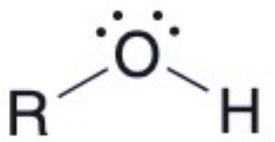
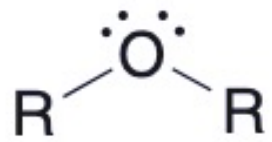
Lesson 12 & 13
Alcohols, Ethers, Epoxides



alcohol



ether



epoxide

Alcohols: Properties & Naming

PROPERTIES

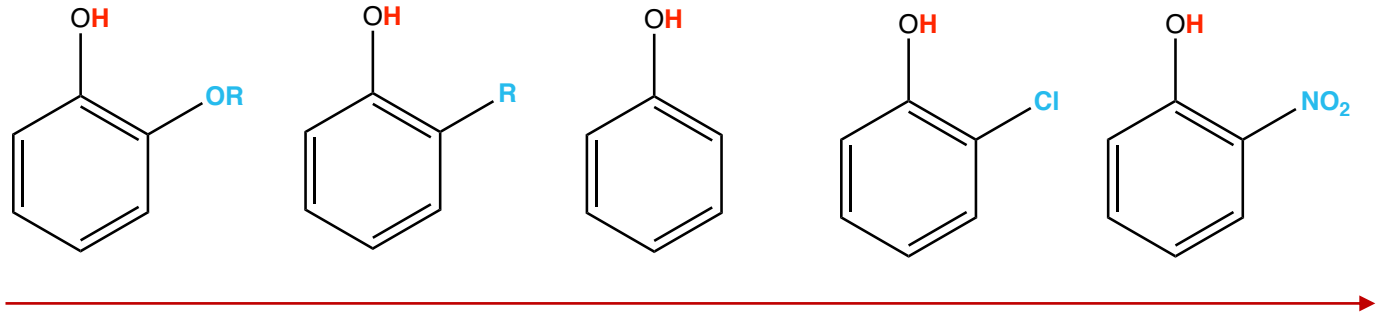
- Weakly acidic
  - Conjugation increases acidity
  - EWGs stabilize conjugate base
  - EDGs destabilize conjugate base
- Polarity
  - Polar OH Group
  - Nonpolar R Group
    - R group length inhibits polarity
- Intermolecular H-Bonds
- H-Bonds with other protic solvents

NOMENCLATURE

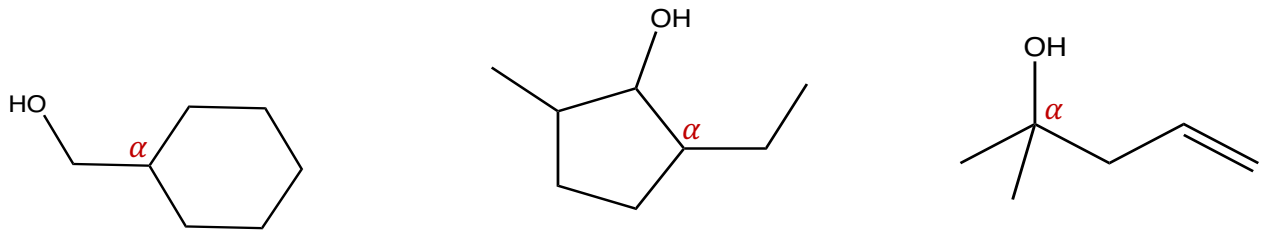
Alcohols > Alkene > Alkynes > Halogens

PRIORITY

- R Groups on α carbon determines 1°/2°/3°







cyclohexylmethanol

1° alcohol

2-ethyl-5-methylcyclopentan-1-ol

2° alcohol

2-methylpent-4-en-2-ol

3° alcohol

Alcohols: Outline

(1) **Review**: Mildly Oxidizing π Bonds

- $KMnO_4$, NaOH, cold – *syn diols*
- 1. OsO_4 2. NMO or t-BuOK – *syn diols*
- mCPBA, H_3O^+ – *trans diols*
- 1. BH_3-THF 2. NaOH, H_2O_2 – *Anti-Mark. OH, syn H, OH*
- 1. $Hg(OAc)_2$, H_2O 2. $NaBH_4$ – *Mark. OH (no rearrange)*
- H_2O, H_2SO_4 – *Mark. of OH (rearrange possible)*

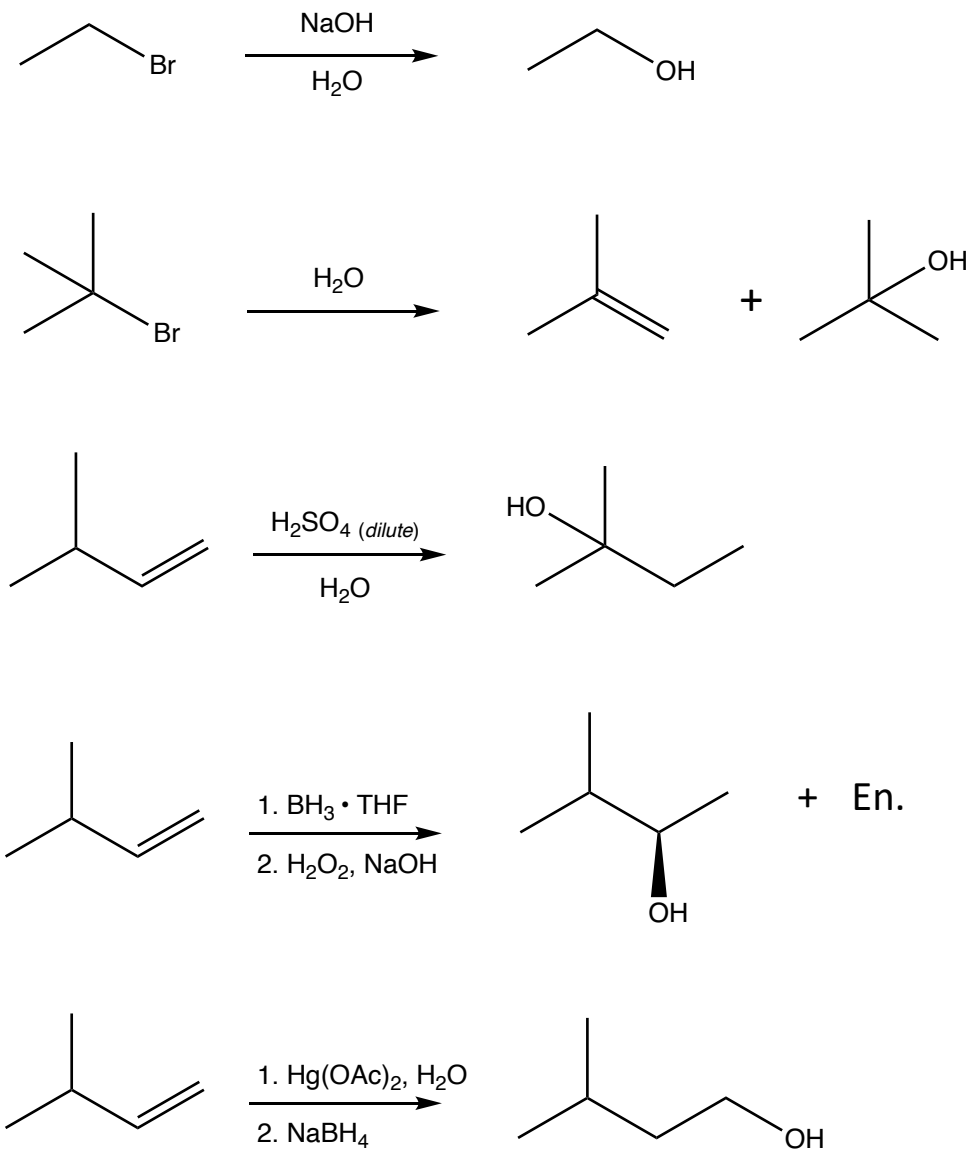
(2) **Review**: Substitution of Alkyl Halides

- ^-OH is strong nucleophile/base
  - SN2 for Me / 1° substrates
  - E2 for 2° / 3° substrates
- H_2O is weak nucleophile/base
  - SN1/E1 for 2° / 3° substrates

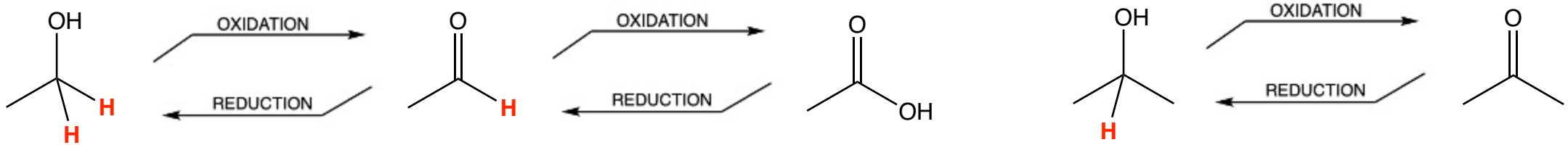
(3) **NEW**: Reducing & Oxidizing Agents

