
LONGHORN RUN
20 23

LONGHORN RUN REGISTRATION IS NOW OPEN!

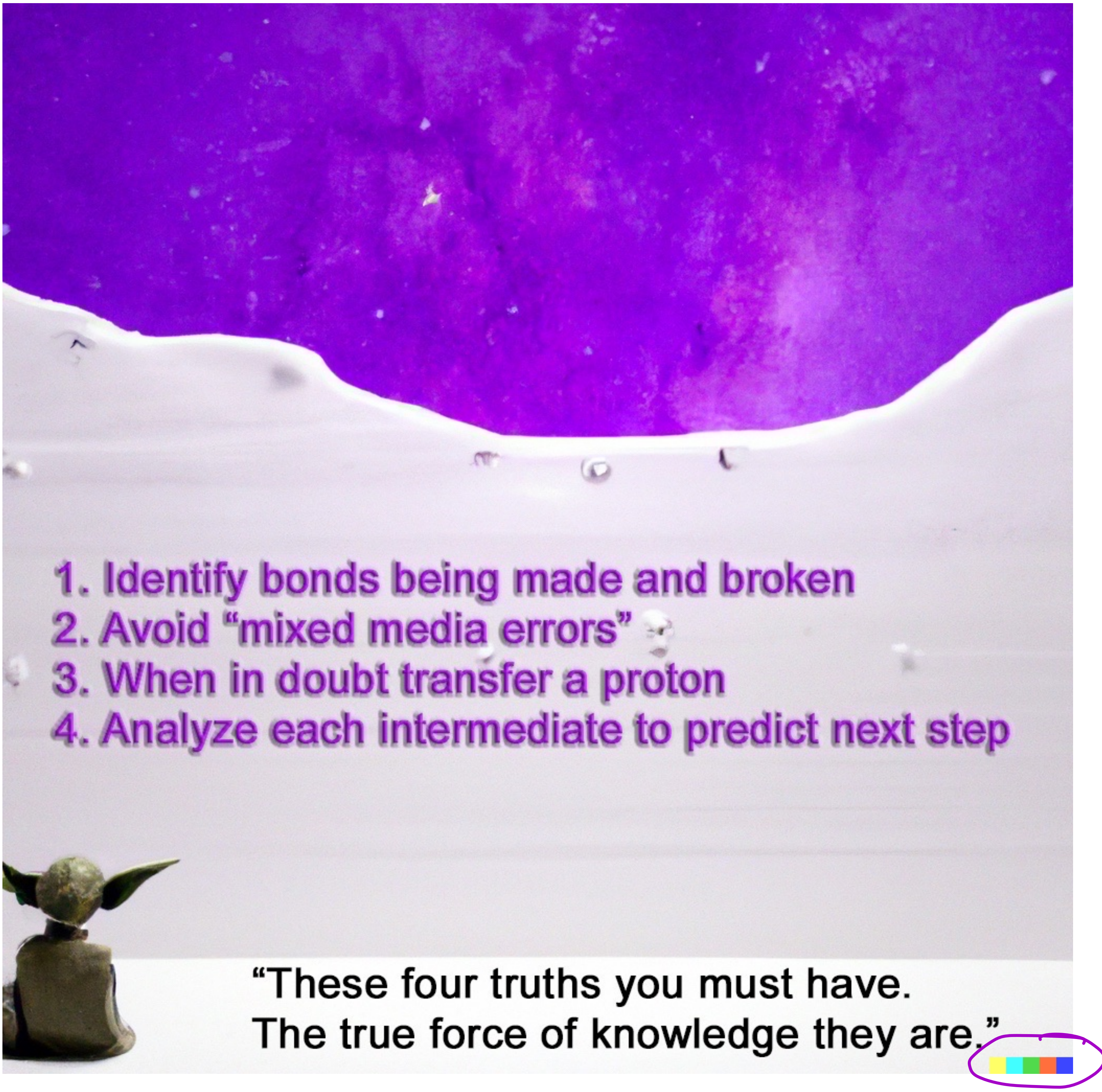
Saturday, April 18
The University of Texas at Austin
5K and 10K Race

Virtual options are available.

EARLY BIRD PRICING

5K: $45.11 | 10K: $50.48

Prices increase March 4


1. Identify bonds being made and broken
2. Avoid “mixed media errors”
3. When in doubt transfer a proton
4. Analyze each intermediate to predict next step
“These four truths you must have.
The true force of knowledge they are.”

For mechanisms, keep the following in mind:

1) Identify the bonds to be made and broken in the overall reaction
2) Avoid "mixed media errors"
   a) In acid, all the intermediates are positively-charged or neutral
   b) In base, all the intermediates are negatively-charged or neutral
   c) In neutral solution → the intermediates could be positively-charged, negatively-charged or neutral
3) When in doubt transfer a proton → protons move very fast
4) Analyze each intermediate carefully to predict the next step

Here are the keys to understanding mechanisms in 320N!!

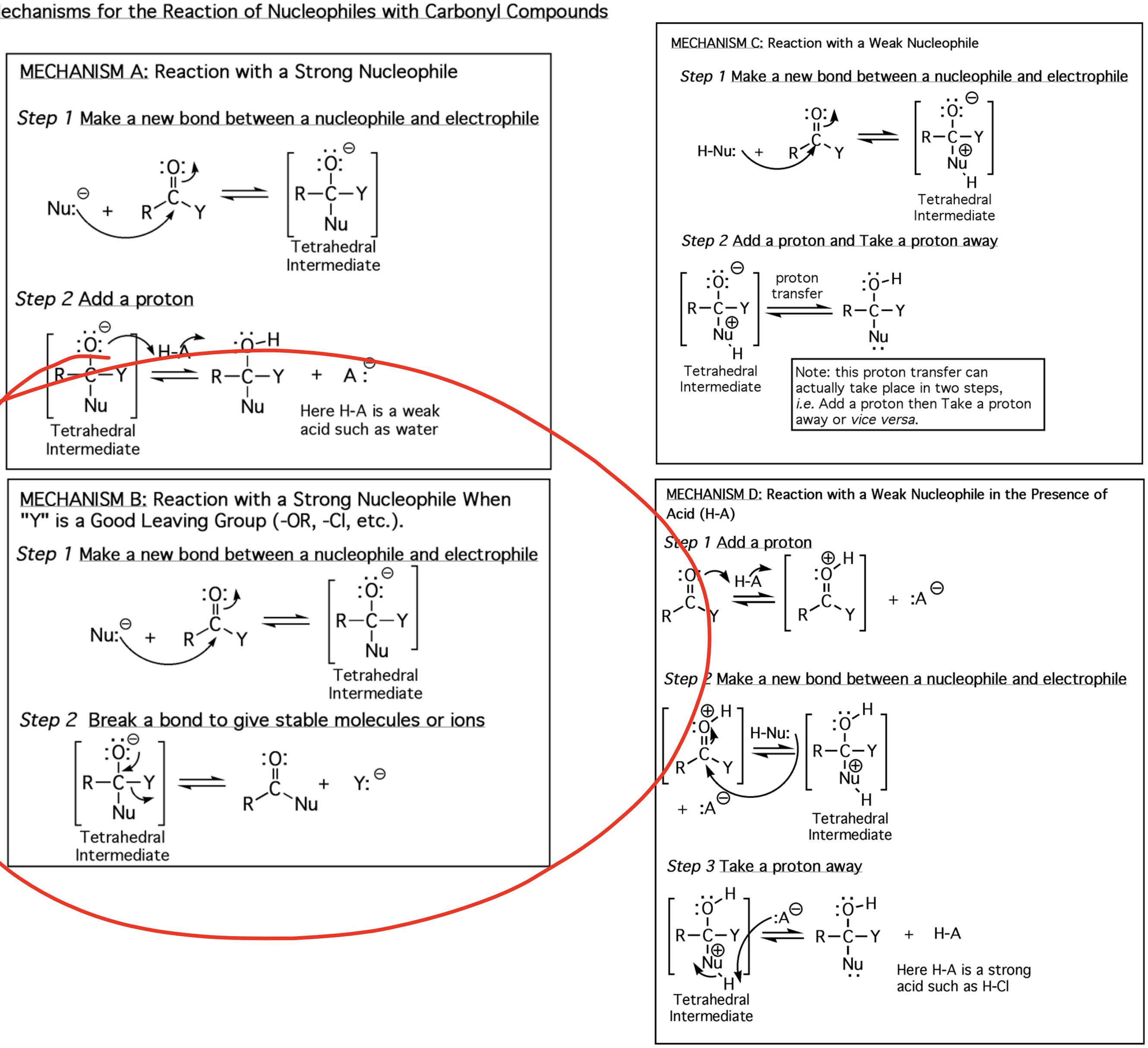
1) There are basically four different mechanisms elements that make up the steps of carbonyl reactions.

