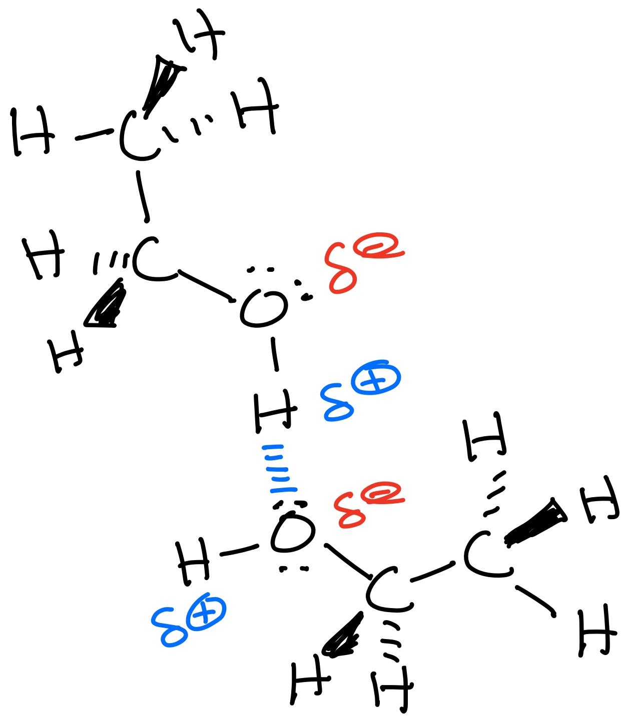
Alcohols $\rightarrow$ R–Ö–H

The OH group can take part in hydrogen bonding



Consequence $\rightarrow$ These molecules are "sticky"

$\Rightarrow$ High Boiling Points

$\Rightarrow$ Good solvent for cations, anions and other polar molecules

Accelerate $S_N1/E1$ reactions!

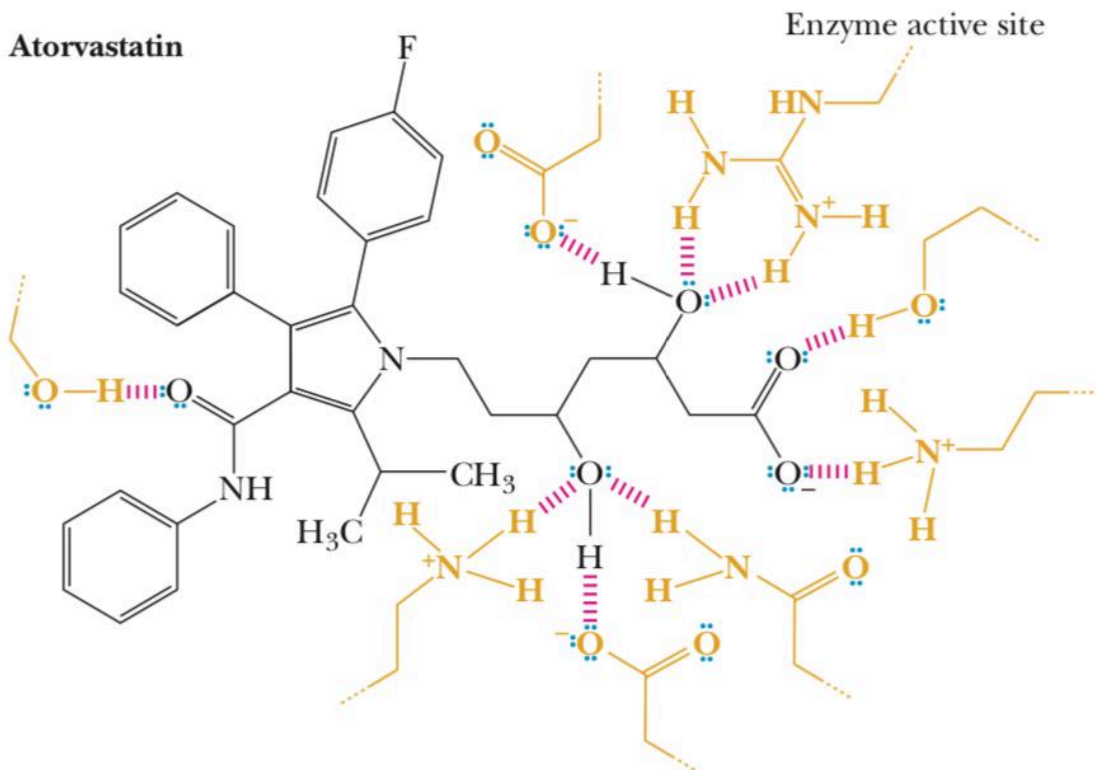


Figure 2
Hydrogen bonding (shown in red) between atorvastatin and the functional groups at the active site of the enzyme HMG-CoA reductase. The nine hydrogen bonds (shown in red), many of which involve hydroxyl groups on atorvastatin or the enzyme surface, help to provide the specificity that directs the binding of the drug to its target enzyme.

Hydrogen bonds between drug molecules and key amino acids of the protein target → Designed on purpose to keep the drug "stuck" to the protein

