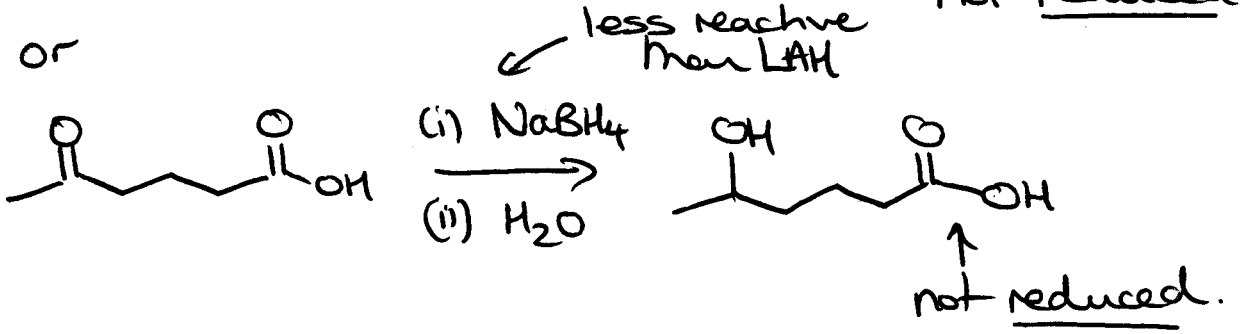




SELECTIVE REDUCTION



or



Lec (17)

(1) Quiz
LOW 6/36 HIGH 38/36 AV 27/36 (74%)
TOO HIGH

Q20 A (120) B (90) C→E <20 each

(2) HMK.
17.4 – 17.6, 17.32 – 17.36, 17.38 – 17.41, 17.43

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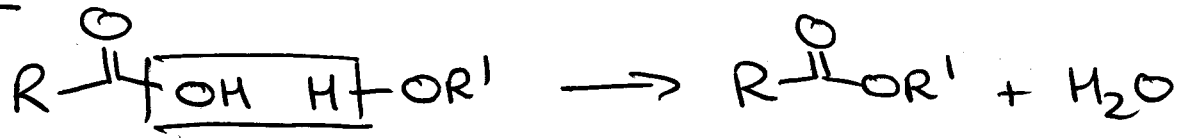
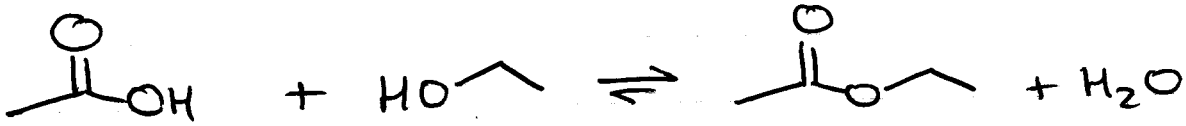
(1) RCO_2H REDUCTION
(2) ESTERIFICATION
(3) ACID CHLORIDES
(4) DECARBOXYLATION
(5) Ch18 CARBOXYLIC ACID DERIVATIVES

(2) ESTERIFICATION

ACID → REVERSIBLE → FISCHER

LASSO





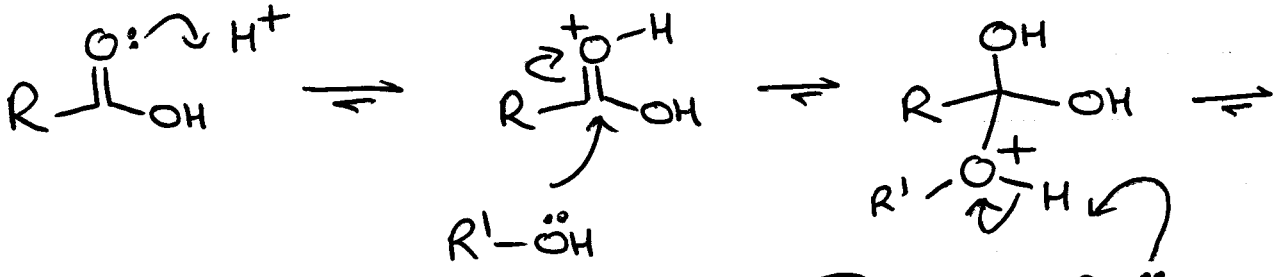
acetic acid — ethanol — ethyl acetate

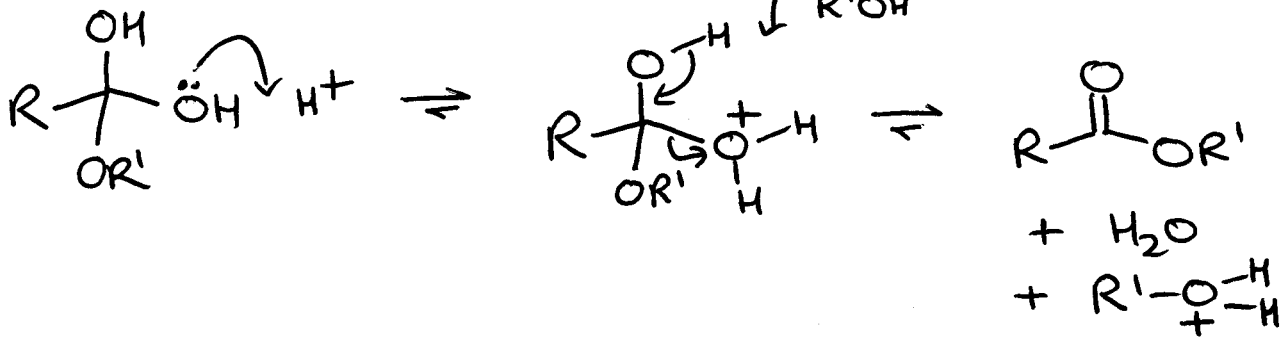
H^+ usually H_2SO_4 or HCl(g)

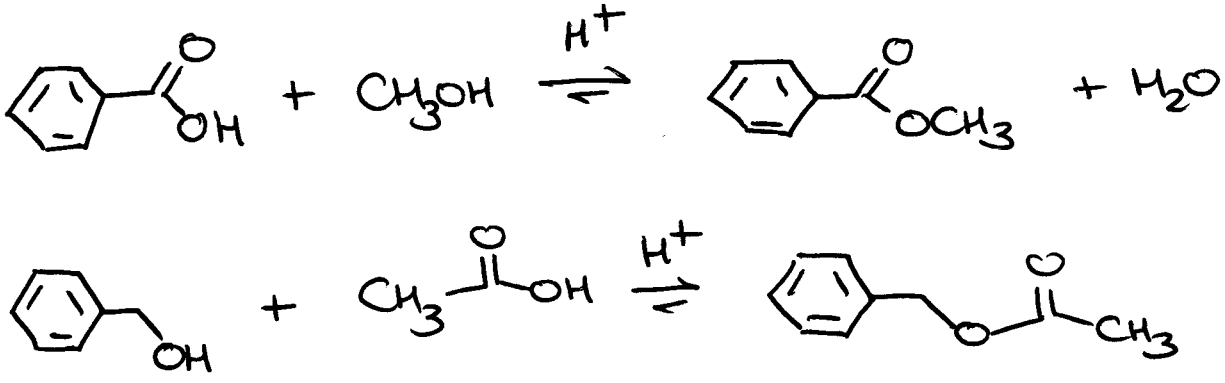
EQUILIBRIUM shifted by:

(i) removing H_2O
(ii) use large xs R'-OH

MECHANISM
(v. important – lots of other similar ones)

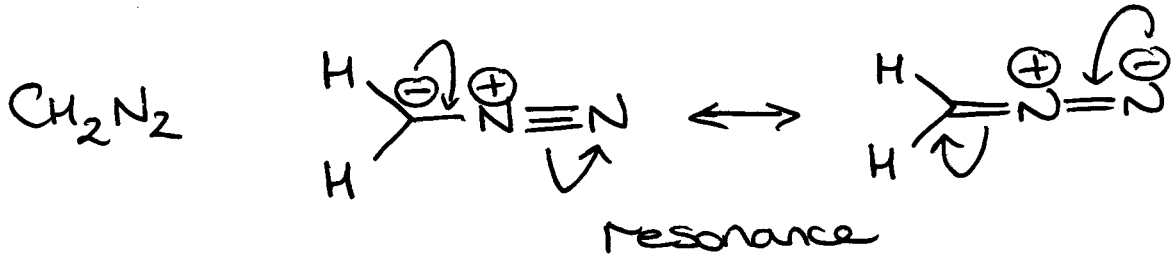


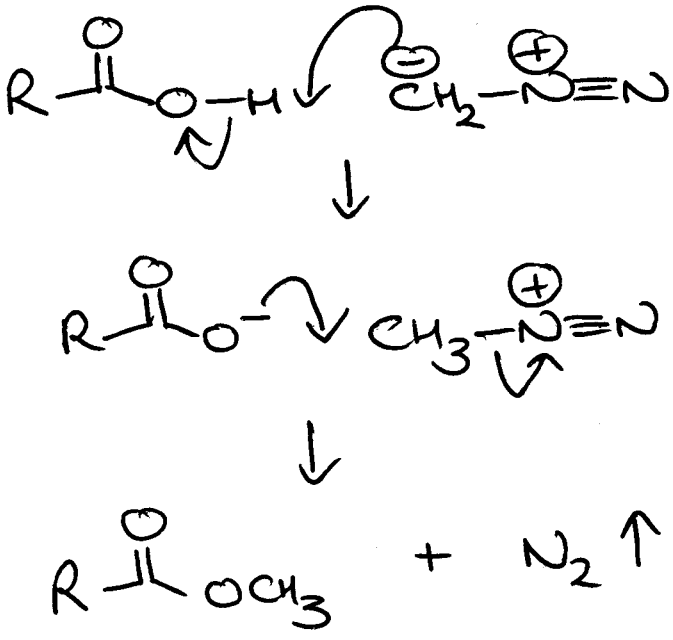




DIAZOMETHANE (METHYL ESTERS)

$$RCO_2H \xrightarrow[\text{ether}]{CH_2N_2} RCO_2Me + N_2\uparrow$$

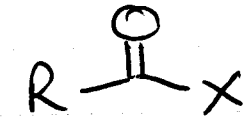




Very mild conditions

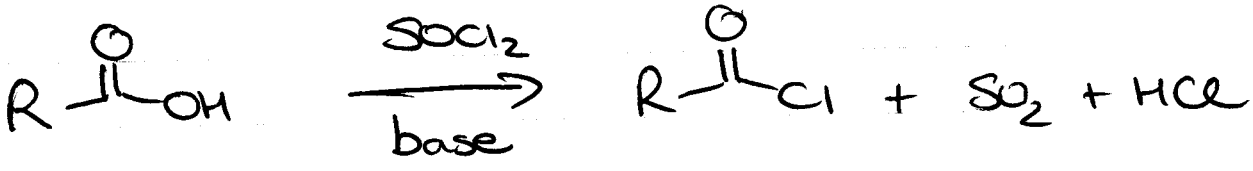
BUT v. dangerous, CH_2N_2 explosive.

③ Conversion to Acid Chlorides

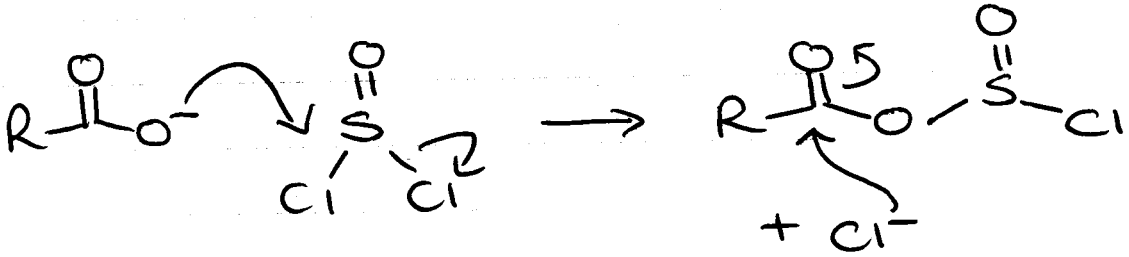


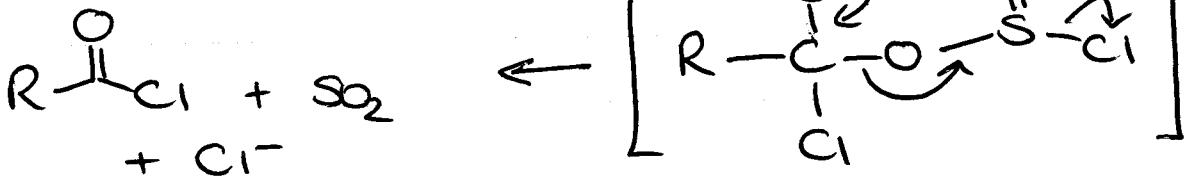
$X = Cl$ (mostly)

acid halides



(R-OH → R-Cl)





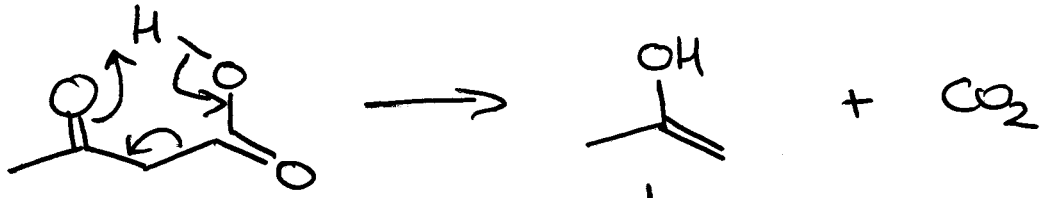
Tetrahedral Intermediate

④ Decarboxylation

Most RCO_2H resistant to this even melting or boiling before it happens

Except:

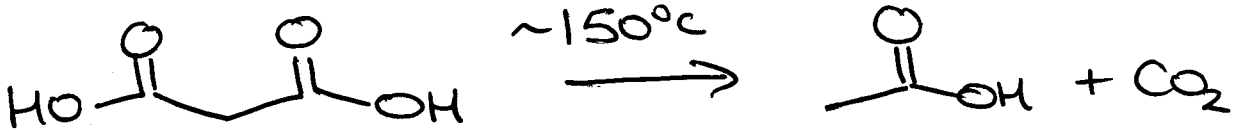
① β-Ketoacids



6-membered cyclic TS

Ketdenol

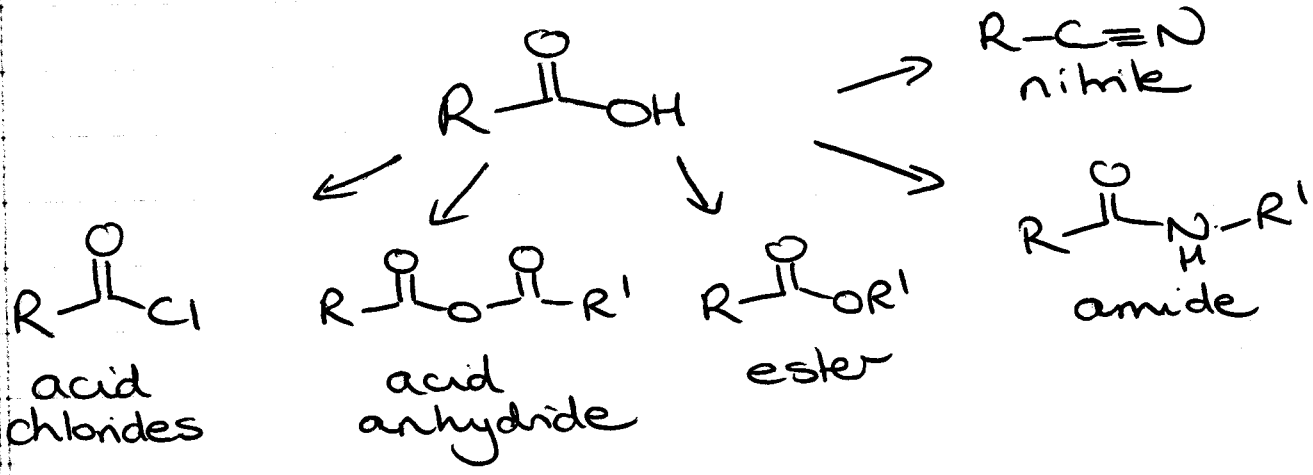
② Malonic acid



need C=O β to carboxyl group

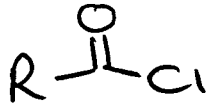
Ch18

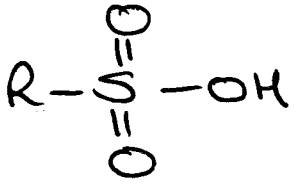
Derivatives of Carboxylic Acids

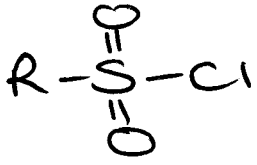


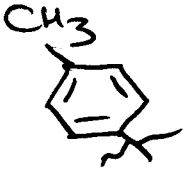
Acid halides (acyl halides)

$(R-C(=O)-)$

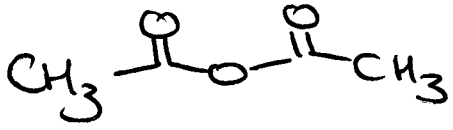


Sulfonic acids 

Sulfonyl chlorides 

If R =  then TsCl

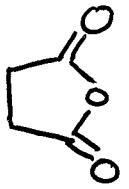
ANHYDRIDES



acetic anhydride

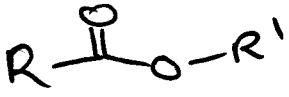
mixed anhydride

cyclic

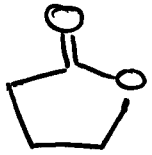


succinic anhydride

ESTERS

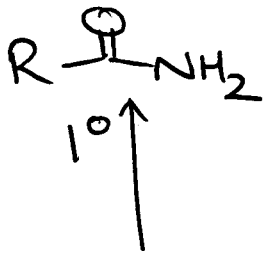


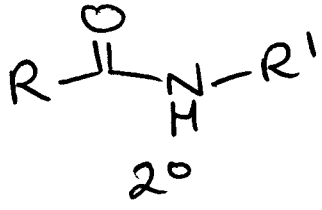
cyclic esters = LACTONES

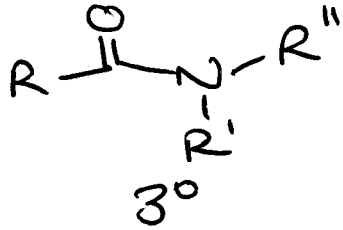


4 BUTANOLACTONE

AMIDES

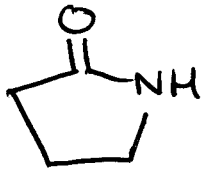






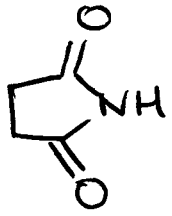
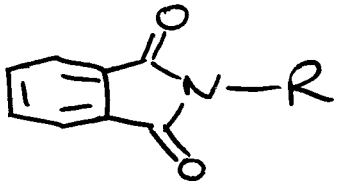
amide bond ~ peptide bond

cyclic amides = LACTAMS

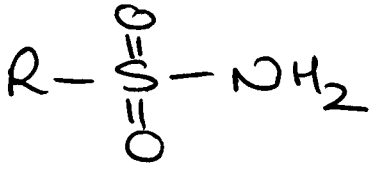


4-BUTANOLACTAM

Imides, two acyl groups on N (usually cyclic)

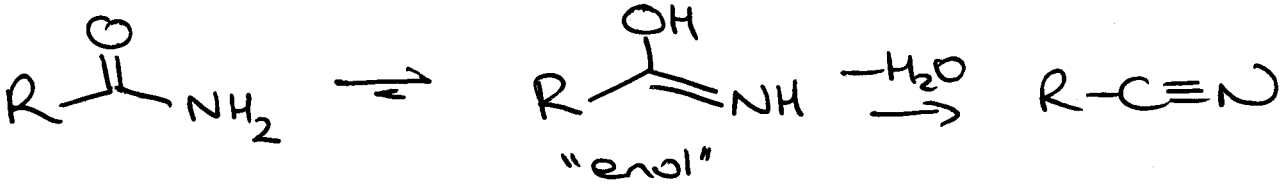
 or 

Sulfonamides



NITRILES

$R-C\equiv N$ CH_3CN acetonitrile (solvent)



"enol"

NEXT: rxns of derivatives.

Lec (18)

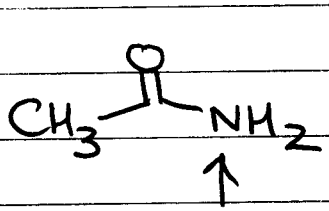
(1) NEXT TUESDAY — HOLIDAY
(2) HMK 18.2–6 18.15

---

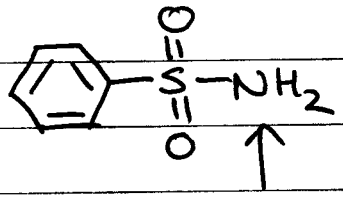
(1) RCO_2H DERIVATIVES INTRO
(2) ACIDITY
(3) GENERAL REACTIVITY
(4) HYDROLYSIS (RXN w/ H_2O)
(5) RXN w/ ALCOHOLS

---

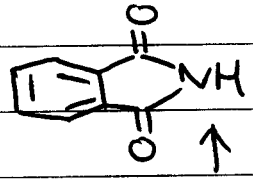
(2) ACIDITY



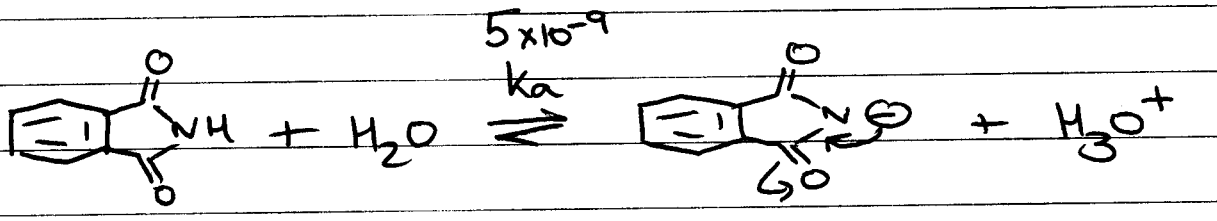
pka 15–17
(amine)

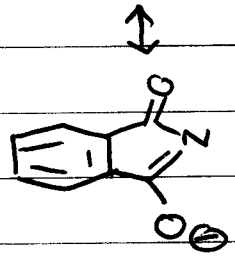


pka ~10
(sulfonamide)



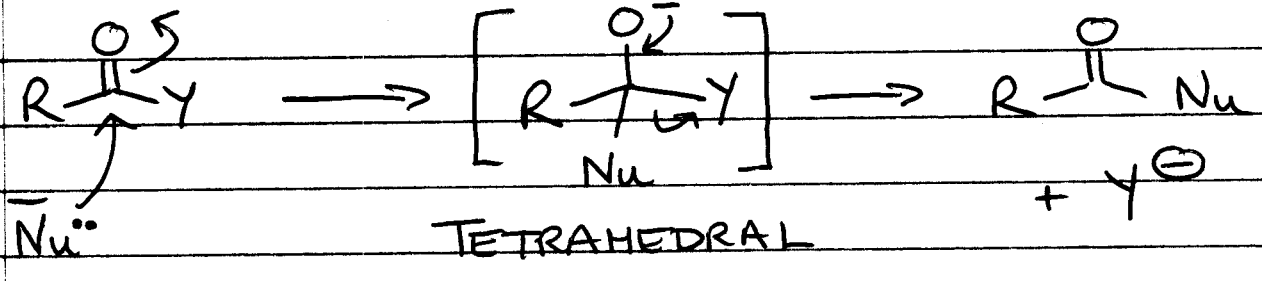
pka ~8
(imide)





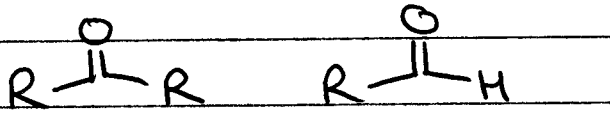
↕ RESONANCE STABILIZED

(3) GENERAL RXN



NUCLEOPHILIC ACYL SUBSTITUTION

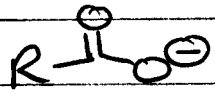
Compare to:



(R^-) (R^- or H^-)

NOT GOOD LEAVING GROUP

NO SUBSTITUTION, JUST ADDITION

	AMIDES	ESTERS	ANHYDRIDES	HALIDES
LG (Y)	$R_2N^\ominus$	$RO^\ominus$		$X^\ominus$

ACID HALIDES / ANHYDRIDES

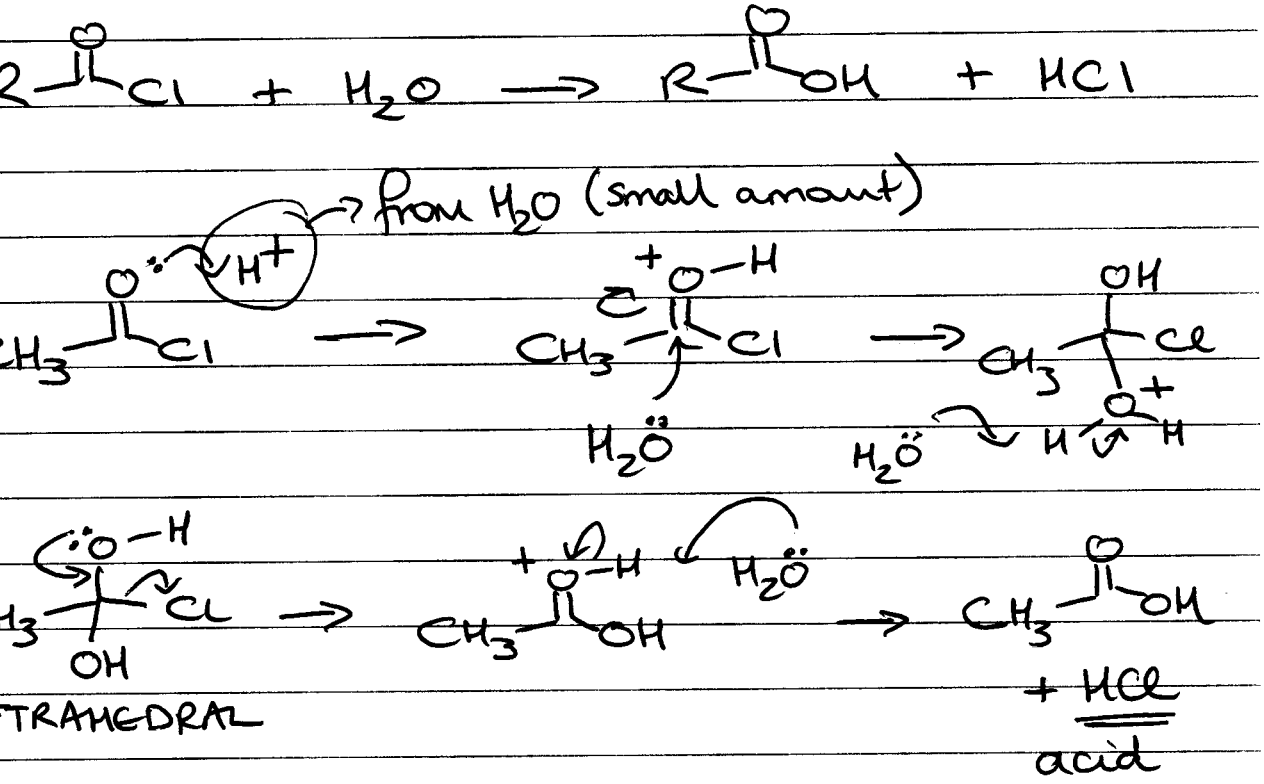
V. reactive → not found in Nature

ESTERS / AMIDES

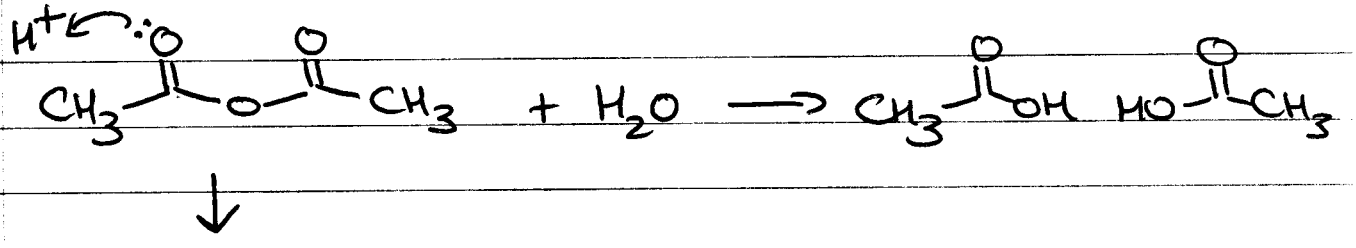
ubiquitous in Nature

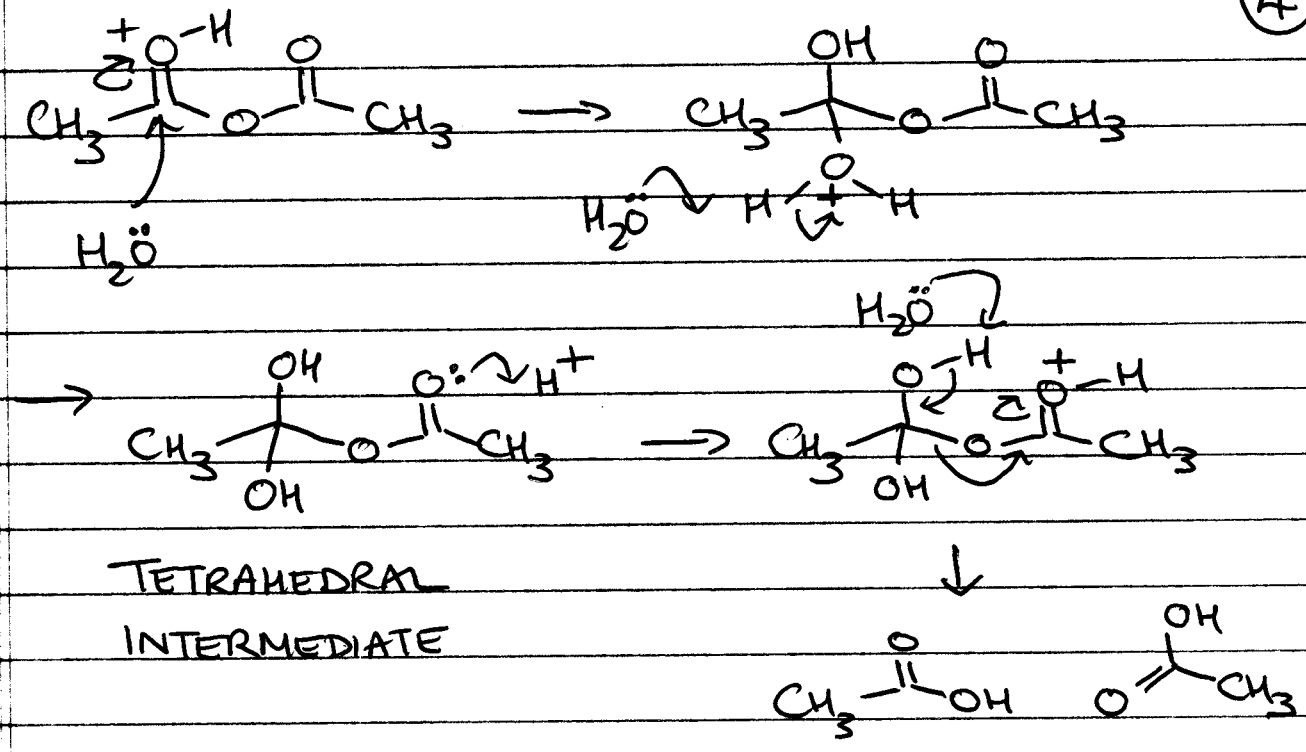
(4) HYDROLYSIS

(i) ACID CHLORIDES



(ii) ACID ANHYDRIDES





TETRAHEDRAL INTERMEDIATE

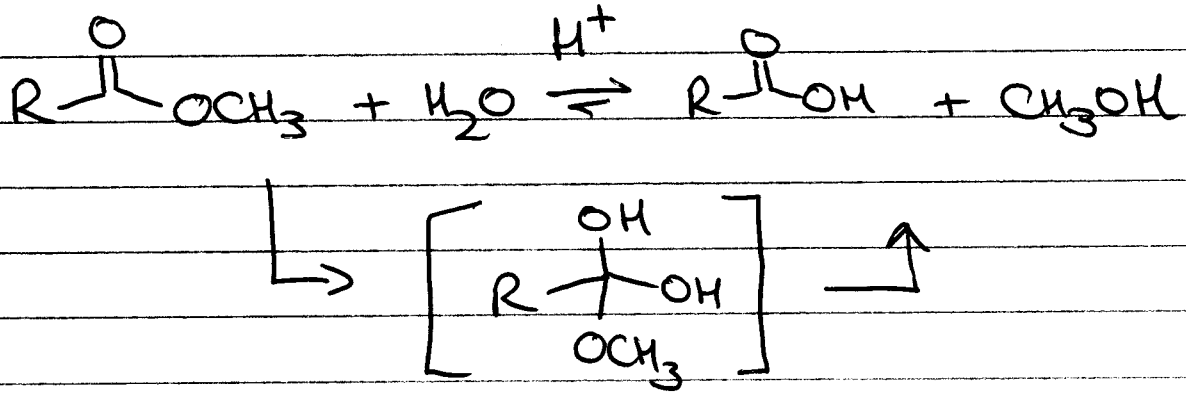
(iii) ESTERS

HYDROLYZED vSLOWLY IN BOILING H_2O

↳ FAST IN AQUEOUS ACID/BASE

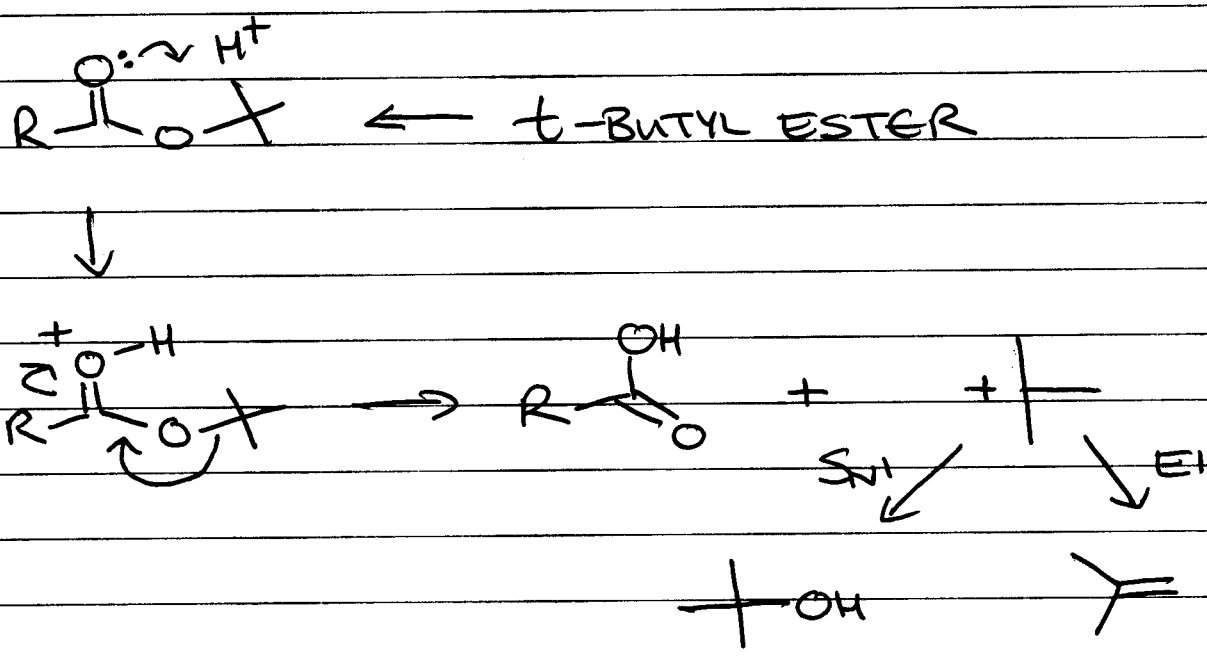
↑

REVERSE OF FISCHER ESTERIFICATION

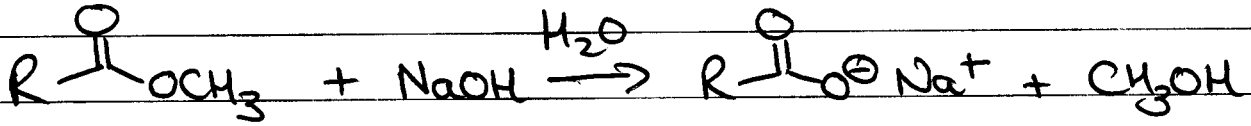


TETRAHEDRAL

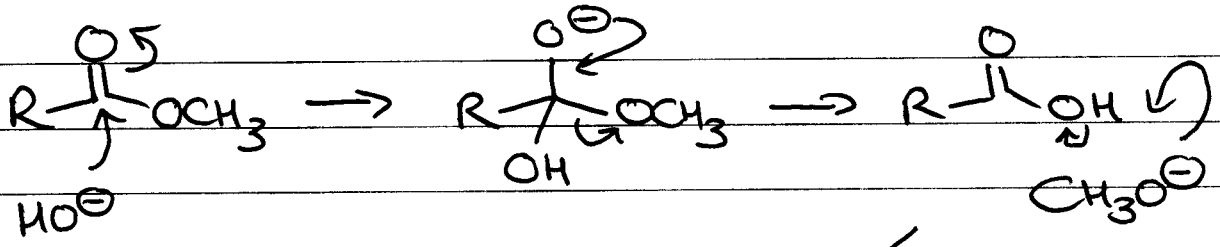
IF POSSIBLE TO FORM STABLE C^+ NEXT TO O

