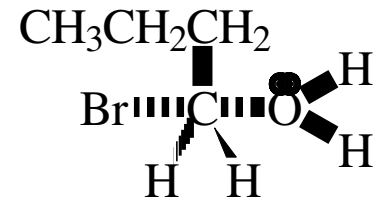


Organic Chemistry, 7th Edition
L. G. Wade, Jr.



Chapter 11

Reactions of Alcohols

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Types of Alcohol Reactions

- Dehydration to alkene
- Oxidation to aldehyde, ketone
- Substitution to form alkyl halide
- Reduction to alkane
- Esterification
- Tosylation
- Williamson synthesis of ether

Summary Table

TABLE 11-1

Types of Reactions of Alcohols

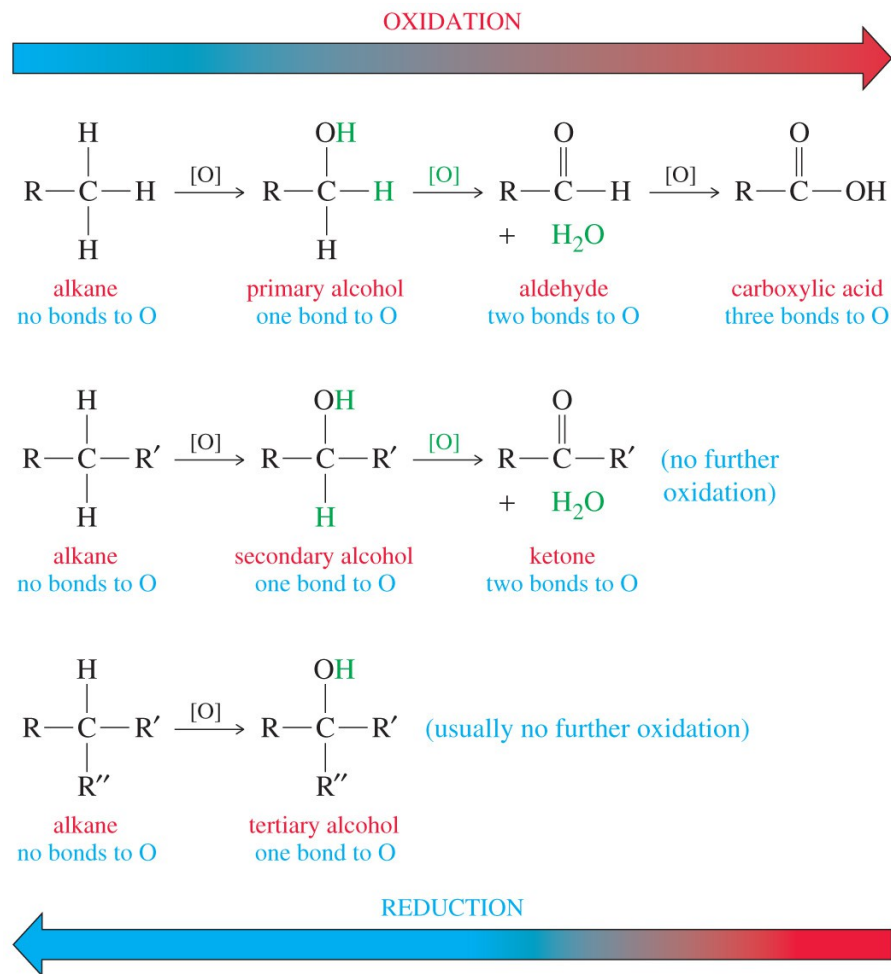
$R-OH$		<i>type of reaction</i>	<i>Product</i>
$R-OH$	dehydration	→	alkenes
$R-OH$	oxidation	→	ketones, aldehydes, acids
$R-OH$	substitution	→	$R-X$ halides
$R-OH$	reduction	→	$R-H$ alkanes
$R-OH$	esterification	→	$R-O-\overset{\text{O}}{\parallel}{C}-R'$ esters
$R-OH$	tosylation	→	$R-OTs$ tosylate esters (good leaving group)
$R-OH$	(1) form alkoxide (2) $R'X$	→	$R-O-R'$ ethers

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Oxidation States

- Easy for inorganic salts:
 - CrO_4^{2-} reduced to Cr_2O_3 .
 - KMnO_4 reduced to MnO_2 .
- **Oxidation**: Gain of O, O_2 , or X_2 ; loss of H_2 .
- **Reduction**: Gain of H_2 (or H^-); loss of O or O_2 ; and loss of X_2 .
- The gain or loss of H^+ , H_2O , HX , etc. is neither an oxidation nor a reduction.

Oxidation States of Carbons



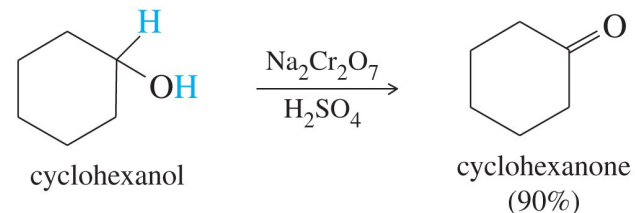
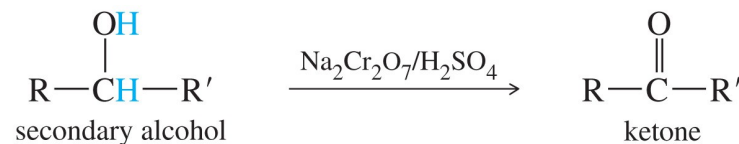
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Oxidation of 2° Alcohols

- 2° alcohol becomes a ketone.
- Oxidizing agent is $\text{Na}_2\text{Cr}_2\text{O}_7/\text{H}_2\text{SO}_4$.
- Active reagent probably is H_2CrO_4 .
- Color change is orange to greenish-blue.



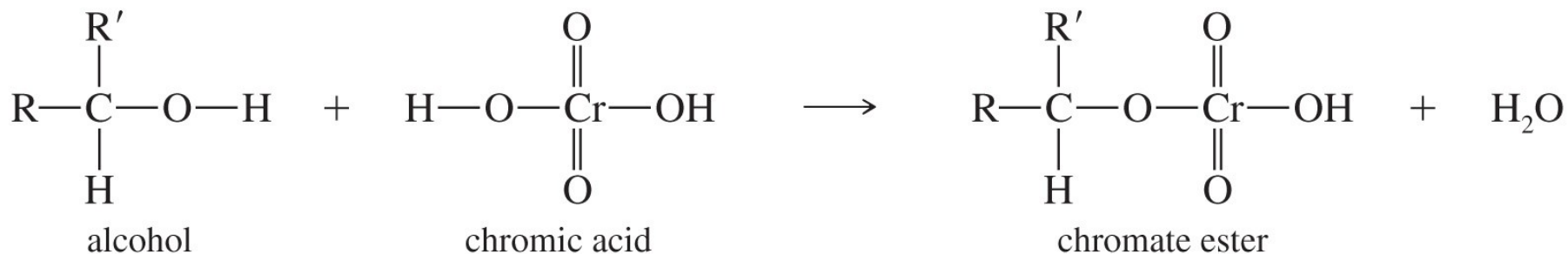
Example



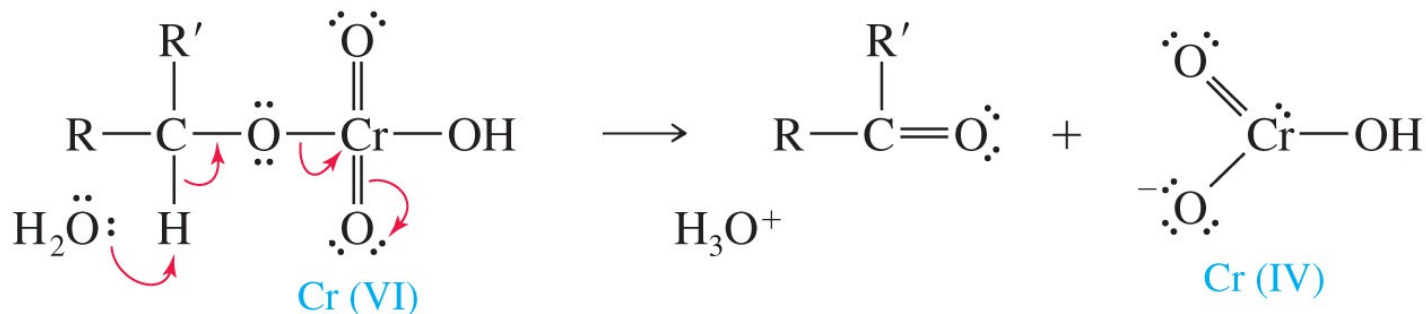
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Oxidation Mechanism

Formation of the chromate ester

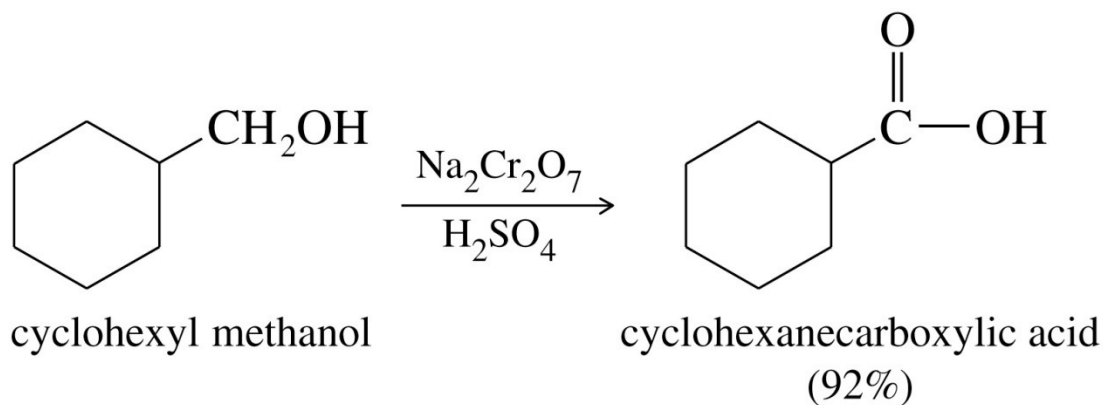


Elimination of the chromate ester and oxidation of the carbinol carbon



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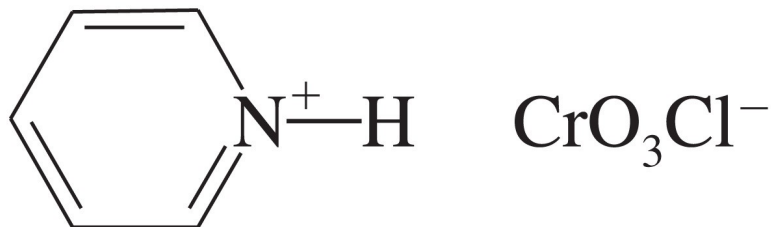
Oxidation of 1° Alcohols to Carboxylic Acids



- Chromic acid reagent oxidizes primary alcohols to carboxylic acids.
- The oxidizing agent is too strong to stop at the aldehyde.

