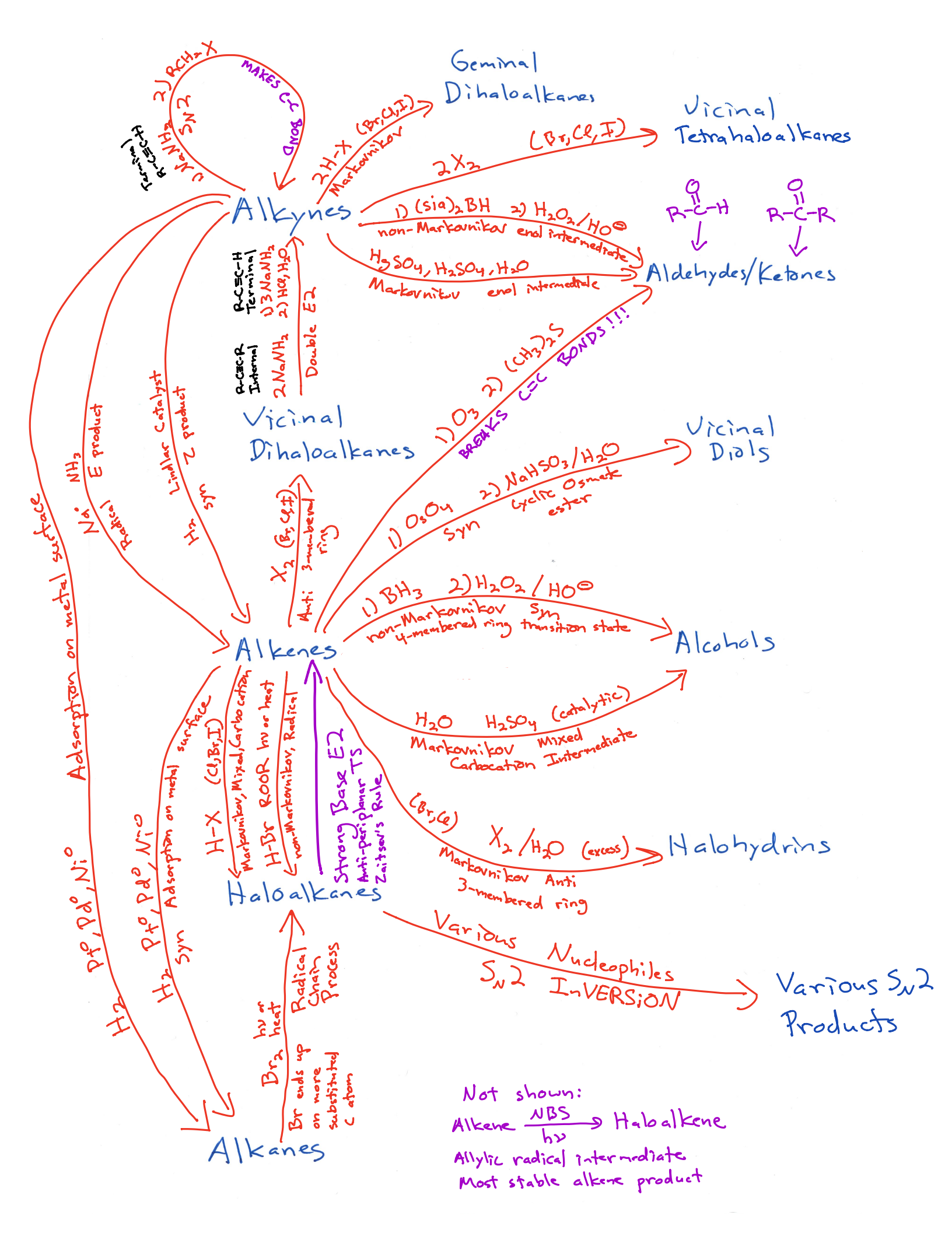
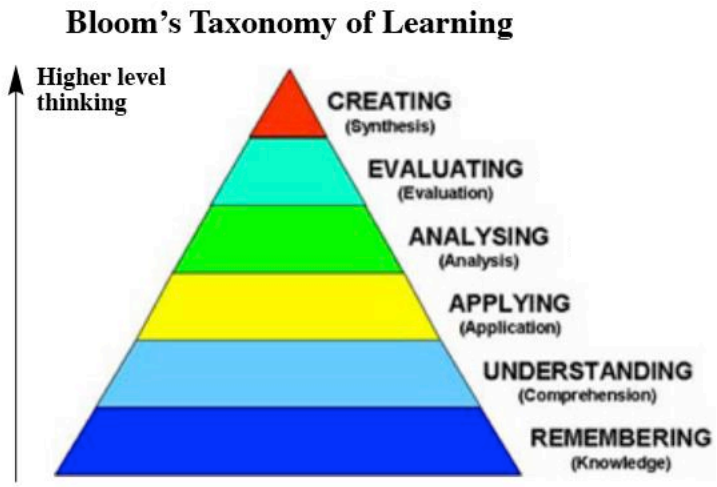
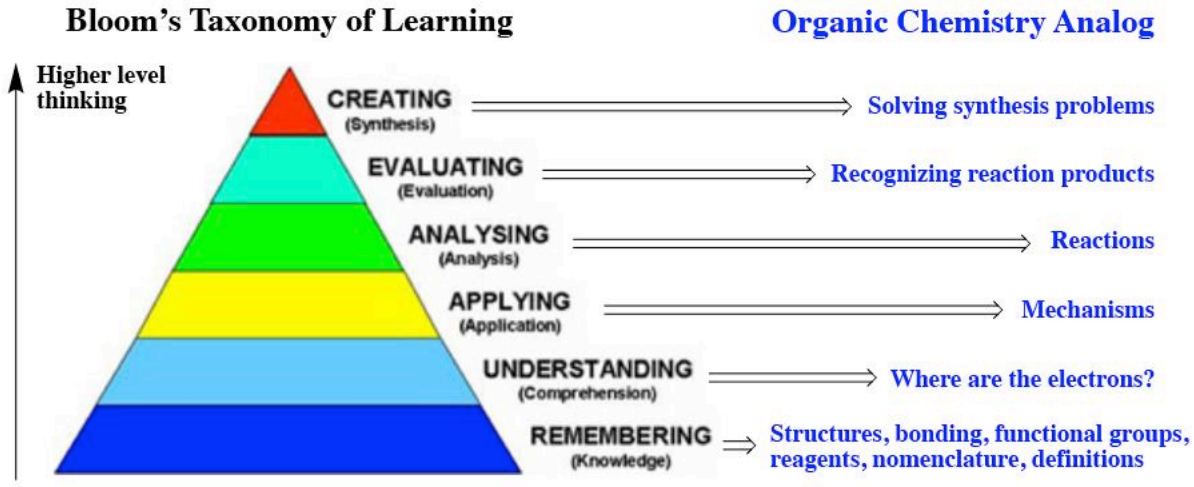

Geminal Dihaloalkanes
Vicinal Tetrahaloalkanes
Alkynes
Aldehydes/Ketones
Vicinal Dihaloalkanes
Vicinal Diols
Alkenes
Alcohols
Haloalkanes
Halohydrins
Alkanes
Various Products
Not shown:
Allylic radical intermediate
Most stable alkene product





A) **You must have your entire roadmap learned** so you can recite the NIRRS parameters for each reagent, i.e. Nature of overall transformation ("locations" on the roadmap), the Intermediate or transition state (carbocation, anti-periplanar etc.), the Reagents and how to designate them, as well as any Regiochemistry (Markovnikov, etc.) and any appropriate Stereochemistry (syn, anti, InVERSiON, scrambled, etc).

B) **Work backwards** (learn to RECOGNIZE the appropriate reagents and starting materials by looking at the products) from the final product. DO NOT try to work forward from the starting materials. Please trust me on this.

C) **Count carbons** in the starting material(s) and product(s) to see if any carbon-carbon bonds need to be broken or made, thereby zeroing in on key steps. This will be far more important next semester, so you should get used to doing this now.

D) **Pretty much all synthesis problems in OChem 1 involve traveling "north or south" on the so-called "I-35"** reactions (alkanes SA, haloalkanes NB/SM, alkenes ATX, vicinal dihaloalkanes Waco, alkynes DFW) at least part way at some point during the synthesis. This is not a promise or a rule, just an observation.





"You can't stop the waves, but you can learn to surf"

Jon Kabat-Zinn


Alkanes
Alkenes
Alkynes
Haloalkanes
Vicinal dihaloalkanes
Ketones and Aldehydes
Carboxylic Acids
Alcohols
Where Electrons Are
Mechanisms
Roadmaps
Stereochemistry
Regiochemistry
ROTD
NIRRS
Motive
Opportunity
Carbocation
Radical
Pi-ways
Golden Rules
Make a Bond
Break a Bond
Add a Proton
Take a Proton
Nucleophiles and Electrophiles
Charge Delocalization
Hyperconjugation
Steric strain
Angle and Torsional Strain
Epoxides
Vicinal Diols
Radical Chain
SN2 vs. E2
SN1 and E1
Anti-periplanar
Markovnikov
Zaitsev

Alcohols → R–O–H

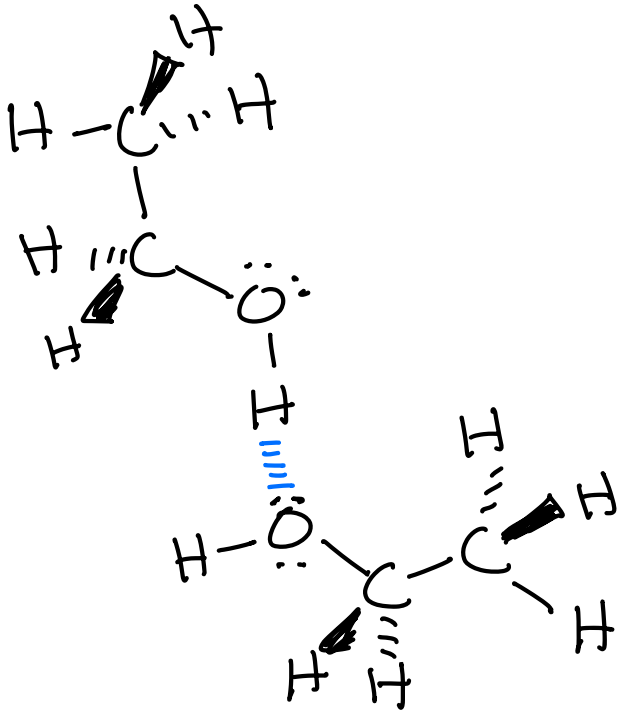


Table 10.1 **Boiling Points and Solubilities in Water of Five Groups of Alcohols and Hydrocarbons of Similar Molecular Weight**

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

General Rules of Solvents

Polar Protic

Polar protic solvents dissolve other polar molecules →

Polar protic solvents →

⇒ See the POTD for today for the main messages here

1) Solvation of cations and anions
2) Solvation of carbocations / anions in S_N1 / E1 reactions
3) Methanol dissolved in water
4) Why pentane and water do not mix

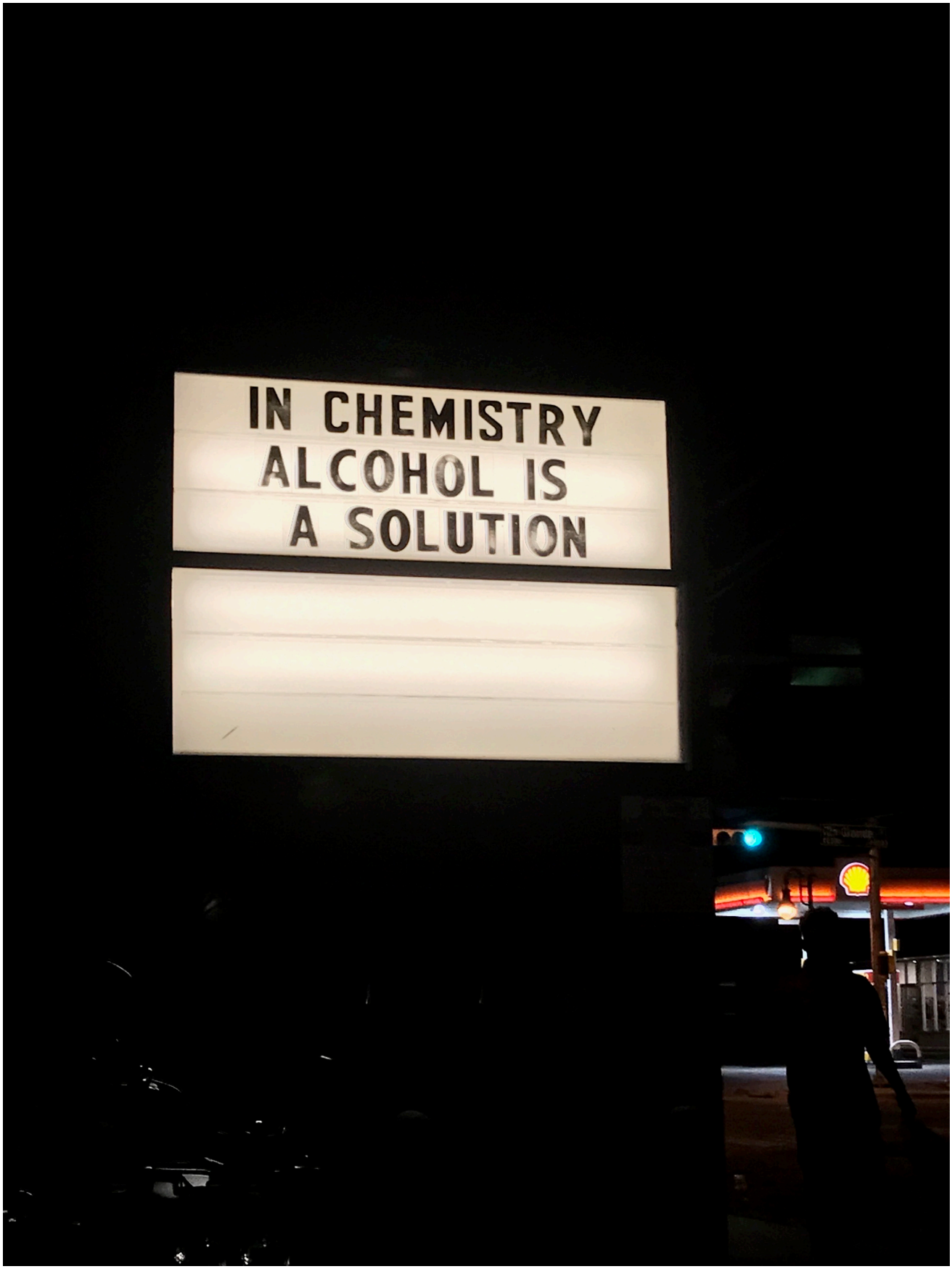

IN CHEMISTRY
ALCOHOL IS
A SOLUTION

Table of Nucleophiles

Strong Nucleophiles

Br^-, I^-, $R\text{-}S^-$, $H\text{-}S^-$, $N{\equiv}C^-$, N_3^-

$R\text{-}C{\equiv}C^-$, $R\text{-}O^-$, $H\text{-}O^-$ **Strong Bases**

Medium Nucleophiles

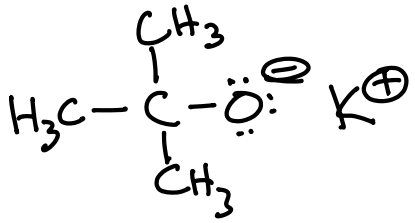
$R\text{-}CO_2^-$, R-S-H, R_2S,
NH_3, RNH_2, R_2NH, NR_3

Weak Nucleophiles

$R\text{-}CO_2H$, R-O-H, H_2O **Very Weak Bases**

Special Case

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



"KOtBu"
or
"$tBuO^-$"

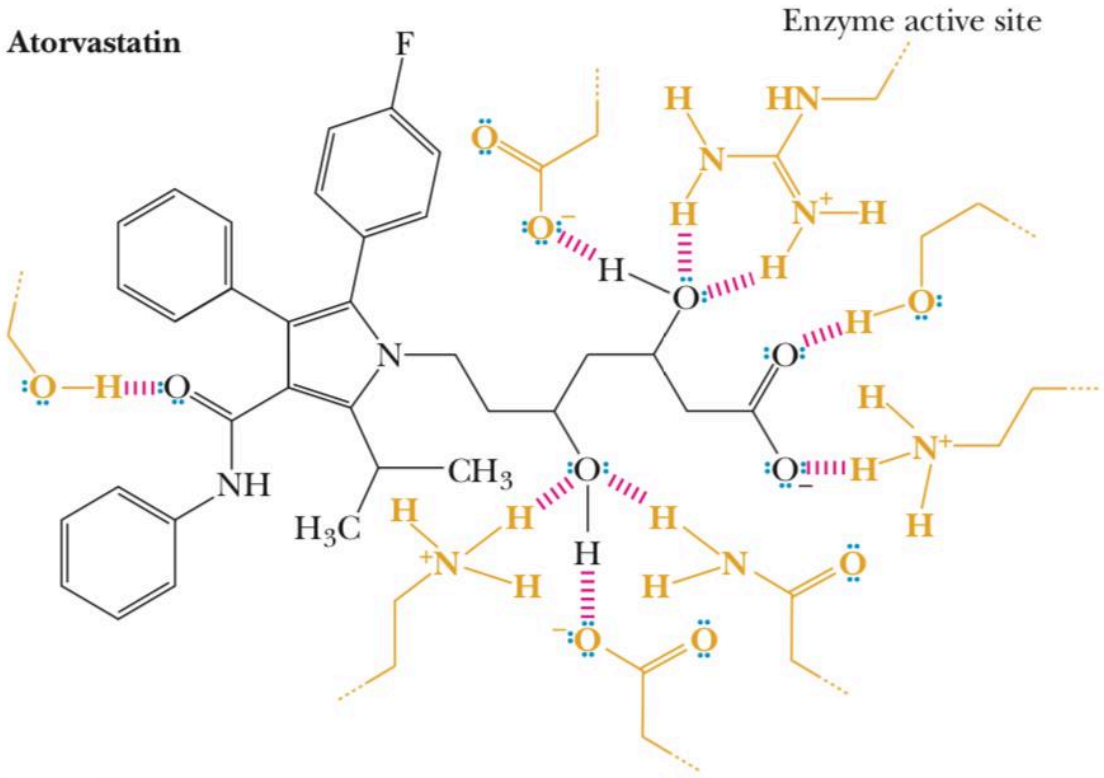


Figure 2

Hydrogen bonding (shown in red) between atorvastatin and the functional groups at the active site of the enzyme HMG-CoA reductase. The nine hydrogen bonds (shown in red), many of which involve hydroxyl groups on atorvastatin or the enzyme surface, help to provide the specificity that directs the binding of the drug to its target enzyme.

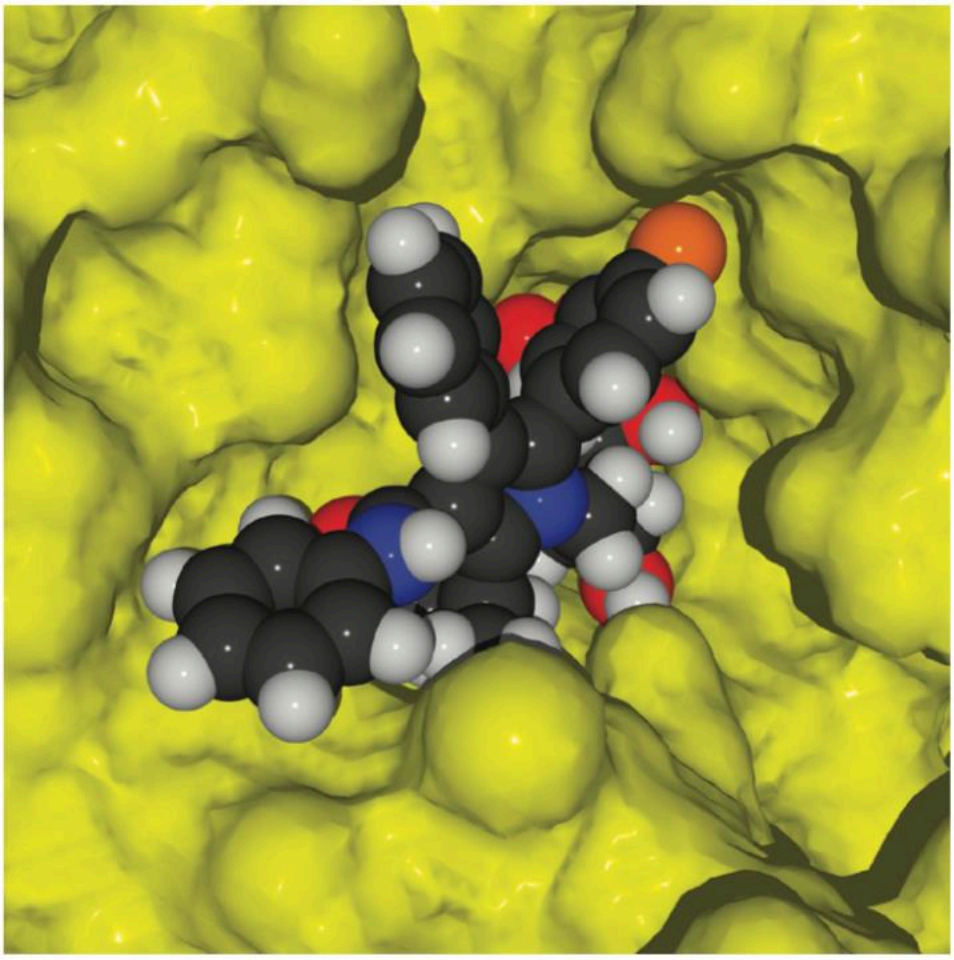


Figure 1

A space-filling model of the cholesterol-lowering drug atorvastatin (Lipitor) bound to the active site of its enzyme target HMG-CoA reductase (shown as a yellow surface). The shape of the drug is complementary to the active site of the enzyme.

<u>Organic Chemistry</u> is the study of carbon-containing molecules.

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You will learn the secret structural reason proteins, the most important molecular machines in our bodies, can support the chemistry of life. 9/9/26

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You will learn how toothpaste works. 9/21/26 9/30/26

You will learn how a single chlorofluorocarbon refrigerant molecule released into the atmosphere can destroy many, many ozone molecules, leading to an enlargement of the ozone hole. 10/26/26

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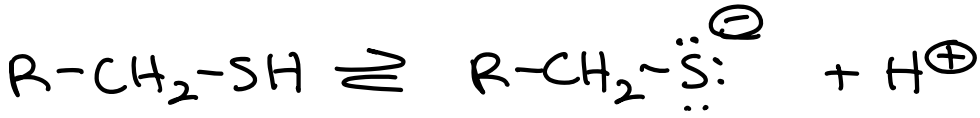
You will learn a reaction that can make nail polish remover from rubbing alcohol.

You will learn how to look at a molecule and accurately predict which atoms will react to make new bonds, and which bonds will break during reactions.

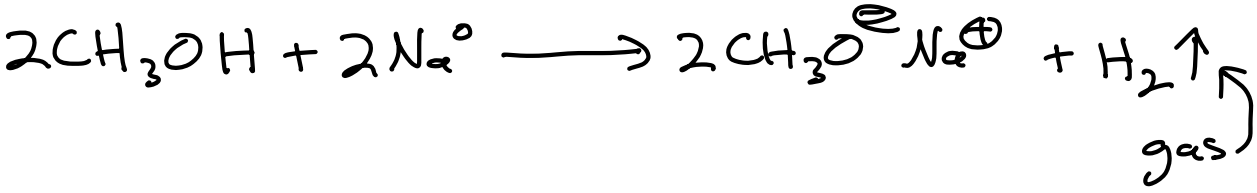
You will learn how to analyze a complex molecule's structure so that you can predict ways to make it via multiple reactions starting with less complex starting molecules.

Alcohols → Acidity and Basicity

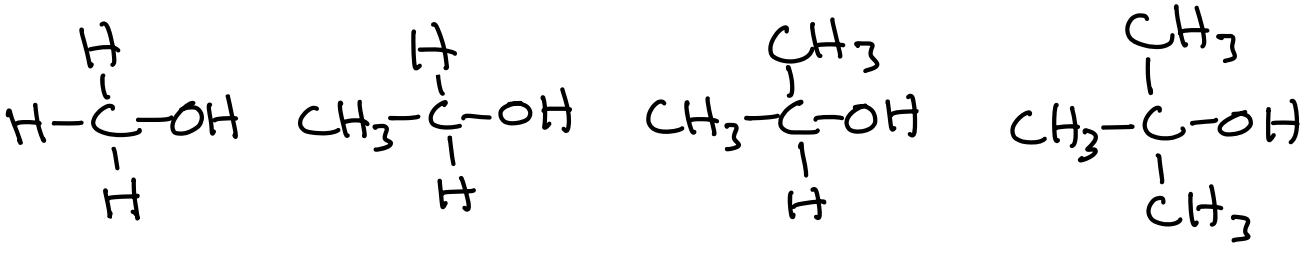




Notice This → $Na^{\circ}, K^{\circ}, Li^{\circ}$



Alcohols → Reaction mechanisms depend on the number of alkyl groups attached on the C atom of C-OH bond.

