File:Dream Team Basketball 1992 Olympic Games Barcelona.jpg

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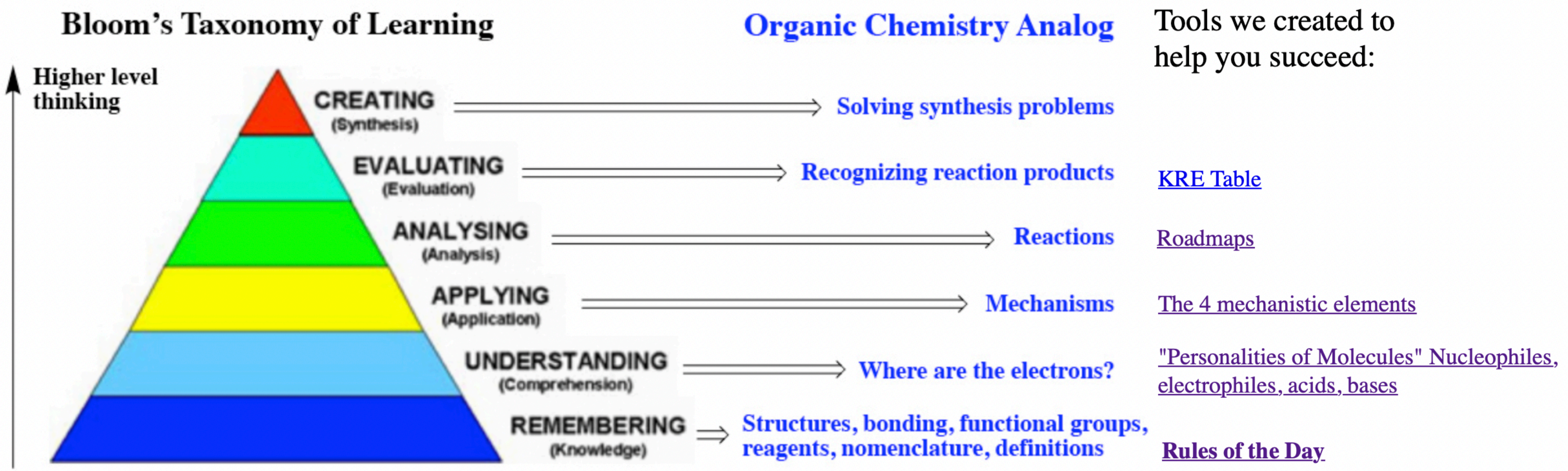
Michael

Robinson

Iverson

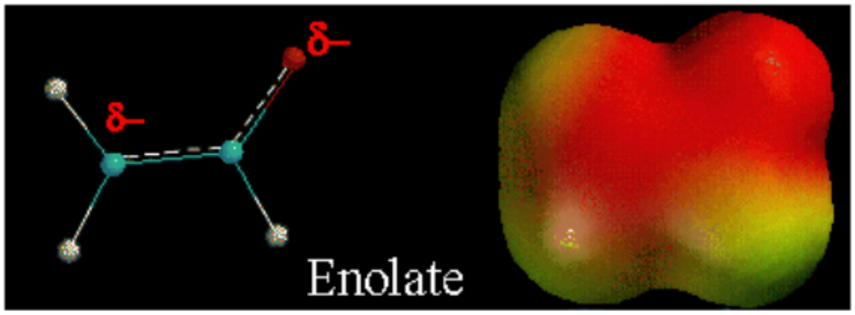


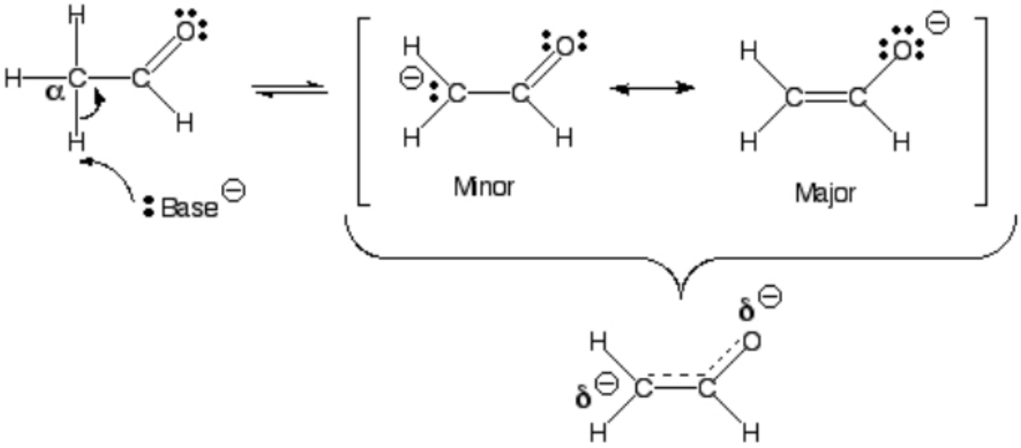
Bloom's Taxonomy of Learning	Organic Chemistry Analog	Tools we created to help you succeed:
CREATING (Synthesis)	Solving synthesis problems	
EVALUATING (Evaluation)	Recognizing reaction products	KRE Table
ANALYSING (Analysis)	Reactions	Roadmaps
APPLYING (Application)	Mechanisms	The 4 mechanistic elements
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**

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!

Enolates as nucleophiles



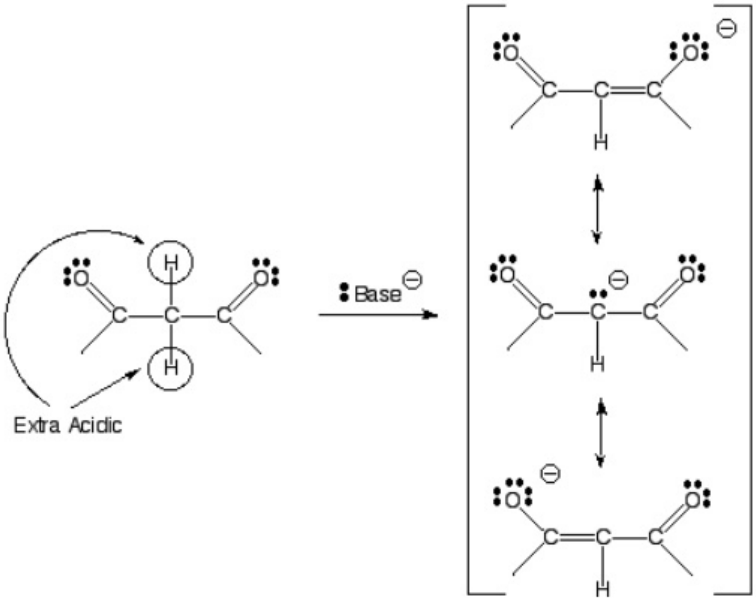


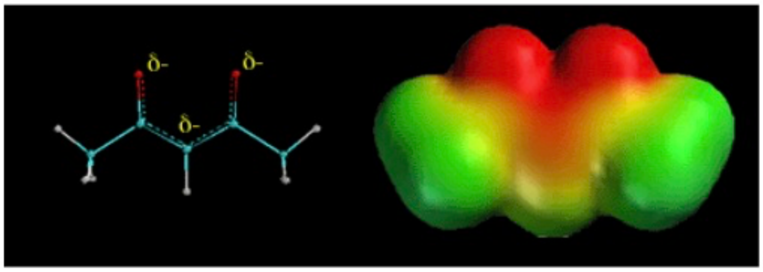
A) Enolates are resonance stabilized, with a partial negative charge on carbon and oxygen.

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.

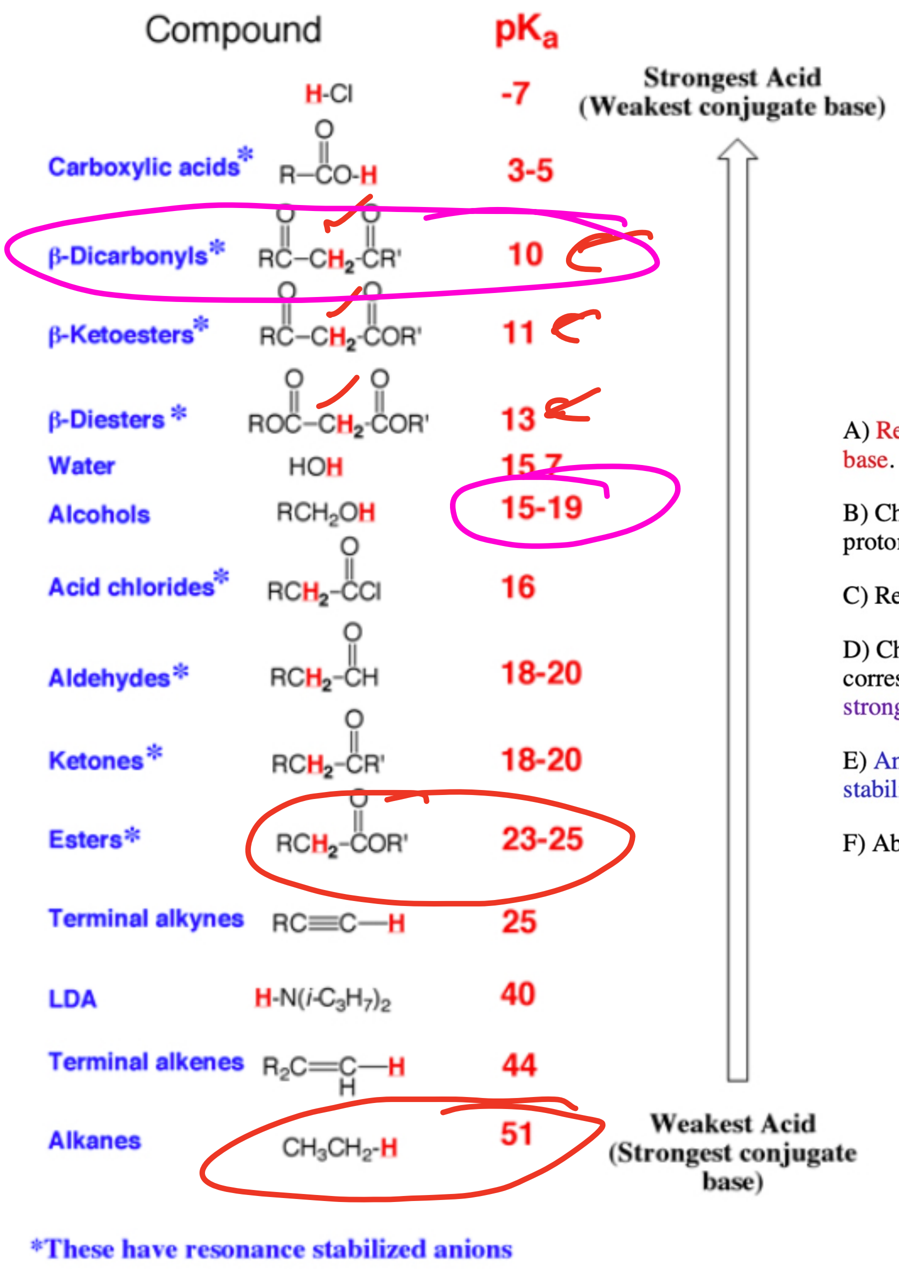
Beta-dicarbonyls have alpha-hydrogens that are extra acidic





The C-H hydrogen atoms between two carbonyl groups are aven more acidic than normal a 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.

Weaker bases are favored at equilibrium



Compound		pKa
	$H\text{-}Cl$	-7
Carboxylic acids*	$R-\overset{\overset{O}{\|}}{C}O\text{-}H$	3-5
β-Dicarbonyls*	$R\overset{\overset{O}{\|}}{C}-CH_2\text{-}\overset{\overset{O}{\|}}{C}R'$	10
β-Ketoesters*	$R\overset{\overset{O}{\|}}{C}-CH_2\text{-}\overset{\overset{O}{\|}}{C}OR'$	11
β-Diesters*	$RO\overset{\overset{O}{\|}}{C}-CH_2\text{-}\overset{\overset{O}{\|}}{C}OR'$	13
Water	HOH	15.7
Alcohols	RCH_2OH	15-19
Acid chlorides*	$RCH_2\text{-}\overset{\overset{O}{\|}}{C}Cl$	16
Aldehydes*	$RCH_2\text{-}\overset{\overset{O}{\|}}{C}H$	18-20
Ketones*	$RCH_2\text{-}\overset{\overset{O}{\|}}{C}R'$	18-20
Esters*	$RCH_2\text{-}\overset{\overset{O}{\|}}{C}OR'$	23-25
Terminal alkynes	$RC{\equiv}C-H$	25
LDA	$H\text{-}N(i\text{-}C_3H_7)_2$	40
Terminal alkenes	$R_2C{=}\underset{H}{C}-H$	44
Alkanes	$CH_3CH_2\text{-}H$	51

Strongest Acid (Weakest conjugate base)

Weakest Acid (Strongest conjugate base)

***These have resonance stabilized anions**

A) Reactions are favored (i.e. have a motive) if they lead to formation of a weaker acid and/or weaker base.

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

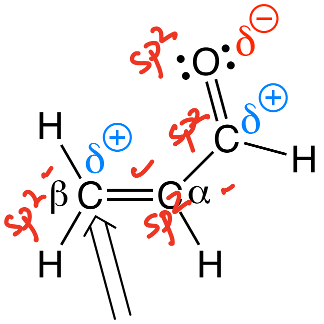
C) Recall that the conjugate base of a stronger acid (lower pKa) is a weaker base.

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

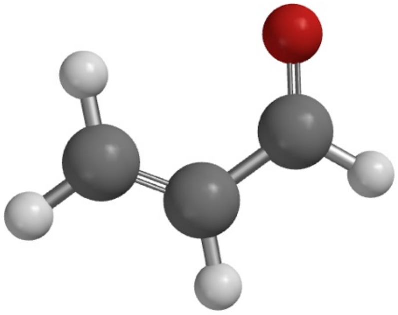
E) Another way to look at it is that the base that is favored at equilibrium is the one that has the more stabilizied anion, i.e. the one with the charge spread around more (electronegative) atoms.

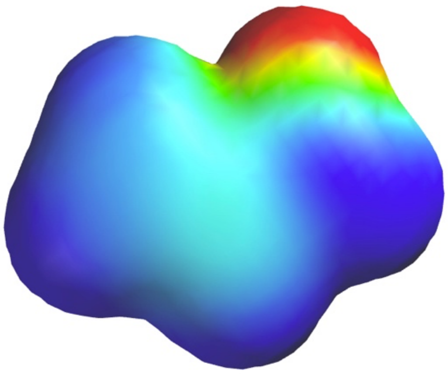
F) Above is a pKa table that we will refer to often.

Conjugate Addition



Nucleophiles react here via conjugate addition





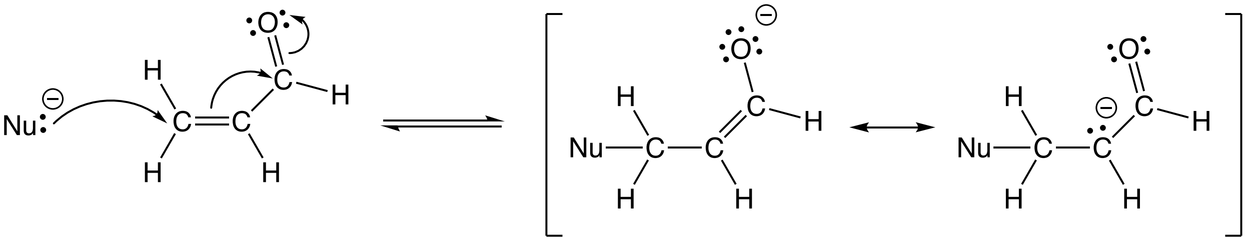
A) Alkenes adjacent to a carbonyl are conjugated and are therefore electrophilic.

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.

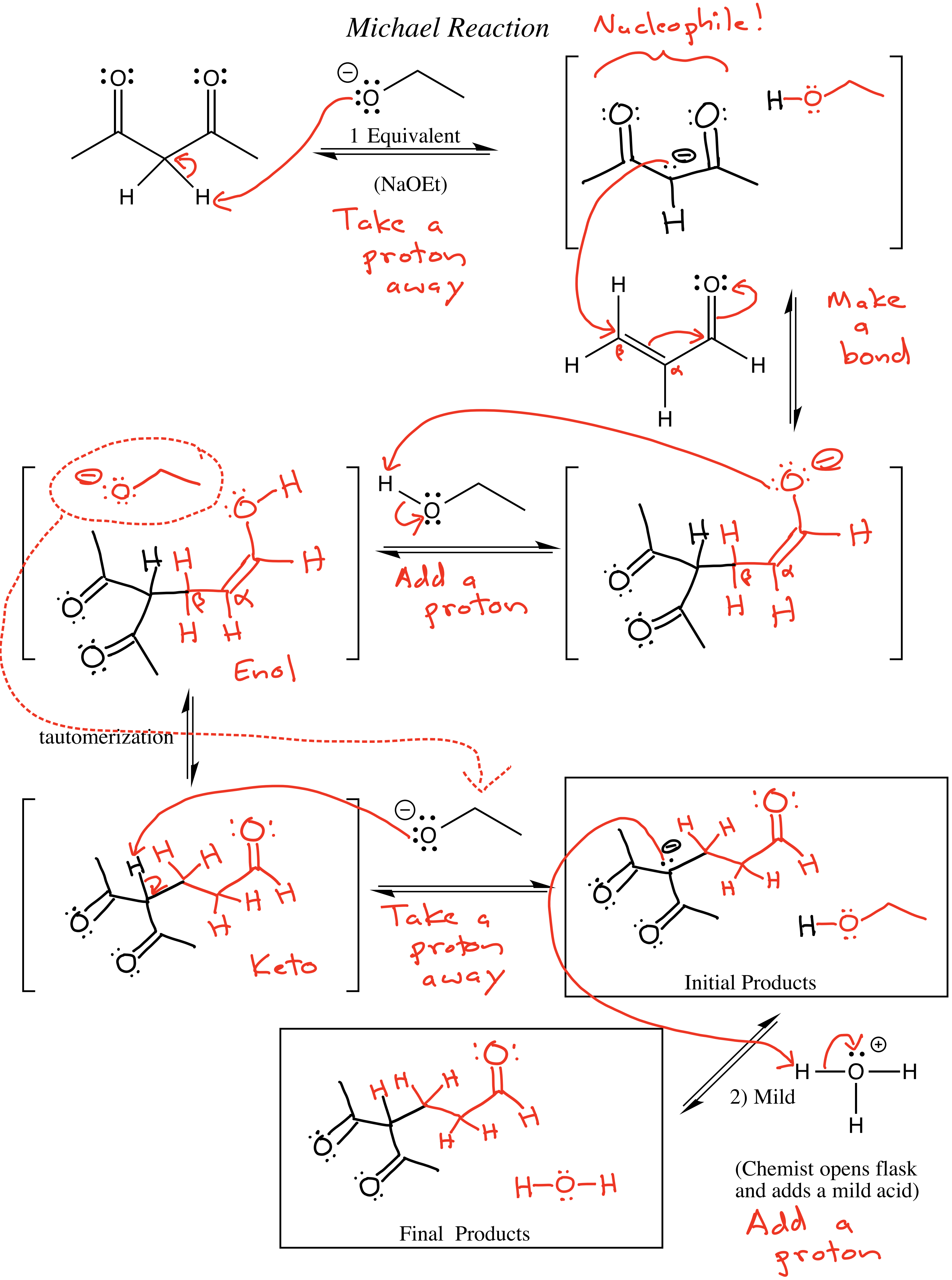
D) Nucleophiles can, however, react at the β carbon atom in a process called conjugate addition.

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

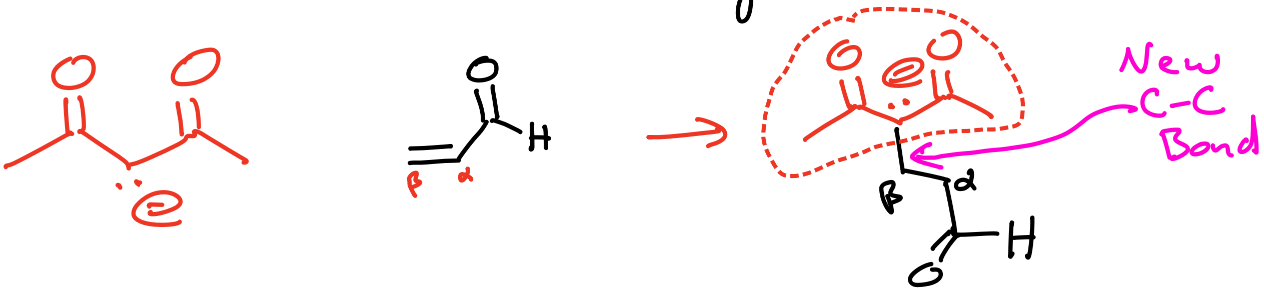


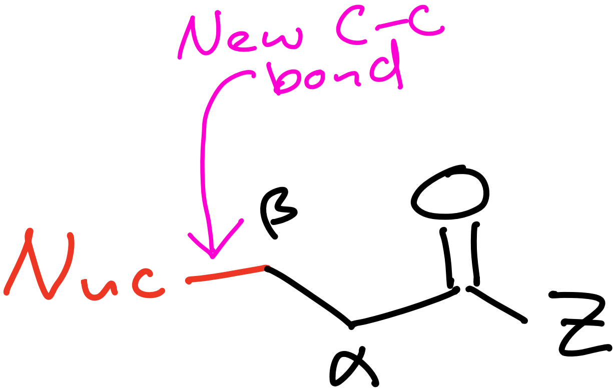
Resonance Stabilized Enolate Anion

Michael Reaction



Overall Balanced Equation

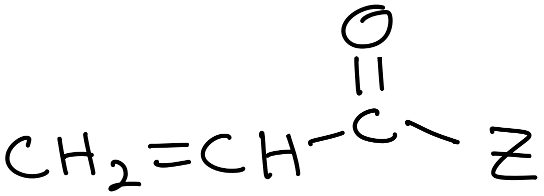




KRE → A nucleophile (Nuc) makes a new C-C bond at the β carbon of a carbonyl

Nucleophiles → β-dicarbonyl
enamine or amine

"Michael Acceptor"



$CH_2{=}CH{-}\overset{\overset{O}{\|}}{C}{-}Z$

Z = H, alkyl, –OR, –NHR′

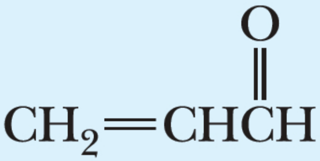
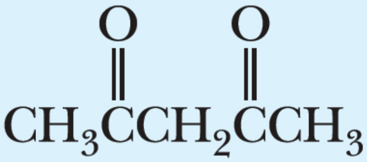
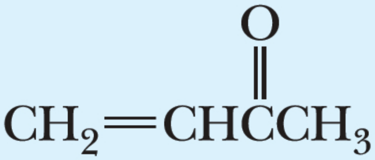
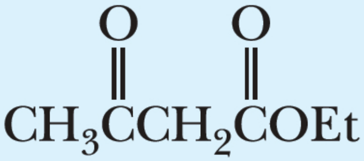
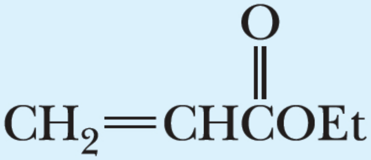
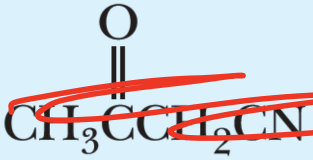
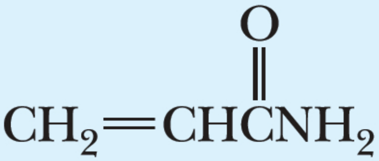
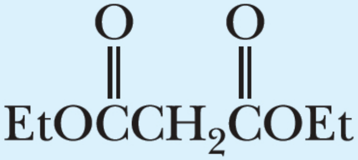
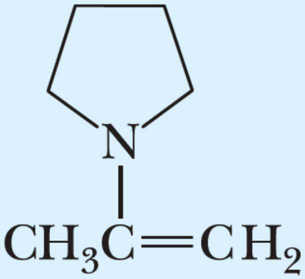
H ← aldehyde

alkyl ← ketone

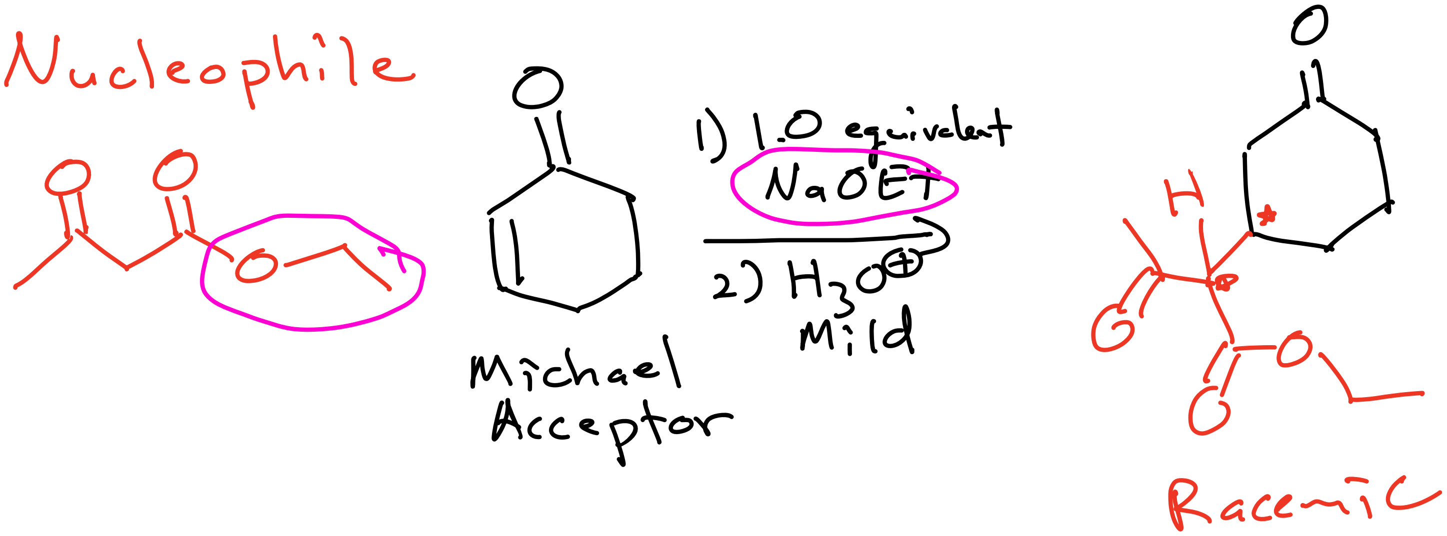
–OR ← ester

–NHR′ ← amide

Table 19.1 Combinations of Reagents for Effective Michael Reactions

These Types of *α,β*-Unsaturated Compounds Are Nucleophile Acceptors in Michael Reactions		These Types of Compounds Provide Effective Nucleophiles for Michael Reactions	
 $CH_2=CH\overset{\overset{O}{\|}}{C}H$	Aldehyde	 $CH_3\overset{\overset{O}{\|}}{C}CH_2\overset{\overset{O}{\|}}{C}CH_3$	*β*-Diketone
 $CH_2=CH\overset{\overset{O}{\|}}{C}CH_3$	Ketone	 $CH_3\overset{\overset{O}{\|}}{C}CH_2\overset{\overset{O}{\|}}{C}OEt$	← Claisen *β*-Ketoester
 $CH_2=CH\overset{\overset{O}{\|}}{C}OEt$	Ester	 ~~$CH_3\overset{\overset{O}{\|}}{C}CH_2CN$~~	~~*β*-Ketonitrile~~
 $CH_2=CH\overset{\overset{O}{\|}}{C}NH_2$	Amide	 $EtO\overset{\overset{O}{\|}}{C}CH_2\overset{\overset{O}{\|}}{C}OEt$	*β*-Diester
~~$CH_2=CHC\equiv N$~~	~~Nitrile~~		Enamine
~~$CH_2=CHNO_2$~~	~~Nitro compound~~	NH_3, RNH_2, R_2NH	Amine

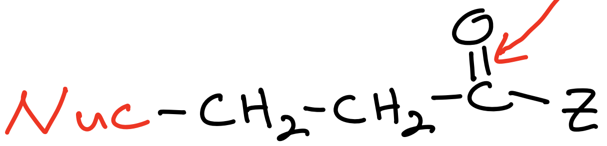
Example


Nucleophile
O
O
O
O
Michael Acceptor
1) 1.0 equivalent NaOEt
2) H3O⊕ Mild
O
H
*
O
O
O
Racemic

Why is conjugate addition (reaction at C=C) favored over reaction at the carbonyl carbon?

Motive - Products

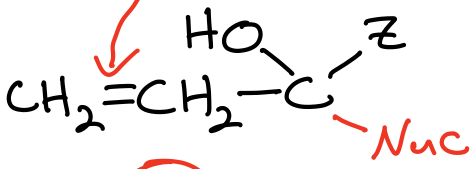
C=O is a stronger bond than C=C



$Nuc-CH_2-CH_2-C(=O)-Z$

Ⓐ

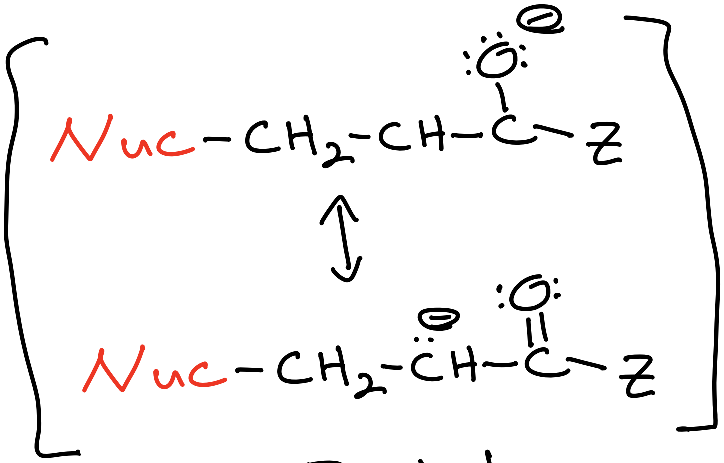
vs.



$CH_2=CH_2-C(OH)(Z)-Nuc$

Ⓑ

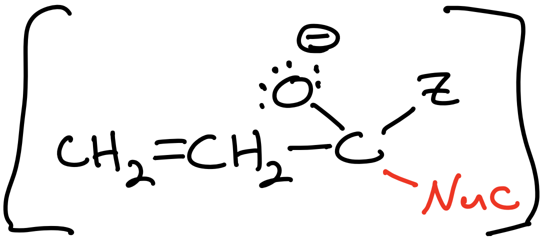
Opportunity - Intermediates



Ⓒ

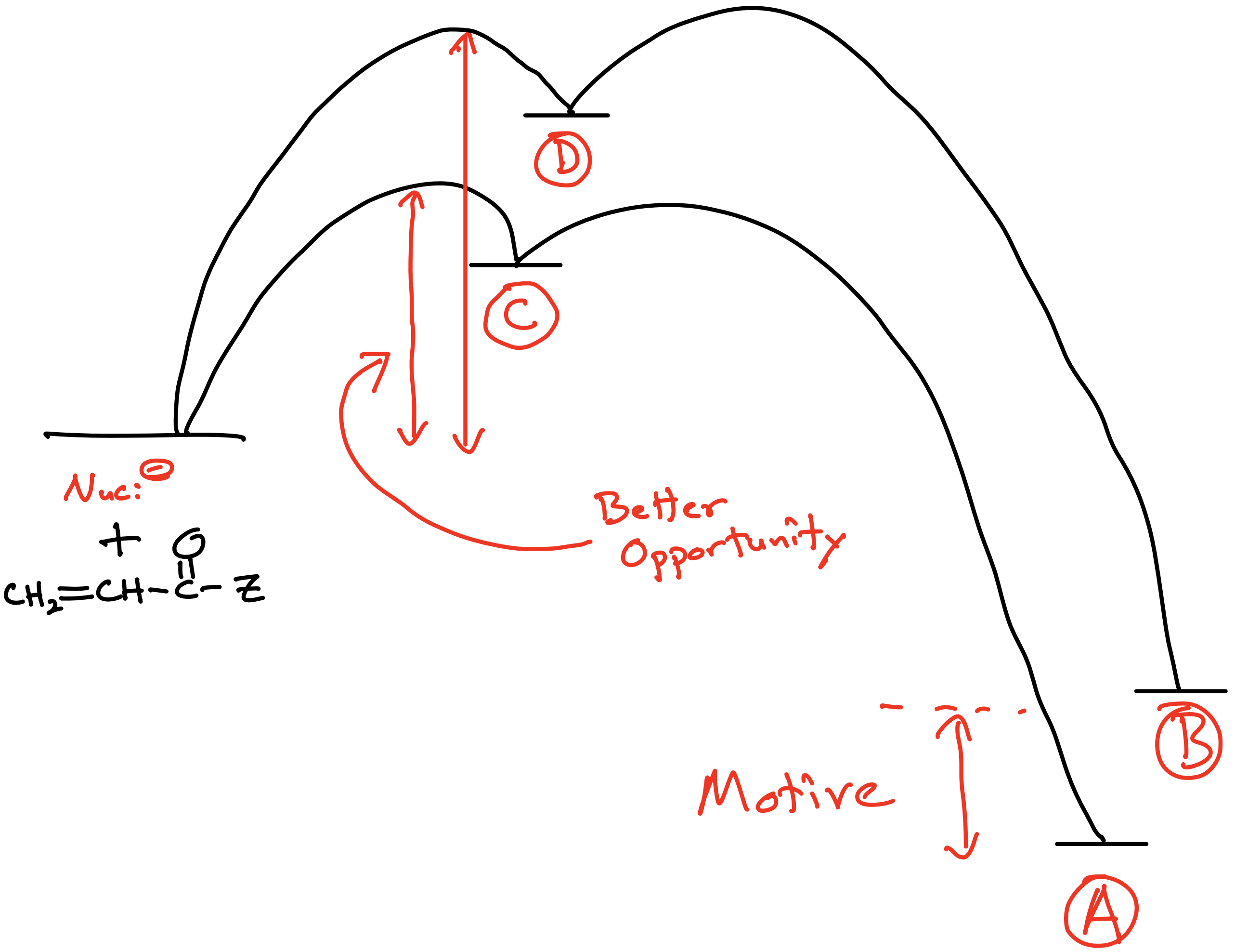
Enolate Intermediate

Stabilized by charge delocalization and a pi-way

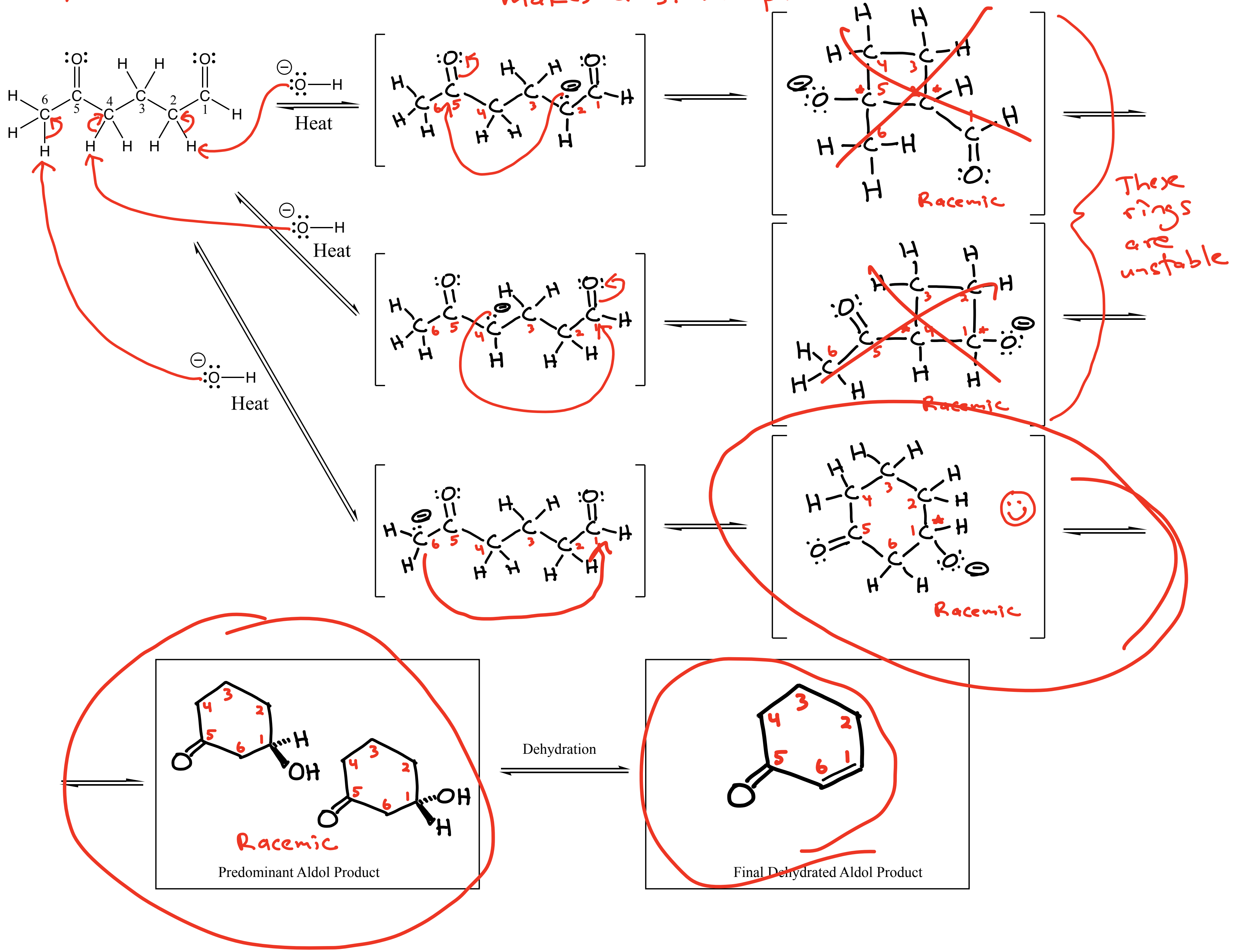


Ⓓ

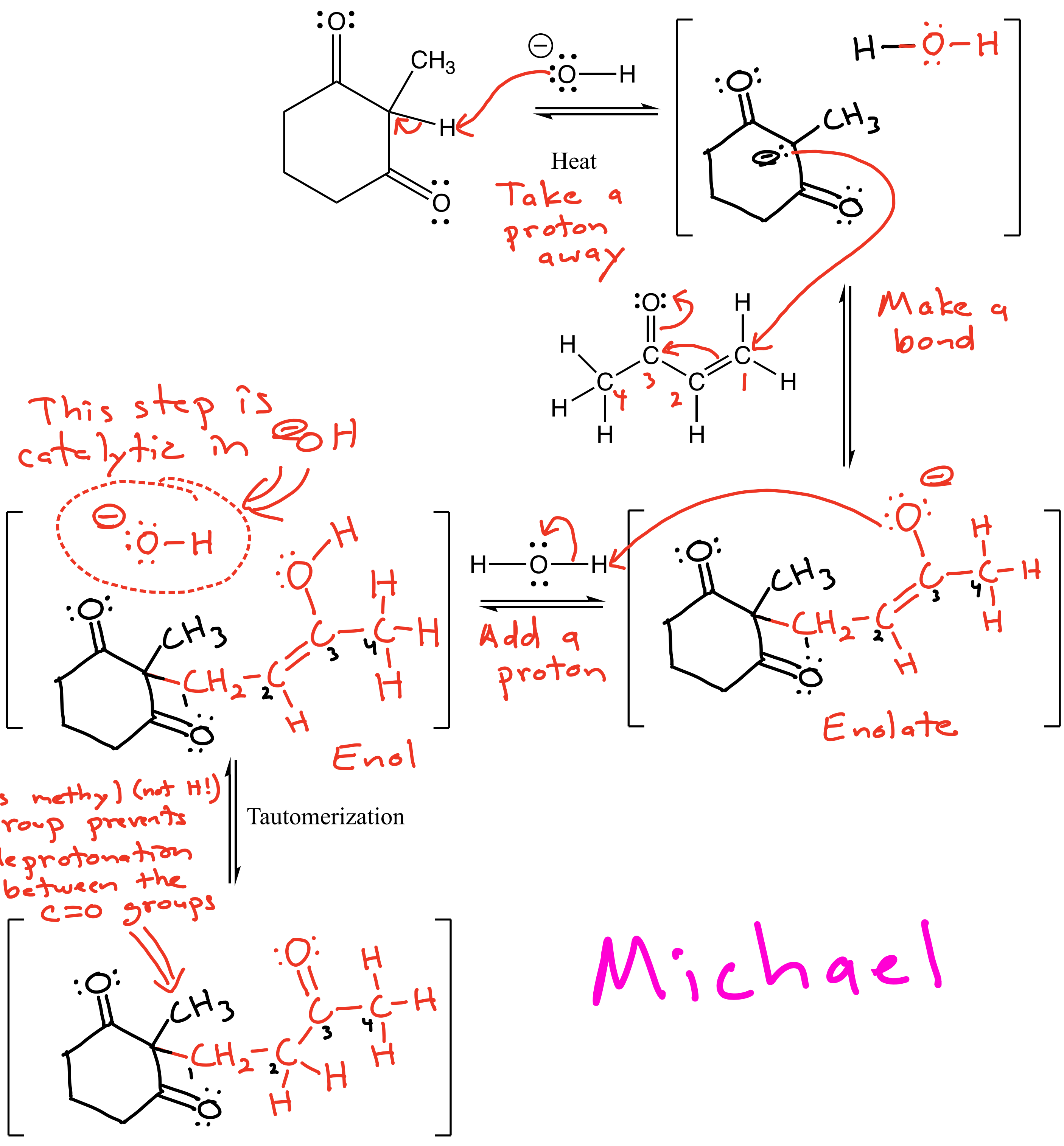
No charge delocalization or pi-way


D
C
Nuc:⊖
+
$CH_2=CH-\overset{O}{\overset{\|}{C}}-Z$
Better Opportunity
Motive
B
A

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



Robinson Annulation Part 1 - Michael Reaction Steps



Take a proton away

Make a bond

Add a proton

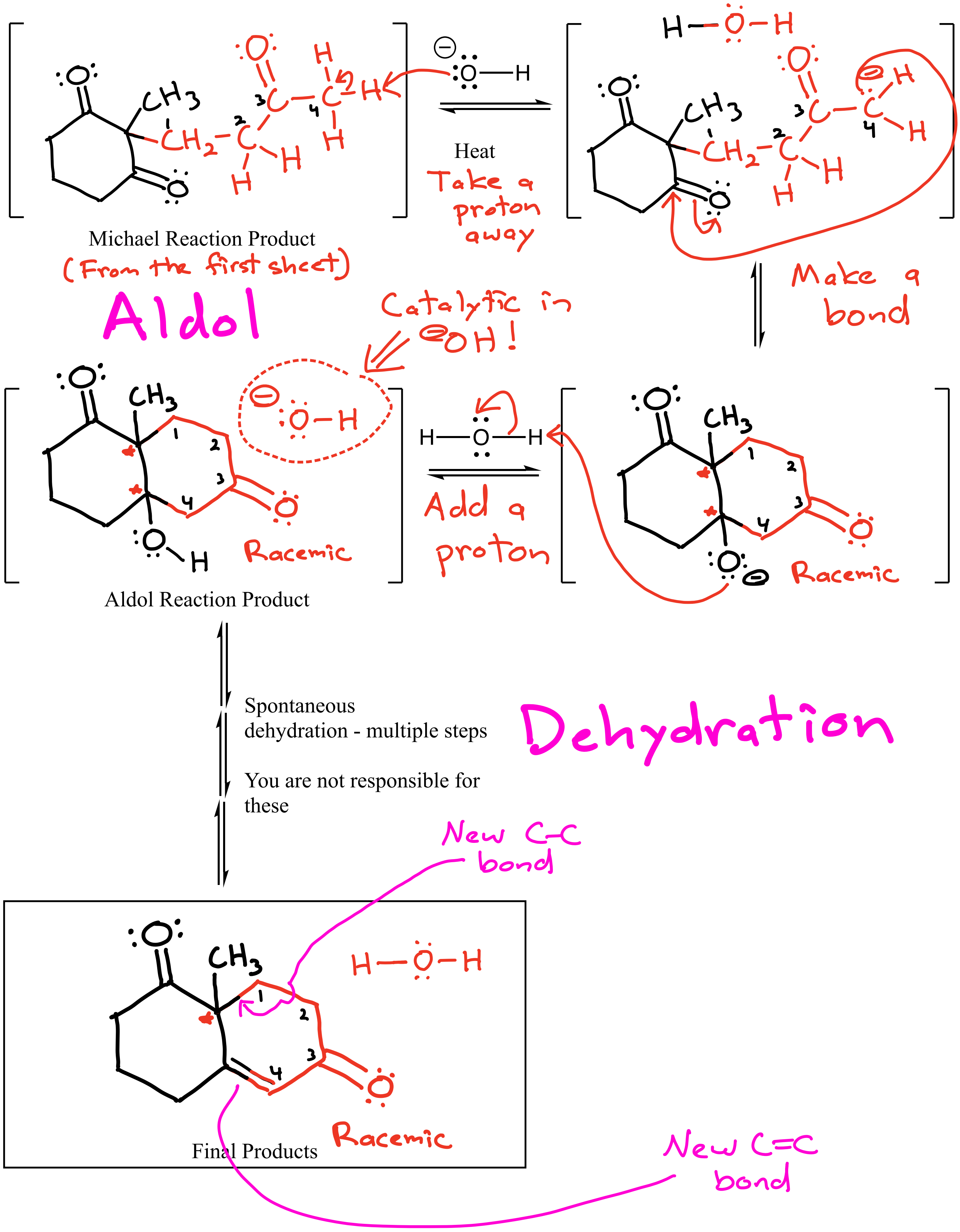
This step is catalytic in ⊖OH

This methyl (not H!) group prevents deprotonation between the C=O groups

Michael Reaction Product

Michael

Robinson Annulation Part 2 - Aldol and Dehydration Steps



Michael Reaction Product

(From the first sheet)

Heat

Take a proton away

Make a bond

Add a proton

Catalytic in ⊖OH!

Racemic

Aldol Reaction Product

Aldol

Spontaneous dehydration - multiple steps

You are not responsible for these

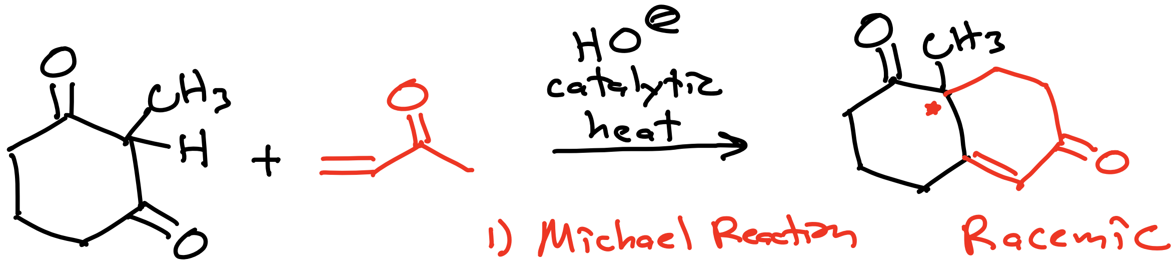
Dehydration

Final Products

New C–C bond

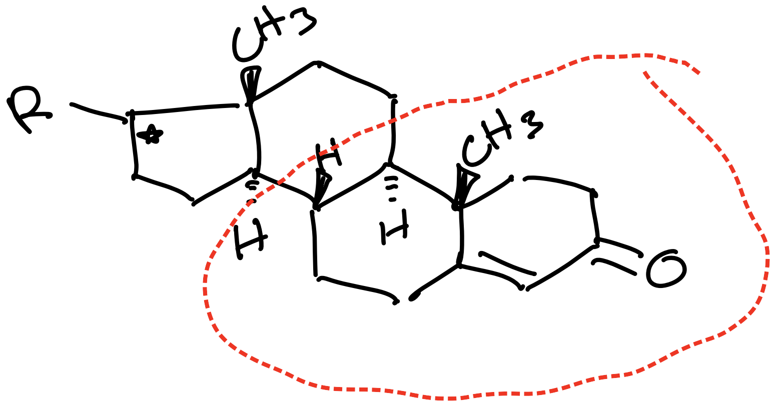
New C=C bond

This is the only Robinson annulation reaction you will see on exams



1) Michael Reaction
2) Aldol Reaction
3) Dehydration

AKA "Dream Team" of reactions that happen in a cascade



The Robinson annulation can be used to assemble complex molecules like this steroid

File:Dream Team Basketball 1992 Olympic Games Barcelona.jpg

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