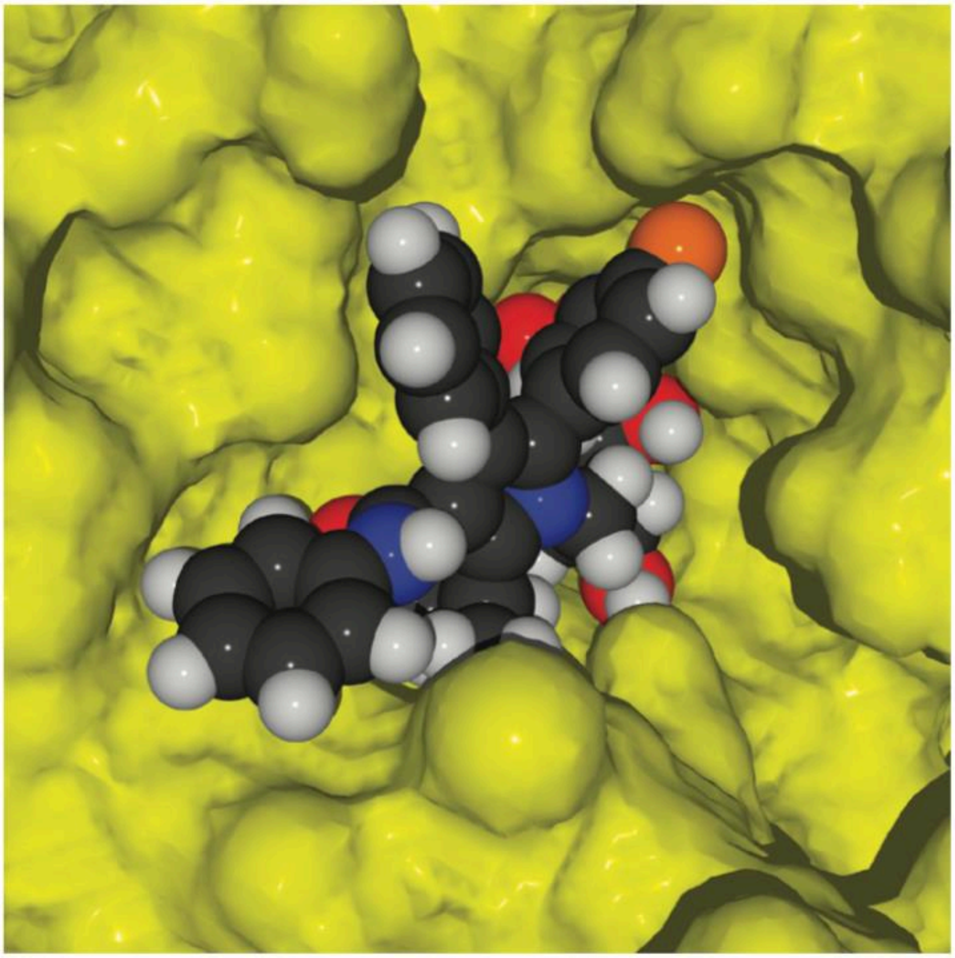


Figure 1

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.

The drug molecule must fit perfectly in three-dimensional space → like a key fits in a lock

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Alcohols → Acidity and Basicity

$$R-CH_2-OH \rightleftharpoons R-CH_2-\ddot{\underset{..}{O}}:^{\ominus} + H^{\oplus}$$

pKa ≅ 16-17

Strong Base

$$R-CH_2-SH \rightleftharpoons R-CH_2-\ddot{\underset{..}{S}}:^{\ominus} + H^{\oplus}$$

pKa ≅ 8-12

Weaker base

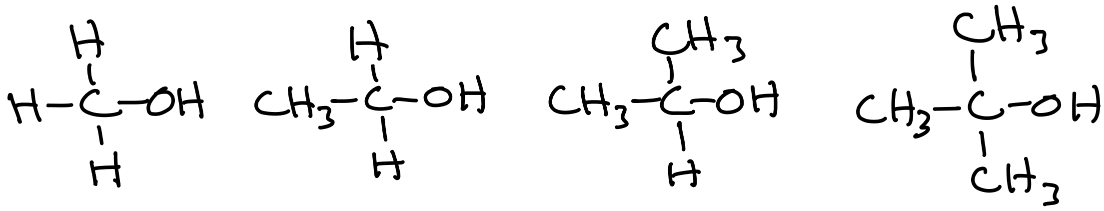
Notice This → Na°, K°, Li°

$$2CH_3OH + 2Na^{\circ} \longrightarrow 2CH_3O^{\ominus}Na^{\oplus} + H_2\uparrow$$

gas

Useful to make alkoxides!

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



Methyl 1° 2° 3°

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

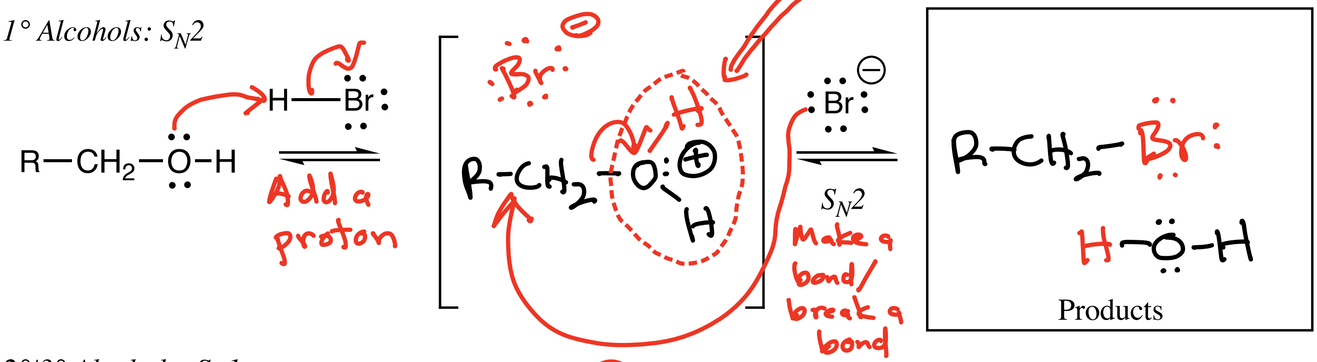
⇒ Recall, the -OH group is a weak nucleophile and weak base (in strong acid)

