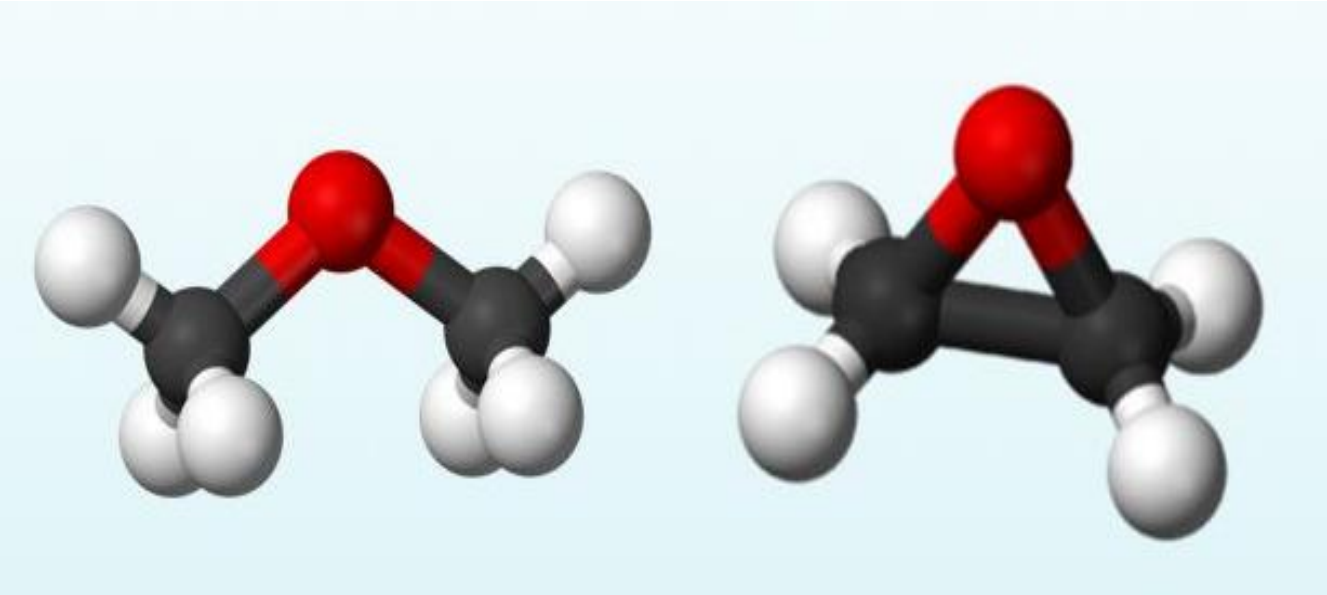


Ethers and Epoxides

Organic Chemistry

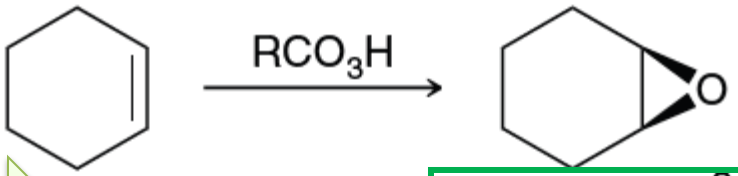
Pharmacy College/ 2nd Stage

Dr.Sham Wali Qurban

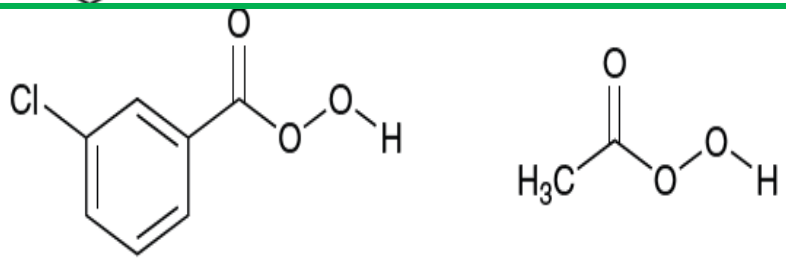
13.8 Preparation of Epoxides

Preparation with Peroxy Acids

Alkenes can be converted into epoxides upon treatment with peroxy acids.



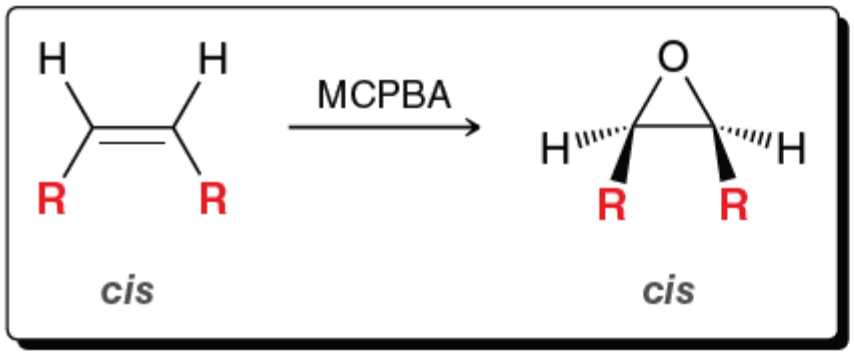
Commonly used peroxy acids include MCPBA and peroxyacetic acid:



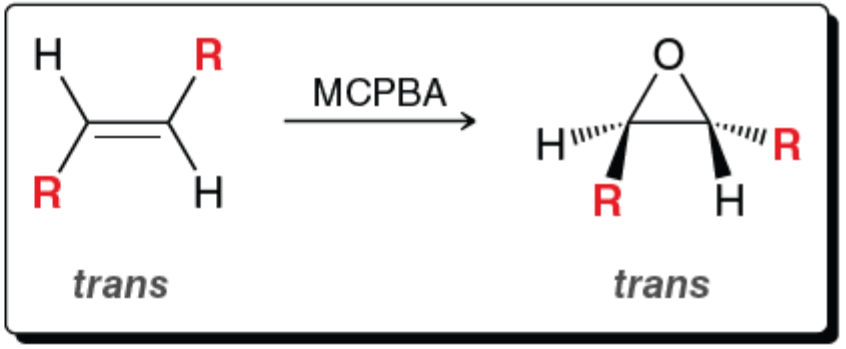
meta-Chloroperoxybenzoic acid (MCPBA)

Peroxyacetic acid

The process is stereospecific.



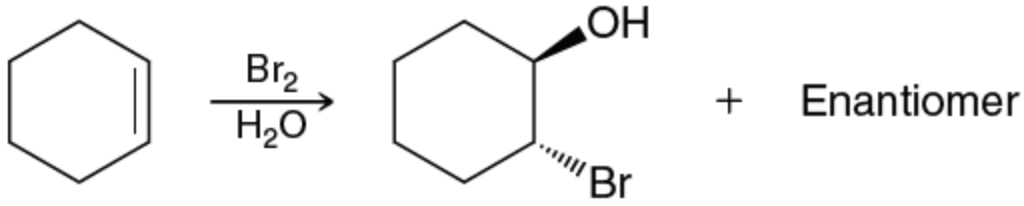
cis *cis*



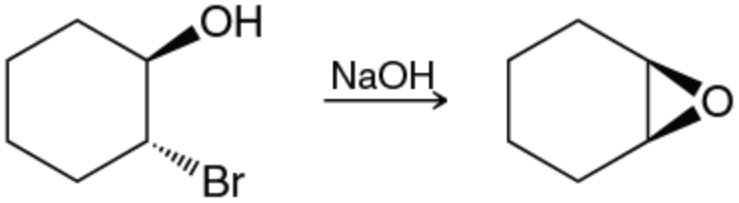
trans *trans*

Preparation from Halohydrins

Alkenes can be converted into halohydrins when treated with a halogen in the presence of water.

