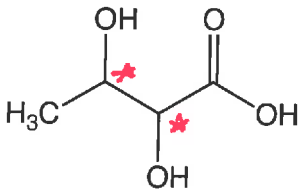
Molecules with 2 chiral centers

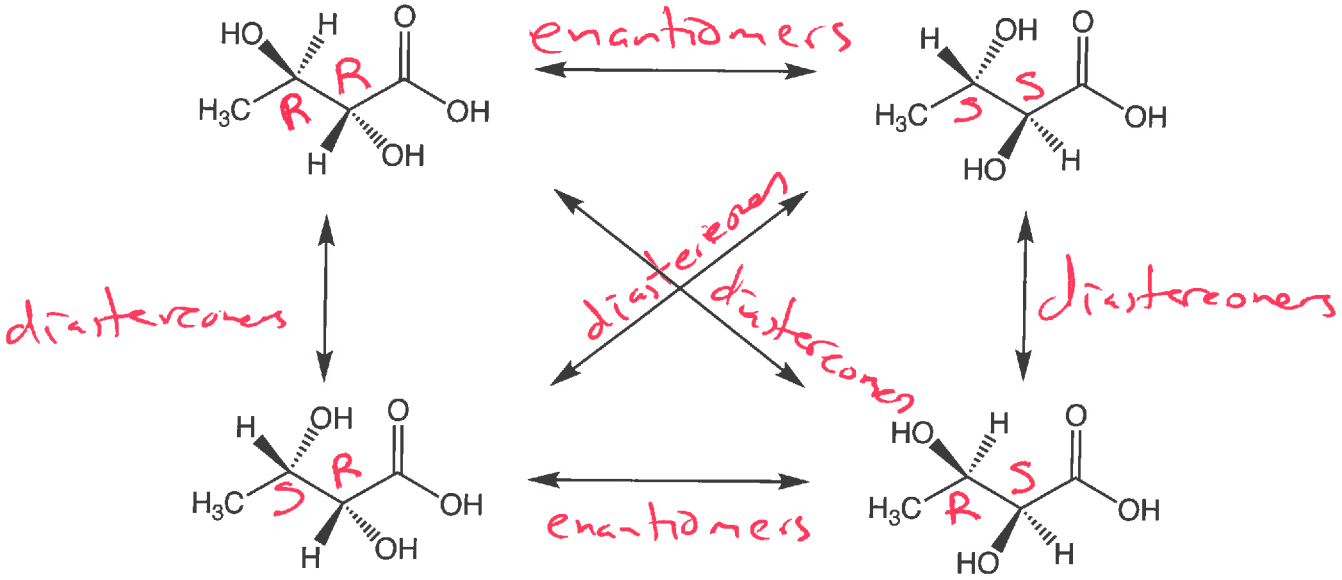
1) If a molecule has "n" chiral centers there are 2^n possible stereoisomers → fewer if symmetry is present ⟹ see "meso"
2) R,R and S,S are enantiomers
   R,S and S,R are enantiomers
   All other pairs ~~are~~ are diastereomers (R,R vs R,S)
3) To identify relationships in stereoisomers → assign R,S to each chiral center and compare those → better than comparing structures directly

4 stereoisomers

$2^2 = 4$

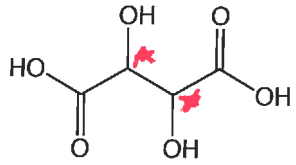


2 chiral centers → no overall symmetry



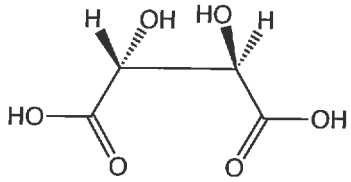
4) A meso compound has chiral centers but is <u>not</u> chiral due to symmetry (i.e. plane of symmetry)

5) You need to draw molecules in the most symmetric conformation possible when looking for symmetry → eclipsed is OK!!! → common

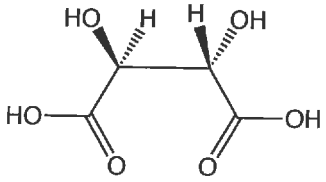


2 chiral centers → symmetry

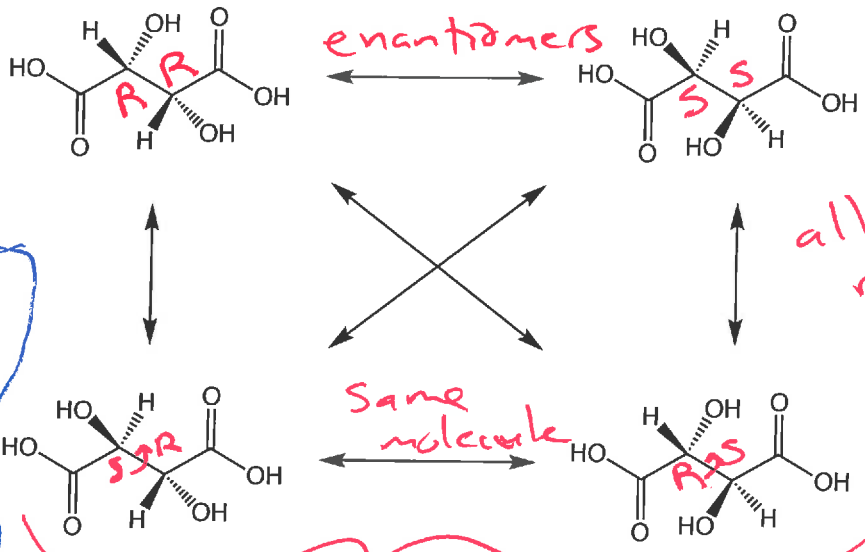
No symetry



No symetry



3 total stereoisomers



same molecule

Almost all mechanisms you will learn are composed of only the following 4 mechanistic elements

1) Make a bond between a nucleophile and an electrophile → a nucleophile and electrophile must be present

2) Break a bond to give stable molecules or ions

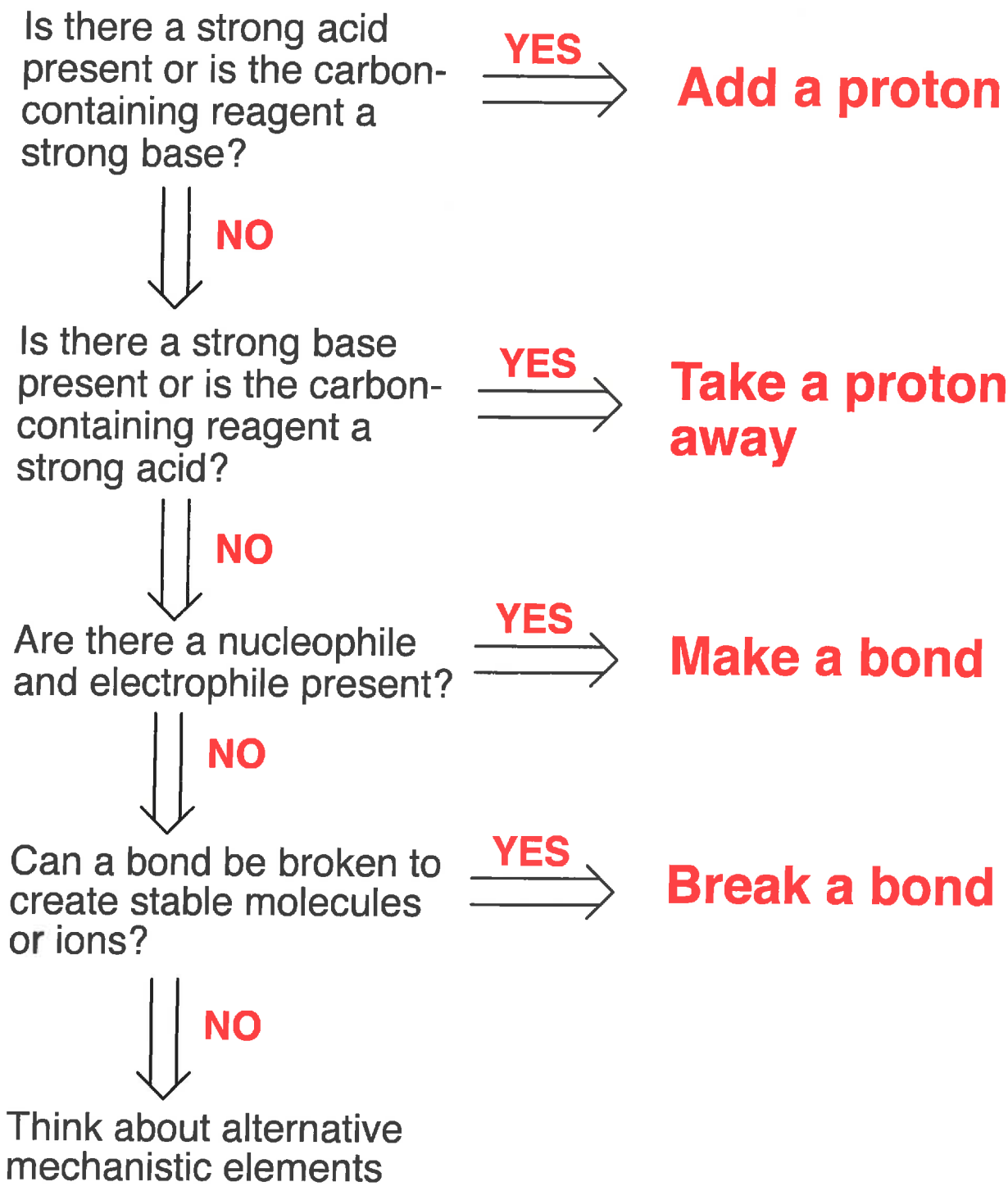
3) Add a proton → if a strong acid is present or your molecule is a base

4) Take a proton away → if a strong base is present or your molecule is a strong acid

These terms are from the point of view of the carbon containing starting material!

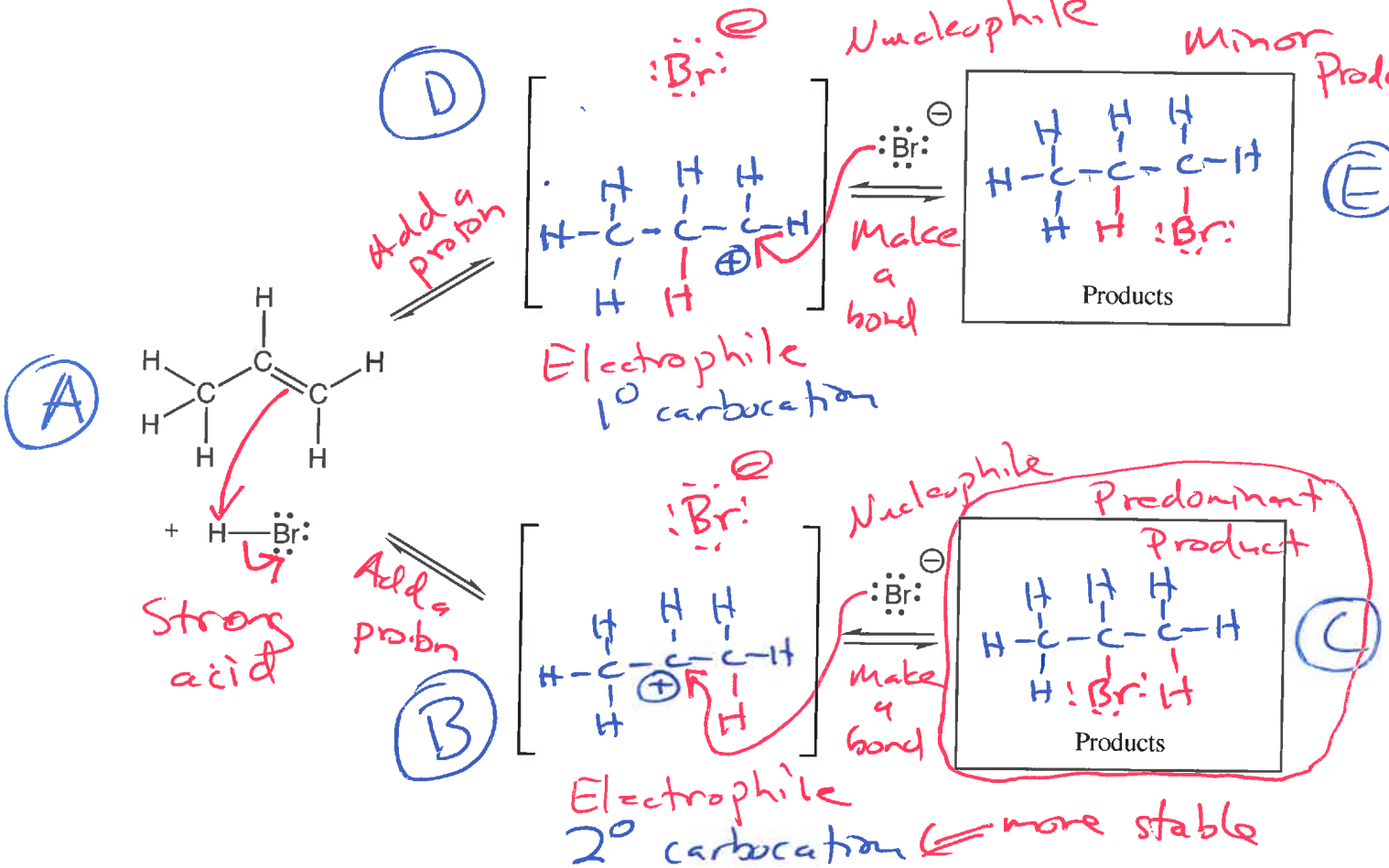
Mechanism Summary

The following questions and mechanistic elements are described from the point of view of the carbon-containing reagent, written in the form of a flowchart.



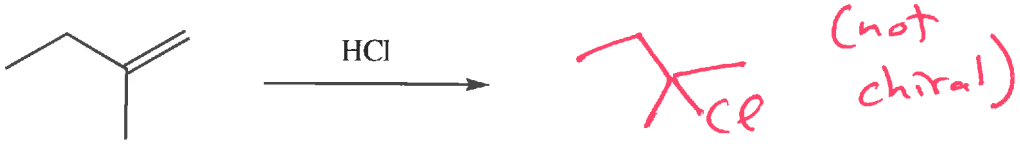
halogens Cl, Br, I

Addition of H-X to an Alkene

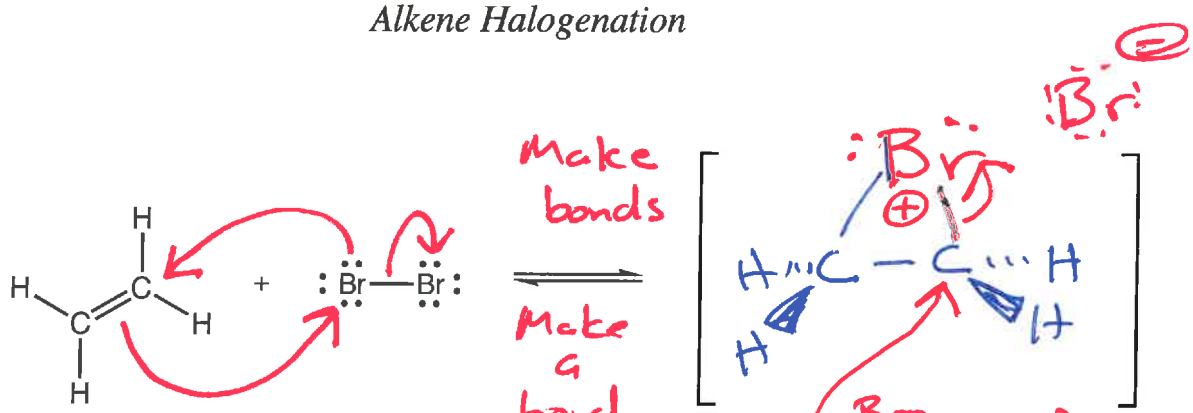


Summary:	Alkenes react with H-X X = Cl, Br, I to give a carbocation intermediate that reacts with X⊖ to give the haloalkane
Regiochemistry:	Markovnikov (Follow Markovnikov's Rule)
Stereochemistry:	Mixed

Example:



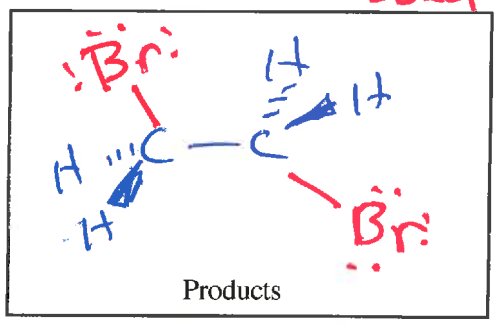
Alkene Halogenation



3-membered ring intermediate

NOT a carbocation

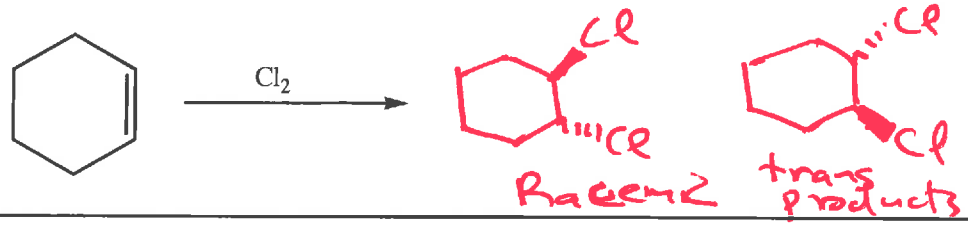
★ → The $Br^{\ominus}$ must attack the face opposite to where the $Br^{\oplus}$ is located → "backside"



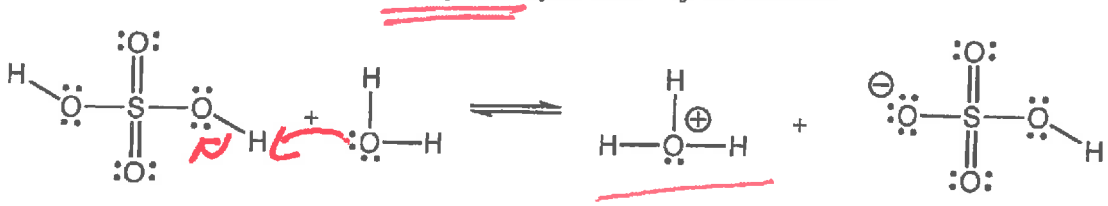
→ "anti" → leads to trans products

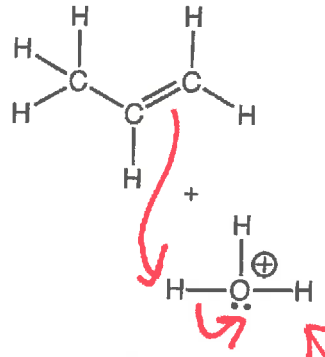
Summary:	Alkenes react with X_2 (Cl_2, Br_2, I_2) to give 3-membered ring intermediate → then a new bond is made from the opposite face
Regiochemistry:	Not applicable
Stereochemistry:	Anti addition → trans products

Example:

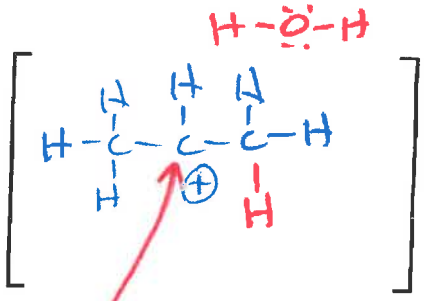


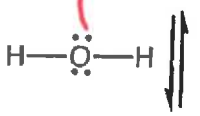
Acid-catalyzed Hydration of an Alkene





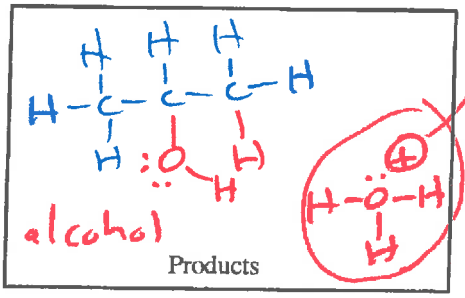
Add a proton



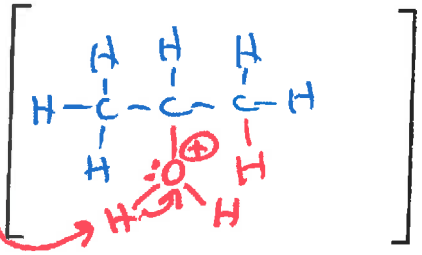


Make a bond

Proton concentration does not change → catalytic



Take a proton away

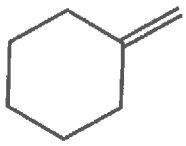


Summary: Add a proton, water bonds to carbocation intermediate, remove a proton to give alcohol

Regiochemistry: Markovnikov's rule

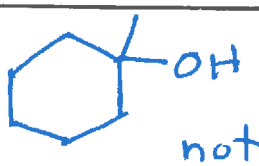
Stereochemistry: Mixed

Example:



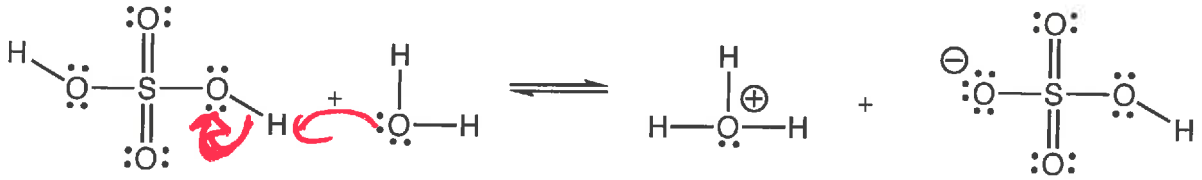
H_2O

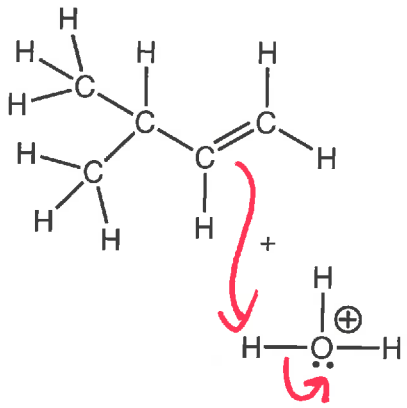
H_2SO_4 (catalytic amount)



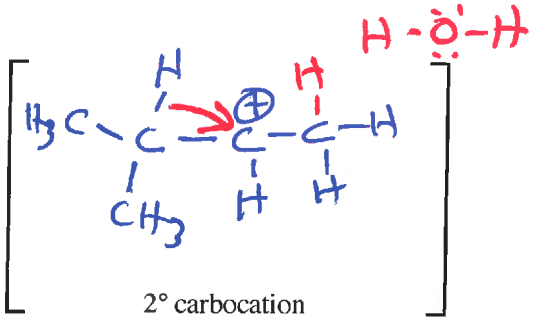
not chiral

Cation Rearrangement

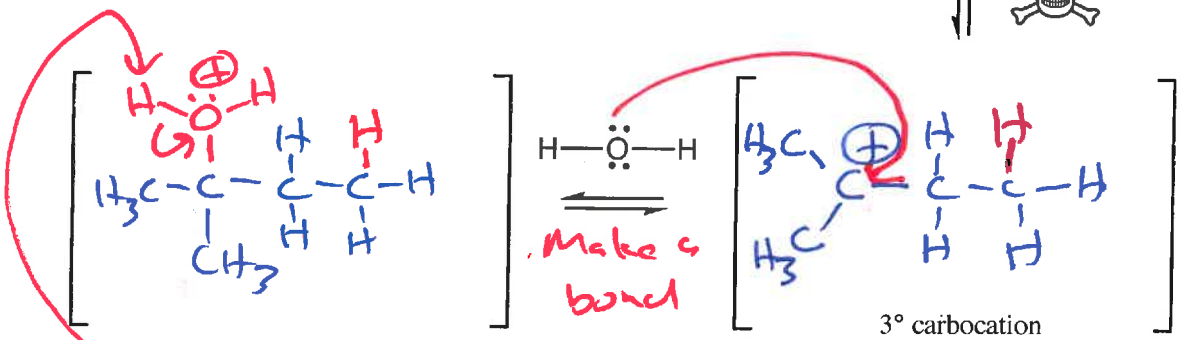


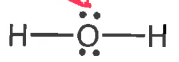


Add a proton

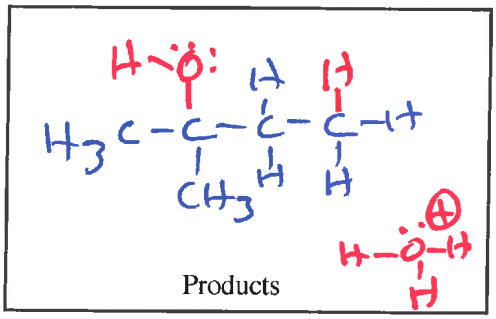


Rearrangement

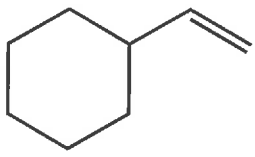




Take a proton away



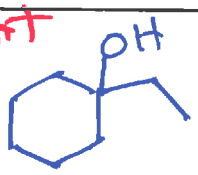
Example:



Assume rearrangement!

H_2O

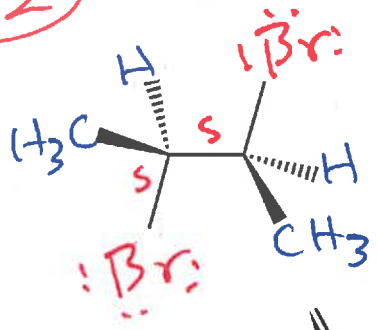
H_2SO_4 (catalytic amount)

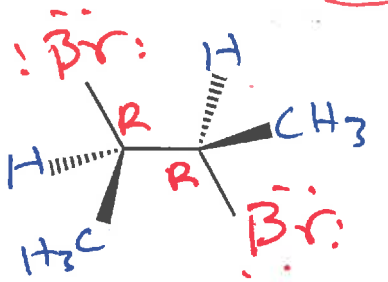


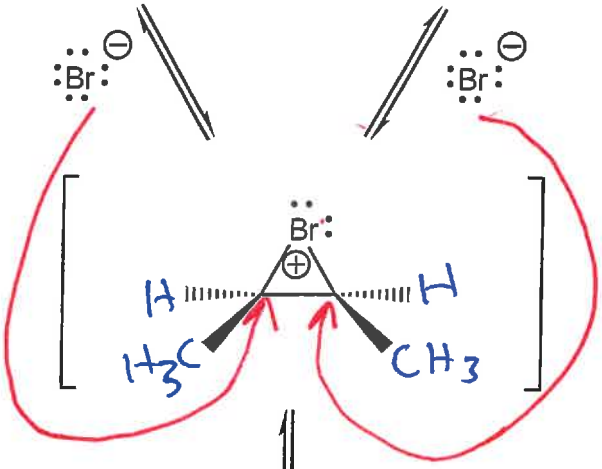
Racemic

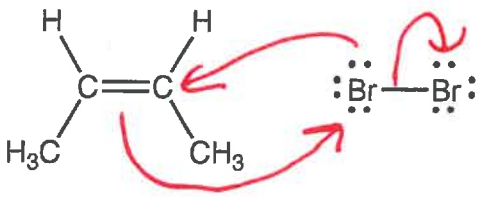
2

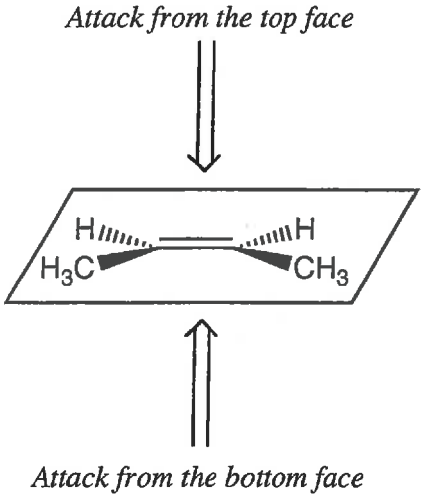
1

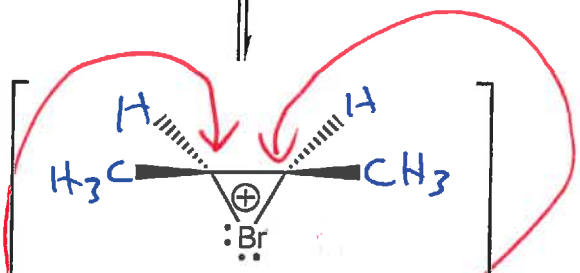


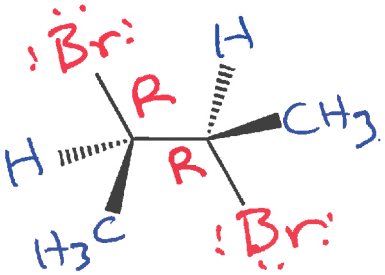


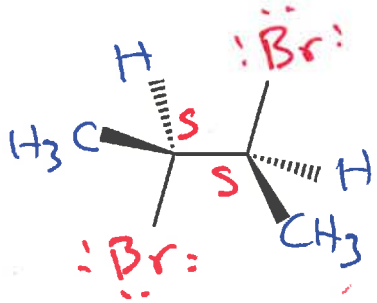








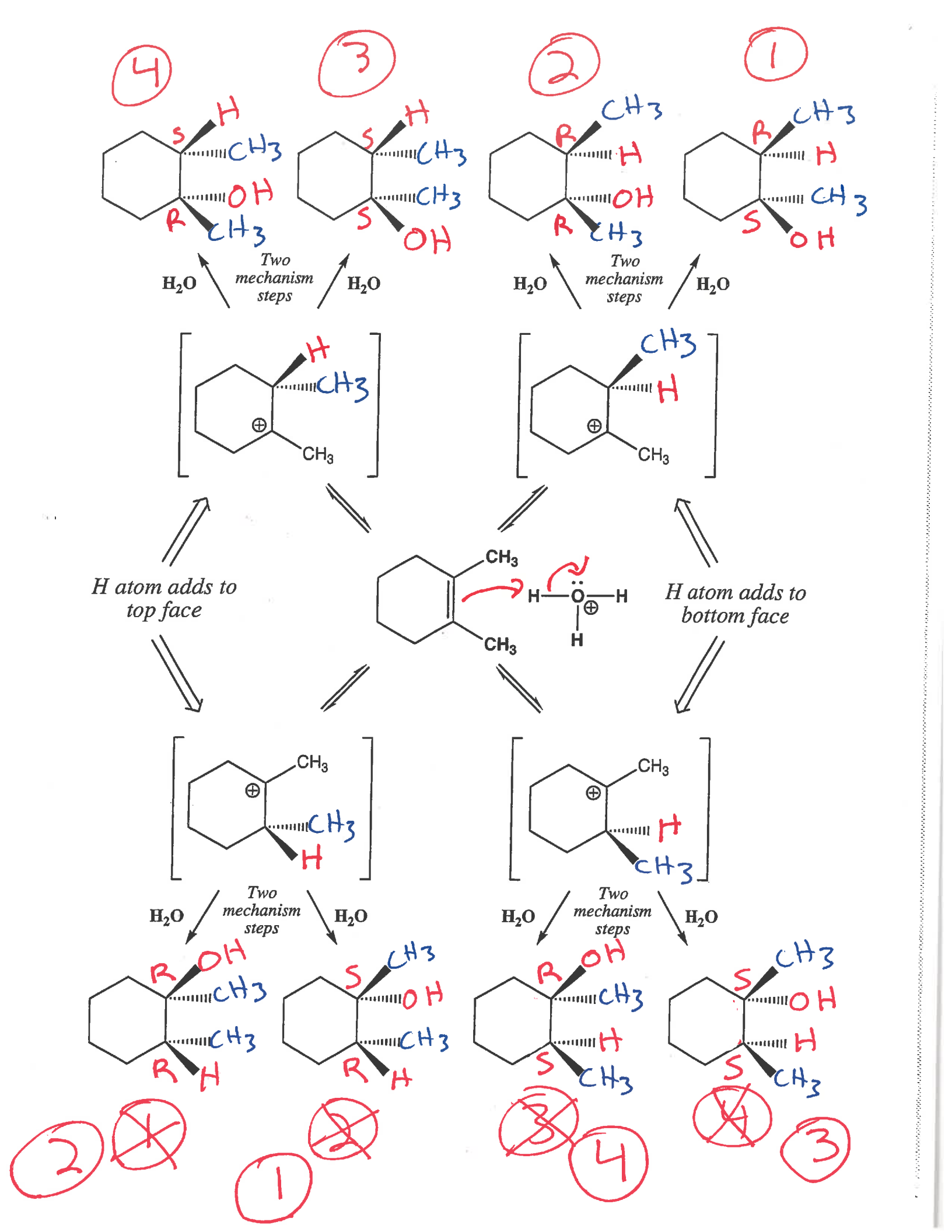




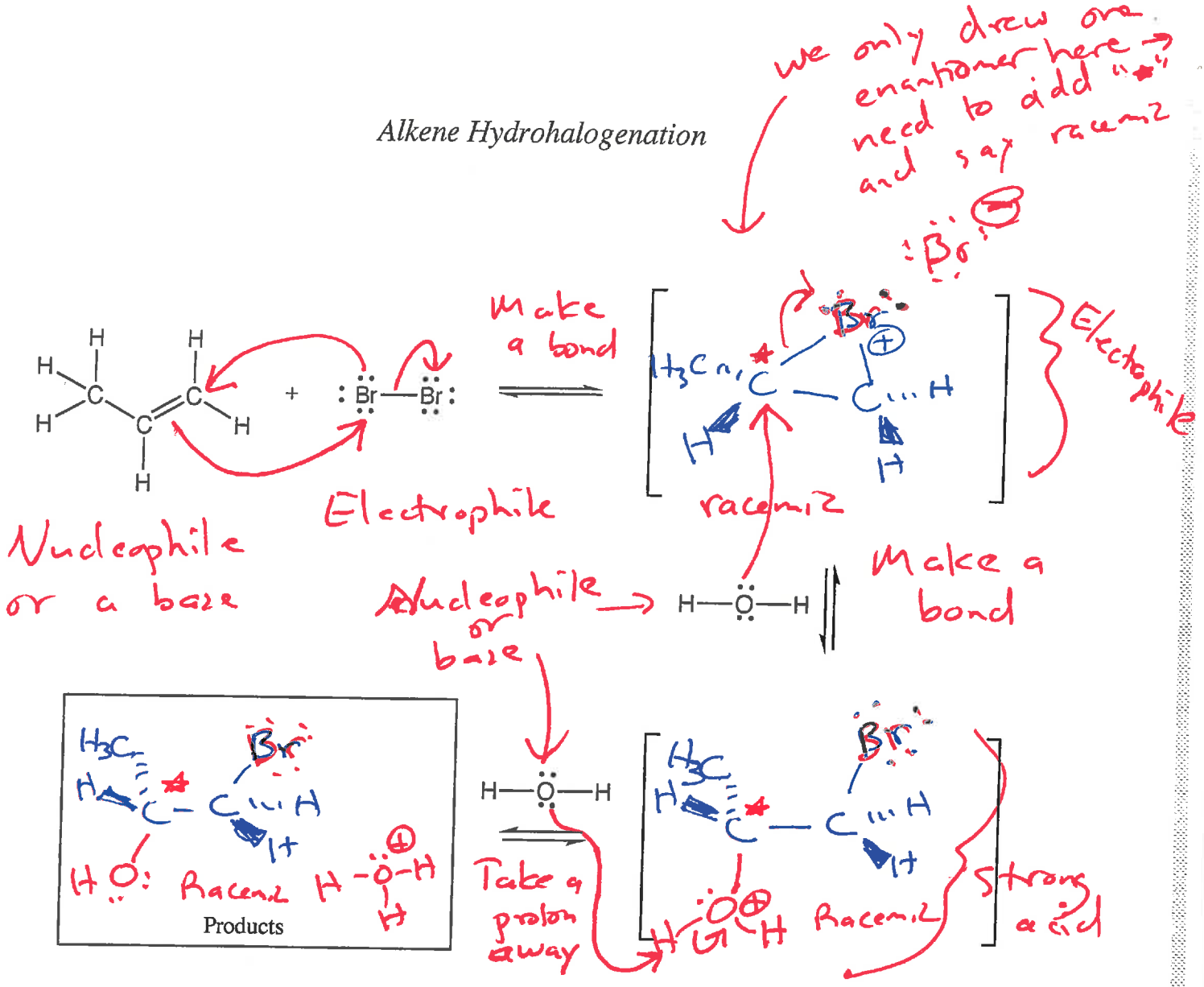
1

2

Racemic


4
3
2
1
H
CH3
OH
S
R
H2O
Two mechanism steps
H2O
Two mechanism steps
H2O
CH3
H
CH3
CH3
CH3
H
CH3
H atom adds to top face
H atom adds to bottom face
H
O
H
H
CH3
CH3
CH3
H
CH3
CH3
H
CH3
H2O
Two mechanism steps
H2O
H2O
Two mechanism steps
H2O
R
OH
CH3
CH3
R
H
S
CH3
OH
CH3
R
H
R
OH
CH3
H
S
CH3
S
CH3
OH
H
S
CH3
2
1
3
4

Alkene Hydrohalogenation

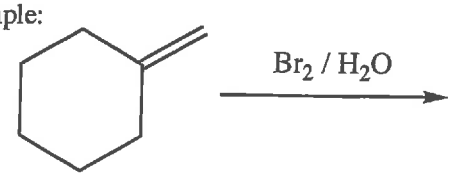


Summary: Br adds to alkene to make a a bromonium ion, water attacks, a proton is removed

Regiochemistry: OH ends up on more substituted Carbon

Stereochemistry: anti → "H_2O attacks from the back"

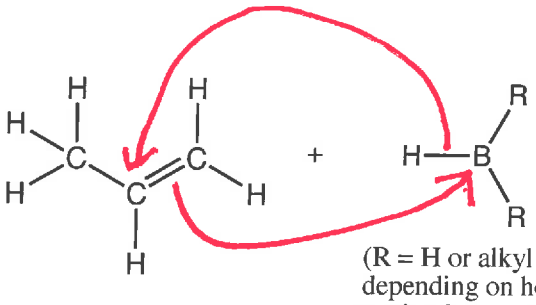
Example:



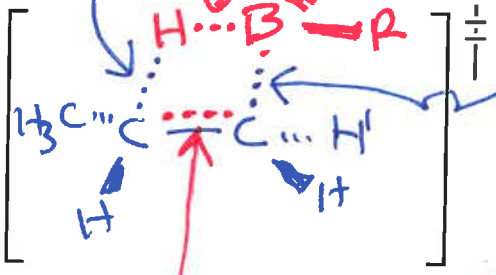
not chiral

Hydroboration-Oxidation

Bonds forming



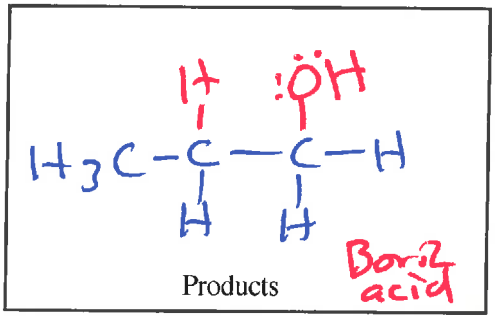
(R = H or alkyl group depending on how far reaction has progressed)



transition state

Bonds that are breaking

H TS on more substituted carbon

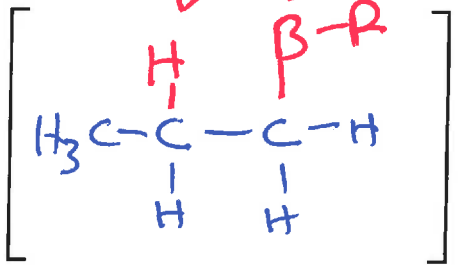


Products

Boric acid

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

(Chemist opens flask and adds new reagent)



Non-Markovnikov!!

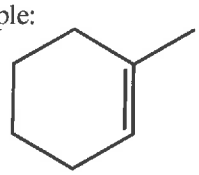
The H and B are on same side of C=C → "Syn"

Summary: Four membered ring transition state! The H and B atoms form bonds at the same time → H on ~~less~~ more substituted carbon atom

Regiochemistry: non-Markovnikov

Stereochemistry: Syn

Example:



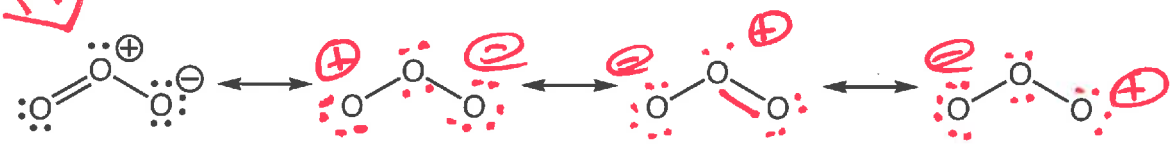
1. BH_3

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

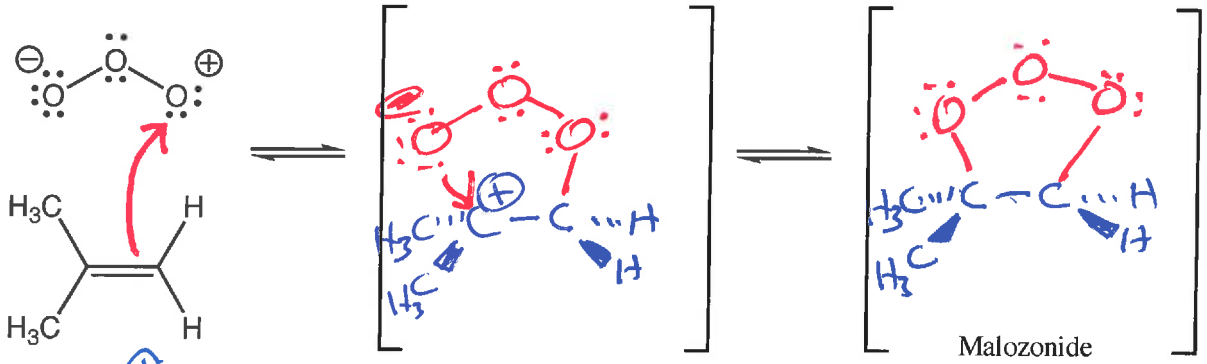
Racemic

"O_3"

Ozonolysis Partial Mechanism



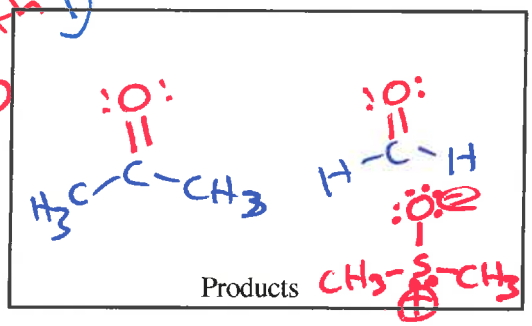
Ozone contributing structures



Replace C=C with two C=O

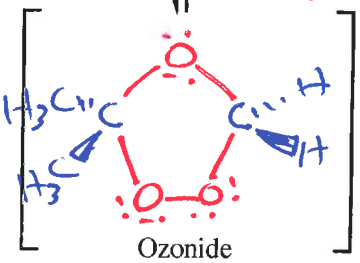
Rearrangement in two steps

Break the C–C bonds



2. $(CH_3)_2S$

(Chemist opens up flask)

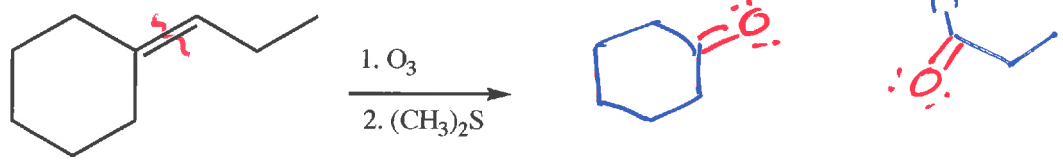


Summary: Alkene, react with ozone (O_3) to give a malozonide then ozonide → reacts with $(CH_3)_2S$ to give 2C=O

Regiochemistry: N/A

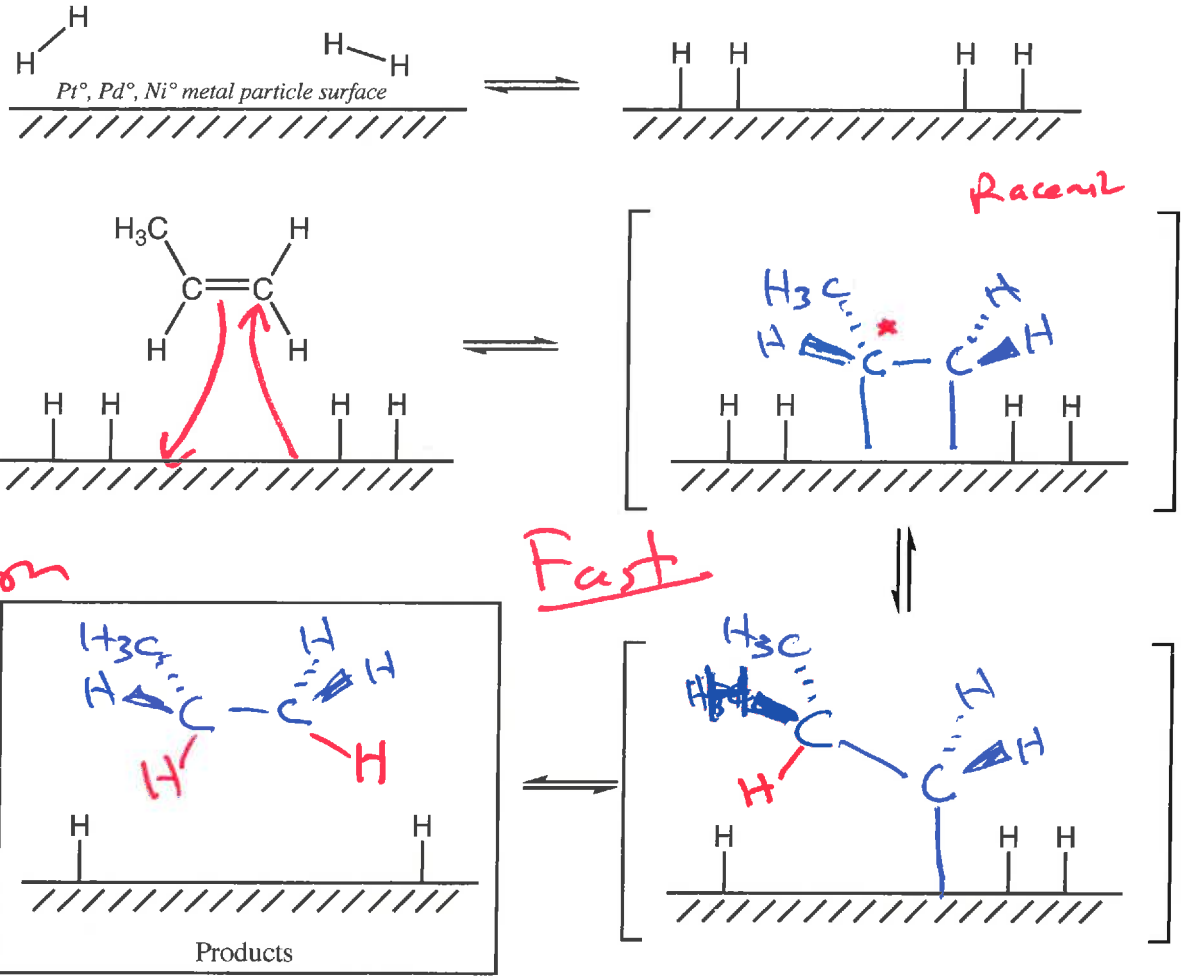
Stereochemistry: N/A

Example:



★ ONLY REACTION THAT BREAKS C–C BONDS

Hydrogenation: H_2 with Pt°, Pd°, Ni°



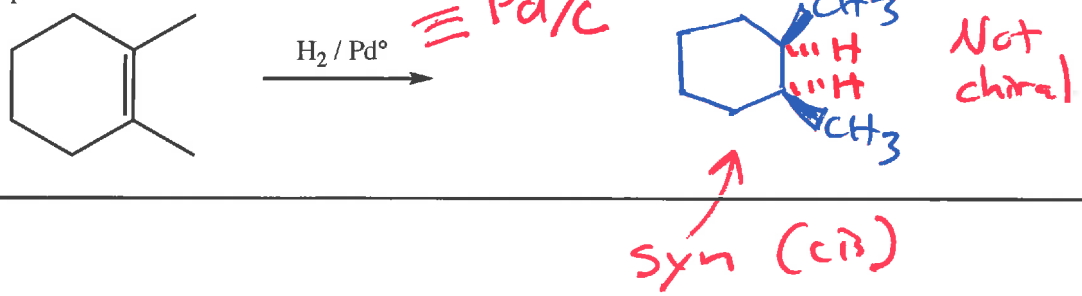
Syn addition geometry

Summary: Alkene → alkane → the H_2 and alkene absorb onto metal surface, new C–H bonds form Syn

Regiochemistry: N/A

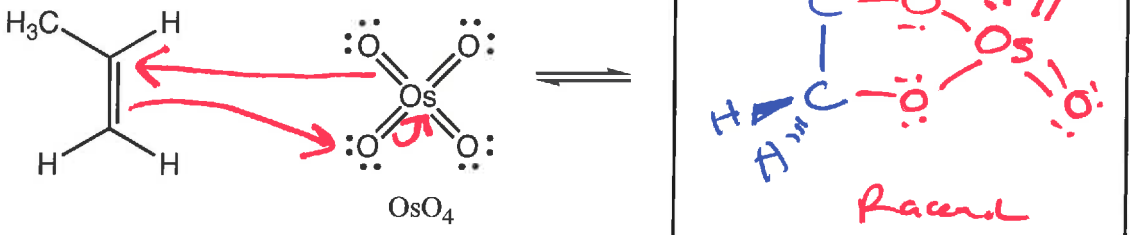
Stereochemistry: Syn

Example:



Osmium Tetroxide → Ozzie Osborne reaction

OsO_4 *Partial Mechanism*

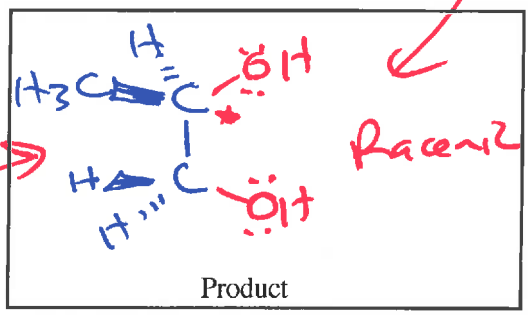


A cyclic osmate ester

"3"

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

"Vicinal diol"

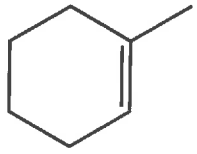


Product

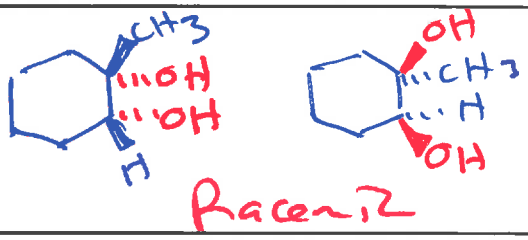
"Syn" addition

Summary:	Alkenes converted to a vicinal diol via a cyclic osmate ester
Regiochemistry:	N/A
Stereochemistry:	Syn addition

Example:



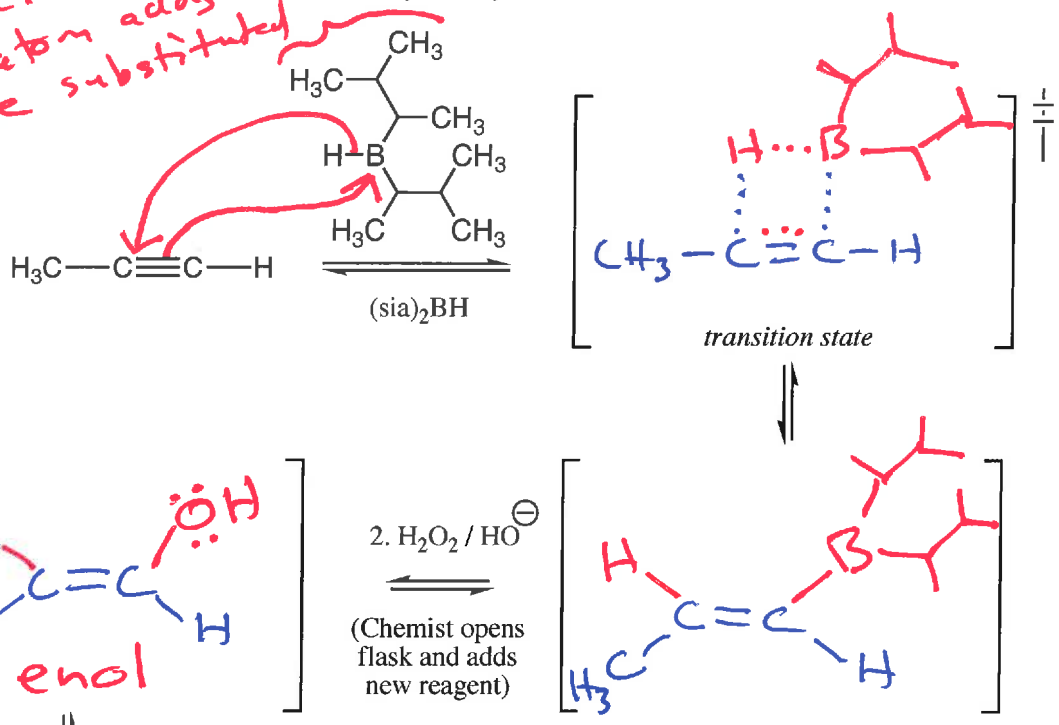
1. OsO_4
2. $NaHSO_3$ / H_2O



.... Bonds being broken
.... Bonds being formed

These "antler" groups provide steric discrimination so the H atom adds to the more substituted C atom

Terminal Alkyne Hydroboration

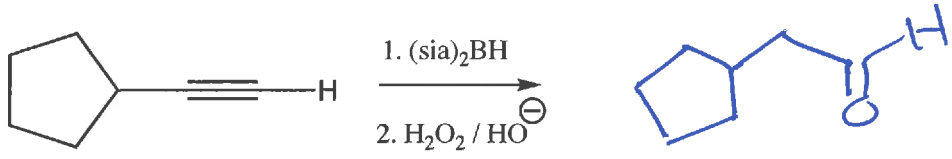


Summary: Syn addition in a four-membered ring transition state to give an enol that tautomerizes to the keto form (aldehyde) final product

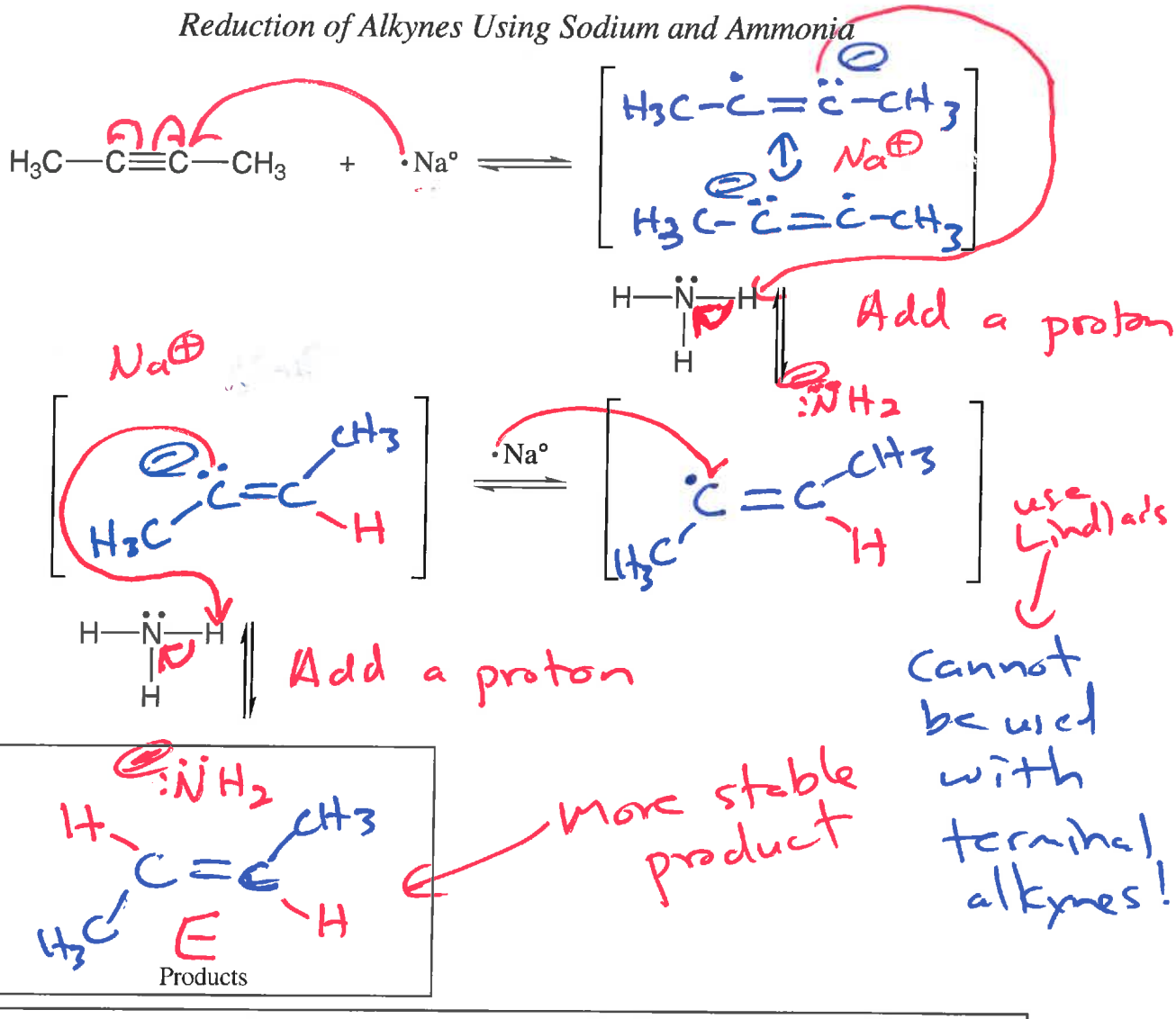
Regiochemistry: Non-Markovnikov (terminal alkynes)