X = Cl, Br, I

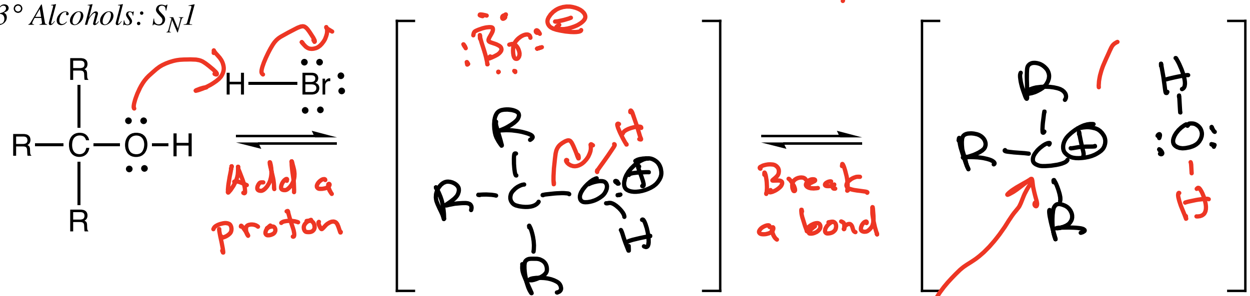
Alcohols + H-X

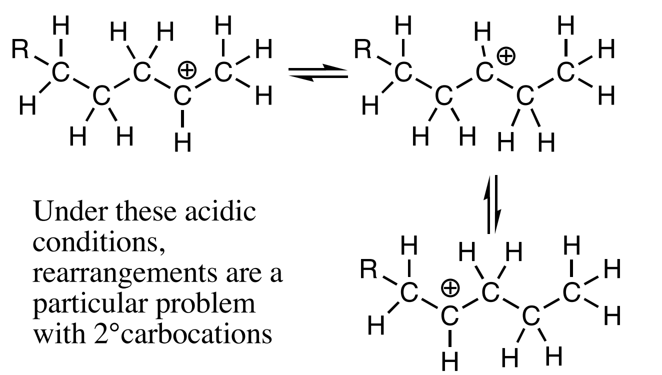
Good leaving group

1° Alcohols: S_N2



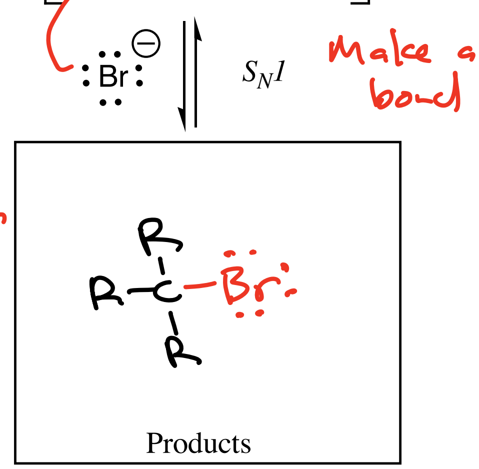
2°/3° Alcohols: S_N1





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

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

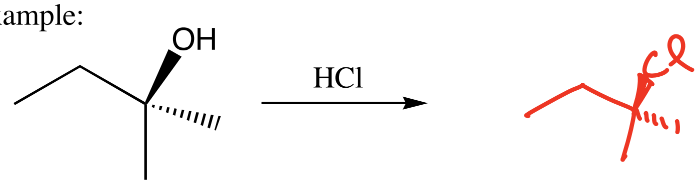


Summary: Reaction of primary alcohols → S_N2
Reaction of secondary/tertiary alcohols → S_N1
The -OH group is converted to a good leaving group by being protonated, followed by S_N2 or S_N1 substitution

Regiochemistry: N/A

Stereochemistry: Chiral tertiary alcohols give scrambled products ← S_N1

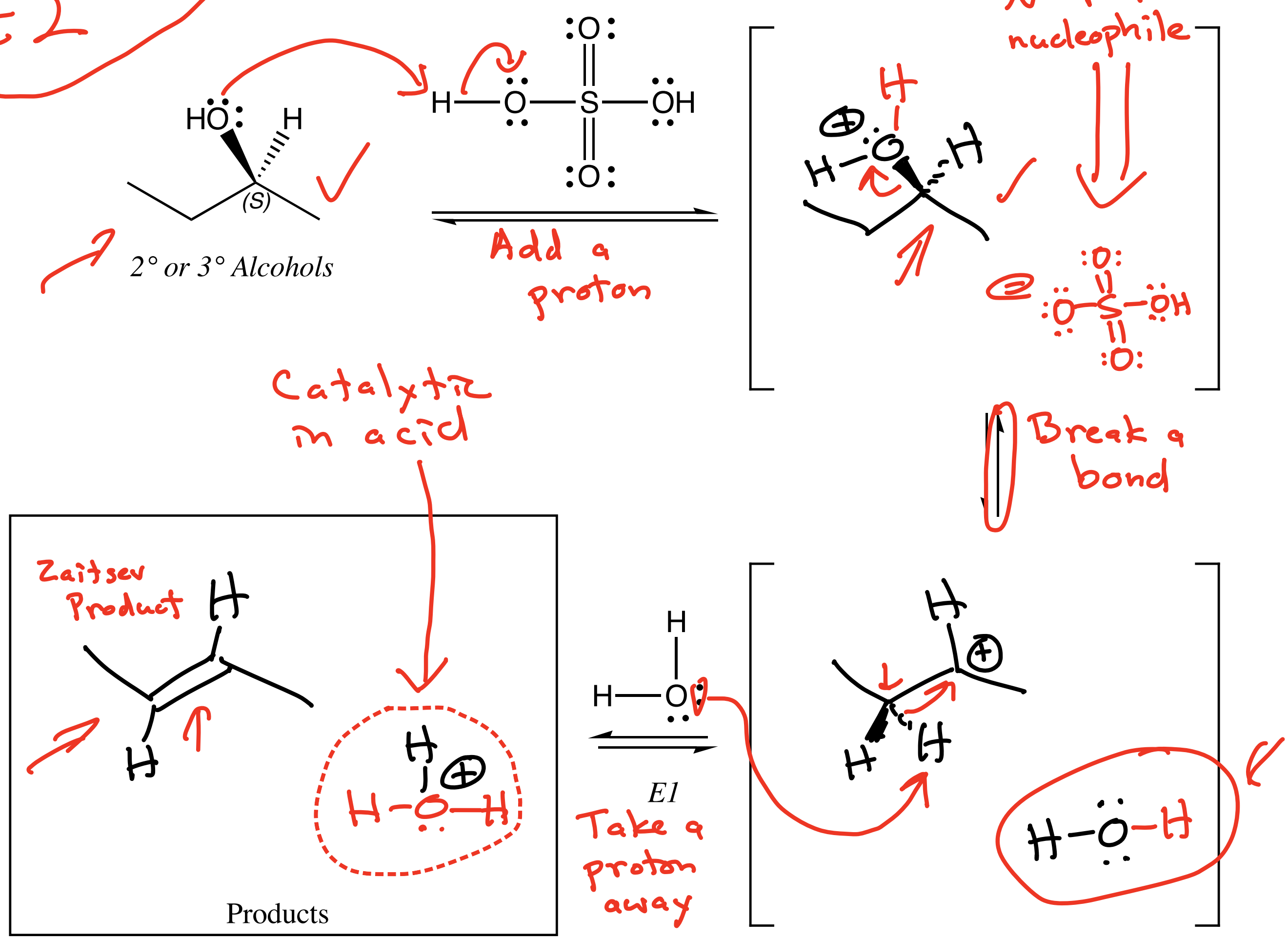
Example:



Not Chiral

1° alcohols react via E2

2° or 3° Alcohol Dehydration → E1

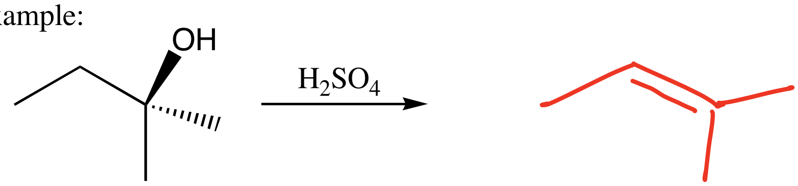


Summary:	The OH group is protonated in strong acid to make a good leaving group, water, which breaks a bond to give a carbocation that has a proton taken away to give the product alkene

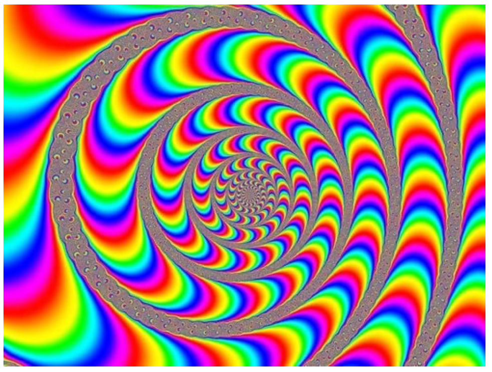
Regiochemistry:	Zaitsev's Rule

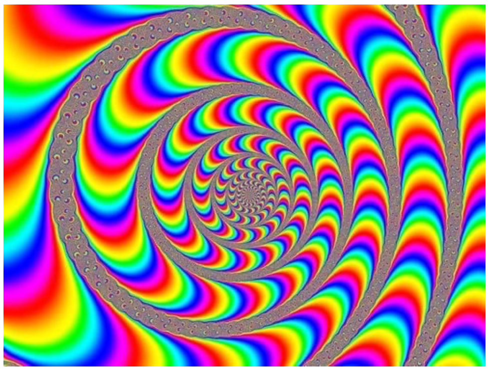
Stereochemistry:	N/A

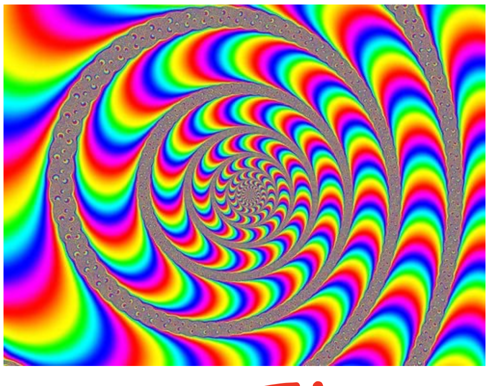
Example:

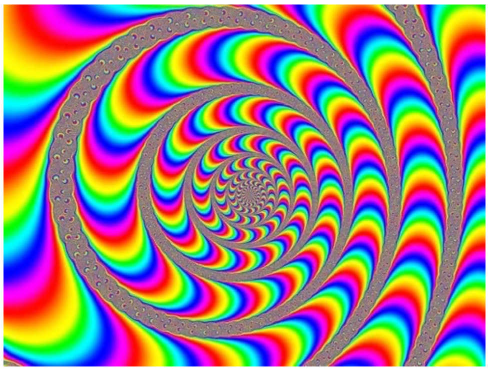


Flashback!!



