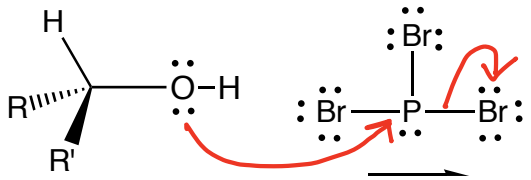
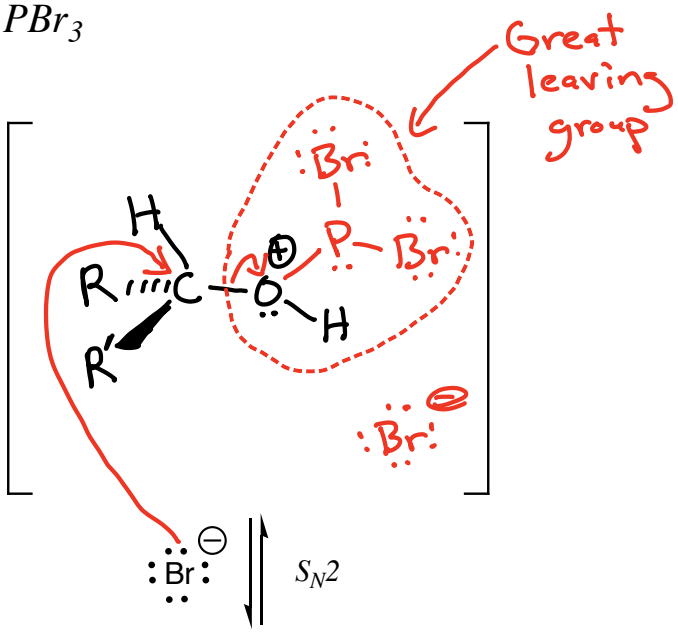
Alcohols + PBr_3



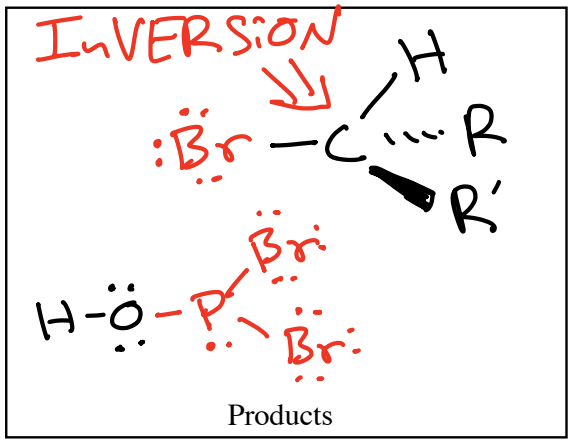
1° or 2° Alcohols

S_N2



Does NOT work with 3° alcohols

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

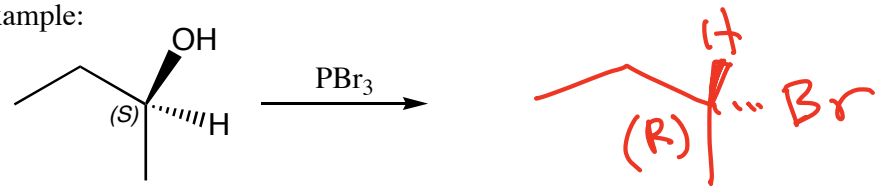


Summary: 1° or 2° alcohols react with PBr_3 via an S_N2 reaction on the P atom to create a good leaving group that undergoes an S_N2 reaction with $Br^\ominus$ at the C atom

Regiochemistry: N/A

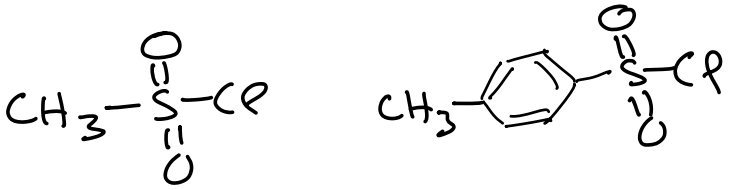
Stereochemistry: INVERSION

Example:



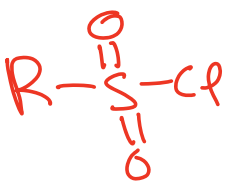
The $SOCl_2$ version of the reaction

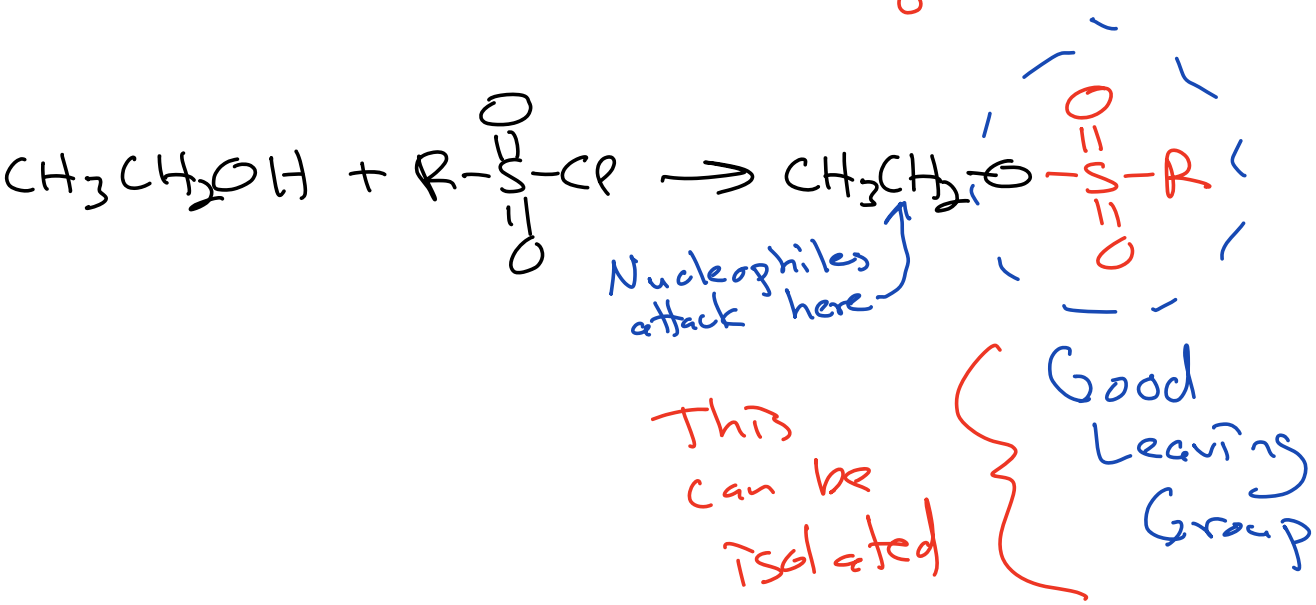
Alkyl Sulfonates



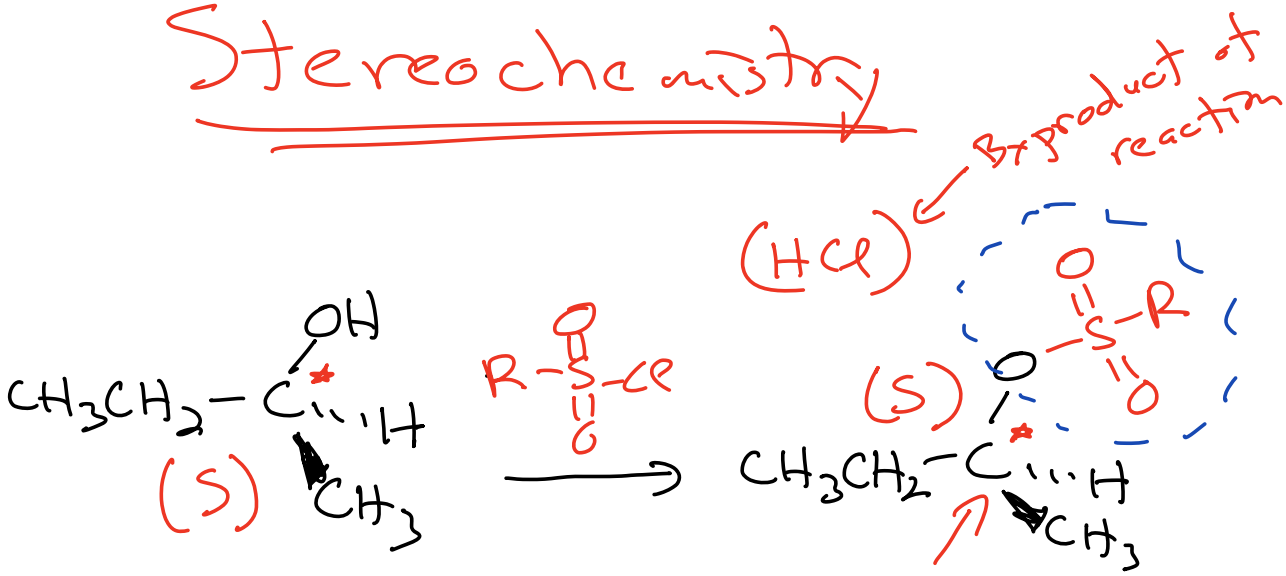
Methanesulfonyl Chloride

p-Toluenesulfonyl Chloride



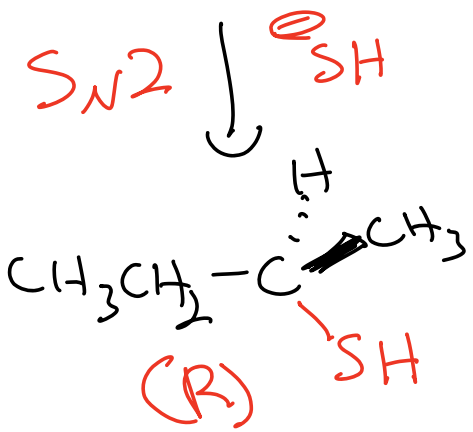


Stereochemistry

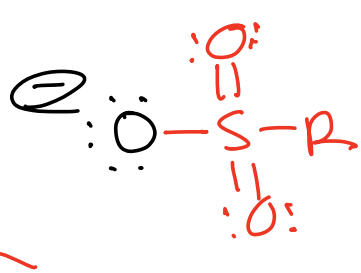


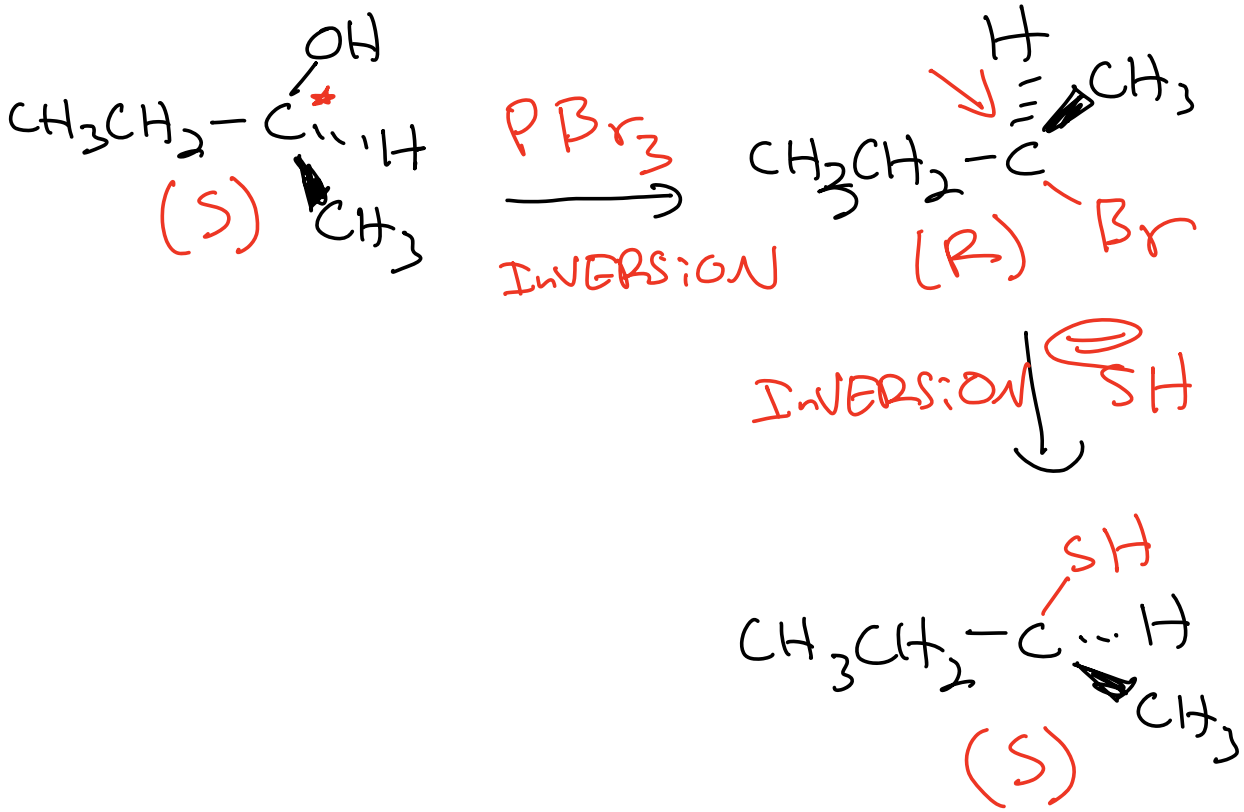
Net ⇒

INVERSION



stabilized by resonance delocalization ⇒ relatively stable anion, explaining why it is such a good leaving group



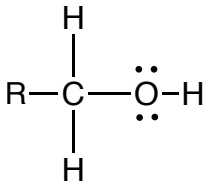


⟹ You can not invert or retain the stereochemistry of a chiral alcohol taking part in S_N2 reactions

