

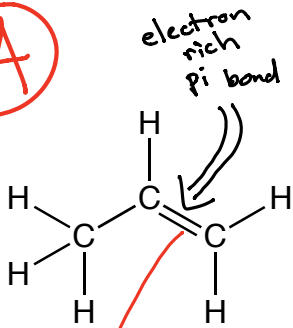
Brackets indicate this is an intermediate

"X" can be Cl, Br, I
Not F

Addition of H-X to an Alkene

Nucleophile

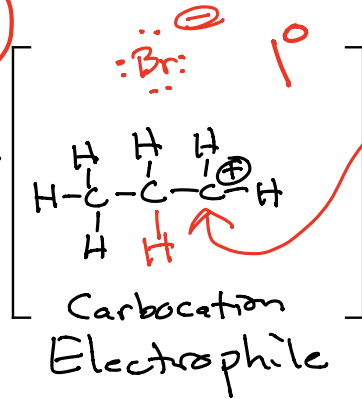
(A)



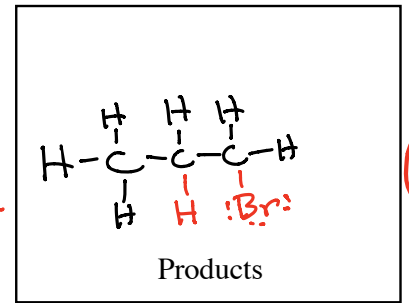
Add a proton

Strong Acid

(B)

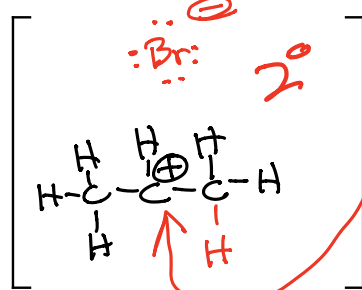


Make a bond

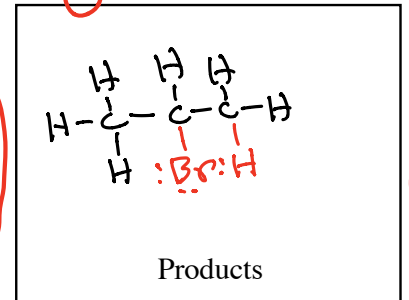


(E)

Major Product



Make a bond



(C)

Markovnikov Product only one to draw

Summary:

Alkene pi bond reacts with H-X to add a proton to create a carbocation intermediate that makes a bond with X⁻ to give the product

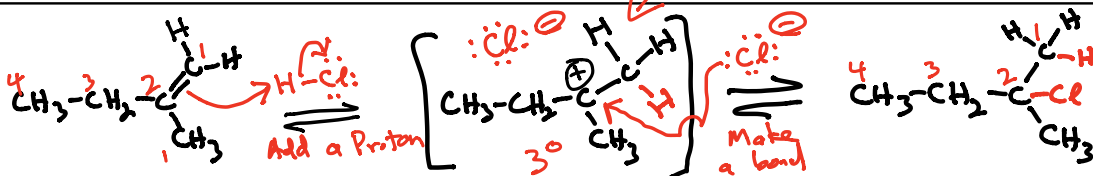
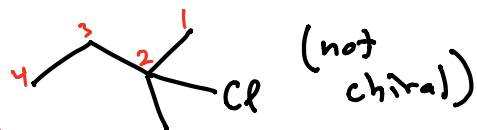
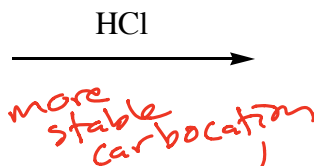
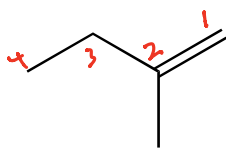
Regiochemistry:

Markovnikov's Rule

Stereochemistry:

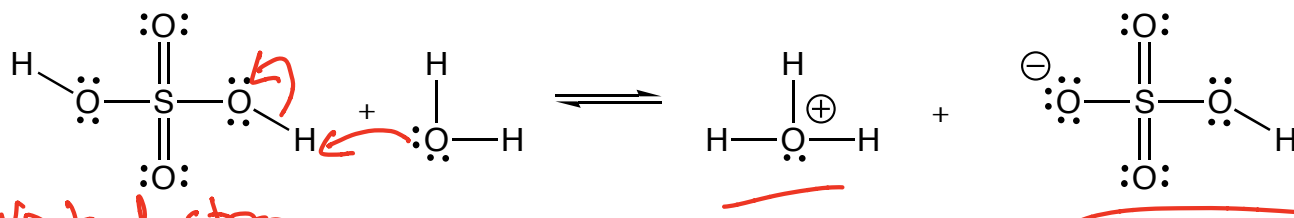
Mixed (time capsule) → Racemic Product

Example:

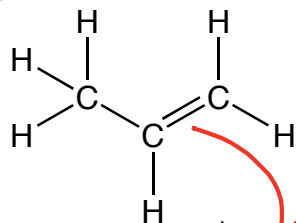


Which constitutional isomer is formed?

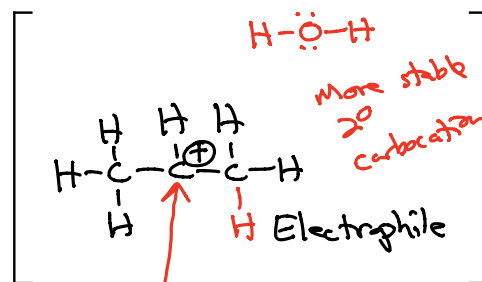
Acid-catalyzed Hydration of an Alkene



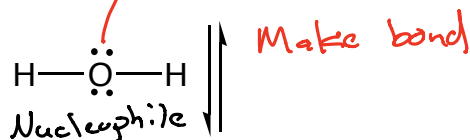
Wicked strong acid



Add a proton

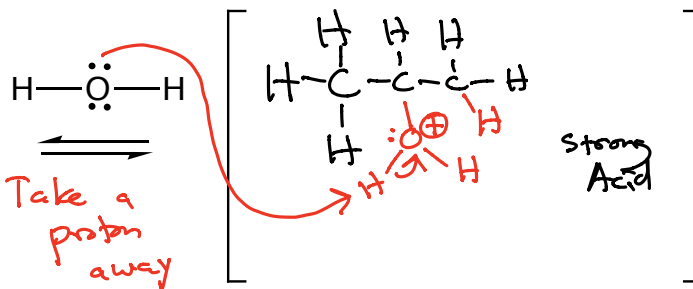
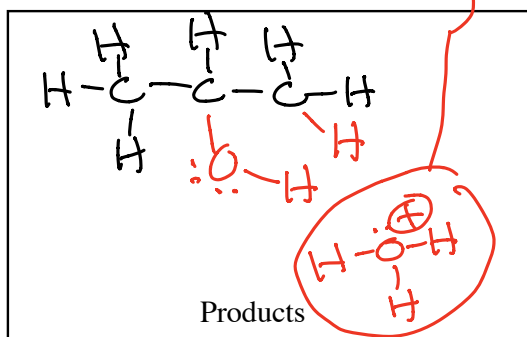


Strong Acid



Make bond

Catalytic in acid → (acid is NOT consumed in reaction)



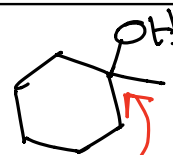
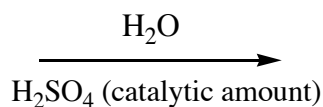
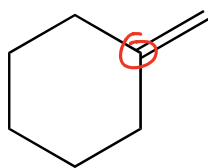
Strong Acid

Summary: Proton adds to make a carbocation, water attacks to make a new bond, take a proton away to make product alcohol

Regiochemistry: Markovnikov's Rule

Stereochemistry: Mixed (time capsule)

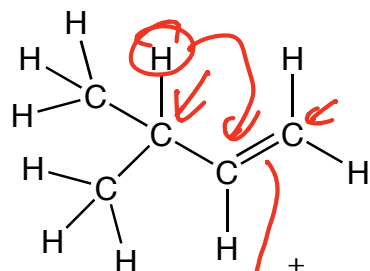
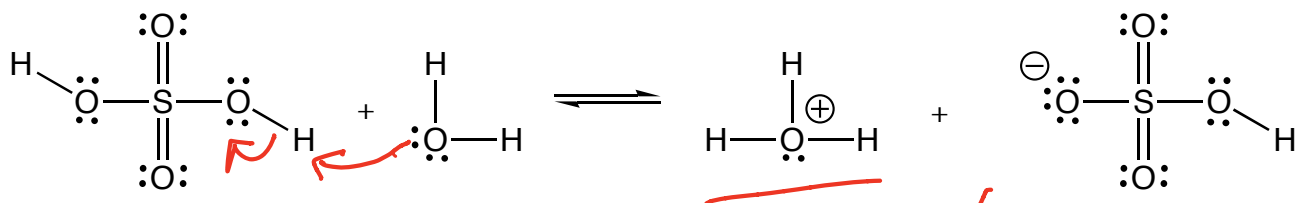
Example:



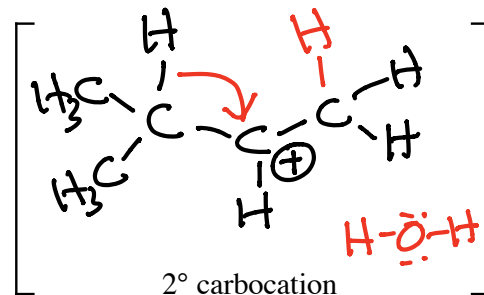
(Not chiral)

-OH on more substituted C atom → Markovnikov

Cation Rearrangement

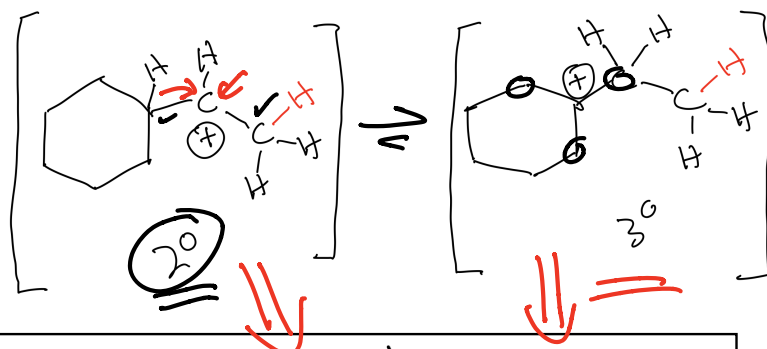
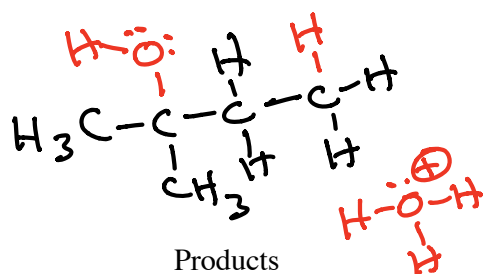
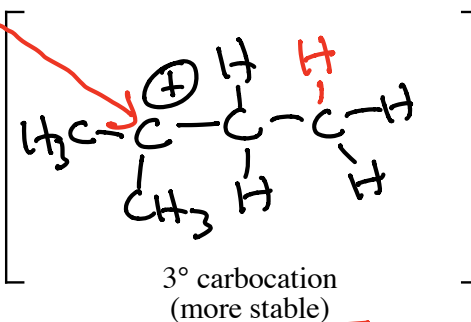
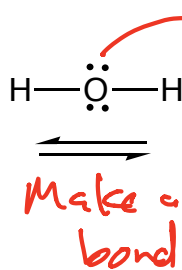
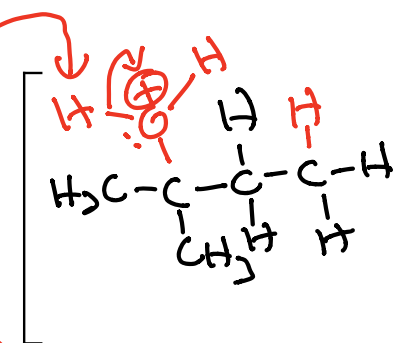


add a proton

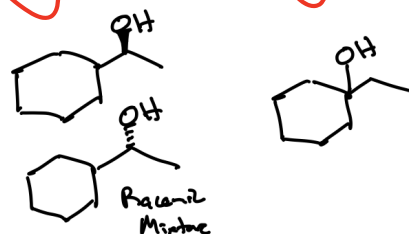
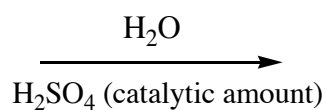
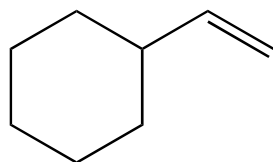


products

Rearrangement

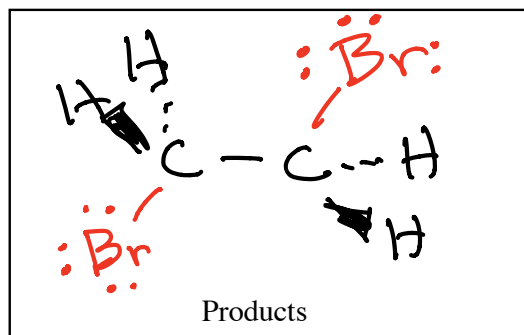
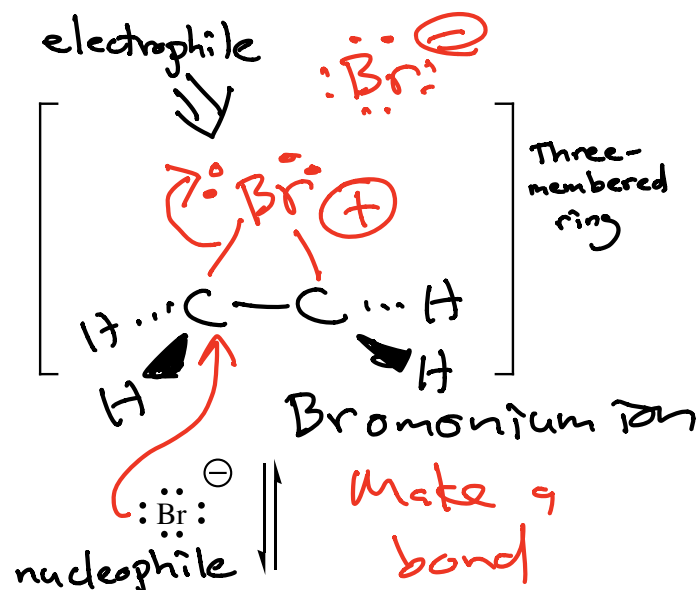
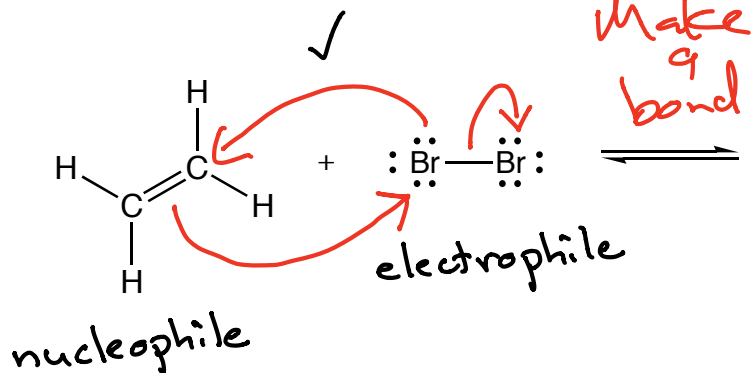


Example:



Alkene Halogenation

$\text{Cl}_2, \text{Br}_2, \text{I}_2$ (not F_2)



Called "anti" addition stereochemistry

The top face of the intermediate is "blocked" by the Br atom, so the Br^- nucleophile must react from the bottom face only.

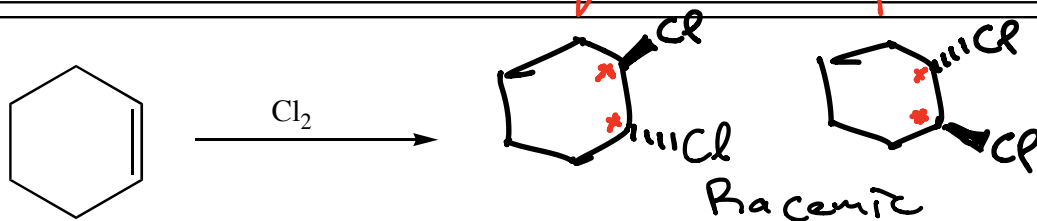
\Rightarrow gives only trans products NEVER CIS

Summary: Alkenes react with X_2 to give a three-membered ring (halonium ion) intermediate, then a new bond is made by X^- from behind the C-X bond (anti stereochemistry)

Regiochemistry: Not applicable \rightarrow Br on both C atoms

Stereochemistry: Anti stereochemistry \rightarrow trans products

Example:



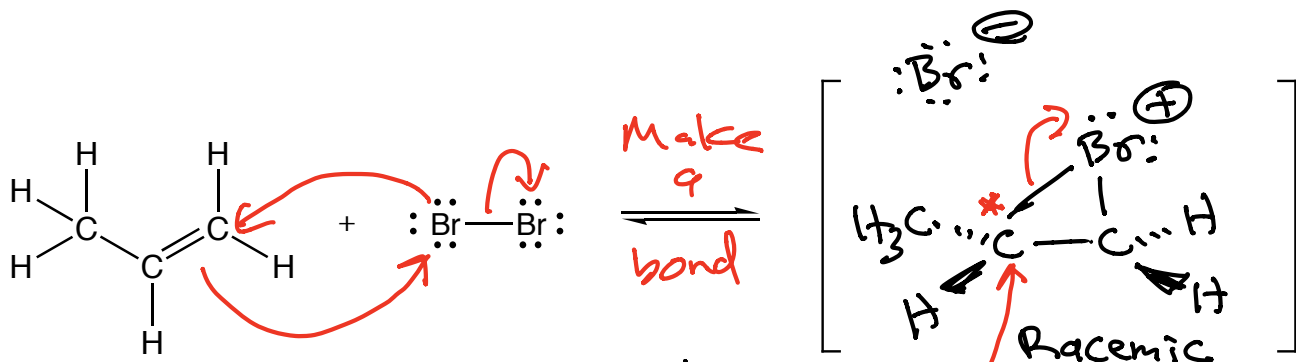
trans products only

Add X_2 to an alkene in the presence of

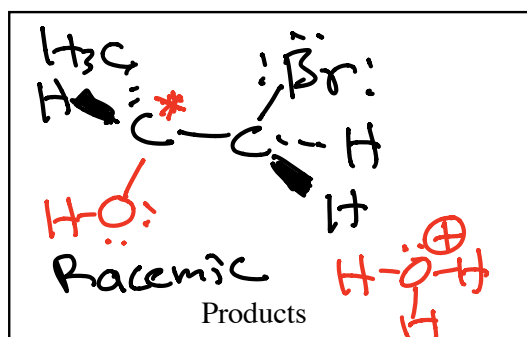
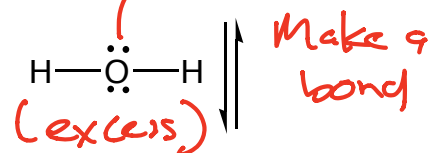
Alkene Hydrohalogenation

excess

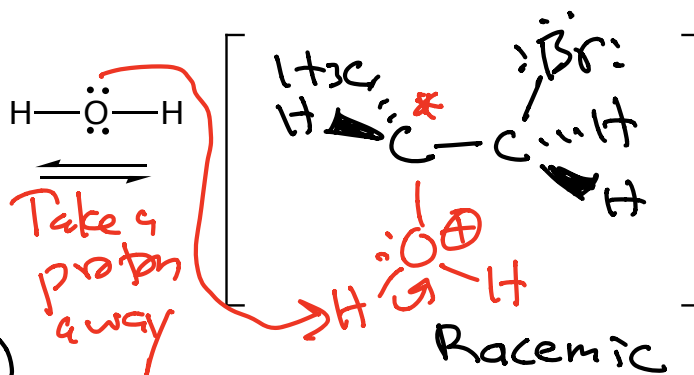
H_2O



Attack by H_2O happens at the more substituted C atom
(see contributing structures above)



(pH drops during rxn)



Summary: Alkene reacts with X_2 to give three-membered ring halonium ion intermediate, H_2O makes a bond with the more substituted C atom, and we take a proton away to give product

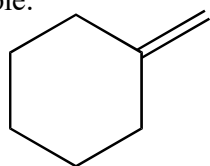
Regiochemistry:

Markovnikov OH on more substituted C

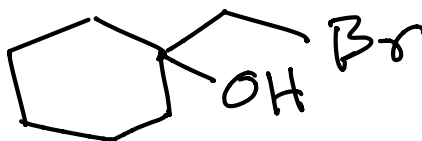
Stereochemistry:

Anti stereochemistry

Example:

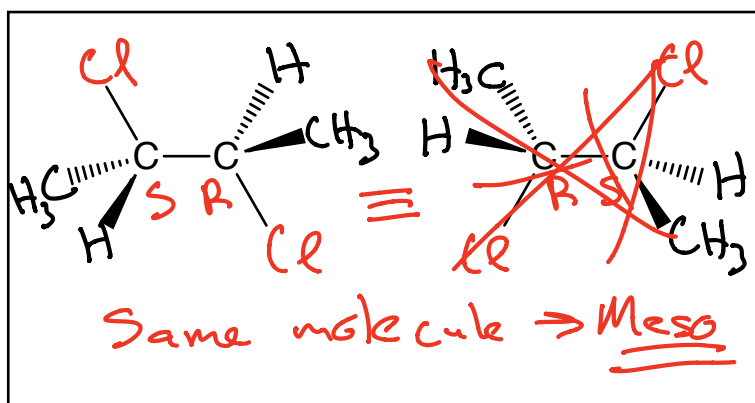
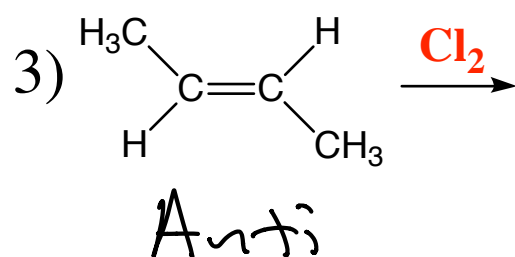
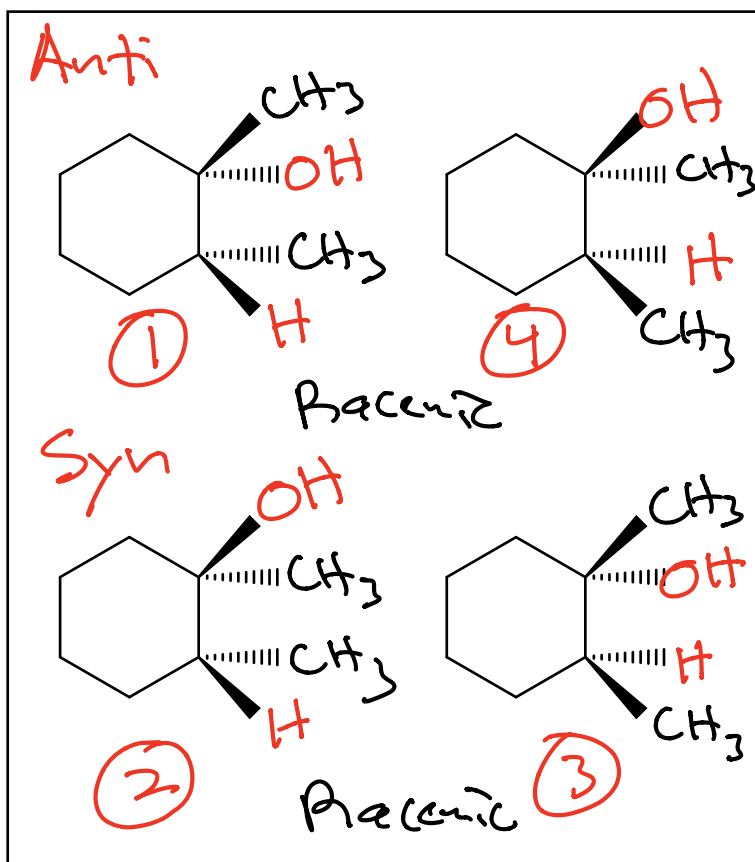
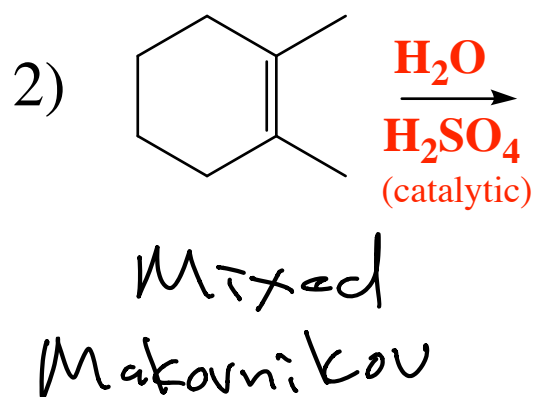
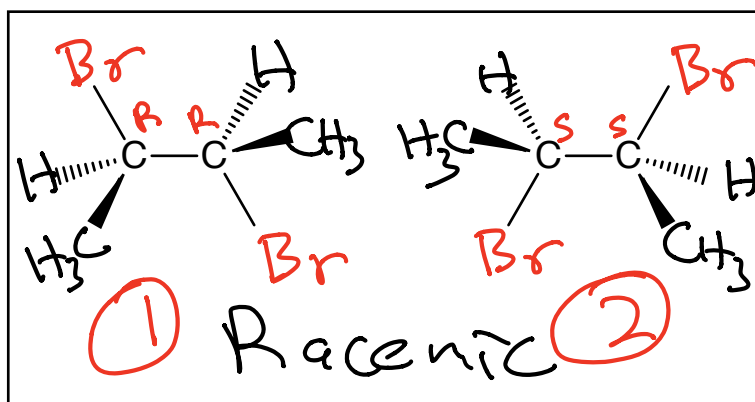
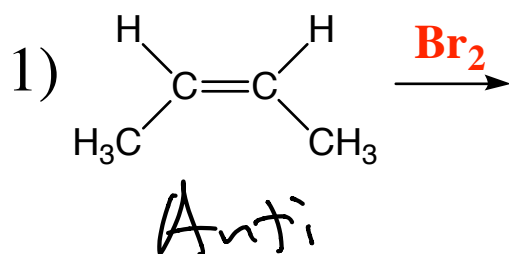


Br_2 / H_2O

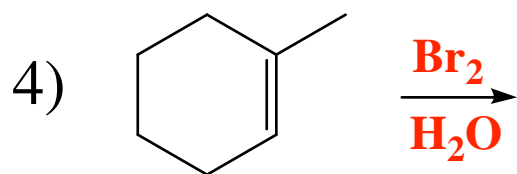


Halohydrin product

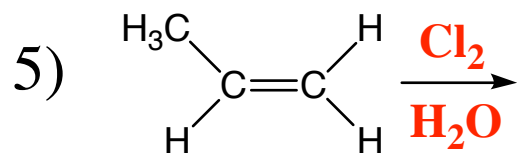
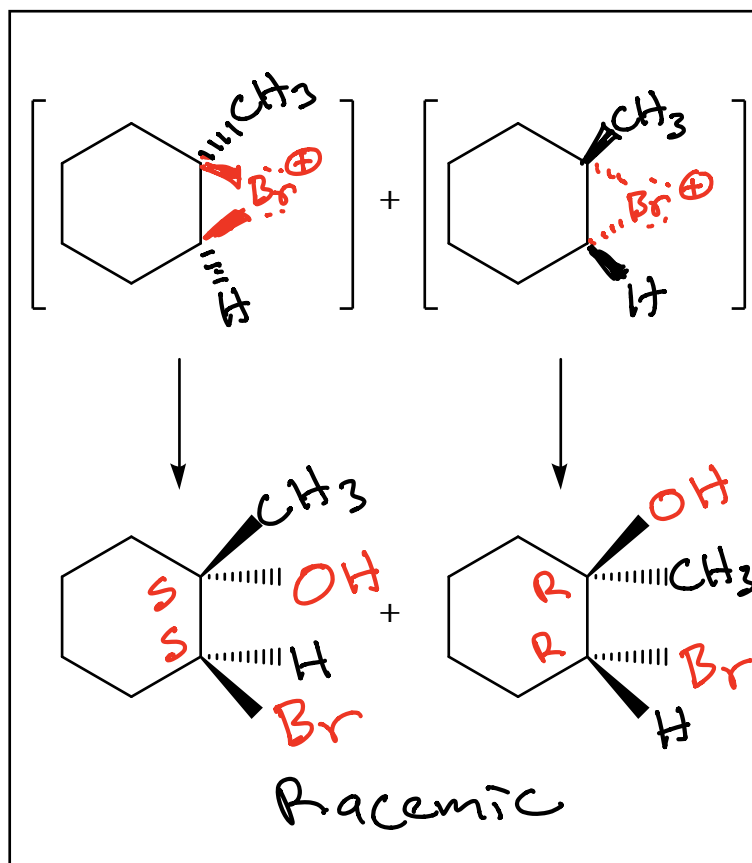
Examples



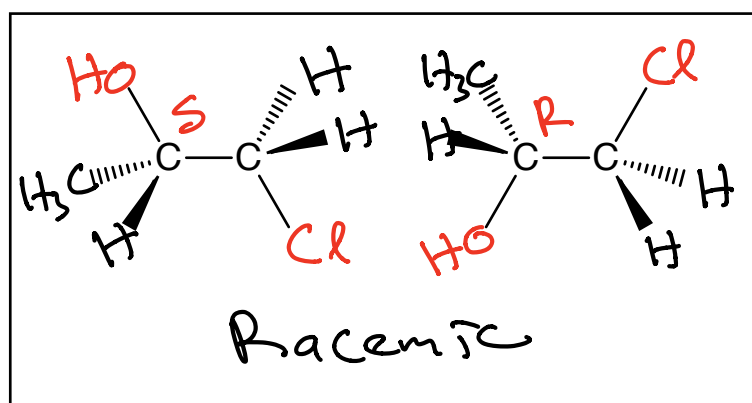
More Examples

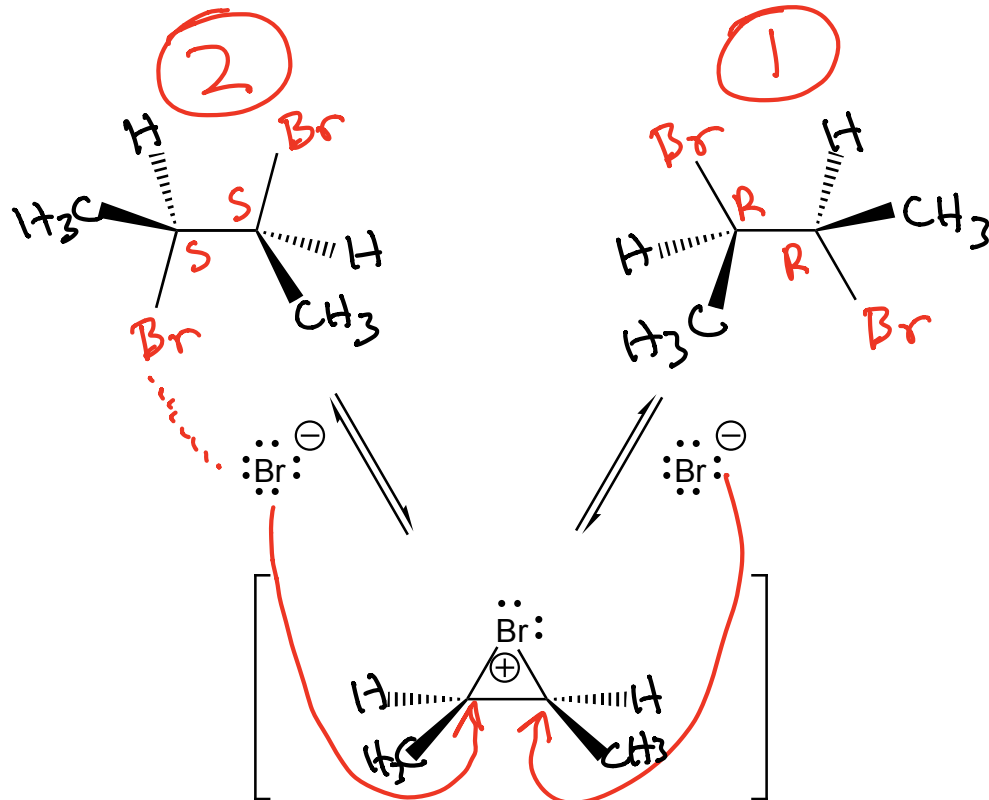


Anti
Markovnikov

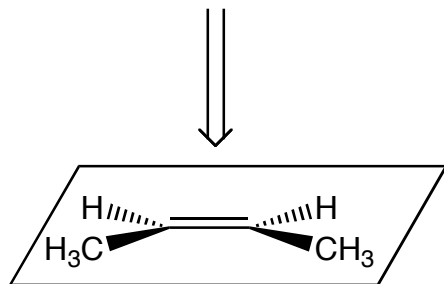


Anti
Markovnikov

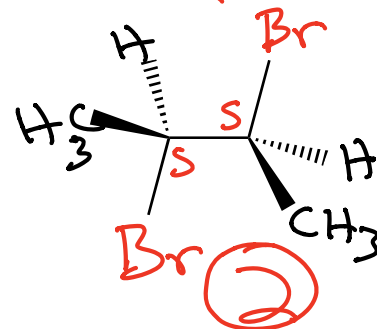
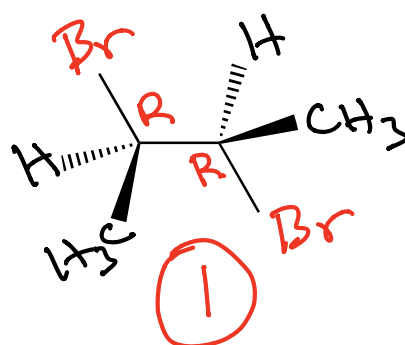
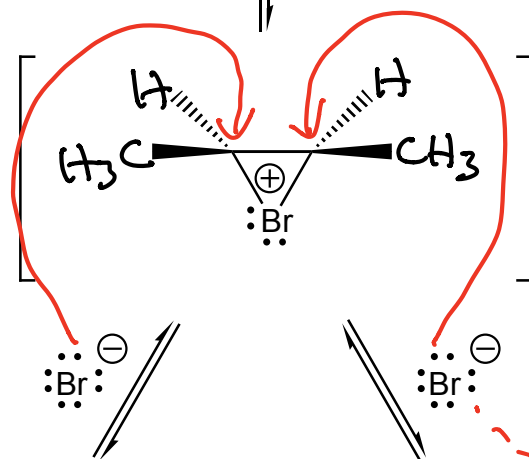
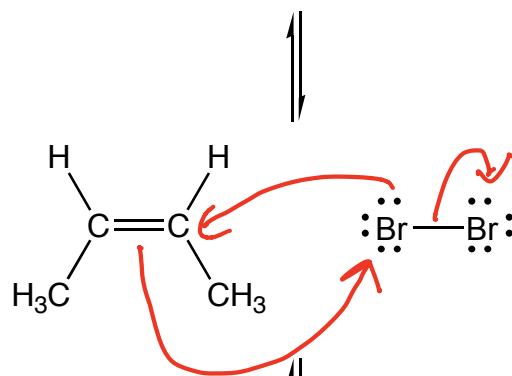




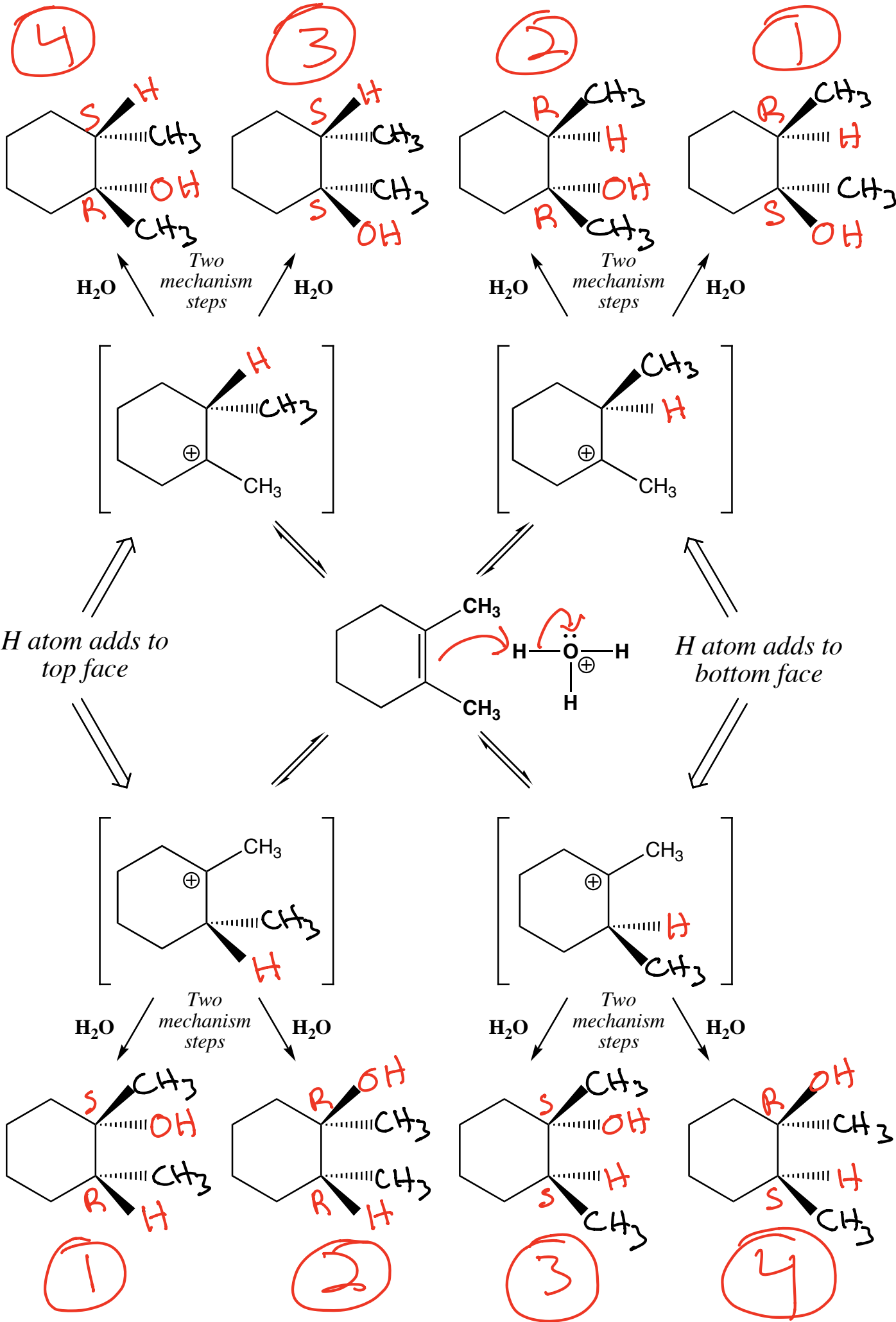
Attack from the top face



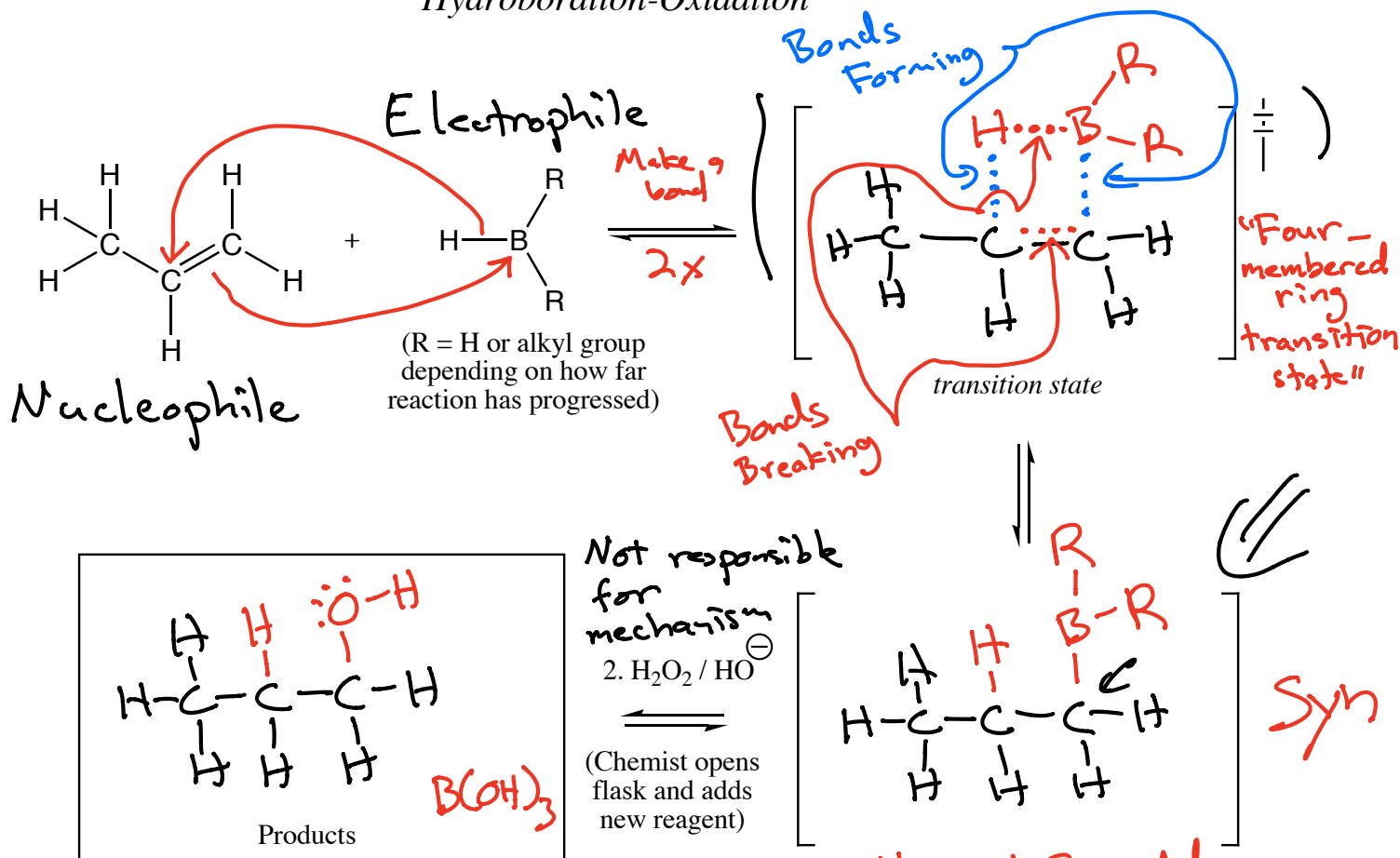
Attack from the bottom face



Anti
Stereospecificity
Only



Hydroboration-Oxidation



H → more substituted carbon

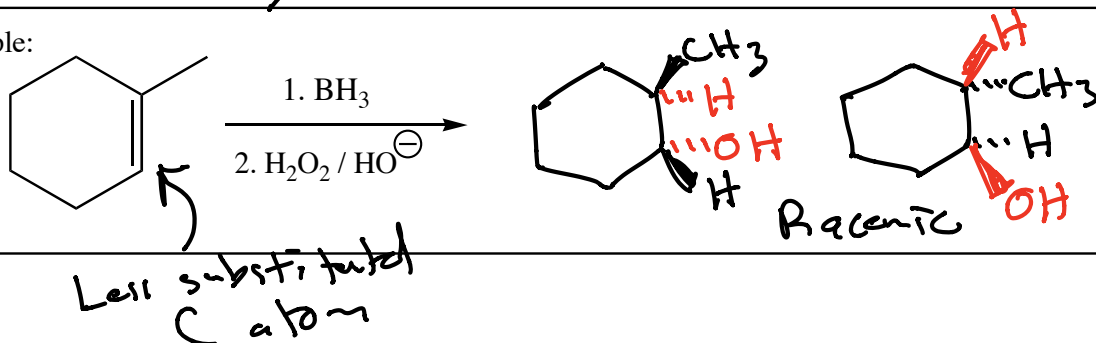
HO → less substituted carbon

Summary: The π bond of the alkene attacks the Lewis acid B atom at the same time a new bond forms between C and H, 4-membered ring transition state

Regiochemistry: non-Markovnikov (opposite to what Markovnikov rule)

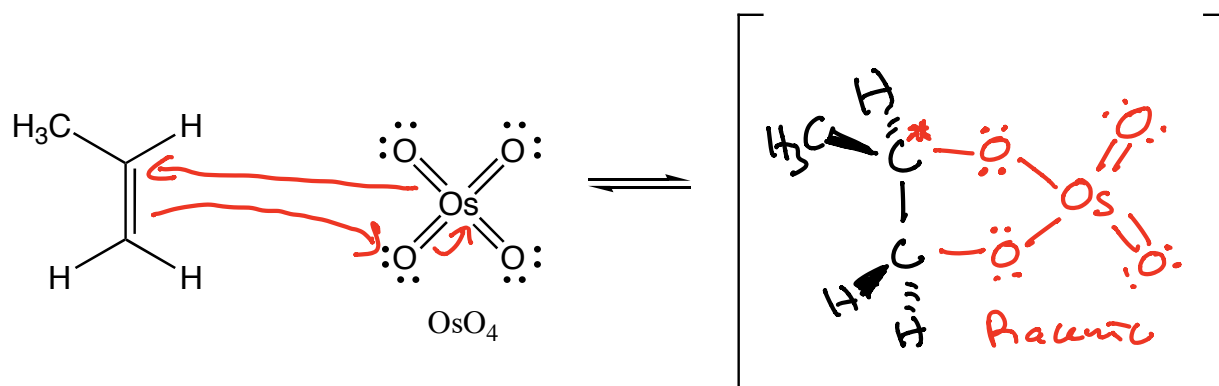
Stereochemistry: Syn

Example:

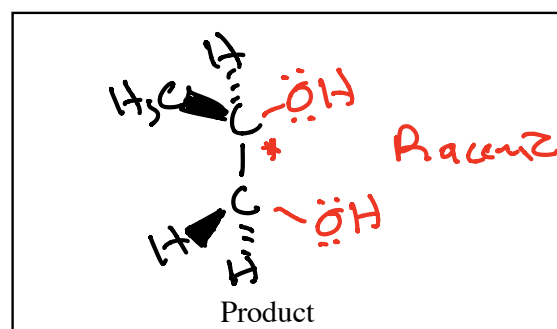


Ozzy Osbourne Reaction

OsO₄ Partial Mechanism



2. NaHSO₃ / H₂O
(Chemist opens up flask) \rightleftharpoons Not responsible for mechanism



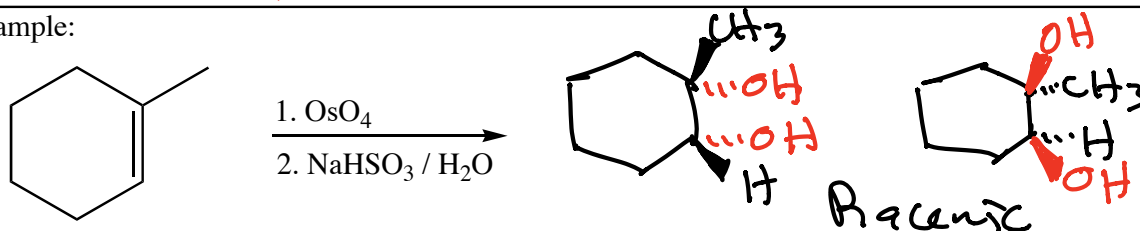
Summary:

Mechanism involves a cyclic osmate ester \rightarrow O atoms add to same face (syn)

Regiochemistry: N/A O atoms on both C atoms

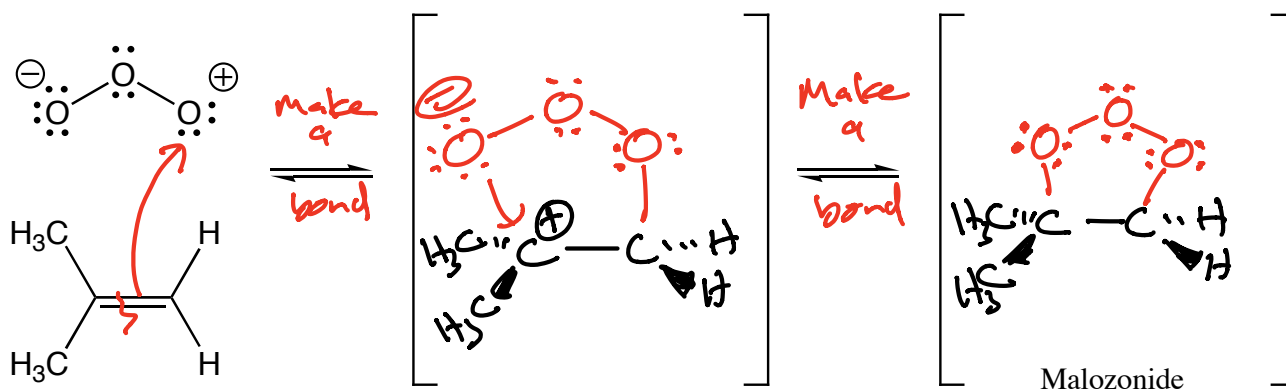
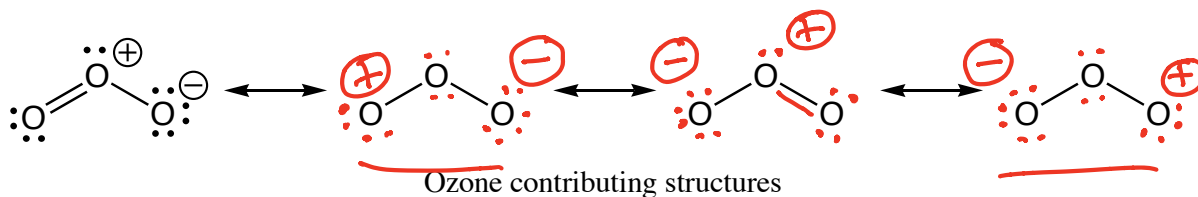
Stereochemistry: Syn

Example:

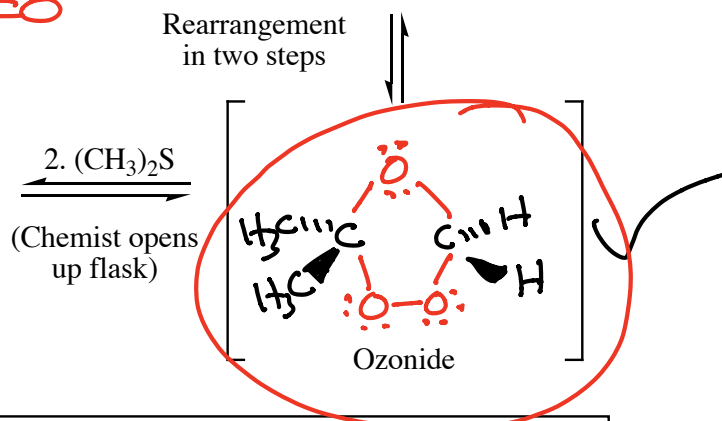
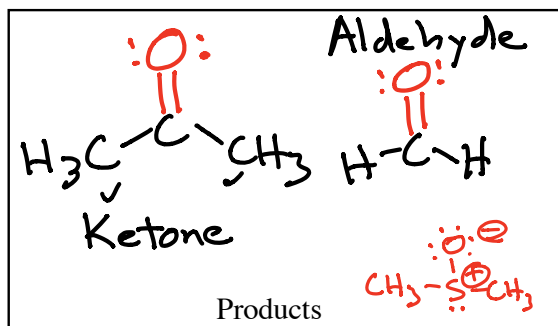


Breaks $C=C$!!!

Ozonolysis Partial Mechanism



Replaced $C=C$ with 2 $C=O$

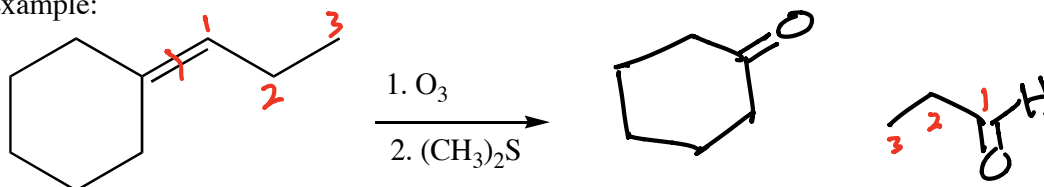


Summary: Reaction of an alkene with O_3 creates an ozonide intermediate that decomposes with the addition of $(CH_3)_2S \rightarrow$ Aldehydes Ketones

Regiochemistry: N/A

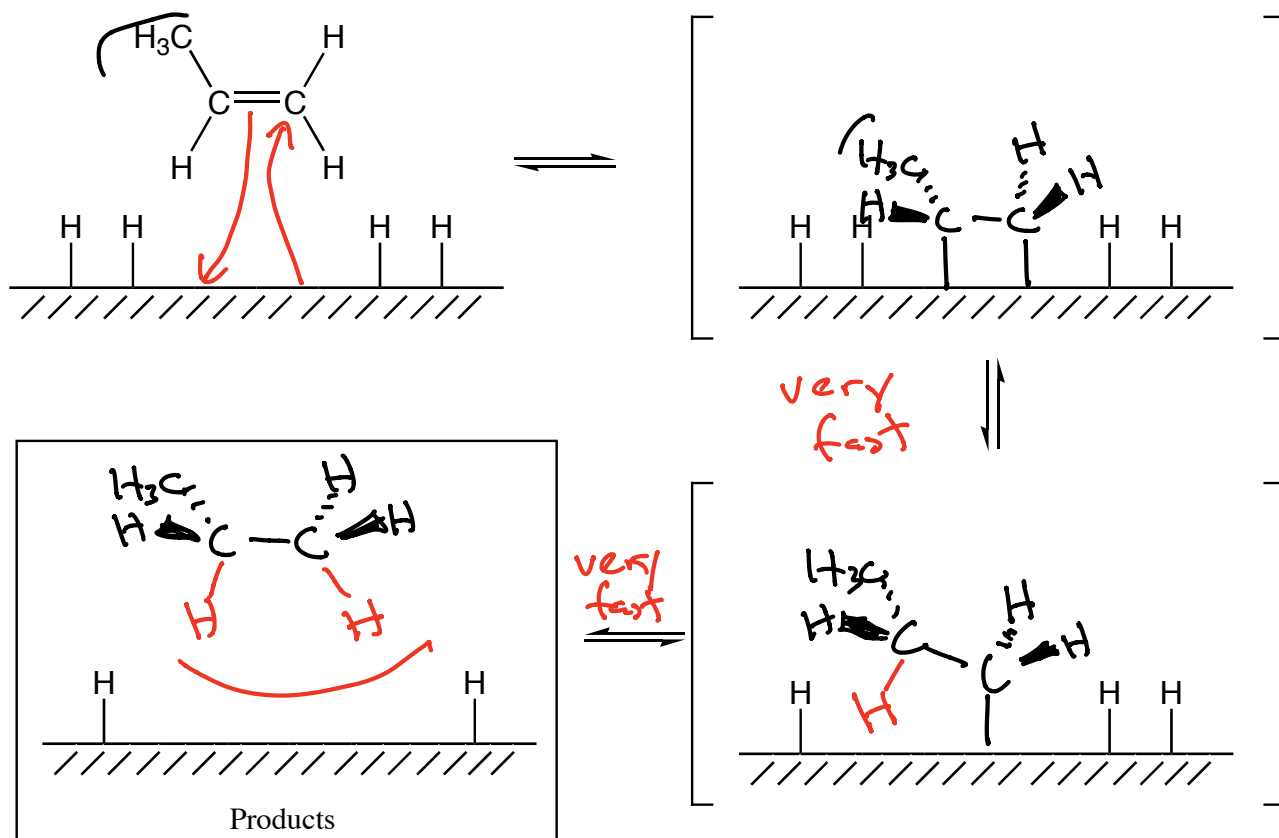
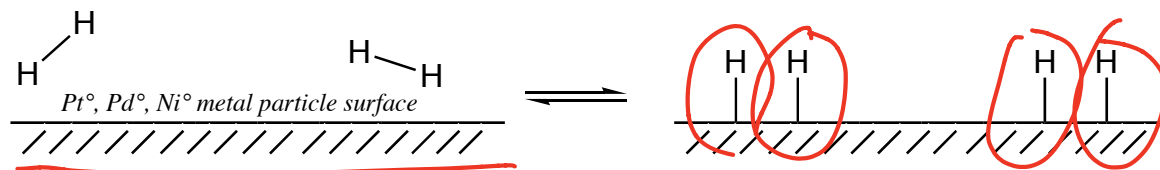
Stereochemistry: N/A

Example:



Converts alkenes to alkanes → overall reduction

Hydrogenation: H_2 with Pt^0 , Pd^0 , Ni^0

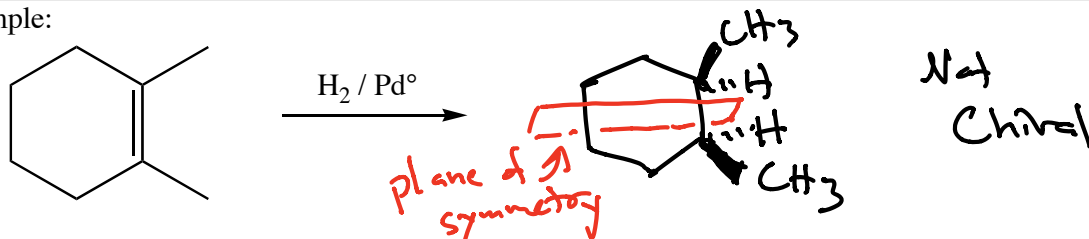


Summary: H_2 adsorbs onto the metal surface
 → Alkene adsorbs onto the metal surface
 → H atoms transfer to both C atoms → on the same face (before the C-C bond rotates)

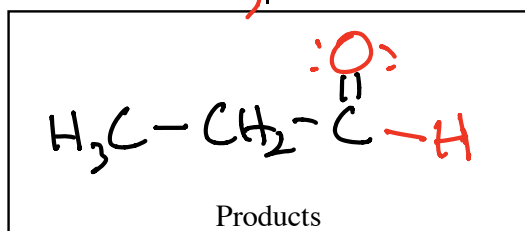
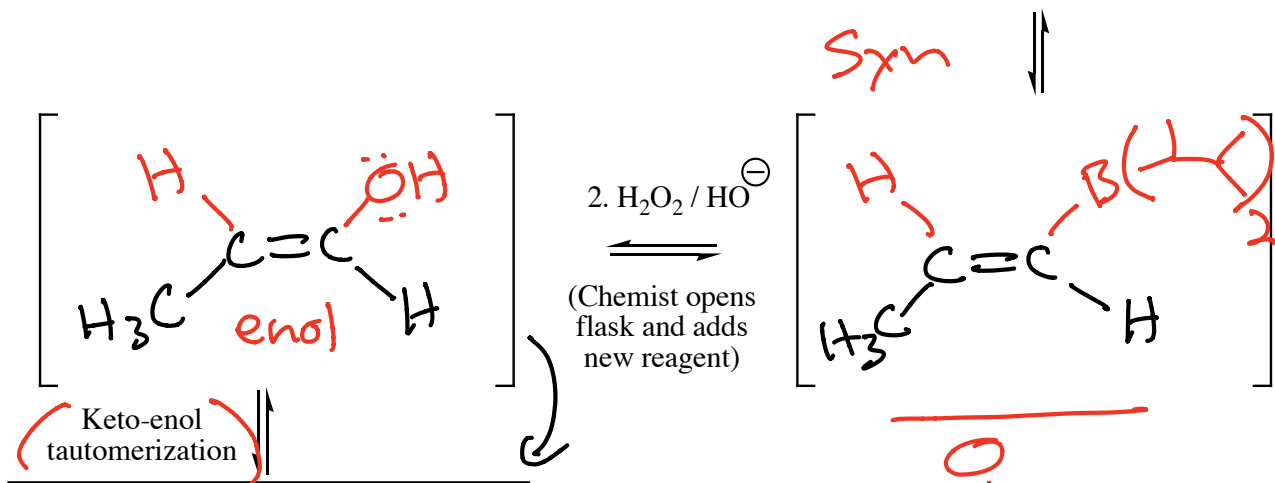
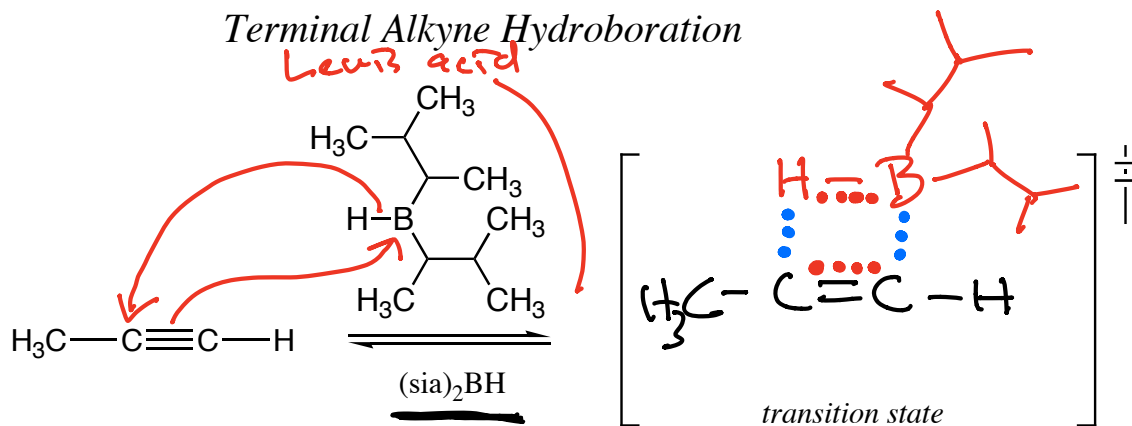
Regiochemistry: N/A

Stereochemistry: Syn addition

Example:



Terminal Alkyne Hydroboration



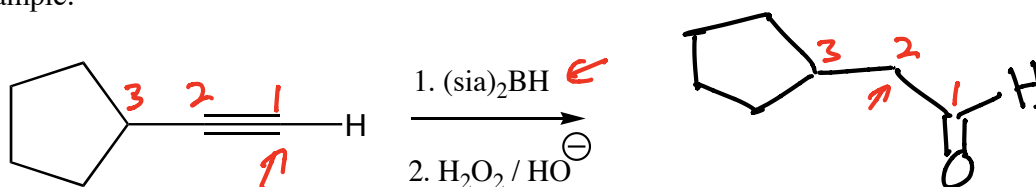
The C is on the C on the end

Summary: The $(\text{sia})_2\text{BH}$ reacts so the B atom is attached to the C atom on the end. Four-membered ring transition makes both bonds simultaneously. $\text{H}_2\text{O}_2 / \text{HO}^- \rightarrow$ makes an enol \rightarrow keto form

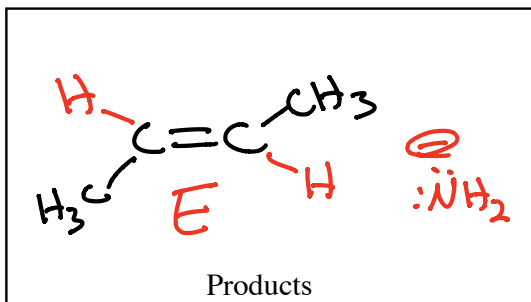
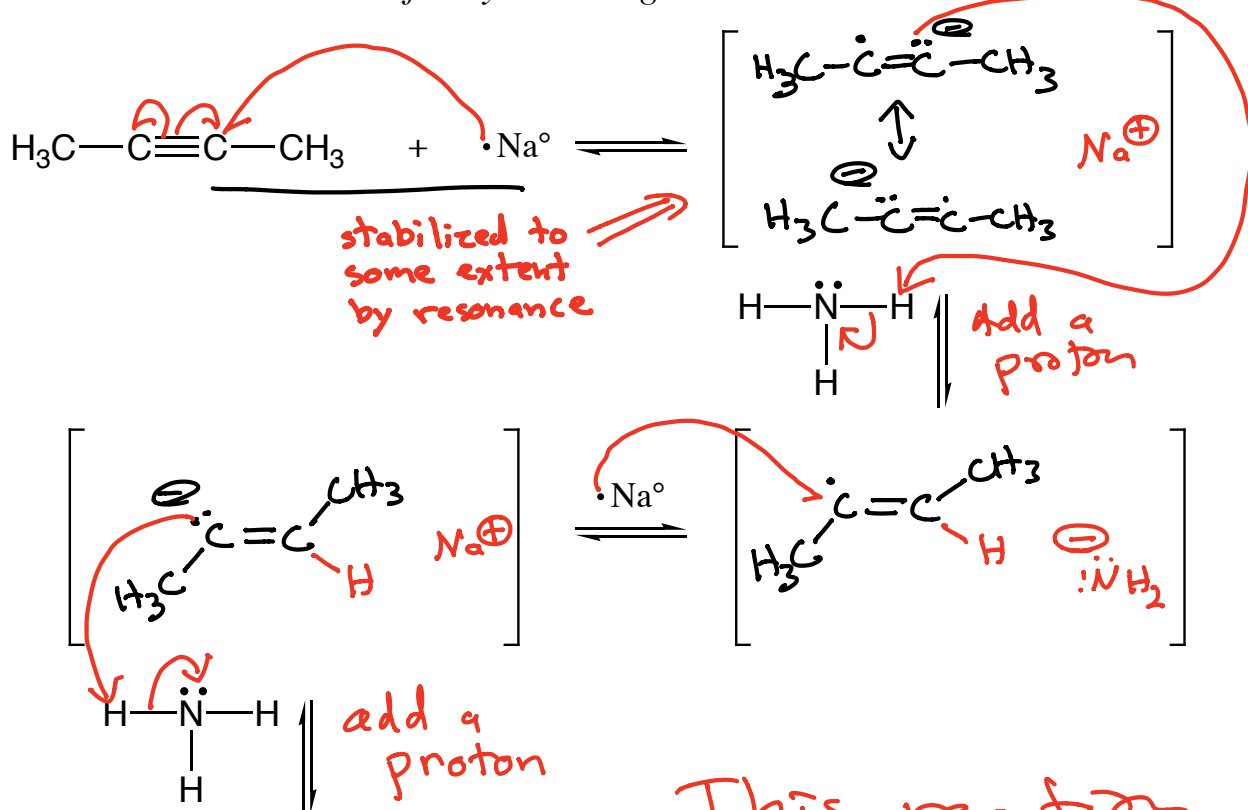
Regiochemistry: non-Markovnikov

Stereochemistry: N/A

Example:



Reduction of Alkynes Using Sodium and Ammonia



This reaction makes the more stable alkene \rightarrow E

Summary:

Alkynes are reduced to alkenes by Na° in NH_3 via two one electron reduction, each of which is followed by a proton transfer from $:\text{NH}_3$

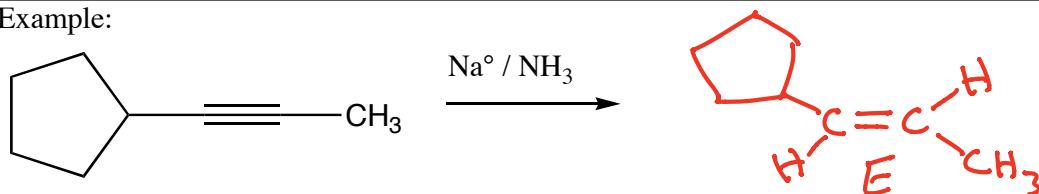
Regiochemistry:

—

Stereochemistry:

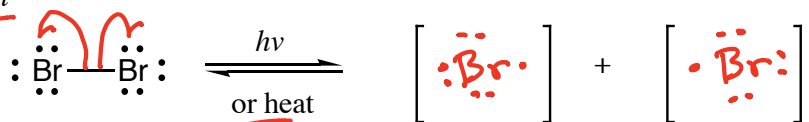
anti \rightarrow E (trans) products

Example:

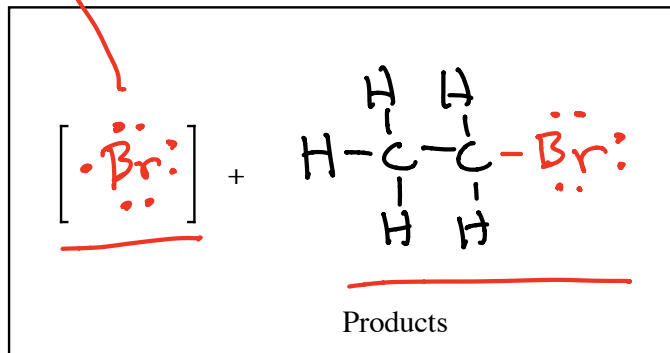
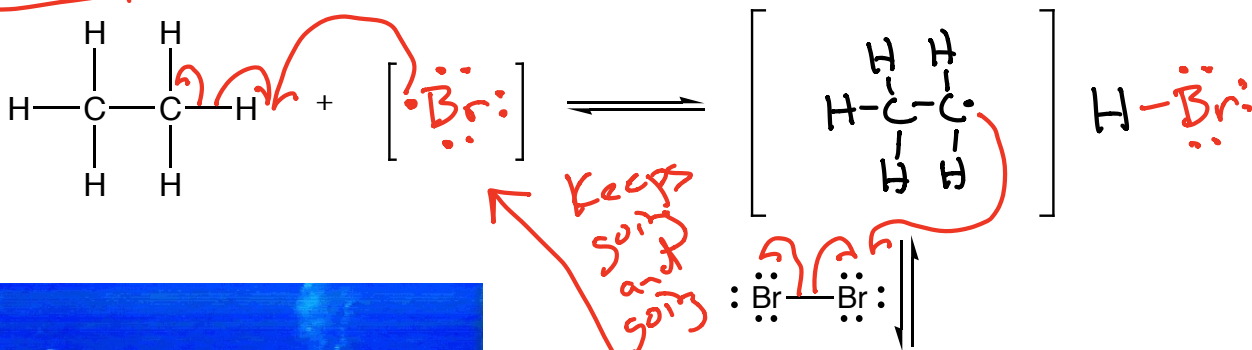


Alkane Free Radical Halogenation

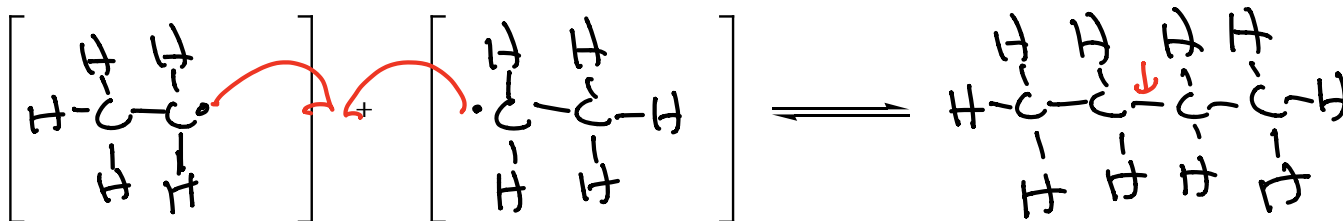
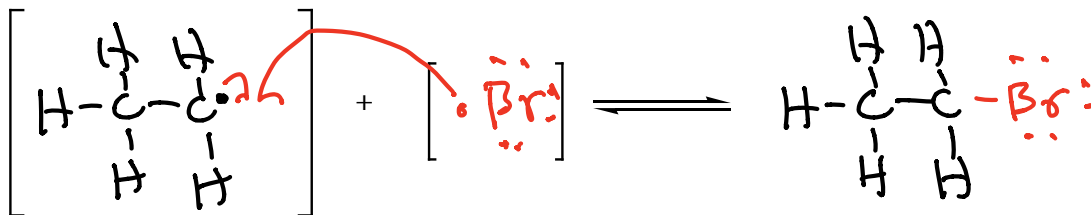
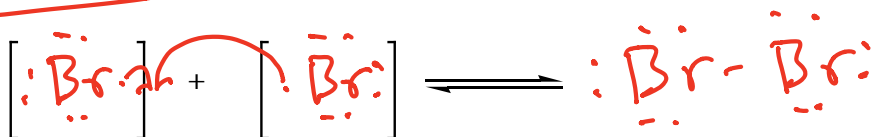
Initiation



Propagation

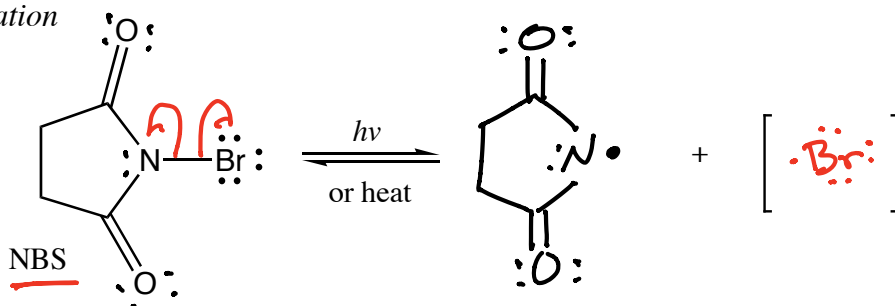


Termination



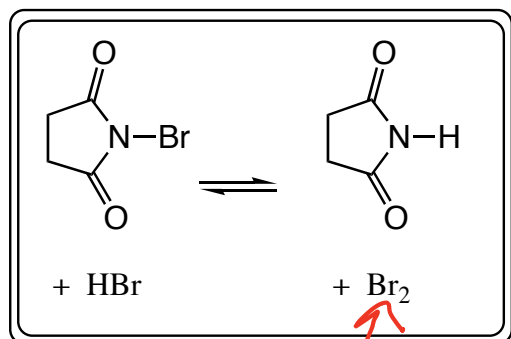
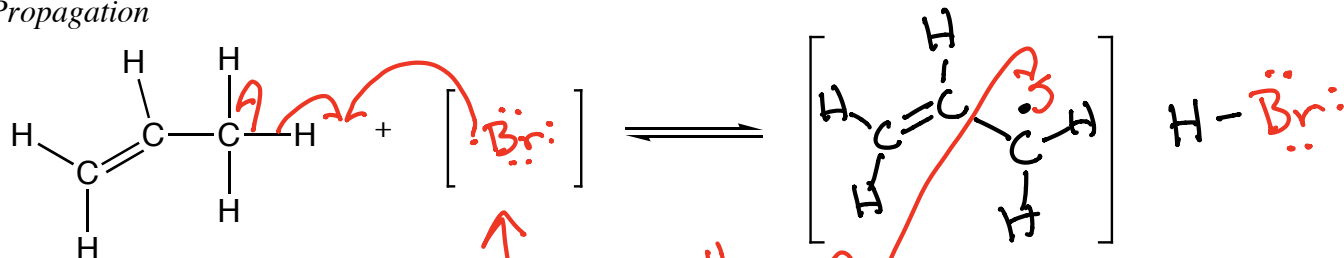
Allylic Halogenation

Initiation

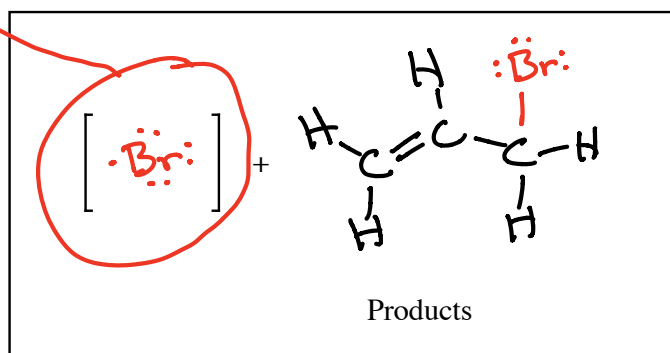


Allylic Radical

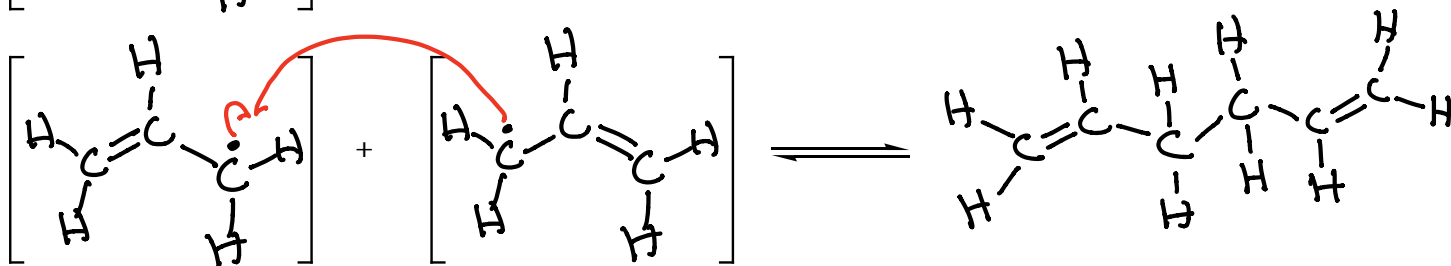
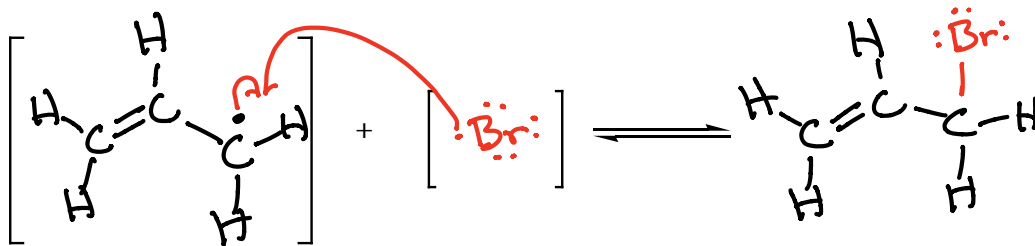
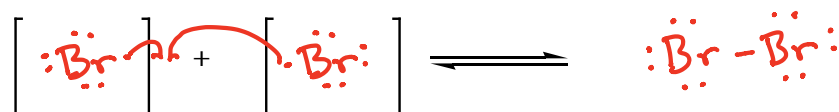
Propagation



only a small amount

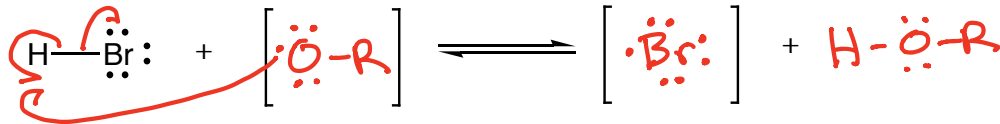
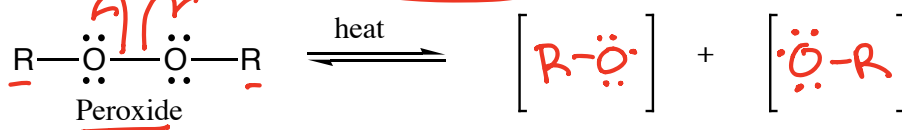


Termination

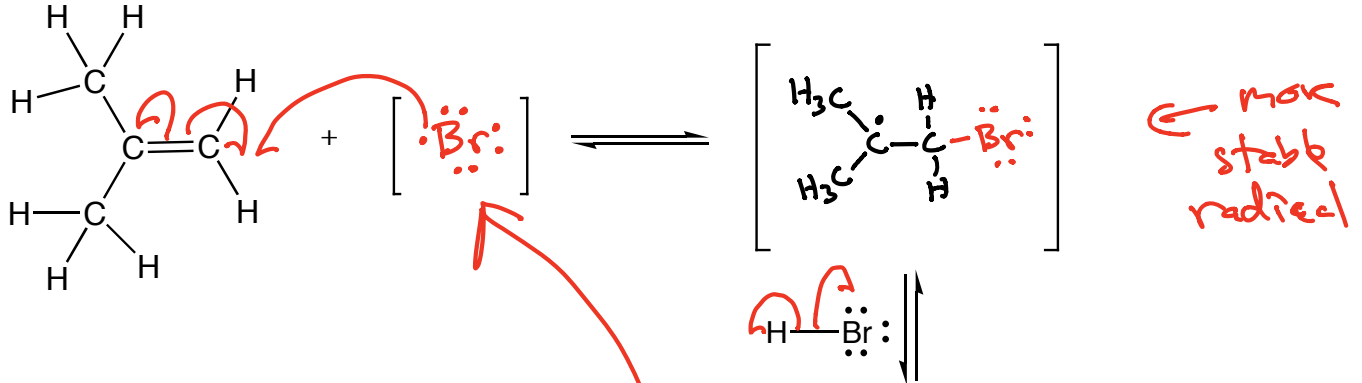


Non-Markovnikov Addition of HBr to an Alkene → in the presence of peroxides

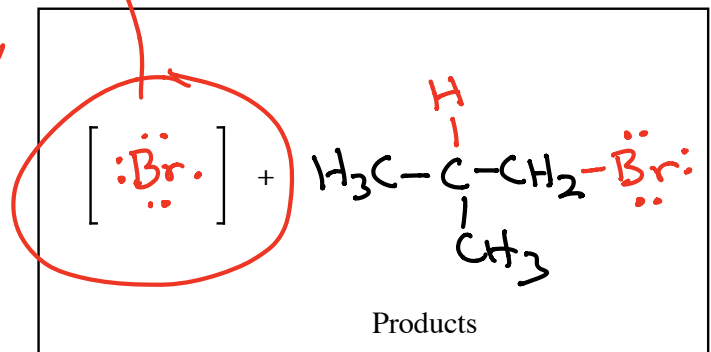
Initiation



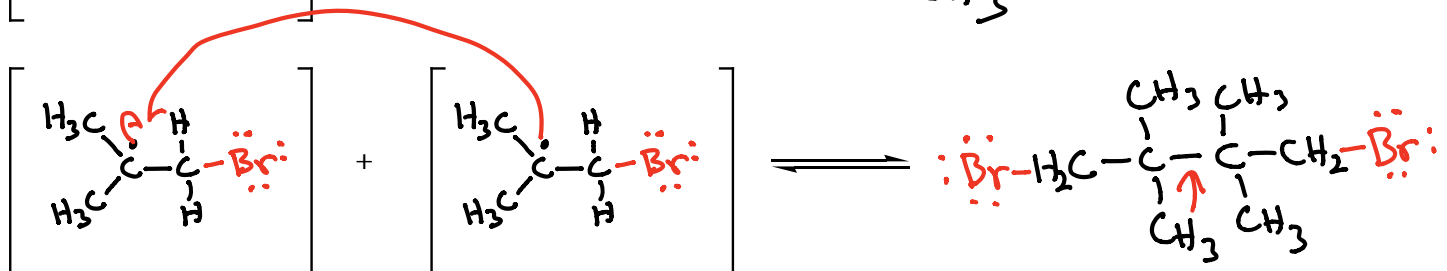
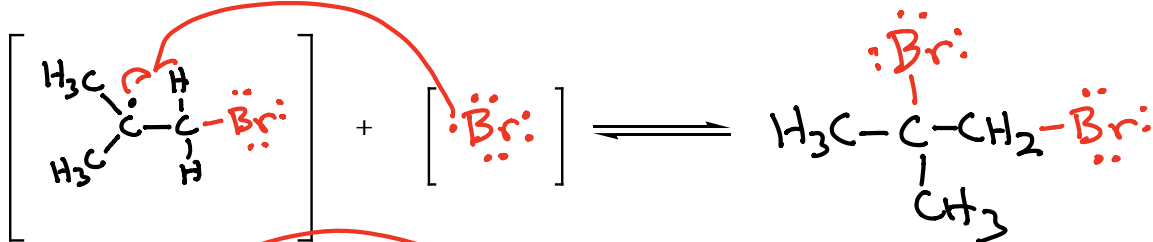
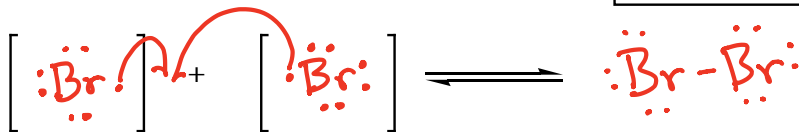
Propagation



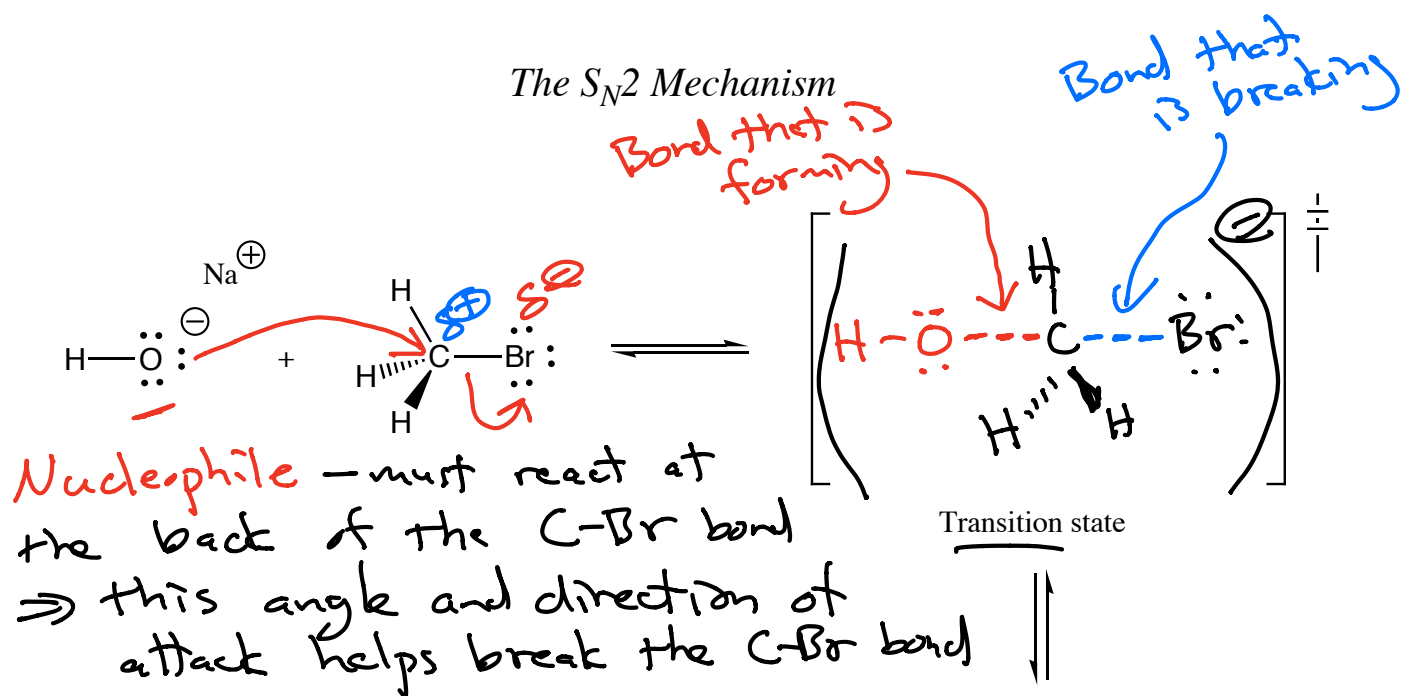
Non-Markovnikov



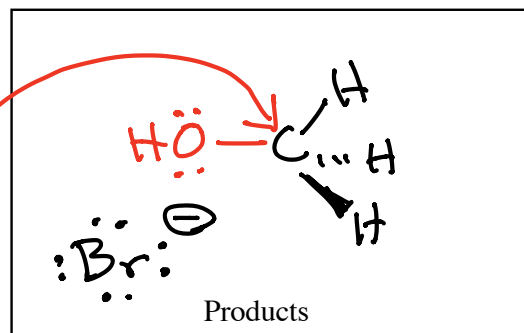
Termination



The S_N2 Mechanism



The configuration at C is inverted

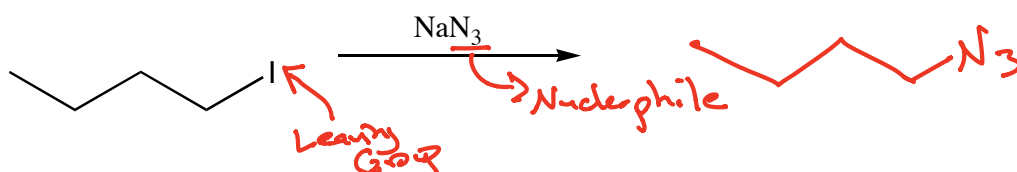


Summary: The nucleophile attacks by making a new bond to C from the back of the C-X bond just as the X leaves.

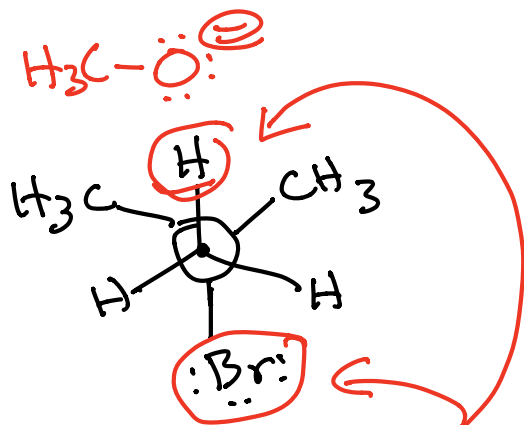
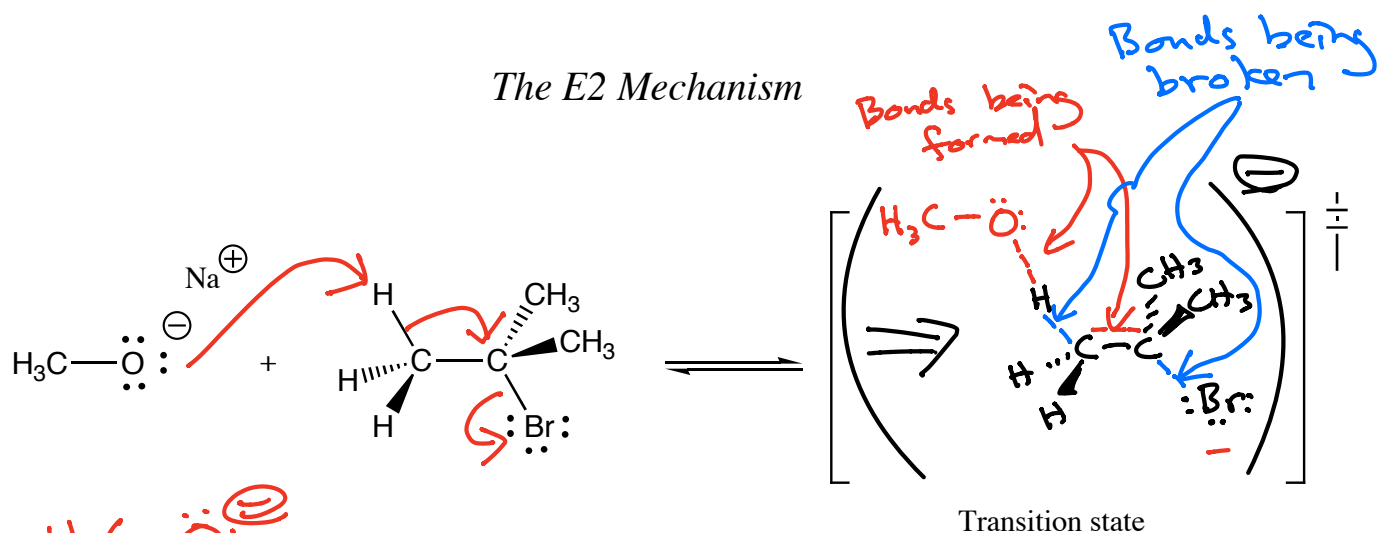
Regiochemistry: N/A

Stereochemistry: **INVERSION** at site of reaction

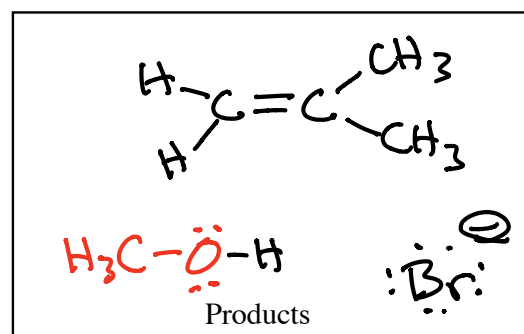
Example:



The E2 Mechanism



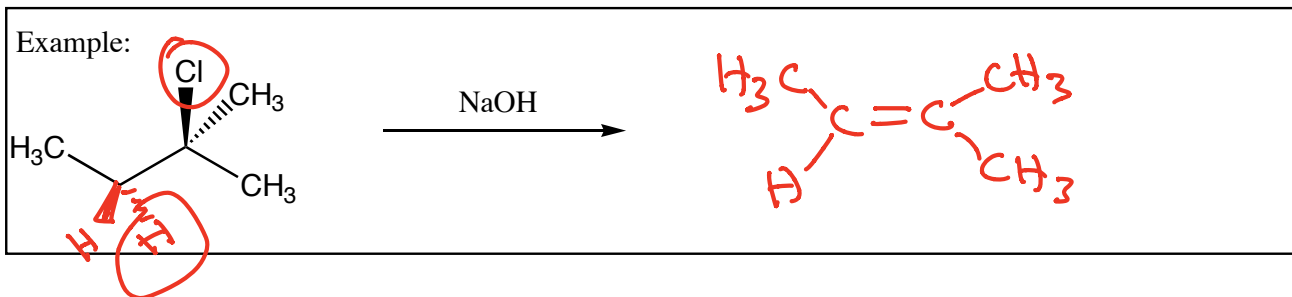
The H that is leaving and the Br must be anti-periplanar



Summary: Base removes an H atom as a pi bond forms and the Br atom leaves
 \rightarrow The H and Br must be anti-periplanar

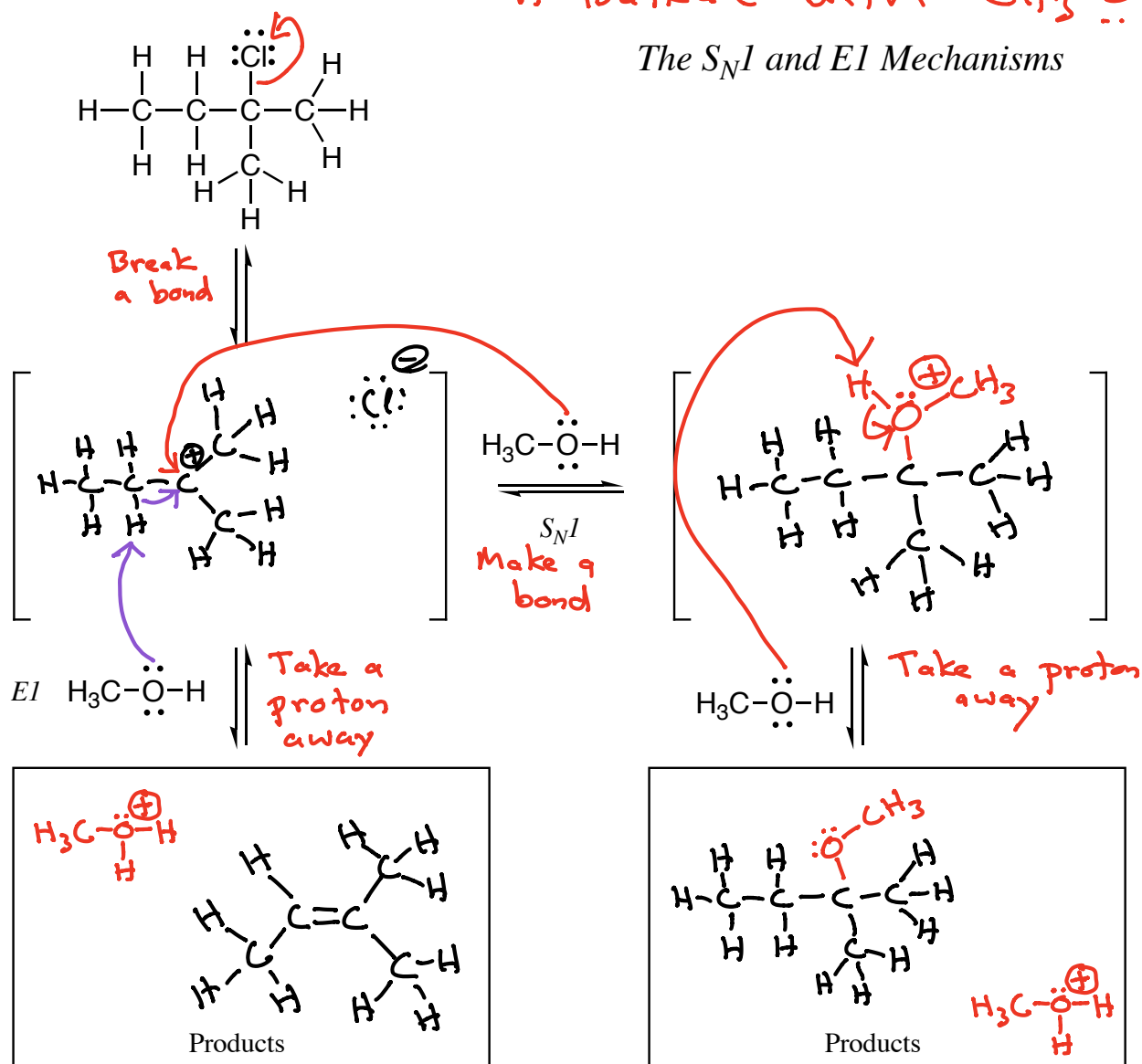
Regiochemistry: Zaitsev's Rule \rightarrow most stable alkene product

Stereochemistry: Determined by anti-periplanar transition state



Haloalkane with $\text{CH}_3\ddot{\text{O}}\text{H}$

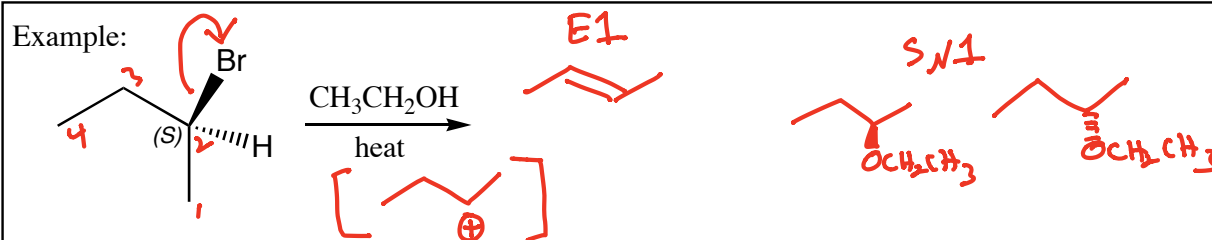
The $\text{S}_{\text{N}}1$ and $\text{E}1$ Mechanisms



Summary: For sterically hindered haloalkanes, the $\text{C}-\text{X}$ bond breaks to give a carbocation intermediate that either reacts as an electrophile ($\text{S}_{\text{N}}1$) or has a proton taken away ($\text{E}1$).

Regiochemistry: $\text{E}1 \rightarrow$ Zaitsev's Rule

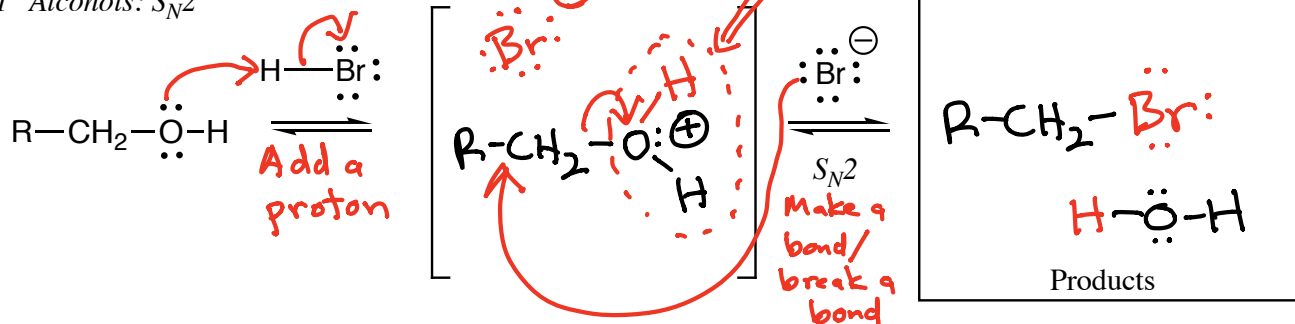
Stereochemistry: $\text{S}_{\text{N}}1 \rightarrow$ Scrambled \rightarrow not quite 1:1 exactly



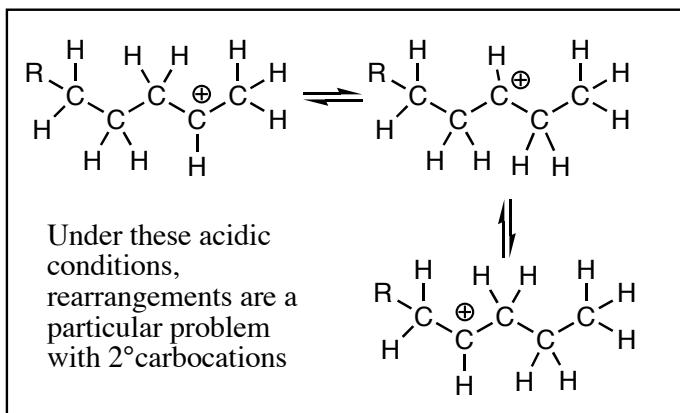
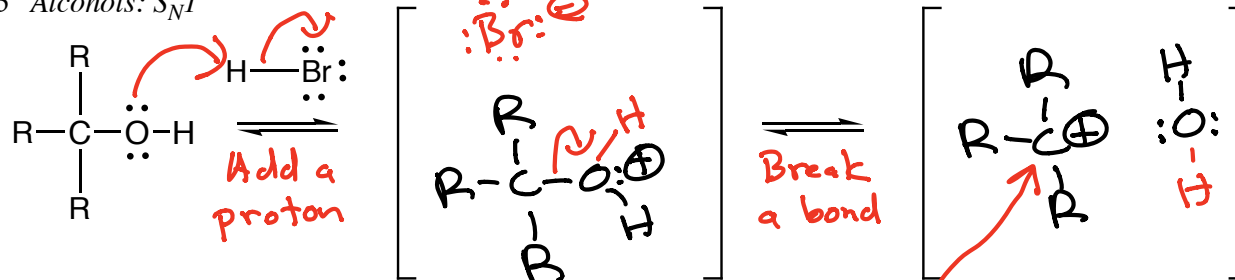
$X = \text{Cl}, \text{Br}, \text{I}$

Alcohols + H-X Good leaving group

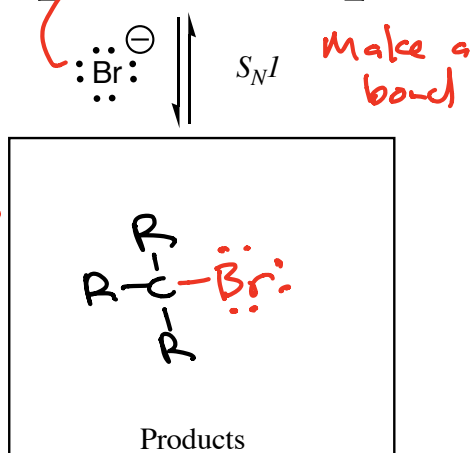
1° Alcohols: $\text{S}_{\text{N}}2$



2°/3° Alcohols: $\text{S}_{\text{N}}1$



Note → The highly acidic nature of this reaction prevents any E1 before the $\text{S}_{\text{N}}1$ is finished

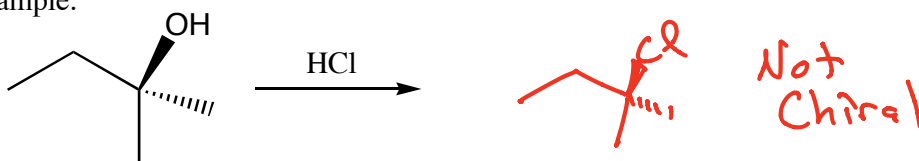


Summary: Reaction of primary alcohols $\rightarrow \text{S}_{\text{N}}2$
 Reaction of secondary/tertiary alcohols $\rightarrow \text{S}_{\text{N}}1$
 The $-\text{OH}$ group is converted to a good leaving group by being protonated, followed by $\text{S}_{\text{N}}2$ or $\text{S}_{\text{N}}1$ substitution

Regiochemistry: N/A

Stereochemistry: Chiral tertiary alcohols give scrambled products $\leftarrow \text{S}_{\text{N}}1$

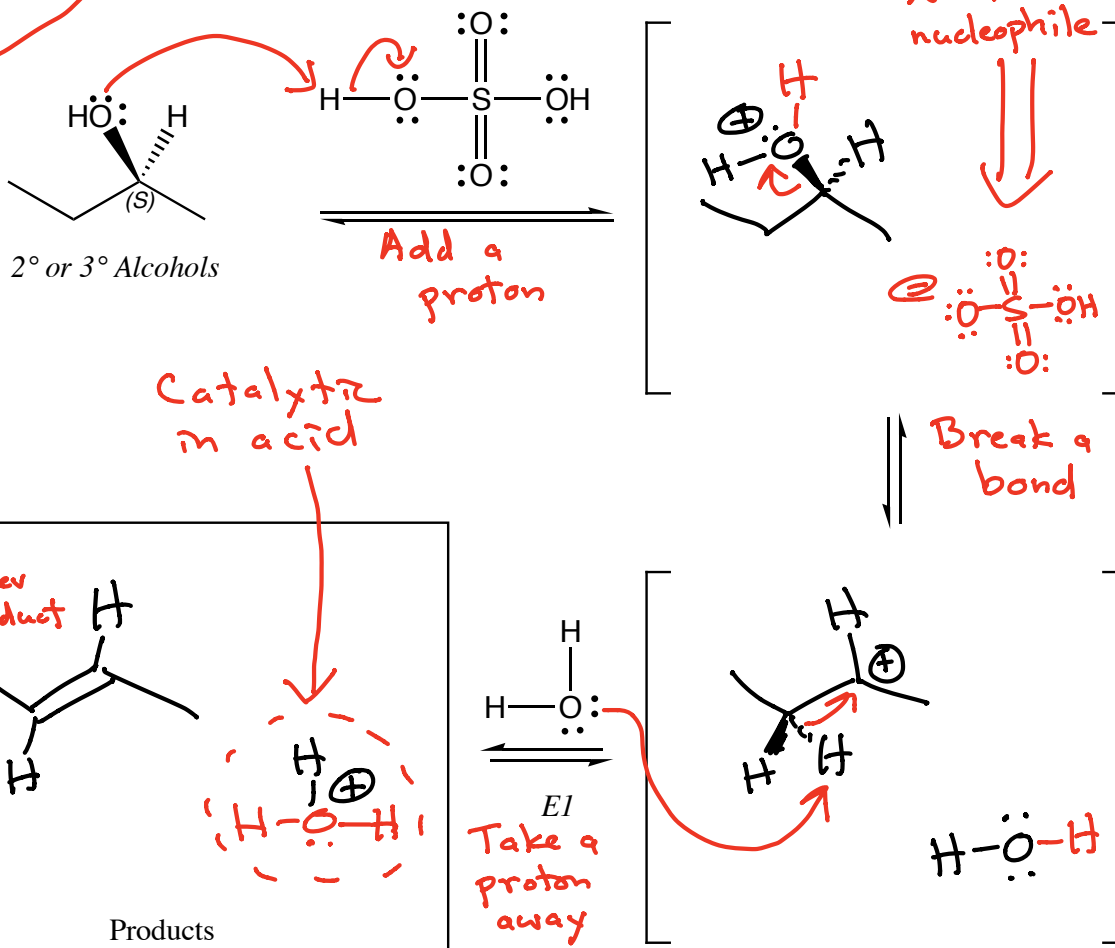
Example:



1° alcohols
react via
E2

2° or 3° Alcohol Dehydration

E1

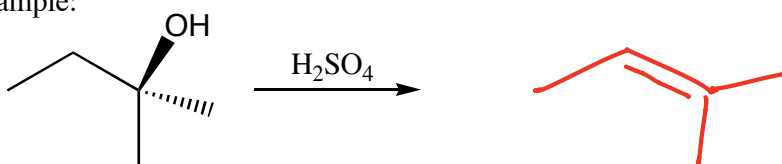


Summary: The OH group is protonated in strong acid to make a good leaving group, water, which breaks a bond to give a carbocation that has a proton taken away to give the product alkene

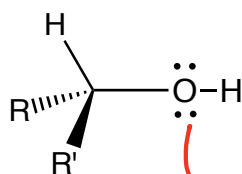
Regiochemistry: Zaitsev's Rule

Stereochemistry: N/A

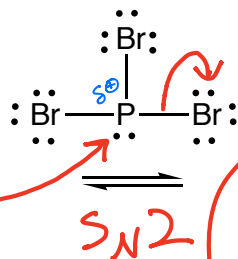
Example:



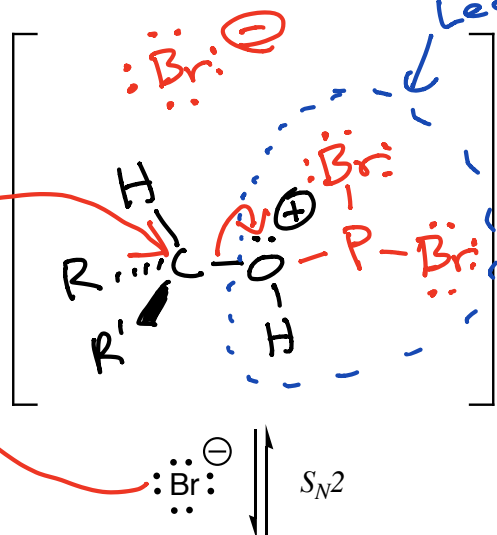
Alcohols + PBr_3 or $(SOCl_2)$



1° or 2° Alcohols

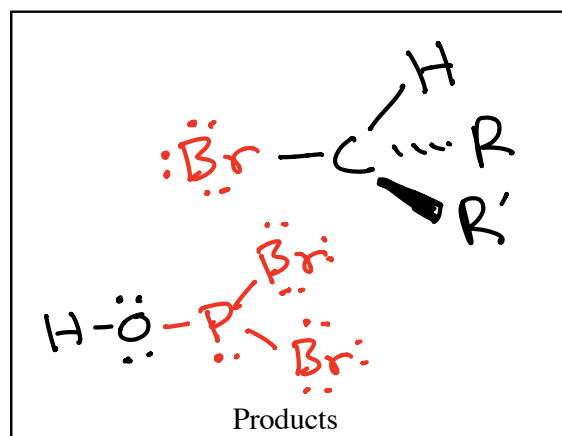


S_N2



Good Leaving Group

S_N2



Does NOT work with 3° alcohols

★ There is an analogous reaction with $SOCl_2$ that converts alcohols into chloroalkanes

Summary: 1° or 2° alcohols react with PBr_3 via an S_N2 reaction on the P atom to create a good leaving group that undergoes an S_N2 reaction with Br^- at the C atom

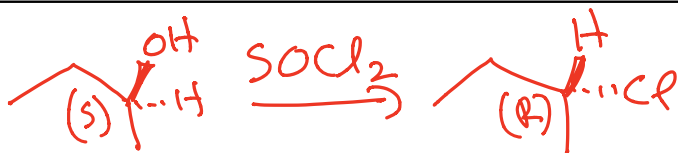
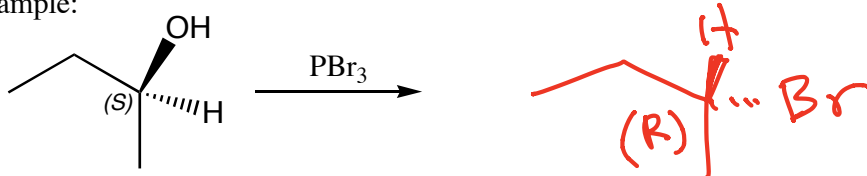
Regiochemistry:

N/A

Stereochemistry:

INVERSION

Example:

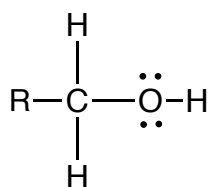


The $SOCl_2$ version of the reaction

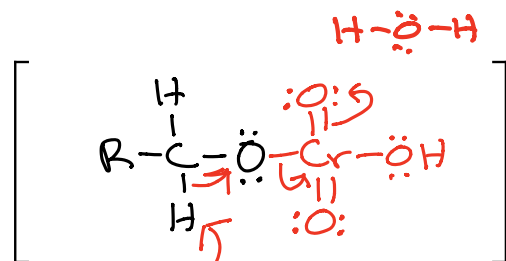
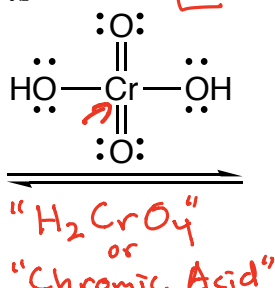
Chromic Acid Oxidation of Alcohols

Called "Jones Reagent" $\left\{ \begin{array}{l} \text{CrO}_3 + \text{H}_2\text{O} \\ \text{or} \\ \text{K}_2\text{CrO}_7 \end{array} \right\} + \text{H}_2\text{SO}_4$

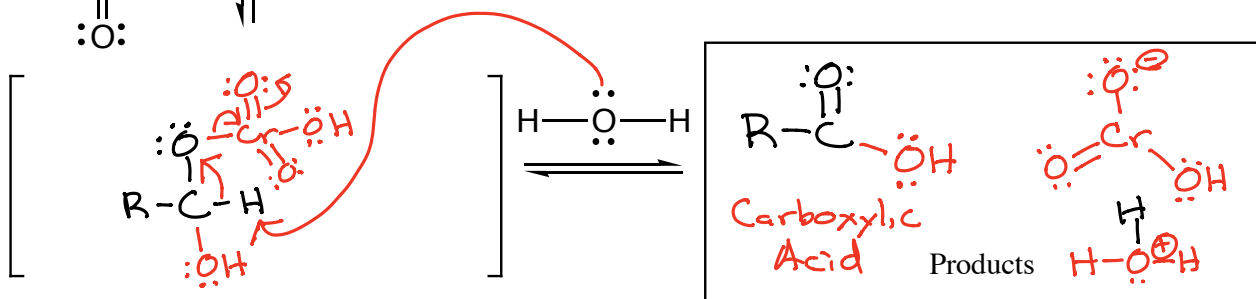
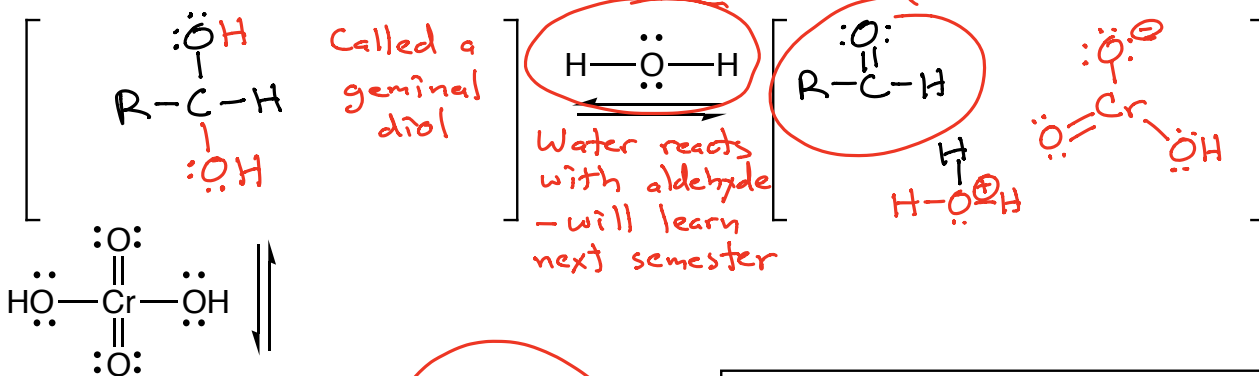
Not responsible for first step



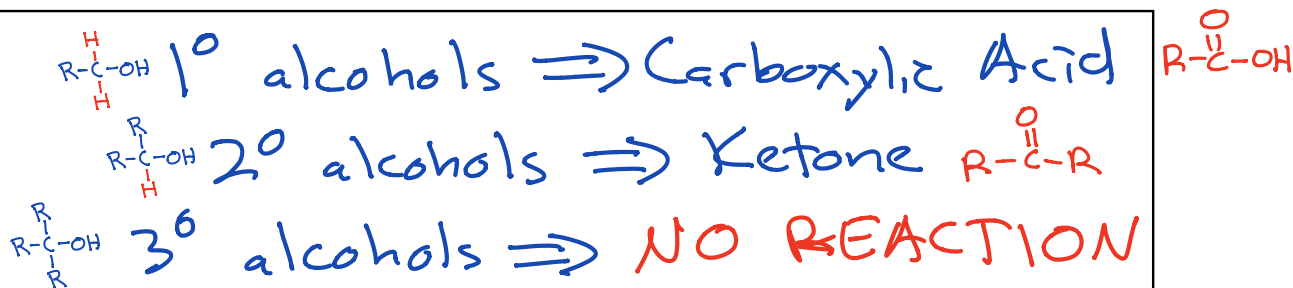
1° Alcohols



Not responsible for this step



Summary:



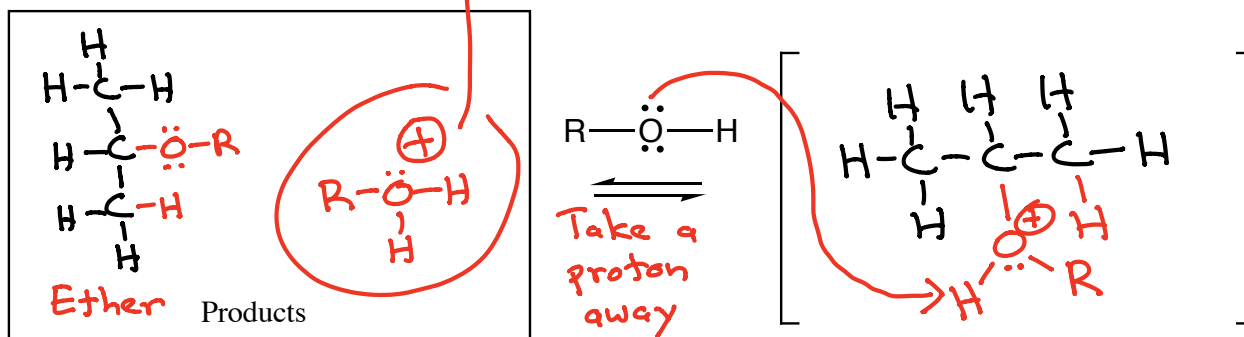
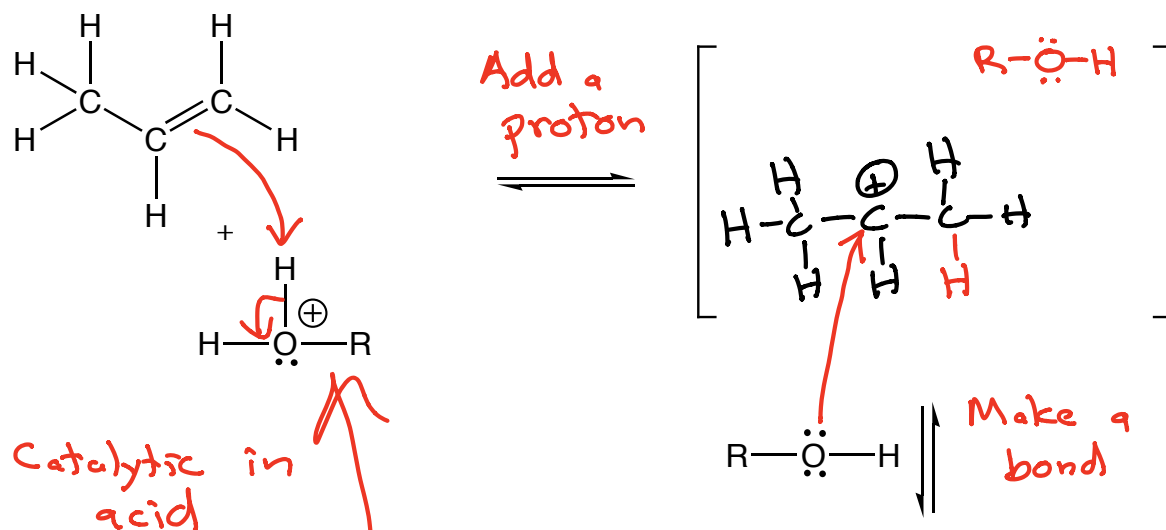
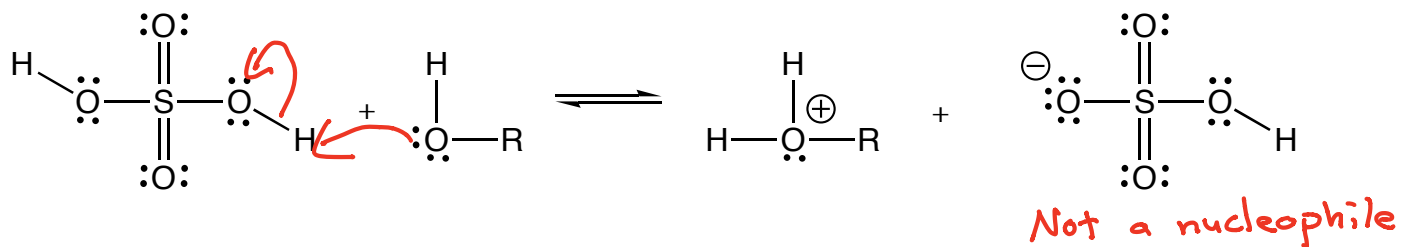
Regiochemistry: N/A

Stereochemistry: N/A

Example:



Acid-catalyzed Reaction of an Alcohol with an Alkene

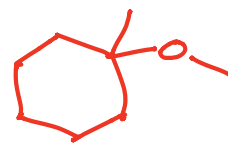
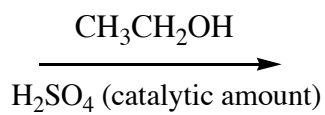
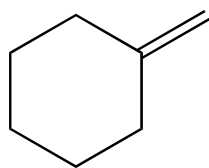


Summary: The alkene is protonated, an alcohol attacks the carbocation \rightarrow take a proton away to give the ether

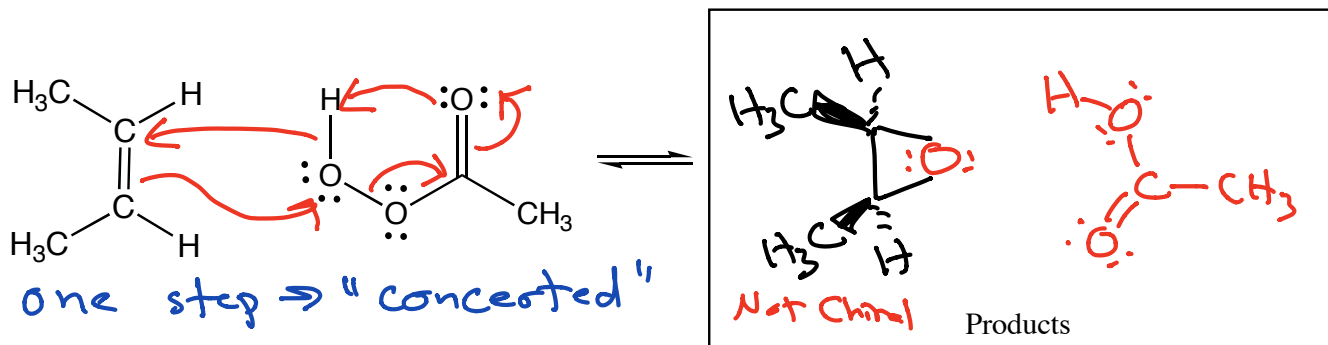
Regiochemistry: Markovnikov

Stereochemistry: Mixed

Example:



Epoxide Formation

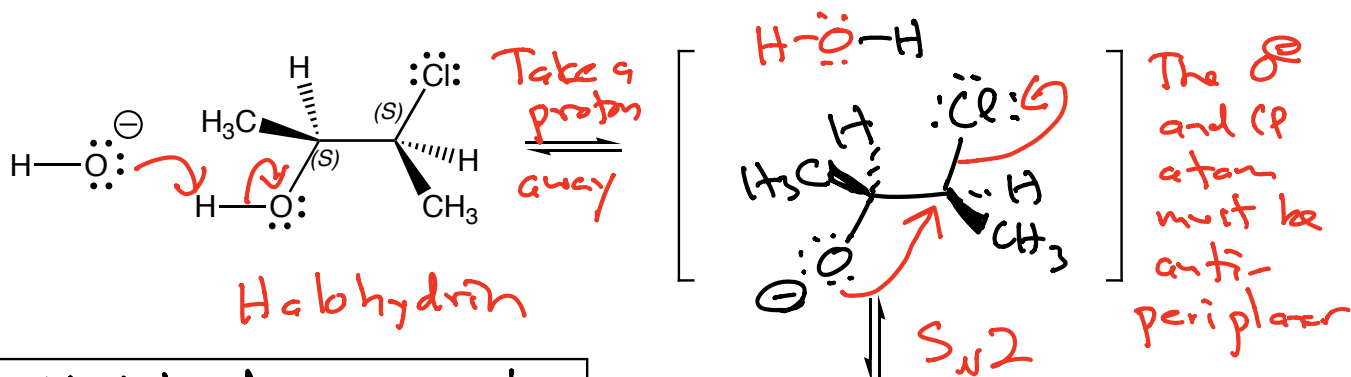
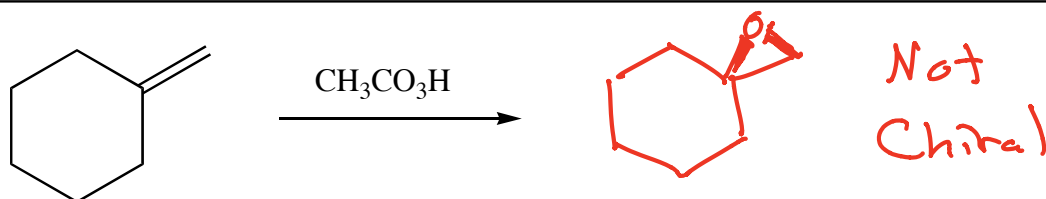


Summary: Alkenes react with peracids in a single concerted step

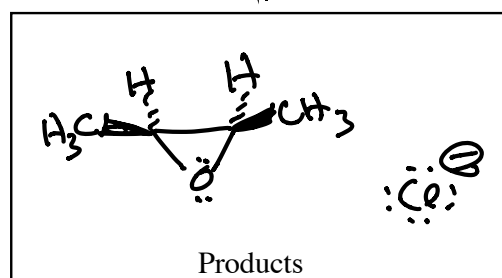
Regiochemistry: N/A

Stereochemistry: Mixed when new chiral centers are created

Example:



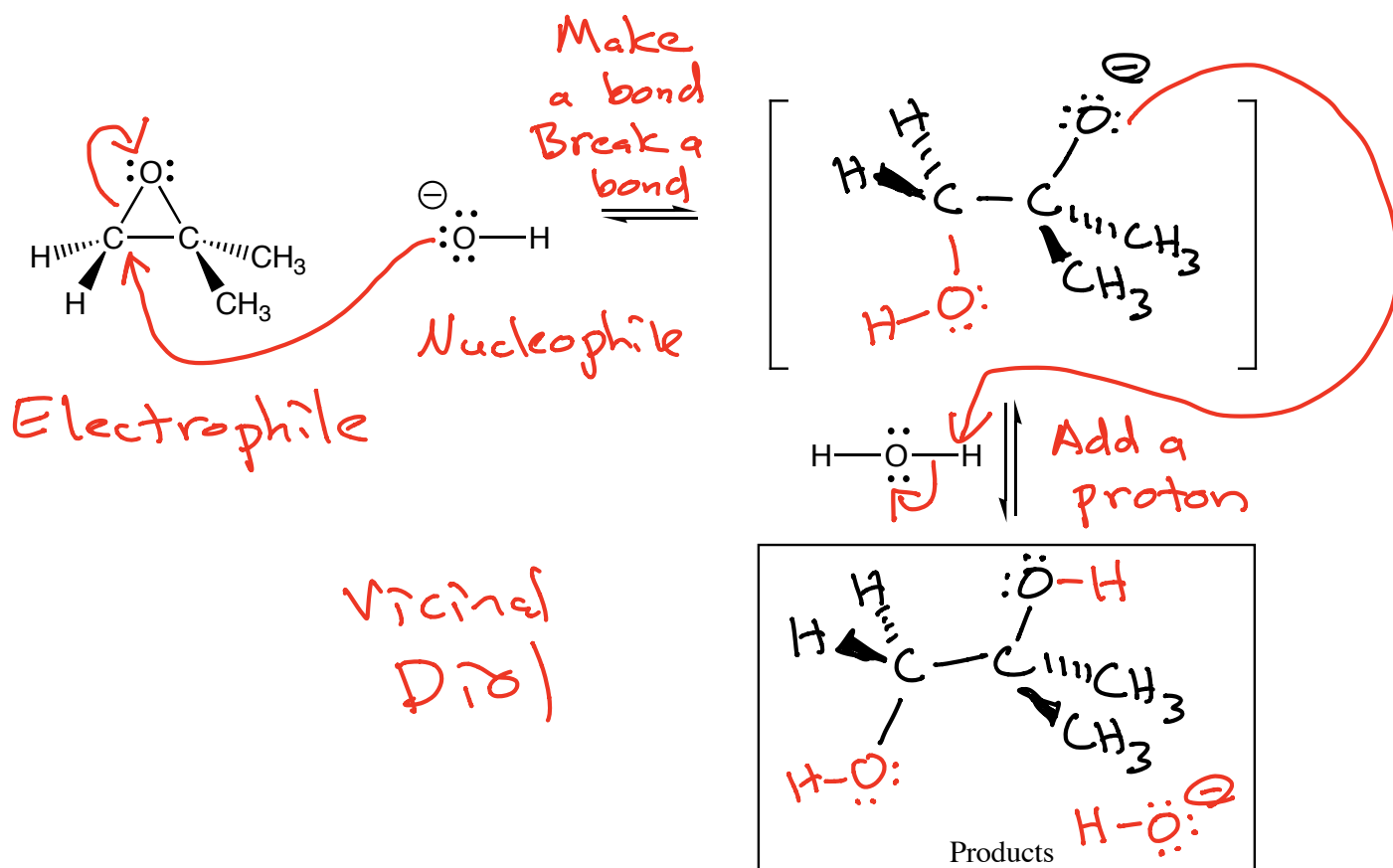
Summary: Halohydrins react in base to give the alkoxide that reacts antiperiplanar to give the epoxide.



Regiochemistry: N/A

Stereochemistry: Antiperiplanar transition state

Nucleophilic ~~Base Promoted~~ Epoxide Opening

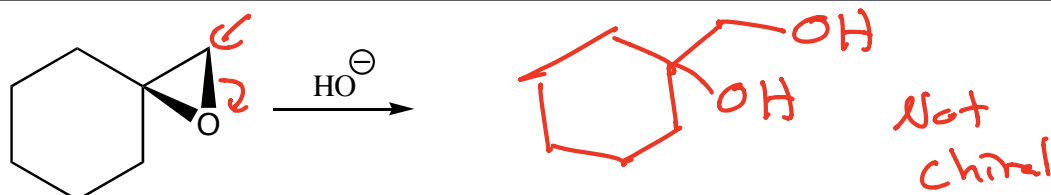


Summary: Epoxides add strong nucleophiles at the less hindered carbon atom

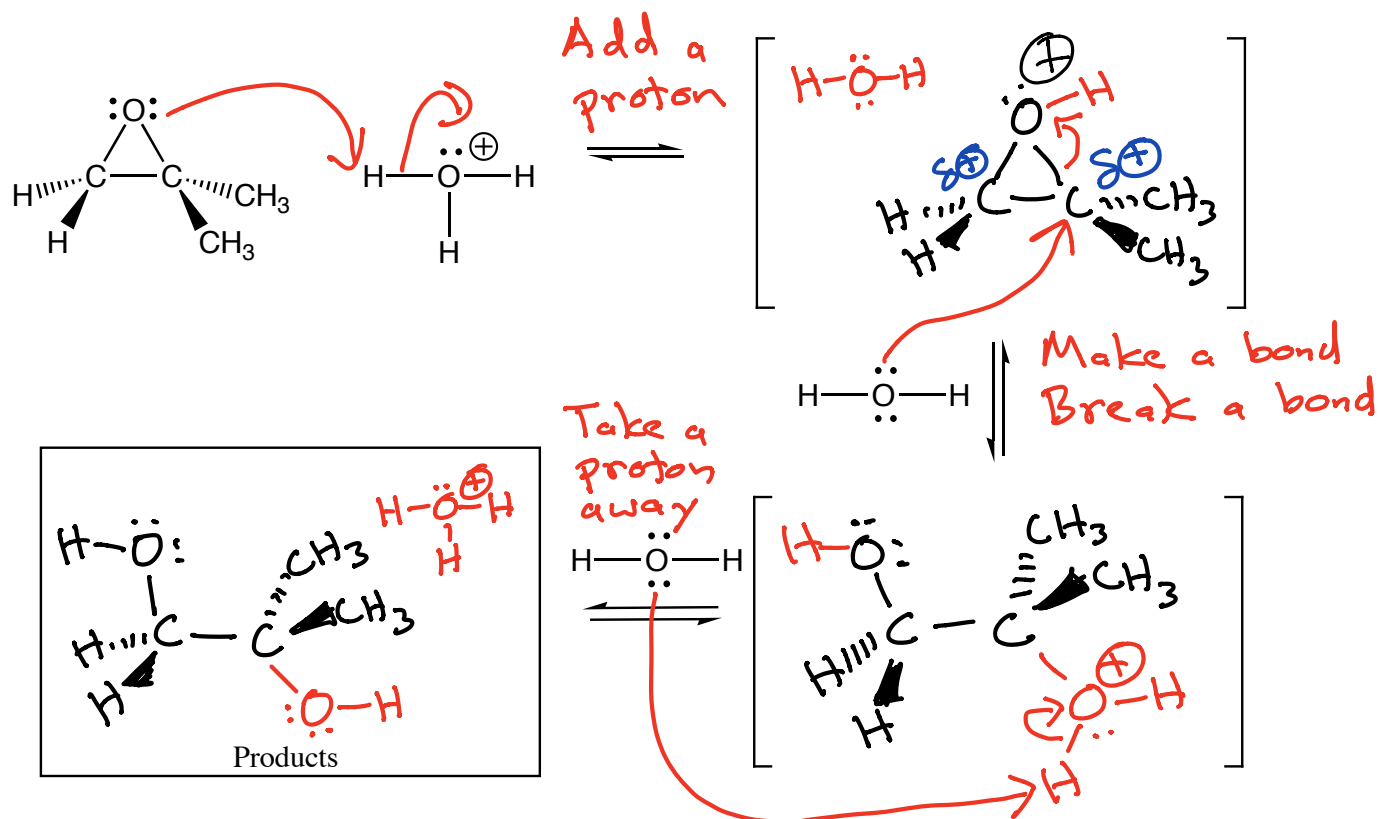
Regiochemistry: Less hindered (non-Markovnikov) ✓

Stereochemistry: Anti addition

Example:



Acid-Catalyzed Epoxide Opening

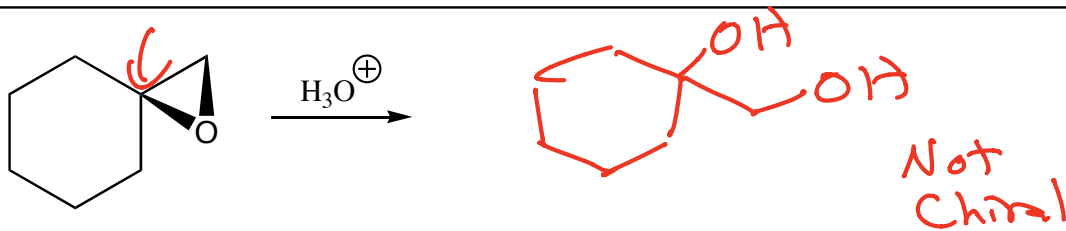


Summary: In acid, epoxides are protonated to give a highly reactive cation intermediate that reacts with nucleophiles at the more highly substituted carbon atom.

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

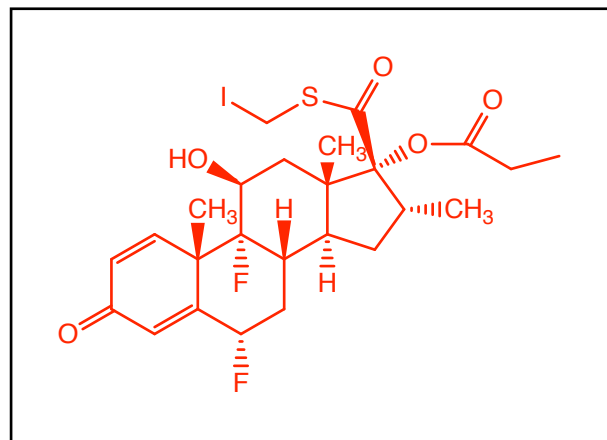
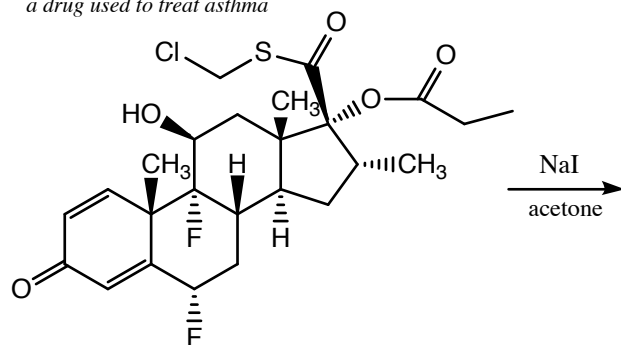
Stereochemistry: Anti

Example:

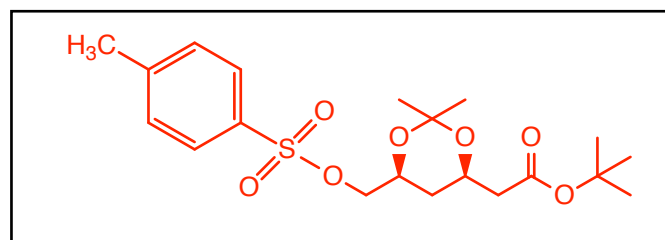
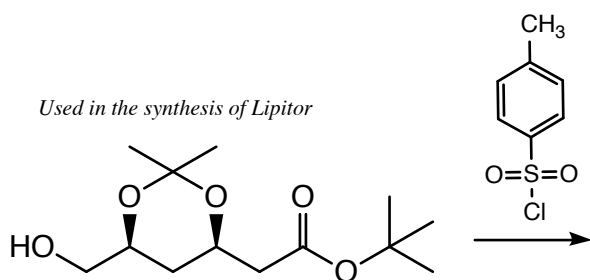


Reactions in the Context of Complex Molecules

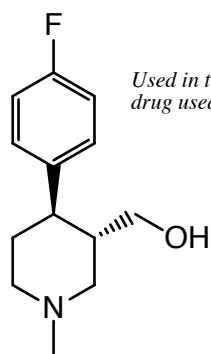
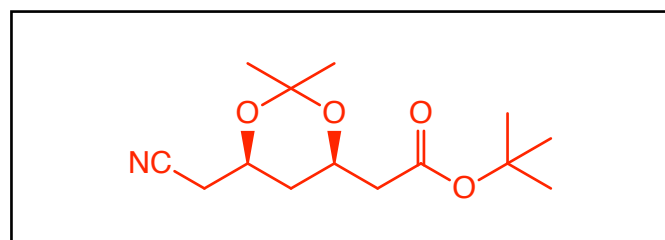
Used in the synthesis of Fluticasone (Flonase),
a drug used to treat asthma



Used in the synthesis of Lipitor

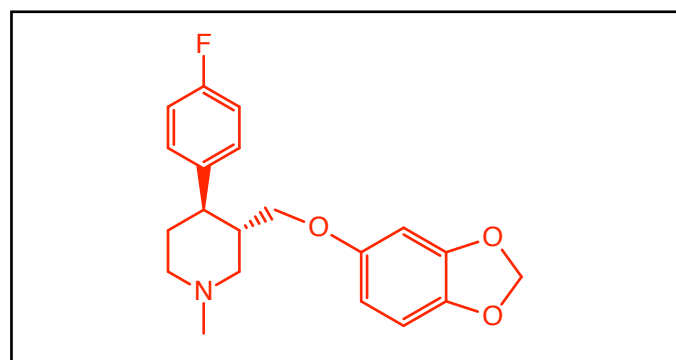
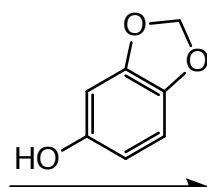
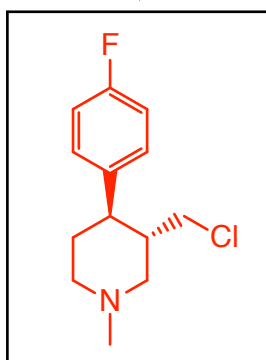


NaCN



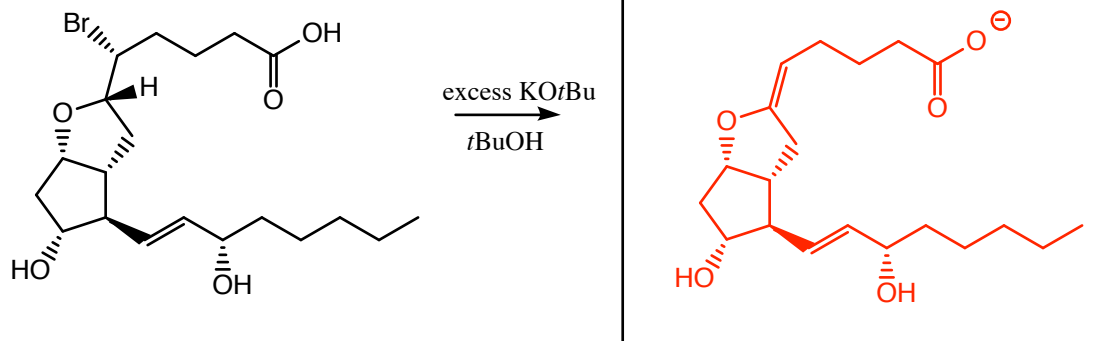
Used in the synthesis of Paxil, a
drug used to treat depression

SOCl₂

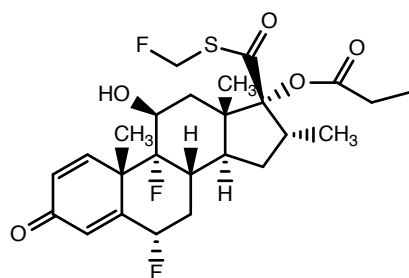
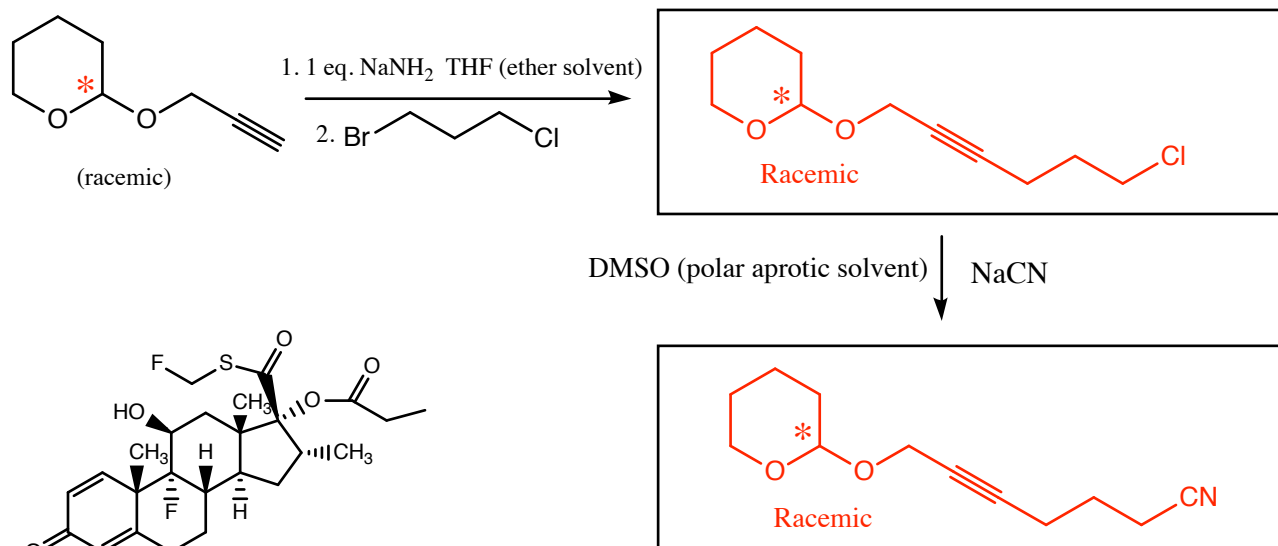


Reactions in the Context of Complex Molecules

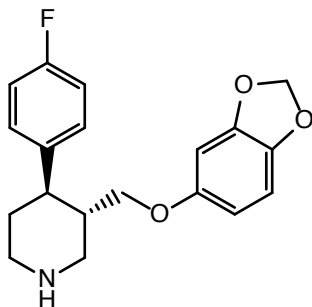
Used in the synthesis of several prostaglandins



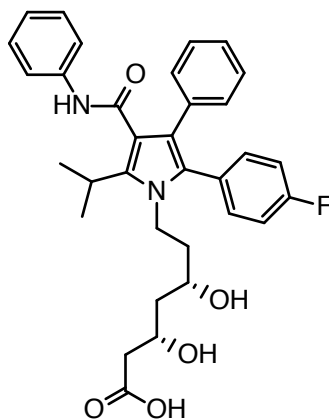
Used in the synthesis of prostaglandin C₂



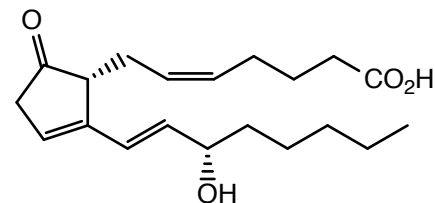
Fluticasone (Flonase)



Paroxetine (Paxil)



Atorvastatin (Lipitor)



Prostaglandin C₂