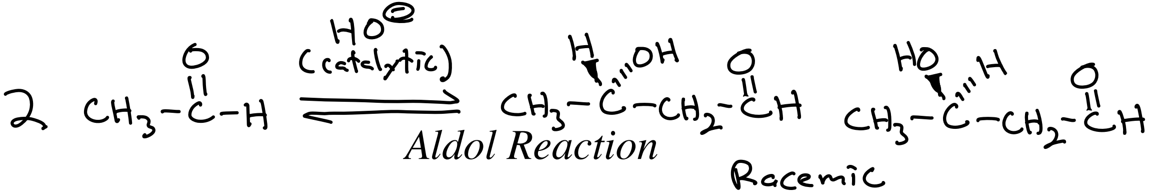
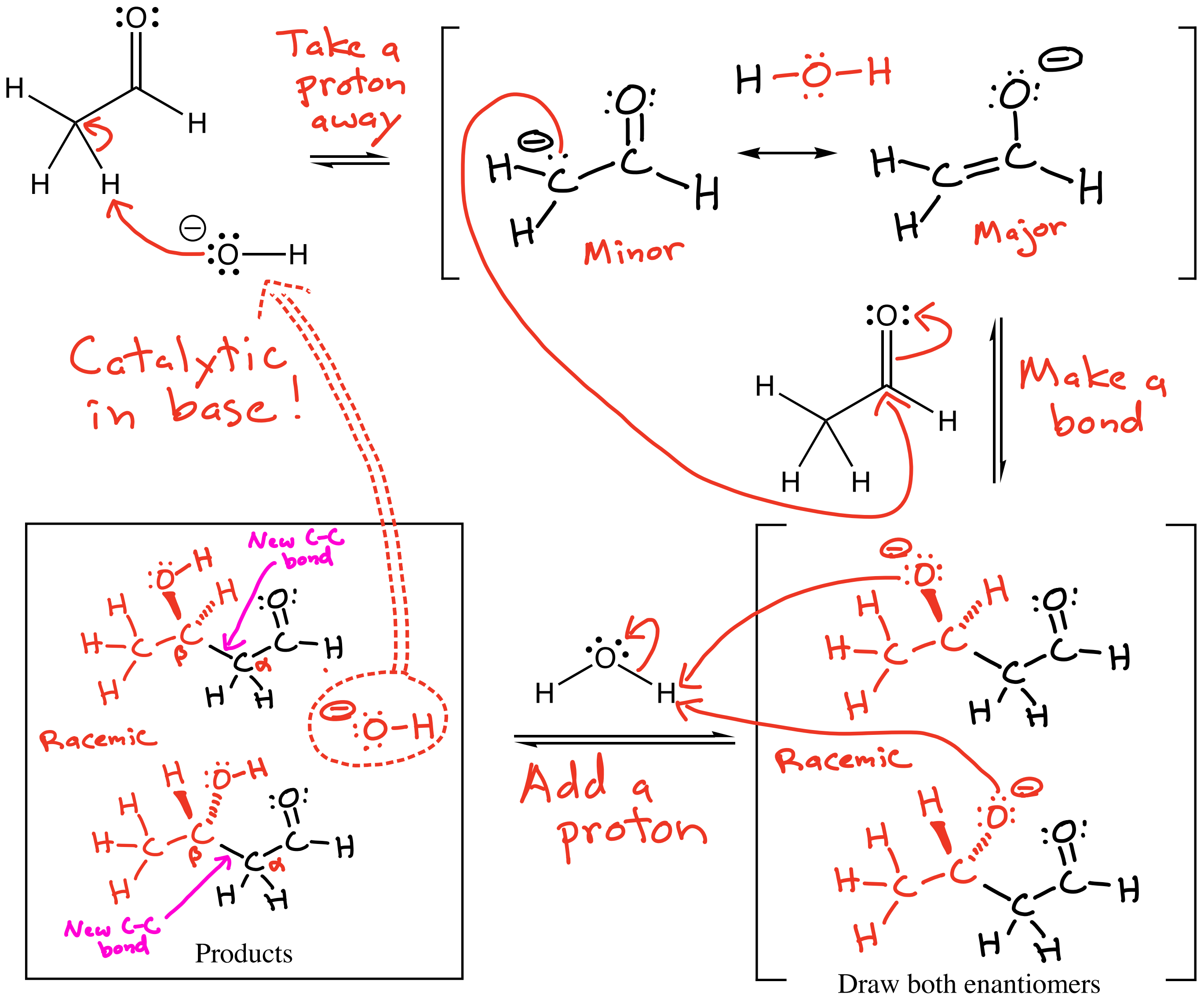


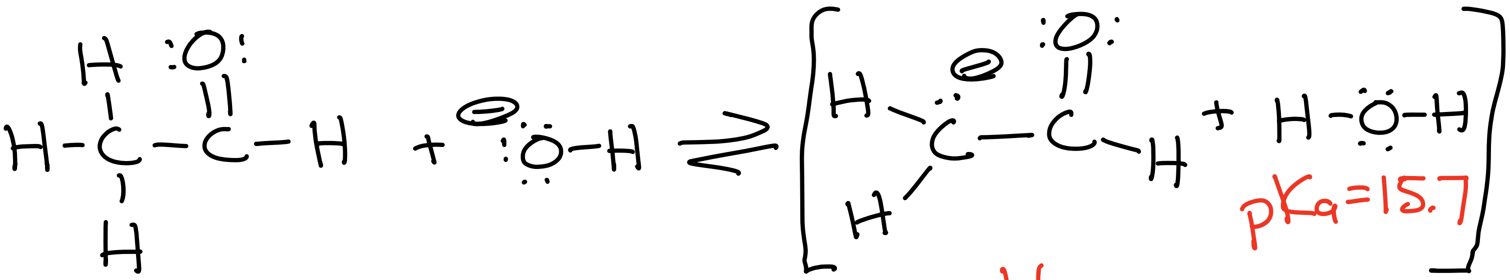


KRE → β-hydroxy aldehyde with a new C–C bond between the aldehyde α and β carbons

Mechanism A

Aldol Reaction Considerations

1) When $HO^{\ominus}$ is used as the base, equilibrium of the first step favors the aldehyde



pKa = 18-20
weaker base

This side favored at equilibrium

There will be excess aldehyde for the enolate to react with

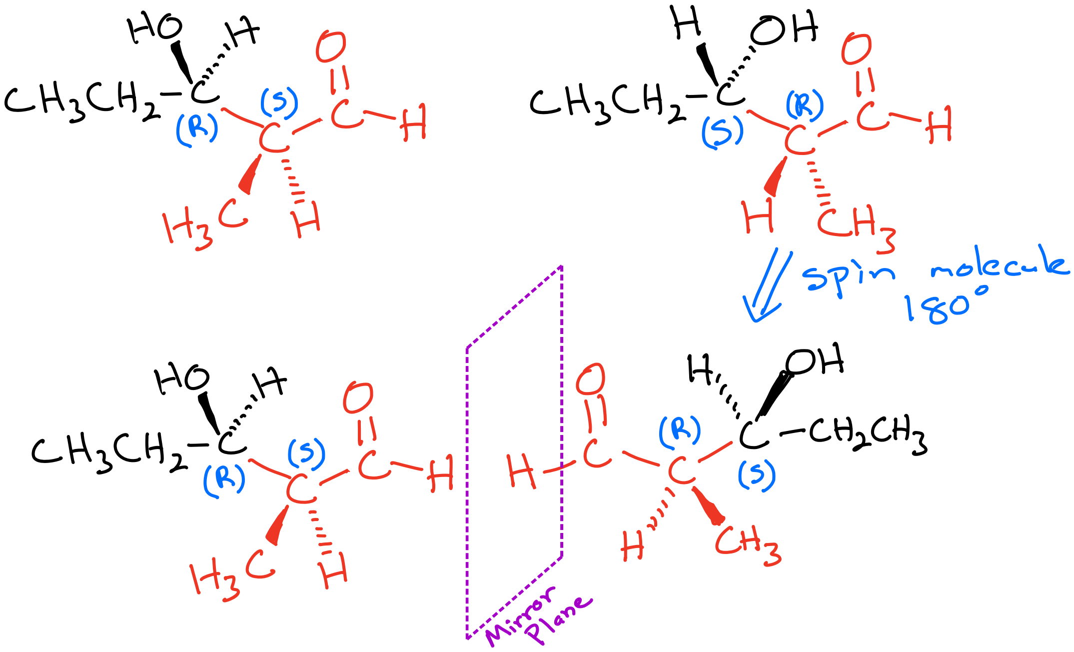
2) Because there is $HO^{\ominus}$ present at the beginning <u>and</u> end of the reaction there is little driving force (motive) for the aldol reaction → the aldol reaction is reversible

3) The aldol reaction is favorable for aldehydes but NOT for ketones

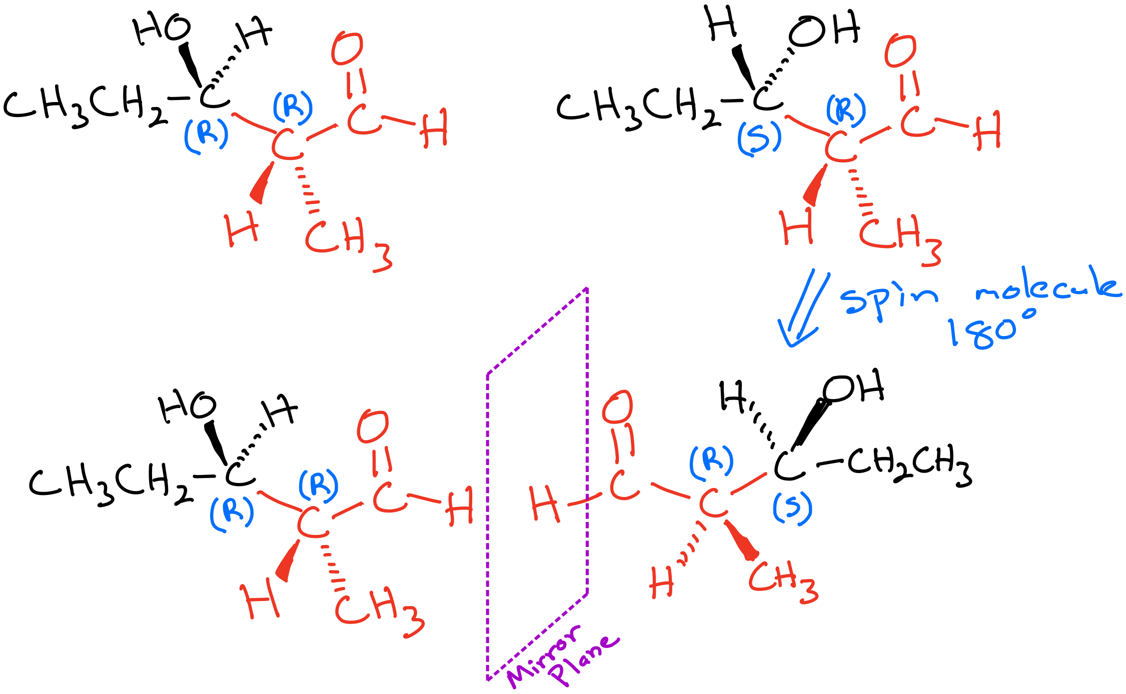
4) The reaction can make two new chiral centers

WAYNE'S WORLD

Enantiomers or Diastereomers?

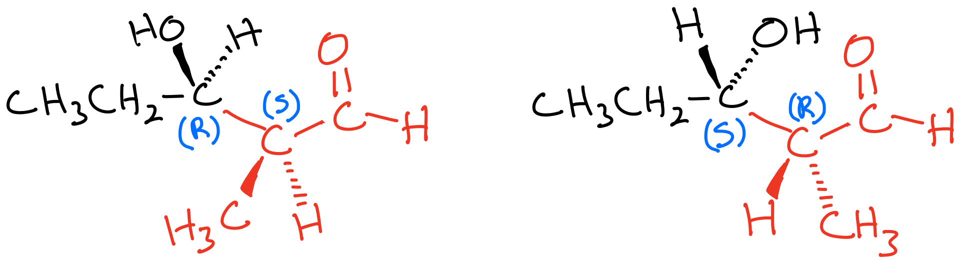


Enantiomers (Section 3.2) Stereoisomers that are nonsuperposable mirror images of each other; refers to a relationship between pairs of objects.

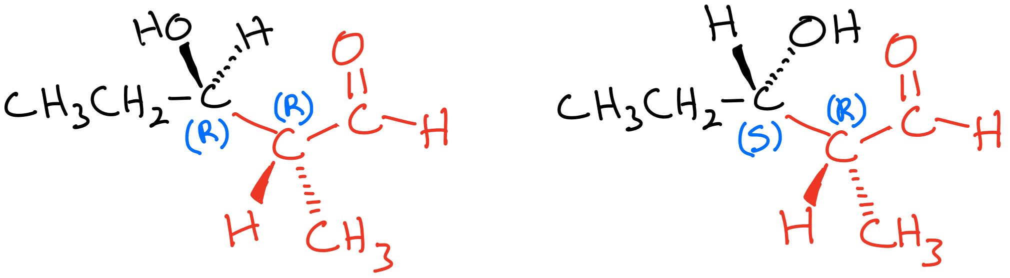


Diastereomers (Section 3.4A) Stereoisomers that are not mirror images of each other; refers to relationships among two or more objects.

Which pair of molecules could be a racemic mixture?

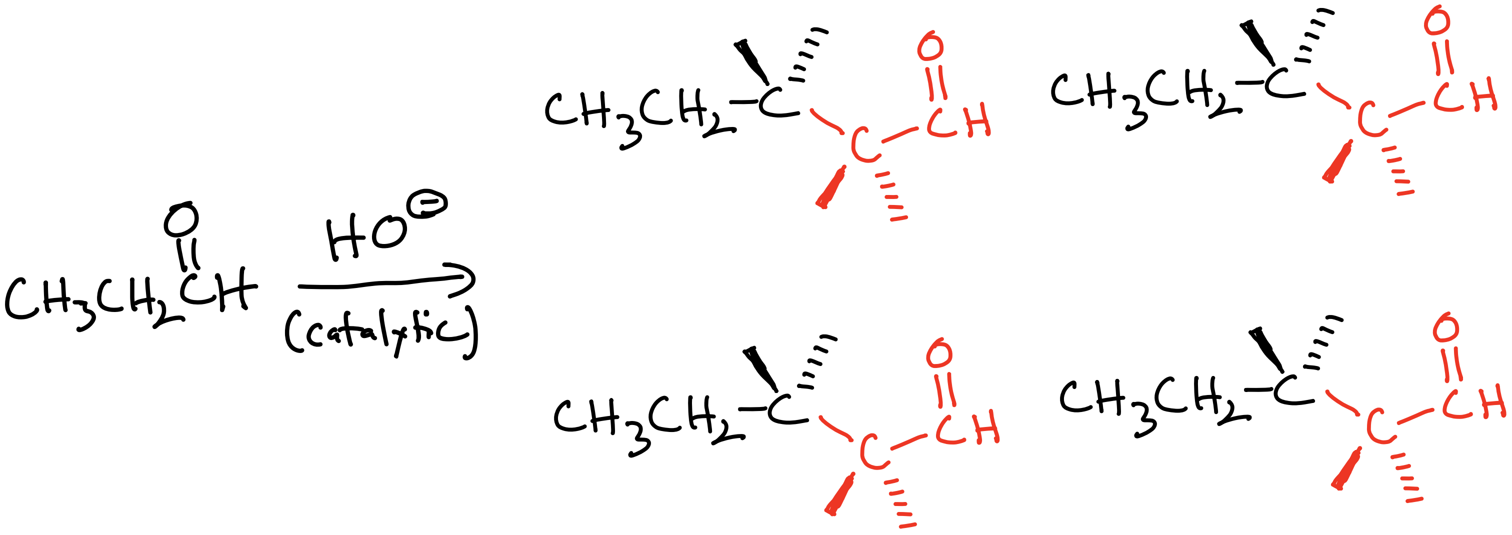


or



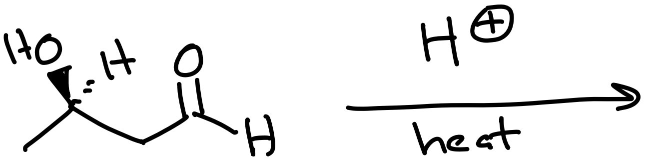
Racemic mixture (Section 3.7C) A mixture of equal amounts of two enantiomers.

Aldol Reaction: 2 new chiral centers



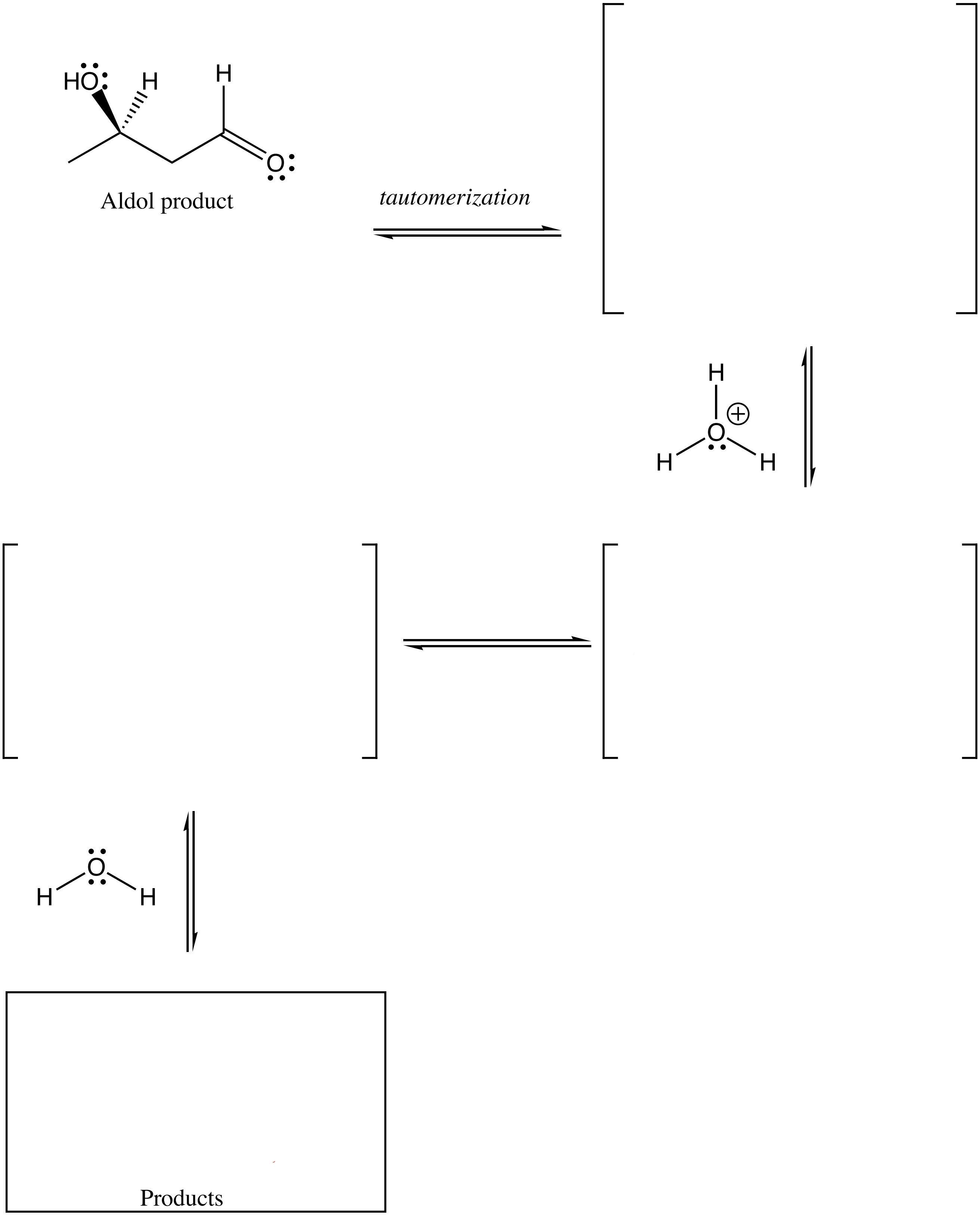
Racemic

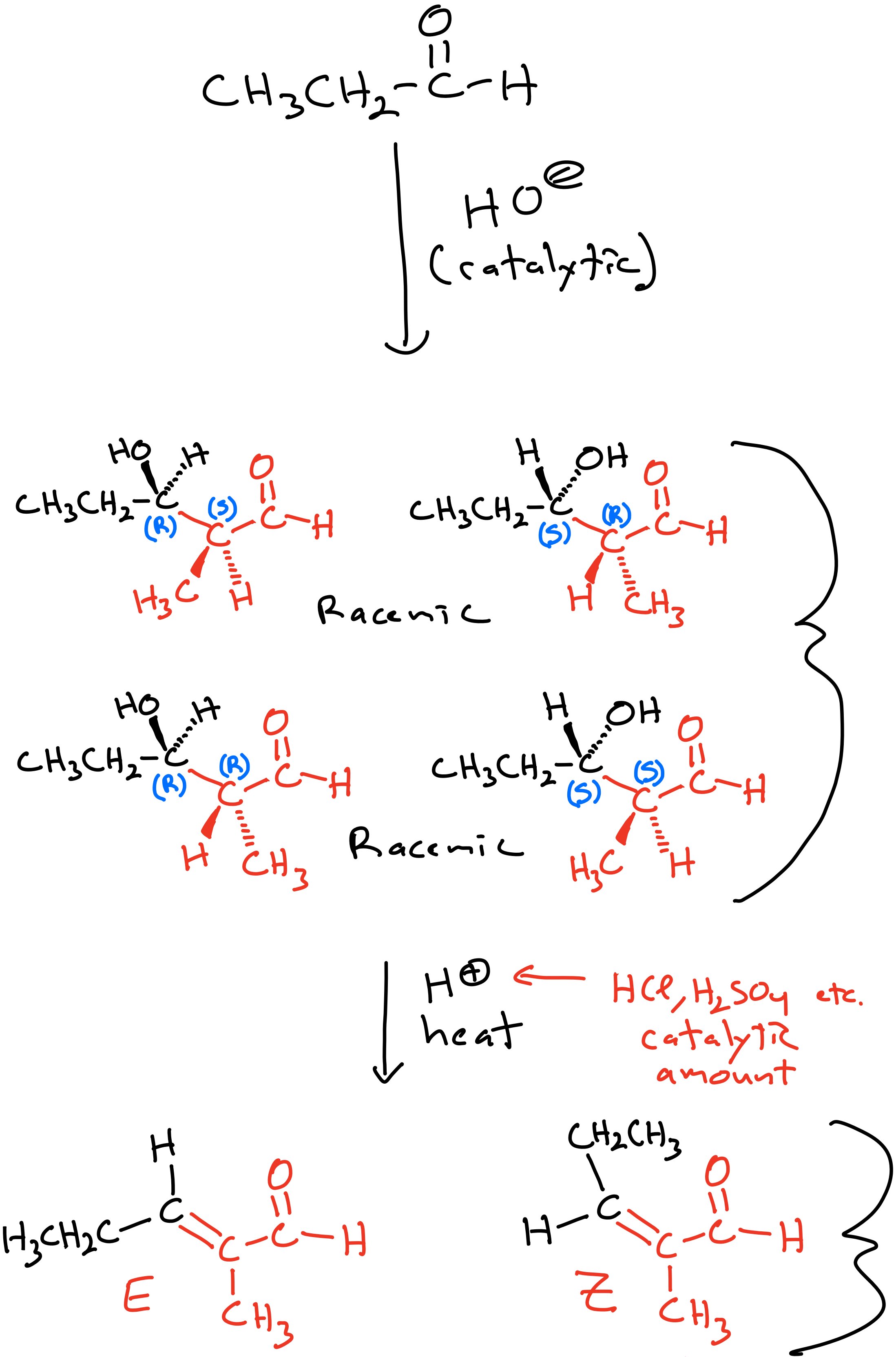
In mild acid with some heating, the aldol product will dehydrate to give an α,β-unsaturated aldehyde.

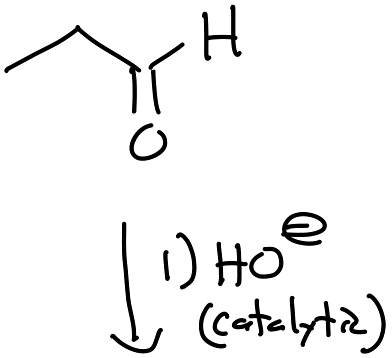


Note: The following mechanism is NOT the simplest you might think of, but it is the one with the lowest energy intermediates (no carbocations, etc.) so this is the correct mechanism

Acid catalyzed dehydration







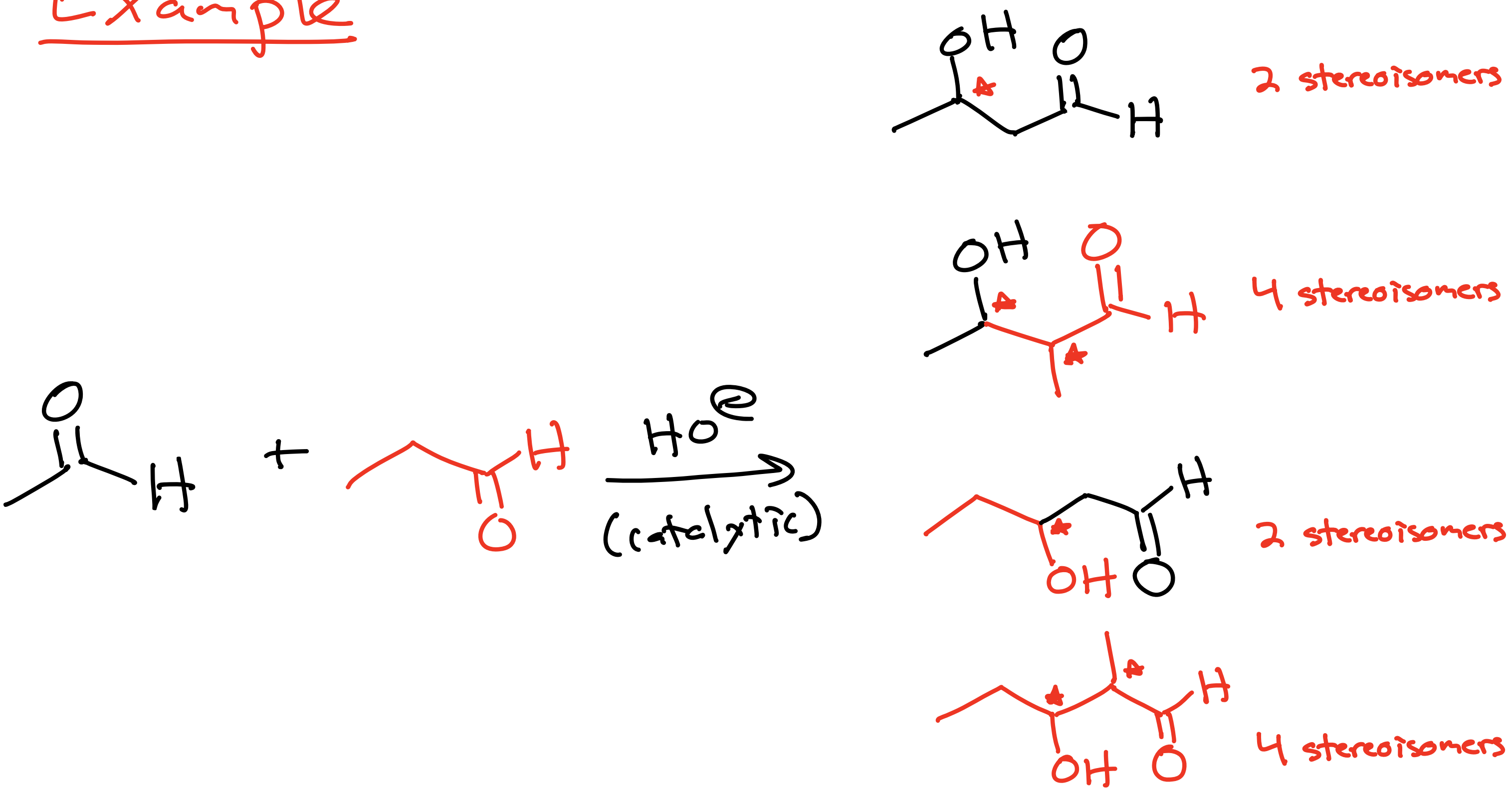
(Need to draw both)

→ The dehydration product is conjugated and therefore stable.

→ The dehydration product can be used in a Michael reaction.

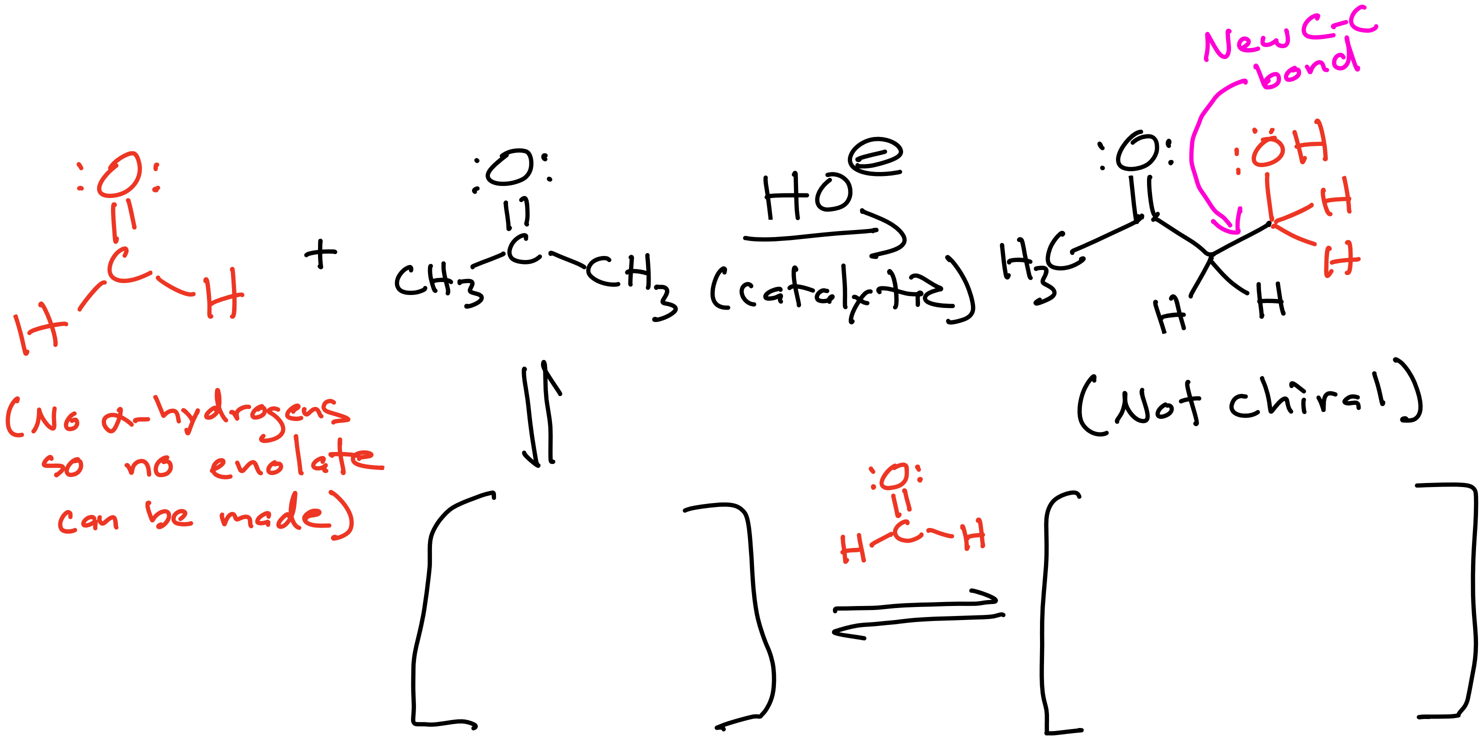
When you run a "mixed" aldol reaction, you generally get far too many reaction products to be useful.

Example

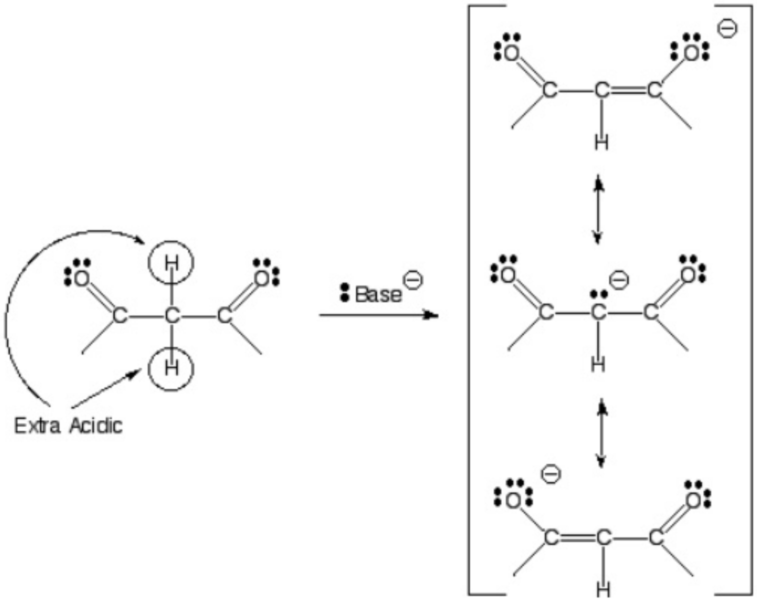


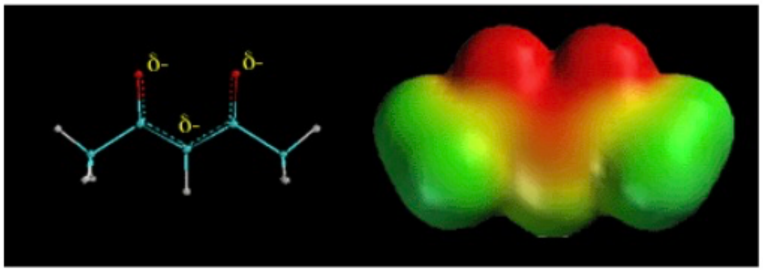
Key Idea ⇒

Strategic Workaround: Use an aldehyde with no α hydrogens and a ketone



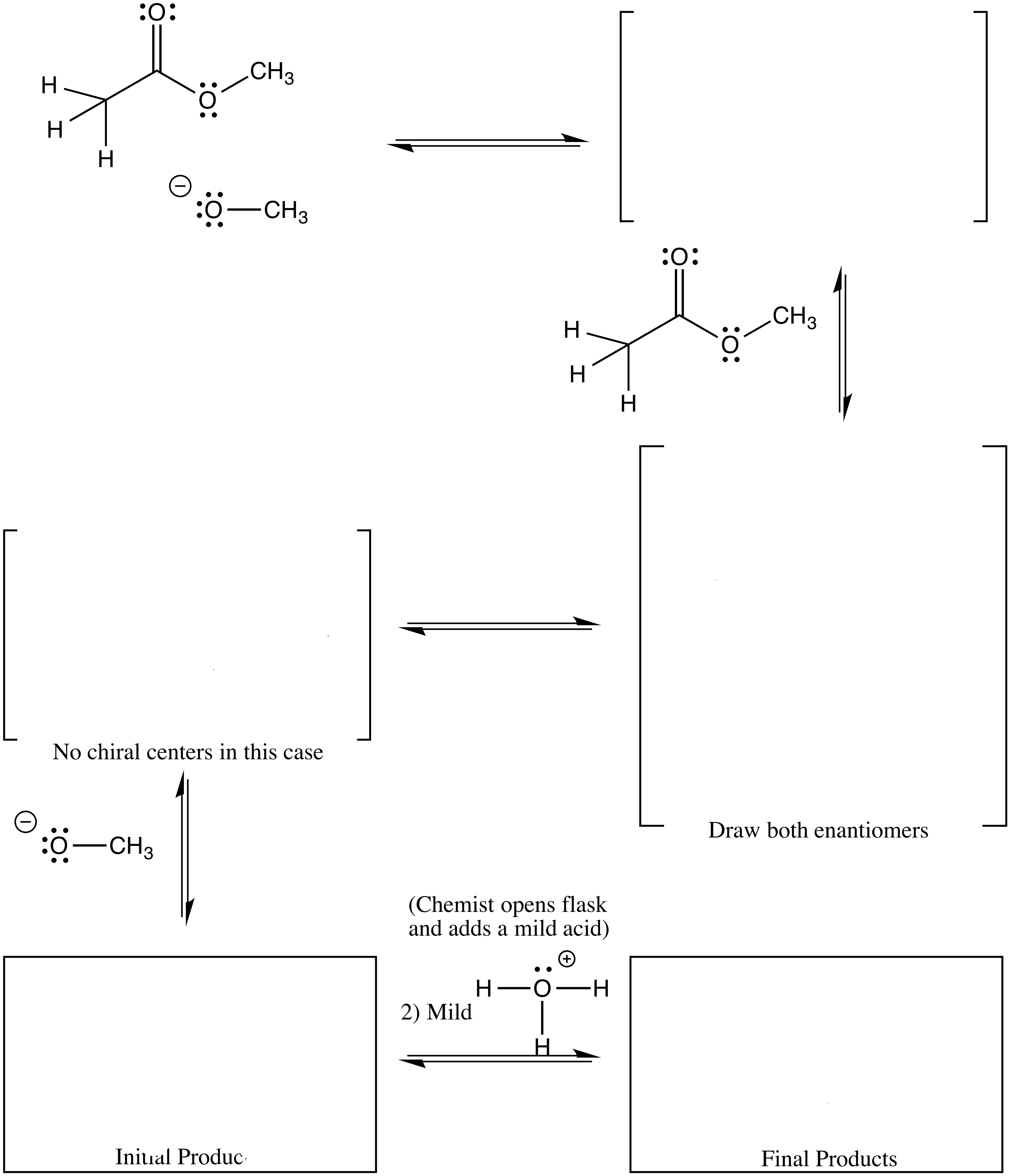
Beta-dicarbonyls have alpha-hydrogens that are extra acidic





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.

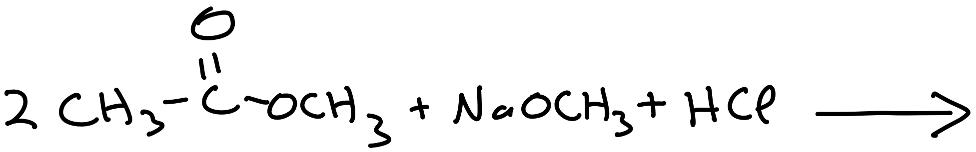
Claisen Condensation



KRE →

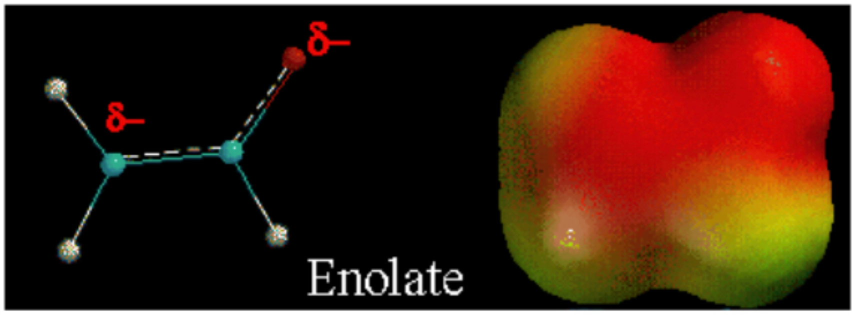
Before we add acid → the last step drives the reaction because we make a relatively stable anion.

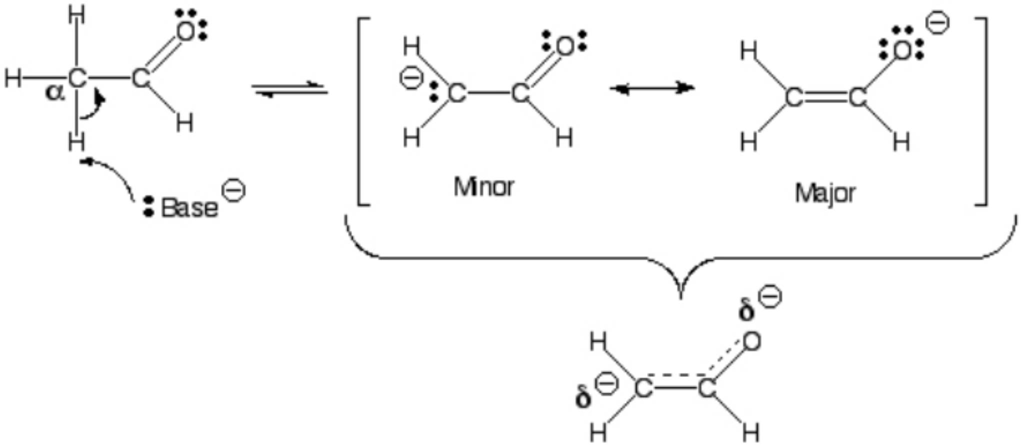
Balanced Equation for the Overall Process



$$2\,CH_3-\overset{\overset{O}{\|}}{C}-OCH_3 + NaOCH_3 + HCl \longrightarrow$$

Enolates as nucleophiles



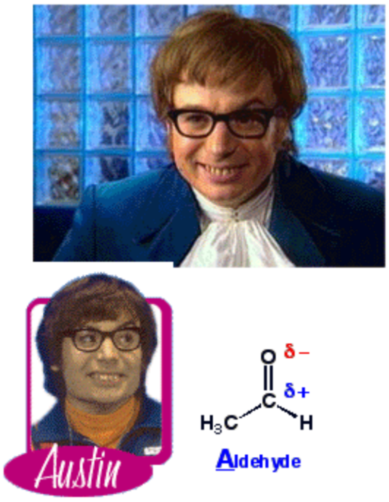


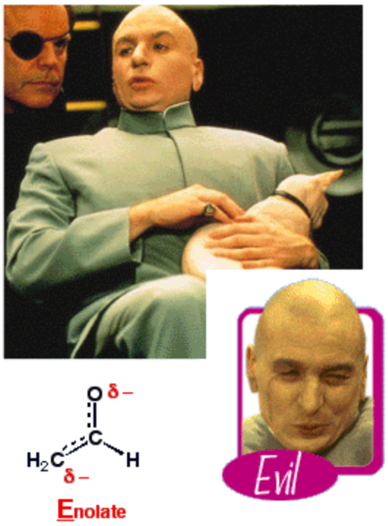
A) Enolates are resonance stabilized, with a partial negative charge on carbon and oxygen.

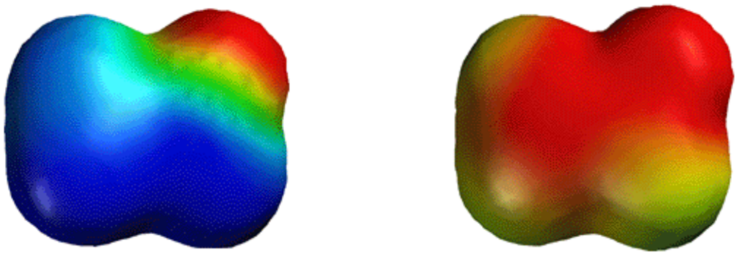
B) Enolates are nucleophiles, so they could react at either the carbon atom or oxygen atom. The partial negative charges give them the **opportunity** to react at either the carbon or oxygen.

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.

Once Again, A Movie Ripping Off Chemistry

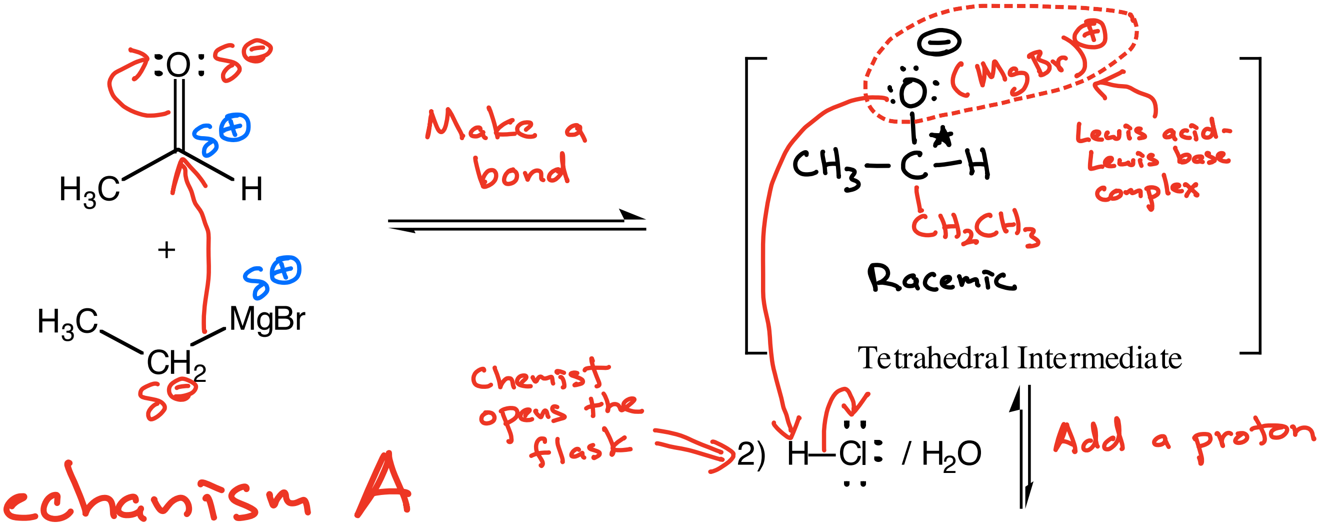






WAYNE'S WORLD

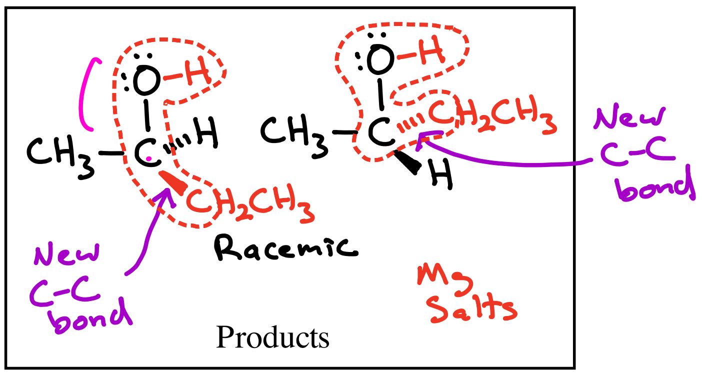
Grignard Reagent Reacting with an Aldehyde or Ketone

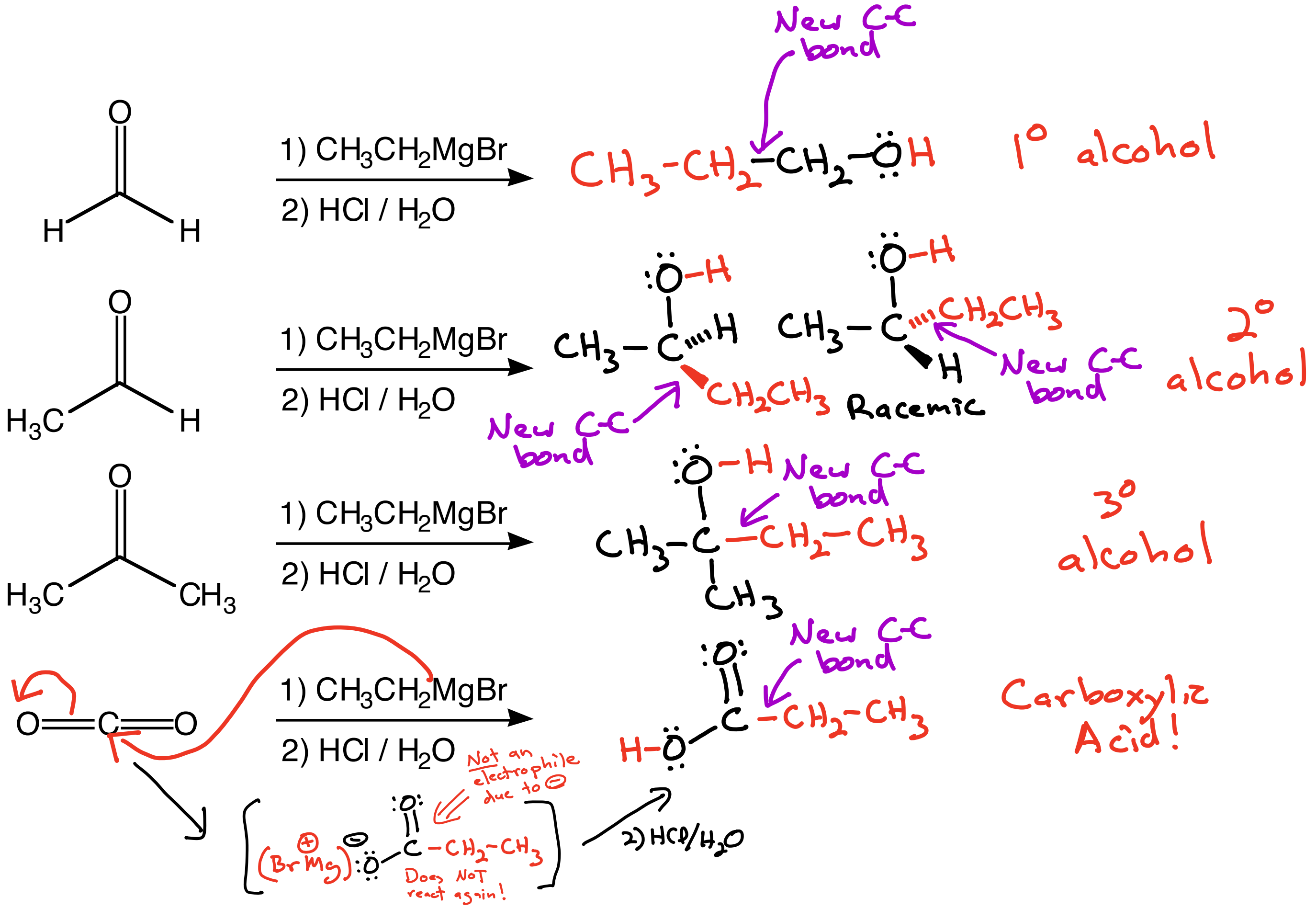


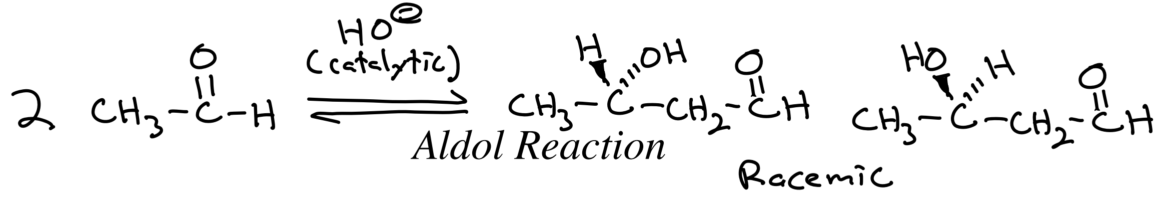
Mechanism A

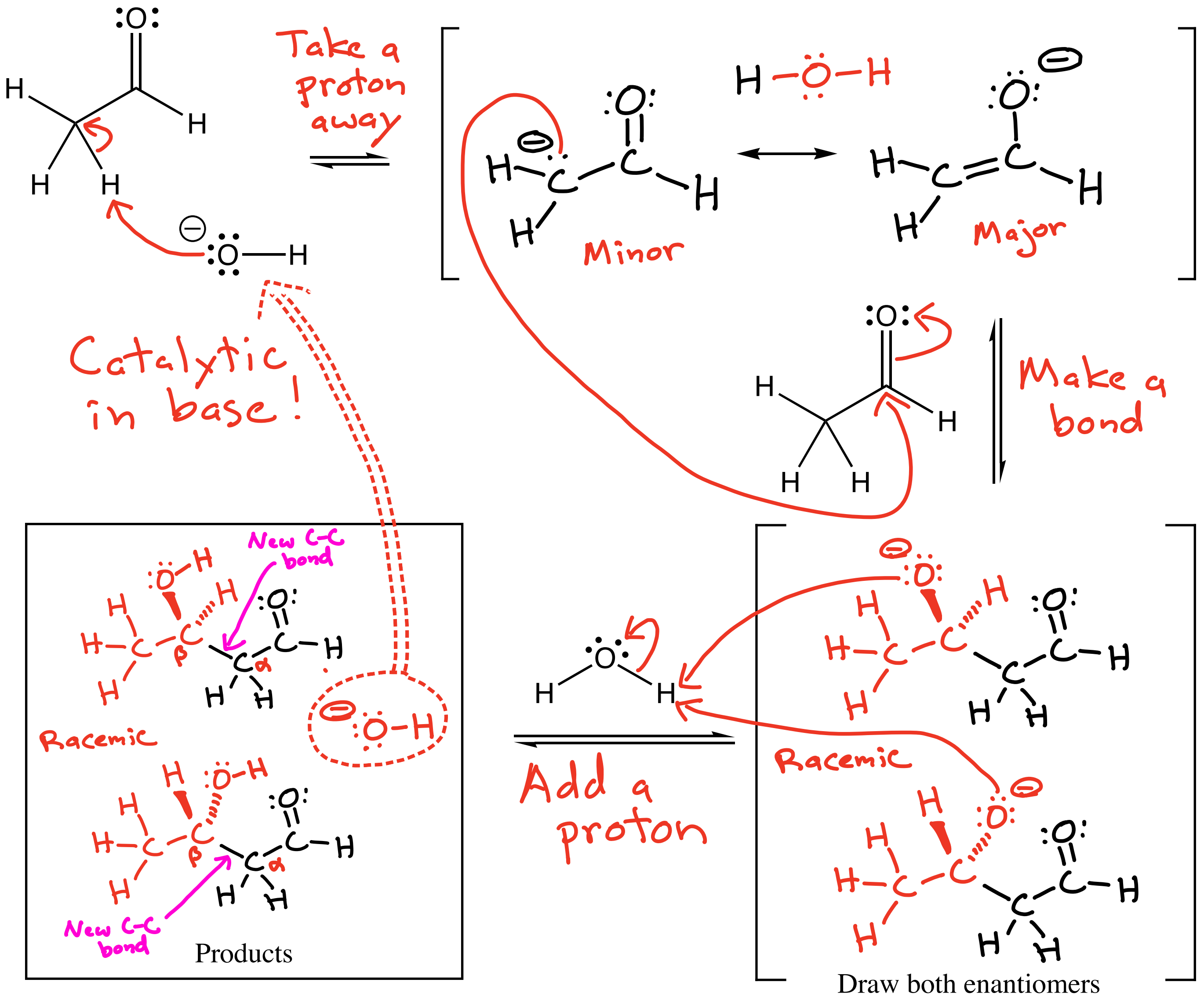
Key Recognition Element (KRE):

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





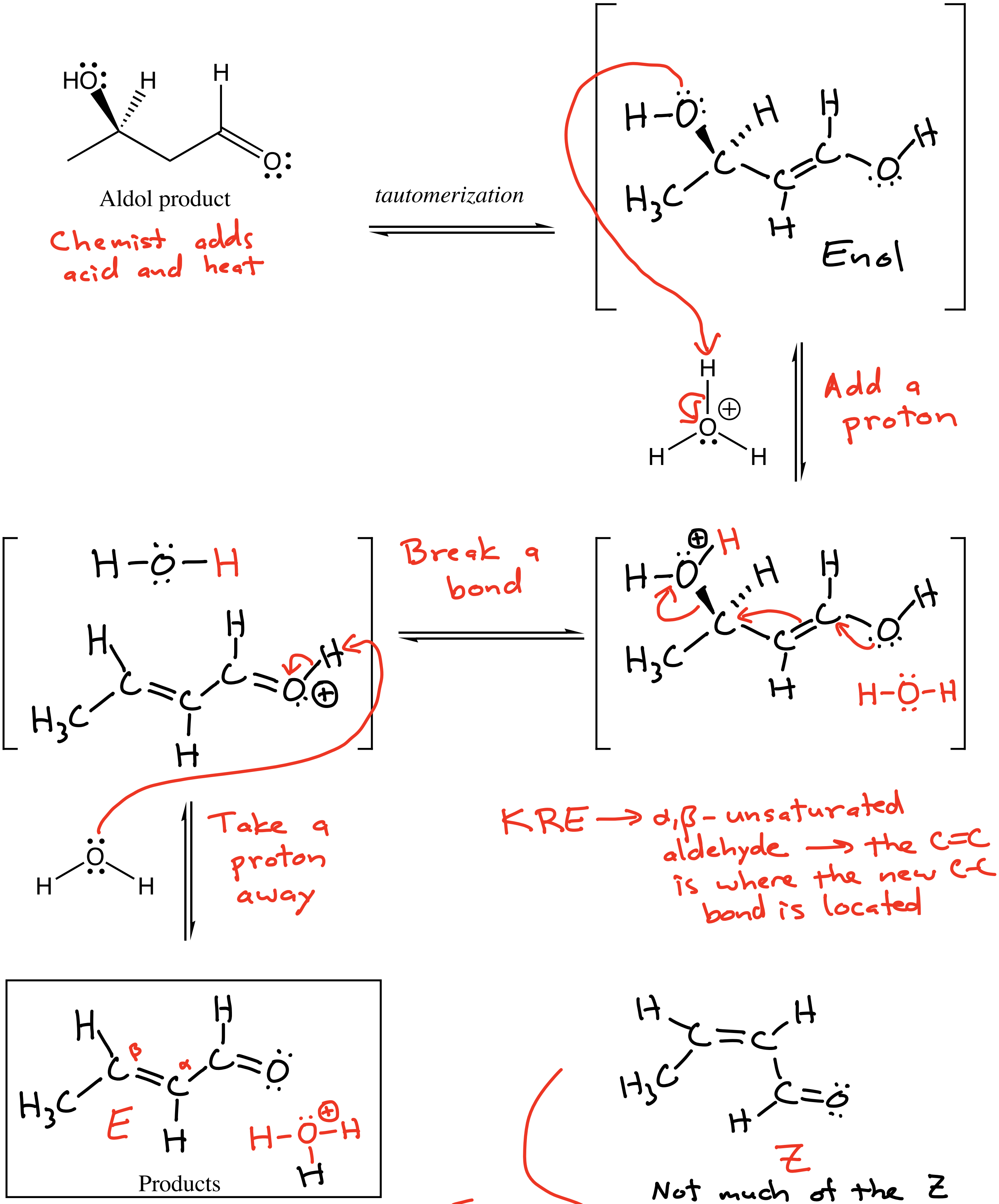




KRE → β-hydroxy aldehyde with a new C–C bond between the aldehyde α and β carbons

Mechanism A

Acid catalyzed dehydration



Chemist adds acid and heat

Add a proton

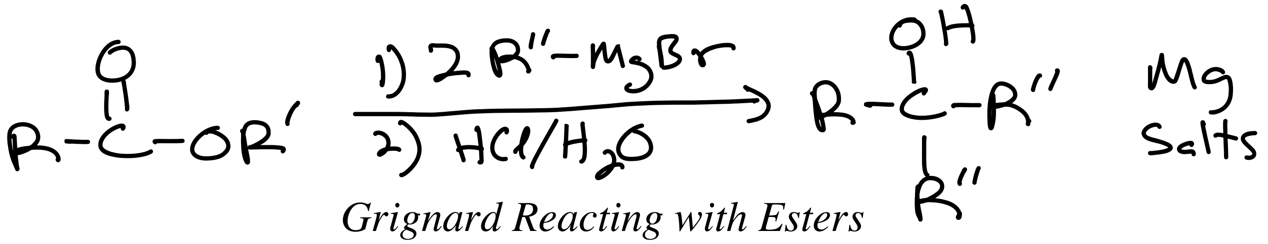
Break a bond

Take a proton away

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

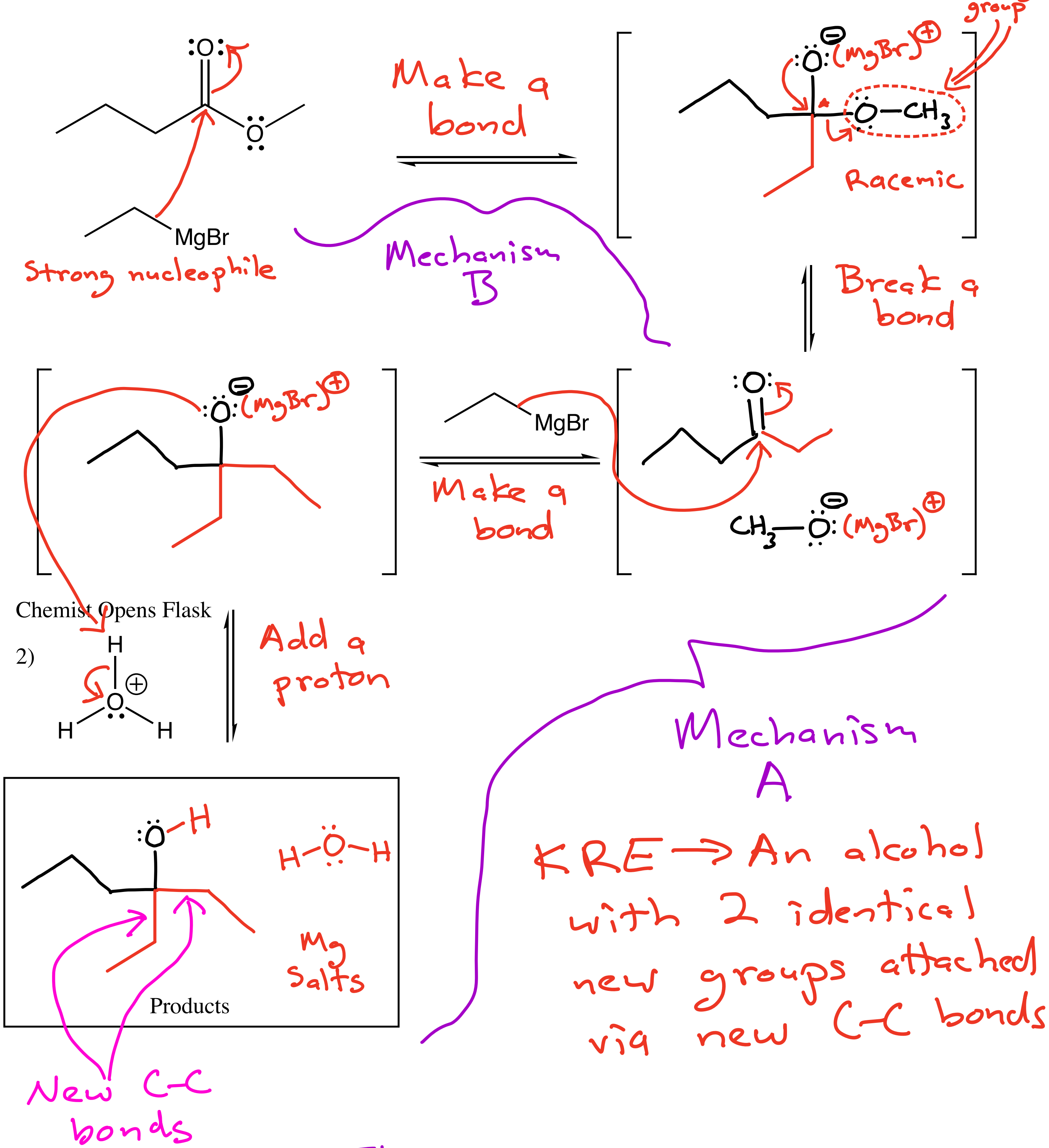
Not much of the Z product is formed because it has significantly more steric strain than E

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



$$\mathrm{R{-}\overset{\overset{O}{\|}}{C}{-}OR'} \xrightarrow[\text{2) HCl/H}_2\text{O}]{\text{1) 2 R''−MgBr}} \mathrm{R{-}\underset{R''}{\overset{OH}{C}}{-}R''} \quad \text{Mg Salts}$$

Grignard Reacting with Esters



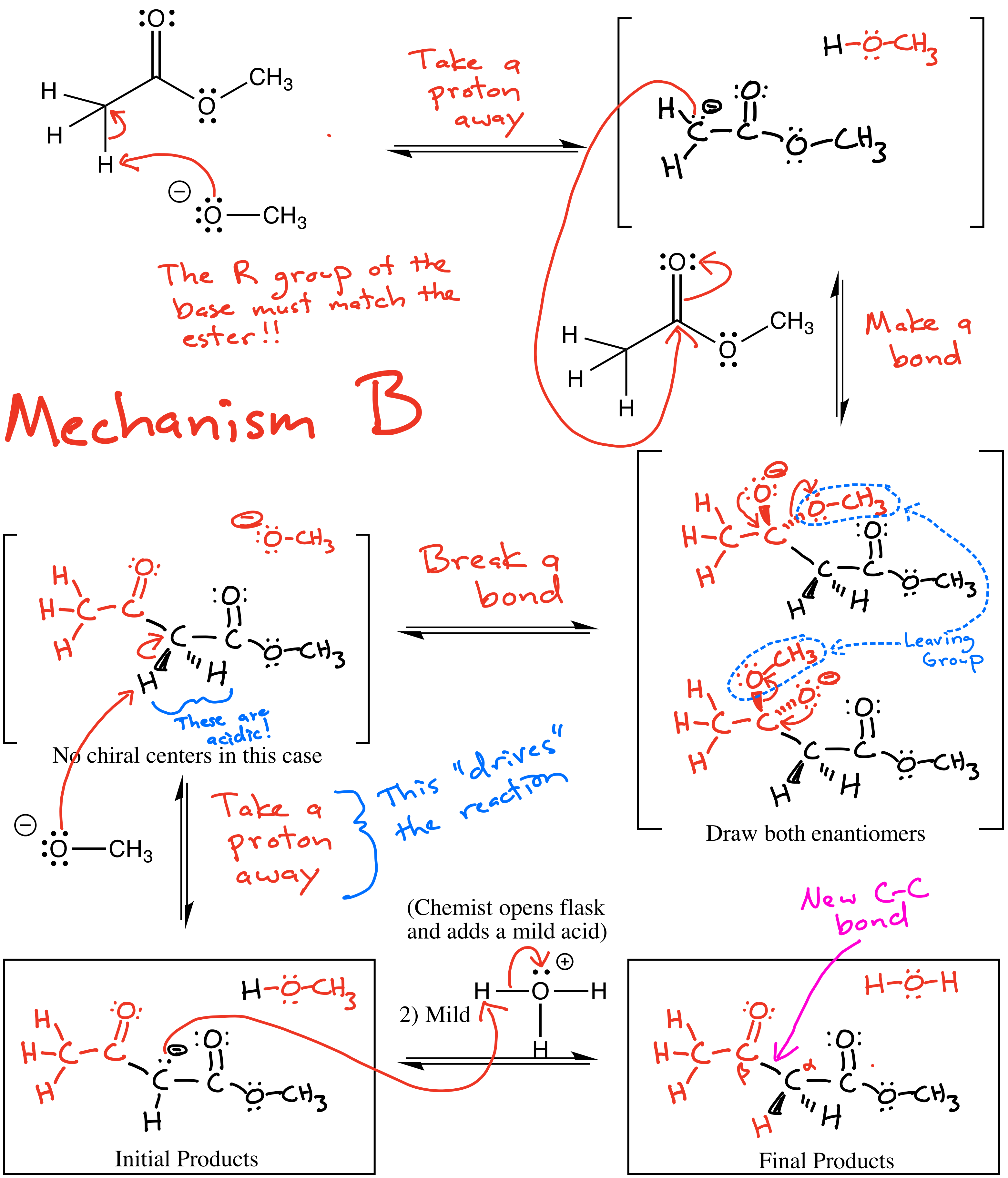
KRE ⇒ An alcohol with 2 identical new groups attached via new C–C bonds

The overall reaction mechanism is Mechanism B followed by Mechanism A

⇒ Same as the next reaction!

Claisen Condensation → "Aldol with Esters"

Mechanism B

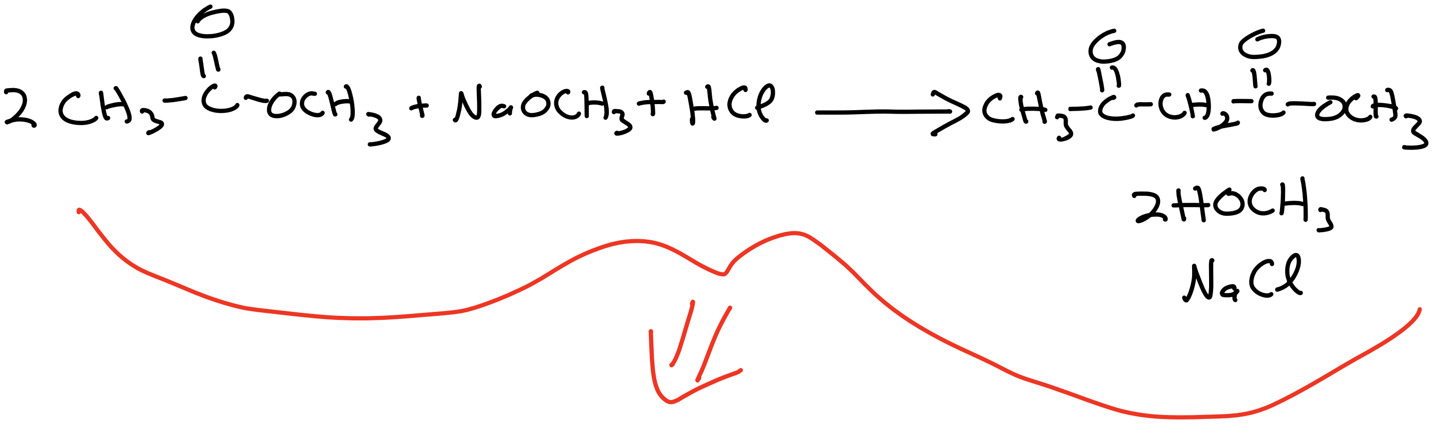


This is a much more stable anion compared to ⊖OCH₃, providing a strong driving force (motive) for the Claisen condensation reaction

KRE → A β-keto ester with a new C-C bond between the α and β carbons

Before we add acid → the last step drives the reaction because we make a relatively stable anion.

Balanced Equation for the Overall Process



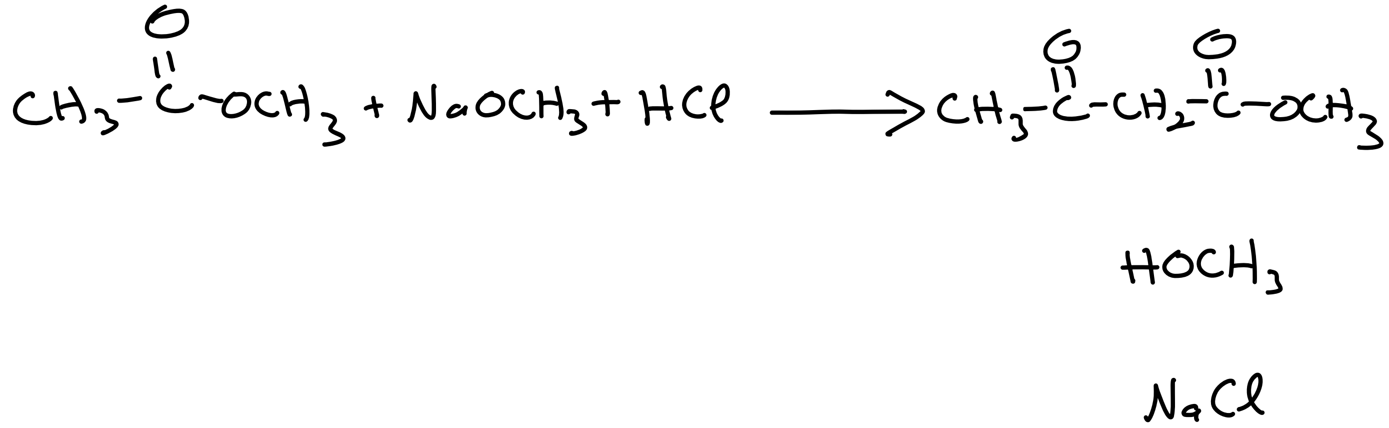
$$2\,CH_3-\overset{O}{\overset{\|}{C}}-OCH_3 + NaOCH_3 + HCl \longrightarrow CH_3-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-OCH_3$$

$2HOCH_3$

$NaCl$

This is the balanced equation that is explained by the mechanism

With the balanced equation in hand we can set up a reaction properly in the lab because we know how much of each reactant is needed → For this we use the notation of "equivalents"

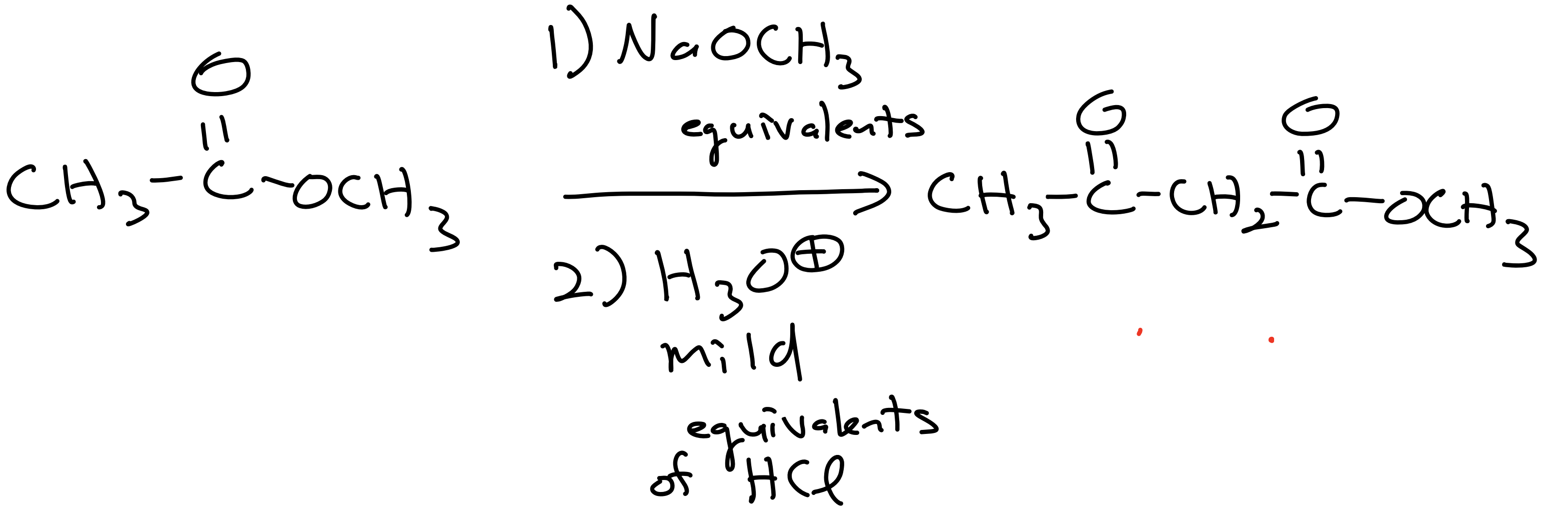


$$\mathrm{CH_3-\overset{O}{\overset{\|}{C}}-OCH_3 + NaOCH_3 + HCl \longrightarrow CH_3-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-OCH_3}$$

$\mathrm{HOCH_3}$

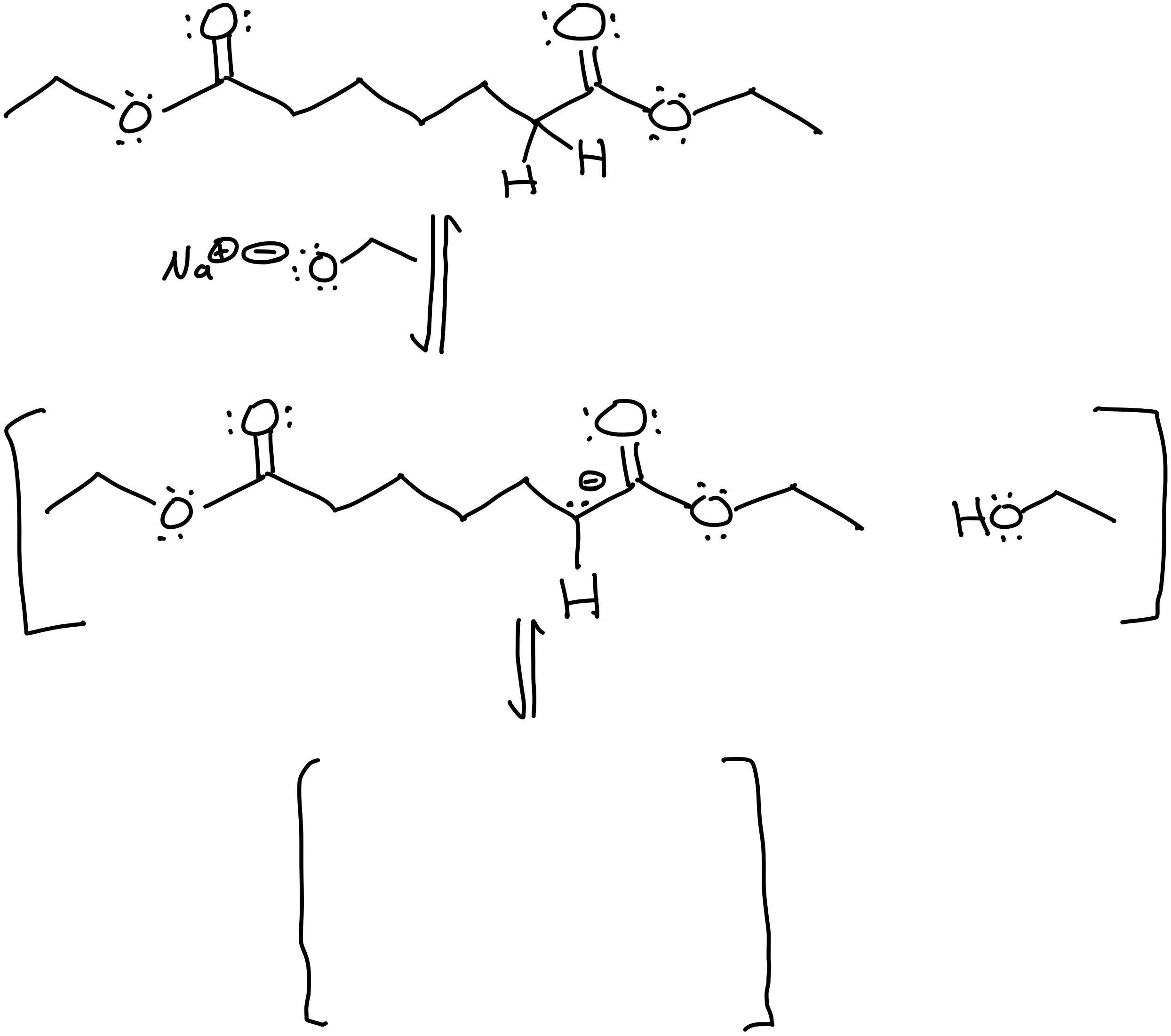
NaCl

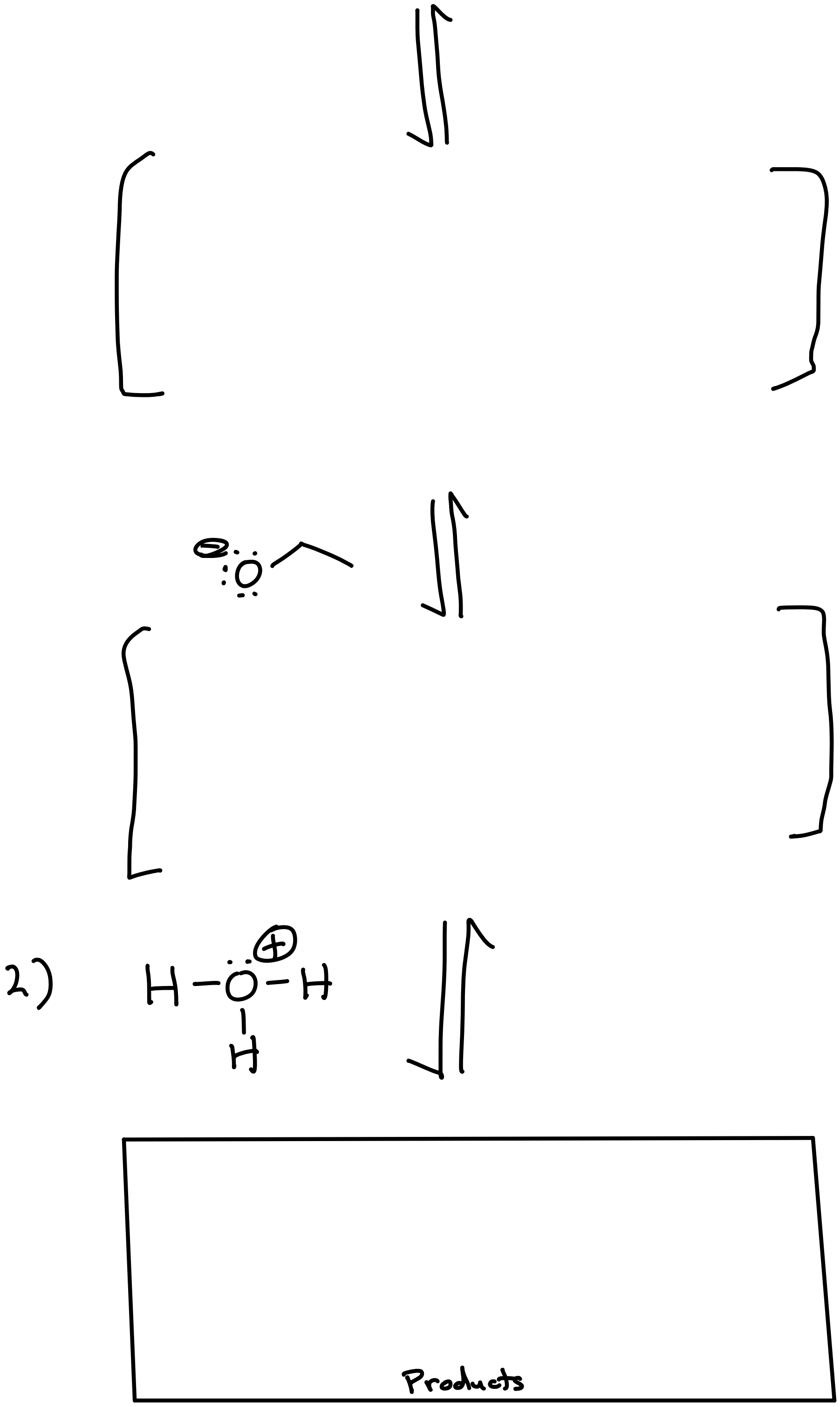
Example of using equivalents



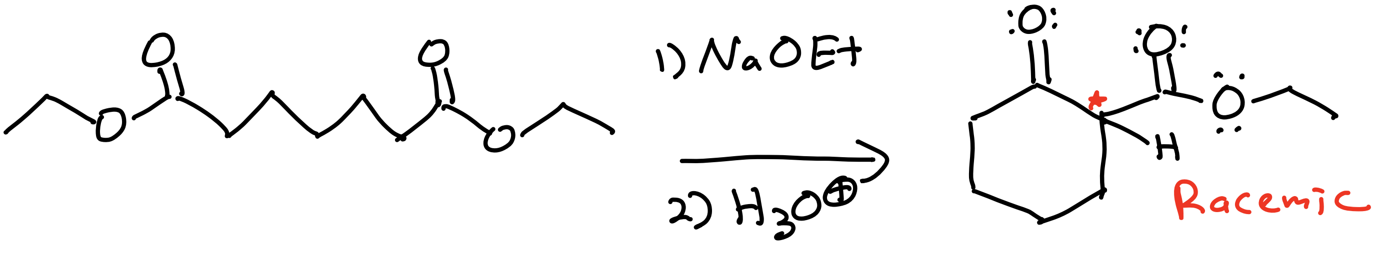
$$CH_3-\overset{O}{\overset{\|}{C}}-OCH_3 \xrightarrow[\text{2) } H_3O^{\oplus} \text{ mild equivalents of } HCl]{\text{1) } NaOCH_3 \text{ equivalents}} CH_3-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-OCH_3$$

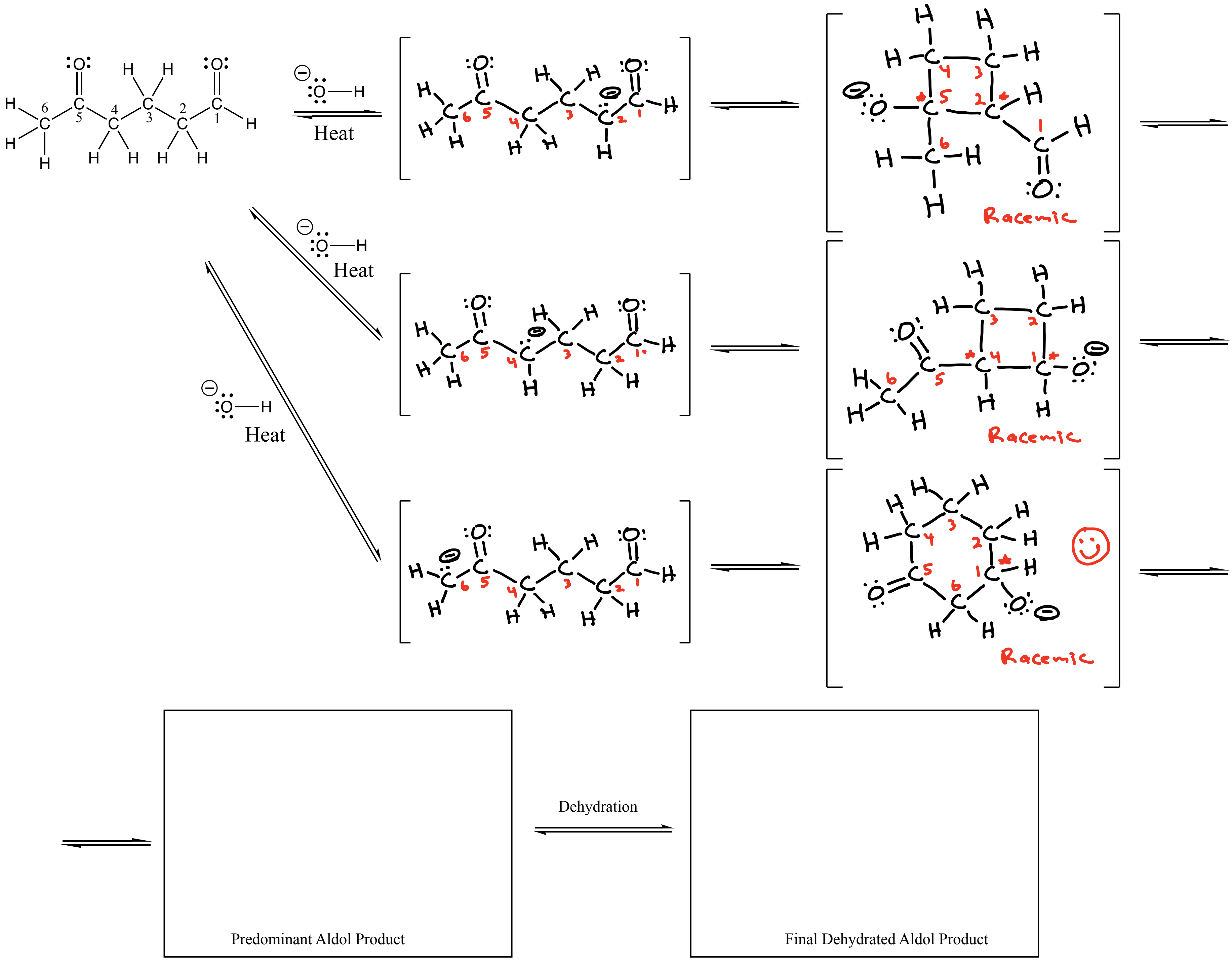
The Dieckmann Condensation → Using a Claisen to make a ring.

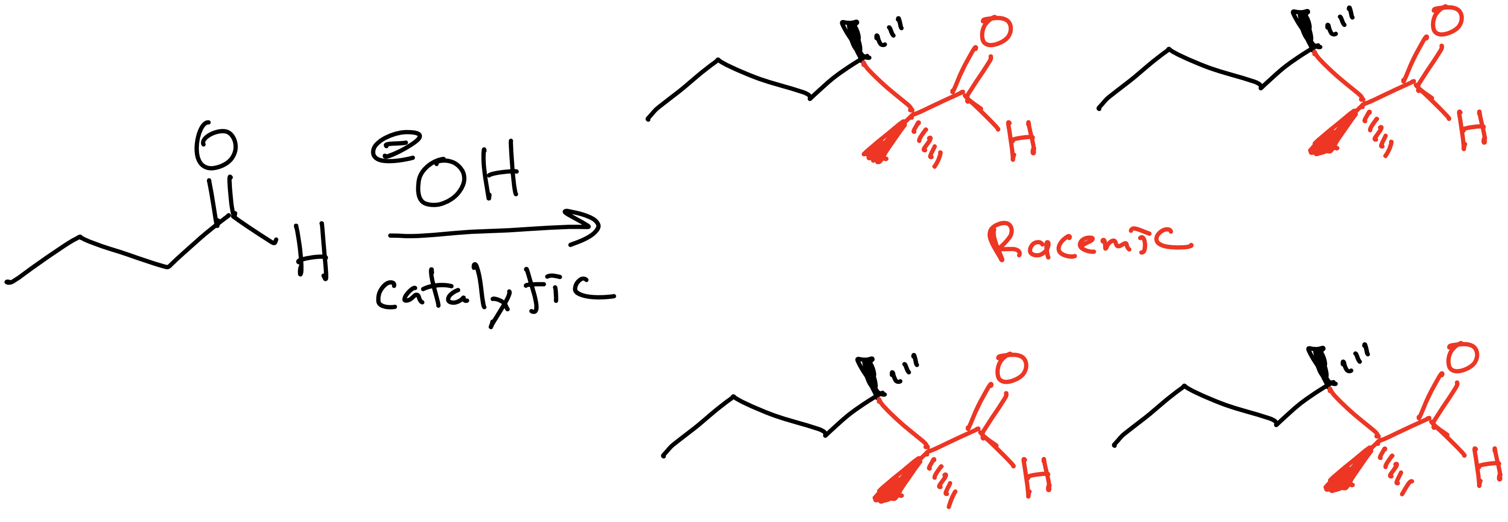




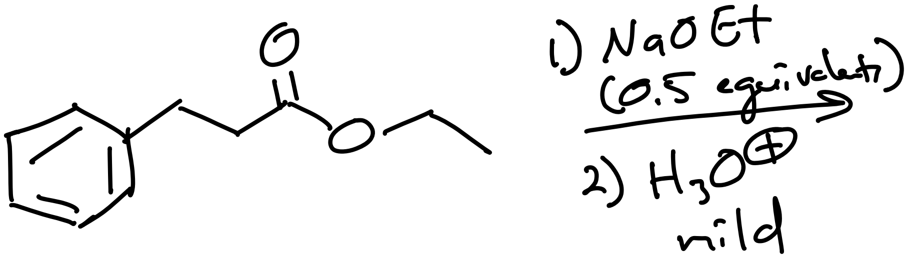
Overall Process



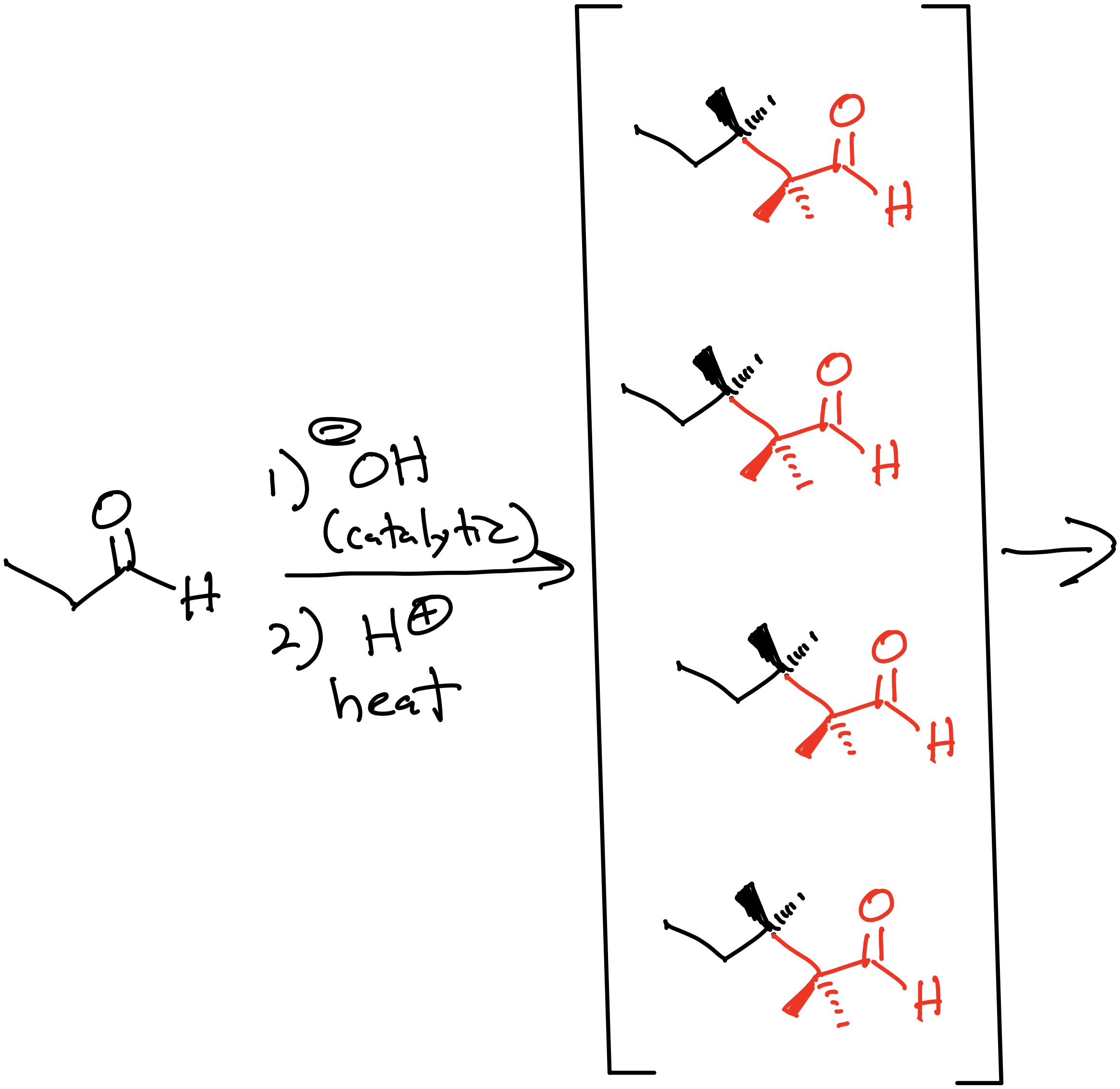

Heat
Heat
Heat
Racemic
Racemic
Racemic
Dehydration
Predominant Aldol Product
Final Dehydrated Aldol Product



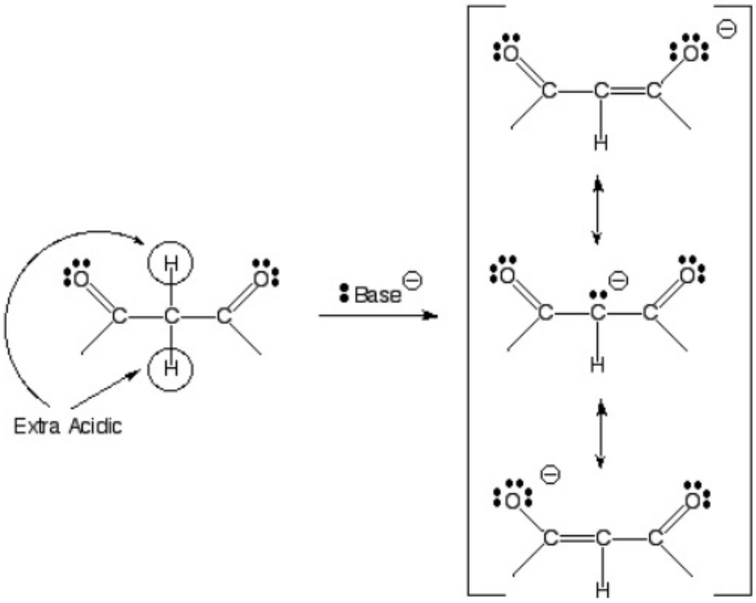
O
H
⊖OH
catalytic
O
H
Racemic

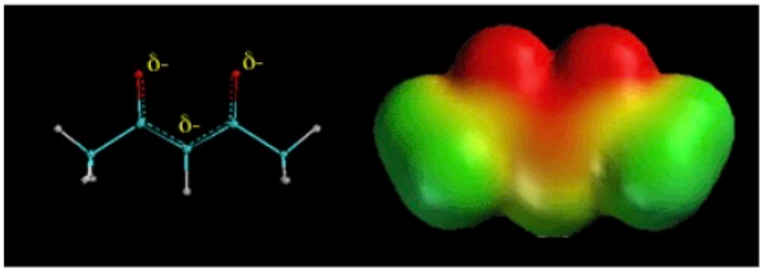


O
O
1) NaOEt
(0.5 equivalents)
2) H₃O⊕
mild


O
H
1) $^{\ominus}$OH
(catalytic)
2) H$^{\oplus}$
heat
O
H
O
H
O
H
O
H

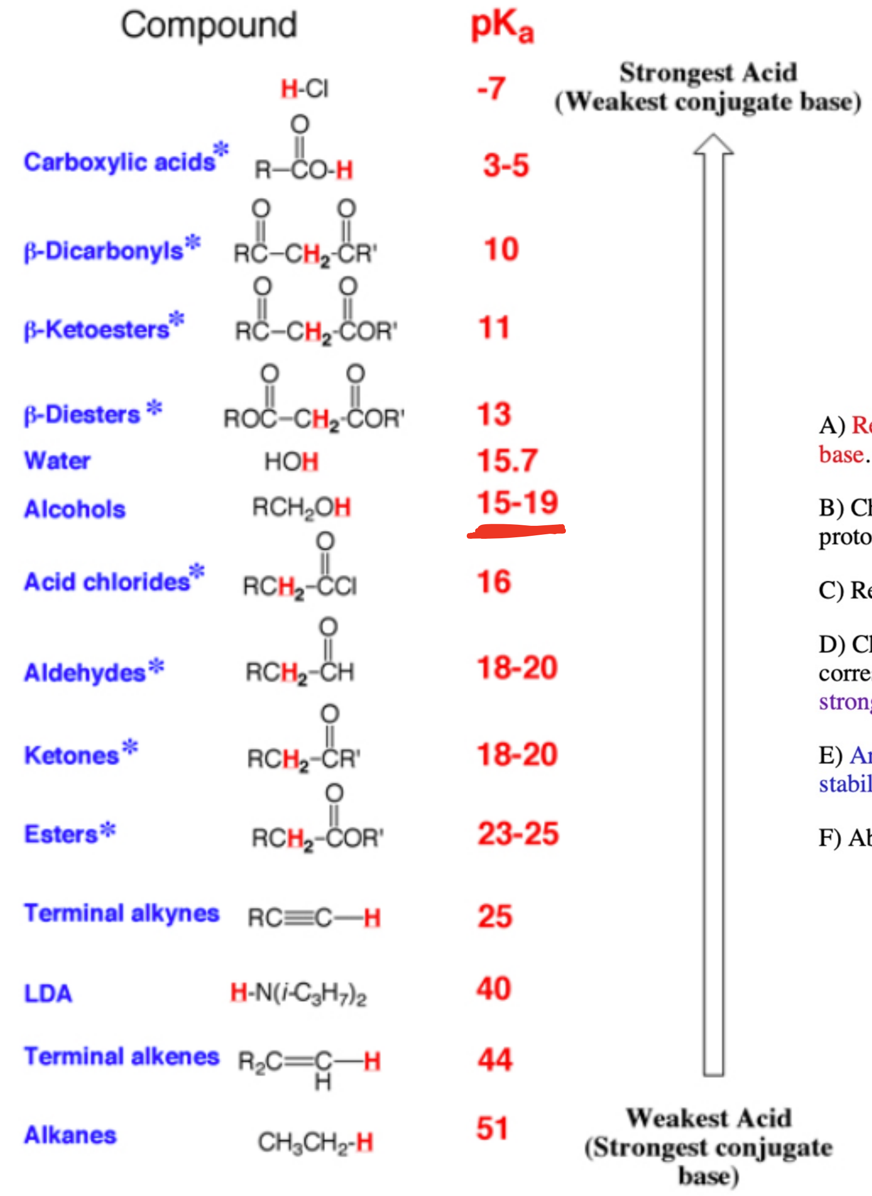
Beta-dicarbonyls have alpha-hydrogens that are extra acidic





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



Compound		pKa
	$H-Cl$	-7
Carboxylic acids*	$R-\overset{O}{C}O-H$	3-5
β-Dicarbonyls*	$R\overset{O}{C}-CH_2-\overset{O}{C}R'$	10
β-Ketoesters*	$R\overset{O}{C}-CH_2-\overset{O}{C}OR'$	11
β-Diesters *	$RO\overset{O}{C}-CH_2-\overset{O}{C}OR'$	13
Water	HOH	15.7
Alcohols	RCH_2OH	15-19
Acid chlorides*	$RCH_2-\overset{O}{C}Cl$	16
Aldehydes*	$RCH_2-\overset{O}{C}H$	18-20
Ketones*	$RCH_2-\overset{O}{C}R'$	18-20
Esters*	$RCH_2-\overset{O}{C}OR'$	23-25
Terminal alkynes	$RC\equiv C-H$	25
LDA	$H-N(i\text{-}C_3H_7)_2$	40
Terminal alkenes	$R_2C=\underset{H}{C}-H$	44
Alkanes	CH_3CH_2-H	51

Strongest Acid
(Weakest conjugate base)

Weakest Acid
(Strongest conjugate base)

*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.

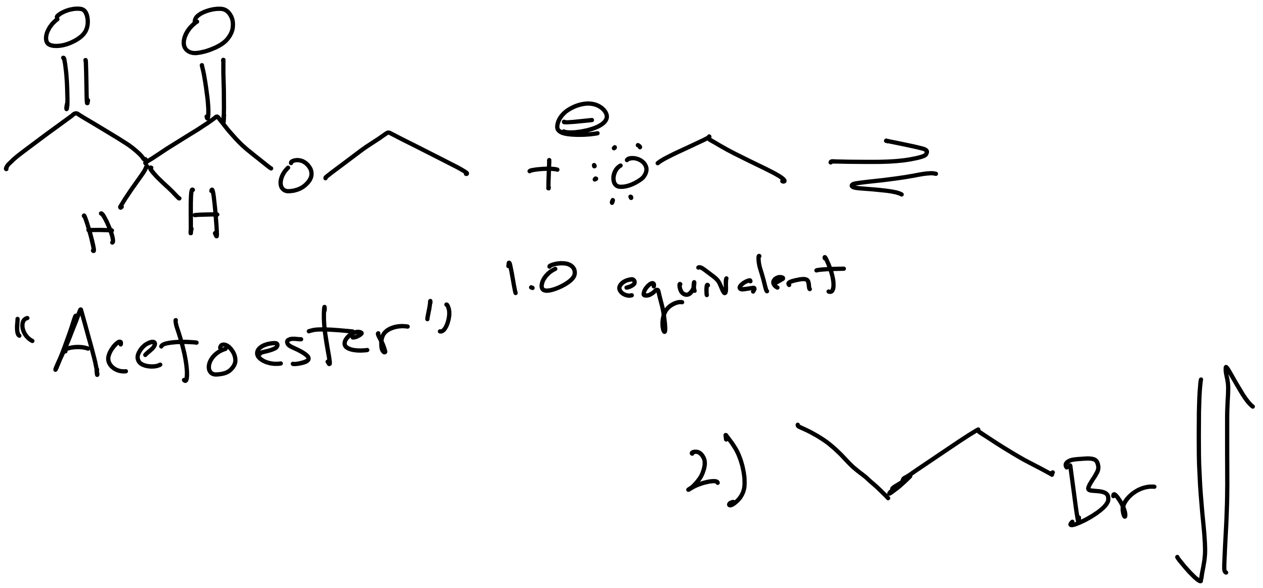
C) Recall that the conjugate base of a stronger acid (lower pKa) is a weaker base.

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.

Acetoester Synthesis



"Acetoester"