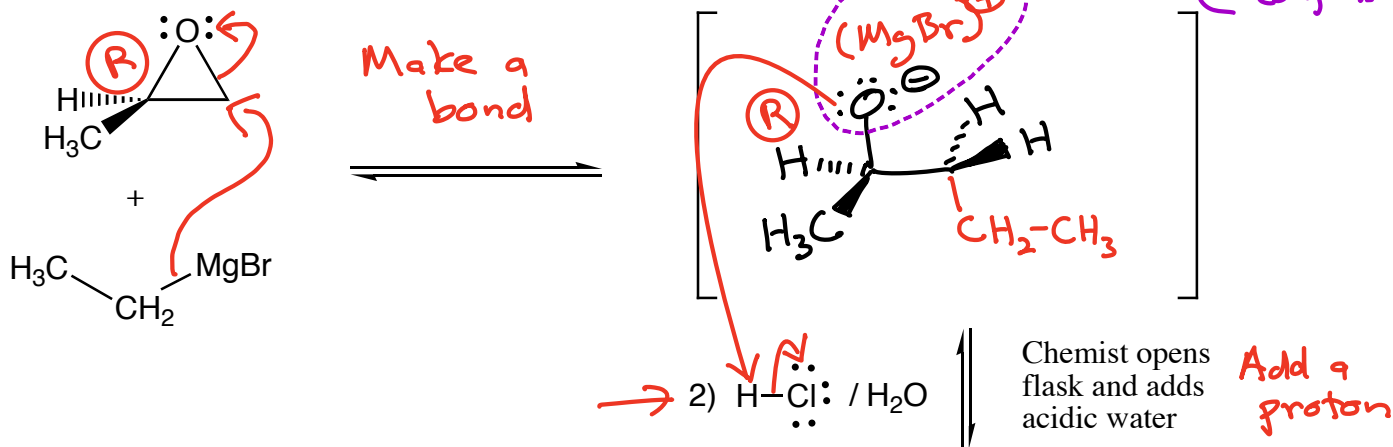


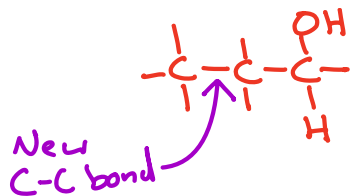
Organolithium and Gilman reagents react the same way as Grignard reagents in this reaction.

Grignard Reagent Reacting with an Epoxide

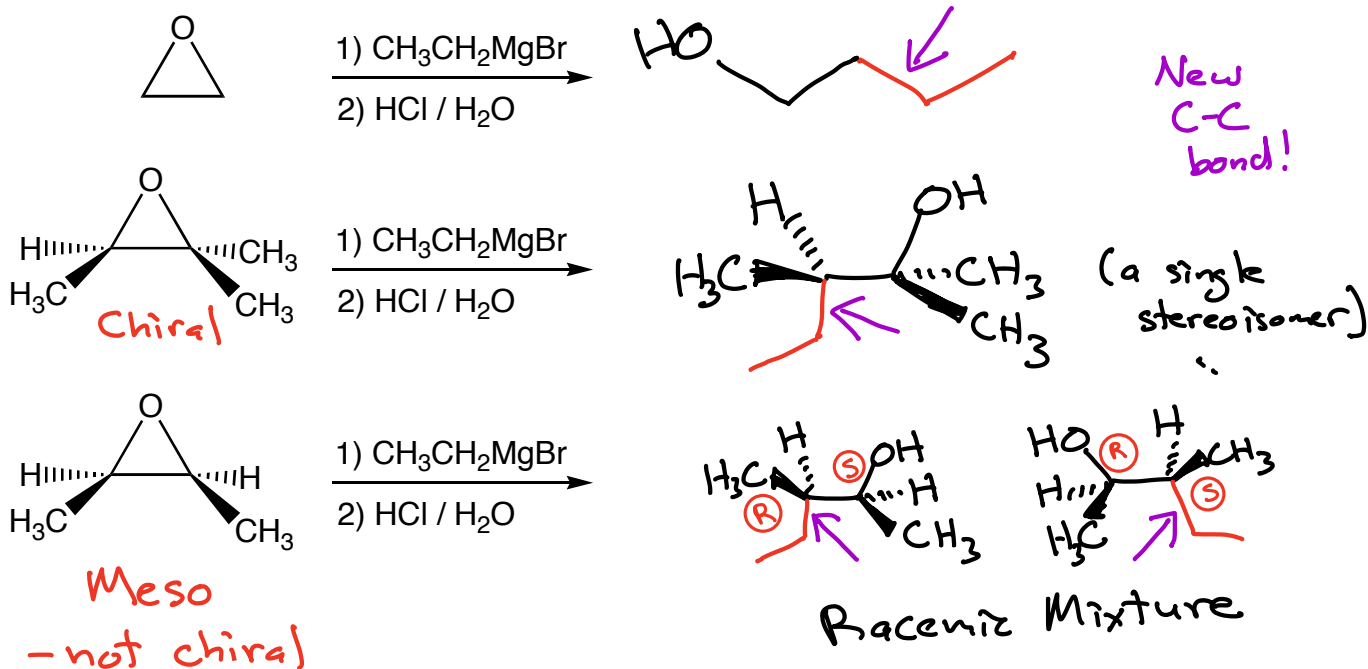
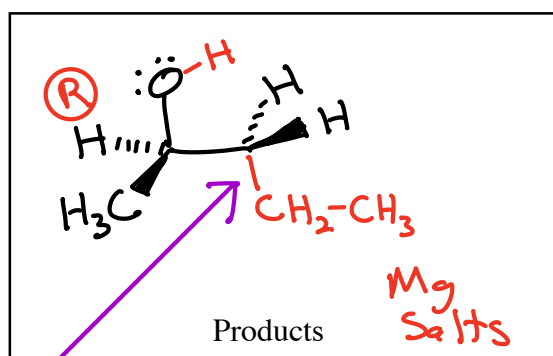


Key Recognition Element (KRE):

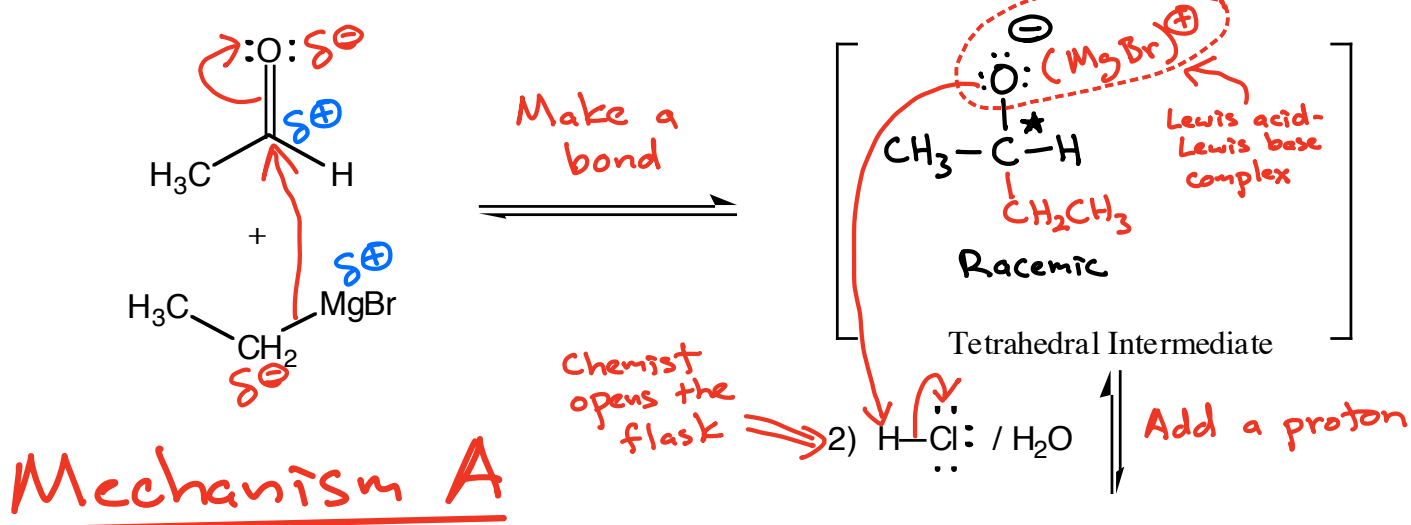
There is a new C-C bond that is two carbon atoms away from an OH group



New C-C bond!

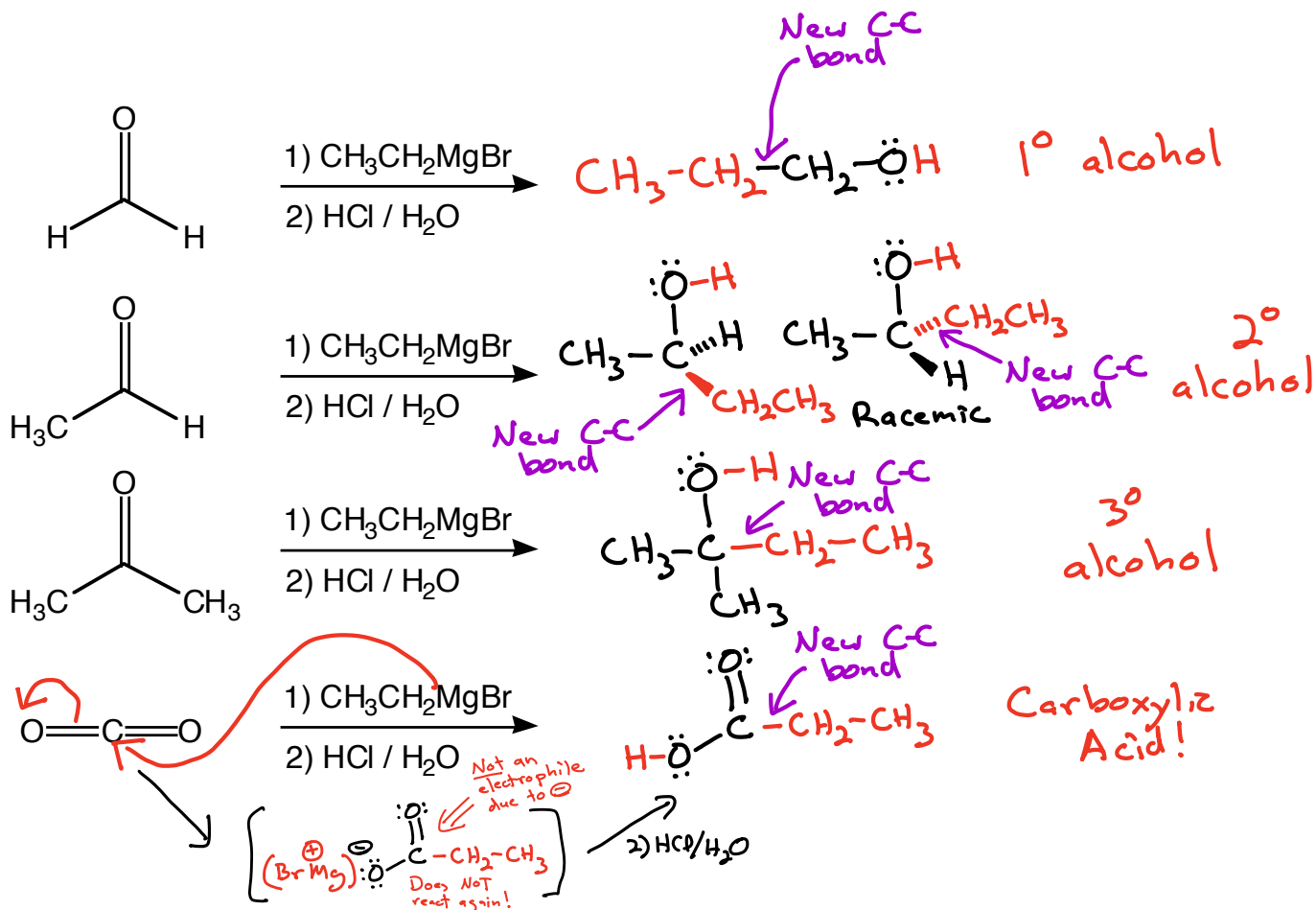
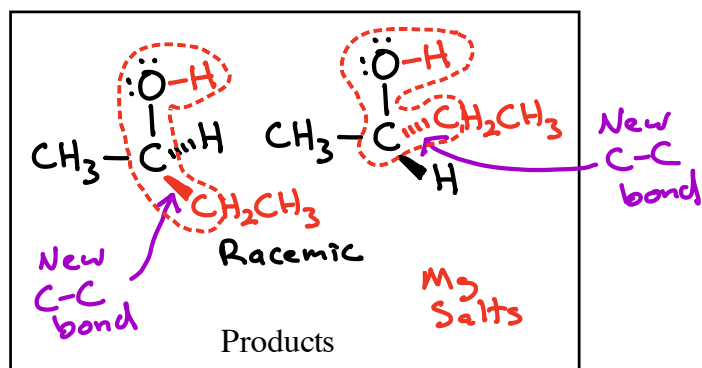


Grignard Reagent Reacting with an Aldehyde or Ketone

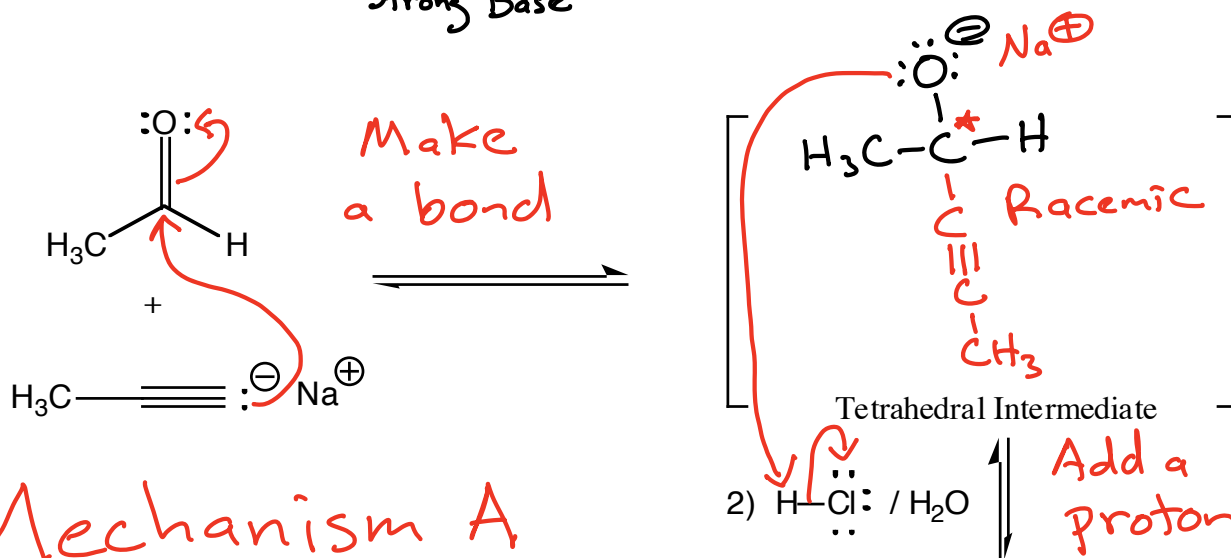
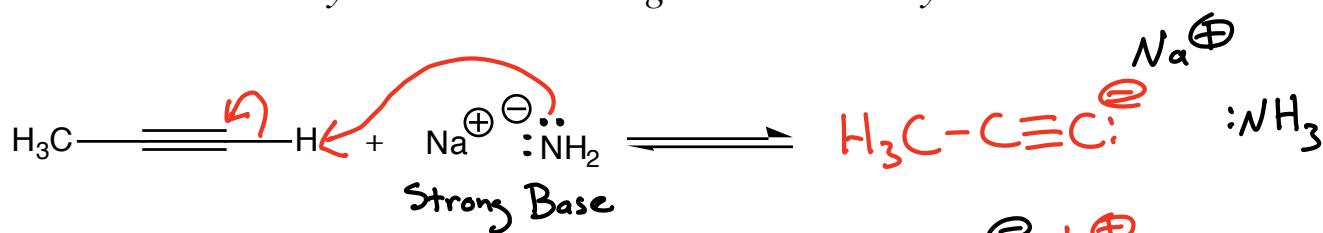


Key Recognition Element (KRE):

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



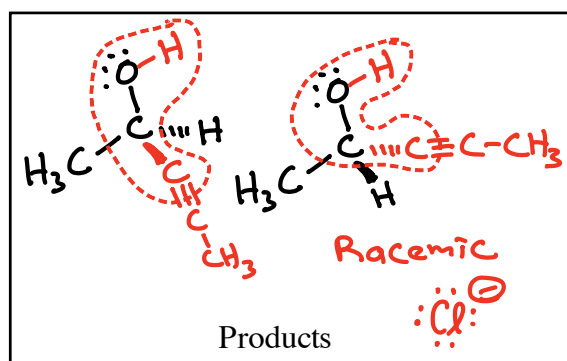
Alkyne Anion Reacting with an Aldehyde or Ketone



Mechanism A

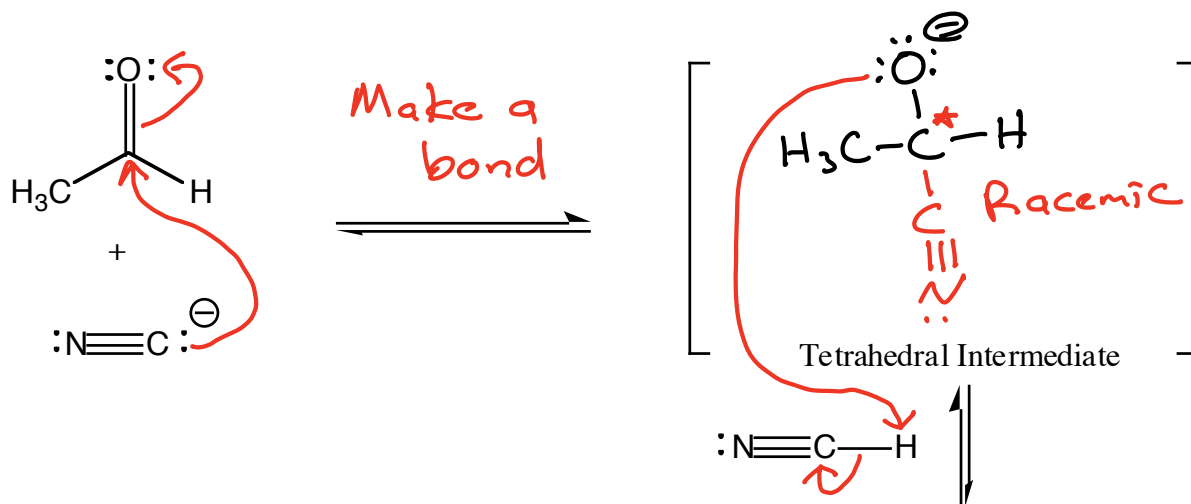
Key Recognition Element (KRE):

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



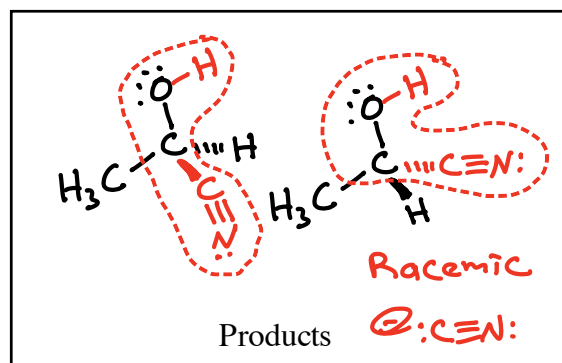
HCN Reacting with an Aldehyde or Ketone

Reacts on the C atom because that makes stronger bonds



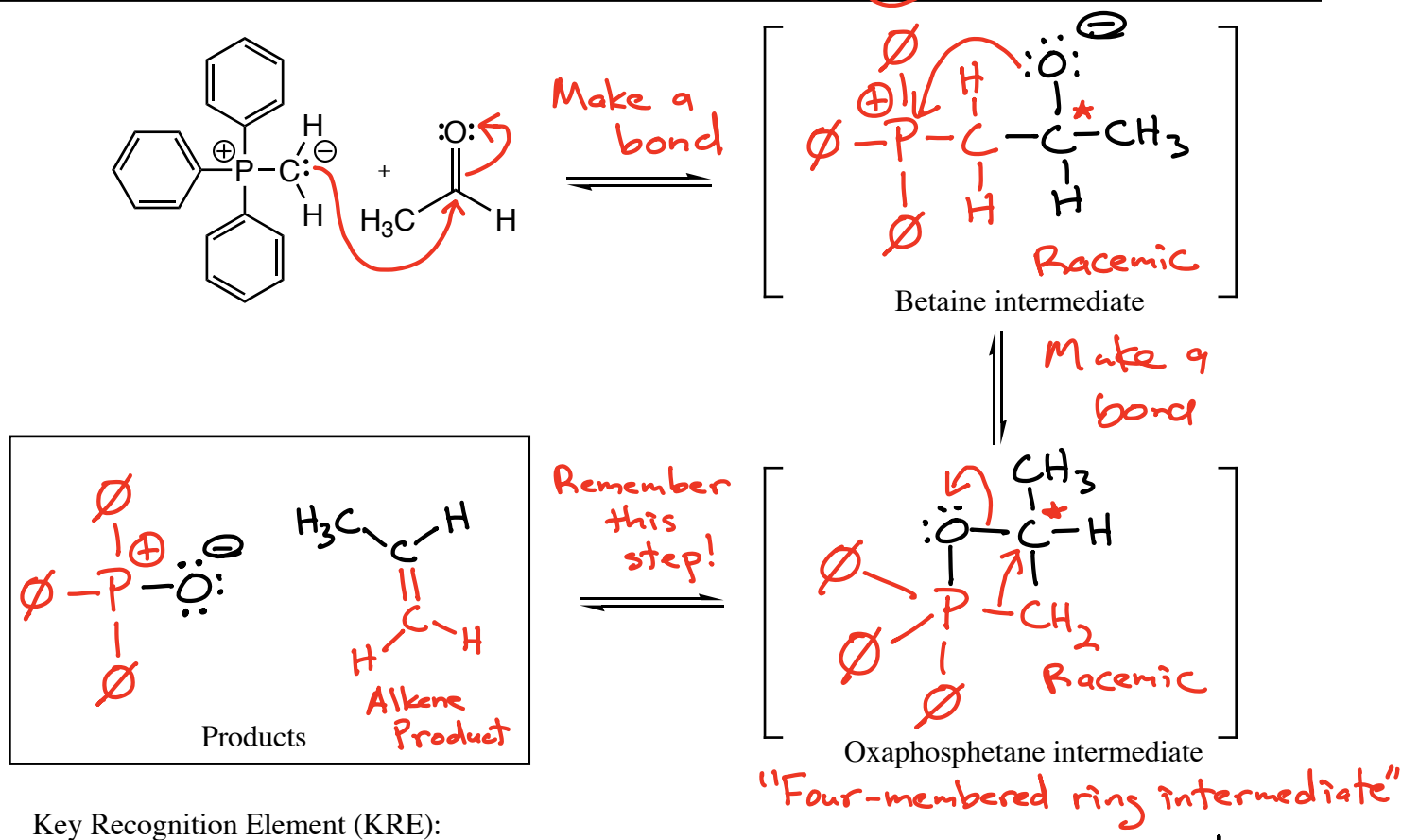
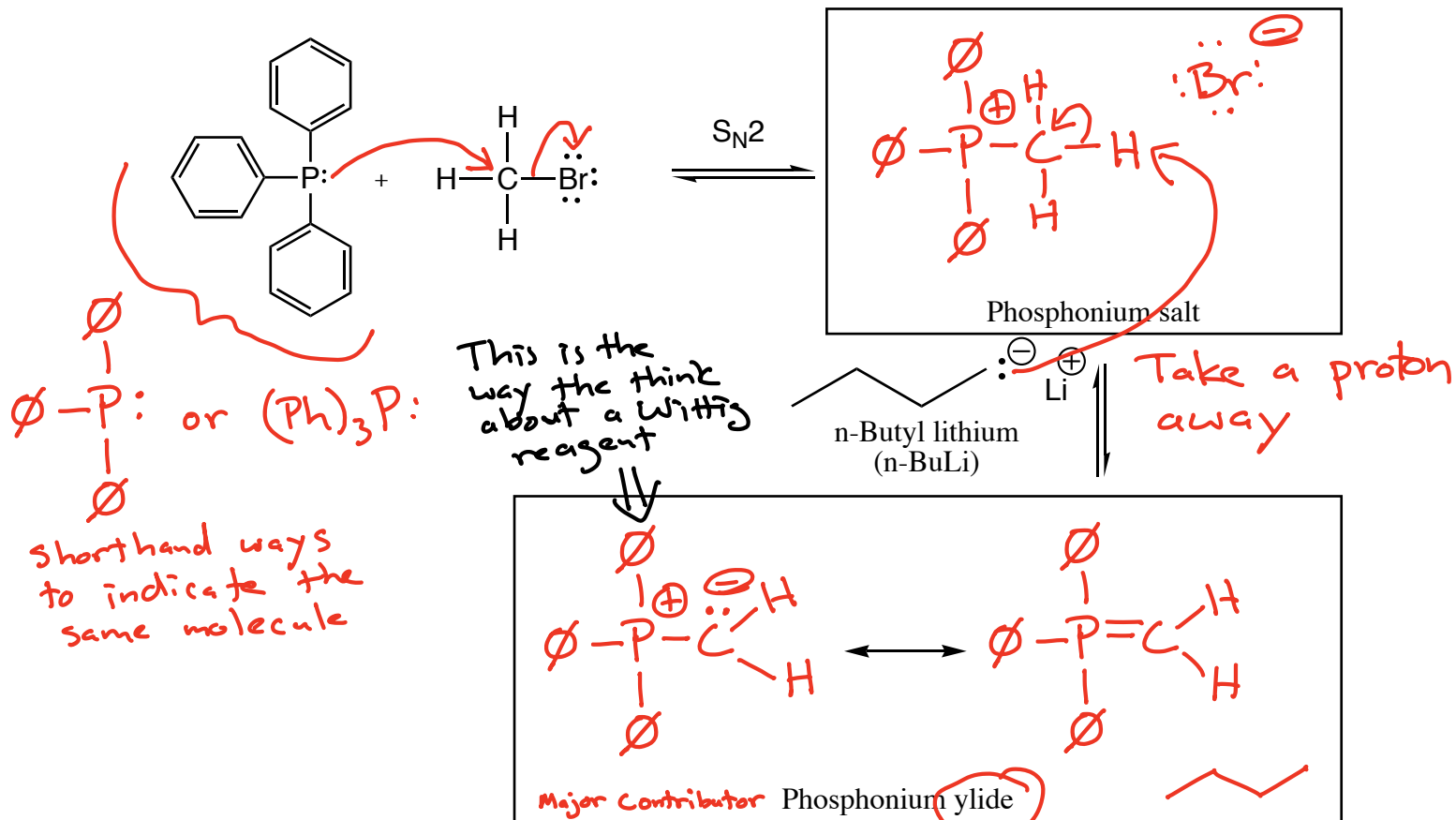
Key Recognition Element (KRE):

Cyanohydrin \rightarrow OH
on a C atom that
made a new C-C
bond to $-\text{C}\equiv\text{N:}$



Time capsule \rightarrow cyanohydrins can be
hydrolyzed in $\text{H}_2\text{SO}_4/\text{H}_2\text{O}$ to
give α -hydroxyacids
"alpha"

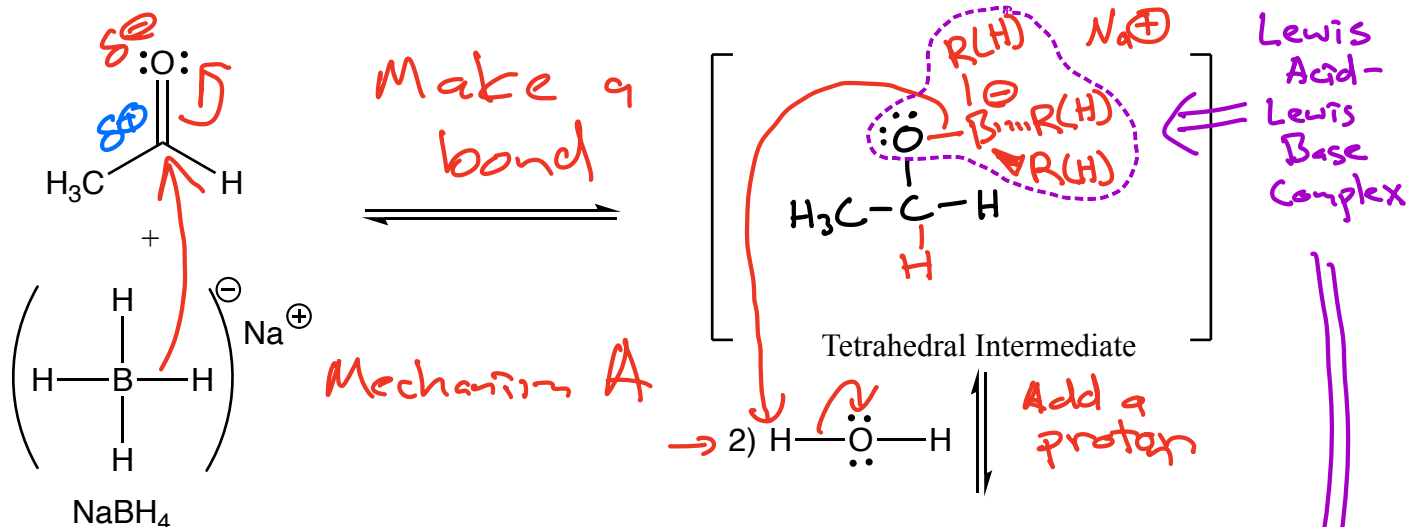
Wittig Reaction



Key Recognition Element (KRE):

Alkene \rightarrow New $\text{C}=\text{C}$ where the $\text{C}=\text{O}$ was!

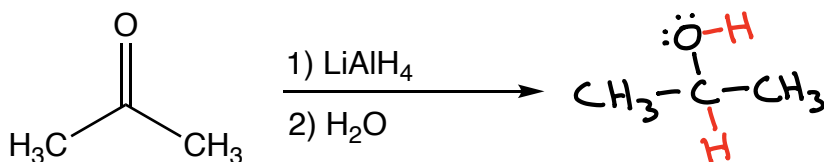
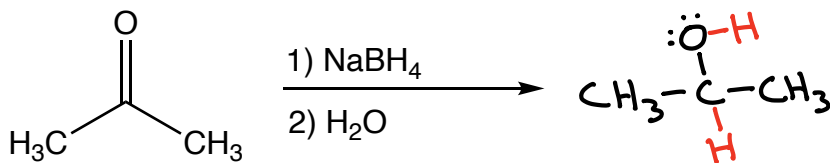
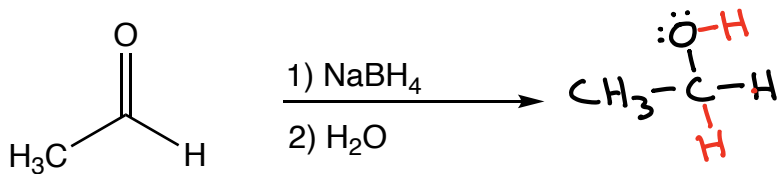
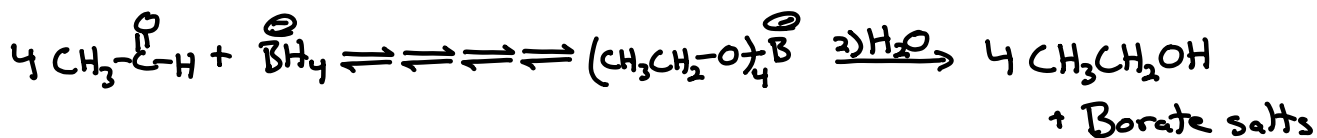
Sodium Borohydride Reacting with an Aldehyde or Ketone



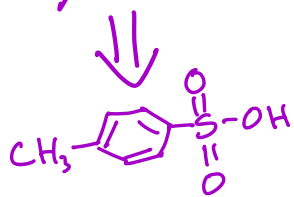
Key Recognition Element (KRE):

An $-\text{OH}$ group where there was a $\text{C}=\text{O}$ of an aldehyde or ketone

All four H of BH_4 react!

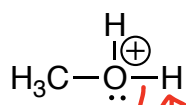


TsOH or H₂SO₄
Tosylic Acid
Acid Catalyzed Hemiacetal and Acetal Formation From an Aldehyde or Ketone

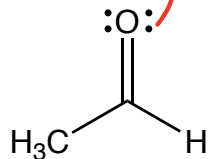


“Hex, does that thing have a hemi in it?” “SWEET!”

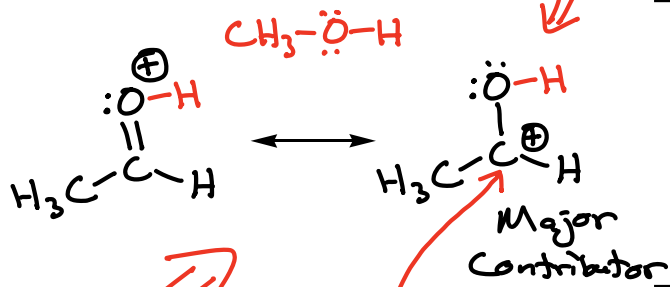
Red Hot Electrophile



Add a proton

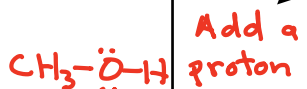
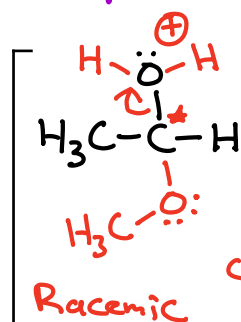


Weak Electrophile

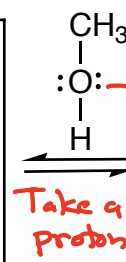
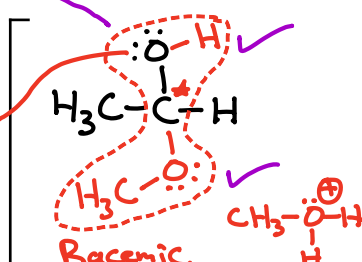


Mechanism

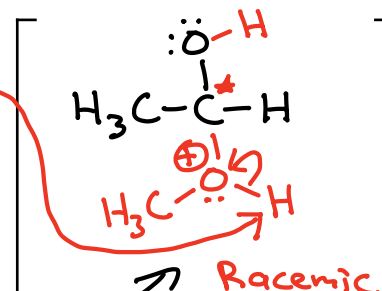
-OH and -OR on the same sp³ C atom



Add a proton



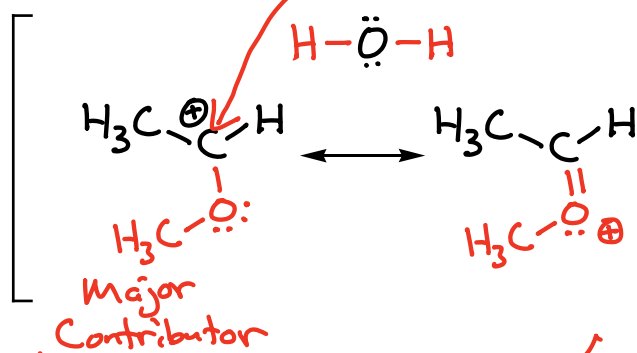
Take a proton away



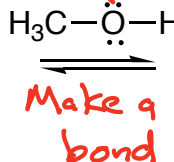
Hemiacetal intermediate

Not stable

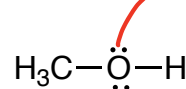
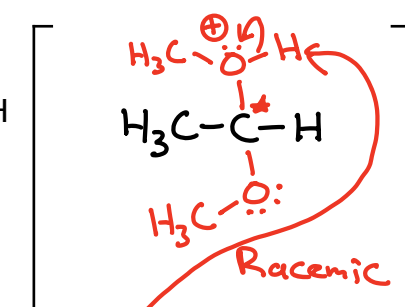
Break a bond



Stabilized by Charge Delocalization



Make a bond



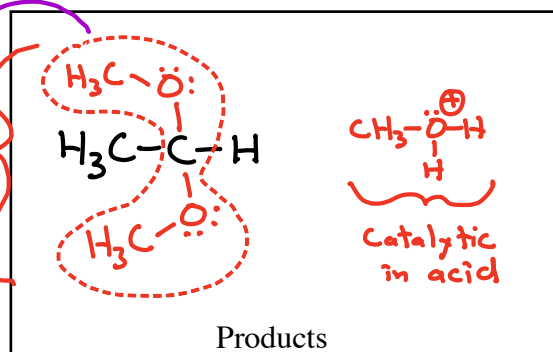
Take a proton away

Key Recognition Element (KRE):

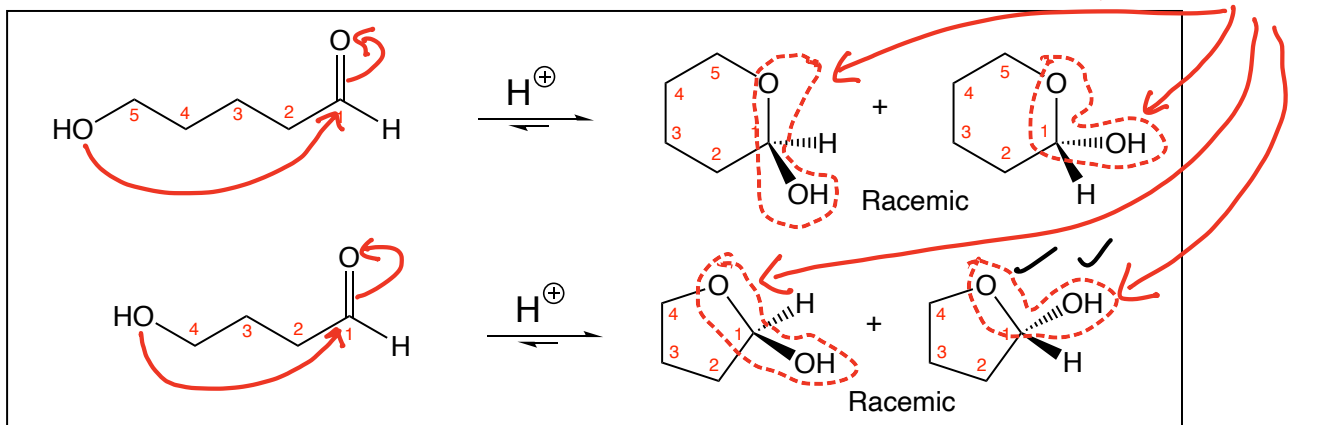
Two -OR on the same sp³ C atom

Two bonds to ether O atoms to an sp³ C atom

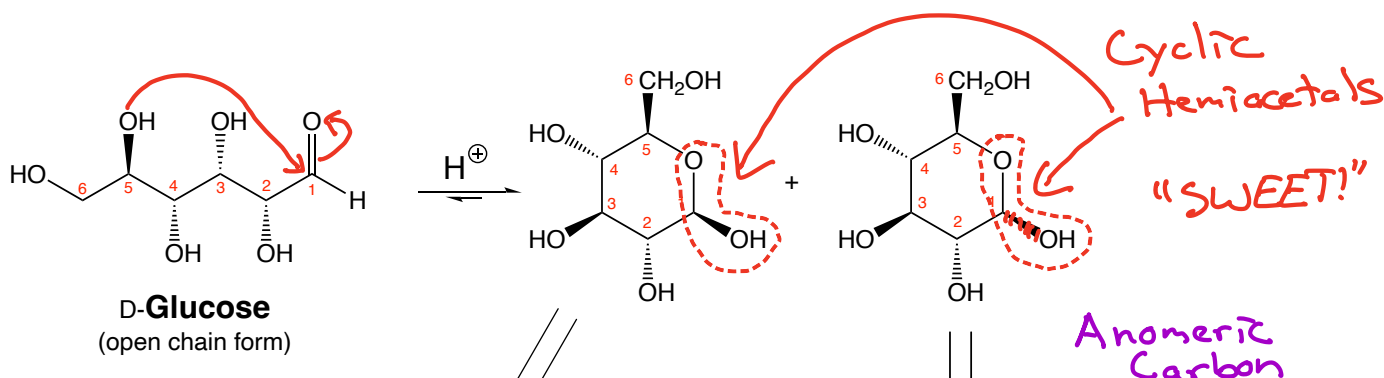
An acetal



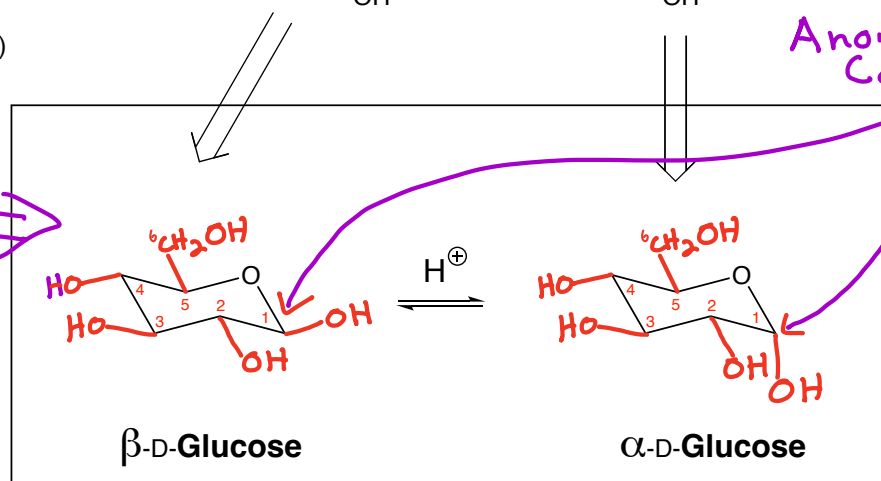
Cyclic Hemiacetals and Carbohydrates



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



This interconversion is called "mutarotation"



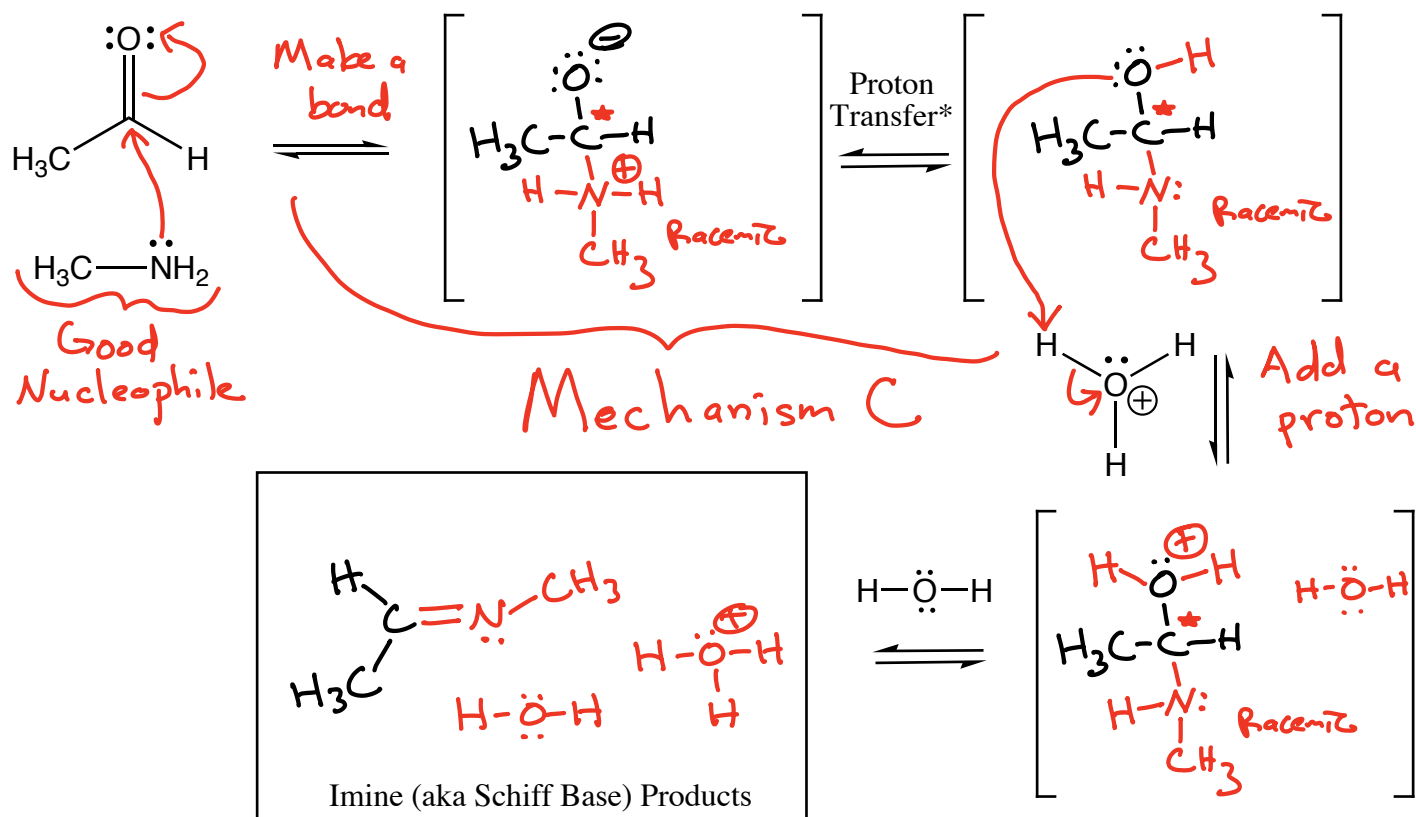
Biochemists call these two forms "anomers"

β -D-Glucopyranose
 means "6-membered ring"

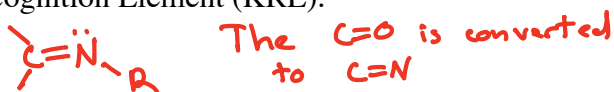
More stable → every group is equatorial!

α -D-Glucopyranose
 Less stable → one -OH is axial

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



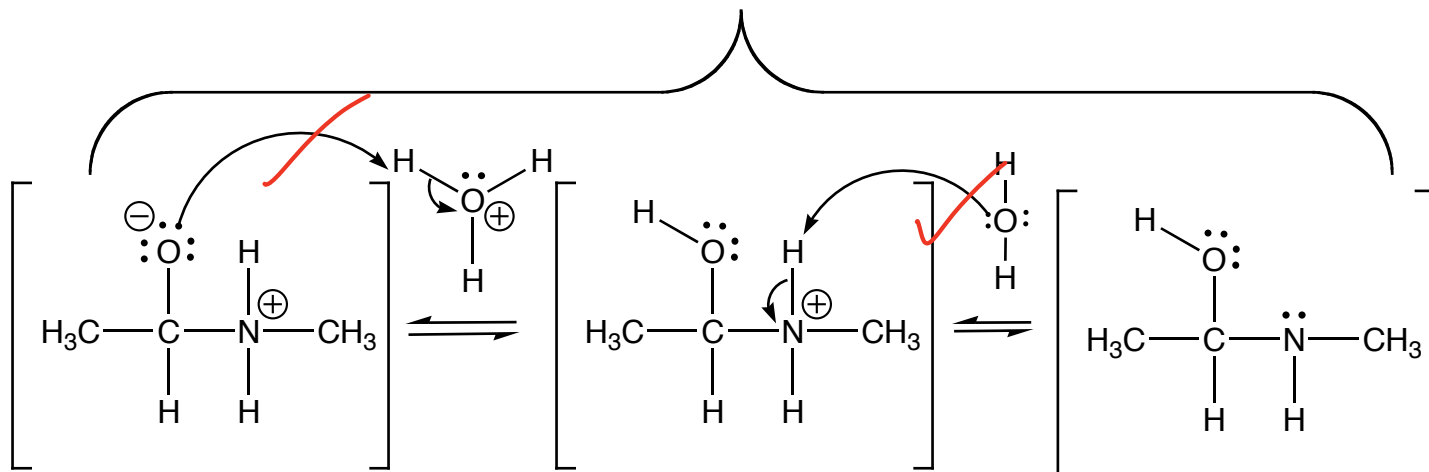
Key Recognition Element (KRE):



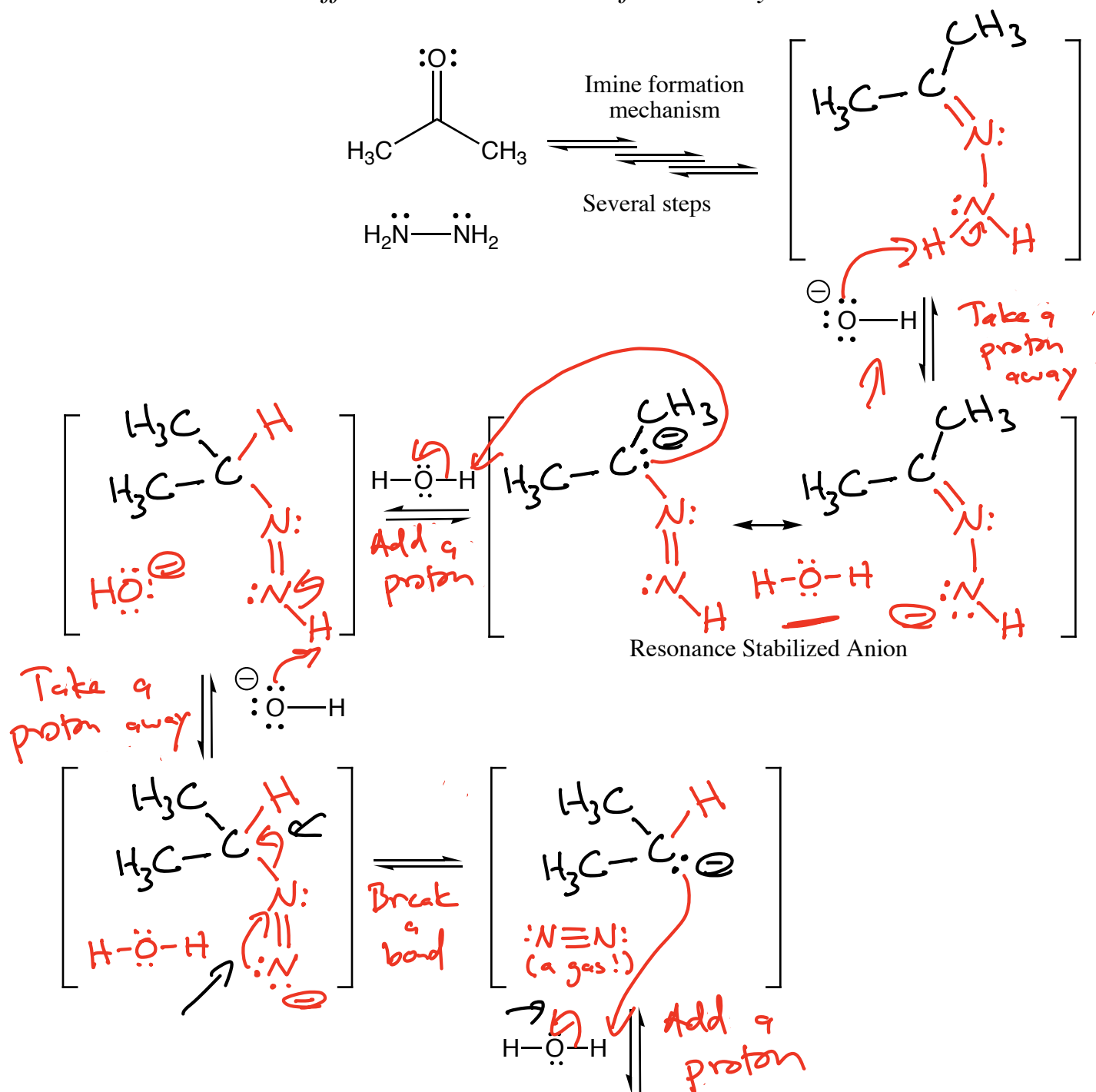
(Note: this last step might actually occur as two steps in some cases.)

* "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. Because of all the ambiguity, we just write "Proton Transfer" and do not bother with arrows.

"Proton Transfer"

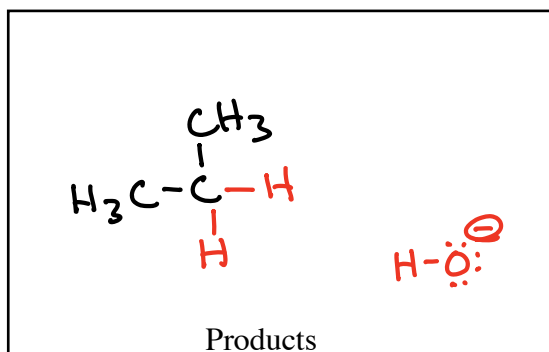


Wolff-Kishner Reduction of an Aldehyde or Ketone



Key Recognition Element (KRE):

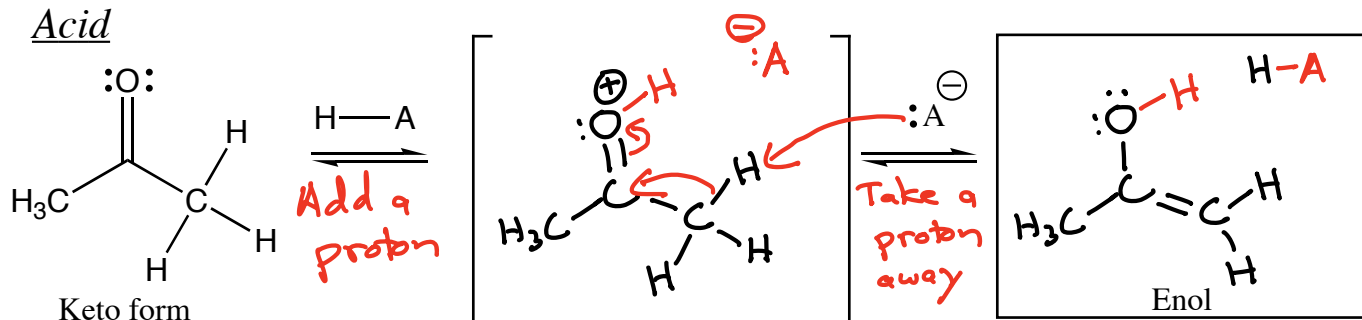
$\sim\text{CH}_2\sim$ where
there was
 $\text{C}=\text{O}$



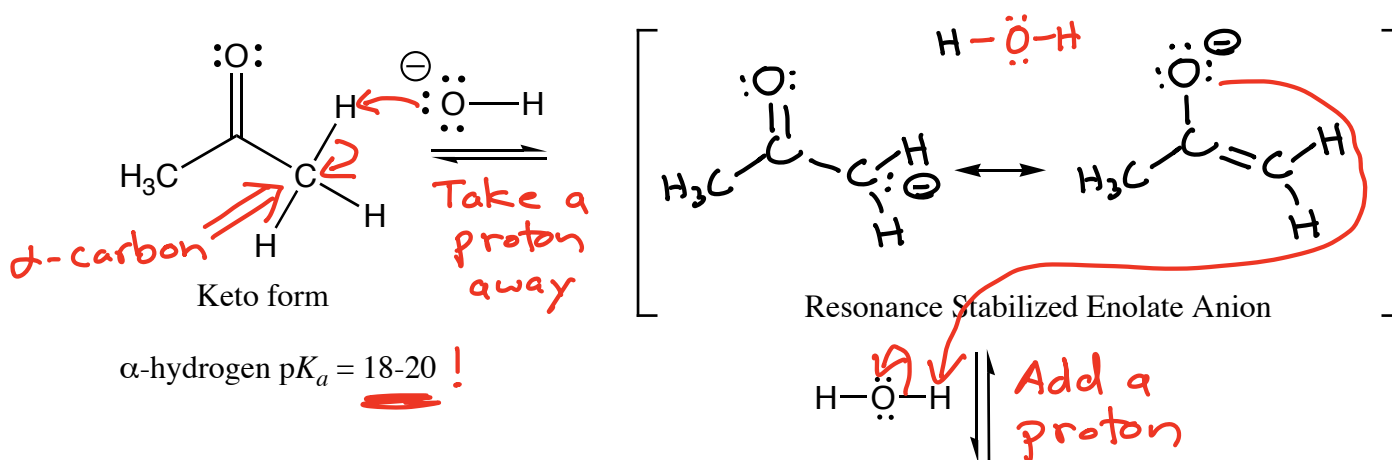
The process of interconverting the keto and enol forms is called "tautomerization"

Keto-Enol Equilibrium Catalyzed by Acid or Base

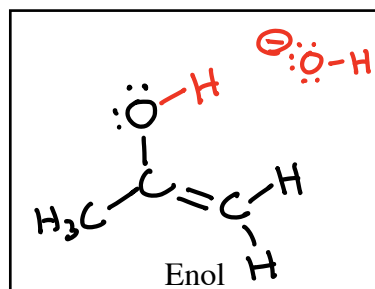
Acid



Base



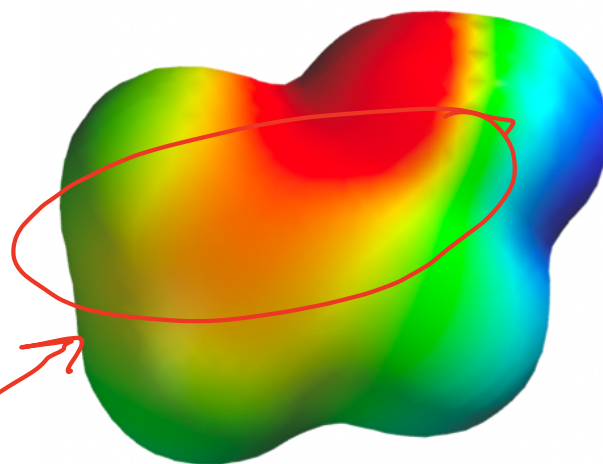
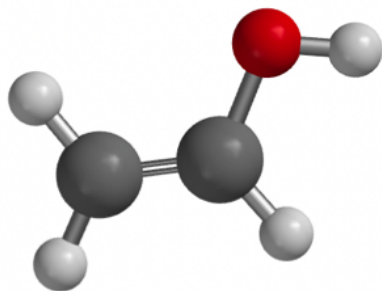
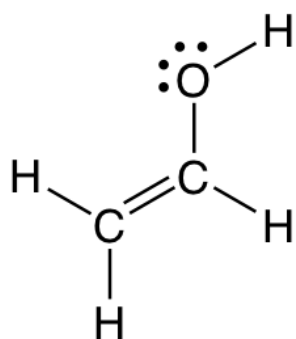
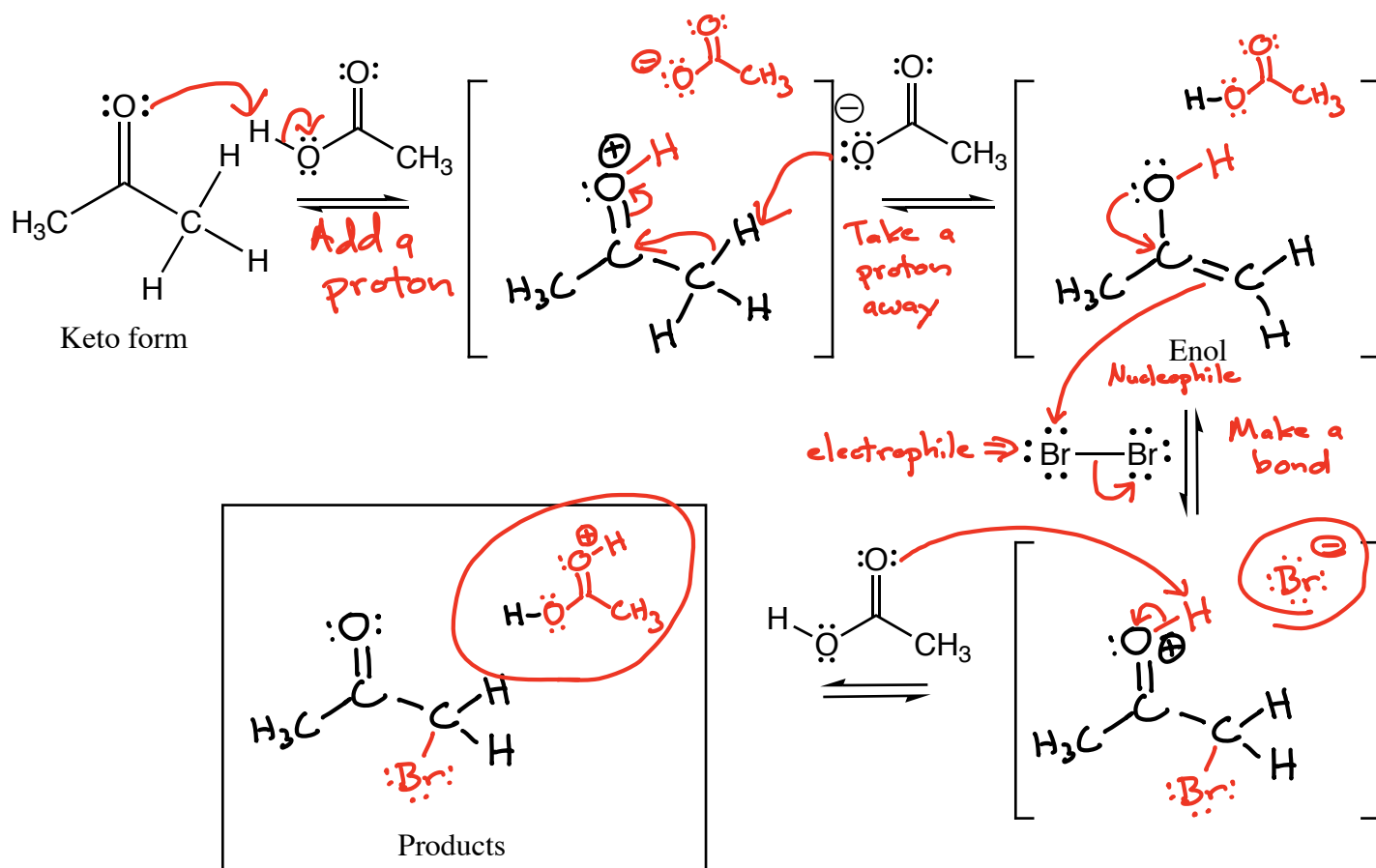
keto and enol forms are called "tautomers"



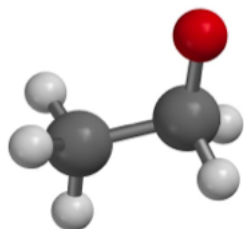
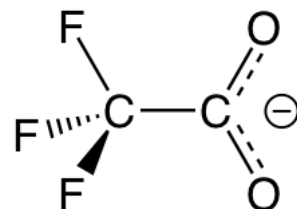
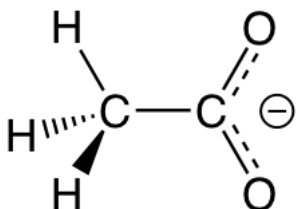
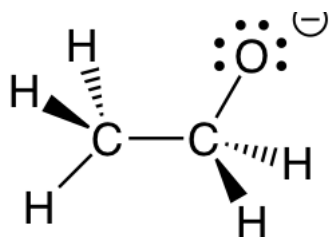
For both aldehydes and ketones, the keto form predominates at equilibrium, because $C=O$ bonds are stronger than $C=C$ bonds.

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

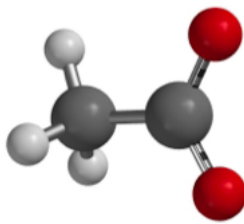
α -Halogenation of an Aldehyde or Ketone Catalyzed by Acid



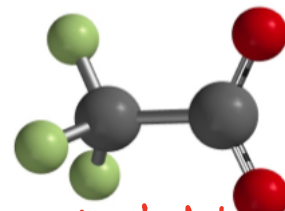
Nucleophile



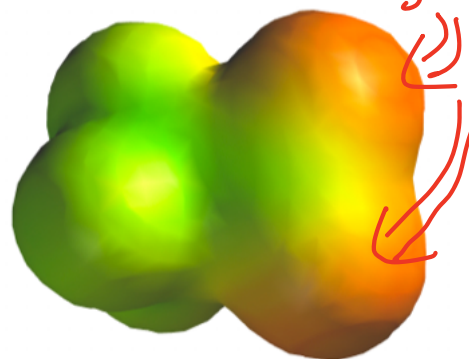
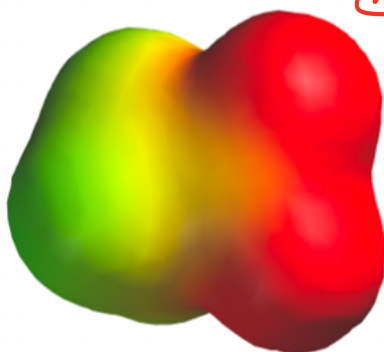
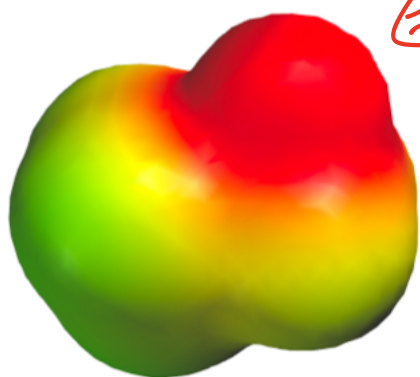
Least
delocalized
⊖ charge



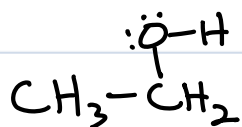
Somewhat
delocalized
⊖ charge



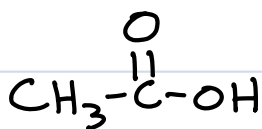
Most delocalized
⊖ charge



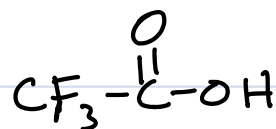
Parent Acids



$$\text{p}K_a \approx 16$$

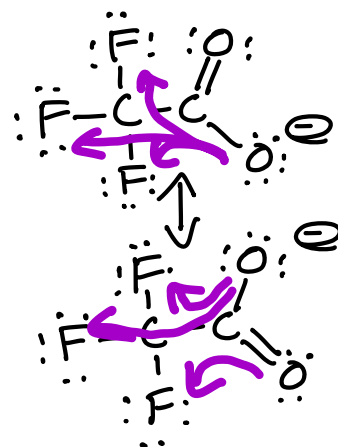
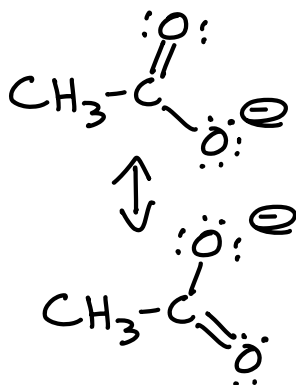
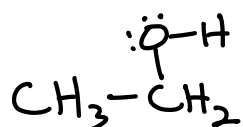


$$\text{p}K_a \approx 3-5$$



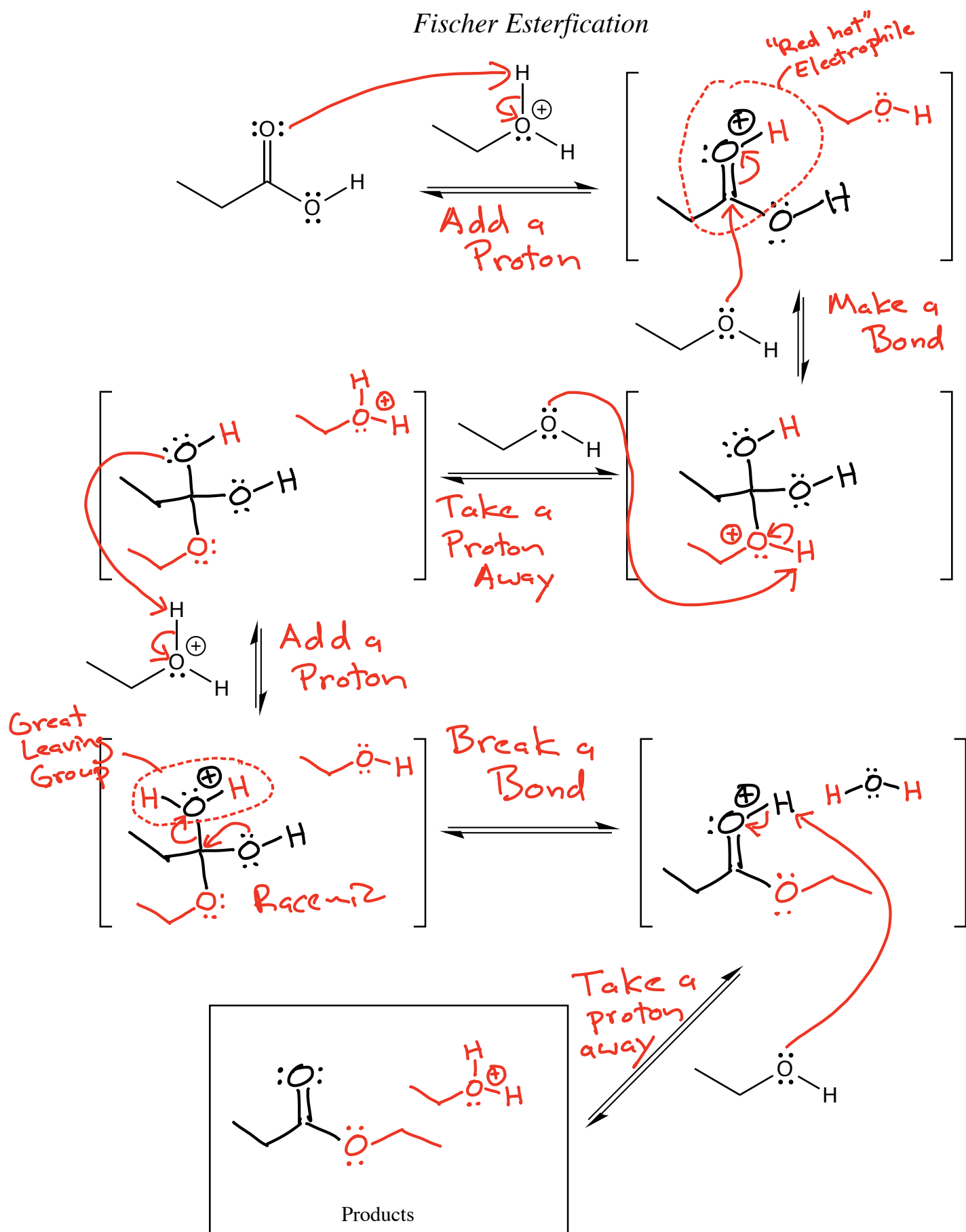
$$\text{p}K_a = 0.3-3$$

Rank acidity by comparing anion stabilities

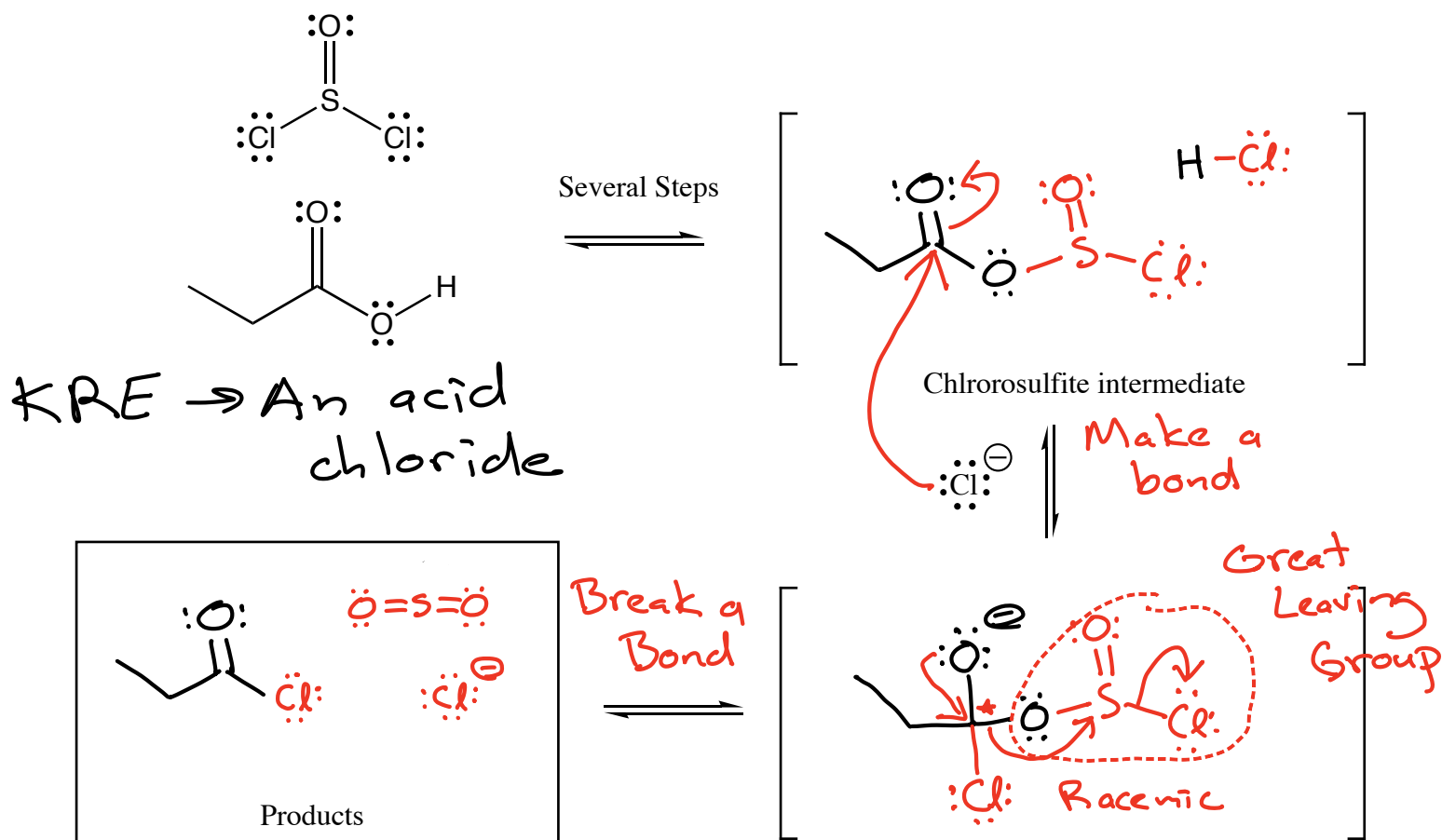


Inductive effect
pulls some ⊖ charge
into F atoms

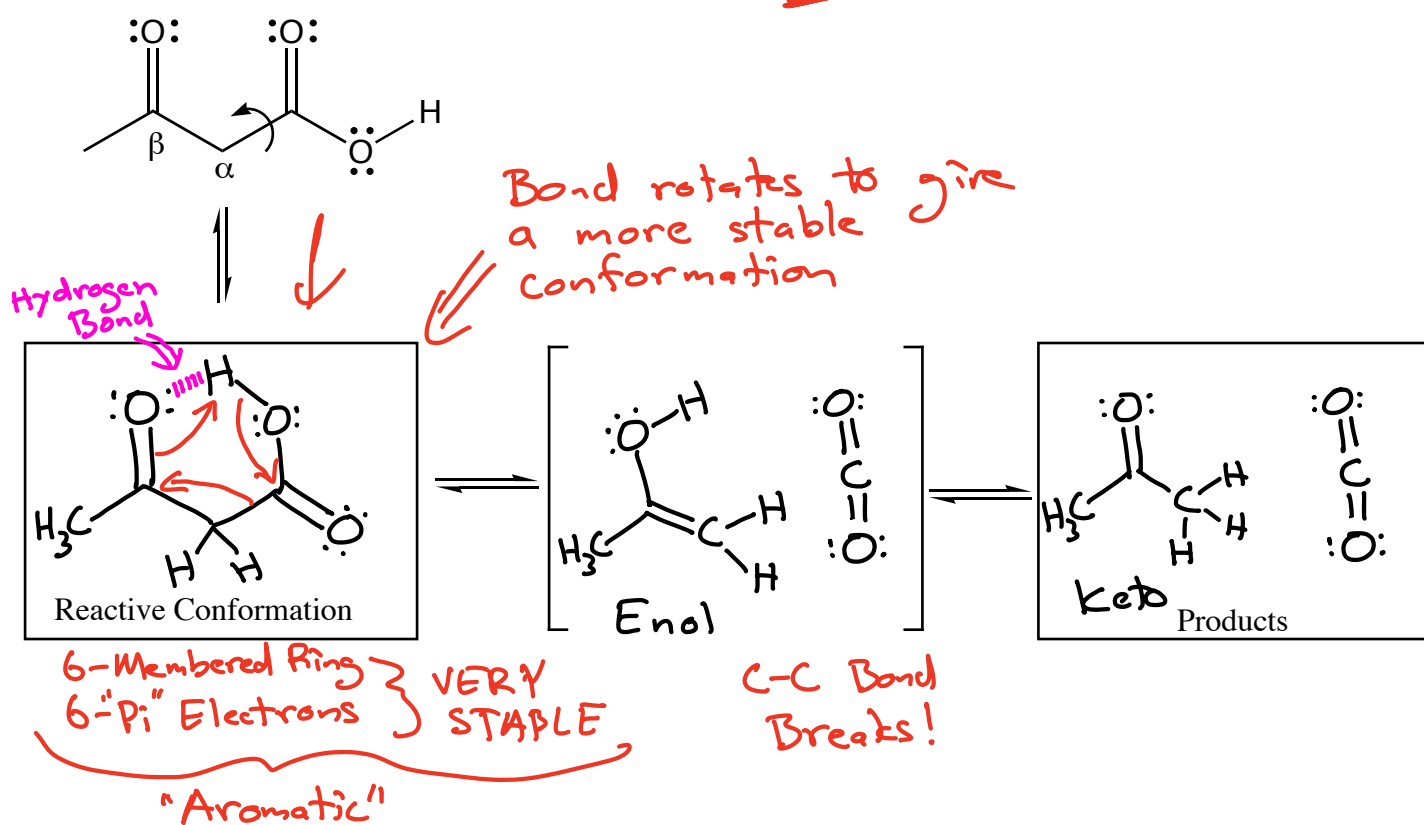
Fischer Esterification



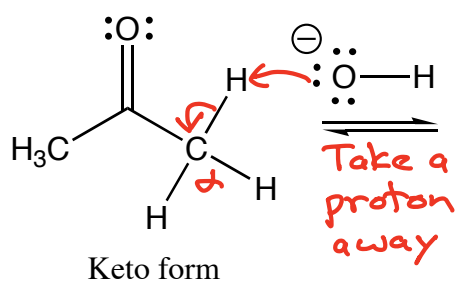
Reaction with Thionyl Chloride



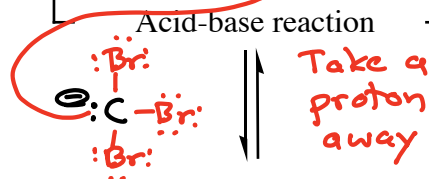
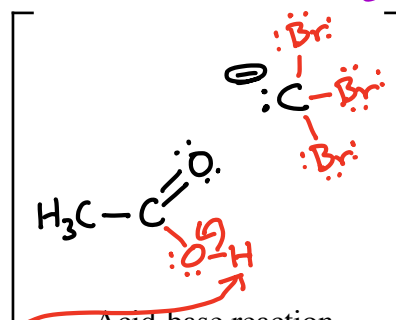
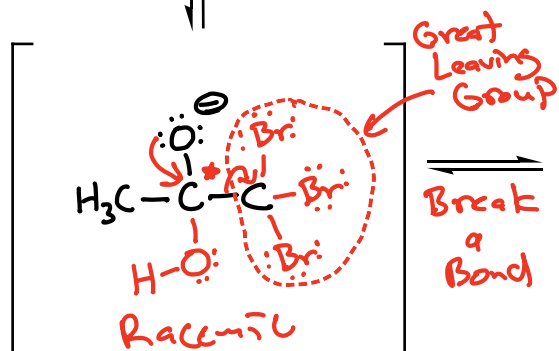
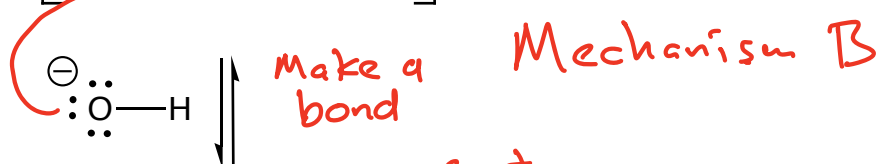
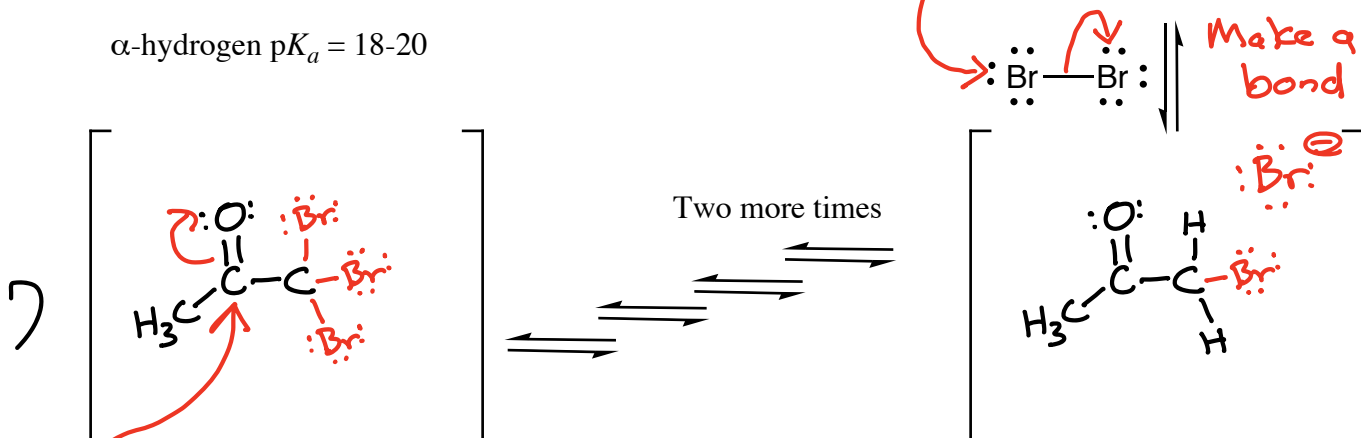
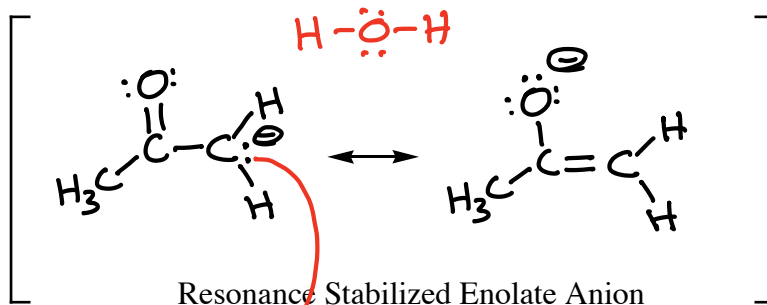
Decarboxylation of a β -Keto Acid



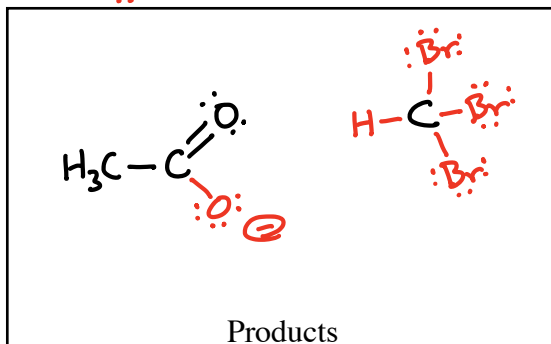
The Haloform Reaction



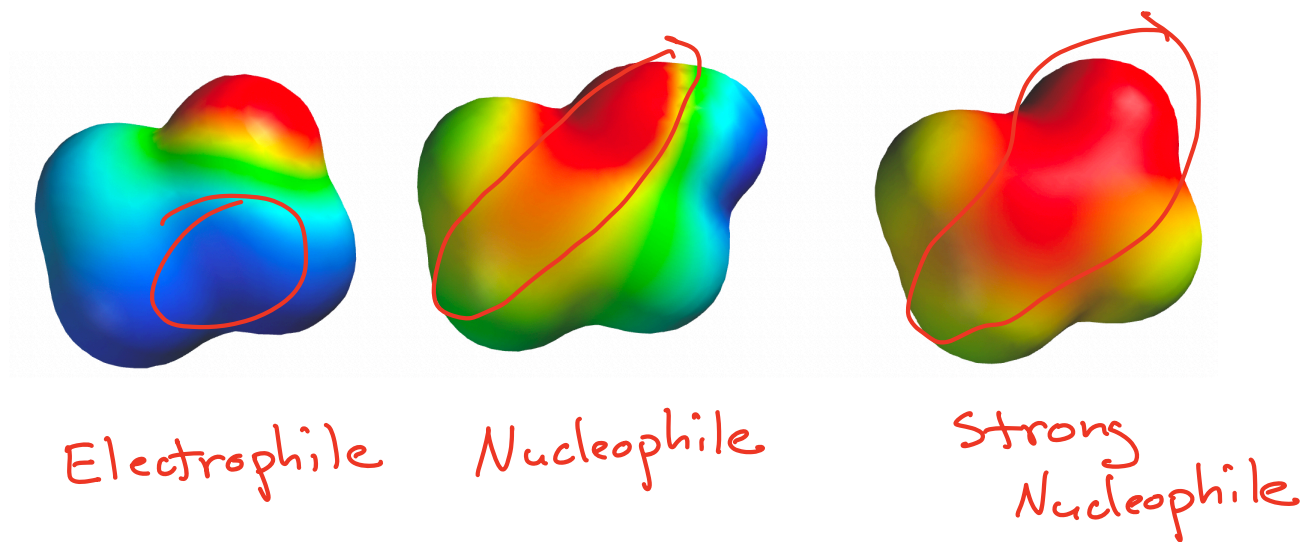
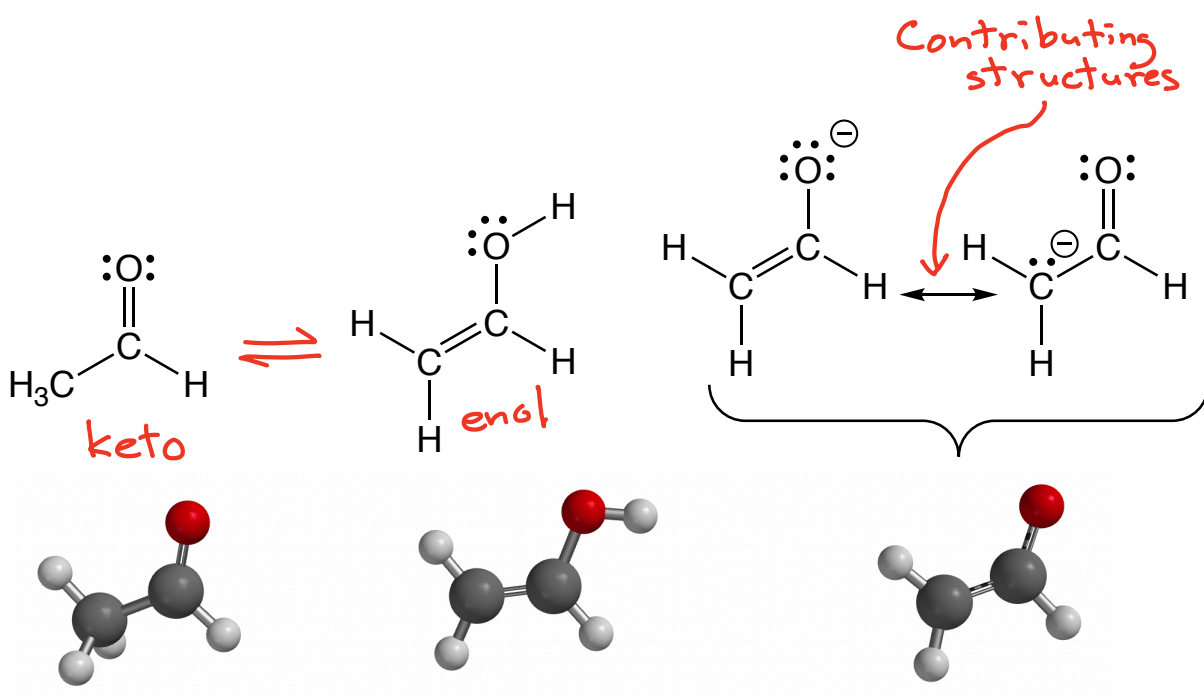
α -hydrogen $pK_a = 18-20$



KRE \rightarrow Break the C-C bond to give a carboxylate and haloform product

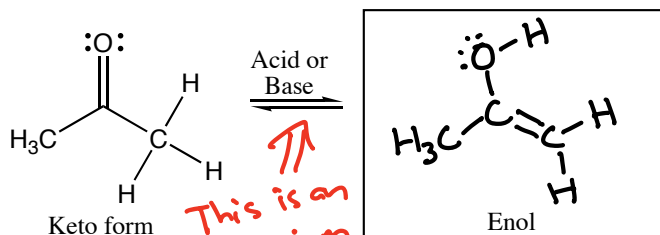


The inductive effect stabilizes the $[O-]$ explaining why $[C(Br)_3]$ is such a good leaving group



Keto-Enol Tautomerization vs. Enolate Resonance

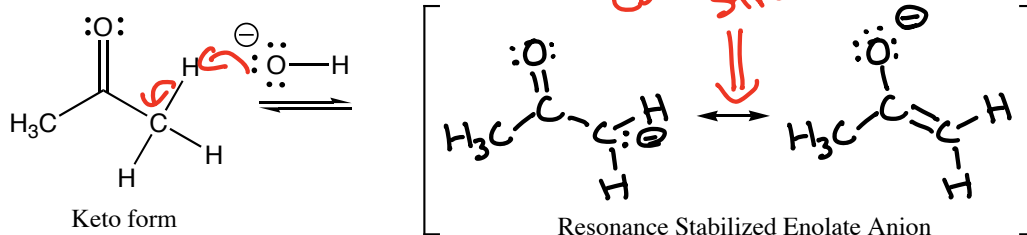
Keto-Enol Tautomerization



Both the keto and enol molecules are Neutral!

This is an equilibrium

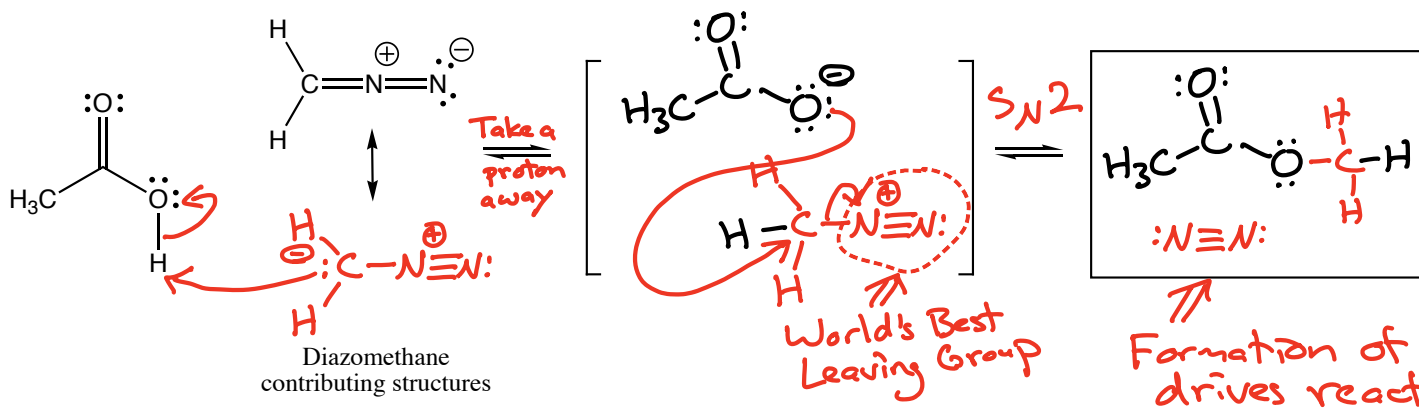
Enolate Resonance



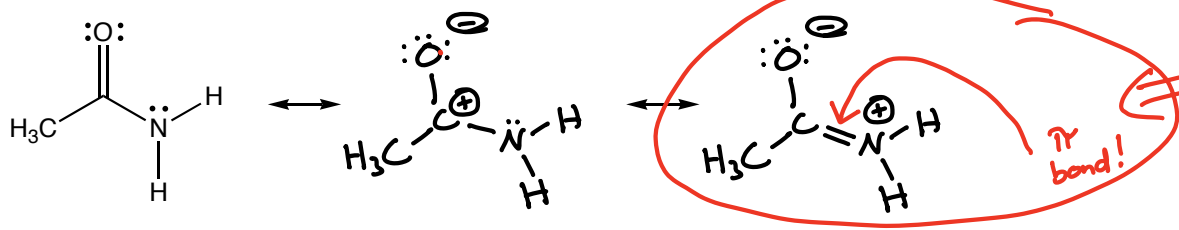
Full \ominus

α -hydrogen $\text{p}K_a = 18-20$

Diazomethane reaction

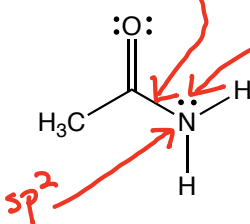


Amide Resonance VERY IMPORTANT!!!!!!



This contributing structure is important and that has big consequences!

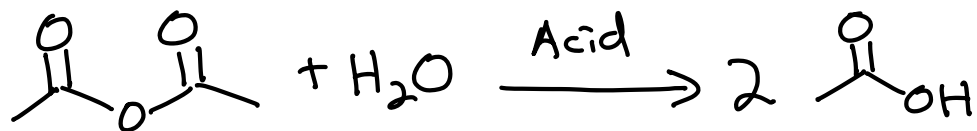
This is a partial π bond so it does NOT rotate at room temperature



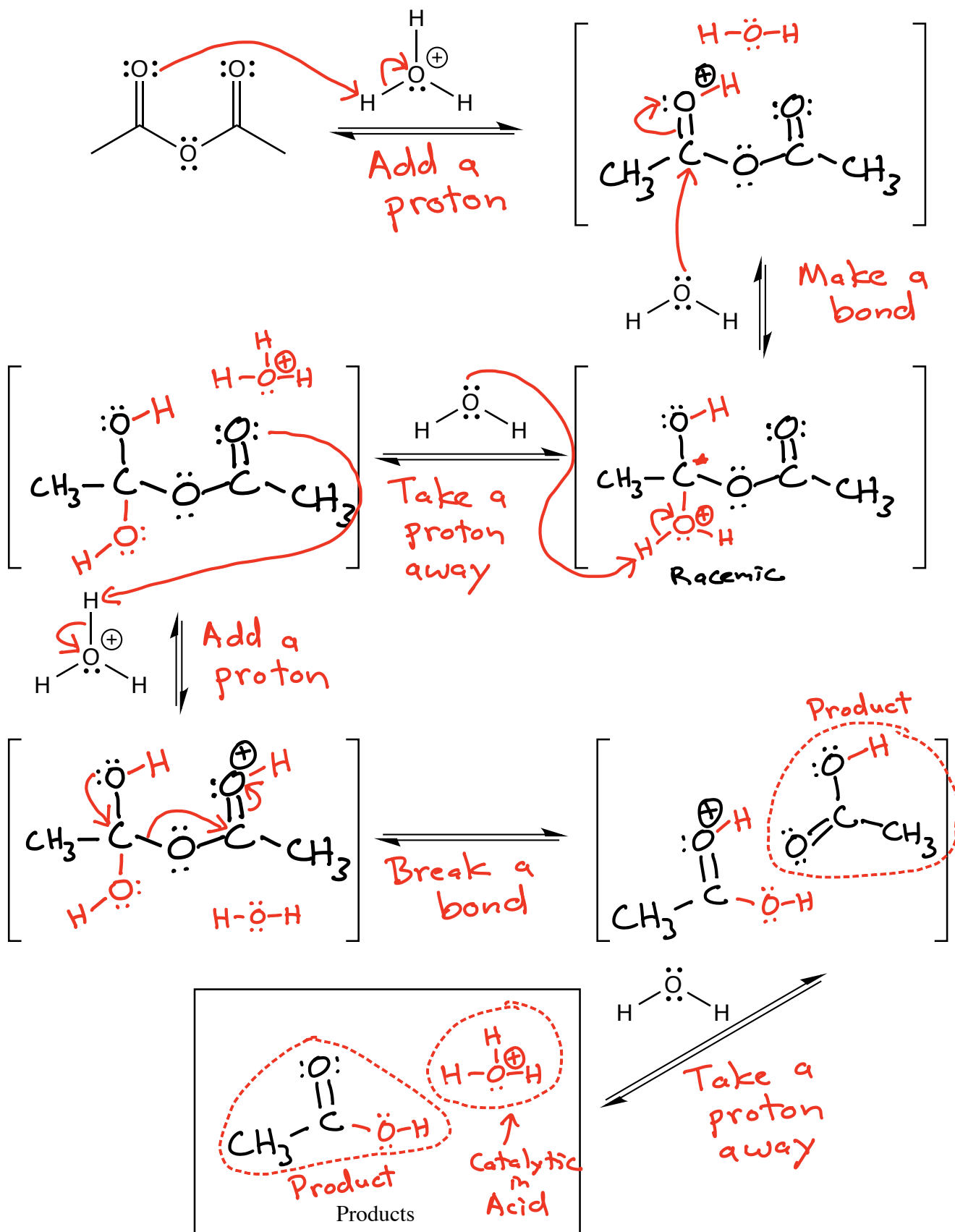
Lone pair is in a 2p orbital!

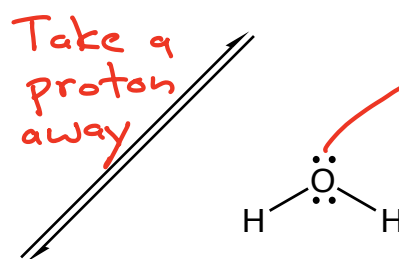
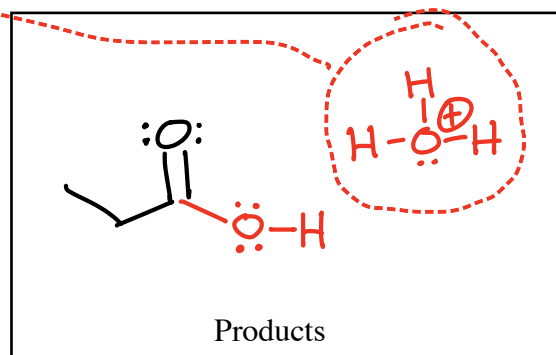
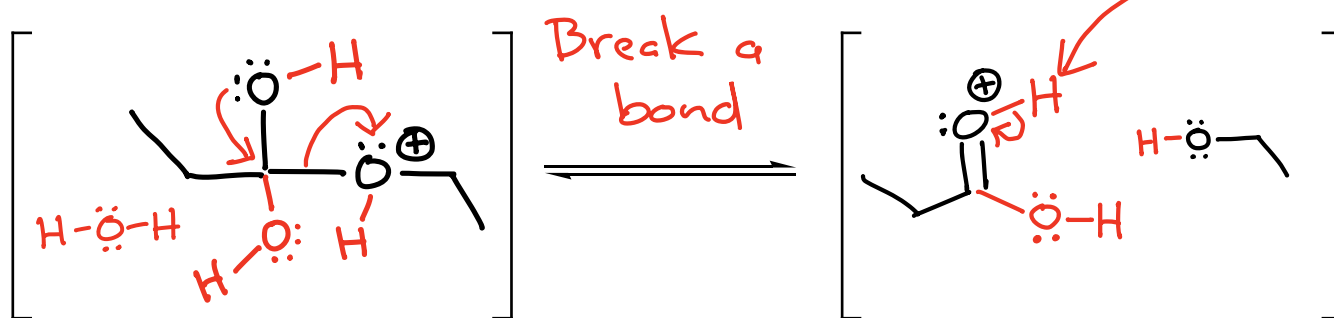
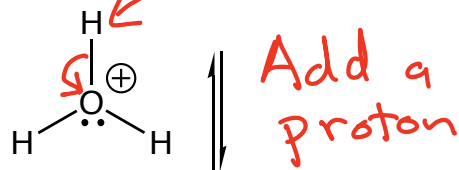
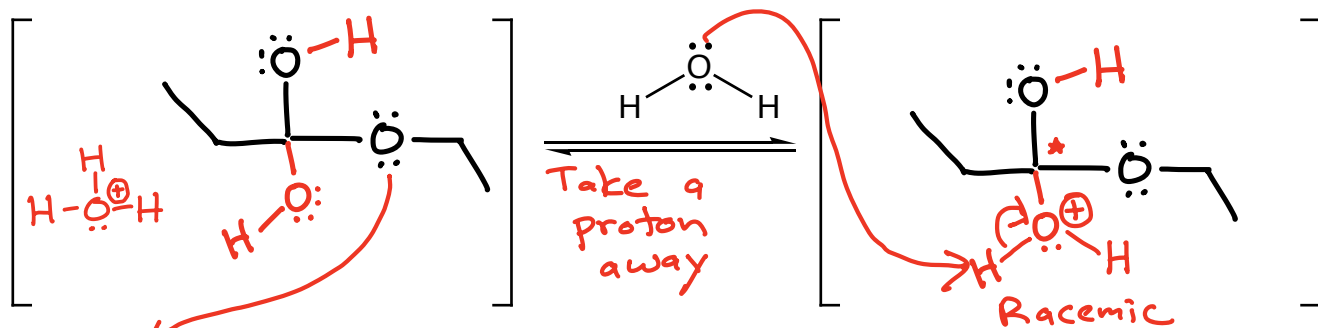
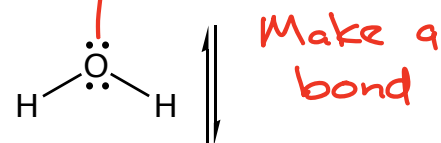
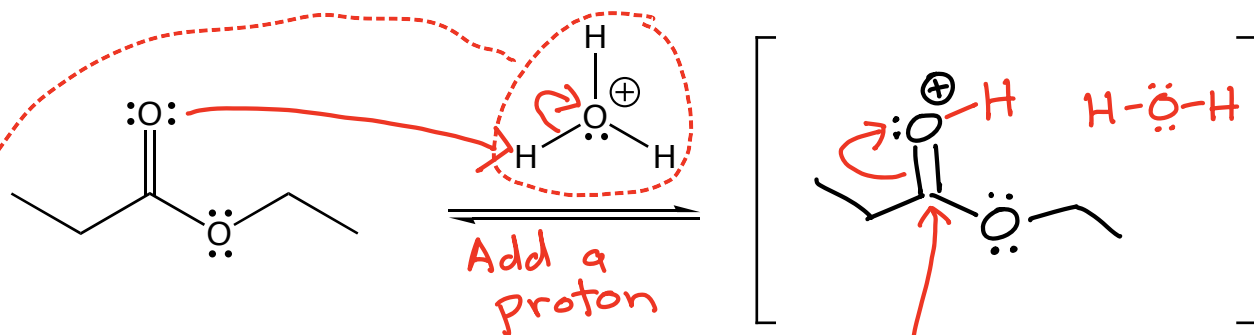
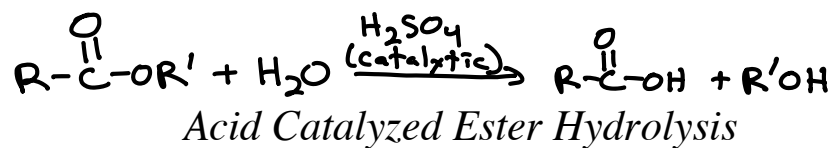
(Golden Rule of Chemistry)

A " π -way" is created from the overlap of 2p orbitals on the O, C, and N atoms \rightarrow 3 atoms, 2 electrons \rightarrow VERY STABILIZING!

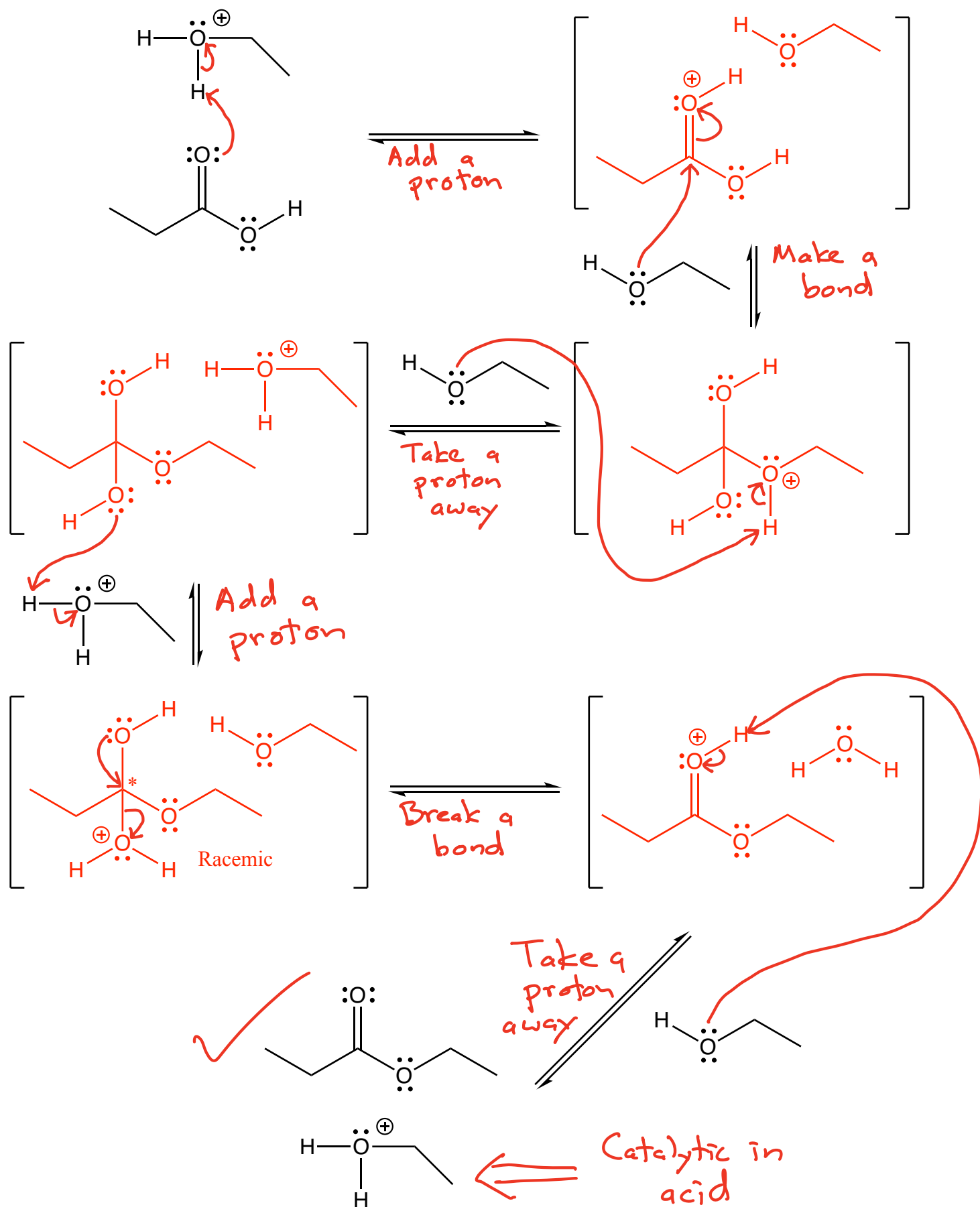


Acid Catalyzed Anhydride Hydrolysis

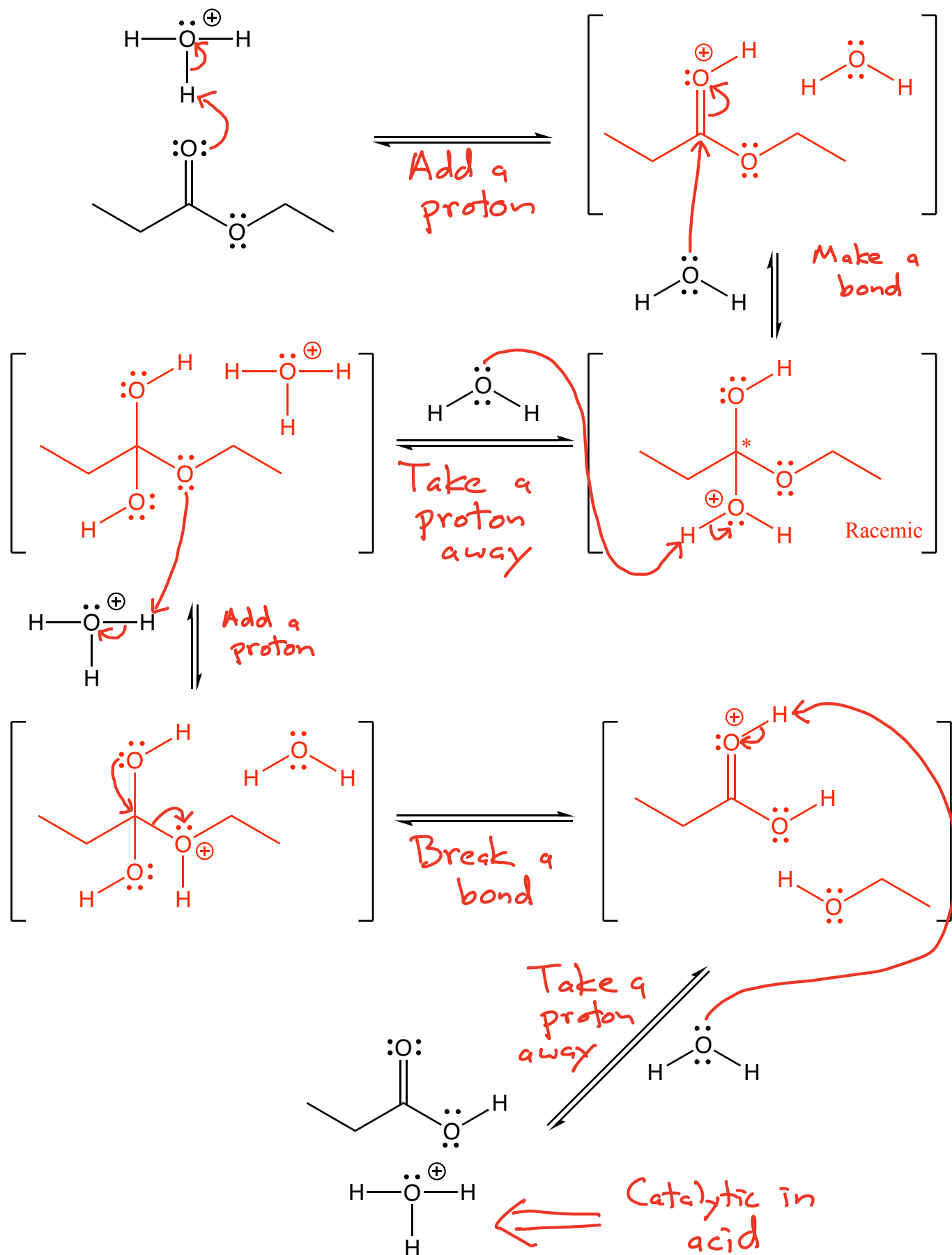


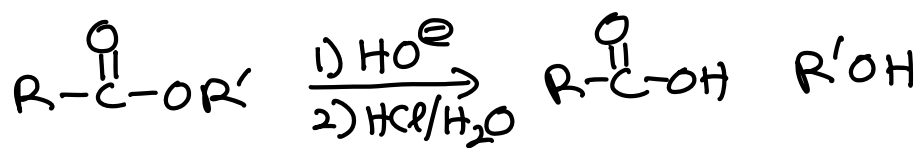


Microscopic Reversibility: Acid Catalyzed Ester Hydrolysis-Fischer Esterification

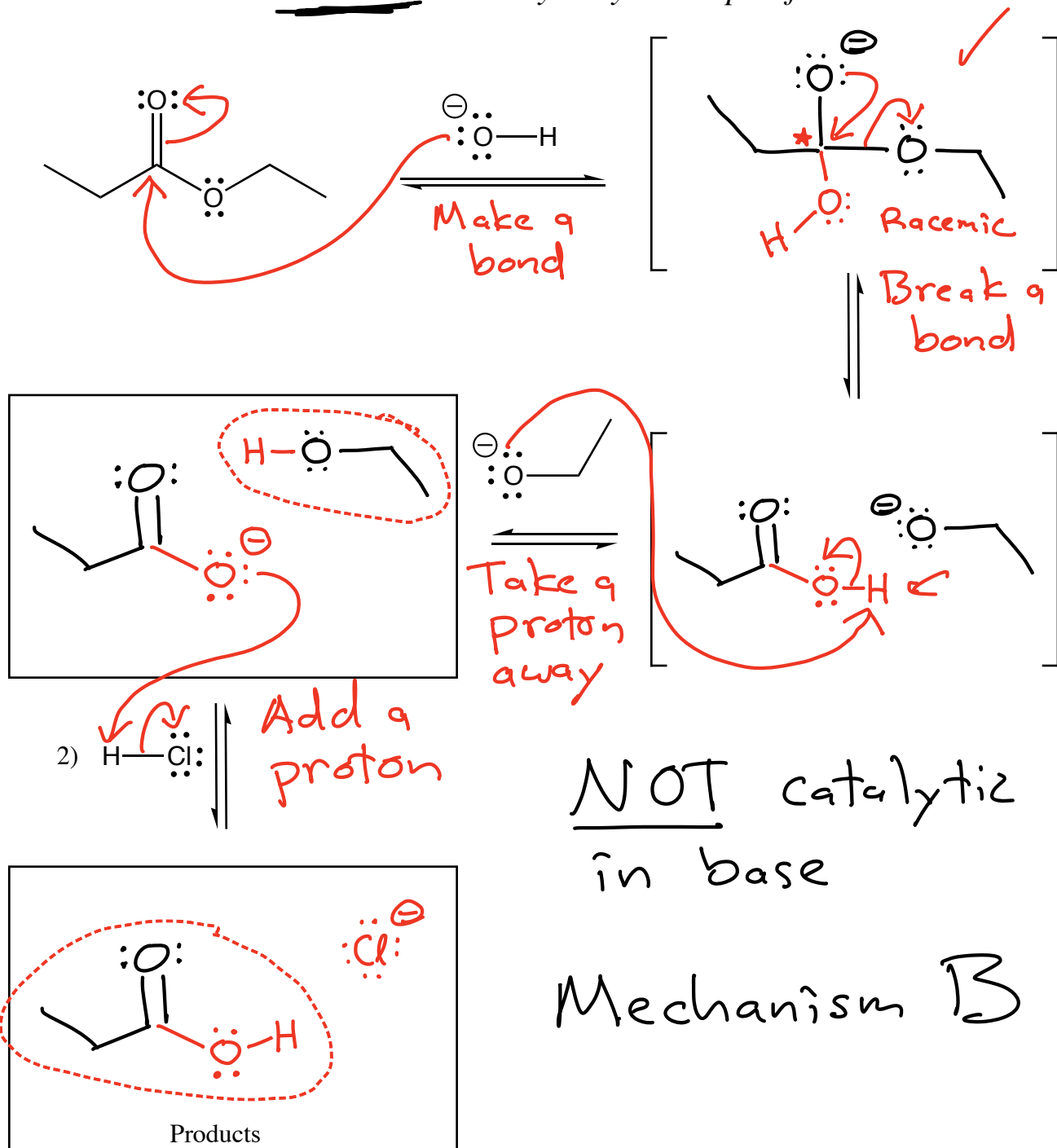


Microscopic Reversibility: Acid Catalyzed Ester Hydrolysis-Fischer Esterification





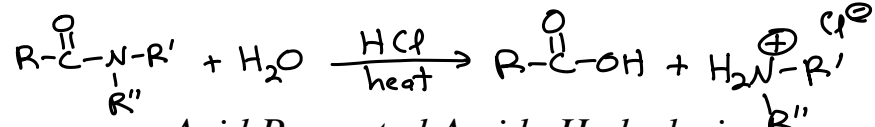
Base-Promoted Ester Hydrolysis - Saponification



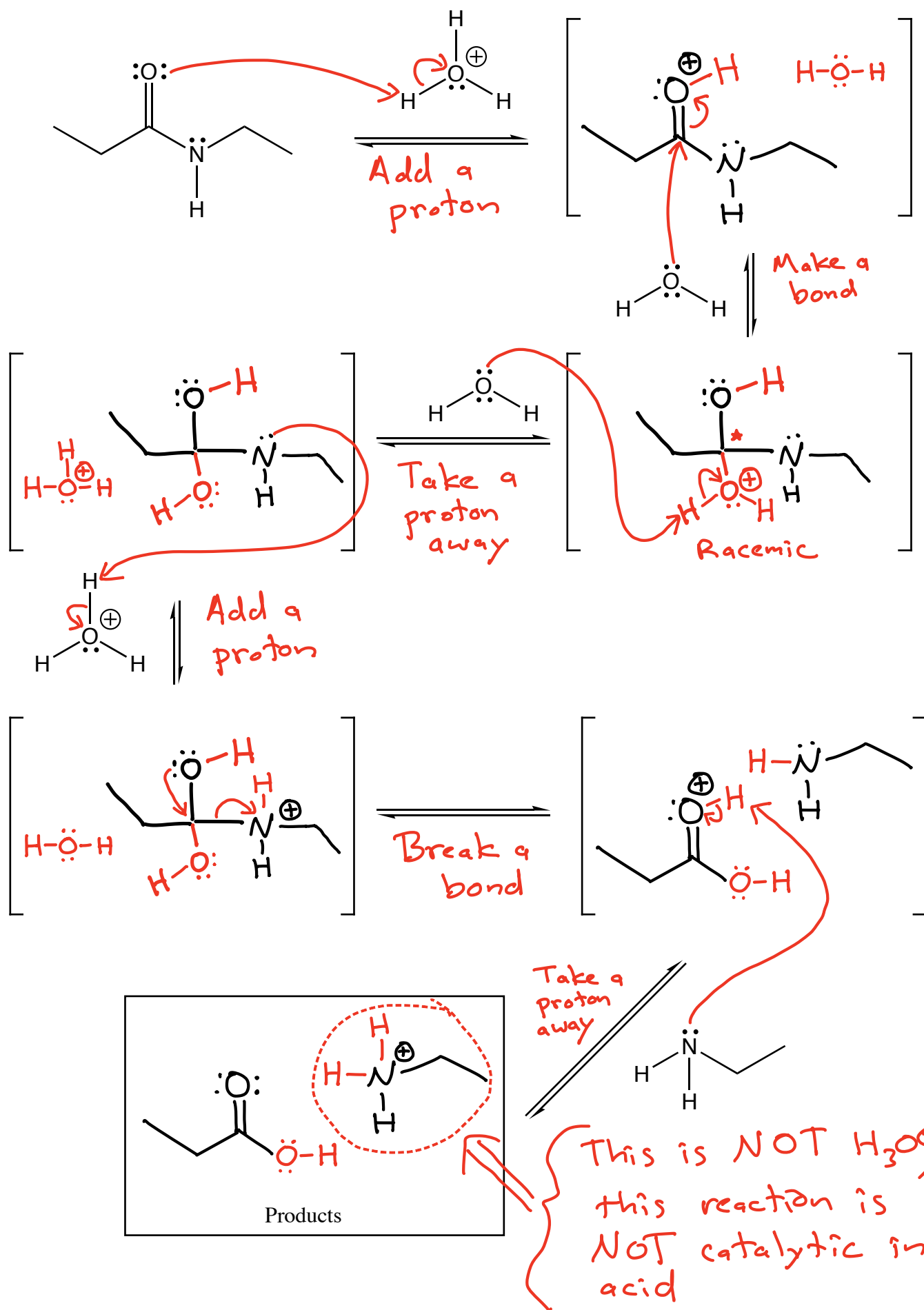
Driving force \rightarrow converts



More stable anion
 \rightarrow favored \rightarrow MOTIVE

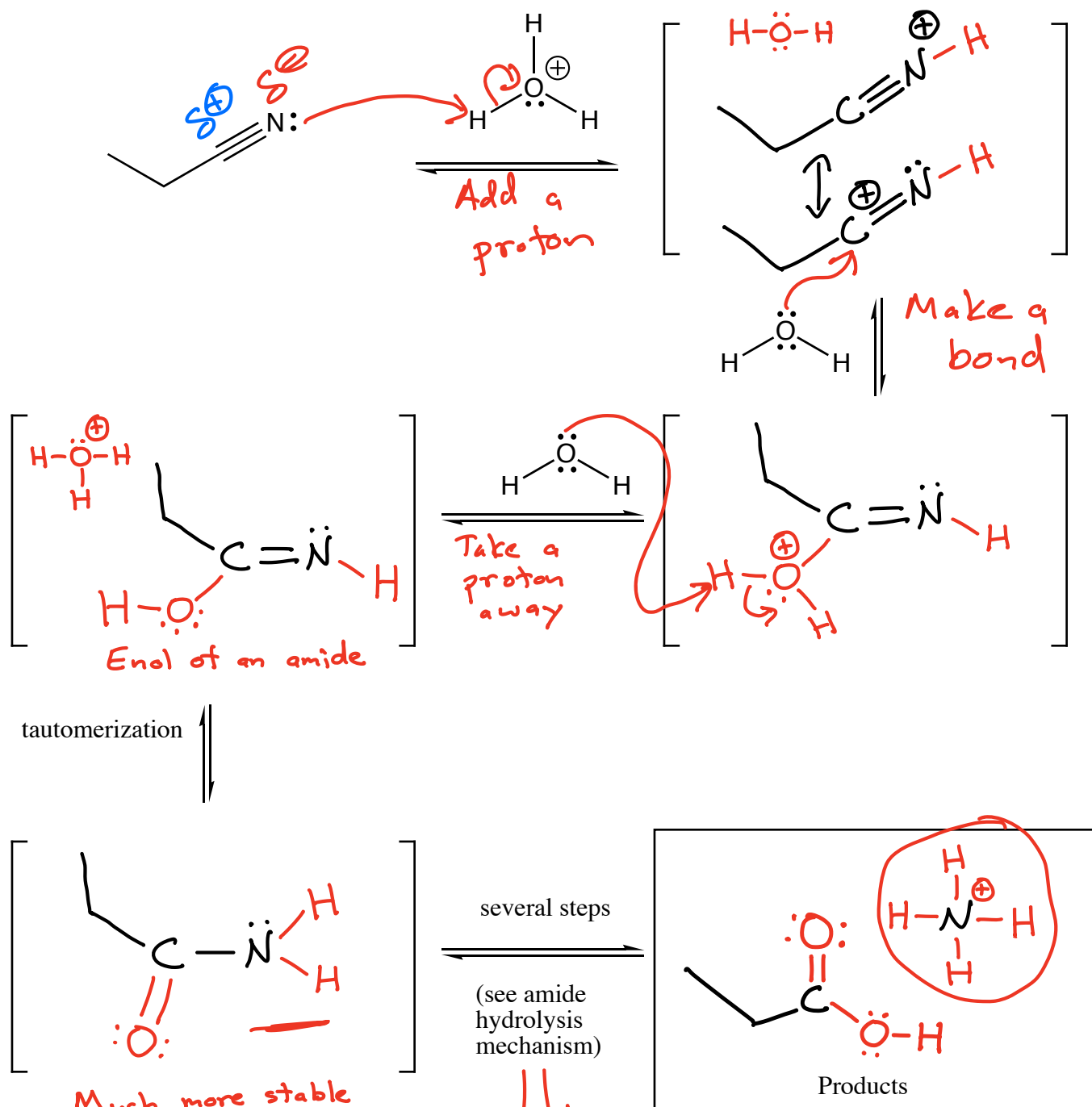


Acid Promoted Amide Hydrolysis



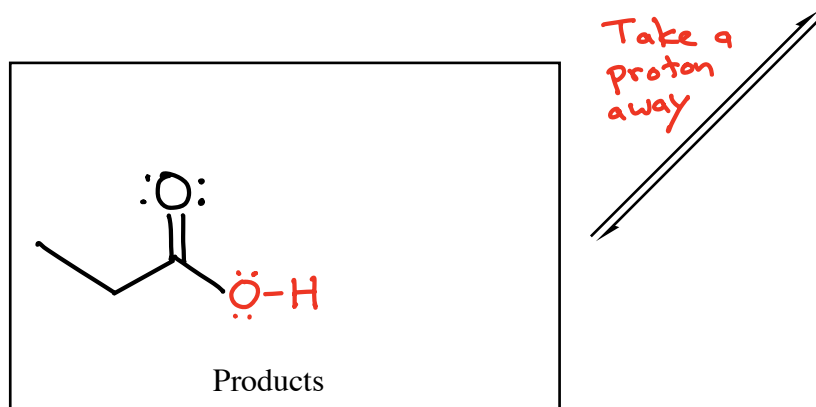
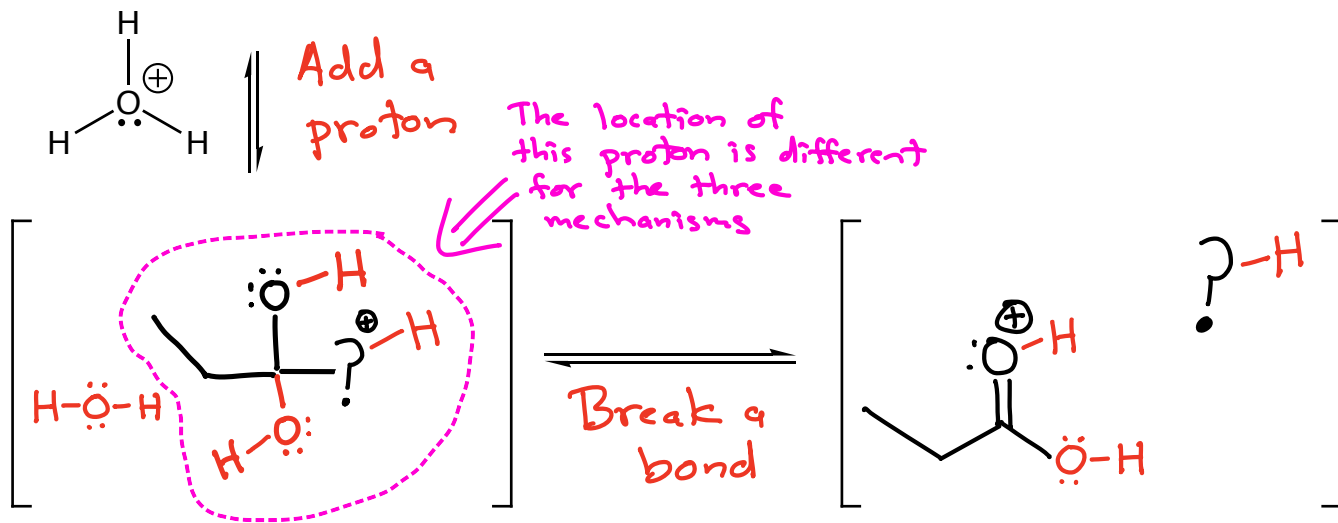
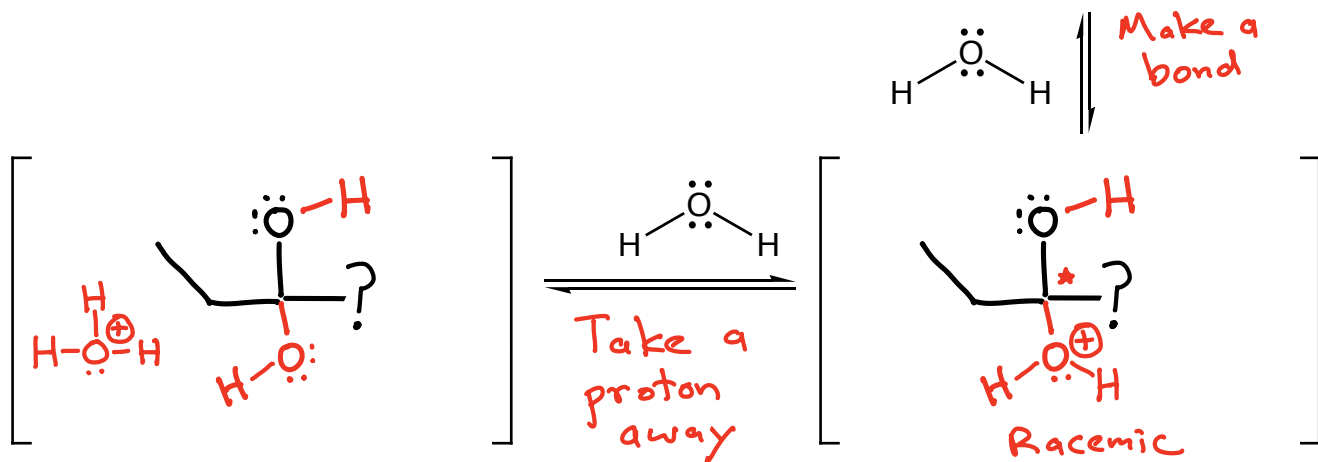
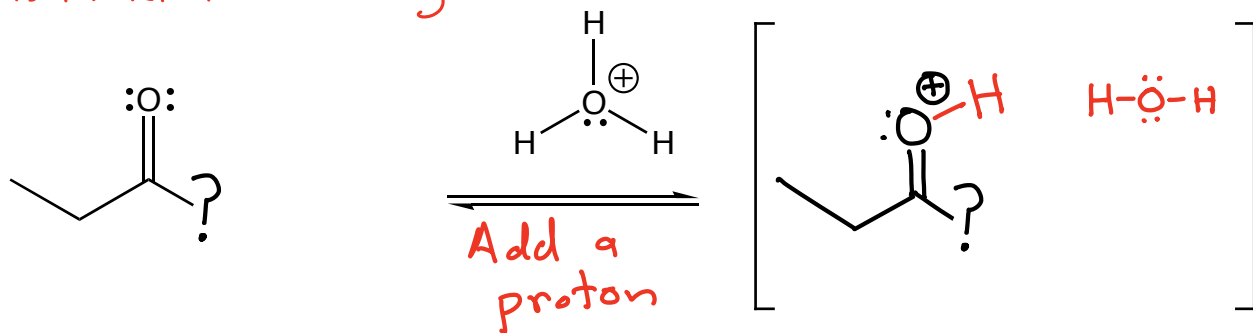


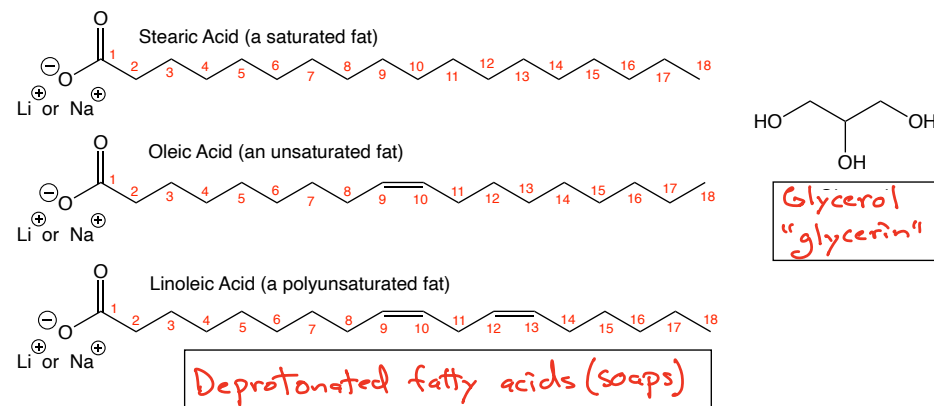
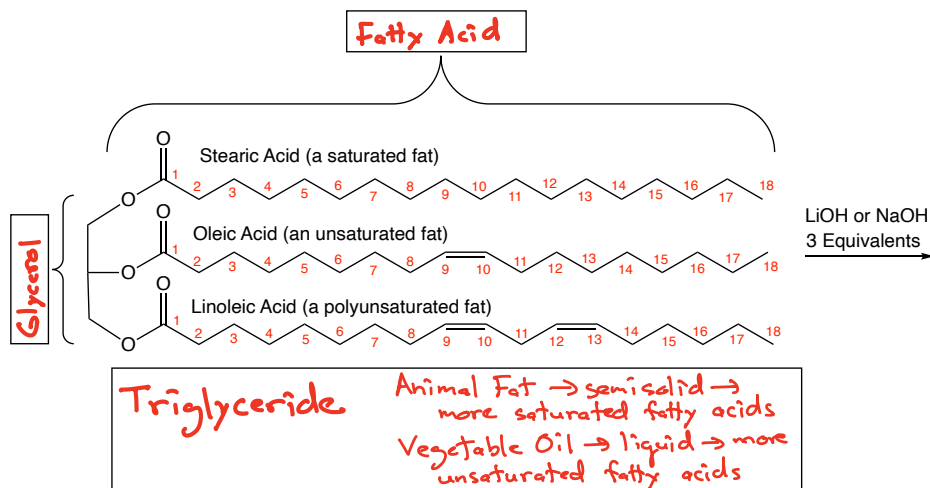
Acid Promoted Nitrile Hydrolysis



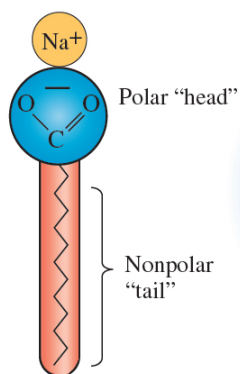
These conditions
 are strong enough
 to hydrolyze
 amides according
 to the mechanism
 we saw as "Acid
 Promoted Hydrolysis
 of an Amide"

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!"

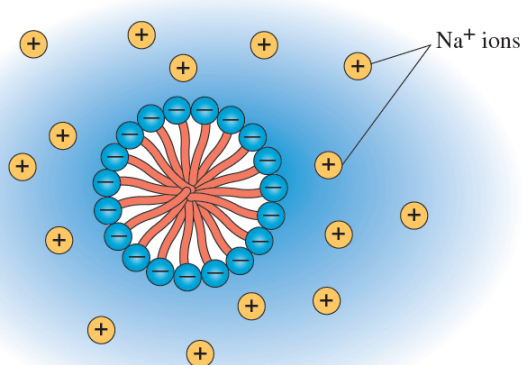




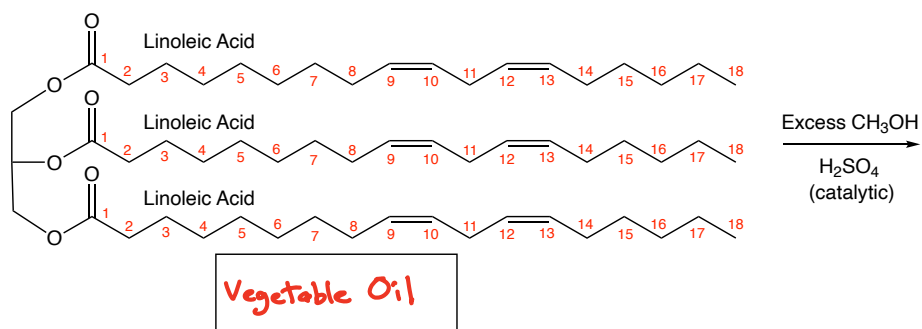
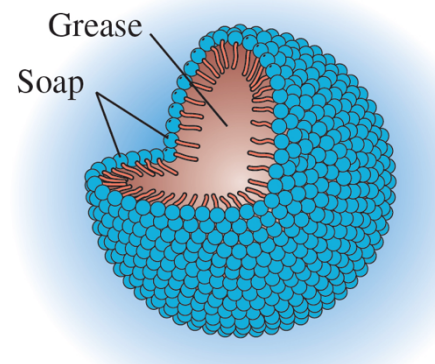
(a) A soap

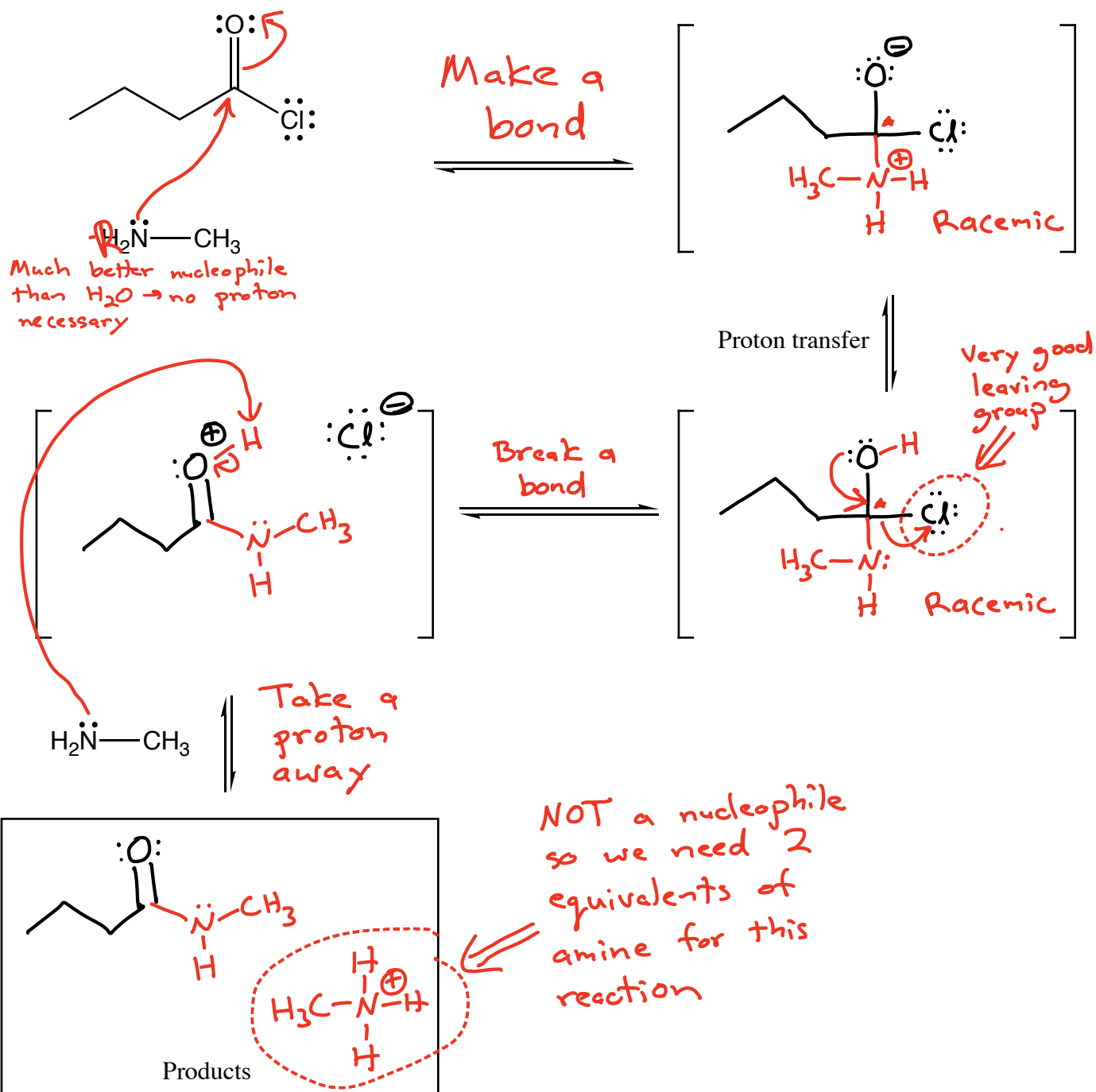
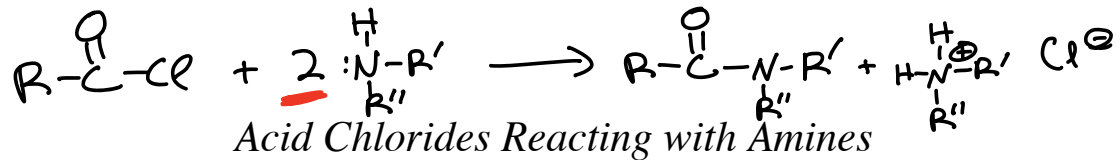


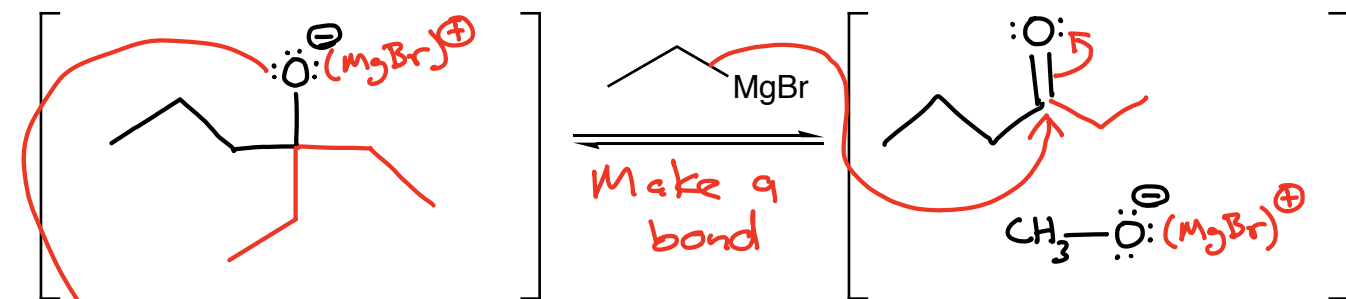
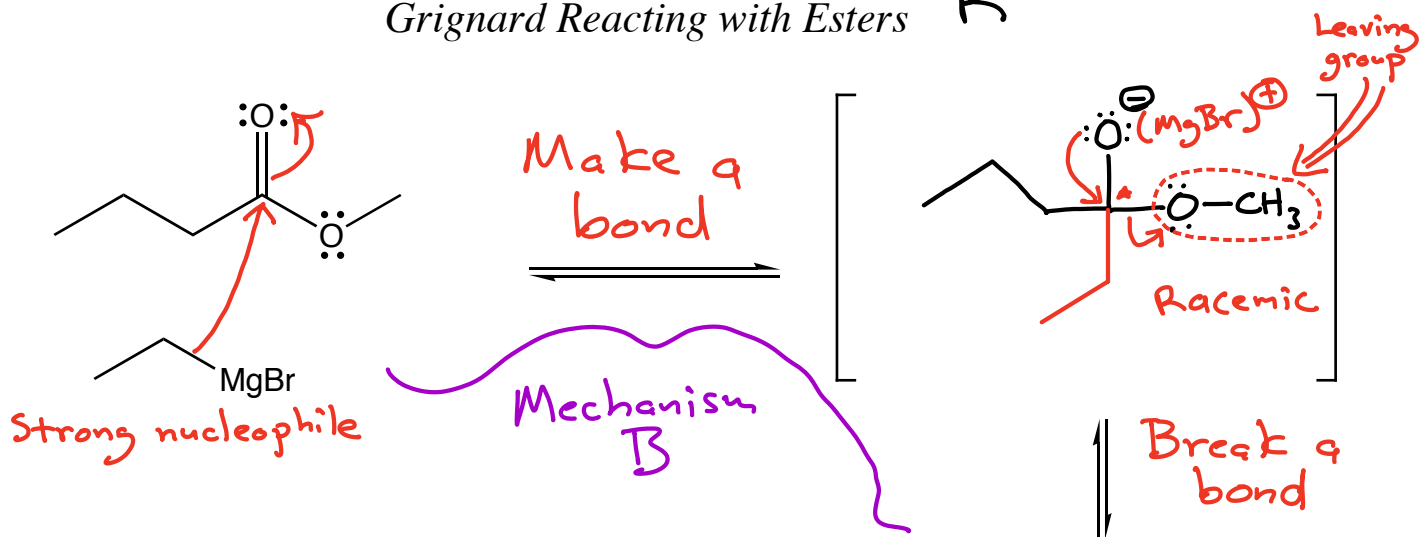
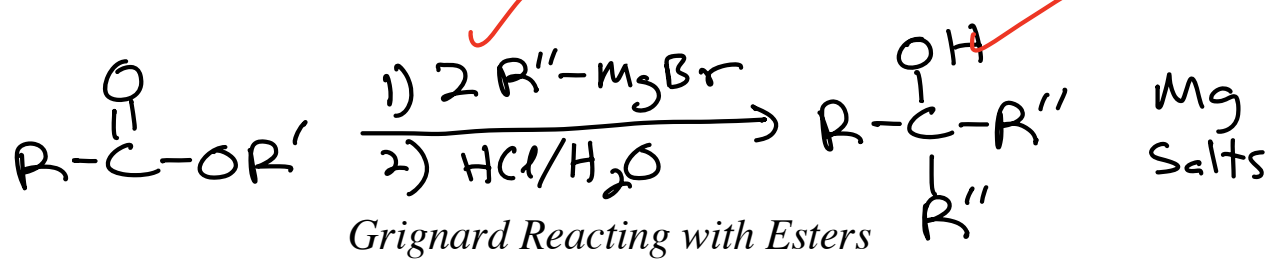
(b) Cross section of a soap micelle in water



Soap micelle with "dissolved" grease

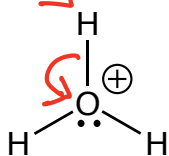




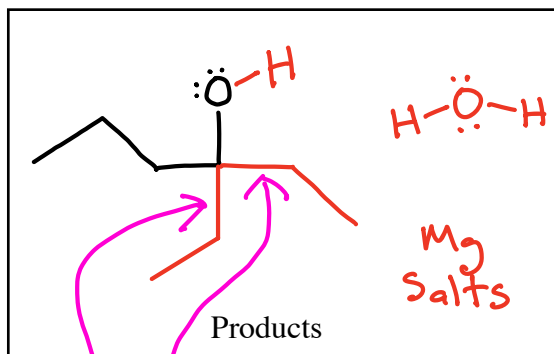


Chemist Opens Flask

2)



Add a proton



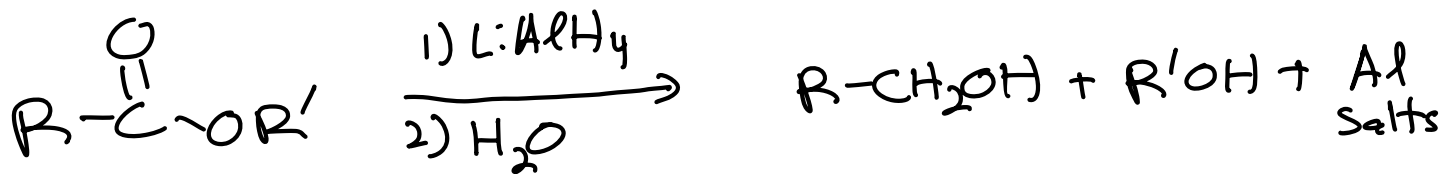
New C-C bonds

Mechanism A

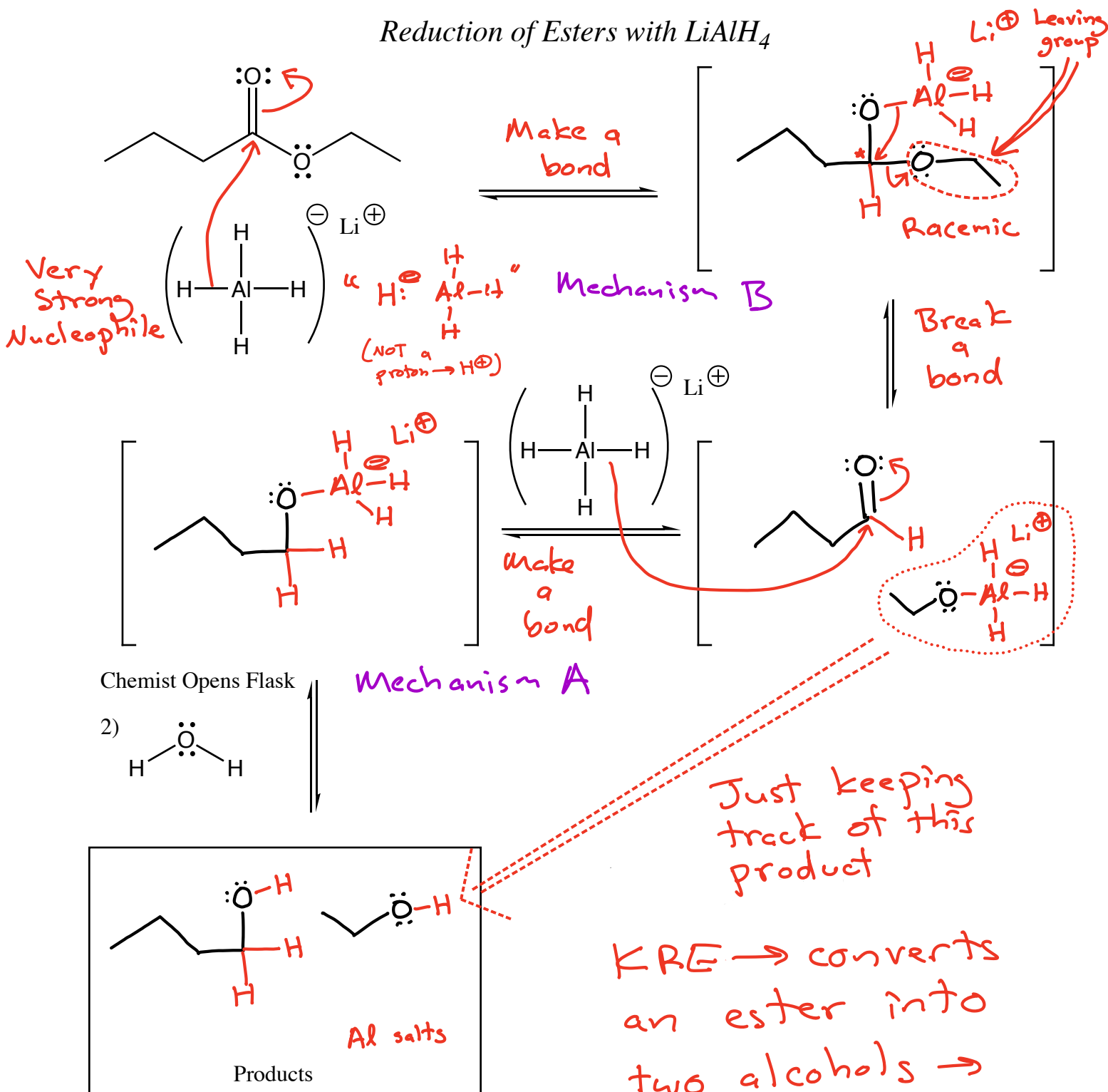
$KRE \rightarrow$ An alcohol with 2 identical new groups attached via new C-C bonds

The overall reaction mechanism is Mechanism B followed by Mechanism A

\Rightarrow Same as the next reaction!

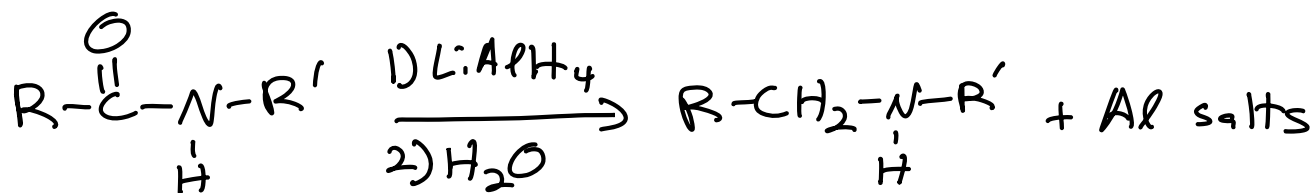


Reduction of Esters with $LiAlH_4$

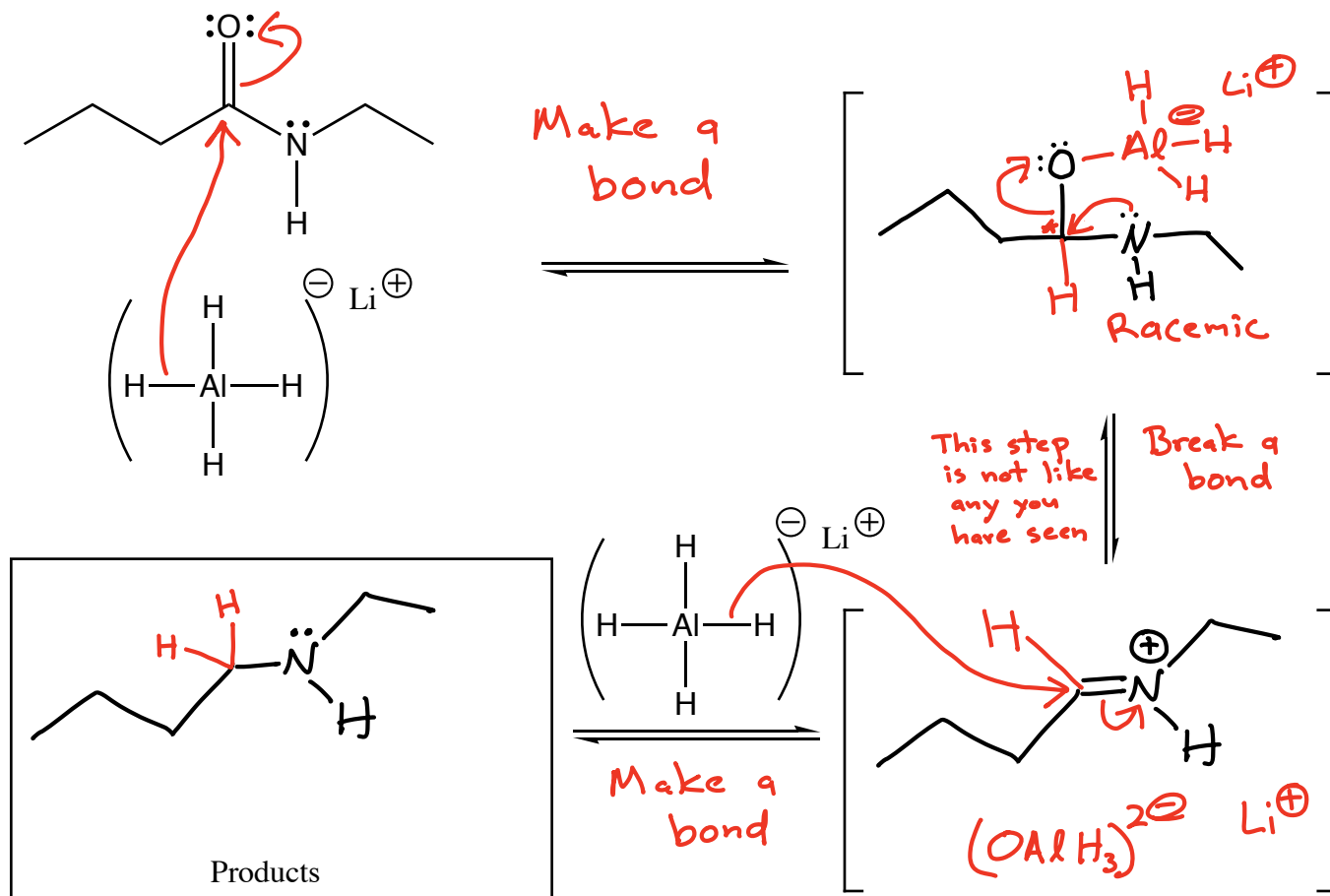


Note the extreme similarities between these last two mechanisms!

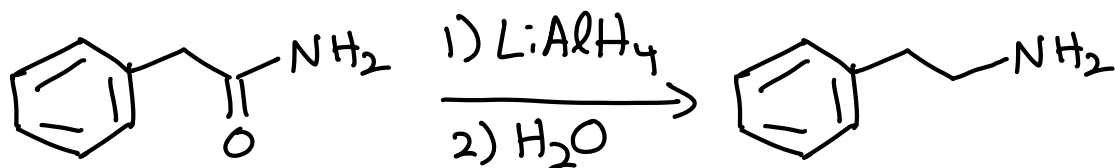
Mechanism B followed by Mechanism A just like the last reaction!



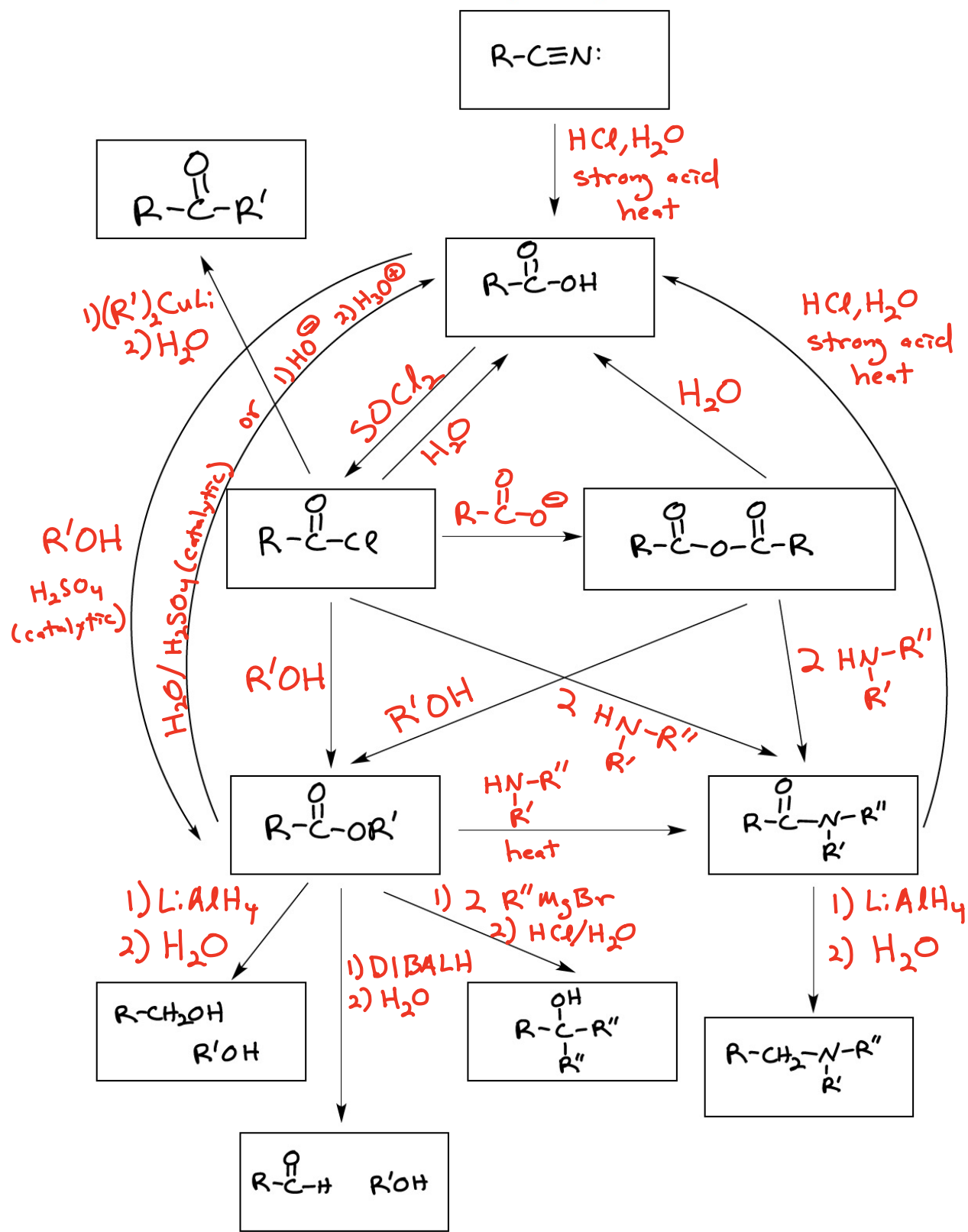
Reduction of Amides with LiAlH_4



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



Weaker bases are favored at equilibrium

Compound		pK _a	
	H-Cl	-7	Strongest Acid (Weakest conjugate base)
Carboxylic acids*	$\text{R}-\text{CO}-\text{H}$	3-5	
β-Dicarbonyls*	$\text{RC}-\text{CH}_2-\text{CR}'$	10	
β-Ketoesters*	$\text{RC}-\text{CH}_2-\text{COR}'$	11	
β-Diesters*	$\text{ROC}-\text{CH}_2-\text{COR}'$	13	
Water	HOH	15.7	
Alcohols	RCH_2OH	15-19	
Acid chlorides*	RCH_2-COCl	16	
Aldehydes*	RCH_2-CHO	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	$\text{R}_2\text{C}=\text{CH}_2$	44	
Alkanes	$\text{CH}_3\text{CH}_2-\text{H}$	51	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_a 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_a) is a weaker base.

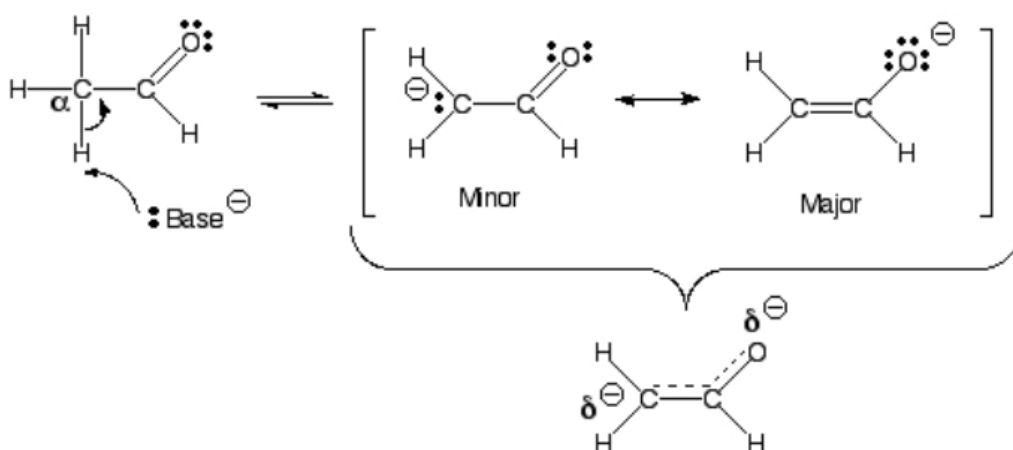
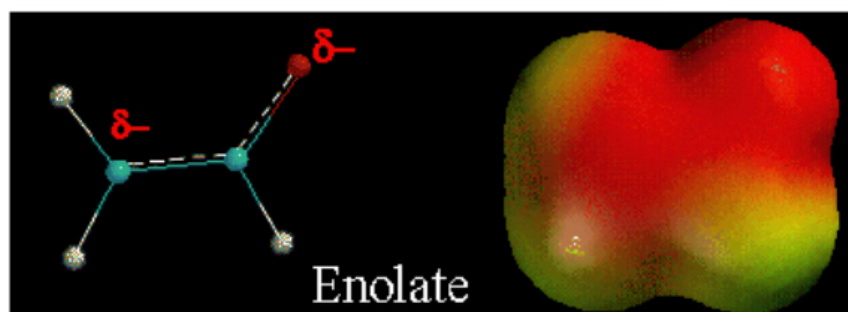
D) Check the pK's of the conjugate acid of the bases on either side of the equation. Lower pK_a value corresponds to stronger acid of the conjugate acid, and thus weaker conjugate base. The base with a stronger conjugate acid (lower pK_a value) will be the weaker base and will be favored at equilibrium.

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.

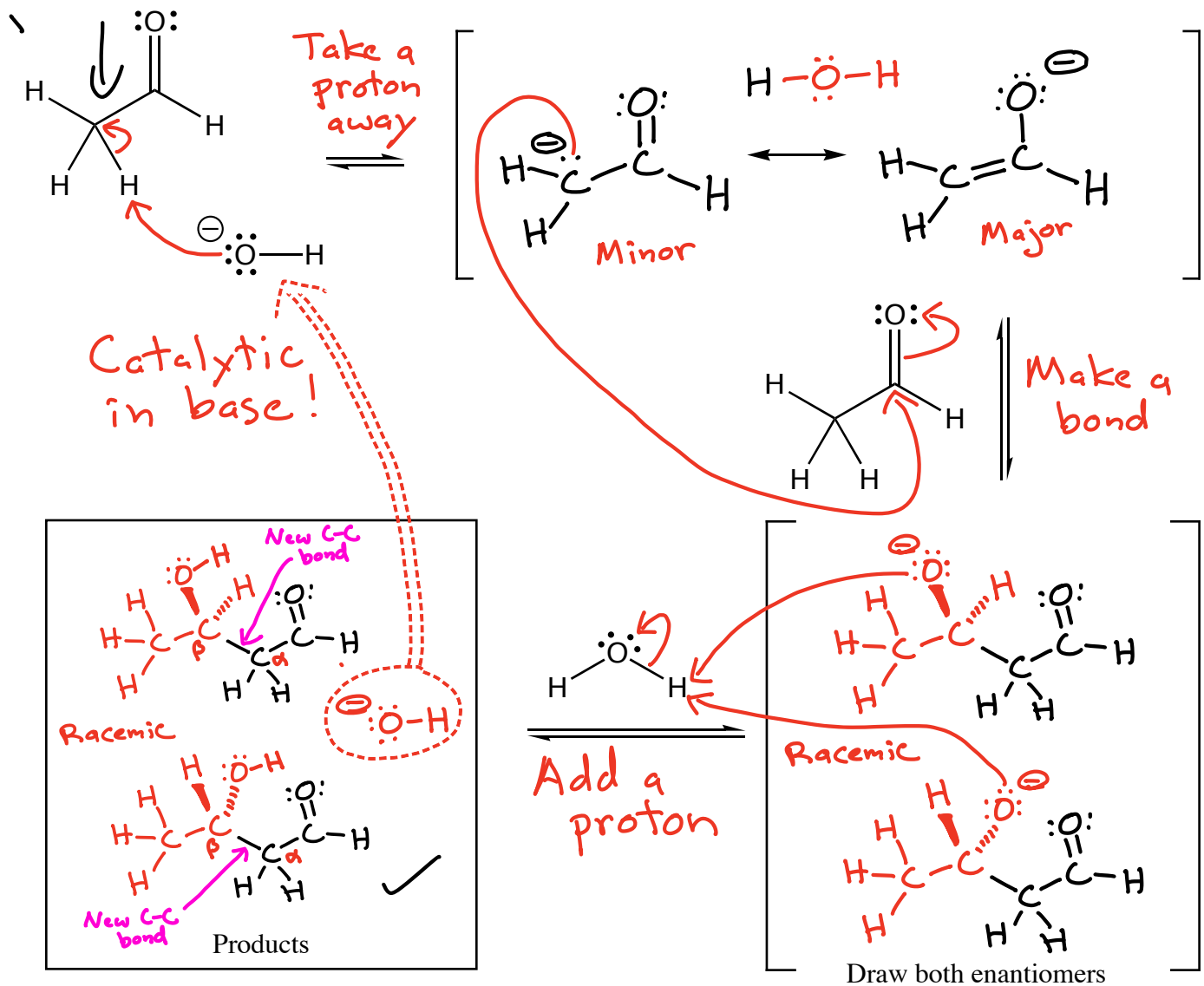
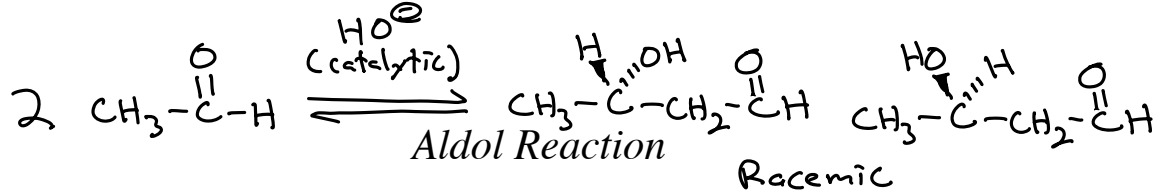
F) Above is a pK_a table that we will refer to often.

*These have resonance stabilized anions

Enolates as nucleophiles



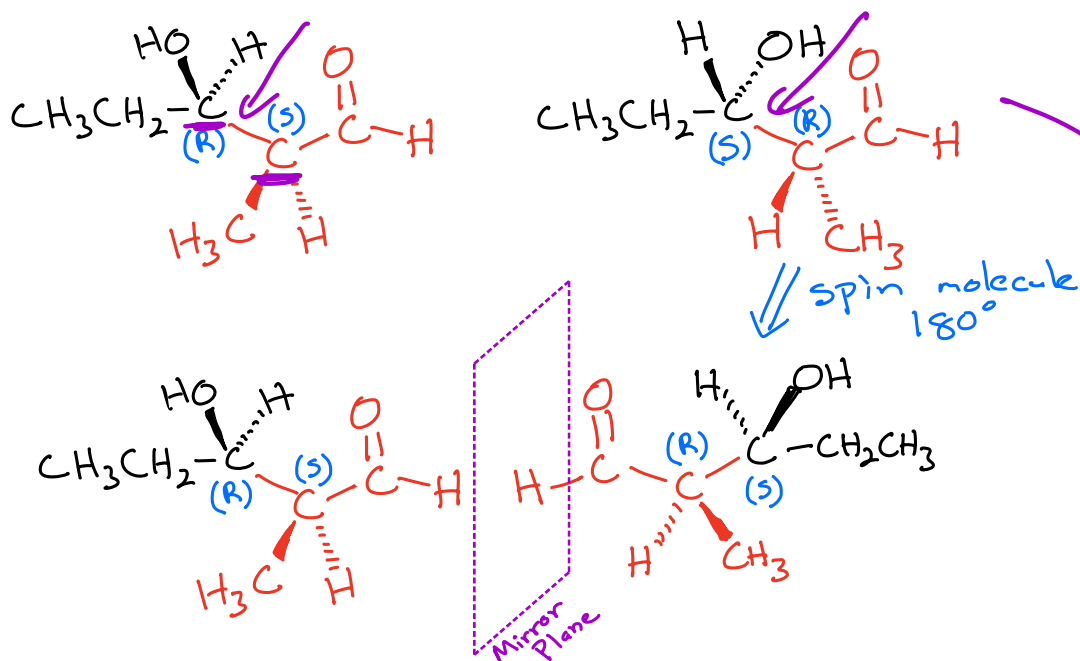
- A) Enolates are resonance stabilized, with a partial negative charge on carbon and oxygen. ✓
- B) Enolates are nucleophiles, so they could react at either the carbon atom or oxygen atom. The partial negative charges give them the **opportunity** to react at either the carbon or oxygen.
- C) Reaction 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.**



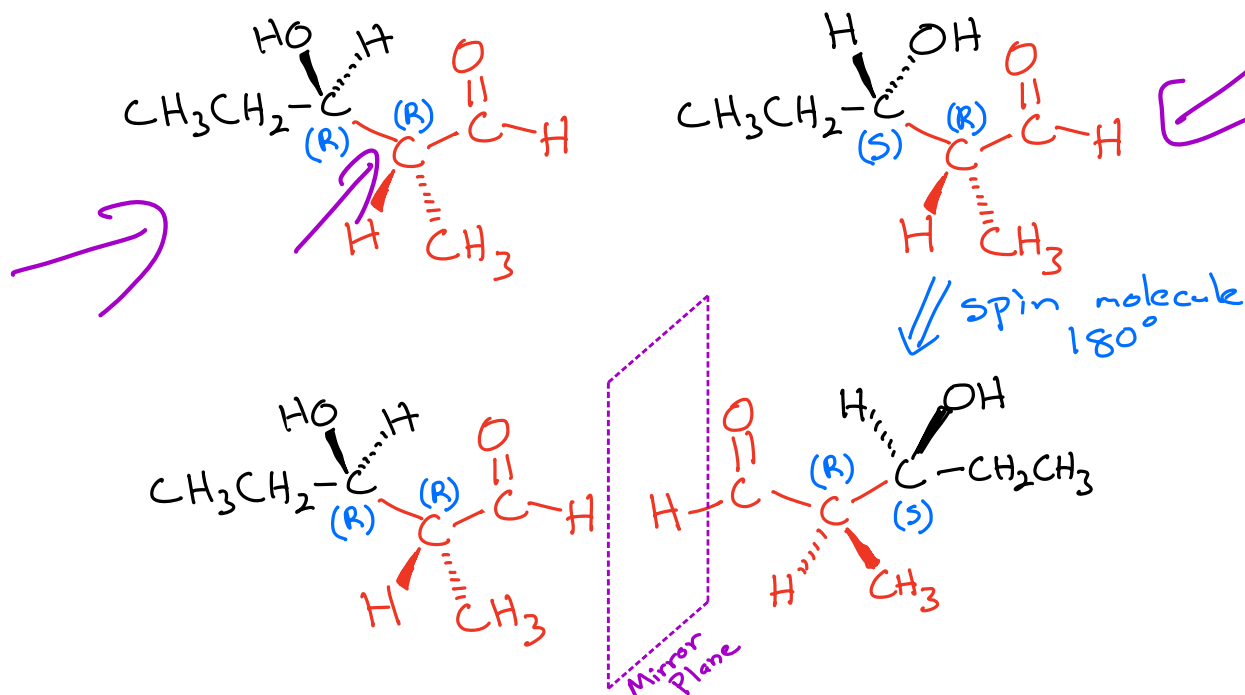
KRE \rightarrow β -hydroxy aldehyde
with a new C-C
bond between the
aldehyde α and β
carbons

Mechanism
A

Enantiomers or Diastereomers?

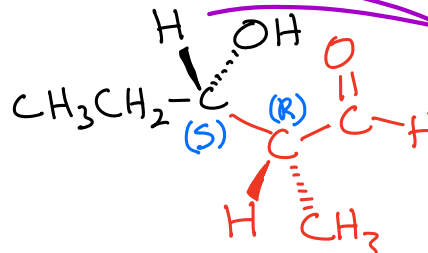
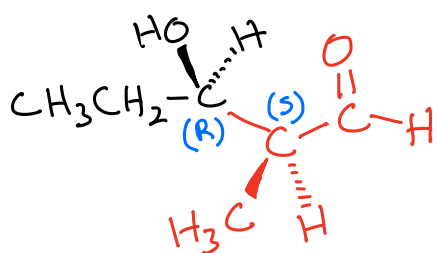


Enantiomers (Section 3.2) Stereoisomers that are nonsuperposable mirror images of each other; refers to a relationship between pairs of objects.

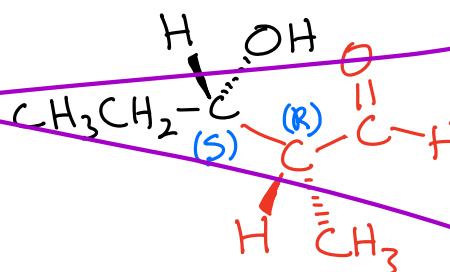
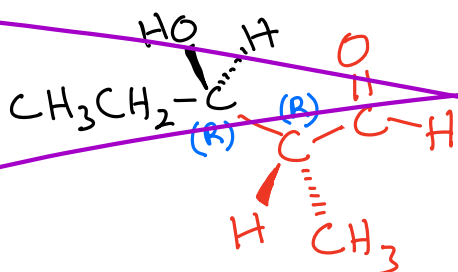


Diastereomers (Section 3.4A) Stereoisomers that are not mirror images of each other; refers to relationships among two or more objects.

Which pair of molecules
could be a racemic mixture?

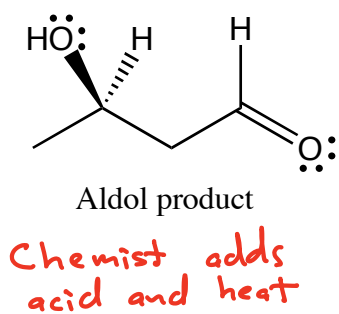


OR

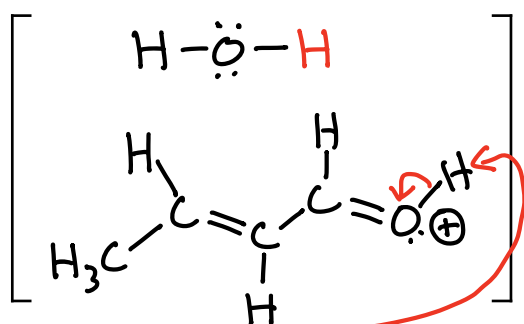
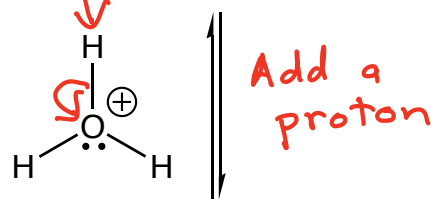
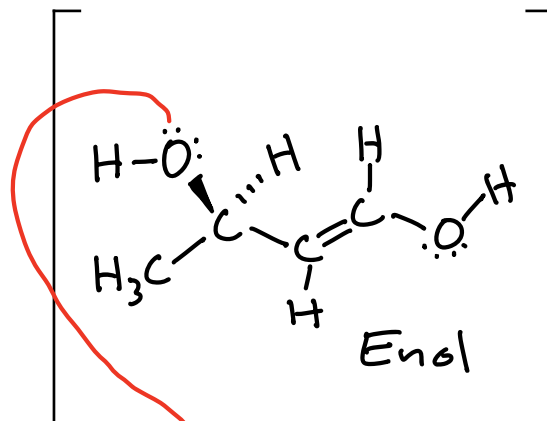


Racemic mixture (Section 3.7C) A mixture of equal amounts of two enantiomers.

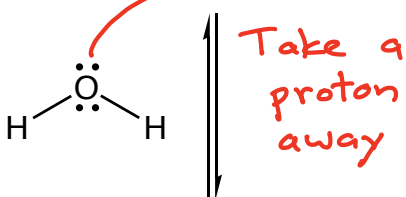
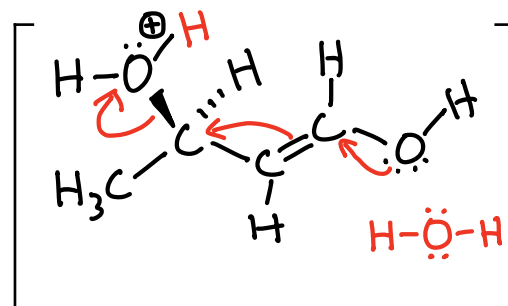
Acid catalyzed dehydration



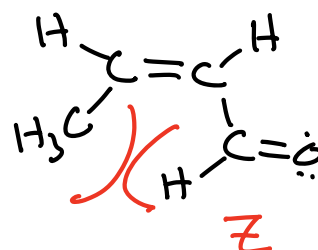
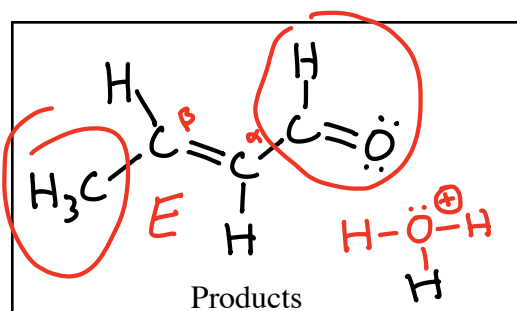
tautomerization



Break a bond



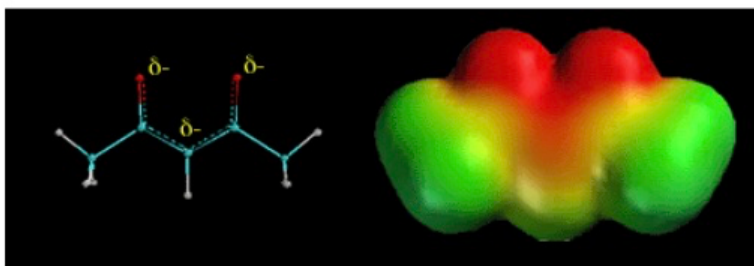
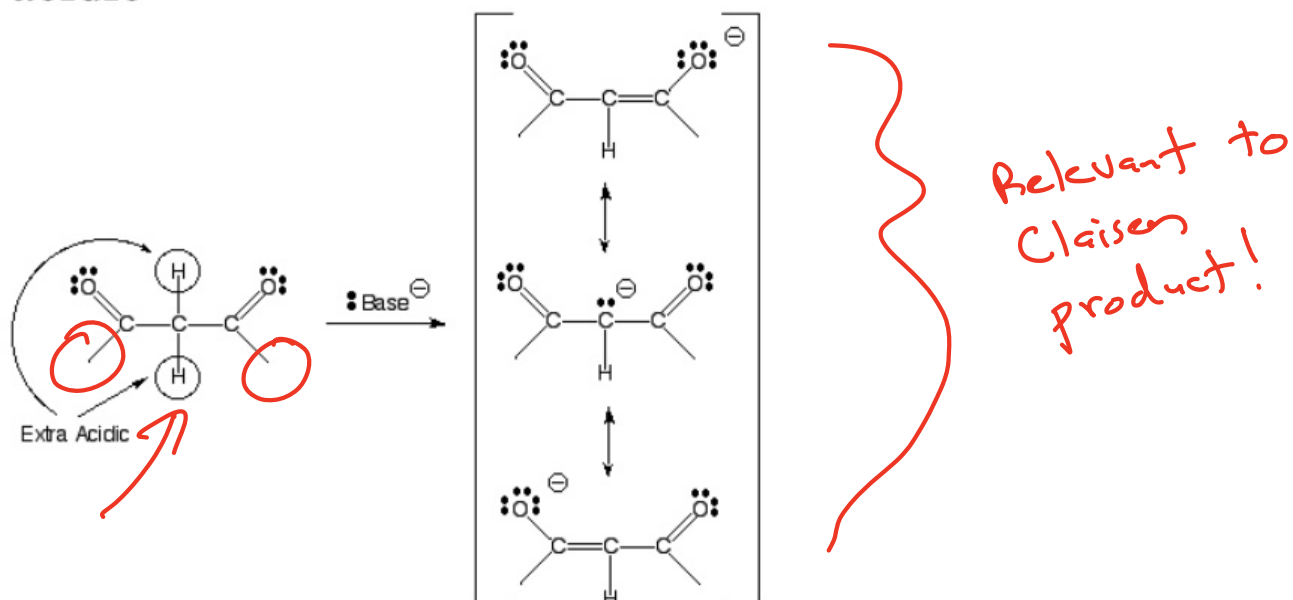
KRE \rightarrow α,β -unsaturated aldehyde \rightarrow the C=C is where the new C-C bond is located



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

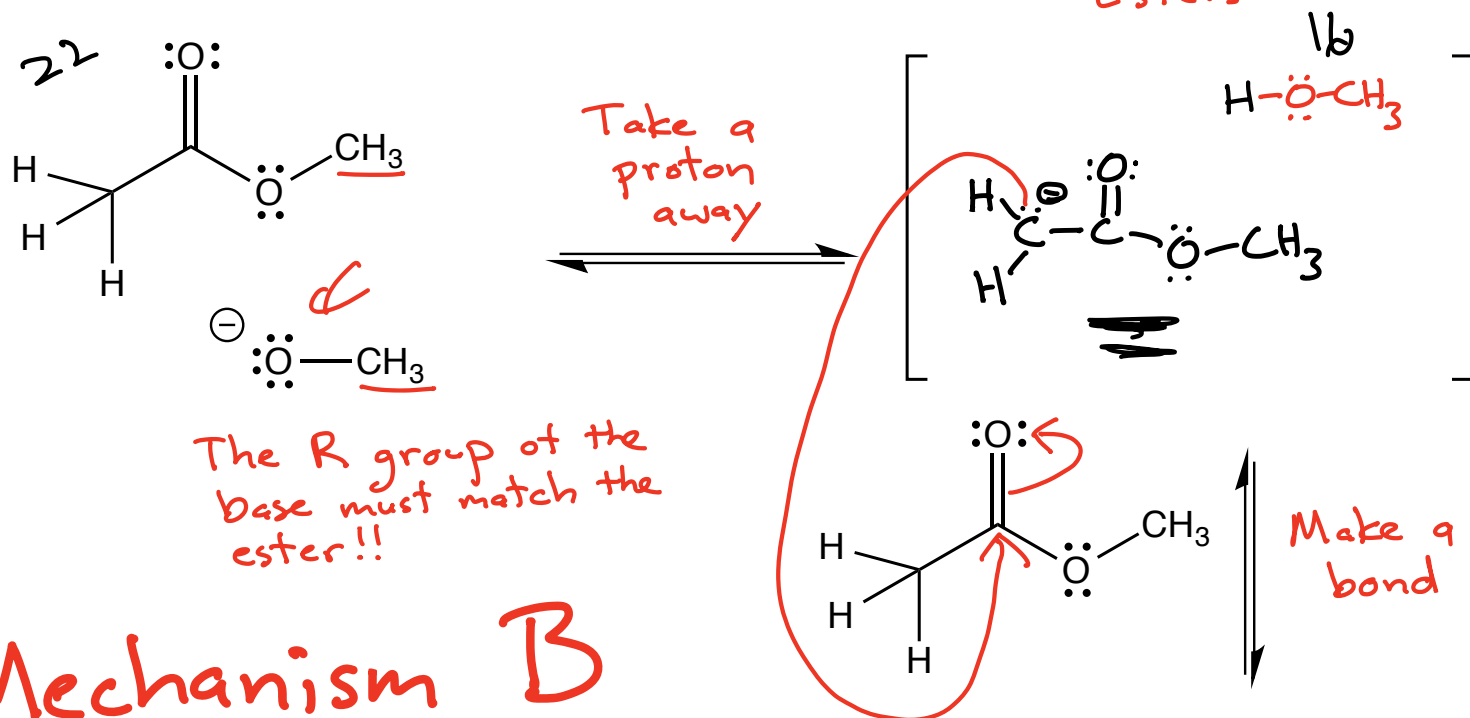
THIS IS UNIQUE TO THIS EXAMPLE
 USUALLY BOTH E AND Z ARE FORMED

Beta-dicarbonyls have alpha-hydrogens that are extra acidic

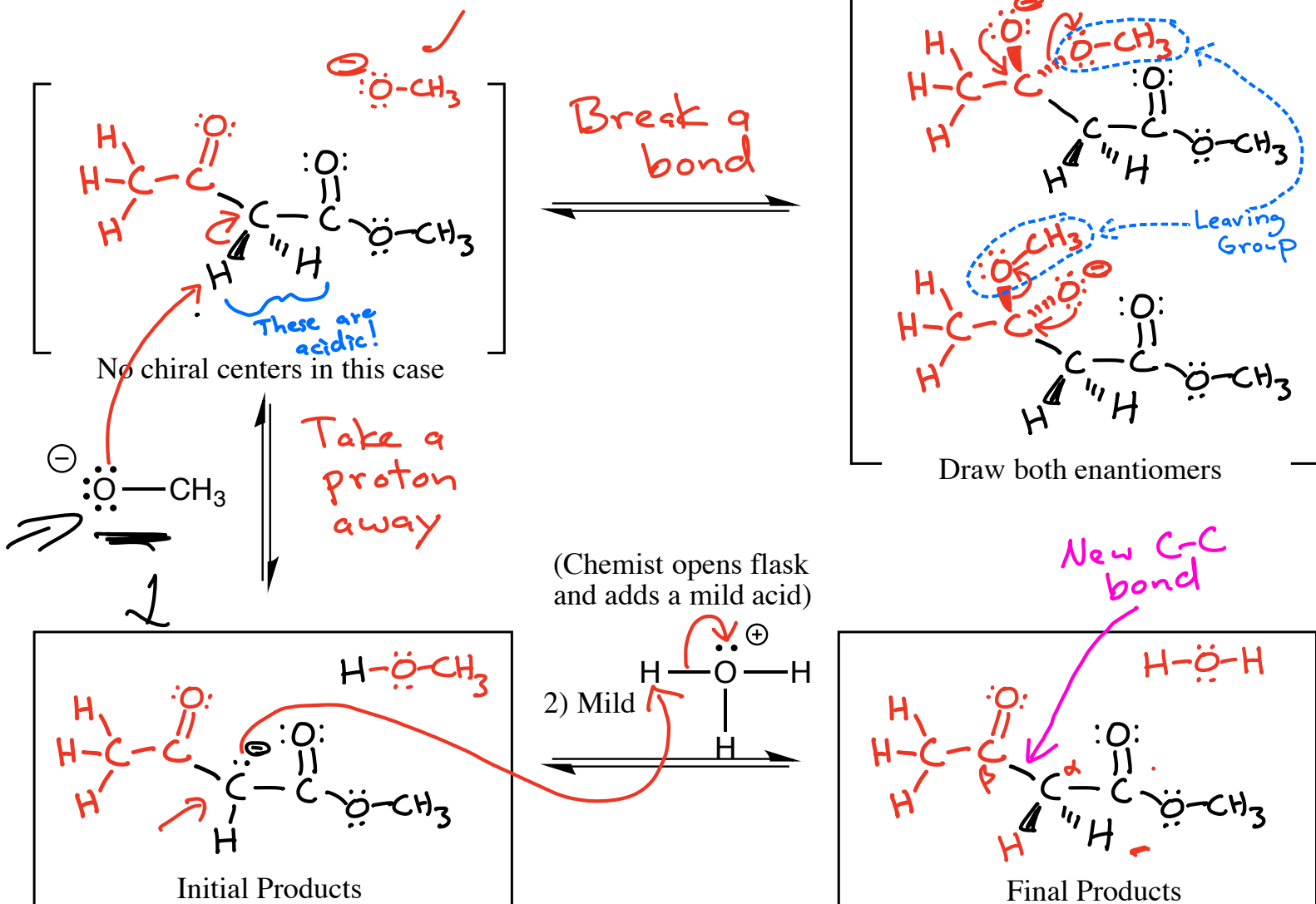


The C-H hydrogen atoms between two carbonyl groups are even more acidic than normal alpha hydrogens because the resulting anion is double resonance stabilized. The above electrostatic potential surface shows how the negative charge (red color) is spread over all three atoms as predicted by the three resonance contributing structures.

Claisen Condensation → "Aldol with Esters"

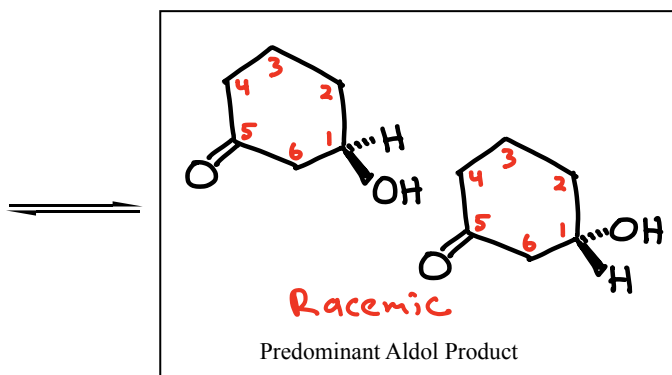
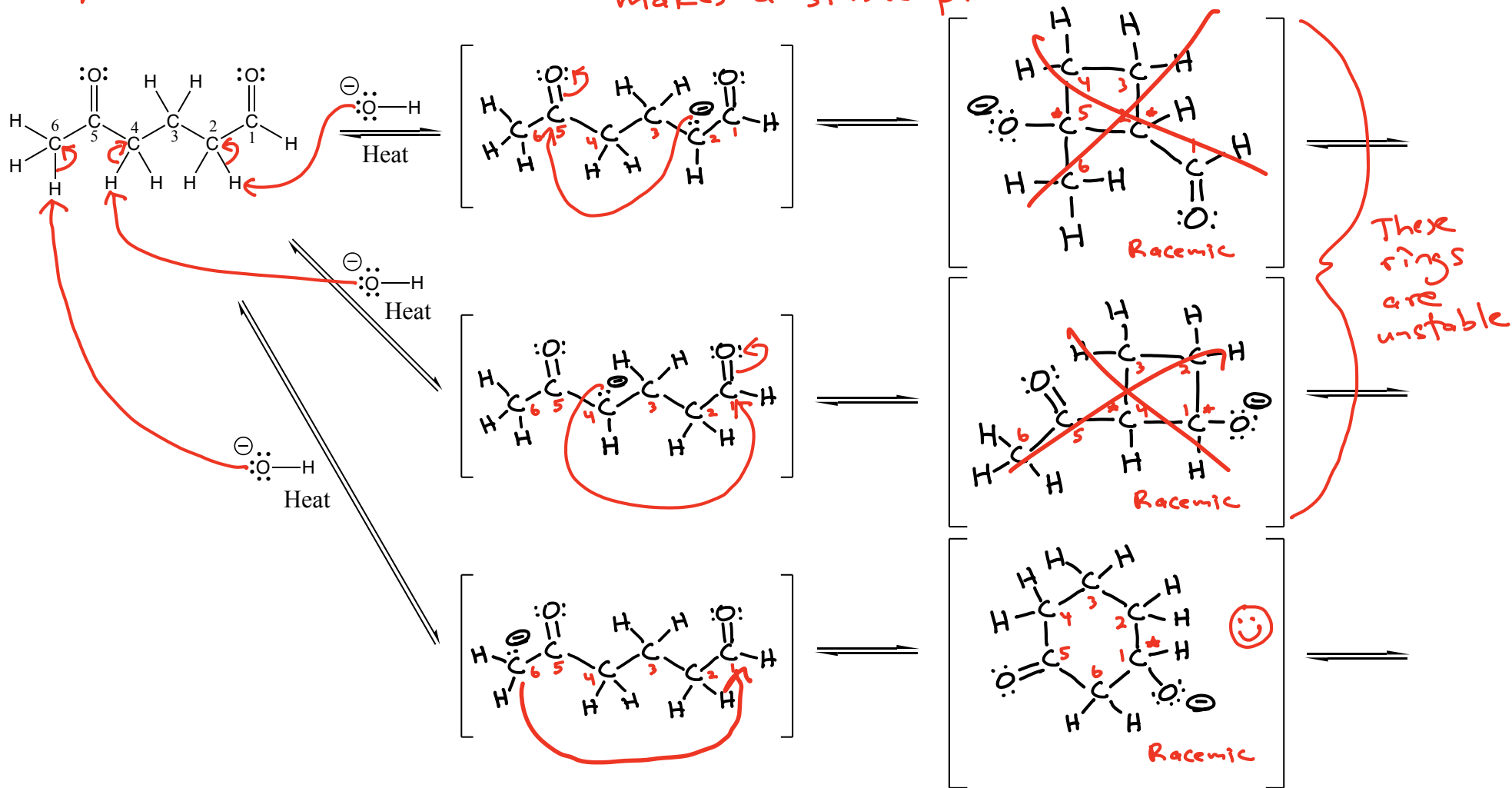


Mechanism B

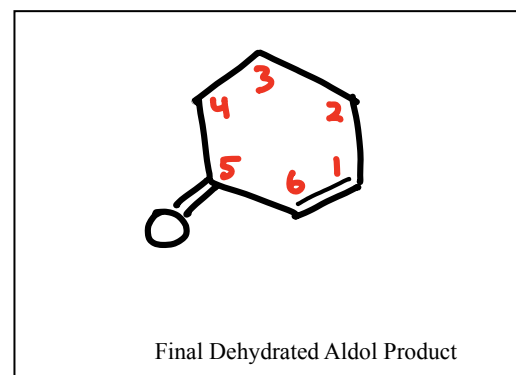


This is a much more stable anion compared to $\ominus\text{OCH}_3$, providing a strong driving force (motive) for the Claisen condensation reaction

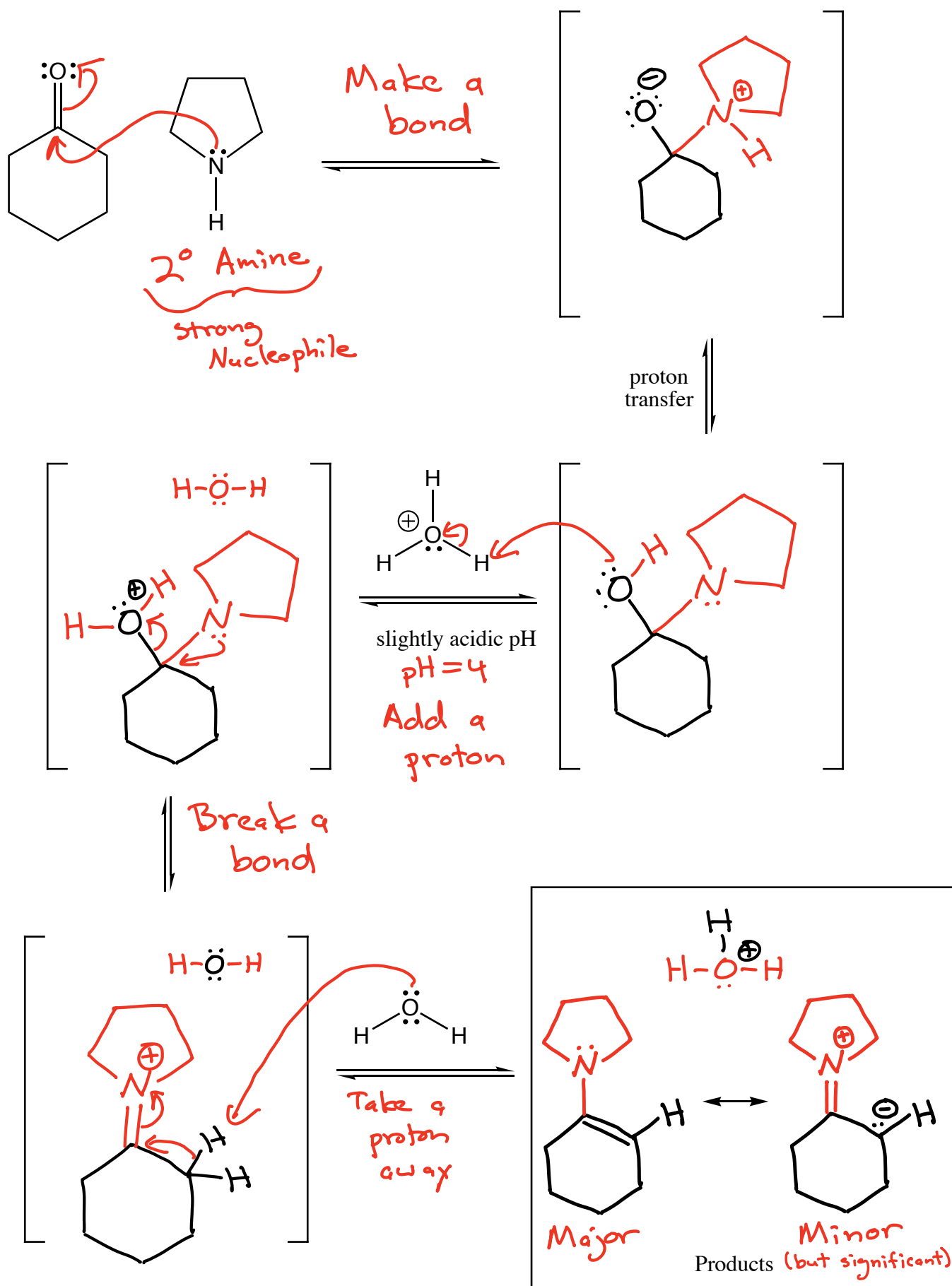
Cyclic Aldol Reaction \rightarrow 3 different enolates are possible, but only one makes a stable product



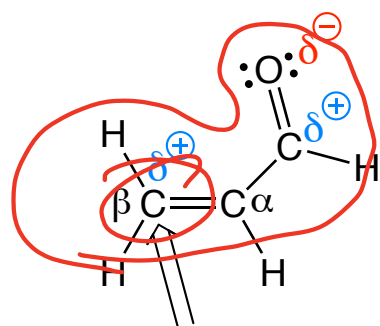
Dehydration



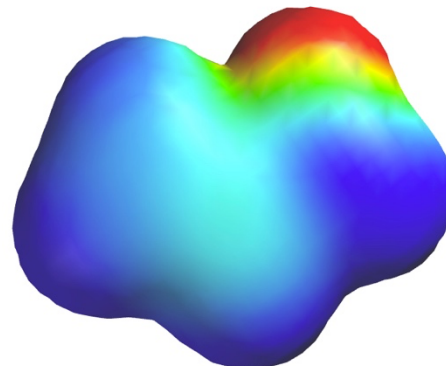
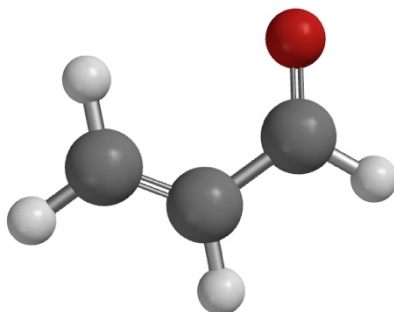
Enamine Formation



Conjugate Addition



Nucleophiles react here via conjugate addition



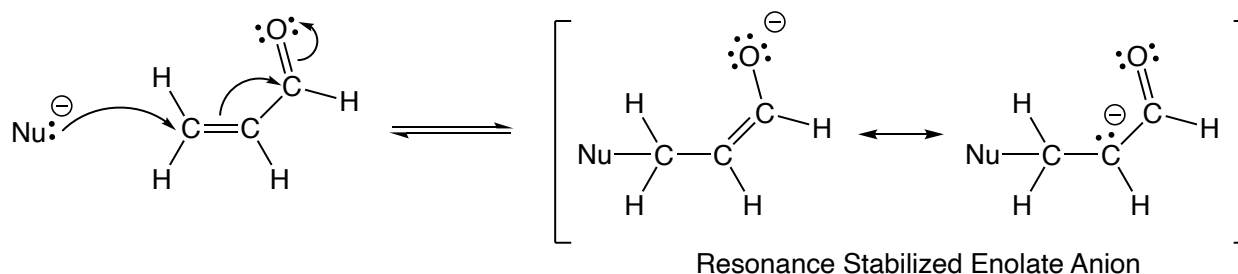
A) Alkenes adjacent to a carbonyl are conjugated and are therefore electrophilic. ✓

B) These species are called α,β unsaturated carbonyl compounds.

C) α,β unsaturated carbonyl compounds are conjugated, in that the pi electrons of the $C=C$ and $C=O$ bonds can delocalize over all four atoms. This lends some degree of extra stabilization to these species, because [pi electrons prefer to delocalize](#).

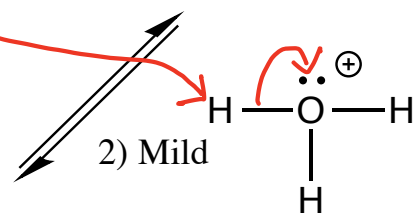
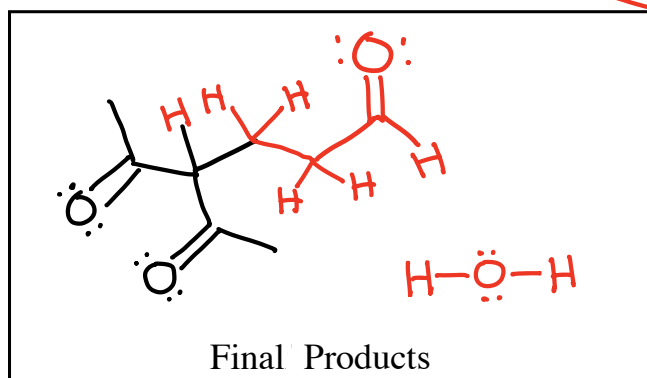
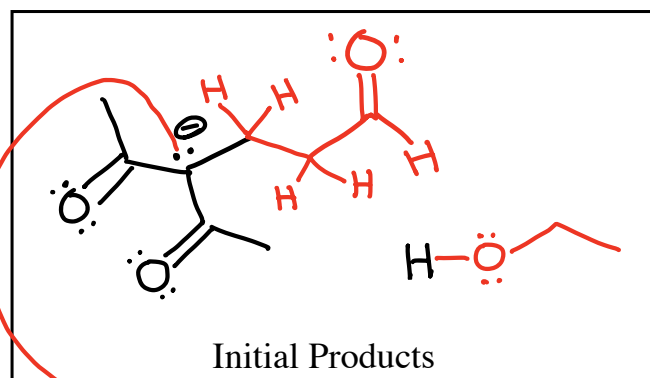
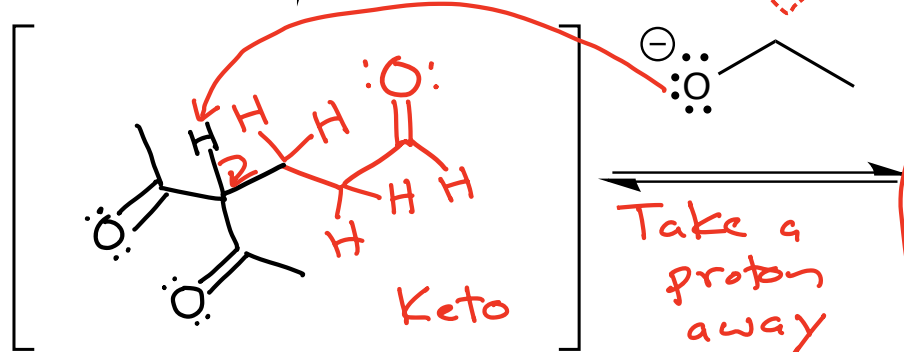
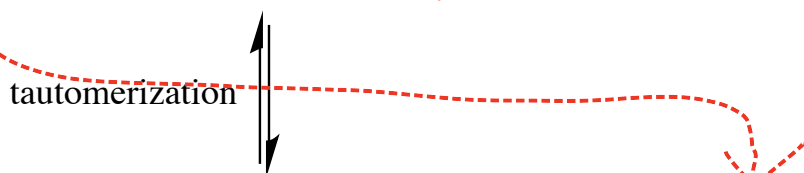
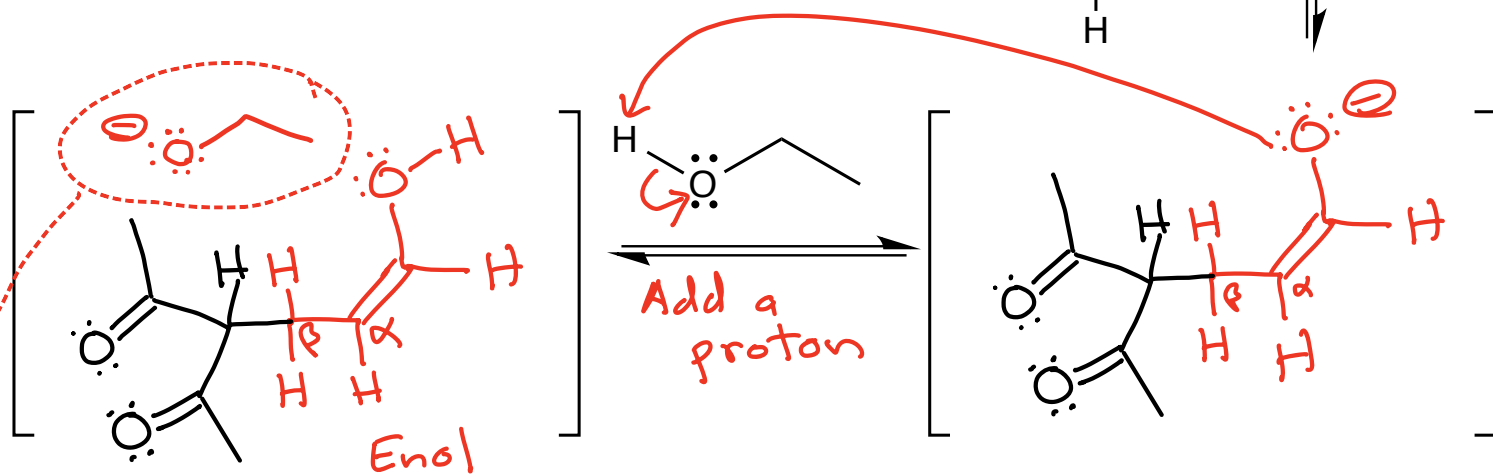
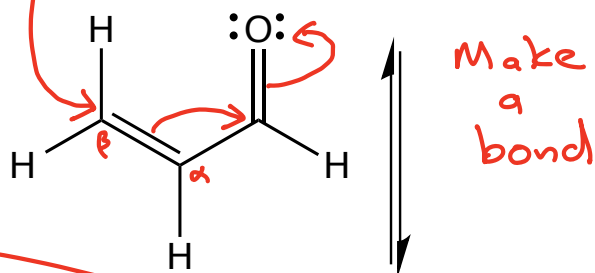
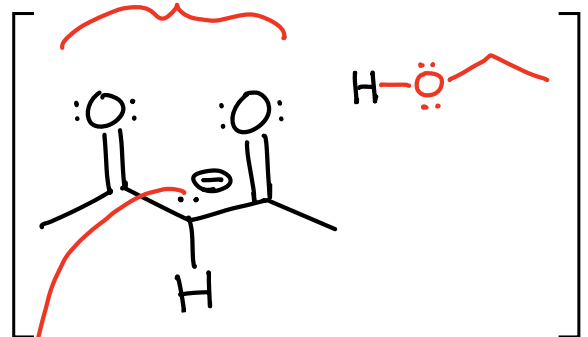
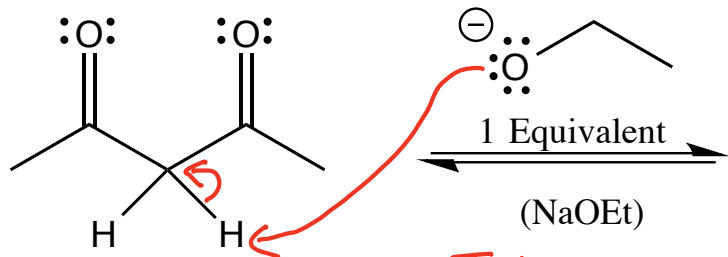
D) Nucleophiles can, however, react at the β carbon atom in a process called conjugate addition.

E) Conjugate addition is favorable because the intermediate formed is a resonance stabilized enolate, thus relatively low energy.



Michael Reaction

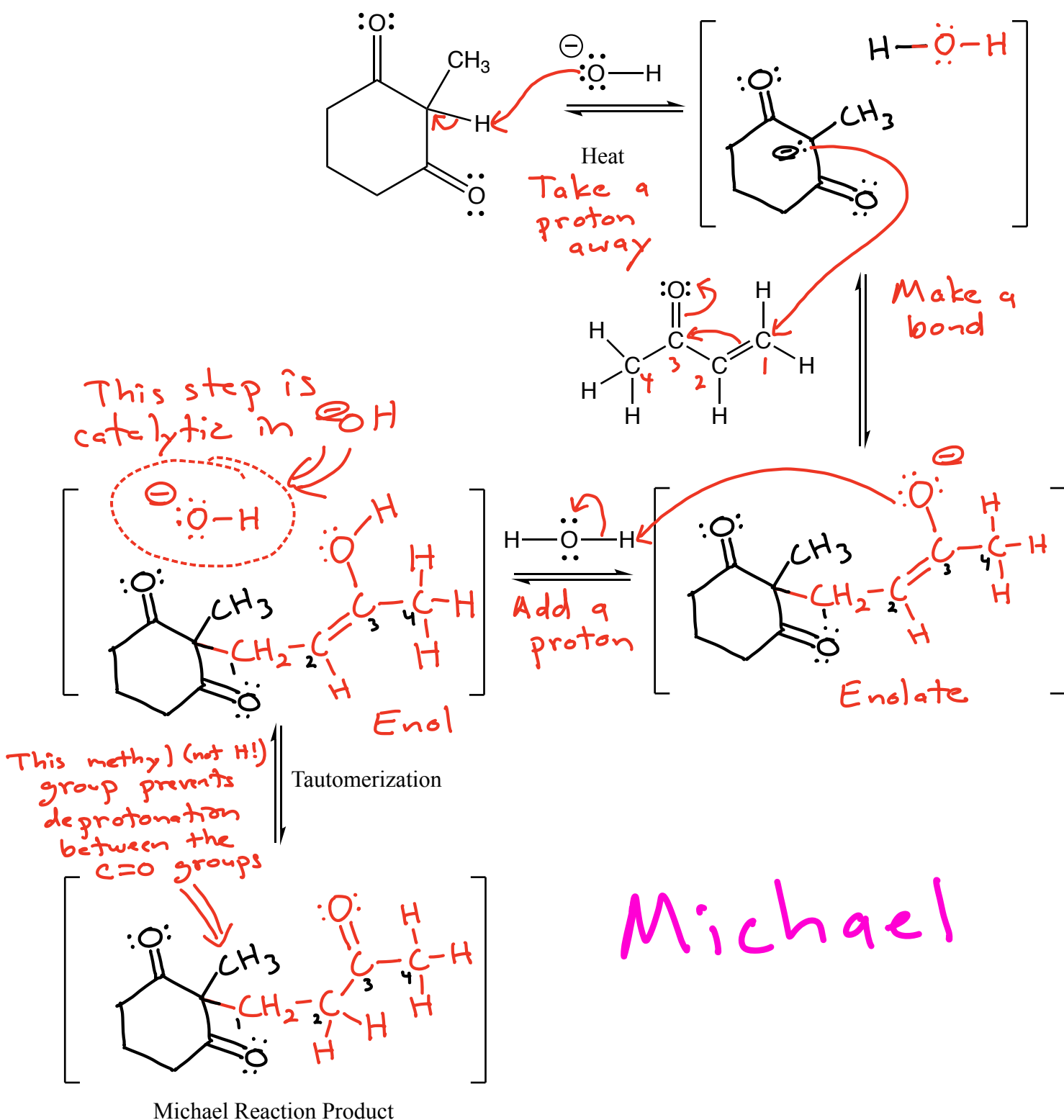
Nucleophile!



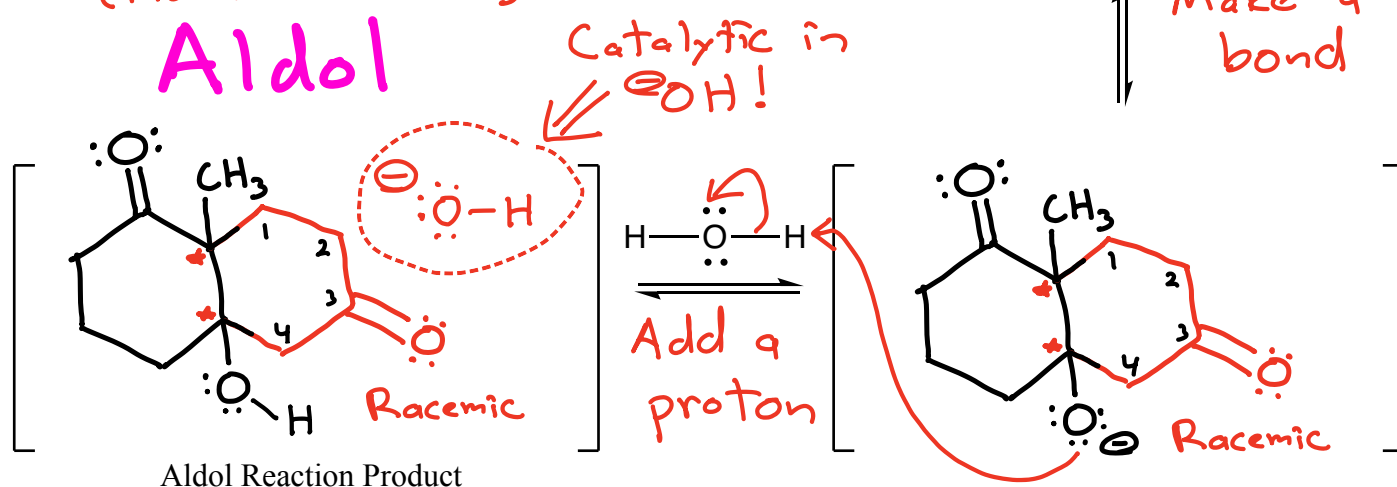
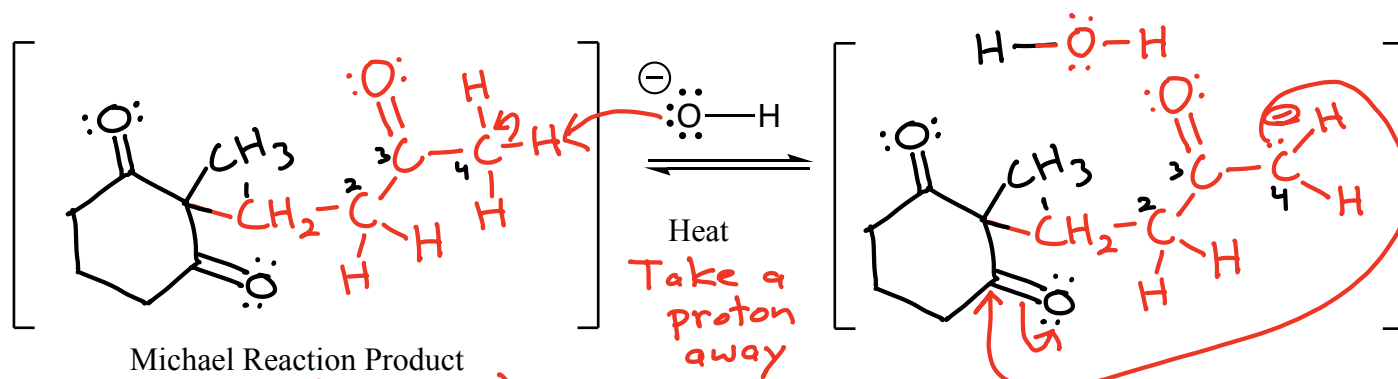
(Chemist opens flask and adds a mild acid)

Add a proton

Robinson Annulation Part 1 - Michael Reaction Steps



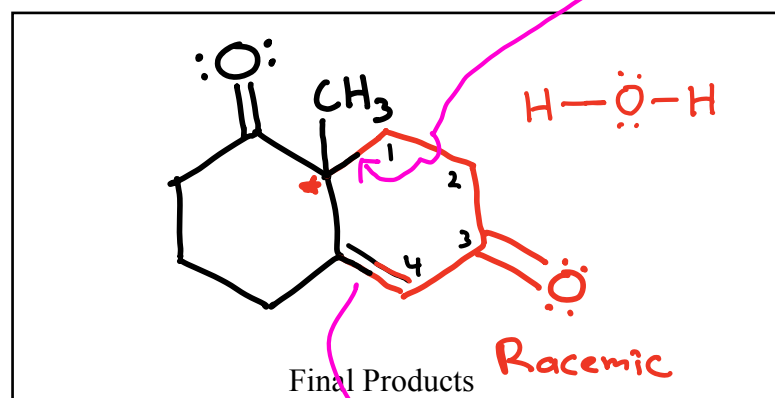
Robinson Annulation Part 2 - Aldol and Dehydration Steps

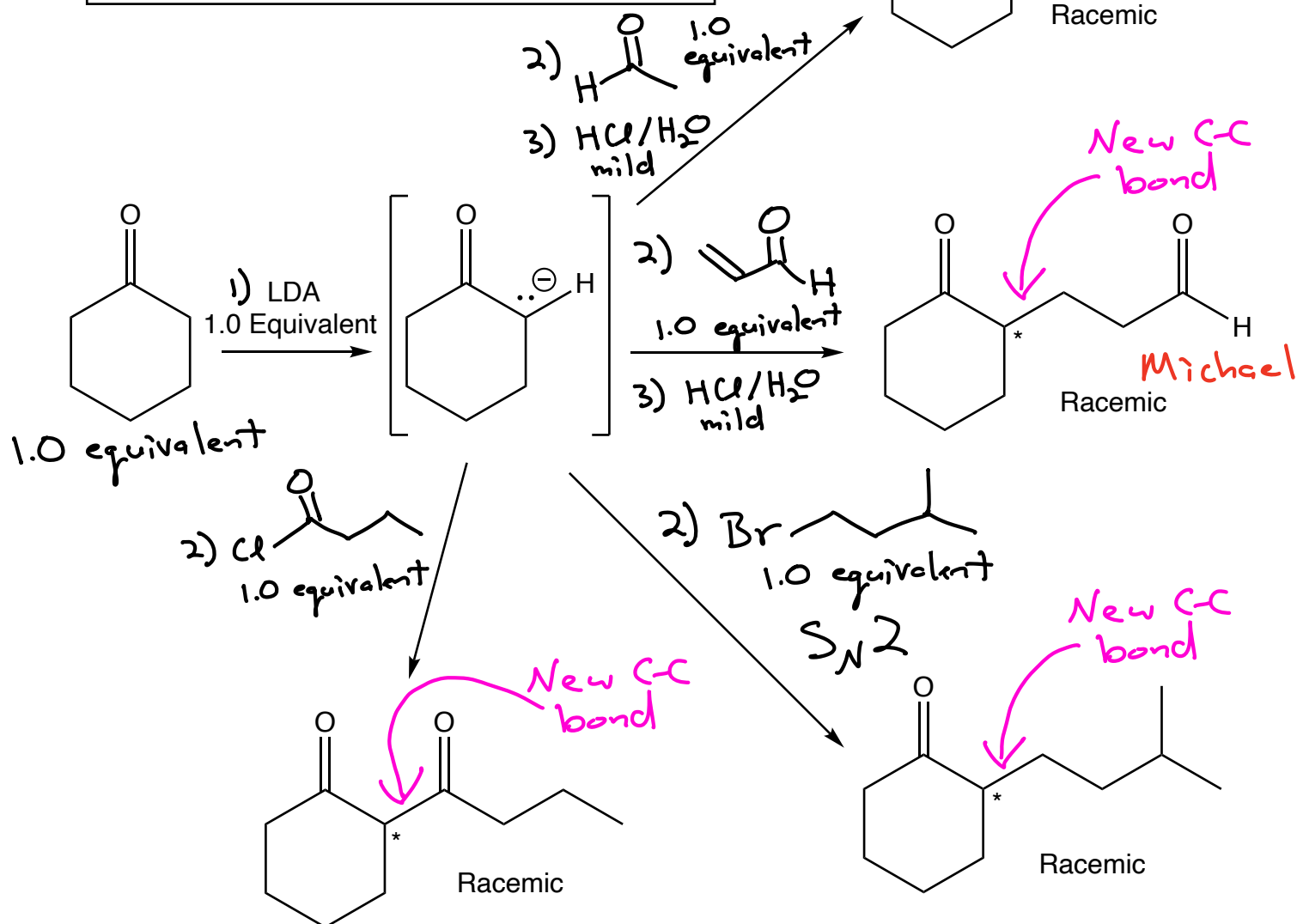
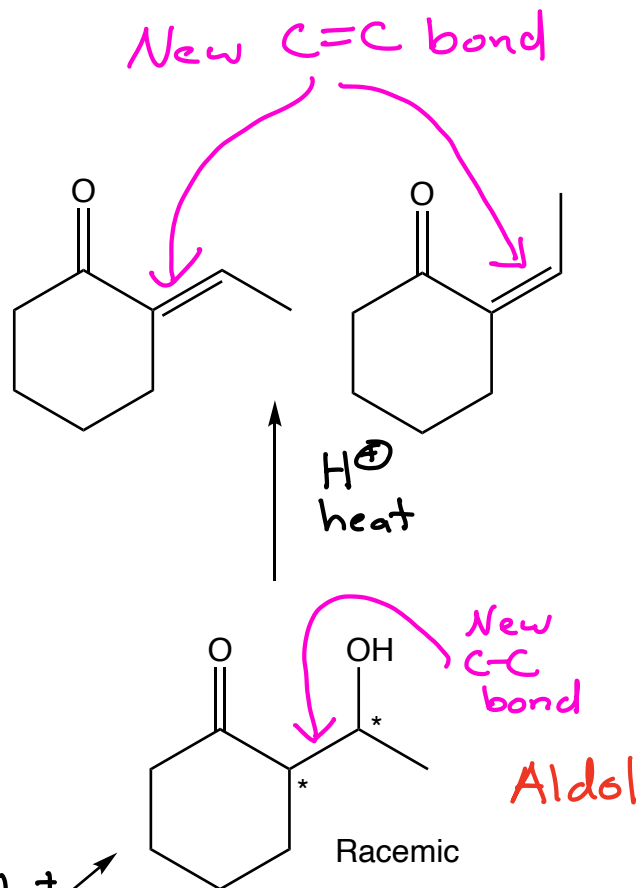
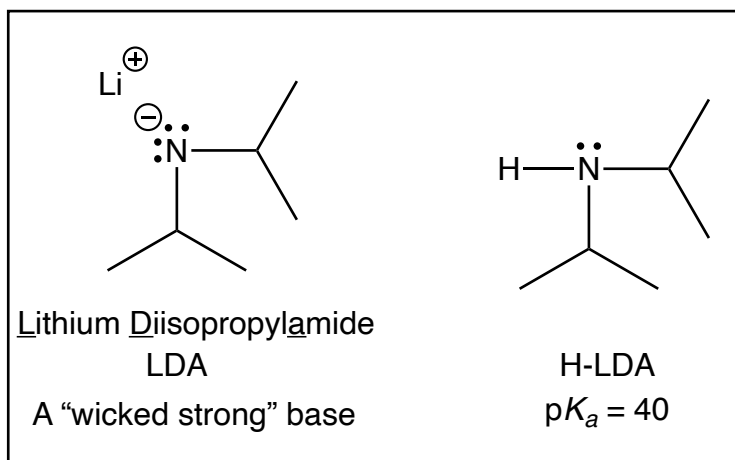


Spontaneous
dehydration - multiple steps

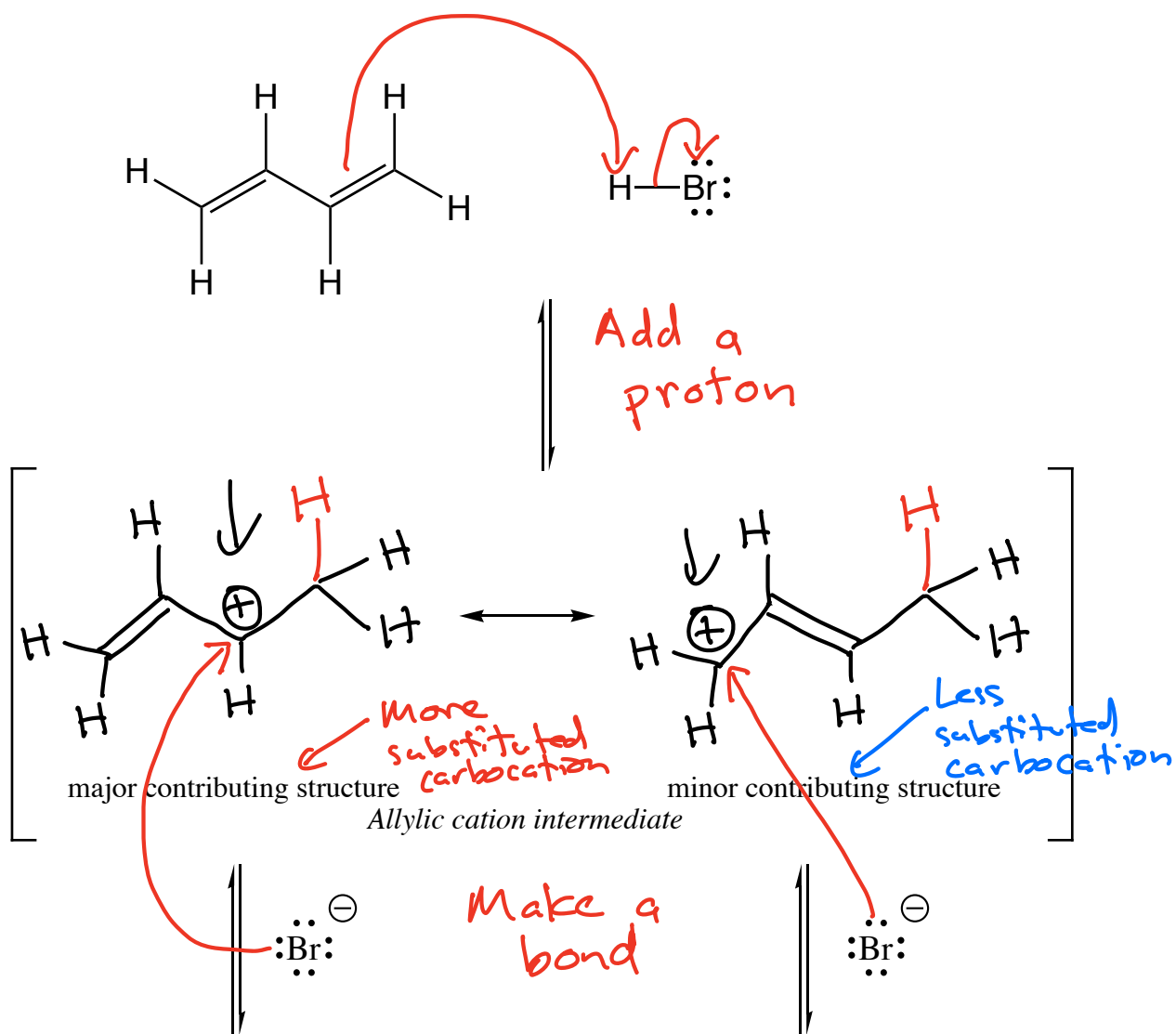
You are not responsible for
these

Dehydration

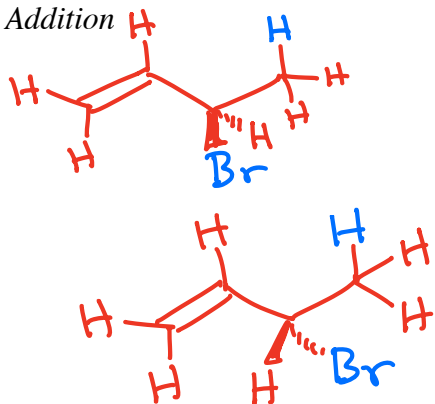




H-X reacting with conjugated dienes

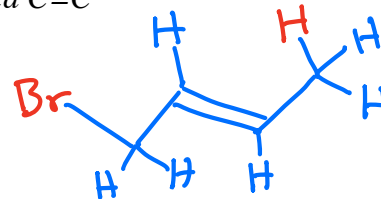


1,2 Addition

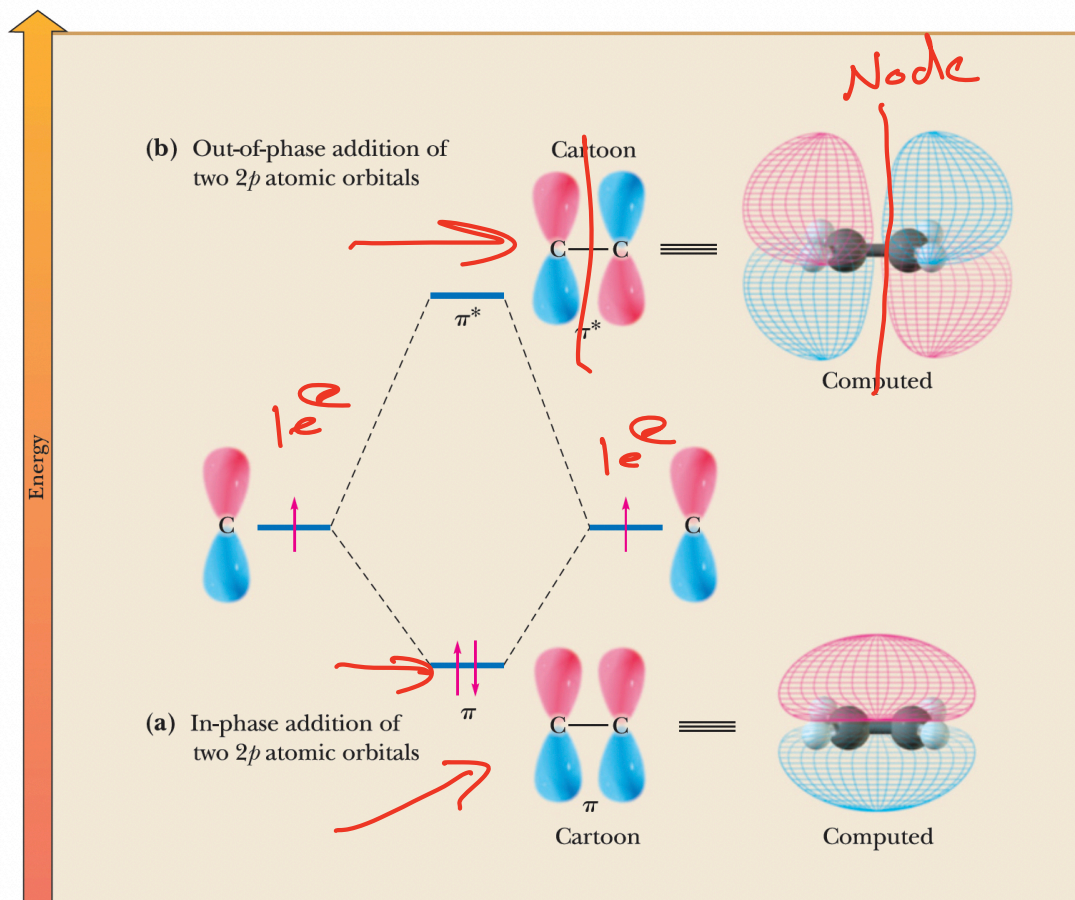


Racemic
Products

1,4 Addition - more stable, more highly substituted $\text{C}=\text{C}$



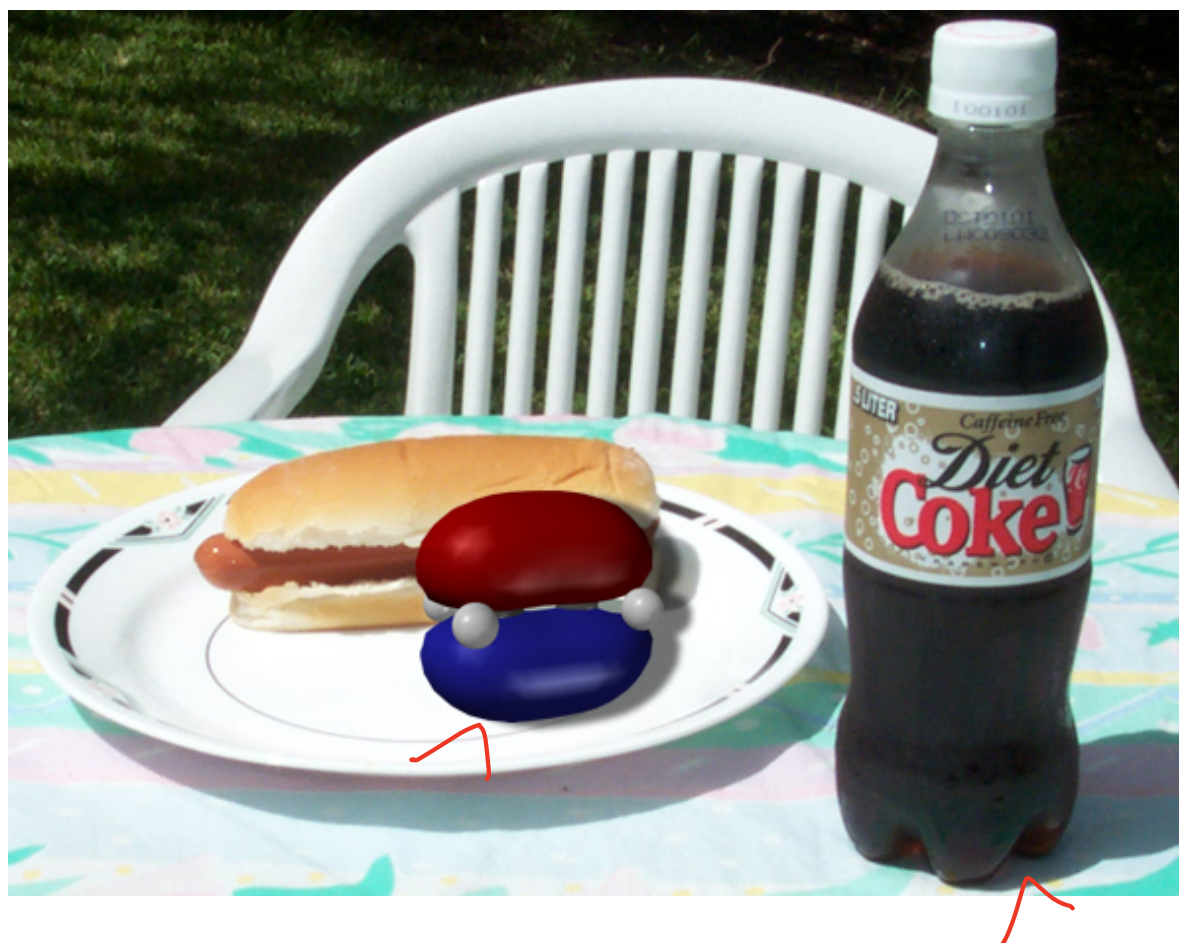
Products

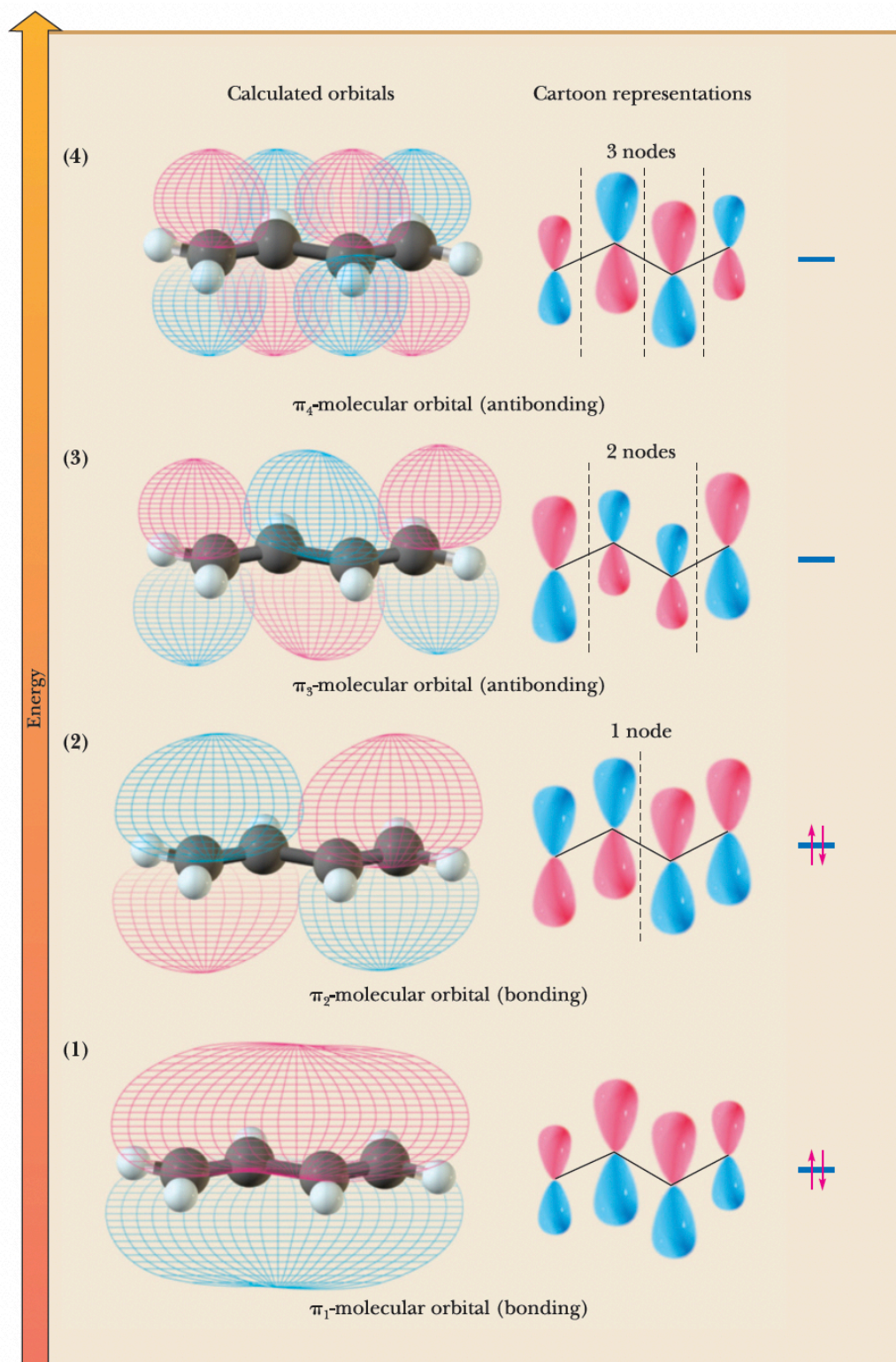


[Watch a video explanation](#)

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

FIGURE 20.2 Structure of 1,3-butadiene—molecular orbital model. Combination of four parallel $2p$ 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.

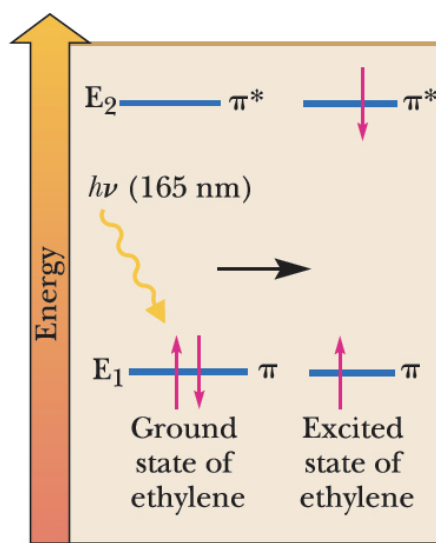


FIGURE 20.6 A $\pi \rightarrow \pi^*$ transition in excitation of ethylene. Absorption of ultraviolet radiation causes a transition of an electron from a π -bonding MO in the ground state to a π -antibonding MO in the excited state. There is no change in electron spin.

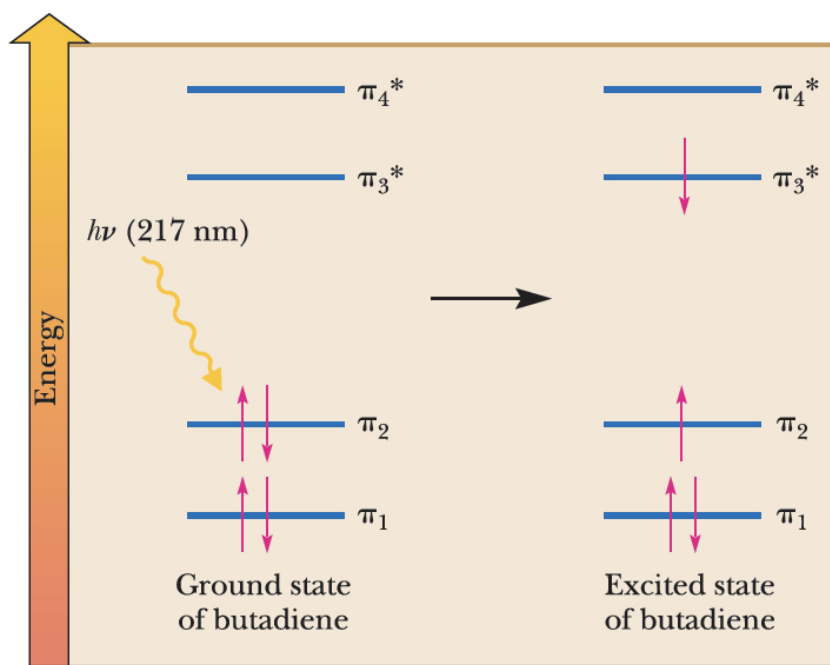
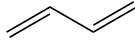
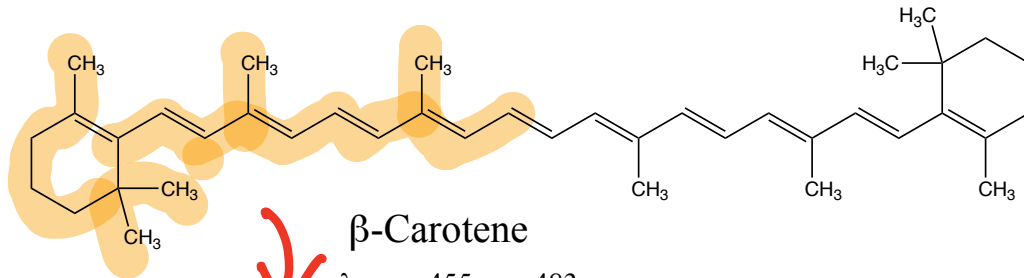


FIGURE 20.7 Electronic excitation of 1,3-butadiene; a $\pi \rightarrow \pi^*$ transition.



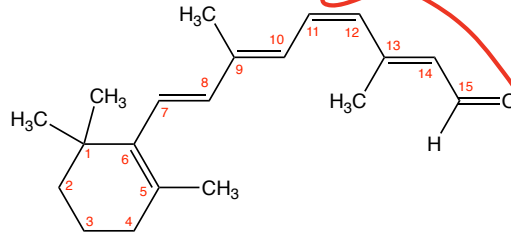
Butadiene

$\lambda_{\text{max}} = 217 \text{ nm}$



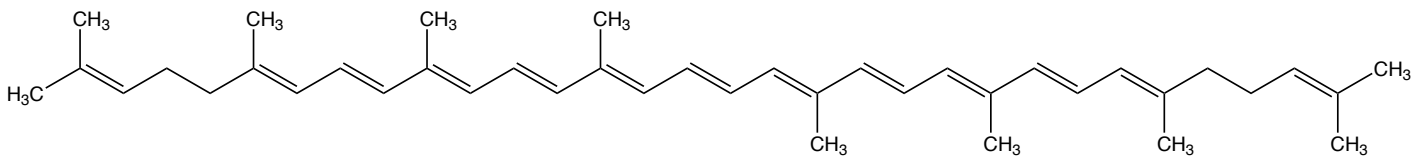
β -Carotene

$\lambda_{\text{max}} = 455 \text{ nm}, 483 \text{ nm}$



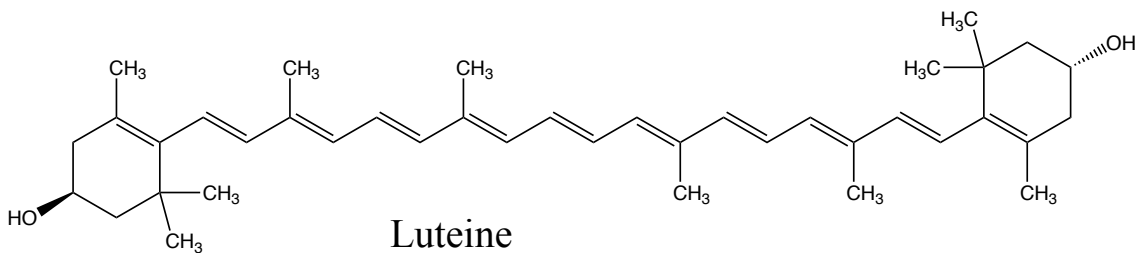
11-*cis*-Retinal

$\lambda_{\text{max}} = 380 \text{ nm}$



Lycopene

$\lambda_{\text{max}} = 443 \text{ nm}, 471 \text{ nm}, 502 \text{ nm}$



Luteine

$\lambda_{\text{max}} = 445 \text{ nm}, 474 \text{ nm}$

← Energy

Light source
↙ ↘

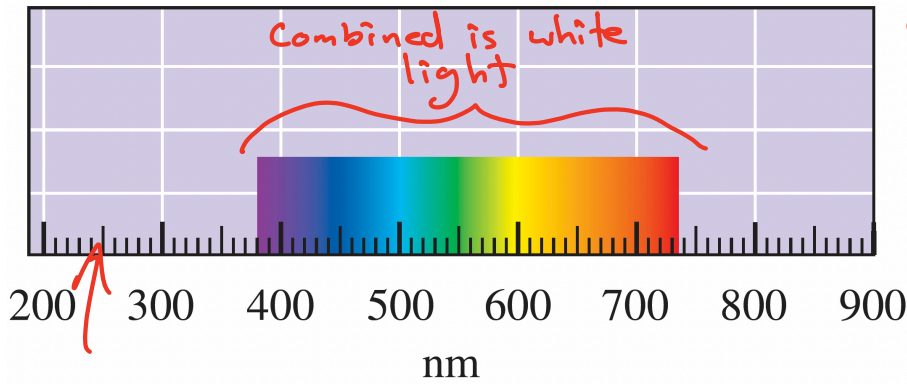
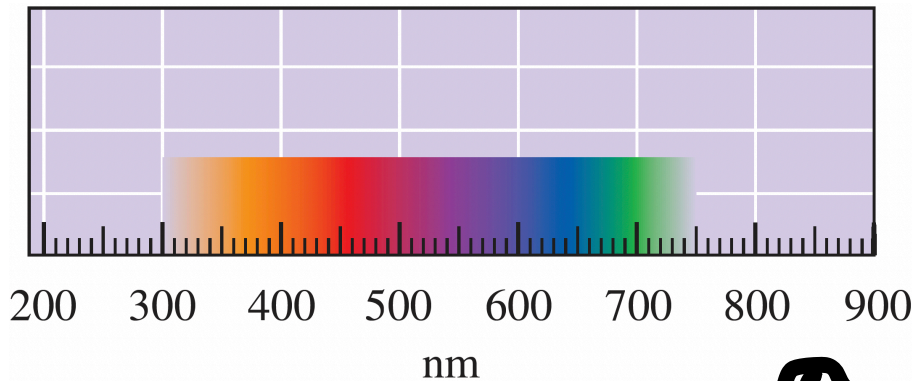
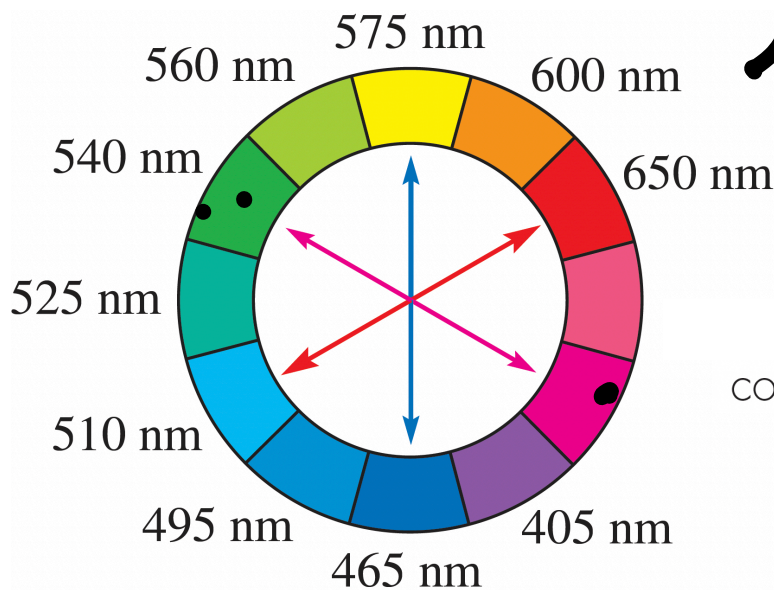


FIGURE 20.5 (a) Visible light color-wavelength correlation.

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



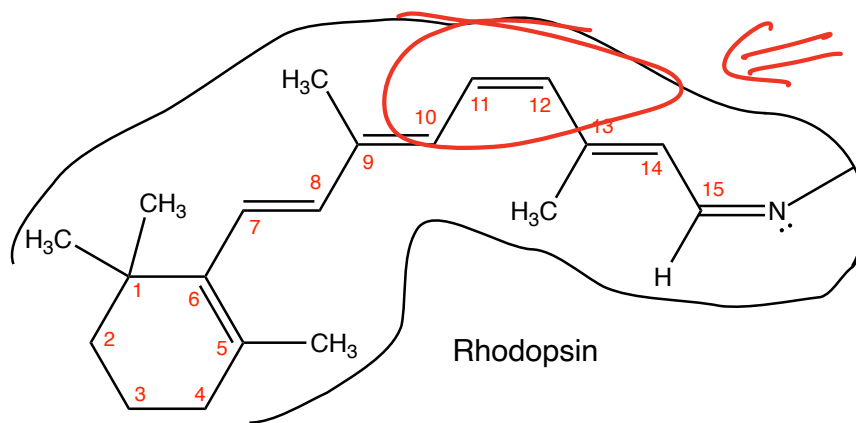
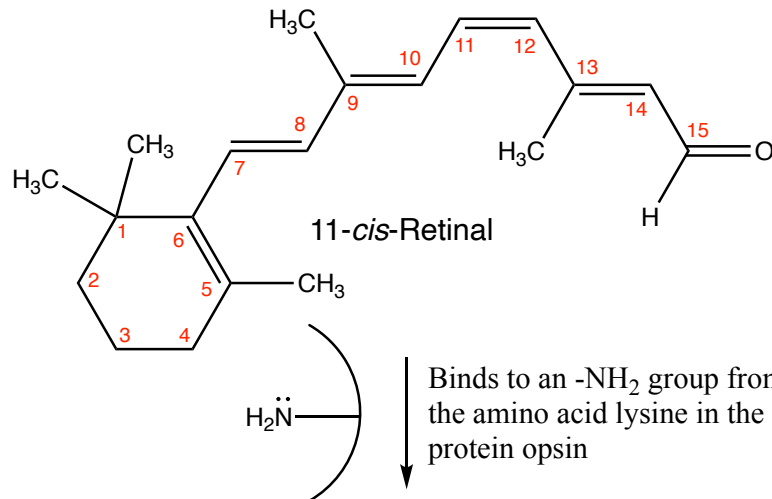
(b) Approximate color of substance (reflected light) if a single wavelength (i.e., the wavelength listed on the numerical scale of the x-axis) is absorbed.



(c) Complementary colors on a color wheel.

Colored arrows are complementary

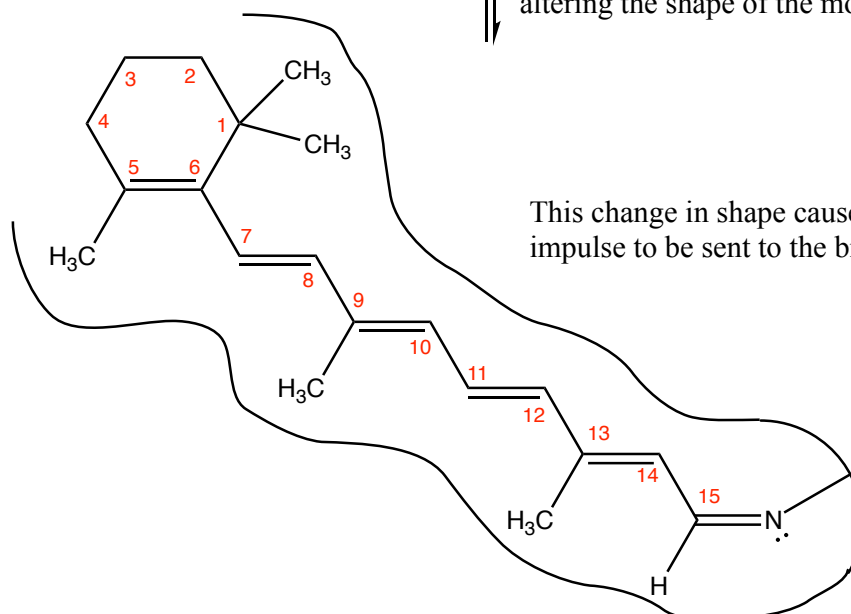
How vision works



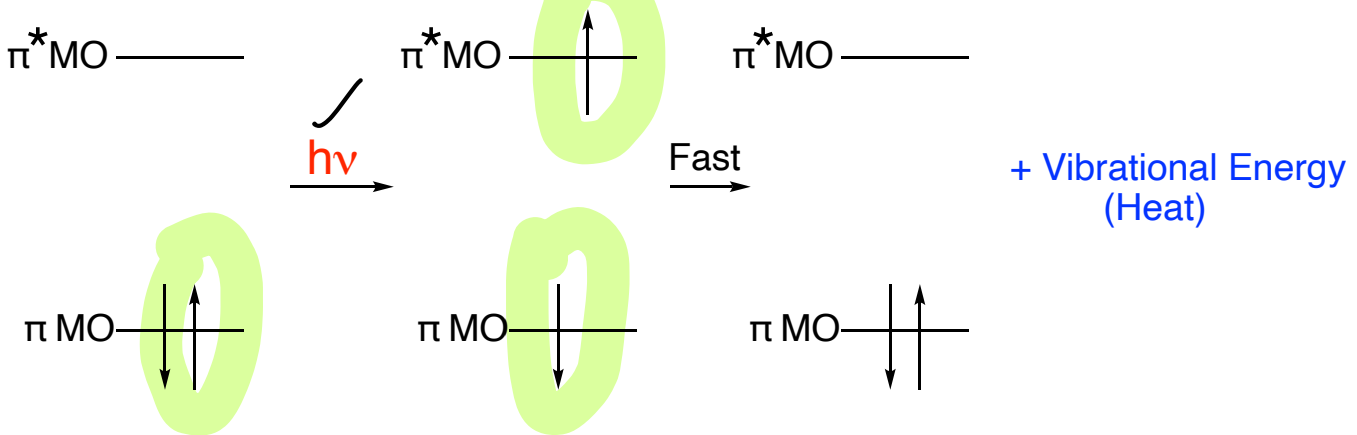
← Absorbing the photon puts an electron into an antibonding π orbital \rightarrow weaken π bond, especially around $\text{C}_{11}=\text{C}_{12}$ so bond can rotate back to more stable *trans* geometry

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

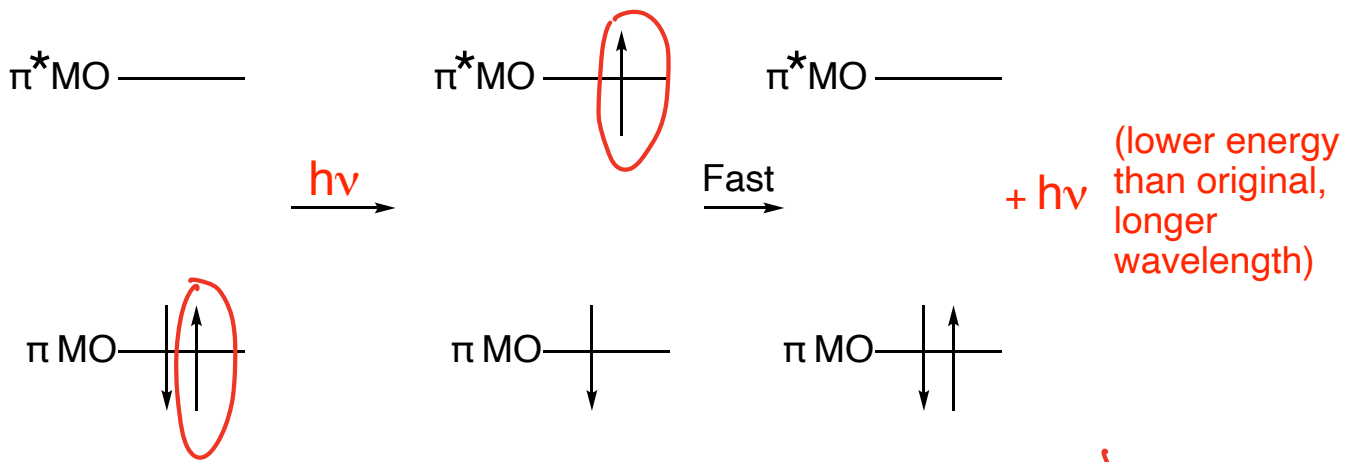
Molecule resets



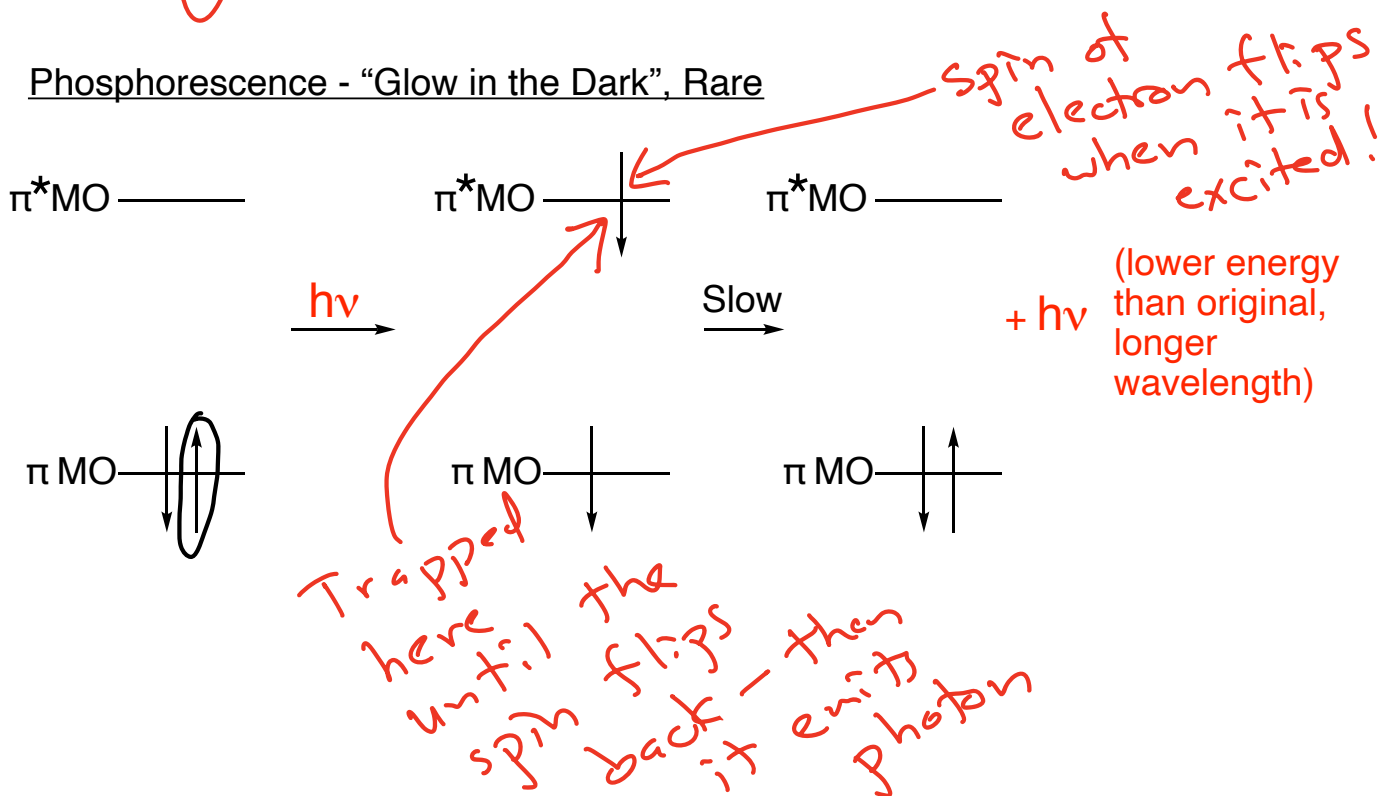
Generation of heat, Most molecules



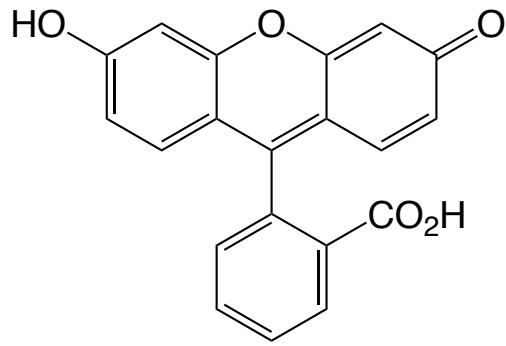
Flourescence - Rigid Molecules, Not uncommon



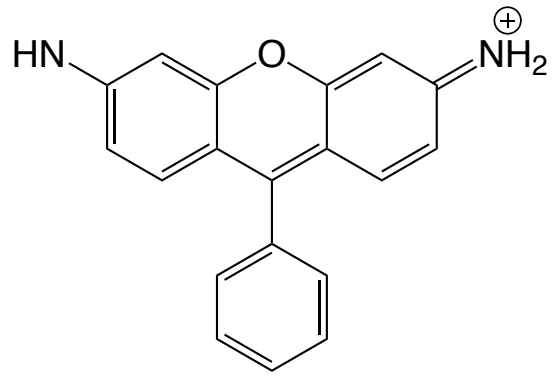
Phosphorescence - "Glow in the Dark", Rare



Flourescence - Rigid Molecules, Not uncommon

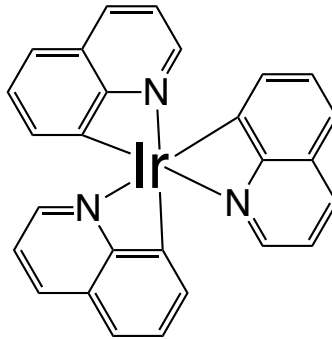


Fluorescein

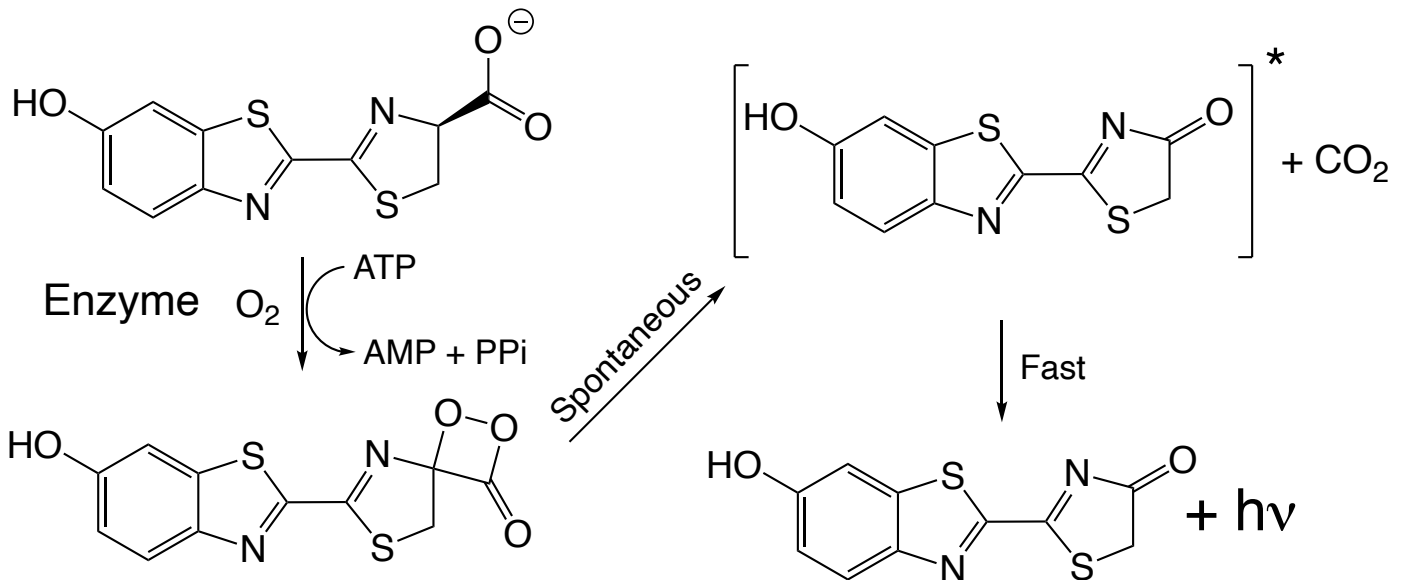


Rhodamine

Phosphorescence - "Glow in the Dark", Rare



Bioluminescence - Fireflies, Deep Sea Creatures - Chemical Reactions



← Energy

Light source

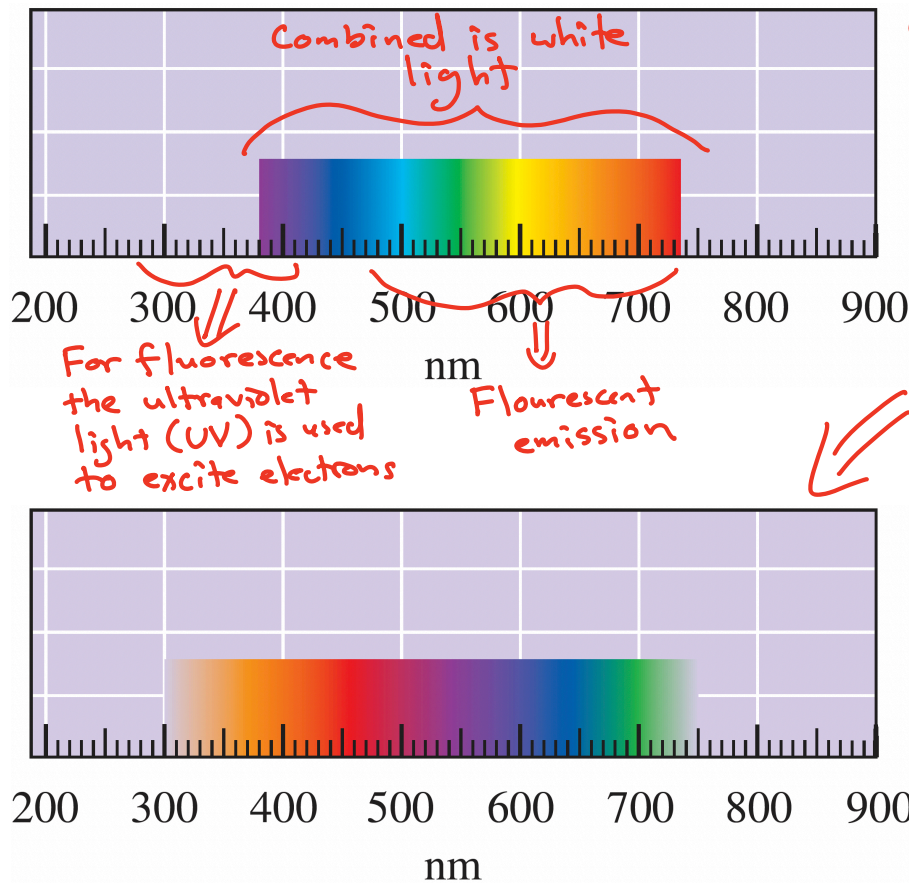
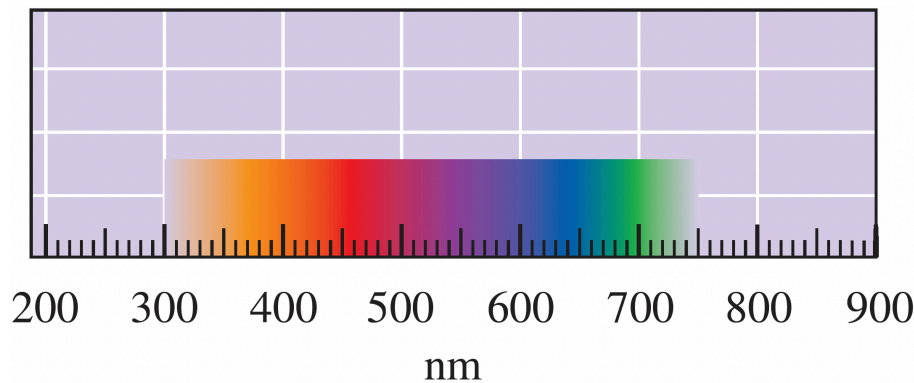
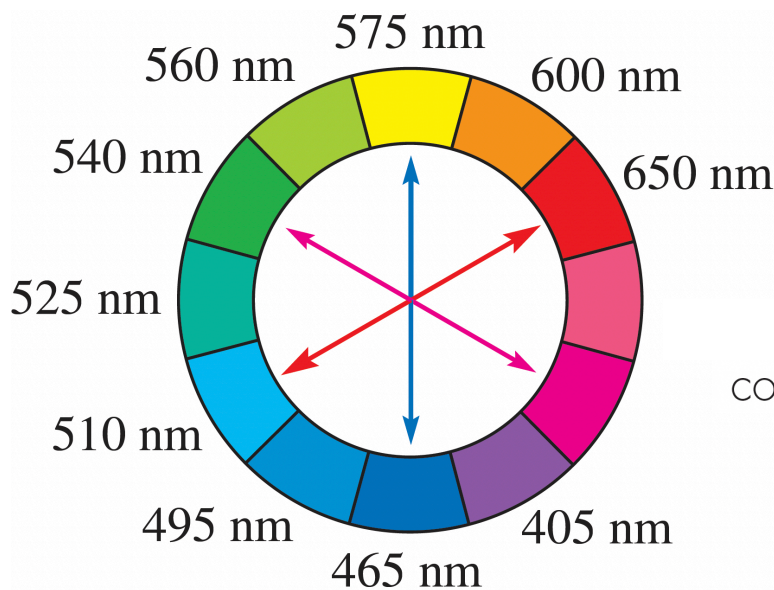


FIGURE 20.5 (a) Visible light color-wavelength correlation.

*** 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.

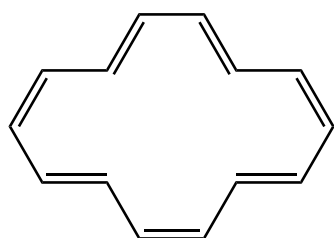
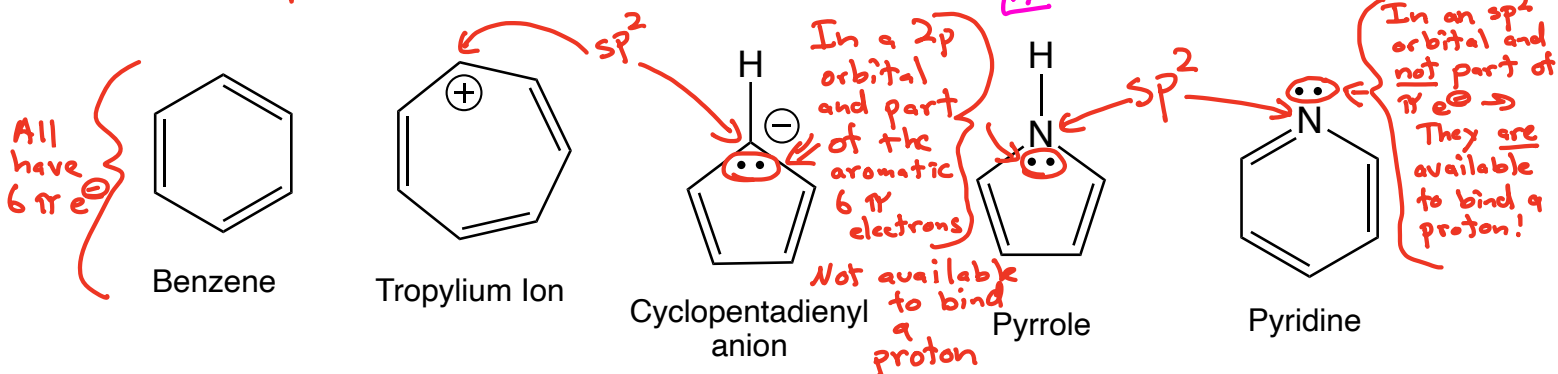


(c) Complementary colors on a color wheel.

Colored arrows are complementary

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, ...)



Annulene

14 π electrons

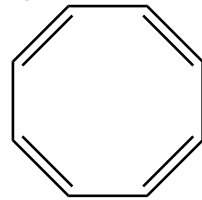
4 π electrons



Cyclobutadiene

Not a stable molecule

8 π electrons



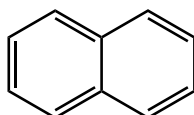
Cyclooctatetraene

Folds so 2p orbitals do not overlap and avoids antiaromaticity

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

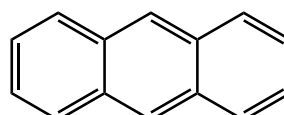
All fused benzene compounds are aromatic no matter the number of π electrons → Not monocyclic so Hückel's $4n+2$ rule does not apply!

10 π electrons

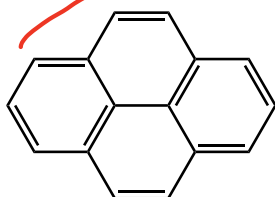


Naphtalene

14 π electrons

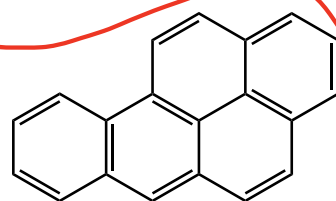


Anthracene



Pyrene

16 π electrons!

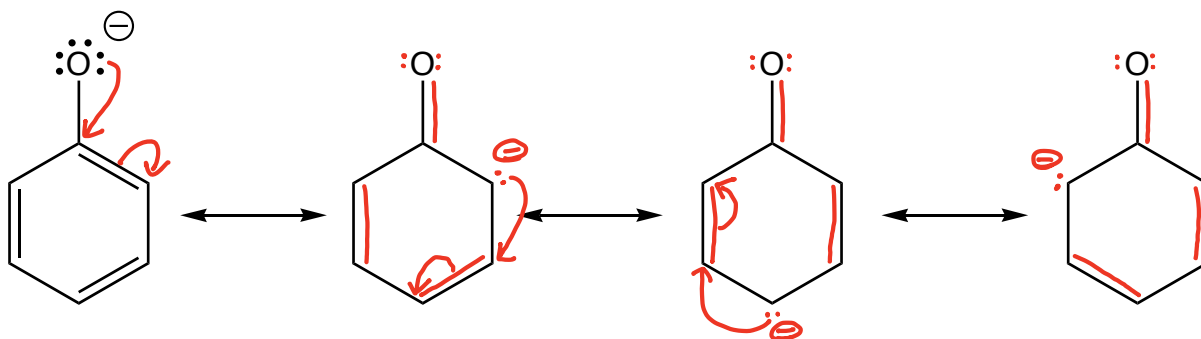


Benzo[α]pyrene

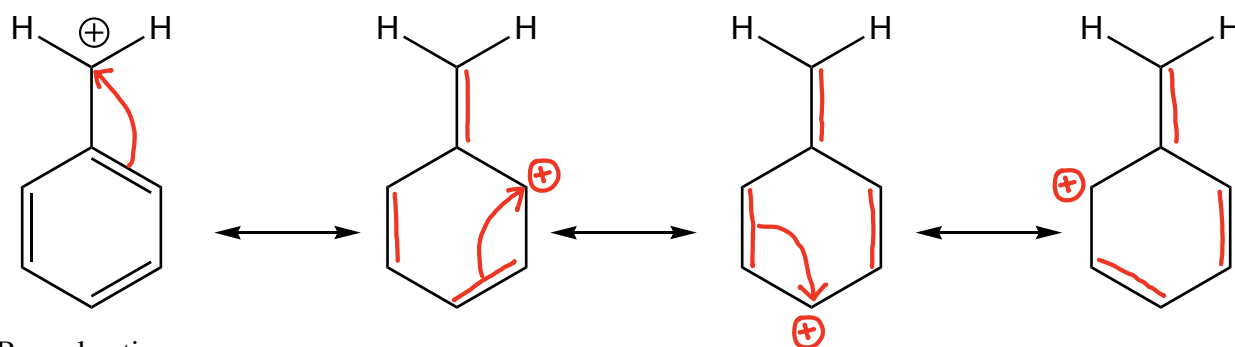
20 π electrons

Still aromatic!

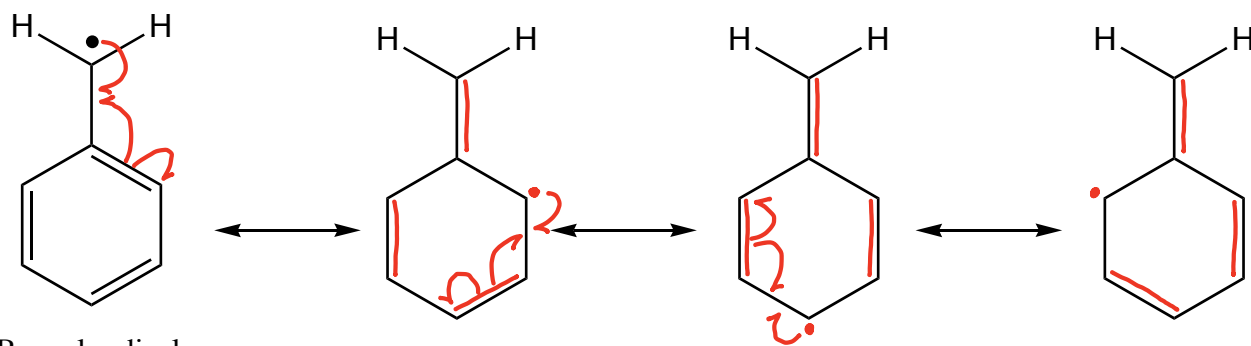
Aromatic resonance stabilization of charged species



Phenoxide anion

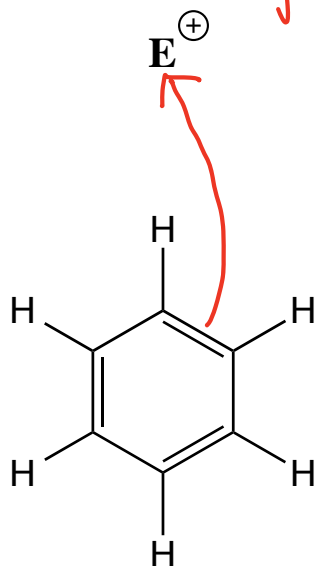


Benzyl cation

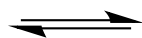


Benzyl radical

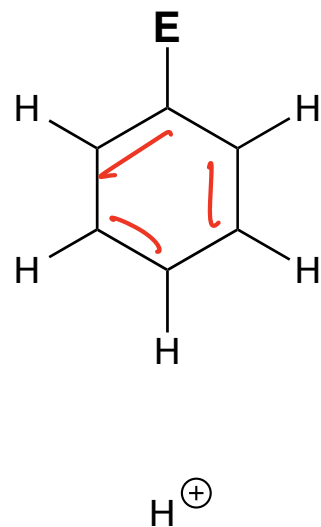
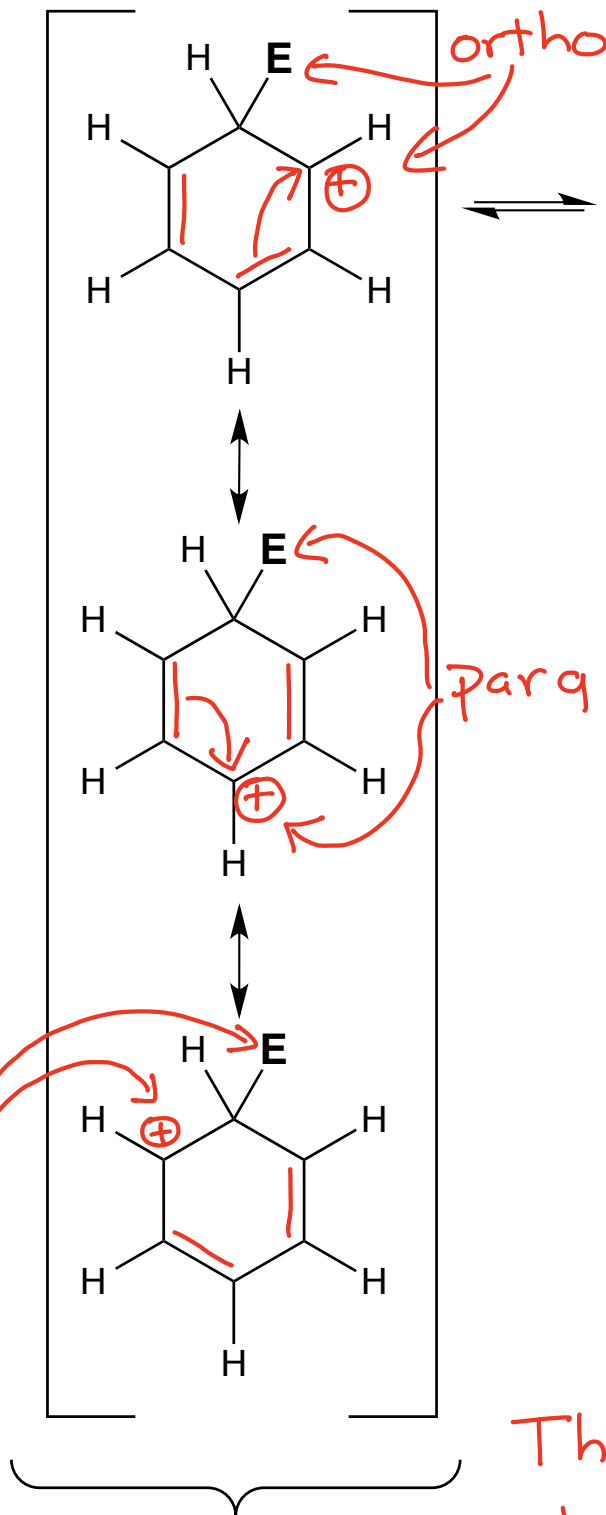
Wicked Strong
Electrophile



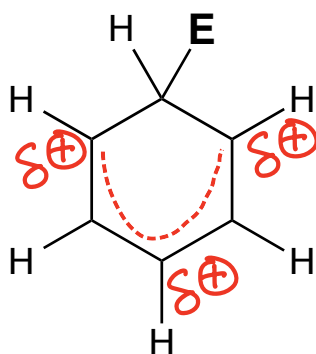
Weak
Nucleophile



ortho



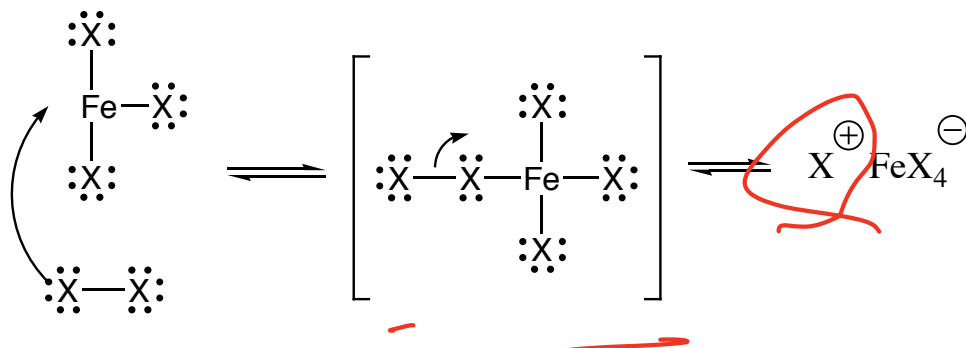
Called the
Arenium Ion



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

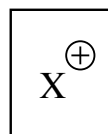
Reagents

Halogenation X_2, FeX_3

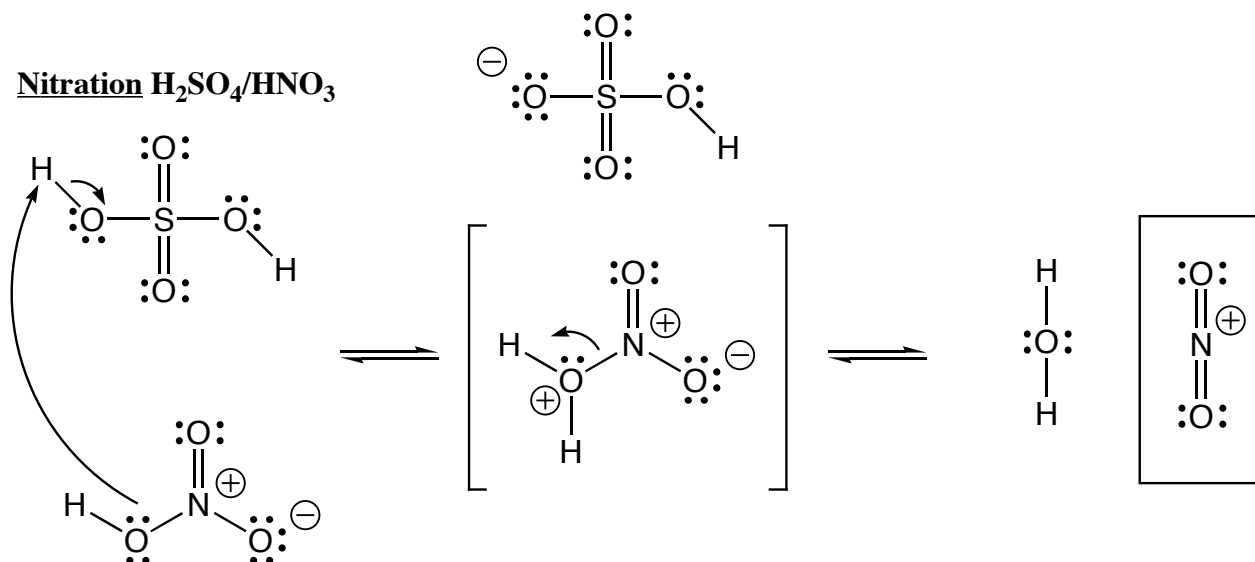


$X = Br, Cl$

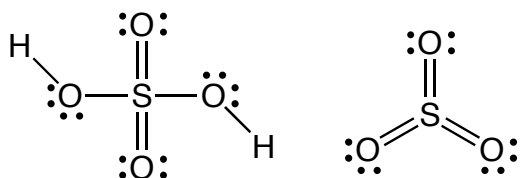
Wicked strong
electrophile



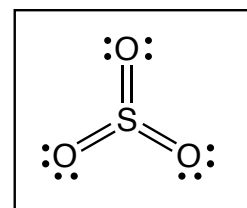
Nitration H_2SO_4/HNO_3



Sulfonation H_2SO_4/SO_3

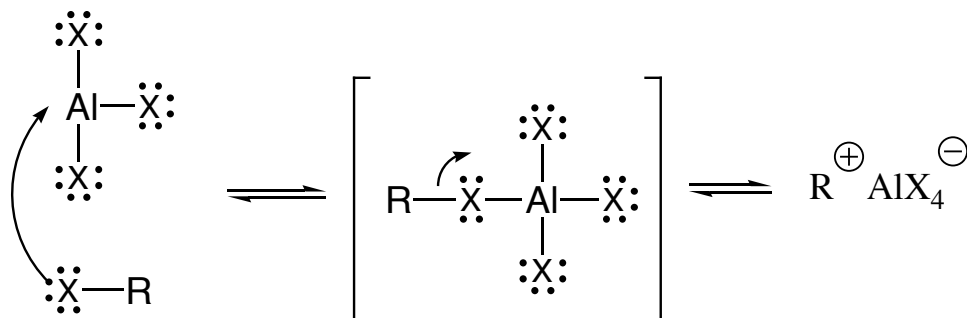


Fuming sulfuric acid
contains both of the
above reagents, the SO_3
is the important one



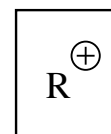
Reagents

Friedel-Crafts Alkylation $R-X, AlX_3$



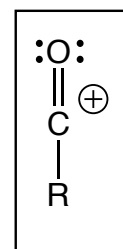
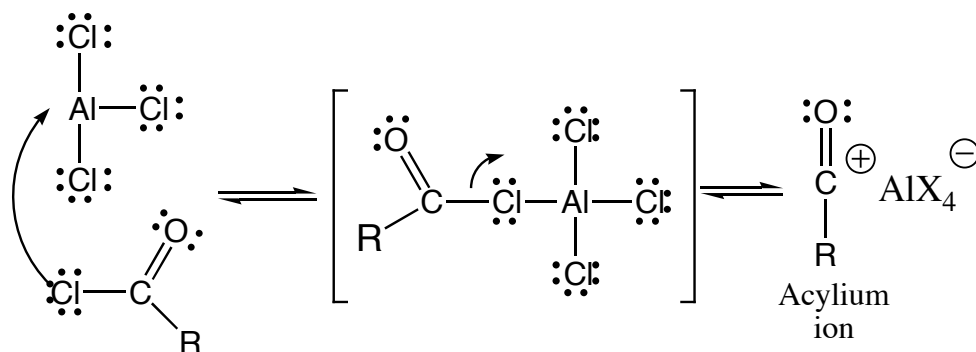
$X = Br, Cl$

Wicked strong
electrophile

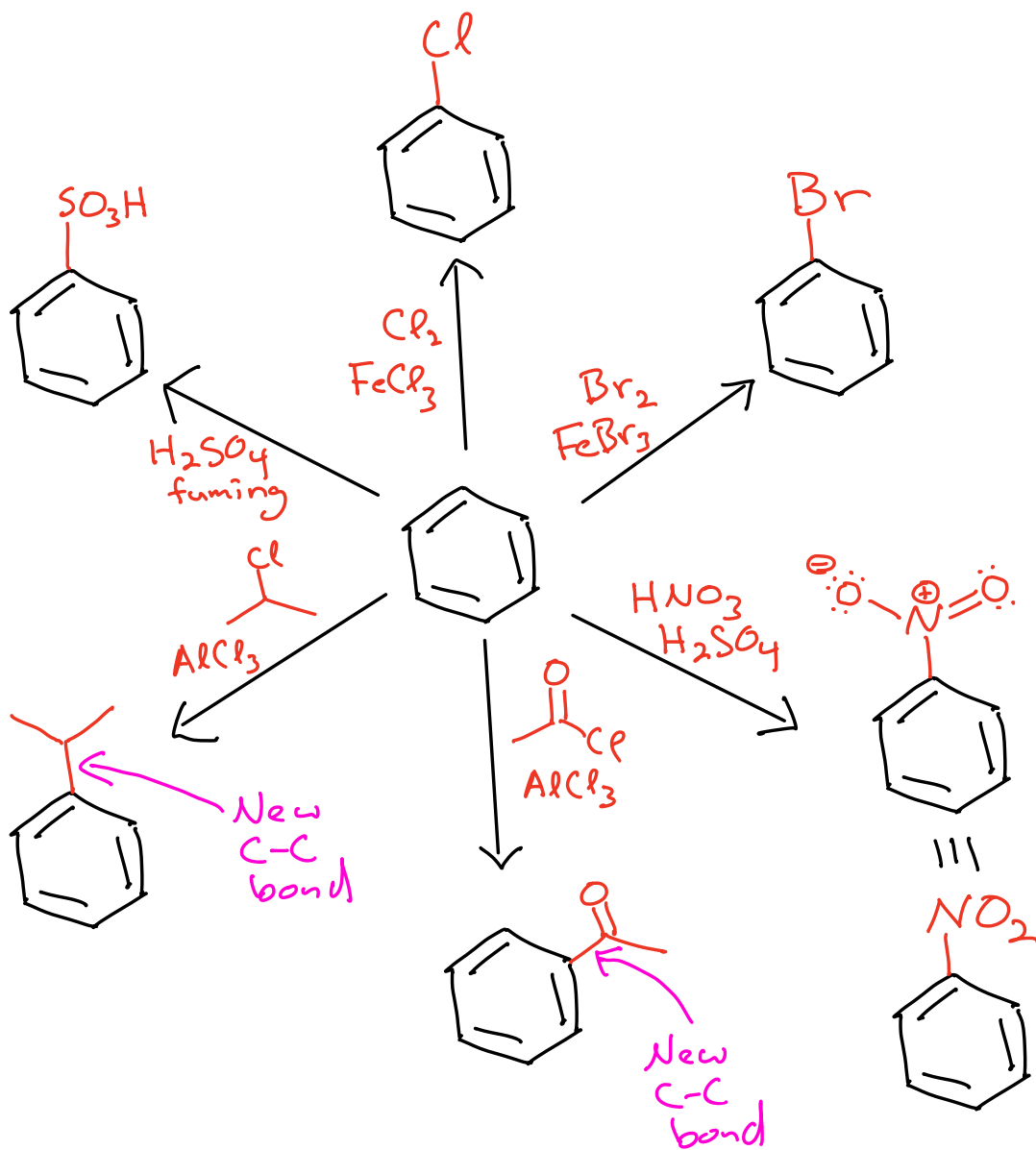


Note this is a
carbocation, so it
will rearrange if it
is a primary or a
rearrangement-
prone secondary
cation

Friedel-Crafts Acylation $RCOCl, AlCl_3$

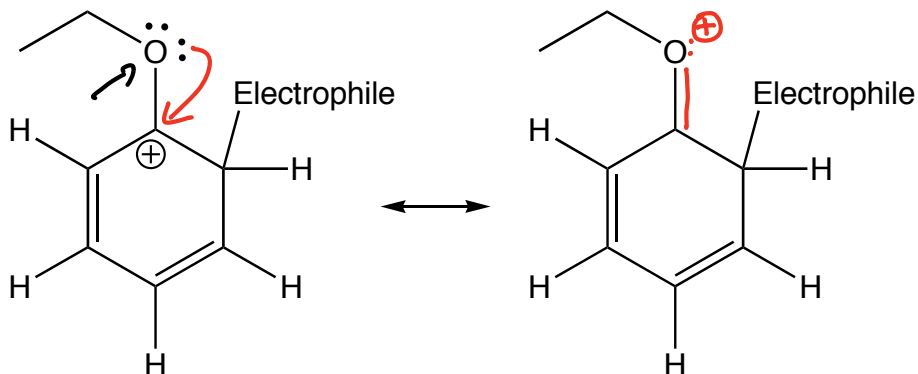


Other notes: 1) It is hard to stop the Friedel-Crafts alkylation after one alkyl group adds (because alkyl groups are "good", that is, activating), but it can be done. 2) Neither Friedel-Crafts reaction works if there is already an electron withdrawing (bad) group on the ring.



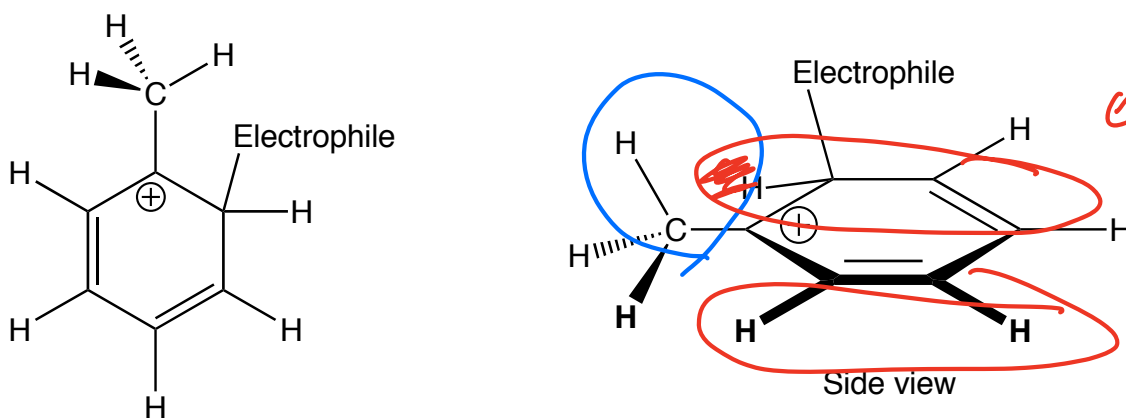
Arenium ion **stabilizing** interactions ← GOOD

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



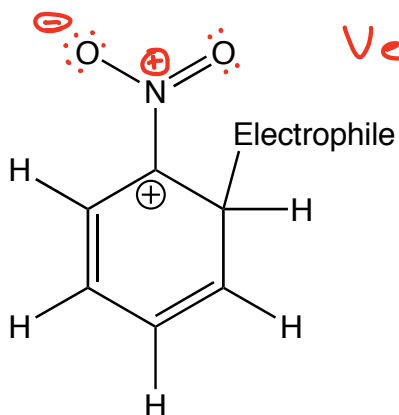
← "pi-pi"
✓
The "Greek interactions"
↓
"sigma-pi"

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

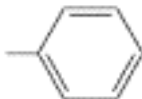


Arenium ion **destabilizing** interaction ← BAD

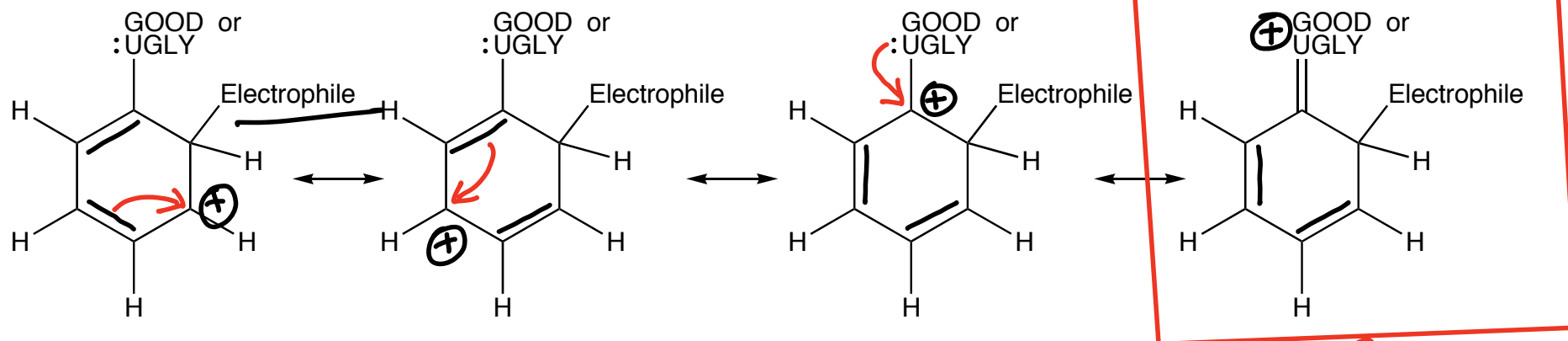
A) **Inductive effect** of electronegative atoms or groups attached to the ring



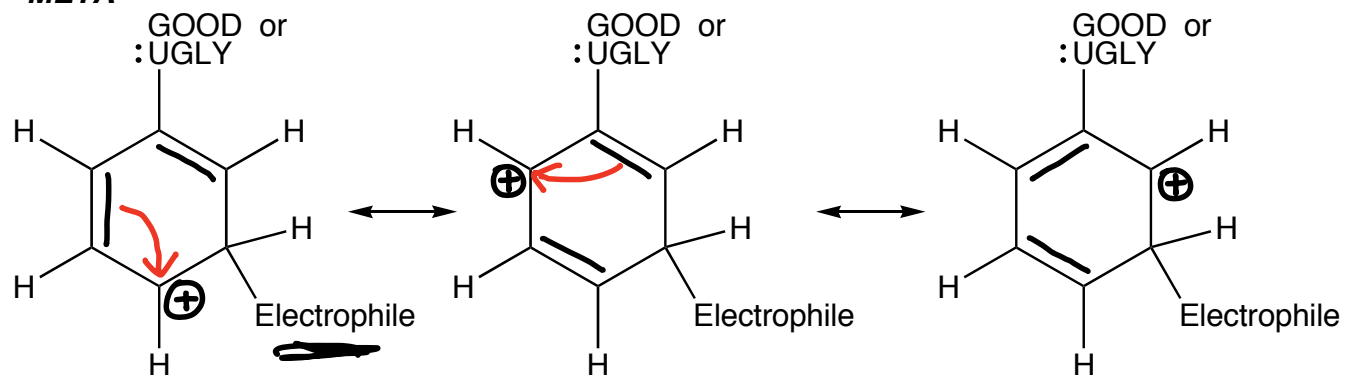
Very electron withdrawing

Ortho-Para Directing	Strongly activating	$\text{--}\ddot{\text{N}}\text{H}_2$ $\text{--}\ddot{\text{N}}\text{HR}$ $\text{--}\ddot{\text{N}}\text{R}_2$ $\text{--}\ddot{\text{O}}\text{H}$ $\text{--}\ddot{\text{O}}\text{R}$	<div>GOOD</div> <p>These all have a lone pair on the atom attached to the ring or they are an alkyl group</p>	Relative importance in directing further substitution
	Moderately activating	$\text{--}\ddot{\text{N}}\text{H}\overset{\text{O}}{\parallel}\text{CR}$ $\text{--}\ddot{\text{N}}\text{H}\overset{\text{O}}{\parallel}\text{CAr}$ $\text{--}\ddot{\text{O}}\overset{\text{O}}{\parallel}\text{CR}$ $\text{--}\ddot{\text{O}}\overset{\text{O}}{\parallel}\text{CAr}$		
	Weakly activating	--R 		
	Weakly deactivating	$\text{--}\ddot{\text{F}}:$ $\text{--}\ddot{\text{Cl}}:$ $\text{--}\ddot{\text{Br}}:$ $\text{--}\ddot{\text{I}}:$ Halogens! UGLY		
Meta Directing	Moderately deactivating	$\text{--}\overset{\text{O}}{\parallel}\text{CH}$ $\text{--}\overset{\text{O}}{\parallel}\text{CR}$ $\text{--}\overset{\text{O}}{\parallel}\text{COH}$ $\text{--}\overset{\text{O}}{\parallel}\text{COR}$ $\text{--}\overset{\text{O}}{\parallel}\text{CNH}_2$ $\text{--}\overset{\text{O}}{\parallel}\text{SOH}$ $\text{--C}\equiv\text{N}$	<div>BAD</div> <p>These all have a pi bond to an electronegative atom on the atom attached to the ring or highly electronegative</p>	
	Strongly deactivating	--NO_2 --NH_3^+ --CF_3 --CCl_3		

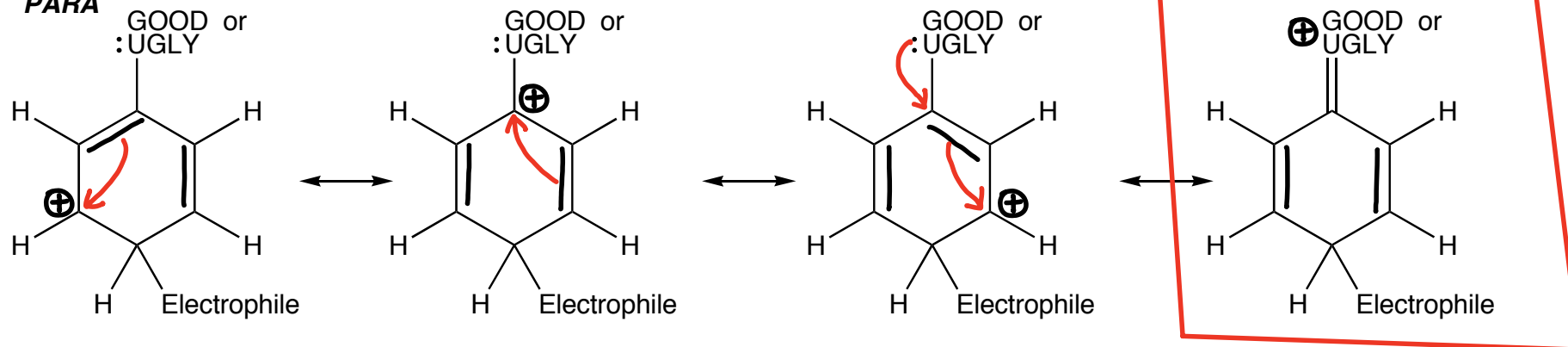
ORTHO



META

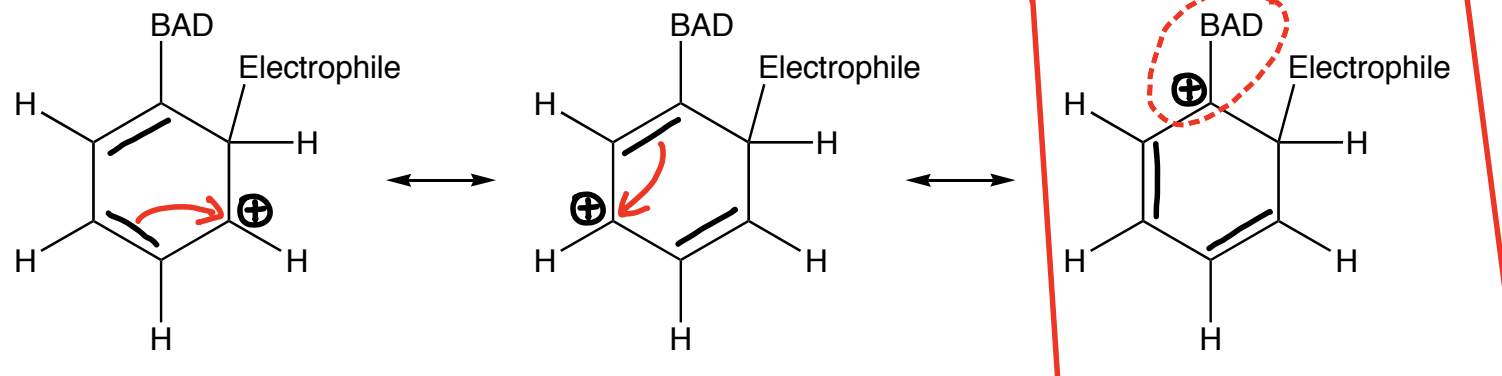


PARA

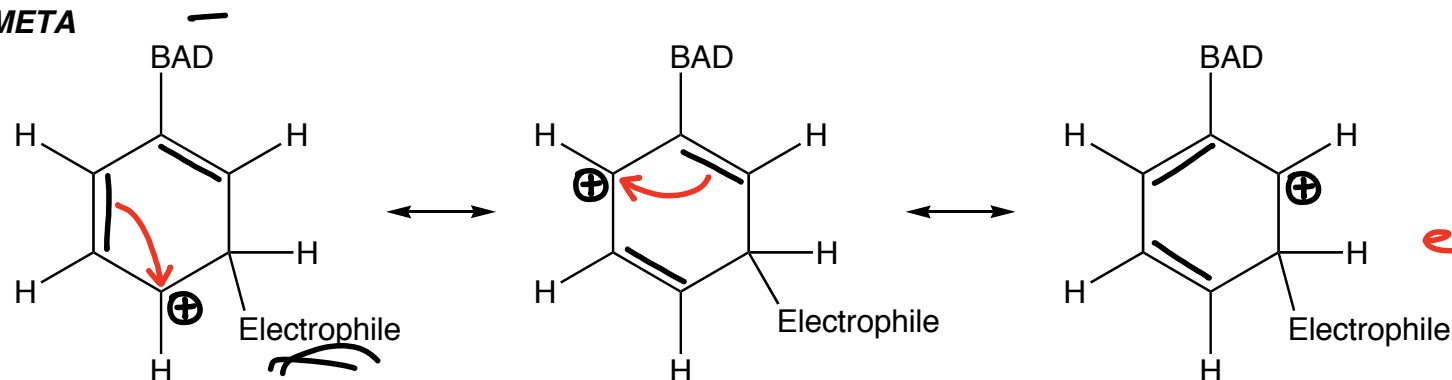


These two explain why ortho, para are preferred

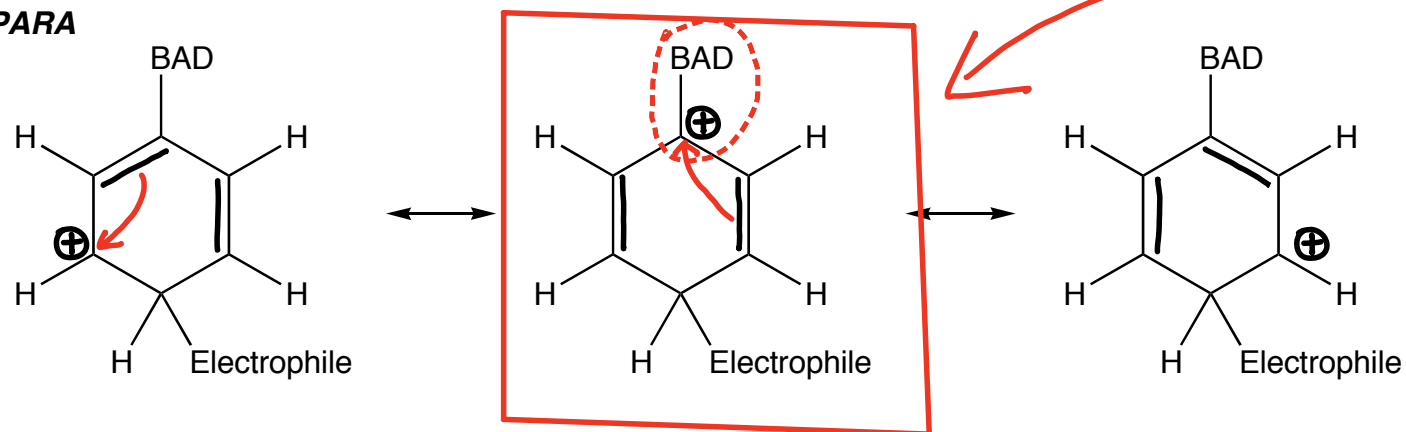
ORTHO



META

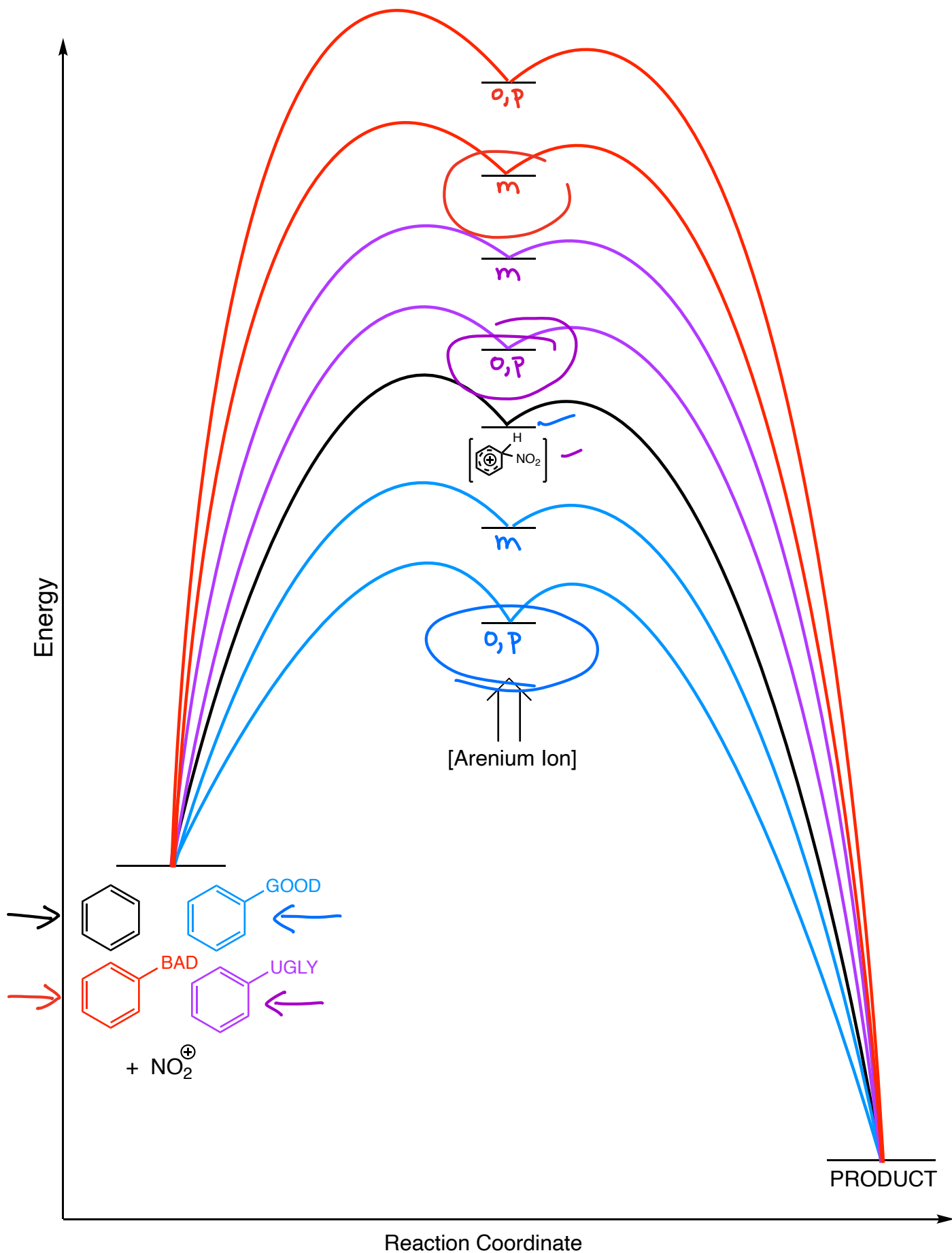


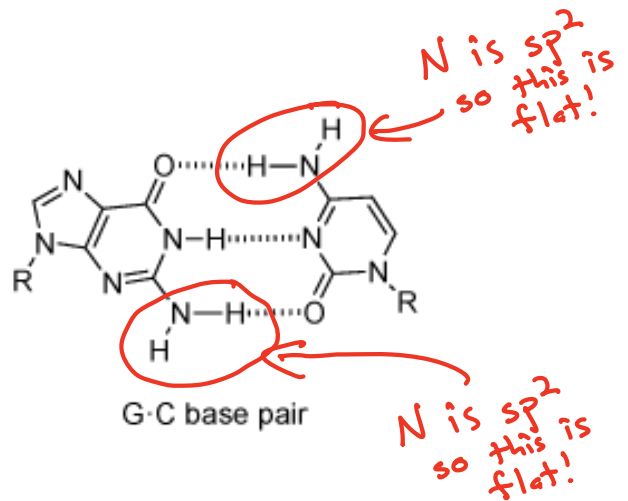
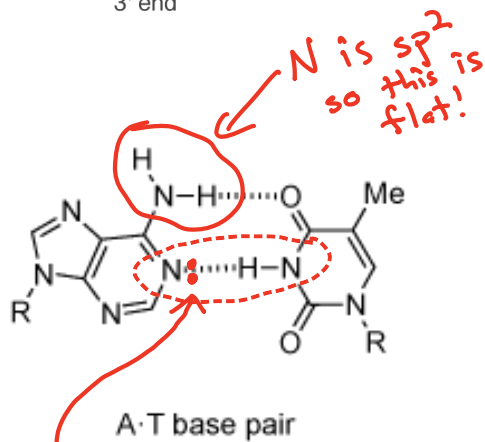
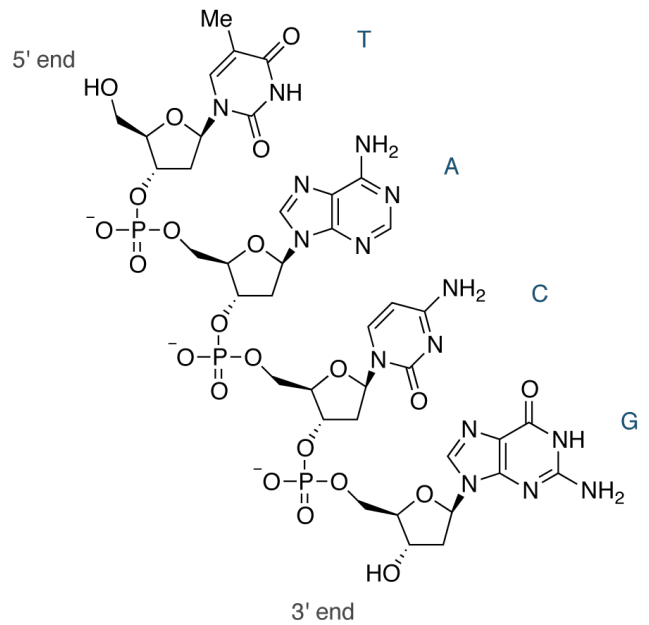
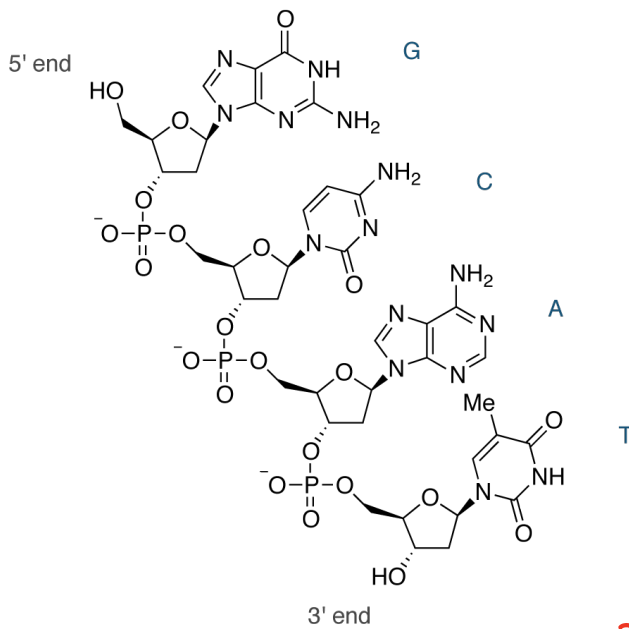
PARA



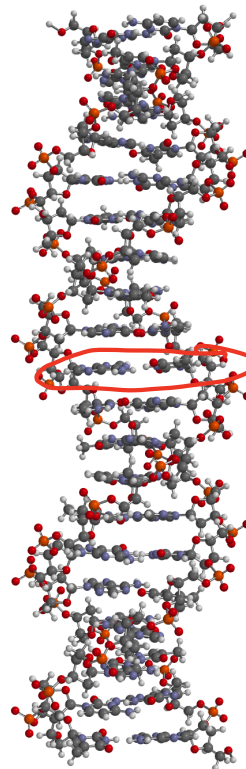
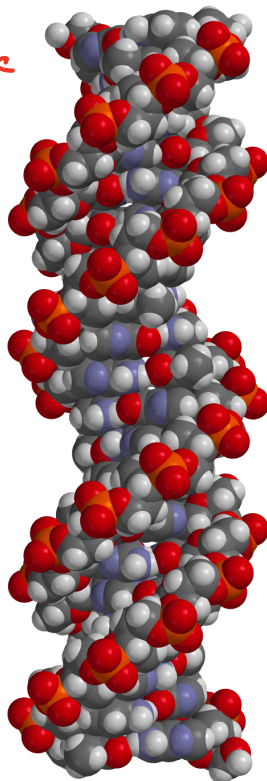
Very destabilizing
explaining why
for BAD
groups

"meta is
better"
No terrible
interaction
meta like
there is
ortho, para



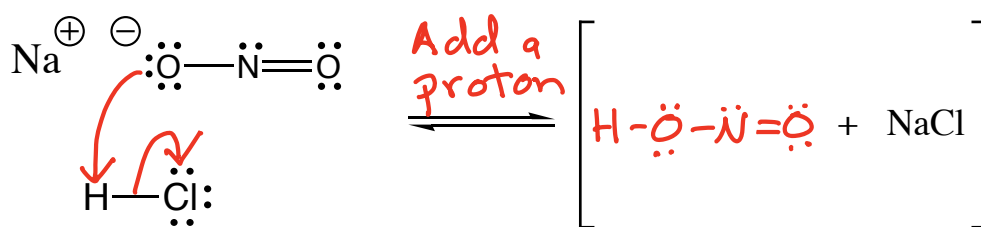


Lone pair is in an sp^2 orbital and available to make a strong hydrogen bond

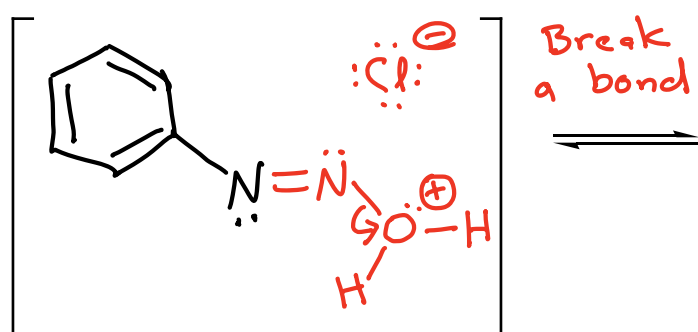
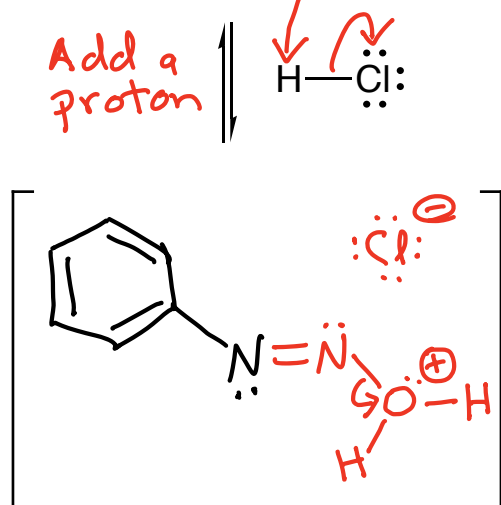
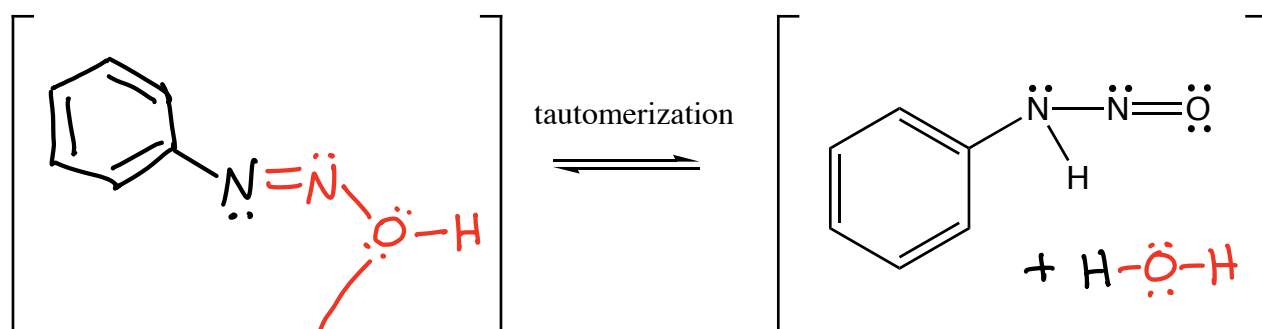
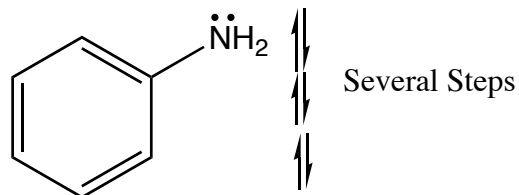


base pairs are flat because N atoms are sp^2

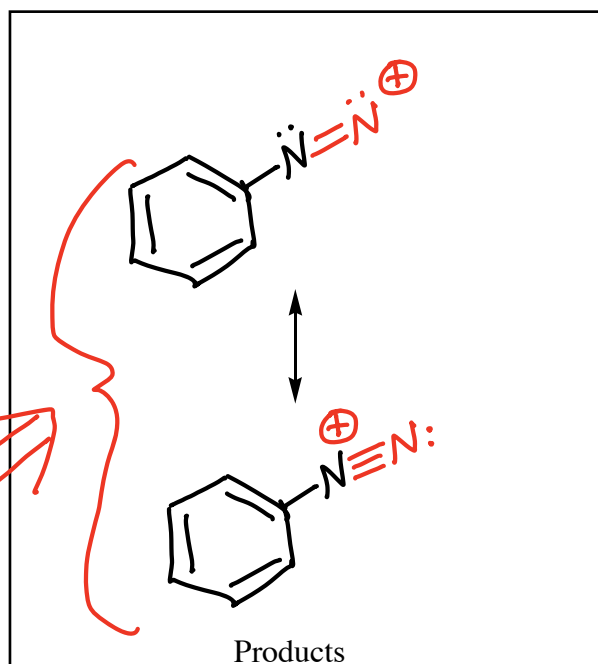
Preparation of Diazoniums, The "Mr. Bill" Reaction



The Mr. Bill reagent

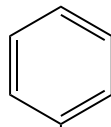
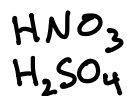
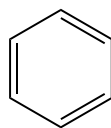


Aryl Diazonium also known as a Diazonium Salt



Products

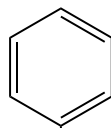
N_2 leaves and is replaced by a variety of reagents \rightarrow Not responsible for mechanisms



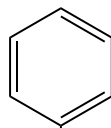
BAD \rightarrow
meta directing



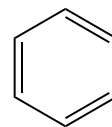
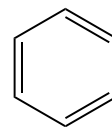
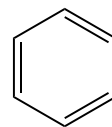
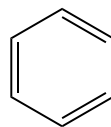
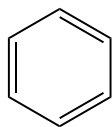
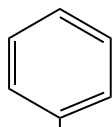
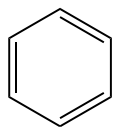
New
Reaction



GOOD
ortho, para
directing



Diazonium
Salt

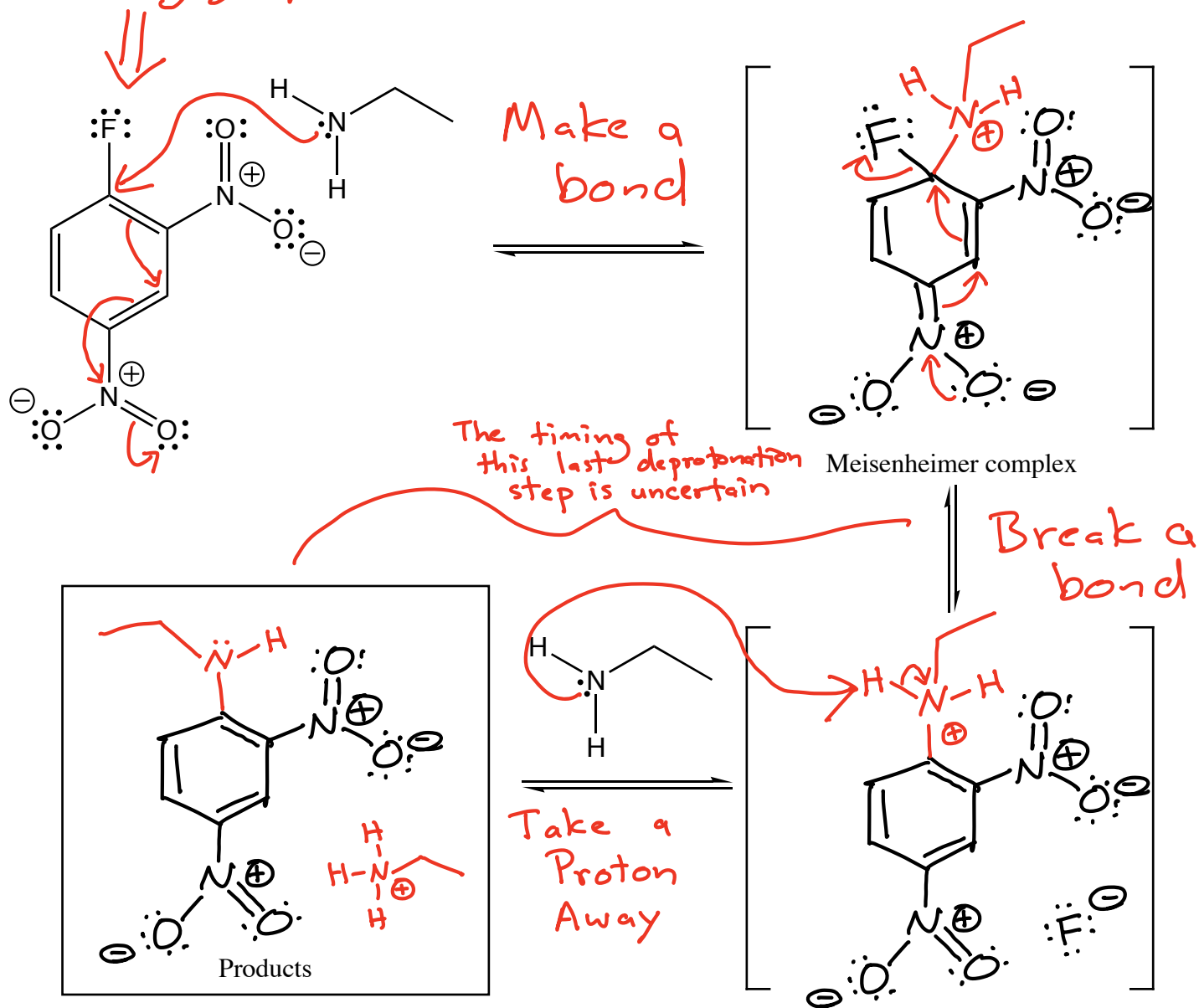


Sandmeyer Reaction



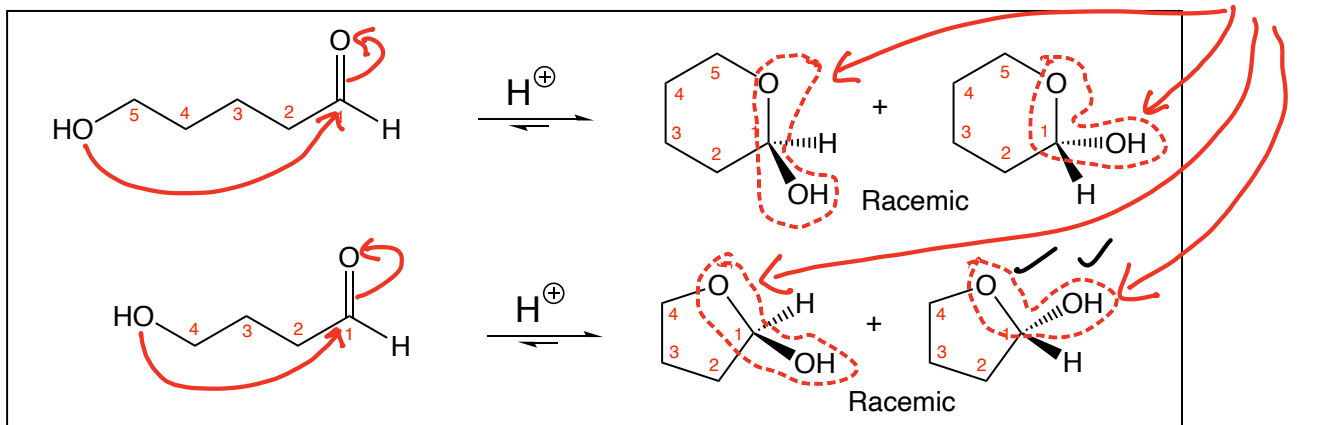
VERY electron deficient aromatic ring because of all the electron withdrawing groups

Nucleophilic Aromatic Substitution

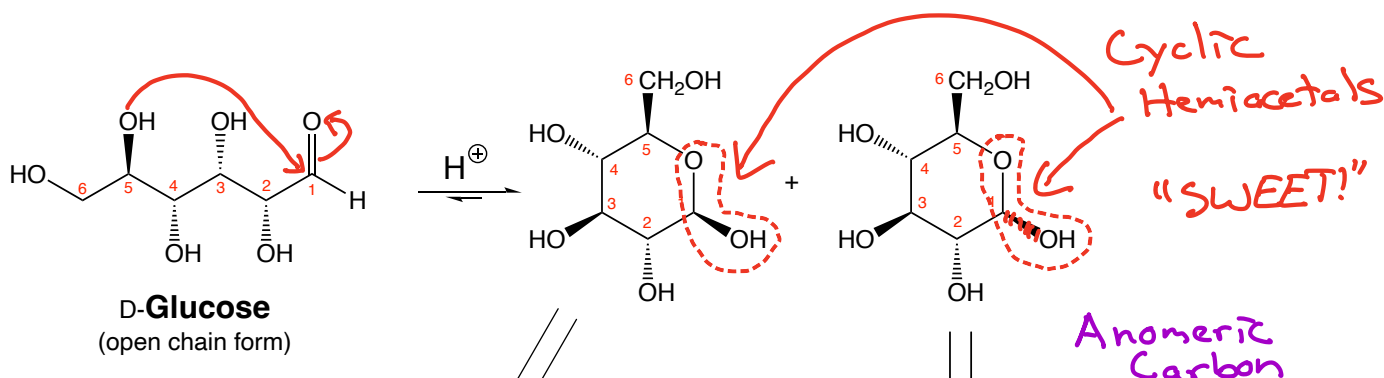


This reaction is relatively rare, and this is the only example you will see in this class

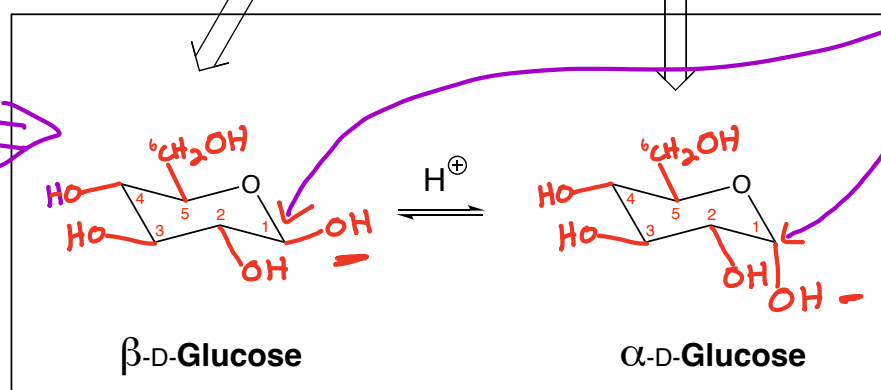
Cyclic Hemiacetals and Carbohydrates



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



This interconversion is called "mutarotation"



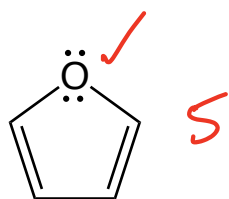
Biochemists call these two forms "anomers"

β -D-Glucopyranose
 means "6-membered ring"

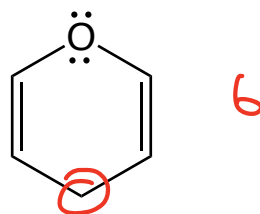
More stable → every group is equatorial!

α -D-Glucopyranose
 Less stable → one -OH is axial

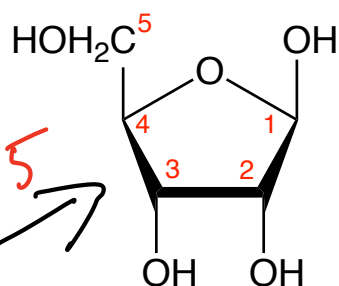
For Glucose:
 " α is axial!"



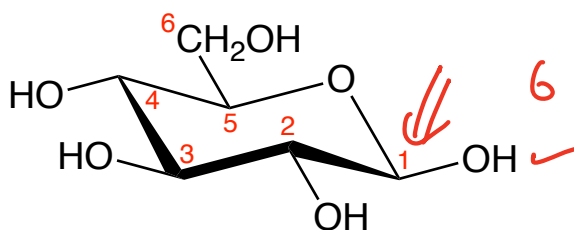
Furan ✓



Pyran

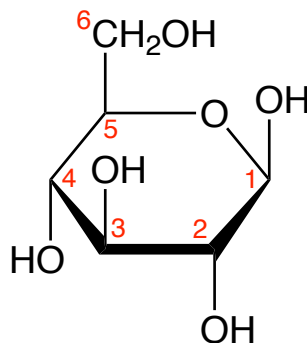


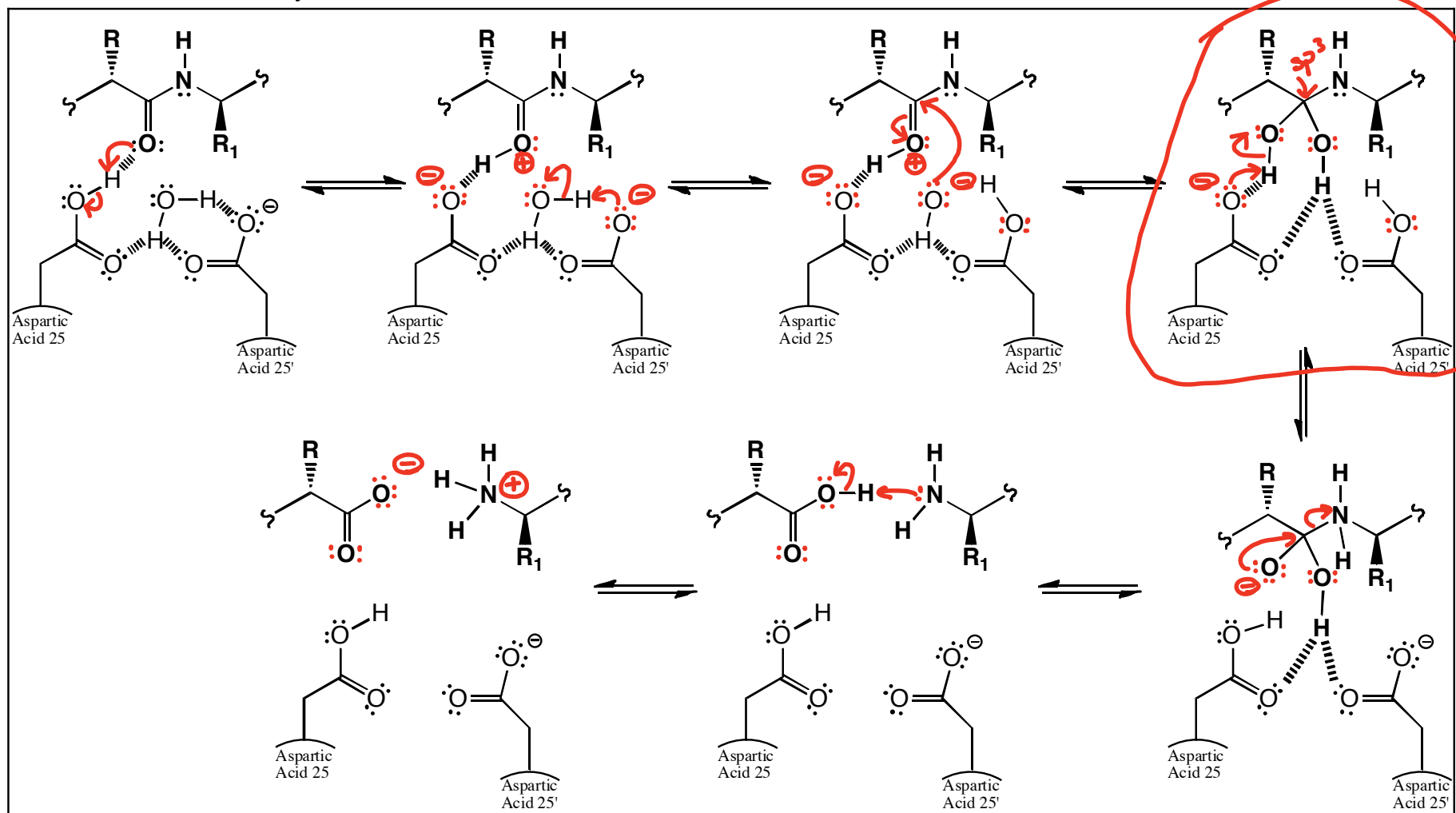
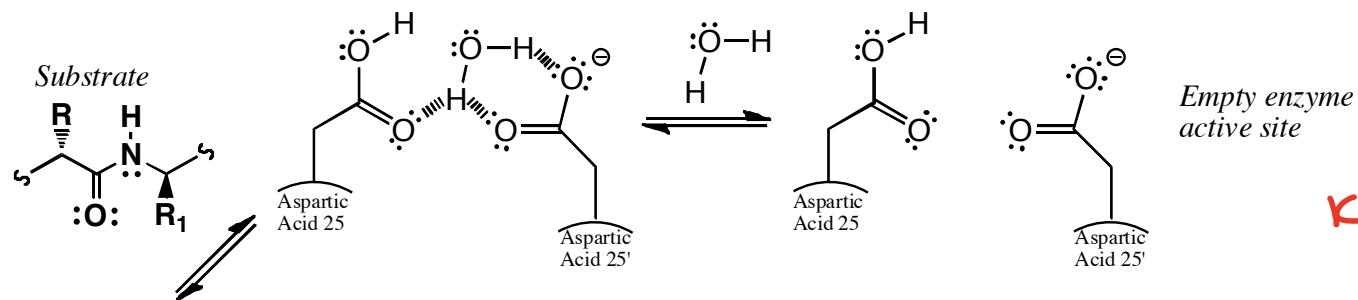
A furanose
 β -D-Ribose
 or β -D-Ribofuranose



A pyranose
 β -D-Glucose
 or β -D-Glucopyranose

This is called a
 Haworth projection





These are probably simultaneous

