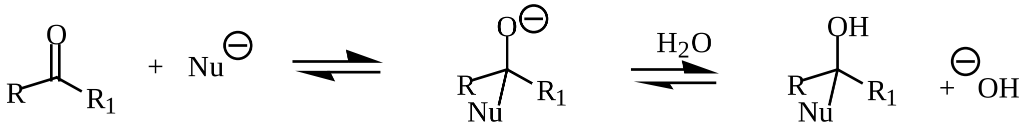
Review:

Base Catalyzed 1,2-addition to carbonyl groups: $\text{H-Nu} + \text{base} \rightarrow \text{Nu:}^{-} + \text{H-base}^{+}$



R_1 = H, carbon group

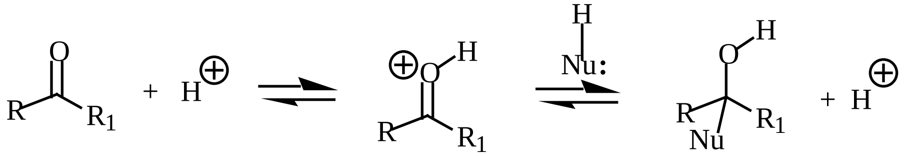
Reversible if $Nu^{\ominus}$ is "stabilized"

e.g., ROH, R_2NH, RO^-, certain carbon anions

Irreversible with simple carbon anions [organometallic reagents]

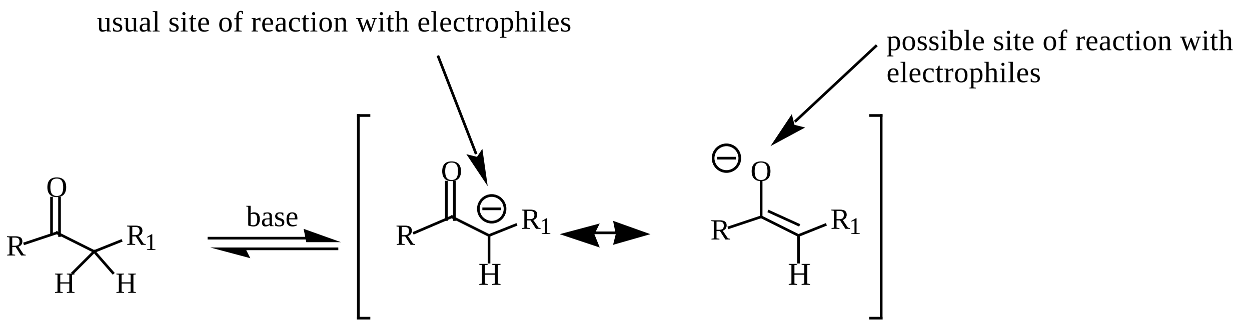
R-Li, R-MgBr, R-Zn-Br

Acid catalyzed:



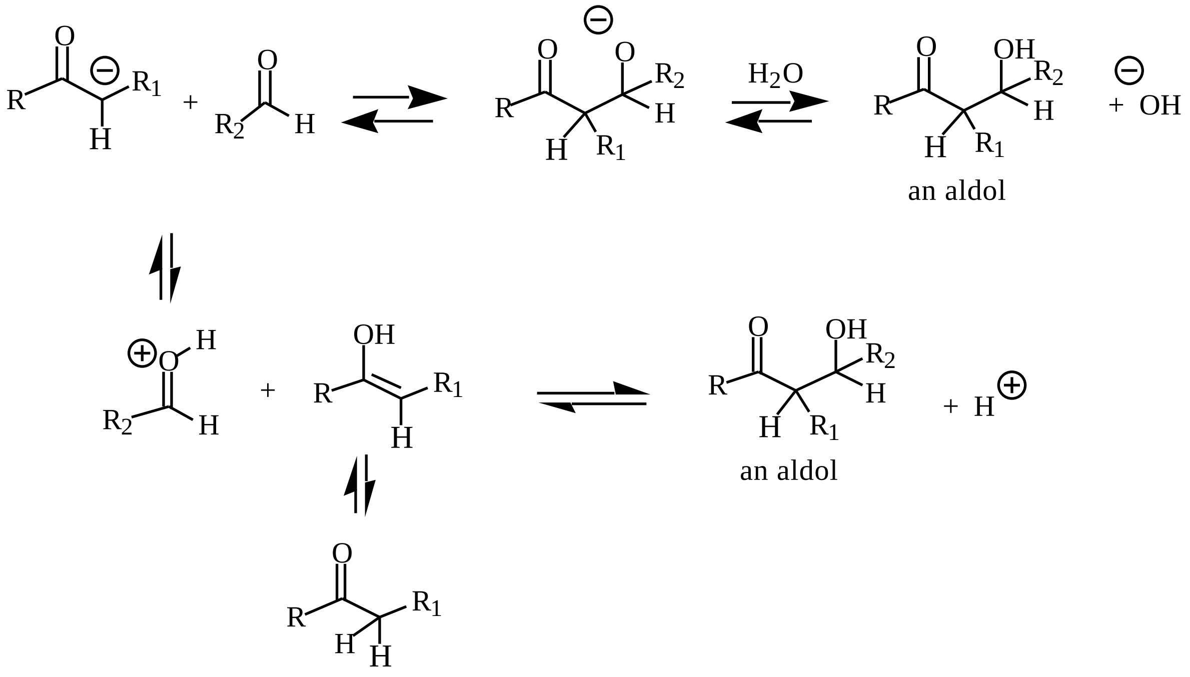
Equilibration is generally favorable (K >1) for aldehydes and unfavorable (K < 1) for ketones, but important electronic and steric effects can influence K_{eq}.

