

## Reactions of Alcohols

Alcohols are versatile organic compounds since they undergo a wide variety of transformations – the majority of which are either oxidation or reduction type reactions.

Oxidation is a loss of electrons

Reduction is a gain of electrons.

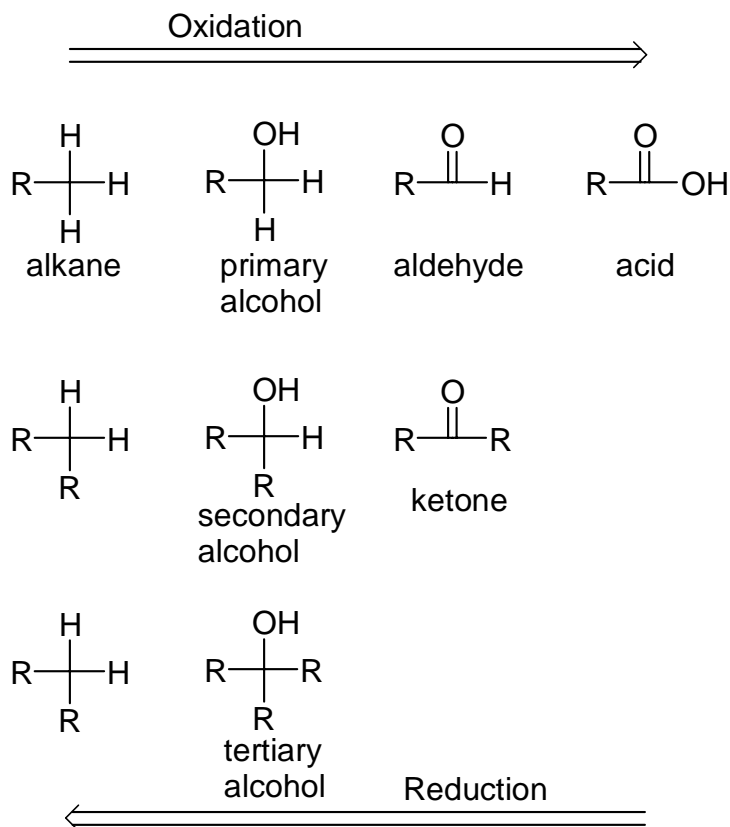
But in organic terms:

Oxidation: loss of H<sub>2</sub>; addition of O or O<sub>2</sub>; addition of X<sub>2</sub> (halogens).

Reduction: addition of H<sub>2</sub> or H<sup>-</sup>; loss of O or O<sub>2</sub>; loss of X<sub>2</sub>.

(Neither an oxidation or reduction: Addition or loss of H<sup>+</sup>, H<sub>2</sub>O, HX).

Oxidation-Reduction Chart:

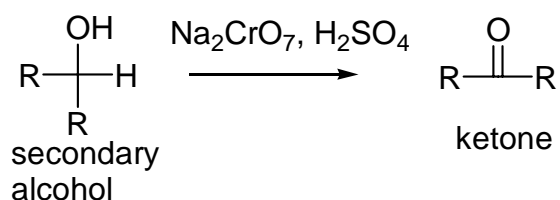


## Oxidation of Alcohols

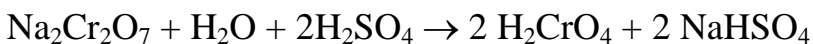
Primary and secondary alcohols are easily oxidized by a variety of reagents.

### Secondary Alcohols

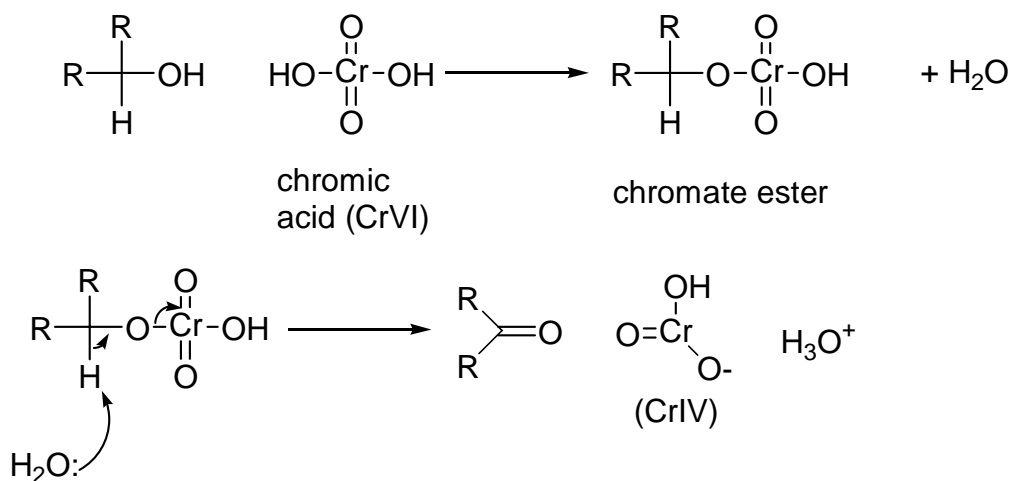
The most common reagent used for oxidation of secondary alcohols to ketones is chromic acid,  $\text{H}_2\text{CrO}_4$ .



Chromic acid is produced in situ by reaction of sodium dichromate, sulfuric acid and water.



### Mechanism of oxidation

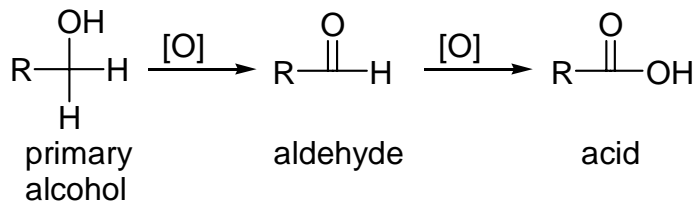


The alcohol and chromic acid produce a chromate ester, which then reductively eliminates the Cr species.

The Cr is reduced (VI  $\rightarrow$  IV), the alcohol is oxidized.

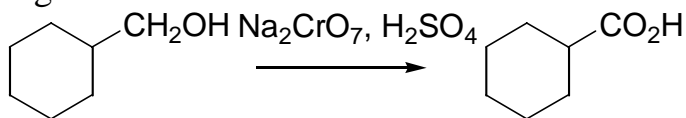
## Oxidation of Primary Alcohols

Primary alcohols are easily oxidized just like secondary alcohols, but the product of oxidation is an aldehyde.

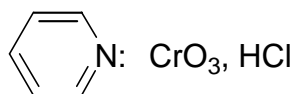


However, the aldehyde can also be easily oxidized to an acid, and this ‘over-oxidation’ is a practical problem.

E.g.

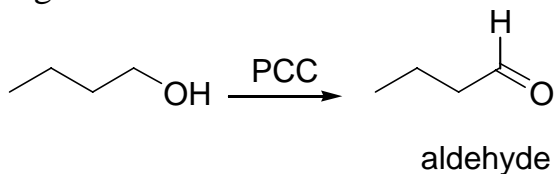


A common reagent that selectively oxidizes a primary alcohol to an aldehyde (and no further) is pyridinium chlorochromate, PCC.



(PCC)

E.g.

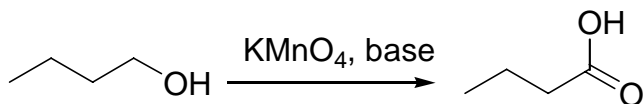


### Tertiary Alcohols

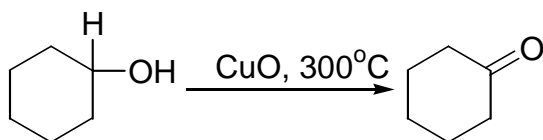
These are resistant to oxidation because they have no hydrogen atoms attached to the oxygen bearing carbon (carbinol carbon).

### Other Oxidizing Reagents

Potassium permanganate is a cheaper but stronger oxidizing agent, and conditions must be controlled carefully.

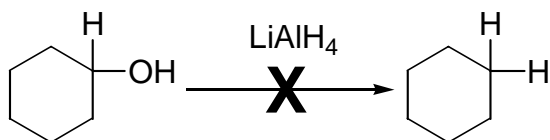


Thermal dehydrogenation is the cheapest method of oxidation but the high temperatures involved limit the applicability of this method.



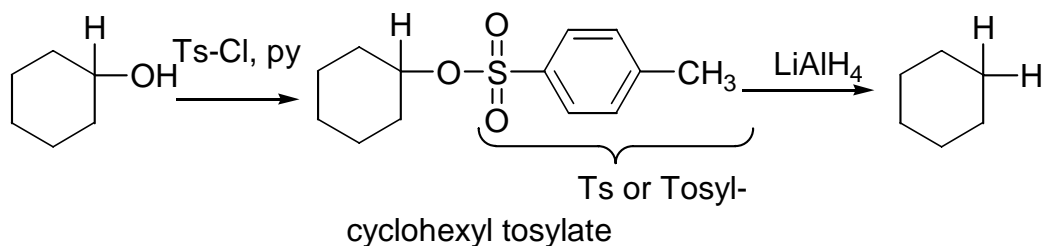
### Reduction of Alcohols

Normally an alcohol cannot be directly reduced to an alkane in one step.



