

Gleevec – Novartis (\$4.65 Billion in sales in 2015). A kinase inhibitor that is a first of its kind pill capable of treating certain blood cancers with only limited side effects. It was designed to combat leukemias with the relatively common “Philadelphia chromosome” (BCR-ABL kinase gene fusion)

Weaker bases are favored at equilibrium

Compound	Chemical Structure	pK _a
	H-Cl	-7
Carboxylic acids*	$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{OH}$	3-5
β-Dicarbonyls*	$\text{RC}-\overset{\text{O}}{\parallel}{\text{C}}-\text{CH}_2-\overset{\text{O}}{\parallel}{\text{C}}-\text{R}'$	10
β-Ketoesters*	$\text{RC}-\overset{\text{O}}{\parallel}{\text{C}}-\text{CH}_2-\overset{\text{O}}{\parallel}{\text{C}}-\text{OR}'$	11
β-Diesters*	$\text{ROC}-\overset{\text{O}}{\parallel}{\text{C}}-\text{CH}_2-\overset{\text{O}}{\parallel}{\text{C}}-\text{OR}'$	13
Water	HOH	15.7
Alcohols	RCH_2OH	15-19
Acid chlorides*	$\text{RCH}_2-\overset{\text{O}}{\parallel}{\text{C}}-\text{Cl}$	16
Aldehydes*	$\text{RCH}_2-\overset{\text{O}}{\parallel}{\text{C}}-\text{H}$	18-20
Ketones*	$\text{RCH}_2-\overset{\text{O}}{\parallel}{\text{C}}-\text{R}'$	18-20
Esters*	$\text{RCH}_2-\overset{\text{O}}{\parallel}{\text{C}}-\text{OR}'$	23-25
Terminal alkynes	$\text{RC}\equiv\text{C}-\text{H}$	25
LDA	$\text{H}-\text{N}(\text{i}-\text{C}_3\text{H}_7)_2$	40
Terminal alkenes	$\text{R}_2\text{C}=\underset{\text{H}}{\text{C}}-\text{H}$	44
Alkanes	$\text{CH}_3\text{CH}_2-\text{H}$	51

Strongest Acid
(Weakest conjugate base)



Weakest Acid
(Strongest conjugate base)

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

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

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

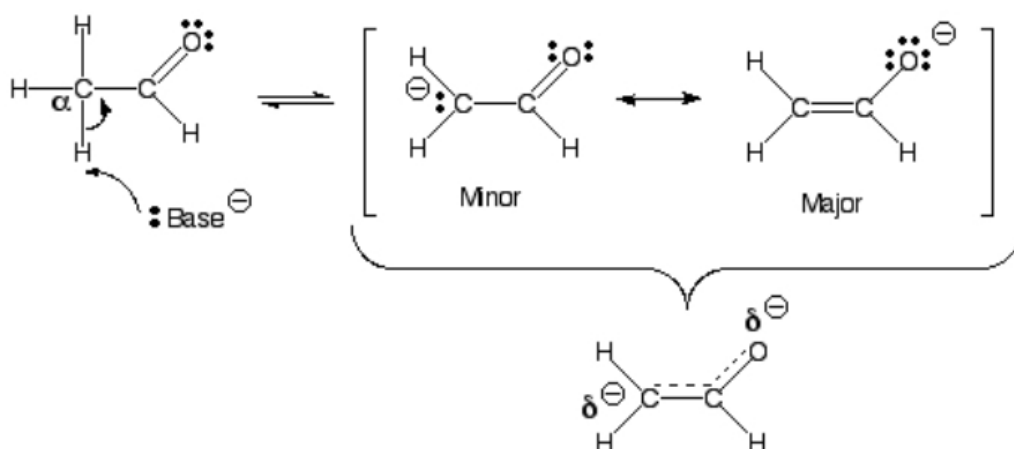
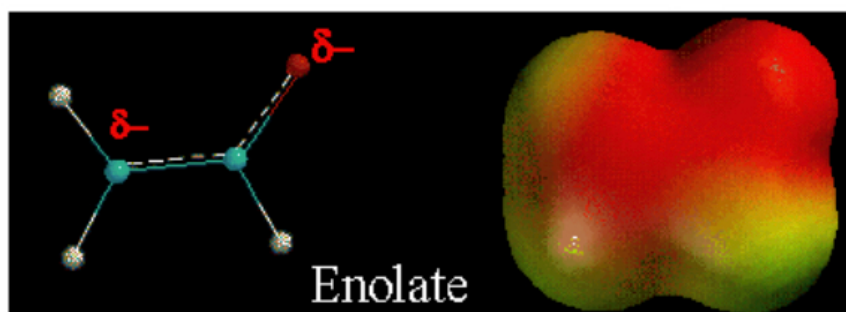
D) Check the pK's of the conjugate acid of the bases on either side of the equation. Lower pK_a value corresponds to stronger acid of the conjugate acid, and thus weaker conjugate base. The base with a stronger conjugate acid (lower pK_a value) will be the weaker base and will be favored at equilibrium.

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

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

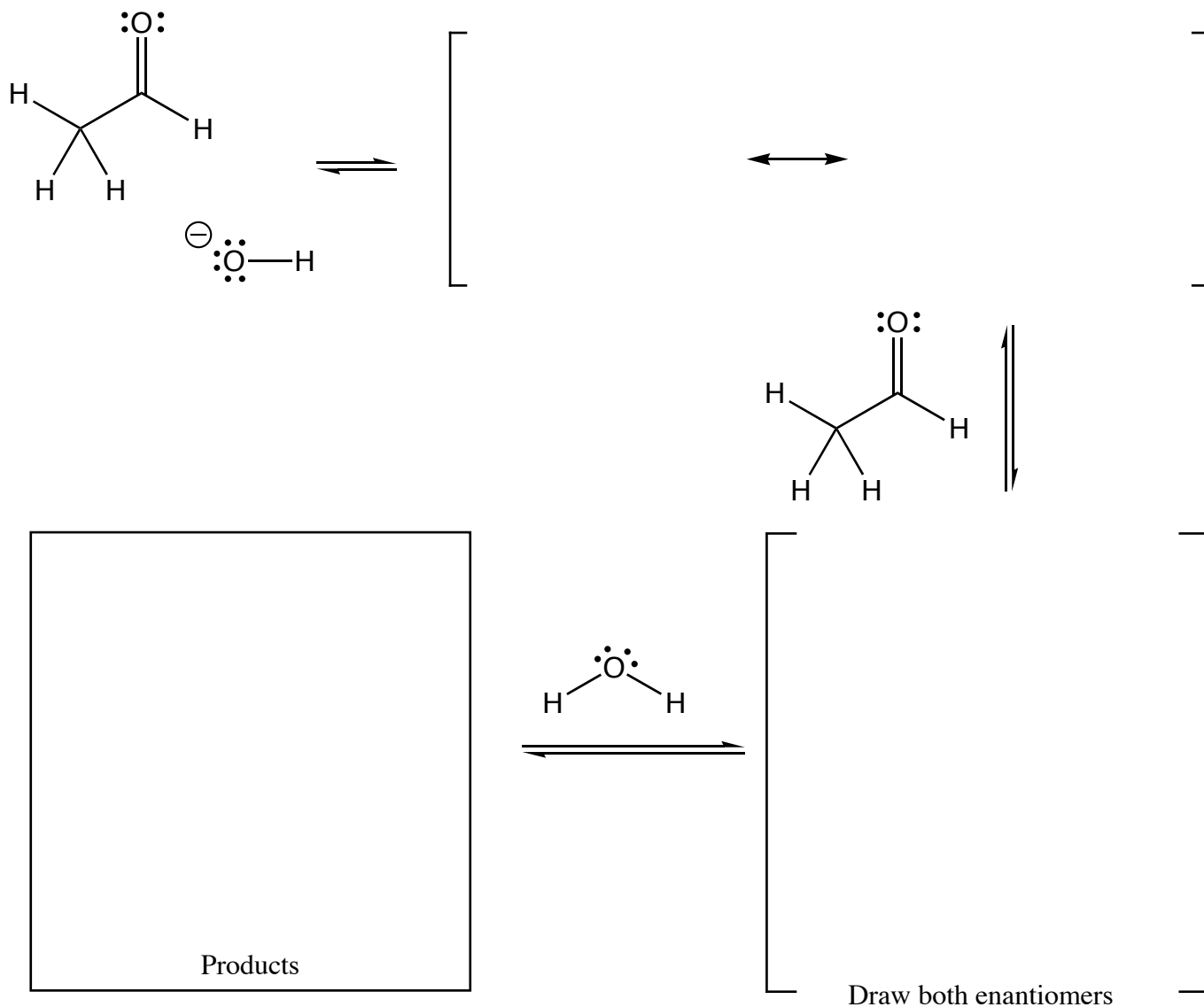
*These have resonance stabilized anions

Enolates as nucleophiles

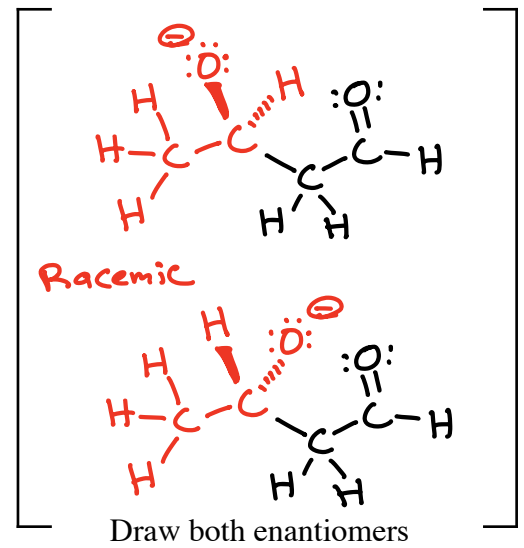
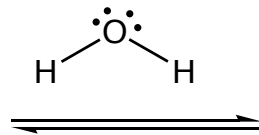
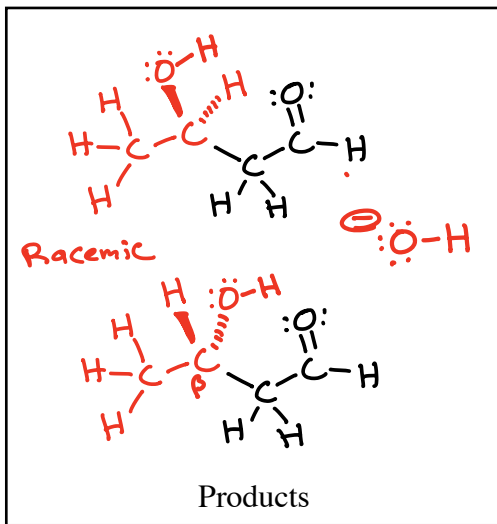
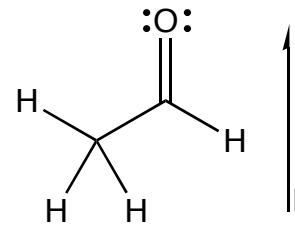
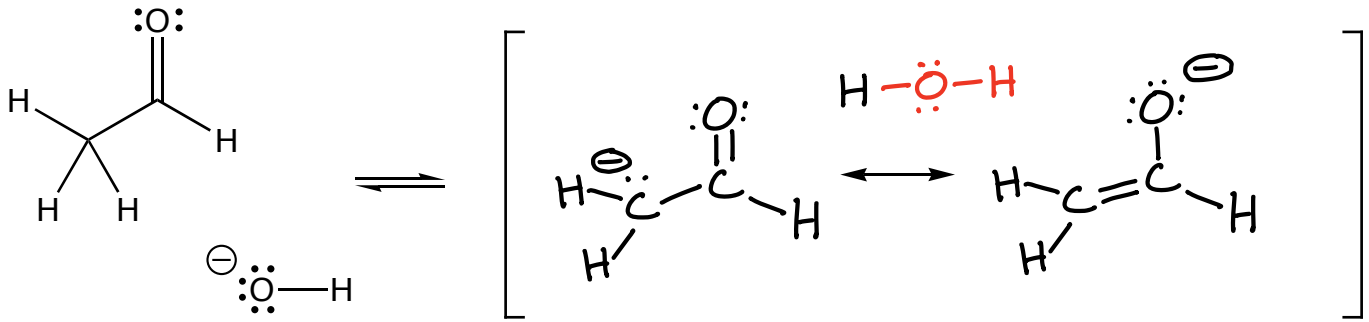
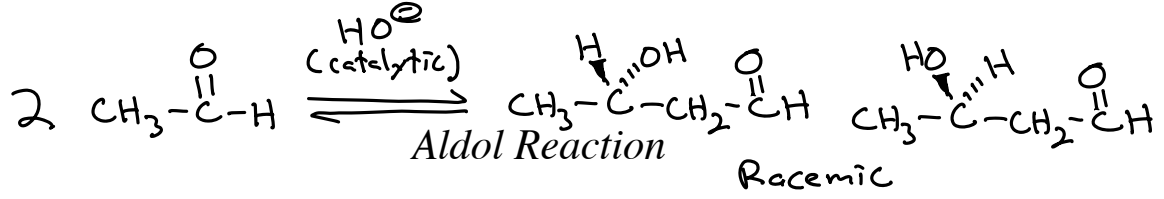


- A) Enolates are resonance stabilized, with a partial negative charge on carbon and oxygen.
- B) Enolates are nucleophiles, so they could react at either the carbon atom or oxygen atom. The partial negative charges give them the **opportunity** to react at either the carbon or oxygen.
- C) Reaction at the carbon atom gives the final product a 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.**

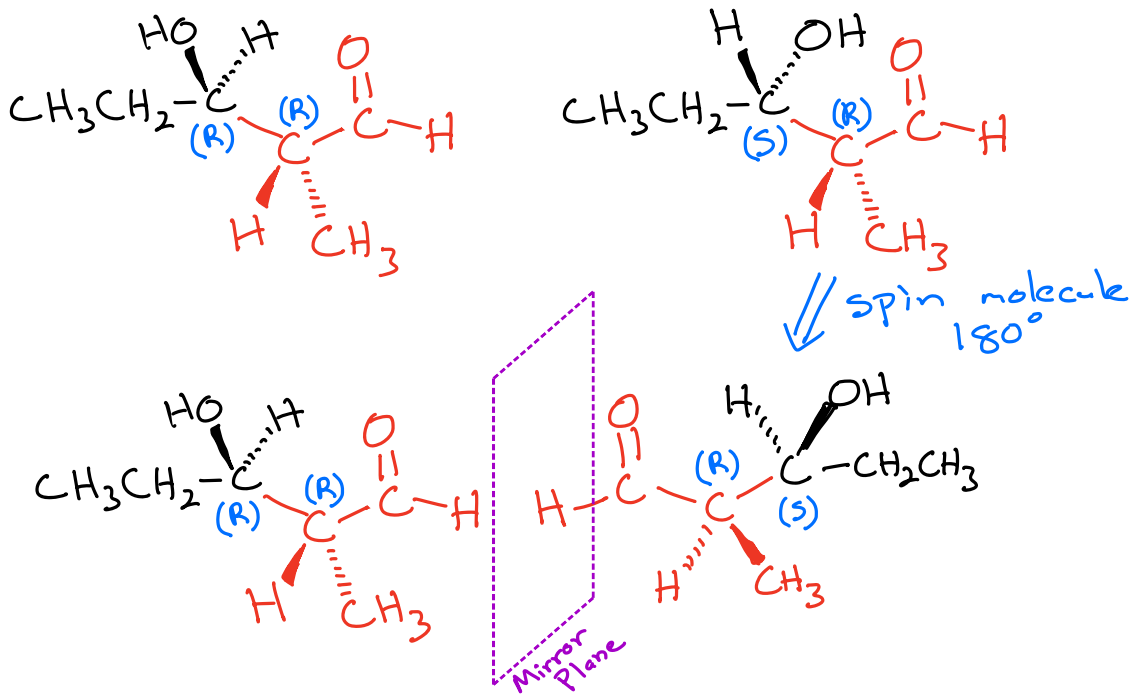
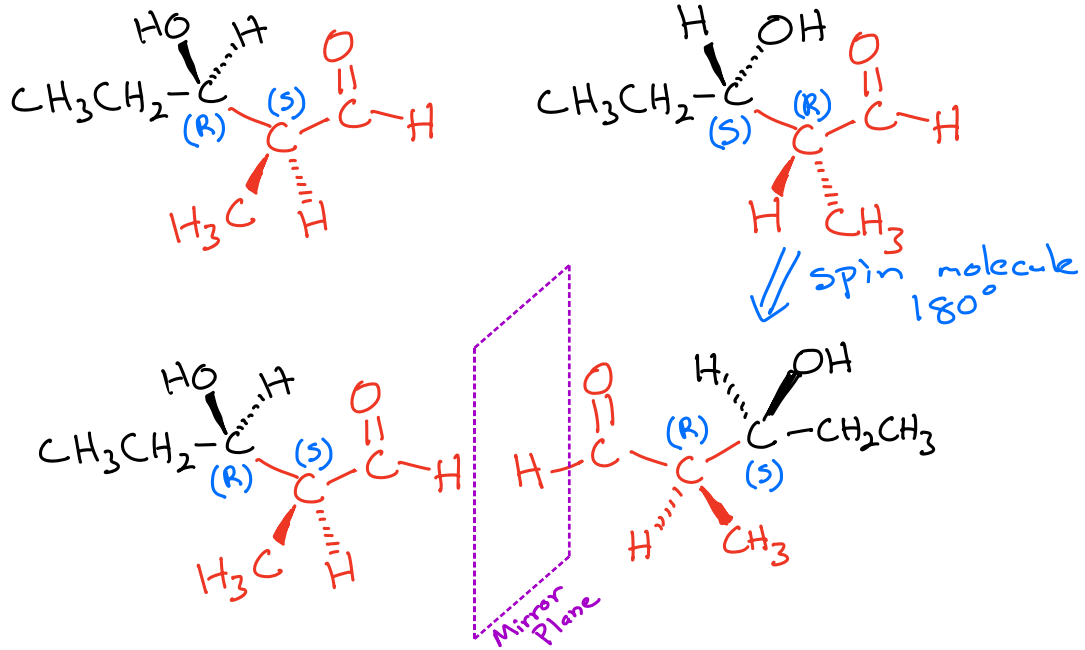
Aldol Reaction



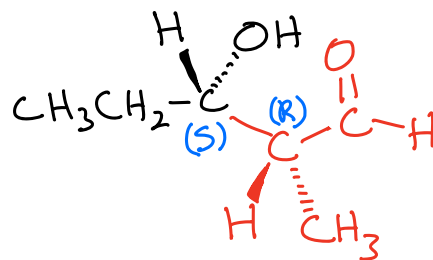
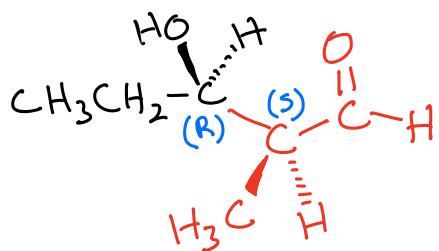
Draw both enantiomers



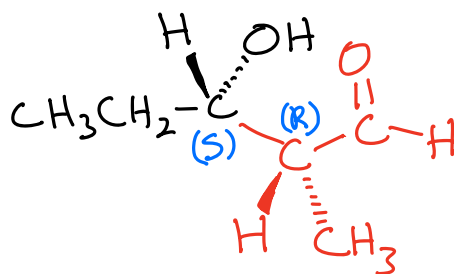
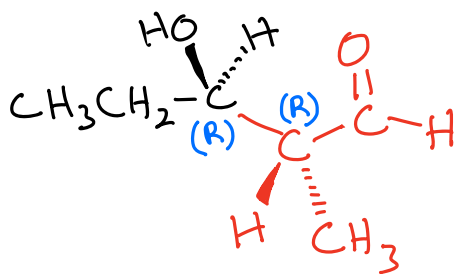
Enantiomers or Diastereomers?



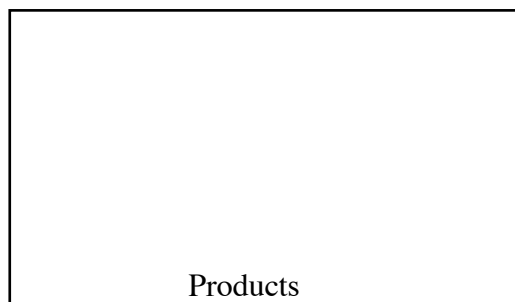
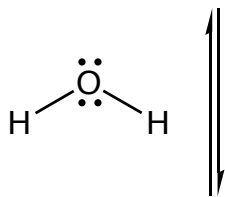
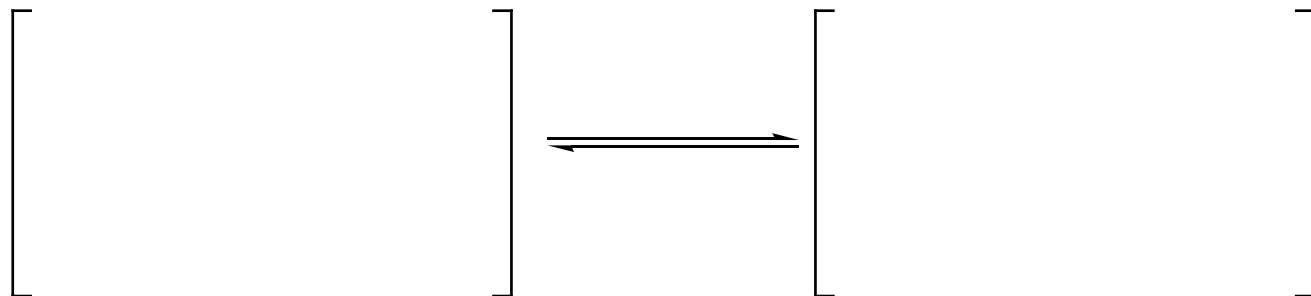
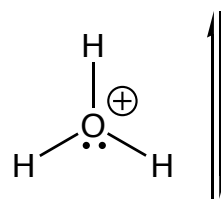
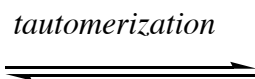
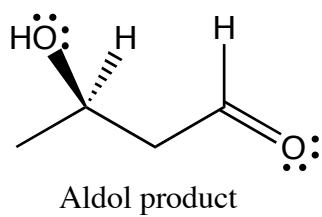
Which pair of molecules could be a racemic mixture?



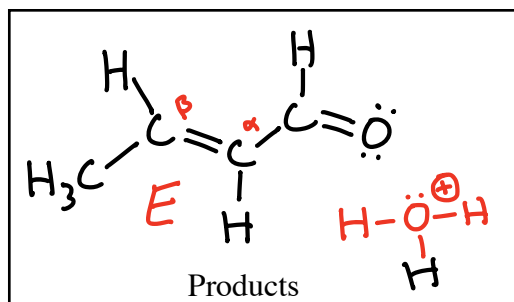
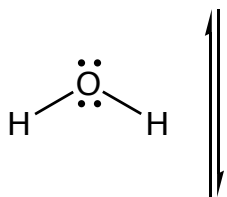
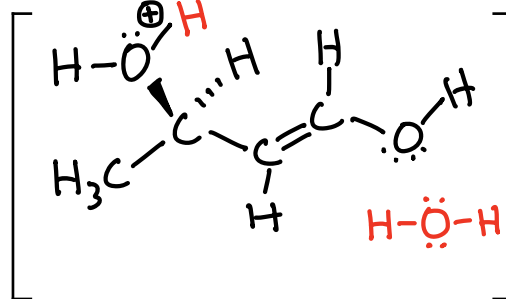
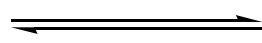
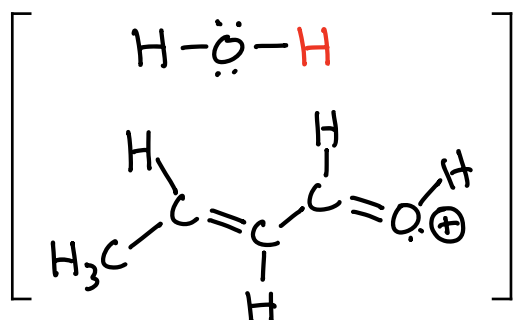
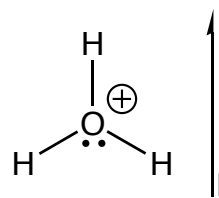
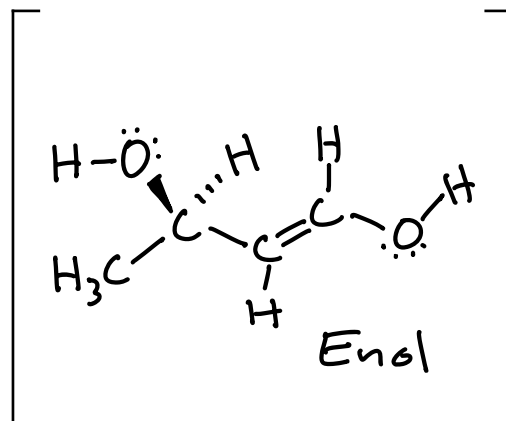
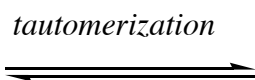
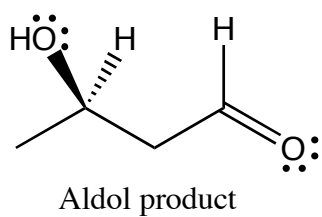
OR



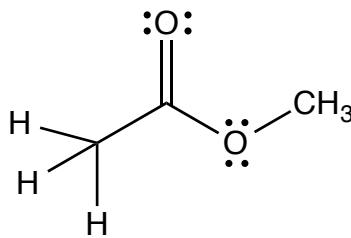
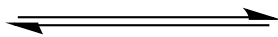
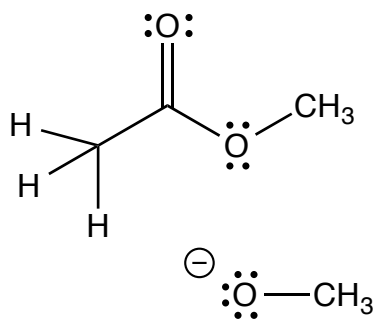
Acid catalyzed dehydration



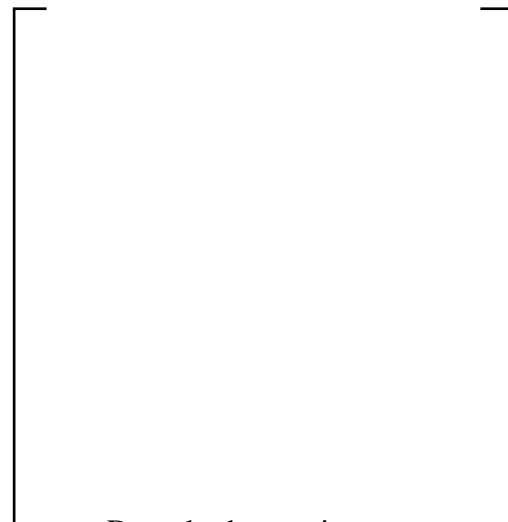
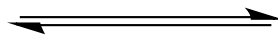
Acid catalyzed dehydration



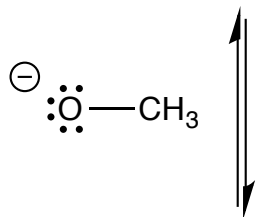
Claisen Condensation



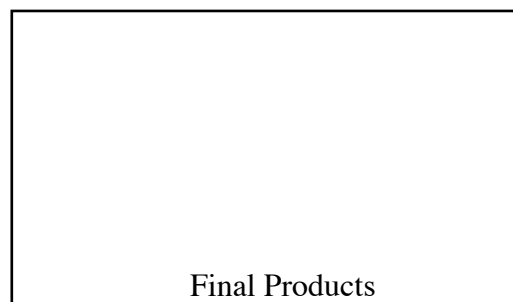
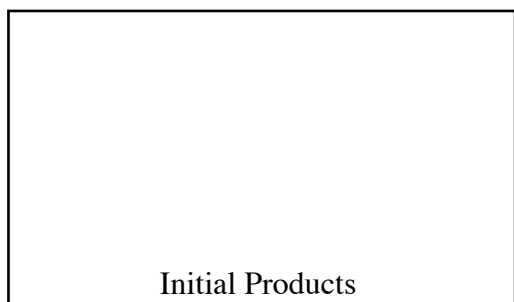
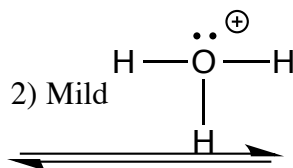
No chiral centers in this case



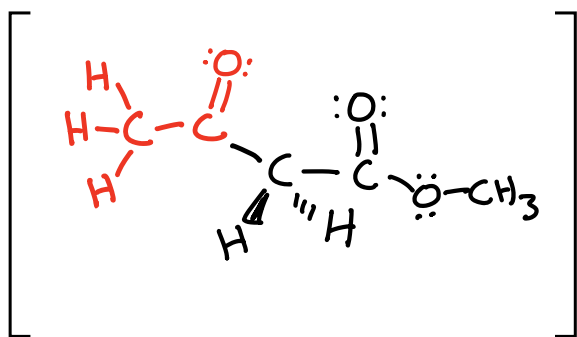
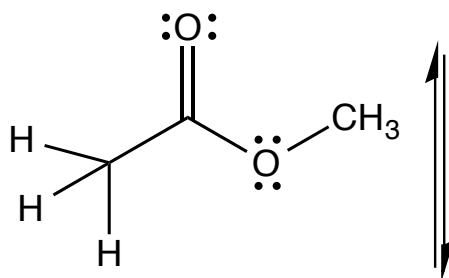
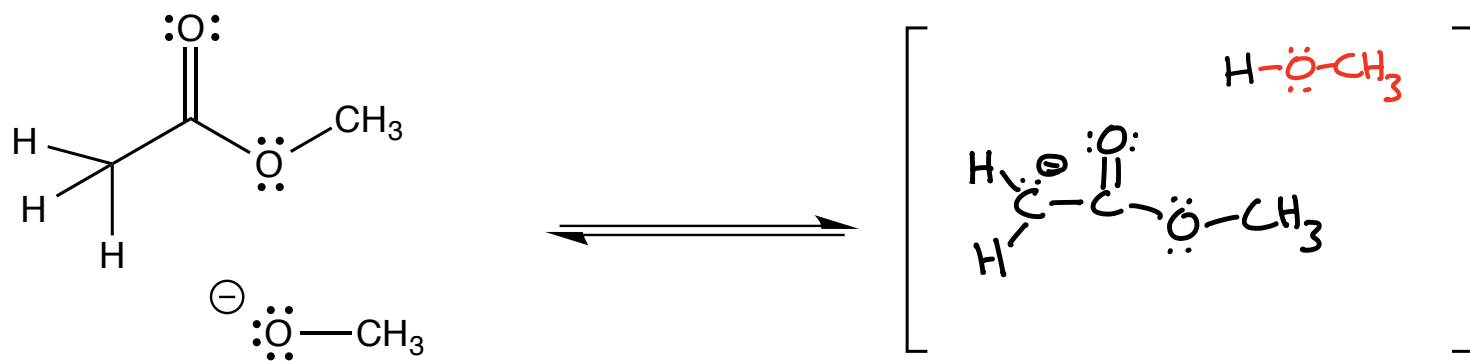
Draw both enantiomers



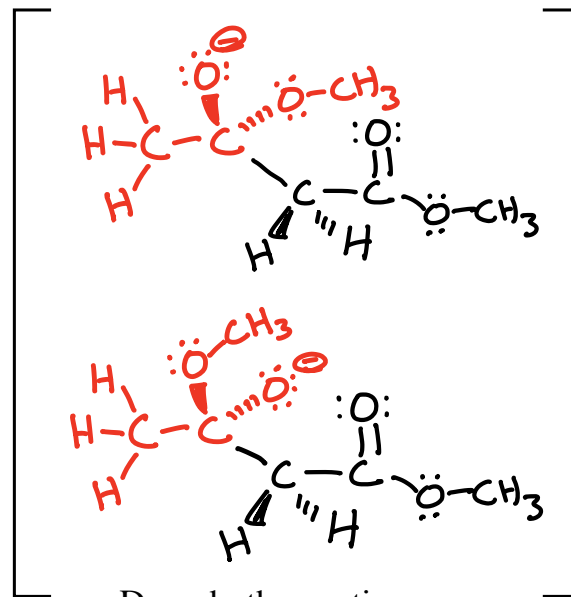
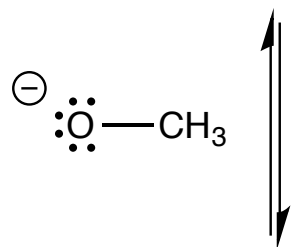
(Chemist opens flask and adds a mild acid)



Claisen Condensation

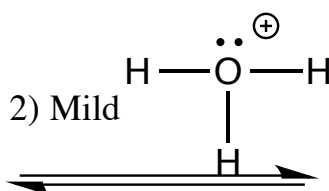


No chiral centers in this case

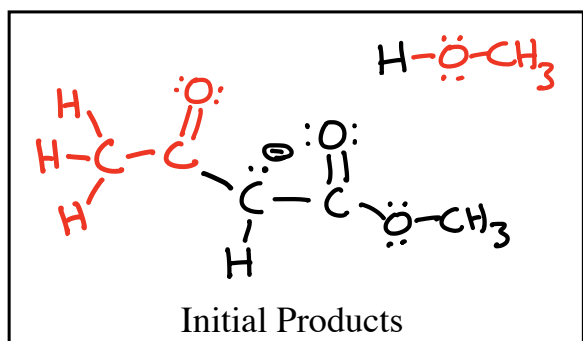


Draw both enantiomers

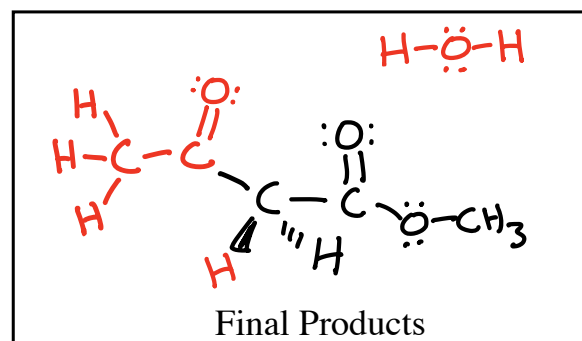
(Chemist opens flask and adds a mild acid)



2) Mild

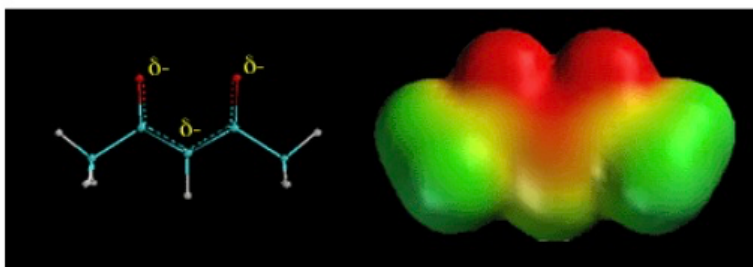
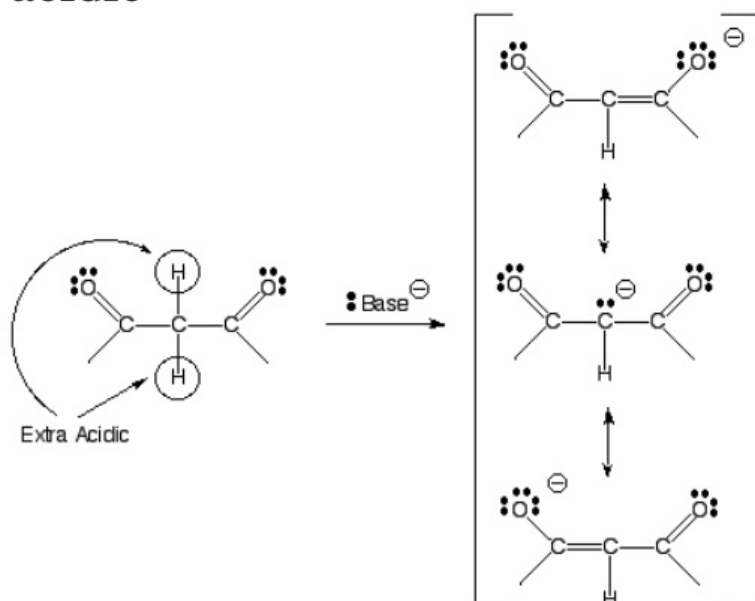


Initial Products



Final Products

Beta-dicarbonyls have alpha-hydrogens that are extra acidic



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