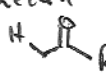
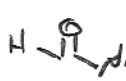
Chapter 19 - Carbonyl chemistry II

(1) Enols & enolates

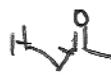
Recall pKa

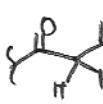
 ~19

 24

 25

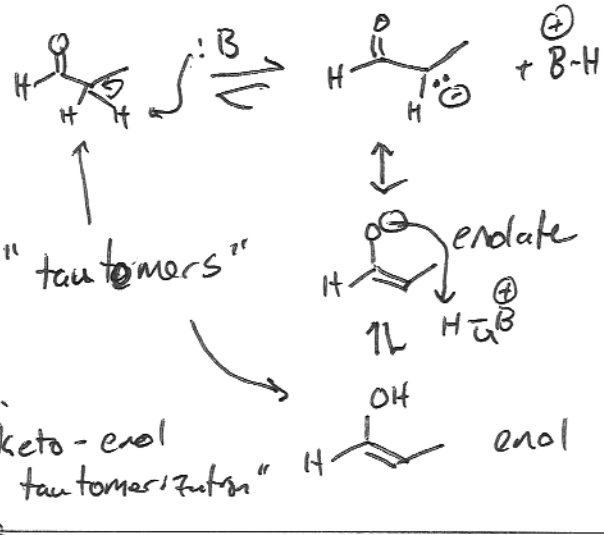
(A) α Hs of carbonyls are acidic

 ~15–20 aldehydes similar to ketones

 ~9 dicarbonyls v. acidic

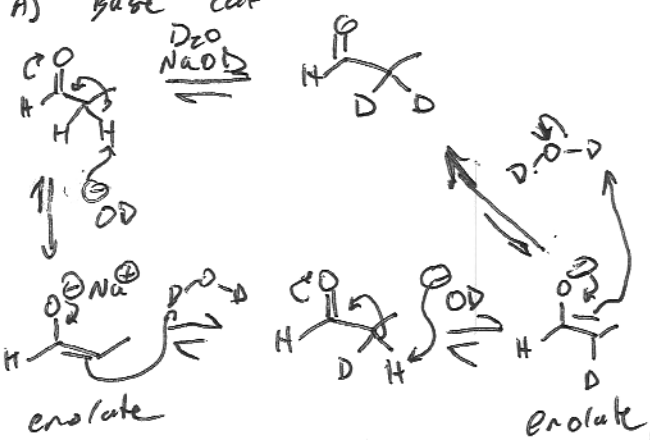
comment on why

(2)

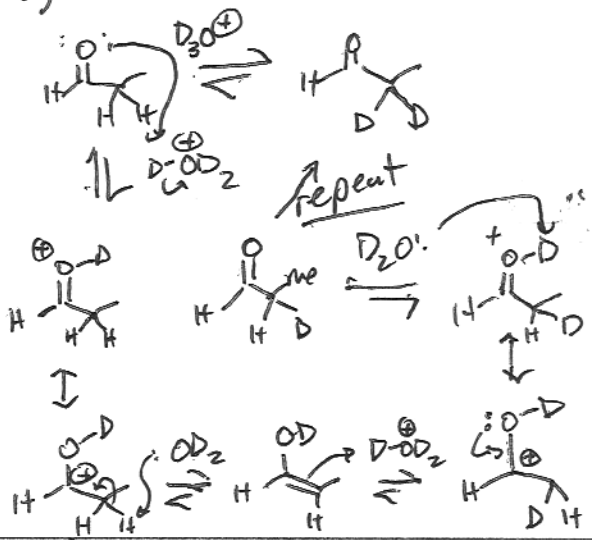


(3) H/D exchange (Acid or Base cat)

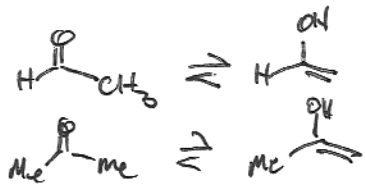
A) Base cat



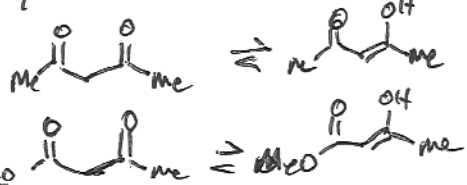
(4) B) Acid cat



(5) Equilibrium Keto/Enol forms



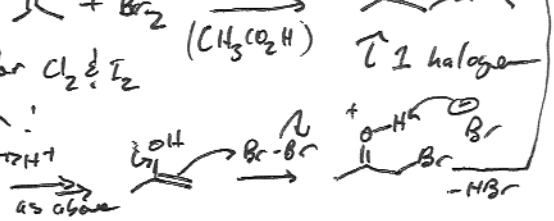
favors keto form for normal aldehydes & ketones



More favorable w/ β-dicarbonyls ∴ conjugation!

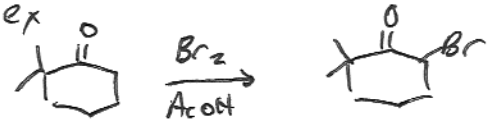
(6) Reactions at the α-carbon

(A) Acid cat Halogenations

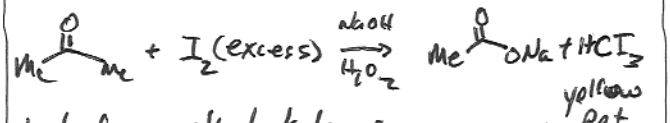
Ex 

also for Cl_2 & I_2

Mech:

ex 

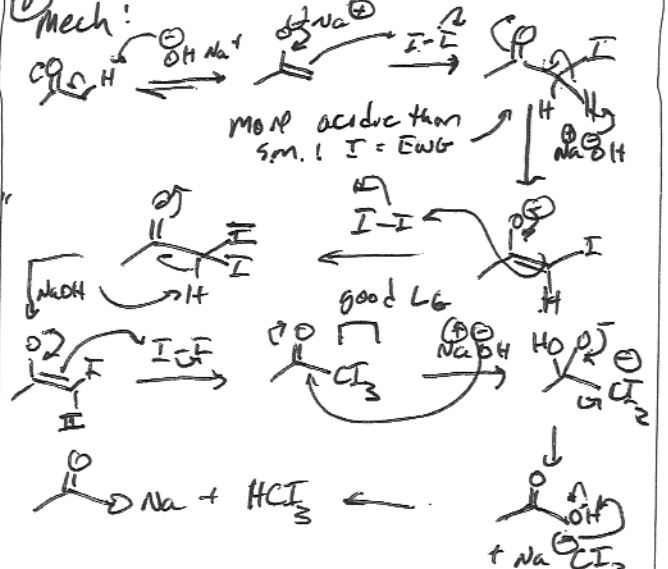
(7) Base cat. Halogenation - Haloform Rxn



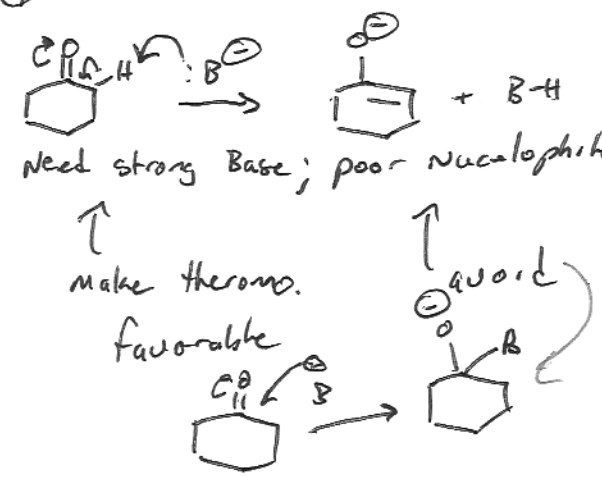
test for methyl ketones

yellow ppt "iodoform"

(8) Mech:



(9) closer look at enolate formation



Need strong Base; poor Nucleophile

make thermo. favorable

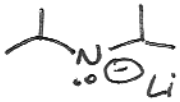
avoid

(10) Common Bases for enolate formation

(1) NaH or KH pka' ~ 35

(2) $tO^{\ominus}K^{\oplus}$ / tOH pka' ~17 (ketones only)

(3) LDA (Lithium diisopropyl amide)



pka' ~ 35

(4) Et_3N: triethylamine pka' ~9

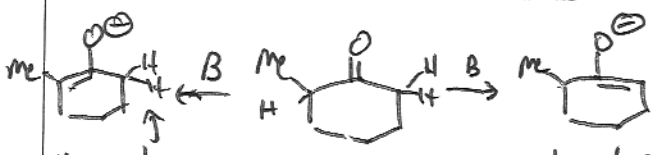
Ex

lithium enolate

(11) Stability of enolates

Thermodynamic vs kinetic

More substituted = more stable



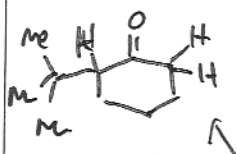
thermodynamic

More sub.
more stable

kinetic

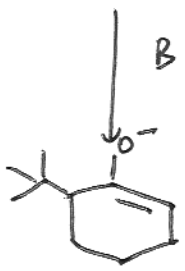
less sub.
less stable

(12) Kinetic enolates form first



which deprotonated first?

less steric encumberance



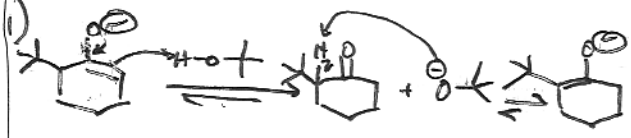
Note: Add ketone to base

kinetic enolate

how to form thermodynamic enolate?

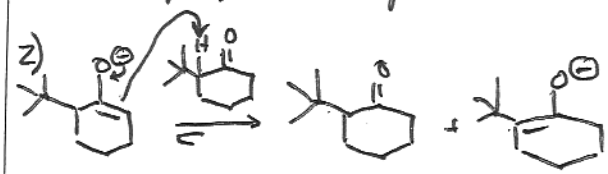
(13) Thermodynamic enolate formation two methods

1)



Run in presence of proton sources

2)

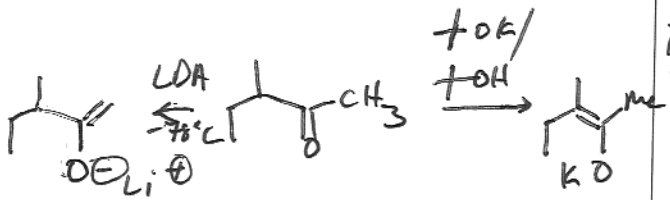


or run w/ excess ketone present
a) add base slowly to ketone or
b) use a "slow" base

(14) Conditions vs enolate geometry:

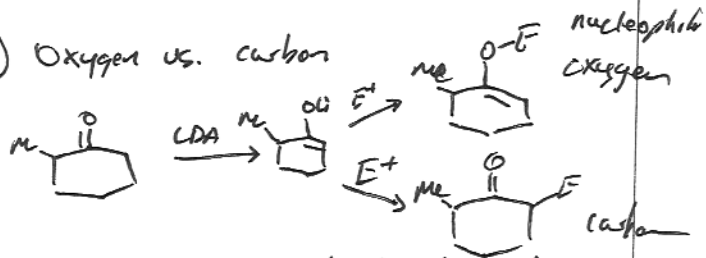
Kinetic	Thermo
- Rapid deprotonation	- slow deprotonation
- Quantitative deprotonation	- Excess ketone
- low temp (T < 0°C)	- Reversible Deprotonation
- strong base	- Higher temp (T > 0°C)
- Irreversible deprotonation	- allow equilibration
Ideal base: LDA, < 0°C	Ideal TEA or $t\text{-}O^-/t\text{-}OH$ at RT

(15) ex



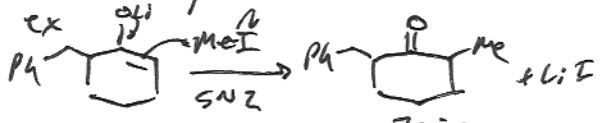
(16) Enolate Rxns with Electrophiles

1) Oxygen vs. carbon



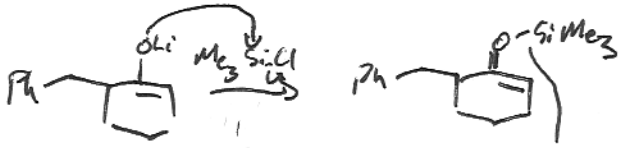
O vs C selectivity depends on nature of electrophile

(17) C-alkylation - most electrophiles



Also w/ ester & amide enolates

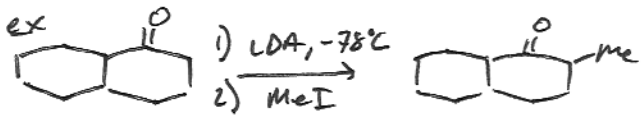
O-alkylation - silicon electrophiles



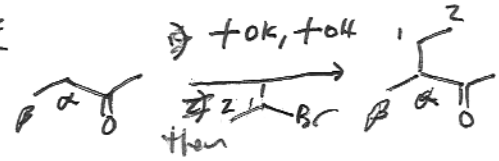
(C-Si 69 kcal/mol)

O-Si strong ~ 120 kcal/mol

(18) C α - alkylations

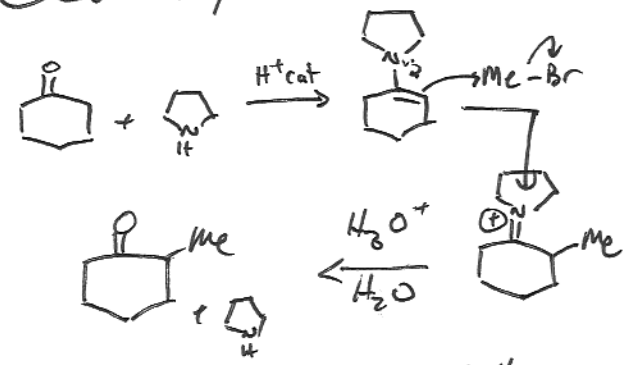


ex



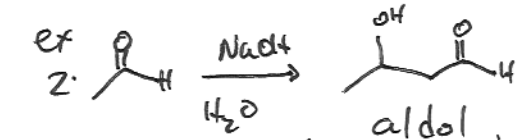
Note these are SN2 rxns! Enolates are basic. Sterically demanding electrophiles, 2° electrophile E2 completes. Limited to MeI, Bn-Br, Et-Br, allyl-Cl etc

(19) α-alkylation via enamines



3 steps - but often better behaved

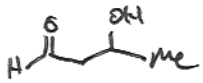
(20) Aldol Reactions



aldol
(aldehyde & alcohol)

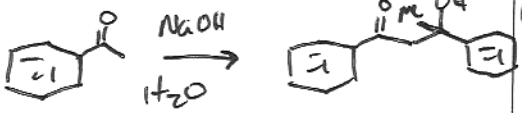
Base cat mech:

Note: carbonyl is both nucleophile & electrophile in this rxn!

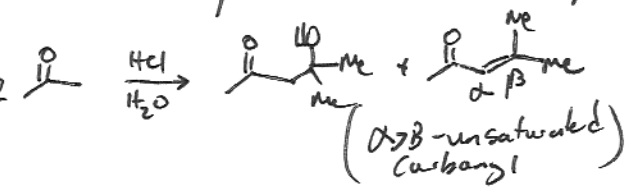


(21)

Ex 2.



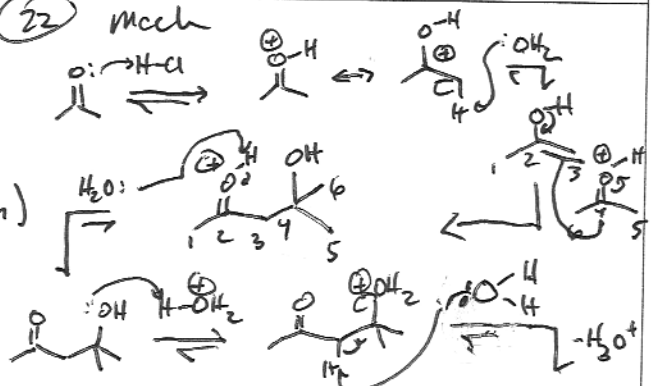
Acid catalyzed Aldol (watch for dehydration)



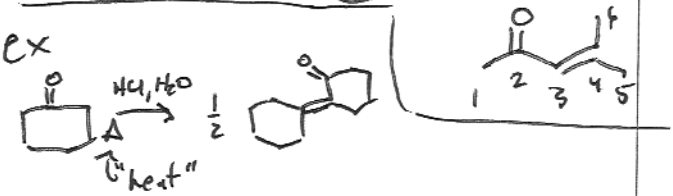
(α,β-unsaturated carbonyl)

(heat + acid favors dehydration product)

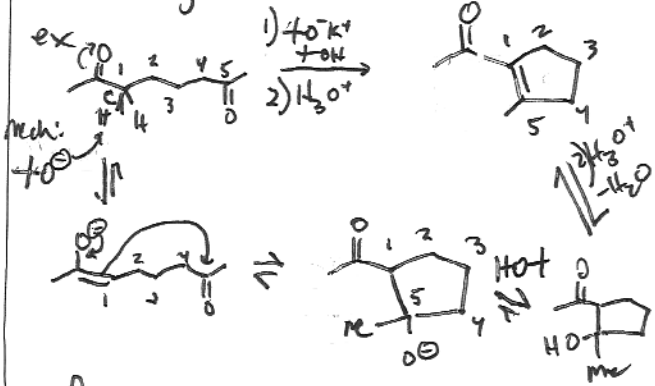
(22) mech



ex



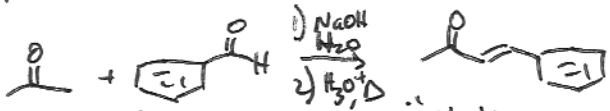
(23) Intramolecular Aldols (Acid or Base cat)
- favorable if 5- or 6-membered ring is formed



form α,β-unsaturated ketone

(24) Aldol cross coupling

method 1



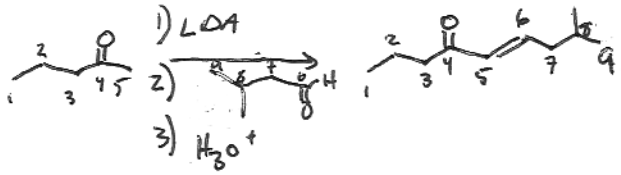
must be electrophile
- no α-hydrogens
∴ can't form enolate

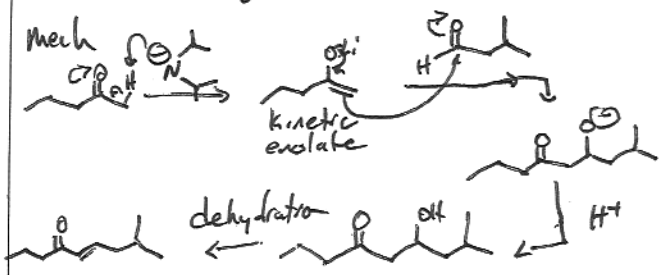
∴ Claisen-Schmidt condensation

force one partner to be electrophile

(25) Cross Aldol method # 2

form kinetic enolate first

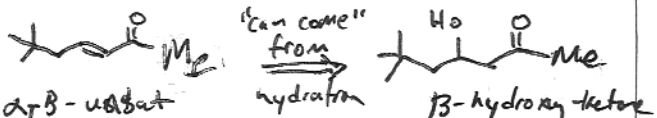


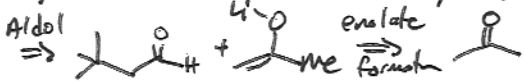


(26) Side note - Retrosynthetic analysis

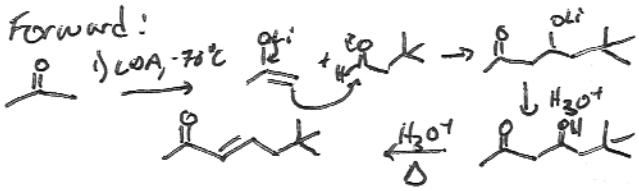
How to make  ?

Work Backward!



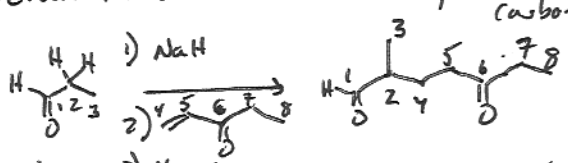


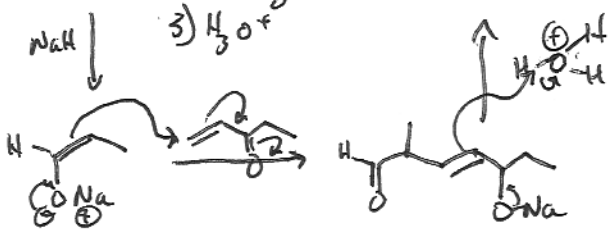
Forward:



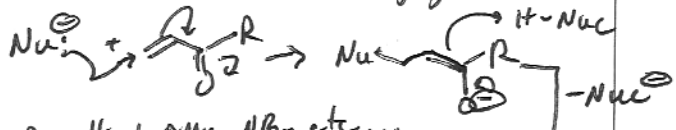
(27) Rxn of α,β-unsaturated Carbonyls

Micheal Reaction = enolate + α,β-unsat carbonyl

ex 

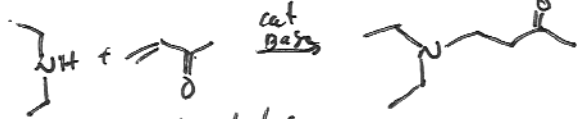


(28) General Rxn "conjugate addition"

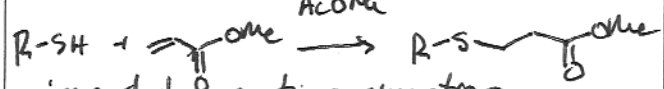


R = alkyl, OMe, NR_2, etc...

a) amine nucleophiles



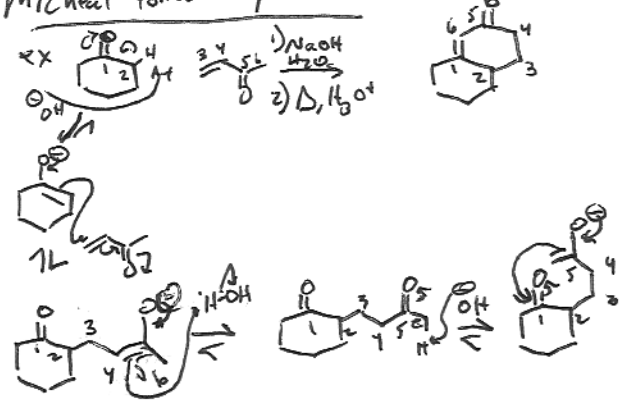
b) sulfur nucleophiles



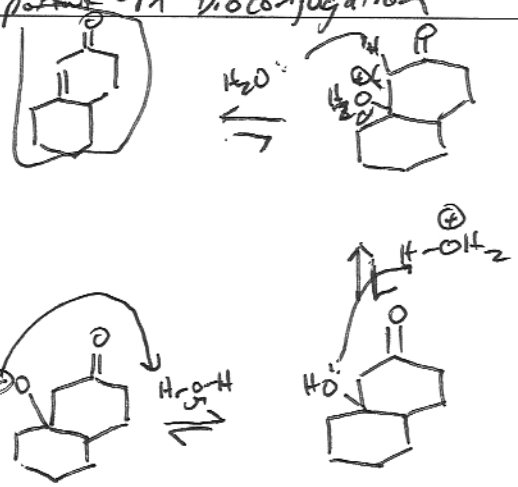
important in bioconjugation

(29) Robinson Annulation: Build 6-membered Rings

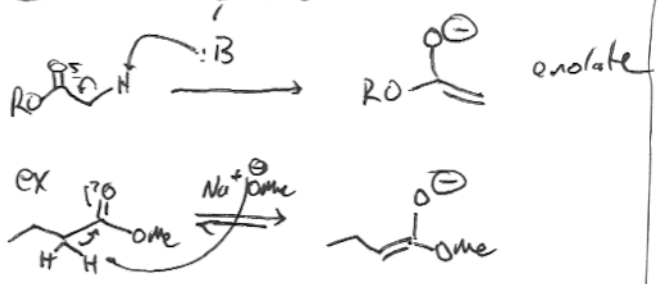
Micheal followed by Aldol



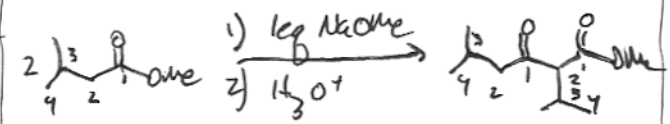
(30)



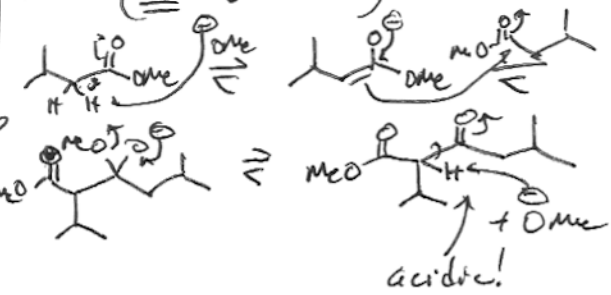
(31) Esters & Enolates



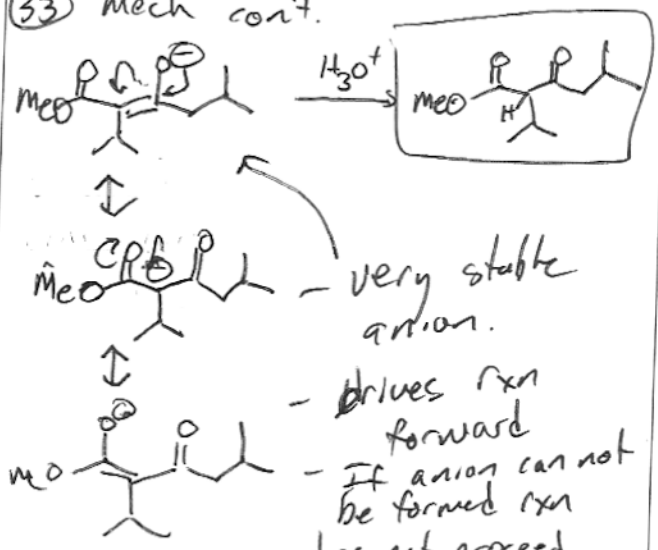
(32) Claisen condensation



Mech (NOT Base cat)

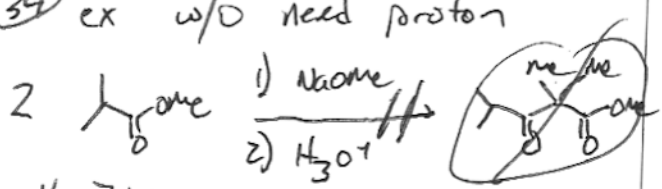


(33) Mech cont.

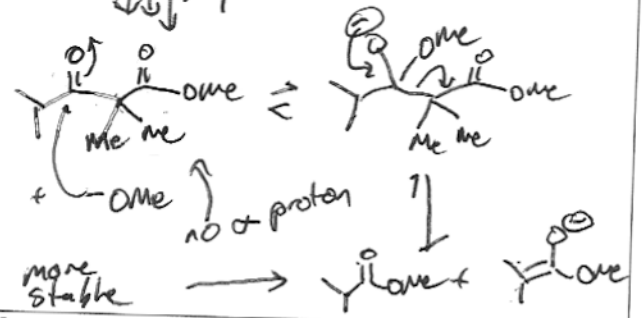


- very stable anion.
- drives rxn forward
- If anion can not be formed rxn does not proceed.

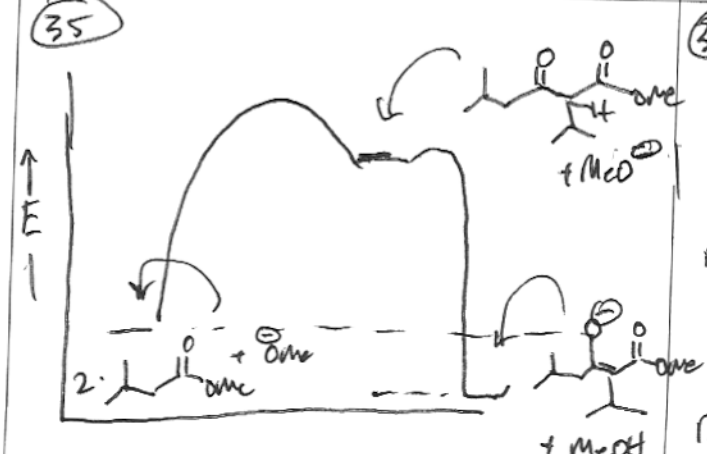
(34) ex w/o need proton



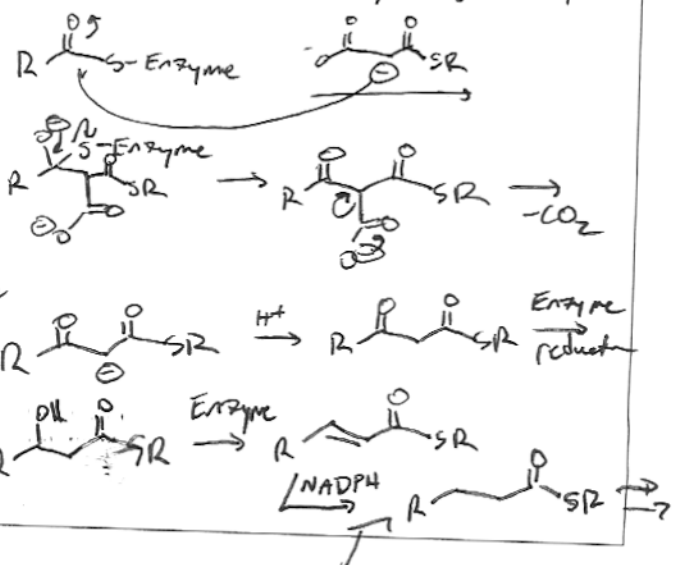
Why? ↓↓↓ steps



(35)



(36) Claisen Cond. in Biology: Fatty Acid Synthesis



sm + 2 carbons

Add 34 here

37 Acid cat. decarboxylation of β-keto esters