The  $-\text{OH}$  group is a poor leaving group so hydride displacement is not a good option – however the hydroxyl group is easily converted into other groups that are superior leaving groups, and allow reactions to proceed.

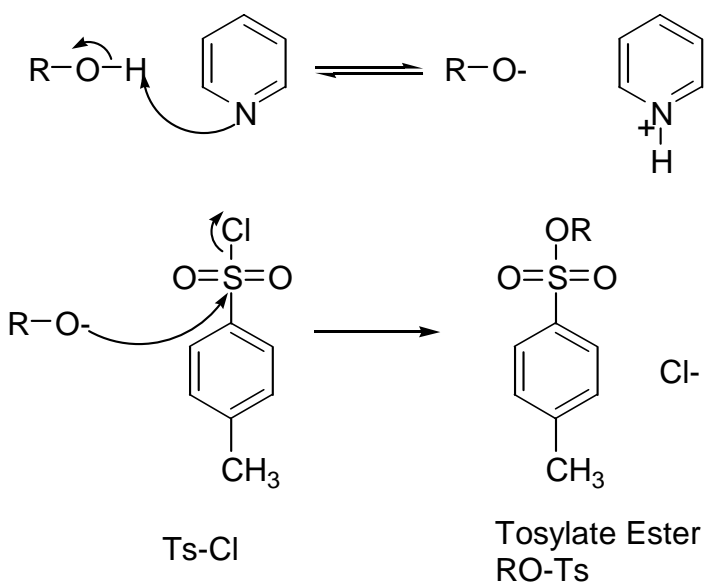
One such conversion involves tosyl chloride, and the formation of a **tosylate**.



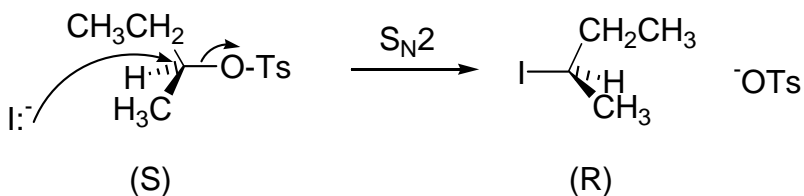
Cyclohexanol will not reduce with  $\text{LiAlH}_4$ , but the corresponding tosylate reduces to cyclohexane very easily.

### Tosylate Esters

These compounds undergo substitution and elimination very easily (often more reactive than alkyl halides).

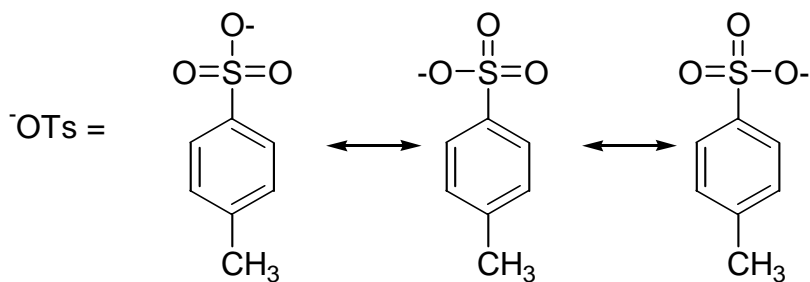


Tosylate esters (tosylates) are typically formed from alcohols with reaction with Ts-Cl and pyridine (py).

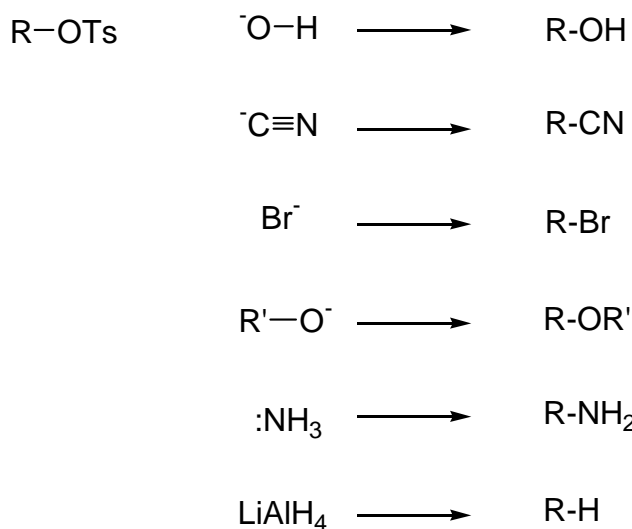


Tosylate groups undergo a variety of  $\text{S}_{\text{N}}2$  reactions.

The tosylate is such a good leaving group because it is a stable anion.

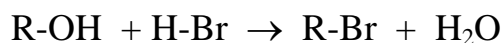


Common  $\text{S}_{\text{N}}2$  transformations of Tosylates:

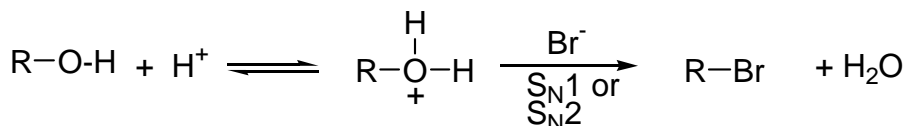


### Alcohols and Hydrohalic Acids

Alkyl halides can also be formed by reaction of alcohols with H-X acids.



In acidic media, the alcohol is in equilibrium with its protonated form.



The  $-\text{OH}$  is a poor leaving group, but  $-\text{OH}_2^+$  is an excellent leaving group, and once the  $-\text{OH}$  is protonated the molecule may take place in a variety of substitution and/or elimination reactions.

The nature of R determines whether the reactions proceed via S<sub>N</sub>1 or S<sub>N</sub>2 mechanisms.

(If R is primary alkyl → S<sub>N</sub>2

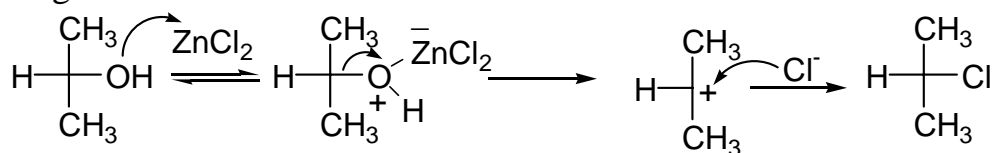
If R is bulky tertiary alkyl → S<sub>N</sub>1).

### Hydrochloric Acid

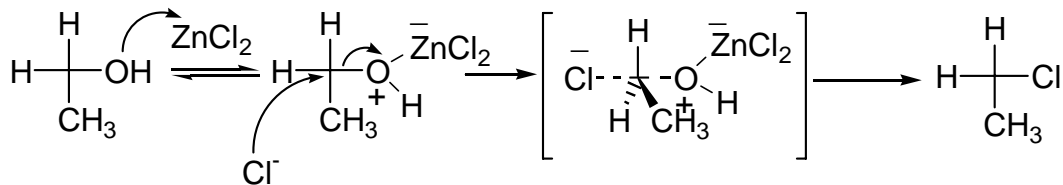
H-Cl reacts in the same way, although often Zinc (II) chloride (a Lewis acid) is added to help compensate for the lower nucleophilicity of chloride ion.

The mixture of HCl and ZnCl<sub>2</sub> is called the Lucas Reagent.

Secondary and tertiary alcohols react via the S<sub>N</sub>1 mechanism with the Lucas reagent.



The ZnCl<sub>2</sub> coordinates to the hydroxyl oxygen, and this generates a far superior leaving group.



Primary alcohols react in a similar fashion except the free cation is not generated, and the substitution is of S<sub>N</sub>2 type.

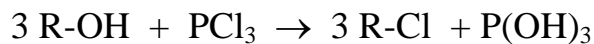
### Limitations of use of H-X

- 1) Only works for H-Cl and H-Br
- 2) Low chemical yields for primary and secondary alcohols
- 3) Often observe competing elimination
- 4) Carbocations can lead to rearranged products

## Phosphorous Halides

Phosphorous halides can convert alcohols to alkyl halides.

E.g.



$\text{PI}_3$  has to be generated *in situ* via reaction of iodine and phosphorous.

E.g.

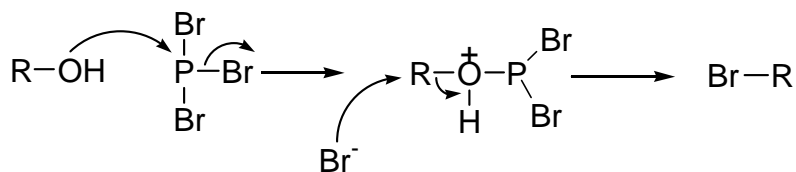


This type of reaction does not work well for tertiary alcohols, and also does not lead to rearranged products.