(4) **NEW**: Grignard Reagents

(5) **NEW**: Protecting Groups

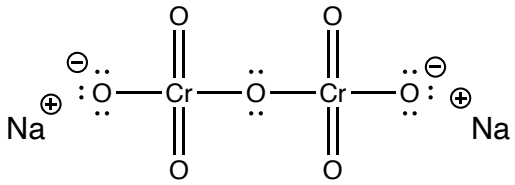


Alcohols: REDOX AGENTS



Oxidizing Agents

JONES



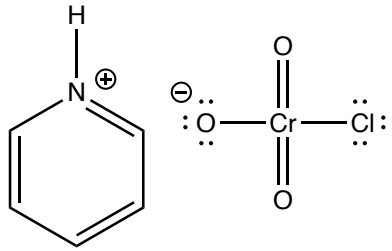
Strong OXID. Agent

1° ——> COOH

2° ——> ketone

Benzylic H —> COOH

PCC



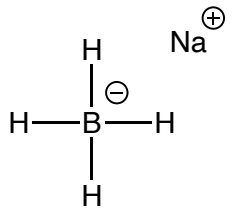
Mild OXID. Agent

1° ——> aldehyde

2° ——> ketone

Reducing Agents

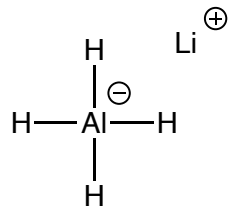
$NaBH_4$



Mild RED. Agent

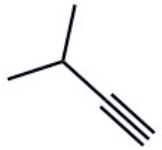
- aldehyde / ketone

LAH



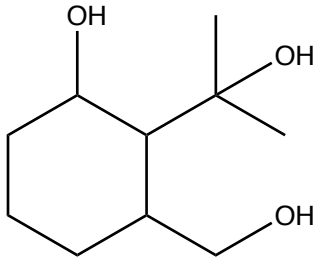
Strong RED. Agent

- aldehyde / ketone
- COOH / esters
- amide / CN / NO_2



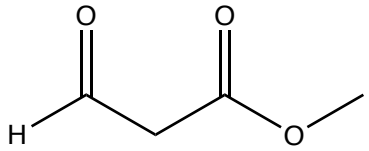
1. $(sia)_2BH$

2. H_2O_2, NaOH
3. $NaBH_4$ / EtOH



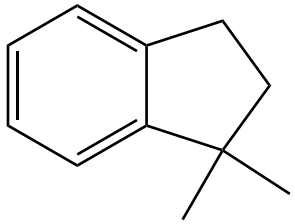
PCC

CH_2Cl_2



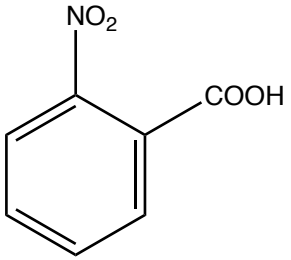
$NaBH_4$

EtOH



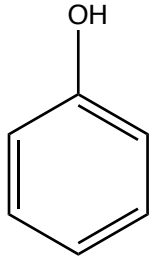
$Na_2Cr_2O_7$

H_2O, H_2SO_4



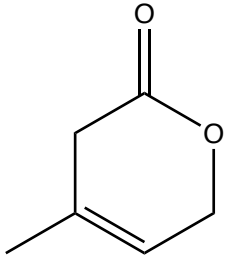
1. $LiAlH_4$

2. H_2O



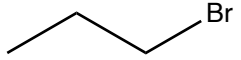
CrO_3, H_2SO_4

H_2O



1. $LiAlH_4$

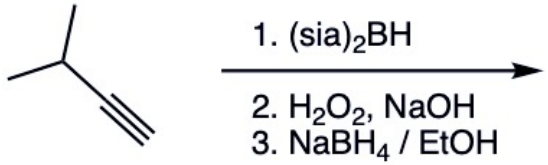
2. H_2O



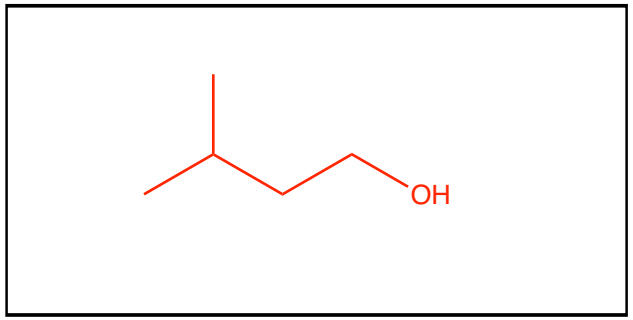
1. NaOH, H_2O

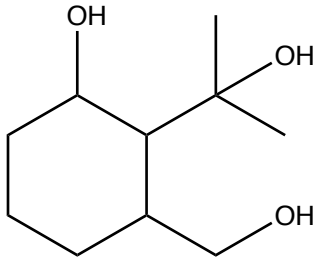
2. $(COCl)_2$, DMSO

ANSWER KEY



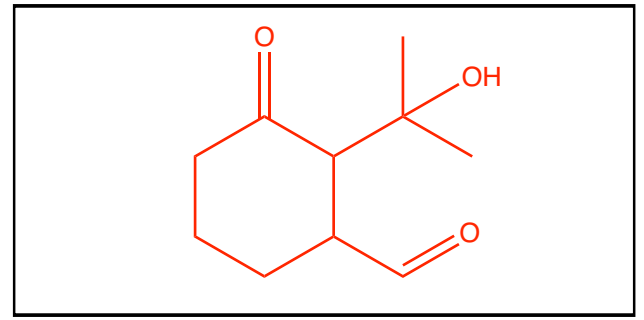
1. $(sia)_2BH$
2. H_2O_2, NaOH
3. $NaBH_4$ / EtOH

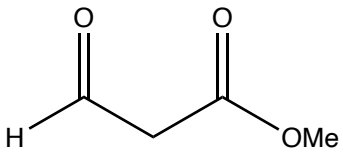




PCC

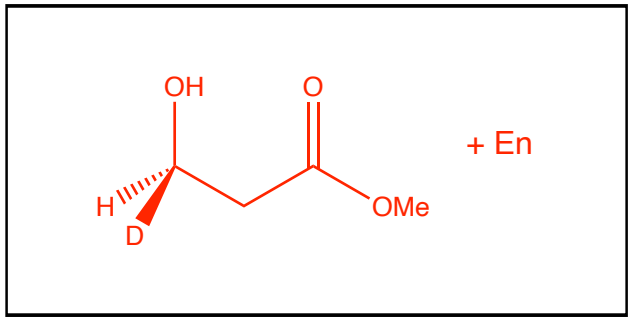
CH_2Cl_2

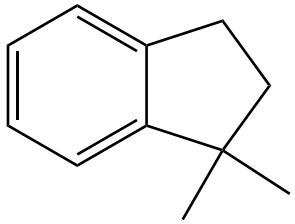




$NaBD_4$

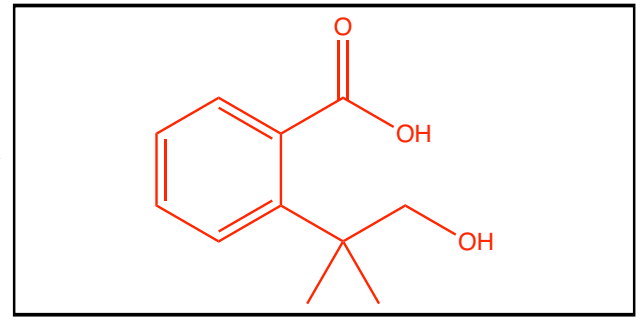
EtOH

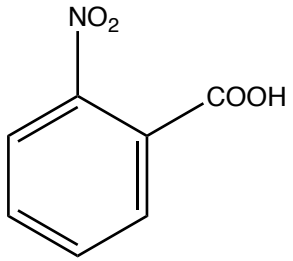




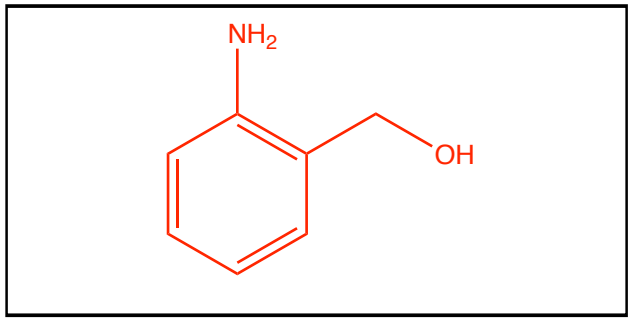
$Na_2Cr_2O_7$

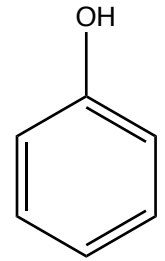
H_2O, H_2SO_4





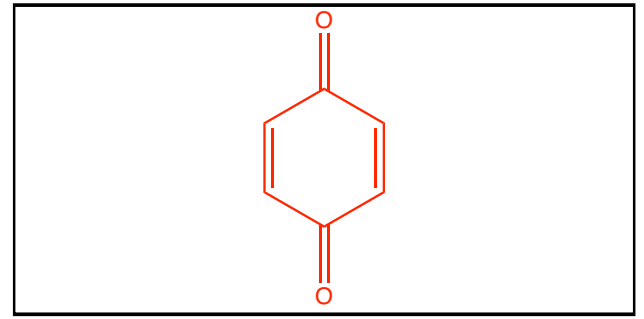
1. $LiAlH_4$
2. H_2O

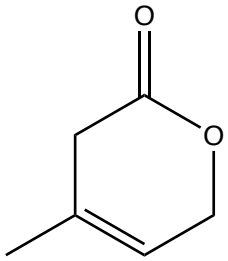




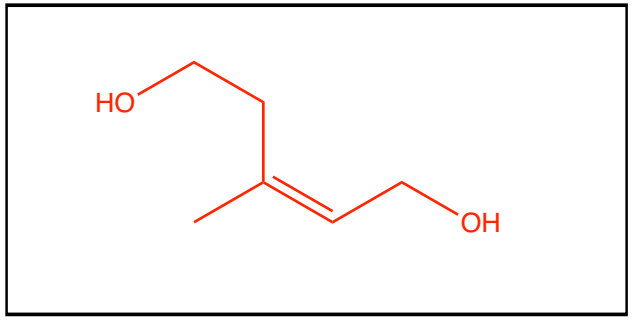
CrO_3, H_2SO_4

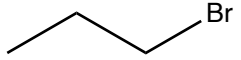
H_2O



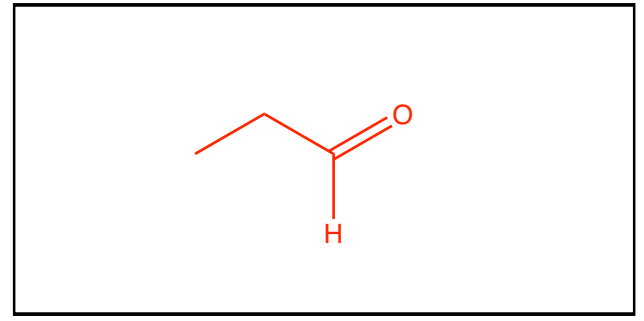


1. $LiAlH_4$
2. H_2O



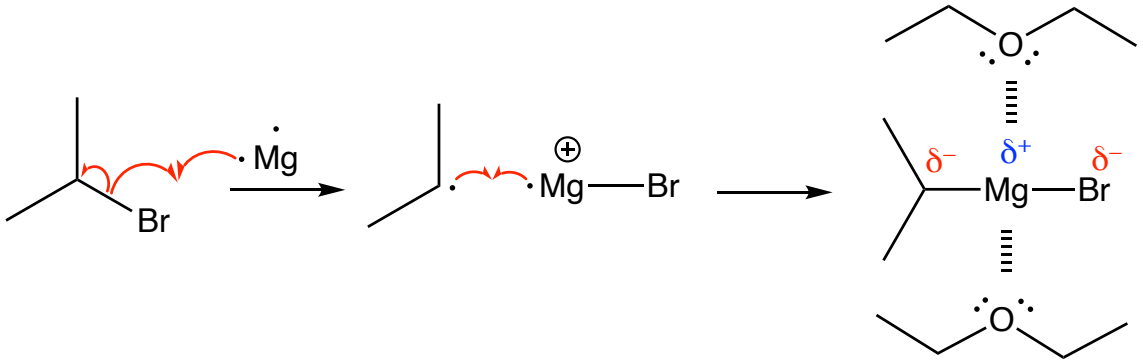


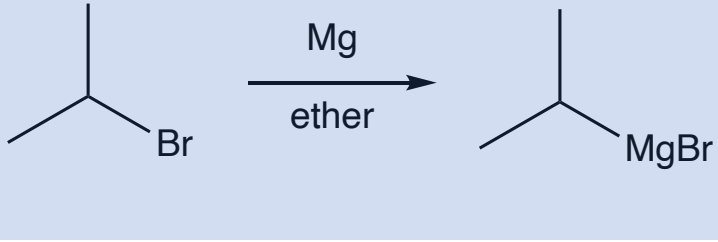
1. NaOH, H_2O
2. $(COCl)_2$, DMSO



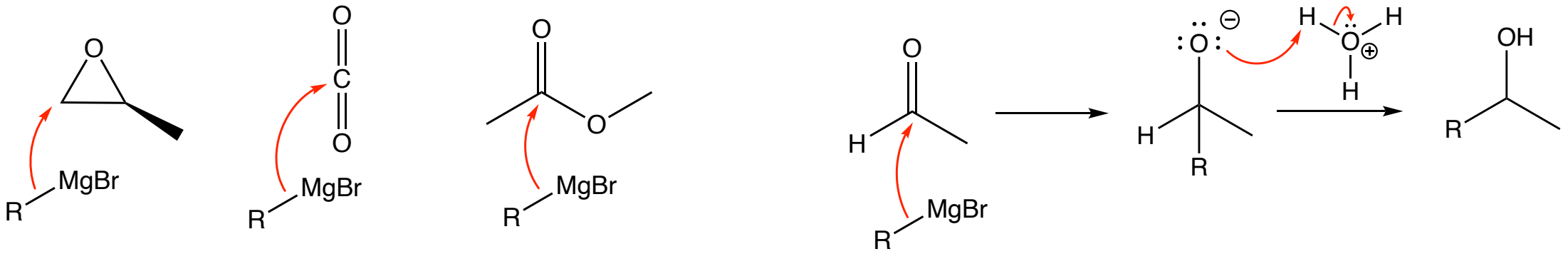
Alcohols: Grignard Reagents

Grignard reagents are carbon nucleophiles/bases formed from any sp^2 or sp^3 alkyl halide with magnesium and ethers (or similarly stabilizing molecules).

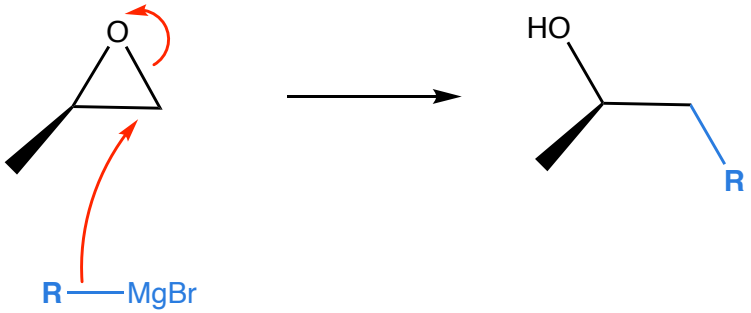




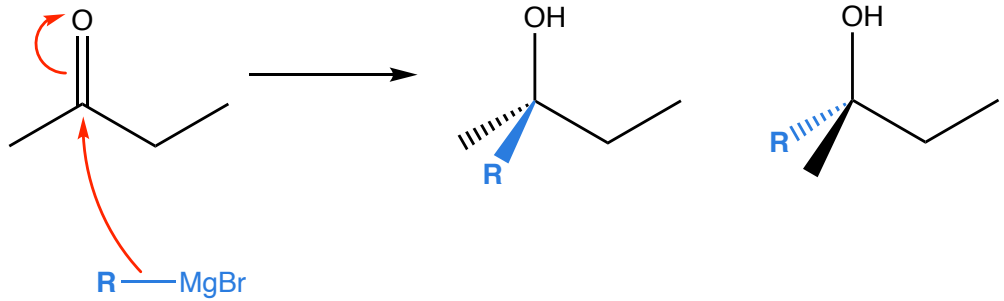
Grignard reagents will attack most electrophiles, so long as an acidic proton-source is absent.