Stereochemistry: N/A

Example:



Reduction of Alkynes Using Sodium and Ammonia

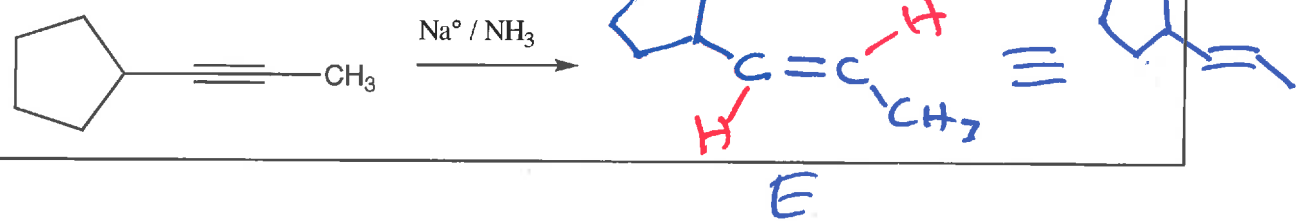


Summary: Alkynes are reduced using Na^0 in NH_3 via two one electron reductions followed by addition of a proton from NH_3

Regiochemistry: — N/A

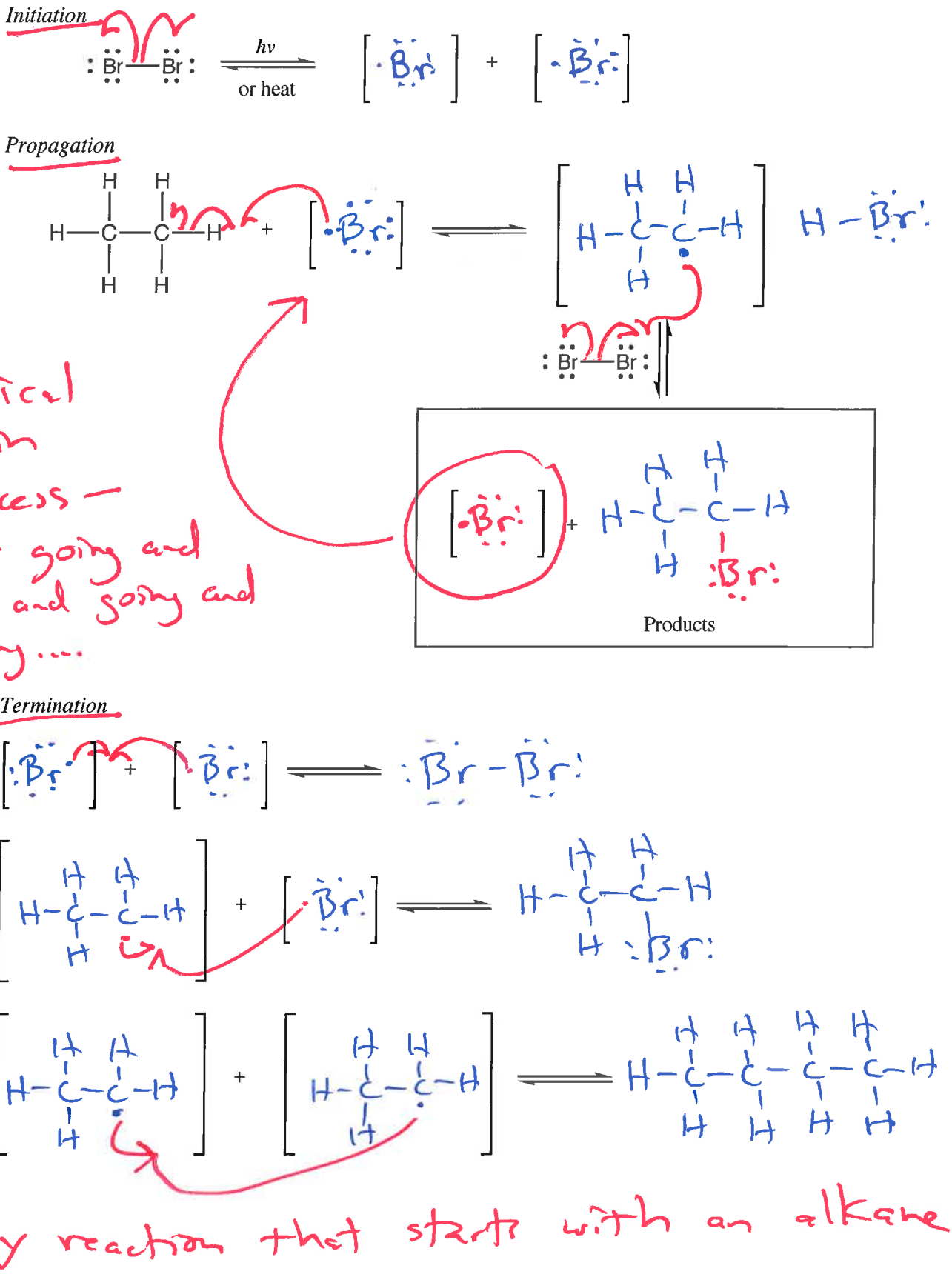
Stereochemistry: anti → trans or E product

Example:



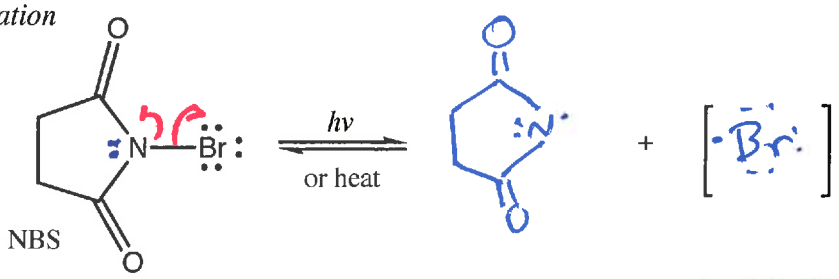
E

Alkane Free Radical Halogenation

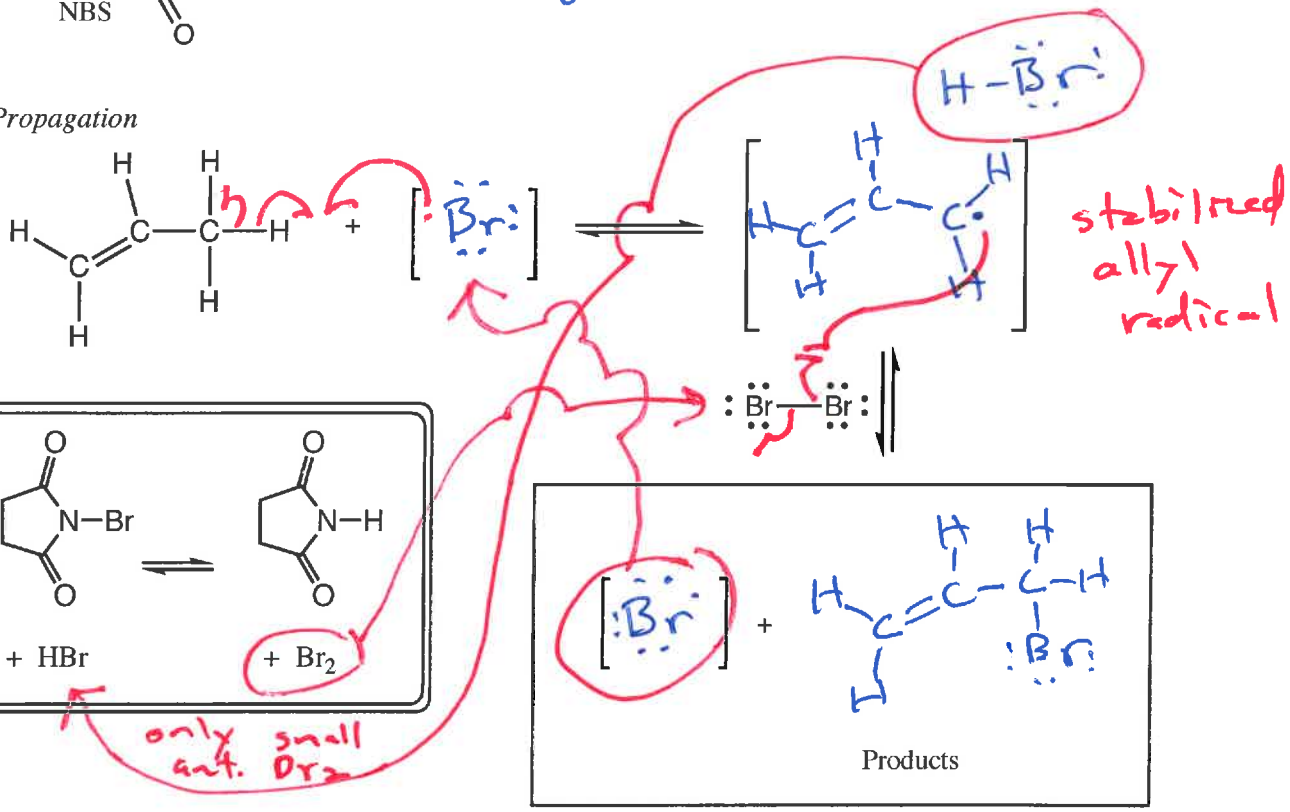


Allylic Halogenation

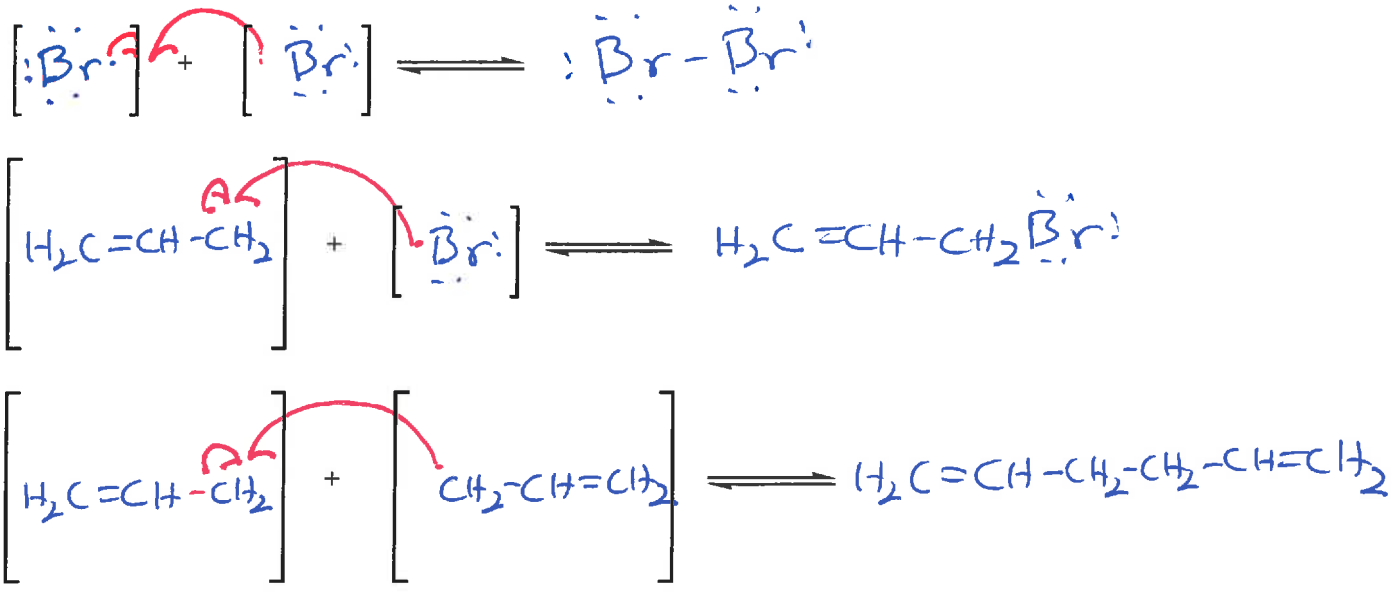
Initiation



Propagation



Termination



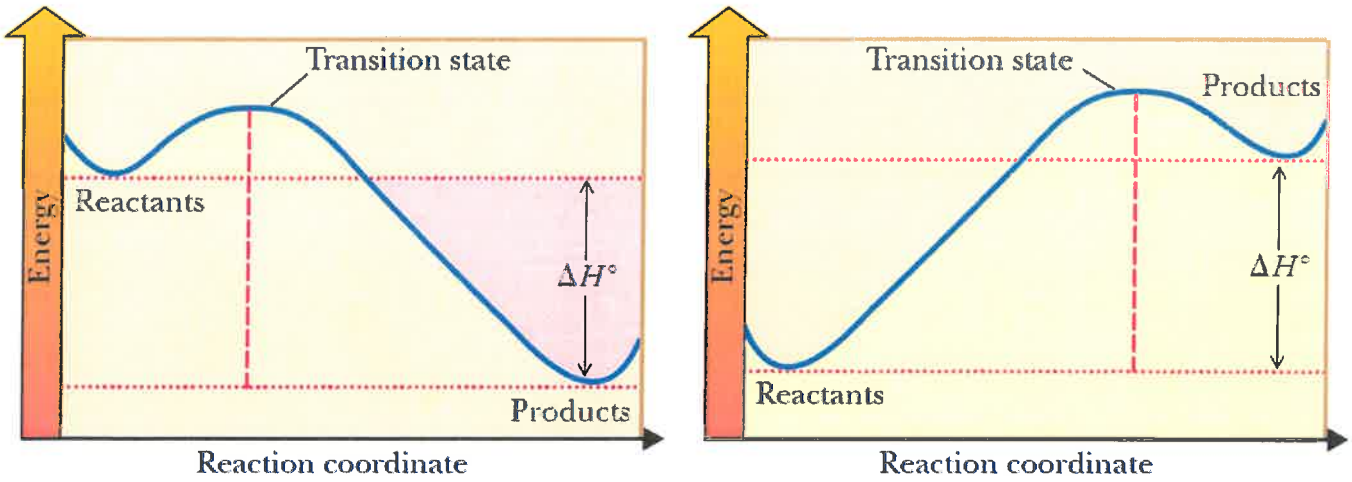


Figure 8.2
Hammond's postulate. Energy diagrams for two one-step reactions. In the exothermic reaction, the transition state occurs early, and its structure resembles that of the reactants. In the endothermic reaction, the transition state occurs late, and its structure resembles that of the products.

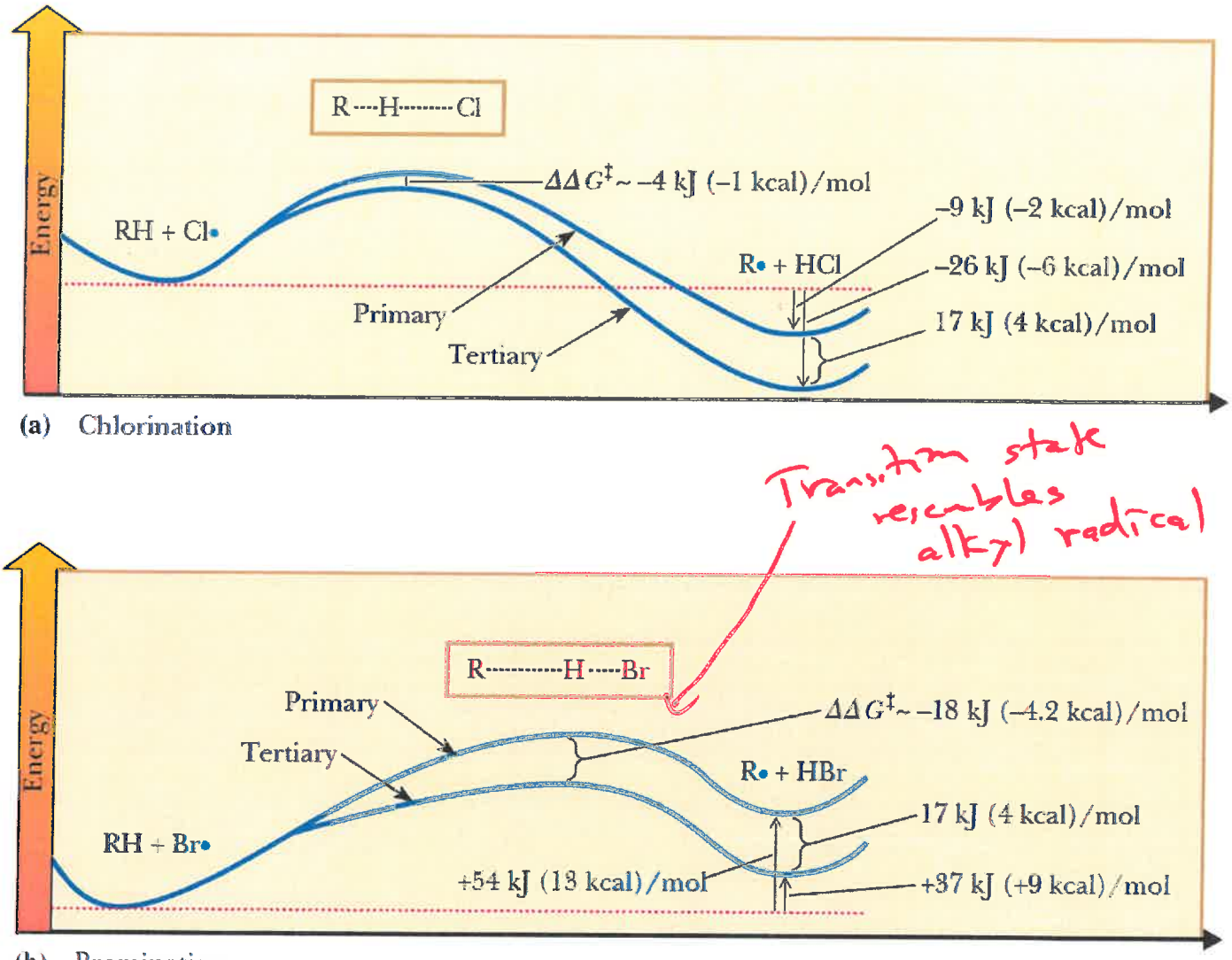
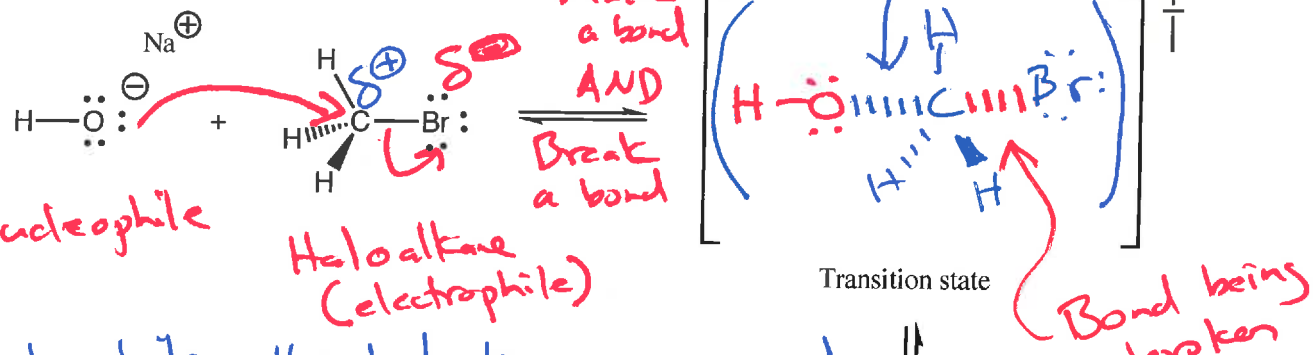


Figure 8.3
Transition states and energetics for hydrogen abstraction in the radical chlorination and bromination of 2-methylpropane (isobutane). The product is the intermediate radical, R·.

