

Alcohols Reactions

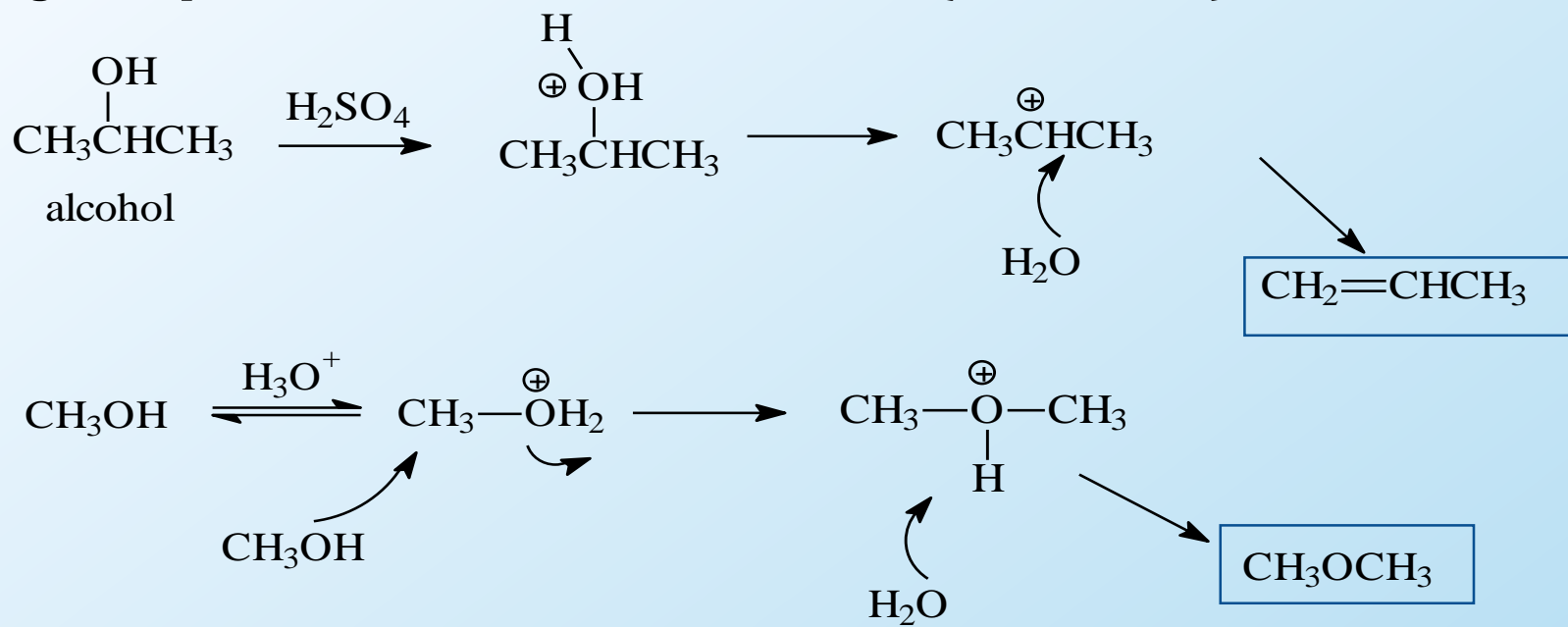
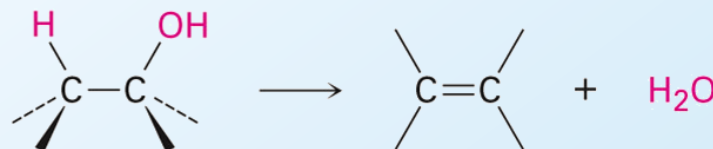
Dr. Sapna Gupta

Types of Alcohol Reactions

- Dehydration to alkene
- Substitution to form alkyl halide
- Tosylation
- Oxidation

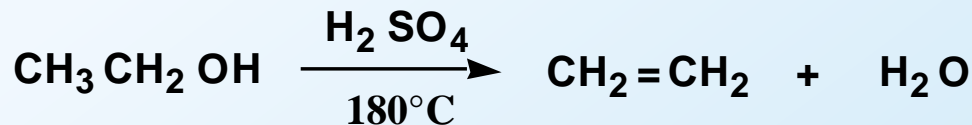
Dehydration Reactions

- Conc. H_2SO_4 produces alkene via E1.
- Carbocation is the intermediate.
- Rearrangement can also occur.
- Zaitsev product is predominant.
- Low temp, 140°C and below, favors ether (substitution – *will cover in ethers*)
- High temp, 180°C and above, favors alkene (elimination)

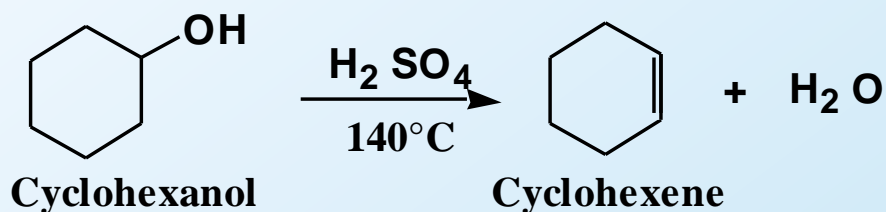


Dehydration Contd...

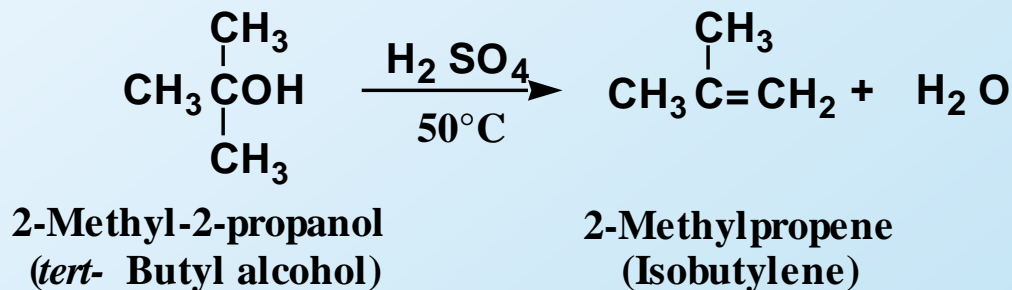
- Primary Alcohols



- Secondary Alcohols

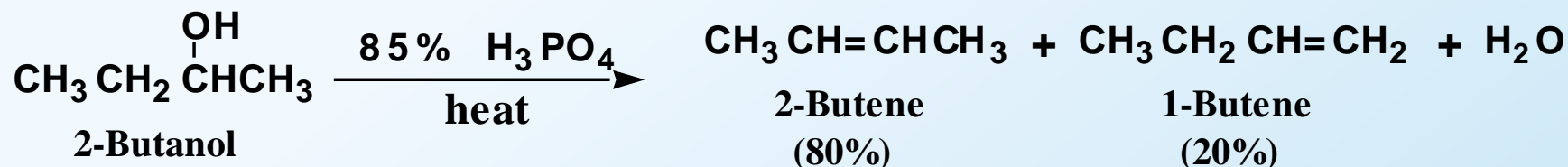


- Tertiary Alcohols

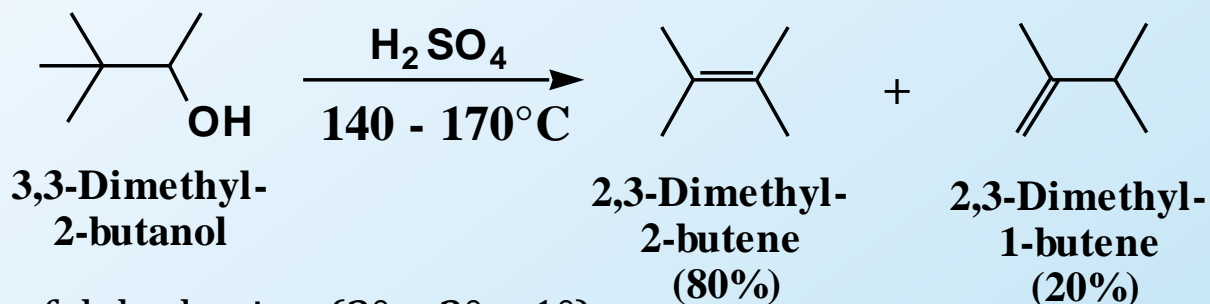


Dehydration Contd...

- Where possible, the alkene having the greater number of substituents on the double bond (the more stable alkene) is the major product (Zaitsev rule).



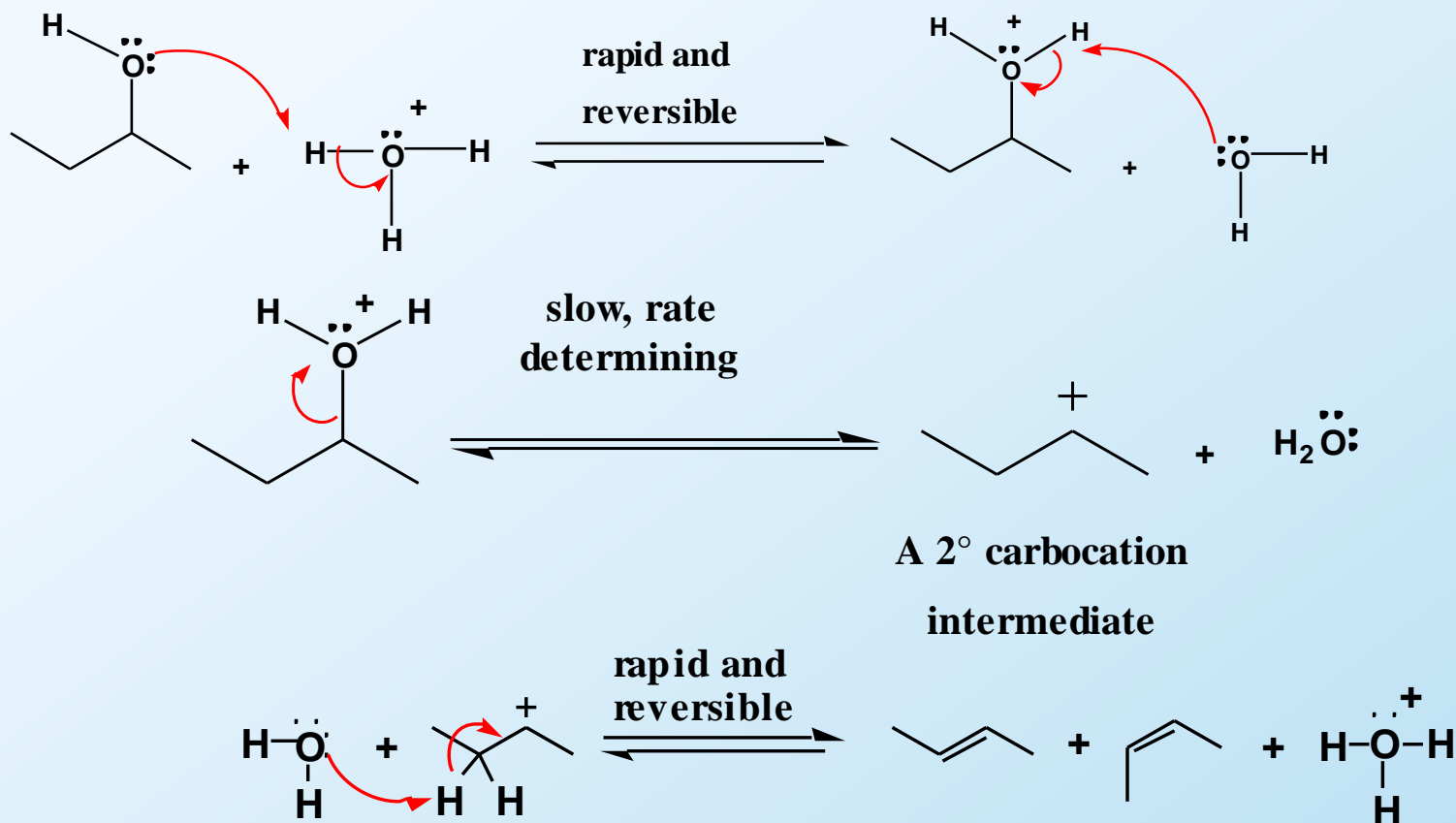
- Dehydration of 1° and 2° alcohols may give rearranged alkenes.



- Ease of dehydration ($3^\circ > 2^\circ > 1^\circ$)

Dehydration - Mechanism

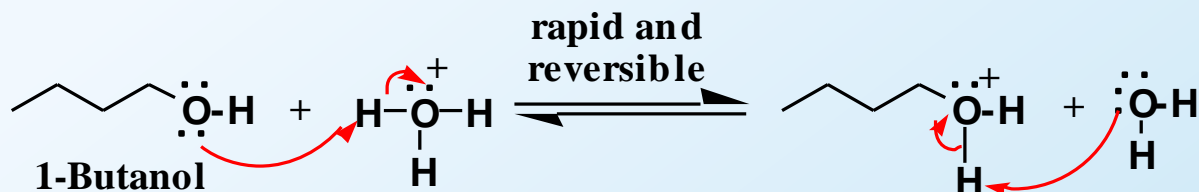
Protonation of alcohol followed by formation of carbocation (*this is where rearrangement can occur*) and finally elimination step (*this is where Zaitsev's product is formed*) gives the alkene.



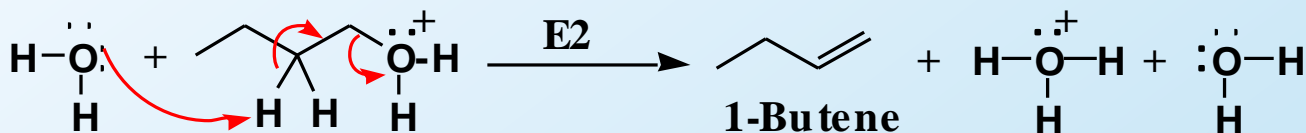
Dehydration – Zaitsev's Product

- Primary alcohols give Zaitsev's (from hydride shift) and Hoffman's product (by regular E2 mechanism).

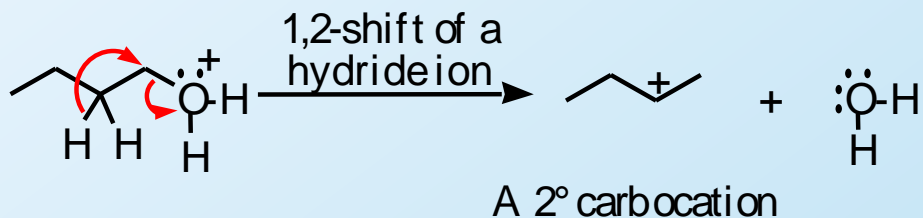
Protonation
of alcohol



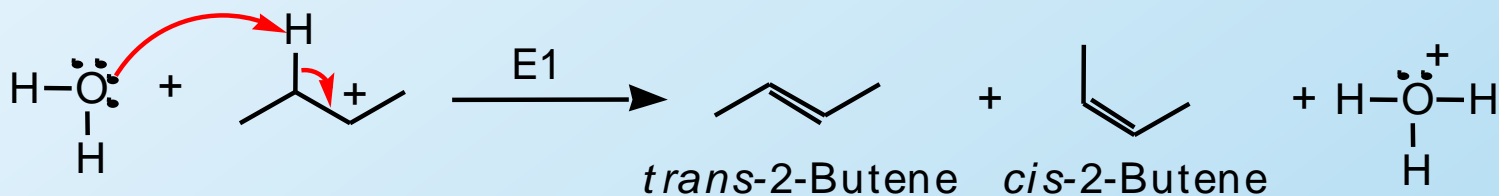
E2 elimination to
give Hoffman's
product



Hydride shift to give a
more stable
carbocation

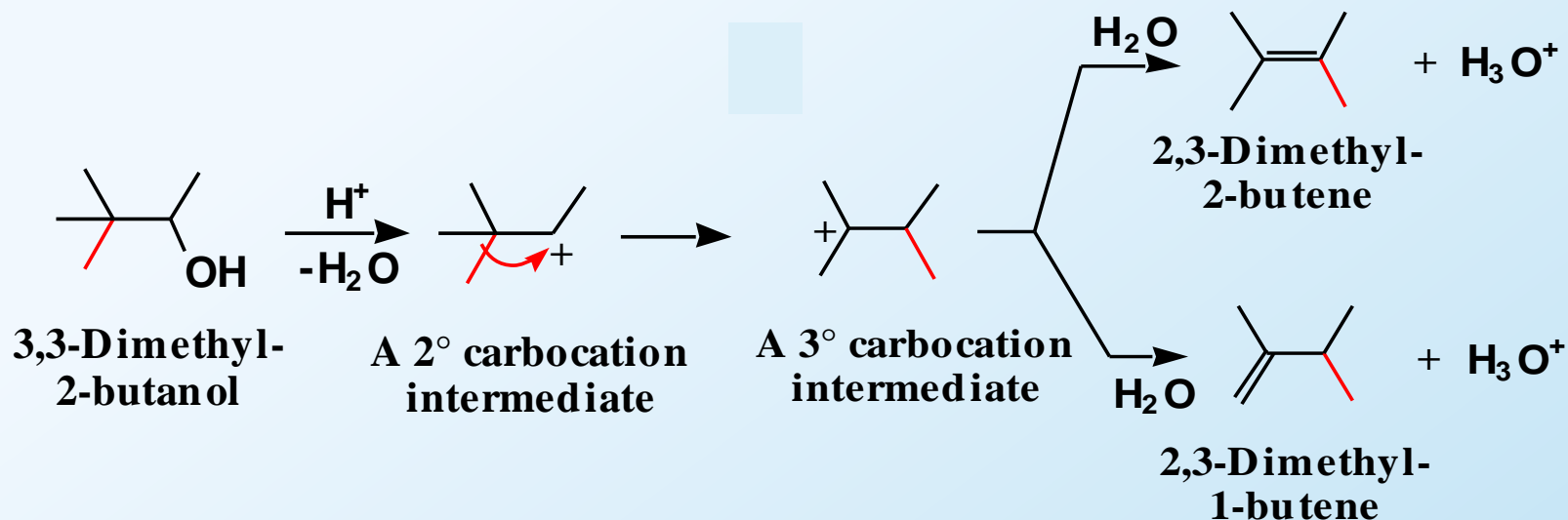


E1 elimination
to give Zaitsev's
product



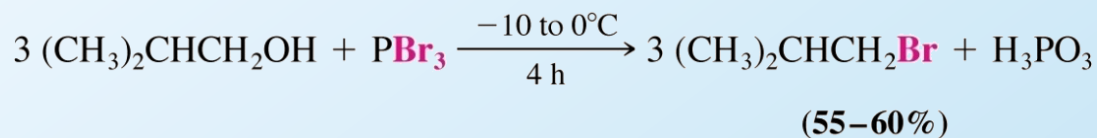
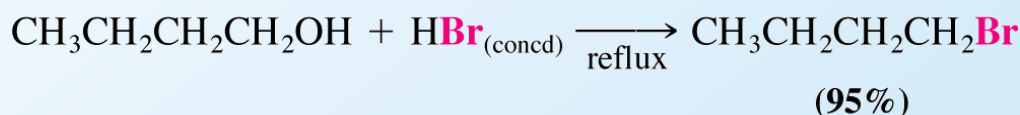
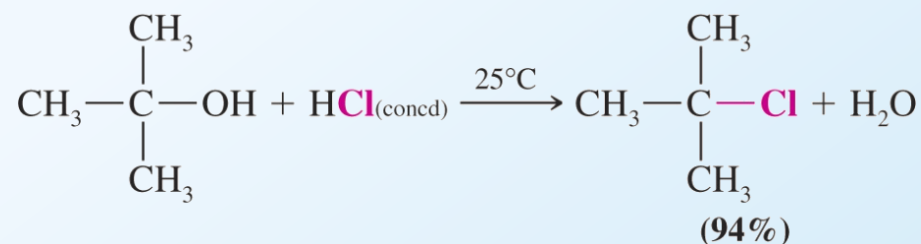
Dehydration - Rearrangement

- This is usually for secondary alcohols and can involve a hydride or methyl shift.

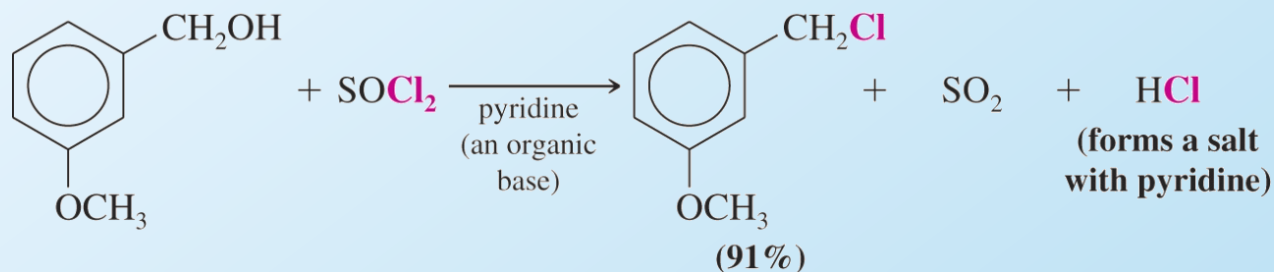


Alkyl Halides from Alcohols

- Hydroxyl groups are poor leaving groups, and as such, are often converted to alkyl halides when a good leaving group is needed
- Three general methods exist for conversion of alcohols to alkyl halides, depending on the classification of the alcohol and the halogen desired. Reagents used are: hydrogen halides, phosphorus tribromide and thionyl chloride.



Can also use PCl_3 or PCl_5 to get alkylhalide



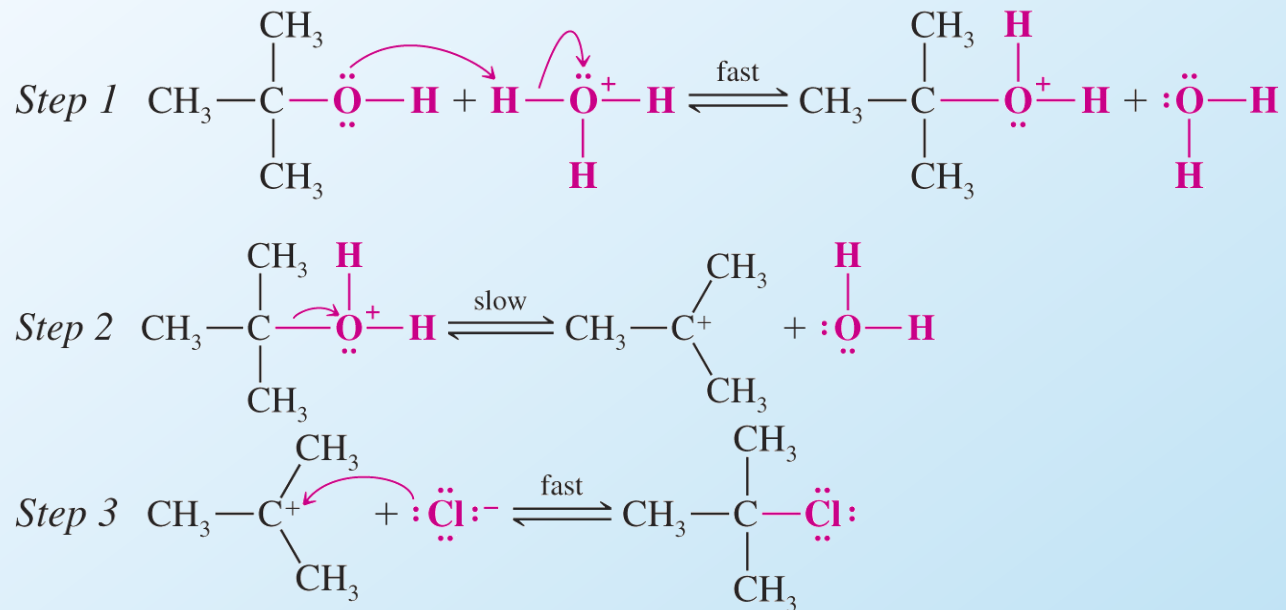
Reaction with Hydrogen Halide contd..

The order of reactivity is as follows

- Hydrogen halide $\text{HI} > \text{HBr} > \text{HCl} > \text{HF}$
- Type of alcohol $3^\circ > 2^\circ > 1^\circ < \text{methyl}$

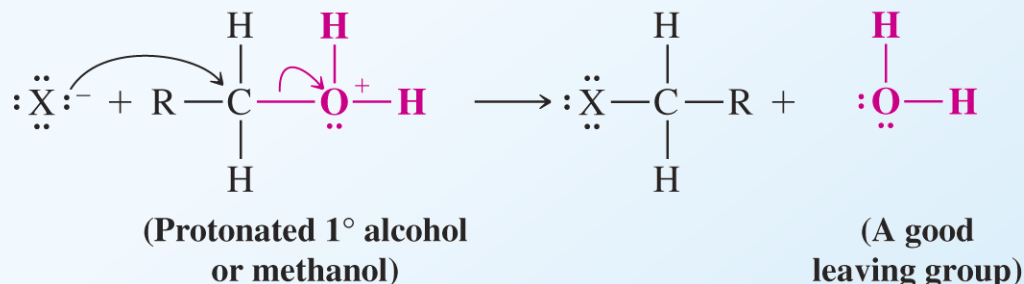
Mechanism of the Reaction of Alcohols with HX:

- $\text{S}_{\text{N}}1$ mechanism for 3° , 2° , allylic and benzylic alcohol.
- These reactions are prone to carbocation rearrangements

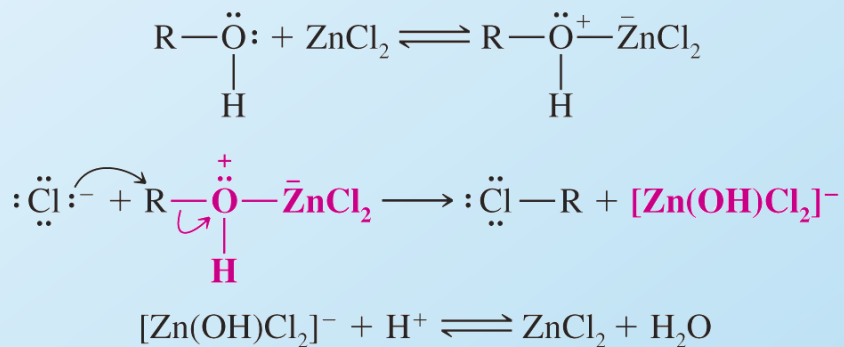


Reaction with Hydrogen Halide contd..

- Primary and methyl alcohols undergo substitution by an S_N2 mechanism

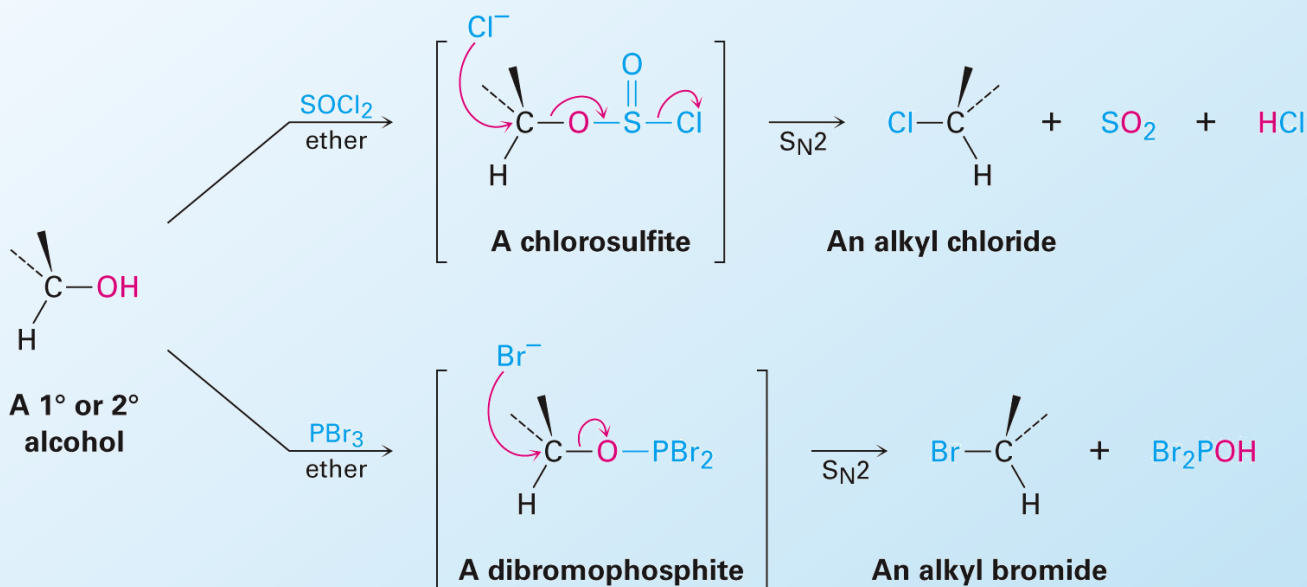
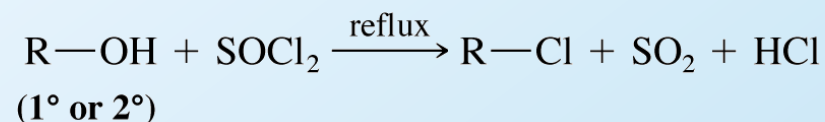
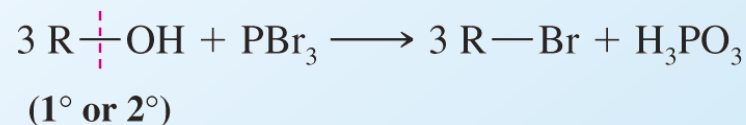


- Reaction with HCl
- Add ZnCl₂, which bonds strongly with -OH, to promote the reaction.
- The chloride product is insoluble.
- Lucas test:** ZnCl₂ in conc. HCl
 - 1° alcohols react slowly or not at all.
 - 2° alcohols react in 1-5 minutes.
 - 3° alcohols react in less than 1 minute.
- Limitation: Carbocation intermediate may rearrange.



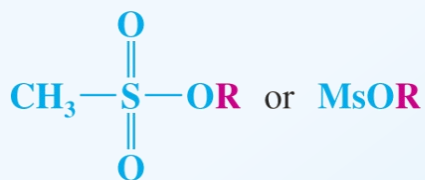
Reaction with PCl_5 and SOCl_2

- Good yields with 1° and 2° alcohols
- PCl_3 for alkyl chloride (but SOCl_2 better)
- PBr_3 for alkyl bromide
- Mechanism is $\text{S}_\text{N}2$ – no rearrangement
- P and I_2 for alkyl iodide (PI_3 not stable)

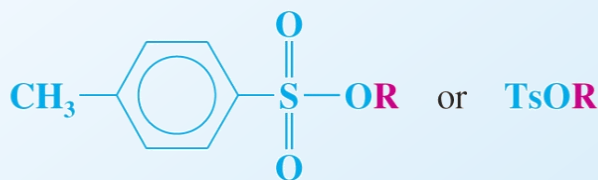


Tosylates and Mesylates

- The hydroxyl group of an alcohol can be converted to a good leaving group by conversion to a sulfonate ester.

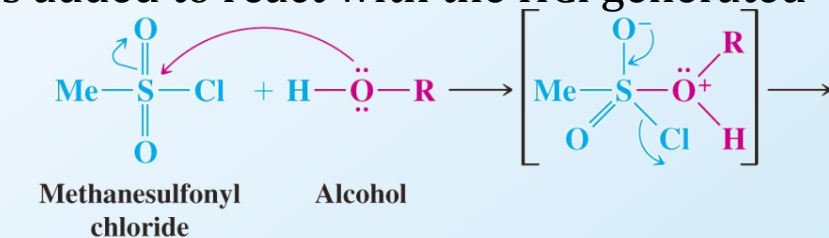


An alkyl mesylate



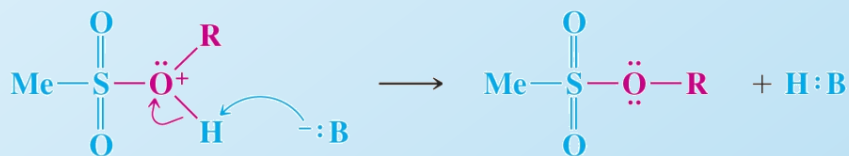
An alkyl tosylate

- Sulfonyl chlorides are used to convert alcohols to sulfonate esters
- Base is added to react with the HCl generated



The alcohol oxygen attacks the sulfur atom of the sulfonyl chloride.

The intermediate loses a chloride ion.



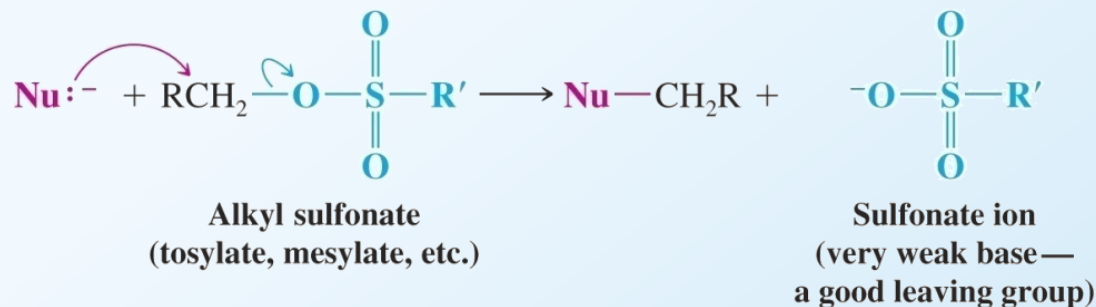
(a base)

Alkyl methanesulfonate

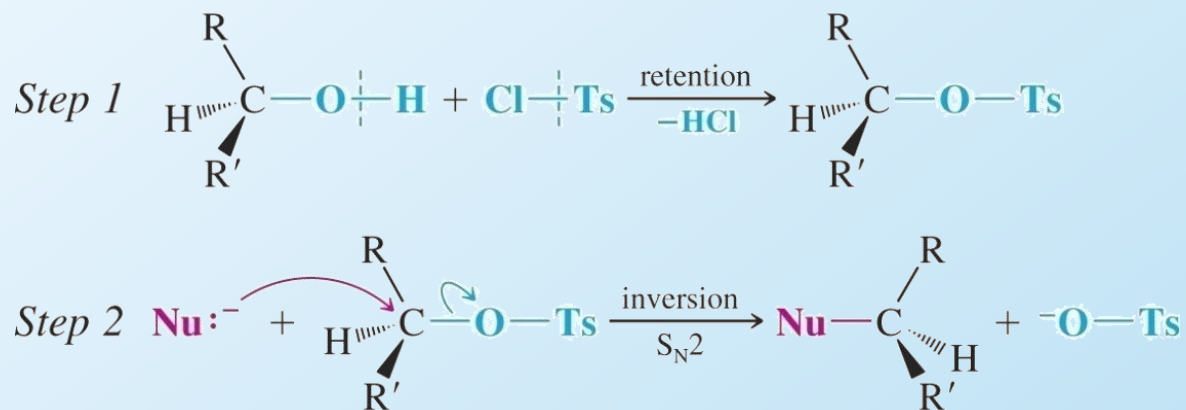
Loss of a proton leads to the product.

Tosylates and Mesylates contd..

- A sulfonate ion (a weak base) is an excellent leaving group

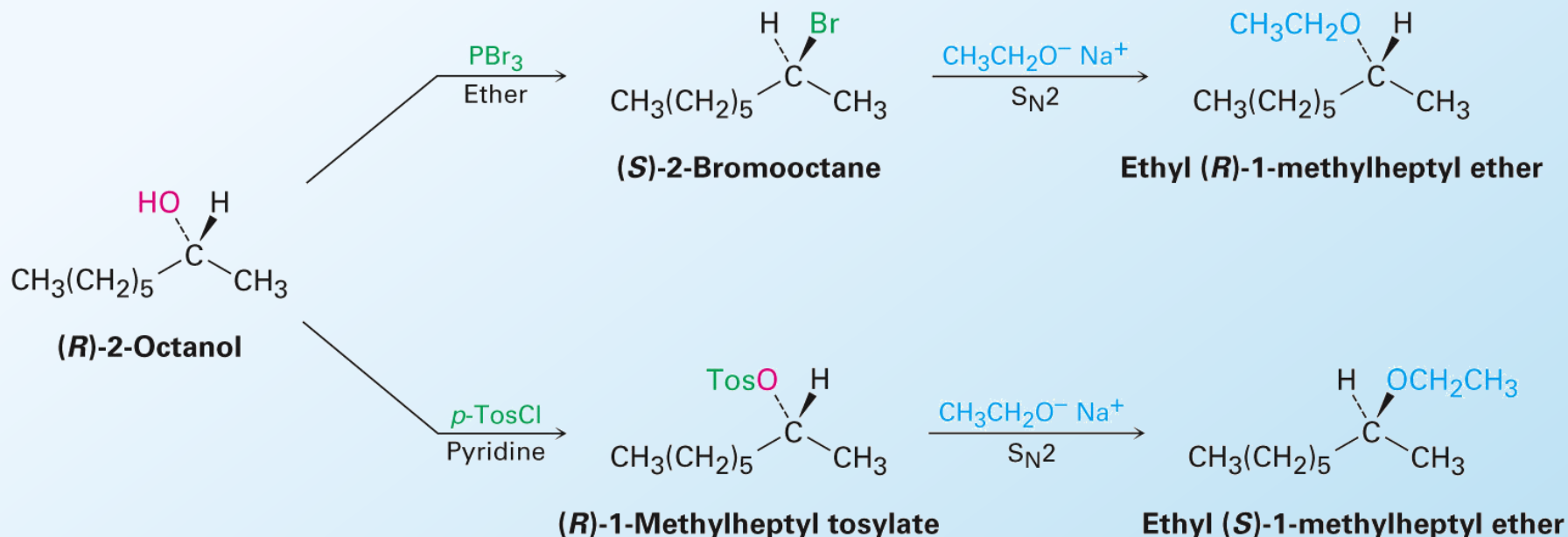


- If the alcohol hydroxyl group is at a stereo center then the overall reaction with the nucleophile proceeds with inversion of configuration ($\text{S}_{\text{N}}2$). The second step to form a sulfonate ester proceeds with retention of configuration.



Stereochemistry of Tosylates

- The S_N2 reaction of an alcohol via an alkyl halide proceeds with *two* inversions, giving product with same arrangement as starting alcohol
- The S_N2 reaction of an alcohol via a tosylate, produces inversion at the chirality center



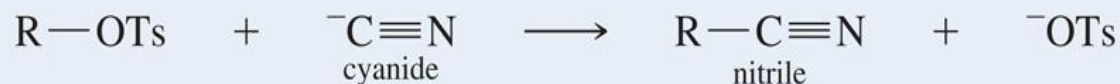
S_N2 Reactions of Tosylates

SUMMARY S_N2 Reactions of Tosylate Esters

With hydroxide produces alcohol



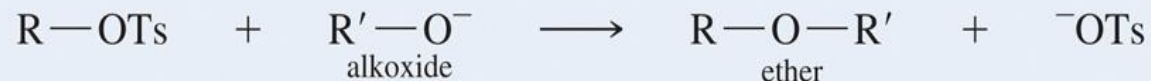
With cyanide produces nitrile



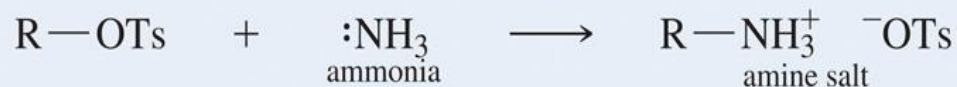
With halide ion produces alkyl halide



With alkoxide ion produces ether



With ammonia produces amine salt

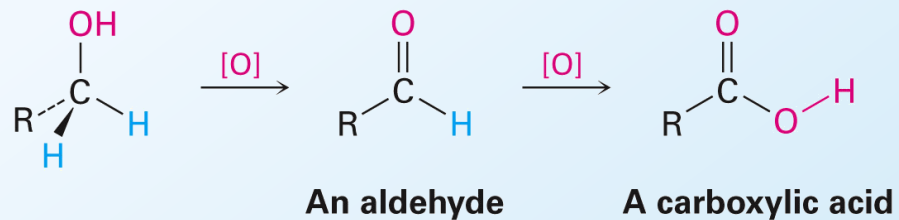


With LiAlH₄ produces alkane

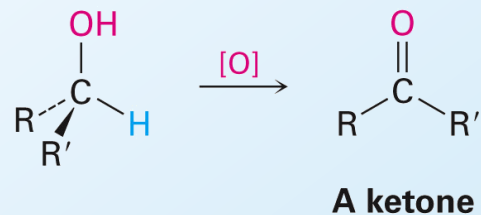


Oxidation of Alcohols

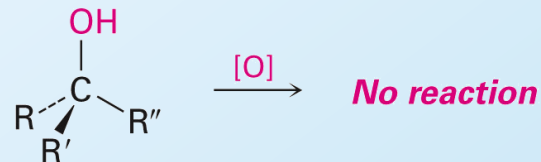
Primary alcohol



Secondary alcohol



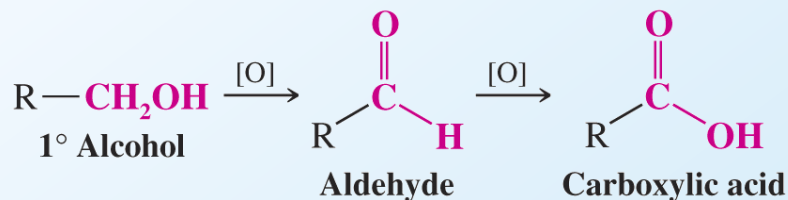
Tertiary alcohol



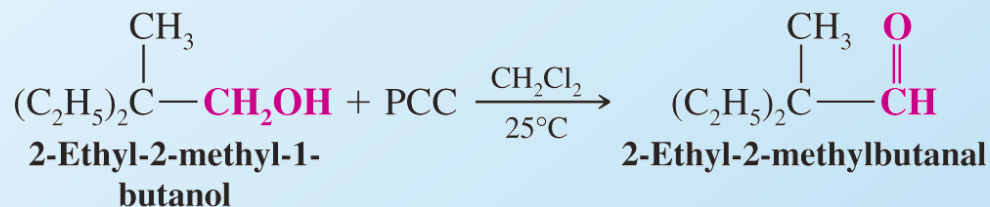
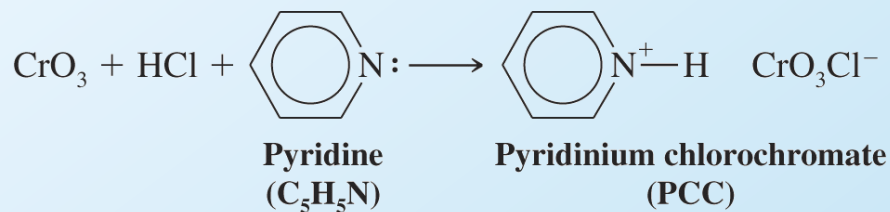
Oxidation of Alcohols contd..

Oxidation of Primary Alcohols to Aldehydes

- A primary alcohol can be oxidized to an aldehyde or a carboxylic acid. The oxidation is difficult to stop at the aldehyde stage and usually proceeds to the carboxylic acid



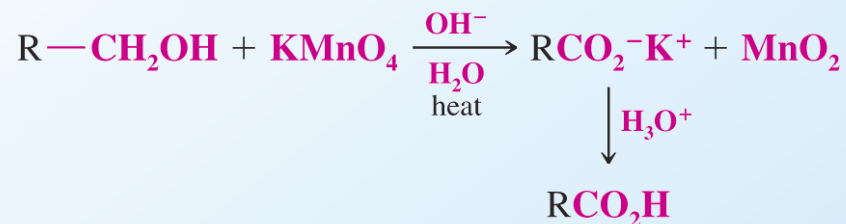
- A reagent which stops the oxidation at the aldehyde stage is pyridinium chlorochromate (PCC)



Oxidation of Alcohols contd...

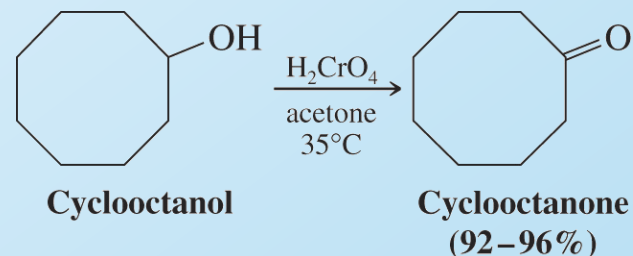
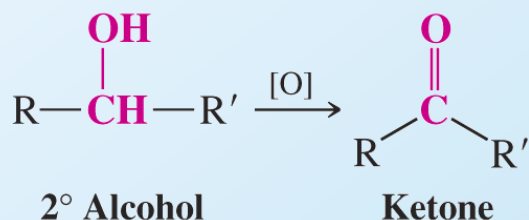
Oxidation of Primary Alcohols to Carboxylic Acids

- Potassium permanganate (KMnO_4) is a typical reagent used for oxidation of a primary alcohol to a carboxylic acid. (a brown precipitate of MnO_2 indicates that oxidation has taken place)



Oxidation of Secondary Alcohols to Ketones

- Oxidation of a secondary alcohol stops at the ketone (e.g. chromic acid (H_2CrO_4) and Jones reagent (CrO_3 in acetone))



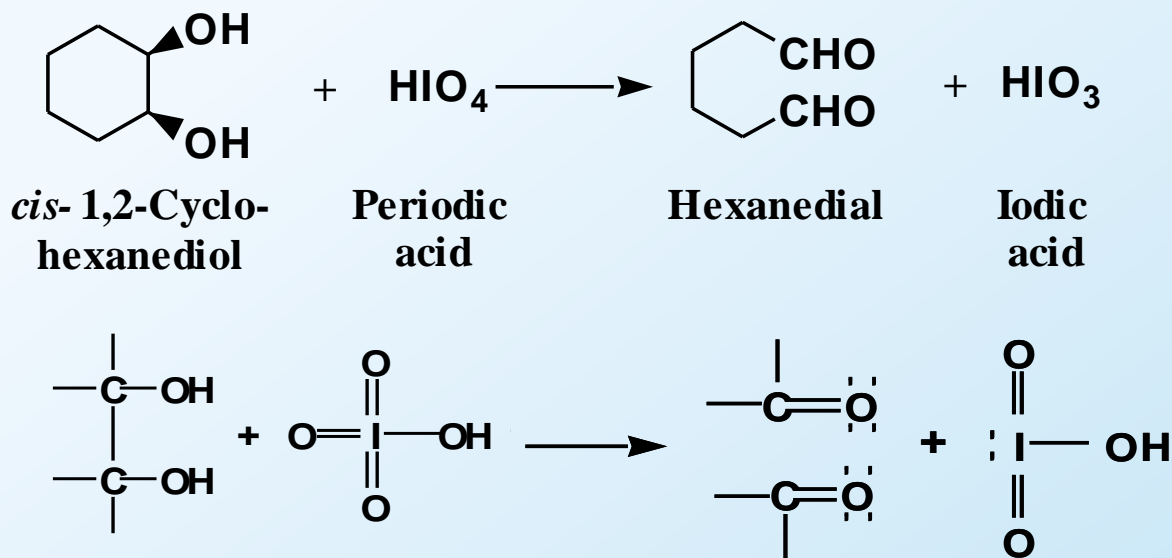
Oxidation of Alcohols contd...

- 3° Alcohols Don't Oxidize
 - Cannot lose 2 H's
 - Basis for chromic acid test

Summary of Oxidation of Alcohols		
Substrate	Product	Reagent
1° Alcohol	Aldehyde	PCC, chromic acid
1° Alcohol	Acid	KMnO ₄
2° Alcohol	Ketone	PCC, chromic acid
3° Alcohol	Don't get oxidized	NR

Oxidation of Glycols

- Glycols (vicinal alcohols) can be cleaved by periodic acid, HIO_4 to give carbonyls – aldehydes or ketones.



Other Oxidizing Agents and Biological Oxidation

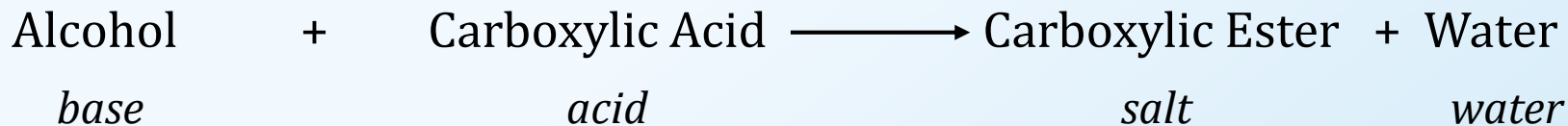
- Other Oxidizing Agents

- Collins reagent: Cr_2O_3 in pyridine
- Jones reagent: chromic acid in acetone
- KMnO_4 (strong oxidizer)
- Nitric acid (strong oxidizer)
- CuO , 300°C (industrial dehydrogenation)

- Biological Oxidation

- Catalyzed by ADH, alcohol dehydrogenase.
- Oxidizing agent is NAD^+ , nicotinamide adenine dinucleotide.
- Ethanol oxidizes to acetaldehyde, then acetic acid, a normal metabolite.
- Methanol oxidizes to formaldehyde, then formic acid, more toxic than methanol.
- Ethylene glycol oxidizes to oxalic acid, toxic.
- Treatment for poisoning is excess ethanol.

Esterification



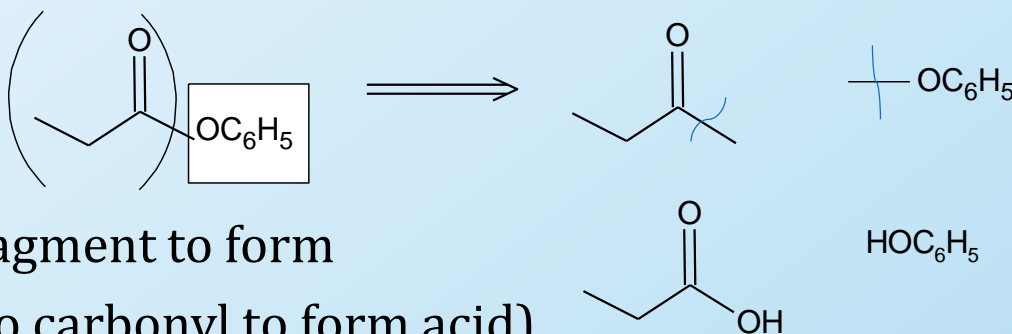
- Acid is needed to catalyze the reaction.
- The reaction is similar to acid base reaction.



For example: what alcohol and acid is required to make $\text{CH}_3\text{CH}_2\text{COOC}_6\text{H}_5$?

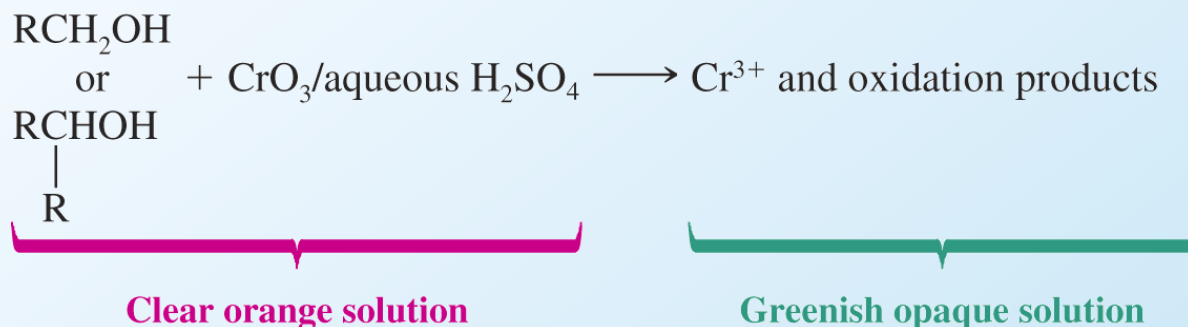
Cleave between the carbonyl
and "O" group.

Add HO-H to the appropriate fragment to form
the acid and alcohol. (OH goes to carbonyl to form acid)



Alcohol Analysis

- A Chemical Test for Primary and Secondary Alcohols
 - Chromium oxide in acid has a clear orange color which changes to greenish opaque if an oxidizable alcohol is present



Key Concepts

- Dehydration of alcohols (Zaitsev's product and rearrangement)
- Synthesis of alkyl halides from alcohols (stereochemistry)
- Mesylates and tosylates (stereochemistry)
- Oxidation of alcohols
- Esterification
- Analysis of alcohols