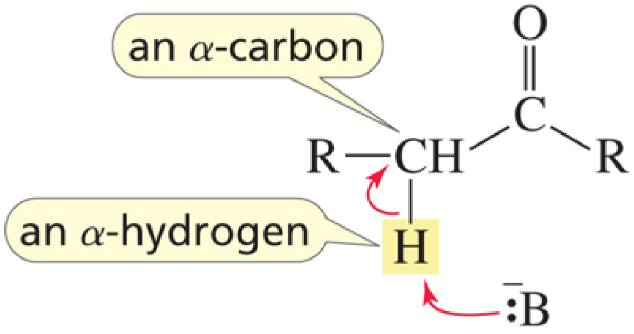
Chapter 17

Reactions at α-C of Carbonyls

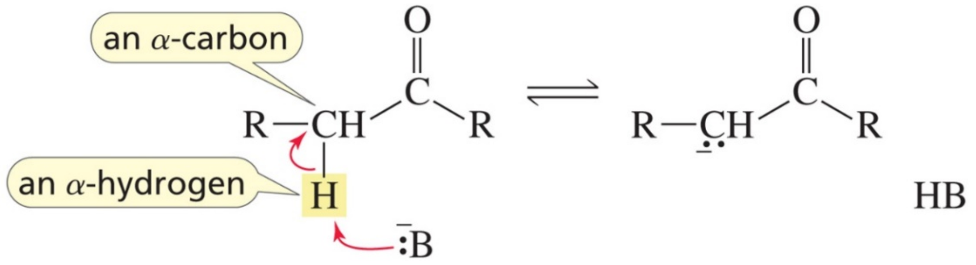
rxns removing α-H

addition/condensation



α-H is acidic.

- removed by (strong) B:



- acidity of carbon acid

carbon acid = sp^3 C–H ≠ carbonic acid

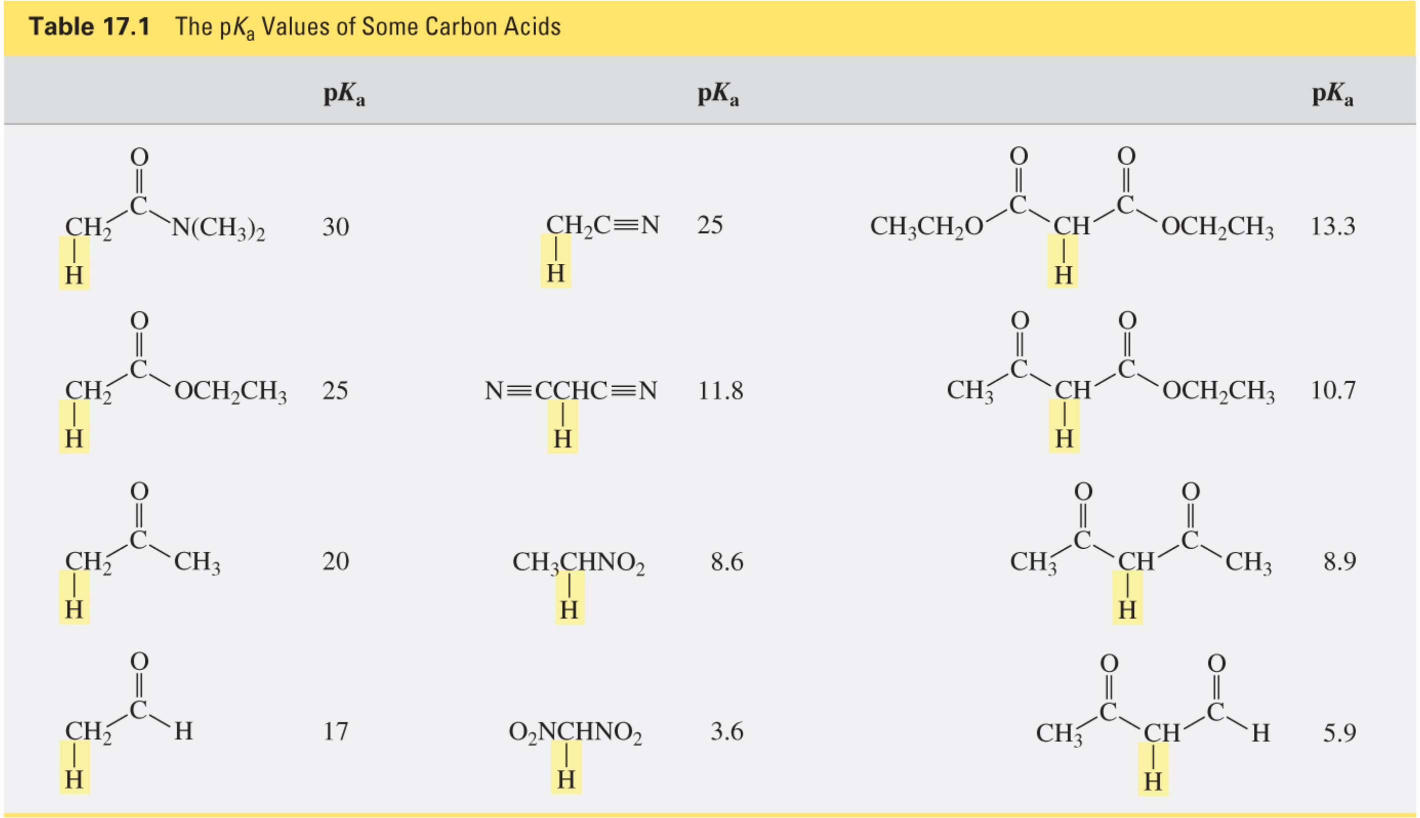


Table 17.1 The pK_a Values of Some Carbon Acids

	pK_a		pK_a		pK_a
$\underset{\substack{\vert\\ H}}{CH_2}-\overset{\substack{O\\ \Vert}}{C}-N(CH_3)_2$	30	$\underset{\substack{\vert\\ H}}{CH_2}C\equiv N$	25	$CH_3CH_2O-\overset{\substack{O\\ \Vert}}{C}-\underset{\substack{\vert\\ H}}{CH}-\overset{\substack{O\\ \Vert}}{C}-OCH_2CH_3$	13.3
$\underset{\substack{\vert\\ H}}{CH_2}-\overset{\substack{O\\ \Vert}}{C}-OCH_2CH_3$	25	$N\equiv C\underset{\substack{\vert\\ H}}{CH}C\equiv N$	11.8	$CH_3-\overset{\substack{O\\ \Vert}}{C}-\underset{\substack{\vert\\ H}}{CH}-\overset{\substack{O\\ \Vert}}{C}-OCH_2CH_3$	10.7
$\underset{\substack{\vert\\ H}}{CH_2}-\overset{\substack{O\\ \Vert}}{C}-CH_3$	20	$CH_3\underset{\substack{\vert\\ H}}{CH}NO_2$	8.6	$CH_3-\overset{\substack{O\\ \Vert}}{C}-\underset{\substack{\vert\\ H}}{CH}-\overset{\substack{O\\ \Vert}}{C}-CH_3$	8.9
$\underset{\substack{\vert\\ H}}{CH_2}-\overset{\substack{O\\ \Vert}}{C}-H$	17	$O_2N\underset{\substack{\vert\\ H}}{CH}NO_2$	3.6	$CH_3-\overset{\substack{O\\ \Vert}}{C}-\underset{\substack{\vert\\ H}}{CH}-\overset{\substack{O\\ \Vert}}{C}-H$	5.9

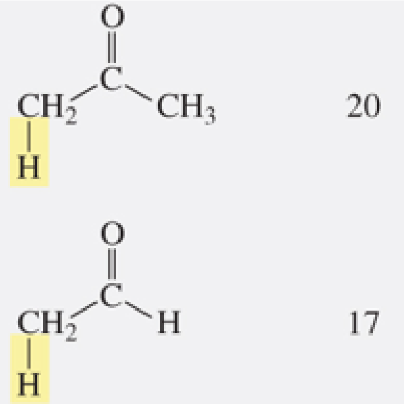
- acidity of α-C (cont'd)

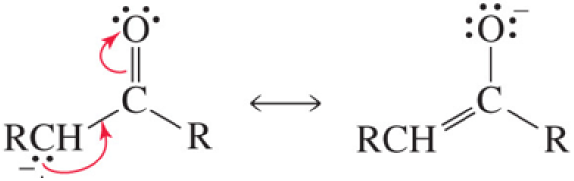
CH_3CH_3

pK_a > 60

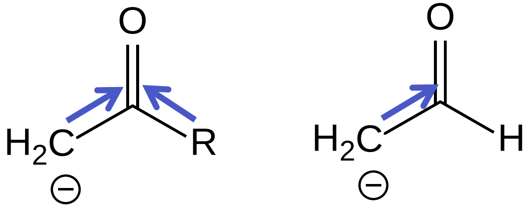
localized electrons

$$CH_3CH_3 \rightleftharpoons CH_3\ddot{C}H_2^- + H^+$$

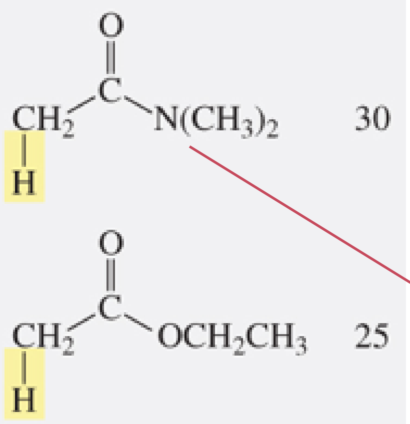


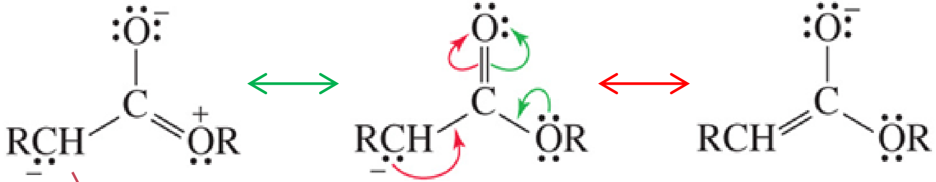


$C:^-$ delocalized
[B: stabilized]
by resonance [–M]



inductive [–I] larger
for RCHO
(no ED [+I] R)

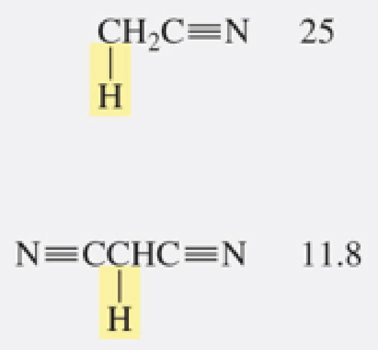


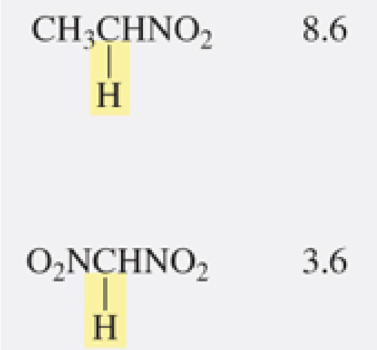


$C:^-$ not delocalized → smaller delocalize'n than for A&K

N: does +M better than O: → smaller delocalize'n

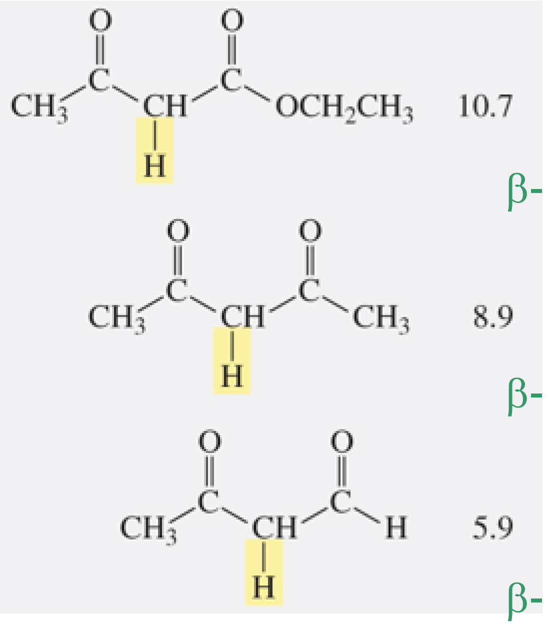
- acidity of α-C (cont'd)





Problem 1
propene

inductive + resonance

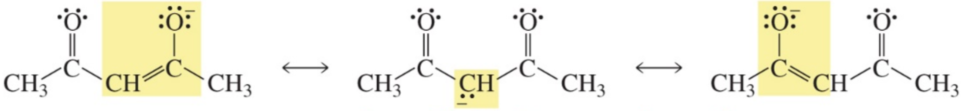


β-ketoester

β-diketone

β-keto aldehyde

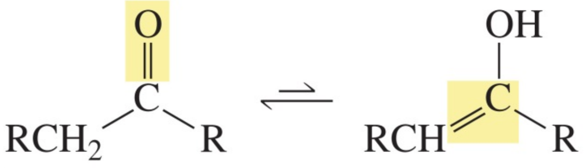
also inductive + resonance



resonance contributors for the 2,4-pentanedione anion

Keto-enol tautomerism

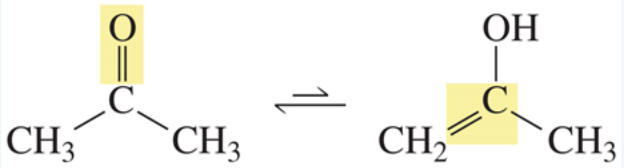
- tautomers = isomers in rapid equilibrium



keto tautomer **enol tautomer**

The equili is tautomerism.

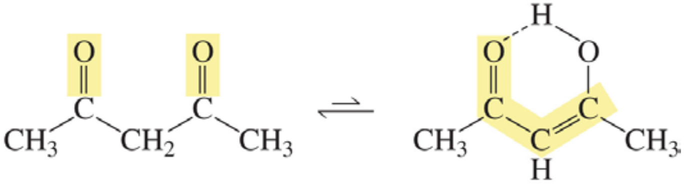
- Very generally, keto tautomer is much more stable. why?



$>$ **99.9%** $<$ **0.1%**

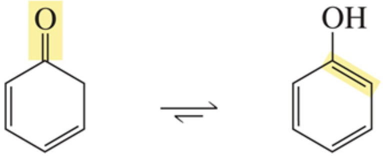
$\Delta H \approx 15$ kcal/mol

$u = \exp[-\Delta G/RT] \approx 1\text{E-}11$



85% **15%**

H-bonding + conjugation

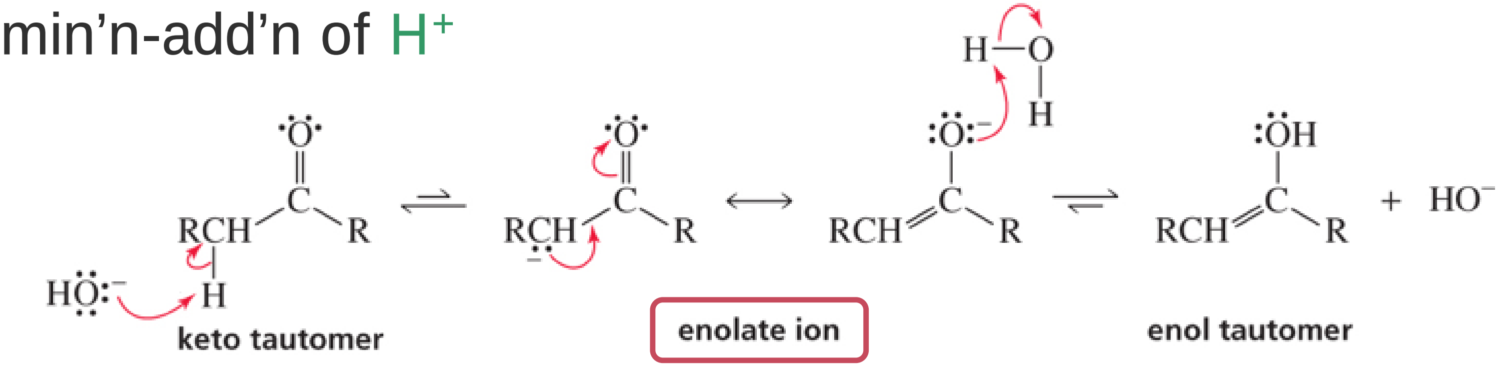


aromaticity

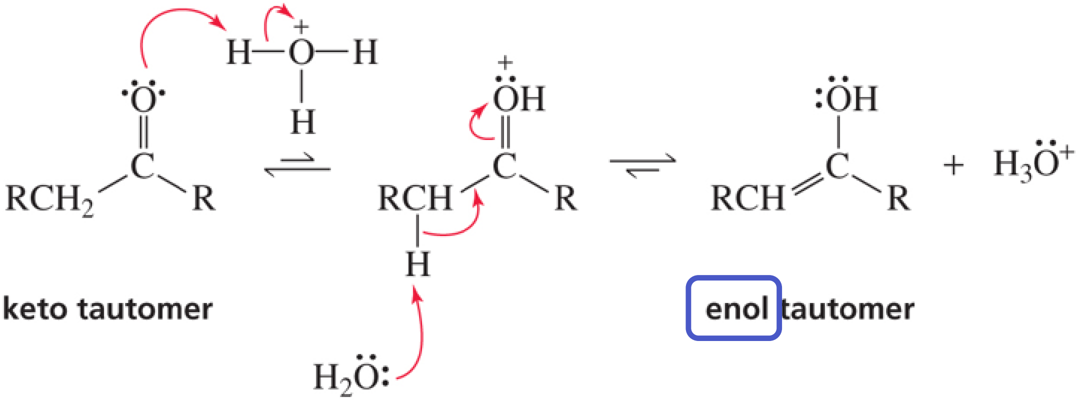
Tautomerization

= interconversion [isomerization] btw tautomers

- base-catalyzed
  - elimin'n-add'n of H^+

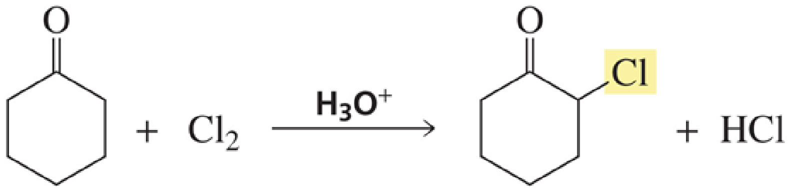


- acid-catalyzed
  - add'n-elimin'n of H^+



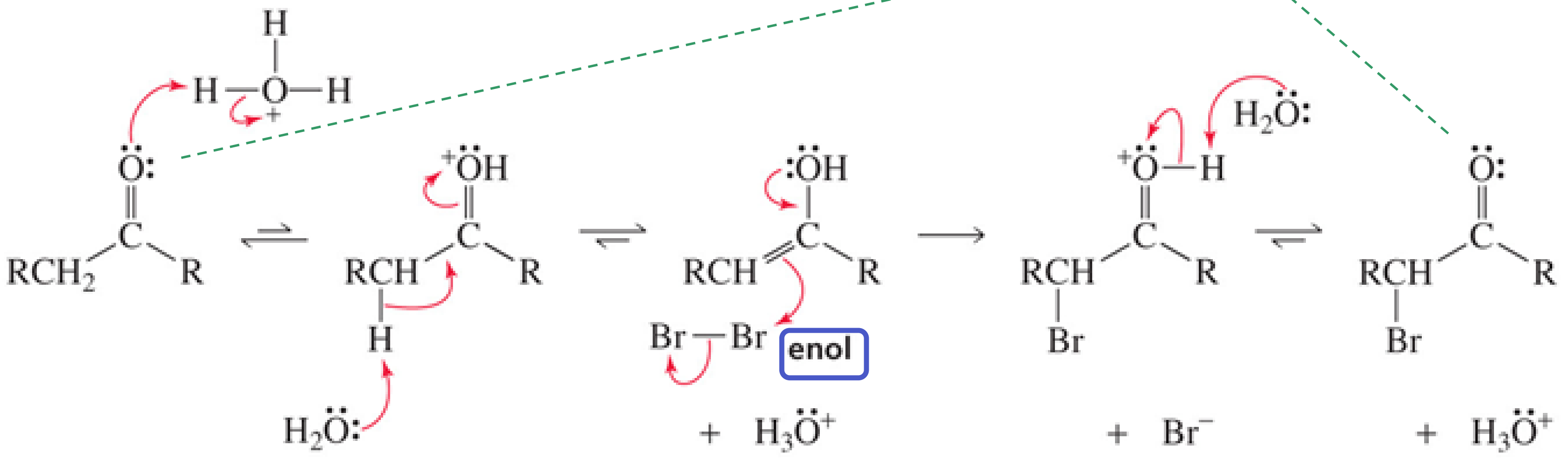
Halogenation of A&K

- α-substitution of X^+ for one or more of α-H^+
- acid-catalyzed → substit'n one of α-H



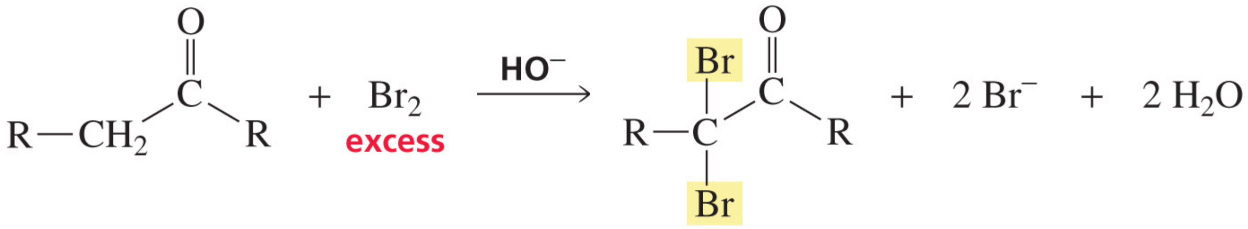
one α-H only
← protonated slower
← O less basic than original
← EW X [Br, Cl]

  - mechanism ~ thru (add'n to) enol

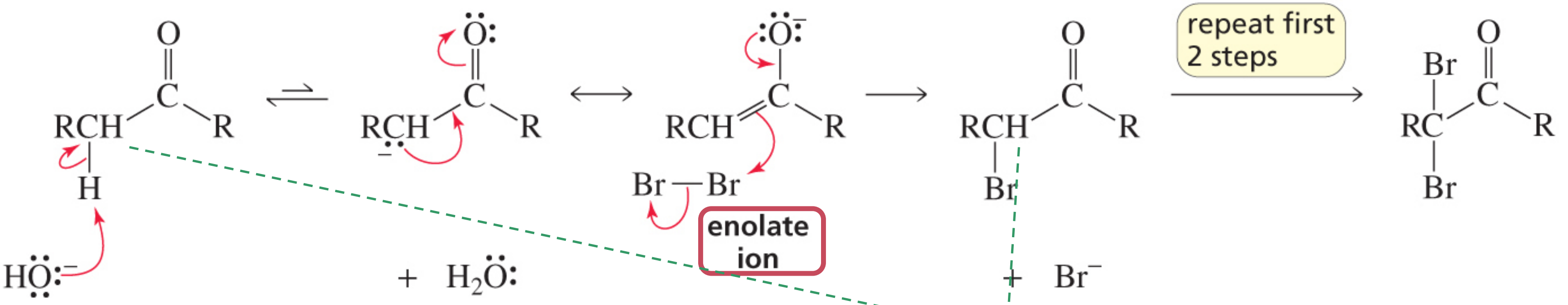


= is Nu: and Br^+ is E^+

- base-promoted ~ all of α-H



  - mechanism ~ thru (add'n to) enolate ion

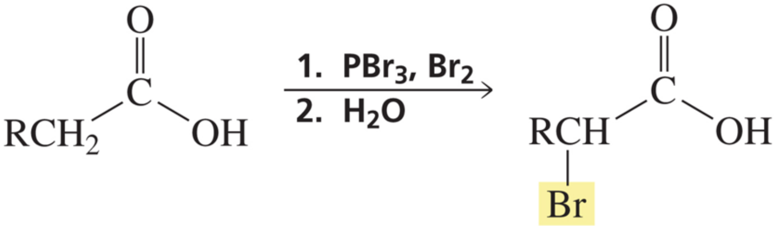


⁻OH neither re-generated
(but consumed) nor contained
still, not catalyze but promote

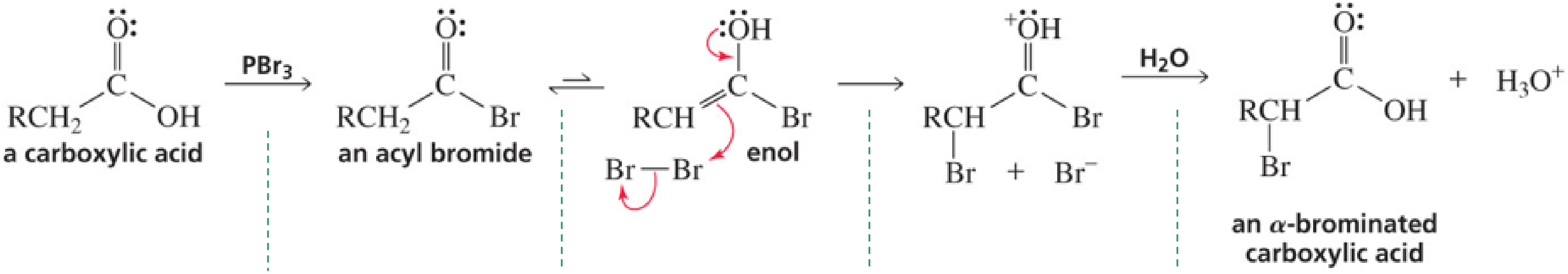
EW Br
→ α-H more acidic than original
→ eliminated faster
→ repeat to all α-H

Halogenation of RCOOH

- Hell-Volhard-Zelinski [HVZ] rxn
- α-H is less acidic than O–H (of RCOOH).
- still, α-substitution possible with PBr_3 (+ Br_2)



  - OH to Br, halogenation, then hydrolysis back to OH



OH to X

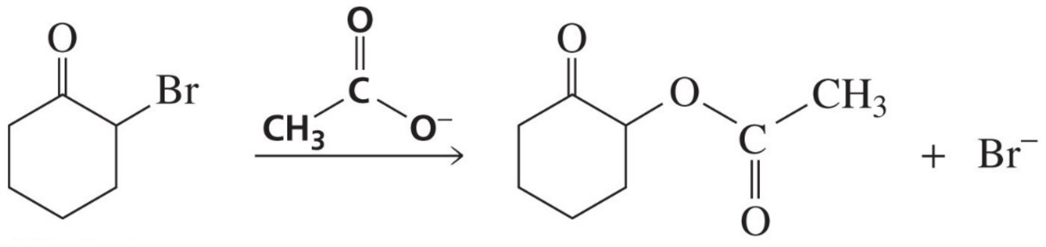
to enol (in acidic)
in basic? no

halogenation

hydrolysis

Rxn of halogenated carbonyls

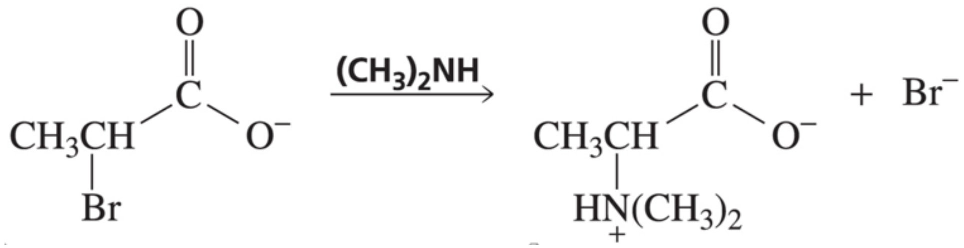
- with weak (or medium) B: [Nu:] → S_N of X



  - why <u>not</u> strong B:? E §9.12

$H_2O < AcO^- < R_2NH < {}^-OH$

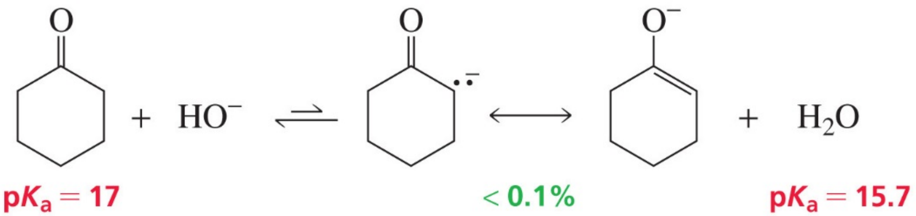
  - the 2nd example p845? stronger and bulky. maybe some E



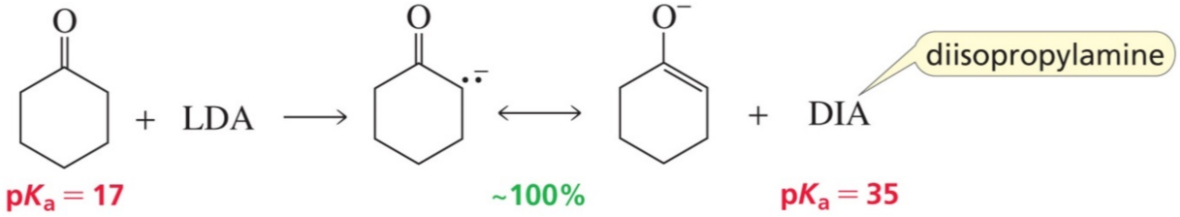
Enolate ion

- is formed when α-H is abstracted (from C=O comp'ds) by B:
- is the rxn interm in basic condition

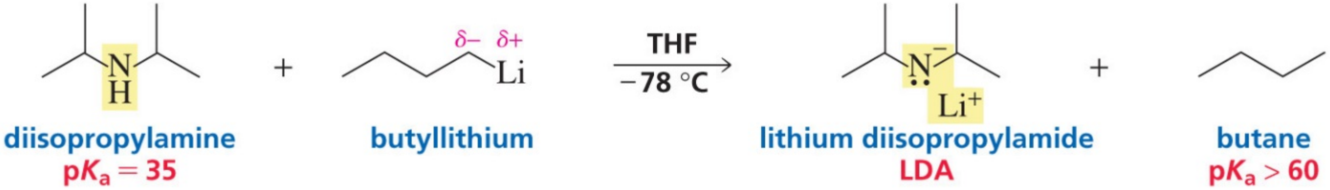
- amount depends on
  - acidity of α-C and basicity of B:



"A-B rxn to weak A and B."

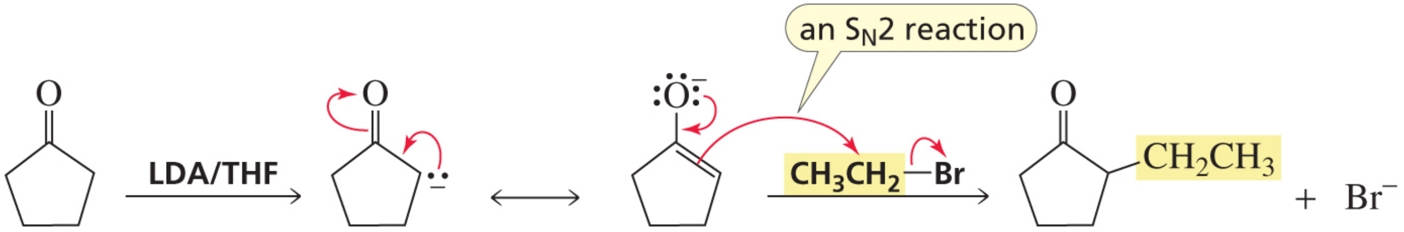


Why LDA not NaNH$_2$?
bulky not to add to C=O

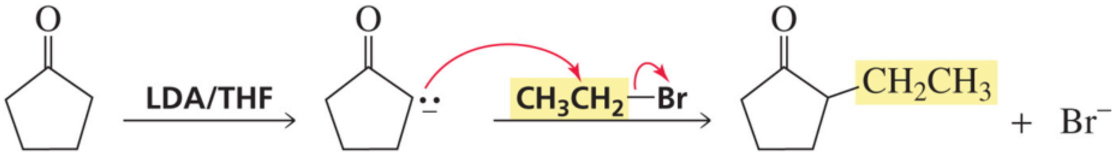


Alkylating α-C → C–C bond

- S_N2 of enolate on (1°) R-X



  - simplified

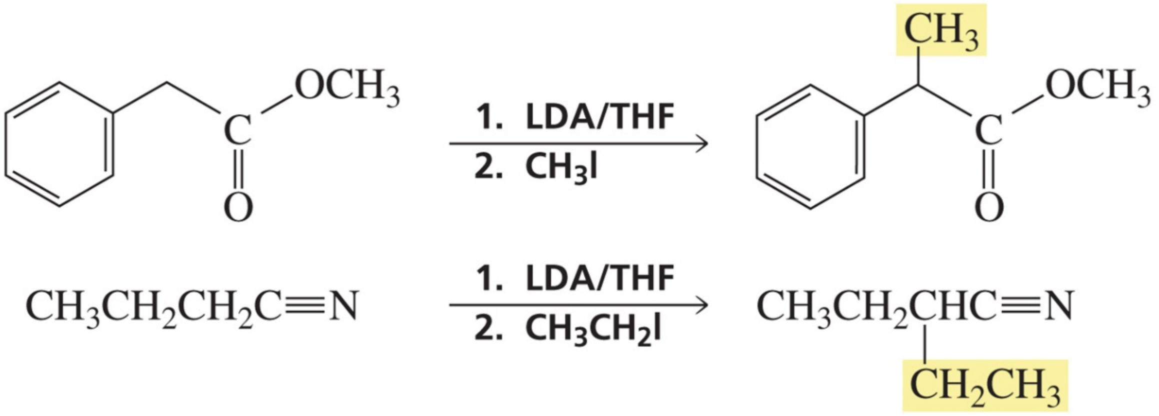


- using (very) strong B: like LDA (then R-X)
- if <u>not</u> [if weaker B: like $^-$OH];

$$\xrightarrow[\text{2. R-X}]{\text{1. LDA/THF}}$$

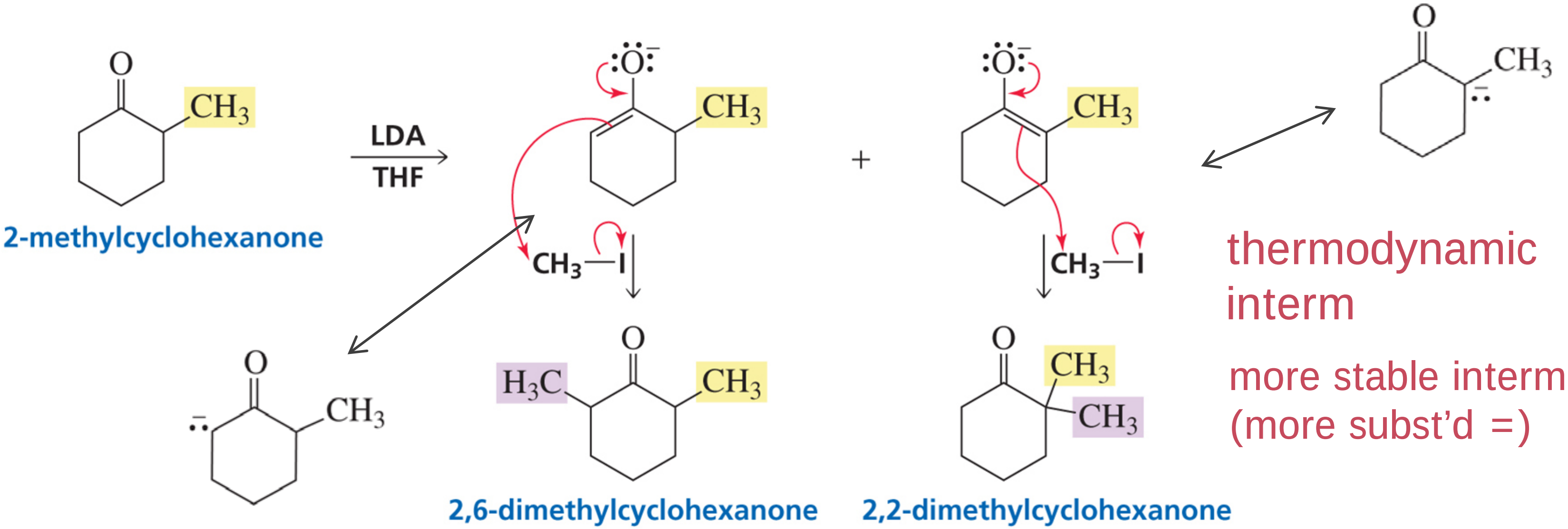
S_N of 1 on 2 only little enolate

- esters and nitriles also alkylated



  - less reactive ~ higher pK_a than A&K

- unsymmetrical ketones → 2 products



thermodynamic interm

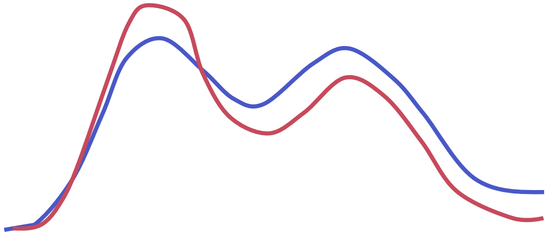
more stable interm
(more subst'd =)

kinetic interm

lower steric
hindrance for B:

at low Temp

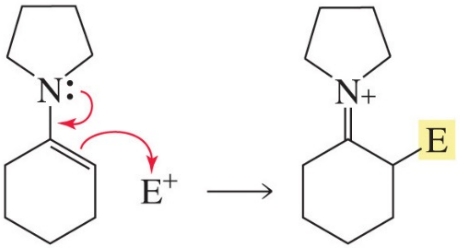
at high Temp



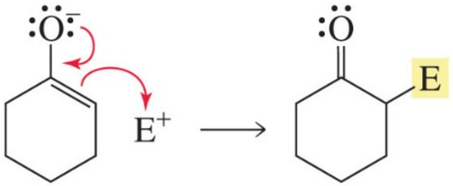
inductive effect?
ED R → thermo interm
more unstable C:⁻;
but, outweighed by
other effects

Alkylation and acylation thru enamine

- enamine similar to enolate as a Nu:

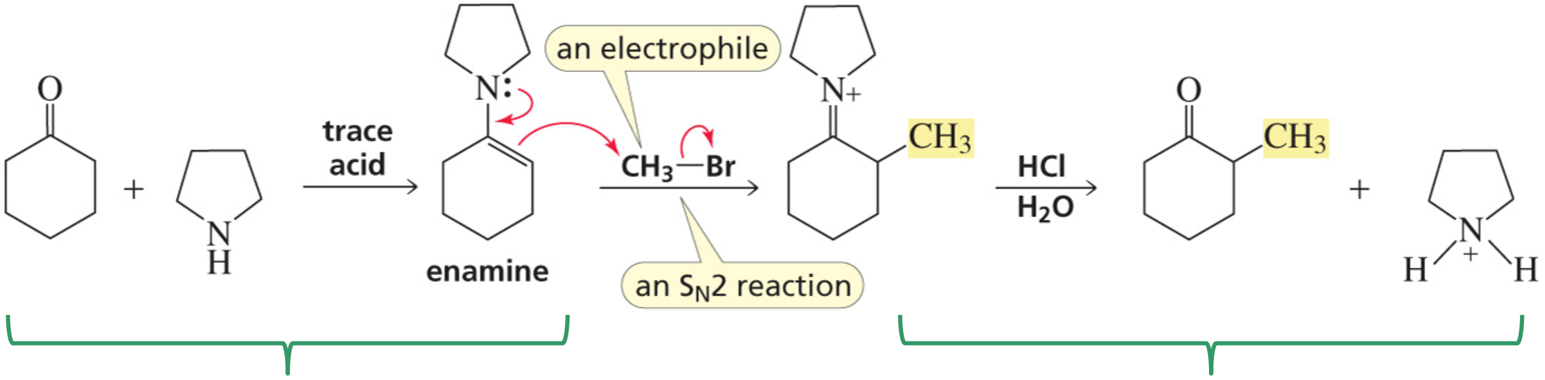


an enamine reacts with an electrophile



an enolate ion reacts with an electrophile

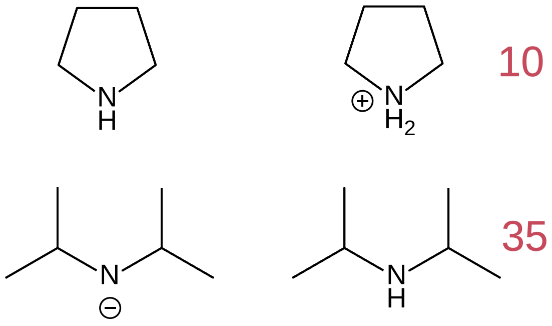
- alkylation thru enamine (interm)



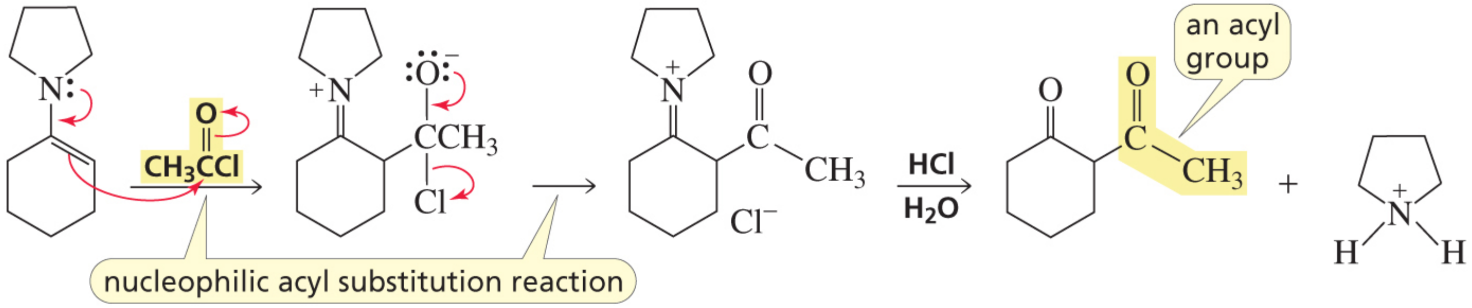
enamine formation
Chapt 16

hydrolysis
[reverse of enamine formation]

- alkylation thru enamine (cont'd)
  - mild alternative to LDA
    - neutral
    - less basic ~ amine vs amide ion
    - gives monoalkylation
      - LDA may over-react → multiple alkylation



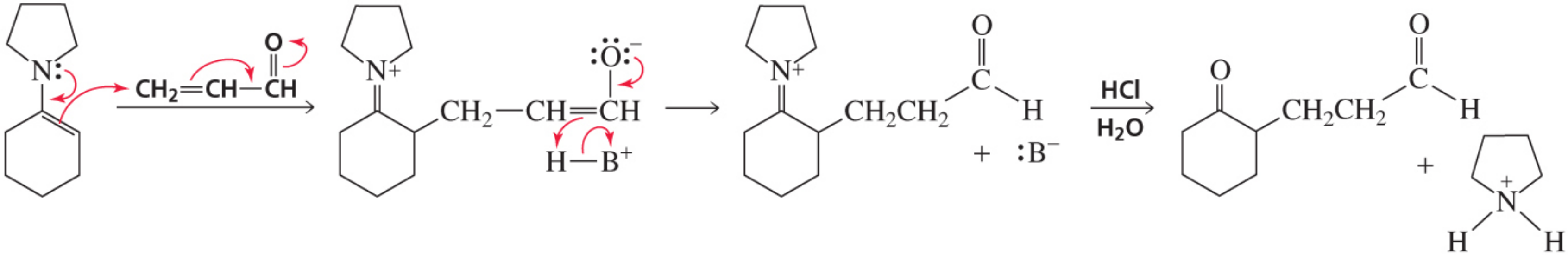
- acylation [+ RCO] also



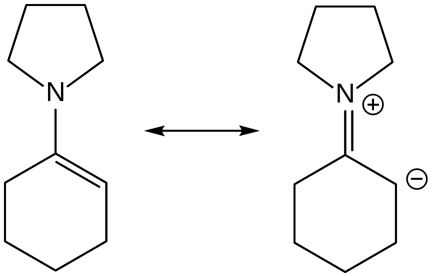
- ➢ acylation with enolate? later

Alkylating β-C

- via enamine



  - (α-C:$^-$ of) enamine is a weak B: [poor Nu:] → conj add’n
    - compared with other C:$^-$ or H:$^-$ See sl#56 of Chapt 16
  - forming 1,5-dicarbonyl comp’d



- Michael reaction [addition]
  - original definition (by Michael) ~ addition of enolate of A or K to α,β-unsat'd carbonyl comp'ds at β-C
  - newer definition ~ 1,4-addition of a doubly stabilized C Nu: to α,β-unsat'd carbonyl comp'ds

β-diketone, β-diester,
β-ketoester, β-ketonitrile

- weak B: → conj add'n

pK$_a$ = 8–10
more acidic than A&K
→ weaker conj B: