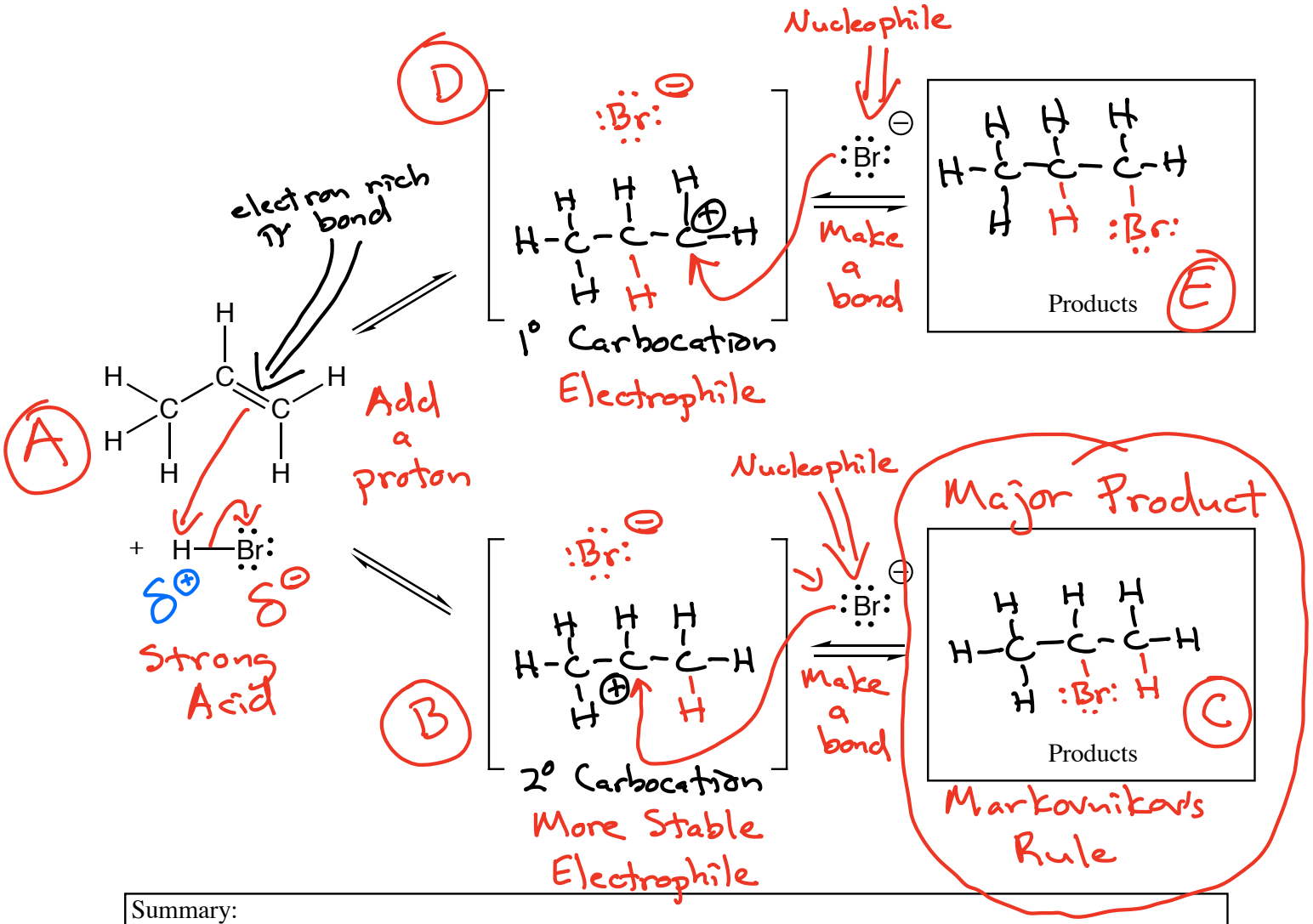
Addition of H-X to an Alkene

X = Cl, Br, I but not F



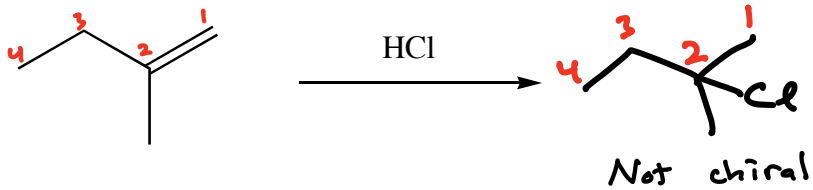
Summary:

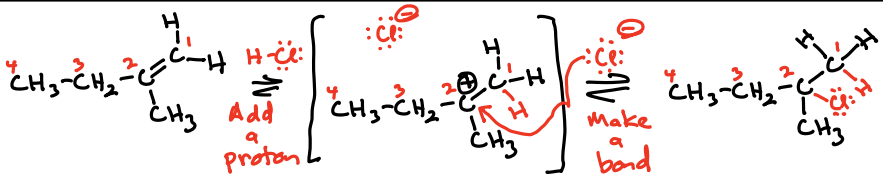
The alkene pi bond reacts with H-X to add a proton to create a carbocation intermediate that makes a bond with $X^{\ominus}$ to give the product

Regiochemistry: Markovnikov's Rule

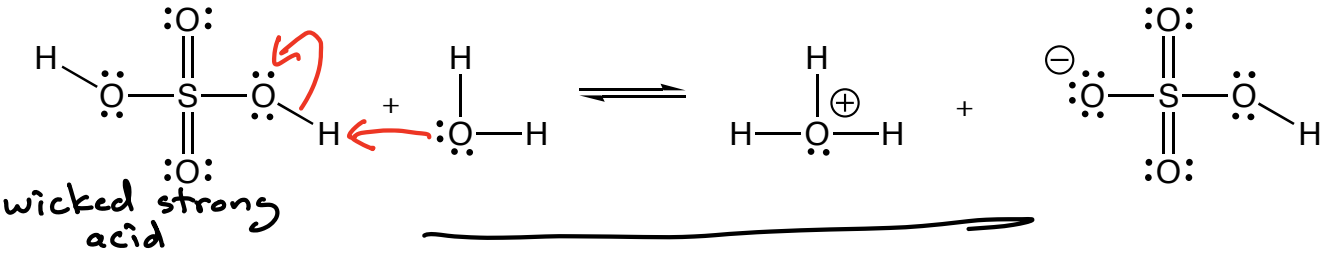
Stereochemistry: Mixed (time capsule) → Racemic Product

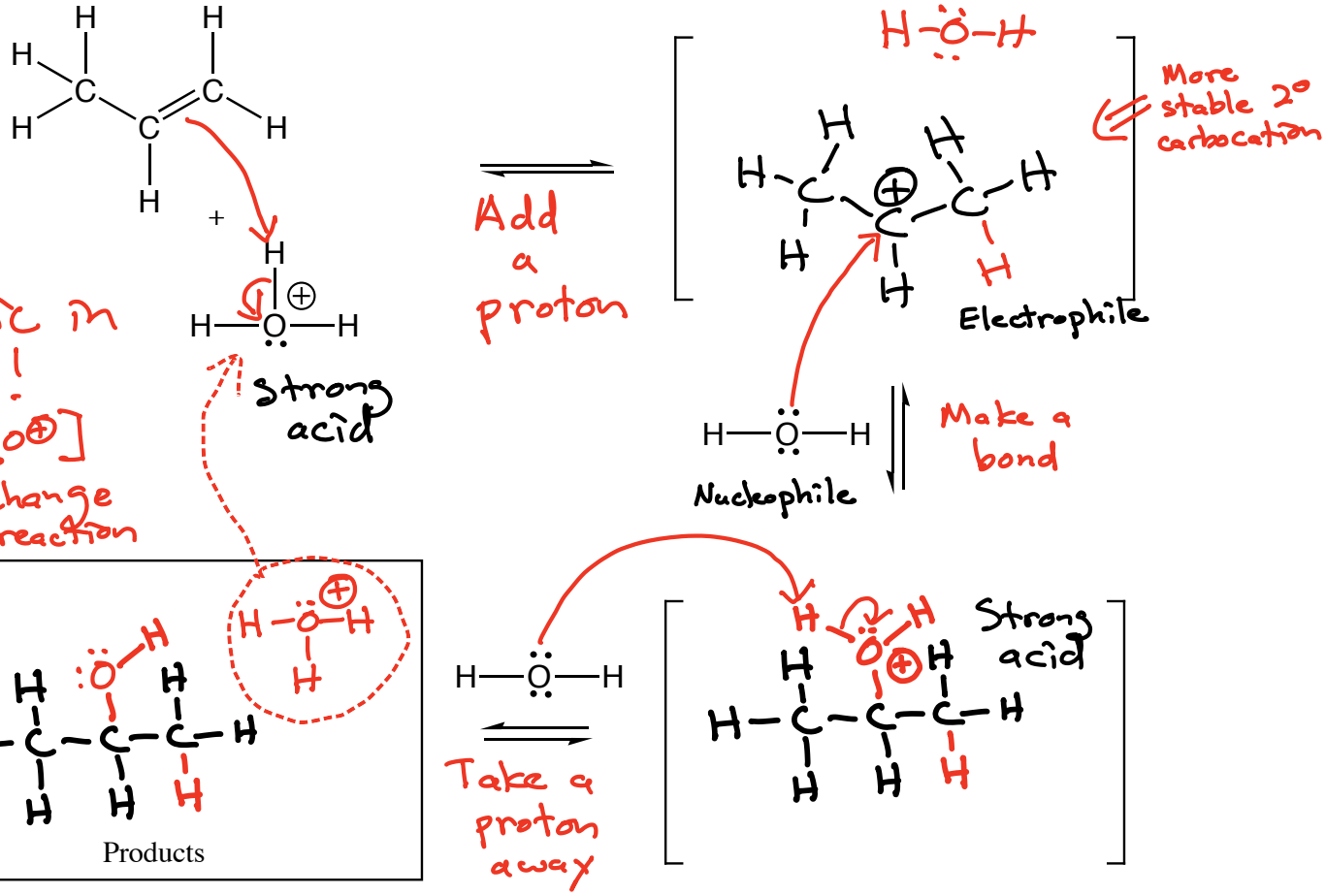
Example:





Acid-catalyzed Hydration of an Alkene

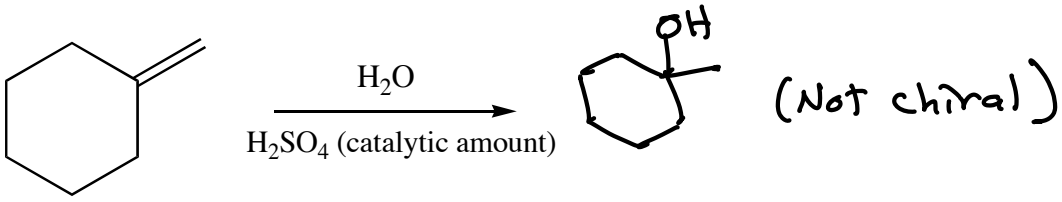




Catalytic in Acid!
⇒ The $[H_3O^{\oplus}]$ does not change during the reaction

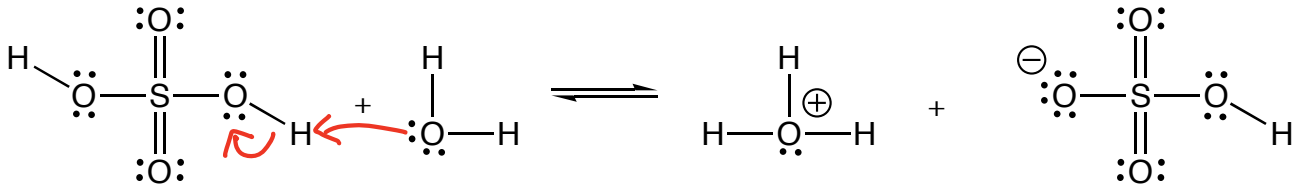
Summary:	Proton adds to make a carbocation intermediate, water attacks to make a new bond, take a proton away to make the product alcohol. Catalytic in $H_3O^{\oplus}$
Regiochemistry:	Markovnikov's Rule
Stereochemistry:	Mixed (time capsule)

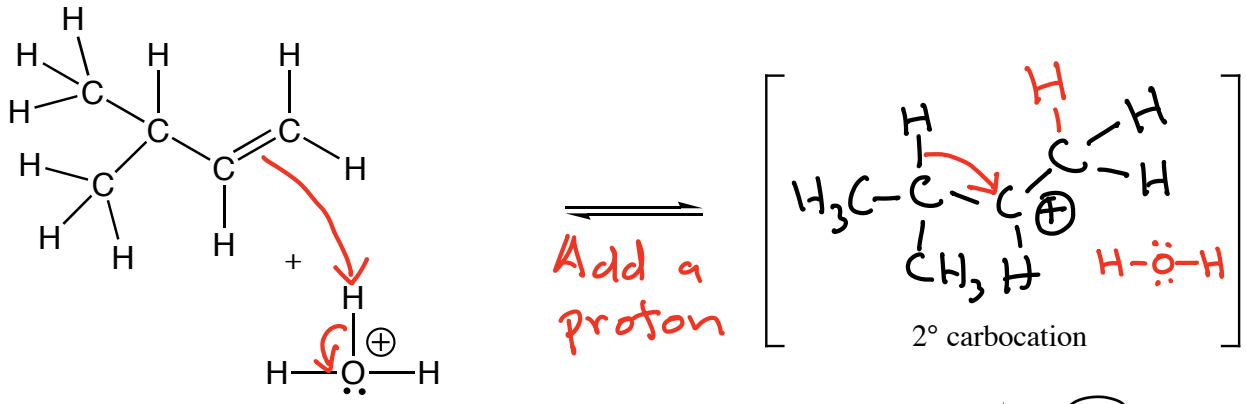
Example:



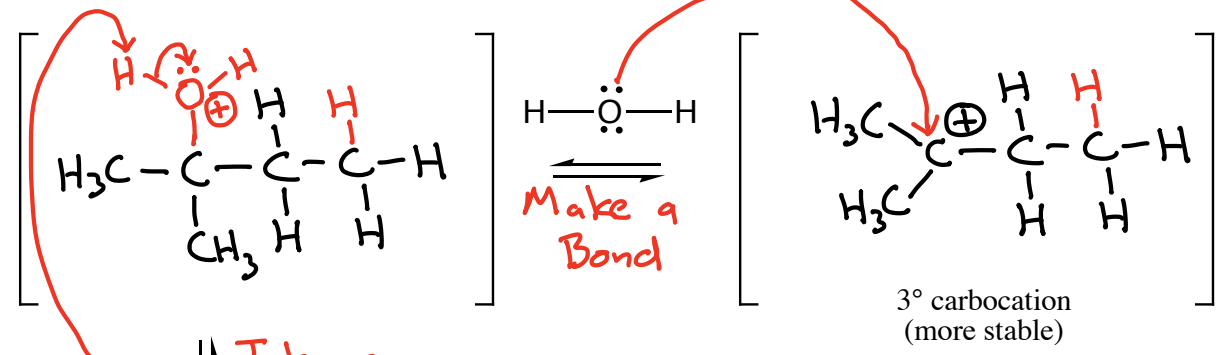
-OH on more substituted C atom ⇒ Markovnikov's Rule

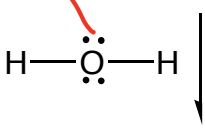
Cation Rearrangement

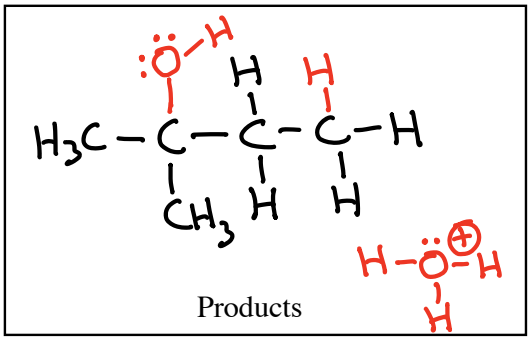


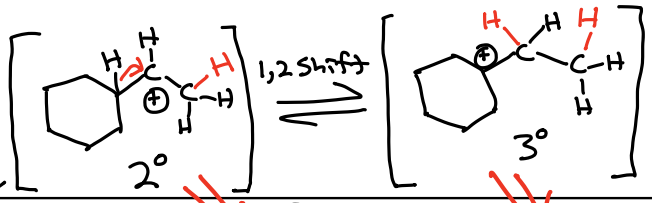


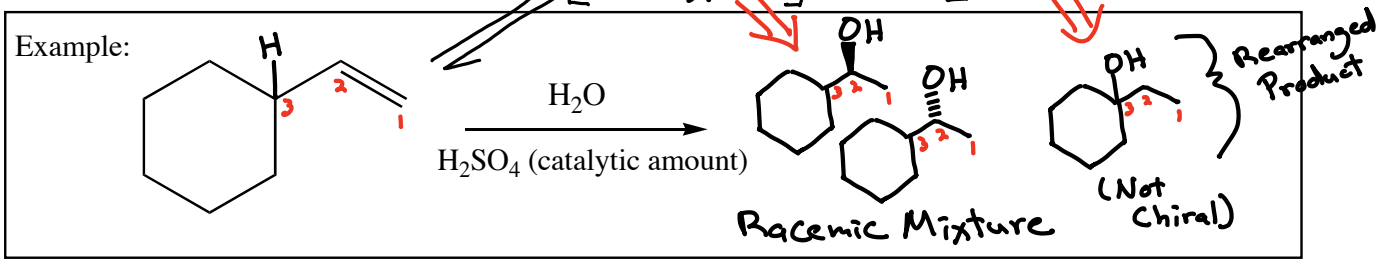
Rearrangement



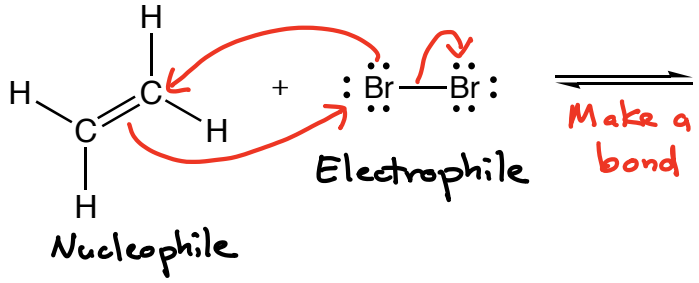


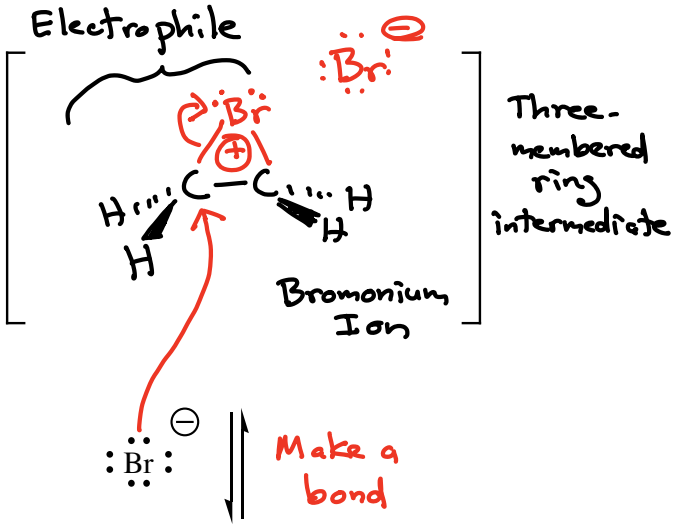






Alkene Halogenation

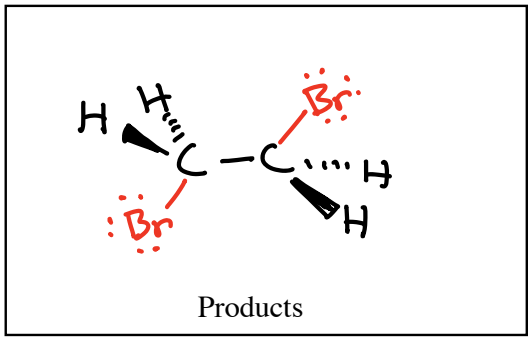




Called "anti" addition stereochemistry

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"

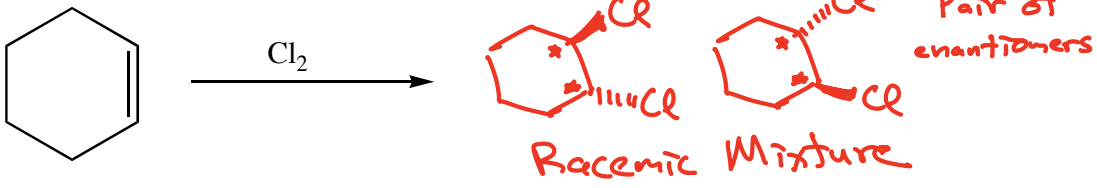


Summary: Alkenes react with X_2 to give a three-membered ring intermediate, then a new bond is made by $X^{\ominus}$ reacting from behind the C–X bond of the intermediate.

