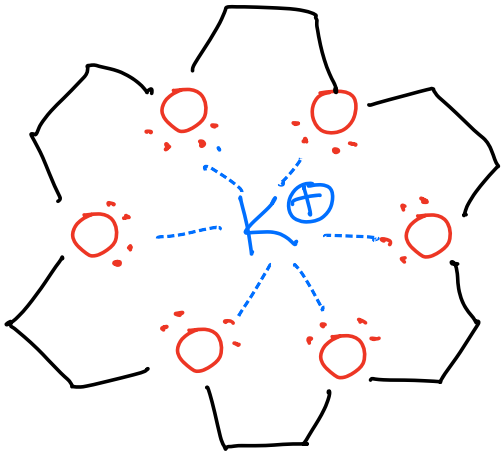
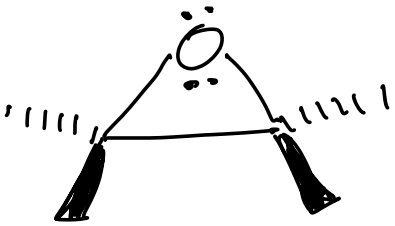

Back
WELCOME TO OUR
REACTION
FESTIVAL

Crown Ethers → bind cations based on the radius of the ion





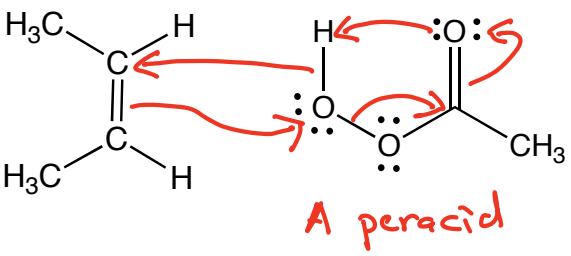
Epoxide

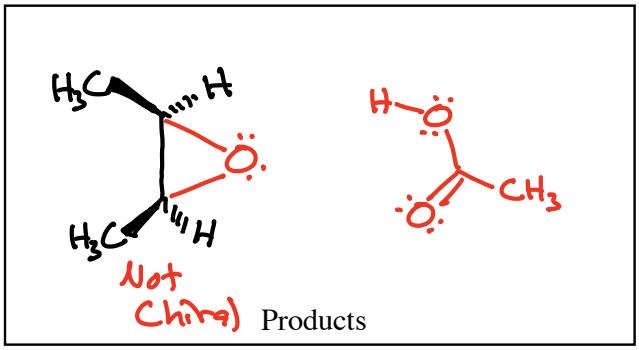
Important because they can be formed from alkenes or halohydrins AND they are good electrophiles → reactions open up three-membered ring, relieving angle strain

Epoxides are also involved in a number of biological processes including oxidative damage

Synthesis of epoxides

Epoxide Formation



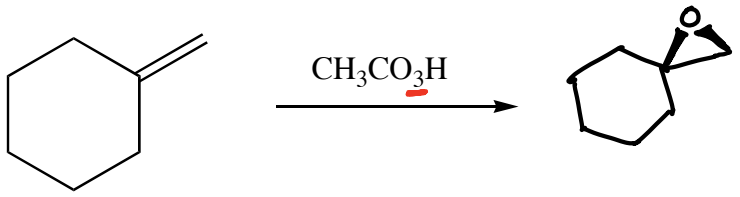


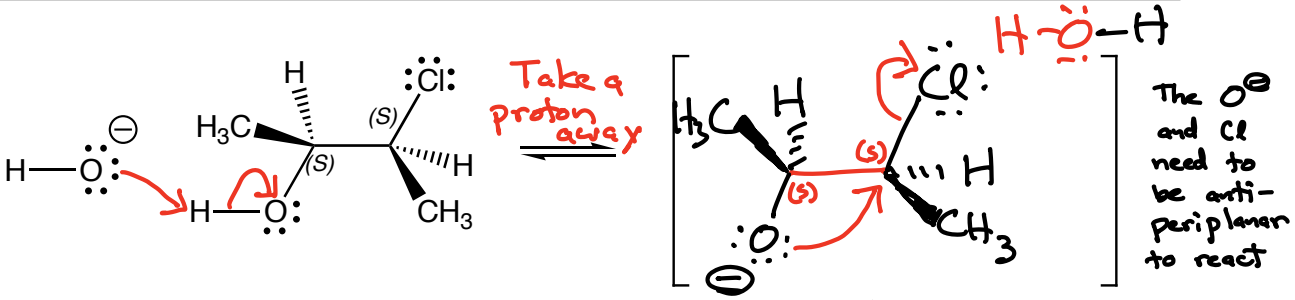
Summary: Alkenes react with peracids in a single concerted step

Regiochemistry: N/A

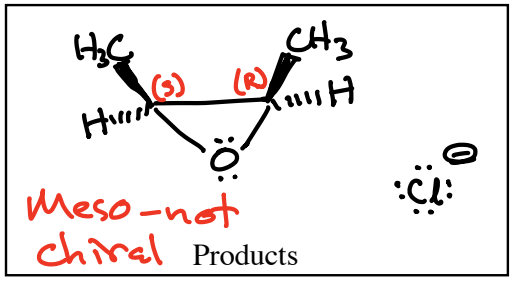
Stereochemistry: Mixed when new chiral centers are created

Example:





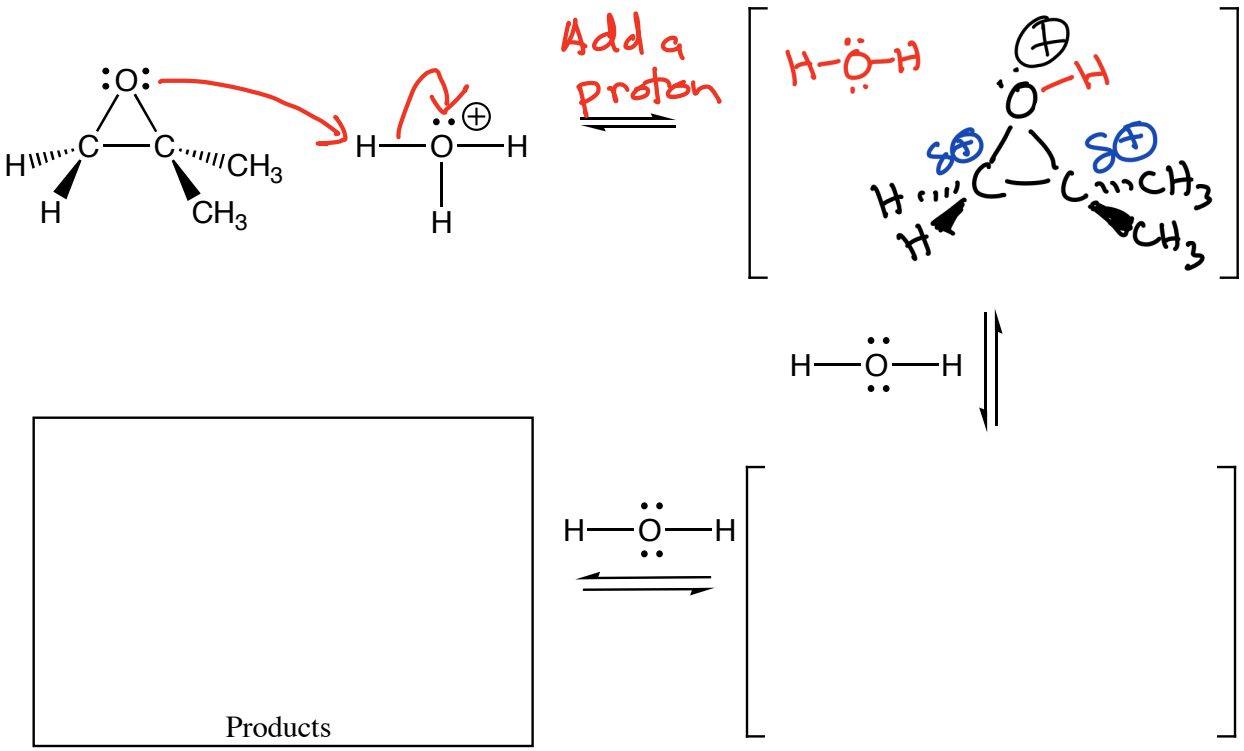
Summary: Halohydrins react in base to give the alkoxide that reacts antiperiplanar to give the epoxide.



Regiochemistry: N/A

Stereochemistry: Antiperiplanar transition state

Acid-Catalyzed Epoxide Opening

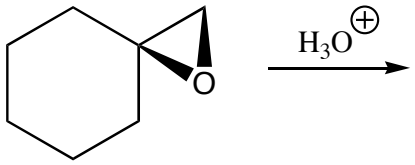


Summary: In acid, epoxides are protonated to give a highly reactive cation intermediate that reacts with nucleophiles at the more highly substituted carbon atom

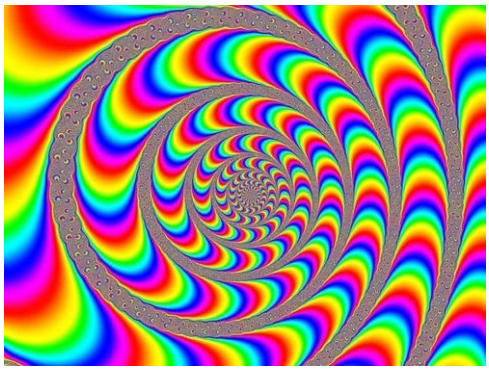
Regiochemistry: "Markovnikov" Attack at more highly substituted C atom

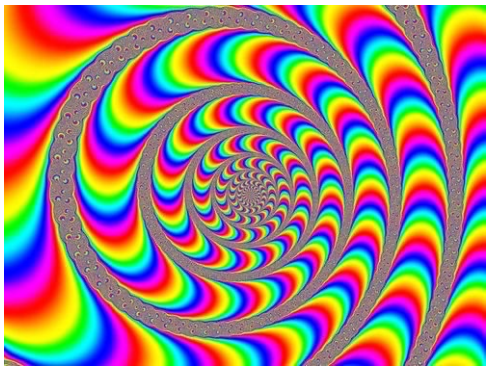
Stereochemistry: Anti

Example:

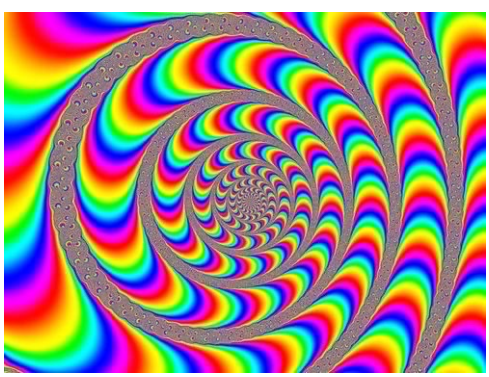


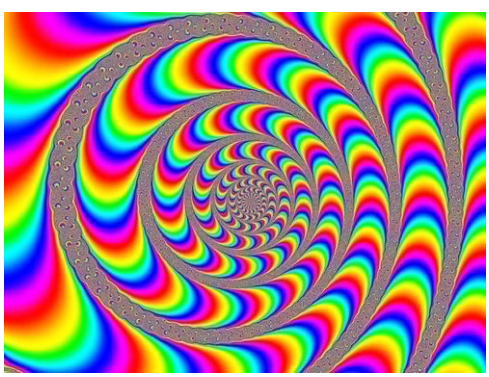
Flashback!



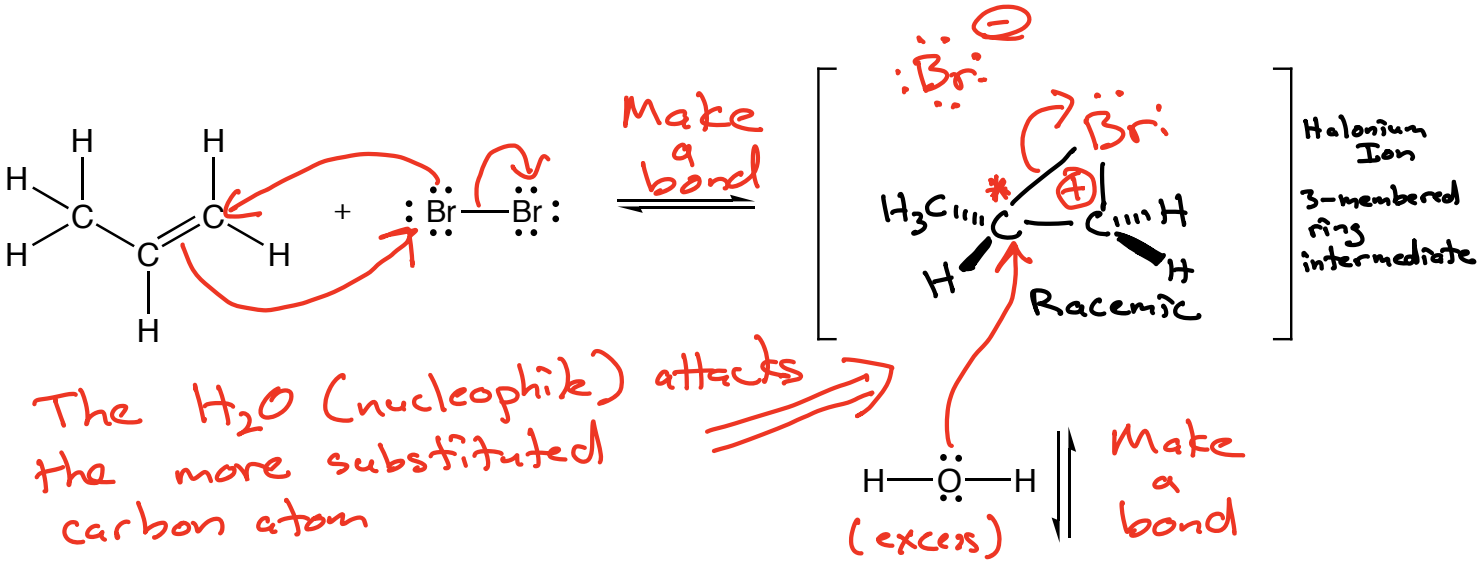


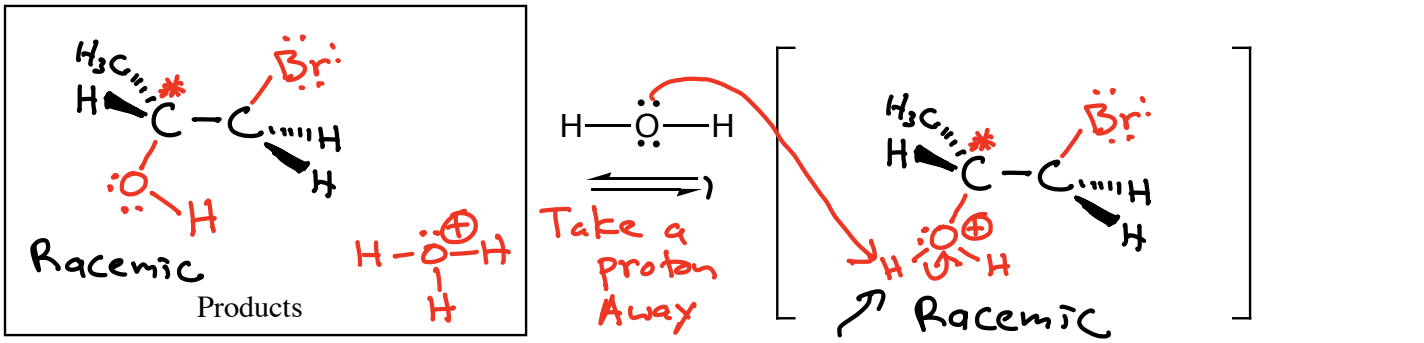






Alkene Hydrohalogenation





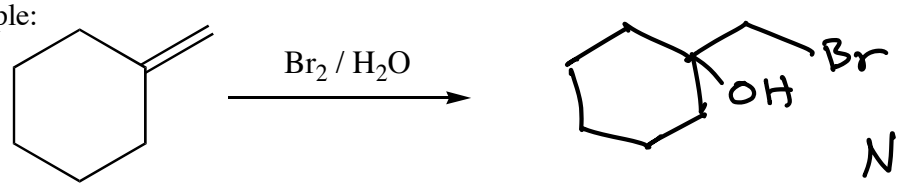
pH drops during the reaction!

Summary: Alkene reacts with X_2 to give a 3-membered ring intermediate (halonium ion) → H_2O attacks the more substituted C atom and we take a proton away to give the halohydrin product.

Regiochemistry: Markovnikov (OH on more substituted C atom)

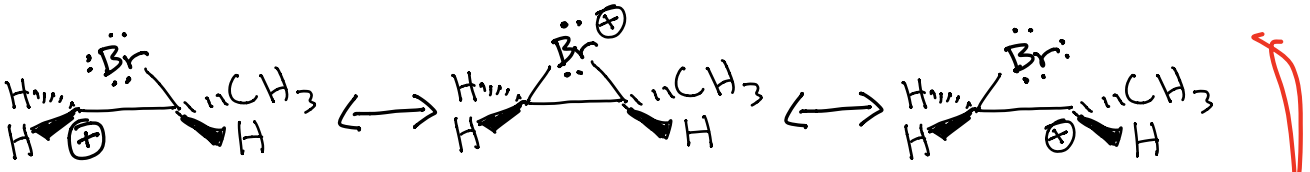
Stereochemistry: Anti

Example:



Not Chiral

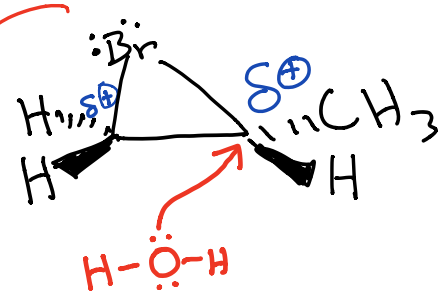
Flashback → Halohydrin Mechanism



Minor Contributor

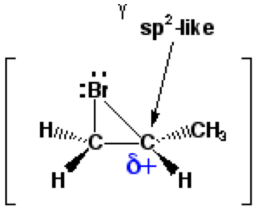
Major Contributor

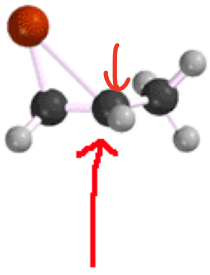
Resonance Hybrid

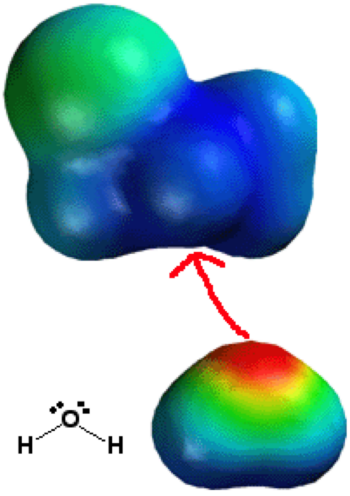


Water attacks the more substituted carbon atom because there is more partial ⊕ charge

From "Pictures of the Day (POTD)" 10-9-20

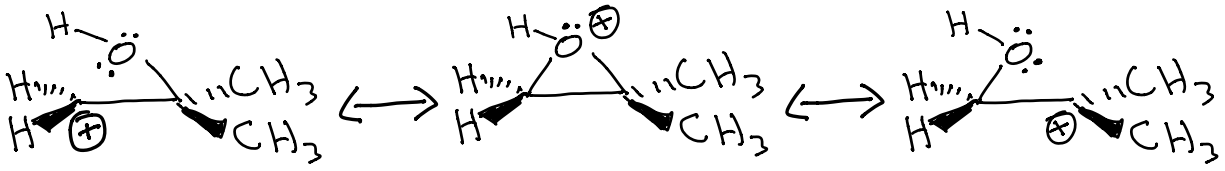






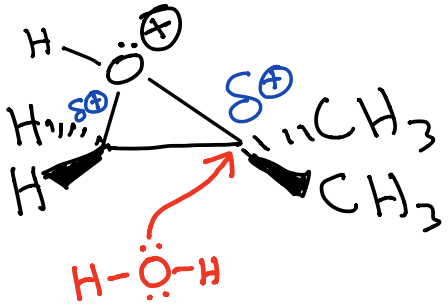
Nucleophiles Attack the More Positively-Charged Carbon Atom From This Face Leading to Markovnikov Regiochemistry and Trans Stereochemistry of Addition

Epoxide in acid



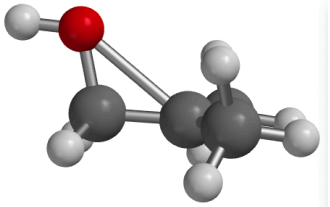
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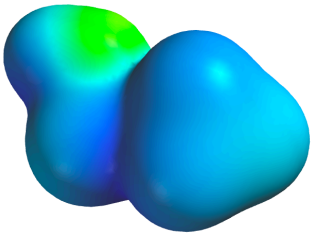
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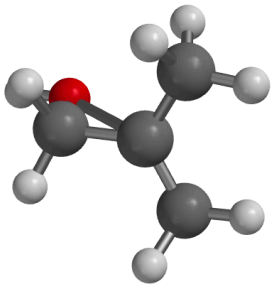
Water attacks the more substituted carbon atom because there is more partial ⊕ charge

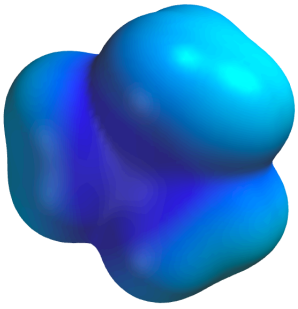
Side View



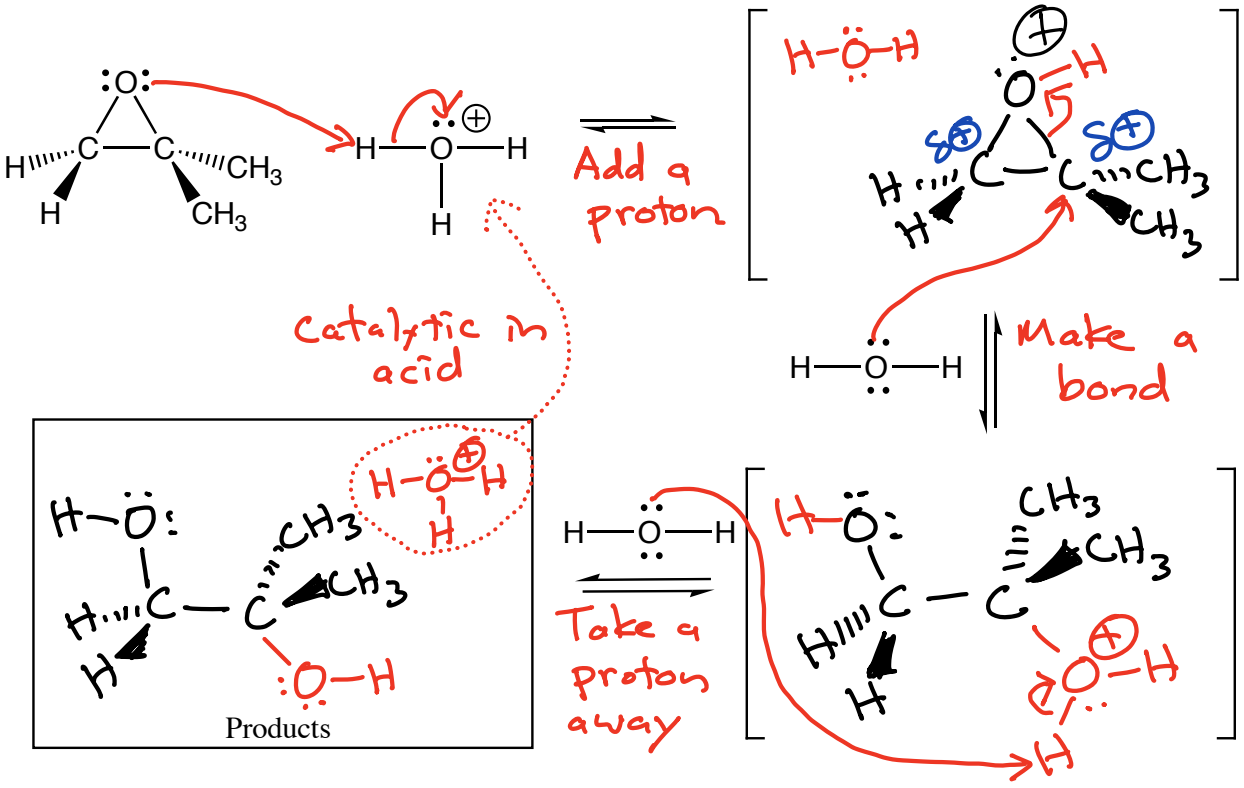


View from Bottom



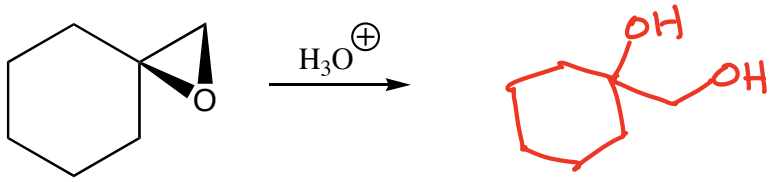


Acid-Catalyzed Epoxide Opening

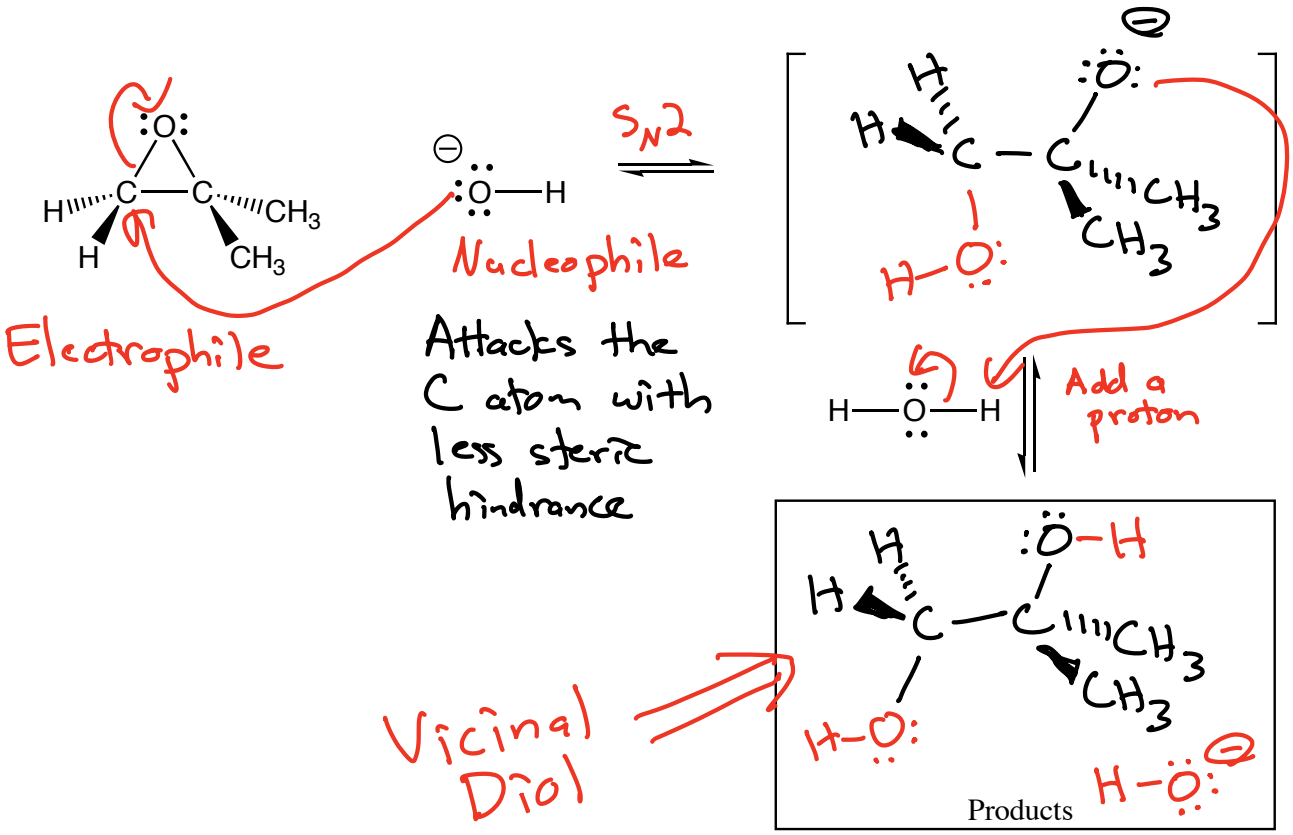


Summary:	In acid, epoxides are protonated to give a highly reactive cation intermediate that reacts with nucleophiles at the more highly substituted carbon atom
Regiochemistry:	"Markovnikov" Attack at more highly substituted C atom
Stereochemistry:	Anti ← !!!

Example:

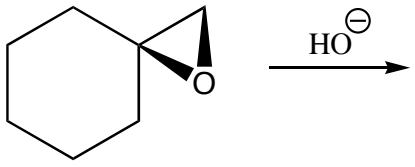


Nucleophilic ~~Base Promoted~~ Epoxide Opening

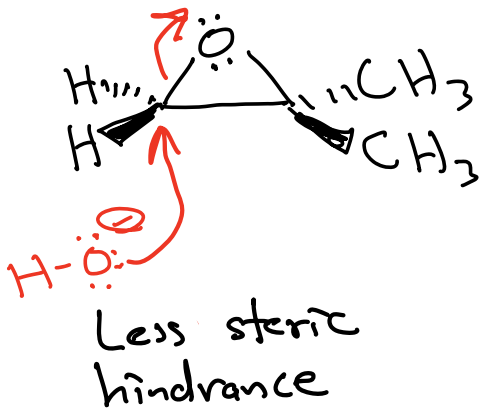


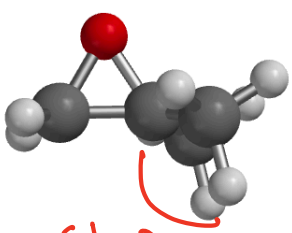
Summary:	Epoxides add strong nucleophiles at the less hindered carbon atom
Regiochemistry:	Less hindered (non-Markovnikov)
Stereochemistry:	Anti addition

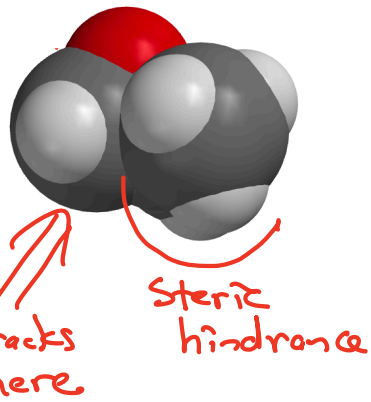
Example:



Epoxide reacting with nucleophile



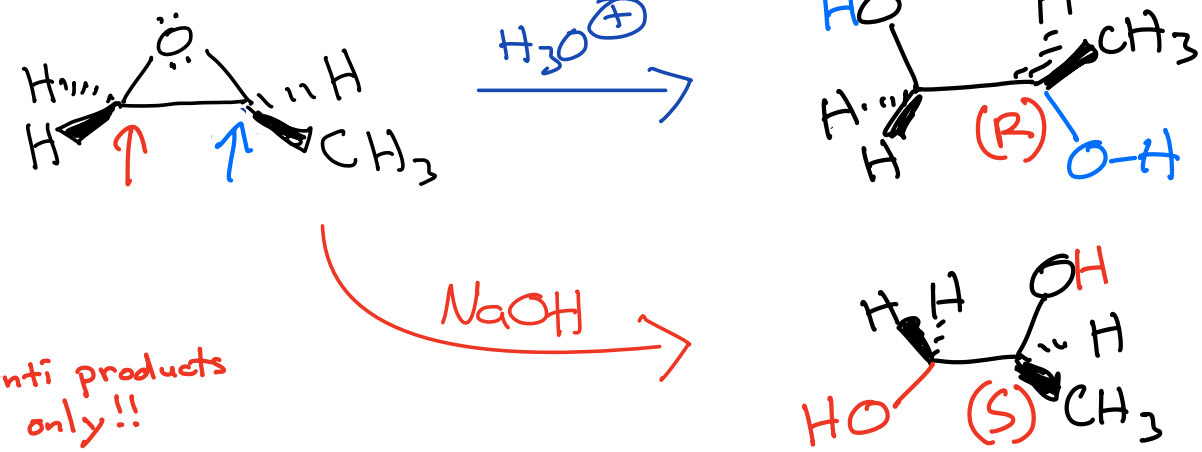




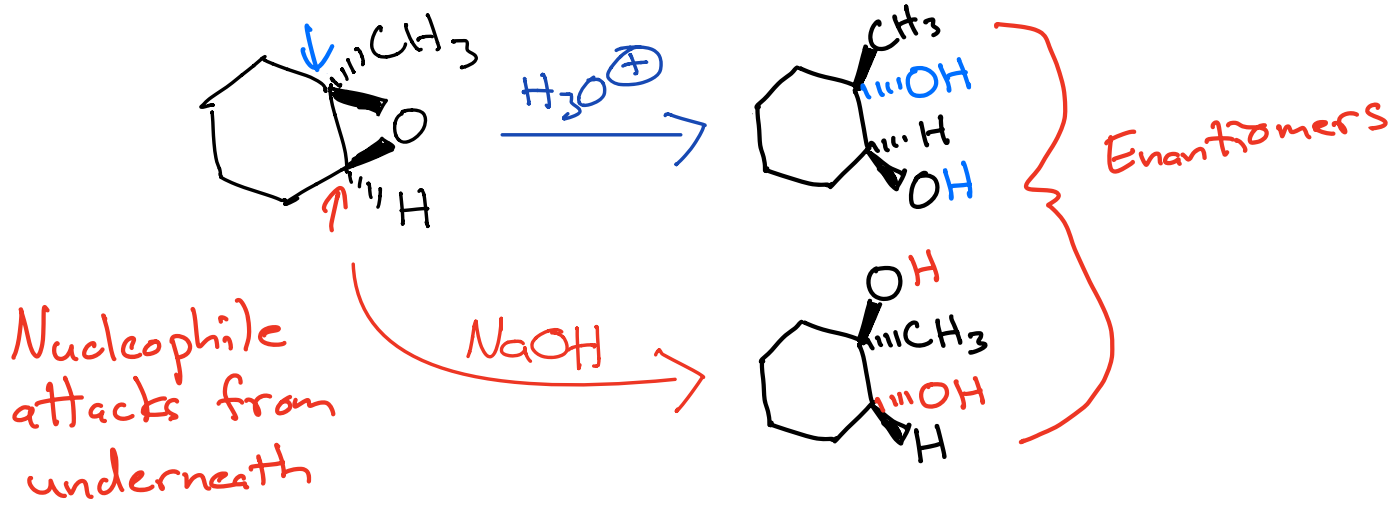


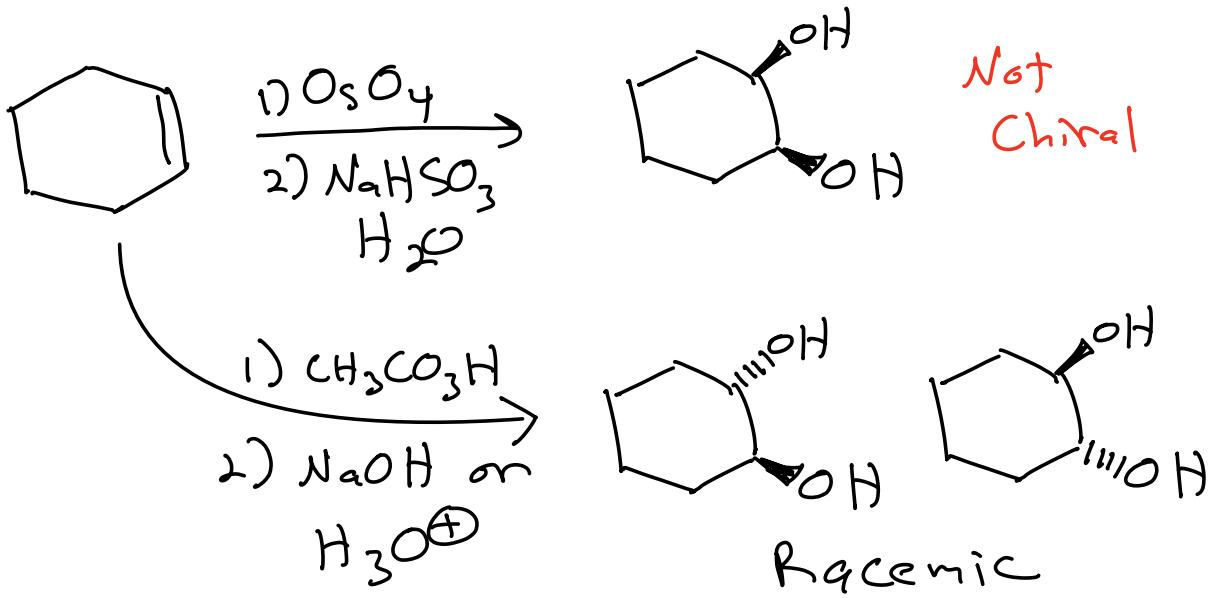
Watch out for the stereochemistry!

Single enantiomer



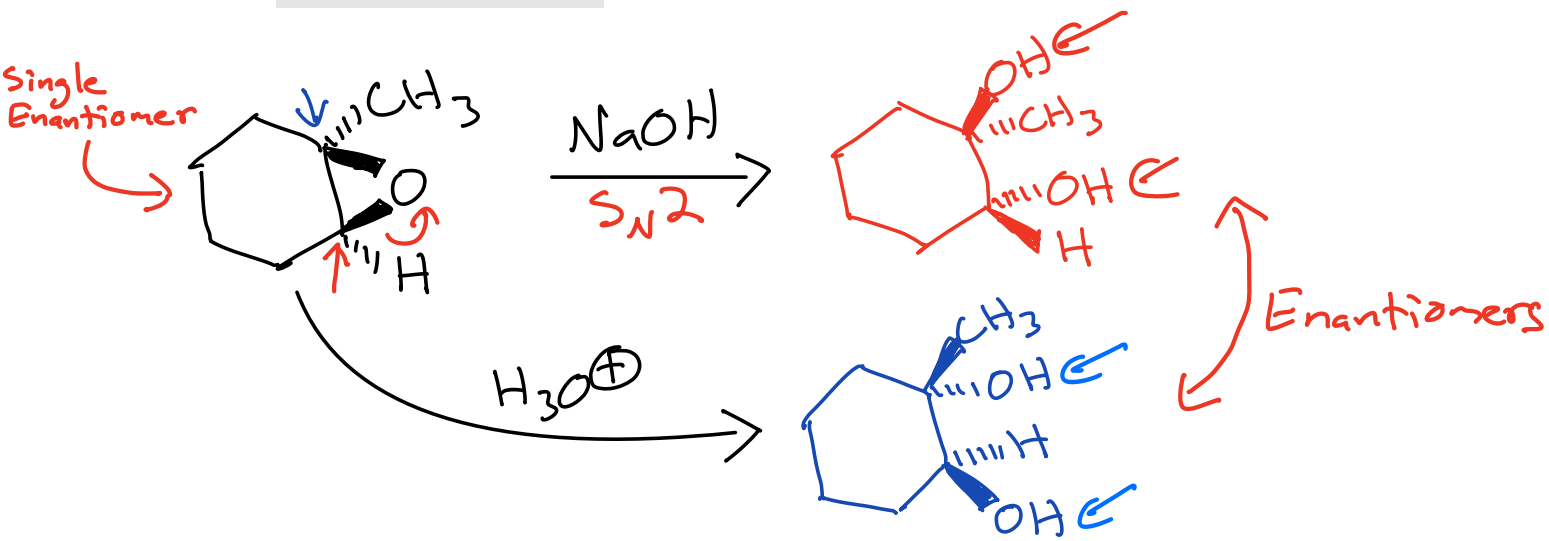
Anti products only!!


CH3
O
H
H3O+
OH
H
OH
CH3
Enantiomers
NaOH
OH
CH3
OH
H
Nucleophile attacks from underneath

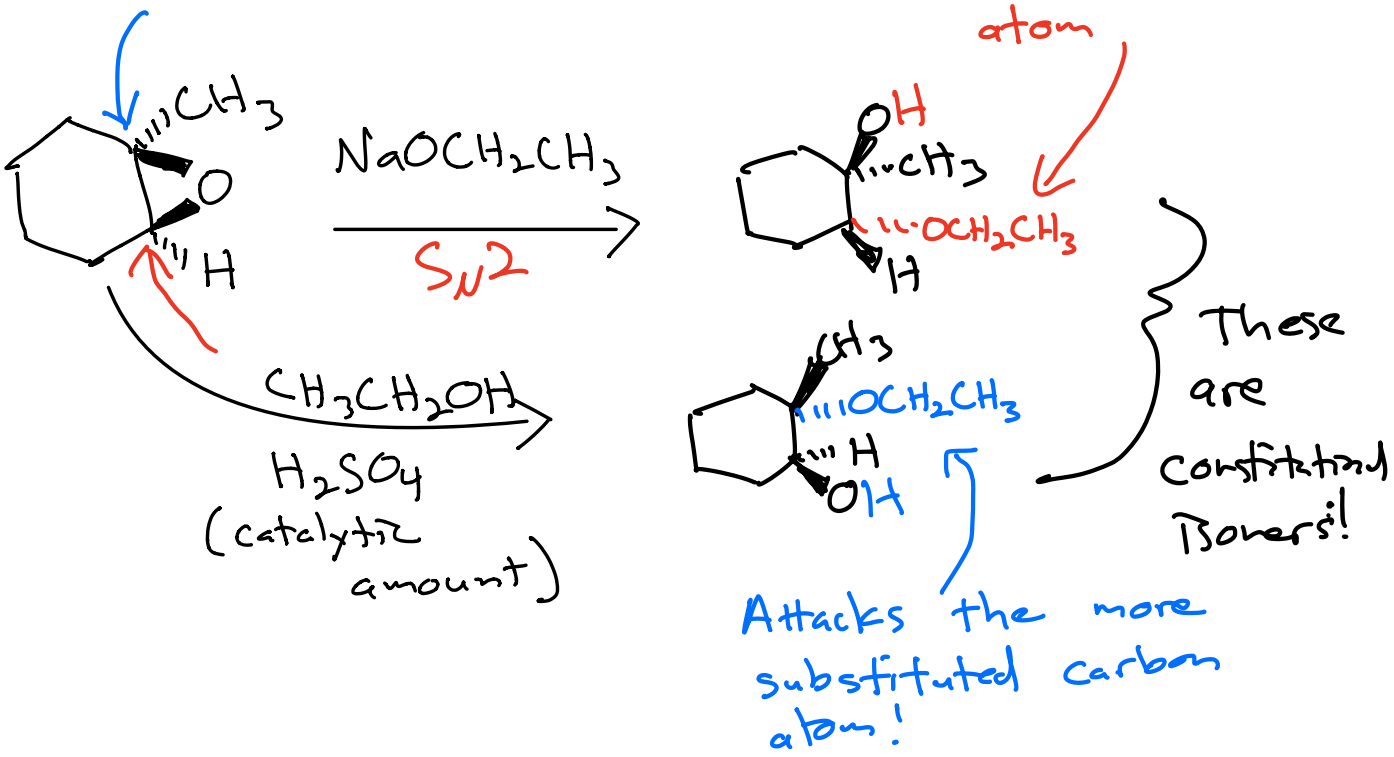




Watch out for the stereochemistry!



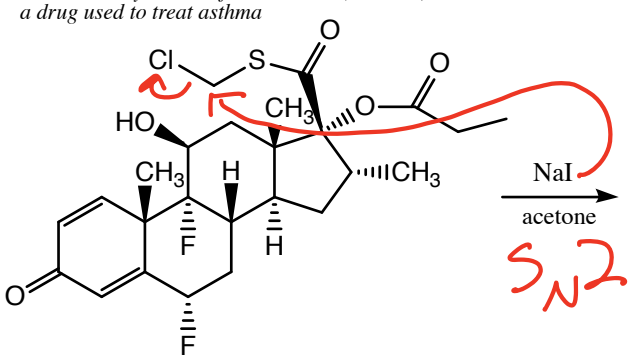
Works with alkoxides and alcohols as well

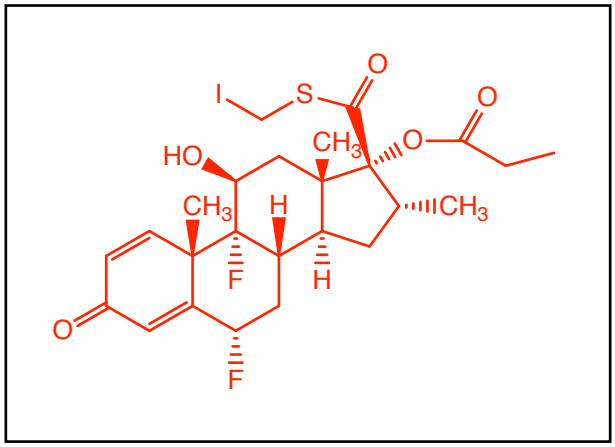


The key paradigm of organic chemistry: Functional groups react the same in complex molecules as they do in simpler ones.

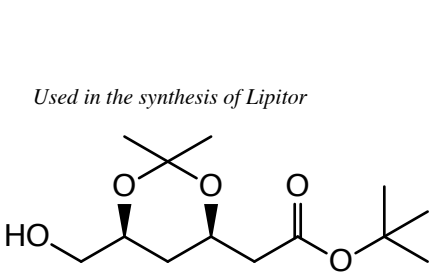
Reactions in the Context of Complex Molecules

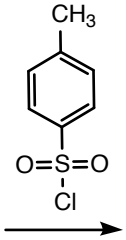
Used in the synthesis of Fluticasone (Flonase), a drug used to treat asthma

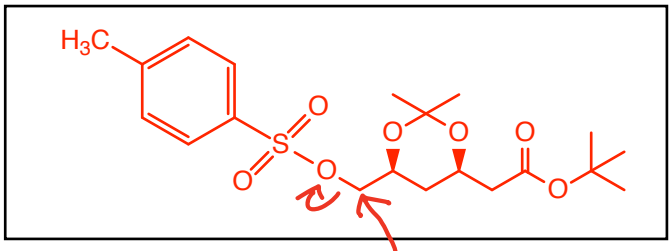




Used in the synthesis of Lipitor

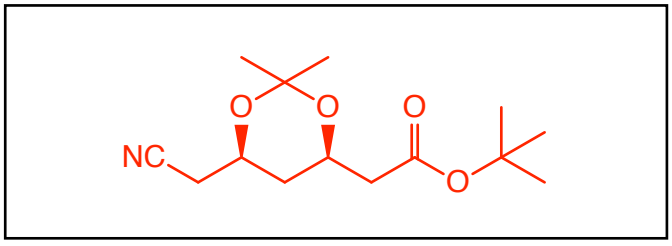




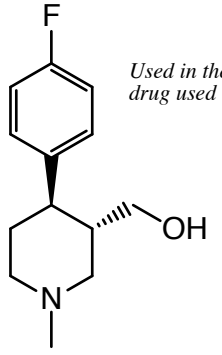


NaCN

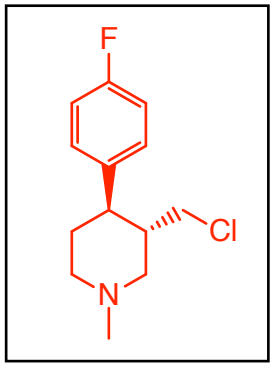
SN2

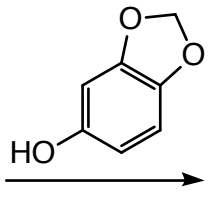


Used in the synthesis of Paxil, a drug used to treat depression

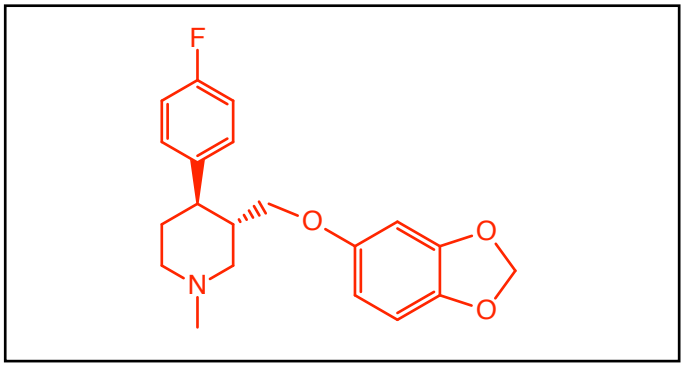


$SOCl_2$



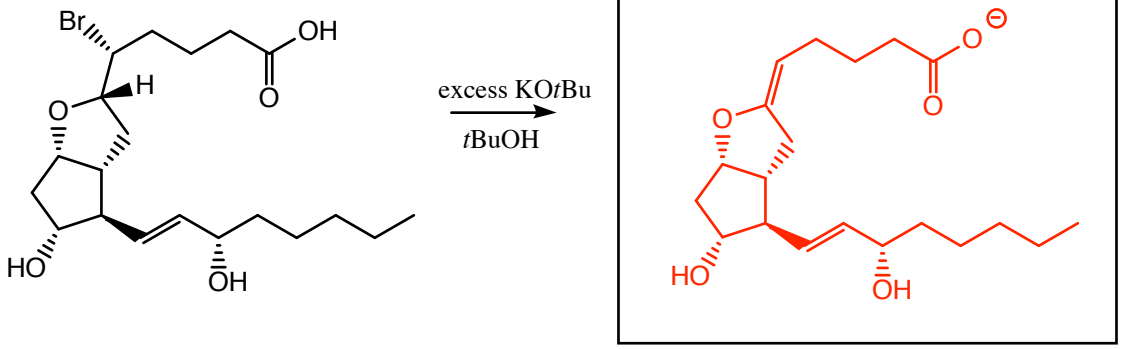


SN2

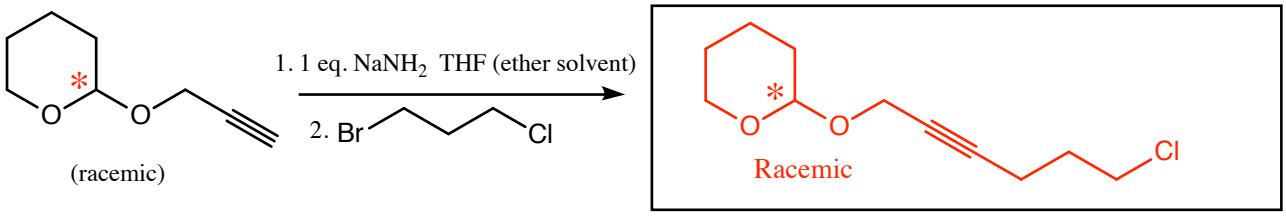


Reactions in the Context of Complex Molecules

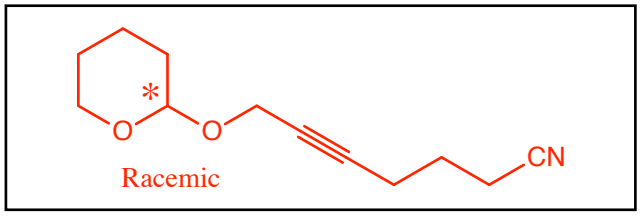
Used in the synthesis of several protaglandins

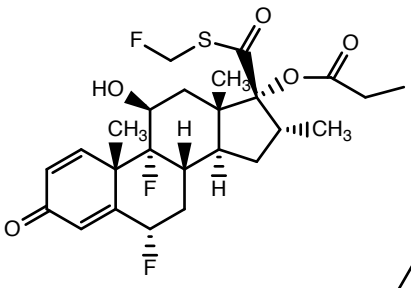


Used in the synthesis of protaglandin C_2

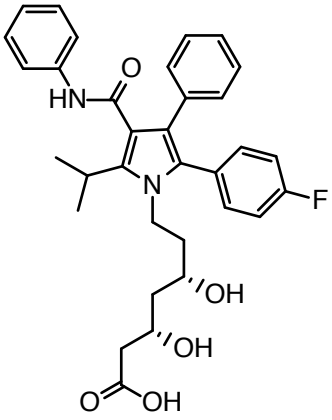


DMSO (polar aprotic solvent) NaCN

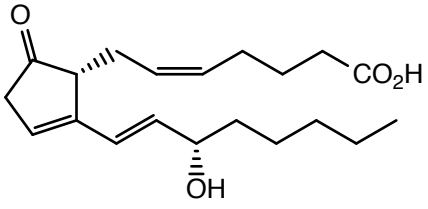




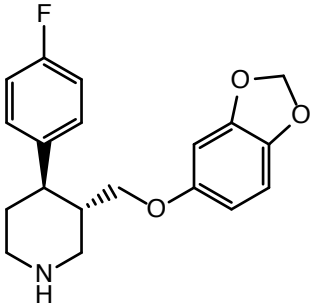
Fluticasone (Flonase)



Atorvastatin (Lipitor)



Prostaglandin C_2



Paroxetine (Paxil)

Here are some things I wish I had said when we were talking about substitution and elimination reactions:

Good leaving group → leaves to create a stable anion or molecule

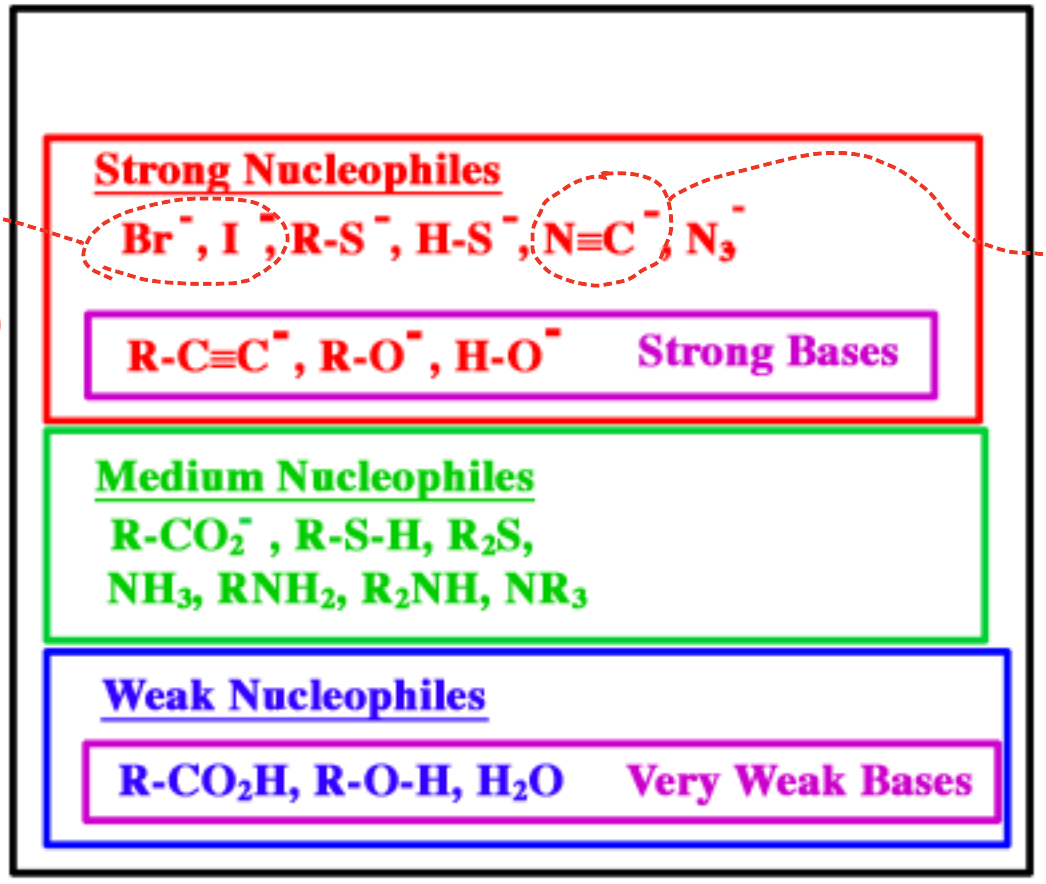


Nucleophiles → not simple to explain what makes a good nucleophile → the Table for reference

Halogens → $Br^{\ominus}$, $I^{\ominus}$ are both good nucleophiles and good leaving groups

HOWEVER → not all nucleophiles are leaving groups!

Table of Nucleophiles

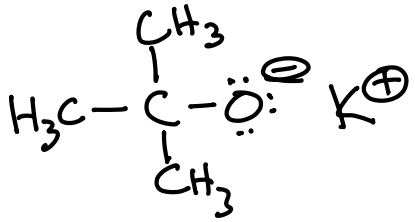


Strong nucleophiles and good leaving groups

$Na^{\oplus}{}^{\ominus}CN$
NaCN
or
$K^{\oplus}{}^{\ominus}CN$
KCN
very useful!

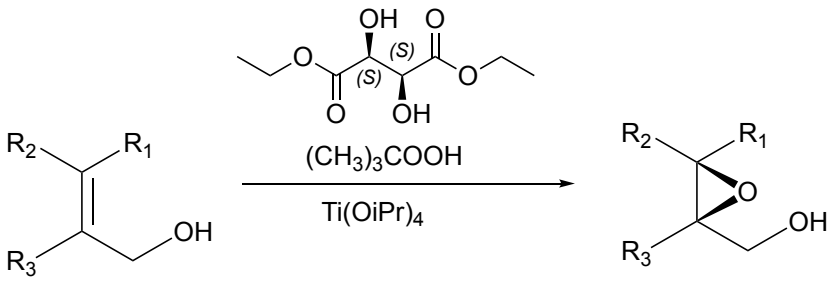
Special Case

***Tert*-Butoxide ($tBuO^-$) is a strong base, but is not a nucleophile due to steric hindrance.**

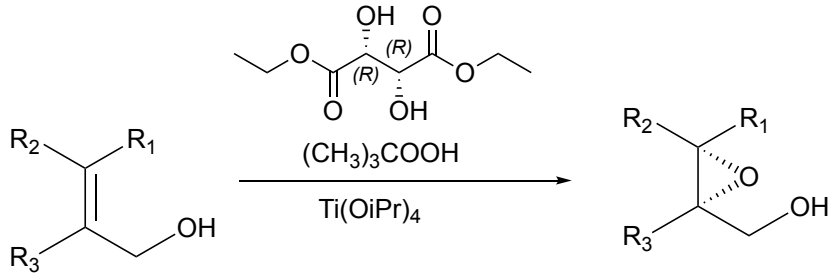


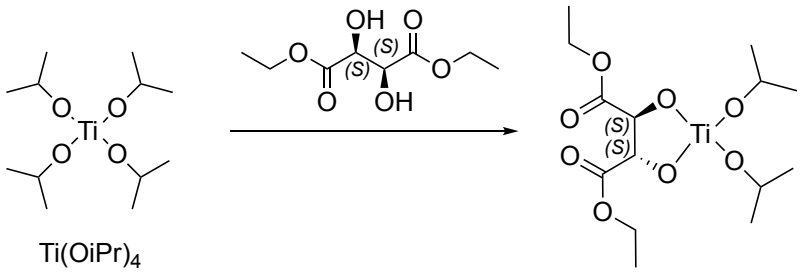
"KOtBu"
or
"tBuO⊖"

The Sharpless Epoxidation 2001 Nobel prize for making single enantiomer products!



R_1, R_2, R_3 can be any alkyl group or H





$Ti(OiPr)_4$

The true situation is more complicated than this

The First Practical Method for Asymmetric Epoxidation

Tsutomu Katsuki, K. Barry Sharpless*[18]

Department of Chemistry, Stanford University
Stanford, California 94305

Received May 5, 1980

Sir:

As revealed in Scheme I, we have discovered a new metal-catalyzed asymmetric epoxidation process which is far more selective than any of the previously described methods[1] for this type of asymmetric transformation. The simplicity of this new method is one of its more attractive aspects; the necessary components [(+) or (−)-diethyl tartrate,[2] titanium tetraisopropoxide, and *tert*-butyl hydroperoxide] are all[3] commercially available at low to moderate cost.[4]

Scheme I

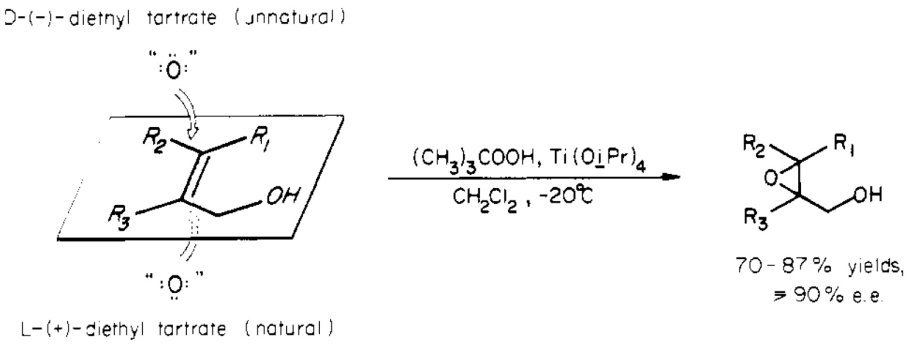
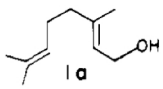
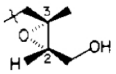
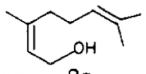
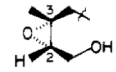
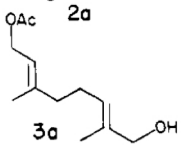
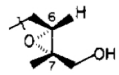
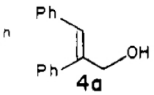
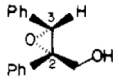
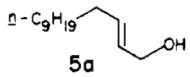
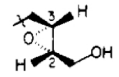
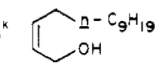
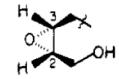
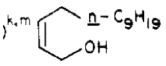
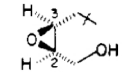
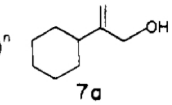
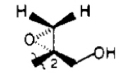


Table I. Asymmetric Epoxidation of Allylic Alcohols[a]

	Allylic Alcohol	Epoxyalcohol	% yield[b]	% e.e.[c]	Configuration[d]
(1)	 1a	1b 	77	95 (Eu, M)	2(S), 3(S)[e]
(2)	 2a	2b 	79	94 (Eu, M)	2(S), 3(R)[f]
(3)	 3a	3b 	70[g]	>95 (Eu)	6(S), 7(S)[g]
(4)[h]	 4a	4b 	87	>95 (Eu)	2(S), 3(S)[i]
(5)	 5a	5b 	79	>95 (M)	2(S), 3(S)[j]
(6)[k]	 6a	6b 	82	90 (M)	2(S), 3(R)[l]
(7)[k,m]	 6a	6c 	80	90 (M)	2(R), 3(S)[m]
(8)[n]	 7a	7b 	81	>95 (M)	2(S)[o]

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Mechanism of the Sharpless Epoxidation Reaction: A DFT Study

Robert D. Bach* and H. Bernhard Schlegel

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ABSTRACT: The Sharpless reaction is an enantioselective epoxidation of prochiral allylic alcohols that employs a Ti(IV) catalyst formed from titanium tetra(isopropoxide), Ti(O-*i*-Pr)$_4$, diethyl tartrate (DET), and the oxidizing agent *tert*-butyl hydroperoxide. The M06-2X DFT functional with the 6-311+G-(d,p) basis set has been employed to model the structures and energetics of the Sharpless epoxidation reaction. The monomeric tetracoordinate titanium(IV) diethyltartrate is thermodynamically strongly favored to dimerize, producing a pentacoordinate catalyst, [Ti(DET)(O-i-Pr)$_2$]$_2$, that is a more reactive chiral epoxidation catalyst. The rapid ligand exchange reactions needed to generate the "loaded" catalyst and to repeat the overall catalytic cycle have been examined and are found to have activation energies that are much lower than the epoxidation barriers. The transition structures and activation energies for the enantioselective epoxidation of allyl alcohol, *trans*-methyl-allyl alcohol and *trans-tert*-butyl-allyl alcohol with the "loaded" Sharpless catalyst, [Ti$_2$(DET)$_2$(O-*i*-Pr)$_2$-(OAllyl)-(OO*t*-Bu)], are presented. The effect of the C═O···Ti interactions on the activation energies and the significance of the O−C−C═C dihedral angle on the enantioselectivity of the epoxidation reaction are discussed.

