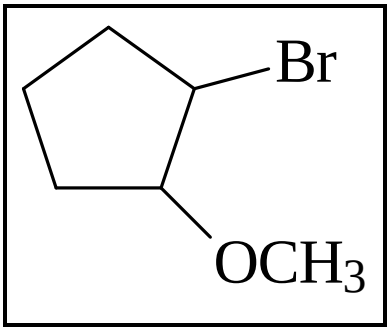
ETHERS

Nomenclature: name both groups, followed by "ether," *eg*

C_6H_5-O-CH_2-CH=CH_2 CH_3CH_2-O-CH_2CH_3

allyl phenyl ether diethyl ether (ether)

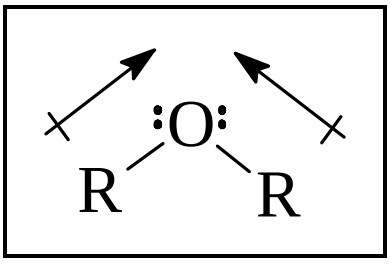
If one group has no simple name, use alkoxy, R-O-, method, *eg*



1-bromo-2-methoxycyclopentane

Physical properties:

Weakly polar, slightly soluble in water.



Preparation

Bimolecular dehydration —

$$2\ ROH \xrightarrow{H_2SO_4} ROR + H_2O$$

- ➢ lower temp than used to form alkene.
- ➢ symmetrical ethers from 1^o and 2^o alcohols (di-tertiary ethers are unstable).

$$ROH + R'OH \xrightarrow{H_2SO_4} ROR + ROR' + R'OR' + H_2O$$

However, if one alcohol is *t*-BuOH, *t*-Bu-O-R will be the major product owing to rapid formation of *t*-Bu^+ carbocation and inability to form *t*-Bu-O-*t*-Bu.

Williamson synthesis —

Used to prepare R-O-R, R'-O-R, Ar-O-R

- ➢ Ar-O-Ar' only when one Ar group has strong electron withdrawing groups [nucleophilic aromatic substitution].

$$R\text{-}X + Na^+\ ^-OR' \longrightarrow R\text{-}O\text{-}R' + NaX$$

$$R\text{-}X + Na^+\ ^-OAr \longrightarrow R\text{-}O\text{-}Ar + NaX$$

$$[R\text{-}OH + Na \longrightarrow R\text{-}O^-\ ^+Na + H_2]$$

[ArOH + NaOH))))))))))> $ArO^{-}{}^{+}Na + H_2O$]

Williamson synthesis works best for methyl, 1° halides:

$CH_3CH_2CH_2O^{-}\ Na^{+} + CH_3CH_2Br \longrightarrow$

$CH_3CH_2O^{-}\ Na^{+} + CH_3CH_2CH_2Br \longrightarrow$

} $CH_3CH_2OCH_2CH_2CH_3$

$(CH_3)_3CO^{-}\ Na^{+} + CH_3Br \longrightarrow (CH_3)_3COCH_3$

$(CH_3)_3CBr + CH_3O^{-}{}^{+}Na \longrightarrow (CH_3)_2C{=}CH_2 + CH_3OH$

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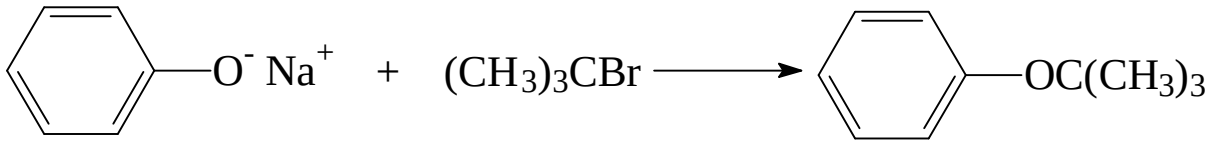
but under mild conditions:



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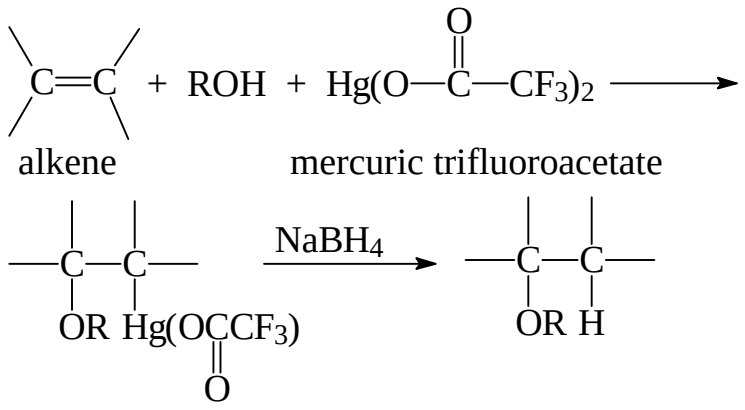
via an S_N1 mechanism. This is successful because the phenoxide anion is not a strong base and does not easily cause E2 elimination.

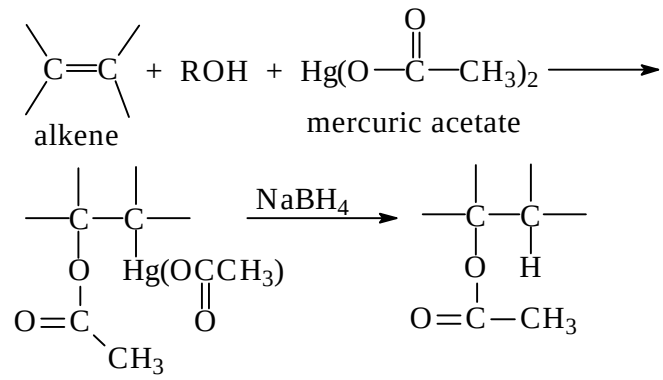
Alkoxymercuration - Demercuration —

This is similar to the preparation of alcohols via oxymercuration-demercuration.