These observations are explained by the reaction mechanism.

### Mechanism

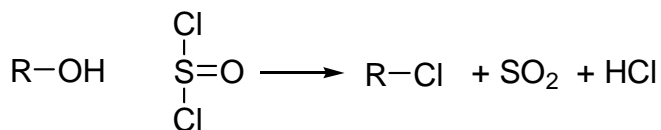
The hydroxyl oxygen displaces a halide (good leaving group) from the Phosphorous.



The liberated halide performs an  $\text{S}_{\text{N}}2$  type attack on the back side of the R group. The positively charged oxygen is a good leaving group.

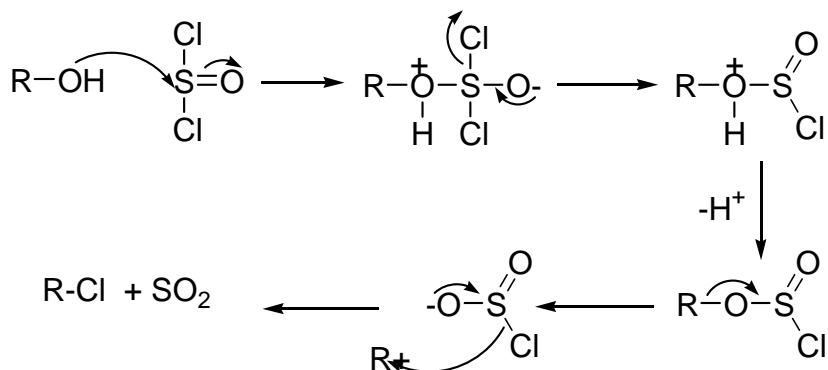
### Thionyl Chloride

Thionyl chloride ( $\text{SOCl}_2$ ) is the usual method of choice for preparing alkyl chlorides from alcohols.



The mechanism is interesting:

The hydroxyl oxygen attacks the electrophilic Sulfur, and from the tetrahedral intermediate a chloride is ejected.



The chlorosulfite ester rearranges with the breaking of the C-O and S-Cl bonds and the formation of the R-Cl bond and a new S-O bond.

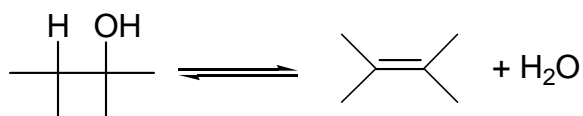
When R is secondary or tertiary, the ionization to a cation probably precedes the Chloride attack, whereas if R is primary the process is probably concerted (Bond breaking and forming at the same time).

### Summary of Best Alcohol to Alkyl Halide Transformations

Class	Chloride	Bromide	Iodide
Primary	SOCl <sub>2</sub>	PBr <sub>3</sub>	P/I <sub>2</sub>
Secondary	SOCl <sub>2</sub>	PBr <sub>3</sub>	P/I <sub>2</sub>
Tertiary	HCl	HBr	HI

### Dehydration Reactions of Alcohols

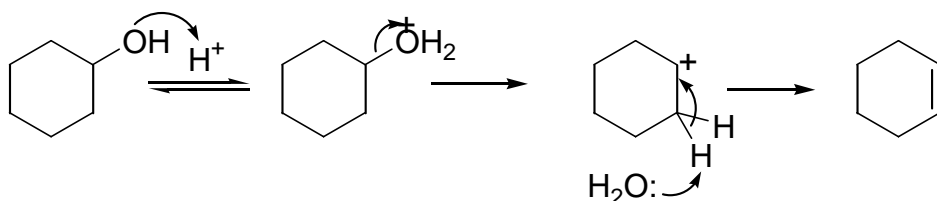
Dehydration of alcohols requires an acidic catalyst to convert the hydroxyl into a good leaving group – this is an equilibrium reaction.



It is possible to force the equilibrium to the right (alkene) by removing one or both of the products.

This is normally achieved either by distillation (alkene is lower boiling than alkyl halide) or the addition of a dehydrating agent.

Alcohol dehydration usually occurs via the E1 mechanism.



The first step is the exothermic protonation of the hydroxyl, followed by the slow, endothermic, rate determining ionization to generate the cation.

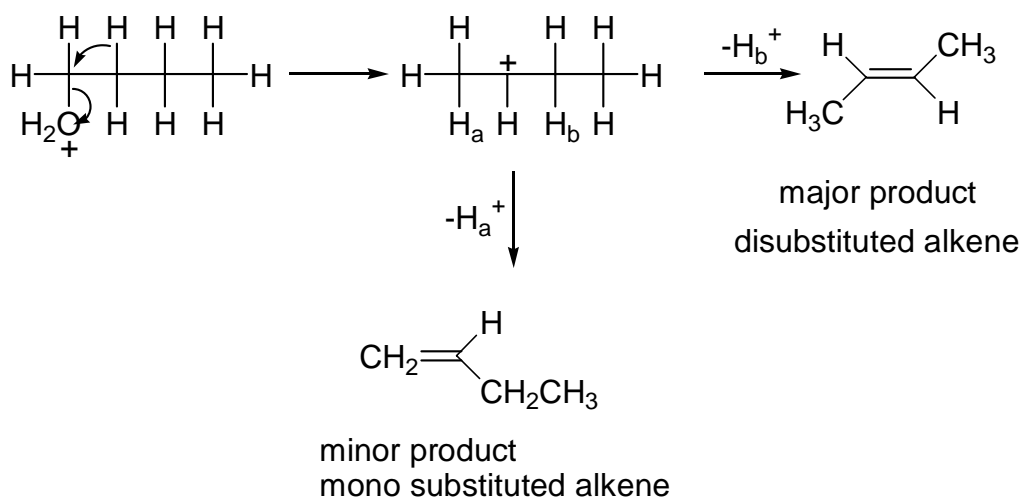
The fast deprotonation is exothermic and produces the alkene.

Figure 11-2

Since the RDS is the formation of the carbocation, the ease of formation dictates the reaction rates of  $3^\circ > 2^\circ > 1^\circ$ .

Rearrangements are common since a free carbocation is involved.

E.g.



After 1-butanol is protonated, the ionization is accompanied by a hydride shift to produce a secondary carbocation.

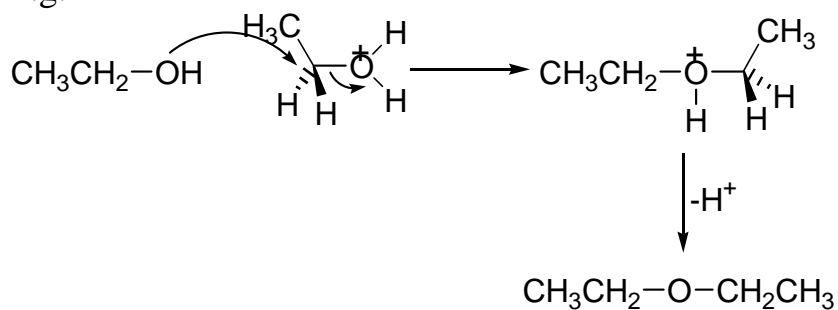
There is a choice of protons to be eliminated, and Saytzeff's rule applies.

### Bimolecular Dehydration to form Ethers

In certain cases, a protonated primary alcohol may be attacked by another molecule of alcohol.

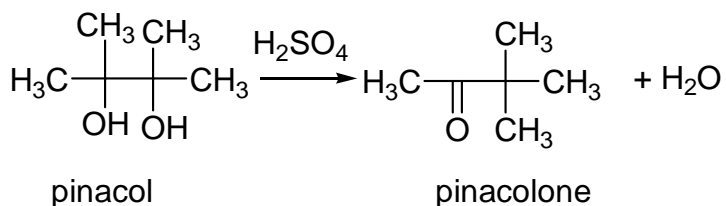
The net result is a dehydration and a formation of an ether.

E.g.



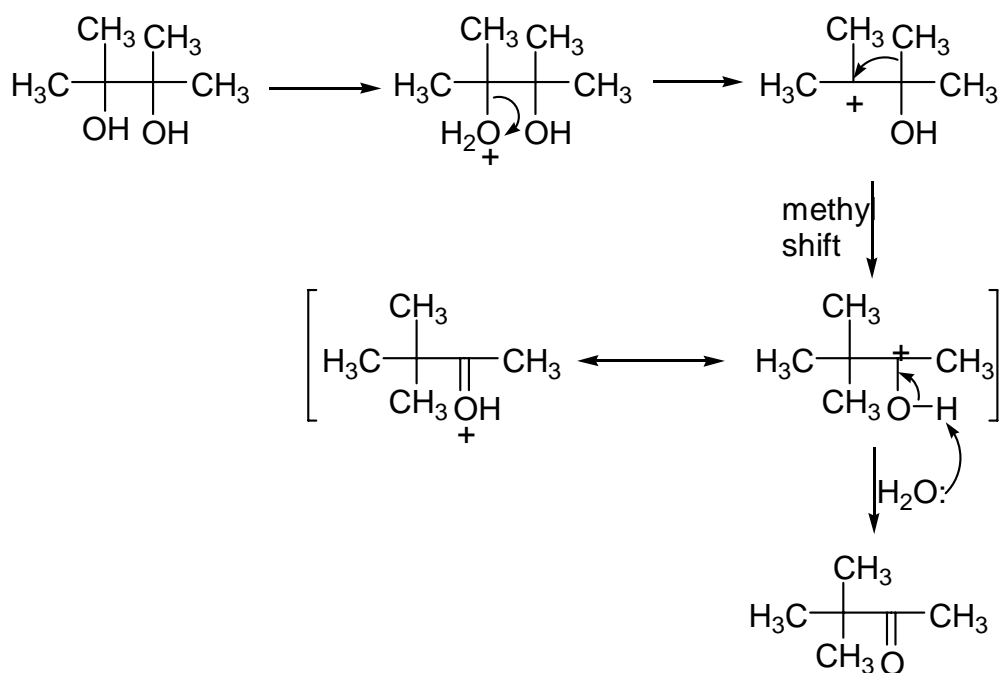
Bimolecular dehydration is best used for the synthesis of symmetrical dialkyl ethers from unhindered primary alcohols.

## Unique Reactions of Diols (Pinacol Rearrangement)



The pinacol rearrangement is a formal dehydration.

### Mechanism



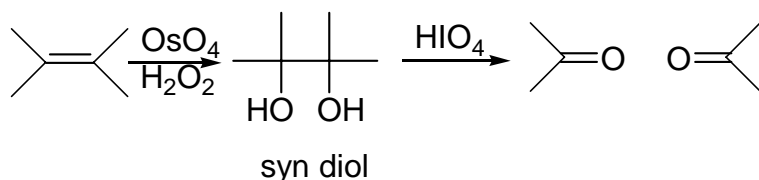
The protonation of the hydroxyl is followed by ionization.

The tertiary carbocation rearranges with a methyl shift to produce a tertiary cation which has the extra benefit of resonance stabilization.

The rearranged product is deprotonated to generate the final product.

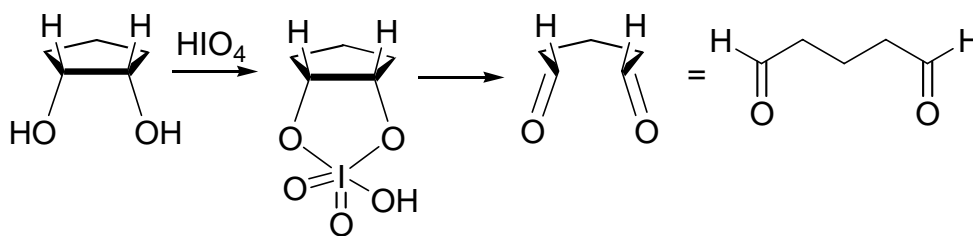
## Cleavage of Glycols

Periodic acid will cleave 1,2 diols to give aldehyde and ketone products.



(The treatment of an alkene to syn hydroxylation followed by periodic acid cleavage is an alternative to the ozonolysis-reduction procedure described earlier).

## Mechanism

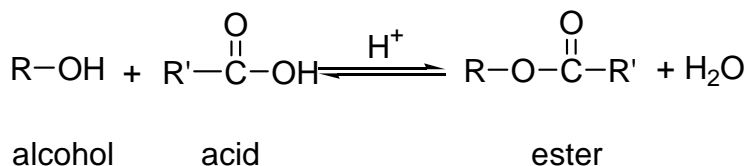


The mechanism involves the formation of a cyclic periodate ester, which cleaves to generate carbonyl groups.

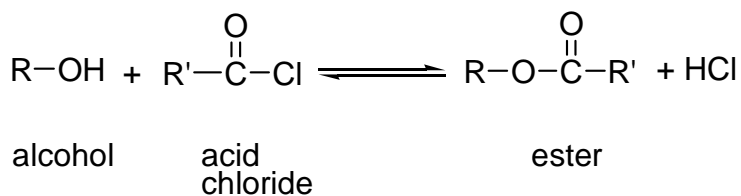
## Esterification of Alcohols

Usually the term ester means the ester of a carboxylic acid.