Special case of nucleophile: **enolate anion** by proton abstraction from a ketone or aldehyde

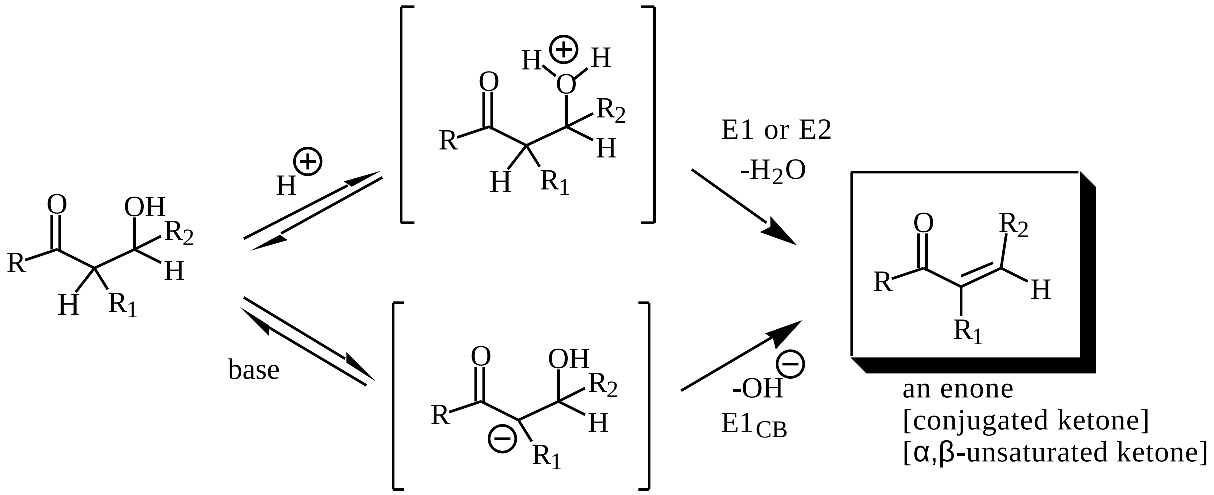


usual site of reaction with electrophiles

possible site of reaction with electrophiles

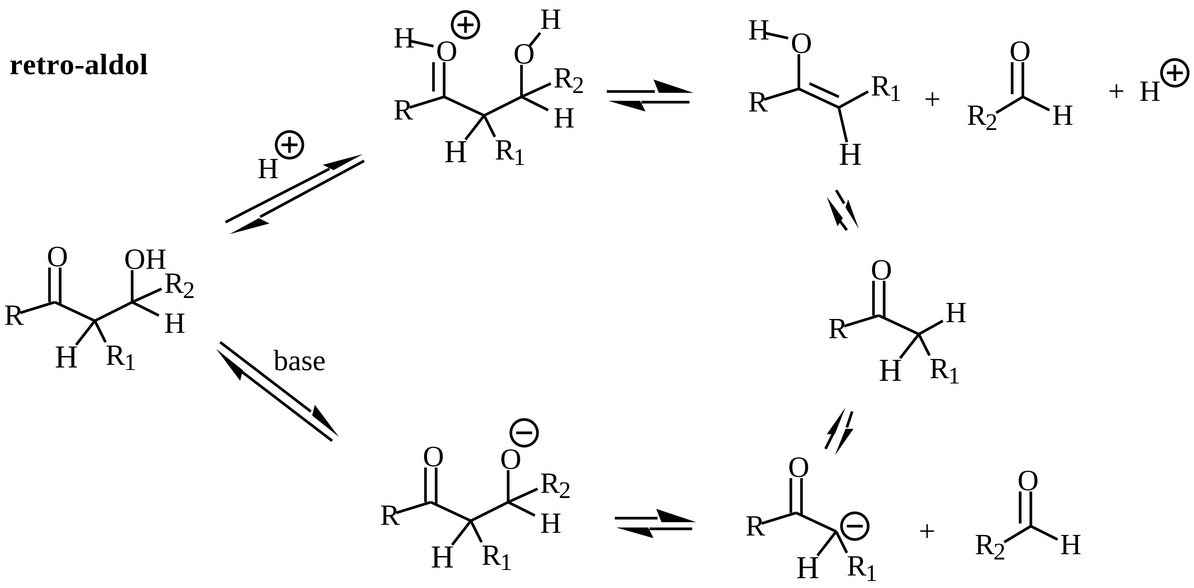


Final Stage:

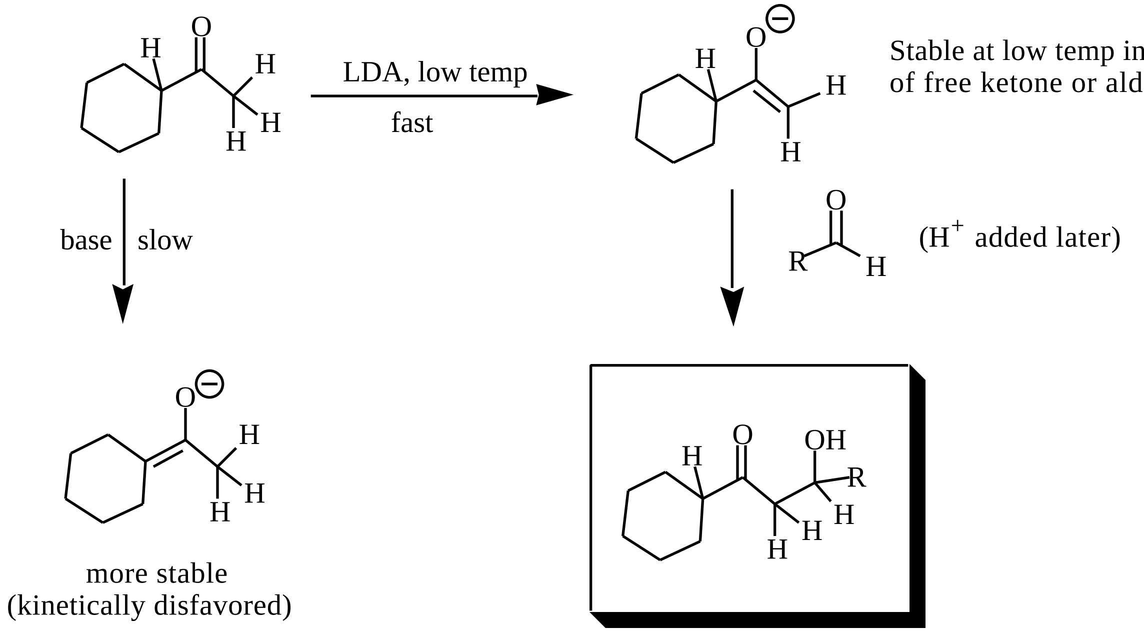


Makes the process irreversible, pulls the various equilibria steps to the right.

retro-aldol



Modern: Selective generation of the enolate anion, add other carbonyl component.



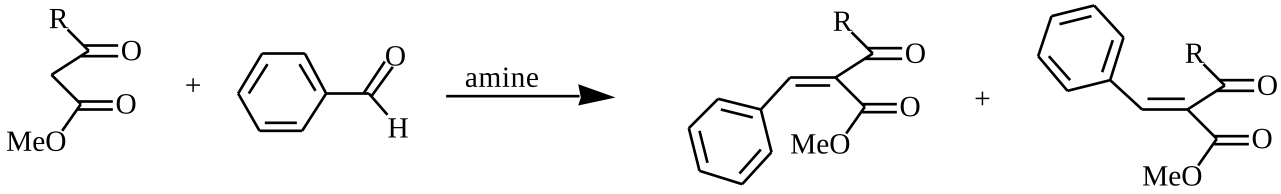
Stable at low temp in absence of free ketone or aldehyde

(H^+ added later)

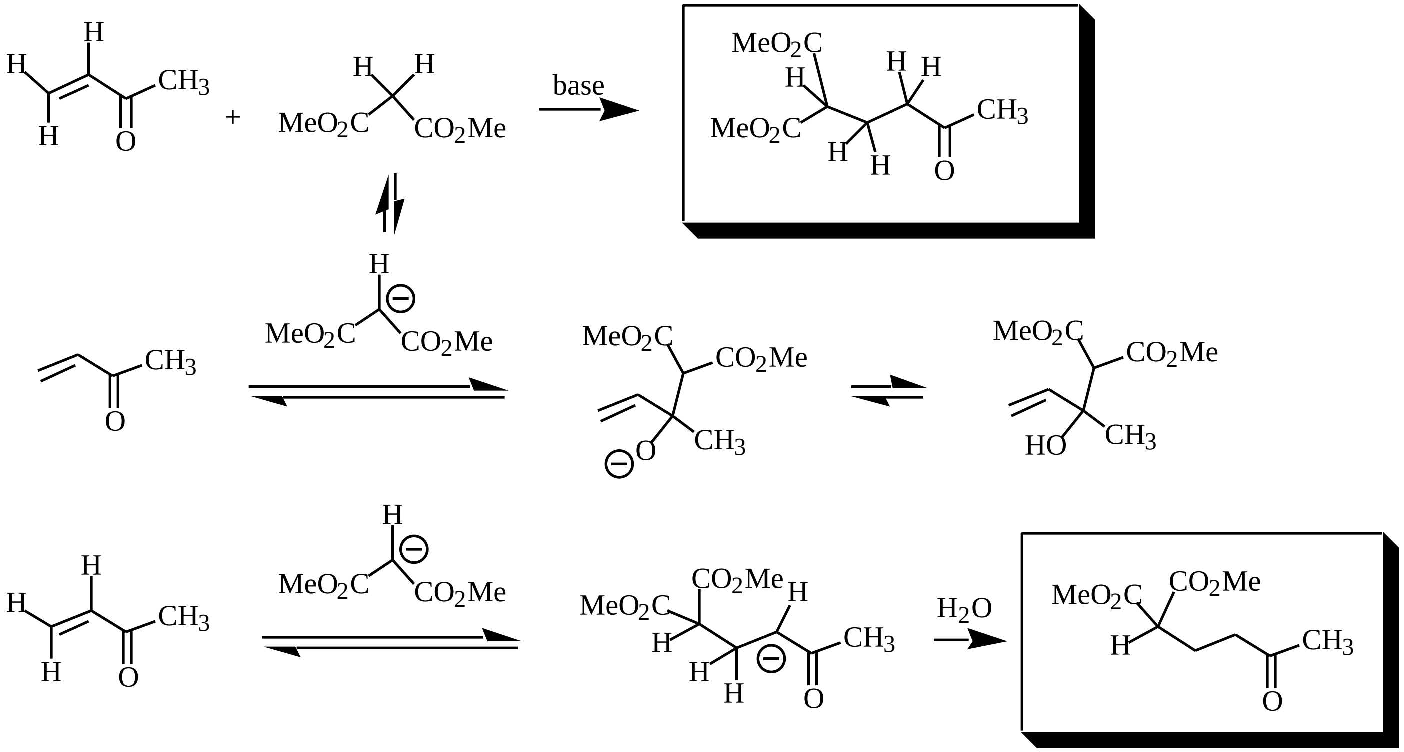
more stable
(kinetically disfavored)

Classics:

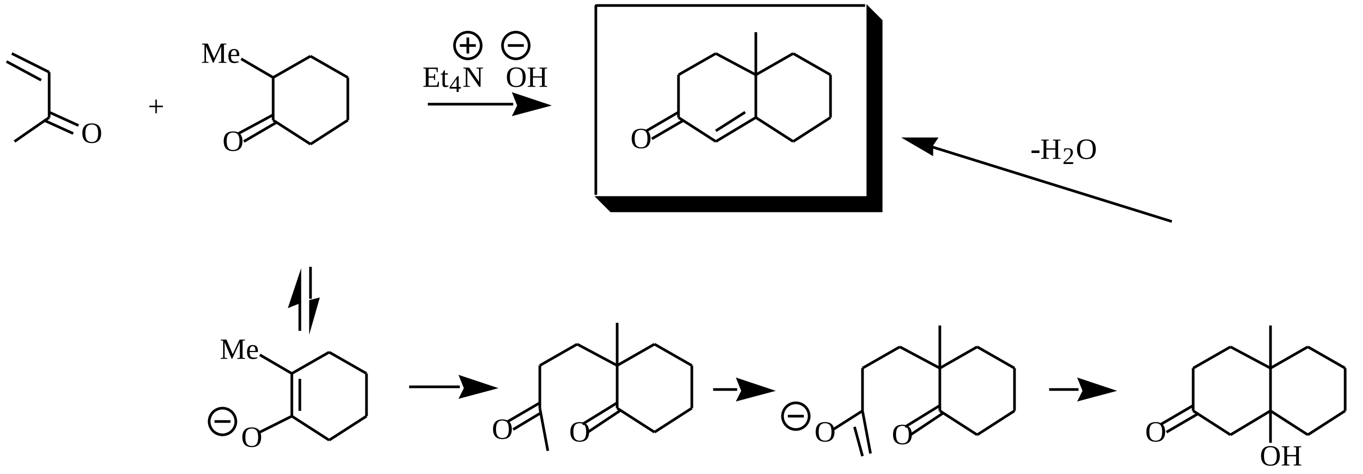
Very stabilized carbanion in one component: Knoevenagel Condensation
elimination of water to drive the process:



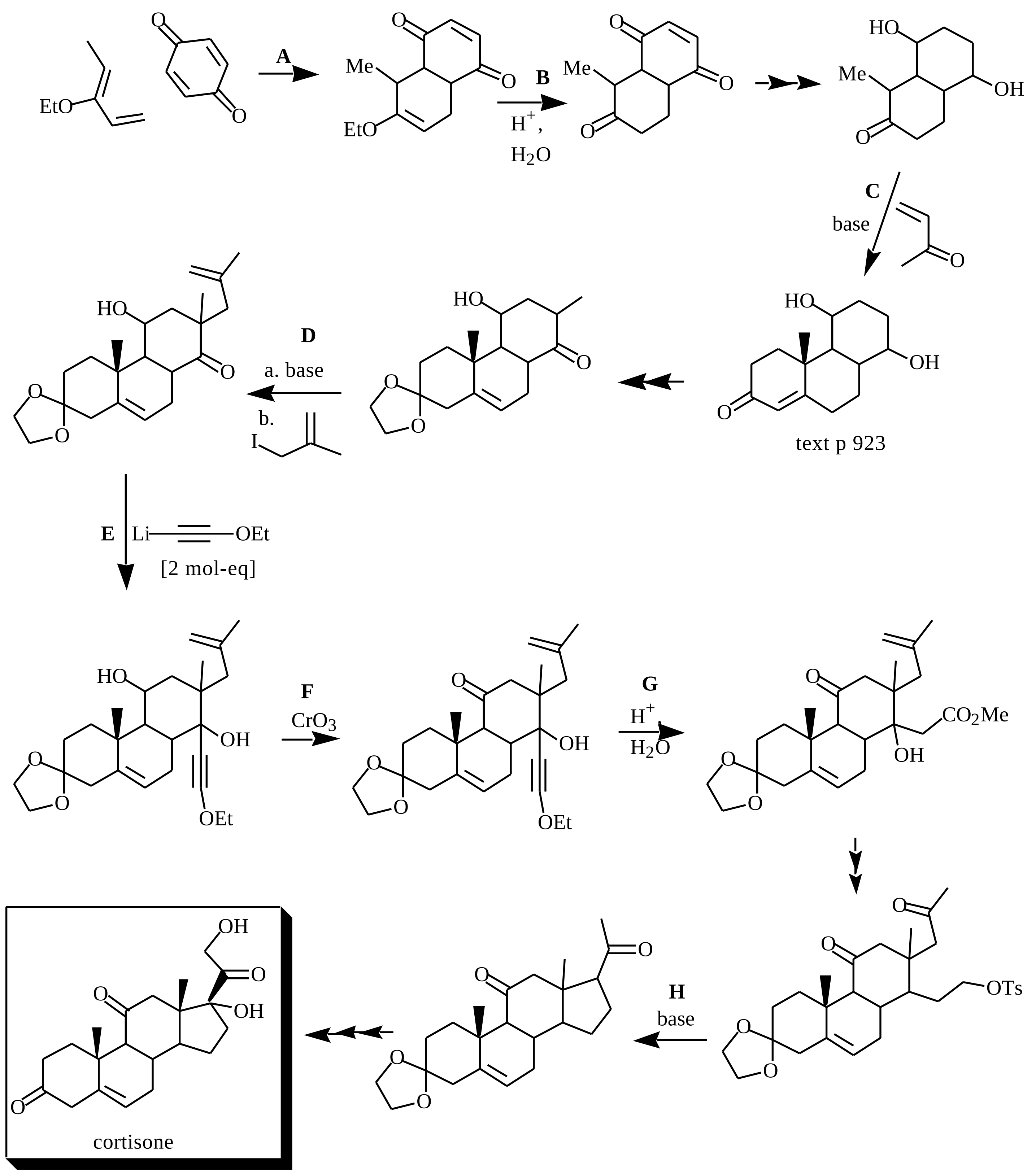
"Conjugate Addition" The Michael Reaction



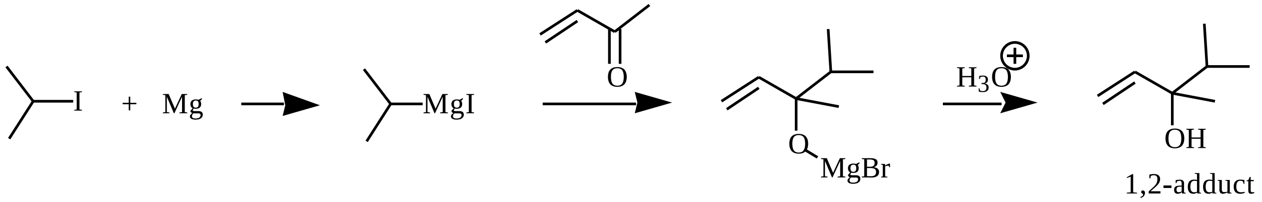
Combination condensation reactions: **Robinson Annulation**



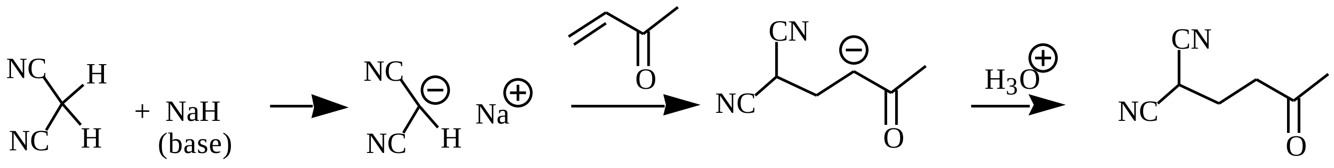
Sarett's Cortisone synthesis:



Note: Reactive Anions tend to react "1,2" at the carbonyl carbon and not reverse

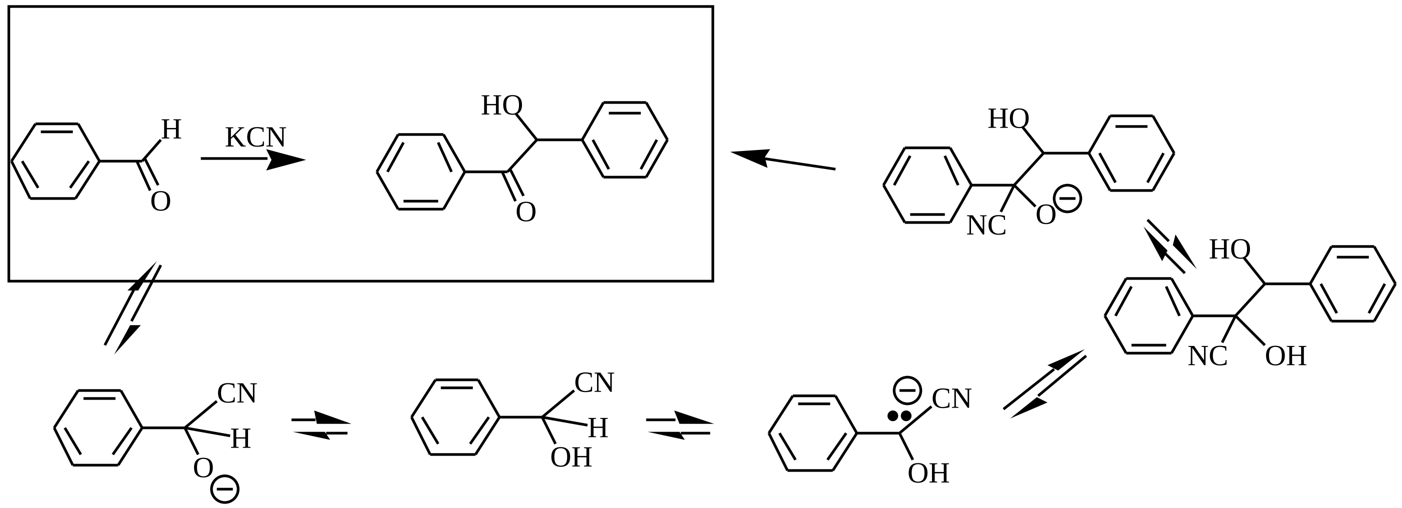


1,2-adduct



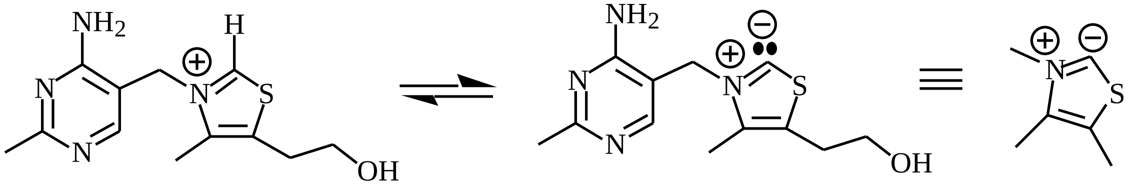
1,4-adduct

The Benzoin reaction and Vitamin B1 [thiamine] Very old:



Role of CN: Add to C=O; favor deprotonation of α-H
Easily formed nucleophile and then a good electron-withdrawing group.
[e.g., HO⁻ does not do the same job. Why?]

Nature's analog of CN: Thiamine--pKa 12.7



highly stablilized carbanion

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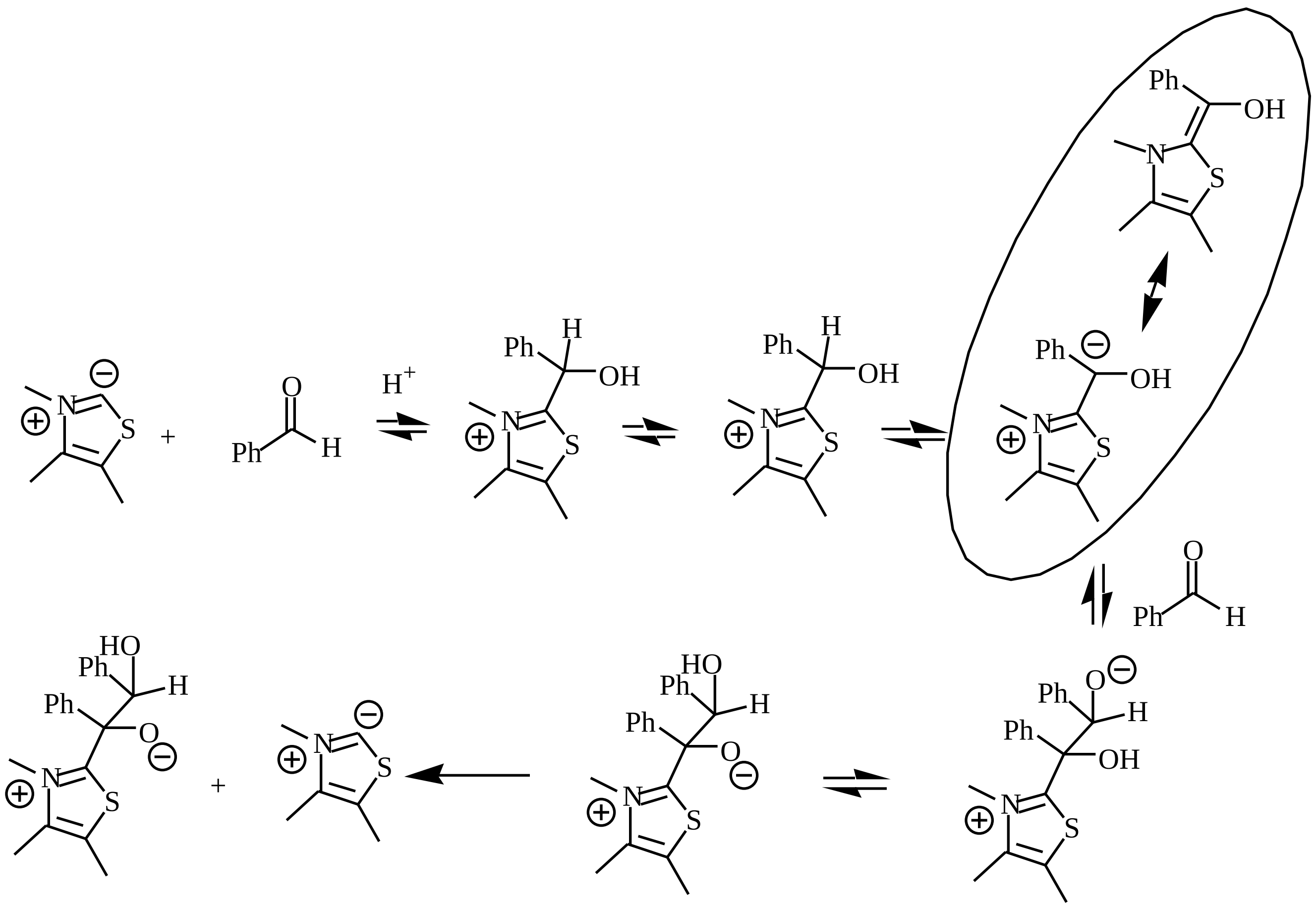
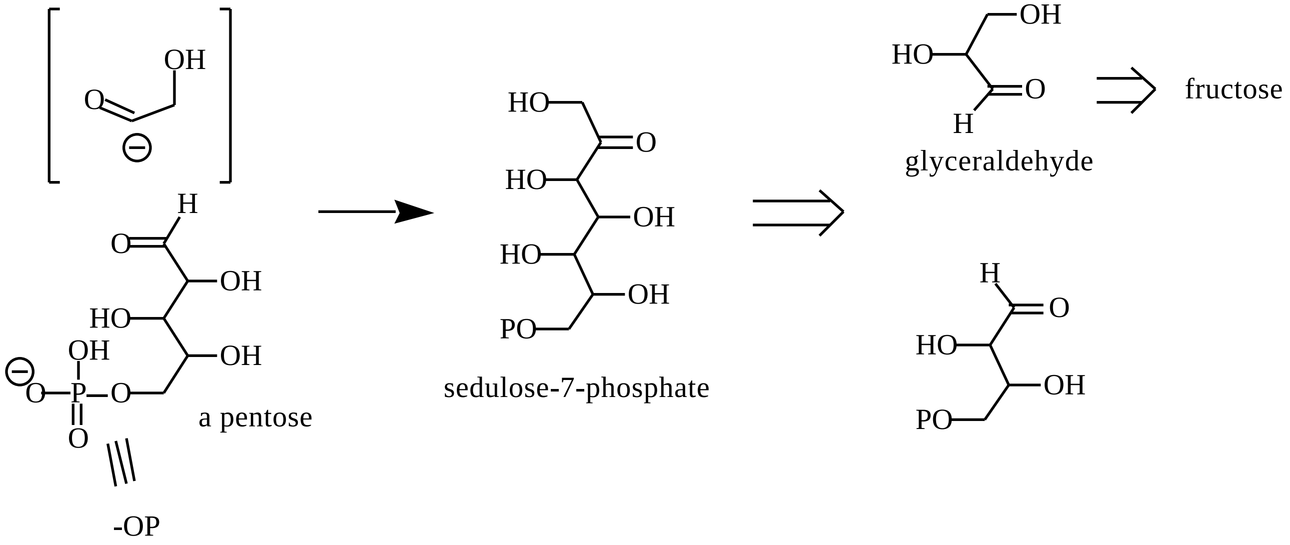
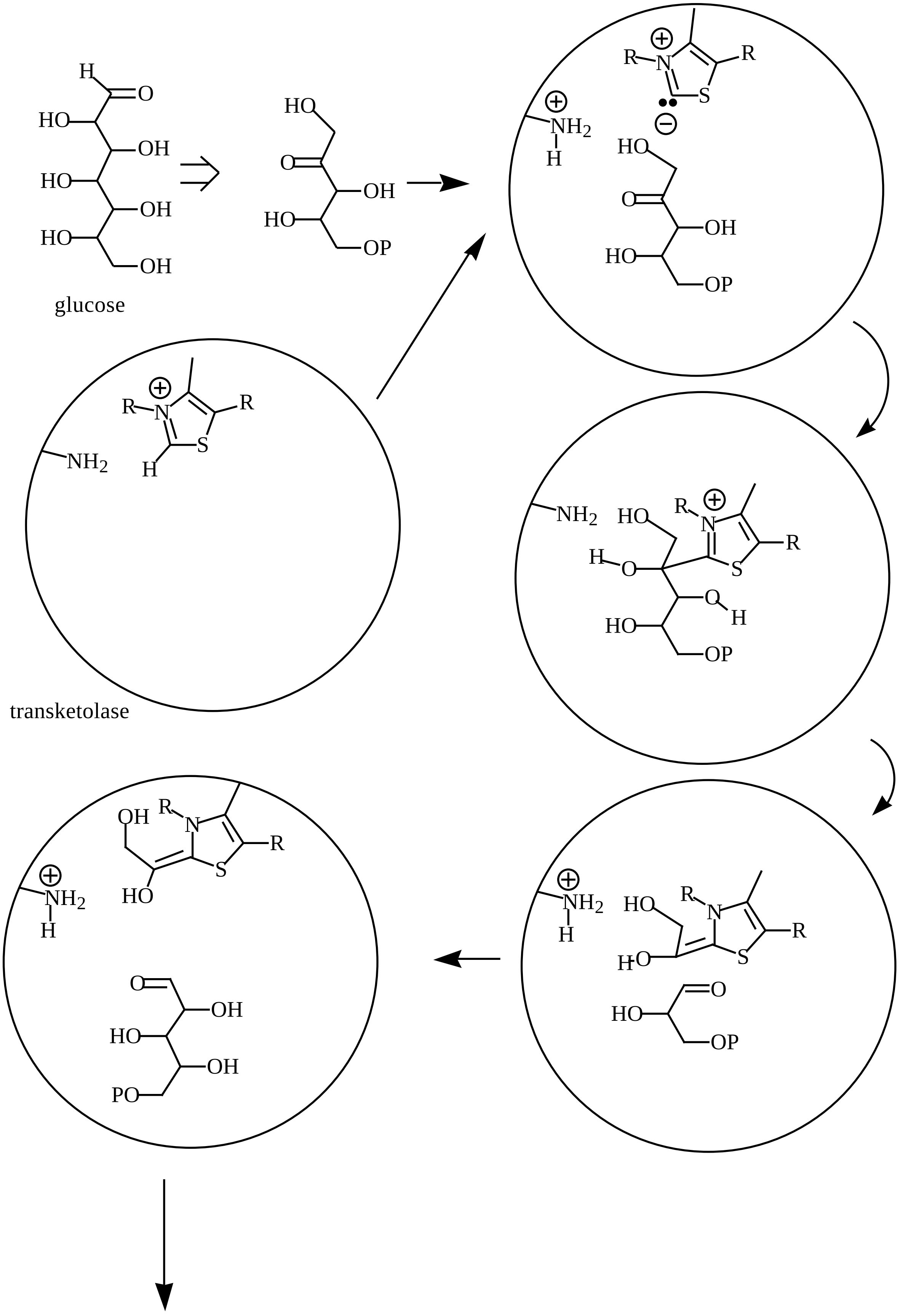