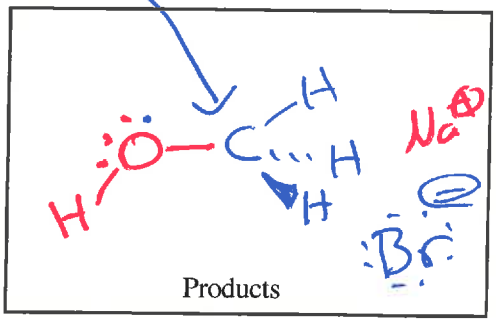
Differences in energy between 3°, 2°, 1° radicals MORE important for Bromine compared to chlorine

⇒ Use Br_2 → it is more selective for free radical halogenation of an alkane

The S_N2 Mechanism



Nucleophile attracted to backside of C–Br bond → this reaction geometry actually assists in breaking the C–Br bond → required geometry

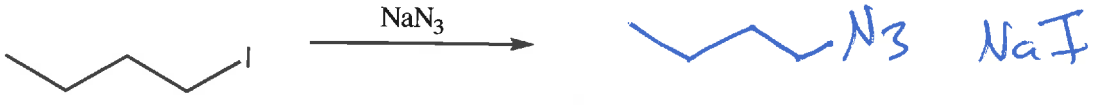


Summary: Nucleophile displaces the leaving group ($Br^{\ominus}$) in a single step

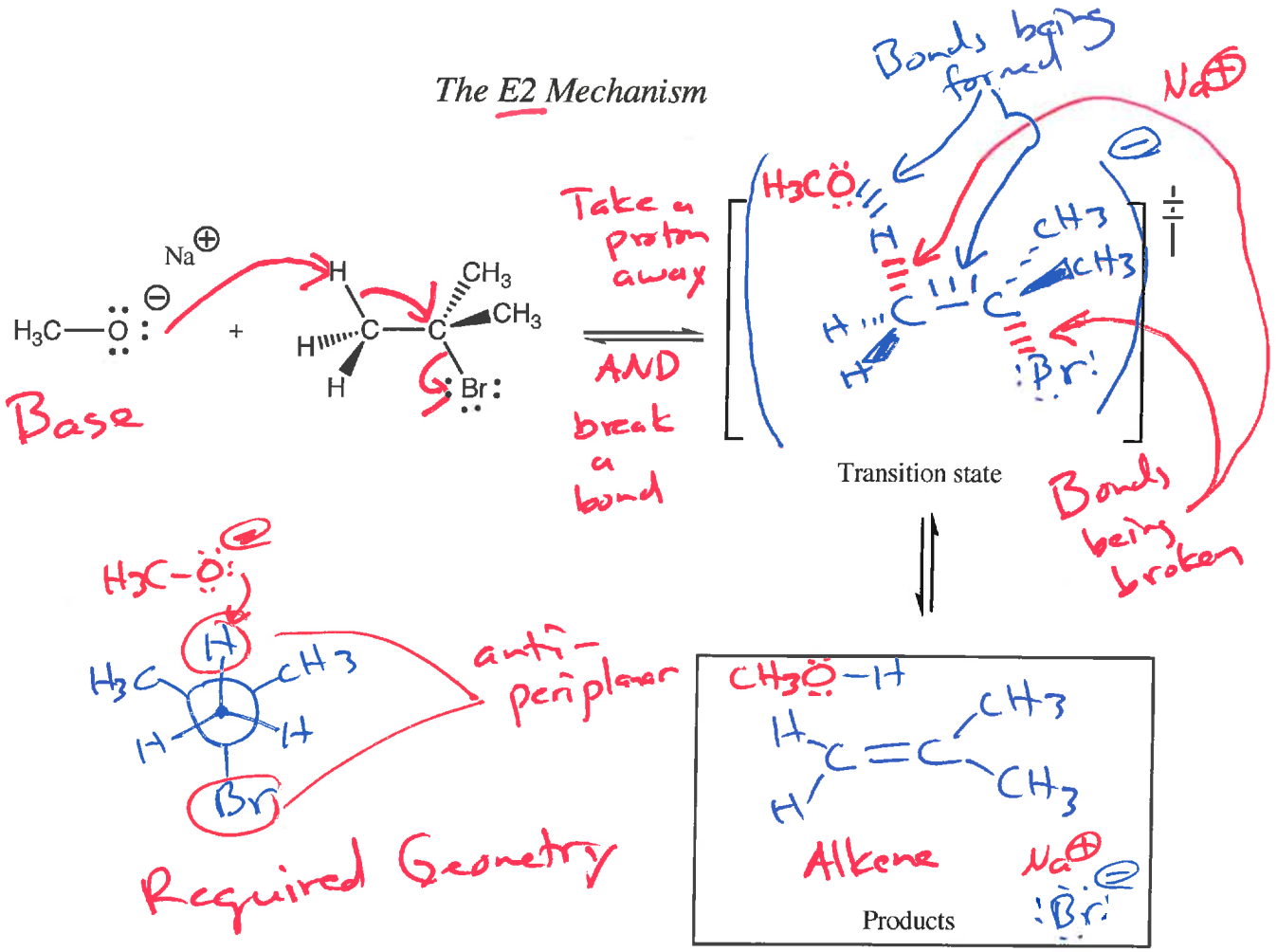
Regiochemistry: N/A

Stereochemistry: INVERSION at site of reaction

Example:



The E2 Mechanism



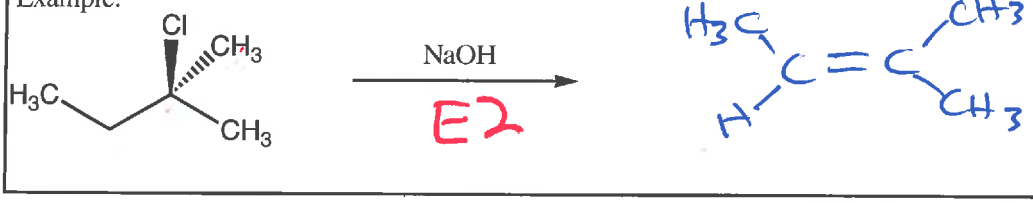
Summary:

Base removes H, making a π bond and losing the halogen (leaving group) → all one step → all must be anti-periplanar

Regiochemistry: Zaitsevs Rule → Make most stable alkene (most substituted)

Stereochemistry: Determined by anti-periplanar transition state

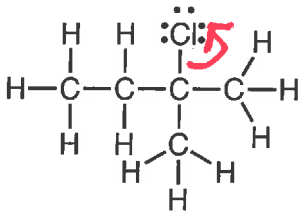
Example:



Always see these together!!

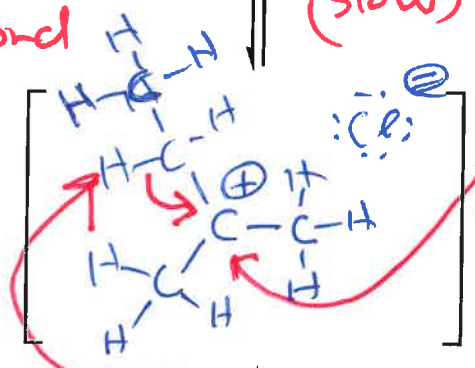
unimolecular → one the haloalkane is part of rate-limiting step

The S_N1 and E1 Mechanisms

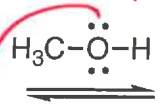


Break a bond

(slow)

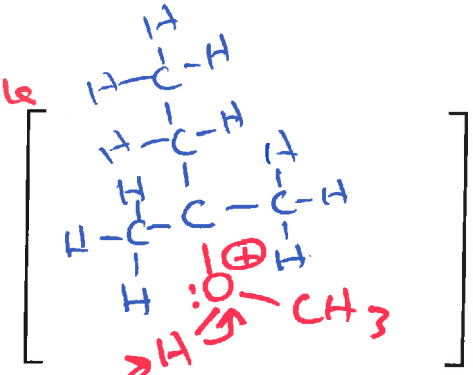


weak nucleophile

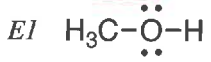


S_N1

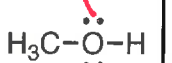
Make a bond



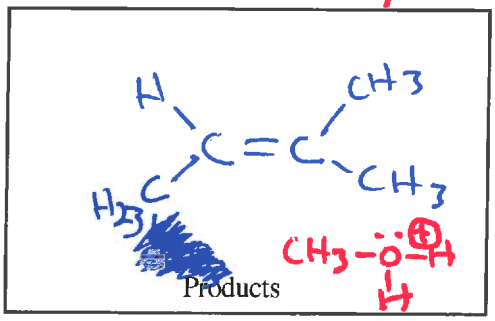
weak base

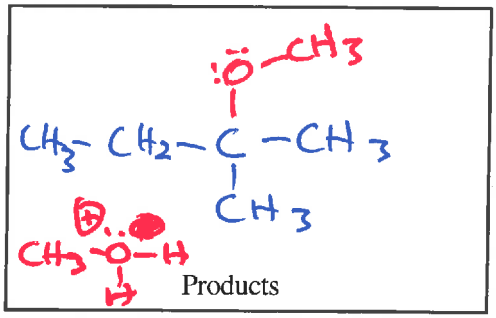
E1 

Take a proton away



Take a proton away





Summary: For sterically hindered haloalkanes, heating causes the halide to leave, the resulting carbocation adds weak nucleophiles (S_N1) or loses a proton to give an alkene (E1)

Regiochemistry: E1 → Zaitsev's Rule → most substituted alkene

Stereochemistry: S_N1 → Stereochemistry is scrambled → not 1:1 exactly

Example:

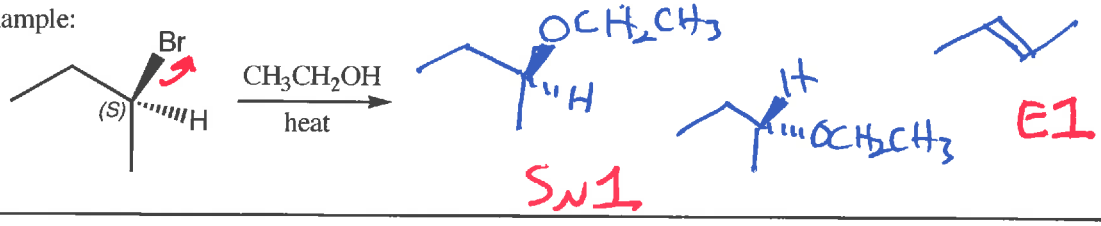
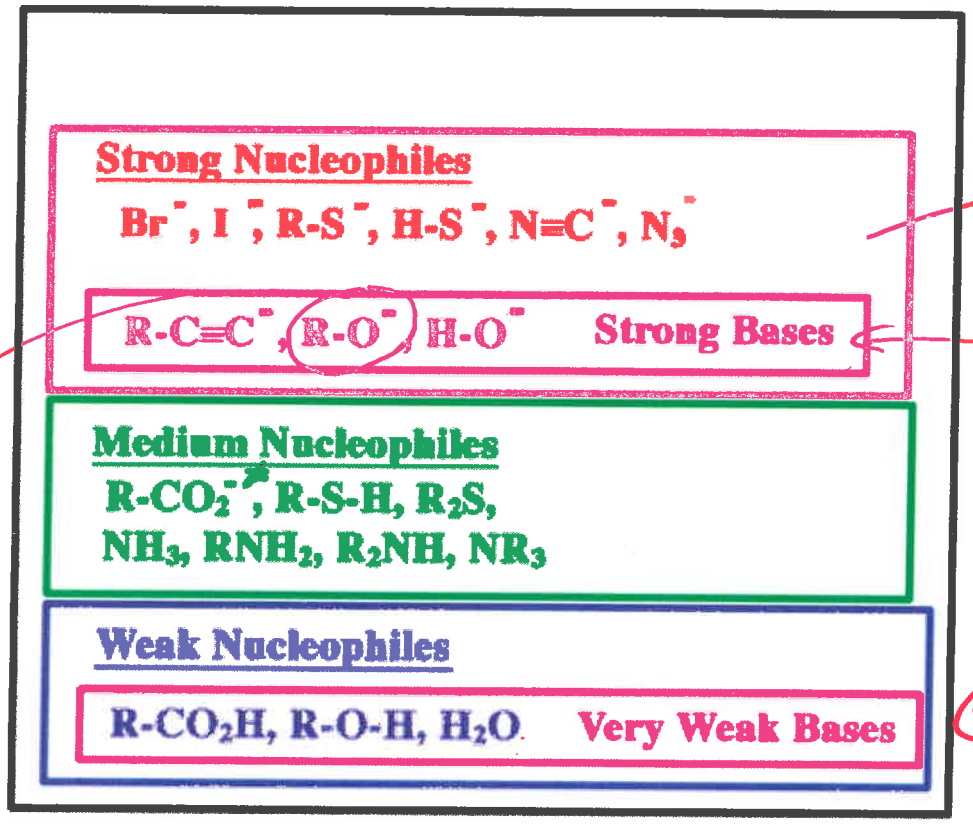


Table of Nucleophiles

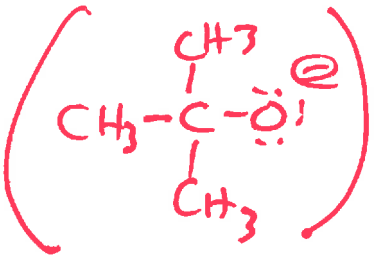


negative charge

Big deal

Special Case

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



Learn this table

Haloalkane

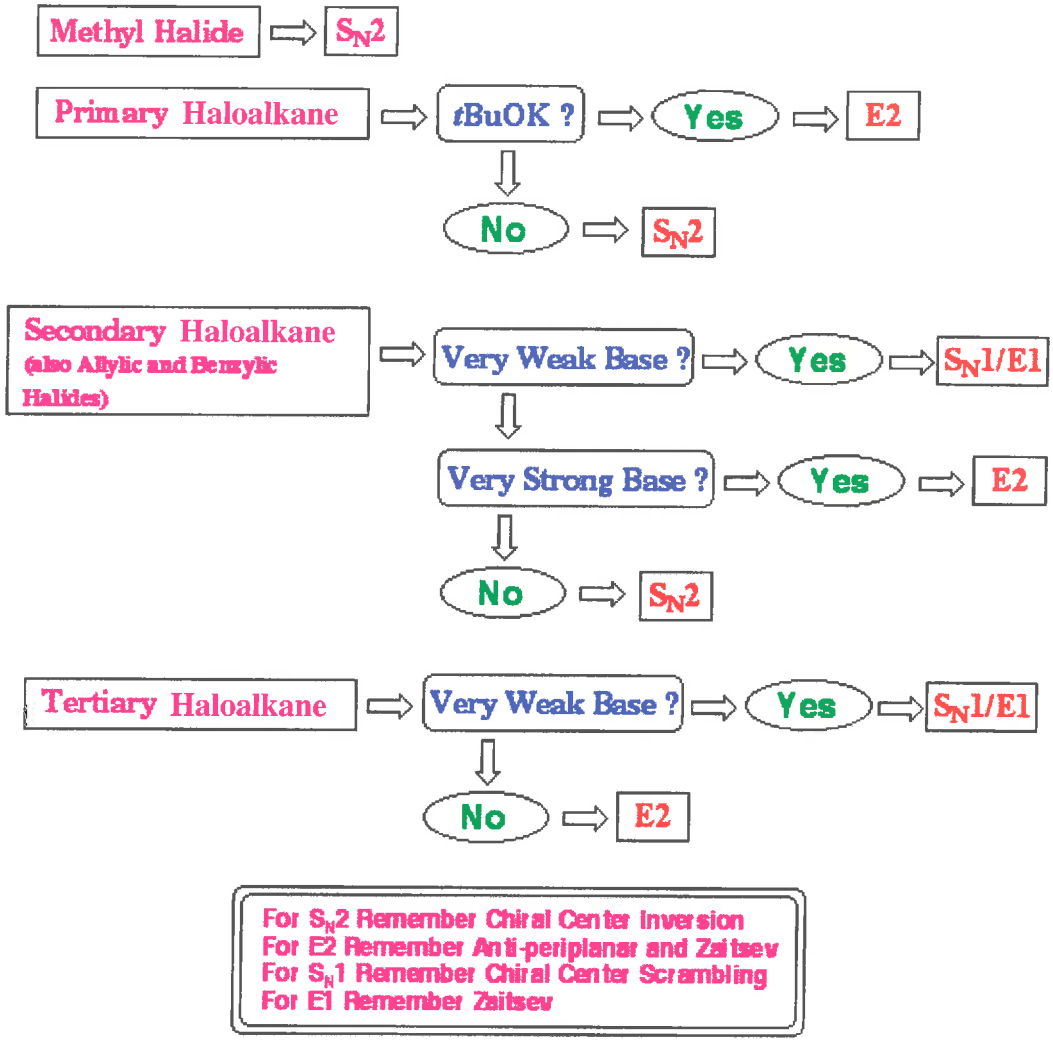
Methyl	Primary	Secondary	Tertiary
CH_3Cl	CH_3CH_2Cl	$CH_3CH(Cl)CH_3$	$(CH_3)_3CCl$