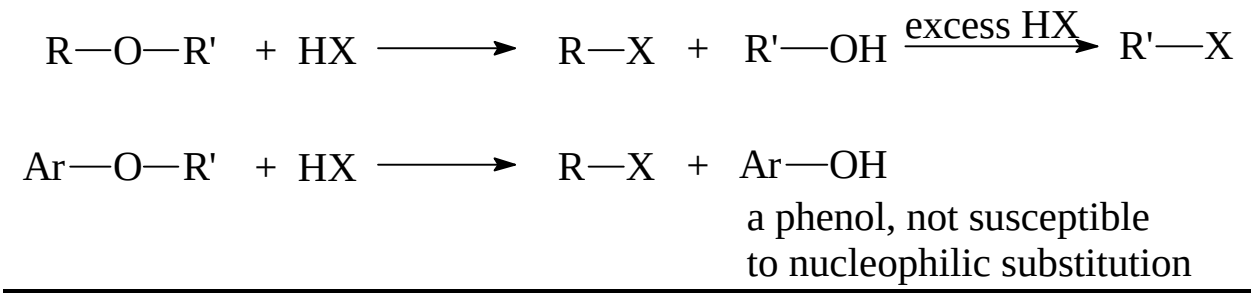
- net Markovnikov additon
- usually no rearrangements
- no competition from elimination

Trifluoroacetate is used rather than acetate because acetate competes with 2º and especially 3º alcohols as the nucleophile.



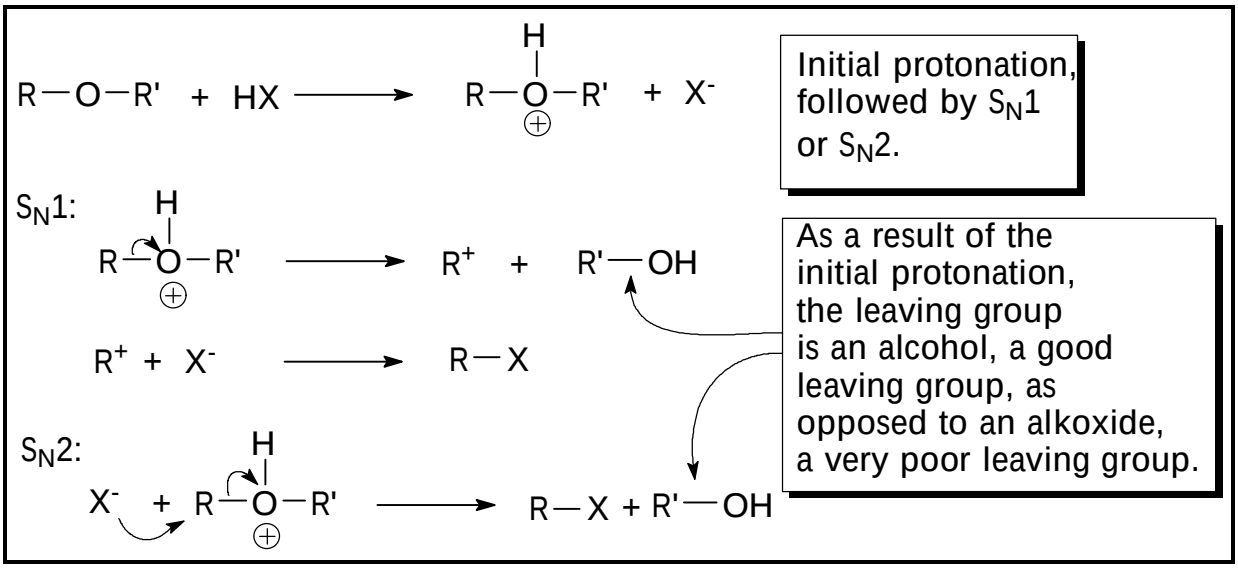
Reactions

Cleavage by Acids —



Reactivity of HX: HI > HBr >> HCl

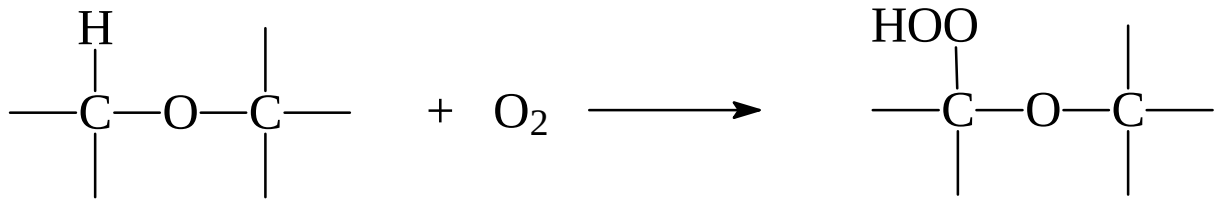
Mechanism —



Usually, S_N1 operates in the case of 3°, allylic, and benzylic groups, and S_N2 in the case of methyl, 1°, and 2°, groups.

Free Radical Attack at a-Hydrogens —

Ethers air oxidize to form explosive peroxides —



These peroxides are explosive. They are higher boiling than the ethers from which they form. Thus, they are concentrated in the distilling flask when contaminated ethers are distilled. The distilling flask is the one you're heating!))))))))> **BOOM!**

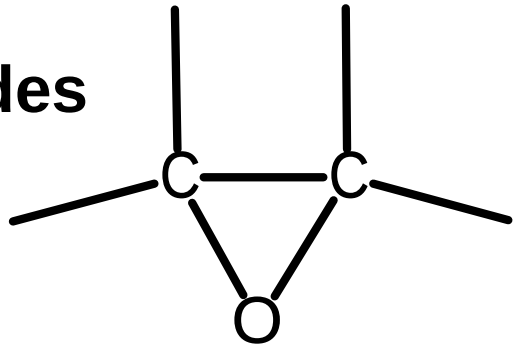
Test ethers that have been exposed to air for a while for the presence of peroxides before distilling:

peroxide + KI(aq)))))))> I_2, (blue color with starch)
or
peroxide + $FeSO_4$ + KCNS))))))> Fe^{+3}, blood-red with CNS^-

Nucleophilic Substitution Under Basic Conditions —

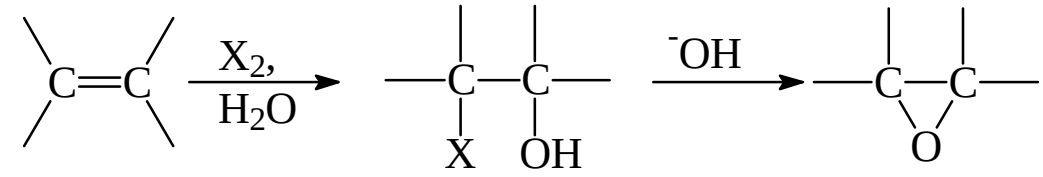
Except for the epoxides, ethers do not undergo nucleophilic substitution without prior protonation: alkoxide ion is a very poor leaving group.

Epoxides

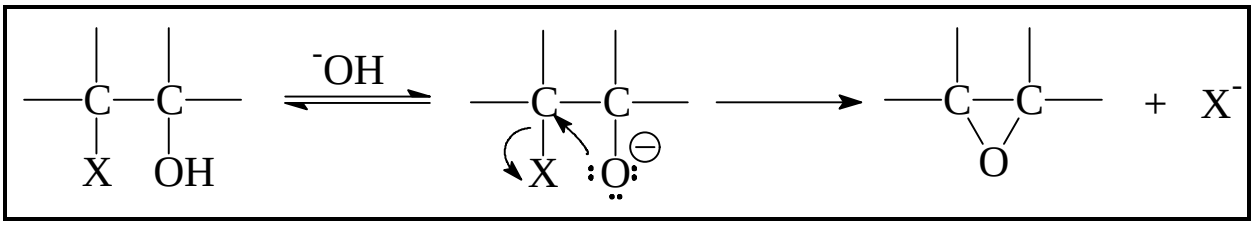


Preparation —

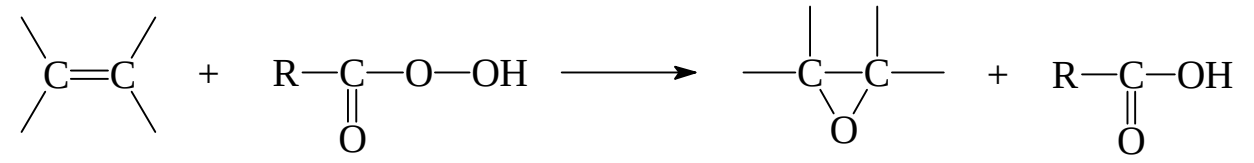
From halohydrins (from alkenes) —



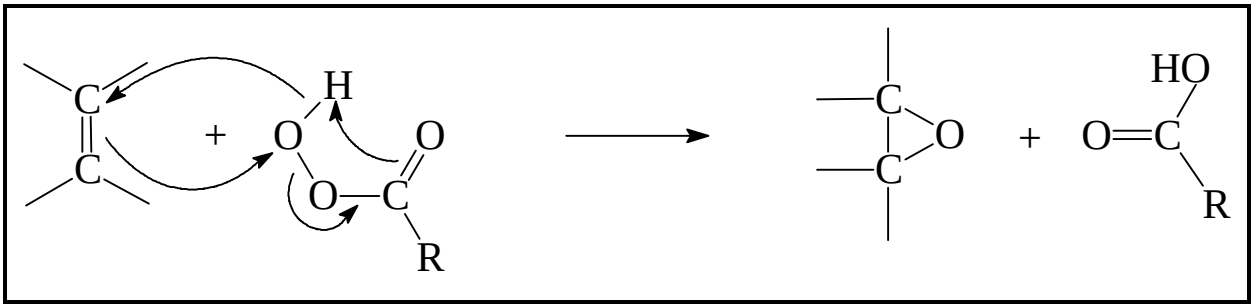
Mechanism —



From Alkenes and Peracids —



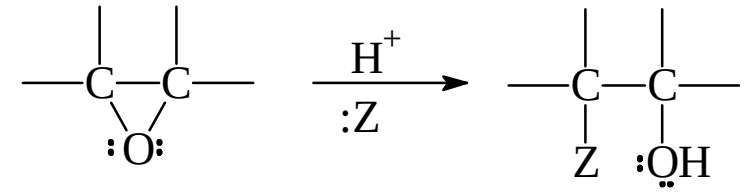
Posssible mechanism (or Bolshoi choreography) —



Reactions —

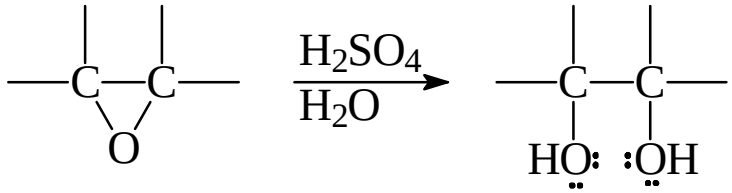
Epoxides are strained and, therefore, reactive toward ring-opening reactions.

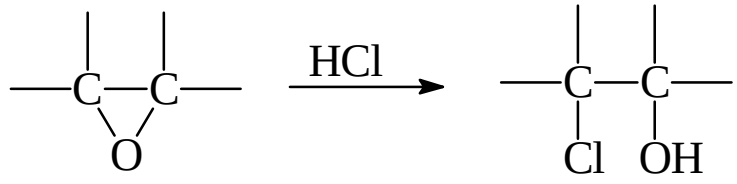
Acid Promoted Cleavage —



This reaction is similar to that of other ethers, except easier owing to the relief of angle strain.

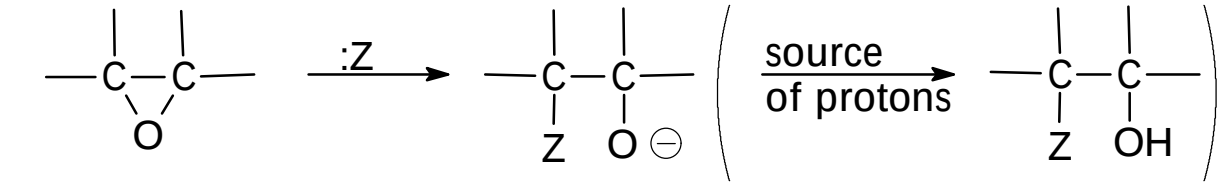
eg



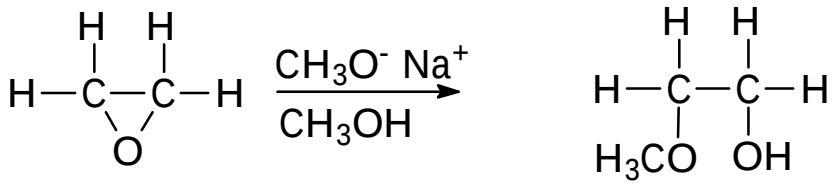


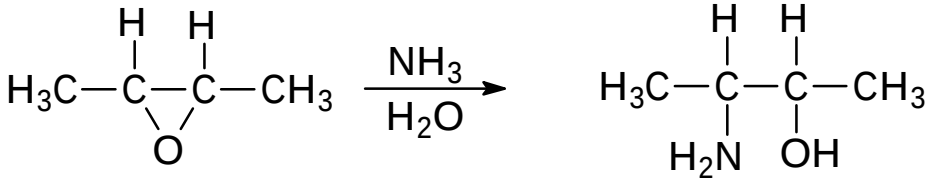
Base Promoted Cleavage —

This reaction type has no counterpart in ordinary ethers. It is only possible for epoxides because of the ring strain.



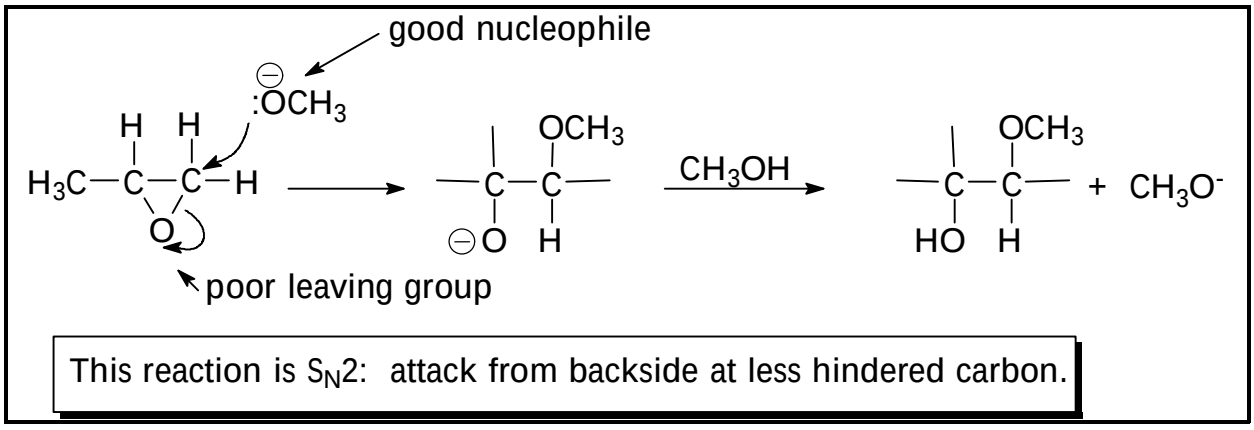
eg





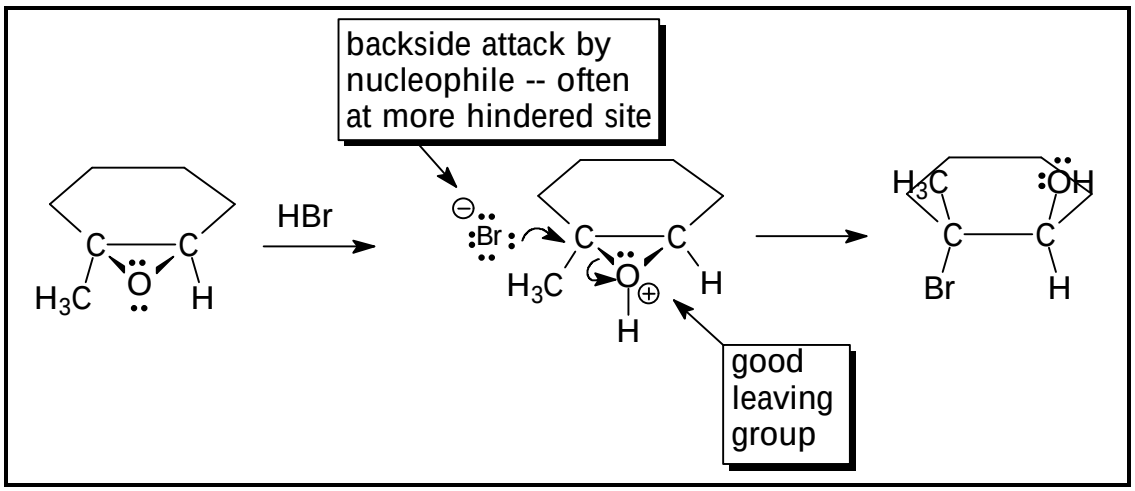
Mechanism of Cleavage —

As seen below, the reaction is basically S_N2 in base promoted cleavage. This means that the nucleophile attacks the backside (opposite the oxygen) of the less sterically hindered carbon preferentially – typical S_N2 behavior.

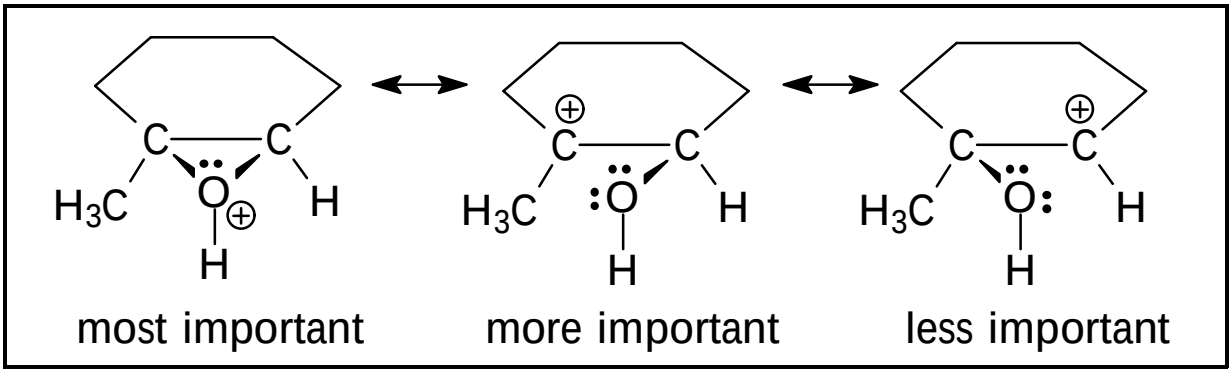


The situation for acid catalyzed cleavage is more complex. These reactions are believed to be “in between” S_N1 and S_N2 in most cases. They are S_N2 in that the attack of the nucleophile is backside. On the other hand, it is often the more highly substituted (more sterically hindered) carbon that is attacked by the nucleophile. This is where the S_N1 character to the reaction comes in: S_N1 is favored at more highly substituted carbon atoms.

Acid promoted —

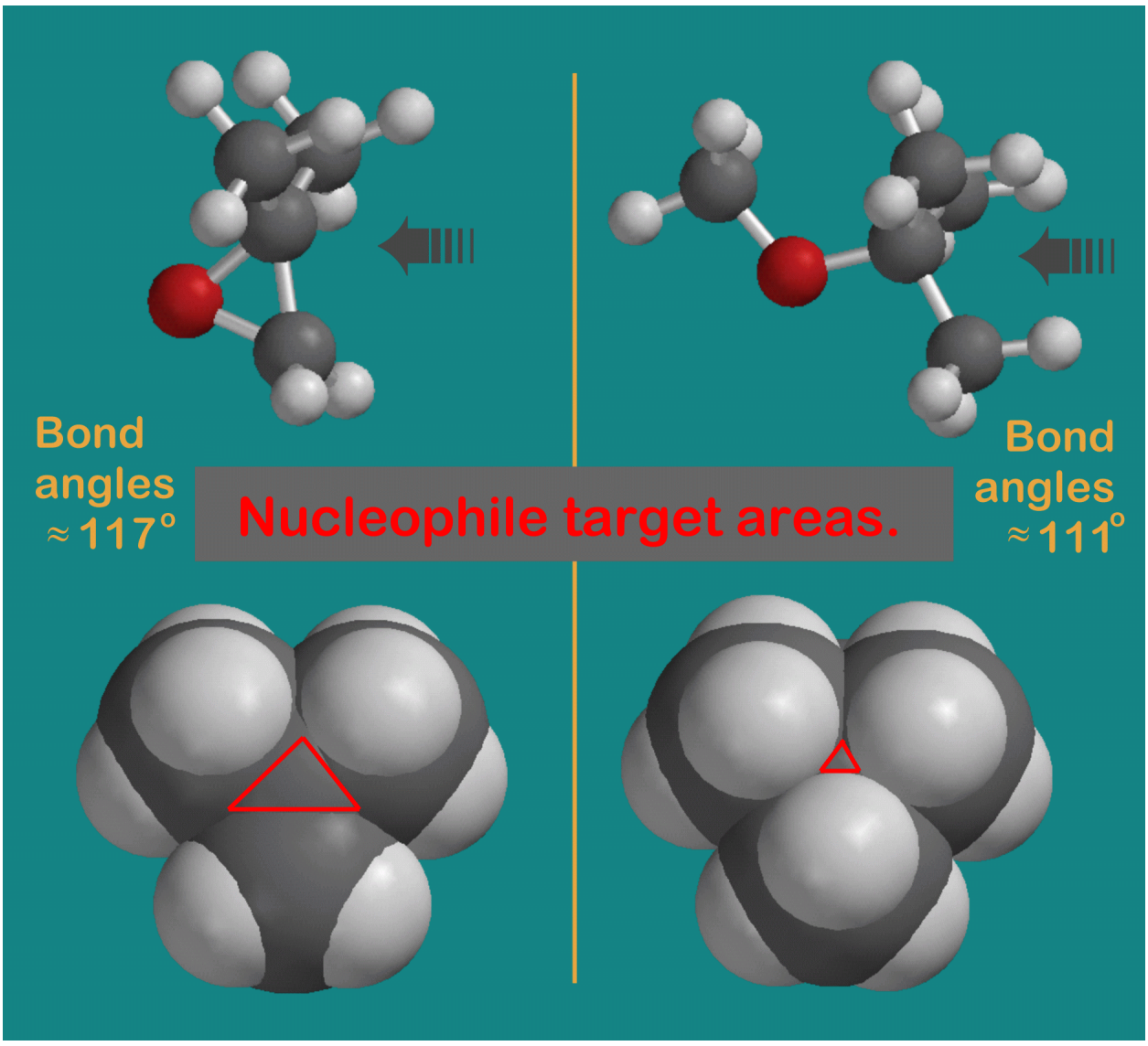


The nucleophile attacks the tertiary carbon because this reaction has considerable "S_N1 character." In other words, the tertiary carbon shares more of the positive charge nominally held by the oxygen.



But how can a tertiary carbon undergo backside attack?!!!

In the case of the strained epoxide, the bond angles around the tertiary carbon are approximately 117° (120° would make the carbon trigonal planar), while in unstrained molecules they are approximately 109°. This allows the nucleophile to make a successful attack, as seen below in the comparison of 2-methyl-1,2-epoxypropane with *t*-butyl methyl ether.



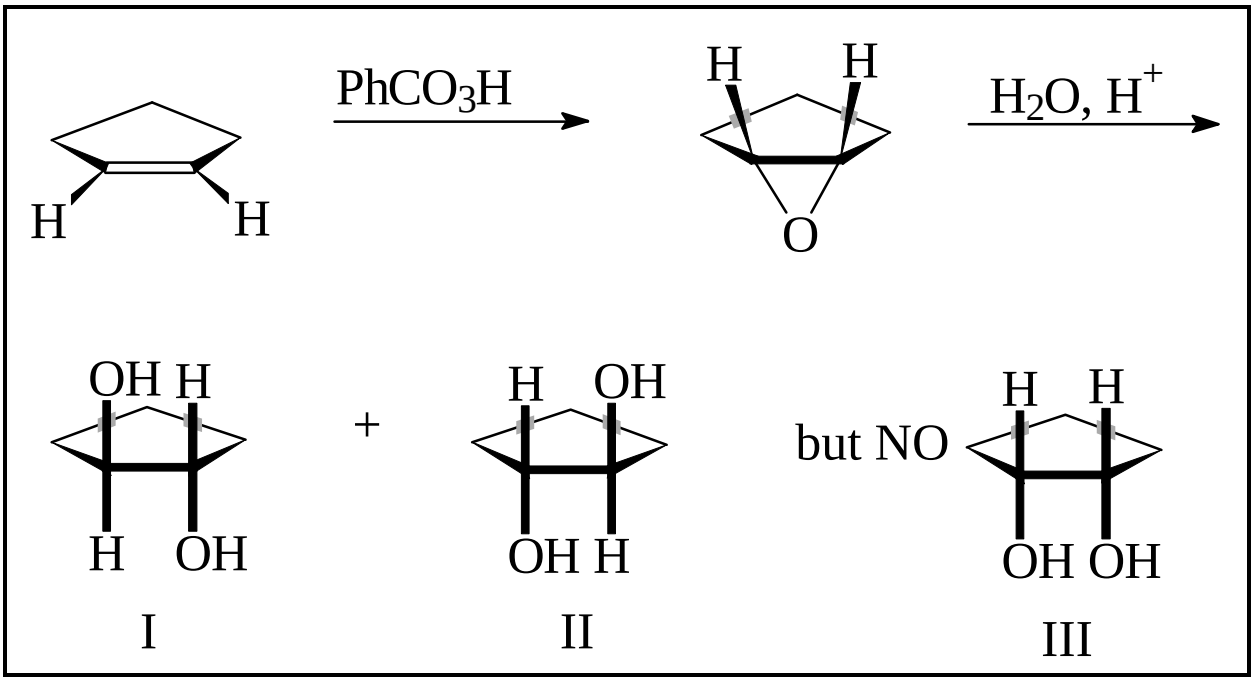
Notice how much larger the nucleophile target area is in the t-butyl group in the epoxide on the left compared to the t-butyl group in the unstrained ether on the right. [The target area in the t-butyl group on the left would likely be even larger when the epoxide is protonated.]

A Summary of the Relationship Between Substrate Structure and Nucleophilic Substitution Mechanism

Functional Group	$-CH_3$	1^o	2^o	3^o
alkyl halides	S_N2	S_N2	S_N2 or S_N1	S_N1 (or E1)
alcohols (protonated)	S_N2	S_N2	S_N1	S_N1 (or E1)
ethers (protonated)	S_N2	S_N2	S_N2	S_N1 (or E1)
Two sites* – rate: 3^o > methyl > 1^o > 2^o				
epoxides (protonated)		S_N2	S_N2	S_N2-S_N1
Two sites* – rate: 3^o > (1^o ~ 2^o)				
epoxides (basic conditions)		S_N2	S_N2	NR/S_N2?
Two sites* – rate: 1^o > 2^o				

*Two sites – Since the oxygen in an ether is joined to two carbon atoms there are two possible sites of nucleophilic attack. If these carbons belong to different classes they will likely react at different rates.

Stereochemistry of Glycol Formation from Epoxides



1) What does the formation of I and II, but NO III, imply with regard to the mechanism of epoxide ring opening under acidic conditions?
   Principally S_N1? Principally S_N2?

2) What is the relationship between the two compounds which are formed, I & II?

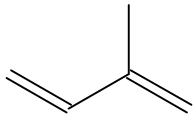
3) What percentage of I + II is I?

4) What is the relationship of the compound that is not formed, III, to I and II?

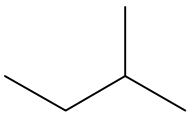
5) How would you make III, starting with cyclopentene?

A Biologically Important Epoxide Ring Opening

Terpenes are important naturally occurring compounds (natural products) that contain the isoprene structural unit repeated 2, 3, 4 or more times.

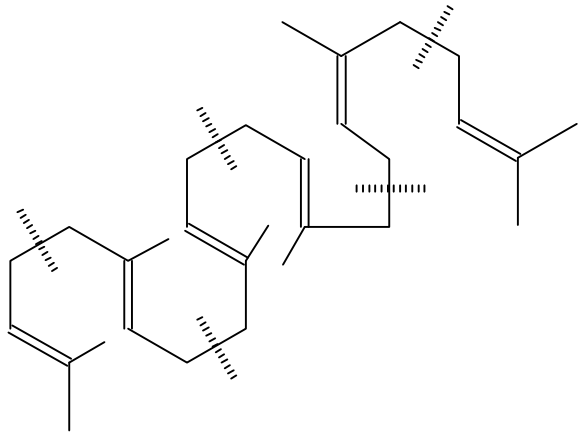


isoprene (2-methyl-1,3-butadiene)



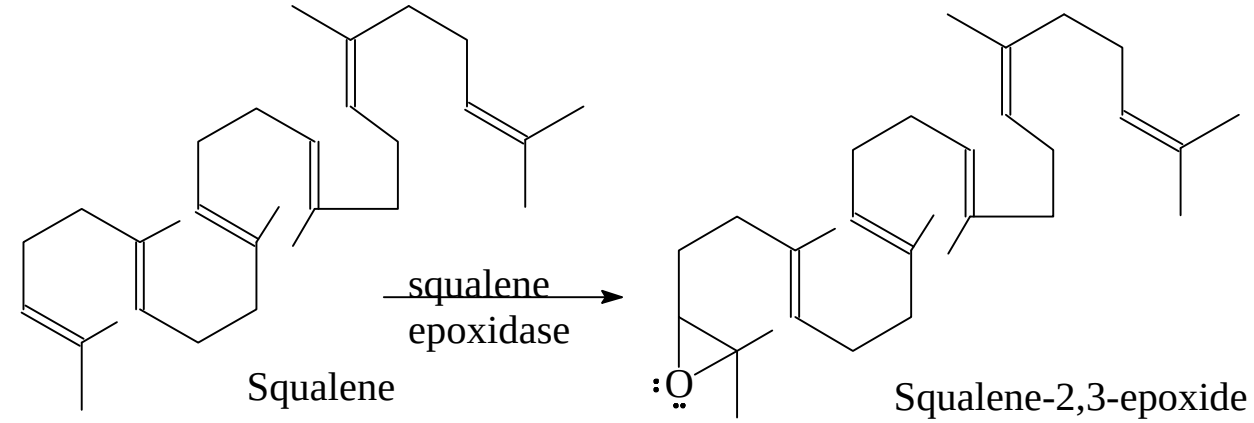
terpene structural unit, may contain multiple bonds, and hetero atoms may be attached

One important terpene is *squalene*. The figure shows the isoprene units in squalene.

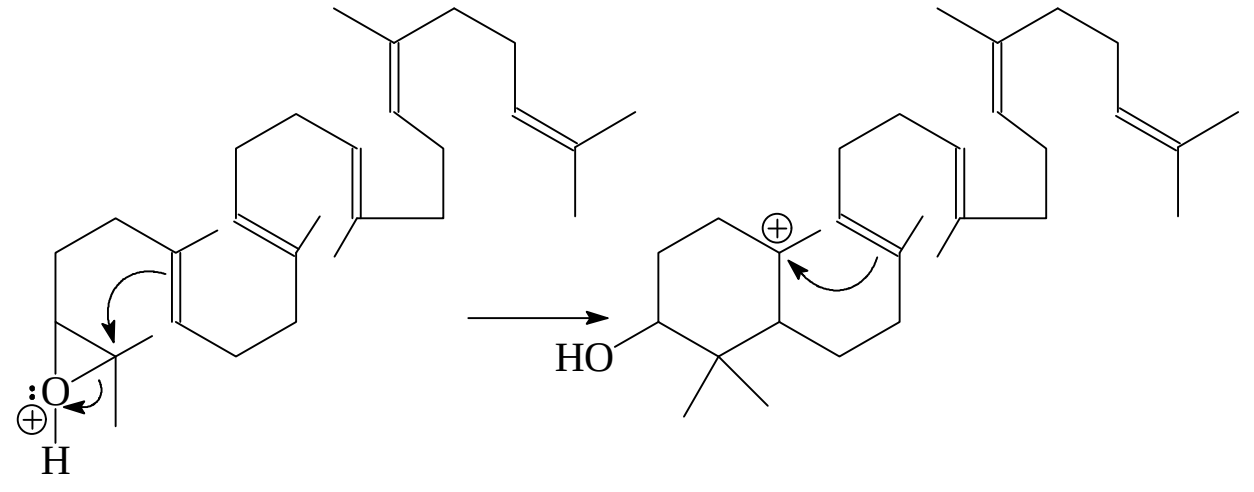


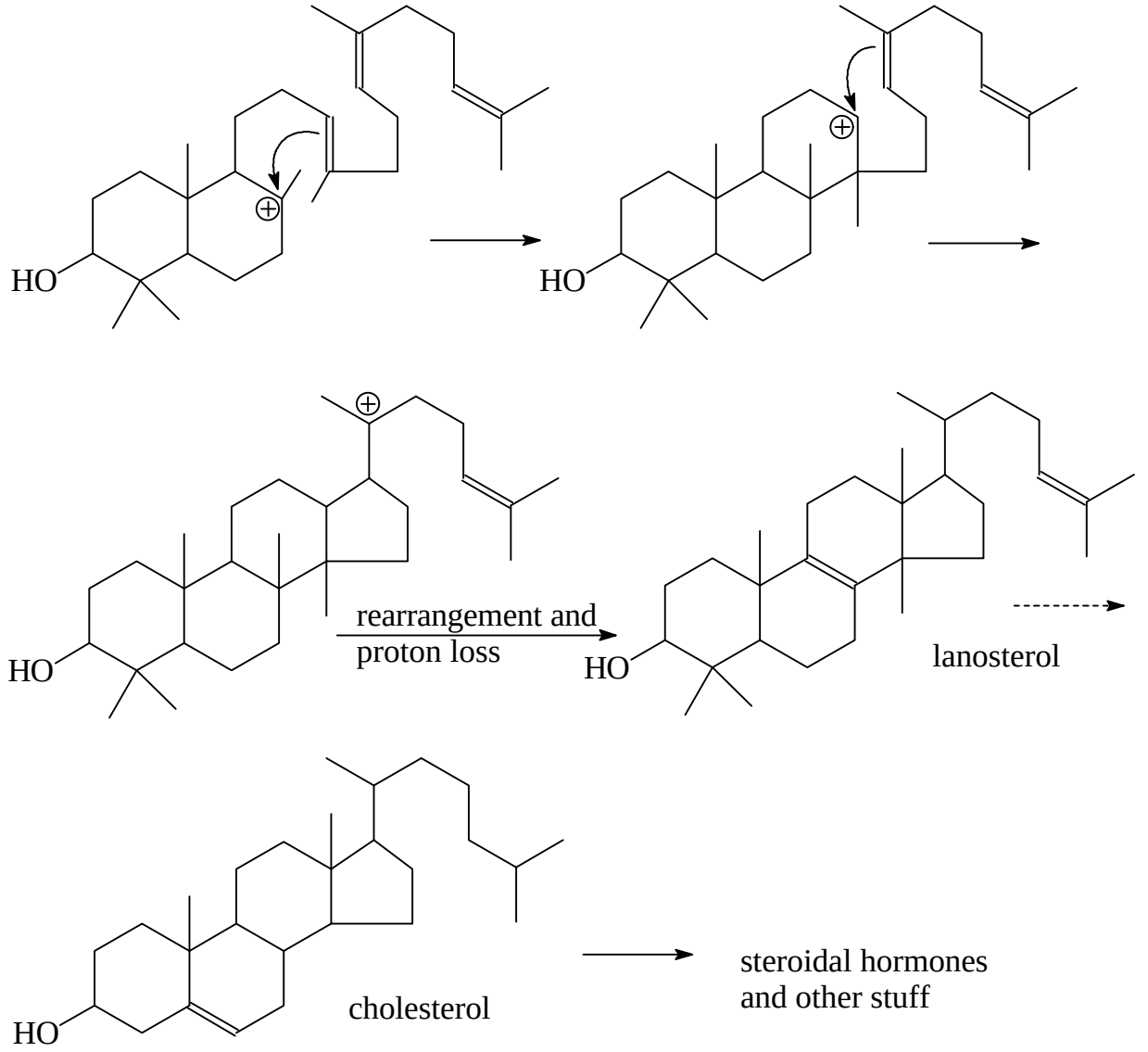
Squalene, emphasizing the isoprene units

Squalene is biochemically oxidized *in vivo* to an epoxide at the Δ-2 double bond by the enzyme *squalene epoxidase*, to give squalene-2,3-epoxide.



The epoxide is protonated (to provide a better leaving group) and the neighboring π-bond makes a nucleophilic attack backside at the #2 carbon, forming a 6-membered ring/3° carbocation. This carbocation undergoes nucleophilic attack by the neighboring π-bond to generate another ring/3° carbocation, *etc.*





The above reactions are enzyme mediated.