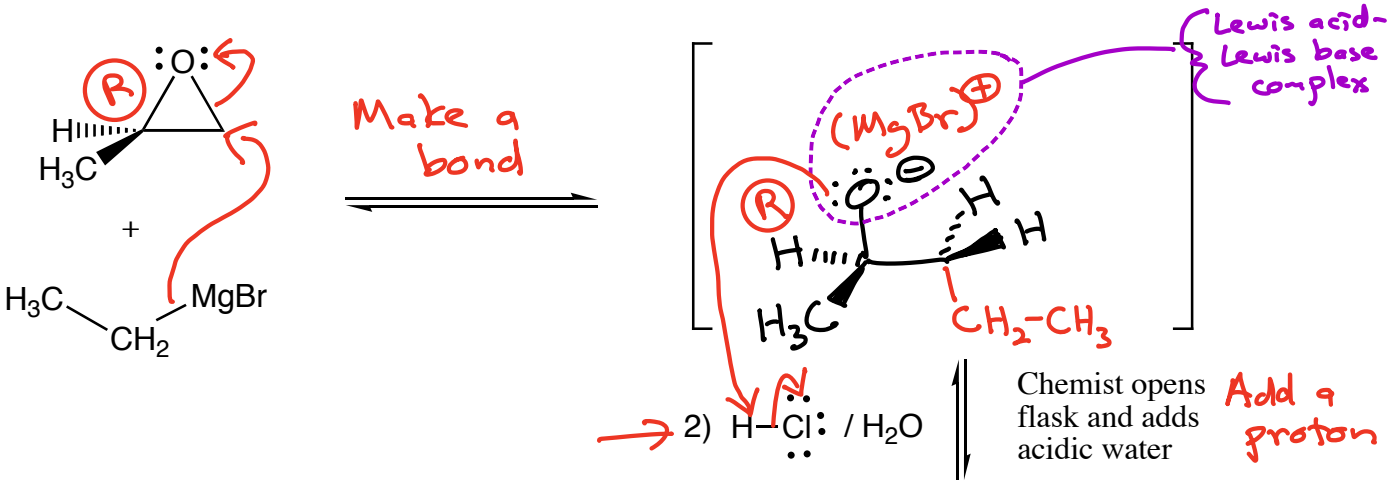
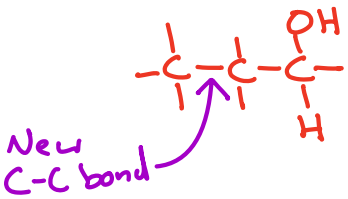
Organolithium and Gilman reagents react the same way as Grignard reagents in this reaction.

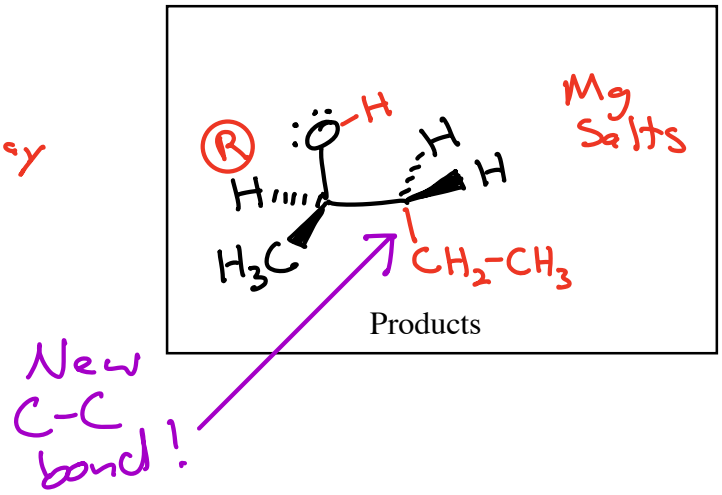
Grignard Reagent Reacting with an Epoxide

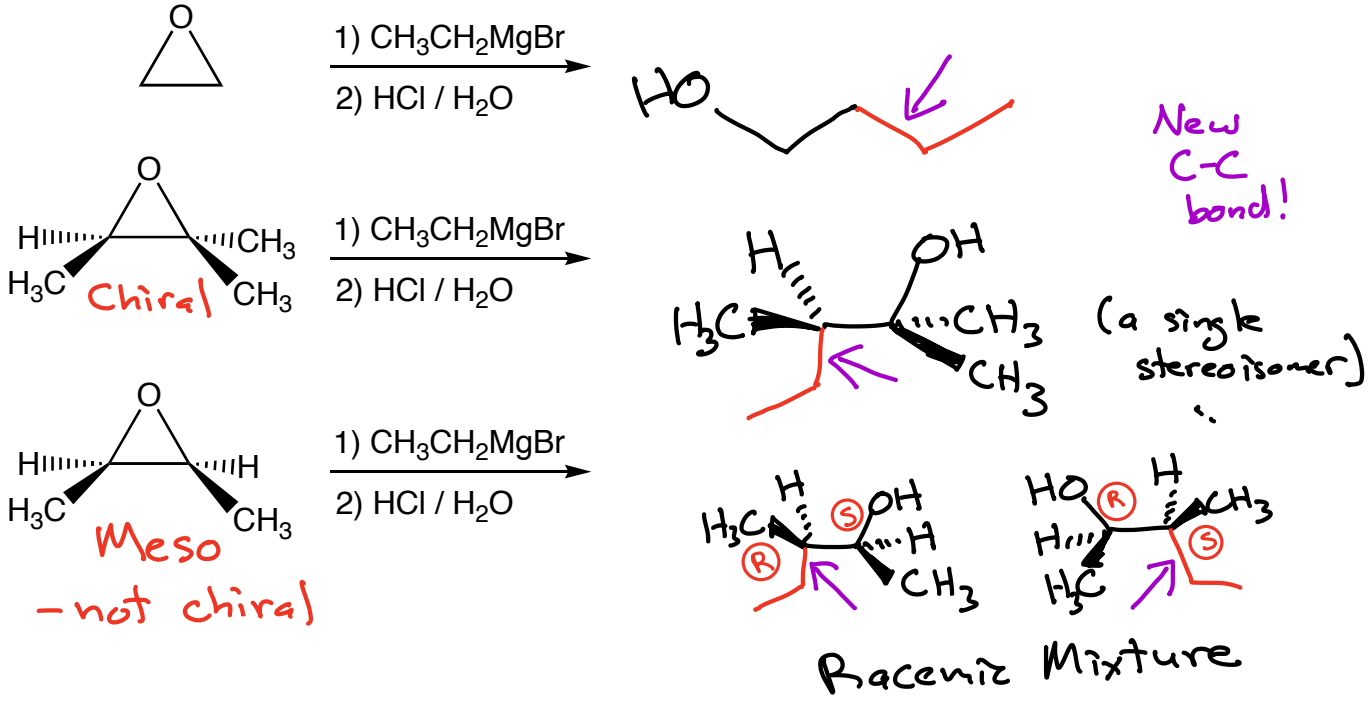


Key Recognition Element (KRE):

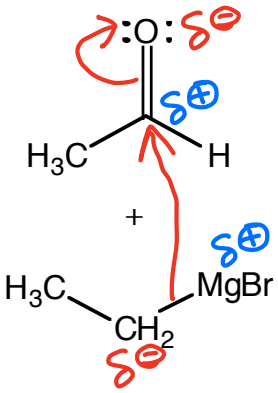
There is a new C-C bond that is two carbon atoms away from an OH group



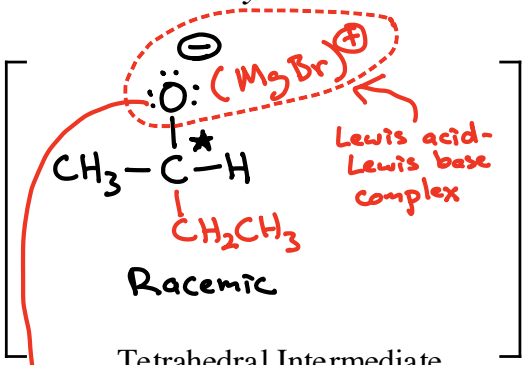




Grignard Reagent Reacting with an Aldehyde or Ketone



Make a bond



Chemist opens the flask

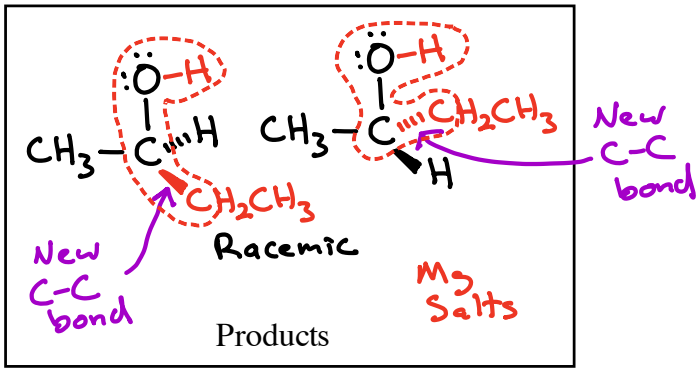
2) $H-Cl: / H_2O$

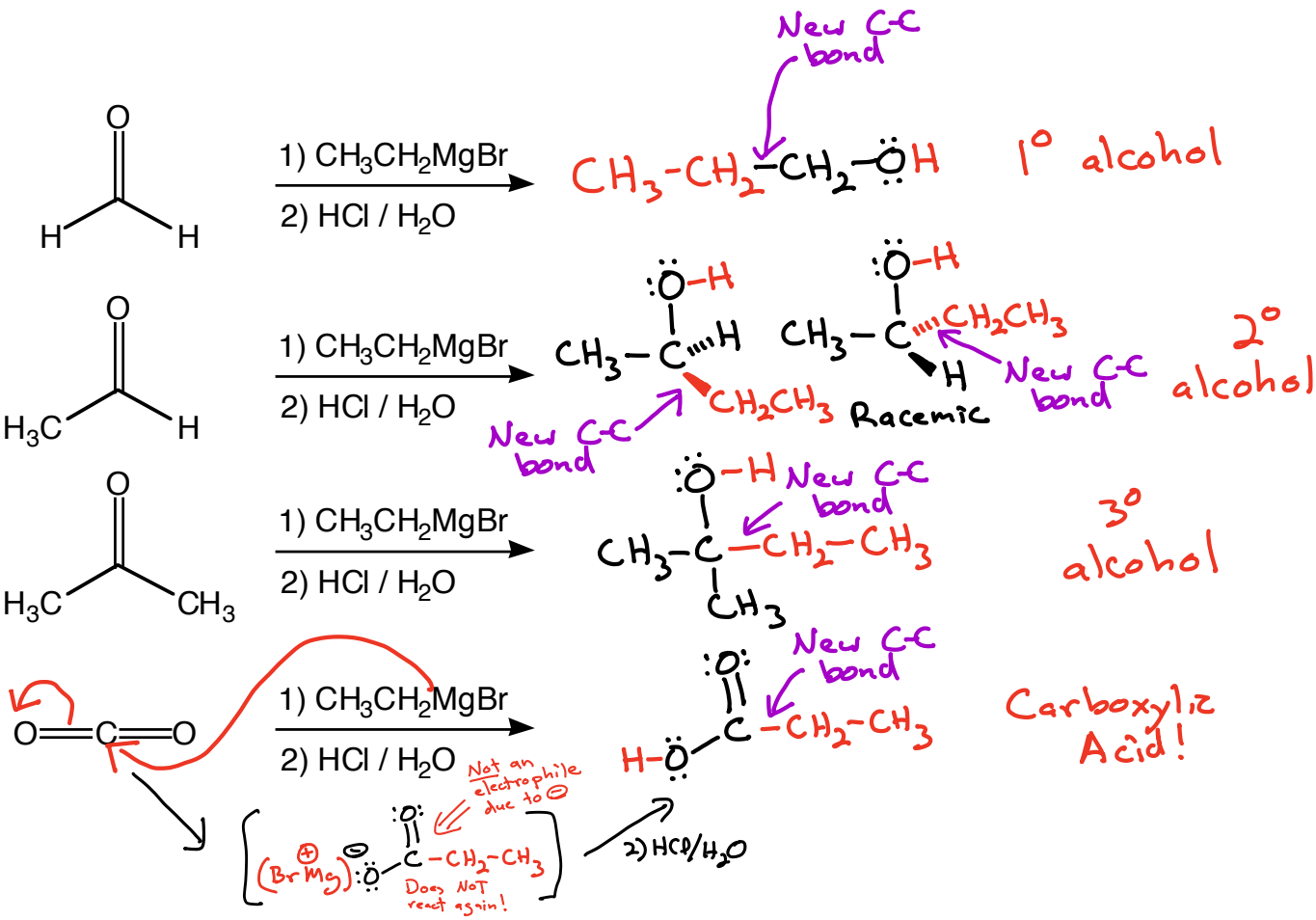
Add a proton

Mechanism A

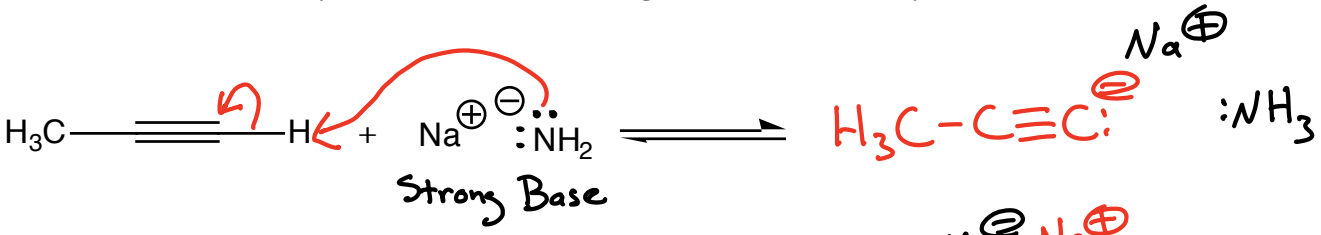
Key Recognition Element (KRE):

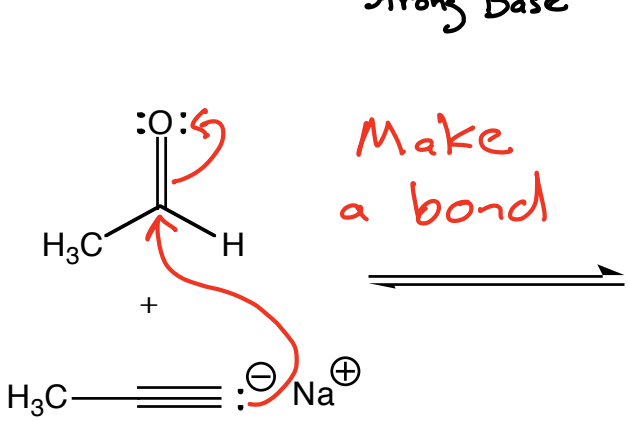
-OH group attached the same C atom as a new C-C bond

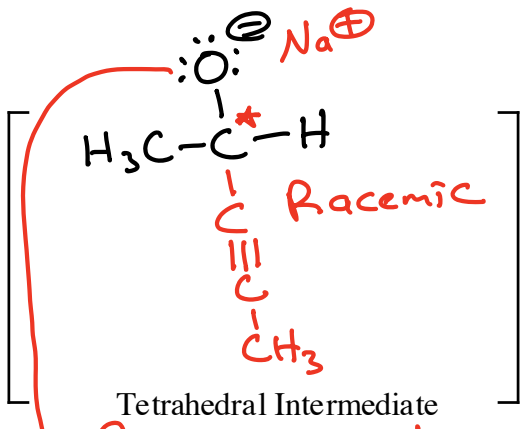


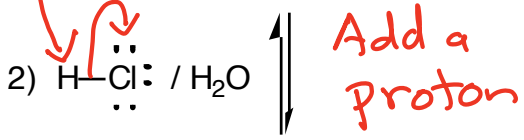


Alkyne Anion Reacting with an Aldehyde or Ketone





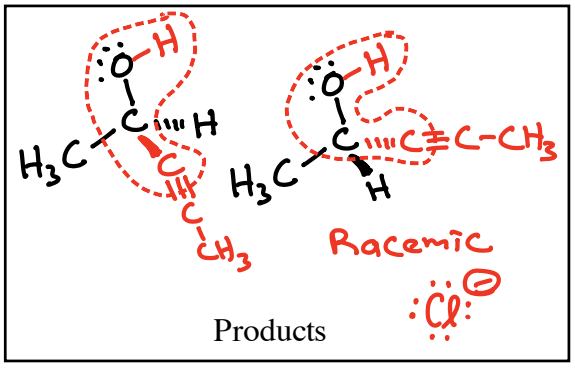




Mechanism A

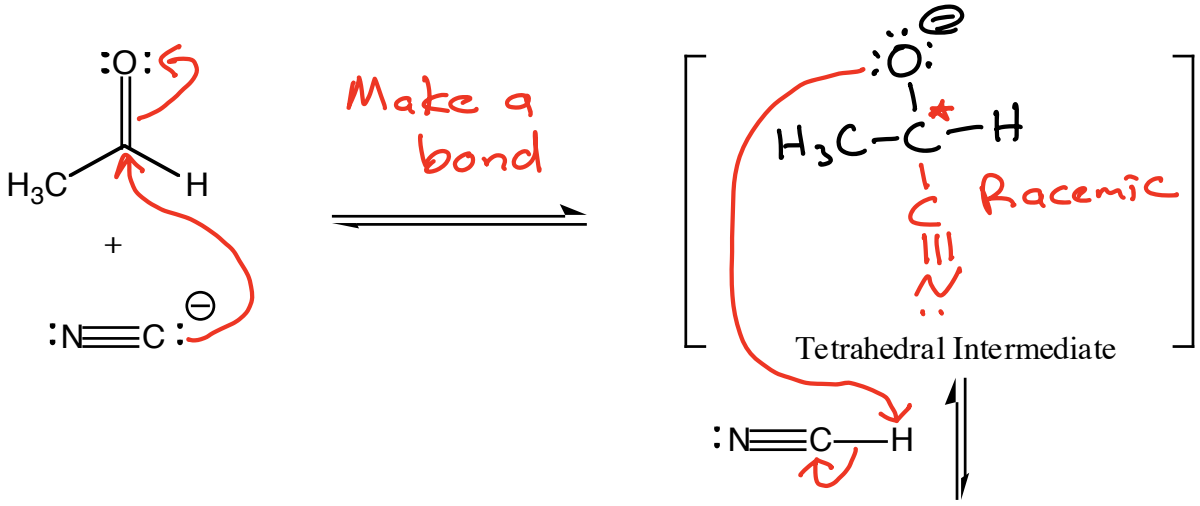
Key Recognition Element (KRE):

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



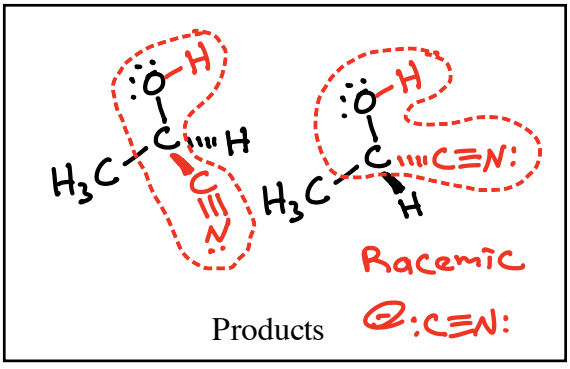
HCN Reacting with an Aldehyde or Ketone

Reacts on the C atom because that makes stronger bonds



Key Recognition Element (KRE):

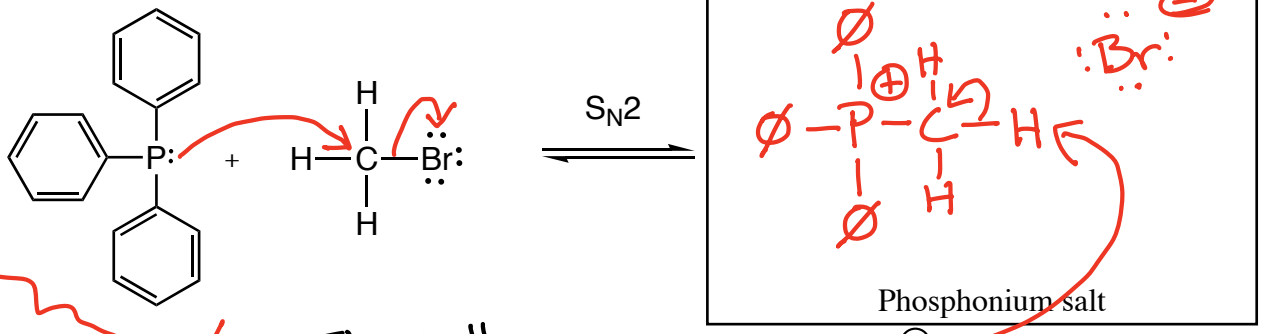
Cyanohydrin → OH on a C atom that made a new C-C bond to −C≡N:



Time capsule → cyanohydrins can be hydrolyzed in H_2SO_4/H_2O to give α-hydroxyacids

"alpha"

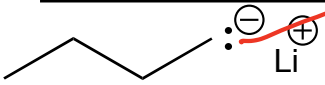
Wittig Reaction



ϕ–P: or $(Ph)_3P$:

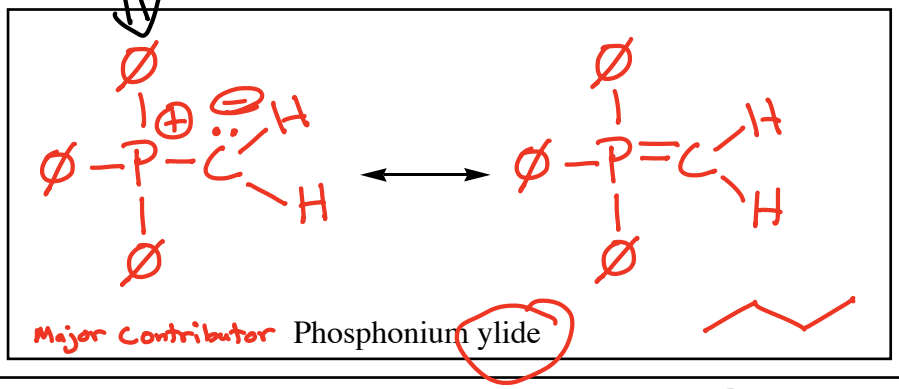
shorthand ways to indicate the same molecule

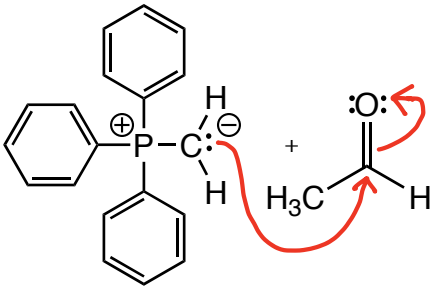
This is the way the think about a Wittig reagent



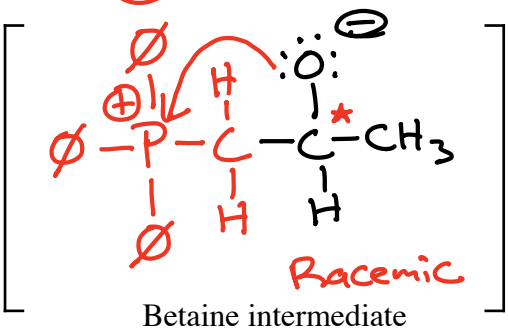
n-Butyl lithium (n-BuLi)

Take a proton away

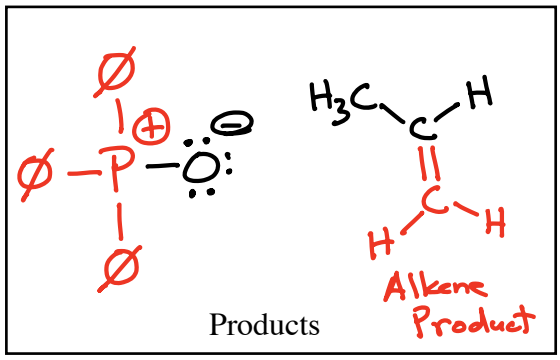




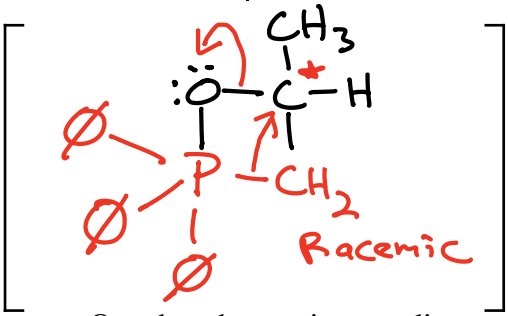
Make a bond



Make a bond



Remember this step!

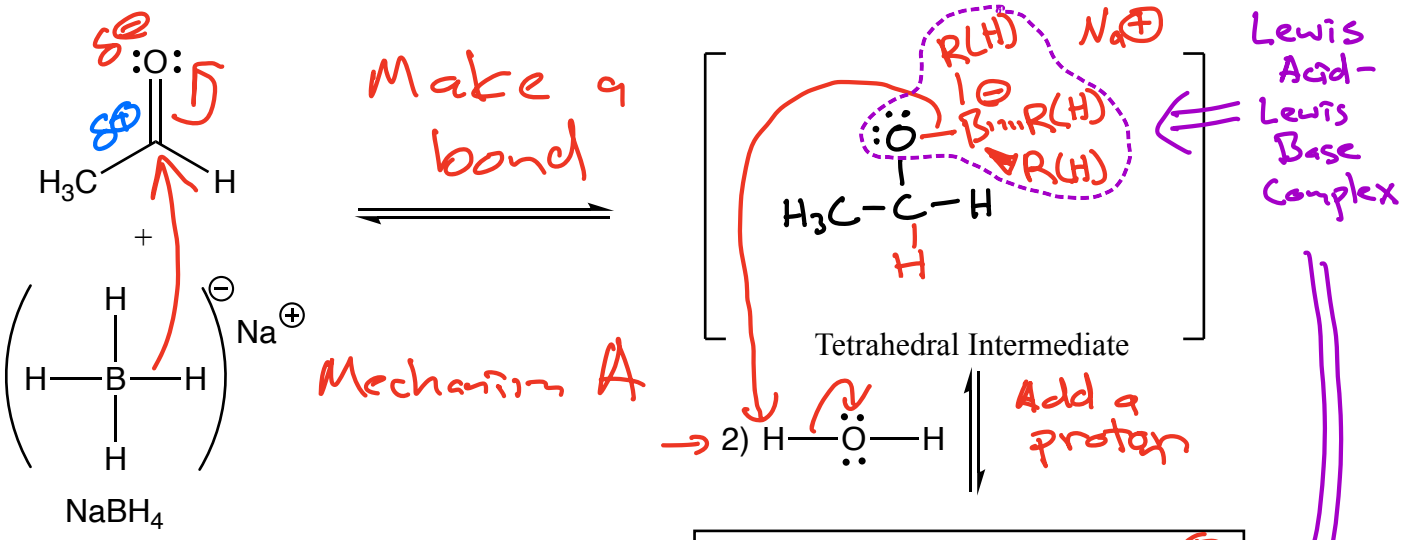


"Four-membered ring intermediate"

Key Recognition Element (KRE):

Alkene → New C=C where the C=O was!

Sodium Borohydride Reacting with an Aldehyde or Ketone

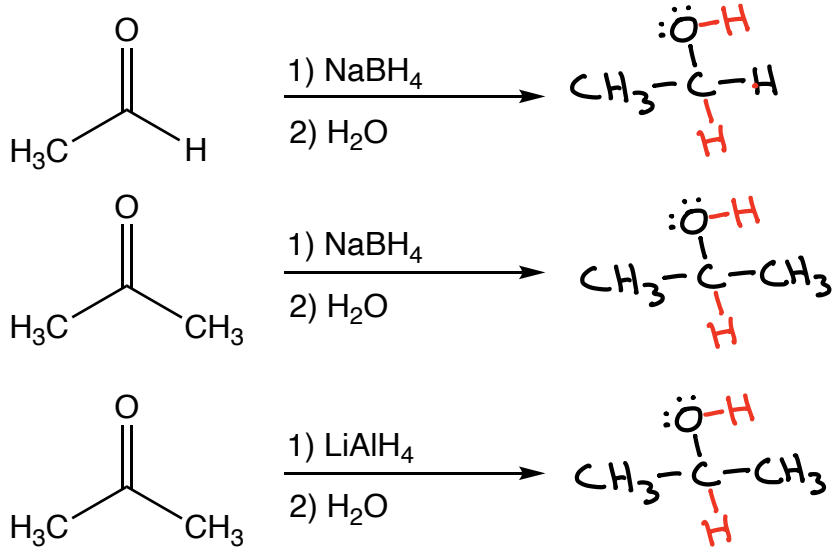


Key Recognition Element (KRE):

An -OH group where there was a C=O of an aldehyde or ketone

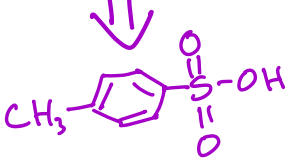
All four H of BH_4^- react!

$$4\ CH_3CHO + BH_4^- \rightleftharpoons\rightleftharpoons\rightleftharpoons\rightleftharpoons (CH_3CH_2O)_4B^- \xrightarrow{2)\ H_2O} 4\ CH_3CH_2OH + \text{Borate salts}$$



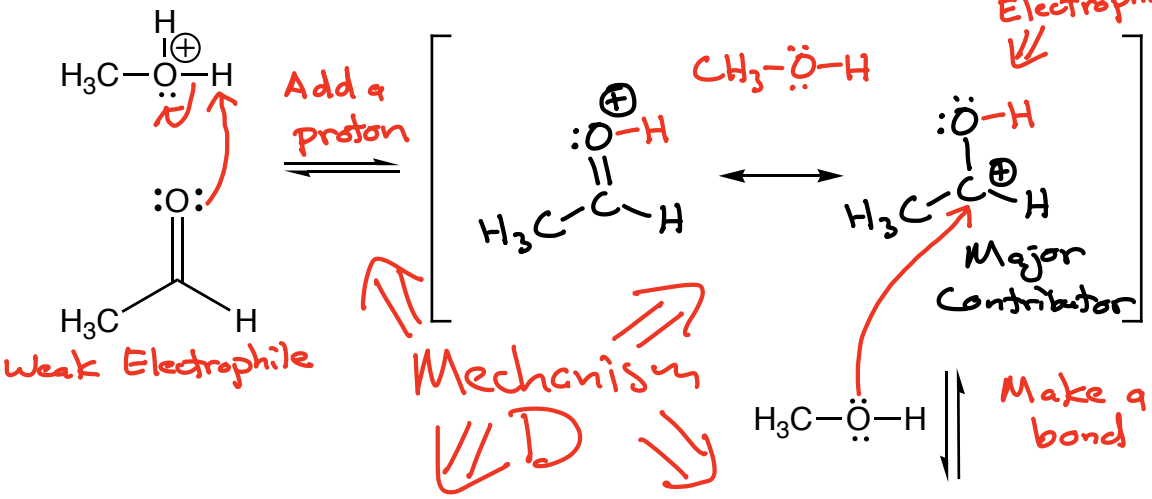
TsOH or H_2SO_4

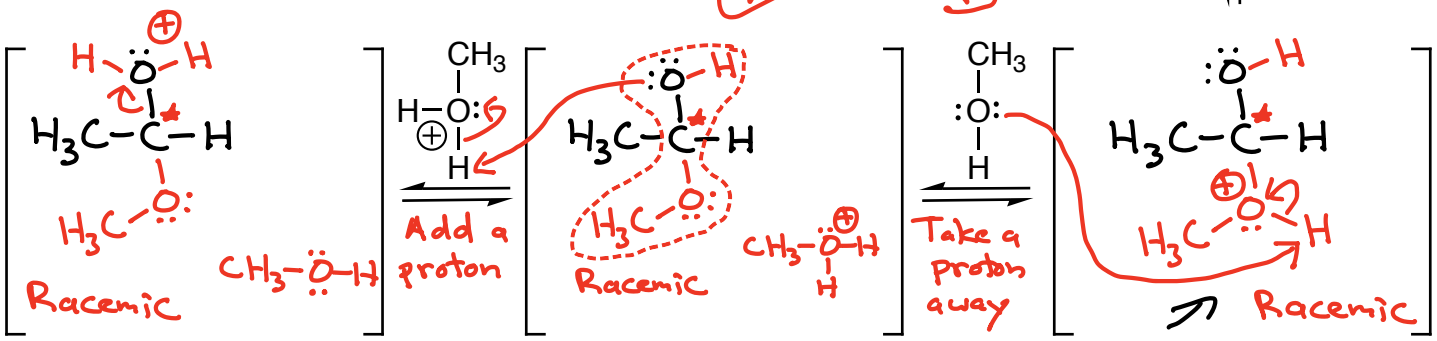
Tosylic Acid



"Hey, does that thing have a heni in it?" "SWEET!" !

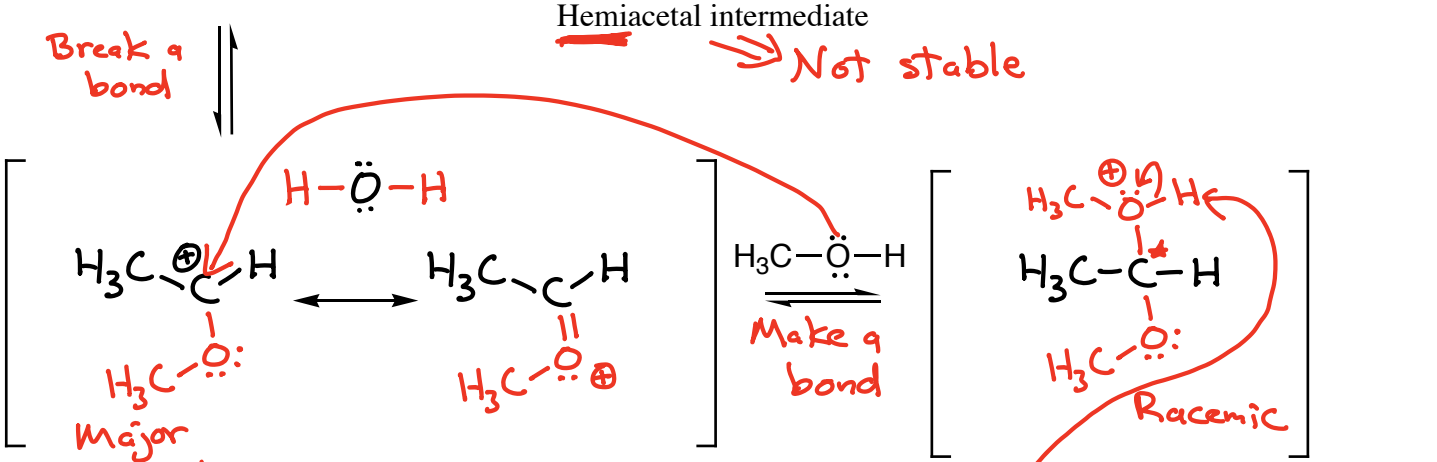
Acid Catalyzed Hemiacetal and Acetal Formation From an Aldehyde or Ketone





Hemiacetal intermediate

Not stable

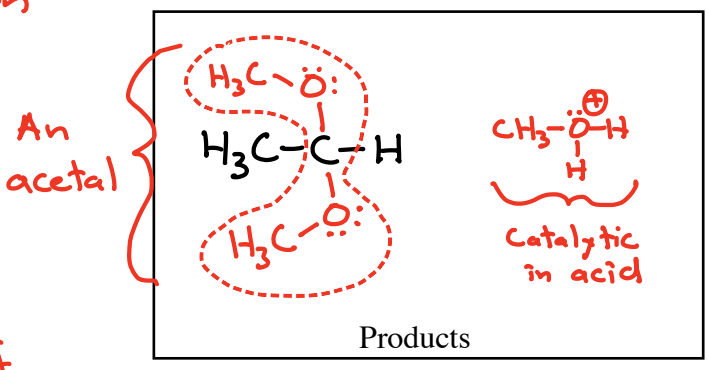


Stabilized by Charge Delocalization

Key Recognition Element (KRE):

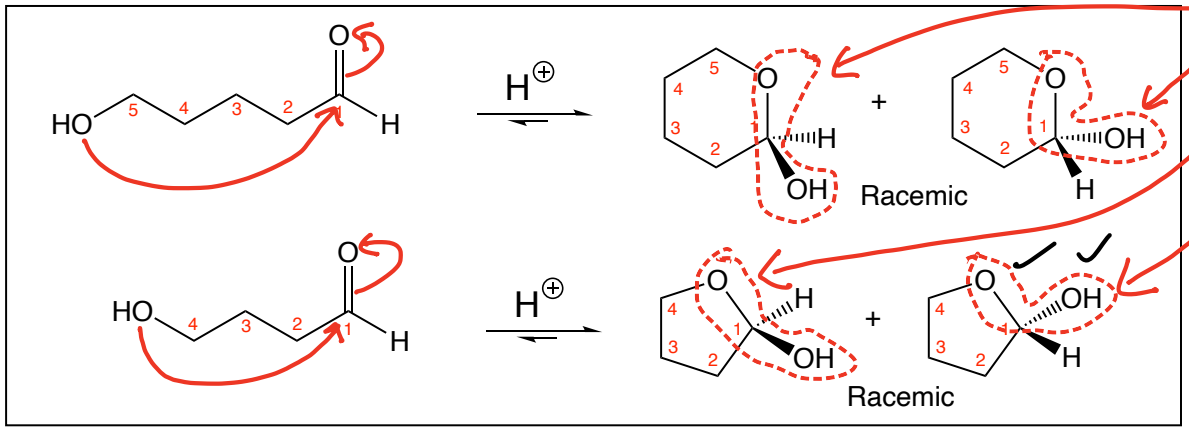
Two bonds to O atoms from an sp^3 C atom

Definition of an acetal

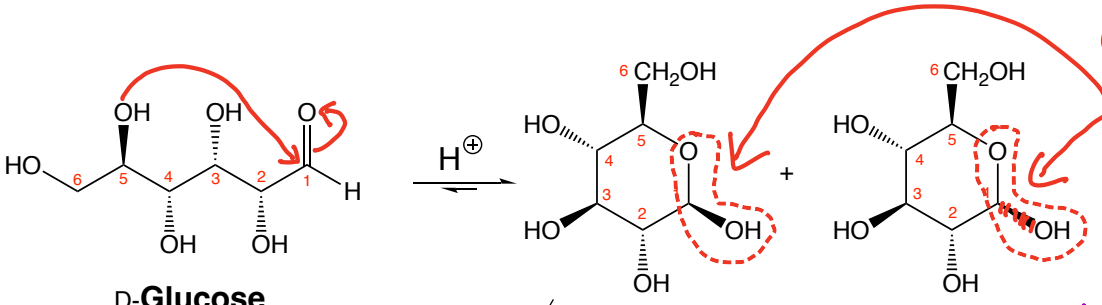


Cyclic Hemiacetals and Carbohydrates

Cyclic hemiacetals



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

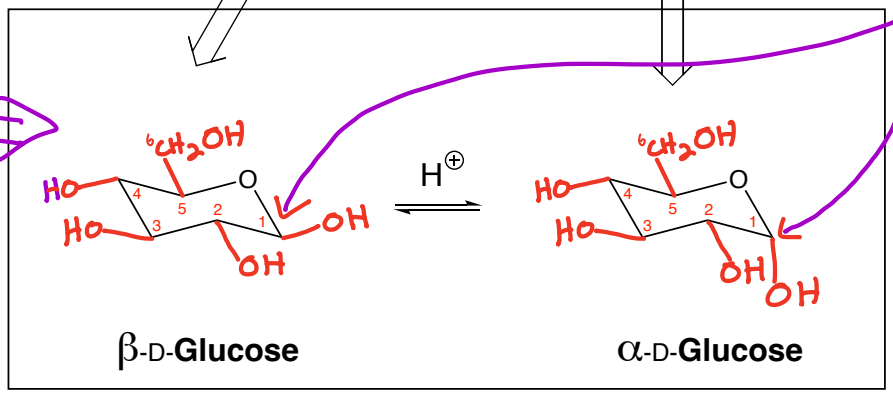


D-**Glucose**
(open chain form)

Cyclic Hemiacetals
"SWEET!"

Anomeric Carbon

This interconversion is called "mutarotation"



Biochemists call these two forms "anomers"

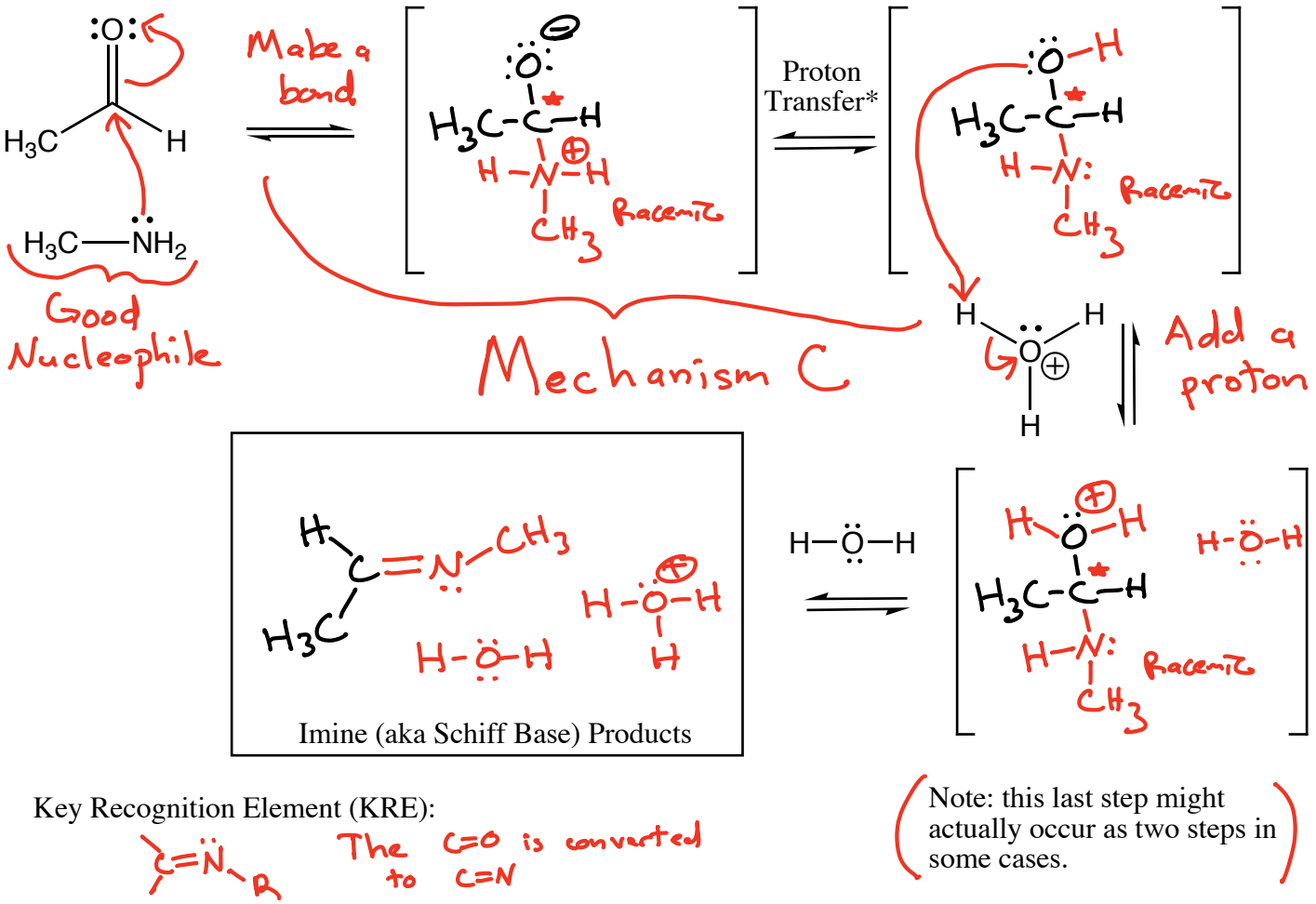
β-D-Glucopyranose
means "6-mebered ring"

More stable → every group is equatorial!

α-D-Glucopyranose

Less stable → one -OH is axial

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



Key Recognition Element (KRE):

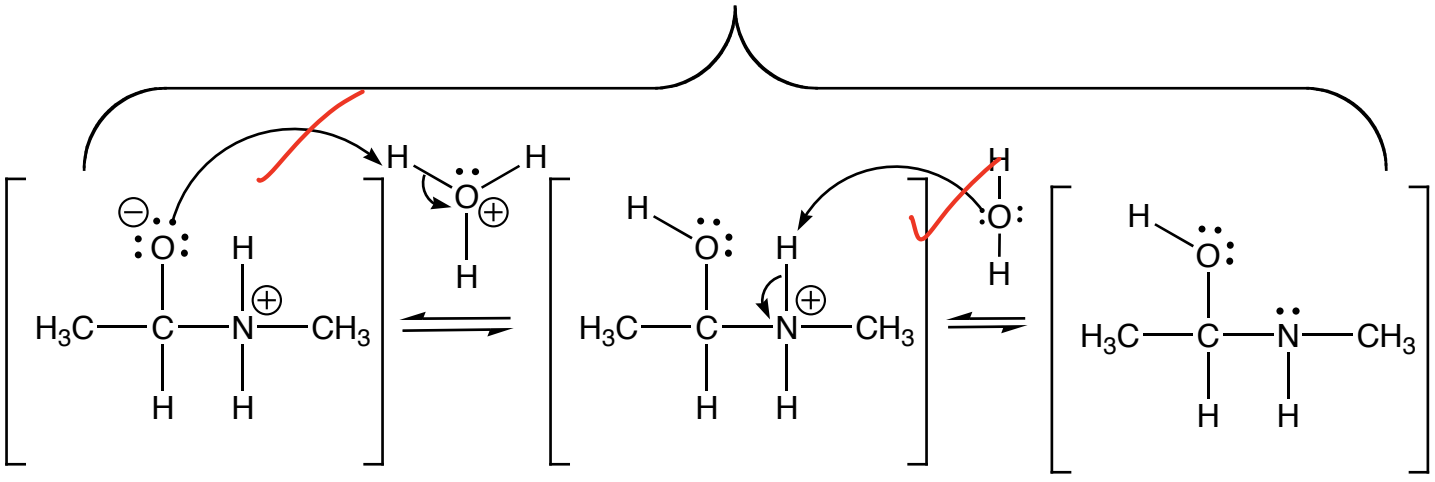
The C=O is converted to C=N

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

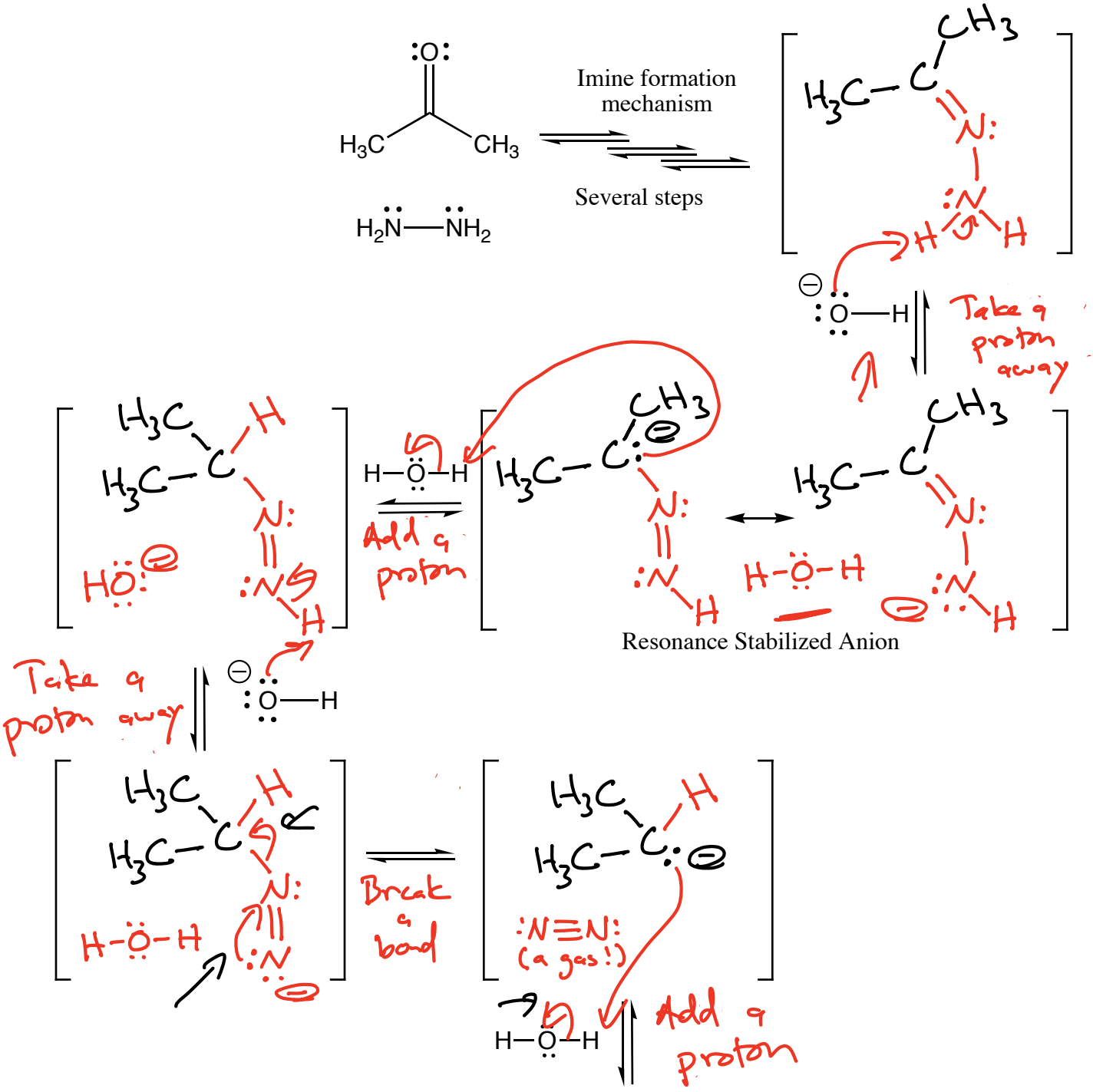
---

* "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. Becuase 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):

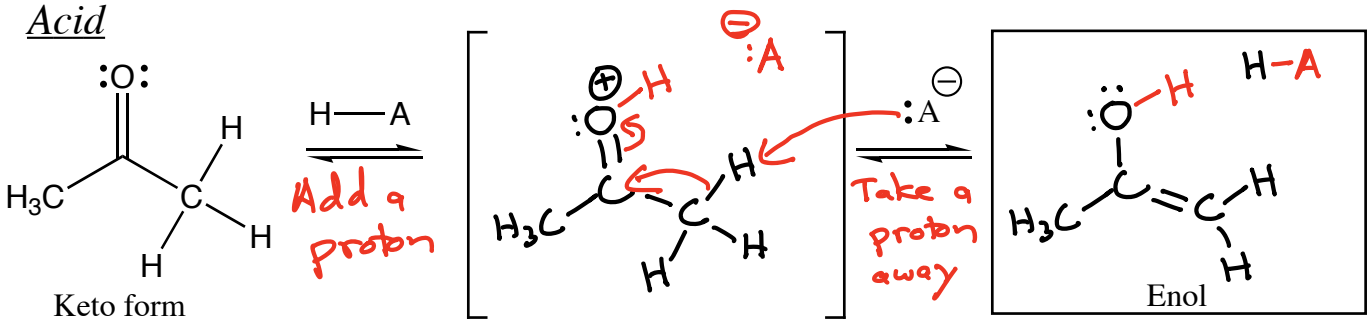
$-CH_2-$ where there was C=O

Products

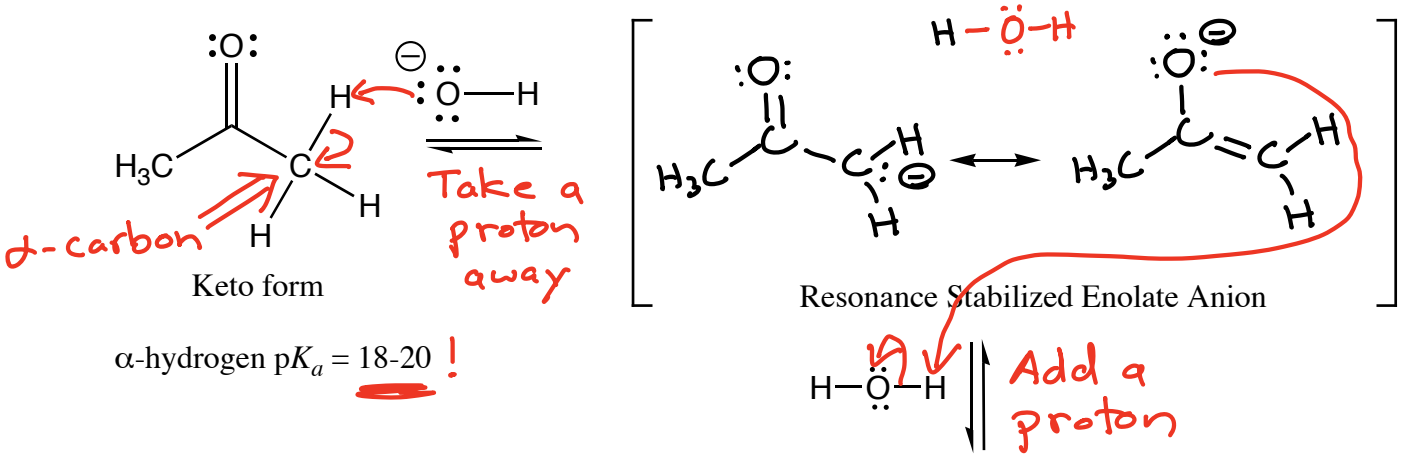
The process of interconverting the keto and enol forms is called "tautomerization"

Keto-Enol Equilibrium Catalyzed by Acid or Base

Acid



Base



α-hydrogen pK_a = 18-20 !

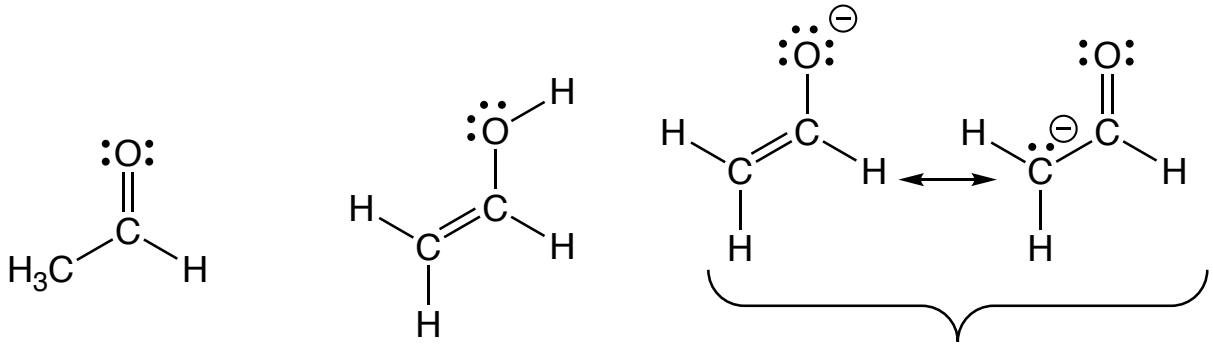
keto and enol forms are called "tautomers"

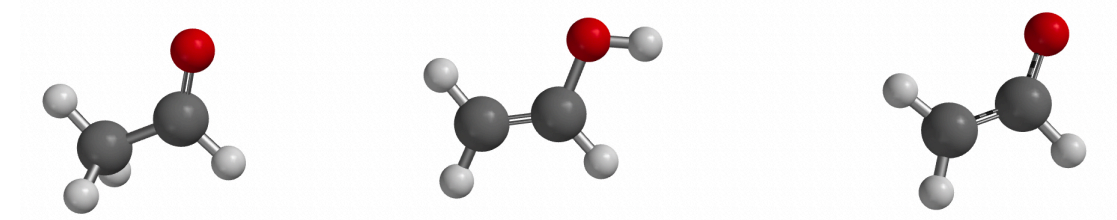
For both aldehydes and ketones, the keto form predominates at equilibrium, because C=O bonds are stronger than C=C bonds.

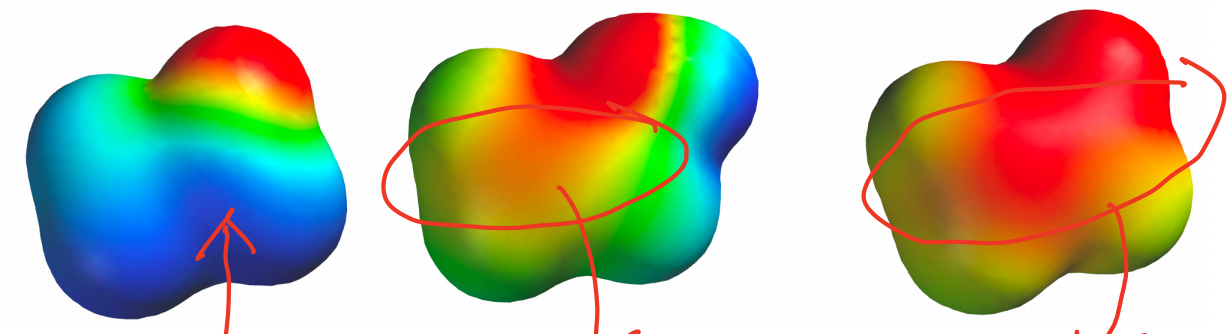
Enols are significant, however, because they react like nucleophile, not carbonyls, and this is important in certain situations.

Changing Personality:

An aldehyde or ketone is a weak electrophile.
An enol of that same aldehyde or ketone has a π bond that is a weak nucleophile!

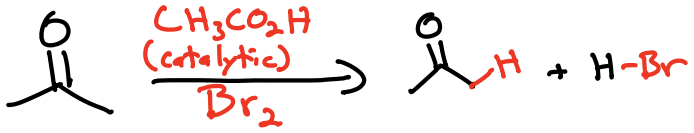


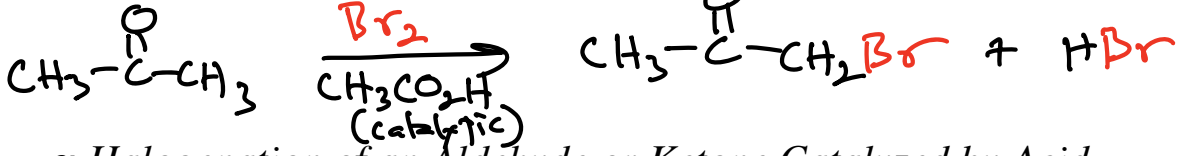




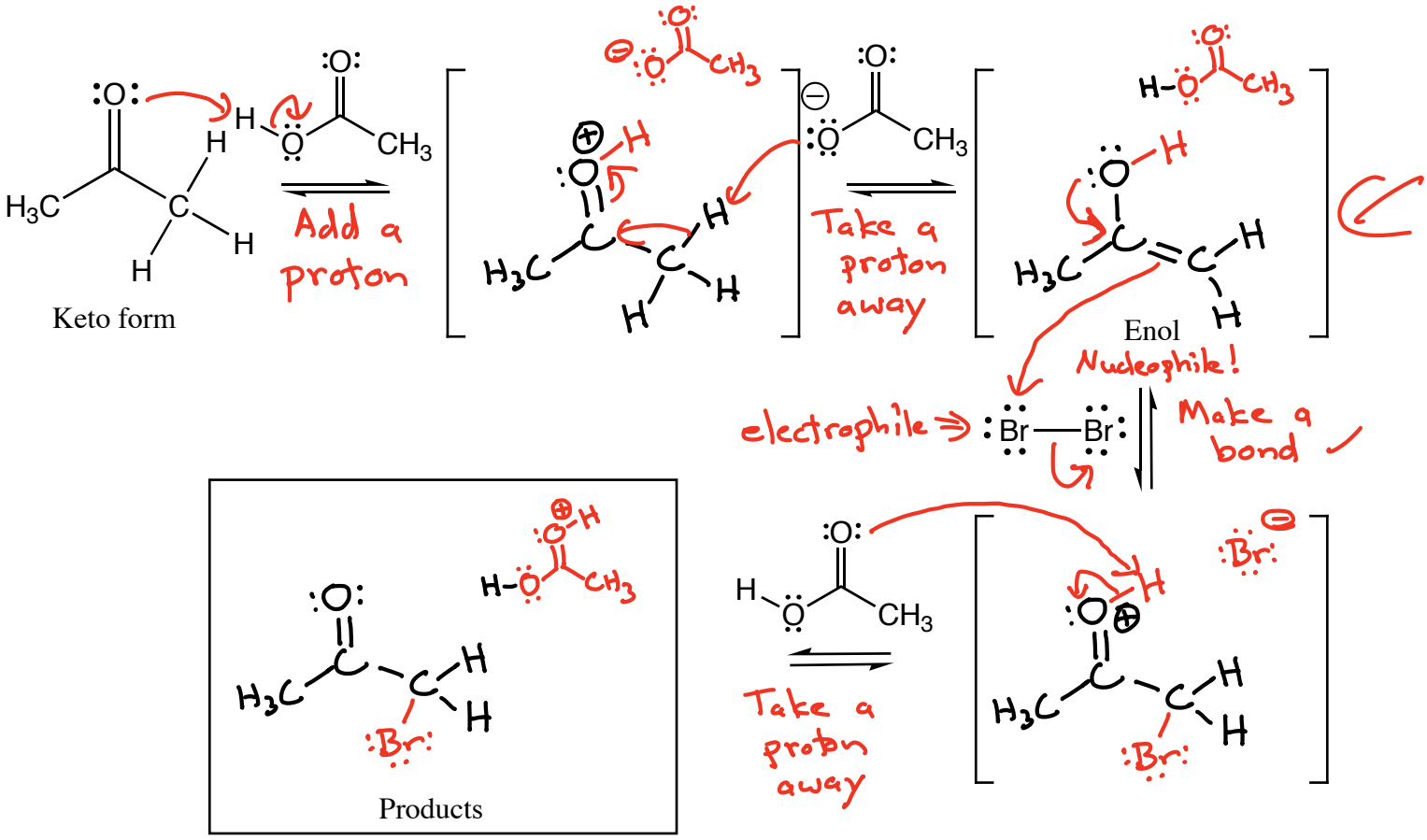
α-Halogenation of Aldehyde or Ketone in Acid

<u>Overall Reaction</u>

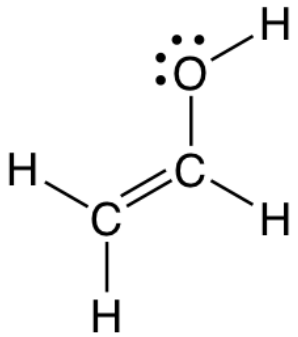


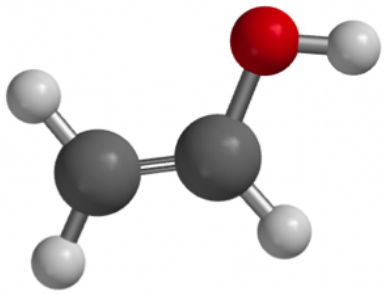


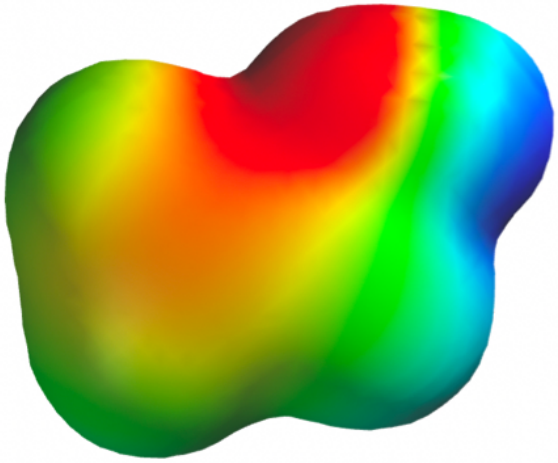
α-Halogenation of an Aldehyde or Ketone Catalyzed by Acid



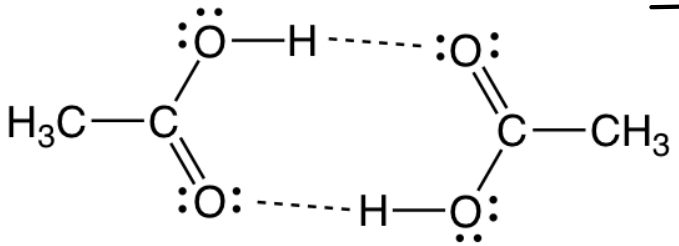
KRG: A new bond to Br at the α-carbon position
Prefers methyl groups

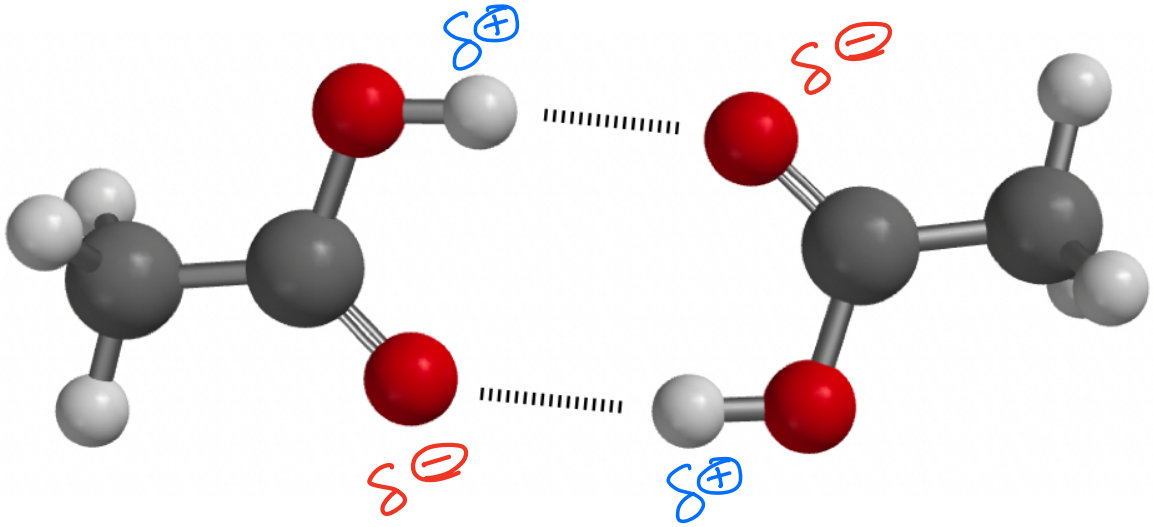


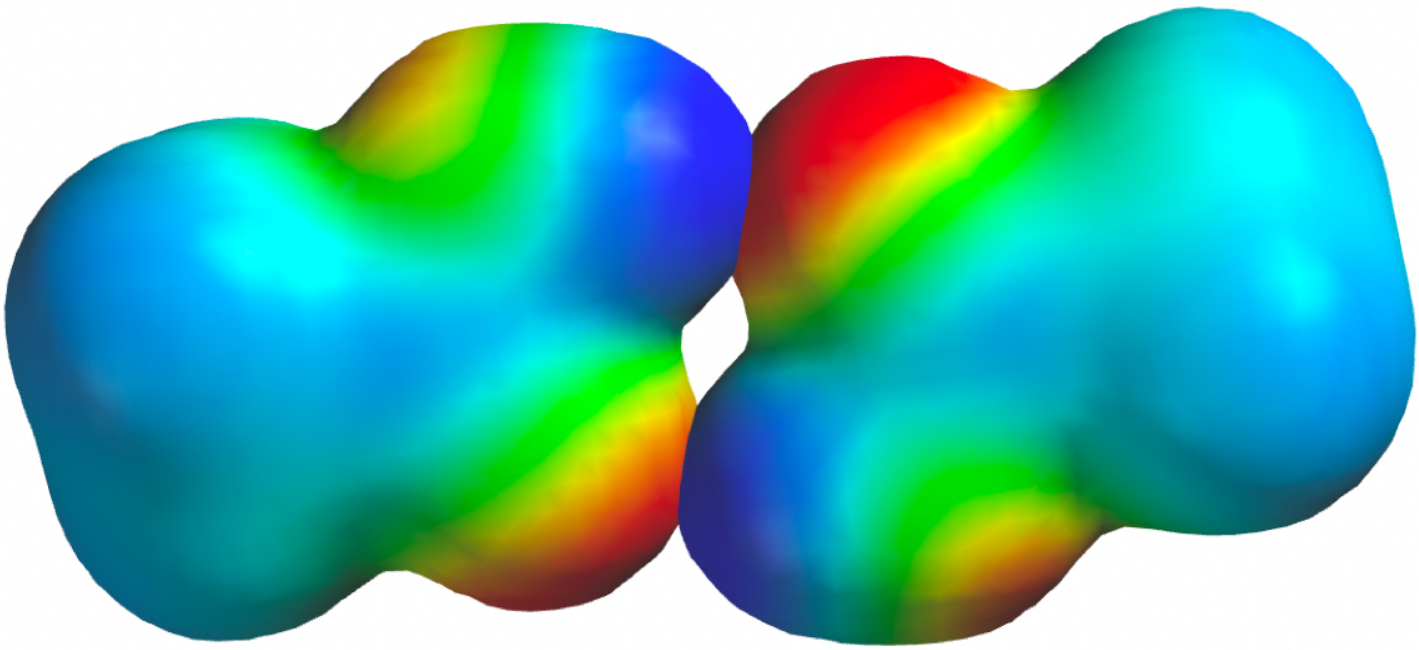


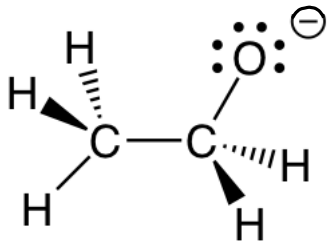


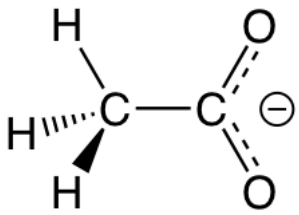
Carboxylic Acids

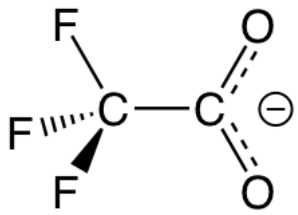


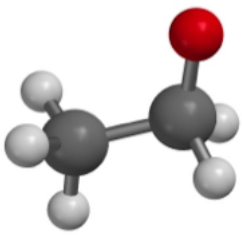


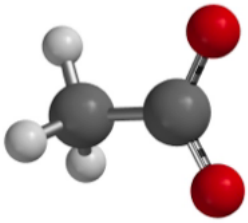


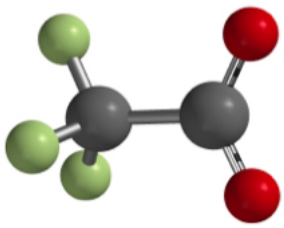


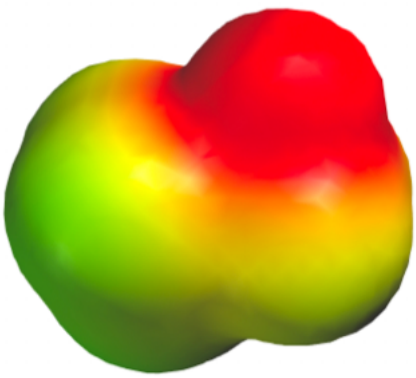


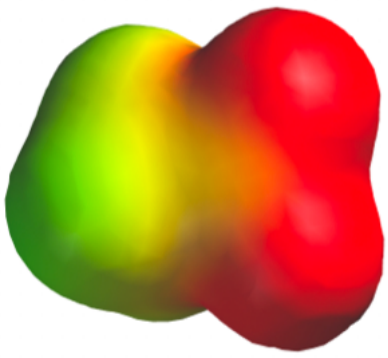


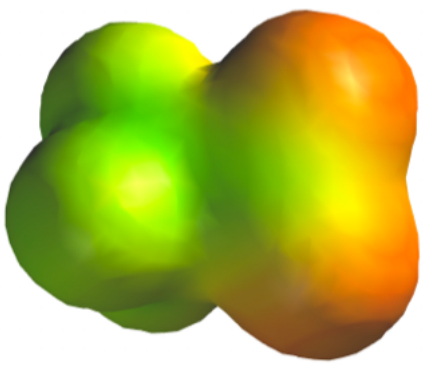




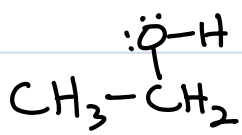


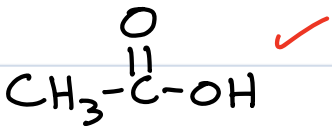


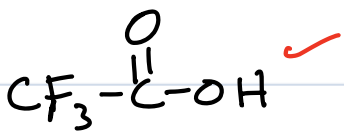




Parent Acids



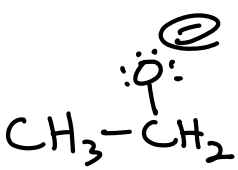


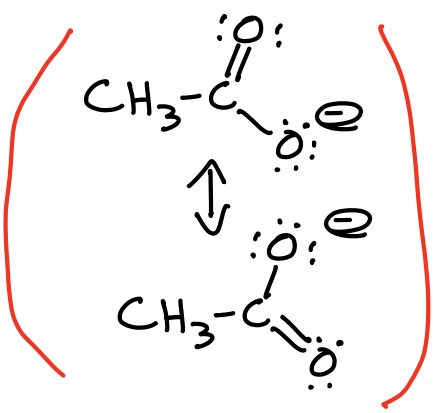


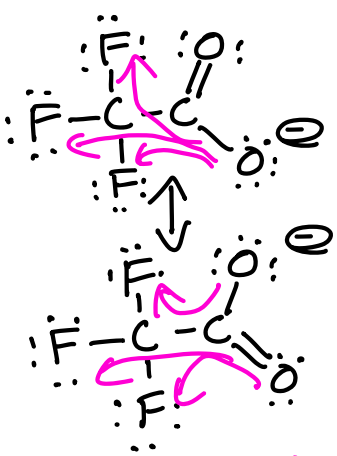
$pK_a = 16$

$pK_a = 3\text{-}5$

$pK_a = 0.3$

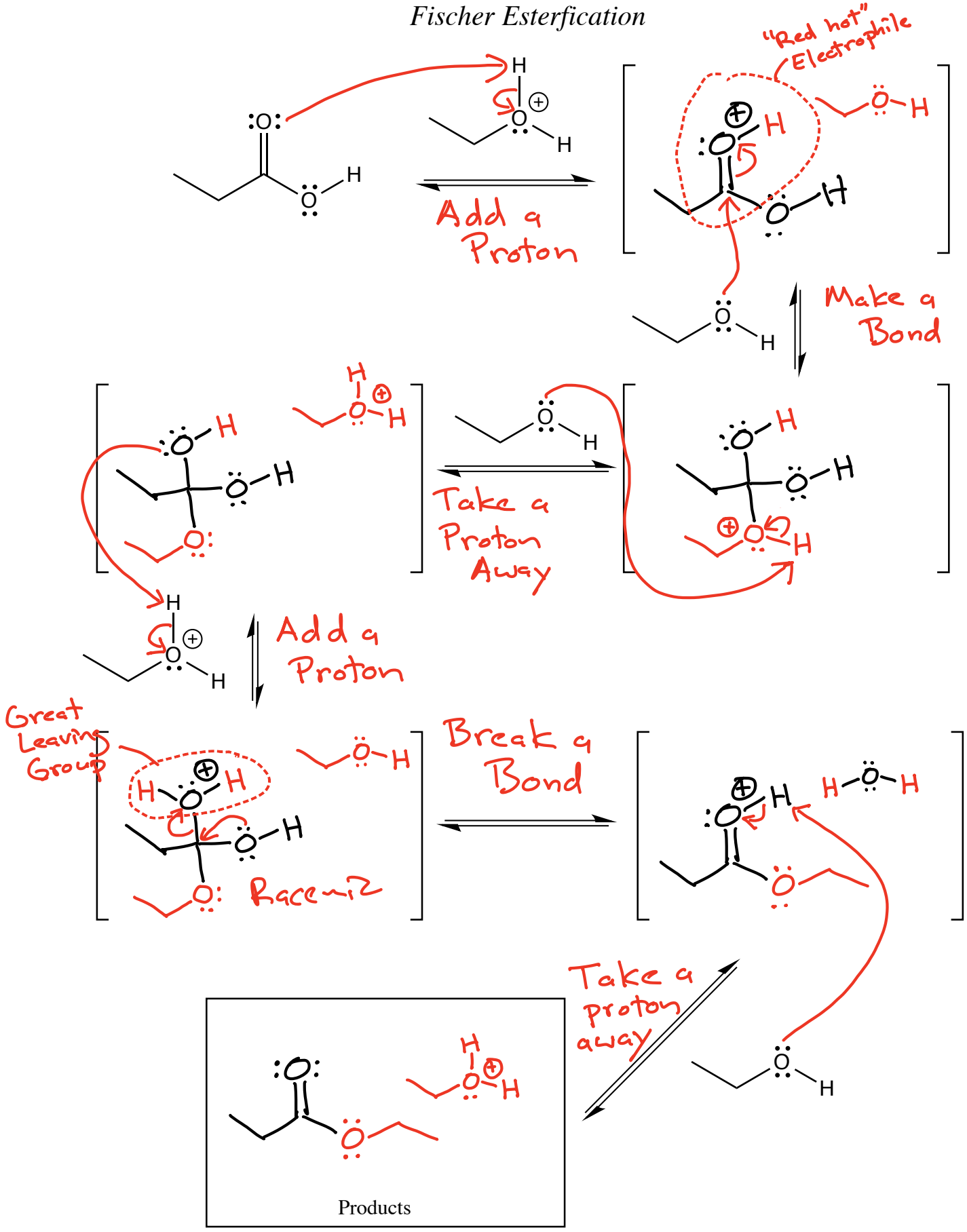




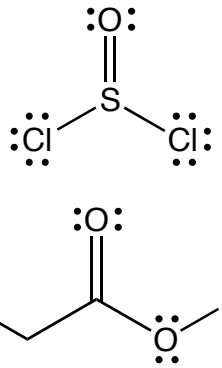


Inductive effect

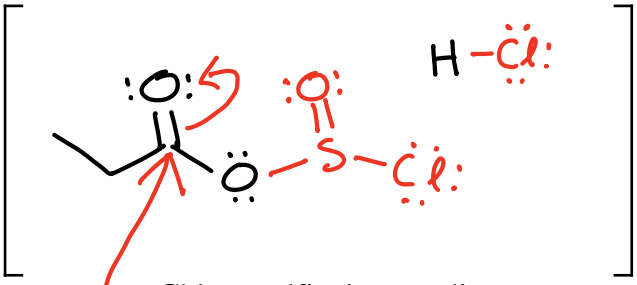
Fischer Esterfication



Reaction with Thionyl Chloride



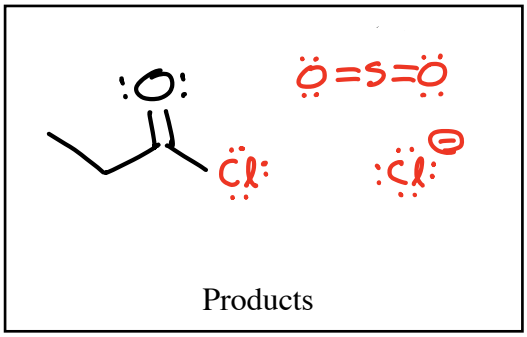
Several Steps



Chlrorosulfite intermediate

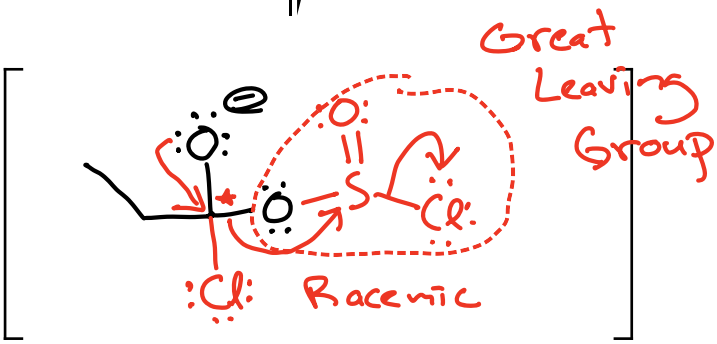
KRE → An acid chloride

Make a bond



Products

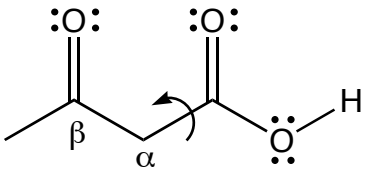
Break a Bond



Great Leaving Group

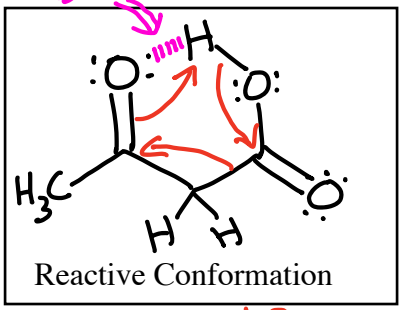
Racemic

Decarboxylation of a β-Keto Acid

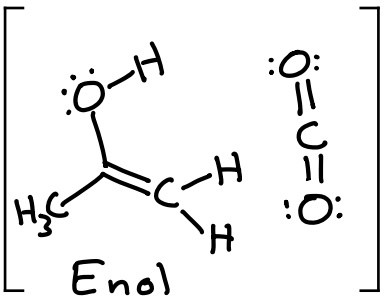


Bond rotates to give a more stable conformation

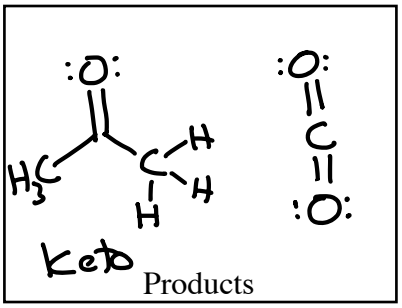
Hydrogen Bond



Reactive Conformation



Enol



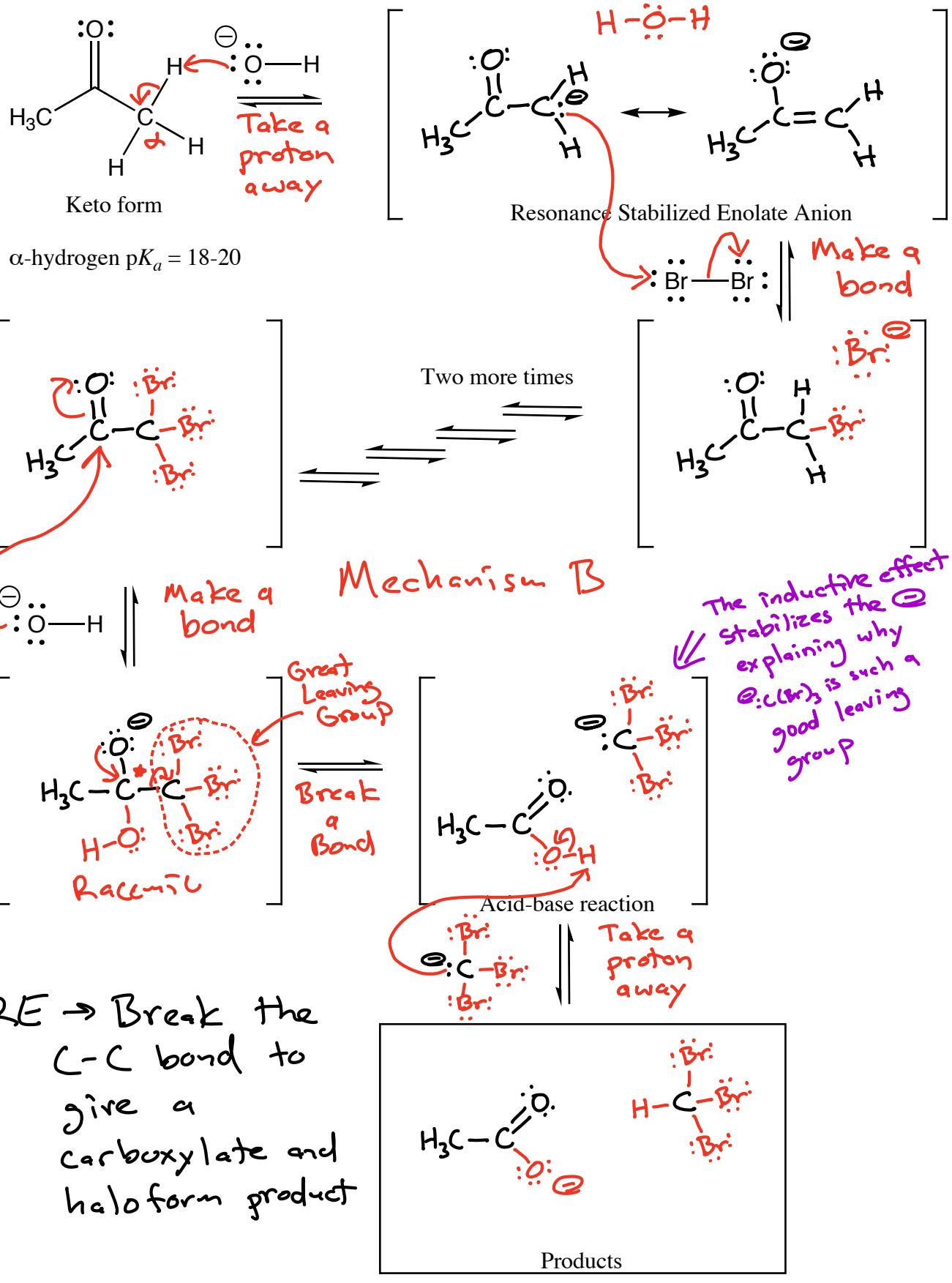
Keto

Products

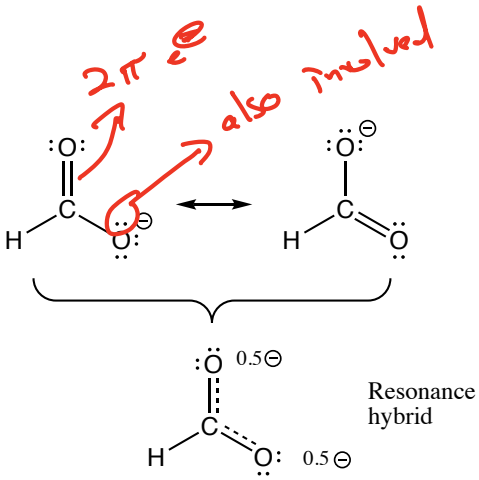
6-Membered Ring
6 "Pi" Electrons
VERY STABLE
"Aromatic"

C-C Bond Breaks!

The Haloform Reaction

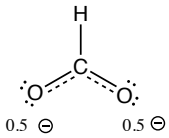


KRE → Break the C-C bond to give a carboxylate and haloform product



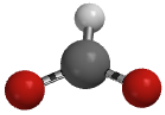
A common situation, and the one many resonance contributing structures describe, occurs when three 2p orbitals combine on adjacent atoms. A good example is the carboxylate anion. When three adjacent 2p orbitals interact (we add the three 2p orbital wave functions $\Psi_{C2pz} + \Psi_{O2pz} + \Psi_{O2pz}$), three new molecular orbitals are produced; a low energy bonding "pi-way", a non-bonding orbital and an antibonding orbital as shown below. This pattern of three molecular orbitals is generally the same whenever three 2p orbitals interact even if there are different atoms involved, for example the enolate ion or allyl cation. There are four electrons in the pi system of the carboxylate anion, (you can see this by looking at either of the contributing structures; two electrons from the pi bond and two from the third lone pair on the negatively charge O atom). Note the non-bonding orbital contains the electron density of two electrons that are paired, do NOT think of it as having one upaired electron on each O atom. I know, weird, but remember it is best to think of bonding electrons as waves, not particles. Note the electron density on only the O atoms of the non-bonding orbital explains why the negative charge is localized on the O atoms in the carboxylate anion.

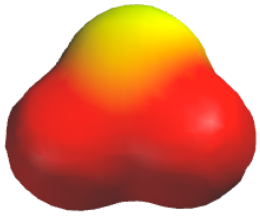
$\Psi_{C2pz} + \Psi_{O2pz} + \Psi_{O2pz}$

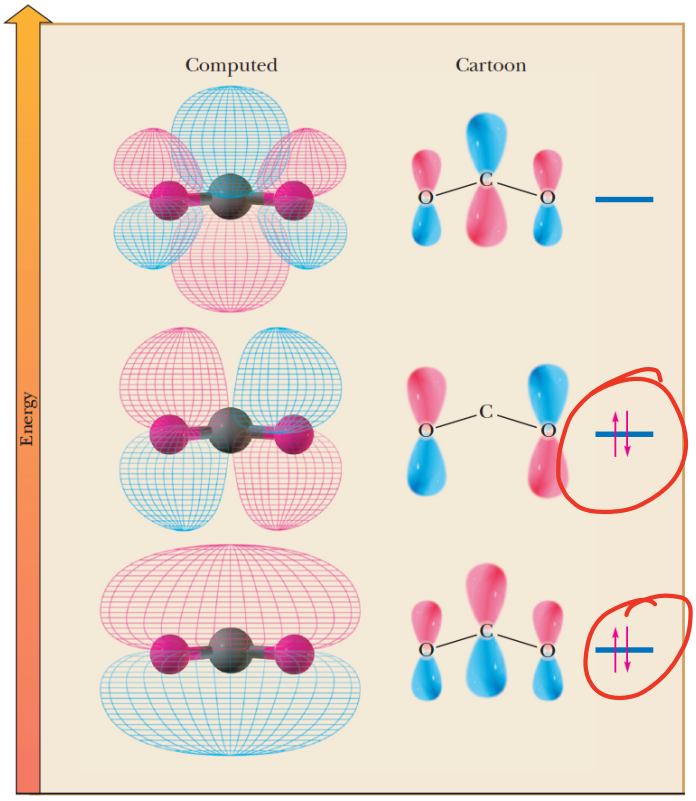


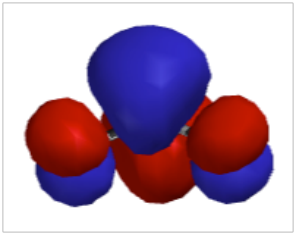
Carboxylate anion

Resonance hybrid

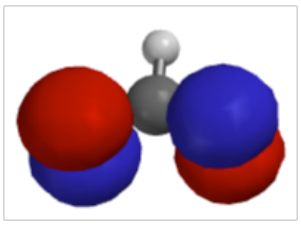




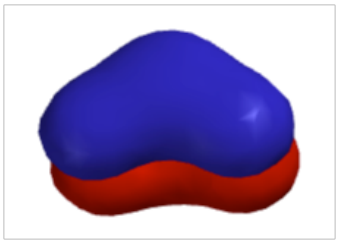




Antibonding orbital



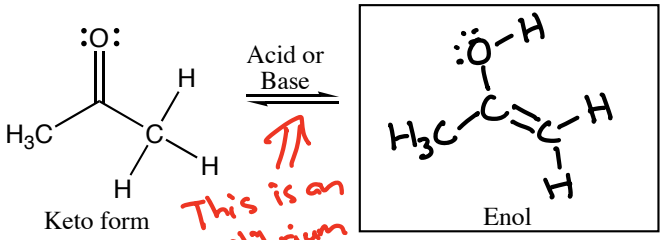
Non-bonding orbital



"π-way" orbital

Keto-Enol Tautomerization vs. Enolate Resonance

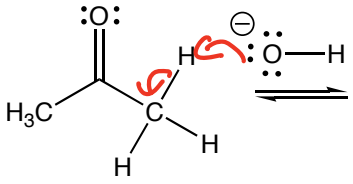
Keto-Enol Tautomerization

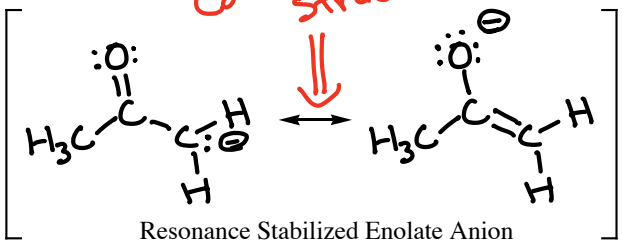


This is an equilibrium

Both the keto and enol molecules are Neutral!

Enolate Resonance



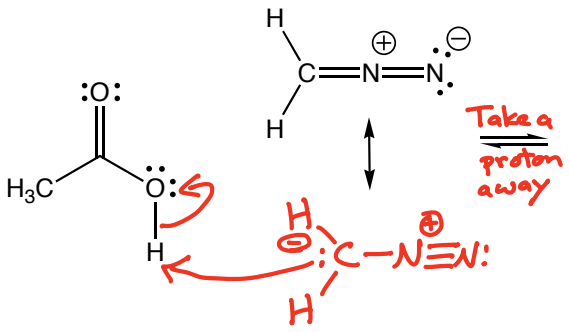


Contributing structures!

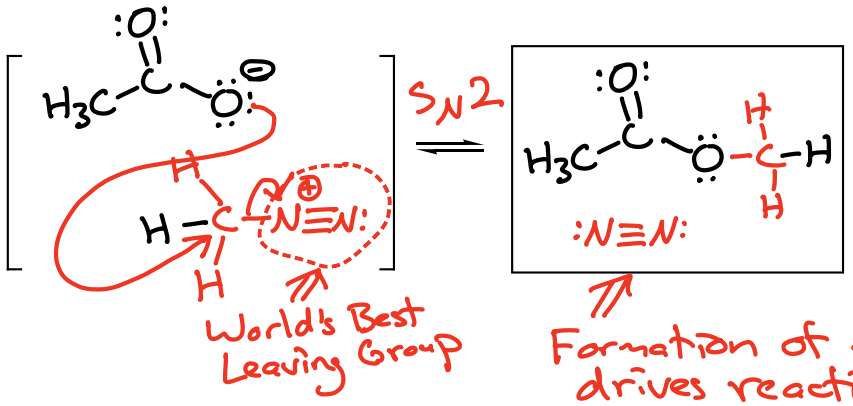
Full ⊖

α-hydrogen pK_a = 18-20

Diazomethane reaction



Take a proton away

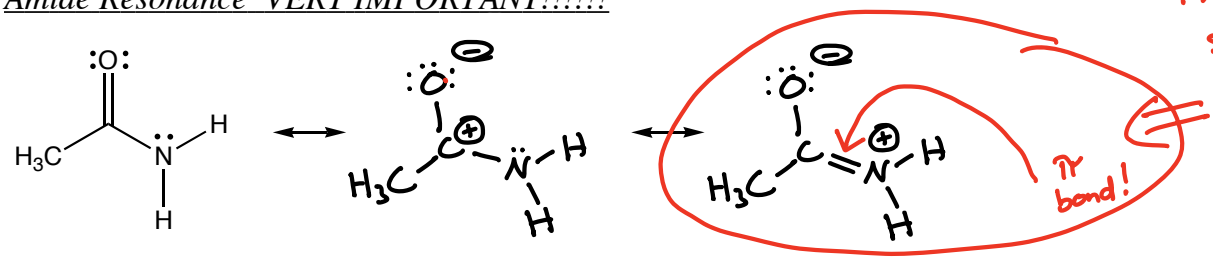


S_N2

World's Best Leaving Group

Formation of N_2 drives reaction!

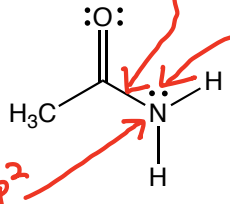
Amide Resonance VERY IMPORTANT!!!!!!



This contributing structure is important and that has big consequences!

π bond!

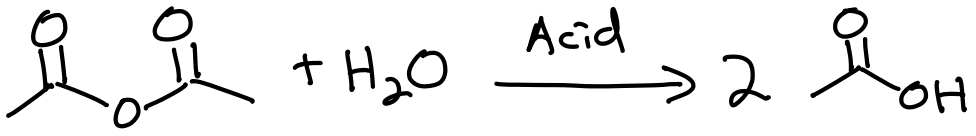
This is a partial π bond so it does NOT rotate at room temperature



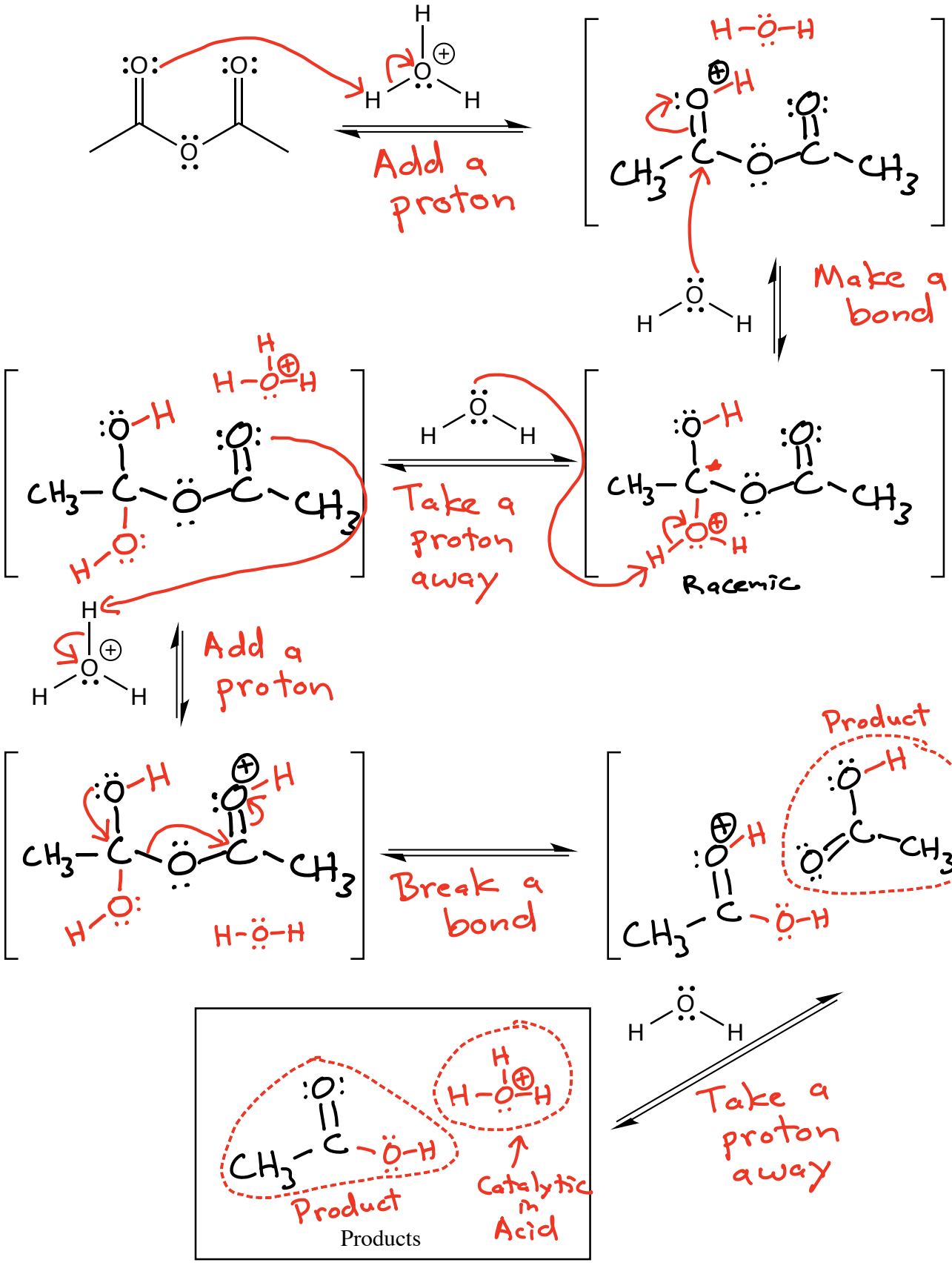
Lone pair is in a 2p orbital!

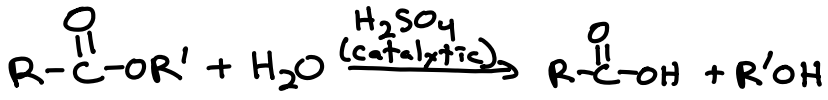
(Golden Rule of Chemistry)

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

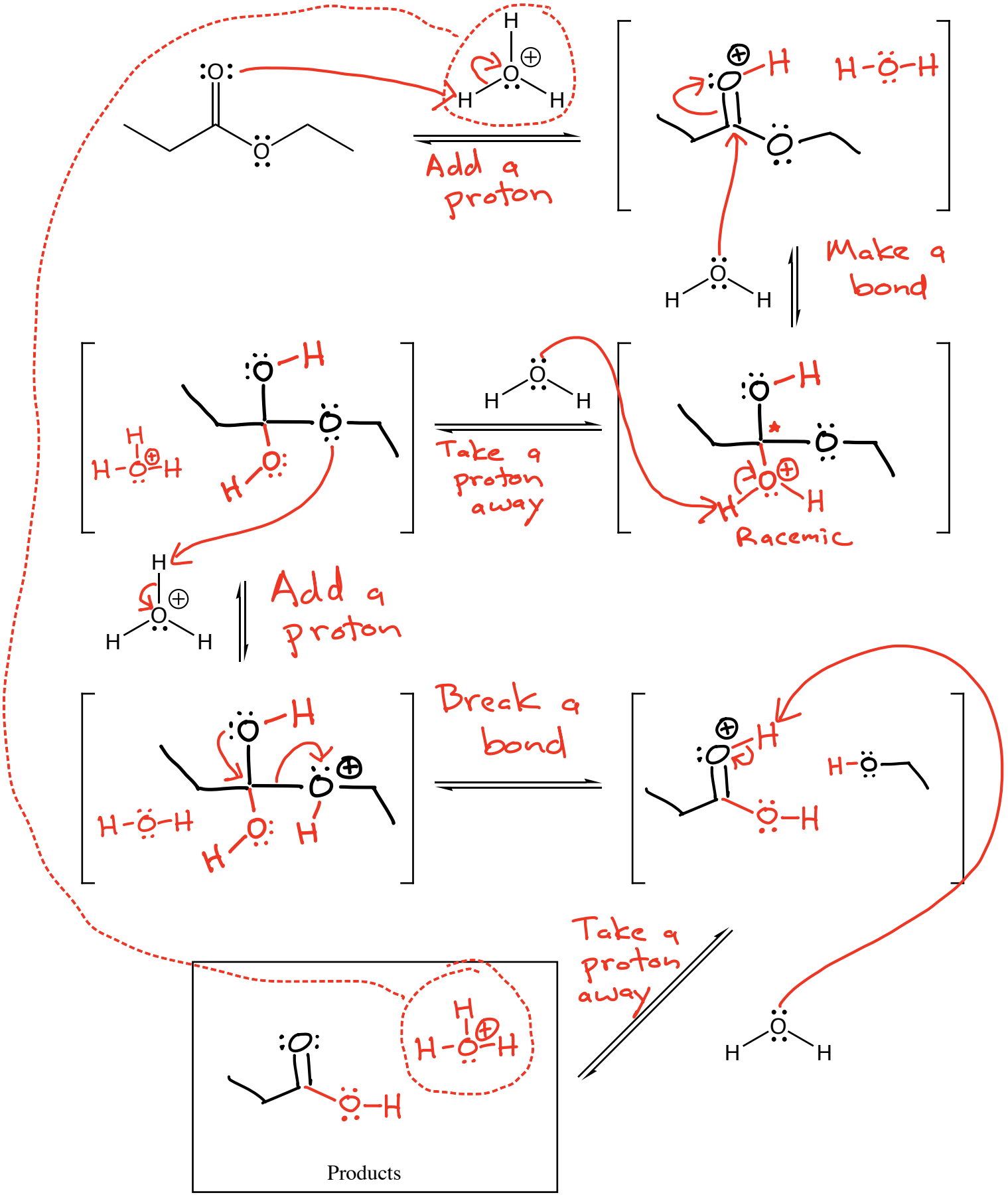


Acid Catalyzed Anhydride Hydrolysis

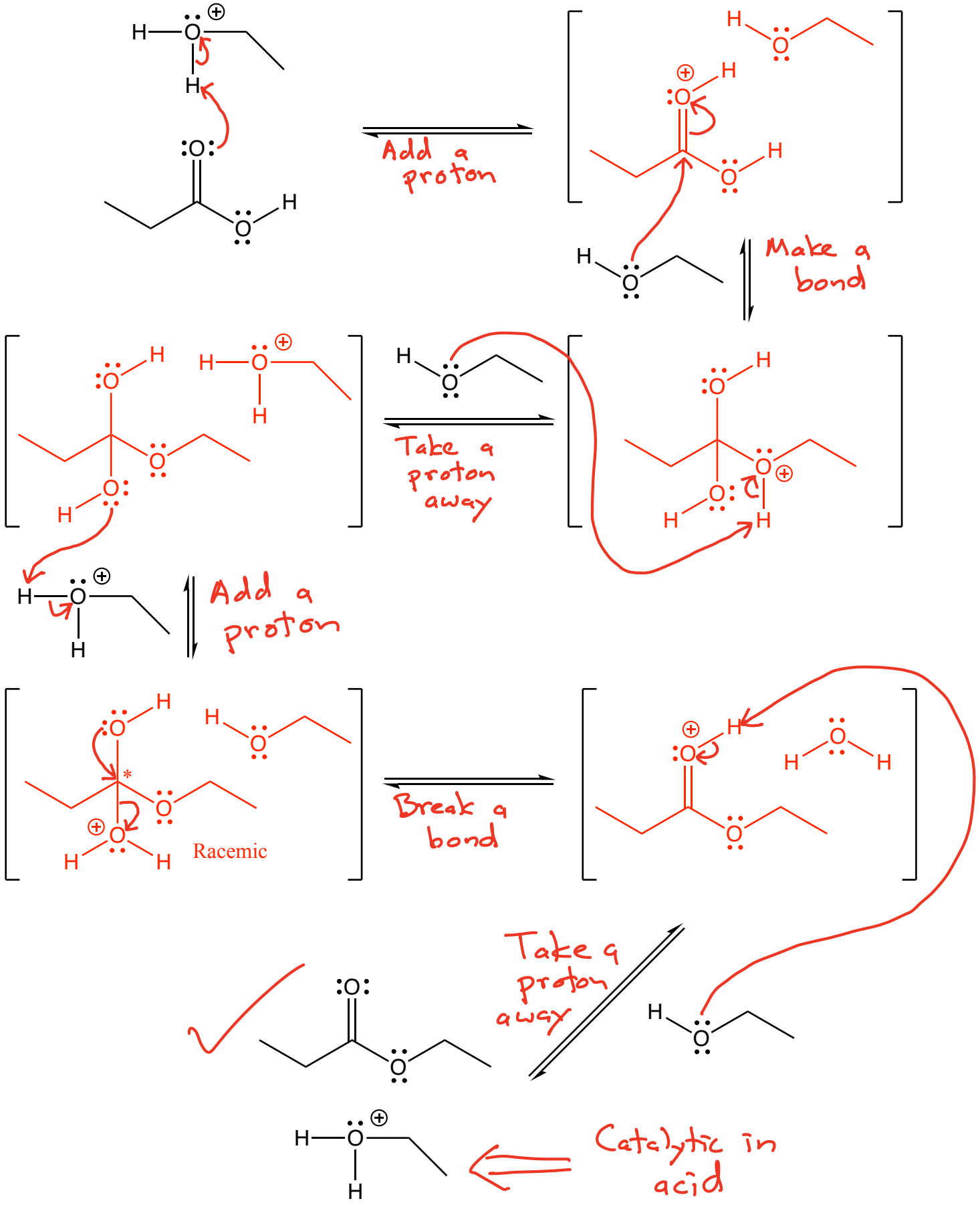




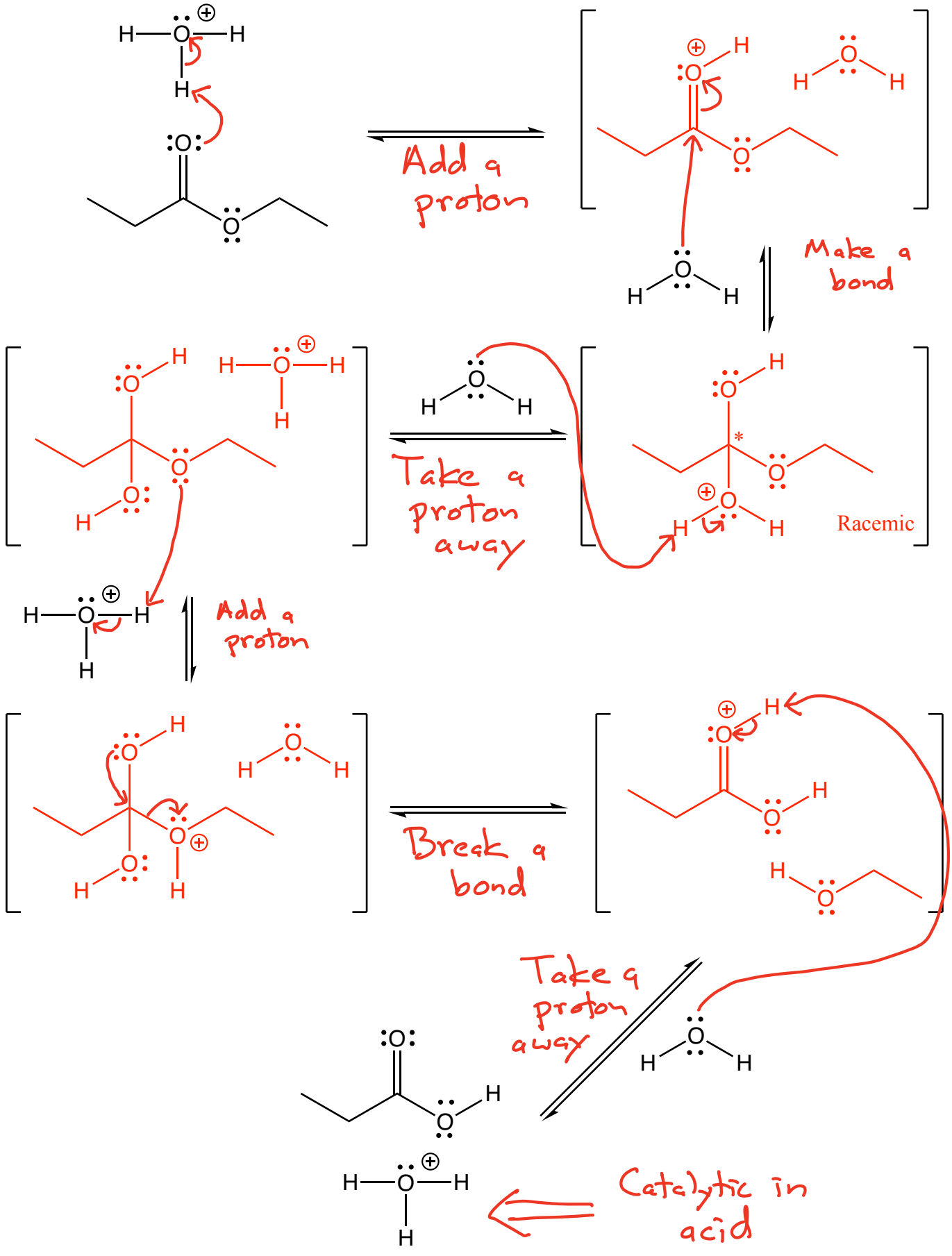
Acid Catalyzed Ester Hydrolysis

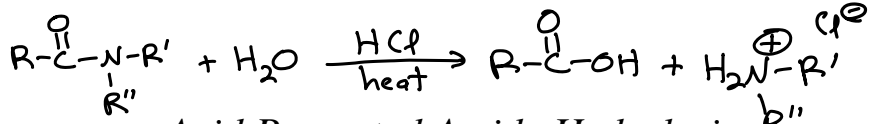


Microscopic Reversibilty: Acid Catalyzed Ester Hydrolysis-Fischer Esterification

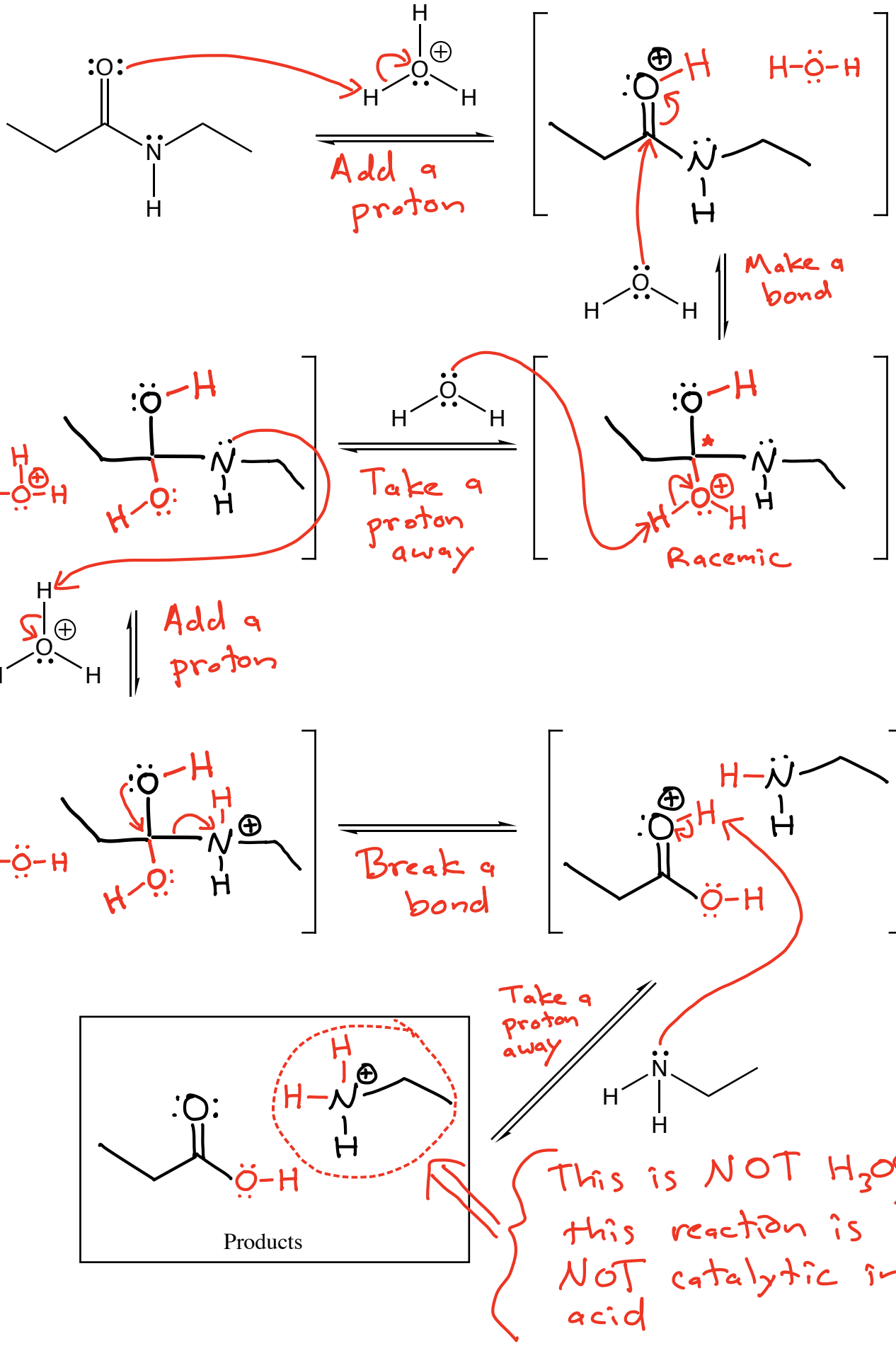


Microscopic Reversibilty: Acid Catalyzed Ester Hydrolysis-Fischer Esterification

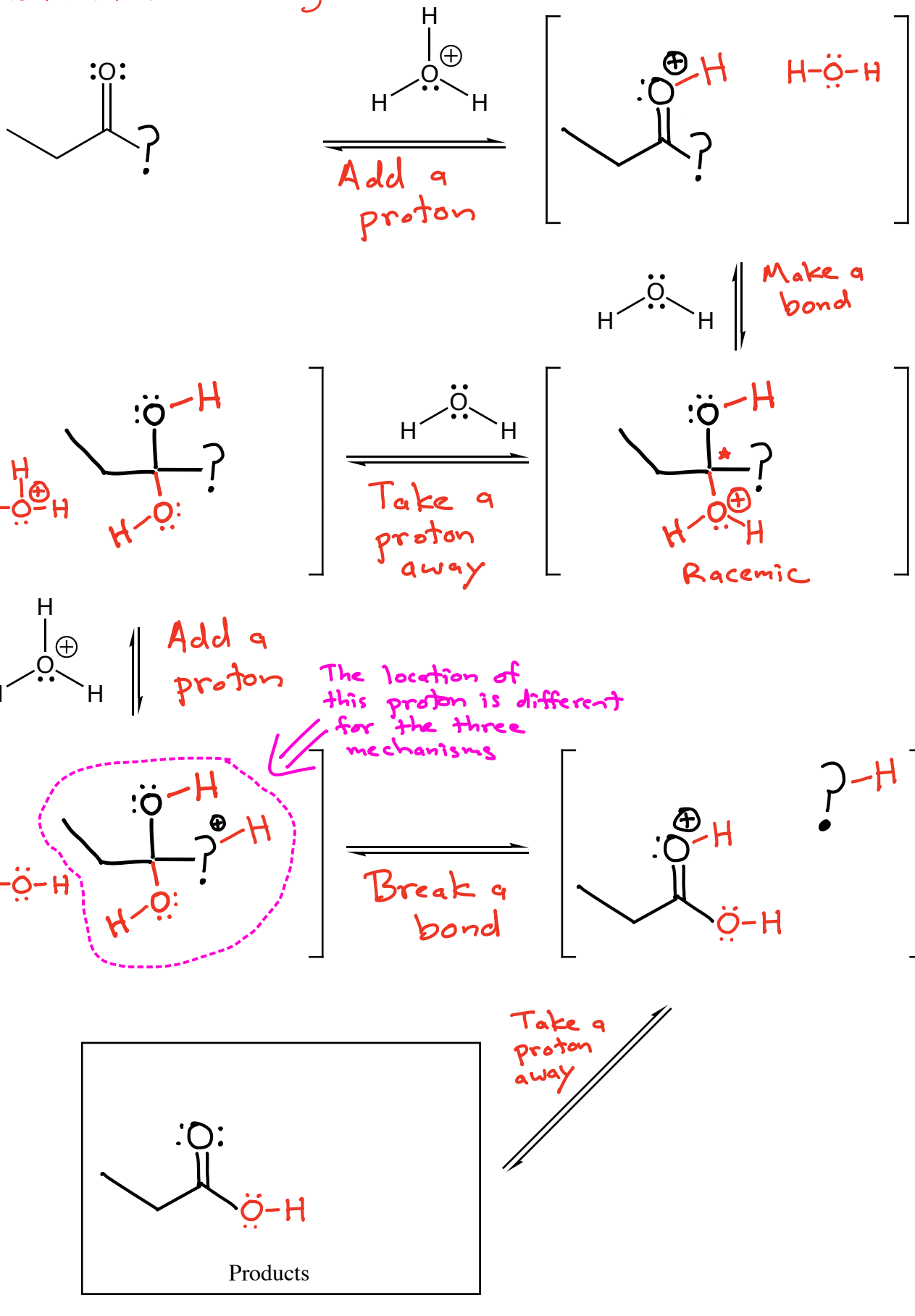




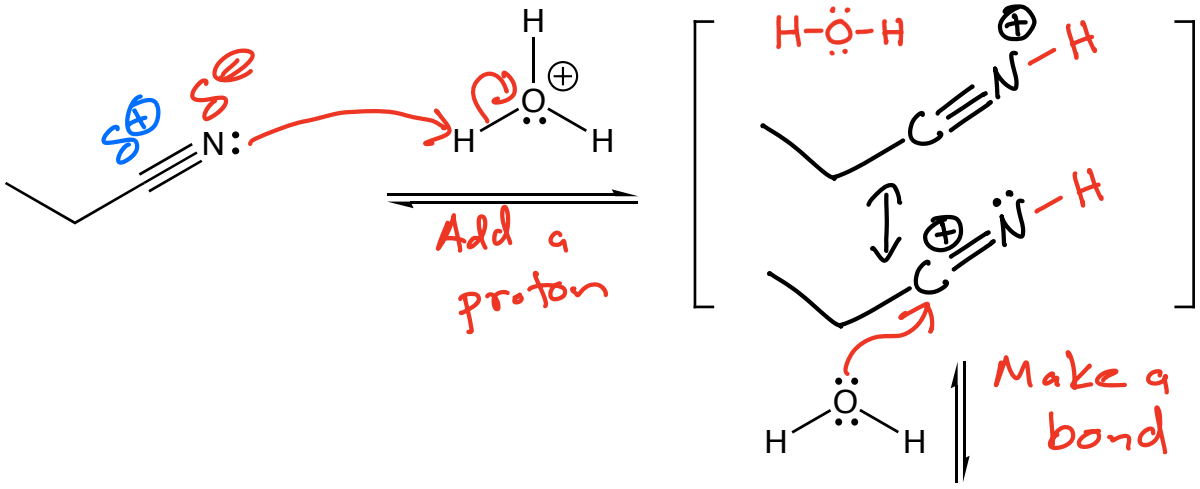
Acid Promoted Amide Hydrolysis

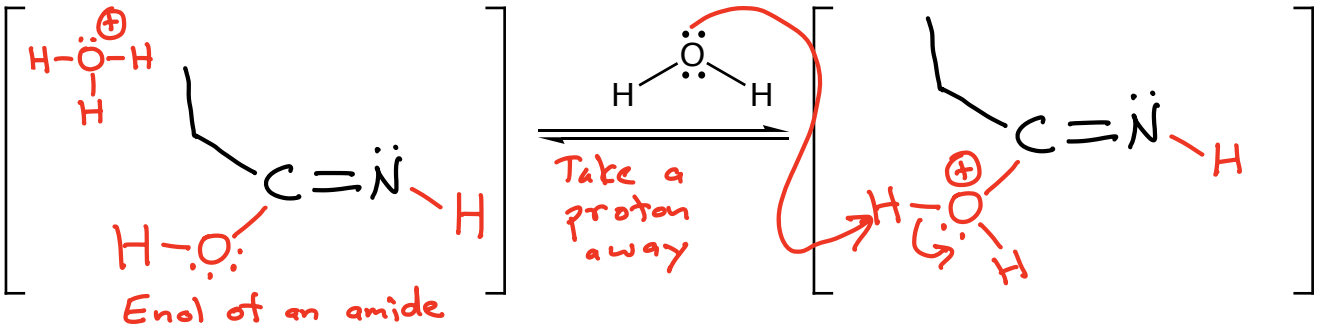


The following mechanism applies to which reaction we have seen? Trick Question → it applies to three reactions → Anhydride, ester and amide hydrolysis in acid! "Same song different verse!"

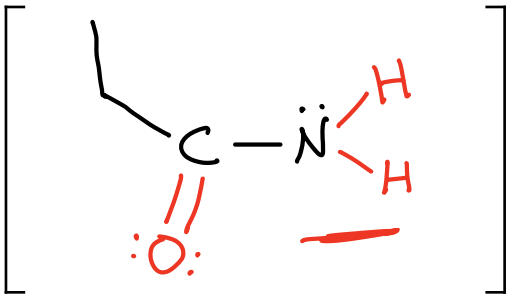


Acid Promoted Nitrile Hydrolysis



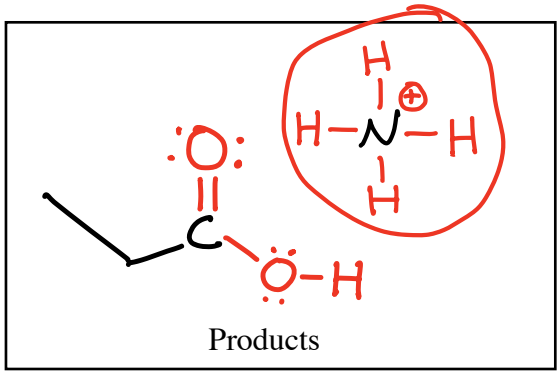


tautomerization

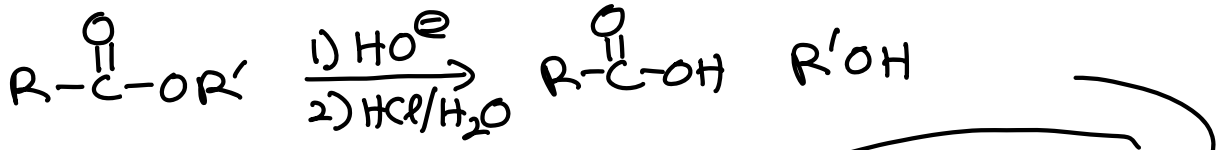


several steps

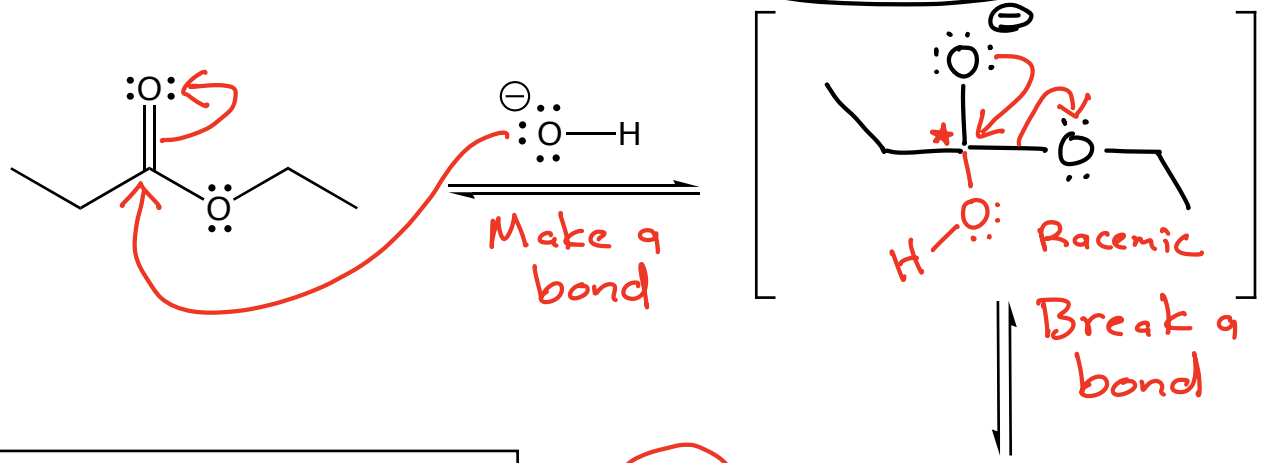
(see amide hydrolysis mechanism)

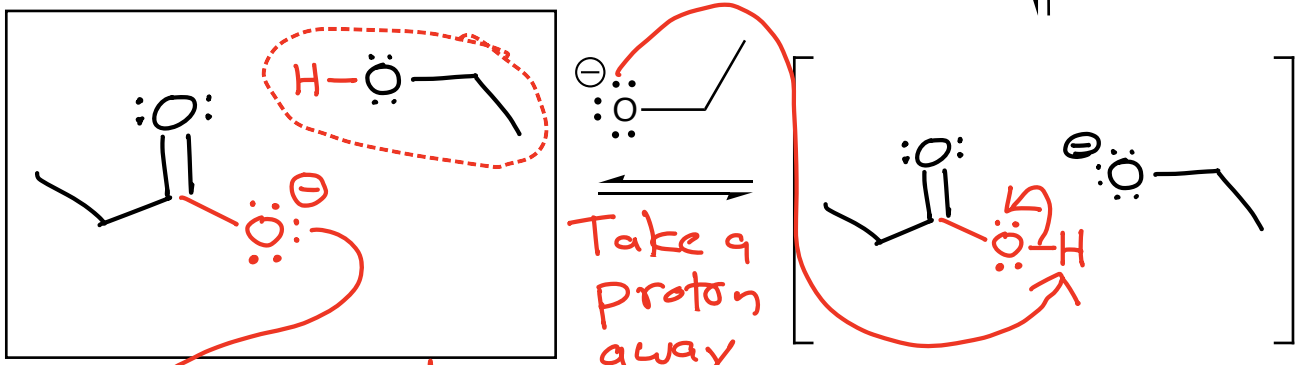


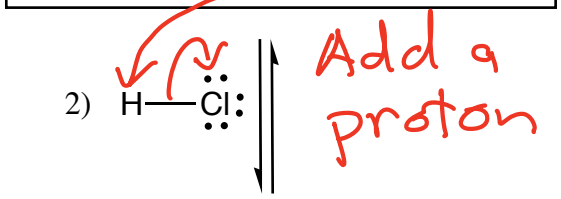
These conditions are strong enough to hydrolyze amides according to the mechanism we saw as "Acid Promoted Hydrolysis of an Amide"



Base-Promoted Ester Hydrolysis - Saponification

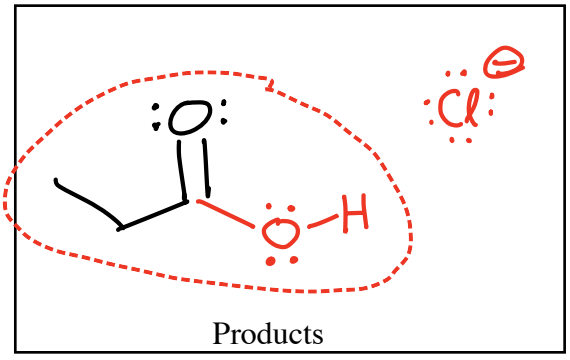






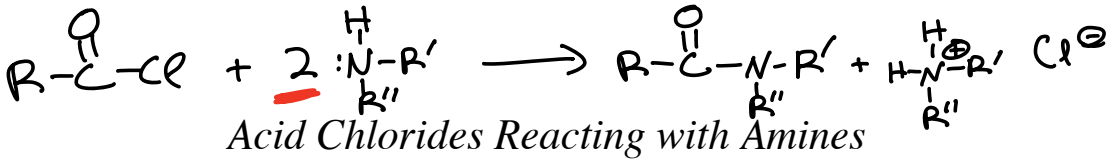
NOT catalytic in base

Mechanism B

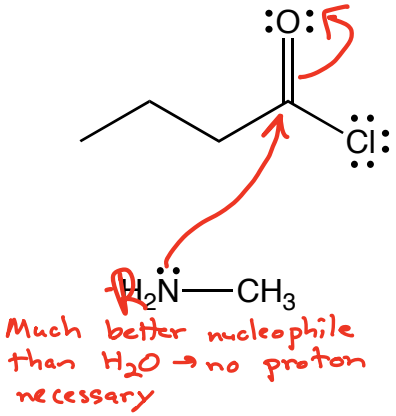


Driving force → converts $HO^{\ominus}$ to $R-C(=O)-O^{\ominus}$

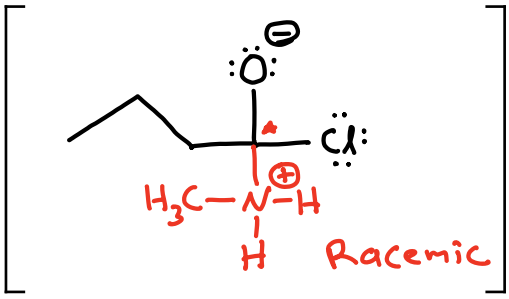
More stable anion → favored → MOTIVE



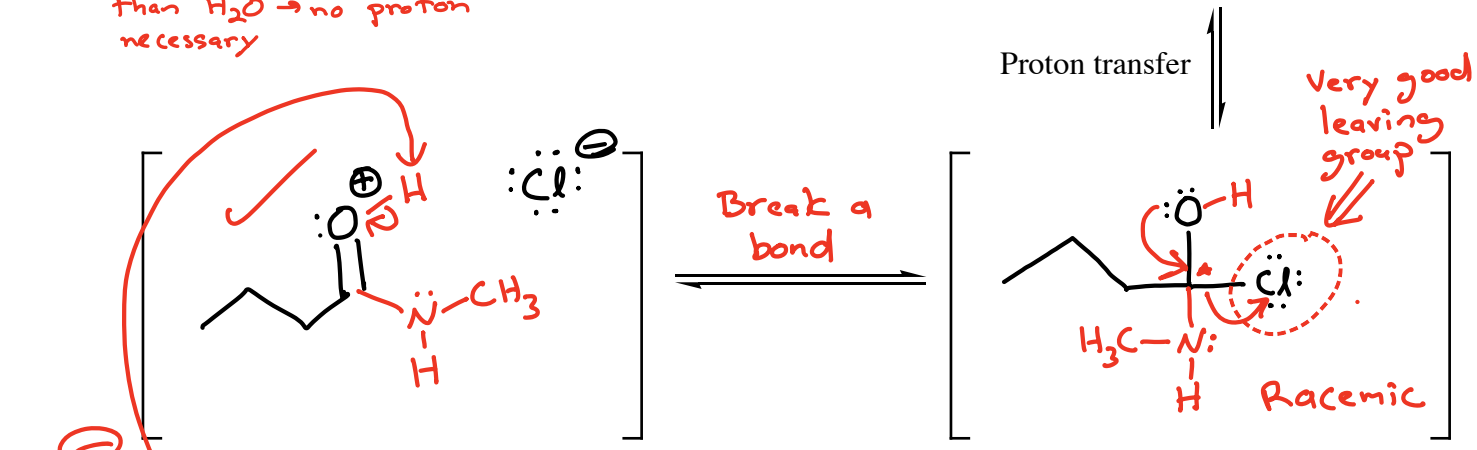
Acid Chlorides Reacting with Amines

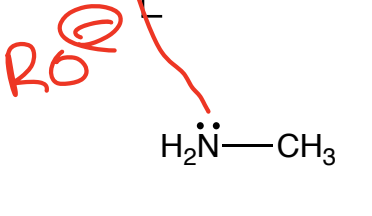


Make a bond

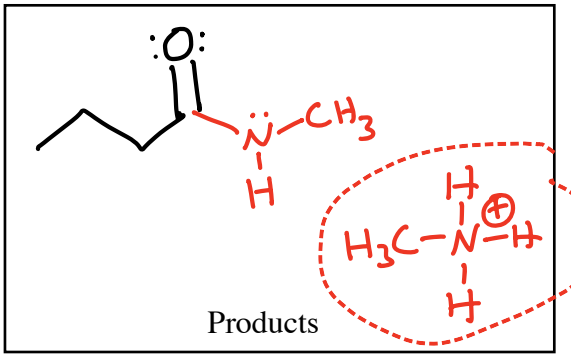


Proton transfer

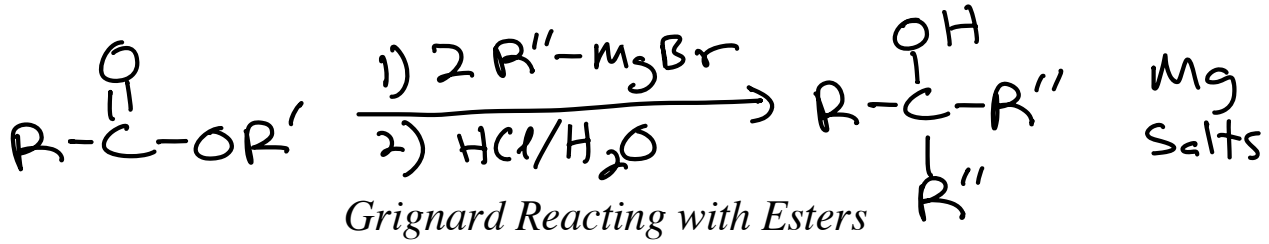




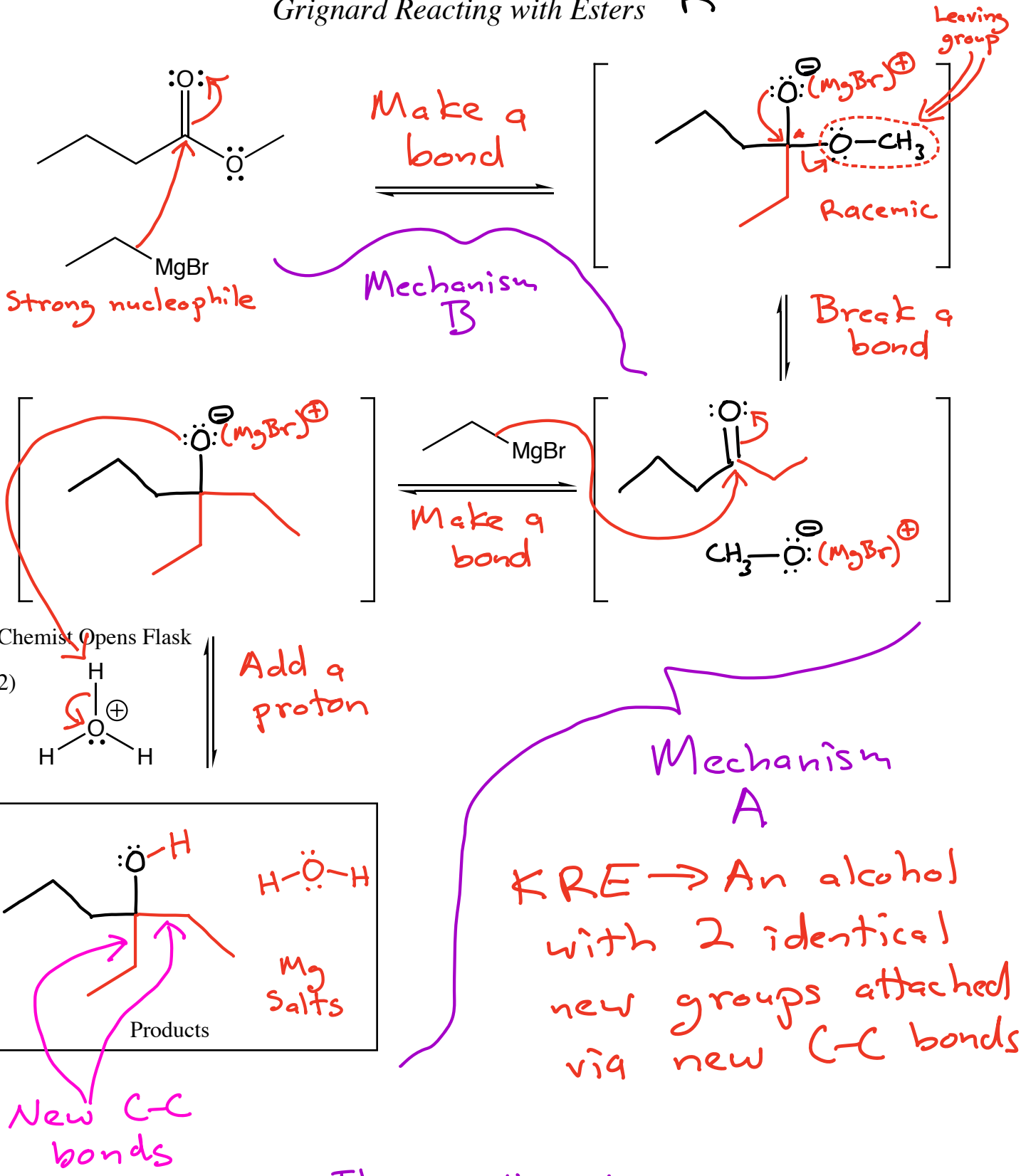
Take a proton away

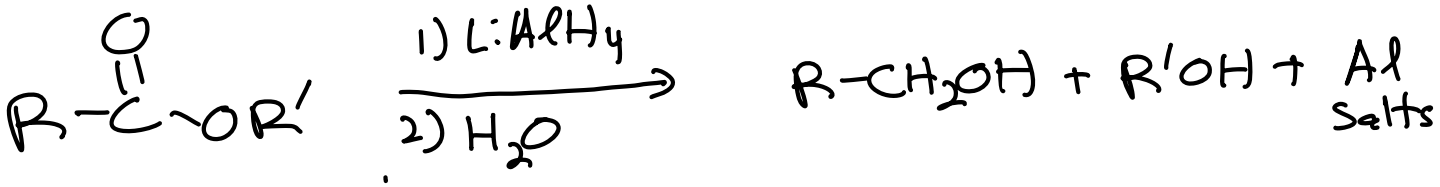


NOT a nucleophile so we need 2 equivalents of amine for this reaction

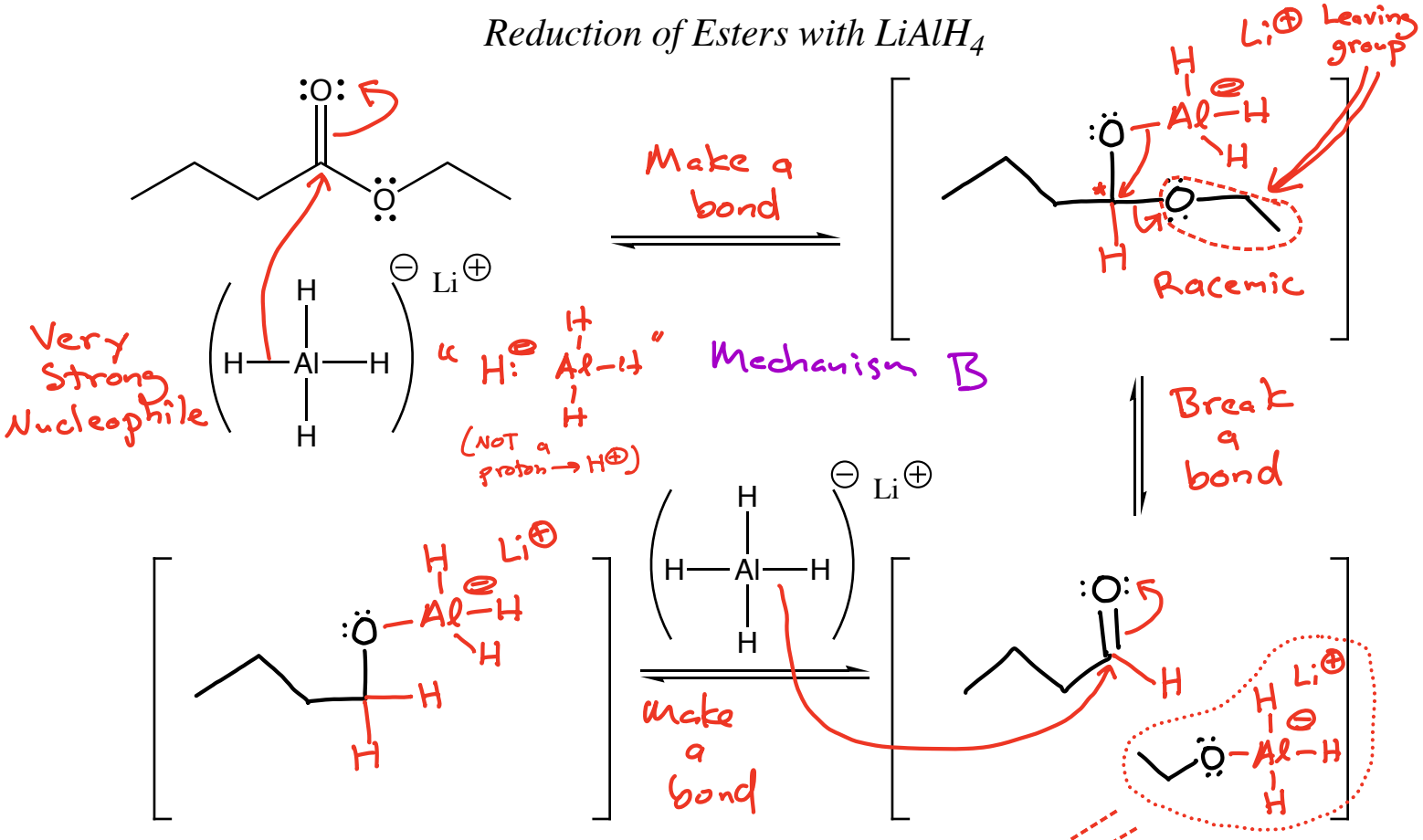


Grignard Reacting with Esters



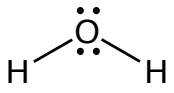


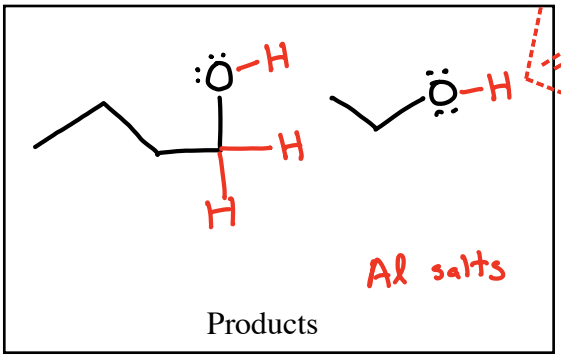
Reduction of Esters with $LiAlH_4$



Chemist Opens Flask

2)

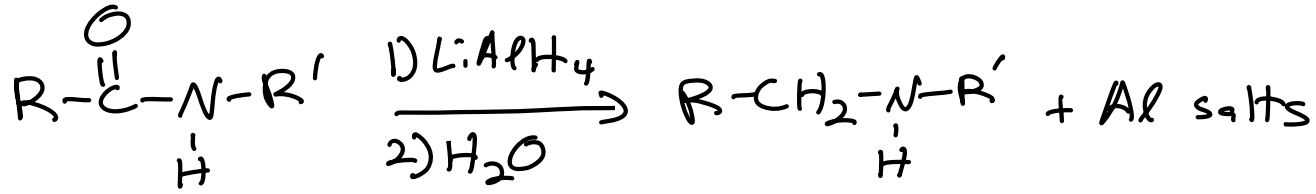




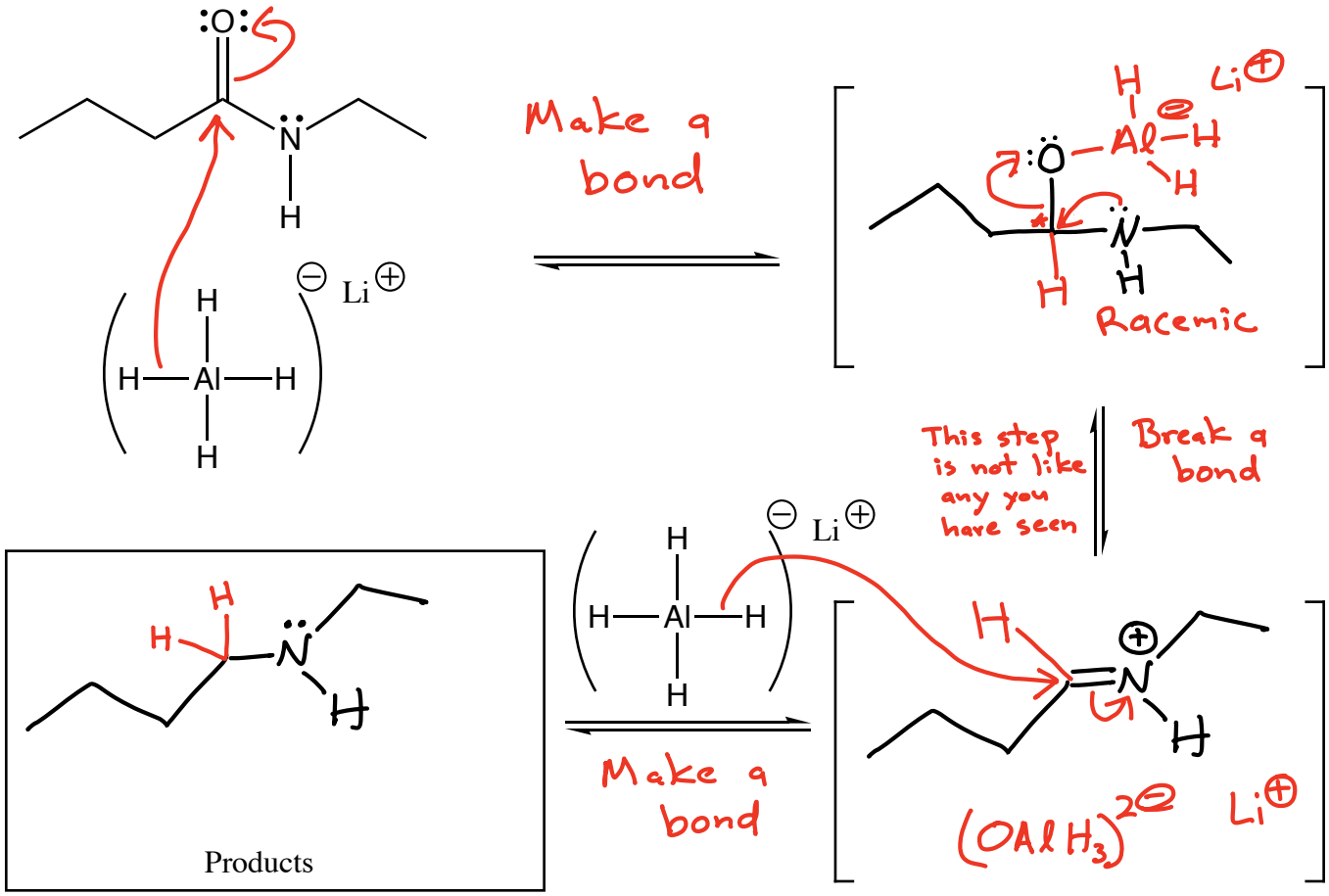
Just keeping track of this product

KRE → converts an ester into two alcohols → breaks C-O bond

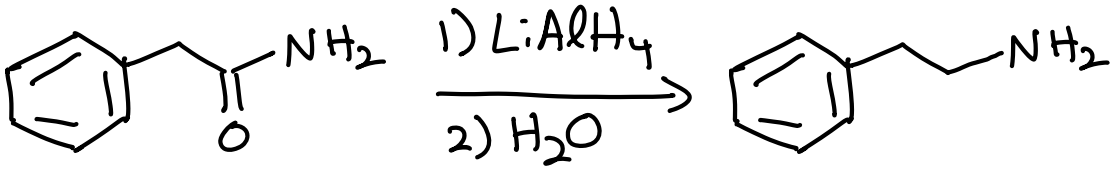
Note the extreme similarities between these last two mechanisms! ⇒ Mechanism B followed by Mechanism A just like the last reaction!



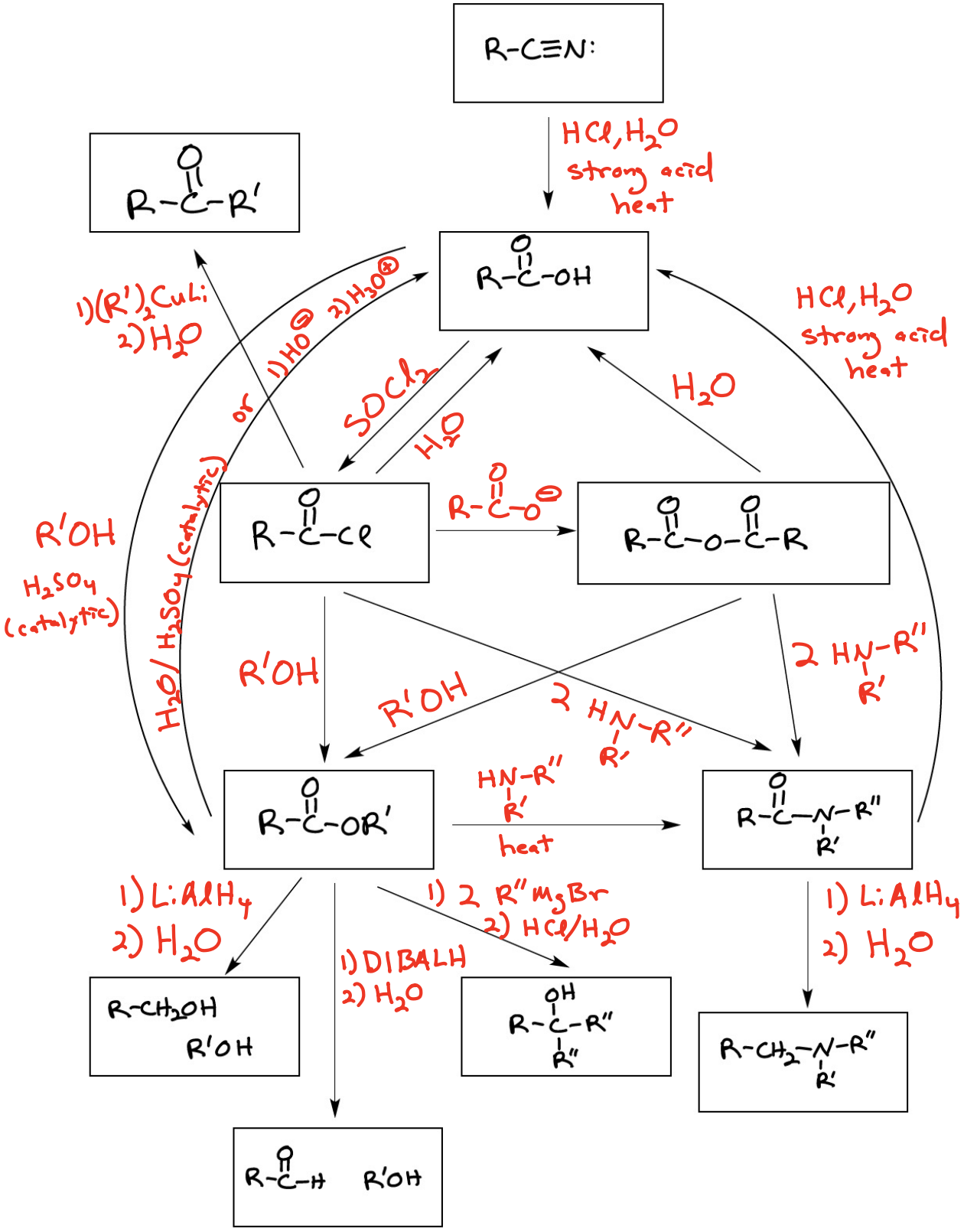
Reduction of Amides with $LiAlH_4$

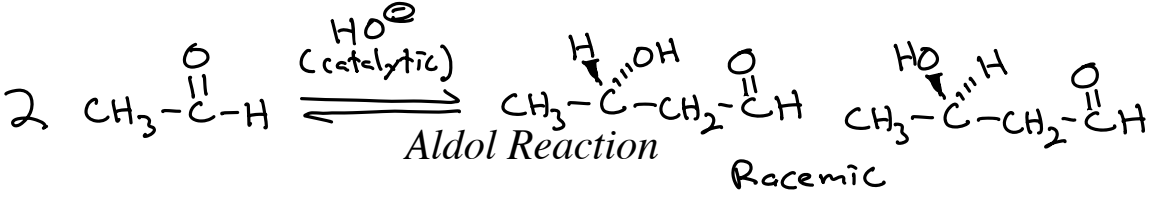


Note: In this reaction the chemist opens the flask and adds water in a second step that quenches any excess $LiAlH_4$. Therefore, you need a second step to add water when using this reaction in synthesis even though it is not shown in the mechanism above.

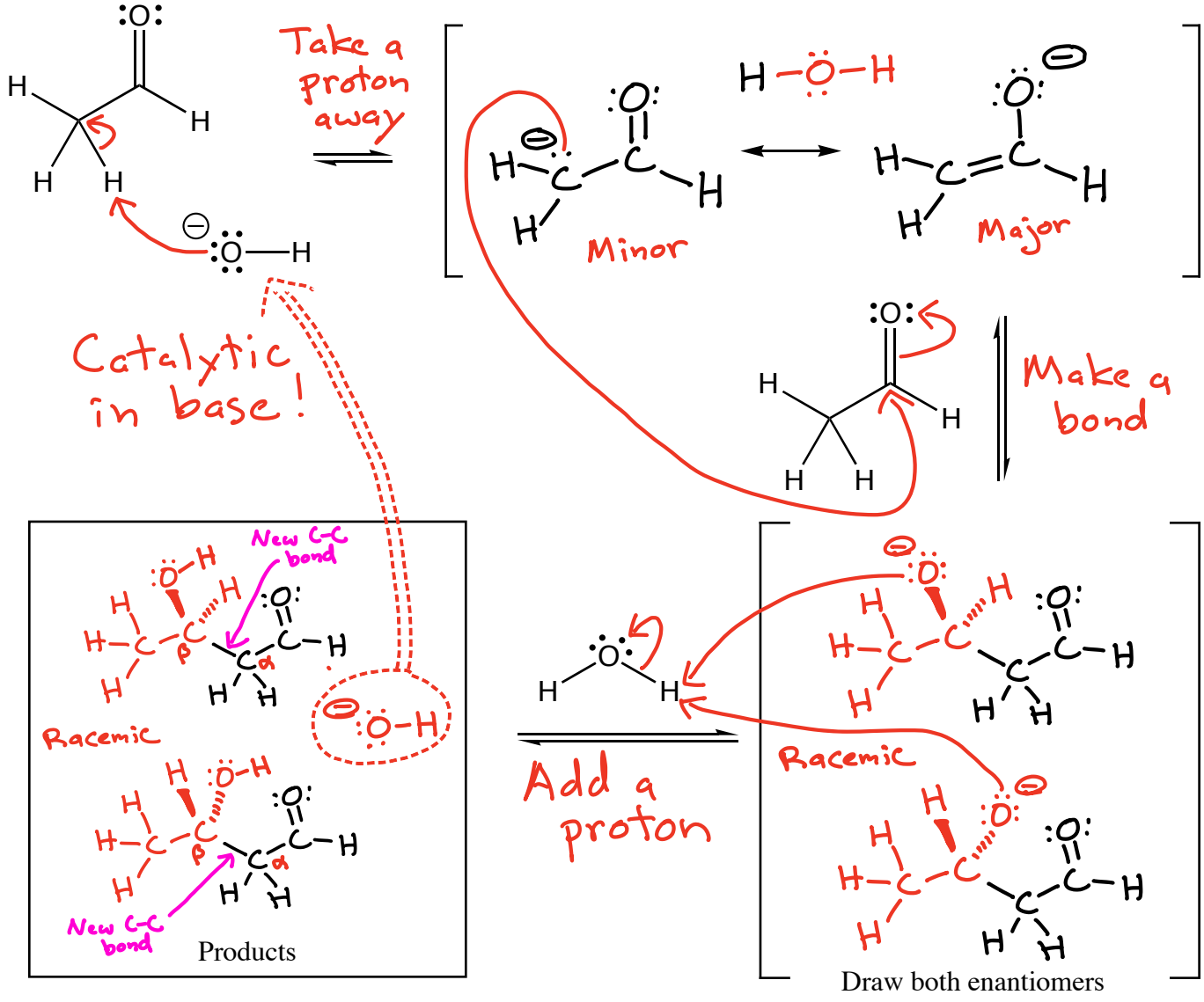


Interconversion of Carboxylic Acid Derivatives





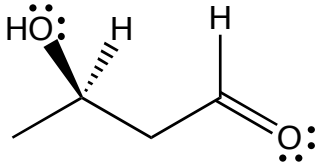
Aldol Reaction



KRE → β-hydroxy aldehyde with a new C-C bond between the aldehyde α and β carbons

Mechanism A

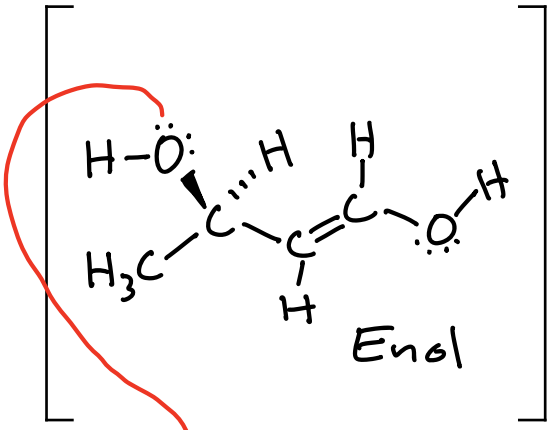
Acid catalyzed dehydration



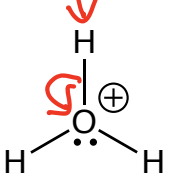
Aldol product

Chemist adds acid and heat

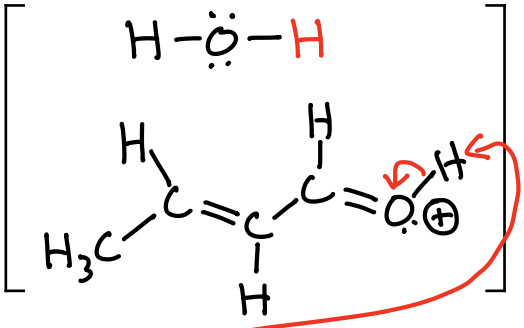
tautomerization



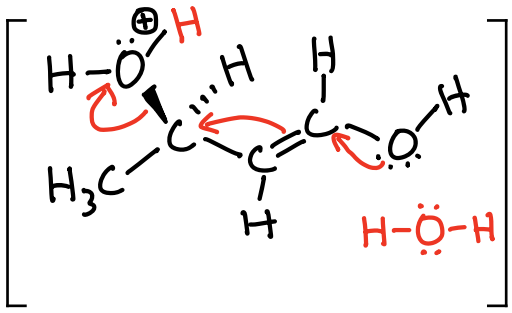
Enol

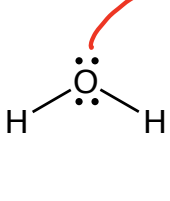


Add a proton



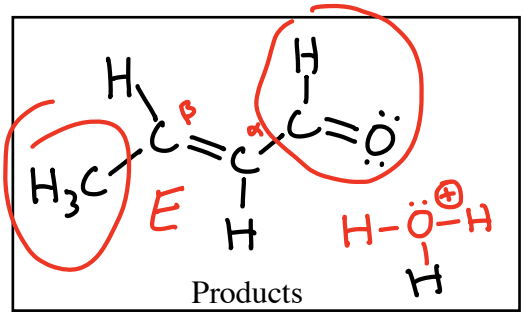
Break a bond





Take a proton away

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

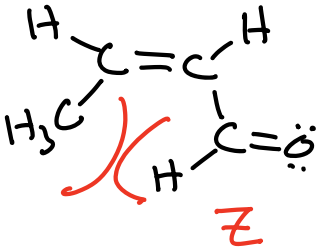


Products

THIS IS UNIQUE TO THIS EXAMPLE

⇓

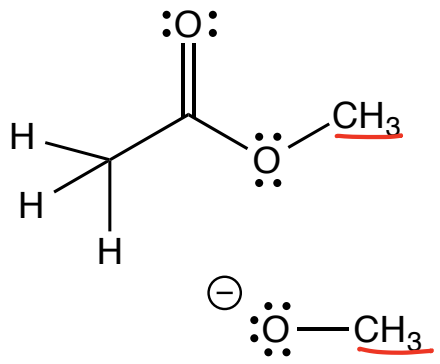
USUALLY BOTH E AND Z ARE FORMED



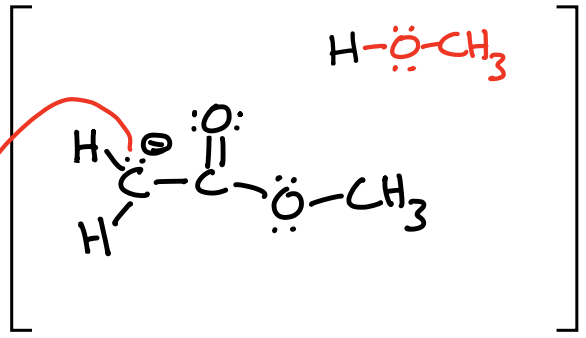
Z

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

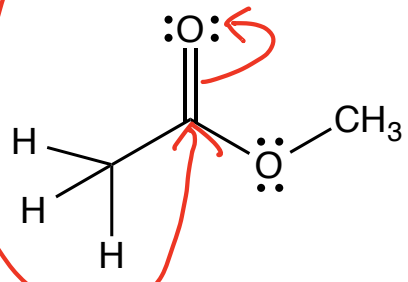
Claisen Condensation → "Aldol with Esters"



Take a proton away

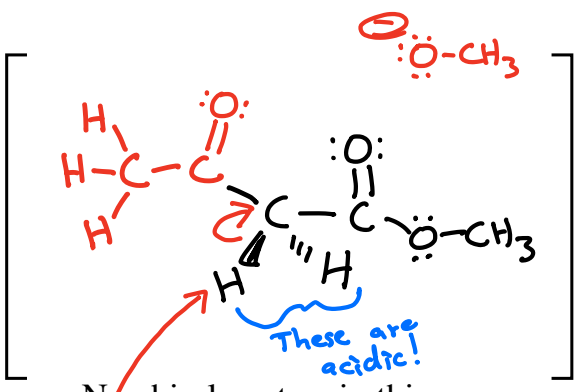


The R group of the base must match the ester!!



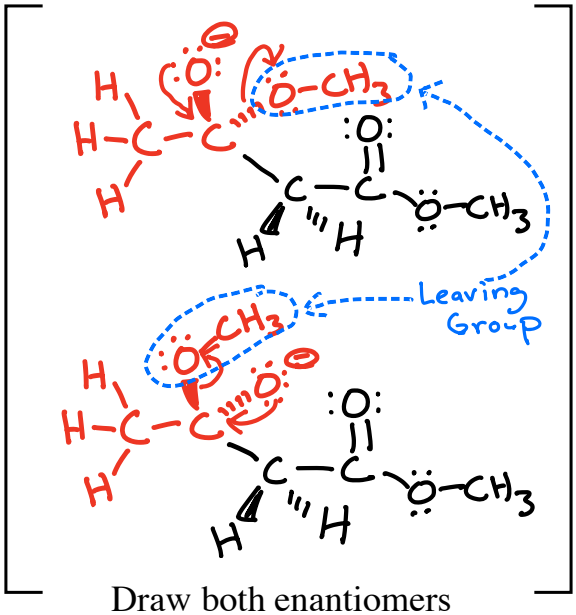
Make a bond

Mechanism B

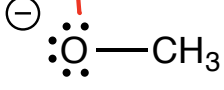


No chiral centers in this case

Break a bond

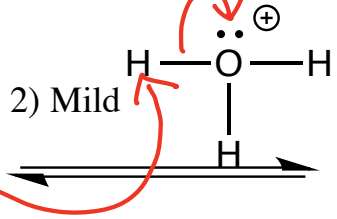


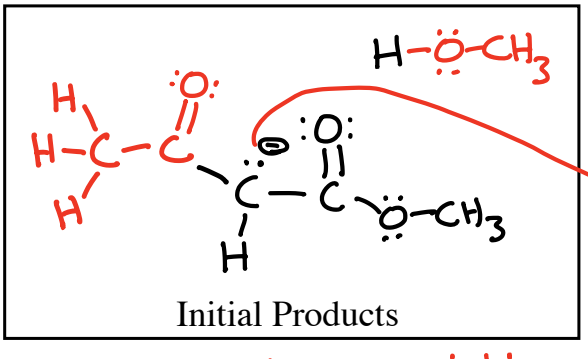
Draw both enantiomers



Take a proton away

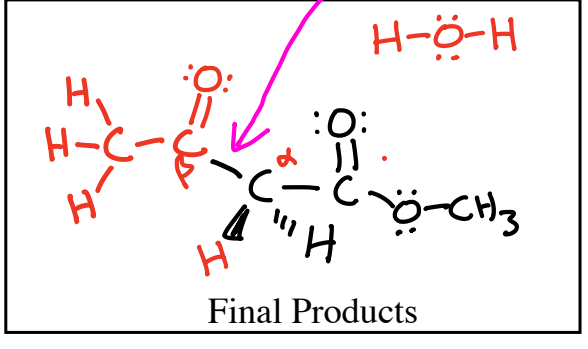
(Chemist opens flask and adds a mild acid)





Initial Products

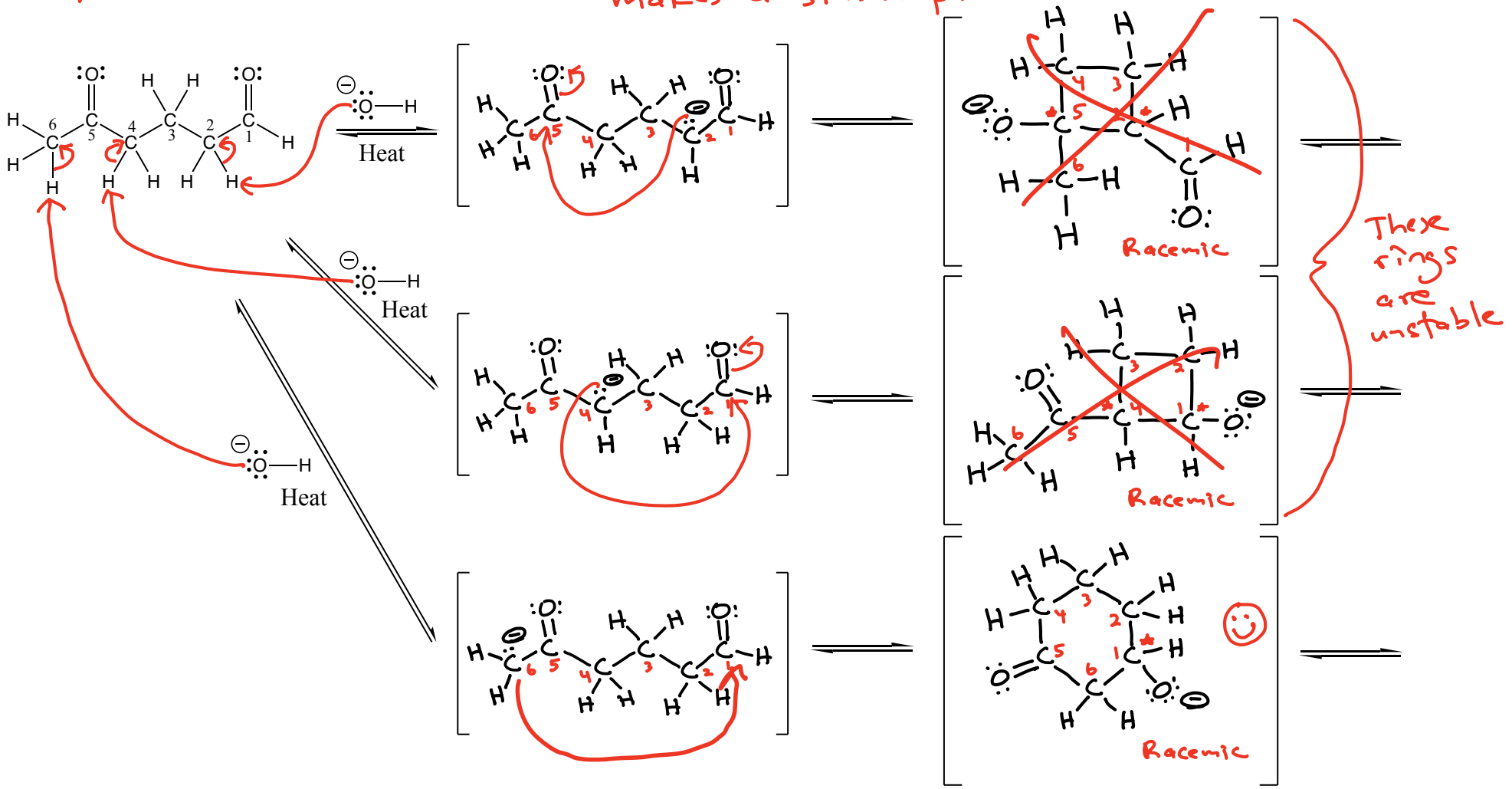
New C–C bond

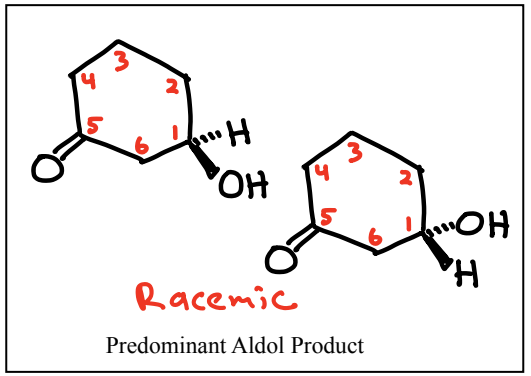


Final Products

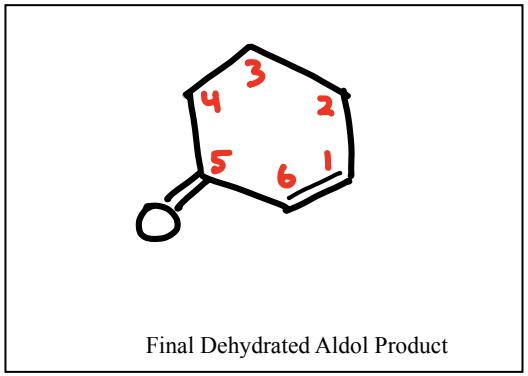
This is a much more stable anion compared to $^{\ominus}OCH_3$, providing a strong driving force (motive) for the Claisen condensation reaction

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

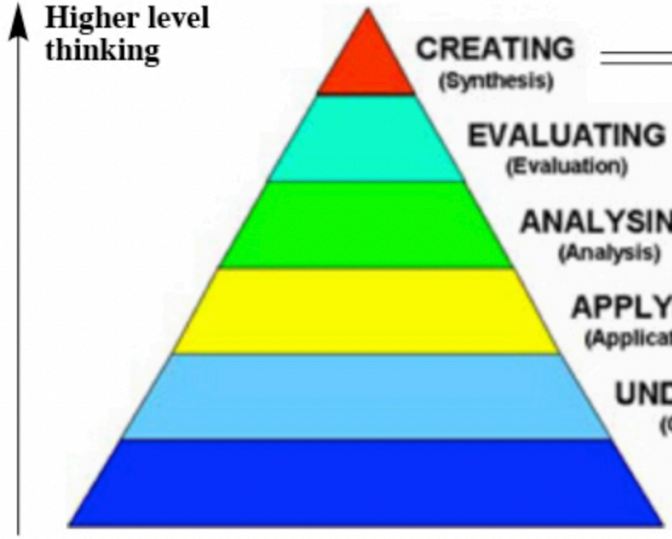




Dehydration



Bloom's Taxonomy of Learning



Organic Chemistry Analog

Solving synthesis problems

Recognizing reaction products

Reactions

Mechanisms

Where are the electrons?

Structures, bonding, functional groups, reagents, nomenclature, definitions

Tools we created to help you succeed:

KRE Table

Roadmaps

The 4 mechanistic elements

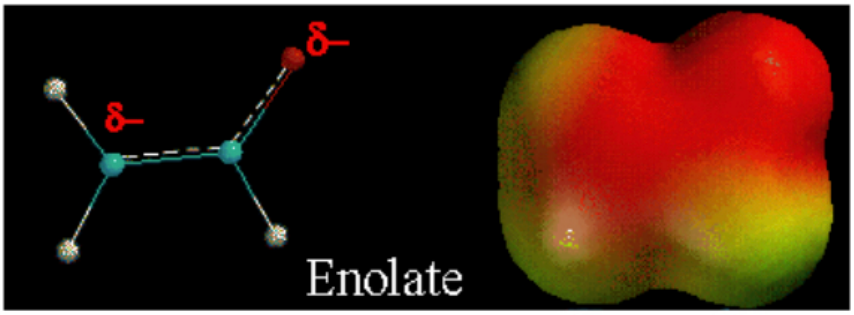
"Personalities of Molecules" Nucleophiles, electrophiles, acids, bases

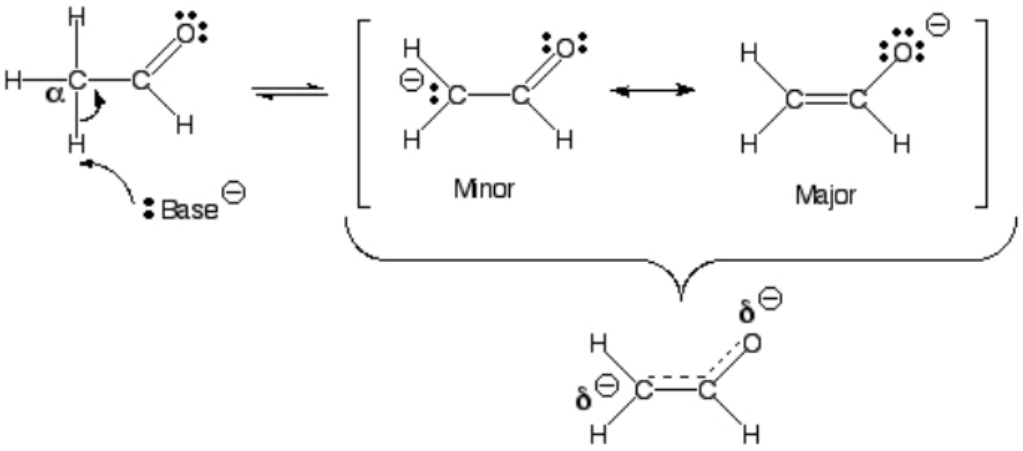
Rules of the Day

Organic chemistry is difficult because it requires higher order thinking. According to Bloom's taxonomy of learning, the lowest level of learning involves pure memorization ("Remembering") As one moves up the pyramid to higher learning, understanding, applying, analysing, evaluating and creating are reached. I believe there are Organic chemistry analogs of all of these, culminating in synthesis which inolves creativity along with all of the other levels of thinking. It is likely that many of you have never been challenged all the way to the top of the Bloom's taxonomy of learning pyramid before, explaining why this feels different and disorienting. DO NOT GIVE UP. As shown on the right, we have created tools to help you master each step up the ladder. On the above diagram you can cllick on the tools listed to go directly to them. Also, if you have any questions about how to study, click here to read about the way I learned to study. I never earned a grade lower than an A after I started using this method during my own college career.

I understand that most of you are headed to the health professions, so you may be wondering if mastering synthesis problems will be important for you. I assert that it is. Solving a synthesis problem involves the detailed evaluation of a complex molecule while looking for KREs, then working backwards to the starting materials by analyzying possible reactions involved by thinking through your roadmaps, possibly applying your understanding of mechanism to make sure you predict the correct product for each reaction. This is the exact type of thinking you will need to diagnose a patient. A patient will present various complex combinations of symptoms, then you must evaluate which of these are important, then analyze, apply and understand how the patient got that way and how to get them back to their starting state (healthy) again. In other words, you will learn the "KREs of diagnosis" then work backwards to understand what happened to the originally healthy patient! Therefore, learning how to solve synthesis problems will teach you how to use higher level thinking skills, exactly the kind you will need to develop as a health care professional!

Enolates as nucleophiles



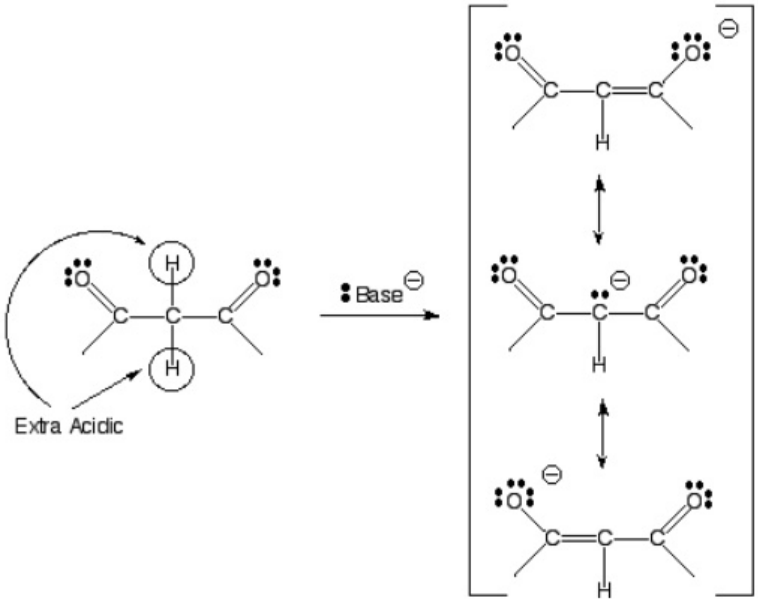


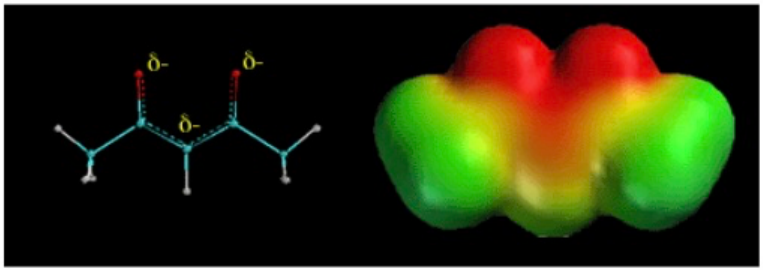
A) Enolates are resonance stabilized, with a partial negative charge on carbon and oxygen.

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 C=O bond, while reaction at the oxygen atom gives the final product a C=C bond. However, C=O bonds are stronger than C=C bonds, so the **motive** is to react at the carbon atom with most electrophiles.

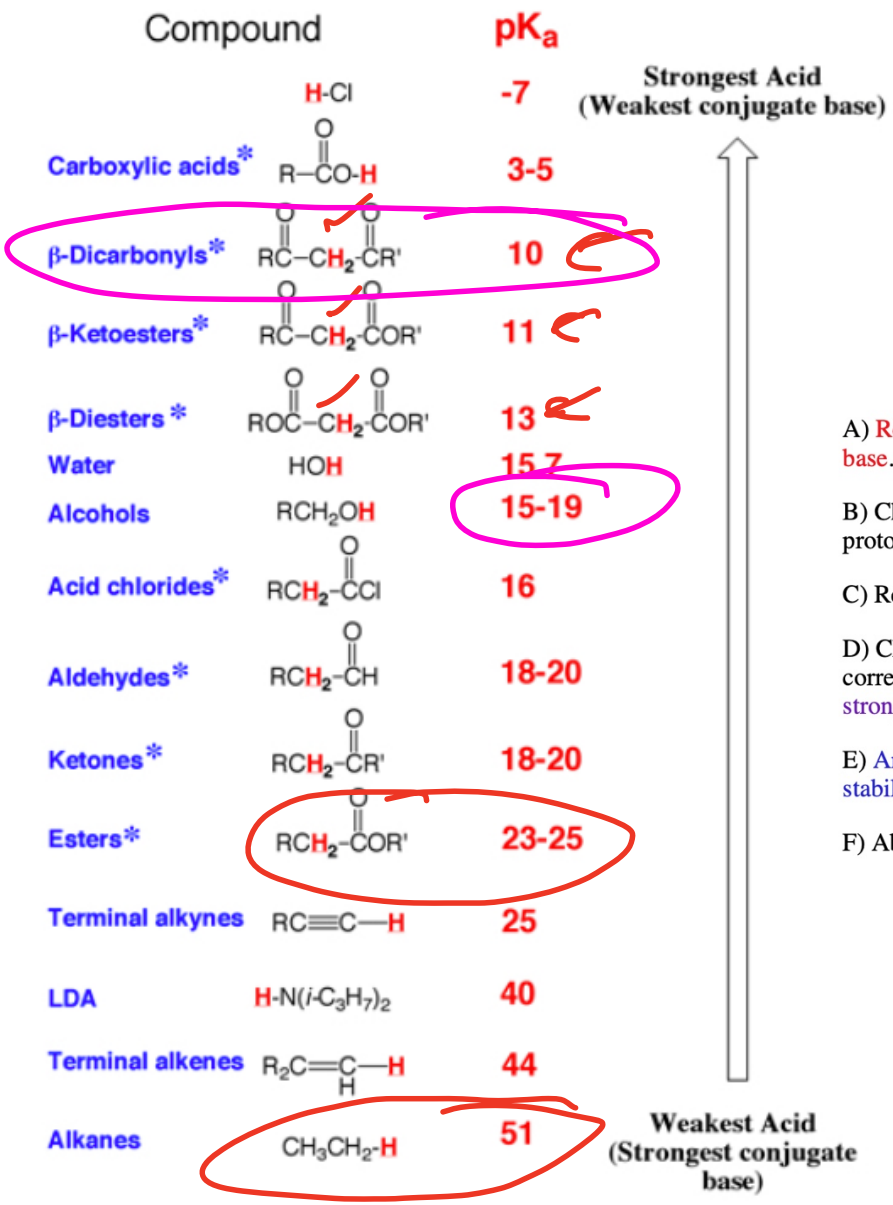
Beta-dicarbonyls have alpha-hydrogens that are extra acidic





The C-H hydrogen atoms between two carbonyl groups are aven more acidic than normal a 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.

Weaker bases are favored at equilibrium



*These have resonance stabilized anions

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

B) Checking pKa values can predict if a reaction has a motive even if there are other steps besides a proton transfer.

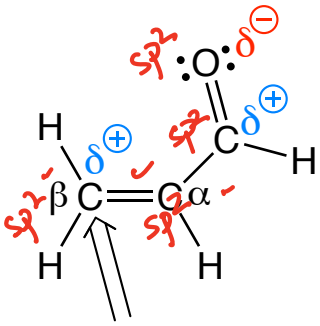
C) Recall that the conjugate base of a stronger acid (lower pKa) is a weaker base.

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

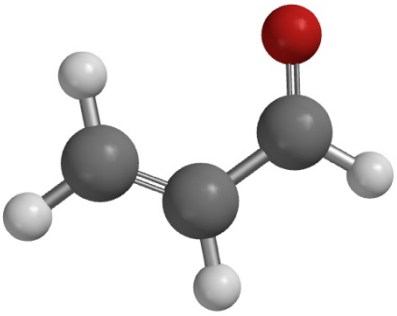
E) Another way to look at it is that the base that is favored at equilibrium is the one that has the more stabilizied anion, i.e. the one with the charge spread around more (electronegative) atoms.

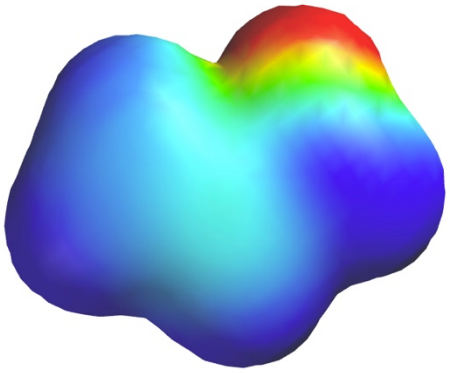
F) Above is a pKa table that we will refer to often.

Conjugate Addition



Nucleophiles react here via conjugate addition





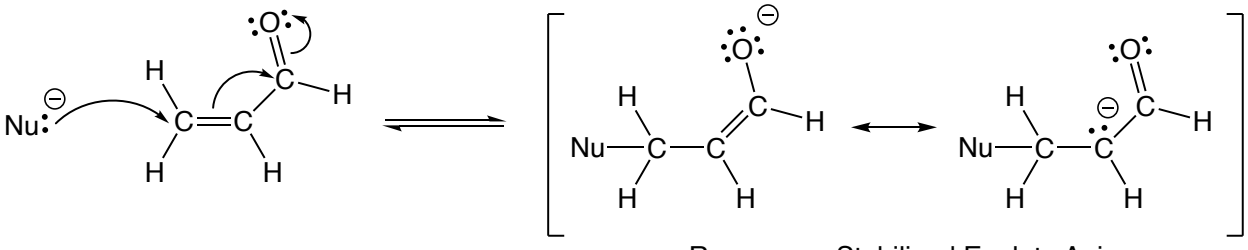
A) Alkenes adjacent to a carbonyl are conjugated and are therefore electrophilic.

B) These species are called α,β unsaturated carbonyl compounds.

C) α,β 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 β 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.



Resonance Stabilized Enolate Anion

Michael Reaction

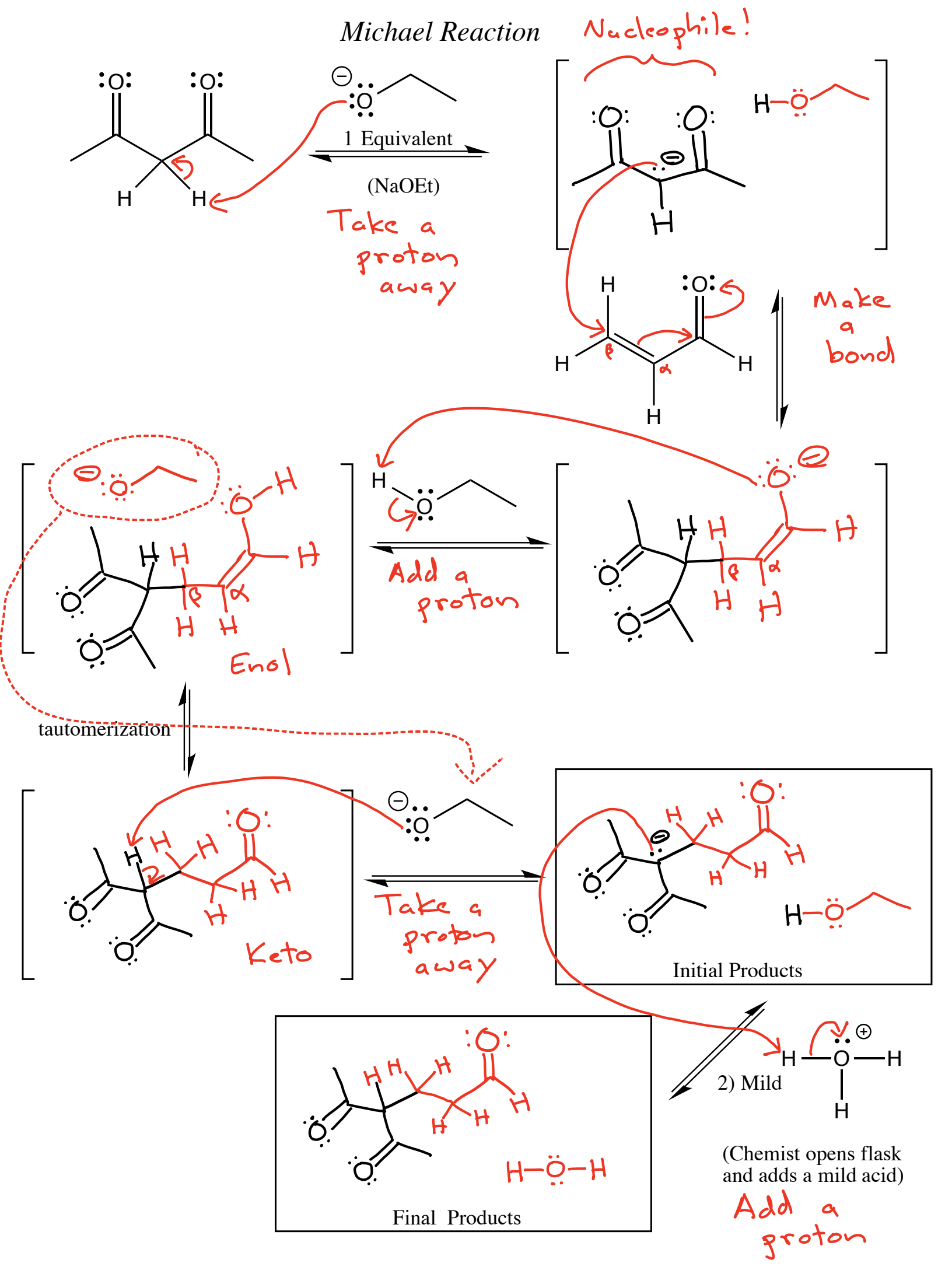
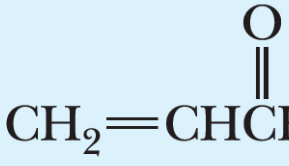
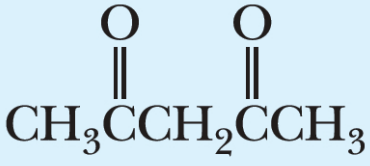
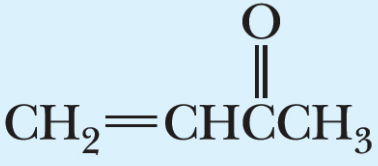
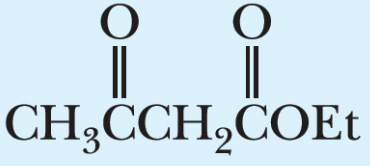
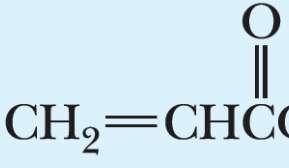
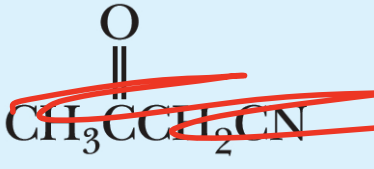
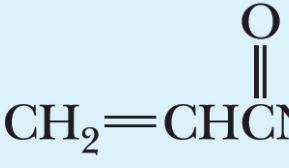
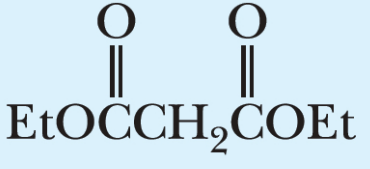
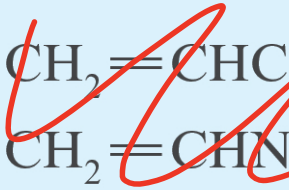
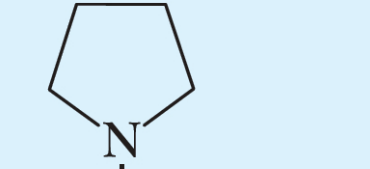
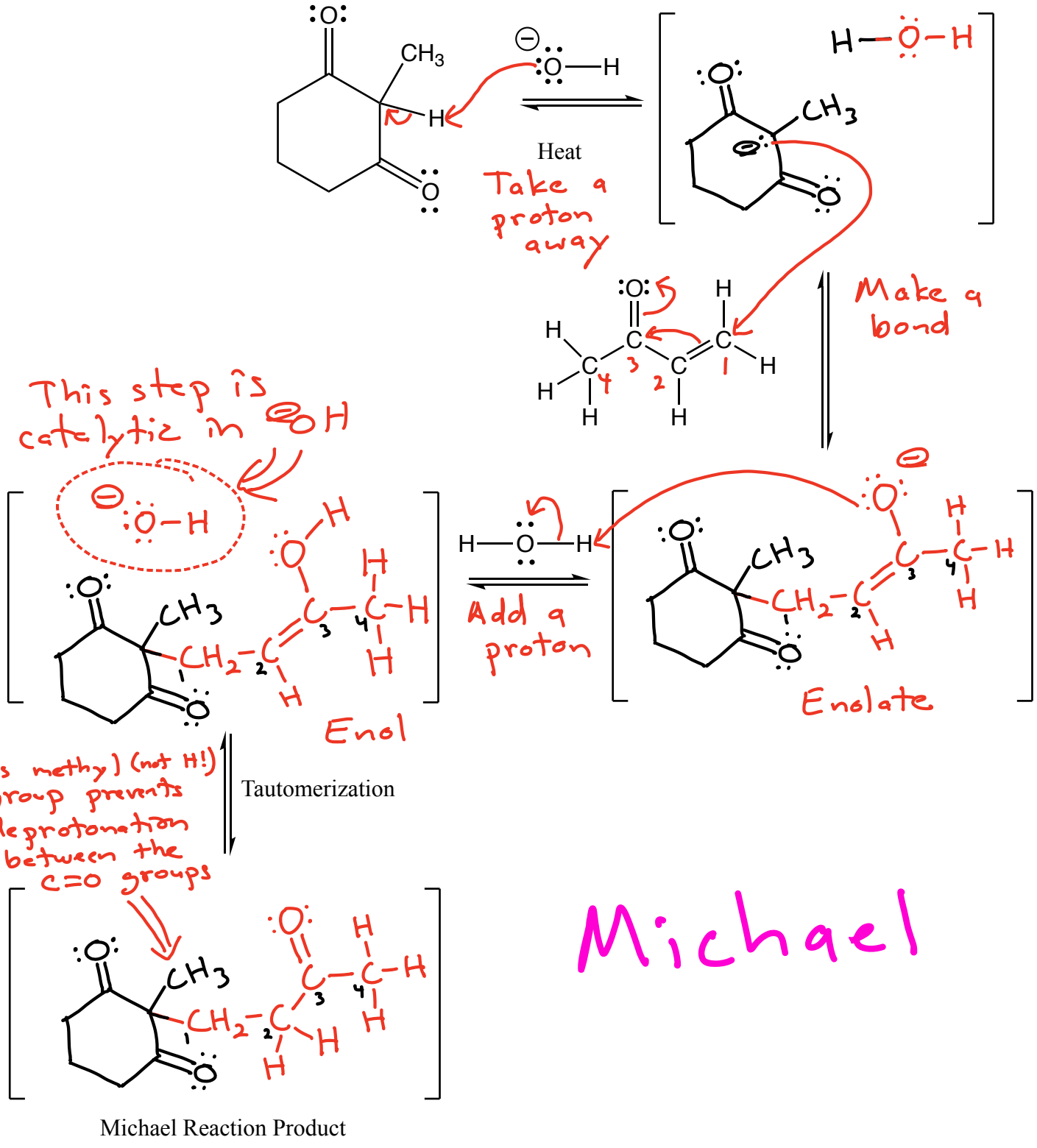


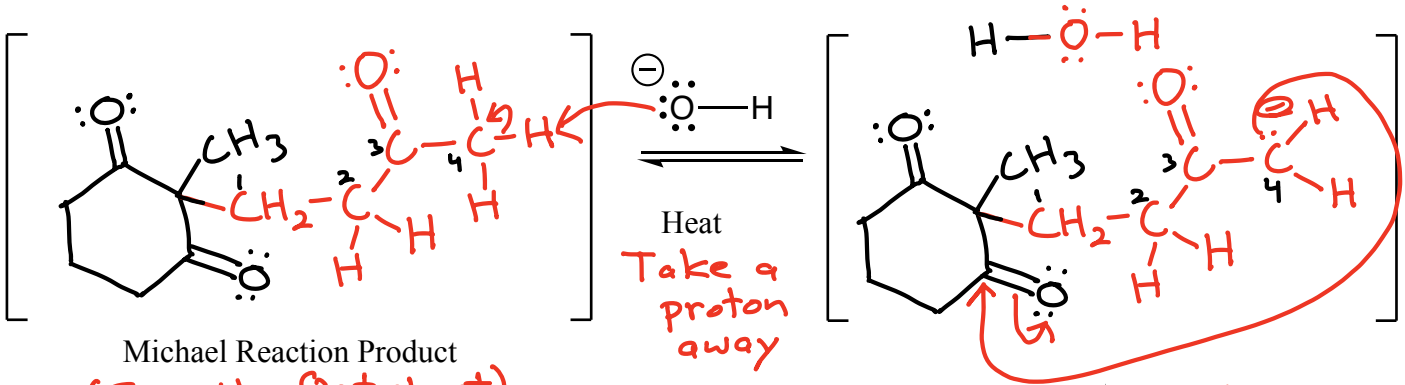
Table 19.1 Combinations of Reagents for Effective Michael Reactions

These Types of α,β-Unsaturated Compounds Are Nucleophile Acceptors in Michael Reactions		These Types of Compounds Provide Effective Nucleophiles for Michael Reactions	
	Aldehyde		β-Diketone
	Ketone		β-Ketoester
	Ester		β-Ketonitrile
	Amide		β-Diester
	Nitrile		Enamine
	Nitro compound	NH_3, RNH_2, R_2NH	Amine

Robinson Annulation Part 1 - Michael Reaction Steps



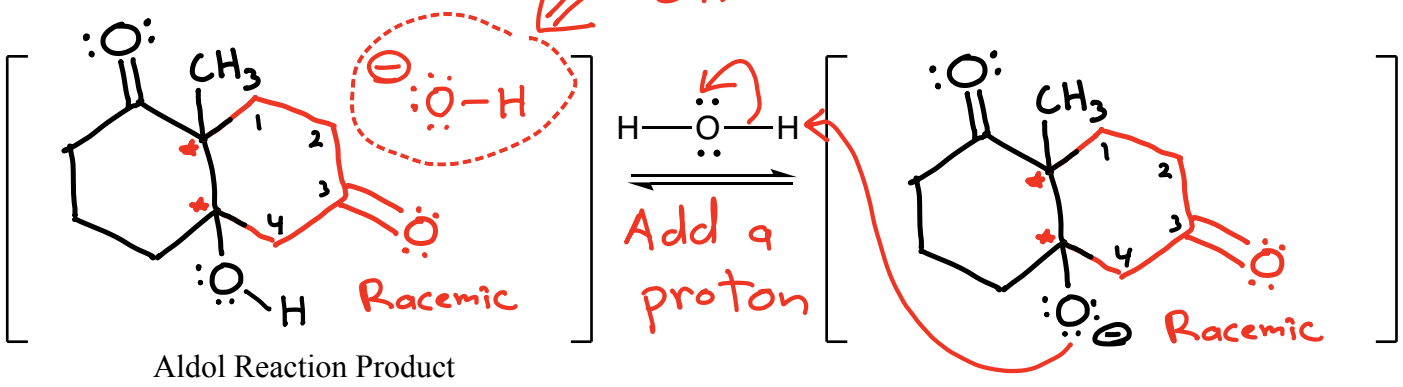
Robinson Annulation Part 2 - Aldol and Dehydration Steps



Michael Reaction Product
(From the first sheet)

Aldol

Catalytic in ⊖OH!

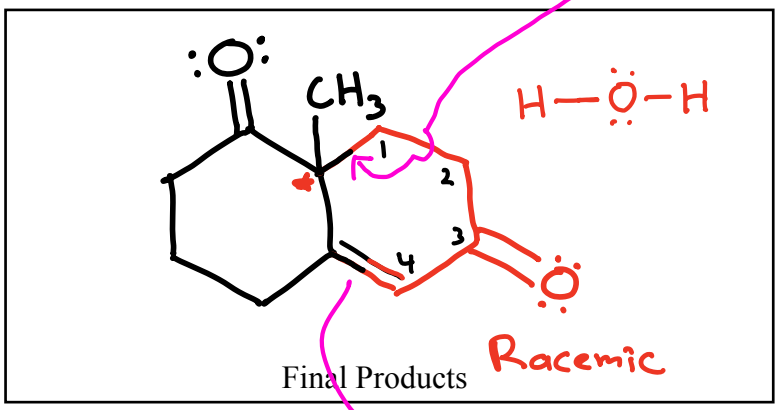


Aldol Reaction Product

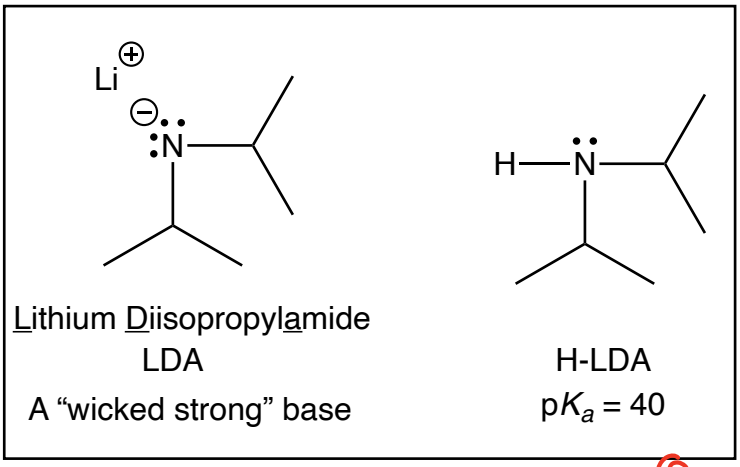
Spontaneous dehydration - multiple steps

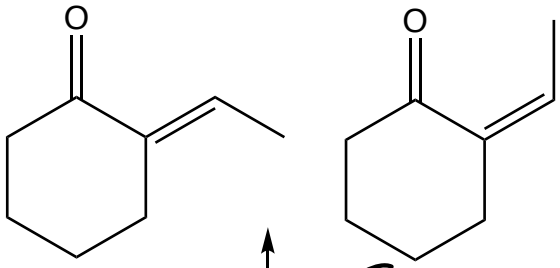
You are not responsible for these

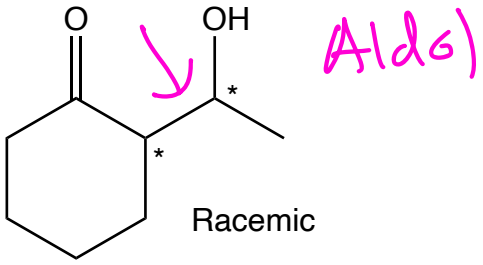
Dehydration

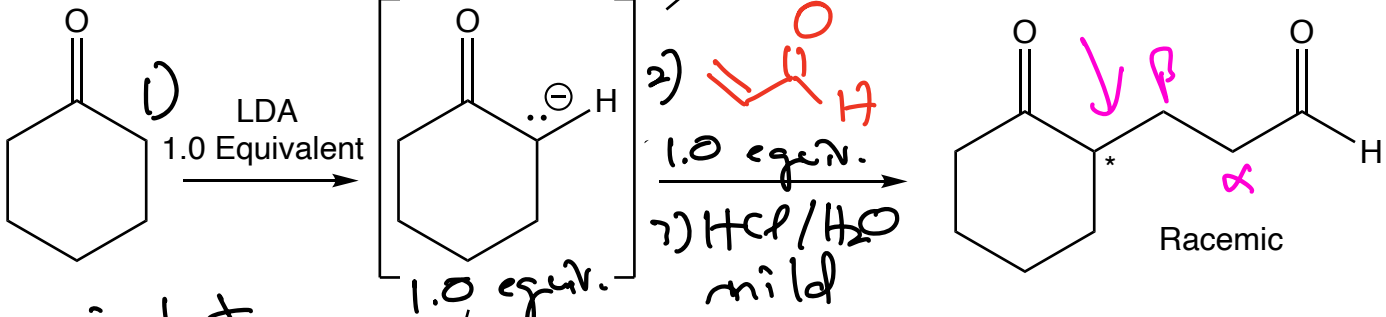


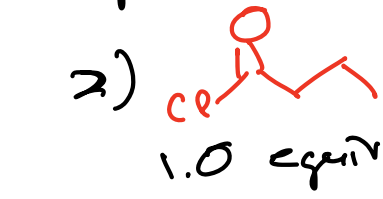
Final Products

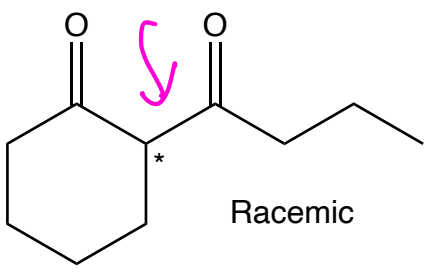

Li
N
H
N
Lithium Diisopropylamide
LDA
A "wicked strong" base
H-LDA
pKa = 40

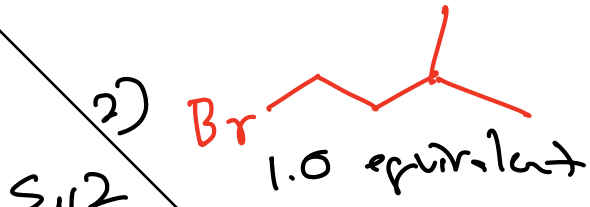

O
O
H⊕
heat

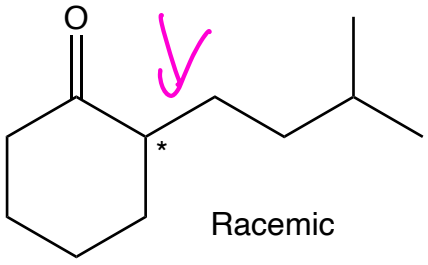

O
OH
Aldol
Racemic


O
1)
LDA
1.0 Equivalent
O
H
1.0 equiv.
2)
1.0 equiv.
3) HCl/H2O
mild
O
O
β
α
H
Racemic

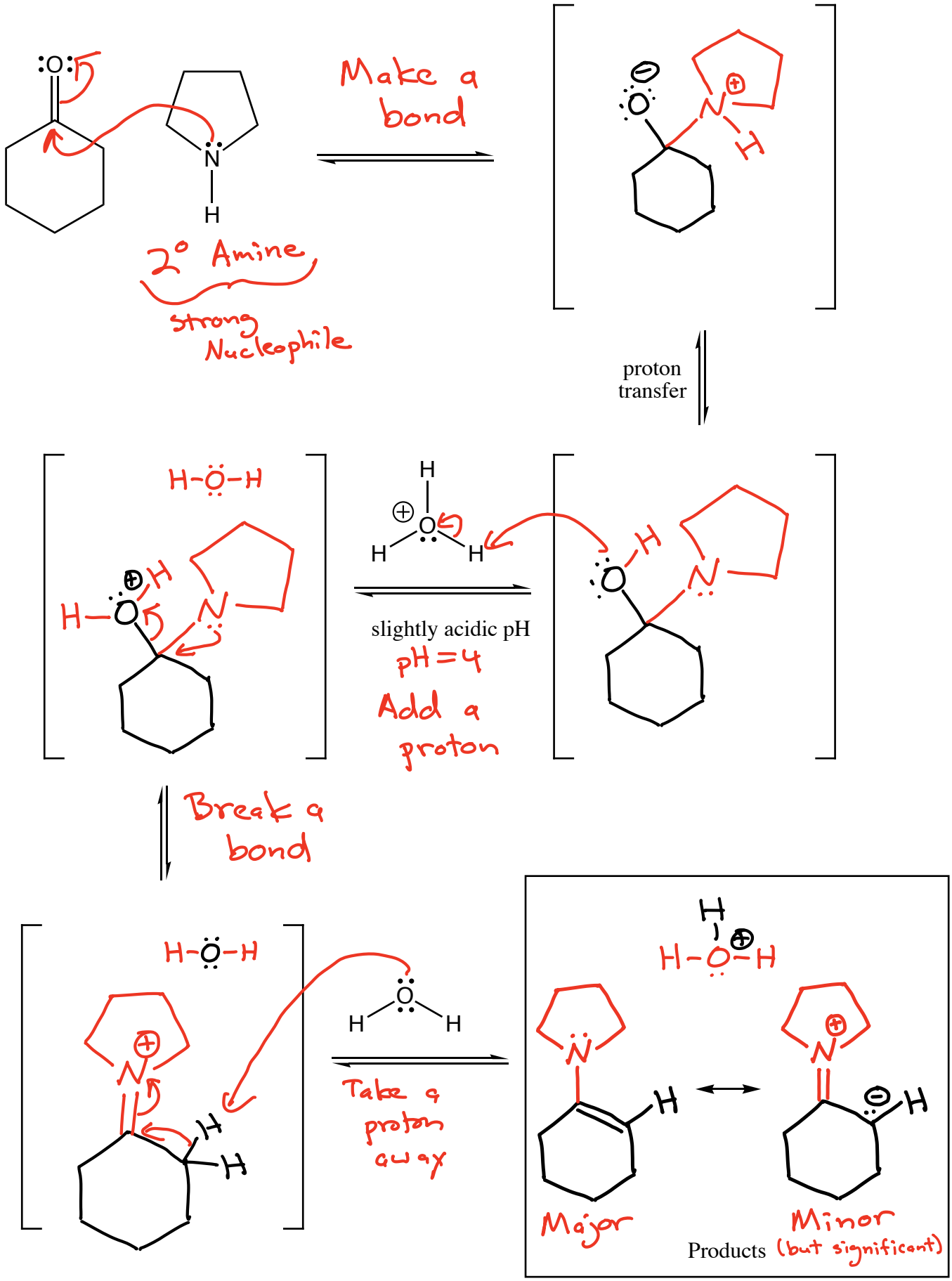

1.0 equivalent
2)
Cl
1.0 equiv.


O
O
Racemic

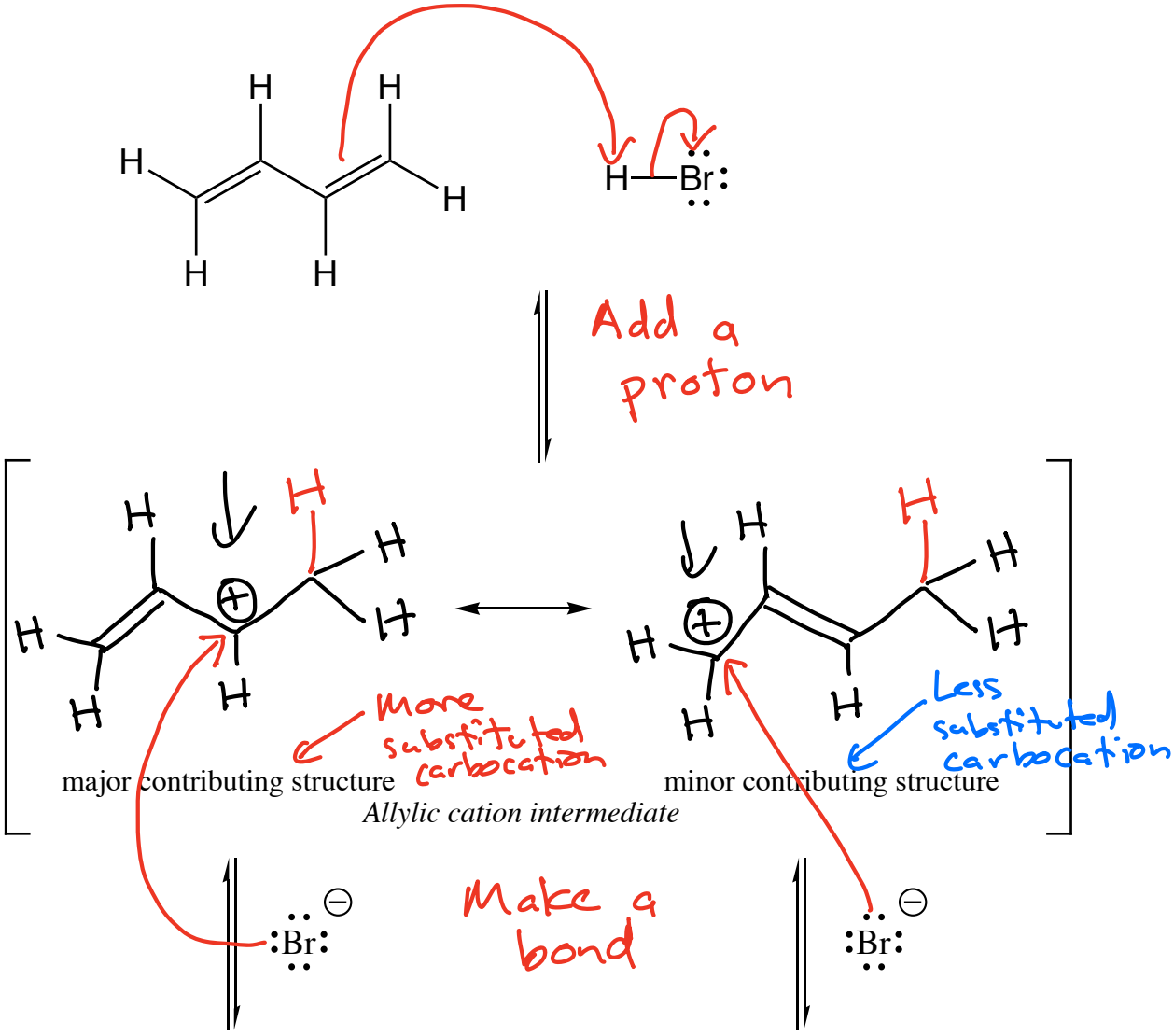

SN2
2)
Br
1.0 equivalent


O
Racemic

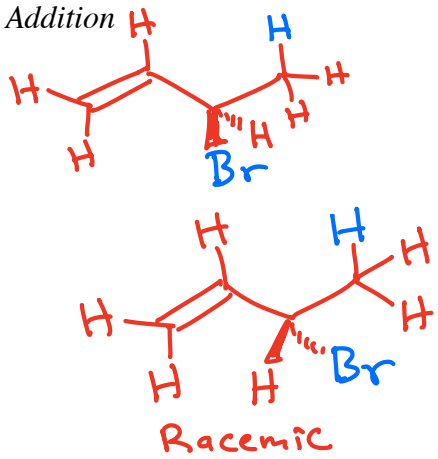
Enamine Formation



H-X reacting with conjugated dienes

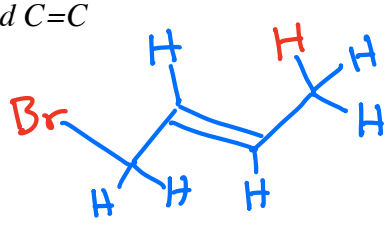


1,2 Addition

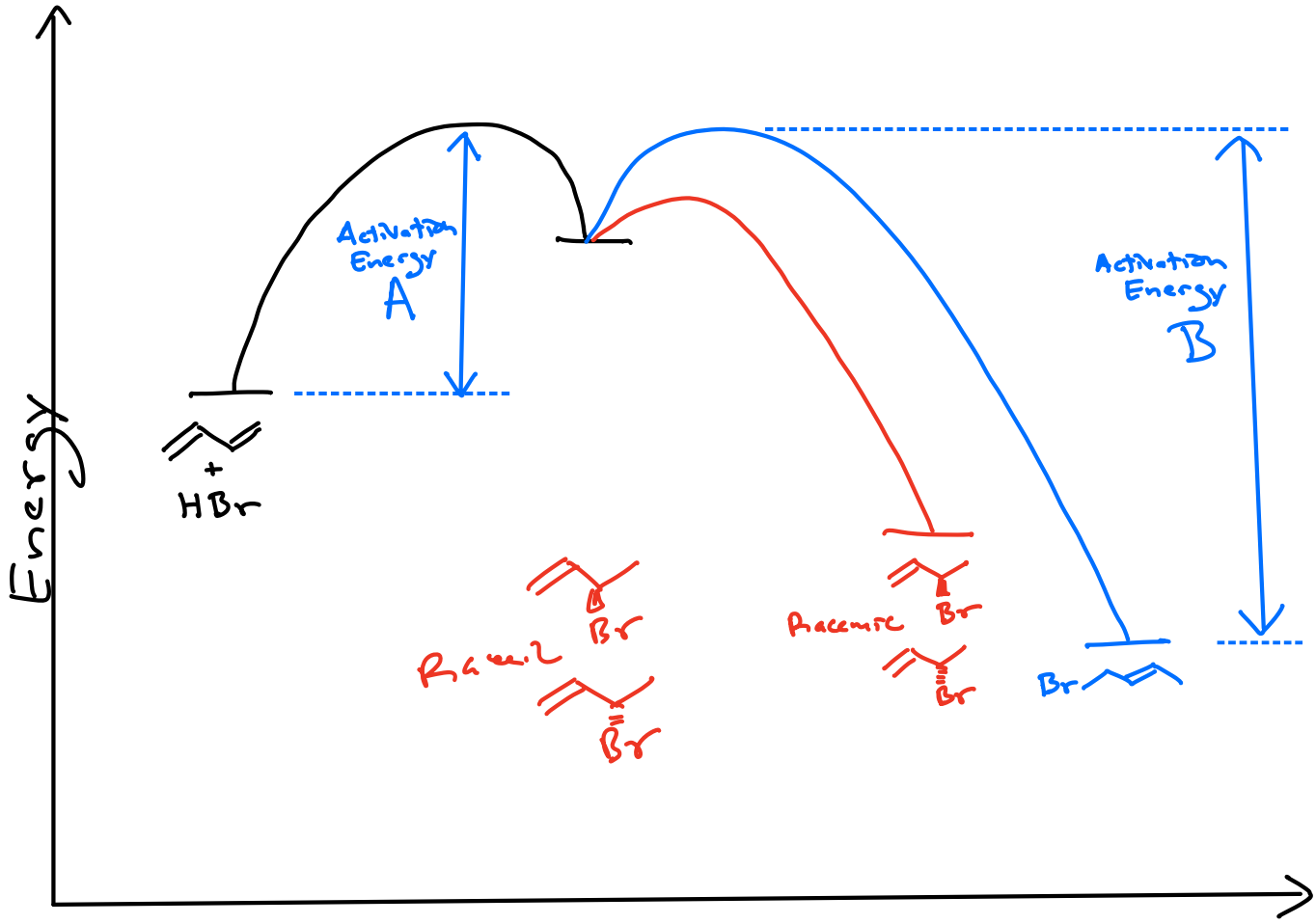


Products

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



Products



Low temperature → Molecules have enough energy to get over activation energy A, but not enough energy to get over activation energy B.

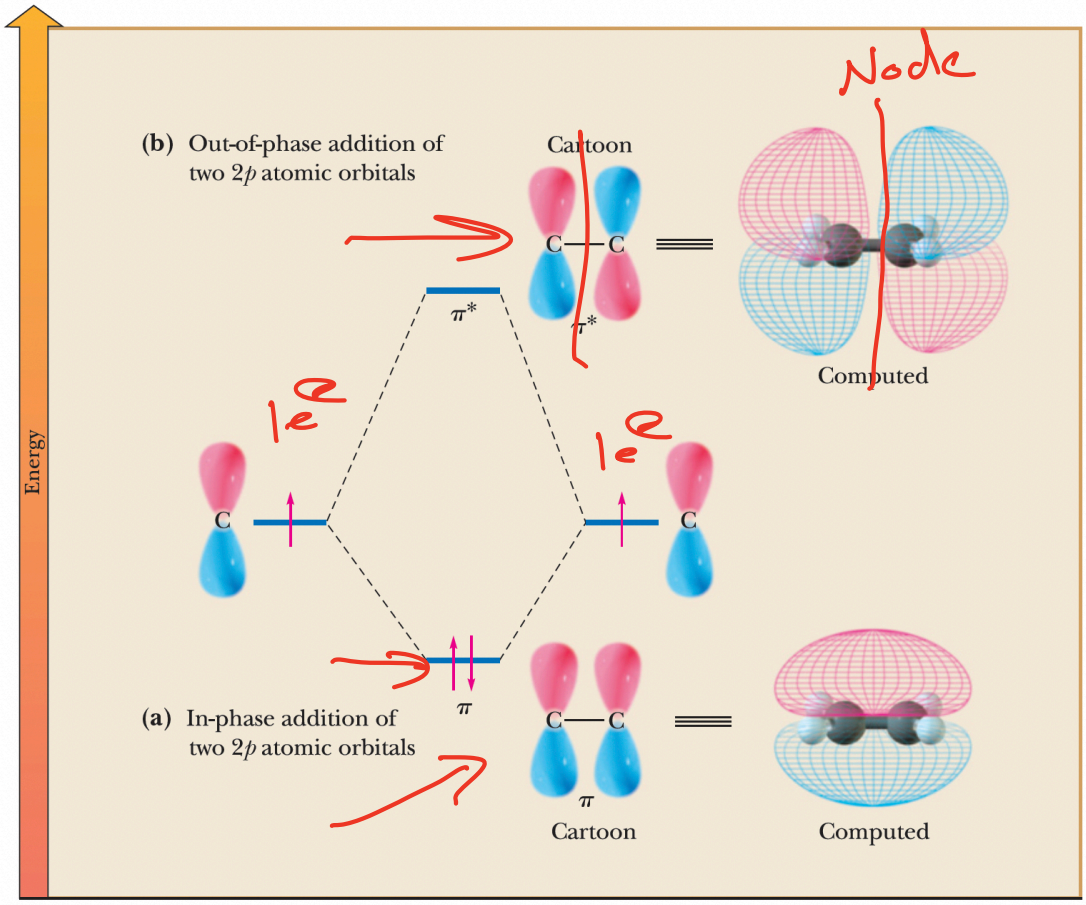
Kinetic Control

"Fastest" wins

High temperature → Molecules have enough energy to get over activation energy A and activation energy B

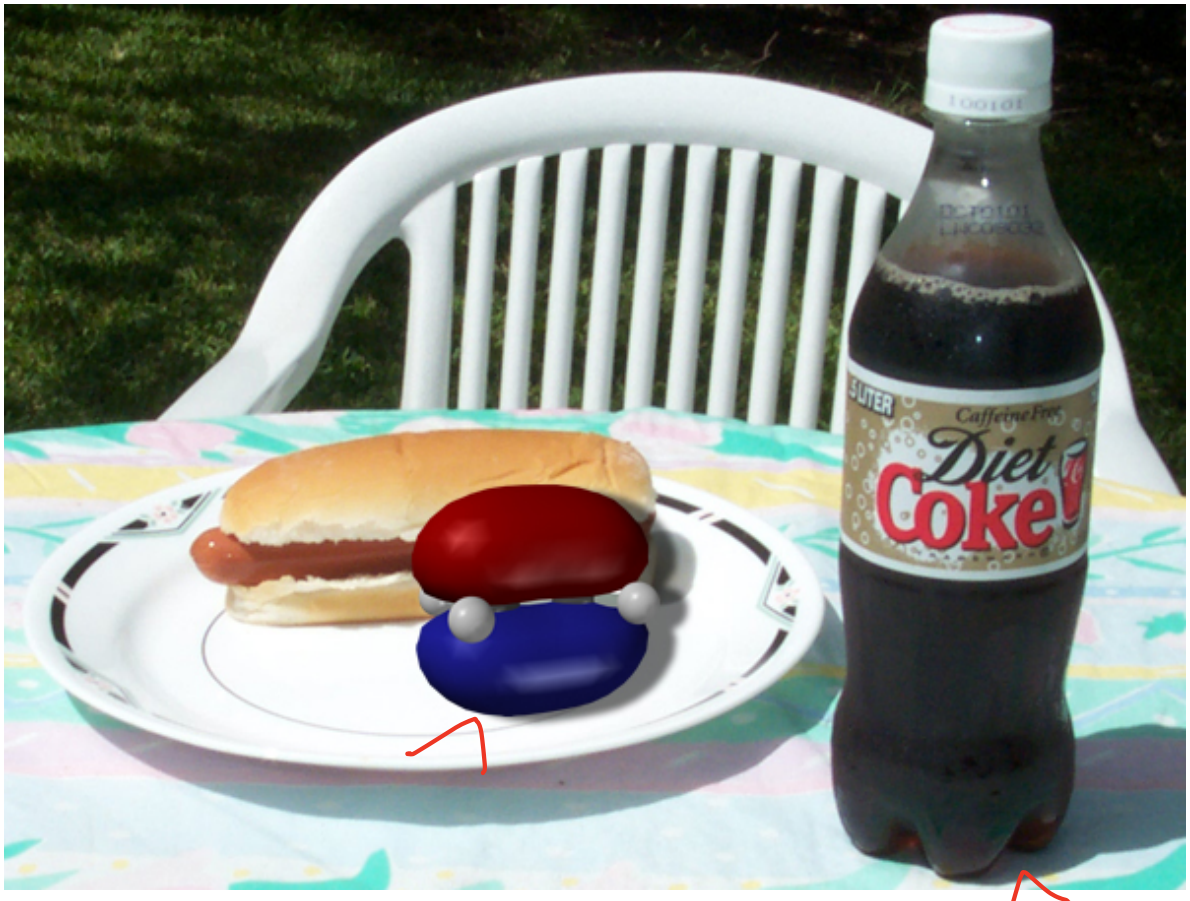
Thermodynamic Control

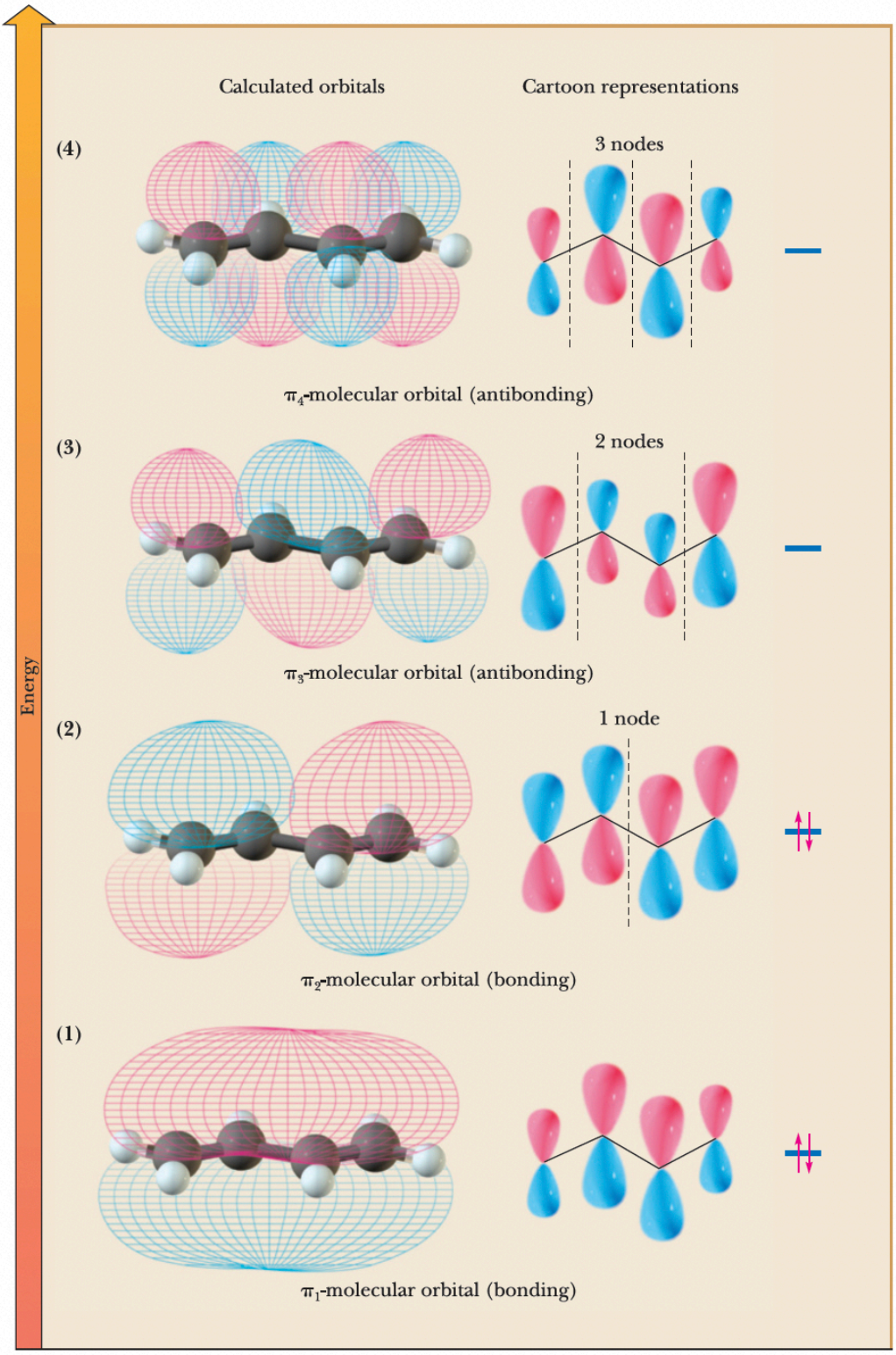
Most stable product wins



Watch a video explanation

FIGURE 1.21
Molecular orbital mixing diagram for the creation of any C—C π bond. (a) Addition of two p atomic orbitals in phase leads to a π orbital that is lower in energy than the two separate starting orbitals. When populated with two electrons, the π orbital gives a π 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 π^* orbital. Population of this orbital with one or two electrons leads to weakening or cleavage of the π bond, respectively.





Watch a video explanation

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

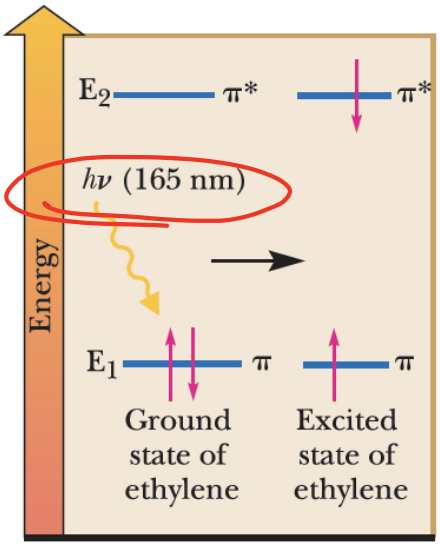


FIGURE 20.6 A $\pi \rightarrow \pi^*$ transition in excitation of ethylene. Absorption of ultraviolet radiation causes a transition of an electron from a π-bonding MO in the ground state to a π-antibonding MO in the excited state. There is no change in electron spin.

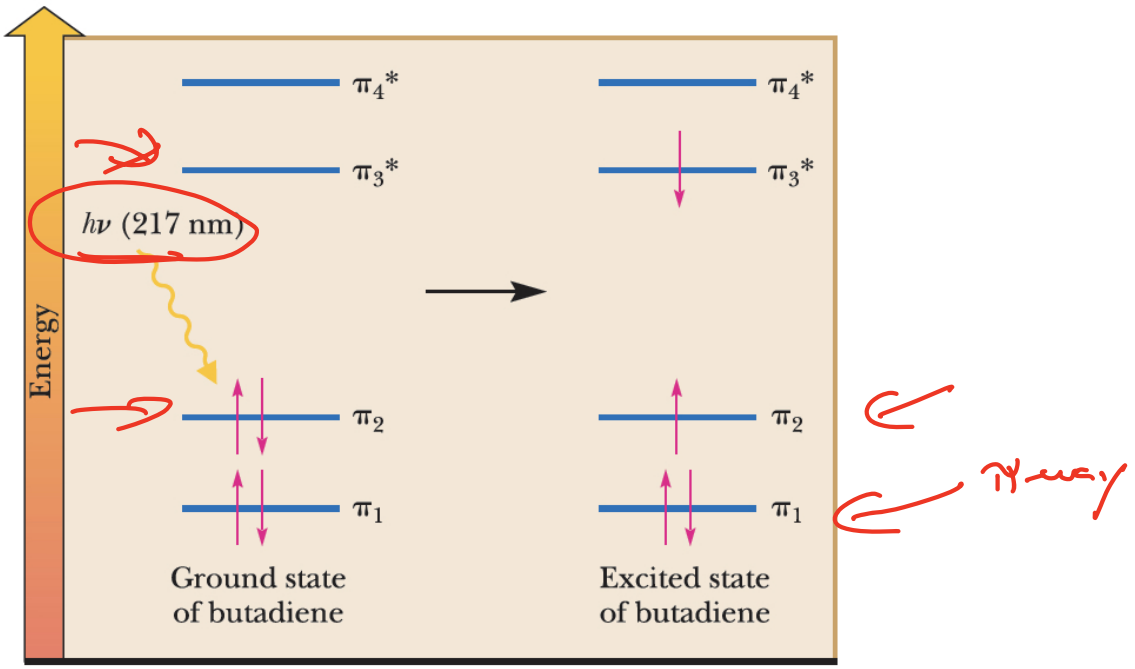


FIGURE 20.7 Electronic excitation of 1,3-butadiene; a $\pi \rightarrow \pi^*$ transition.

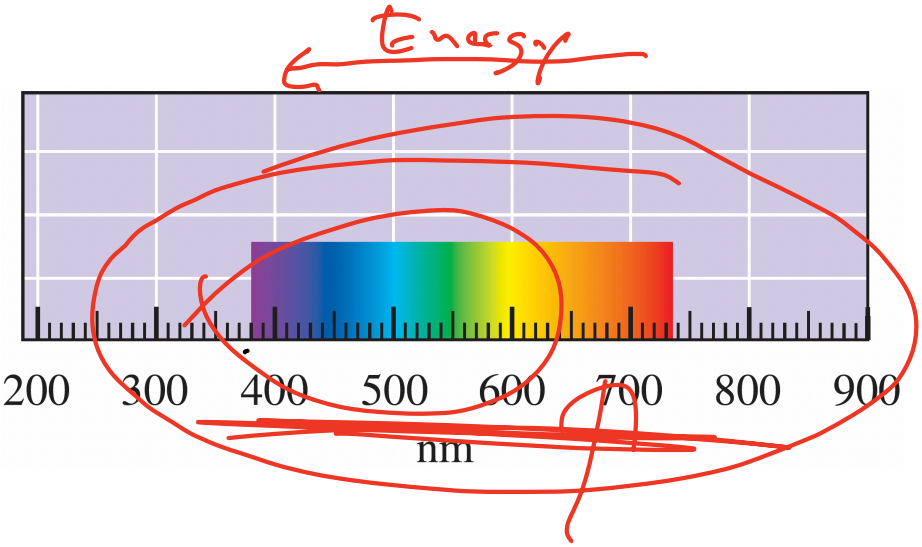
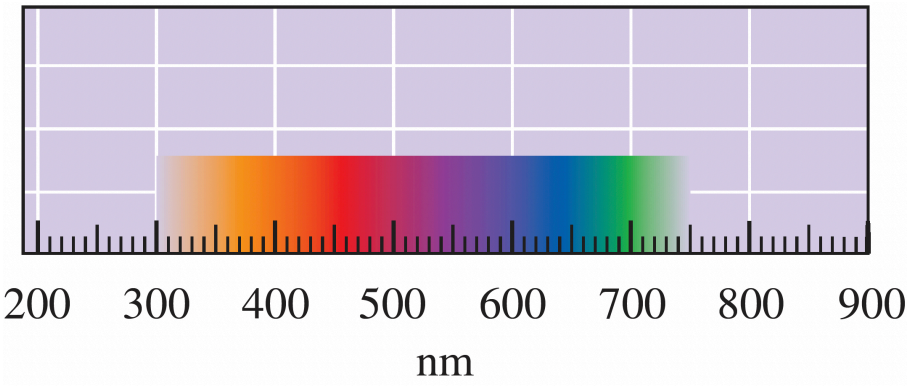
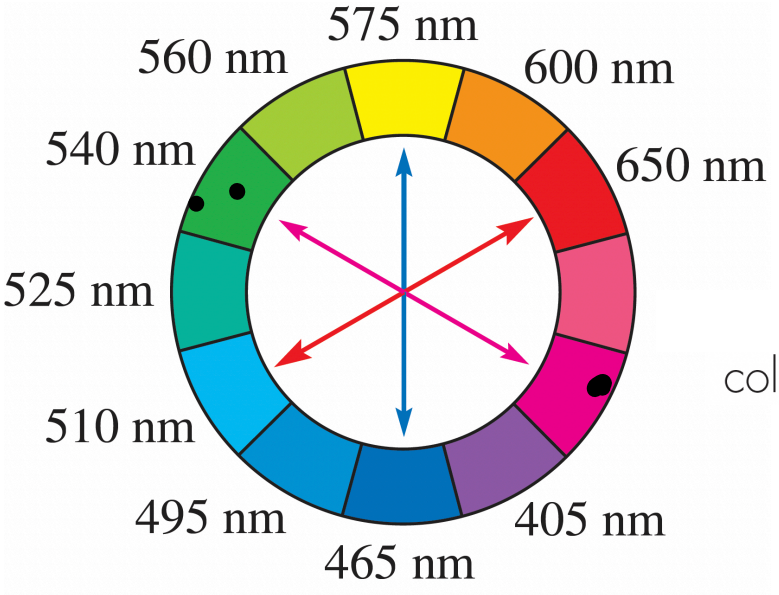


FIGURE 20.5 (a) Visible light color-wavelength correlation.



(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.