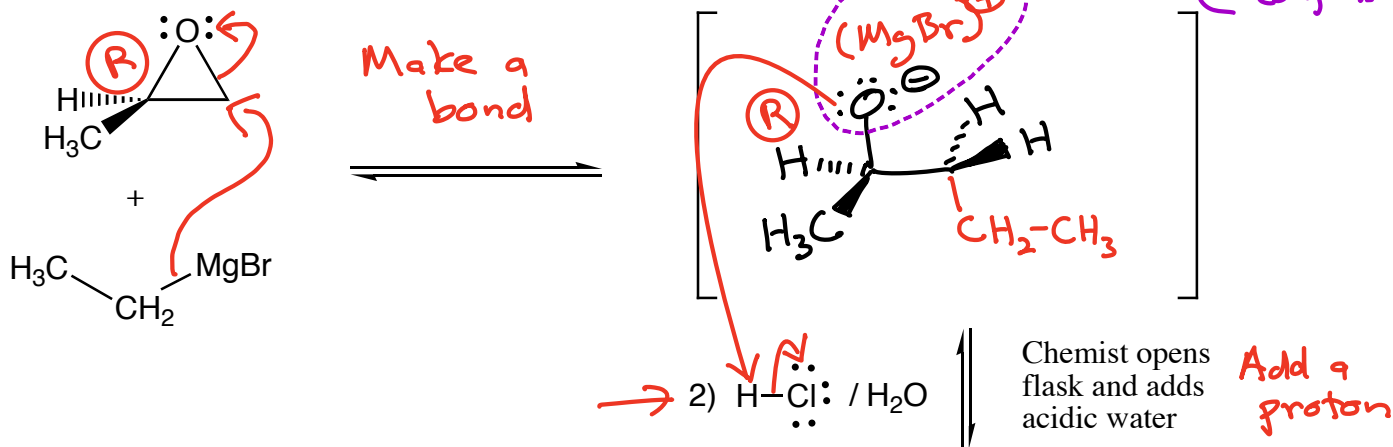


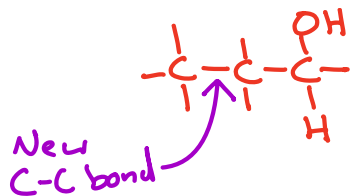
Organolithium and Gilman reagents react the same way as Grignard reagents in this reaction.

*Grignard Reagent Reacting with an Epoxide*

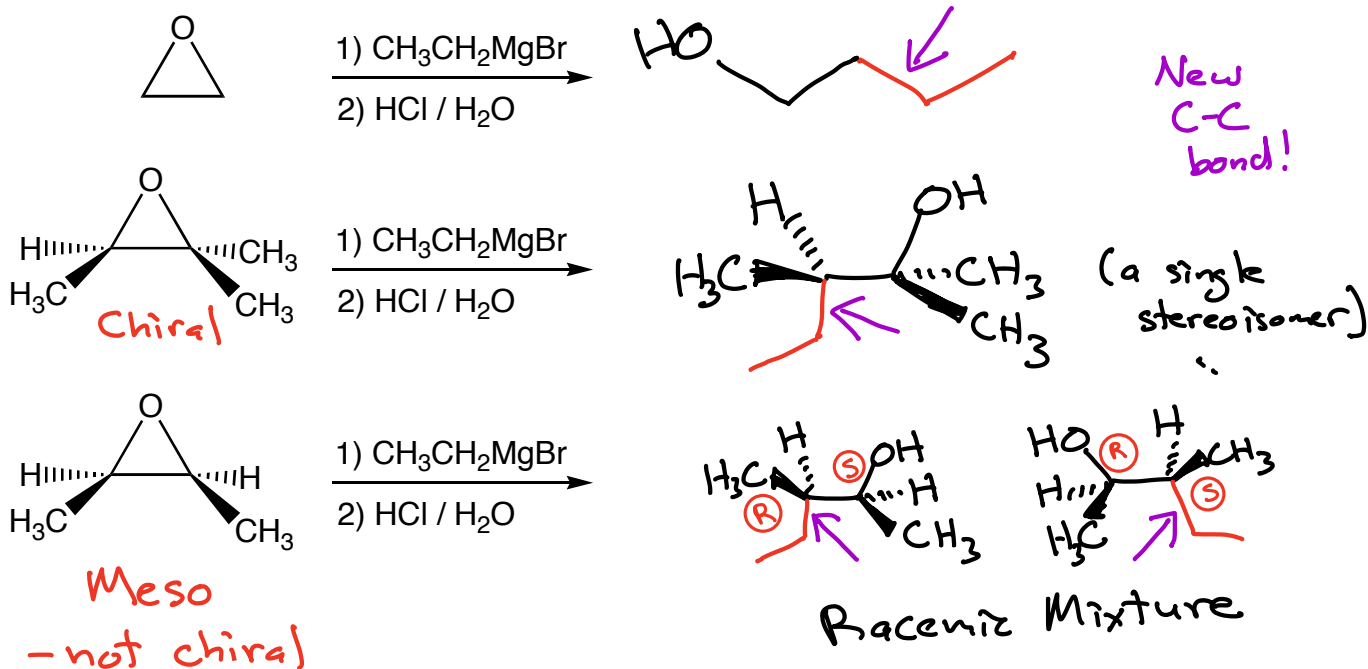
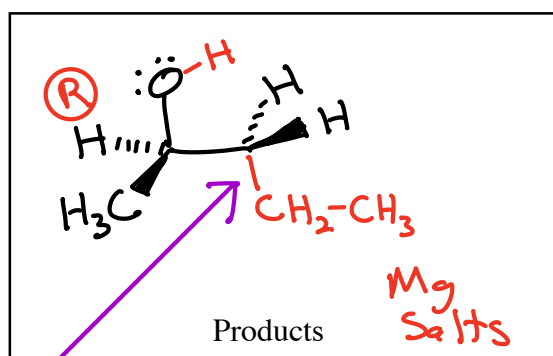


Key Recognition Element (KRE):

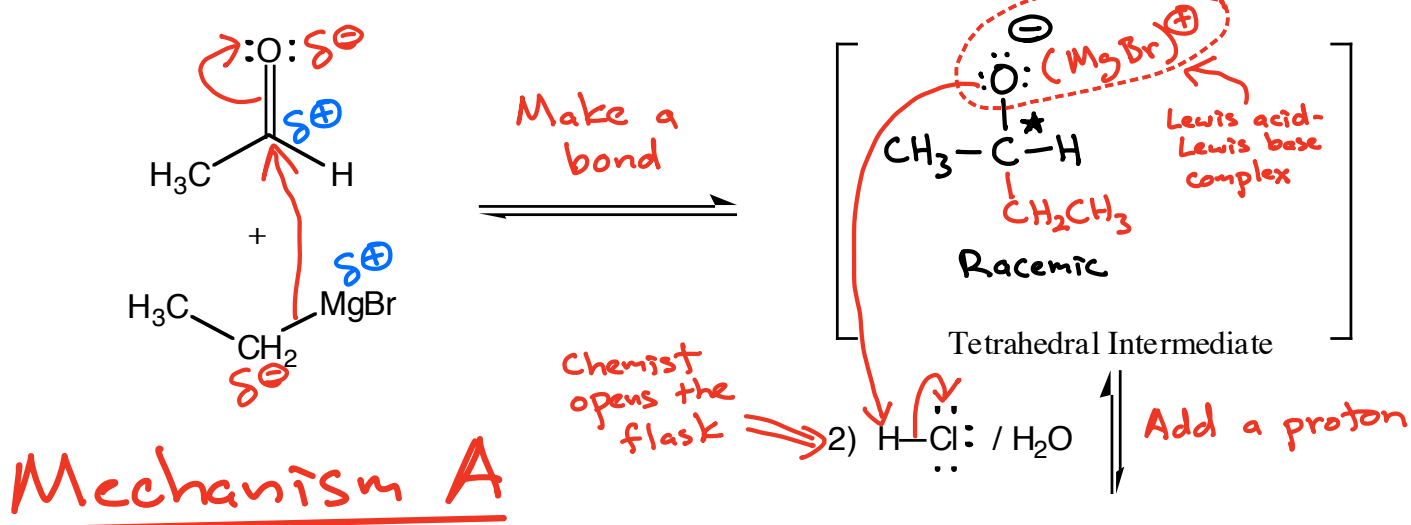
There is a new C-C bond that is two carbon atoms away from an OH group



New C-C bond!

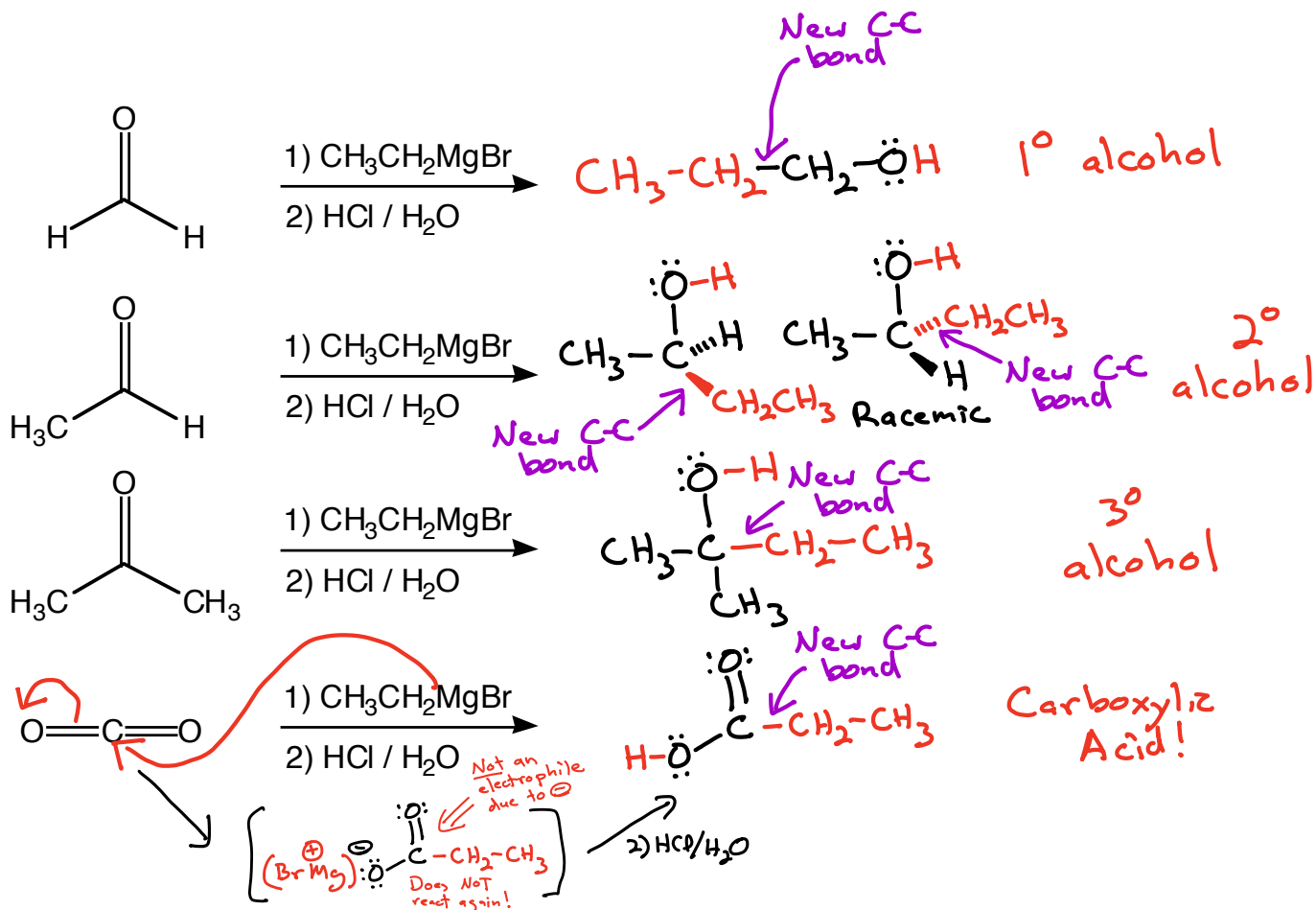
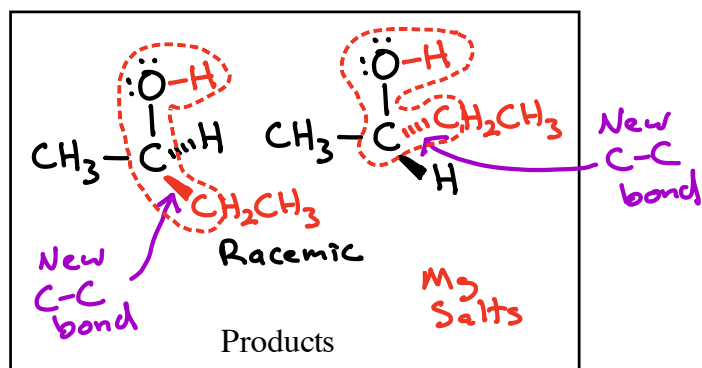


## Grignard Reagent Reacting with an Aldehyde or Ketone

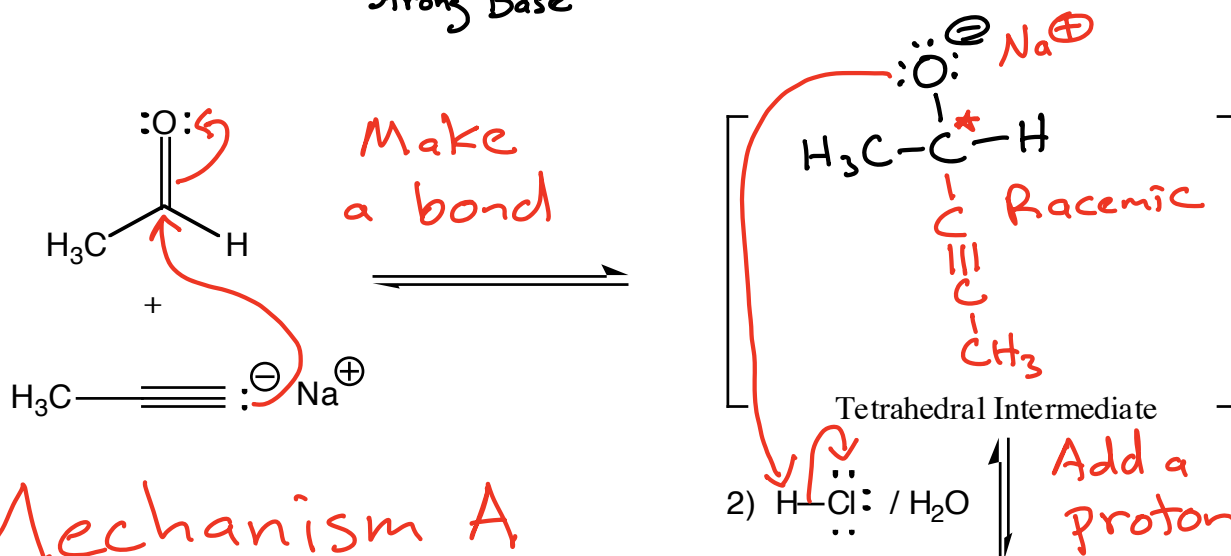
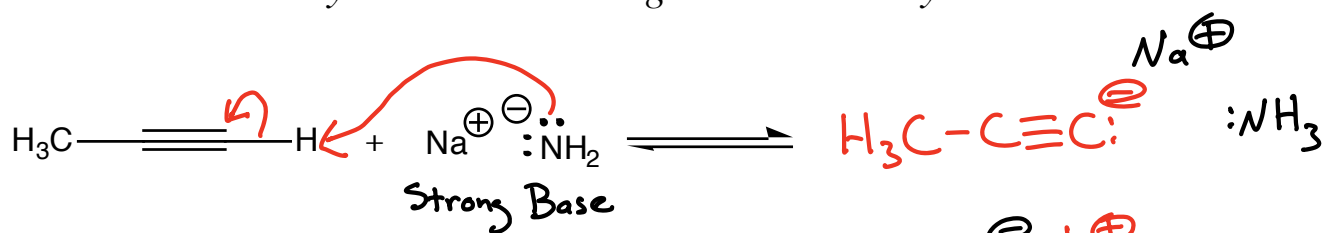


Key Recognition Element (KRE):

-OH group attached the same C atom as a new C-C bond



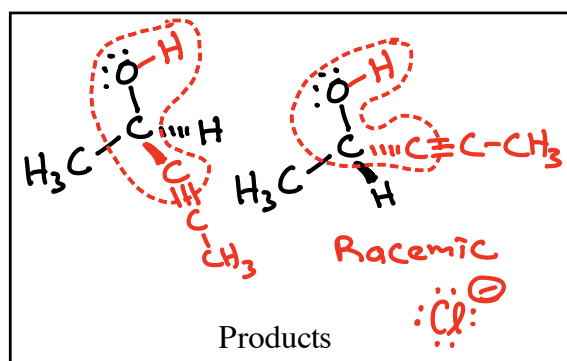
# Alkyne Anion Reacting with an Aldehyde or Ketone



## Mechanism A

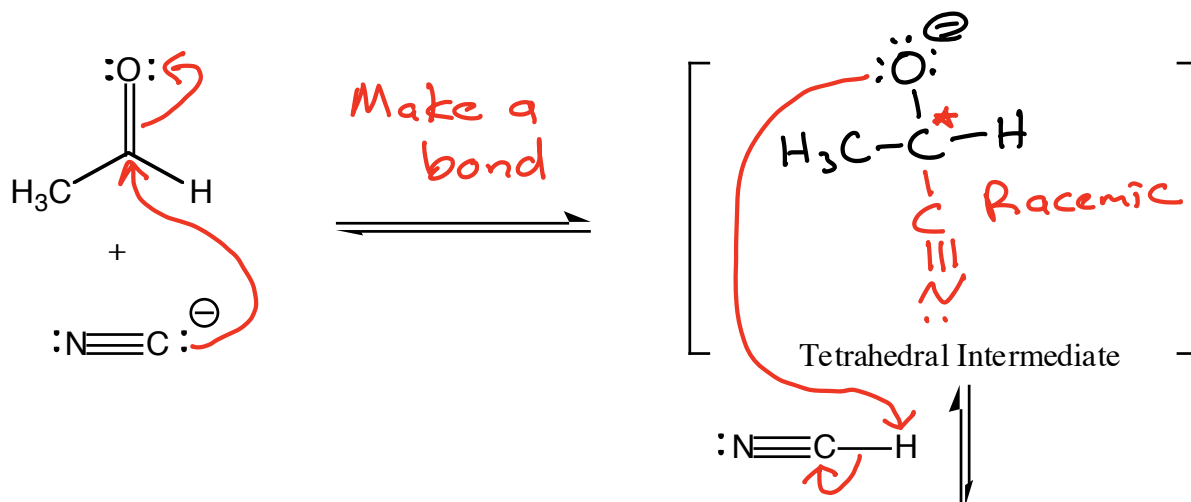
Key Recognition Element (KRE):

OH group on the carbon that makes a new C-C bond to an sp C atom (alkyne)



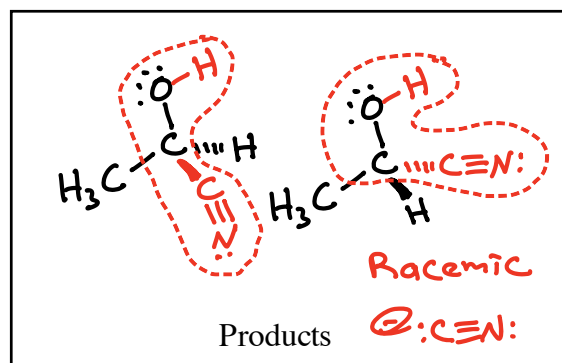
## HCN Reacting with an Aldehyde or Ketone

Reacts on the C atom because that makes stronger bonds



Key Recognition Element (KRE):

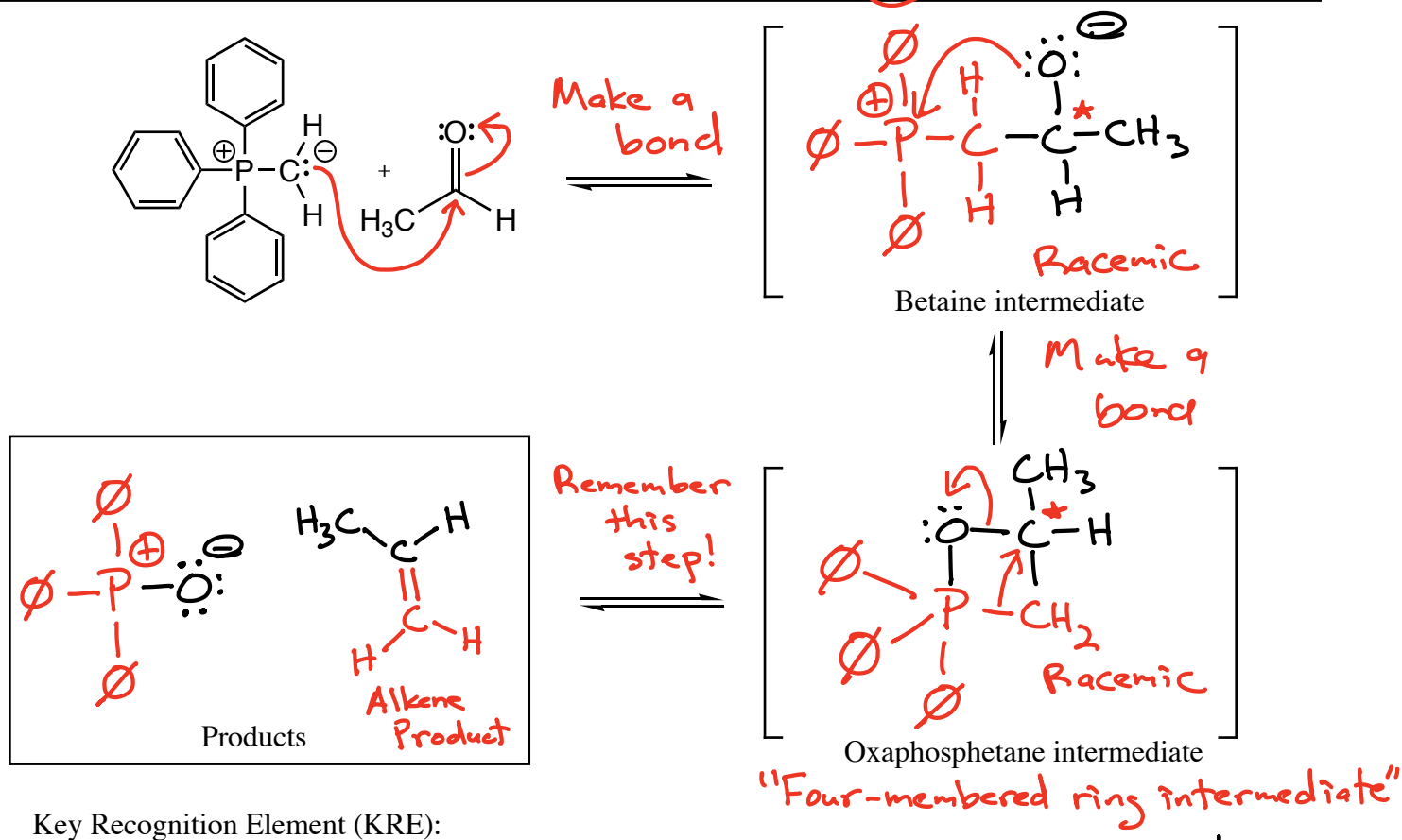
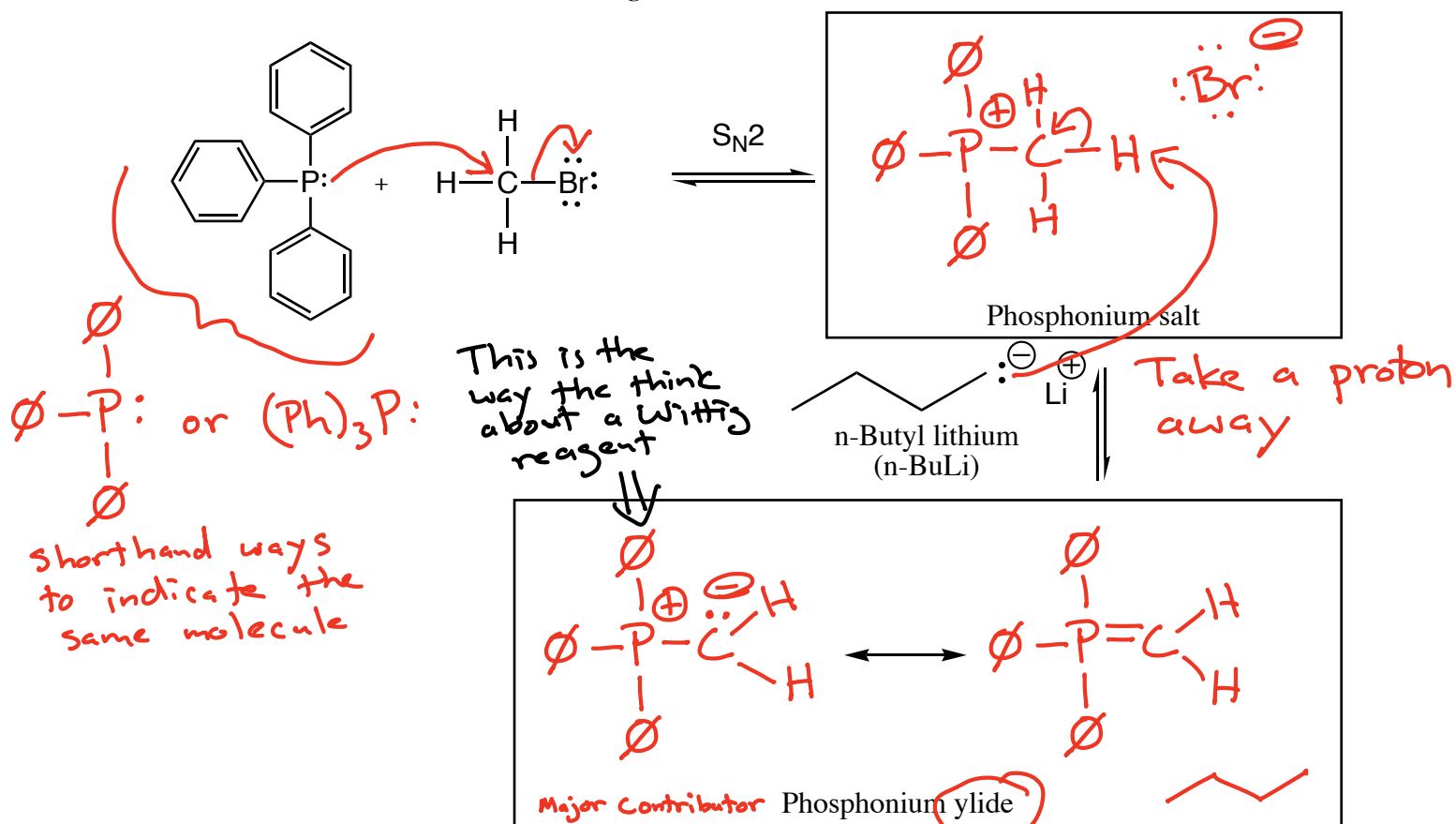
Cyanohydrin  $\rightarrow$  OH  
on a C atom that  
made a new C-C  
bond to  $-\text{C}\equiv\text{N:}$



Time capsule  $\rightarrow$  cyanohydrins can be  
hydrolyzed in  $\text{H}_2\text{SO}_4/\text{H}_2\text{O}$  to  
give  $\alpha$ -hydroxyacids  
"alpha"



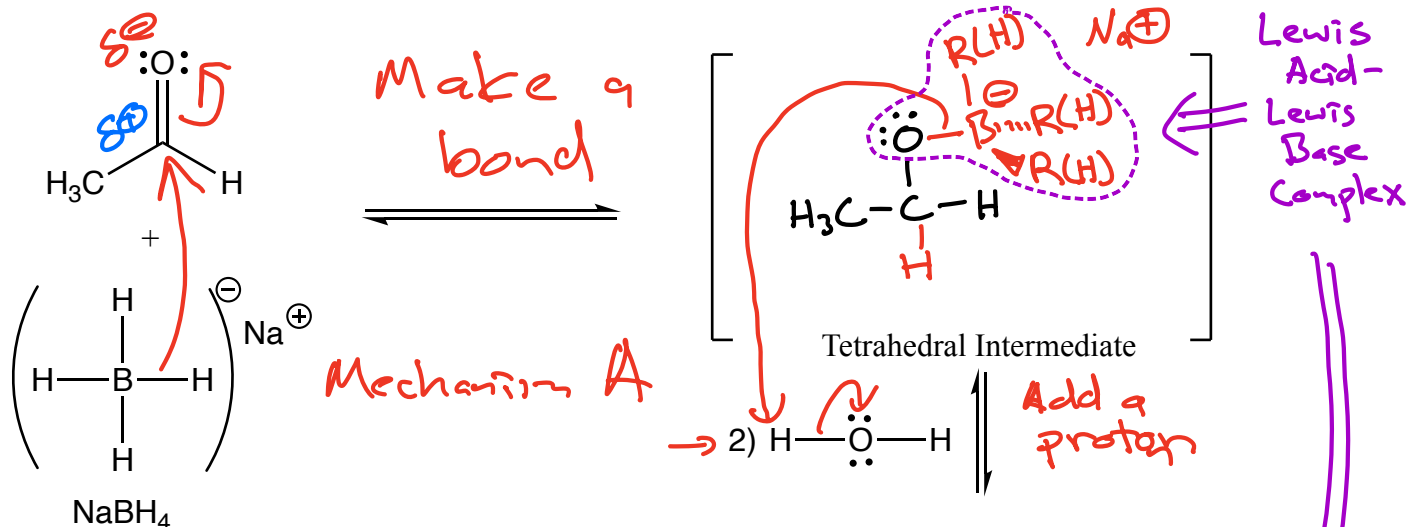
# Wittig Reaction



Key Recognition Element (KRE):

Alkene  $\rightarrow$  New  $\text{C}=\text{C}$  where the  $\text{C}=\text{O}$  was!

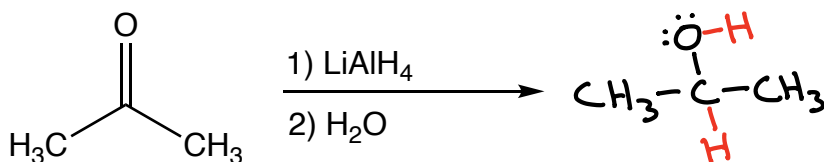
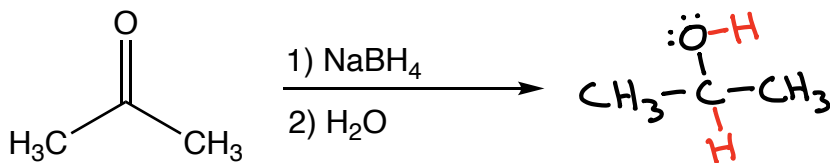
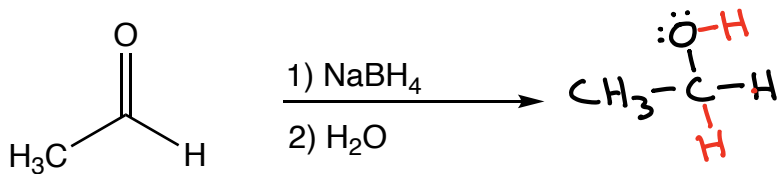
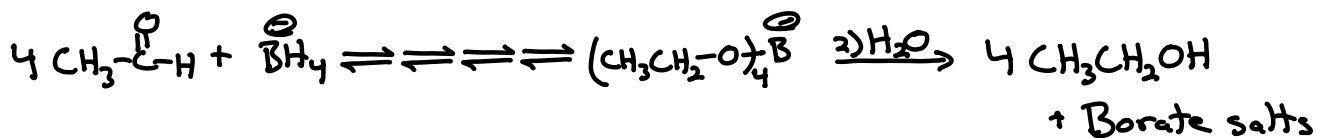
## Sodium Borohydride Reacting with an Aldehyde or Ketone



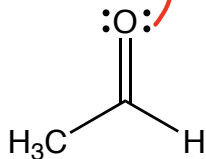
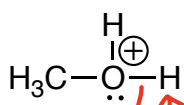
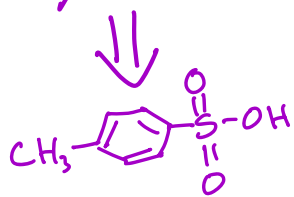
Key Recognition Element (KRE):

An  $-\text{OH}$  group where there was a  $\text{C=O}$  of an aldehyde or ketone

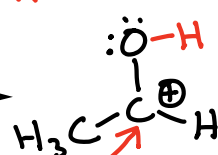
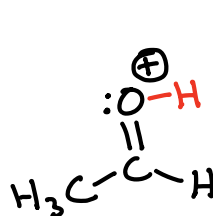
All four H of  $\text{BH}_4^-$  react!



**TsOH or H<sub>2</sub>SO<sub>4</sub>**  
**Tosylic Acid**  
*Acid Catalyzed Hemiacetal and Acetal Formation From an Aldehyde or Ketone*



Add a proton

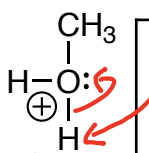
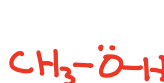
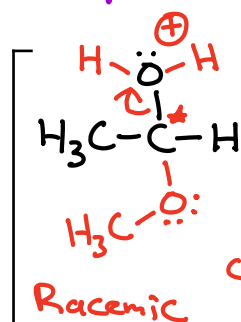


Red Hot Electrophile

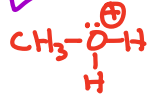
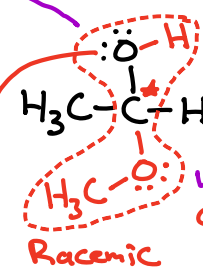
Make a bond

Mechanism

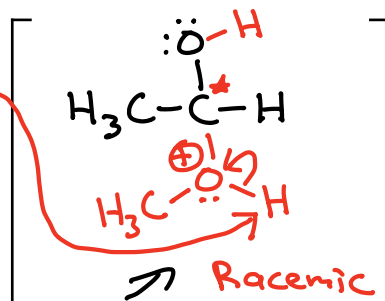
-OH and -OR on the same sp<sup>3</sup> C atom



Add a proton



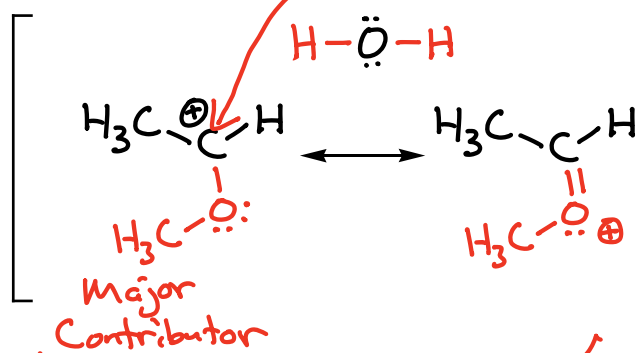
Take a proton away



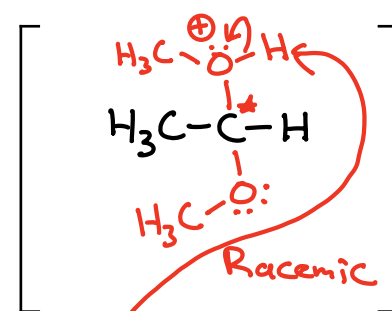
Hemiacetal intermediate

Not stable

Break a bond



Make a bond



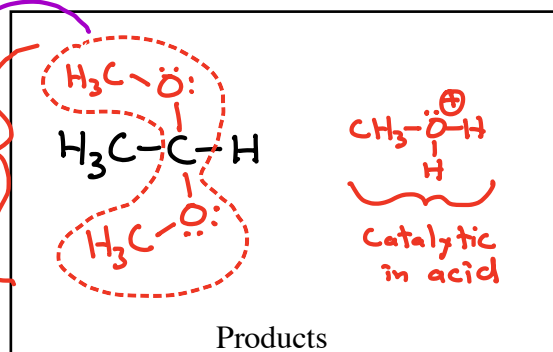
Stabilized by Charge Delocalization

Key Recognition Element (KRE):

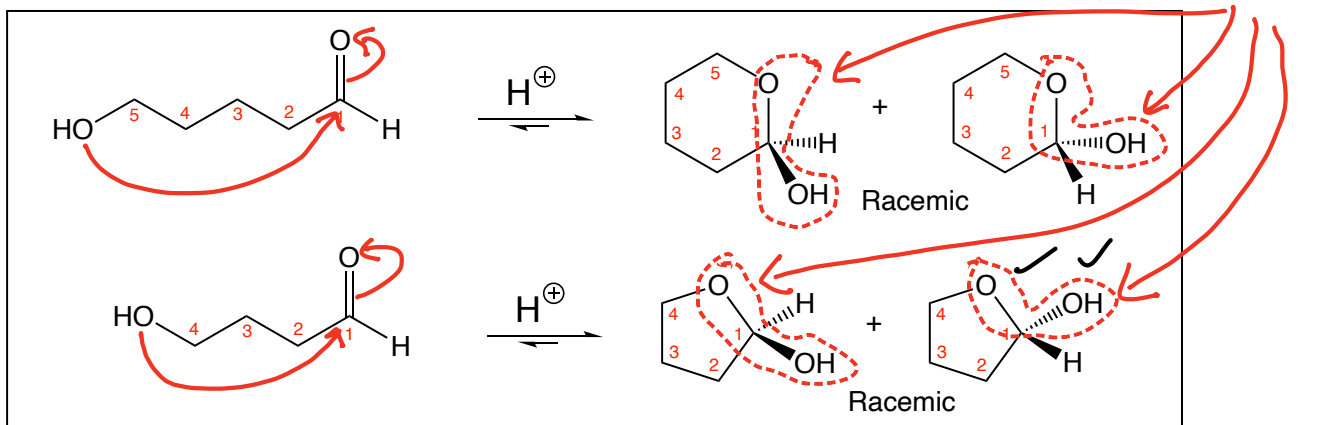
Two -OR on the same sp<sup>3</sup> C atom

Two bonds to ether O atoms to an sp<sup>3</sup> C atom

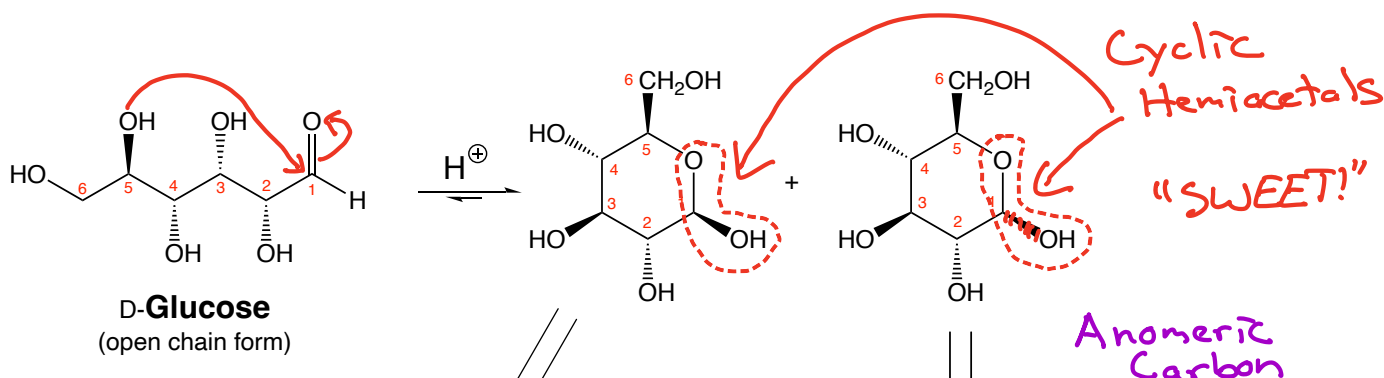
An acetal



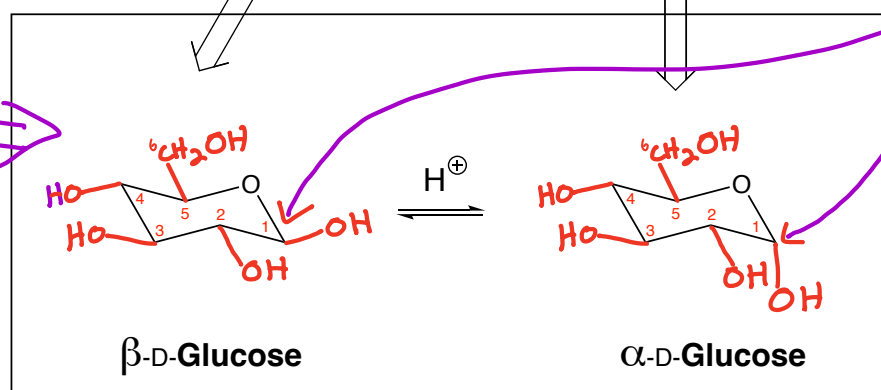
# Cyclic Hemiacetals and Carbohydrates



The cyclic form of hemiacetals are stable - "SWEET!"  
 → The chelate effect



This interconversion is called "mutarotation"



Biochemists call these two forms "anomers"

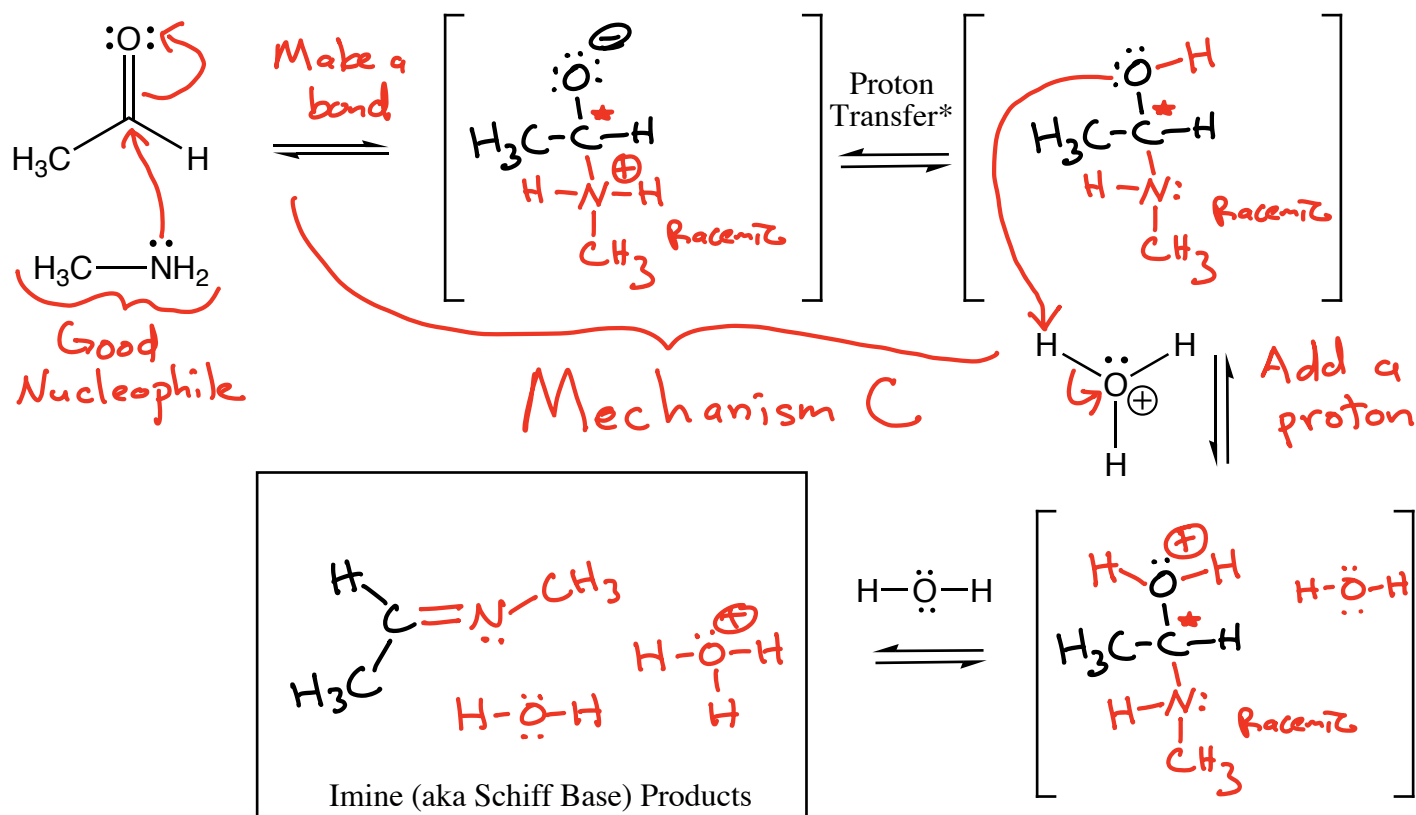
$\beta$ -D-Glucopyranose  
 means "6-membered ring"

More stable → every group is equatorial!

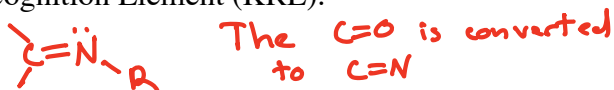
$\alpha$ -D-Glucopyranose

Less stable → one -OH is axial

## Formation of an Imine (Schiff Base) From an Aldehyde or Ketone Reacting with an Amine



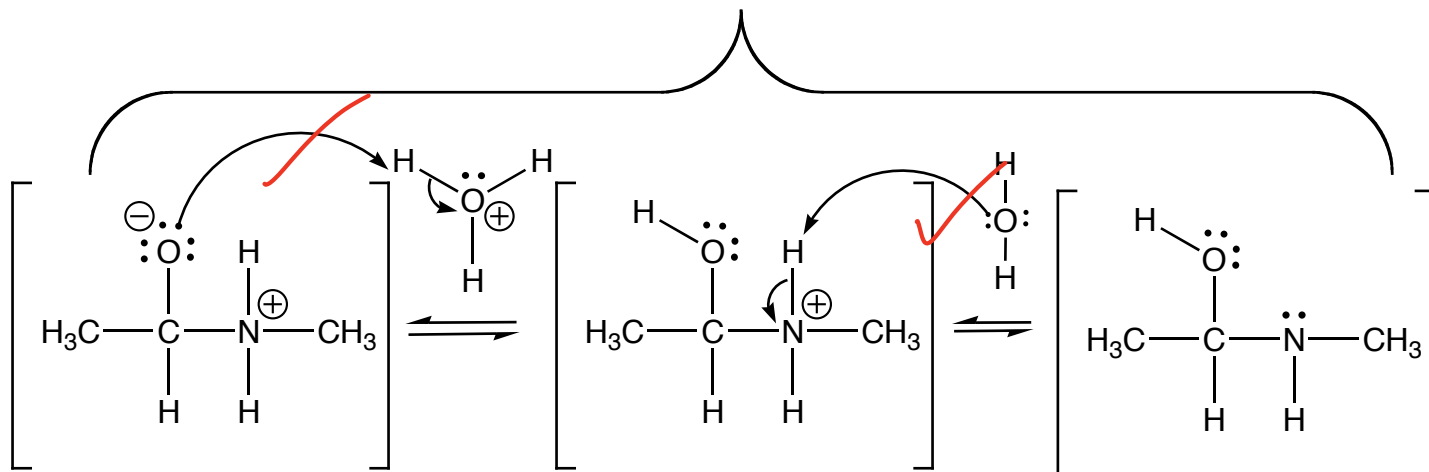
Key Recognition Element (KRE):



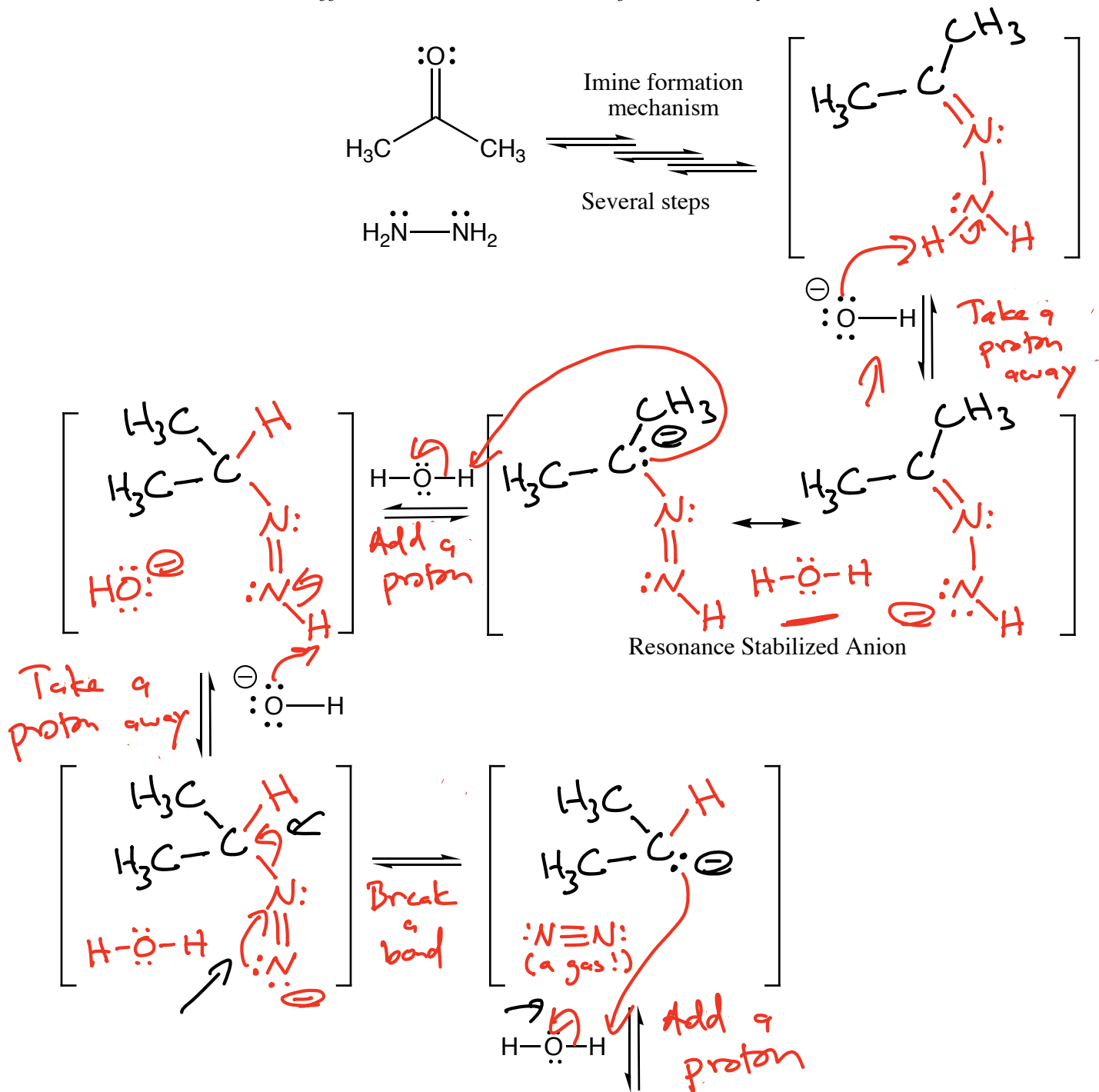
(Note: this last step might actually occur as two steps in some cases.)

\* "Proton Transfer" refers to a situation in which a proton moves from one part of a molecule to another on the SAME MOLECULE. We do not draw arrows for proton transfer steps because that would be deceptive. In some cases, the same proton may move from one part of the molecule to the other directly, but in other cases, solvent molecules may be involved as indicated in the following scheme. To make things even more interesting, the following two steps might even be reversed in some cases. Because of all the ambiguity, we just write "Proton Transfer" and do not bother with arrows.

"Proton Transfer"

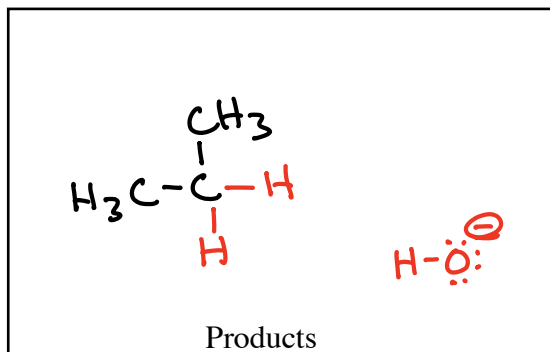


### Wolff-Kishner Reduction of an Aldehyde or Ketone



Key Recognition Element (KRE):

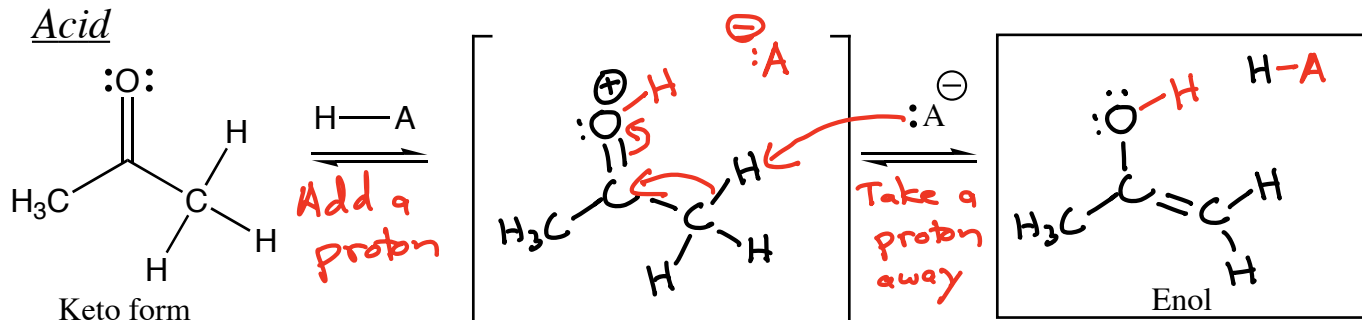
-CH<sub>2</sub>- where there was C=O



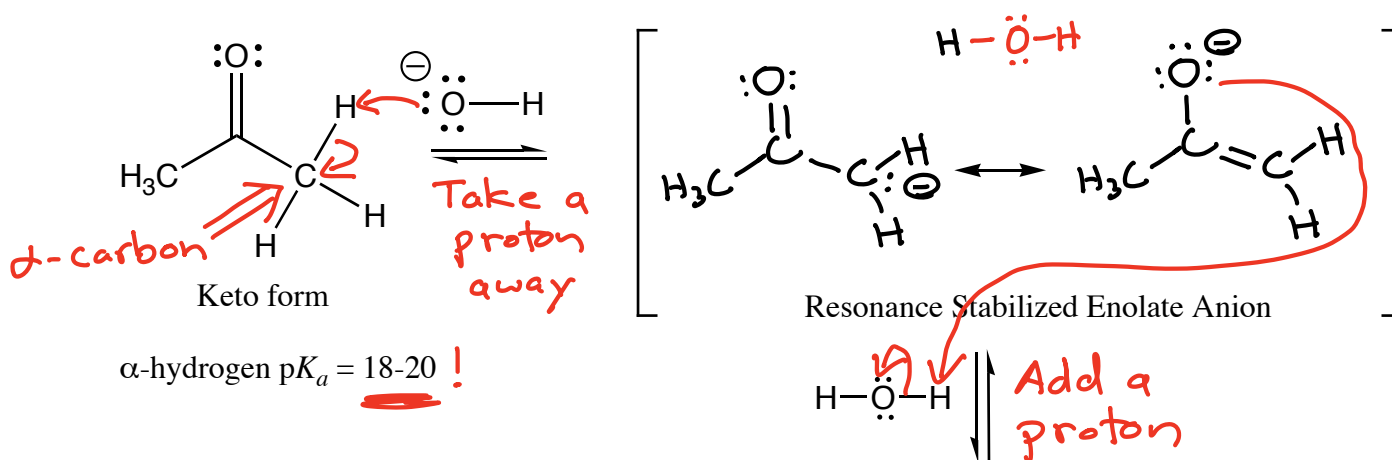
The process of interconverting the keto and enol forms is called "tautomerization"

*Keto-Enol Equilibrium Catalyzed by Acid or Base*

Acid

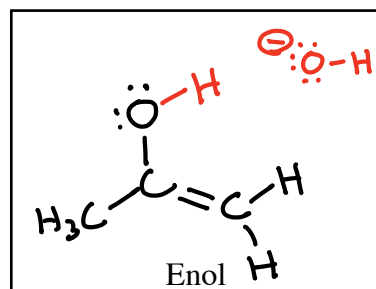


Base



$\alpha$ -hydrogen  $\text{p}K_a = 18-20$  !

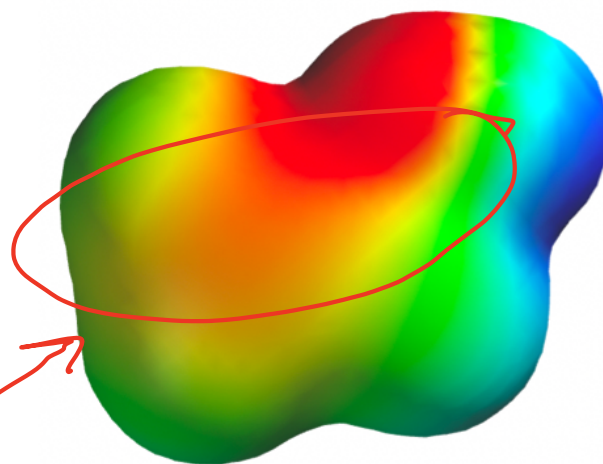
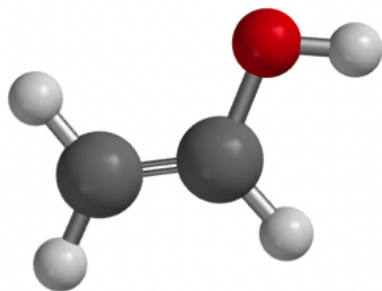
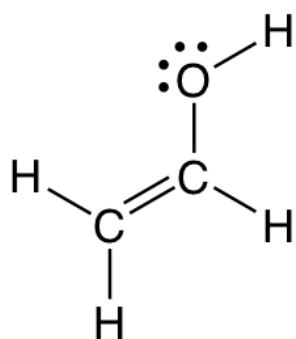
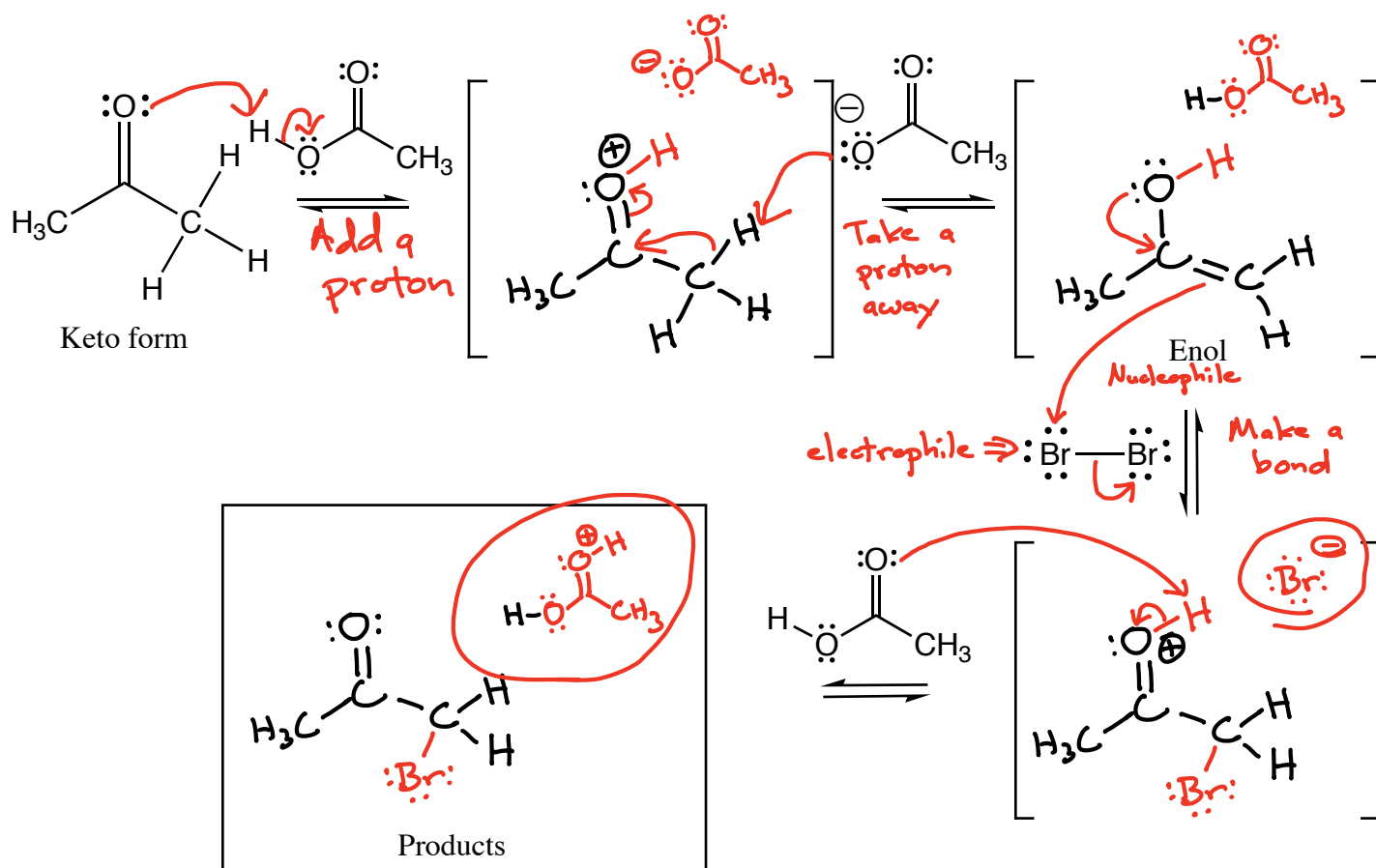
keto and enol forms are called "tautomers"



For both aldehydes and ketones, the keto form predominates at equilibrium, because  $\text{C}=\text{O}$  bonds are stronger than  $\text{C}=\text{C}$  bonds.

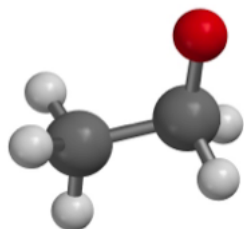
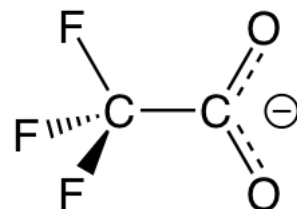
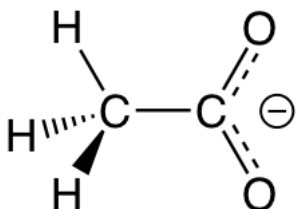
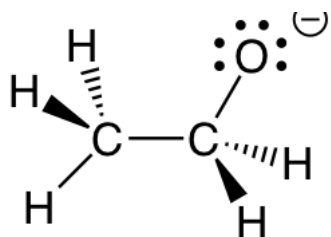
Enols are significant, however, because they react like nucleophile, not carbonyls, and this is important in certain situations.

# *$\alpha$ -Halogenation of an Aldehyde or Ketone Catalyzed by Acid*

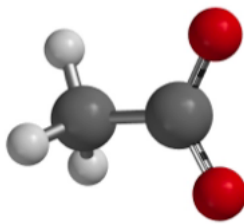


Nucleophile

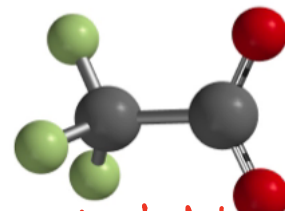




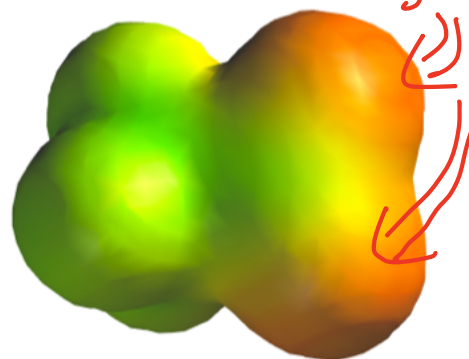
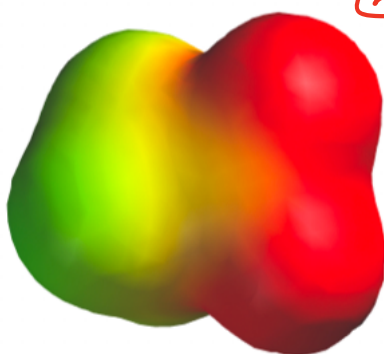
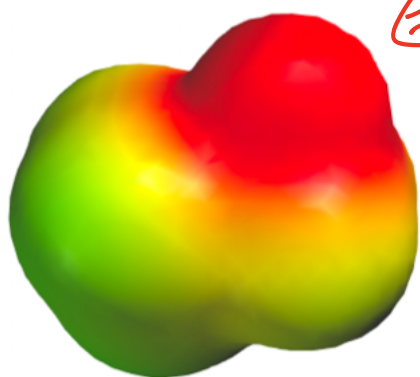
Least  
delocalized  
⊖ charge



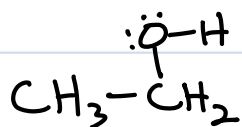
Somewhat  
delocalized  
⊖ charge



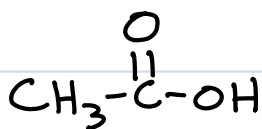
Most delocalized  
⊖ charge



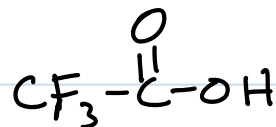
## Parent Acids



$$\text{p}K_a \approx 16$$

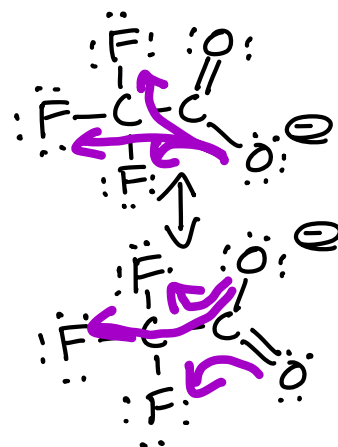
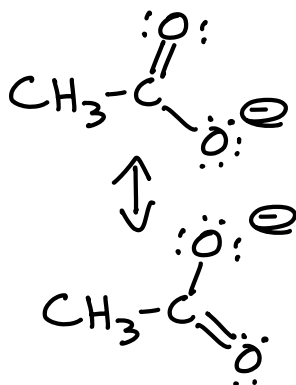
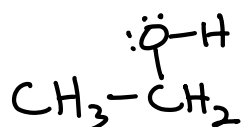


$$\text{p}K_a \approx 3-5$$



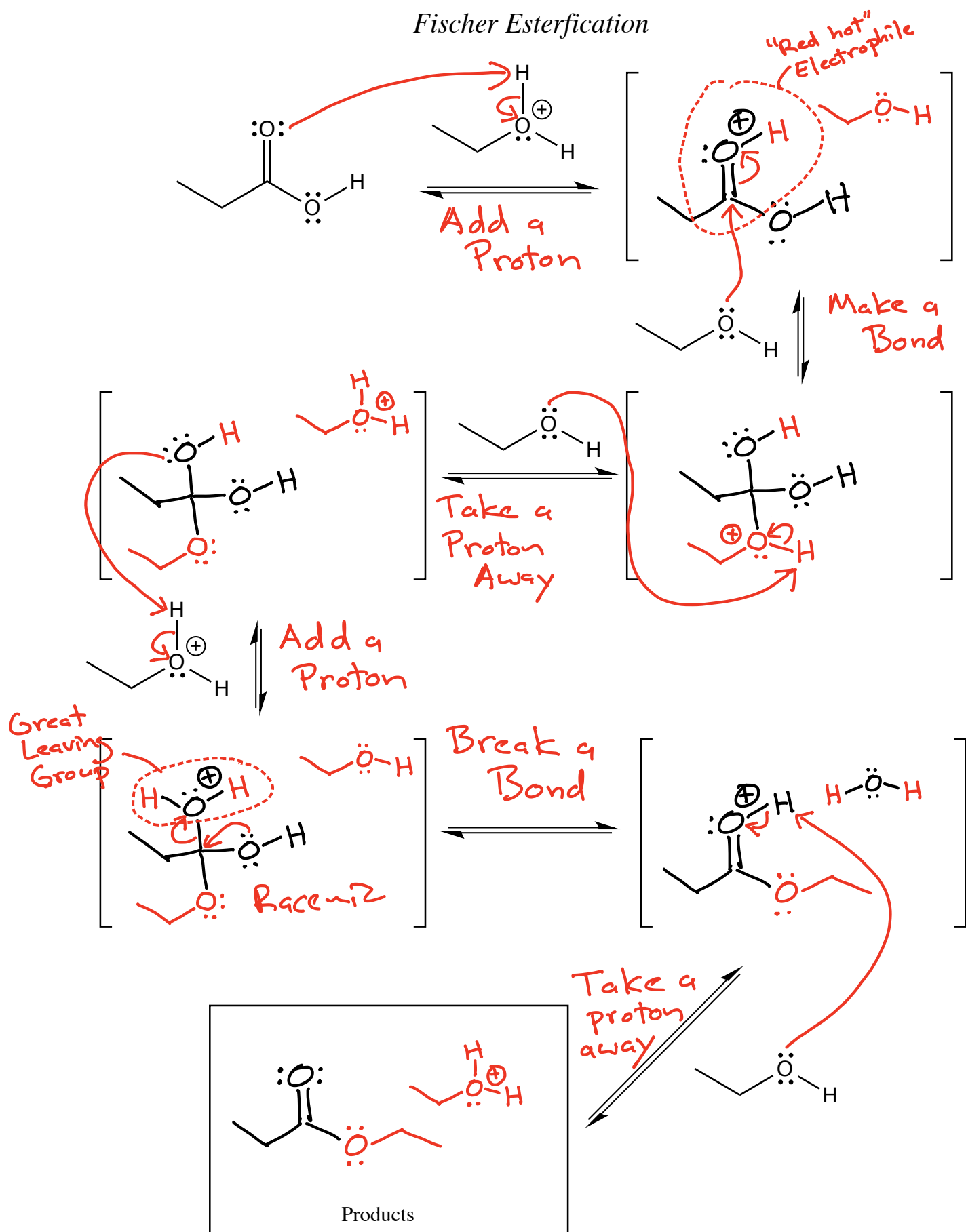
$$\text{p}K_a = 0.3-3$$

Rank acidity by comparing anion stabilities

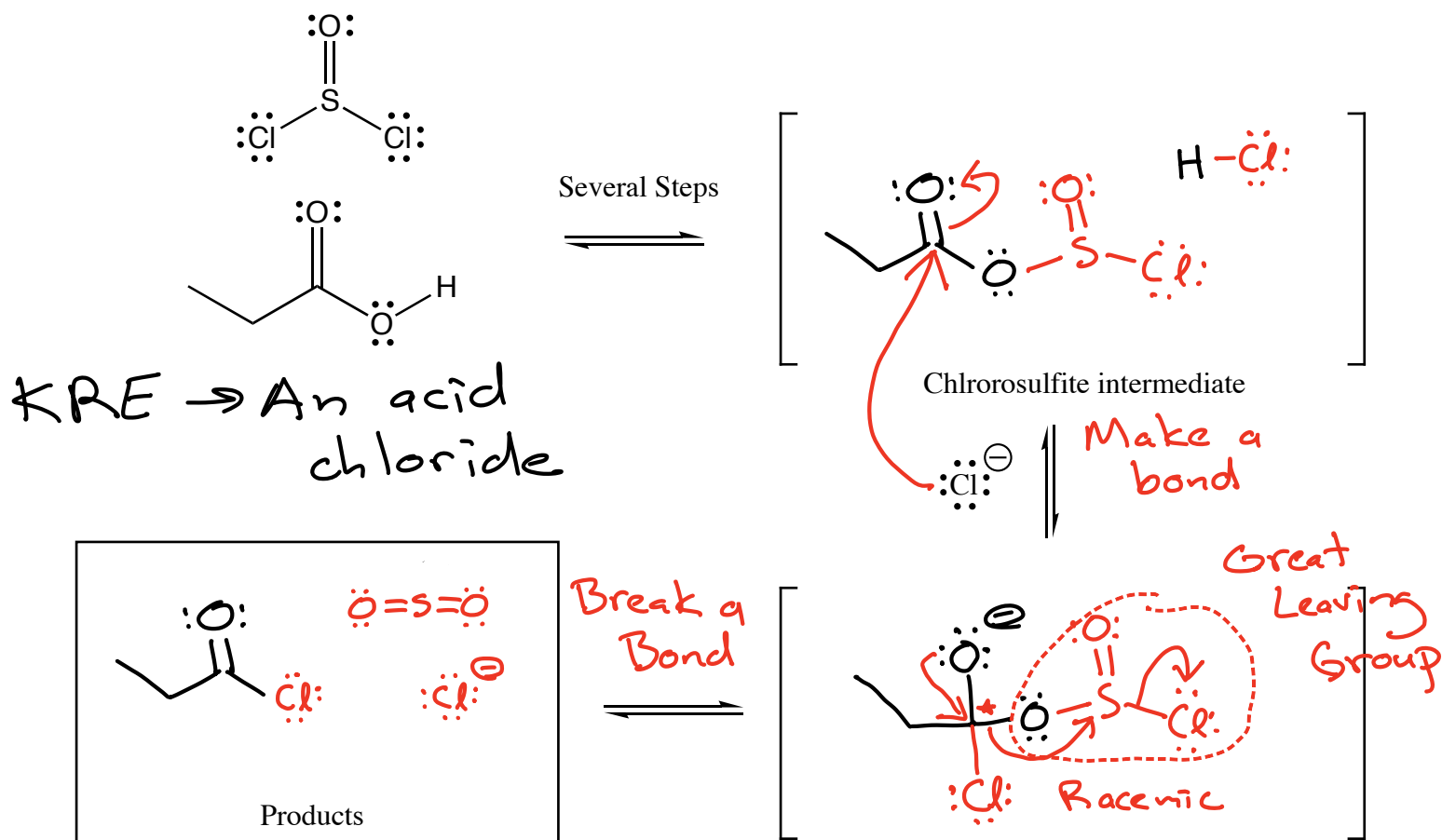


Inductive effect  
pulls some ⊖ charge  
into F atoms

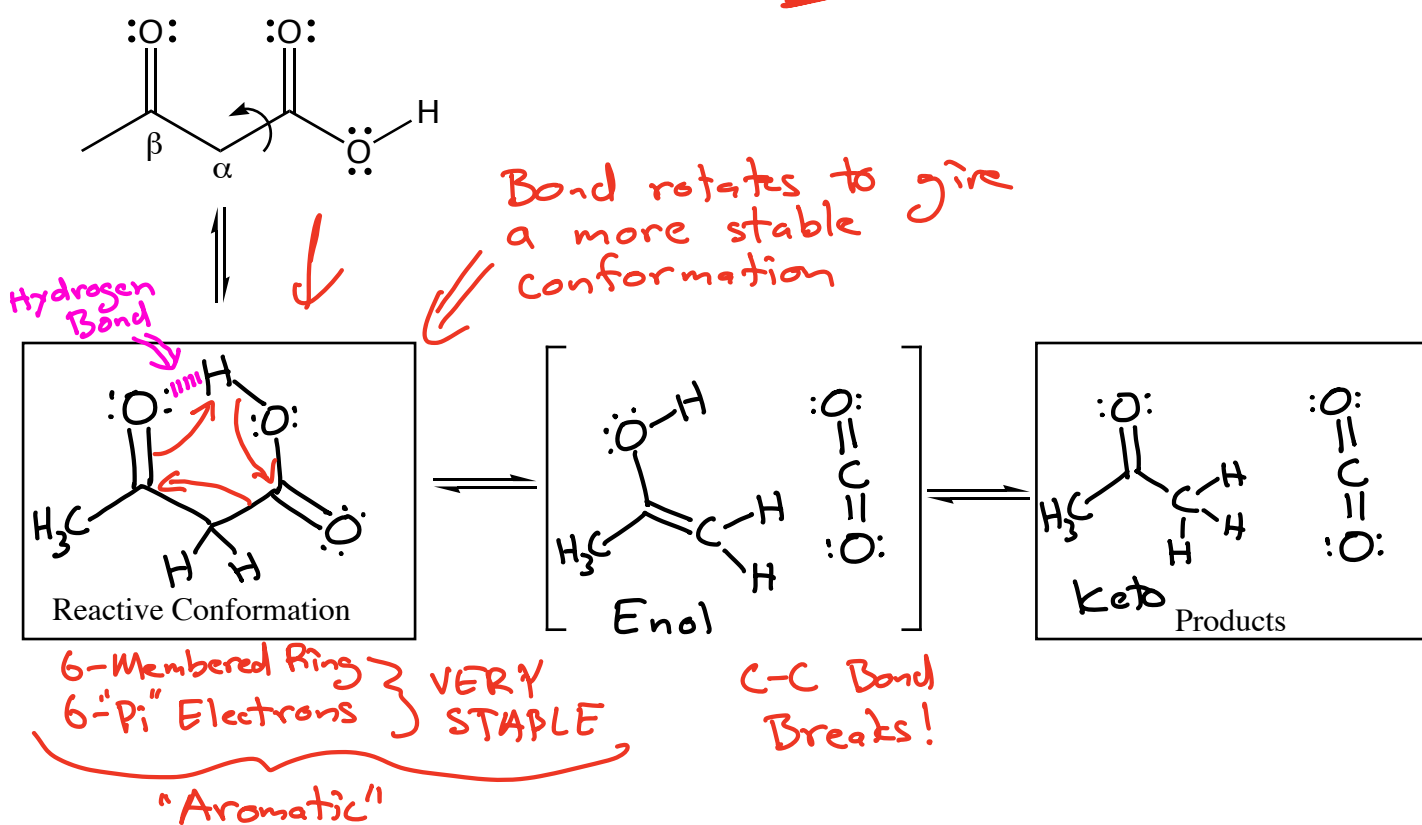
# Fischer Esterification



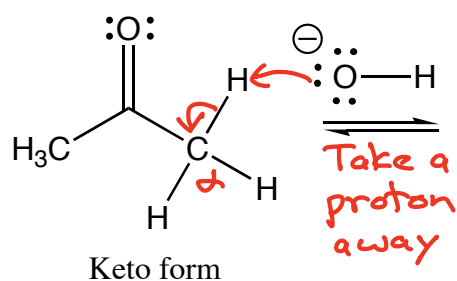
## Reaction with Thionyl Chloride



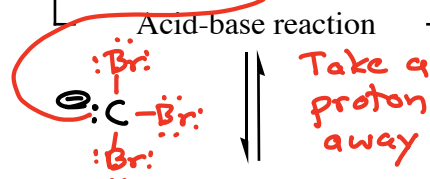
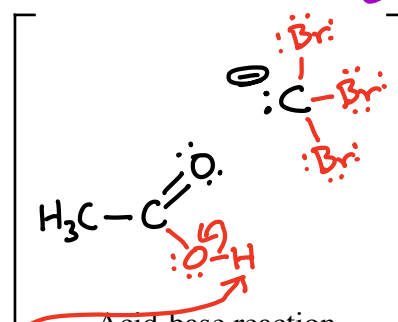
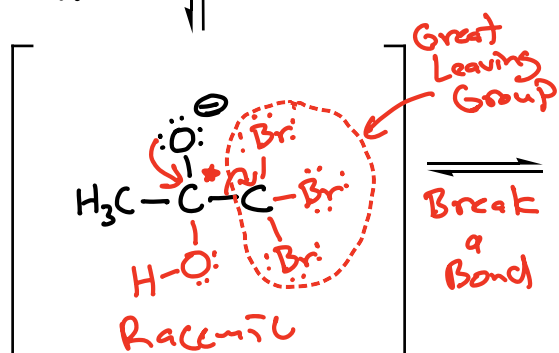
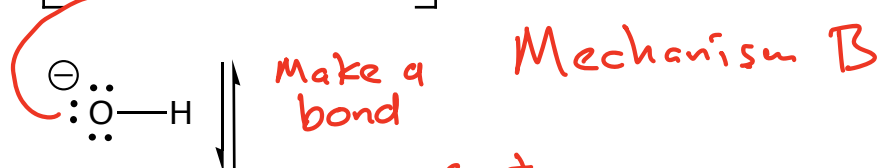
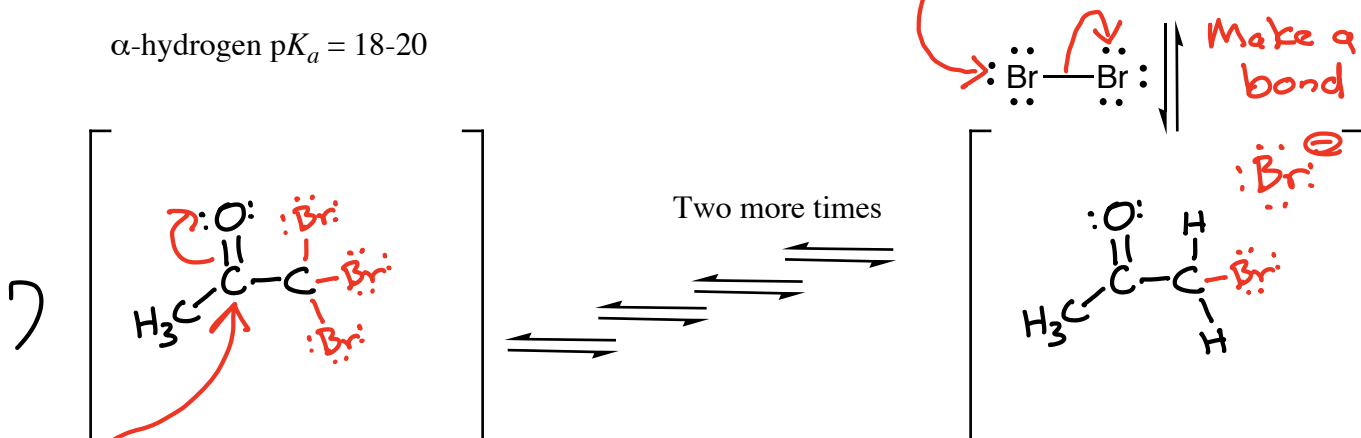
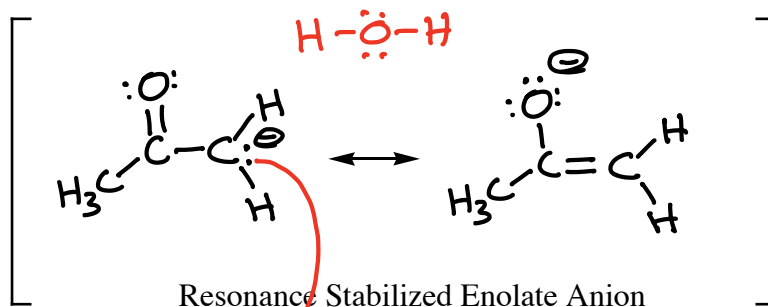
## Decarboxylation of a $\beta$ -Keto Acid



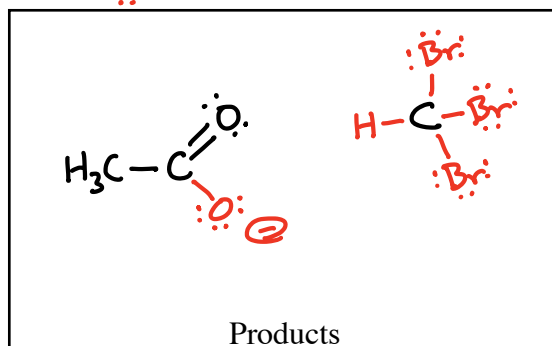
# The Haloform Reaction



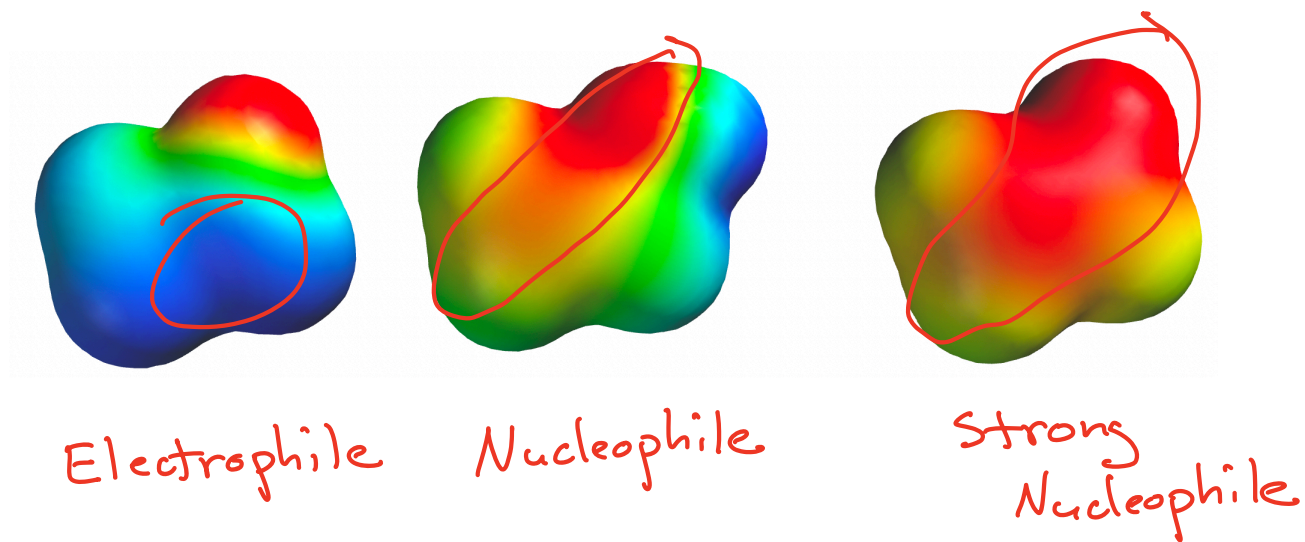
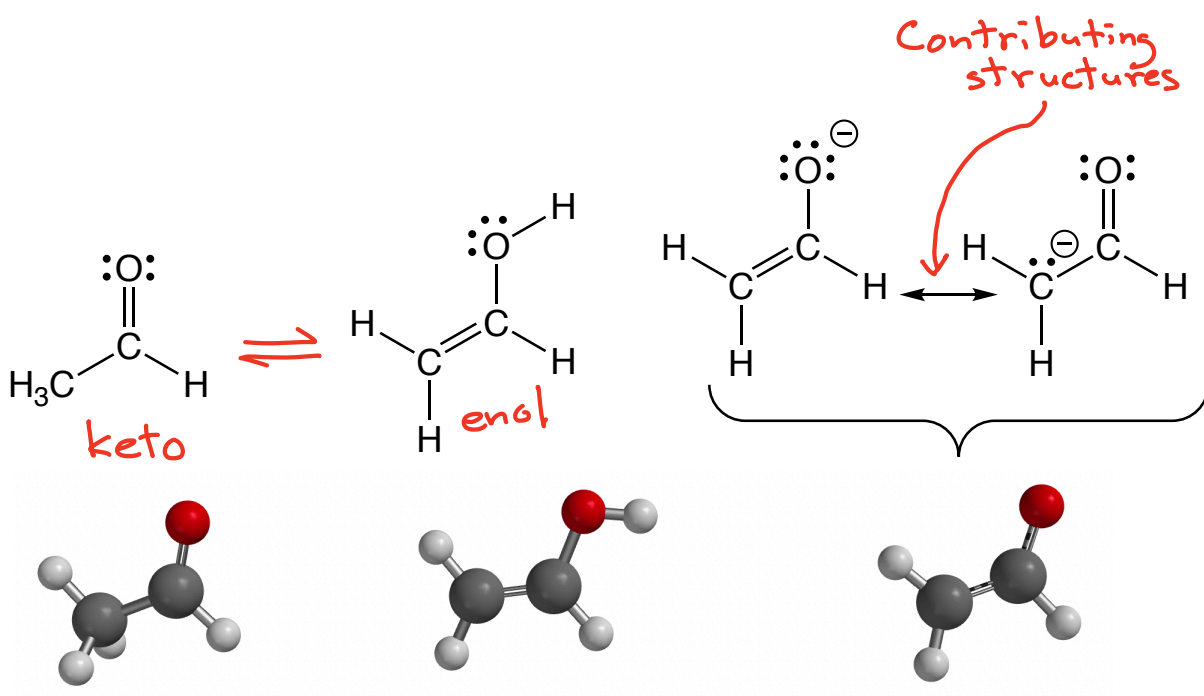
$\alpha$ -hydrogen  $pK_a = 18-20$



KRE  $\rightarrow$  Break the C-C bond to give a carboxylate and haloform product

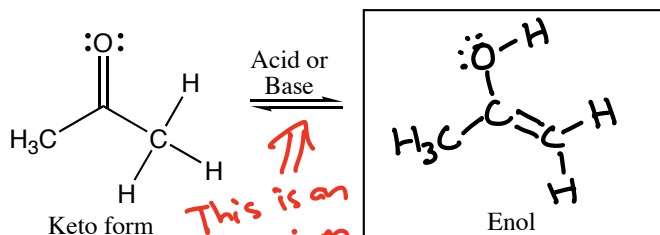


The inductive effect stabilizes the  $\ominus$  explaining why  $\ominus C(Br)_3$  is such a good leaving group



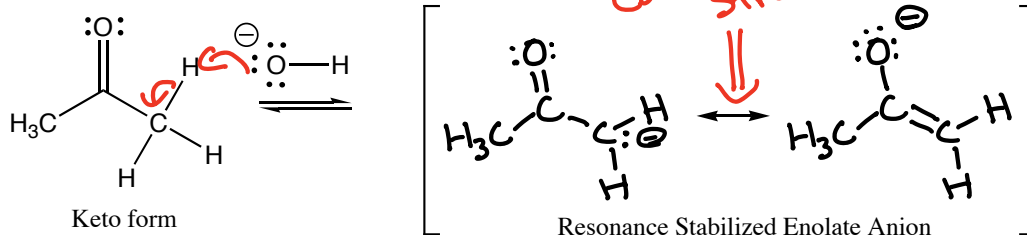
## Keto-Enol Tautomerization vs. Enolate Resonance

### Keto-Enol Tautomerization



Both the keto and enol molecules are Neutral!

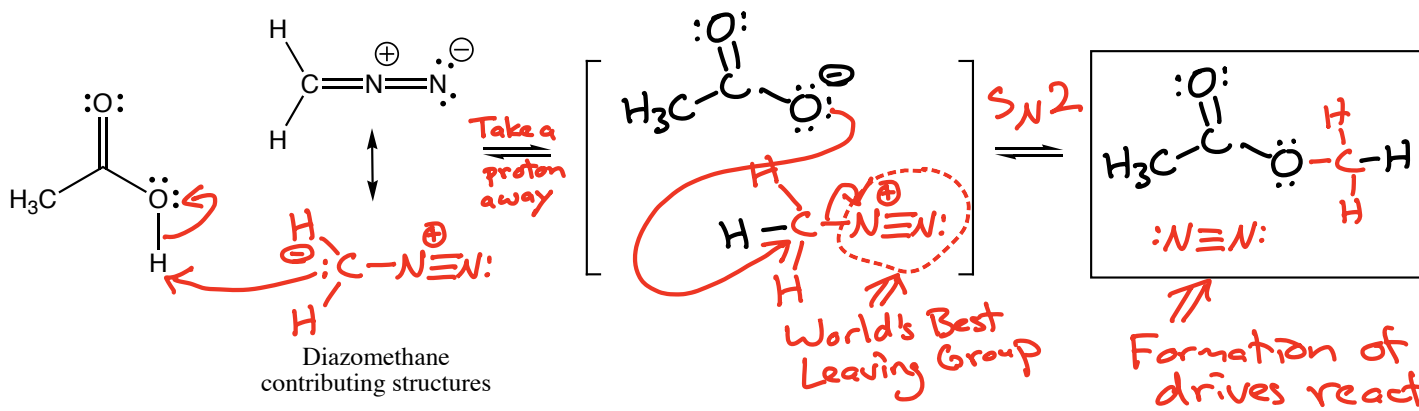
### Enolate Resonance



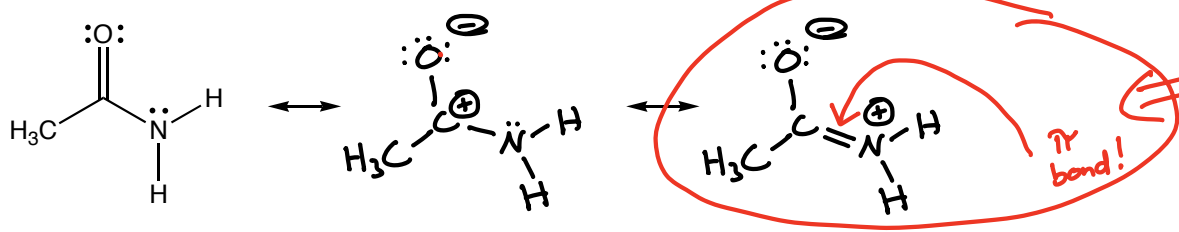
Full  $\ominus$

$\alpha$ -hydrogen  $\text{p}K_a = 18-20$

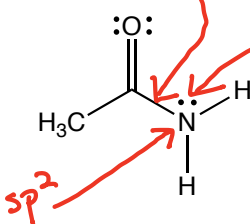
### Diazomethane reaction



### Amide Resonance VERY IMPORTANT!!!!!!



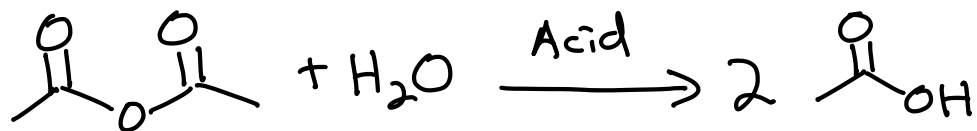
This is a partial  $\pi$  bond so it does NOT rotate at room temperature



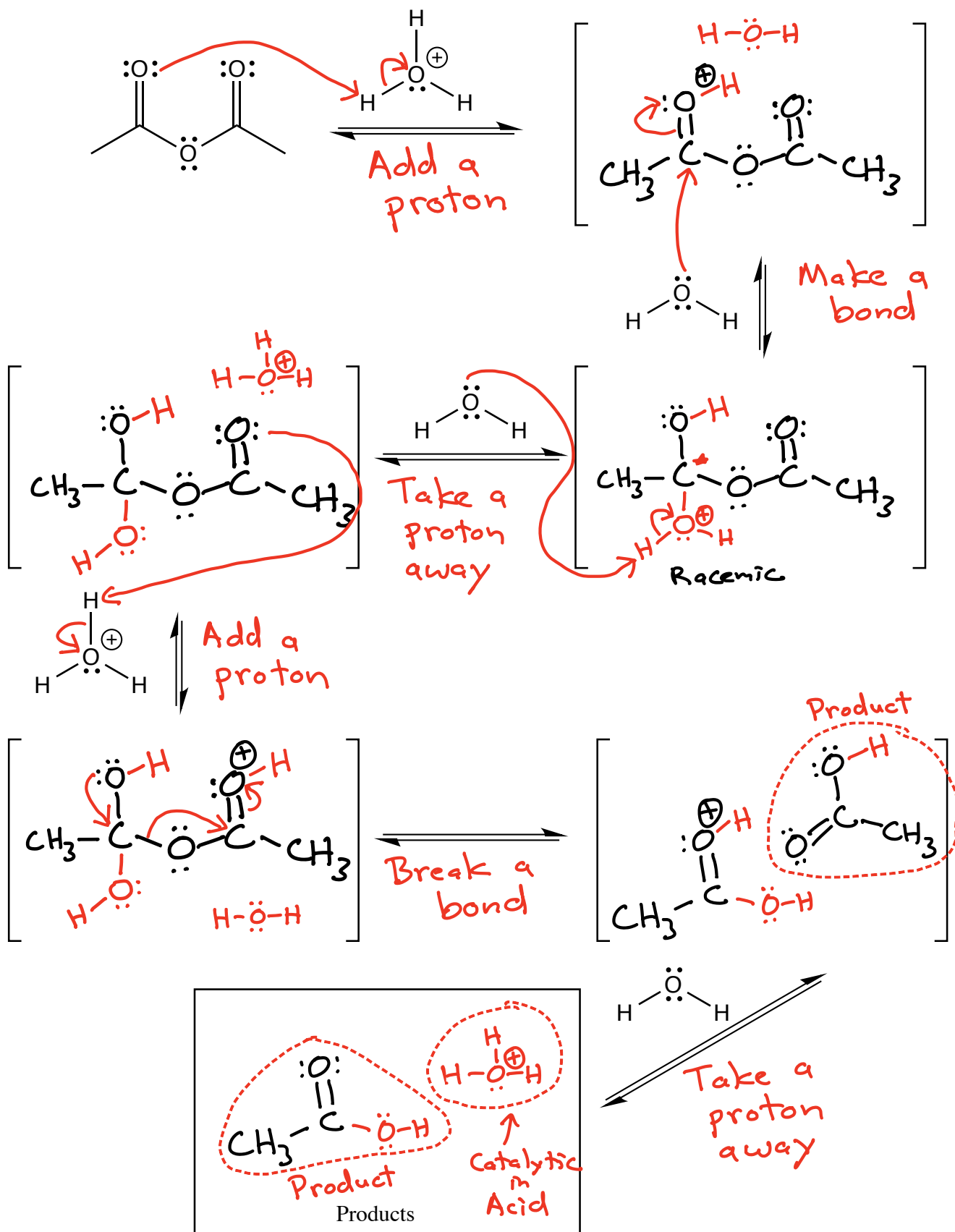
Lone pair is in a 2p orbital!

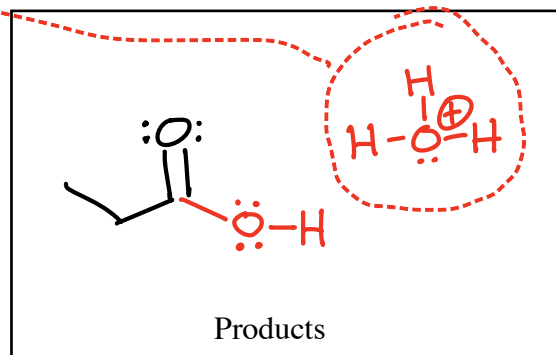
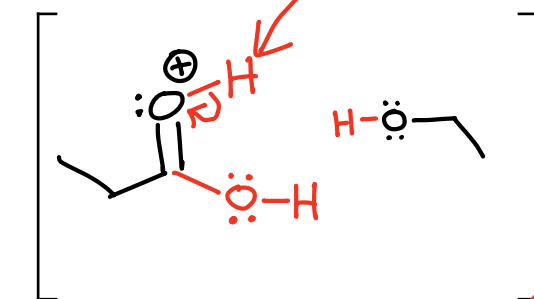
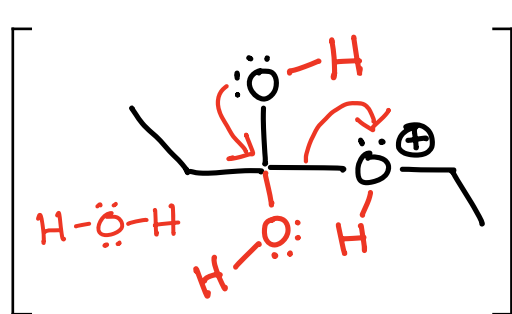
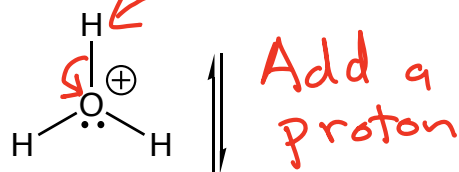
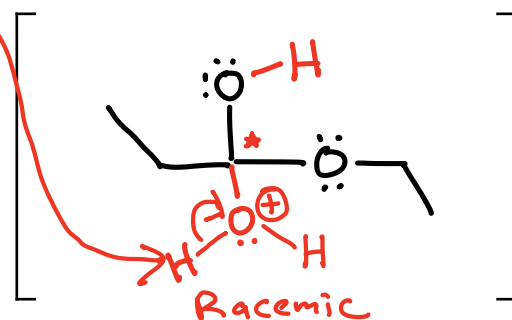
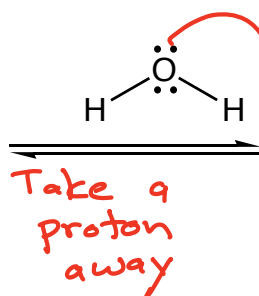
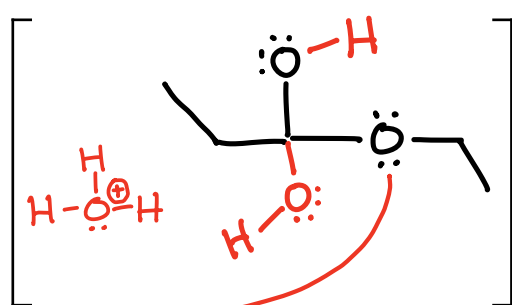
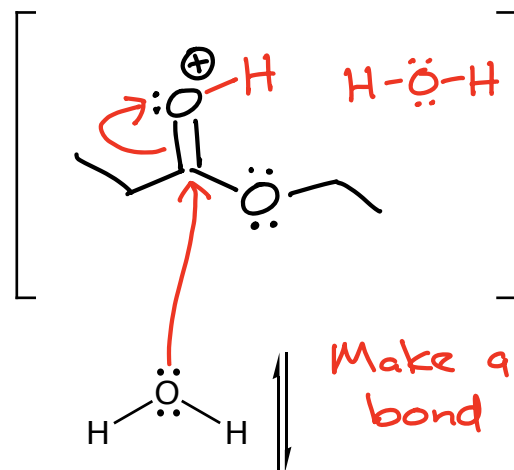
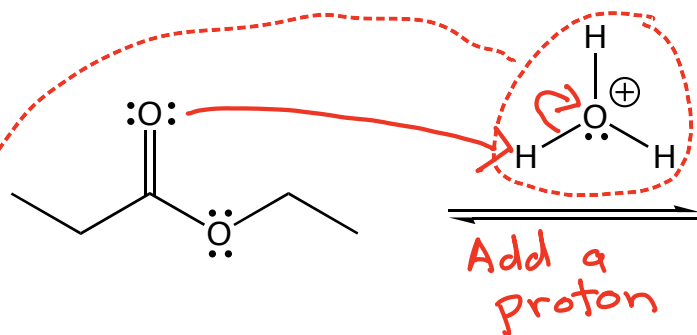
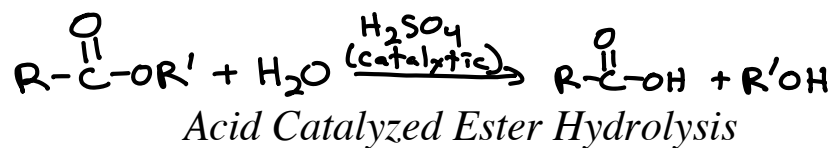
(Golden Rule of Chemistry)

A " $\pi$ -way" is created from the overlap of 2p orbitals on the O, C, and N atoms  $\rightarrow$  3 atoms, 2 electrons  $\rightarrow$  VERY STABILIZING!



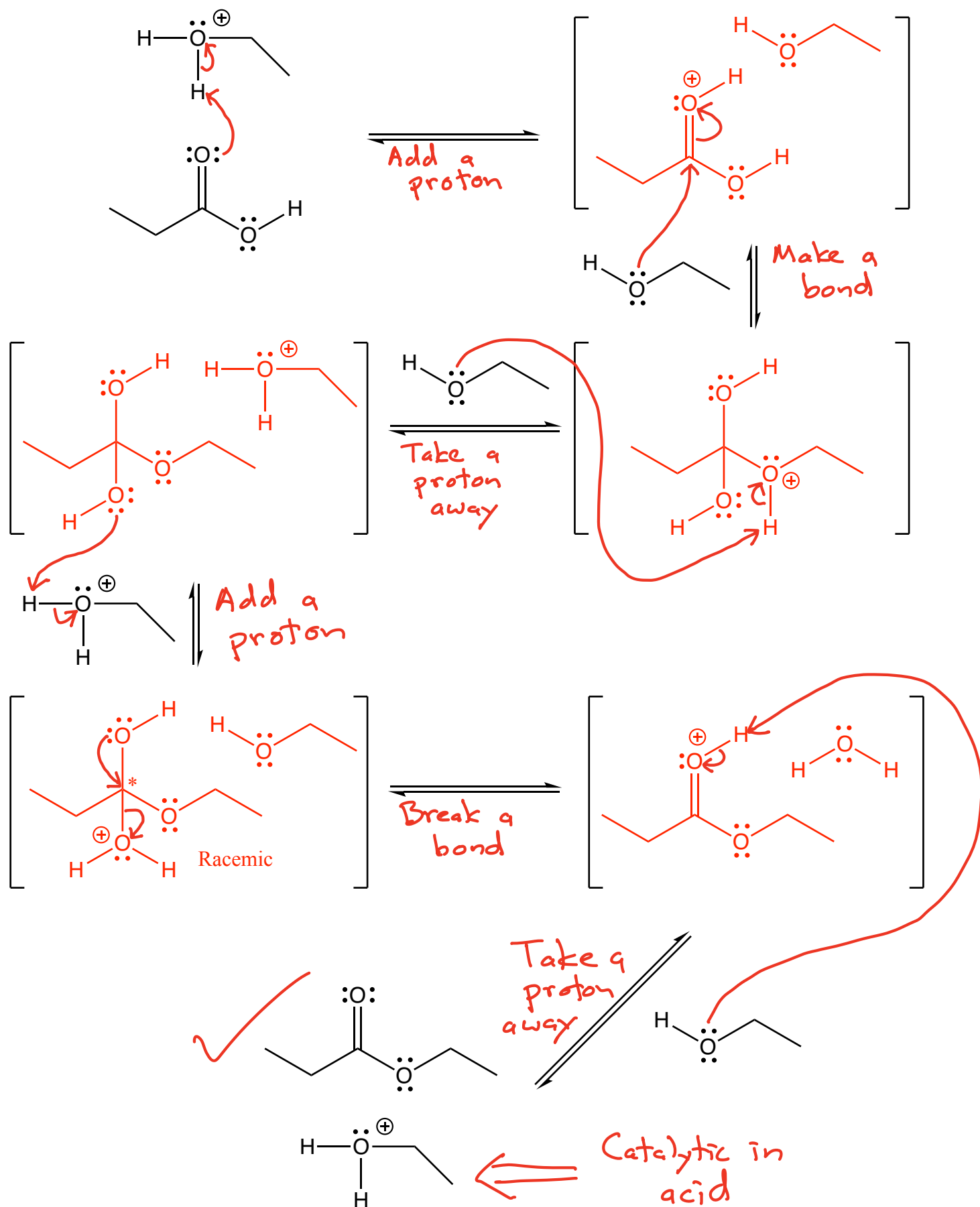
### Acid Catalyzed Anhydride Hydrolysis



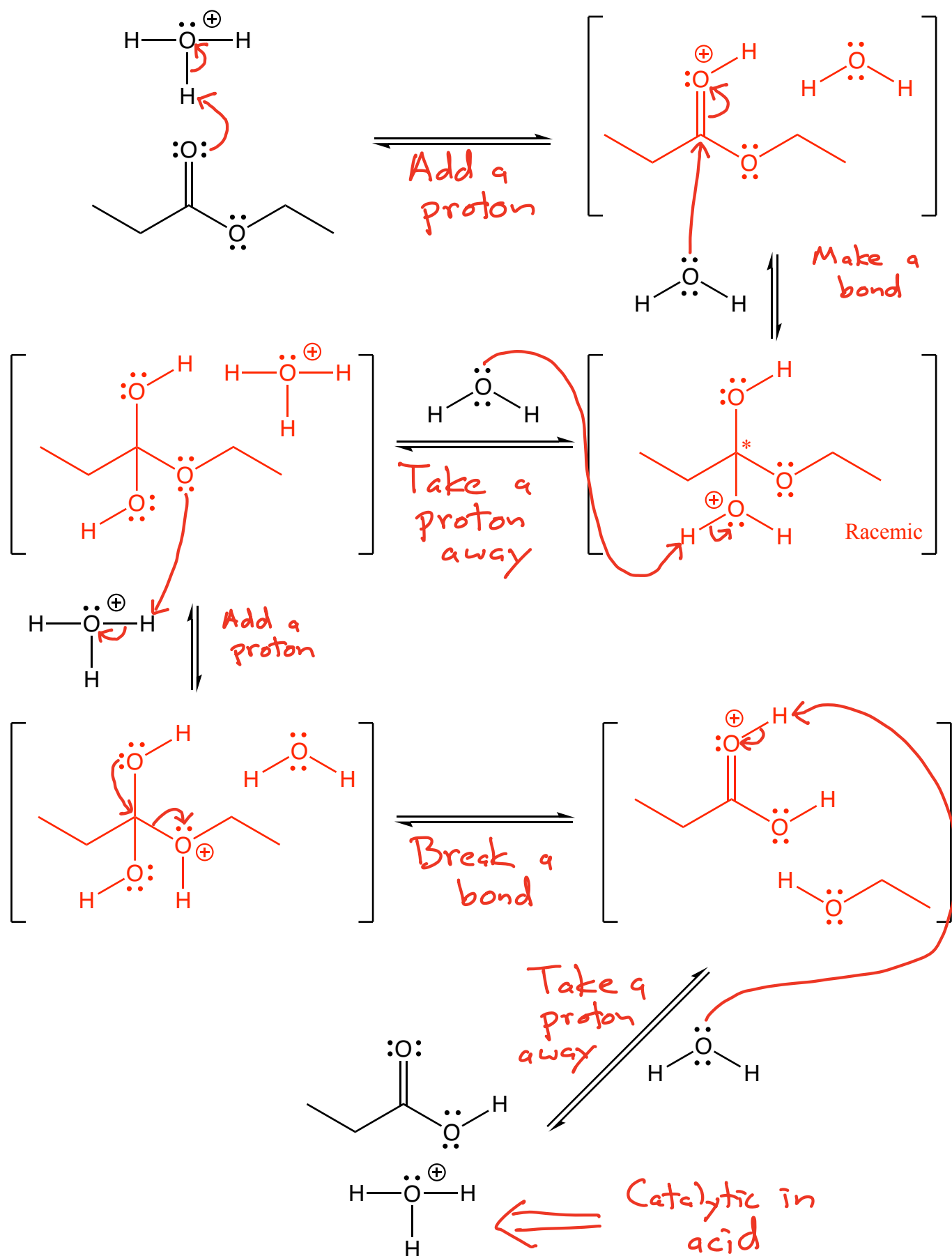


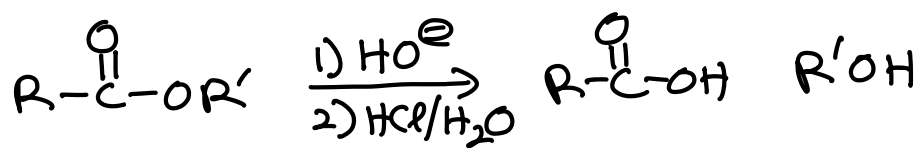


*Microscopic Reversibility: Acid Catalyzed Ester Hydrolysis-Fischer Esterification*

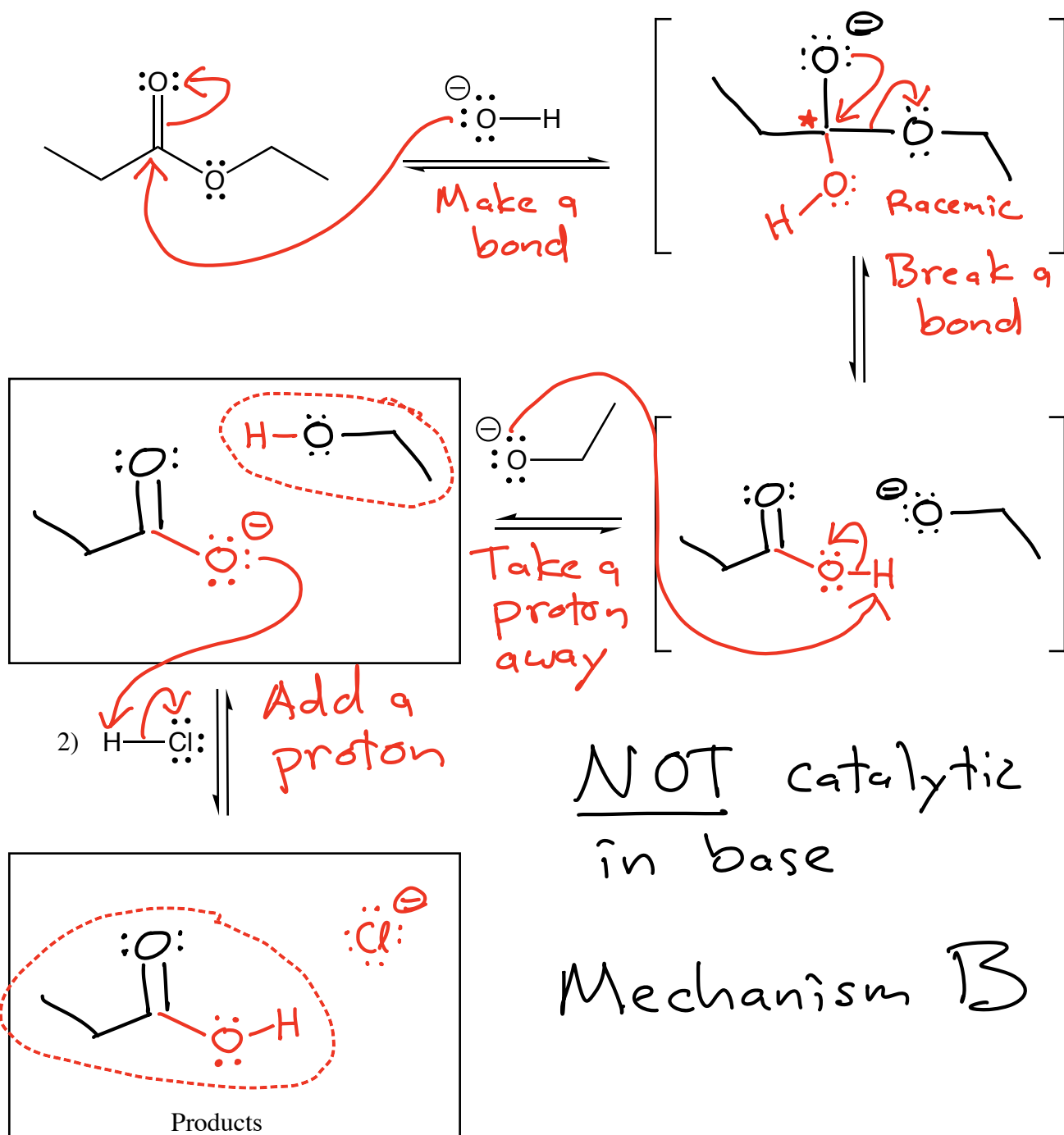


*Microscopic Reversibility: Acid Catalyzed Ester Hydrolysis-Fischer Esterification*





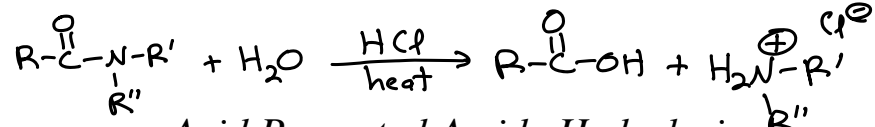
Base-Promoted Ester Hydrolysis - Saponification



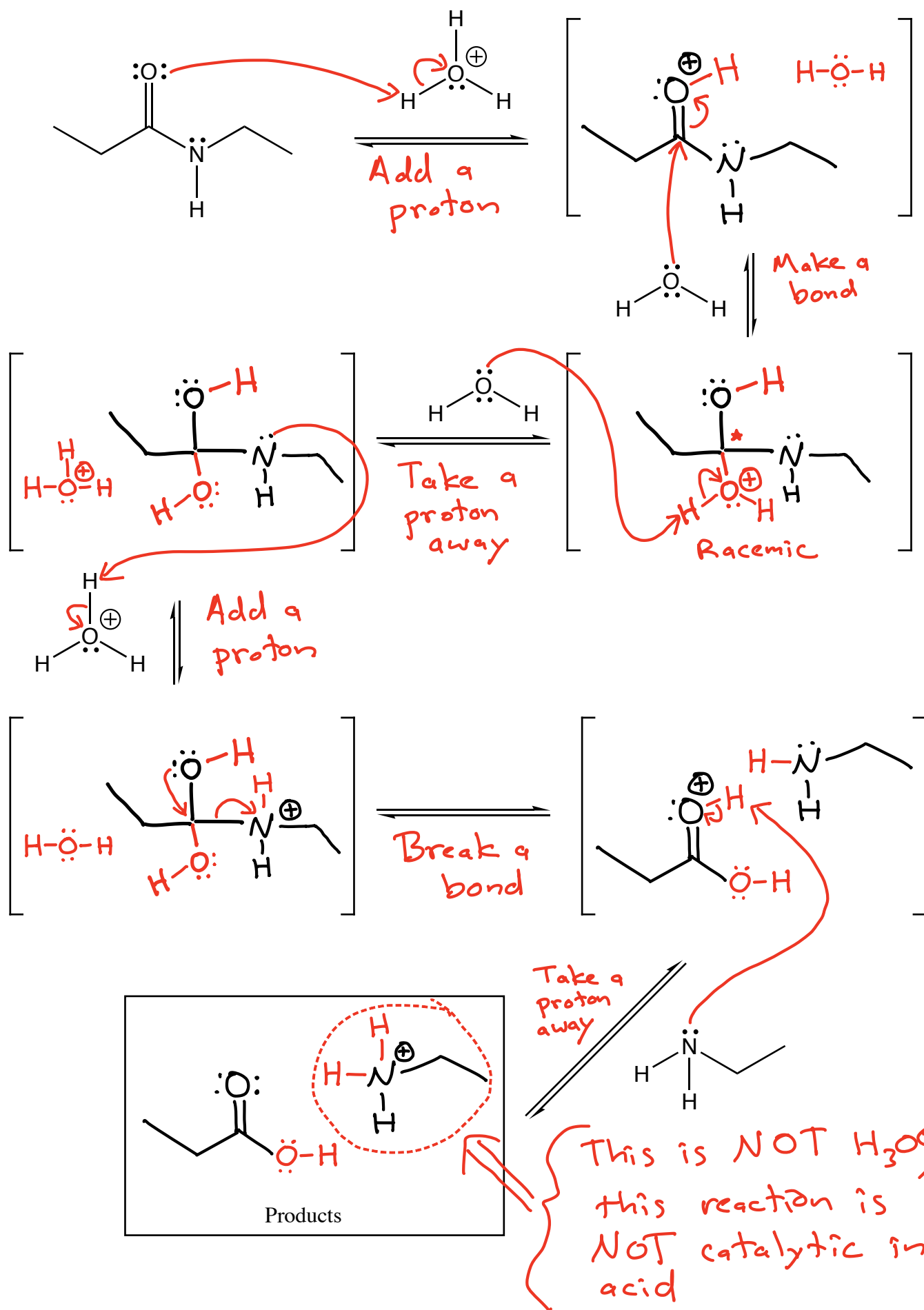
Driving force  $\rightarrow$  converts



More stable anion  
 $\rightarrow$  favored  $\rightarrow$  MOTIVE

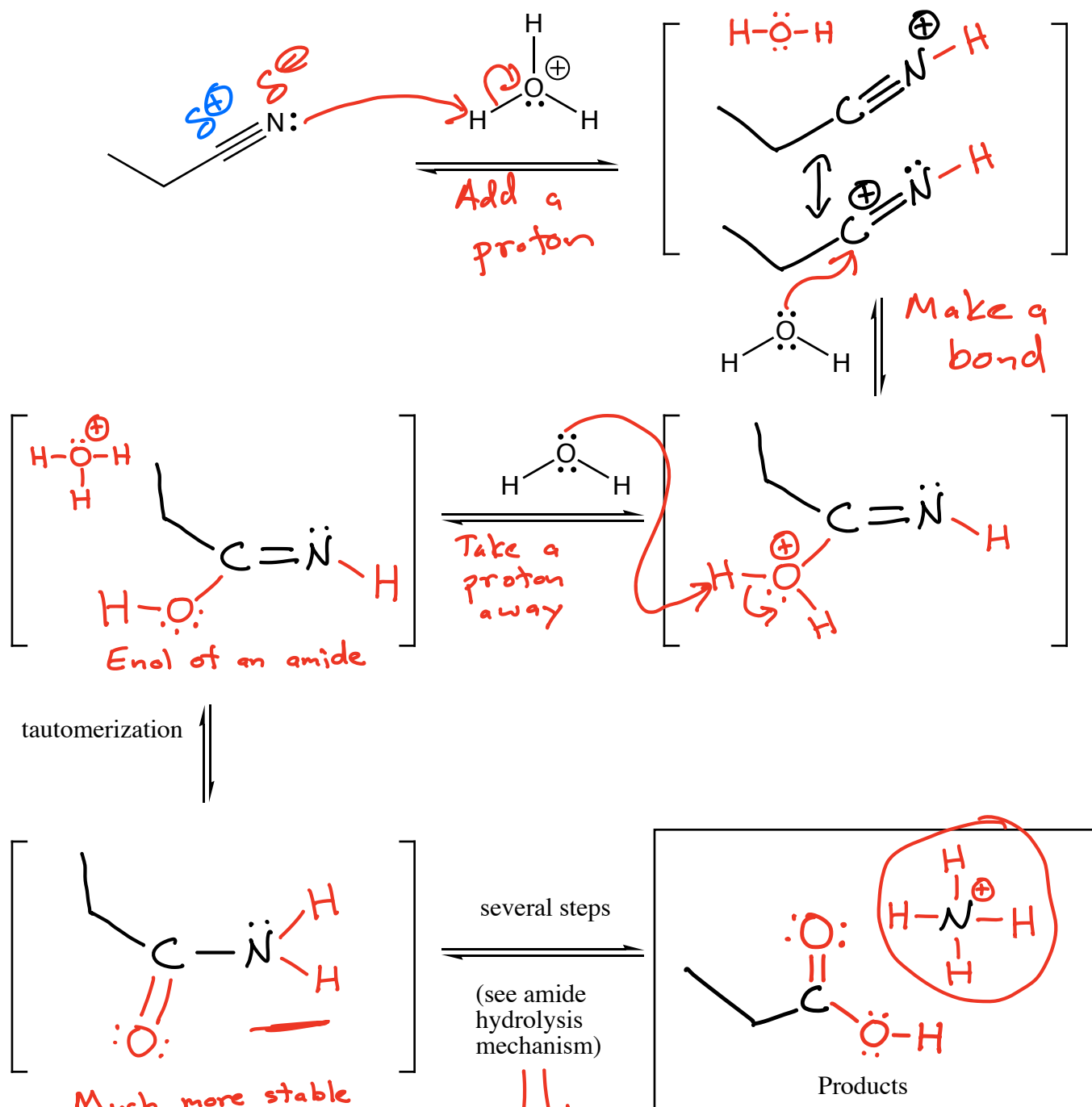


### Acid Promoted Amide Hydrolysis



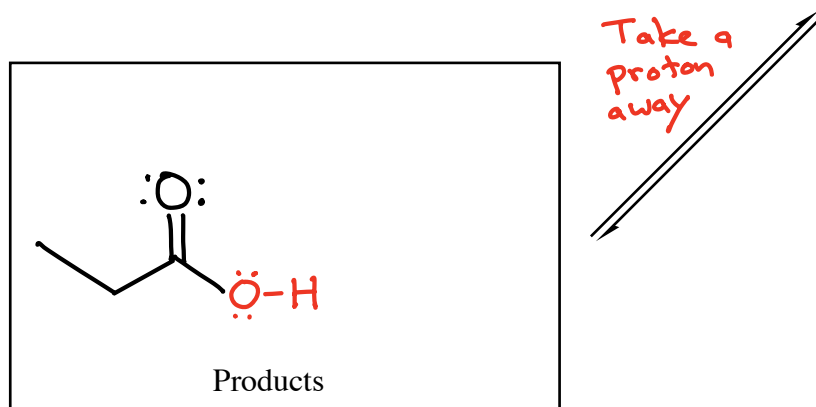
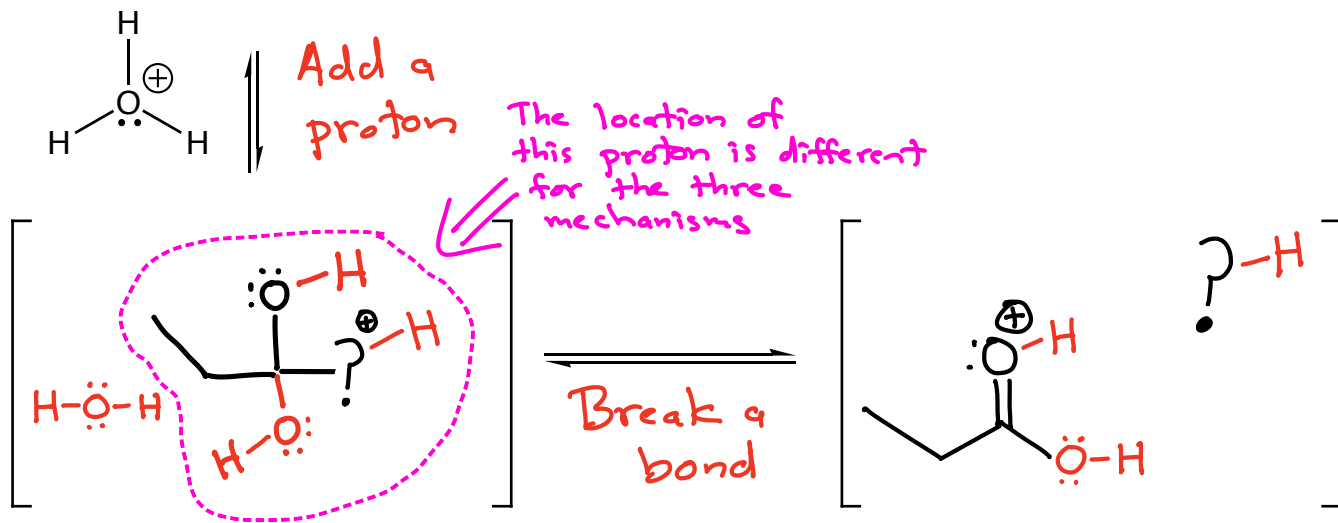
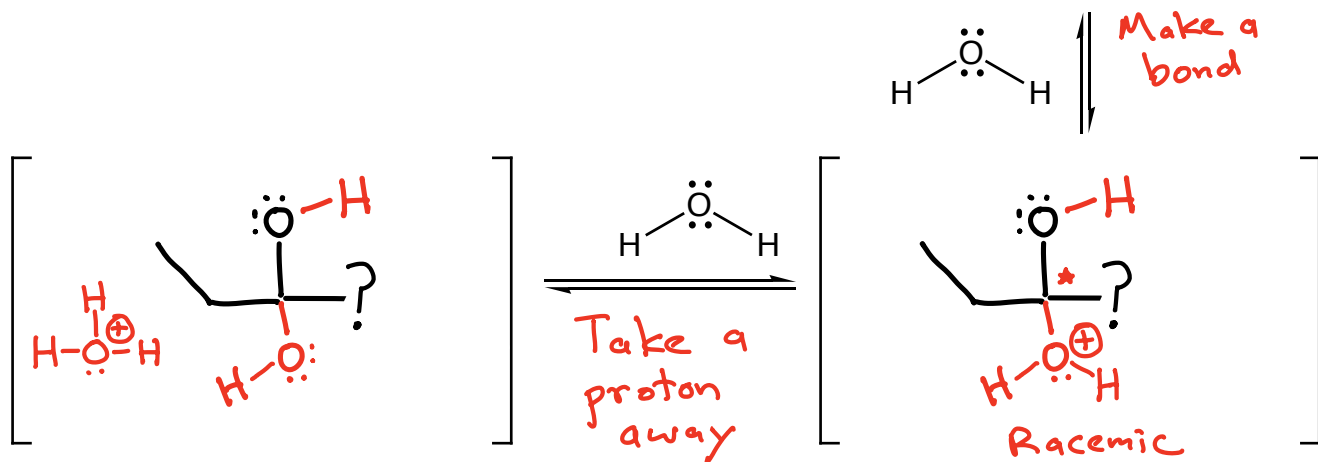
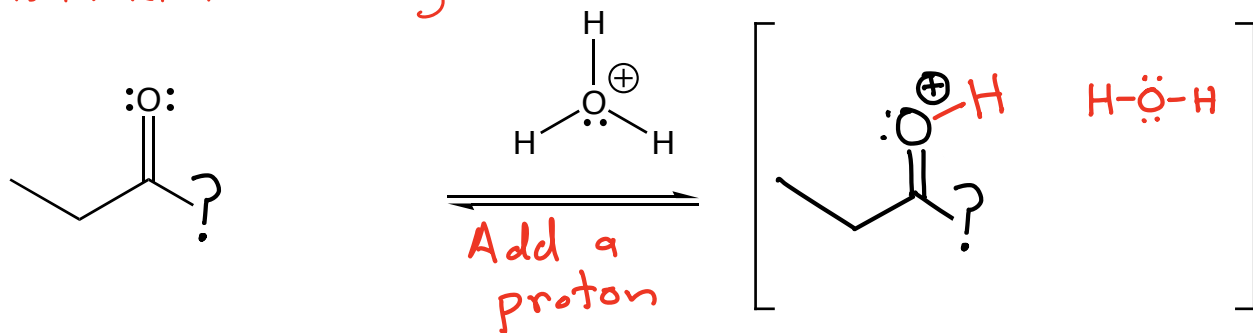


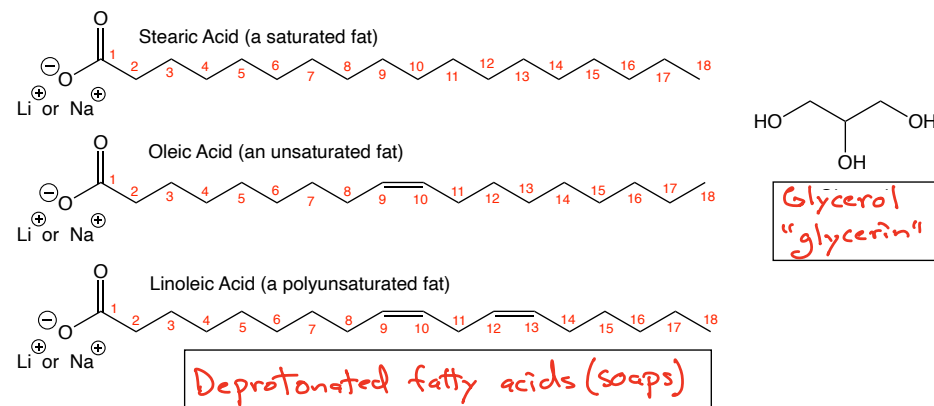
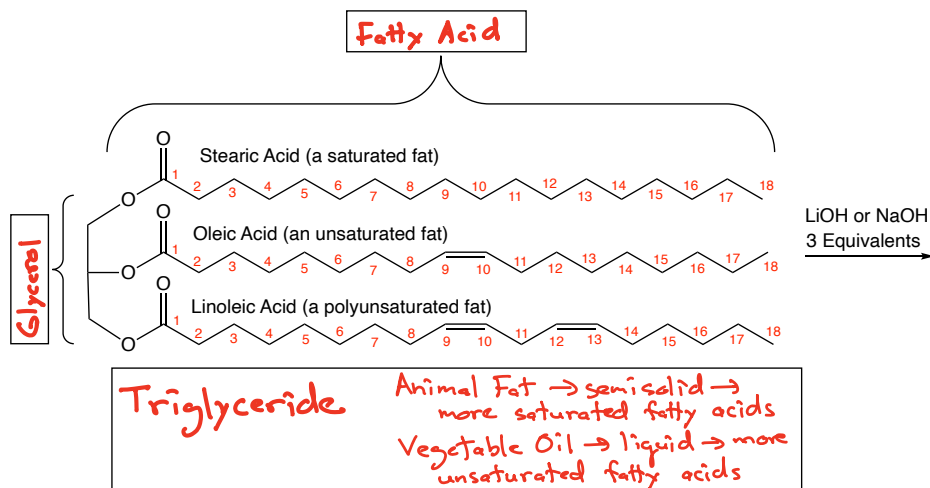
### Acid Promoted Nitrile Hydrolysis



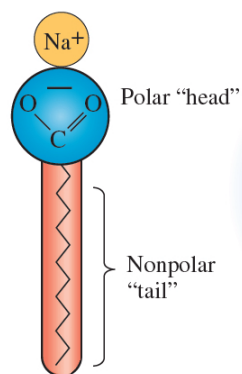
These conditions  
 are strong enough  
 to hydrolyze  
 amides according  
 to the mechanism  
 we saw as "Acid  
 Promoted Hydrolysis  
 of an Amide"

The following mechanism applies to which reaction we have seen? Trick Question → it applies to three reactions → Anhydride, ester and amide hydrolysis in acid! "Same song different verse!"

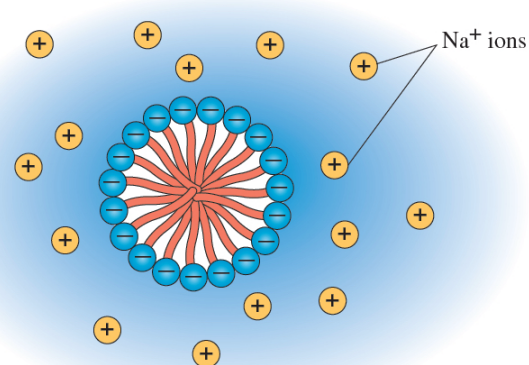




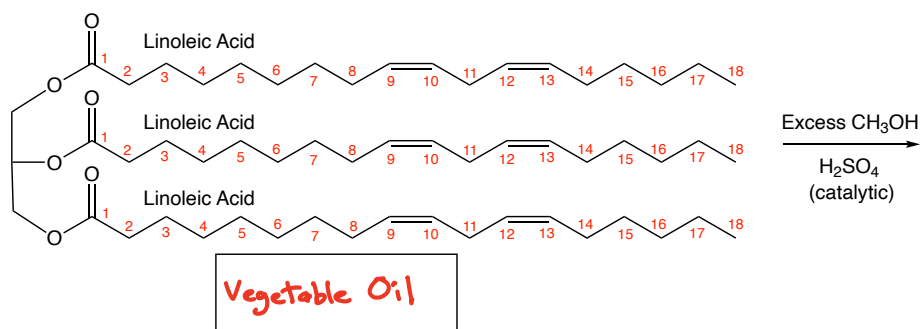
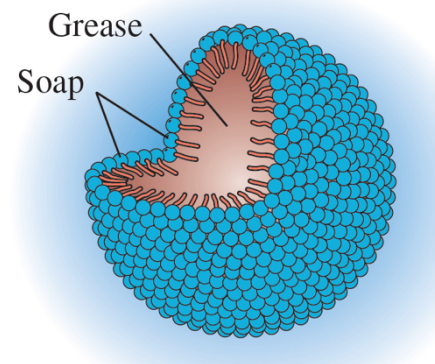
(a) A soap

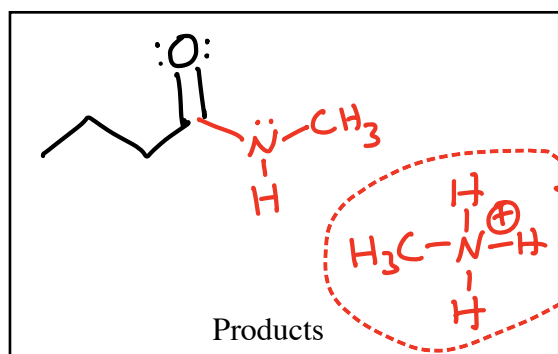
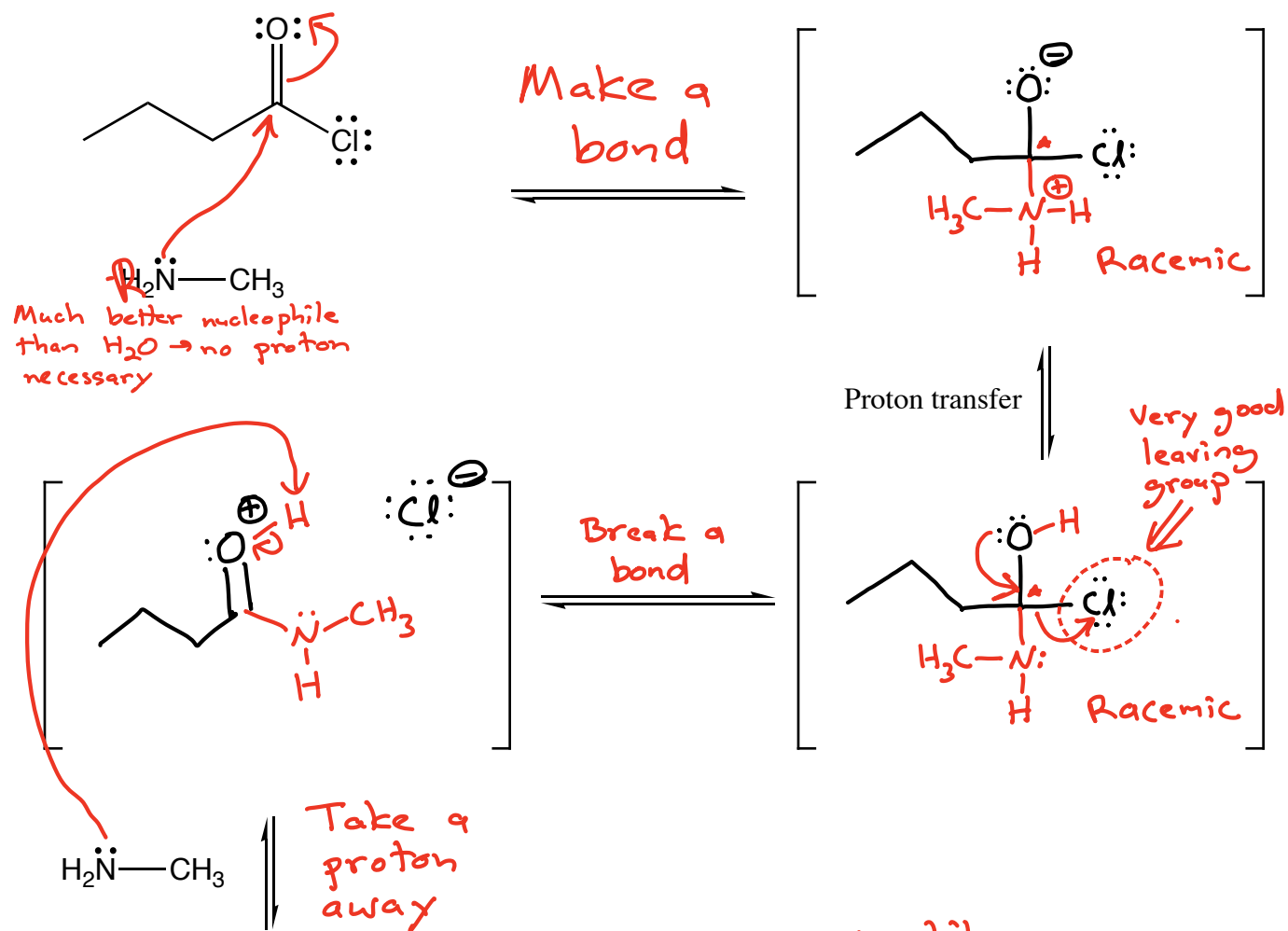
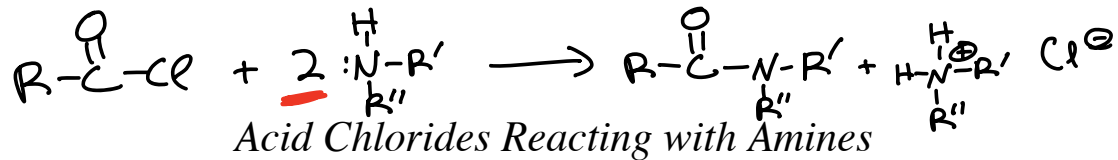


(b) Cross section of a soap micelle in water



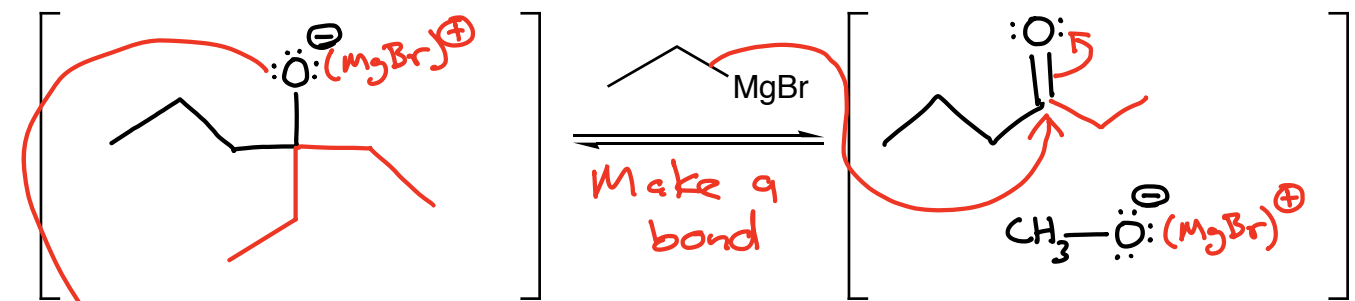
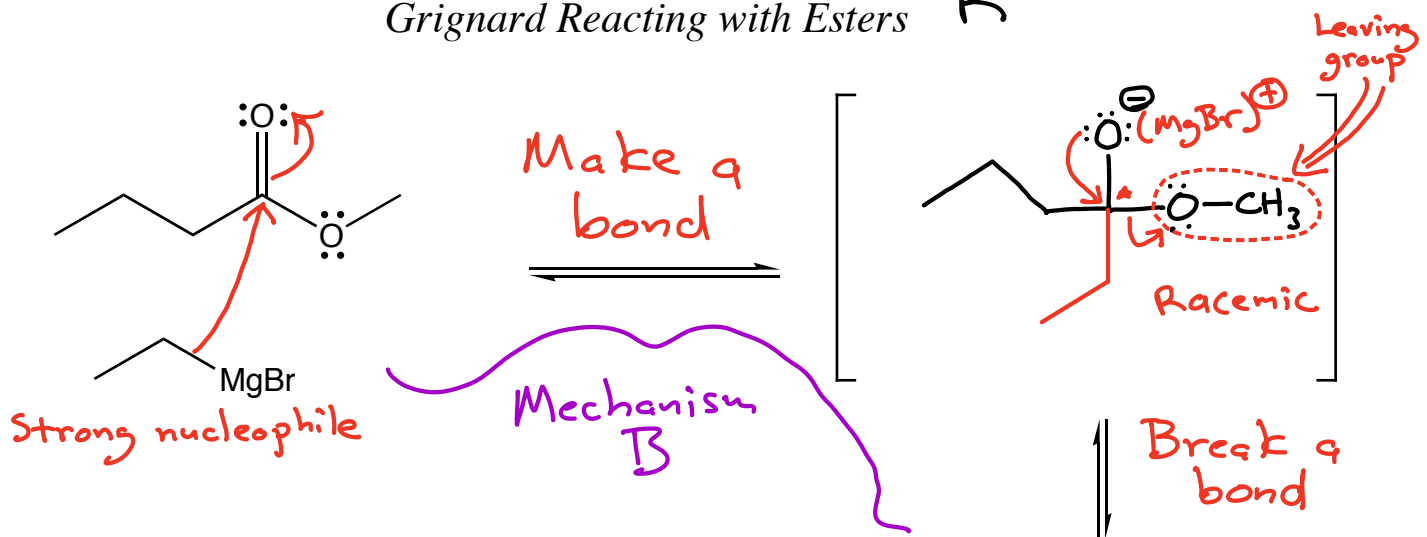
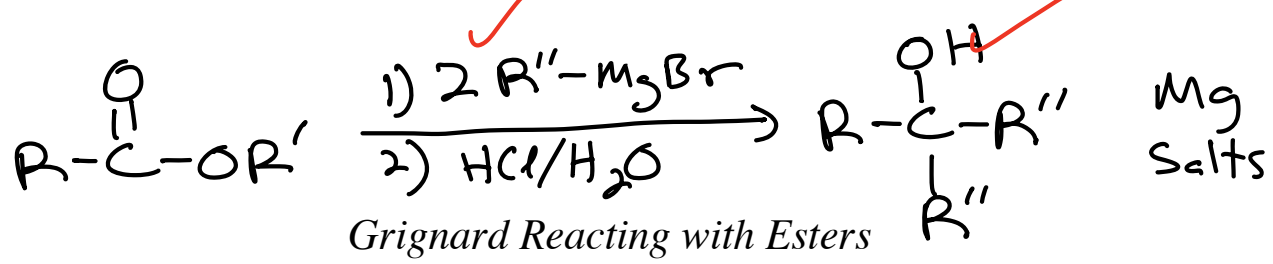
Soap micelle with "dissolved" grease





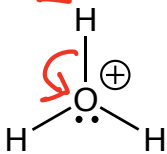
NOT a nucleophile  
so we need 2  
equivalents of  
amine for this  
reaction



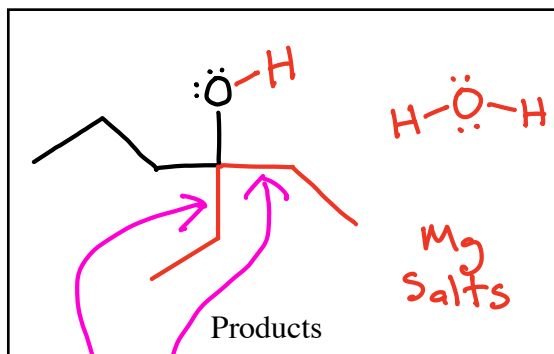


Chemist Opens Flask

2)



Add a proton



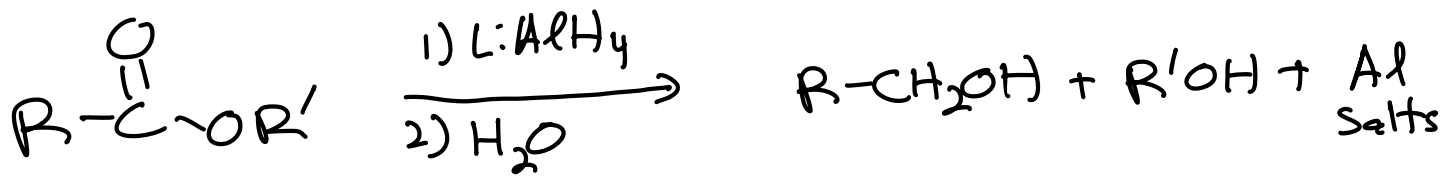
New C-C bonds

Mechanism A

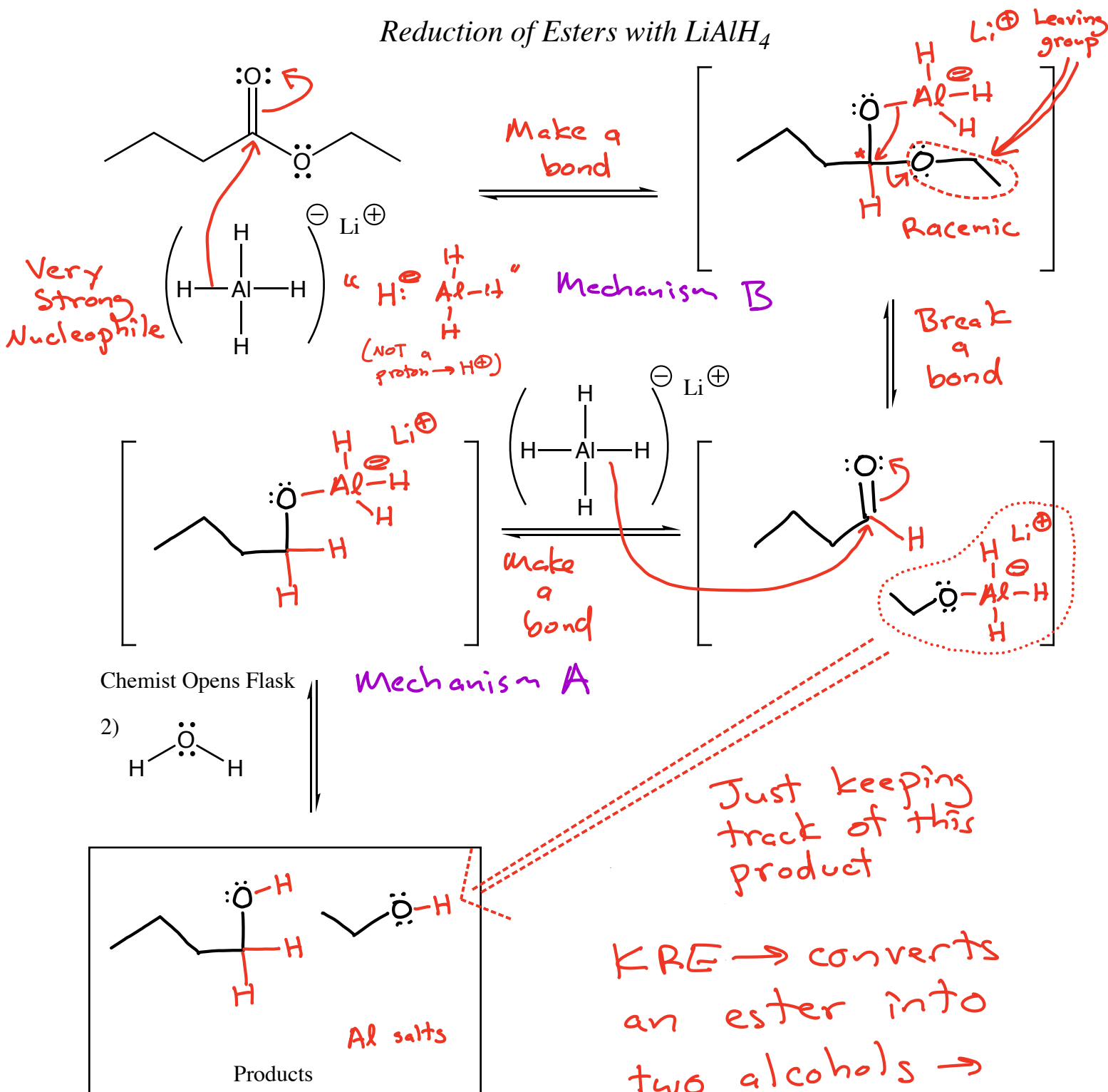
$KRE \rightarrow$  An alcohol with 2 identical new groups attached via new C-C bonds

The overall reaction mechanism is Mechanism B followed by Mechanism A

$\Rightarrow$  Same as the next reaction!

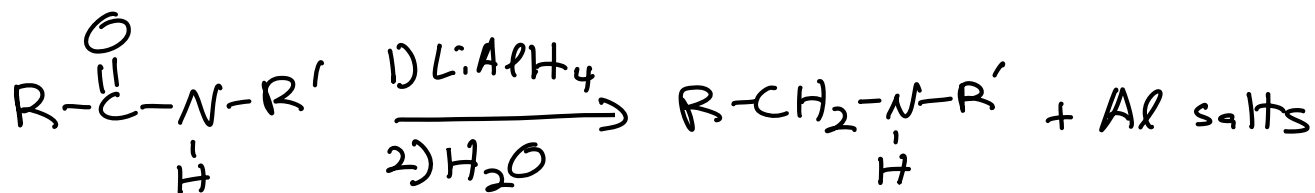


### Reduction of Esters with $LiAlH_4$

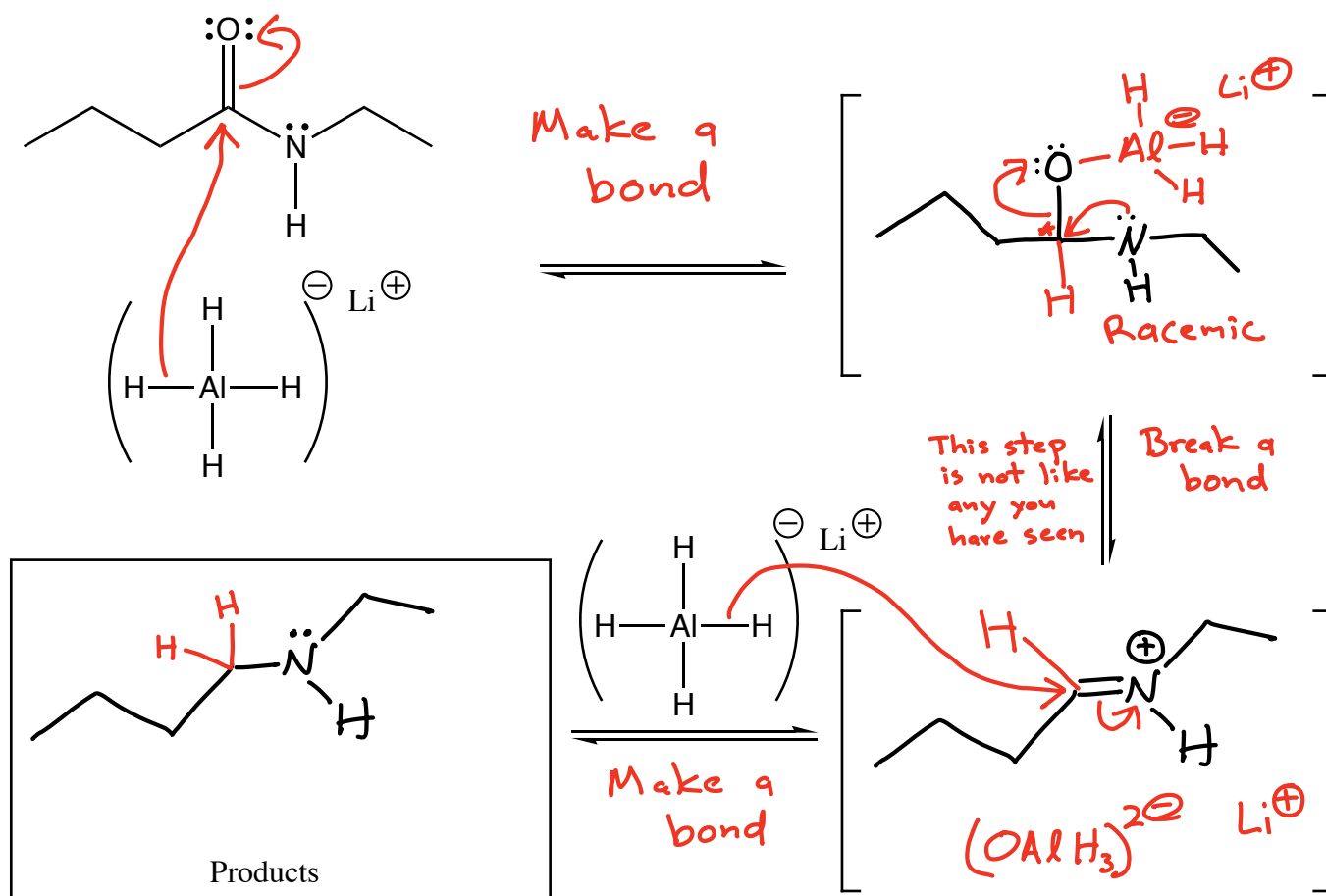


Note the extreme similarities between these last two mechanisms!

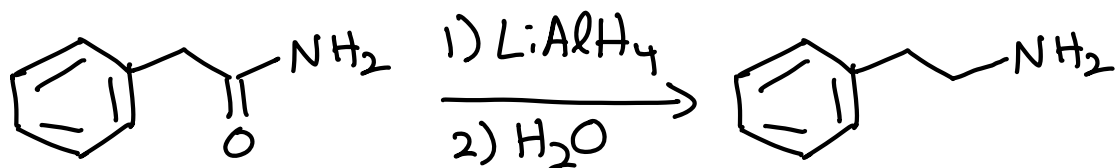
$\Rightarrow$  Mechanism B followed by Mechanism A just like the last reaction!



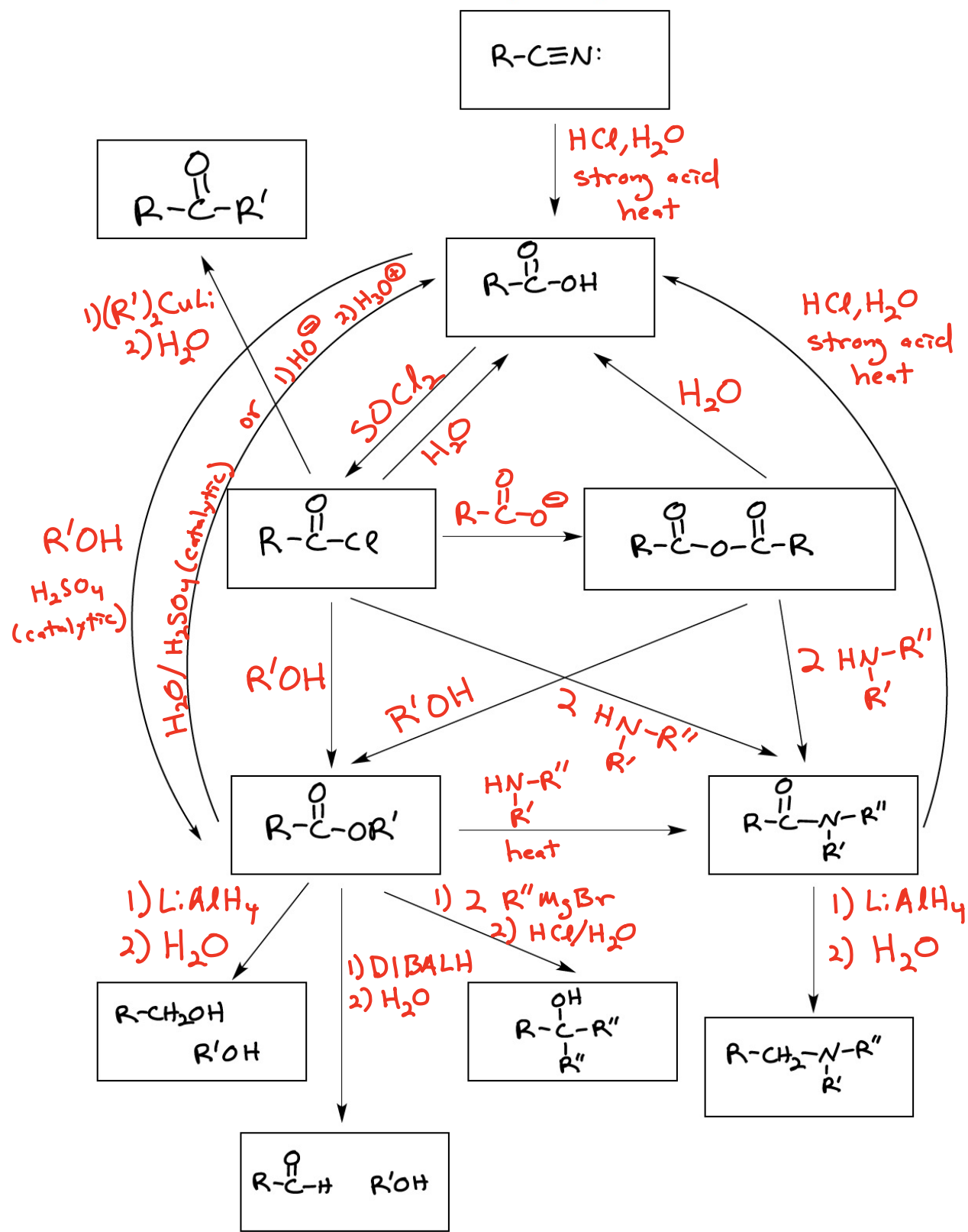
Reduction of Amides with  $\text{LiAlH}_4$



Note: In this reaction the chemist opens the flask and adds water in a second step that quenches any excess  $\text{LiAlH}_4$ . Therefore, you need a second step to add water when using this reaction in synthesis even though it is not shown in the mechanism above.



# Interconversion of Carboxylic Acid Derivatives



# Weaker bases are favored at equilibrium

Compound		pK <sub>a</sub>	
	$\text{H-Cl}$	-7	Strongest Acid (Weakest conjugate base)
Carboxylic acids*	$\text{R-CO-H}$	3-5	
β-Dicarbonyls*	$\text{RC(=O)-CH}_2\text{-C(=O)R'}$	10	
β-Ketoesters*	$\text{RC(=O)-CH}_2\text{-C(=O)OR'}$	11	
β-Diesters*	$\text{ROC(=O)-CH}_2\text{-C(=O)OR'}$	13	
Water	$\text{HOH}$	15.7	
Alcohols	$\text{RCH}_2\text{OH}$	15-19	
Acid chlorides*	$\text{RCH}_2\text{-COCl}$	16	
Aldehydes*	$\text{RCH}_2\text{-CHO}$	18-20	
Ketones*	$\text{RCH}_2\text{-C(=O)R'}$	18-20	
Esters*	$\text{RCH}_2\text{-C(=O)OR'}$	23-25	
Terminal alkynes	$\text{RC}\equiv\text{C-H}$	25	
LDA	$\text{H-N}(i\text{-C}_3\text{H}_7)_2$	40	
Terminal alkenes	$\text{R}_2\text{C=CH-H}$	44	
Alkanes	$\text{CH}_3\text{CH}_2\text{-H}$	51	Weakest Acid (Strongest conjugate base)

A) Reactions are favored (i.e. have a motive) if they lead to formation of a weaker acid and/or weaker base.

B) Checking pK<sub>a</sub> values can predict if a reaction has a motive even if there are other steps besides a proton transfer.

C) Recall that the conjugate base of a stronger acid (lower pK<sub>a</sub>) is a weaker base.

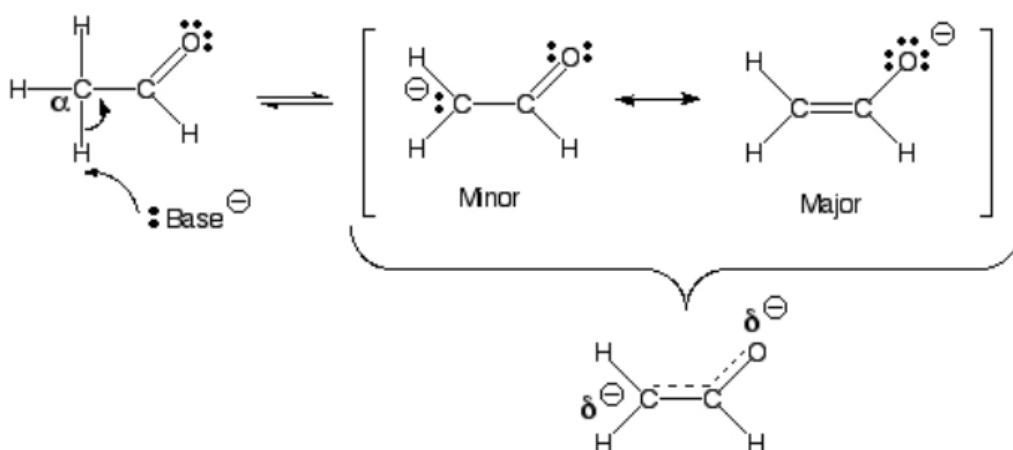
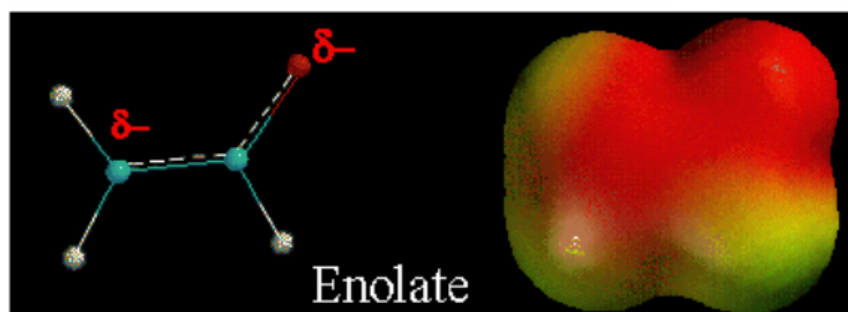
D) Check the pK's of the conjugate acid of the bases on either side of the equation. Lower pK<sub>a</sub> value corresponds to stronger acid of the conjugate acid, and thus weaker conjugate base. The base with a stronger conjugate acid (lower pK<sub>a</sub> value) will be the weaker base and will be favored at equilibrium.

E) Another way to look at it is that the base that is favored at equilibrium is the one that has the more stabilized anion, i.e. the one with the charge spread around more (electronegative) atoms.

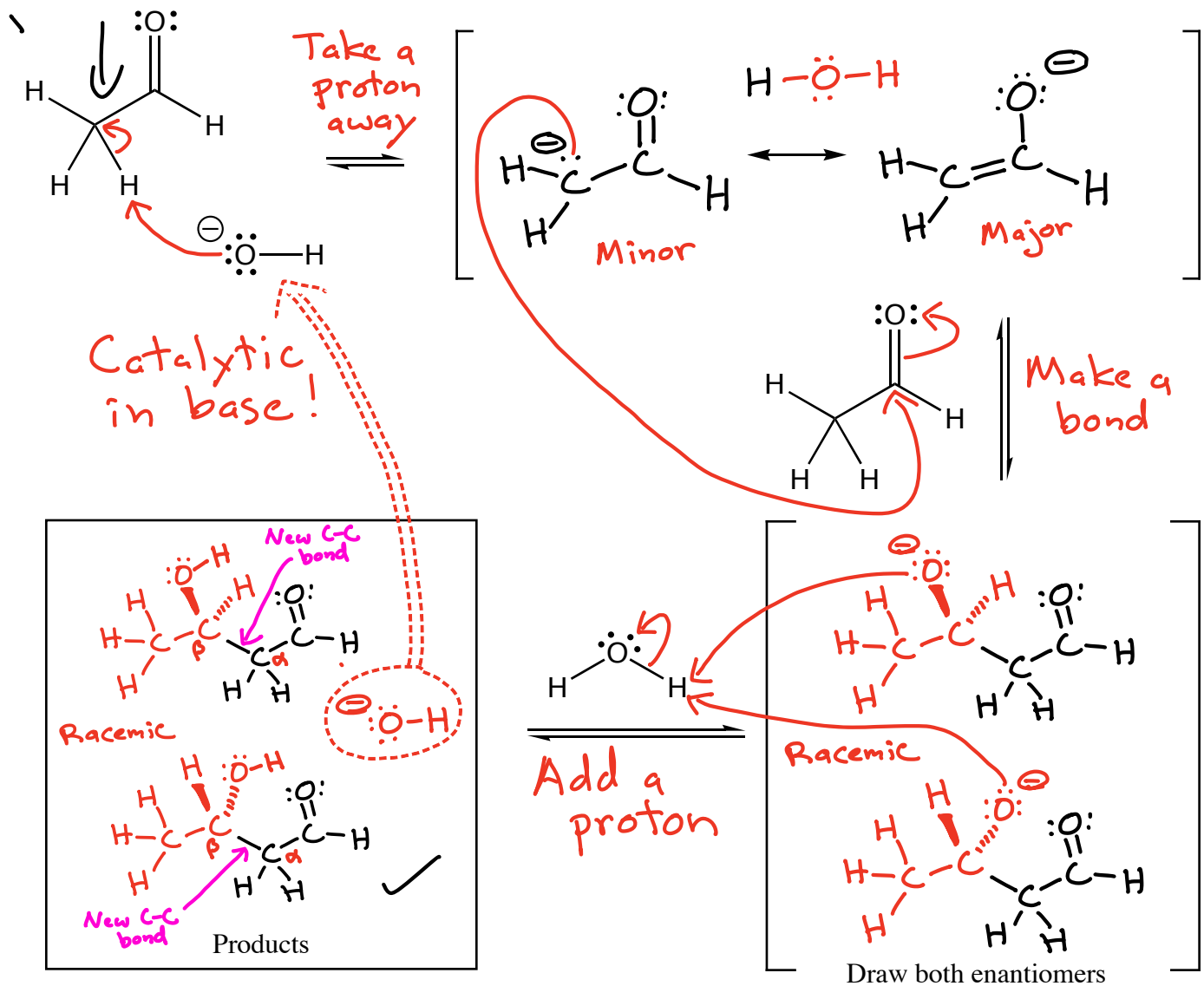
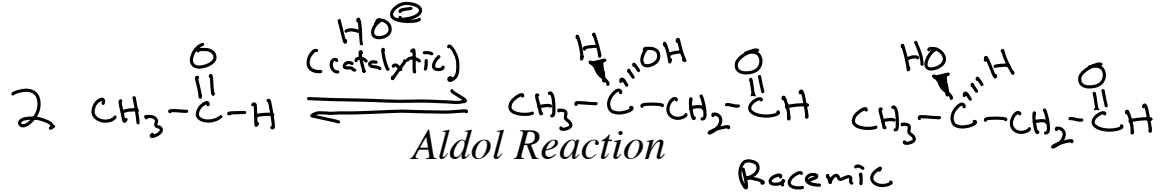
F) Above is a pK<sub>a</sub> table that we will refer to often.

\*These have resonance stabilized anions

# Enolates as nucleophiles



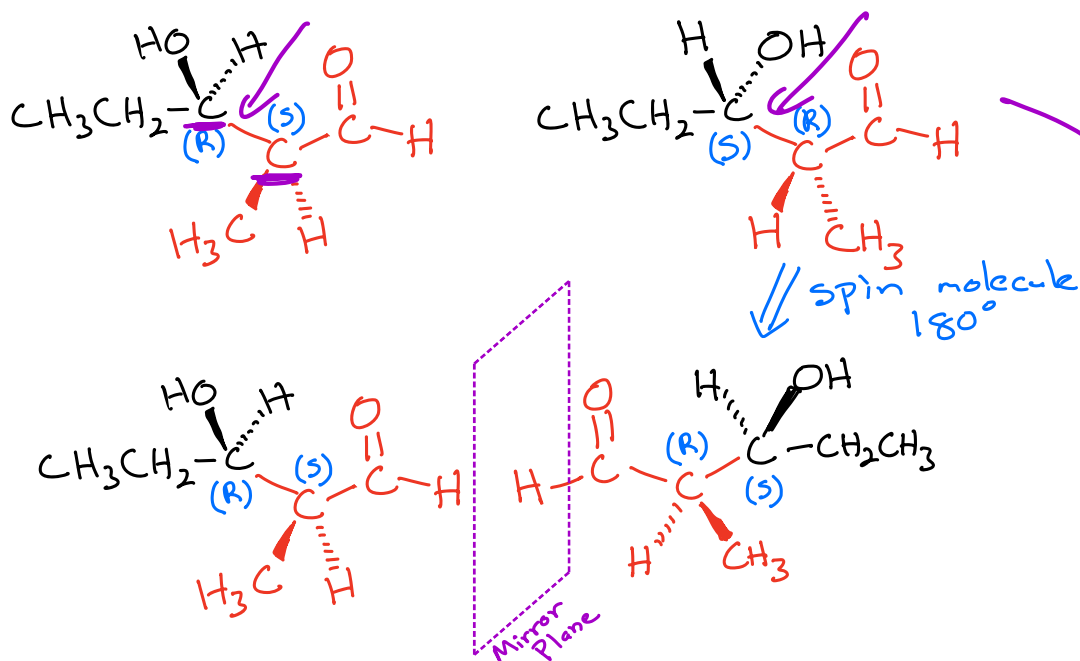
- A) Enolates are resonance stabilized, with a partial negative charge on carbon and oxygen. ✓
- B) Enolates are nucleophiles, so they could react at either the carbon atom or oxygen atom. The partial negative charges give them the **opportunity** to react at either the carbon or oxygen.
- C) Reaction at the carbon atom gives the final product a  $\text{C}=\text{O}$  bond, while reaction at the oxygen atom gives the final product a  $\text{C}=\text{C}$  bond. However,  $\text{C}=\text{O}$  bonds are stronger than  $\text{C}=\text{C}$  bonds, so the **motive is to react at the carbon atom with most electrophiles.**



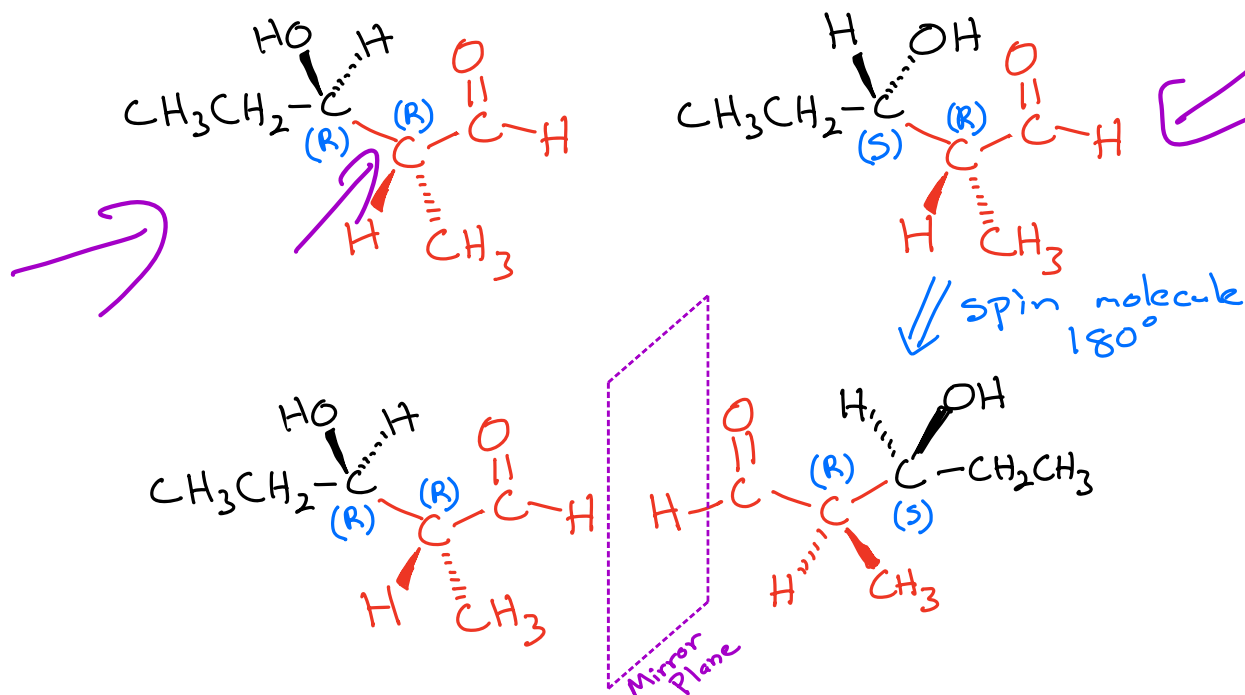
KRE  $\rightarrow$   $\beta$ -hydroxy aldehyde  
with a new C-C  
bond between the  
aldehyde  $\alpha$  and  $\beta$   
carbons

Mechanism  
A

# Enantiomers or Diastereomers?



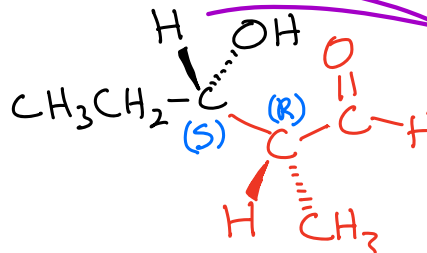
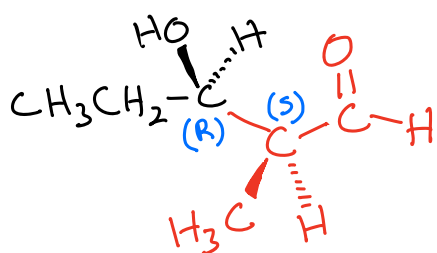
**Enantiomers** (Section 3.2) Stereoisomers that are nonsuperposable mirror images of each other; refers to a relationship between pairs of objects.



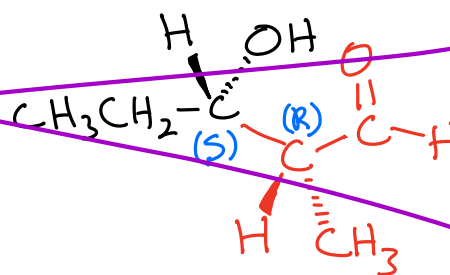
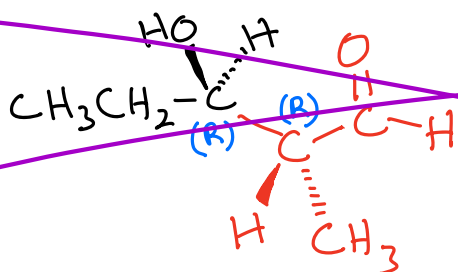
**Diastereomers** (Section 3.4A) Stereoisomers that are not mirror images of each other; refers to relationships among two or more objects.



Which pair of molecules  
could be a racemic mixture?

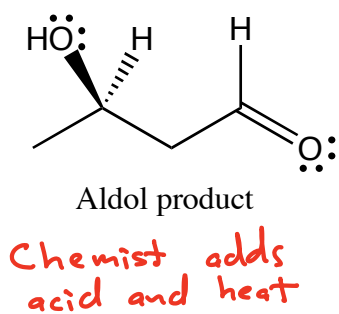


OR

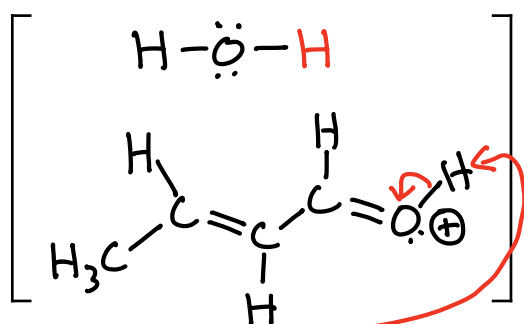
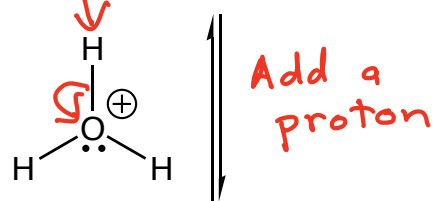
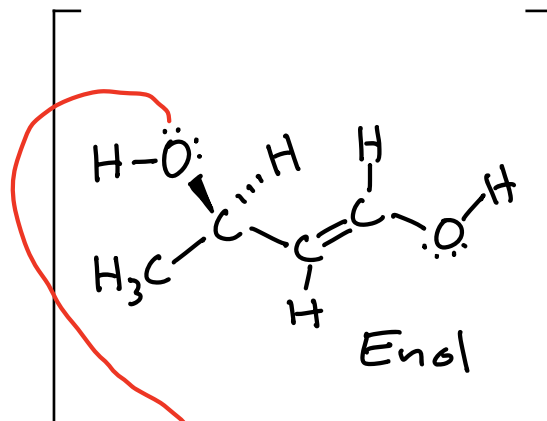


**Racemic mixture** (Section 3.7C) A mixture of equal amounts of two enantiomers.

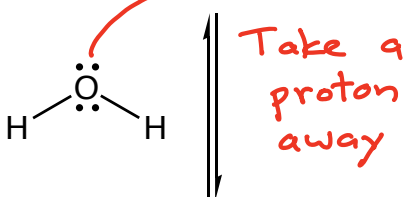
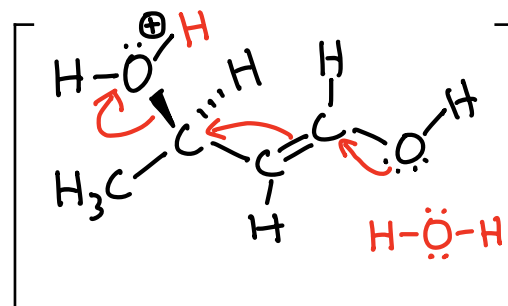
# Acid catalyzed dehydration



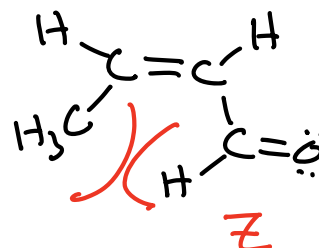
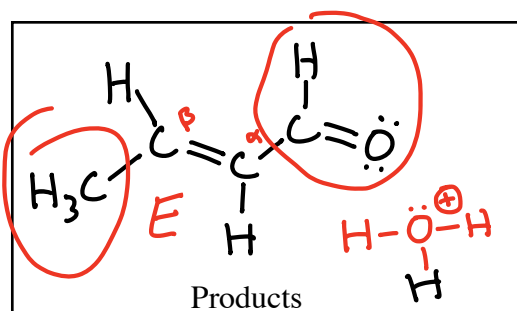
tautomerization



Break a bond



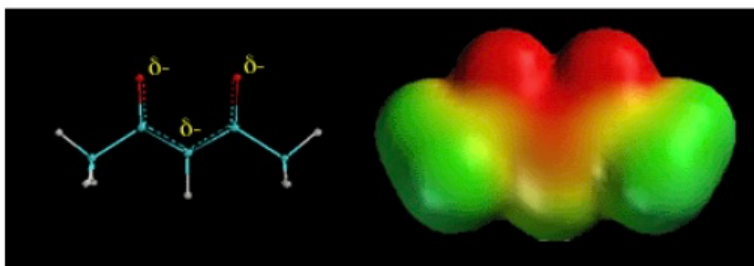
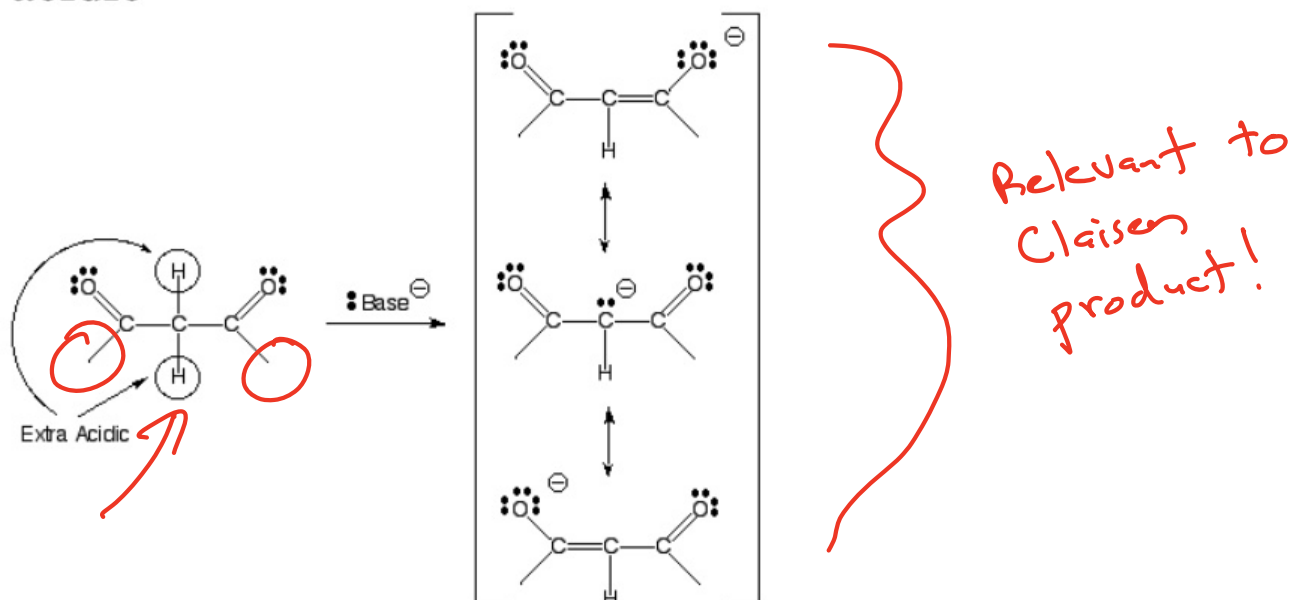
KRE → α,β-unsaturated aldehyde → the C=C is where the new C-C bond is located



Not much of the Z product is formed because it has significantly more steric strain than E

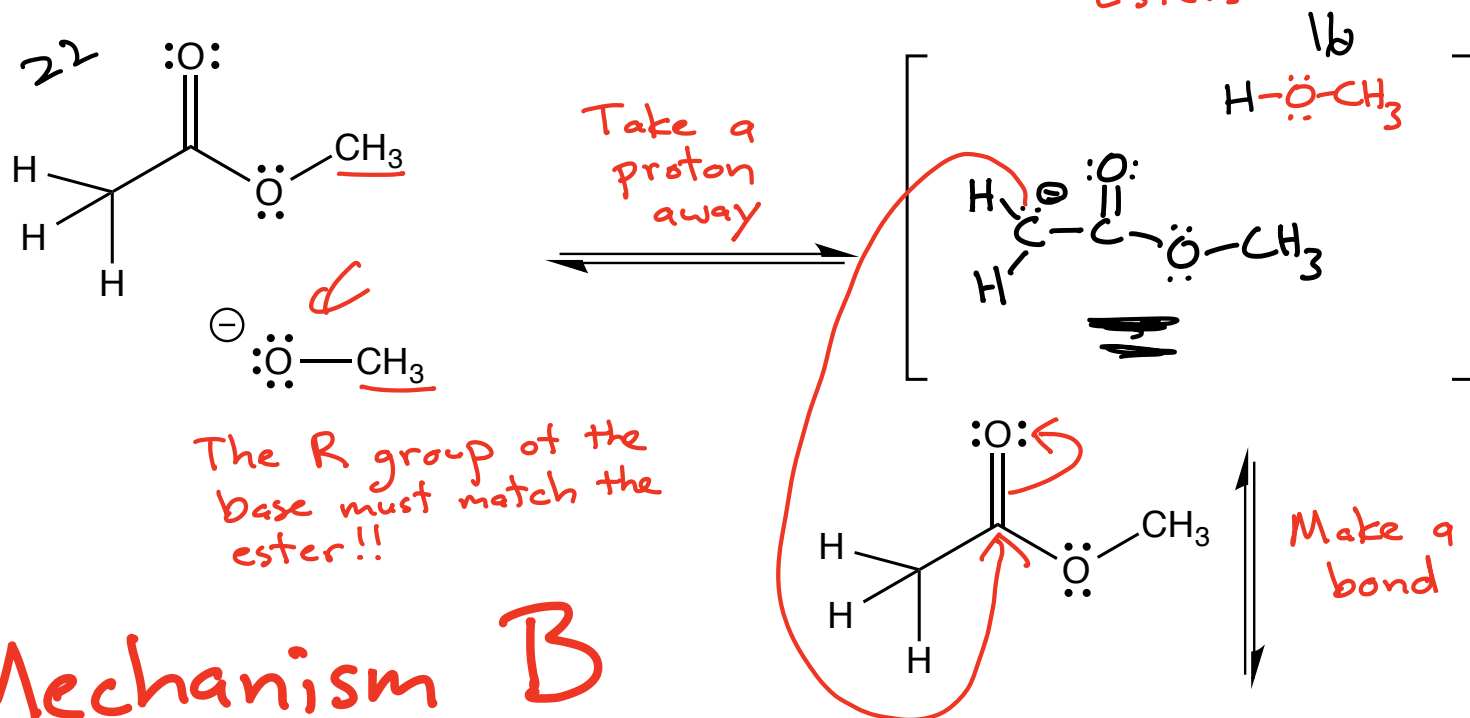
THIS IS UNIQUE TO THIS EXAMPLE  
 ↓  
 USUALLY BOTH E AND Z ARE FORMED

Beta-dicarbonyls have alpha-hydrogens that are extra acidic

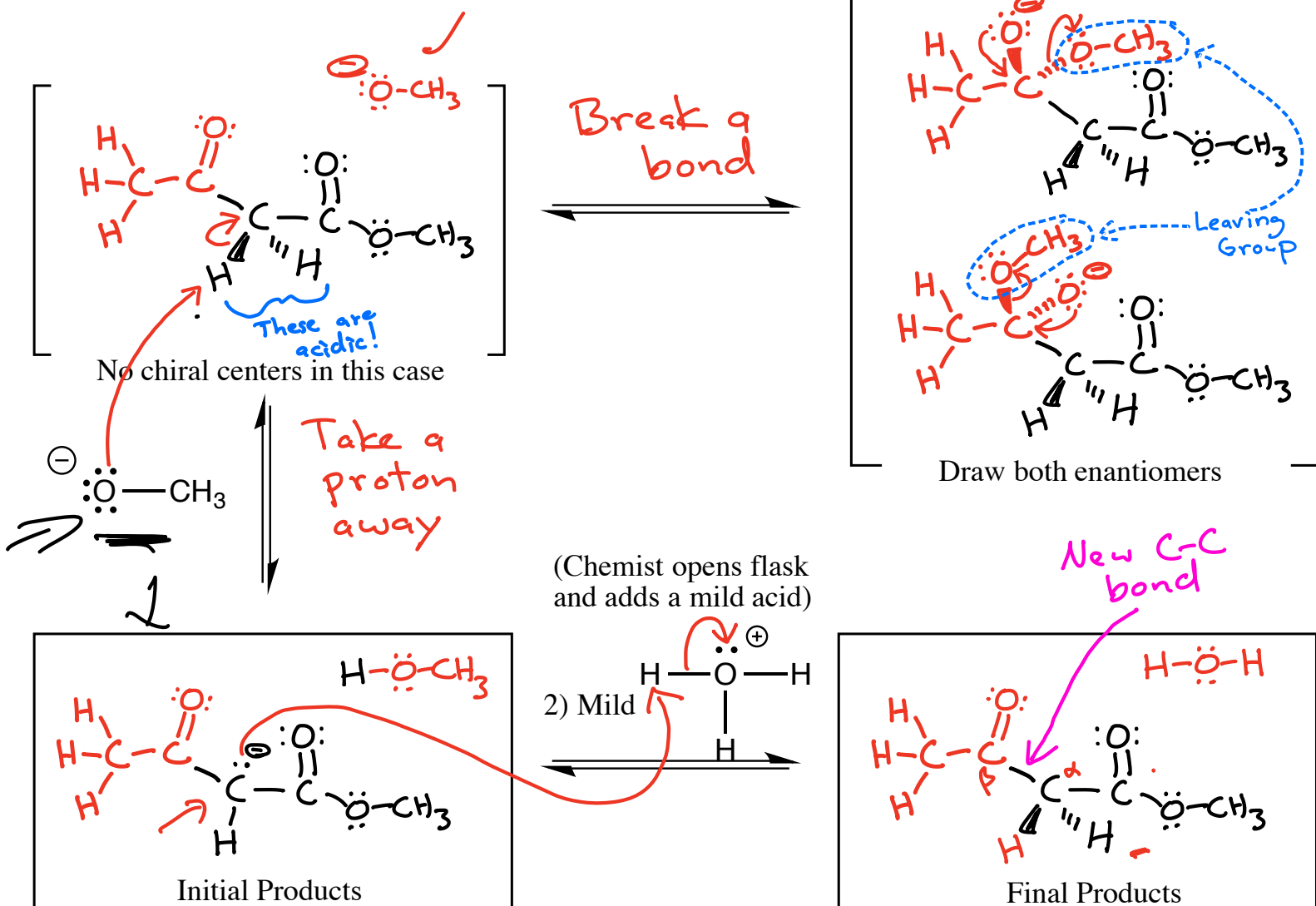


The C-H hydrogen atoms between two carbonyl groups are even more acidic than normal alpha hydrogens because the resulting anion is double resonance stabilized. The above electrostatic potential surface shows how the negative charge (red color) is spread over all three atoms as predicted by the three resonance contributing structures.

# Claisen Condensation → "Aldol with Esters"

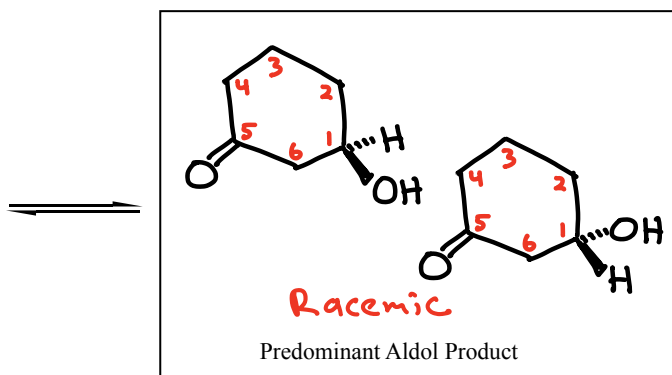
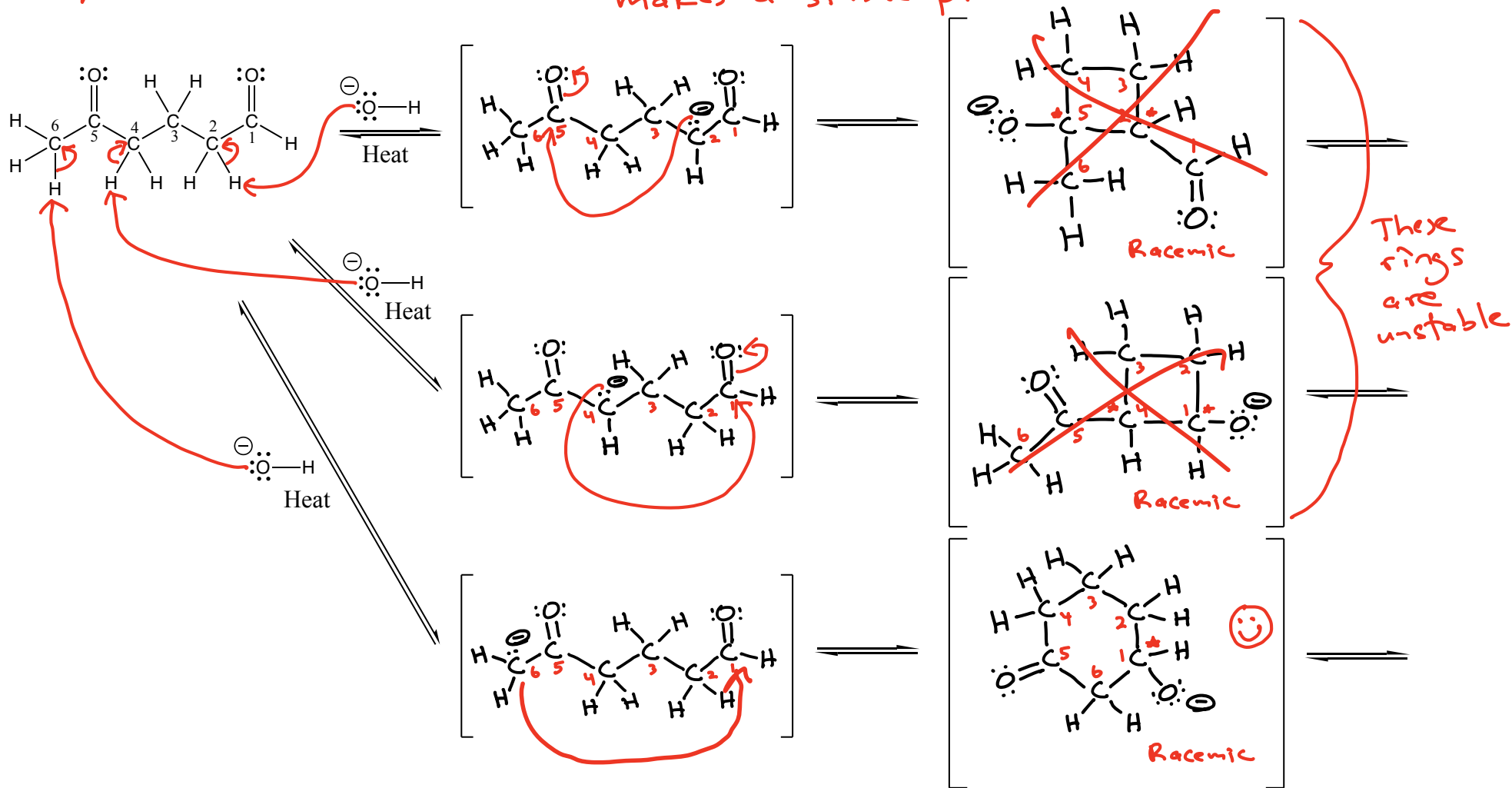


## Mechanism B

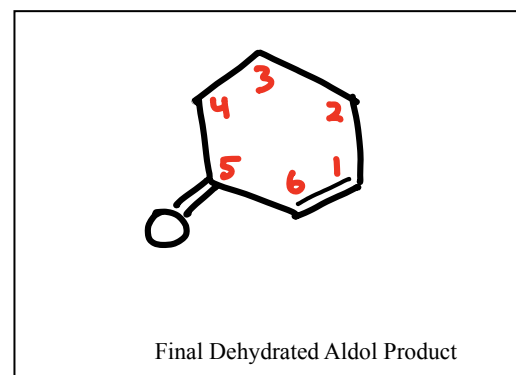


This is a much more stable anion compared to  $\text{CH}_3\text{O}^-$ , providing a strong driving force (motive) for the Claisen condensation reaction

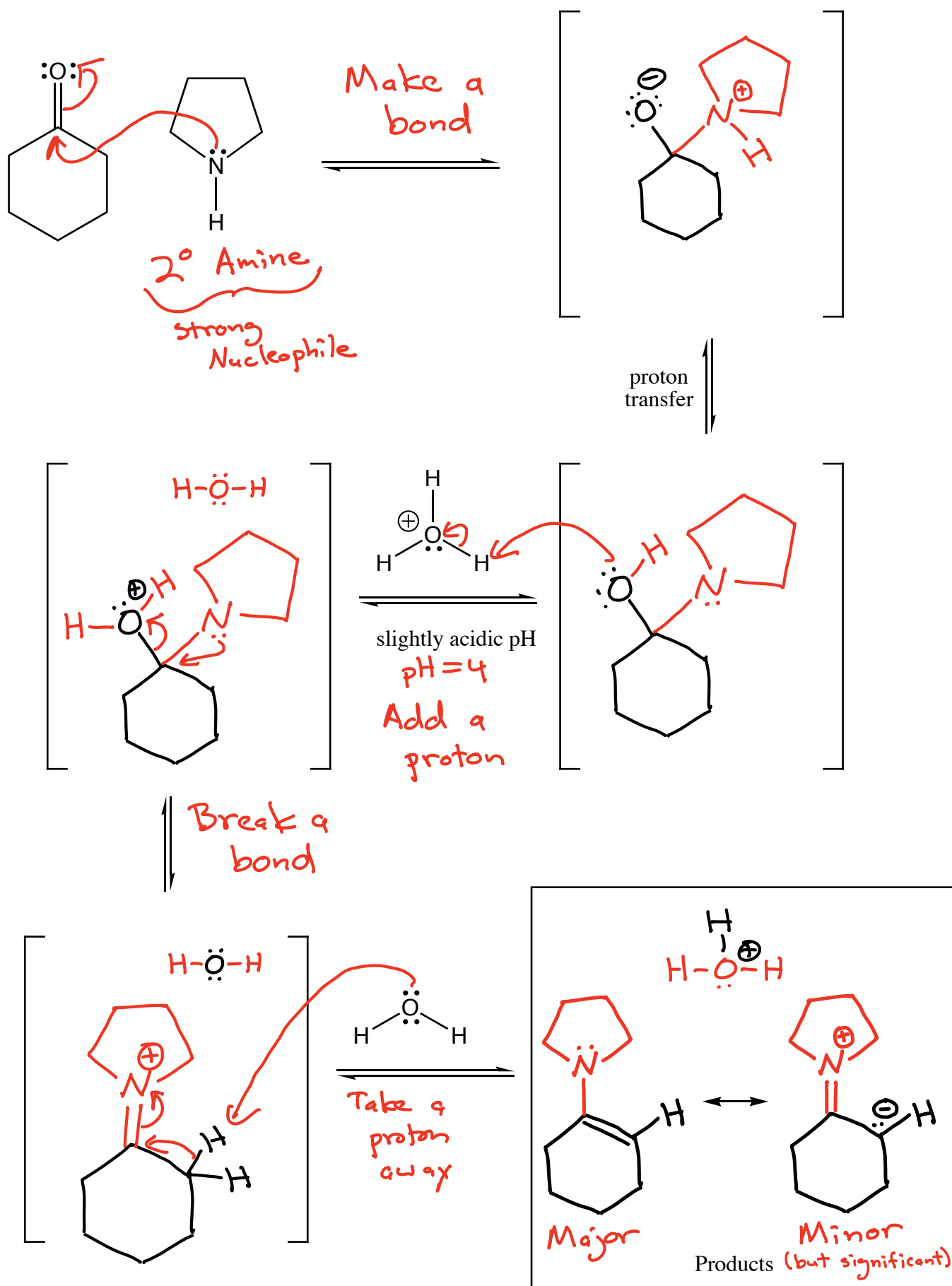
Cyclic Aldol Reaction  $\rightarrow$  3 different enolates are possible, but only one makes a stable product



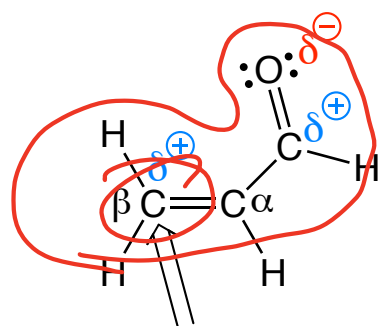
Dehydration



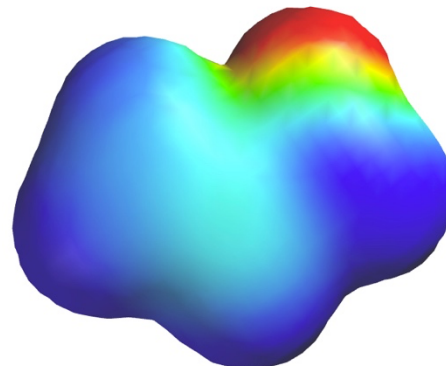
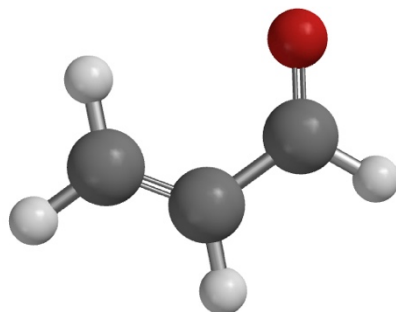
## Enamine Formation



# Conjugate Addition



Nucleophiles react here via conjugate addition



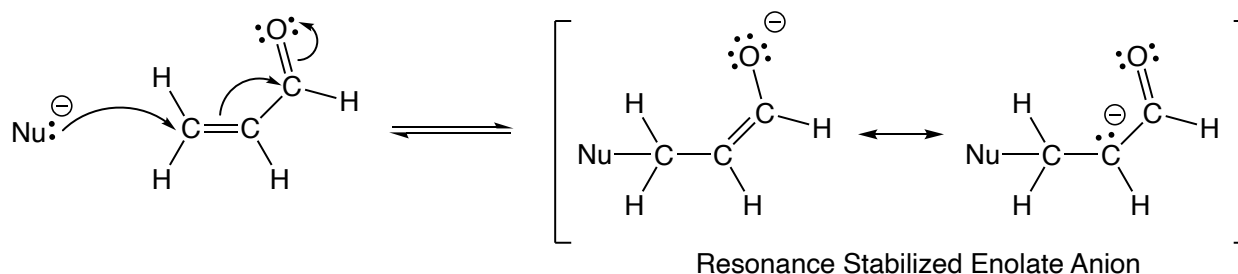
A) Alkenes adjacent to a carbonyl are conjugated and are therefore electrophilic. ✓

B) These species are called  $\alpha,\beta$  unsaturated carbonyl compounds.

C)  $\alpha,\beta$  unsaturated carbonyl compounds are conjugated, in that the pi electrons of the  $C=C$  and  $C=O$  bonds can delocalize over all four atoms. This lends some degree of extra stabilization to these species, because [pi electrons prefer to delocalize](#).

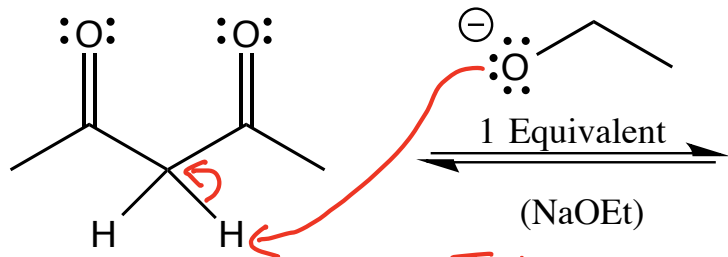
D) Nucleophiles can, however, react at the  $\beta$  carbon atom in a process called conjugate addition.

E) Conjugate addition is favorable because the intermediate formed is a resonance stabilized enolate, thus relatively low energy.

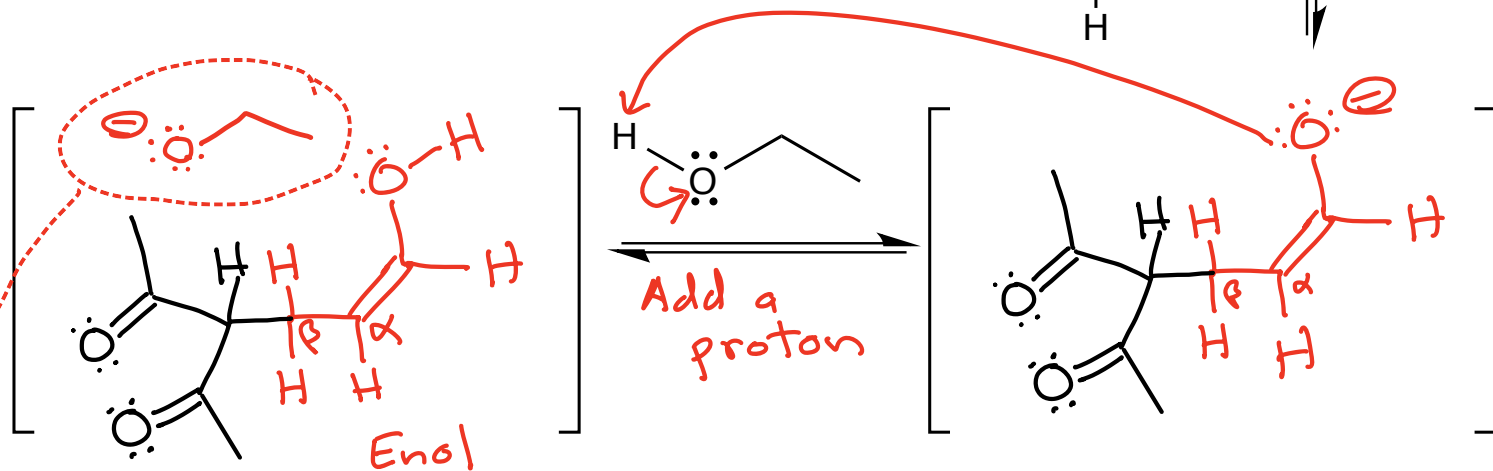
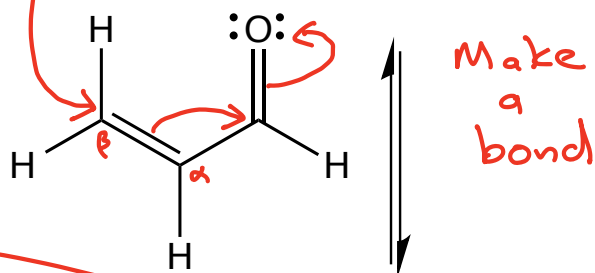
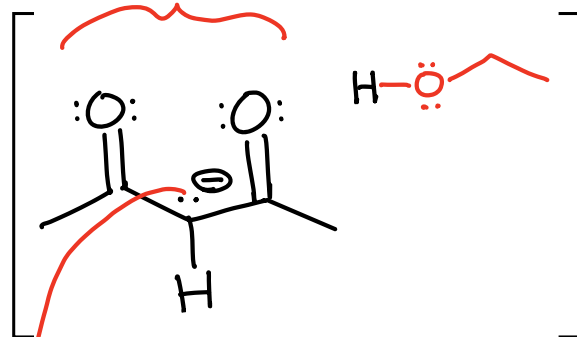


# Michael Reaction

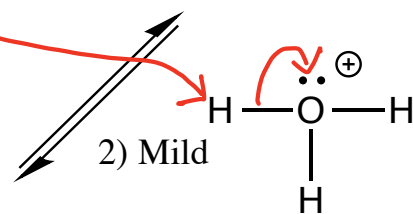
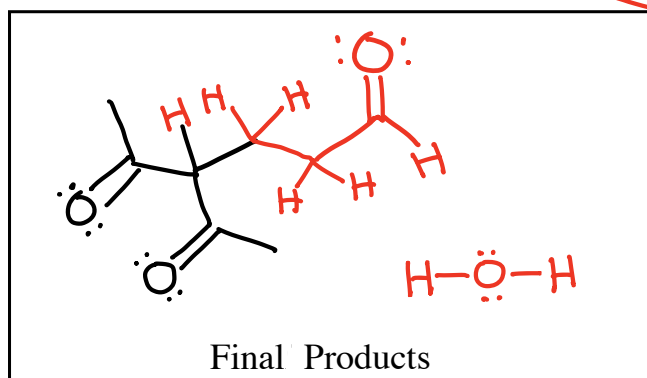
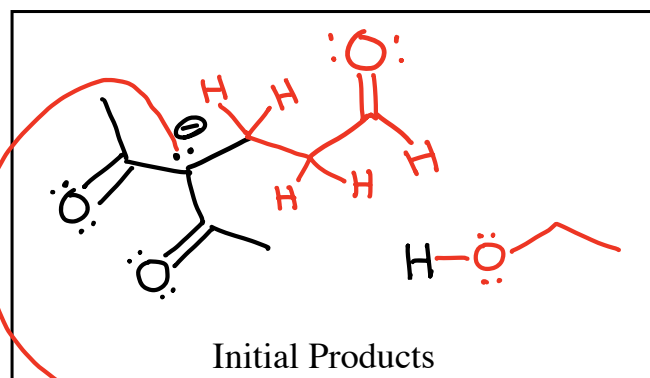
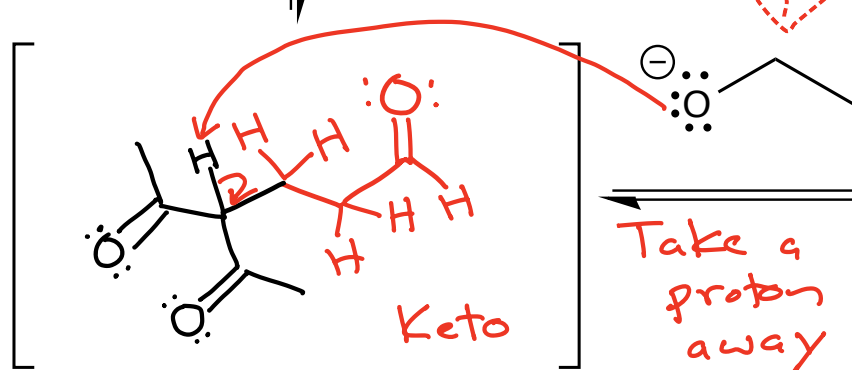
Nucleophile!



Take a proton away



tautomerization

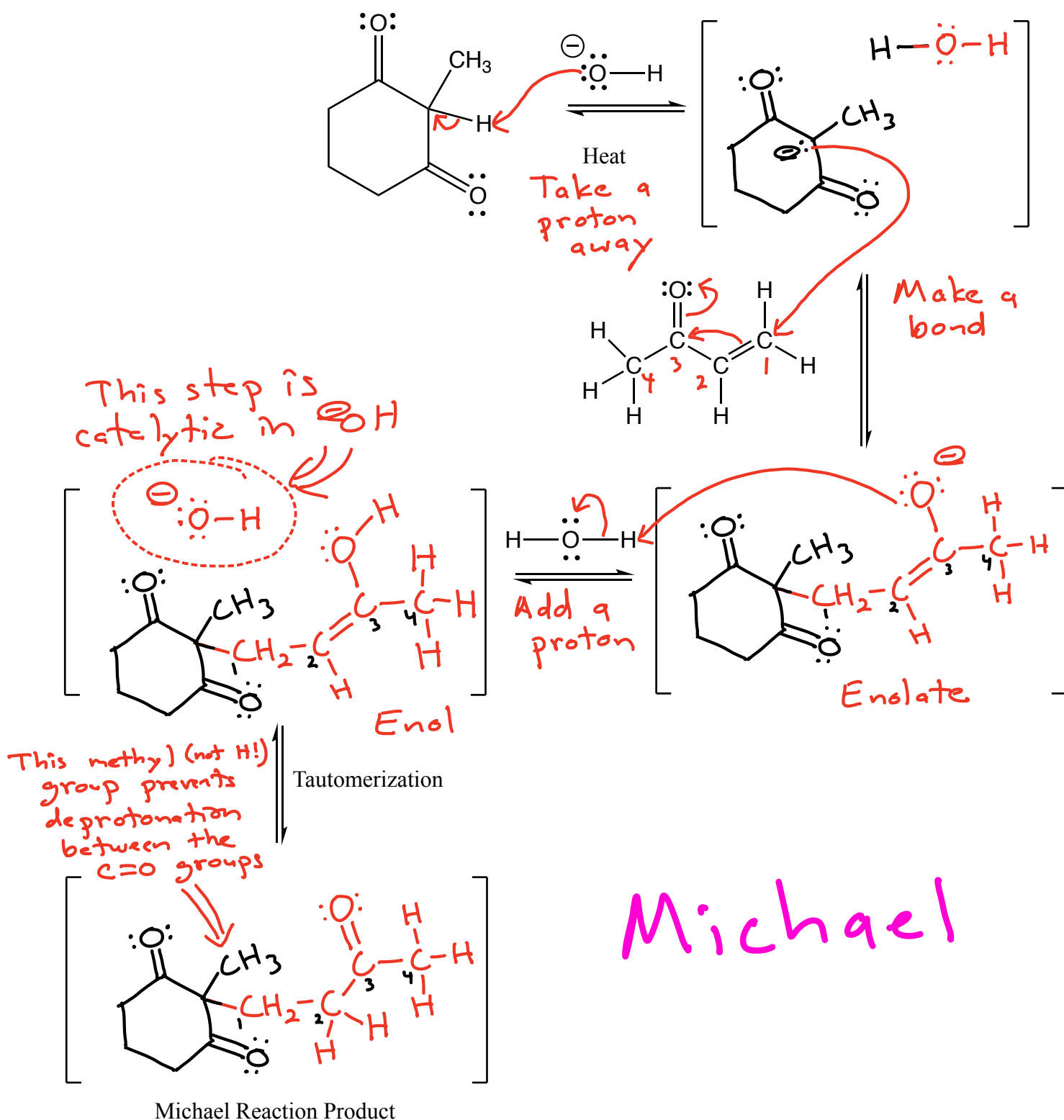


(Chemist opens flask and adds a mild acid)

Add a proton

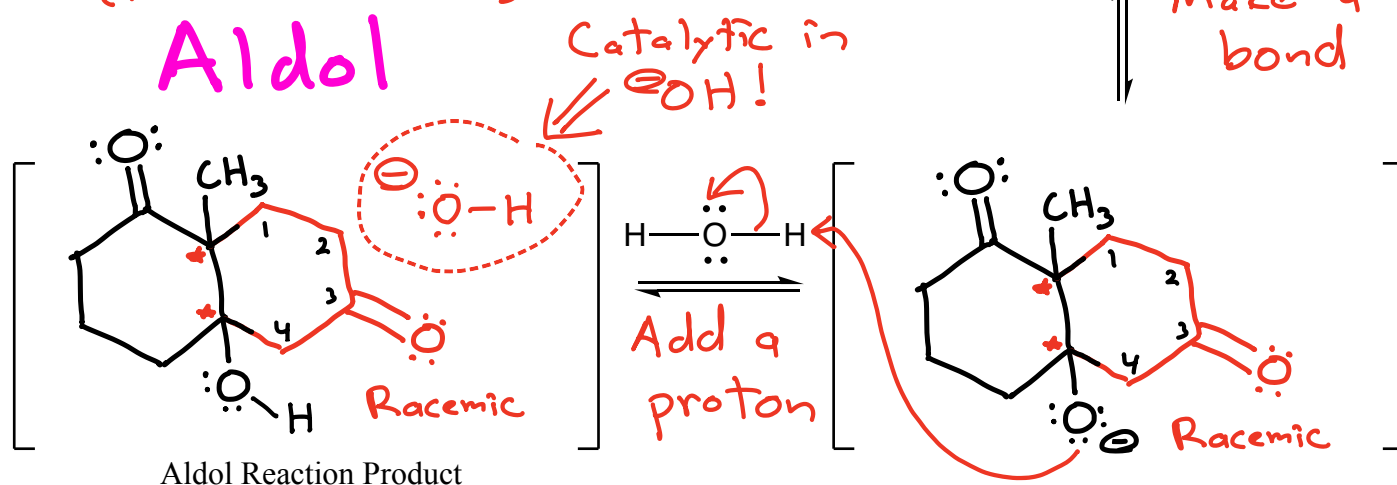
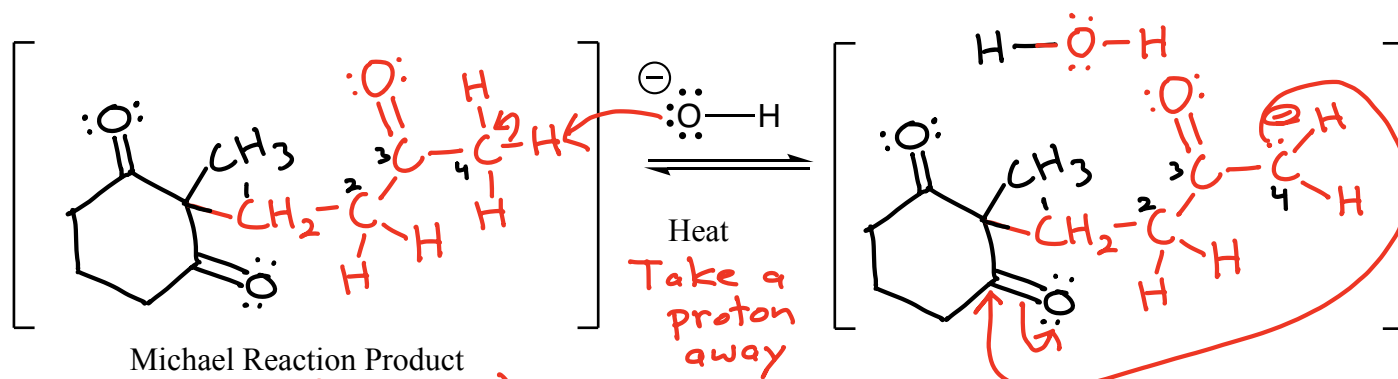


## Robinson Annulation Part 1 - Michael Reaction Steps



Michael

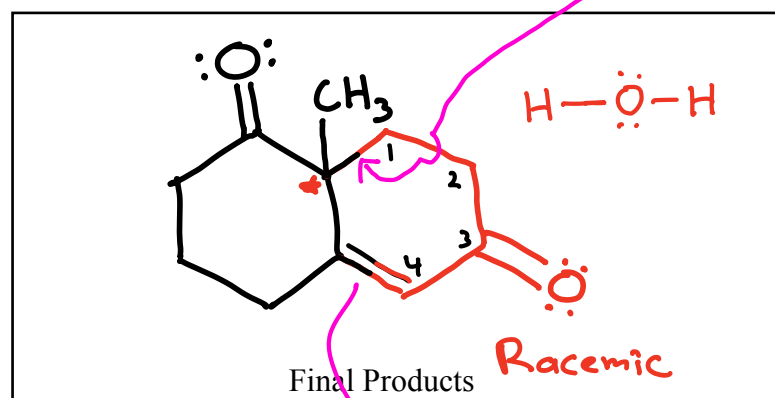
## Robinson Annulation Part 2 - Aldol and Dehydration Steps

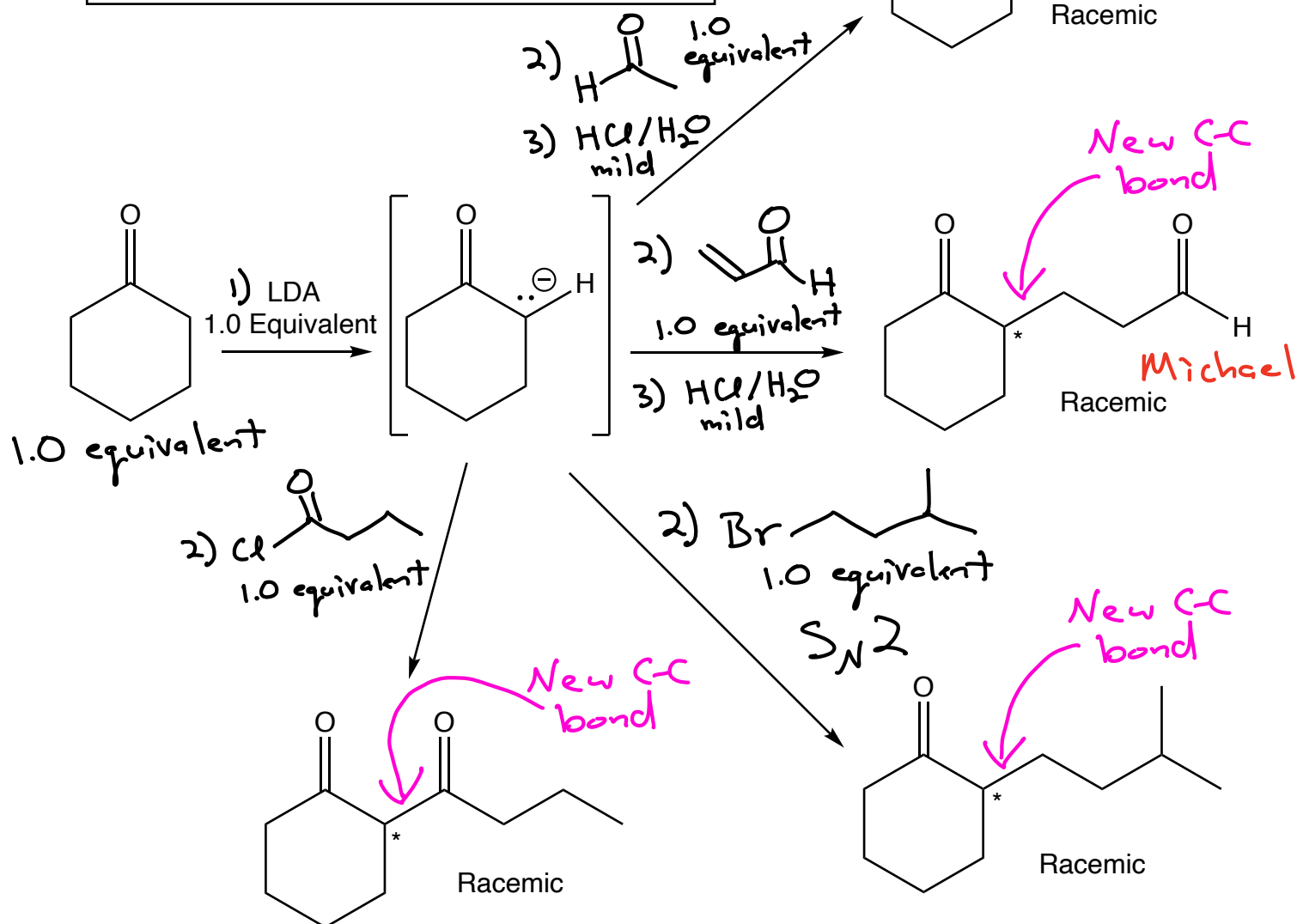
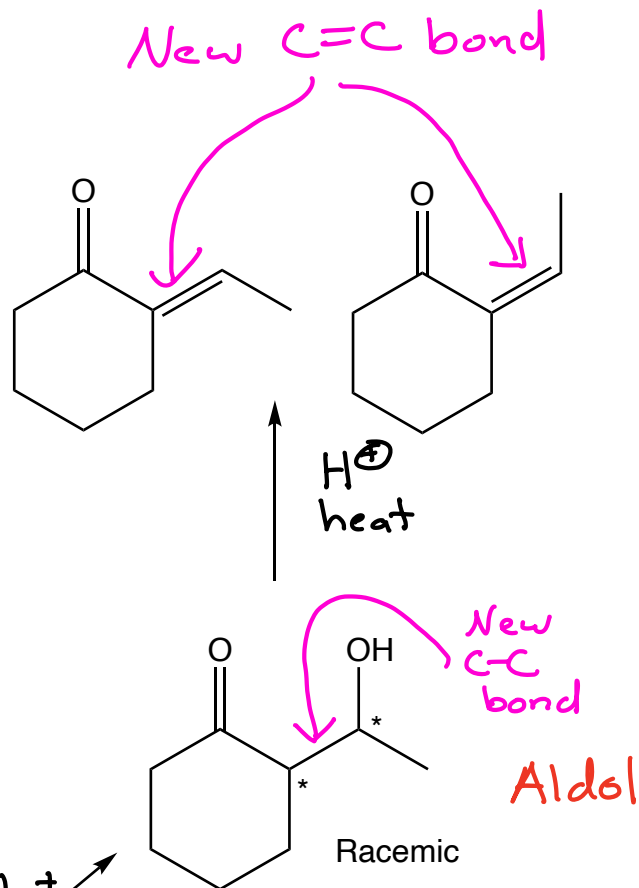
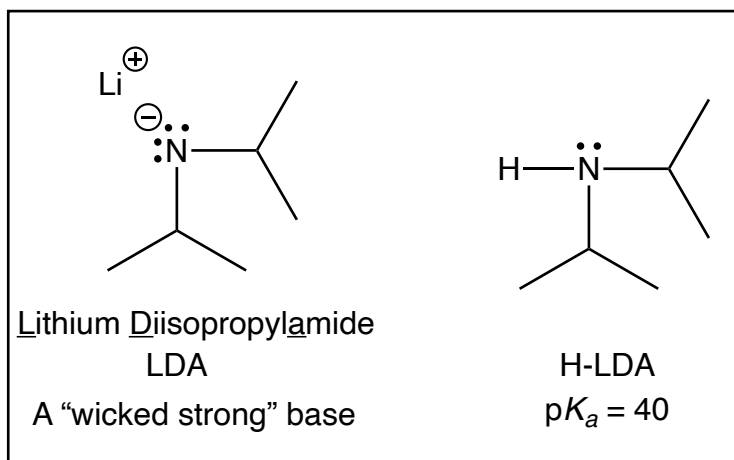


Spontaneous  
dehydration - multiple steps

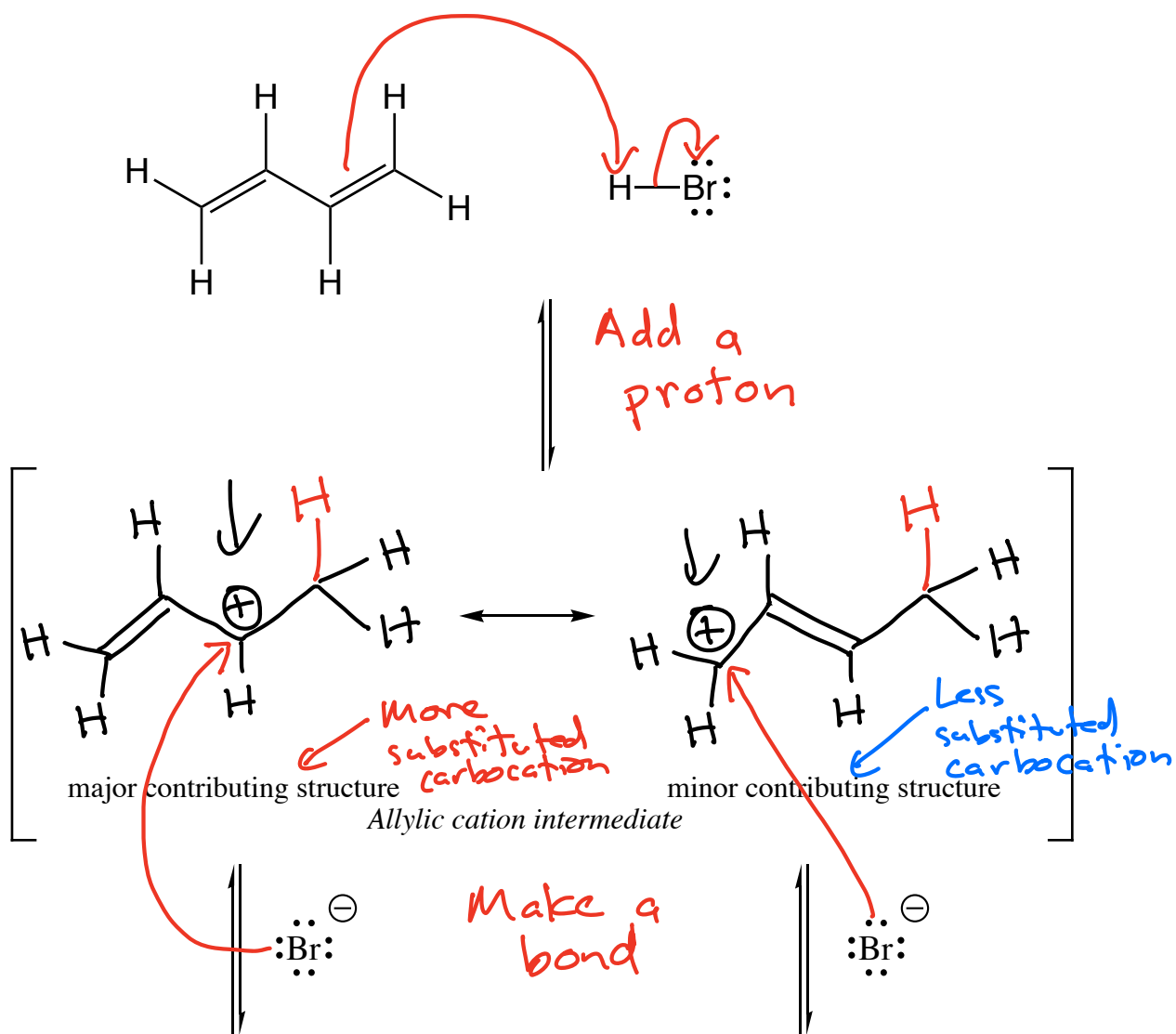
You are not responsible for  
these

**Dehydration**

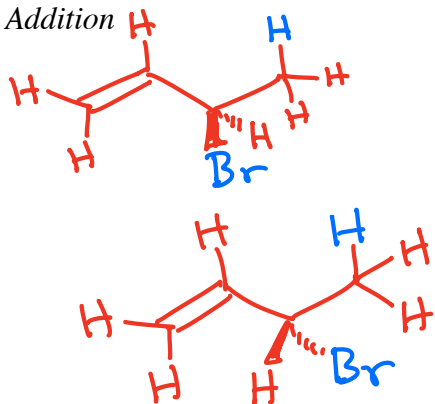




# *H-X reacting with conjugated dienes*

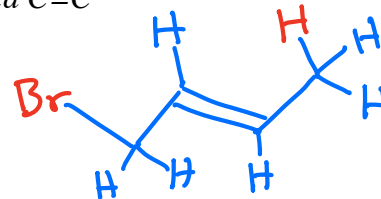


*1,2 Addition*

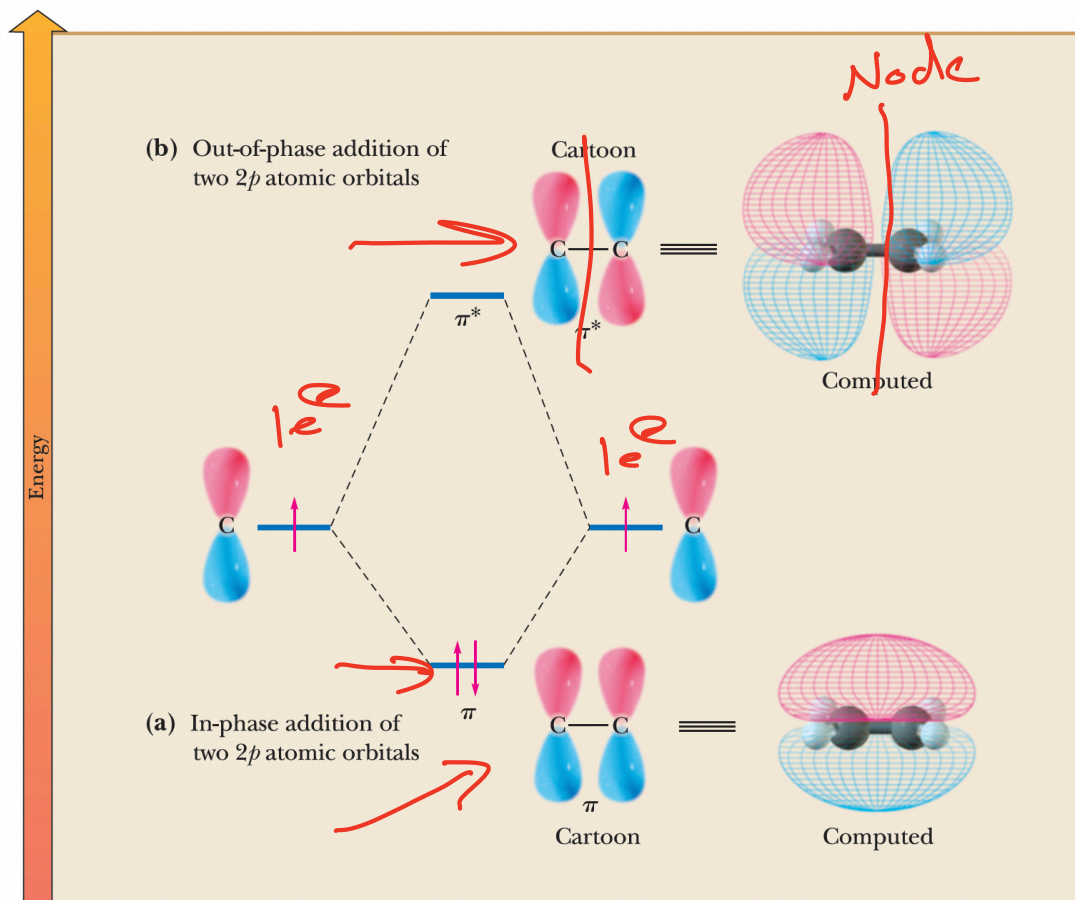


*Racemic*  
Products

*1,4 Addition - more stable, more highly substituted C=C*



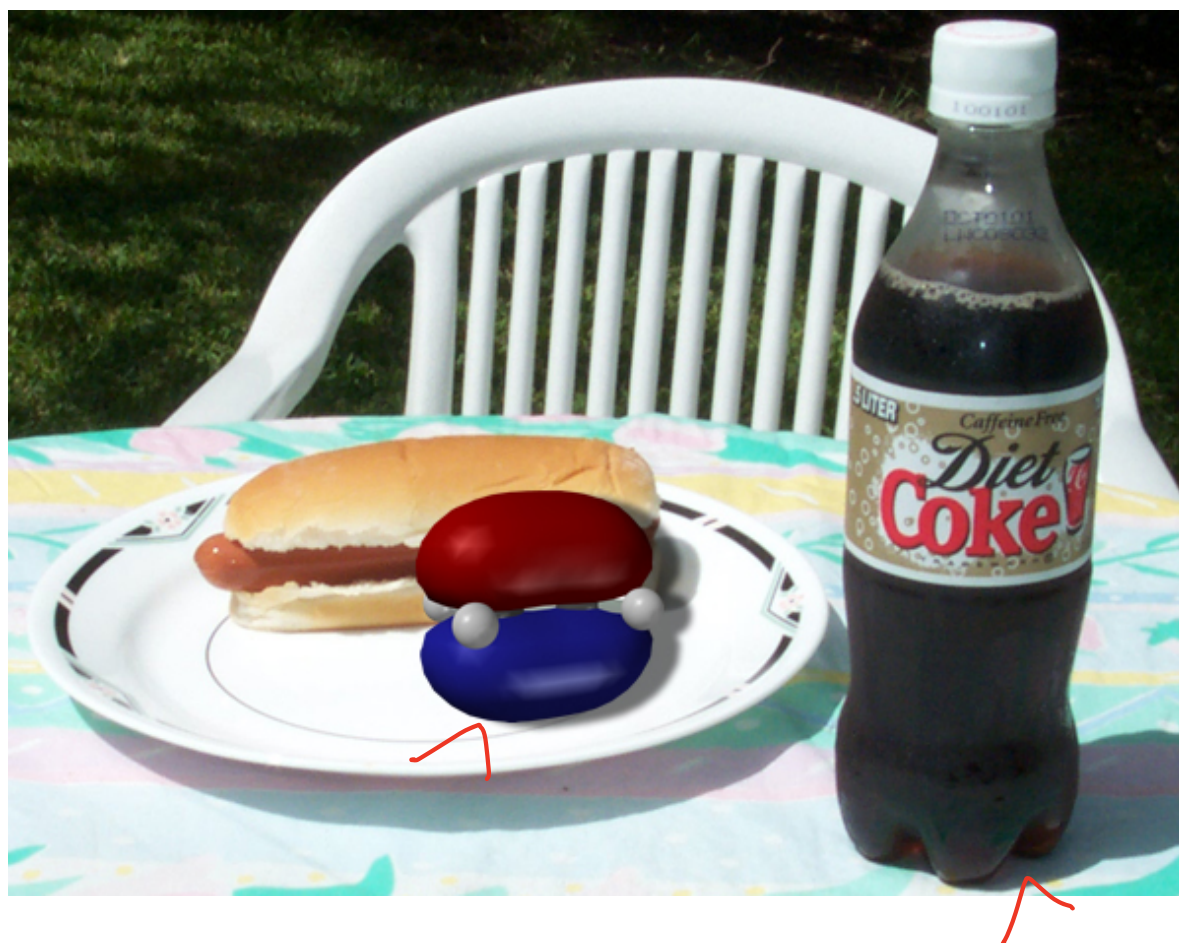
Products



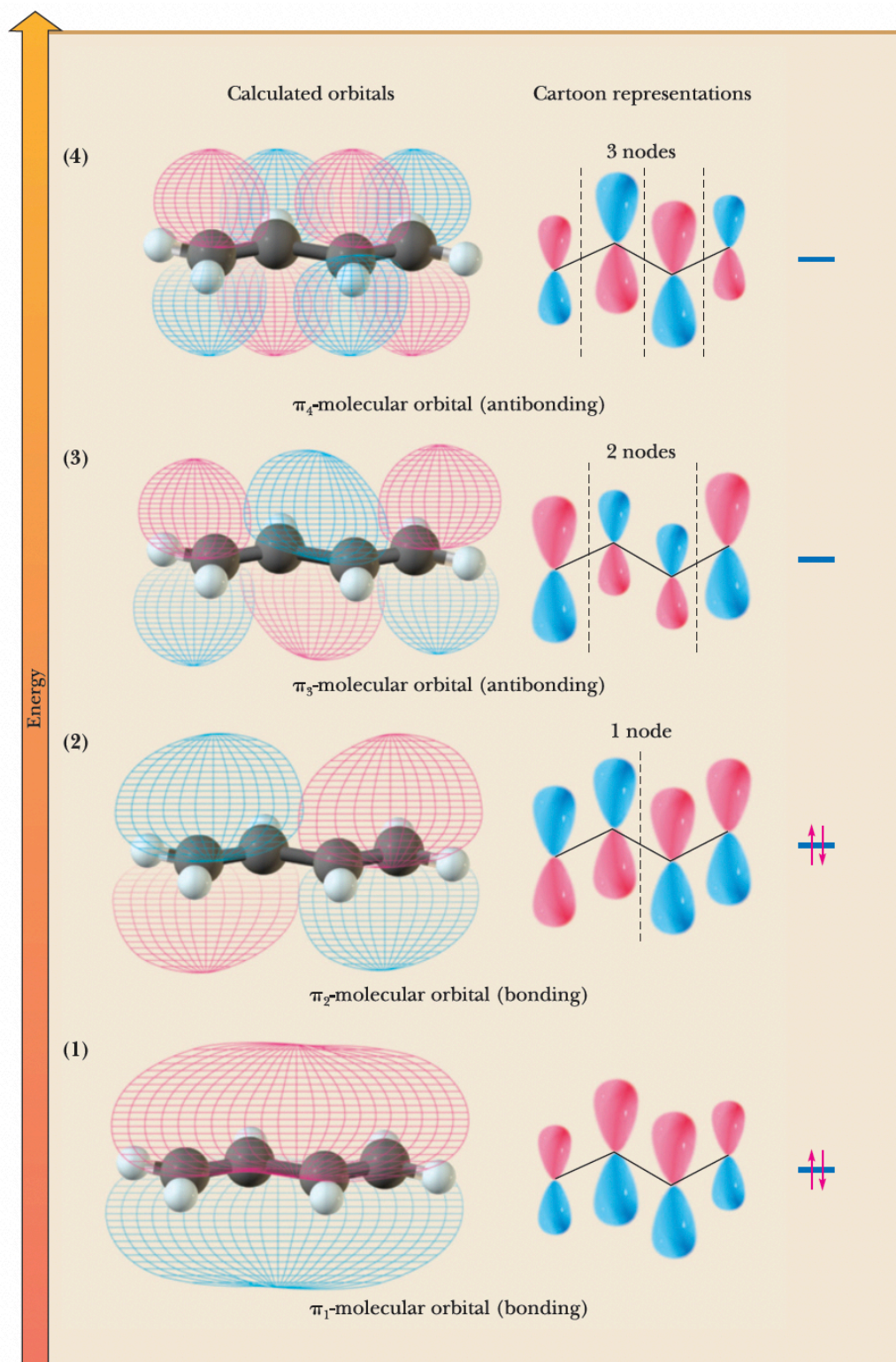
[Watch a video explanation](#)

**FIGURE 1.21**

Molecular orbital mixing diagram for the creation of any C—C  $\pi$  bond. (a) Addition of two  $p$  atomic orbitals in phase leads to a  $\pi$  orbital that is lower in energy than the two separate starting orbitals. When populated with two electrons, the  $\pi$  orbital gives a  $\pi$  bond. (b) Addition of the  $p$  orbitals in an out-of-phase manner (meaning a reversal of phasing in one of the starting orbitals) leads to a  $\pi^*$  orbital. Population of this orbital with one or two electrons leads to weakening or cleavage of the  $\pi$  bond, respectively.