Pyridinium Chlorochromate (PCC)

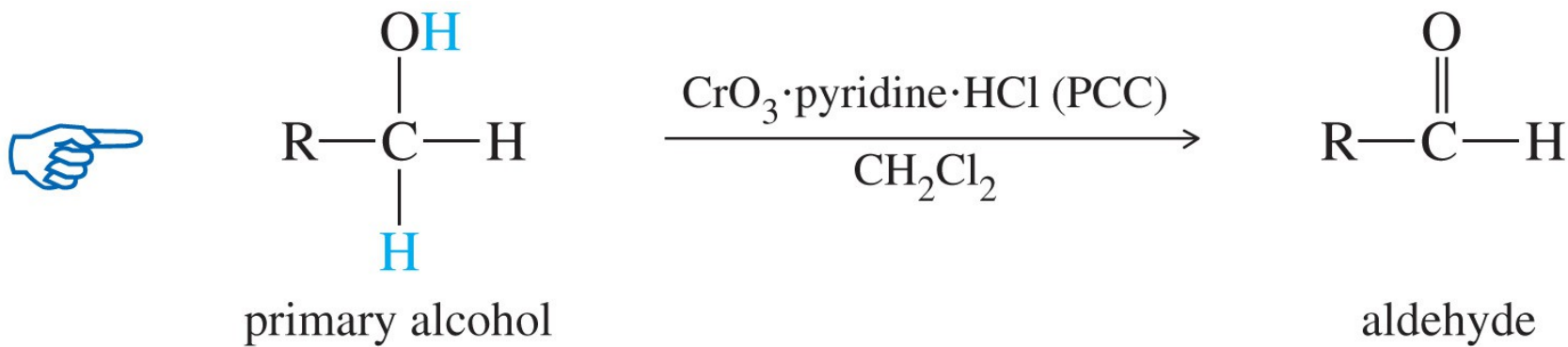
Pyridinium chlorochromate (PCC):



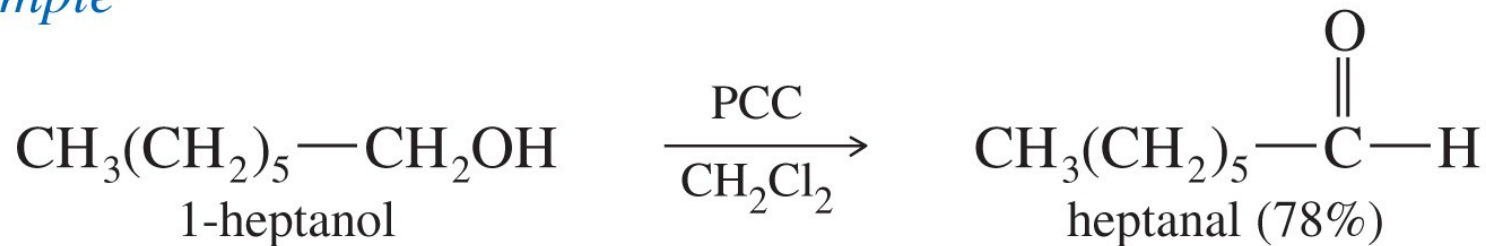
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- PCC is a complex of chromium trioxide, pyridine, and HCl.
- Oxidizes primary alcohols to aldehydes.
- Oxidizes secondary alcohols to ketones.

Pyridinium Chlorochromate (PCC)



Example



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3° Alcohols Cannot Be Oxidized

- Carbon does not have hydrogen, so oxidation is difficult and involves the breakage of a C—C bond.
- Chromic acid test is for primary and secondary alcohols because tertiary alcohols do not react.

Summary of Alcohol Oxidations

To Oxidize	Product	Reagent
2° alcohol	ketone	chromic acid (or PCC)
1° alcohol	aldehyde	PCC
1° alcohol	carboxylic acid	chromic acid

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Other Oxidation Reagents

- CuO, 300°C (industrial dehydrogenation)
- Collins reagent: Cr₂O₃ in pyridine
- Jones reagent: chromic acid in acetone
- KMnO₄ (strong oxidizer)
- Nitric acid (strong oxidizer)
- Swern oxidation: dimethylsulfoxide, with oxalyl chloride and hindered base, oxidizes 2° alcohols to ketones and 1° alcohols to aldehydes.

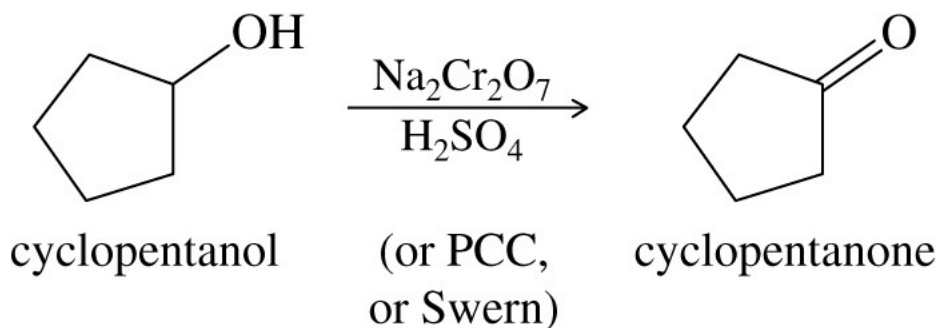
Solved Problem 1

Suggest the most appropriate method for each of the following laboratory syntheses.

(a) cyclopentanol \longrightarrow cyclopentanone

Solution

Many reagents are available to oxidize a simple secondary alcohol to a ketone. For a laboratory synthesis, however, dehydrogenation is not practical, and cost is not as large a factor as it would be in industry. Most labs would have chromium trioxide or sodium dichromate available, and the chromic acid oxidation would be simple. PCC and the Swern oxidation would also work, although these reagents are more complicated to prepare and use.



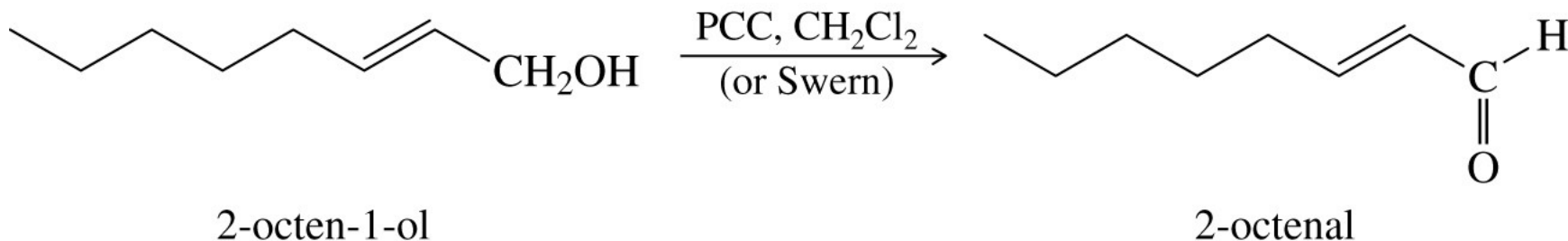
Solved Problem 1 (Continued)

Suggest the most appropriate method for each of the following laboratory syntheses.

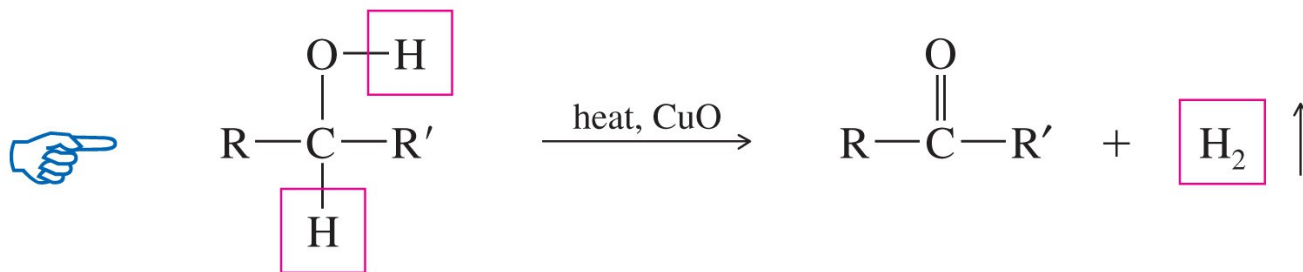
(b) 2-octen-1-ol \longrightarrow 2-octenal (structure below)

Solution

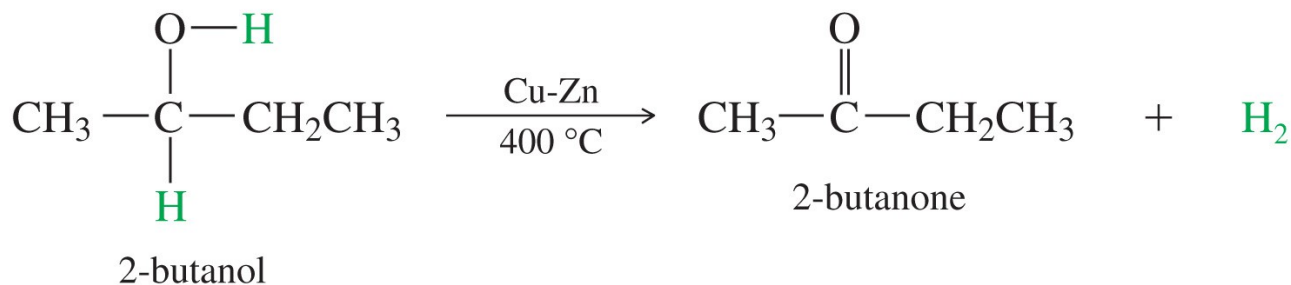
This synthesis requires more finesse. The aldehyde is easily over-oxidized to a carboxylic acid, and the double bond reacts with oxidants such as KMnO_4 . Our choices are limited to PCC or the Swern oxidation.



Dehydrogenation of Alcohols



Example



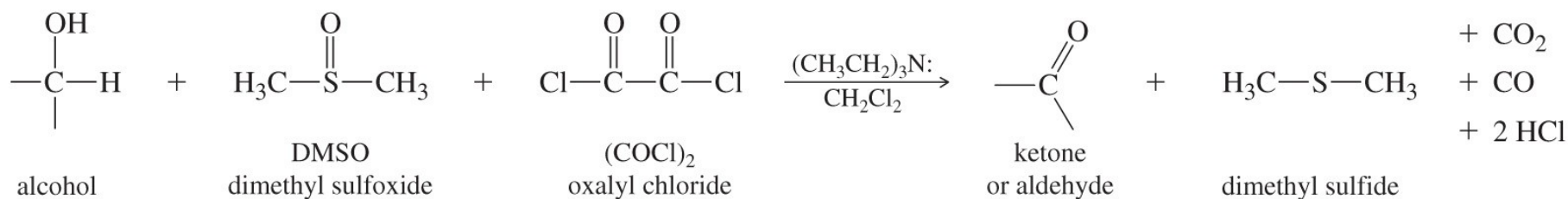
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The dehydrogenation of alcohols is not used in laboratory settings because many compounds do not survive the reaction temperature of 300°C.

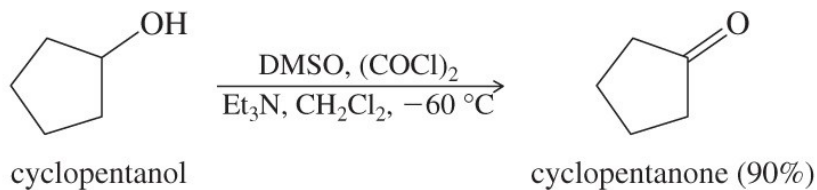
Swern Oxidation

- This reaction uses dimethyl sulfoxide (DMSO) as the oxidizing agent along with oxalyl chloride and pyridine.
- Primary alcohols can be oxidized to the aldehyde.
- Secondary alcohols can be oxidized to the corresponding ketone with this reaction as well.
- The by-products of this reaction can be easily separated from the products, making this a convenient reaction.

Example of the Swern Oxidation



Examples

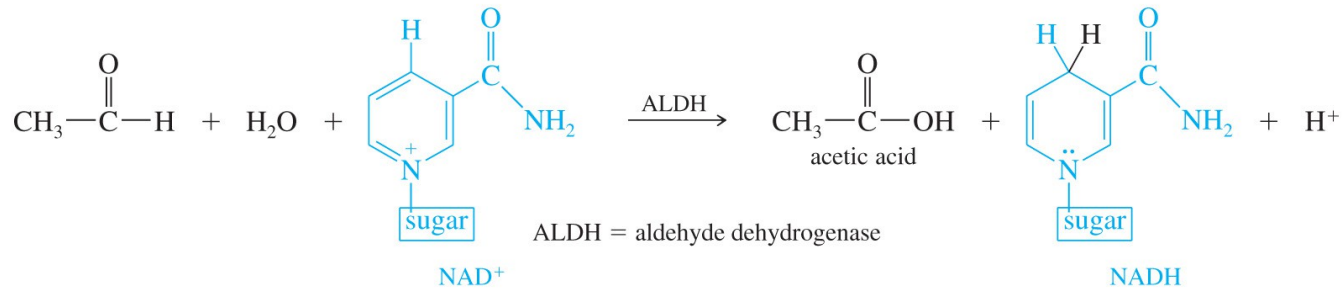
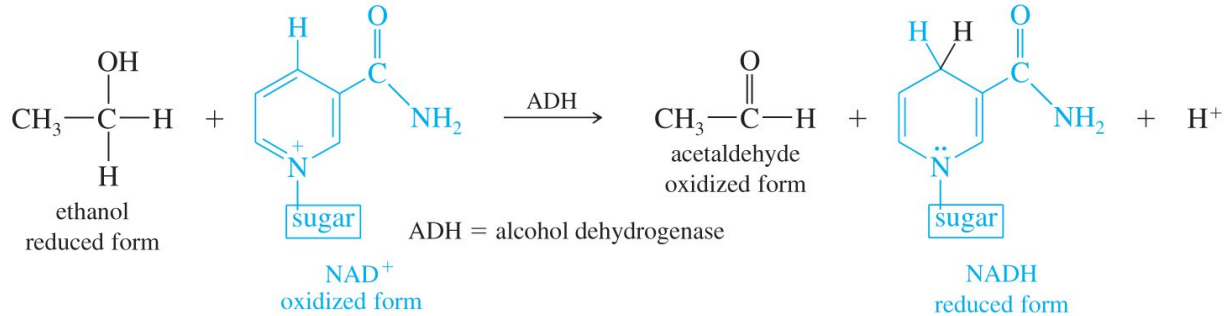


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Biological Oxidation

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

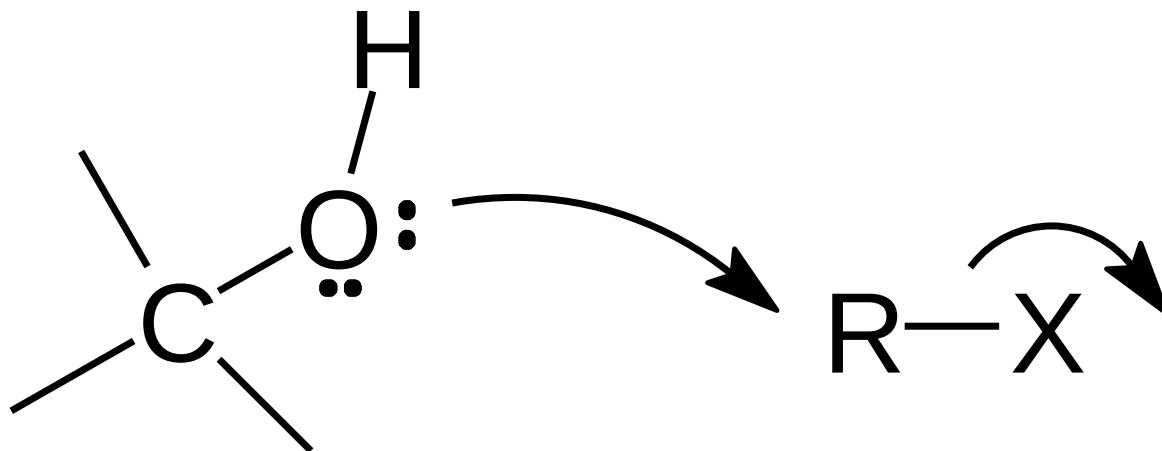
Enzymatic Oxidation



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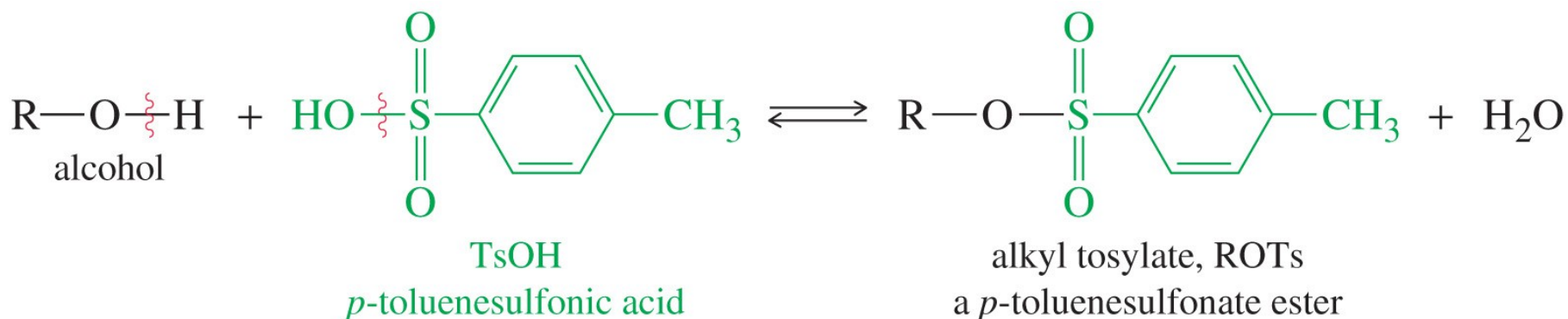
Alcohol dehydrogenase catalyzes an oxidation: the removal of two hydrogen atoms from an alcohol molecule. The oxidizing agent is called nicotinamide adenine dinucleotide (NAD^+).

Alcohol as a Nucleophile



- ROH is a weak nucleophile.
- RO⁻ is a strong nucleophile.
- New O—C bond forms; O—H bond breaks.

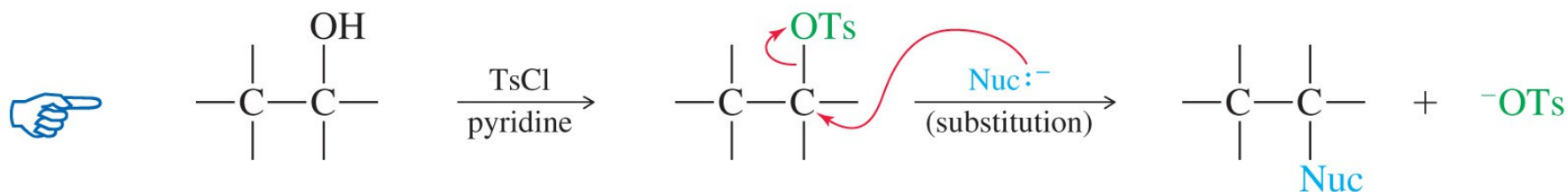
Alcohol as an Electrophile



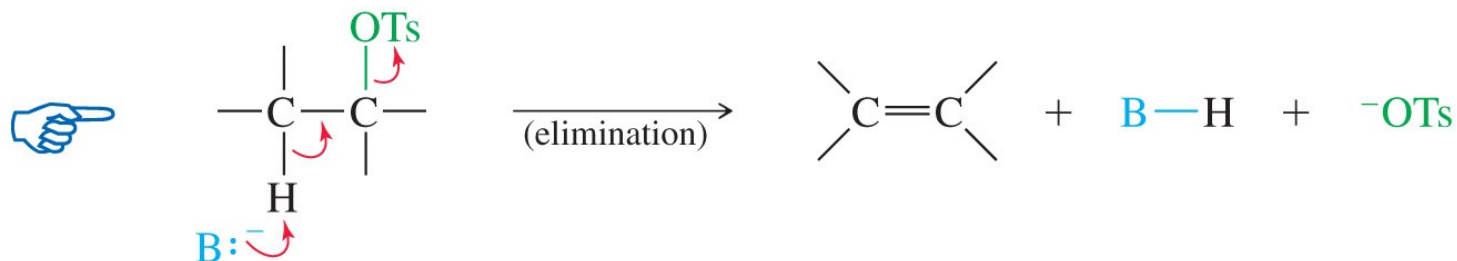
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- OH⁻ is not a good leaving group.
- Protonation of the hydroxyl group converts it into a good leaving group (H₂O).
- Alcohols can be converted to a tosylate ester.
- The tosylate group is an excellent leaving group.