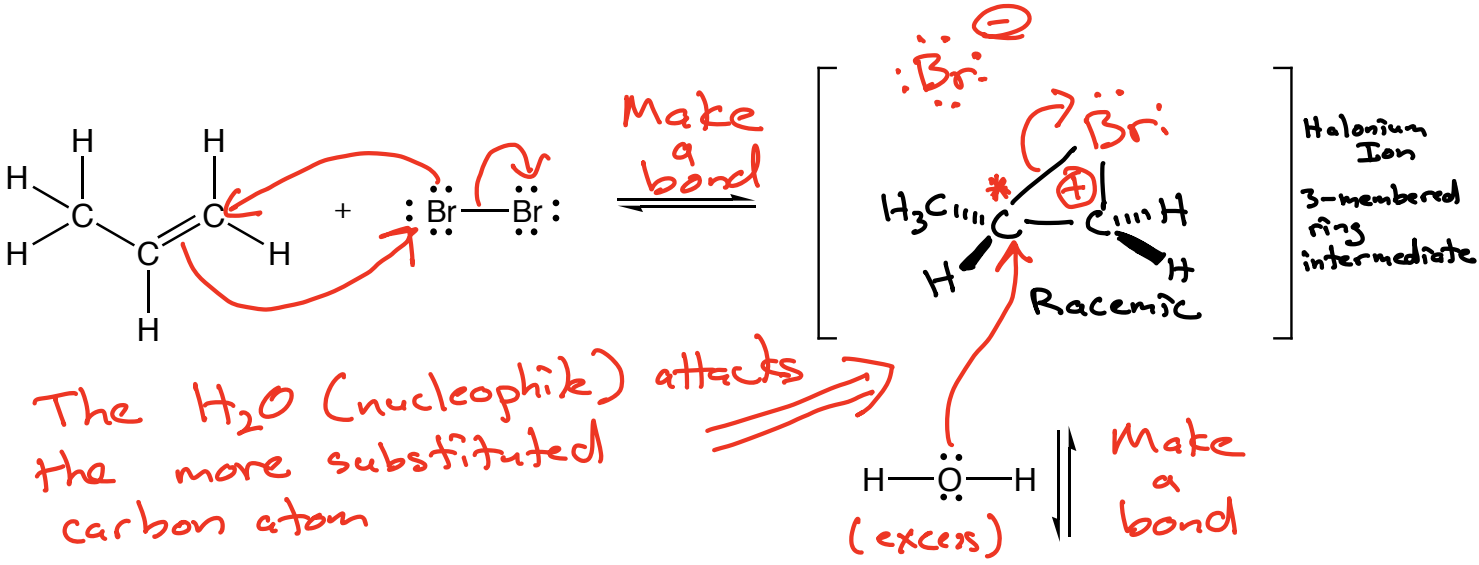
Regiochemistry: Not applicable → Br is on both atoms

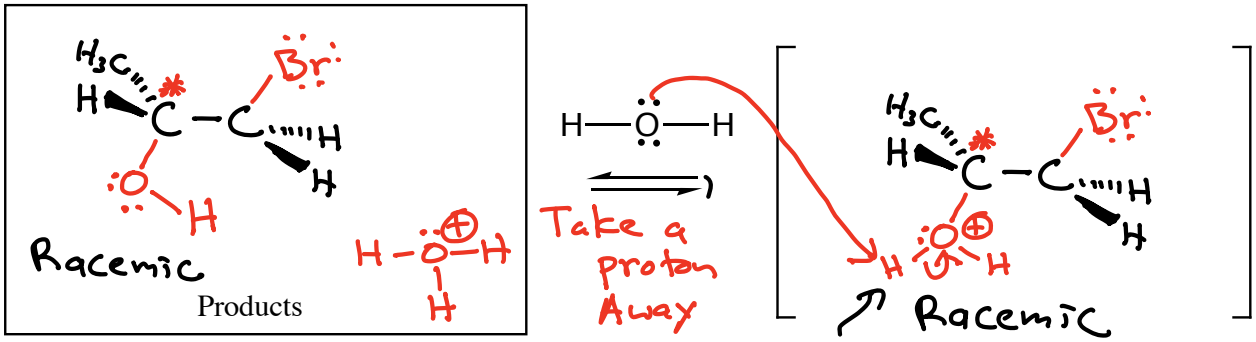
Stereochemistry: Anti addition geometry → trans products

Example:



Alkene Hydrohalogenation





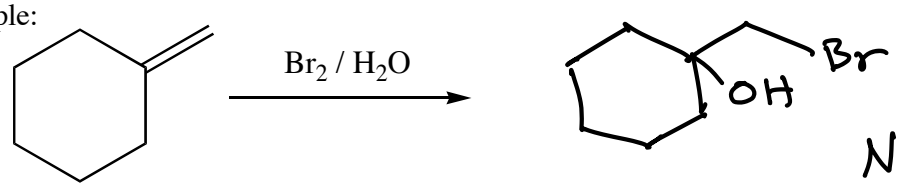
pH drops during the reaction!

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)

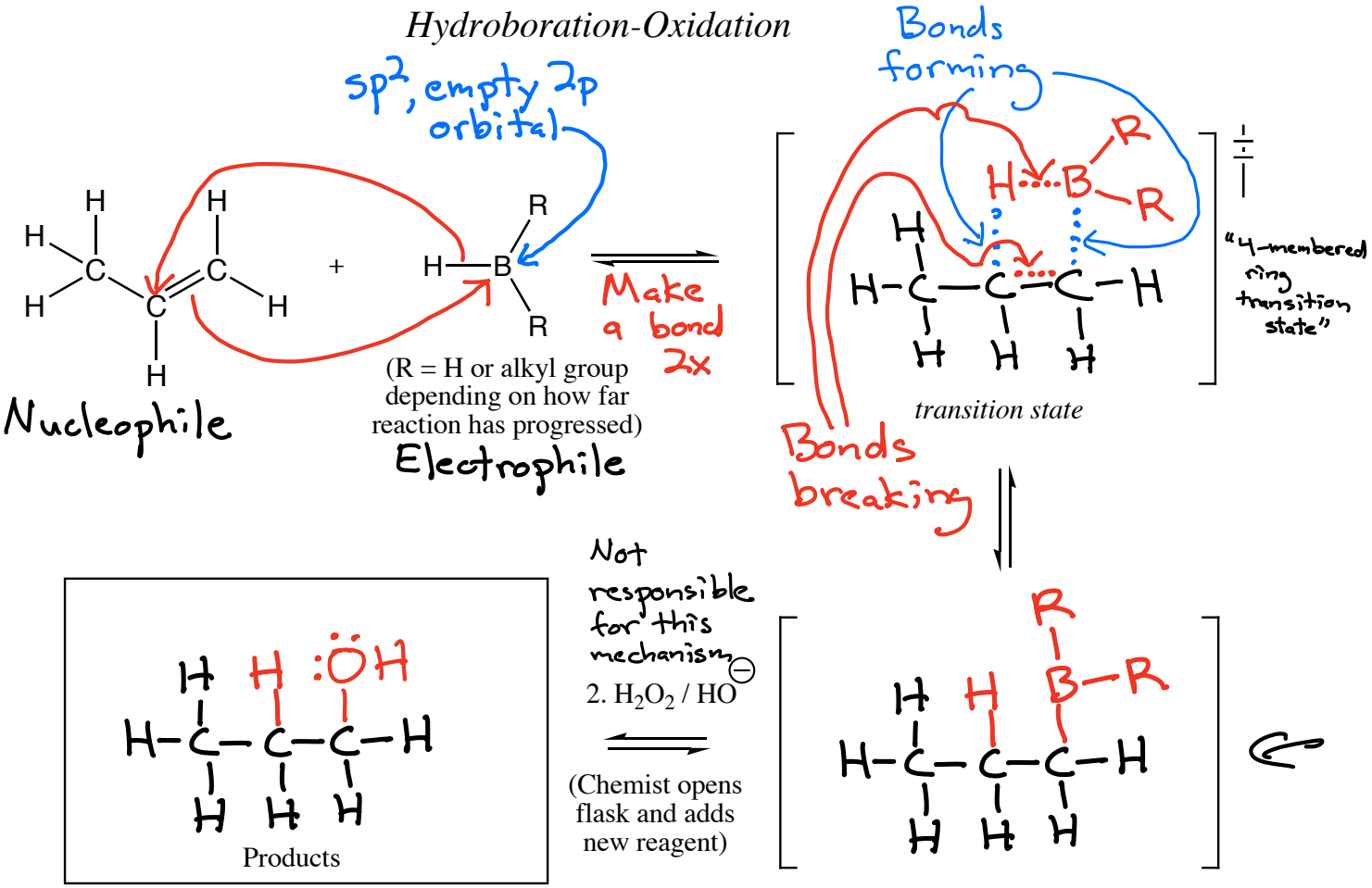
Stereochemistry: Anti

Example:



Not Chiral

Hydroboration-Oxidation



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

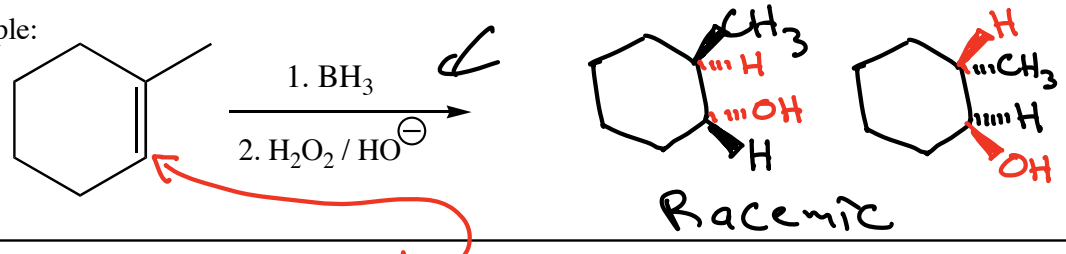
H and OH are syn

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"

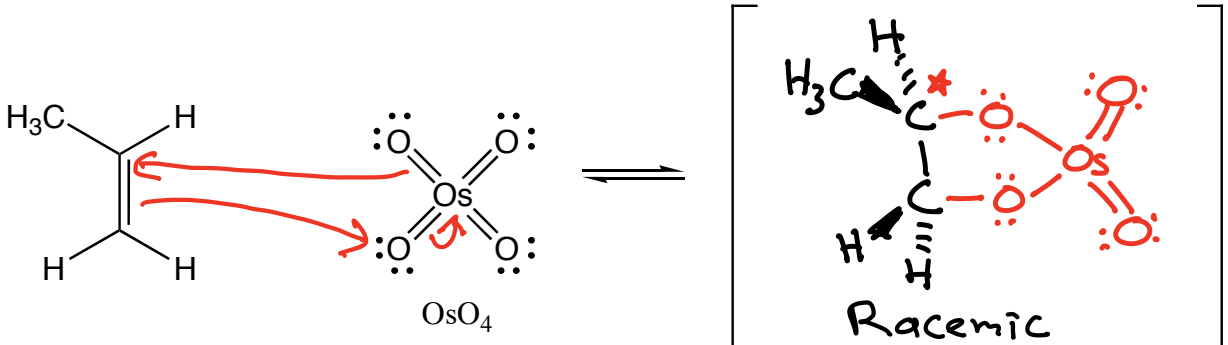
Regiochemistry: Non-Markovnikov

Stereochemistry: Syn

Example:



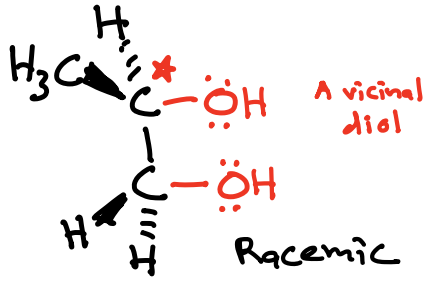
OsO_4 *Partial Mechanism*



A cyclic osmate ester

2. $NaHSO_3$ / H_2O
(Chemist opens up flask)

Not responsible for mechanism



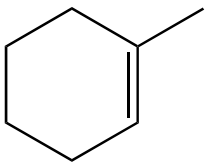
Product

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

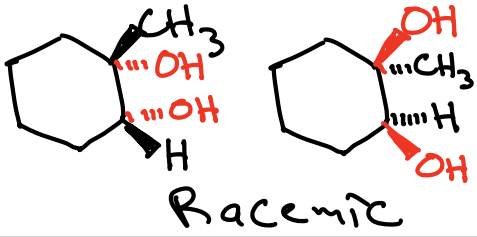
Regiochemistry: N/A

Stereochemistry: Syn

Example:

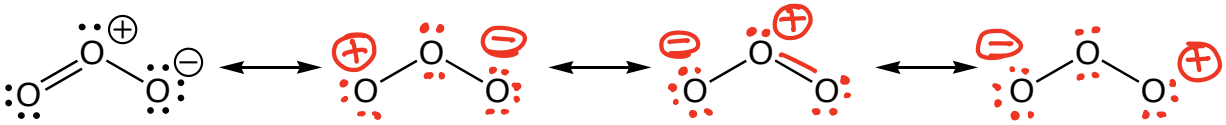


1. OsO_4
2. $NaHSO_3$ / H_2O

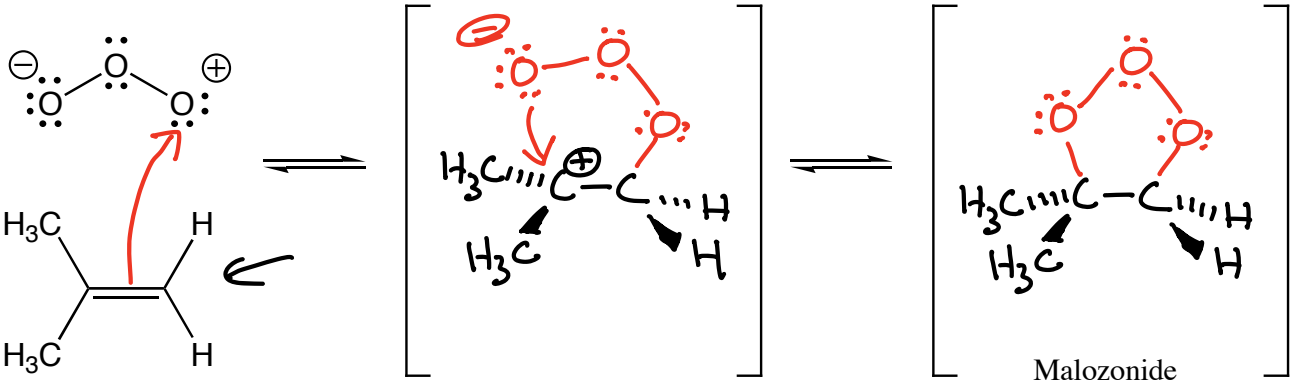


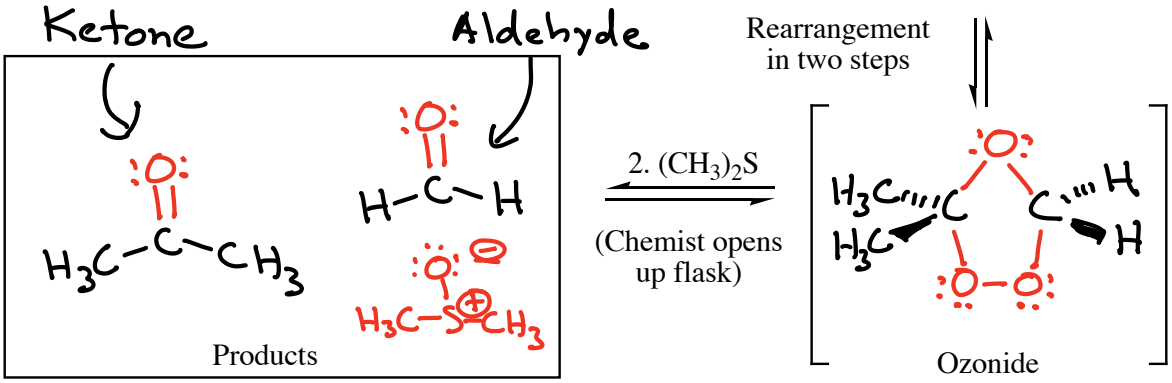
This breaks C=C bonds !!!