A) Make a bond between a nucleophile and an electrophile
B) Break a bond to give stable molecules or ions
C) Add a proton
D) Take a proton away

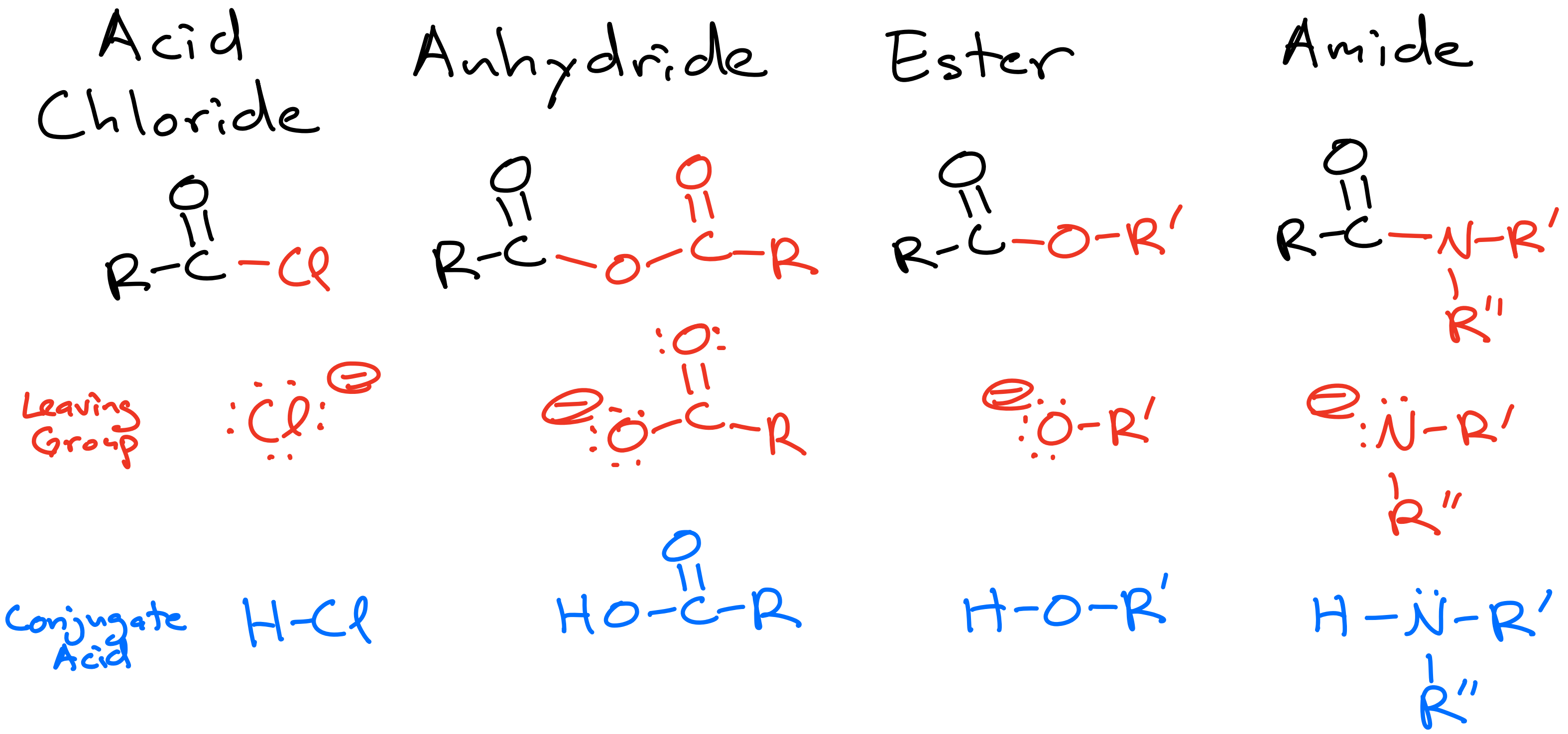
2) These same four mechanism elements describe most of the other mechanisms you have/will learn!!! (Yes, organic chemistry really is this simple if you look at it this way!!)

There are basically four different mechanisms that describe the vast majority of carbonyl reactions and these mechanisms are different combinations/ordering of the four mechanism elements listed above. In this class, I have termed them "Mechanism A", "Mechanism B", "Mechanism C", and "Mechanism D". They all involve a nucleophile attacking the partially positively charged carbon atom of the carbonyl to create a tetrahedral intermediate. Different reaction mechanisms are distinguished by the timing of protonation of the oxygen atom as well as the presence or absence of a leaving group attached to the carbonyl.

Four Mechanisms for the Reaction of Nucleophiles with Carbonyl Compounds



From Last Thursday's Lecture:



	Acid Chloride	Anhydride	Ester	Amide
Conjugate Acid	H–Cl	HO–C(=O)–R	H–O–R′	H–N(R″)–R′
pKa	-7	3-5	16	38

← Anion Stability

← Better Leaving Group Ability

← Reactivity of Carboxylic Acid Derivative

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

Characteristic Reactions of Carboxylic Acid Derivatives

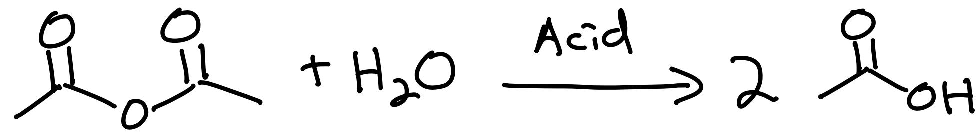
Mechanism B

The key issue is leaving group ability

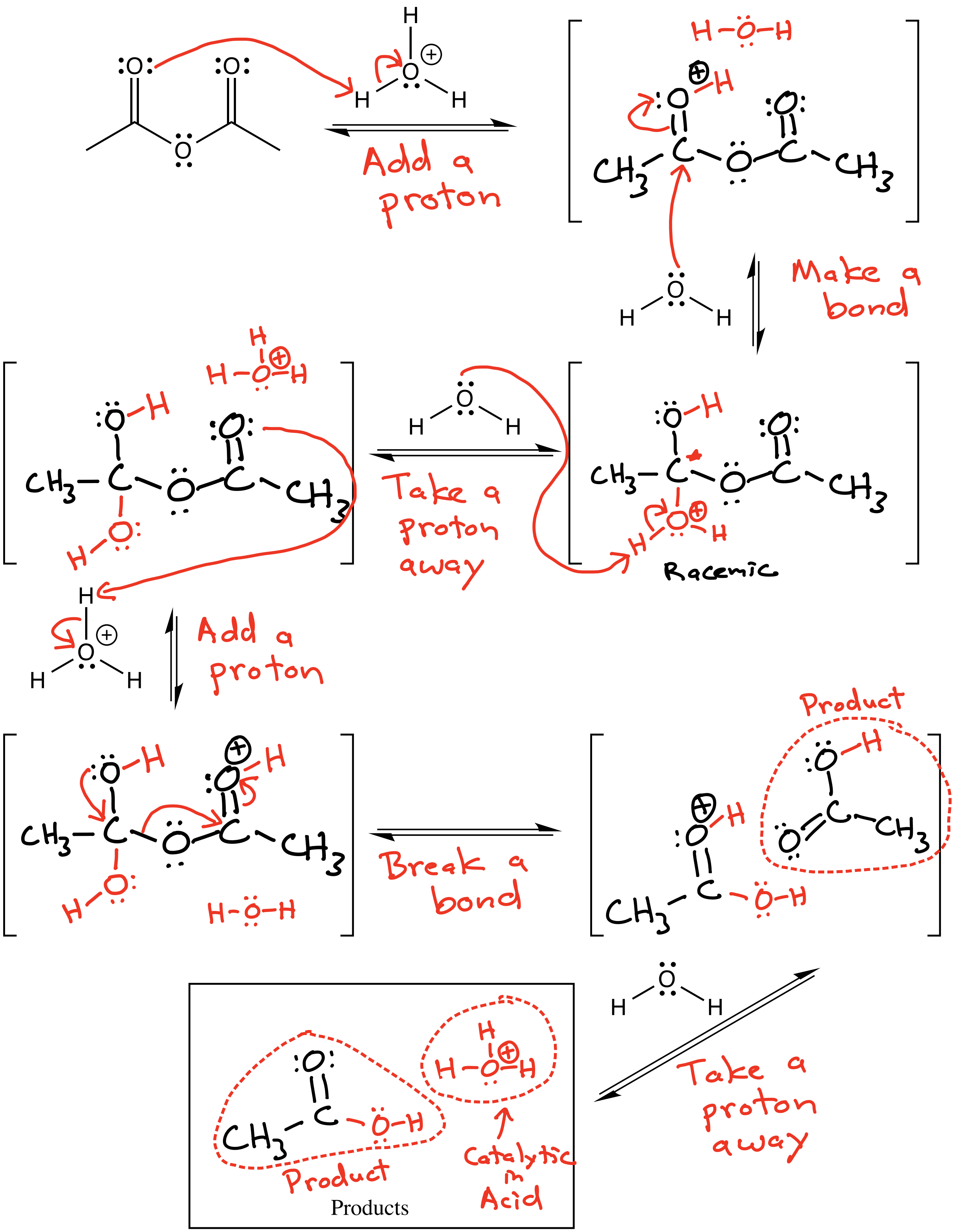
Both depend on anion stability:

- The more stable the anion of the leaving group, the better the leaving group ability ⇒ the more reactive the carboxylic acid derivative

- The relative leaving group ability is correlated with the pKa of the leaving group conjugate acid

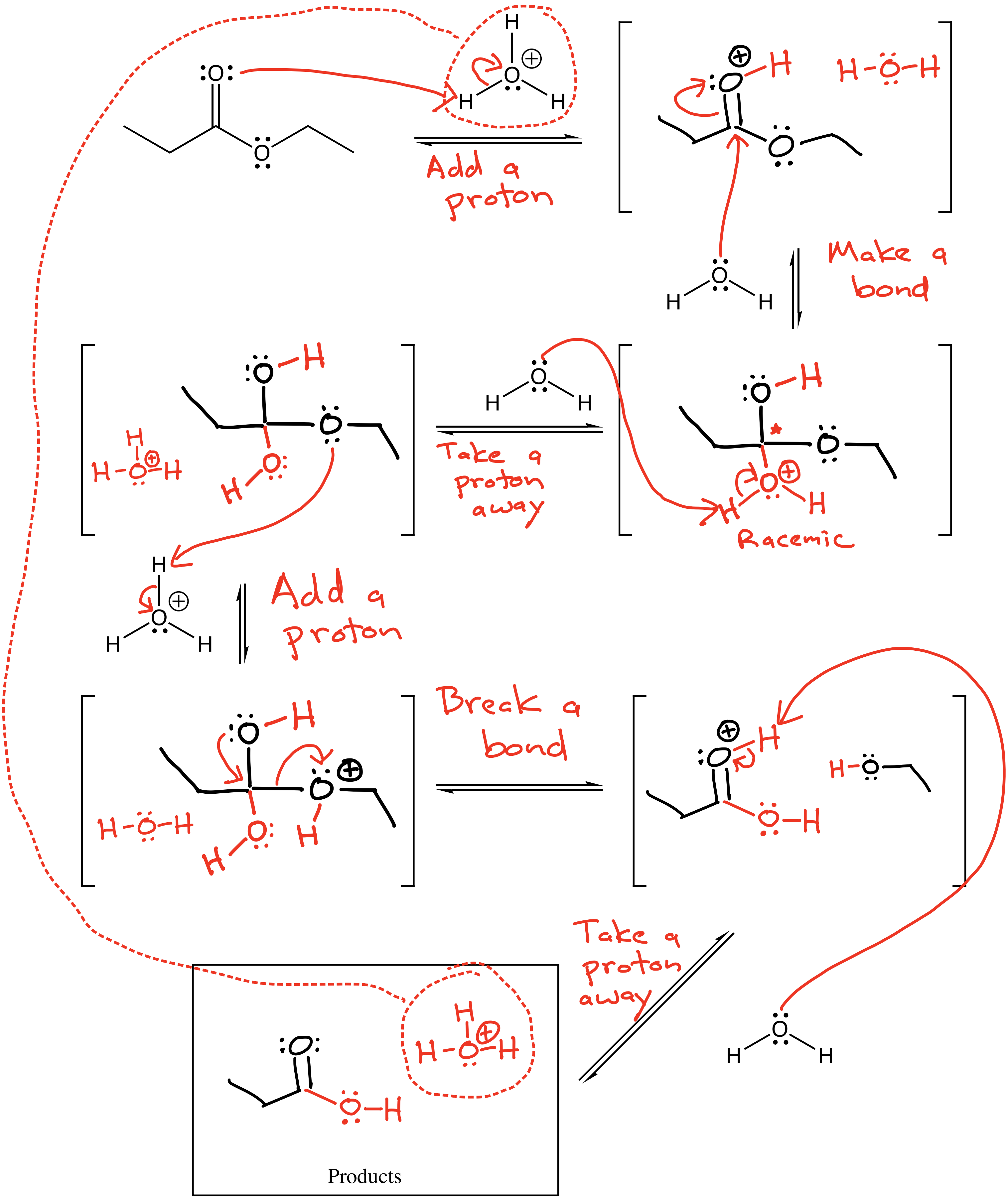


Acid Catalyzed Anhydride Hydrolysis



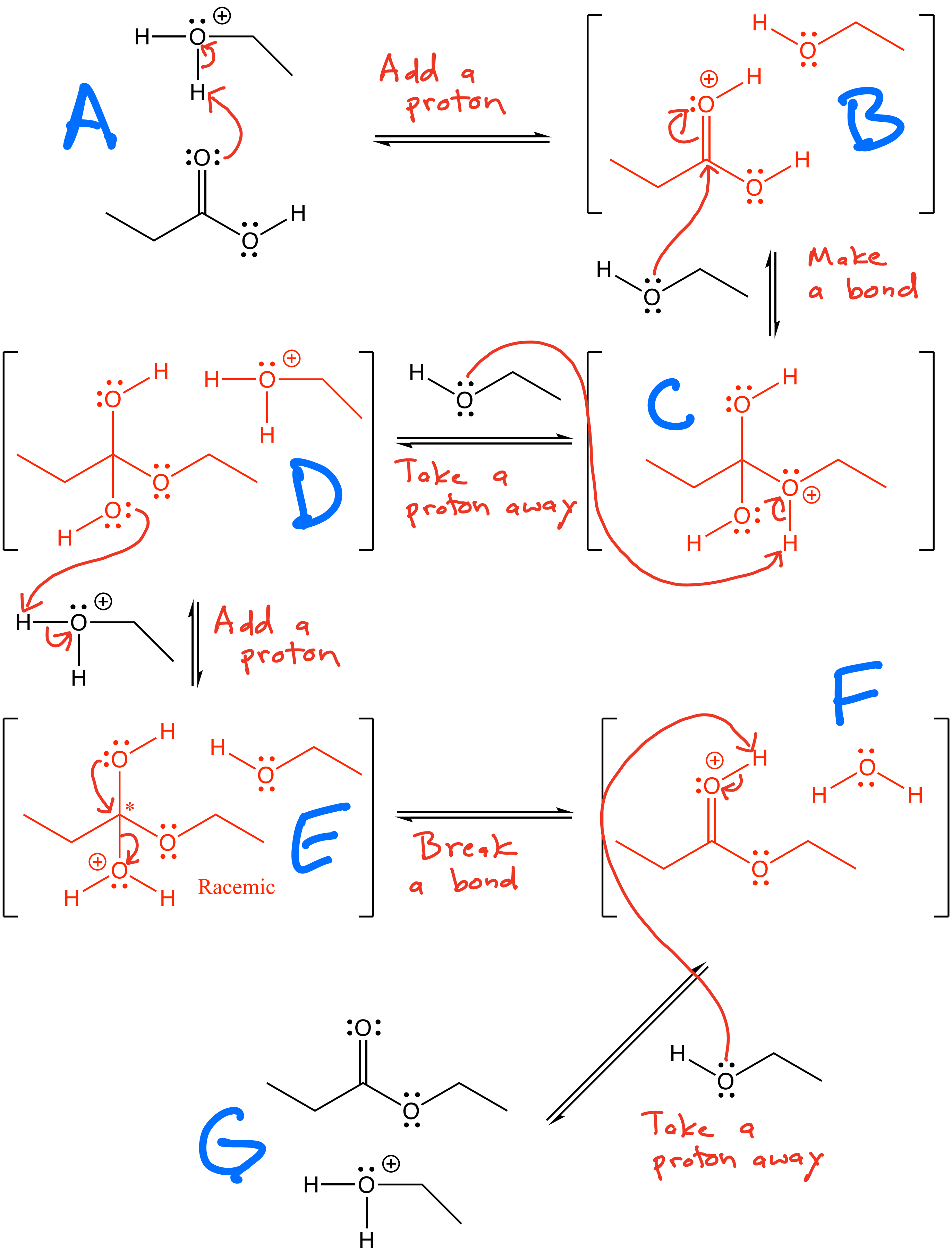
$$R-\overset{O}{\overset{\|}{C}}-OR' + H_2O \xrightarrow[\text{(catalytic)}]{H_2SO_4} R-\overset{O}{\overset{\|}{C}}-OH + R'OH$$

Acid Catalyzed Ester Hydrolysis



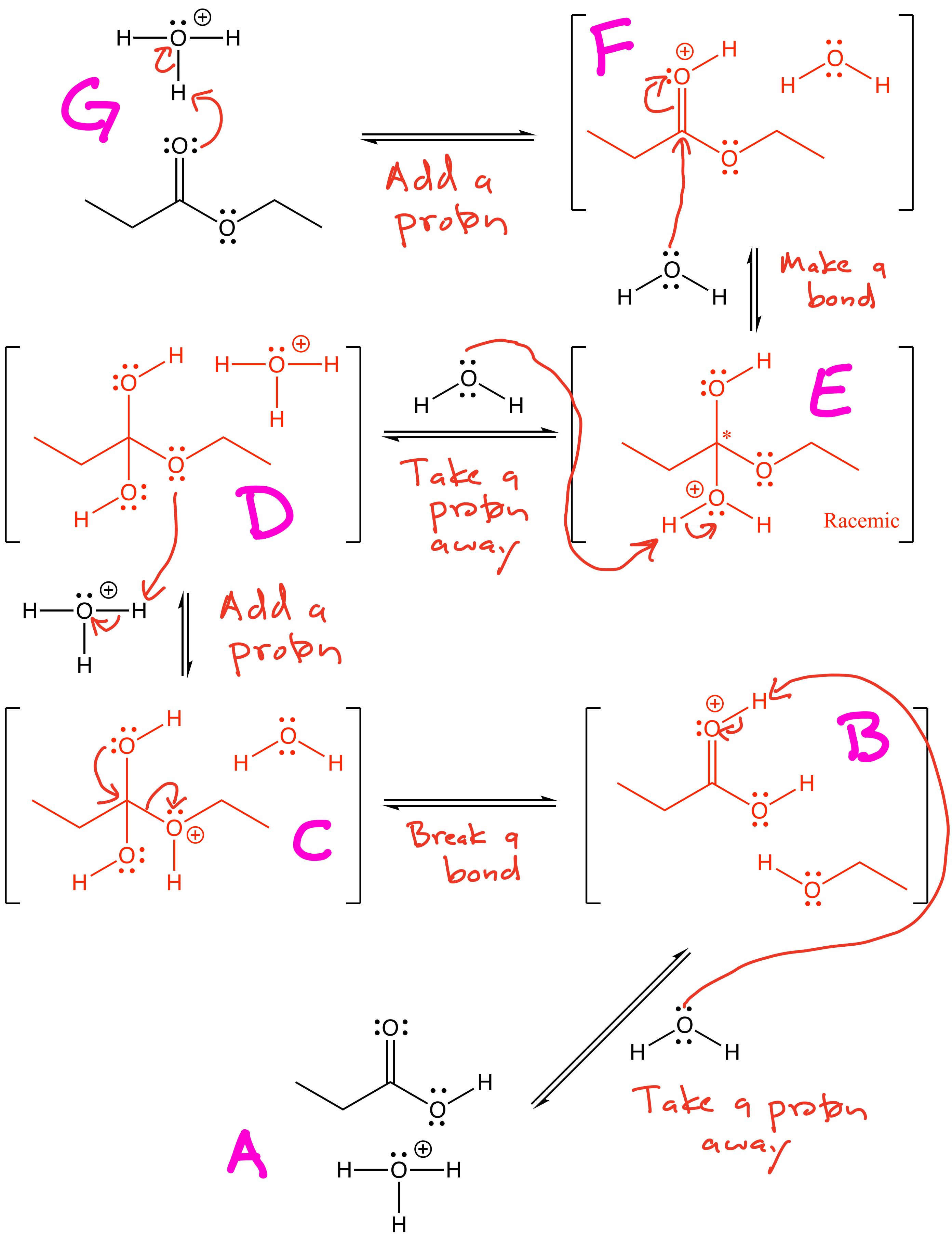
$$R\text{-}\overset{O}{\overset{\|}{C}}\text{-}OH + R'OH \xrightarrow[\text{(catalytic)}]{H_2SO_4} R\text{-}\overset{O}{\overset{\|}{C}}\text{-}OR' + H_2O$$

Microscopic Reversibilty: Acid Catalyzed Ester Hydrolysis-Fischer Esterification



$$R\text{-}\overset{O}{\overset{\|}{C}}\text{-}OR' + H_2O \xrightarrow[\text{(catalytic)}]{H_2SO_4} R\text{-}\overset{O}{\overset{\|}{C}}\text{-}OH + R'OH$$

Microscopic Reversibilty: Acid Catalyzed Ester Hydrolysis-Fischer Esterification



Fischer esterification →

$$R\text{-}\overset{O}{\overset{\|}{C}}\text{-}OH + R'OH \underset{}{\overset{H_2SO_4\ (\text{catalytic})}{\rightleftharpoons}} R\text{-}\overset{O}{\overset{\|}{C}}\text{-}OR' + H\text{-}O\text{-}H$$

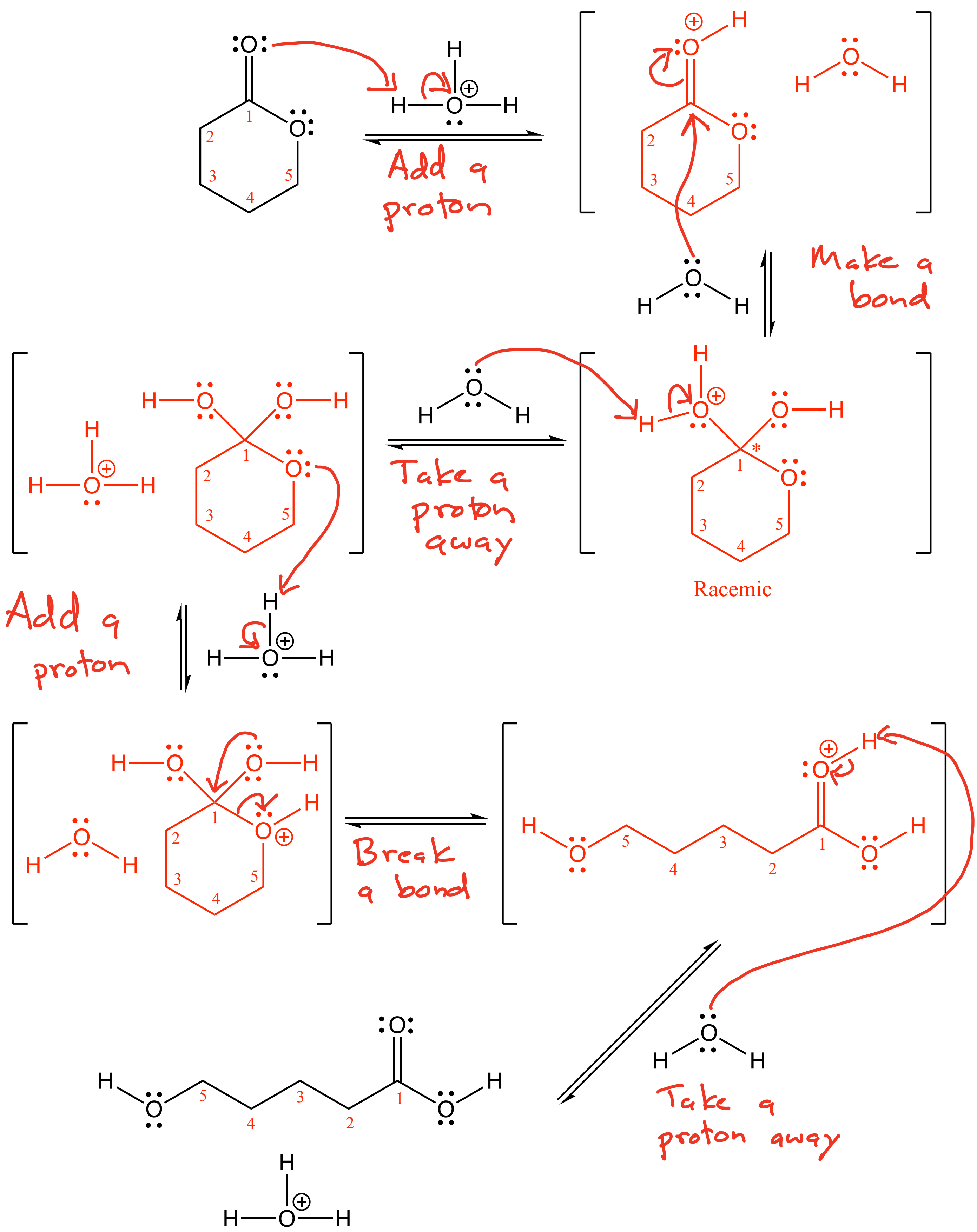
← Ester hydrolysis

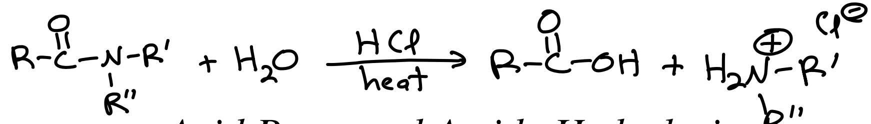
This reaction is reversible

It has the same mechanism in both directions!

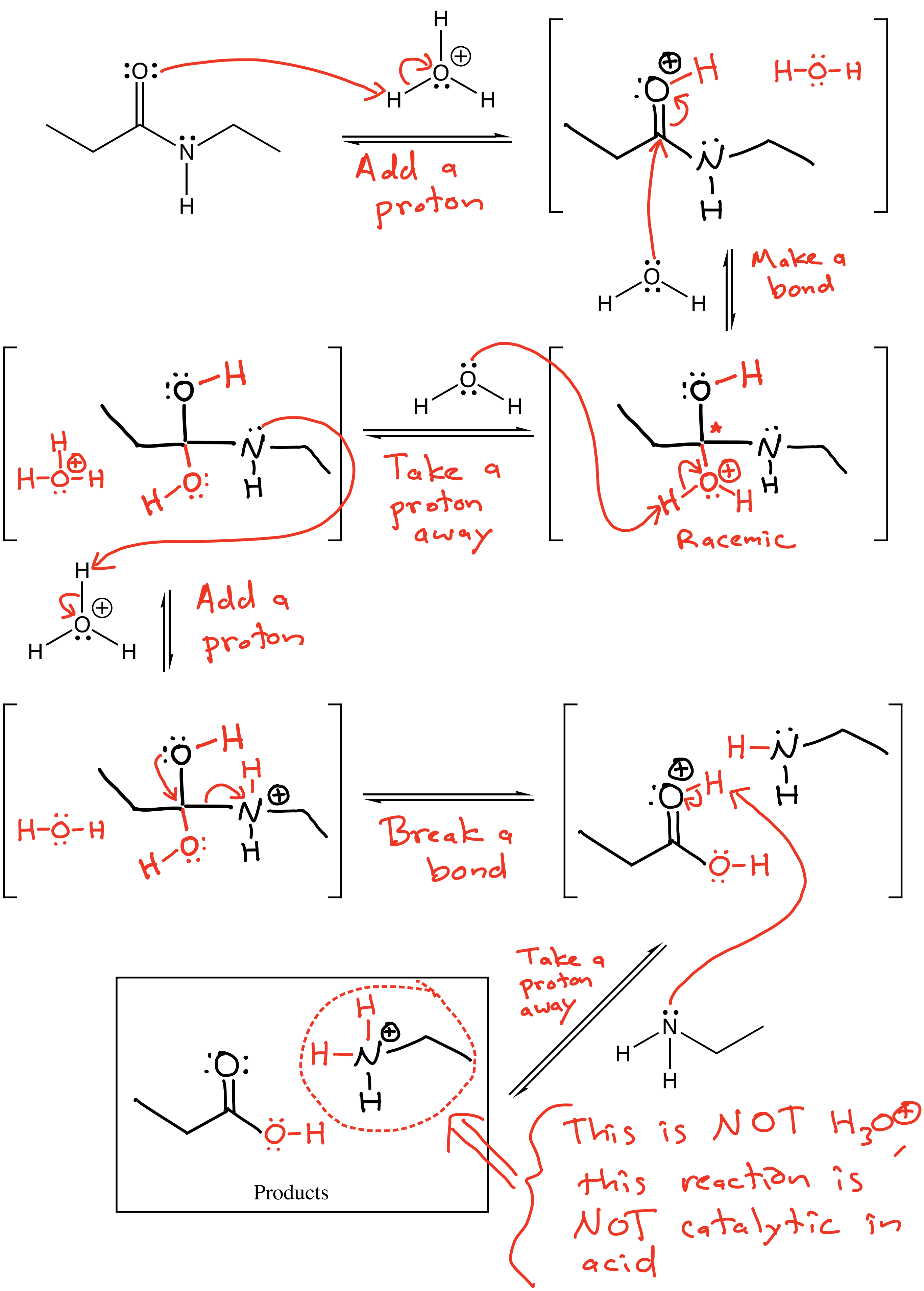
Important general rule
⇓
Microscopic Reversibility → The mechanism of a reversible process is the same (same intermediates) in both directions!

Microscopic Reversibilty: Acid Catalyzed Ester Hydrolysis-Fischer Esterification

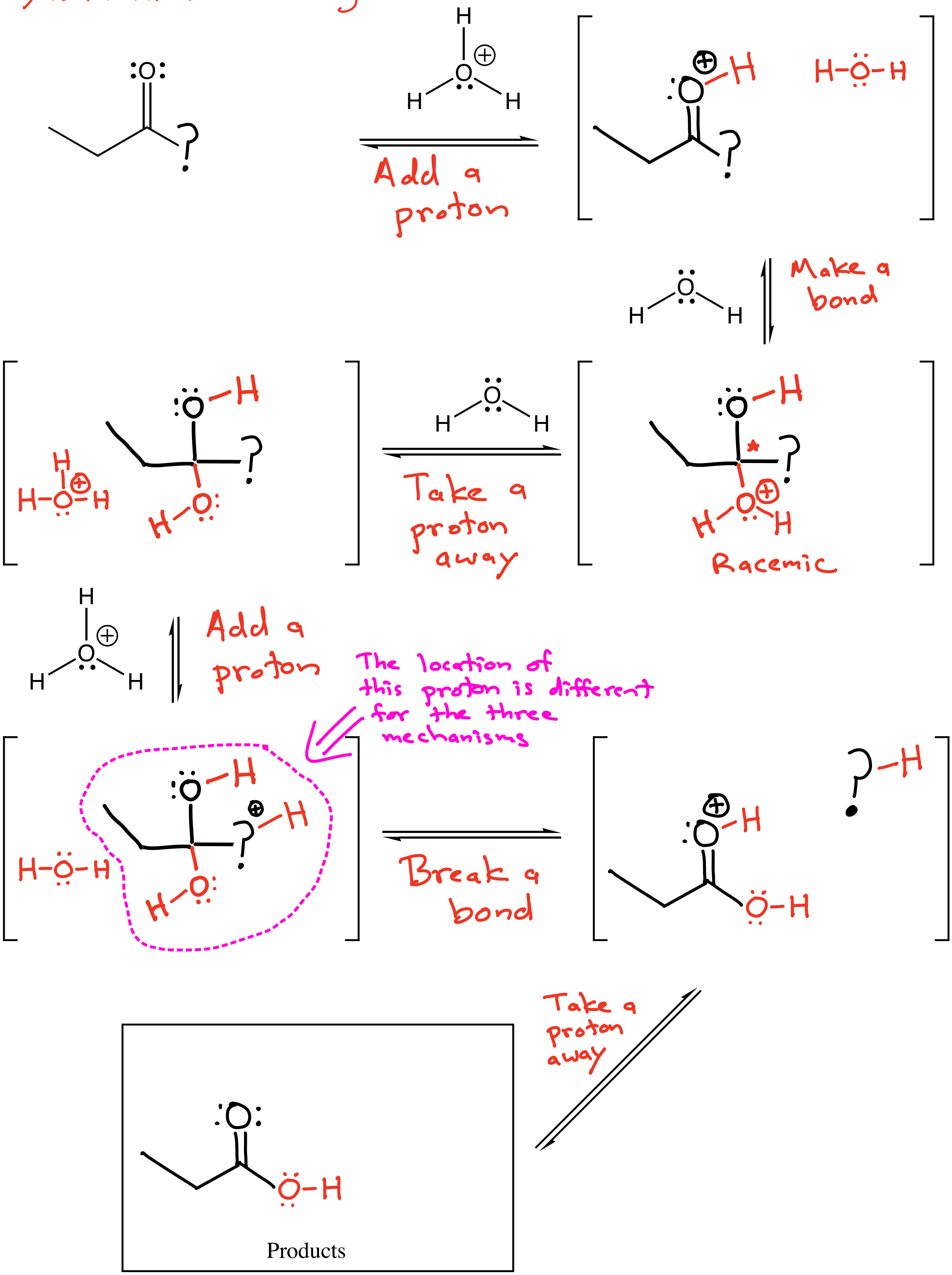




Acid Promoted Amide Hydrolysis

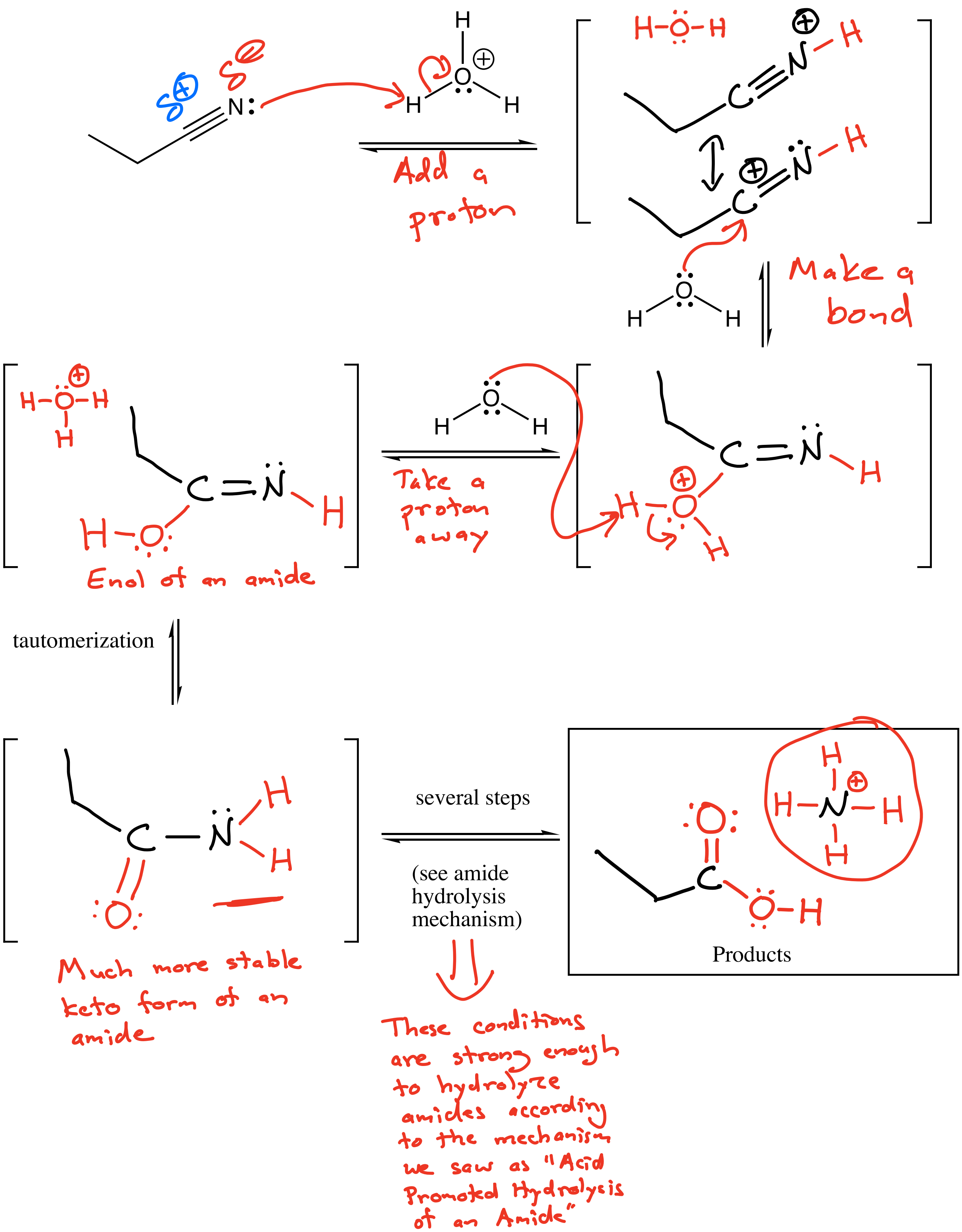


The following mechanism applies to which reaction we have seen? Trick Question → it applies to three reactions → Anhydride, ester and amide hydrolysis in acid! "Same song different verse!"

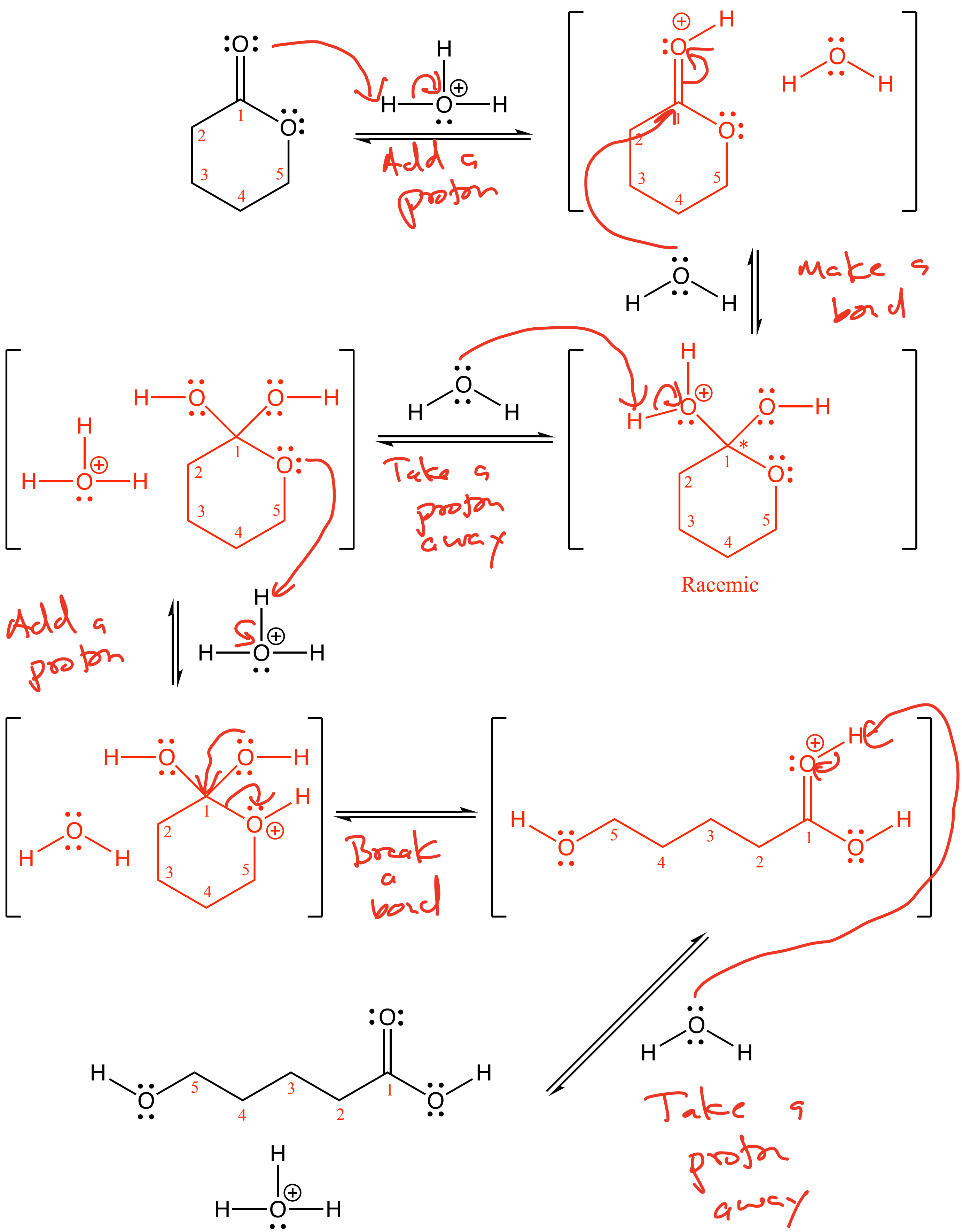


$$R-C\equiv N: + 2\,H_2O \xrightarrow[\text{heat}]{HCl} R-\overset{O}{\overset{\|}{C}}-OH + \overset{\oplus}{N}H_4\ Cl^{\ominus}$$

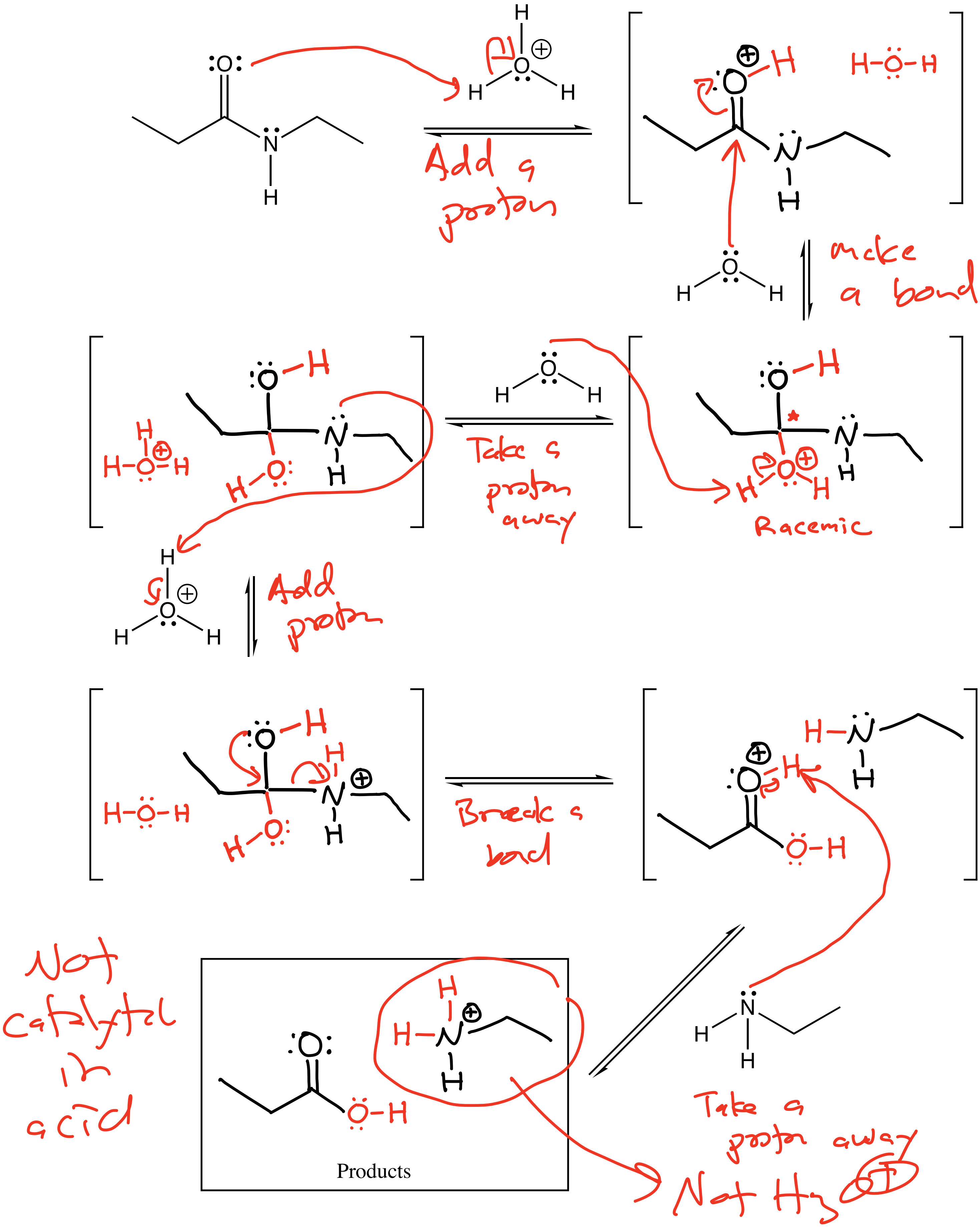
Acid Promoted Nitrile Hydrolysis

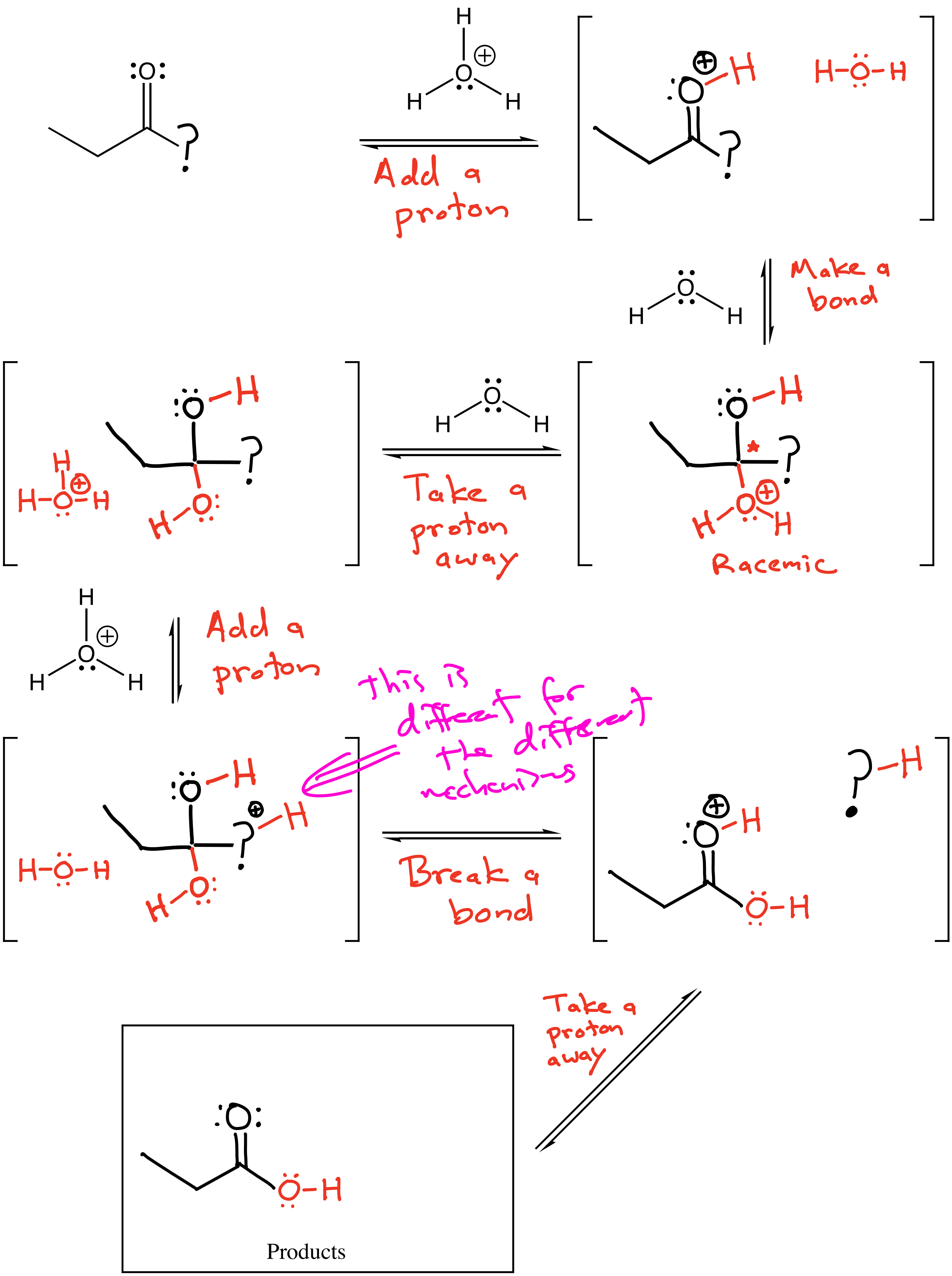


Microscopic Reversibilty: Acid Catalyzed Ester Hydrolysis-Fischer Esterification



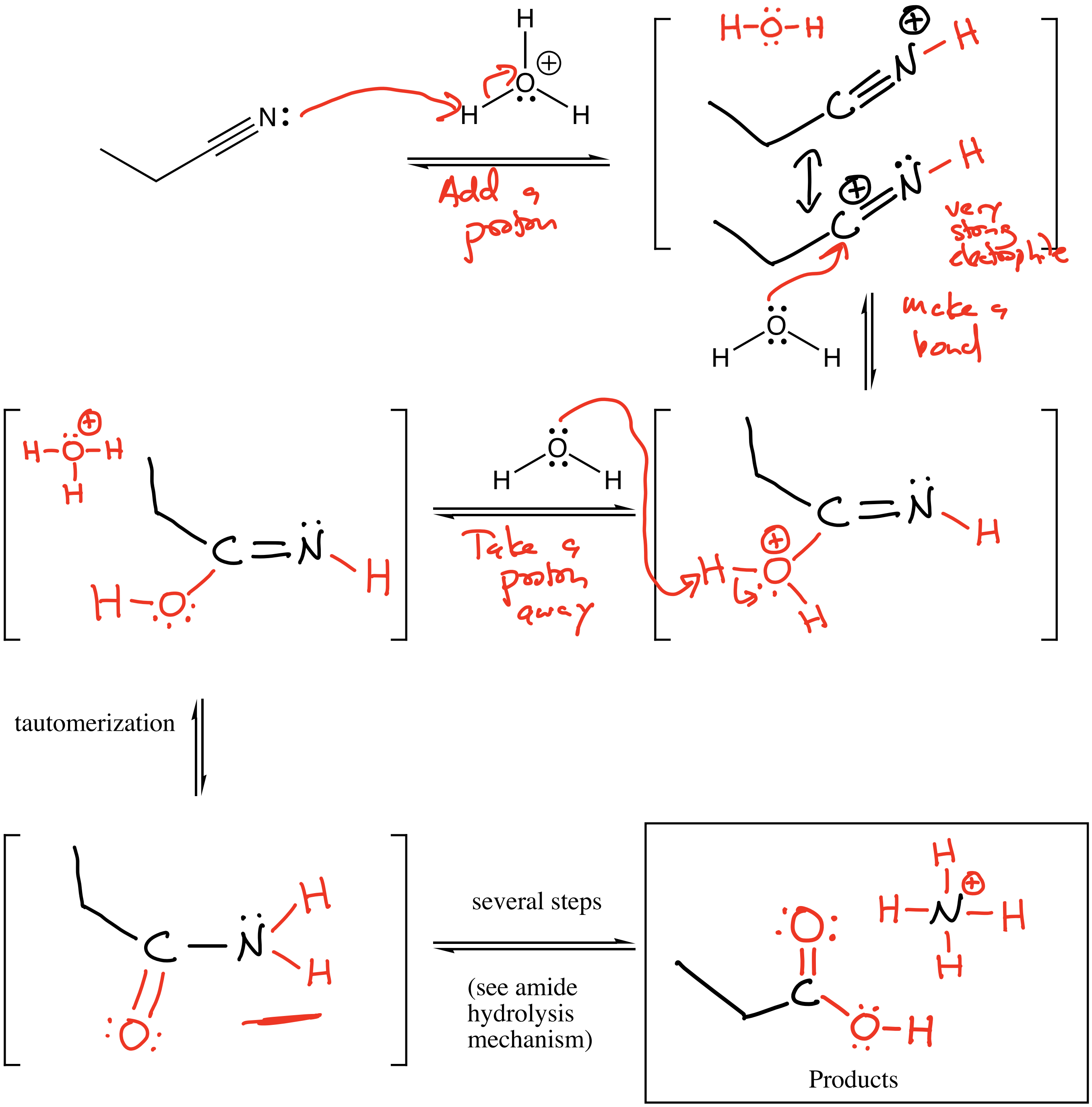
Acid Promoted Amide Hydrolysis

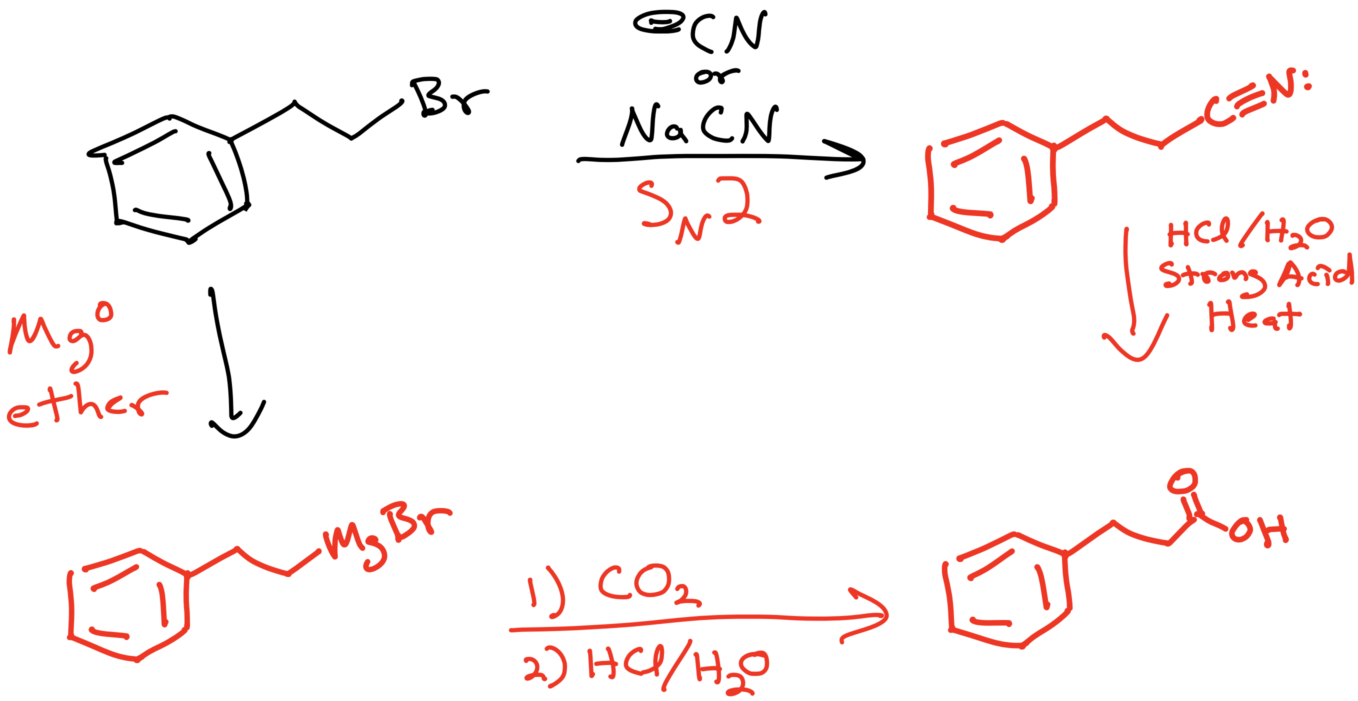


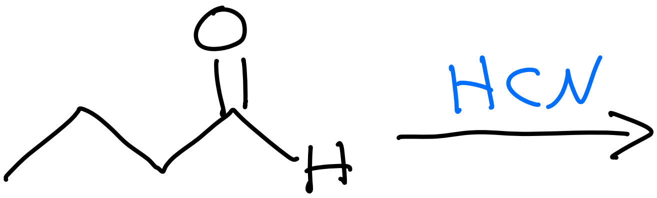

Add a proton
Make a bond
Take a proton away
Racemic
Add a proton
this is different for the different mechanisms
Break a bond
Take a proton away
Products

$$R-C\equiv N: + 2H_2O \xrightarrow[\text{heat}]{HCl} R-\overset{O}{\overset{\|}{C}}-OH + \overset{\oplus}{N}H_4$$

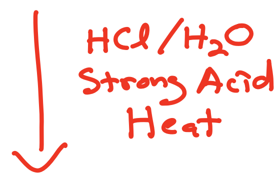
Acid Promoted Nitrile Hydrolysis




Br
⊖CN
or
NaCN
SN2
C≡N:
HCl/H2O
Strong Acid
Heat
Mg0
ether
MgBr
1) CO2
2) HCl/H2O
O
OH


O
H
HCN

KRE →


HCl/H2O
Strong Acid
Heat