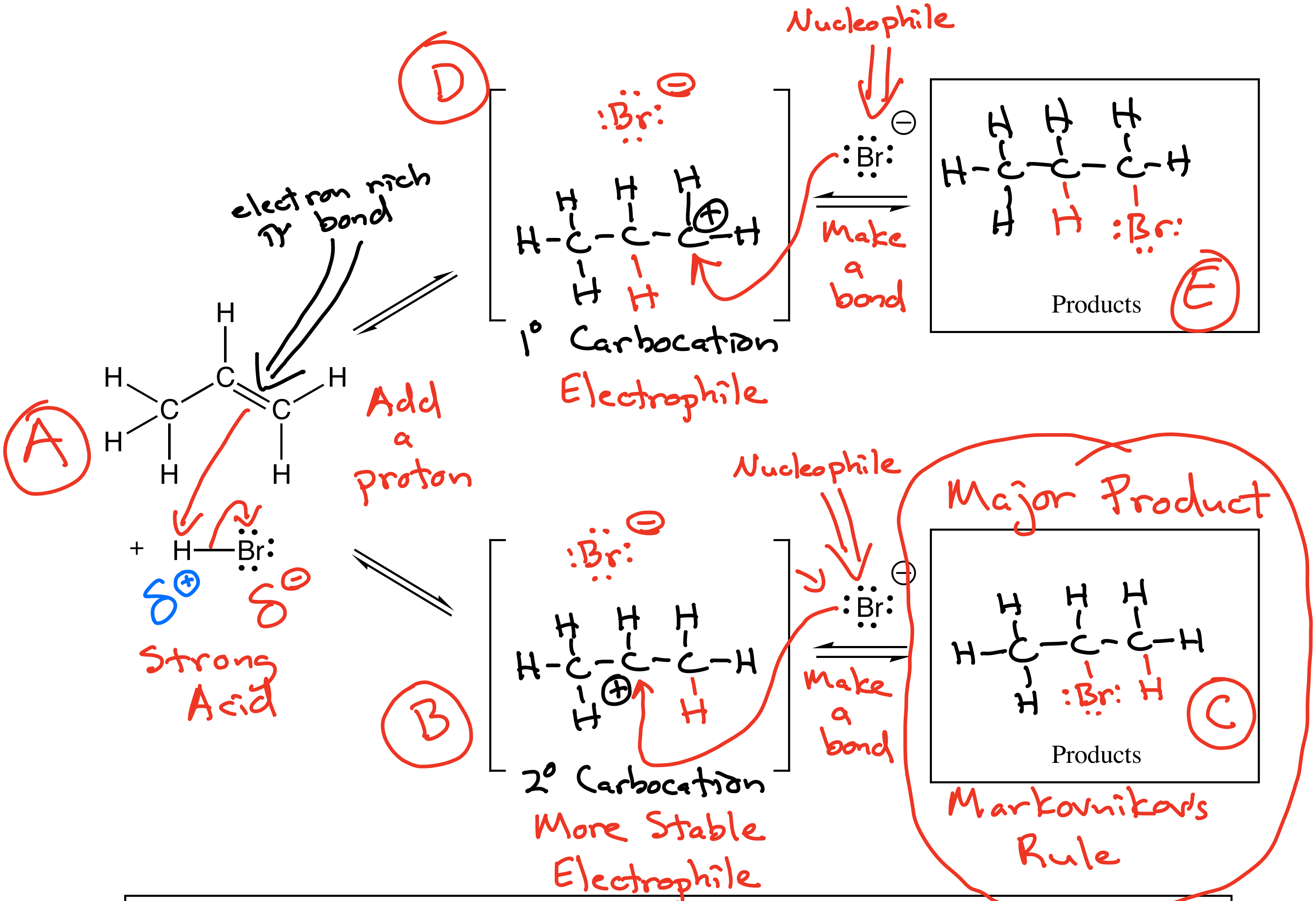
Addition of H-X to an Alkene

X = Cl, Br, I
but not F



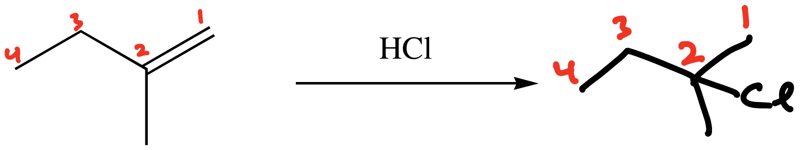
Summary:

The alkene pi bond reacts with H-X to add a proton to create a carbocation intermediate that makes a bond with $X^{\ominus}$ to give the product

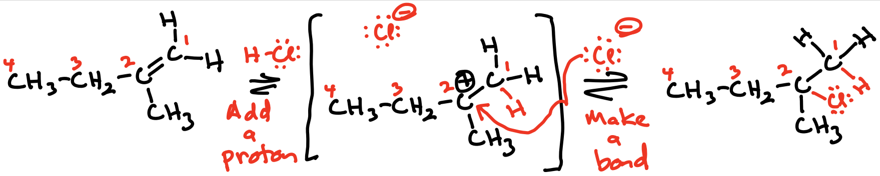
Regiochemistry: Markovnikov's Rule

Stereochemistry: Mixed (time capsule) → Racemic Product

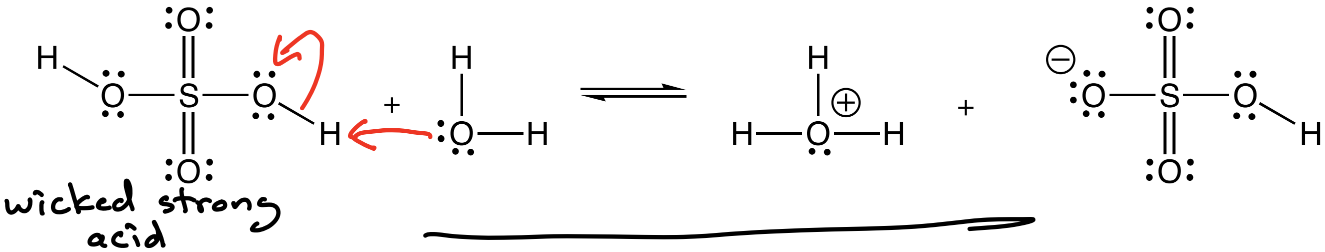
Example:

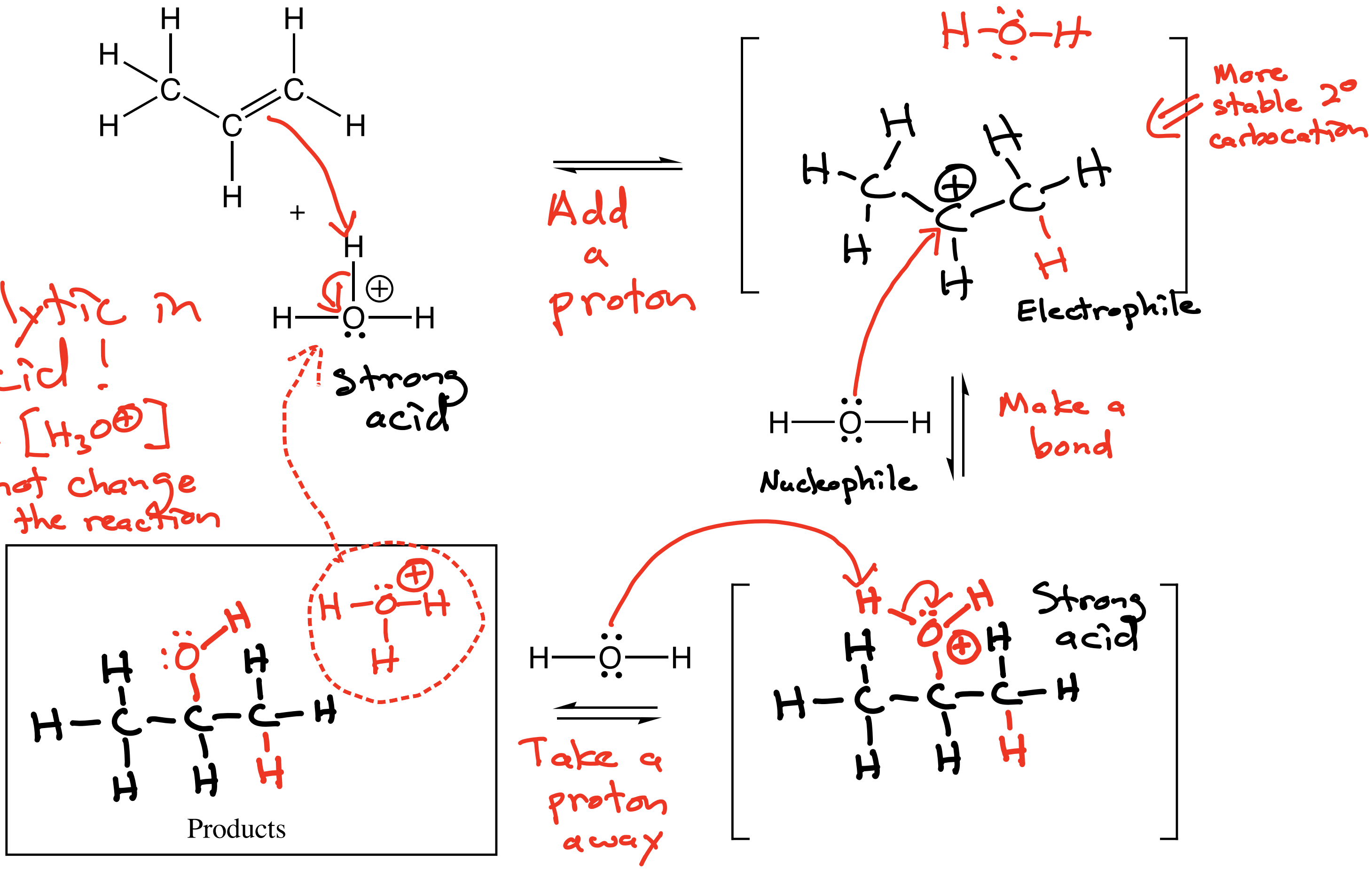


Not chiral



Acid-catalyzed Hydration of an Alkene





Catalytic in Acid!

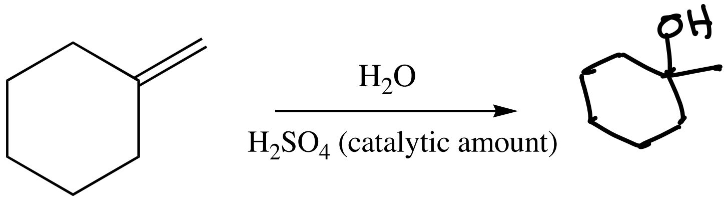
⇒ The $[H_3O^{\oplus}]$ does not change during the reaction

Summary: Proton adds to make a carbocation intermediate, water attacks to make a new bond, take a proton away to make the product alcohol. Catalytic in $H_3O^{\oplus}$

Regiochemistry: Markovnikov's Rule

Stereochemistry: Mixed (time capsule)

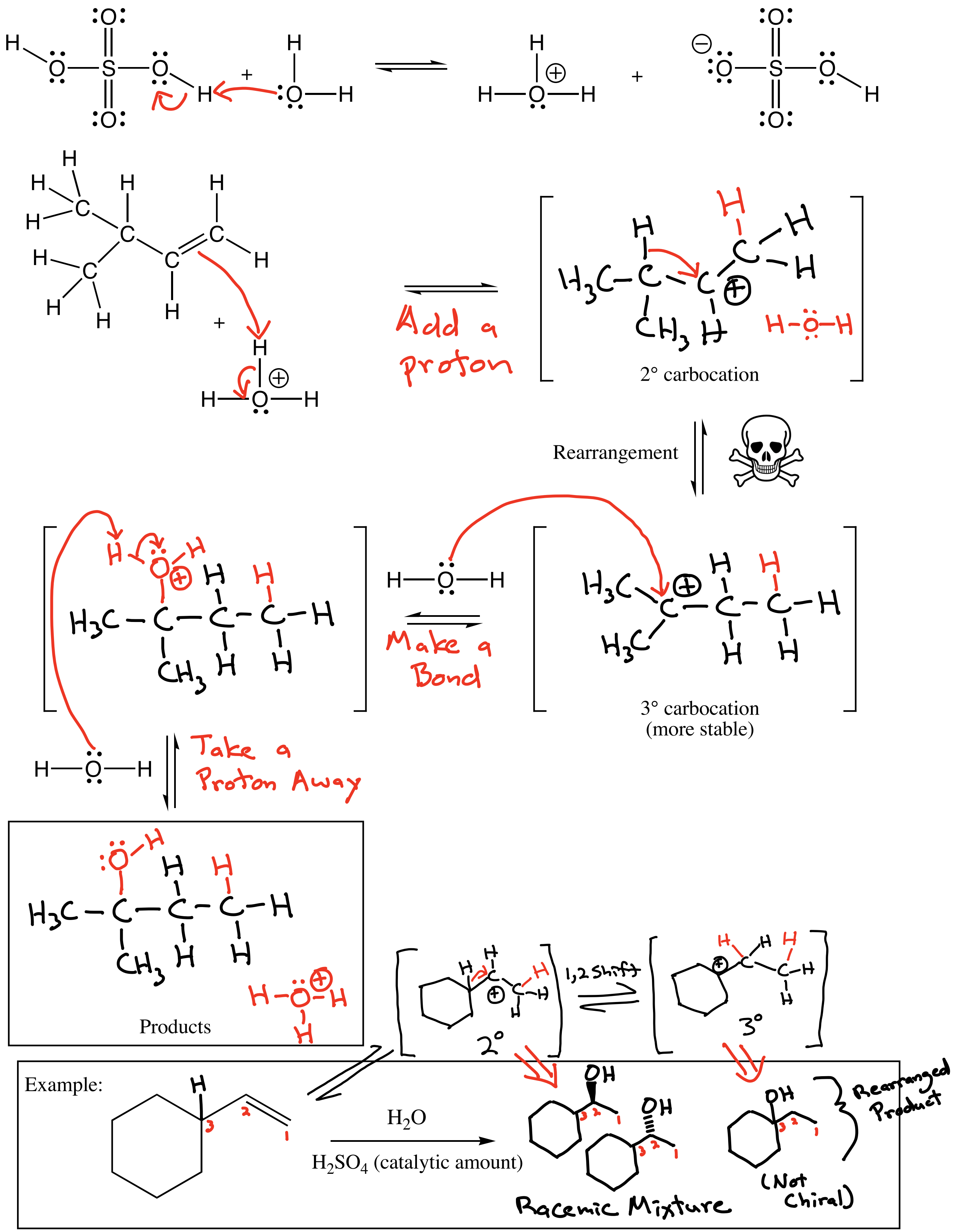
Example:



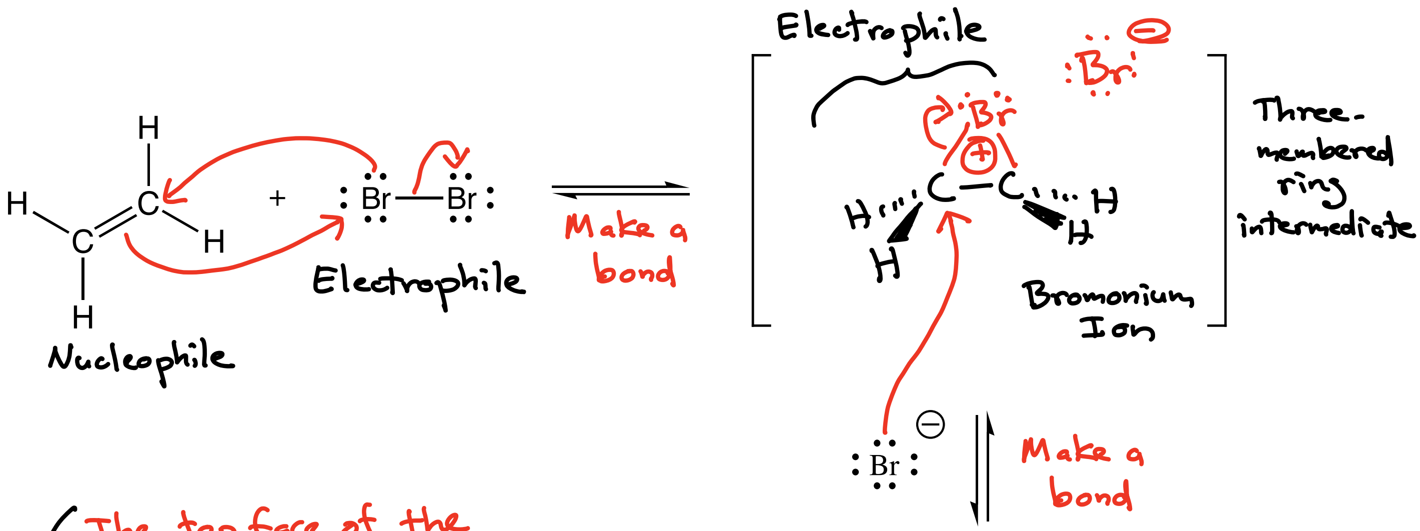
(Not chiral)

–OH on more substituted C atom ⇒ Markovnikov's Rule

Cation Rearrangement



Alkene Halogenation

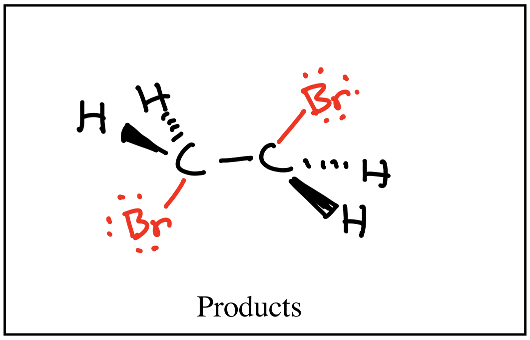


Called "anti" addition stereochemistry

The top face of the intermediate is "blocked" by the Br atom, so the :Br:⊖ nucleophile must react from the opposite face

⇓

Gives only a "trans" product—never "cis"



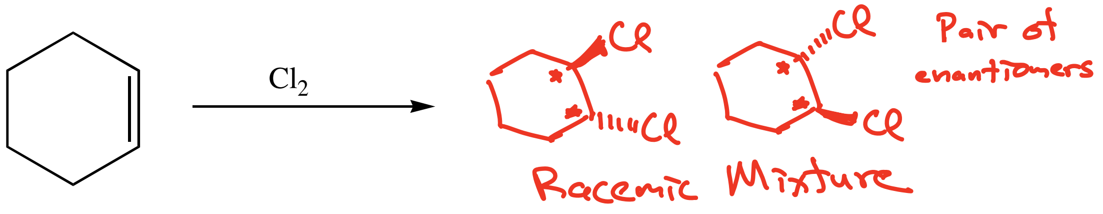
Products

Summary: Alkenes react with X_2 to give a three-membered ring intermediate, then a new bond is made by $X^{\ominus}$ reacting from behind the C–X bond of the intermediate.