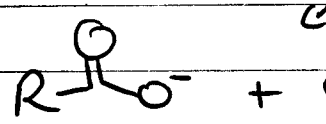


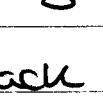
BASIC HYDROLYSIS – SAPONIFICATION

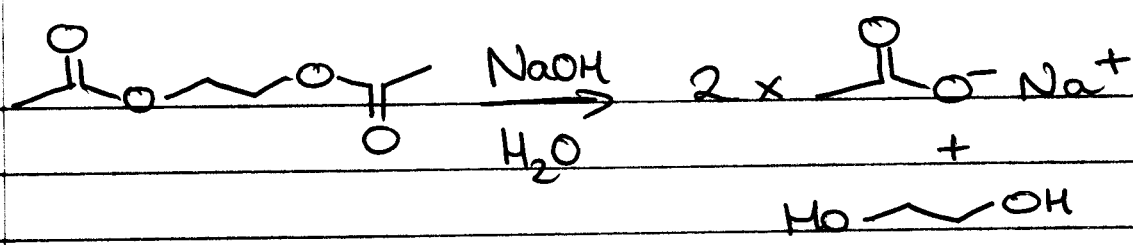


unlike acid,
stoichiometric not catalytic



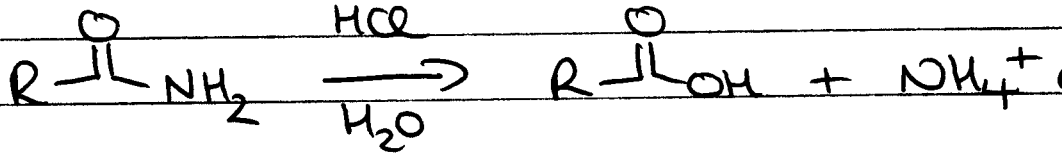


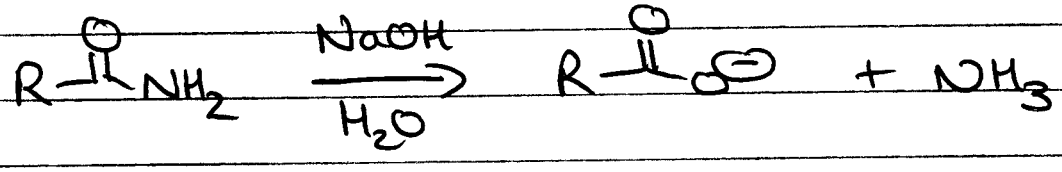
NOT REVERSIBLE, ROH doesn't attack 



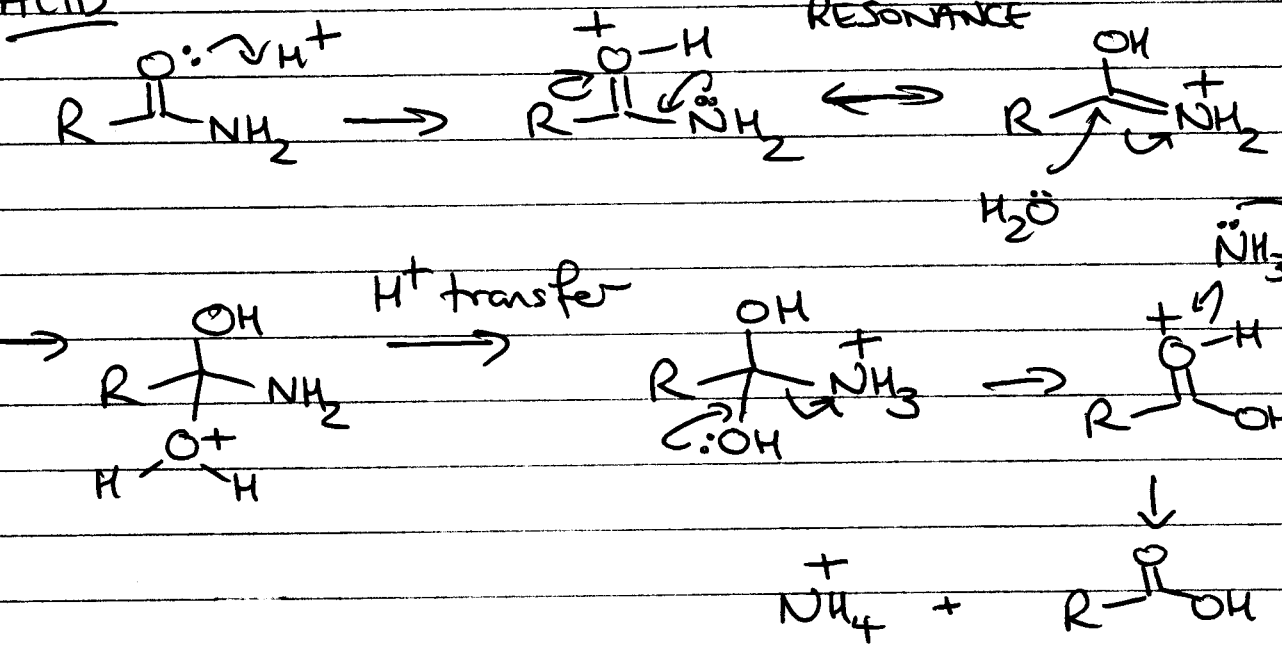
(iv) AMIDES — HARSH CONDITIONS

ACID or BASE — STOICHIOMETRIC

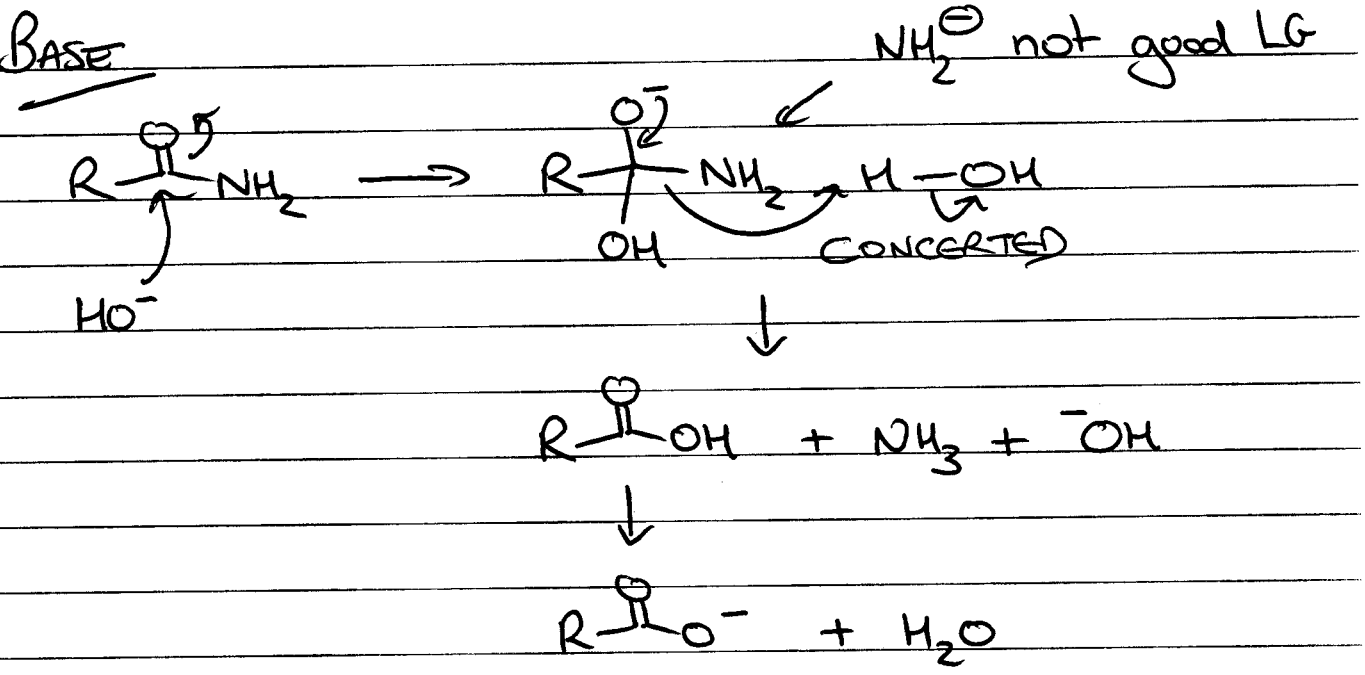


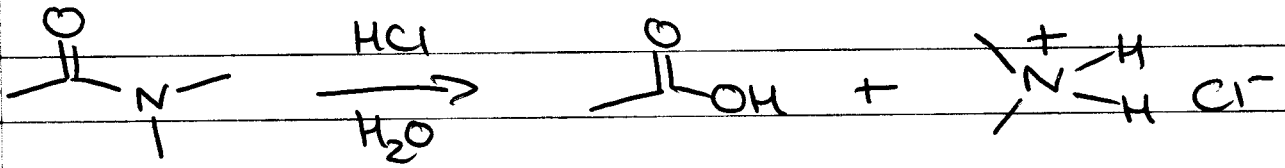


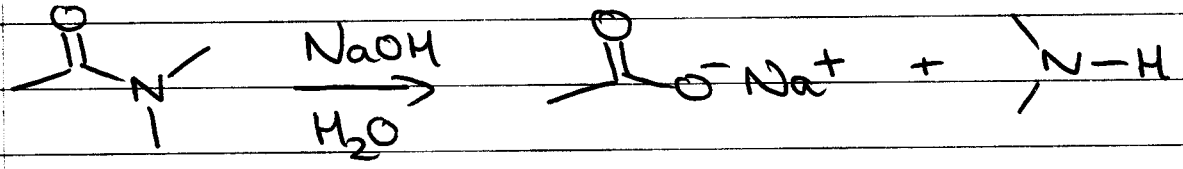
ACID



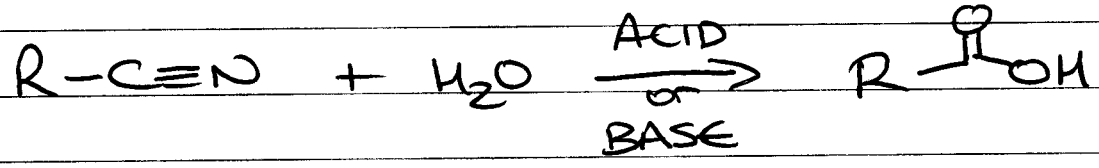
BASE





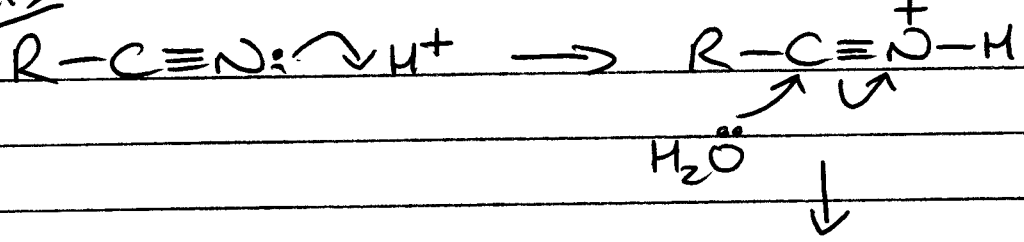


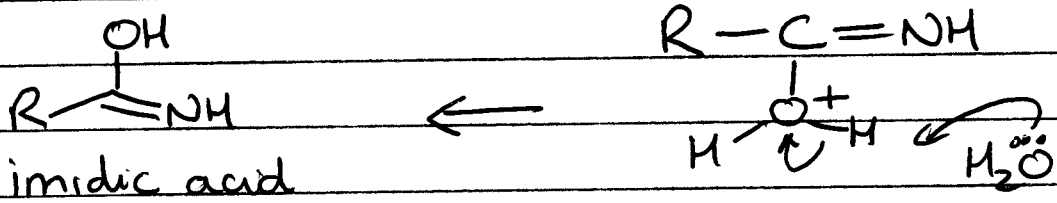
(V) HYDROLYSIS OF NITRILES (R-CN)



CONDITIONS for R-CN hydrolysis harsher than for AMIDES

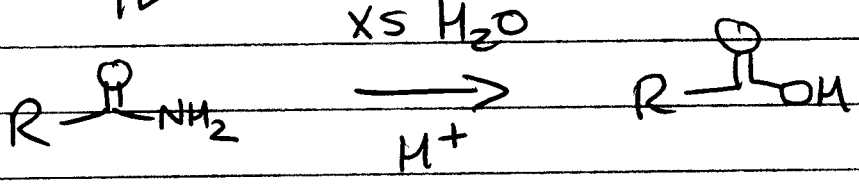
ACID





imidic acid

"enol"

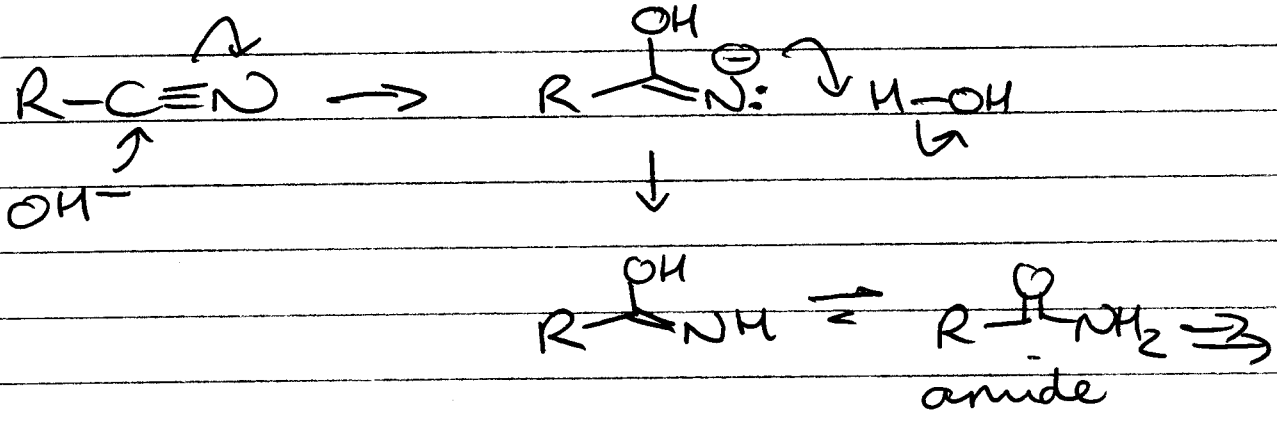


amide

Can ONLY stop at AMIDE using H_2SO_4 (cat) and STOICHIOMETRIC H_2O

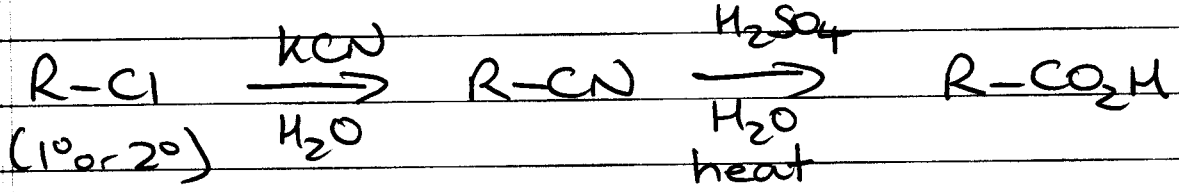
NOT GOOD METHOD of MAKING AMIDES

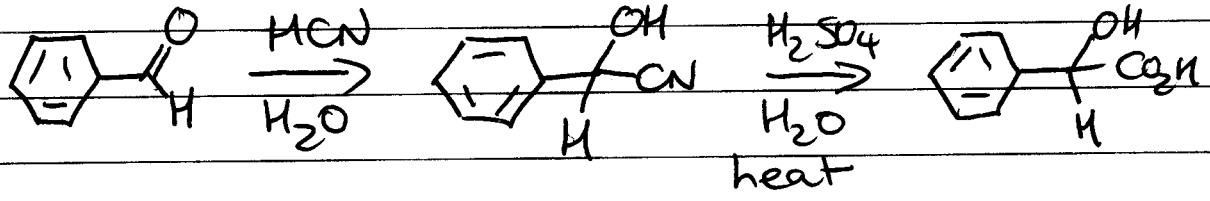
BASE



amide

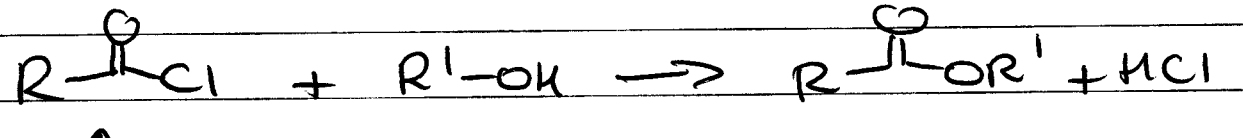
USEFUL FOR SYNTHESIS





(5) RXNS w/ ALCOHOLS

(i) ACID CHLORIDES

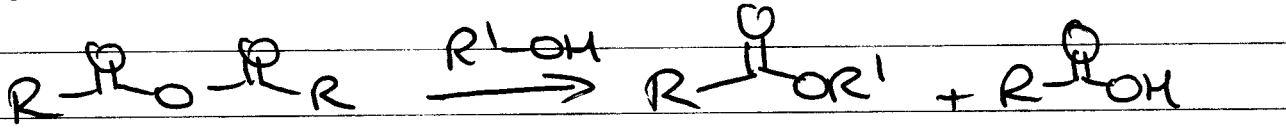


↑ so reactive, not catalyst req.

If ester or alcohol is acid sensitive, a 3° amine (Et_3N / py) is added to neutralize acid.

MECH like H-OH, but R-OH

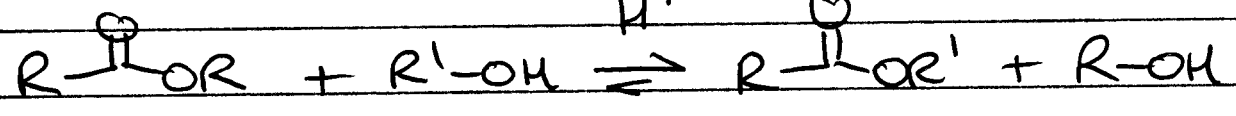
(ii) ACID ANHYDRIDES



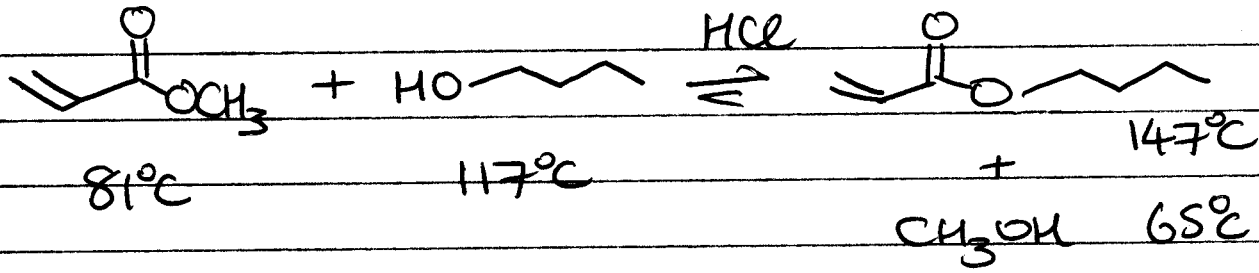
Catalyzed by H^+ / 3° AMINES

Again MECH like H–OH, but R–OH

(iii) ESTERS



TRANSESTERIFICATION



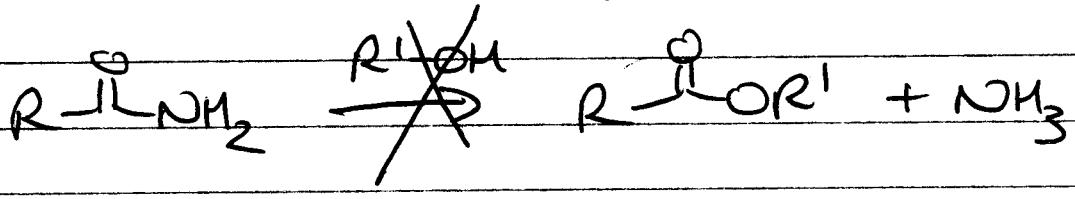
EQUILIBRIUM

Boil off CH_3OH ⟶

⟵ LARGE XS OF CH_3OH

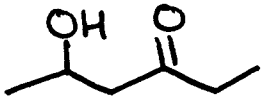
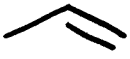
(iv) AMIDES

DO NOT REACT w/ R'–OH



LEC (19)

(1) HMK 18.7 – 18.11
(2) MIDTERM MONDAY NOV 17th
A – K ROLFE 1200
L – Z CS 76
(3) SYNTHESIS OF THE WEEK

 from 

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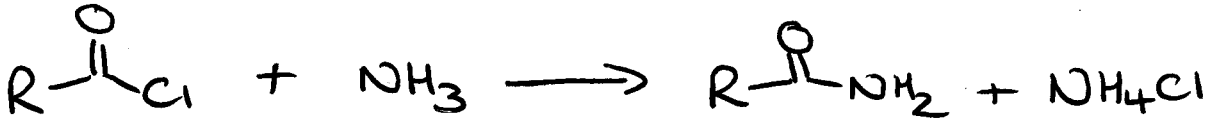
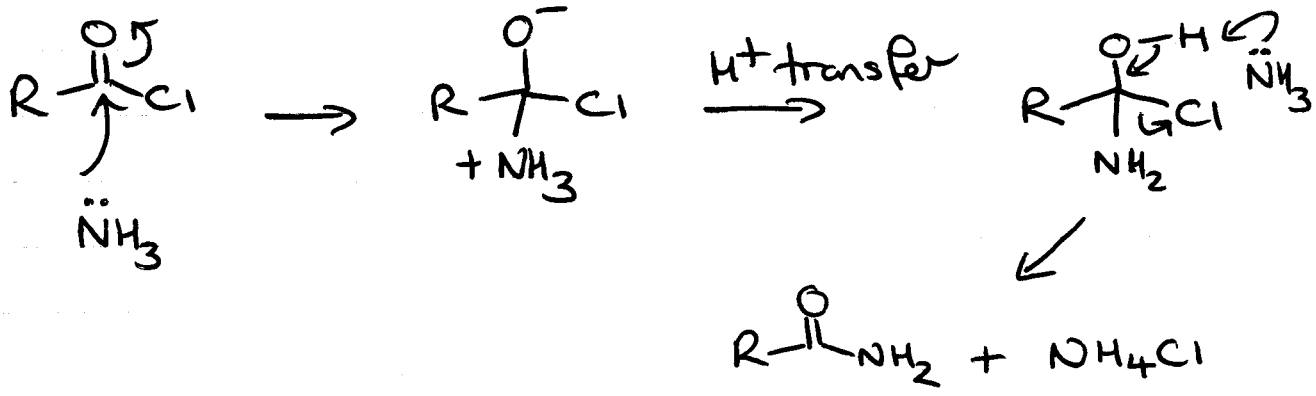
(1) HYDROLYSIS (RXN w/ H_2O)
(2) RXN w/ ALCOHOLS
(3) RXN w/ AMINES or AMMONIA
(4) $RCOCl + RCO_2^{\ominus}$
(5) RXN w/ ORGANOMETALLICS
(6) REDUCTION

---

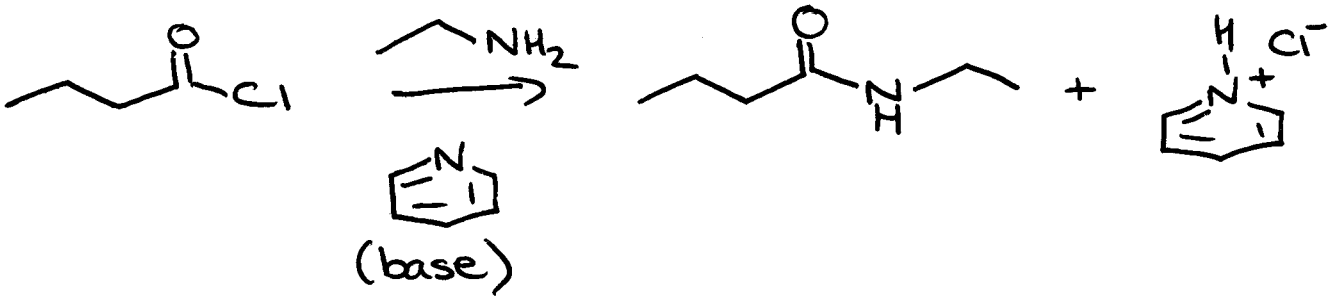
(3) RXN w/ NH_3 or RNH_2

(i) ACID CHLORIDE

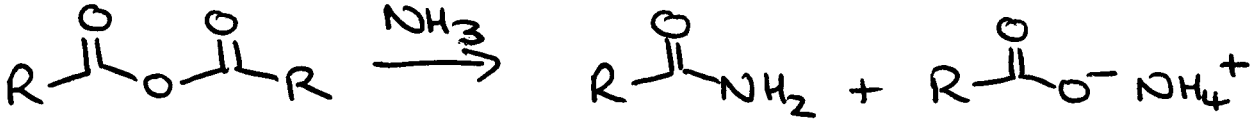


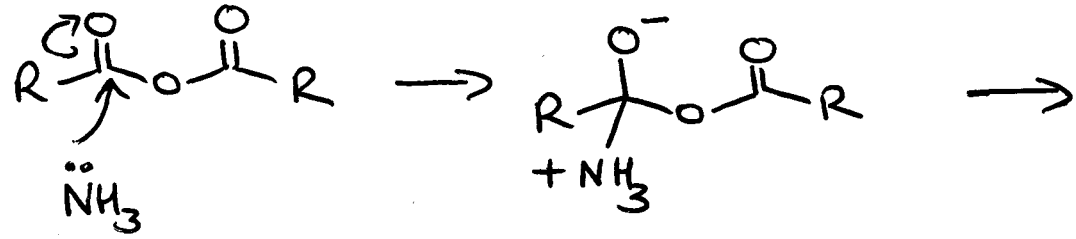


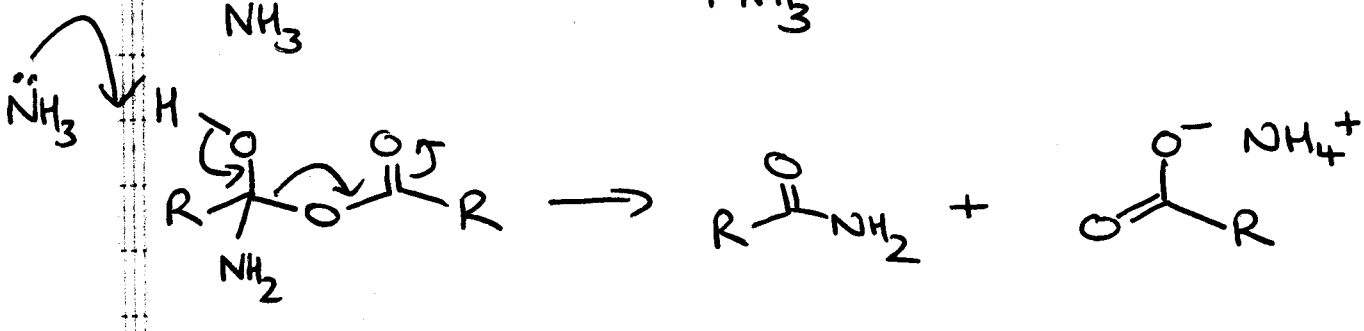
W/ AMINE



(ii) ACID ANHYDRIDES







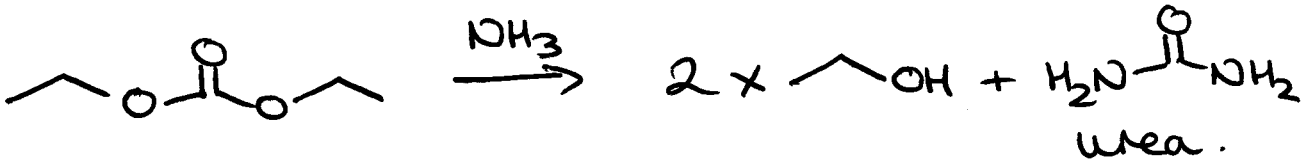
(iii) ESTERS
(not as reactive as RCOCl, anhydrides)

WRITE OUT MECHANISM FOR HNK

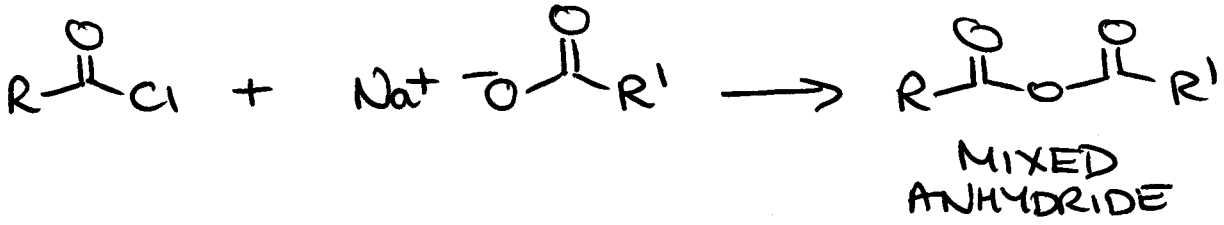
(iv) AMIDES
DO NOT REACT w/ NH_3 or AMINES