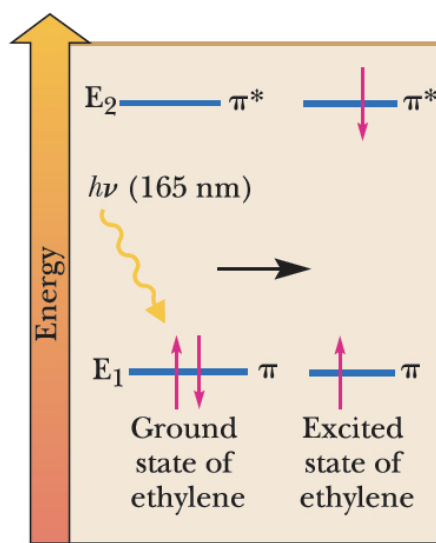




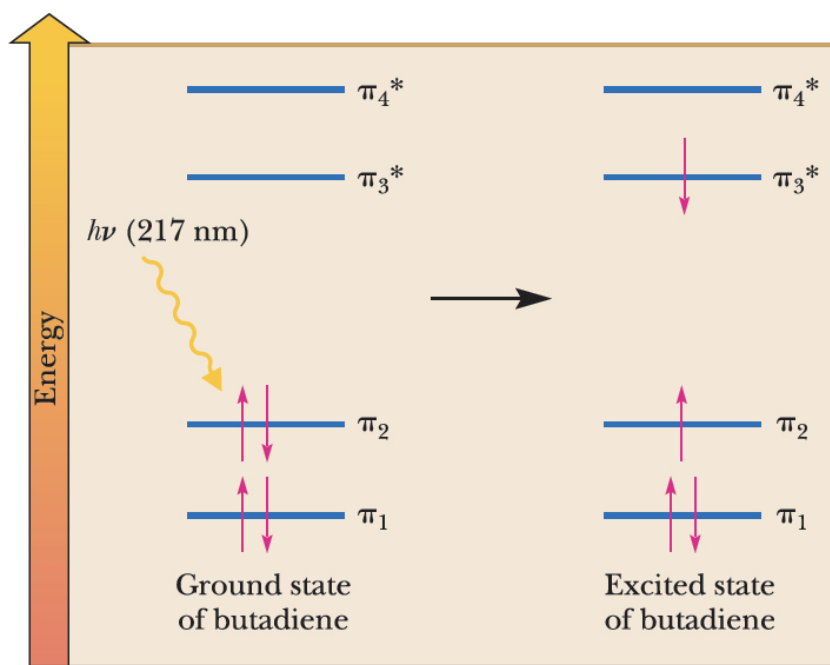


Watch a video explanation

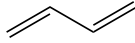
**FIGURE 20.2** Structure of 1,3-butadiene—molecular orbital model. Combination of four parallel  $2p$  atomic orbitals gives two  $\pi$ -bonding MOs and two  $\pi$ -antibonding MOs. In the ground state, each  $\pi$ -bonding MO is filled with two spin-paired electrons. The  $\pi$ -antibonding MOs are unoccupied.



**FIGURE 20.6** A  $\pi \rightarrow \pi^*$  transition in excitation of ethylene. Absorption of ultraviolet radiation causes a transition of an electron from a  $\pi$ -bonding MO in the ground state to a  $\pi$ -antibonding MO in the excited state. There is no change in electron spin.

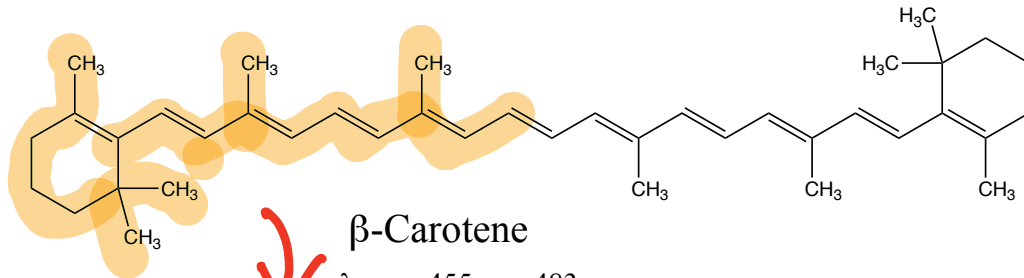


**FIGURE 20.7** Electronic excitation of 1,3-butadiene; a  $\pi \rightarrow \pi^*$  transition.



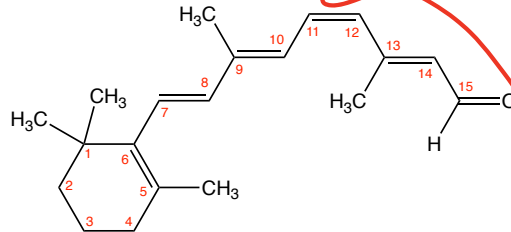
Butadiene

$\lambda_{\text{max}} = 217 \text{ nm}$



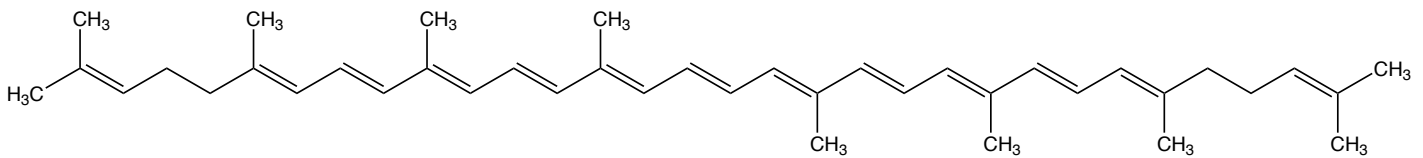
$\beta$ -Carotene

$\lambda_{\text{max}} = 455 \text{ nm}, 483 \text{ nm}$



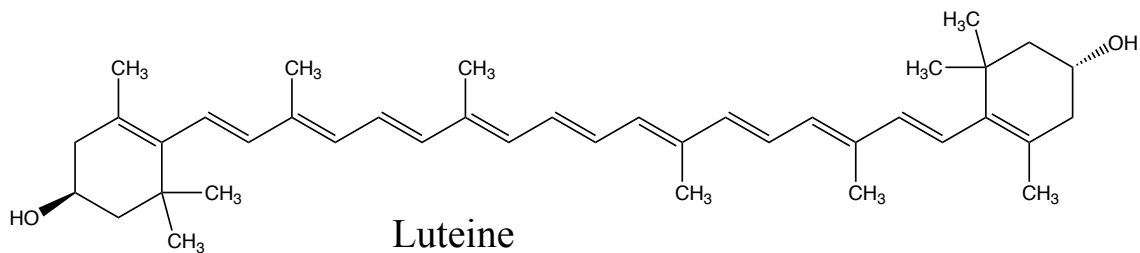
11-*cis*-Retinal

$\lambda_{\text{max}} = 380 \text{ nm}$



Lycopene

$\lambda_{\text{max}} = 443 \text{ nm}, 471 \text{ nm}, 502 \text{ nm}$



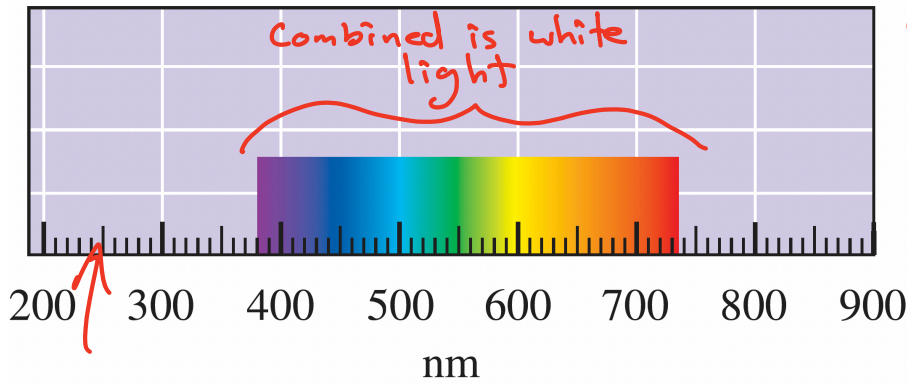
Luteine

$\lambda_{\text{max}} = 445 \text{ nm}, 474 \text{ nm}$



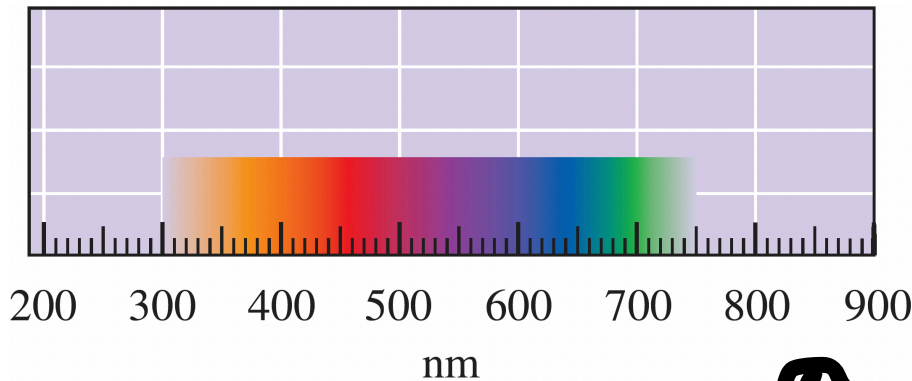
← Energy

Light source  
↙↘

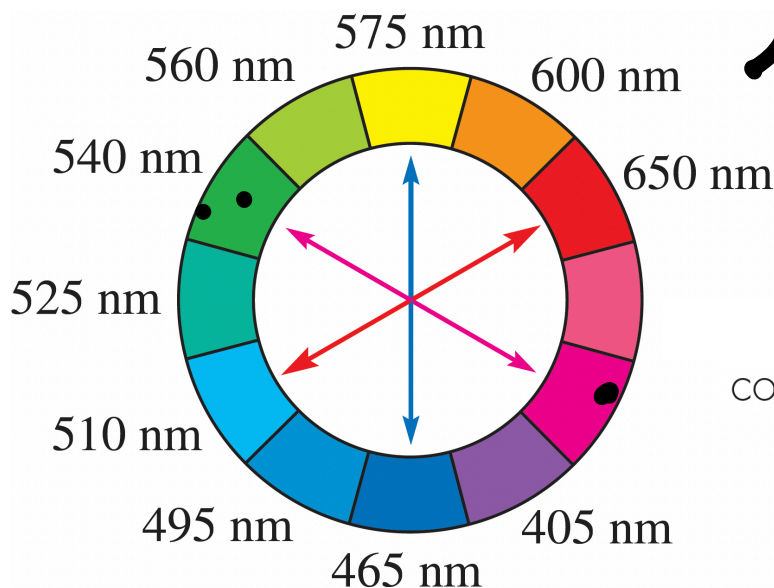


**FIGURE 20.5** (a) Visible light color-wavelength correlation.

\*\*\* We "see" the wavelengths reflected minus the wavelengths absorbed \*\*\*



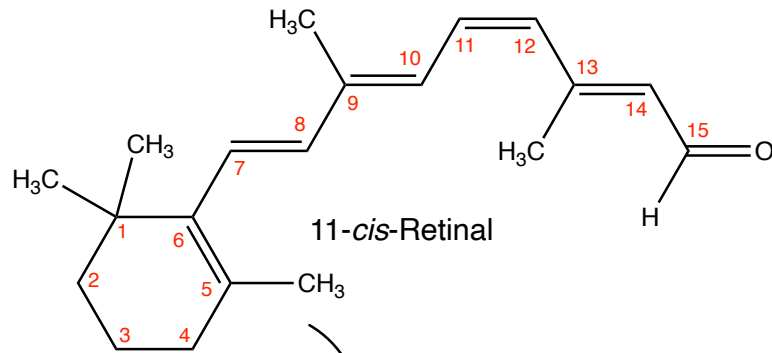
(b) Approximate color of substance (reflected light) if a single wavelength (i.e., the wavelength listed on the numerical scale of the x-axis) is absorbed.



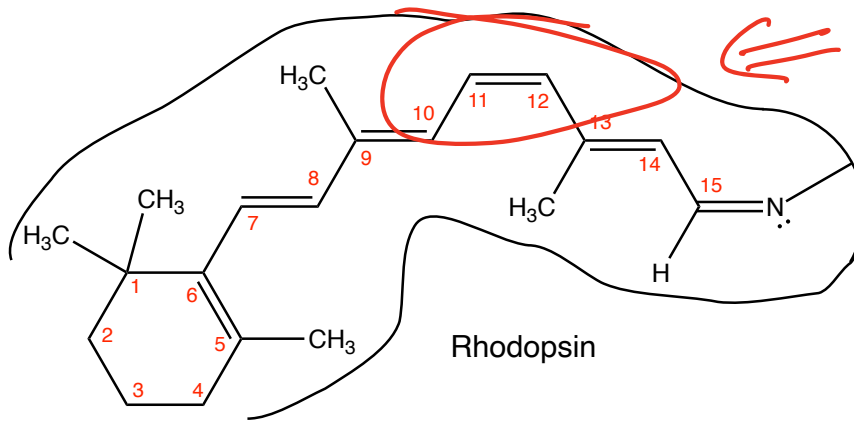
(c) Complementary colors on a color wheel.

Colored arrows are complementary

# How vision works

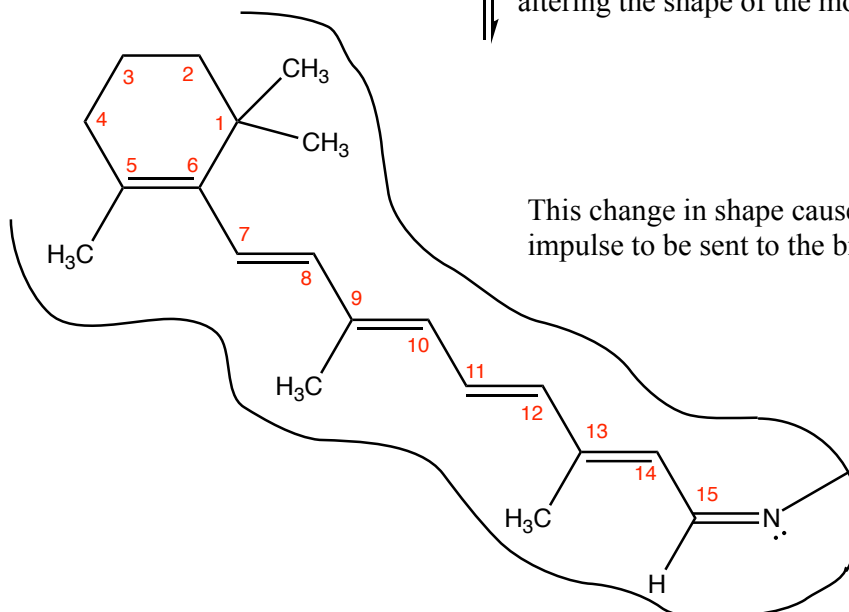


Binds to an  $\text{-NH}_2$  group from the amino acid lysine in the protein opsin

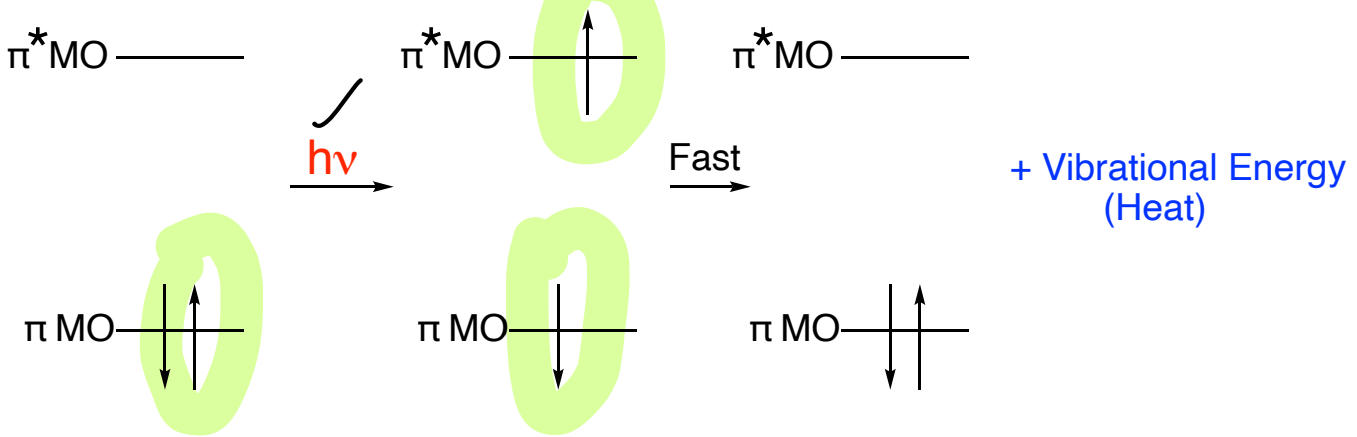


Absorbing the photon puts an electron into an antibonding  $\pi$  orbital  $\rightarrow$  weaken  $\pi$  bond, especially around  $\text{C}_{11}=\text{C}_{12}$  so bond can rotate back to more stable trans geometry

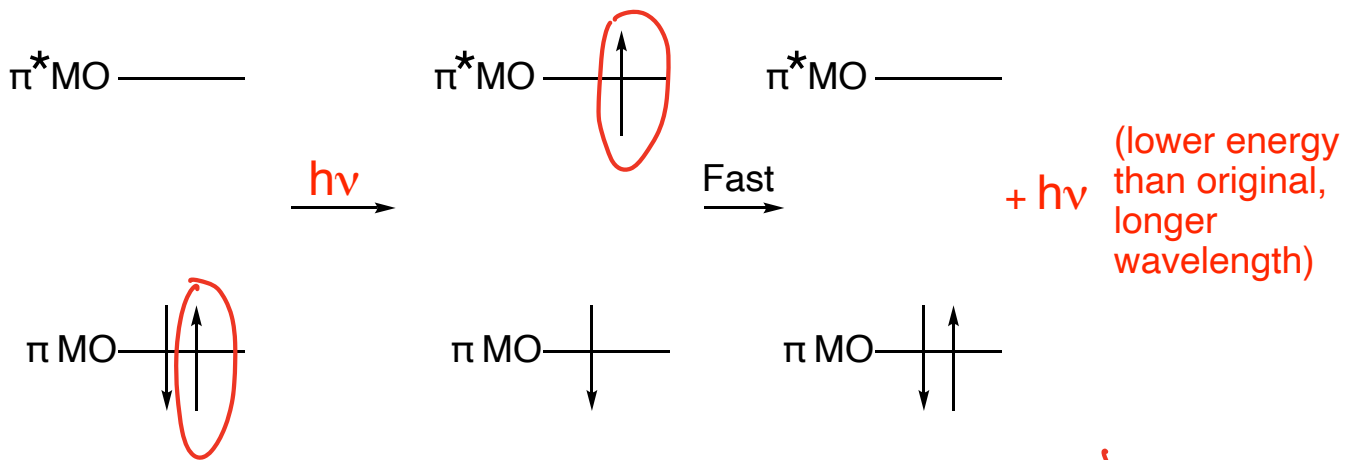
A photon of visible light is absorbed by the retinal, isomerizing the *cis* bond to *trans*, dramatically altering the shape of the molecule



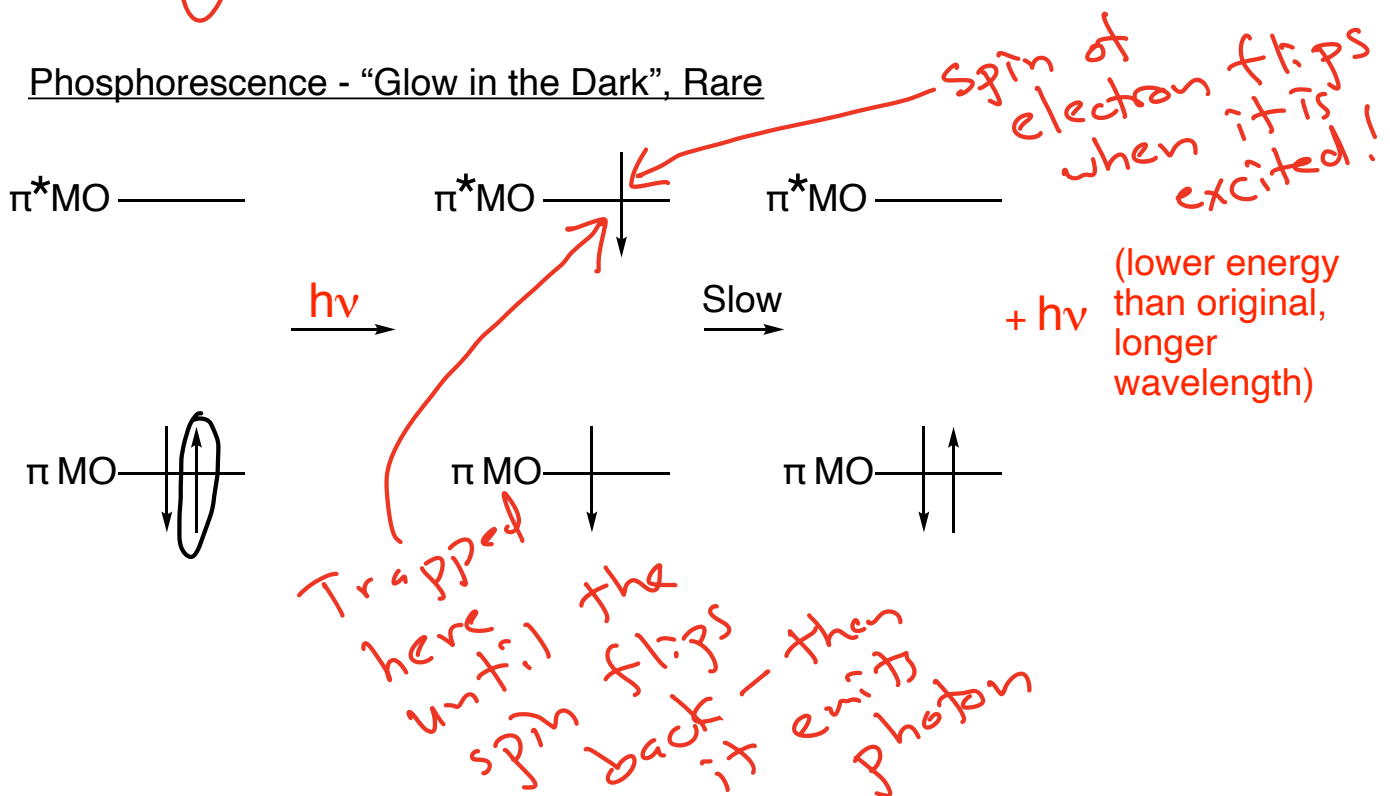
### Generation of heat, Most molecules



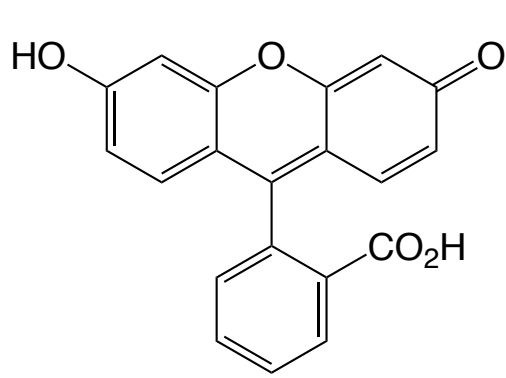
### Fluorescence - Rigid Molecules, Not uncommon



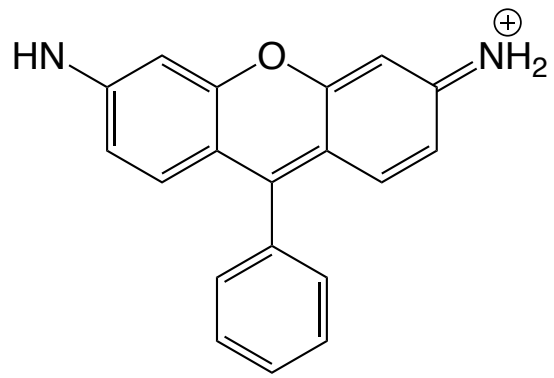
### Phosphorescence - "Glow in the Dark", Rare



## Flourescence - Rigid Molecules, Not uncommon

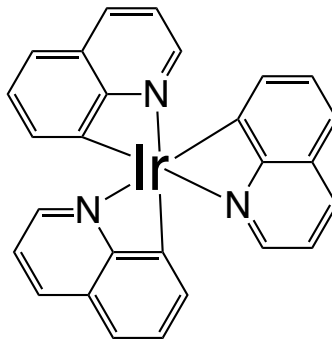


Fluorescein

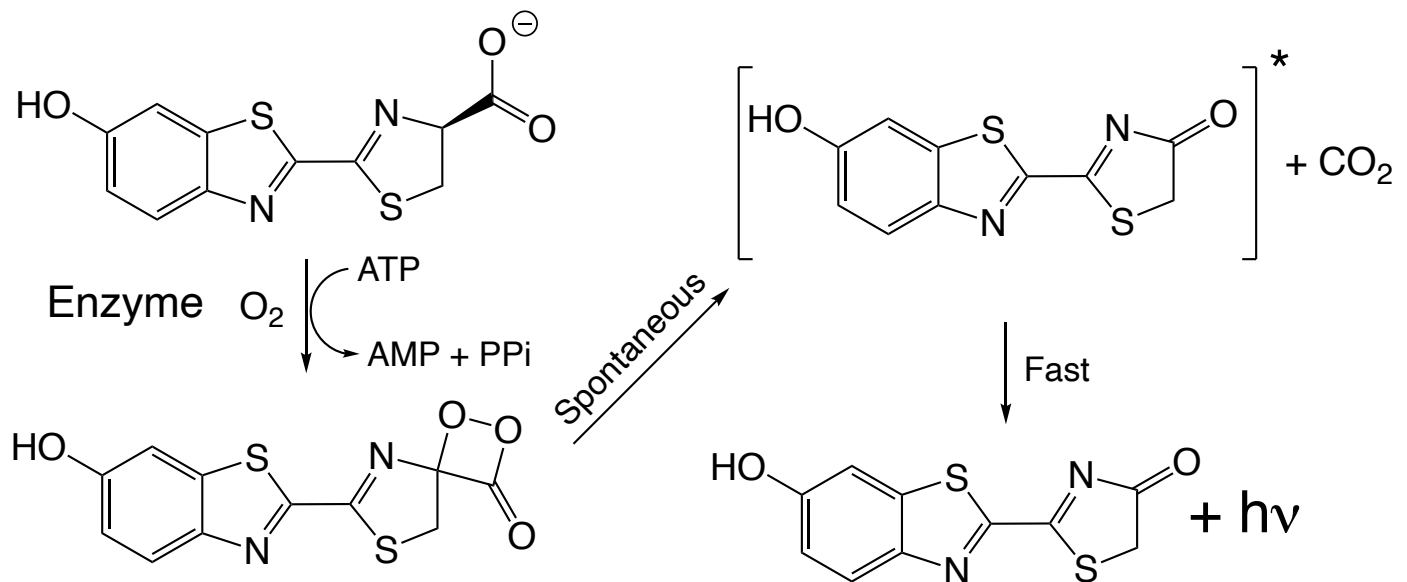


Rhodamine

## Phosphorescence - "Glow in the Dark", Rare

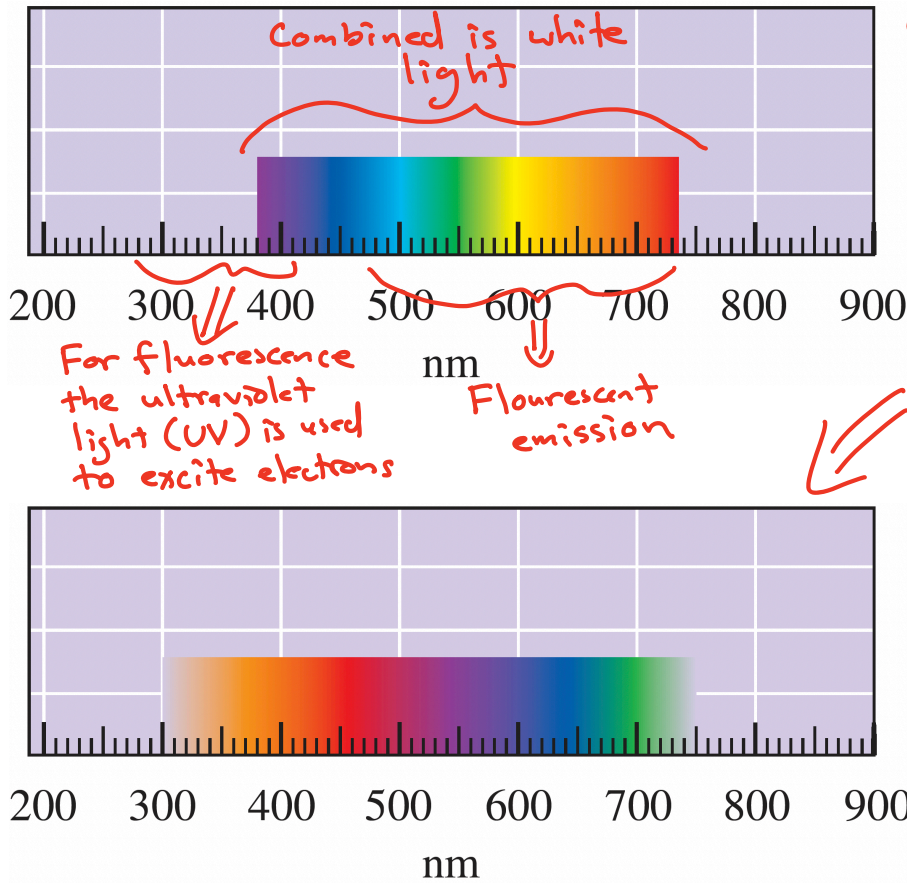


## Bioluminescence - Fireflies, Deep Sea Creatures - Chemical Reactions



← Energy

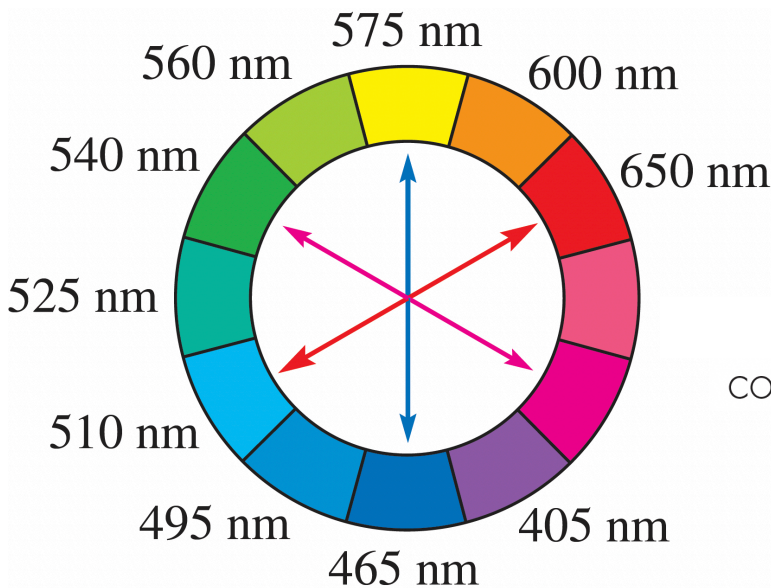
Light source



**FIGURE 20.5** (a) Visible light color-wavelength correlation.

\*\*\* We "see" the wavelengths reflected minus the wavelengths absorbed \*\*\*

(b) Approximate color of substance (reflected light) if a single wavelength (i.e., the wavelength listed on the numerical scale of the x-axis) is absorbed.



(c) Complementary colors on a color wheel.

Colored arrows are complementary