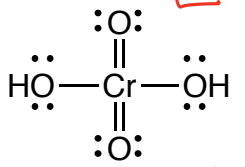
Chromic Acid Oxidation of Alcohols

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

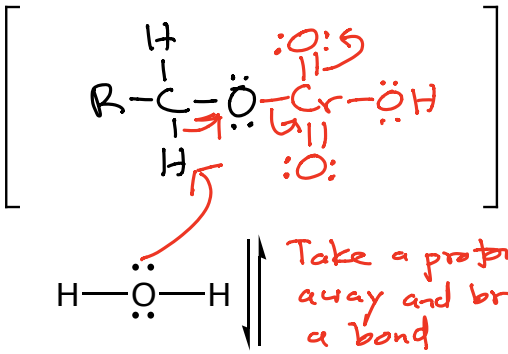
Not responsible for first step



1° Alcohols

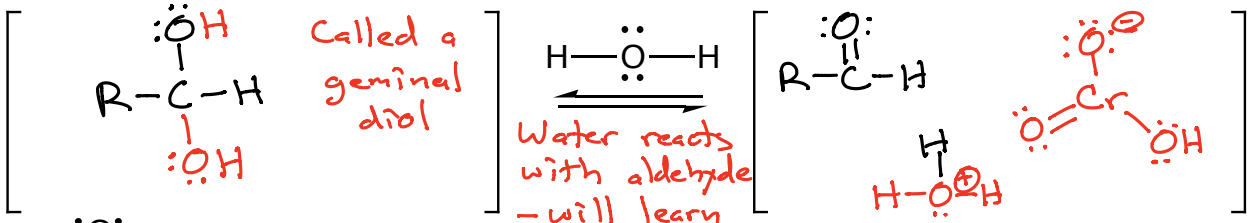


"H_2CrO_4" or "Chromic Acid"



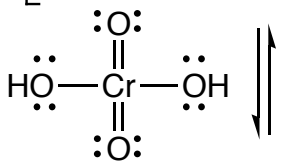
Take a proton away and break a bond

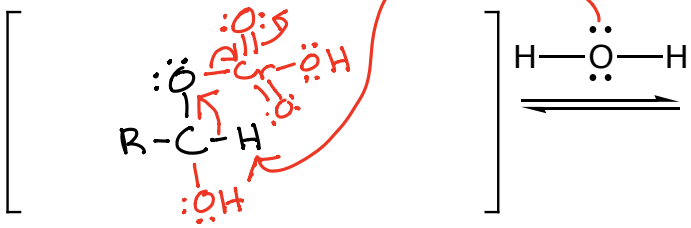
Not responsible for this step

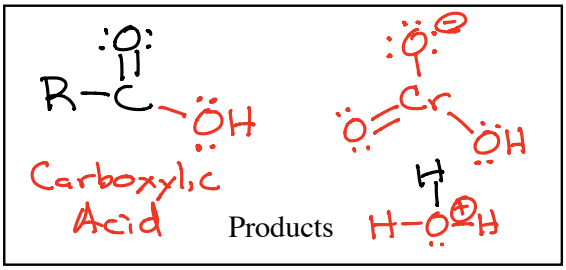


Called a geminal diol

Water reacts with aldehyde – will learn next semester



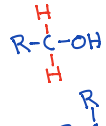




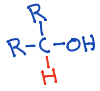
Carboxylic Acid

Products

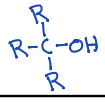
Summary:



1° alcohols ⇒ Carboxylic Acid



2° alcohols ⇒ Ketone

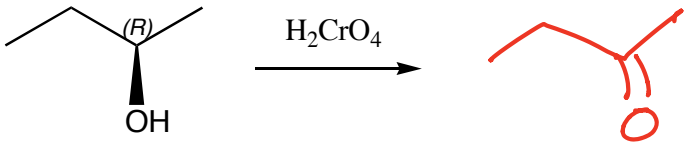


3° alcohols ⇒ NO REACTION

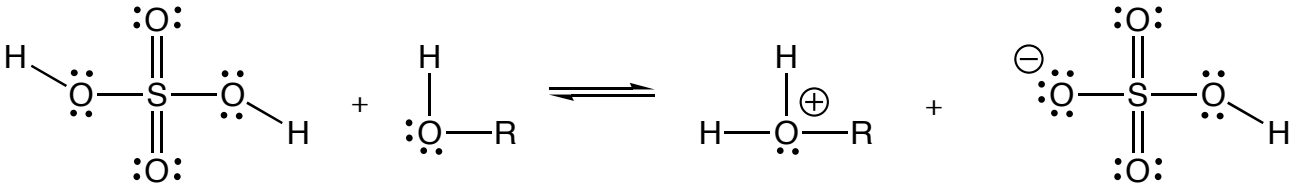
Regiochemistry: N/A

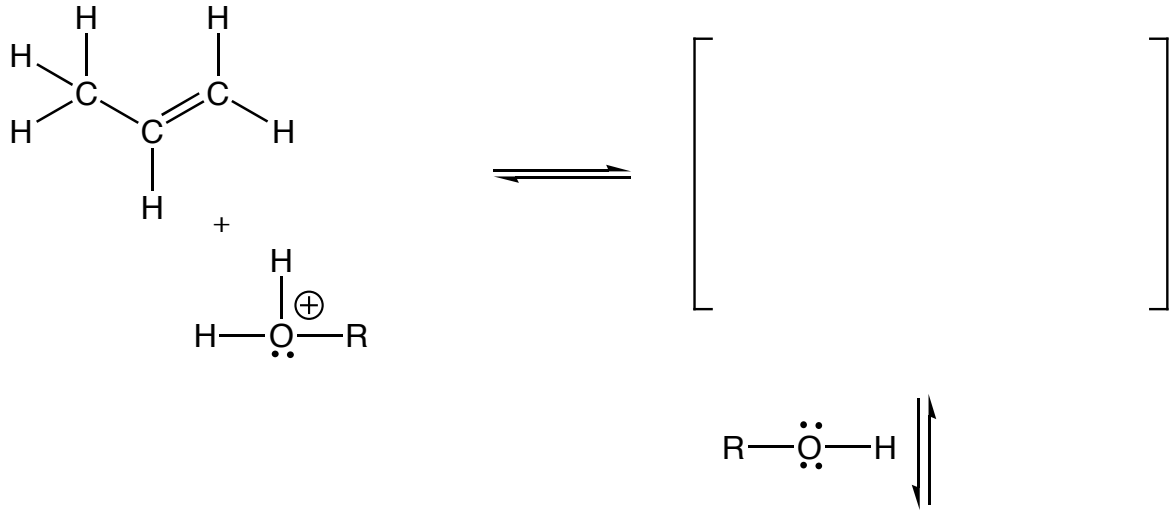
Stereochemistry: N/A

Example:



Acid-catalyzed Reaction of an Alcohol with an Alkene





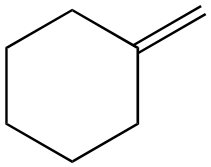
Products

Summary:

Regiochemistry:

Stereochemistry:

Example:

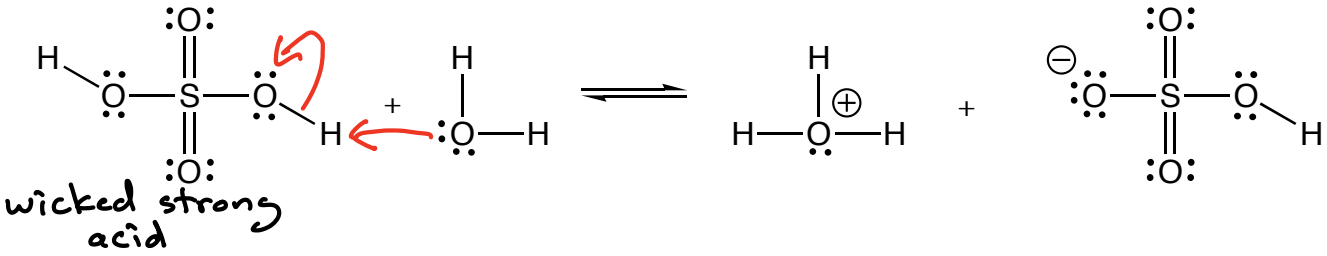


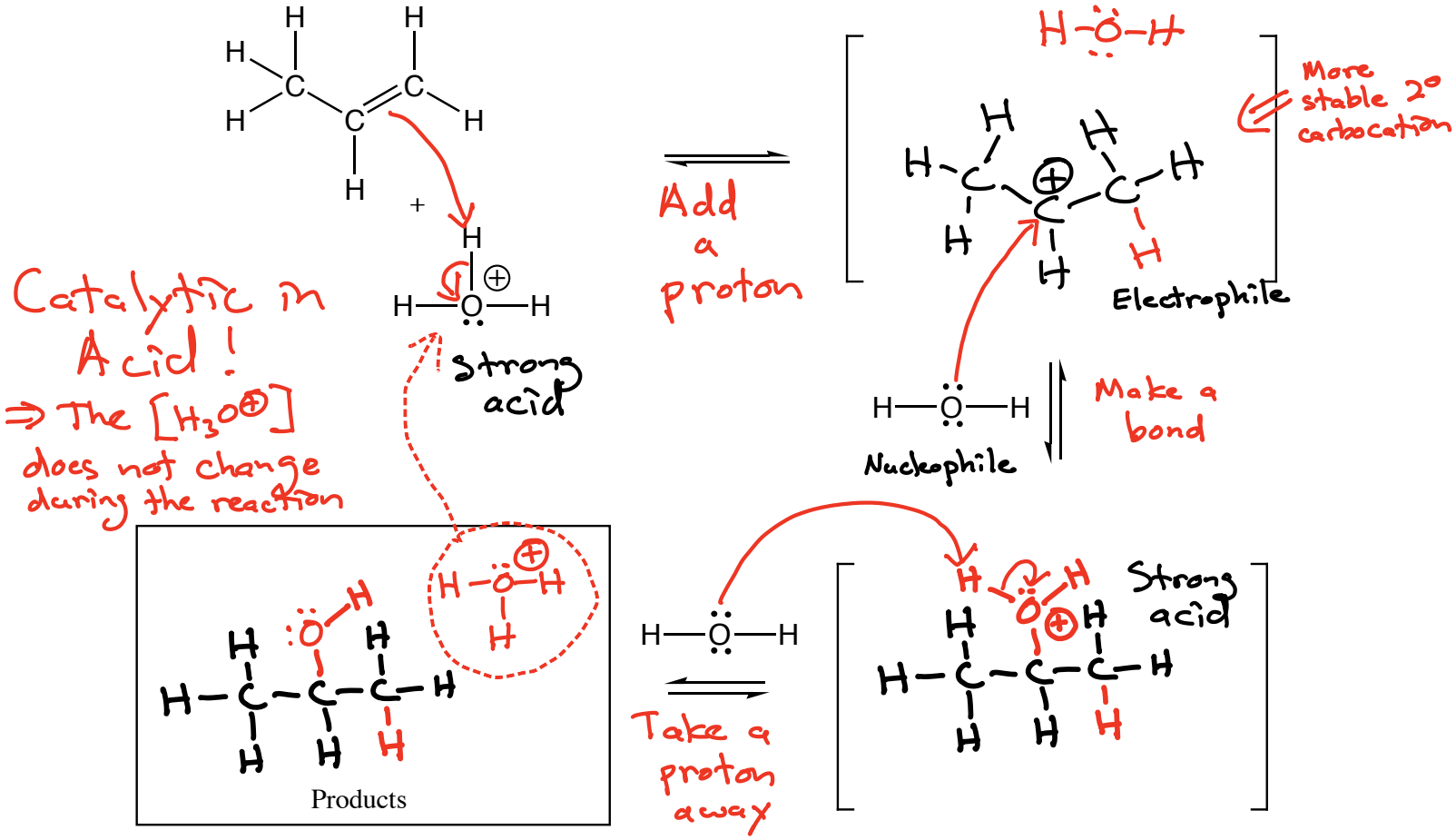
CH_3CH_2OH

H_2SO_4 (catalytic amount)

Flashback to October 4

Acid-catalyzed Hydration of an Alkene



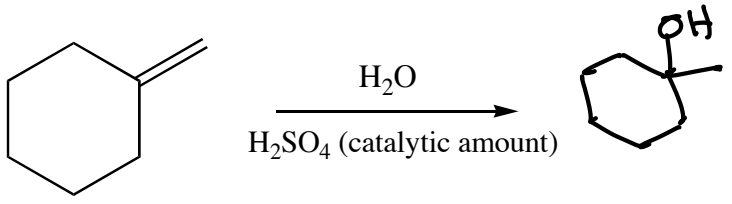


Summary: Proton adds to make a carbocation intermediate, water attacks to make a new bond, take a proton away to make the product alcohol. Catalytic in $H_3O^{\oplus}$

Regiochemistry: Markovnikov's Rule

Stereochemistry: Mixed (time capsule)

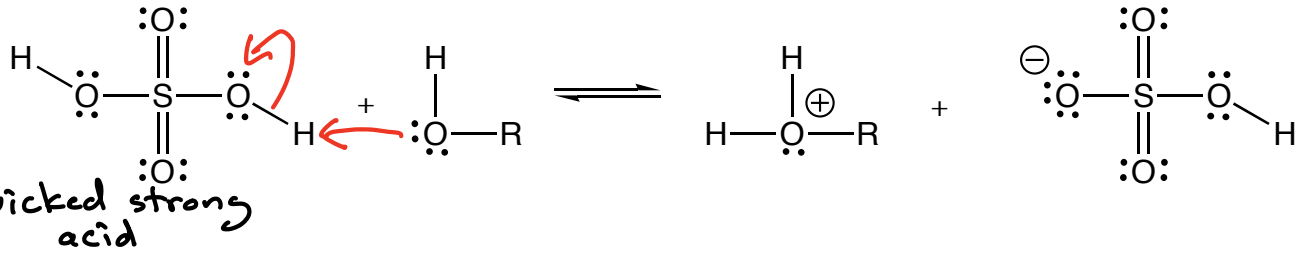
Example:



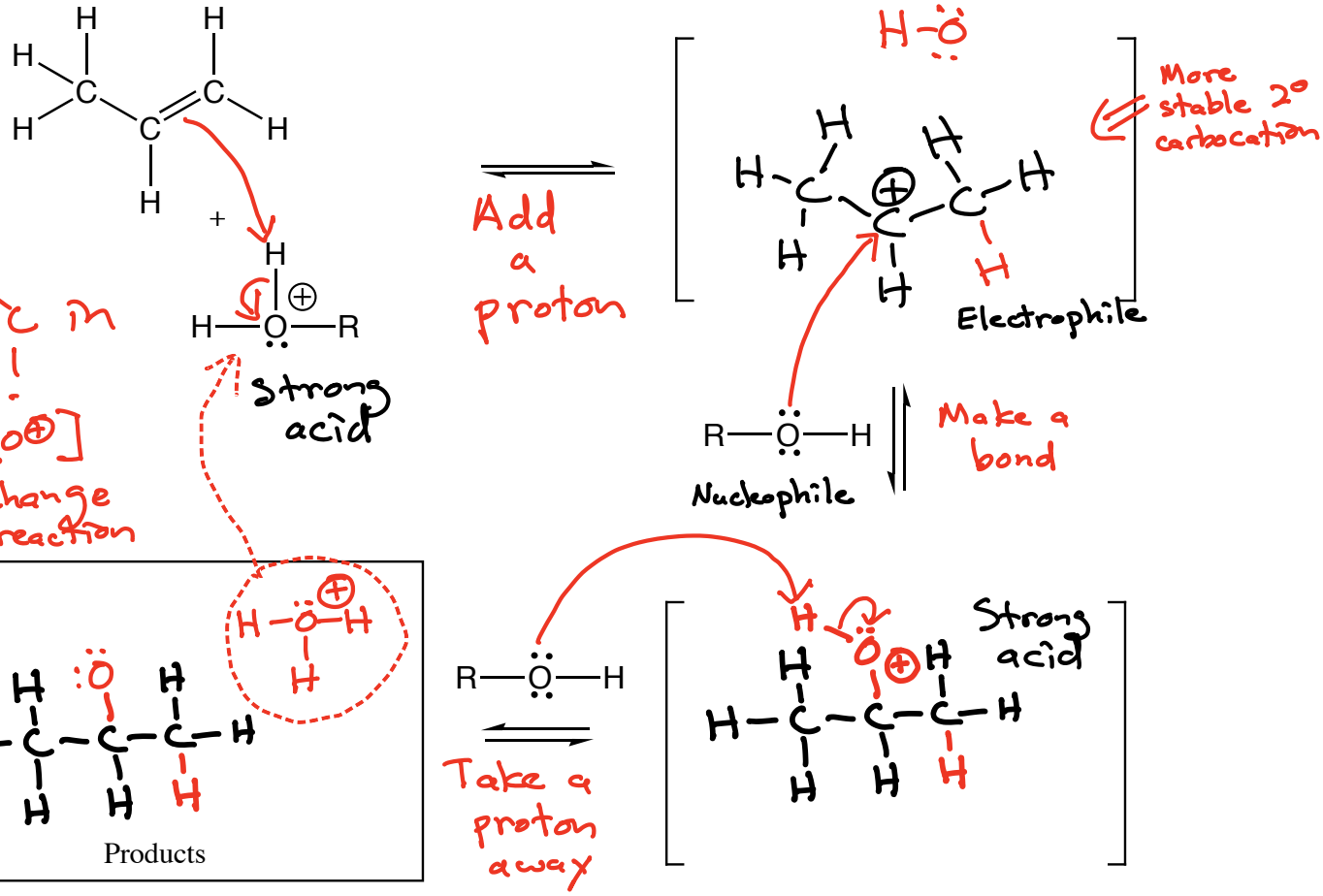
(Not chiral)

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

Acid-catalyzed Reaction of an Alcohol with an Alkene



wicked strong acid

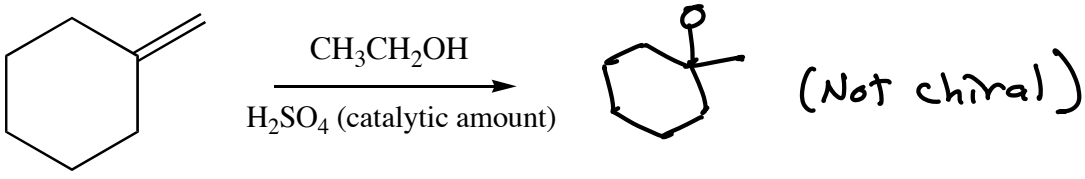


Catalytic in Acid!

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

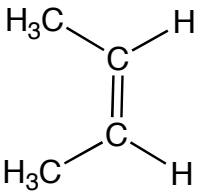
Summary:	Proton adds to make a carbocation intermediate, attacks to make a new bond, take a proton away to make the product. Catalytic in $H_3O^{\oplus}$
Regiochemistry:	Markovnikov's Rule
Stereochemistry:	Mixed

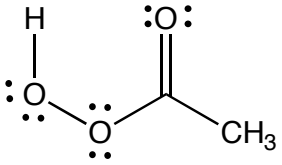
Example:



(Not chiral)

Epoxide Formation





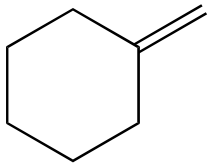
Products

Summary: Alkenes react with peracids in a single concerted step

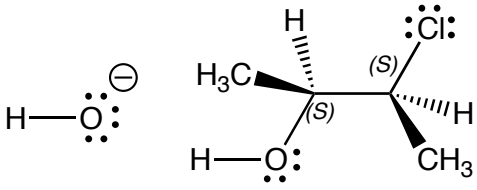
Regiochemistry: N/A

Stereochemistry: Mixed when new chiral centers are created

Example:



CH_3CO_3H



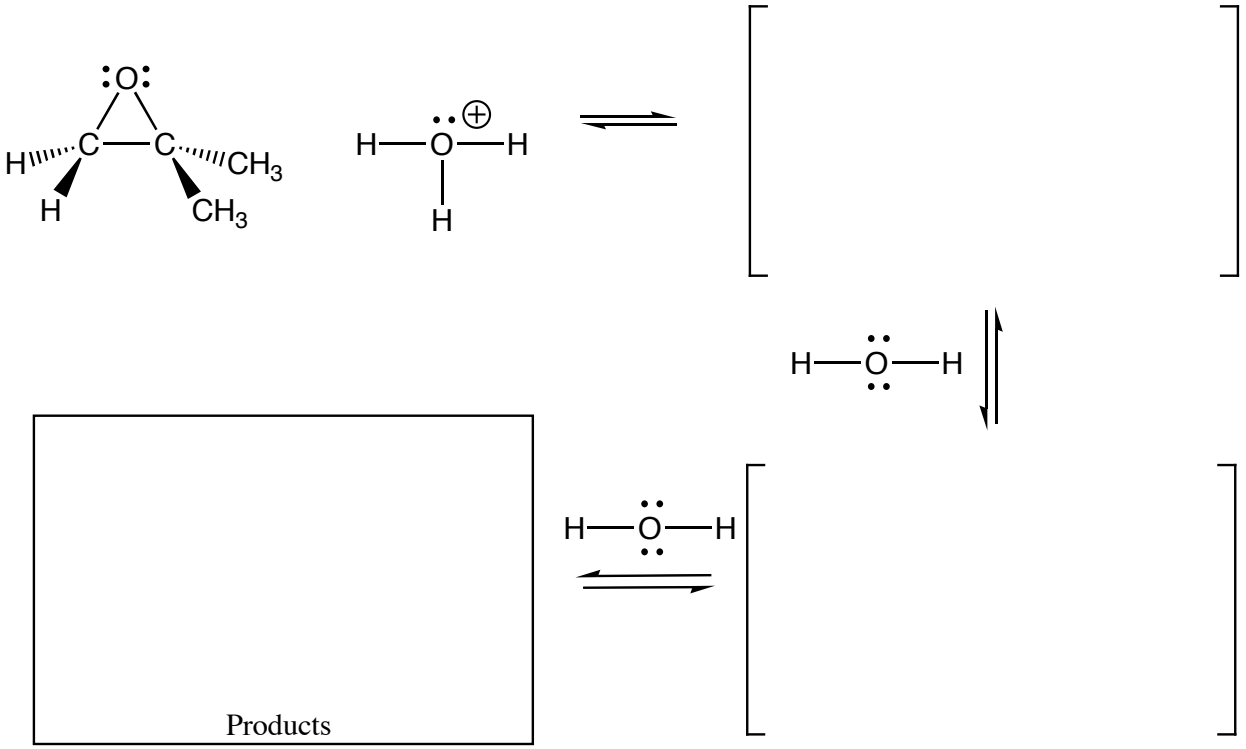
Products

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

Regiochemistry: N/A

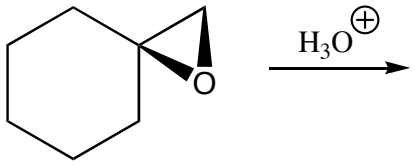
Stereochemistry: Antiperiplanar transition state

Acid-Catalyzed Epoxide Opening



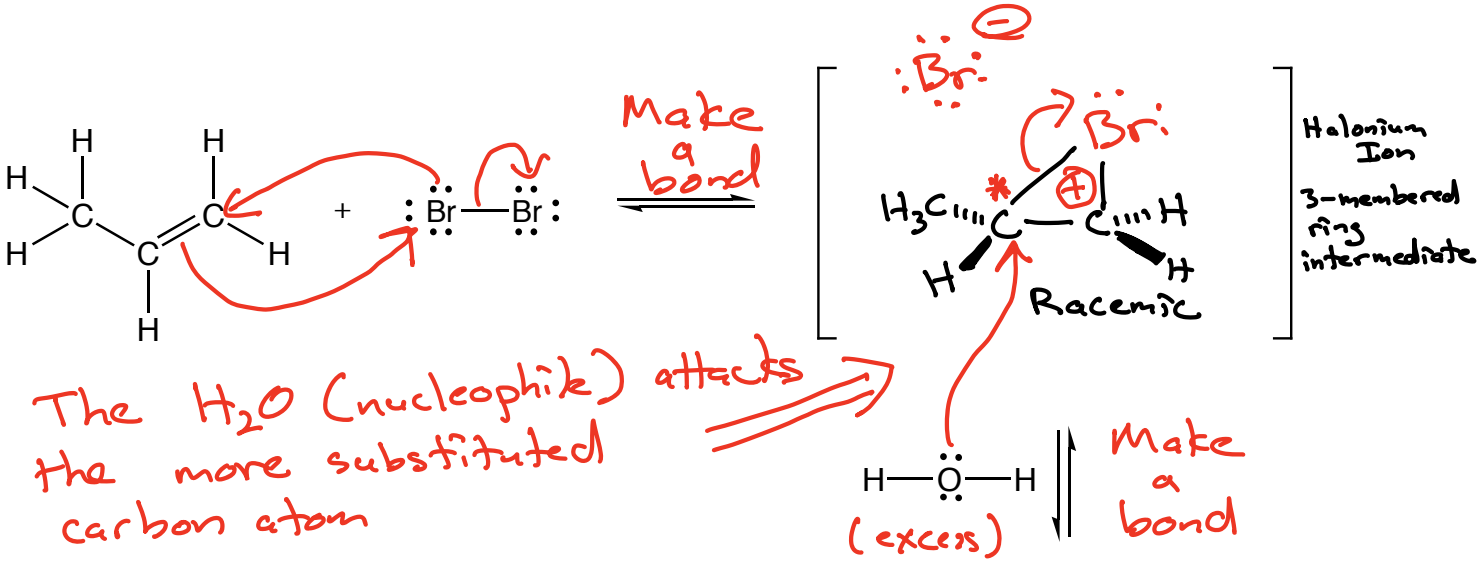
Summary:	In acid, epoxides are protonated to give a highly reactive cation intermediate that reacts with nucleophiles at the more highly substituted carbon atom
Regiochemistry:	"Markovnikov" Attack at more highly substituted C atom
Stereochemistry:	Anti

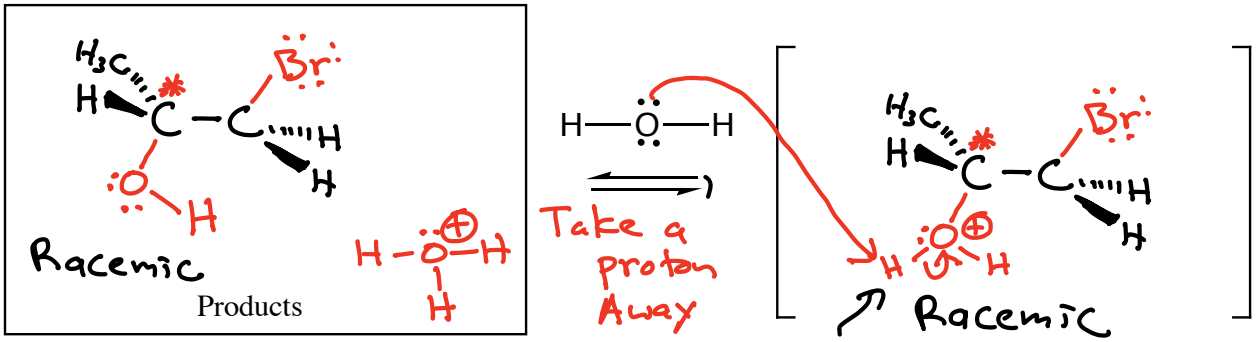
Example:



Flashback to October 11

Alkene Hydrohalogenation





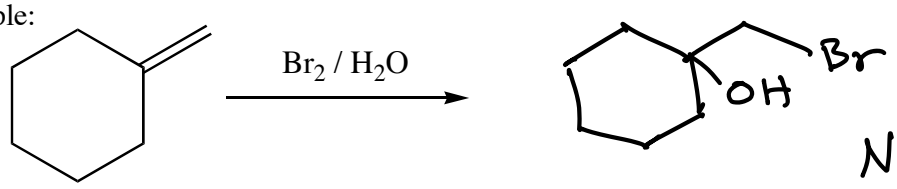
pH drops during the reaction!