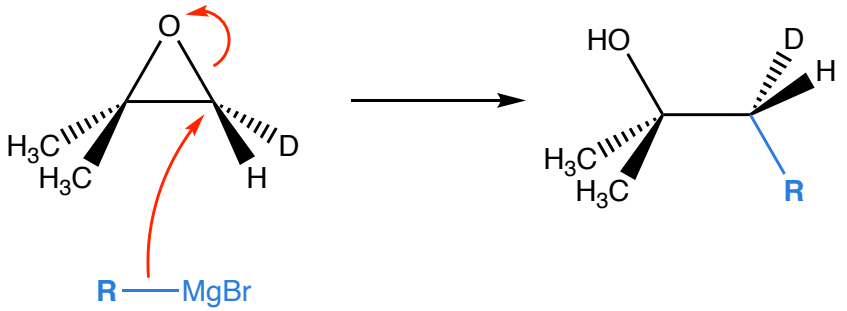
Grignard: Carbonyls vs. Epoxides



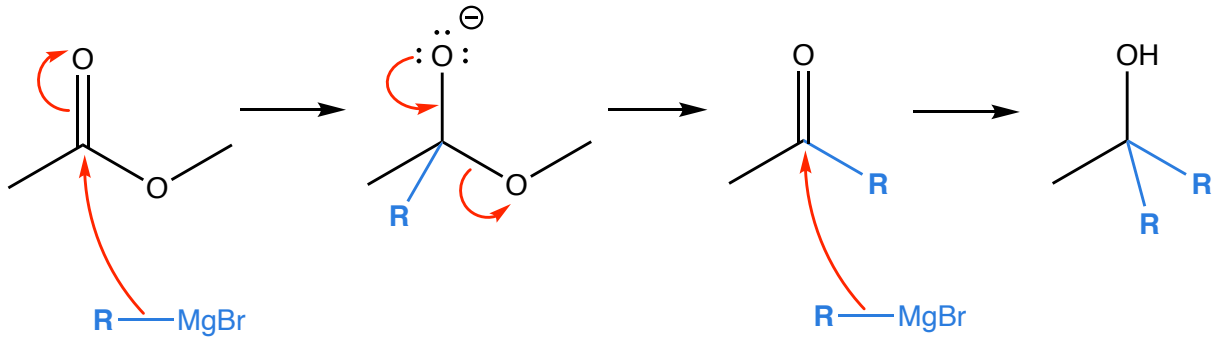
Grignard bonds at **β-carbon** for epoxides, and results in stereochemistry inversion via S_N2.



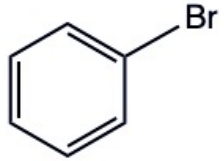
Grignard bonds at **α-carbon** for carbonyls, and results in racemization by attacking planar electrophile.



Stereochemistry shows **S_N2 inversion** by initially pointing H & D down then pointing them up.



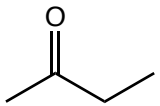
Grignard uniquely attacks **esters** *twice*, as the carbonyl group reforms by the -OR acting as a leaving group.



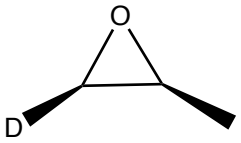
Mg

O

1.



2. H_2O

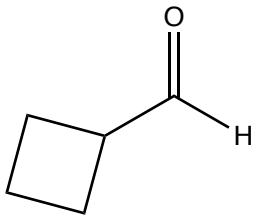


1. PrMgBr

2. H_2O

1. TsCl / pyr

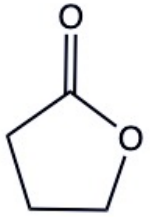
2. NaOMe



1. EtMgBr

2. H_2O

H_2SO_4 (conc.)

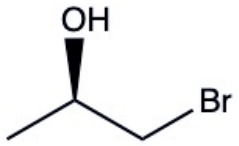


1. xs CH_3MgBr

2. H_2O

H_2SO_4 (conc.)

heat

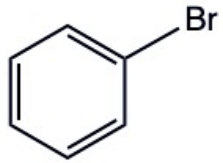


NaH

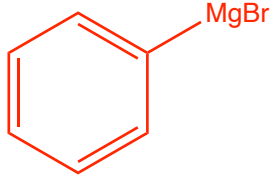
1. CH_3CH_2MgBr

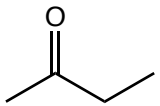
2. H_2O

ANSWER KEY

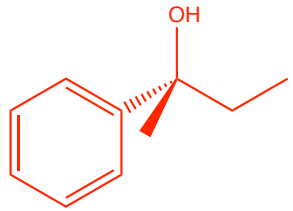


Mg, O

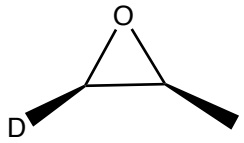


1. 

2. H_2O

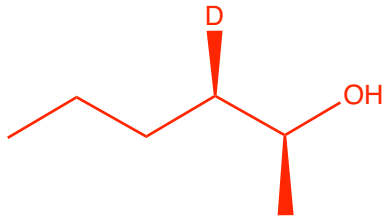


+ En



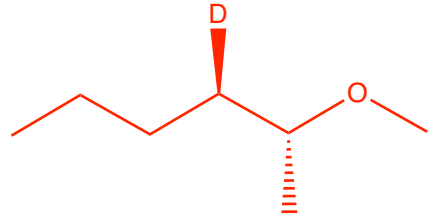
1. PrMgBr

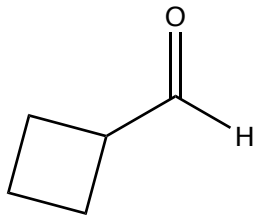
2. H_2O



1. TsCl / pyr

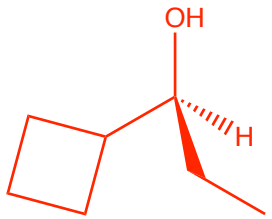
2. NaOMe





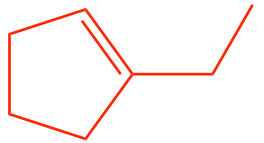
1. EtMgBr

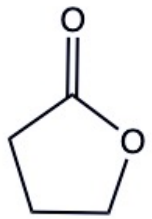
2. H_2O



+ En

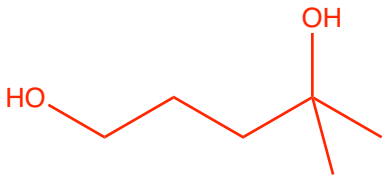
H_2SO_4 (conc.)





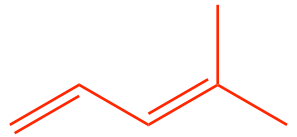
1. xs CH_3MgBr

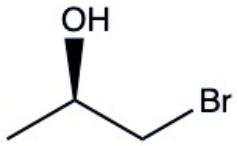
2. H_2O



H_2SO_4 (conc.)

heat



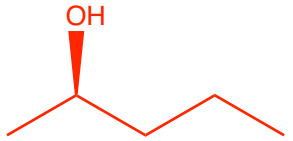


NaH



1. CH_3CH_2MgBr

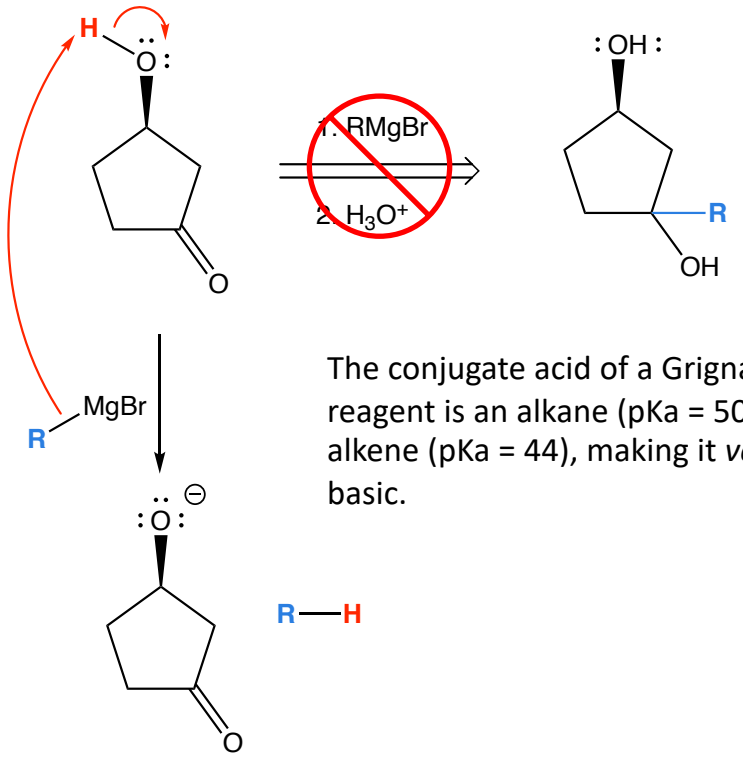
2. H_2O



Grignard: Protecting Groups

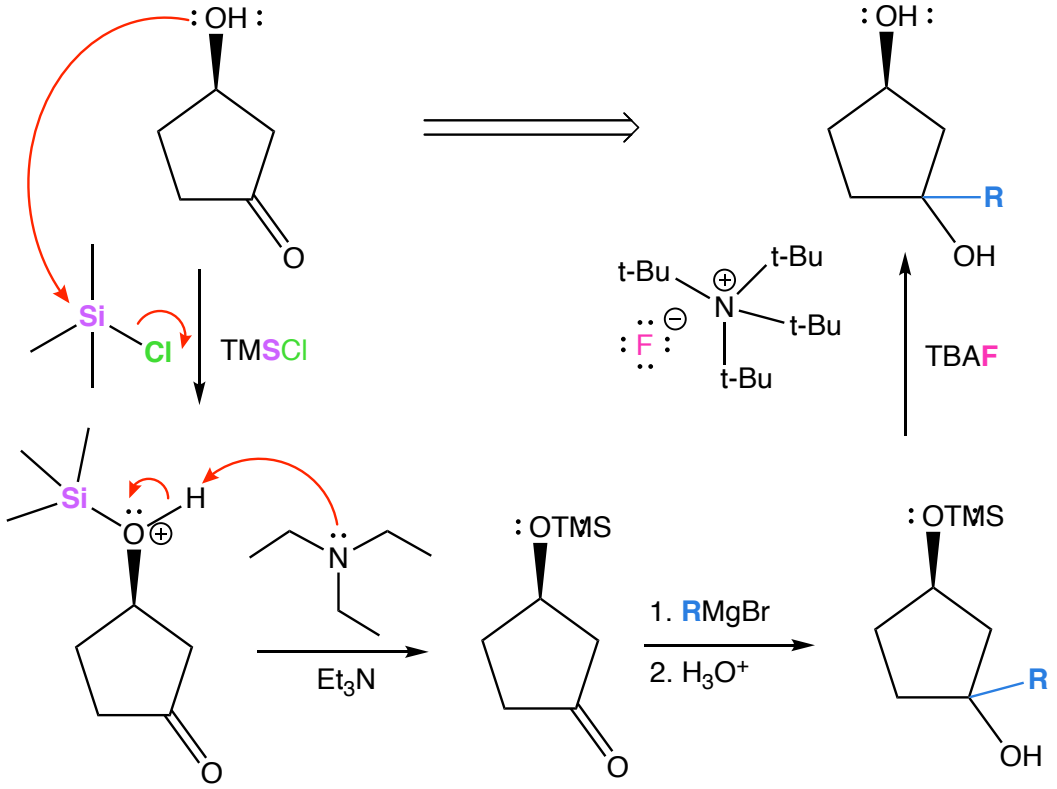
To prevent undesired side reactions of Grignard reagents—very basic nucleophiles—with any protic components of the substrate, a protecting group must be used.

Using a Grignard reagent in the presence of alcohol (a.k.a. acidic proton) is not useful.

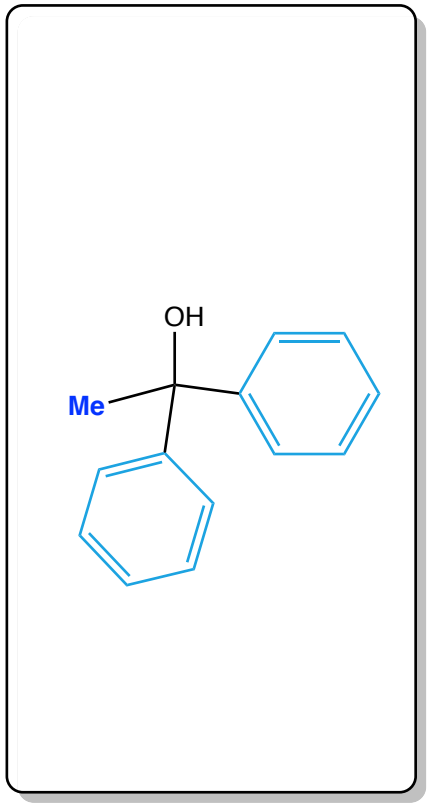


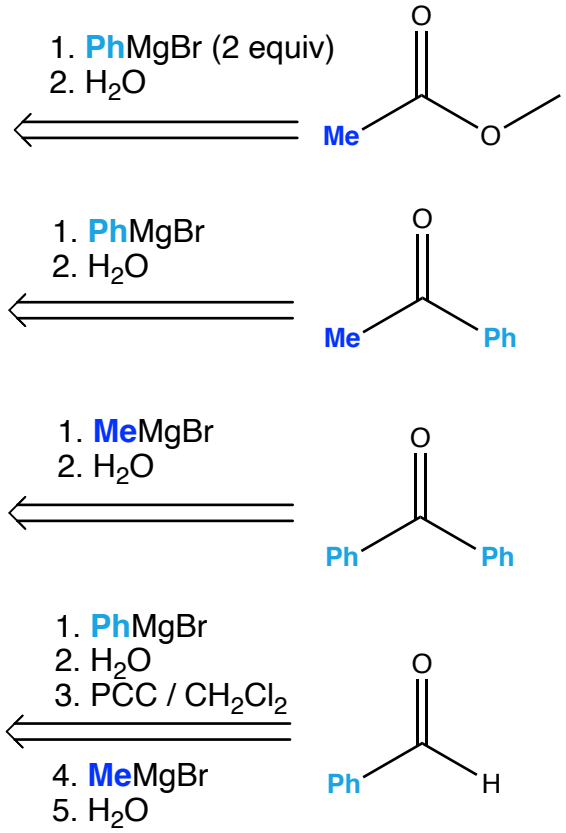
The conjugate acid of a Grignard reagent is an alkane (pKa = 50) or alkene (pKa = 44), making it *very* basic.

Turning an alcohol into a **silyl ether** creates an inert group that is still easily removed with fluoride ions.



Grignard: Synthesizing Strategies





From **Ester**: Grignard reacts *twice* with esters
- carbonyl reforms because alkoxide is a good enough leaving group

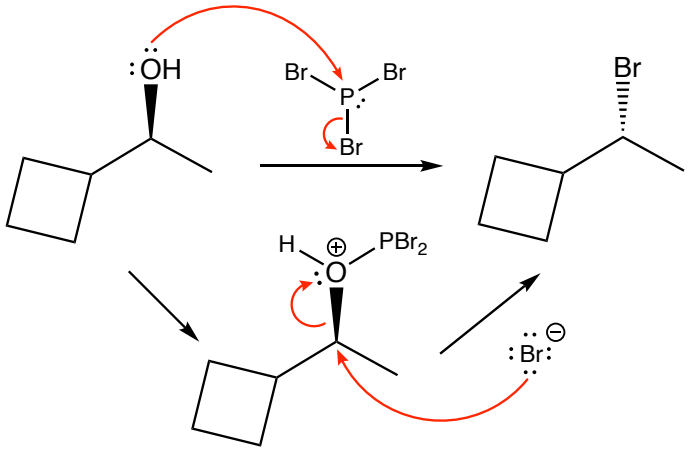
From **Ketone**: Grignard reacts *once* with ketones
- R groups can vary to provide multiple options for synthesis

From **Aldehyde**: Grignard reacts *once* or *twice*
- forms 2° alcohol first
- oxidizing agent reforms carbonyl so Grignard can attack again.

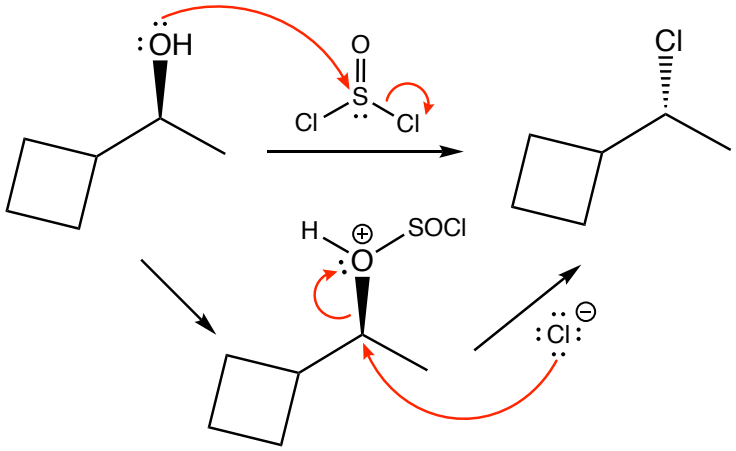
Alcohols: New Reagents

New reagents have been added to create alkyl halides from alcohols. The biggest difference in utility between these new reagents—PBr_3 or $SOCl_2$—and the more familiar ones—HBr and HCl—can be observed when reacting with 2° alcohols.

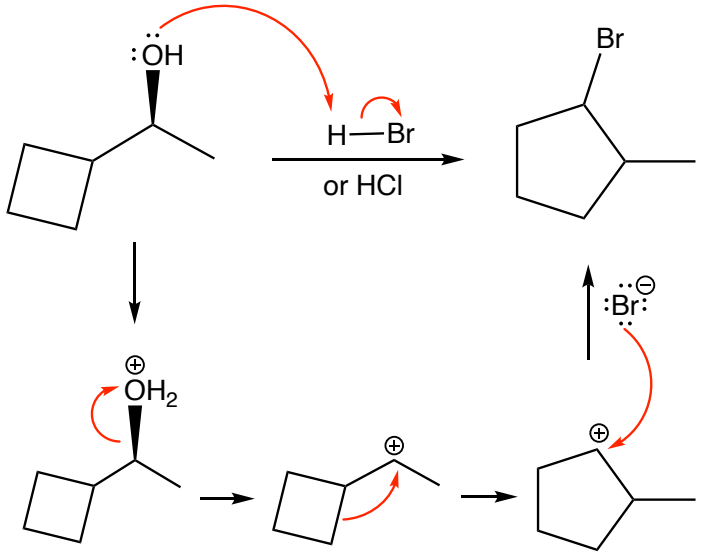
PBr_3 and **PCl_3** (S_n2)



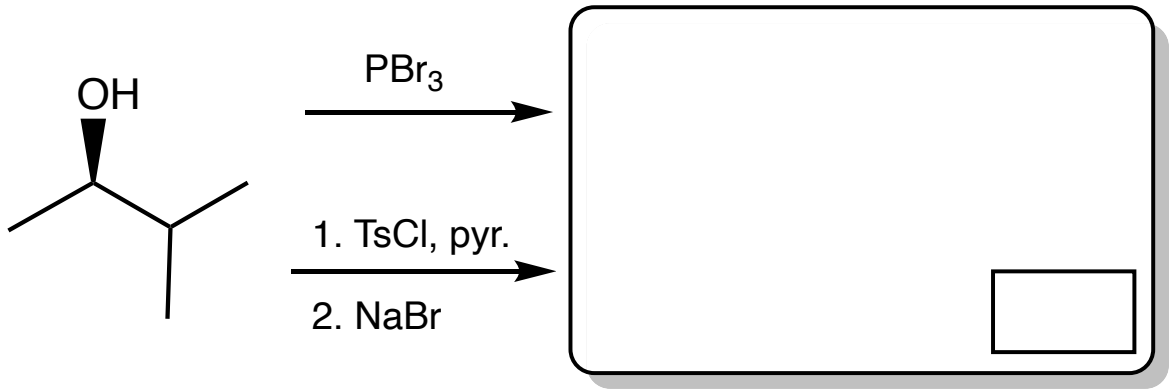
$SOCl_2$ and **$SOBr_2$** (S_n2)

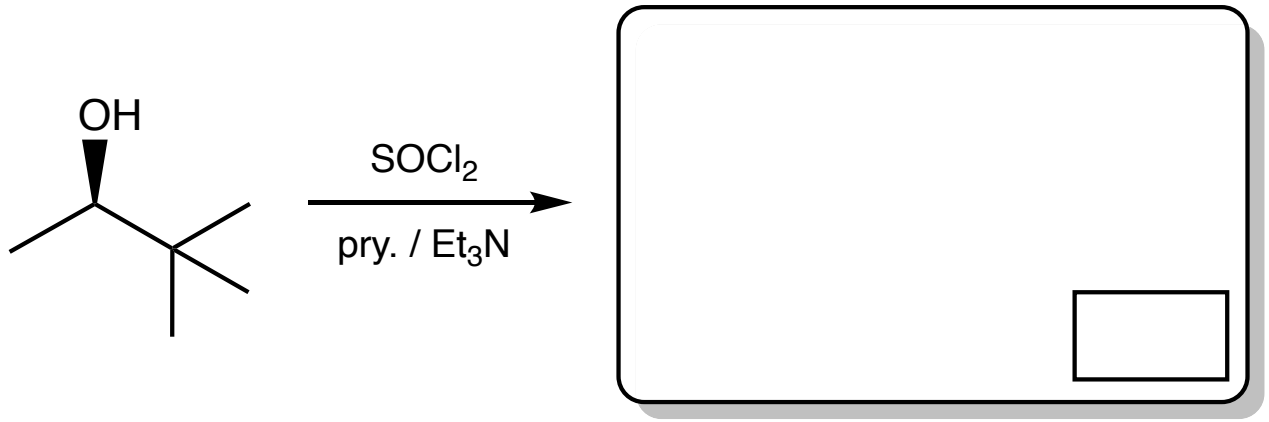


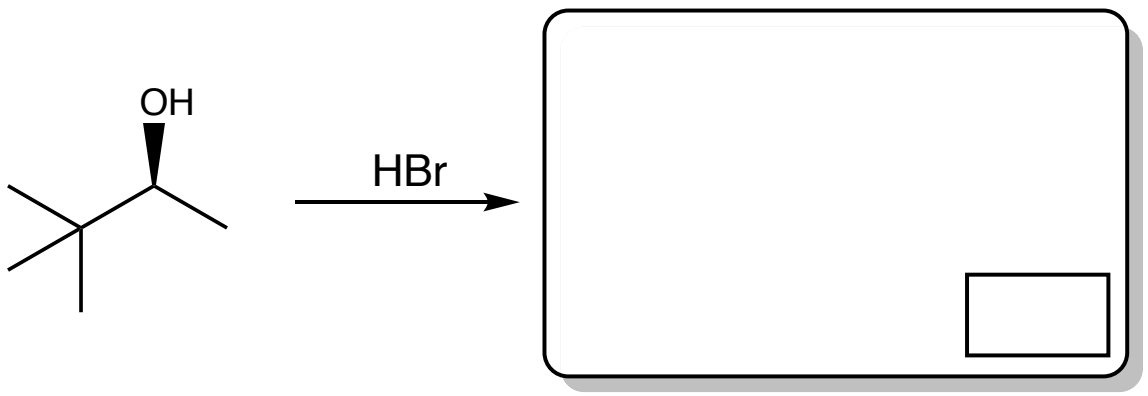
HBr and **HCl/$ZnCl_2$** (S_n1)

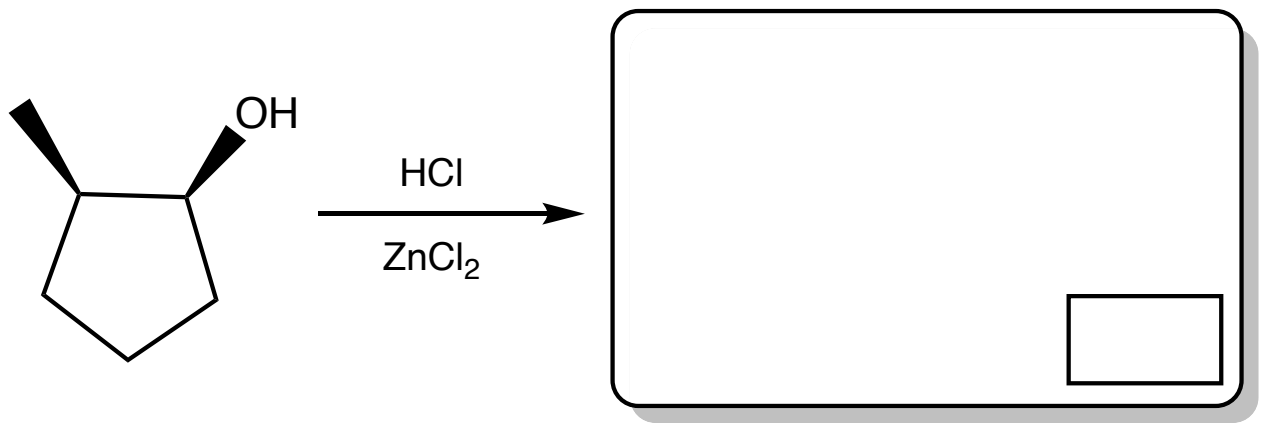


PBr_3 and $SOCl_2$ react only via S_N2 with 2° alcohols, while HBr/HCl react S_N1, incurring rearrangement.

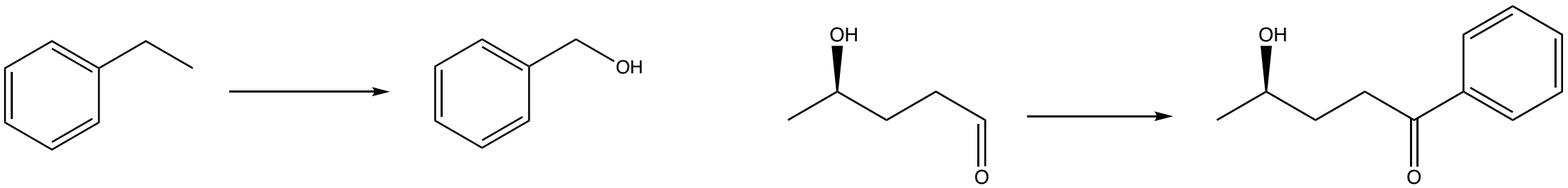

OH
PBr3
1. TsCl, pyr.
2. NaBr


OH
SOCl2
pry. / Et3N

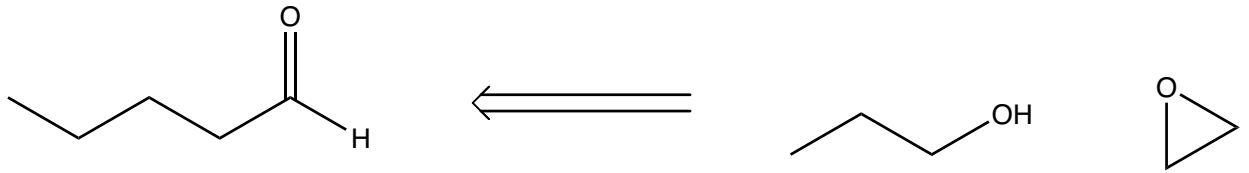

OH
HBr


OH
HCl
ZnCl2

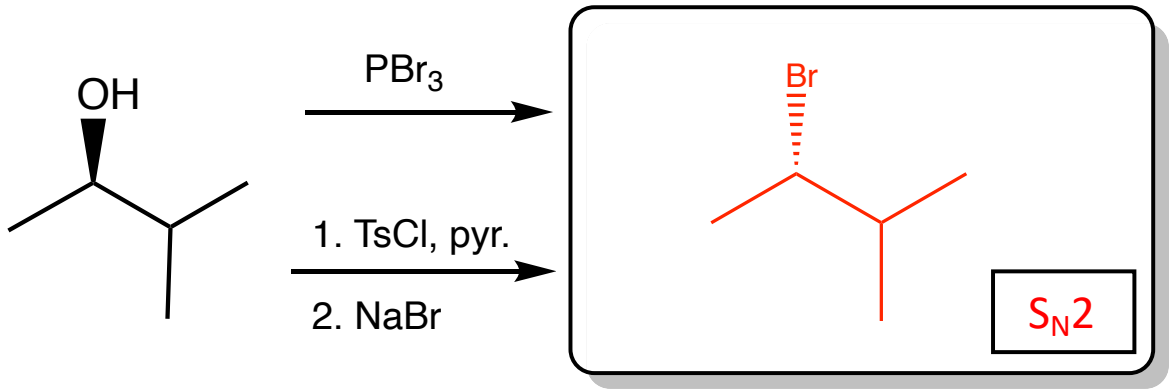
Write in the missing reagent(s) to form the complete the following reactions:

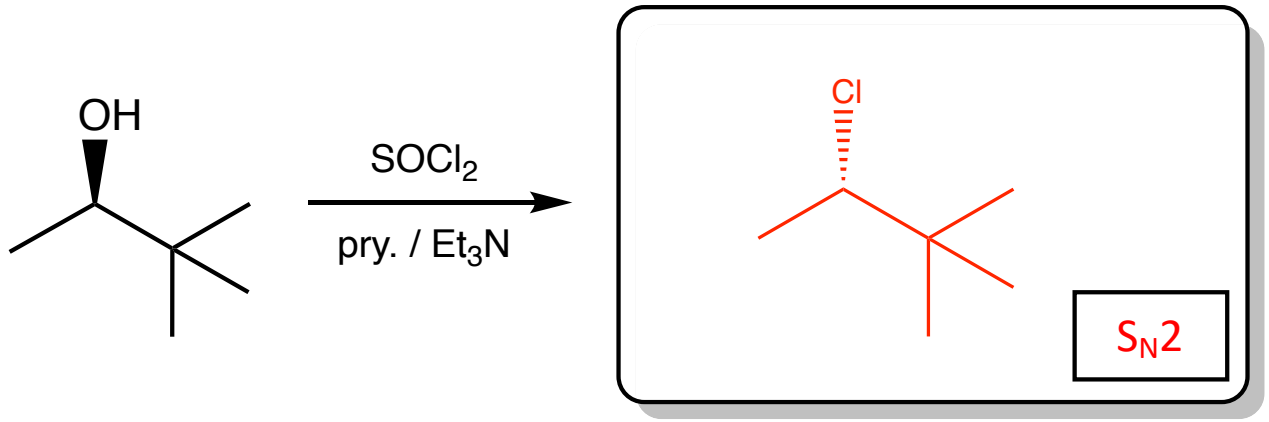


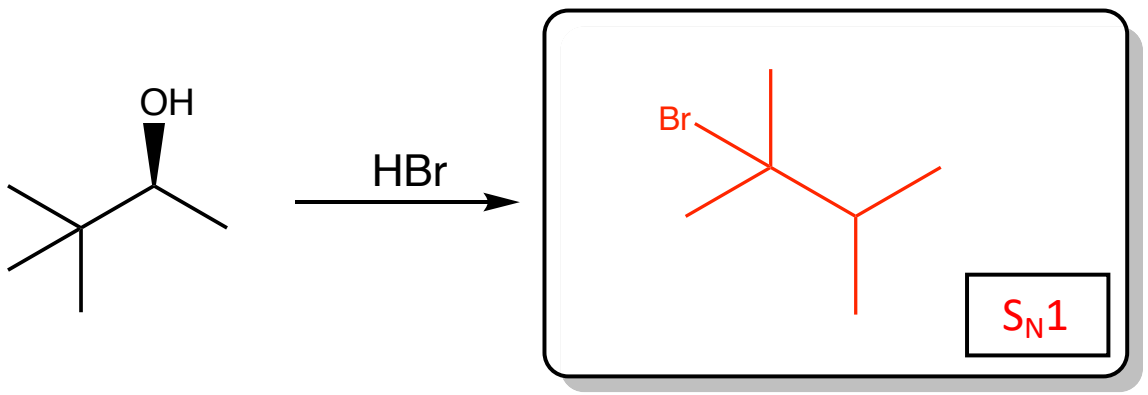
Propose an efficient synthesis strategy to form **pentanal** using propanol and oxirane as your only carbon sources.

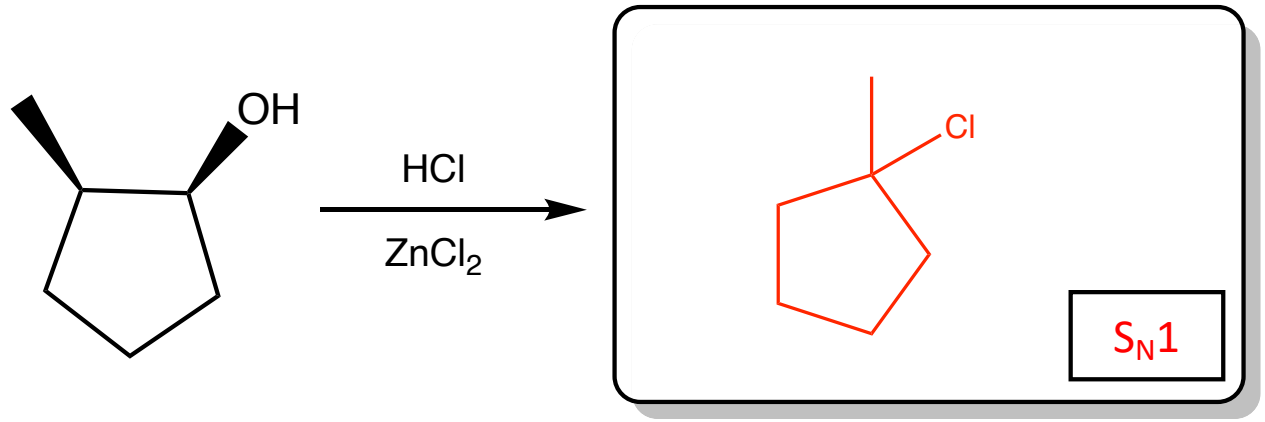


ANSWER KEY


OH
PBr_3
1. TsCl, pyr.
2. NaBr
Br
S_N2

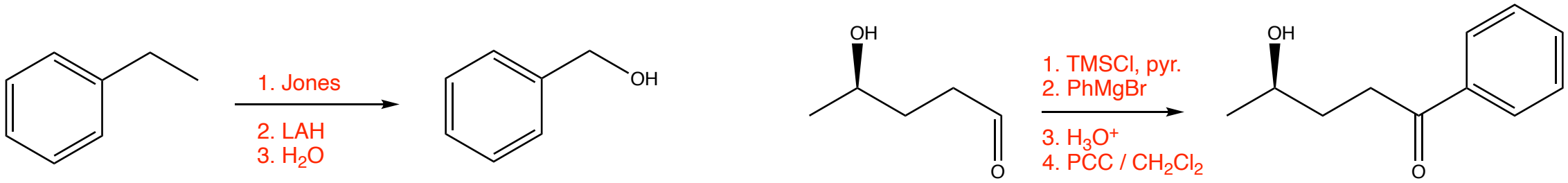

OH
$SOCl_2$
pry. / Et_3N
Cl
S_N2


OH
HBr
Br
S_N1

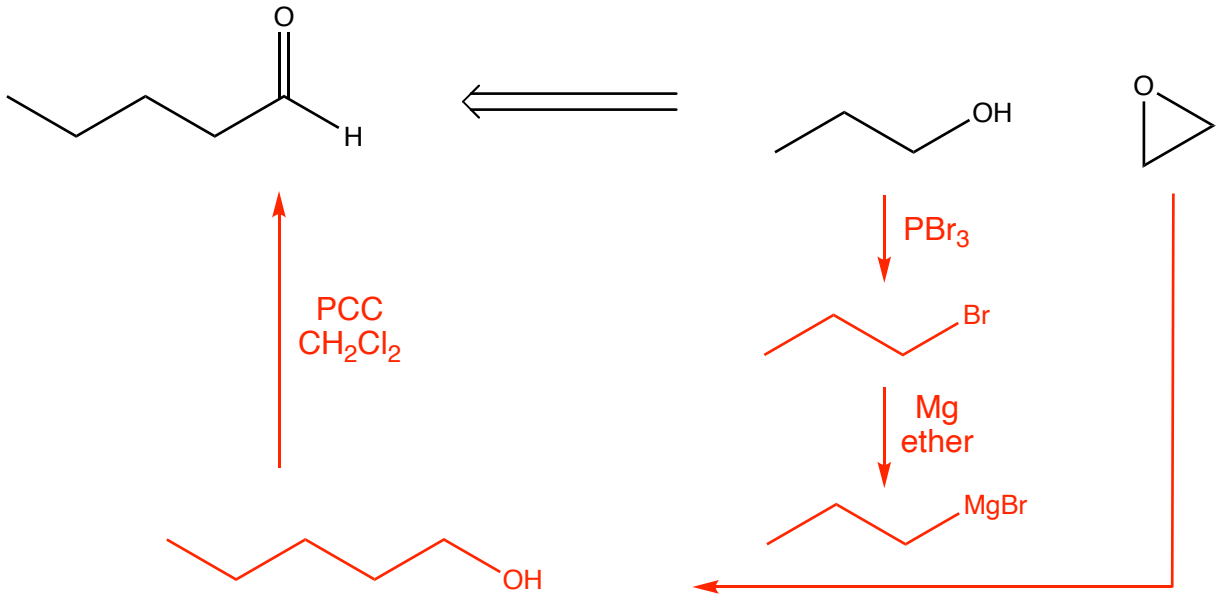

OH
HCl
$ZnCl_2$
Cl
S_N1

ANSWER KEY

Write in the missing reagent(s) to form the complete the following reactions:



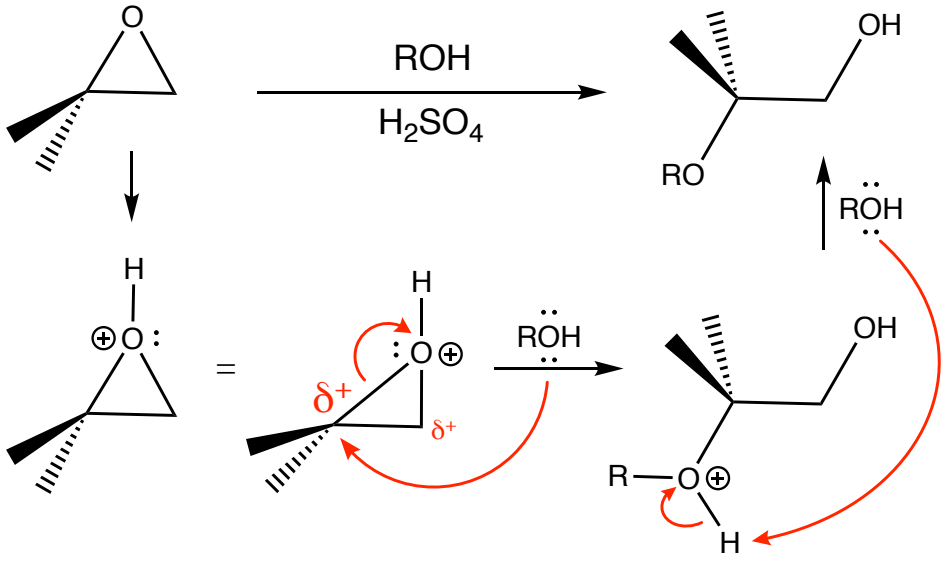
Propose an efficient synthesis strategy to form **pentanal** using propanol and oxirane as your only carbon sources.



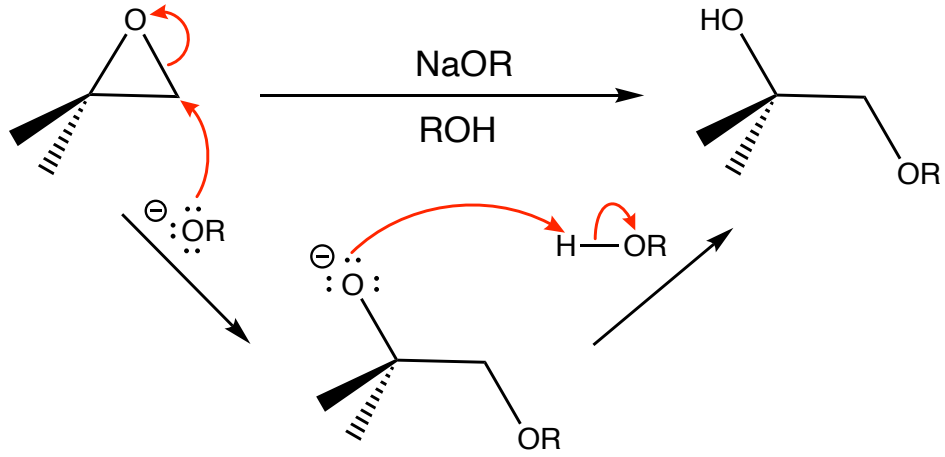
Ethers: Opening an Epoxide

Nucleophiles attack **more substituted** side in **acidic** conditions and the **less substituted** side in **basic** conditions. Both conditions follow the basic rules of SN2, in which the nucleophile attacks the more exposed, weaker bond.

ACIDIC



BASIC



Acidic Nucleophiles:
- H_2O, H^+
- ROH, H^+
- SH_2, H^+
- HBr or HCl

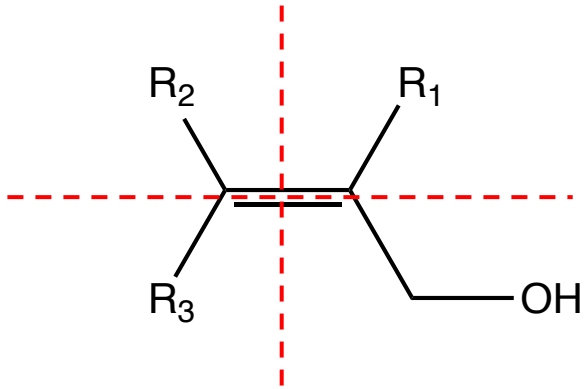
Basic Nucleophiles:
- ^-OH
- ^-OR
- ^-SR
- $^-NH_2$
- ^-CN
- ^-Nuc (etc…)
- ^-R (via Grignard)
- ^-H (via LAH)

Ethers: Sharpless Epoxidation

Typically forming epoxides from alkenes results in enantiomers. Sharpless Epoxidation forms a specific enantiomer but requires an **allylic OH group**.

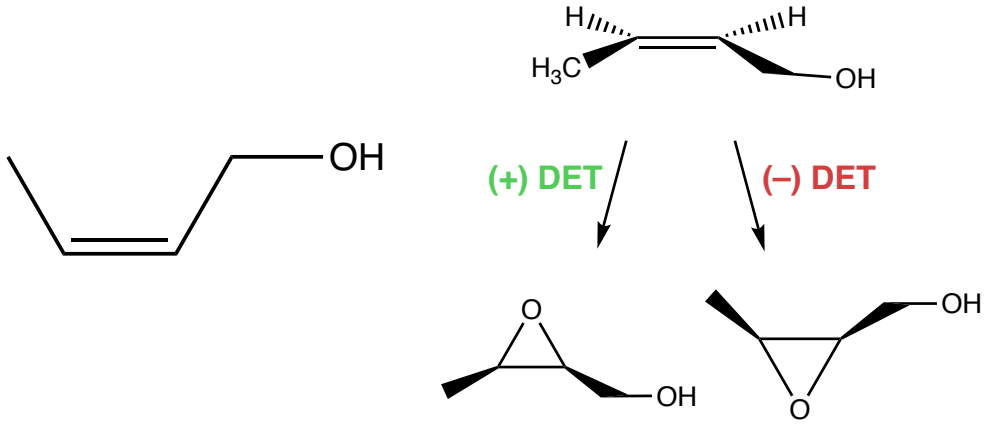
The oxidant is t-butyl hydroperoxide, written $(CH_3)_3C–OOH$ (abbrev. TBHP). The catalyst is titanium tetraisopropoxide, written $Ti[O\textit{i}\text{-}Pr]_4$. The additive that imparts chirality is **diethyl tartrate** (**DET**).

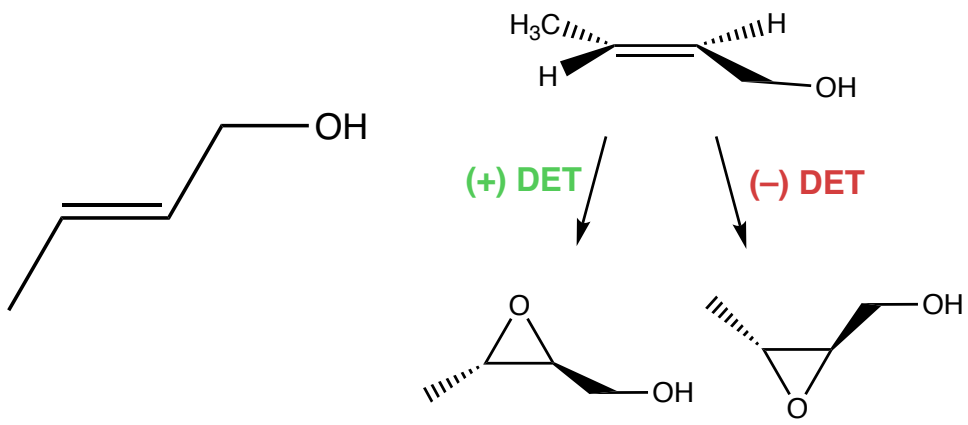
Selecting (+)/(–) DET and placing the **allylic OH in the lower left** quadrant, helps to predict the enantiomeric product.



(+) DET – epoxide forms *above*

(–) DET – epoxide forms *below*

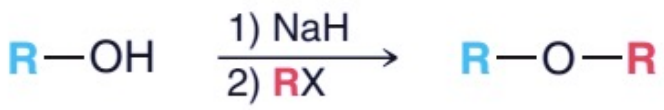




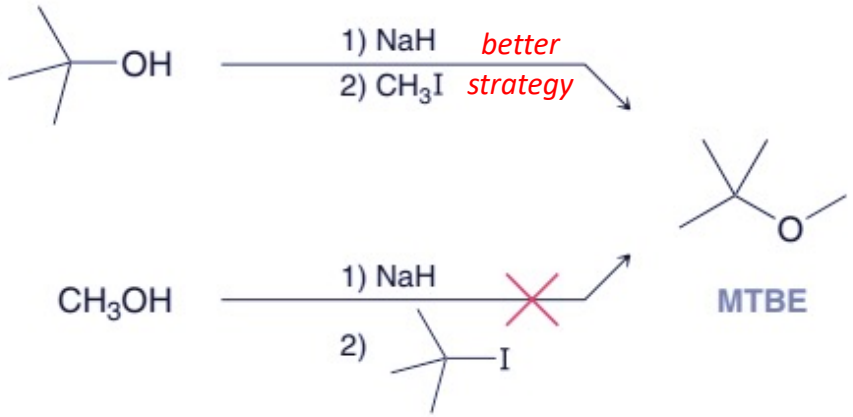
Ethers: Synthesis & Breakdown

Ethers are synthesized and broken down through two major pathways: Williamson Synthesis & Acidic Cleavage.

WILLIAMSON ETHER SYNTHESIS

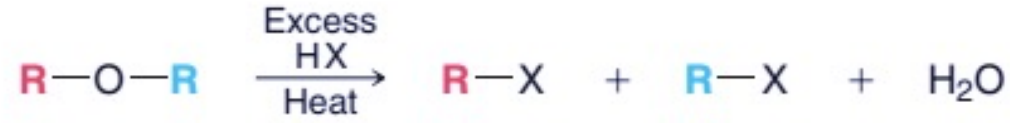


Typically, it's an S_N2 reaction, so the alkyl halide should be a Me or 1° sp^3 substrate.



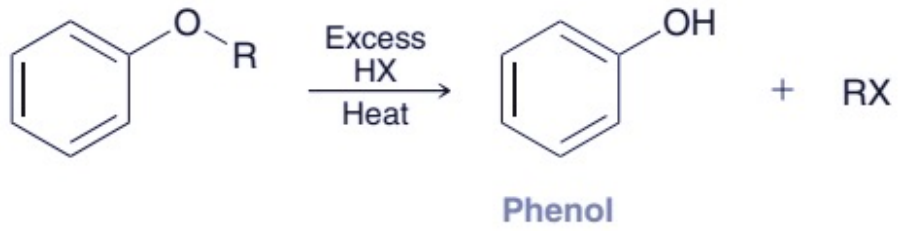
NaOH deprotonates PhOH, NaH deprotonates ROH

ACIDIC CLEAVAGE



Typically, it's an S_N2 reaction, but it can be S_N1 if ether is 3°.

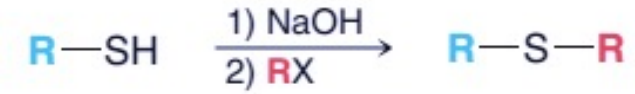
HI or HBr are preferred acids: (1) Both are strong acids
(2) I^- and Br^- are great Nuc



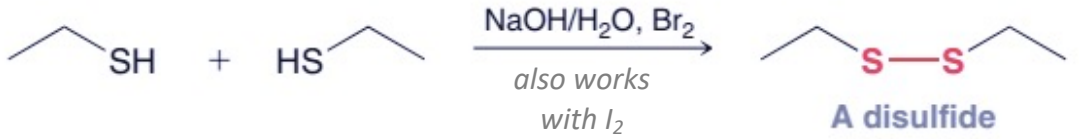
sp^2 ethers <u>*cannot*</u> undergo acidic cleavage.

Ethers: Sulfides, etc.

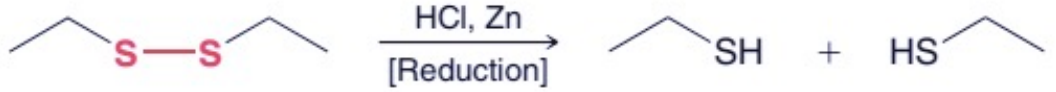
Thiol ethers (i.e. sulfides) are formed from thiols similar to the Williamson Ether Synthesis. Since thiols are more acidic than most alcohols, NaOH is generally always an appropriate base.



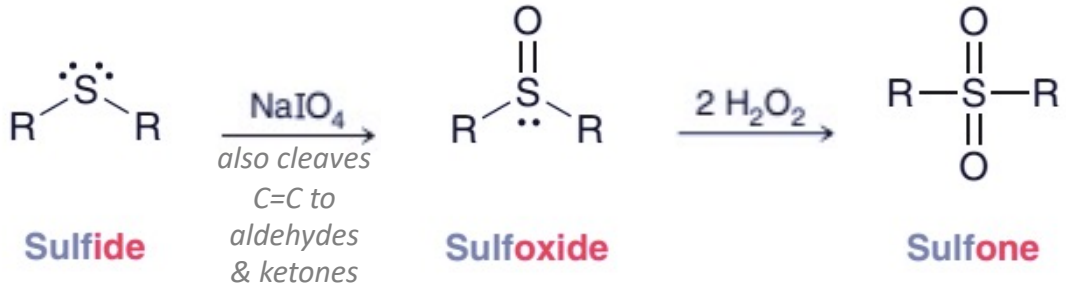
Thiols are oxidized to form disulfides via molecular bromide or iodide and NaOH.



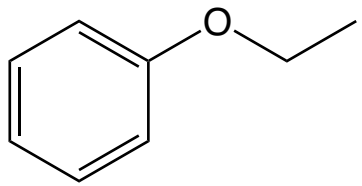
Disulfide bonds are reduced via Zn, HCl.

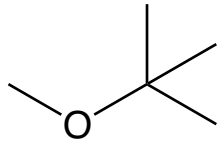


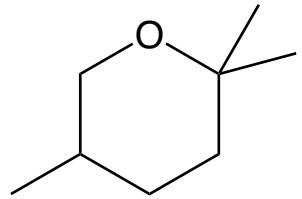
Sulfides are oxidized to sulfoxides via $NaIO_4$ (sodium periodate) and to sulfones via H_2O_2 (hydrogen peroxide).

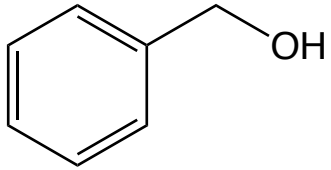


Propose the most efficient synthesis for the formation of the following ethers:

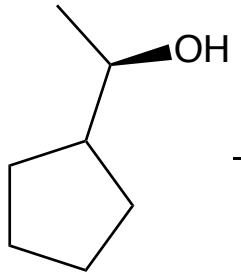
a) 

b) 

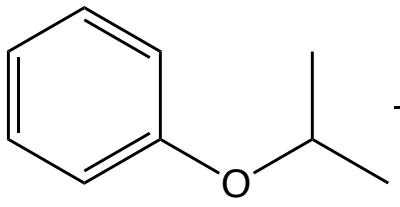
c) 



1. NaH
2. PhBr

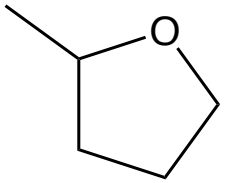


1. NaH
2. EtBr



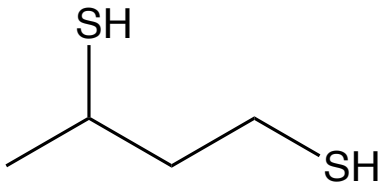
HI xs

heat



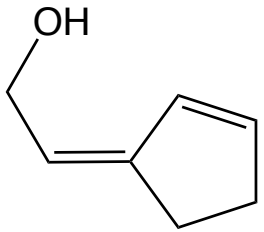
HBr (1 eq.)

heat



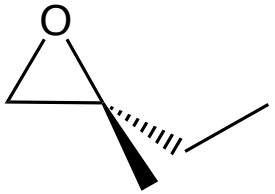
Br_2

NaOH



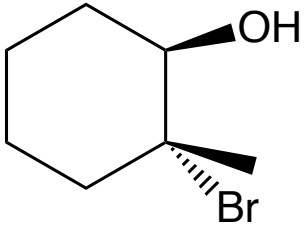
$Ti[O\textit{i}\text{-}Pr]_4$
TBHP

(+) DET



1. $NaSCH_3$

2. $NaIO_4$



1. NaH

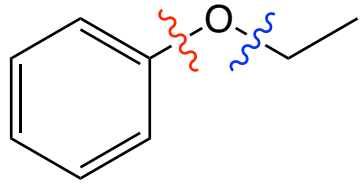
2. $LiAlD_4$

3. H_2O

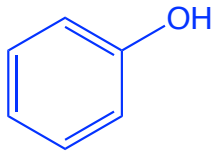
ANSWER KEY

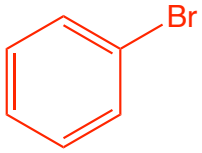
Propose the most efficient synthesis for the formation of the following ethers:

a)





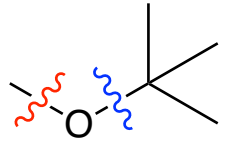


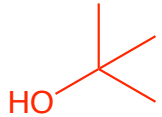


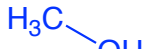


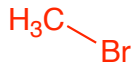
Blue is more efficient: PhO^- attacks 1° alkyl halide. PhBr cannot undergo S_n1 or S_n2.

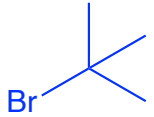
b)





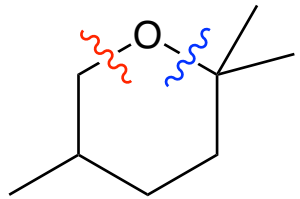


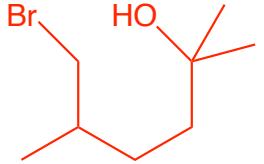


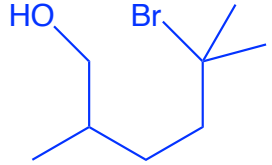


Red is more efficient: t-BuO^- attacks Me alkyl halide via Sn2. t-BuBr undergoes S_n1.

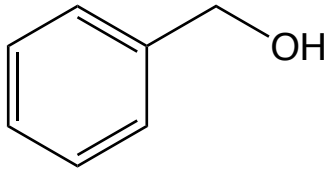
c)







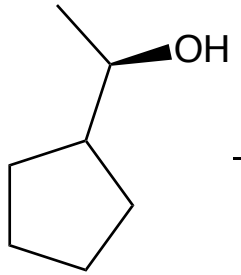
Red is more efficient: 3° RO^- attacks 1° alkyl halide via S_n2. Blue must undergo S_n1.



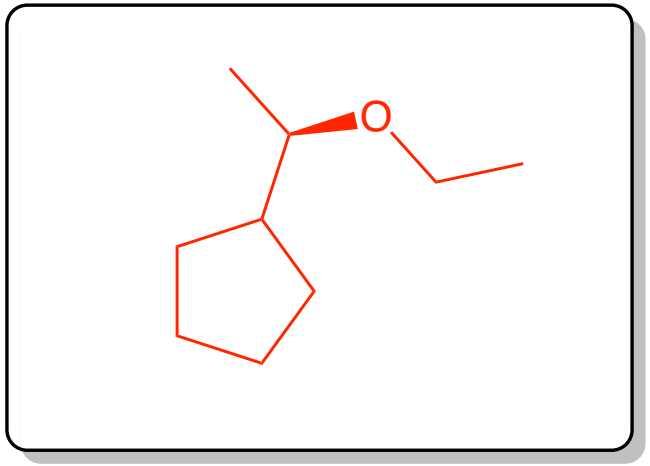
1. NaH
2. PhBr

No RXN

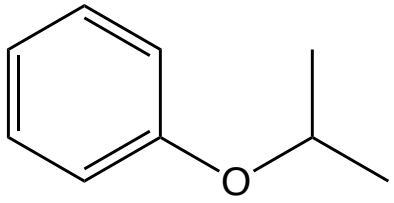
PhBr cannot undergo S_n1 or S_n2 attack.



1. NaH
2. EtBr

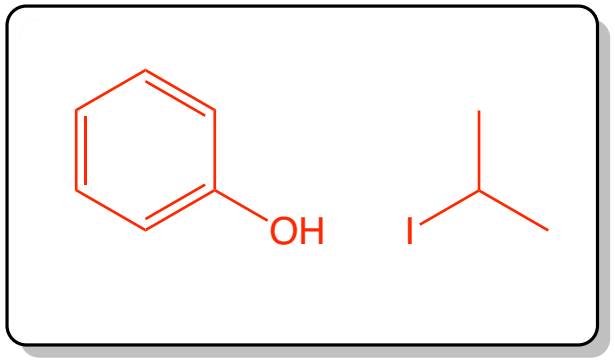


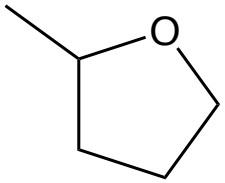
ANSWER KEY



HI xs

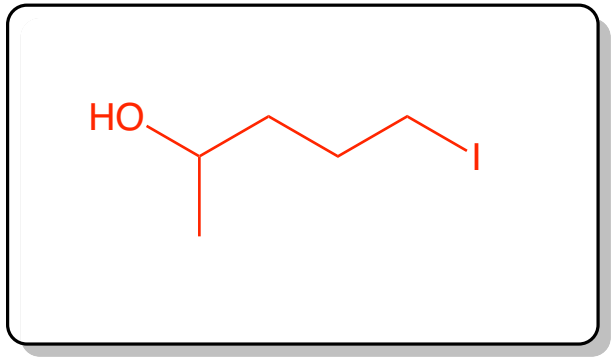
heat

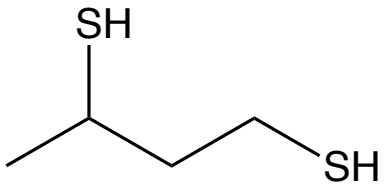




HBr (1 eq.)

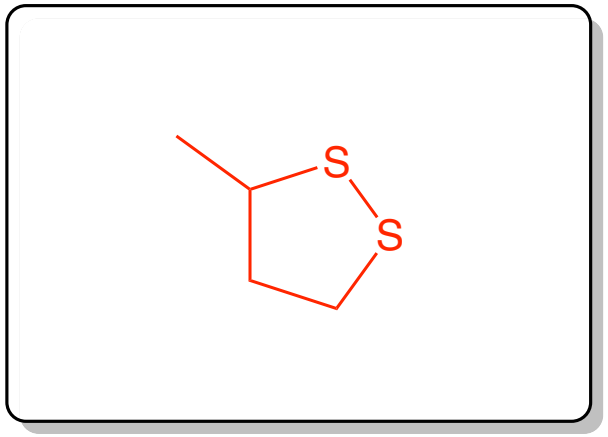
heat

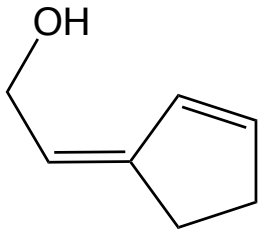




Br_2

NaOH

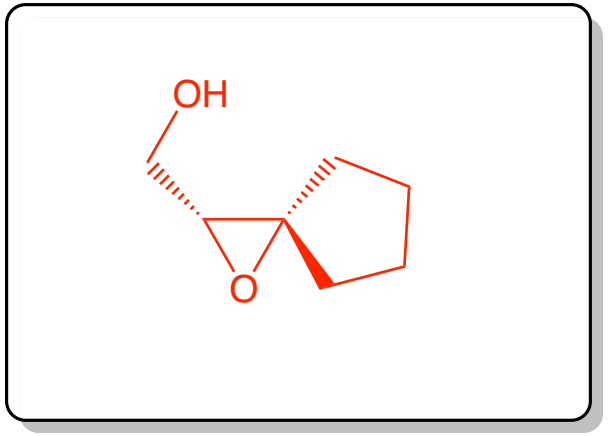


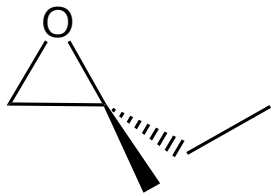


$Ti[O\textit{i}\text{-}Pr]_4$

TBHP

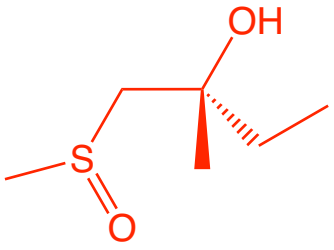
(+) DET

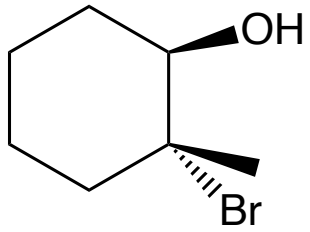




1. $NaSCH_3$

2. $NaIO_4$

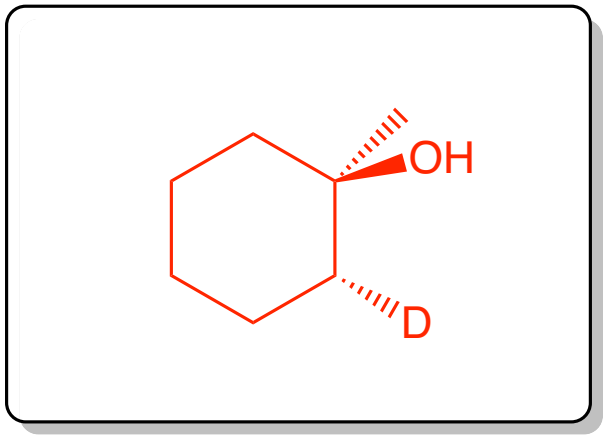




1. NaH

2. $LiAlD_4$

3. H_2O



SUMMARY: Alcohols

- **Alkenes —> Alcohols**
  - H_2O, H_2SO_4
  - a) $Hg(OAc)_2$, H_2O b) $NaBH_4$
  - a) BH_3-THF b) OH, H_2O_2
- **Alcohols —> Alkyl Halides**
  - PBr_3 or PCl_3 –via S_N2
  - $SOCl_2$ or $SOBr_2$ –via S_N2
  - HBr or HCl/$ZnCl_2$ – likely via S_N1
- **Oxidation**: ROH —> C=O
  - PCC / CH_2Cl_2 – 1° to aldehyde
  - Swern: DMSO, $(COCl)_2$ – 1° to aldehyde
  - Jones: $Na_2Cr_2O_7$, H_2SO_4 – 1° to COOH
- **Reduction**: C=O —> ROH
  - $NaBH_4$ / ROH – ketones/aldehydes
  - 1) $LiAlH_4$ 2) H_2O – ketones/aldeh., COOH/COOR
  - H_2, Pt/C – alkenes, alkynes, benzylic C=O

ROH ——> alkene ——> alcohol

Grignard strategy:

Carbonyl – adds to alpha carbon

Aldehyde – adds 1, can oxidize to add again

Ester – adds twice to alpha

Epoxide – adds to beta carbon

Protecting Group: TMSCl, pyr. followed by TBAF

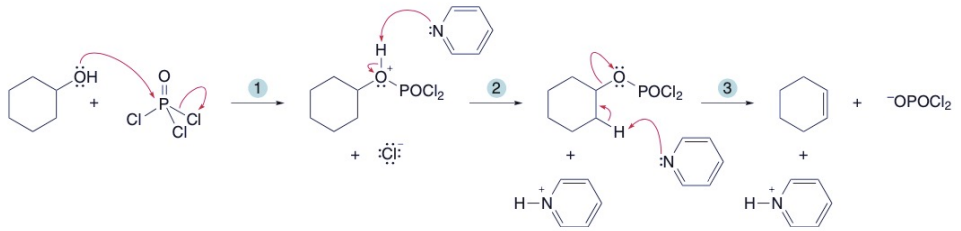
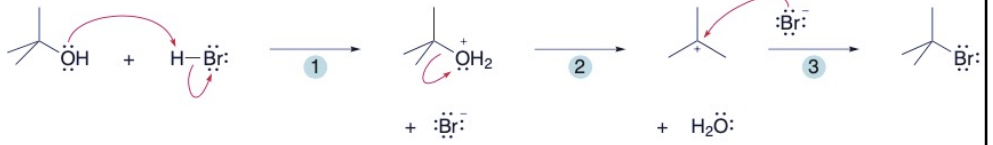
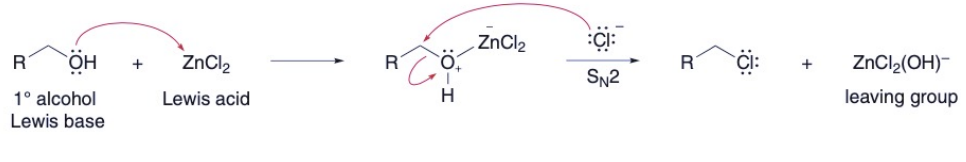
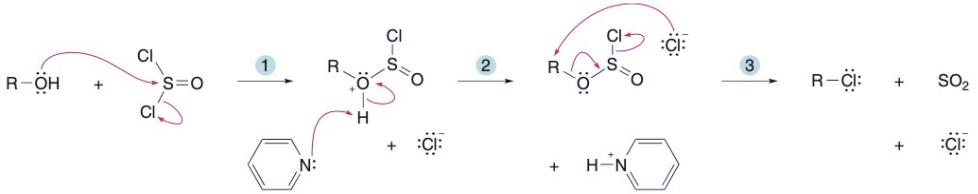
SUMMARY: Ethers, Thiols

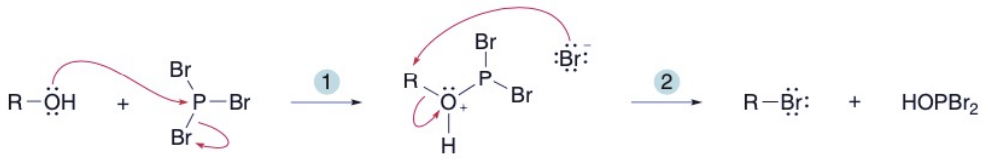
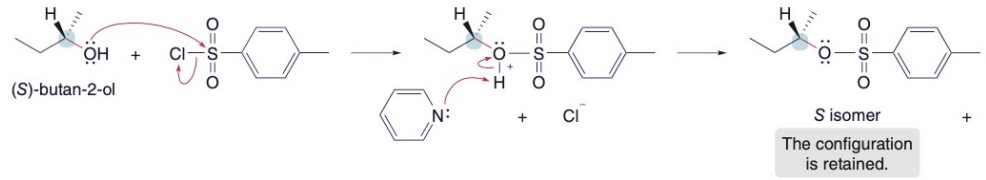
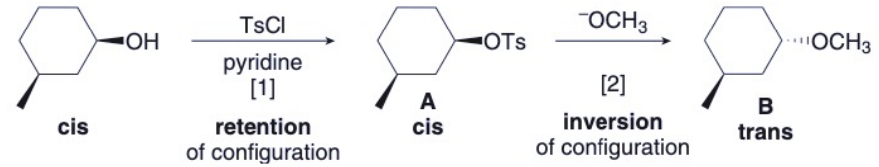
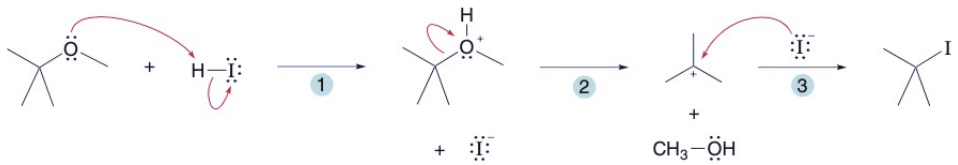
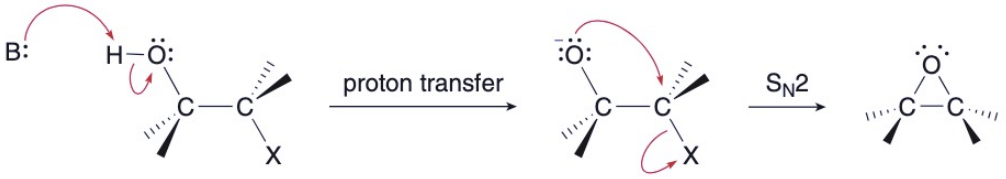
- **Alkenes —> Epoxides**
  - Peroxyacid – RCO_3H (ex. mCPBA)
  - Halohydrin – a) Br_2, H_2O b) NaH
- **Ether Formation**
  - Acid-Catalysis: 2 ROH H_3O^+
    - Forms symmetrical ether
  - Williamson (S_n2): ROH 1) Base 2) R–X
    - Alkyl halide should be Me or 1°
- **Ether Breakdown**
  - Acid Catalysis: xs HI or HBr (heat)
- **Thiol Formation**
  - 1) NaOH 2) R–X
- **Sulfides**
  - Oxidation – Br_2, NaOH
  - Reduction – Zn, HCl

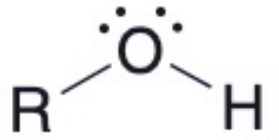
Epoxide Opening:

ACIDIC

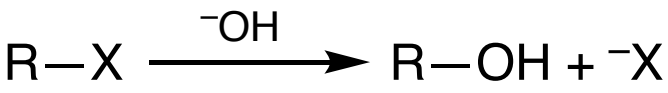
BASIC

Reaction	Example	Reagent(s)	Notes
Acid-Catalyzed Dehydration of ROH *(w. rearrangement)*		H_2SO_4 (*concentrated*) heat	Rate increases 1° > 2° > 3° • via E2 – 1° (unstable carbocation) • via E1 – 2°, 3°
Acid-Catalyzed Dehydration of ROH *(w/o rearrangement)*		$POCl_3$ / excess pyr	No rearrangement occurs because no carbocation forms.
Form Alkyl Halides from ROH		HI HBr	Halides act as more effective nucleophiles than bases. • via S_N2 – Me, 1° • via S_N1 – 2°, 3°
Form Alkyl Chlorides from ROH		HCl / $ZnCl_2$	$ZnCl_2$ added to increase electrophilicity of alcohol • via S_N2 – Me, 1° • via S_N1 – 2°, 3°
Form 1°/2° Alkyl Chlorides from ROH		$SOCl_2$ / pyr $SOBr_2$ / pyr.	Can be used with Me, 1° or 2° alcohols • S_N2 only

Reaction	Example	Reagent(s)	Notes
Form 1°/2° Alkyl Halide from ROH		PBr_3 or PCl_3	Can be used with Me, 1°, or 2° alcohols • S_N2 only
Tosylation & Mesylation		TsCl / pyr TfCl / pyr MsCl/ pyr	No rearrangement occurs because no carbocation forms. Retains absolute configuration.
Alkylation from Tosylates		1. TsCl / pyr 2. Nuc	Net inversion of stereochemistry • S_N2
Acid-Catalyzed Cleavage of Ethers		HX (2 equiv.) X = Br or I	Cleavage depends on type of R groups: • via S_N2 – Me or 1° • via S_N1 – 2° or 3°
Formation of Epoxide from Halohydrin		NaH or Li	Basic – attack less-substituted side Acidic – attack more-substituted side

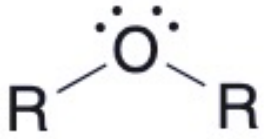


ALCOHOLS

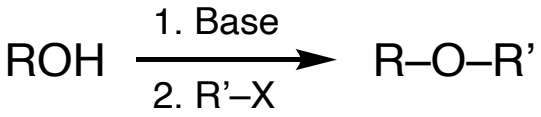


HYDROXIDE S_N2 of 1° ALKYL HALIDE
2° alkyl halides are possible, but will form an E2 side product.

– does *not* have a good LG
→ can create better LG with:
- TsCl, MsCl, TfCl
- Halic acids (e.g. HCl, HBr)
  – result in substitution
- Other strong acids (e.g. H_2SO_4)
  – result in elimination



ETHERS

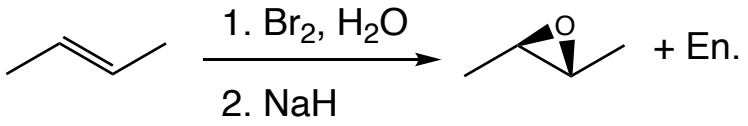


WILLIAMSON ETHER SYNTHESIS: S_N2
The preferred path uses the less sterically-hindered alkyl halide (Me or 1°).

– does *not* have a good LG
→ undergoes fewer reactions
– requires strong acid and heat to react and breakdown



EPOXIDES



SYNTHESIS via HALOHYDRIN: S_N2
Another pathway is using peroxy acids (RCO_3H) via alkene.

– does *not* have a good LG
→ opens due to **ring strain**
– reacts with vast variety of reagents:
- Base – attacks less sub. .
- Acid – attacks more sub.