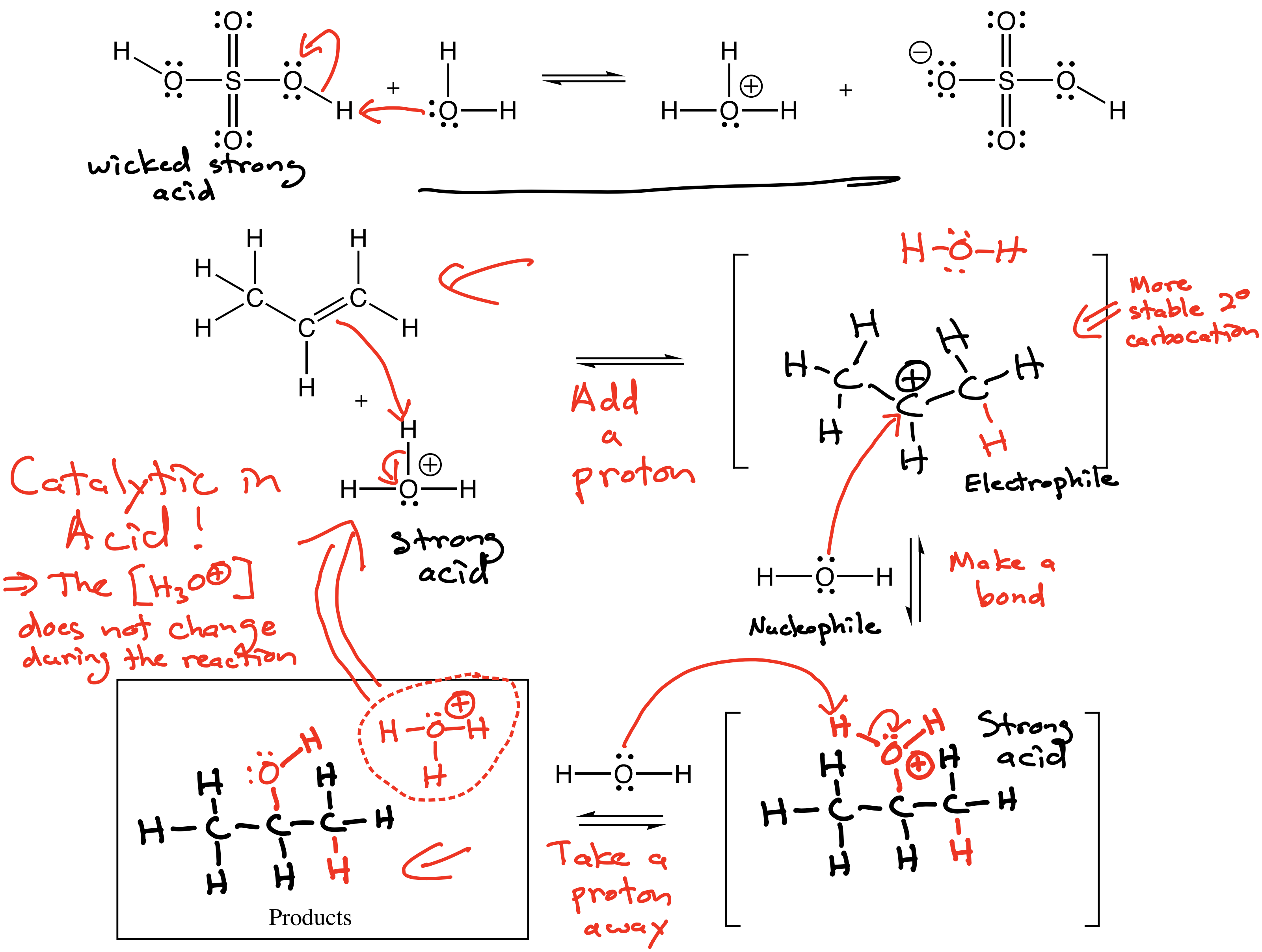






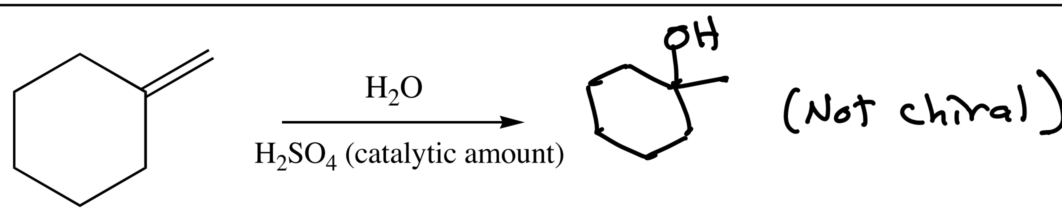
Flashback!!

Acid-catalyzed Hydration of an Alkene



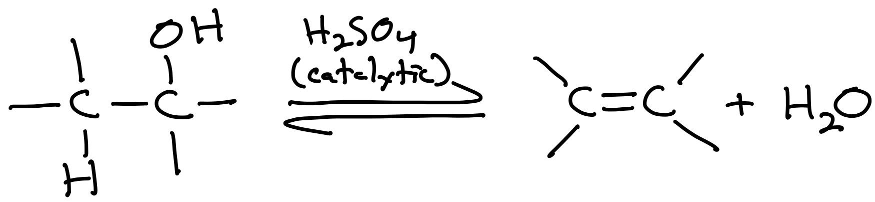
Summary: Proton adds to make a carbocation intermediate, water attacks to make a new bond, take a proton away to make the product alcohol. Catalytic in $H_3O^{\oplus}$
Regiochemistry: Markovnikov's Rule
Stereochemistry: Mixed (time capsule)

Example:



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

Microscopic Reversibility → Reversible reaction mechanisms have the same intermediates in both directions. → Compare the last two mechanisms!



This reaction is REVERSIBLE!

Le Chatlier's Principle ⇒

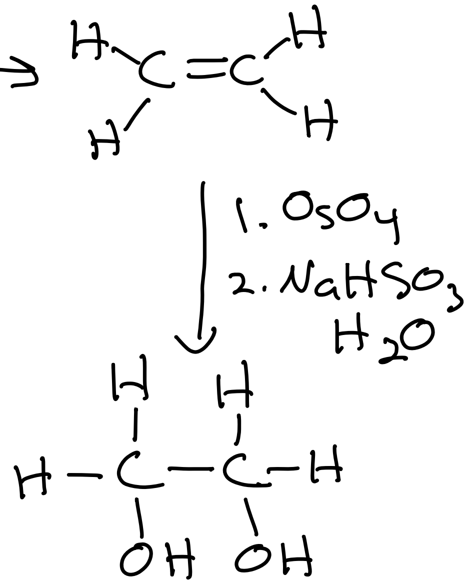
If we add water → we drive the reaction to the alcohol product

If we remove the water as it is formed → we drive the reaction to the alkene product

Anti-freeze

$CH_3CH_2OH \xrightarrow[\text{(catalytic)}]{H_2SO_4}$

"Vodka"



"Antifreeze"

35% – 95% ethanol

Usually ~40%

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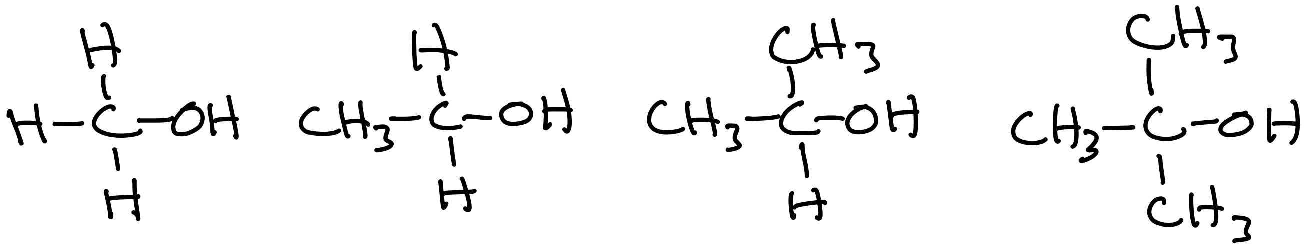
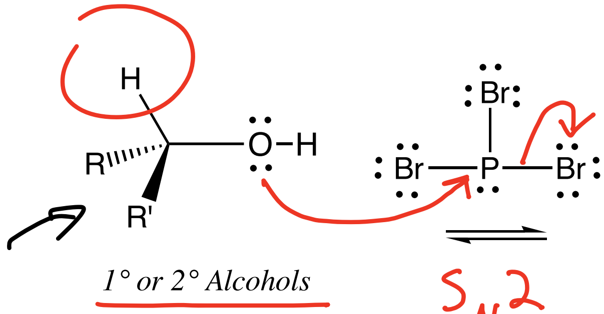
Alcohols → Reaction mechanisms depend on the number of alkyl groups attached on the C atom of C-OH bond.

