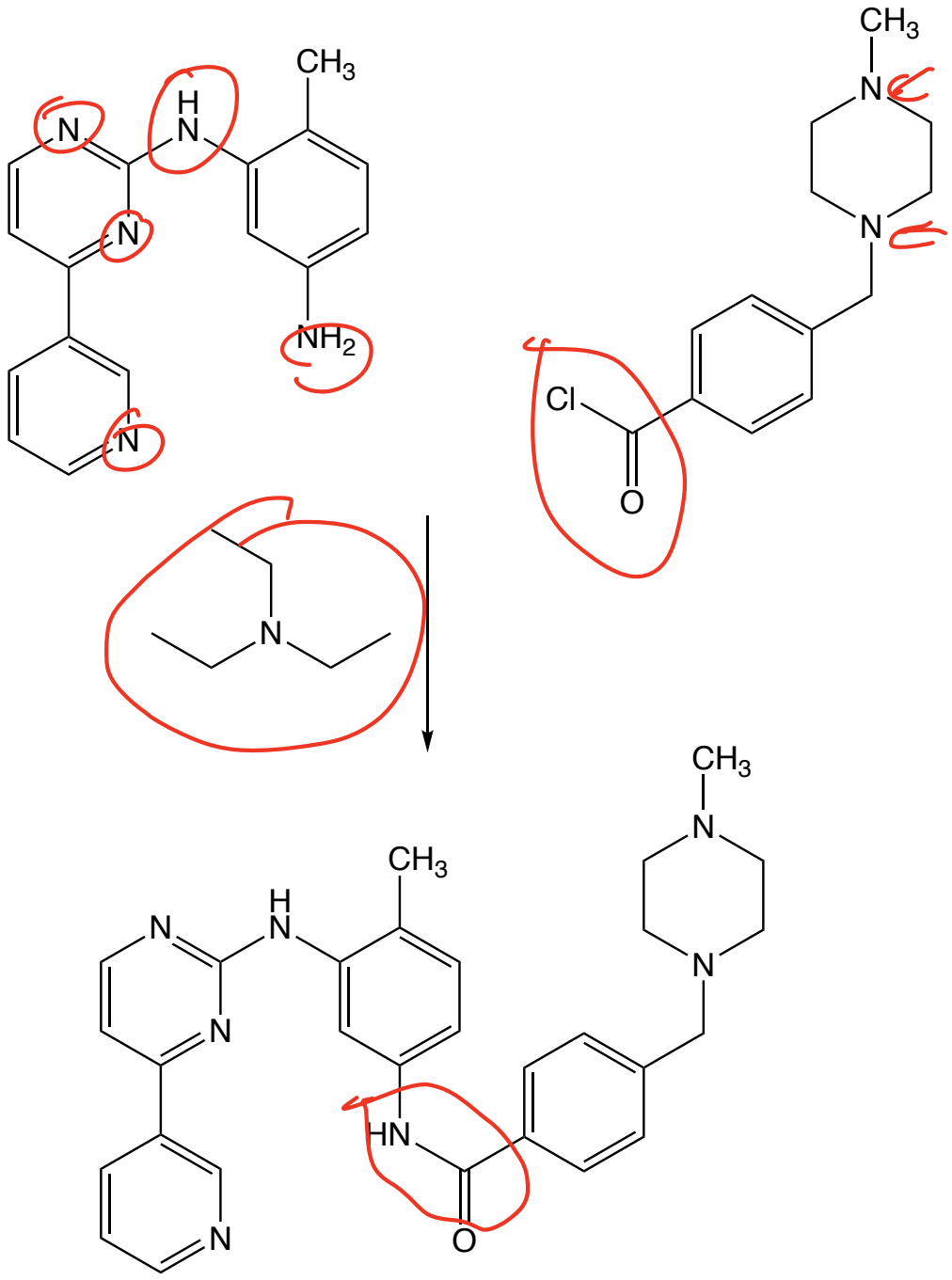
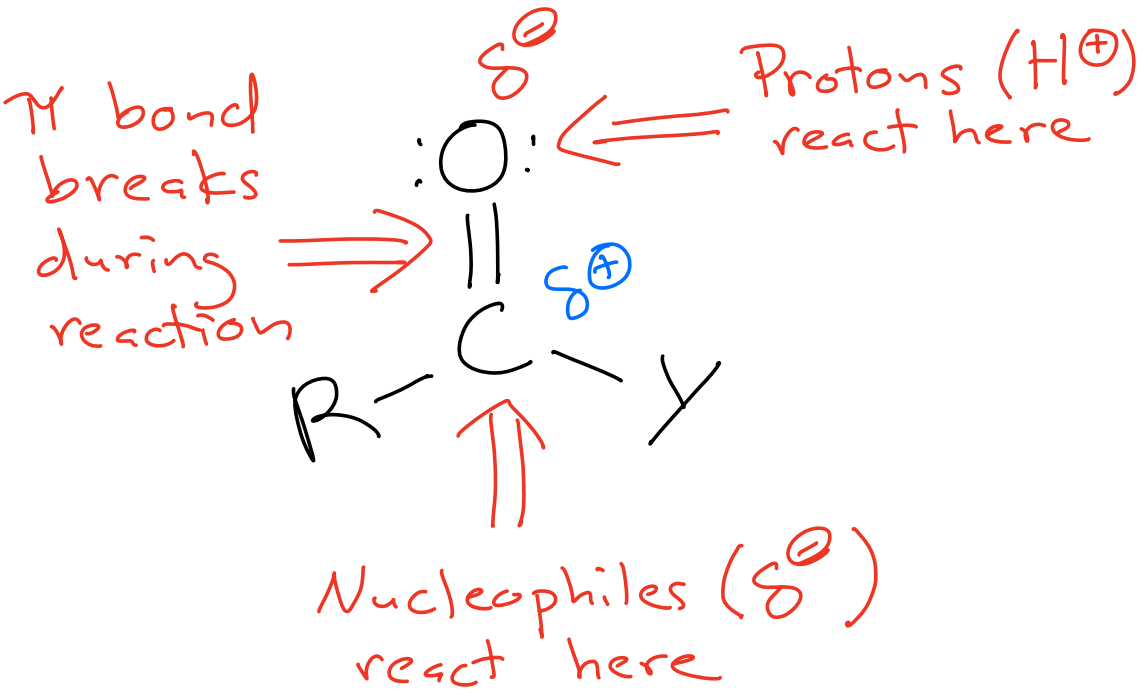
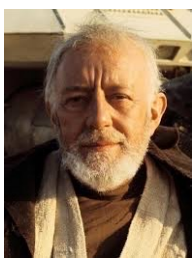


Gleevec – Novartis ($4.65 Billion in sales in 2015). A kinase inhibitor, that is a first of its kind pill capable of treating certain blood cancers with only limited side effects. It was designed to combat leukemias with the relatively common "Philadelphia chromosome" (BCR-ABL kinase gene fusion)

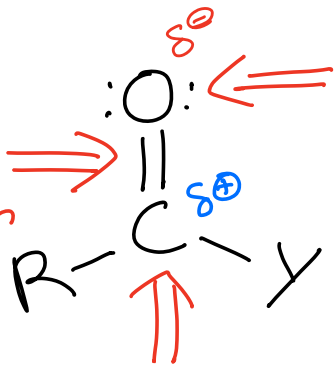

π bond breaks during reaction
δ⊖
Protons (H⊕) react here
δ⊕
R
C
Y
Nucleophiles (δ⊖) react here

Carbonyl Death Star

Old "pi bond" Kenobi



π bond breaks during reaction



Han "The Proton" Solo

"Nuc" Skywalker

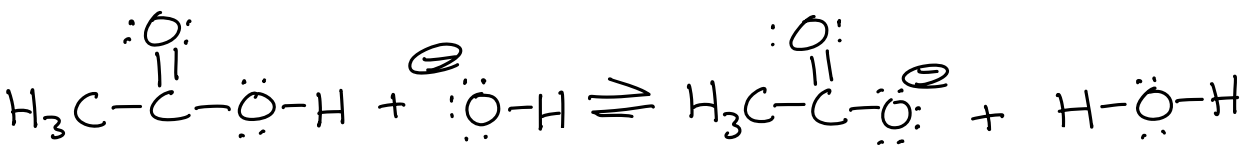
"sp^3 O"

"$S_N2/E2$"

Equilibrium favors formation of the weaker base and weaker acid

⇓ more stable anion

⇓ higher pK_a



$pK_a = 4.78$ ⇑ less stable anion

⇑ more stable anion

⇑ weaker base!

$pK_a = 15.7$ ⇑ larger pK_a so weaker acid

Bottom line → position of equilibrium favors the side with the more stable anion

Amounts to a thermodynamic driving force (motive) for a reaction

Weaker bases are favored at equilibrium

Compound		pK_a
	H-Cl	-7
Carboxylic acids*	R–CO-H	3-5
β-Dicarbonyls*	RC–CH_2-CR'	10
β-Ketoesters*	RC–CH_2-COR'	11
β-Diesters*	ROC–CH_2-COR'	13
Water	HOH	15.7
Alcohols	RCH_2OH	15-19
Acid chlorides*	RCH_2-CCl	16
Aldehydes*	RCH_2-CH	18-20
Ketones*	RCH_2-CR'	18-20
Esters*	RCH_2-COR'	23-25
Terminal alkynes	RC≡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.

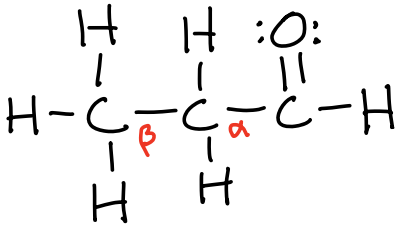
B) Checking pKa values can predict if a reaction has a motive even if there are other steps besides a proton transfer.

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.

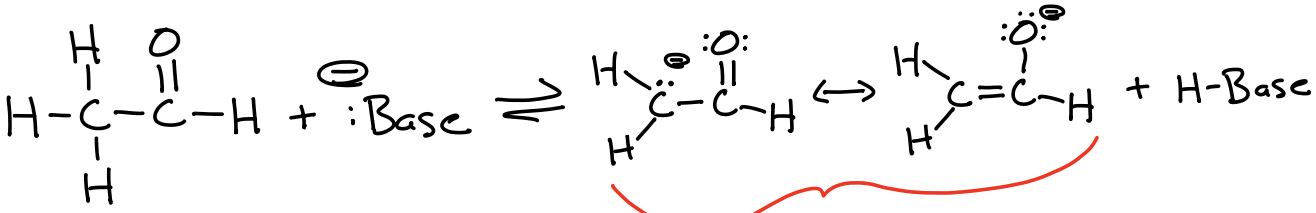
F) Above is a pKa table that we will refer to often.



The C atom adjacent to a carbonyl is called the α carbon. The next C atom is called the β carbon.

The H atoms on the α carbon are called α hydrogens

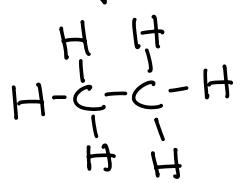
α hydrogens are extremely acidic for a C-H bond



$pK_a = 18$

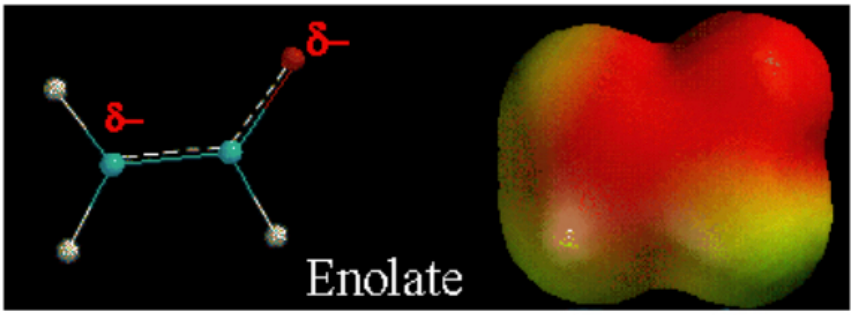
Stabilized by delocalization of ⊖ charge and a π-way

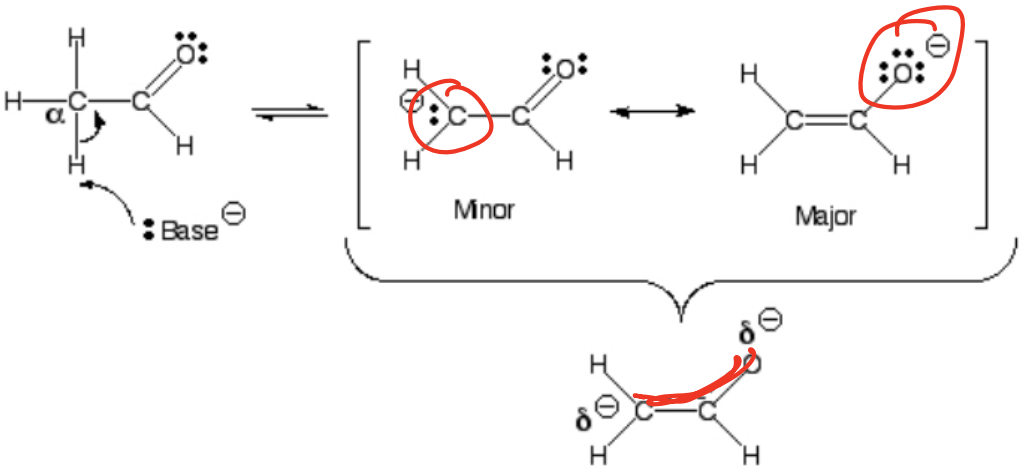
Compare:



$pK_a = 51$

Enolates as nucleophiles

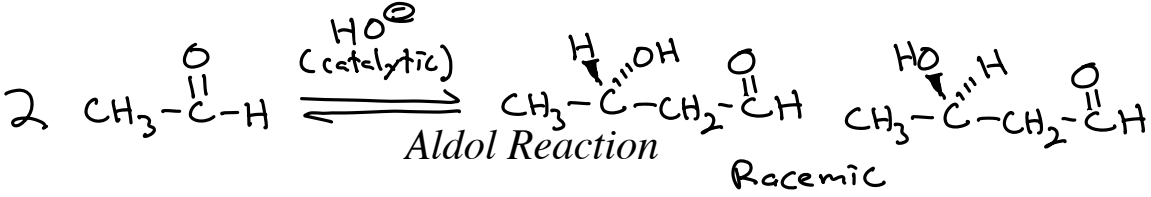




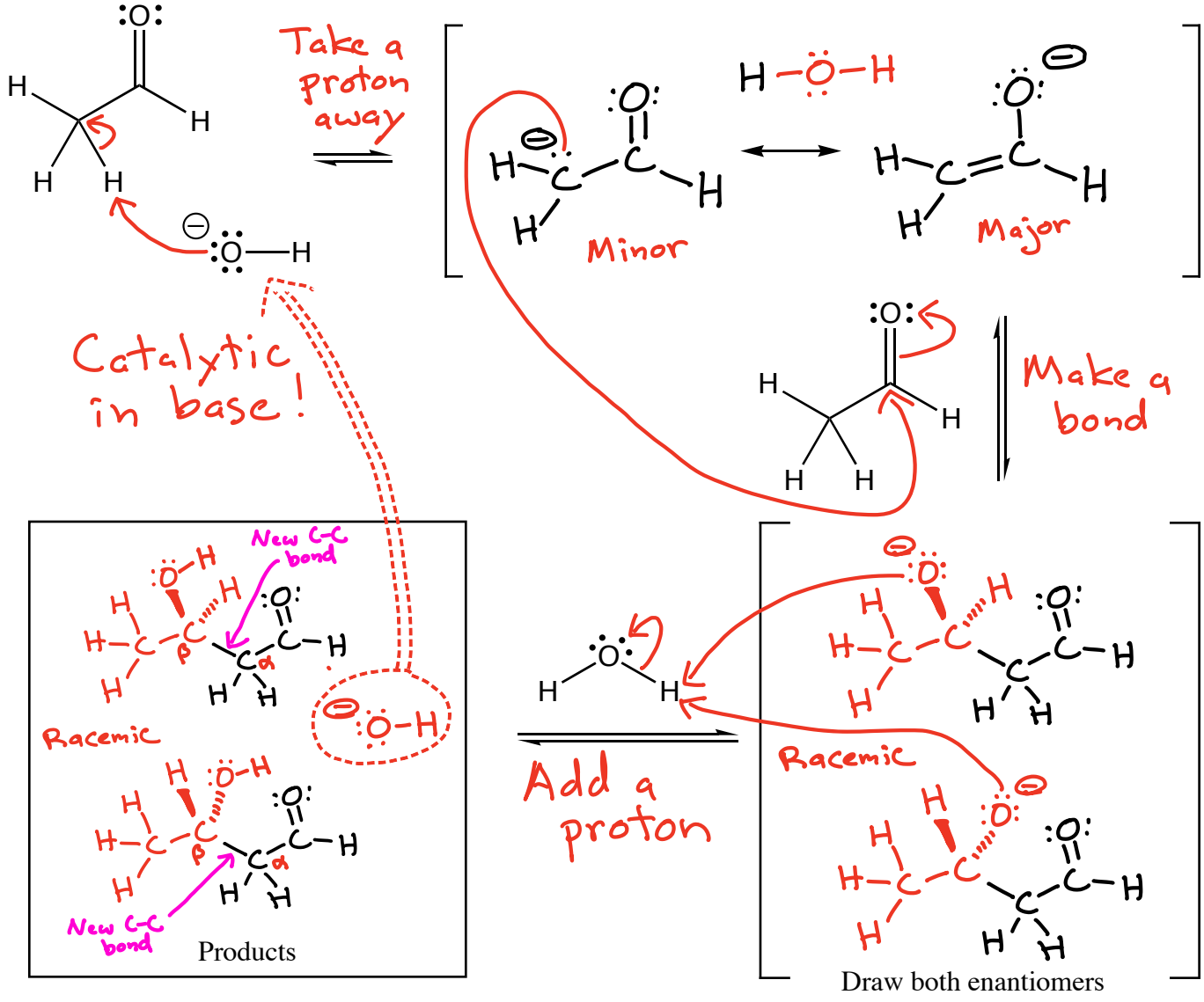
A) Enolates are resonance stabilized, with a partial negative charge on carbon and oxygen.

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.



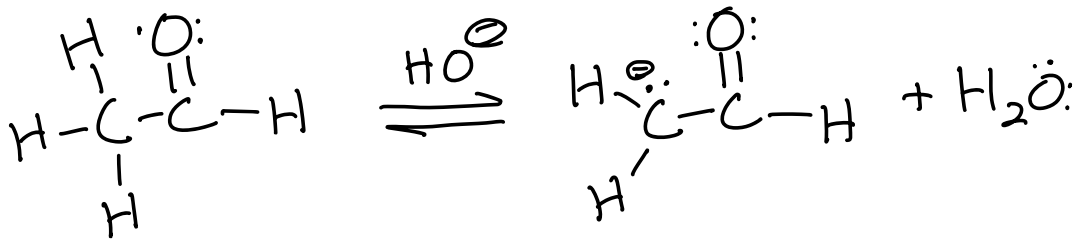
Aldol Reaction



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

Mechanism A

Another Movie Rips Off Organic Chemistry



Aldehyde

Enolate

Is Attacked By Enolate ✓

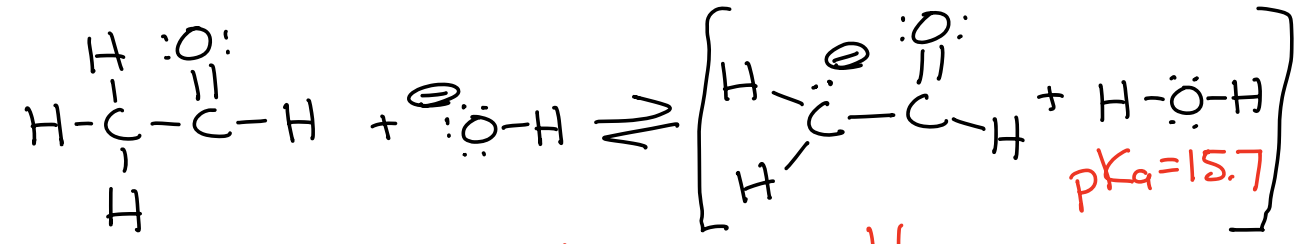
Attacks Aldehyde ✓

Austin Powers

Dr. Evil

Aldol Reaction Considerations

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



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 and 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