

11

Organic Chemistry

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Foote**

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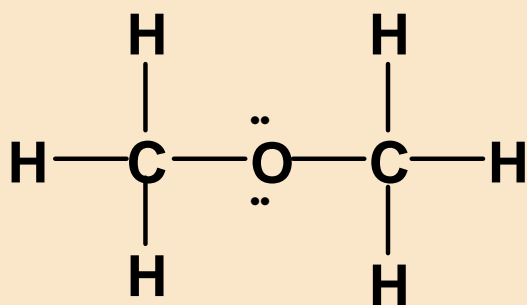
Ethers & Epoxides

Chapter 11

11-2

11 Structure

- u The functional group of an ether is an oxygen atom bonded to two carbon atoms
- u Oxygen is sp^3 hybridized with bond angles of approximately 109.5° . In dimethyl ether, the C-O-C bond angle is 110.3°

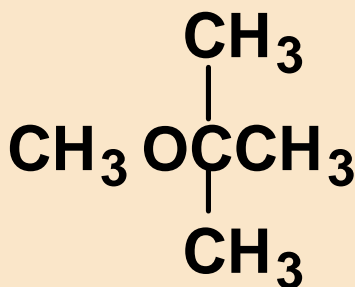


11 Nomenclature: ethers

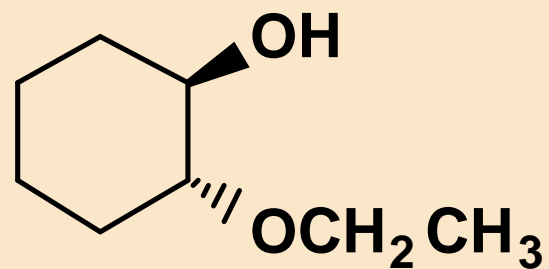
- u **IUPAC:** the longest carbon chain is the parent. Name the OR group as an alkoxy substituent
- u **Common names:** name the groups attached to oxygen followed by the word **ether**



Ethoxyethane
(Diethyl ether)



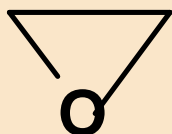
2-Methoxy-2-methylpropane
(tert-Butyl methyl ether)



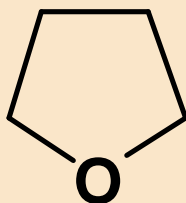
trans-2-Ethoxycyclohexanol

11 Nomenclature: ethers

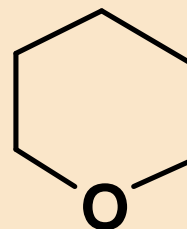
- u Although cyclic ethers have IUPAC names, their common names are more widely used
 - IUPAC: prefix ox- shows oxygen in the ring. The suffixes **-irane**, **-etane**, **-olane**, and **-ane** show three, four, five, and six atoms in a saturated ring.



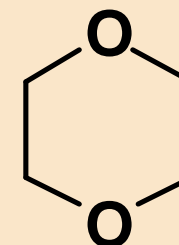
Oxirane
(Ethylene
oxide)



Oxolane
(Tetrahydro-
furan, THF)



Oxane
(Tetrahydro-
pyran, THP)



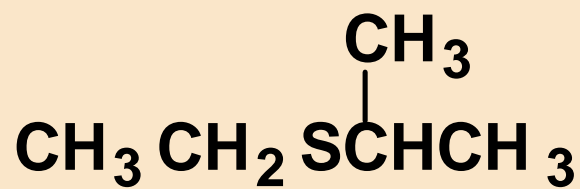
1,4-Dioxane

11 Nomenclature: sulfides

- u Sulfide: the sulfur analog of an ether
- u Name the alkyl or aryl groups attached to sulfur followed by the word **sulfide**



Dimethyl sulfide



Ethyl isopropyl sulfide

11 Nomenclature: sulfides

- u The functional group of a disulfide is an -S-S- group
- u Name the alkyl or aryl groups bonded to sulfur followed by the word **disulfide**



Dimethyl disulfide

11 Physical Properties

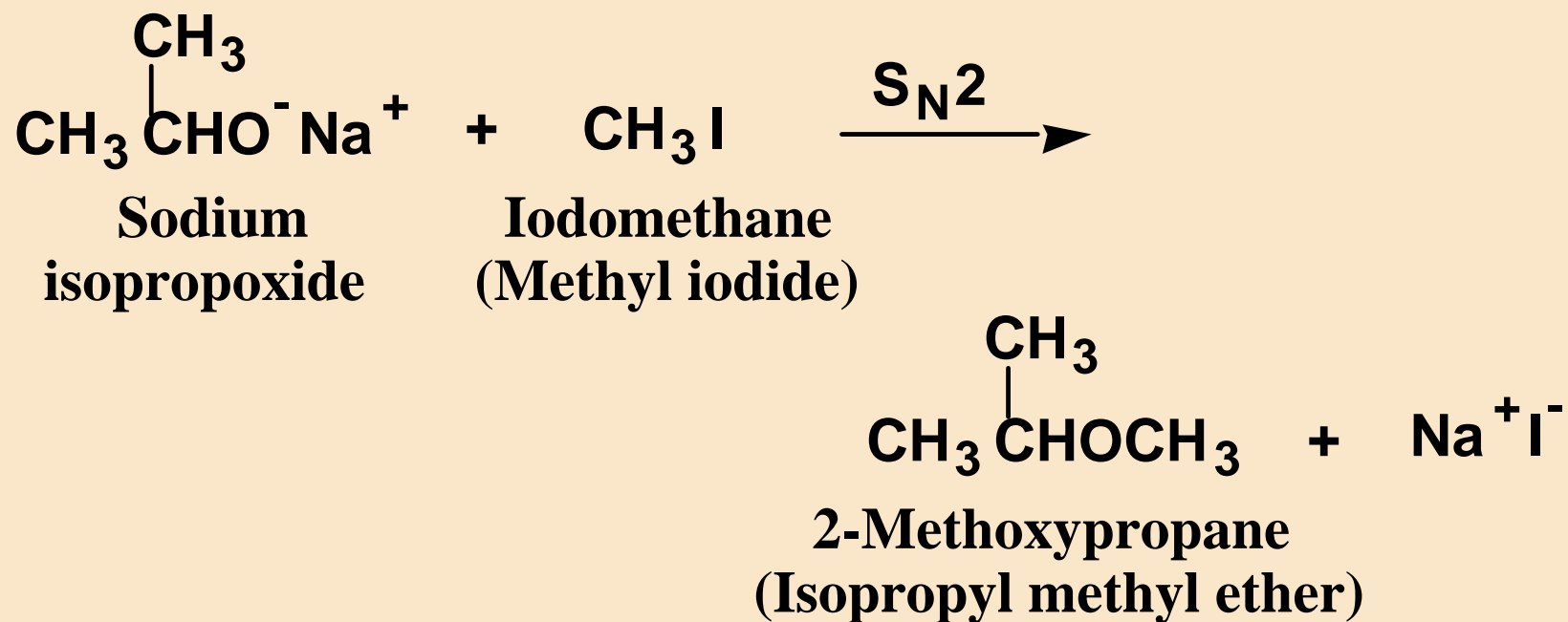
- u Ethers are polar molecules; oxygen bears a partial negative charge and each carbon a partial positive charge

11 Physical Properties

- u Ethers are polar molecules, but because of steric hindrance, only weak dipole-dipole attractive forces exist between their molecules in the pure liquid state
- u Boiling points of ethers are
 - lower than alcohols of comparable MW and
 - close to those of hydrocarbons of comparable MW
- u Ethers hydrogen bond with H₂O and are more soluble in H₂O than are hydrocarbons

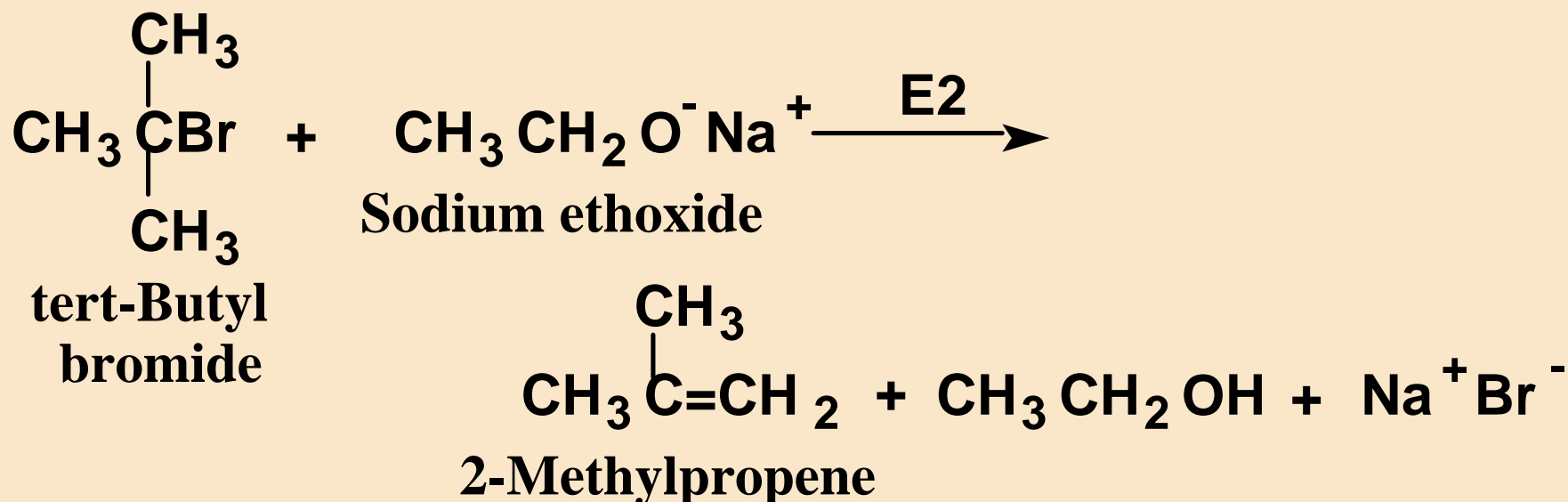
11 Preparation of Ethers

- u **Williamson ether synthesis:** S_N2 displacement of halide, tosylate, or mesylate by alkoxide ion



11 Preparation of Ethers

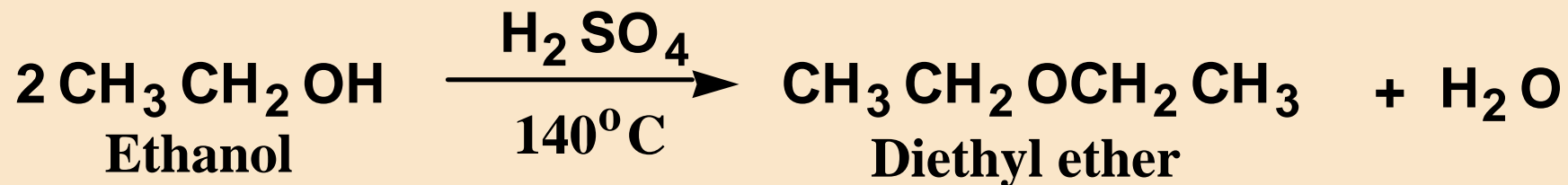
- u Williamson ether synthesis: yields are
- highest with methyl and 1° halides,
 - lower with 2° halides (competing β -elimination)
 - fails with 3° halides (β -elimination only)



11 Preparation of Ethers

u Acid-catalyzed dehydration of alcohols

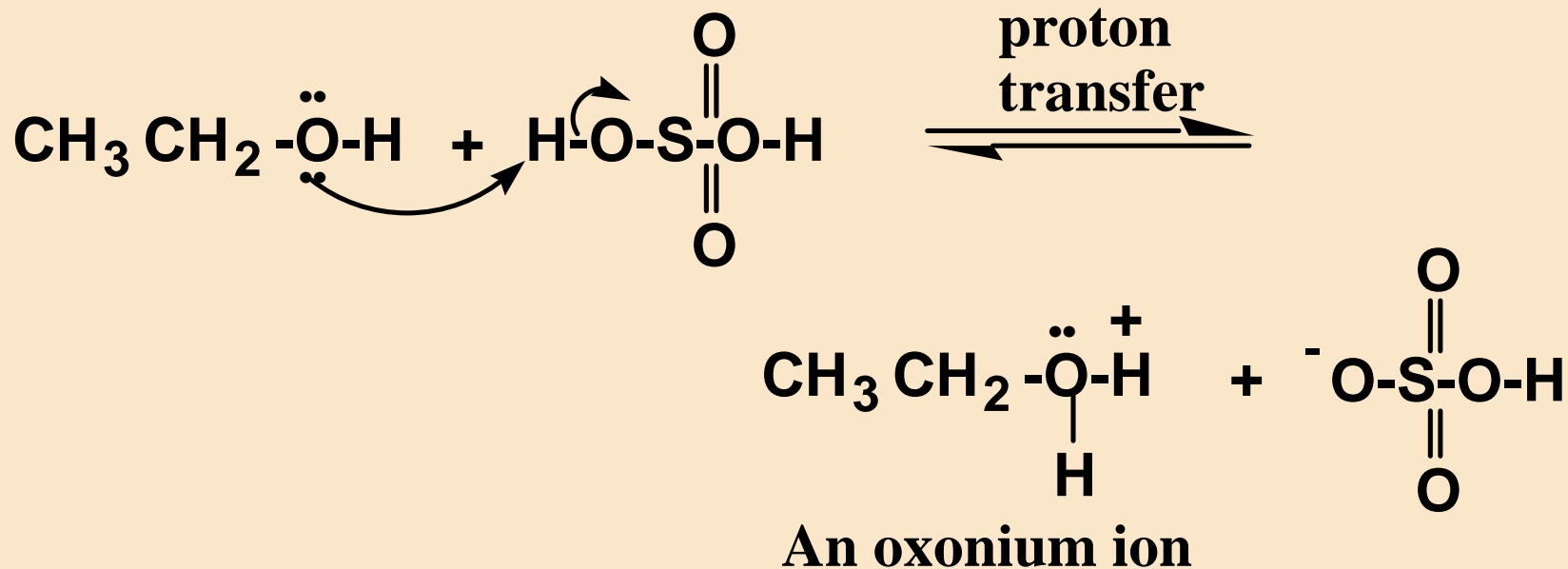
- diethyl ether and several other ethers are made on an industrial scale this way
- a specific example of an S_N2 reaction in which a poor leaving group is converted to a better one