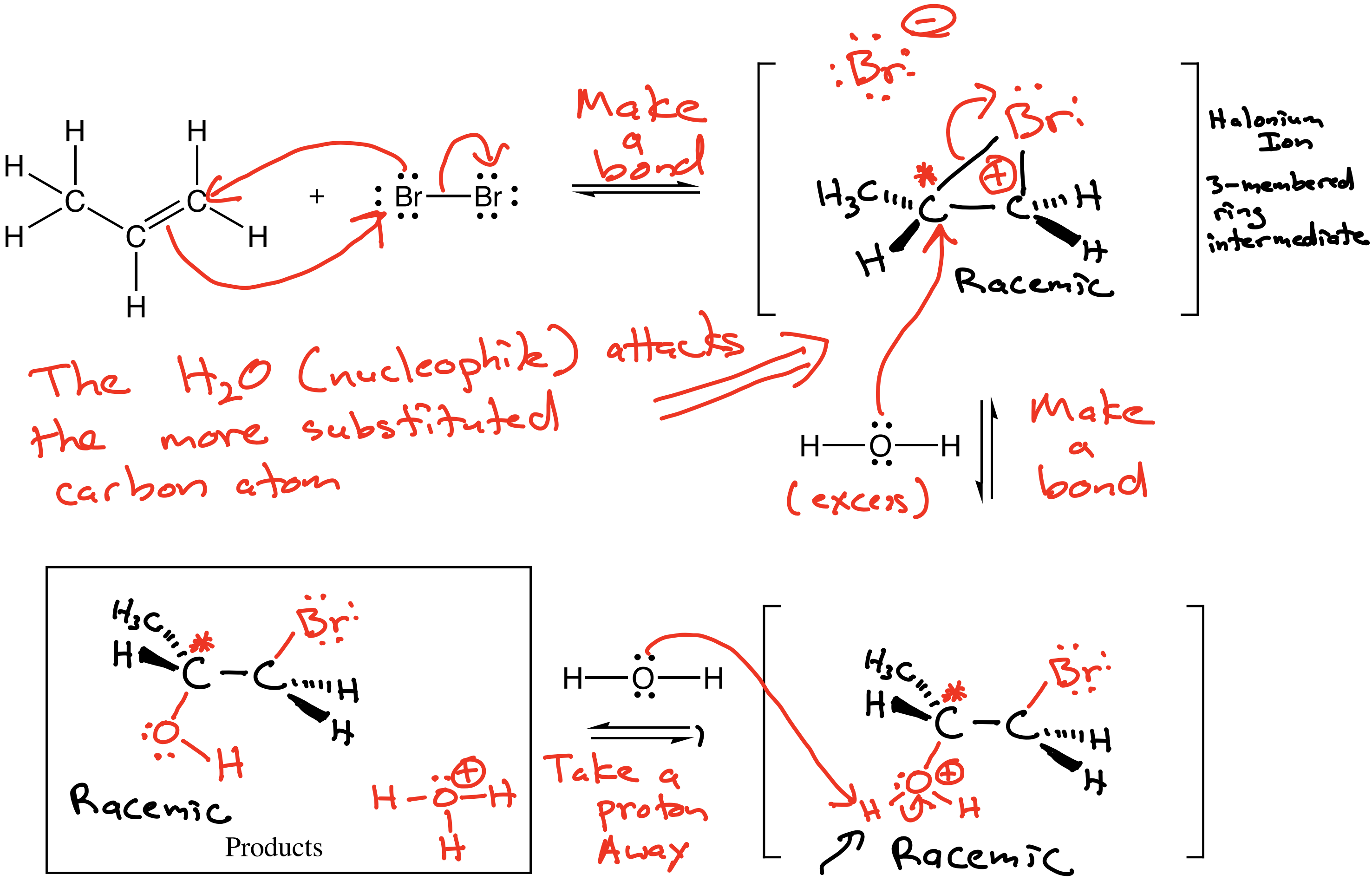
Regiochemistry: Not applicable → Br is on both atoms

Stereochemistry: Anti addition geometry → trans products

Example:



Alkene Hydrohalogenation



The H_2O (nucleophile) attacks the more substituted carbon atom

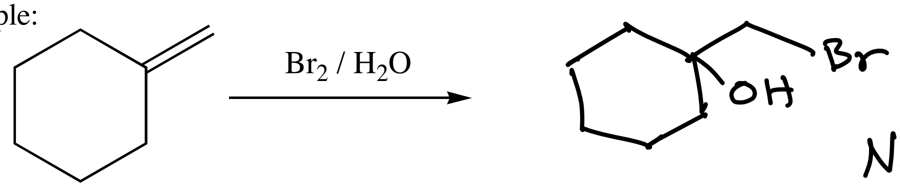
pH drops during the reaction!

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)

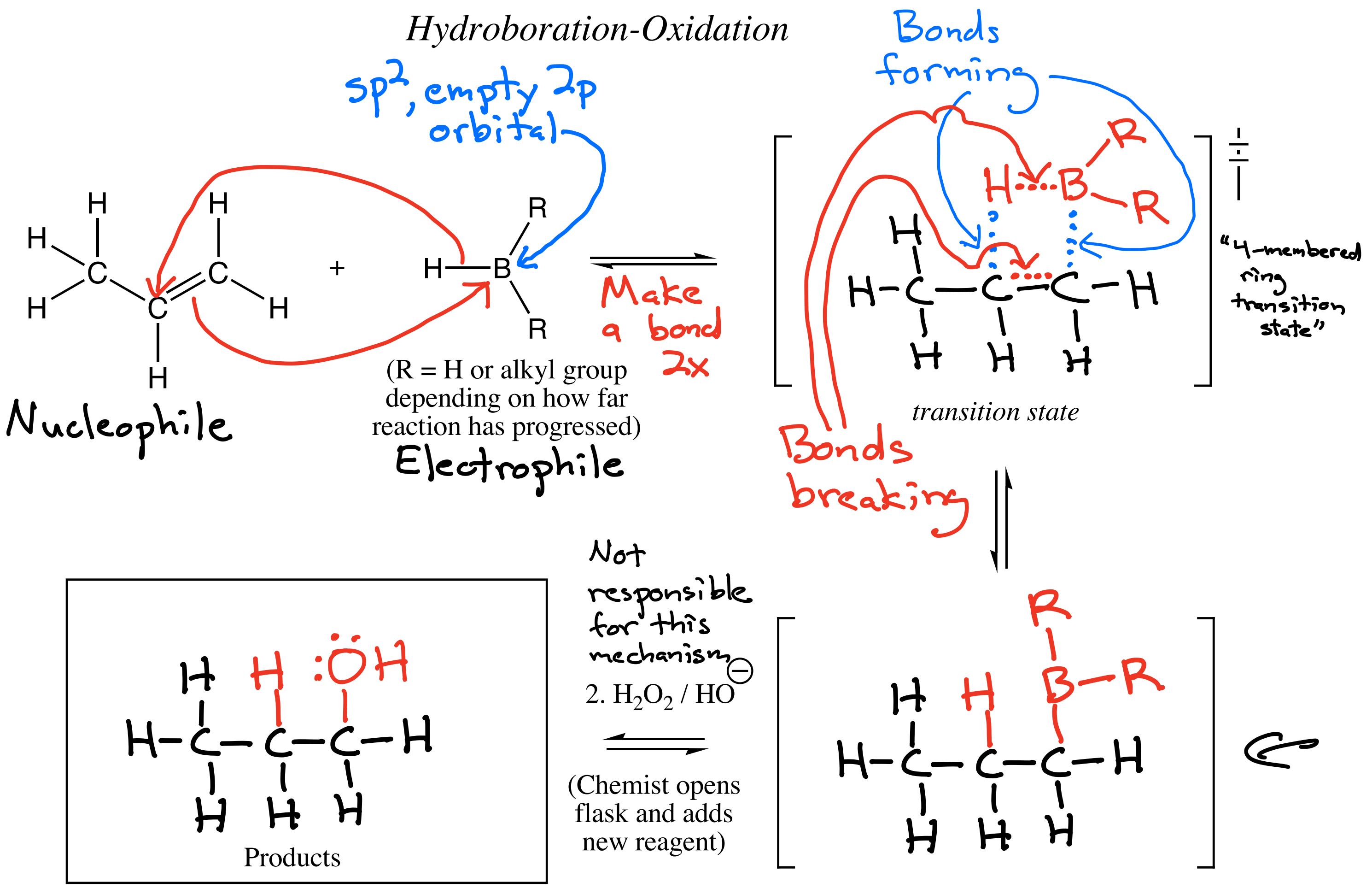
Stereochemistry: Anti

Example:



Not Chiral

Hydroboration-Oxidation



H → More substituted C atom
OH → Less substituted C atom } Steric strain in the first transition state

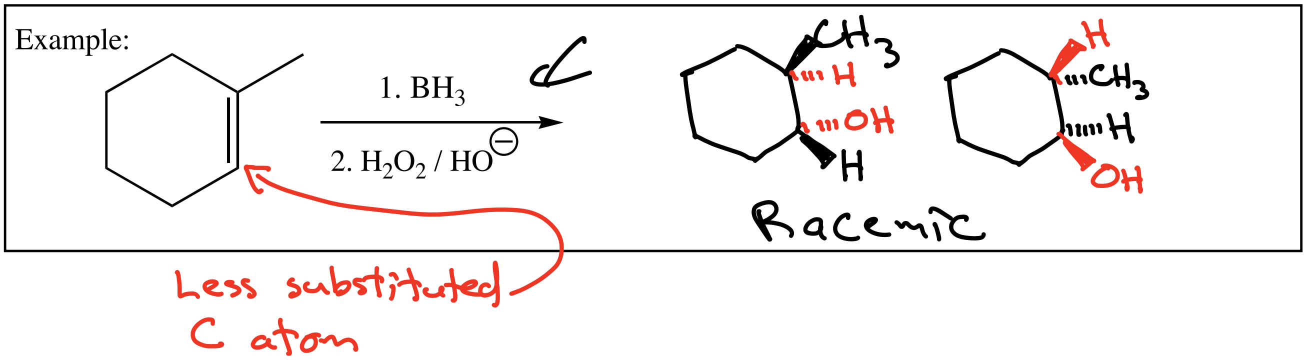
H and OH are syn

Summary: The pi bond of the alkene attacks the Lewis acid (electrophile) B atom at the same time a new bond forms between C and H. In 2nd step OH replaces $B(R)_2$. "4-membered ring transition state"

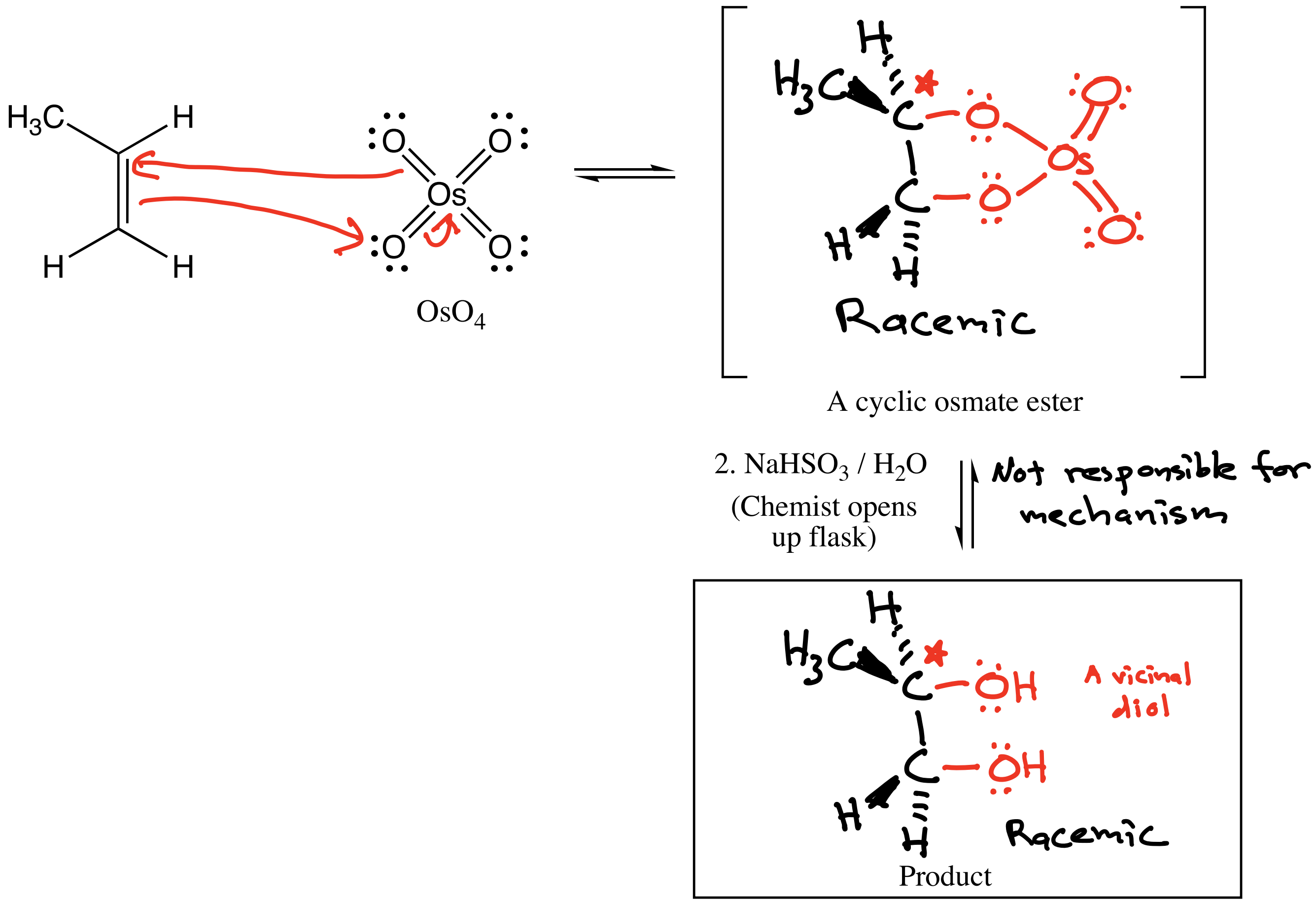
Regiochemistry: Non-Markovnikov

Stereochemistry: Syn

Example:



OsO_4 Partial Mechanism

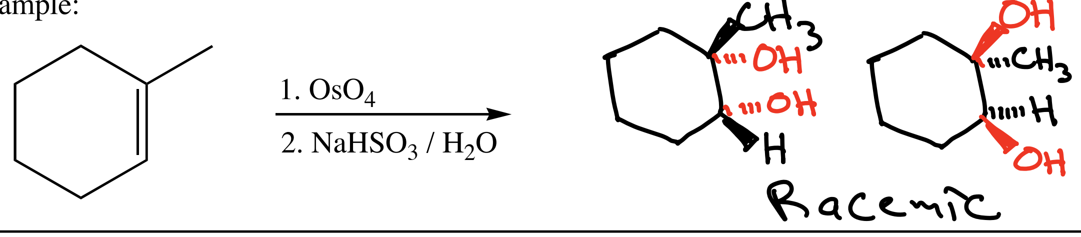


Summary: The mechanism involves a cyclic osmate ester, explaining the syn stereochemistry of addition.

Regiochemistry: N/A

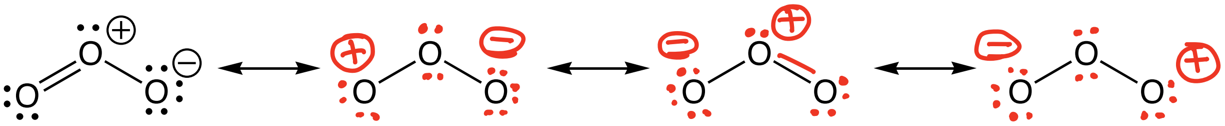
Stereochemistry: Syn

Example:

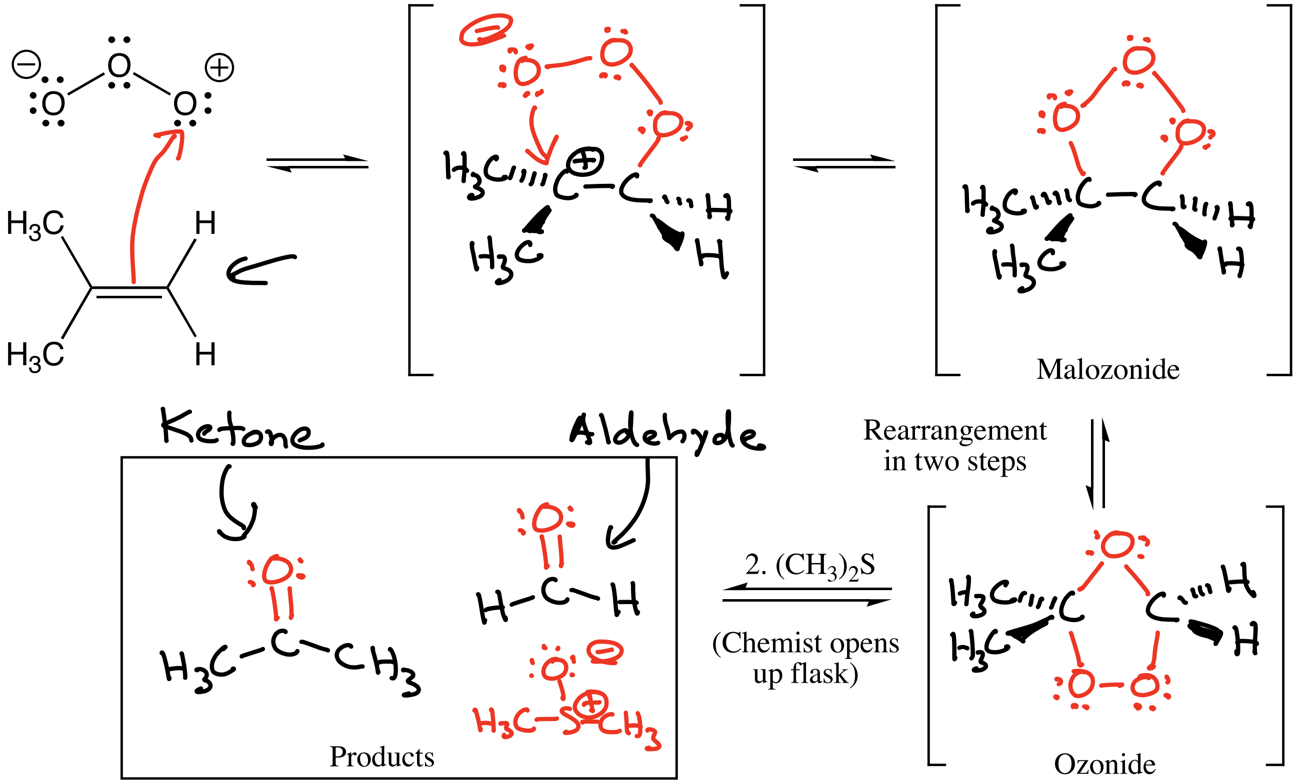


This breaks C=C bonds !!!

Ozonolysis Partial Mechanism



Ozone contributing structures

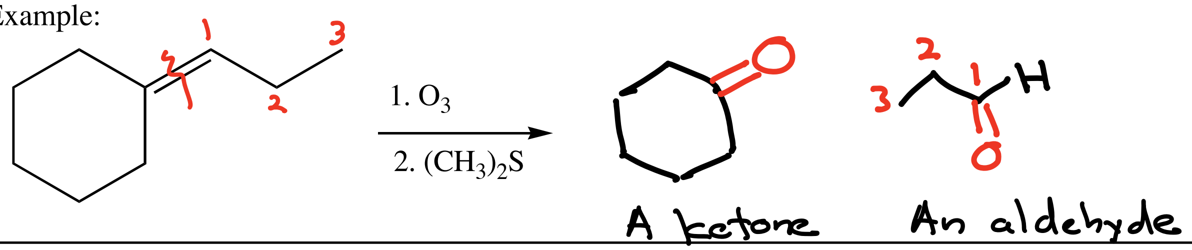


Summary: Reaction of an alkene with O_3 gives a malozonide than an ozonide intermediate (the C=C pi bond then C–C sigma bond is broken). Adding $(CH_3)_2S$ decomposes the ozonide into ketone and aldehyde products Breaks C=C bond!

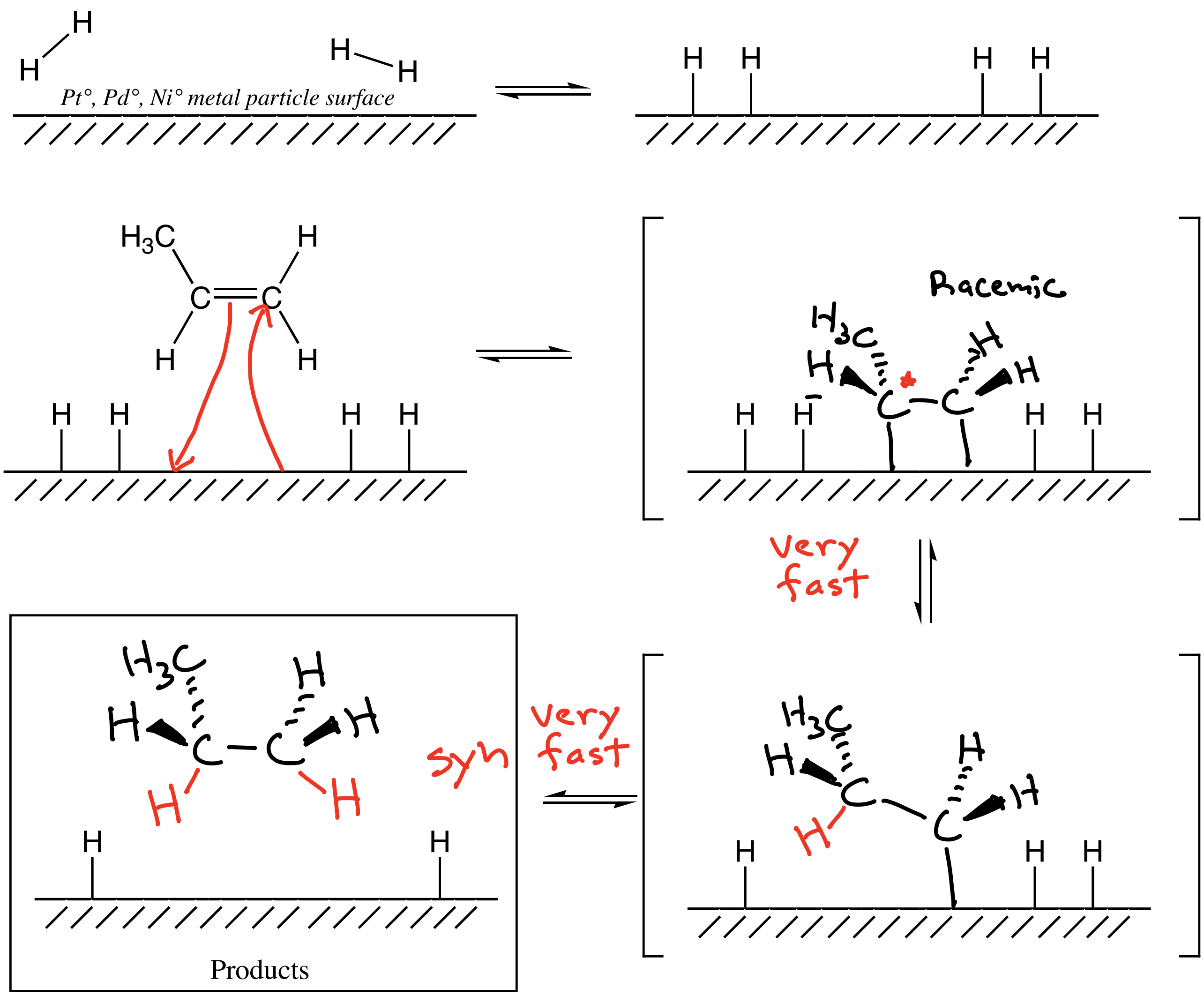
Regiochemistry: N/A

Stereochemistry: N/A

Example:



Hydrogenation: H_2 with Pt°, Pd°, Ni°

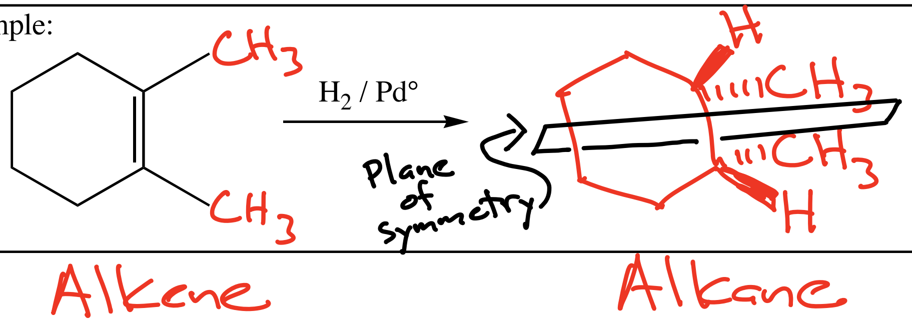


Summary: H_2 adsorbs onto the metal surface. The alkene adsorbs onto the metal surface. H atoms transfer to both C atoms → on the same face → before the C-C bond rotates

Regiochemistry: N/A

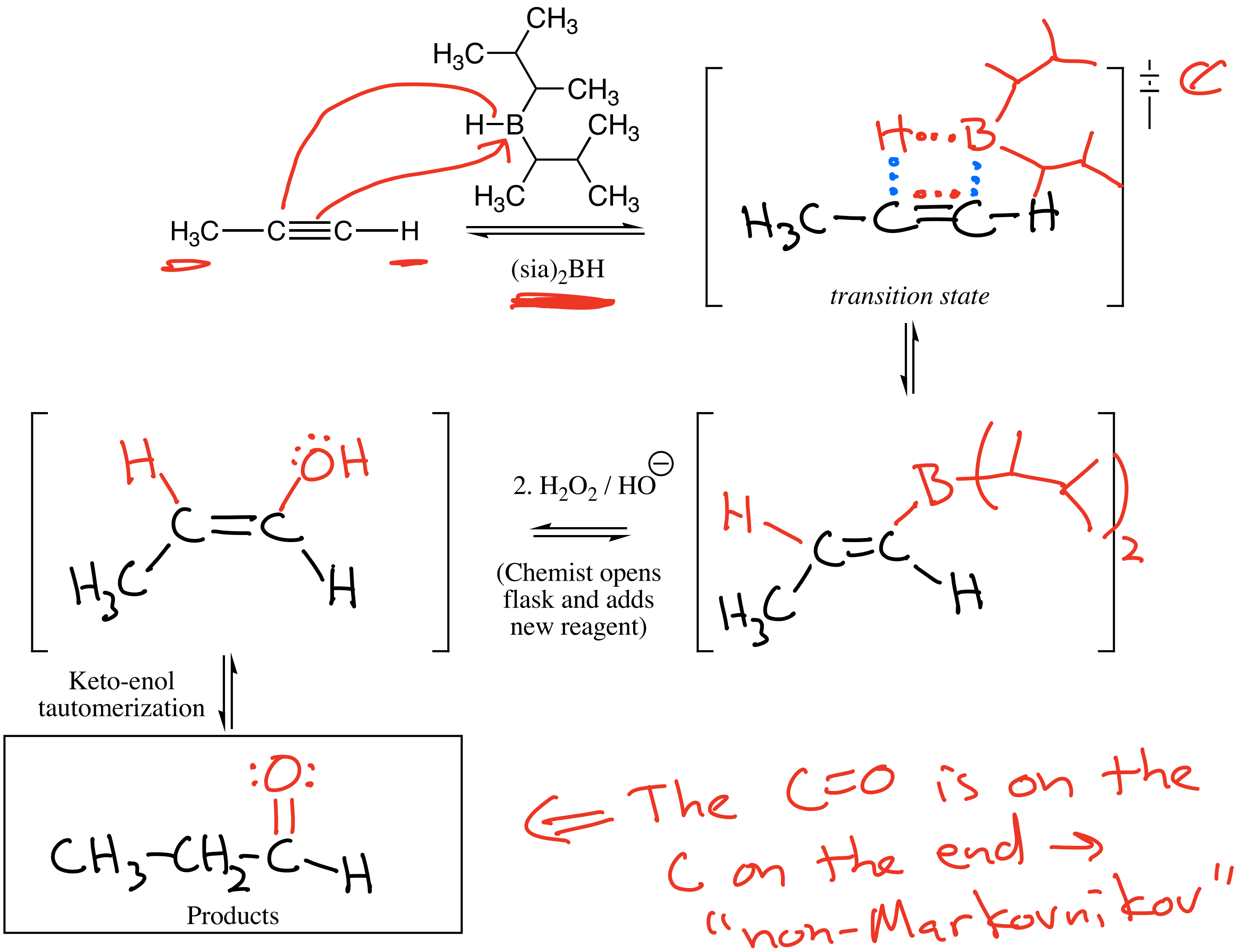
Stereochemistry: Syn

Example:



Not Chiral

Terminal Alkyne Hydroboration



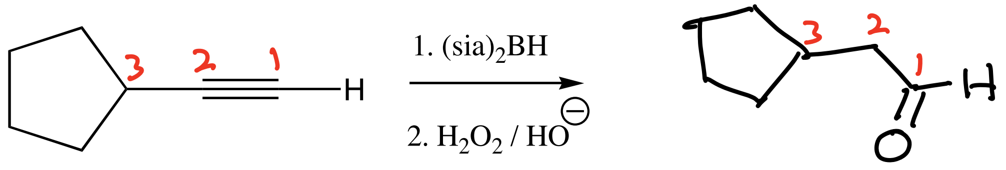
⇐ The C=O is on the C on the end → "non-Markovnikov"

Summary: The $(sia)_2BH$ reacts so the B atom attaches to the C atom on the end. The four-membered ring transition states makes both bonds simultaneously. 2. $H_2O_2/HO^{\ominus}$ → enol → keto

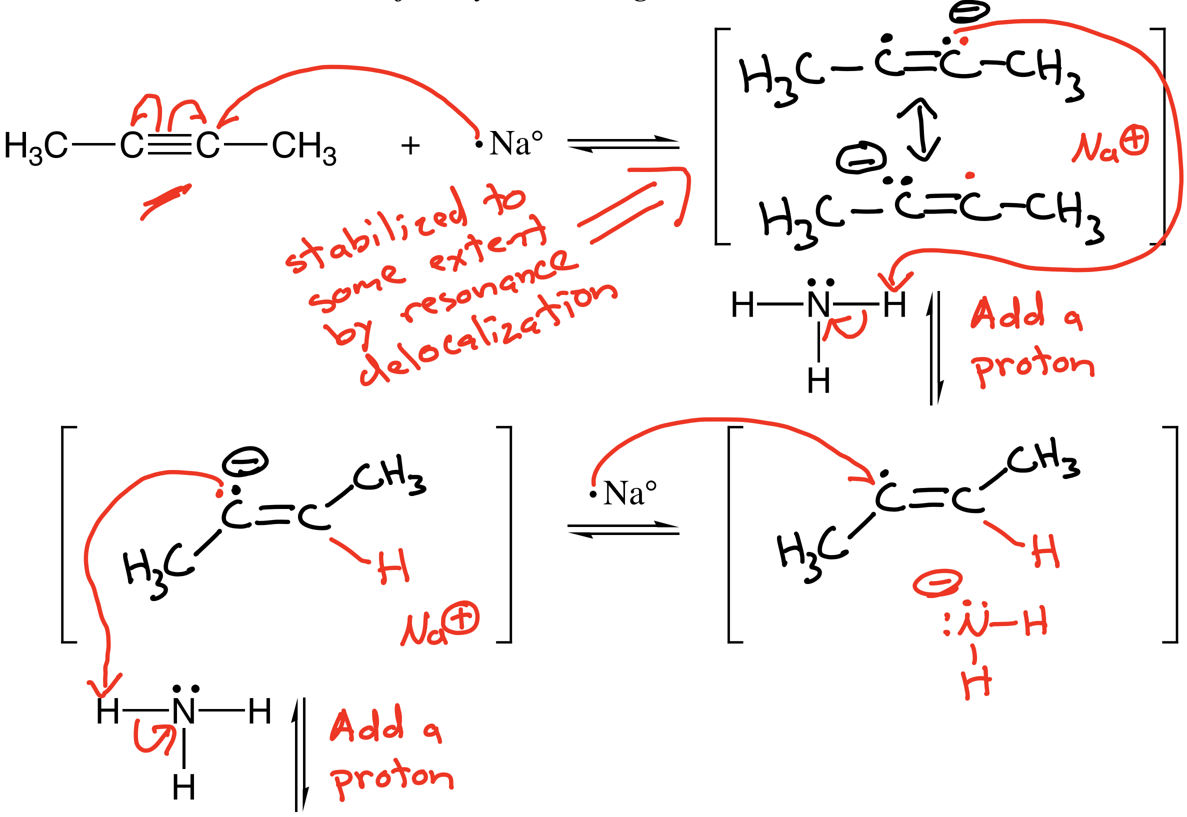
Regiochemistry: non-Markovnikov

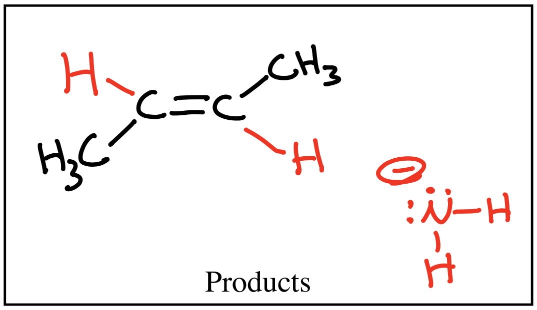
Stereochemistry: N/A

Example:



Reduction of Alkynes Using Sodium and Ammonia





Products

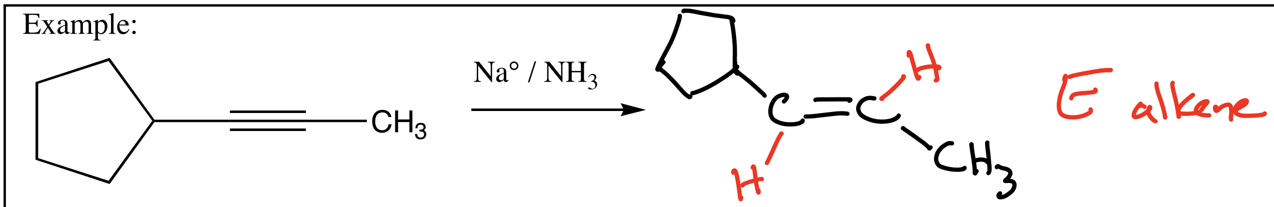
This reaction makes the more stable E alkene

Summary: Alkynes are reduced to E alkenes by Na° in NH_3 via two one-electron reductions by Na°, each of which is followed by adding a proton from the NH_3 solvent

Regiochemistry: N/A

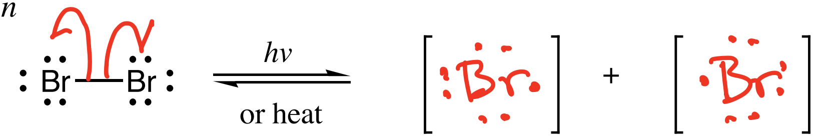
Stereochemistry: Anti → E products

Example:

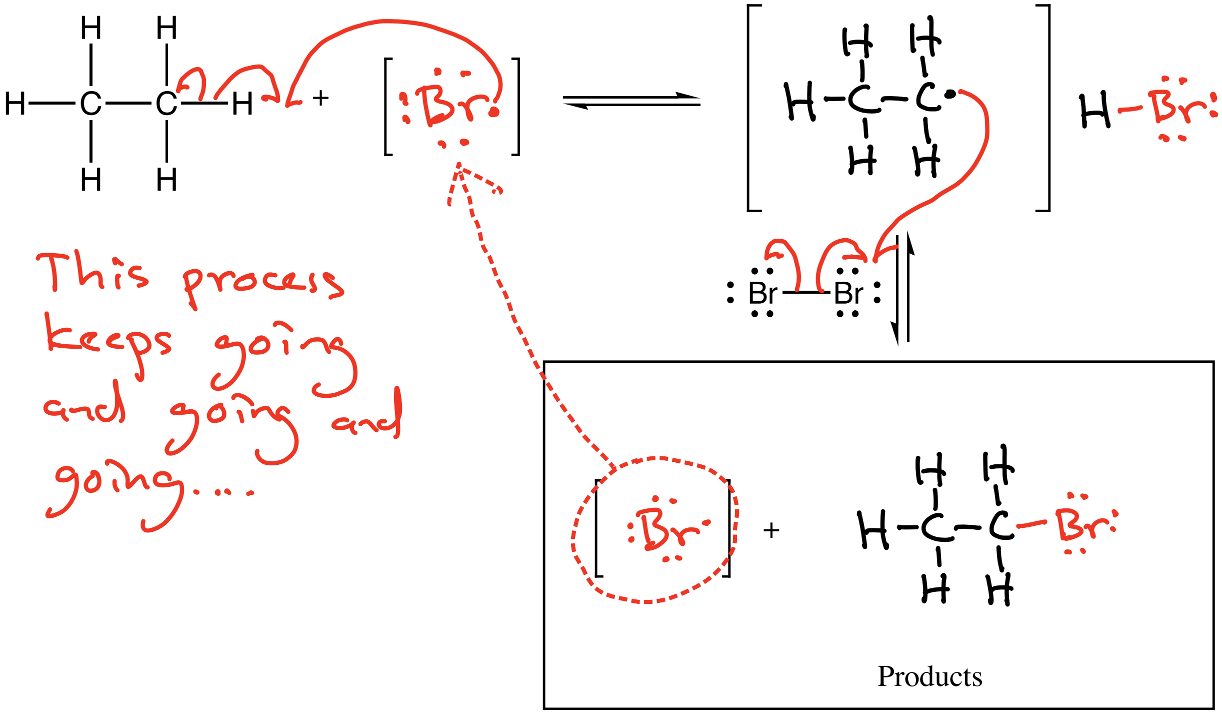


Alkane Free Radical Halogenation

Initiation

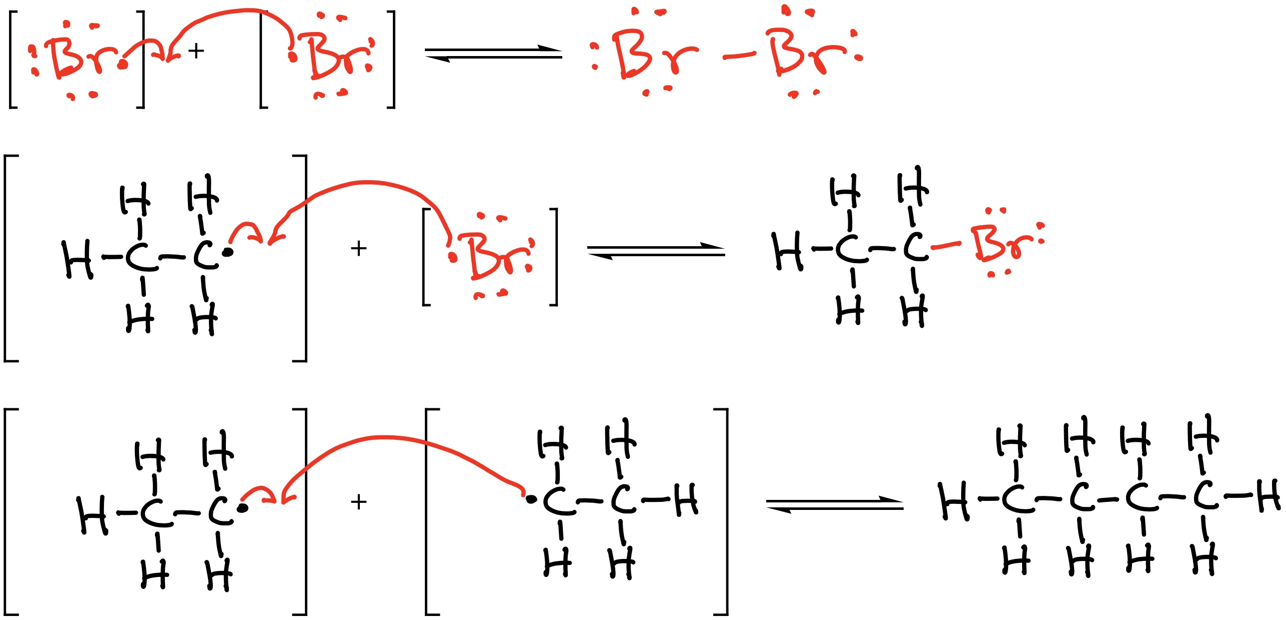


Propagation

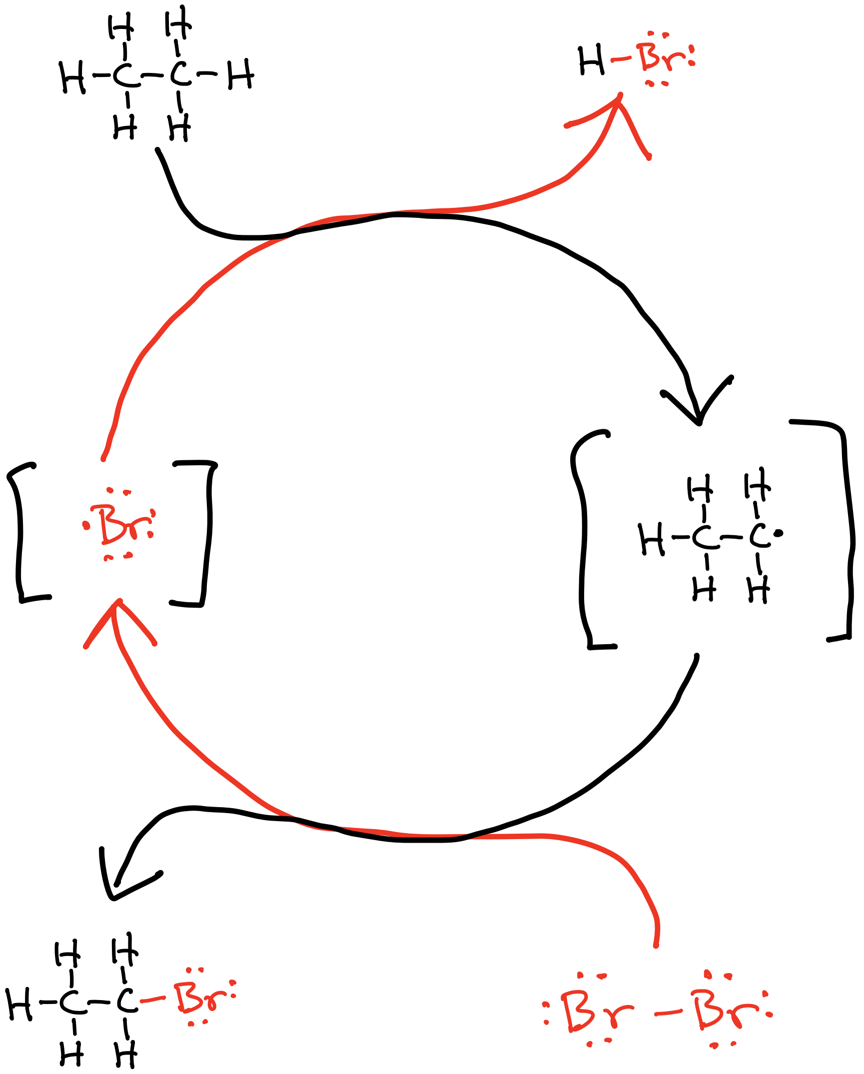


This process keeps going and going and going....

Termination

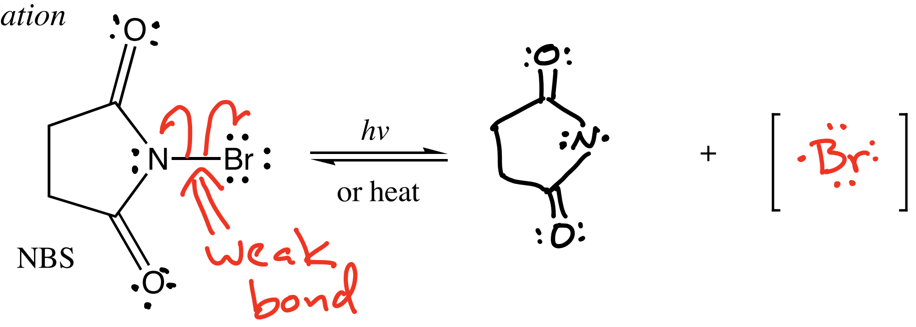


Propagation Process Diagram

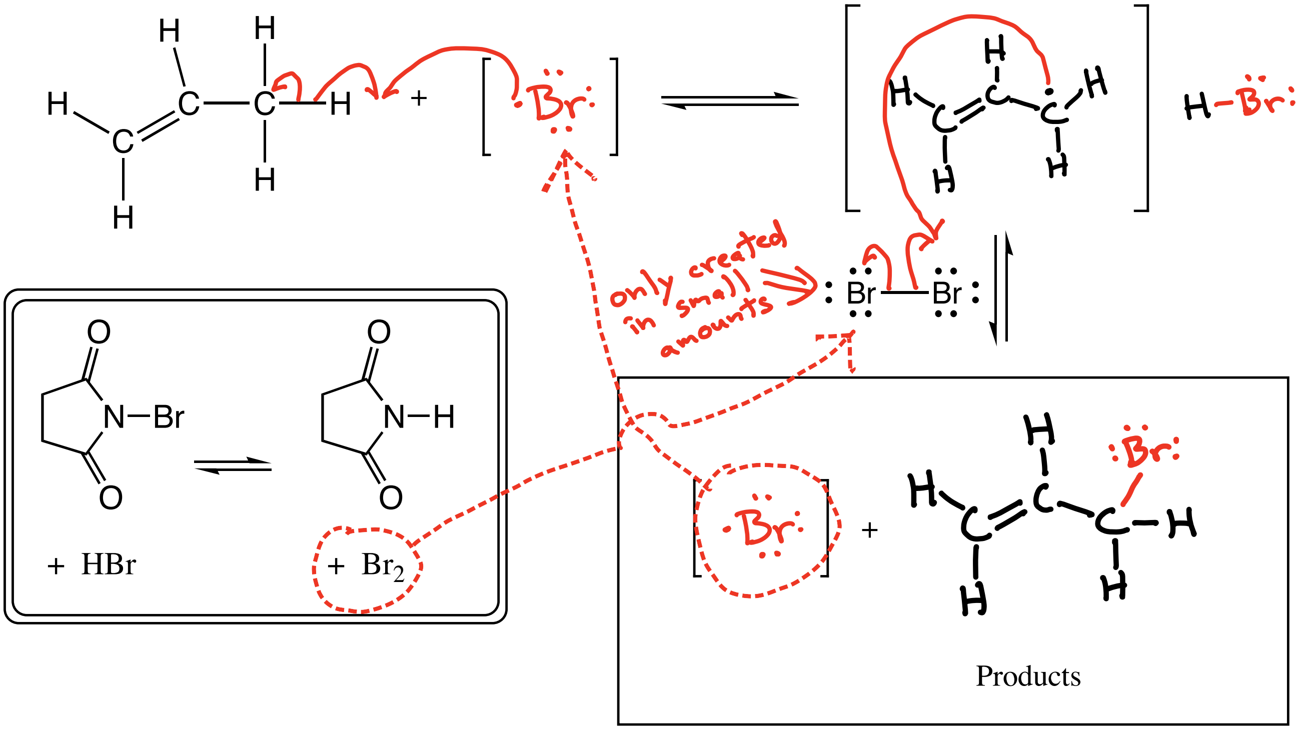


Allylic Halogenation

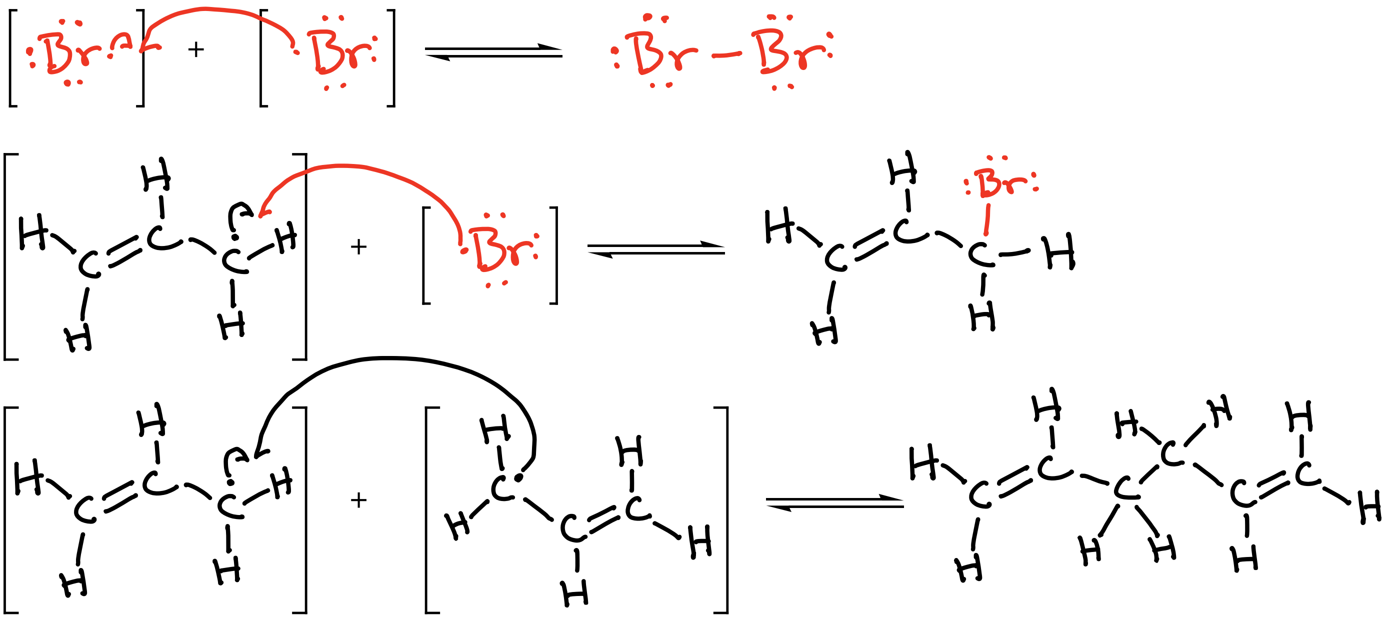
Initiation



Propagation

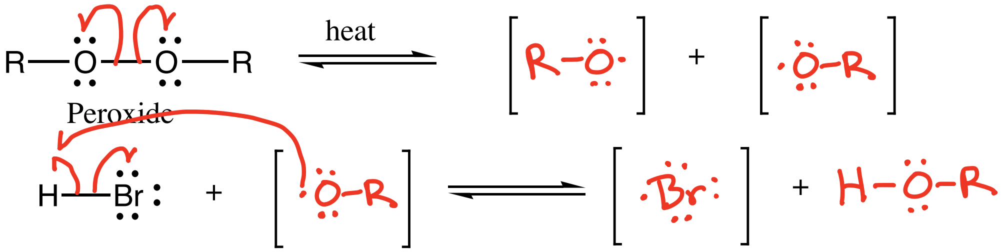


Termination

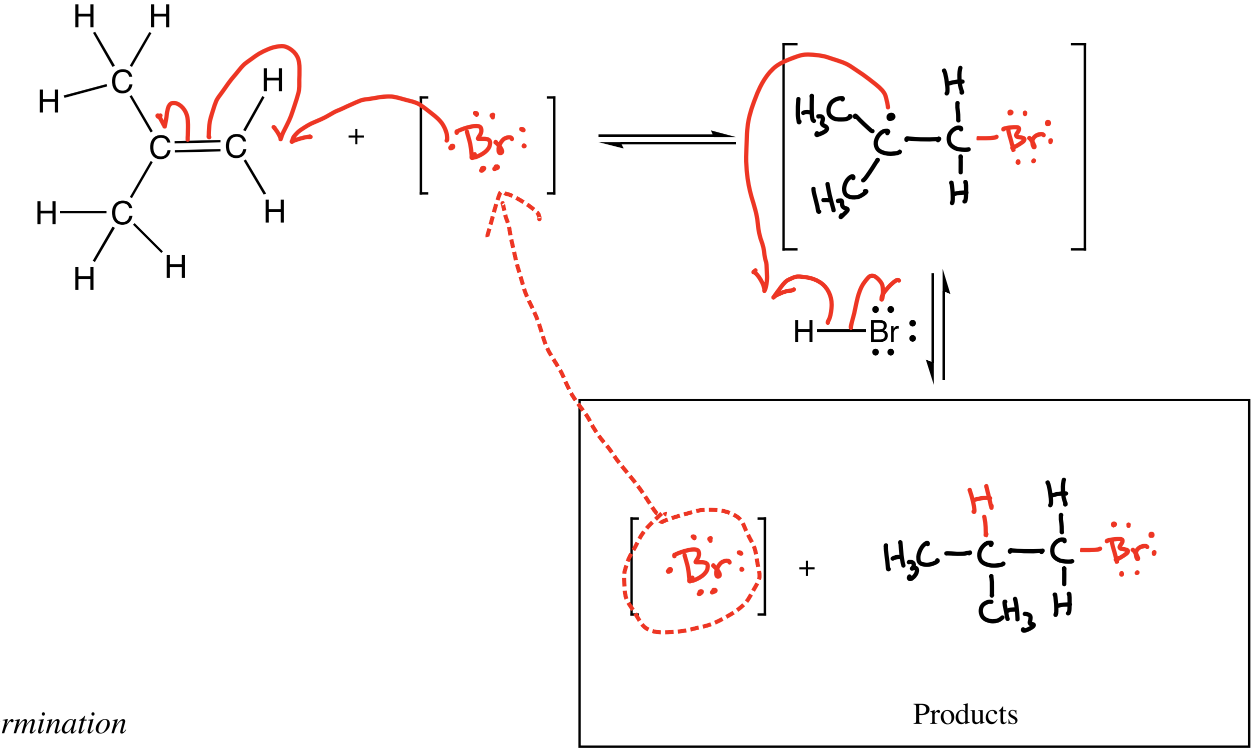


Non-Markovnikov Addition of HBr to an Alkene

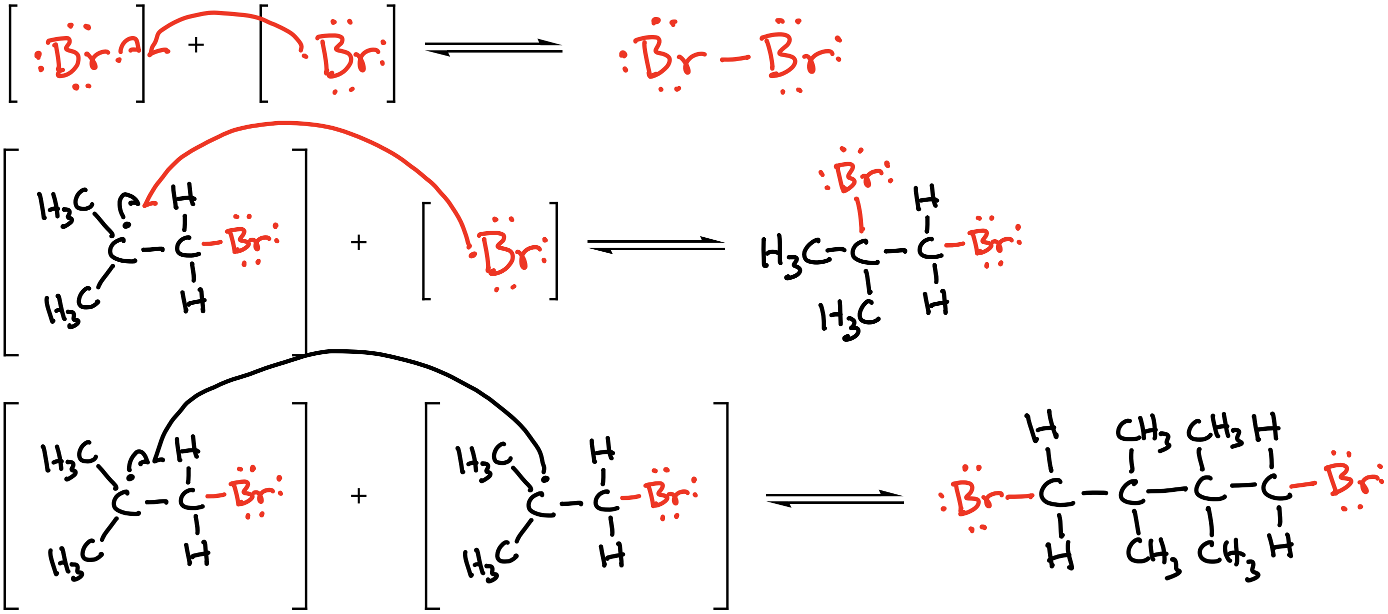
Initiation



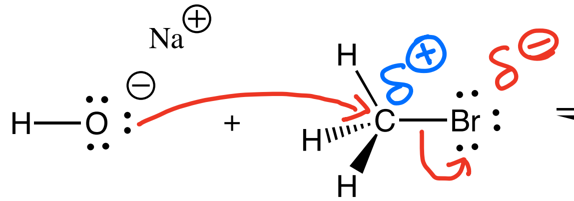
Propagation



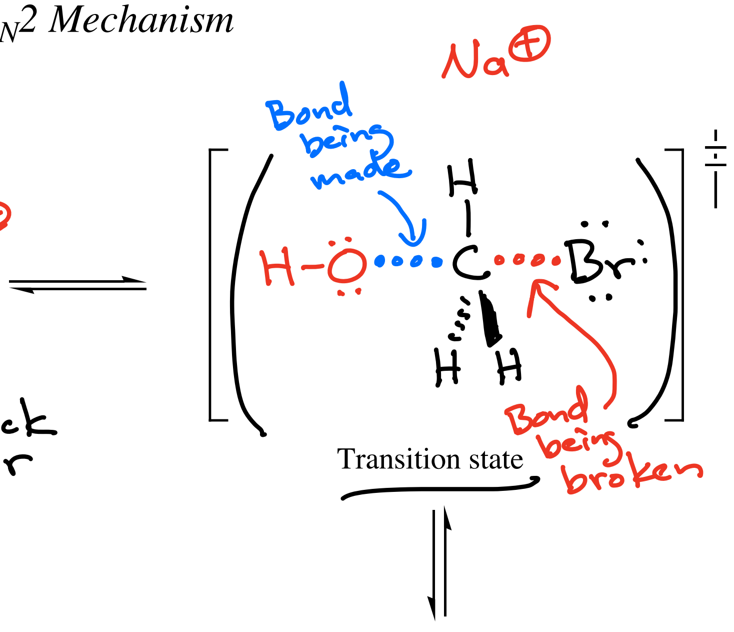
Termination

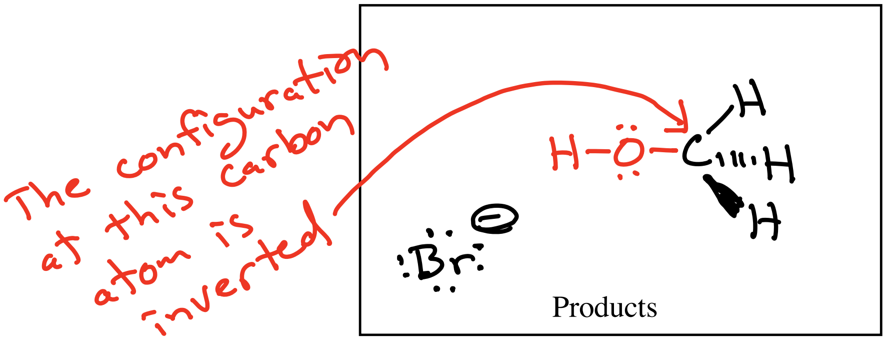


The S_N2 Mechanism



Nucleophile → must attack at the back of the C-Br bond. ⇒ This angle and direction of attack helps break the C-Br bond



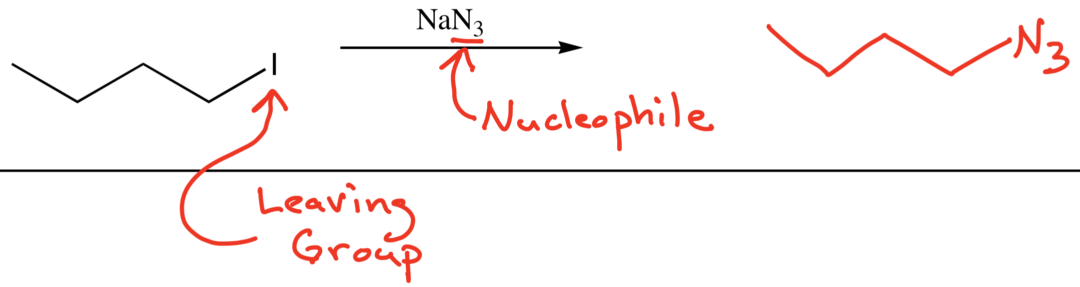


Summary: The nucleophile attacks by making a new bond to C from the back of the C-X bond just as X leaves

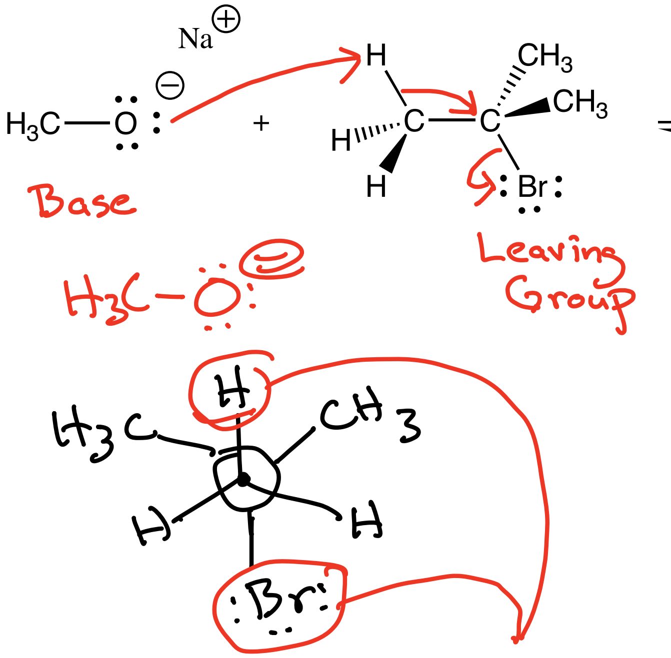
Regiochemistry: N/A

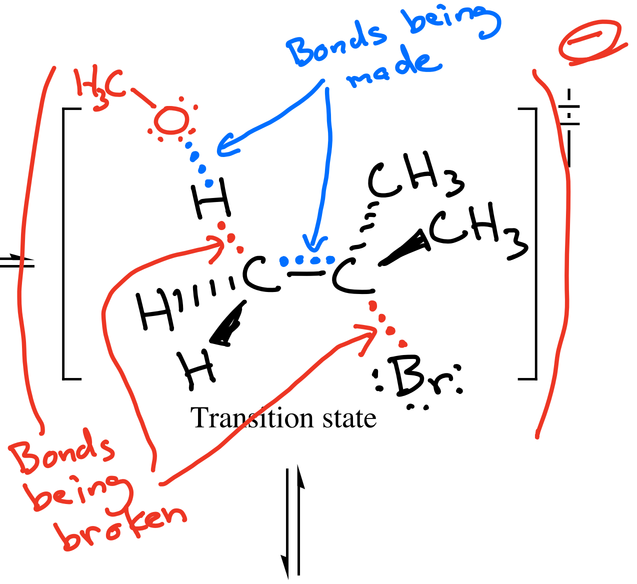
Stereochemistry: INVERSION at the site of reaction

Example:

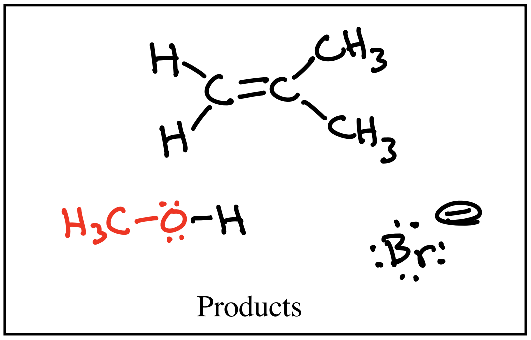


The E2 Mechanism





Transition state



Products

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

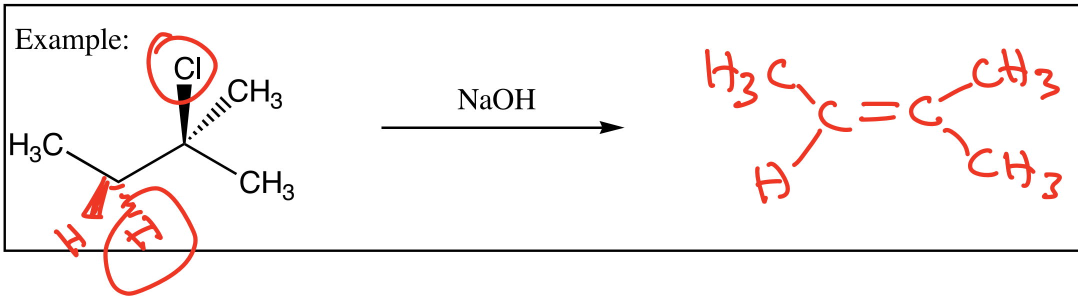
Summary: Base removes an H atom as a pi bond forms and the Br atom leaves

→ The H and Br must be anti-periplanar

Regiochemistry: Zaitsev's Rule → most stable alkene product

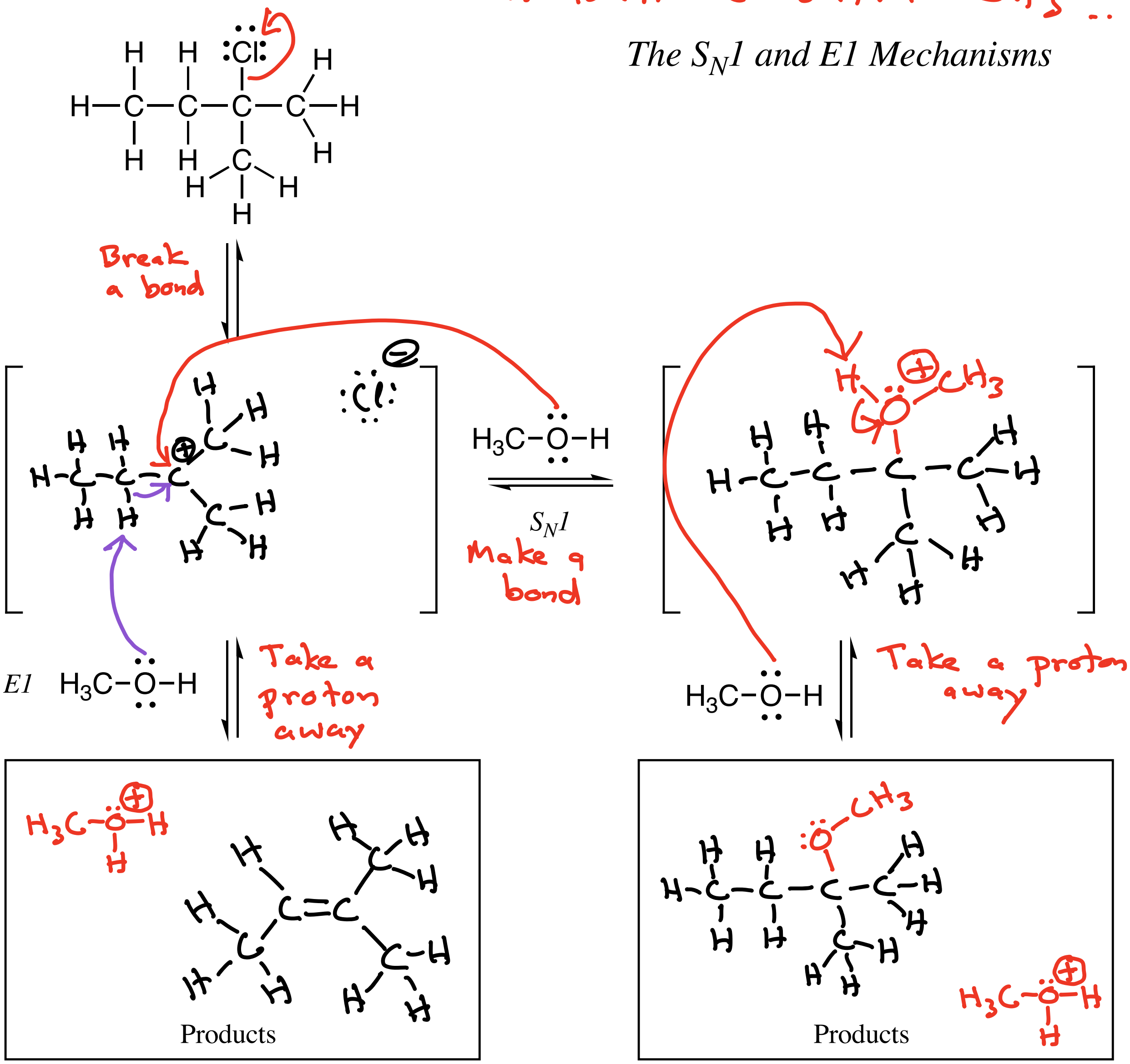
Stereochemistry: Determined by anti-periplanar transition state

Example:



Haloalkane with $CH_3-\ddot{O}-H$

The S_N1 and E1 Mechanisms

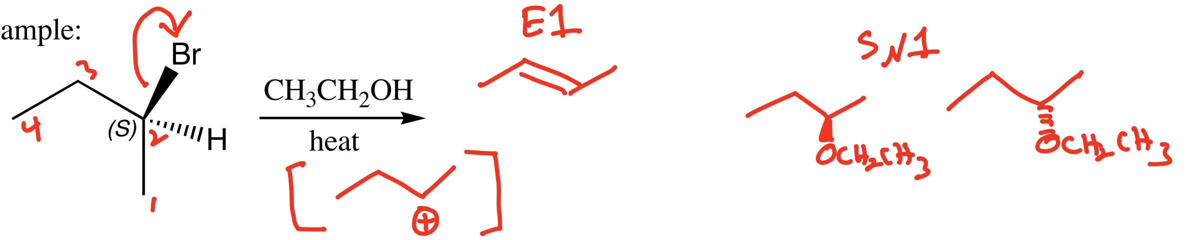


Summary: For sterically hindered haloalkanes, the C-X bond breaks to give a carbocation intermediate that either reacts as an electrophile (S_N1) or has a proton taken away (E1)

Regiochemistry: E1 → Zaitsev's Rule

Stereochemistry: S_N1 → Scrambled → not quite 1:1 exactly

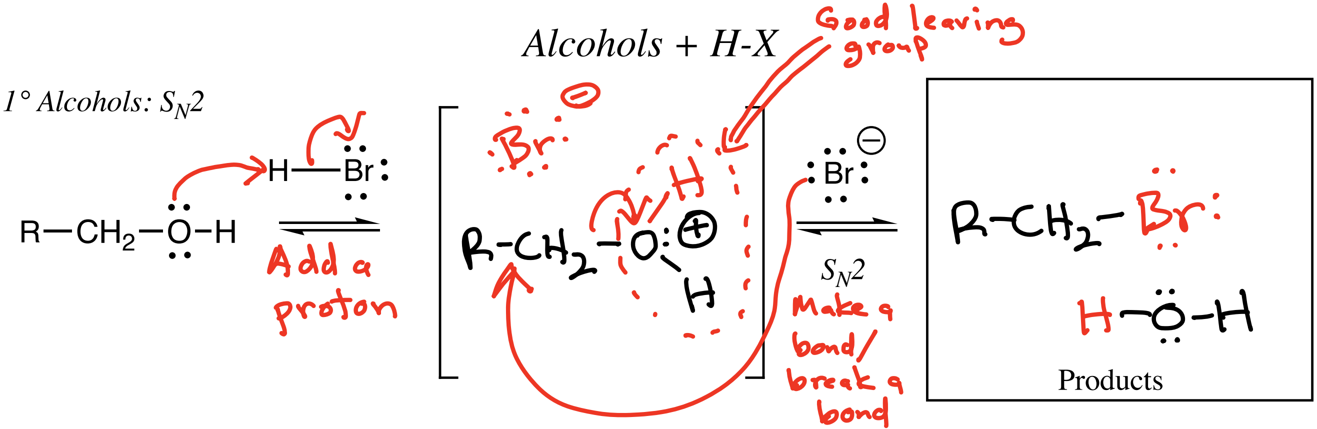
Example:



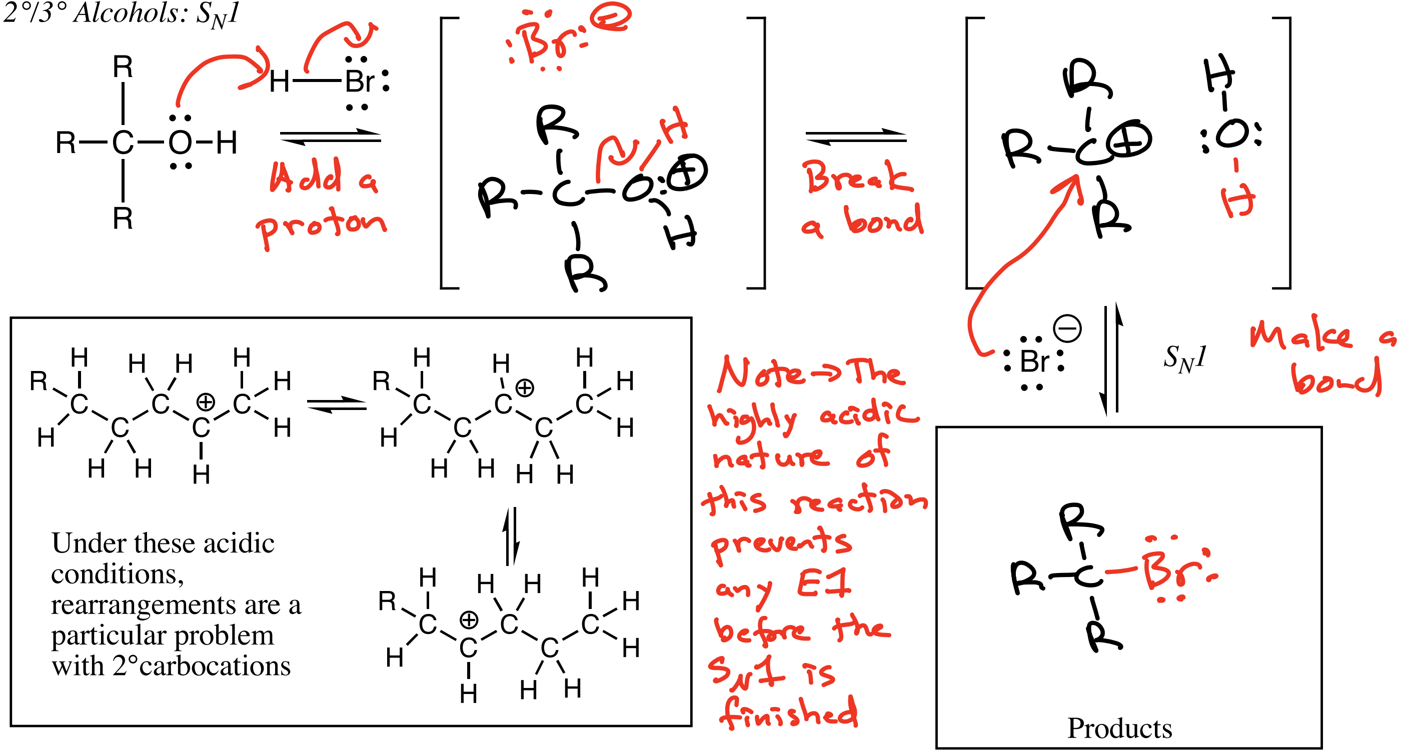
X = Cl, Br, I

Alcohols + H-X

1° Alcohols: S_N2



2°/3° Alcohols: S_N1



Under these acidic conditions, rearrangements are a particular problem with 2°carbocations

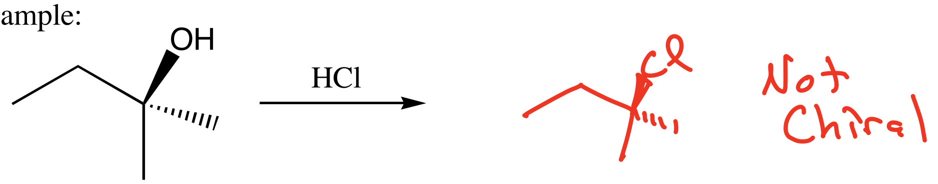
Note → The highly acidic nature of this reaction prevents any E1 before the S_N1 is finished

Summary: Reaction of primary alcohols → S_N2
Reaction of secondary/tertiary alcohols → S_N1
The -OH group is converted to a good leaving group by being protonated, followed by S_N2 or S_N1 substitution

Regiochemistry: N/A

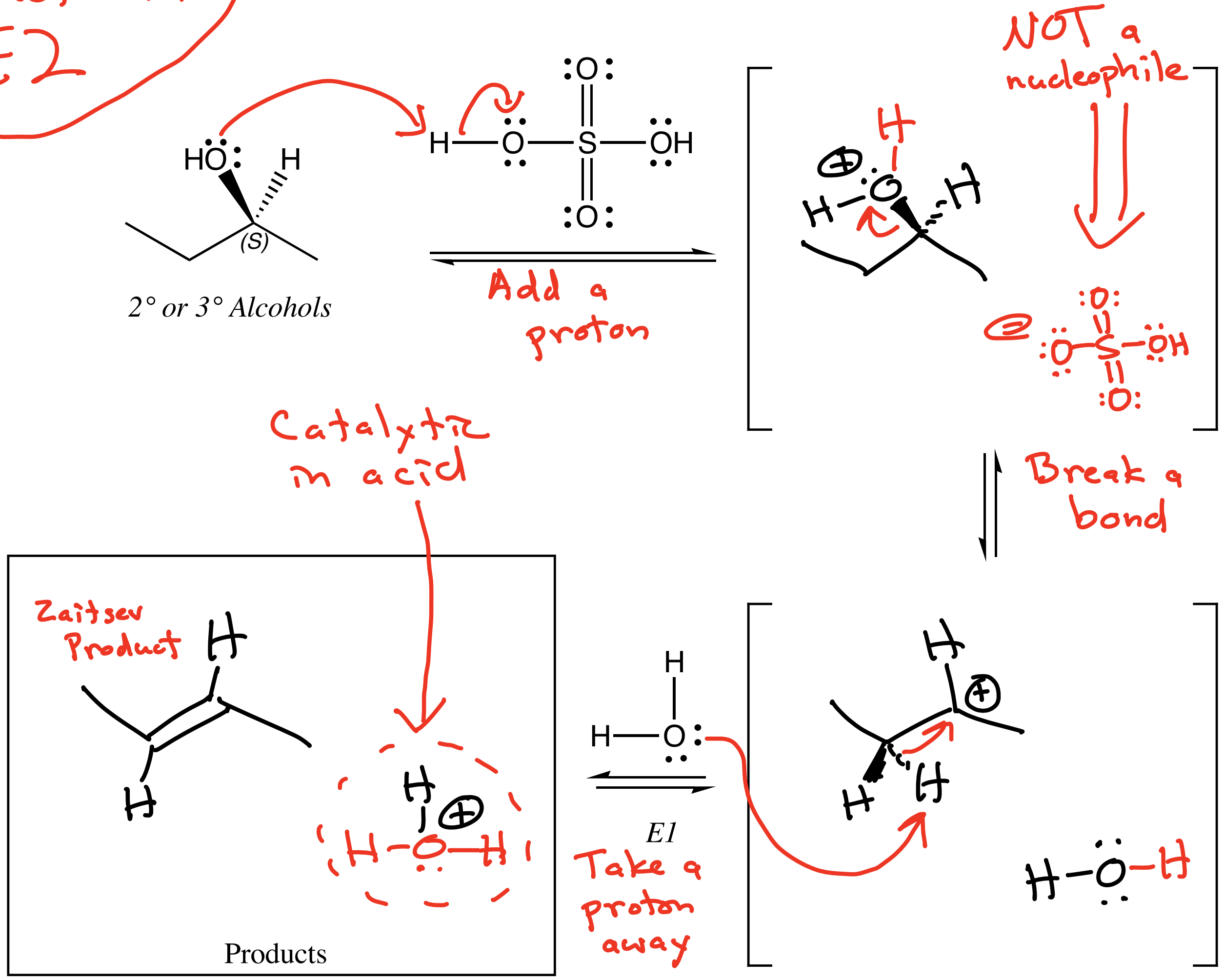
Stereochemistry: Chiral tertiary alcohols give scrambled products ← S_N1

Example:



1° alcohols react via E2

2° or 3° Alcohol Dehydration → E1

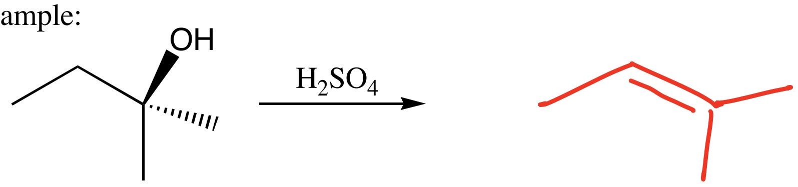


Summary: The OH group is protonated in strong acid to make a good leaving group, water, which breaks a bond to give a carbocation that has a proton taken away to give the product alkene

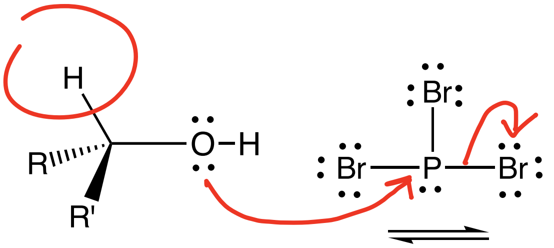
Regiochemistry: Zaitsev's Rule

Stereochemistry: N/A

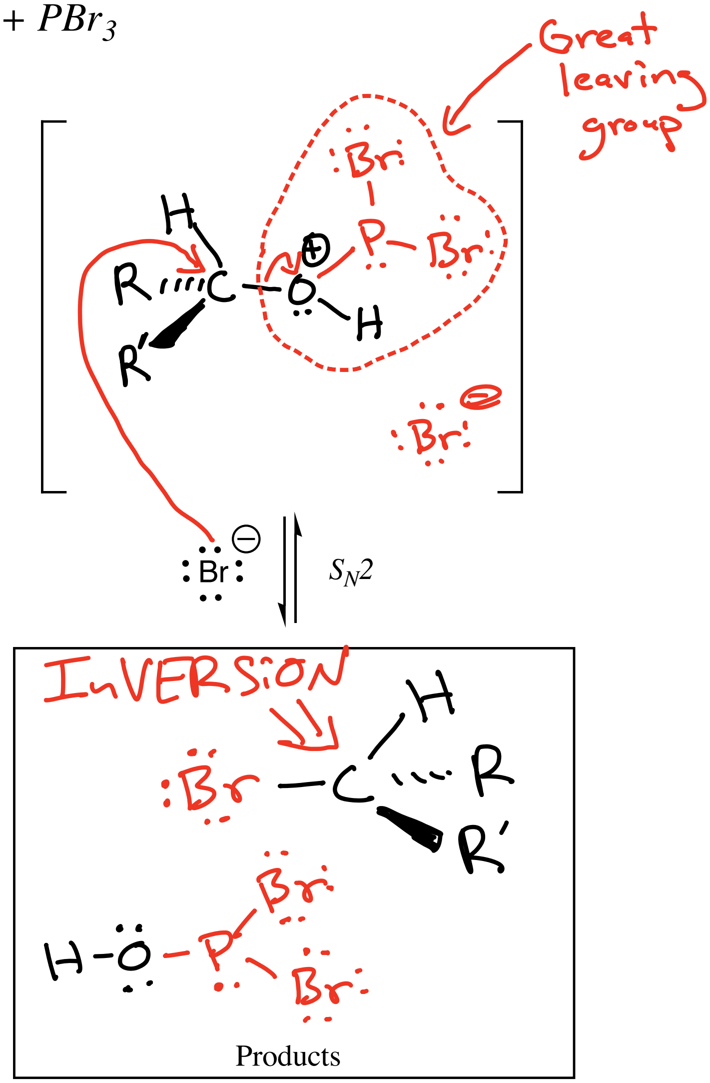
Example:



Alcohols + PBr_3



1° or 2° Alcohols



Does NOT work with 3° alcohols

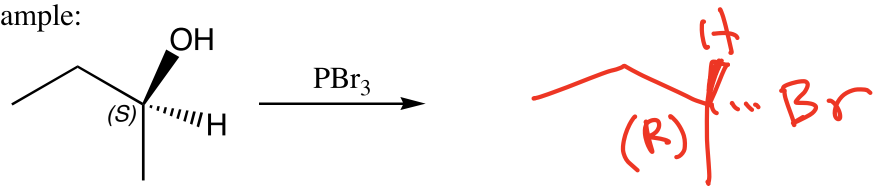
☆ There is an analogous reaction with $SOCl_2$ that converts alcohols into chloroalkanes

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 $Br^{\ominus}$ at the C atom

Regiochemistry: N/A

Stereochemistry: INVERSION

Example:

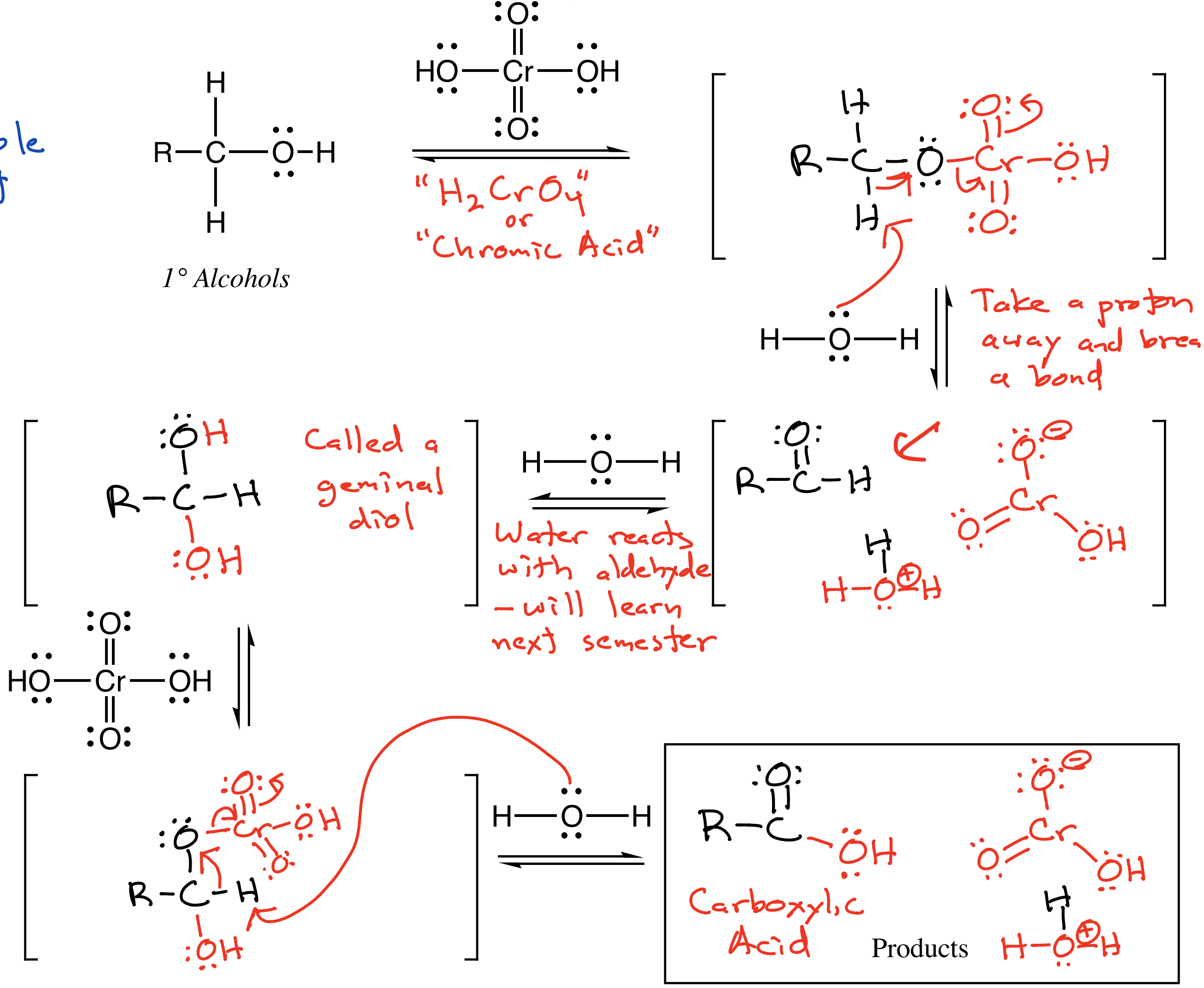


The $SOCl_2$ version of the reaction

Called "Jones Reagent" $\left(\begin{matrix} CrO_3 + H_2O \\ \text{or} \\ K_2Cr_2O_7 \end{matrix}\right) + H_2SO_4$

Chromic Acid Oxidation of Alcohols

Not responsible for first step


1° Alcohols

"H_2CrO_4" or "Chromic Acid"

Take a proton away and break a bond

Called a geminal diol

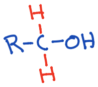
Water reacts with aldehyde – will learn next semester

Carboxylic Acid

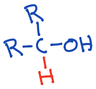
Products

Not responsible for this step

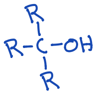
Summary:


1° alcohols ⇒ Carboxylic Acid

$R-\overset{O}{\overset{\|}{C}}-OH$


2° alcohols ⇒ Ketone

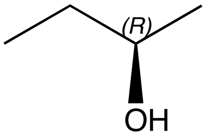
$R-\overset{O}{\overset{\|}{C}}-R$


3° alcohols ⇒ NO REACTION

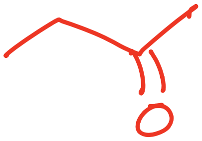
Regiochemistry: N/A

Stereochemistry: N/A

Example:

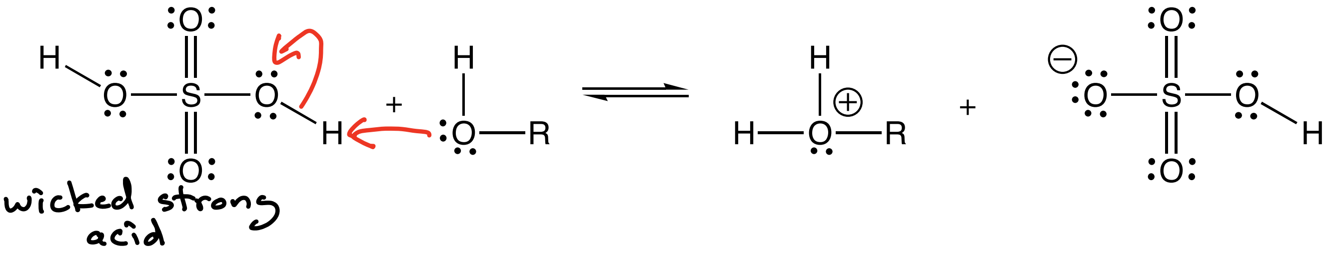


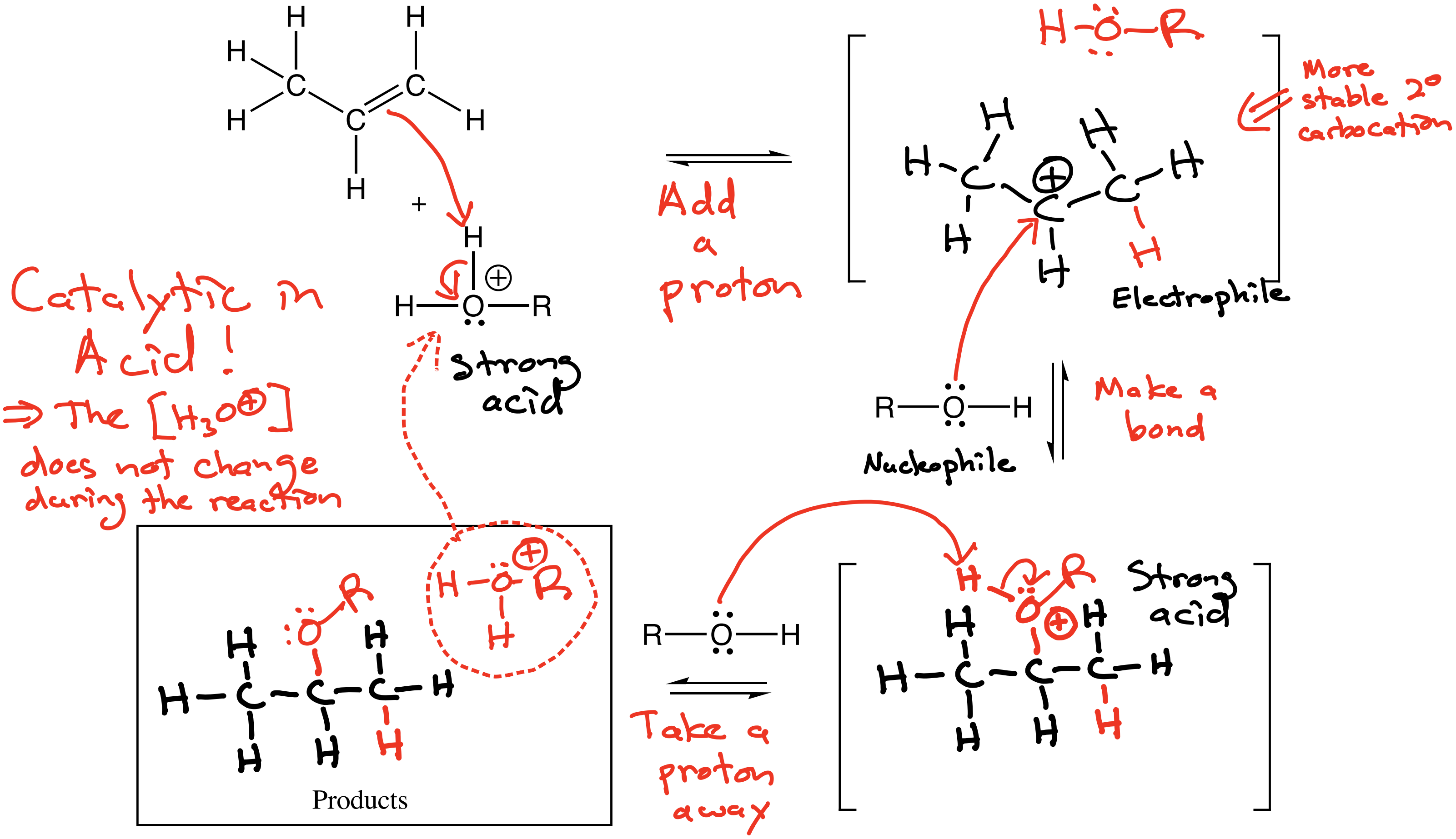
$\xrightarrow{H_2CrO_4}$



Ketone

Acid-catalyzed Reaction of an Alcohol with an Alkene

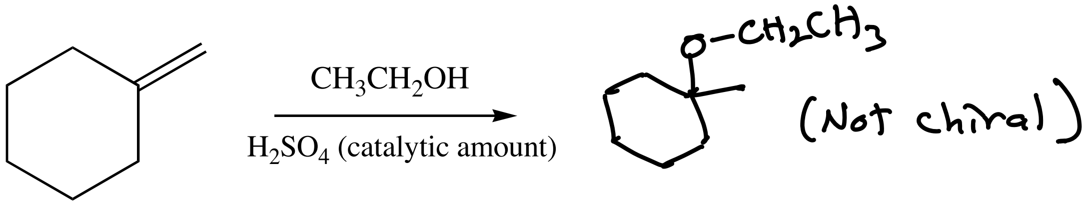




Catalytic in Acid!
⇒ The $[H_3O^{\oplus}]$ does not change during the reaction

Summary:	Proton adds to make a carbocation intermediate, alcohol attacks to make a new bond, take a proton away to make the product ether. Catalytic in $H_3O^{\oplus}$
Regiochemistry:	Markovnikov's Rule
Stereochemistry:	Mixed

Example:

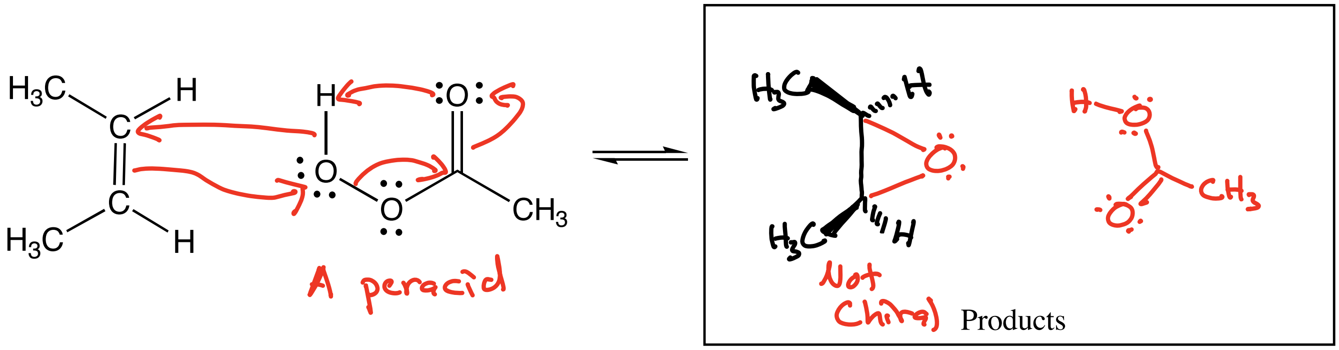

CH_3CH_2OH

H_2SO_4 (catalytic amount)

(Not chiral)

Synthesis of epoxides

Epoxide Formation

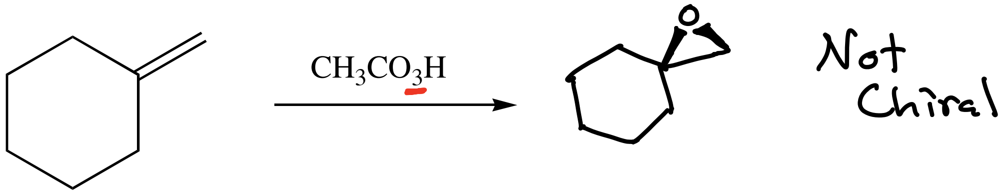


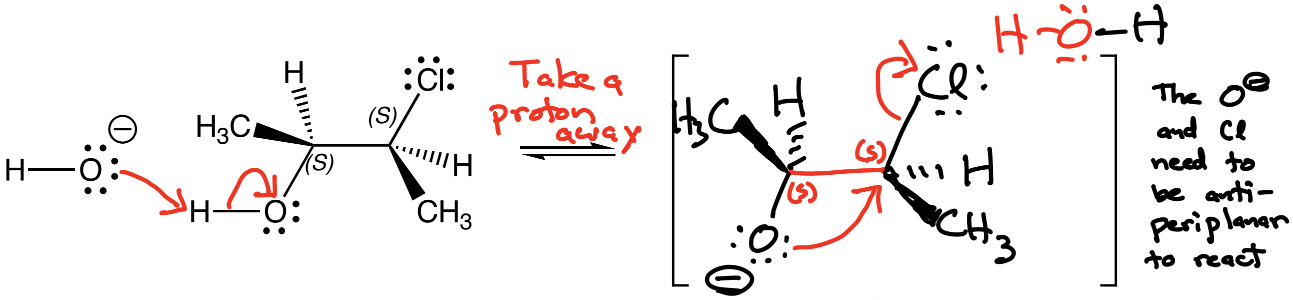
Summary: Alkenes react with peracids in a single concerted step

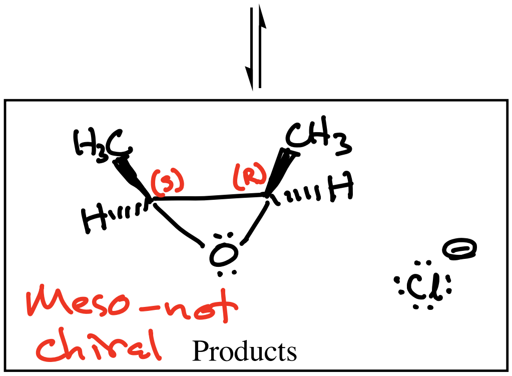
Regiochemistry: N/A

Stereochemistry: Mixed when new chiral centers are created

Example:





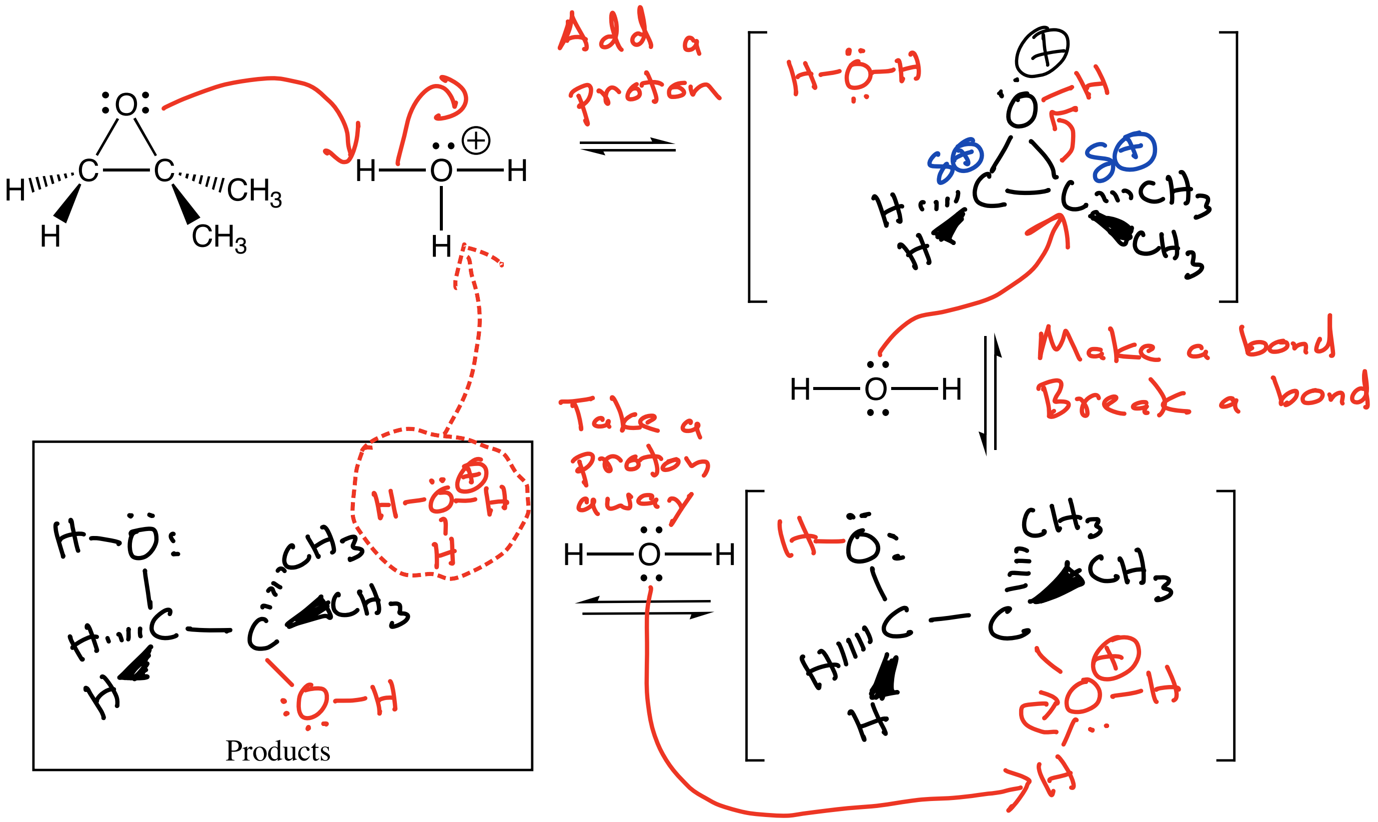


Summary: Halohydrins react in base to give the alkoxide that reacts antiperiplanar to give the epoxide.

Regiochemistry: N/A

Stereochemistry: Antiperiplanar transition state

Acid-Catalyzed Epoxide Opening

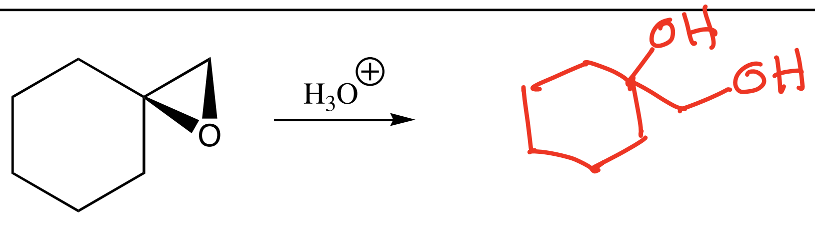


Summary: In acid, epoxides are protonated to give a highly reactive cation intermediate that reacts with nucleophiles at the more highly substituted carbon atom

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

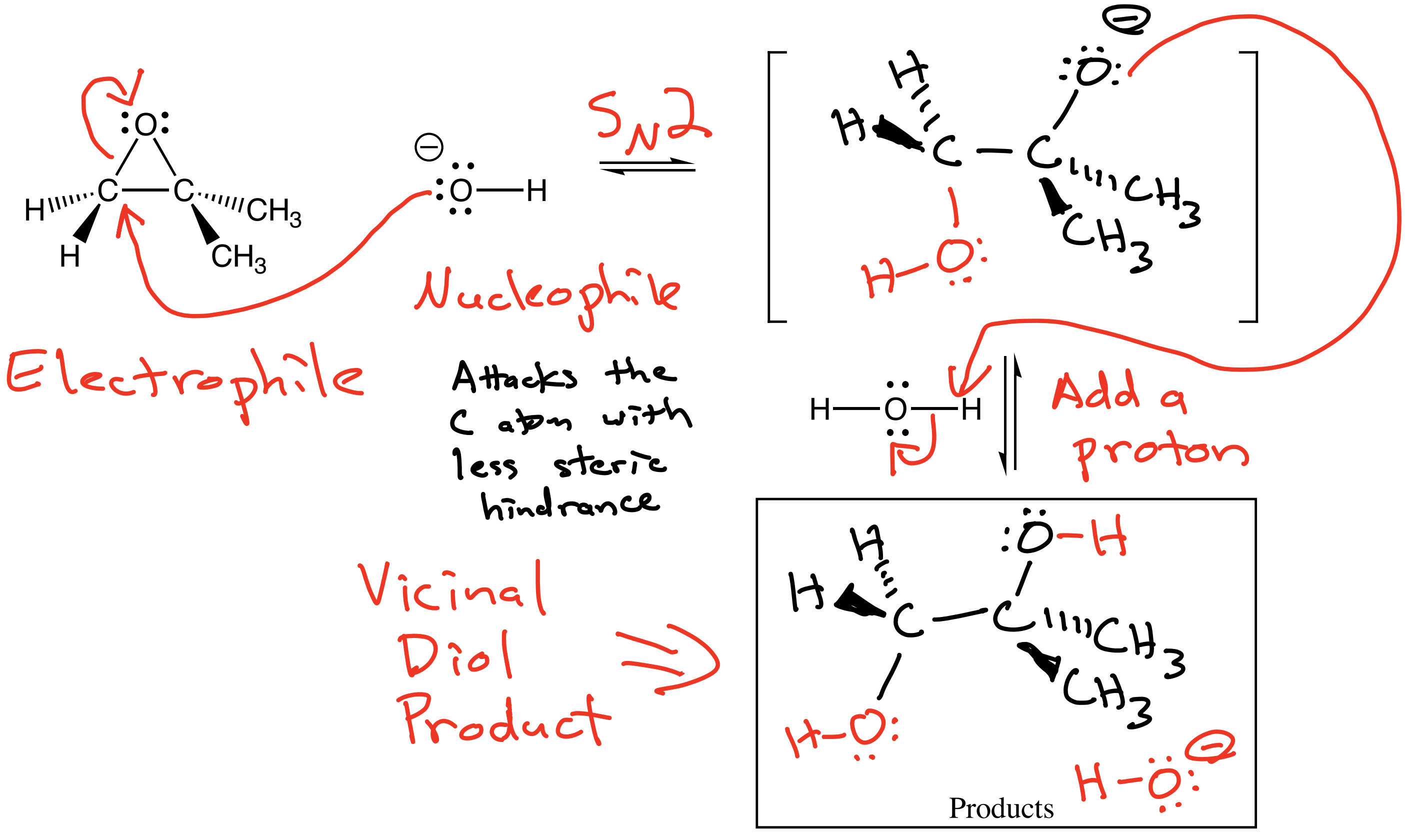
Stereochemistry: Anti

Example:



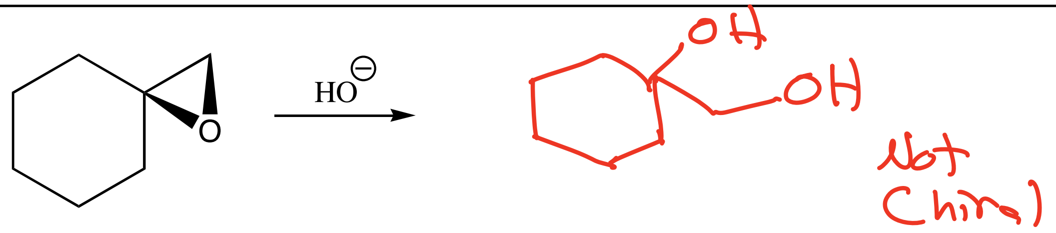
Not Chiral

Nucleophilic
~~Base Promoted~~ Epoxide Opening

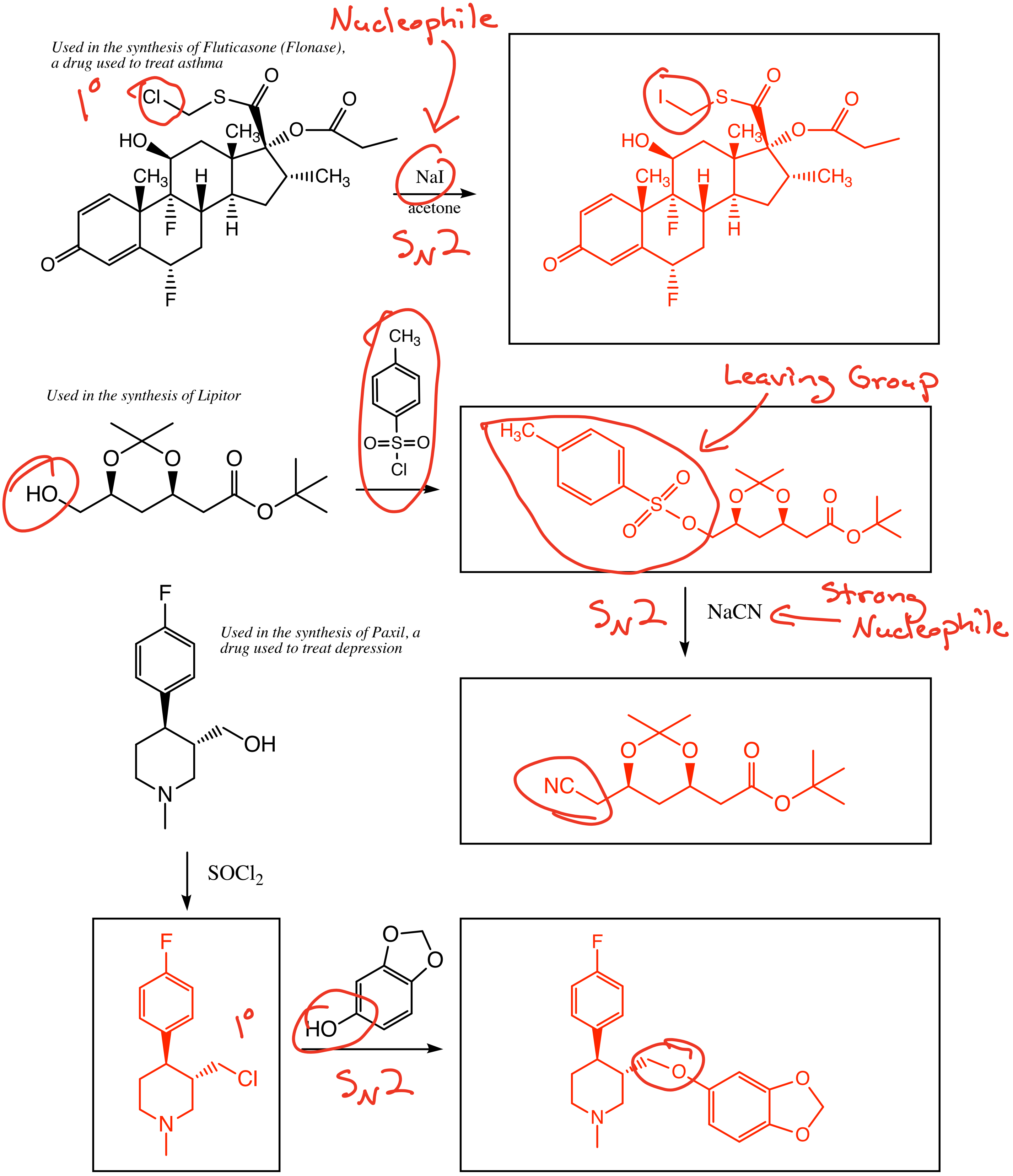


Summary:	Epoxides add strong nucleophiles at the less hindered carbon atom
Regiochemistry:	Less hindered (non-Markovnikov) ✓
Stereochemistry:	Anti addition

Example:



Reactions in the Context of Complex Molecules



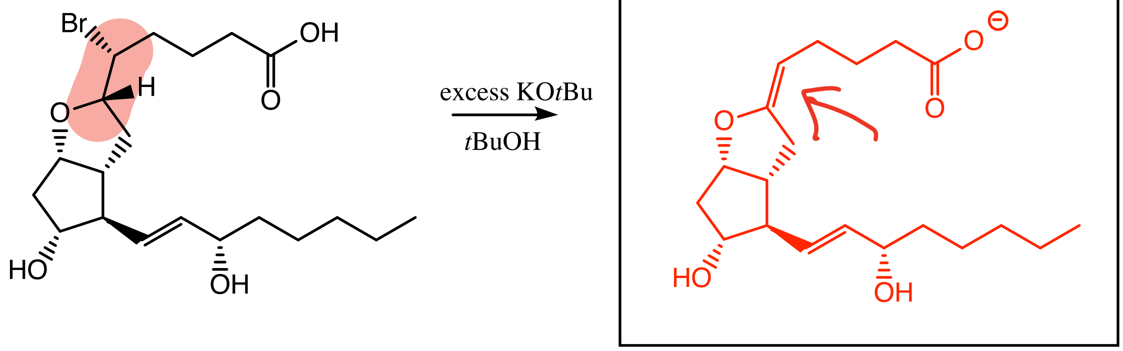
Used in the synthesis of Fluticasone (Flonase), a drug used to treat asthma

Used in the synthesis of Lipitor

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

Reactions in the Context of Complex Molecules

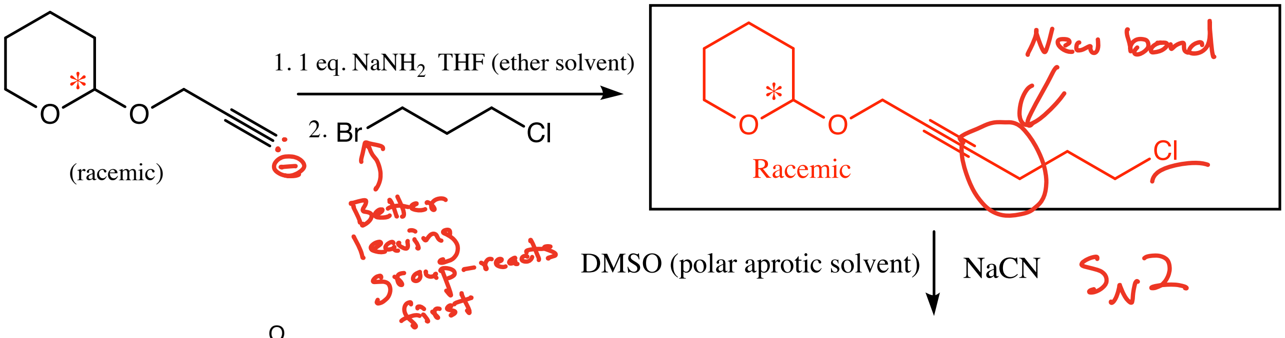
Used in the synthesis of several protaglandins



excess KO*t*Bu

*t*BuOH

Used in the synthesis of protaglandin C_2



(racemic)

1. 1 eq. $NaNH_2$ THF (ether solvent)

2. Br⁀⁀Cl

Better leaving group-reacts first

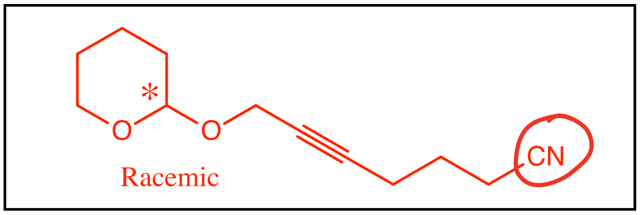
New bond

Racemic

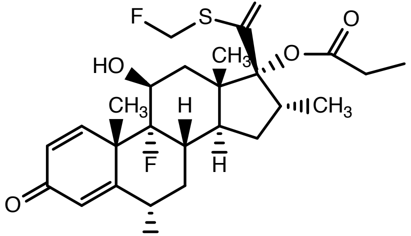
DMSO (polar aprotic solvent)

NaCN

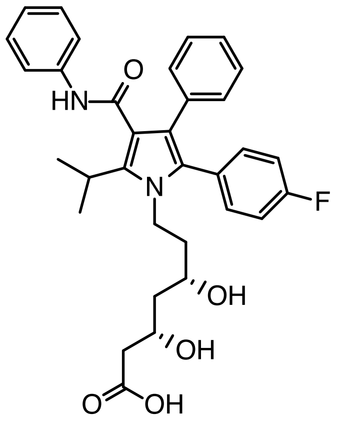
S_N2



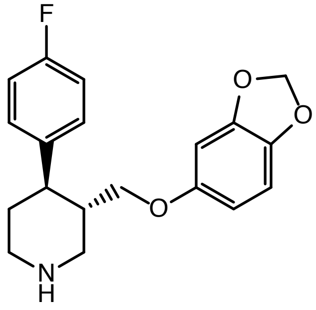
Racemic



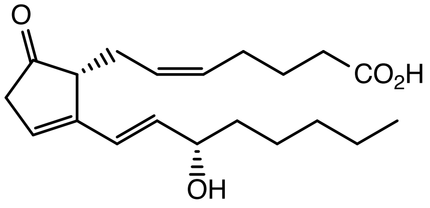
Fluticasone (Flonase)



Atorvastatin (Lipitor)



Paroxetine (Paxil)



Prostaglandin C_2