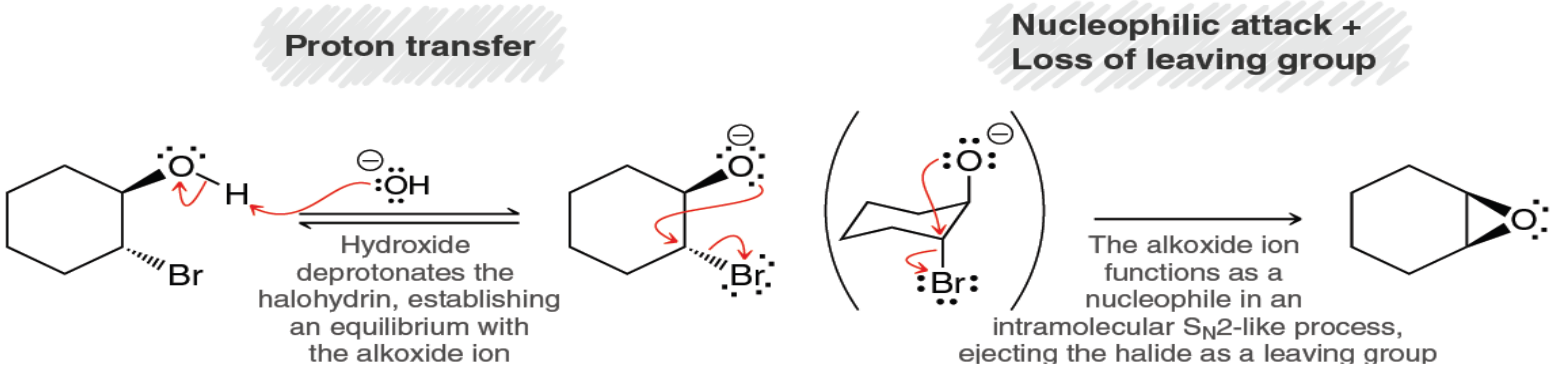


Halohydrins can be converted into epoxides upon treatment with a strong base:

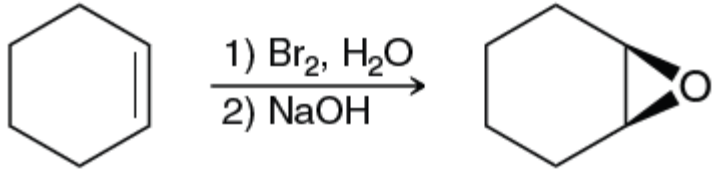


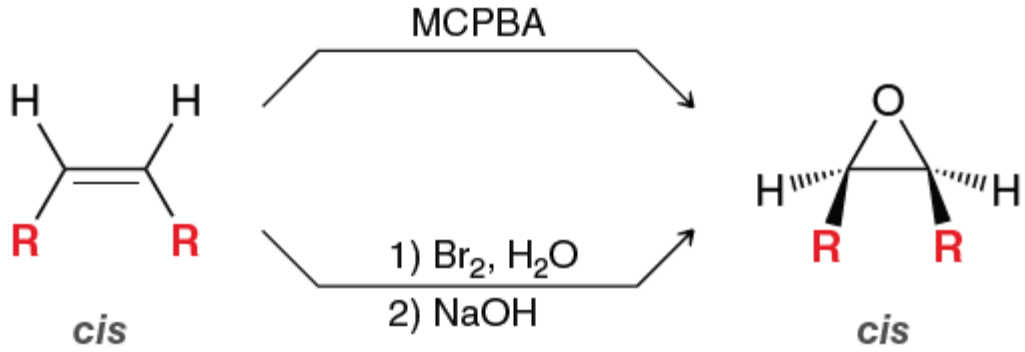
The process is achieved via an intramolecular Williamson ether synthesis. An alkoxide ion is formed, which then functions as a nucleophile in an intramolecular S_N2 like Process.

MECHANISM 13.4 EPOXIDE FORMATION FROM HALOHYDRINS

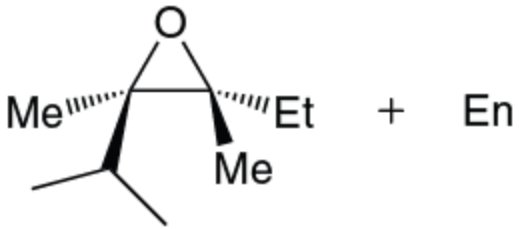


This provides us with another way of forming an epoxide from an alkene:





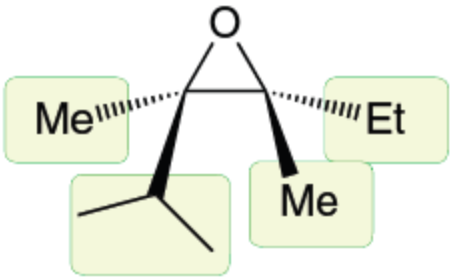
Example: Identify a starting material and reagents that can be used to prepare the following epoxide:



+ En

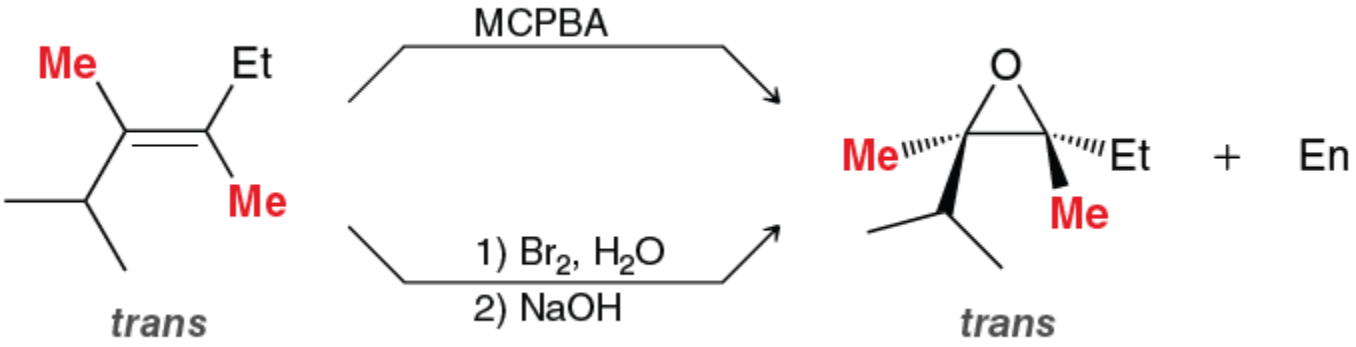
STEP 1

Identify the four groups attached to the epoxide ring.



STEP 2

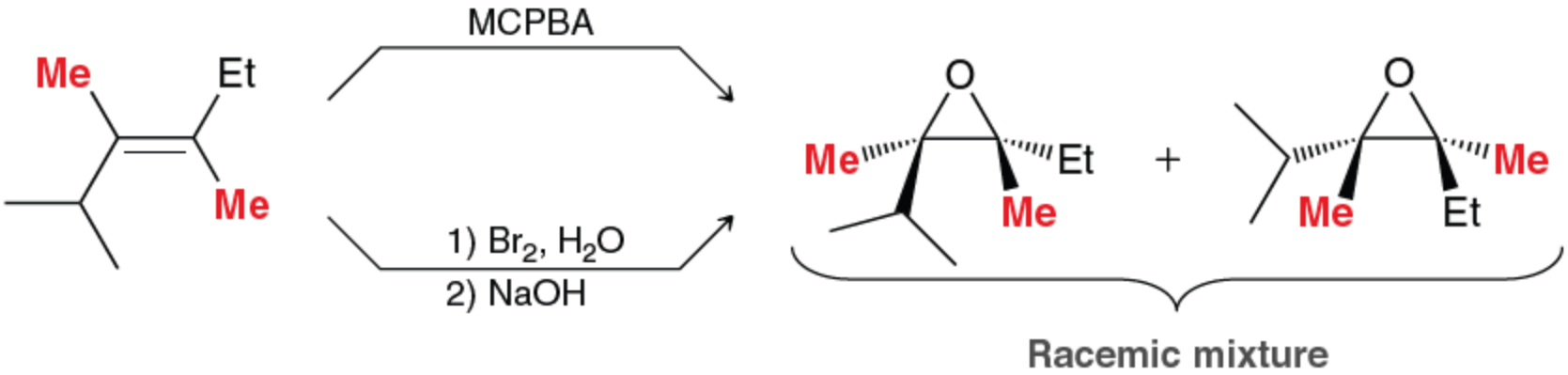
Identify the relative configuration of the four groups in the starting alkene.

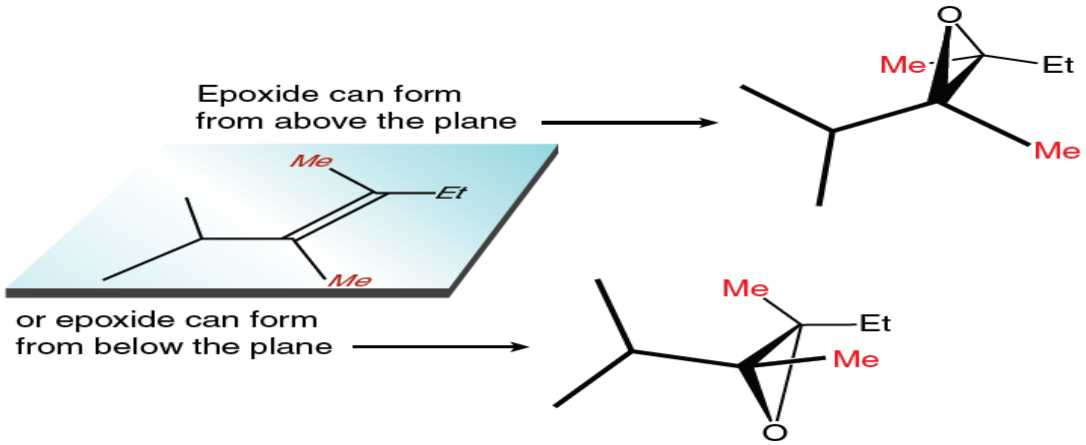


+ En

13.9 Enantioselective Epoxidation

When forming an epoxide that is chiral, each of the previous methods will provide a racemic mixture:





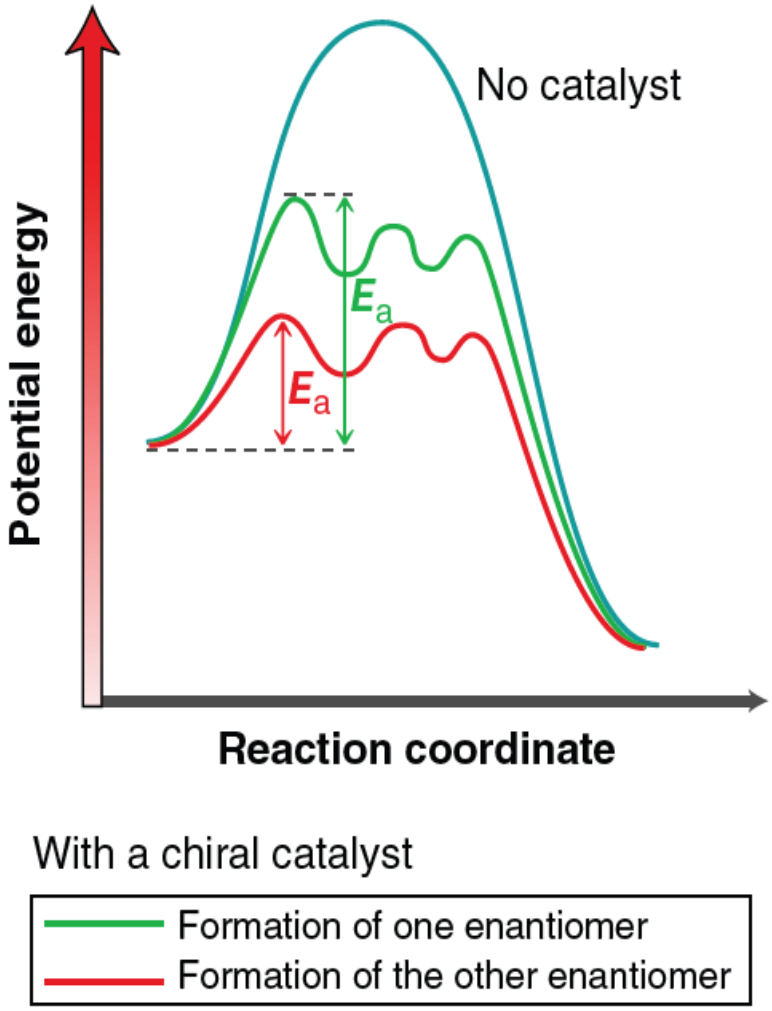
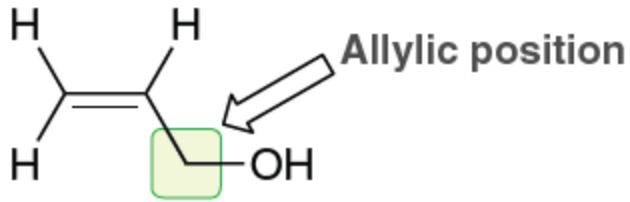
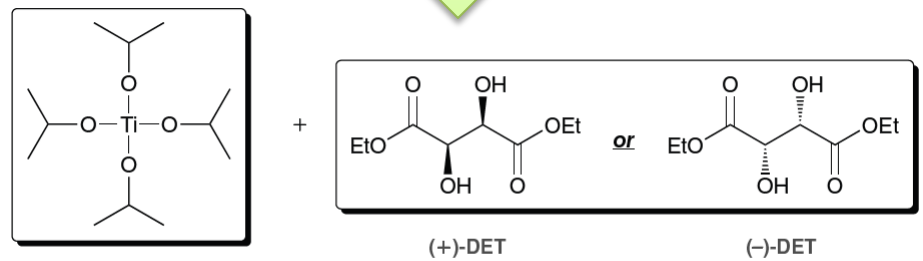


FIGURE 13.3
An energy diagram that depicts the effect of a chiral catalyst. The formation of one enantiomer is more effectively catalyzed than the other.

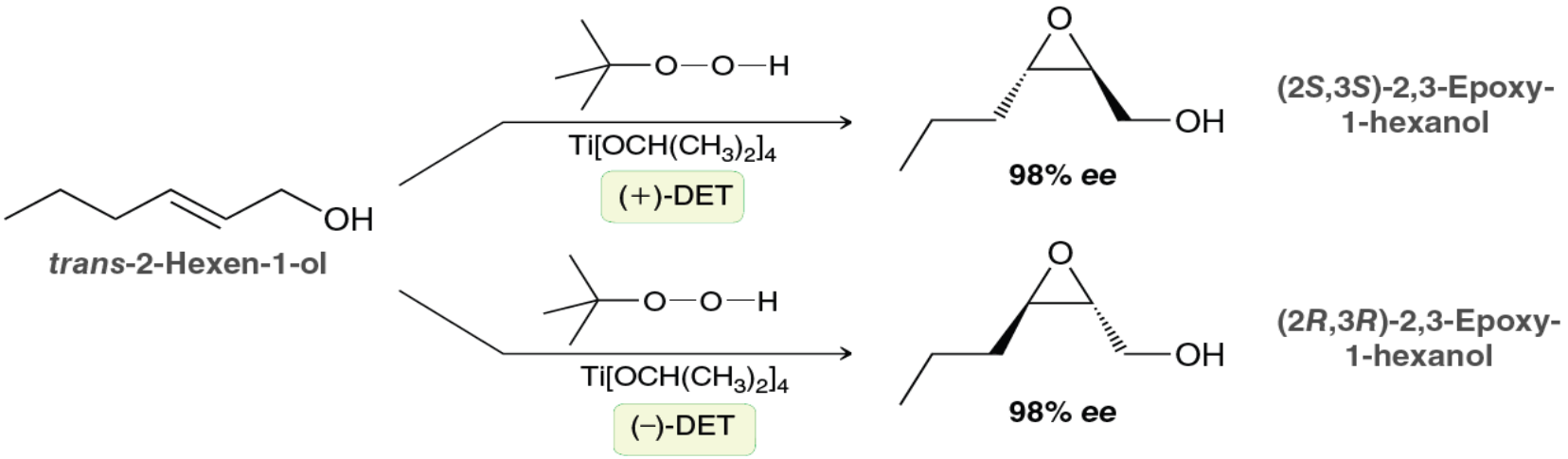


Sharpless' catalyst is comprised of titanium tetraisopropoxide and one enantiomer of diethyl tartrate (DET):

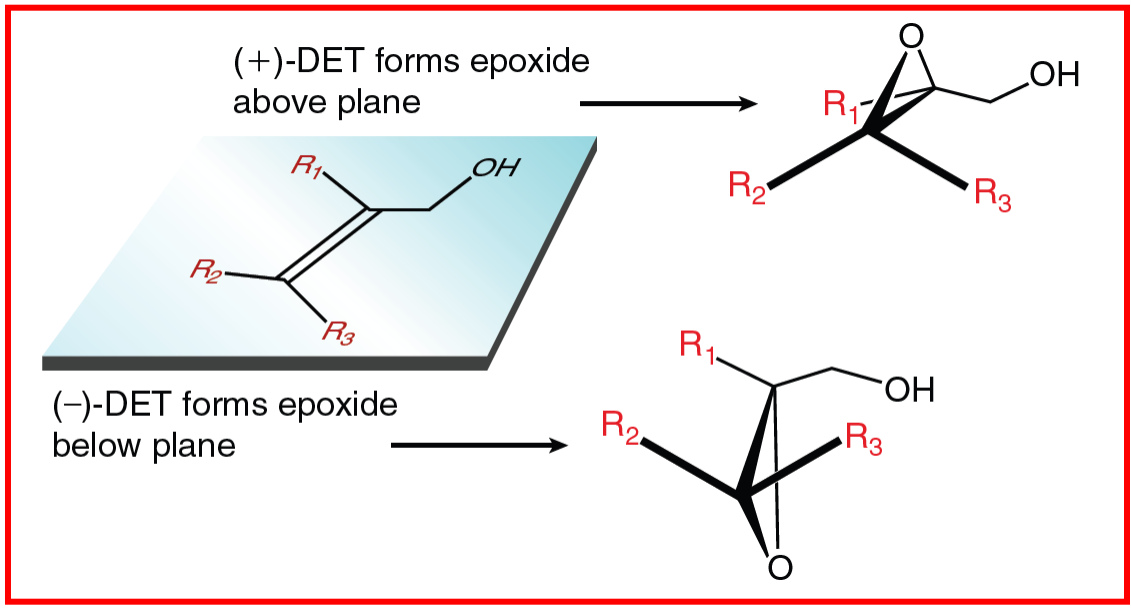


$Ti[OCH(CH_3)_2]_4$
Titanium tetraisopropoxide

Either one can be used. By choosing between (+)-DET or (–)-DET, it is possible to control which enantiomer is obtained