In general, an acid and alcohol generate an ester and water. This is called a Fischer esterification.

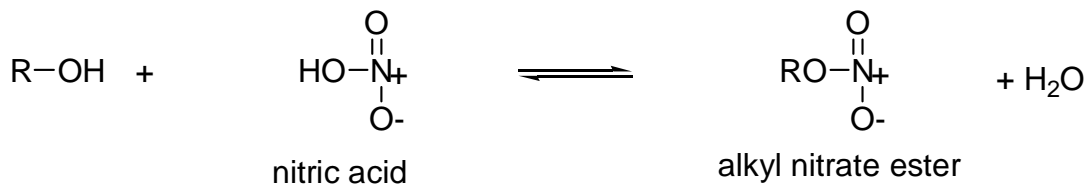
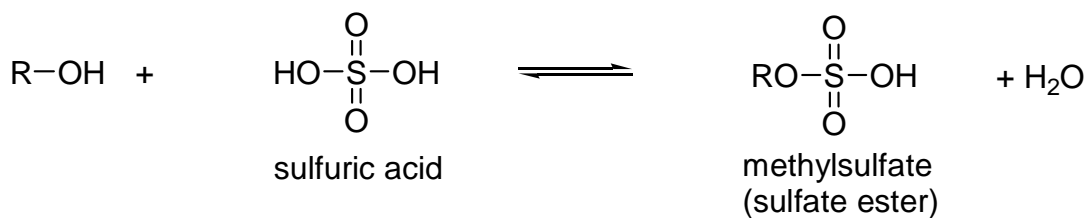
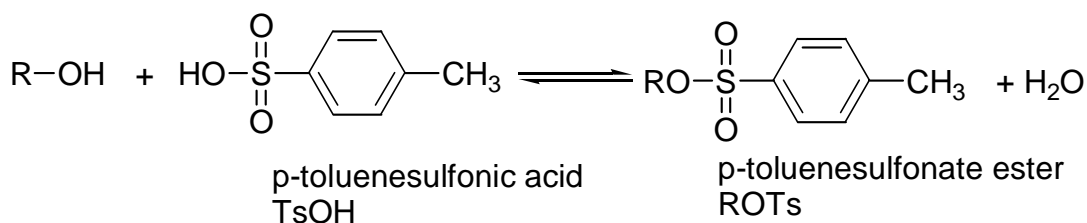


Acid chlorides provide another route to producing esters.

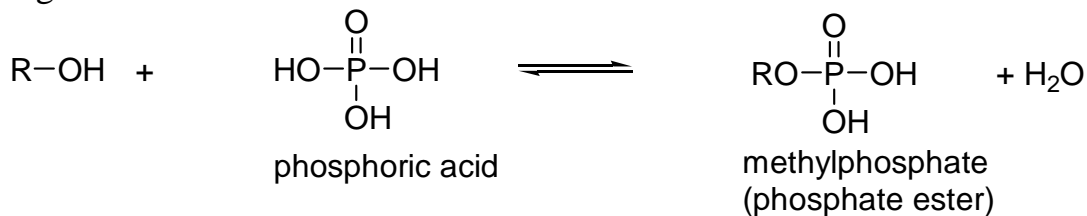


### Esters of Inorganic Acids

Just as alcohols form esters with carboxylic acids, they also form esters with inorganic acids.

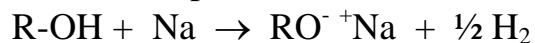


Phosphate esters are important in nature since they link the nucleotide bases together in DNA.



### Reactions of Alkoxides

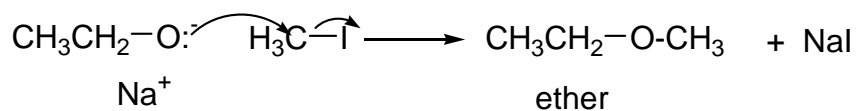
Alkoxide ions are produced when metals like Na or K are added to alcohols.



The sodium (or potassium) alkoxides are strong bases and nucleophiles.

Alkoxides can react with primary alkyl halides (or tosylates) to produce ethers.

This is the Williamson Ether synthesis, and it involves  $\text{S}_{\text{N}}2$  displacement with back side attack of the alkoxide.



Normally this reaction is limited to unhindered primary alkyl halides, otherwise elimination tends to be the preferred mode of reaction.