



A few hundred to now thousands  
Endangered





From 15 cranes last century  
to 831 today  
Endangered

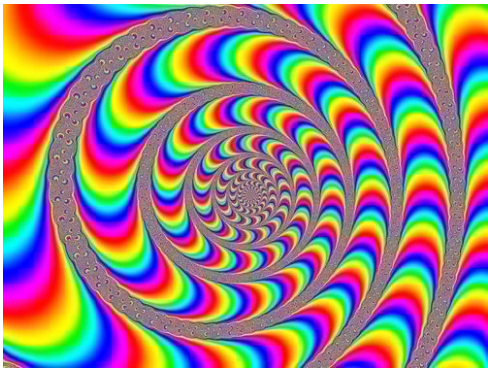




10,000 and declining fast!

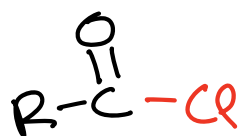
Newly listed as endangered



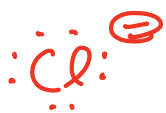




Acid Chloride



Leaving Group



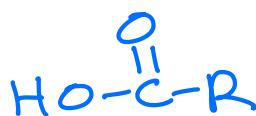
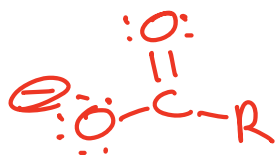
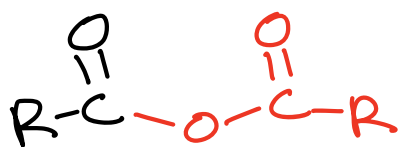
Conjugate Acid



pK<sub>a</sub>

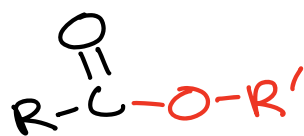
-7

Anhydride



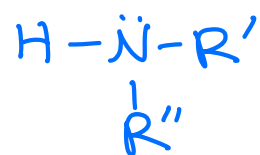
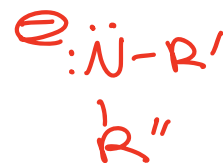
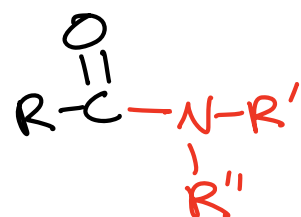
3-5

Ester



16

Amide



38

← Anion Stability

← Better Leaving Group Ability

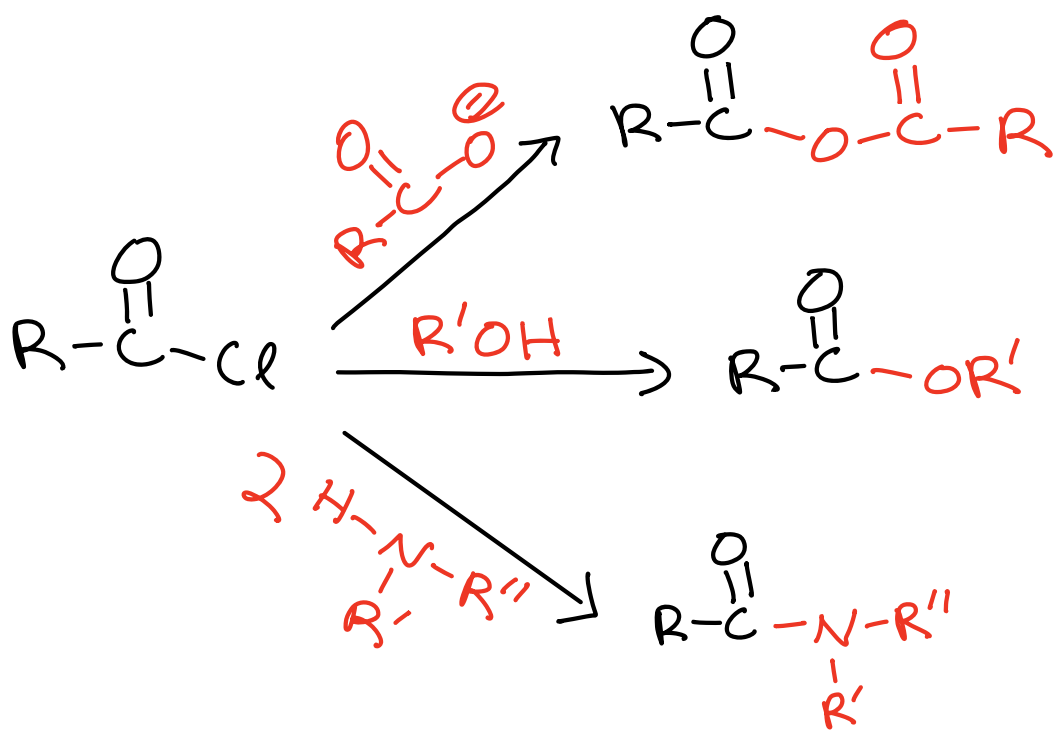
← Reactivity of Carboxylic Acid Derivative

Think of carboxylic acid derivatives  
⇒ C=O with a leaving group attached

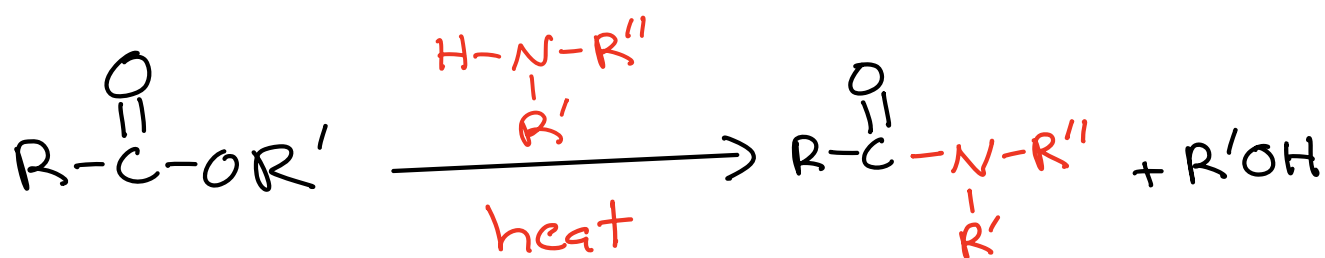
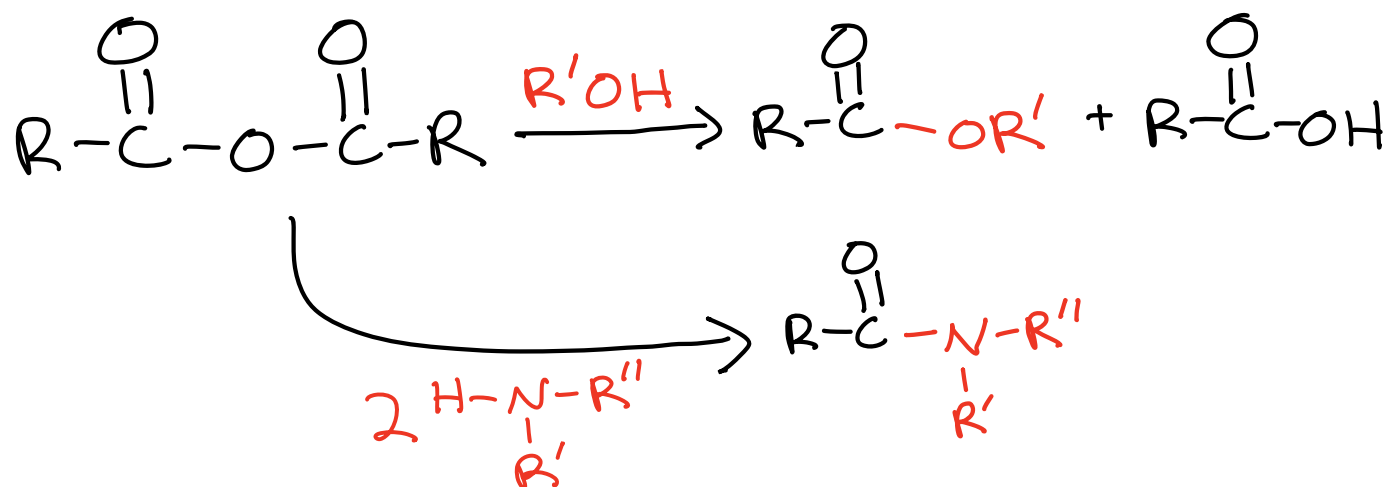


Here is the big rule → You can make any of the less reactive carboxylic acid derivatives from any of the more reactive carboxylic acid derivatives using the appropriate nucleophiles

Note: Acid chlorides and anhydrides spontaneously react with nucleophiles at room temperature, esters usually need some heat.







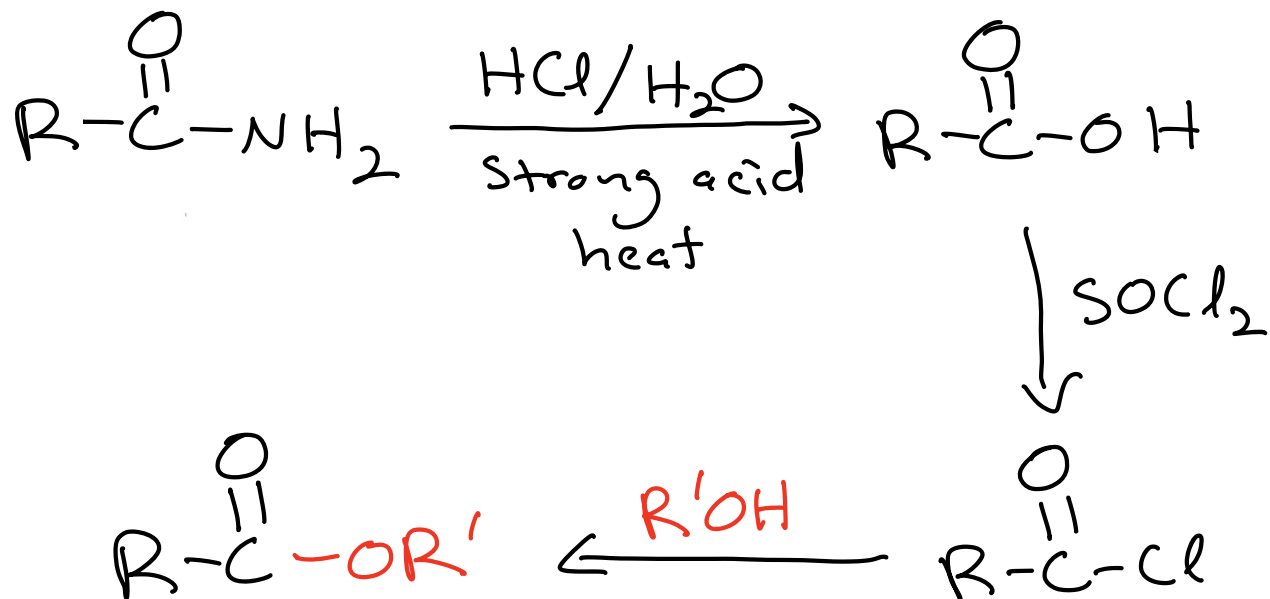
Note: For the last reaction, only 1 equivalent of  $\text{H}-\underset{\text{R}'}{\underset{|}{\text{N}}}-\text{R}''$

is used because the leaving group  $\text{R}'\ddot{\text{O}}:\ominus$  is a much stronger base than  $\text{H}-\underset{\text{R}'}{\underset{|}{\text{N}}}-\text{R}''$

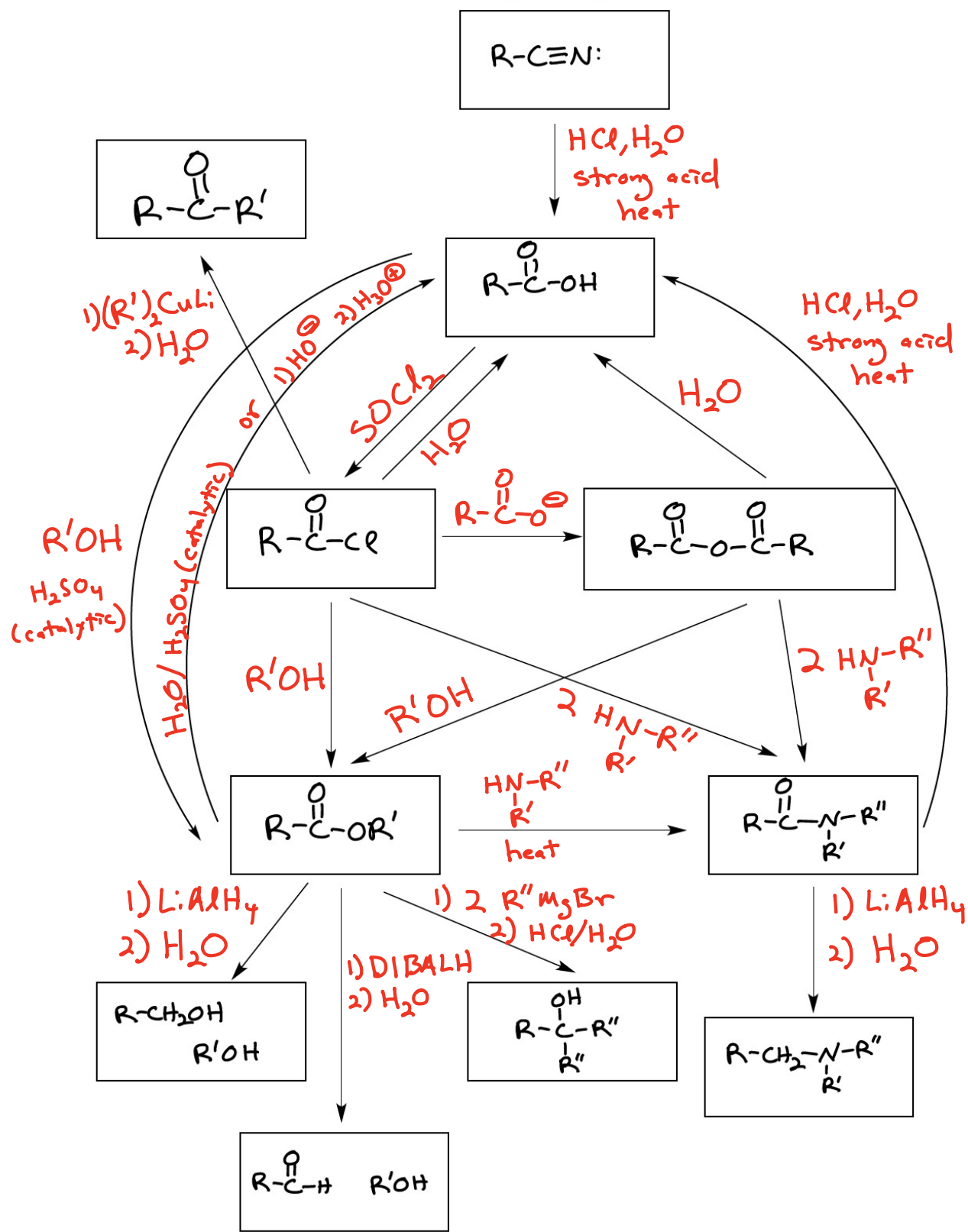


However: You can make a less stable carboxylic acid derivative from a more stable carboxylic acid derivative, but only if you:

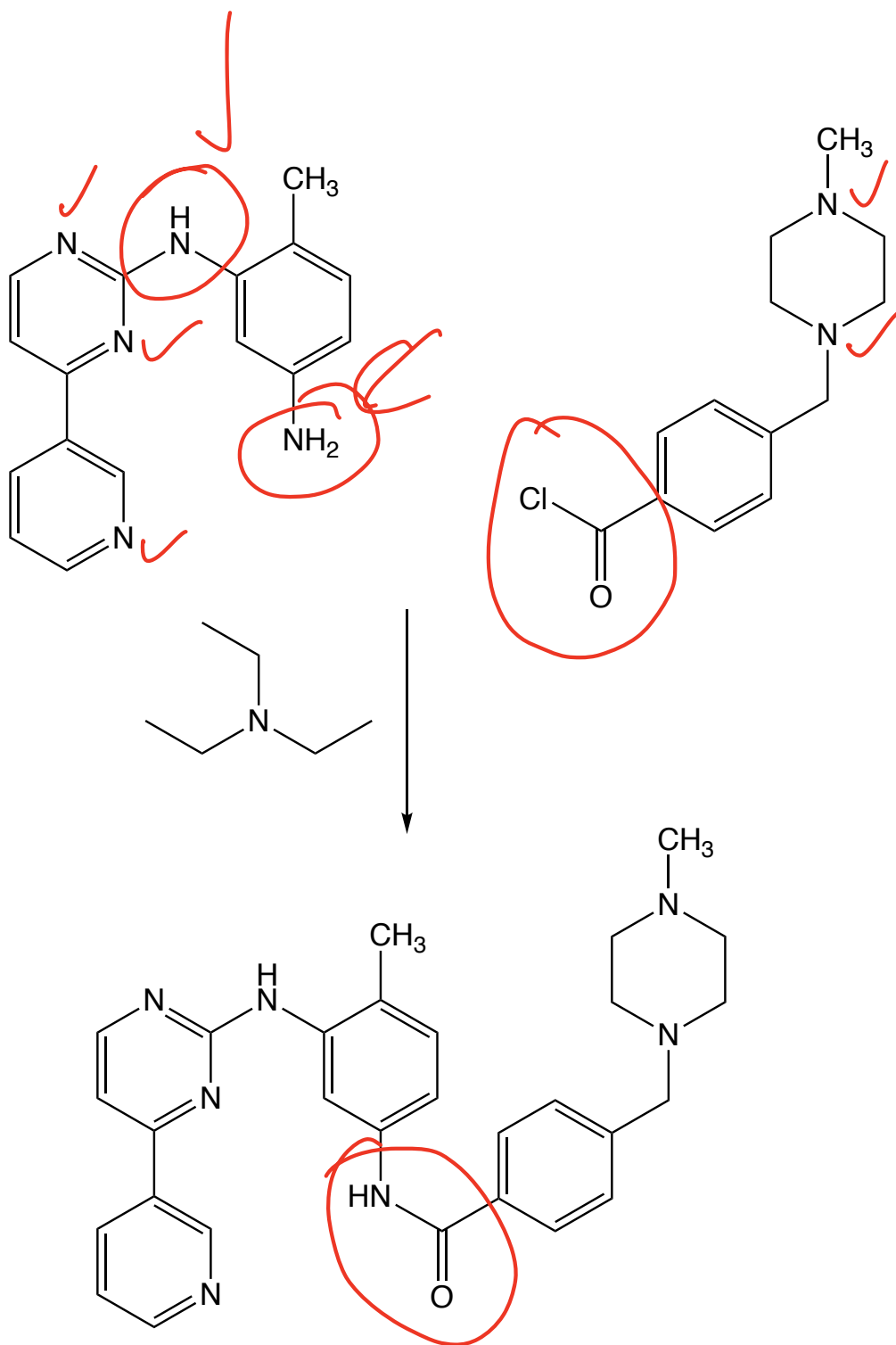
- 1) You hydrolyze the carboxylic acid derivative to the carboxylic acid
- 2) You react the carboxylic acid with  $\text{SOCl}_2$  to make an acid chloride



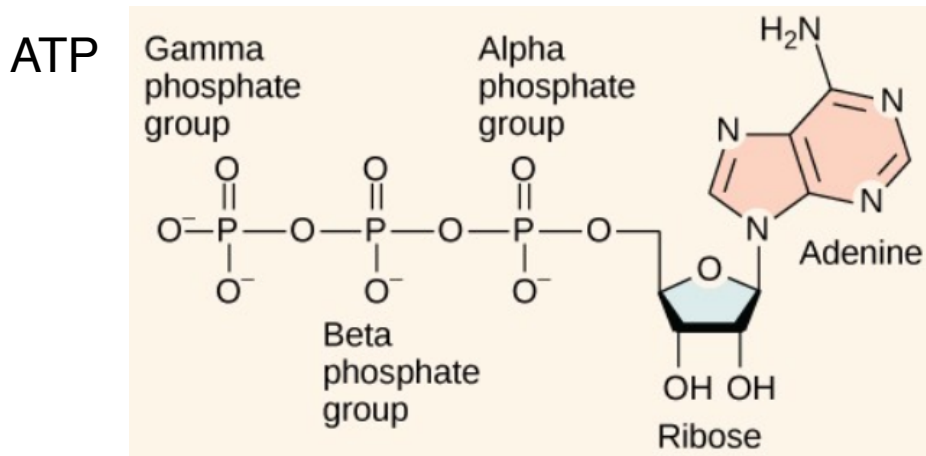
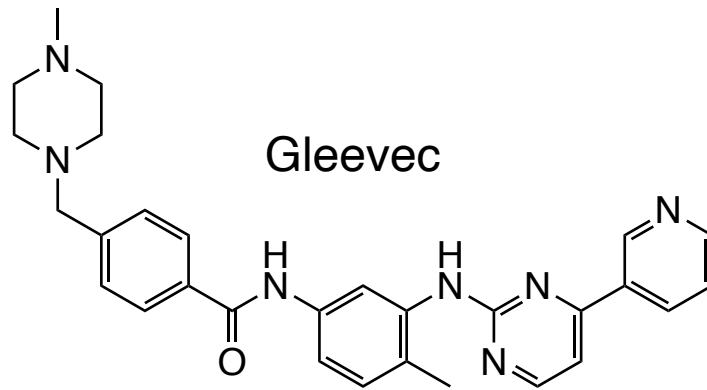
Interconversion of Carboxylic Acid Derivatives



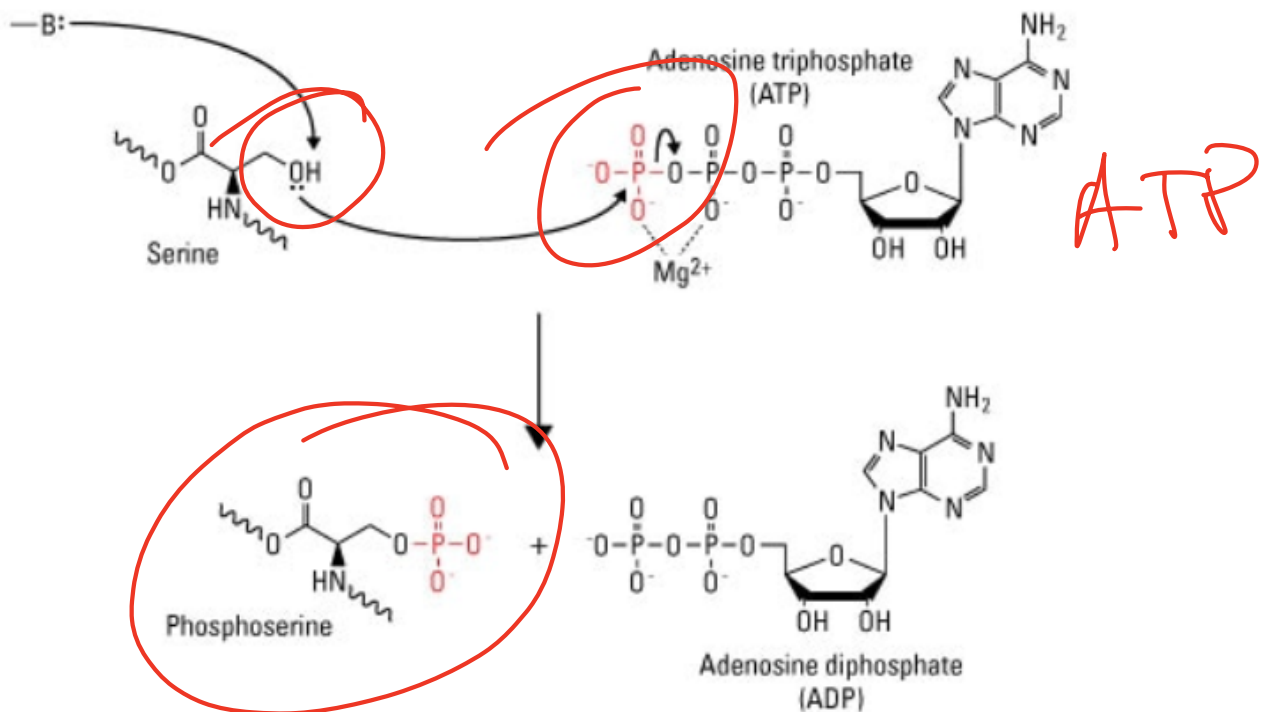




**Gleevec** – Novartis (\$4.65 Billion in sales in 2015). A kinase inhibitor, that is a first of its kind pill capable of treating certain blood cancers with only limited side effects. It was designed to combat leukemias with the relatively common “Philadelphia chromosome” (BCR-ABL kinase gene fusion)



How Kinases Work:



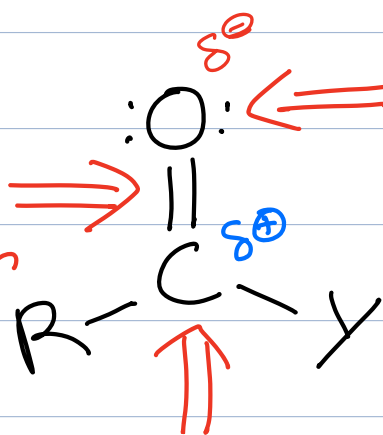


# Carbonyl Death Star

Old  
"pi bond"  
Kenobi



$\pi$  bond  
breaks  
during  
reaction



Protons ( $\text{H}^+$ )  
react here

Han  
"The  
Proton"  
Solo



Nucleophiles ( $\delta^-$ )  
react here

"Nuc" Skywalker



" $\text{sp}^3 \text{O}$ "

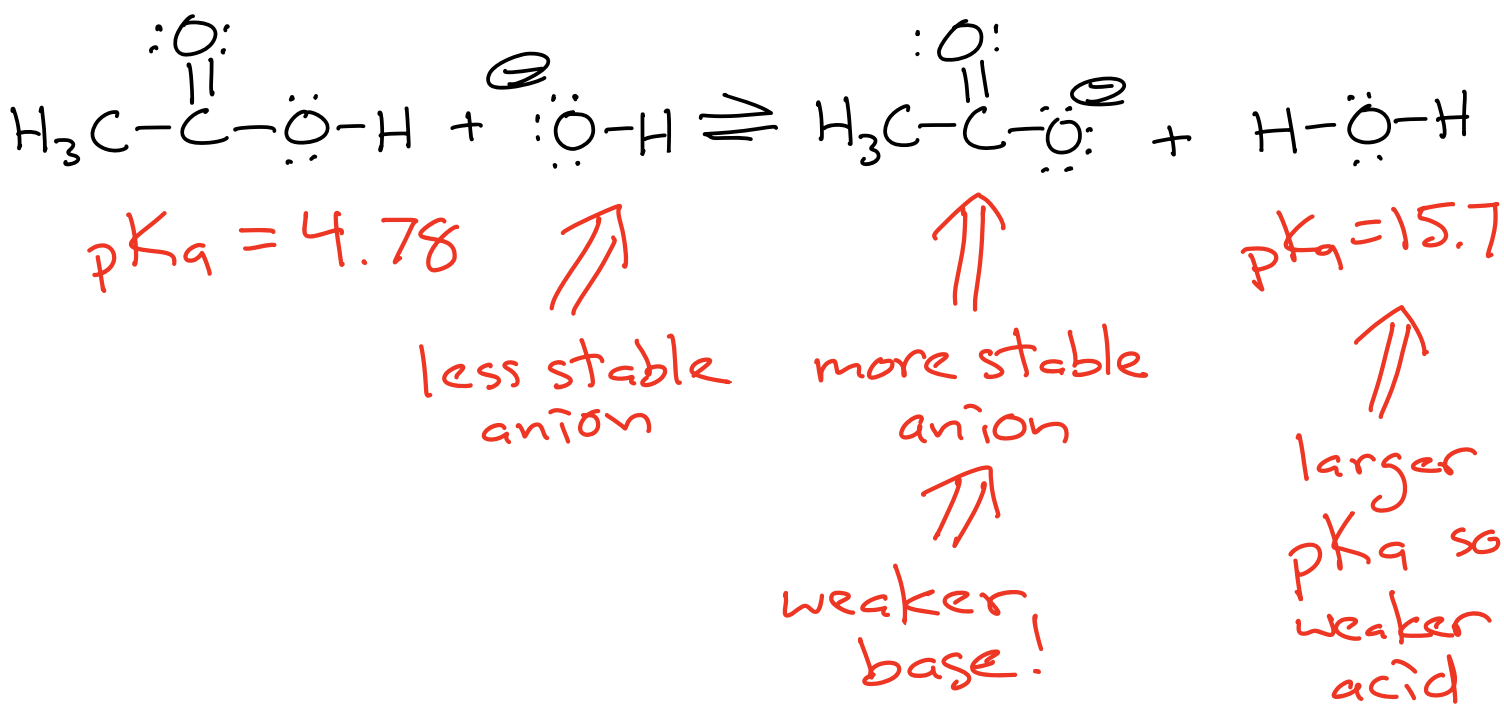


" $\text{S}_\text{N}2/\text{E}2$ "

Equilibrium favors formation of the weaker base and weaker acid

⇓  
more stable anion

⇓  
higher pKa



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	Chemical Structure	pK <sub>a</sub>
	H-Cl	-7
Carboxylic acids*	$\text{R}-\text{C}(=\text{O})-\text{OH}$	3-5
β-Dicarbonyls*	$\text{RC}(=\text{O})-\text{CH}_2-\text{C}(=\text{O})\text{R}'$	10
β-Ketoesters*	$\text{RC}(=\text{O})-\text{CH}_2-\text{C}(=\text{O})\text{OR}'$	11
β-Diesters*	$\text{ROC}(=\text{O})-\text{CH}_2-\text{C}(=\text{O})\text{OR}'$	13
Water	HOH	15.7
Alcohols	$\text{RCH}_2\text{OH}$	15-19
Acid chlorides*	$\text{RCH}_2-\text{C}(=\text{O})\text{Cl}$	16
Aldehydes*	$\text{RCH}_2-\text{C}(=\text{O})\text{H}$	18-20
Ketones*	$\text{RCH}_2-\text{C}(=\text{O})\text{R}'$	18-20
Esters*	$\text{RCH}_2-\text{C}(=\text{O})\text{OR}'$	23-25
Terminal alkynes	$\text{RC}\equiv\text{C}-\text{H}$	25
LDA	$\text{H}-\text{N}(\text{i-C}_3\text{H}_7)_2$	40
Terminal alkenes	$\text{R}_2\text{C}=\text{C}-\text{H}$	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<sub>a</sub> values can predict if a reaction has a motive even if there are other steps besides a proton transfer.

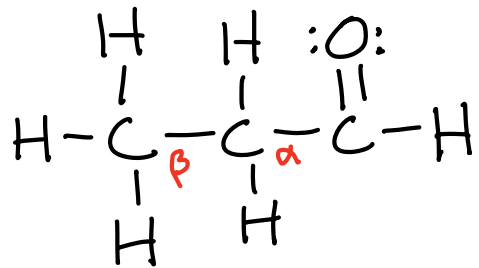
C) Recall that the conjugate base of a stronger acid (lower pK<sub>a</sub>) is a weaker base.

D) Check the pK's of the conjugate acid of the bases on either side of the equation. Lower pK<sub>a</sub> value corresponds to stronger acid of the conjugate acid, and thus weaker conjugate base. The base with a stronger conjugate acid (lower pK<sub>a</sub> 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<sub>a</sub> table that we will refer to often.

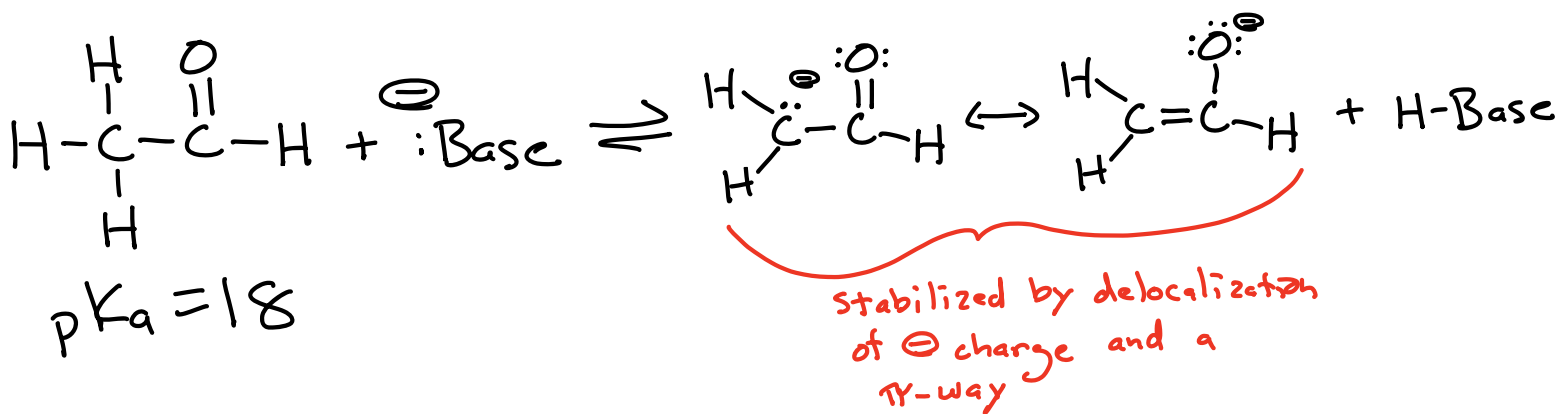
\*These have resonance stabilized anions



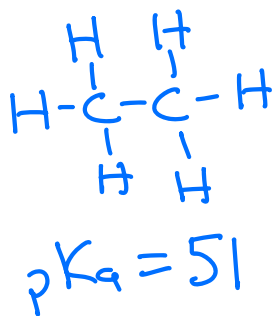
The C atom adjacent to a carbonyl is called the  $\alpha$  carbon. The next C atom is called the  $\beta$  carbon.

The H atoms on the  $\alpha$  carbon are called  $\alpha$  hydrogens

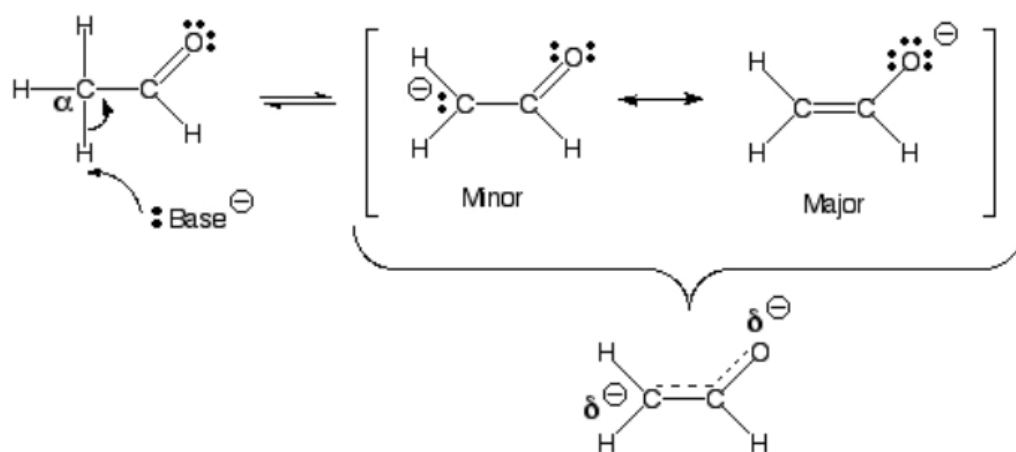
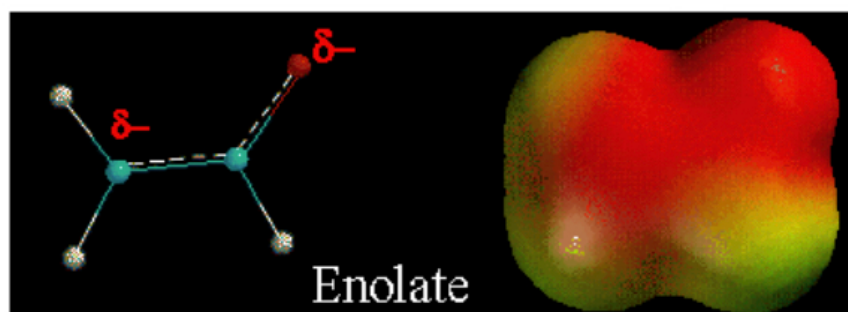
$\alpha$  hydrogens are extremely acidic for a C-H bond



Compare:

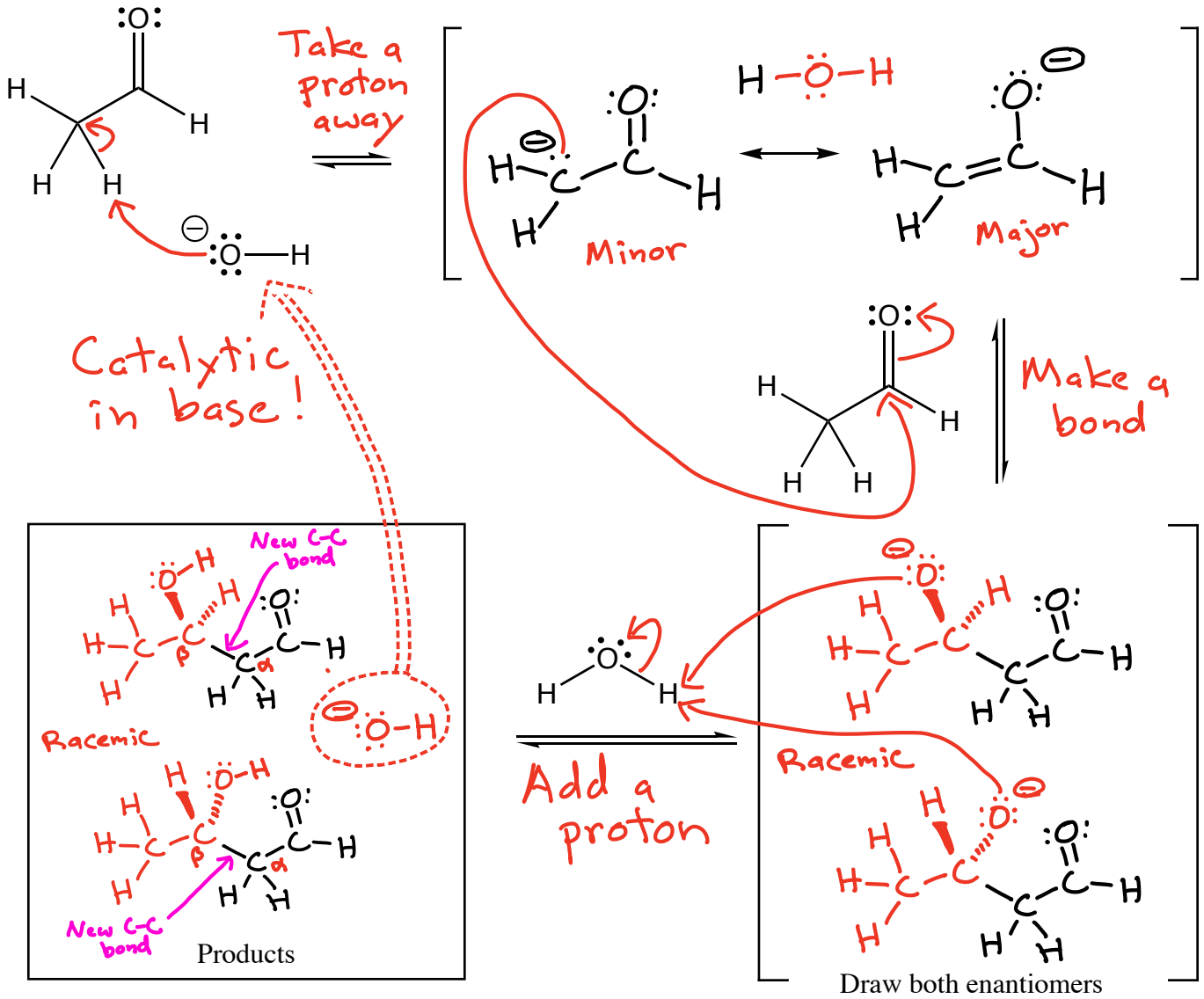
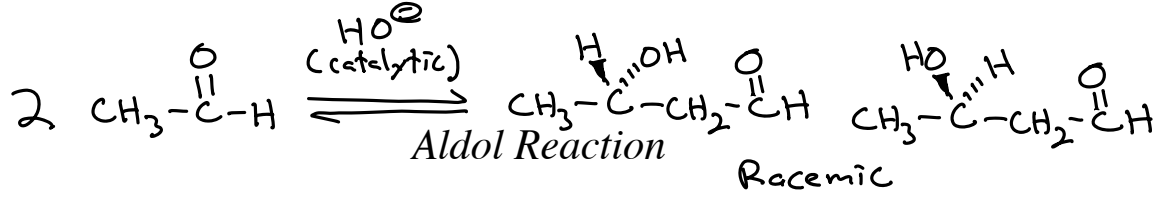


# Enolates as nucleophiles



- 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.**

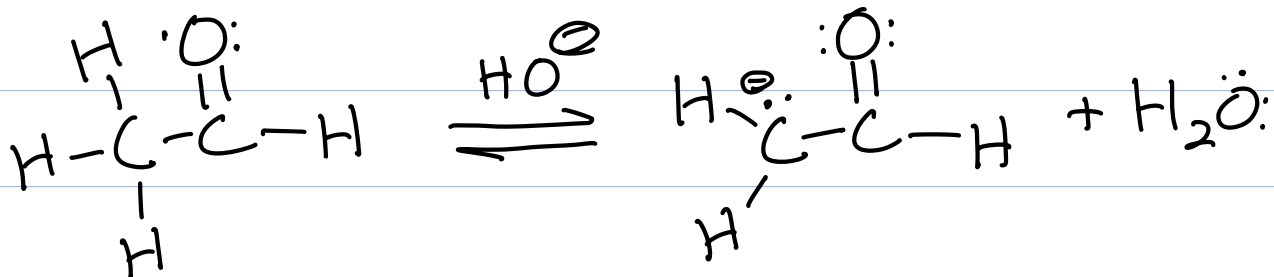




KRE → β-hydroxy aldehyde  
with a new C-C  
bond between the  
aldehyde α and β  
carbons

Mechanism  
A

# Another Movie Rips Off Organic Chemistry



Aldehyde

Enolate

Is Attacked  
By Enolate

Attacks  
Aldehyde

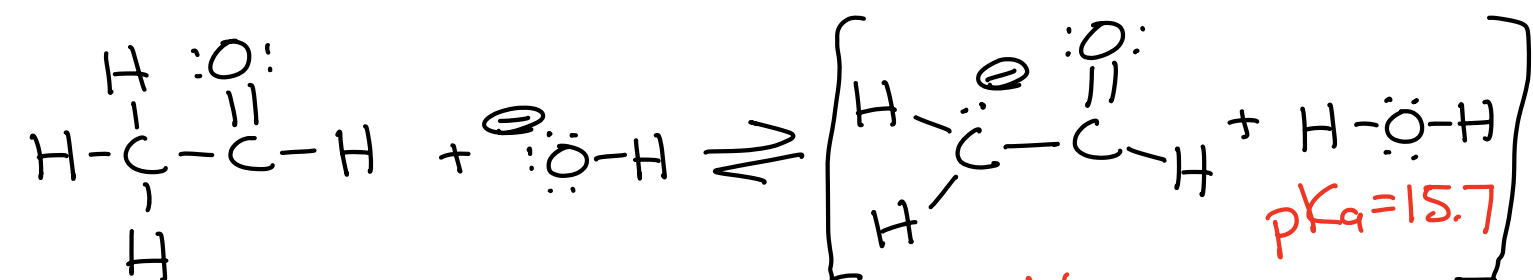
Austin Powers

Dr. Evil



# Aldol Reaction Considerations

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



$pK_a = 18-20$   
weaker base

This side favored at equilibrium

There will be excess aldehyde for the enolate to react with

2) Because there is  $\text{HO}^\ominus$  present at the beginning and end of the reaction there is little driving force (motive) for the aldol reaction  $\rightarrow$  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