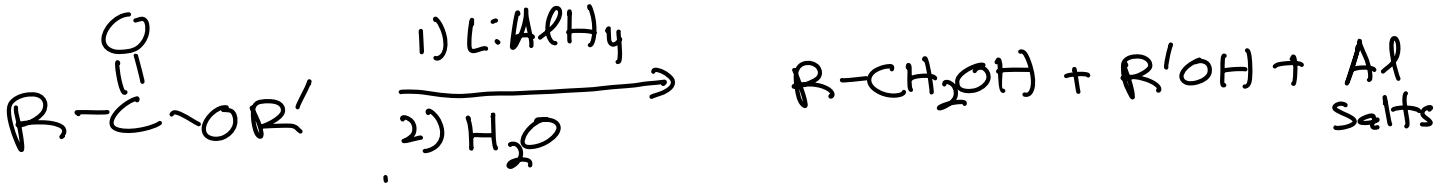
↑ A few hundred to now thousands Endangered

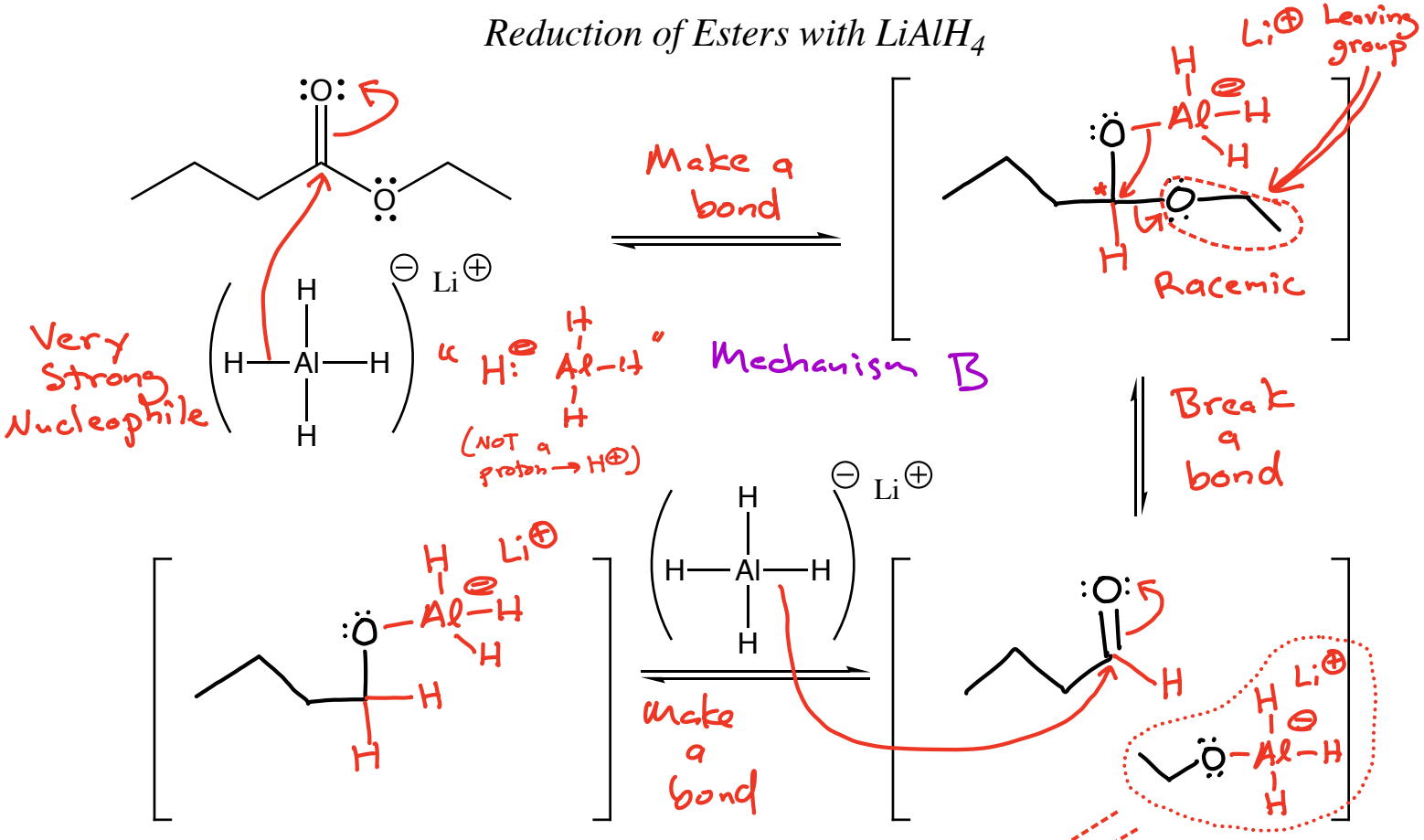
From 15 cranes last century
to 831 today
Endangered

10,000 and declining fast!

Newly listed as endangered

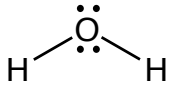


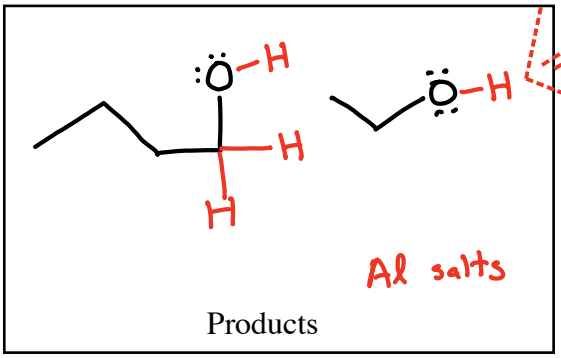
Reduction of Esters with $LiAlH_4$



Chemist Opens Flask

2)



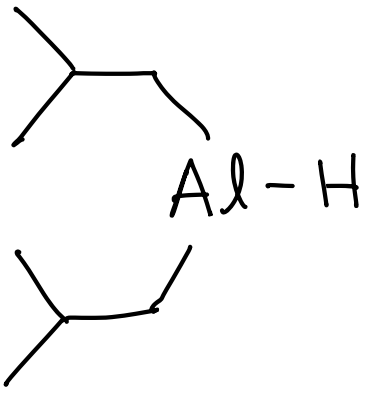


Just keeping track of this product

KRE → converts an ester into two alcohols → breaks C-O bond

Note the extreme similarities between these last two mechanisms! ⇒ Mechanism B followed by Mechanism A just like the last reaction!