NOTE:

CARBONATES

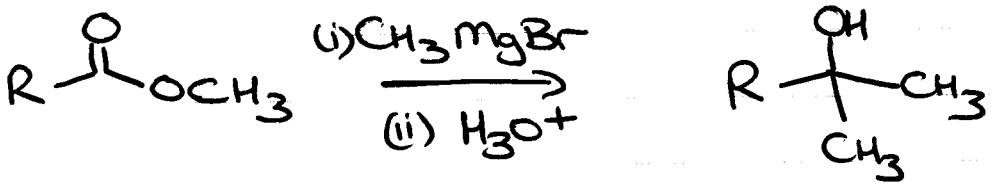


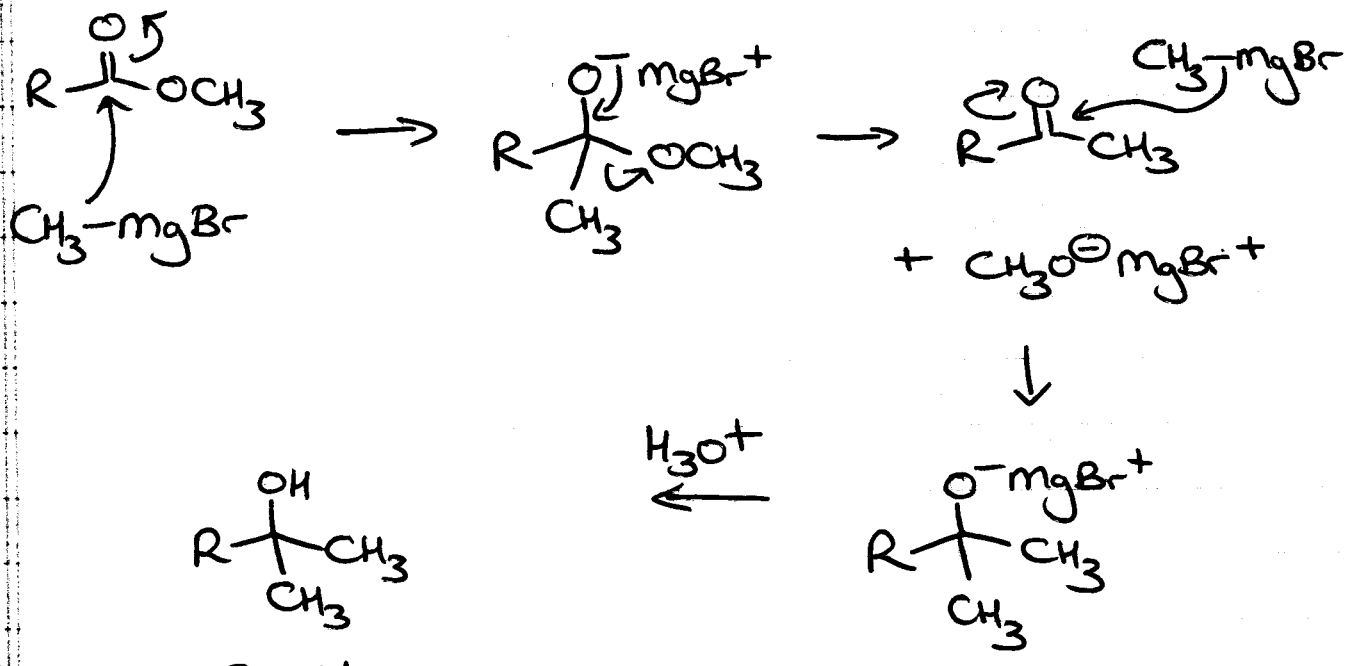
(4) $RCOCl + RCO_2^{\ominus}$



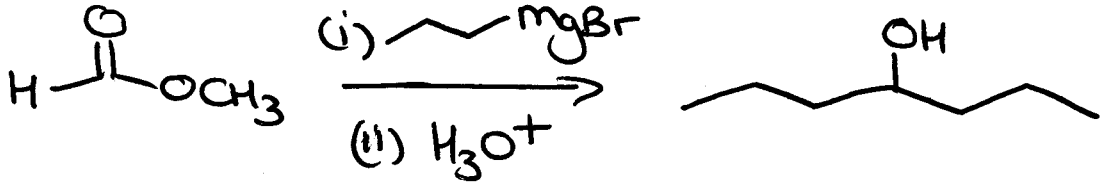
(5) ORGANOMETALLICS

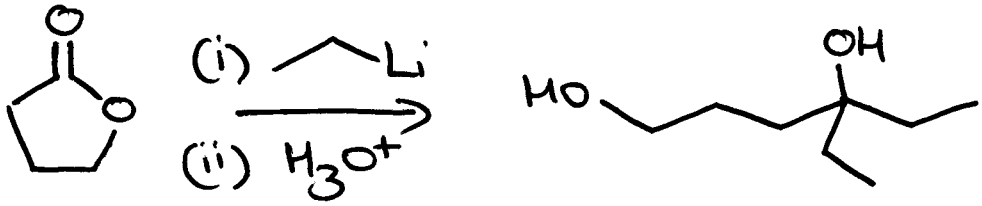
– ESTER + GRIGNARD (or ORGANOLITHIUM)



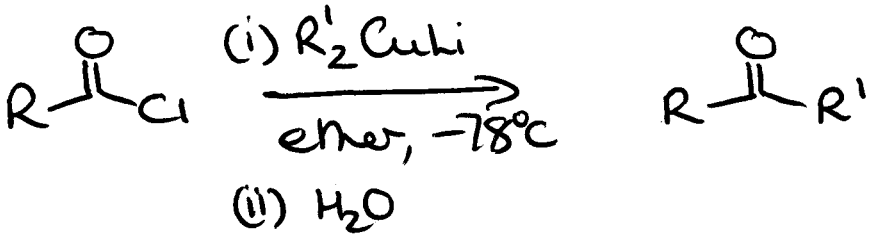


KETONE MORE REACTIVE THAN ESTER





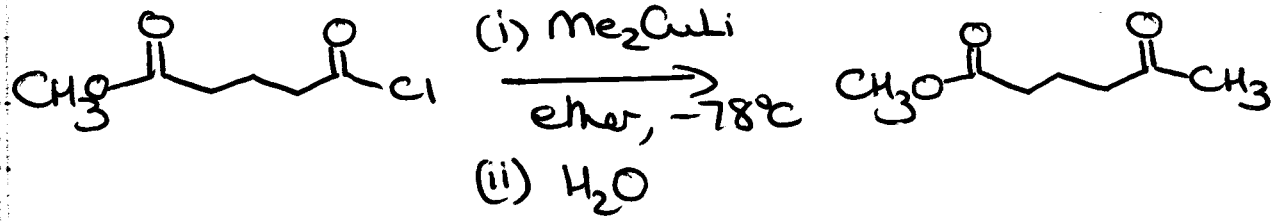
GILMAN + ACID CHLORIDE



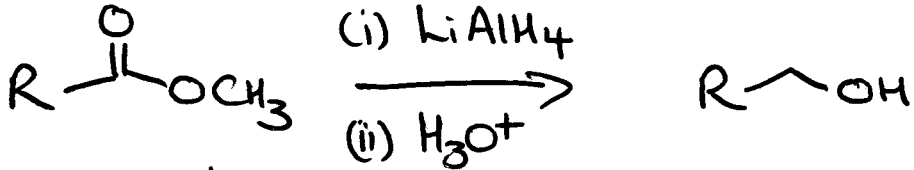
NOTE: KETONE DOES NOT REACT FURTHER

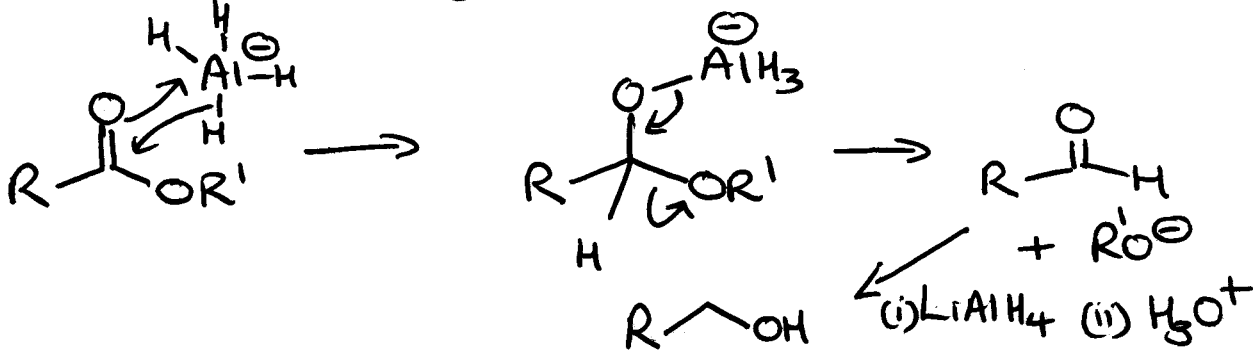
At −78°C, GILMAN only RXN w/ 

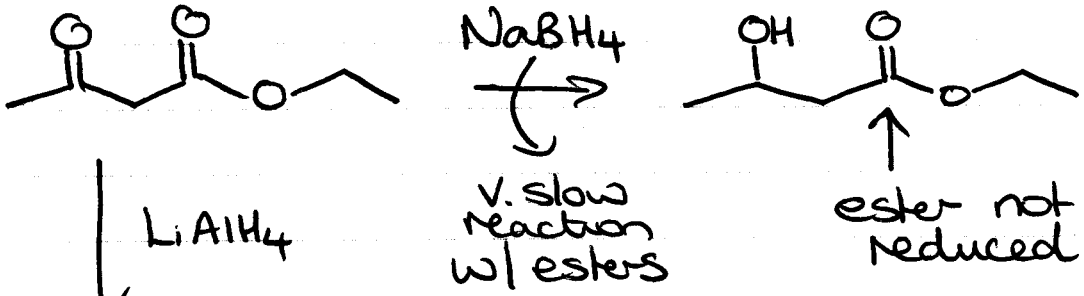
no rxn w/ aldelyde, ketone, esters, amides, anhydrides, nitriles



⑥ REDUCTION

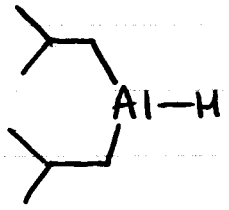




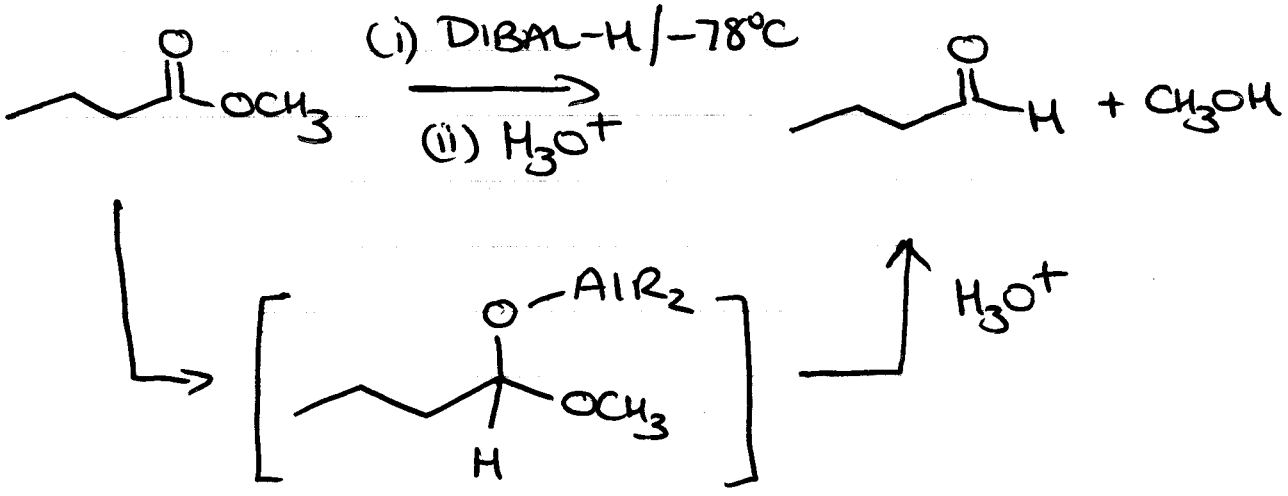


? ← write down what you would get

DIBAL-H



= DIISOBUTYLALUMINUM HYDRIDE



DOES NOT ELIMINATE $OCH_3^{\ominus}$ at low temp

At rt, 1° alcohol is formed (like $LiAlH_4$)

NEXT — AMIDES

LEC 20

① HMK 18.12, 18.20 – 18.53

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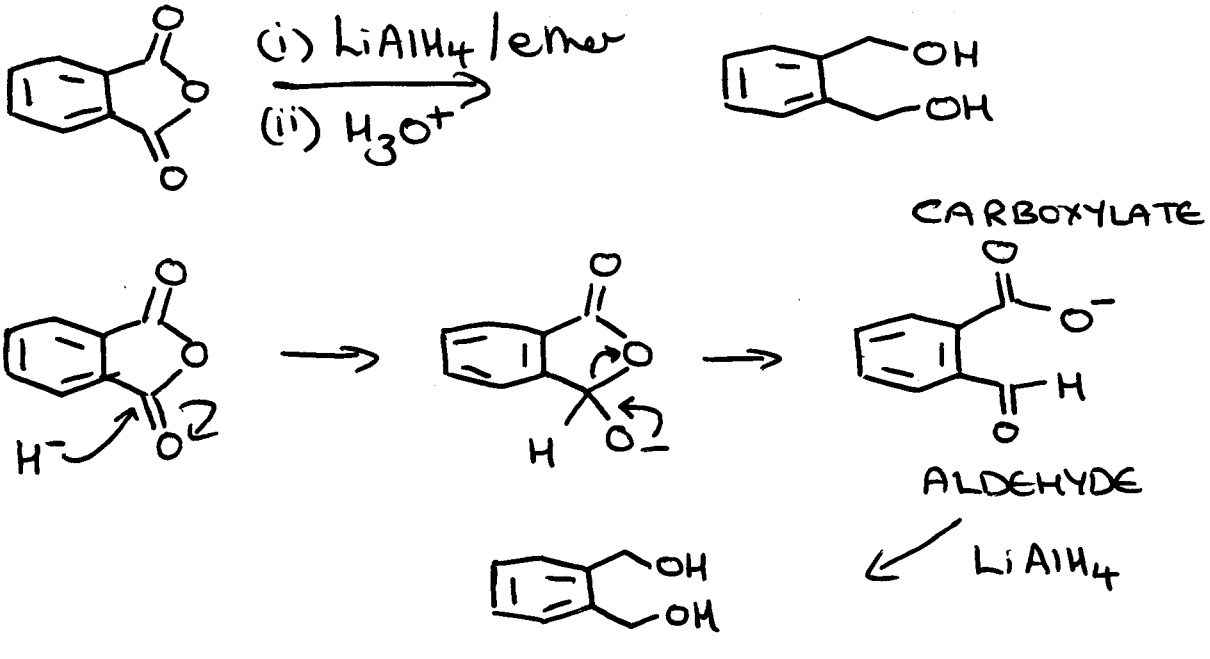
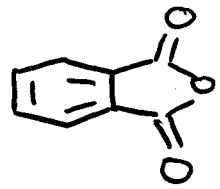
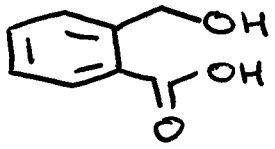
① RXN w/ ORGANOMETALLICS
② REDUCTION
③ REARRANGEMENTS

② REDUCTION continued

ANHYDRIDES

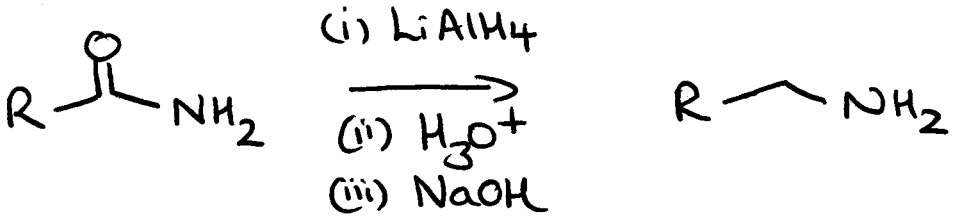


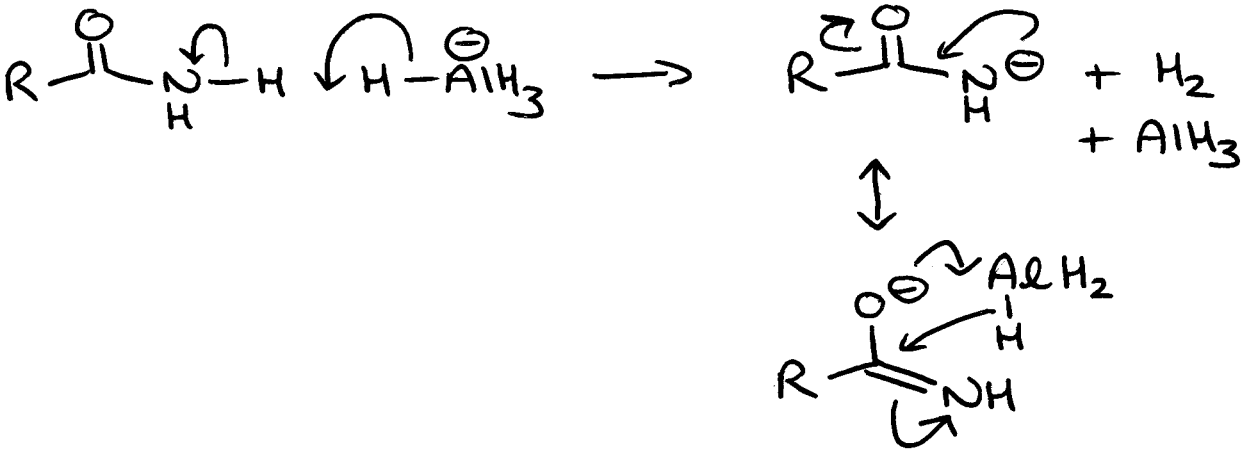

(i) NaBH4
(ii) H3O+

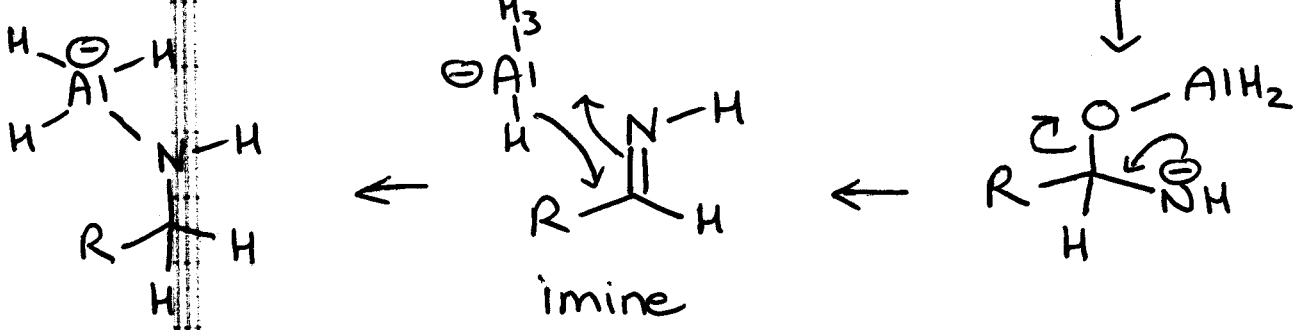

OH
OH
O

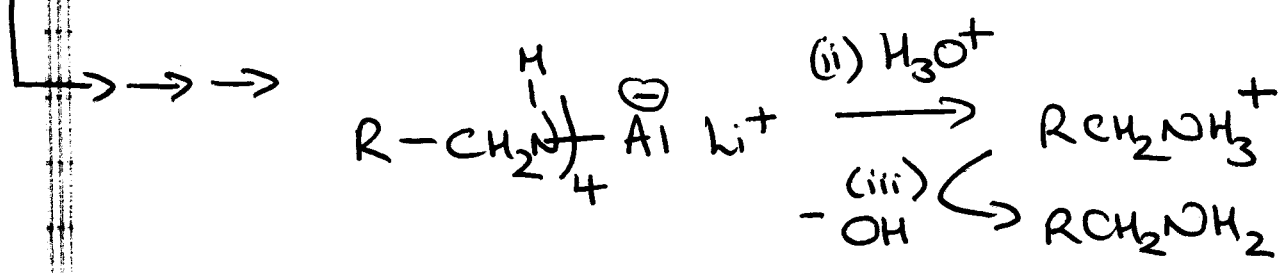
WHY?

Amides

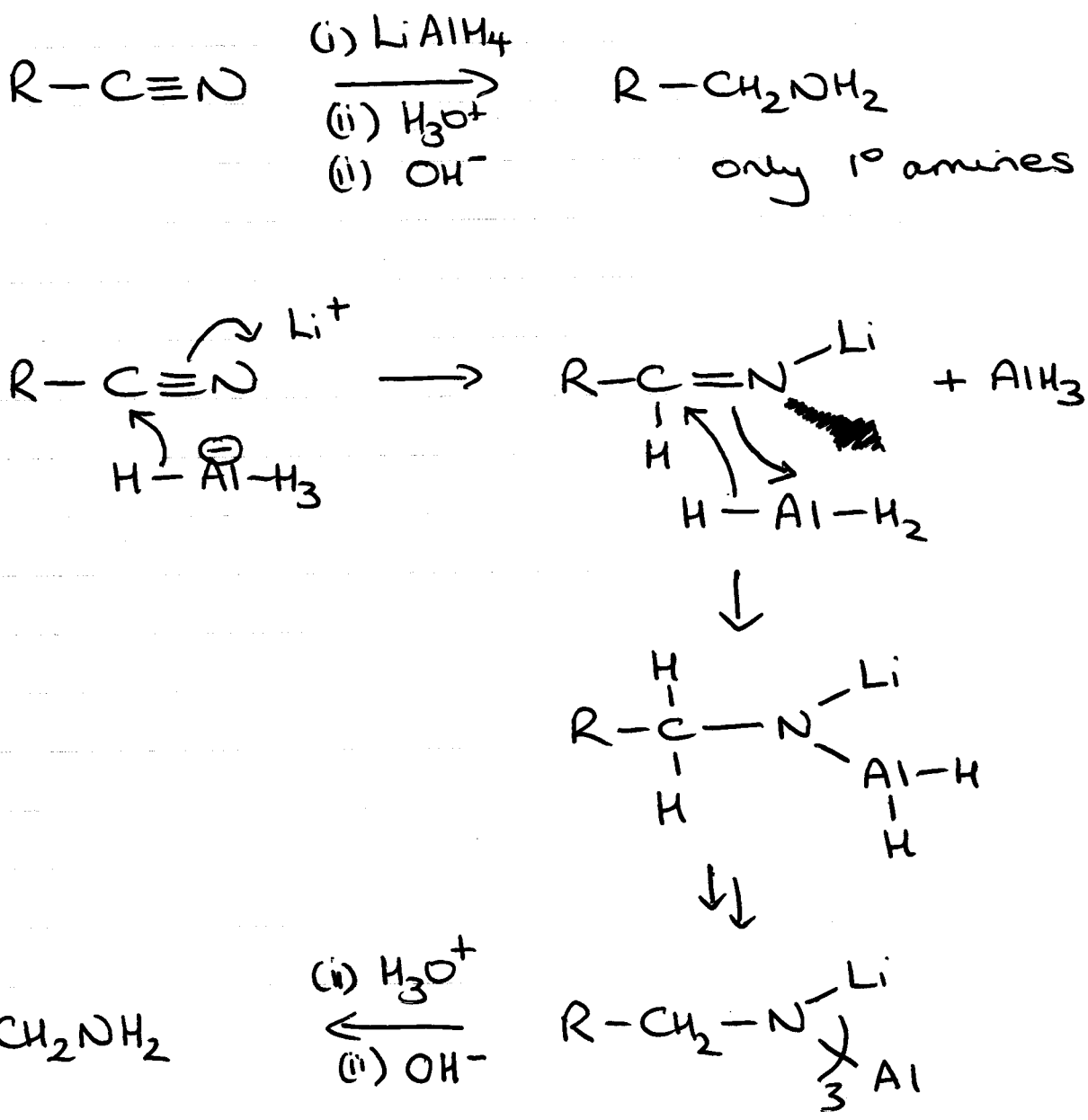

(i) LiAlH4
(ii) H3O+
(iii) NaOH
R
NH2
R
NH2

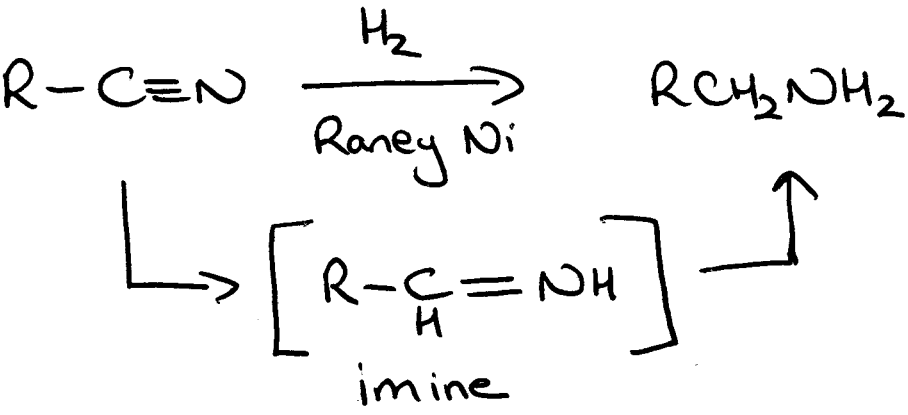

R
N
H
H
H
AlH3
R
N
H
+ H2
+ AlH3
AlH2
O
H
R
NH

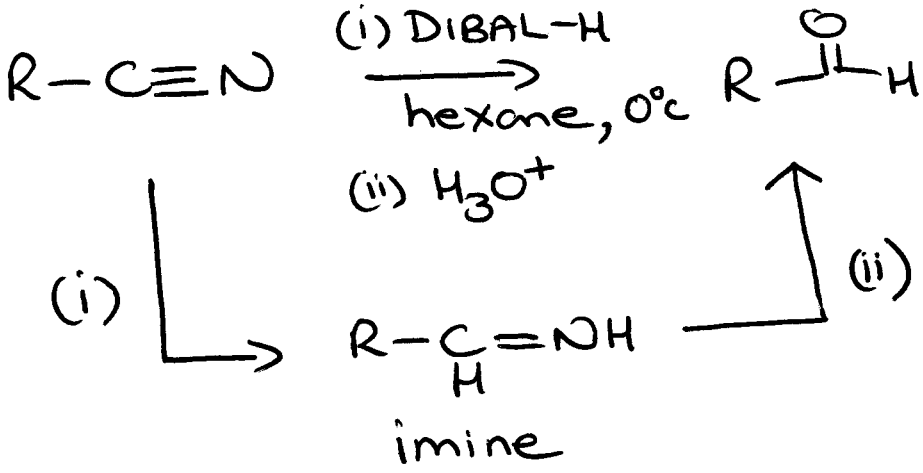

AlH2
O
R
NH
H3
Al
N
H
R
H
imine
H
Al
N
H
R
H
H


H
R
CH2
N
4
Al
Li+
(ii) H3O+
RCH2NH3+
(iii)
- OH
RCH2NH2

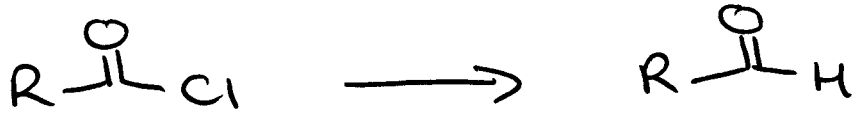
NITRILES


R–C≡N
(i) LiAlH4
(ii) H3O+
(ii) OH−
R–CH2NH2
only 1° amines
Li+
H–Al–H3
+ AlH3
RCH2NH2
(i) H3O+
(ii) OH−
3 Al


R–C≡N
H2
Raney Ni
RCH2NH2
imine



ACID CHLORIDES



H_2, $Pd|BaSO_4$,  , sulfur

ROSENMUND REDUCTION

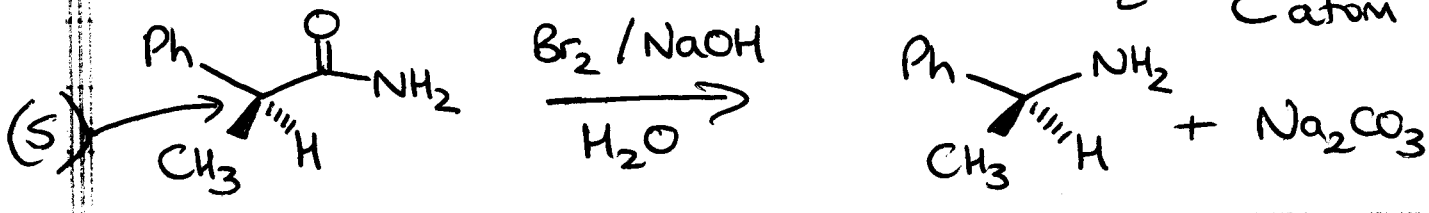
or

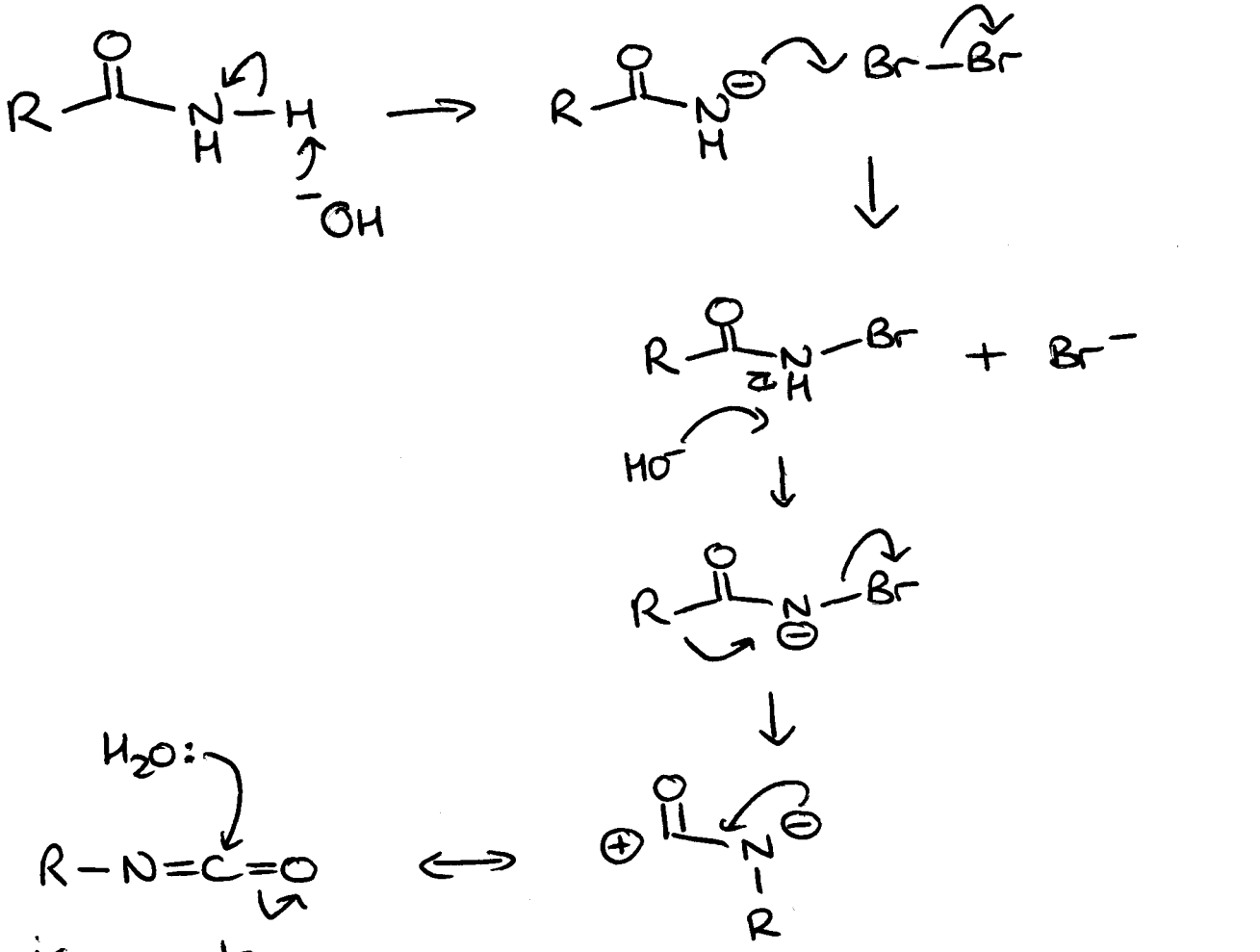
quite unreactive H^- → will react w/ RCOCl, not RCHO

(i) $LiAlH(O^tBu)_3$, THF, −78°C
(ii) H_3O^+

(3) REARRANGEMENTS

(i) HOFMANN REARRANGEMENT



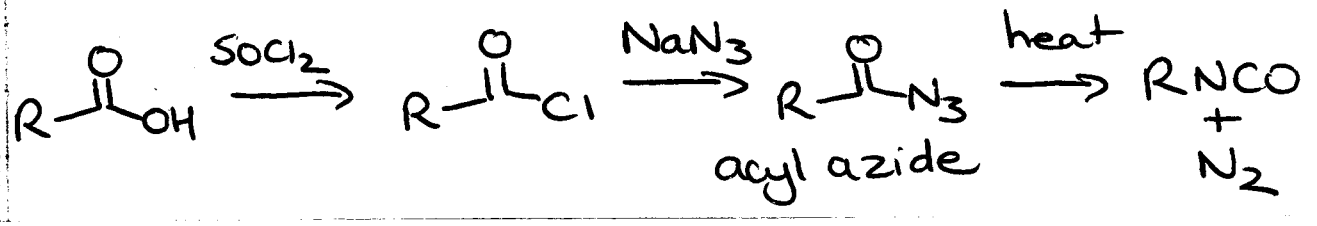


isocyanate

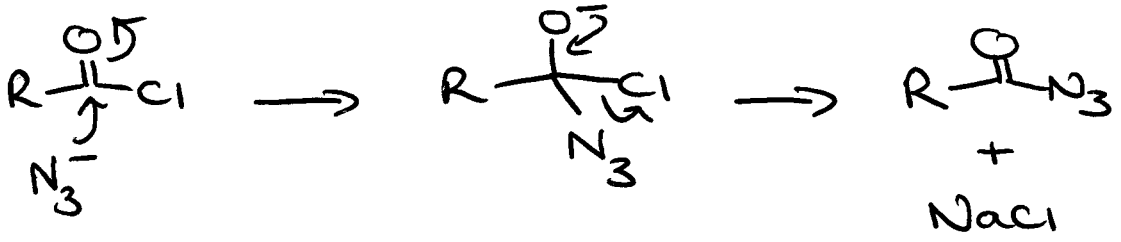
carbanic acid

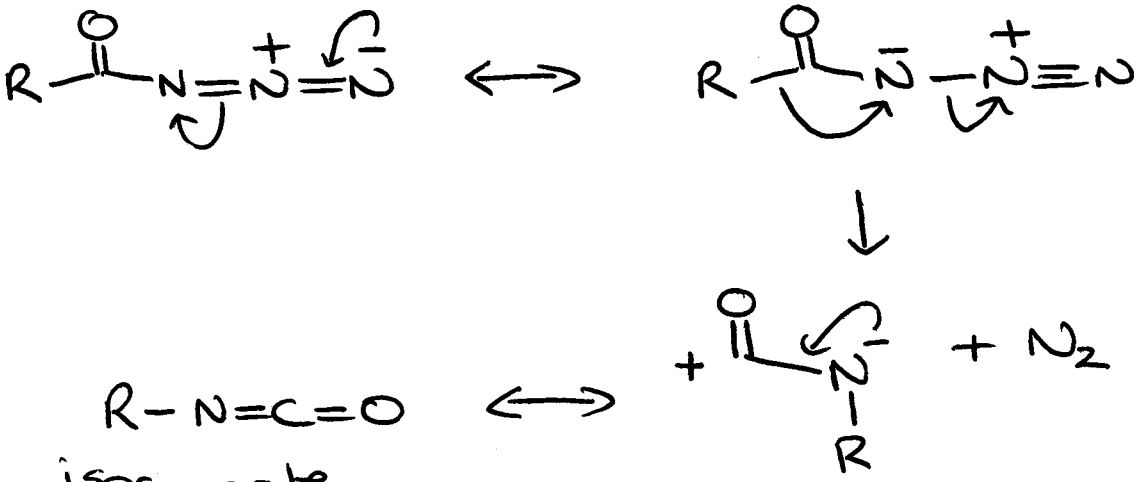
amine $R-NH_2$ + CO_2

(ii) CURTIUS REARRANGEMENT

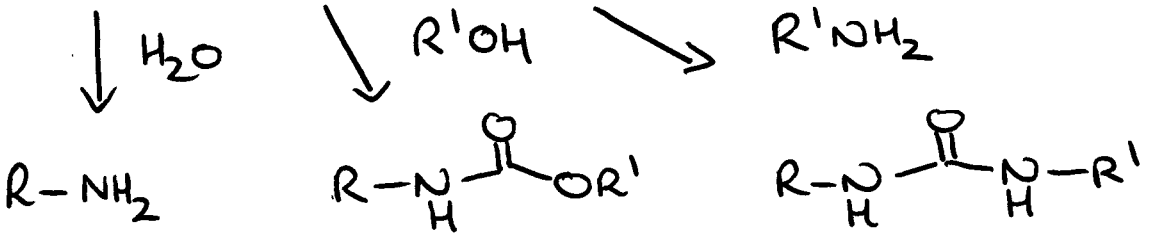


acyl azide



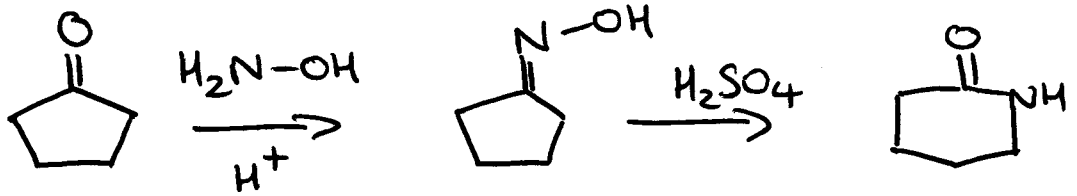


isocyanate

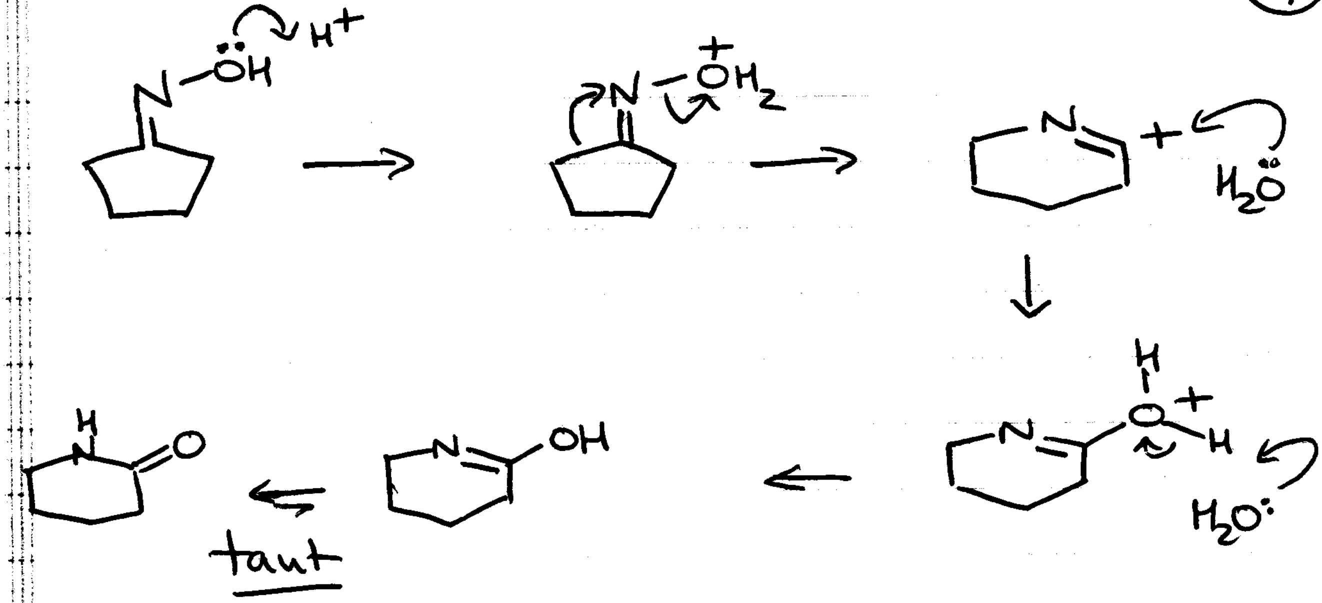


carbamate urea

(iii) BECKMANN REARRANGEMENT



oxime lactam


H+
taut

Lec (21)

(1) MIDTERM MON 17th
A-K ROLFE 1200
L-Z CS 76

(2) HMK
16.10-11, 16.46-16.53

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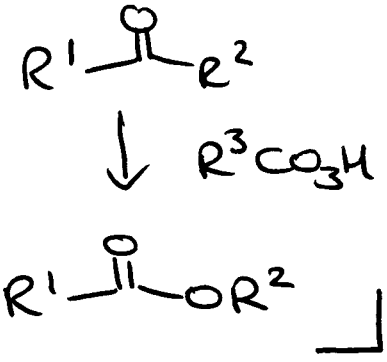
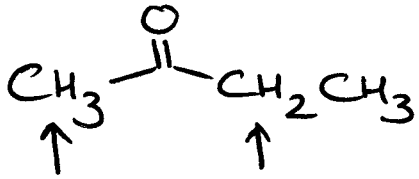
(1) BAEYER-VILLIGER
(2) REARRANGEMENT
(3) α- REACTIVITY

B-V

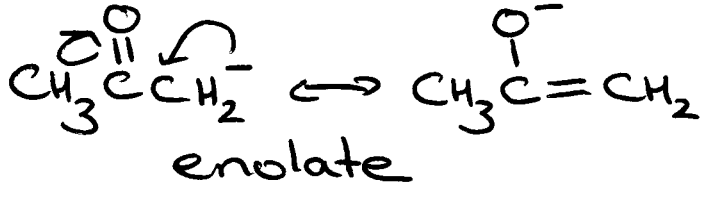


(3)



α hydrogens → relatively acidic

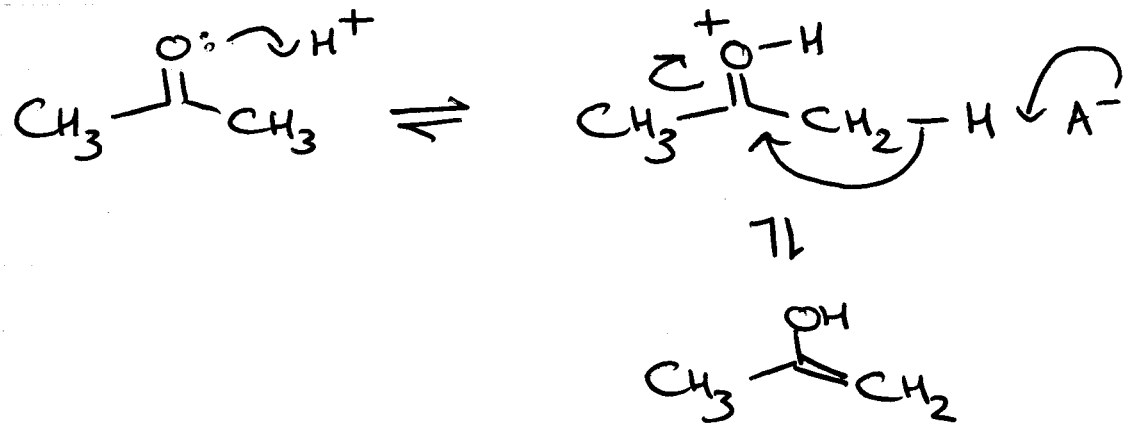
	pka
CH_3CH_2OH	16
CH_3CCH_2-H	20 ← anion is resonance stabilized
$CH_3C\equiv C-H$	25
CH_3CH_2-H	51



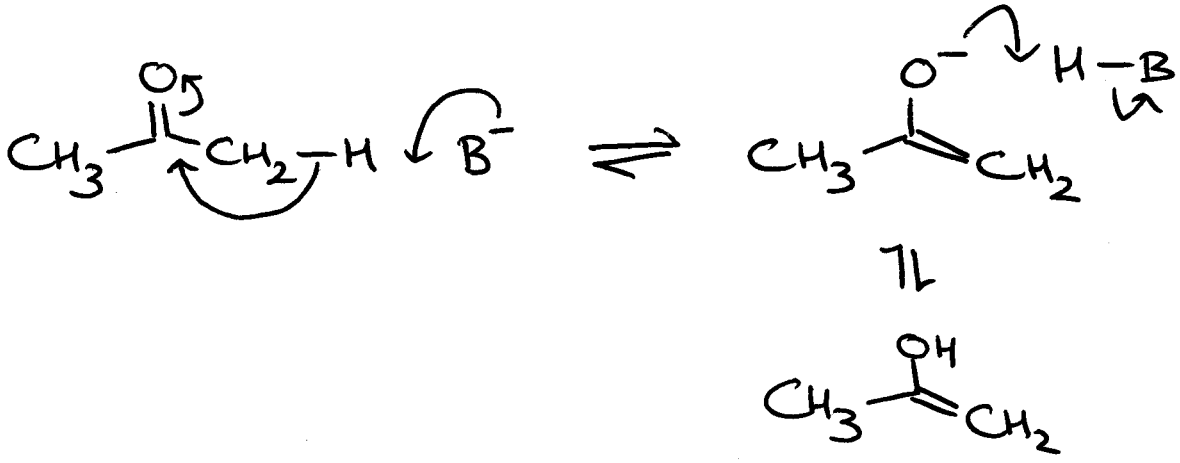
enolate

KETO-ENOL TAUTOMERIZATION

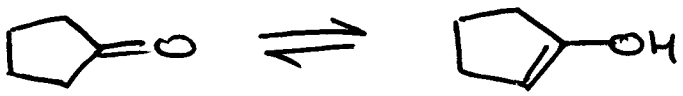
ACID CATALYZED (HA)



BASE CATALYZED (B^-)



POSITION of EQUILIBRIUM



% enol at EQ

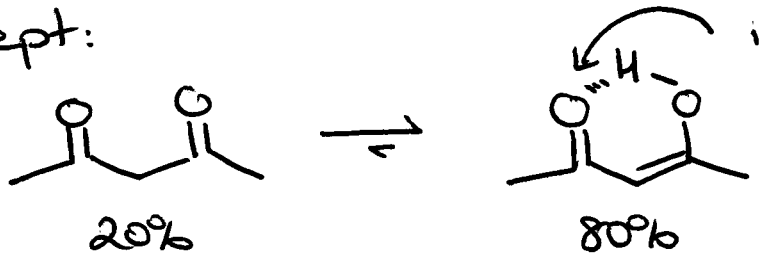
1×10^{-6}

FOR SIMPLE ALDEHYDES / KETONES,

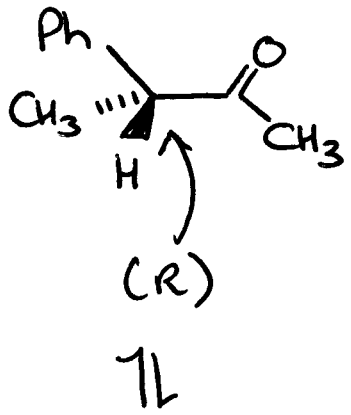
C=O stronger than C=C

equilibrium lies on keto side

xcept:

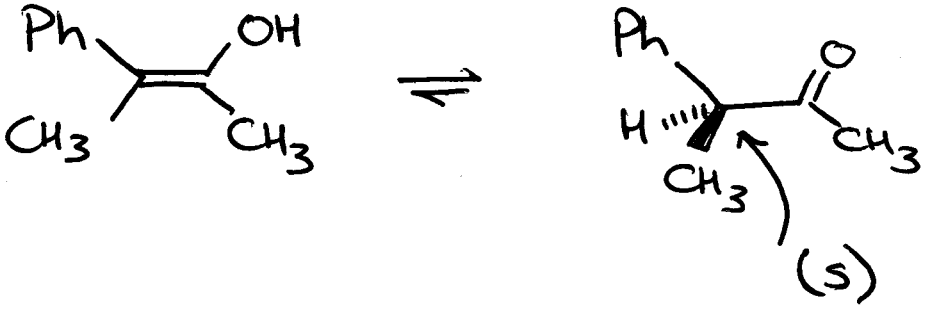


RACEMIZATION



DISSOLVE IN EtOH
optical activity remains

(ADD trace acid or base)
HCl(g) NaOEt

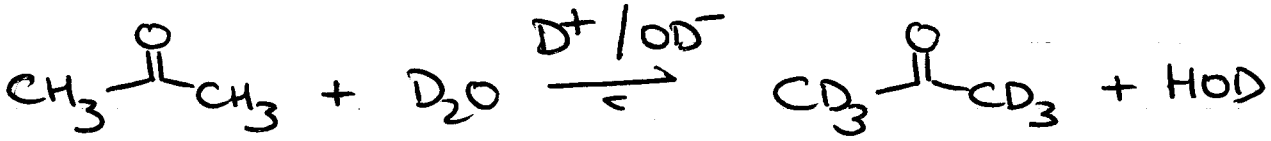


NEED at LEAST one α-H

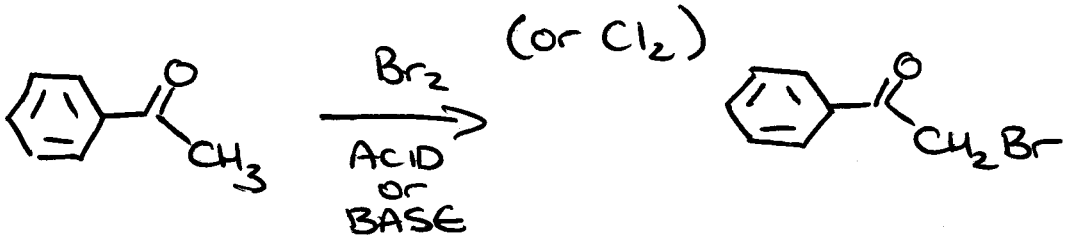
- DEUTERIUM EXCHANGE

ALDEHYDE/KETONE w/ α-H

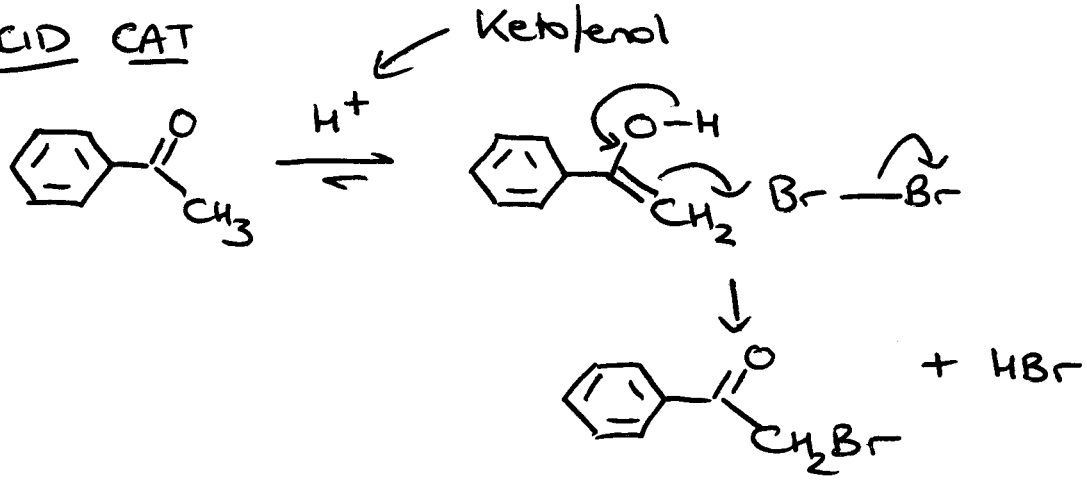
dissolve in D_2O w/ D^+ or ^-OD



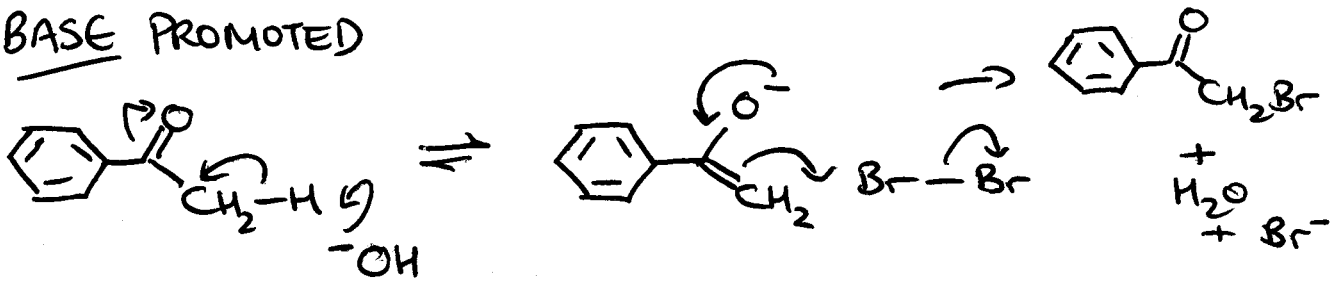
- α – HALOGENATION

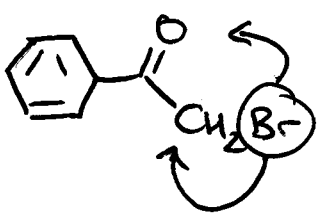


ACID CAT



BASE PROMOTED





makes H more acidic

⇓

Base reaction leads to Polyhalogeration

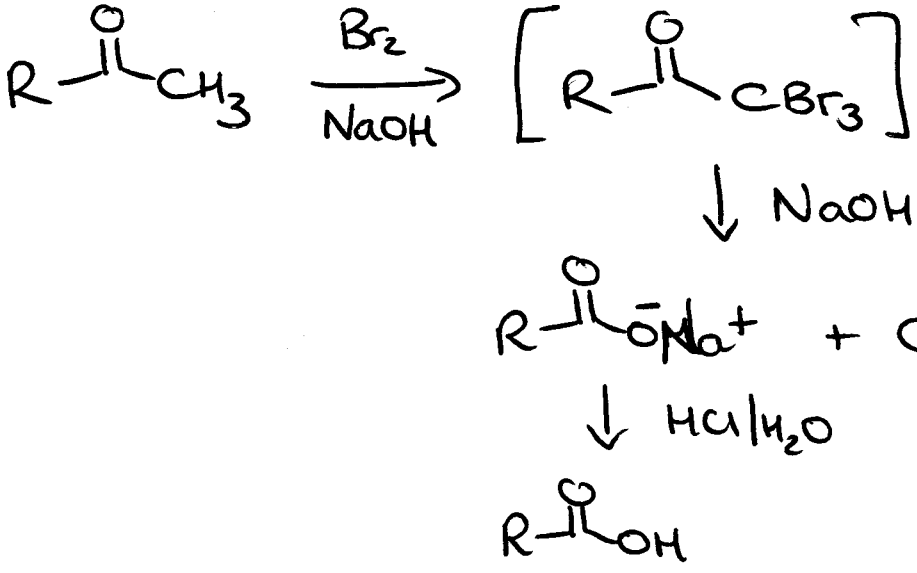
→ NOT SYNTHETICALLY USEFUL

makes C=O less basic

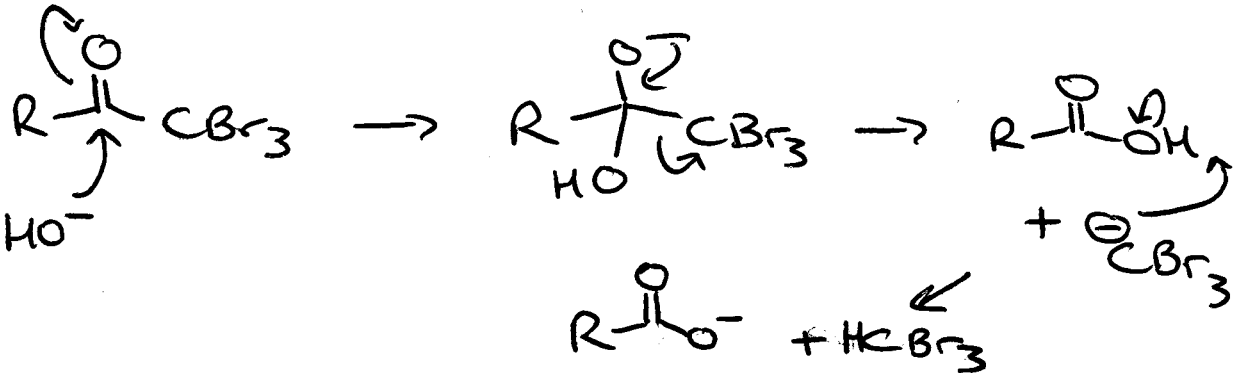
⇓

H^+ can be stopped at single halogeration

Xcept METHYL KETONES



MALOFORM REACTION



LEC (22)

(1) MIDTERM *

AVERAGE = 50/100 LOW = 5 HIGH = 100 1/2

most improved = +51 41 1/2 → 92 1/2

(2) HMK 19.1, 19.2, 19.3

* RULES

① TEXAS CARBONS (OXYGENS) ② MECHANISMS (no other reagents)

③ SYNTHESIS – RIGHT DIRECTION

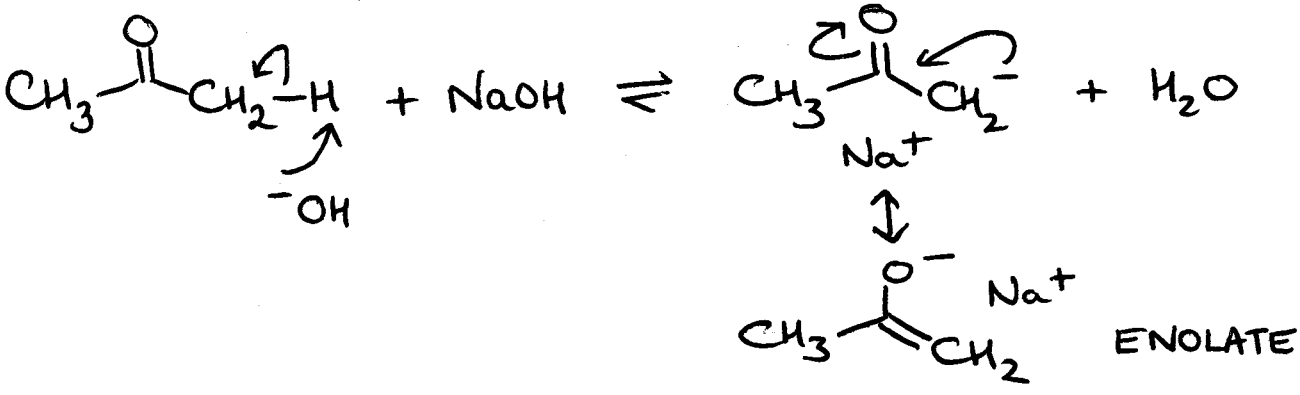
α – REACTIVITY – INTRO

① ALDOL

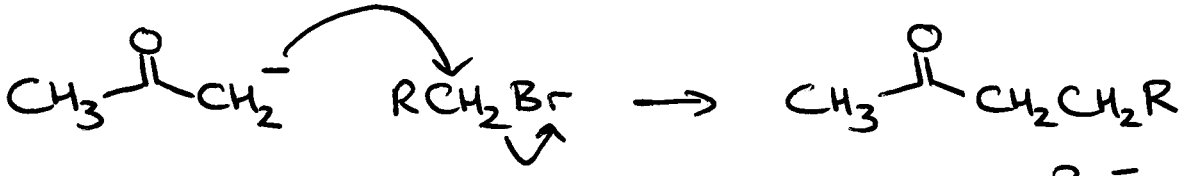
② CROSSED ALDOLS

③ CYCLIC ALDOLS

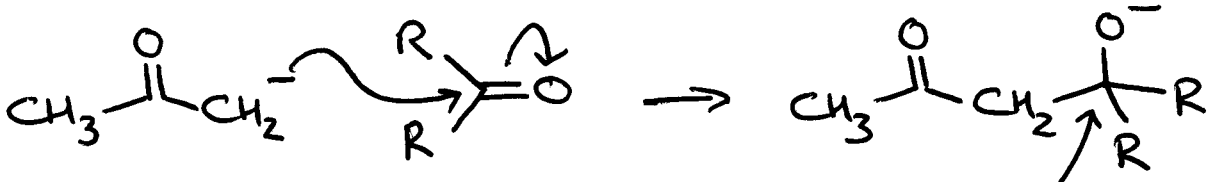
INTRO



Nuc in S_N2 rxns



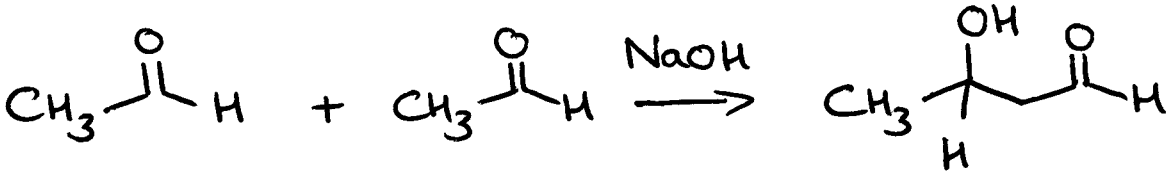
Nuc in CARBONYL addition rxns



tetrahedral intermediate

---

(1) ALDOL RXN



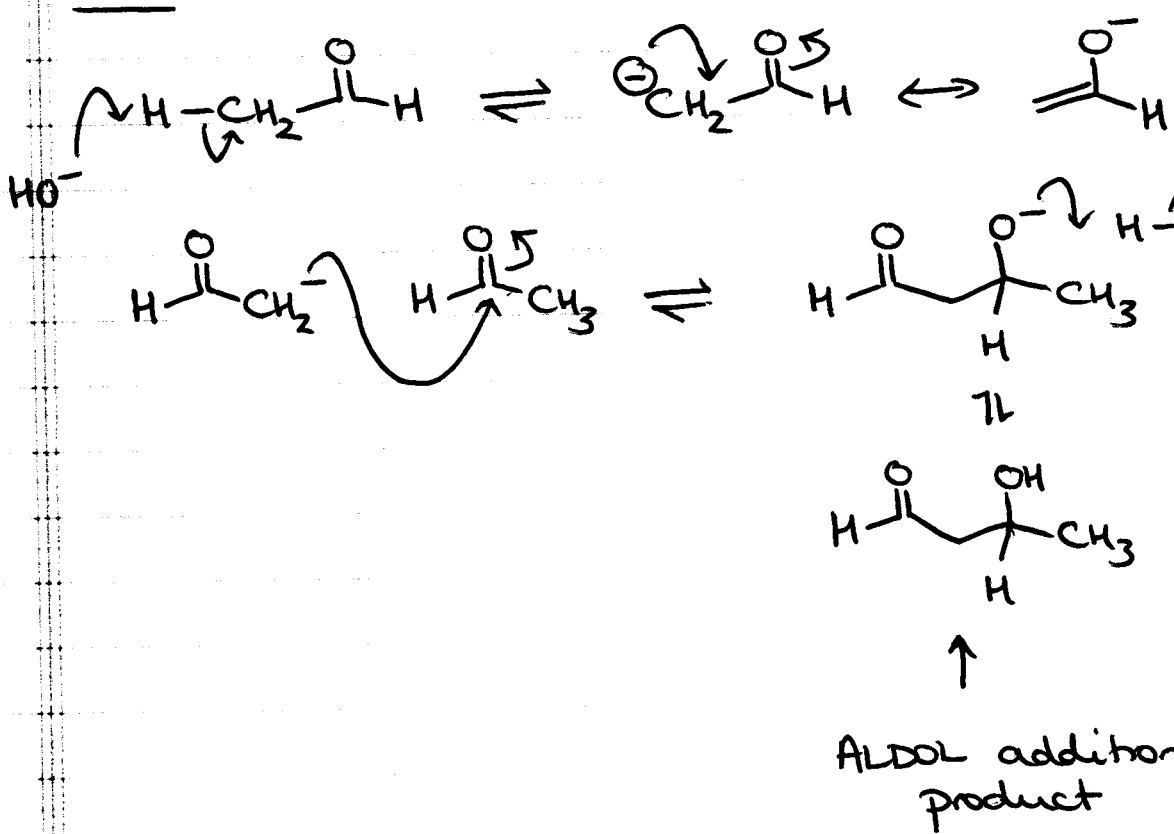
<u>aldehyde</u> + <u>alcohol</u>

NOT HOW IT WORKS

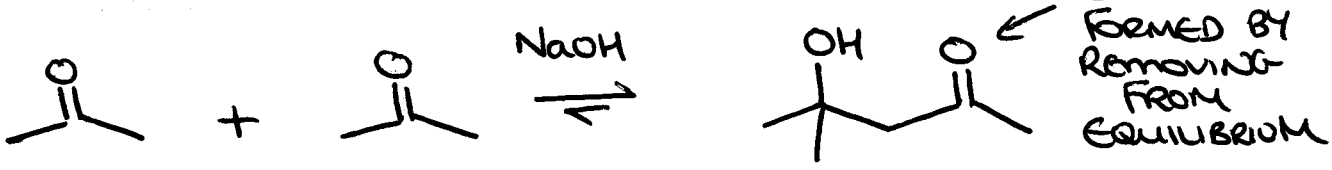
β- HYDROXY ALDEHYDE

ACID or BASE catalyzed.

Base



For ALDEHYDES, equilibrium lies to right
i.e., ALDOL product favored

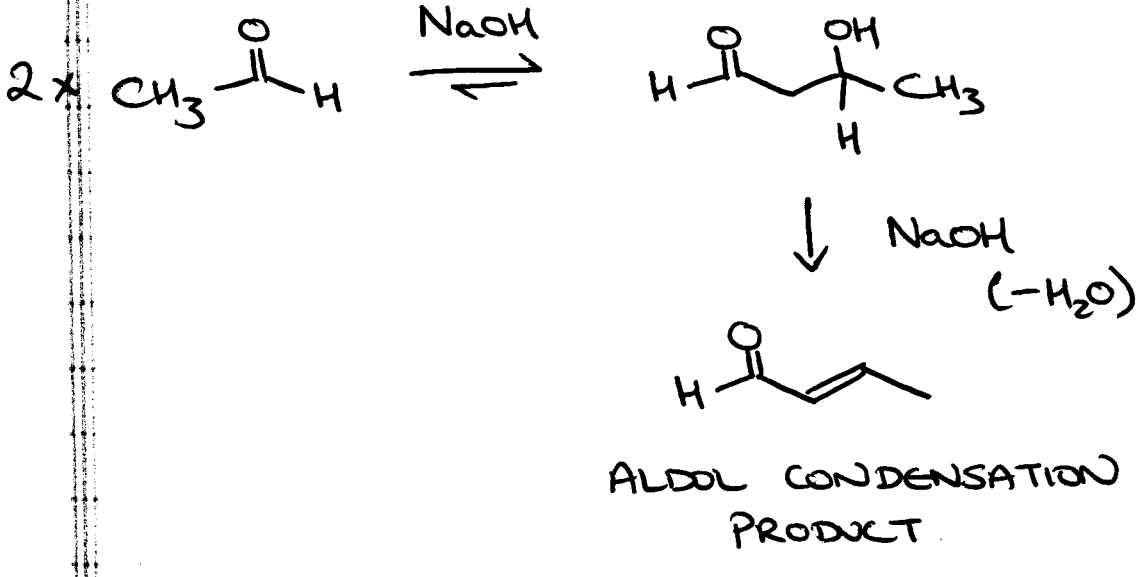


β-HYDROXY KETONE

EQUILIBRIUM lies to left (Ketones less electrophilic than aldehydes)

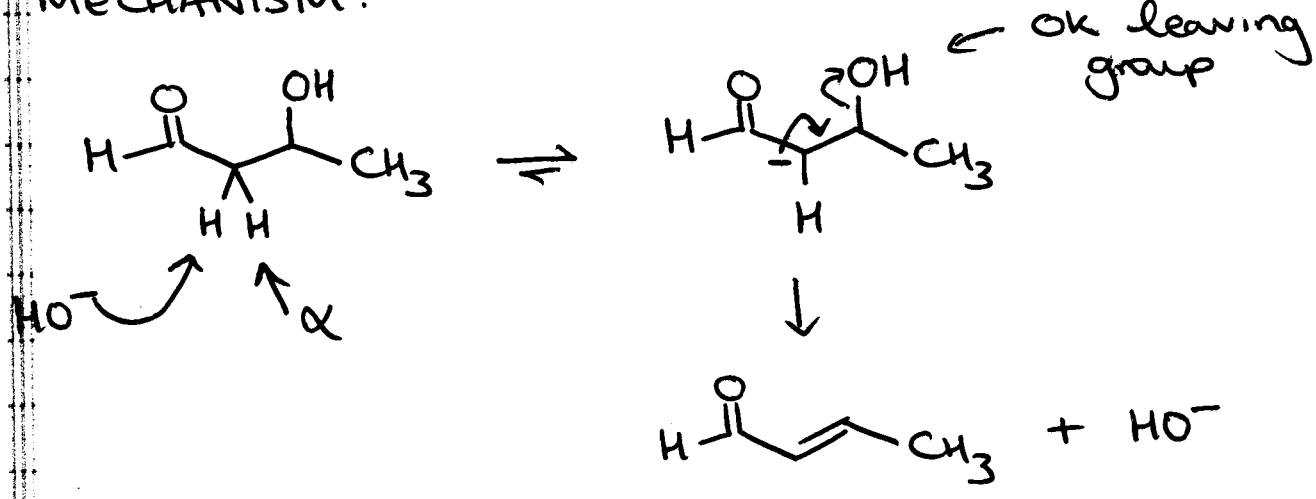
IMPORTANT IN <u>CROSSED ALDOL</u> RXNS...

- MORE SEVERE CONDITIONS
(higher temp, more conc base)
⟶ DEHYDRATION



ALDOL CONDENSATION PRODUCT

MECHANISM:



NOTE:

BASE-CATALYZED DEHYDRATION OF SIMPLE ALCOHOLS IS NOT KNOWN

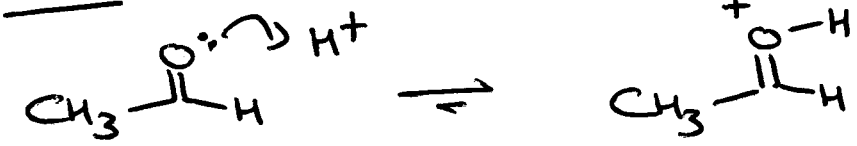
BUT

(i) α–H → relatively acidic

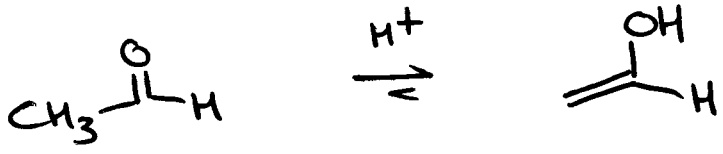
(ii) PRODUCT is CONJUGATED ⇒ stable

ACID

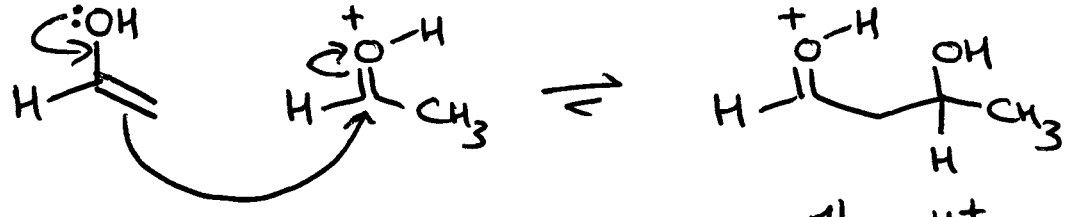
(i)

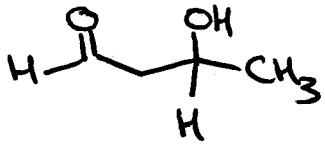


(ii)

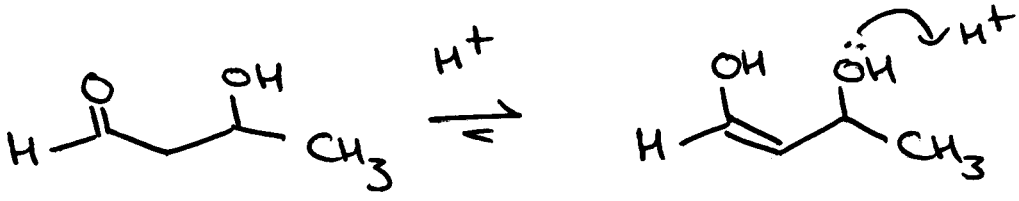


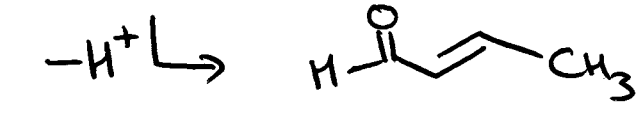
(iii)



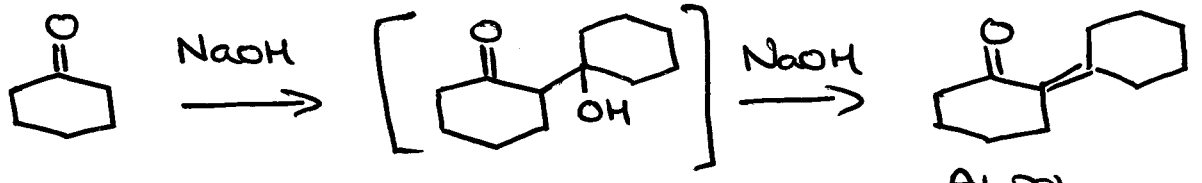


ACID cat ALDOL almost always give DEHYDRATED PRODUCT



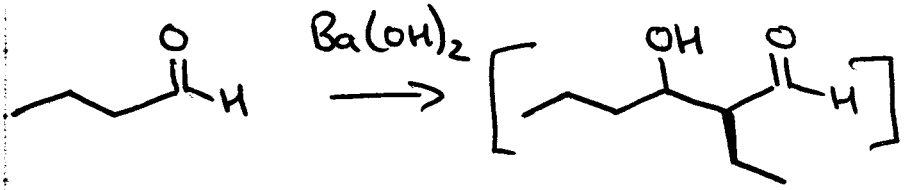


EXAMPLES

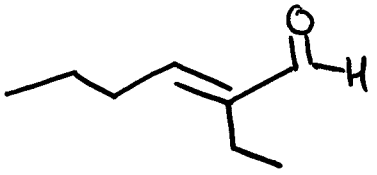


ALDOL ADDITION

ALDOL CONDENSATION

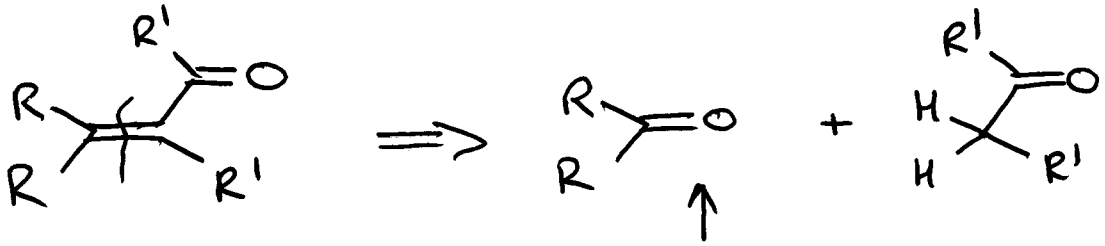


ADDITION PRODUCT

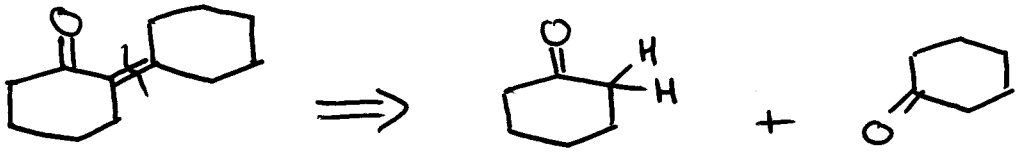


CONDENSATION PRODUCT

SPOTTING ALDOL PRODUCTS

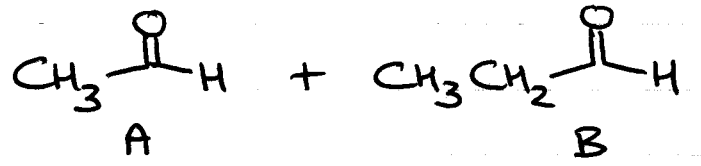


add "O" add "H_2"

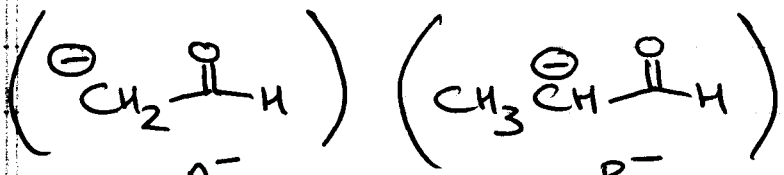


(2) CROSSED ALDOL RXNS

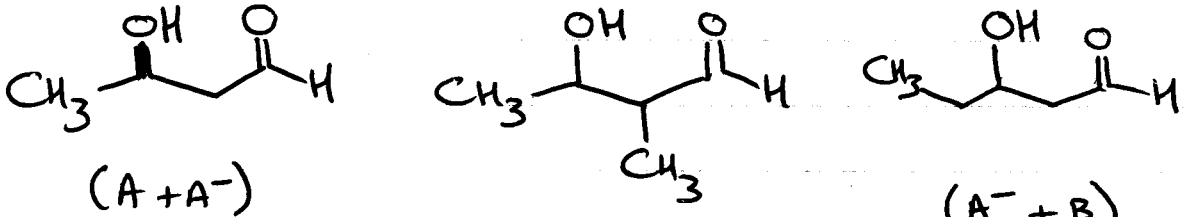
⇒ PRODUCT MIXTURES



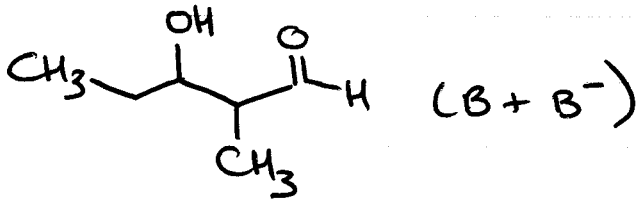
A B



A^- B^-



$(A + A^-)$ $(A + B^-)$ $(A^- + B)$



$(B + B^-)$

4 PRODUCTS

HMK: WRITE MECHANISM FOR FORMATION OF EACH PRODUCT.

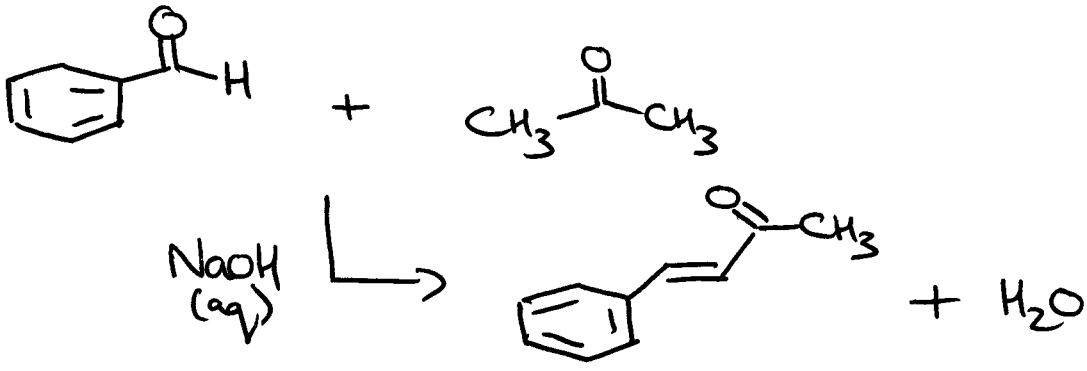
CROSSED ALDOLS ARE USED WHEN:

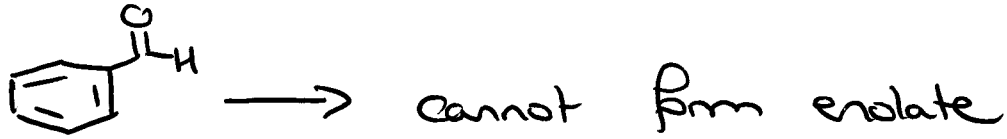
A + B ← (LESS REACTIVE C=O)
↑ no α Hs (cannot form enolate)

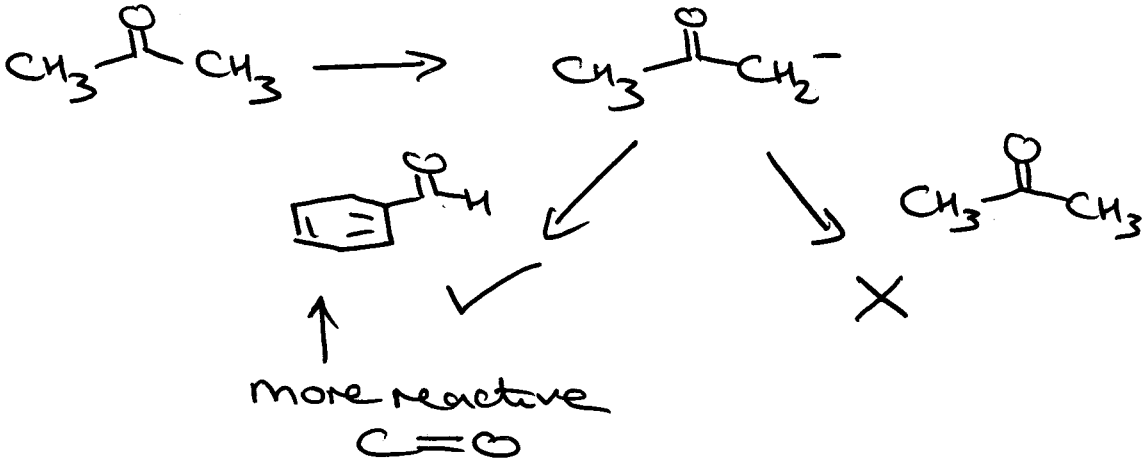
SO ONCE B^- ENOLATE FORMED, ONLY REACTS WITH A.

CLAISEN-SCHMIDT RXN

KETONE w/ α Hs reacts w/ aromatic aldehyde (no α H)

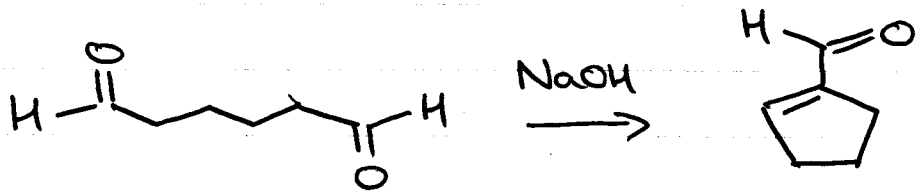






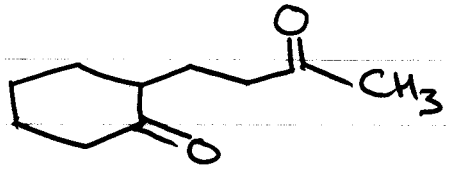
OTHER Ø αH aldehydes:

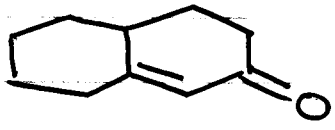
(3) CYCLIC ALDOLS



Write mechanism for HMK

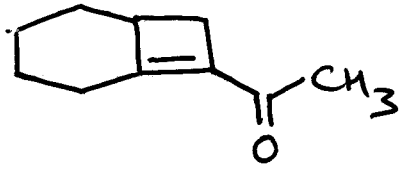
GOOD for forming 5, 6 membered rings





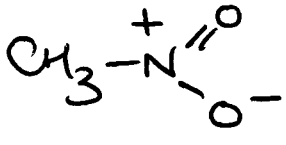
THIS ONE

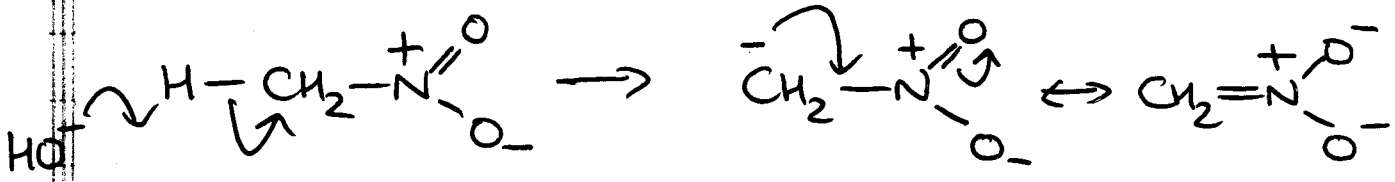
or

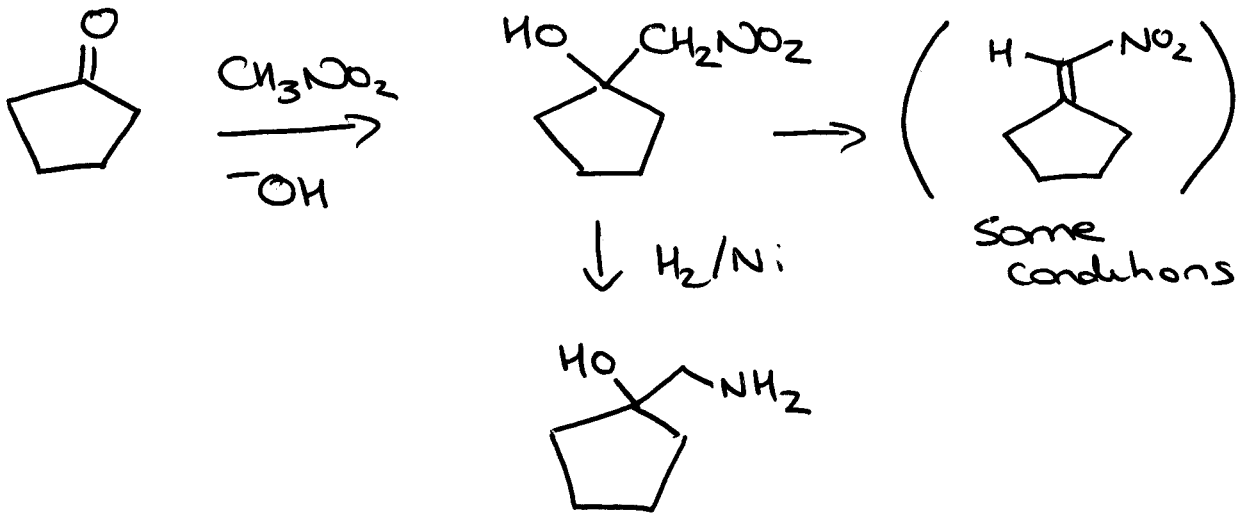


NO

(4) NITROALKANES






O
CH_3NO_2
^-OH
HO
CH_2NO_2
H
NO_2
Some
conditions
H_2/Ni
HO
NH_2

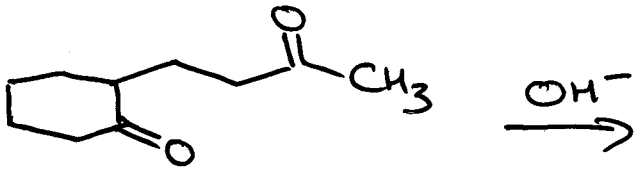
LEC (23)

(1) HMK 19.4 – 19.12

---

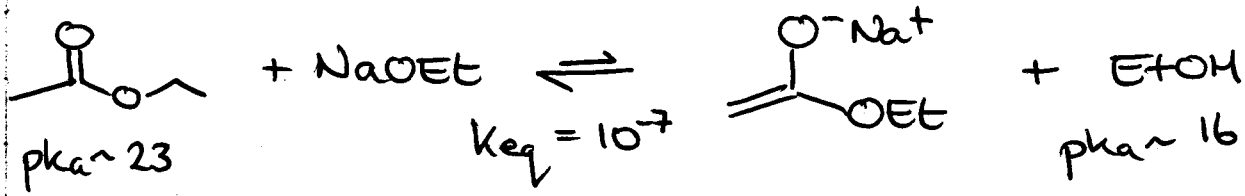
(1) CYCLIC ALDOLS

(2) NITROALKANES
(3) DIRECTED ALDOL
(4) CLAISEN COND...
(5) DIECKMANN COND...
(6) ENAMINES



(2) NITROALKANES (last lecture)

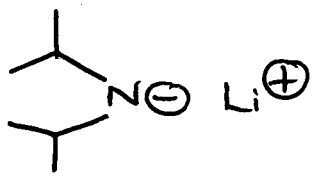
(3) DIRECTED ALDOLS



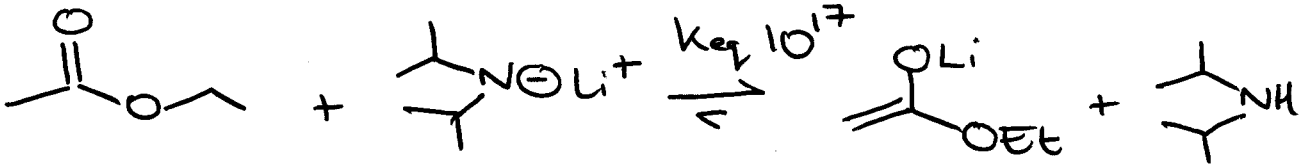
USE STRONGER BASE

→ DRIVE ENOLATE FORMATION TO COMPLETION

LDA – Lithium Diisopropylamide

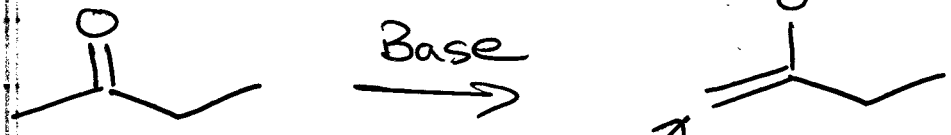


Strong base / Poor nucleophile (sterics) → does not add to C=O



pka~23 pka~40

ESSENTIALLY IRREVERSIBLE →



non equivalent α Hs

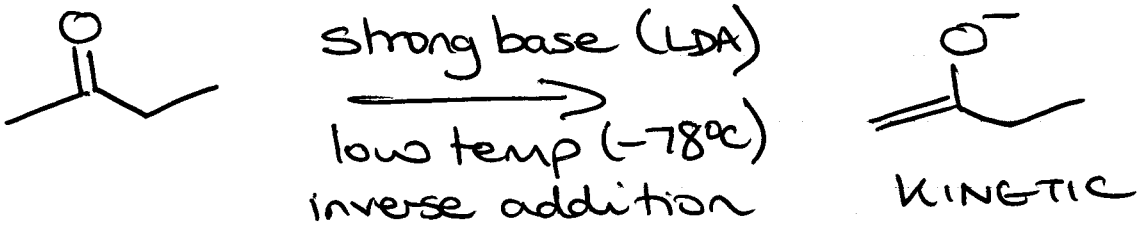
more accesible H

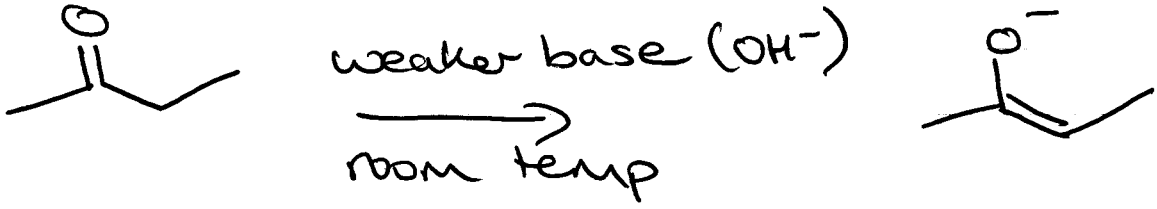
OR

KINETIC ENOLATE (RATE)

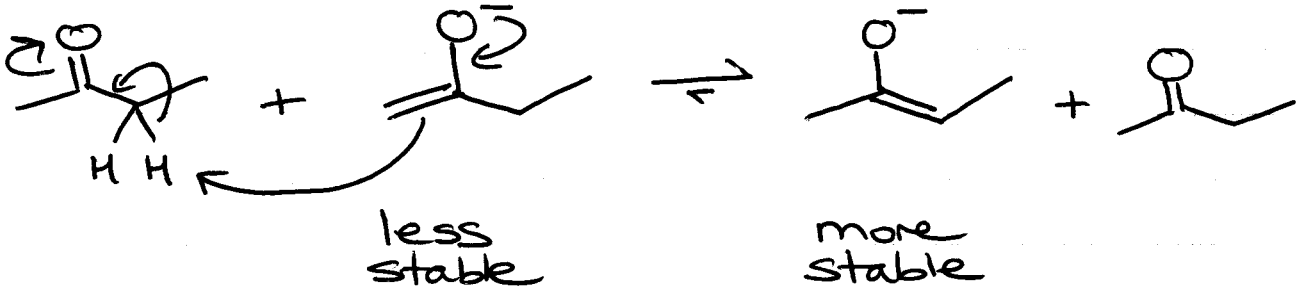
THERMO ENOLATE (STABILITY)

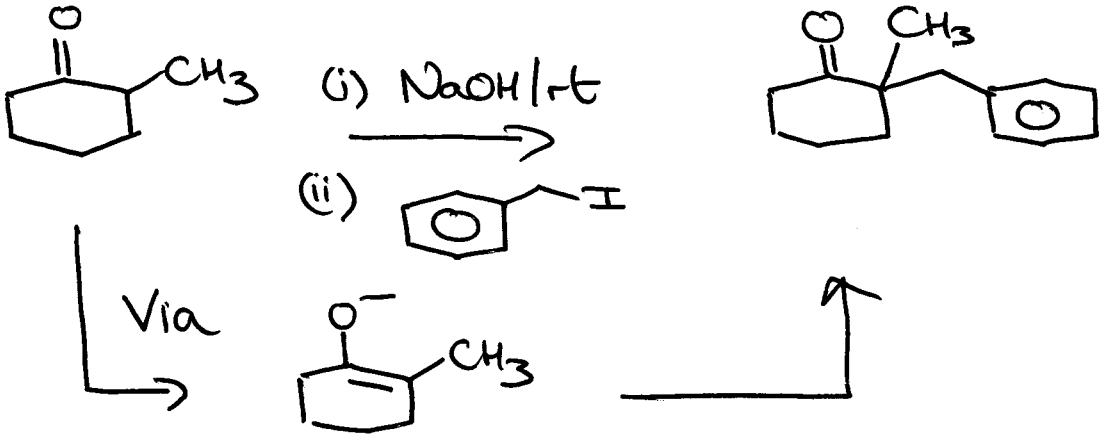
more sub C=C bond

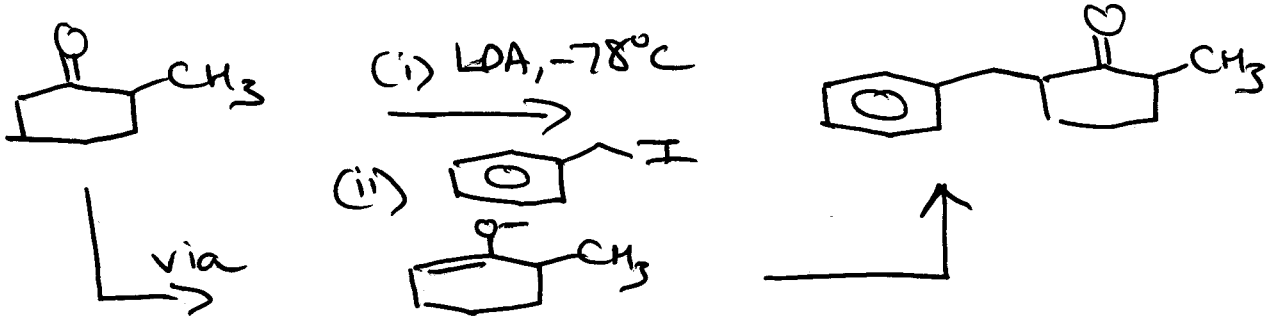




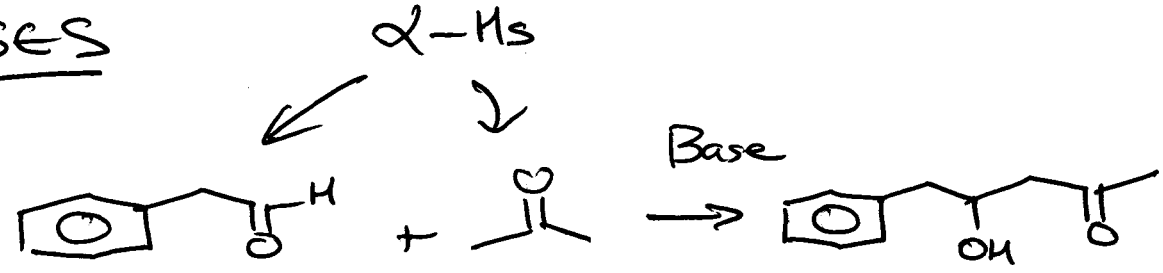
ENOLATE EXCHANGE (XS KETONE)