S_N2 favored ← steric hindrance on backside of C-Cl bond → S_N2 prevented

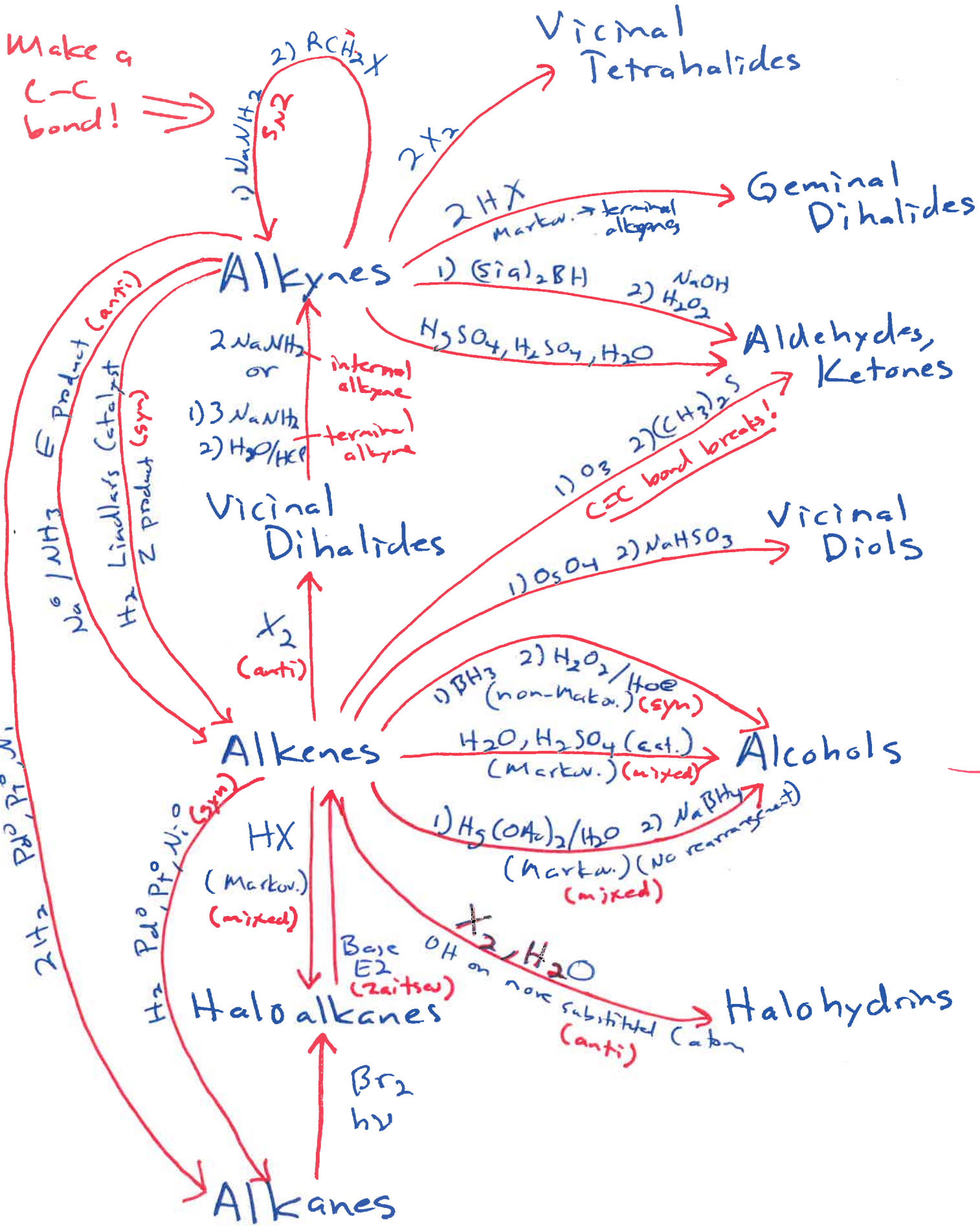
S_N1 / E1 not happening! ← carbocation stability → Favors S_N1/E1

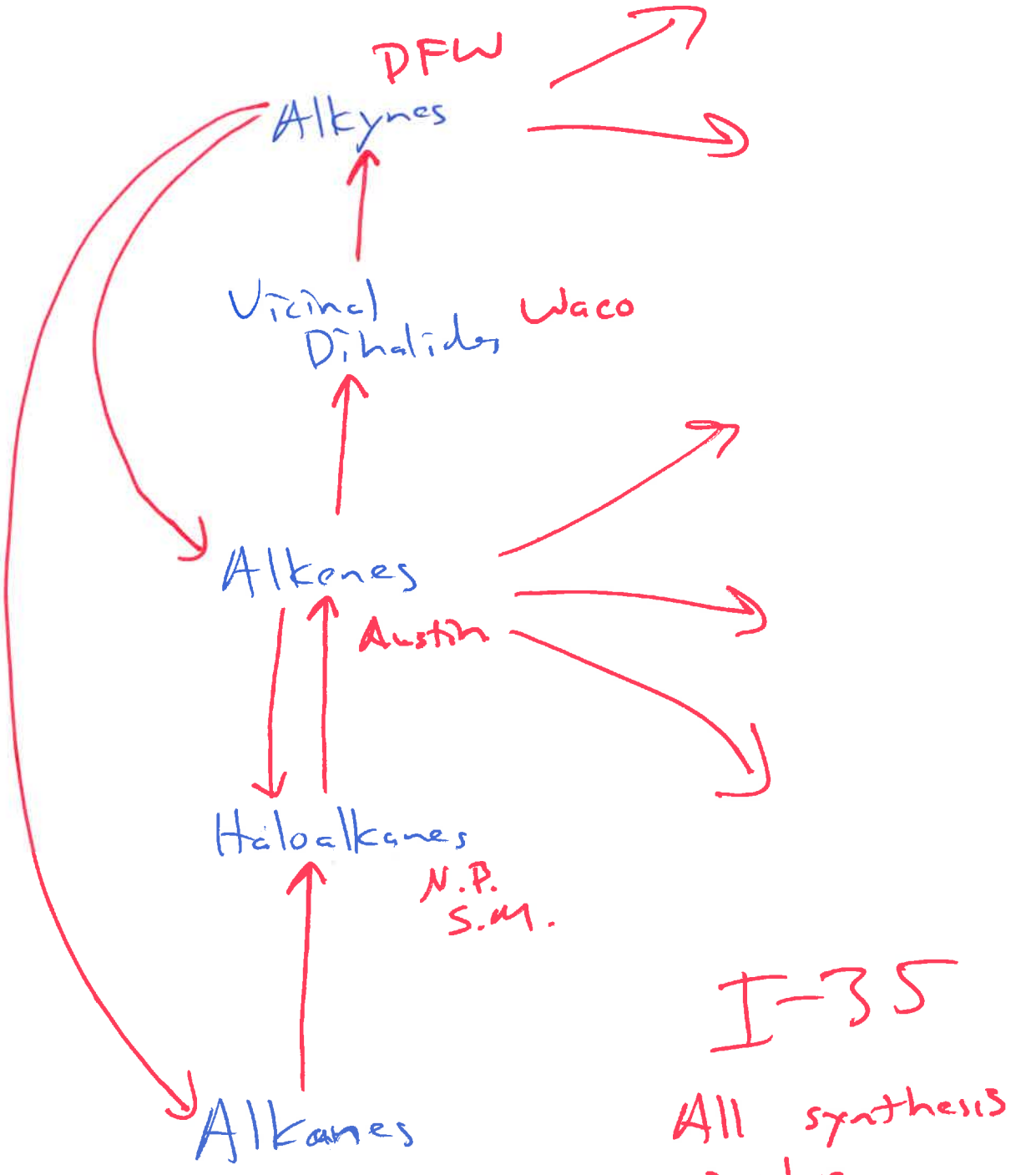
Stronger base favors E2 over S_N2

Substitution/Elimination Decision Map



For S_N2 Remember Chiral Center Inversion
For E2 Remember Anti-periplanar and Zaitsev
For S_N1 Remember Chiral Center Scrambling
For E1 Remember Zaitsev


Make a C–C bond!
1) NaNH2
2) RCH2X
SN2
Alkynes
2 X2
Vicinal Tetrahalides
2 HX
Markov. → terminal alkynes
Geminal Dihalides
1) (Sia)2BH
2) NaOH, H2O2
H3SO4, H2SO4, H2O
Aldehydes, Ketones
2 NaNH2 or 1) 3 NaNH2 2) H2O/HEP
internal alkyne
terminal alkyne
Vicinal Dihalides
1) O3 2) (CH3)2S
C=C bond breaks!
1) OsO4 2) NaHSO3
Vicinal Diols
Na° / NH3
E Product (anti)
H2 Lindlar's Catalyst
Z product (syn)
X2 (anti)
Alkenes
1) BH3 2) H2O2 / HOe
(non-Markov.) (syn)
H2O, H2SO4 (cat.)
(Markov.) (mixed)
Alcohols
1) Hg(OAc)2 / H2O 2) NaBH4
(Markov.) (No rearrangement)
(mixed)
Pd°, Pt°, Ni°
2 H2
Pd°, Pt°, Ni°
H2 (syn)
HX
(Markov.)
(mixed)
Base OH on more substituted Carbon
E2 (Zaitsev)
X2, H2O
Haloalkanes
Halohydrins
(anti)
Br2
hν
Alkanes



I-35

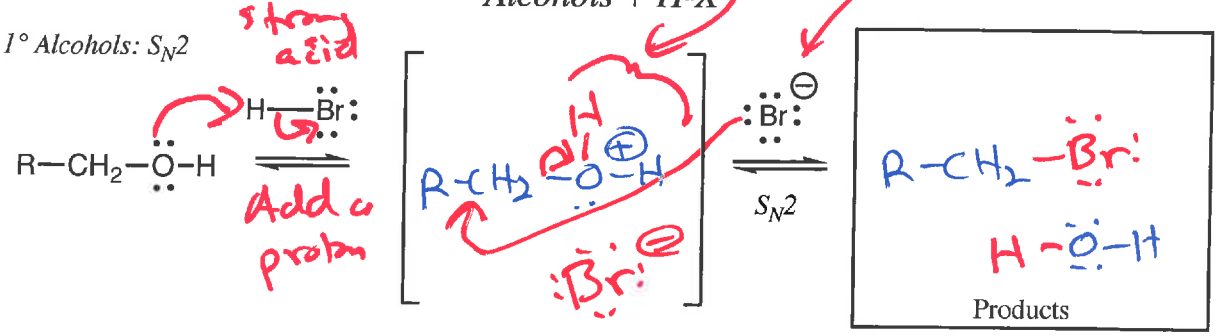
All synthesis involve travel on this I-35

Table 10.1 Boiling Points and Solubilities in Water of Five Groups of Alcohols and Hydrocarbons of Similar Molecular Weight

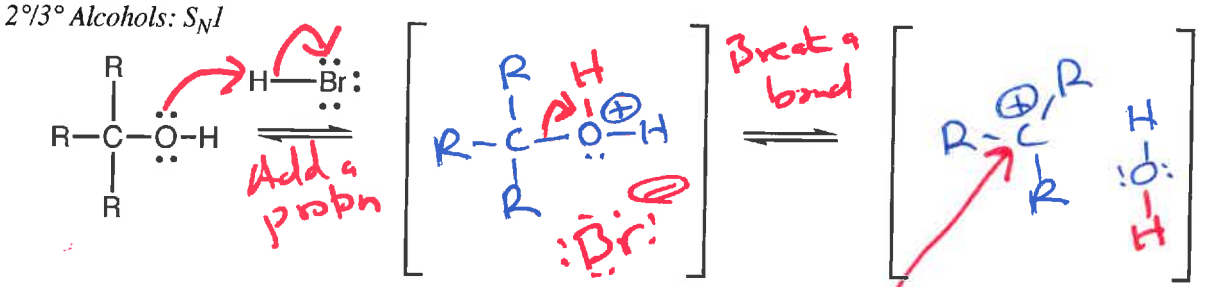
Structural Formula	Name	Molecular Weight (g/mol)	Boiling Point (°C)	Solubility in Water
CH_3OH	Methanol	32	65	Infinite
CH_3CH_3	Ethane	30	−89	Insoluble
CH_3CH_2OH	Ethanol	46	78	Infinite
$CH_3CH_2CH_3$	Propane	44	−42	Insoluble
$CH_3CH_2CH_2OH$	1-Propanol	60	97	Infinite
$CH_3CH_2CH_2CH_3$	Butane	58	0	Insoluble
$CH_3CH_2CH_2CH_2OH$	1-Butanol	74	117	8 g/100 g
$CH_3CH_2CH_2CH_2CH_3$	Pentane	72	36	Insoluble
$HOCH_2CH_2CH_2CH_2OH$	1,4-Butanediol	90	230	Infinite
$CH_3CH_2CH_2CH_2CH_2OH$	1-Pentanol	88	138	2.3 g/100 g
$CH_3CH_2CH_2CH_2CH_2CH_3$	Hexane	86	69	Insoluble

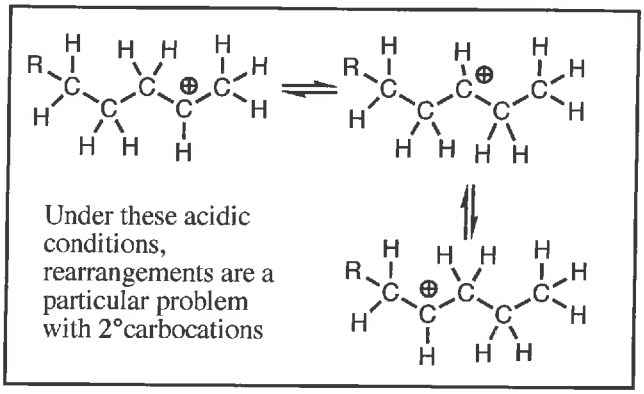
Alcohols + H-X

1° Alcohols: S_N2



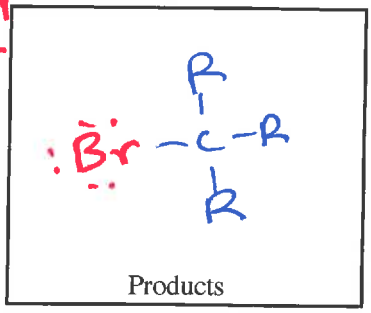
2°/3° Alcohols: S_N1





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

Note: very little E1 because these are acidic conditions!

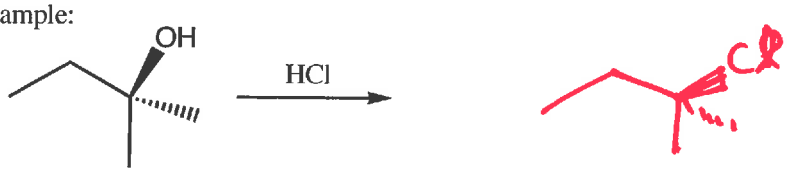


Summary: Reaction of the OH group as a ~~weak~~ ~~nucleophile~~/base with H-X leads to good leaving group (H_2O) → S_N2 (1°) or S_N1 (2°, 3°) no E1!

Regiochemistry: N/A

Stereochemistry: Scrambled if starting w/ chiral alcohol

Example:

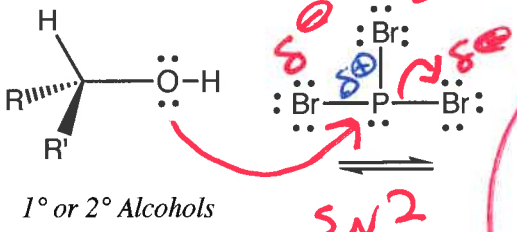


Electrophile

1° and 2° not 3°

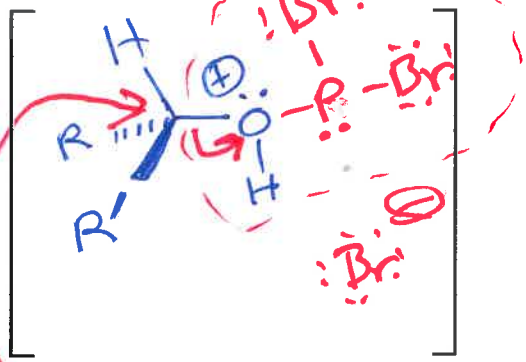
Very good (leaving group!!

Alcohols + PBr_3



1° or 2° Alcohols

S_N2



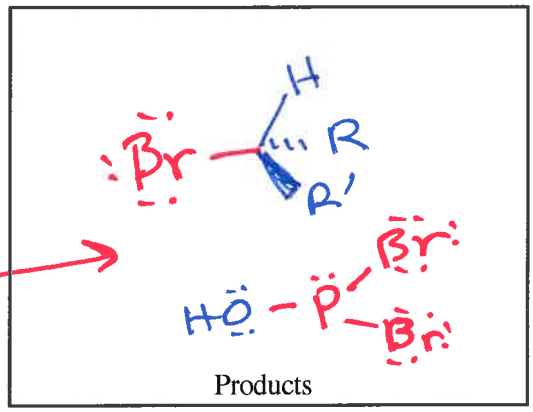
S_N2

There is an analogous reaction using $SOCl_2$ to turn –OH into –Cl

$RCH_2OH \xrightarrow{SOCl_2} RCH_2Cl$

No carbocation so NO rearrangement

INVERSION at chiral carbon



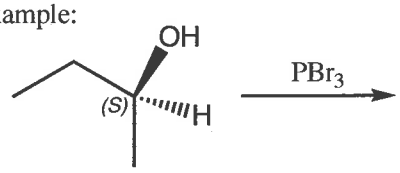
Products

Summary: 1° or 2° alcohol reacts as a nucleophile with PBr_3 to give a very good leaving group, setting up an S_N2 reaction with Br^-

Regiochemistry: N/A

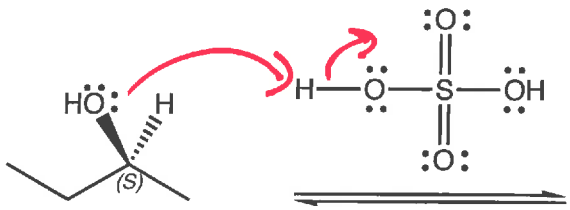
Stereochemistry: INVERSION

Example:



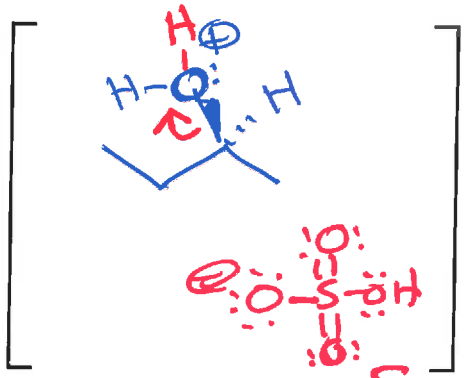
INVERSION

2° or 3° Alcohol Dehydration



2° or 3° Alcohols

Add a proton

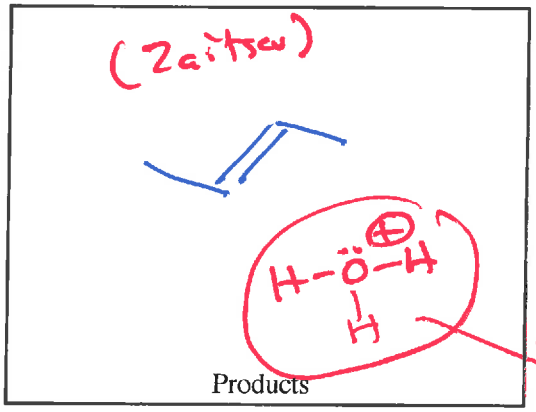


Break a bond

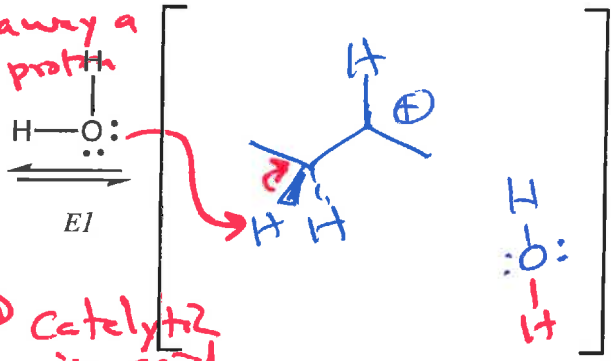
Not a nucleophile

1° alcohols react via E2

E1



Take away a proton



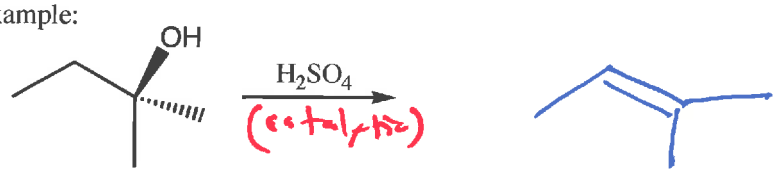
Catalyst in acid

Summary: An alcohol is protonated, the H_2O departs to give a carbocation (2° and 3° alcohols), that loses a proton to give an alkene. 1° alcohols lose the proton as the H_2O departs → E2

Regiochemistry: Zaitsev

Stereochemistry: N/A

Example:

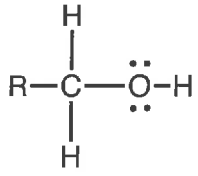


Called "Jones Reagent"

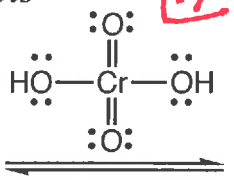
$(CrO_3 + H_2O$ or $K_2Cr_2O_7) + H_2SO_4$

Chromic Acid Oxidation of Alcohols

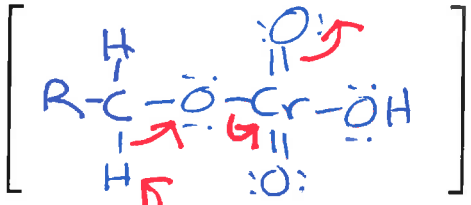
Not responsible for first step

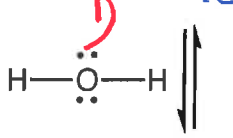


1° Alcohols

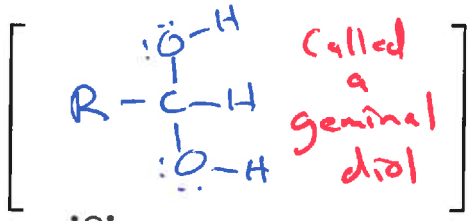


H_2CrO_4 or Chromic Acid

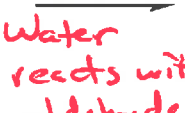




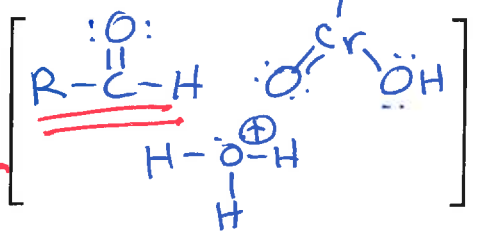
Not responsible for this step

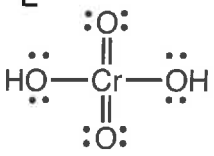


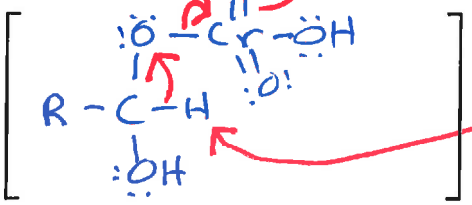
Called a geminal diol

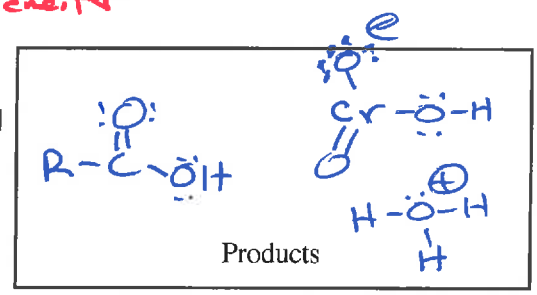


Water reacts with aldehyde – will learn next semester





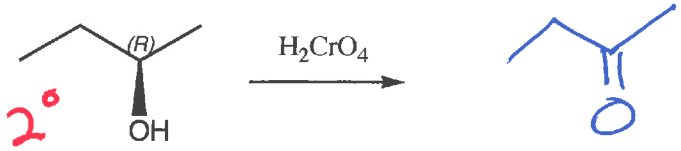




Products

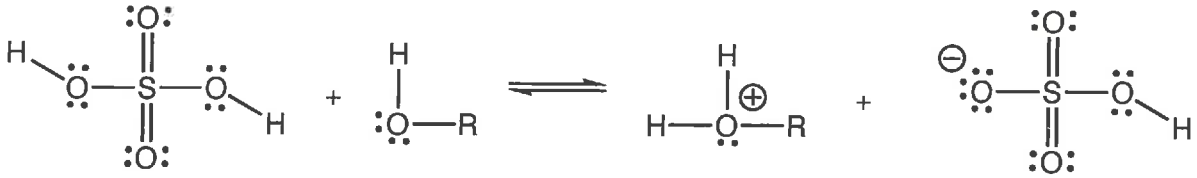
Summary:	1° alcohols ⇒ carboxylic acids 2° alcohols ⇒ ketones 3° alcohols ⇒ No Reaction!
Regiochemistry:	N/A
Stereochemistry:	N/A

Example:

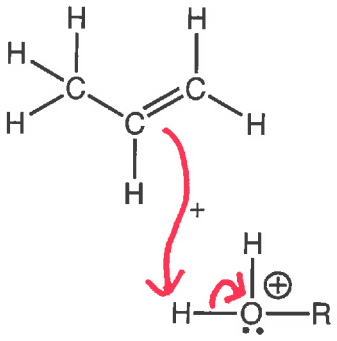


Ketone

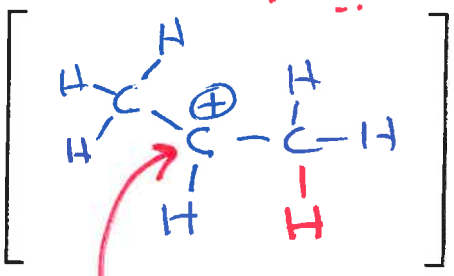
Acid-catalyzed Reaction of an Alcohol with an Alkene



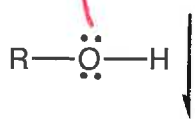
watch for rearrangement



add a proton



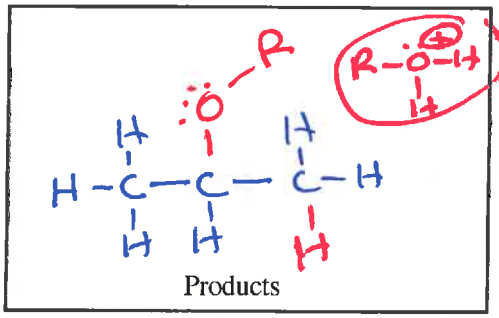
R-Ö-H



make a bond

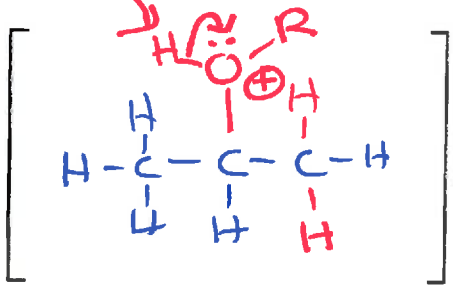
catalytic in acid

ether



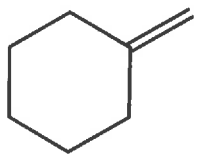
Products

take a proton away



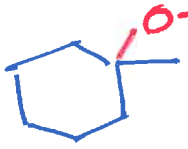
Summary:	Alkenes react with alcohols in acid to give ethers
Regiochemistry:	Markovnikov
Stereochemistry:	Mixed

Example:



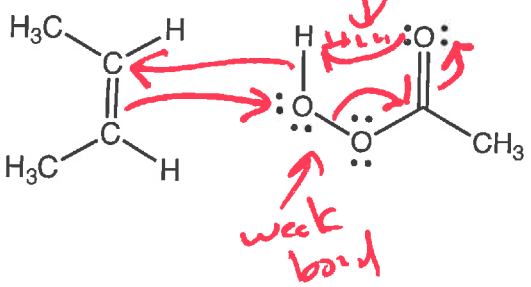
CH_3CH_2OH

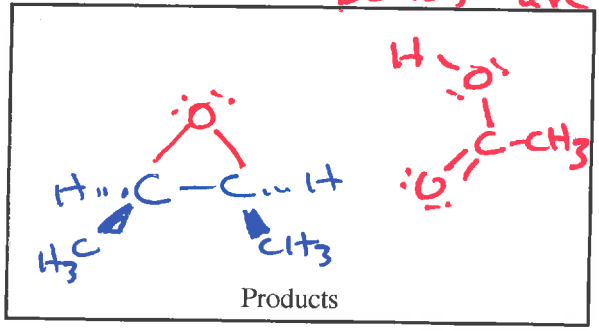
H_2SO_4 (catalytic amount)



not chiral

Epoxide Formation





hydrogen bond → keeps molecule in reactive conformation

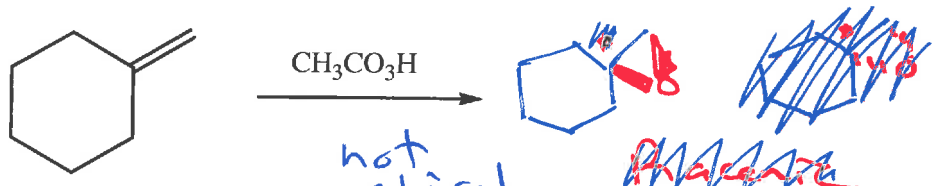
Motive → The O-O bond is weak → product Bonds are stronger

Summary: Alkenes react with peracids to make epoxides in a single step

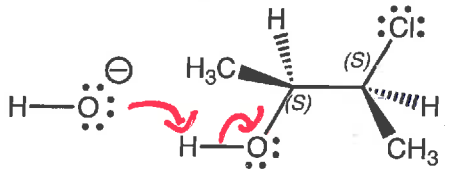
Regiochemistry: N/A

Stereochemistry: Mixed

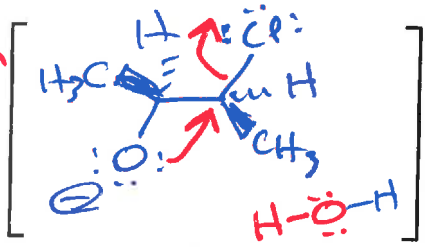
Example:



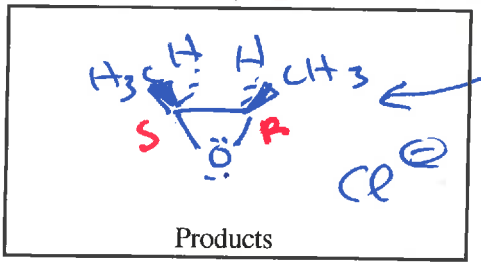
alkene
H_2O/X_2



take a proton away



make a bond (in same molecule)



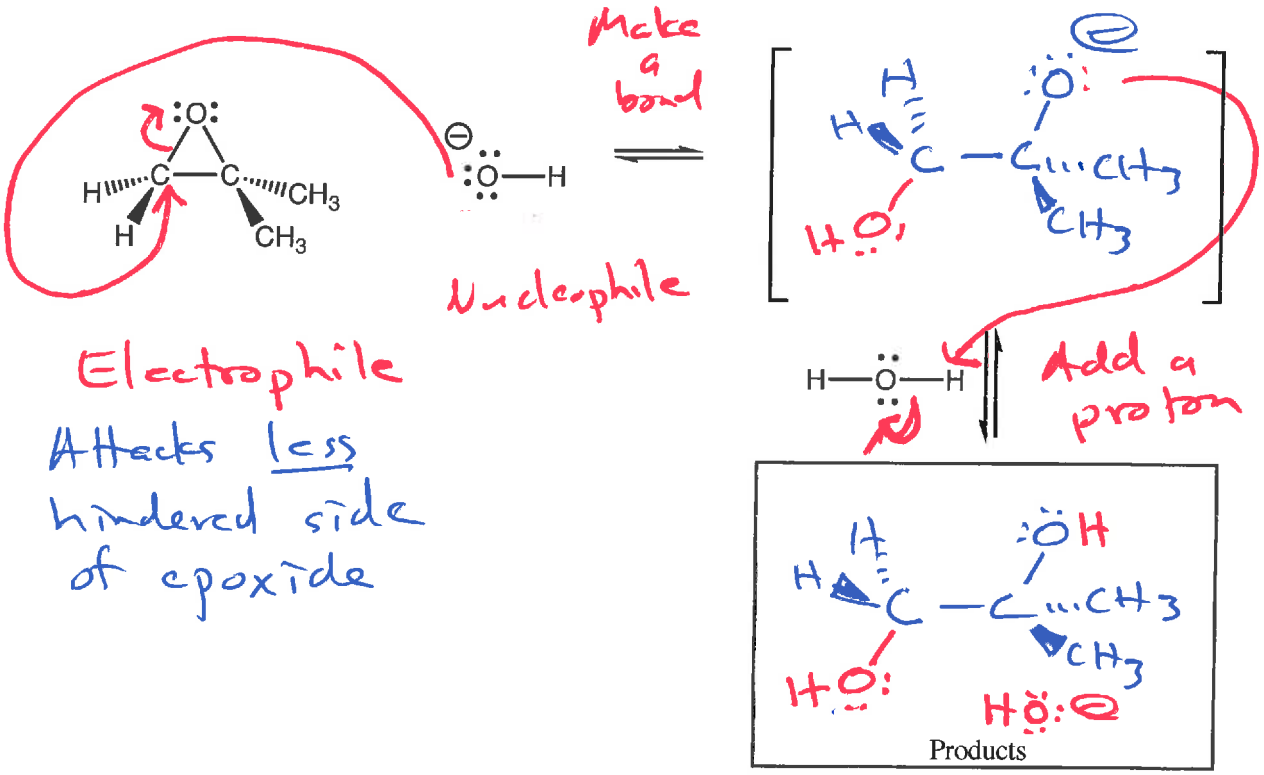
Summary: Halohydrins react in basic to give epoxides

Regiochemistry: N/A

Stereochemistry: Antiperiplanar transition state / INVERSION

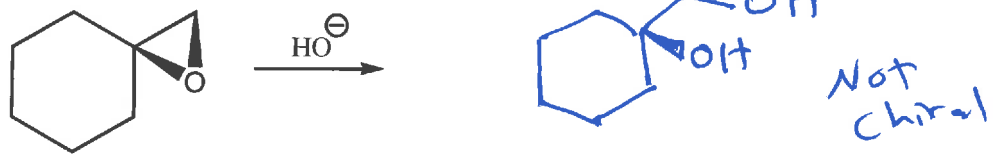
Nucleophilic

~~Base-Promoted~~ Epoxide Opening

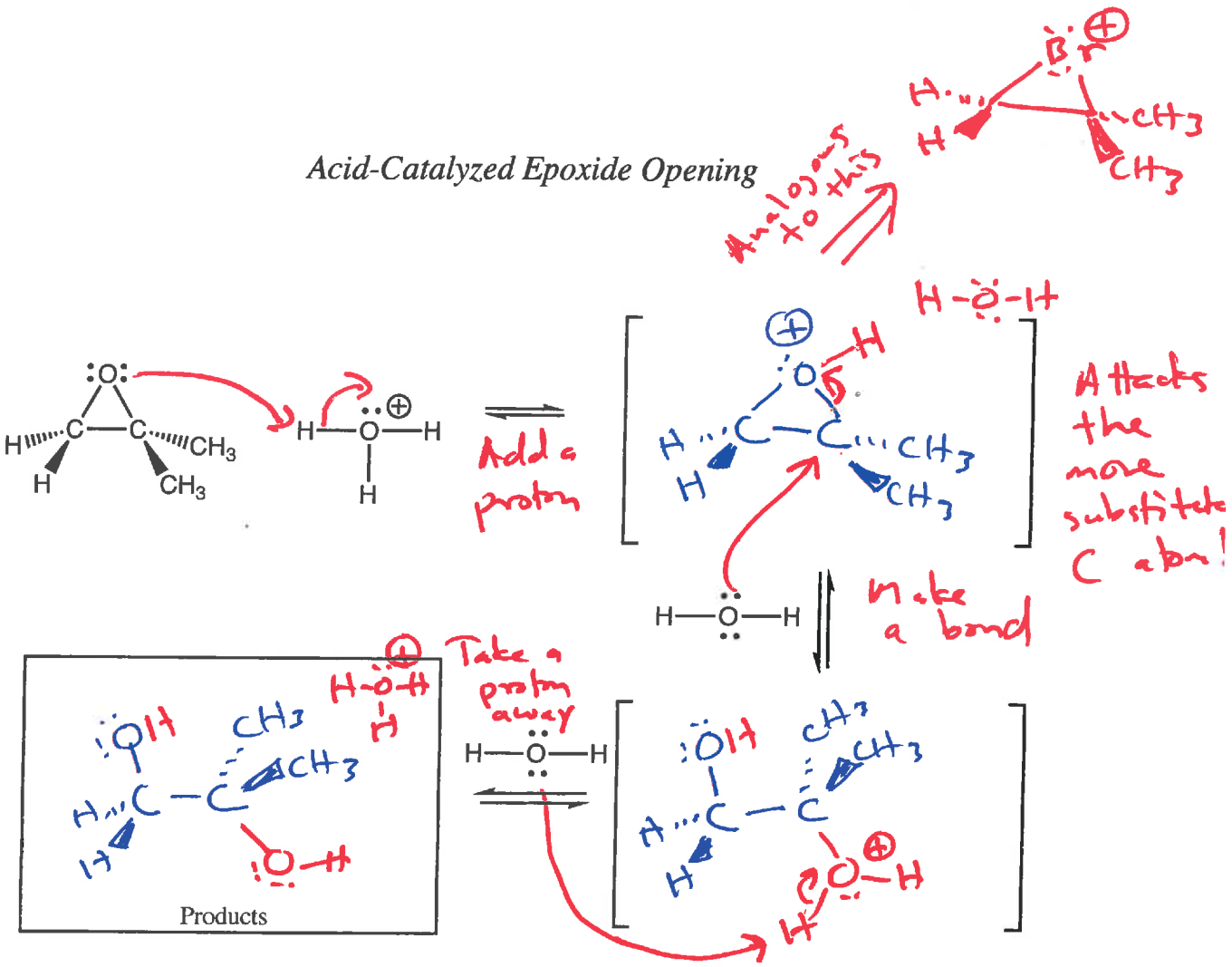


Summary:	Epoxides react with nucleophiles at the less hindered ~~site~~ C atom.
Regiochemistry:	Less Hindered
Stereochemistry:	Anti addition

Example:

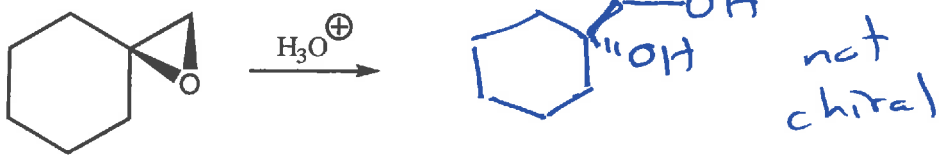


Acid-Catalyzed Epoxide Opening

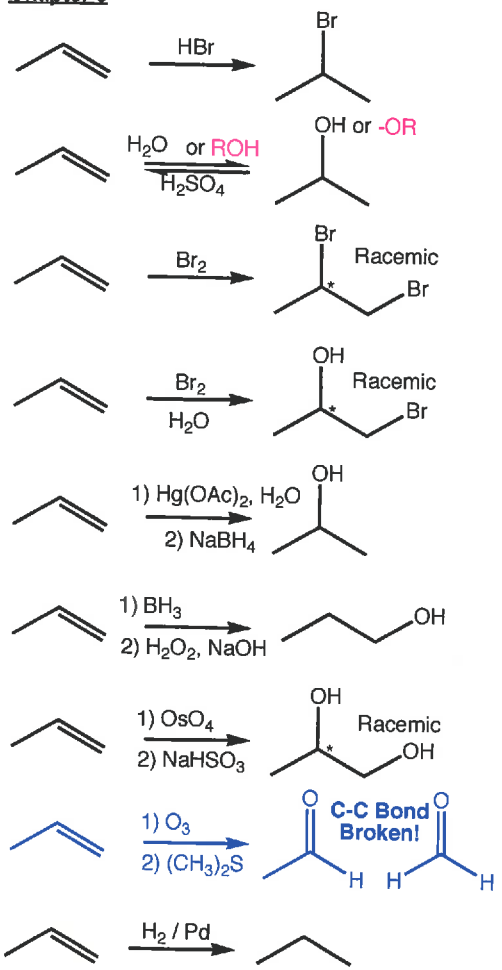


Summary:	An acid, epoxides add nucleophiles to the more substituted C atom
Regiochemistry:	More substituted
Stereochemistry:	Anti addition

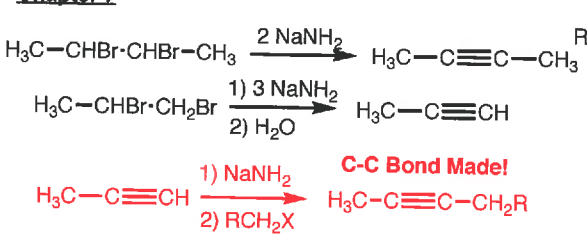
Example:

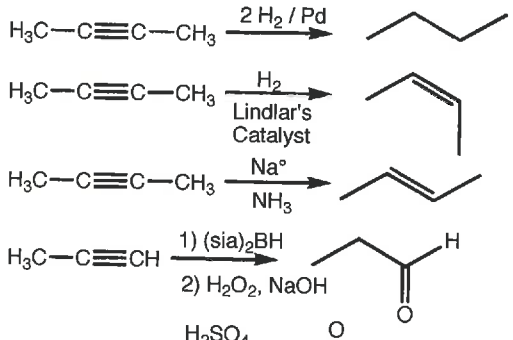


Chapter 6

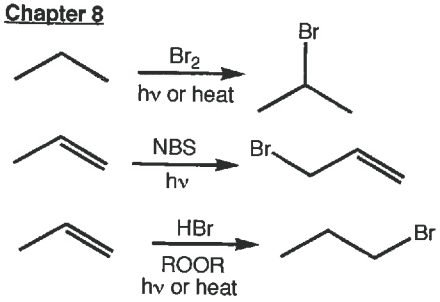


Chapter 7

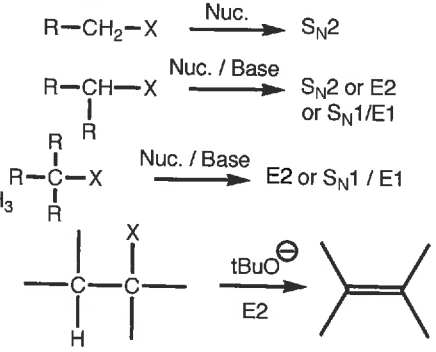




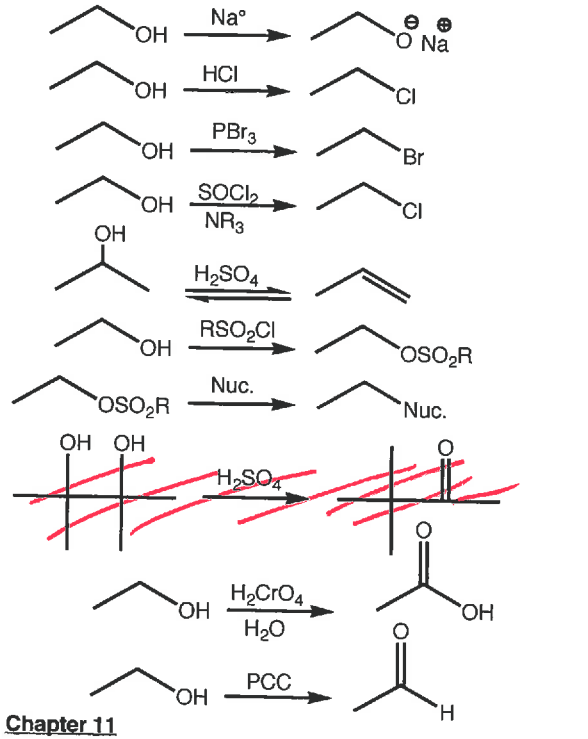
Chapter 8



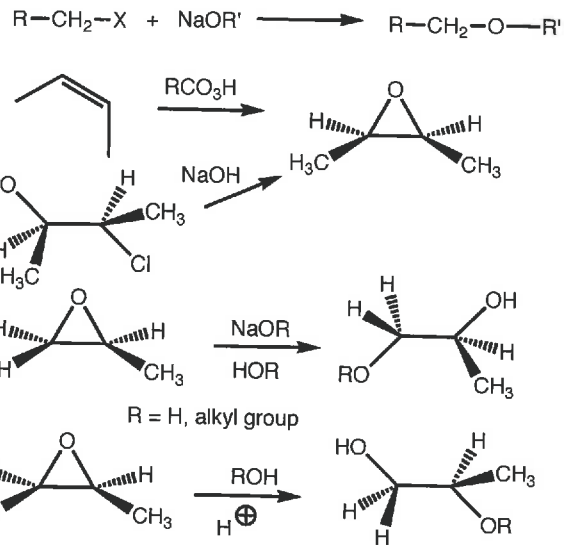
Chapter 9

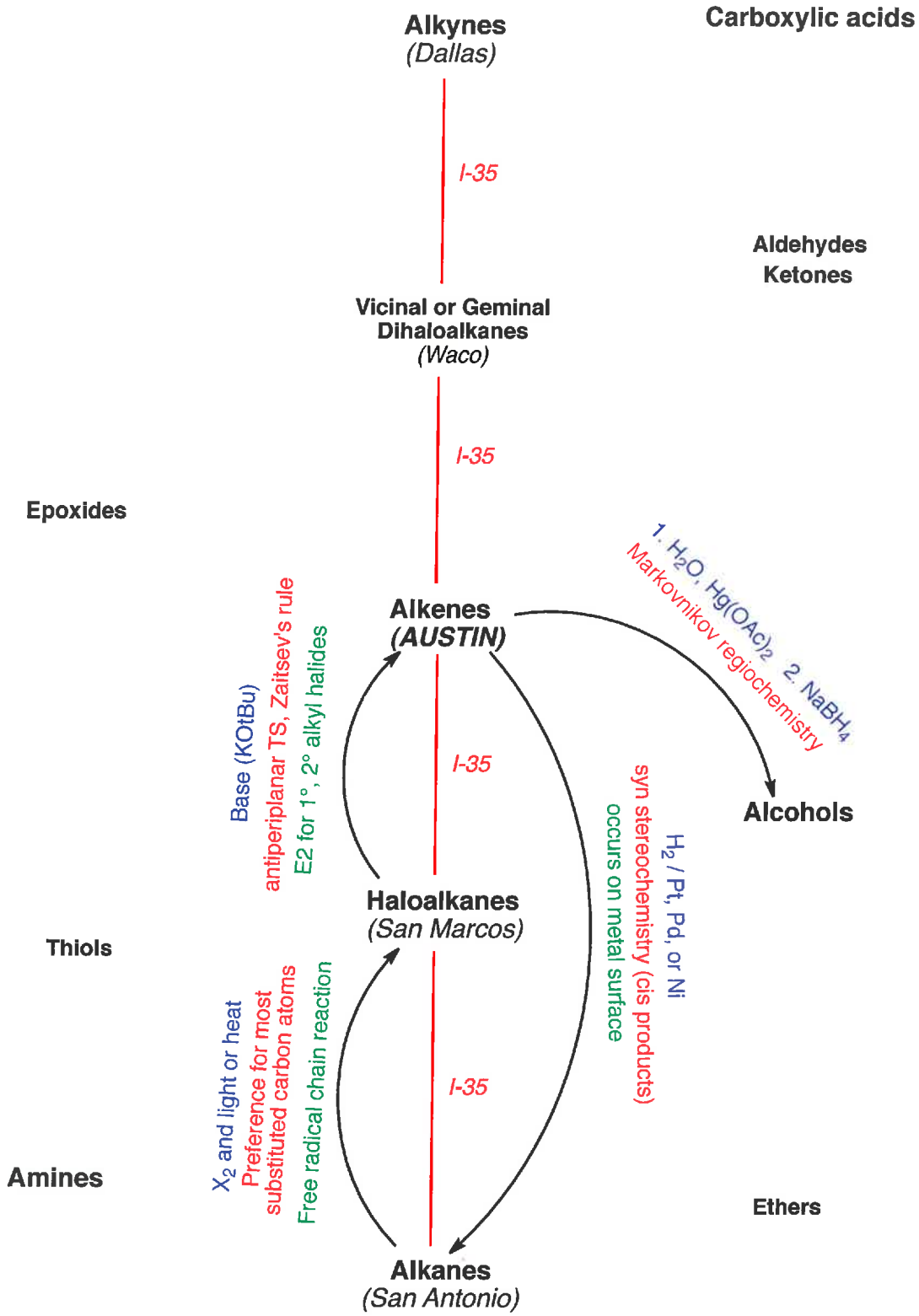


Chapter 10



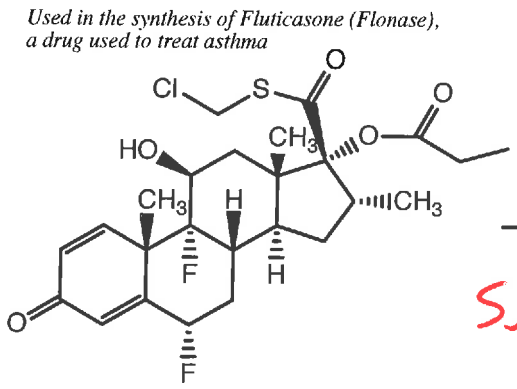
Chapter 11




Alkynes
(Dallas)
Carboxylic acids
I-35
Aldehydes
Ketones
Vicinal or Geminal
Dihaloalkanes
(Waco)
I-35
Epoxides
1. H_2O, $Hg(OAc)_2$ 2. $NaBH_4$
Markovnikov regiochemistry
Alkenes
(AUSTIN)
Base (KOtBu)
antiperiplanar TS, Zaitsev's rule
E2 for 1°, 2° alkyl halides
I-35
Alcohols
H_2 / Pt, Pd, or Ni
syn stereochemistry (cis products)
occurs on metal surface
Haloalkanes
(San Marcos)
Thiols
X_2 and light or heat
Preference for most
substituted carbon atoms
Free radical chain reaction
I-35
Amines
Ethers
Alkanes
(San Antonio)

Reactions in the Context of Complex Molecules

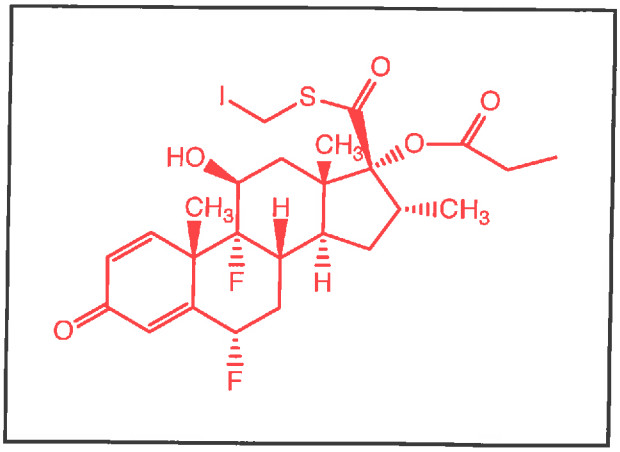
Used in the synthesis of Fluticasone (Flonase), a drug used to treat asthma



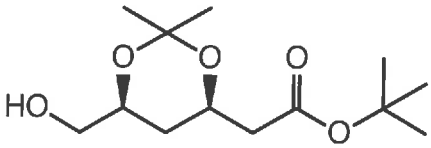
NaI

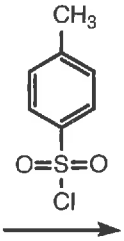
acetone

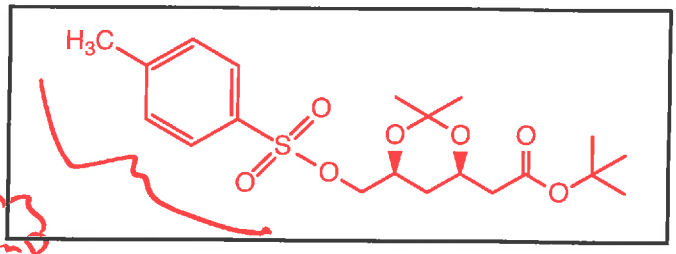
S_N2



Used in the synthesis of Lipitor

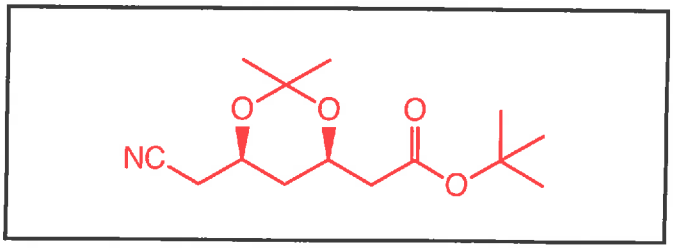




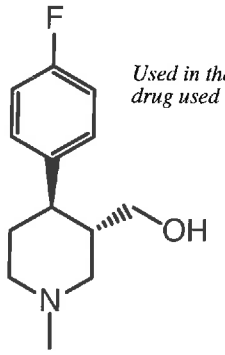


Leaving Group

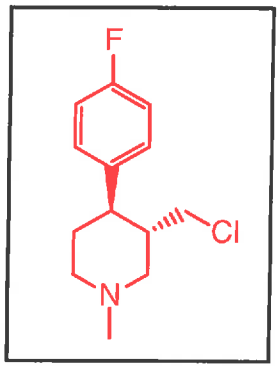
NaCN S_N2

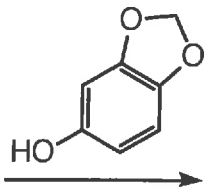


Used in the synthesis of Paxil, a drug used to treat depression

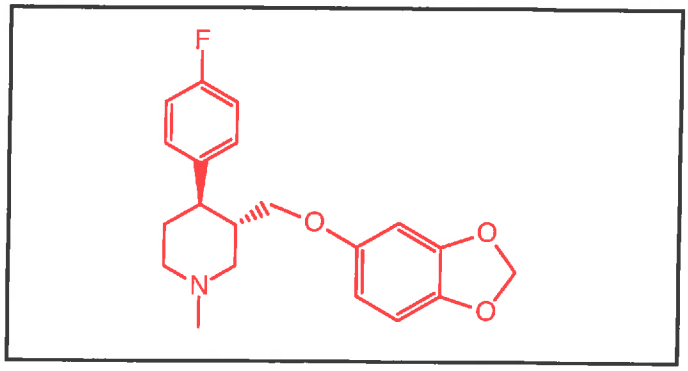


$SOCl_2$



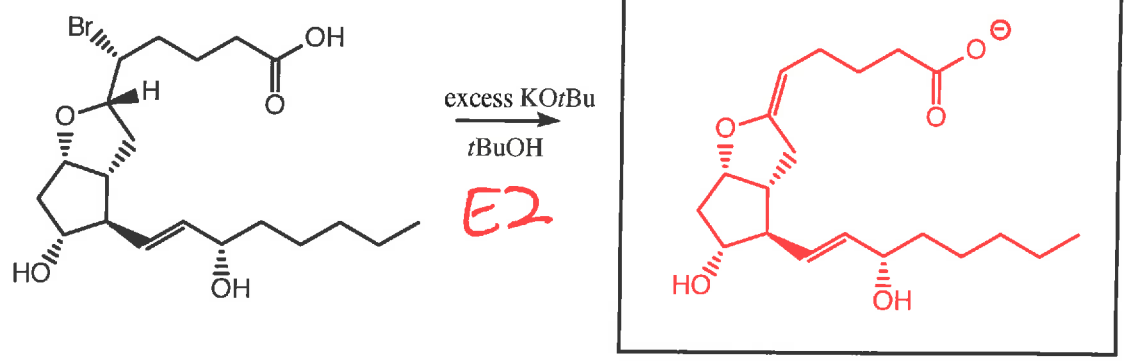


S_N2

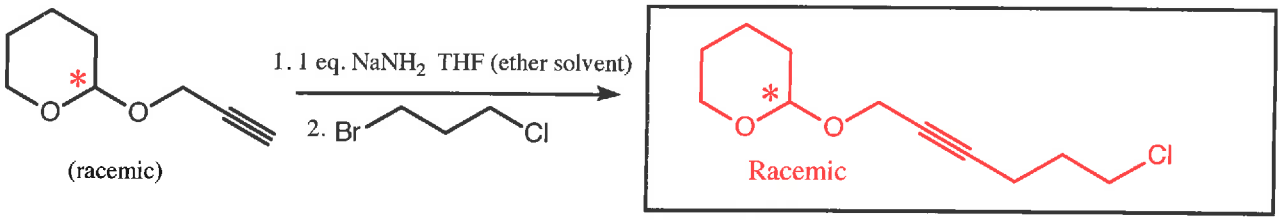


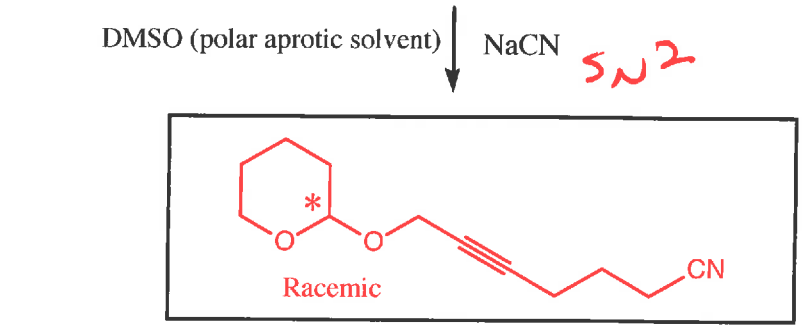
Reactions in the Context of Complex Molecules

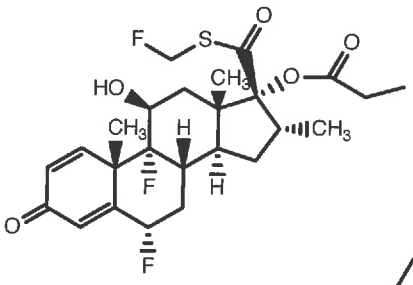
Used in the synthesis of several protaglandins



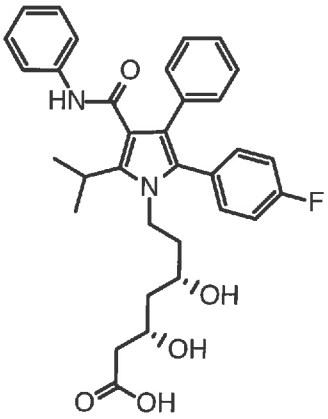
Used in the synthesis of protaglandin C_2

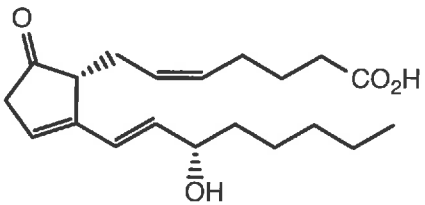




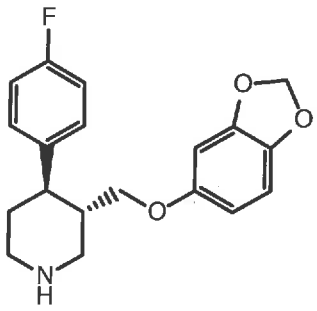


Fluticasone (Flonase)





Prostaglandin C_2



Paroxetine (Paxil)

Atorvastatin (Lipitor)