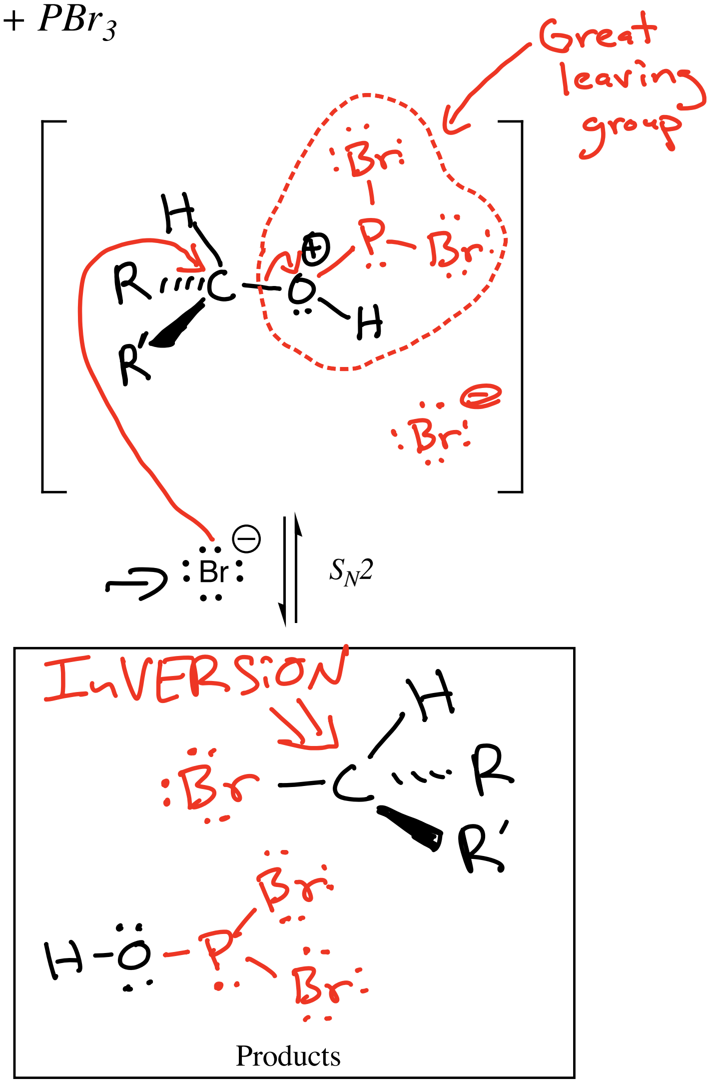


The -OH is not a leaving group but several reactions involve conversion of the -OH group into a good leaving group

Recall, the -OH group is a weak $\boxed{\text{nucleophile}}$ and weak base (in strong acid)

Alcohols + PBr_3





Does NOT work with 3° alcohols

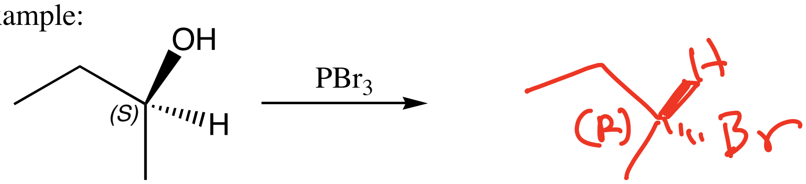
There is an analogous reaction with $SOCl_2$ that converts an -OH group into –Cl, also with INVERSION of stereochemistry

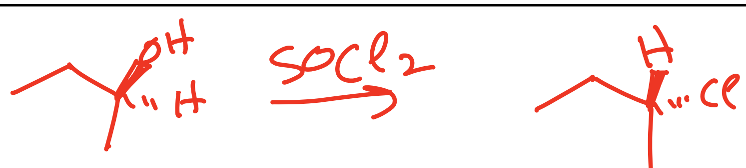
Summary: 1° or 2° alcohols react with PBr_3 via an S_N2 reaction at the P atom to create a great leaving group that undergoes an S_N2 reaction with Br^- at the C atom

Regiochemistry: N/A

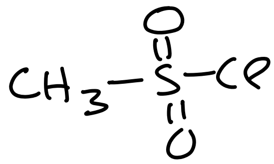
Stereochemistry: INVERSION

Example:

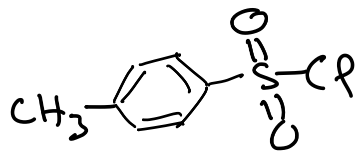




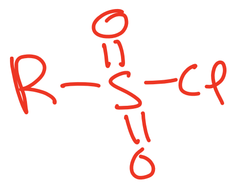
Alkyl Sulfonates

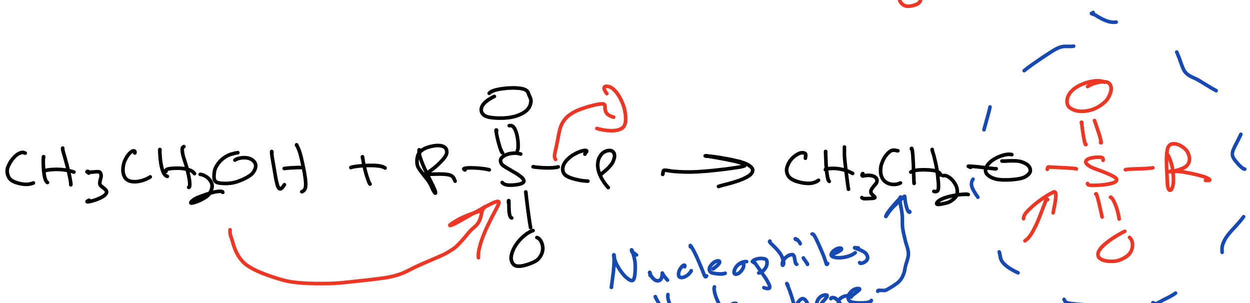


Methanesulfonyl Chloride



p-Toluenesulfonyl Chloride

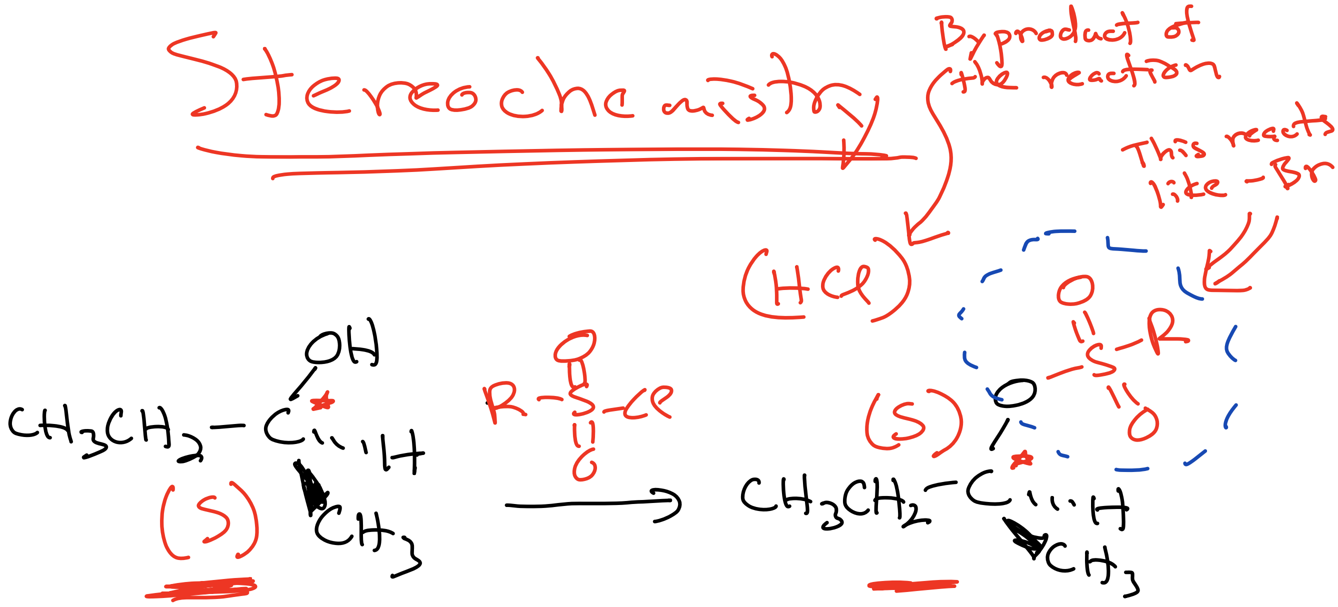




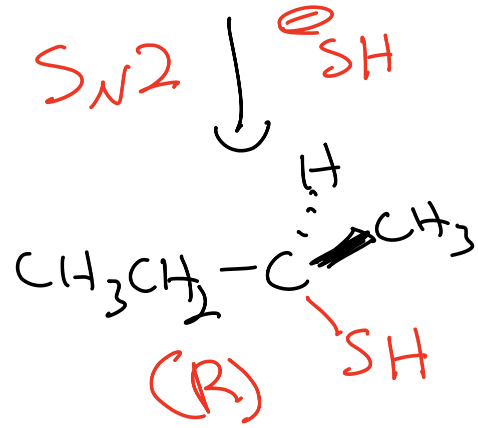
This can be isolated

Good Leaving Group

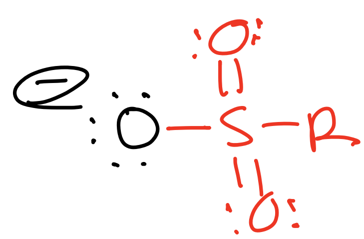
Stereochemistry

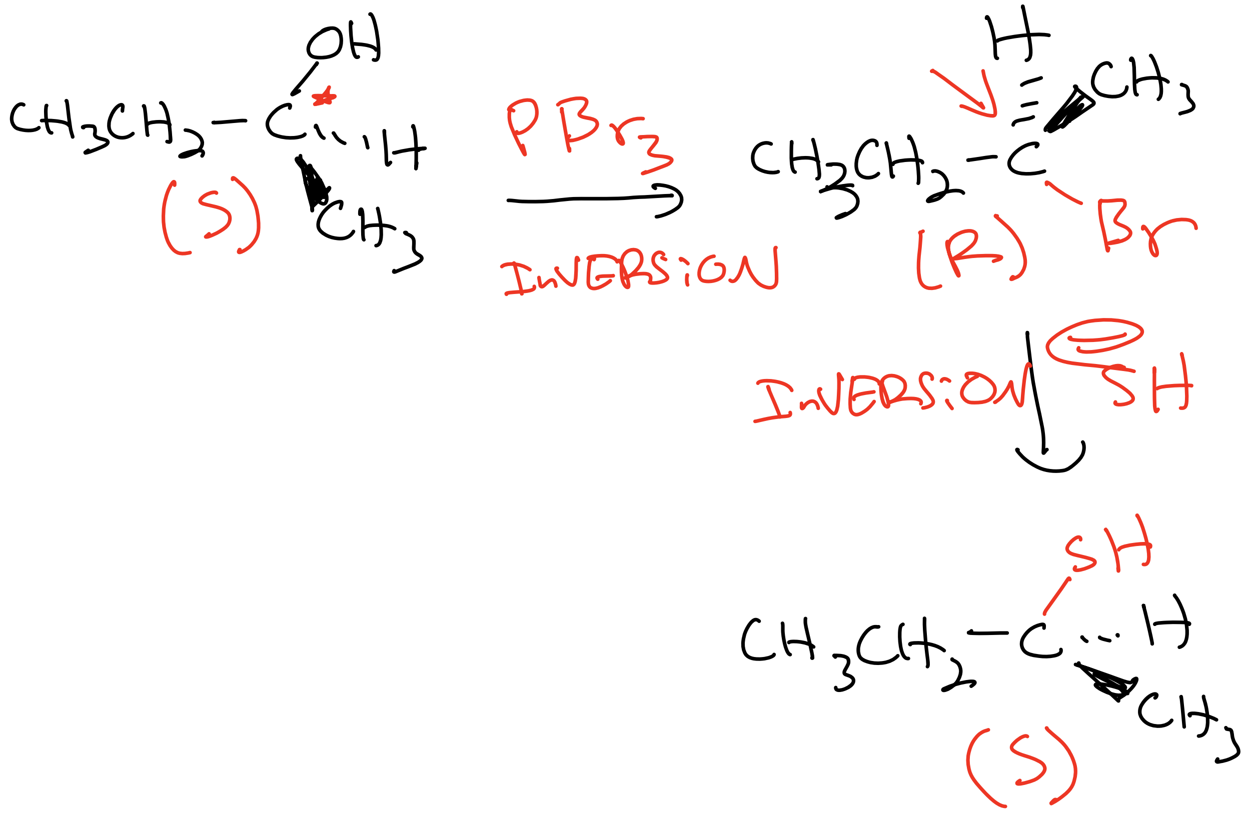


Net ⇒ INVERSION



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

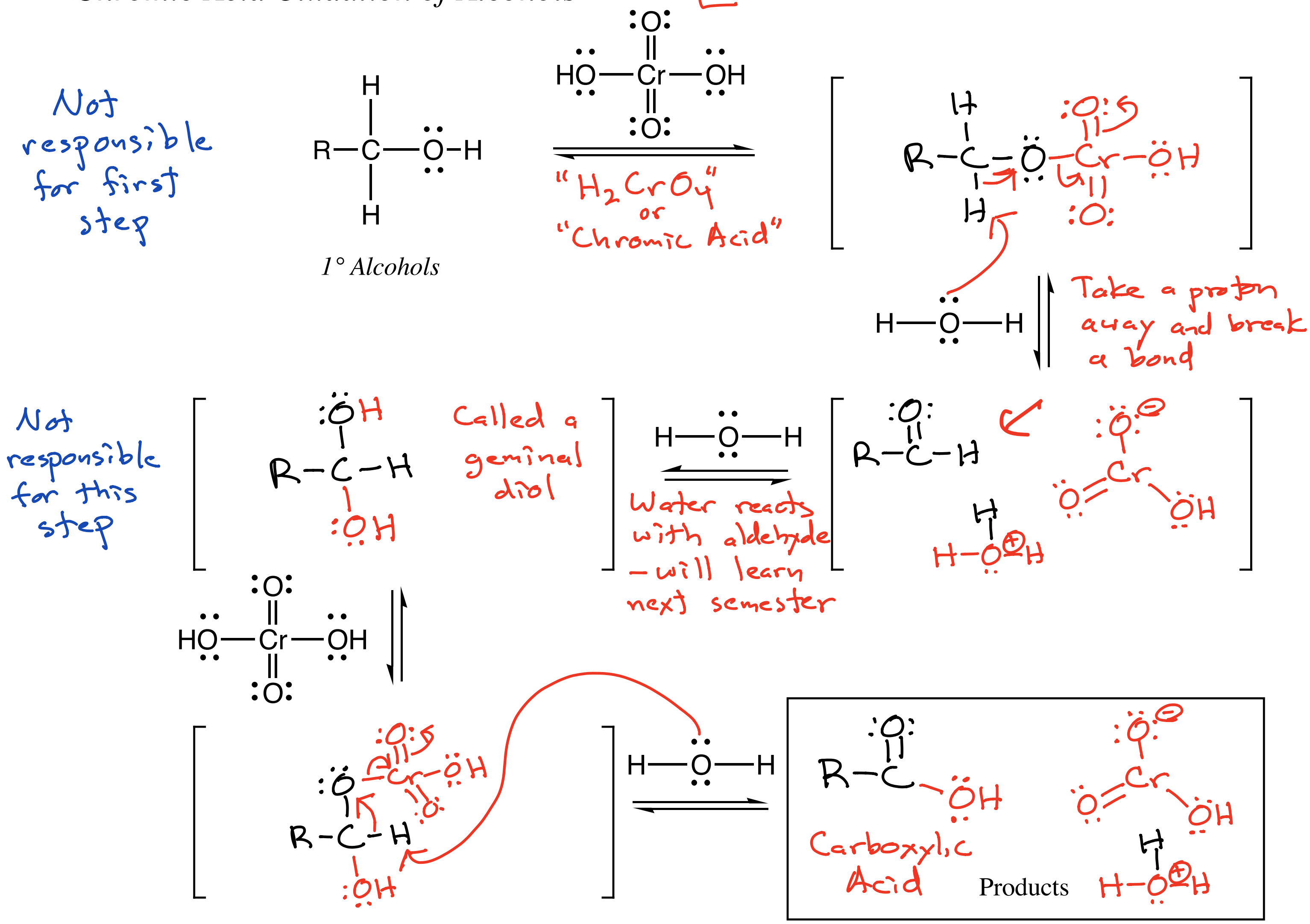




⟹ You can net invert or retain the stereochemistry of a chiral alcohol taking part in S_N2 reactions

Chromic Acid Oxidation of Alcohols

Called "Jones Reagent" ($CrO_3 + H_2O$ or $K_2Cr_2O_7$) + H_2SO_4



Summary:

$1°$ alcohols ⇒ Carboxylic Acid R-C(=O)-OH

$2°$ alcohols ⇒ Ketone R-C(=O)-R

$3°$ alcohols ⇒ NO REACTION

Regiochemistry: N/A

Stereochemistry: N/A

Example: