https://www.youtube.com/watch?v=iKLXEAPjwAw&t=10s

BEAUMONT ENTERPRISE

Brain cancer patient wins Gusher Marathon

By **Avi Zaleon**
Updated March 11, 2013 11:27 a.m.

Iram Leon and daughter Kiana Leon finish the Gusher Marathon in 3 hours 7 minutes and 35 seconds taking first place in the full marathon on Saturday, March 9, 2013. Photo taken: Randy Edwards/The Enterprise

A man racing against time crossed the finish line. His daughter, snugly sitting in a stroller he had been pushing for just over 26 miles, gained a memory that may live longer than her father.

"This is supposed to eat away at my memory in the end," Iram Leon said of the cancer in his left temporal lobe. "But I hope this memory is one of the last things to go and one she never loses."

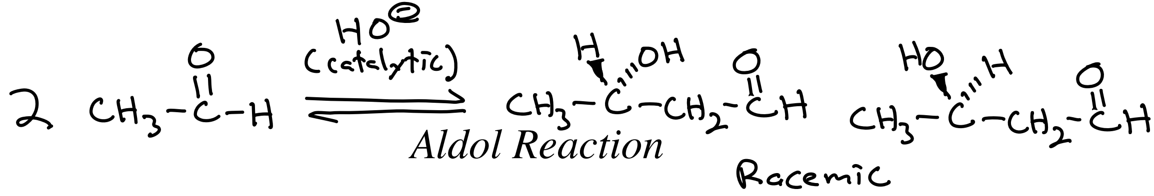
Leon is 32 years old. He said his doctors have told him, "we're probably not going to beat this. We're just hoping to get you to 40."

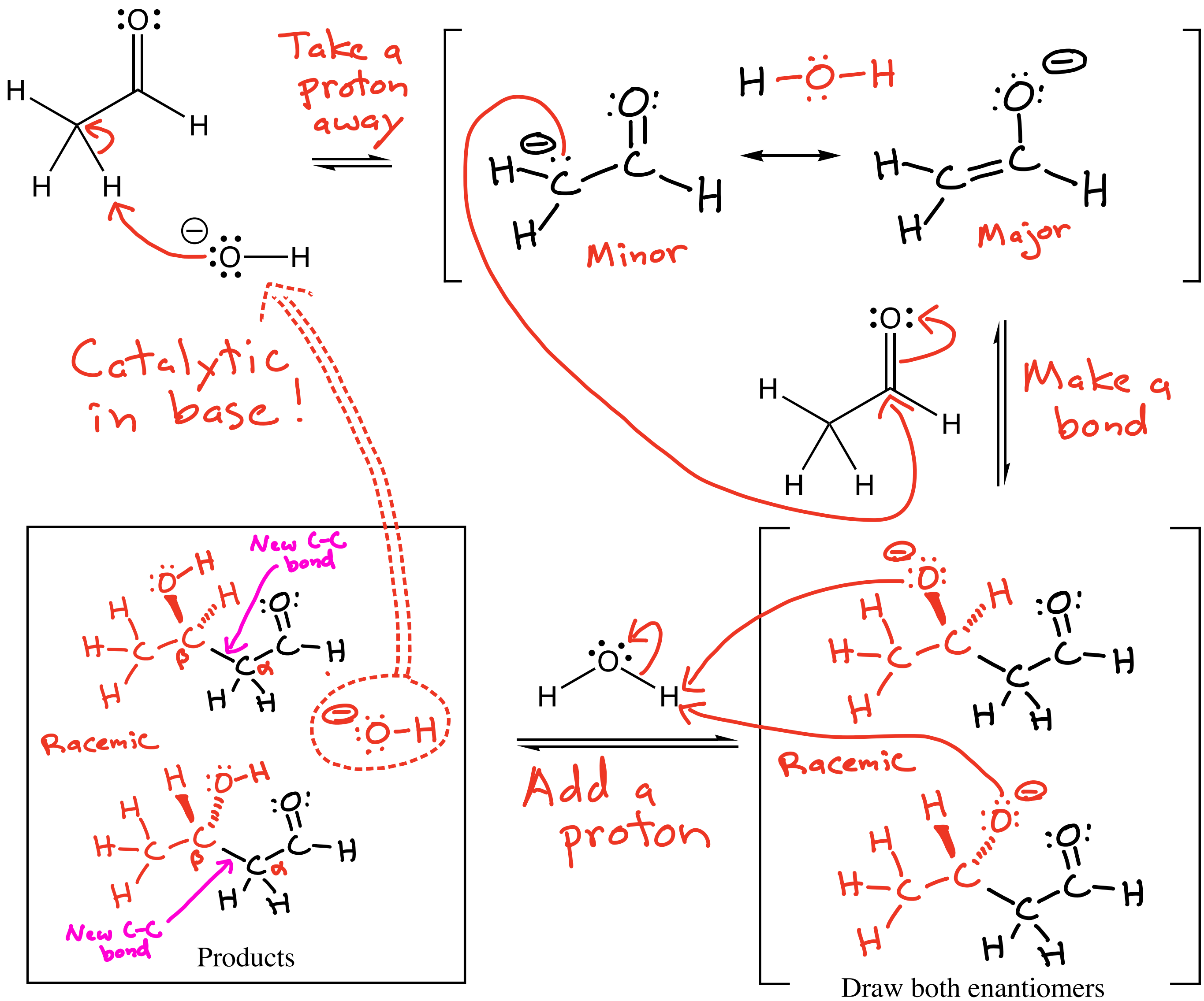
Hello Dr. Iverson,
You may not remember me, but I was in your organic chemistry class last semester.

This past summer I was diagnosed with lymphoma cancer. Initially I had lost all hope, I kept asking myself "why me?" and kept thinking of all things I hadn't accomplished in my lifetime. Nevertheless, I soon got over that fact and started my chemotherapy treatments. Each treatment got worse and worse as I experienced more and more of the side effects. At night I couldn't fall asleep from all psychological and financial stress, couldn't eat because of mouth sores, and when I did eat I would feel sick and nauseated. It wasn't until my third treatment that I remembered the many times you told the class that running could help quality of life. It took a couple of weeks for me to convince myself to start running but I eventually started slowly.I never thought how great of an affect physical activity could have. I was never obese so I never gave running or cardio any thought. As I started running on a regular basis I started seeing my symptoms disappear slowly. Soon when I would come back from running I suddenly had an appetite, regardless of the mouth sores I was hungry enough to eat. My sleeping schedule was started falling into place because I was so tired after running. My stress levels decreased enough that I could see the difference. Best of all it gave me something to do during my days at home, saving me from depression.

Running saved my life Dr. Iverson.

Thanks again,



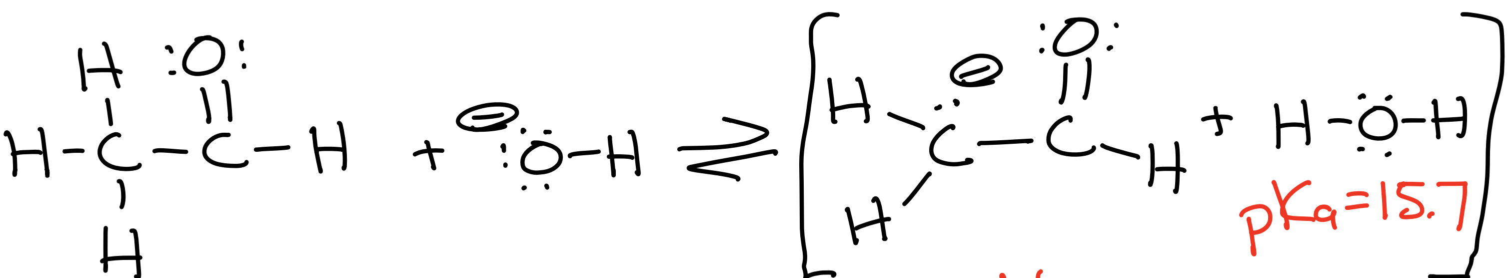


KRE → β-hydroxy aldehyde with a new C–C bond between the aldehyde α and β carbons

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

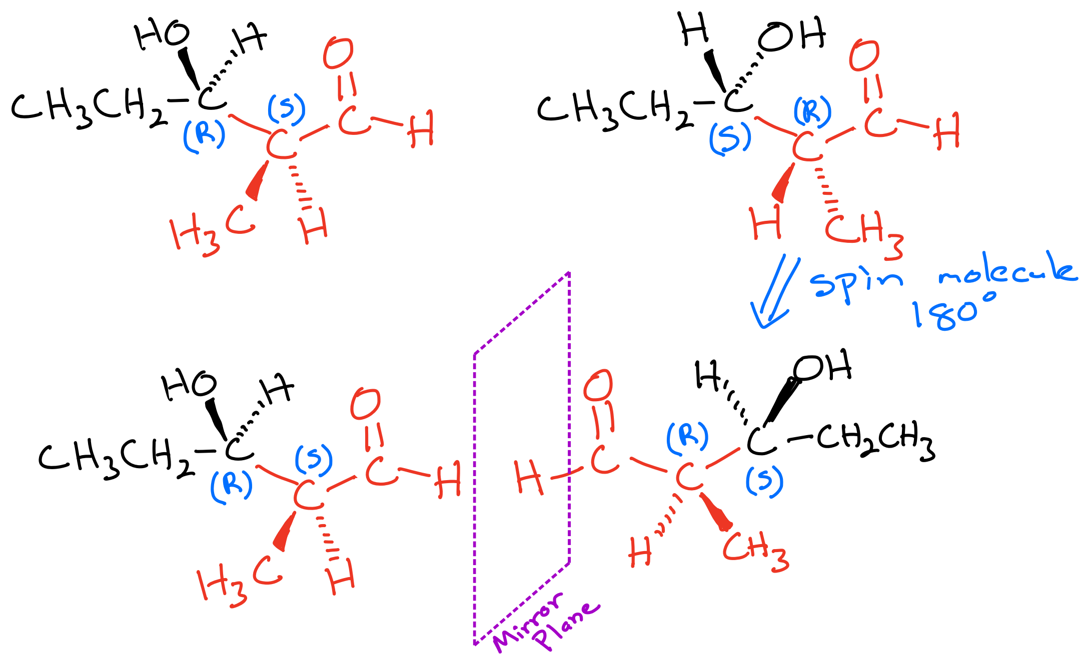
This side favored at equilibrium ⇒ There will be excess aldehyde for the enolate to react with

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

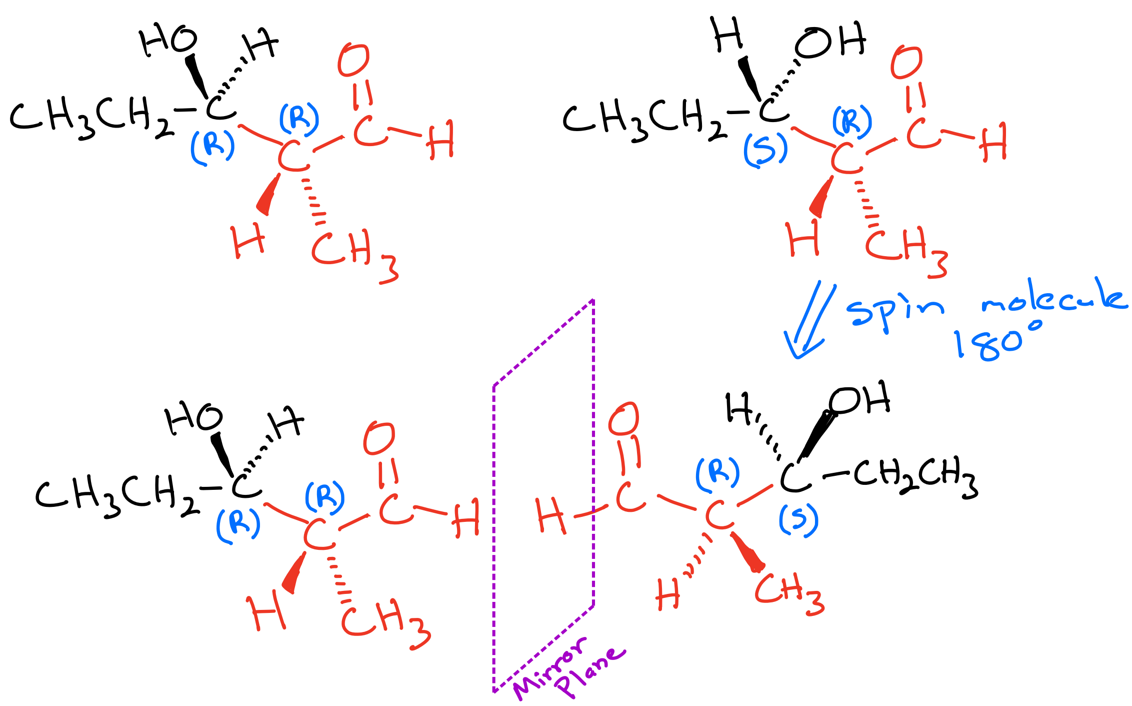
3) The aldol reaction is favorable for aldehydes but NOT for ketones

4) The reaction can make two new chiral centers

Enantiomers or Diastereomers?

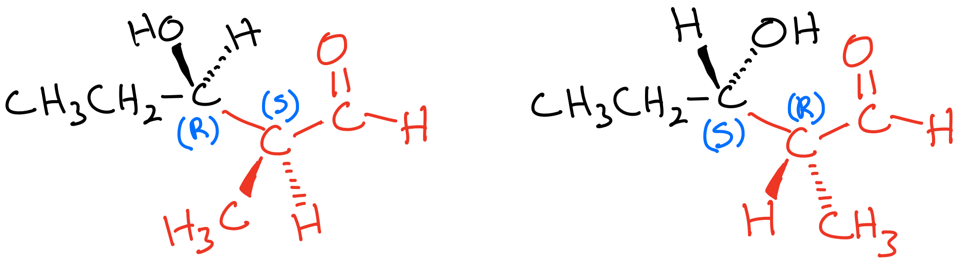


Enantiomers (Section 3.2) Stereoisomers that are nonsuperposable mirror images of each other; refers to a relationship between pairs of objects.

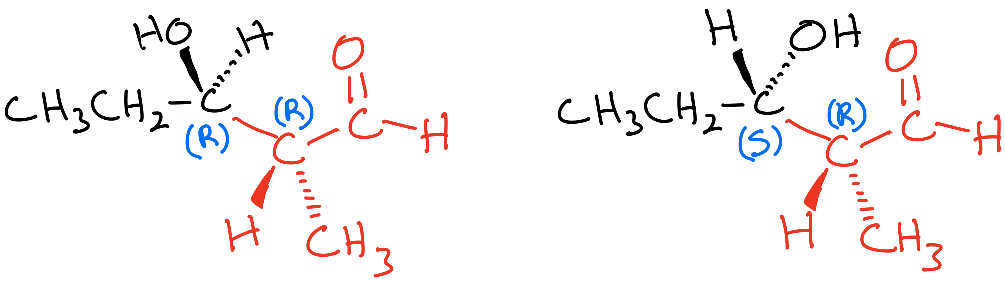


Diastereomers (Section 3.4A) Stereoisomers that are not mirror images of each other; refers to relationships among two or more objects.

Which pair of molecules could be a racemic mixture?

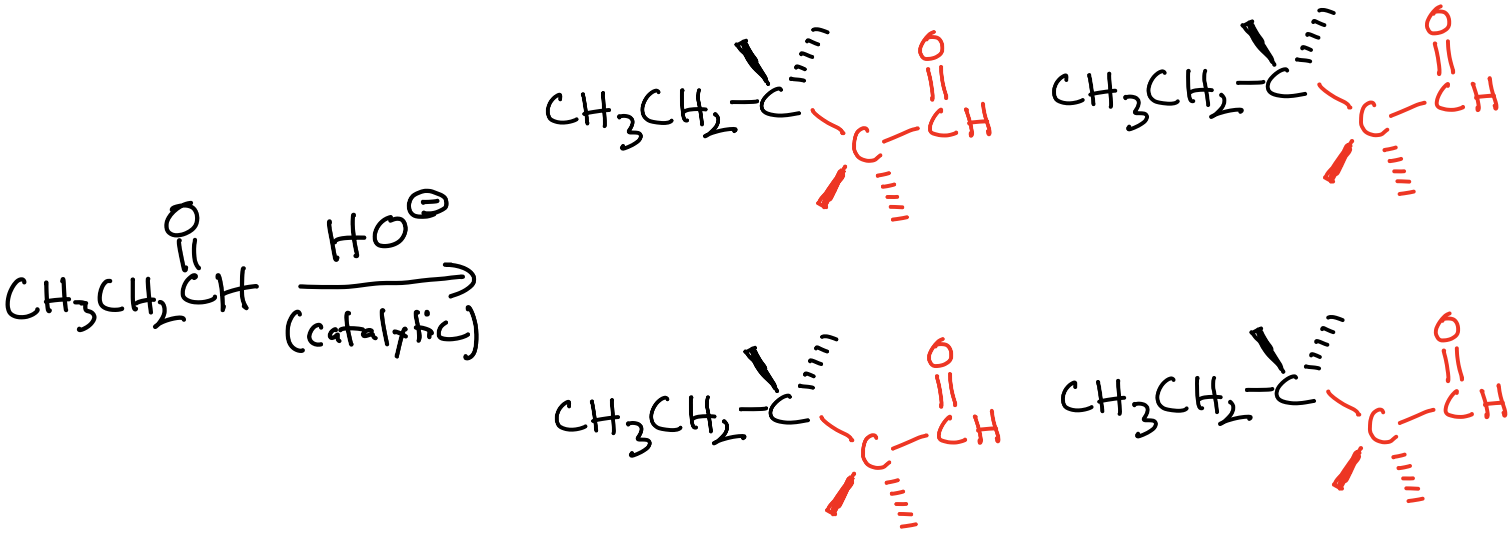


or



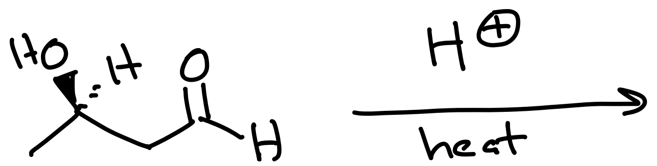
Racemic mixture (Section 3.7C) A mixture of equal amounts of two enantiomers.

Aldol Reaction: 2 new chiral centers



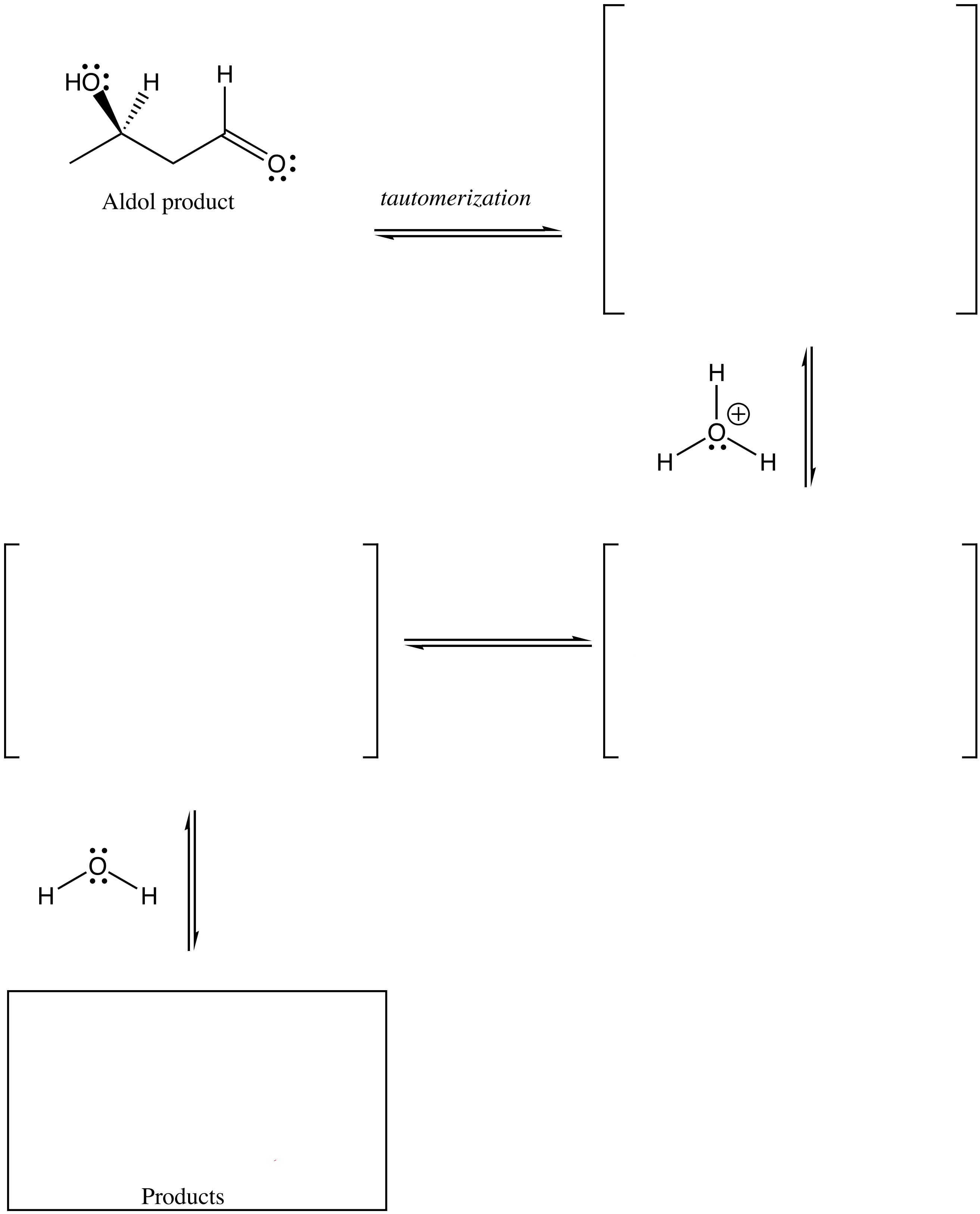
Racemic

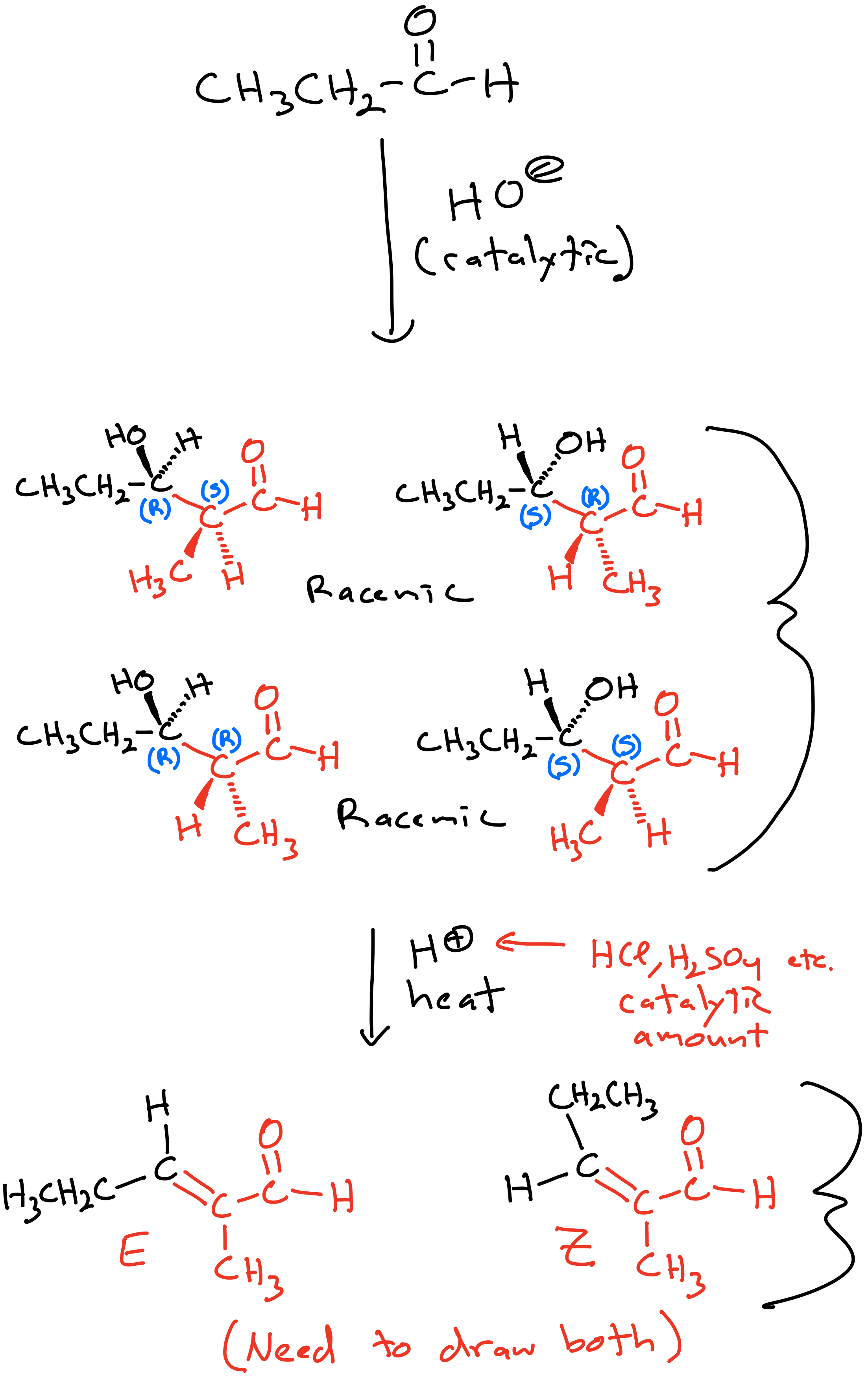
In mild acid with some heating, the aldol product will dehydrate to give an α,β-unsaturated aldehyde.

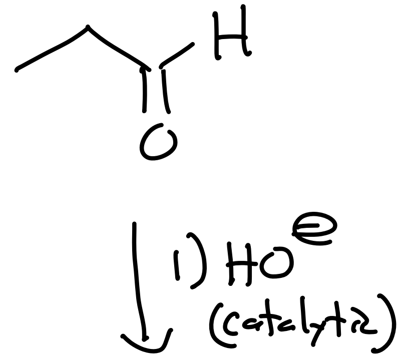


Note: The following mechanism is NOT the simplest you might think of, but it is the one with the lowest energy intermediates (no carbocations, etc.) so this is the correct mechanism

Acid catalyzed dehydration




CH3CH2-C(=O)-H
HO⊖
(catalytic)
(R) (S) (S) (R)
Racemic
(R) (R) (S) (S)
Racemic
H⊕
heat
HCl, H2SO4 etc.
catalytic
amount
E
Z
(Need to draw both)

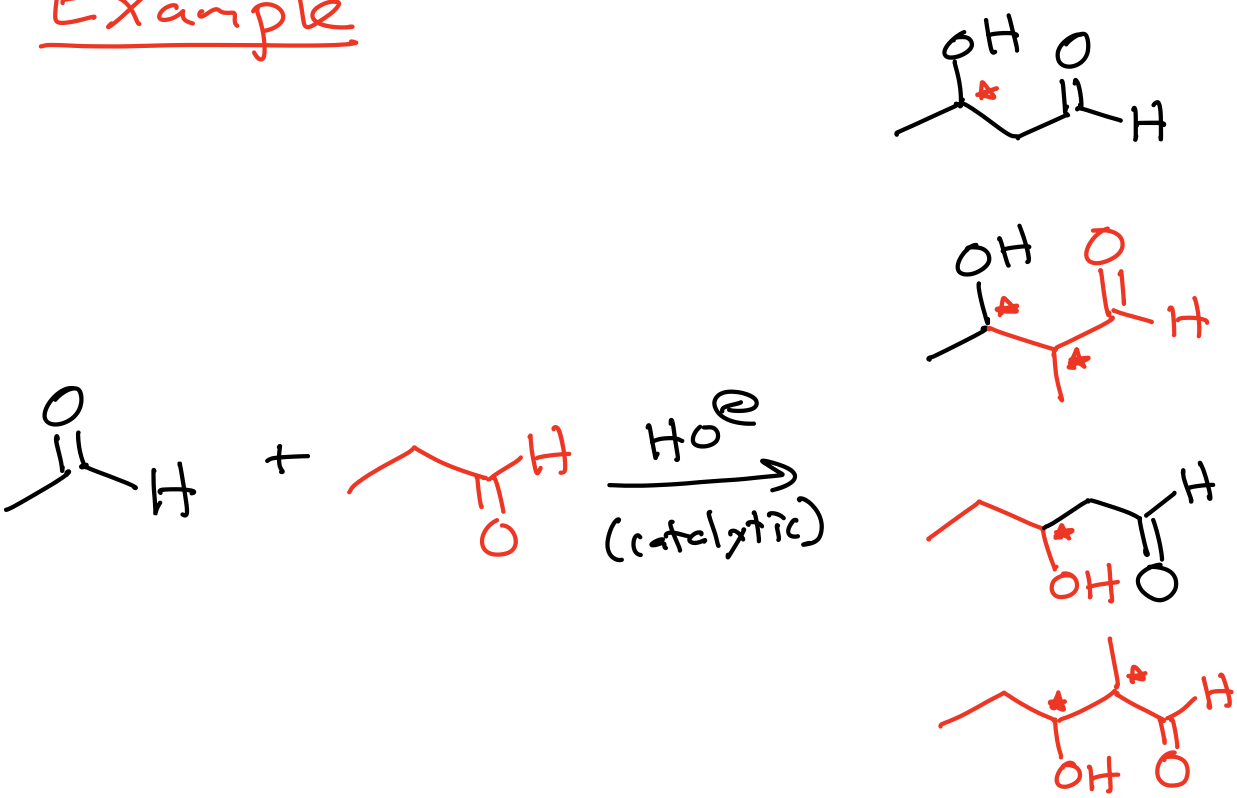

H
O
1) HO⊖
(catalytic)

→ 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

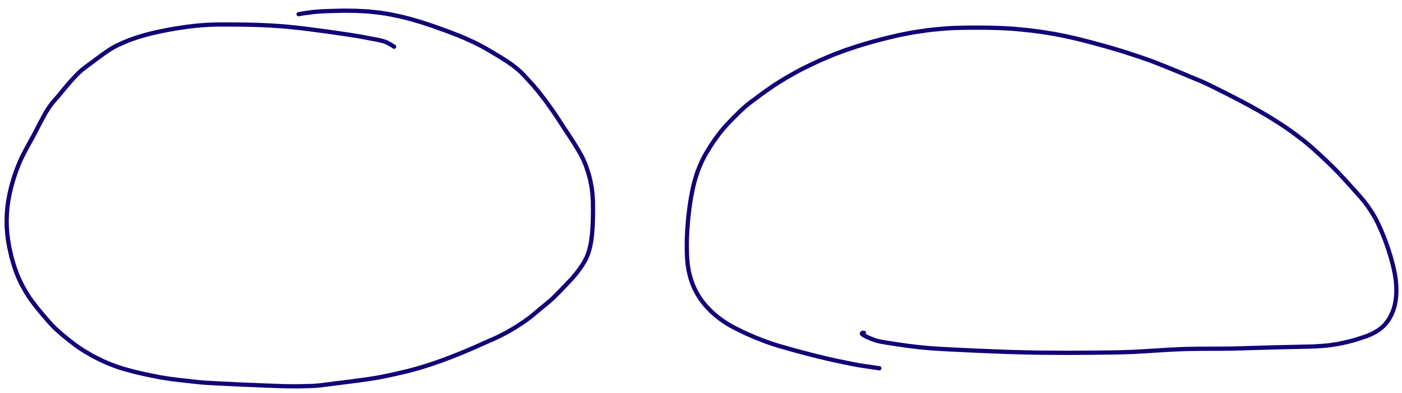


2 stereoisomers

4 stereoisomers

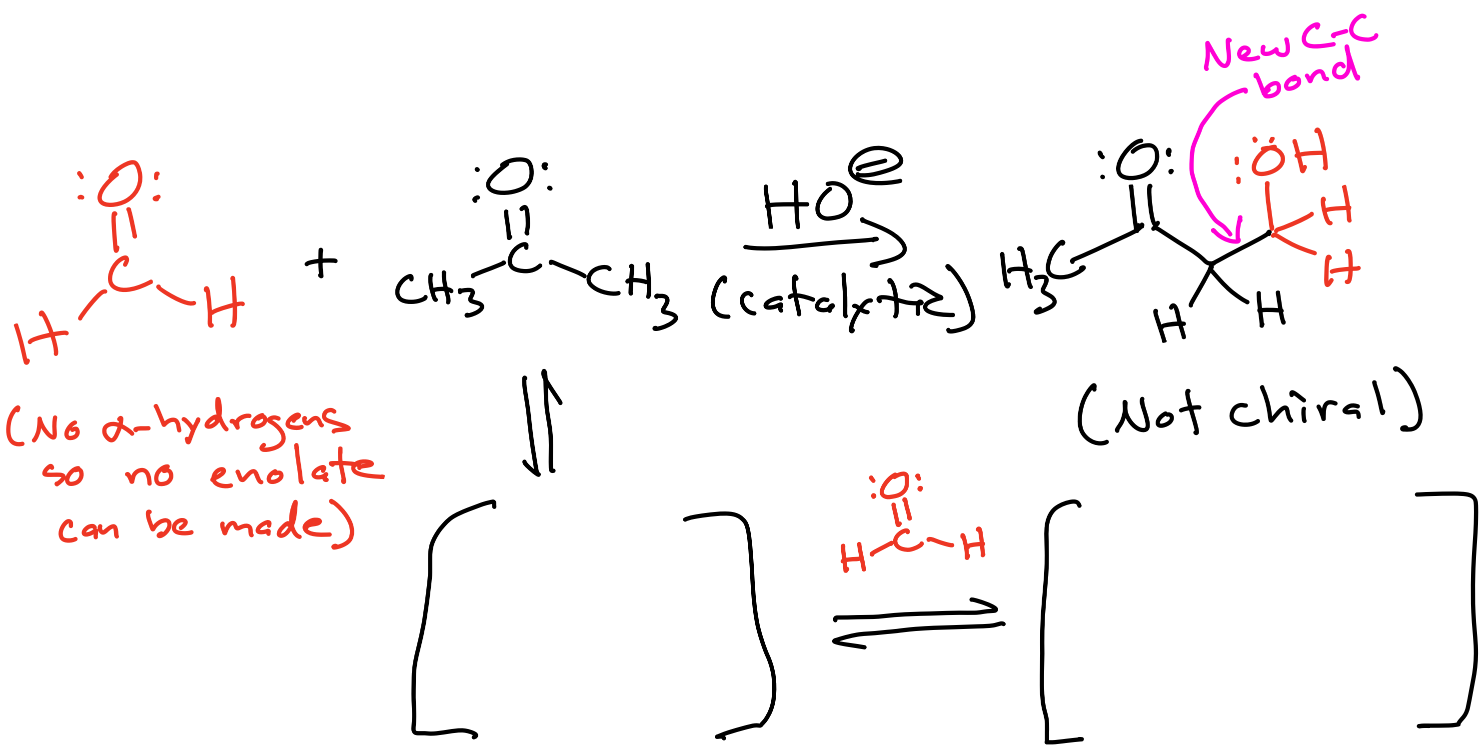
2 stereoisomers

4 stereoisomers

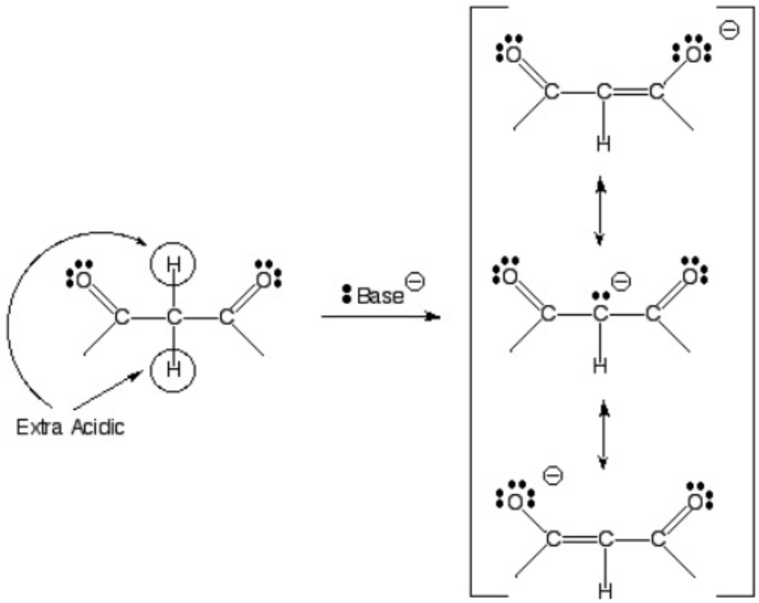


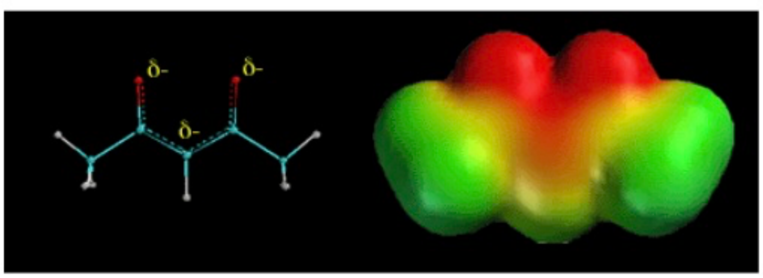
Key Idea ⇒

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



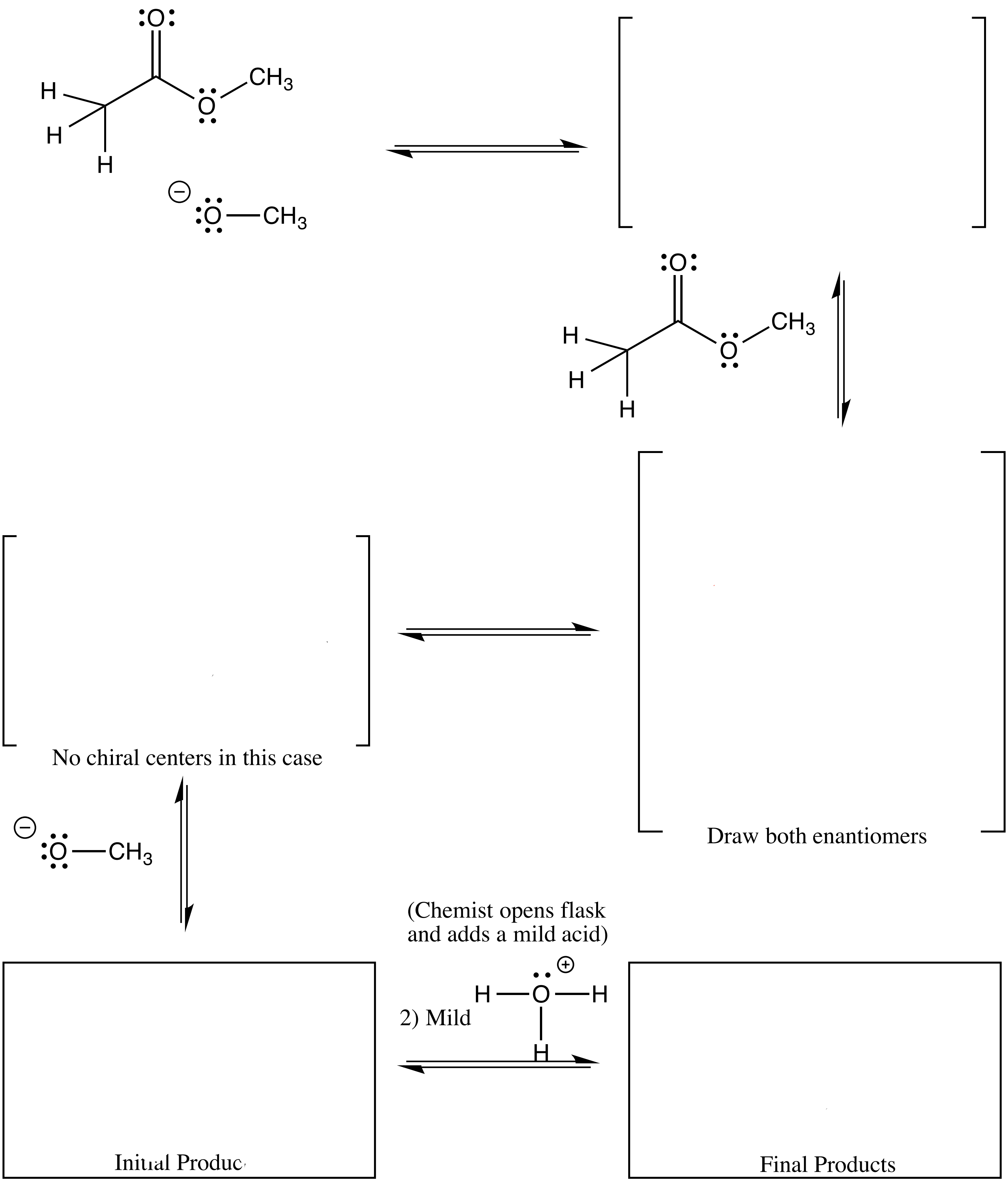
Beta-dicarbonyls have alpha-hydrogens that are extra acidic





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



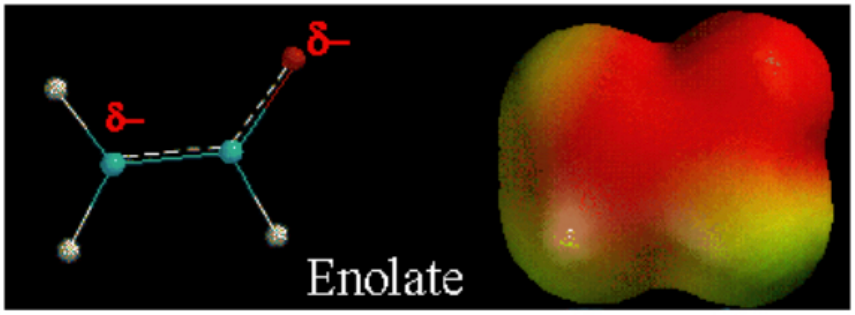
KRE →

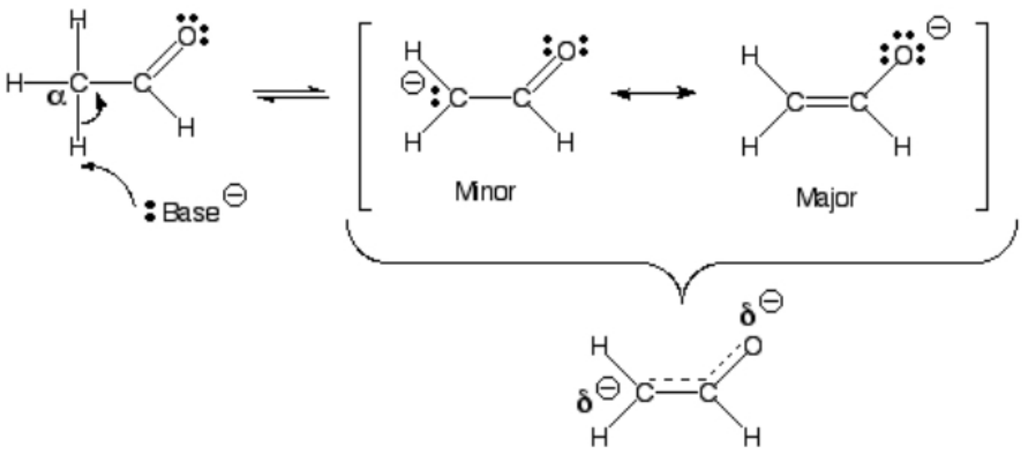
Before we add acid → the last step drives the reaction because we make a relatively stable anion.

Balanced Equation for the Overall Process

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

Enolates as nucleophiles



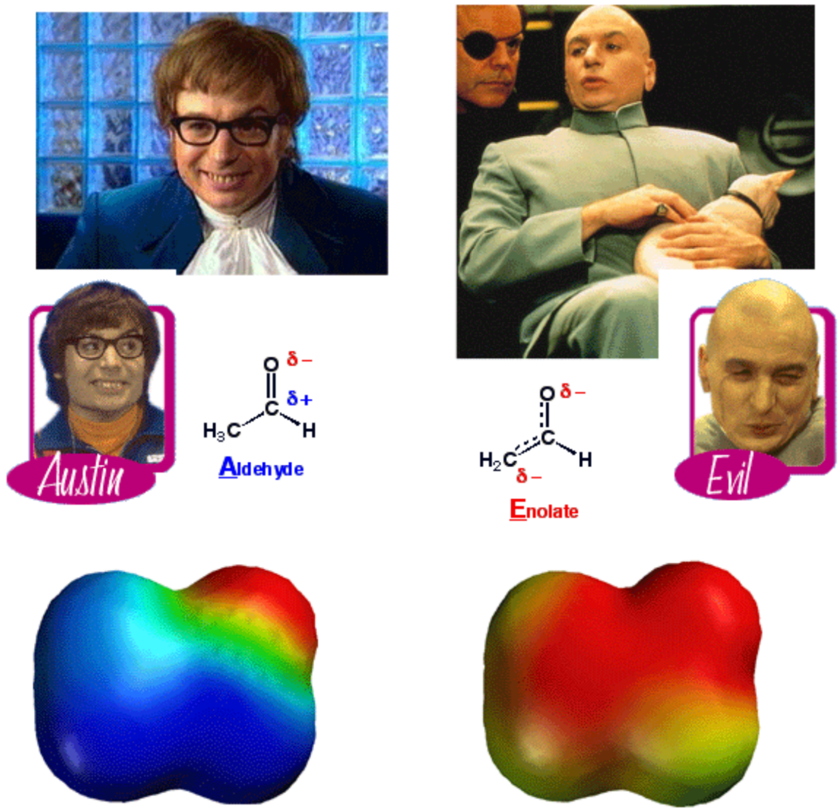


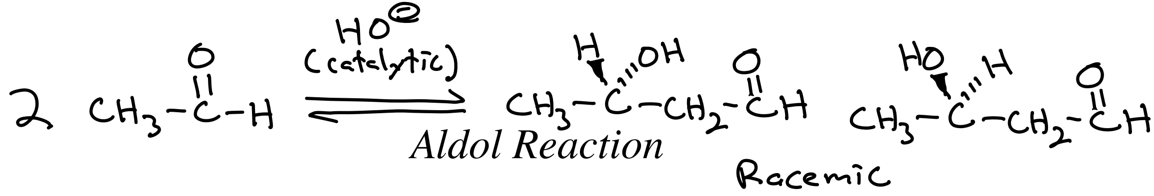
A) Enolates are resonance stabilized, with a partial negative charge on carbon and oxygen.

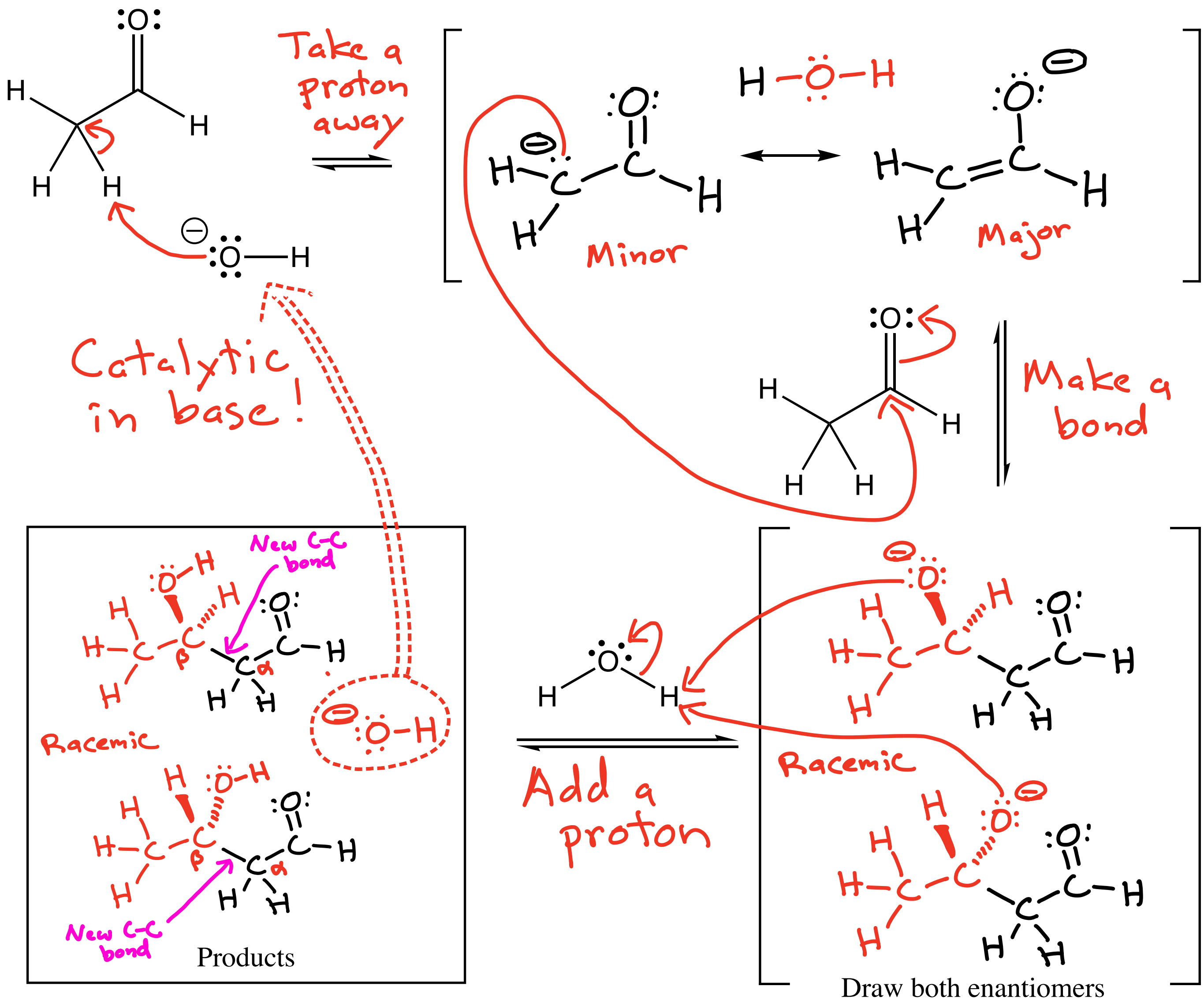
B) Enolates are nucleophiles, so they could react at either the carbon atom or oxygen atom. The partial negative charges give them the **opportunity** to react at either the carbon or oxygen.

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



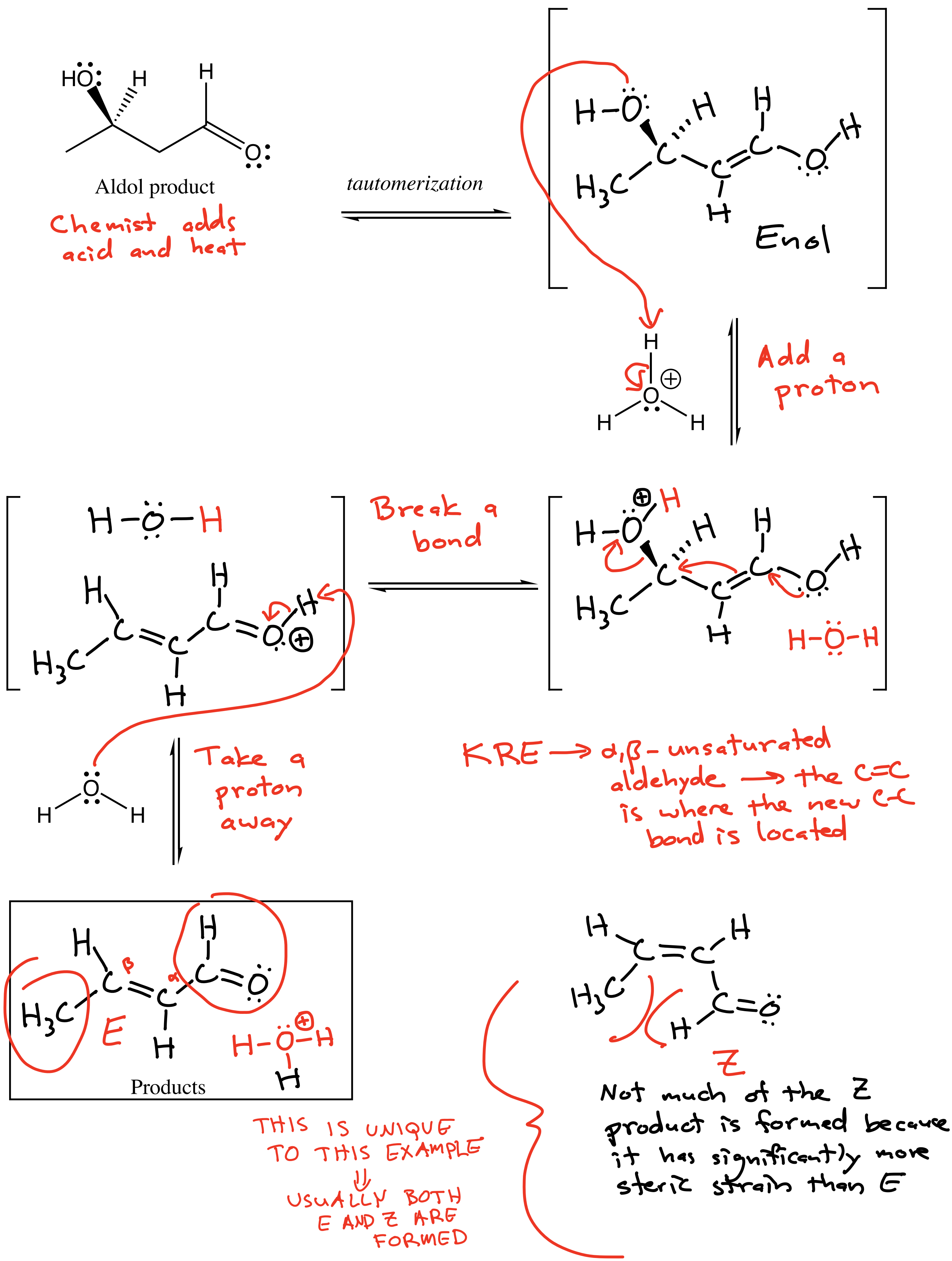




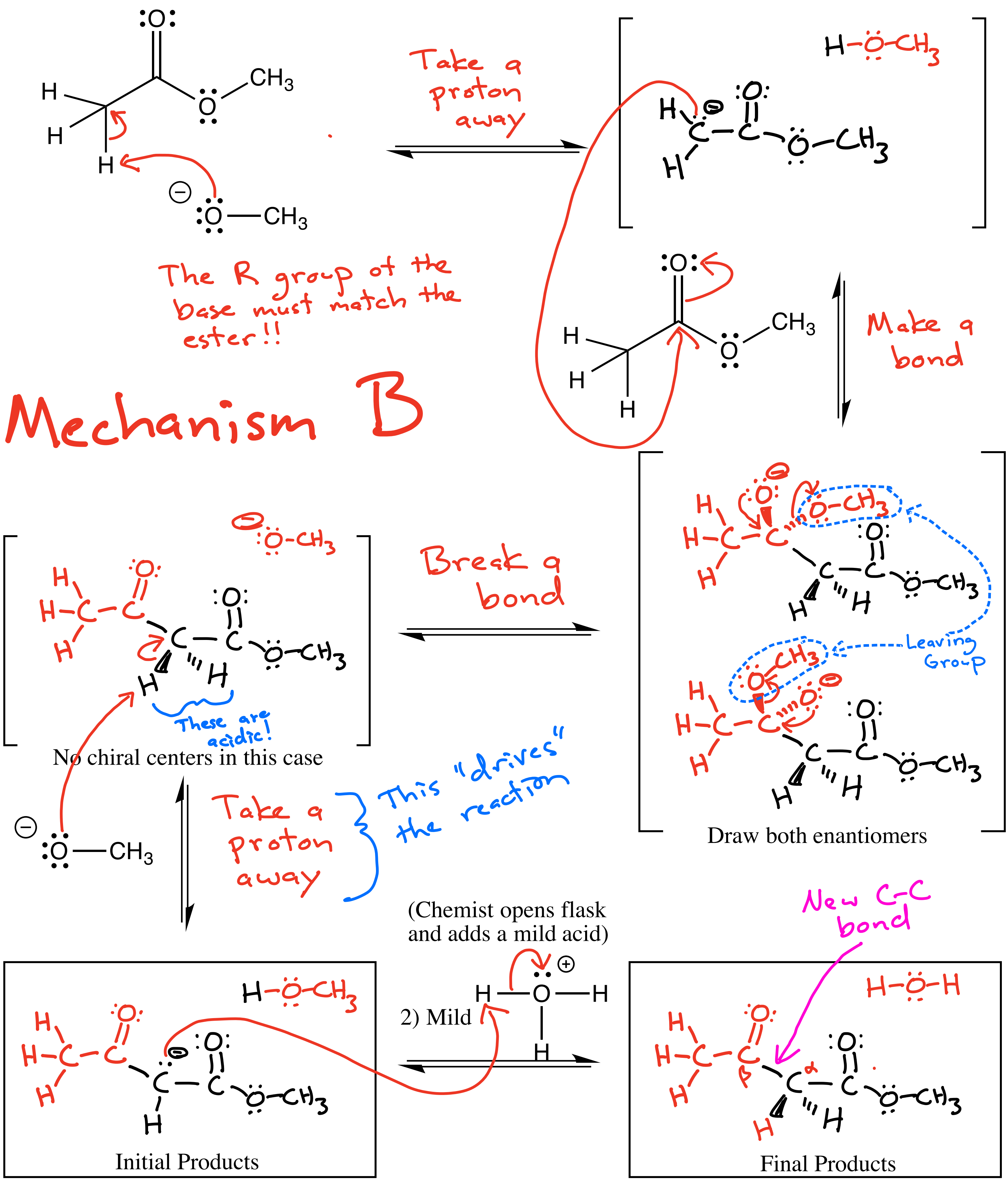
KRE → β-hydroxy aldehyde with a new C–C bond between the aldehyde α and β carbons

Mechanism A

Acid catalyzed dehydration



Claisen Condensation → "Aldol with Esters"



This is a much more stable anion compared to ⊖OCH_3, 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

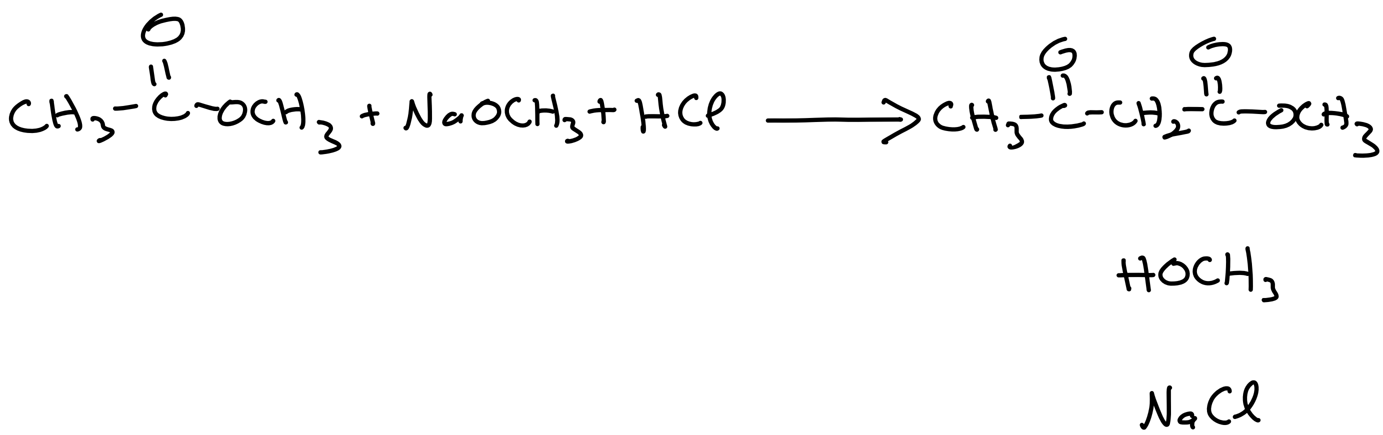
$$2\,CH_3-\overset{\overset{O}{\|}}{C}-OCH_3 + NaOCH_3 + HCl \longrightarrow CH_3-\overset{\overset{O}{\|}}{C}-CH_2-\overset{\overset{O}{\|}}{C}-OCH_3$$

$$2HOCH_3$$

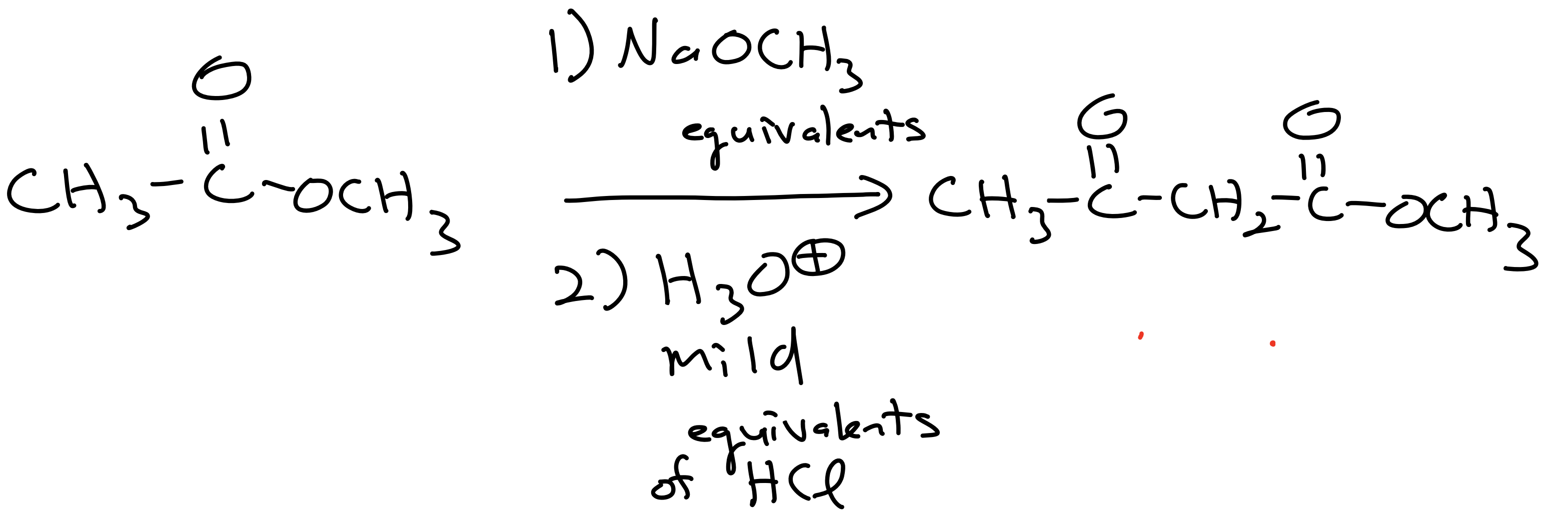
$$NaCl$$

This is the balanced equation that is explained by the mechanism

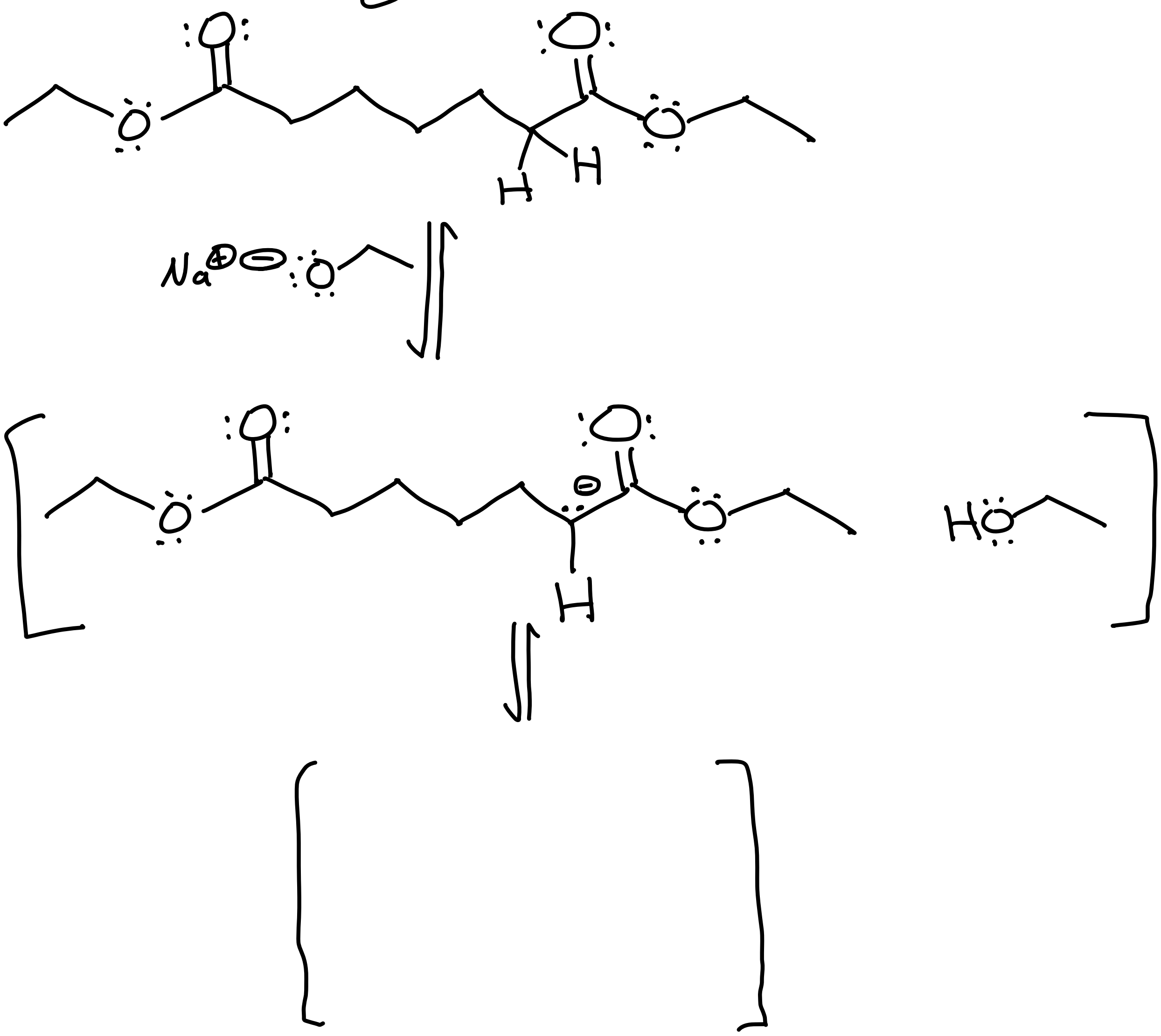
With the balanced equation in hand we can set up a reaction properly in the lab because we know how much of each reactant is needed → For this we use the notation of "equivalents"

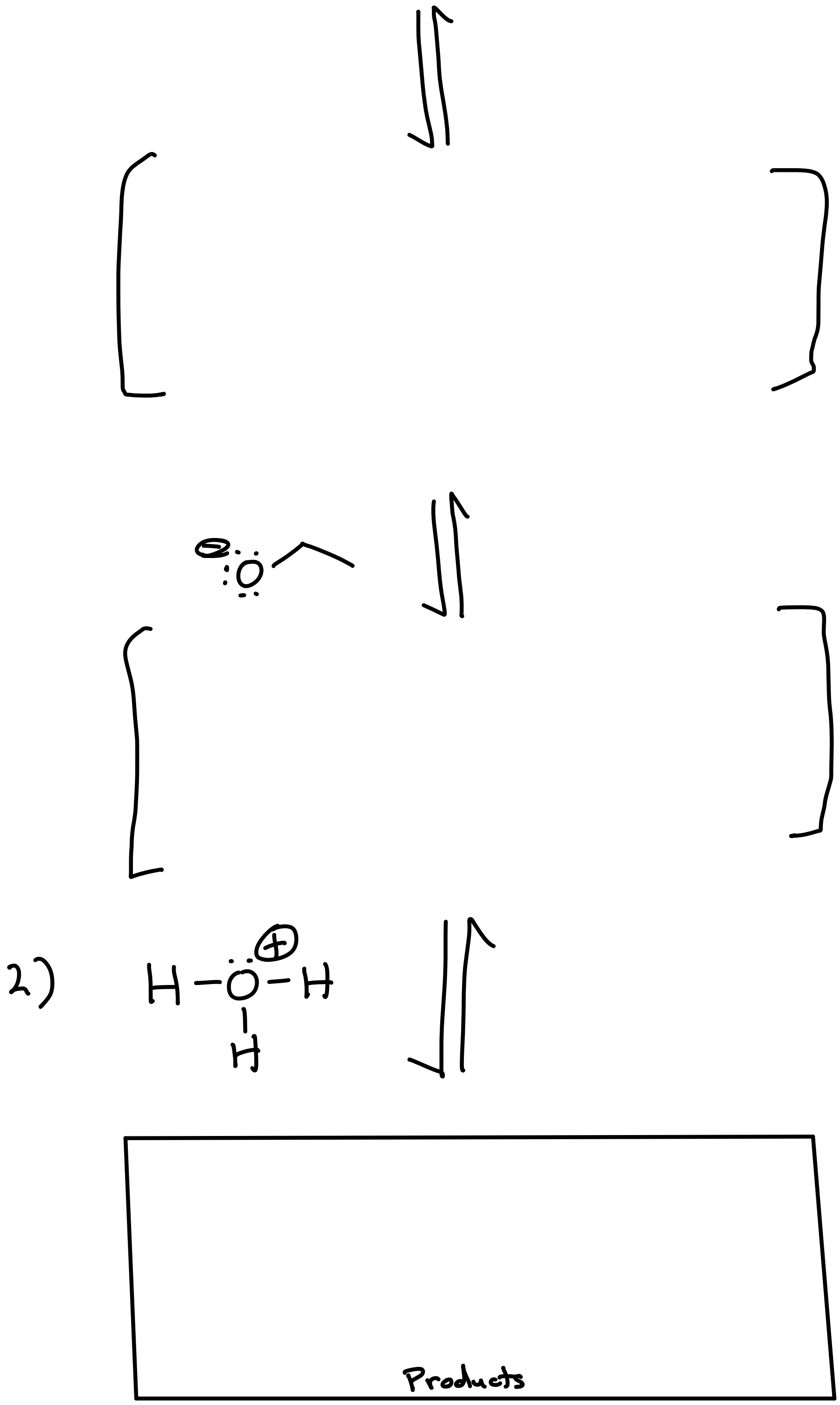


Example of using equivalents

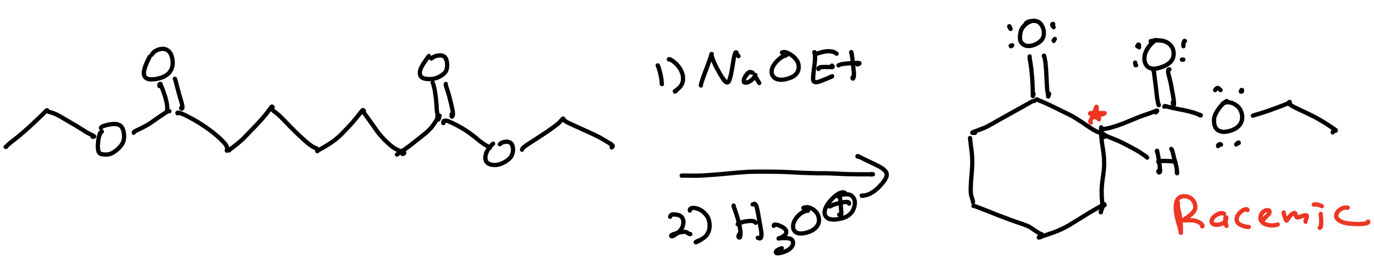


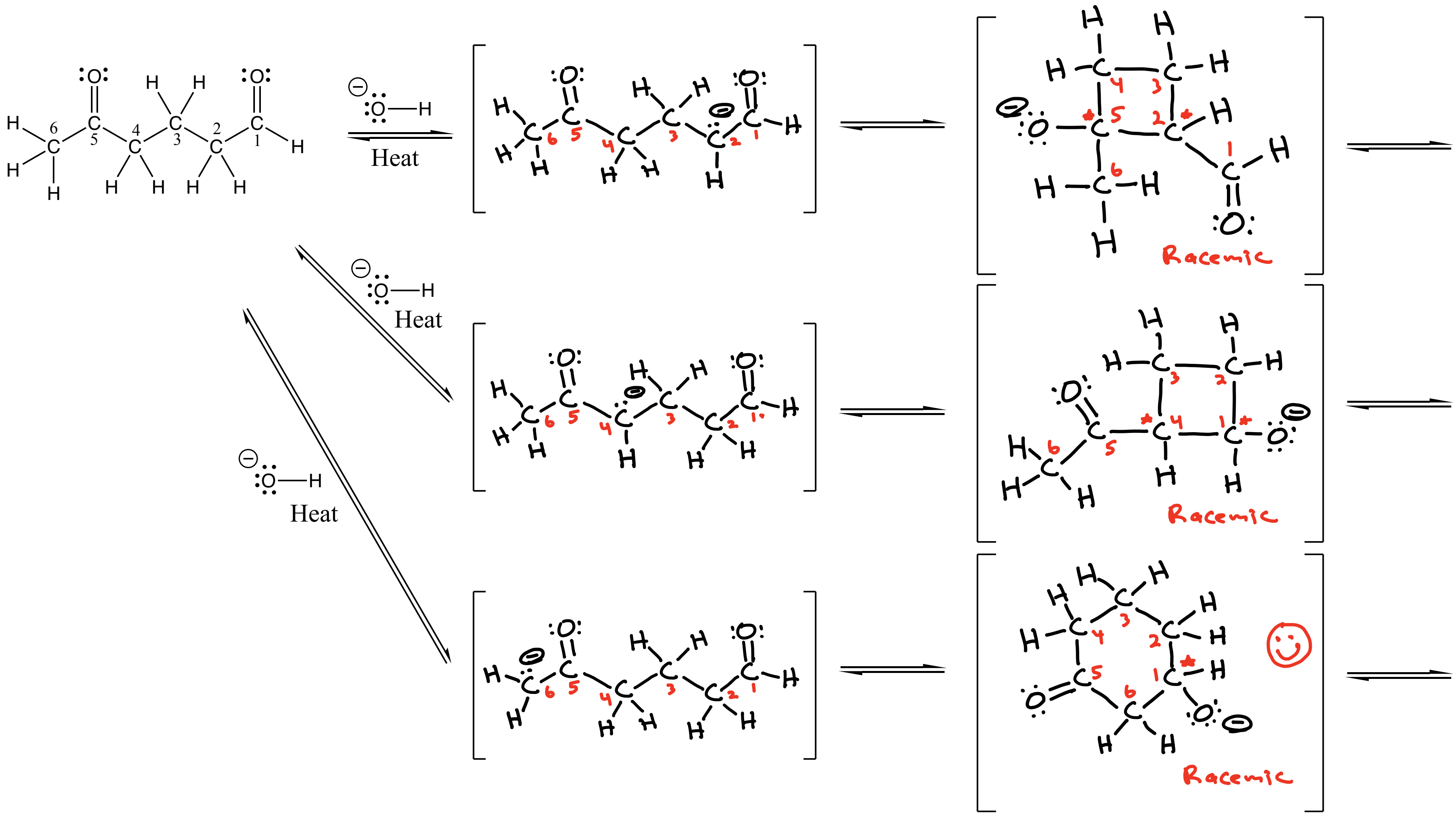
The Dieckmann Condensation → Using a Claisen to make a ring.





Overall Process



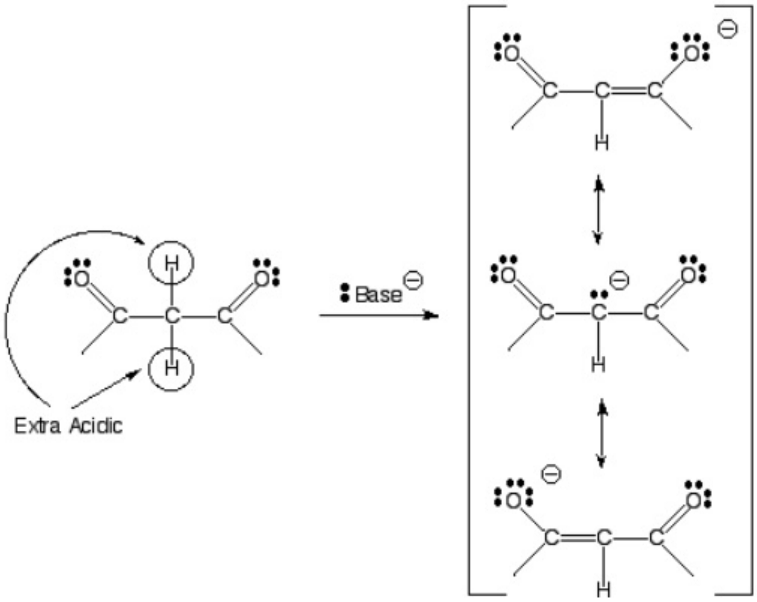


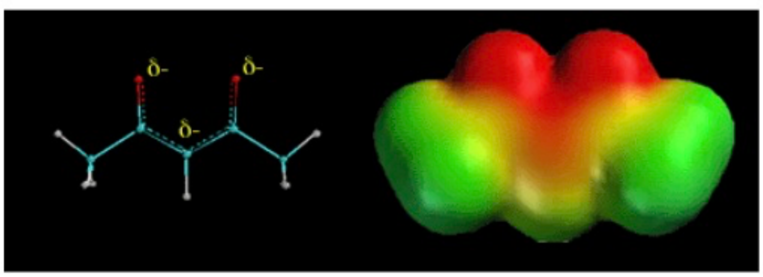
Dehydration

Predominant Aldol Product

Final Dehydrated Aldol Product

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