Substitution and Elimination Reactions Using Tosylates

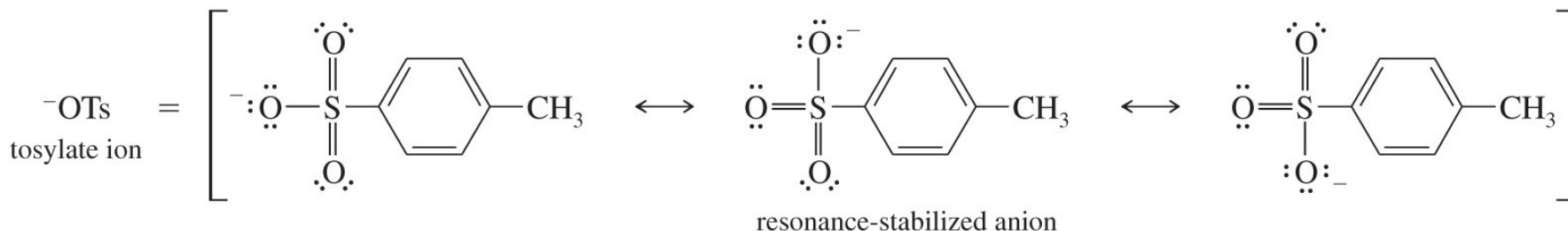
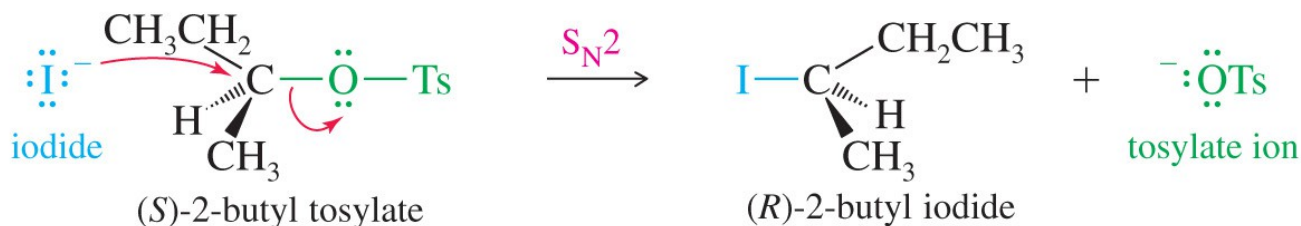


or elimination:



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S_N2 Reactions with Tosylates



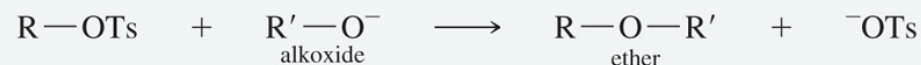
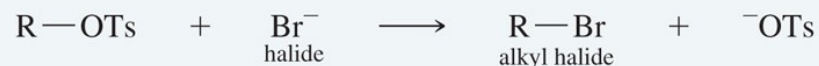
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- The reaction shows the S_N2 displacement of the tosylate ion (-OTs) from (S)-2-butyl tosylate with inversion of configuration.
- The tosylate ion is a particularly stable anion, with its negative charge delocalized over three oxygen atoms.

Summary of Tosylate Reactions

SUMMARY

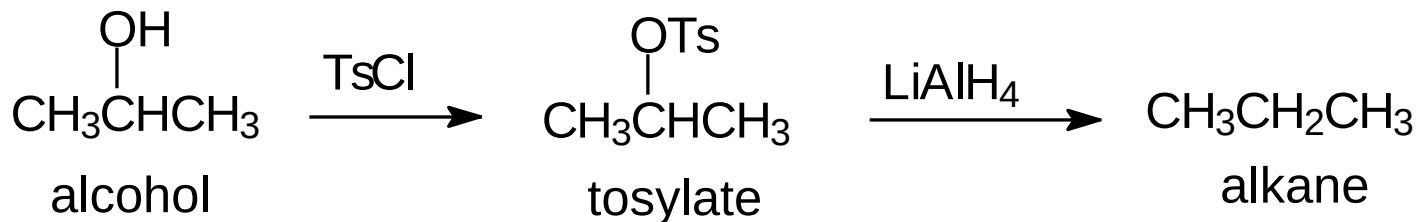
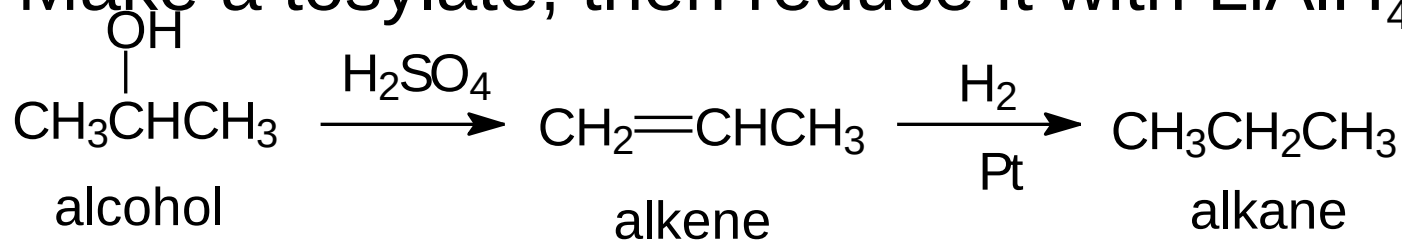
S_N2 Reactions of Tosylate Esters



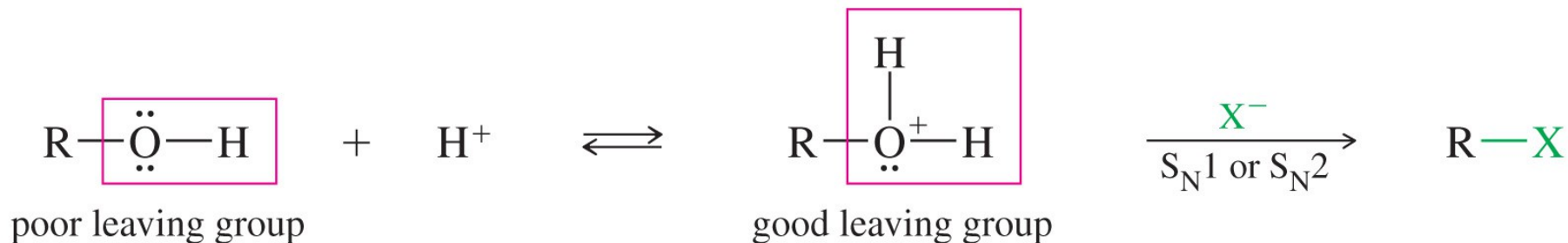
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Reduction of Alcohols

- Dehydrate with concentrated H_2SO_4 , then add H_2 .
- Make a tosylate, then reduce it with LiAlH_4 .



Reaction of Alcohols with Acids

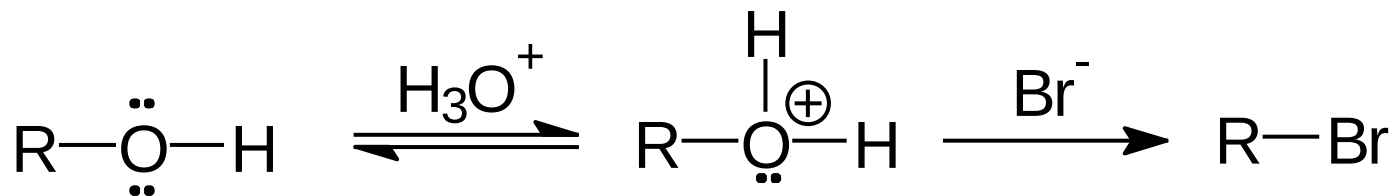


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- The hydroxyl group is protonated by an acid to convert it into a good leaving group (H_2O).
- Once the alcohol is protonated a substitution or elimination reaction can take place.

Reaction with HBr

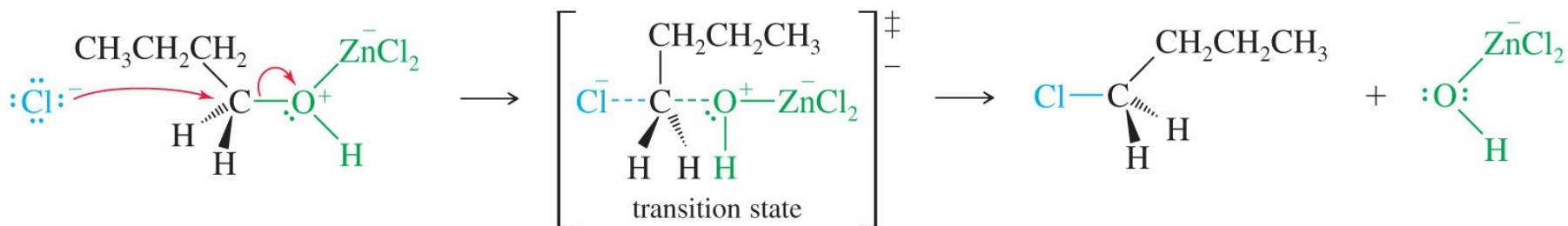
- -OH of alcohol is protonated.
- -OH_2^+ is good leaving group.
- 3° and 2° alcohols react with Br^- via $\text{S}_\text{N}1$.
- 1° alcohols react via $\text{S}_\text{N}2$.



Reaction with HCl

- Chloride is a weaker nucleophile than bromide.
- Add ZnCl_2 , which bonds strongly with $-\text{OH}$, to promote the reaction.
- The chloride product is insoluble.
- Lucas test: ZnCl_2 in concentrated HCl:
 - 1° alcohols react slowly or not at all.
 - 2° alcohols react in 1-5 minutes.
 - 3° alcohols react in less than 1 minute.

S_N2 Reaction with the Lucas Reagent

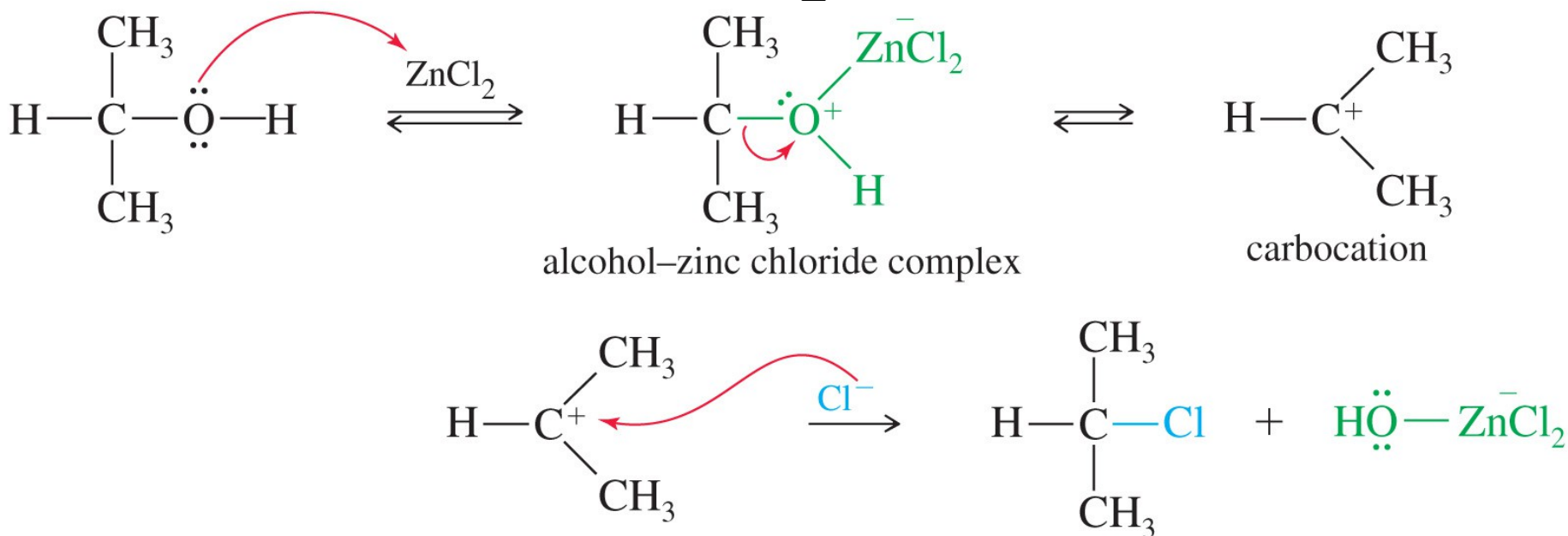


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- Primary alcohols react with the Lucas reagent (HCl and ZnCl_2) by the S_N2 mechanism.
- Reaction is very slow. The reaction can take from several minutes to several days.

S_N1 Reaction with the Lucas

Reagent



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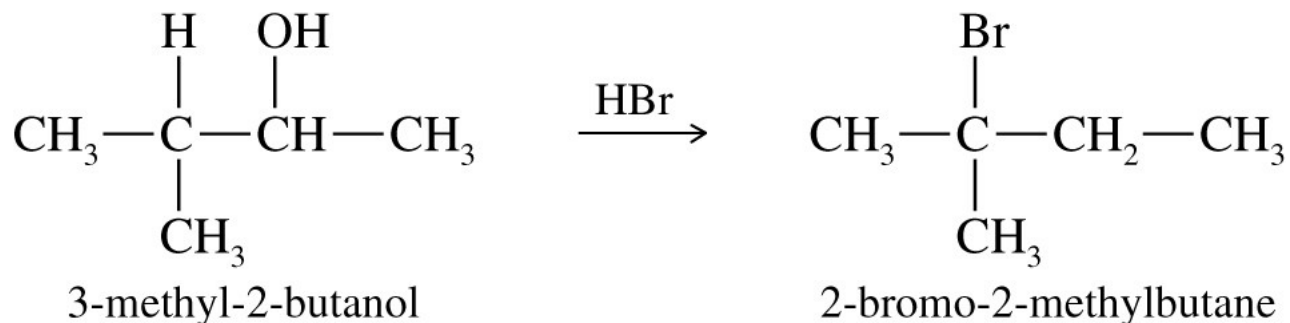
Secondary and tertiary alcohols react with the Lucas reagent (HCl and ZnCl₂) by the S_N1 mechanism.

Limitations of HX Reactions

- Poor yields of alkyl chlorides from primary and secondary alcohols.
- Elimination competes with substitution.
- Carbocation intermediate may undergo a rearrangement.
- Limited ability to make alkyl halides.

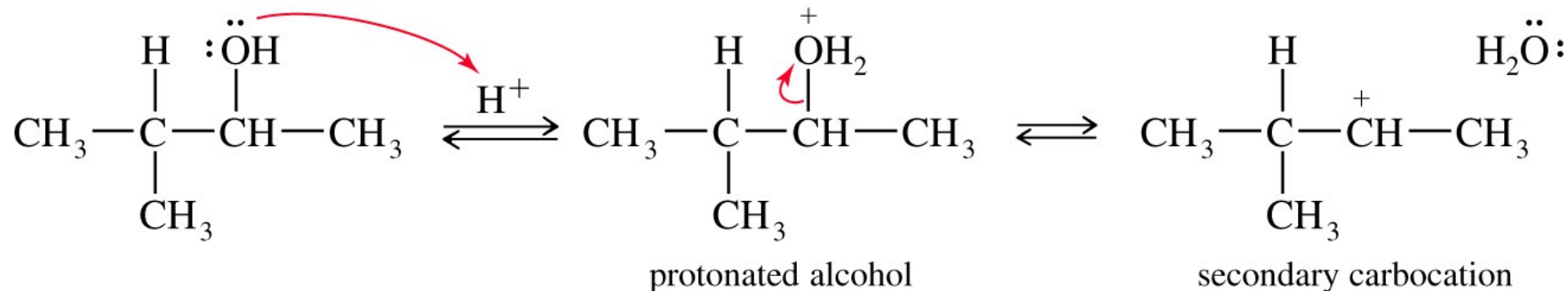
Solved Problem 2

When 3-methyl-2-butanol is treated with concentrated HBr, the major product is 2-bromo-2-methylbutane. Propose a mechanism for the formation of this product.



Solution

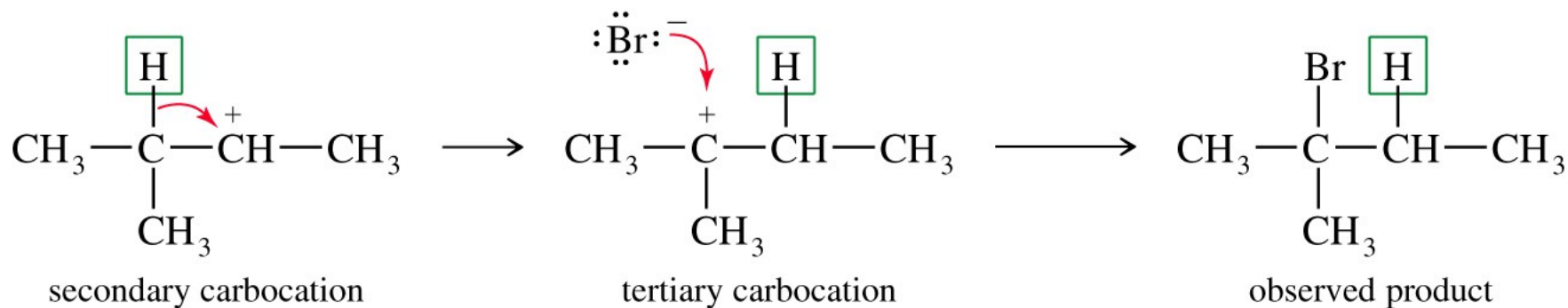
The alcohol is protonated by the strong acid. This protonated secondary alcohol loses water to form a secondary carbocation.



Solved Problem 2 (Continued)

Solution (Continued)

A hydride shift transforms the secondary carbocation into a more stable tertiary cation. Attack by bromide leads to the observed product.

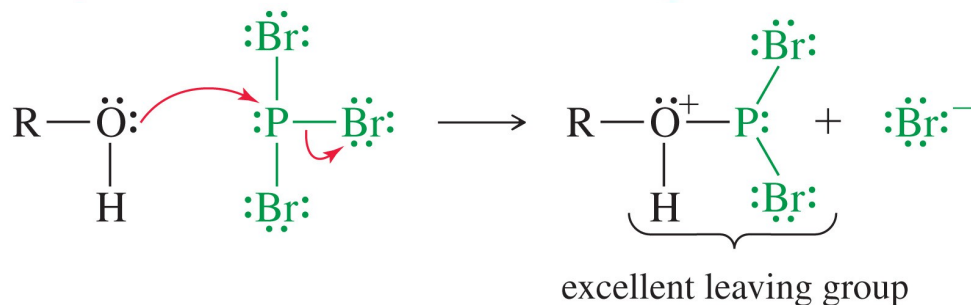


Reactions with Phosphorus Halides

- Good yields with 1° and 2° alcohols.
- PCl_3 for alkyl chlorides (but SOCl_2 better).
- PBr_3 for alkyl bromides.
- P and I_2 for alkyl iodides (PI_3 not stable).

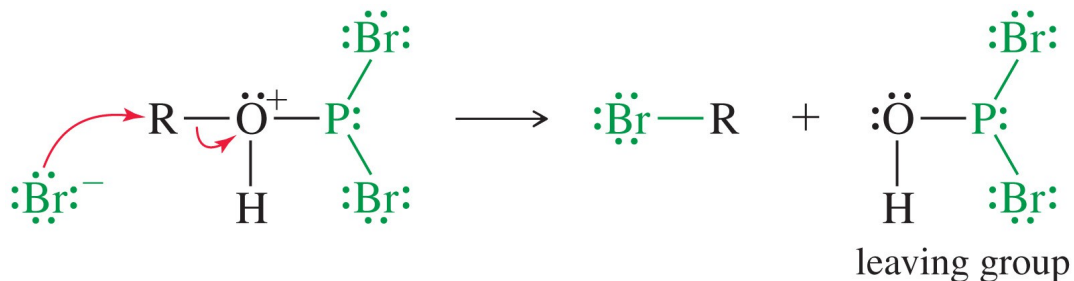
Mechanism with PBr_3

Step 1: Displacement of bromide ion, forming an excellent leaving group.



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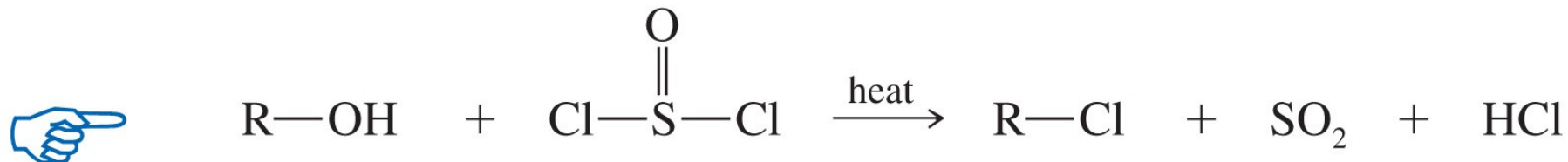
Step 2: $\text{S}_{\text{N}}2$ attack on the alkyl group.



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- Oxygen attacks the phosphorus, displacing one of the halides.
- Br^- attacks back-side ($\text{S}_{\text{N}}2$).

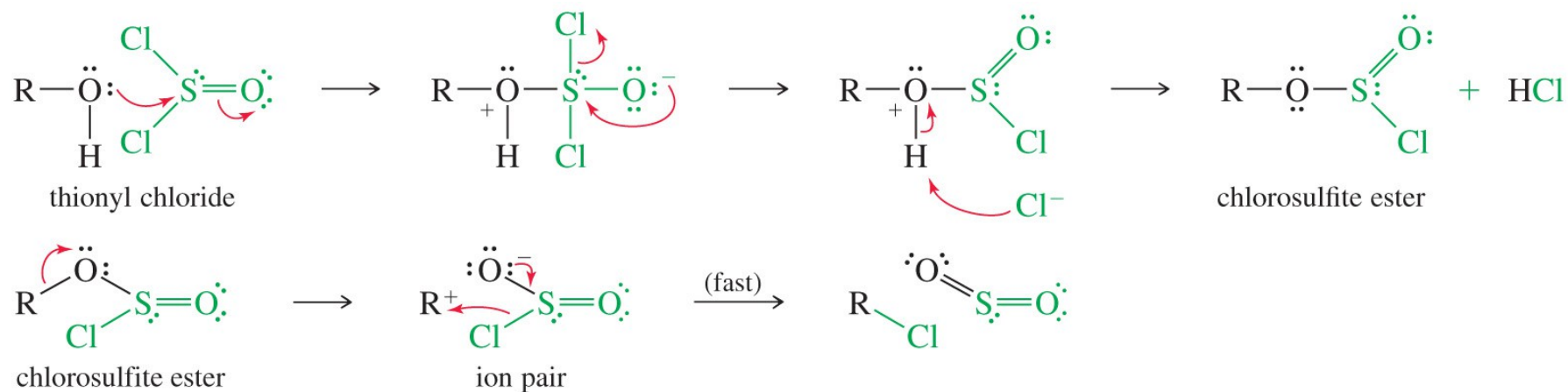
Reaction of Alcohols with Thionyl Chloride



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- Thionyl chloride (SOCl_2) can be used to convert alcohols into the corresponding alkyl chloride in a simple reaction that produces gaseous HCl and SO_2 .

Mechanism of Thionyl Chloride Reaction

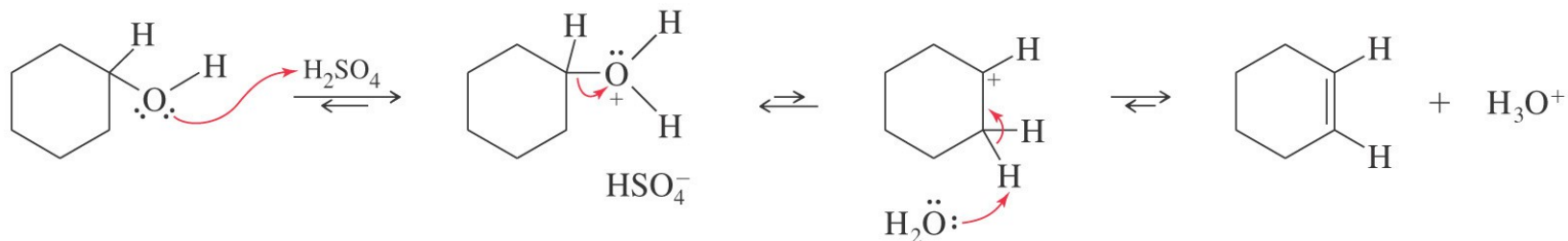


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Dehydration Reactions

- Concentrated H_2SO_4 produces alkene.
- Carbocation intermediate
- Zaitsev product
- Bimolecular dehydration produces ether.
- Low temp, 140°C and below, favors ether formation.
- High temp, 180°C and above, favors alkene formation.

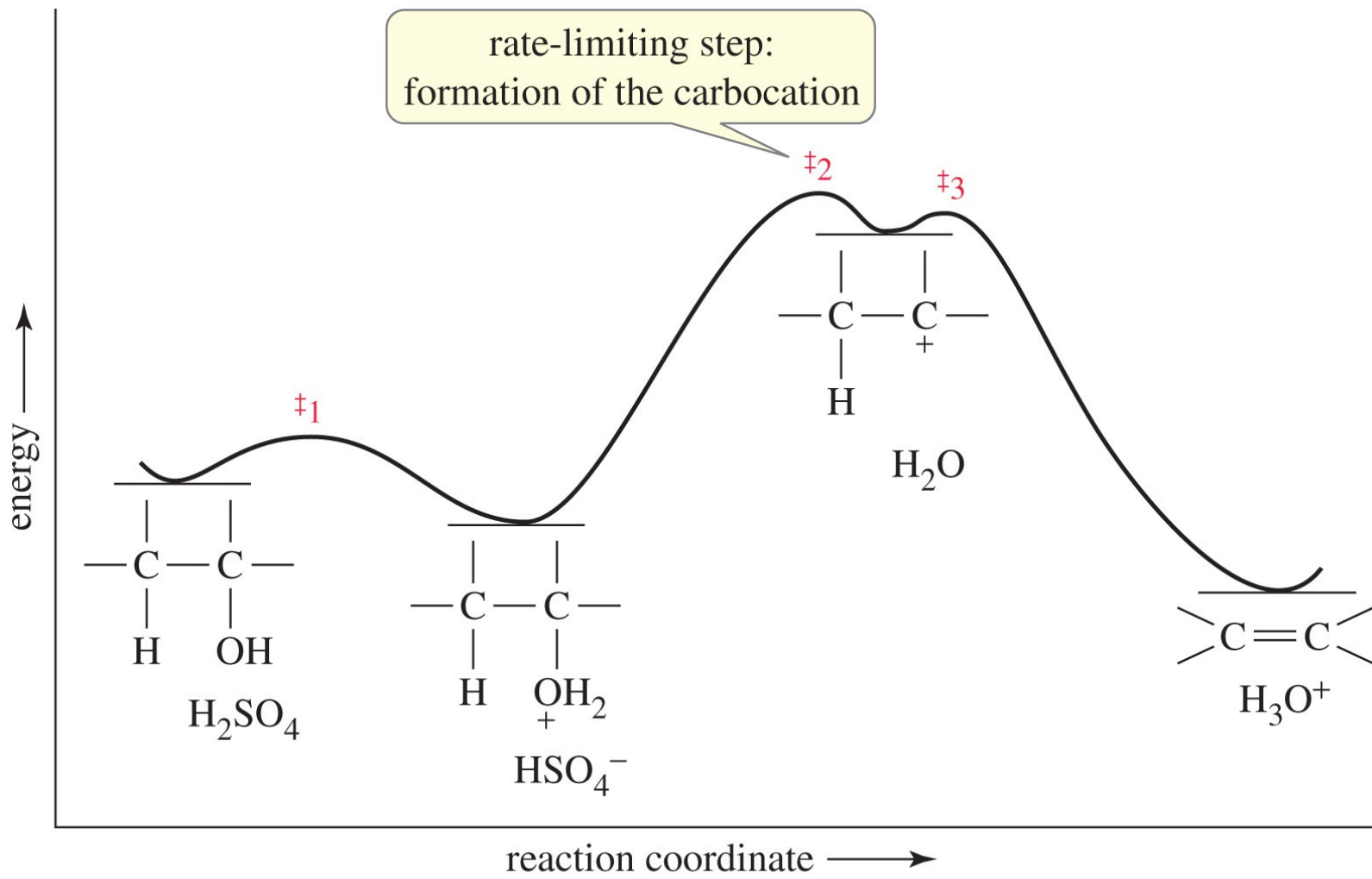
Dehydration of Cyclohexanol



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- The dehydration of cyclohexanol with H_2SO_4 has three steps: Protonation of the hydroxide, loss of water, and deprotonation.
- Alcohol dehydration generally takes place through the E1 mechanism. Rearrangements are possible.
- The rate of the reaction follows the same rate as the ease of formation of carbocations: $3^\circ > 2^\circ > 1^\circ$.

Energy Diagram, E1



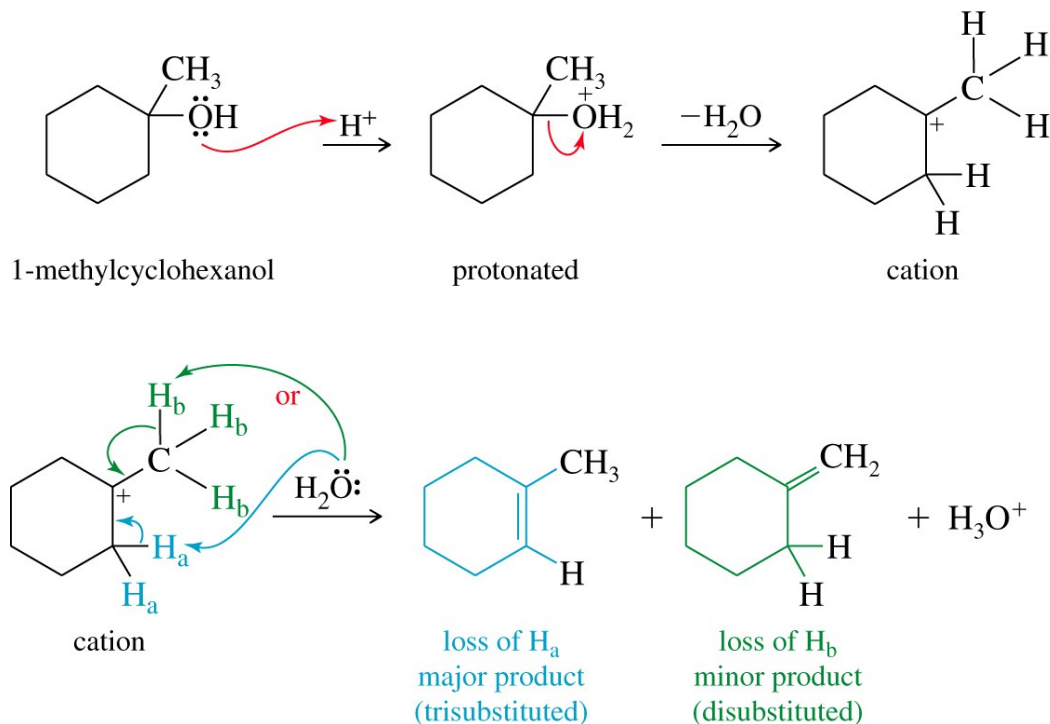
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Solved Problem 3

Predict the products of sulfuric acid-catalyzed dehydration of 1-methylcyclohexanol

Solution

1-Methylcyclohexanol reacts to form a tertiary carbocation. A proton may be abstracted from any one of three carbon atoms. The two secondary atoms are equivalent, and abstraction of a proton from one of these carbons leads to the trisubstituted double bond of the major product. Abstraction of a methyl proton leads to the disubstituted double bond of the minor product.

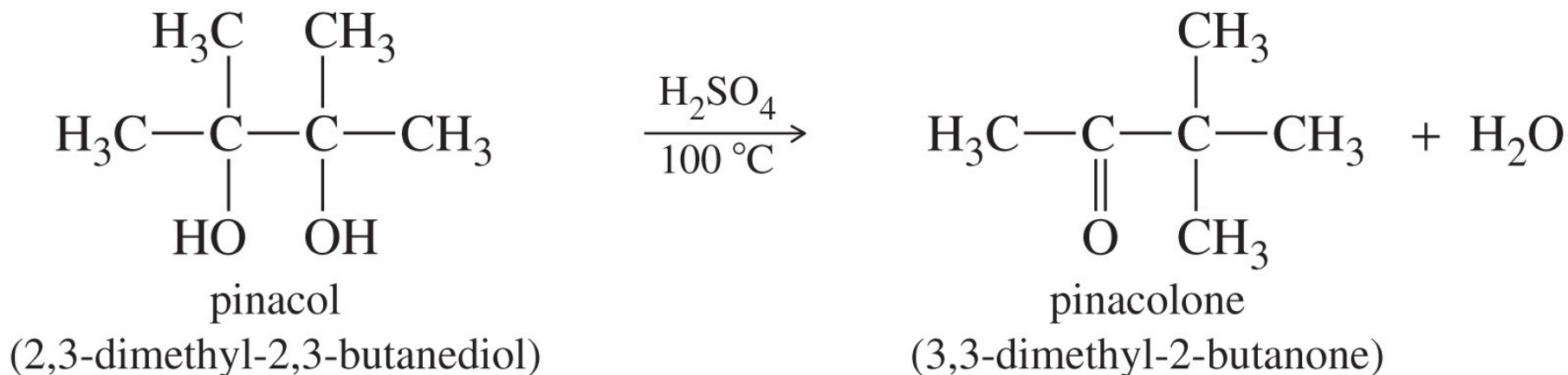


Unique Reactions of Diols

Vicinal diols can undergo the following two reactions:

- Pinacol rearrangement
- Periodic acid cleavage

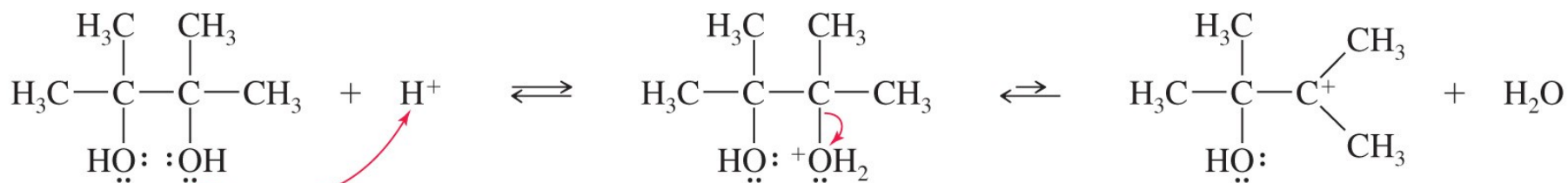
Pinacol Rearrangement



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- In the pinacol rearrangement, a vicinal diol converts to the ketone (pinacolone) under acidic conditions and heat.
- The reaction is classified as a dehydration since a water molecule is eliminated from the starting material.

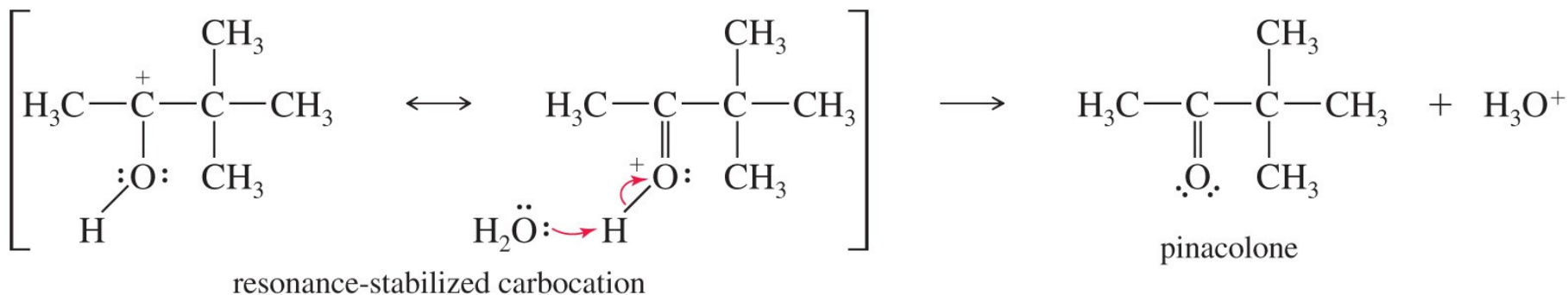
Mechanism of the Pinacol Rearrangement



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- The first step of the rearrangement is the protonation and loss of a water molecule to produce a carbocation.

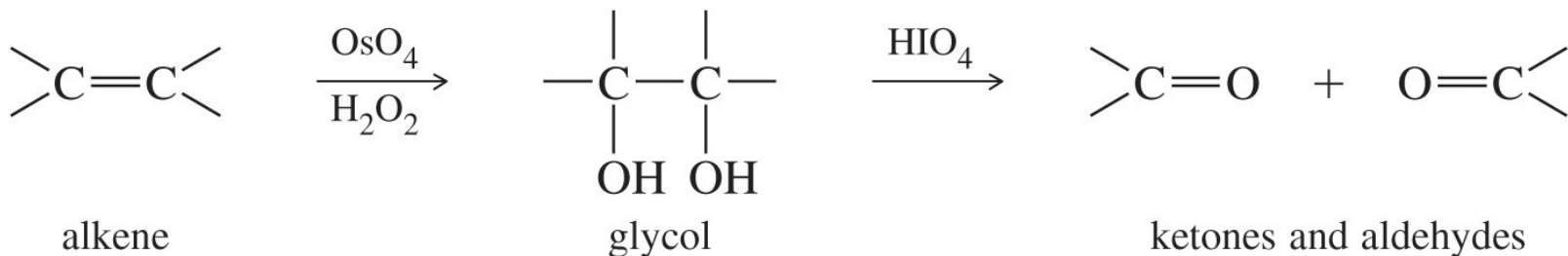
Mechanism of the Pinacol Rearrangement (Continued)



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- There is a methyl shift to form a resonance-stabilized carbocation, which upon deprotonation by water, yields the pinacolone product.

Periodic Cleavage of Glycols



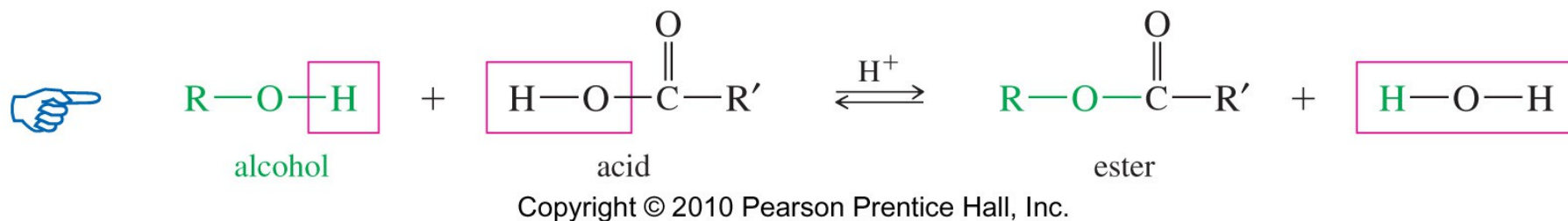
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- Glycols can be oxidatively cleaved by periodic acid (HIO_4) to form the corresponding ketones and aldehydes.
- This cleavage can be combined with the hydroxylation of alkenes by osmium tetroxide or cold potassium permanganate to form the glycol and the cleavage of the glycol with periodic acid.
- Same products formed as from ozonolysis of the corresponding alkene.

Esterification

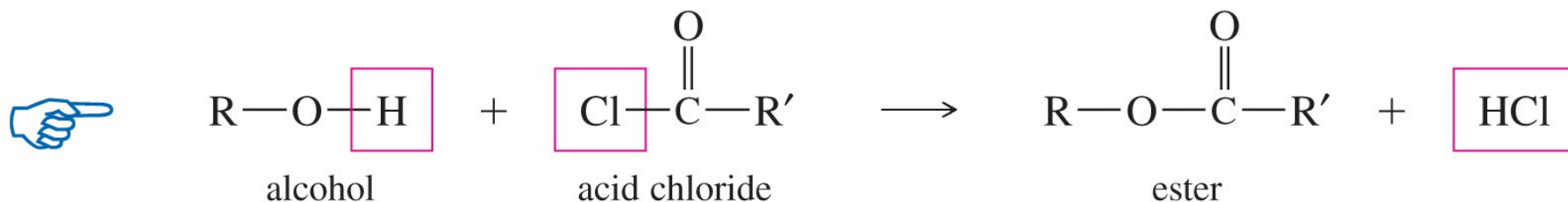
- Fischer: Alcohol + carboxylic acid
- Tosylate esters
- Sulfate esters
- Nitrate esters
- Phosphate esters

Fischer Esterification



- Reaction of an alcohol and a carboxylic acid produces an ester.
- Sulfuric acid is a catalyst.
- The reaction is an equilibrium between starting materials and products, and for this reason, the Fischer esterification is seldom used to prepare esters.

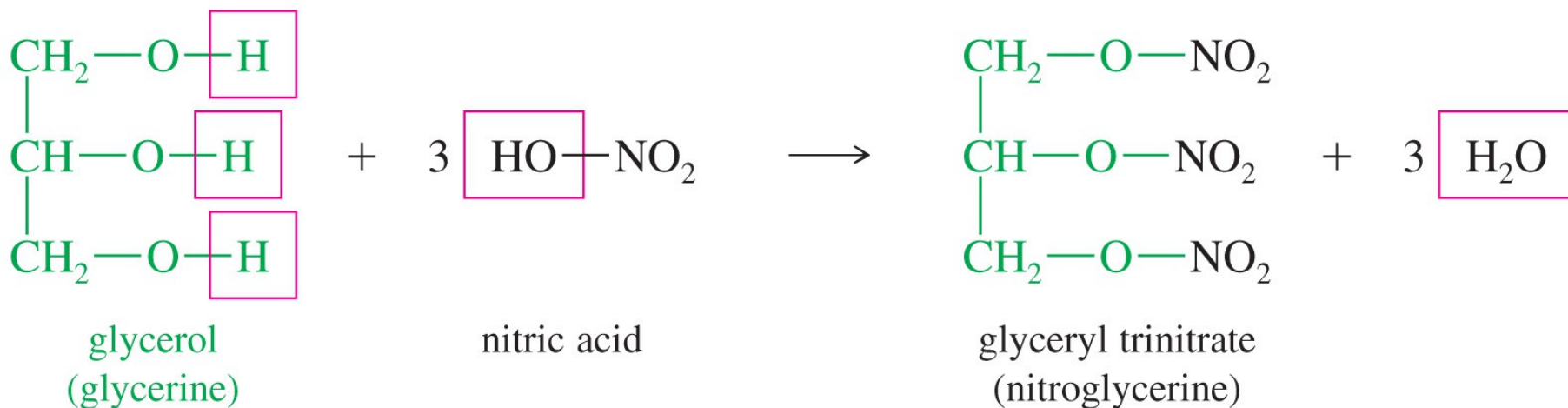
Reaction of Alcohols with Acyl Chlorides



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- The esterification reaction achieves better results by reacting the alcohol with an acyl chloride.
- The reaction is exothermic and produces the corresponding ester in high yields with only HCl as a by-product.

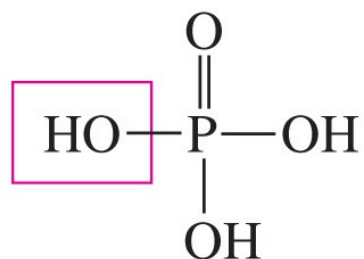
Nitrate Esters



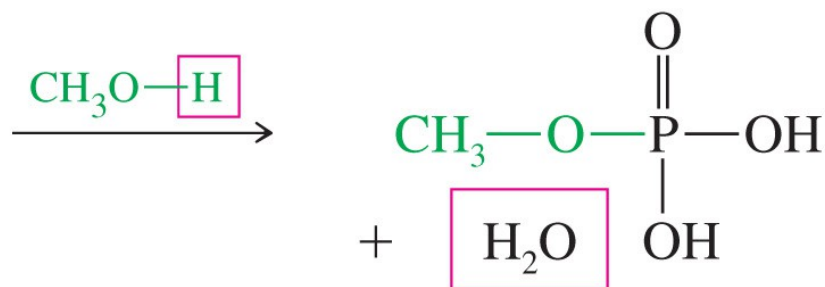
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- The best known nitrate ester is nitroglycerine, whose systematic name is glyceryl trinitrate.
- Glyceryl nitrate results from the reaction of glycerol (1,2,3-propanetriol) with three molecules of nitric acid.

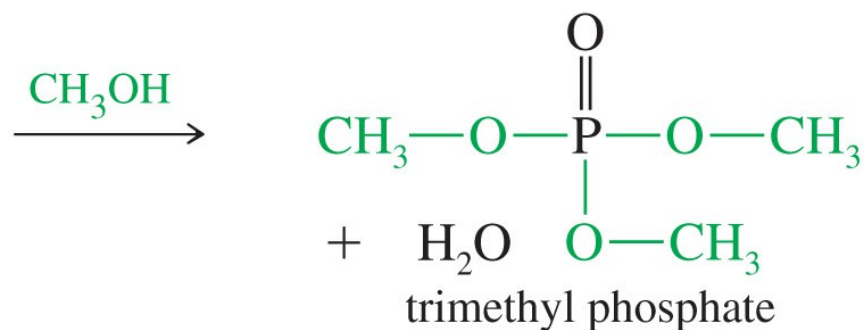
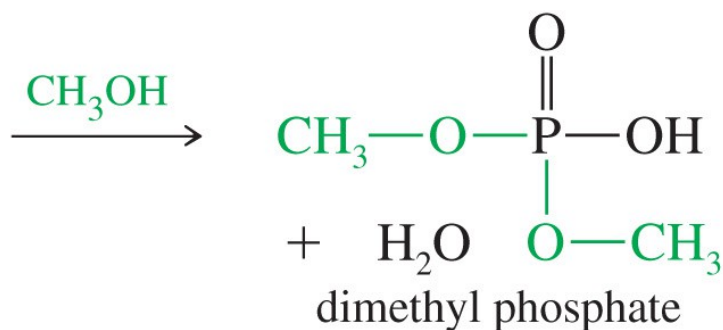
Phosphate Esters



phosphoric acid

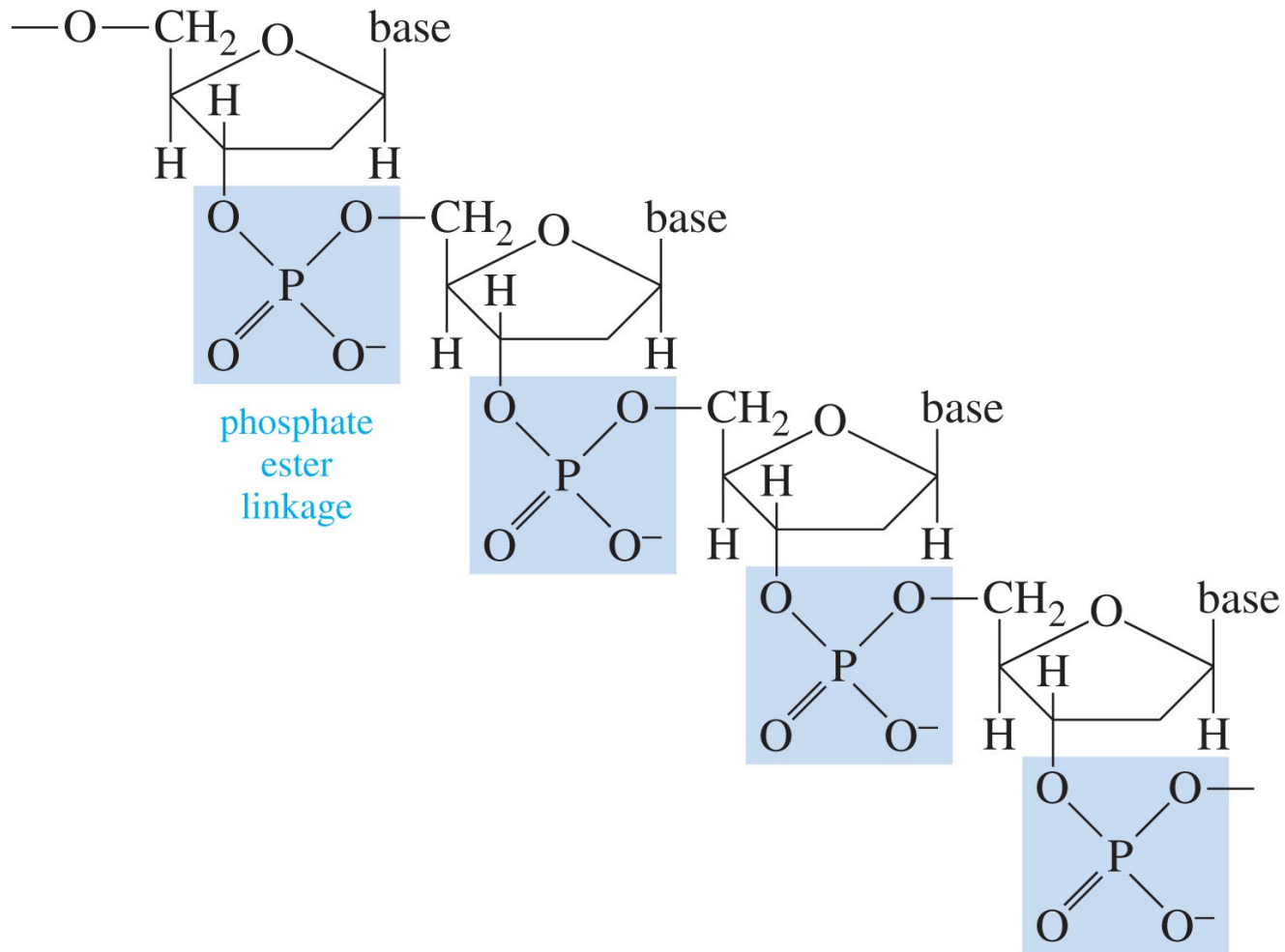


monomethyl phosphate



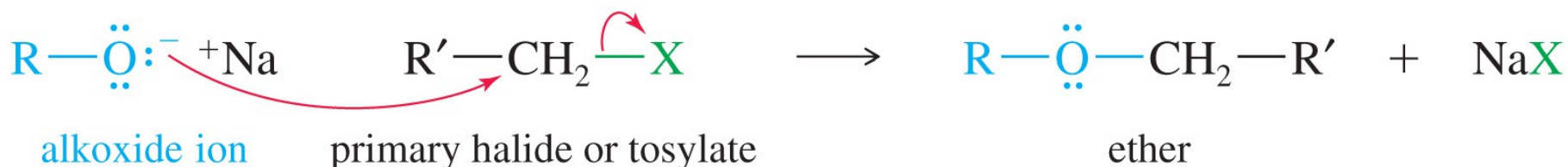
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Phosphate Esters in DNA



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Alkoxide Ions: Williamson Ether Synthesis



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- Ethers can be synthesized by the reaction of alkoxide ions with primary alkyl halides in what is known as the Williamson ether synthesis.
- This is an S_N2 displacement reaction and as such, works better with primary alkyl halides to facilitate back-side attack.
- If a secondary or tertiary alkyl halide is used, the alkoxide will act as a base and an elimination will take place.