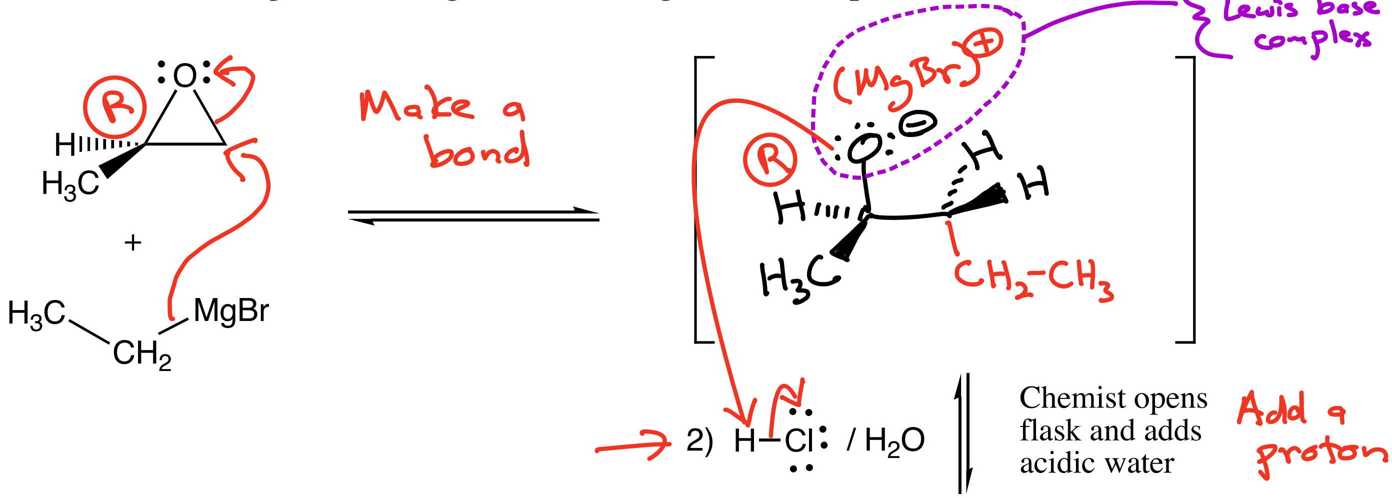
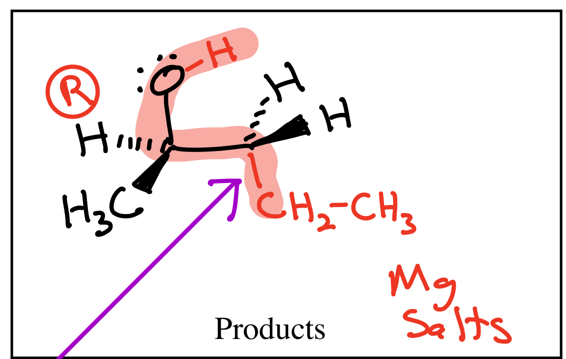
Organolithium and Gilman reagents react the same way as Grignard reagents in this reaction.

Grignard Reagent Reacting with an Epoxide

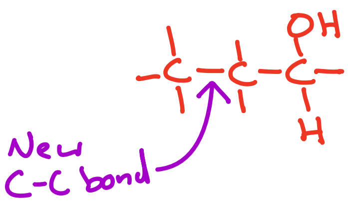


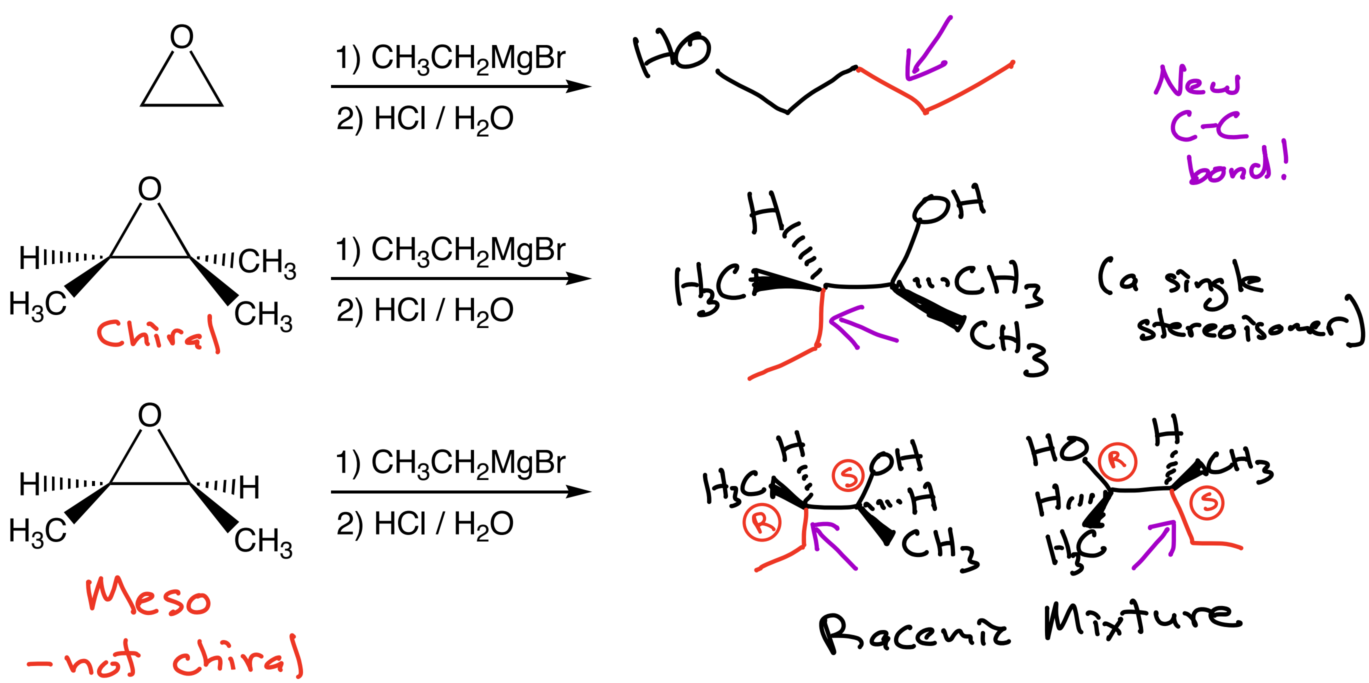


New C-C bond!

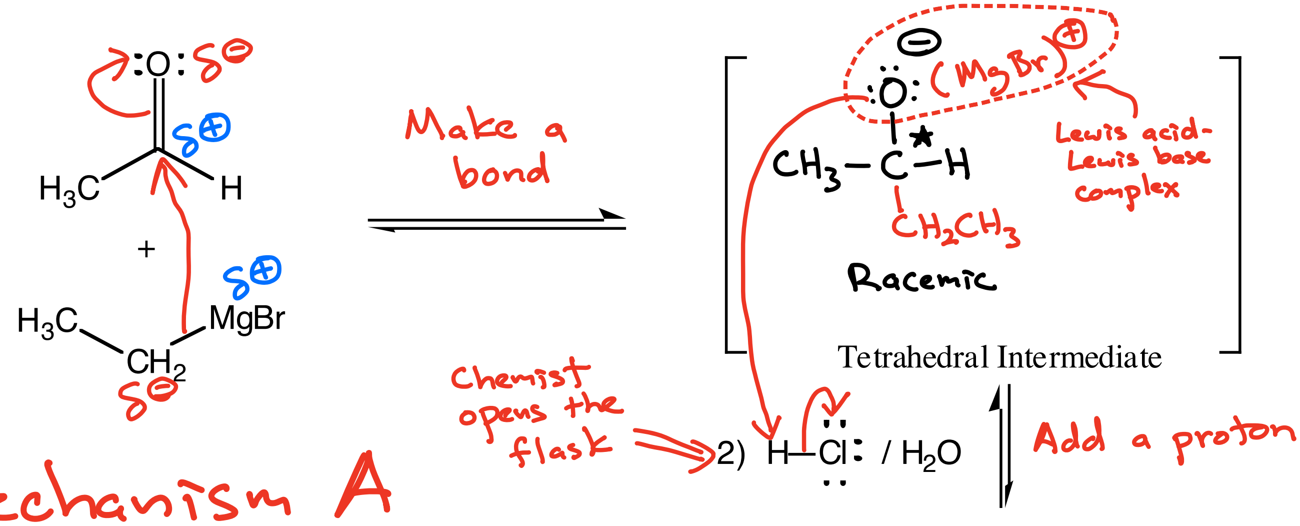
Key Recognition Element (KRE):

There is a new C-C bond that is two carbon atoms away from an OH group





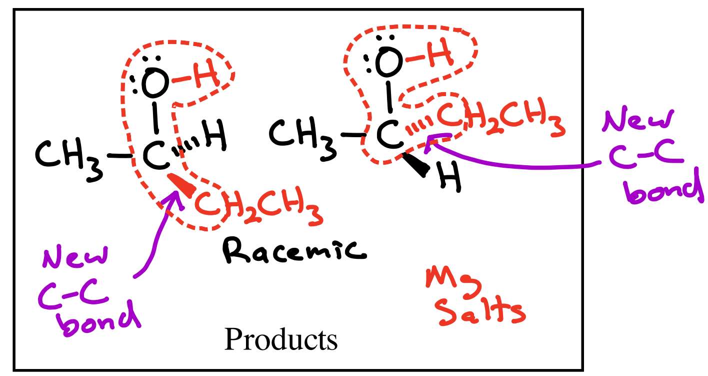
Grignard Reagent Reacting with an Aldehyde or Ketone

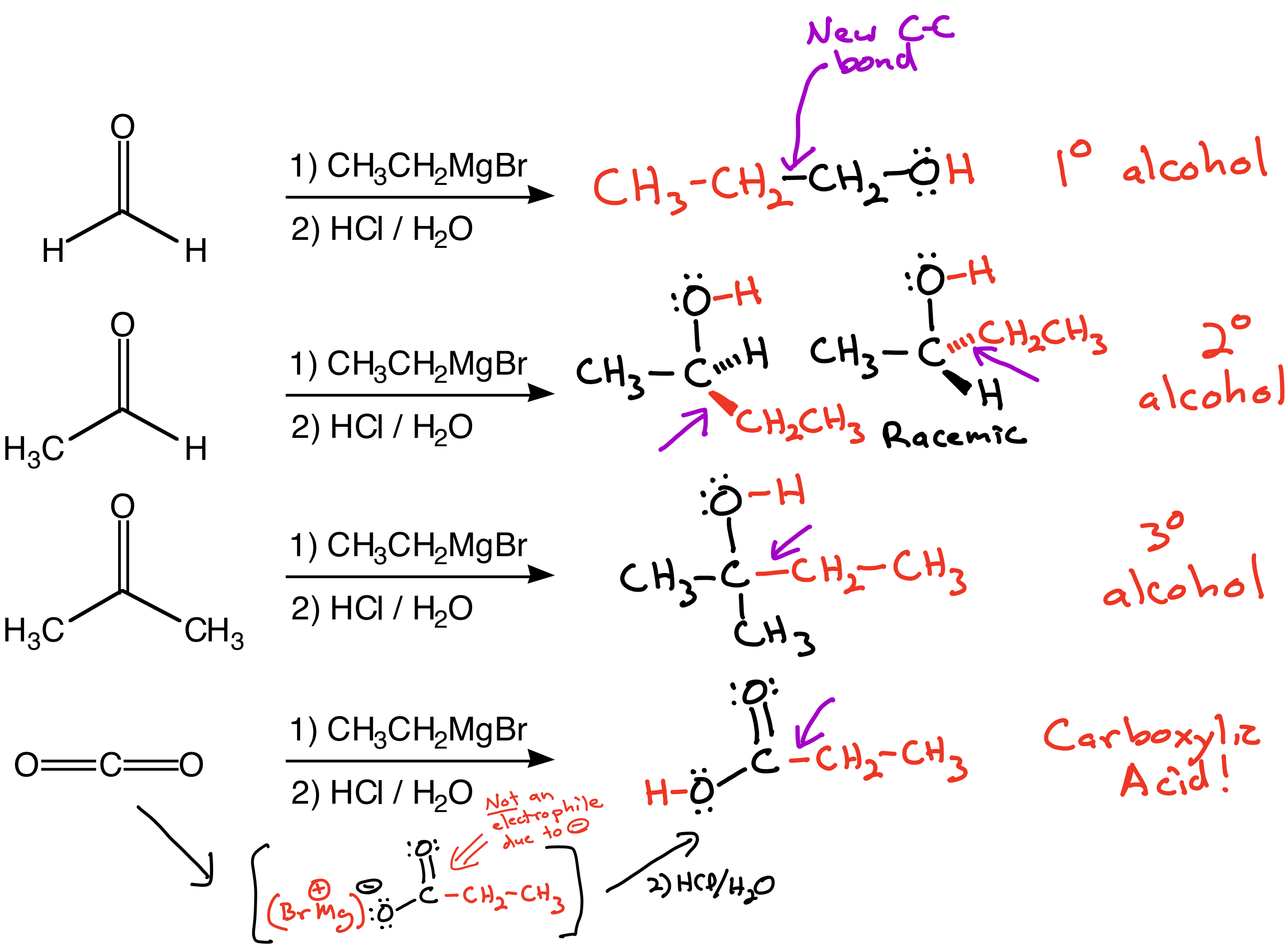


Mechanism A

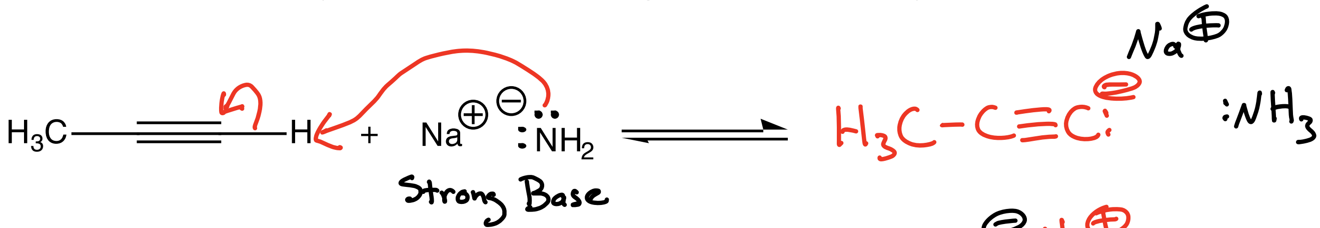
Key Recognition Element (KRE):

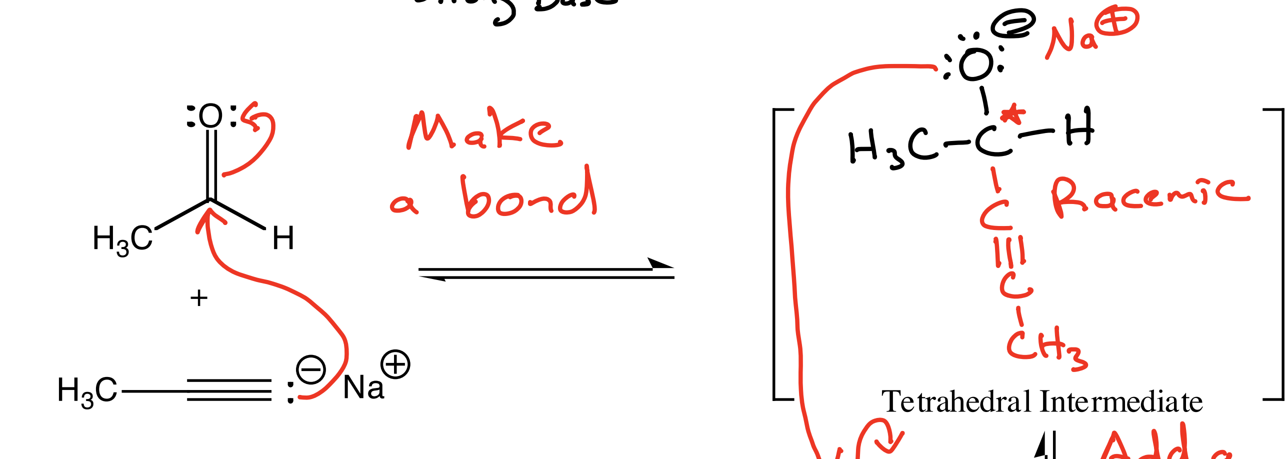
-OH group attached the same C atom as a new C–C bond





Alkyne Anion Reacting with an Aldehyde or Ketone

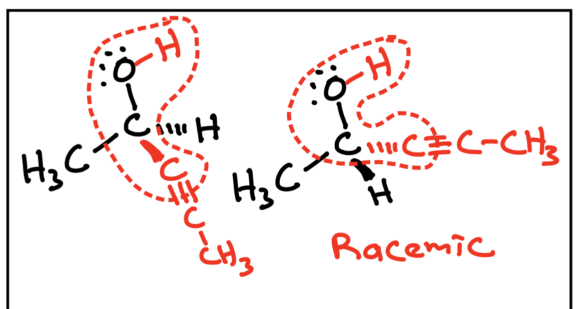




Mechanism A

Key Recognition Element (KRE):

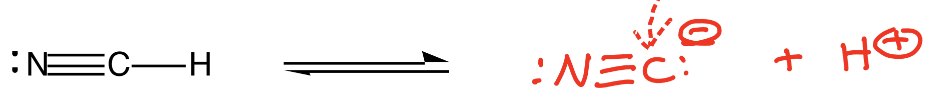
OH group on the carbon that makes a new C-C bond to an sp C atom (alkyne)

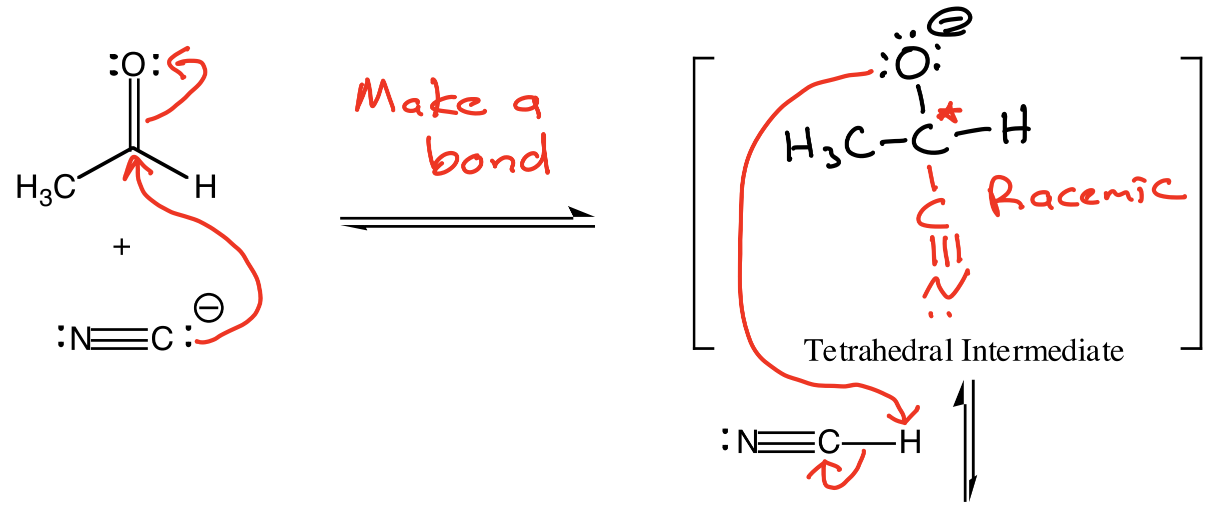


Products

HCN Reacting with an Aldehyde or Ketone

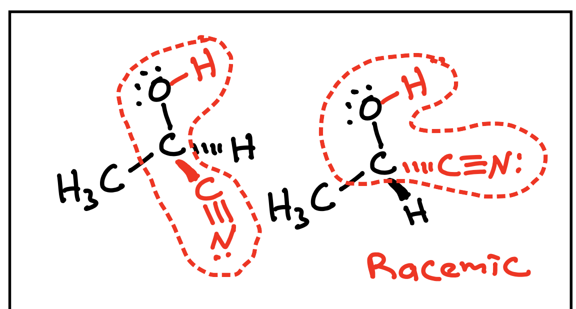
Reacts on the C atom because that makes stronger bonds





Key Recognition Element (KRE):

Cyanohydrin → OH on a C atom that made a new C–C bond to –C≡N:

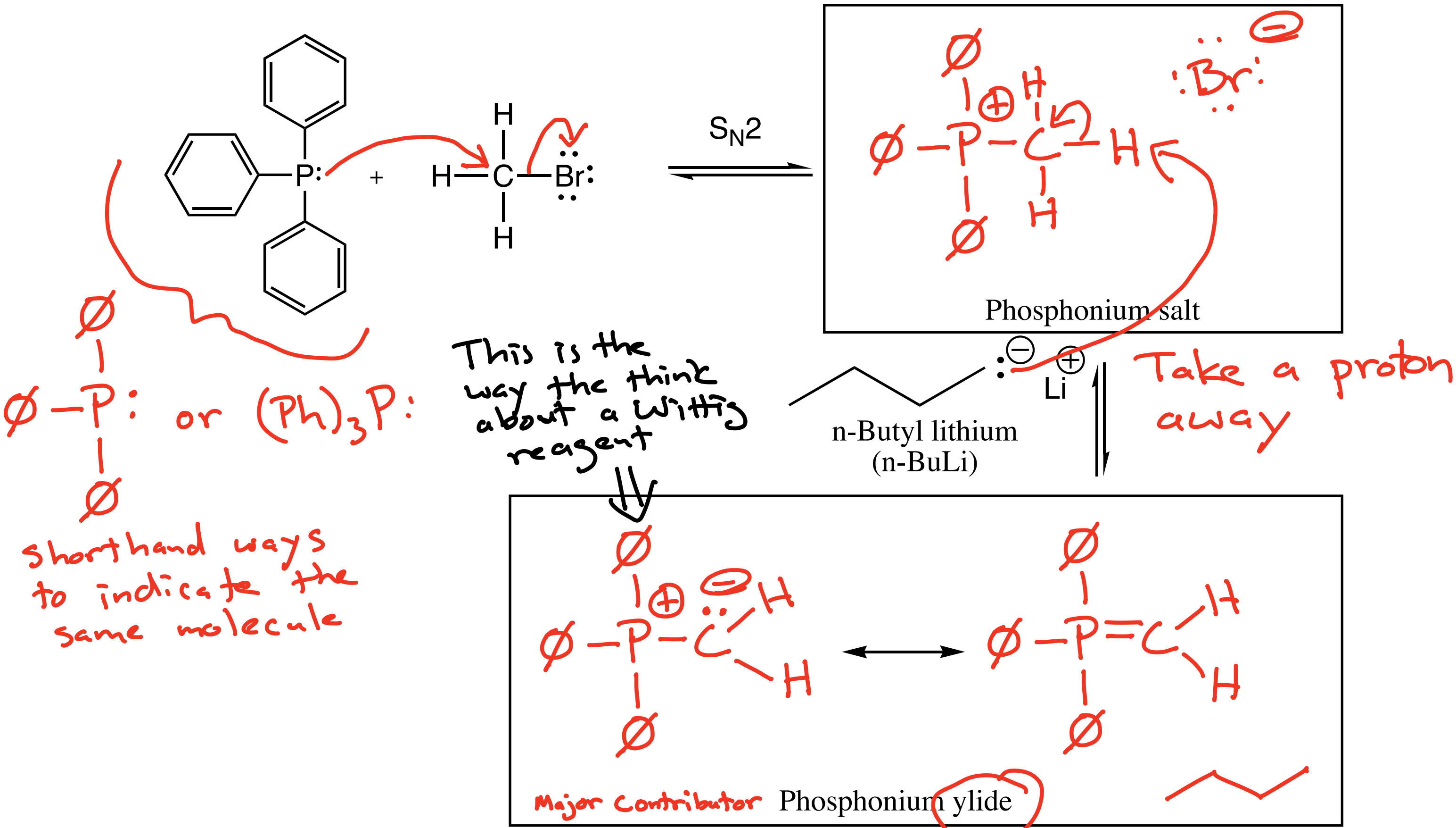


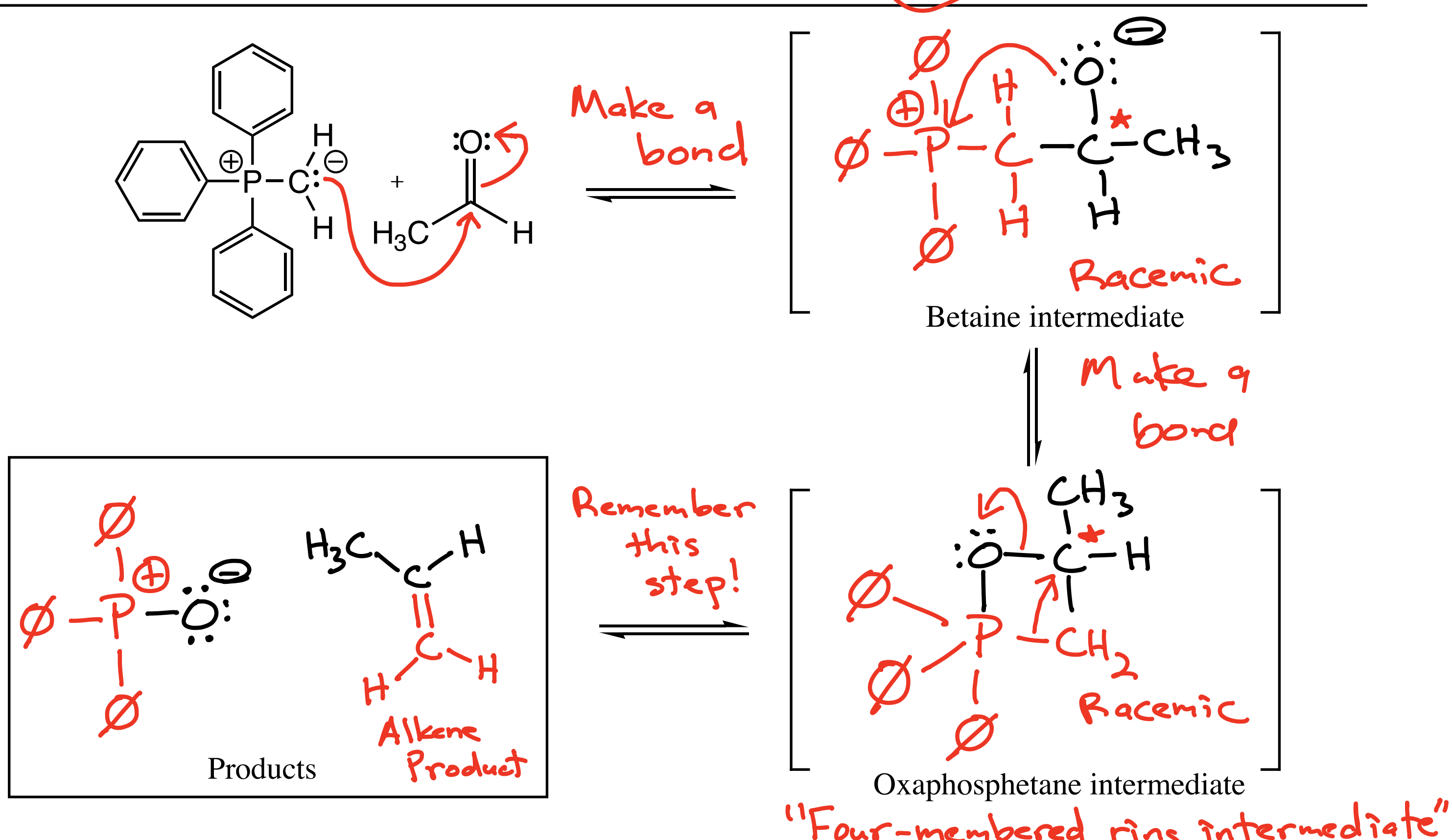
Products

Time capsule → cyanohydrins can be hydrolyzed in H_2SO_4/H_2O to give α-hydroxyacids

"alpha"

Wittig Reaction



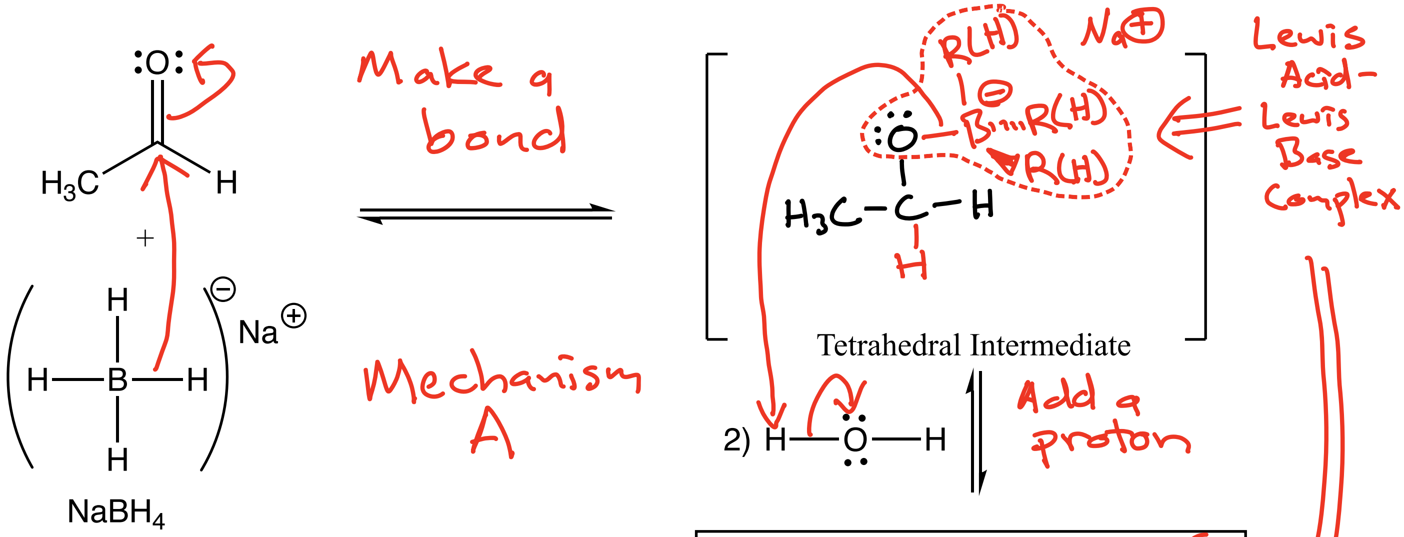


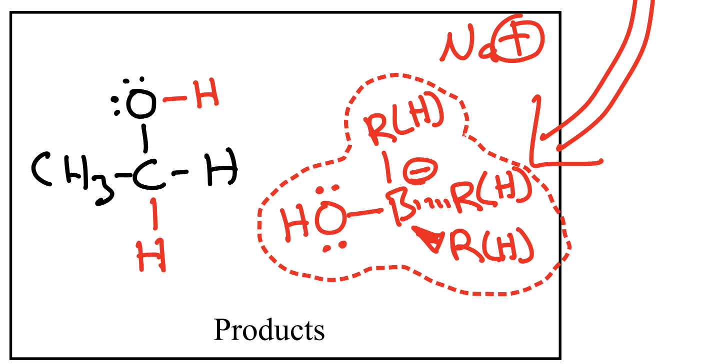
Key Recognition Element (KRE):

Alkene → New C=C where the C=O was!

or LiAlH4

Sodium Borohydride Reacting with an Aldehyde or Ketone





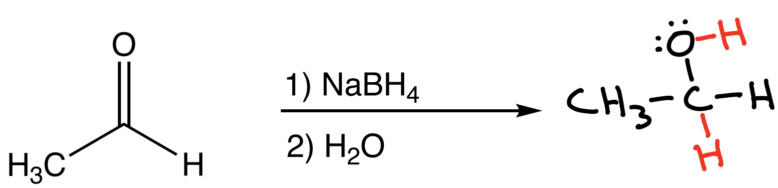
Key Recognition Element (KRE):

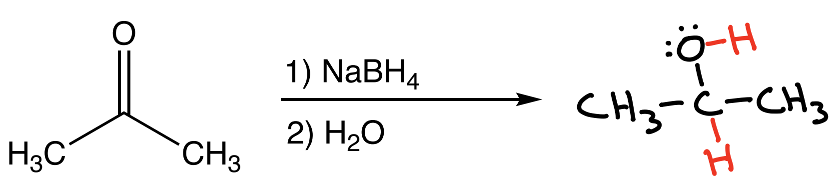
An -OH group where there was a C=O of an aldehyde or ketone

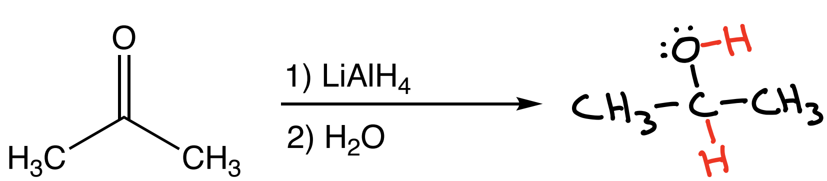
All four H of $\overset{\ominus}{B}H_4$ react!

$$4\ CH_3-\overset{O}{\overset{\|}{C}}-H + \overset{\ominus}{B}H_4 \rightleftharpoons\rightleftharpoons\rightleftharpoons\rightleftharpoons (CH_3CH_2-O)_4\overset{\ominus}{B} \xrightarrow{2)\ H_2O} 4\ CH_3CH_2OH$$

+ Borate salts



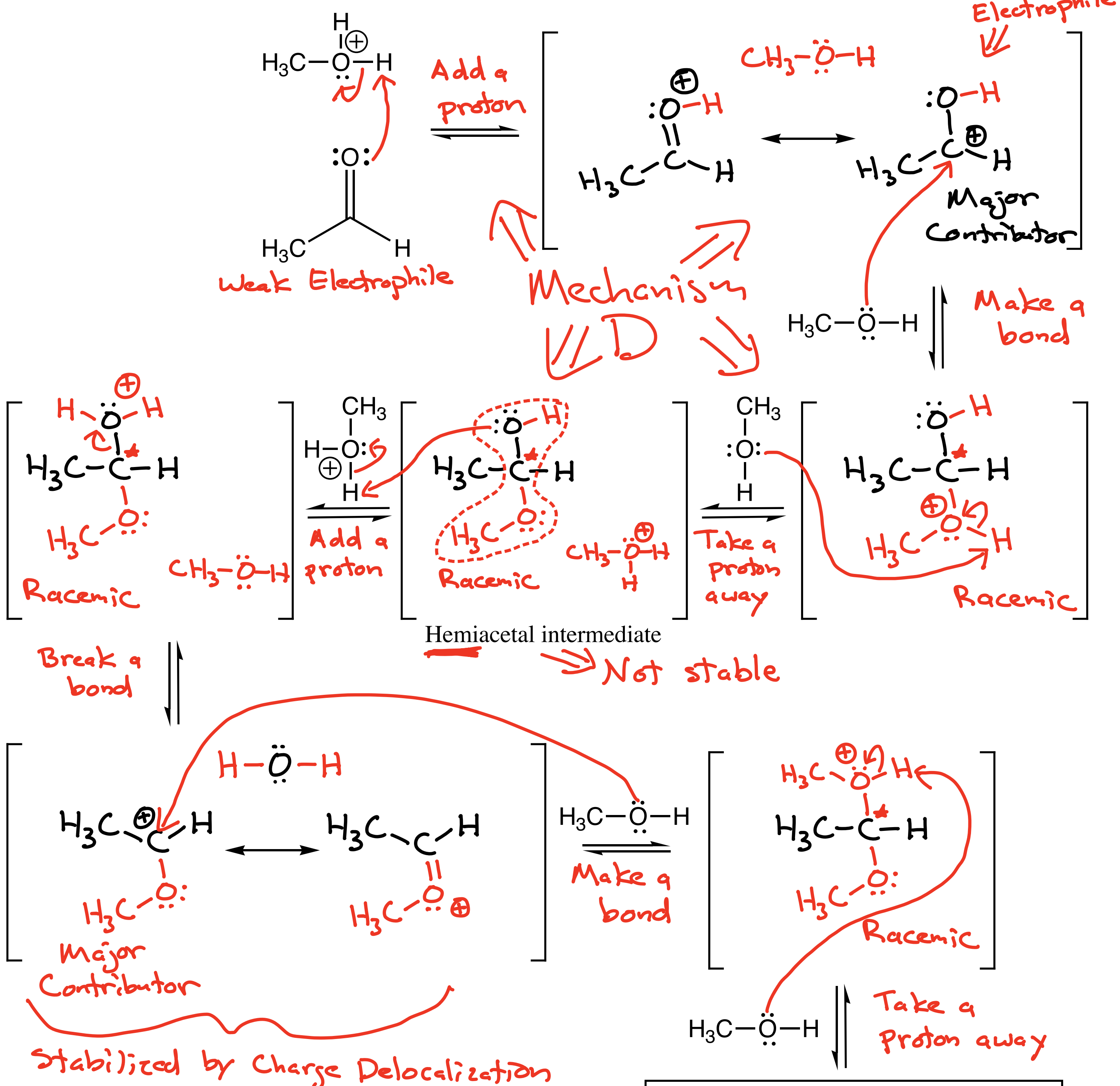




H_2SO_4

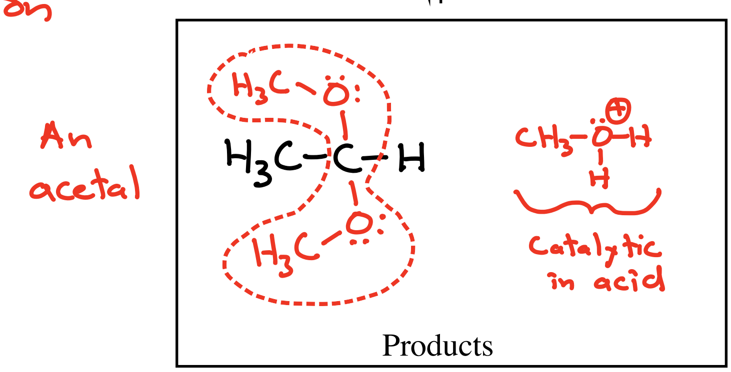
"Hey, does that thing have a hemi in it?" "SWEET!" !

Acid Catalyzed Hemiacetal and Acetal Formation From an Aldehyde or Ketone



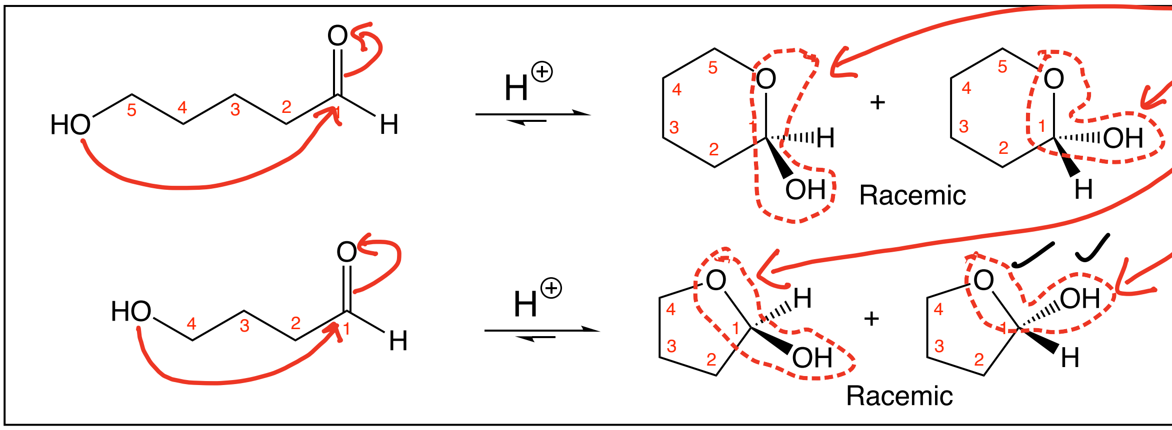
Key Recognition Element (KRE):

Two bonds to O atoms from an sp^3 C atom

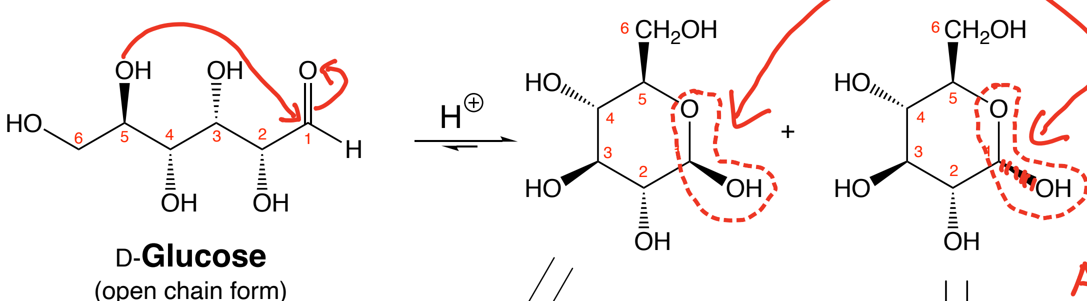


Cyclic Hemiacetals and Carbohydrates

Cyclic hemiacetals



The cyclic form of hemiacetals are stable - "SWEET!"
→ The chelate effect

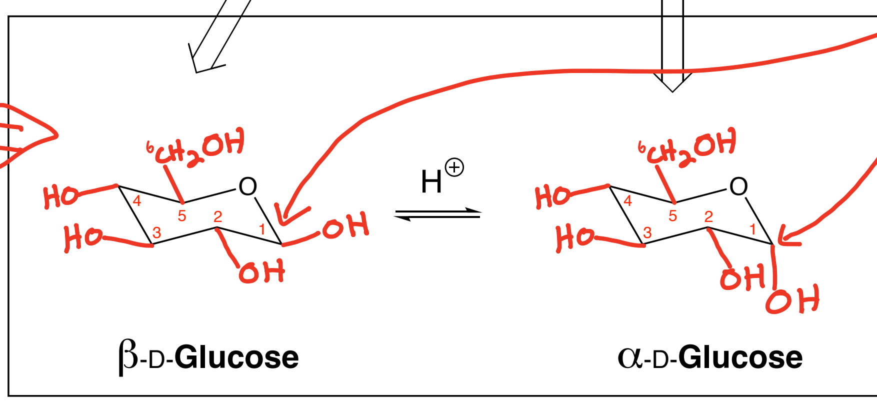


Cyclic Hemiacetals

"SWEET!"

Anomeric Carbon

This interconversion is called "mutarotation"



β-D-Glucopyranose

α-D-Glucopyranose

means "6-mebered ring"

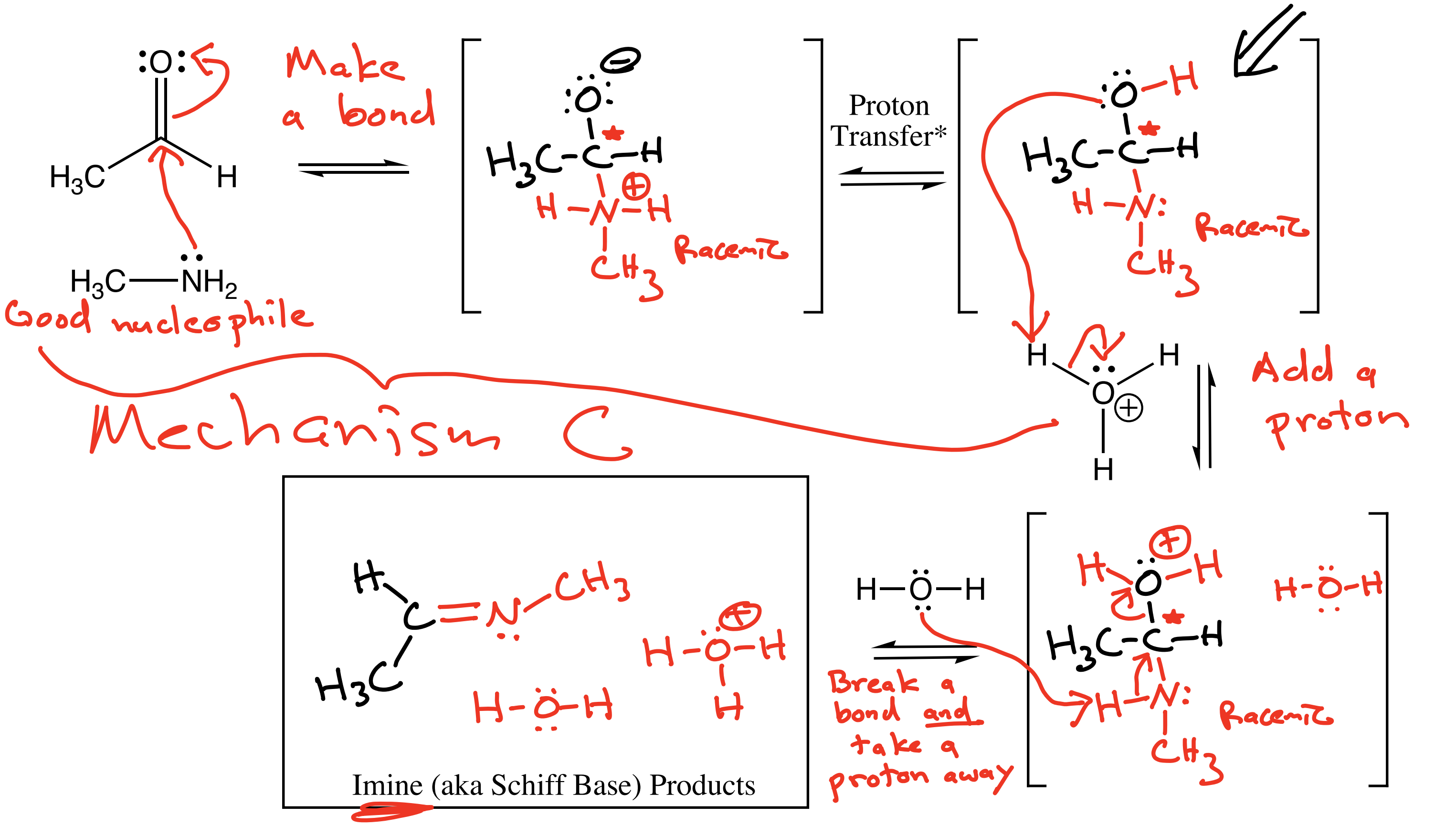
Biochemists call these two forms "anomers"

Less stable → one -OH is axial

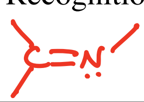
More stable → every group is equatorial!

Formation if an Imine (Schiff Base) From an Aldehyde or Ketone Reacting with an Amine

Aminal Intermediate



Key Recognition Element (KRE):



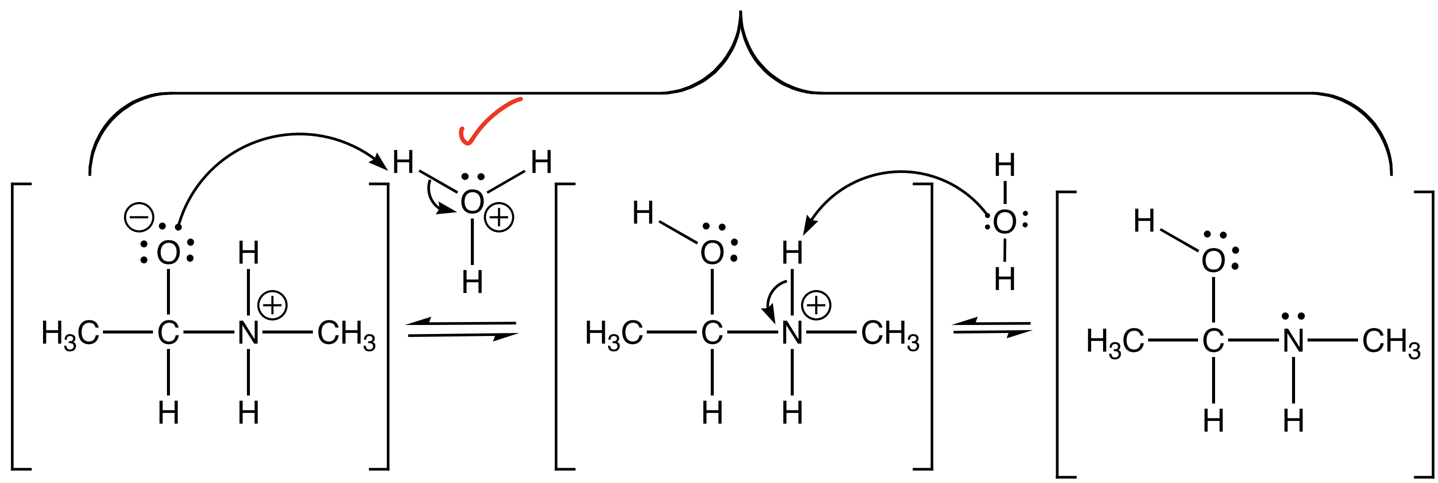
The C=O is replaced by C=N

Note: this last step might actually occur as two steps in some cases.

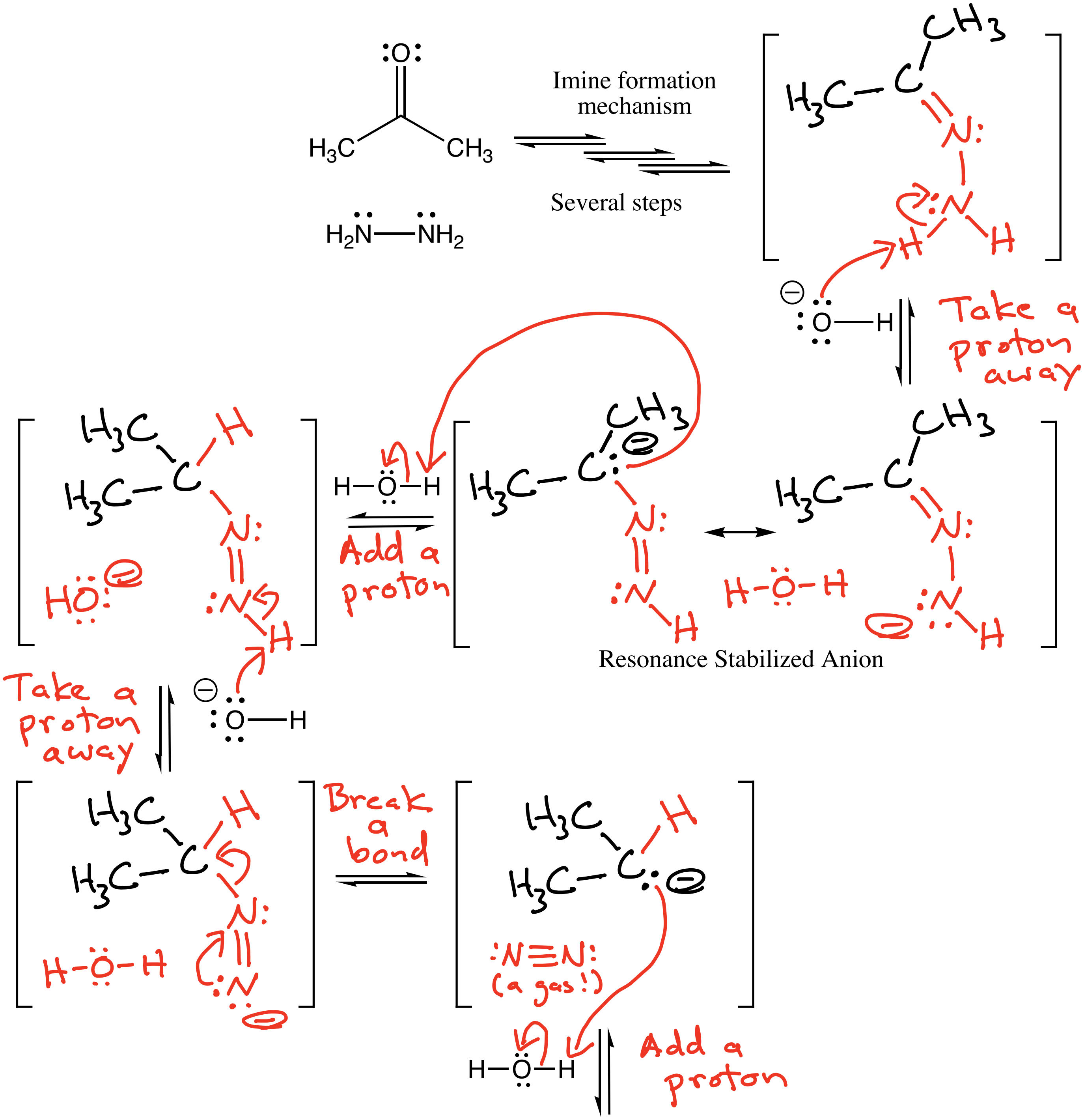
---

* "Proton Transfer" refers to a situation in which a proton moves from one part of a molecule to another on the SAME MOLECULE. We do not draw arrows for proton transfer steps because that would be deceptive. In some cases, the same proton may move from one part of the molecule to the other directly, but in other cases, solvent molecules may be involved as indicated in the following scheme. To make things even more interesting, the following two steps might even be reversed in some cases. Becuase of all the ambiguity, we just write "Proton Transfer" and do not bother with arrows.

"Proton Transfer"

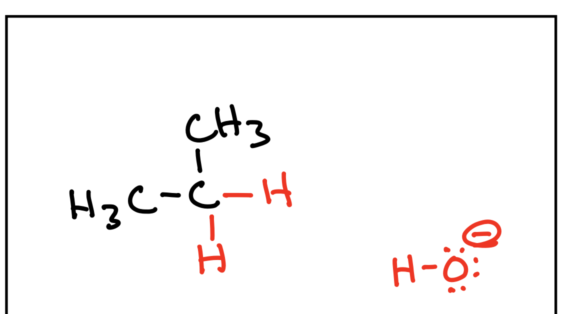


Wolff-Kishner Reduction of an Aldehyde or Ketone



Key Recognition Element (KRE):

-CH₂- group where there was a carbonyl of a ketone or aldehyde

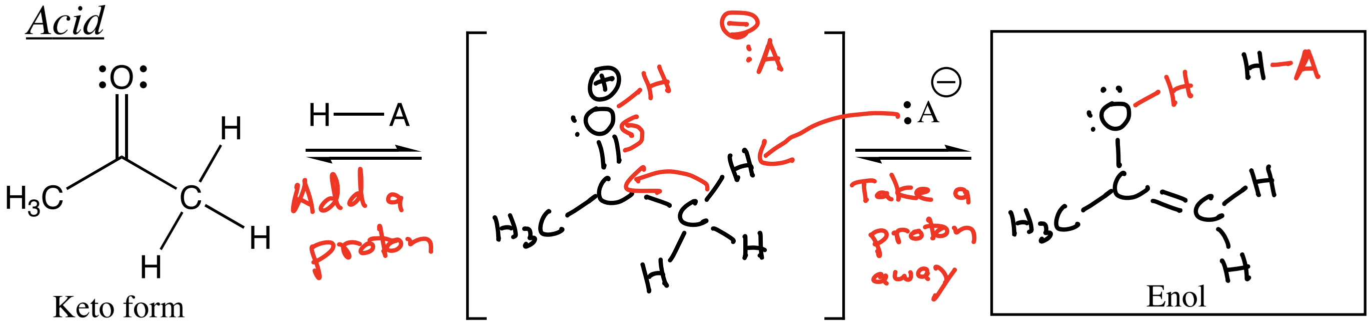


Products

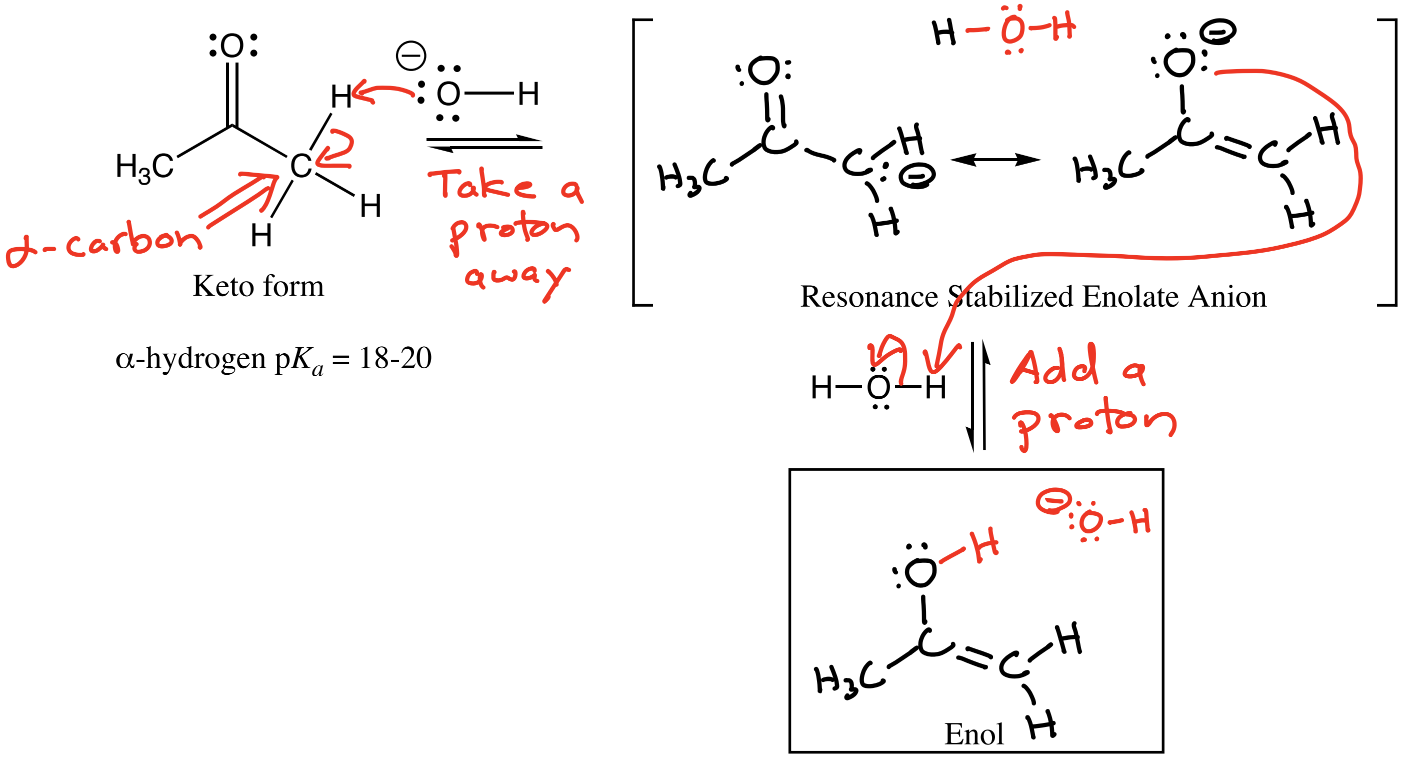
Tautomerization

Keto-Enol Equilibrium Catalyzed by Acid or Base

Acid



Base

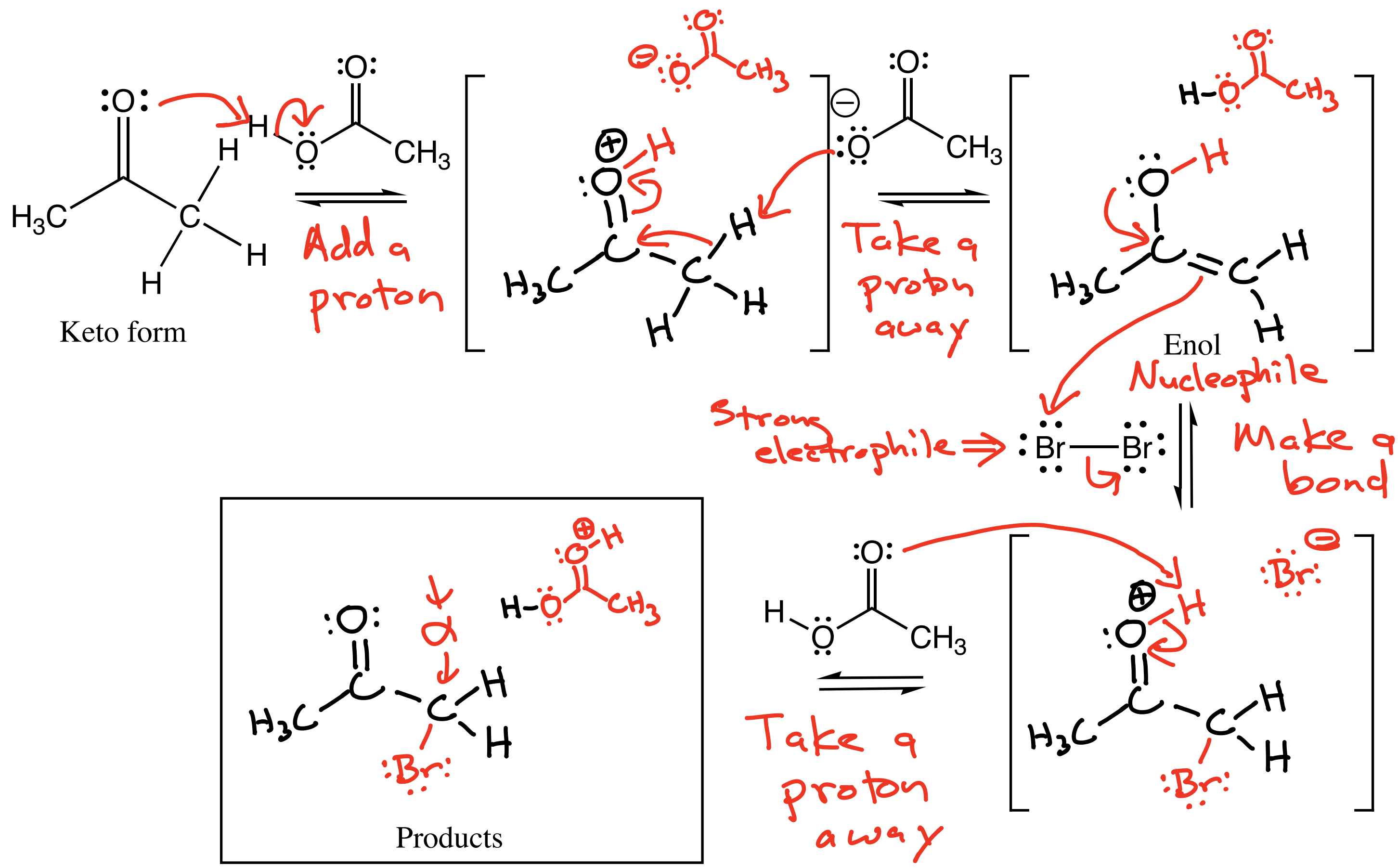


α-hydrogen pK_a = 18-20

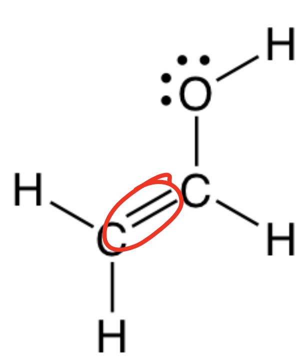
For both aldehydes and ketones, the keto form predominates at equilibrium, because C=O bonds are stronger than C=C bonds.

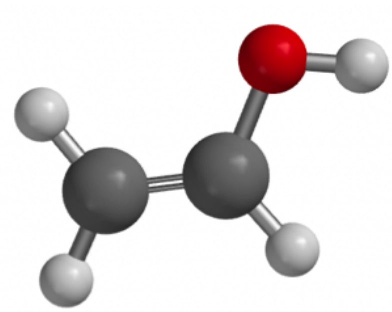
Enols are significant, however, because they react like nucleophile, not carbonyls, and this is important in certain situations.

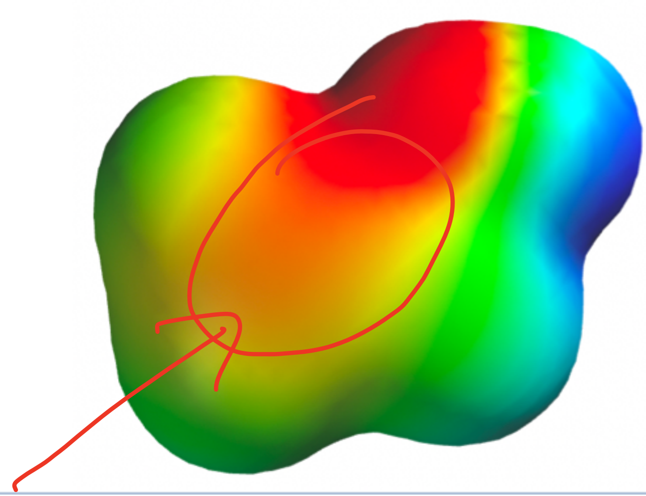
α-Halogenation of an Aldehyde or Ketone Catalyzed by Acid



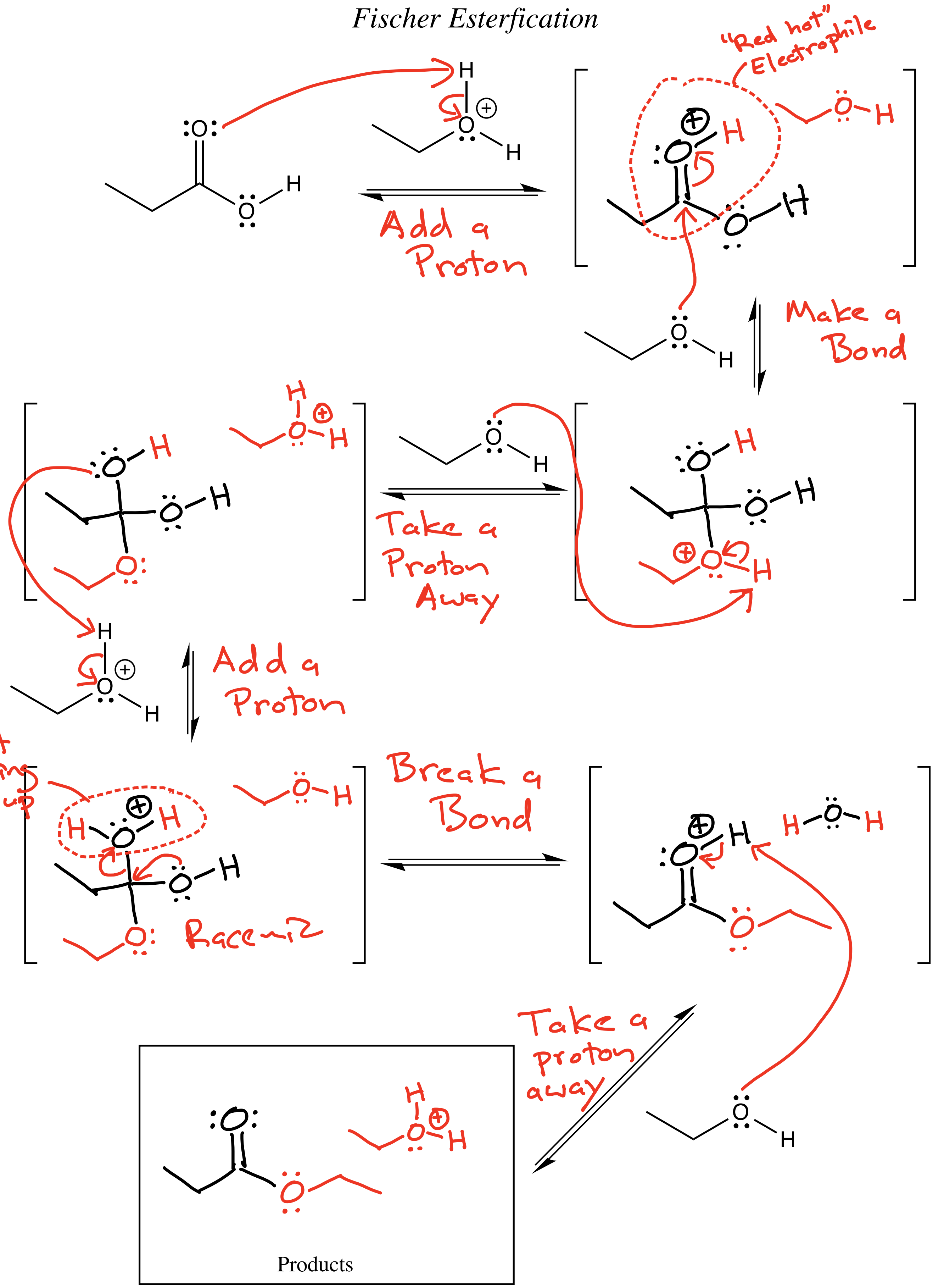
KRE: A new bond to Br at the α-carbon position



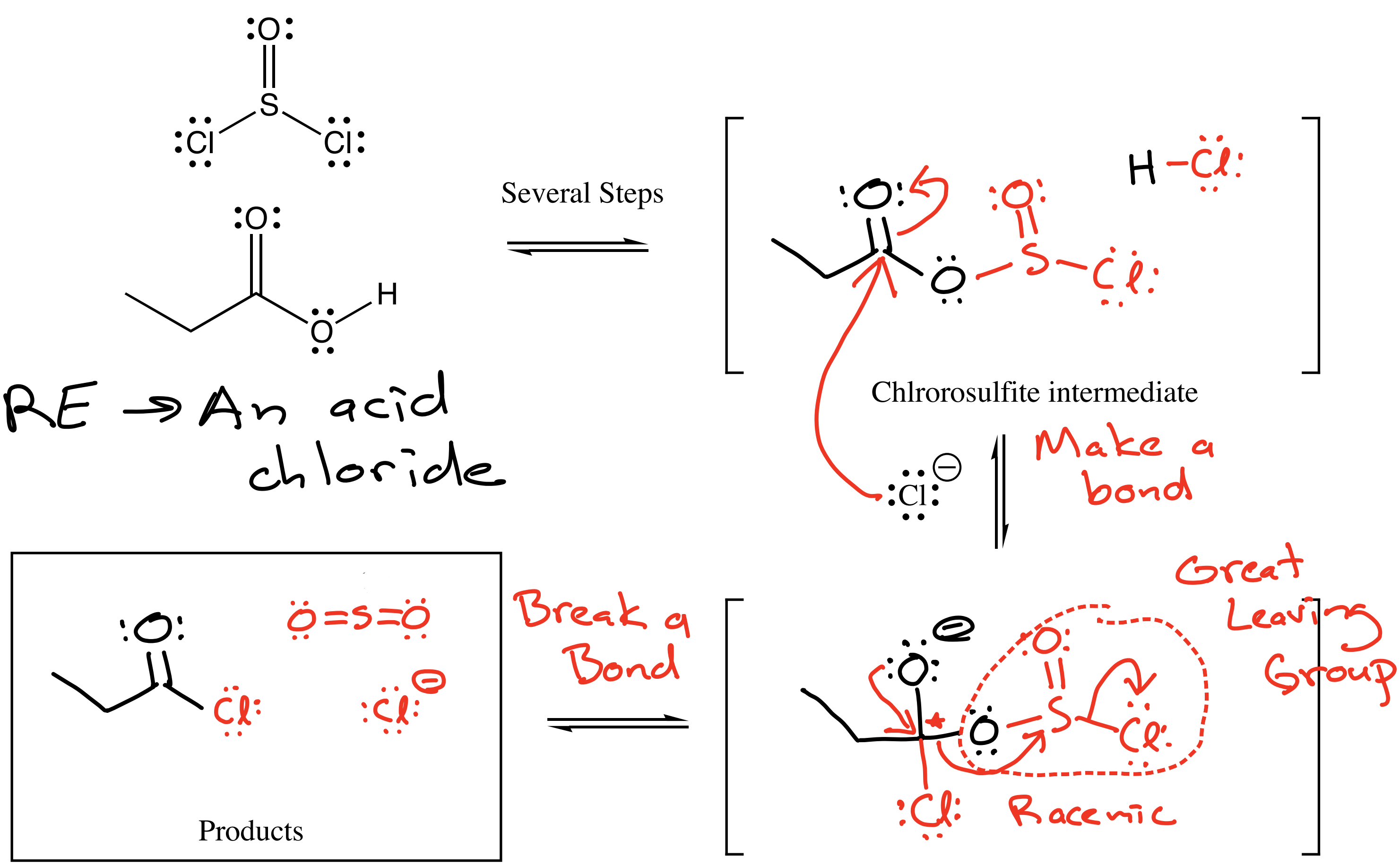




Fischer Esterfication

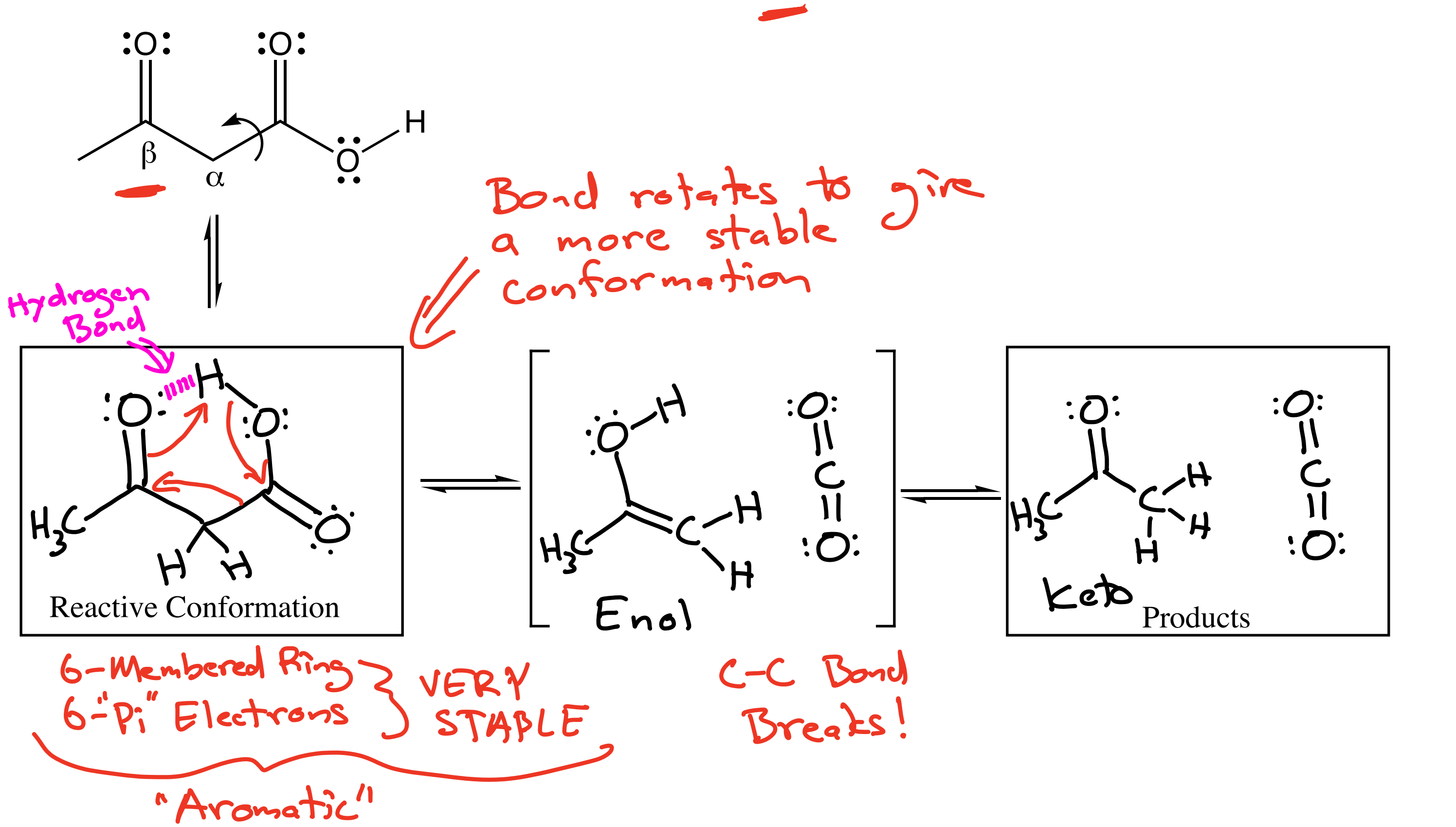


Reaction with Thionyl Chloride

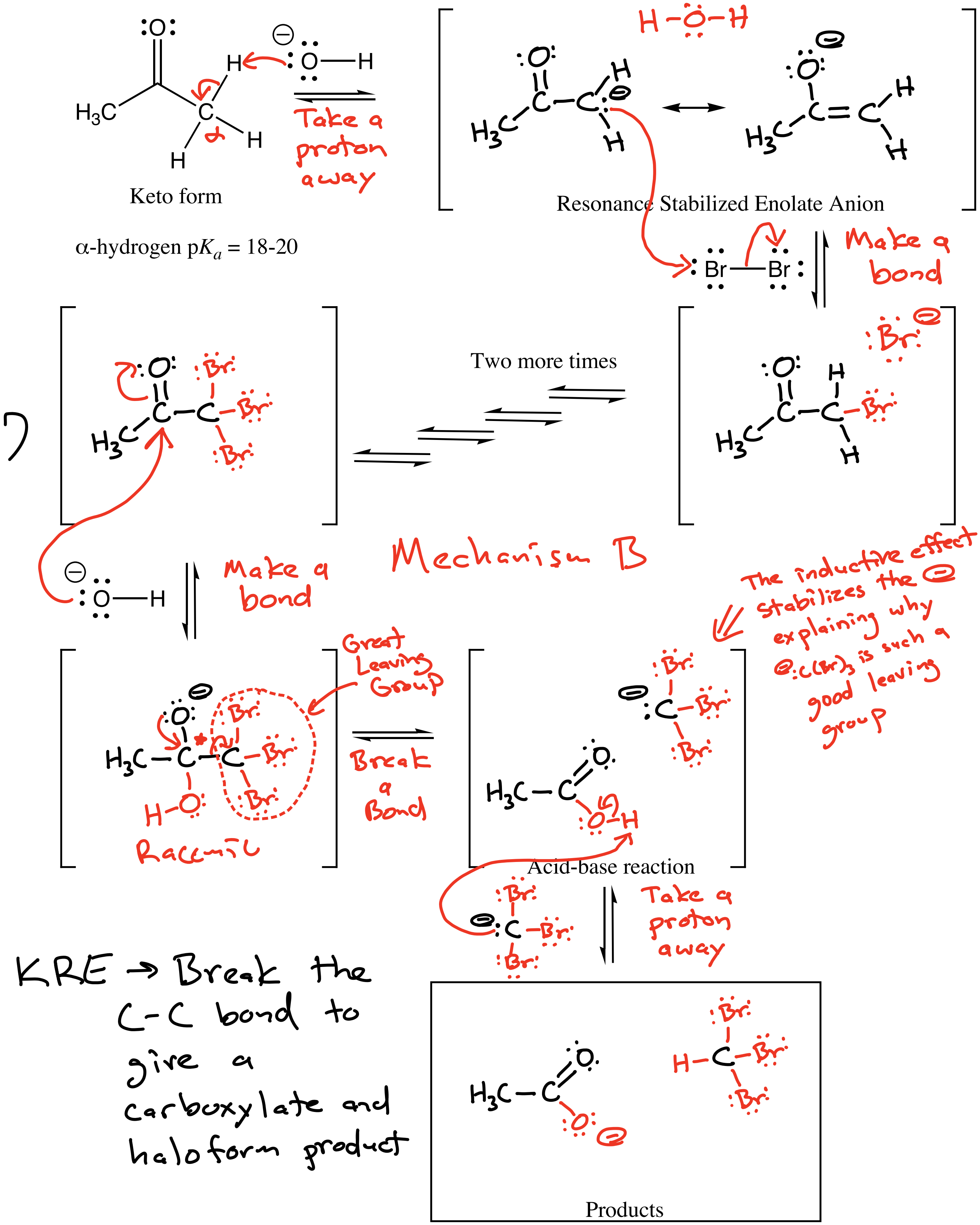


KRE → An acid chloride

Decarboxylation of a β-Keto Acid



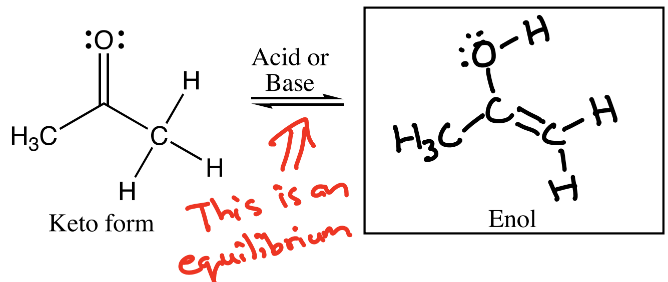
The Haloform Reaction



KRE → Break the C–C bond to give a carboxylate and haloform product

Keto-Enol Tautomerization vs. Enolate Resonance

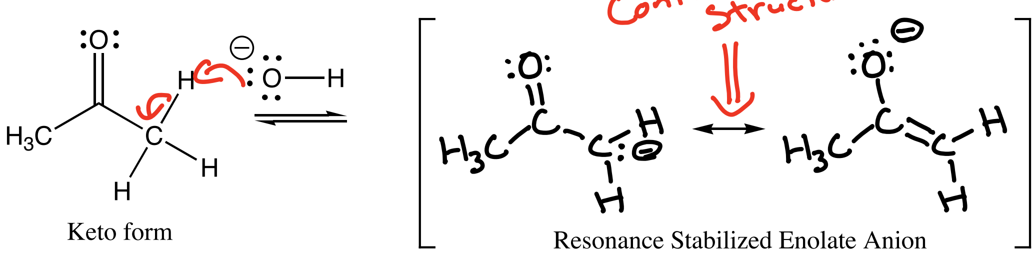
Keto-Enol Tautomerization



Both the keto and enol molecules are Neutral!

Enolate Resonance

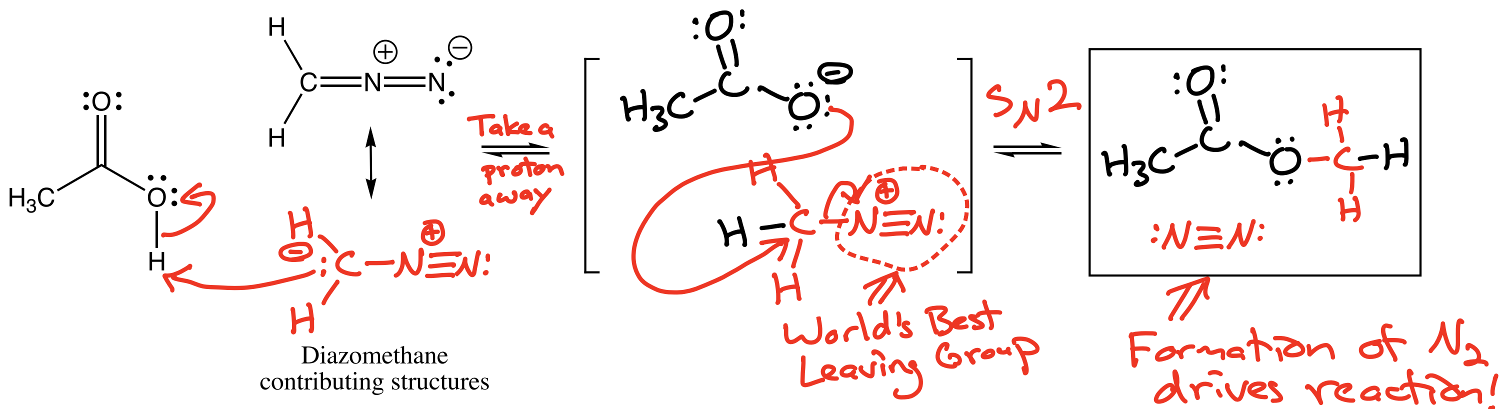
Contributing structures!



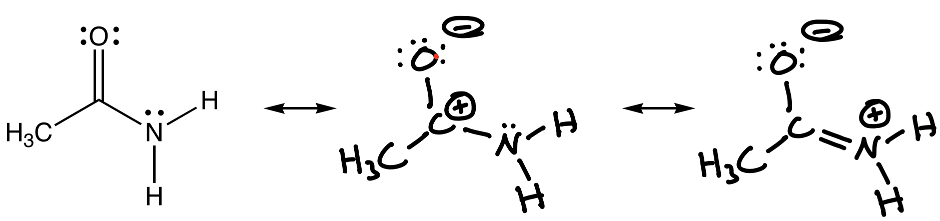
Full ⊖

α-hydrogen pK_a = 18-20

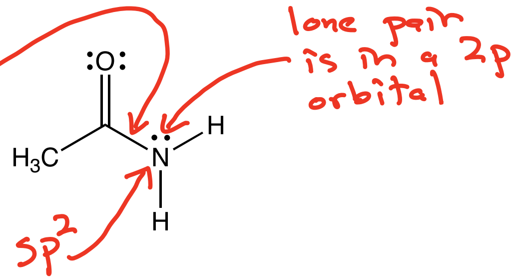
Diazomethane reaction

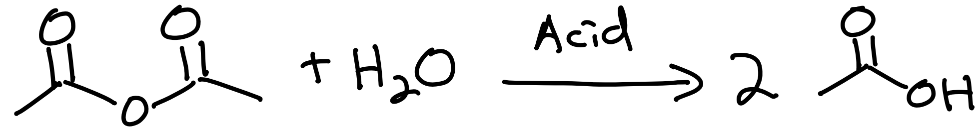


Amide Resonance VERY IMPORTANT!!!!!!

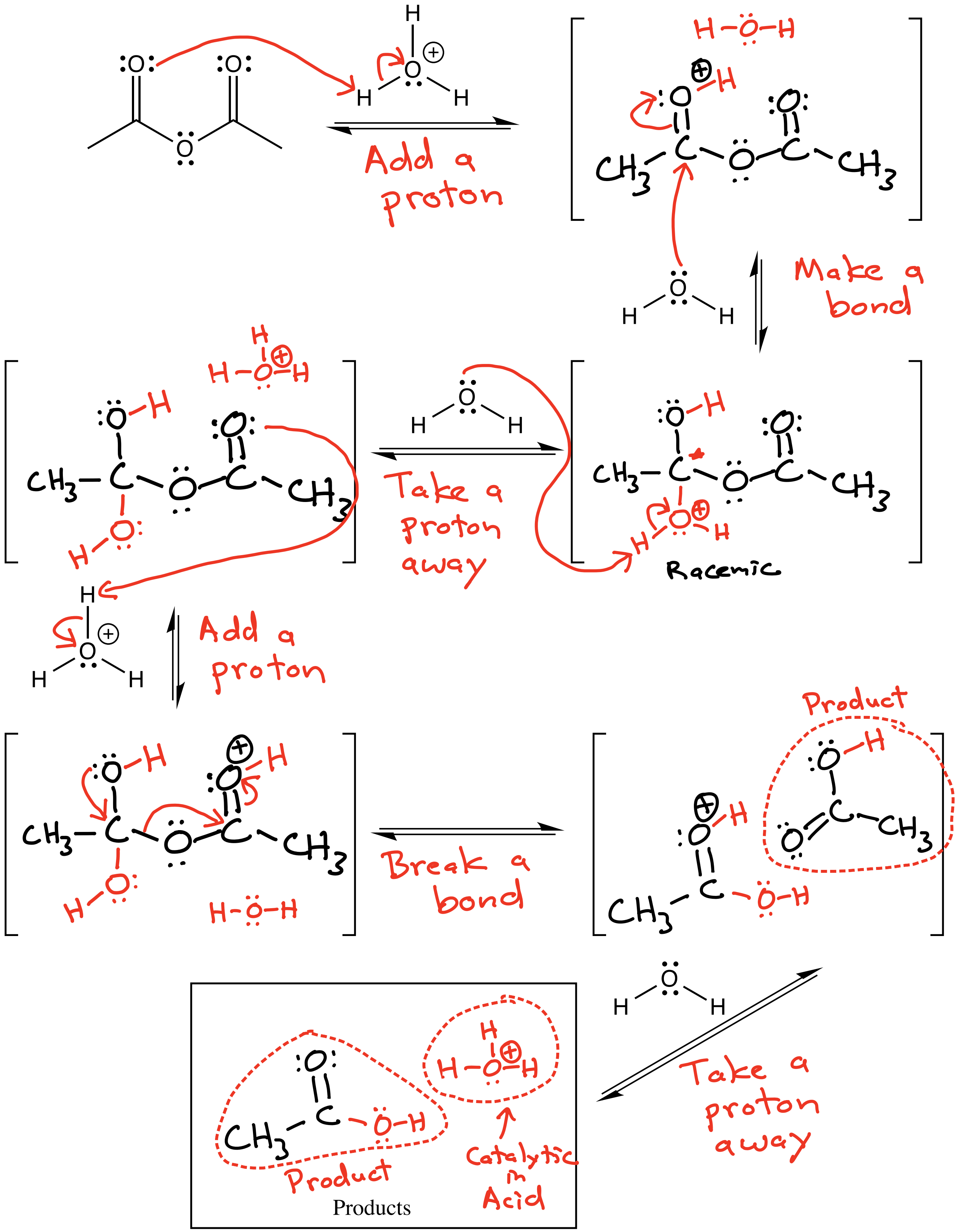


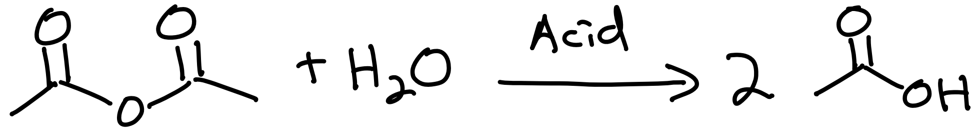
This is a partial π bond so it does not rotate at room temperature



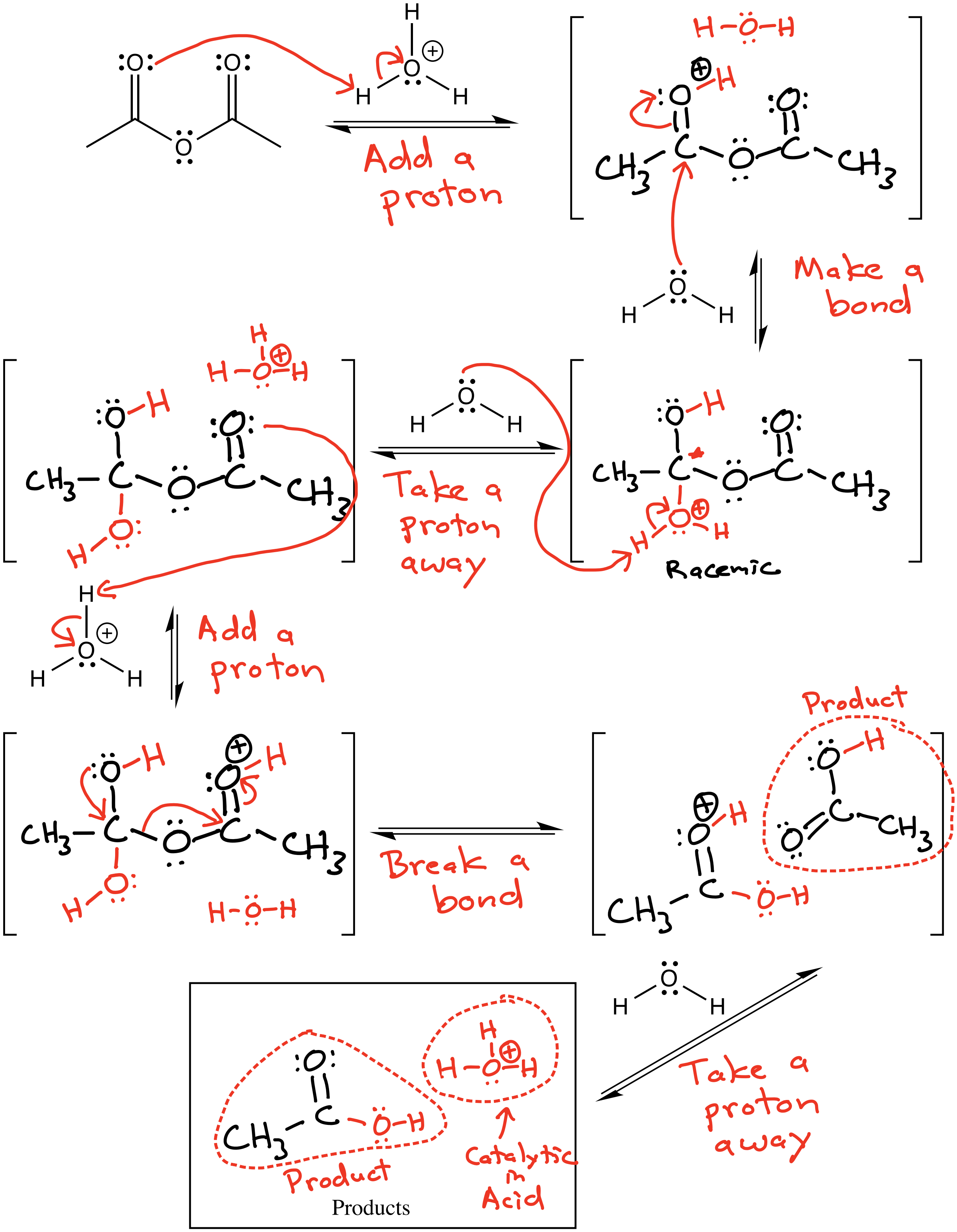


Acid Catalyzed Anhydride Hydrolysis



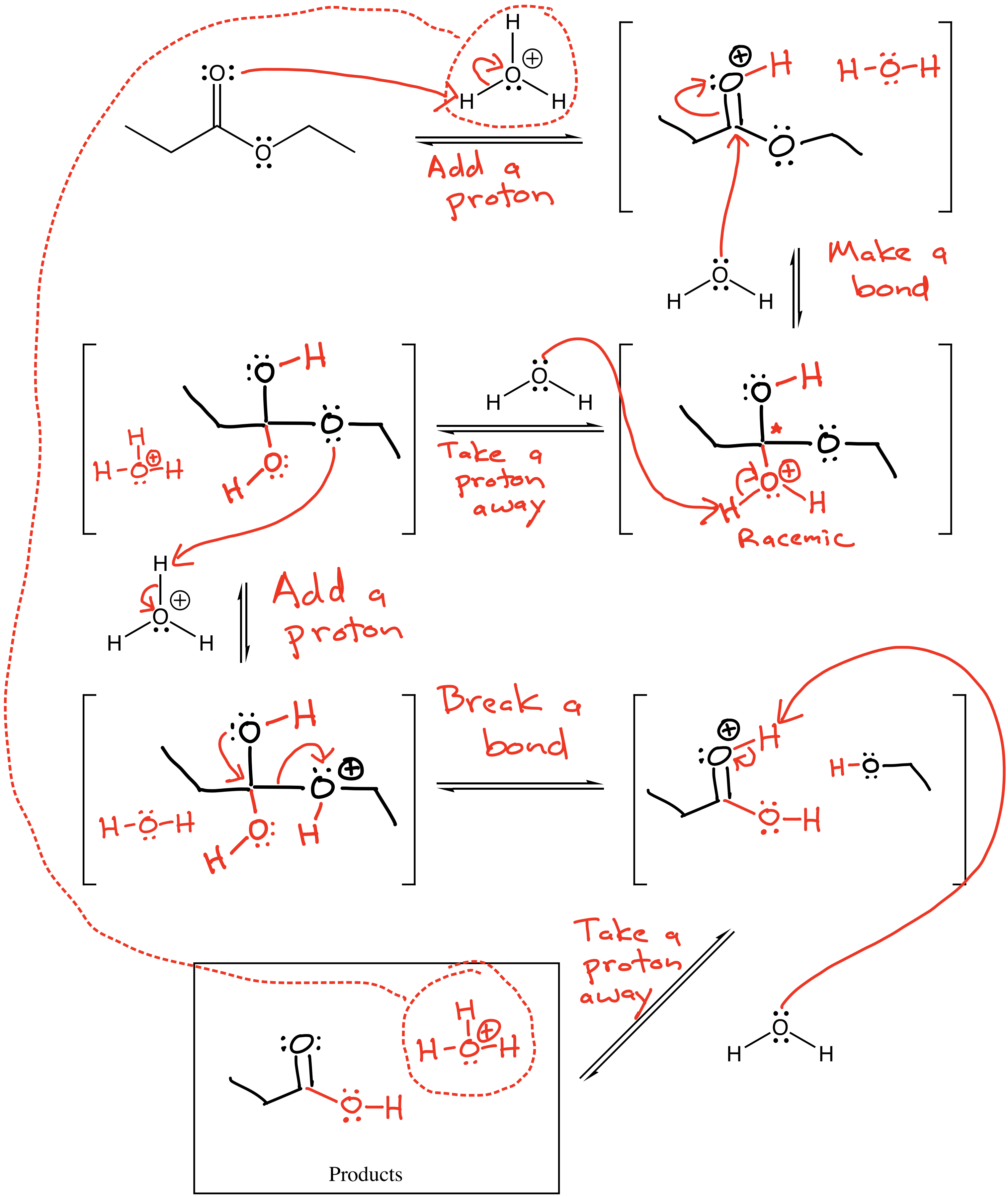


Acid Catalyzed Anhydride Hydrolysis

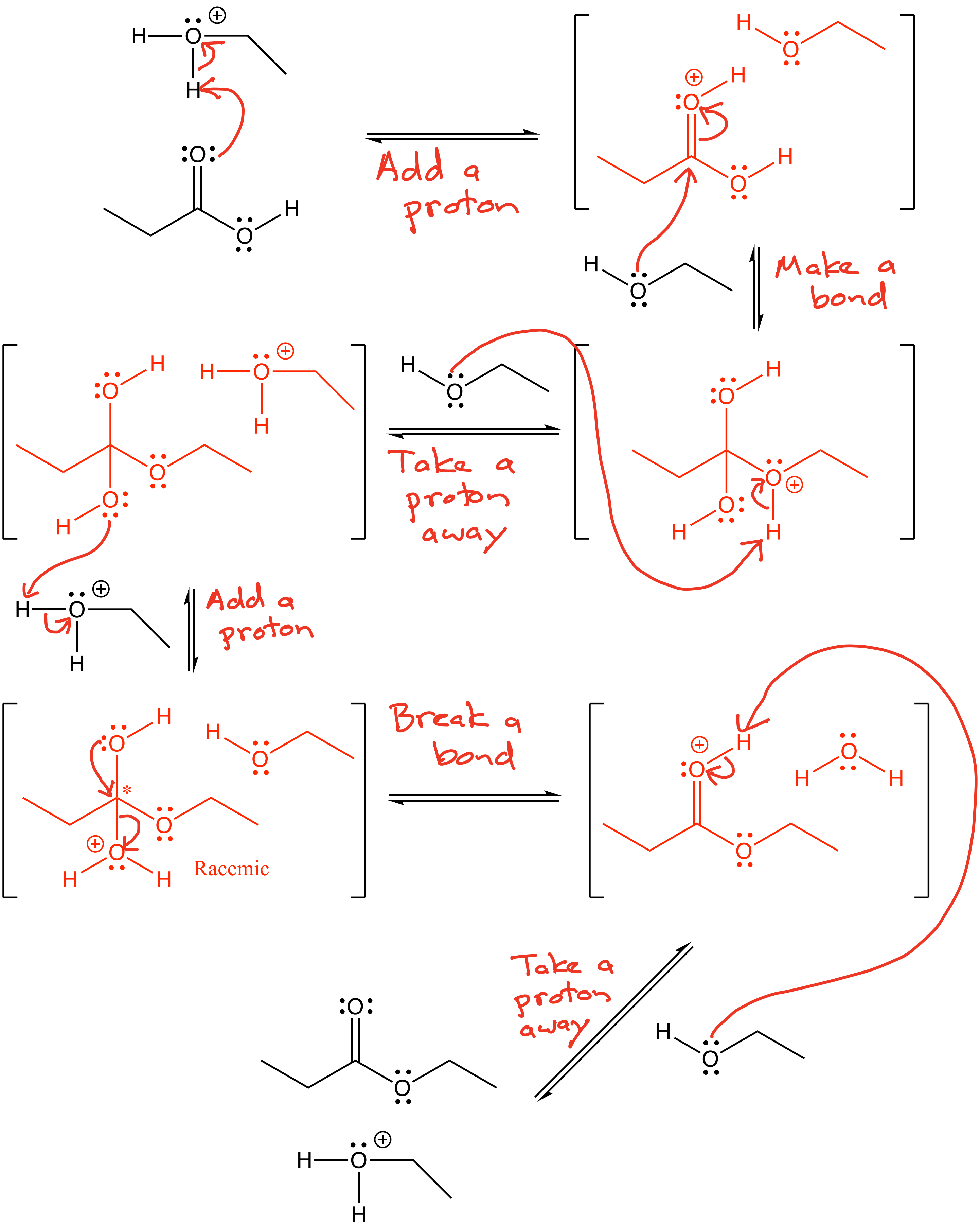


$$R-\overset{O}{\overset{\|}{C}}-OR' + H_2O \xrightarrow[(catalytic)]{H_2SO_4} R-\overset{O}{\overset{\|}{C}}-OH + R'OH$$

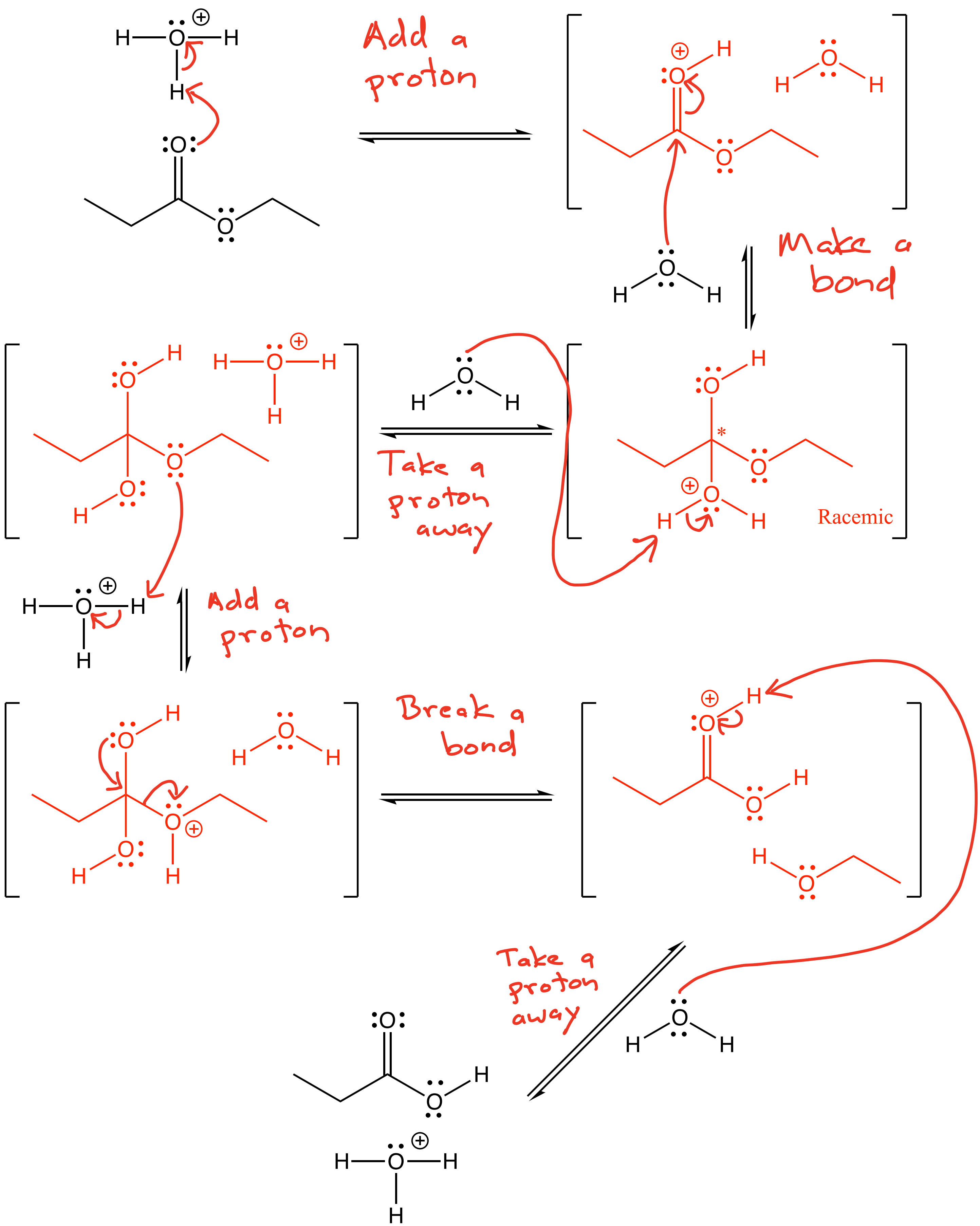
Acid Catalyzed Ester Hydrolysis



Microscopic Reversibilty: Acid Catalyzed Ester Hydrolysis-Fischer Esterification

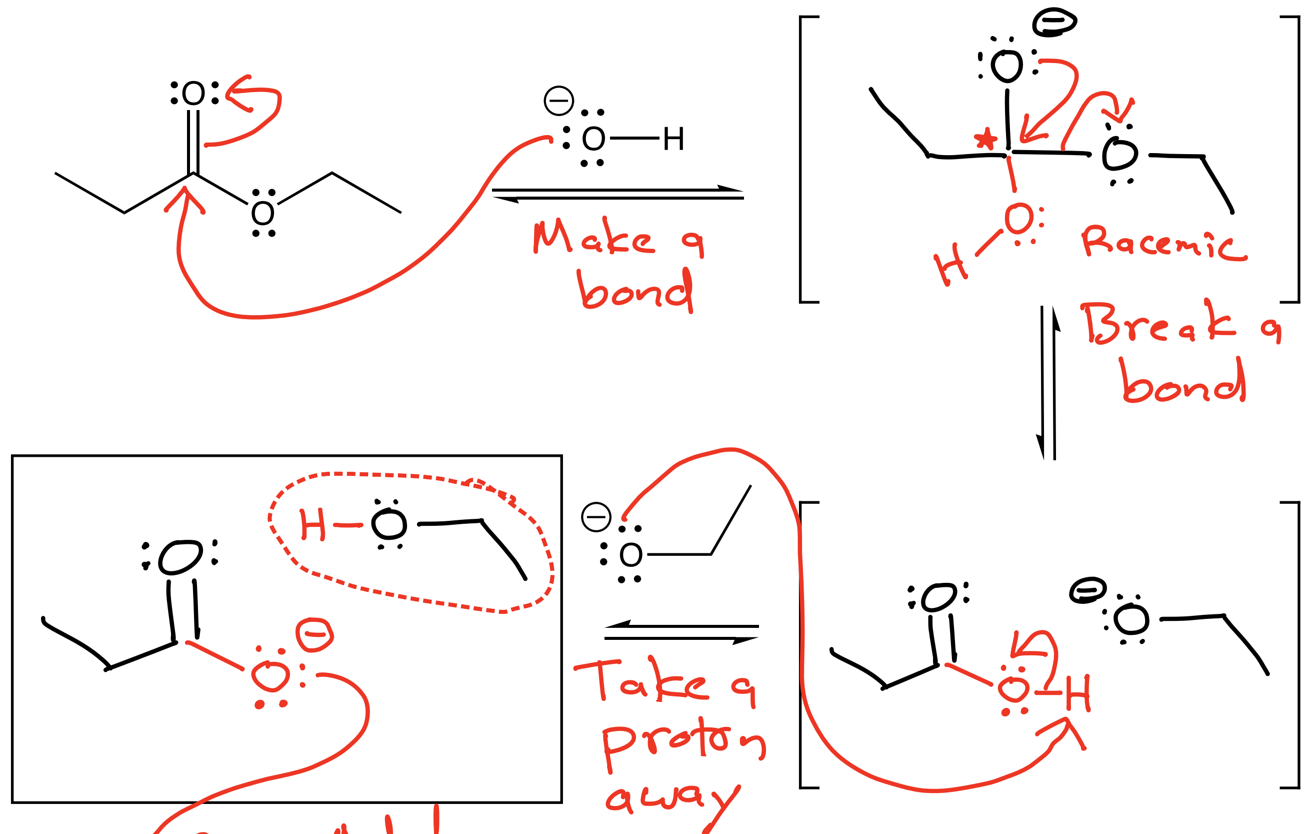


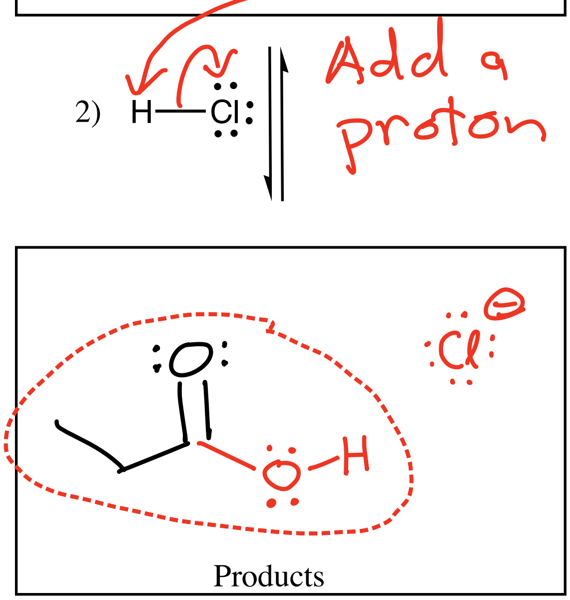
Microscopic Reversibilty: Acid Catalyzed Ester Hydrolysis-Fischer Esterification



$$R-\overset{O}{\overset{\|}{C}}-OR' \xrightarrow[2)\ HCl/H_2O]{1)\ HO^{\ominus}} R-\overset{O}{\overset{\|}{C}}-OH \quad R'OH$$

Base-<u>Promoted</u> Ester Hydrolysis - Saponification





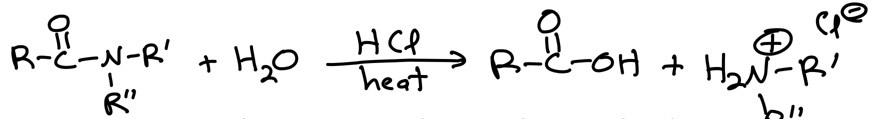
<u>NOT</u> catalytic in base

Mechanism B

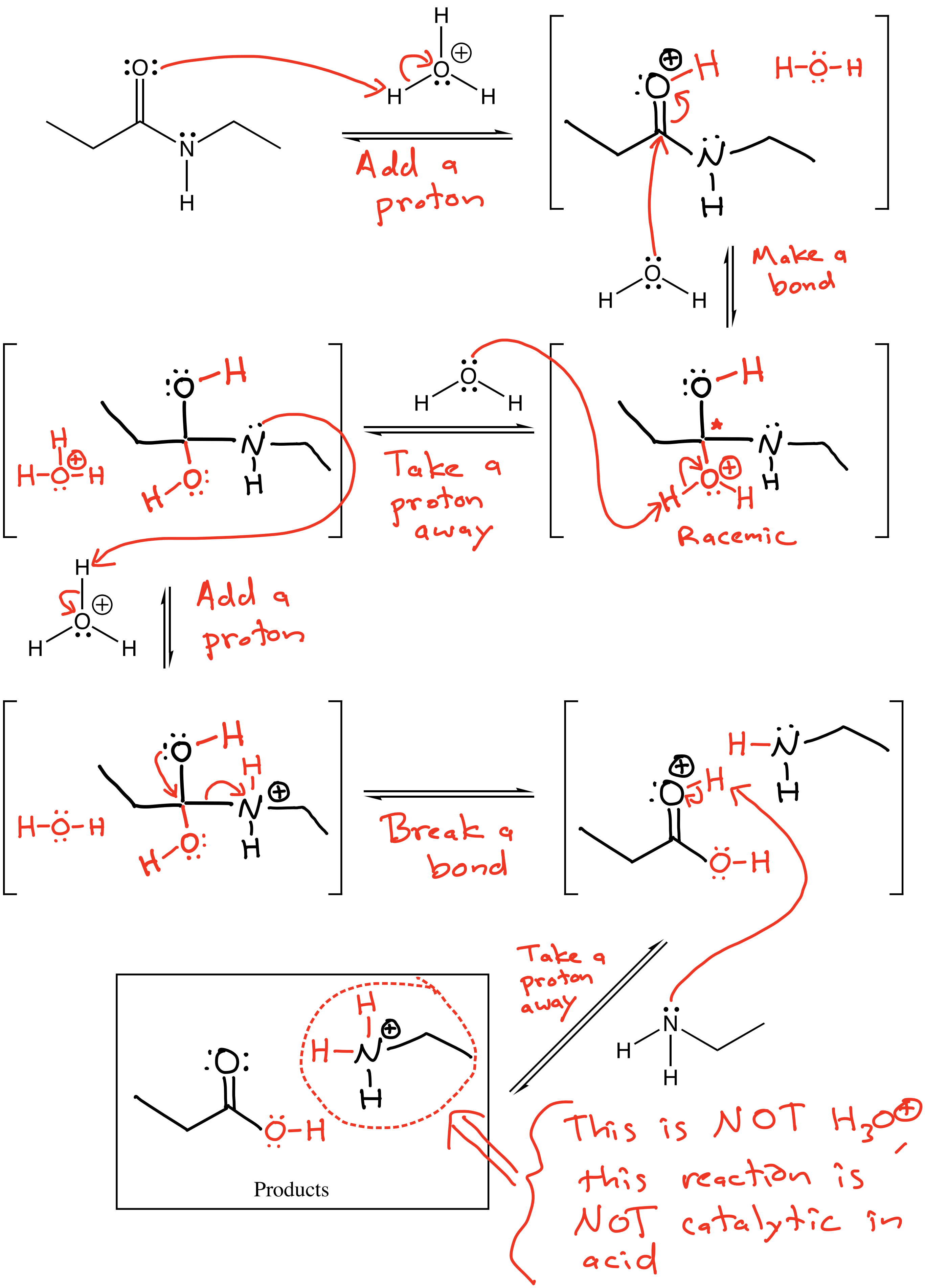
Driving force → converts

$HO^{\ominus}$ to $R-\overset{O}{\overset{\|}{C}}-O^{\ominus}$

More stable anion → favored → MOTIVE

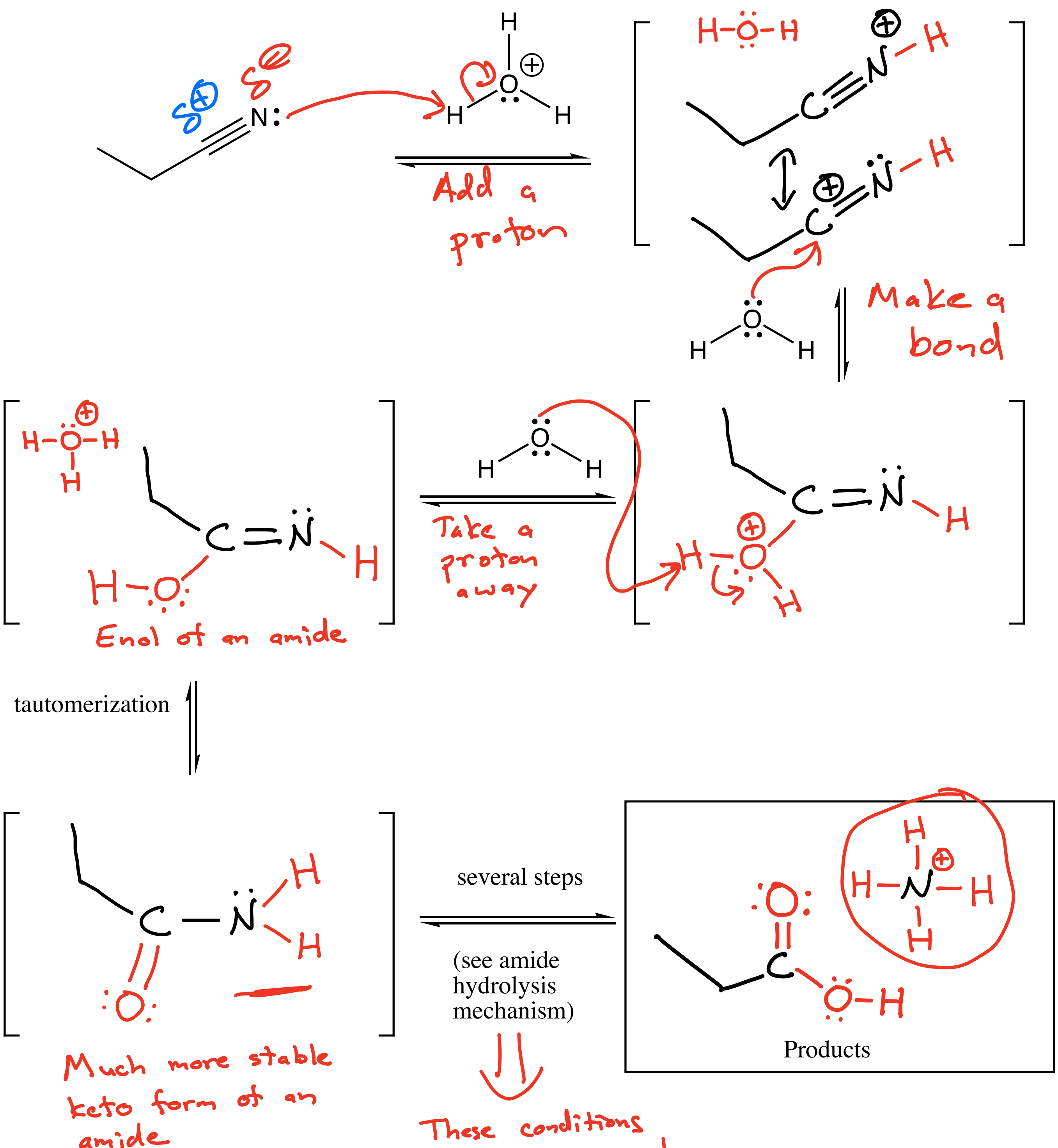


Acid Promoted Amide Hydrolysis

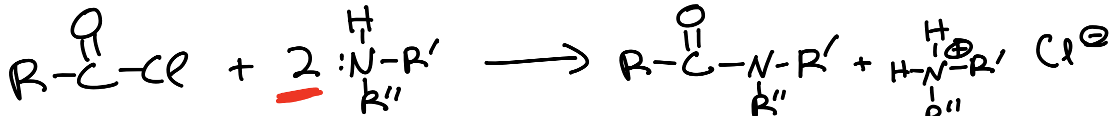


$$R-C\equiv N: + 2H_2O \xrightarrow[\text{heat}]{HCl} R-\overset{\overset{O}{\|}}{C}-OH + \overset{\oplus}{N}H_4\ Cl^{\ominus}$$

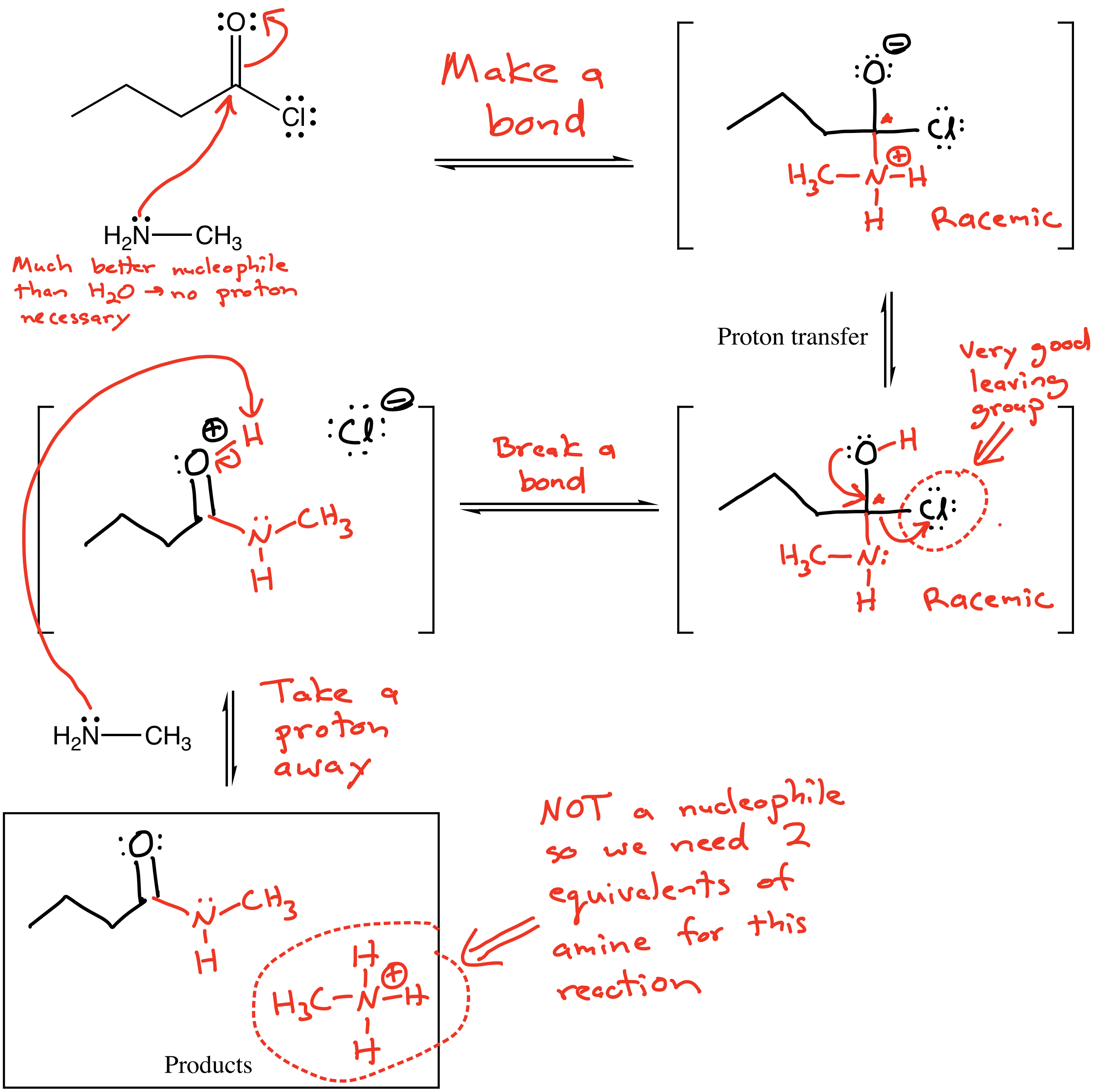
Acid Promoted Nitrile Hydrolysis

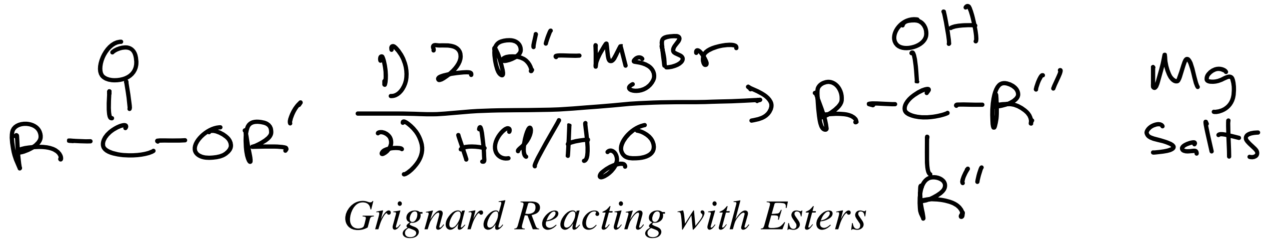


These conditions are strong enough to hydrolyze amides according to the mechanism we saw as "Acid Promoted Hydrolysis of an Amide"

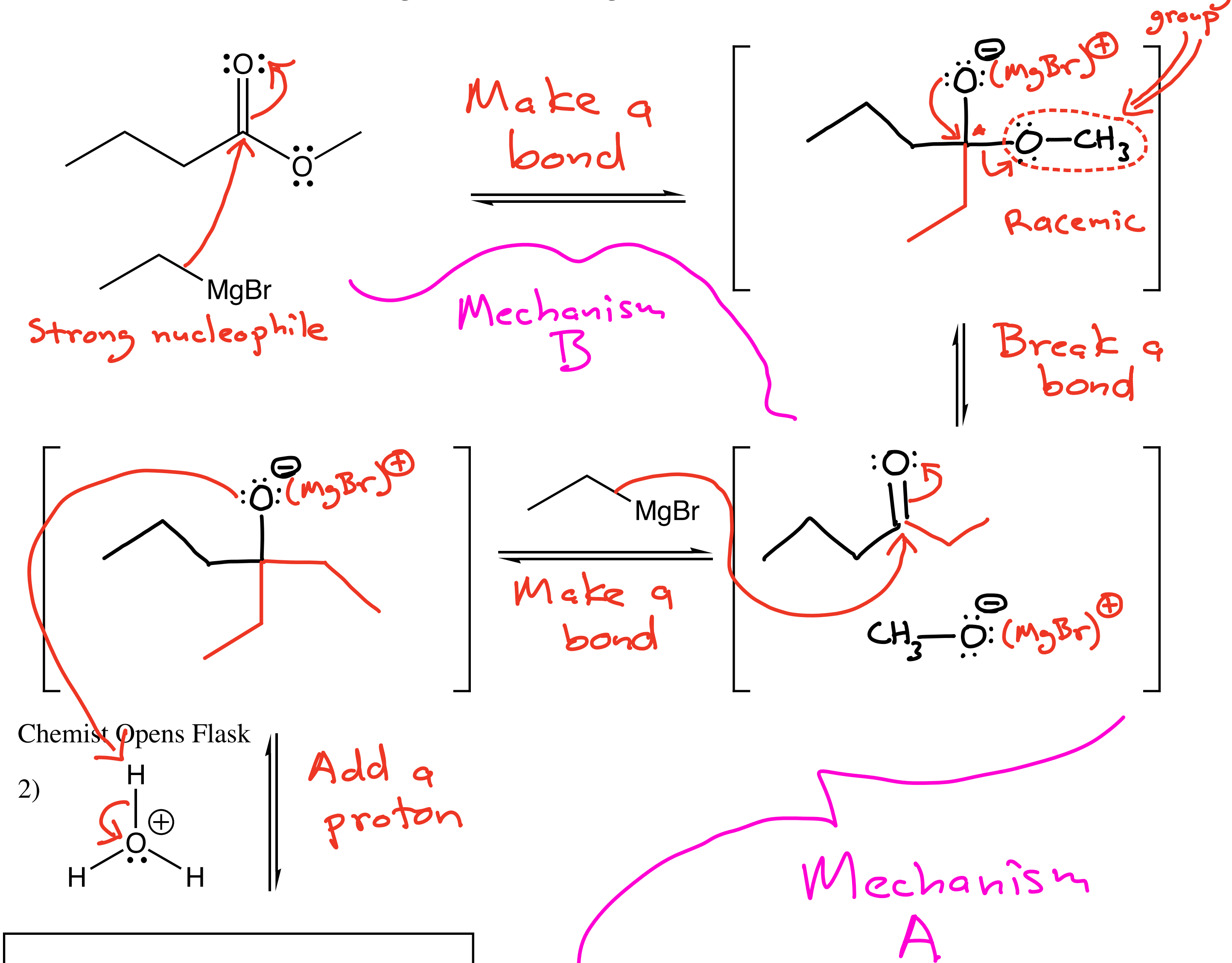


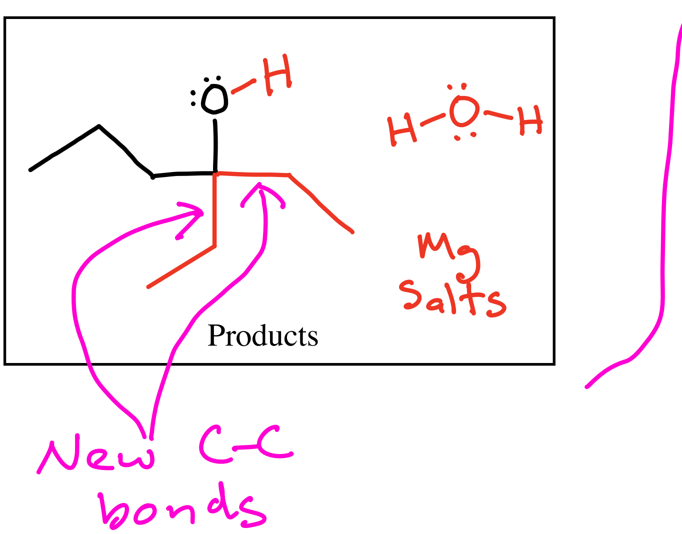
Acid Chlorides Reacting with Amines



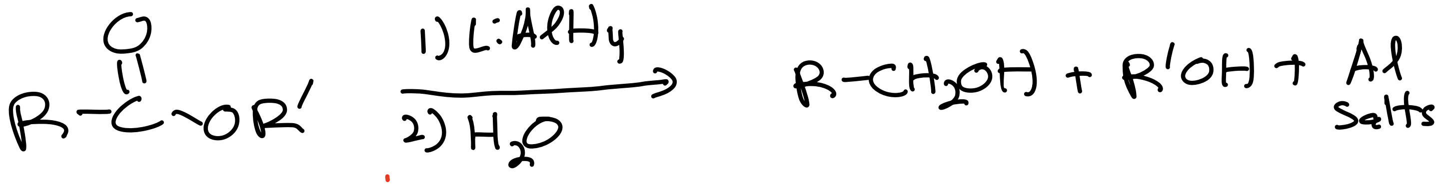


Grignard Reacting with Esters

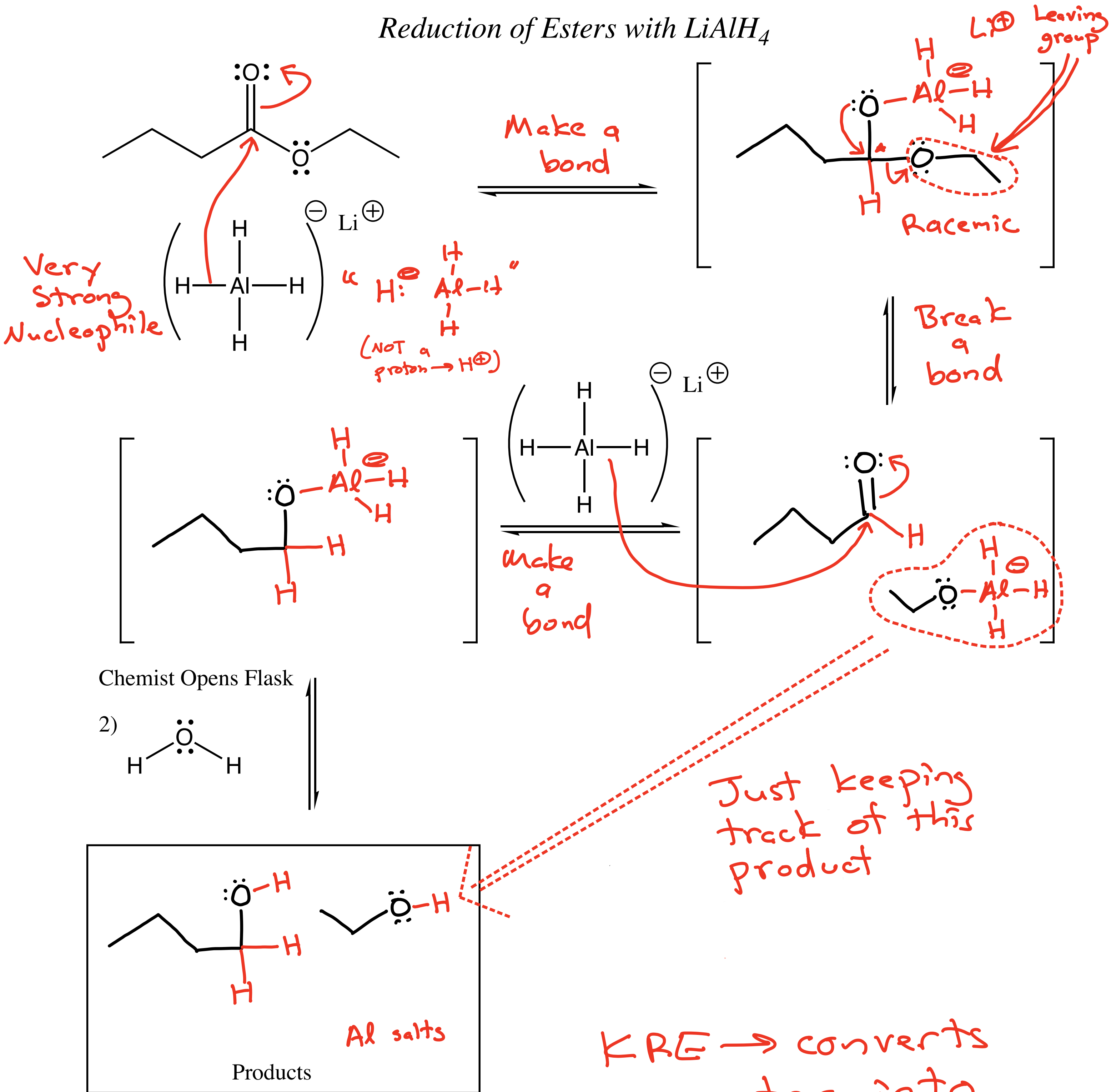




KRE → An alcohol with 2 identical new groups attached via new C–C bonds

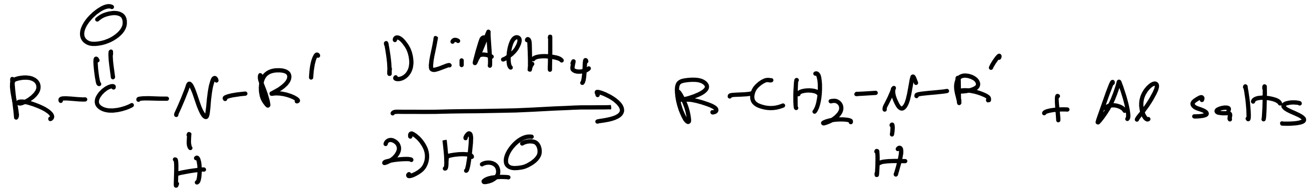


Reduction of Esters with $LiAlH_4$

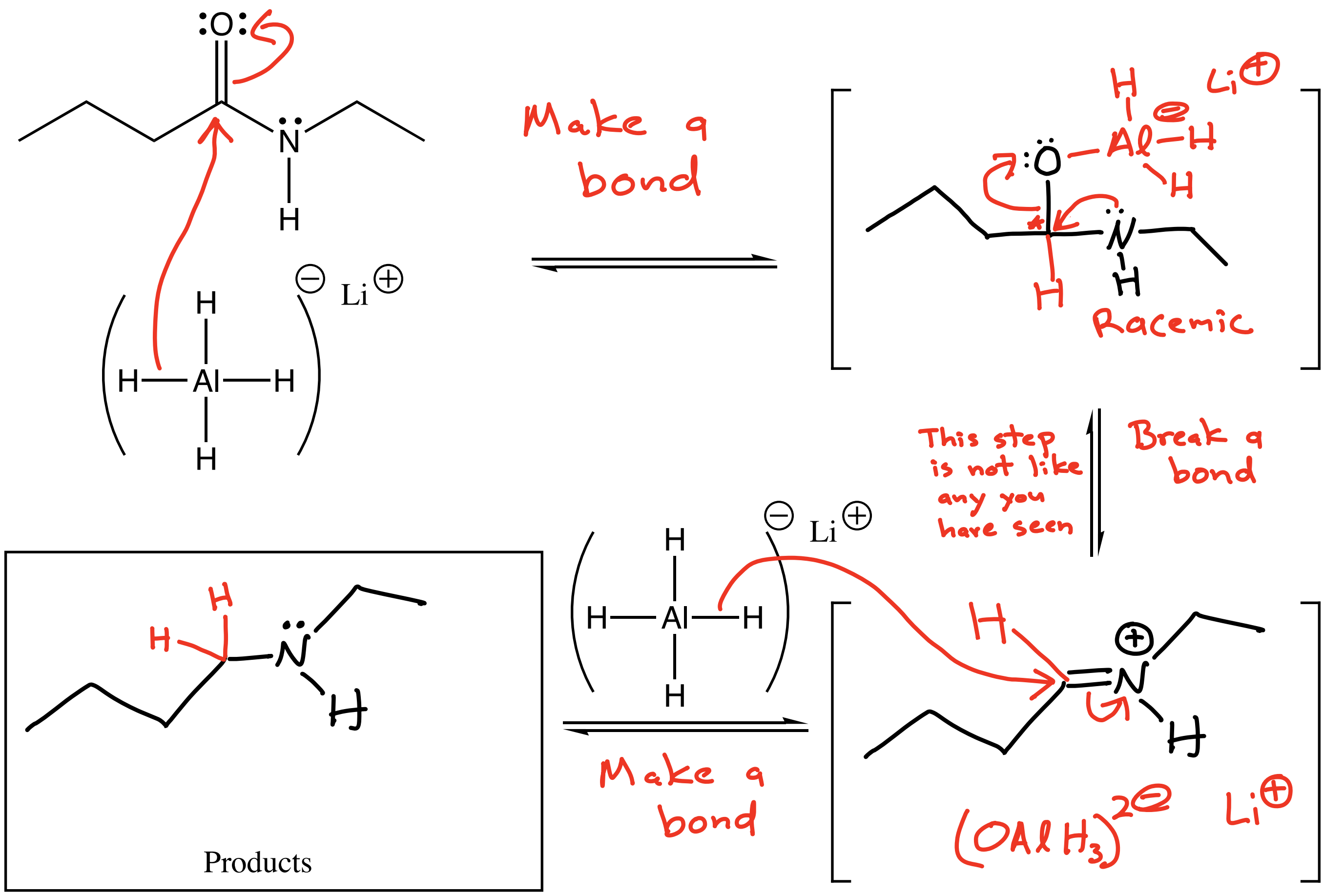


KRE → converts an ester into two alcohols → breaks C–O bond

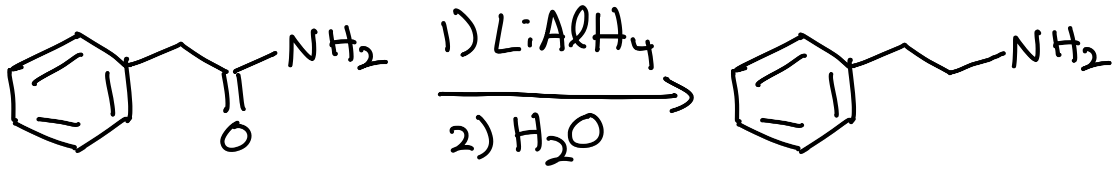
Note the extreme similarities between these last two mechanisms!



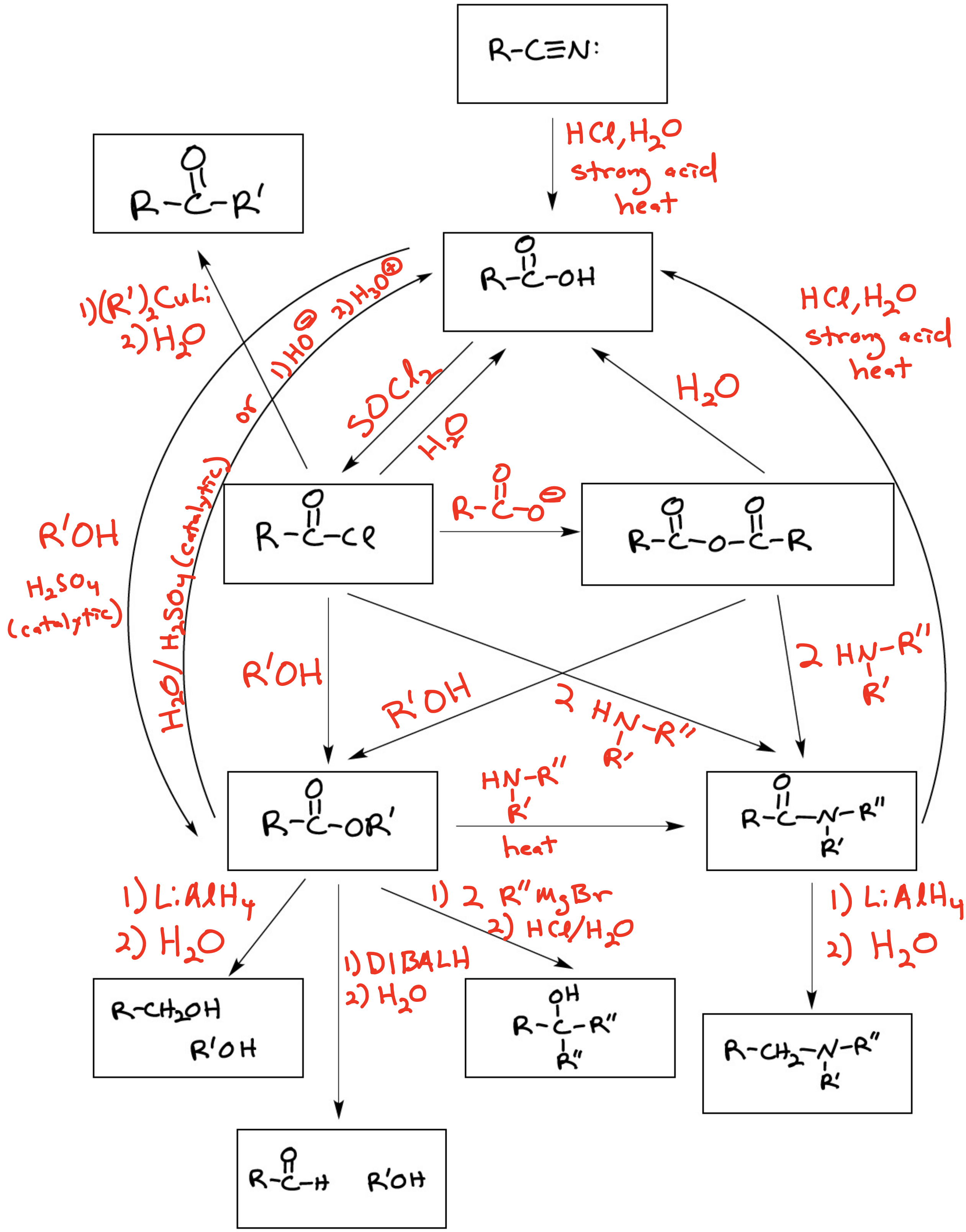
Reduction of Amides with $LiAlH_4$

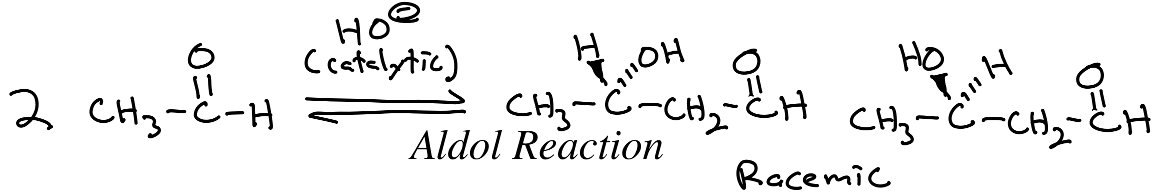


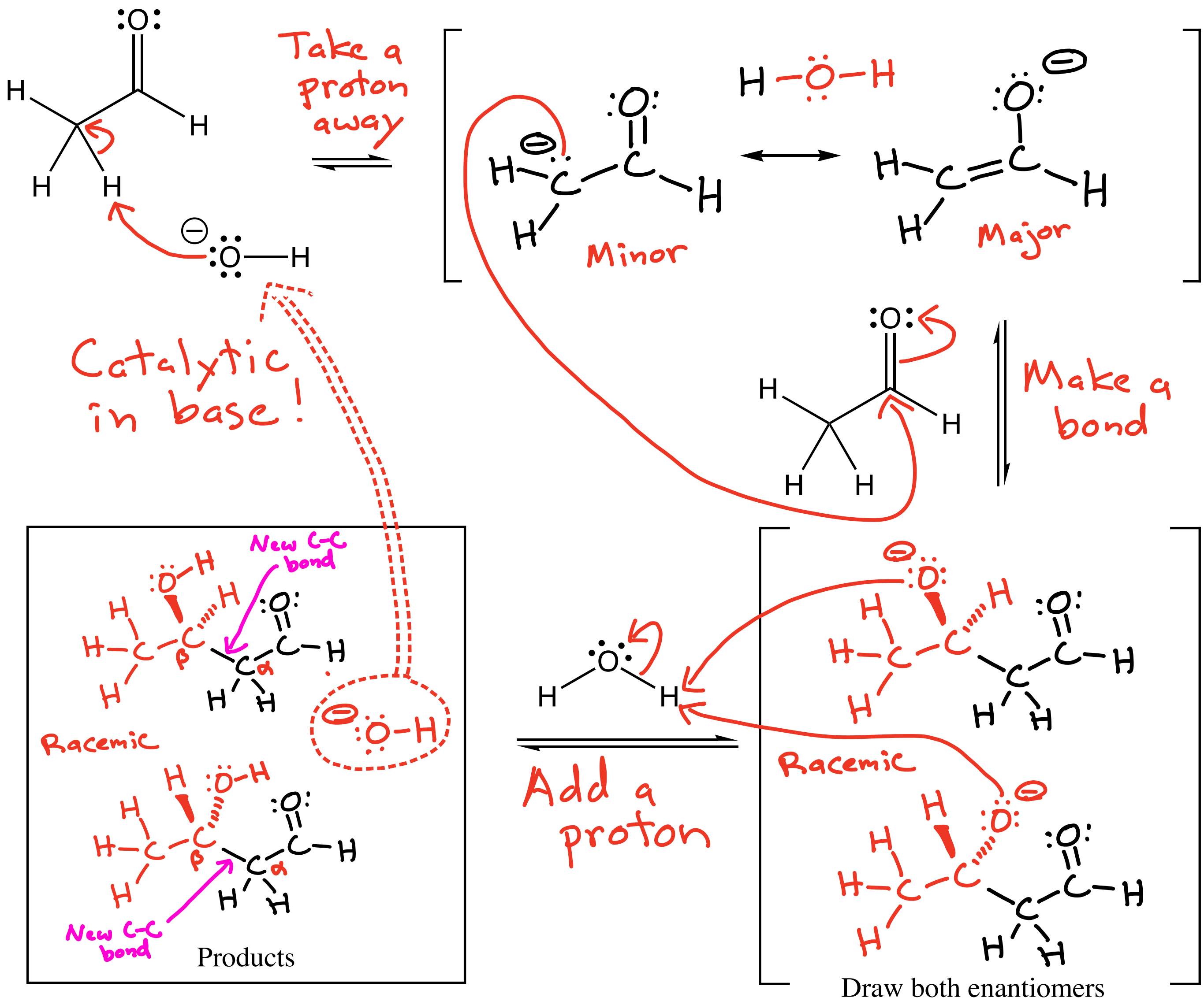
Note: In this reaction the chemist opens the flask and adds water in a second step that quenches any excess $LiAlH_4$. Therefore, you need a second step to add water when using this reaction in synthesis even though it is not shown in the mechanism above.



Interconversion of Carboxylic Acid Derivatives



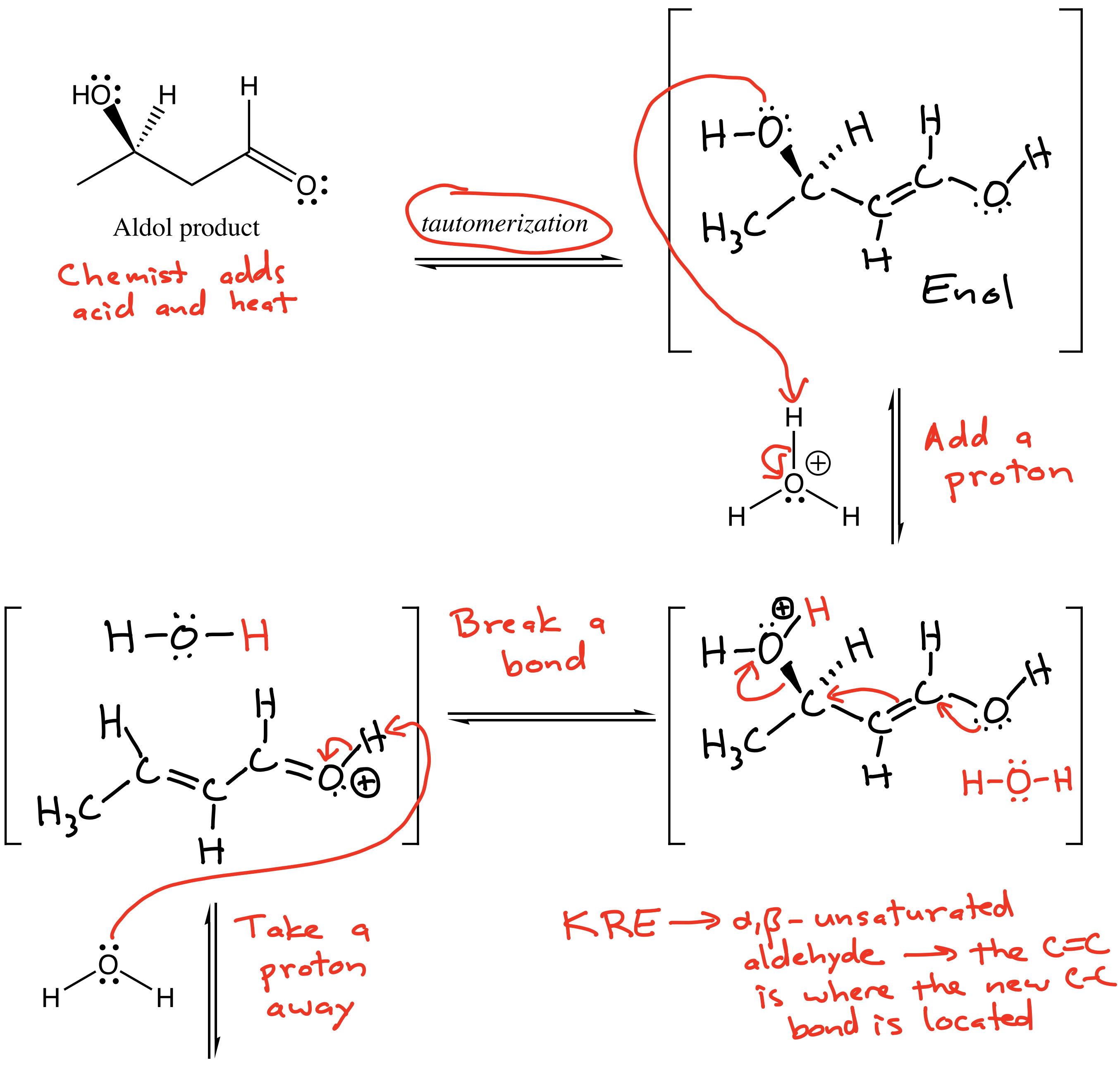


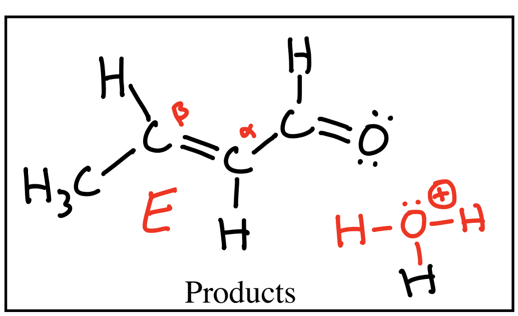


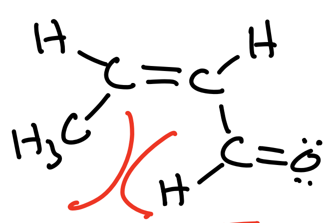
KRE → β-hydroxy aldehyde with a new C–C bond between the aldehyde α and β carbons

Mechanism A

Acid catalyzed dehydration





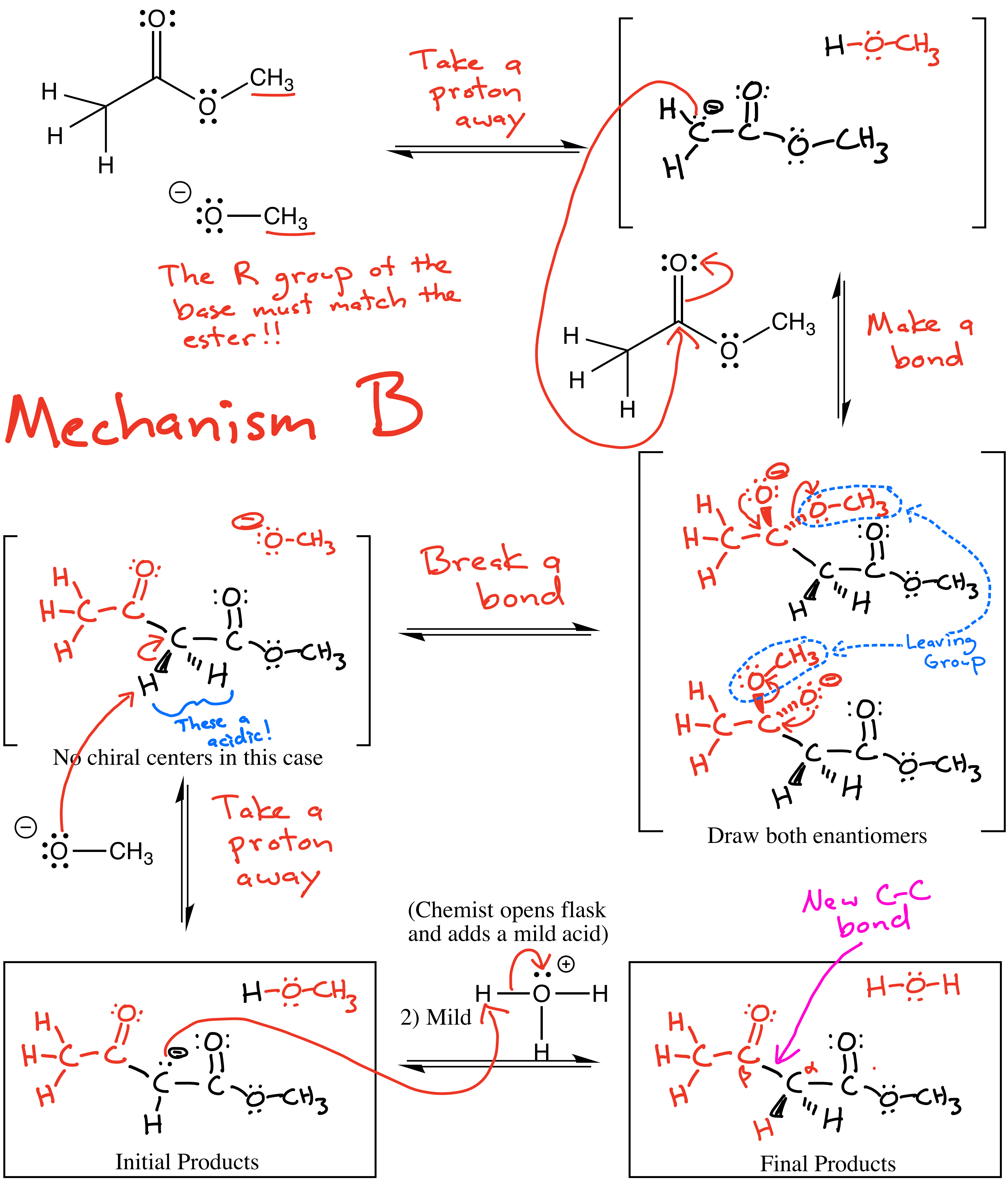


Not much of the Z product is formed because it has significantly more steric strain than E

THIS IS UNIQUE TO THIS EXAMPLE
⇓
USUALLY BOTH E AND Z ARE FORMED

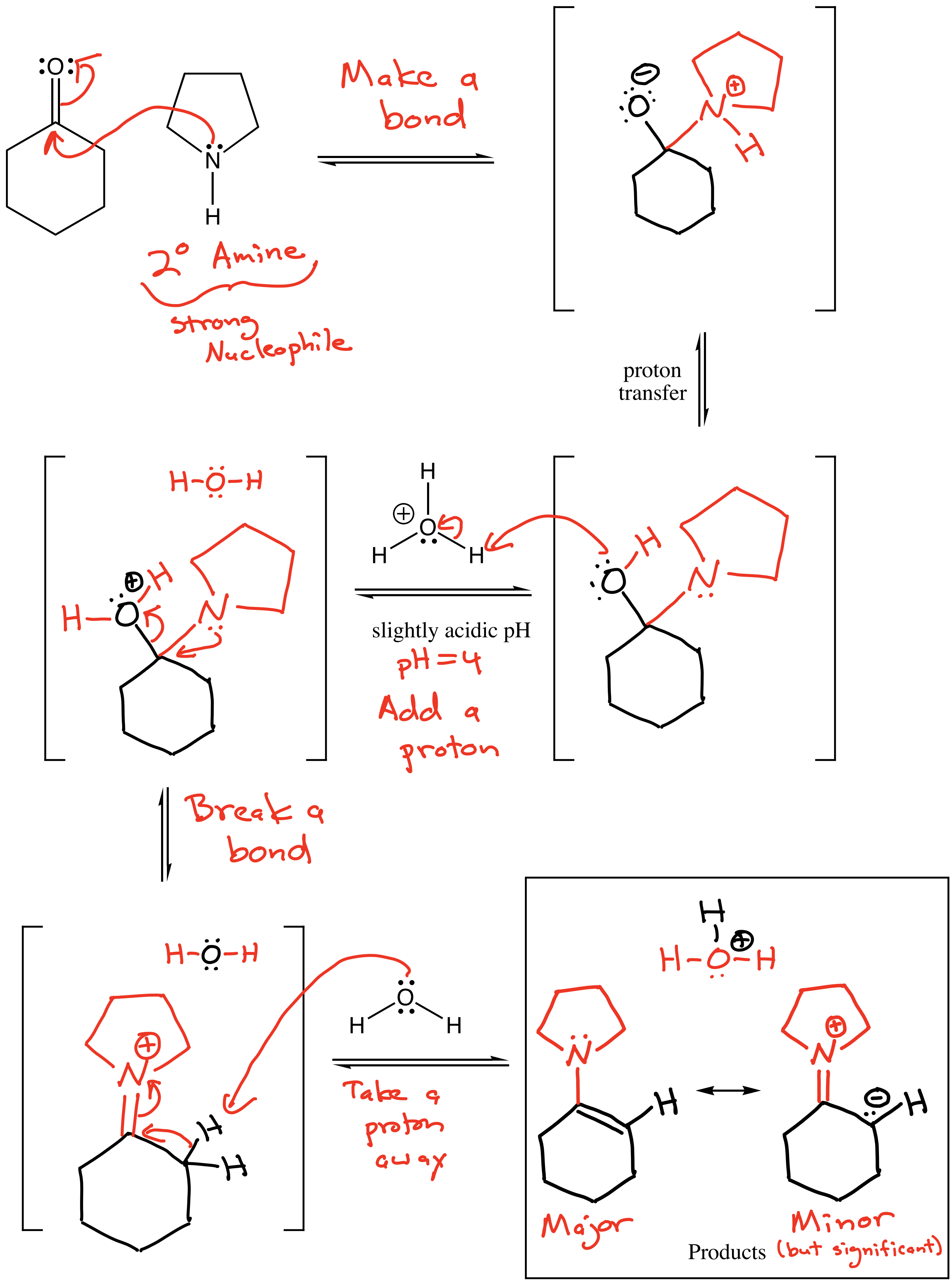
Claisen Condensation → "Aldol with Esters"

Mechanism B

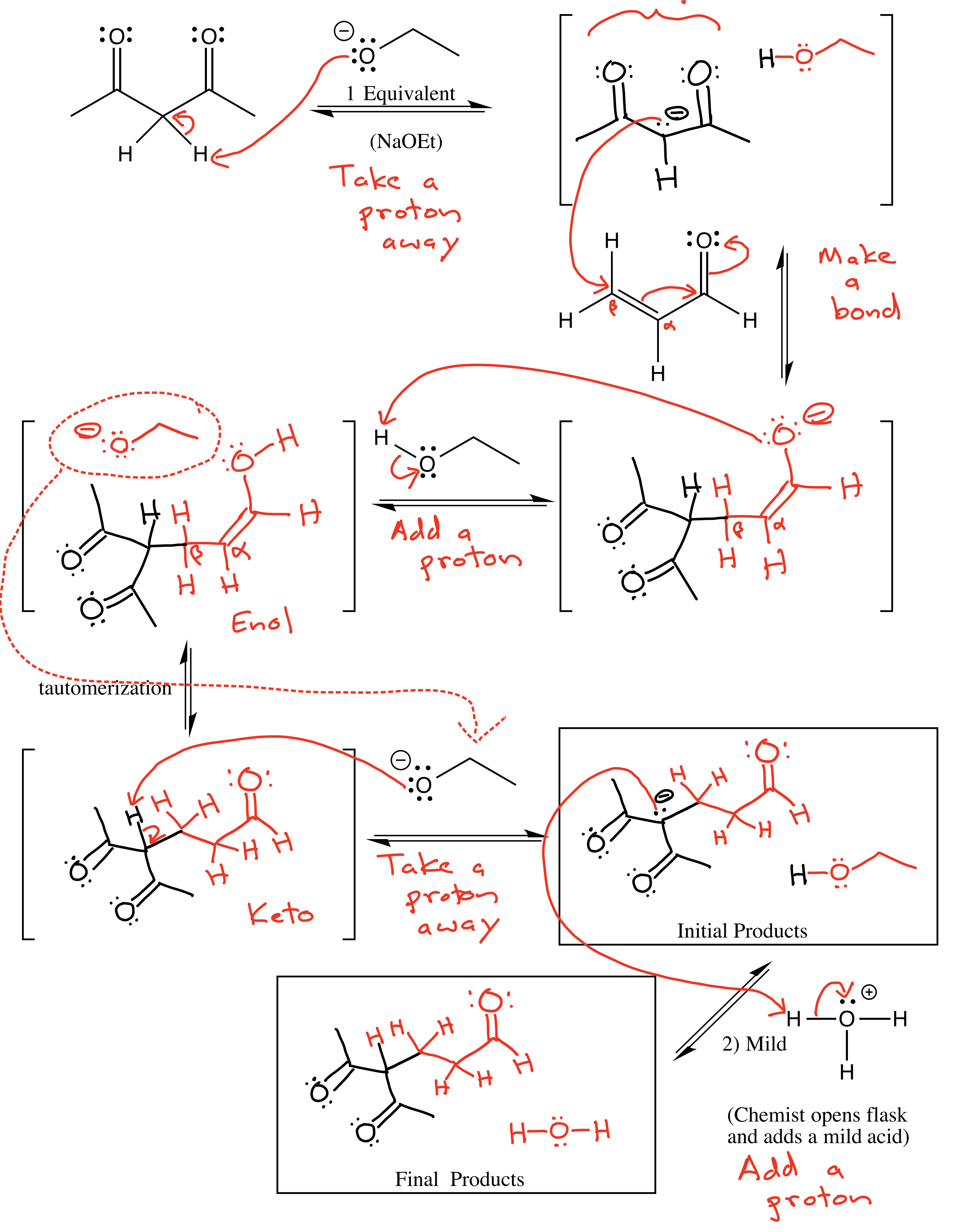


This is a much more stable anion compared to ⊖OCH3, providing a strong driving force (motive) for the Claisen condensation reaction

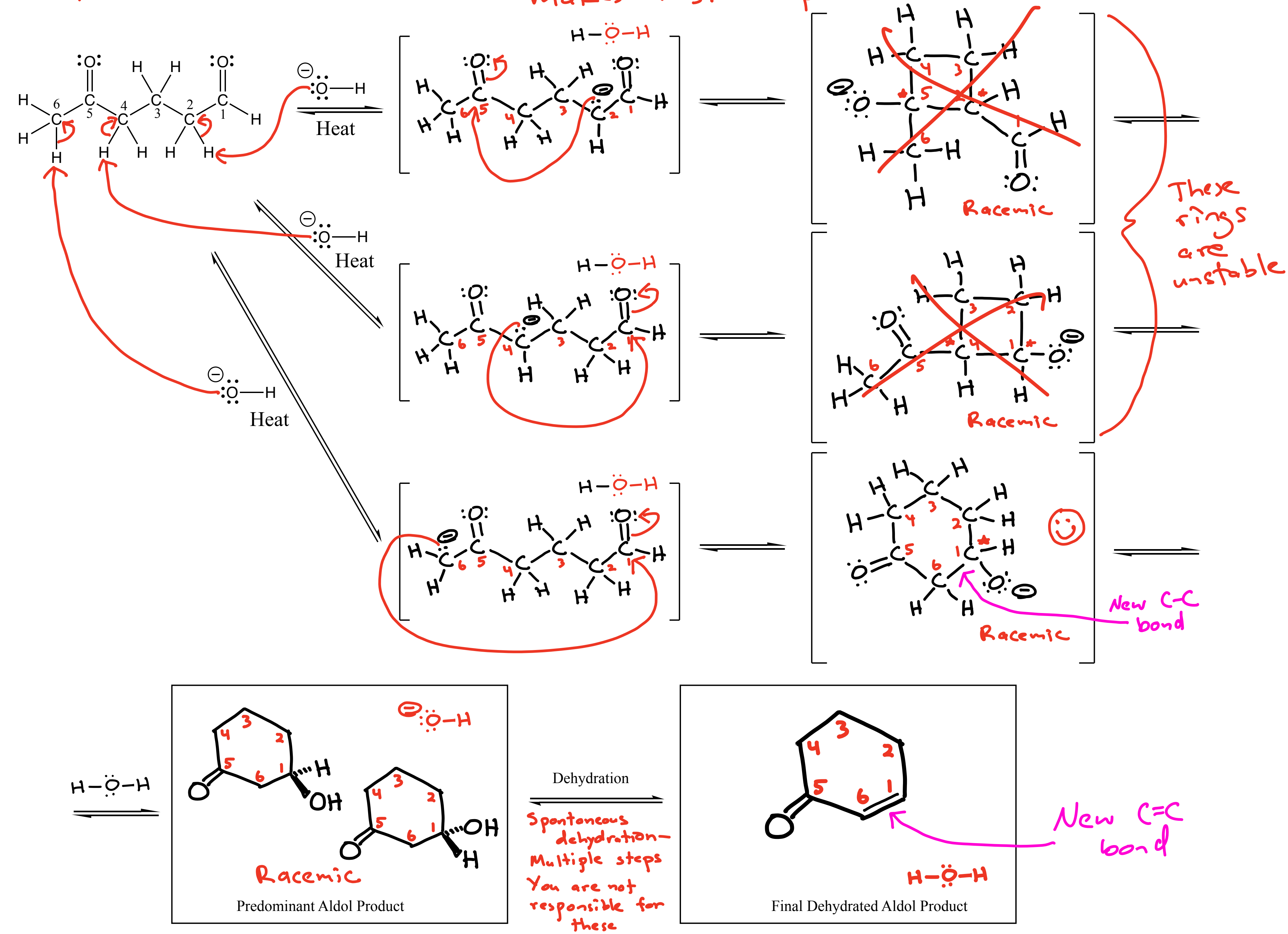
Enamine Formation



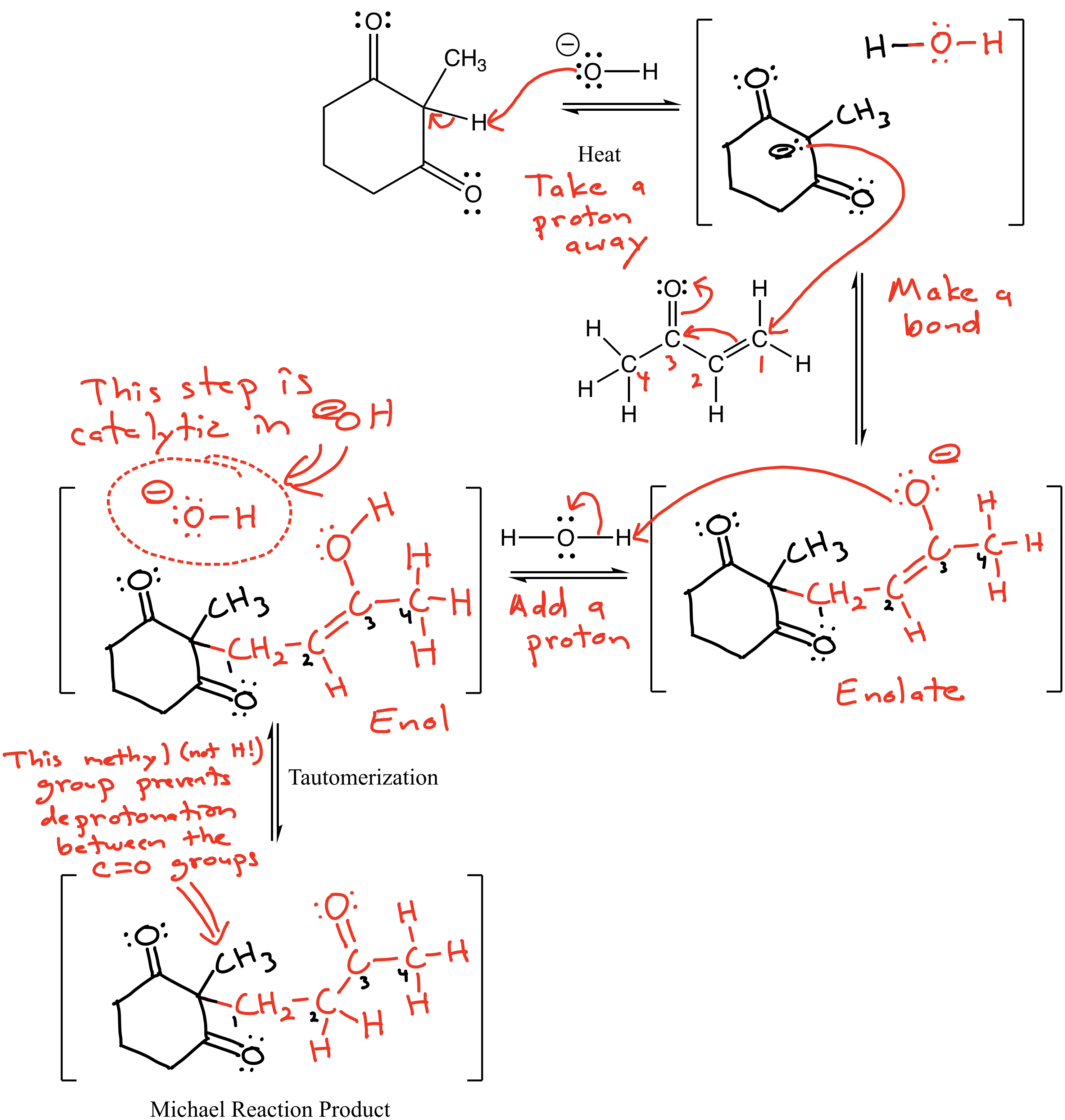
Michael Reaction



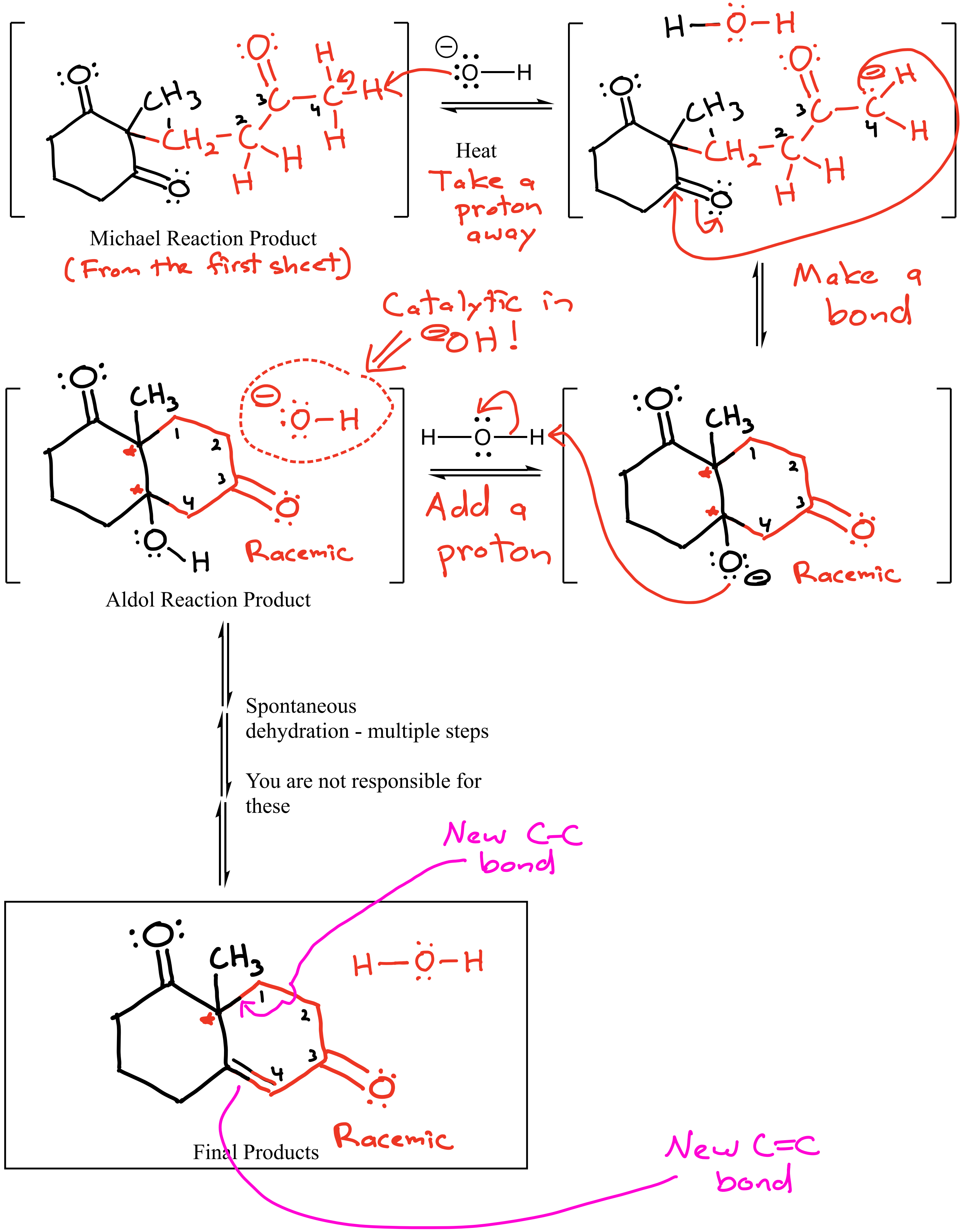
Cyclic Aldol Reaction → 3 different enolates are possible, but only one makes a stable product

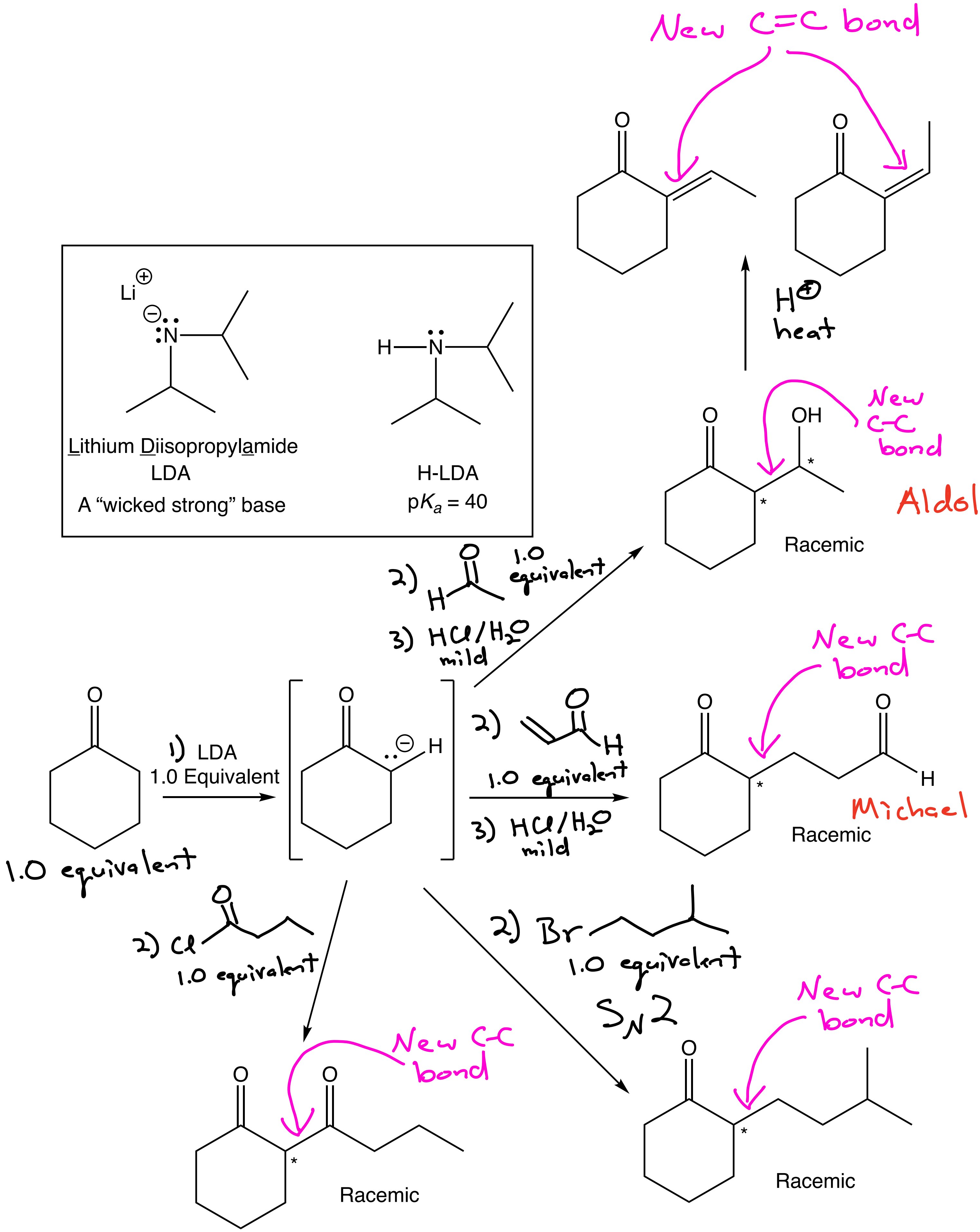


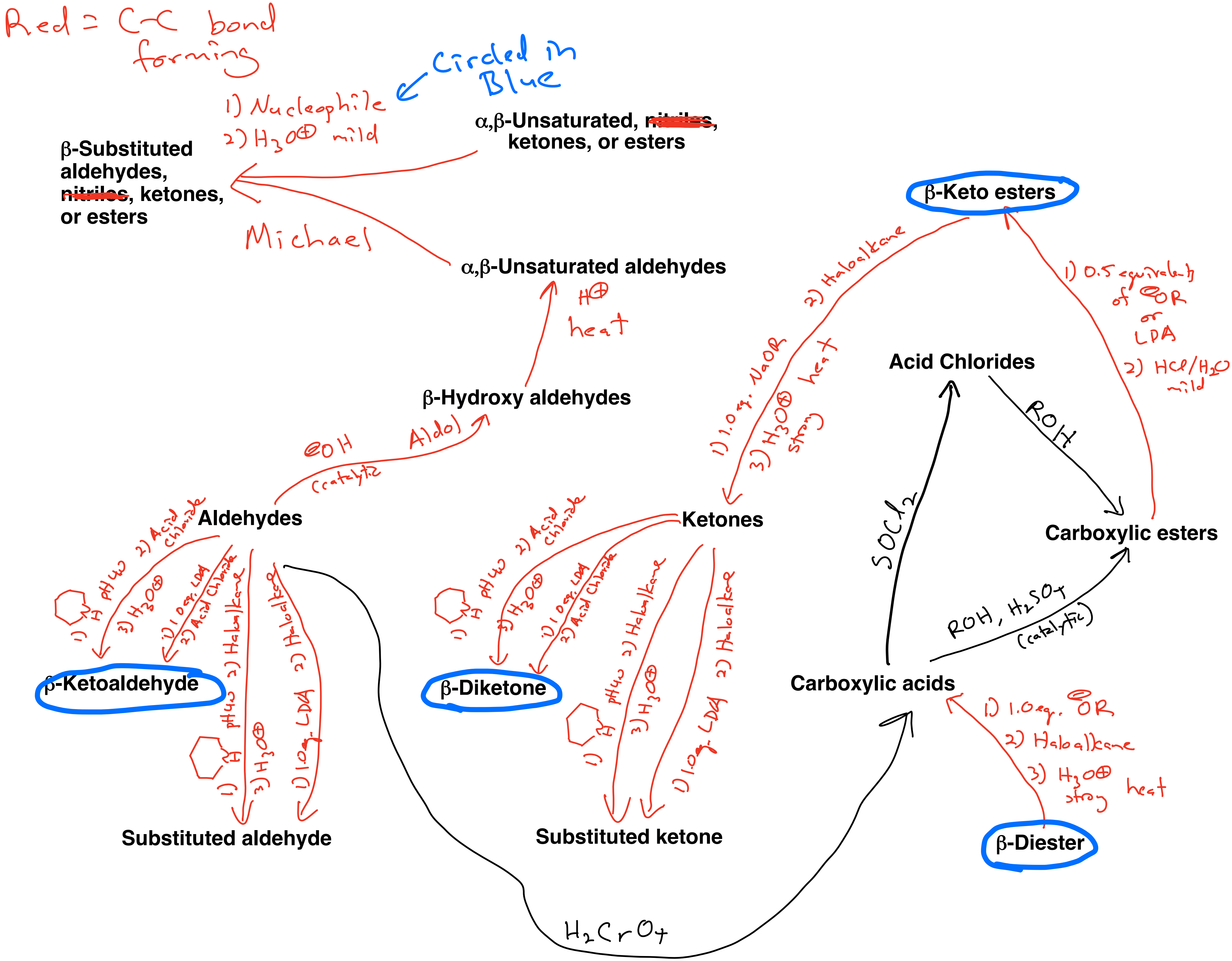
Robinson Annulation Part 1 - Michael Reaction Steps

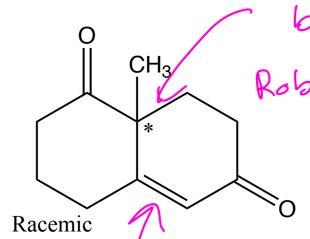


Robinson Annulation Part 2 - Aldol and Dehydration Steps




New C=C bond
O
O
H⊕
heat
Li⊕
N
H
N
Lithium Diisopropylamide
LDA
A "wicked strong" base
H-LDA
pK_a = 40
New C-C bond
O
OH
*
*
Racemic
Aldol
2) 1.0 equivalent
H
O
3) HCl/H$_2$O mild
New C-C bond
O
O
H
*
Racemic
Michael
O
1) LDA
1.0 Equivalent
1.0 equivalent
O
H
2) O H
1.0 equivalent
3) HCl/H$_2$O mild
2) Cl
O
1.0 equivalent
2) Br
1.0 equivalent
S_N2
New C-C bond
O
O
*
Racemic
New C-C bond
O
*
Racemic


Red = C-C bond forming
Circled in Blue
1) Nucleophile
2) $H_3O^{\oplus}$ mild
α,β-Unsaturated, ~~nitriles~~, ketones, or esters
β-Substituted aldehydes, ~~nitriles~~, ketones, or esters
Michael
α,β-Unsaturated aldehydes
$H^{\oplus}$
heat
β-Hydroxy aldehydes
$^{\ominus}OH$
(catalytic)
Aldol
β-Keto esters
2) Haloalkane
1) 1.0 eq. NaOR
3) $H_3O^{\oplus}$ strong
heat
1) 0.5 equivalents of $^{\ominus}OR$ or LDA
2) HCl/H_2O mild
Acid Chlorides
ROH
$SOCl_2$
Carboxylic esters
ROH, H_2SO_4 (catalytic)
Carboxylic acids
1) 1.0 eq. $^{\ominus}OR$
2) Haloalkane
3) $H_3O^{\oplus}$ strong
heat
β-Diester
Aldehydes
Ketones
2) Acid chloride
$pH_{4\text{-}5}$
3) $H_3O^{\oplus}$
1) 1.0 eq. LDA
2) Acid Chloride
2) Haloalkane
2) Haloalkane
1) 1.0 eq. LDA
β-Ketoaldehyde
β-Diketone
Substituted aldehyde
Substituted ketone
H_2CrO_4

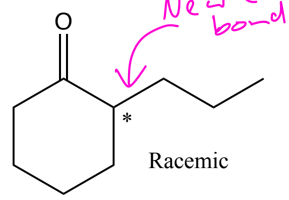


Racemic

New C-C bond

Robinson

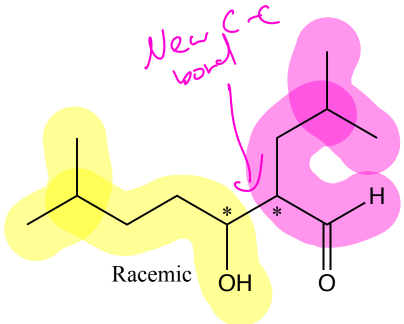
New C=C bond



Racemic

New C-C bond

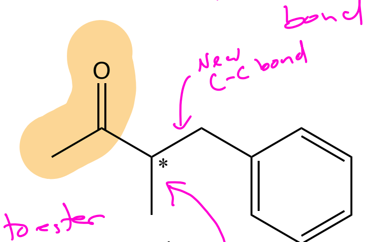
Enamine or LDA and S_N2



Racemic

New C-C bond

Aldol !!

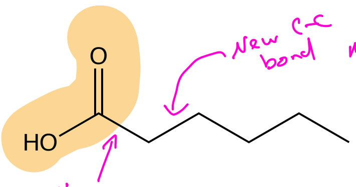


Racemic

New C-C bond

Acetoester

New C-C bond

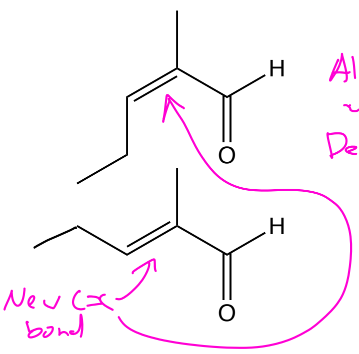


New C-C bond

Malonic Ester Synthesis

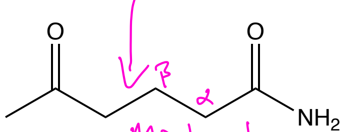
New C-C bond

Grignard + CO_2



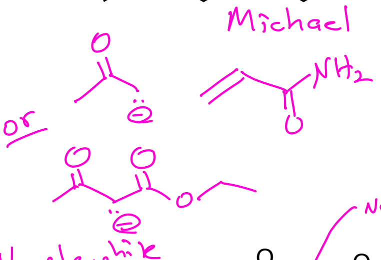
Aldol with Dehydration

New C=C bond

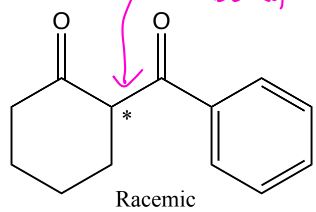


New C-C bond

Michael



Nucleophile

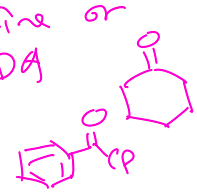


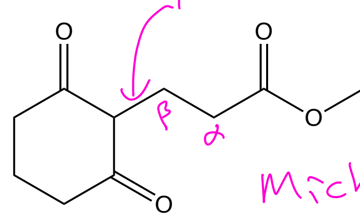
Racemic

New C-C bond

enamine or LDA

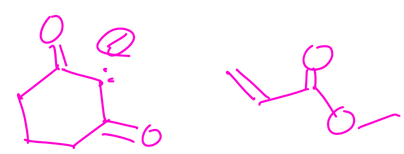
Add

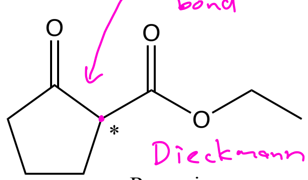




New C-C bond

Michael

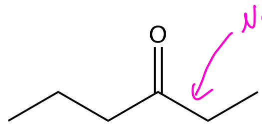




New C-C bond

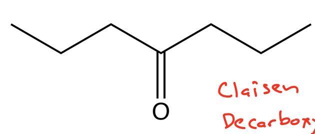
Dieckmann

Racemic

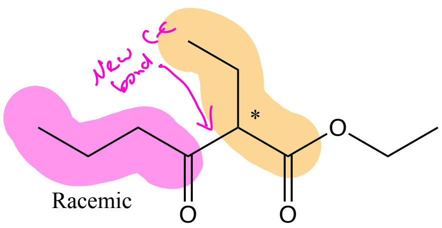


New C-C bond

Gilman



Claisen with Decarboxylation

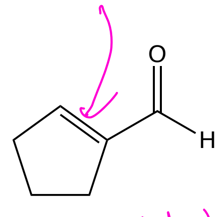


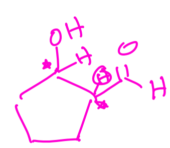
New C-C bond

Racemic

Claisen

New C=C bond





Racemic

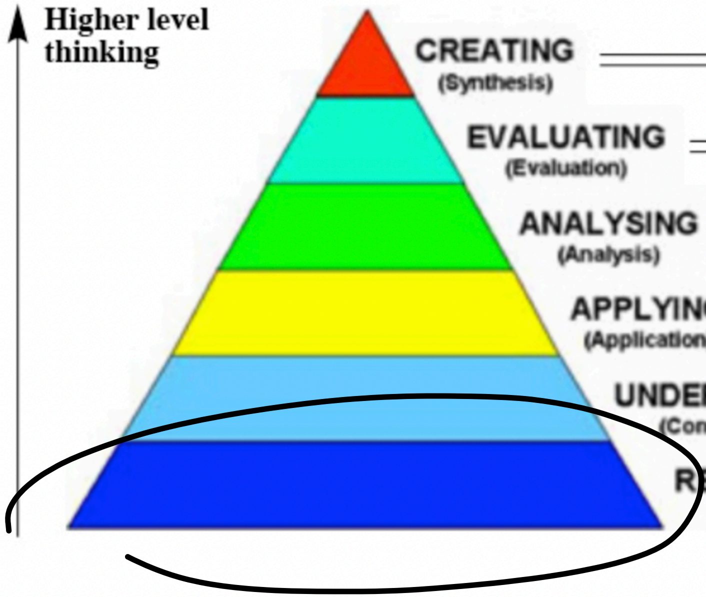
Cyclic aldol dehydration

Bloom's Taxonomy of Learning

Organic Chemistry Analog

Tools we created to help you succeed:

Higher level thinking

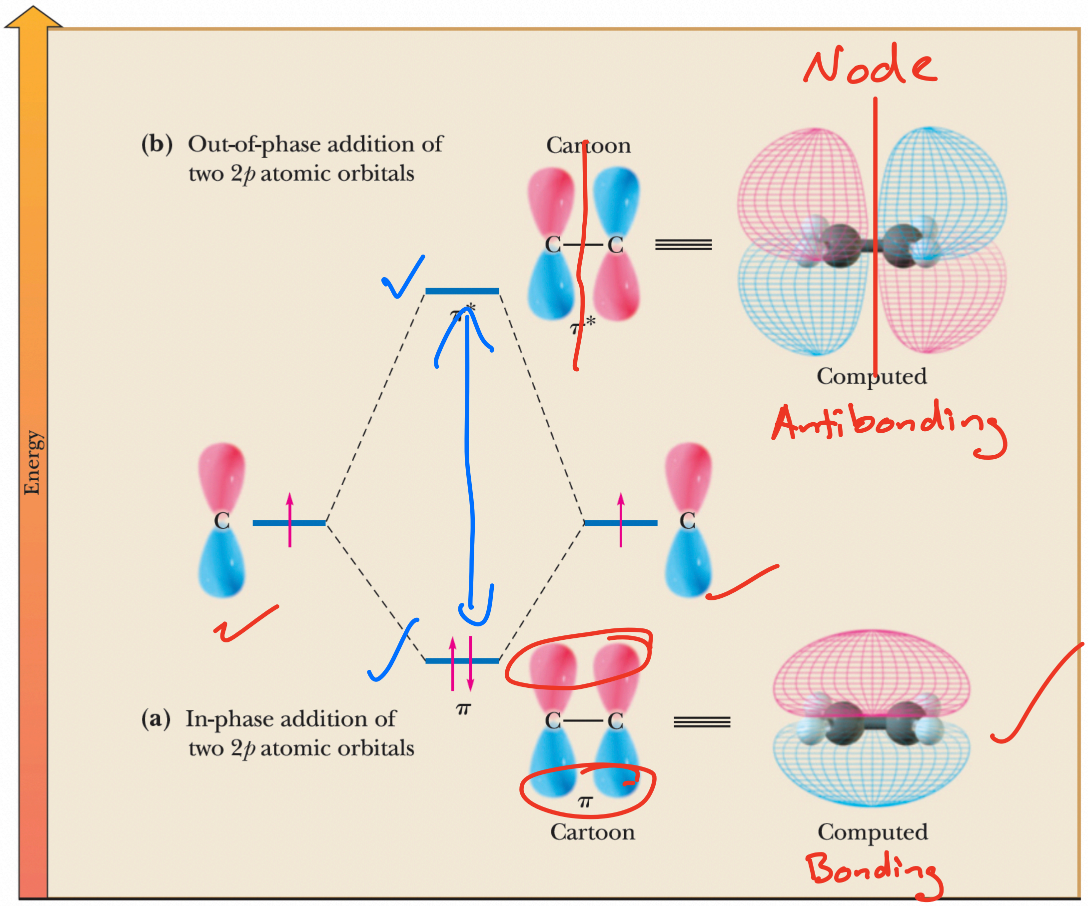


	Organic Chemistry Analog	Tools
CREATING (Synthesis)	Solving synthesis problems	Homework 9
EVALUATING (Evaluation)	Recognizing reaction products	KRE Table
ANALYSING (Analysis)	Reactions	Roadmaps Homework 8
APPLYING (Application)	Mechanisms	The 4 mechanistic elements
UNDERSTANDING (Comprehension)	Where are the electrons?	"Personalities of Molecules" Nucleophiles, electrophiles, acids, bases
REMEMBERING (Knowledge)	Structures, bonding, functional groups, reagents, nomenclature, definitions	Rules of the Day

There are no short cuts to the top →
you cannot just "remember" any more

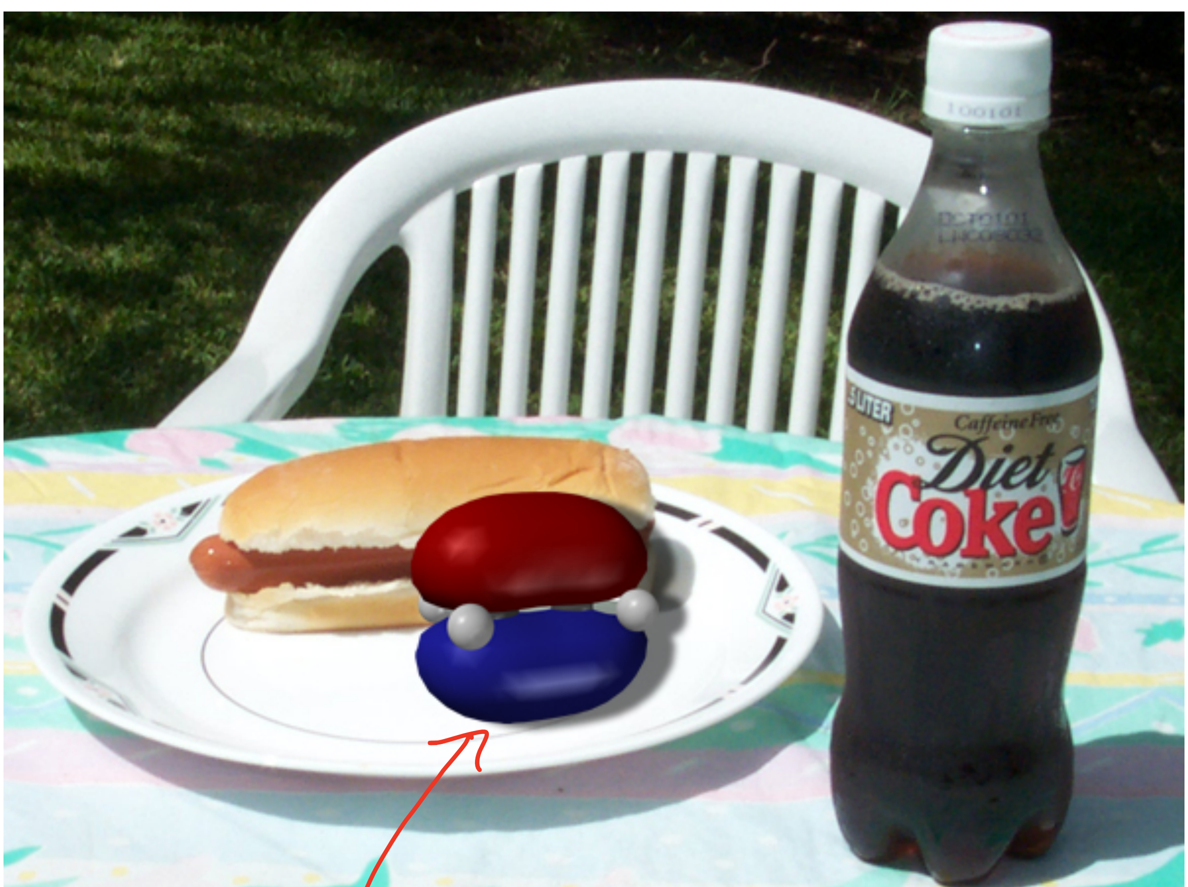
Organic chemistry is difficult because it requires higher order thinking. According to Bloom's taxonomy of learning, the lowest level of learning involves pure memorization ("Remembering") As one moves up the pyramid to higher learning, understanding, applying, analysing, evaluating and creating are reached. I believe there are Organic chemistry analogs of all of these, culminating in synthesis which inolves creativity along with all of the other levels of thinking. It is likely that many of you have never been challenged all the way to the top of the Bloom's taxonomy of learning pyramid before, explaining why this feels different and disorienting. DO NOT GIVE UP. As shown on the right, we have created tools to help you master each step up the ladder. On the above diagram you can cllick on the tools listed to go directly to them. Also, if you have any questions about how to study, click here to read about the way I learned to study. I never earned a grade lower than an A after I started using this method during my own college career.

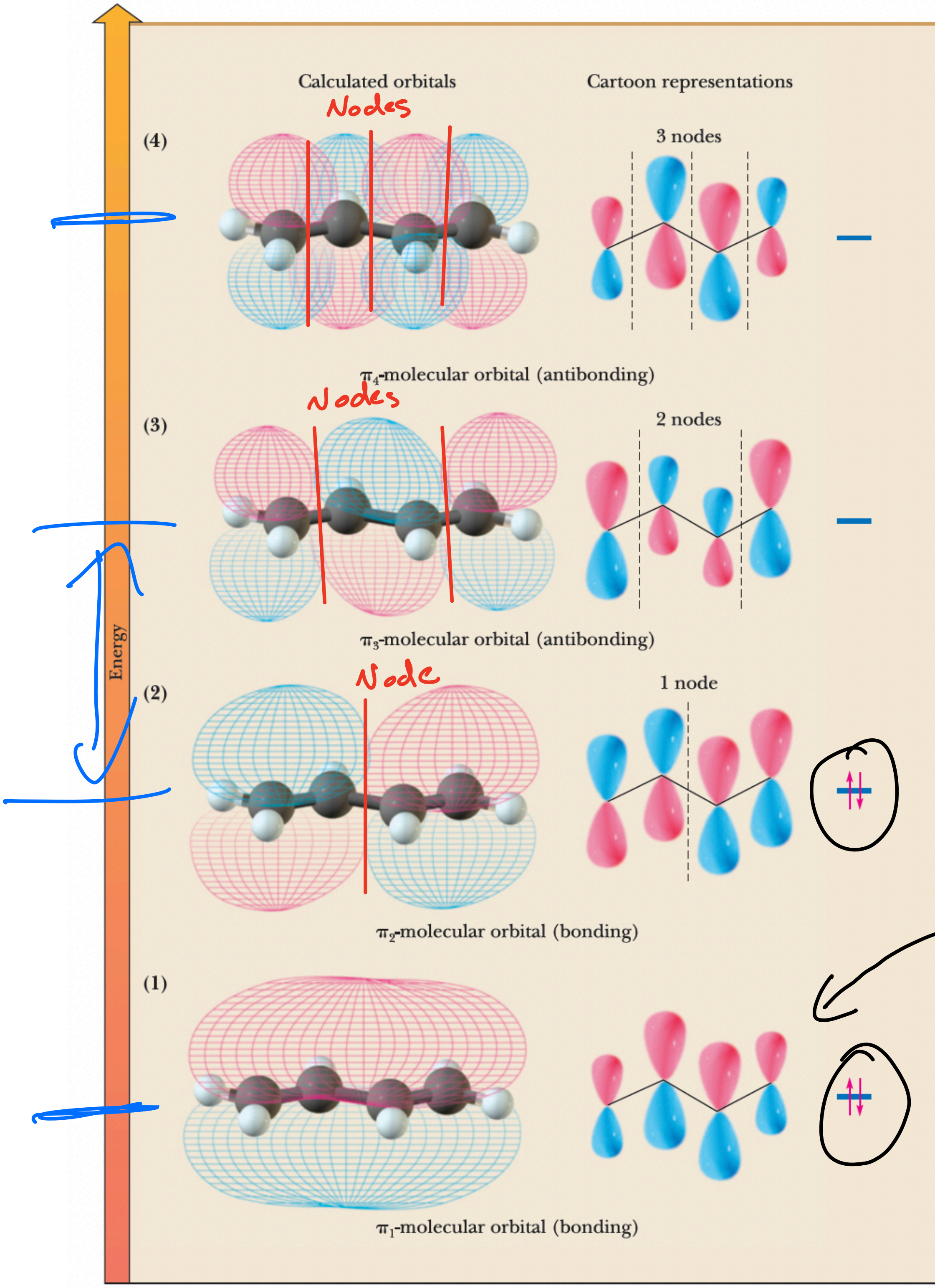
I understand that most of you are headed to the health professions, so you may be wondering if mastering synthesis problems will be important for you. I assert that it is. Solving a synthesis problem involves the detailed evaluation of a complex molecule while looking for KREs, then working backwards to the starting materials by analyzying possible reactions involved by thinking through your roadmaps, possibly applying your understanding of mechanism to make sure you predict the correct product for each reaction. This is the exact type of thinking you will need to diagnose a patient. A patient will present various complex combinations of symptoms, then you must evaluate which of these are important, then analyze, apply and understand how the patient got that way and how to get them back to their starting state (healthy) again. In other words, you will learn the "KREs of diagnosis" then work backwards to understand what happened to the originally healthy patient! Therefore, learning how to solve synthesis problems will teach you how to use higher level thinking skills, exactly the kind you will need to develop as a health care professional!



Watch a video explanation

FIGURE 1.21 Molecular orbital mixing diagram for the creation of any C—C π bond. (a) Addition of two p atomic orbitals in phase leads to a π orbital that is lower in energy than the two separate starting orbitals. When populated with two electrons, the π orbital gives a π bond. (b) Addition of the p orbitals in an out-of-phase manner (meaning a reversal of phasing in one of the starting orbitals) leads to a π^* orbital. Population of this orbital with one or two electrons leads to weakening or cleavage of the π bond, respectively.



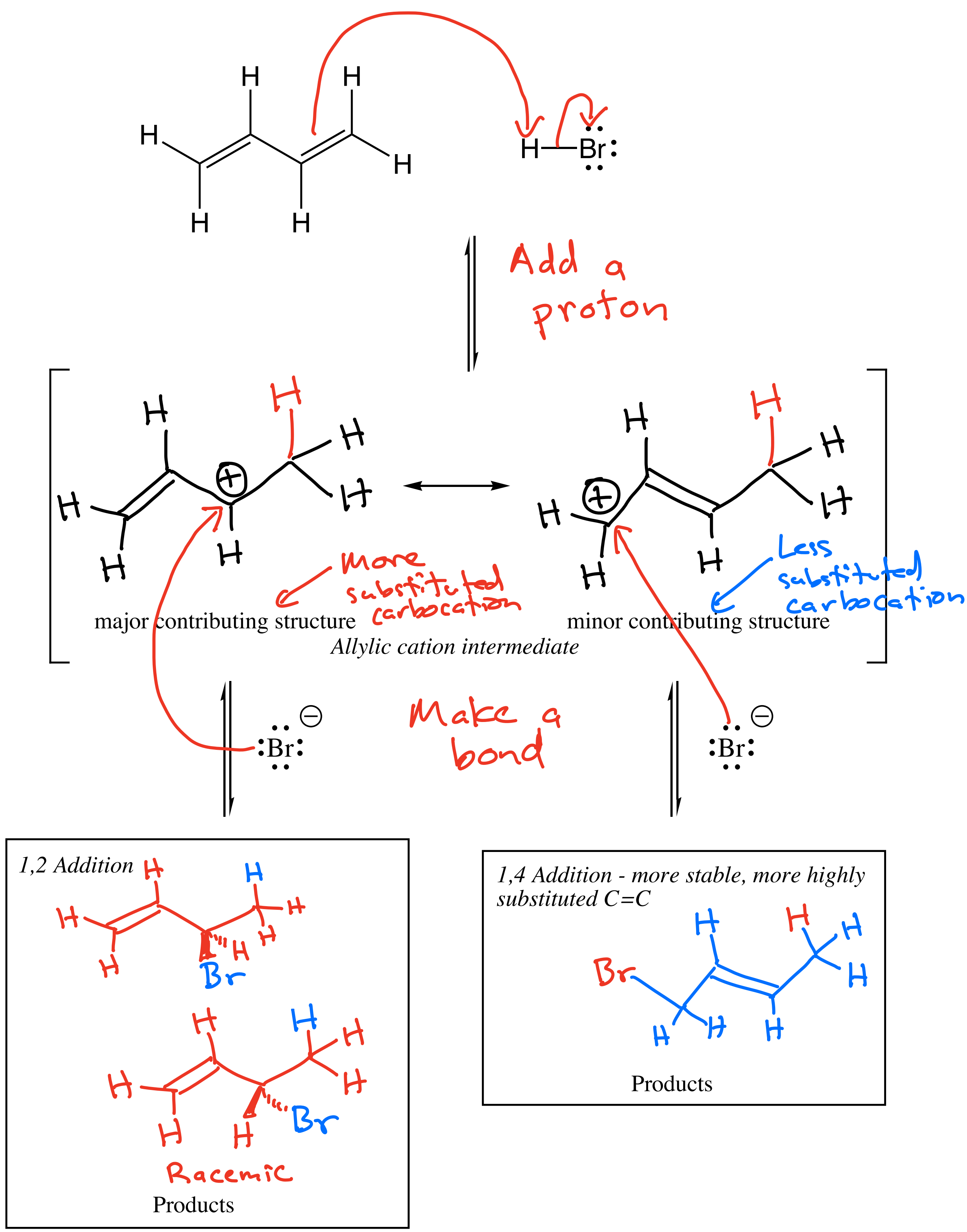


Watch a video explanation

"π-way" orbital → a "highway" for π electrons

FIGURE 20.2 Structure of 1,3-butadiene—molecular orbital model. Combination of four parallel 2*p* atomic orbitals gives two π-bonding MOs and two π-antibonding MOs. In the ground state, each π-bonding MO is filled with two spin-paired electrons. The π-antibonding MOs are unoccupied.

H-X reacting with conjugated dienes



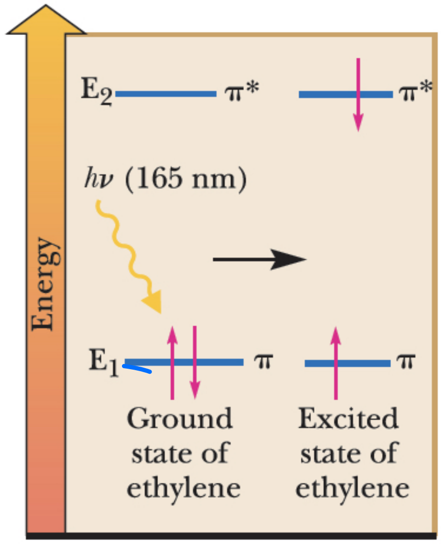


FIGURE 20.6 A $\pi \rightarrow \pi^*$ transition in excitation of ethylene. Absorption of ultraviolet radiation causes a transition of an electron from a π-bonding MO in the ground state to a π-antibonding MO in the excited state. There is no change in electron spin.

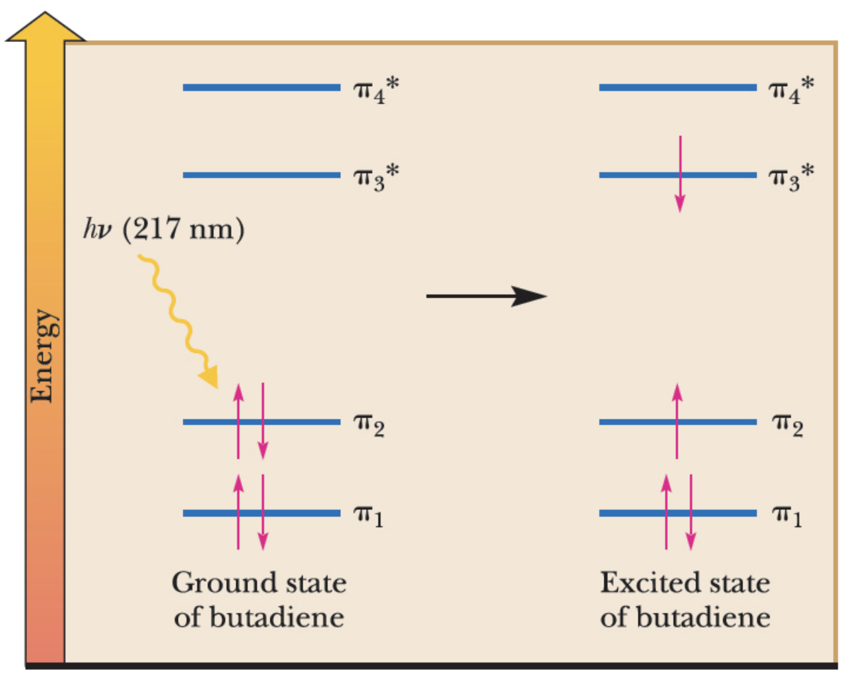
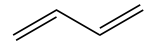
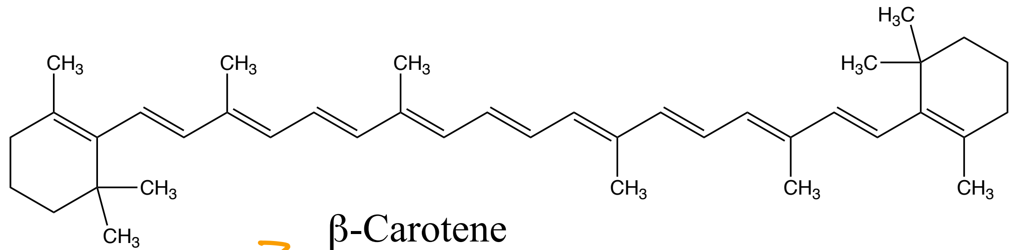


FIGURE 20.7 Electronic excitation of 1,3-butadiene; a $\pi \rightarrow \pi^*$ transition.



Butadiene

λ_{max} = 217 nm

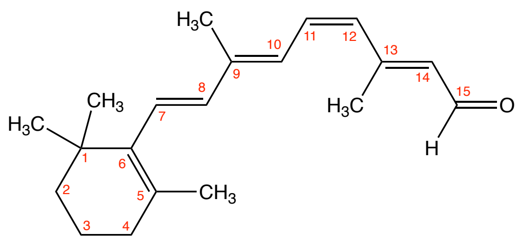


β-Carotene

λ_{max} = 455 nm, 483 nm

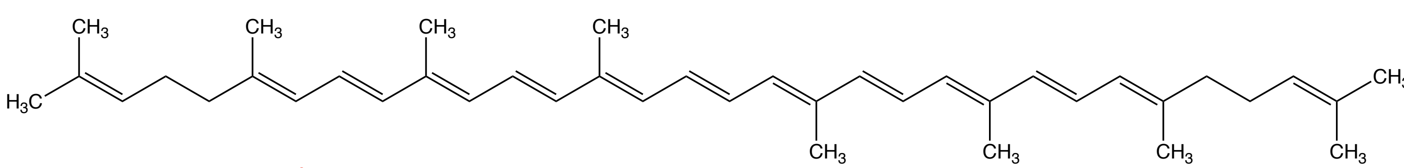
The orange color in carrots

β-Carotene is converted to 11-cis-retinal in our bodies



11-*cis*-Retinal

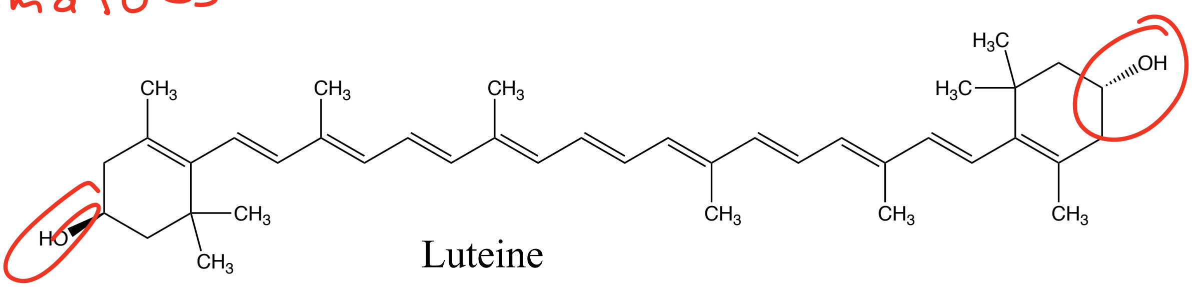
λ_{max} = 380 nm



Lycopene

λ_{max} = 443 nm, 471 nm, 502 nm

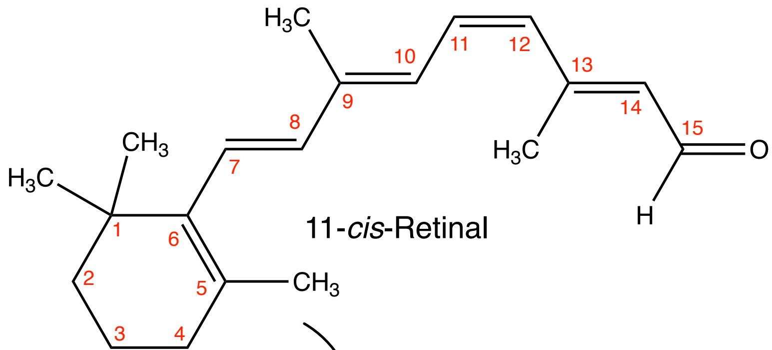
The red color of tomatoes



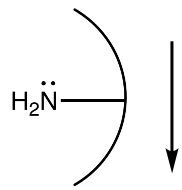
Luteine

λ_{max} = 445 nm, 474 nm

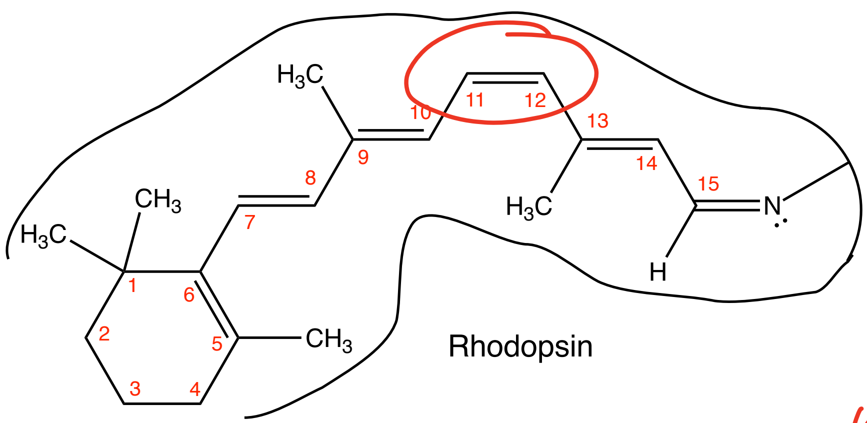
How vision works



11-*cis*-Retinal



Binds to an $-NH_2$ group from the amino acid lysine in the protein opsin

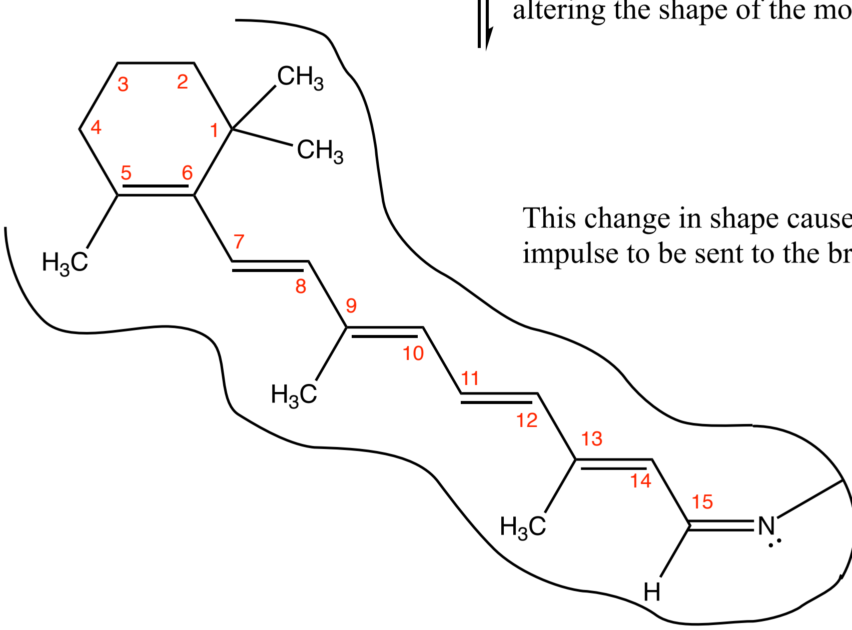


Rhodopsin

As the light is absorbed, a bonding π electron is excited into a π antibonding orbital → that effectively breaks the $C_{11}-C_{12}$ π bond so it can rotate to the more stable all trans form!

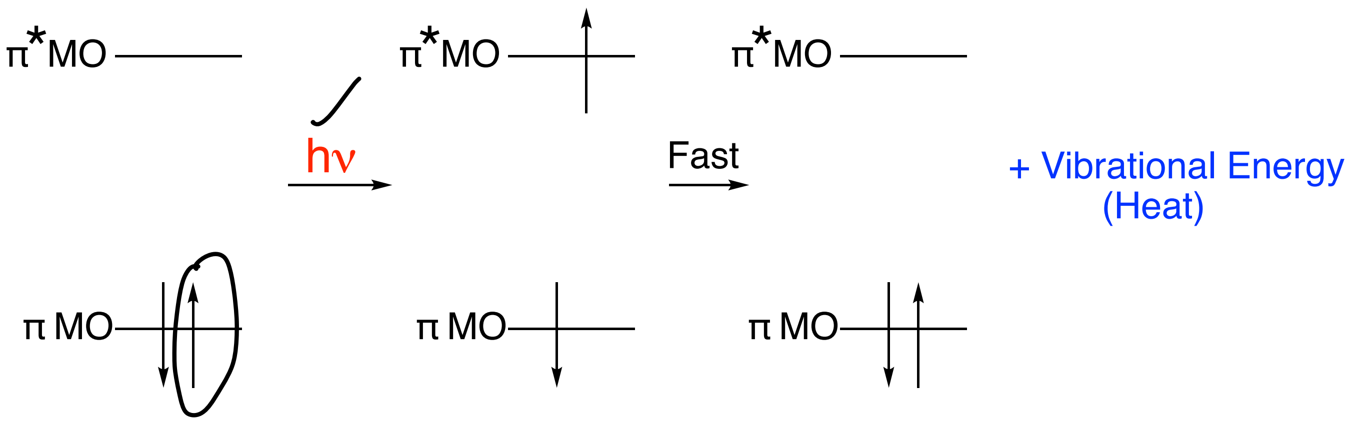
Molecule resets

A photon of visible light is absorbed by the retinal, isomerizing the *cis* bond to *trans*, dramatically altering the shape of the molecule

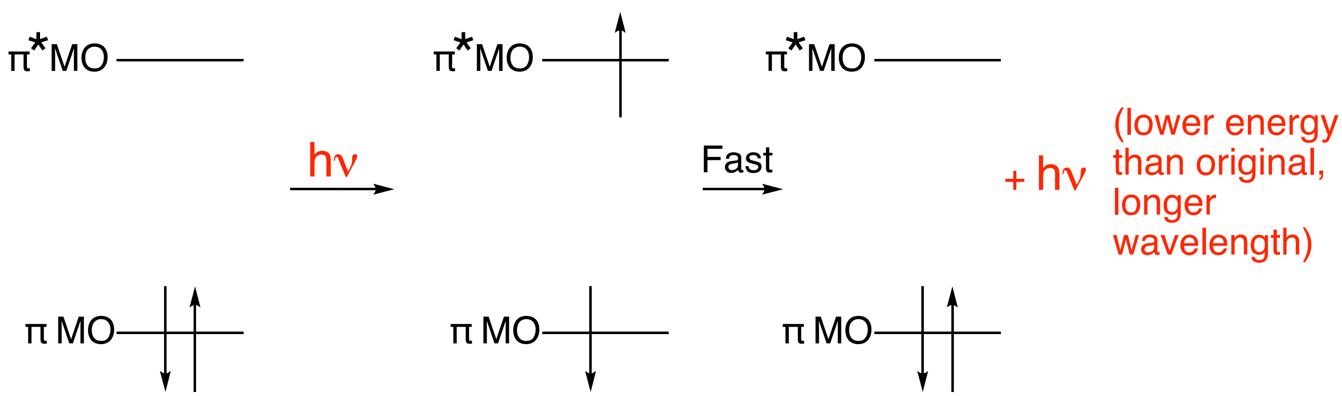


This change in shape causes a nerve impulse to be sent to the brain

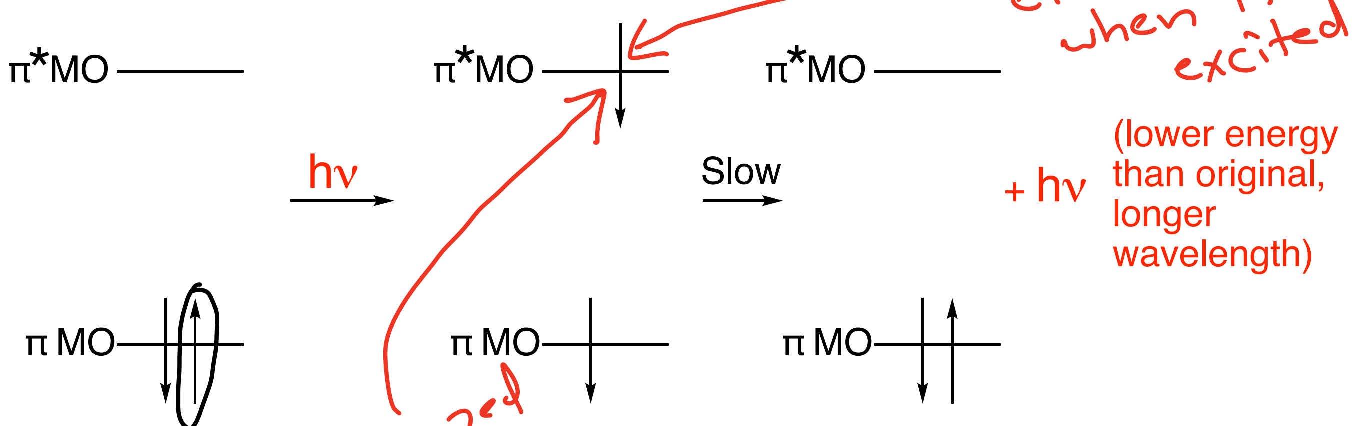
Generation of heat, Most molecules



Flourescence - Rigid Molecules, Not uncommon



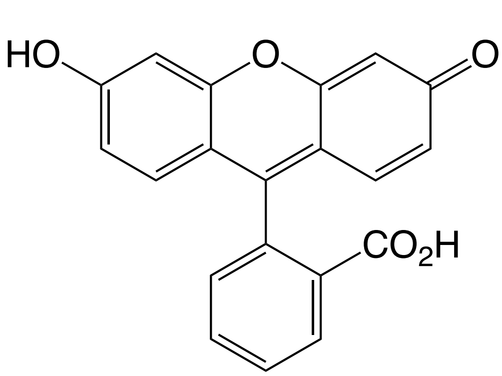
Phosphorescence - "Glow in the Dark", Rare



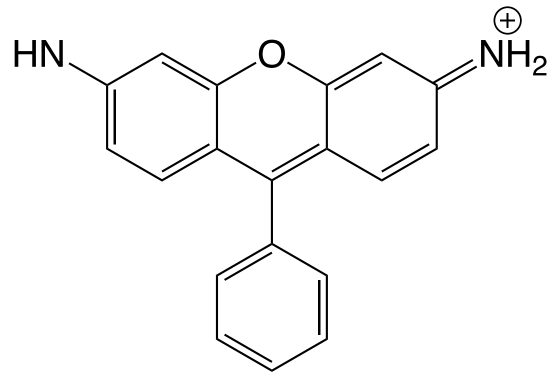
spin of electron flips when it is excited!

Trapped here until the spin flips back – then it emits photon

Flourescence - Rigid Molecules, Not uncommon

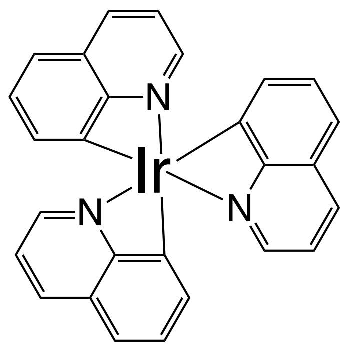


Fluorescein



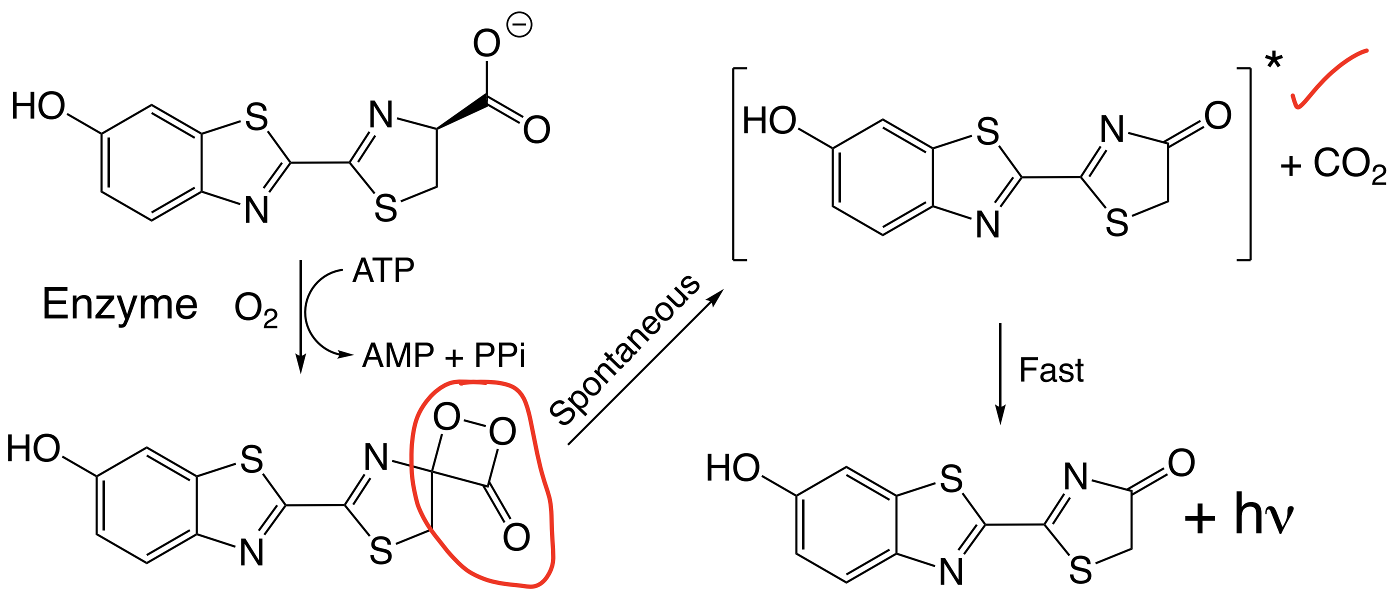
Rhodamine

Phosphorescence - “Glow in the Dark”, Rare



The metal is responsible for the electron spin flipping upon absorbing a photon

Bioluminescence - Fireflies, Deep Sea Creatures - Chemical Reactions

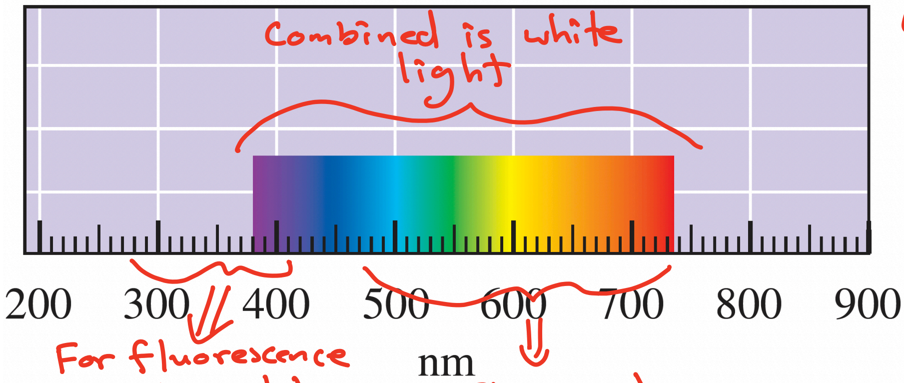


http://photobiology.info/Branchini2.html

Energy

Light source

Combined is white light

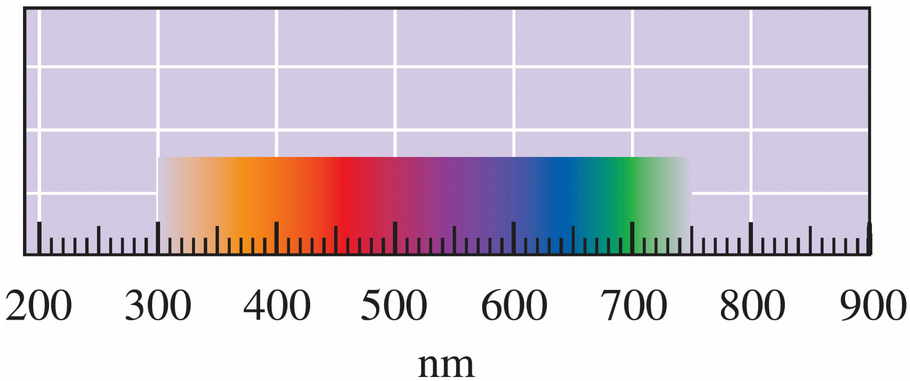


For fluorescence the ultraviolet light (UV) is used to excite electrons

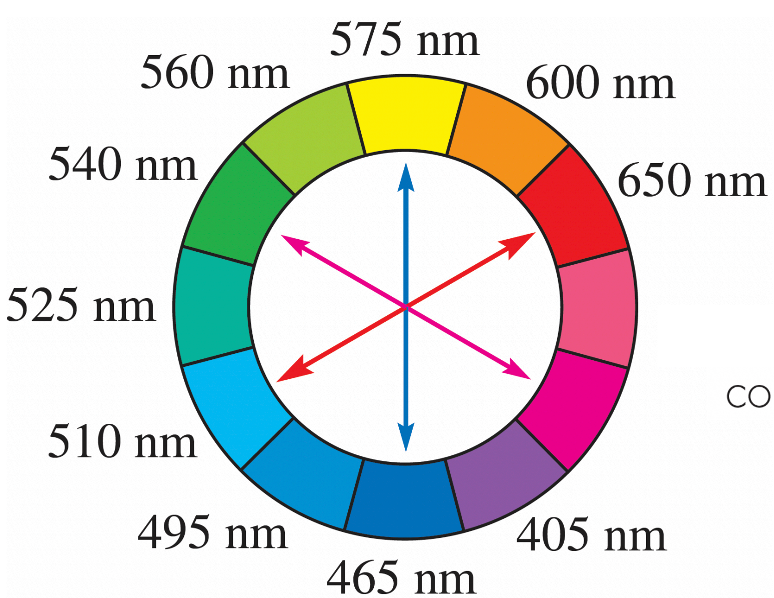
Flourescent emission

FIGURE 20.5 (a) Visible light color-wavelength correlation.

*** We "see" the wavelengths reflected minus the wavelengths absorbed ***

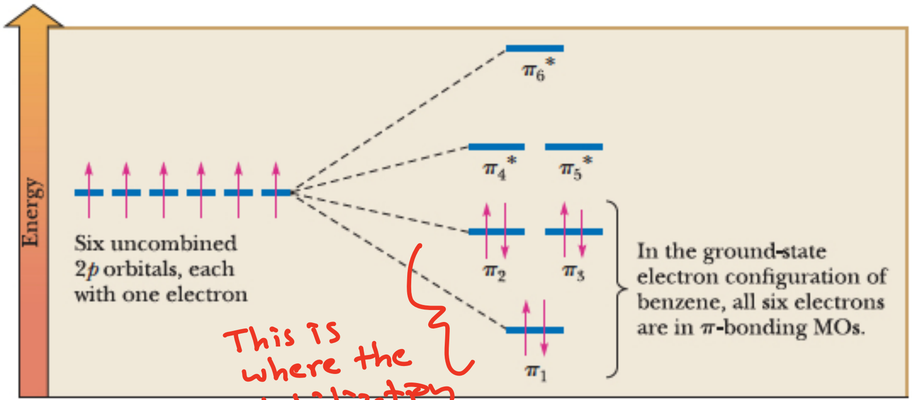


(b) Approximate color of substance (reflected light) if a single wavelength (i.e., the wavelength listed on the numerical scale of the *x*-axis) is absorbed.



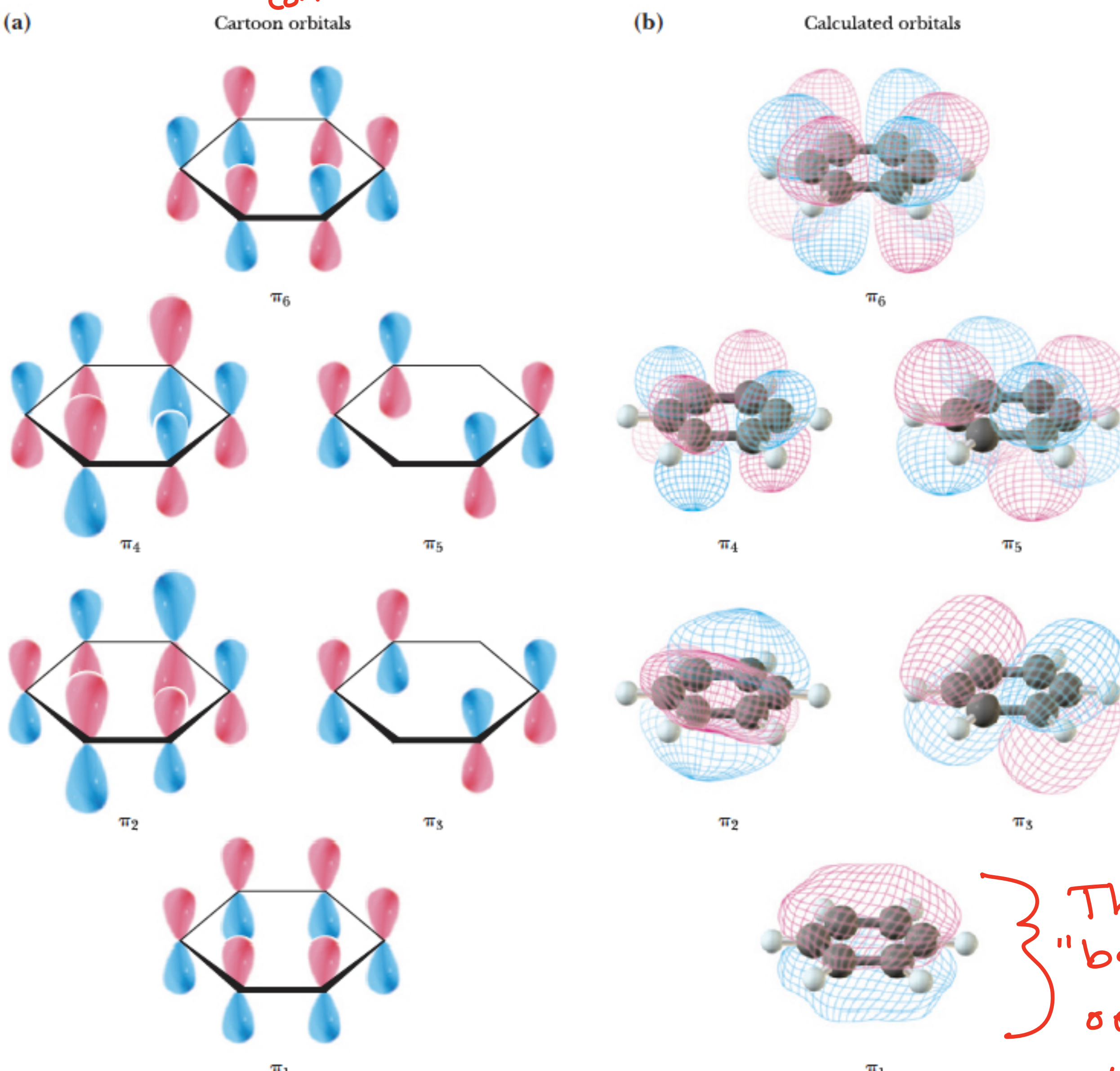
Colored arrows are complementary

(c) Complementary colors on a color wheel.



This is where the stabilization comes from

FIGURE 21.2 The molecular orbital representation of the π bonding in benzene.



The "bagel" orbital

⇓

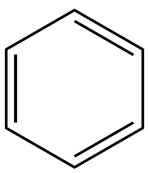
a super stable circular "π-way"

FIGURE 21.3 Orbitals for the π system of benzene. (a) Cartoon representations of the six calculated orbitals that chemists routinely draw. These pictures accentuate the fact that various combinations of parallel 2p orbitals lead to the π system of benzene. (b) Calculated orbitals. The three lowest in energy are occupied with electrons (see Figure 21.2). The lowest of these orbitals is the image most chemists use for the π system of benzene: a torus of electron density above and below the ring.

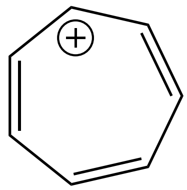
Hückel's Aromaticity Criteria

1) All ring atoms are sp^2 (they have a 2p orbital)
2) Flat (so the 2p orbitals overlap)
3) Monocyclic (Rule 4) only applies to single rings)
4) 4n+2 pi electrons (2,6,10,14....)

All have 6 π $e^{\ominus}$

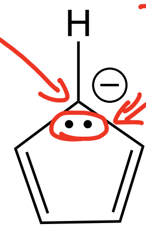


Benzene



Tropylium Ion

sp^2

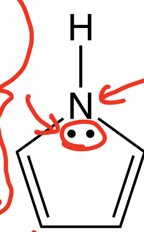


Cyclopentadienyl anion

In a 2p orbital and part of the aromatic 6 π electrons

Not available to bind a proton

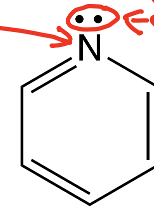
Pyrrole is NOT a base



Pyrrole

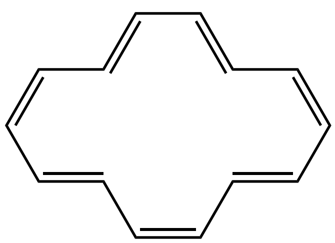
sp^2

Pyridine is a base!



Pyridine

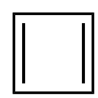
In an sp^2 orbital and not part of π $e^{\ominus}$ → They are available to bind a proton!



Annulene

14 π electrons

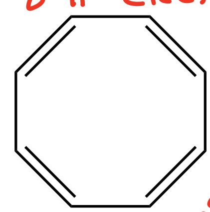
4 π electrons



Cyclobutadiene

Not a stable molecule

8 π electrons



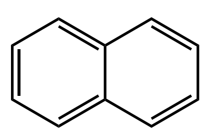
Cyclooctatetraene

Folds so 2p orbitals do not overlap and avoids antiaromaticity

Antiaromatic → These are much less stable than predicted as simple alkenes

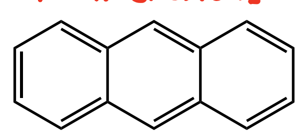
All fused benzene compounds are aromatic no matter the number of π electrons → Not monocyclic so Hückel's 4n+2 rule does not apply!

10 π electrons



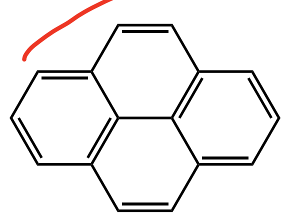
Naphtalene

14 π electrons



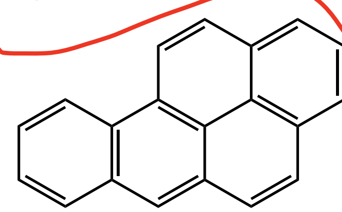
Anthracene

Still aromatic!



Pyrene

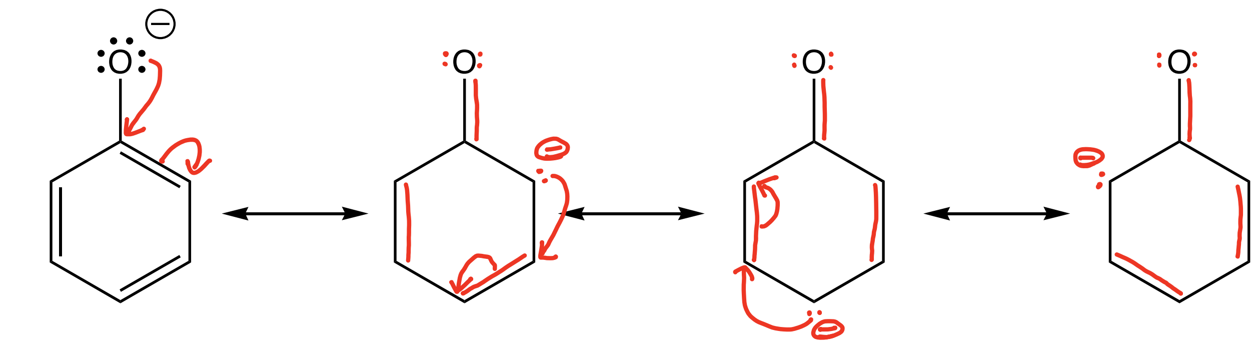
16 π electrons!



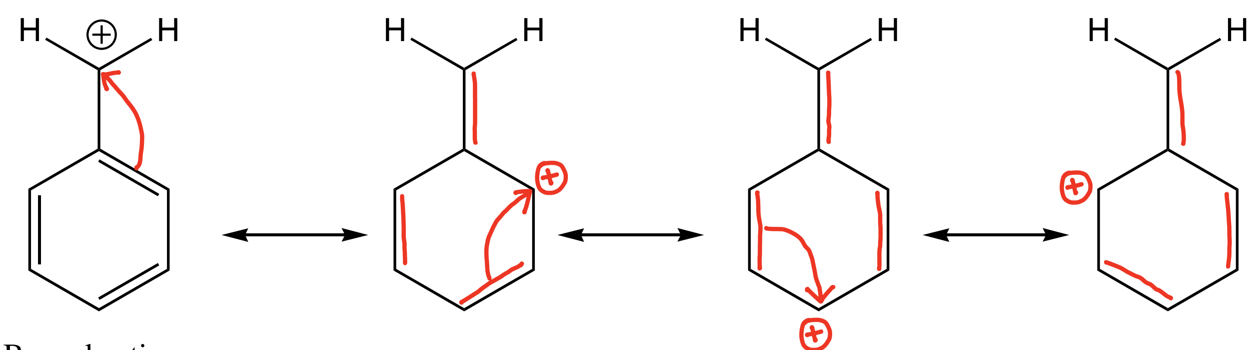
Benzo[α]pyrene

20 π electrons

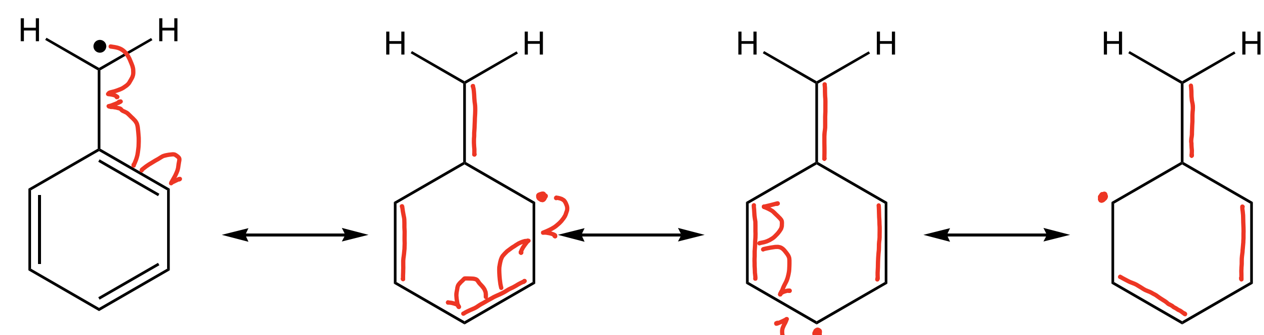
Aromatic resonance stabilization of charged species



Phenoxide anion

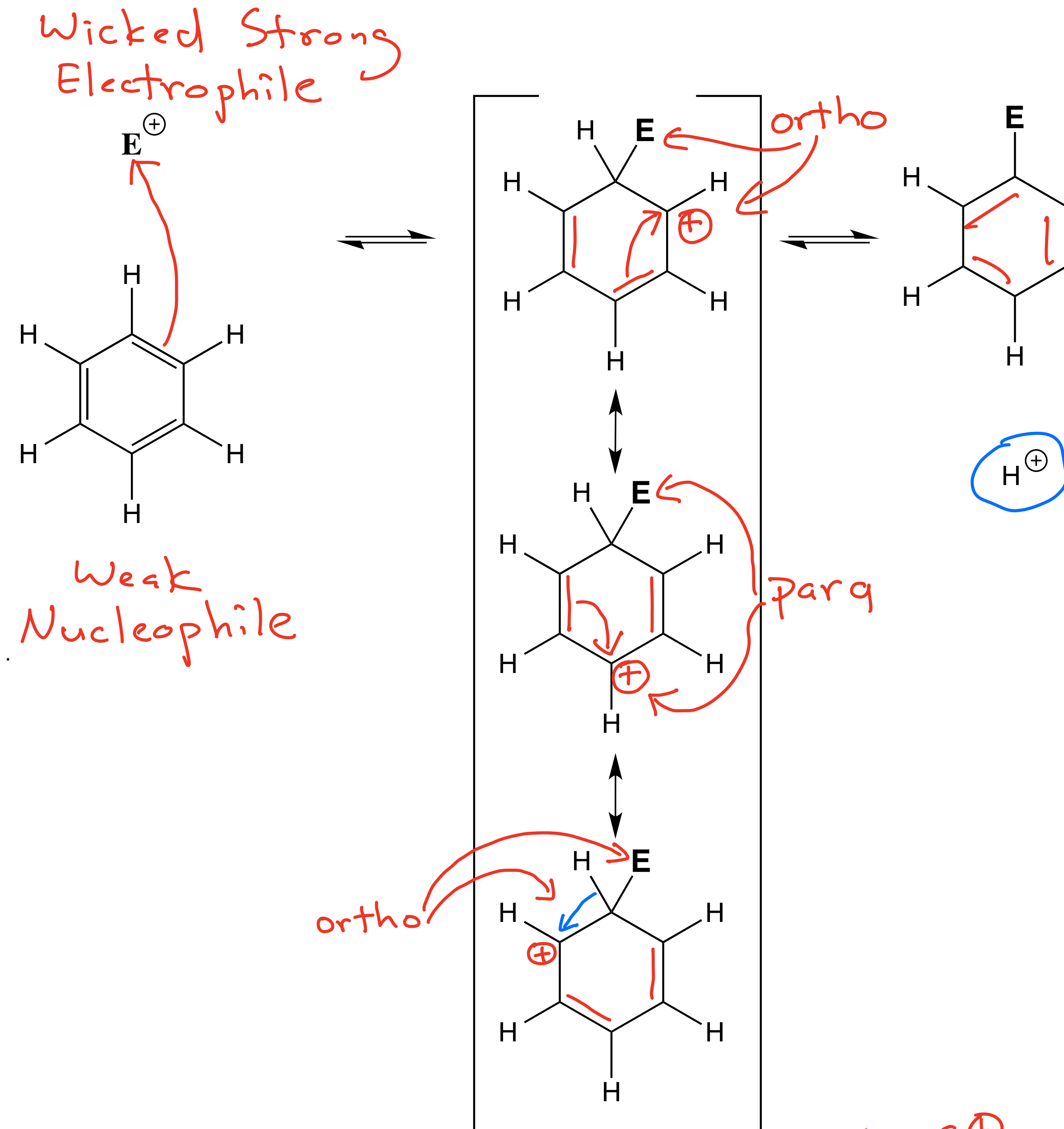


Benzyl cation

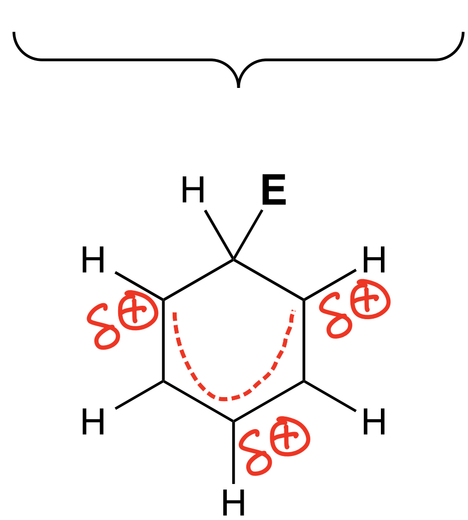


Benzyl radical

Benzene rings stabilize anions, cations and radicals (Golden Rules 5,6 and 7)



Called the Arenium Ion



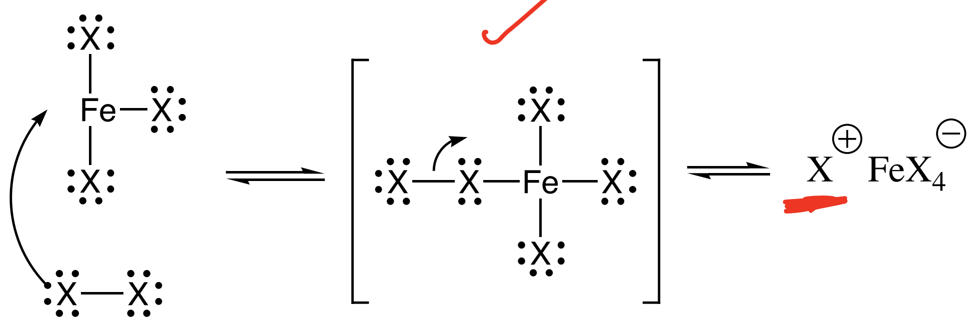
The δ⊕ is located ortho and para to where the new bond to "E" is located

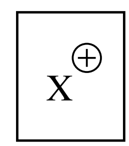
Reagents

Wicked strong electrophile

$\underline{\mathbf{E}^{\oplus}}$

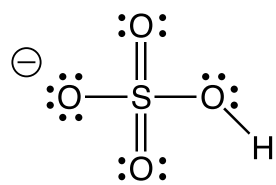
Halogenation X_2, FeX_3

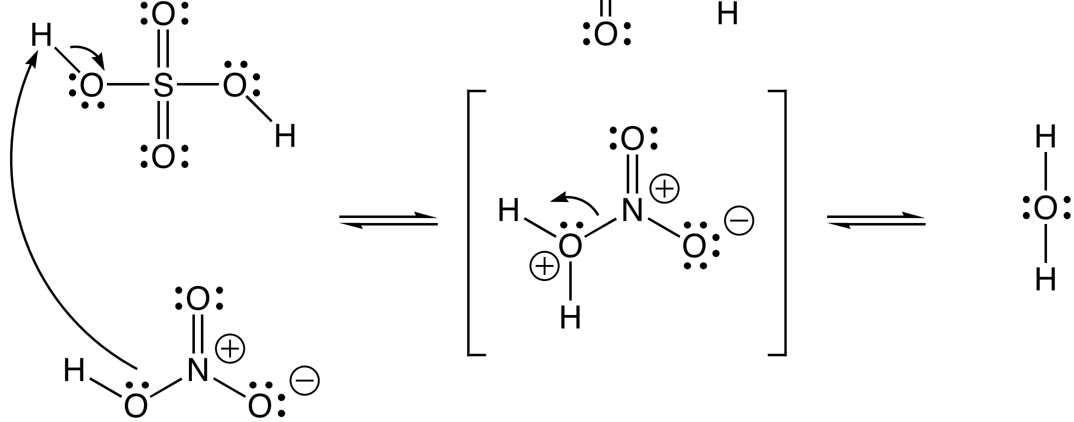


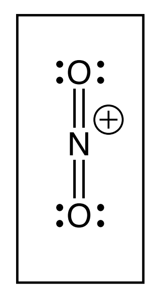


X = Br, Cl

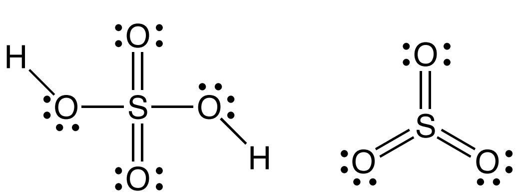
Nitration H_2SO_4/HNO_3

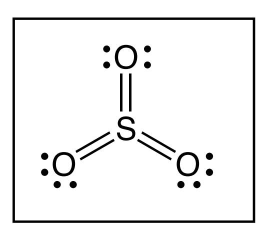






Sulfonation H_2SO_4/SO_3





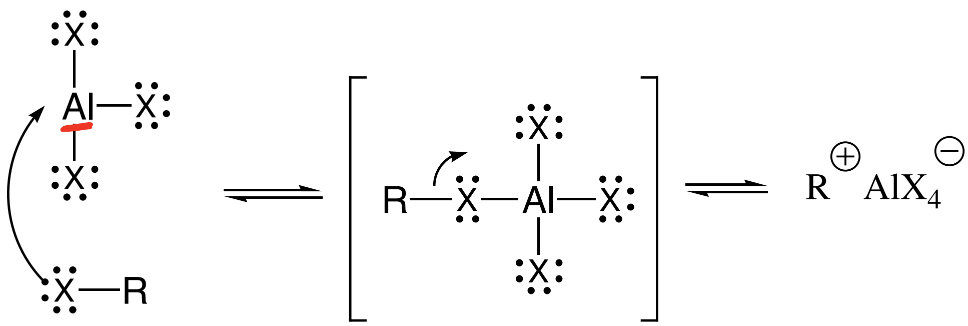
Fuming sulfuric acid contains both of the above reagents, the SO_3 is the important one

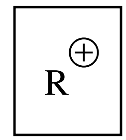
Wicked strong electrophile

Reagents

$\underline{E^{\oplus}}$

Friedal-Crafts Alkylation **R-X, AlX_3**

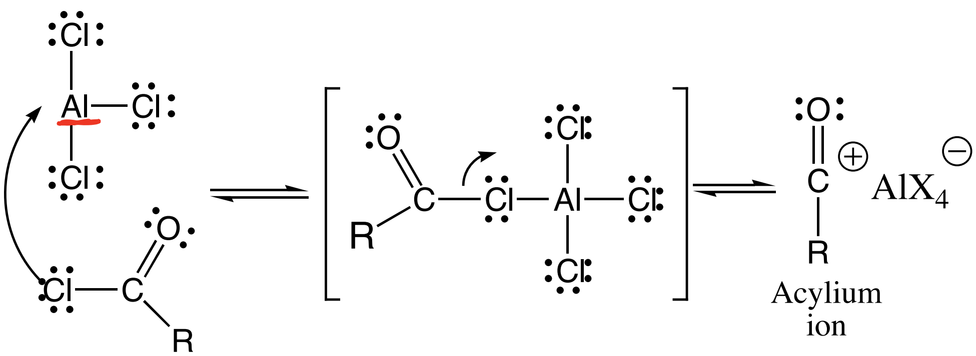




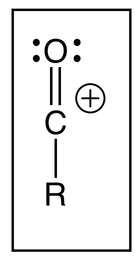
X = Br, Cl

Note this is a carbocation, so it will rearrange if it is a primary or a rearrangment-prone secondary cation

Friedal-Crafts Acylation **RCOCl, $AlCl_3$**



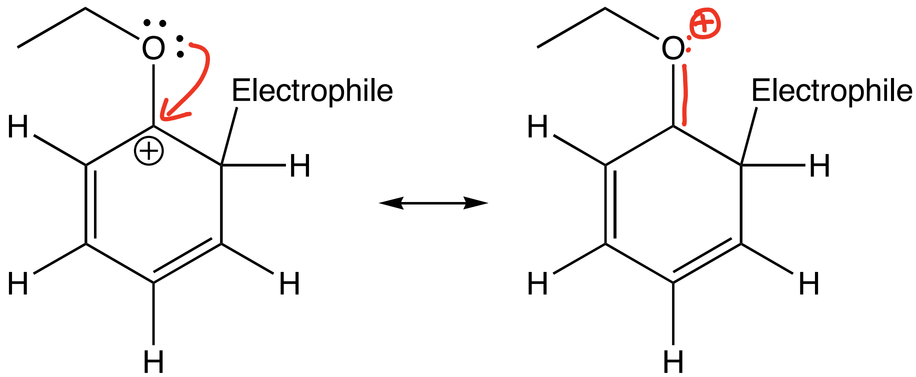
Acylium ion



Other notes: 1) It is hard to stop the Friedel-Crafts alkylation after one alkyl group adds (because alkyl groups are "good", that is, activating), but it can be done. 2) Neither Friedel-Crafts reaction works if there is already an electron withdrawing (bad) group on the ring.

Arenium ion ***stabilizing*** interactions ← GOOD

A) **Pi donation**, a resonance effect for atoms with lone pairs attached to the ring

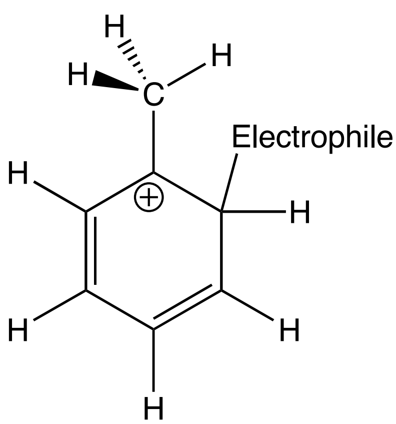


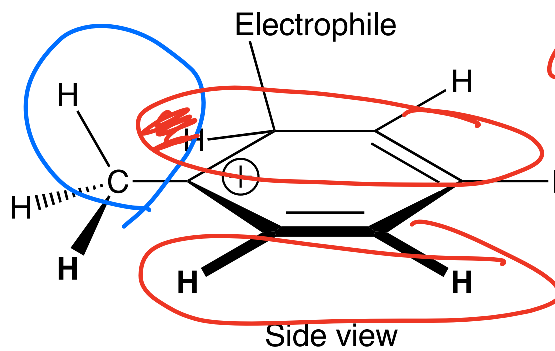
"pi-pi"

The "Greek interactions"

"sigma-pi"

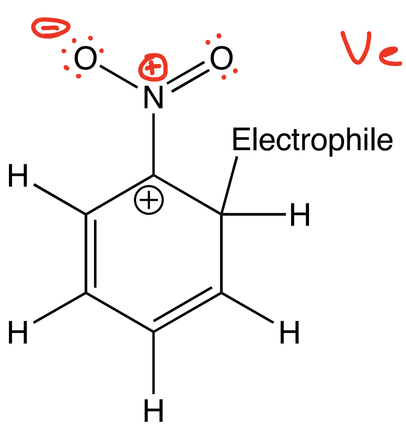
B) **Hyperconjugation** for alkyl groups attached to the ring



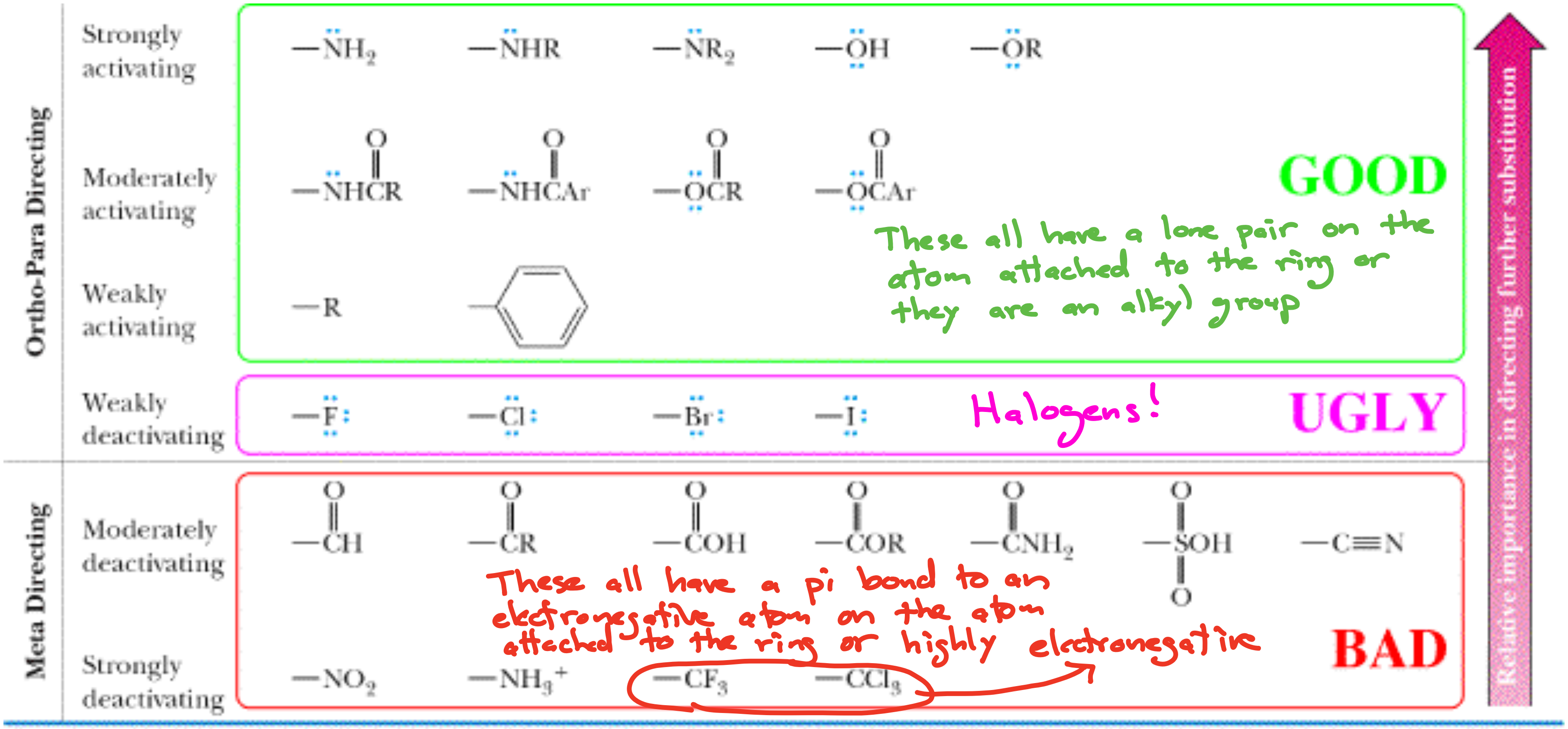


Arenium ion ***destabilizing*** interaction ← BAD

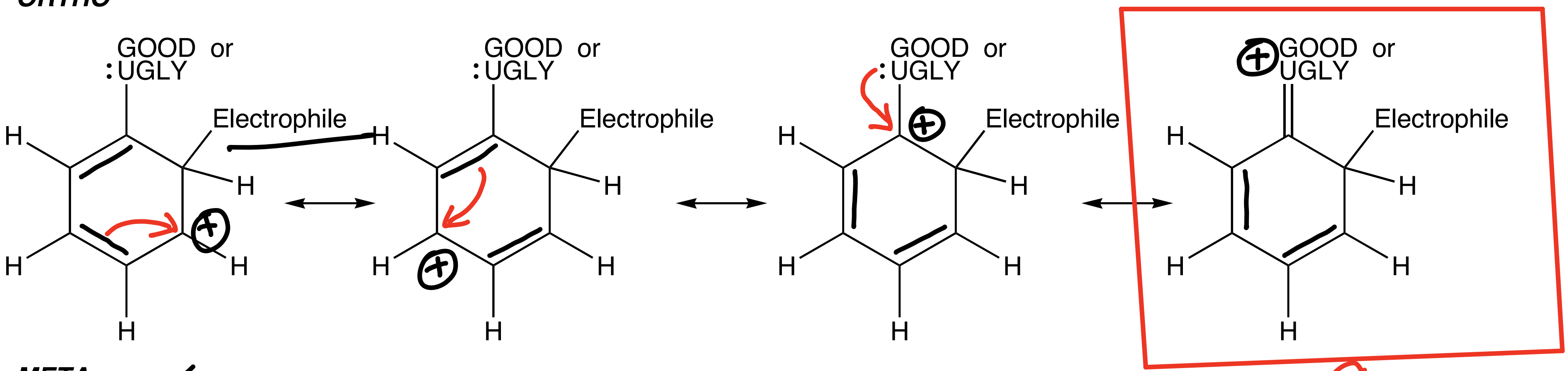
A) **Inductive effect** of electronegative atoms or groups attached to the ring



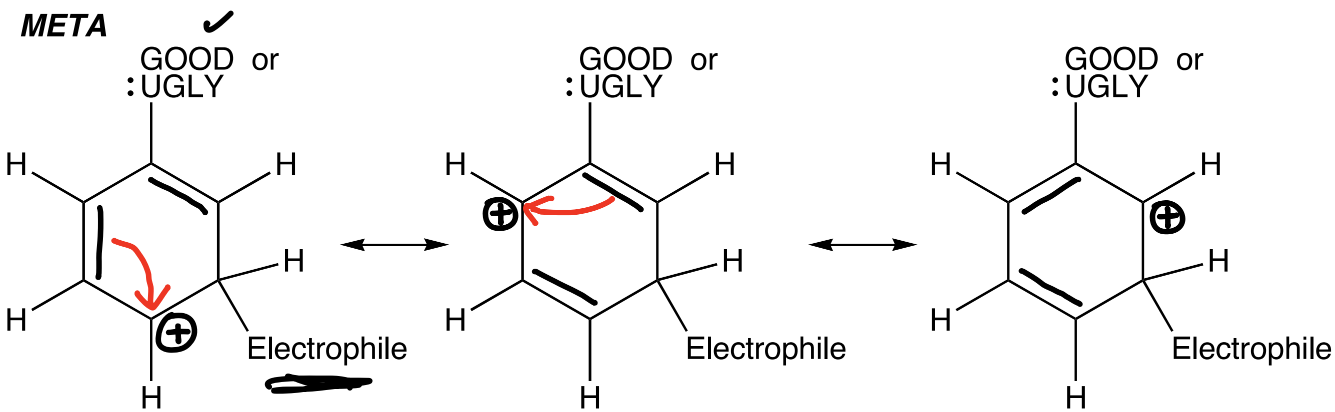
Very electron withdrawing


Ortho-Para Directing
Meta Directing
Strongly activating
—NH2 —NHR —NR2 —OH —OR
Moderately activating
—NHCR —NHCAr —OCR —OCAr
Weakly activating
—R
GOOD
These all have a lone pair on the atom attached to the ring or they are an alkyl group
Weakly deactivating
—F: —Cl: —Br: —I:
Halogens!
UGLY
Moderately deactivating
—CH —CR —COH —COR —CNH2 —SOH —C≡N
Strongly deactivating
—NO2 —NH3+ —CF3 —CCl3
These all have a pi bond to an electronegative atom on the atom attached to the ring or highly electronegative
BAD
Relative importance in directing further substitution

ORTHO

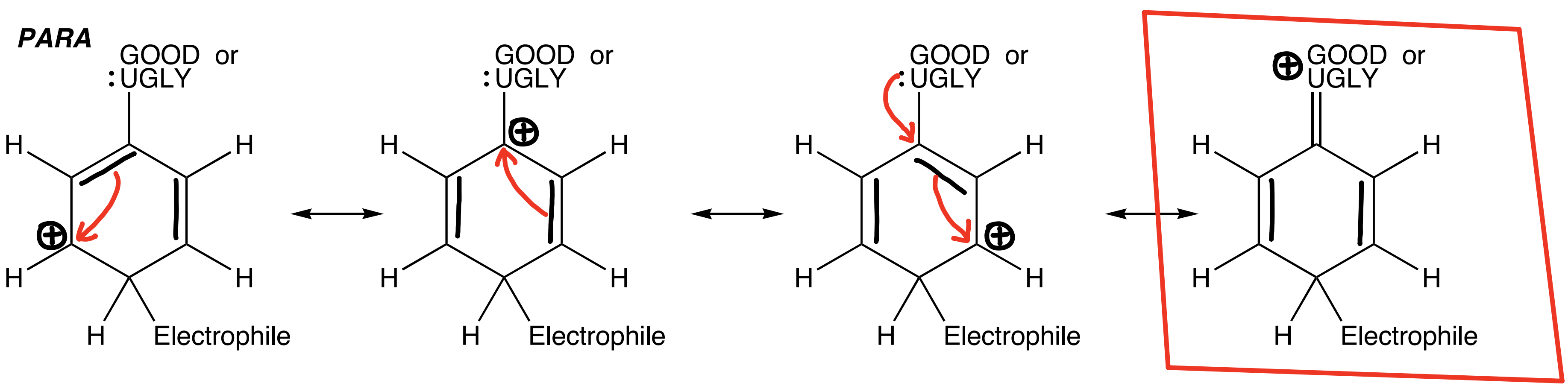


META

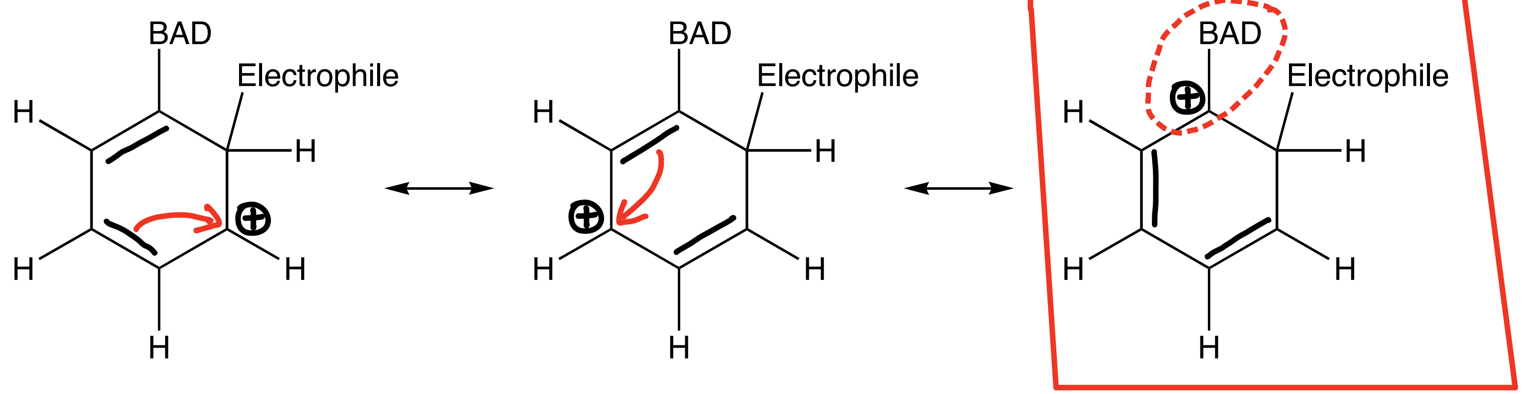


These two explain why ortho, para are preferred

PARA

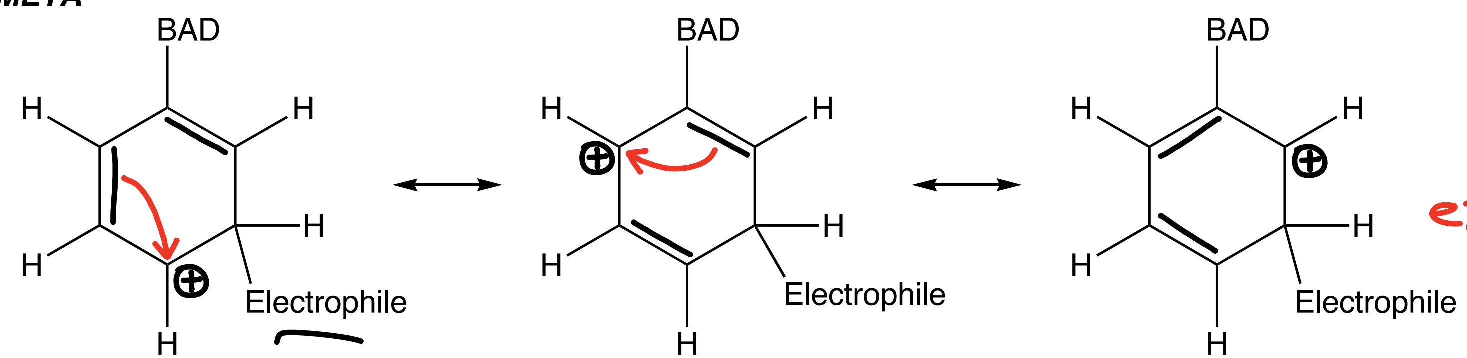


ORTHO



Very destabilizing explaining why for BAD groups

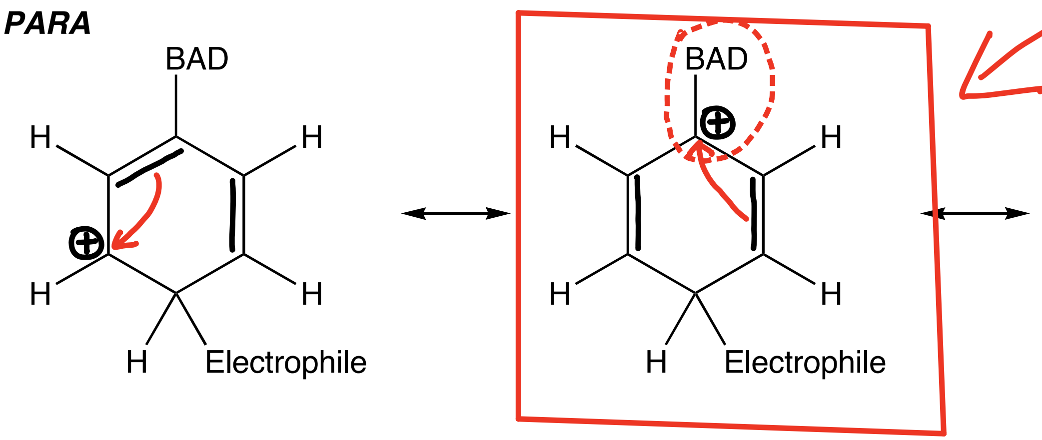
META

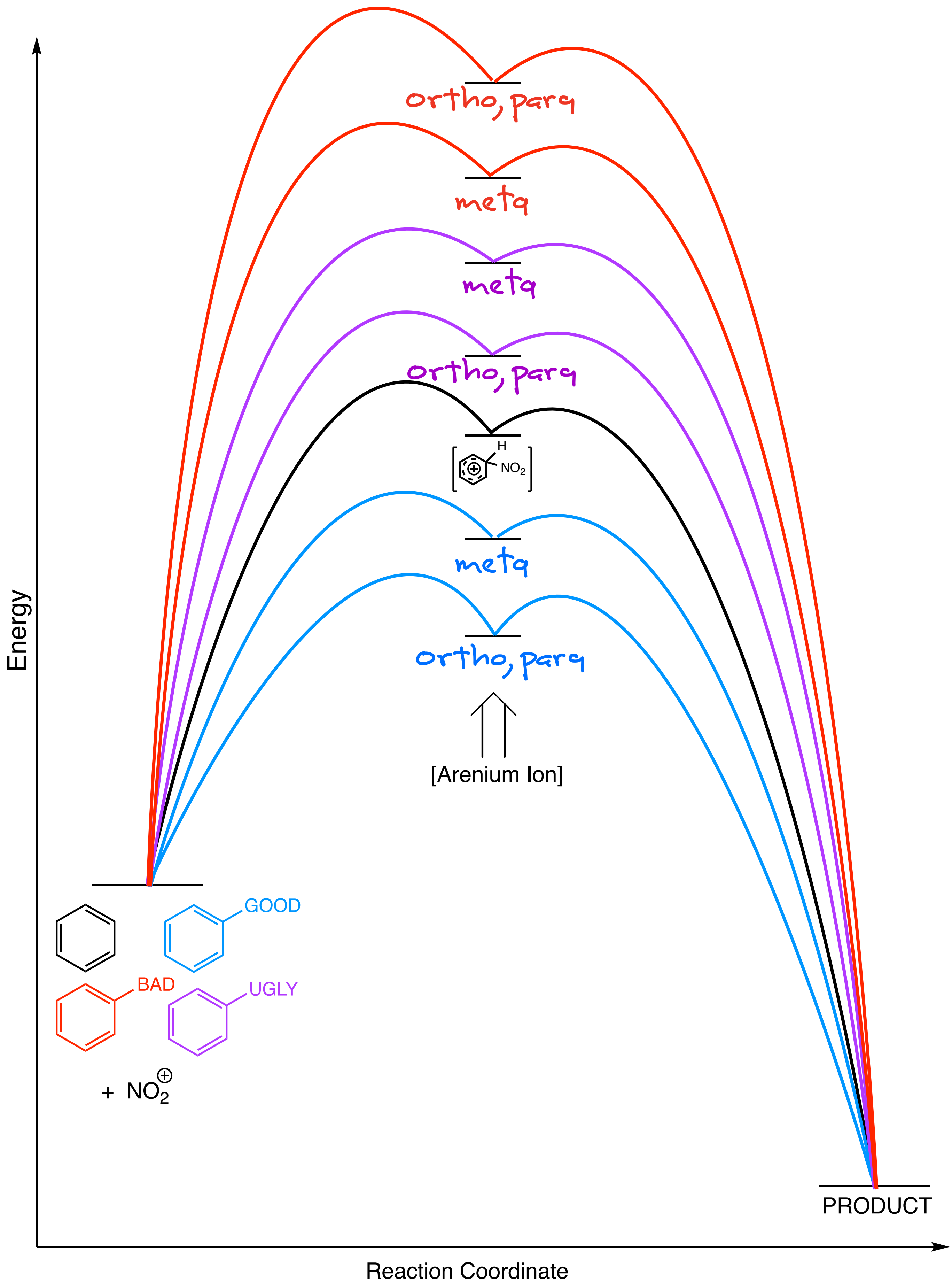


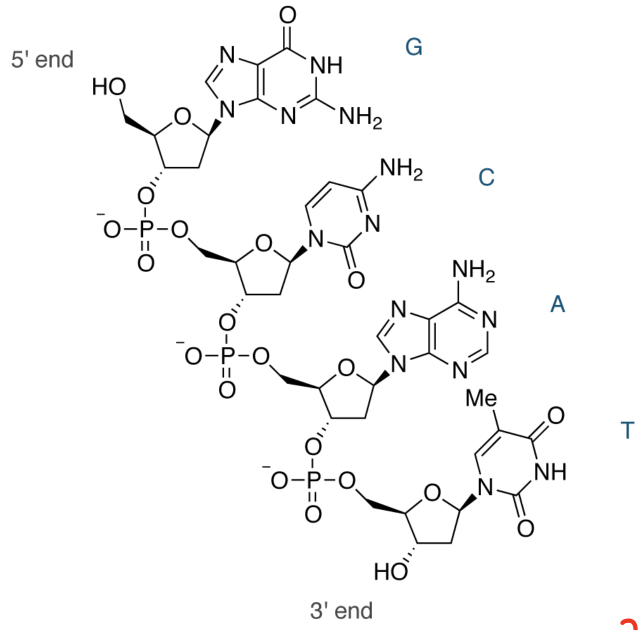
"meta is betta"

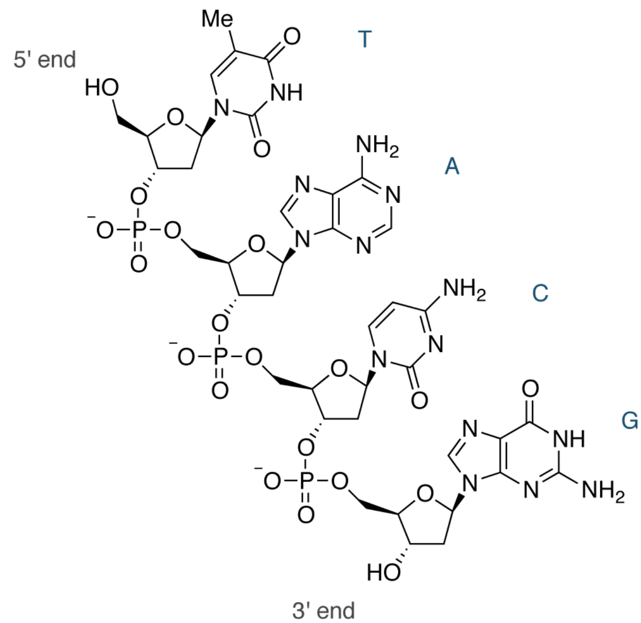
No terrible interaction meta like there is ortho, para

PARA

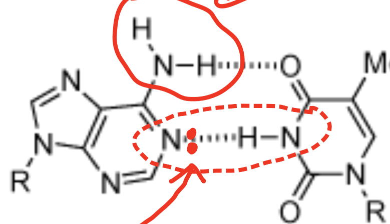



ortho, para
meta
meta
ortho, para
H
NO_2
meta
ortho, para
[Arenium Ion]
Energy
GOOD
BAD
UGLY
+ $NO_2^{\oplus}$
PRODUCT
Reaction Coordinate





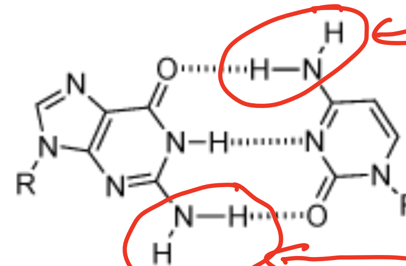
N is sp^2 so this is flat!



A·T base pair

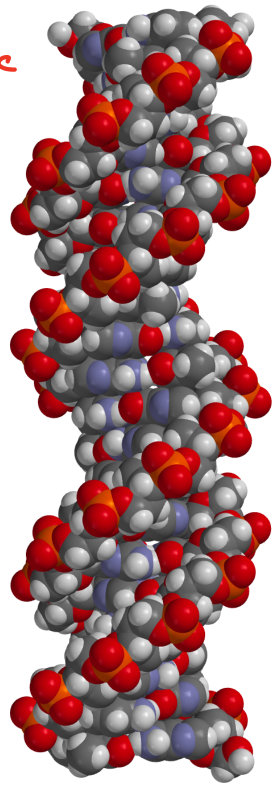
Lone pair is in an sp^2 orbital and available to make a strong hydrogen bond

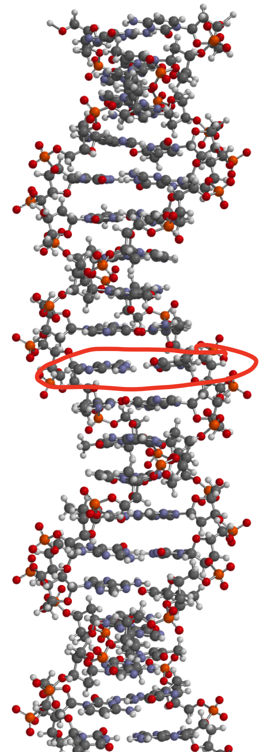
N is sp^2 so this is flat!



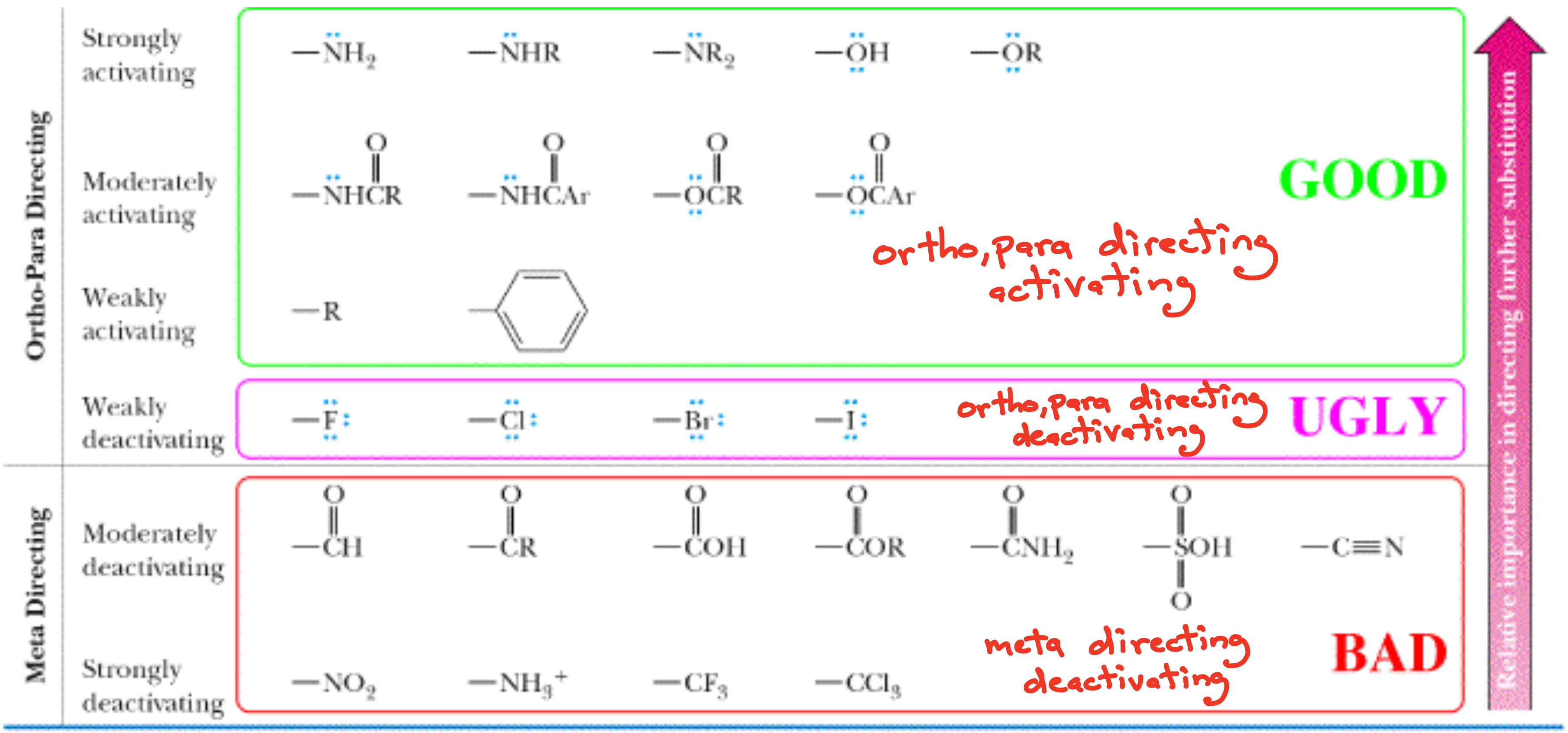
G·C base pair

N is sp^2 so this is flat!

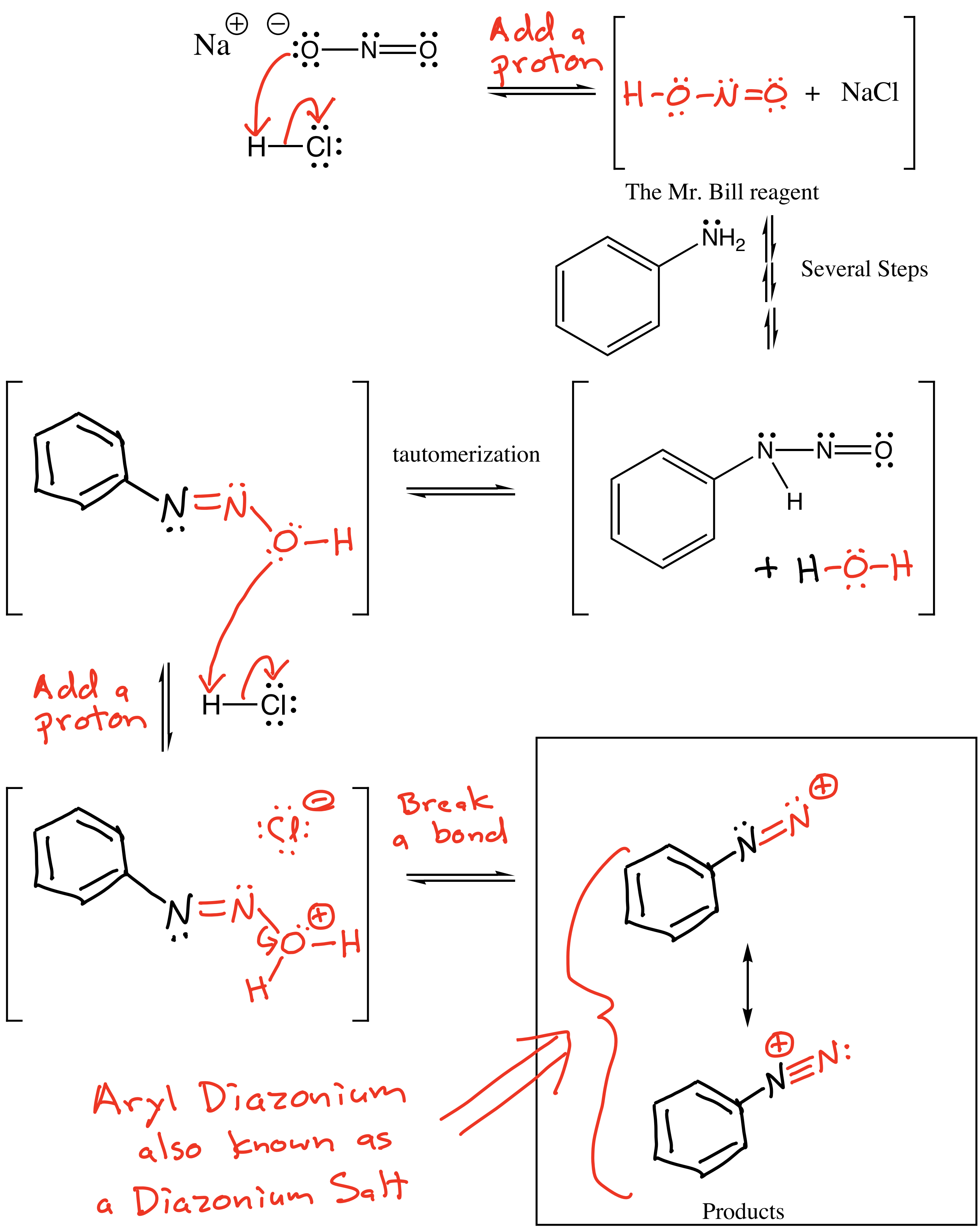




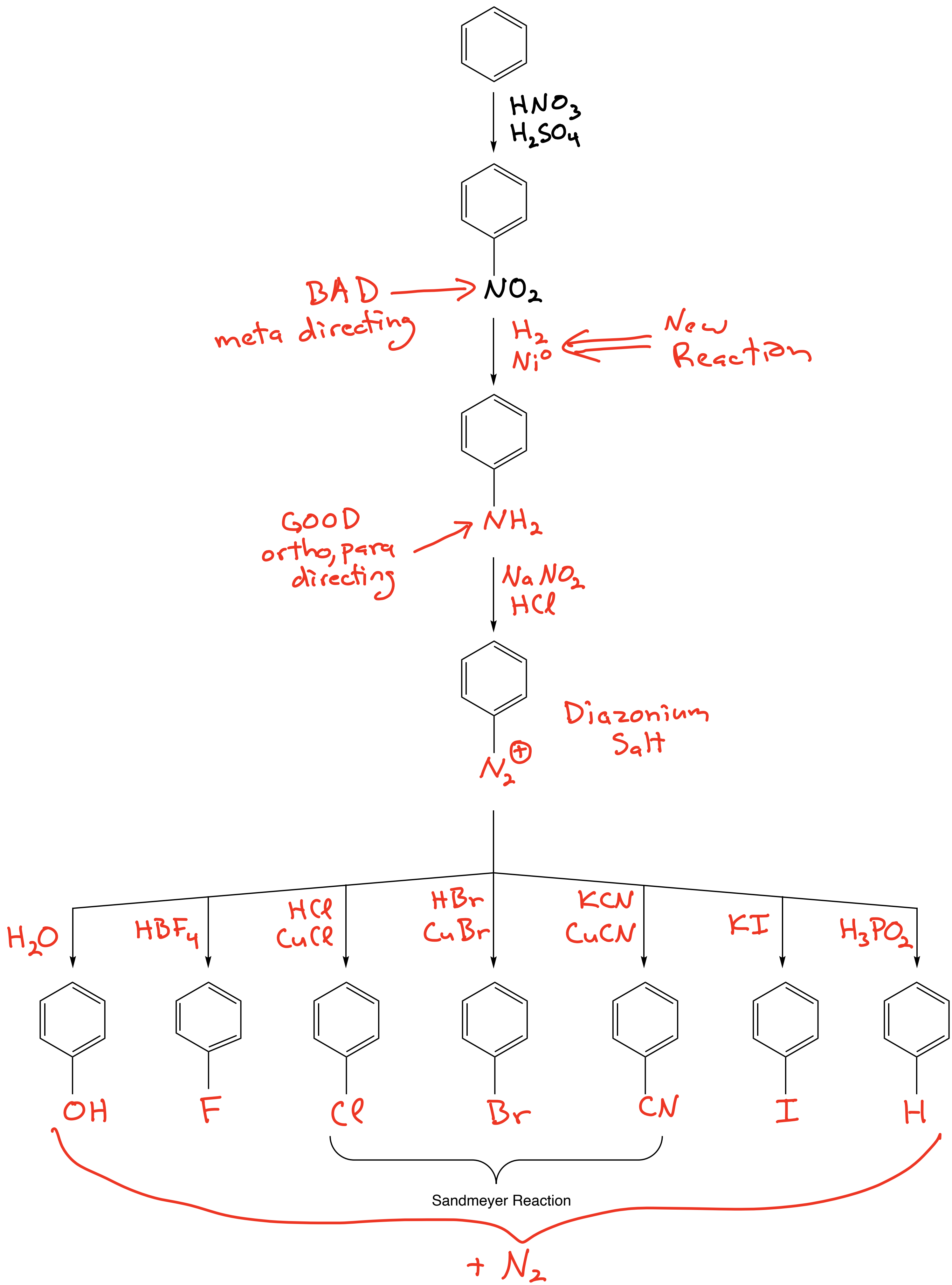
base pairs are flat because N atoms are sp^2


Ortho-Para Directing
Strongly activating
—NH2 —NHR —NR2 —OH —OR
Moderately activating
—NHCR —NHCAr —OCR —OCAr
GOOD
ortho,para directing activating
Weakly activating
—R
Weakly deactivating
—F: —Cl: —Br: —I:
ortho,para directing deactivating
UGLY
Meta Directing
Moderately deactivating
—CH —CR —COH —COR —CNH2 —SOH —C≡N
Strongly deactivating
—NO2 —NH3+ —CF3 —CCl3
meta directing deactivating
BAD
Relative importance in directing further substitution

Preparation of Diazoniums, The "Mr. Bill" Reaction

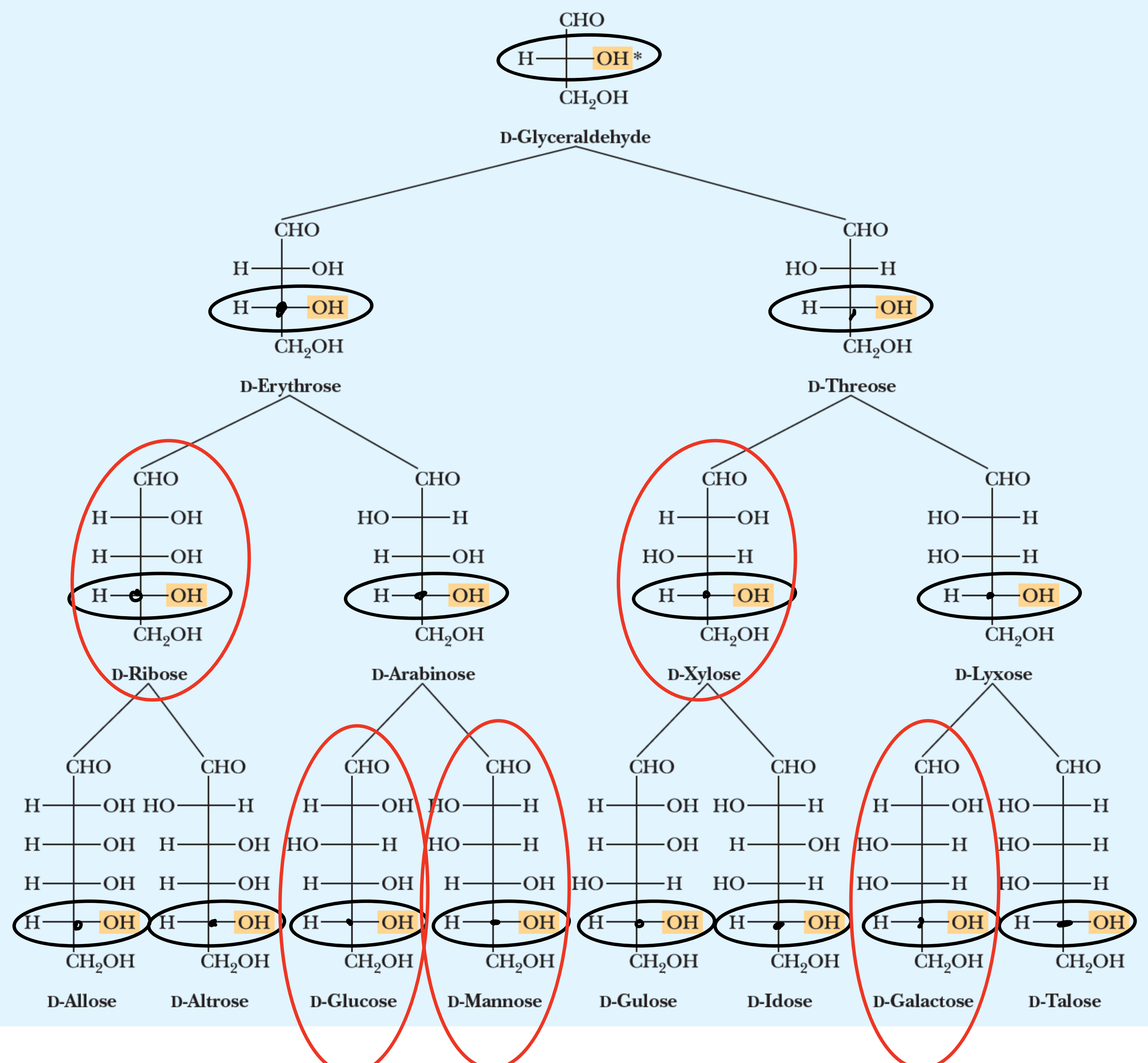


N_2 leaves and is replaced by a variety of reagents → Not responsible for mechanisms

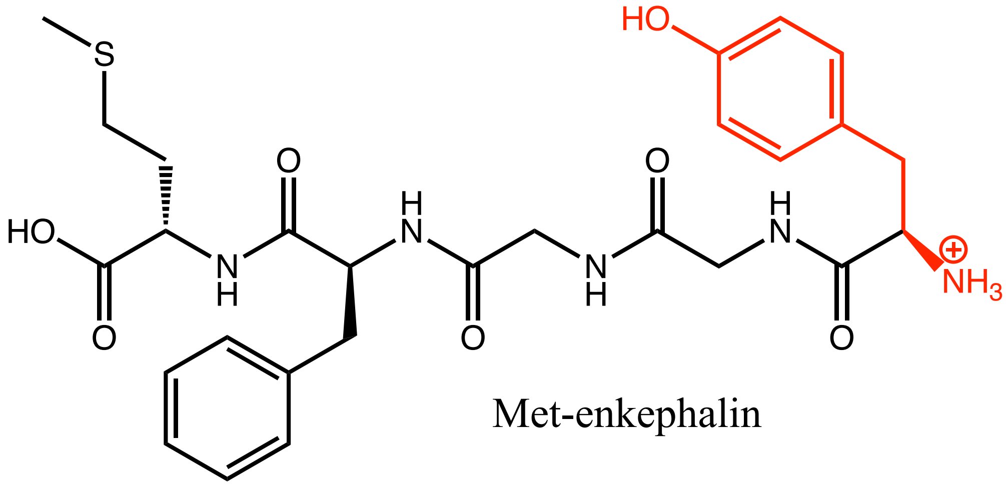


HNO3
H2SO4
BAD
meta directing
NO2
H2
Ni°
New Reaction
GOOD
ortho, para
directing
NH2
NaNO2
HCl
Diazonium
Salt
N2⊕
H2O
HBF4
HCl
CuCl
HBr
CuBr
KCN
CuCN
KI
H3PO2
OH
F
Cl
Br
CN
I
H
Sandmeyer Reaction
+ N2

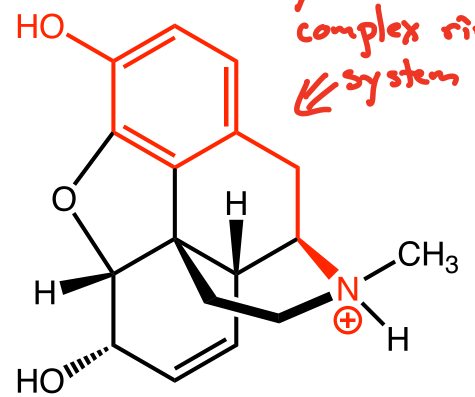
Table 25.1 **Configurational Relationships Among the Isometric D-Aldotetroses, D-Aldopentoses, and D-Aldohexoses**



The carbohydrates circled in red are the most common.



Met-enkephalin

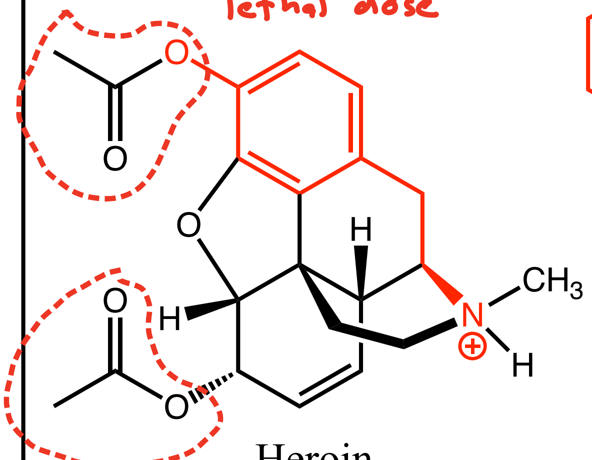


Morphine

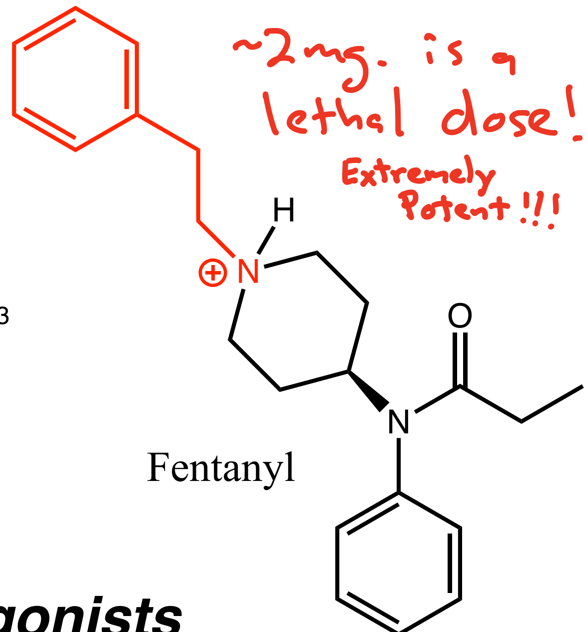
VERY difficult to synthesize this complex ring system

Isolated from poppies grown in the Middle East

>100 mg. is a lethal dose



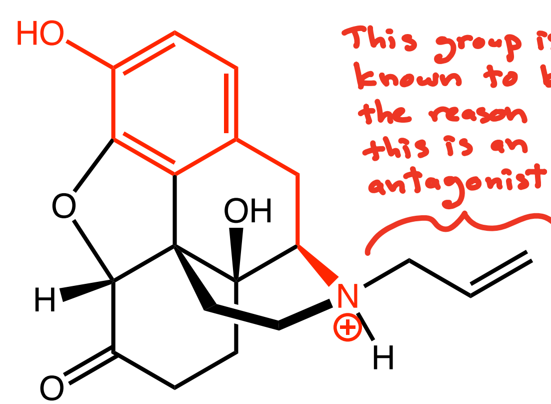
Heroin



Fentanyl

~2mg. is a lethal dose!

Extremely Potent!!!



Naloxone

This group is known to be the reason this is an antagonist

Mu-Receptor Agonists

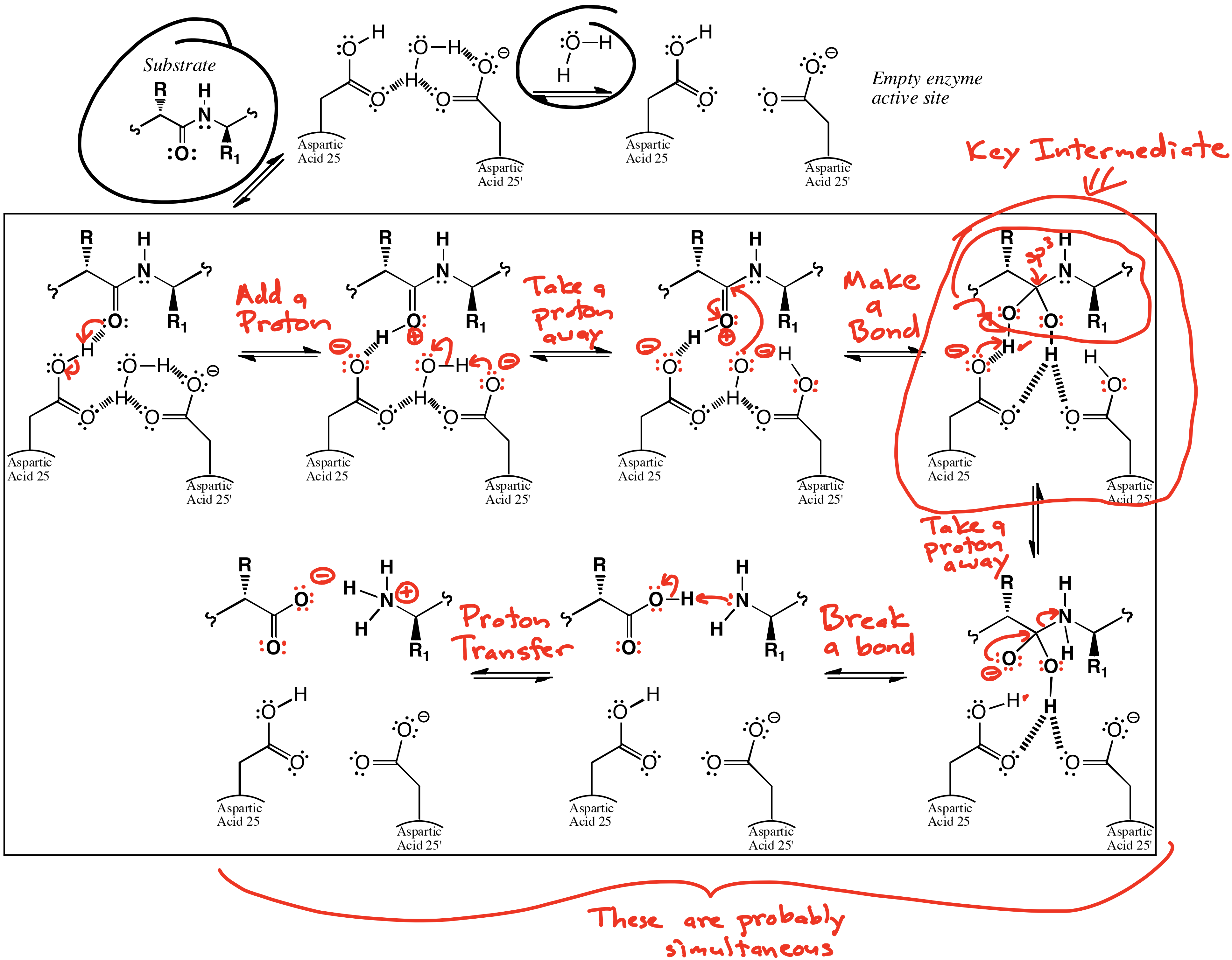
Antagonist

Means it binds to receptor and activates it

Too easy! {VERY easy to make!

Synthesized from natural morphine analog in a couple of easy steps

Means it binds to receptor but does not activate it



Substrate
Empty enzyme active site
Aspartic Acid 25
Aspartic Acid 25'
Key Intermediate
Add a Proton
Take a proton away
Make a Bond
sp3
Take a proton away
Break a bond
Proton Transfer
These are probably simultaneous

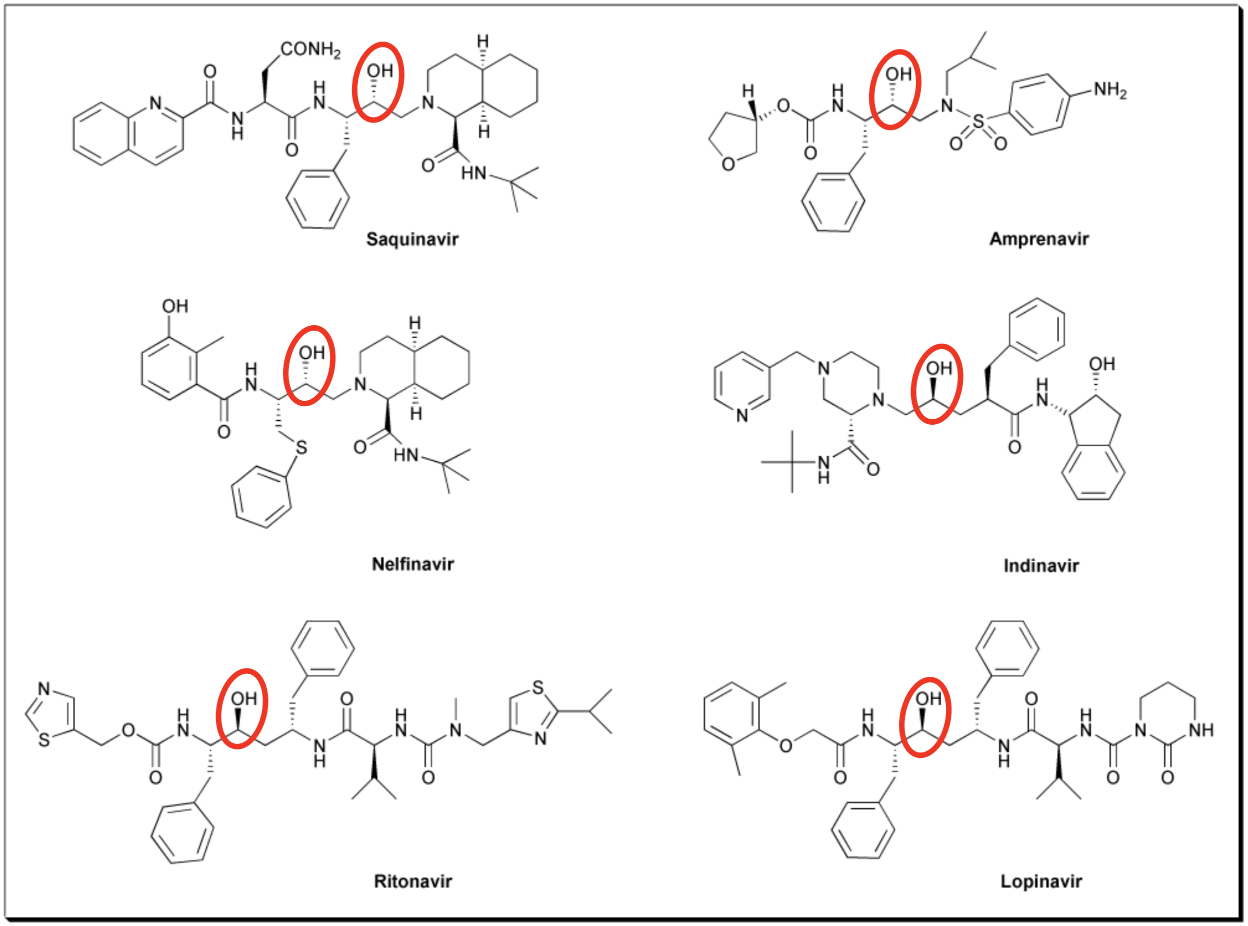
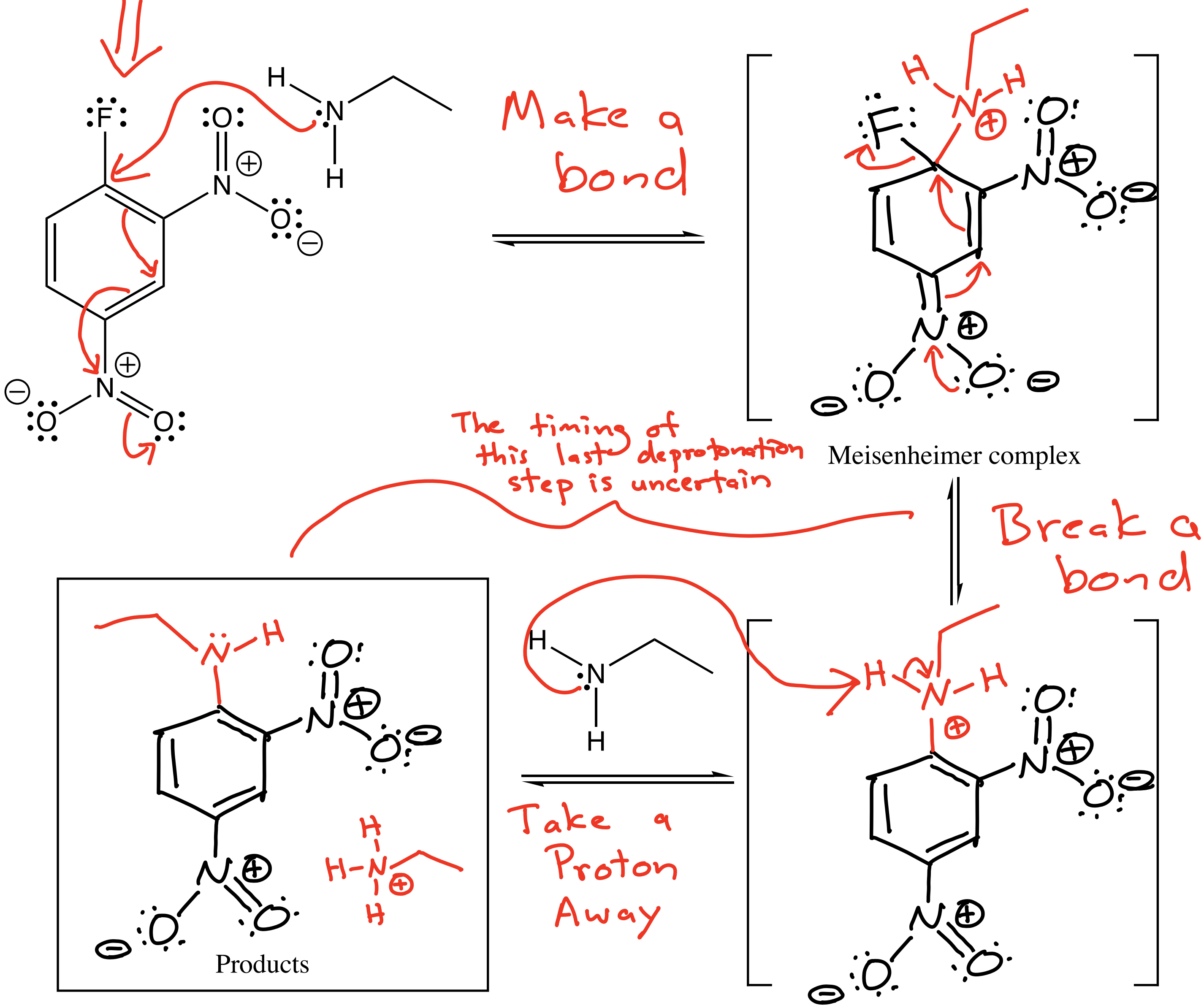


Fig. 10 FDA approved HIV-1 protease inhibitors.

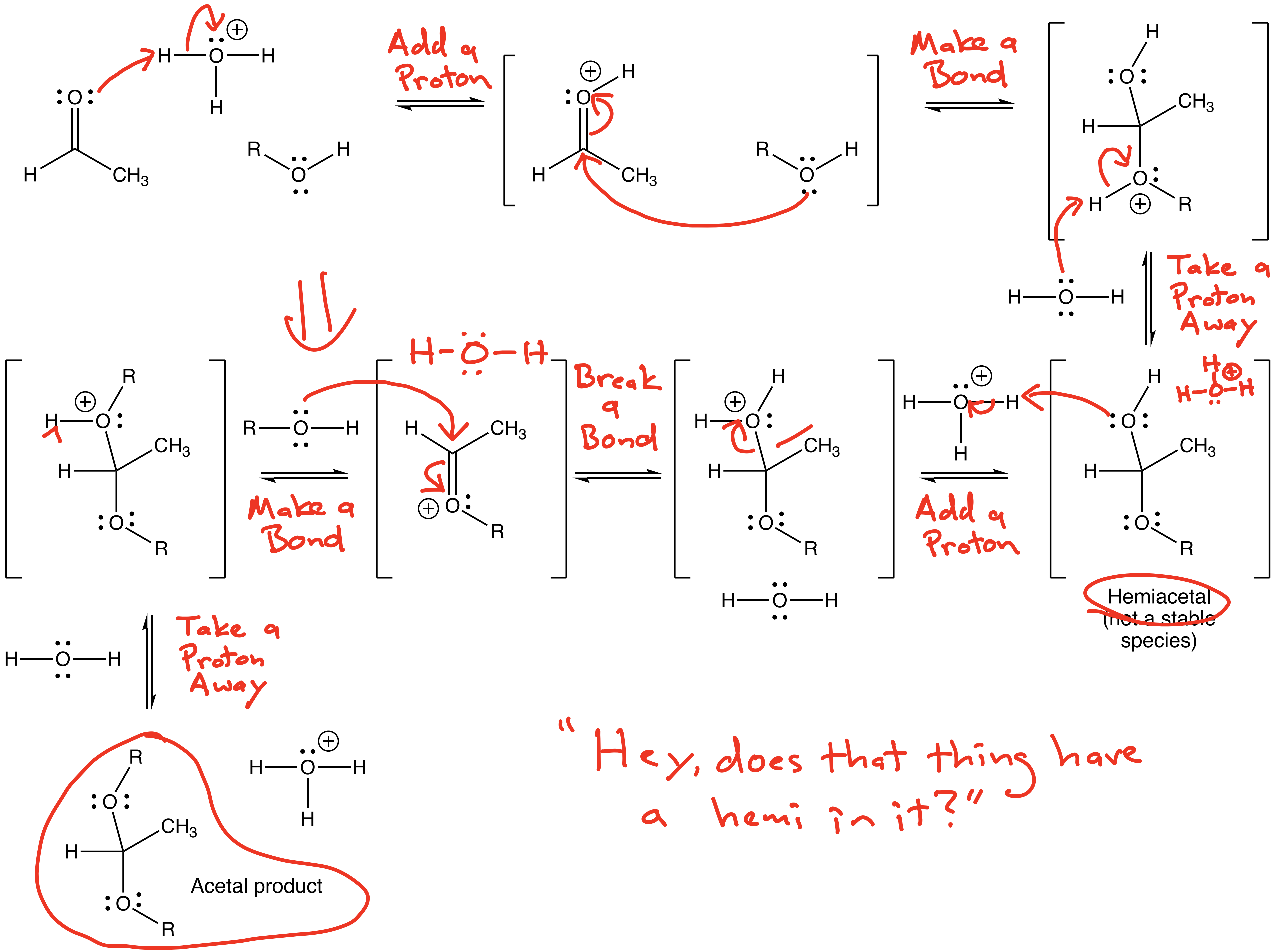
All of these resemble the key intermediate with an sp^3 C atom and an -OH group

VERY electron deficient aromatic ring because of all the electron withdrawing groups

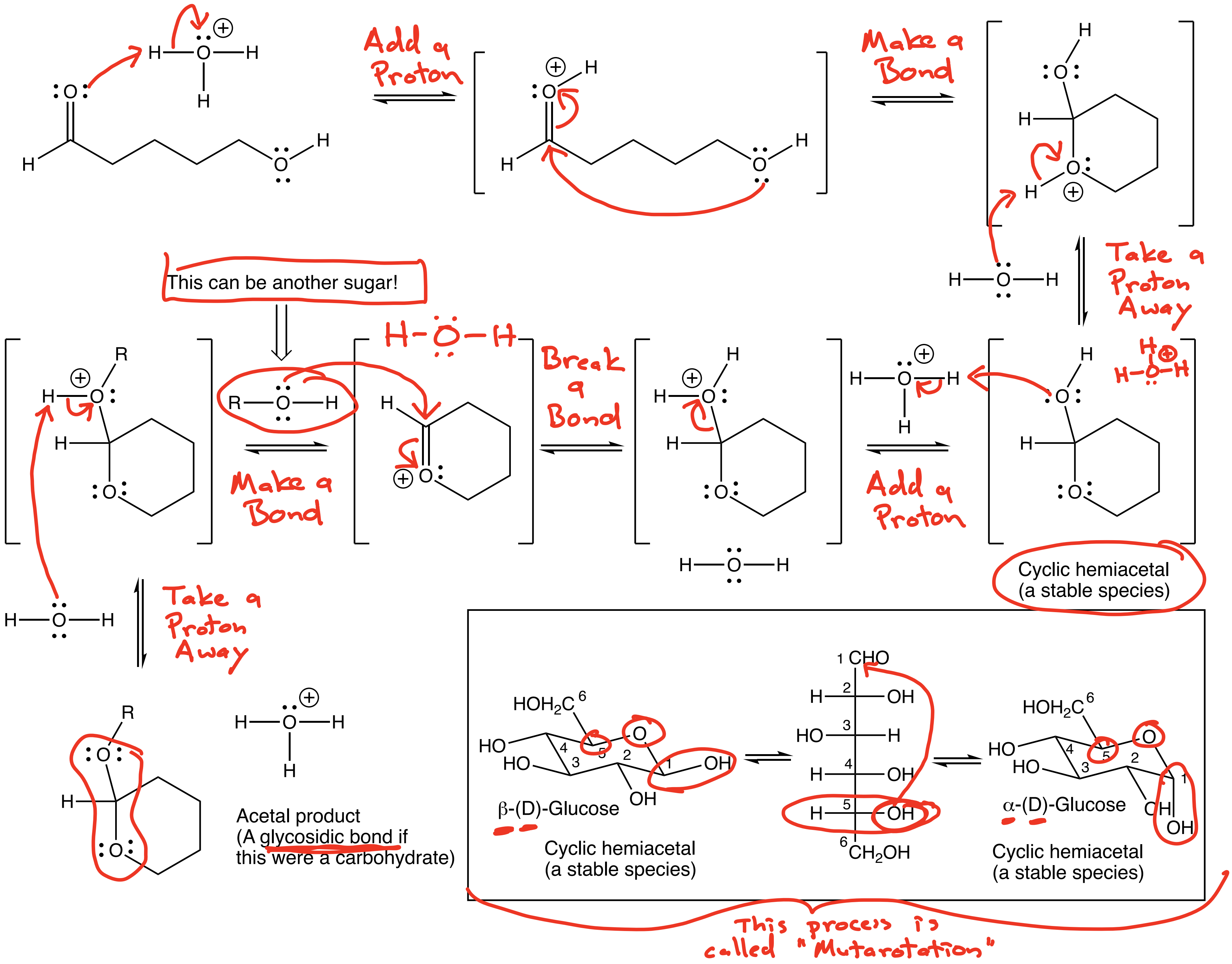
Nucleophilic Aromatic Substitution

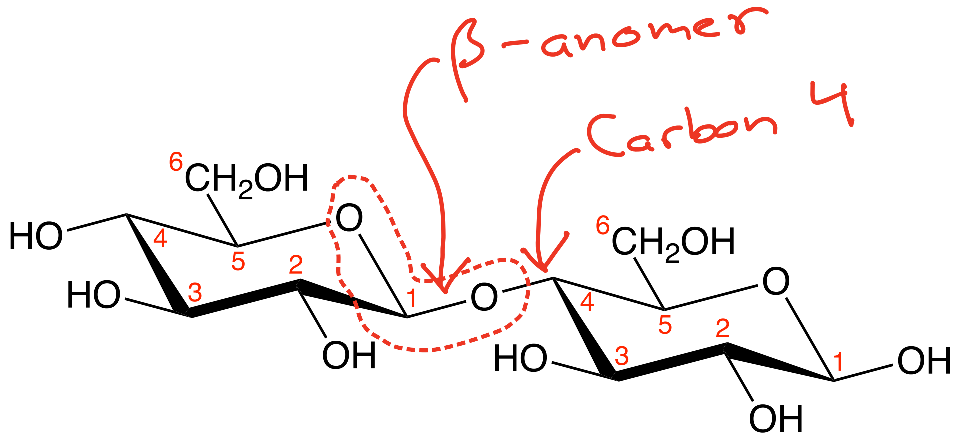


This reaction is relatively rare, and this is the only example you will see in this class

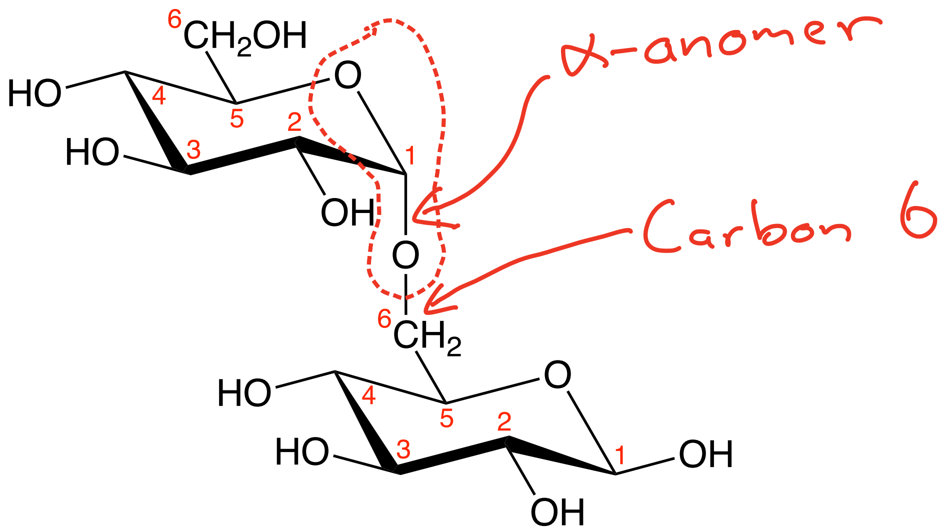


"Hey, does that thing have a hemi in it?"


Add a Proton
Make a Bond
Take a Proton Away
This can be another sugar!
Break a Bond
Add a Proton
Make a Bond
Cyclic hemiacetal
(a stable species)
Take a Proton Away
Acetal product
(A glycosidic bond if
this were a carbohydrate)
β-(D)-Glucose
Cyclic hemiacetal
(a stable species)
α-(D)-Glucose
Cyclic hemiacetal
(a stable species)
This process is called "Mutarotation"

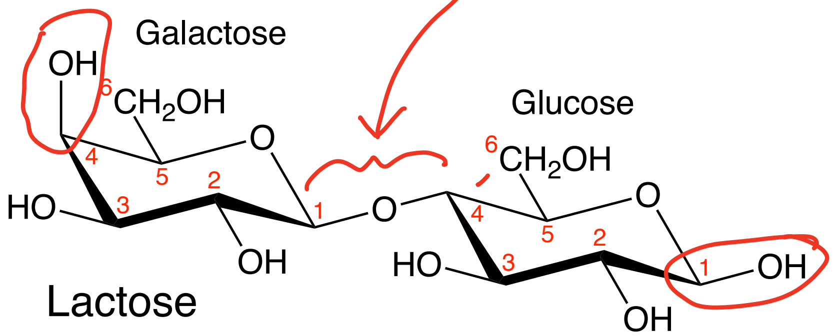


This is a β-1,4-Glycosidic Bond

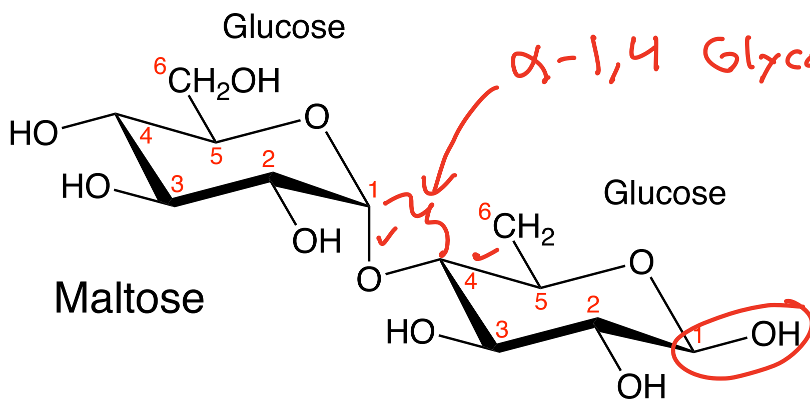


This is an α-1,6-Glycosidic Bond

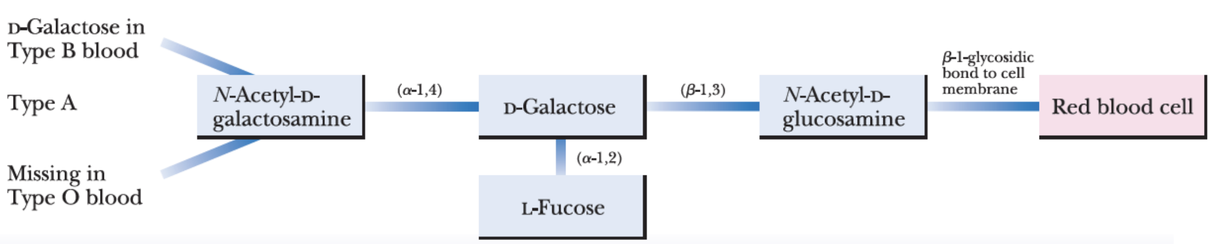
β-1,4 Glycosidic bond

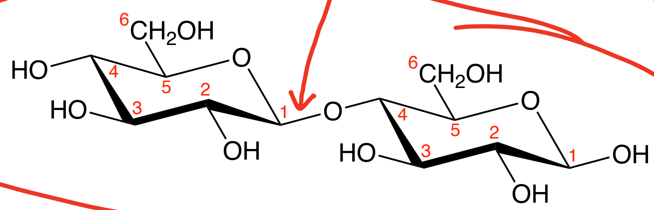


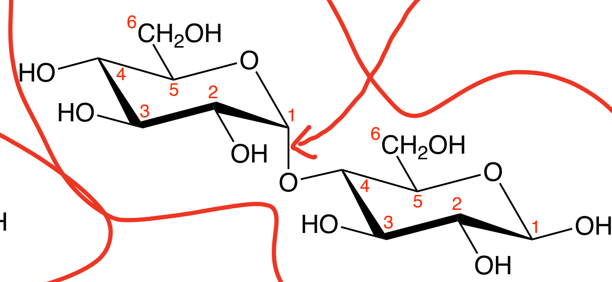
α-1,4 Glycosidic bond

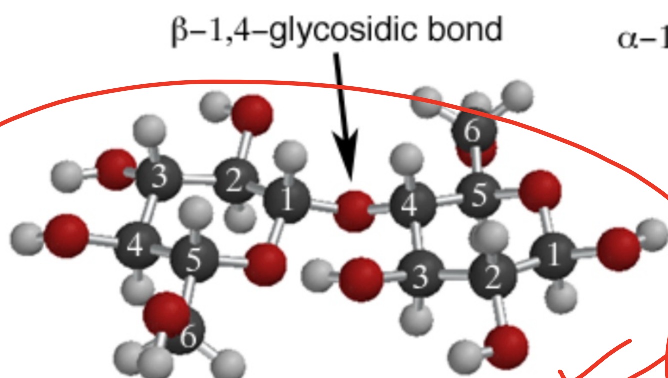


We can link more carbohydrates together, always at Carbon 1, with α or β linkages at carbons 2, 3, 4 or 6

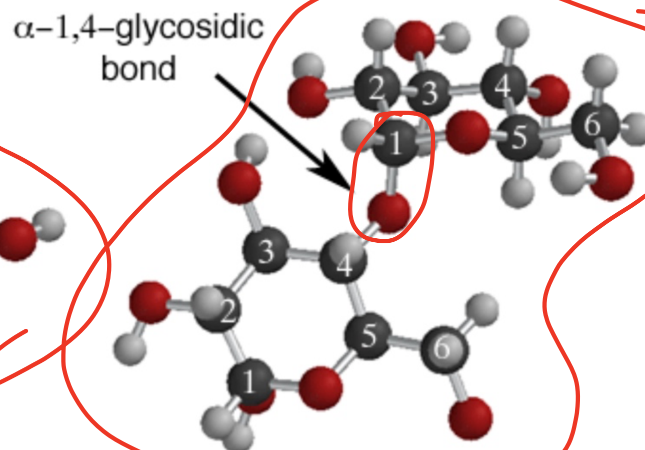






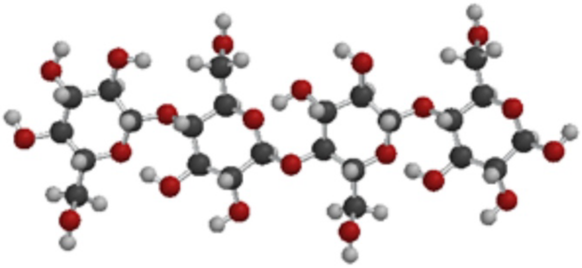


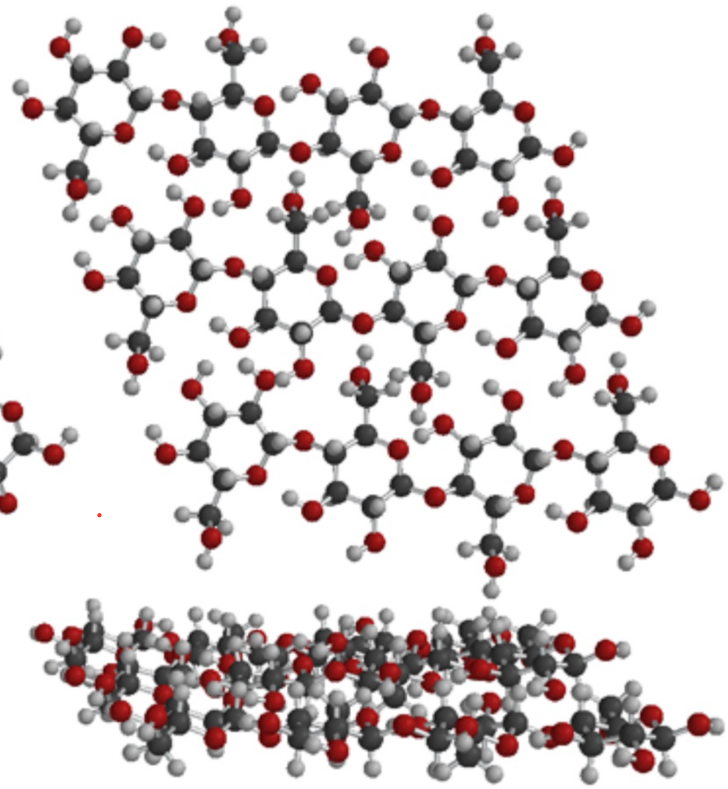
β-1,4-D-glucose



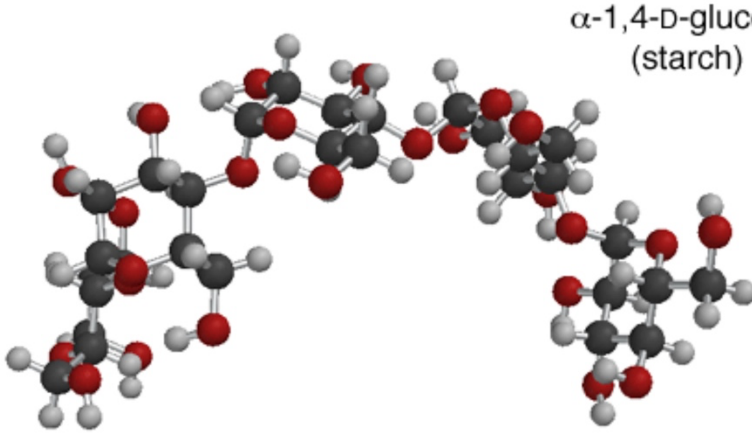
α-1,4-D-glucose

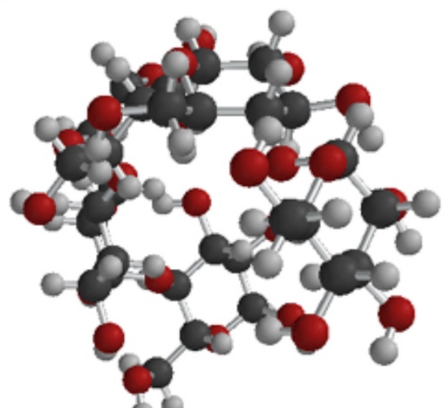
β-1,4-D-glucose
(cellulose)



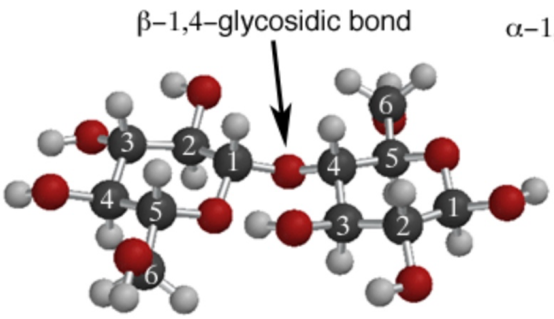


α-1,4-D-glucose
(starch)

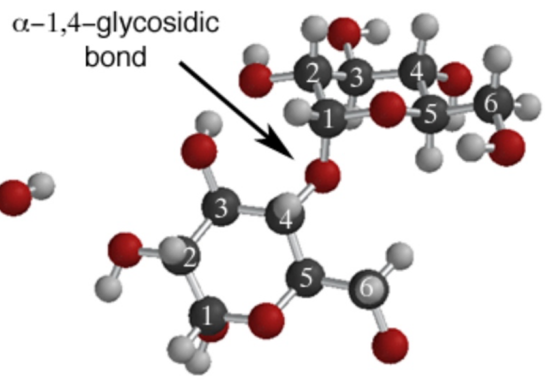




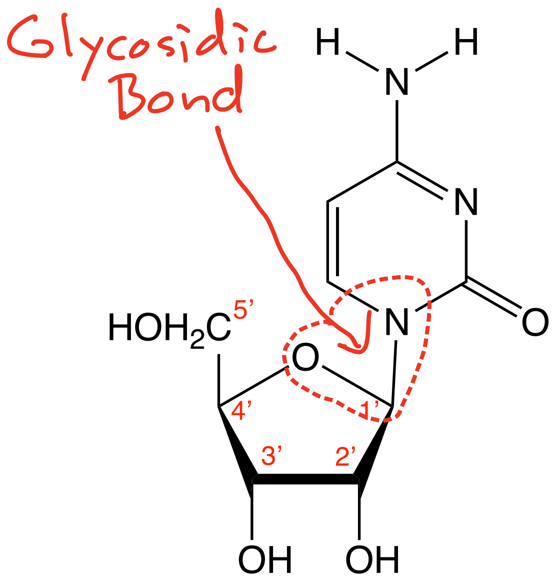
VS.



β-1,4-D-glucose



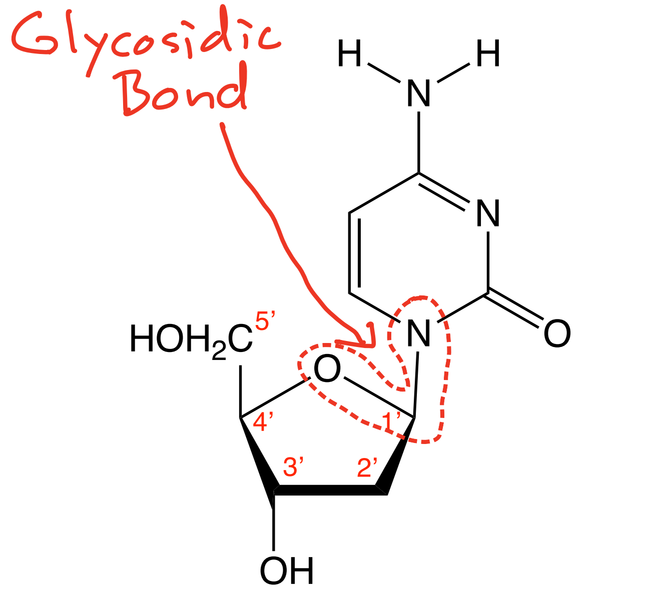
α-1,4-D-glucose



D-Ribose

⇓

RNA



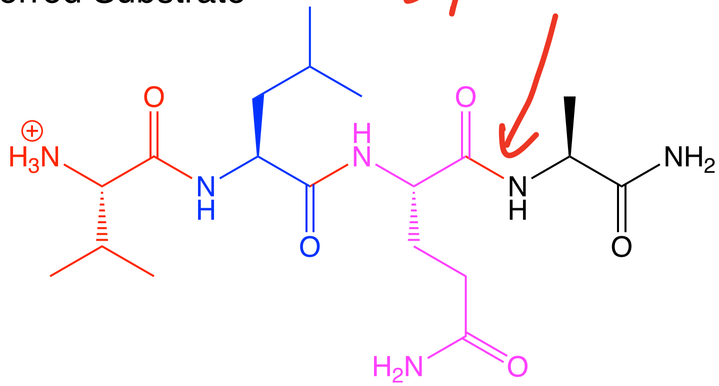
D-2'-Deoxyribose

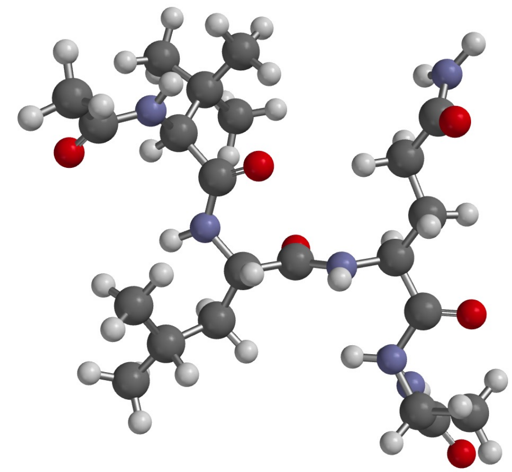
⇓

DNA

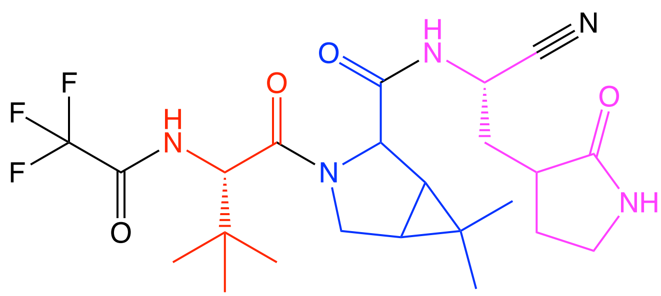
This bond is cleaved by the enzyme

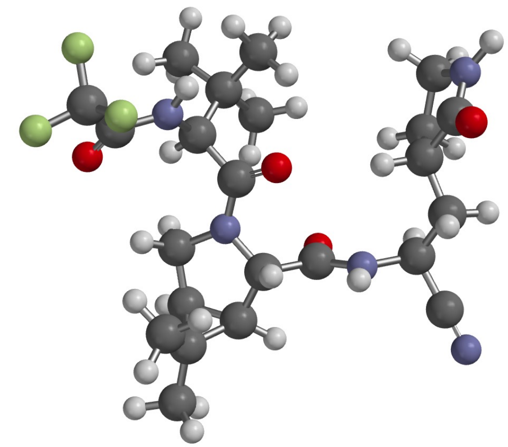
Preferred Substrate



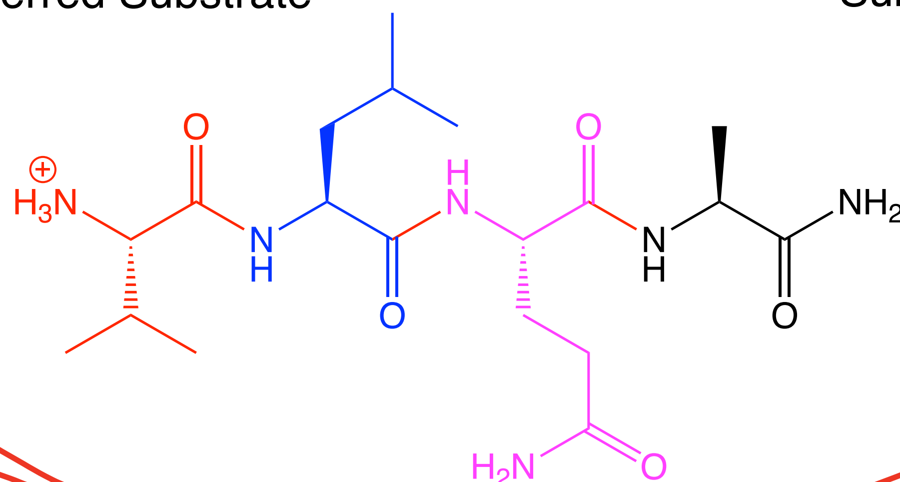


Paxlovid

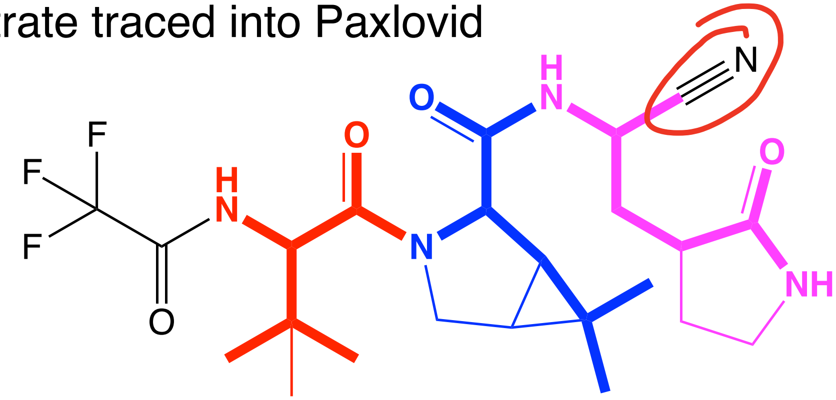




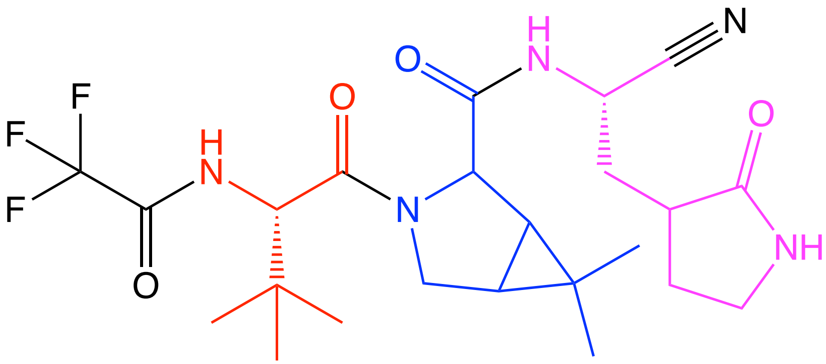
Preferred Substrate

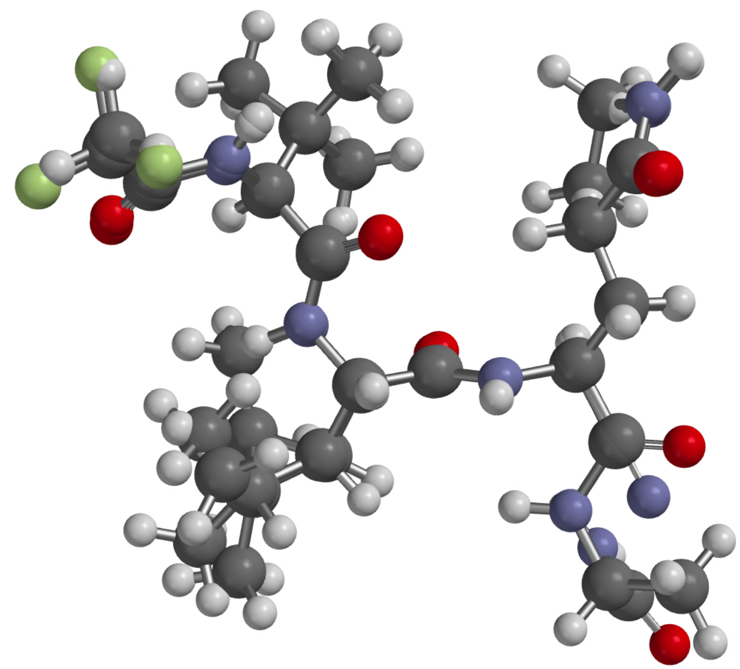


Substrate traced into Paxlovid



Paxlovid





<u>Organic Chemistry</u> is the study of carbon-containing molecules. This class has two points.

The first point of the class is to understand the organic chemistry of living systems. We will teach you how to think about and understand the most amazing molecules on the planet!!

You will learn how MRI scans work. 1/12/23

You will learn the basic principles of pharmaceutical science and how many drugs work. 1/19/23

You will learn about the special bond that holds carbohydrates such as glucose in six-membered rings, connects carbohydrate monomers together to make complex carbohydrate structures and is critical to DNA and RNA structure. 1/26/23

You will learn how soap is made from animal fat and how it works to keep us clean. 2/16/23

You will learn the important structural reason proteins, the most important molecular machines in our bodies, can support the chemistry of life. 2/14/23

You will learn how important antibiotics like penicillins work, including ones that make stable covalent bonds as part of their mode of action. 3/7/23

You will learn why carrots are orange and tomatoes are red. 3/28/23

You will learn the very cool reason that the DNA and RNA bases are entirely flat so they can stack in the double helix structure. 4/13/23

You will learn even more about why fentanyl is such a devastating part of the opioid problem and how Naloxone is an antidote for a fentanyl overdose. 4/18/23

You will learn even more details about why Magic Johnson is still alive, decades after contracting HIV, and how the same strategy is being used to fight COVID. 4/18/23

You will learn about the surprising chemical reason the Pfizer and Moderna mRNA vaccines elicit strong immune responses. 4/20/23

The second point of organic chemistry is the synthesis of complex molecules from simpler ones by making and breaking specific bonds, especially carbon-carbon bonds.

You will learn how carbon-metal bonds lead to new carbon-carbon bonds. 1/17/23

You will learn how most reactions of carbonyl compounds involve only the four common mechanistic elements operating in only a few common patterns. 1/17/23

You will learn how, by simply adding a catalytic amount of base like HO^- to aldehydes or ketones, you can make new carbon-carbon bonds, giving complicated and useful products. 2/28/23

You will learn a reaction that can convert vinegar and vodka into a common solvent. 2/16/23

You will learn why molecules with six-membered rings and alternating double bonds are stable. 3/30/23

You will learn a reaction that can turn model airplane glue into a powerful explosive. 4/18/23

Most important, you will develop powerful critical thinking skills:

1. You will learn how to look at a molecule and accurately predict which atoms will react to make new bonds, and which bonds will break during reactions.
2. You will learn how to analyze a complex molecule's structure so that you can predict ways to make it via multiple reactions starting with less complex starting molecules.