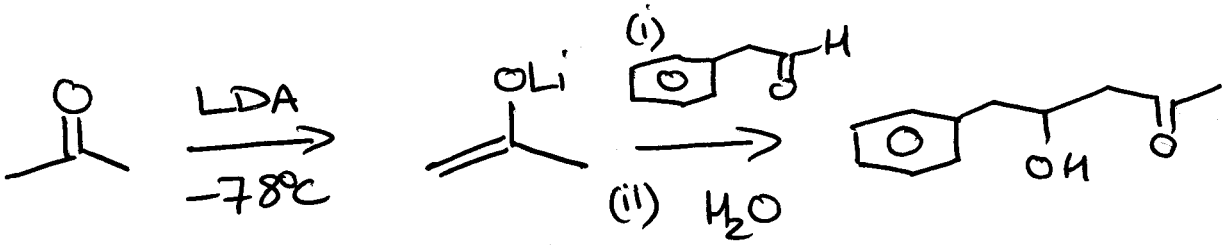


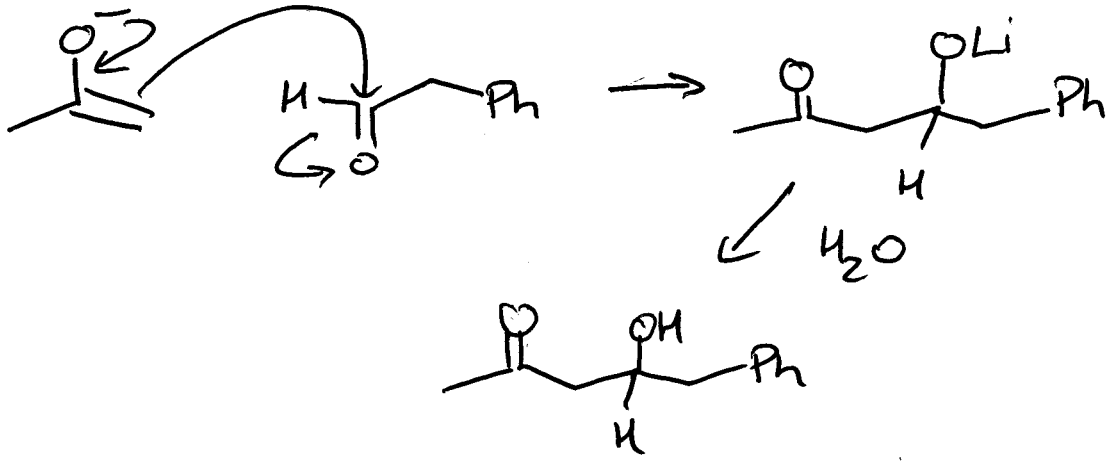


USES

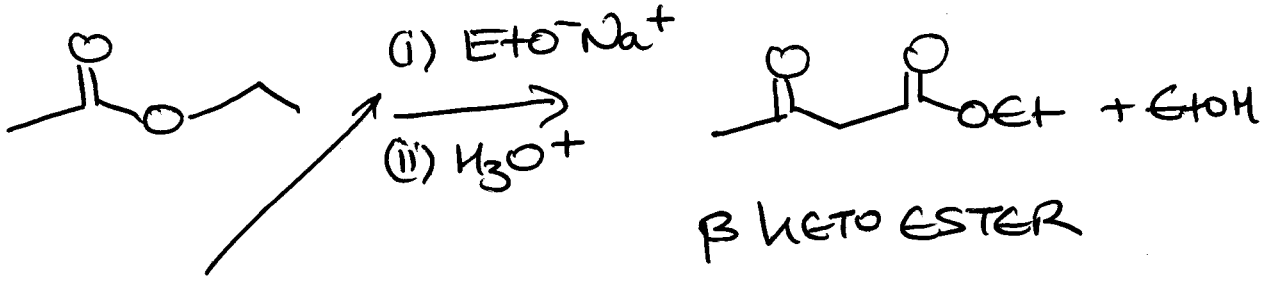


Use NaOEt → 4 products



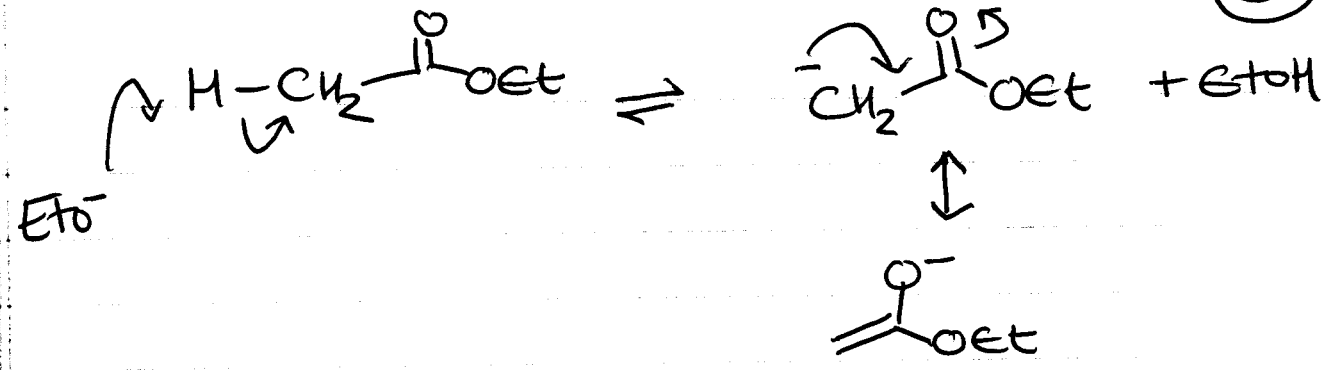


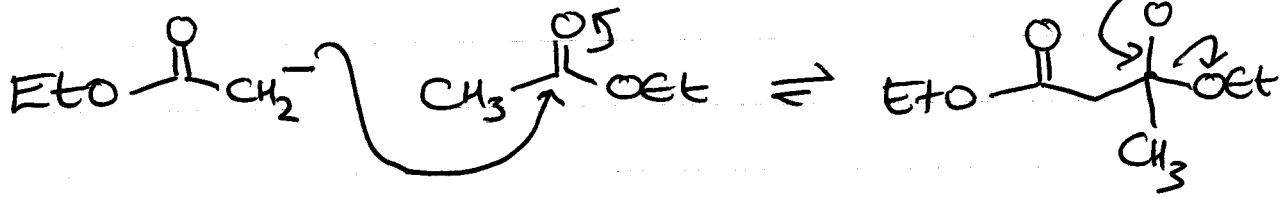
(4) CLAISEN



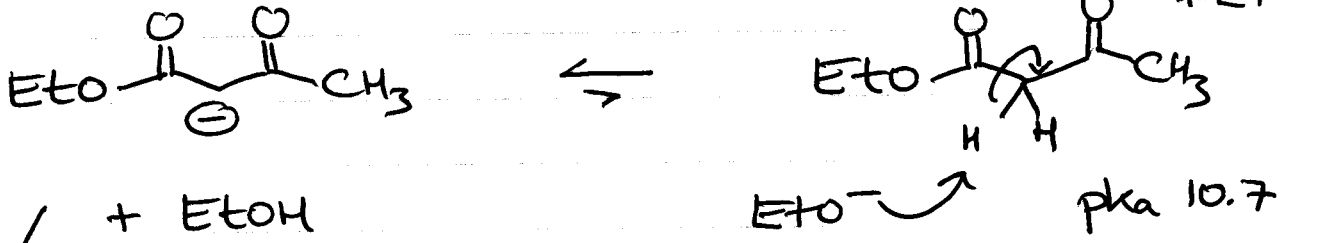
β KETO ESTER

Use base, but not OH^- ⇒ HYDROLYZE ESTER





tetrahedral intermediate

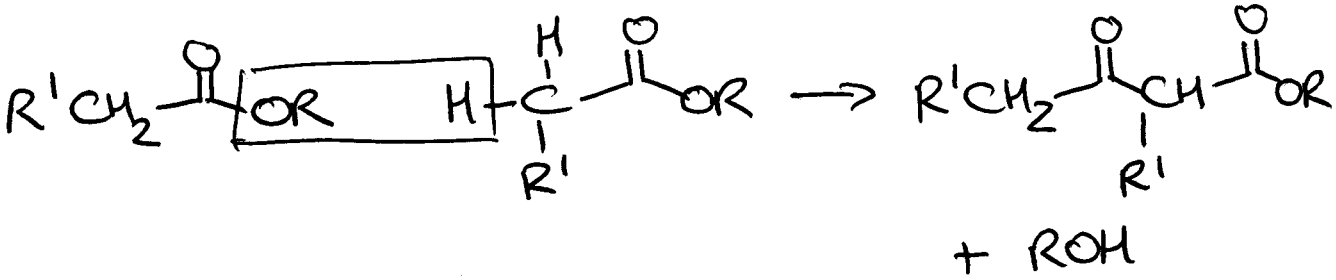


ACID WORK UP

+ EtOH
pka ~16

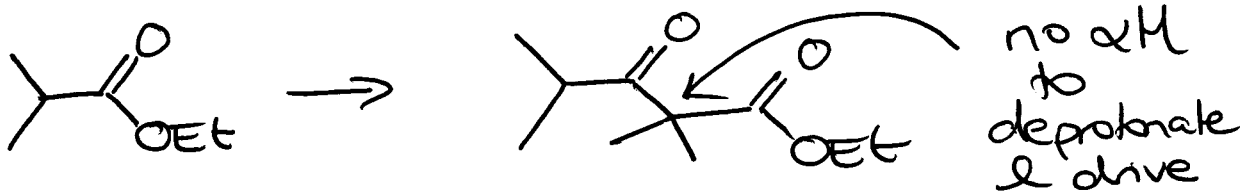
← DRIVES EQUILIBRIUM

GENERAL SCHEME



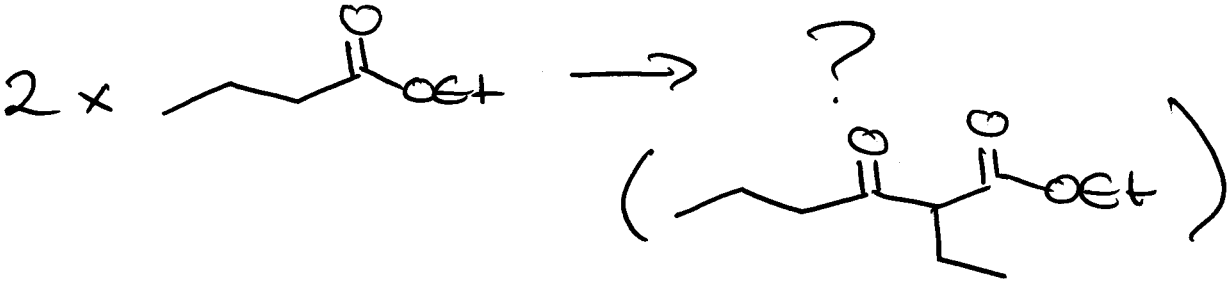
NEED 2 α Hs

one to enolize
one to drive rxn to completion



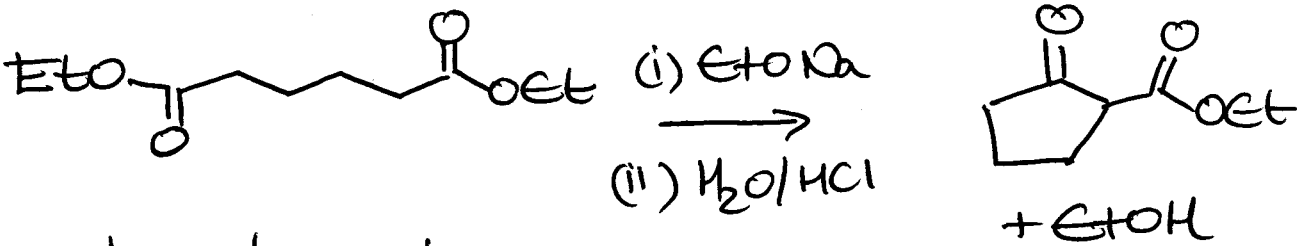
possible product
- but does not form

DO THIS ONE



+ EtOH

(5) INTRAMOLECULAR CLAISEN
(give 5/6 MEM RING => DIECKMANN)



+ EtOH

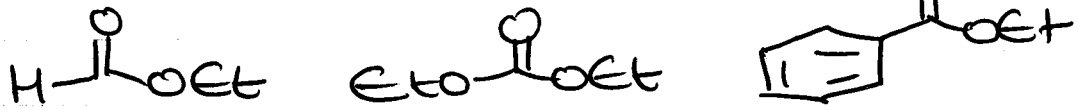
write out mechanism

Crossed CLAISENS

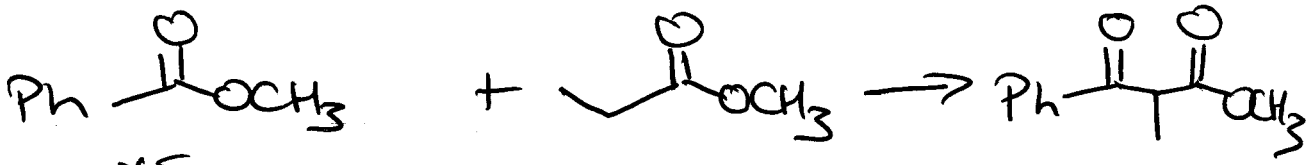
2 esters each w/ 2 αH

↳ (could give 4 β ketoesters)

use 1 ester w/ no αH



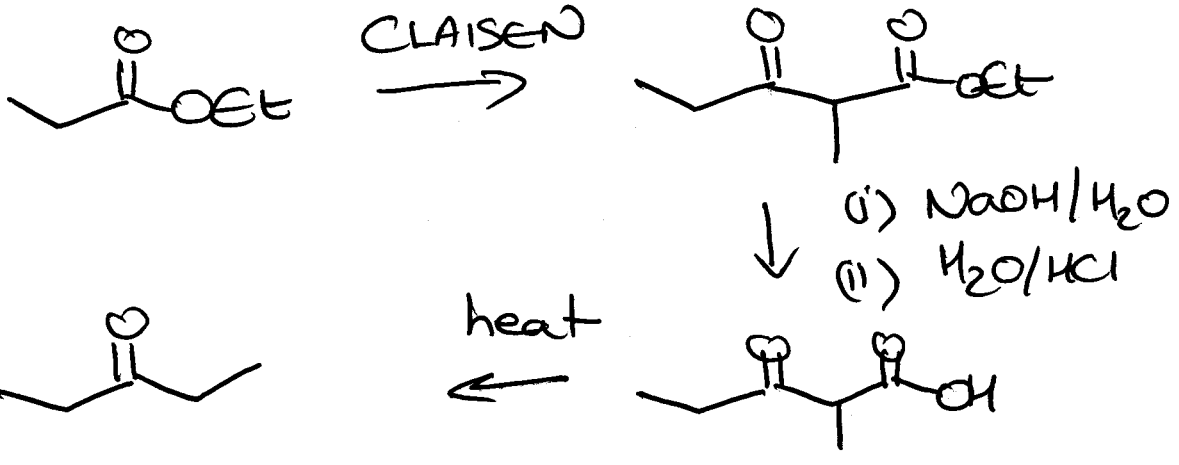
and then used in xs



xs

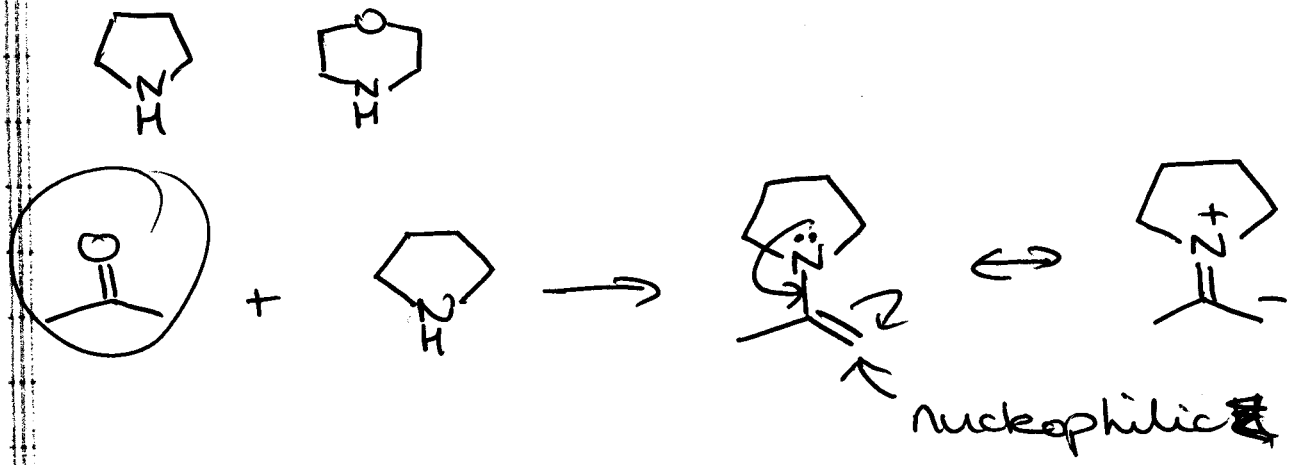
(CANNOT form enolate)

β KETOESTERS

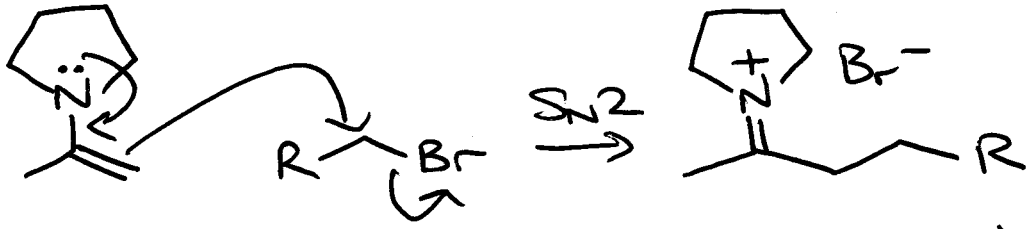


(6) ENAMINES

Rxn C=O w/ secondary amines

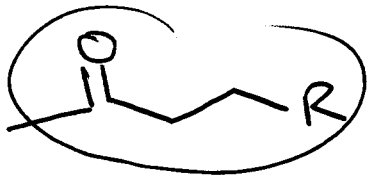


(1) ALKYLATION

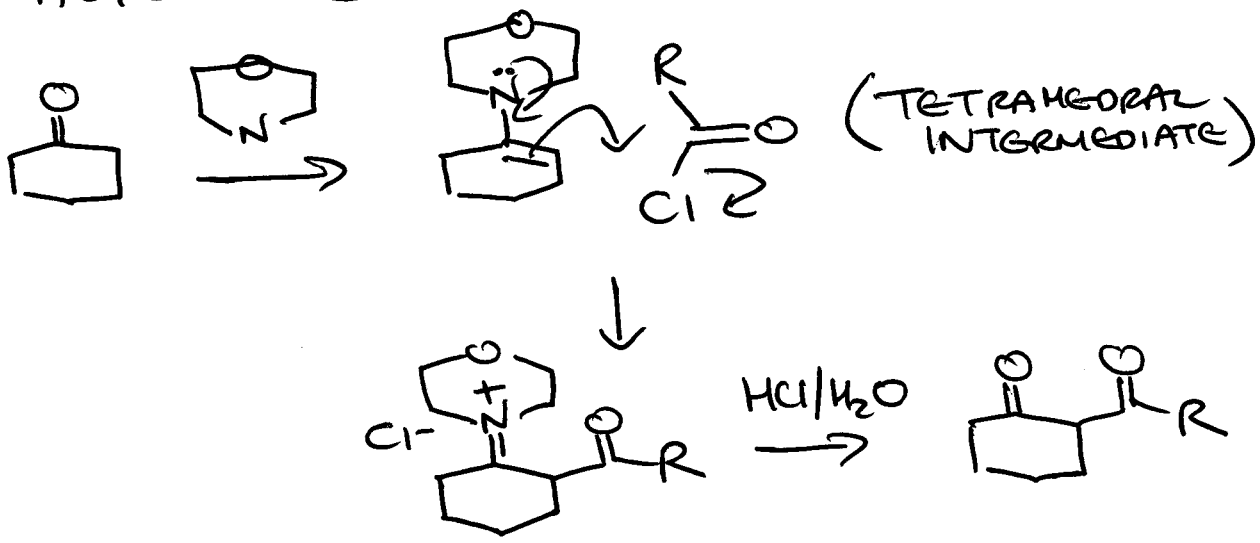


iminium salt

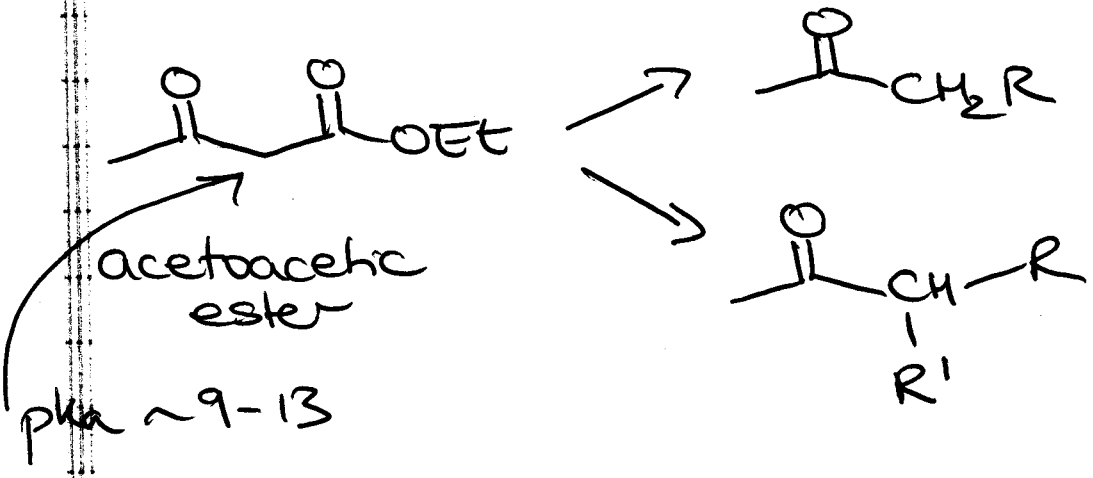
$\downarrow H_3O^+$

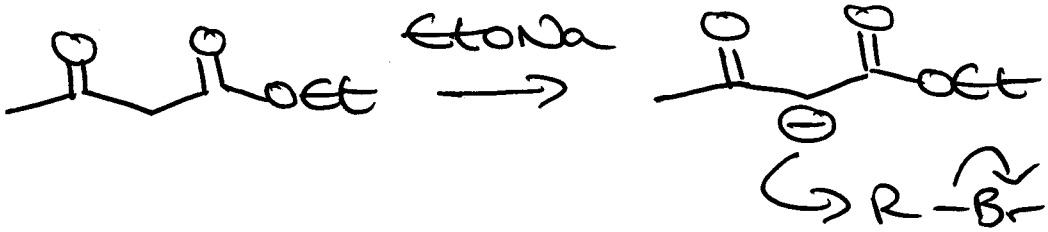


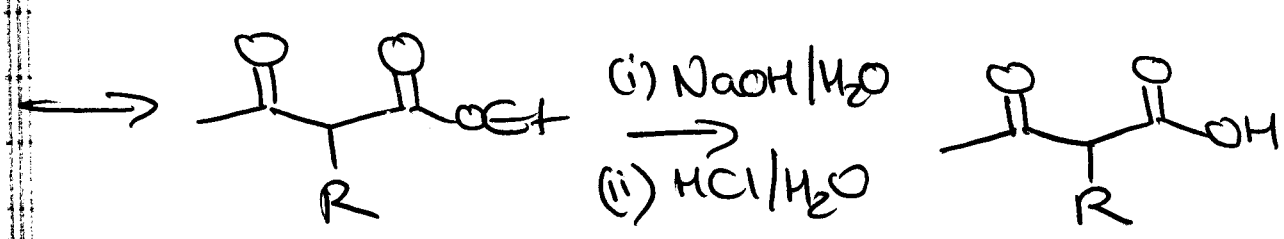
(11) ACYLATION

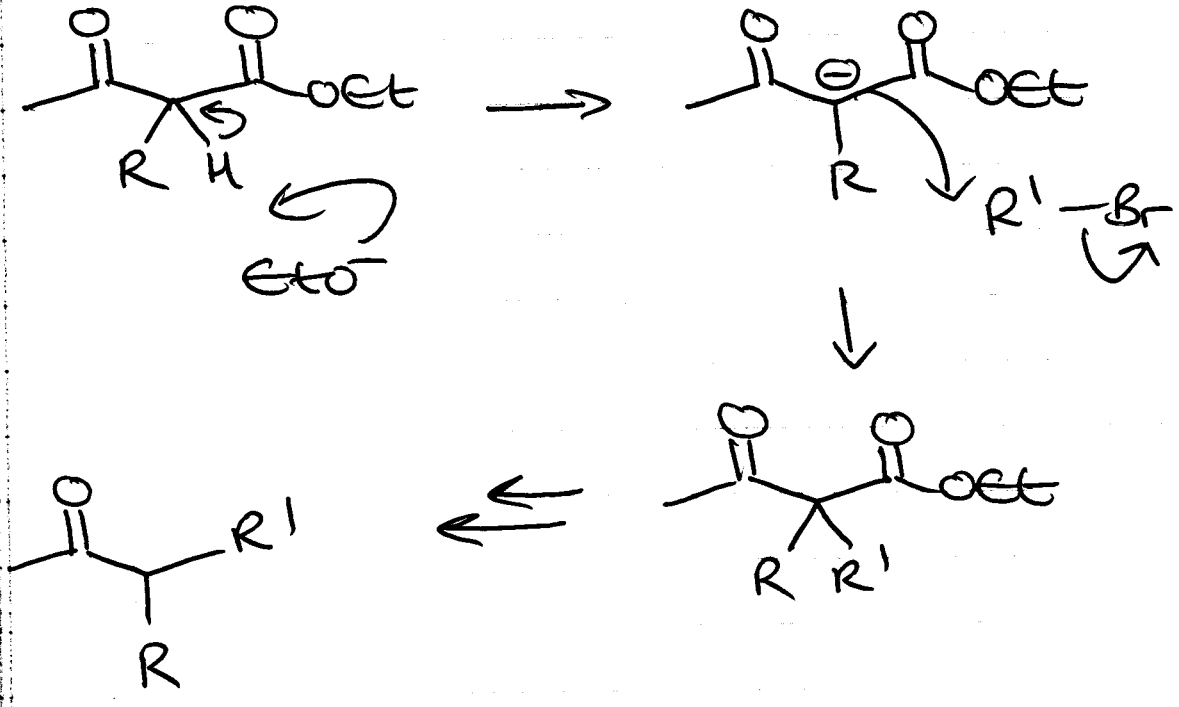


(7) ACETOACETIC ESTER SYNTHESIS

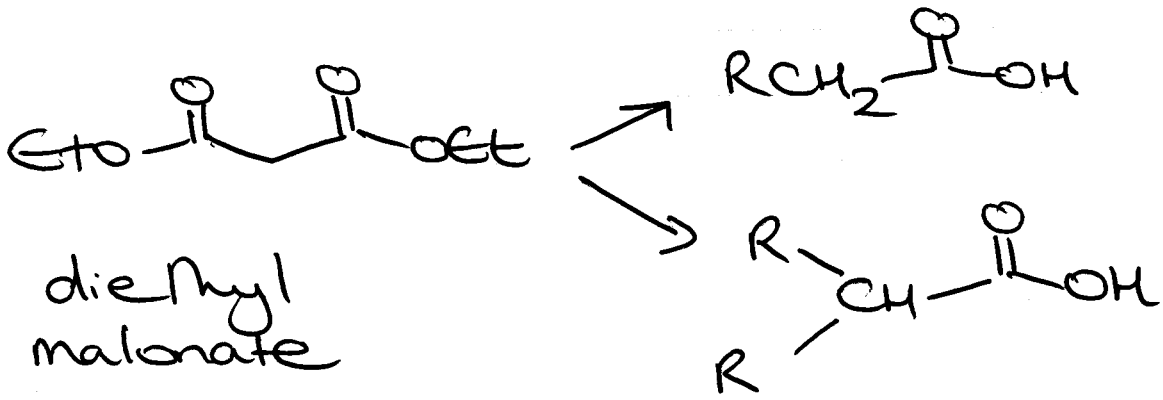








MALONIC ESTER SYNTHESIS

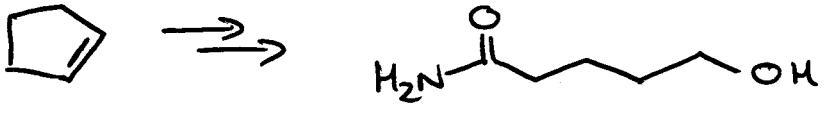


diethyl malonate

LEC (24)

(1) HMK 19.13 – 19.63

(2) SYNTHESIS OF THE WEEK



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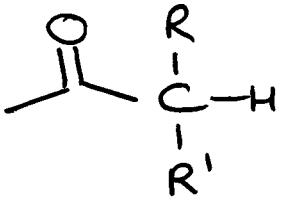
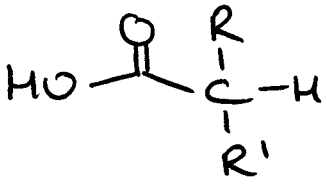
(1) DIECKMANN CONDENSATION
(2) ENAMINES
(3) ACETOACETIC ESTER SYNTHESIS
(4) MALONIC ESTER SYNTHESIS
(5) CONJUGATE ADDITION

Summary

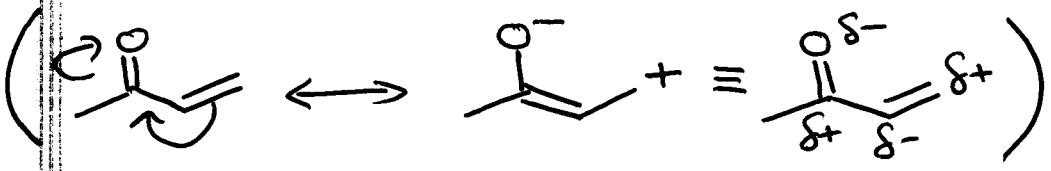


ACETOACETIC ROUTE

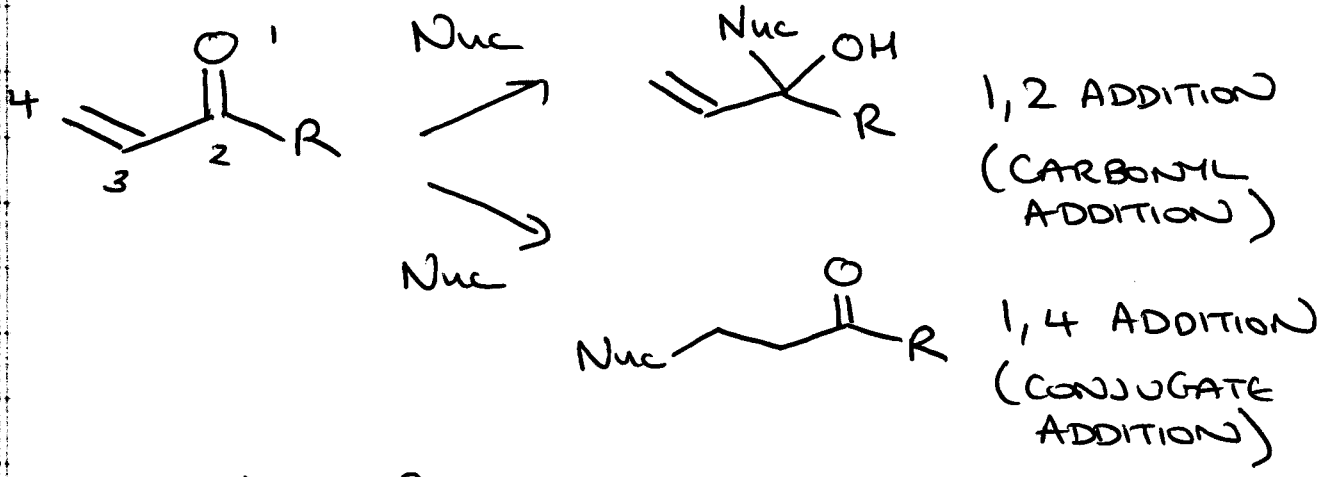


MALONIC ROUTE

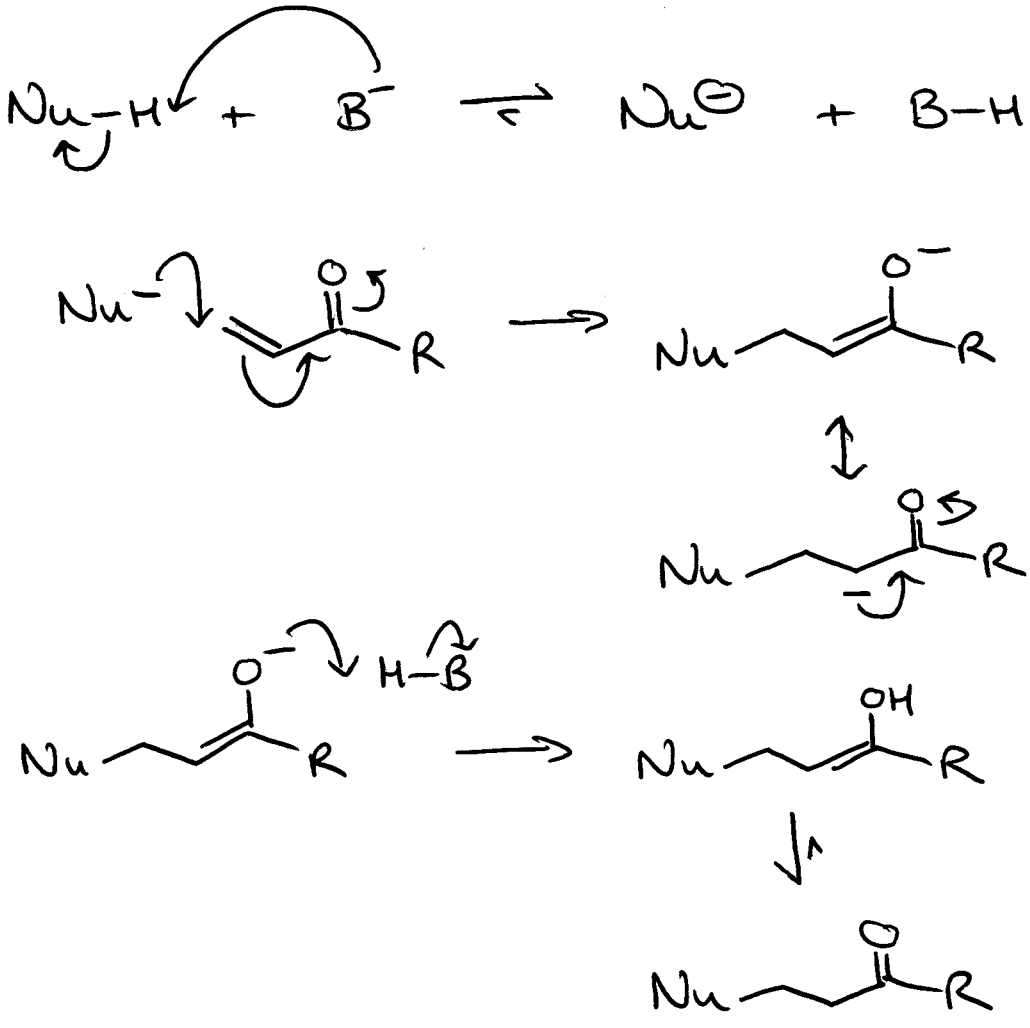
(R or R' may be H)



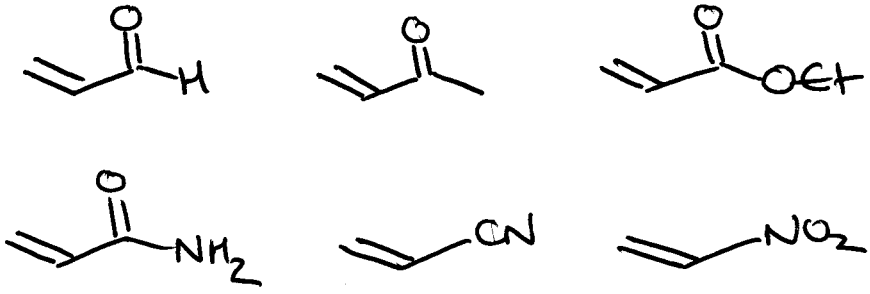
(5) CONJUGATE ADDITION



- Mechanism of CONJUGATE ADDITION

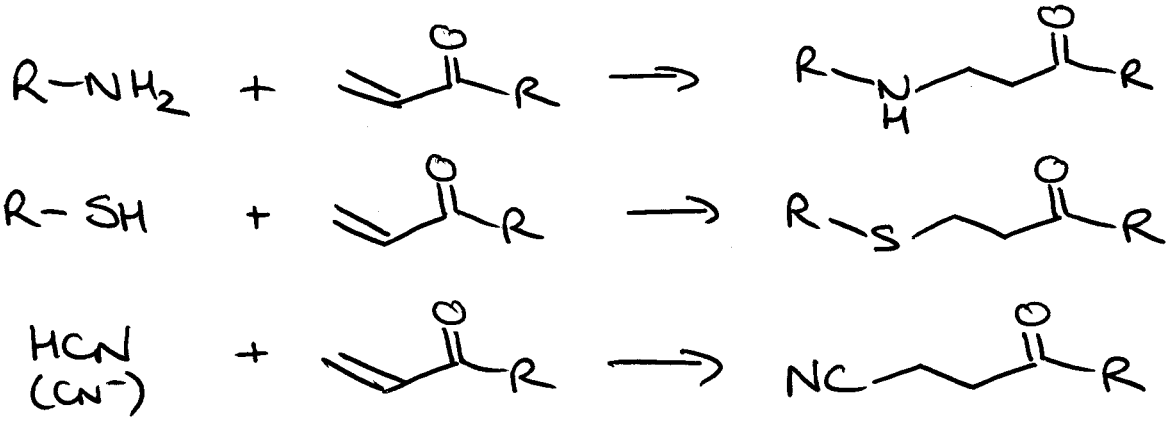


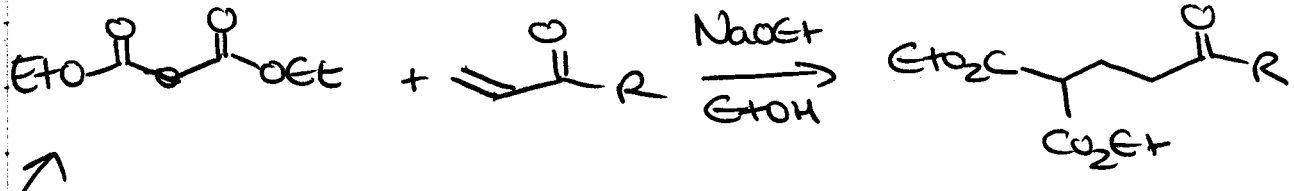
MICHAEL ACCEPTORS



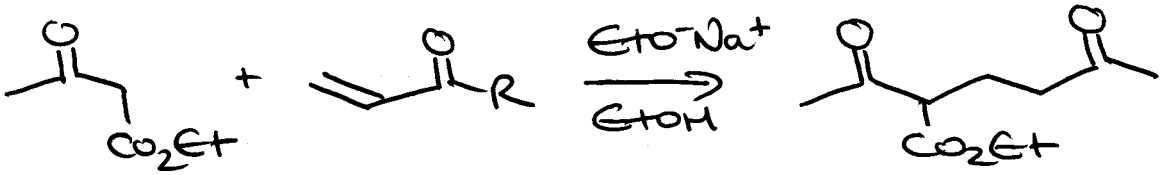
MICHAEL NUCLEOPHILES (WEAK BASES)

CN^-, AMINES, THIOLS, ENOLATES, ENAMINES

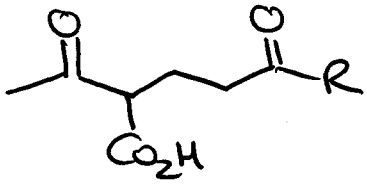




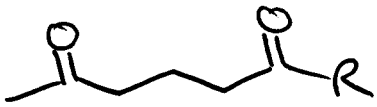
CARBANION = MICHAEL ADDITION



(i) NaOH / H_2O
(ii) HCl / H_2O

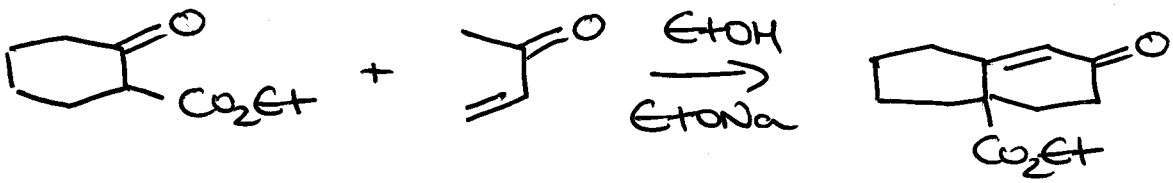


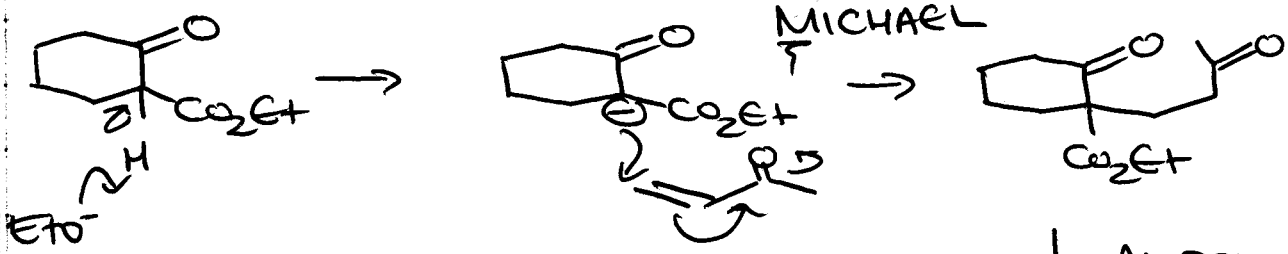
heat



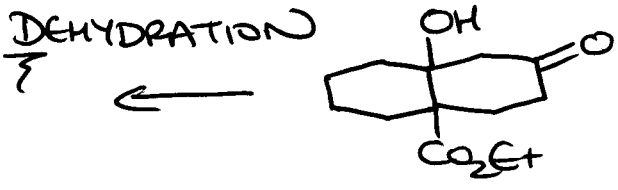
ROBINSON ANNULATION (MAD RXN)

MICHAEL – ALDOL – DEHYDRATION



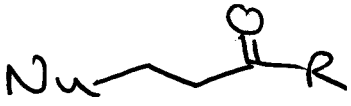


ALDOL

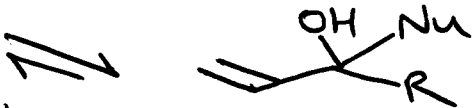


1,2 vs 1,4

CONJUGATE ADDITION



THERMO
C=O stronger
C=C

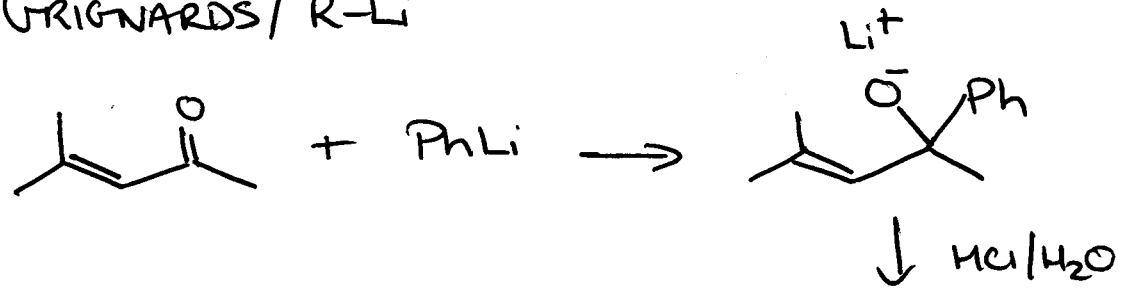


faster,
but reversible w/ nuc that are weak bases

Kinetic

CARBONYL ADDITION

GRIGNARDS / R-Li

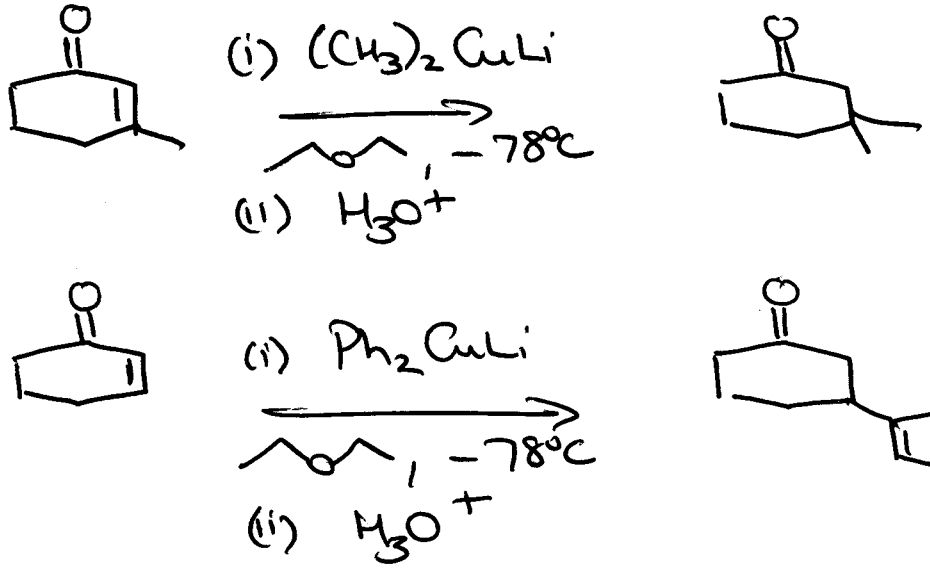


(NON REVERSIBLE C=O ADDITION)

1,2 ADDITION

HOWEVER:

GILMAN (1,4 ADDITION)



LEC (25)

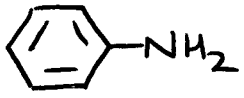
(1) QUIZ MONDAY 15 QUESTION
MULTIPLE CHOICE

---

(1) CONJUGATE ADDITION
(2) AMINES – INTRO
(3) IMINES

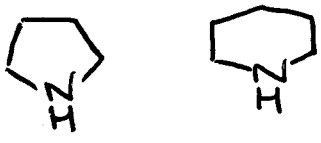
(2) AMINES – NUCLEOPHILIC / BASIC

$R\text{-}NH_2$ R_2NH R_3N R_4N^+
1° 2° 3° 4°

aromatic  aniline

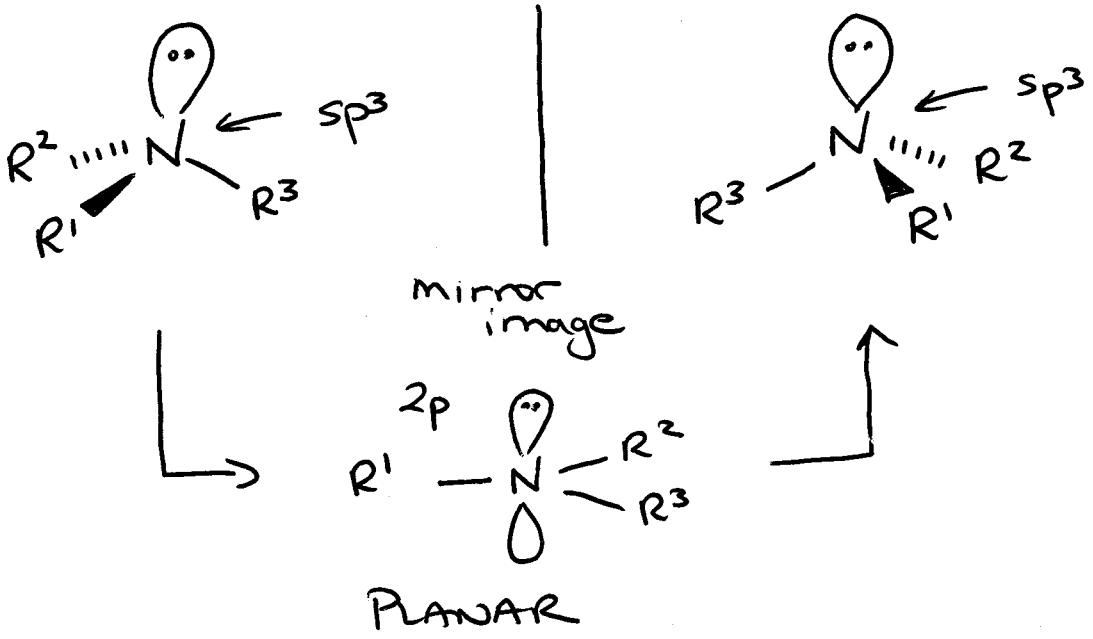
heterocyclic –

aromatic 

non aromatic 

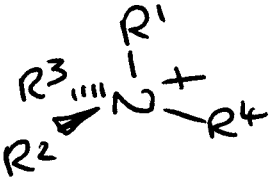
- Nomenclature X

- CHIRALITY



PYRAMIDAL INVERSION
NH_3 at rt, 2×10^{11} s^{-1}

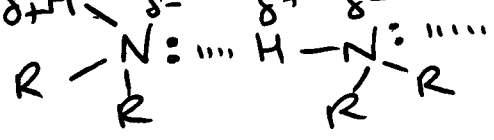
Cannot resolve.

Quat ammonium ions 

can be resolved.

- Physical Prop

1°, 2° polar H bonds



Spectroscopy X

– Basicity

1° — 3° alkyl amines

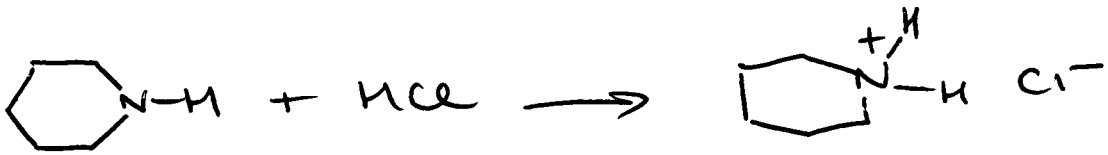
$R_3\overset{+}{N}-H + H_2O \rightleftharpoons R_3N + H_3O^+$

pka ~ 10–11

pka ~ 4.5

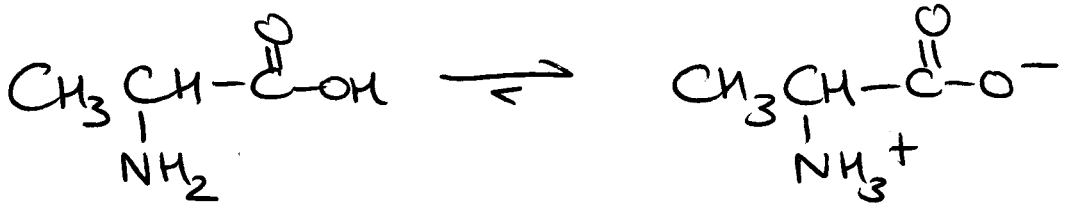
REACTIONS w/ ACIDS

AMINE + STRONG ACID (HCl) ⟶ AMINE–H^+ (Cl^-)



AMINO ACIDS

ZWITTERION



AMINES

- Alkylation NH_3
- Azides
- Tiffereau-Demjanov
- Hofmann Elimination
- Cope Elimination

LEC (26)

(1) FINAL MONDAY 8th 3–6 pm
A–K CS 76
L–Z MATH SCIENCE 4000A

(2) CNSI LECTURE
Steve Quake - Caltech
"BIOLOGICAL LARGE SCALE INTEGRATION" by FRIDAY

(3) HMK: 22.5–8, 10, 11, 14, 15, 29, 32–34, 36–39, 49–52, 54

(4) RESEARCH

---

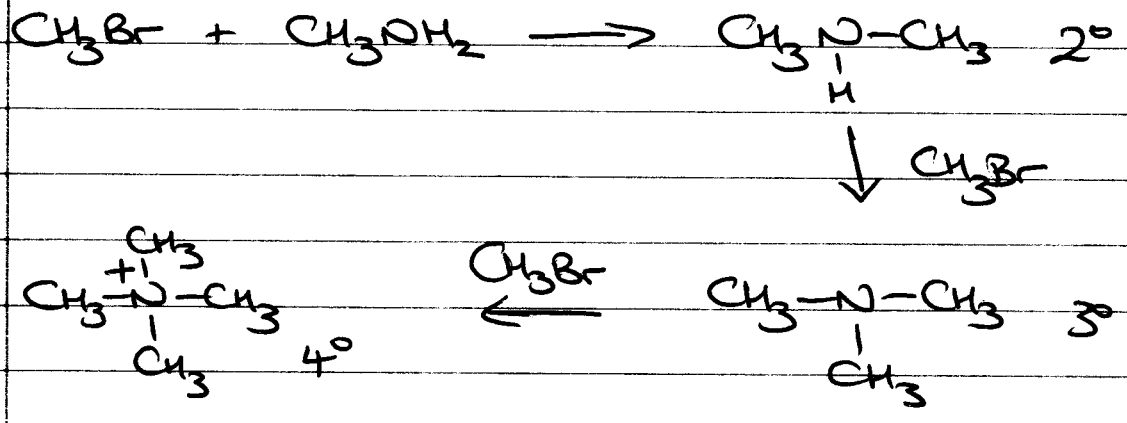
(1) BASICITY
(2) RXNS w/ ACIDS
(3) ALKYLATION OF AMINES
(4) ALKYLATION OF AZIDE
(5) NITROUS ACID
(6) ELIMINATION RXNS

---

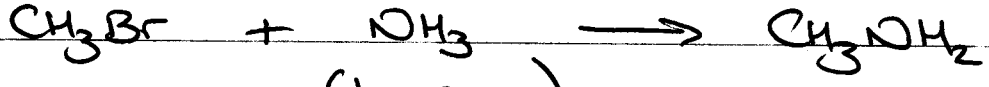
(3) ALKYLATION

$$CH_3Br + NH_3 \xrightarrow{SN2} CH_3NH_2 + HBr$$

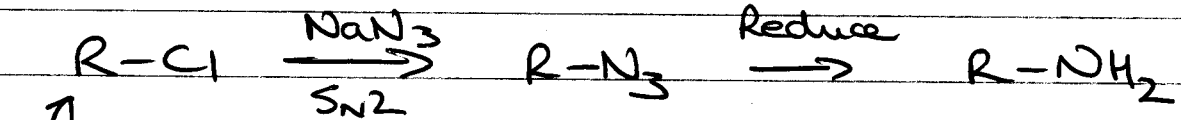
1° amine



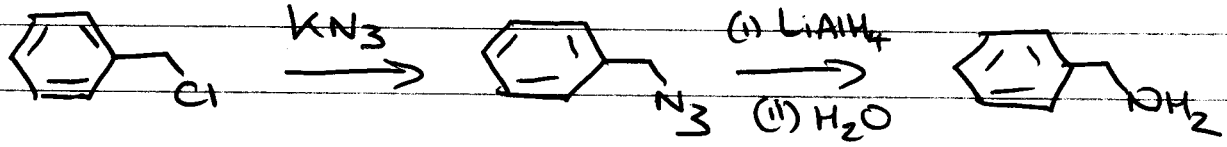
mix of products



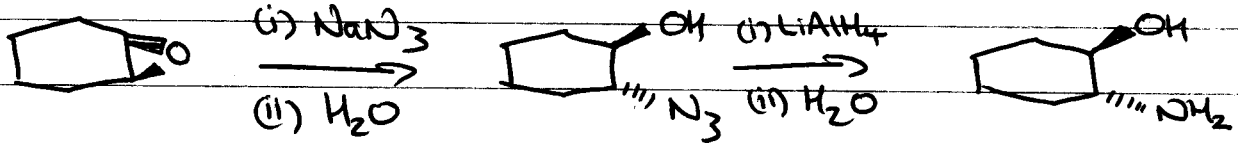
(4) ALKYLATION of AZIDE



1°/2°



OPEN EPOXIDES

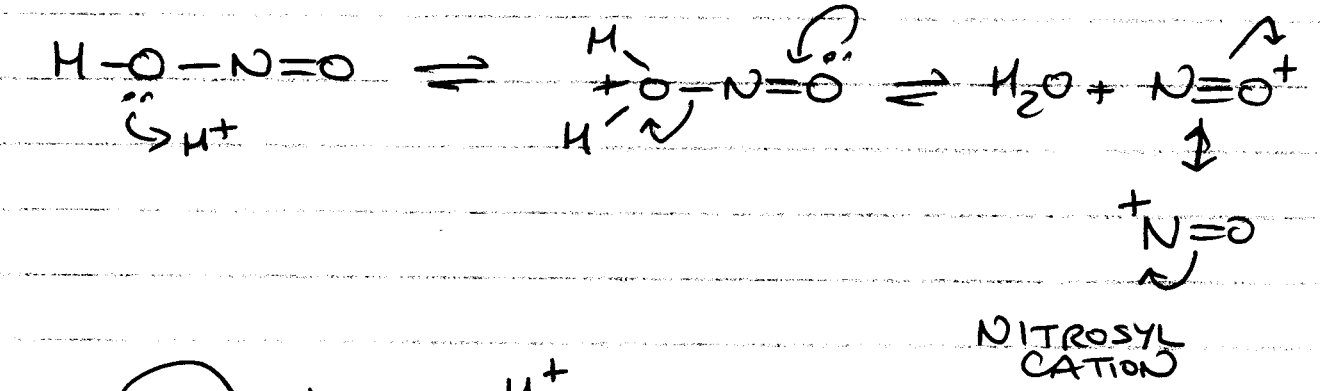


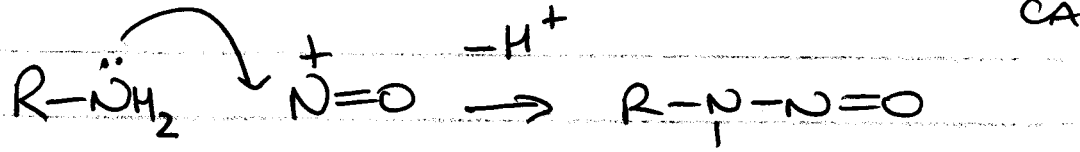
(5) NITROUS ACID

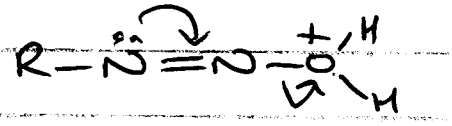
$$R-NH_2 \xrightarrow[HCl,\ 0^\circ C]{NaNO_2} \text{Product Mixture}$$

$$NaNO_2 + HCl \longrightarrow HNO_2 + NaCl$$

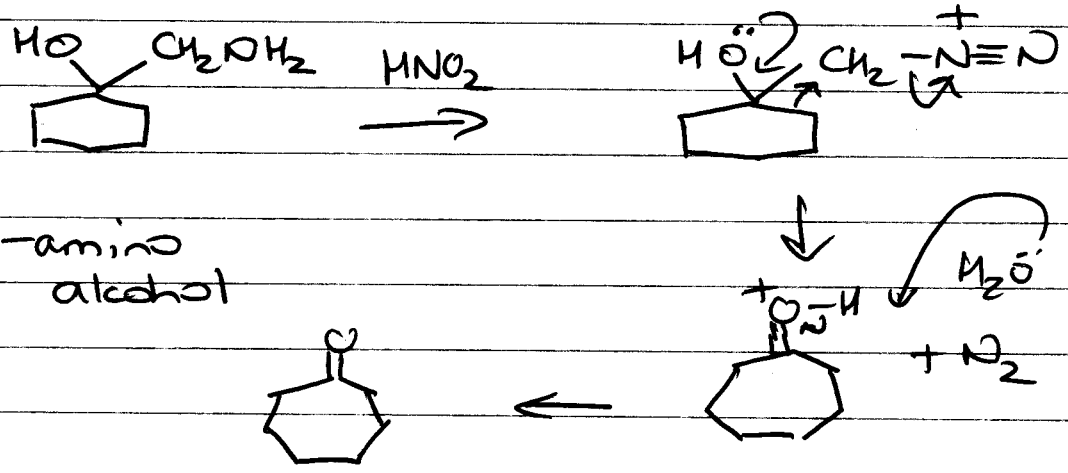
nitrous acid



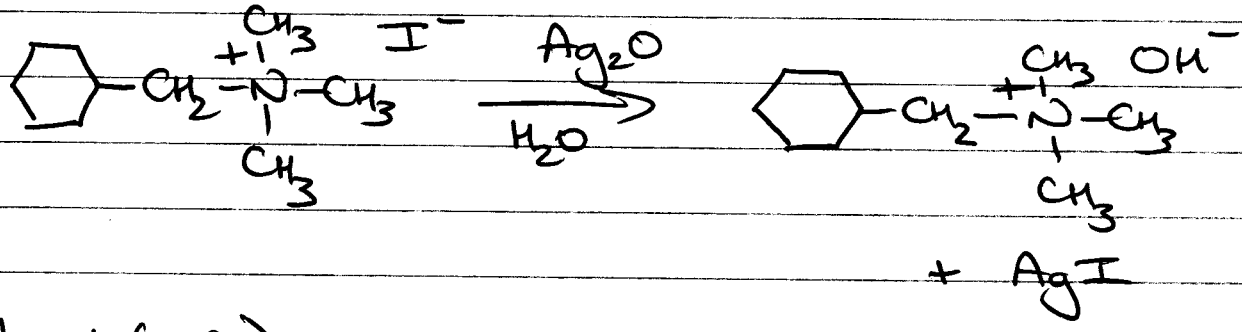




TIFFENEAU-DEMJANOV RXN

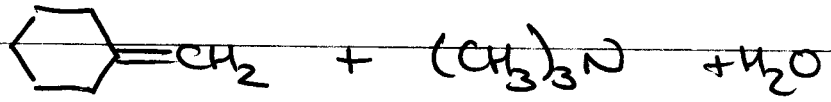


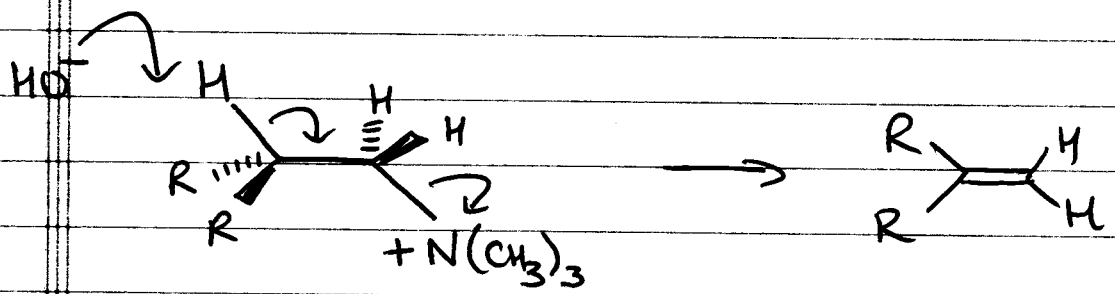
(6) ELIMINATION



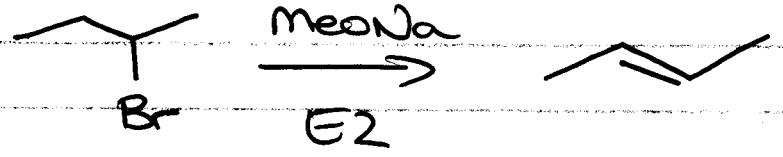
heat (150°C)

HOFMANN ELIMINATION

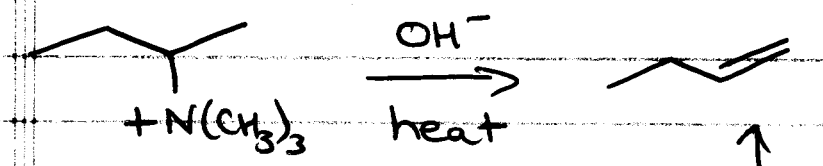




- β-PROTON
- CONCERTED
- ANTI- RELATIONSHIP



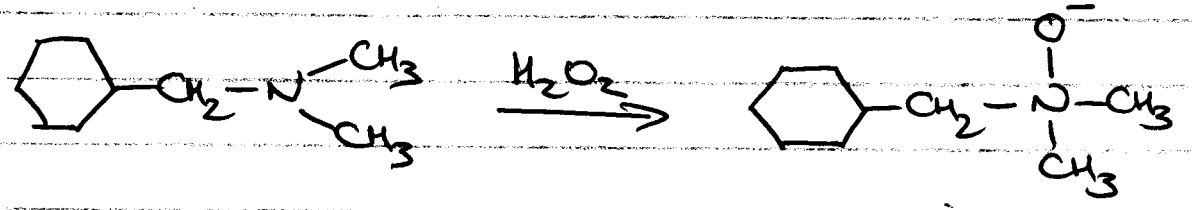
ZAITSEV



HOFMANN

Least sub alkene

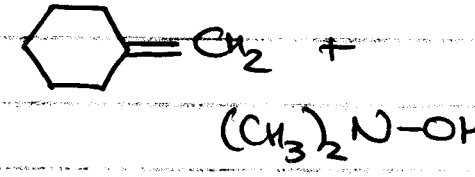
STERICS — least hindered β-H



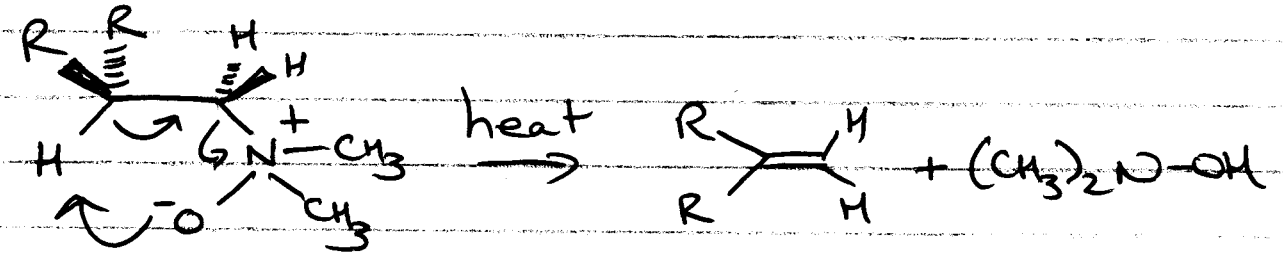
amine oxide

COPE ELIMINATION

heat, 150°C

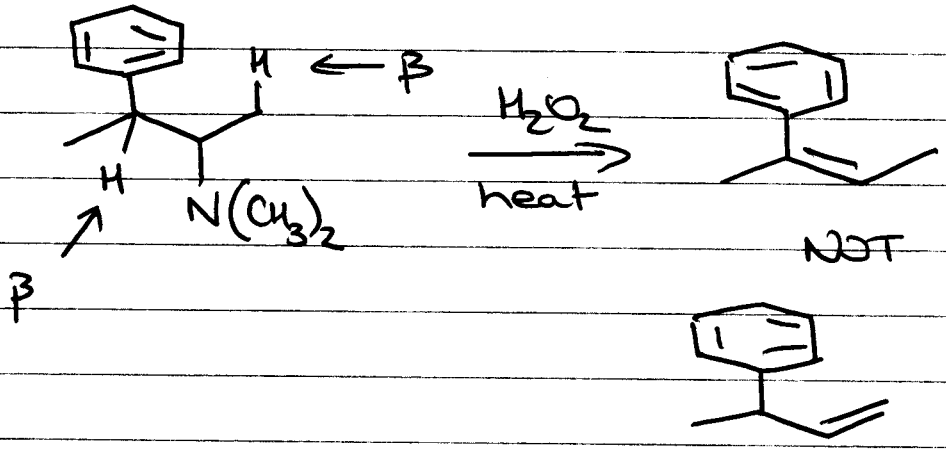


β-PROTON / CONCERTED / SYN



If 2 or more β-H ⇒ little selectivity

UNLESS CONJUGATED



LEC (27) REVIEW

(1) FINAL MONDAY 3–6pm — STAMPS
A–K CS76
L–Z MATH SCIENCE 4000A

(2) ALL EXTRA CREDIT BY MIDNIGHT TONIGHT

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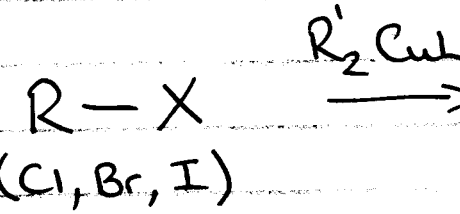
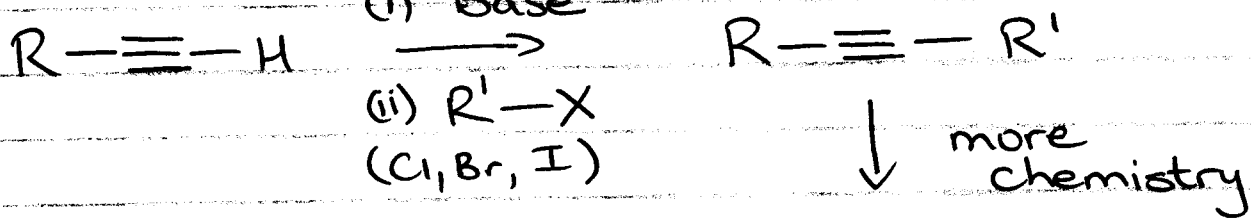
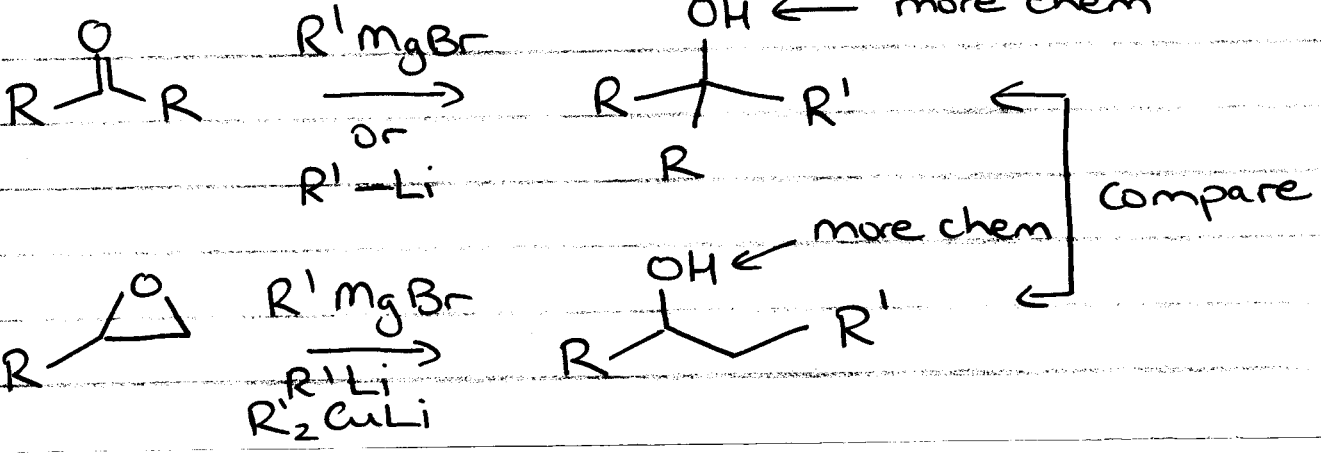
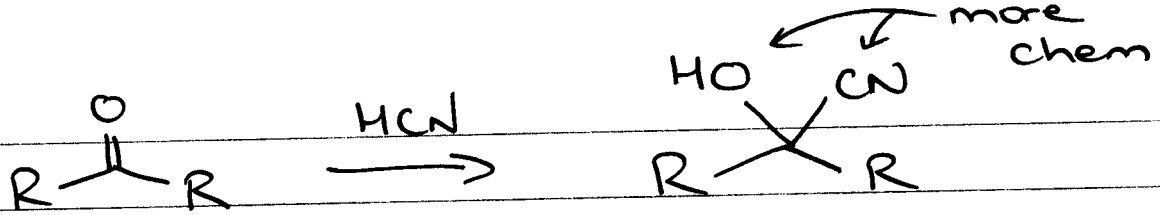
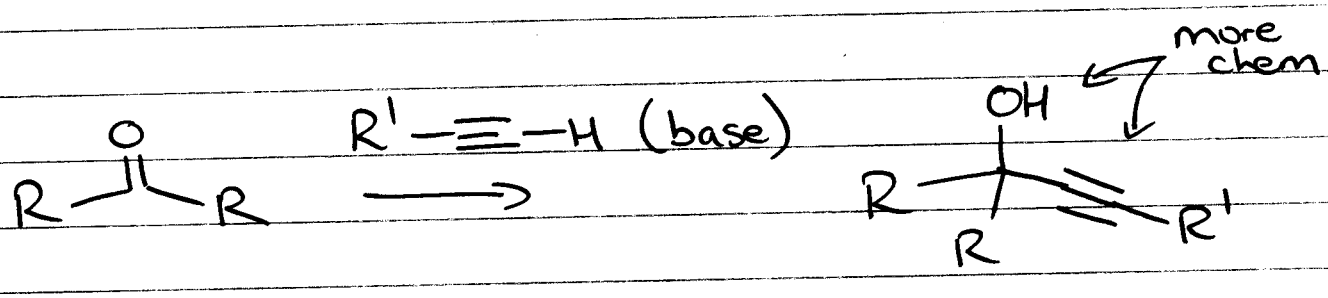
(1) C–C BOND FORMATION
(2) FG-I OVERVIEW (not comprehensive)

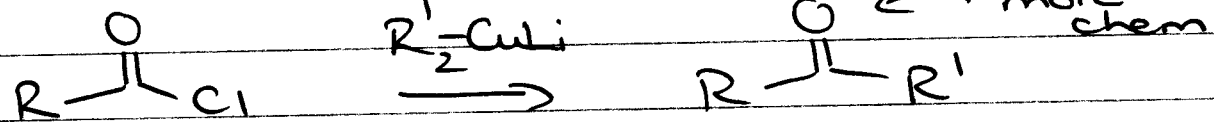


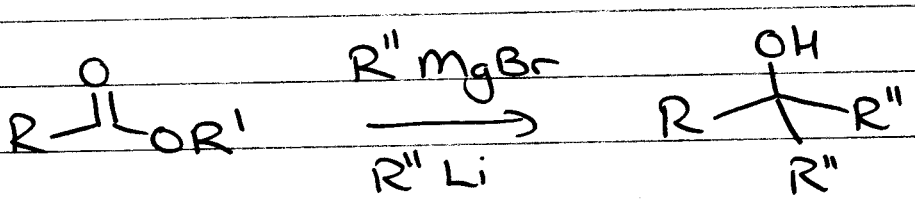


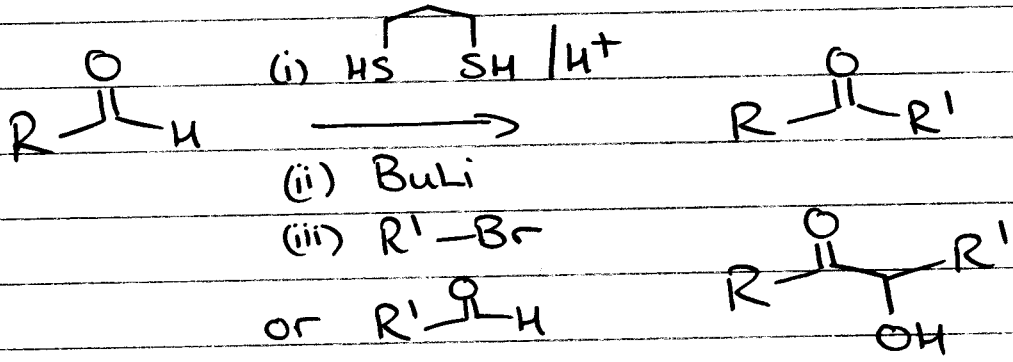




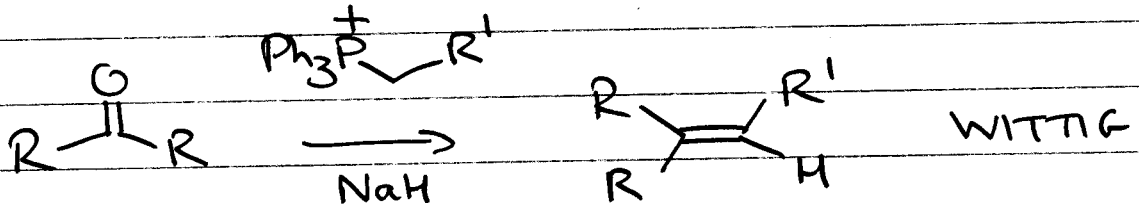




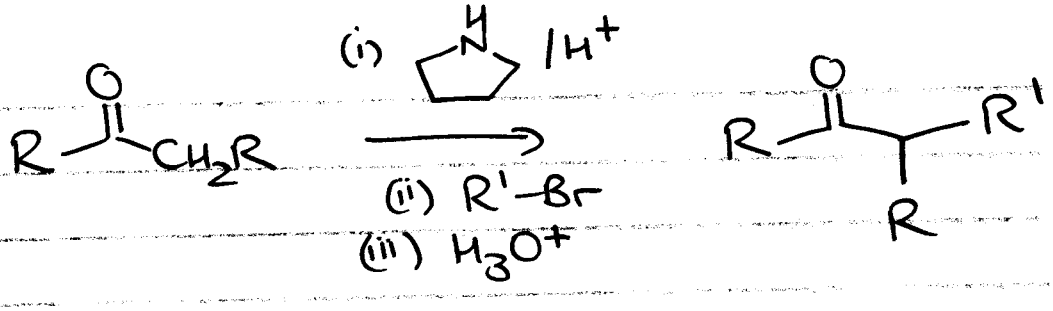


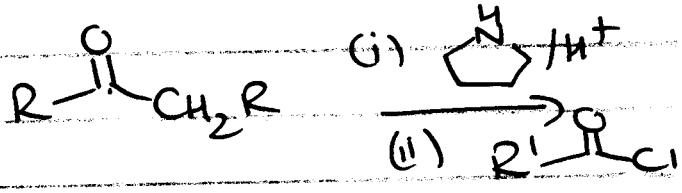


α-HYDROXY KETONE

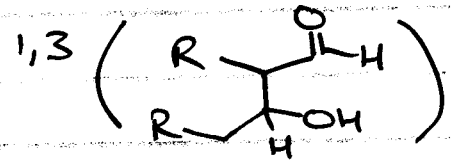


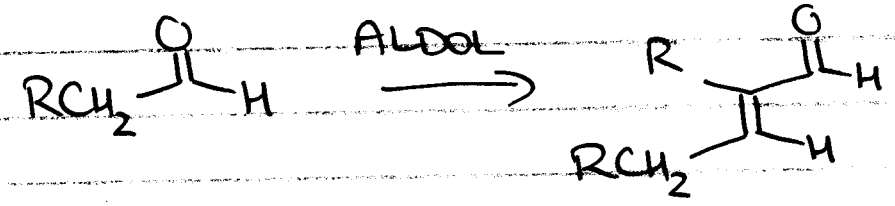
WITTIG



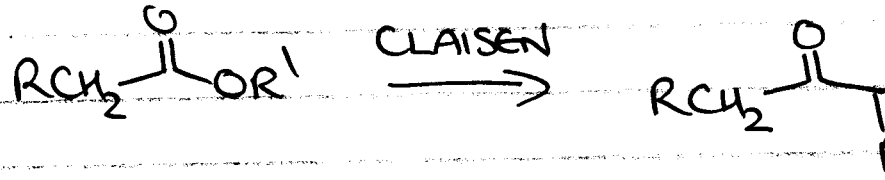


1,3 DIKETONE

1,3 

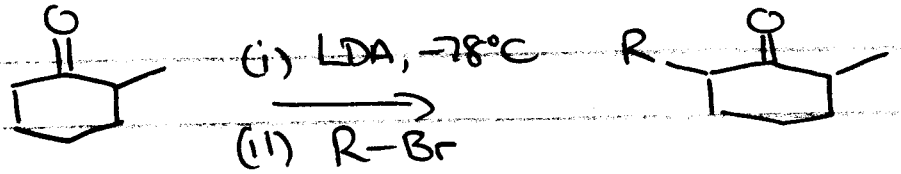


α–β unsat aldehyde or ketone

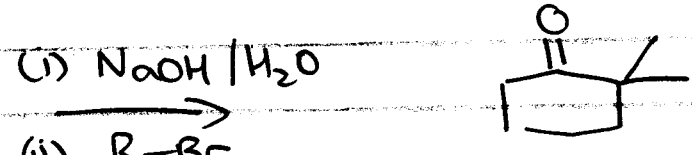


1,3

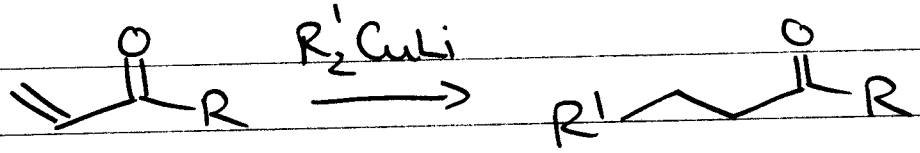
β–KETO ESTER

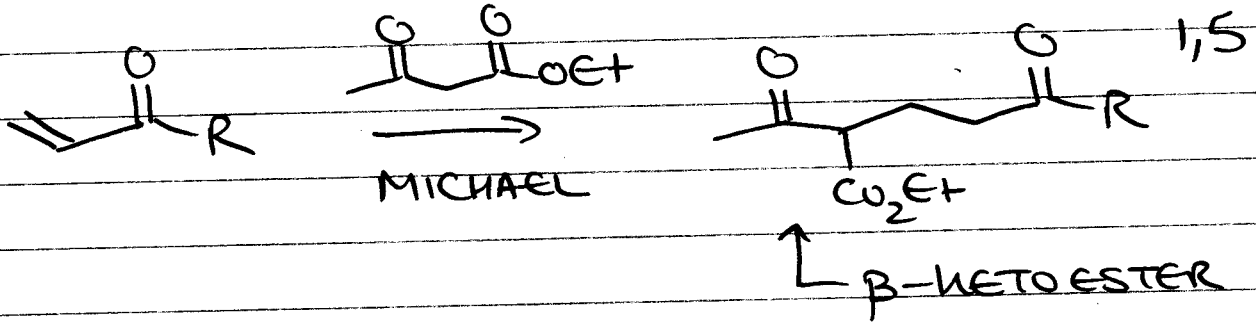


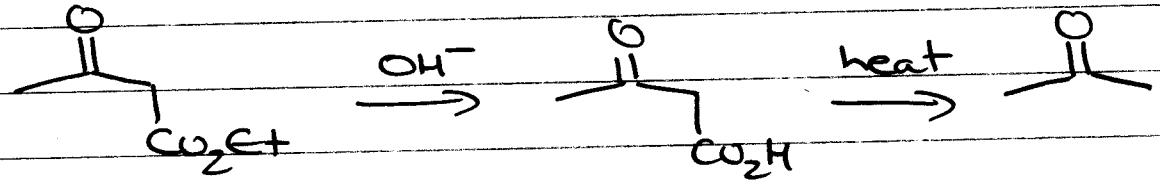
KINETIC



THERMO

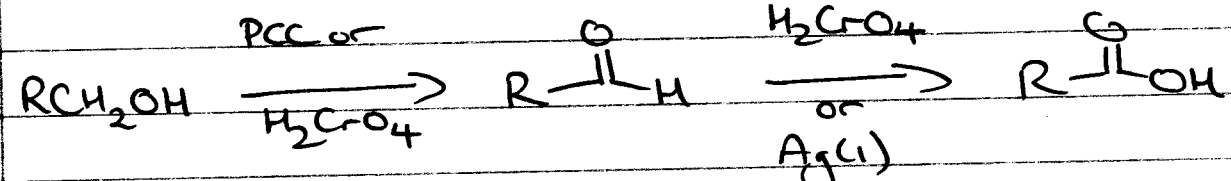


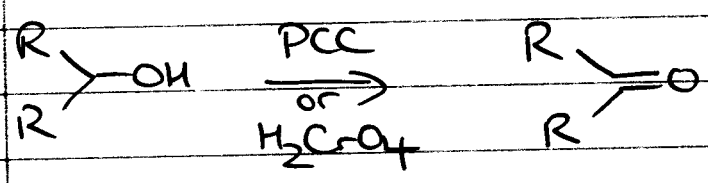


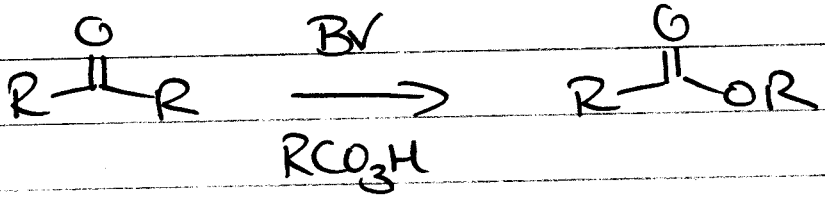


FUNCTIONAL GROUP INTERCONVERSION

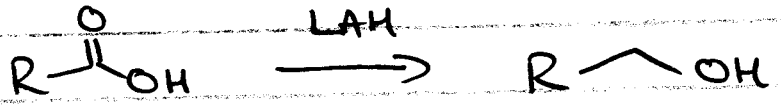
OXIDATION

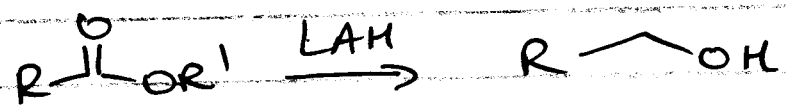


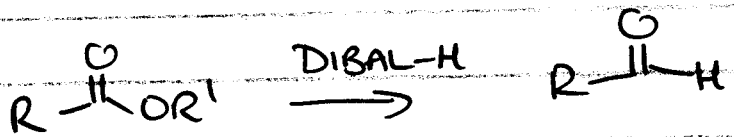


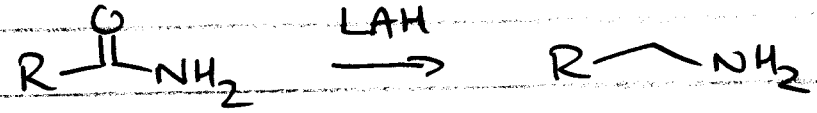


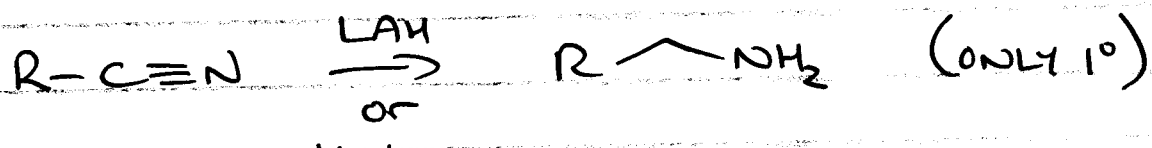
REDUCTIONS

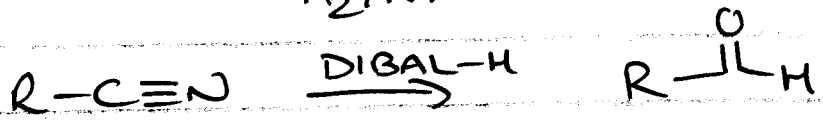

LAH

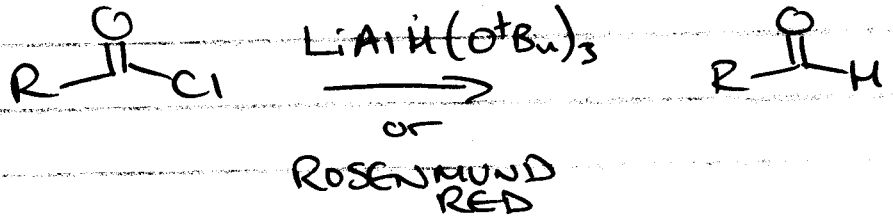

LAH

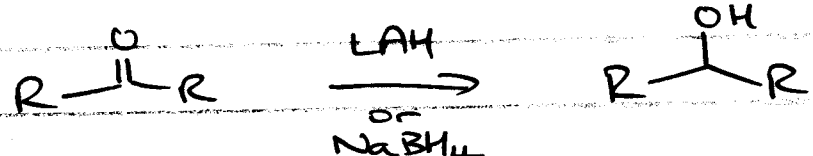

DIBAL-H

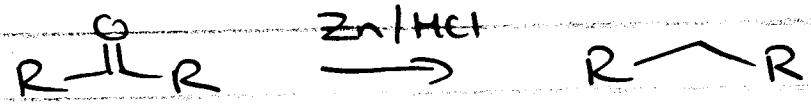

LAH

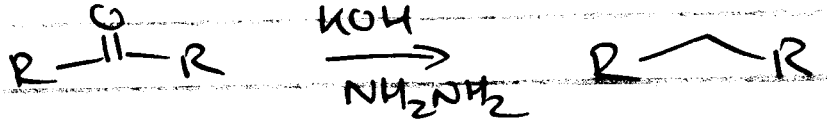

LAH
or
H2/Ni
(ONLY 1°)

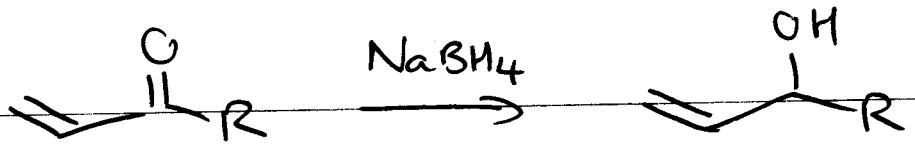

DIBAL-H

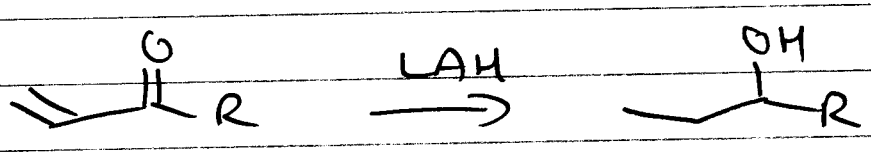

LiAlH(OtBu)3
or
ROSENMUND
RED

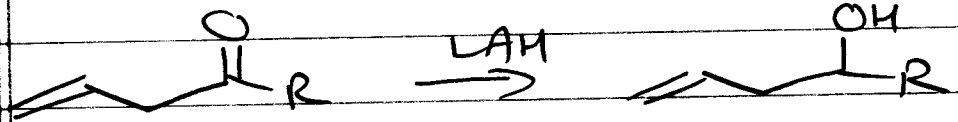

LAH
or
NaBH4

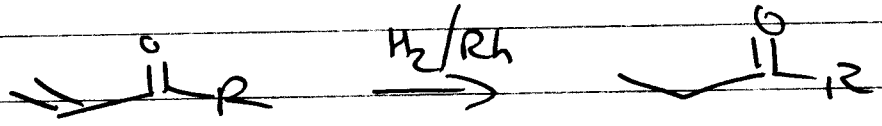

Zn/HCl

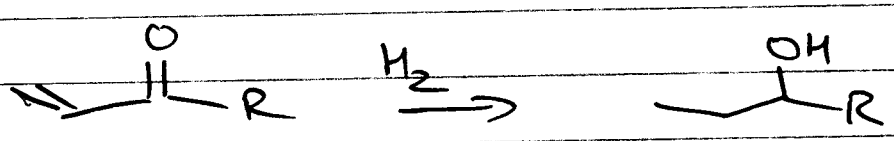

KOH
NH2NH2

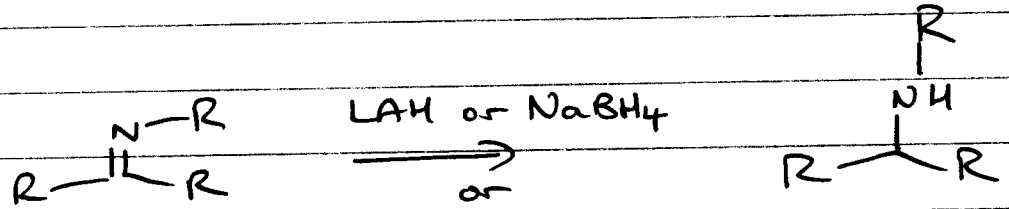

O
R
NaBH4
OH
R

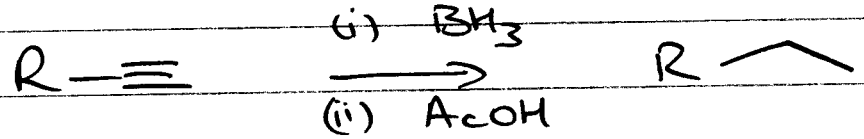

O
R
LAH
OH
R

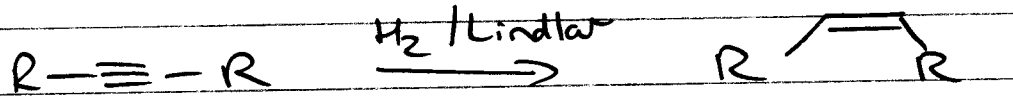

O
R
LAH
OH
R

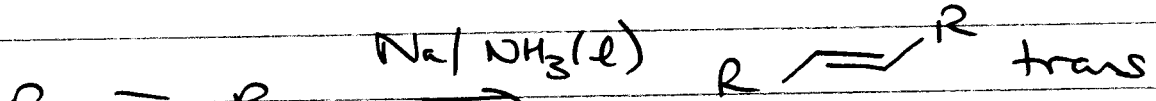

O
R
H2/Rh
O
R

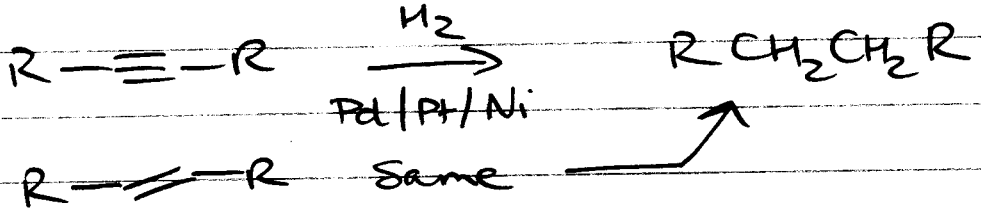

O
R
H2
Pt/Ni
OH
R

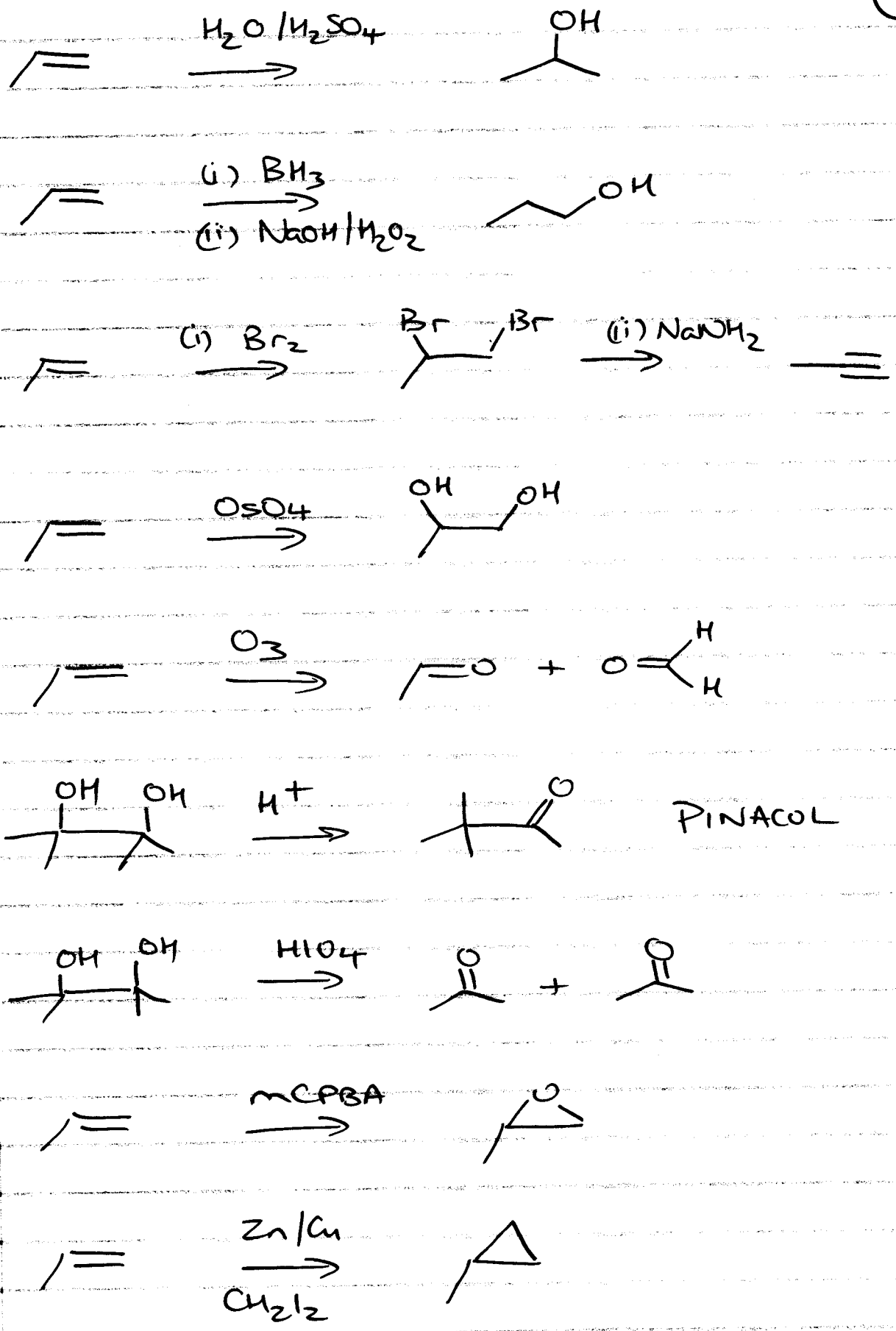

N
R
R
R
LAH or NaBH4
or
Ni/H2
R
NH
R
R

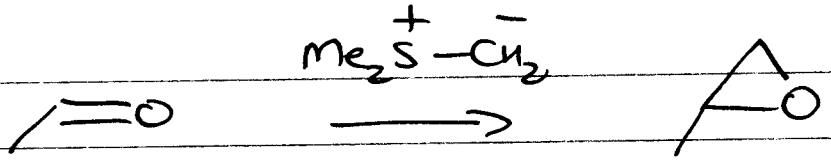

R
(i) BH3
(ii) AcOH
R

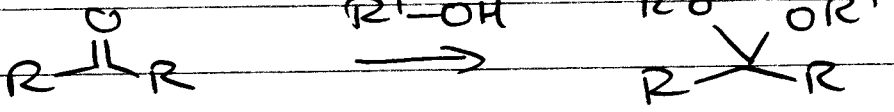

R
R
H2/Lindlar
R
R
cis

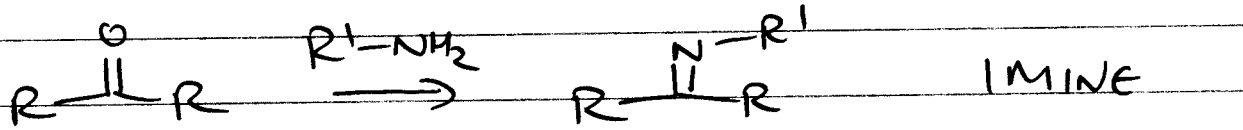

R
R
Na/NH3(l)
R
R
trans

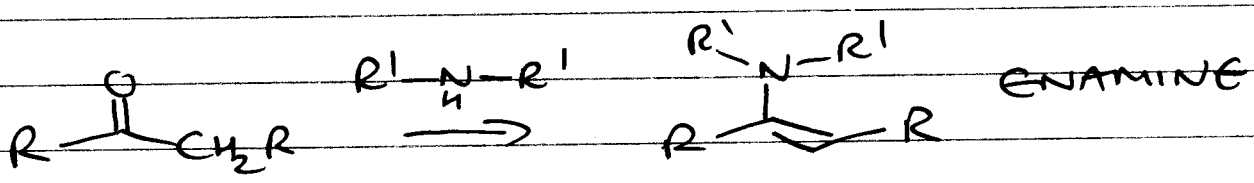

R
R
H2
Pd/Pt/Ni
R
R
Same
RCH2CH2R


H2O / H2SO4
OH
(i) BH3
(ii) NaOH / H2O2
OH
(i) Br2
Br
Br
(ii) NaNH2
OsO4
OH
OH
O3
O
O
H
H
OH
OH
H+
O
PINACOL
OH
OH
HIO4
O
O
mCPBA
O
Zn / Cu
CH2I2






IMINE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