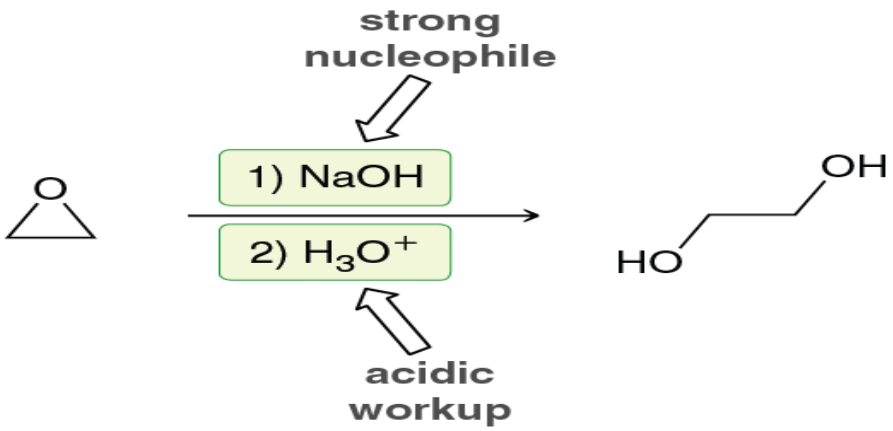
To predict the product of a **Sharpless asymmetric epoxidation**, orient the molecule so that the allylic hydroxyl group appears in the upper right corner. When positioned in this way, (+)DET gives epoxide formation above the plane, and (–)DET gives epoxide formation below the plane.



A method for predicting the product of a Sharpless epoxidation.

13.10 Ring- Opening Reactions of Epoxides

- **Reactions of Epoxides with Strong Nucleophiles**



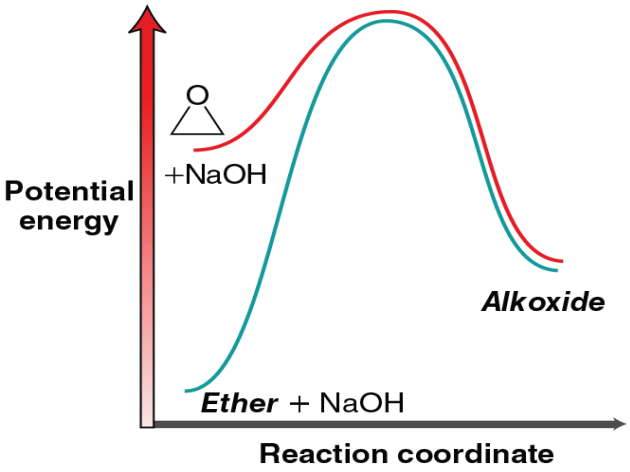
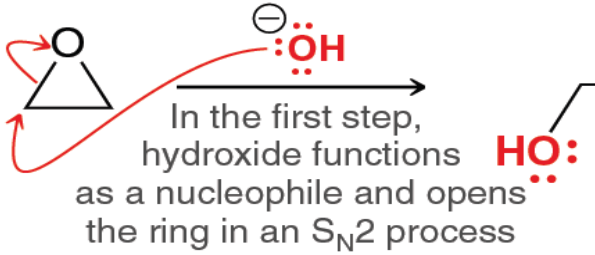


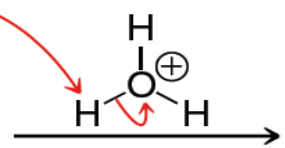
FIGURE 13.5
An energy diagram showing the effect of using a high-energy substrate in an S_N2 reaction.

Nucleophilic attack

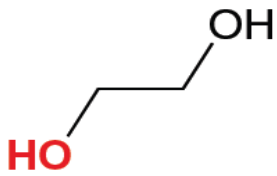


In the first step, hydroxide functions as a nucleophile and opens the ring in an S_N2 process

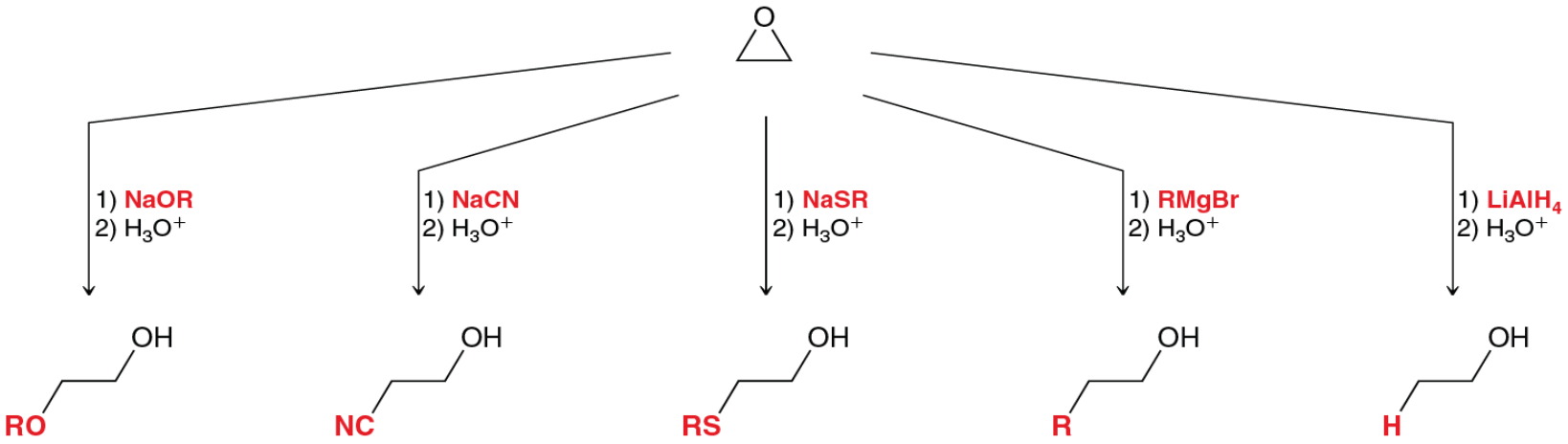
Proton transfer



After the reaction is complete, an acid is introduced into the reaction flask, and the alkoxide ion is protonated

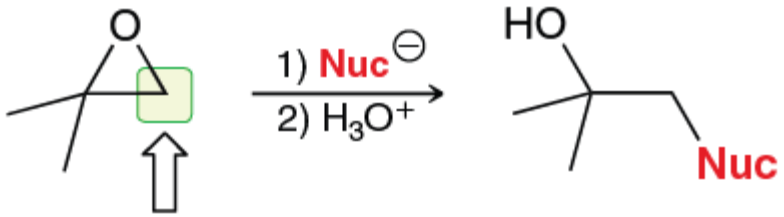


Many strong nucleophiles can be used to open an epoxide.

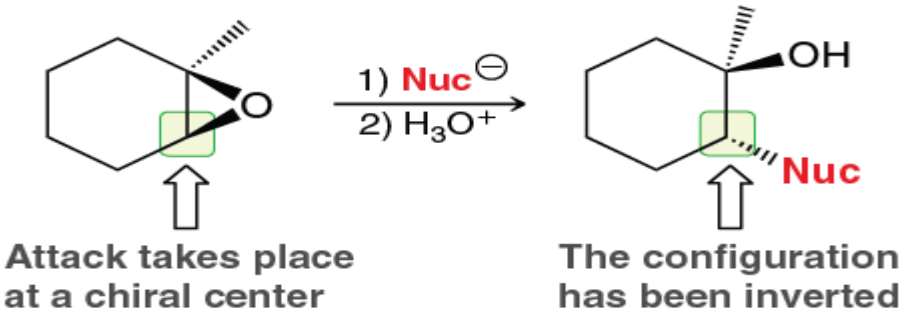


These reactions exhibit two important features that must be considered:

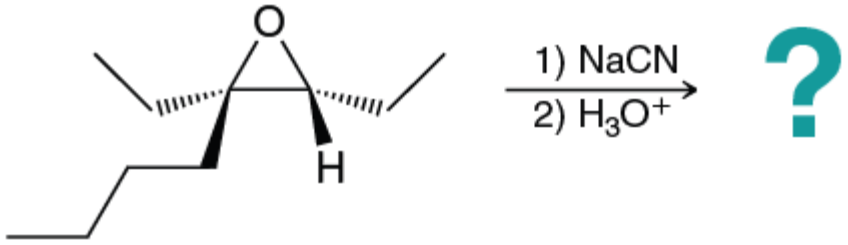
1. *Regiochemistry*. When the starting epoxide is unsymmetrical, the nucleophile attacks at the less substituted (less hindered) position.