11 Preparation of Ethers

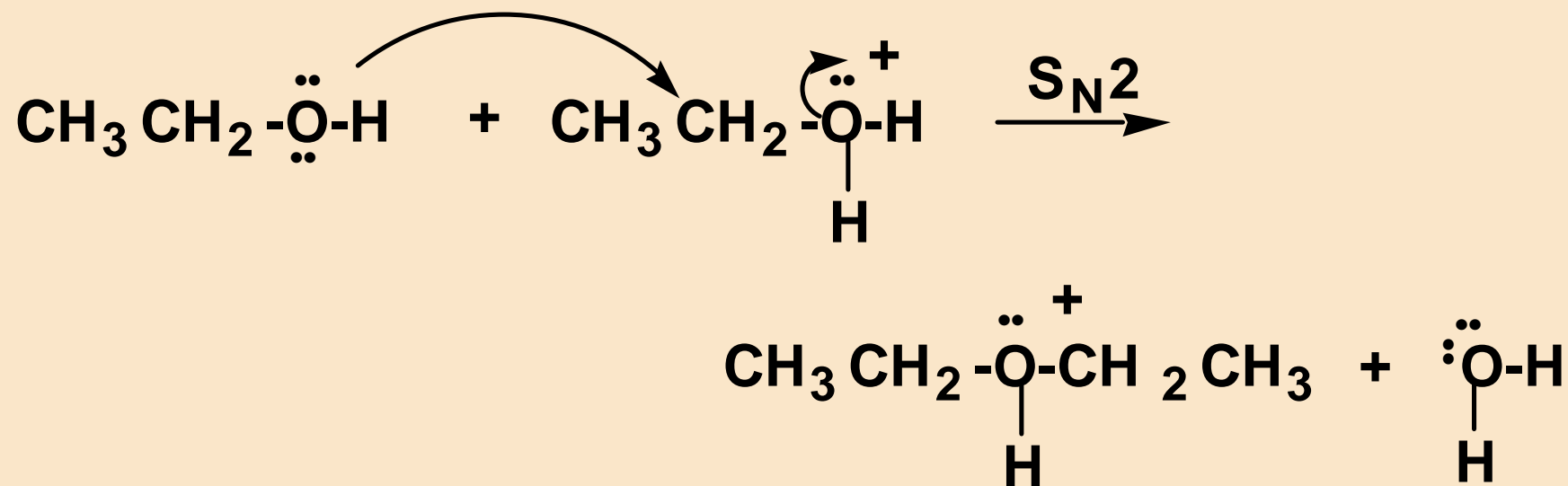
- u A three-step mechanism for acid-catalyzed dehydration of alcohols to ethers

Step 1: proton transfer to form an oxonium ion



11 Preparation of Ethers

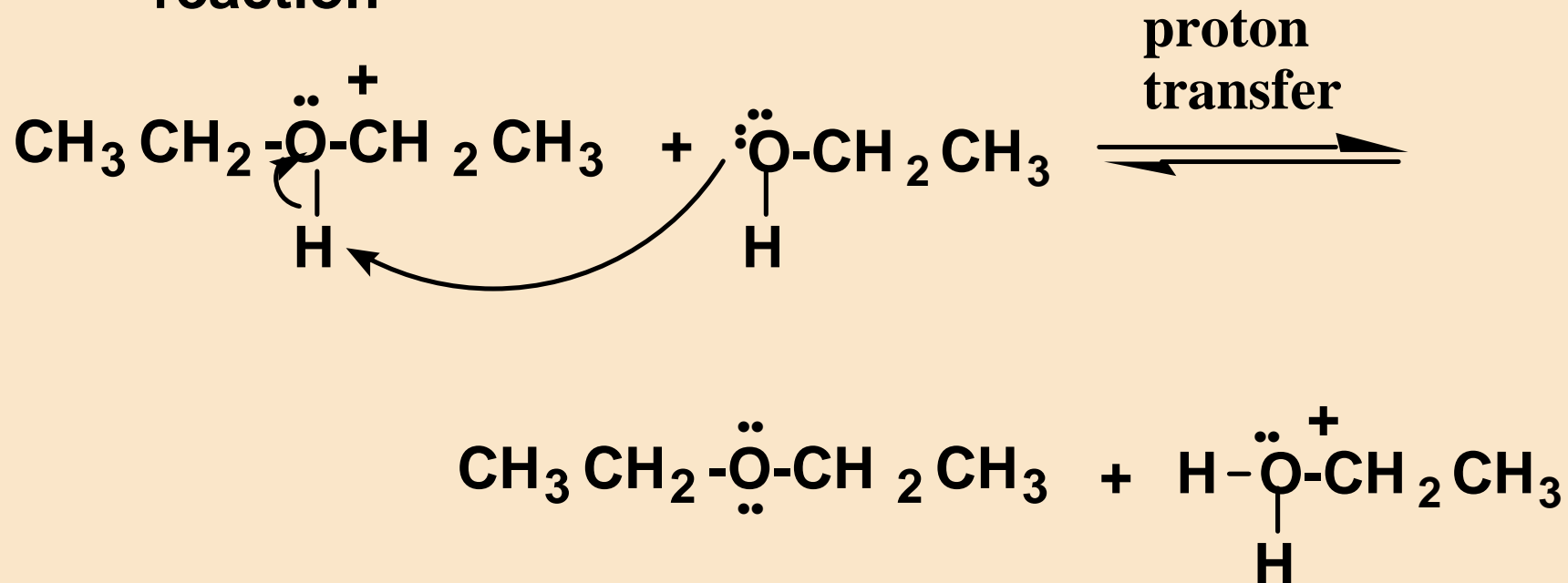
Step 2: nucleophilic displacement of OH_2^+ by the OH group of the alcohol to give a new oxonium ion



A new oxonium ion

11 Preparation of Ethers

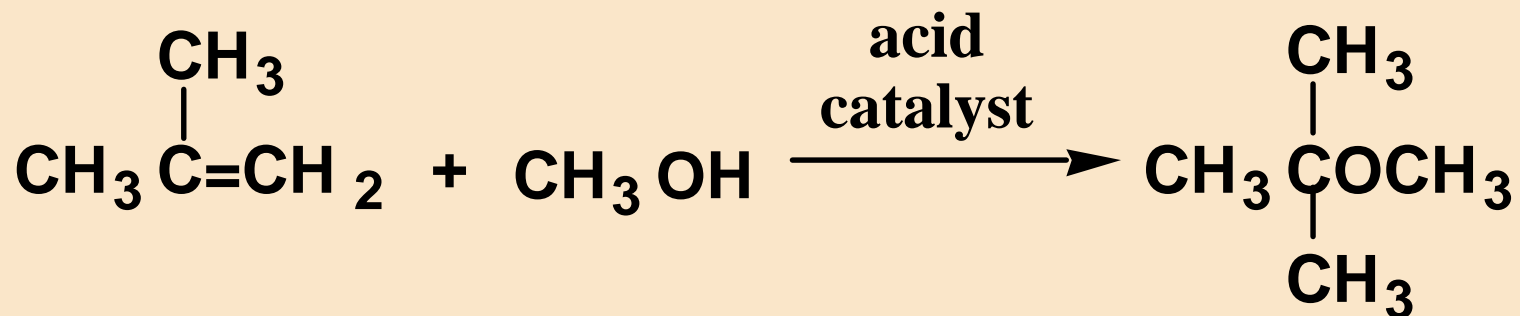
Step 3: proton transfer to solvent to complete the reaction



11 Preparation of Ethers

u Acid-catalyzed addition of alcohols to alkenes.
Yields are highest using

- an alkene that can form a stable carbocation
- methanol or a 1° alcohol

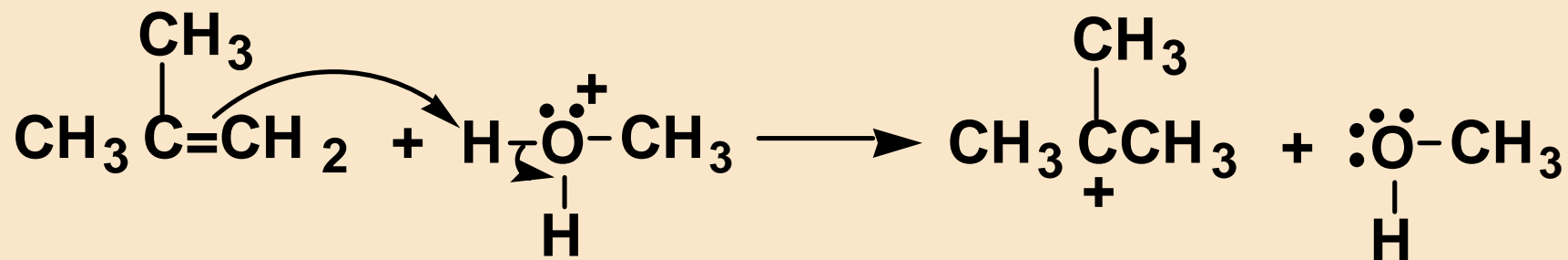


2-Methoxy-2-methylpropane
(tert-Butyl methyl ether)

11 Preparation of Ethers

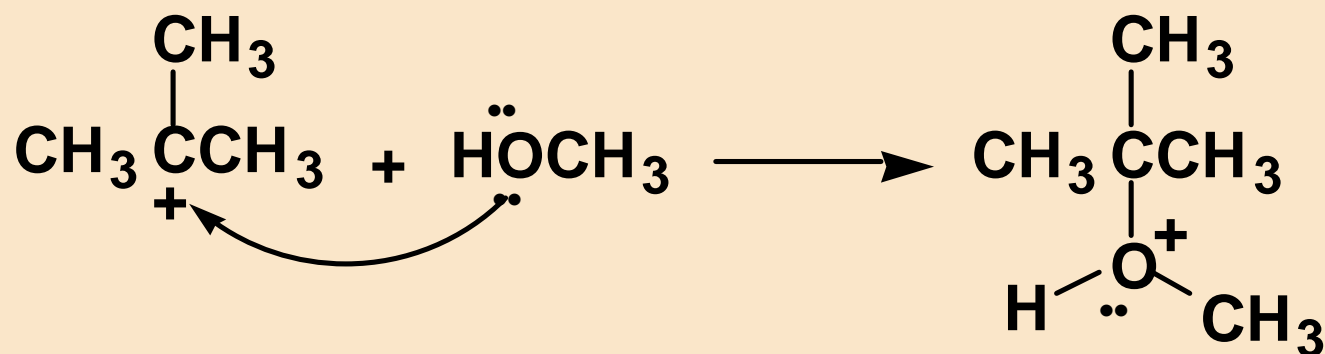
- u A three-step mechanism for the addition of an alcohol to an alkene

Step 1: protonation of the alkene to form a carbocation



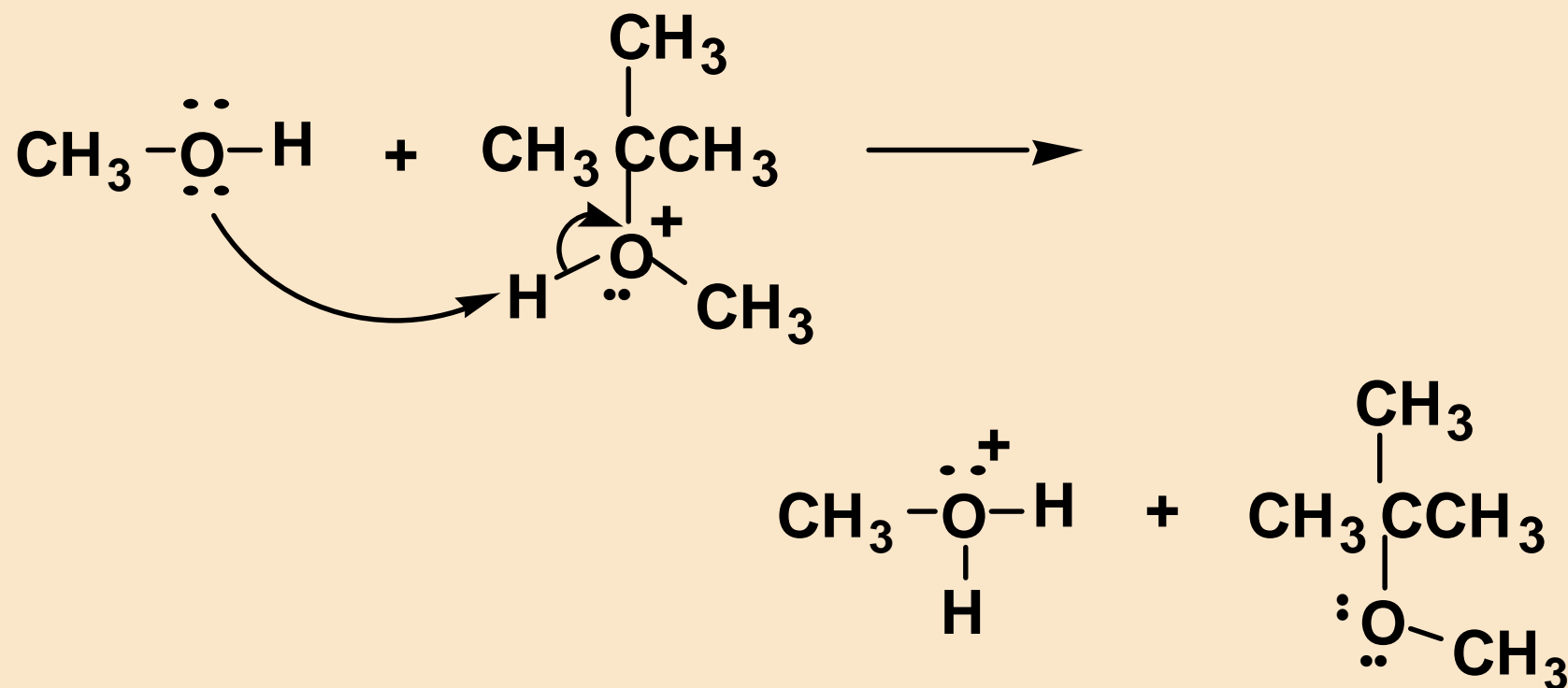
11 Preparation of Ethers

Step 2: reaction of the alcohol (a Lewis base) with the carbocation (a Lewis acid)



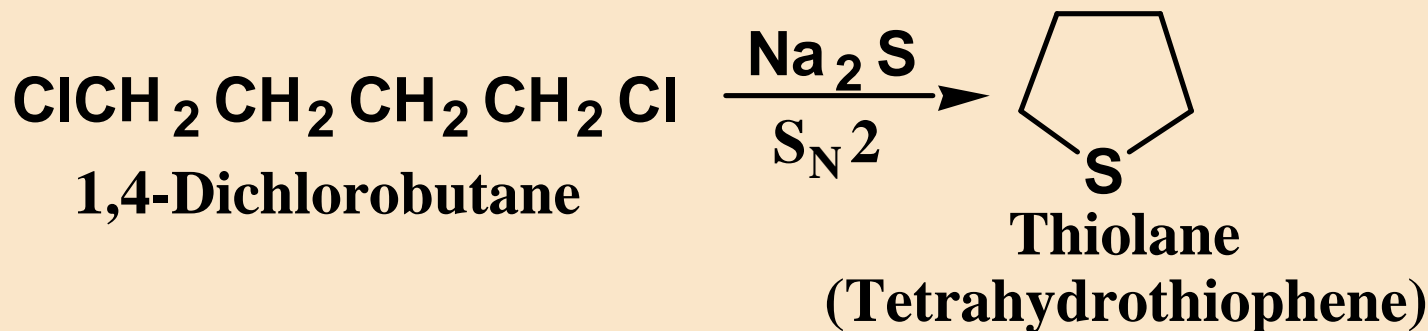
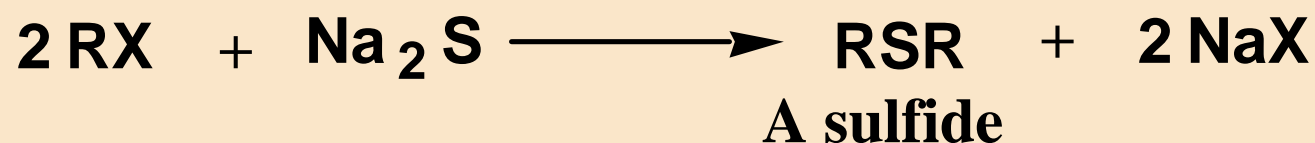
11 Preparation of Ethers

Step 3: proton transfer to solvent to complete the reaction



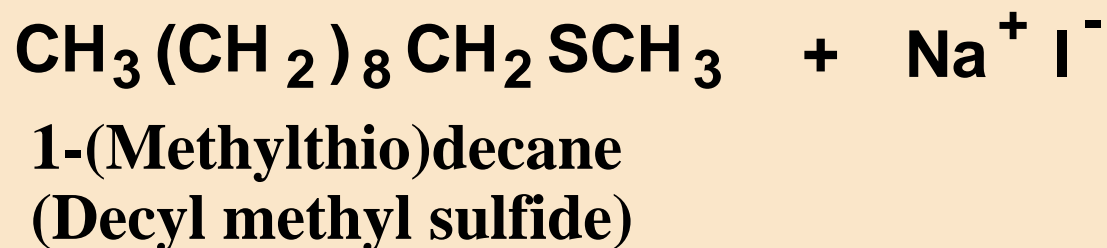
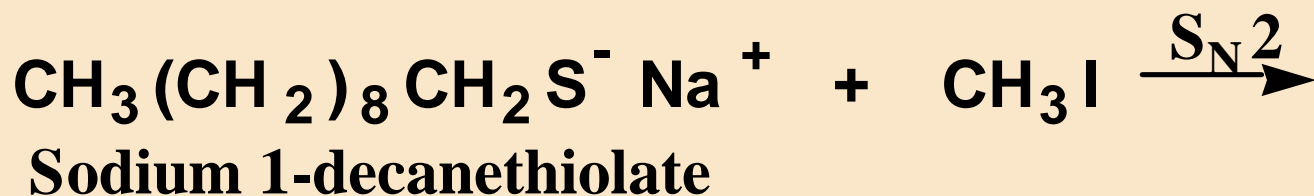
11 Preparation of Sulfides

- u Symmetrical sulfides, R_2S , are prepared by treatment of 1 mol of Na_2S with 2 mol of an alkyl halide. This method can also be used to prepare five- and six-membered cyclic sulfides



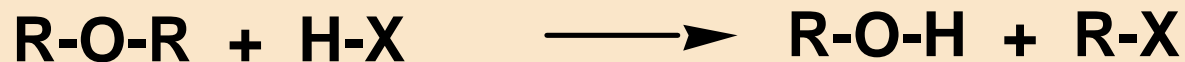
11 Preparation of Sulfides

- u **Unsymmetrical sulfides: convert a thiol to its sodium salt and then treat this salt with an alkyl halide (a variation on the Williamson ether synthesis)**



11 Cleavage of Ethers

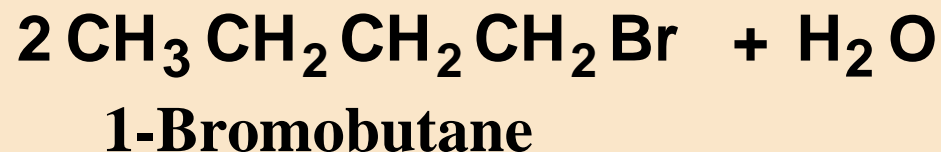
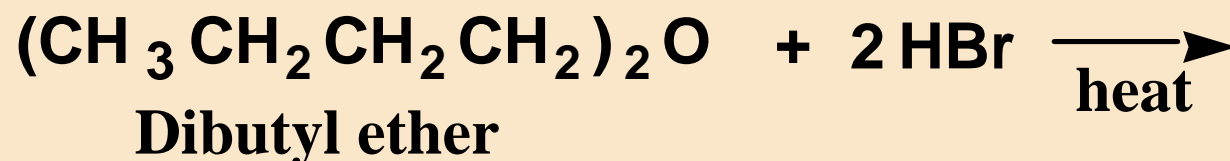
- u Ethers are cleaved by HX to an alcohol and an alkyl halide



- cleavage requires both a strong acid and a good nucleophile, hence the use of concentrated HI (57%) and HBr (48%)
- cleavage by concentrated HCl (38%) is less effective, primarily because Cl^- is a weaker nucleophile in water than either I^- or Br^-

11 Cleavage of Ethers

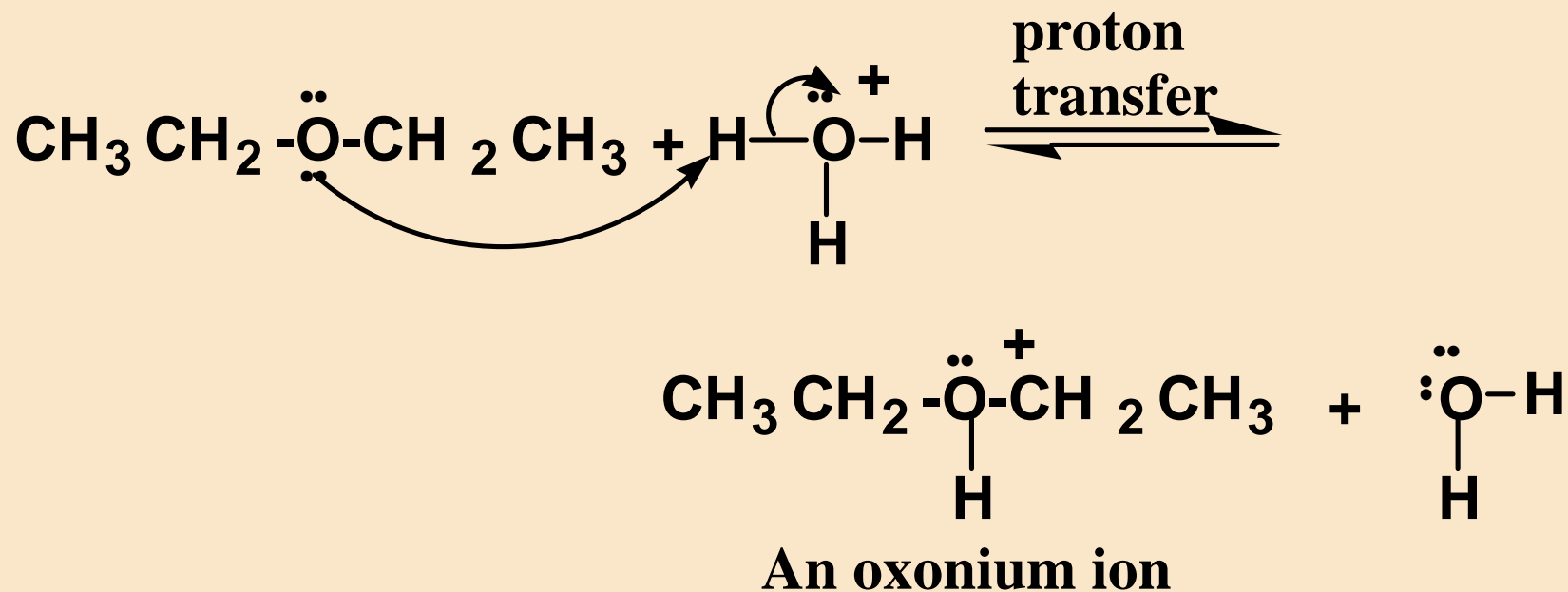
- u A dialkyl ether is cleaved to two moles of alkyl halide



11 Cleavage of Ethers

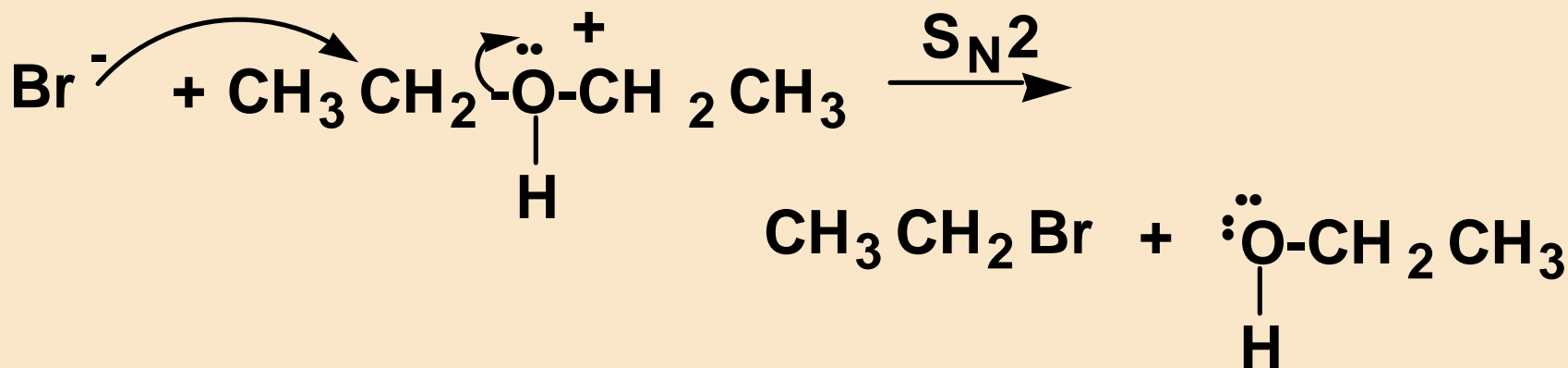
- u The mechanism for HBr and HI cleavage of 1° and 2° dialkyl ethers is divided into two steps

Step 1: proton transfer to the oxygen atom of the ether to form an oxonium ion



11 Cleavage of Ethers

Step 2: Nucleophilic displacement on the primary carbon

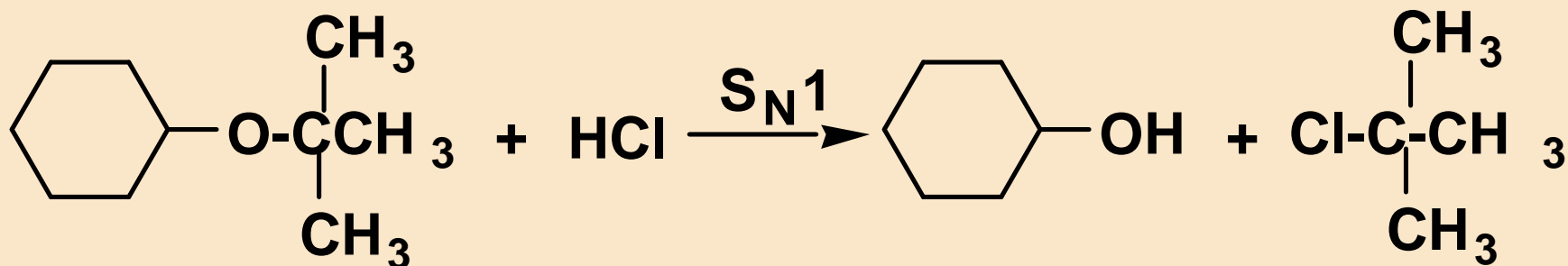


- The alcohol is then converted to the alkyl bromide or iodide by another $\text{S}_{\text{N}}2$ reaction (Section 8.3)

11 Cleavage of Ethers

u 3° and benzylic ethers are particularly sensitive to cleavage by HX

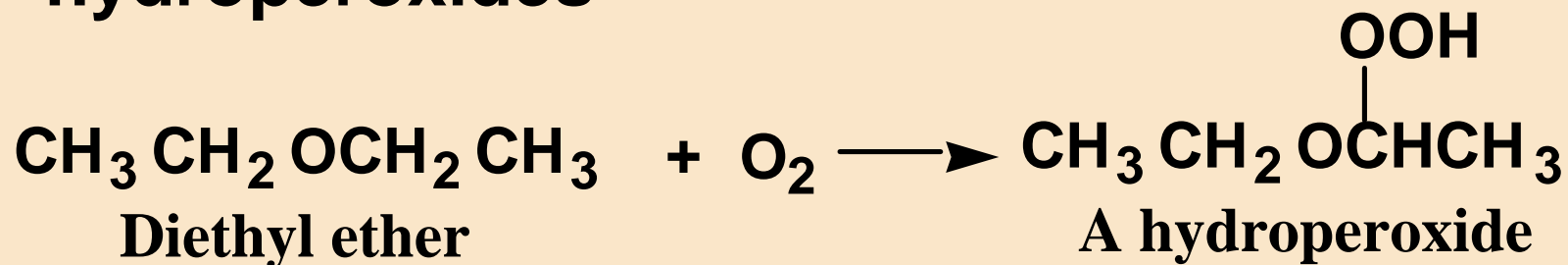
- tert-butyl ethers are cleaved by HCl at room temp



- in this case, protonation of the ether oxygen is followed by C-O cleavage to give the tert-butyl cation

11 Oxidation of Ethers

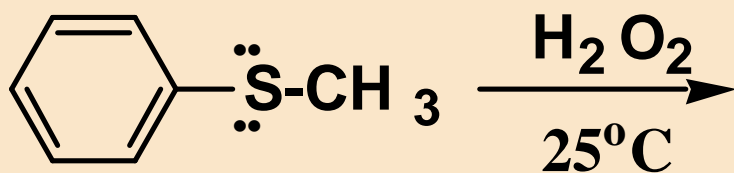
- u Ethers react with O_2 at a C-H bond adjacent to the ether oxygen to form explosive hydroperoxides



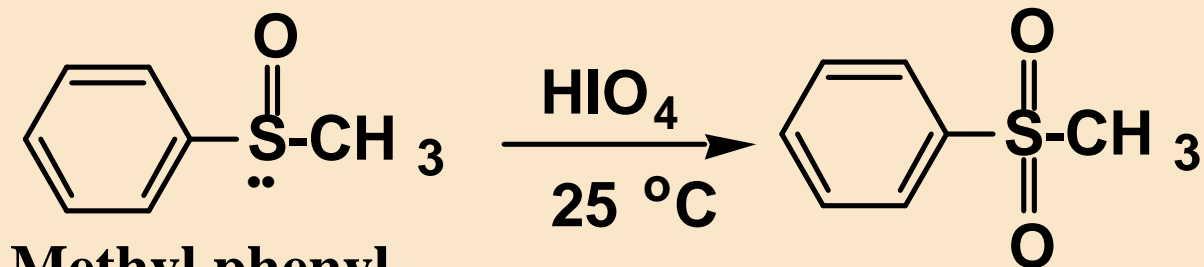
- u **Hydroperoxide**: a compound containing the **OOH** group

11 Oxidation Sulfides

- u Sulfides can be oxidized to sulfoxides and sulfones, by the proper choice of experimental conditions



Methyl phenyl
sulfide

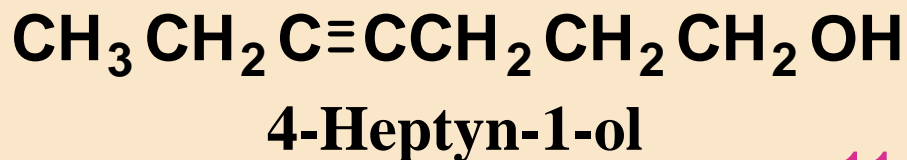
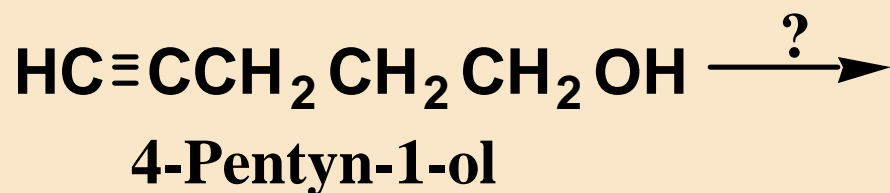


Methyl phenyl
sulfoxide

Methyl phenyl
sulfone

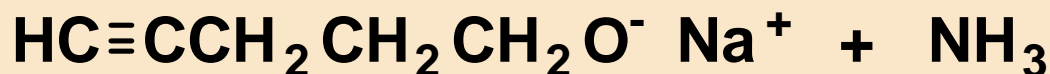
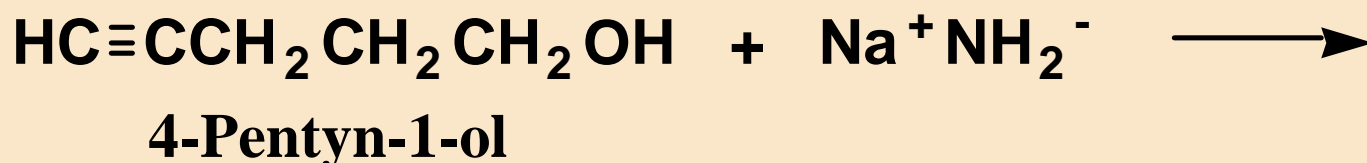
11 Ethers - Protecting Grps

- u When dealing with compounds containing two or more functional groups, it is often necessary to protect one of them (to prevent its reaction) while reacting at the other
- u Suppose you wish to carry out this transformation



11 Ethers - Protecting Grps

- The new C-C bond can be formed by alkylation of the acetylide anion (Section 10.5)
- The OH group, however, is more acidic (pK_a 16-18) than the terminal alkyne (pK_a 25)
- treating the compound with 1 mol of NaNH_2 will form the alkoxide anion rather than the acetylide



11 Ethers - Protecting Grps

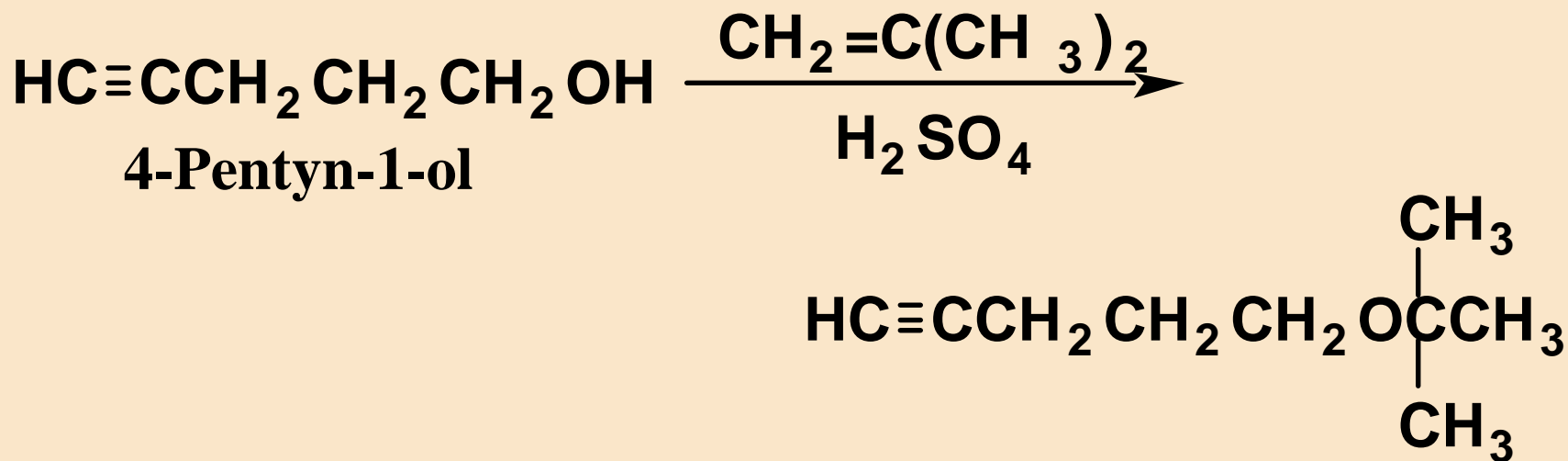
- u A protecting group must be
 - easy to add
 - easy to remove
 - resistant to the reagents used to transform the unprotected group

- u In this chapter, we discuss three -OH protecting groups
 - tert-butyl ether group
 - trimethylsilyl (TMS) group
 - tetrahydropyranyl (THP) group

11 Ethers - Protecting Grps

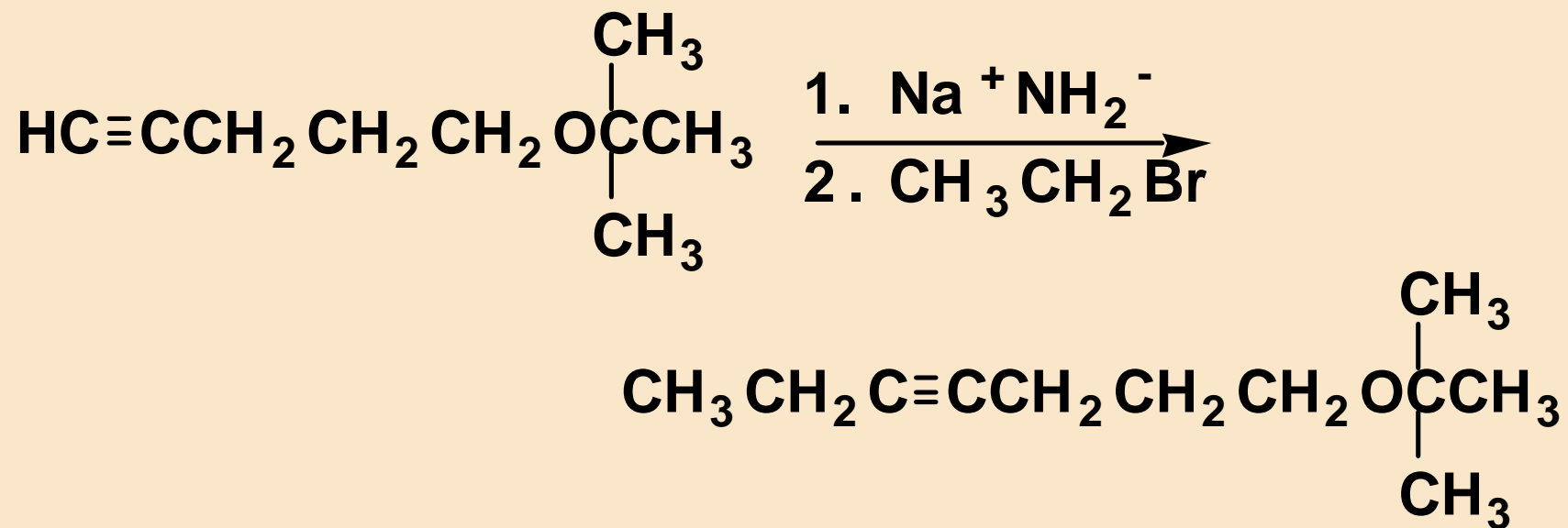
u The tert-butyl protecting group

- formed by treatment of an alcohol with 2-methylpropene in the presence of an acid catalyst



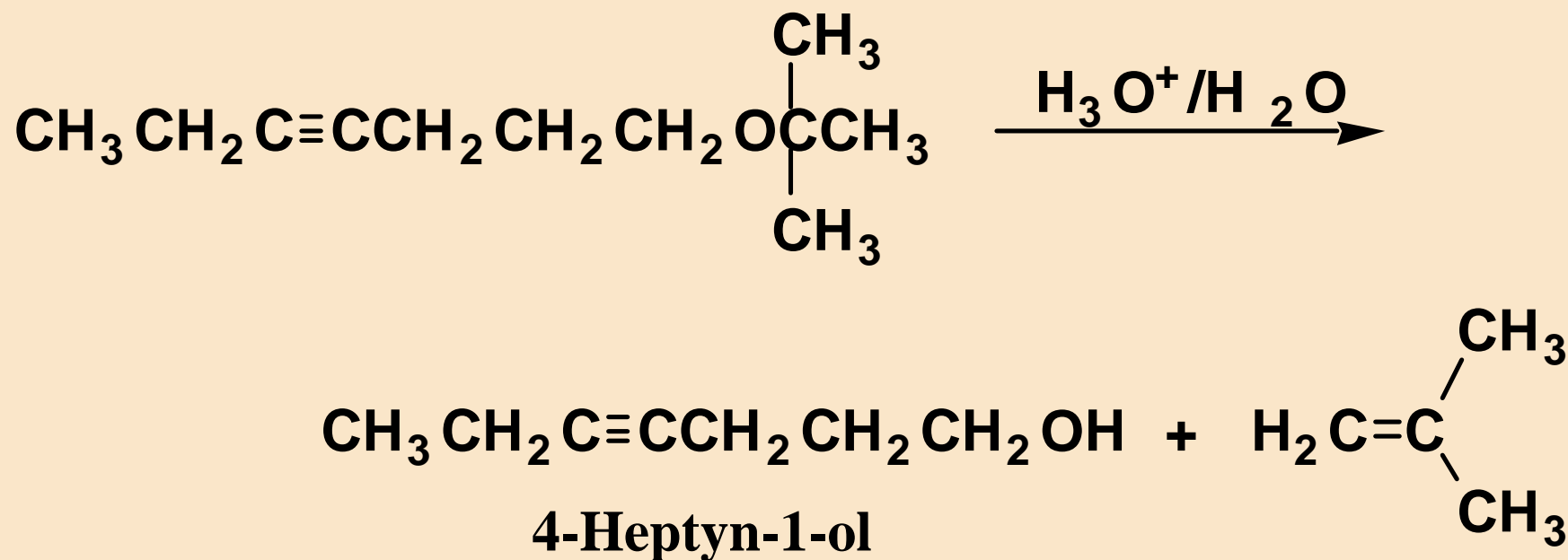
11 Ethers - Protecting Grps

- the protected compound is then alkylated



11 Ethers - Protecting Grps

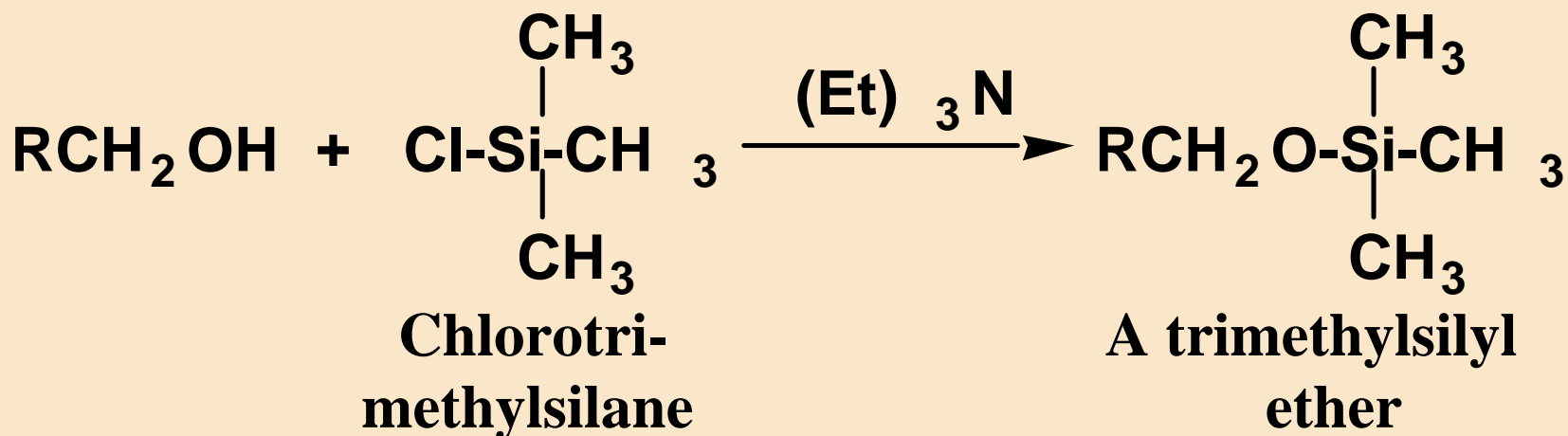
- the tert-butyl group is removed by treatment with aqueous acid



11 Ethers - Protecting Grps

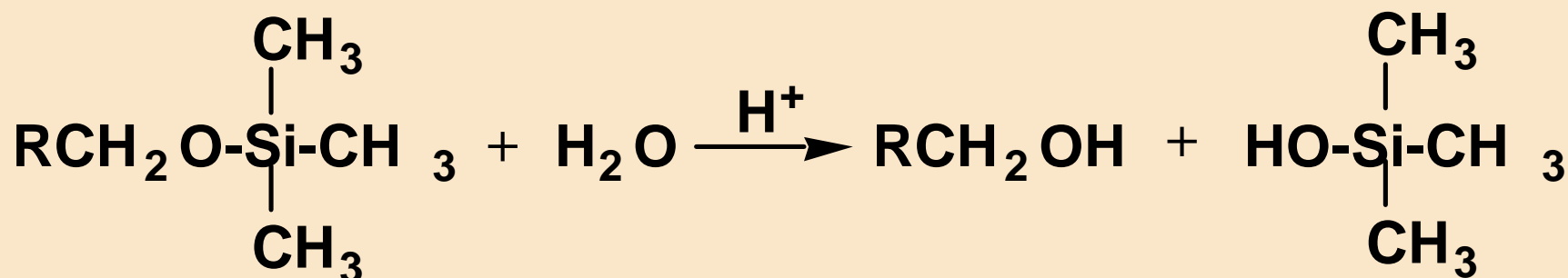
u Trimethylsilyl (TMS) group

- treat the alcohol with chlorotrimethylsilane in the presence of a 3° amine, such as triethylamine
- the function of the 3° amine is to neutralize the HCl



11 Ethers - Protecting Grps

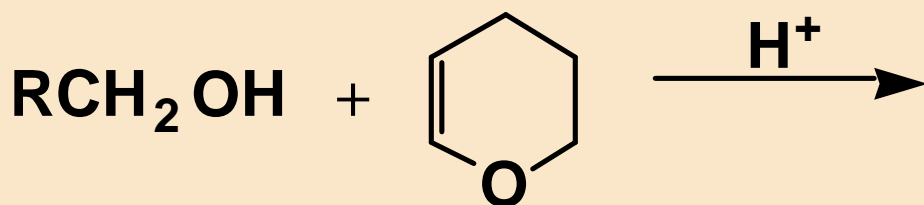
- u The TMS group is removed by treatment with aqueous acid or with F⁻ in the form of tetrabutylammonium fluoride



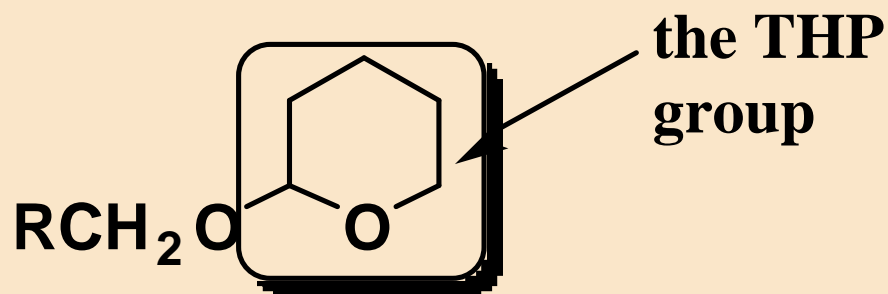
A trimethylsilyl
ether

11 Ethers - Protecting Grps

- u The tetrahydropyranyl (THP) group is used to protect OH groups of 1° and 2° alcohols. We discuss the chemistry of this group in Chapter 15.



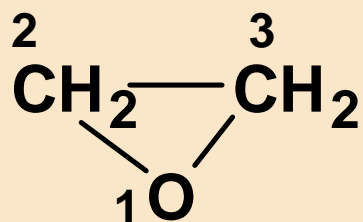
Dihydropyran



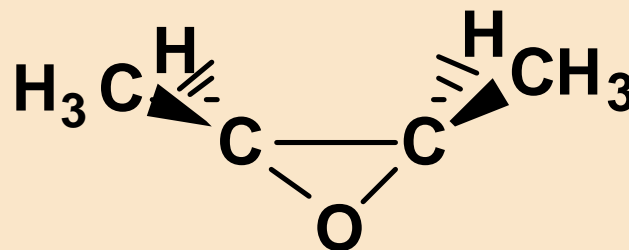
A tetrahydropyranyl ether

11 Epoxides

- u Epoxide: a cyclic ether in which oxygen is one atom of a three-membered ring
- u Simple epoxides are named as derivatives of oxirane.



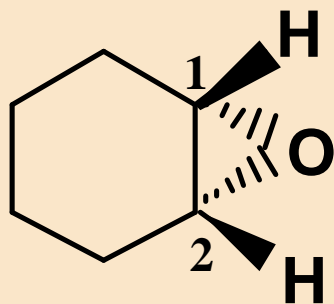
Oxirane
(Ethylene oxide)



cis-2,3-Dimethyloxirane
(cis-2-Butene oxide)

11 Epoxides

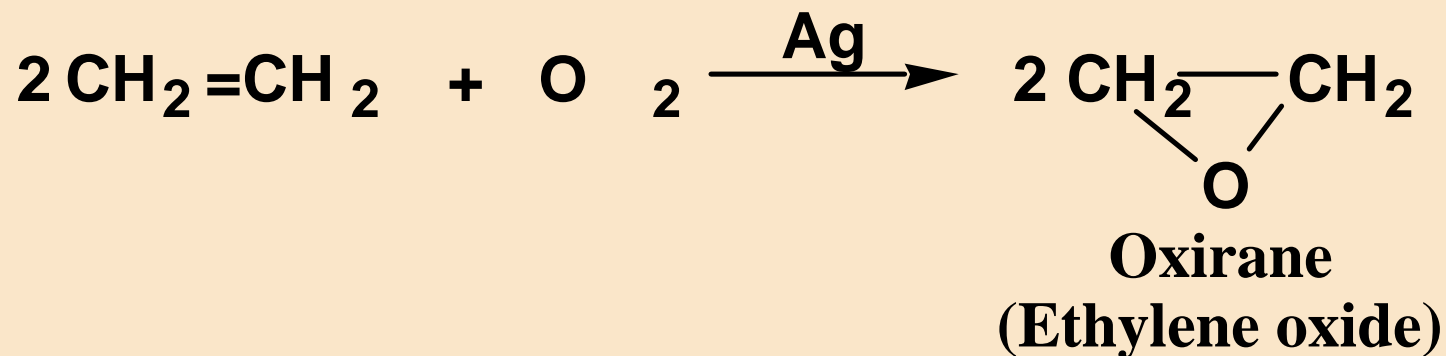
- u Where the epoxide is part of another ring system, it is shown by the prefix epoxy-
- u Common names are derived from the name of the alkene from which the epoxide is formally derived



1,2-Epoxycyclohexane
(Cyclohexene oxide)

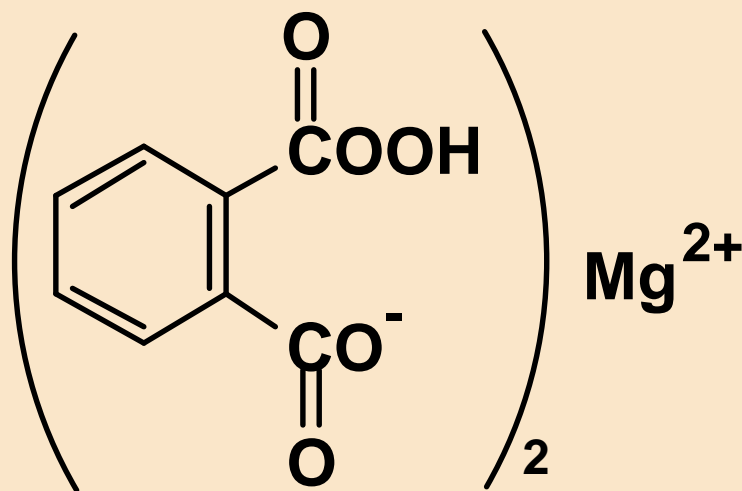
11 Synthesis of Epoxides-1

- u Ethylene oxide, one of the few epoxides manufactured on an industrial scale, is prepared by air oxidation of ethylene

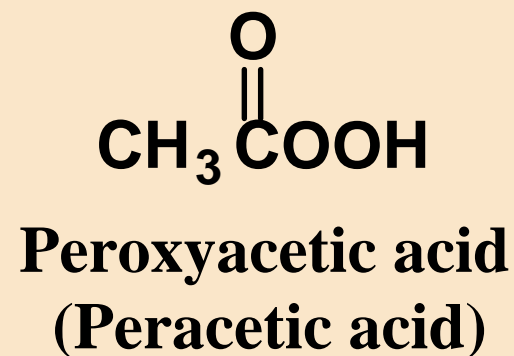


11 Synthesis of Epoxides-2

- u The most common laboratory method for synthesis of epoxides is oxidation of an alkene using a peroxycarboxylic acid (a peracid)

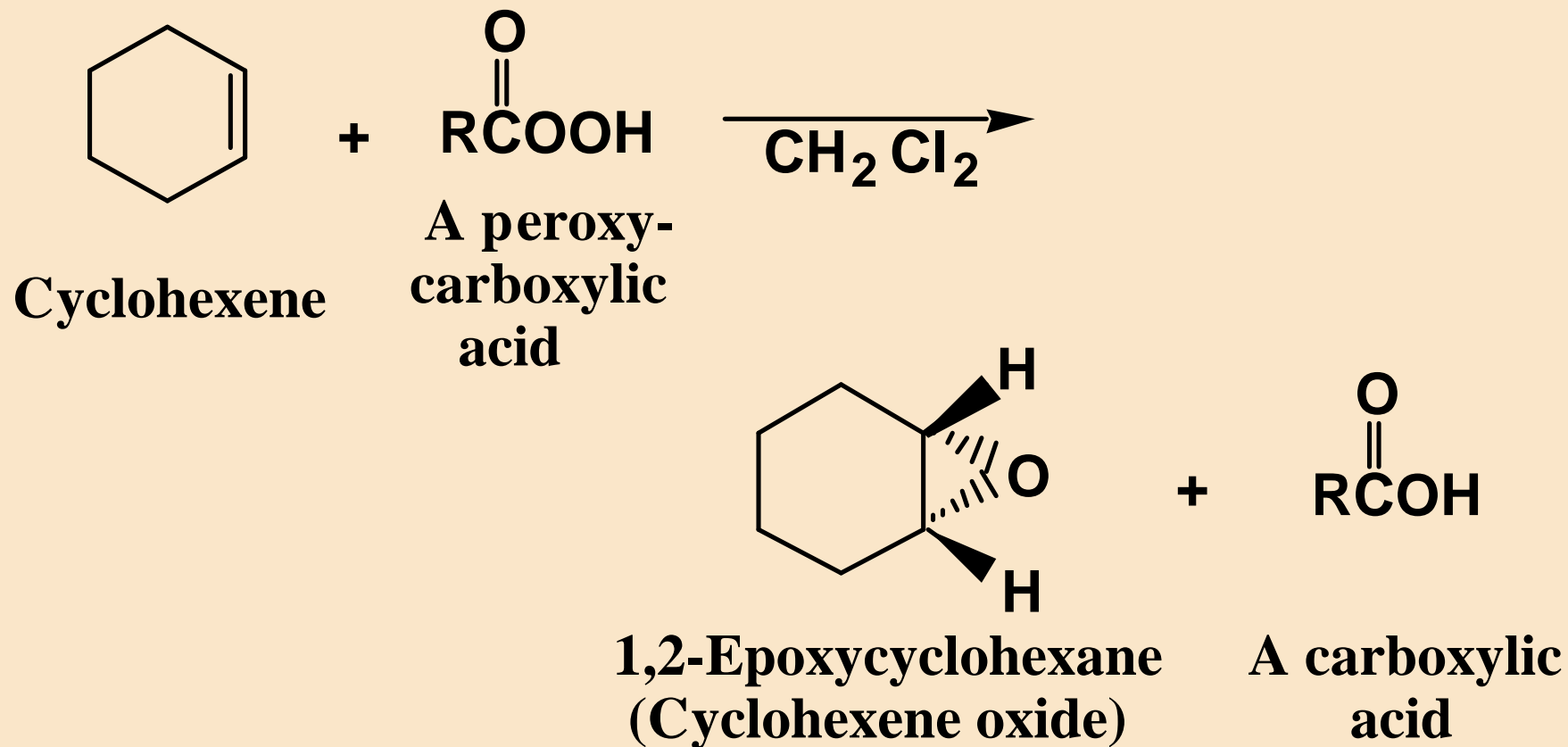


Magnesium monoperoxyphthalate
(MMPP)



11 Synthesis of Epoxides-2

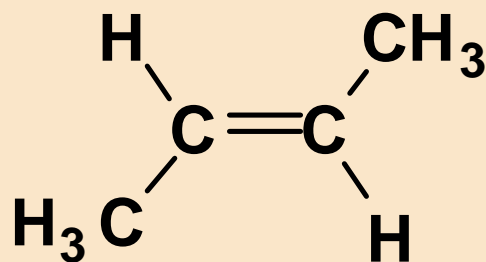
u Epoxidation of cyclohexene



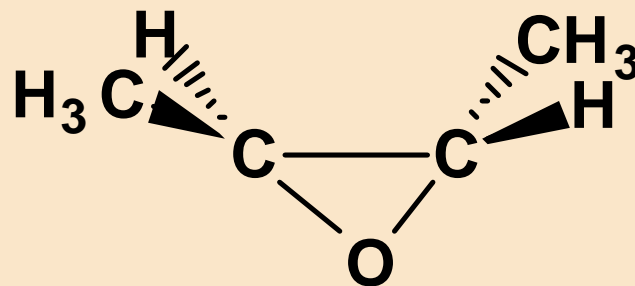
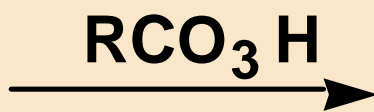
11 Synthesis of Epoxides-2

u Epoxidation is stereoselective:

- epoxidation of cis-2-butene gives only cis-2,3-dimethyloxirane and
- epoxidation of trans-2-butene gives only trans-2,3-dimethyloxirane



trans-2-Butene



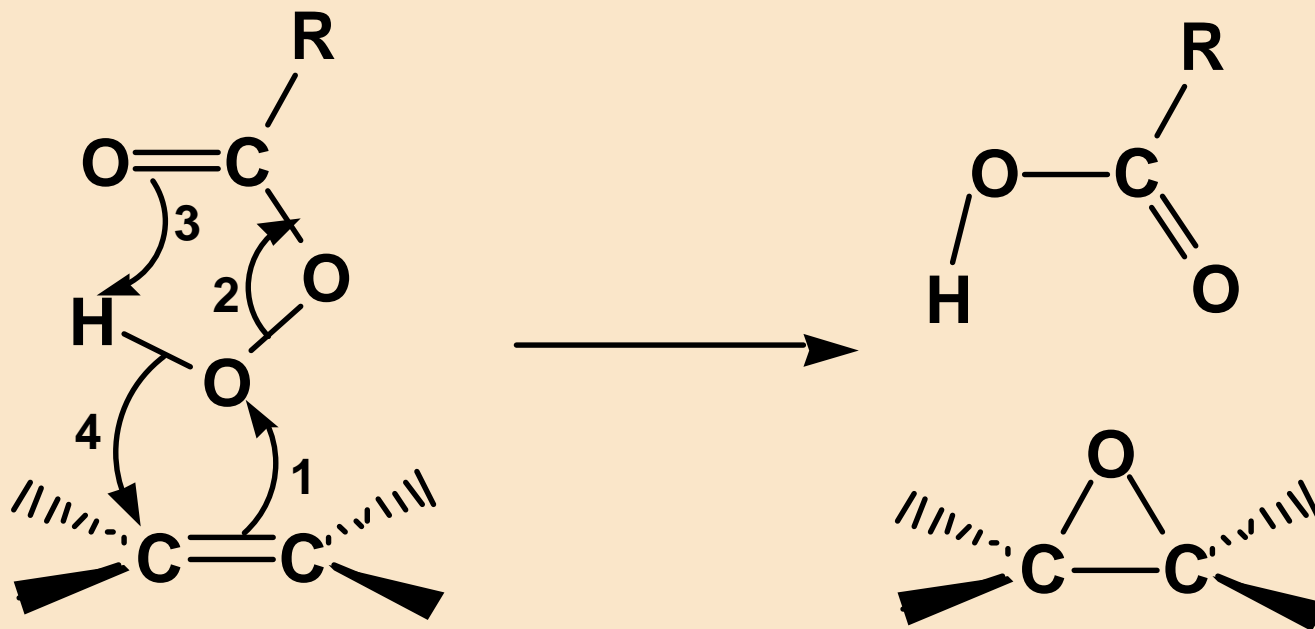
trans-2,3-Dimethyloxirane

11 Synthesis of Epoxides-2

- u **A mechanism for alkene epoxidation must take into account that the reaction**
 - **takes place in nonpolar solvents, which means that no ions are involved**
 - **is stereoselective with retention of the alkene configuration, which means that even though the pi bond is broken, at no time is there free rotation about the remaining sigma bond**

11 Synthesis of Epoxides-2

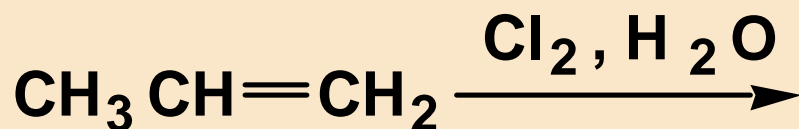
u A mechanism for alkene epoxidation



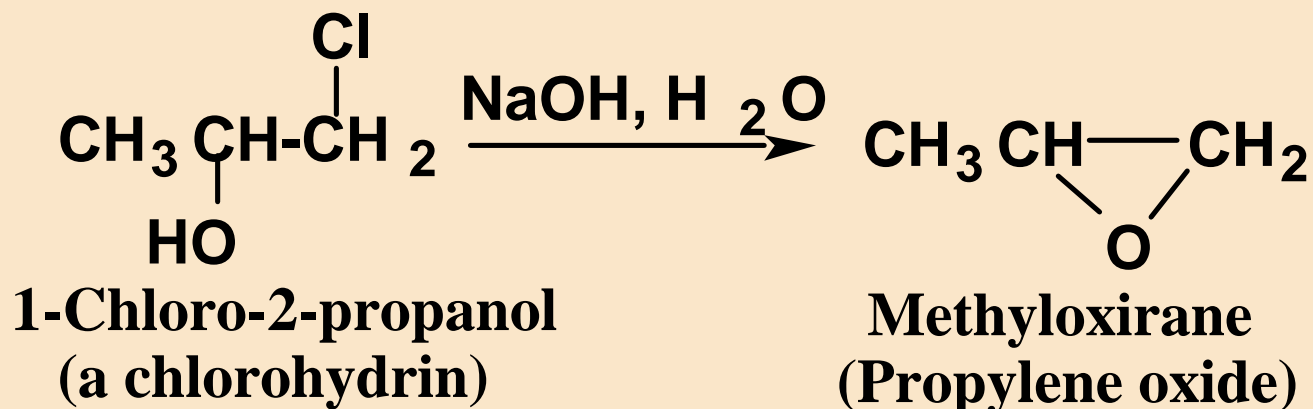
11 Synthesis of Epoxides-3

u A second general method involves

1. treatment of an alkene with Cl_2 or Br_2 in H_2O to form a halohydrin
2. treatment of the halohydrin with base, causing an internal $\text{S}_{\text{N}}2$



Propene

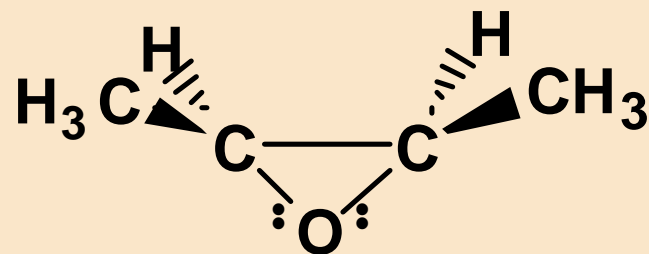
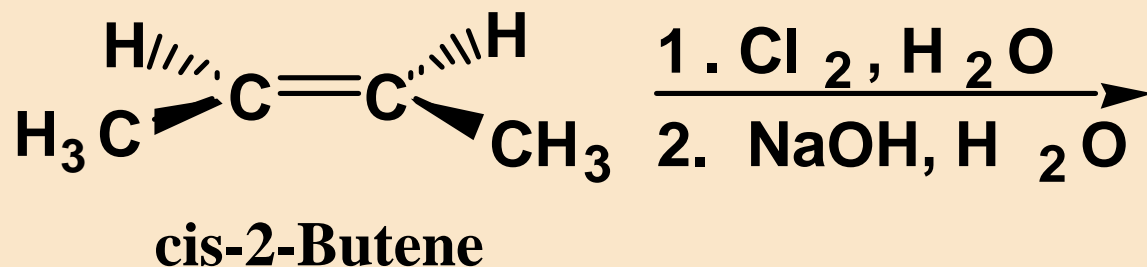


1-Chloro-2-propanol
(a chlorohydrin)

Methyloxirane
(Propylene oxide)

11 Synthesis of Epoxides-3

- u Each step is stereoselective
 - anti stereoselective for halohydrin formation
 - inversion of configuration for the S_N2 reaction
- u Given this stereoselectivity, show that cis-2-butene gives cis-2,3-dimethyloxirane

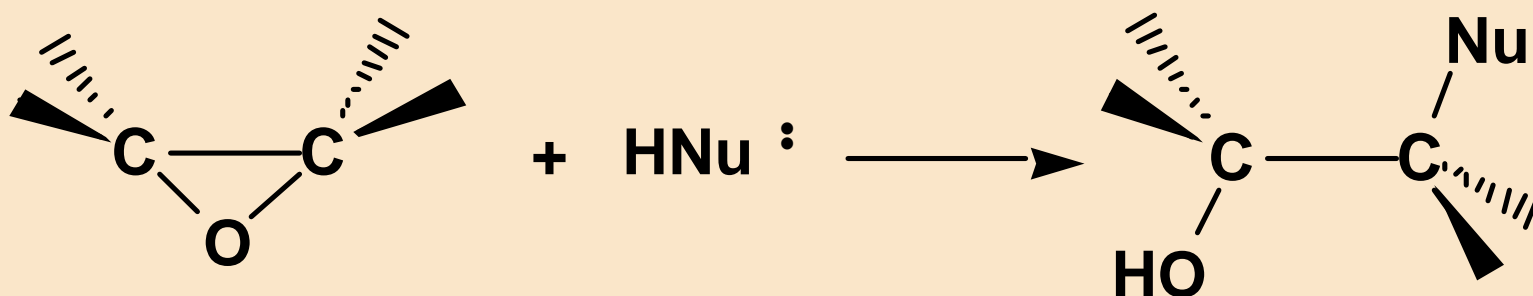


cis-2,3-Dimethyloxirane

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11 Reactions of Epoxides

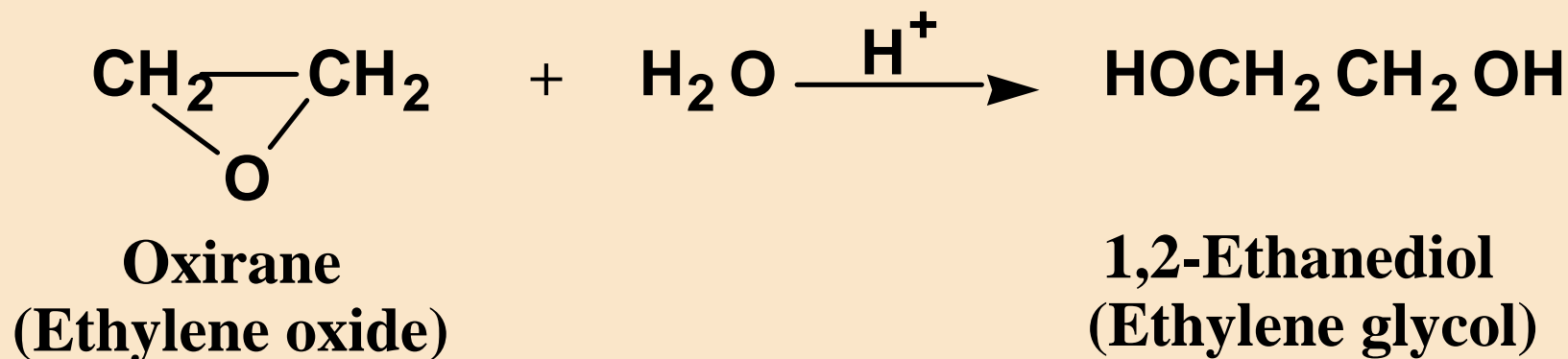
- u Because of the strain associated with the three-membered ring, epoxides readily undergo a variety of ring-opening reactions



11 Reactions of Epoxides

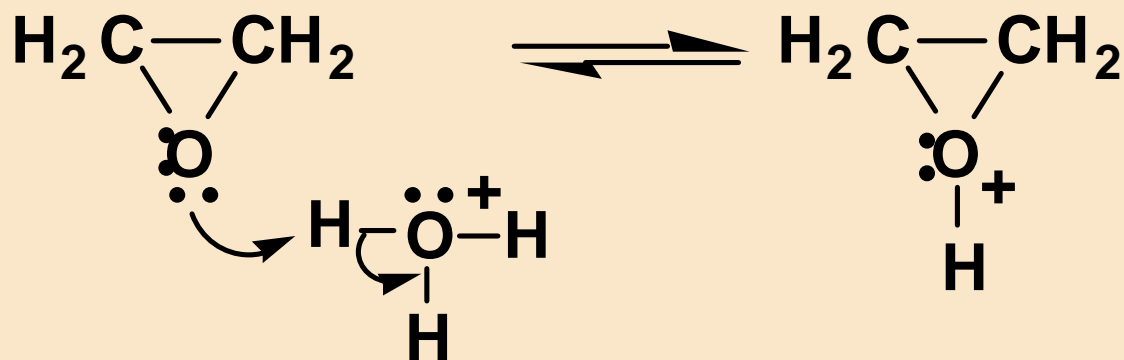
u Acid-catalyzed ring opening

- in the presence of an acid catalyst, epoxides are hydrolyzed to glycols



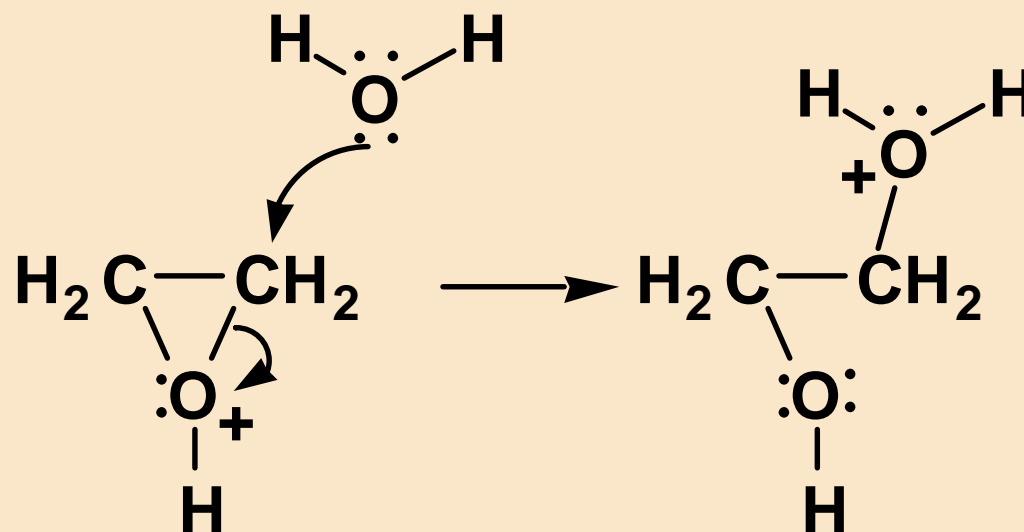
11 Reactions of Epoxides

Step 1: proton transfer to the epoxide to form a bridged oxonium ion intermediate



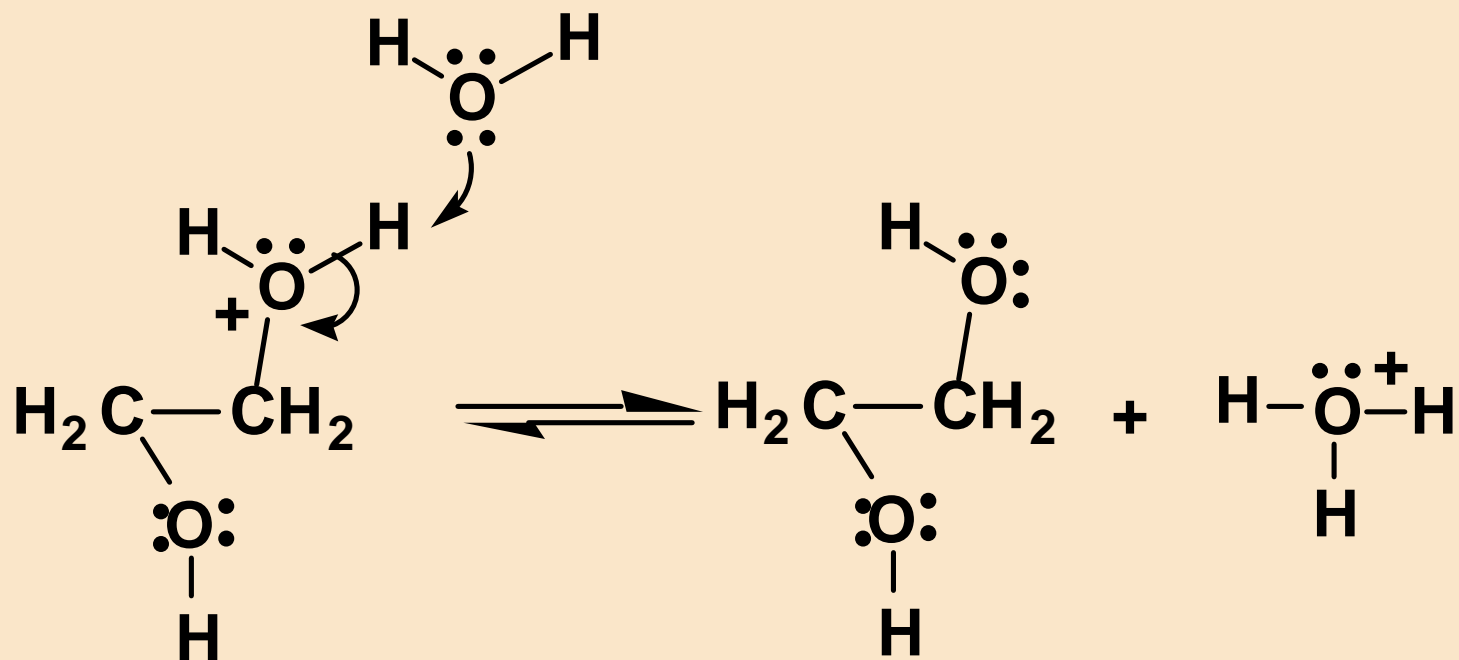
11 Reactions of Epoxides

Step 2: attack of H₂O from the side opposite the oxonium ion bridge

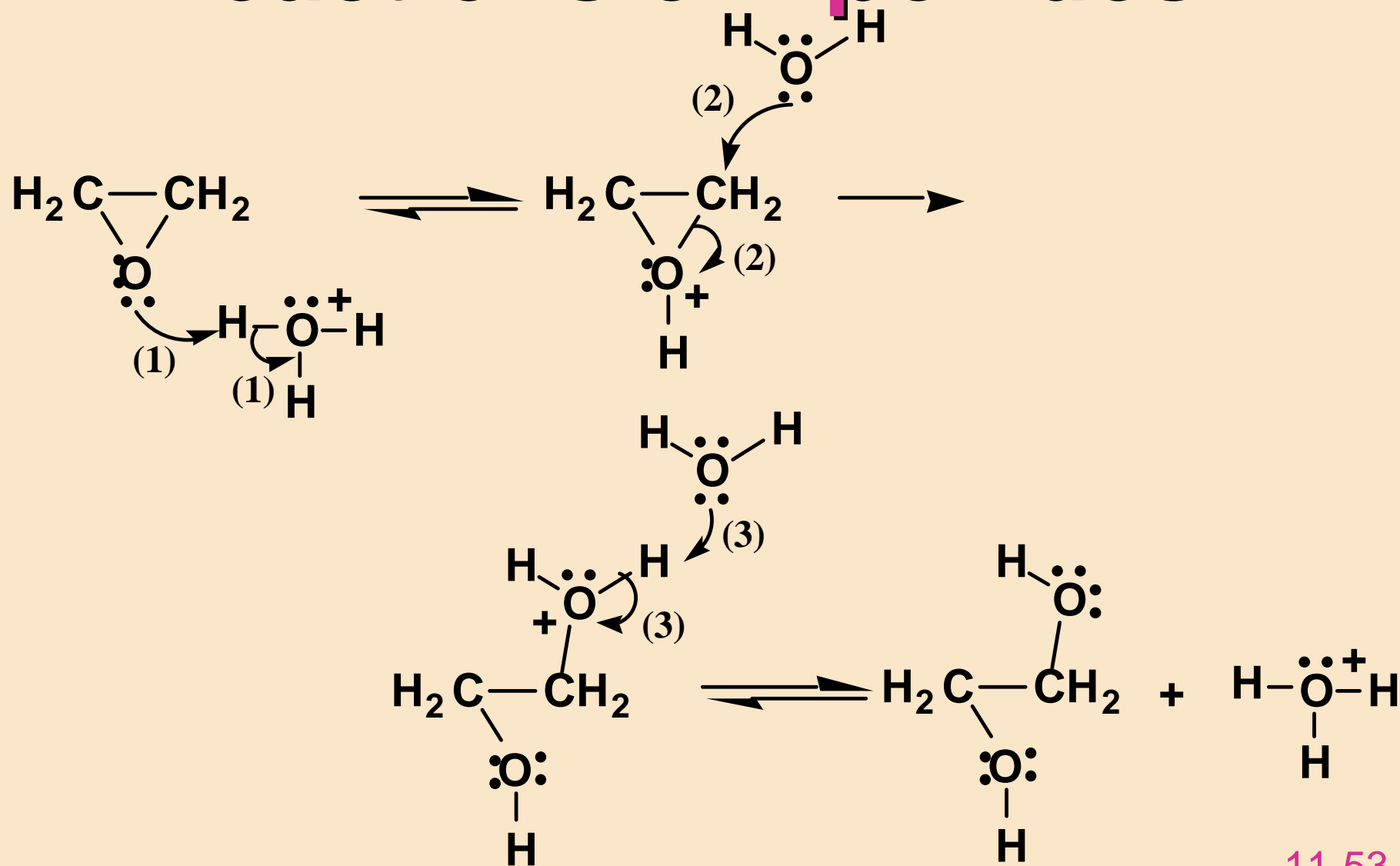


11 Reactions of Epoxides

Step 3: proton transfer to solvent to complete the hydrolysis

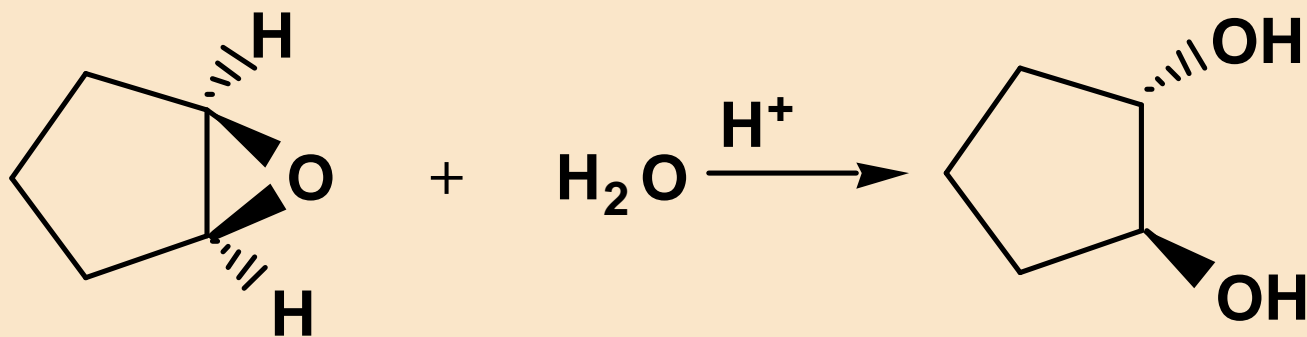


11 Reactions of Epoxides



11 Reactions of Epoxides

- u Attack of the nucleophile on the protonated epoxide shows anti stereoselectivity
 - hydrolysis of an epoxycycloalkane gives a trans-1,2-diol

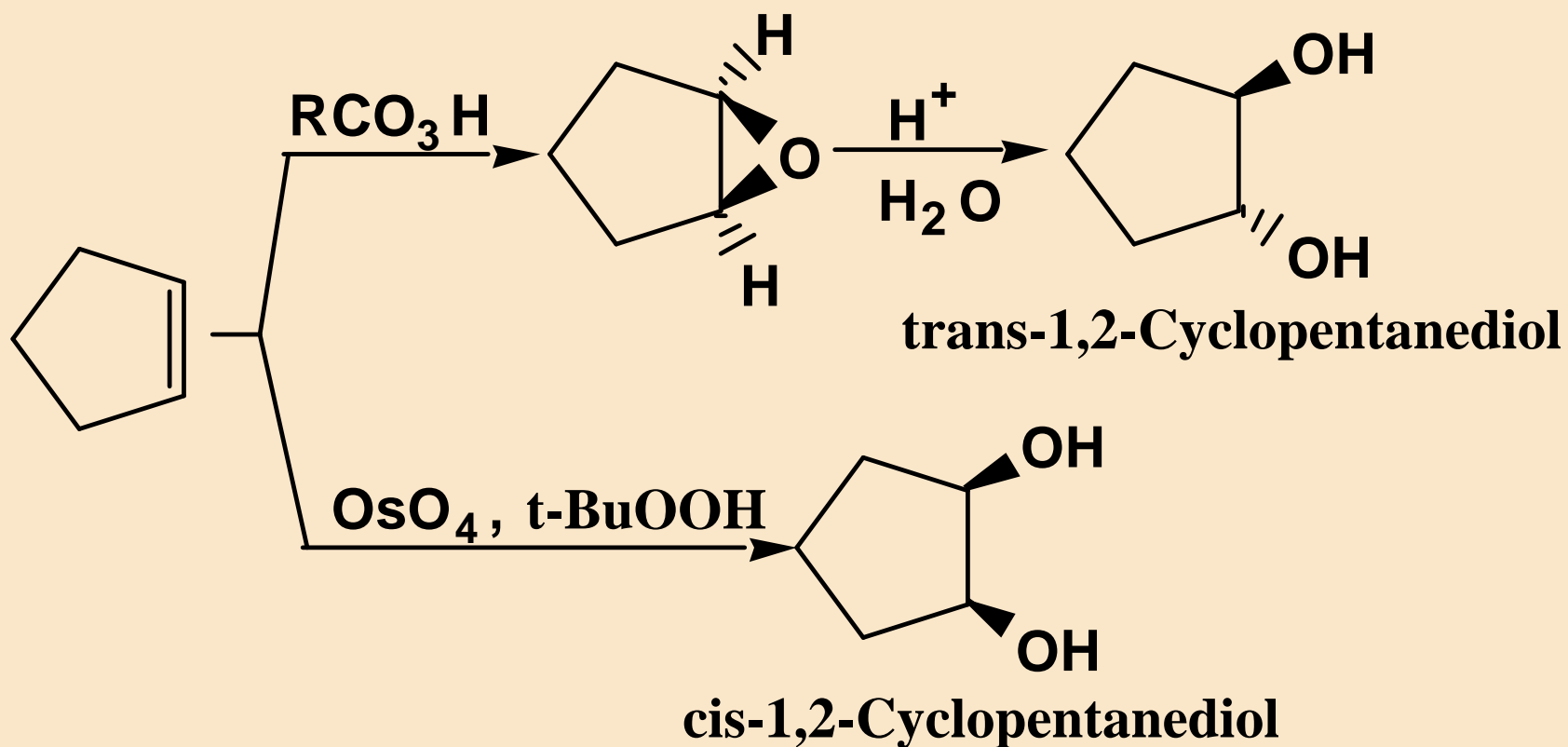


1,2-Epoxy-cyclopentane
(Cyclopentene oxide)

trans-1,2-Cyclopentanediol

11 Reactions of Epoxides

- u Compare the stereochemistry of the glycols formed by these two methods

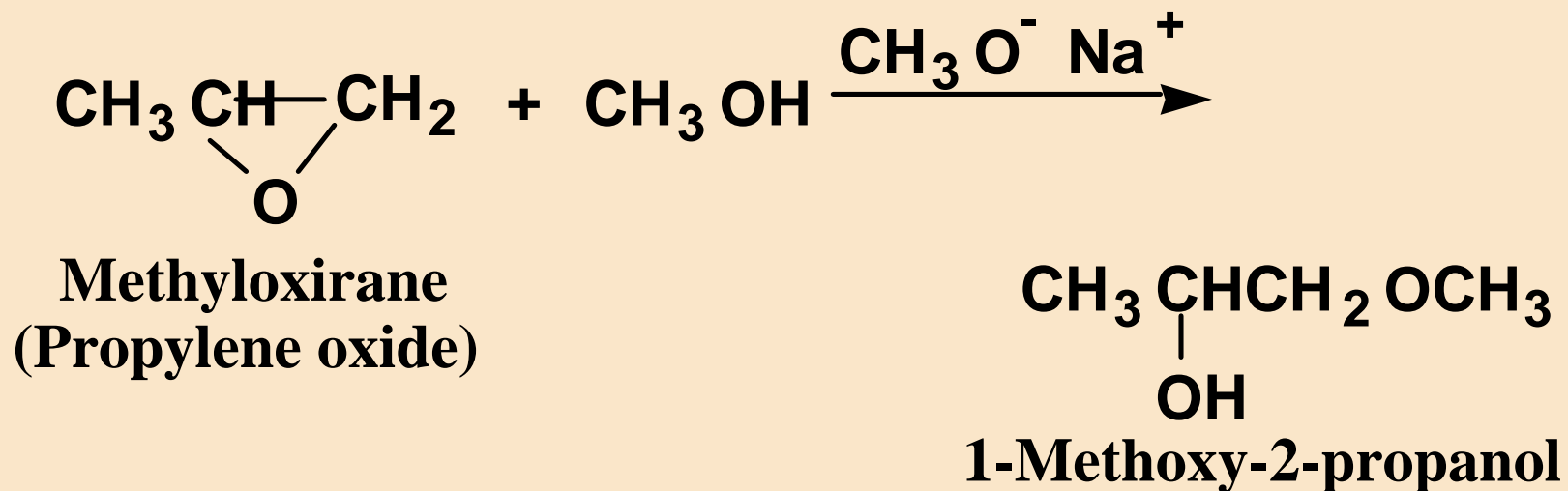


11 Reactions of Epoxides

- u Ethers are not normally susceptible to attack by nucleophiles
- u Because of the strain associated with the three-membered epoxide ring, epoxides undergo nucleophilic ring opening readily

11 Reactions of Epoxides

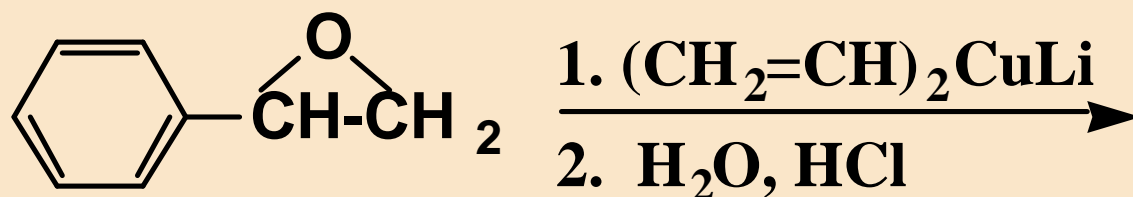
- u Their nucleophilic ring openings show a stereoselectivity typical of S_N2 reactions, namely inversion of configuration at the carbon from which oxygen is displaced



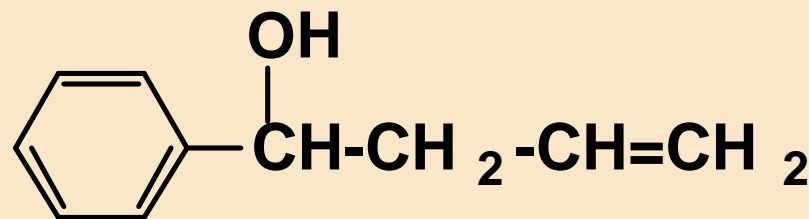
11 Reactions of Epoxides

u Reaction of epoxides with Gilman reagents is an important method for forming new C-C bonds

- ring opening shows typical S_N2 regioselectivity

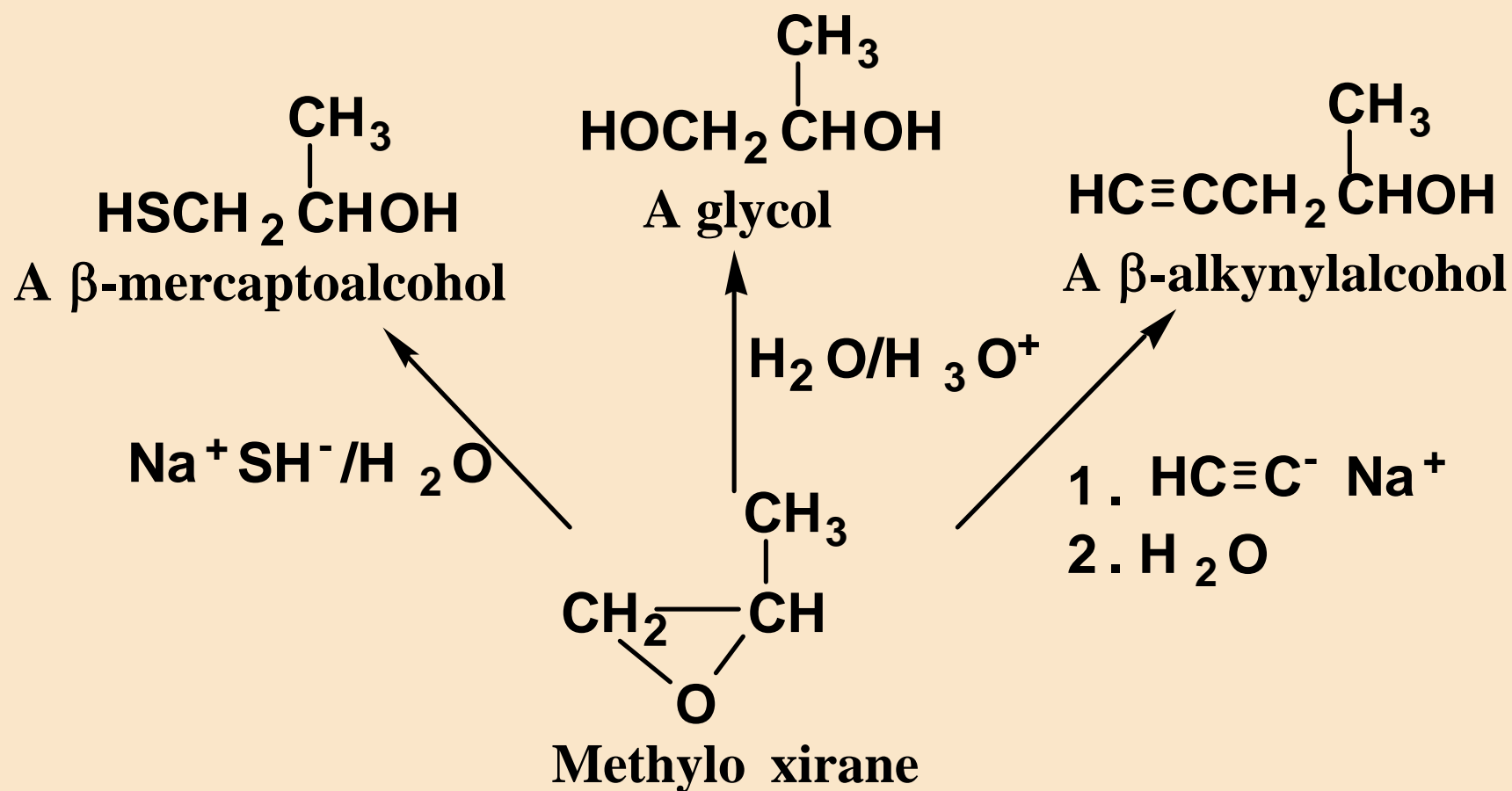


Styrene oxide

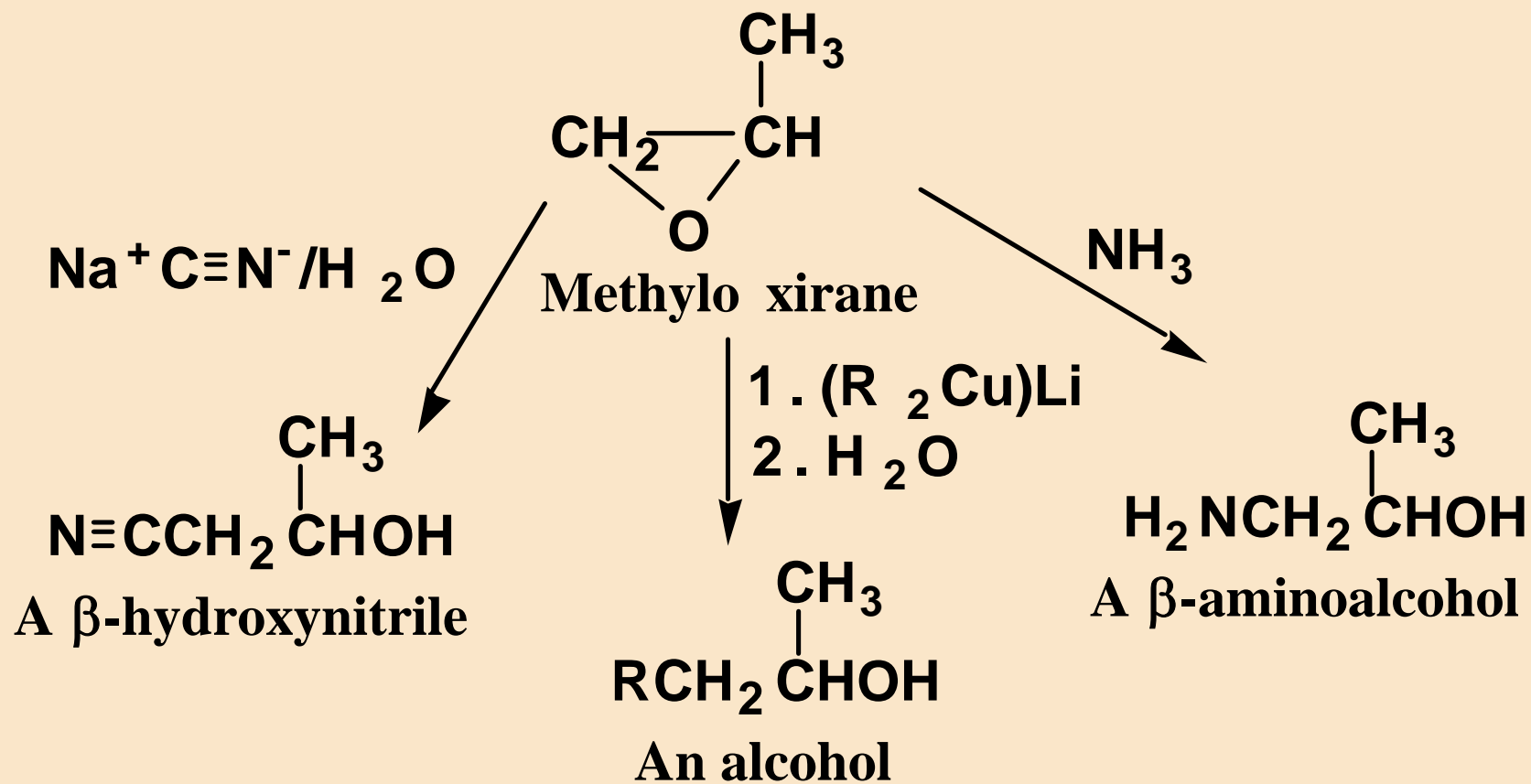


1-Phenyl-3-buten-1-ol

11 Reactions of Epoxides

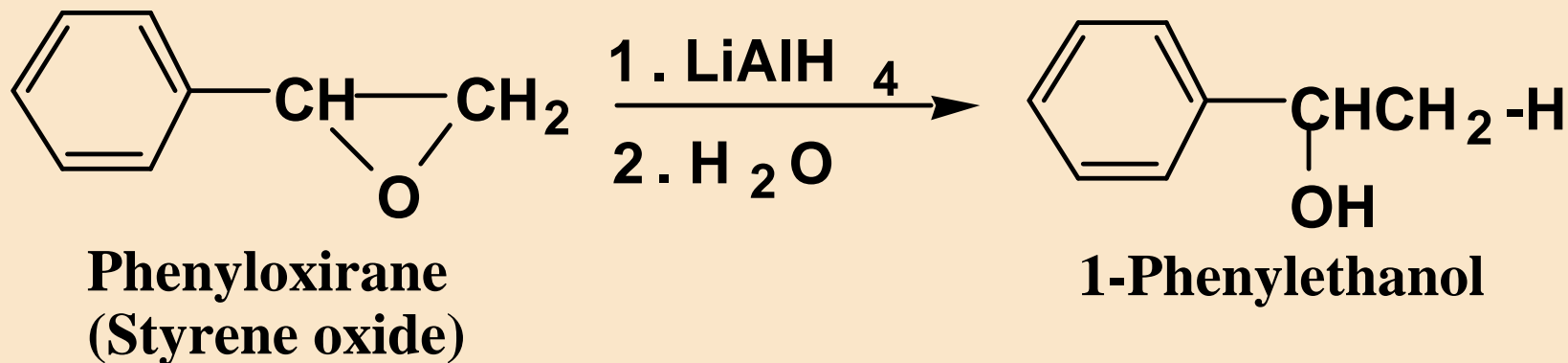


11 Reactions of Epoxides



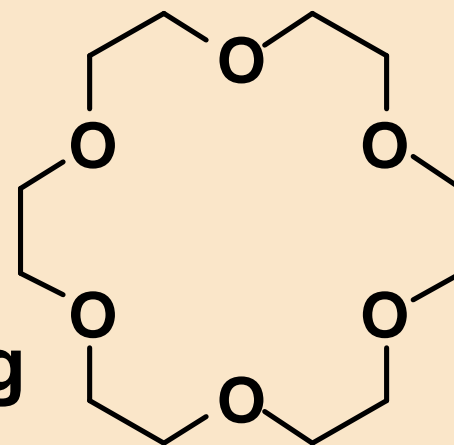
11 Reactions of Epoxides

- u Treatment of an epoxide with lithium aluminum hydride, LiAlH_4 , reduces the epoxide to an alcohol
 - the nucleophile attacking the epoxide ring is hydride ion, H^-



11 Crown Ethers

- u **Crown ether:** a cyclic polyether derived from ethylene glycol or a substituted ethylene glycol
- u The parent name is **crown**, preceded by a number describing the size of the ring and followed by the number of oxygen atoms in the ring. For example, 18-crown-6



18-Crown-6

11 Crown Ethers

- u 18-crown-6 viewed through the plane of the molecule and from above. Pink spheres are unshared pairs of electrons on oxygen

11 Crown Ethers

- u The diameter of the cavity created by the repeating oxygen atoms is comparable to the diameter of alkali metal cations
 - when potassium ion is inserted into the cavity of 18-crown-6, the unshared pairs of electrons on the six oxygens provide very effective solvation for K^+
 - 18-crown-6 does not coordinate well with Na^+ (it is slightly smaller) or with Li^+ (it is considerably smaller)

11

Ethers

&

Epoxides

K⁺

End of Chapter 11

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