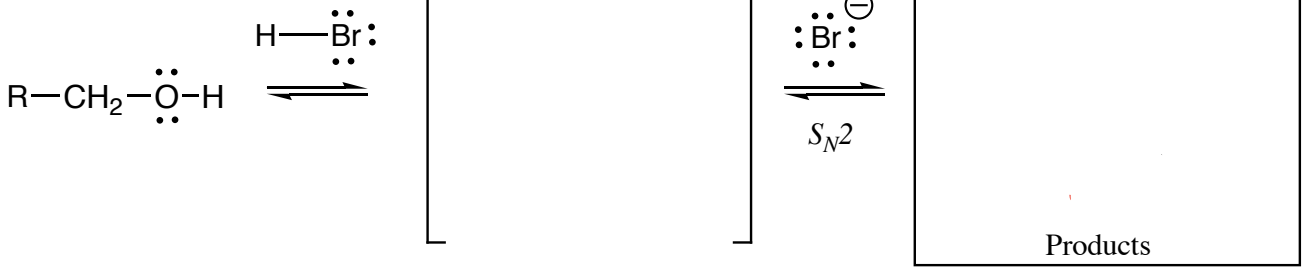


The -OH is not a leaving group but several reactions involve conversion of the -OH group into a good leaving group

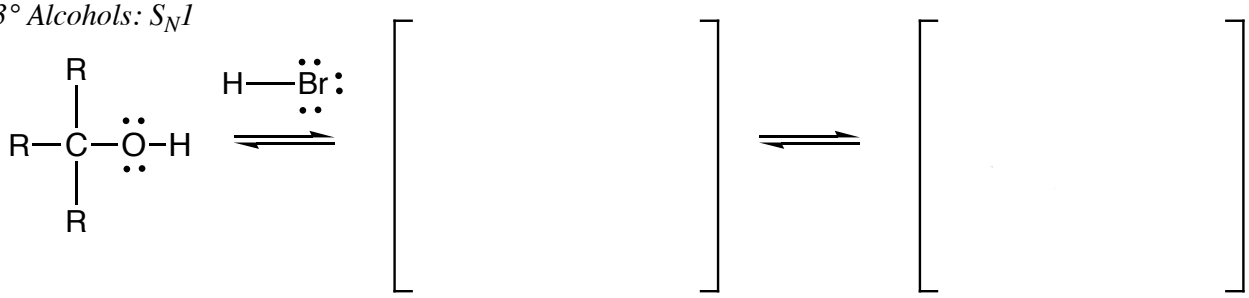
Recall, the -OH group is a weak nucleophile and weak base (in strong acid)

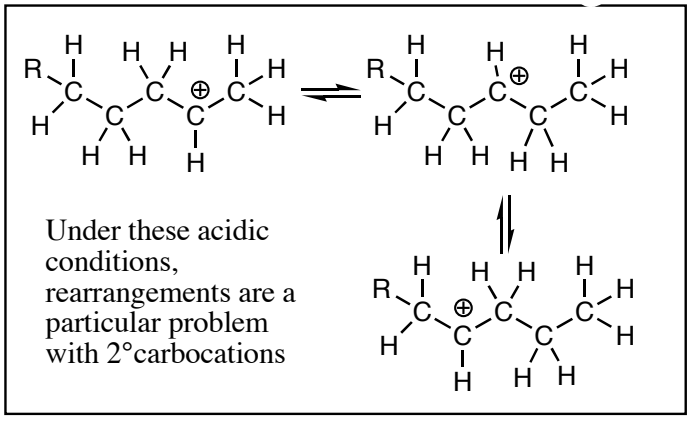
Alcohols + H-X

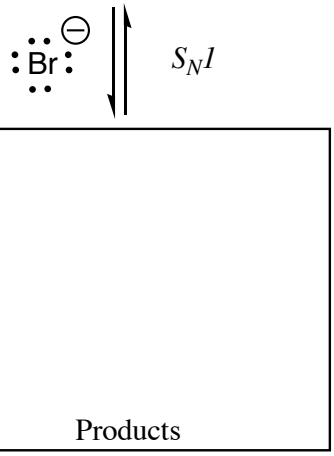
1° Alcohols: S_N2



2°/3° Alcohols: S_N1





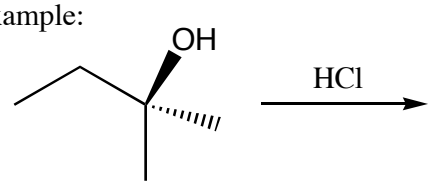


Summary: Reaction of primary alcohols → S_N2
Reaction of secondary/tertiary alcohols → S_N1
The —OH group is converted to a good leaving group by protonation

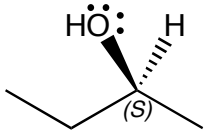
Regiochemistry:

Stereochemistry:

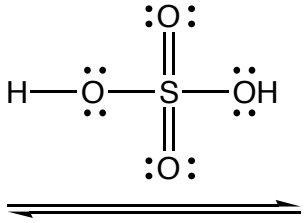
Example:



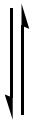
2° or 3° Alcohol Dehydration

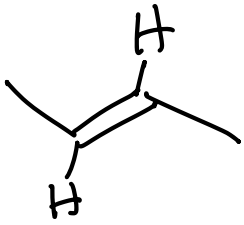


2° or 3° Alcohols

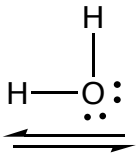








Products



E1

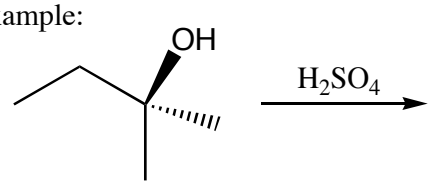


Summary: The OH group is protonated in strong acid to make a good leaving group (H_2O), which breaks a bond to give a carbocation that has a proton taken away → E1 (No S_N1!)

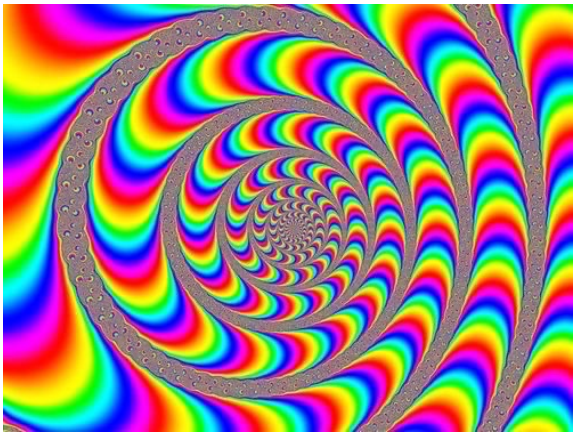
Regiochemistry:

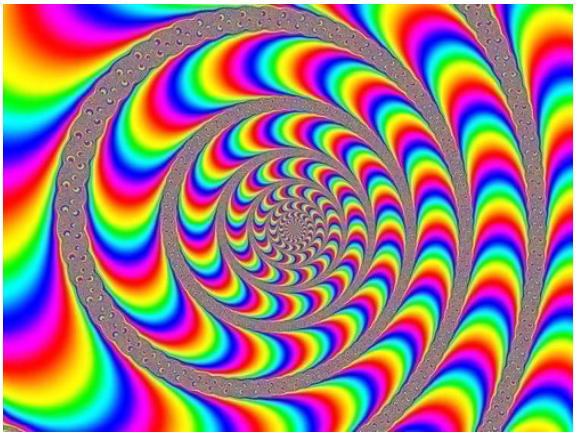
Stereochemistry:

Example:

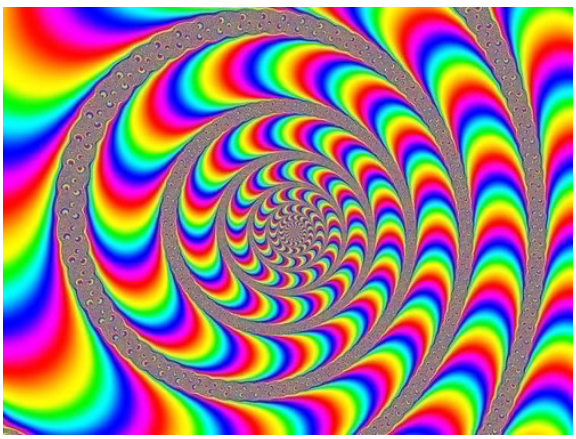


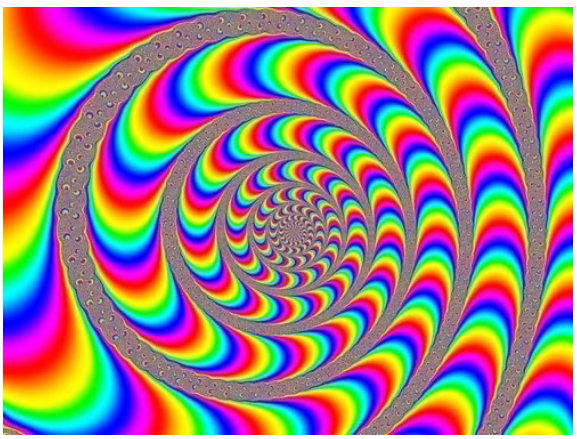
Flashback!!



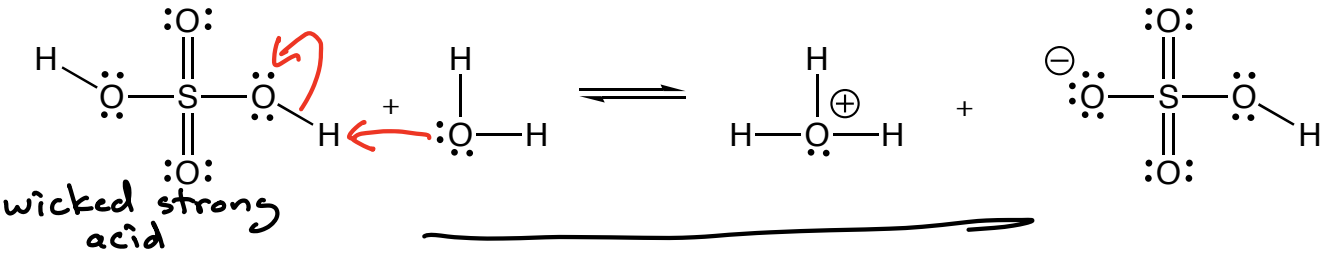


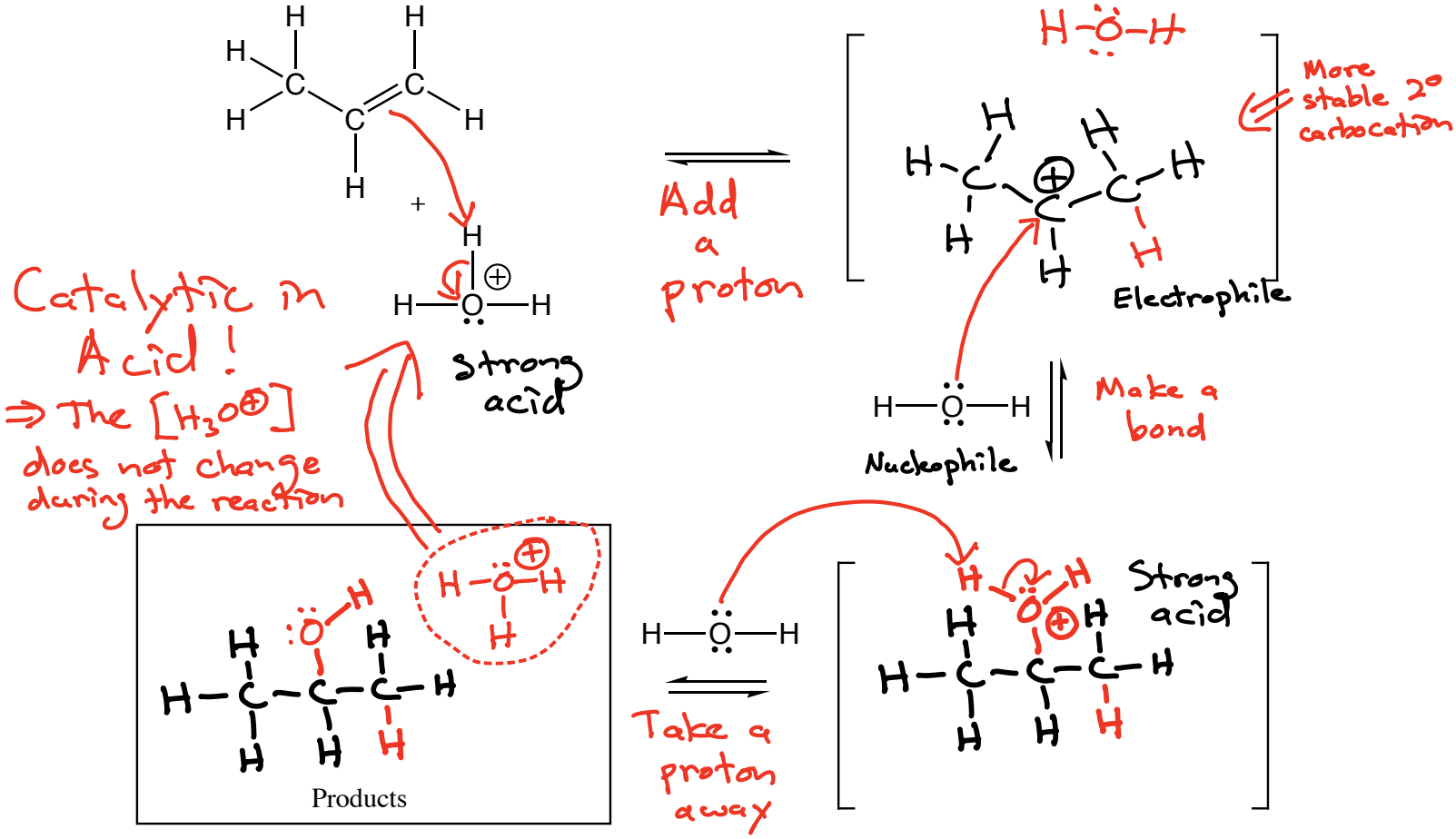






Acid-catalyzed Hydration of an Alkene



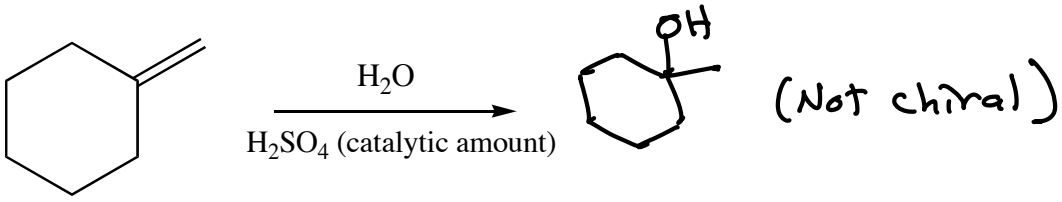


Summary: Proton adds to make a carbocation intermediate, water attacks to make a new bond, take a proton away to make the product alcohol. Catalytic in $H_3O^{\oplus}$

Regiochemistry: Markovnikov's Rule

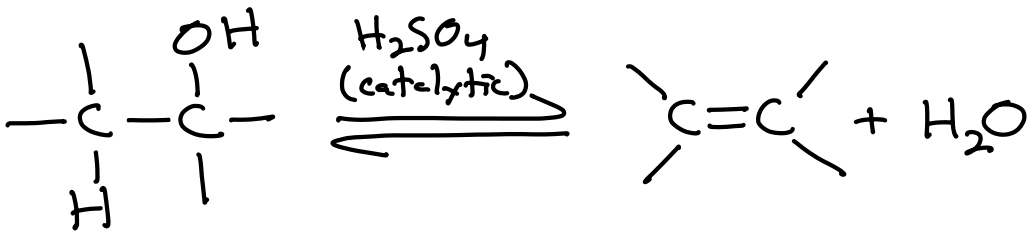
Stereochemistry: Mixed (time capsule)

Example:



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

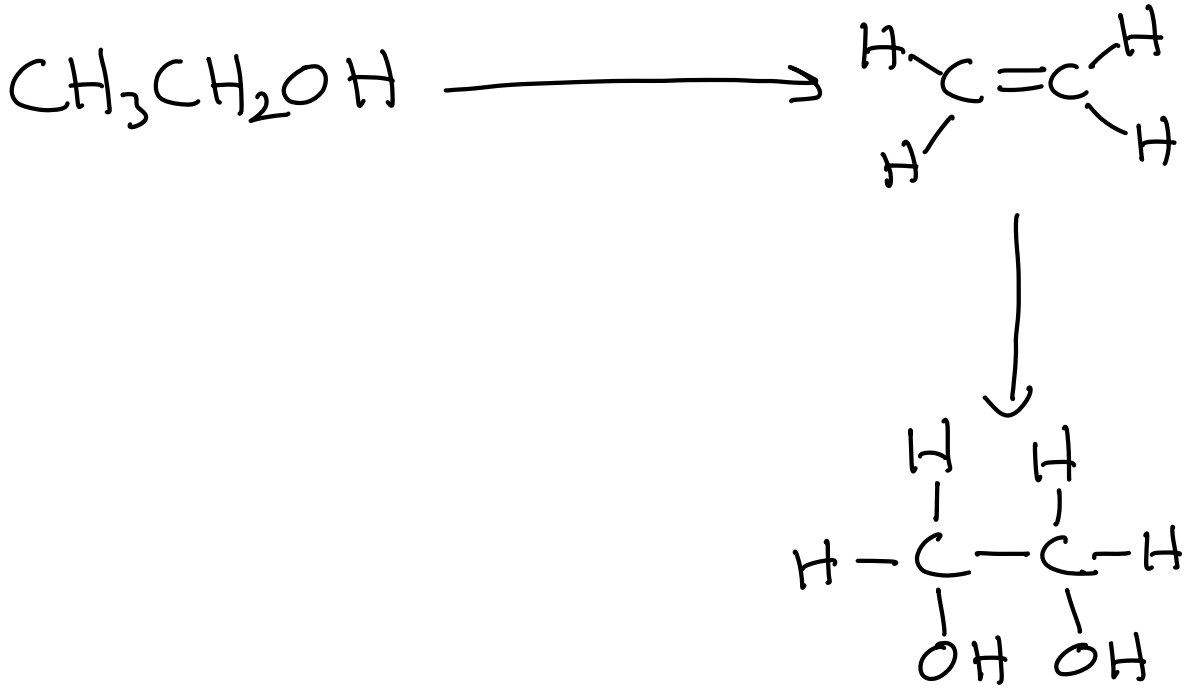
Microscopic Reversibility →



Le Chatlier's Principle ⇒

If we add water →

If we remove the water as it is formed →


CH3CH2OH
H
C
C
H
H
H
H
H
H
C
C
H
OH
OH

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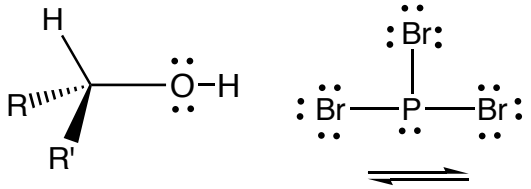
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Alcohols + PBr_3



1° or 2° Alcohols





S_N2

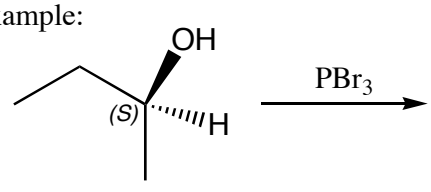
Products

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

Regiochemistry:

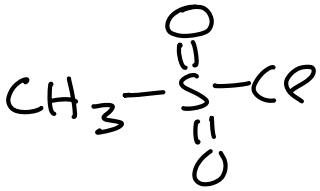
Stereochemistry:

Example:

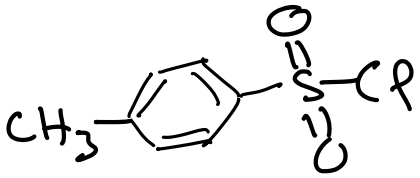




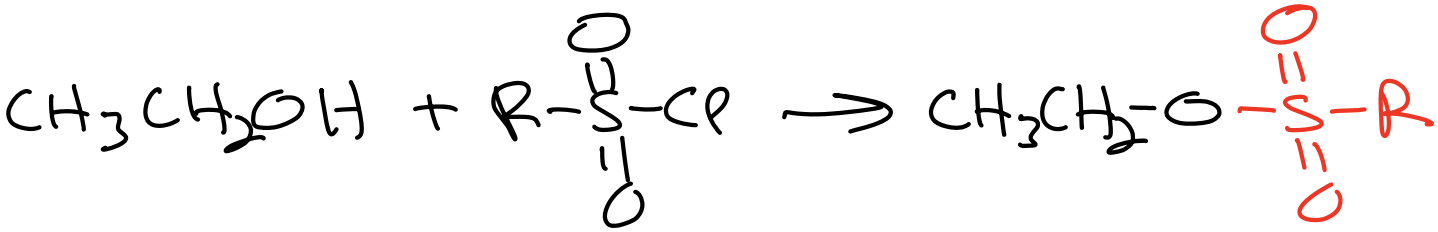
Alkyl Sulfonates



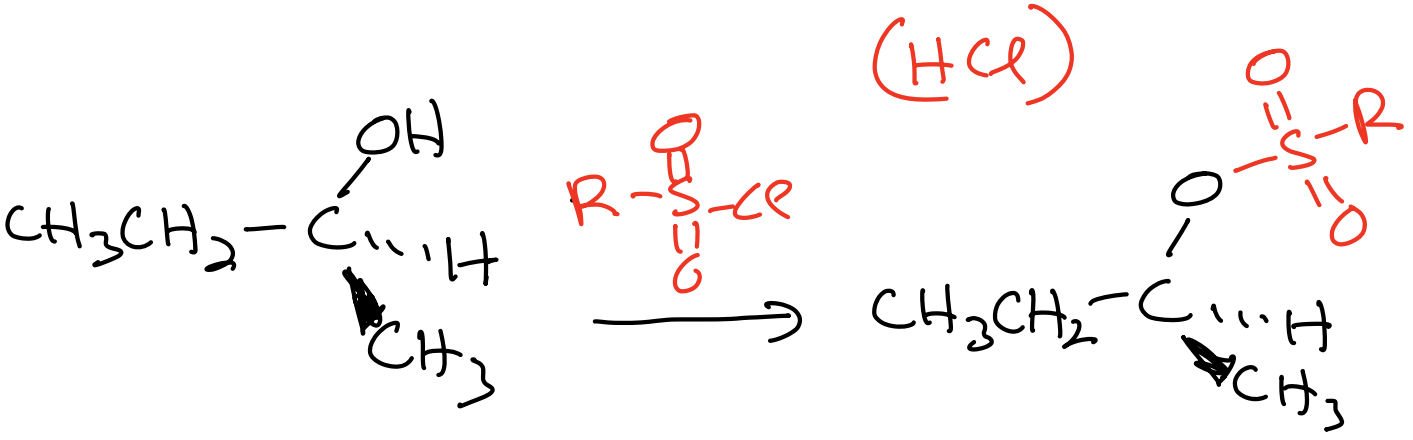
Methanesulfonyl Chloride

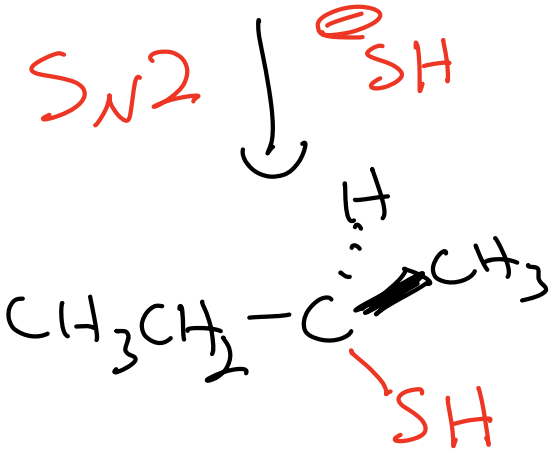


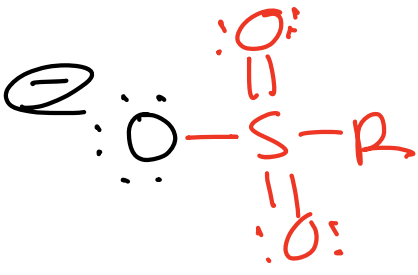
p-Toluenesulfonyl Chloride

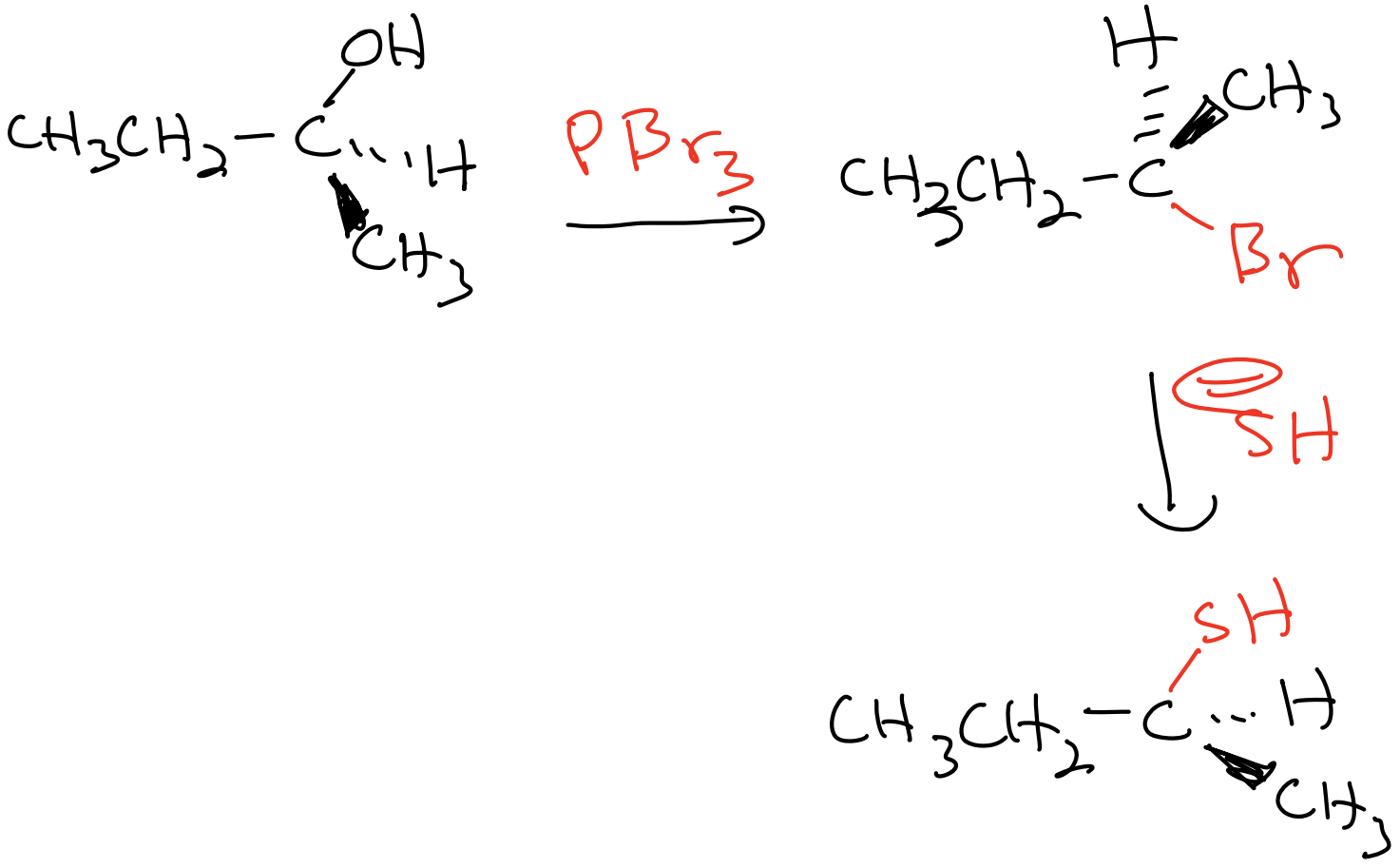


Stereochemistry







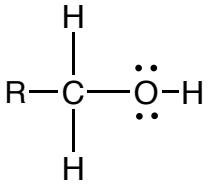


⟹ You can net invert or retain the stereochemistry of a chiral alcohol taking part in SN2 reactions

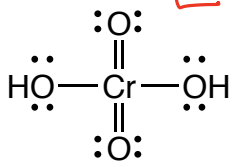
Chromic Acid Oxidation of Alcohols

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

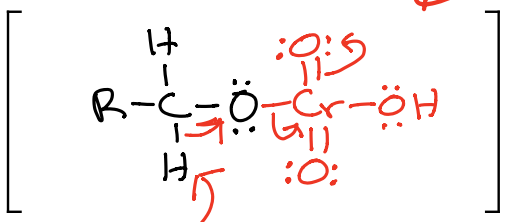
Not responsible for first step

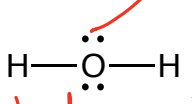


1° Alcohols



"H_2CrO_4" or "Chromic Acid"

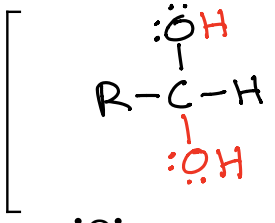




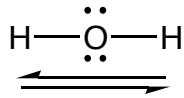
Take a proton away and break a bond

Aldehyde

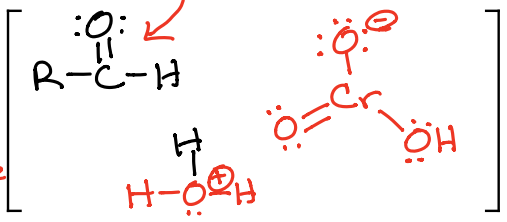
Not responsible for this step

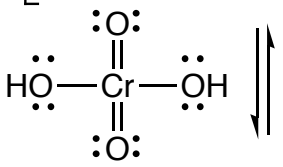


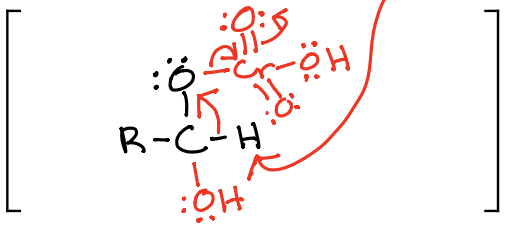
Called a geminal diol

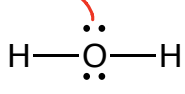


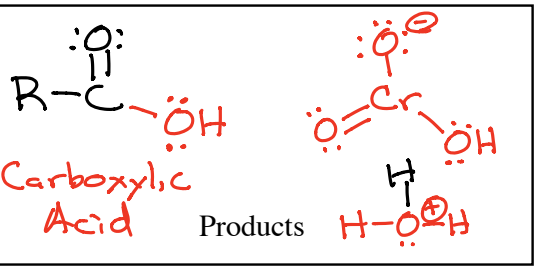
Water reacts with aldehyde – will learn next semester







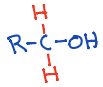




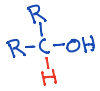
Carboxylic Acid

Products

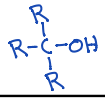
Summary:



1° alcohols ⇒ Carboxylic Acid → 



2° alcohols ⇒ Ketone → 

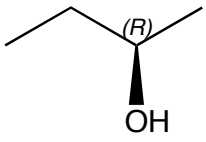


3° alcohols ⇒ NO REACTION

Regiochemistry: N/A

Stereochemistry: N/A

Example:

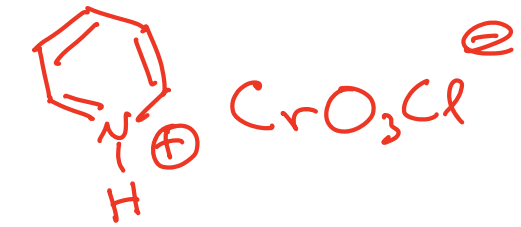


H_2CrO_4

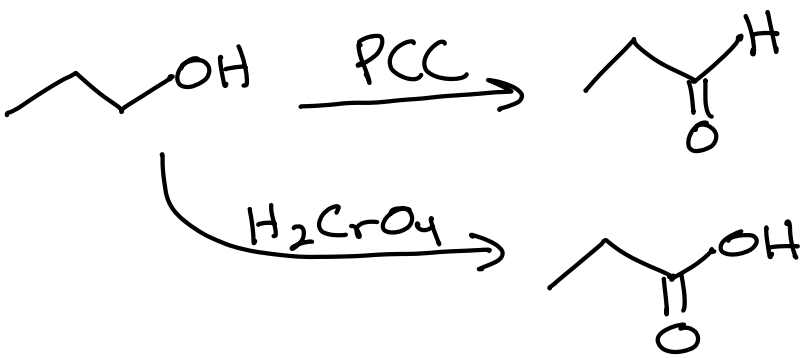


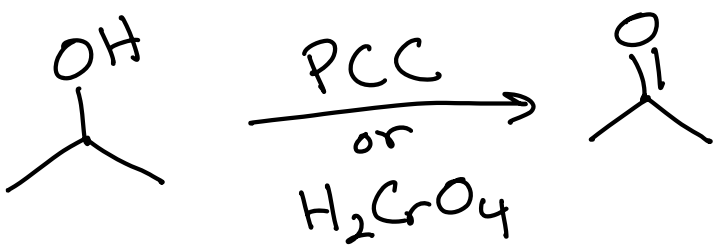
Ketone

A chromic acid-like reagent WITHOUT WATER will stop at the when using a as starting material



PCC





<u>Organic Chemistry</u> is the study of carbon-containing molecules.

This class has two points.

The first point of the class is to understand the organic chemistry of living systems. We will teach you how to think about and understand the most amazing things on the planet!!

Water is essential for life, you will learn why water has such special properties. 8/25/26

You will learn the secret structural reason proteins, the most important molecular machines in our bodies, can support the chemistry of life. 9/9/26

You will learn why when you take Advil for pain, exactly half of what you take works, and the other half does nothing.

You will learn how toothpaste works. 9/21/26 9/30/26

You will learn how a single chlorofluorocarbon refrigerant molecule released into the atmosphere can destroy many, many ozone molecules, leading to an enlargement of the ozone hole. 10/26/26

You will learn how medicines like Benadryl, Seldane, and Lipitor work.

You will learn how Naloxone is an antidote for an opioid overdose.

You will learn why Magic Johnson is still alive, decades after contracting HIV.

You will learn how MRI scans work.

The second point of organic chemistry is the synthesis of complex molecules from simpler ones by making and breaking specific bonds.

You will learn how to understand movies of reaction mechanisms like alkene hydration. 10/5/26

You will learn reactions that once begun, will continue reacting such that each product molecule created starts a new reaction until all the starting material is used up. 10/26/26

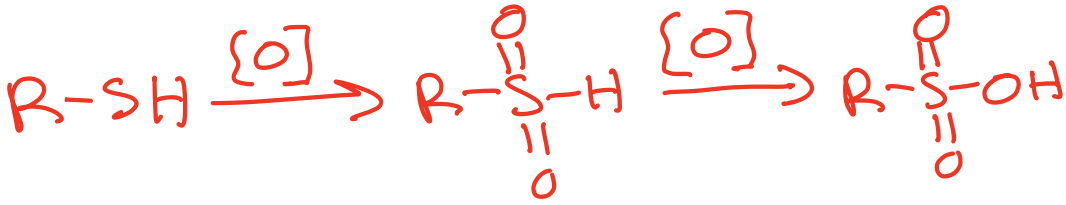
You will learn reactions that can make antifreeze from vodka.

You will learn a reaction that can make nail polish remover from rubbing alcohol.

You will learn how to look at a molecule and accurately predict which atoms will react to make new bonds, and which bonds will break during reactions.

You will learn how to analyze a complex molecule's structure so that you can predict ways to make it via multiple reactions starting with less complex starting molecules.

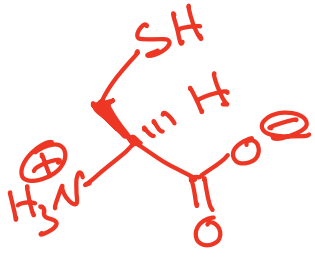
Thiols → R–S–H



In the presence of O_2:

$$2\ R\text{-}SH + \tfrac{1}{2}O_2 \longrightarrow R\text{-}S\text{-}S\text{-}R + H_2O$$

Dissulfide Bond



The amino acid cysteine (Cys)

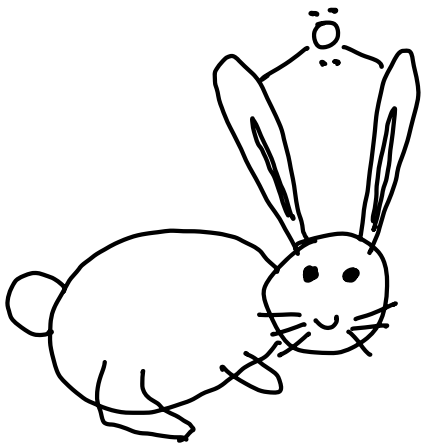
Dissulfide bonds between cysteine residues that are far apart in the sequence, but overlap in three-dimensions, provide covalent links that stabilize folded protein structures

Ethers → R–Ö–R

↳ Unreactive under most conditions

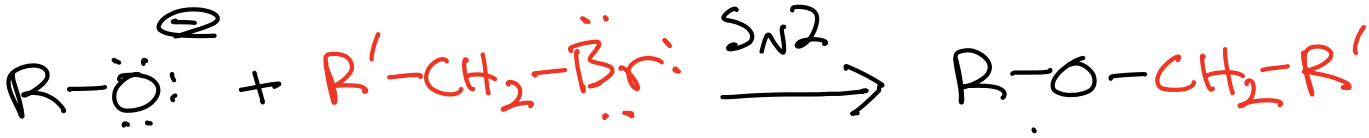


Diethyl ether



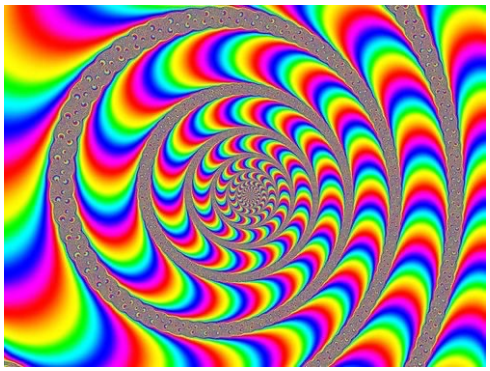
How to make ethers

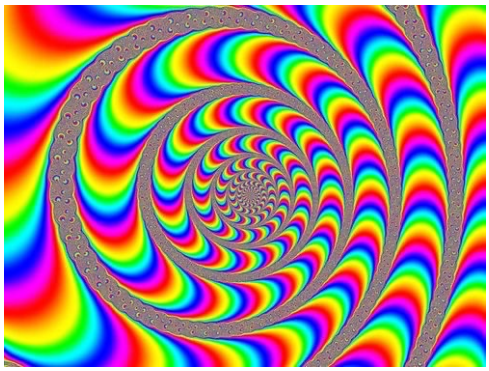
Williamson Ether Synthesis



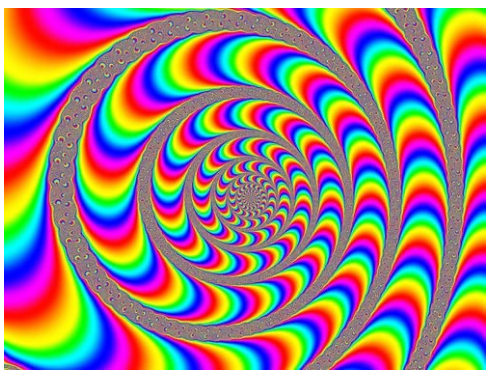
You can also react alkenes with alcohols in the presence of catalytic amounts of H_2SO_4 to make ethers:

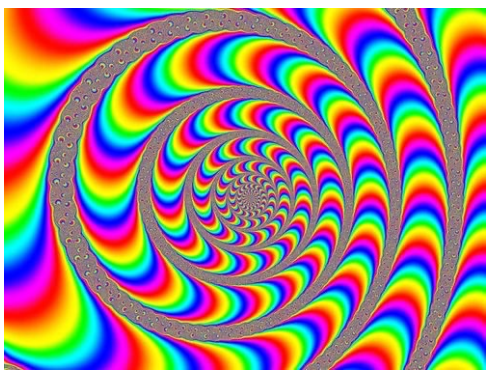
Flashback!!





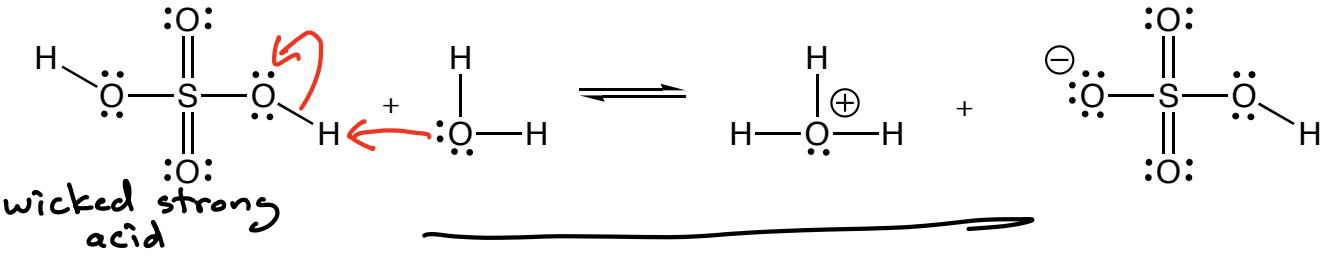


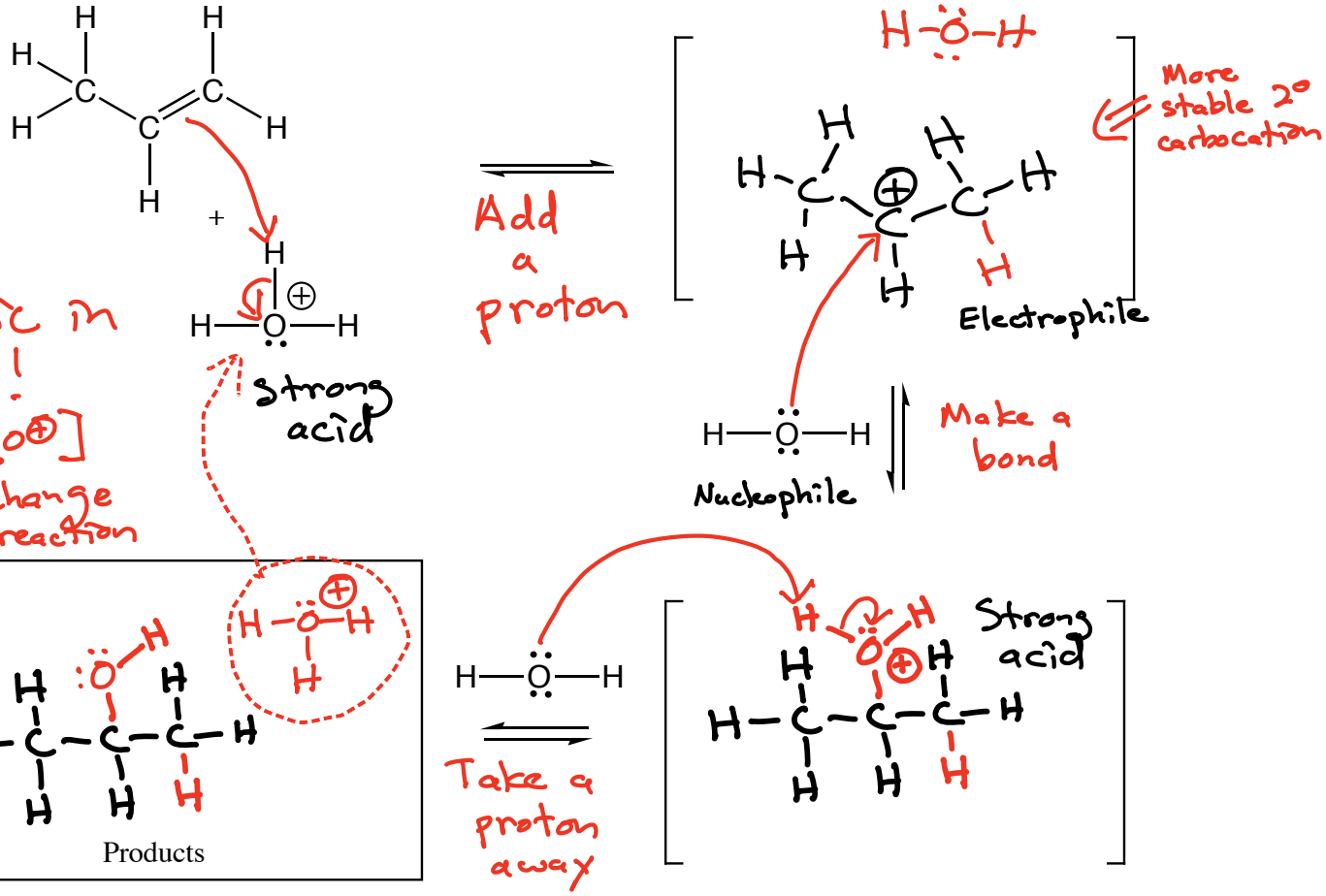




Flashback!!

Acid-catalyzed Hydration of an Alkene

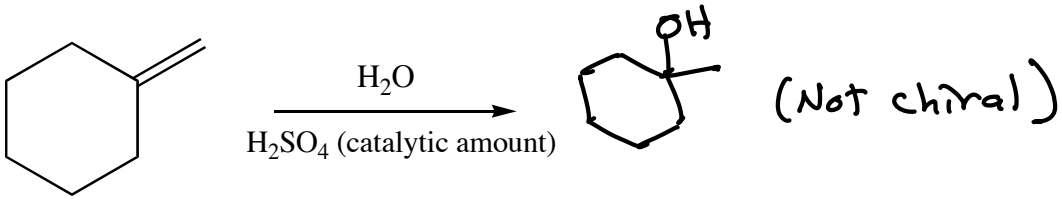




Catalytic in Acid!
⇒ The $[H_3O^{\oplus}]$ does not change during the reaction

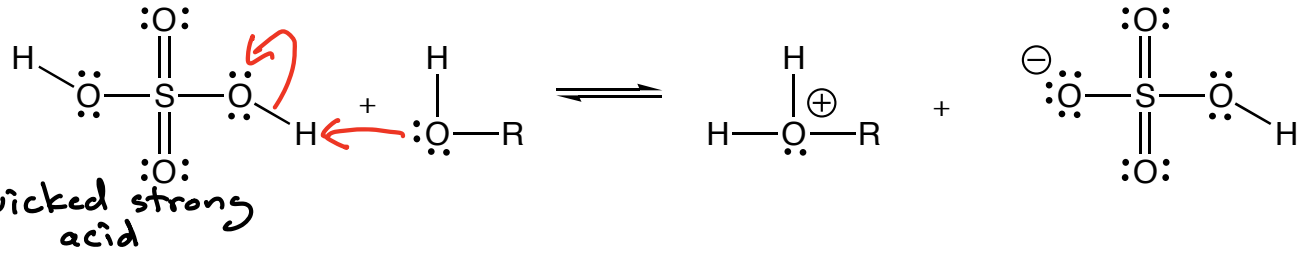
Summary:	Proton adds to make a carbocation intermediate, water attacks to make a new bond, take a proton away to make the product alcohol. Catalytic in $H_3O^{\oplus}$
Regiochemistry:	Markovnikov's Rule
Stereochemistry:	Mixed (time capsule)

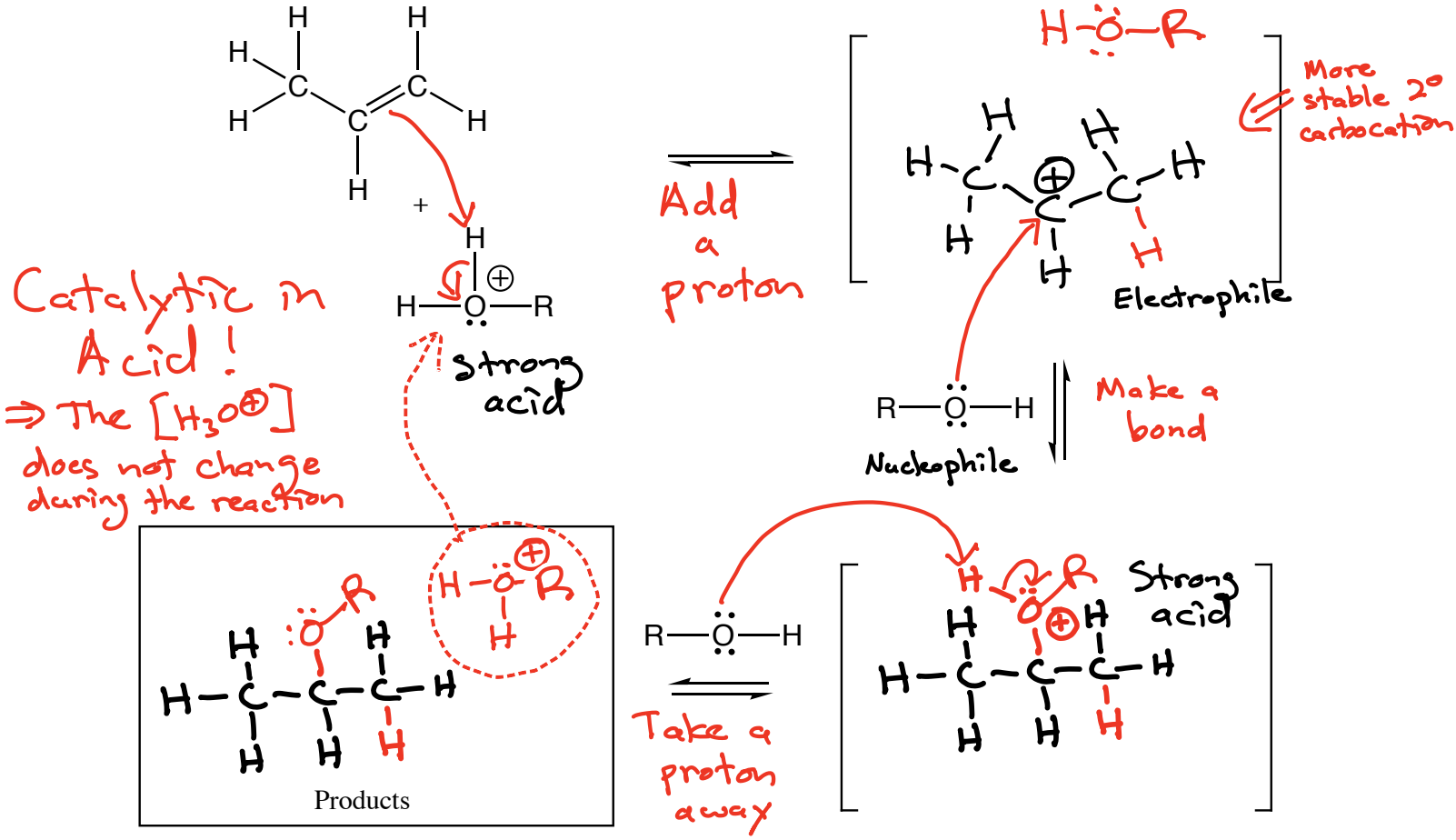
Example:



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

Acid-catalyzed Reaction of an Alcohol with an Alkene



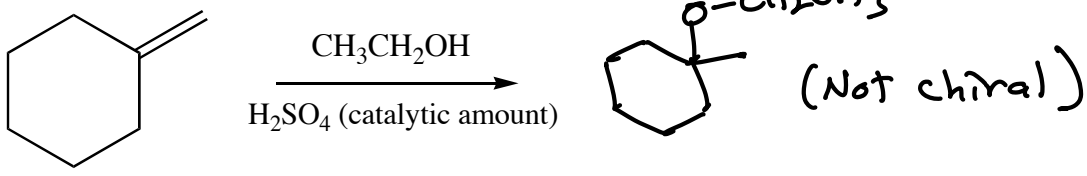


Summary: Proton adds to make a carbocation intermediate, alcohol attacks to make a new bond, take a proton away to make the product ether. Catalytic in $H_3O^{\oplus}$

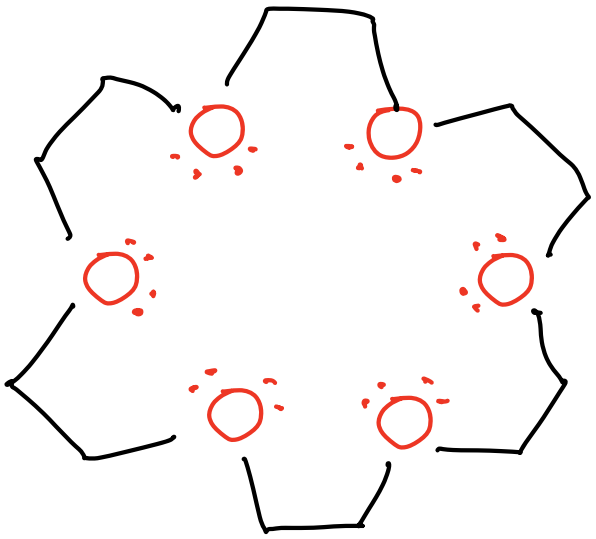
Regiochemistry: Markovnikov's Rule

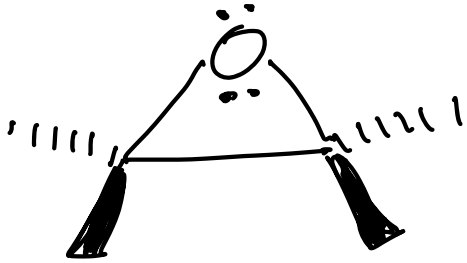
Stereochemistry: Mixed

Example:



Crown Ethers → bind cations based on



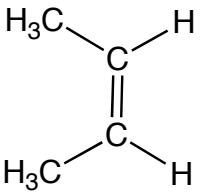


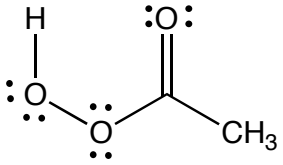
Epoxide

Important because they can be formed from alkenes or halohydrins AND

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

Epoxide Formation





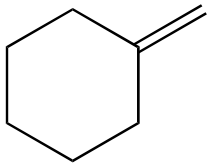
Products

Summary: Alkenes react with peracids in a single concerted step

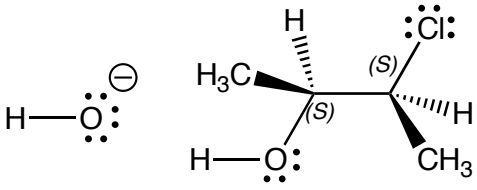
Regiochemistry: N/A

Stereochemistry: Mixed when new chiral centers are created

Example:



CH_3CO_3H



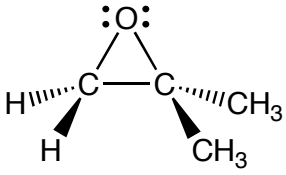
Products

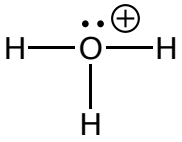
Summary: Halohydrins react in base to give the alkoxide that reacts antiperiplanar to give the epoxide.

Regiochemistry: N/A

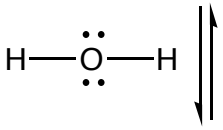
Stereochemistry: Antiperiplanar transition state

Acid-Catalyzed Epoxide Opening

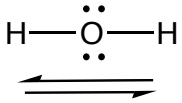








Products



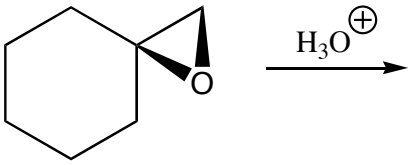


Summary: In acid, epoxides are protonated to give a highly reactive cation intermediate that reacts with nucleophiles at the more highly substituted carbon atom

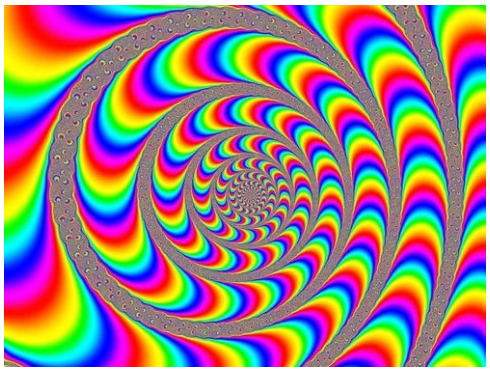
Regiochemistry: "Markovnikov" Attack at more highly substituted C atom

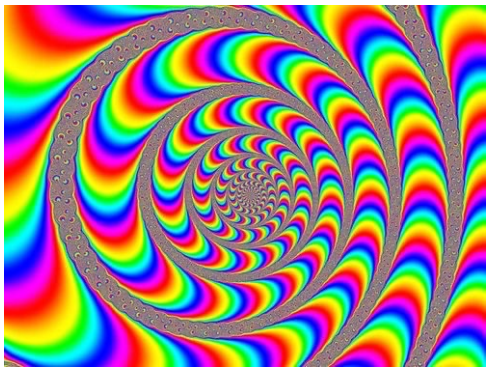
Stereochemistry: Anti

Example:

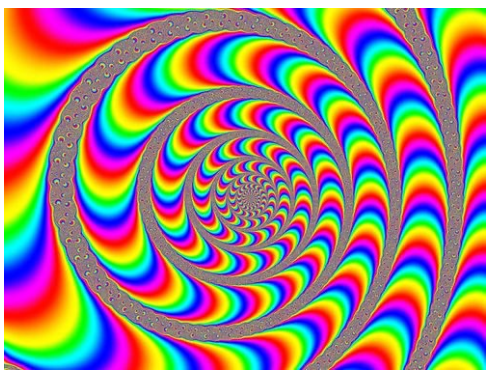


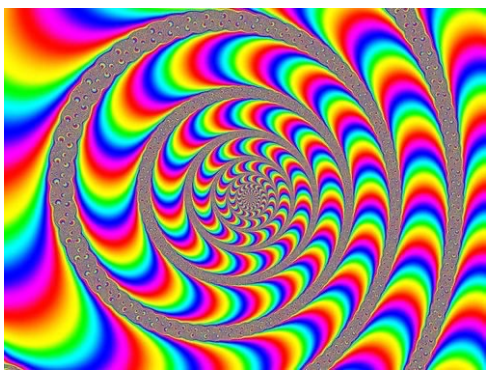
Flashback!!





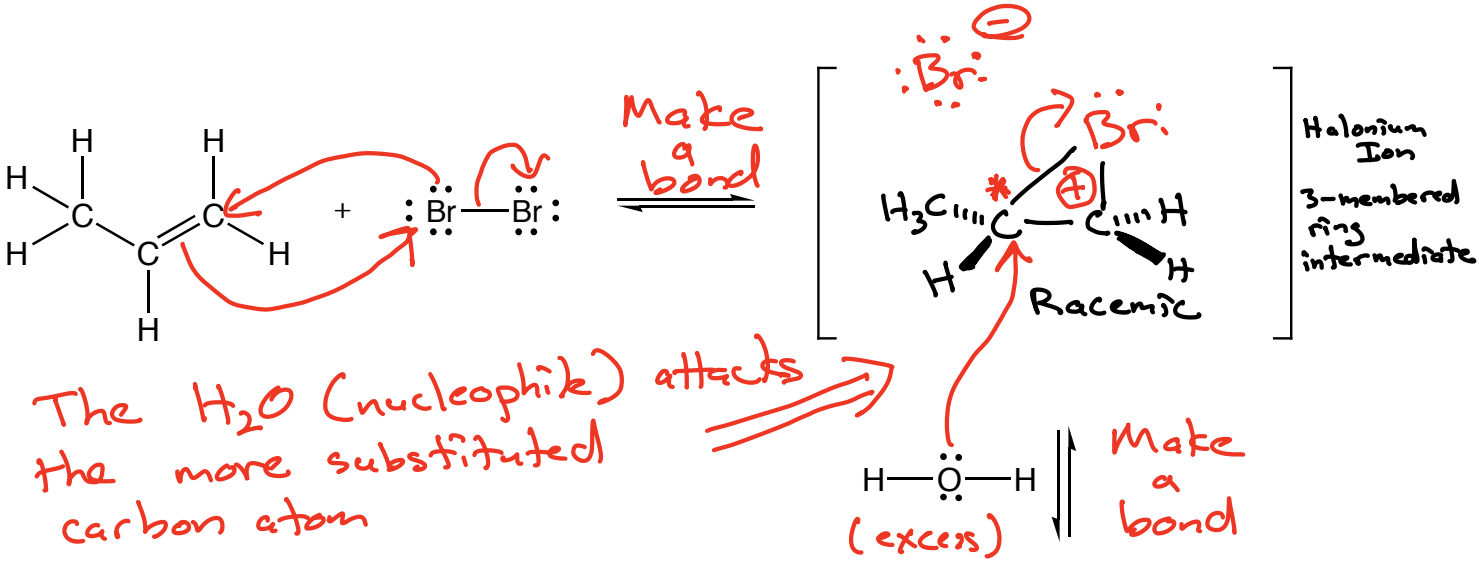


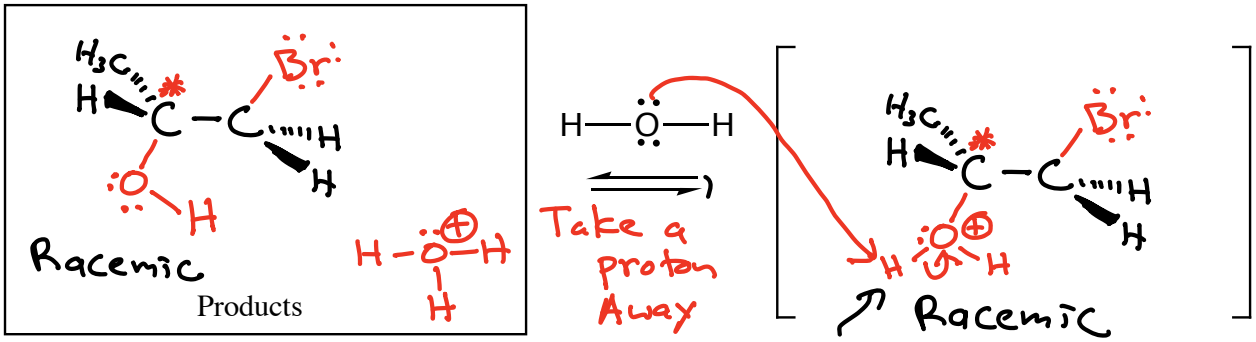




Flashback!!

Alkene Hydrohalogenation





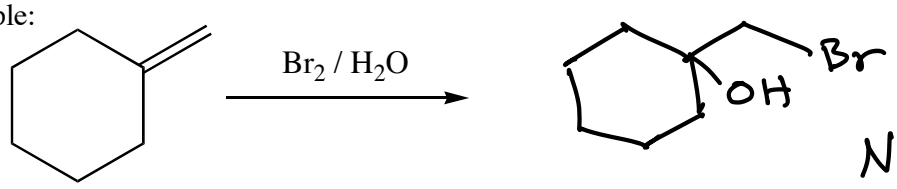
pH drops during the reaction!

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

Regiochemistry: Markovnikov (OH on more substituted C atom)

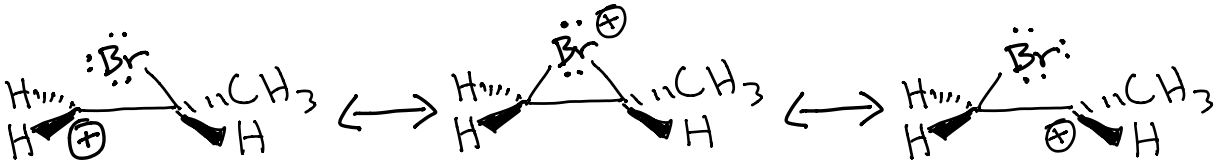
Stereochemistry: Anti

Example:



Not Chiral

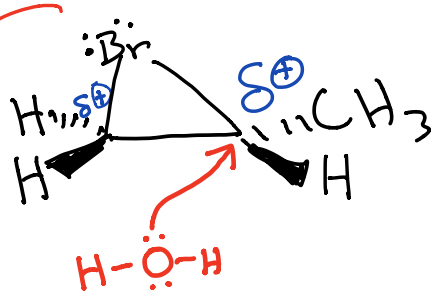
Flashback → Halohydrin Mechanism



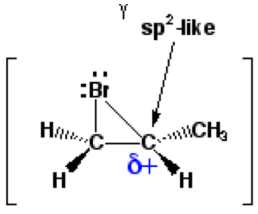
Minor Contributor

Major Contributor

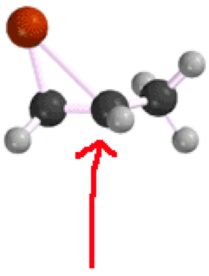
Resonance Hybrid

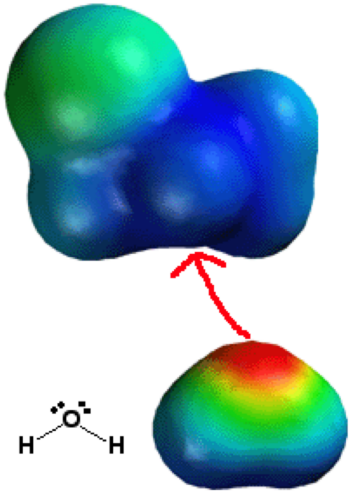


Water attacks the more substituted carbon atom because there is more partial ⊕ charge



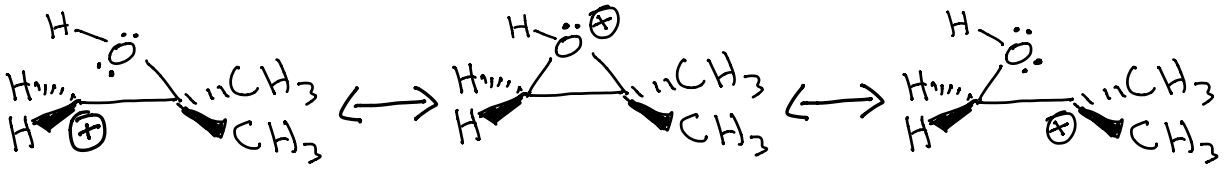
Resonance hybrid

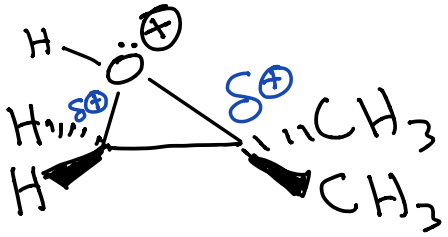




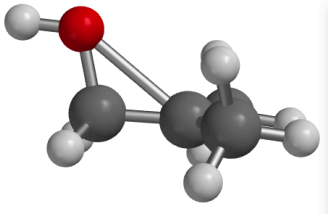
Nucleophiles Attack the More Positively-Charged Carbon Atom From This Face Leading to Markovnikov Regiochemistry and Trans Stereochemistry of Addition

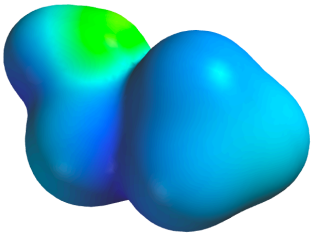
Epoxide in acid

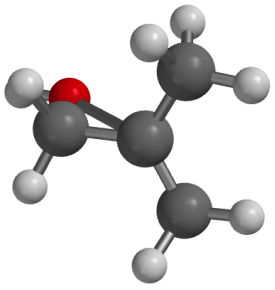


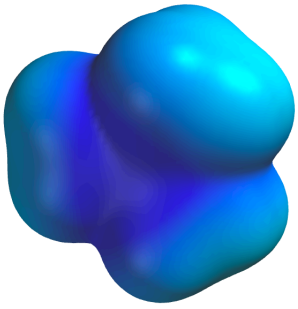




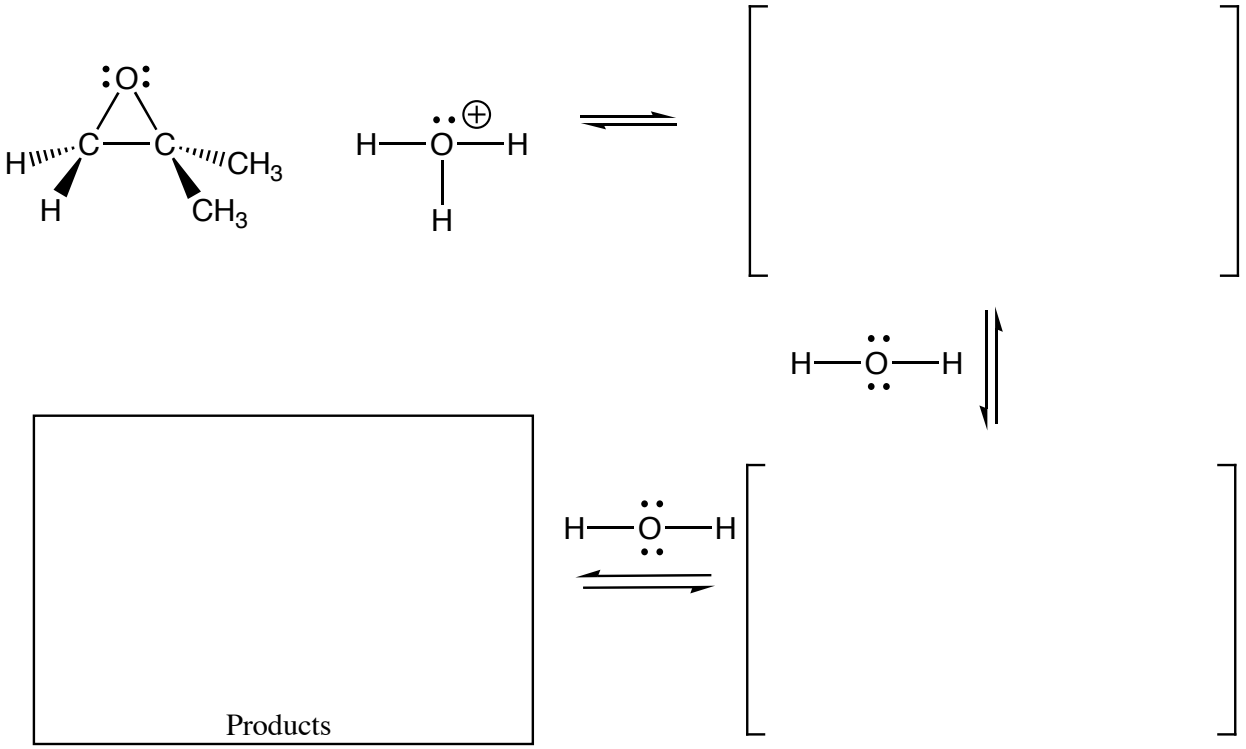






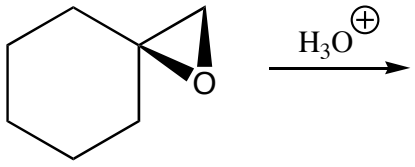


Acid-Catalyzed Epoxide Opening

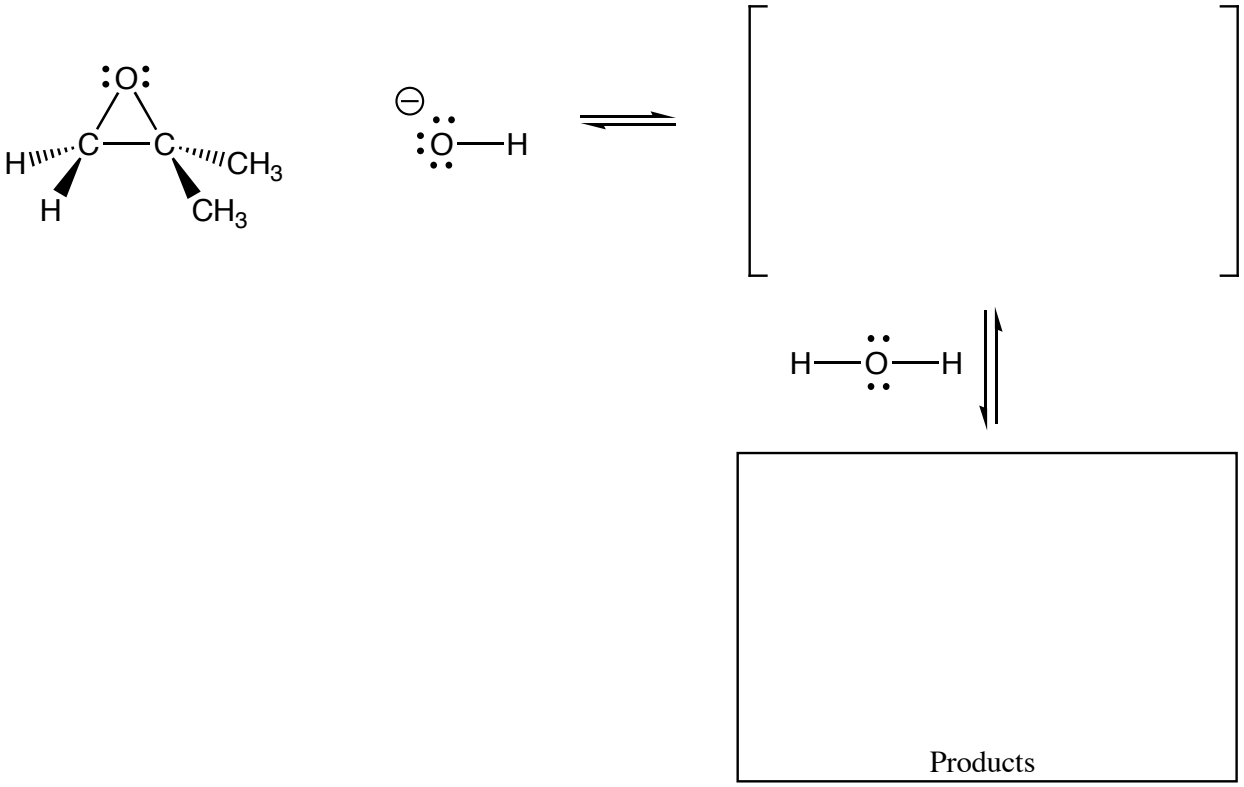


Summary:	In acid, epoxides are protonated to give a highly reactive cation intermediate that reacts with nucleophiles at the more highly substituted carbon atom
Regiochemistry:	"Markovnikov" Attack at more highly substituted C atom
Stereochemistry:	Anti

Example:

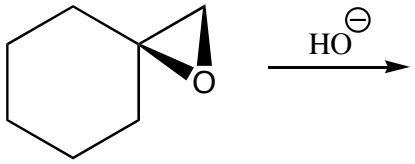


Nucleophilic ~~Base Promoted~~ Epoxide Opening

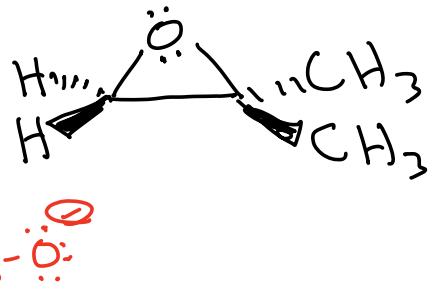


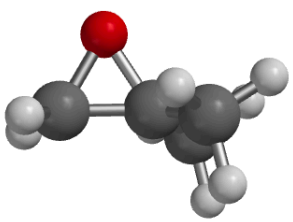
Summary:	Epoxides add strong nucleophiles at the less hindered carbon atom
Regiochemistry:	Less hindered (non-Markovnikov)
Stereochemistry:	Anti addition

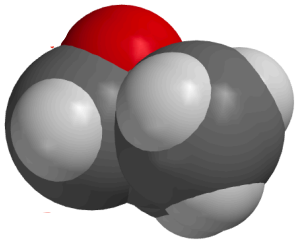
Example:



Epoxide reacting with nucleophile



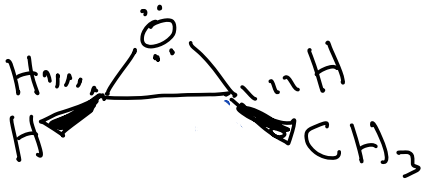




H-O⊖

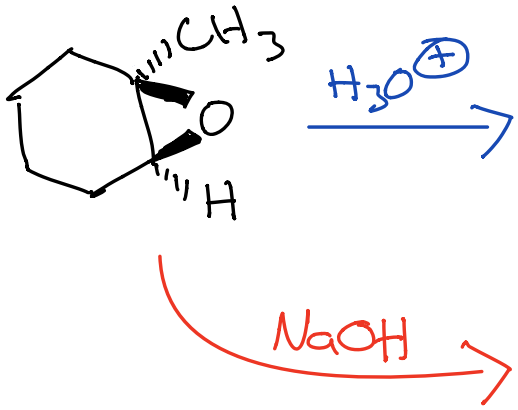


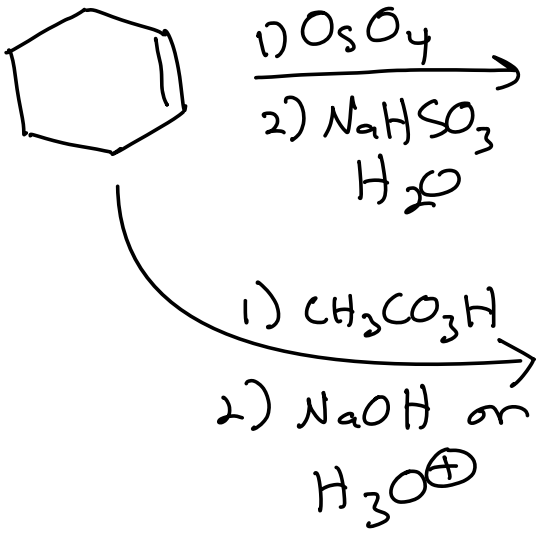
Watch out for the stereochemistry!



$H_3O^{\oplus}$ →

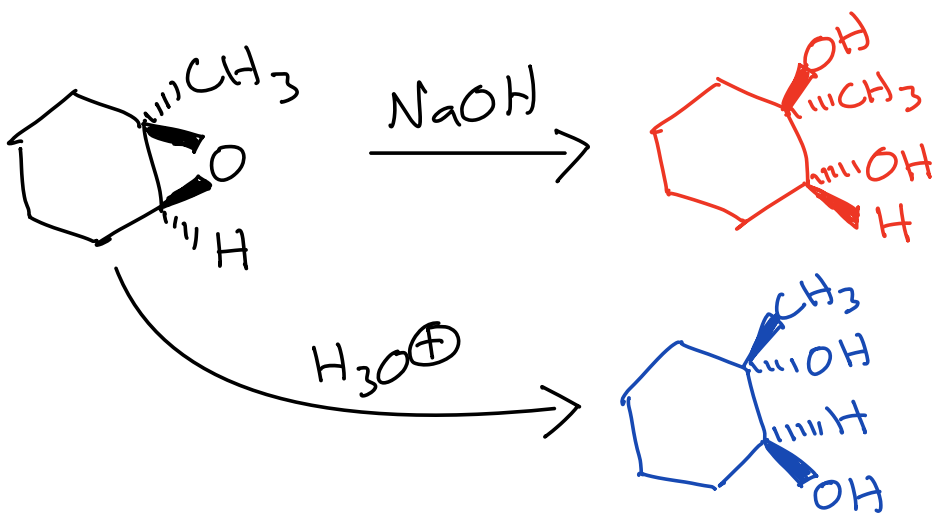
NaOH →


CH3
O
H
H3O⊕
NaOH





Watch out for the stereochemistry!



Works with alkoxides and alcohols as well