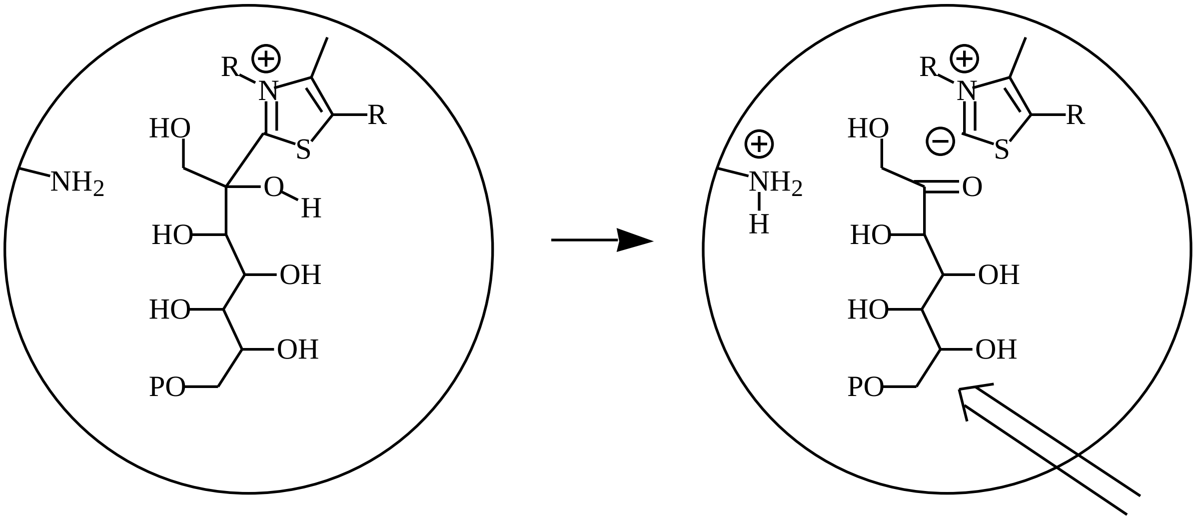
Biological CARBANION Reactions: The Pentose Phosphate Pathway

Overall: 3 Glucose → 2 Fructose + glyceraldehyde + 3 CO_2

C_6 C_6 C_3

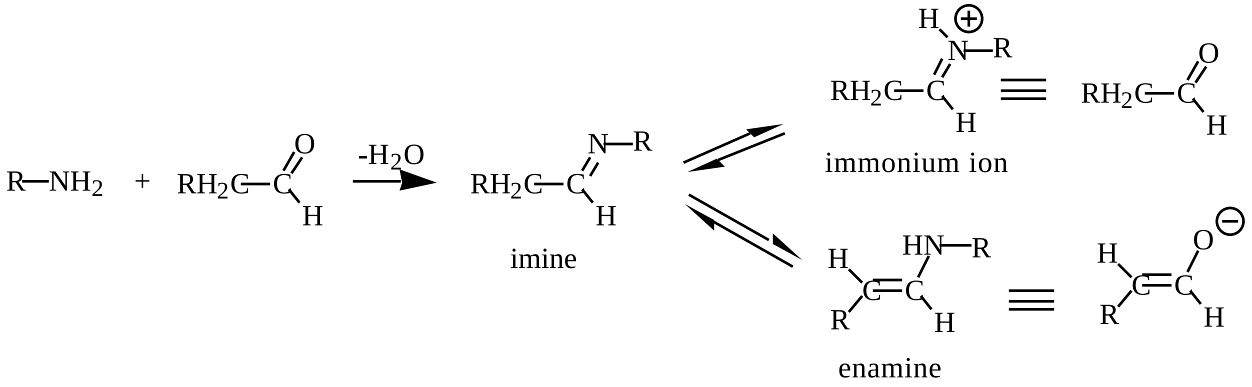


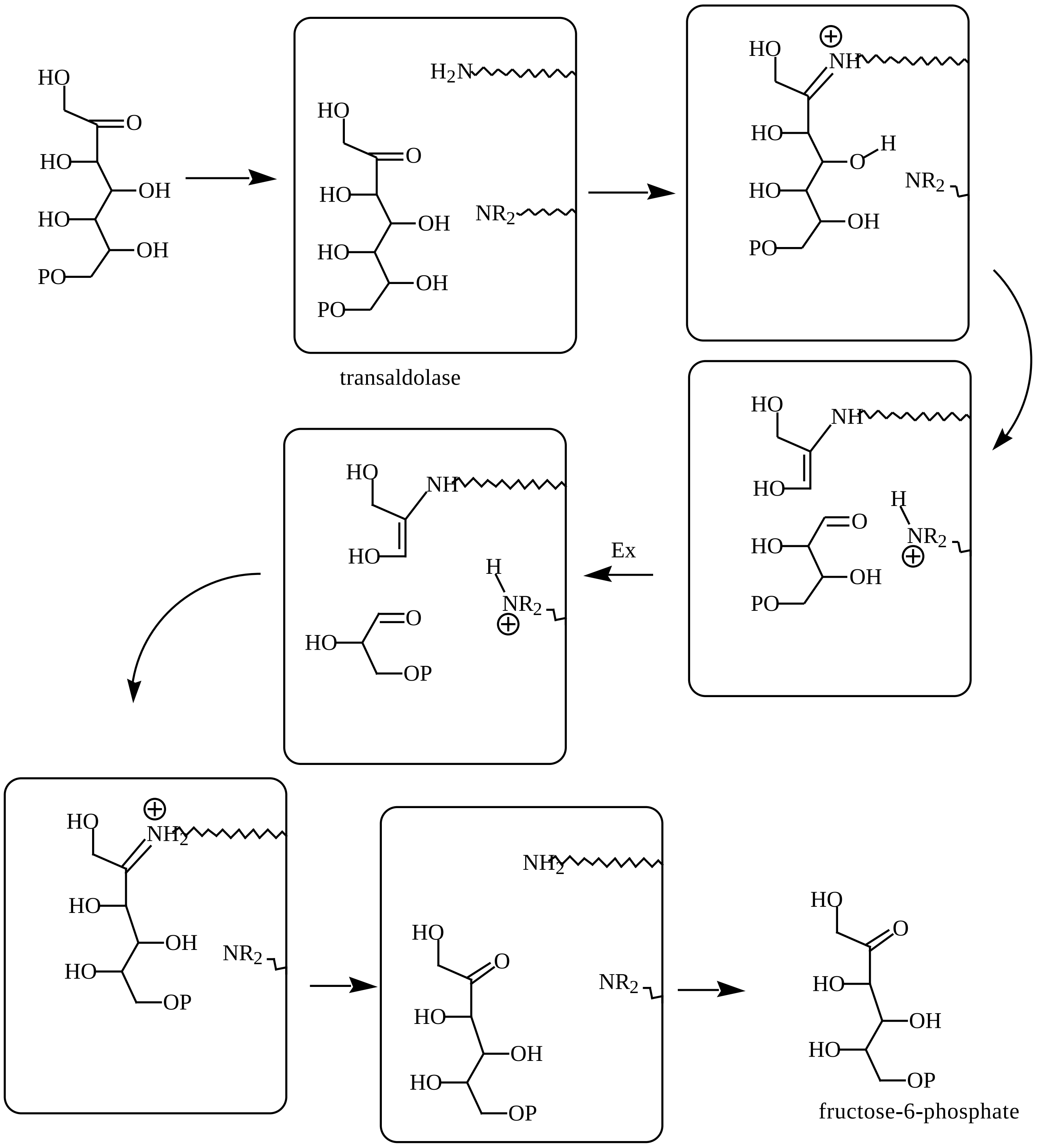

glucose
transketolase
HO
OH
OP
PO
O
H
NH2
N
S
R



sedulose-7-phosphate

Parallel Role of Imines/immonium ions/enamines:




HO
O
HO
OH
HO
OH
PO
H2N
NR2
transaldolase
NH
H
O
NR2
PO
Ex
NH
H
NR2
OP
NH2
NR2
fructose-6-phosphate