



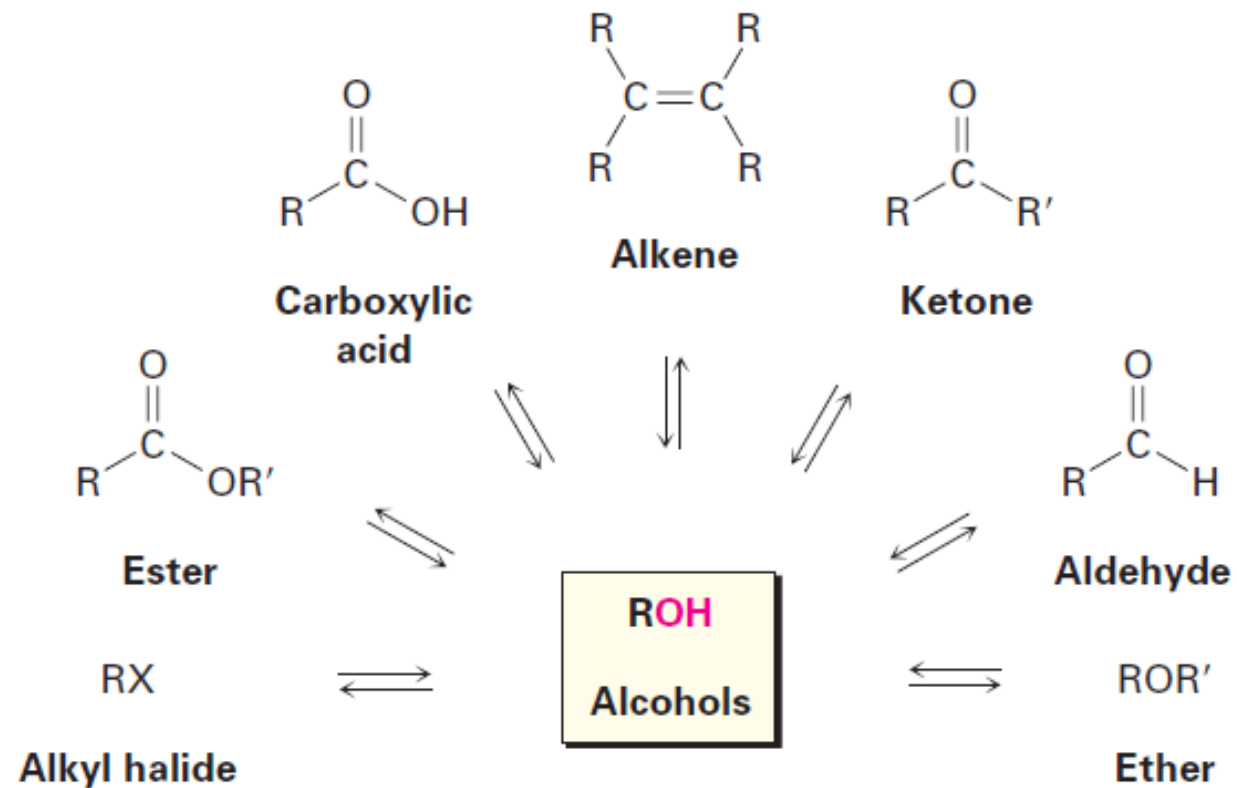
# Pharmaceutical organic chemistry Alcohol – Lecture 3

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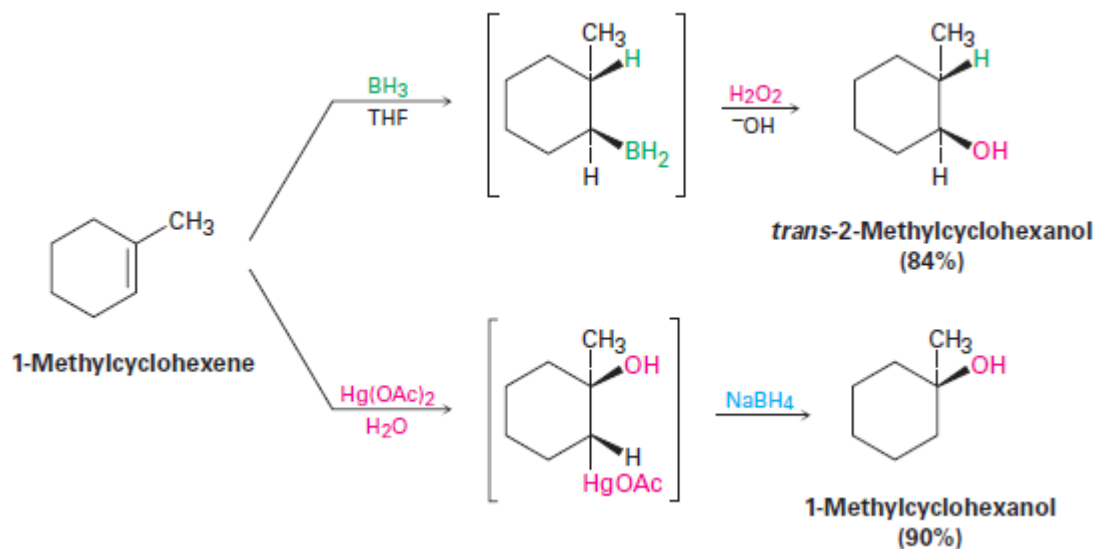
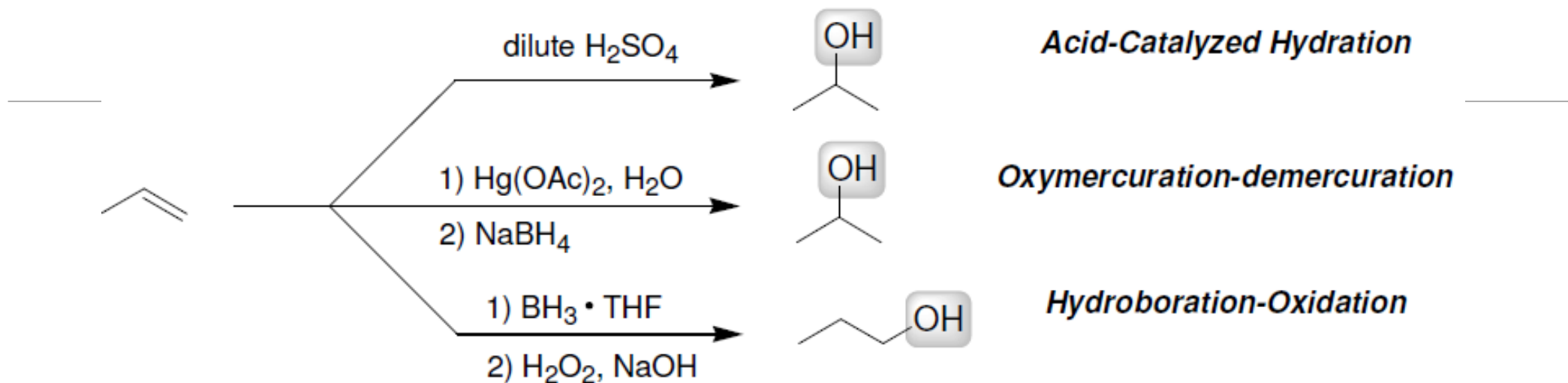
DR. JEHAD ALMALITI

# Alcohol - Preparation

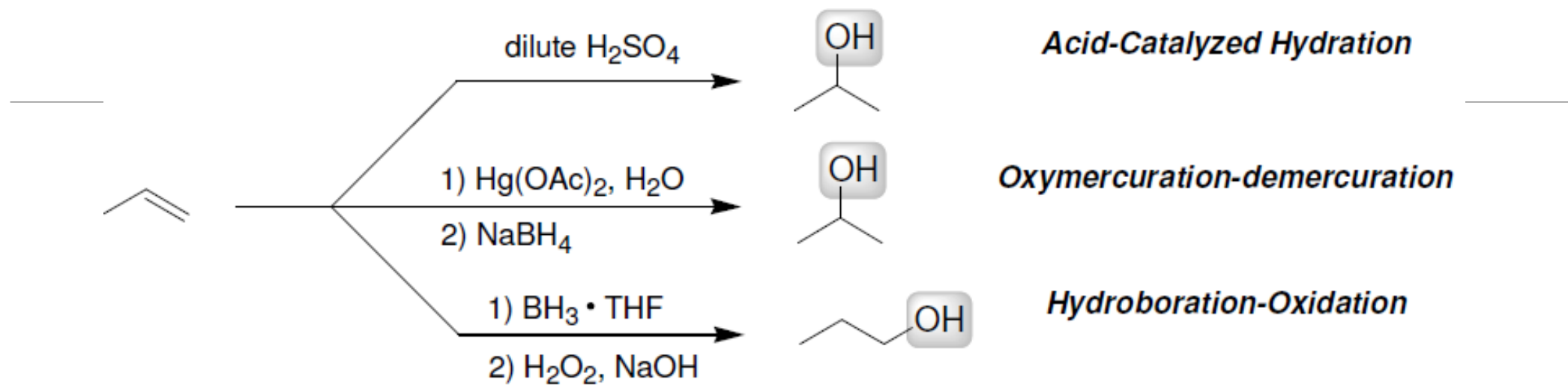
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# Alcohol – Preparation – Alkene Hydration

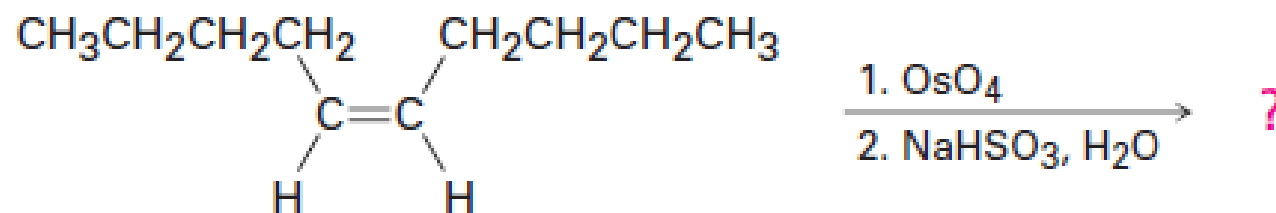
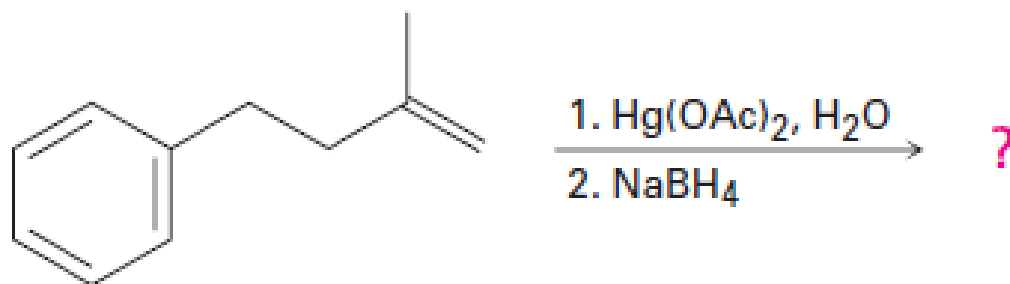
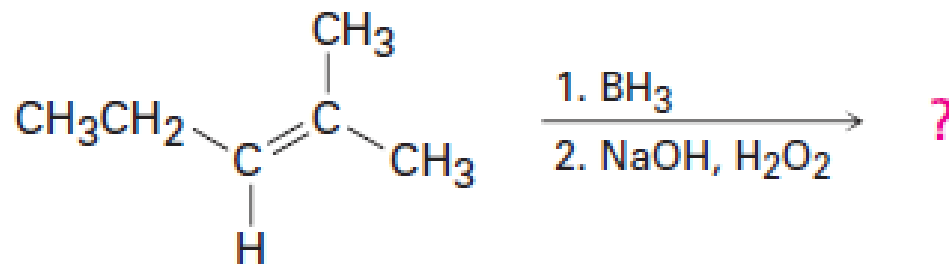


# Alcohol – Preparation – Alkene Hydration



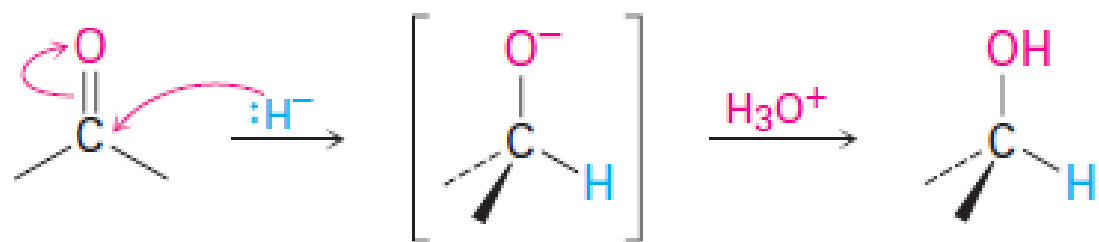
# Alcohol – Preparation – Alkene Hydration

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# Alcohol – Preparation – Carbonyl Reduction

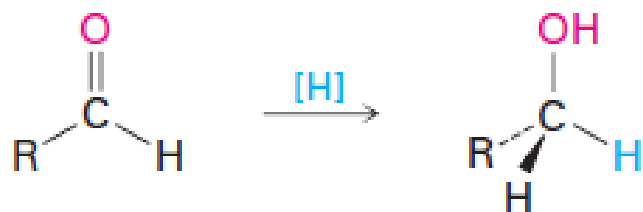
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A carbonyl compound

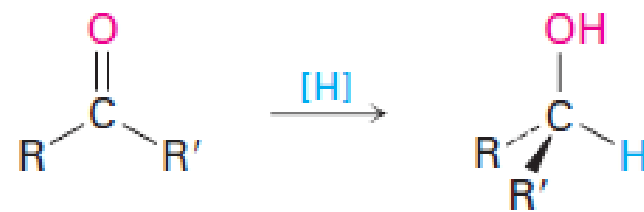
An alkoxide ion intermediate

An alcohol



An aldehyde

A primary alcohol

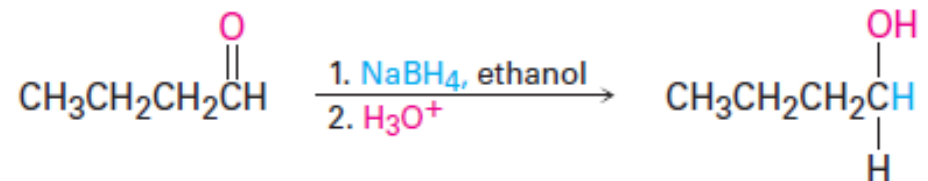


A ketone

A secondary alcohol

# Alcohol – Preparation – Carbonyl Reduction

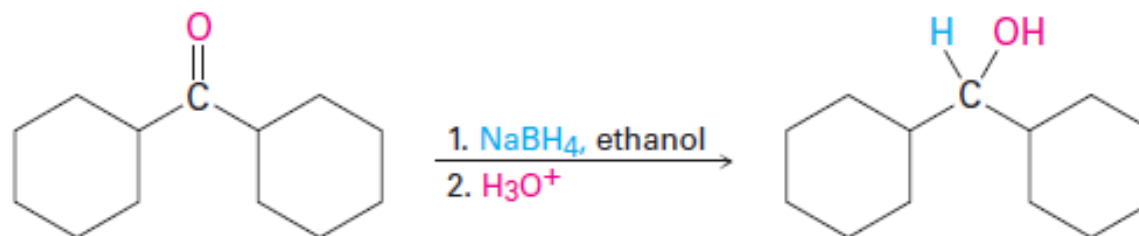
## Aldehyde reduction



Butanal

1-Butanol (85%)  
(a 1° alcohol)

## Ketone reduction



Dicyclohexyl ketone

Dicyclohexylmethanol (88%)  
(a 2° alcohol)

$\text{LiAlH}_4$  is much more reactive than  $\text{NaBH}_4$   
but also more dangerous

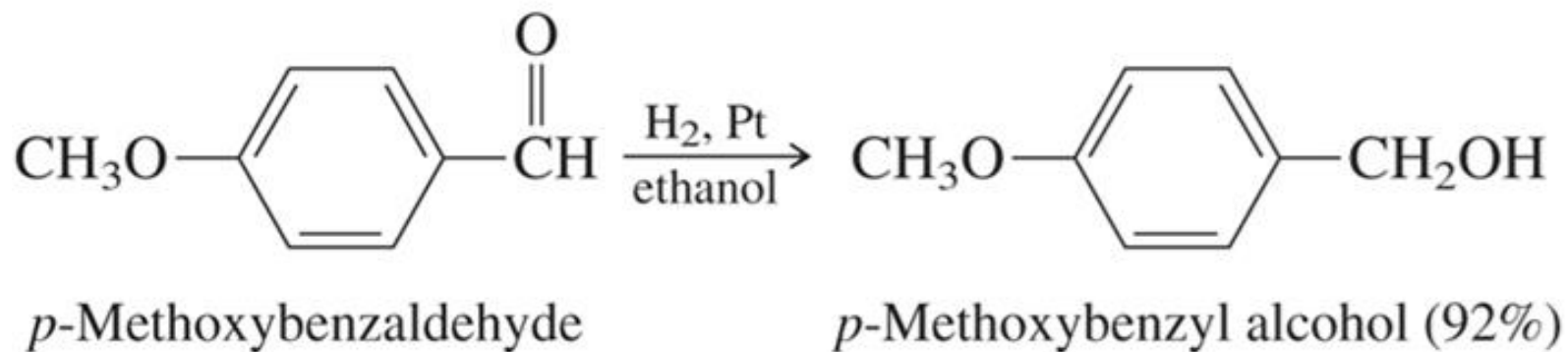
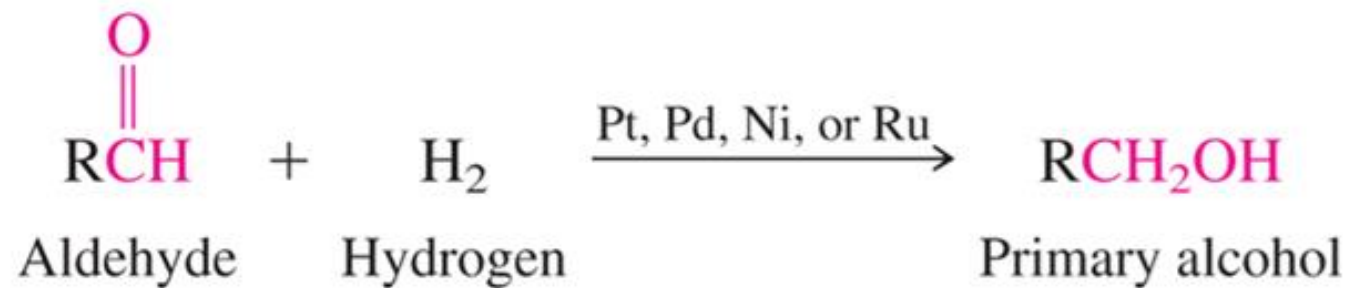
# Question

Which one of the isomeric alcohols of formula  $C_5H_{12}O$  can be prepared by  $LiAlH_4$  reduction of a ketone?

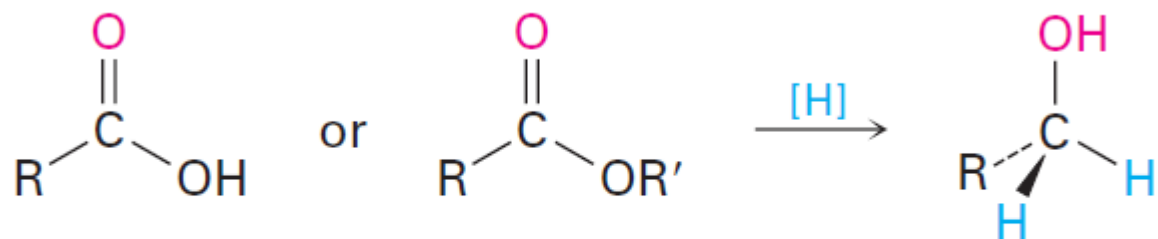
- A) 1-pentanol
- B) 2-methyl-2-butanol
- C) 3-methyl-2-butanol
- D) 2,2-dimethyl-1-propanol

# Alcohol – Preparation – Carbonyl Reduction

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# Alcohol preparation – Carboxylic acid and ester reduction

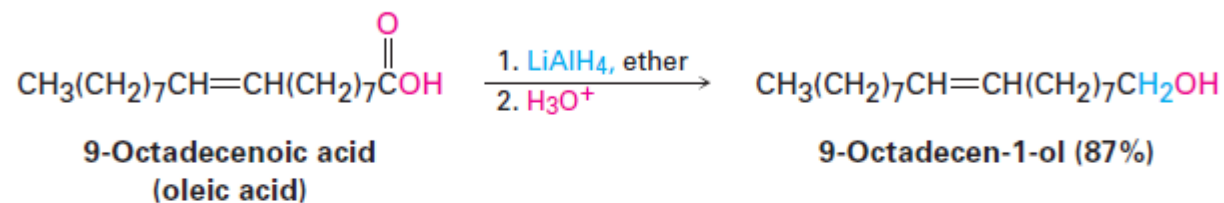


**A carboxylic acid**

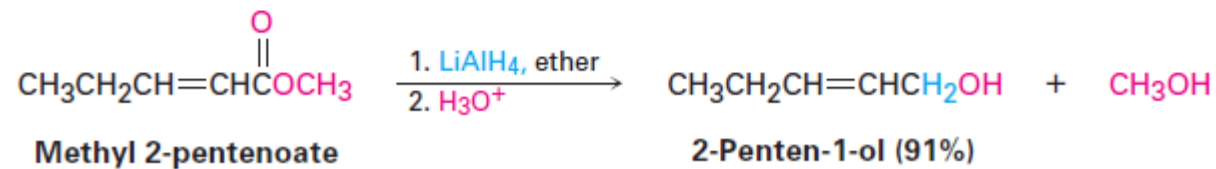
**An ester**

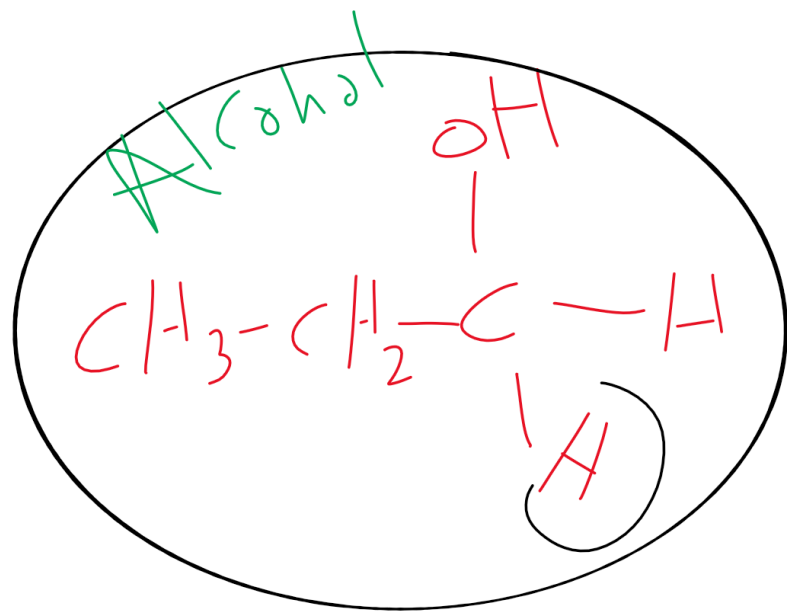
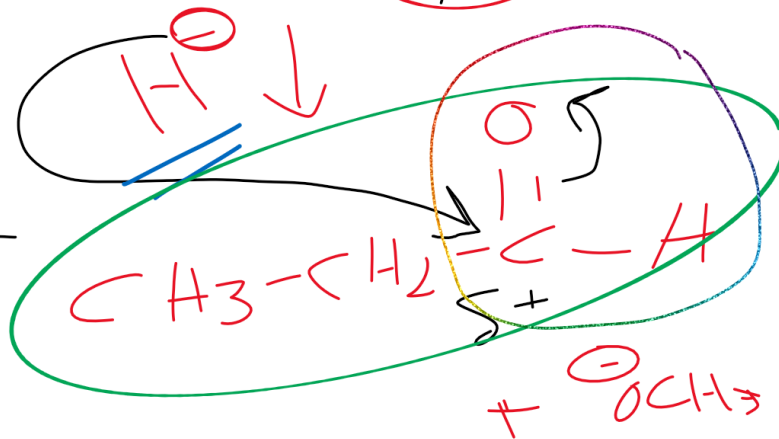
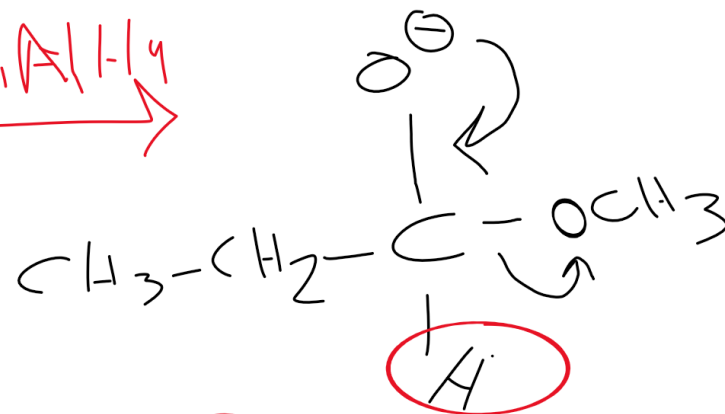
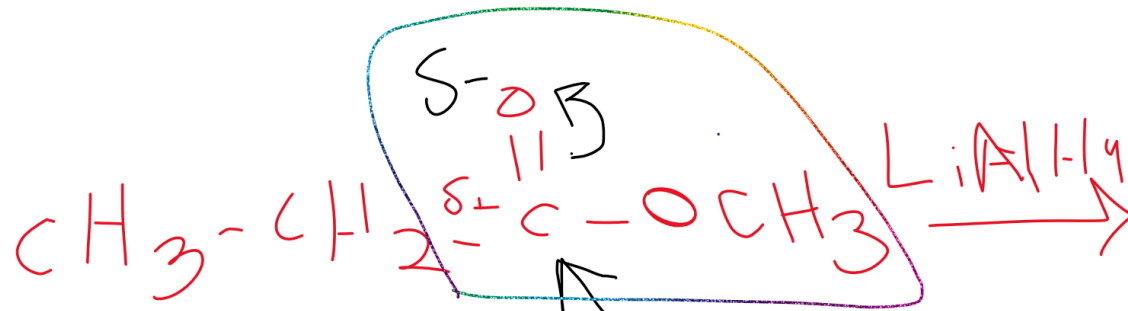
**A primary alcohol**

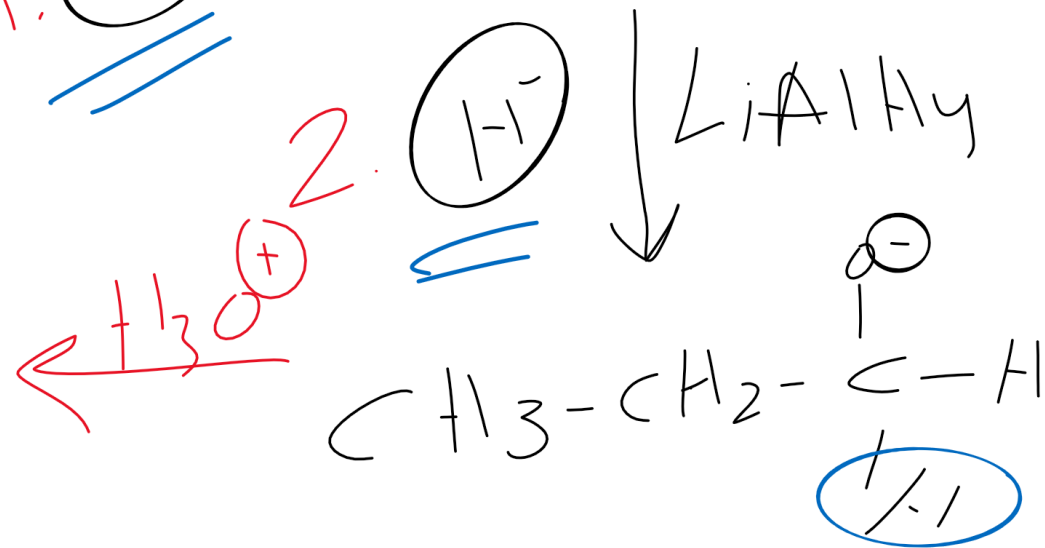
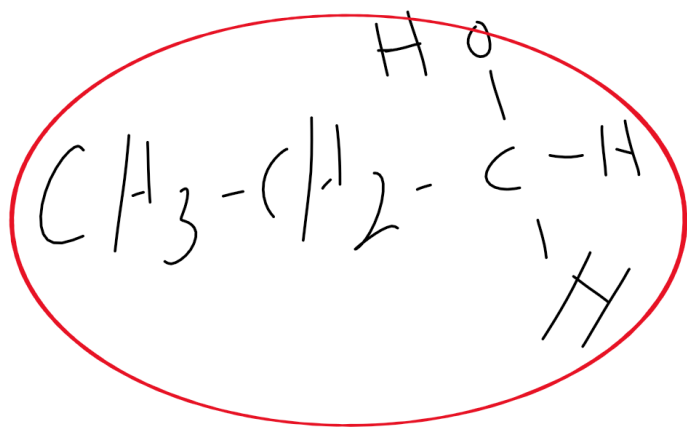
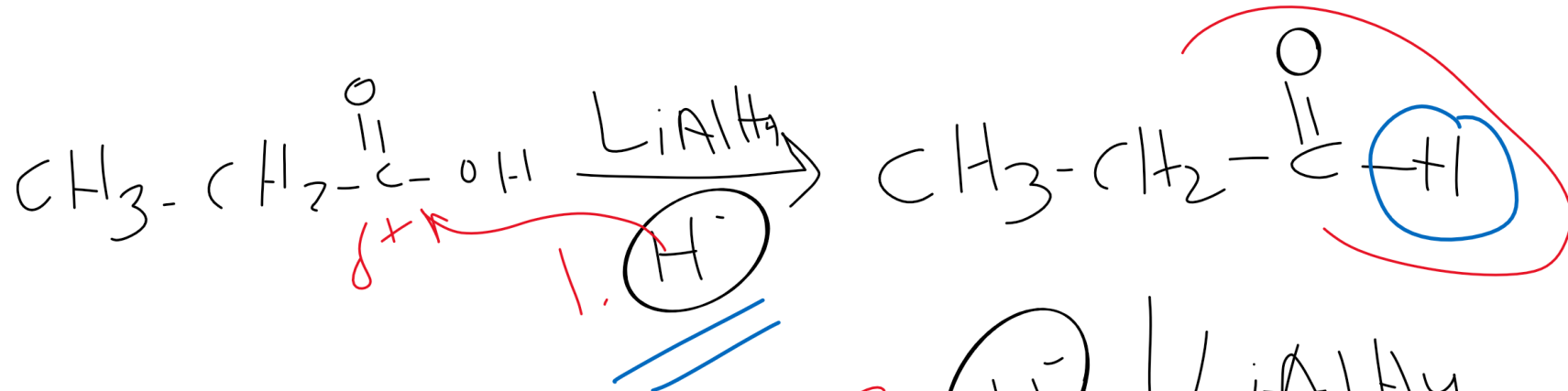
Carboxylic acid reduction



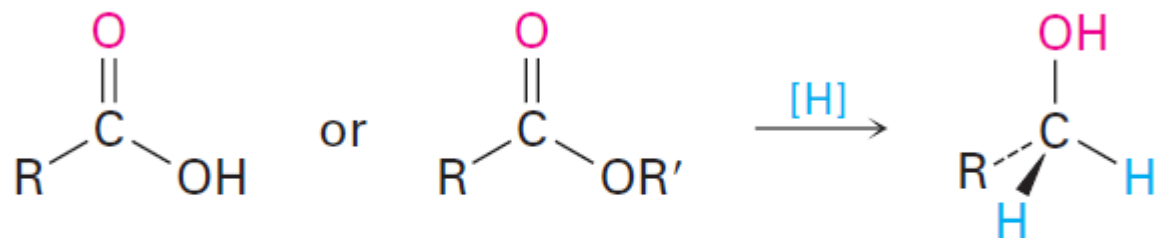
Ester reduction







# Alcohol preparation – Carboxylic acid and ester reduction

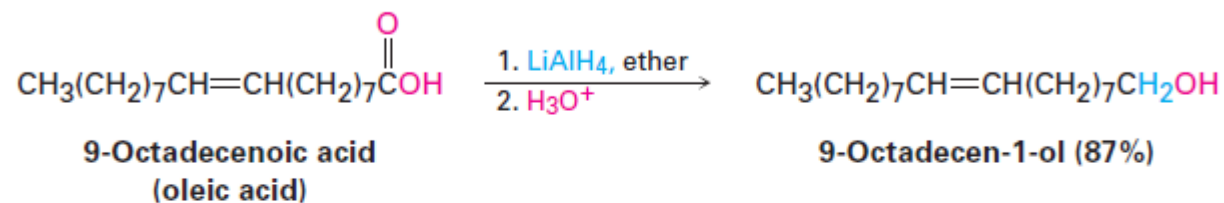


**A carboxylic acid**

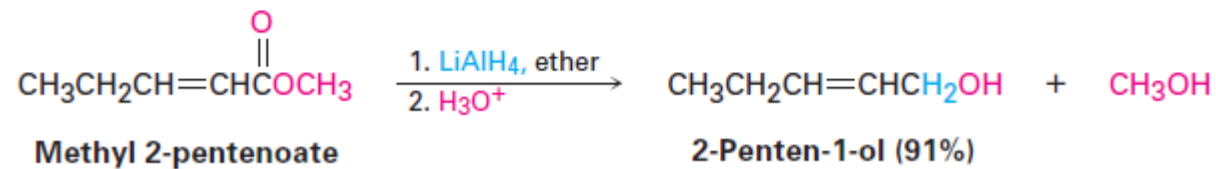
**An ester**

**A primary alcohol**

**Carboxylic acid reduction**



**Ester reduction**



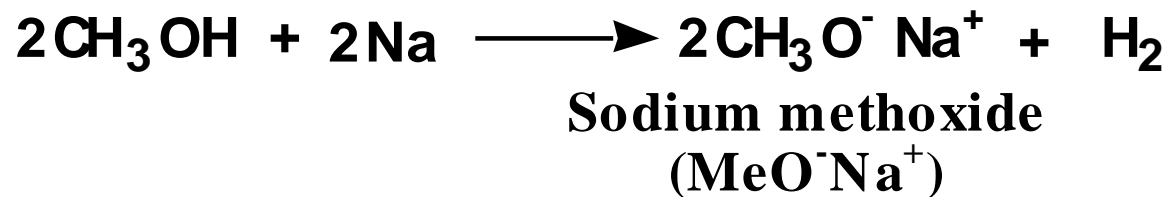
# ALCOHOL REACTIONS

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# Reaction with Metals

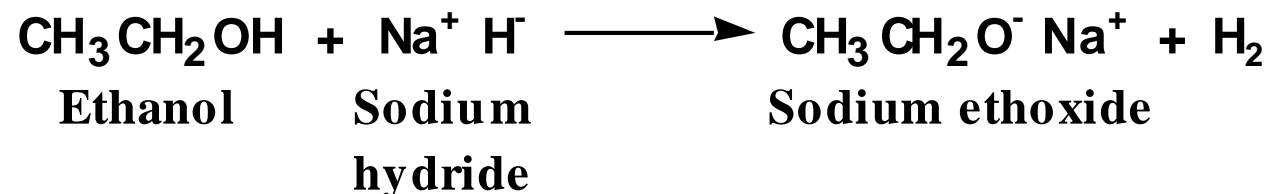
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Alcohols react with Li, Na, K, and other active metals to liberate hydrogen gas and form metal alkoxides



Alcohols are also converted to metal alkoxides by reaction with bases stronger than the alkoxide ion

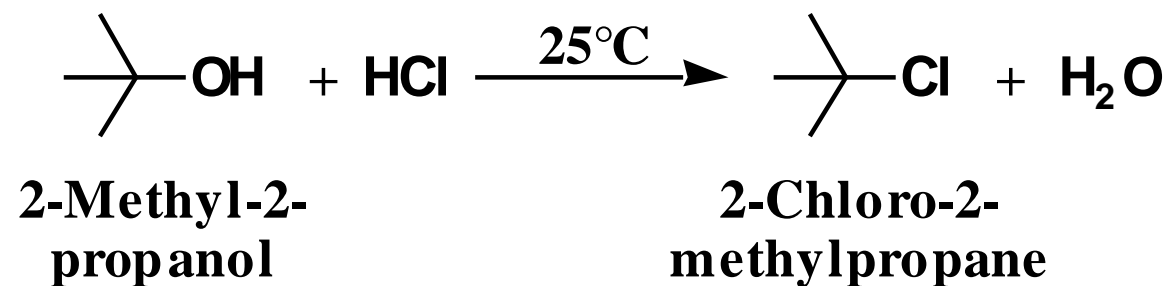
- one such base is sodium hydride



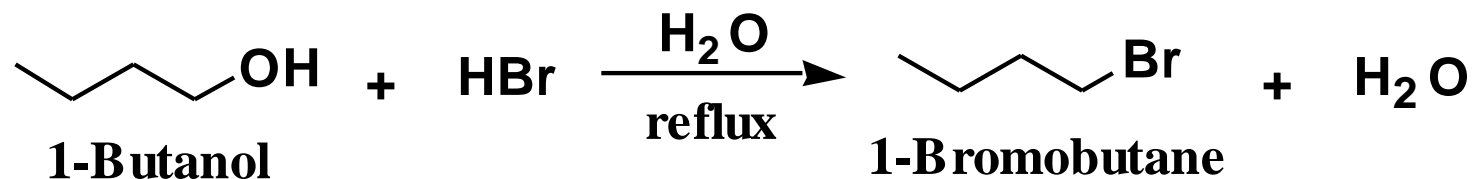
# Reaction with HX

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- 3° alcohols react very rapidly with HCl, HBr, and HI



- low-molecular-weight 1° and 2° alcohols are unreactive under these conditions
- 1° and 2° alcohols require concentrated HBr and HI to form alkyl bromides and iodides



# Reaction with HX

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Based on

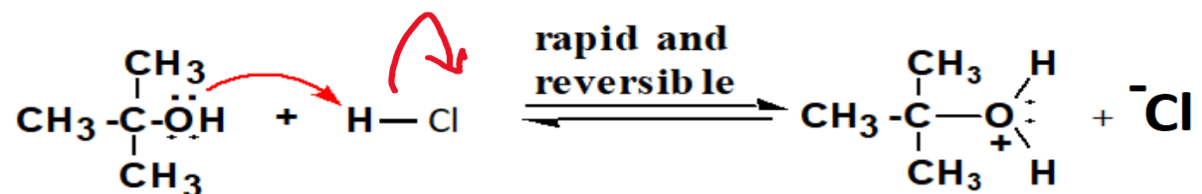
- the relative ease of reaction of alcohols with HX ( $3^\circ > 2^\circ > 1^\circ$ )

Chemists propose that reaction of  $2^\circ$  and  $3^\circ$  alcohols with HX

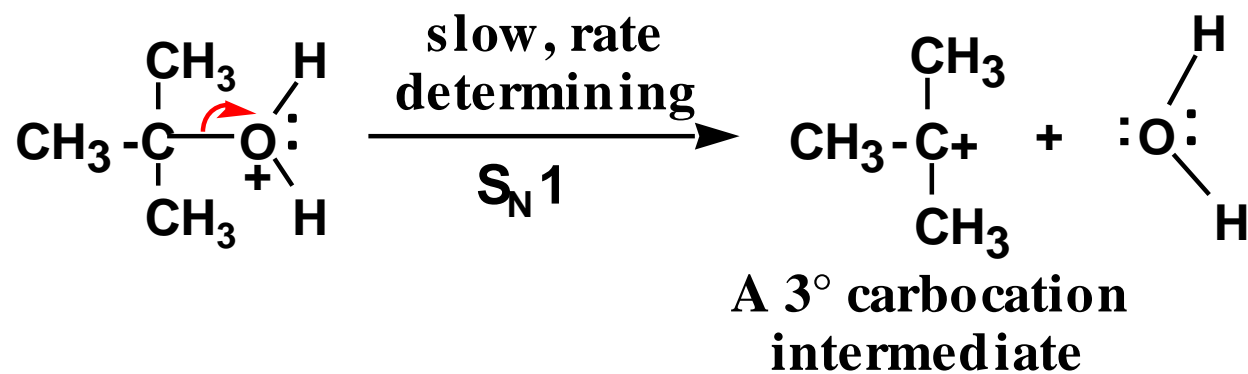
- occurs by an  $S_N1$  mechanism, and
- involves a carbocation intermediate

# Reaction with HX - S<sub>N</sub>1

Step 1: proton transfer to the OH group gives an oxonium ion



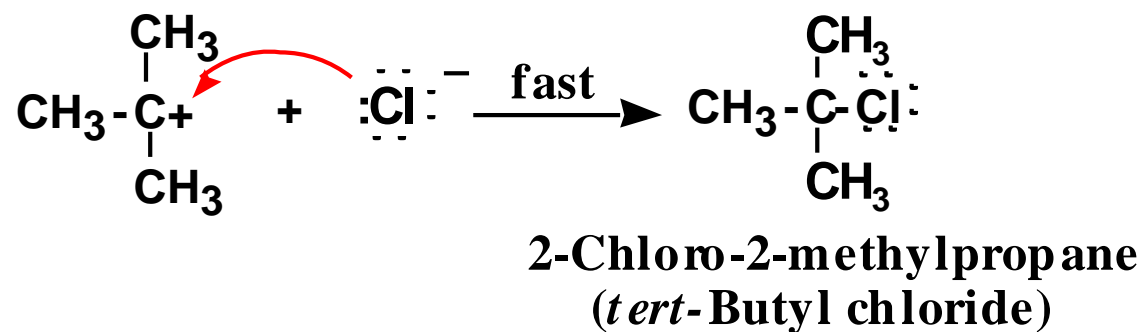
Step 2: loss of H<sub>2</sub>O gives a carbocation intermediate



# Reaction with HX - S<sub>N</sub>1

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Step 3: reaction of the carbocation intermediate (an electrophile) with halide ion (a nucleophile) gives the product

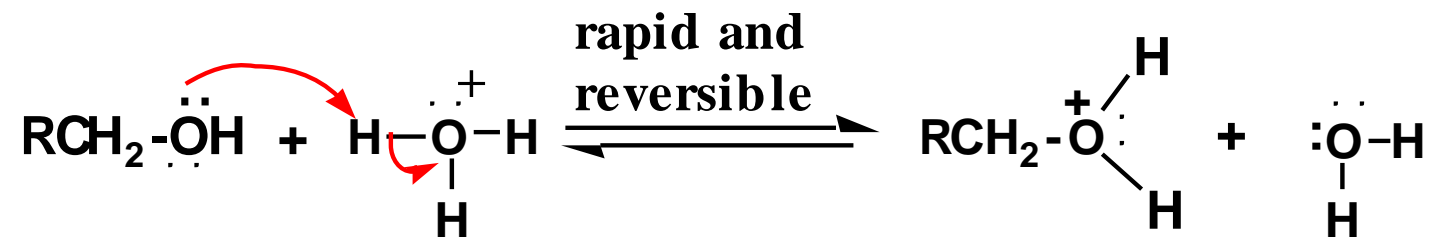


# Reaction with HX - S<sub>N</sub>2

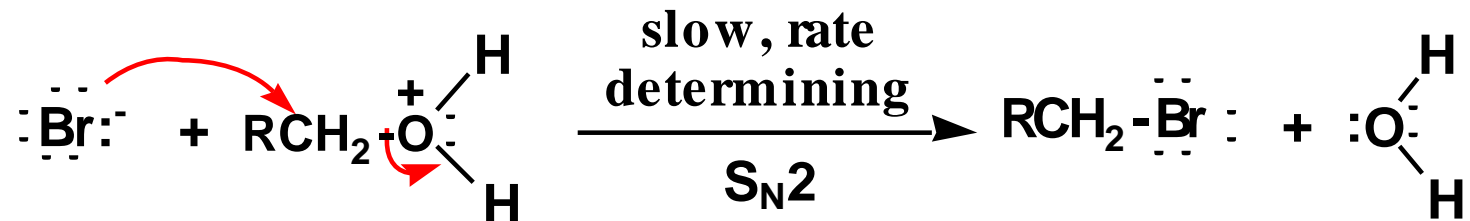
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1° alcohols react with HX by an S<sub>N</sub>2 mechanism

Step 1: rapid and reversible proton transfer



Step 2: displacement of HOH by halide ion

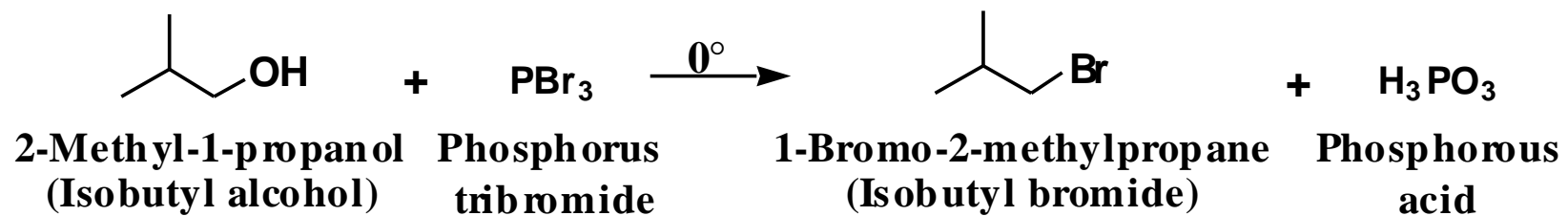


# Reaction with $\text{PBr}_3$

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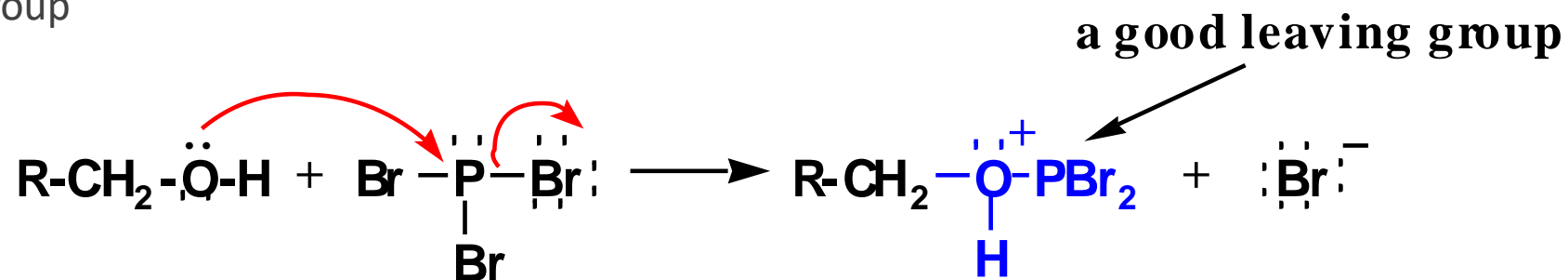
An alternative method for the synthesis of  $1^\circ$  and  $2^\circ$  bromoalkanes is reaction of an alcohol with phosphorus tribromide

- this method gives less rearrangement than with  $\text{HBr}$



# Reaction with PBr<sub>3</sub>

Step 1: formation of a protonated dibromophosphite converts H<sub>2</sub>O, a poor leaving group, to a good leaving group



Step 2: displacement by bromide ion gives the alkyl bromide