Ozonolysis Partial Mechanism



Ozone contributing structures



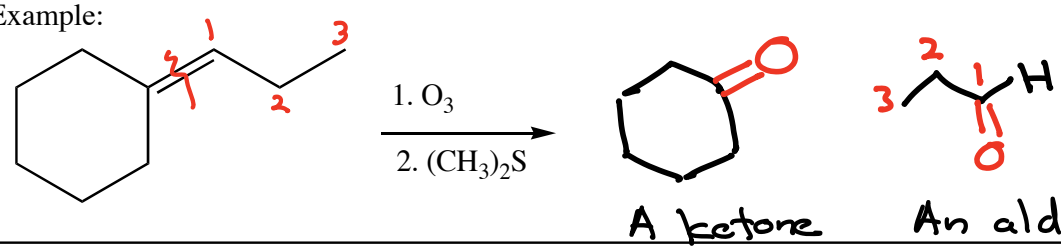


Summary: Reaction of an alkene with O_3 gives a malozonide than an ozonide intermediate (the C=C pi bond then C-C sigma bond is broken). Adding $(CH_3)_2S$ decomposes the ozonide into ketone and aldehyde products Breaks C=C bond!

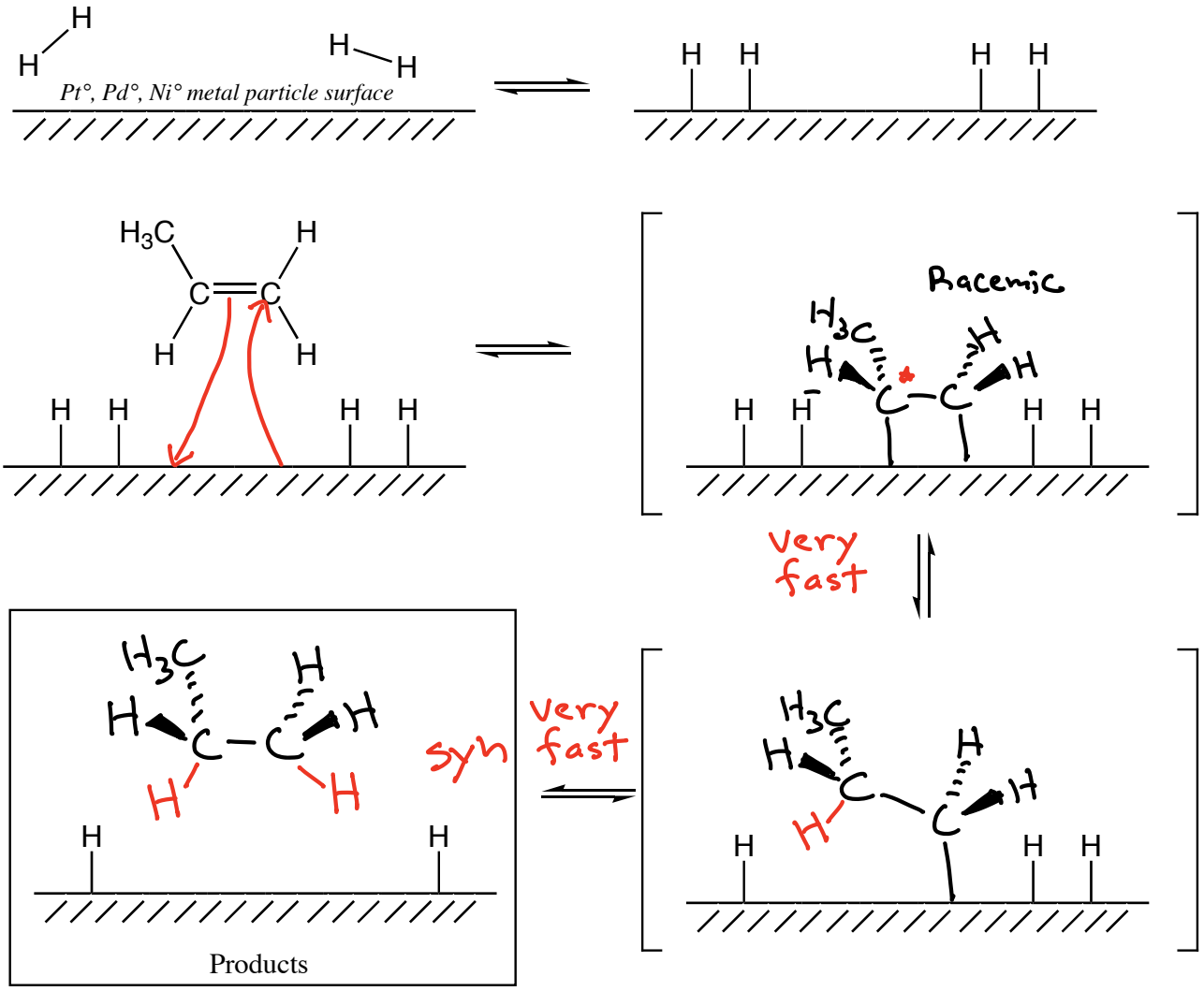
Regiochemistry: N/A

Stereochemistry: N/A

Example:



Hydrogenation: H_2 with Pt°, Pd°, Ni°

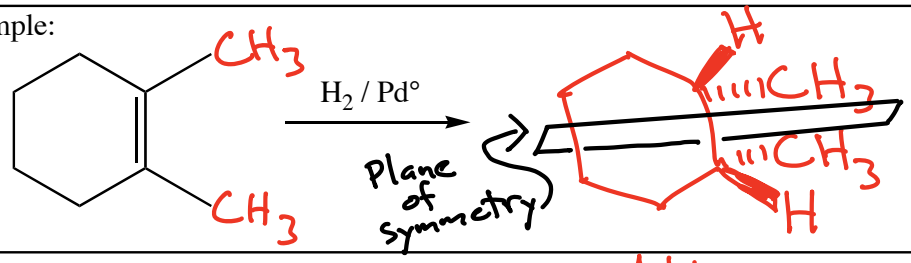


Summary: H_2 adsorbs onto the metal surface. The alkene adsorbs onto the metal surface. H atoms transfer to both C atoms → on the same face → before the C-C bond rotates

Regiochemistry: N/A

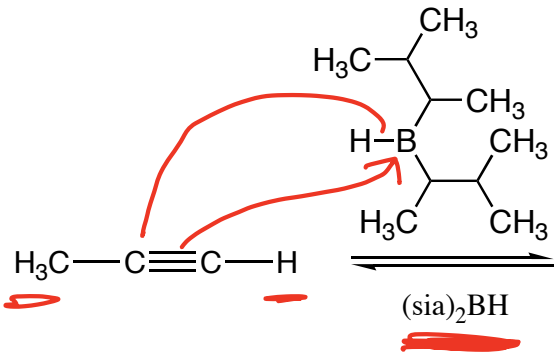
Stereochemistry: Syn

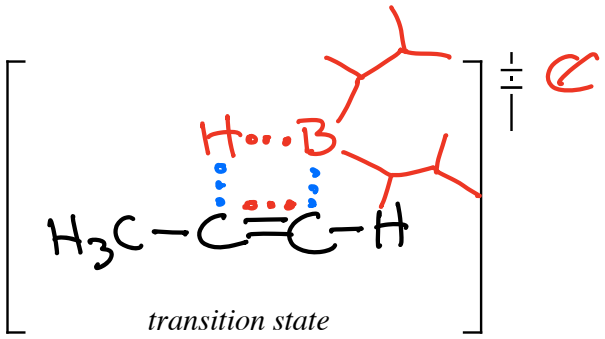
Example:

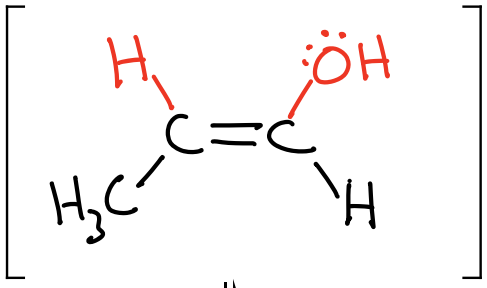


Alkene Alkane

Terminal Alkyne Hydroboration

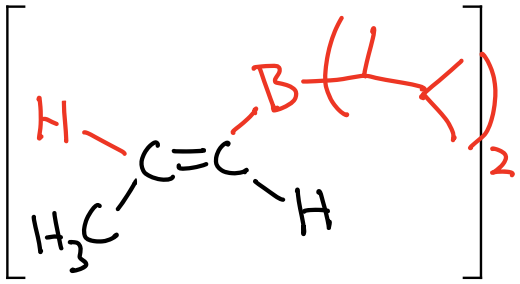




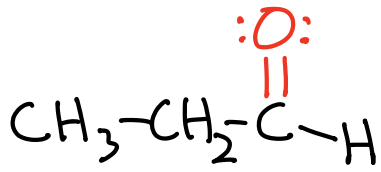


2. H_2O_2 / $HO^{\ominus}$

(Chemist opens flask and adds new reagent)



Keto-enol tautomerization



Products

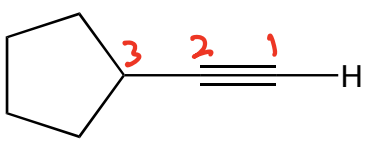
⇐ The C=O is on the C on the end → "non-Markovnikov"

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

Regiochemistry: non-Markovnikov

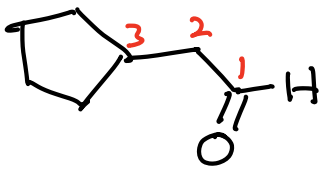
Stereochemistry: N/A

Example:

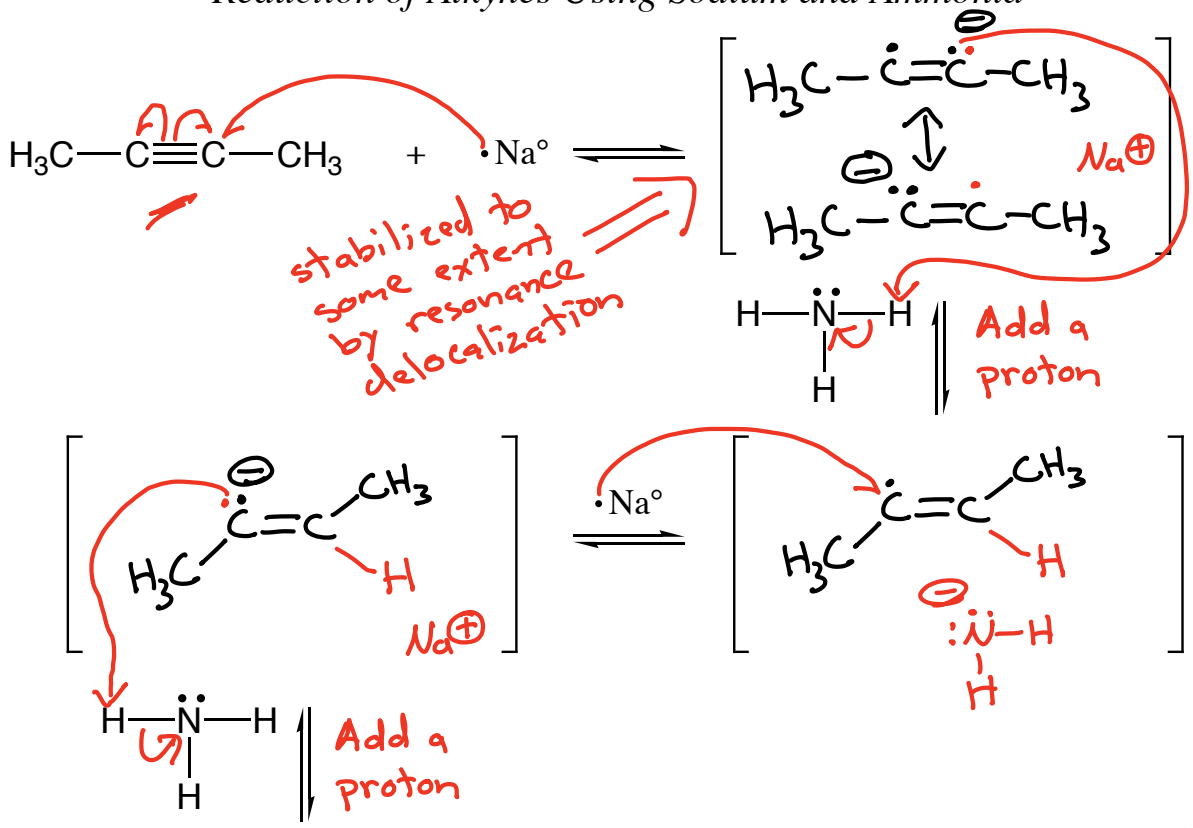


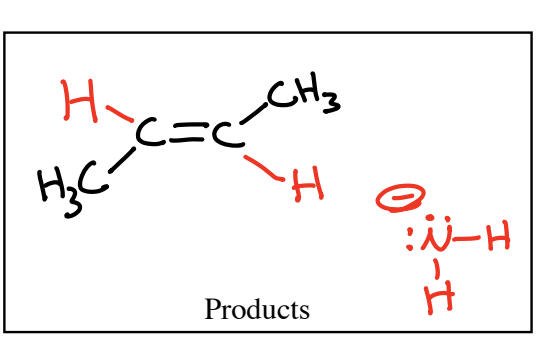
1. $(sia)_2BH$

2. H_2O_2 / $HO^{\ominus}$



Reduction of Alkynes Using Sodium and Ammonia





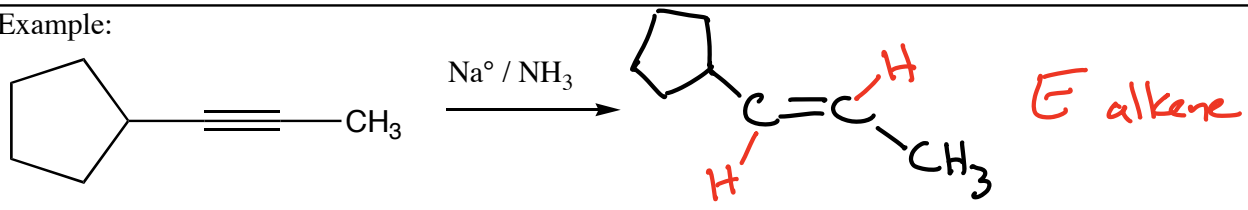
This reaction makes the more stable E alkene

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

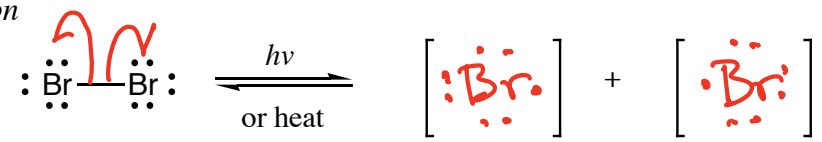
Stereochemistry: Anti → E products

Example:

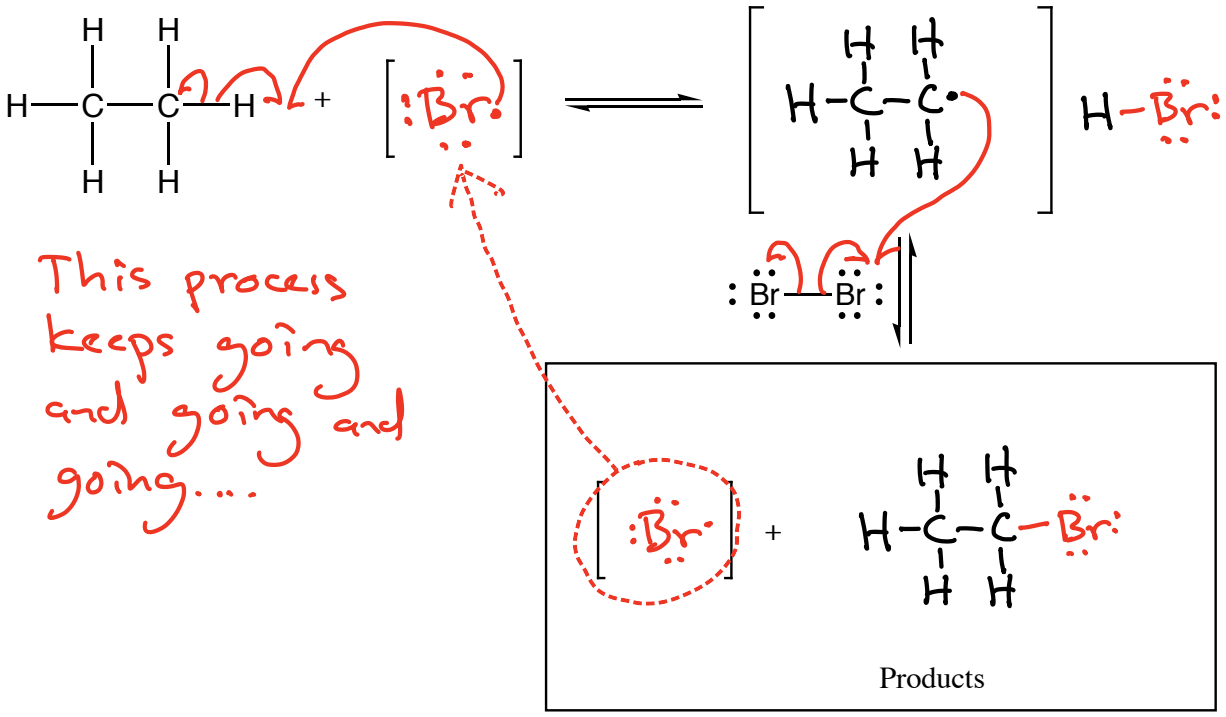


Alkane Free Radical Halogenation

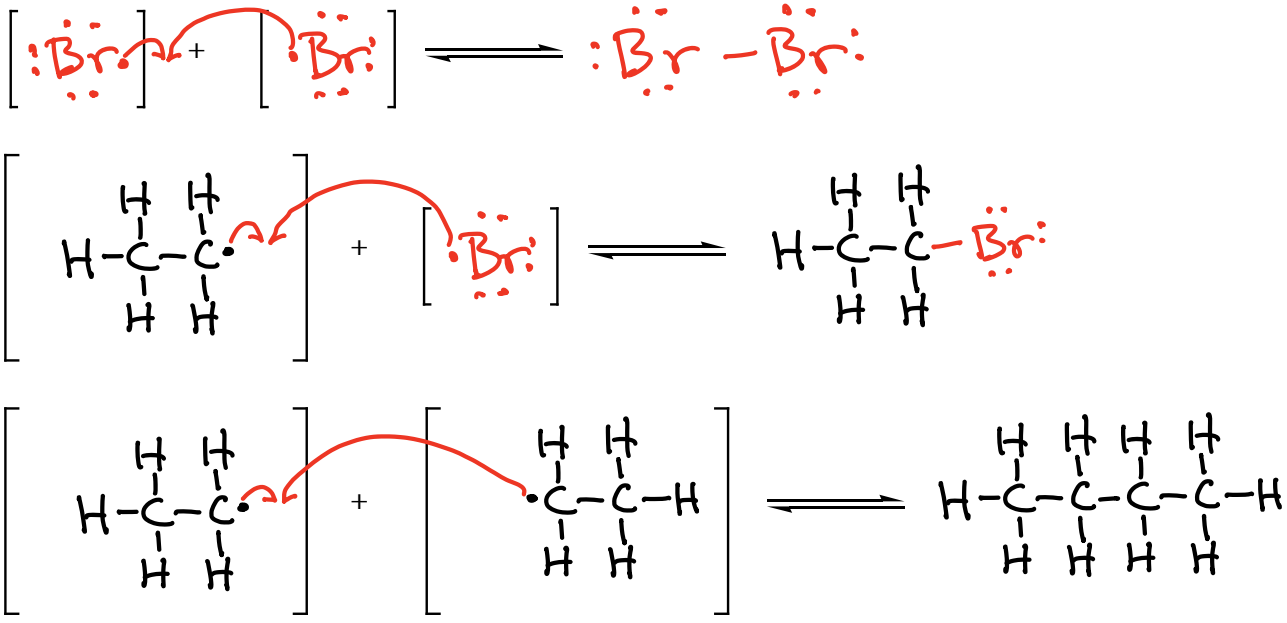
Initiation



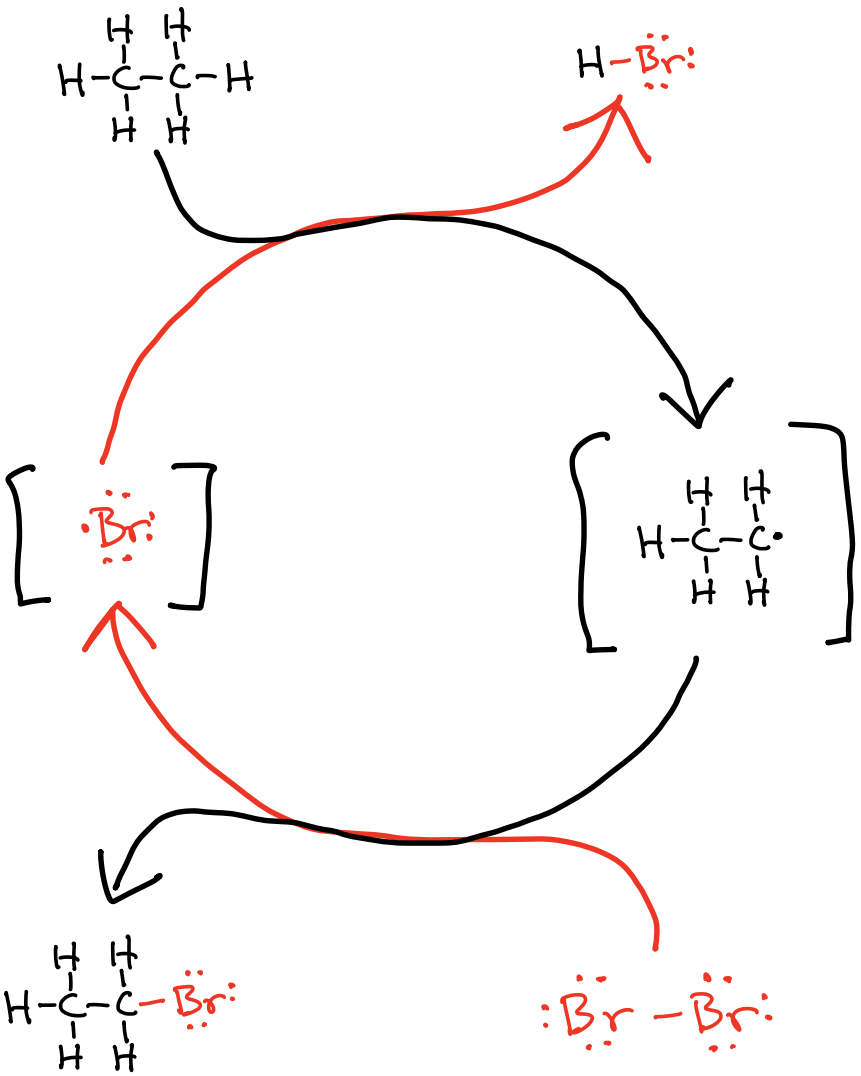
Propagation



Termination

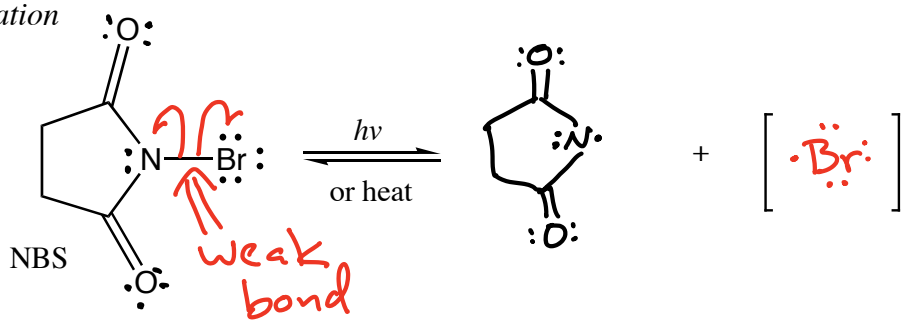


Propagation Process Diagram

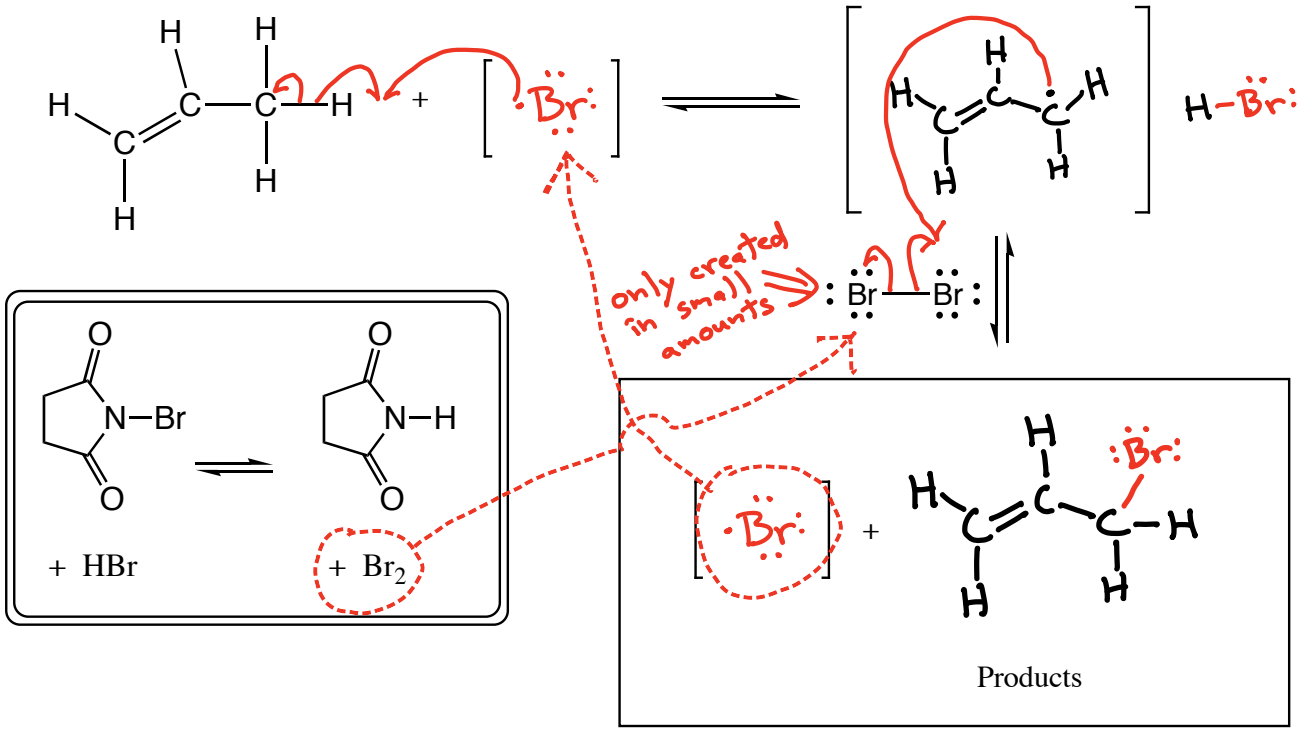


Allylic Halogenation

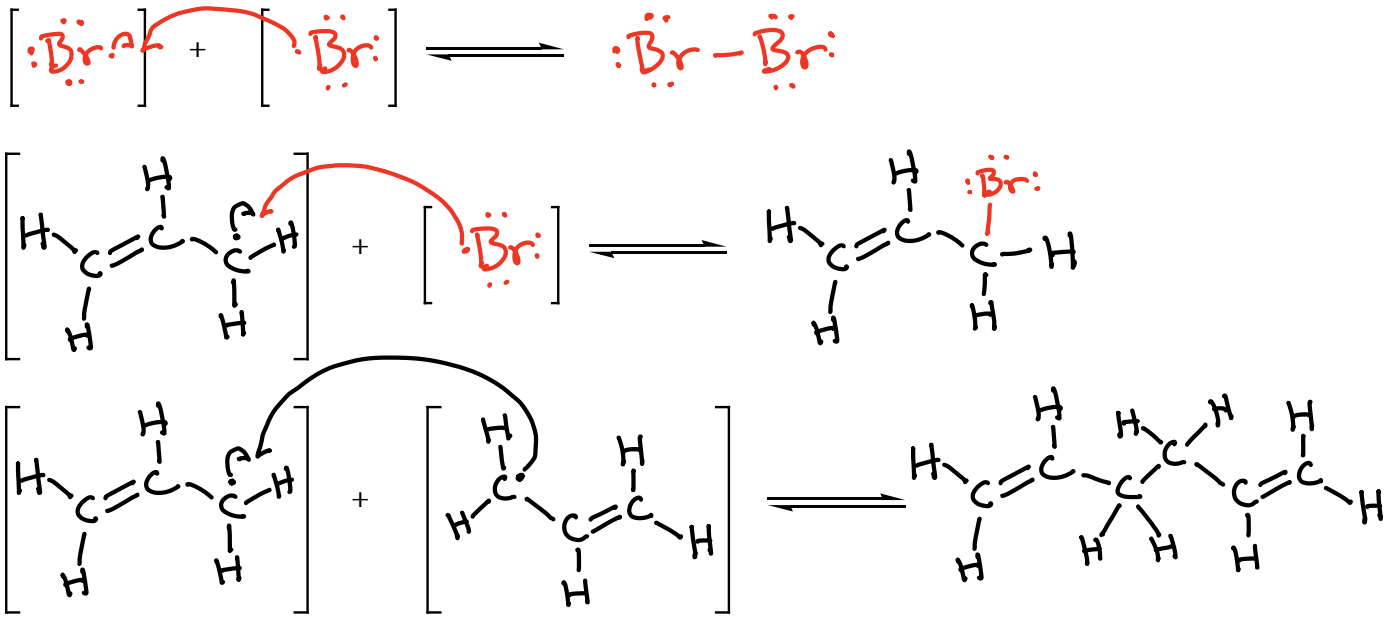
Initiation



Propagation

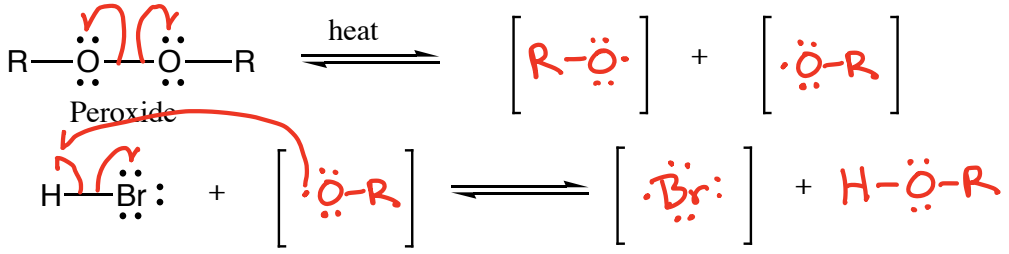


Termination

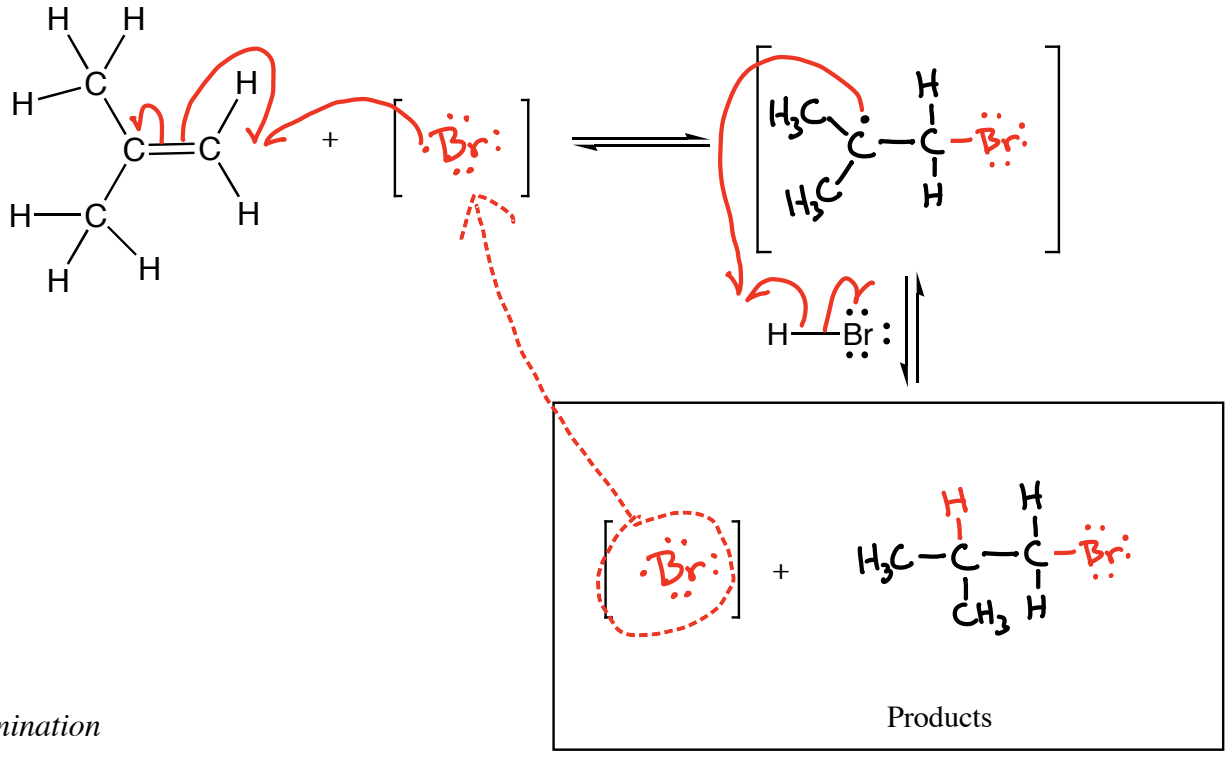


Non-Markovnikov Addition of HBr to an Alkene

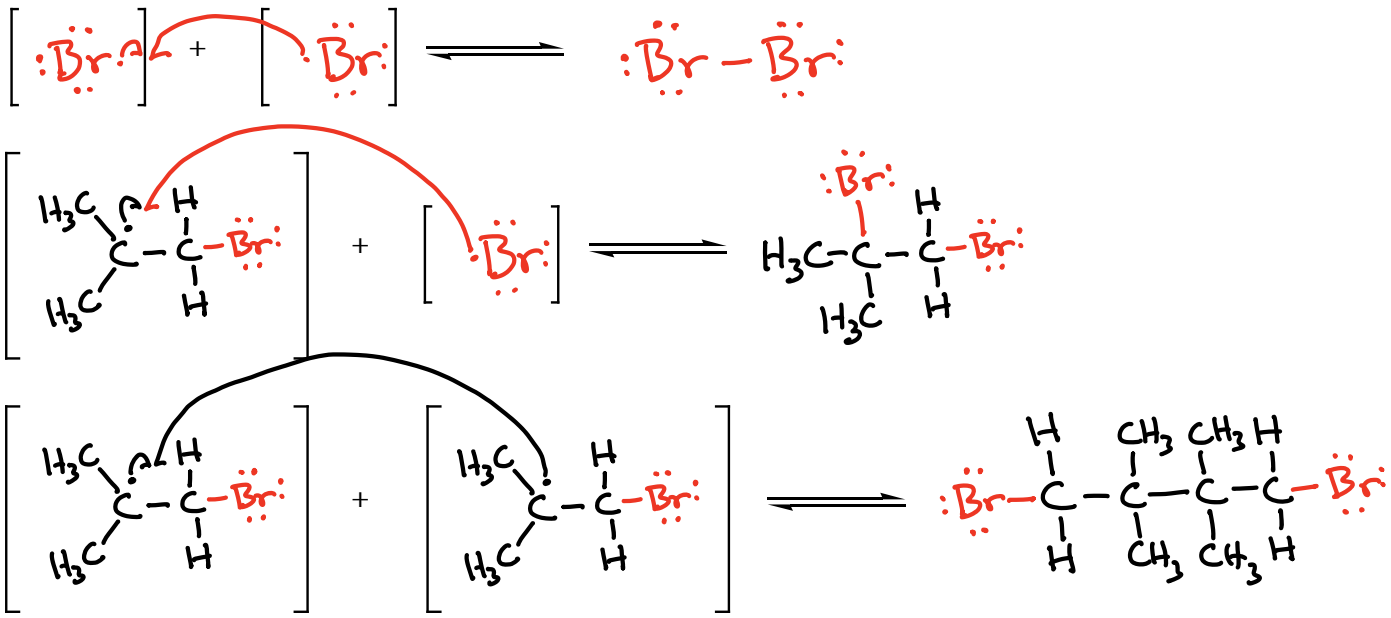
Initiation



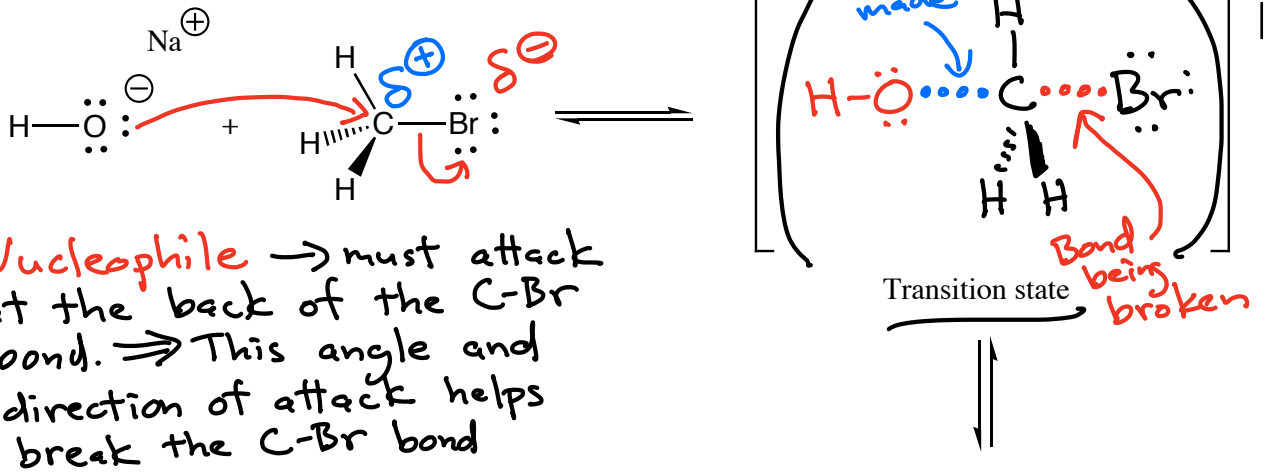
Propagation



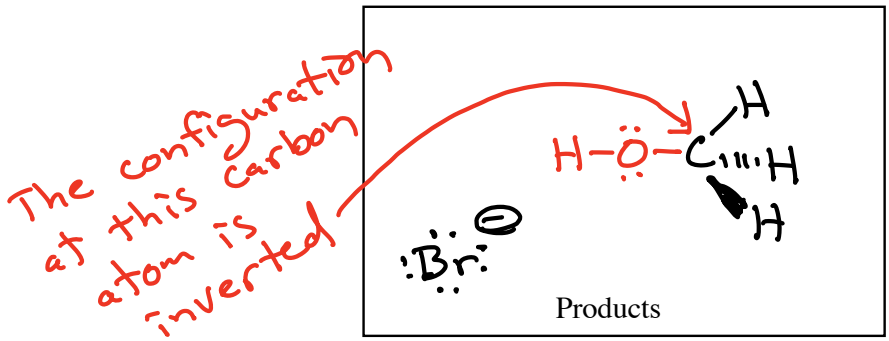
Termination



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

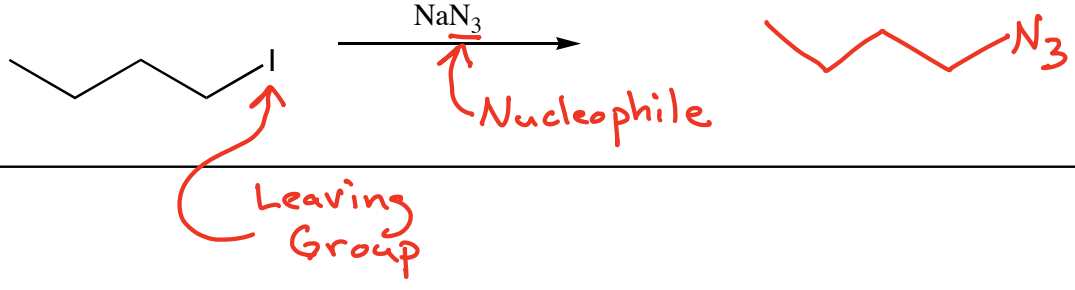


Summary: The nucleophile attacks by making a new bond to C from the back of the C-X bond just as X leaves

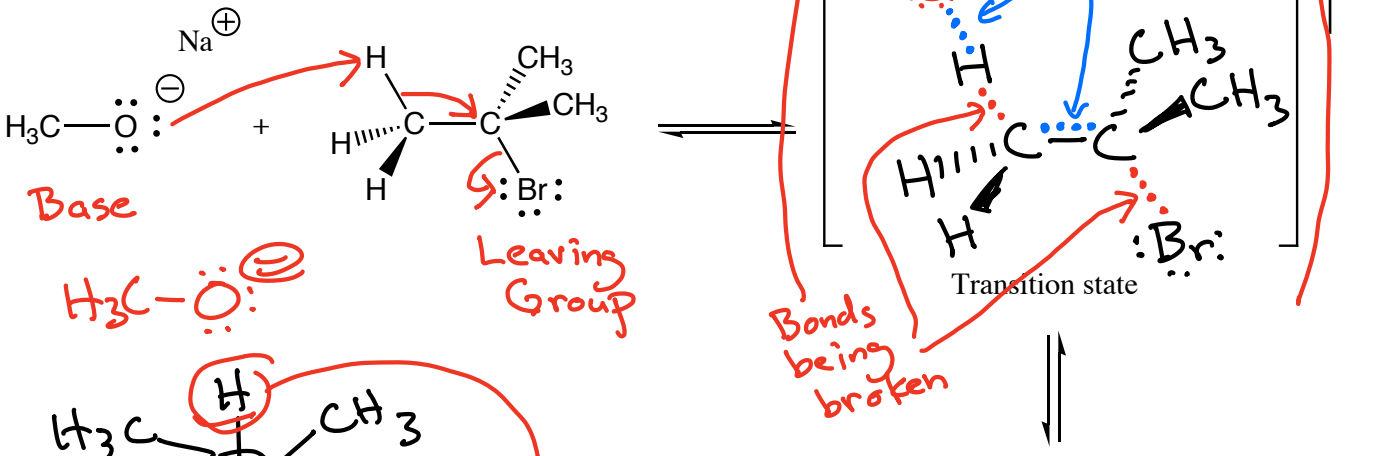
Regiochemistry: N/A

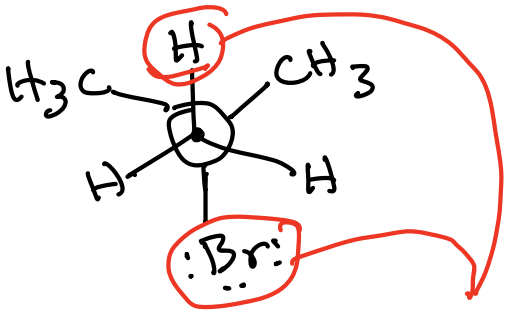
Stereochemistry: INVERSION at the site of reaction

Example:

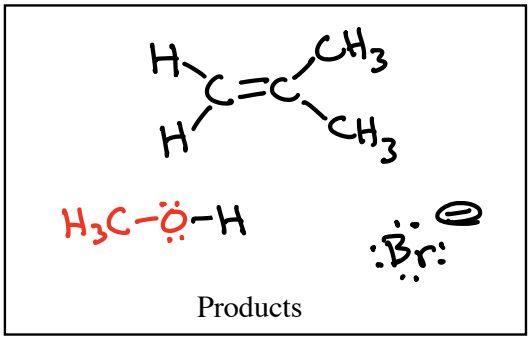


The E2 Mechanism





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

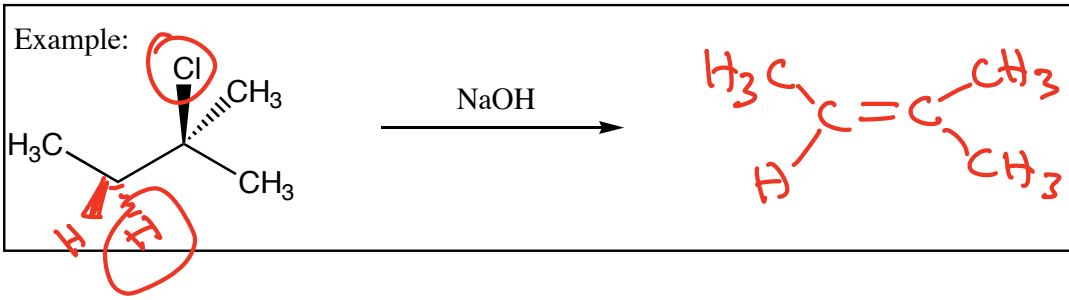