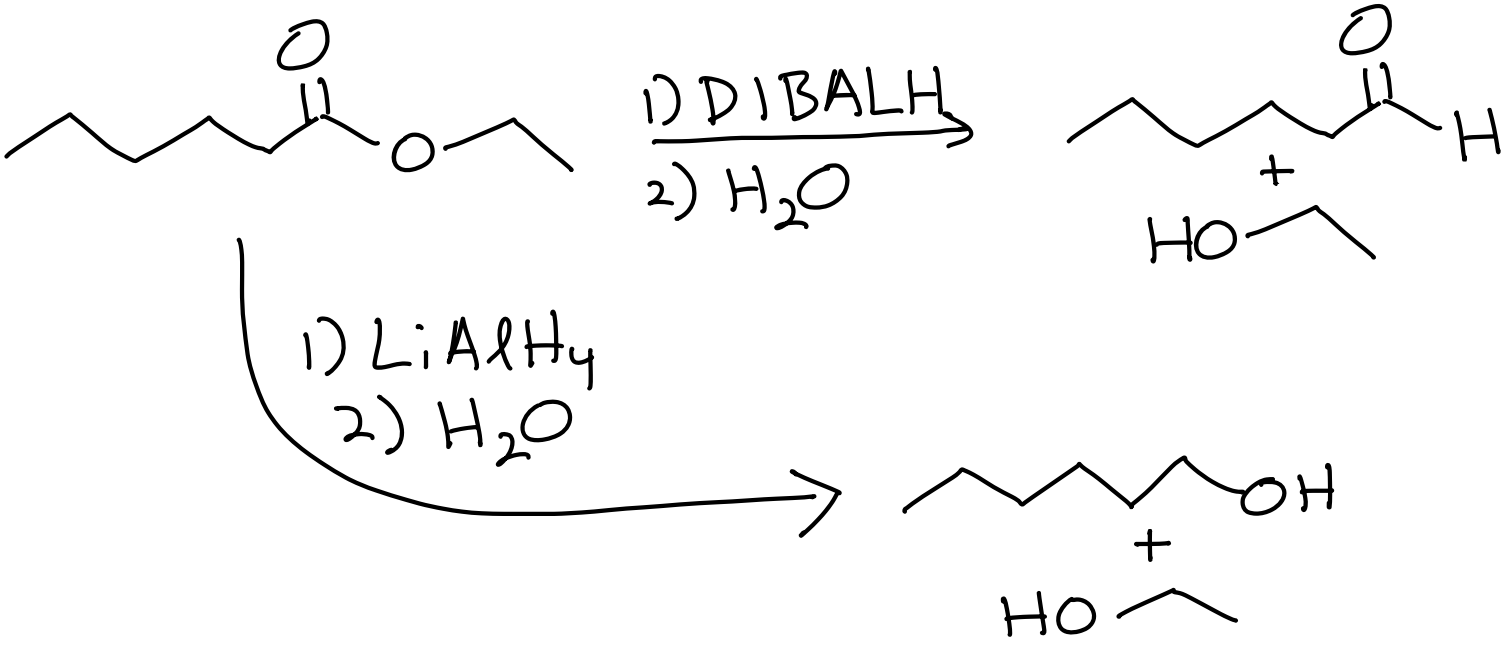
Note: An aldehyde is produced as an intermediate when esters react with $LiAlH_4$

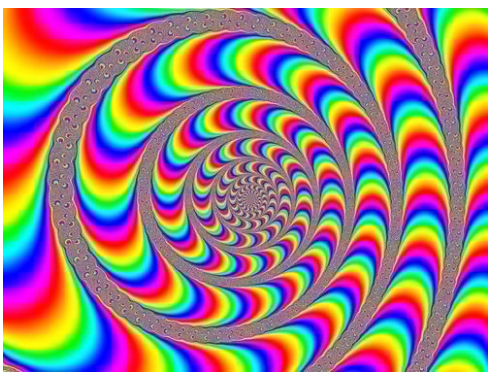


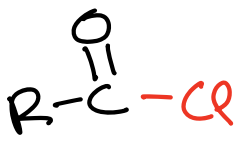
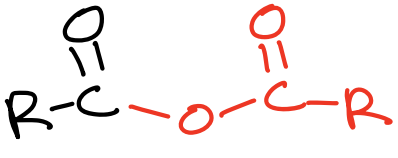
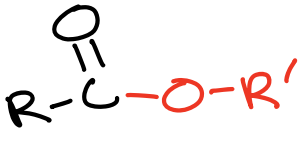
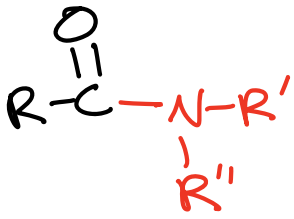
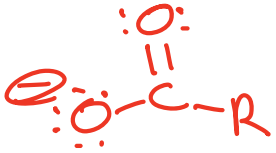
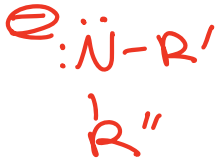
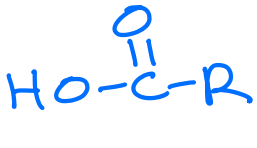
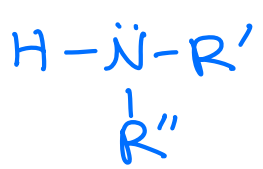
Diisobutylaluminum hydride

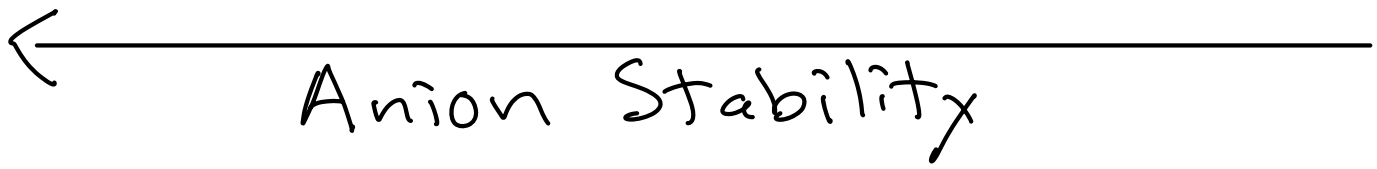
DIBALH

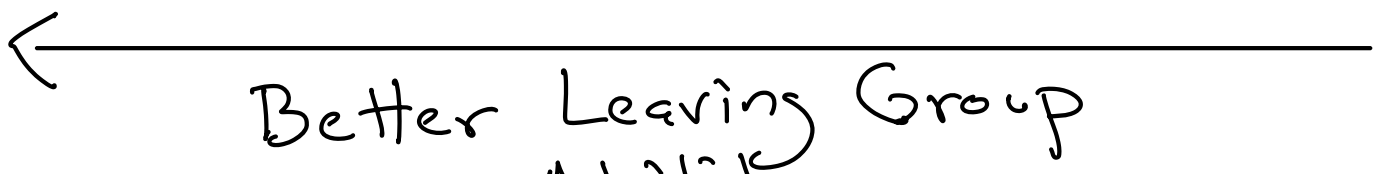
→ Reaction stops at the aldehyde!

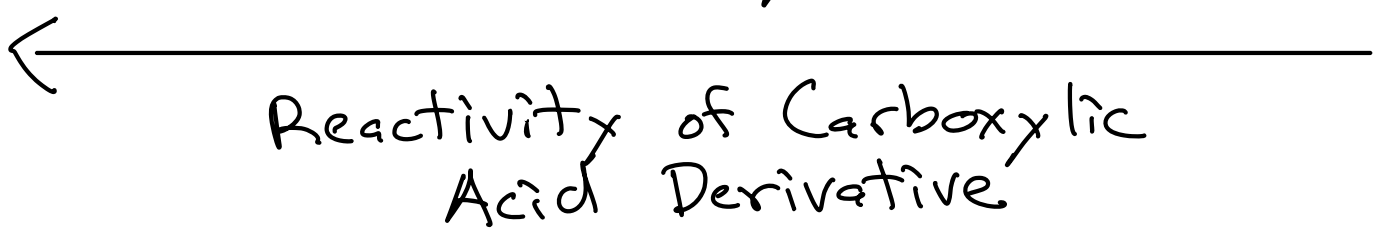




	Acid Chloride	Anhydride	Ester	Amide
				
Leaving Group				
Conjugate Acid				
pK_a	-7	3-5	16	38



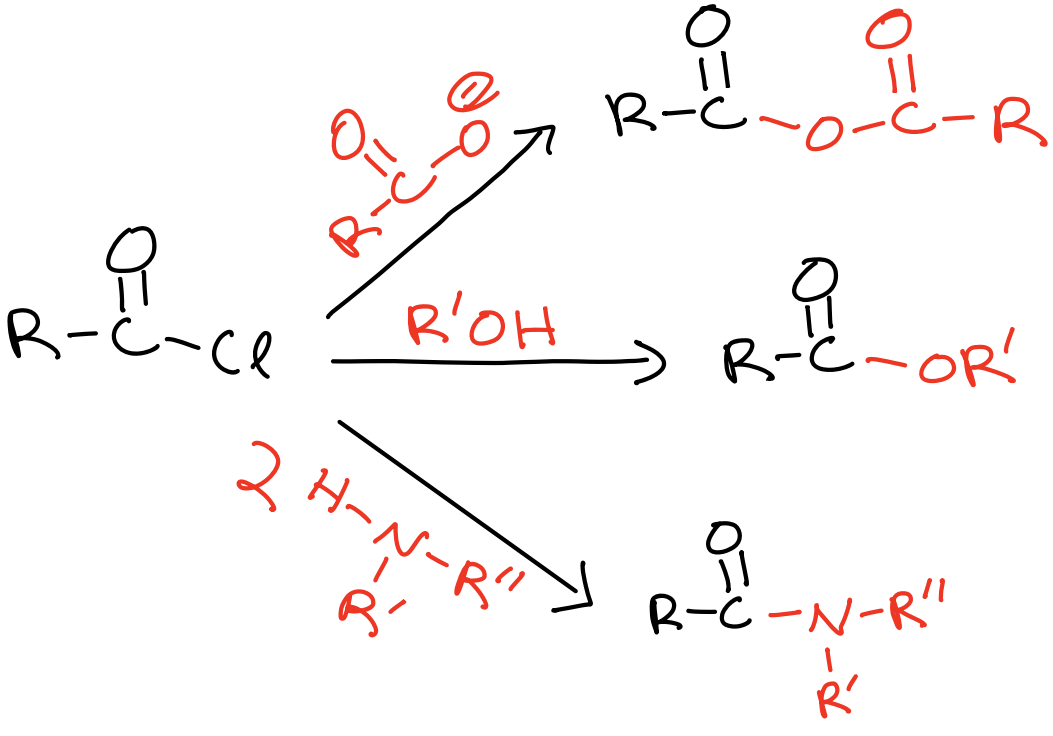


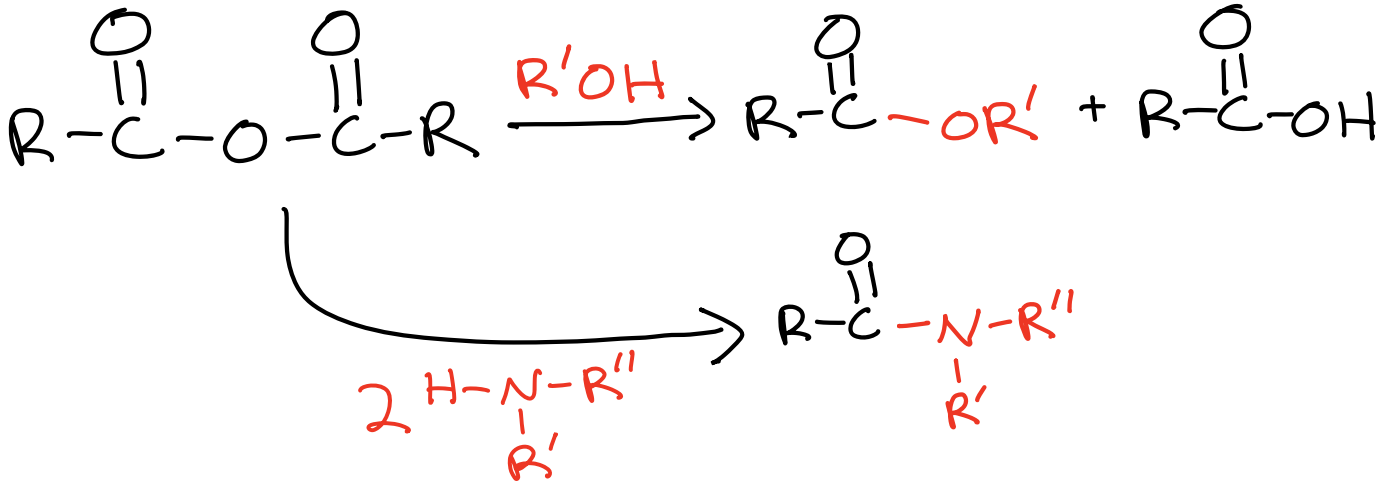


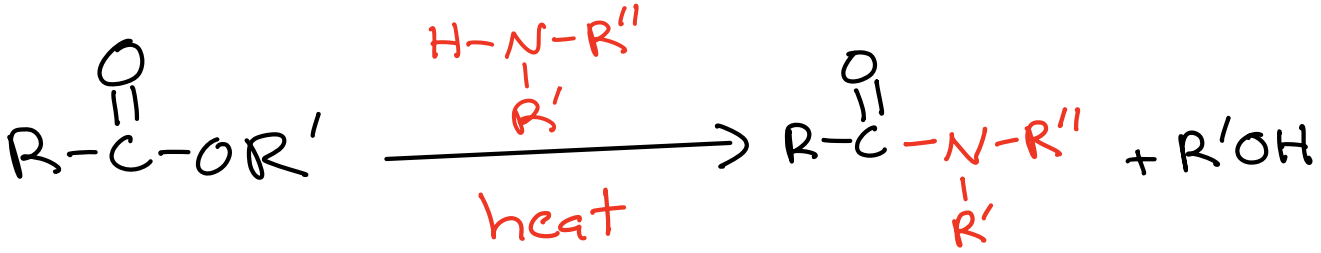
Think of carboxylic acid derivatives
$\Rightarrow$ C=O with a leaving group attached

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.



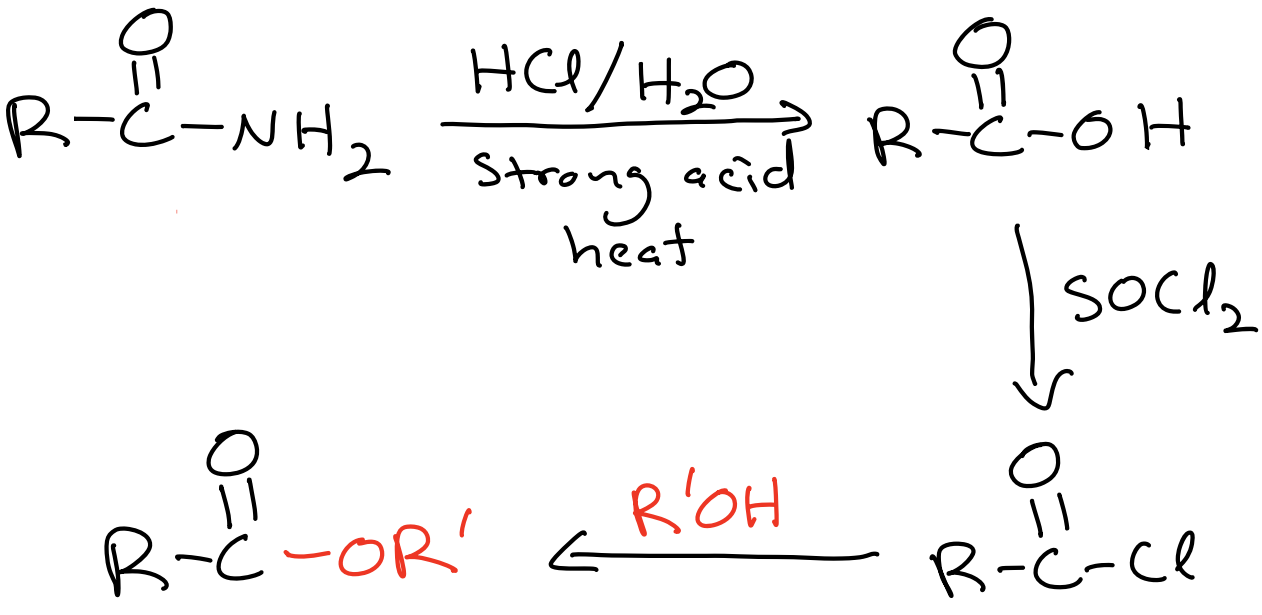




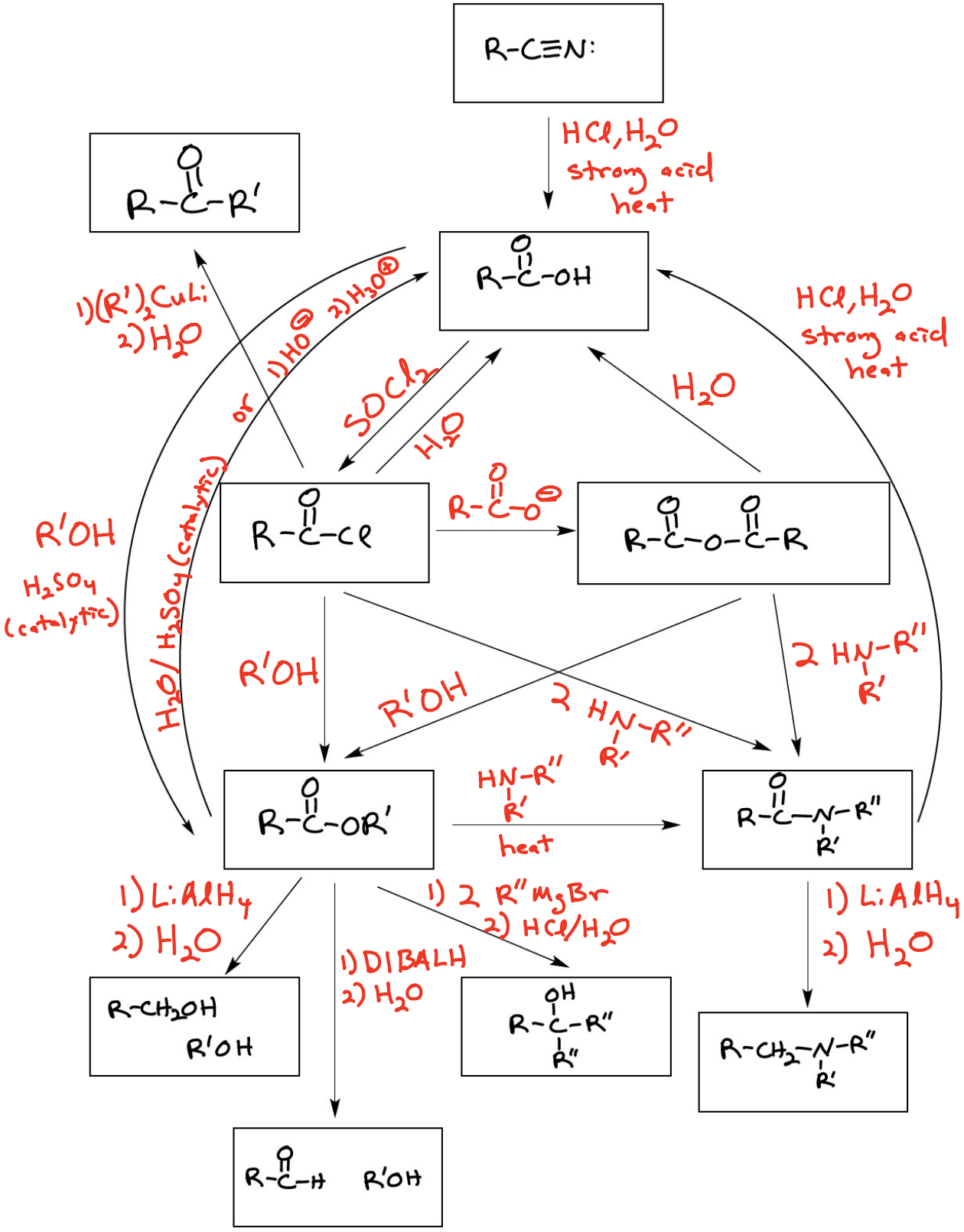
Note: For the last reaction, only 1 equivalent of $HN(R'')(R')$ is used because the leaving group $R'O^-$ is a much stronger base than $HN(R'')(R')$

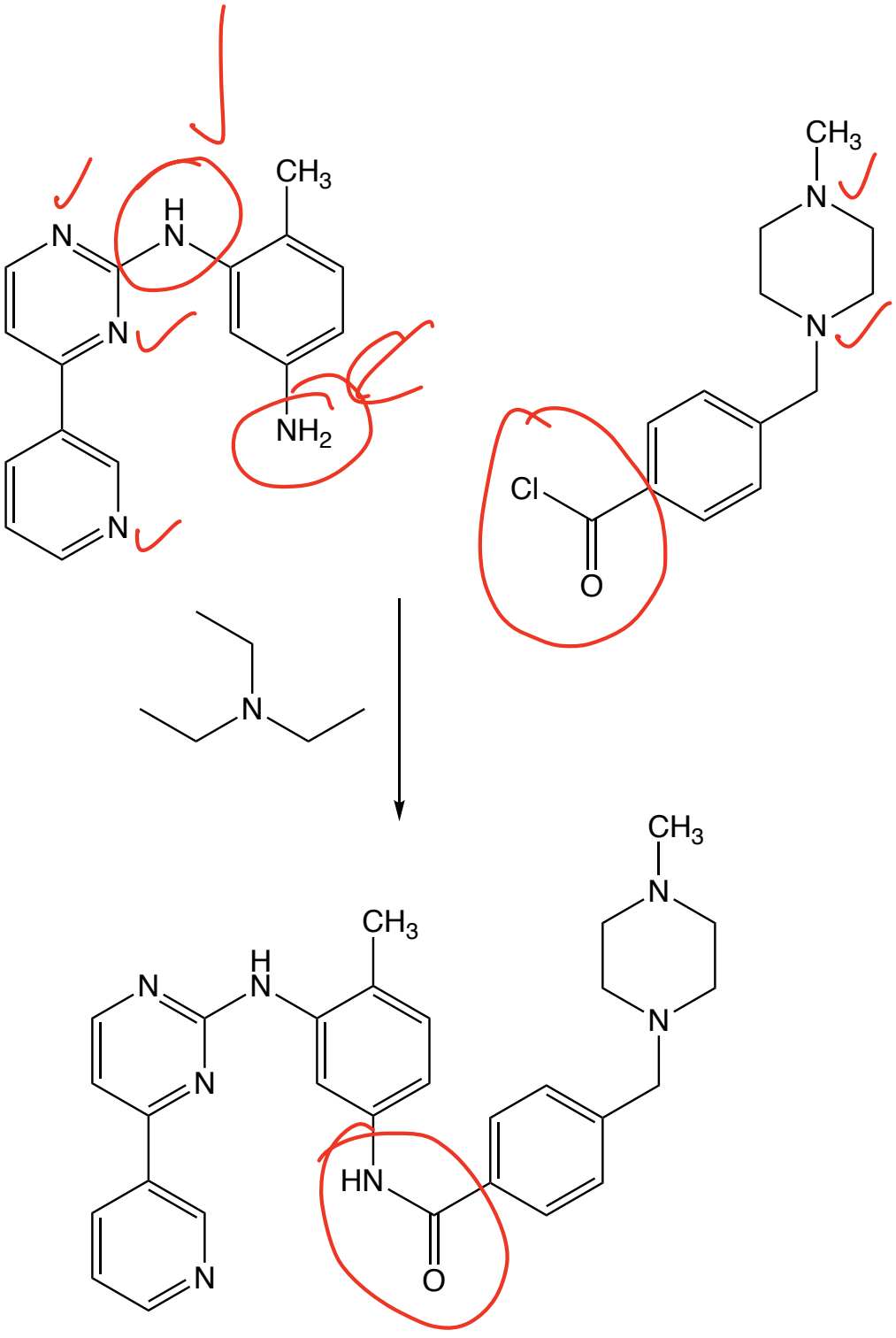
However: You can make a less stable carboxylic acid derivative from a more stable carboxylic acid derivative, but only if you:

1) You hydrolyze the carboxylic acid derivative to the carboxylic acid
2) You react the carboxylic acid with $SOCl_2$ to make an acid chloride

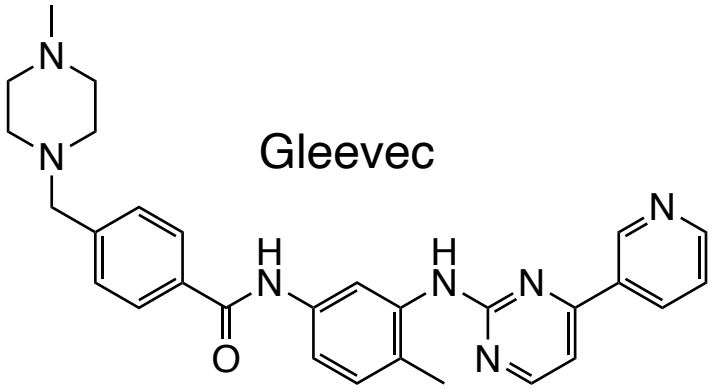


Interconversion of Carboxylic Acid Derivatives

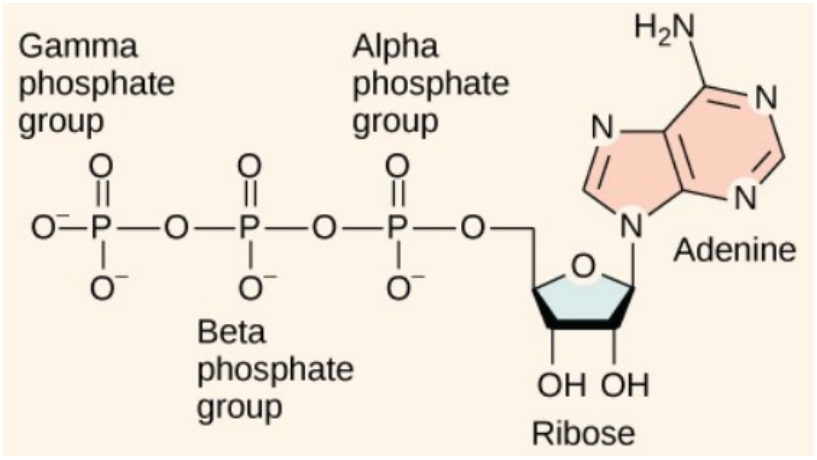




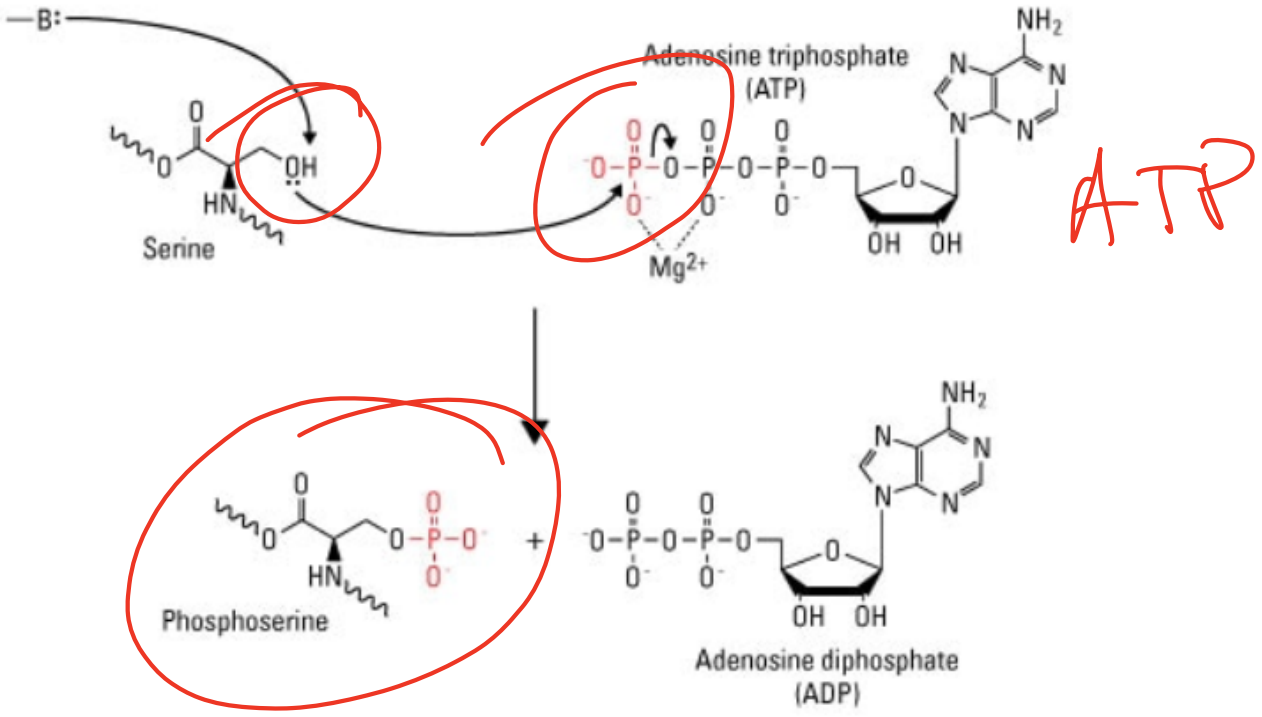
Gleevec – Novartis ($4.65 Billion in sales in 2015). A kinase inhibitor, that is a first of its kind pill capable of treating certain blood cancers with only limited side effects. It was designed to combat leukemias with the relatively common "Philadelphia chromosome" (BCR-ABL kinase gene fusion)



ATP



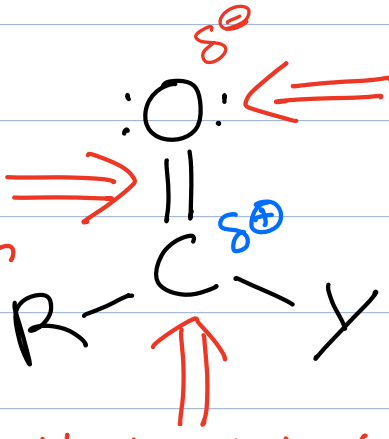
How Kinases Work:



Carbonyl Death Star

Old "pi bond" Kenobi

π bond breaks during reaction



Protons ($H^{\oplus}$) react here

Han "The Proton" Solo

Nucleophiles($\delta^{\ominus}$) react here

"Nuc" Skywalker

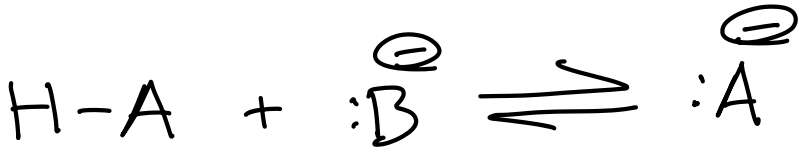
"sp^3 O"

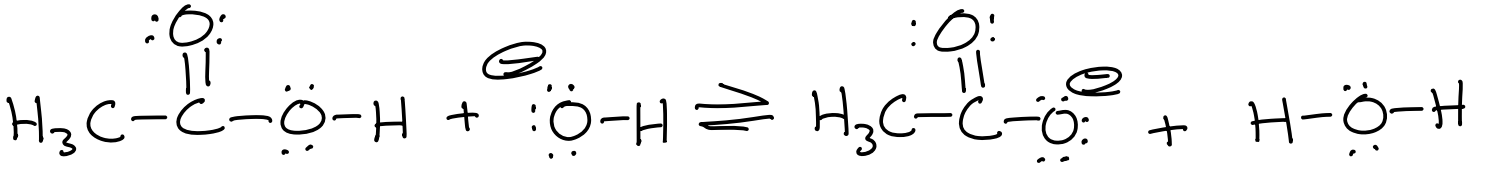
"$S_N2/E2$"

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!

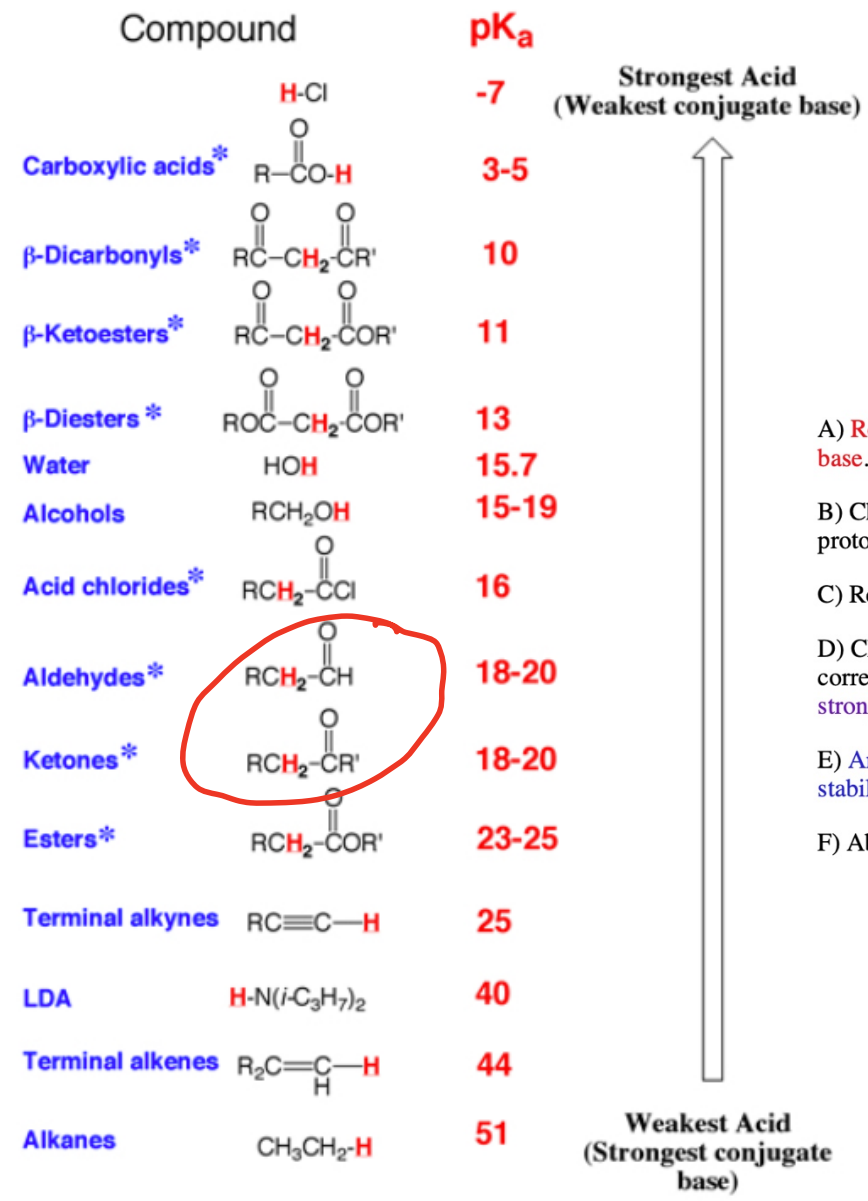
$pK_a = 15.7$

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



*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.

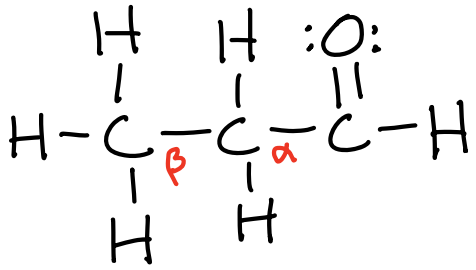
B) Checking pKa values can predict if a reaction has a motive even if there are other steps besides a proton transfer.

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.

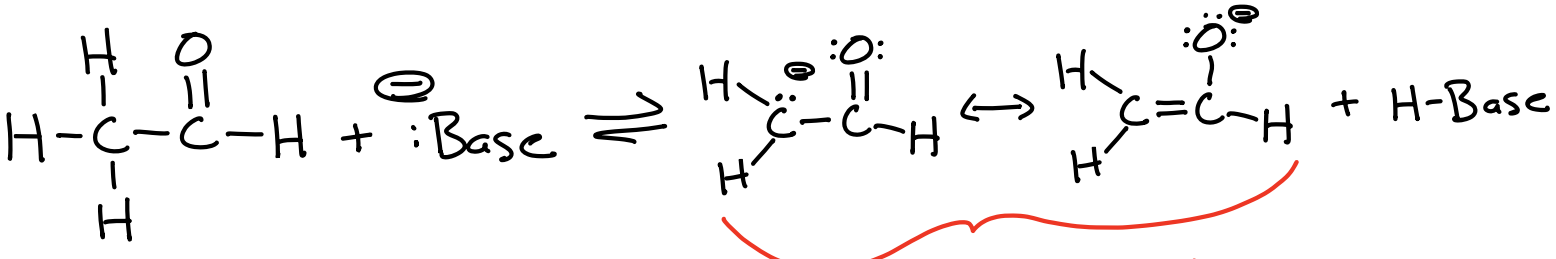
F) Above is a pKa table that we will refer to often.



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

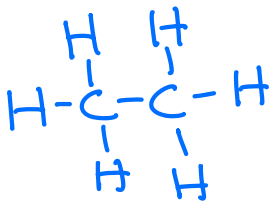
α hydrogens are extremely acidic for a C-H bond



$pK_a = 18$

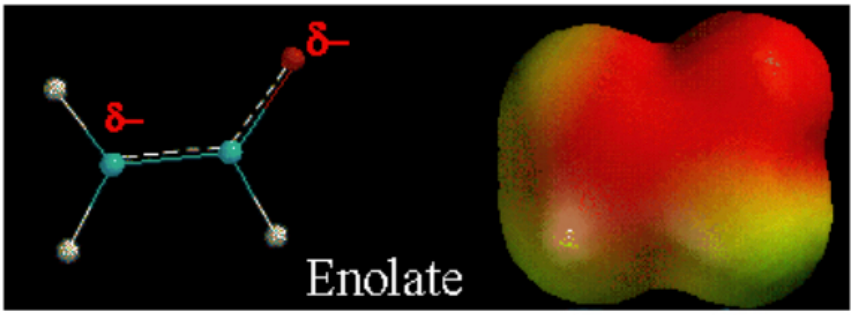
Stabilized by delocalization of ⊖ charge and a π-way

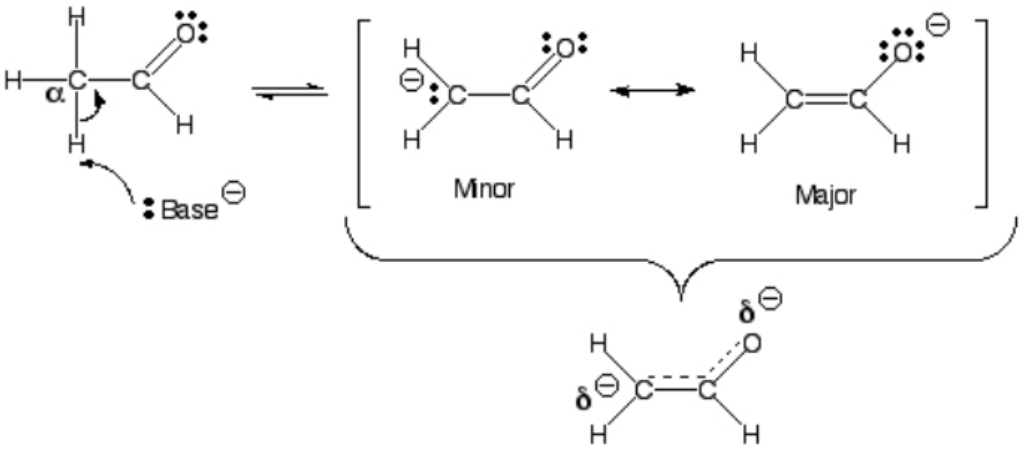
Compare:



$pK_a = 51$

Enolates as nucleophiles

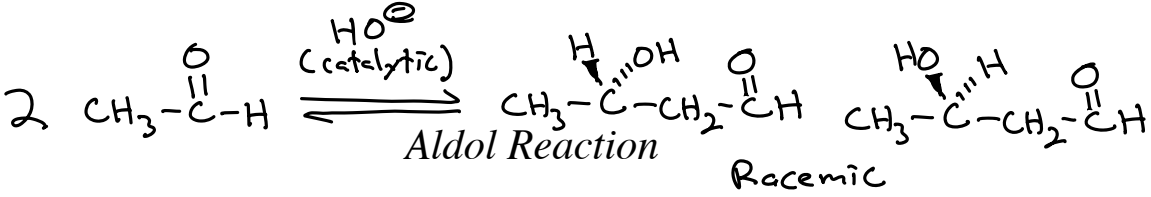




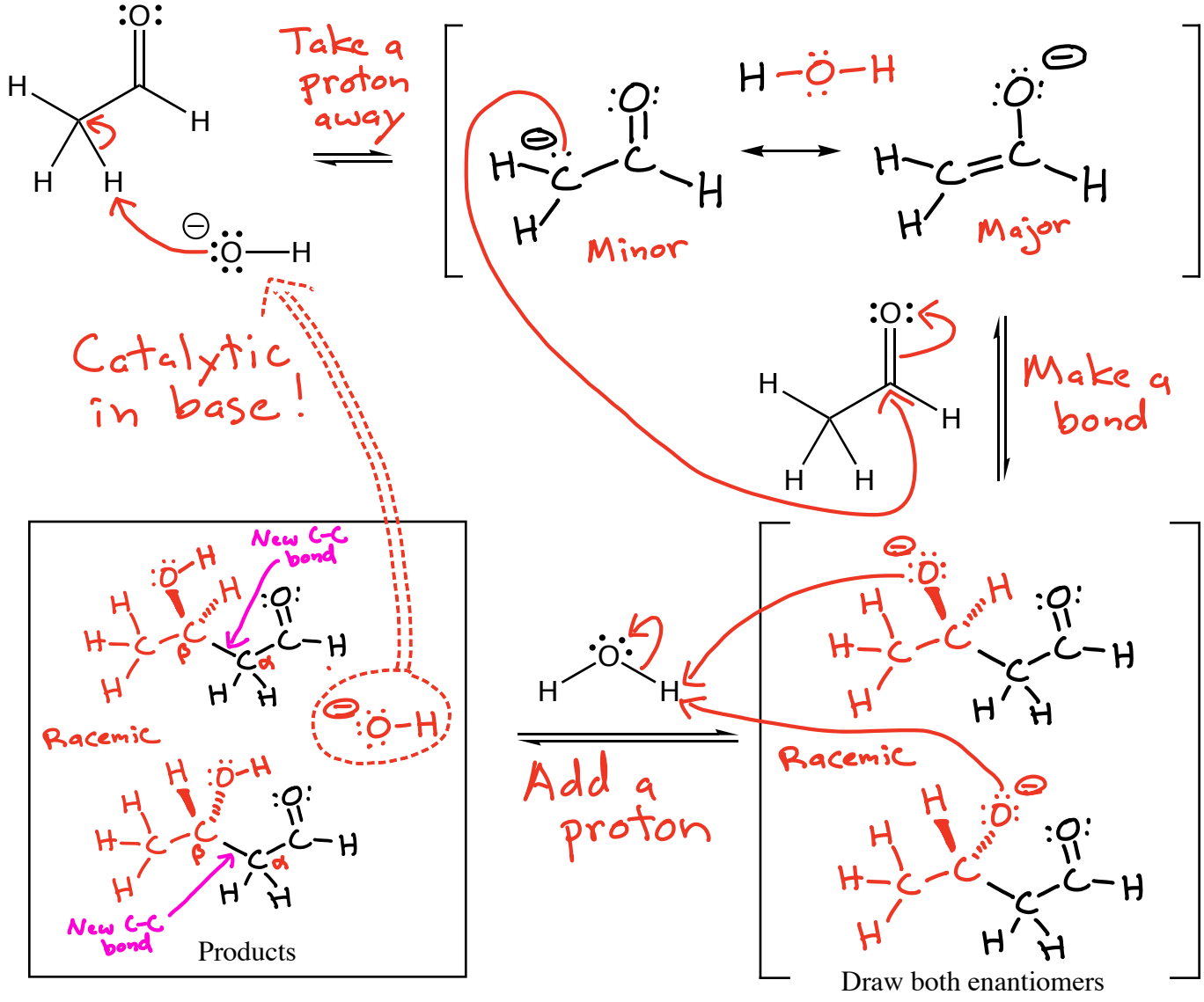
A) Enolates are resonance stabilized, with a partial negative charge on carbon and oxygen.

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.



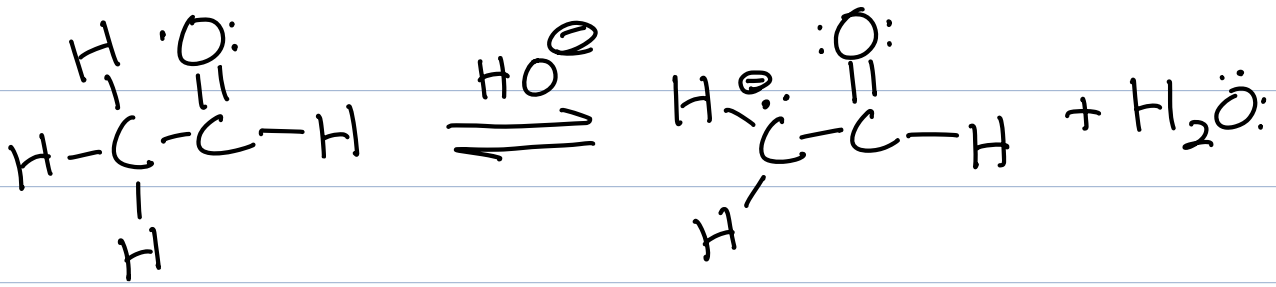
Aldol Reaction



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