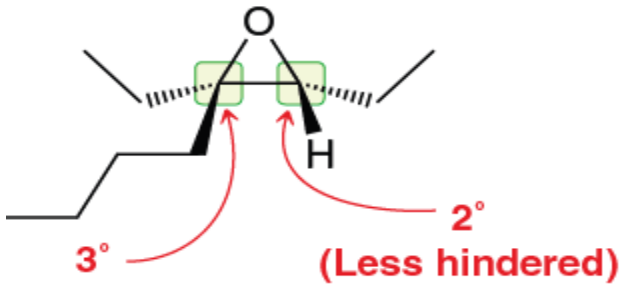


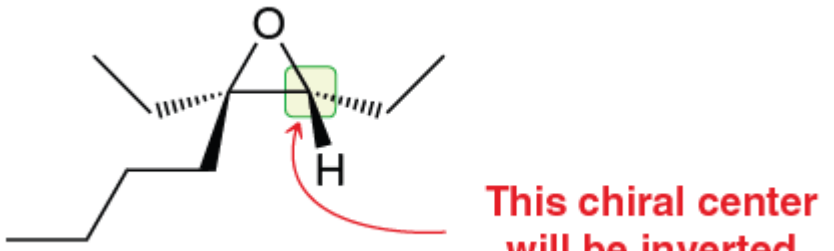
2. *Stereochemistry.* When the attack takes place at a chiral center, inversion of configuration is observed.



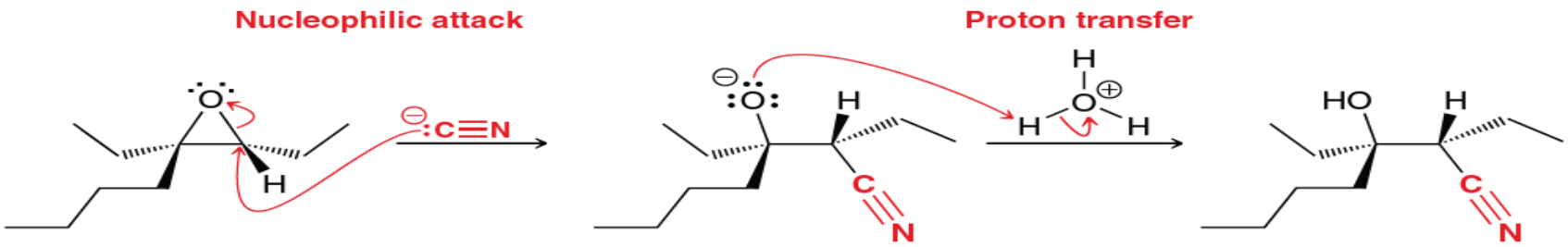
13.4 Predict the major product of the following reaction and draw a mechanism for its formation:



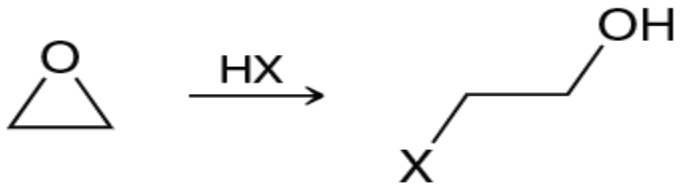


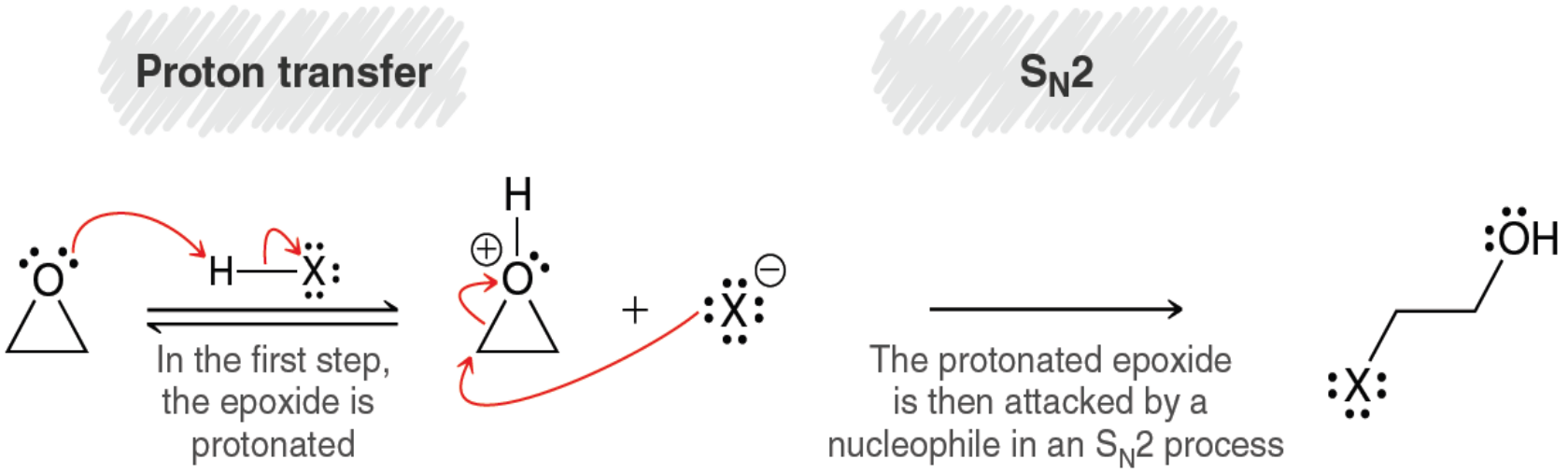


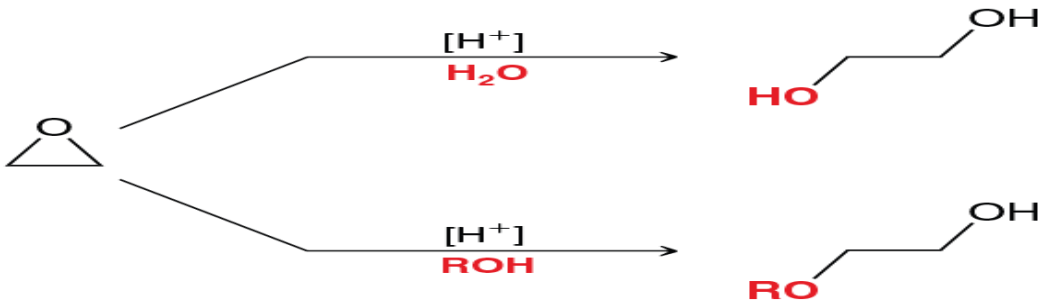
Solution 13.4

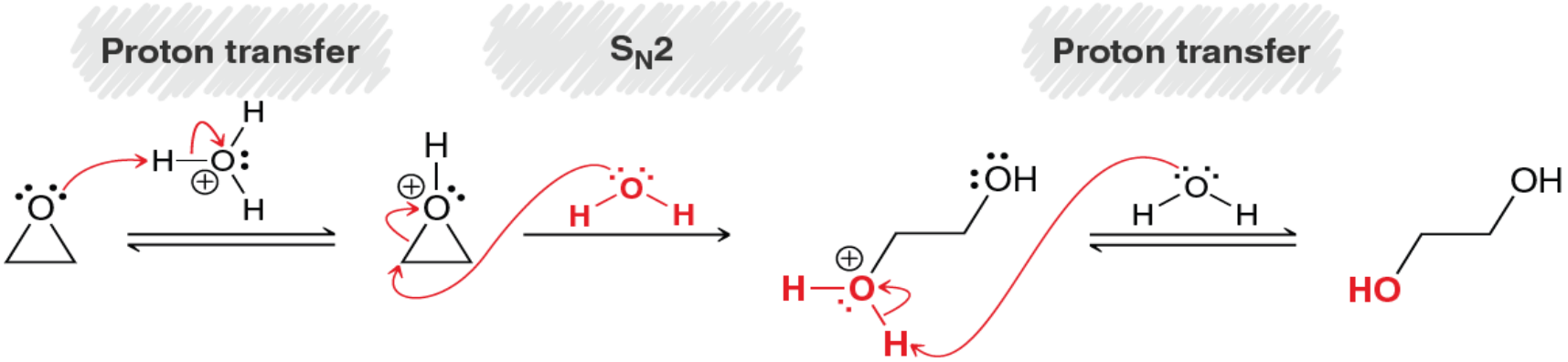


Acid- Catalyzed Ring Opening

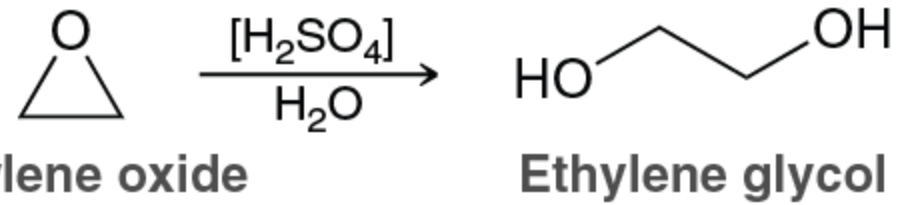




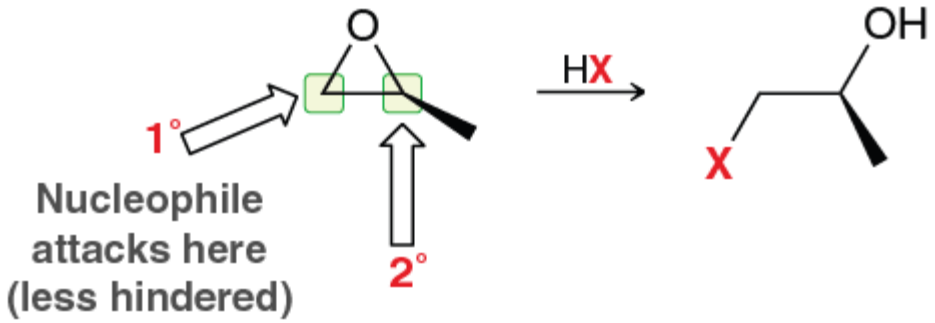




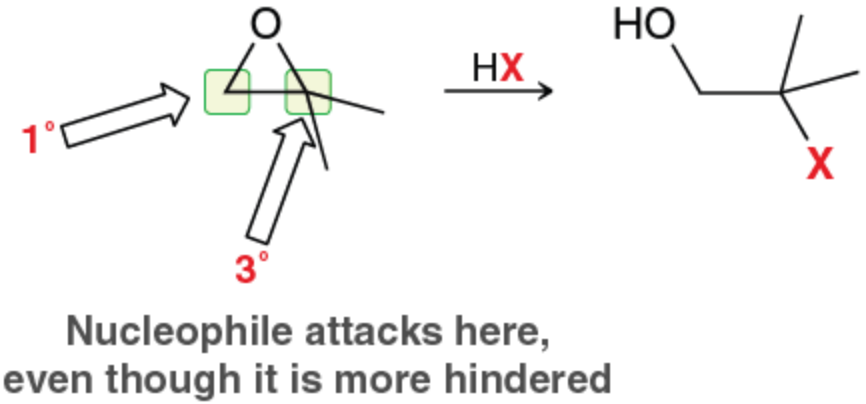
- **The process above is used for the mass production of ethylene glycol.**



We have seen that there are two important features of ringopening reactions: the regiochemical outcome and the stereochemical outcome.

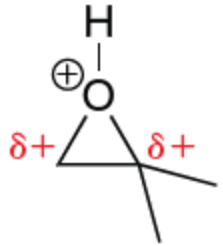


However, when one side of the epoxide is a tertiary position, the reaction is observed to occur at the more substituted, tertiary site.

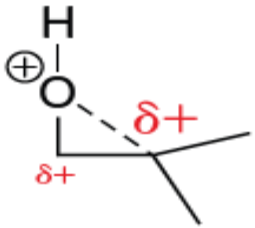


The more dominant factor is an ***electronic* effect**. A protonated epoxide is positively charged, and the positively charged oxygen atom withdraws electron density from the two carbon atoms of the epoxide.

They both have partial carbocationic character. Nevertheless, these two carbon atoms are not equivalent in their ability to support a partial positive charge.



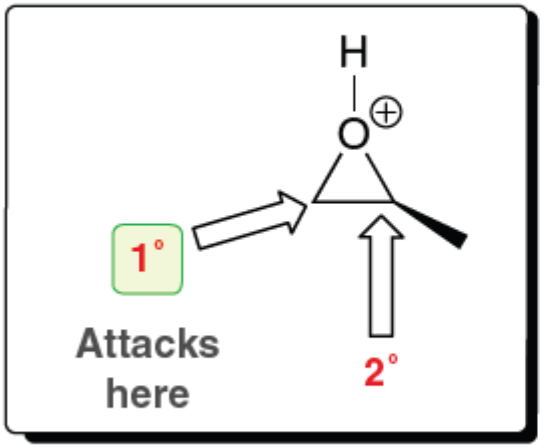
The tertiary position has significantly more partial carbocationic character than the primary position. The protonated epoxide is therefore more accurately drawn in the following way:



There are two important consequences of this analysis:

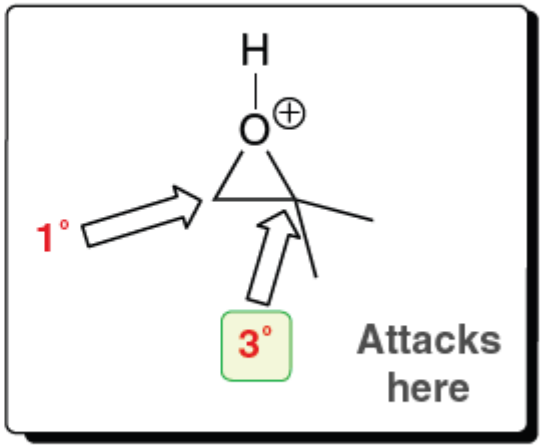
1. The more substituted carbon is a stronger electrophile and is therefore more susceptible to nucleophilic attack;
2. The more substituted carbon has significant carbocationic character, which means that its geometry is described as somewhere between tetrahedral and trigonal planar, allowing nucleophilic attack to occur at that position even though it is tertiary.

Primary vs. secondary



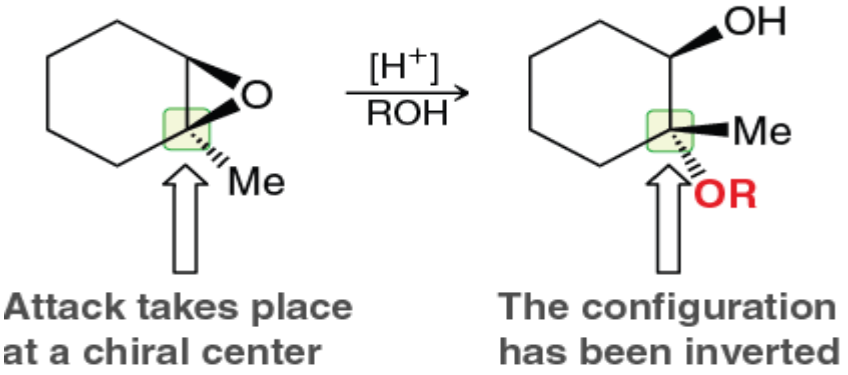
Dominant factor = *steric effect*

Primary vs. tertiary

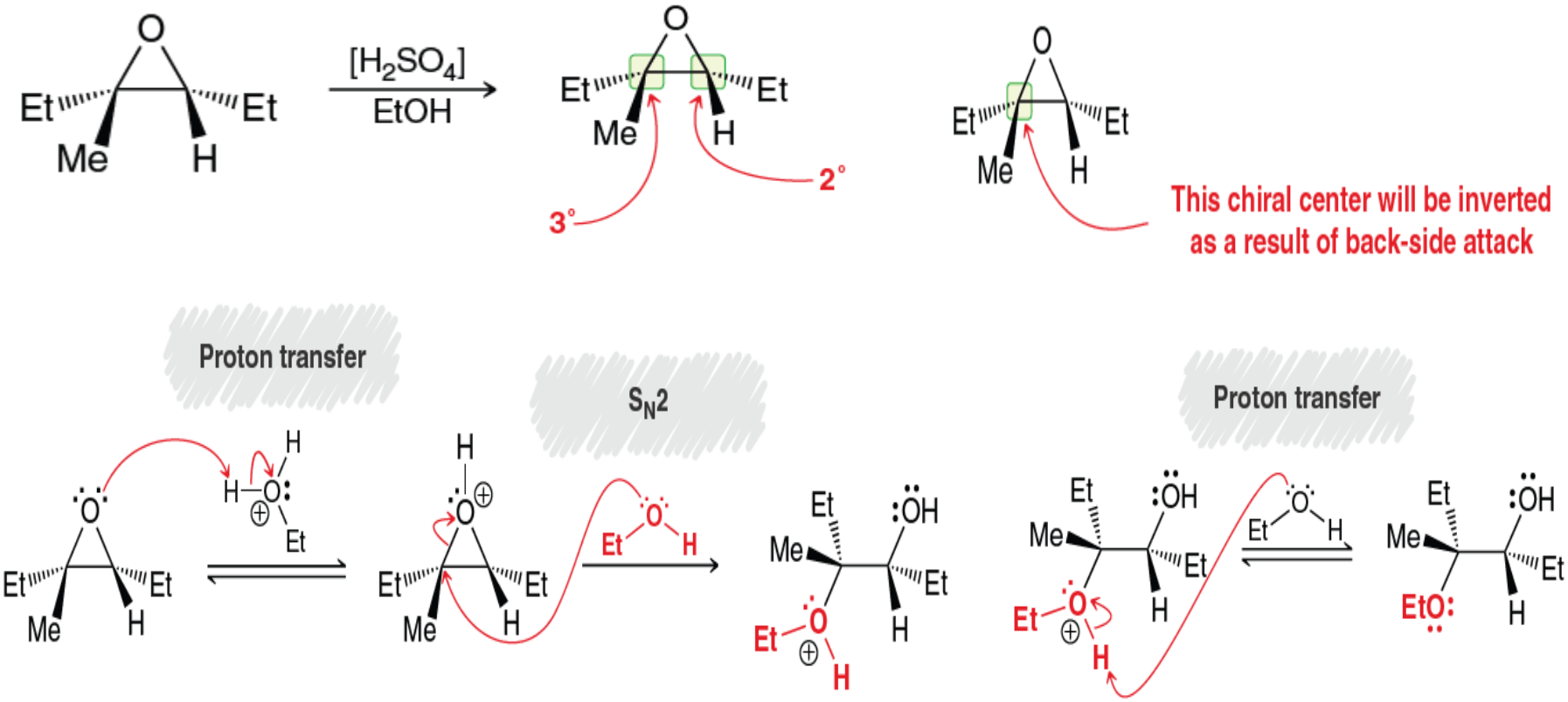


Dominant factor = *electronic effect*

The stereochemistry



13.5 Predict the major product of the reaction below and draw a likely mechanism for its formation:

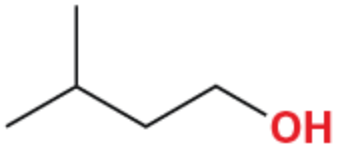


13.11 Thiols and Sulfides

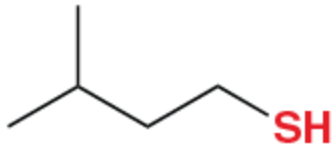
➢ Thiols

Sulfur is directly below oxygen in the periodic table (in the same column), and therefore, many oxygencontaining compounds have sulfur analogs. Sulfur analogs of alcohols contain an SH group in place of an OH group and are called **thiols**.

The nomenclature of thiols is similar to that of alcohols, but the suffi x of the name is “thiol” instead of “ol”:

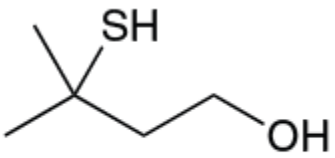


3-Methyl-1-butanol



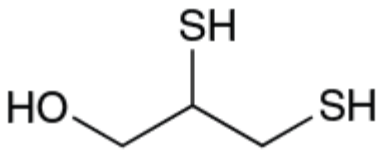
3-Methyl-1-butanethiol

When another functional group is present in the compound, the SH group is named as a substituent and is called a **mercapto group**:



3-Mercapto-3-methyl-1-butanol

- The name “mercapto” is derived from the fact that thiols were once called mercaptans.
- The ability of thiols to form complexes with mercury as well as other metals is put to good use by the drug called dimercaprol, which is used to treat mercury and lead poisoning.



Dimercaprol
(2,3-dimercapto-1-propanol)

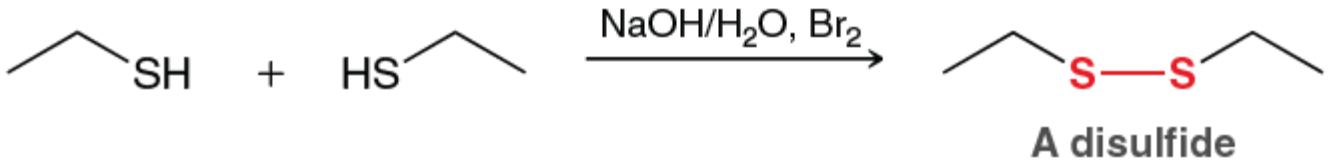
Thiols are most notorious for their pungent,unpleasant odors.

- Methanethiol is added to natural gas so that gas leaks can be easily detected. If you have ever smelled a gas leak, you were smelling the methanethiol (CH_3SH) in the natural gas, as natural gas is odorless.

Thiols can be prepared via an S_N2 reaction between sodium hydrosulfide (**NaSH**) and a suitable **alkyl halide**; for example:

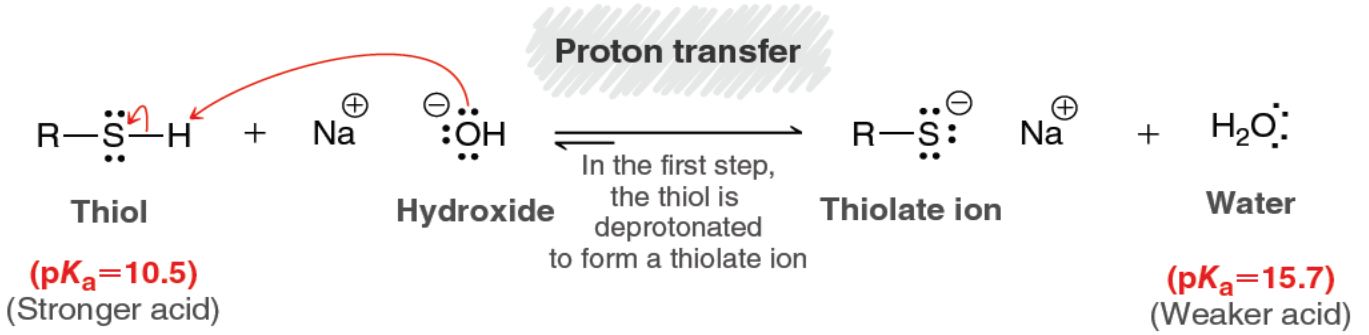
This reaction can occur even at secondary substrates without competing E2 reactions, because the hydrosulfide ion (HS^-) is an excellent nucleophile and a poor base. When this nucleophile attacks a chiral center, inversion of configuration is observed.

Thiols easily undergo oxidation to produce **disulfides**.

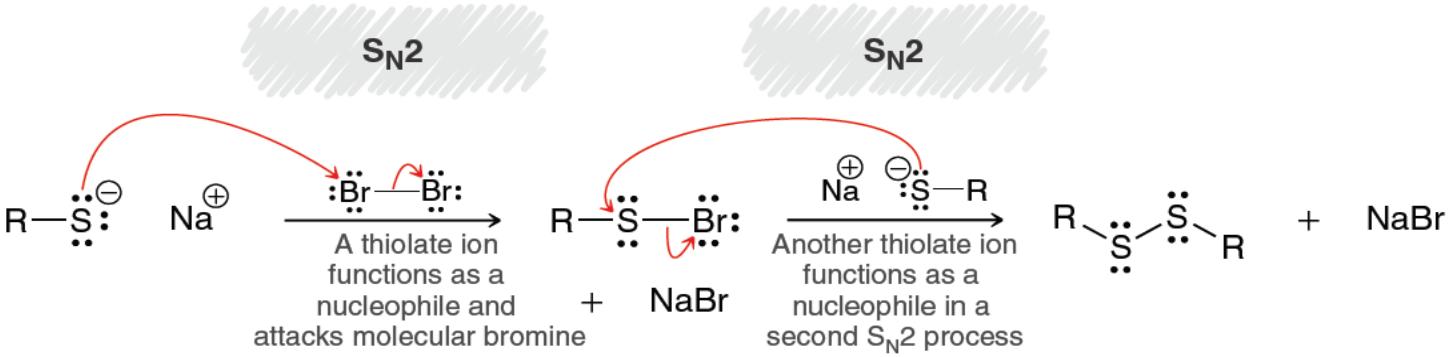


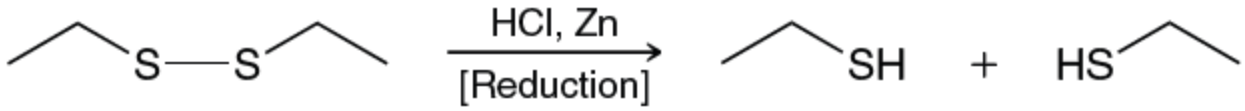
MECHANISM 13.7 OXIDATION OF THIOLS

DEPROTONATION OF THE THIOL



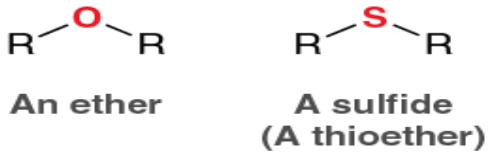
FORMATION OF THE DISULFIDE





➢ Sulfides

The sulfur analogs of ethers are called **sulfides**, or thioethers.

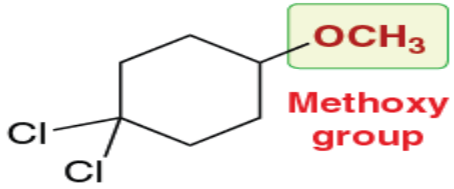


An ether — A sulfide (A thioether)

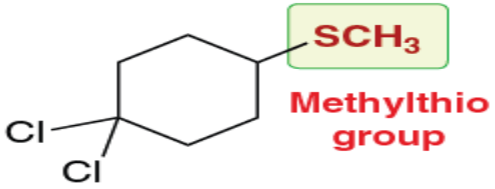
Nomenclature of sulfides is similar to that of ethers. Common names are assigned using the suffix **"sulfide"** instead of "ether."

Diethyl ether — Diethyl sulfide

More complex sulfides are named systematically, much the way ethers are named, with the alkoxy group being replaced by an **alkylthio group**.

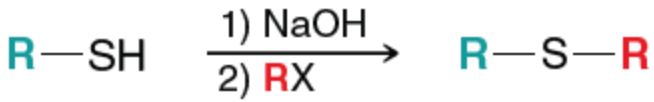


1,1-Dichloro-4-methoxycyclohexane

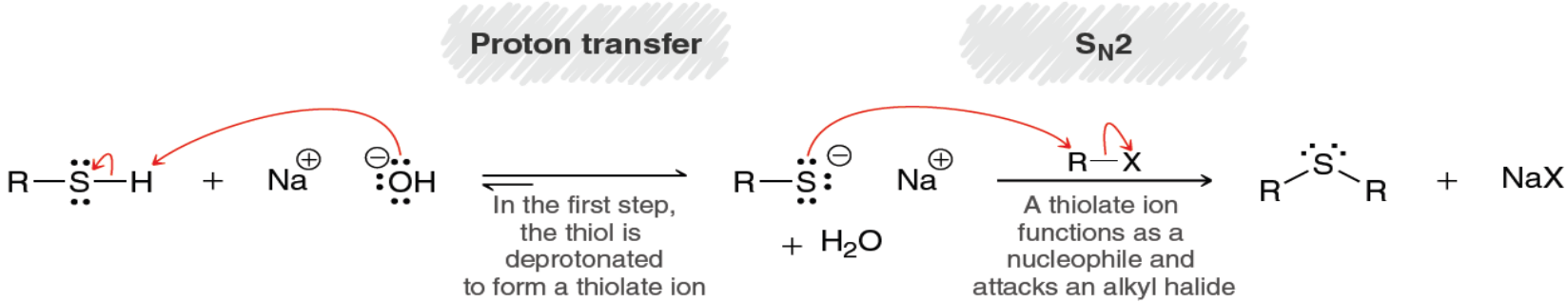


1,1-Dichloro-4-(methylthio)cyclohexane

Sulfides can be prepared from thiols in the following way:

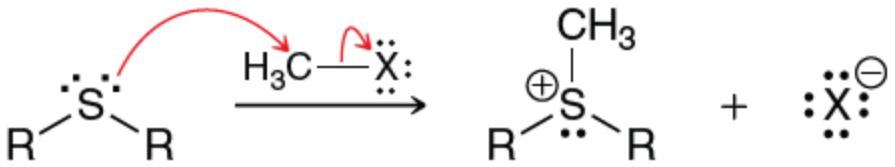


MECHANISM 13.8 PREPARATION OF SULFIDES FROM THIOLS

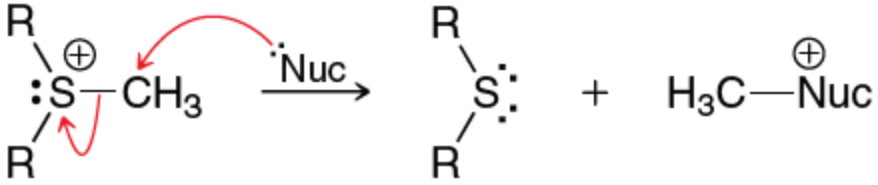


Since sulfides are structurally similar to ethers, we might expect sulfides to be as unreactive as ethers, but this is not the case. Sulfides undergo several important reactions.

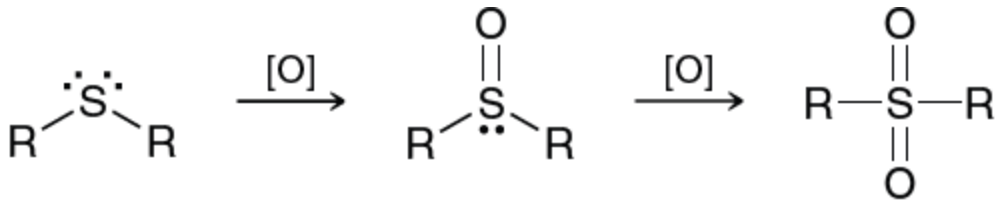
1. Sulfides will attack alkyl halides in an S_N2 process.



The product of this step is a powerful alkylating agent, because it is capable of transferring a methyl group to a nucleophile.

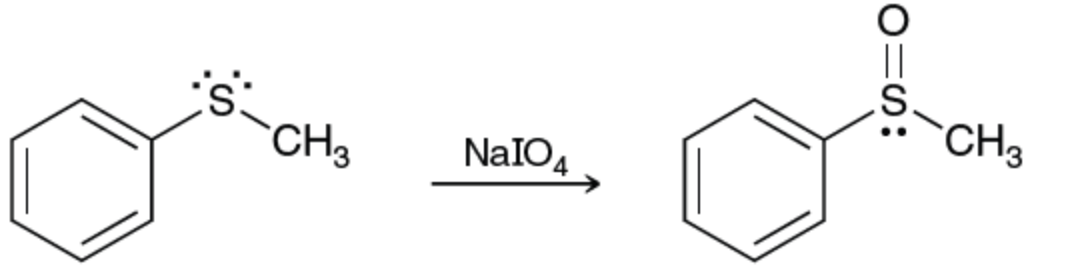


2. Sulfides also undergo oxidation to give **sulfoxides** and then **sulfones**.



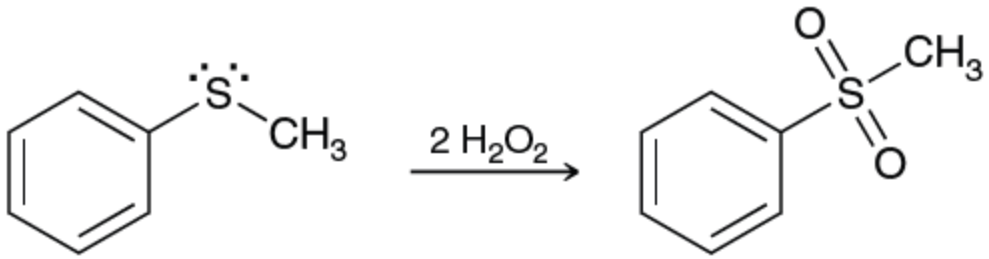
Sulfide Sulfoxide Sulfone

Sodium *meta* periodate, **NaIO4** an oxidizing reagent that will not oxidize the sulfoxide.

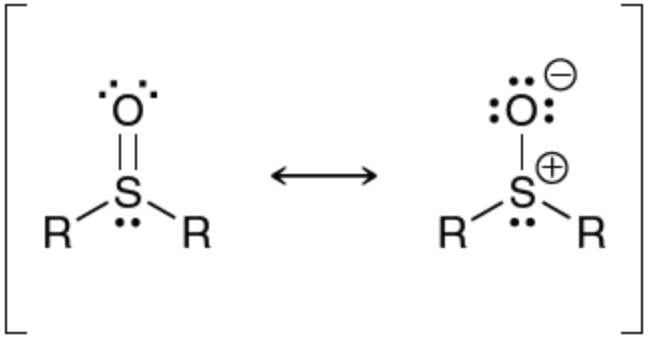


Methyl phenyl sulfide Methyl phenyl sulfoxide

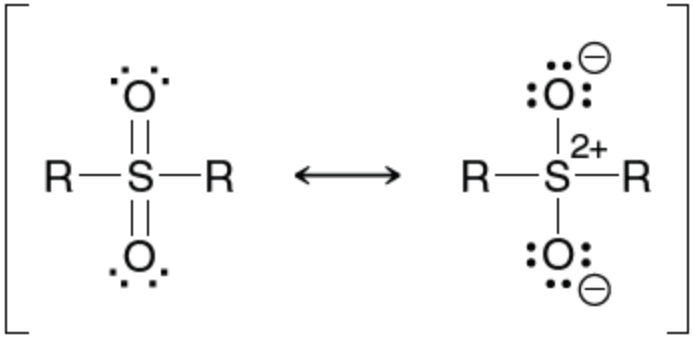
If the sulfone is the desired product, then two equivalents of hydrogen peroxide can be used.



Methyl phenyl sulfide Methyl phenyl sulfone



Sulfoxides can be drawn as
either one of these resonance structures



Sulfones can be drawn as
either one of these resonance structures

The ease with which sulfides are oxidized renders them ideal reducing agents in a wide variety of applications. For example, **DMS (dimethyl sulfide)** is used as a reducing agent in ozonolysis. The by-product is **dimethyl sulfoxide (DMSO).**