Summary: Base removes an H atom as a pi bond forms and the Br atom leaves → The H and Br must be anti-periplanar

Regiochemistry: Zaitsev's Rule → most stable alkene product

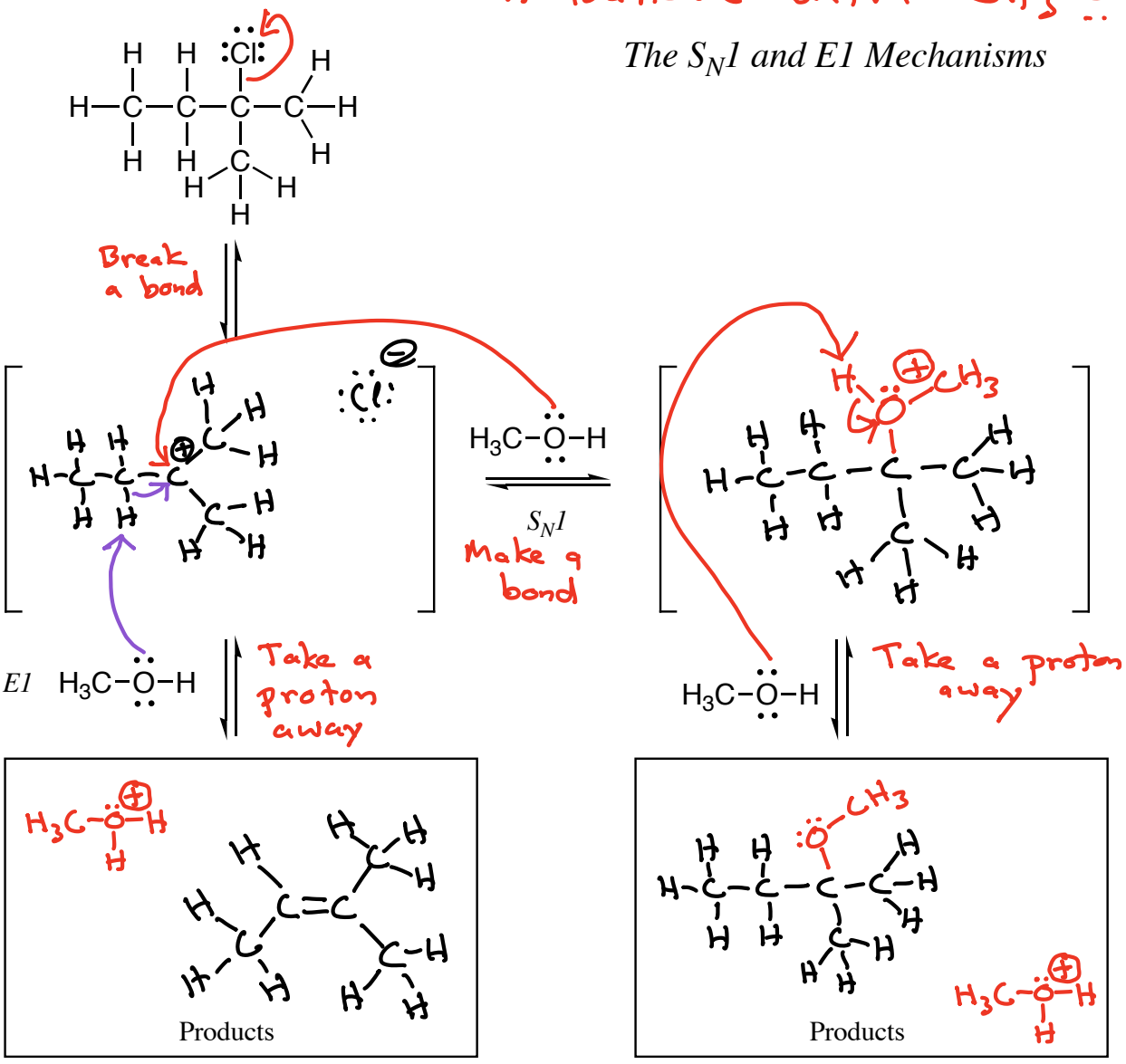
Stereochemistry: Determined by anti-periplanar transition state

Example:



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

The S_N1 and E1 Mechanisms

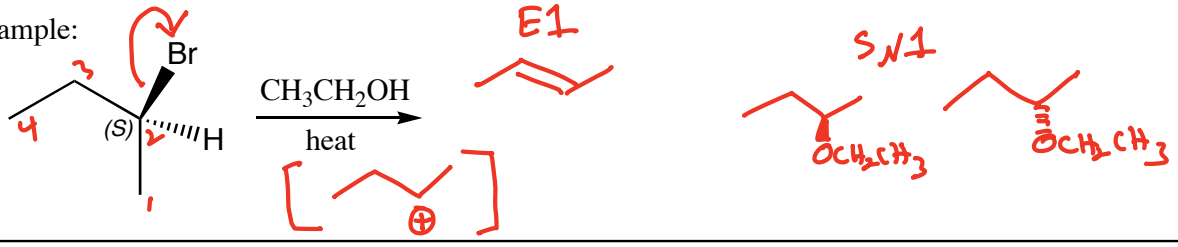


Summary: For sterically hindered haloalkanes, the C-X bond breaks to give a carbocation intermediate that either reacts as an electrophile (S_N1) or has a proton taken away (E1)

Regiochemistry: E1 → Zaitsev's Rule

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

Example:

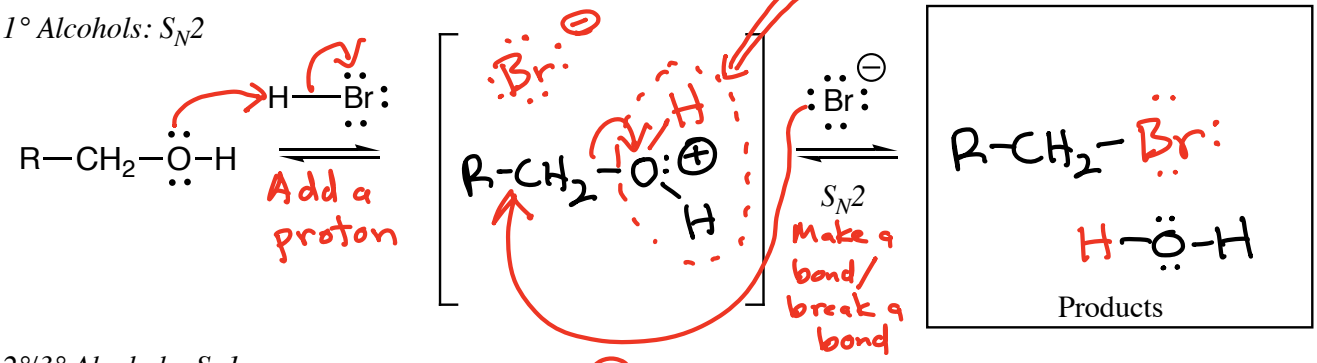


X = Cl, Br, I

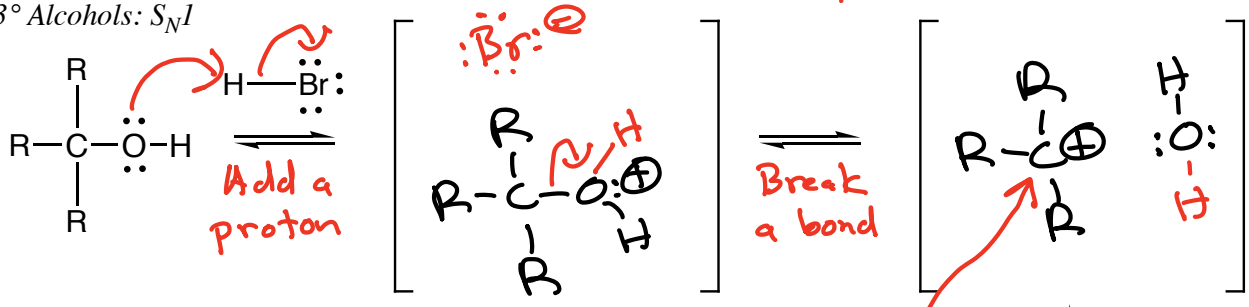
Alcohols + H-X

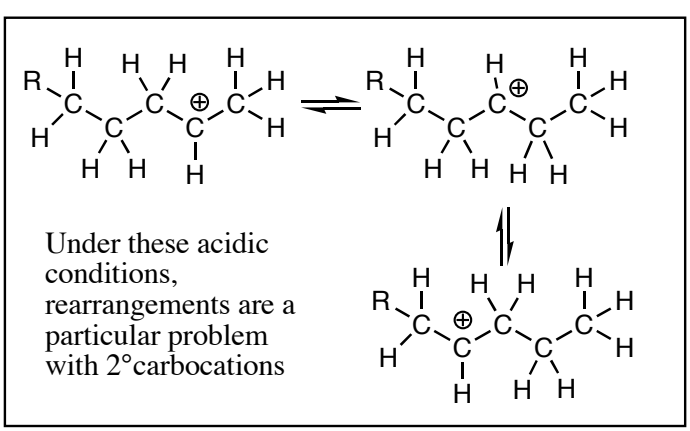
Good leaving group

1° Alcohols: S_N2

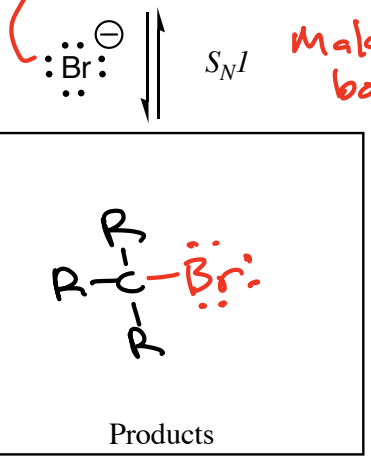


2°/3° Alcohols: S_N1





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

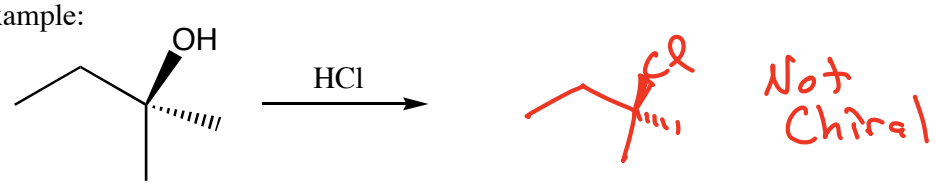


Summary: Reaction of primary alcohols → S_N2
Reaction of secondary/tertiary alcohols → S_N1
The -OH group is converted to a good leaving group by being protonated, followed by S_N2 or S_N1 substitution

Regiochemistry: N/A

Stereochemistry: Chiral tertiary alcohols give scrambled products ← S_N1

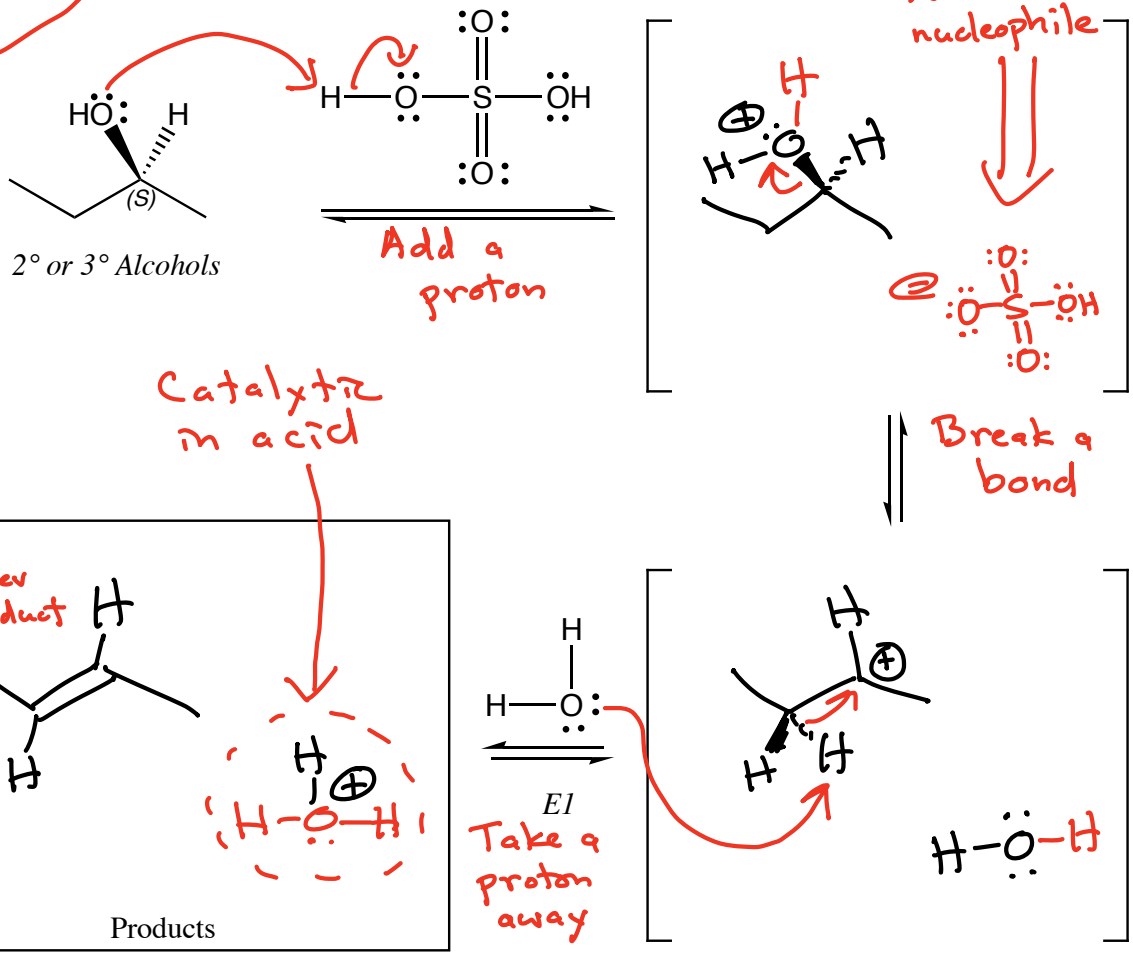
Example:



Not Chiral

1° alcohols react via E2

2° or 3° Alcohol Dehydration → E1

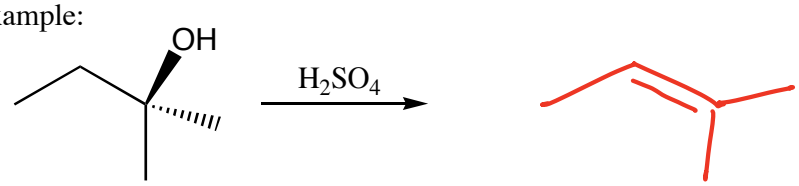


Summary: The OH group is protonated in strong acid to make a good leaving group, water, which breaks a bond to give a carbocation that has a proton taken away to give the product alkene

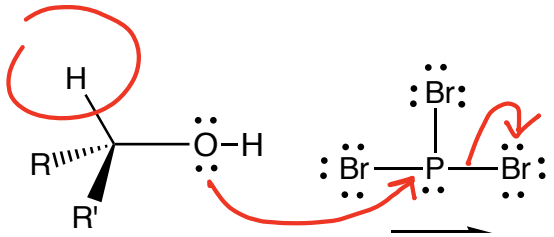
Regiochemistry: Zaitsev's Rule

Stereochemistry: N/A

Example:

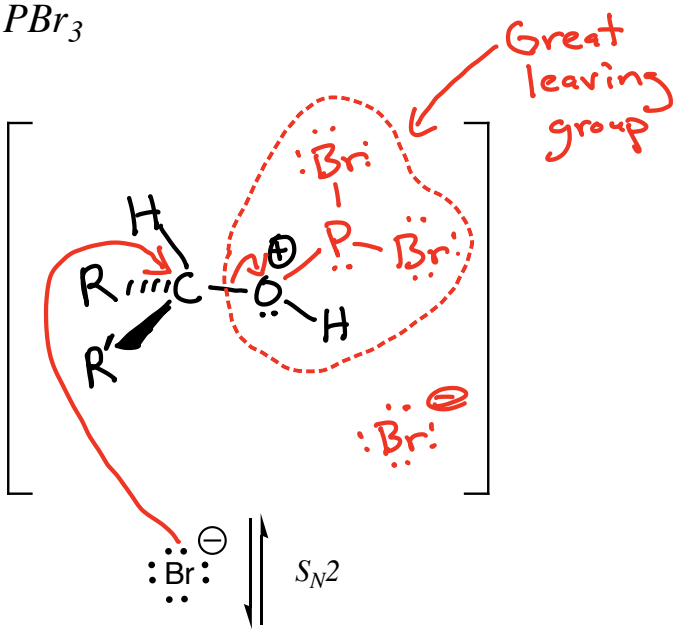


Alcohols + PBr_3



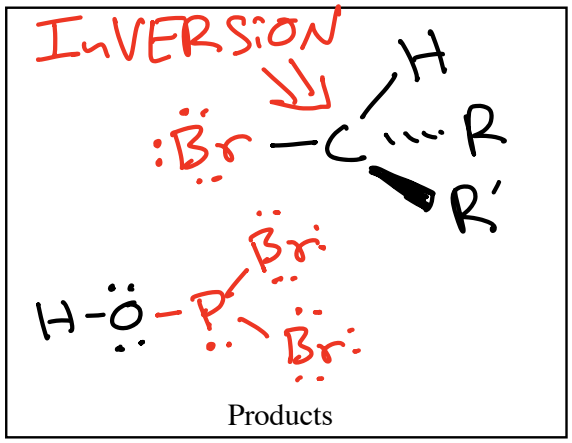
1° or 2° Alcohols

S_N2



Does NOT work with 3° alcohols

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

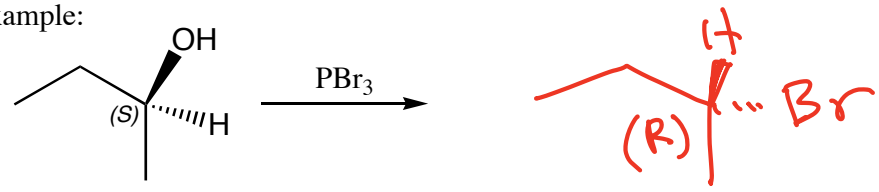


Summary: 1° or 2° alcohols react with PBr_3 via an S_N2 reaction on the P atom to create a good leaving group that undergoes an S_N2 reaction with $Br^{\ominus}$ at the C atom

Regiochemistry: N/A

Stereochemistry: INVERSION

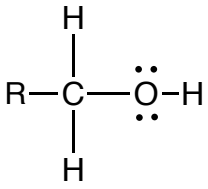
Example:



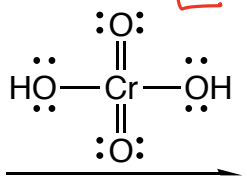
Chromic Acid Oxidation of Alcohols

Called "Jones Reagent" ($CrO_3 + H_2O$ or K_2CrO_7) + H_2SO_4

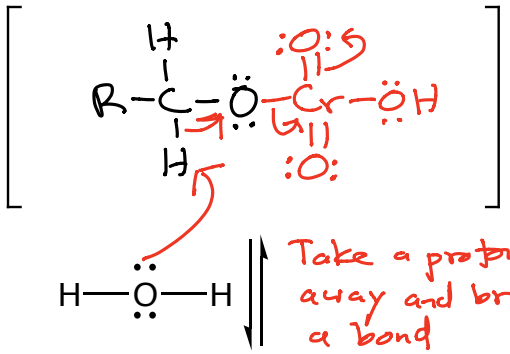
Not responsible for first step



1° Alcohols

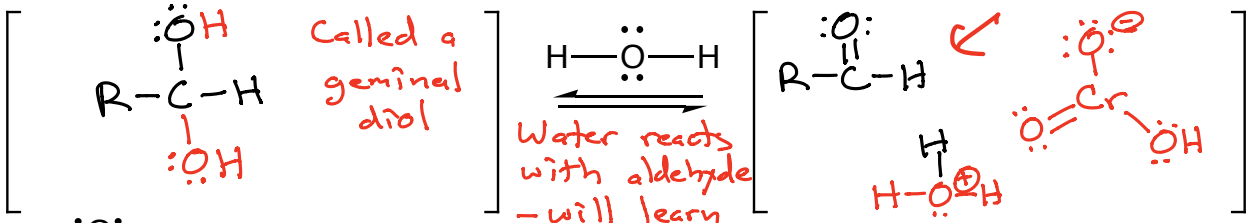


"H_2CrO_4" or "Chromic Acid"



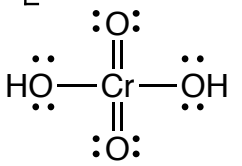
Take a proton away and break a bond

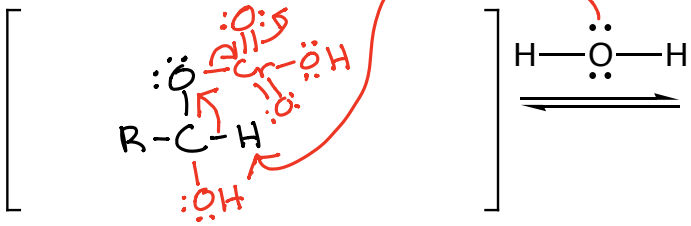
Not responsible for this step

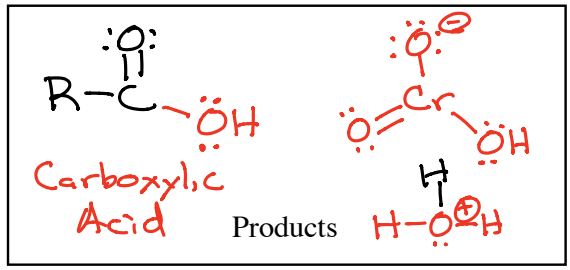


Called a geminal diol

Water reacts with aldehyde – will learn next semester



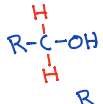




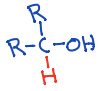
Carboxylic Acid

Products

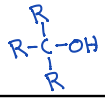
Summary:



1° alcohols ⇒ Carboxylic Acid



2° alcohols ⇒ Ketone

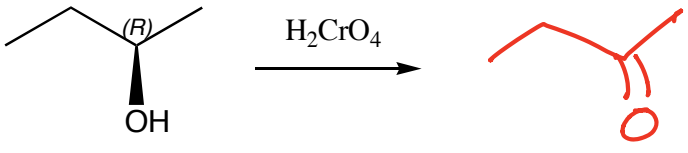


3° alcohols ⇒ NO REACTION

Regiochemistry: N/A

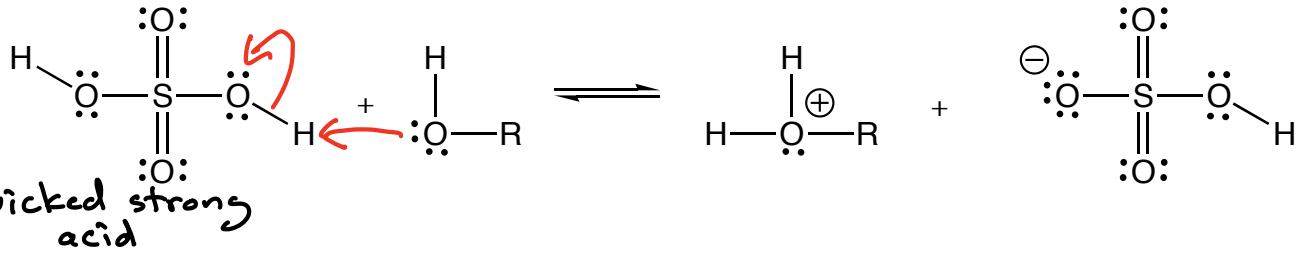
Stereochemistry: N/A

Example:

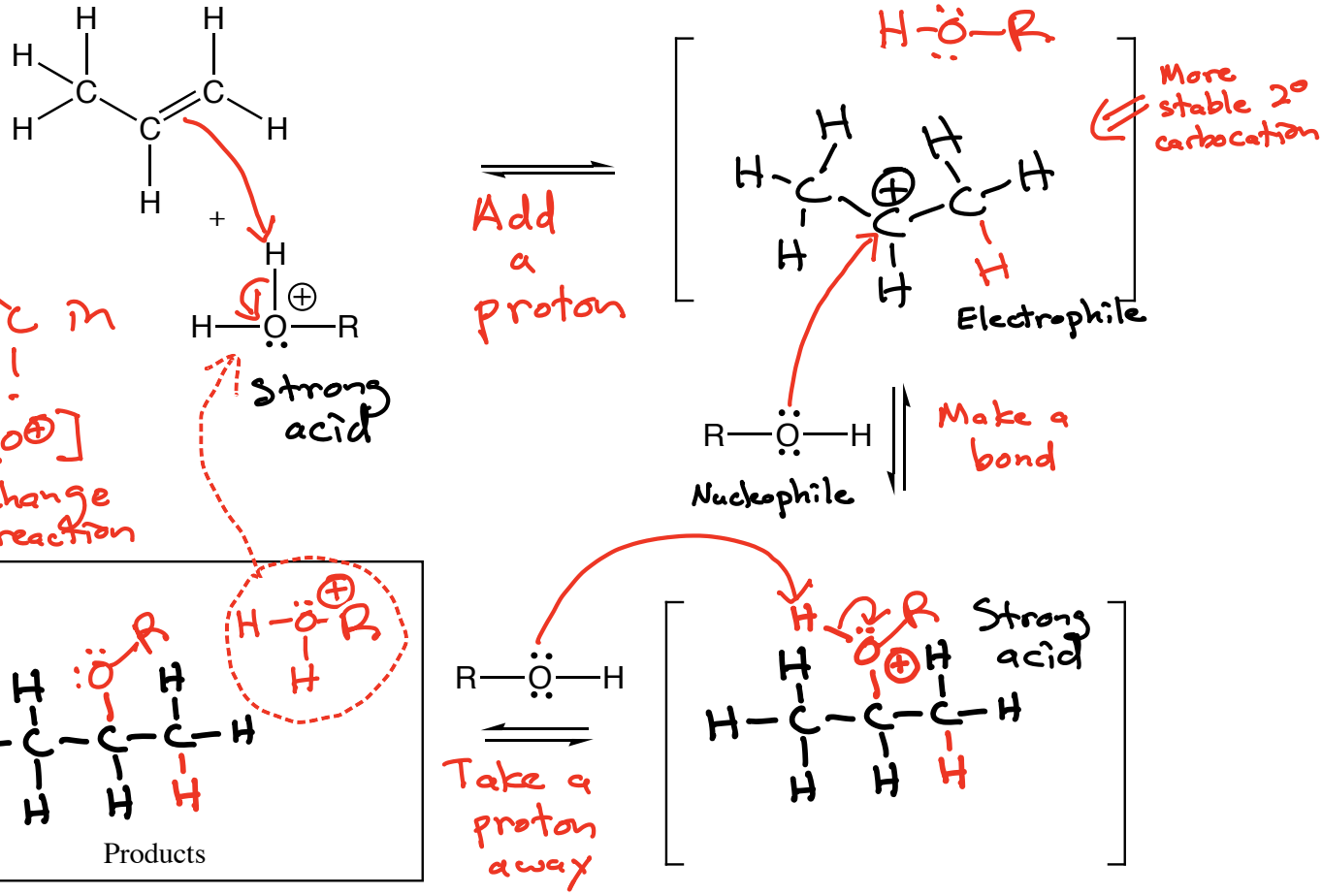


Ketone

Acid-catalyzed Reaction of an Alcohol with an Alkene



wicked strong acid

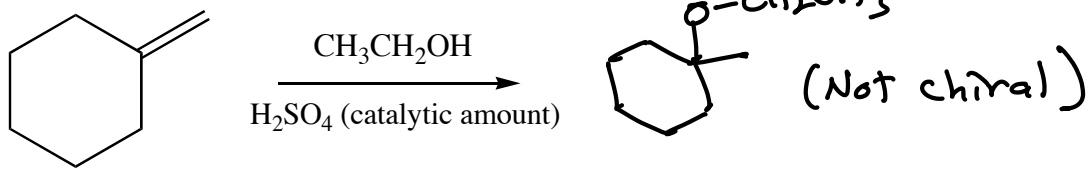


Catalytic in Acid!

⇒ 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

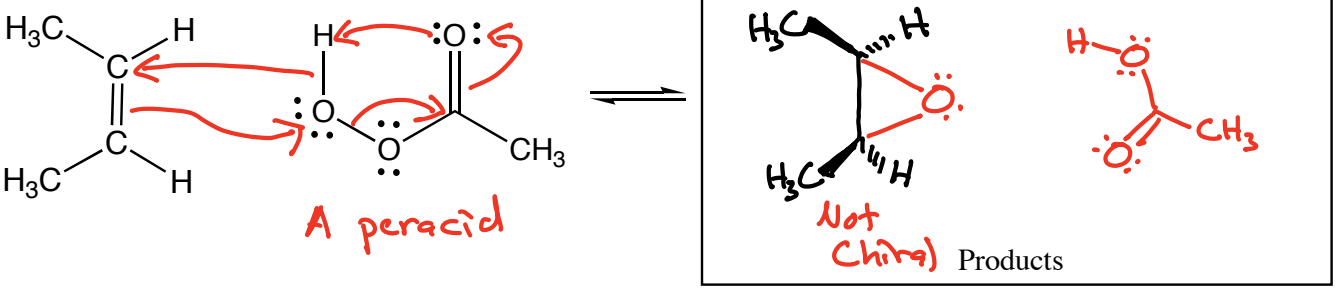
Example:



(Not chiral)

Synthesis of epoxides

Epoxide Formation

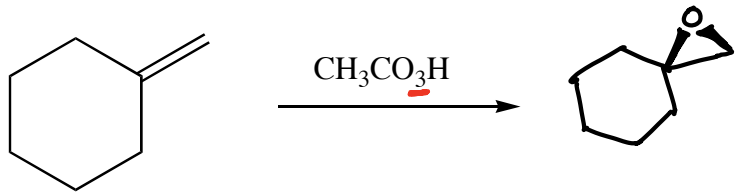


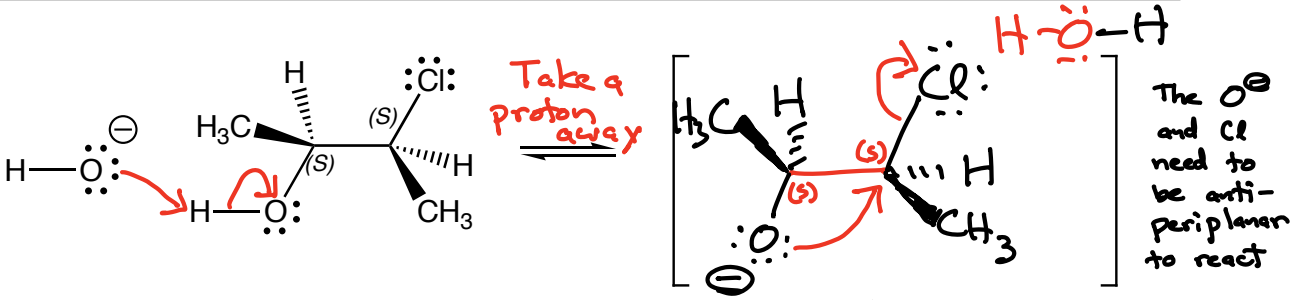
Summary: Alkenes react with peracids in a single concerted step

Regiochemistry: N/A

Stereochemistry: Mixed when new chiral centers are created

Example:



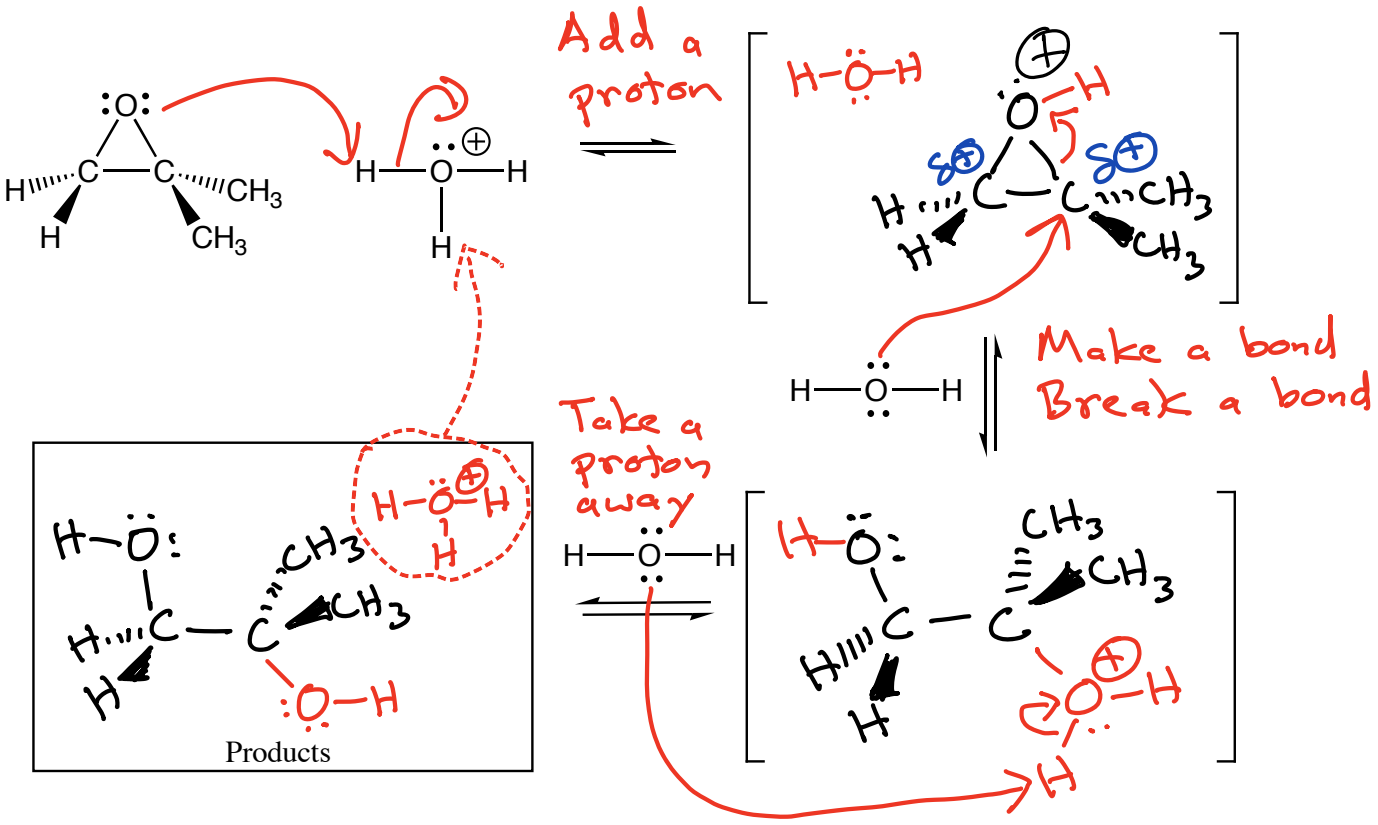


Summary: Halohydrins react in base to give the alkoxide that reacts antiperiplanar to give the epoxide.

Regiochemistry: N/A

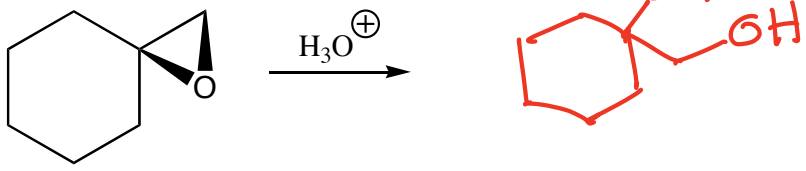
Stereochemistry: Antiperiplanar transition state

Acid-Catalyzed Epoxide Opening

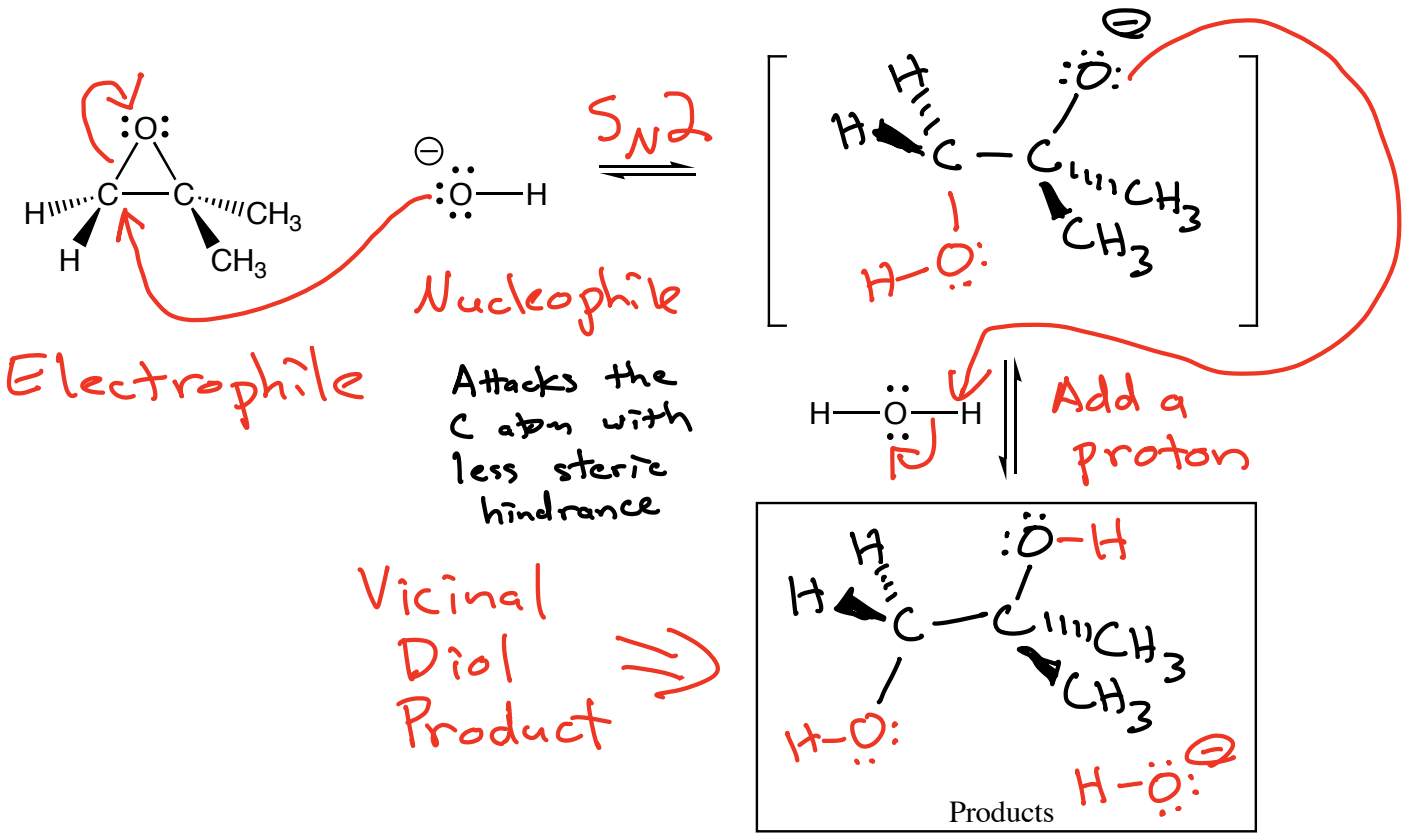


Summary:	In acid, epoxides are protonated to give a highly reactive cation intermediate that reacts with nucleophiles at the more highly substituted carbon atom
Regiochemistry:	"Markovnikov" Attack at more highly substituted C atom
Stereochemistry:	Anti

Example:

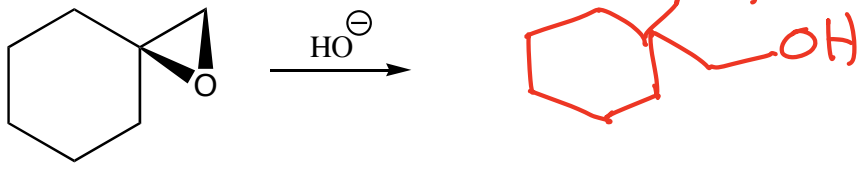


Nucleophilic ~~Base Promoted~~ Epoxide Opening



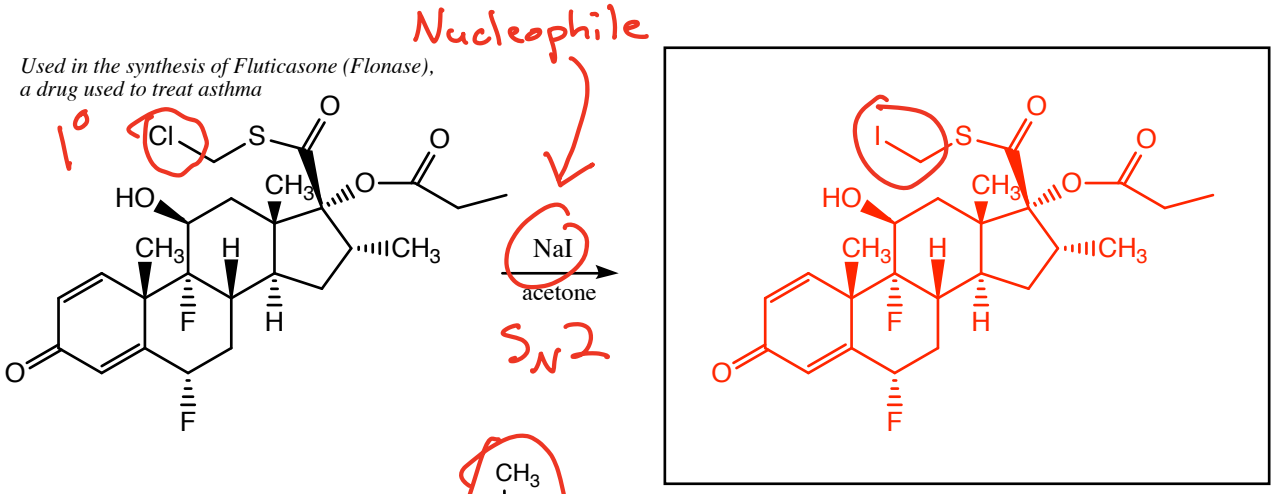
Summary:	Epoxides add strong nucleophiles at the less hindered carbon atom
Regiochemistry:	Less hindered (non-Markovnikov) ✓
Stereochemistry:	Anti addition

Example:

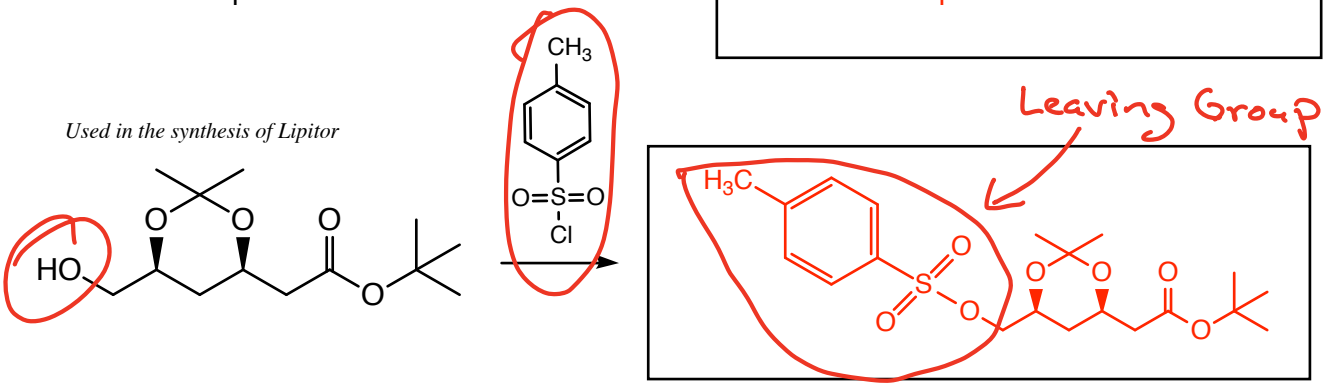


Reactions in the Context of Complex Molecules

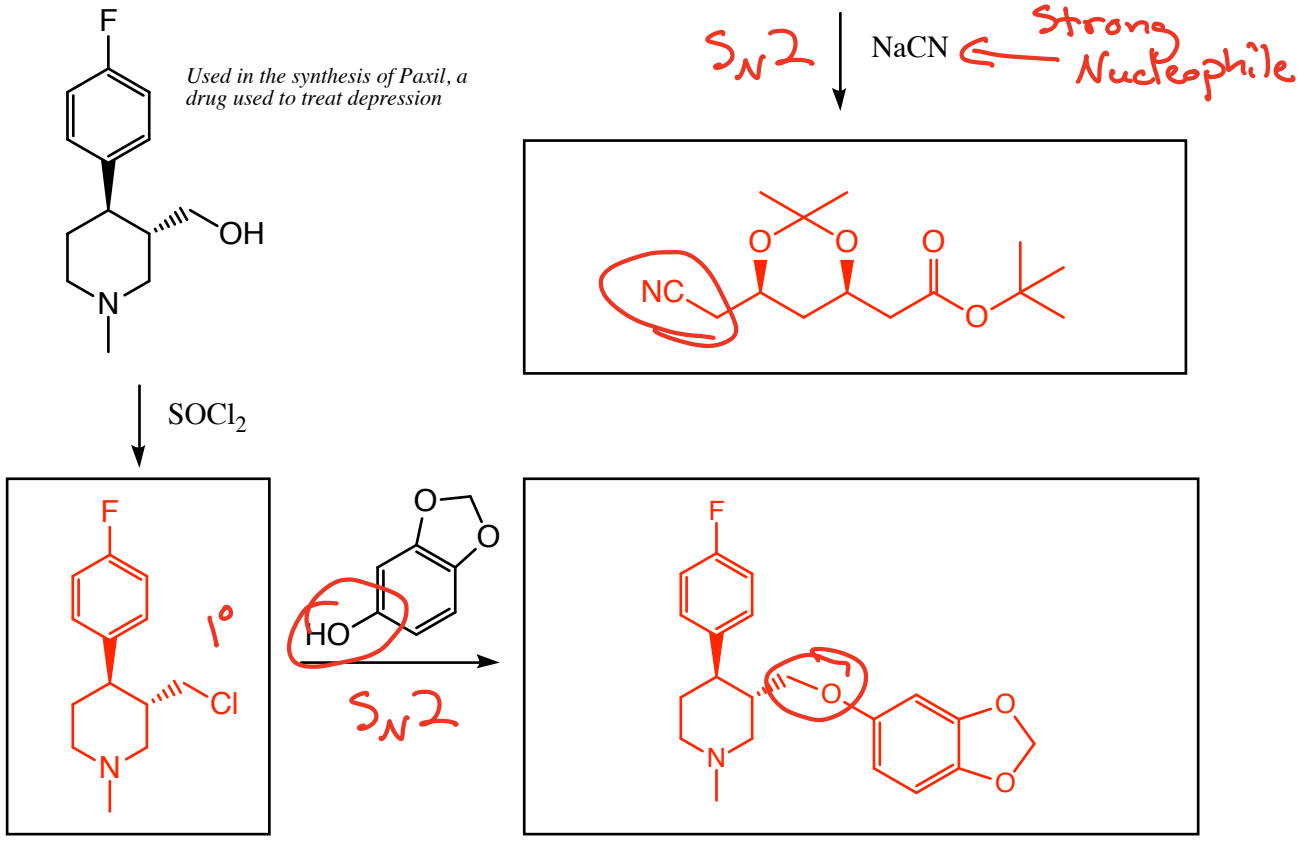
Used in the synthesis of Fluticasone (Flonase), a drug used to treat asthma



Used in the synthesis of Lipitor

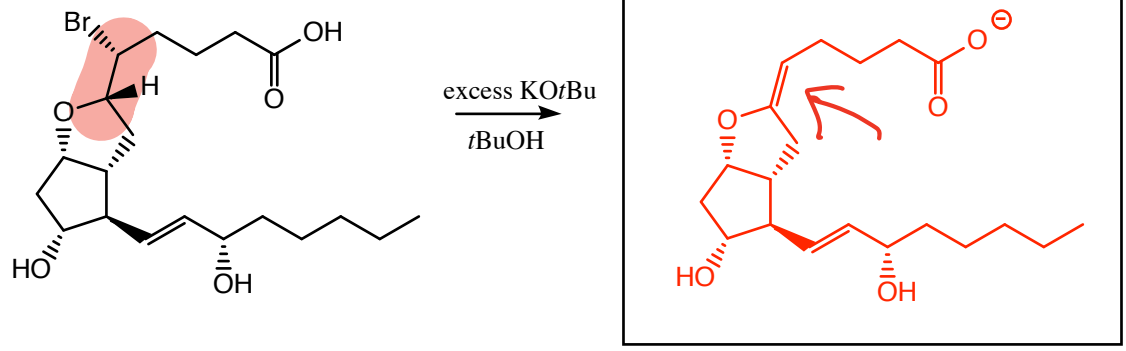


Used in the synthesis of Paxil, a drug used to treat depression

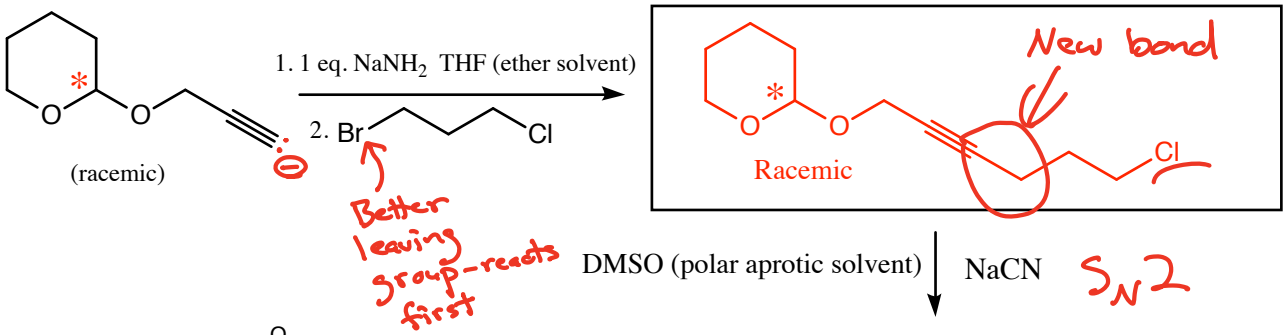


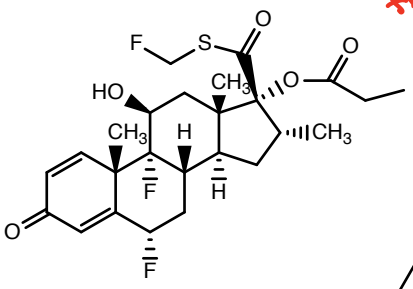
Reactions in the Context of Complex Molecules

Used in the synthesis of several protaglandins

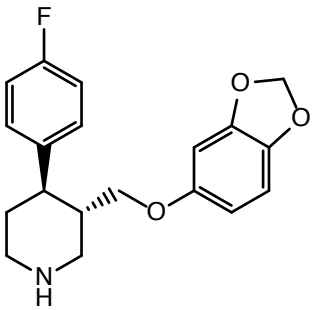


Used in the synthesis of protaglandin C_2

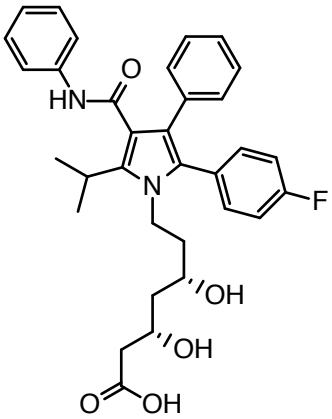




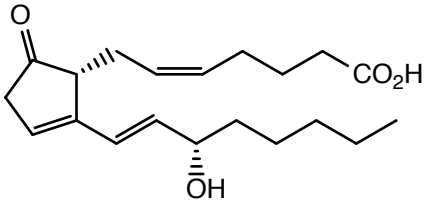
Fluticasone (Flonase)



Paroxetine (Paxil)



Atorvastatin (Lipitor)



Prostaglandin C_2

Geminal
Dihaloalkanes

Vicinal
Tetrahaloalkanes

Alkynes

Aldehydes/Ketones

Vicinal
Dihaloalkanes

Vicinal
Diols

Alkenes

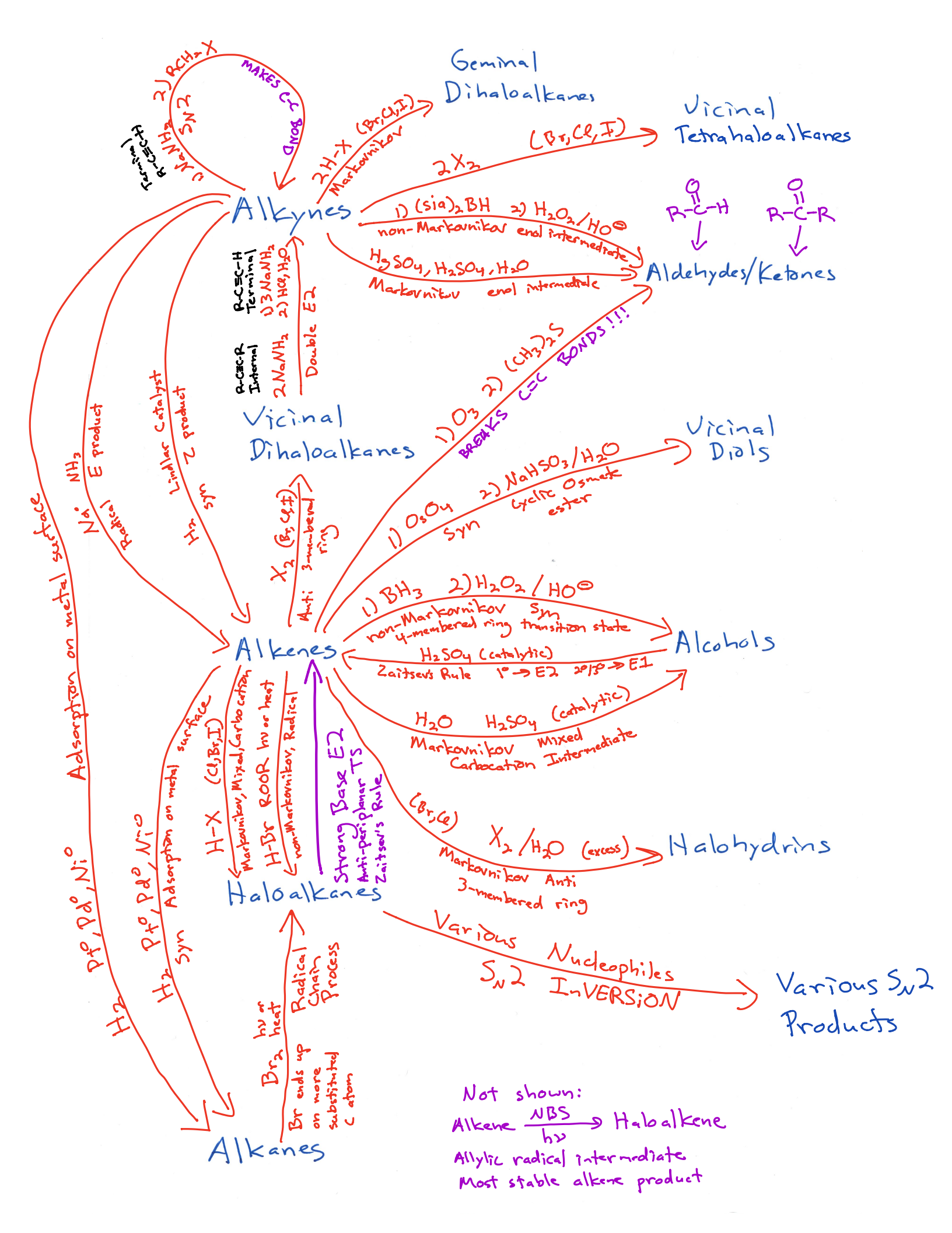
Alcohols

Halohydrins

Haloalkanes

Various S_N2
Products

Alkanes


Terminal RC≡CH
1) NaNH2
2) RCH2X
SN2
MAKES C-C
DOES
Geminal Dihaloalkanes
2 H-X (Br,Cl,I)
Markovnikov
Vicinal Tetrahaloalkanes
(Br, Cl, I)
2 X2
Alkynes
1) (sia)2BH 2) H2O2/HO⊖
non-Markovnikov enol intermediate
H2SO4, H2SO4, H2O
Markovnikov enol intermediate
Aldehydes/Ketones
R-C(=O)-H
R-C(=O)-R
R-C≡C-H Terminal
1) 3 NaNH2
2) H⊕, H2O
R-C≡C-R Internal
2 NaNH2
Double E2
Vicinal Dihaloalkanes
1) O3 2) (CH3)2S
BREAKS C=C BONDS!!!
1) OsO4
Syn
2) NaHSO3/H2O
cyclic Osmate ester
Vicinal Diols
X2 (Br, Cl, I)
Anti
3-membered ring
Adsorption on metal surface
Pt°, Pd°, Ni°
H2
Na° NH3
Radical
E product
Lindlar Catalyst
Z product
H2
syn
Alkenes
1) BH3 2) H2O2 / HO⊖
non-Markovnikov
4-membered ring transition state
Syn
Alcohols
H2SO4 (catalytic)
Zaitsev's Rule
1° → E2 2°/3° → E1
H2O H2SO4 (catalytic)
Markovnikov
Mixed Carbocation Intermediate
(Br, Cl)
X2 / H2O (excess)
Halohydrins
Markovnikov Anti
3-membered ring
H-X (Cl, Br, I)
Markovnikov, Mixed, Carbocation
H-Br ROOR hv or heat
non-Markovnikov, Radical
Strong Base E2
Anti-periplanar TS
Zaitsev's Rule
Haloalkanes
Various Nucleophiles
SN2
INVERSION
Various SN2 Products
Pt°, Pd°, Ni°
H2
Adsorption on metal surface
syn
Br2
hv or heat
Radical Chain Process
Br ends up on more substituted C atom
Alkanes
Not shown:
Alkene NBS / hv → Haloalkene
Allylic radical intermediate
Most stable alkene product

Geminal Dihaloalkanes

Vicinal Tetrahaloalkanes

Alkynes (DFW)

Carboxylic Acids

Aldehydes, Ketones

Vicinal Diols

Vicinal or Geminal Dihaloalkanes (Waco)

Epoxides

Alkenes (Austin)

Alcohols

Halohydrins

Allylic Halides

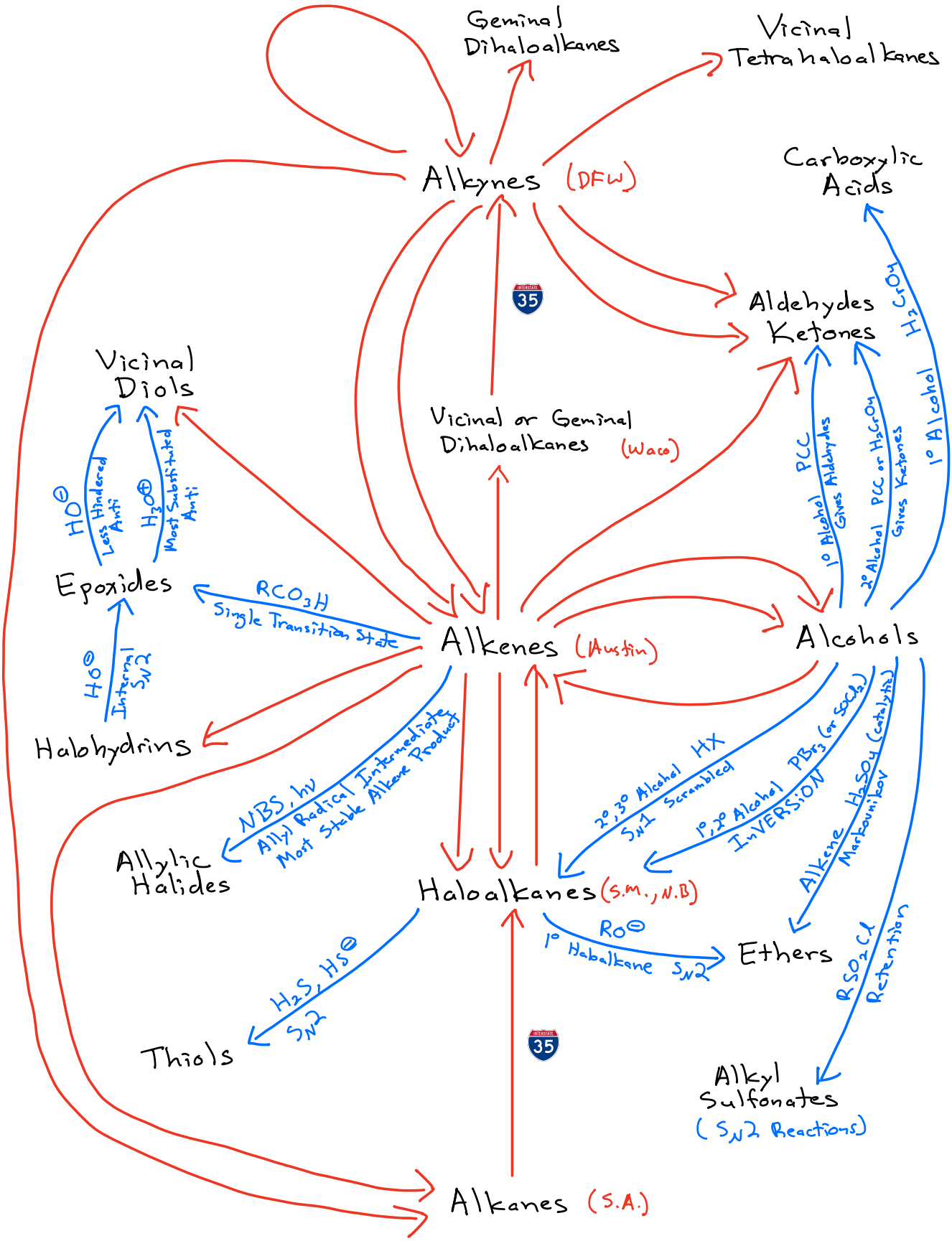
Haloalkanes (S.M., N.B)

Ethers

Throls

Alkyl Sulfonates

Alkanes (S.A.)


Geminal Dihaloalkanes
Vicinal Tetrahaloalkanes
Alkynes (DFW)
Carboxylic Acids
Aldehydes Ketones
Vicinal Diols
Vicinal or Geminal Dihaloalkanes (Waco)
Epoxides
Alkenes (Austin)
Alcohols
Halohydrins
Allylic Halides
Haloalkanes (S.M., N.B)
Ethers
Thiols
Alkyl Sulfonates (SN2 Reactions)
Alkanes (S.A.)
HO⊖ Less Hindered Anti
H3O⊕ Most Substituted Anti
H⊖ Internal SN2
RCO3H Single Transition State
PCC 1° Alcohol Gives Aldehydes
2° Alcohol PCC or H2CrO4 Gives Ketones
H2CrO4 1° Alcohol
NBS, hv Allyl Radical Intermediate Most Stable Alkene Product
3°,2° Alcohol HX SN1 Scrambled
1°,2° Alcohol PBr3 (or SOCl2) INVERSION
Alkene H2SO4 (catalytic) Markovnikov
RSO2Cl Retention
H2S, HS⊖ SN2
R⊖ 1° Haloalkane SN2