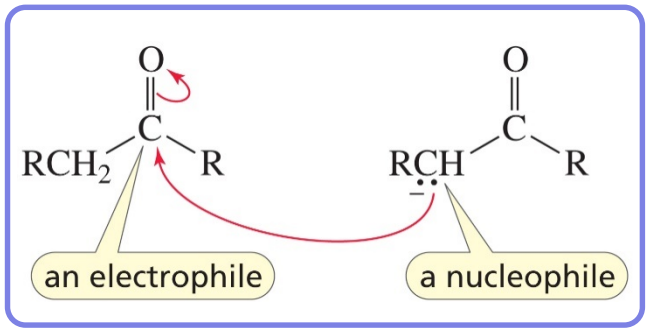
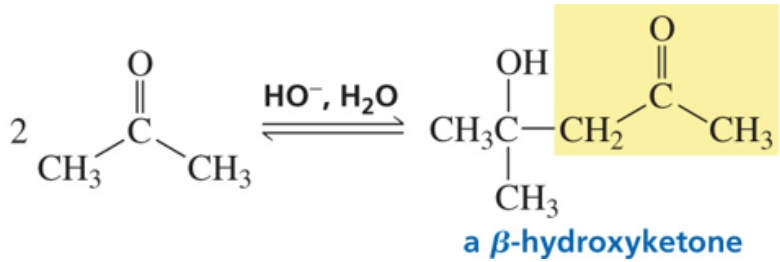
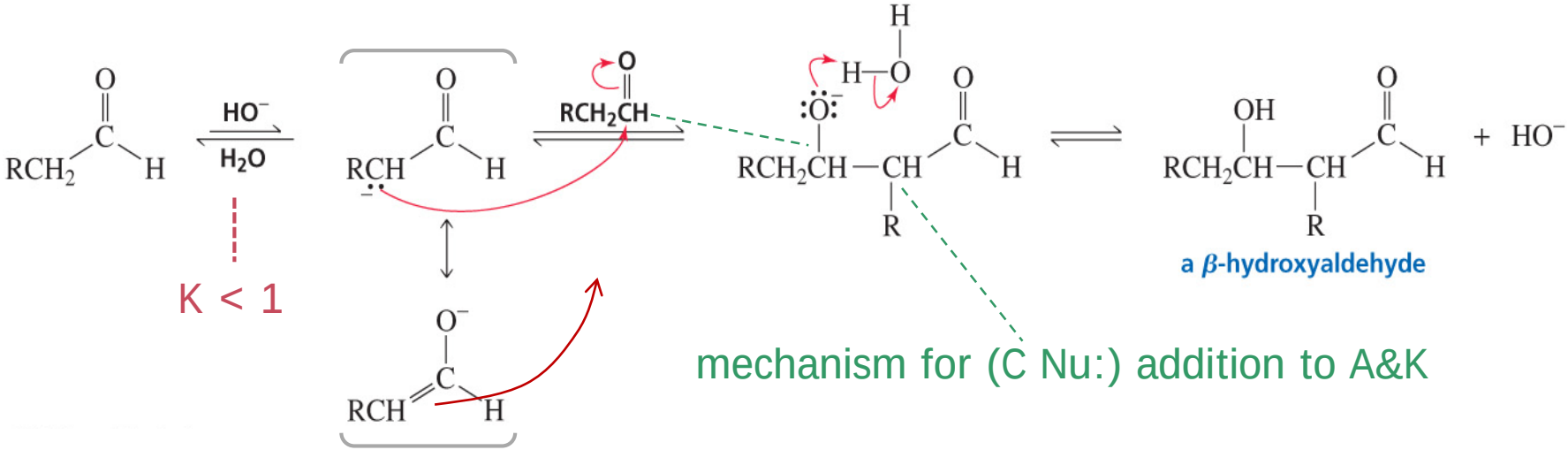
Aldol addition

- addition of enolate Nu: to e-philic C of C=O of A&K



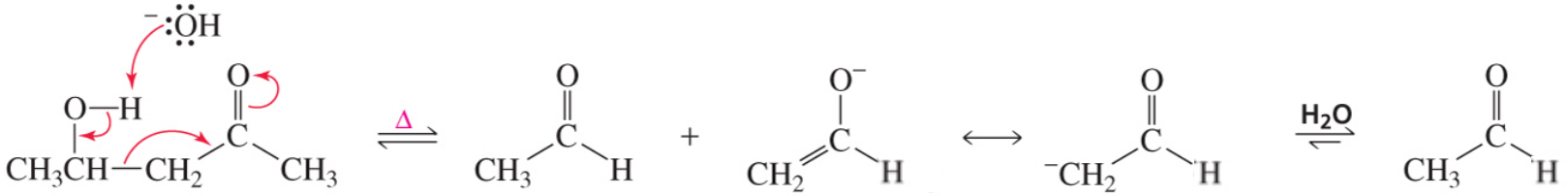


  - between two molecules of the same comp'd
  - resulting in β-hydroxyketone or β-hydroxyalhehyde [aldol]



mechanism for (C Nu:) addition to A&K

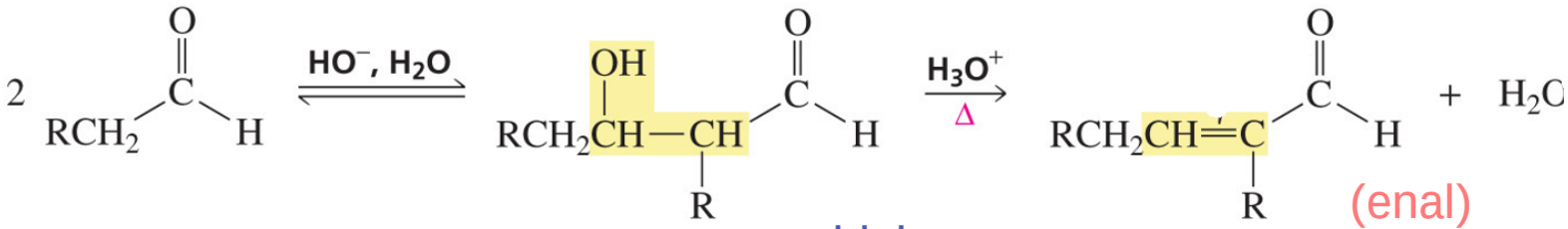
- possible also in acidic condition (thru enol) Look up the internet.
- If in basic, weaker B: like $^{-}$OH should be used.
  - weaker than enolate → K < 1 → only small part enolated → 2nd molecule for rxn present
  - what if strong B: like LDA used?
- Rxn of ketone is slower than aldehyde.
- reversible (and reverse favored) pKa of 17 vs 16
  → remove product for good yield
- retro-aldol addition = reverse rxn of aldol addition



Aldol condensation

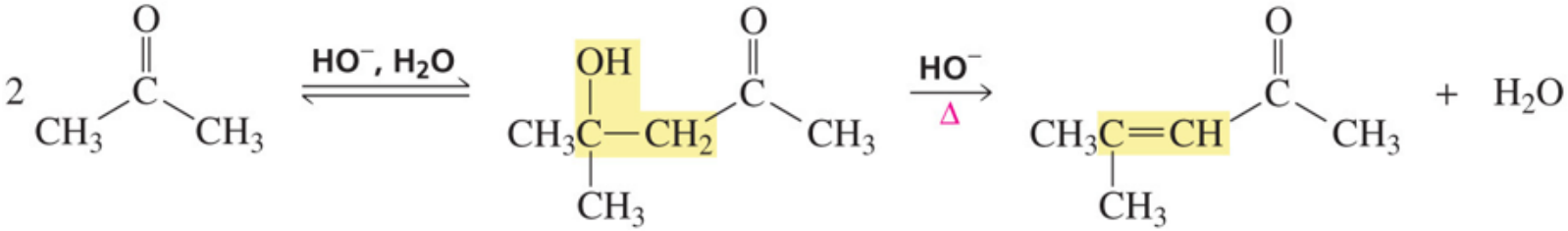
- aldol addition followed by dehydration
  - to form α,β-unsat'd A&K [(enal &) enone]
  - condensation [縮合] ~ A + B → A-B – C (C = small molecule)

(C-C bond)



aldol

(enal)
enone

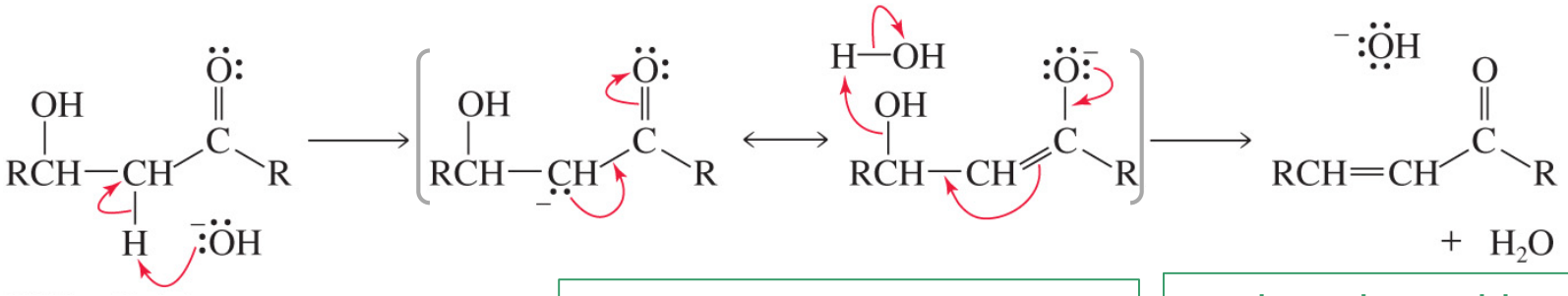


- in acidic or basic condition with heat
  - The whole condensation can be in acidic (thru enol) or basic.

See Wikipedia 'aldol condensation'.

- mechanism = E1cB

E1cb = the 3rd elim'n mechanism

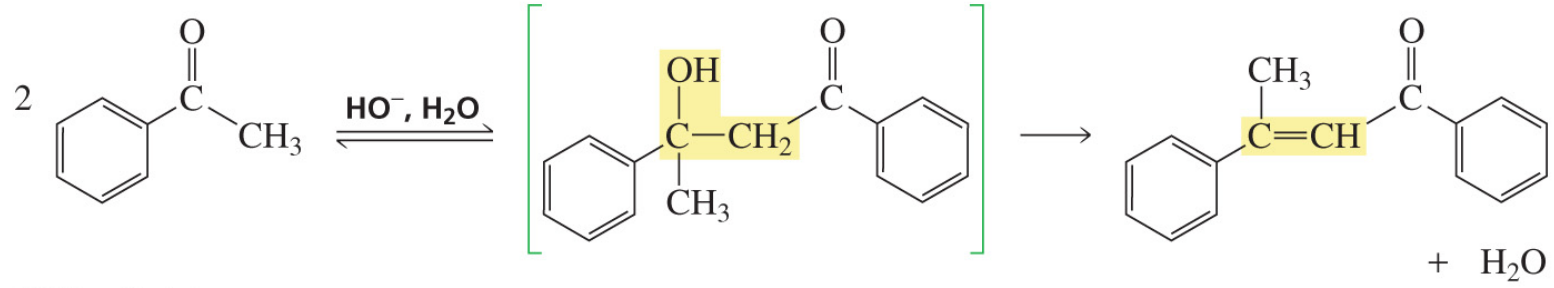


E1cB for poor L (leave later) & stable interm a/o product

Interm is conj B: of reactant. resonance stabilized
→ H can leave

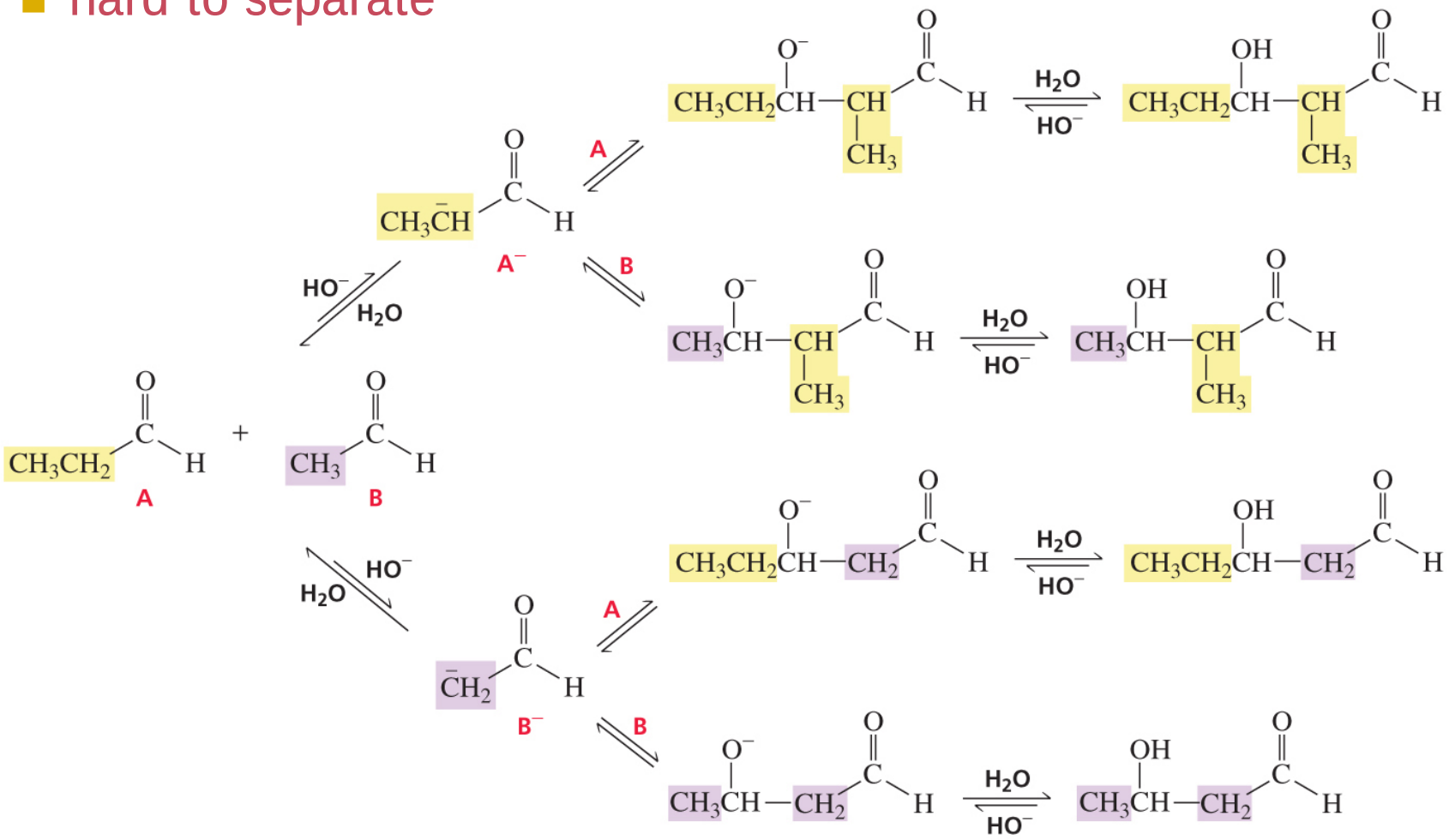
product also stable (conjugated)
→ OH can leave.

- aldol condensation in one step (w/o heat)
  - when the product is much stabilized

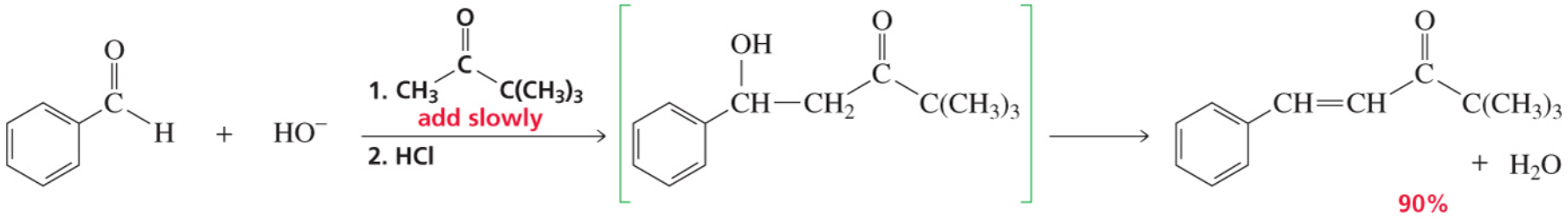


Crossed [mixed] aldol rxn

- from 2 different A or K to 4 products
  - hard to separate



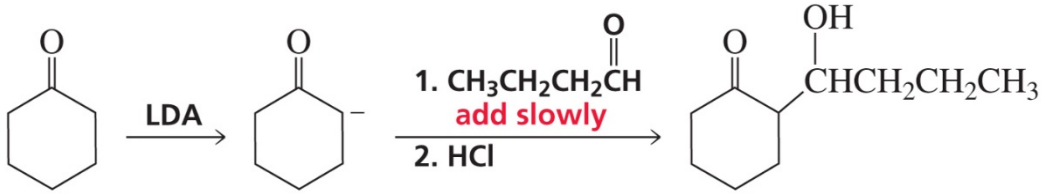
- want 1 product?
  - Add enolizable slowly to {non-enolizable/$^{-}$OH} solution



    - Claisen-Schmidt condensation

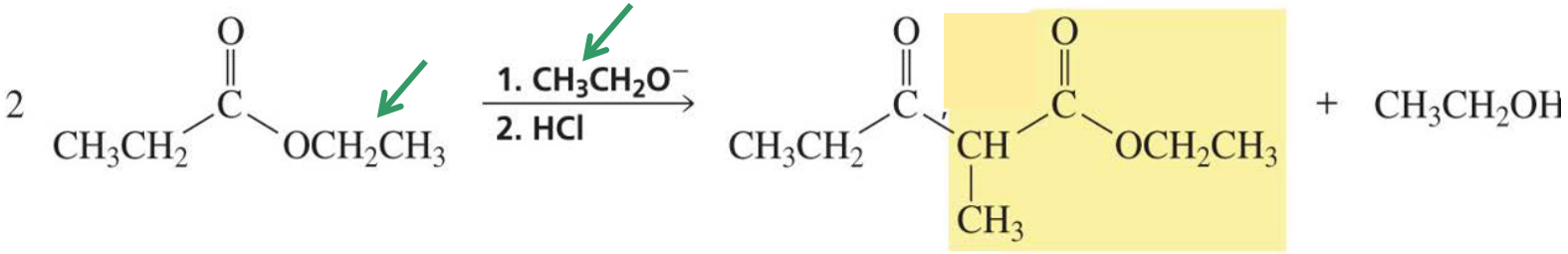
resonance-stabilized
effective

- what if both enolizable?
  - enolate one with LDA, and then add the other slowly

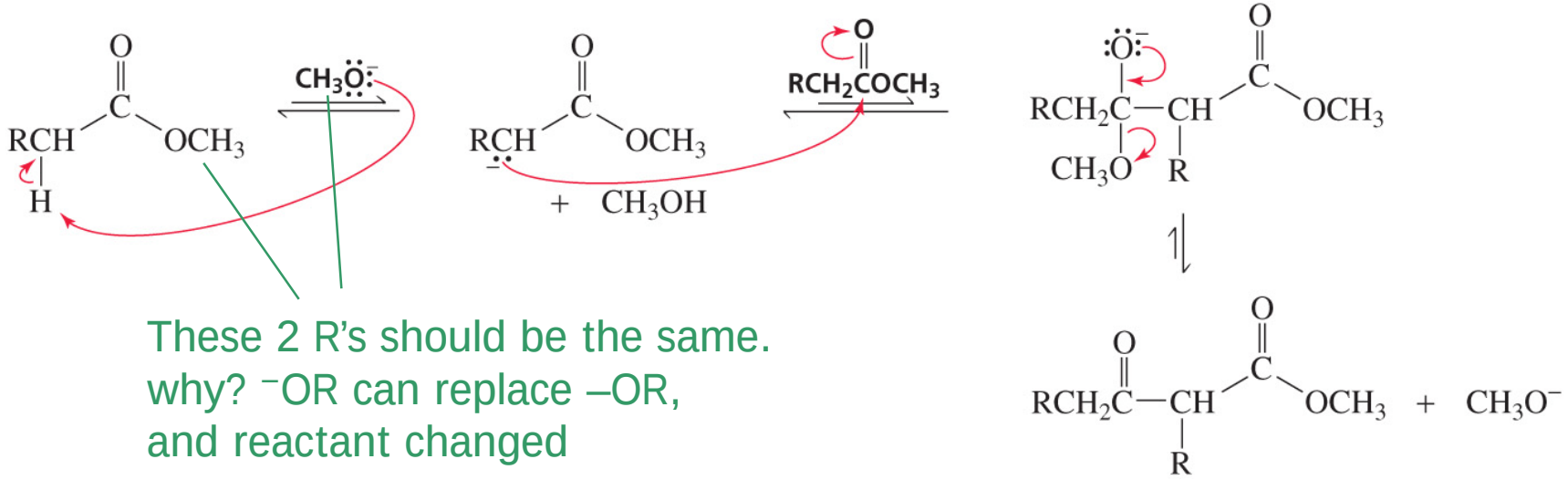


Claisen (ester) condensation

- two molecules of ester condensed to β-keto ester

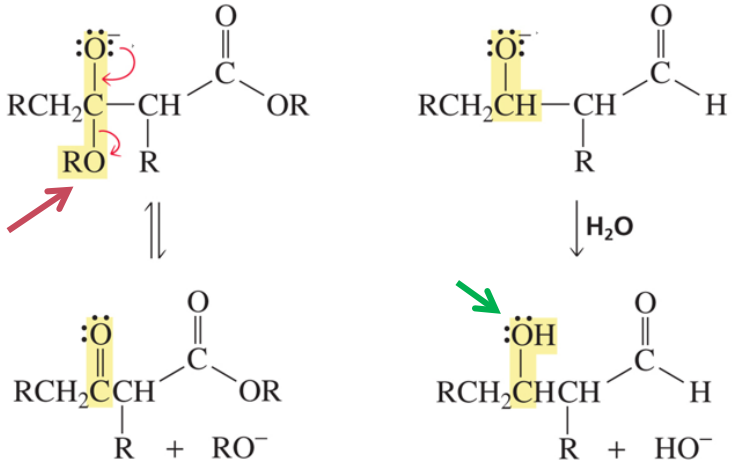


- mechanism ~ add'n-elim'n

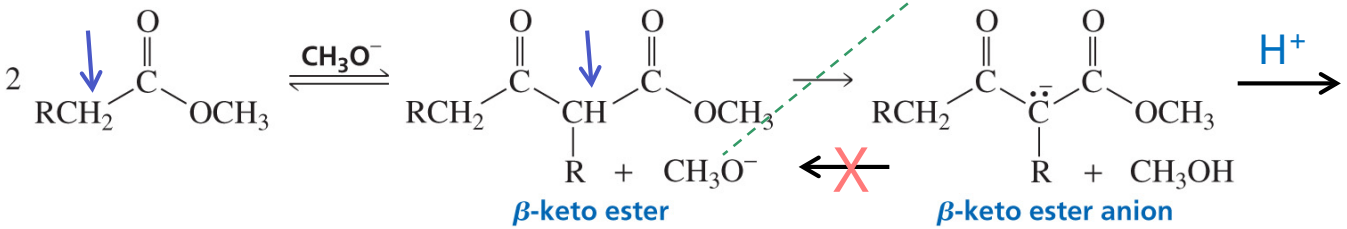


These 2 R's should be the same.
why? ⁻OR can replace –OR,
and reactant changed

- Claisen vs aldol
  - Claisen ~ ester ~ add'n-elim'n → β-keto
  - Aldol ~ A&K ~ addition → β-hydroxyl

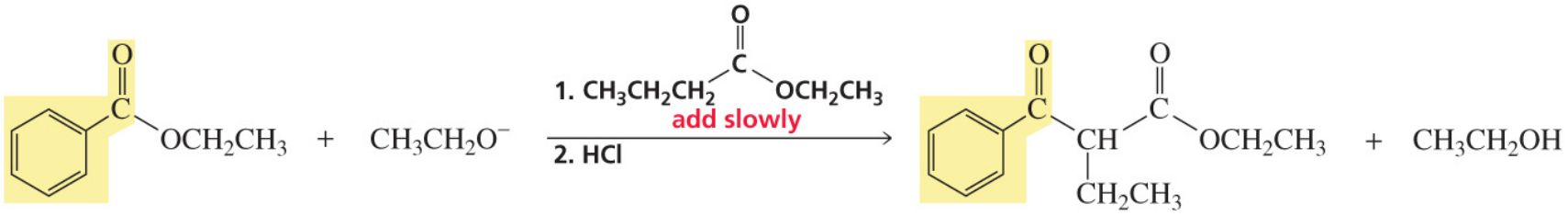


- reversible (and reverse favored) pKa of 25 vs 16
  - to push forward, use equivalent amount of base
    - to take H to ester anion (isolated and protonated)
  - Claisen condens'n effective only for esters with 2 α-H's

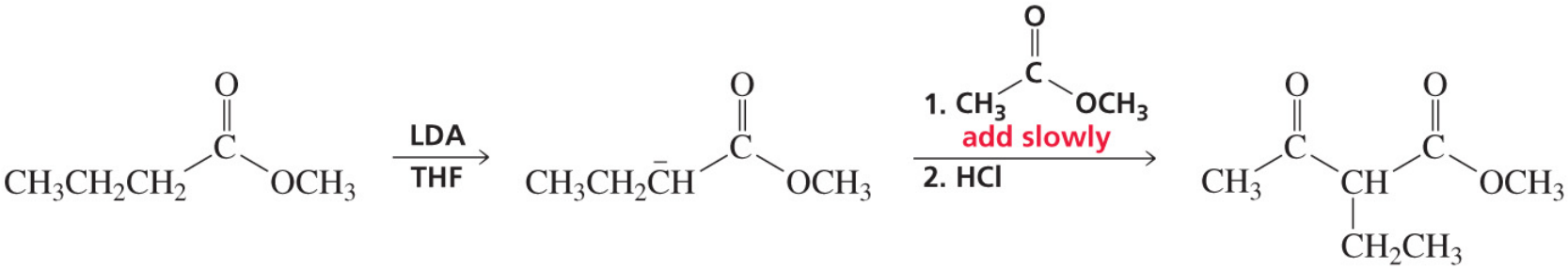


Crossed Claisen condens'n

- to obtain 1 product
  - when one ester has no α-H [not enolizable]



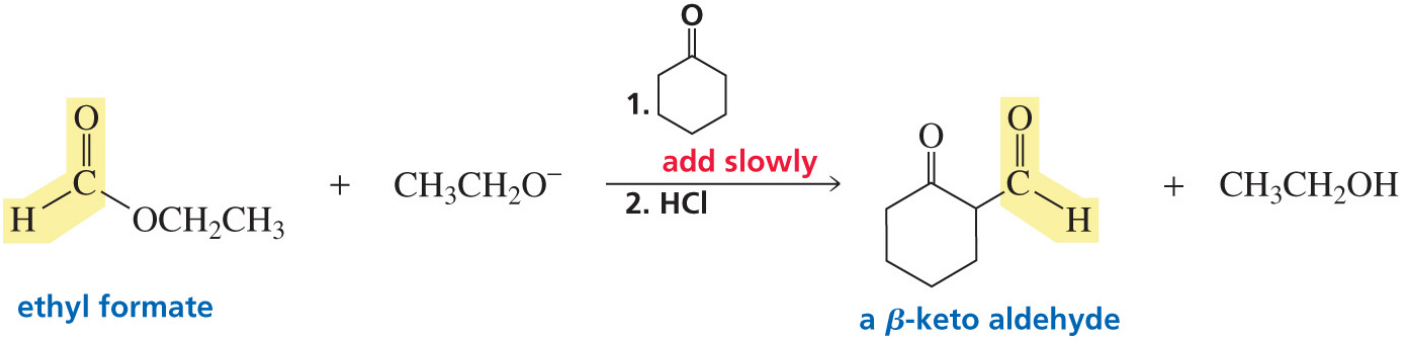
    - add ester-enolaizable slowly
  - when both have α-H [enolizable]



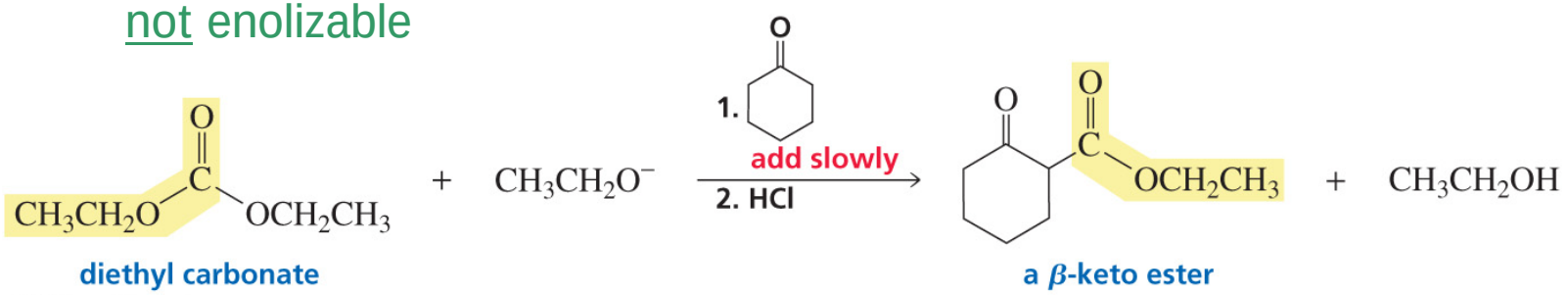
    - ester-enolate one and add the other slowly

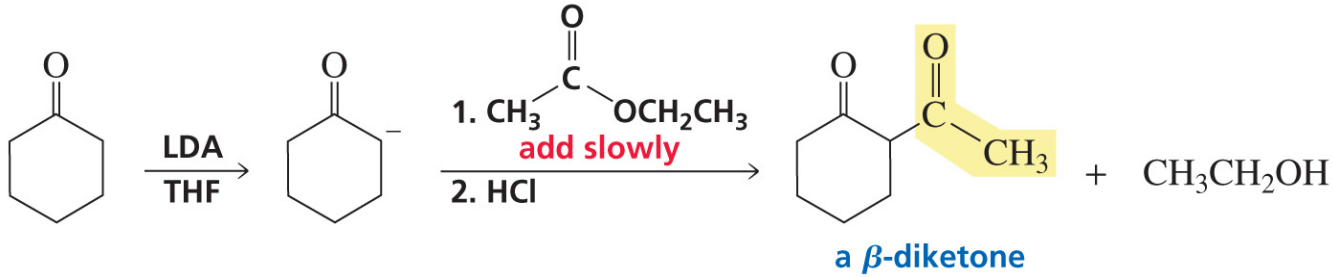
Ketone-ester crossed condens'n

- the same techniques can be used



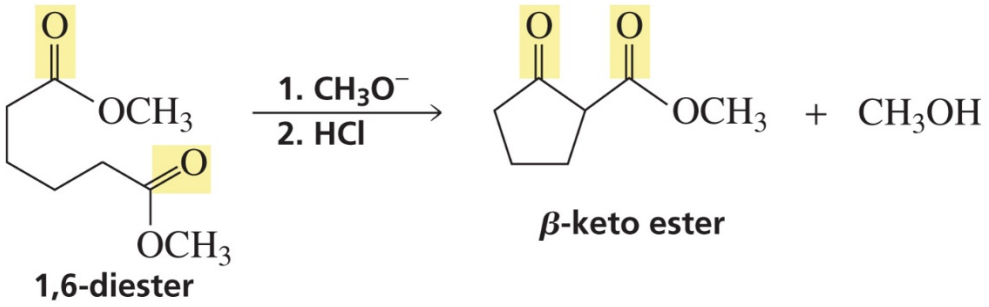
not enolizable



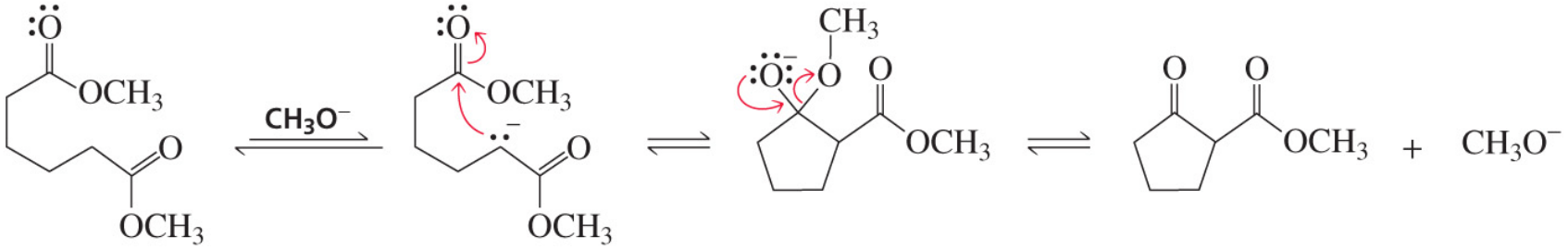


Intramolecular condensations

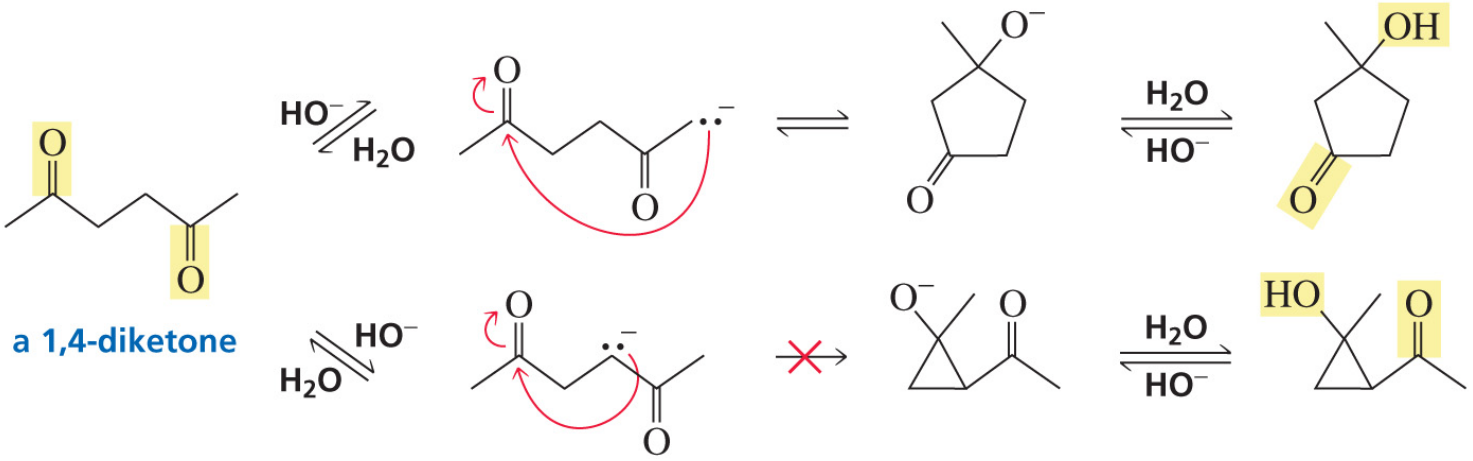
- intramolecular rxn readily occurs
  - when 2 ft'nal groups can react
  - to form 5- or 6-membered ring
- intramolecular Claisen condens'n = Diekmann condens'n



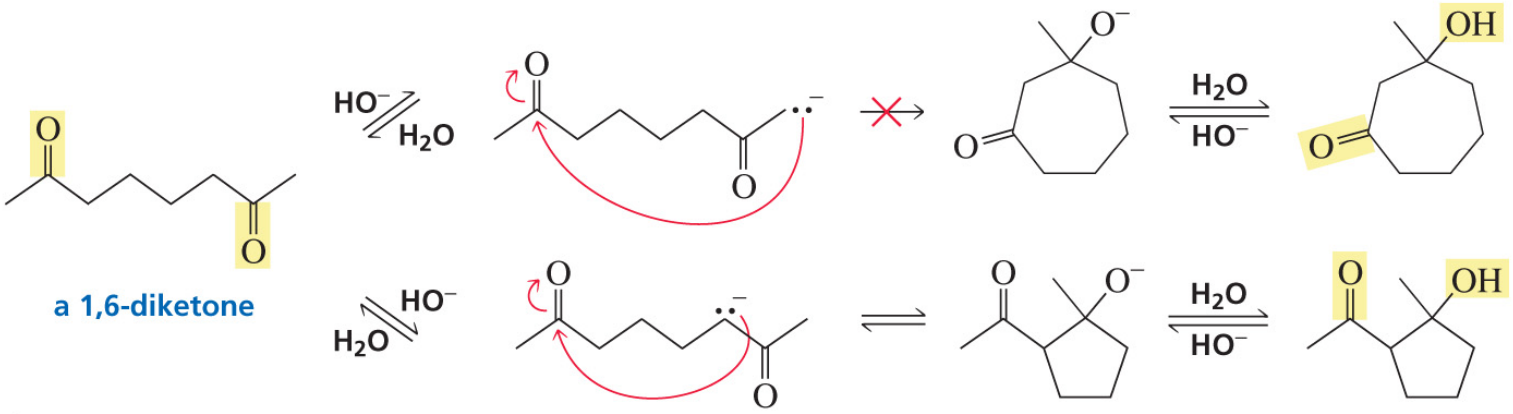
use enough B:
for completion



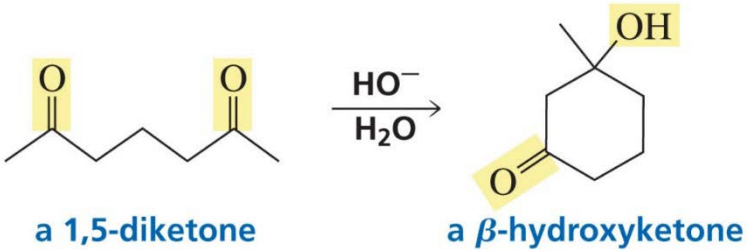
- intramolecular aldol addition
  - 1,4-diketone → 5-membered ring hydroxyl ketone



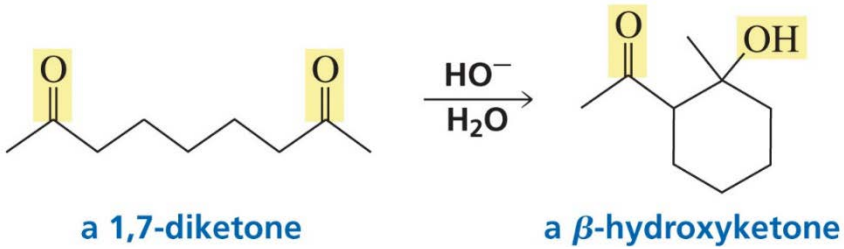
  - 1,6-diketone → also 5-membered ring hydroxyl ketone



- 1,5- and 1,7-diketone → 6-membered ring hydroxyl ketone



a 1,5-diketone a β-hydroxyketone

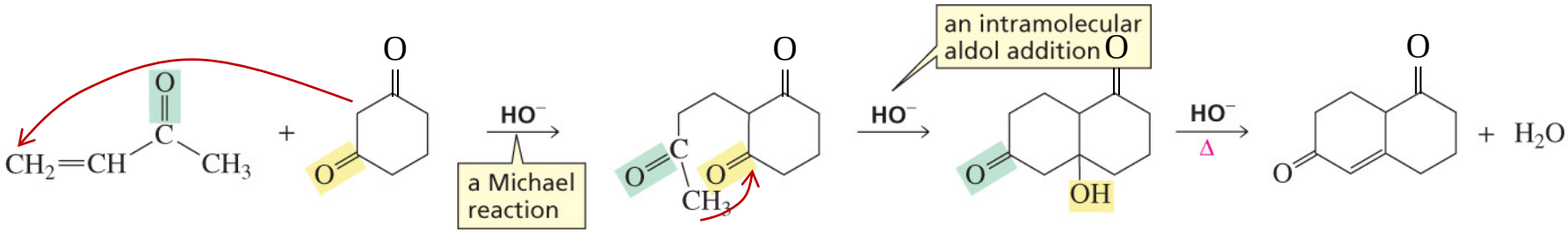


a 1,7-diketone a β-hydroxyketone

Robinson annulation

annulation = ring formation

- Michael and aldol together
  - to form α,β-unsat'd cyclic ketone
  - Michael addition followed by intramolecular aldol condens'n

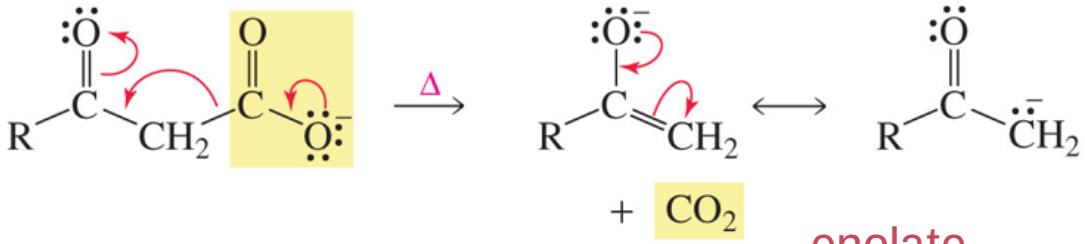


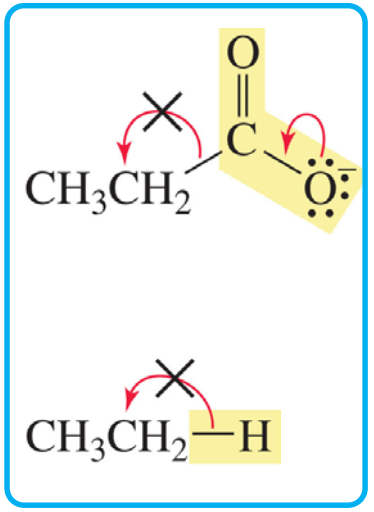
a fused ring

- Follow 'problem-solving strategy' on p866.
- Read 'retroynthetic analysis' on p867.

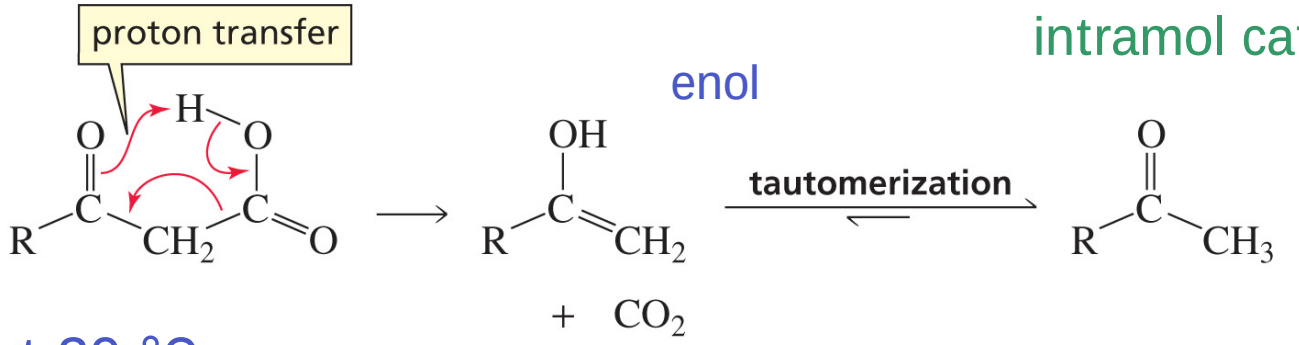
Decarboxylation [$-CO_2$]

- $-CO_2$ from –COO(H) w/ 3-oxo [β-keto]
  - when the left is stable
- from carboxylate (in basic condition)



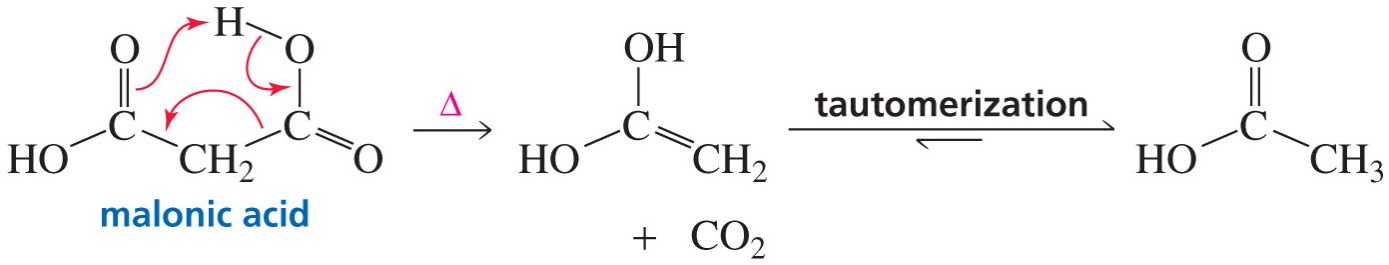


  - at 50 °C
- from RCOOH (in acidic condition) ~ easier, faster

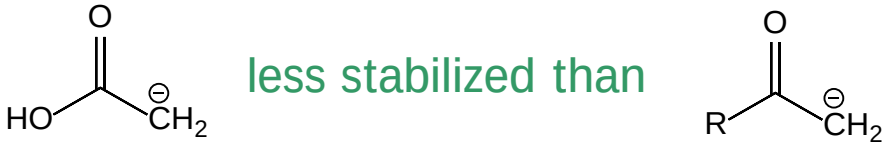


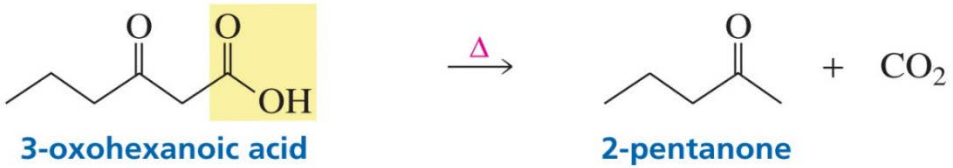
  - at 30 °C

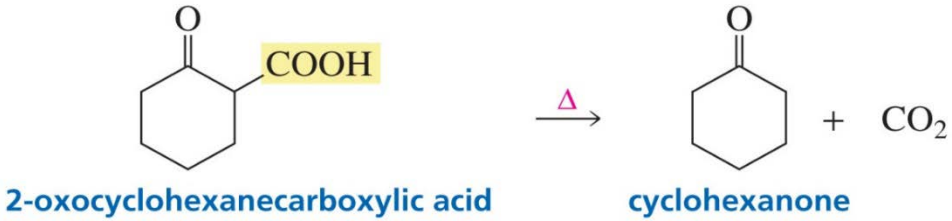
- from dicarboxylic acid (to RCOOH) ~ slower



- at 135 °C
- why? pK_a

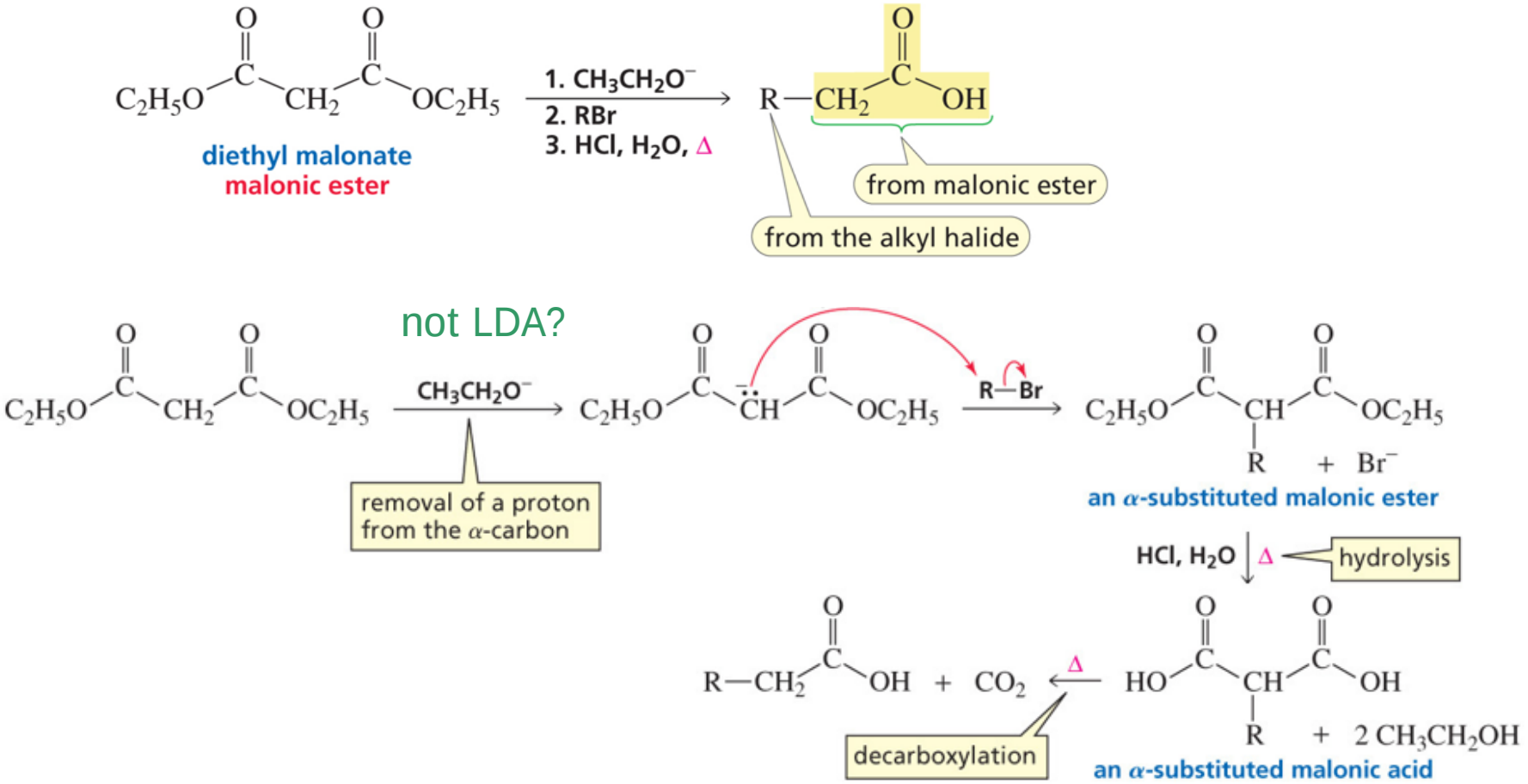




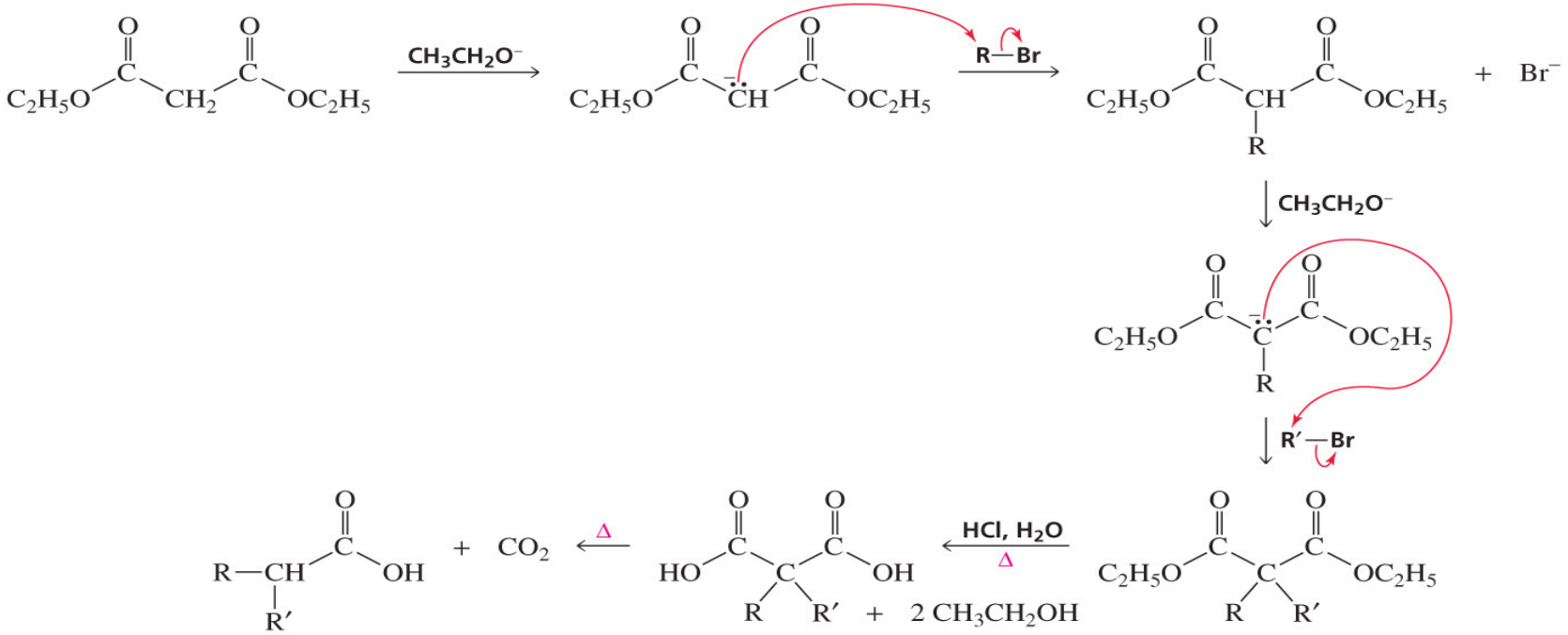


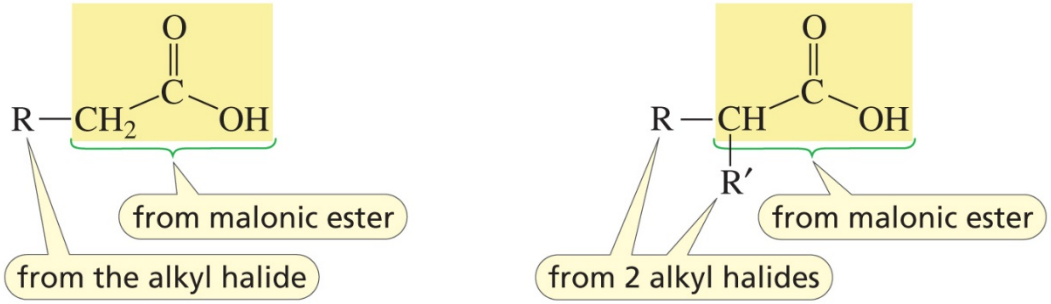
Malonic ester synthesis

- alkylation-hydrolysis-decarboxylation starting from malonic ester to form RCOOH



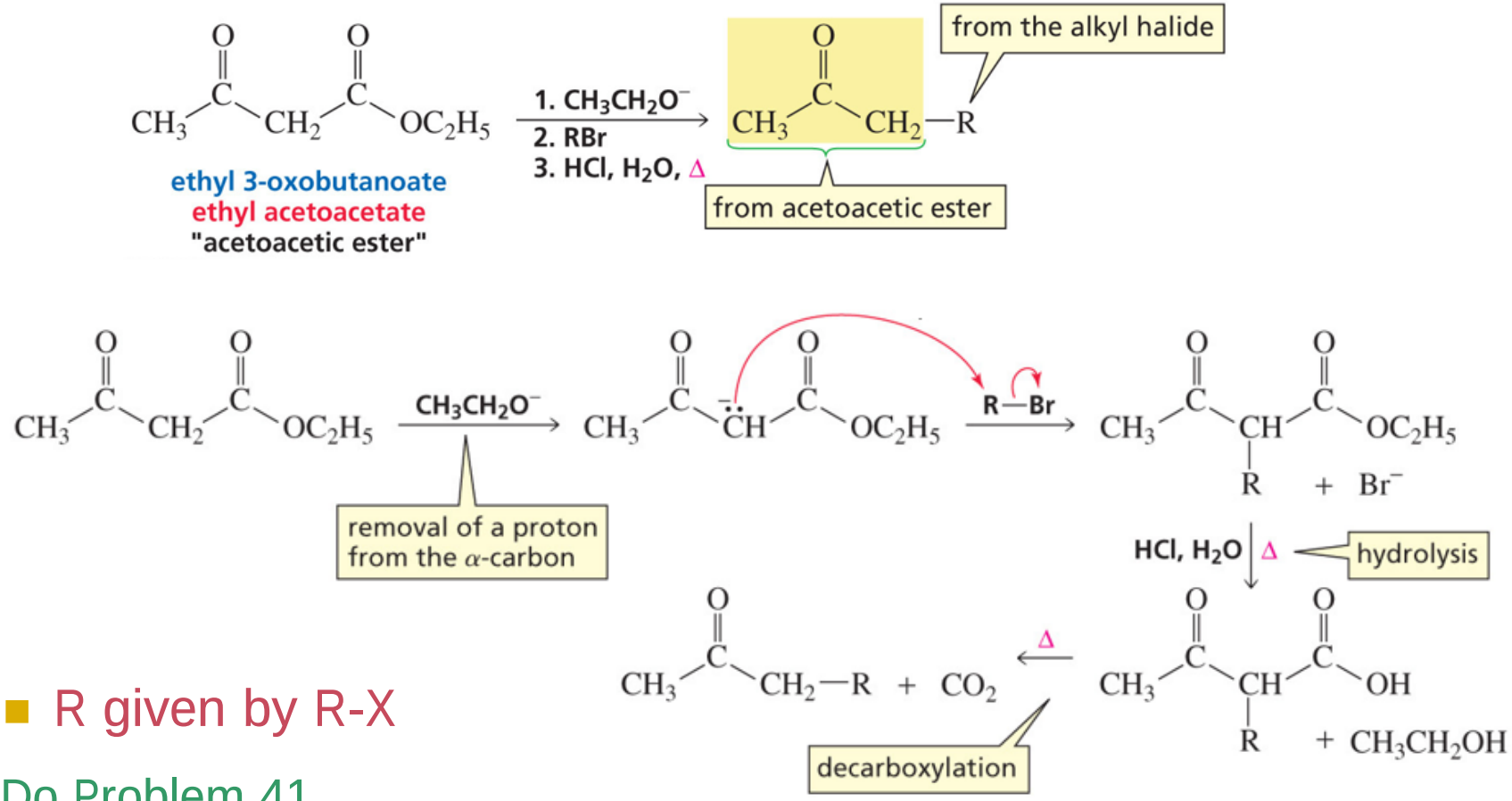
- double alkylation → 2 R's





Acetoacetic ester synthesis

- alkylation-hydrolysis-decarboxylation starting from acetoacetic ester to form methyl ketone

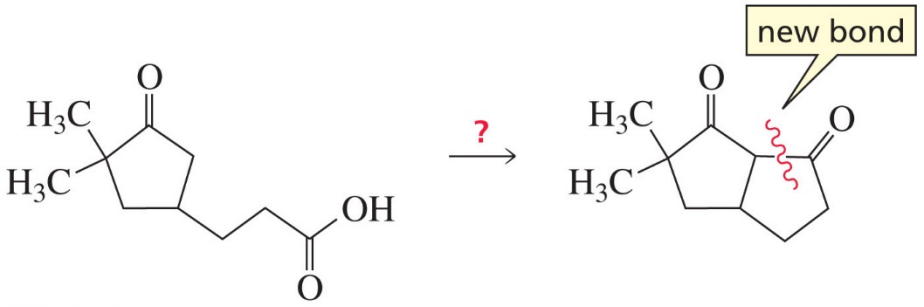


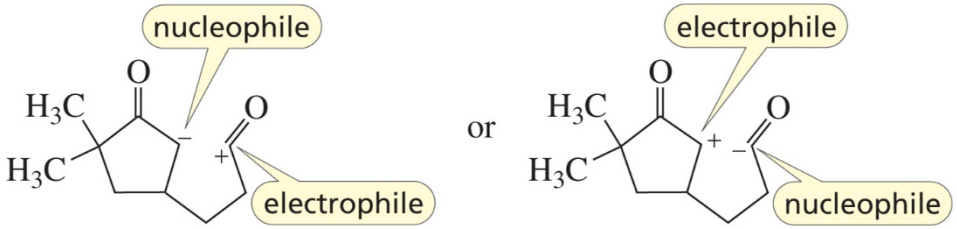
  - R given by R-X

➢ Do Problem 41

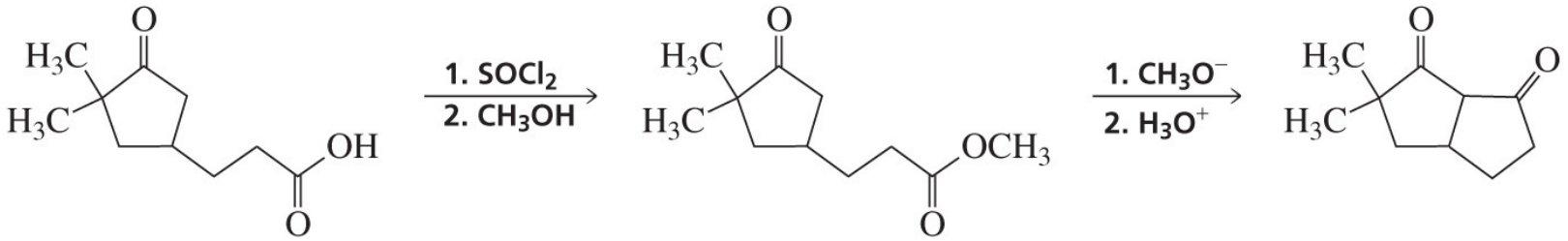
Making new C-C bonds

- locate the C's to be linked → C^+ and C^- → type of rxn



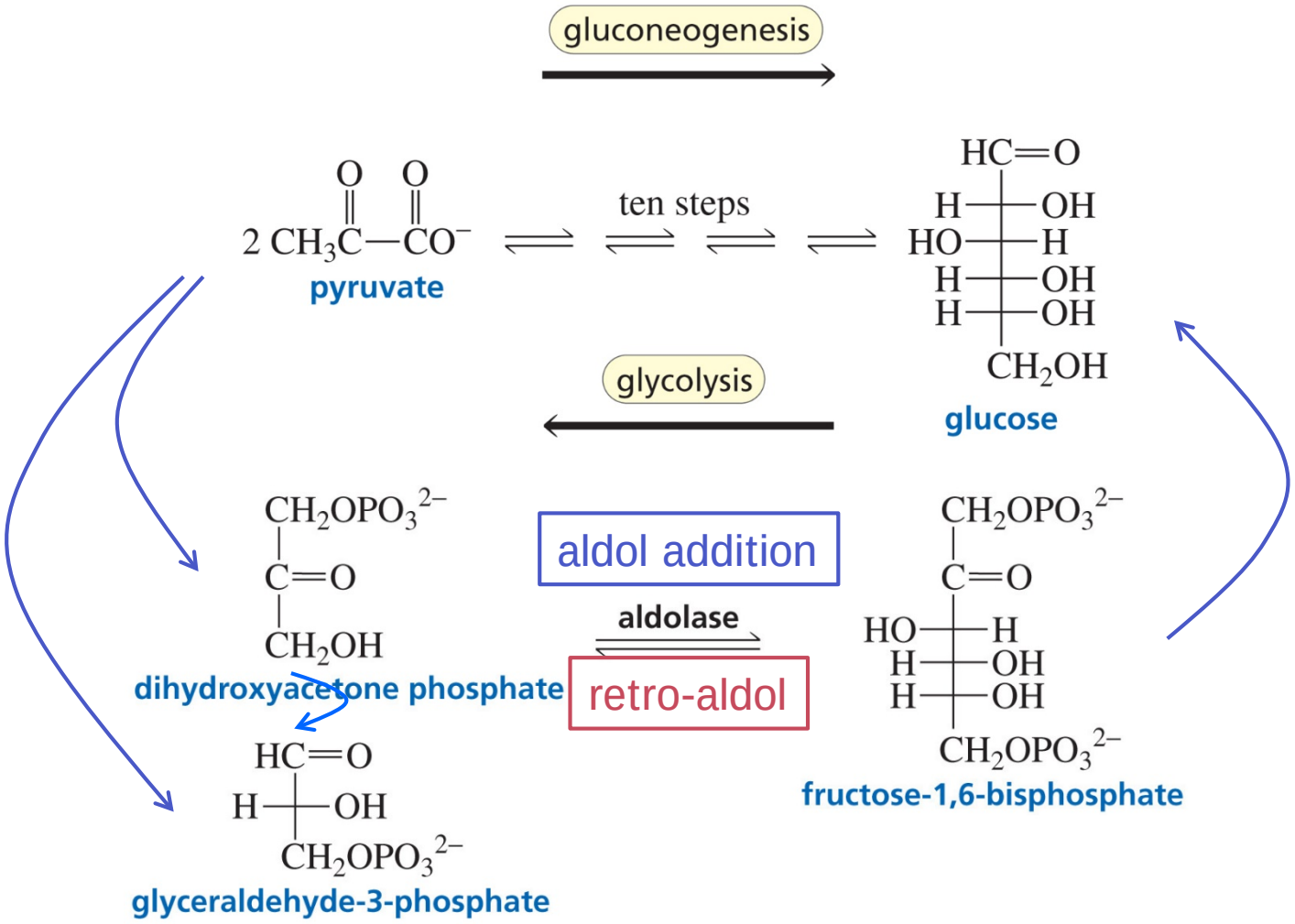


better ← α-C of ketone, removable OH

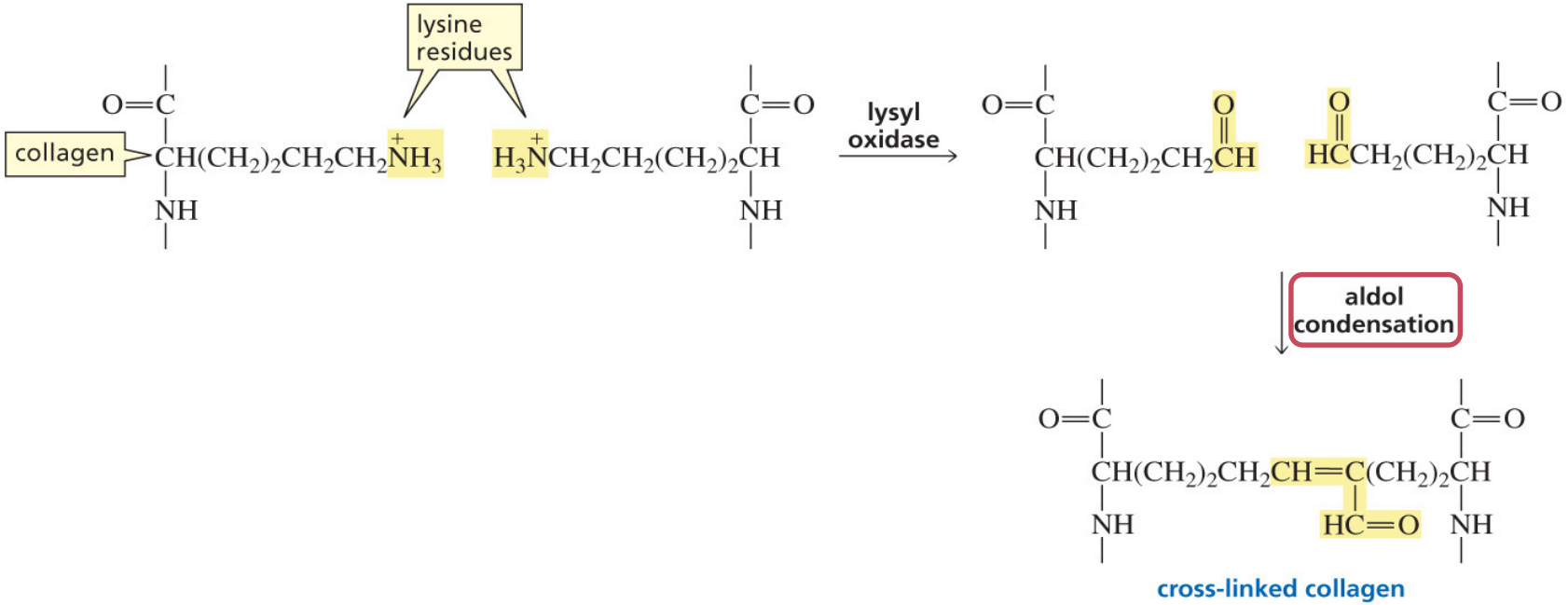


Biological rxn's at α-C

- gluconeogenesis-glycolysis



- cross-linking of collagen [a protein] → aging



Summary

- α-H is acidic: A&K more acidic.
- rxn thru enolate, enamine, or enol $=\!-O^- > =\!-NR_2 > =\!-OH$
- halogenation
- alkylation
- Michael reaction
- Aldol addition/condensation of A&K
- Claisen (ester) condensation
- Crossed additions and condensations
- miscellaneous
  - annulation, decarboxylation, malonic and acetoacetic ester synthesis