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)

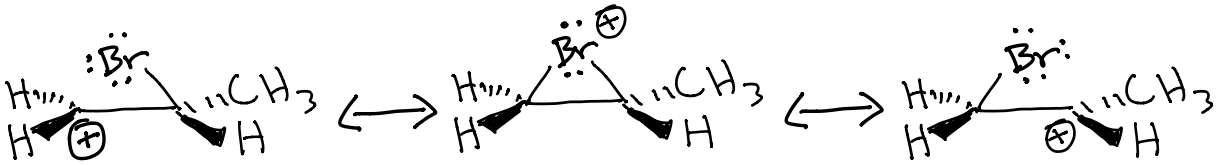
Stereochemistry: Anti

Example:



Not Chiral

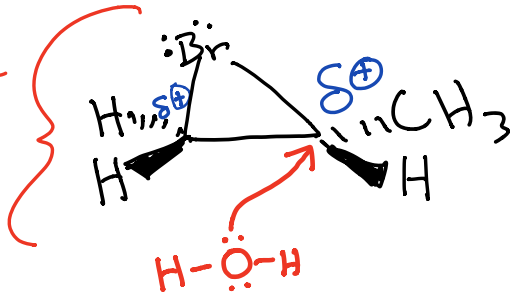
Flashback → Halohydrin Mechanism



Minor Contributor

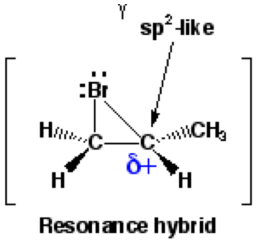
Major Contributor

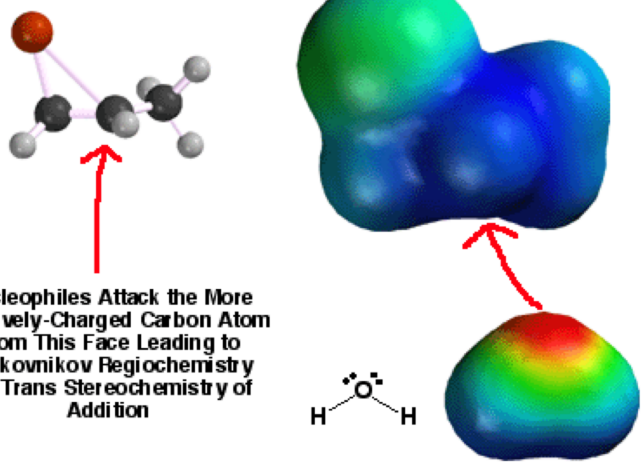
Resonance Hybrid



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

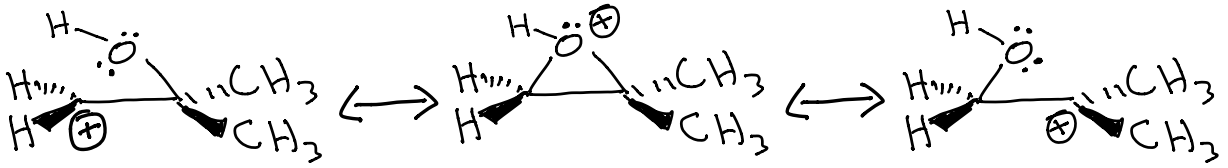
From "Pictures of the Day (PotD)" 10-9-20





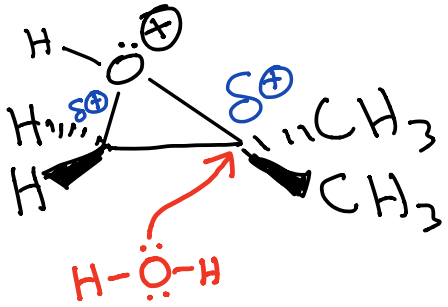
Nucleophiles Attack the More Positively-Charged Carbon Atom From This Face Leading to Markovnikov Regiochemistry and Trans Stereochemistry of Addition

Epoxide in acid



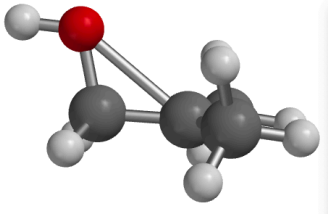
Minor Contributor

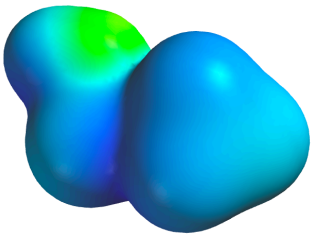
Major Contributor



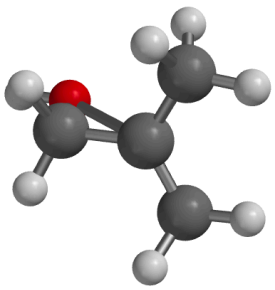
Water attacks the more substituted carbon atom because there is more partial ⊕ charge

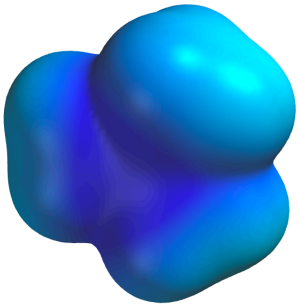
Side View



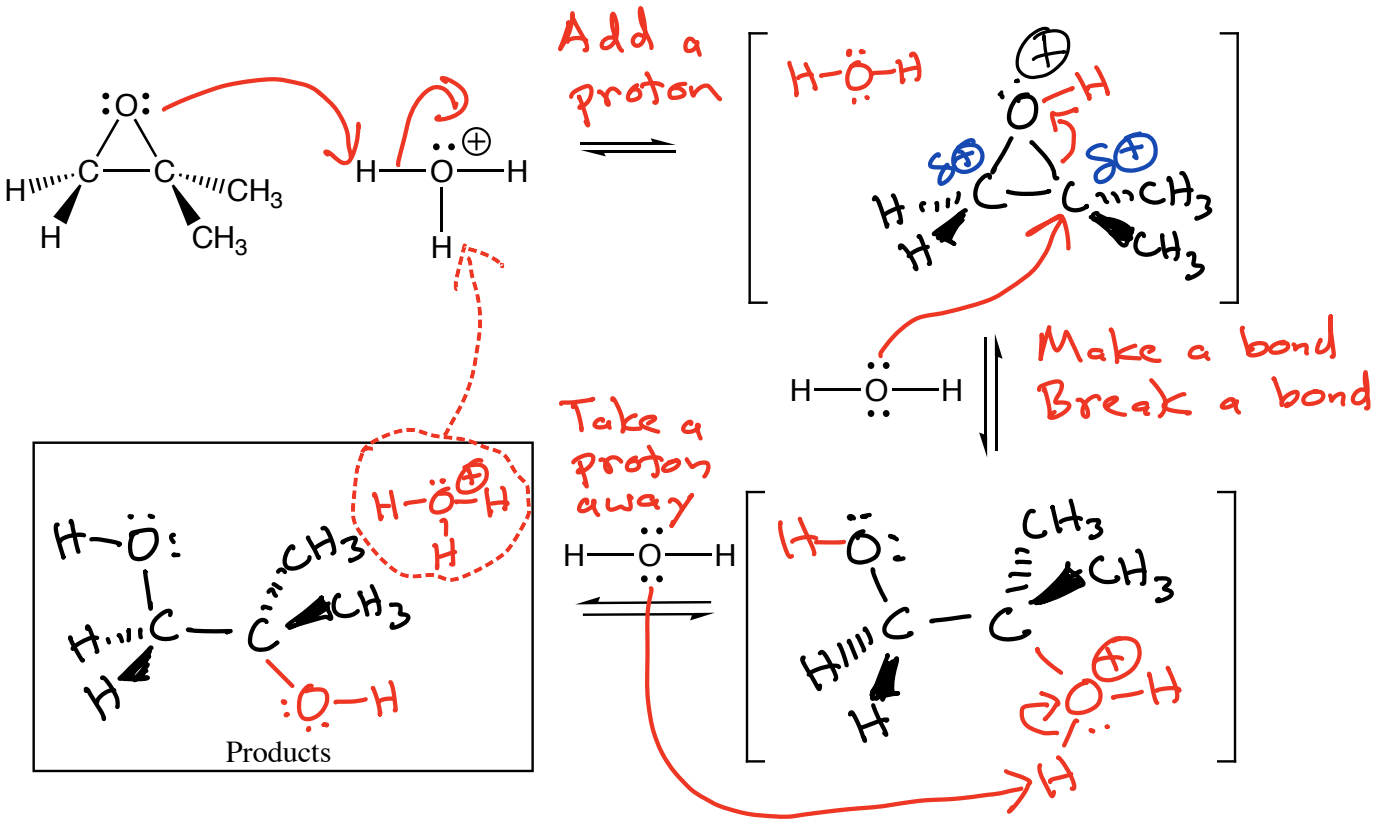


View from Bottom



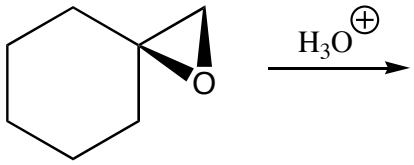


Acid-Catalyzed Epoxide Opening

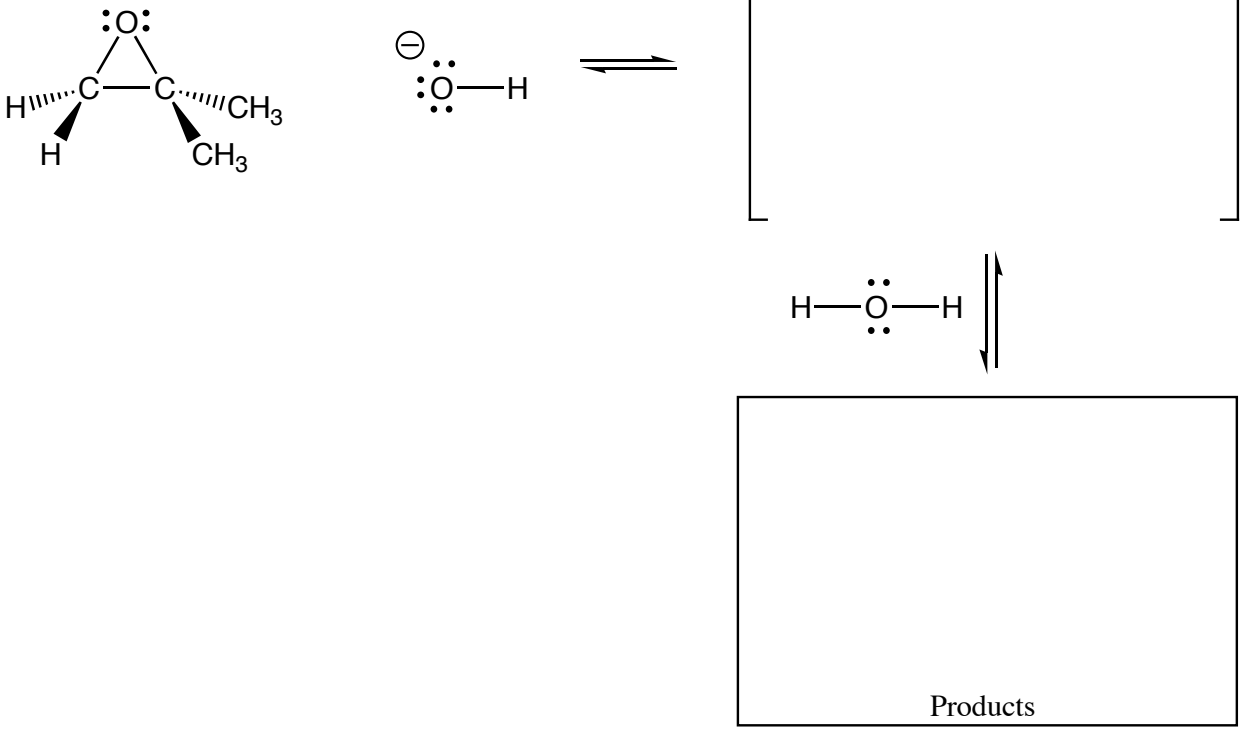


Summary:	In acid, epoxides are protonated to give a highly reactive cation intermediate that reacts with nucleophiles at the more highly substituted carbon atom
Regiochemistry:	"Markovnikov" Attack at more highly substituted C atom
Stereochemistry:	Anti

Example:

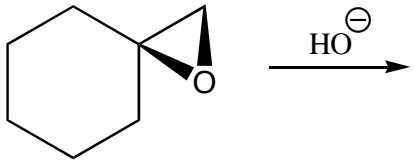


Nucleophilic ~~Base Promoted~~ Epoxide Opening

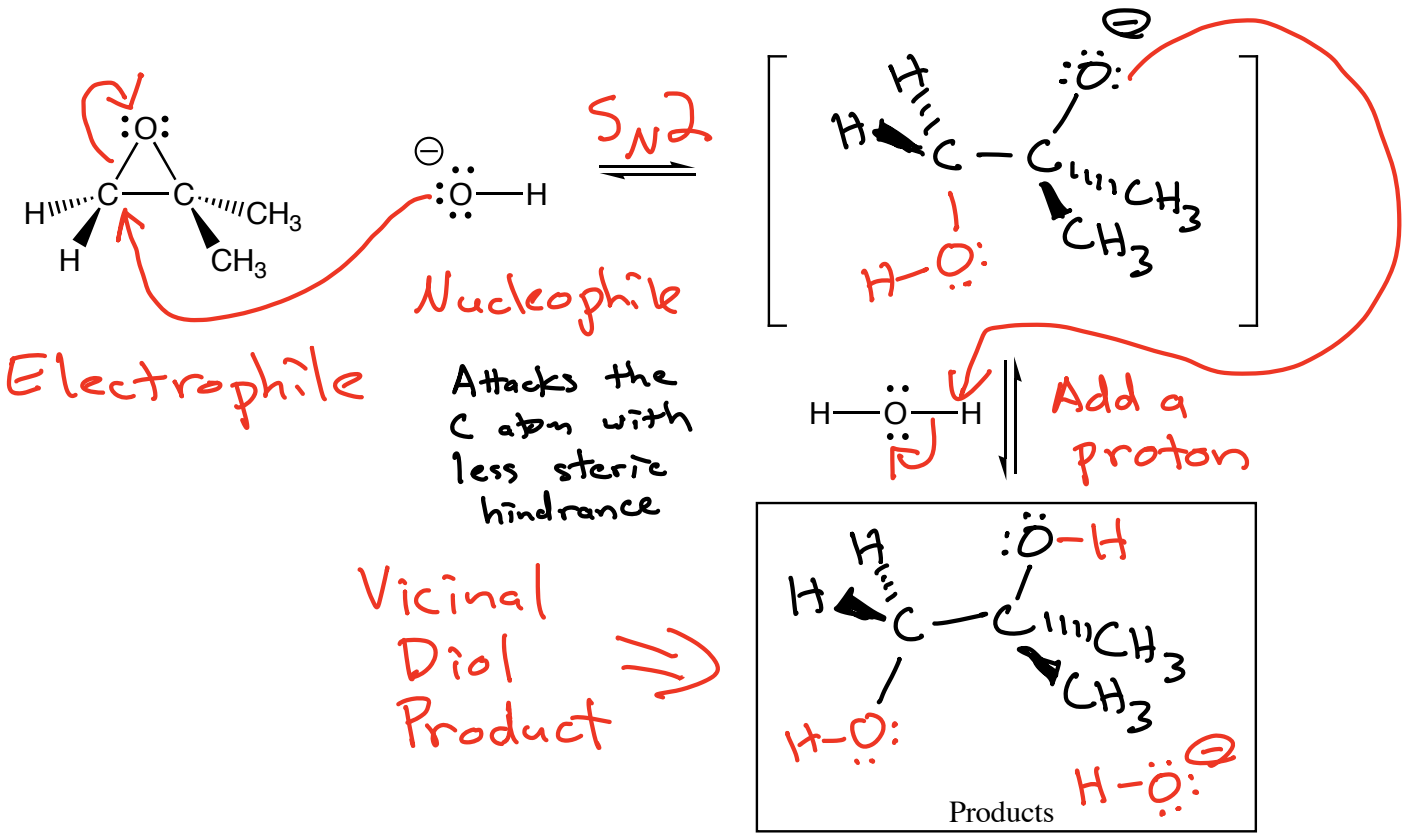


Summary:	Epoxides add strong nucleophiles at the less hindered carbon atom
Regiochemistry:	Less hindered (non-Markovnikov)
Stereochemistry:	Anti addition

Example:

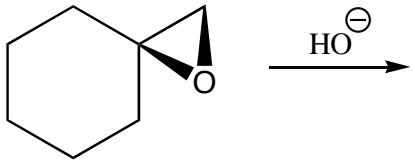


Nucleophilic ~~Base Promoted~~ Epoxide Opening

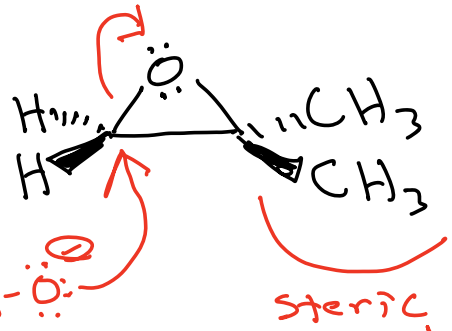


Summary:	Epoxides add strong nucleophiles at the less hindered carbon atom
Regiochemistry:	Less hindered (non-Markovnikov)
Stereochemistry:	Anti addition

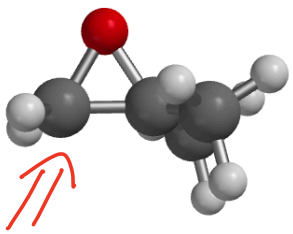
Example:



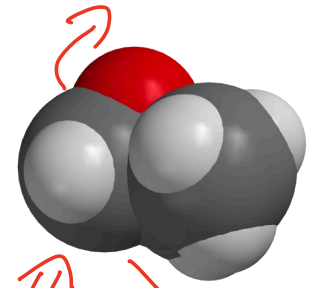
Epoxide reacting with nucleophile



Nucleophile attacks less hindered carbon

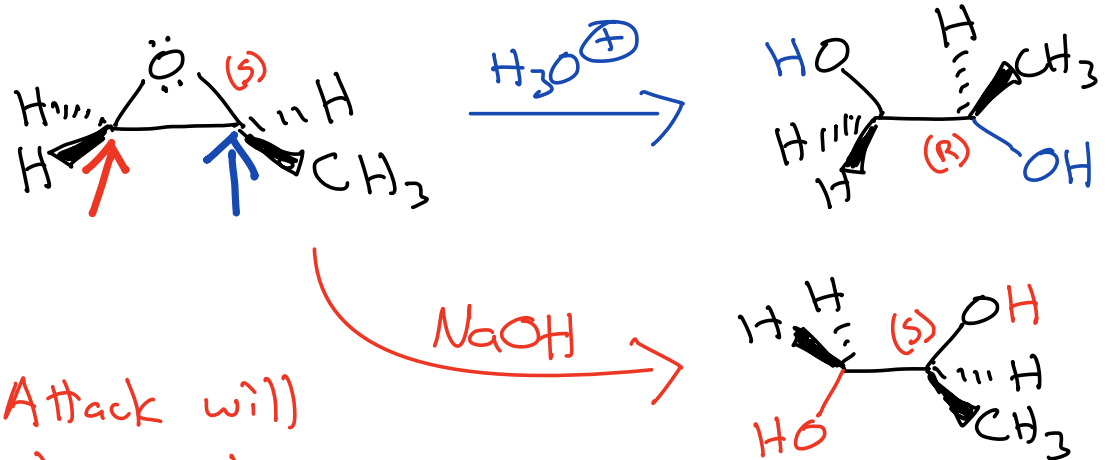


Steric Hindrance → blocks attack at this carbon

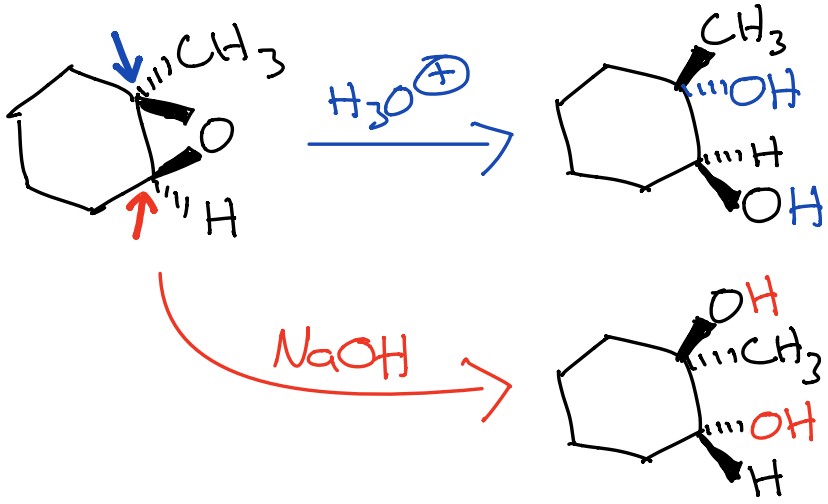


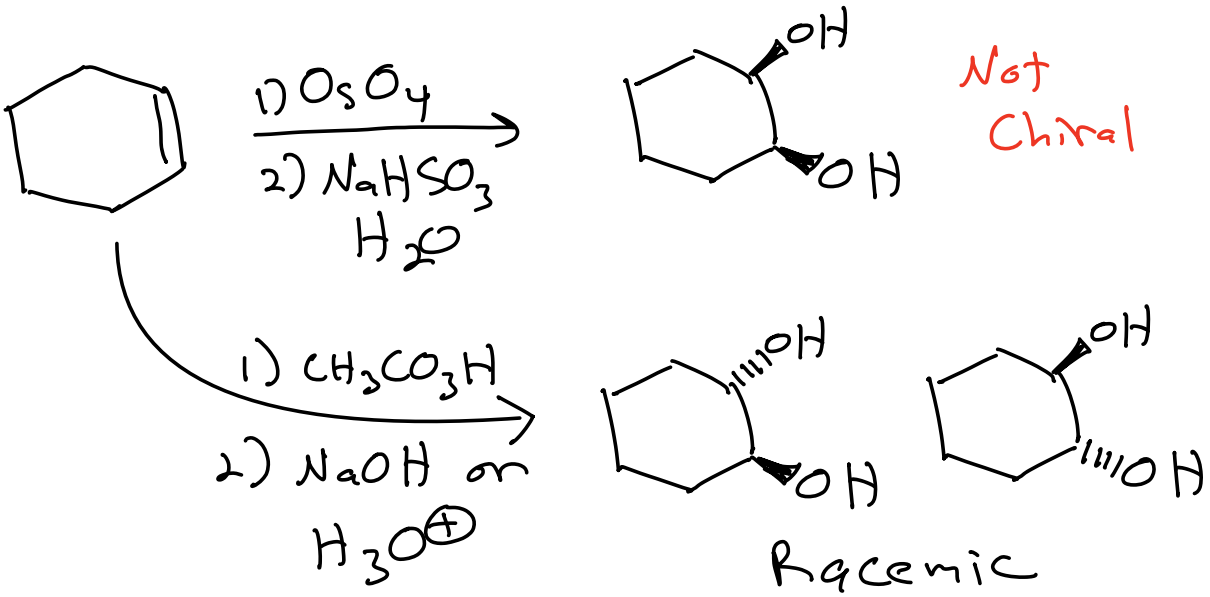
Steric Hindrance

Watch out for the stereochemistry!

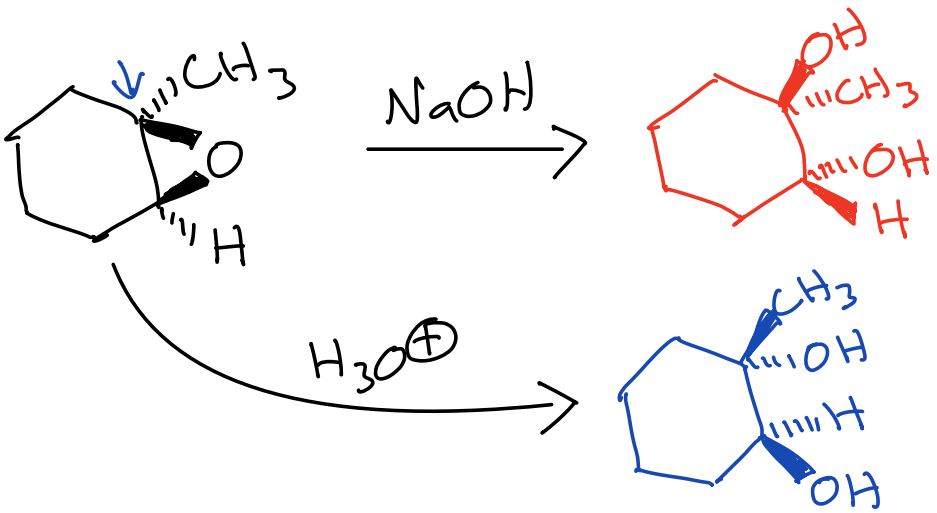


Attack will always be from underneath → back of C-O bond

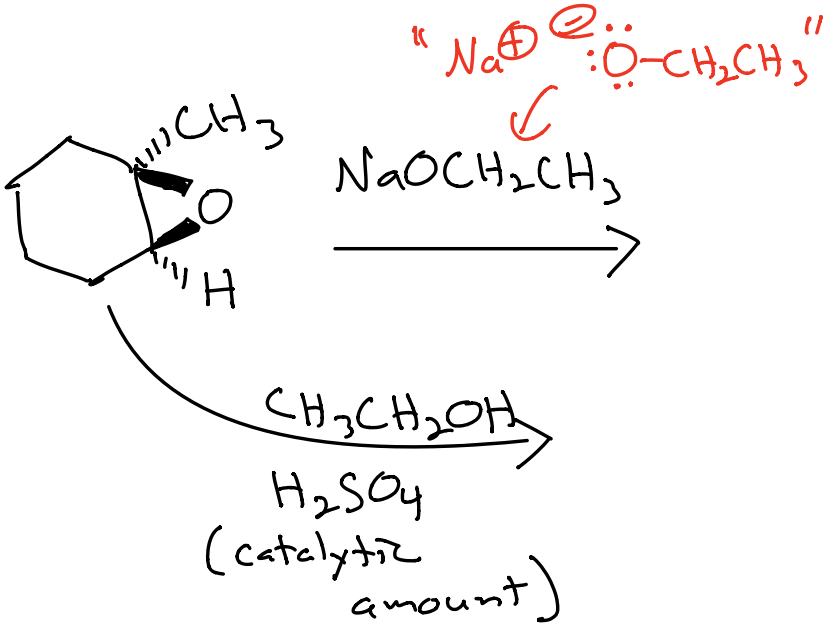

CH3
O
H
H3O⊕
CH3
OH
H
OH
NaOH
OH
CH3
OH
H



Watch out for the stereochemistry!

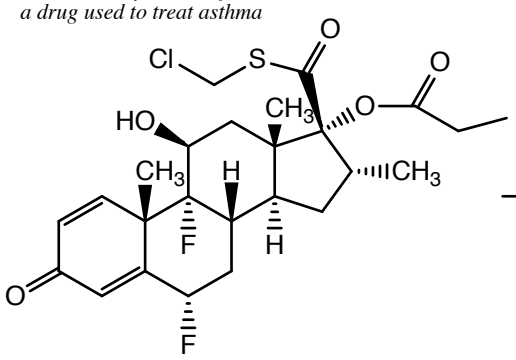


Works with alkoxides and alcohols as well)



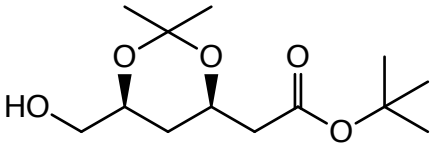
Reactions in the Context of Complex Molecules

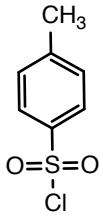
Used in the synthesis of Fluticasone (Flonase), a drug used to treat asthma



NaI

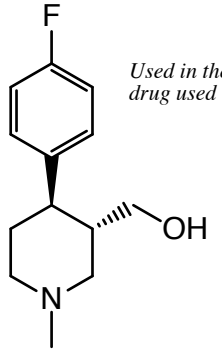
acetone





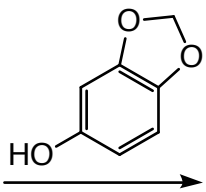
Used in the synthesis of Lipitor

NaCN



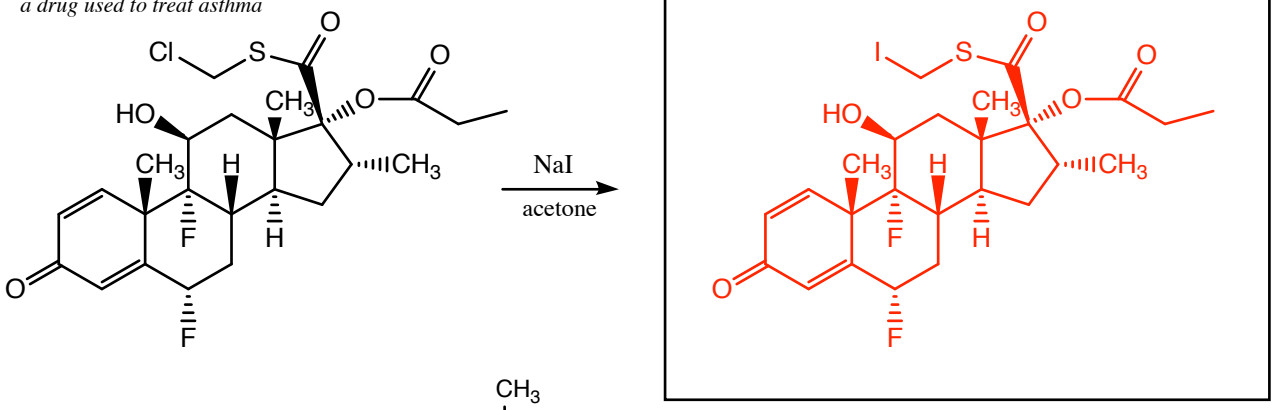
Used in the synthesis of Paxil, a drug used to treat depression

$SOCl_2$

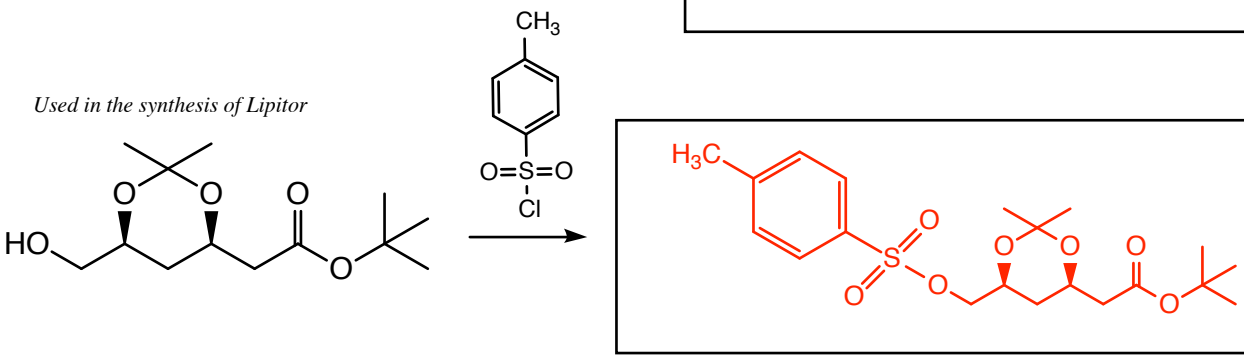


Reactions in the Context of Complex Molecules

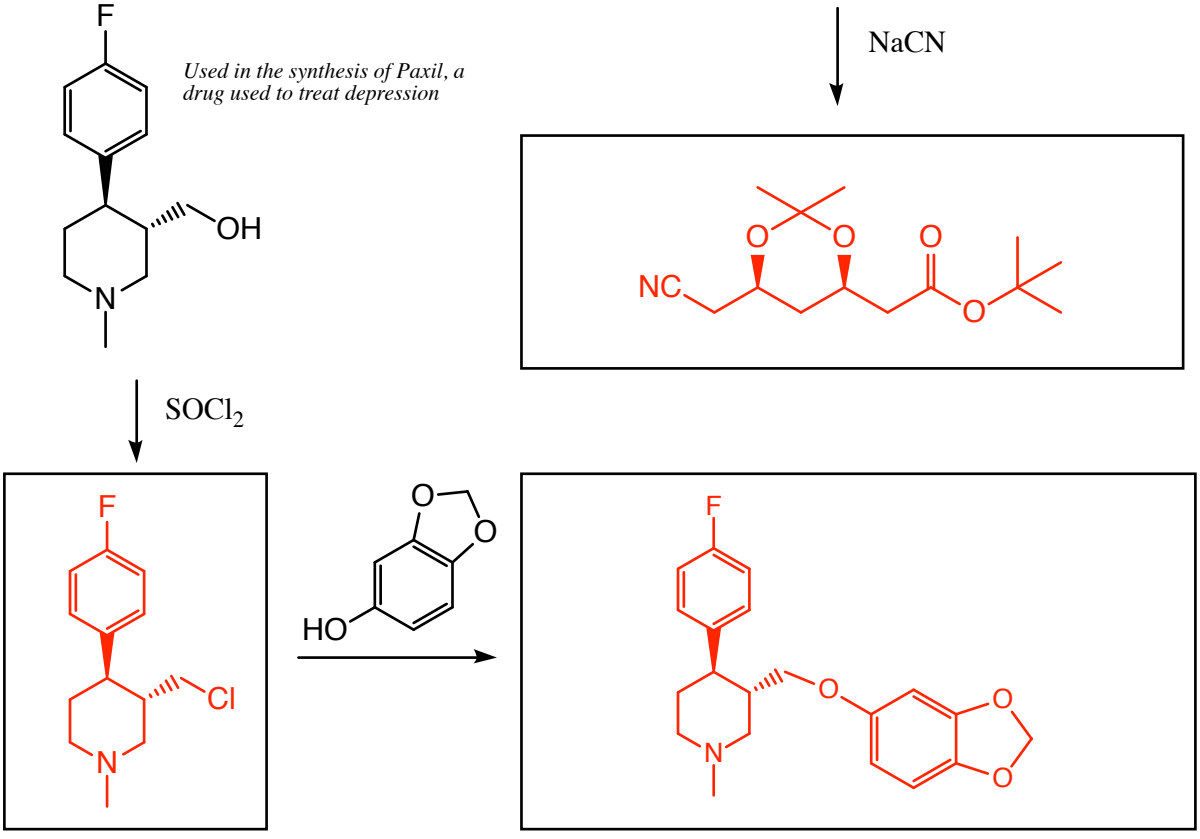
Used in the synthesis of Fluticasone (Flonase), a drug used to treat asthma



Used in the synthesis of Lipitor

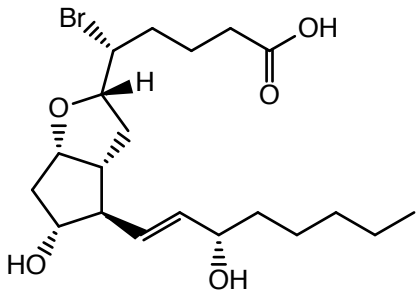


Used in the synthesis of Paxil, a drug used to treat depression



Reactions in the Context of Complex Molecules

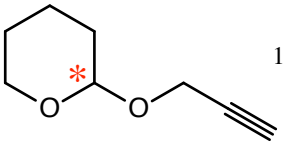
Used in the synthesis of several protaglandins



excess KO*t*Bu

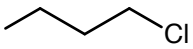
*t*BuOH

Used in the synthesis of protaglandin C_2

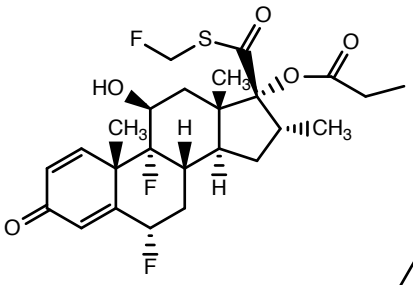


(racemic)

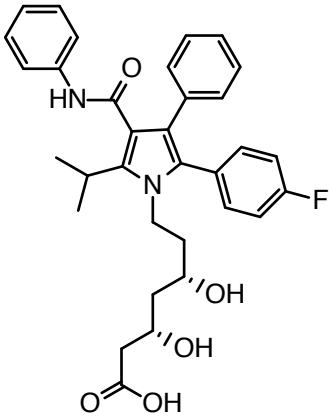
1. 1 eq. $NaNH_2$ THF (ether solvent)

2. 

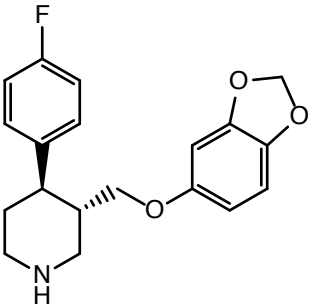
DMSO (polar aprotic solvent) | NaCN



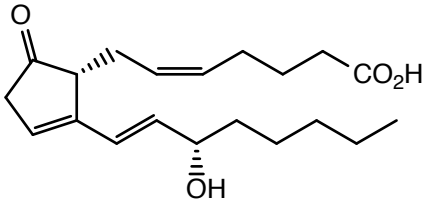
Fluticasone (Flonase)



Atorvastatin (Lipitor)



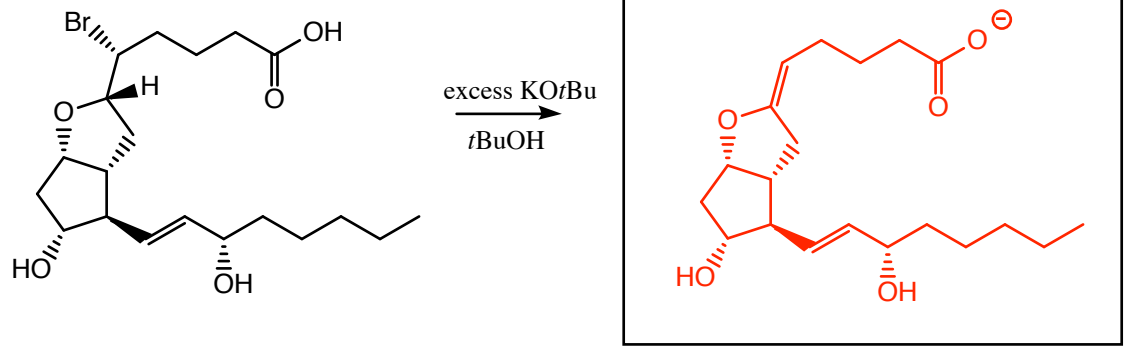
Paroxetine (Paxil)



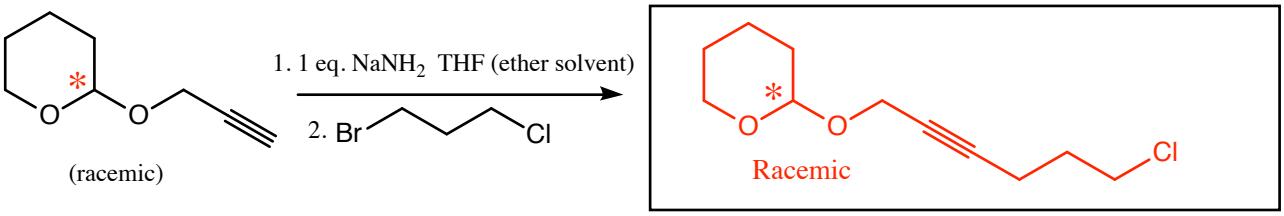
Prostaglandin C_2

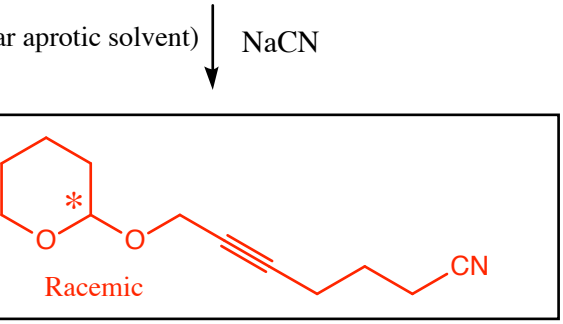
Reactions in the Context of Complex Molecules

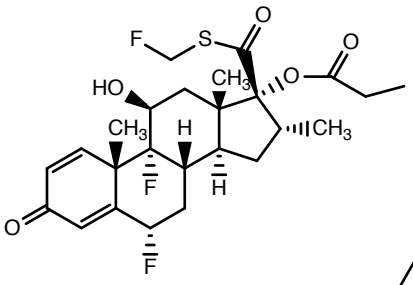
Used in the synthesis of several protaglandins



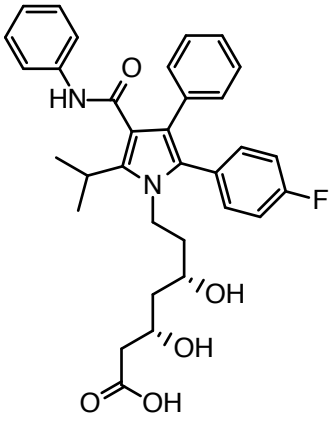
Used in the synthesis of protaglandin C_2



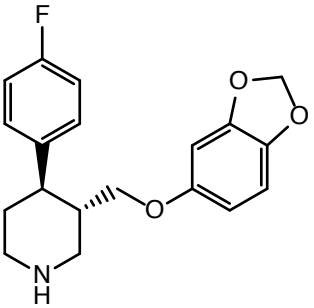




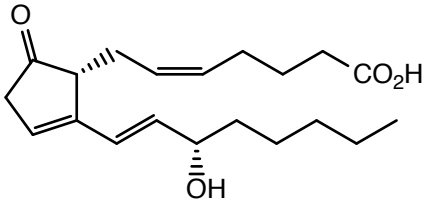
Fluticasone (Flonase)



Atorvastatin (Lipitor)



Paroxetine (Paxil)



Prostaglandin C_2

To understand NMR you need to know the following:

A. Physics: Moving charge generates a magnetic field, and a moving magnetic field causes charges to move in a conductor.

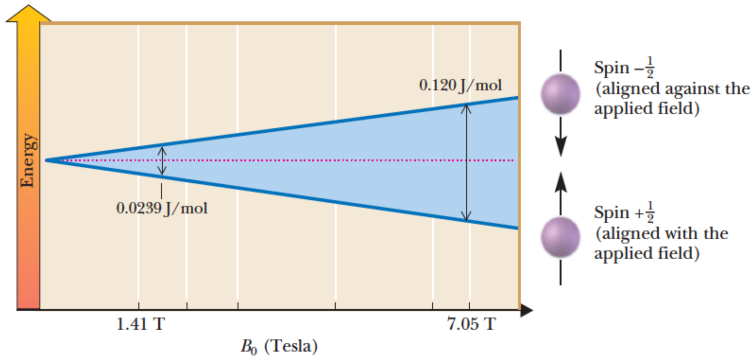
B. Atomic nuclei, like electrons, have a quantum mechanical property of "spin". Spin can be thought of as a small magnetic field around the nucleus created as if the positive charge of the nucleus were circulating.

C. NMR, nuclear magnetic resonance, is used to assign structures of organic molecules.

D. We care about the nuclei ^{1}H and ^{13}C since these are commonly found in organic molecules and they have spin quantum numbers of 1/2.

E. Nuclei with spin quantum number 1/2 are quantized in one of two orientations, "+1/2" (lower energy) or "-1/2"(higher energy) in the presence of an external magnetic field, that is, with and against the external field, respectively.

F. **The difference in energy between the +1/2 and -1/2 nuclear spin states is proportional to the strength of the magnetic field felt by the nucleus.**

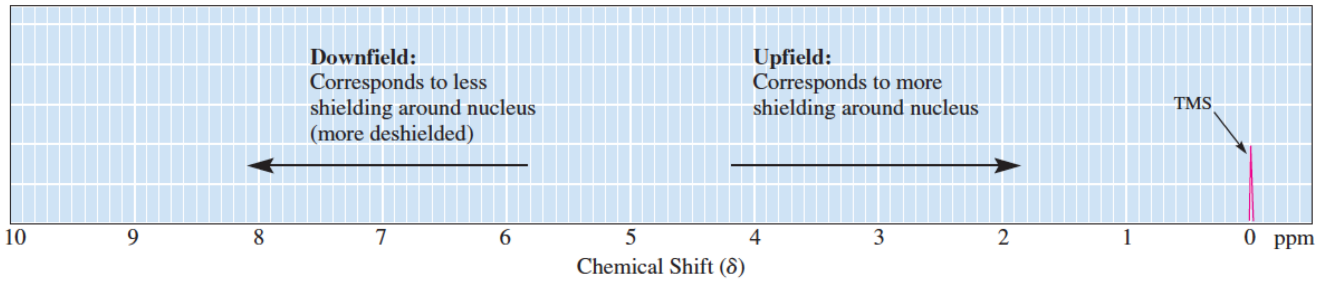


G. Electron density is induced to circulate in a strong external magnetic field, which in turn produces a magnetic field that opposes the external magnetic field. This **shields** nuclei from the external magnetic field. The greater the electron density around a nucleus, the more shielded it is, and the lower the energy (frequency) of electromagnetic radiation required to flip its nuclear spin.

H. The hybridization state of carbon atoms attached to an H atom influences shielding in predictable ways by removing differing amounts of electron density around adjacent nuclei.

I. Electron density in pi bonds also has a large effect on H atom shielding because pi electrons are more free to circulate in an a magnetic field compared to electron density in sigma bonds. Geometry of the pi bond is important.

J. Adjacent nuclei have magnetic fields associated with their spins. The spins of equivalent adjacent nuclei can be either +1/2 or -1/2, and at room temperature they are found in about a 50:50 mixture at any given nucleus (very slight excess of lower energy +1/2). These can add to give n+1 different spin combinations in the proportions predicted by Pascal's triangle. Each different spin combination produces a different magnetic field, which leads to n+1 splittings in the peaks of the NMR spectra of the adjacent (no more than three bonds away) nuclei.



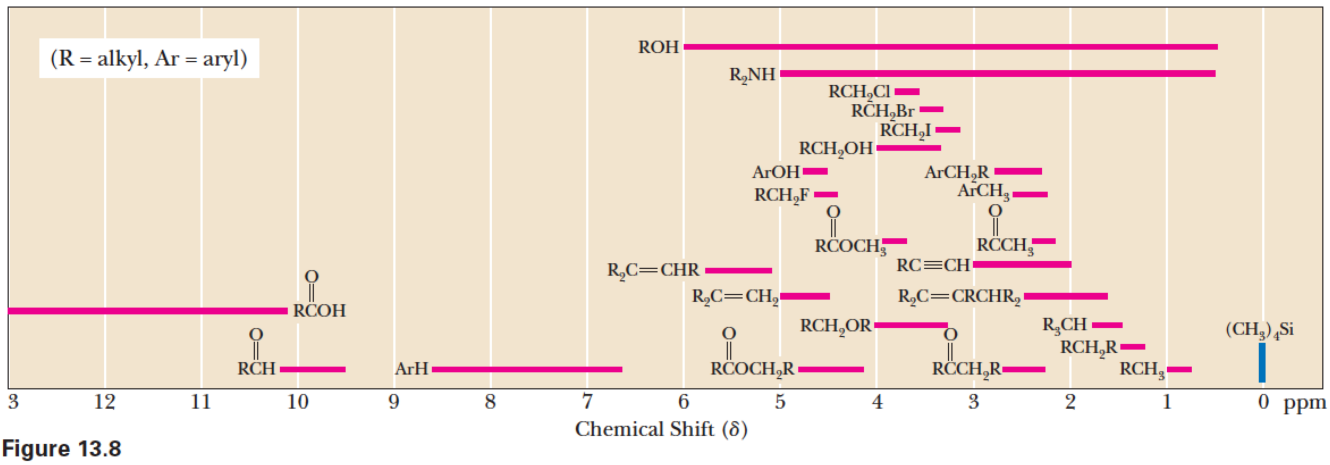


Figure 13.8
Average values of chemical shifts of representative types of hydrogens. These values are approximate. Other atoms or groups in the molecules may cause signals to appear outside of these ranges.

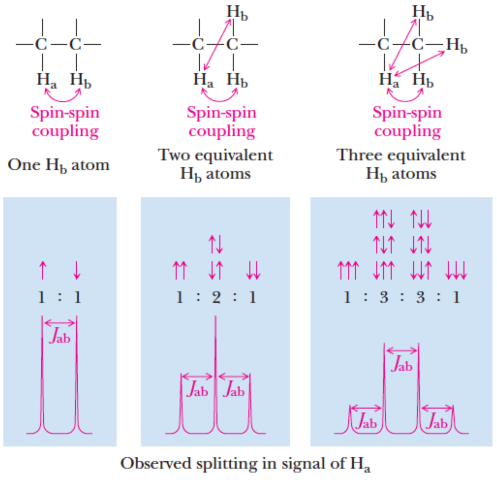


Figure 13.15
The origins of signal splitting patterns. Each arrow represents an H_b nuclear spin orientation.

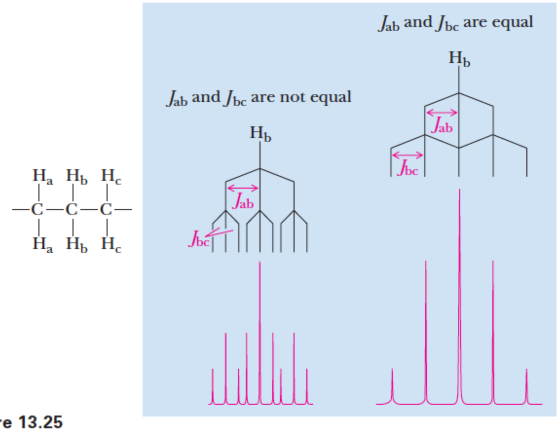


Figure 13.25
Simplification of signal splitting that occurs when coupling constants are the same.

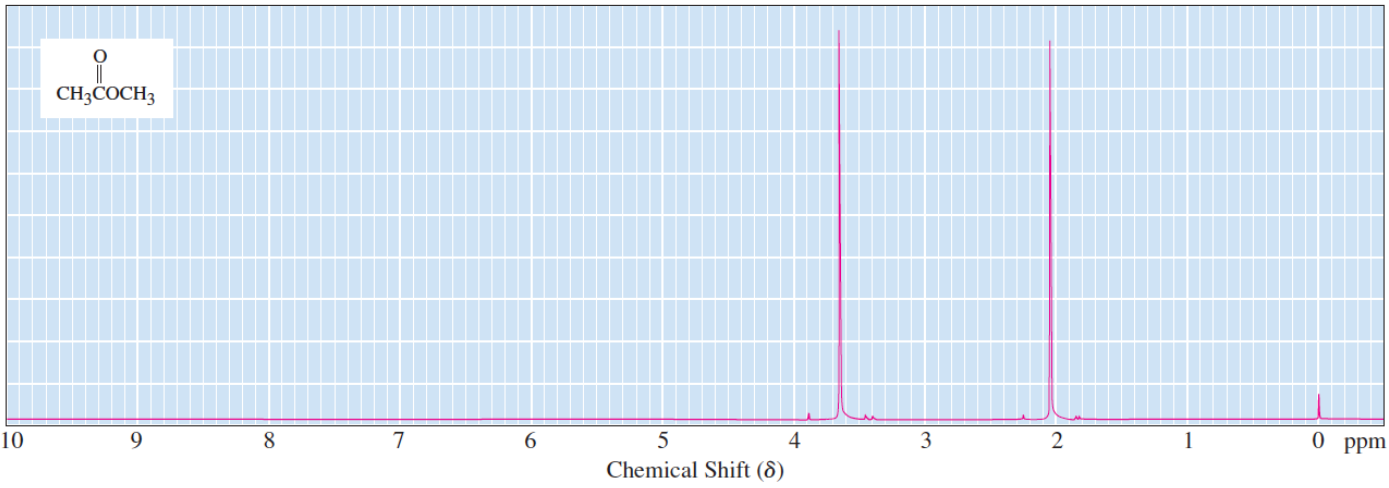


Figure 13.5
^{1}H-NMR spectrum of methyl acetate

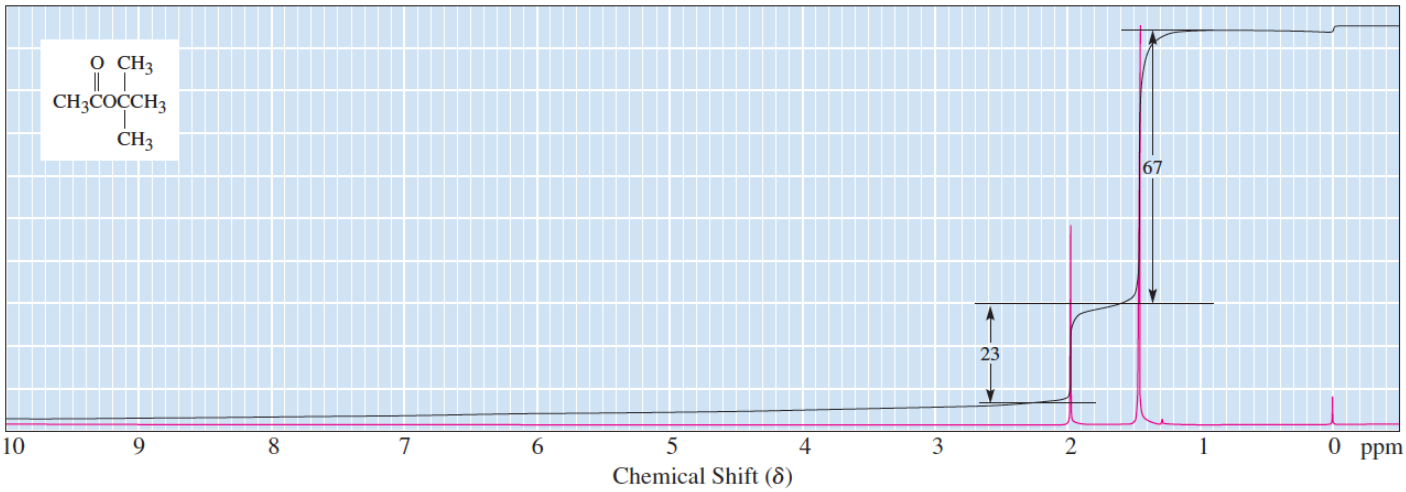


Figure 13.7
^{1}H-NMR spectrum of *tert*-butyl acetate showing the integration. The total vertical rise of 90 chart divisions corresponds to 12 hydrogens, 9 in one set and 3 in the other.

J. Adjacent nuclei have magnetic fields associated with their spins. The spins of equivalent adjacent nuclei can be either +1/2 or -1/2, and at room temperature they are found in about a 50:50 mixture at any given nucleus (very slight excess of lower energy +1/2). These can add to give n+1 different spin combinations in the proportions predicted by Pascal's triangle. Each different spin combination produces a different magnetic field, which leads to n+1 splittings in the peaks of the NMR spectra of the adjacent (no more than three bonds away) nuclei.

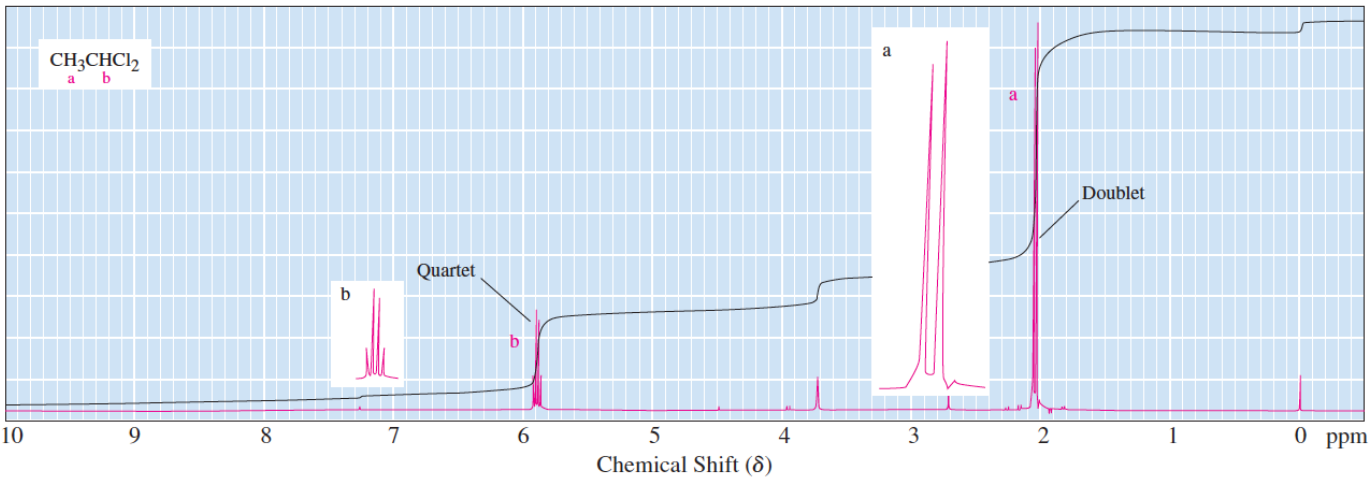


Figure 13.12
^{1}H-NMR spectrum of 1,1-dichloroethane.

K. THEORY: When there are two sets of adjacent H atoms, the number of peaks multiply. For example, a CH_2 group with a CH_2 group and a CH_3group on either side should show 3 x 4 = 12 splittings! You can say this group is a "triplet of quartets" (or a "quartet of triplets").

L. WHAT YOU WILL SEE IN REALITY : For alkyl groups complex splittings simplify because coupling constants ("J") are all about the same. In practice, if there are n adjacent H atoms, equivalent or not, you will see n+1 peaks. This is an approximation, but almost always true on spectra taken with all but the most sophisticated NMR spectrometers.

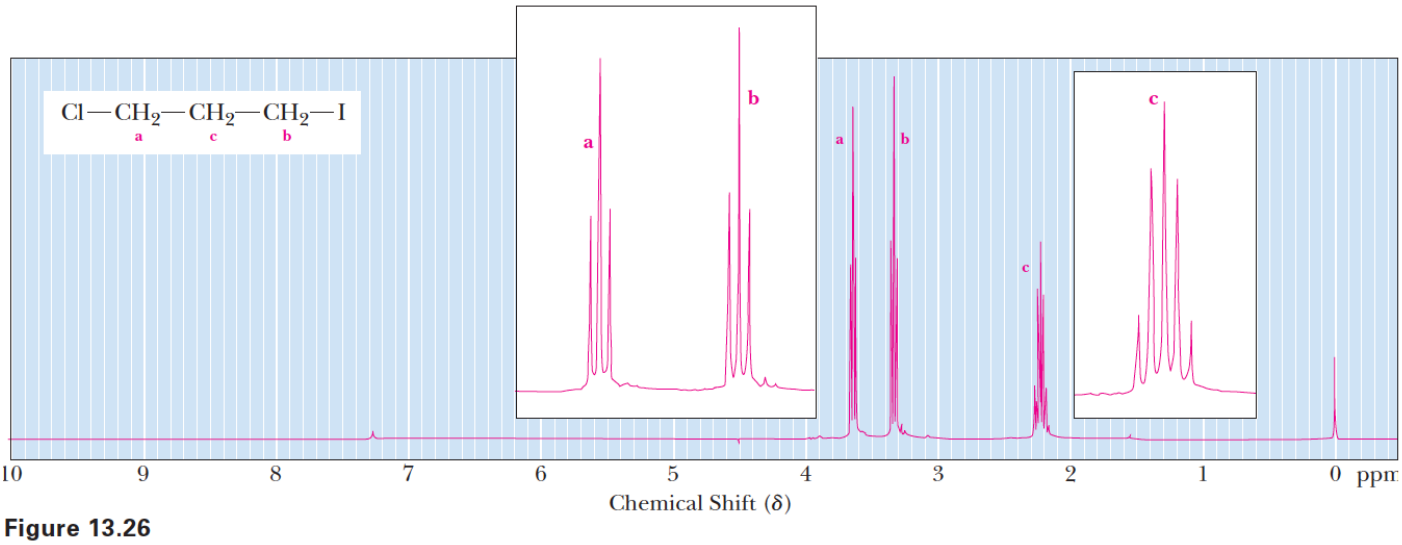
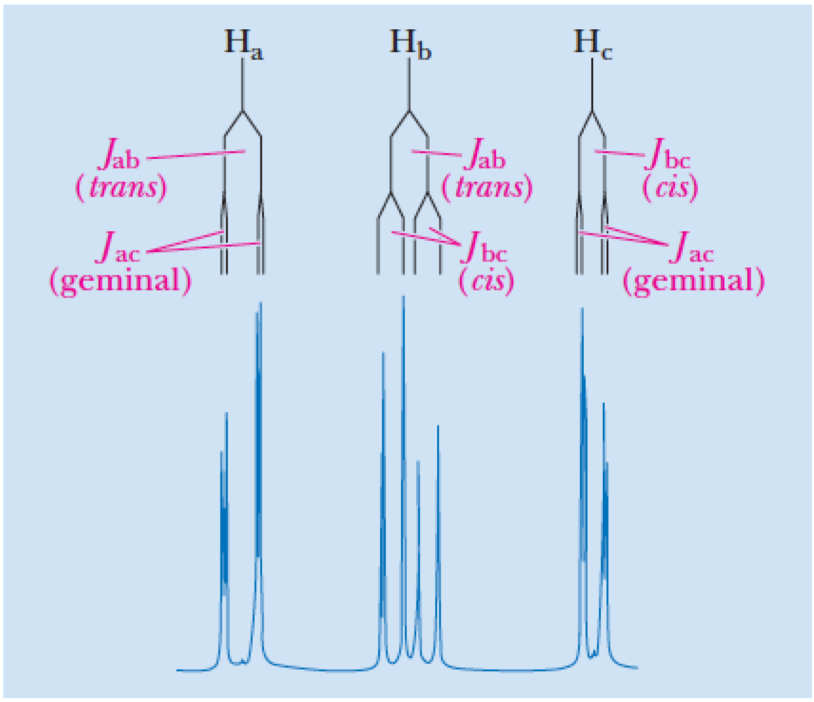


Figure 13.26
300 MHz ^{1}H-NMR spectrum of
1-chloro-3-iodopropane

M. For alkenes or ring structures such as cyclopropanes the splitting does not simplify (no bond rotation) and you see full multiplicative splitting ("doublet of doublets", etc.) Click here to go to Pictures of the Day for today in which the NMR spectra for an alkene and a cyclic structure are explained.Geminal coupling can be important for rings and alkenes.



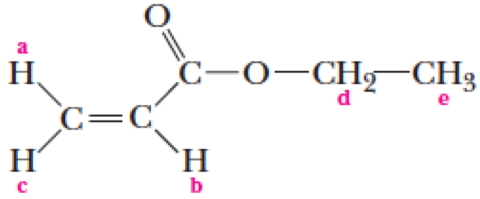


Figure 13.22
Tree diagrams for the complex coupling seen for the alkenyl H atoms in the ^{1}H-NMR spectrum of ethyl propenoate.

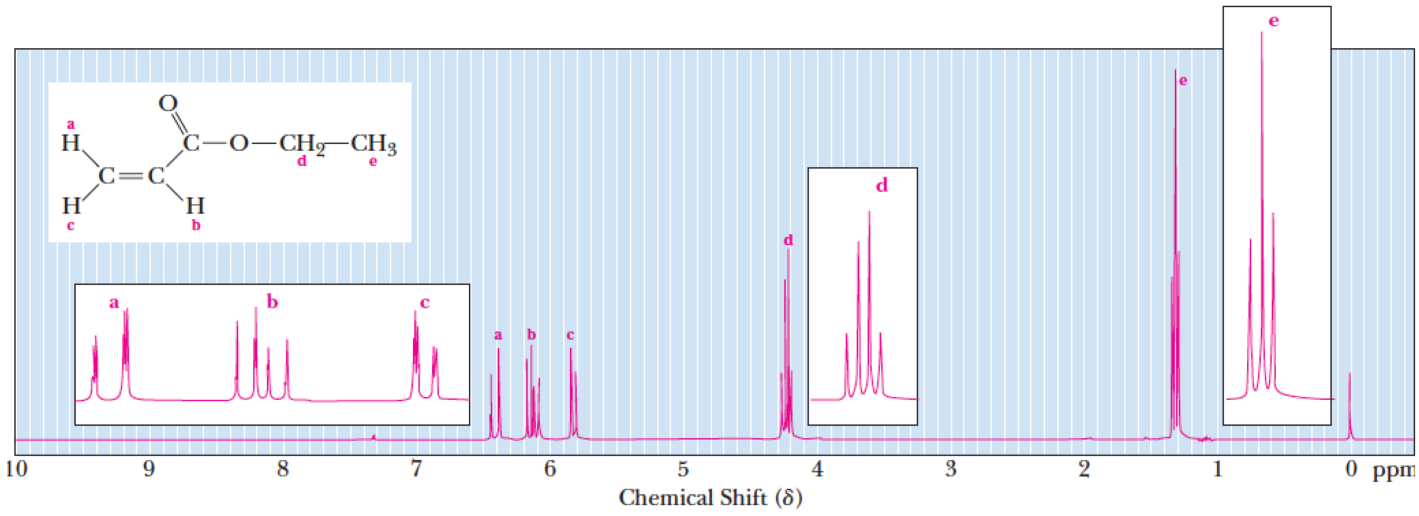


Figure 13.21
300 MHz ^{1}H-NMR spectrum of ethyl propenoate.

More NMR Essentials:

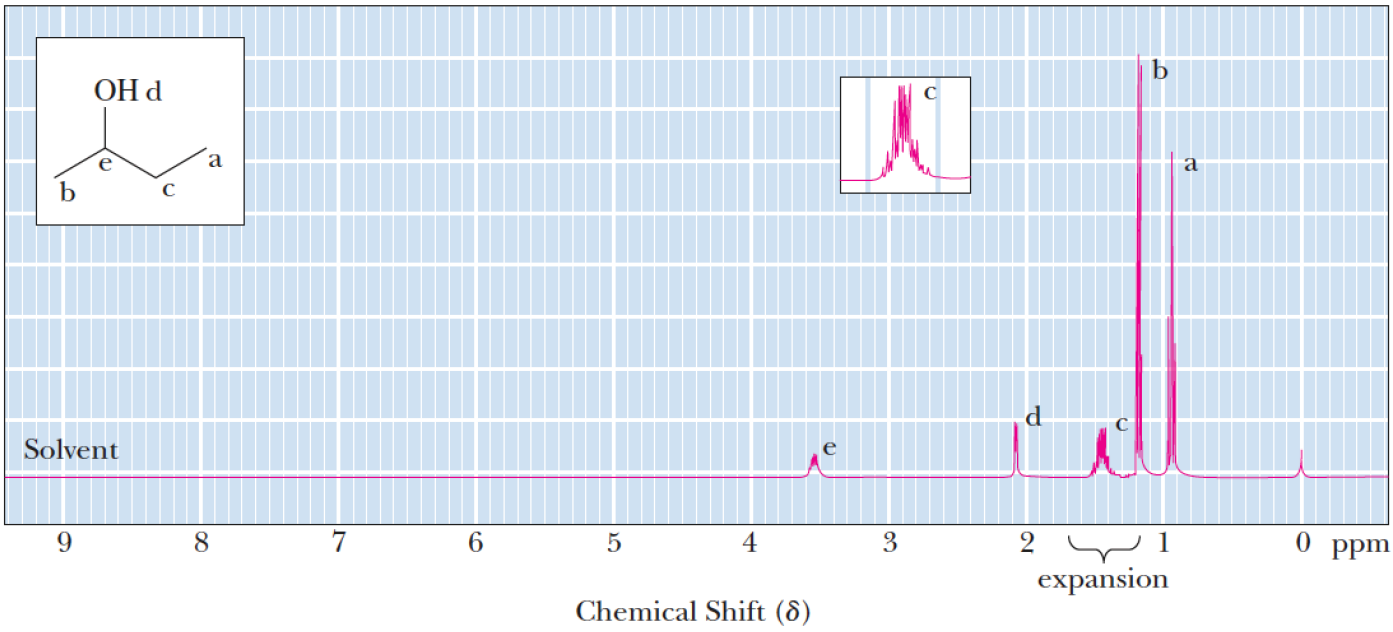
N. Non-equivalent H atoms on the same C atom can split each other (called geminal coupling), for example on alkenes or small rings. This coupling usually has very small coupling constants, so is difficult to see on some spectra.

O. Deuterium atoms do not show up in ^{1}H-NMR spectra, so deuerated solvents are used to dissolve NMR samples.

P. The H atoms of relatively acidic functional groups (alcohols, carboxylic acids, amines) exchange rapidly, so they often do not split adjacent protons, and they can be replaced (signal disappears) with deuterium by adding a drop of D_2O to the NMR sample.

Q. H-bonding changes the location of a signal for H-bonding groups in a concentration dependent manner explaining why -OH and -NH_2 group signals can vary so much in location.

R. The splitting of a -CH_2- group adjacent to a chiral center will be "messed up", that is split into many peaks. This is useful for identifying chiral centers in molecules.



S. When solving NMR spectra problems:

1) Determine number and relative integrations of signals predicted for a given structure
2) Make sure the splitting pattern matches with the spectrum for each signal and
3) If the number and relative integrations as well as splitting patterns match with the spectra, compare expected chemical shifts with those of the signals in the spectra.

The popular medical diagnostic technique of magnetic resonance imaging (MRI) is based on the same principles as NMR, namely the flipping (i.e. resonance) of nuclear spins of H atoms by radio frequency irradiation when a patient is placed in a strong magnetic field. Magnetic field gradients are used to gain imaging information, and rotation of the gradient around the center of the object gives imaging in an entire plane (i.e. slice inside patient). In an MRI image, you are looking at individual slices that when stacked make up the three-dimensional image of relative amounts of H atoms, especially the H atoms from water and fat, in the different tissues [Memorize the preceding passage, as it will be worth 14 points on the final. No I am not kidding, 14 points right there.]