有機化學乙

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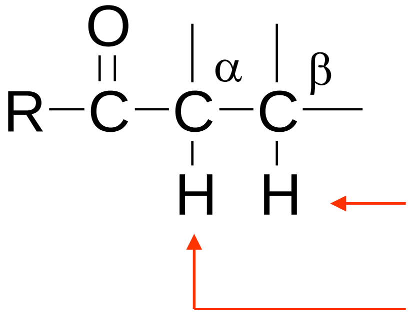
Chapter 18
Aldehydes and Ketones (II) — The chemistry at α-position

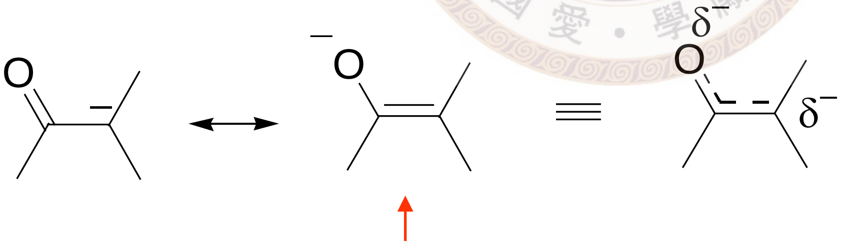
※ The acidity of α-hydrogen



β-hydrogen pK$_a$ ~40-50

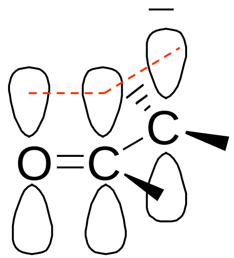
α-hydrogen pK$_a$ ~19-20

Reason:



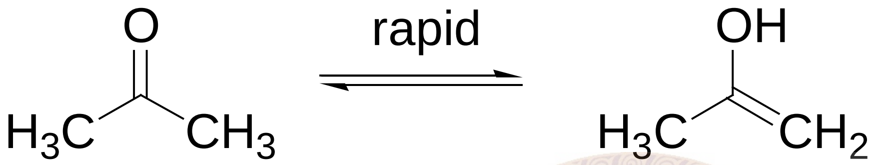
better: negative charge on oxygen

MO:



a delocalized anion

※ Keto-enol tautomerization (互變異構)

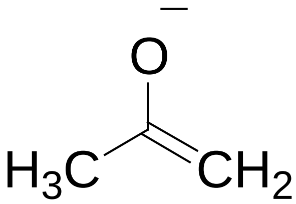


keto form

enol form

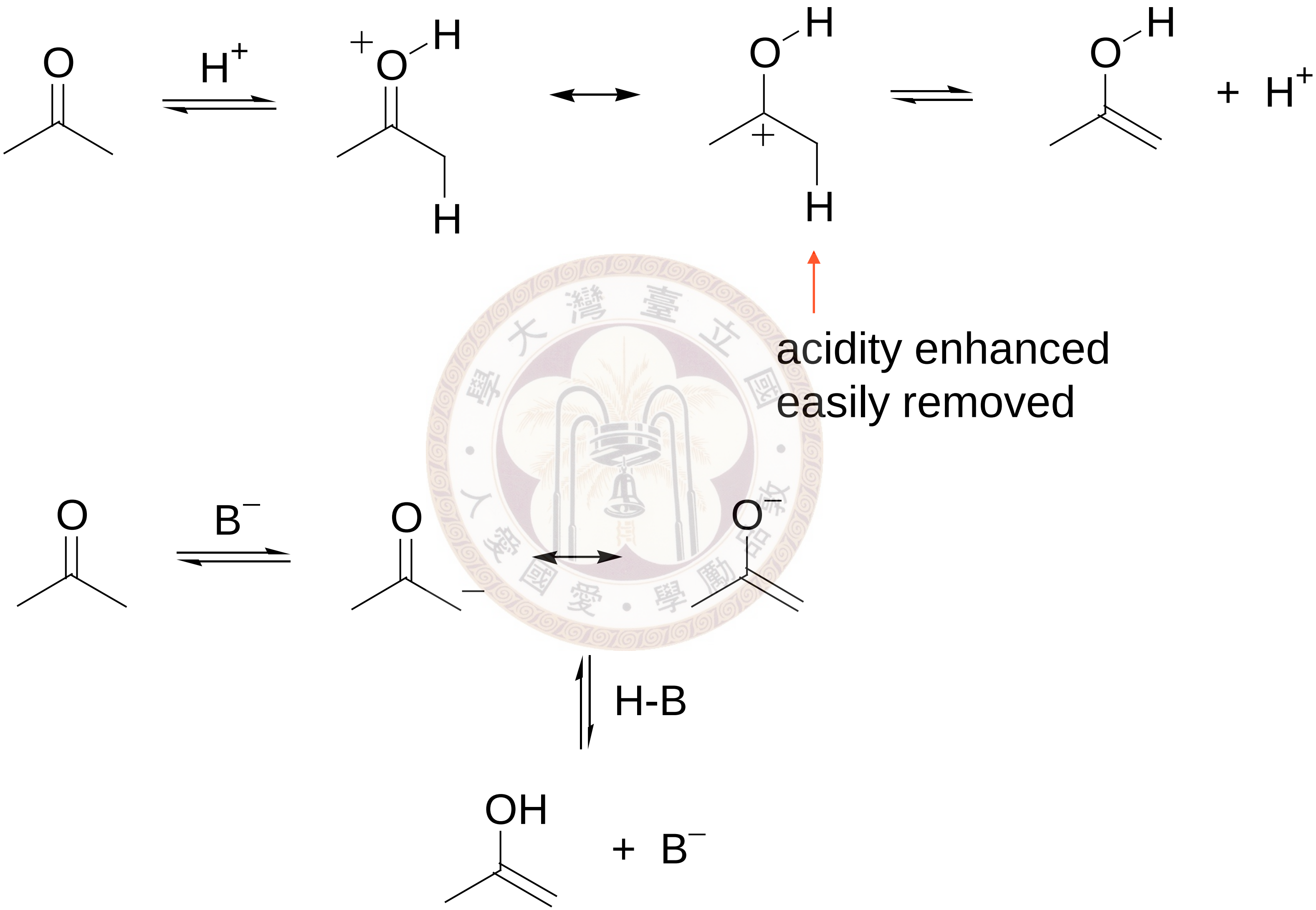
Two different isomer in rapid equilibrium
→ tautomerization

Keto form and enol form are tautomers to each other

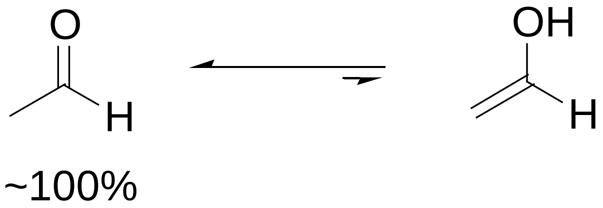


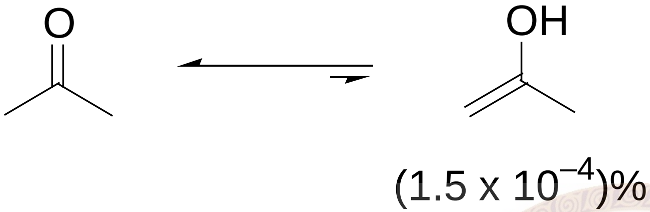
enolate

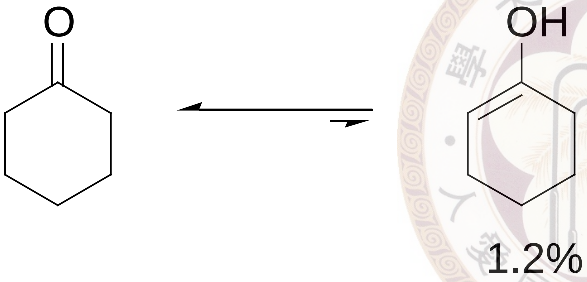
✓ This tautomerization is catalyzed by acid or base



acidity enhanced
easily removed

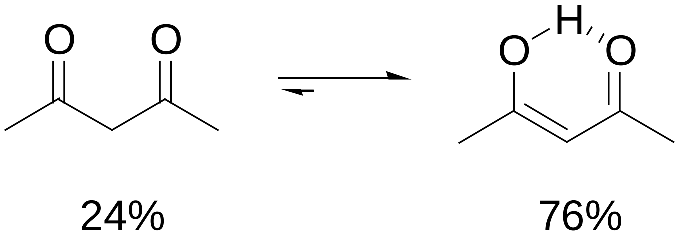




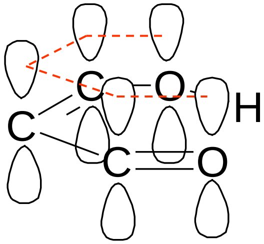


more stable double bond
→ higher enol content

1,3-dicarbonyls

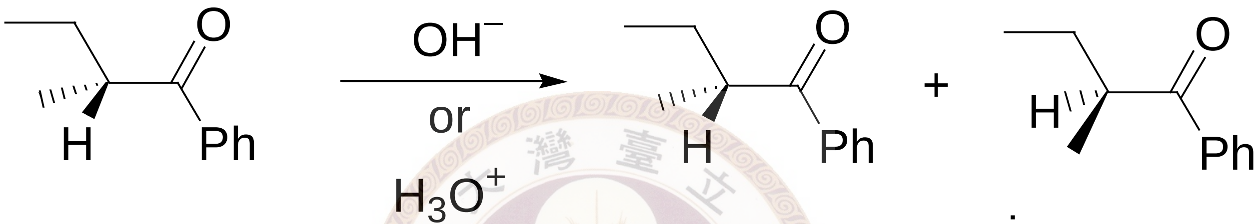


a conjugated system



※ Reactions via enols and enolate ions

◎ Racemization

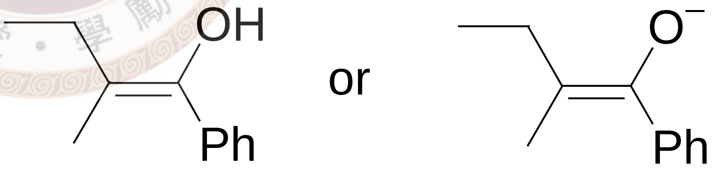


R-(+)

racemic

Reason:

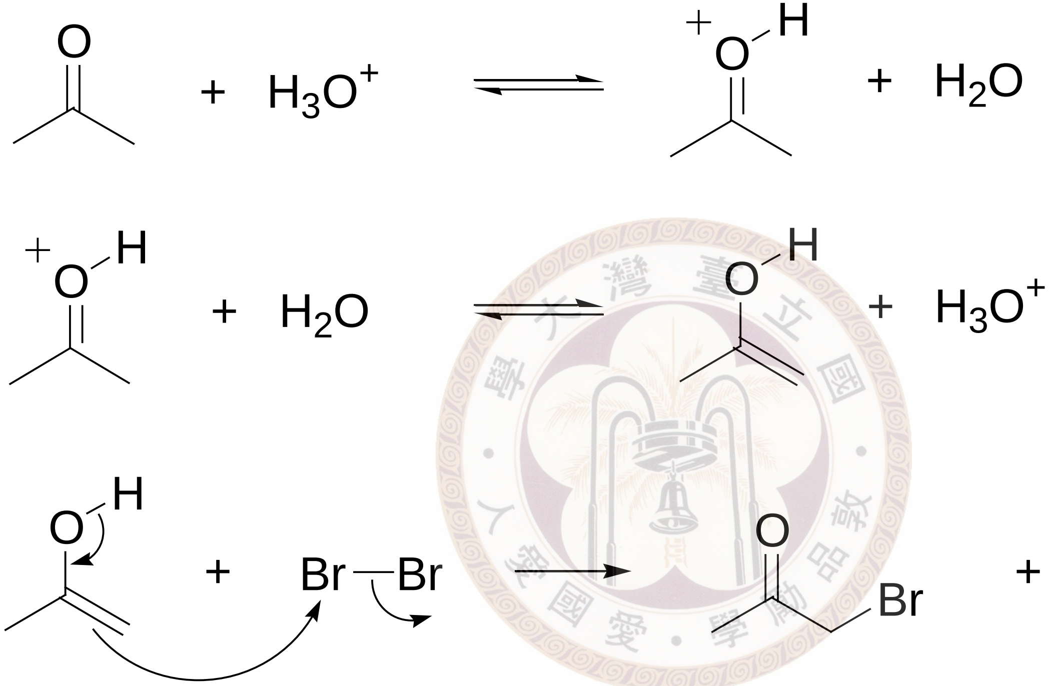
goes through



achiral

◎ Halogenation

✓ Acid catalyzed



fast

slow

fast

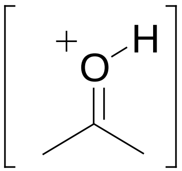
△ Rate is independent of $[Br_2]$

△ The enol formation is rate determining step

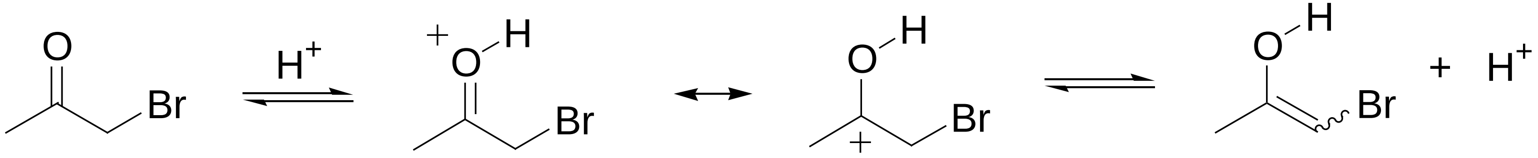
△ Acid enhances the rate of enolization

→ increases the overall rate

rate ∝



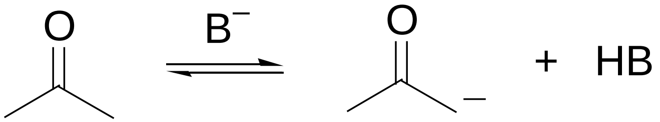
△ Can stop at monobromination



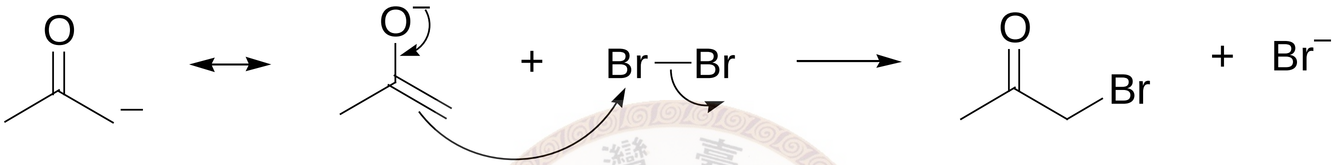
destabilized by inductive effect of Br

→ enol formation is slower

✓ Base promoted

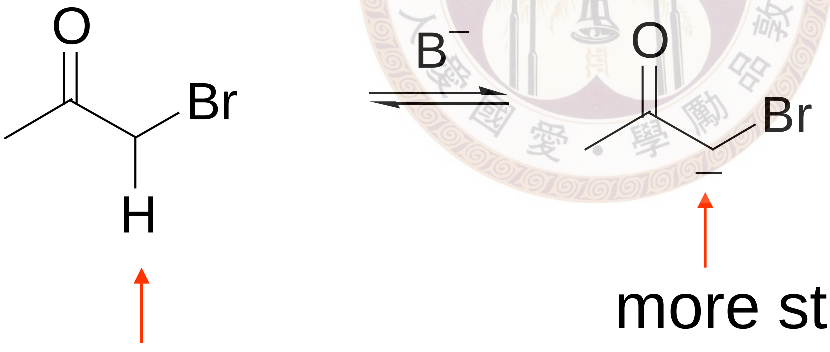


slow



fast

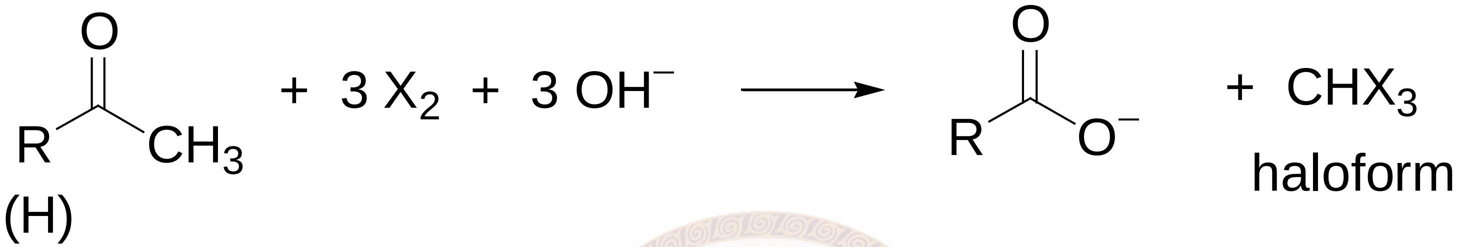
△ Polyhalogenation occurs



more acidic

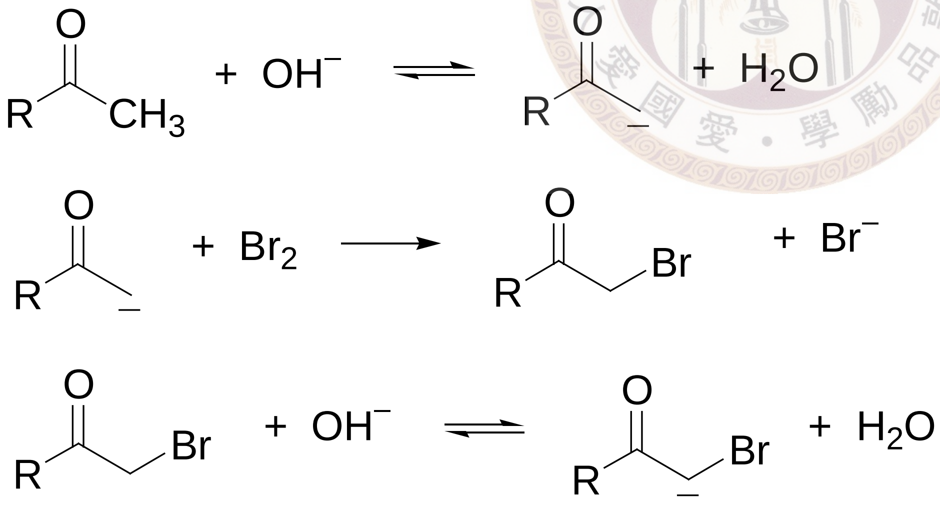
more stabilized by
inductive effect of Br
→ forms more easily

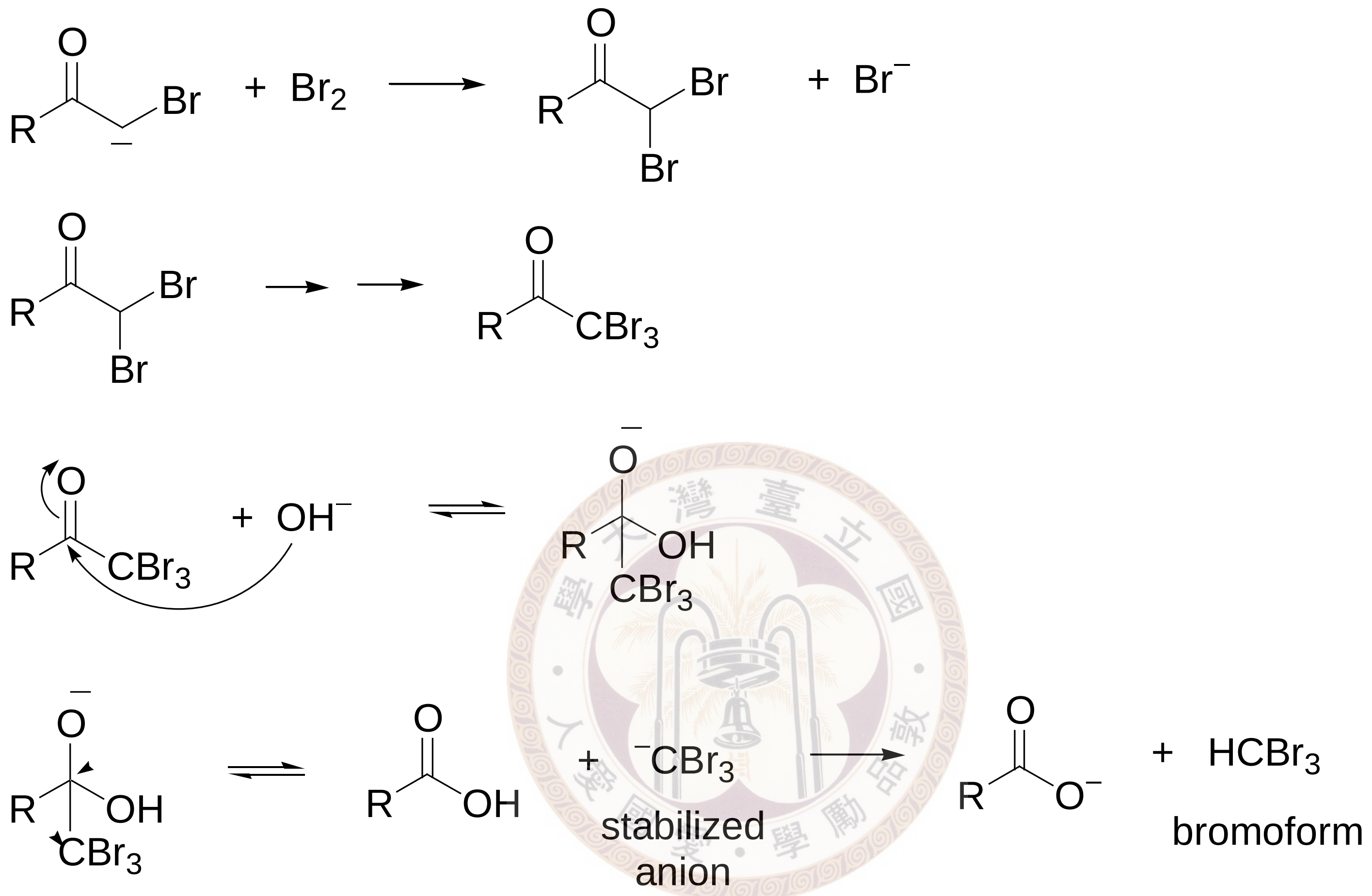
※ The haloform (鹵仿) reaction

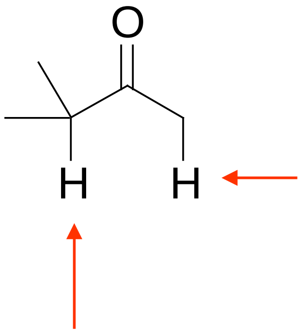


*A method to prepare carboxylic acid

Mechanism:



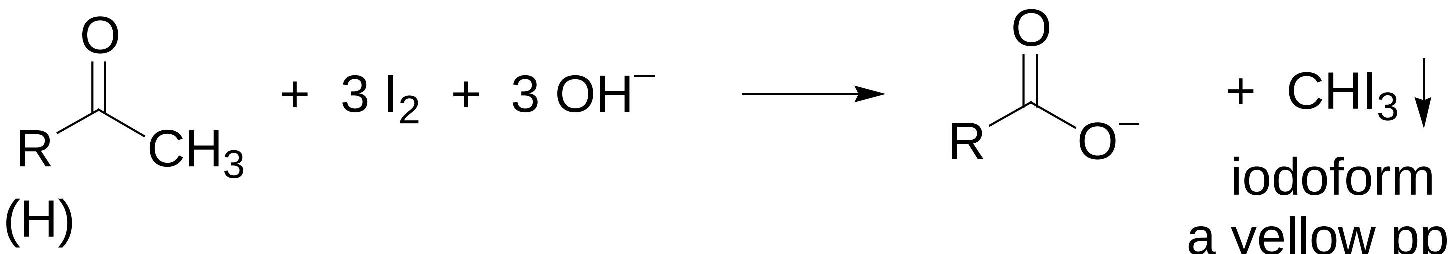




kinetically more acidic due to steric effect

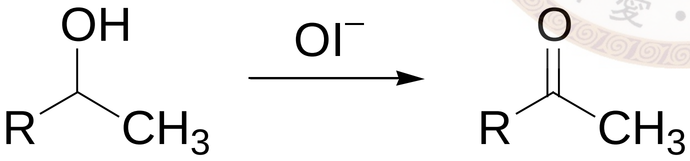
halogenation here is a side reaction

◎ The iodoform (碘仿) test



iodoform
a yellow ppt.

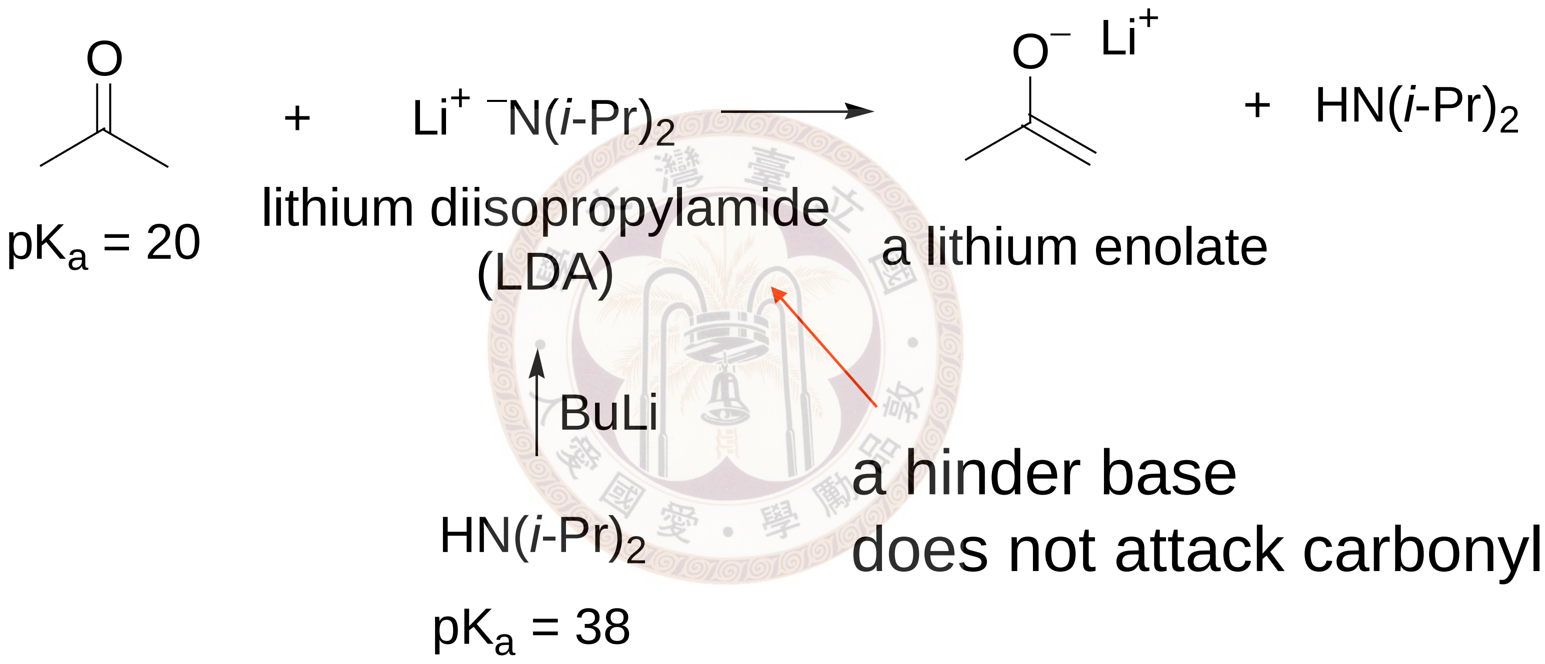
indication of a methyl ketone or acetaldehyde



also gives a positive iodoform test

※ Enolates

✓ Generation



$pK_a = 20$

+ $Li^+ \; ^-N(i\text{-}Pr)_2$

lithium diisopropylamide
(LDA)

$O^- \; Li^+$

a lithium enolate

+ $HN(i\text{-}Pr)_2$

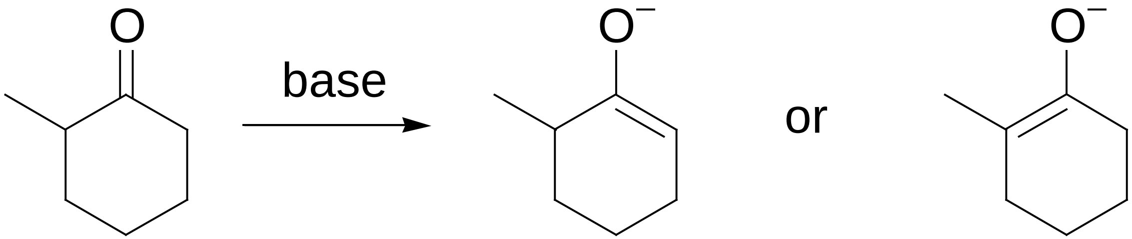
BuLi

$HN(i\text{-}Pr)_2$

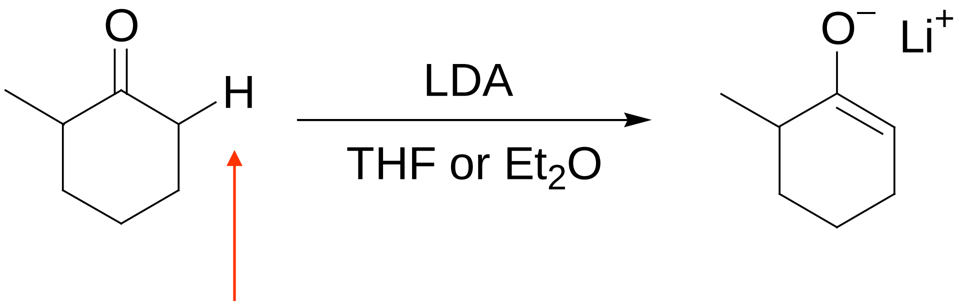
$pK_a = 38$

a hinder base
does not attack carbonyl

✓ Kinetic vs thermodynamic enolate



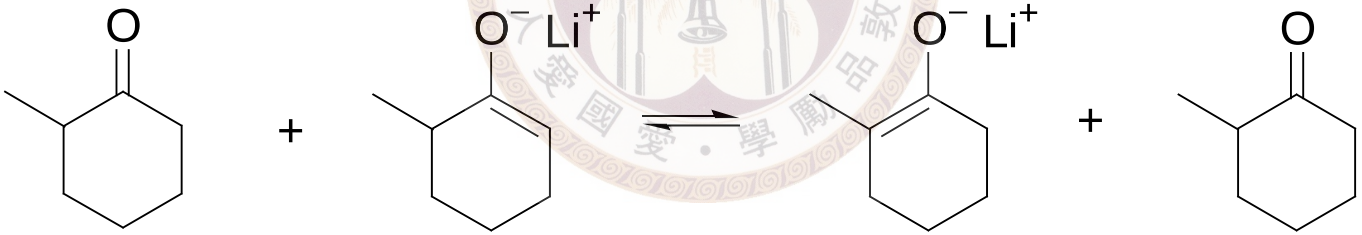
thermodynamically more stable
→ thermodynamic enolate

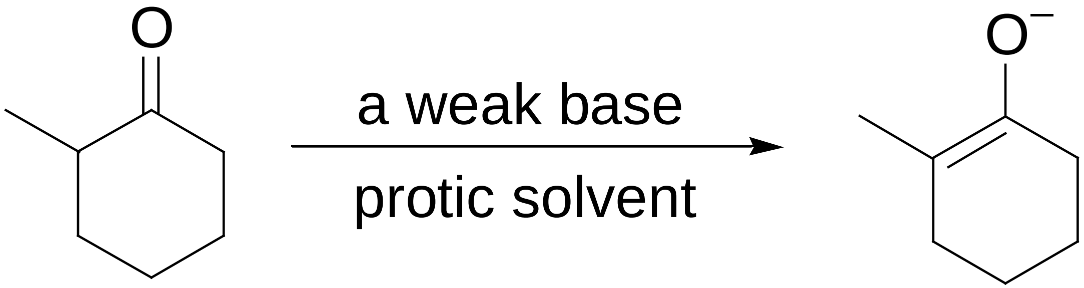


formed faster kinetically
→ kinetic enolate

less hinder
attacked by LDA faster

*Add ketone slowly to LDA to avoid equilibration

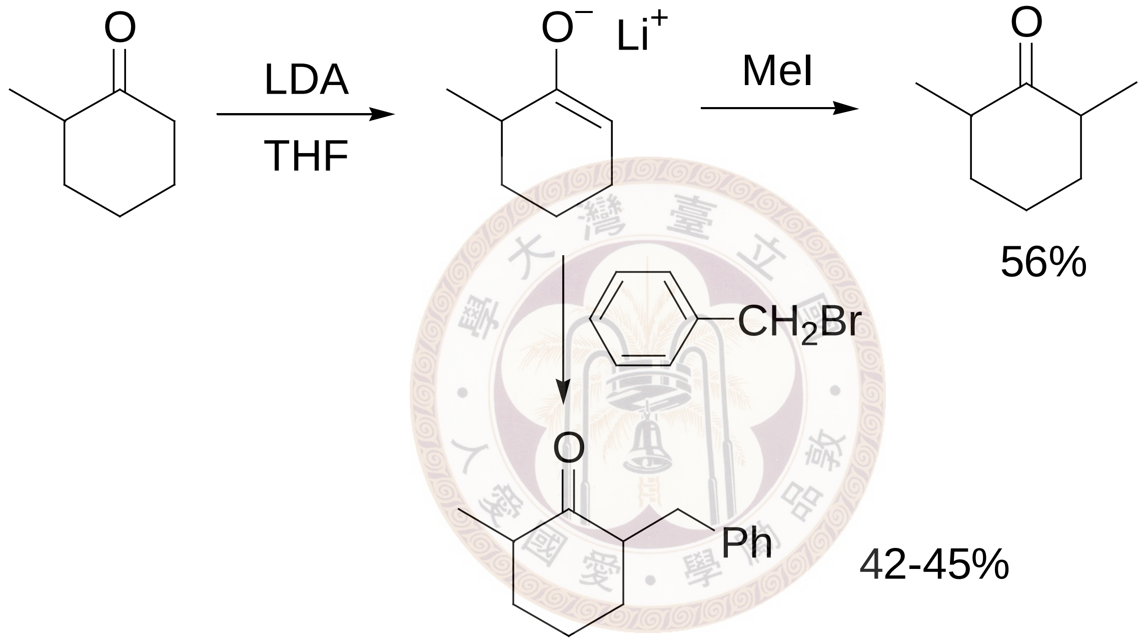




例: NaOEt/EtOH

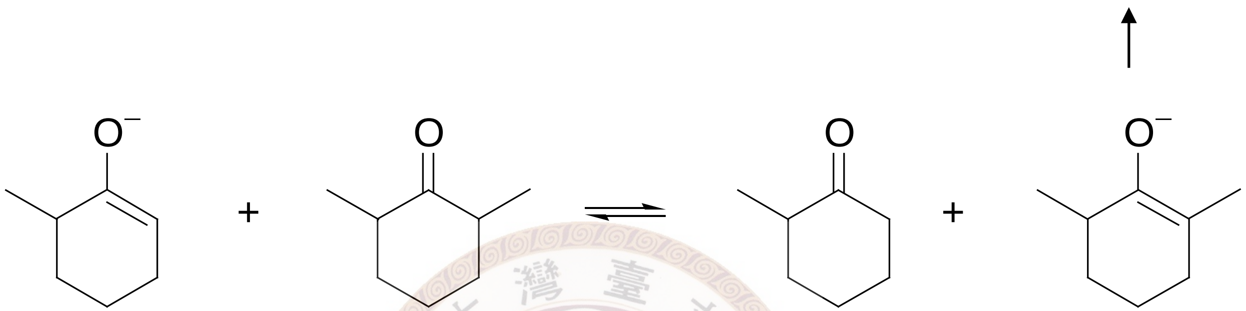
reversible condition → gives thermodynamic enolate

※ Alkylation



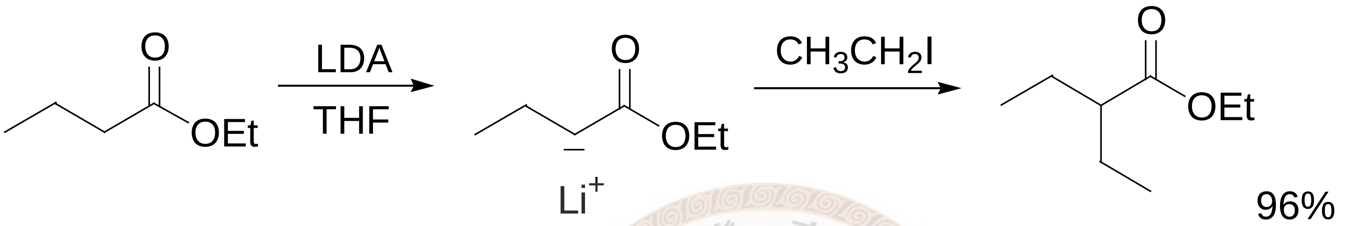
- ✓ Only works for reactive halides
- ✓ Technically: enolate adds to halide

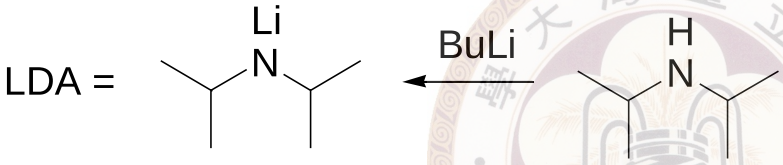
✓ Problem: polyalkylation



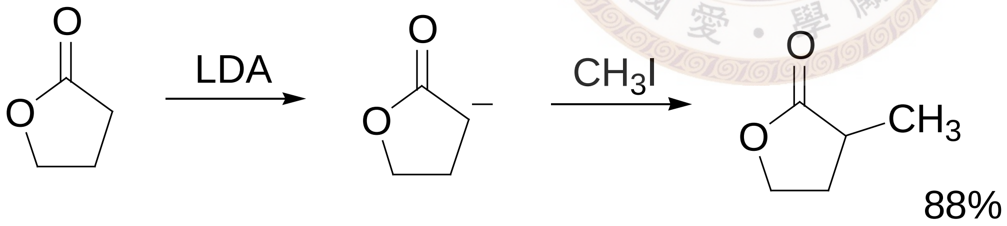
*Proton exchange is more serious for slow alkylation

※ Direct alkylation of esters

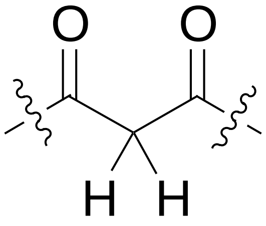




lithium diisopropylamide



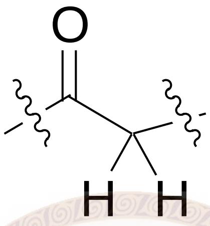
※ Enolates of β-dicarbonyl compounds



pKa 9~11

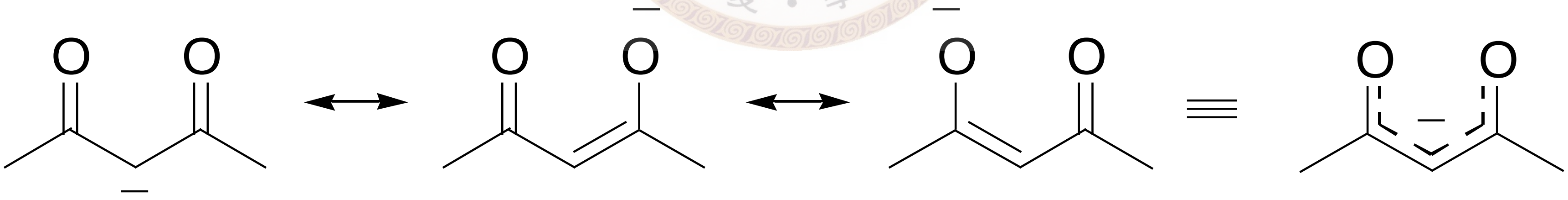
More acidic

cf.



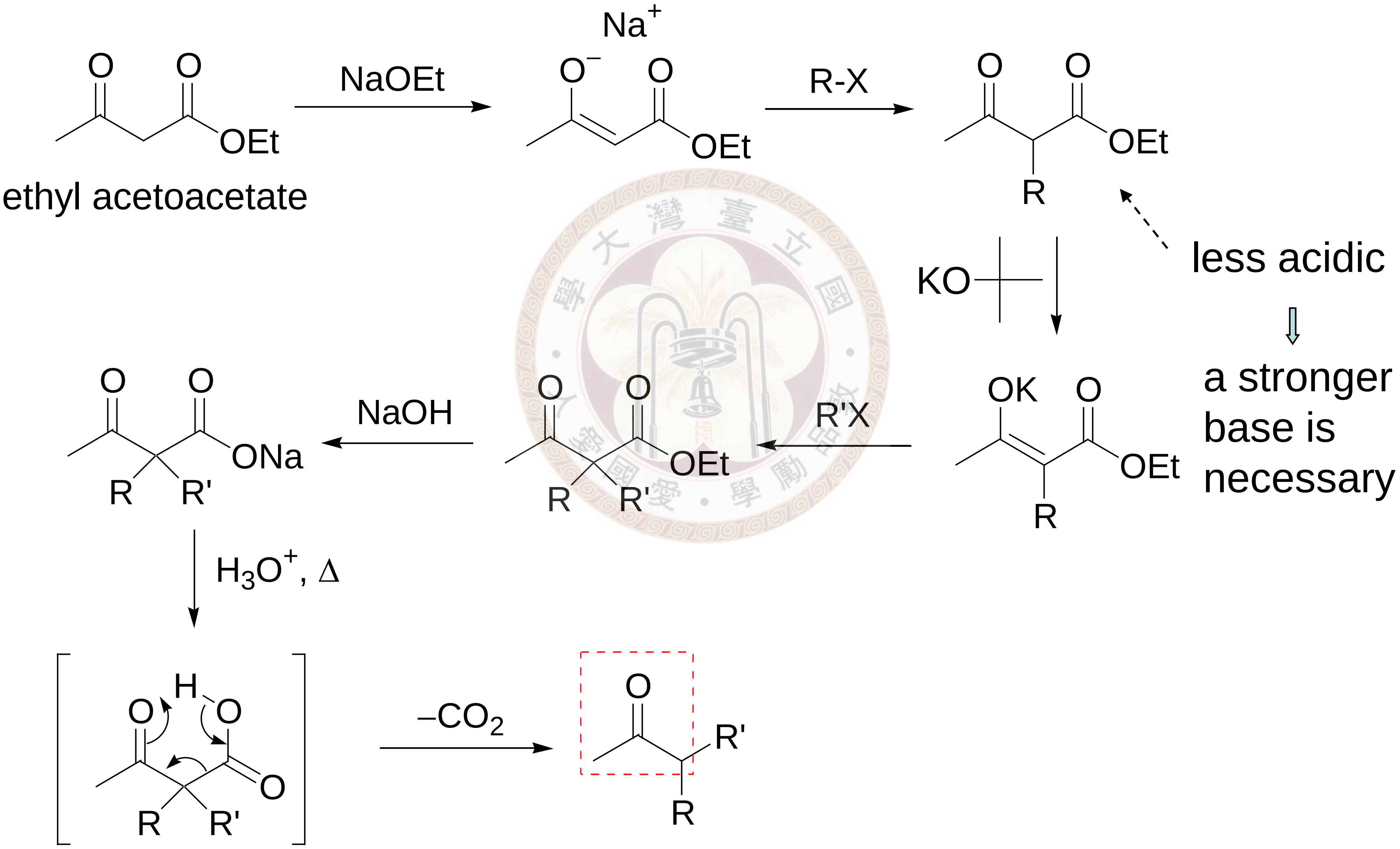
pKa 18~20

Reason:



Resonance stabilized enolate

※ The acetoacetic ester synthesis

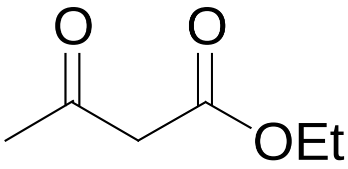


less acidic

⇩

a stronger base is necessary

Overall:

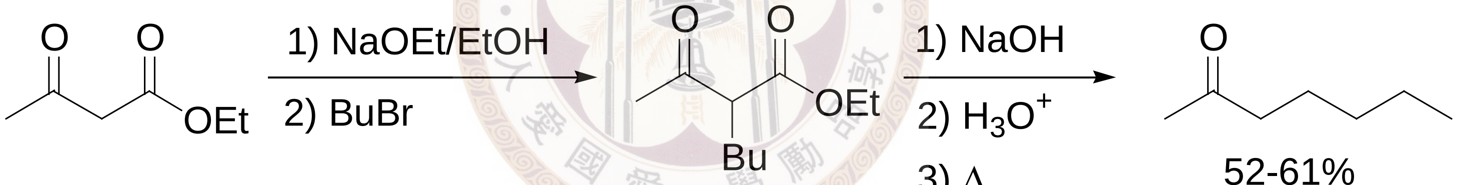


is a synthetic equivalent of acetone

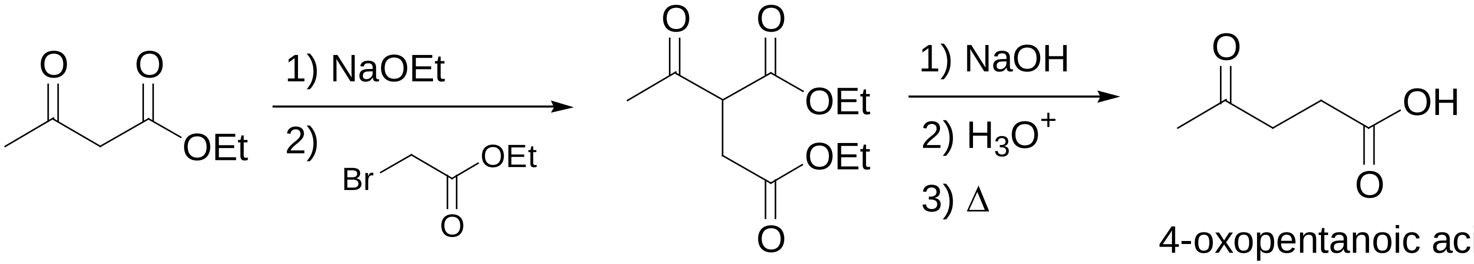
Q: Why not use acetone directly?

A: Polyalkylation, aldol condensation

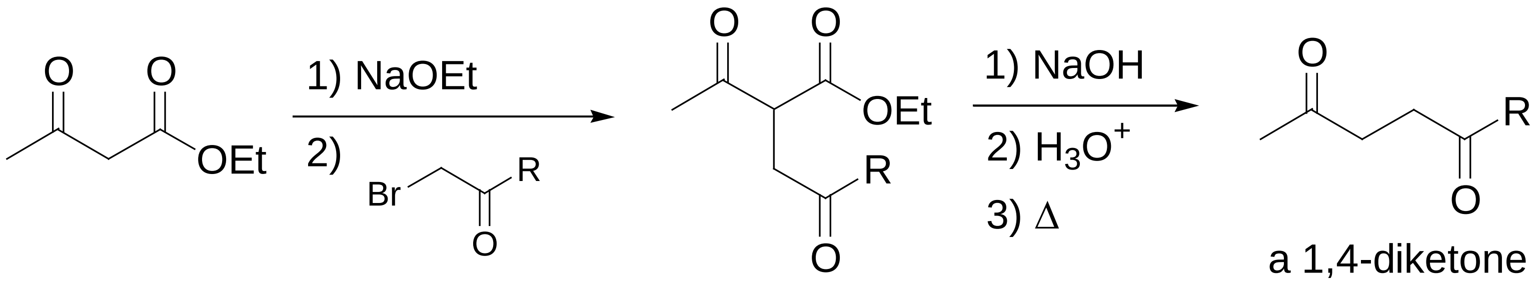
例

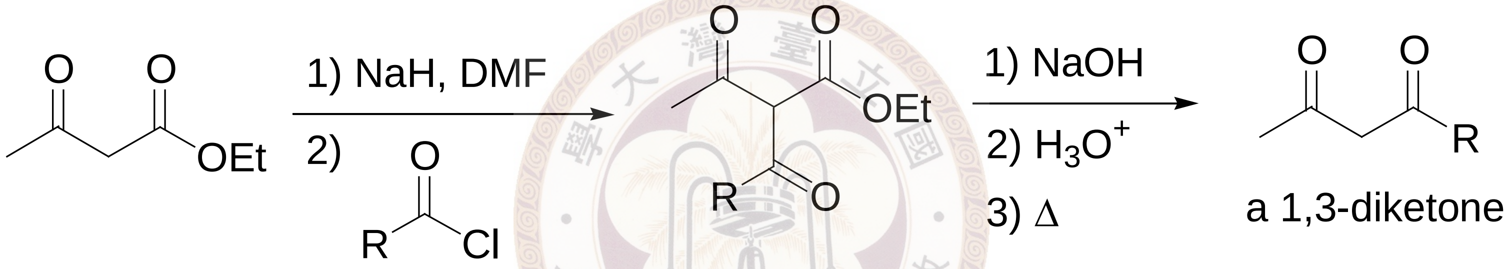


52-61%
overall

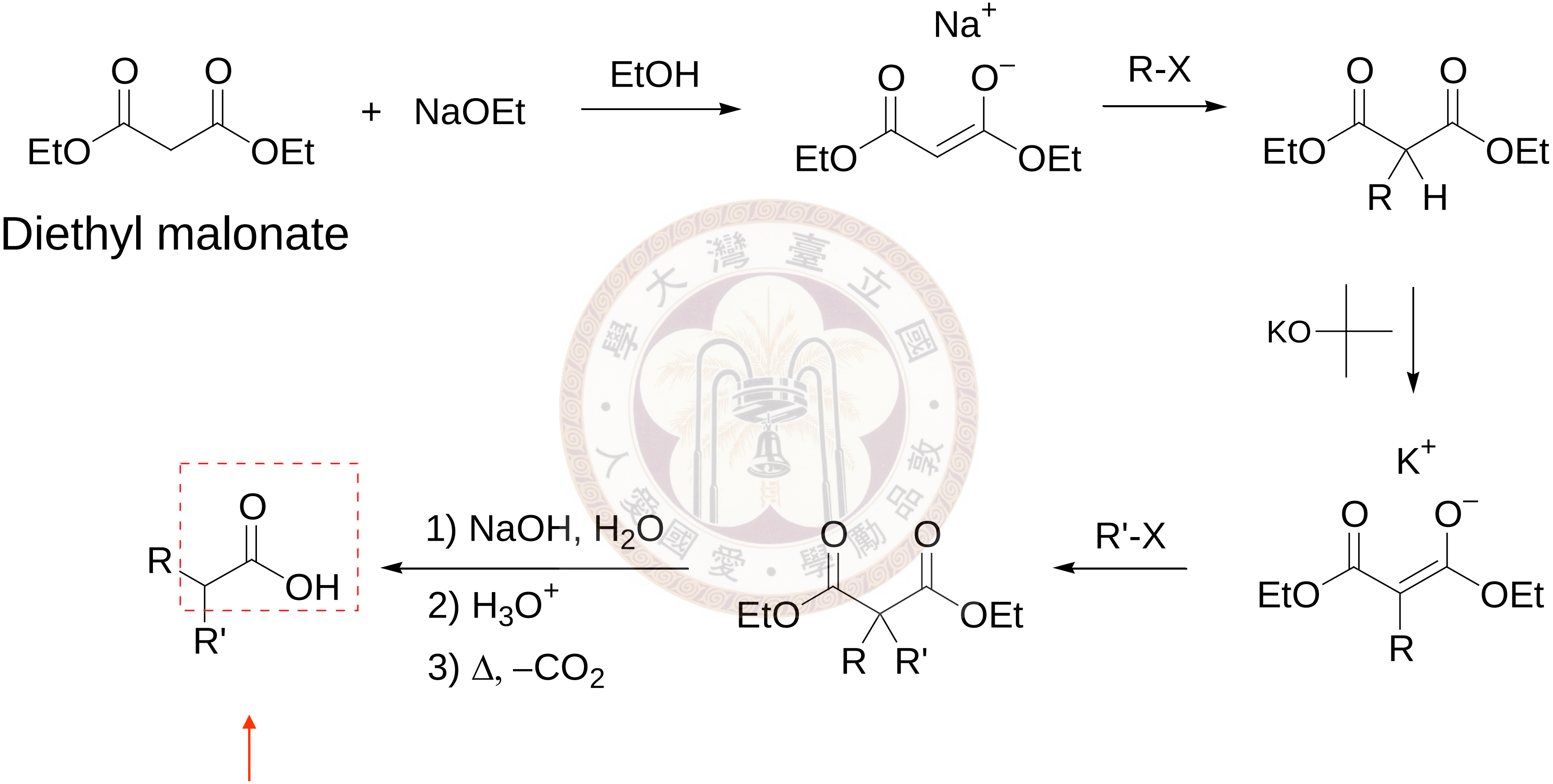


4-oxopentanoic acid


1) NaOEt
2) Br R O
OEt
1) NaOH
2) H_3O^+
3) Δ
a 1,4-diketone

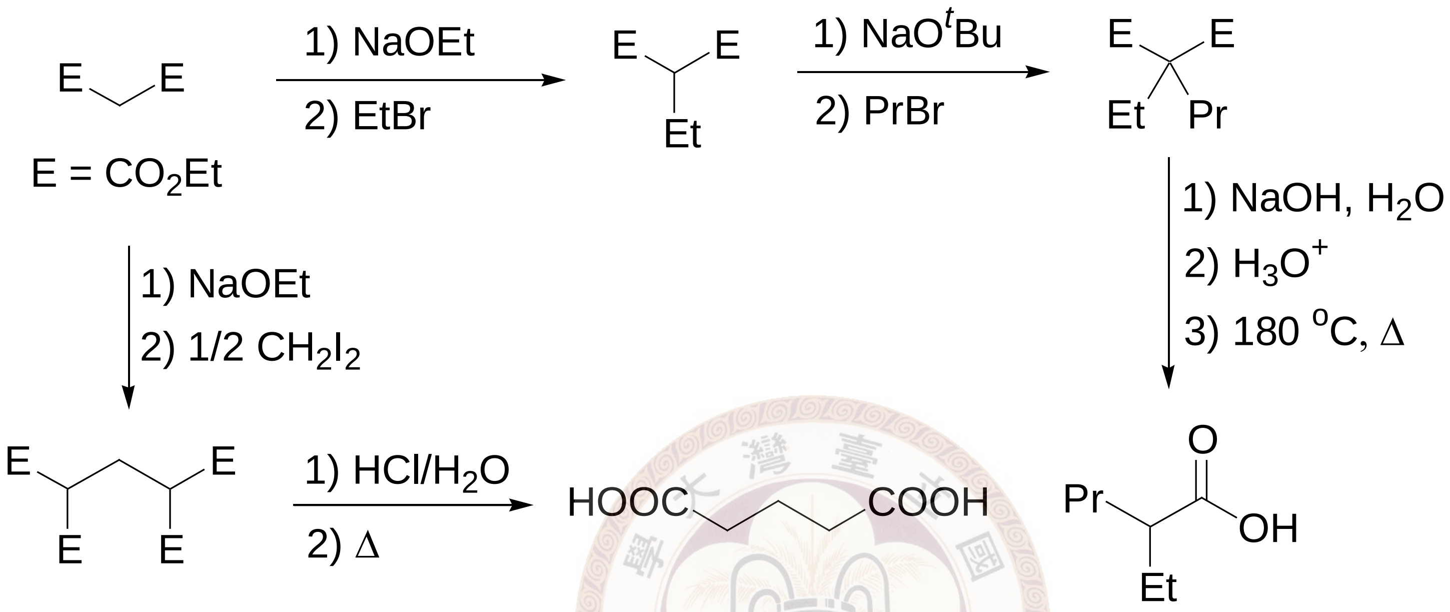

1) NaH, DMF
2) R Cl O
OEt
1) NaOH
2) H_3O^+
3) Δ
a 1,3-diketone

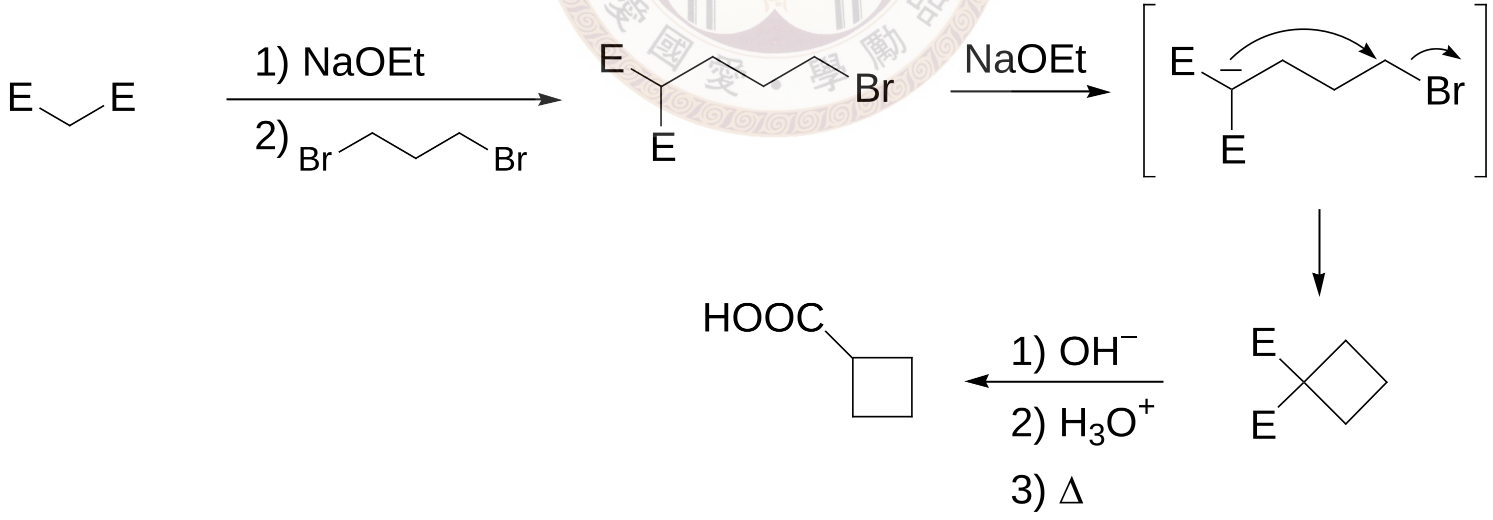
※ Malonic ester synthesis



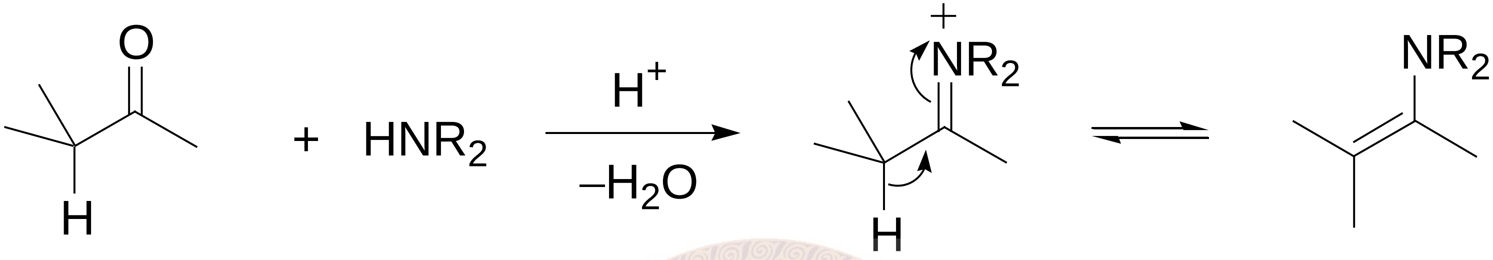
Diethyl malonate

Malonic ester is a synthetic equivalent of acetic acid


E
E
E = CO2Et
1) NaOEt
2) EtBr
E
E
Et
1) NaOtBu
2) PrBr
E
E
Et
Pr
1) NaOH, H2O
2) H3O+
3) 180 oC, Δ
1) NaOEt
2) 1/2 CH2I2
E
E
E
E
1) HCl/H2O
2) Δ
HOOC
COOH
O
Pr
OH
Et

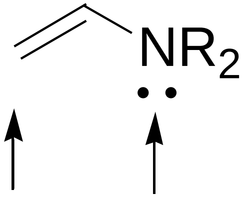

E
E
1) NaOEt
2) Br
Br
E
E
Br
NaOEt
E
–
E
Br
E
E
1) OH–
2) H3O+
3) Δ
HOOC

※ Enamines



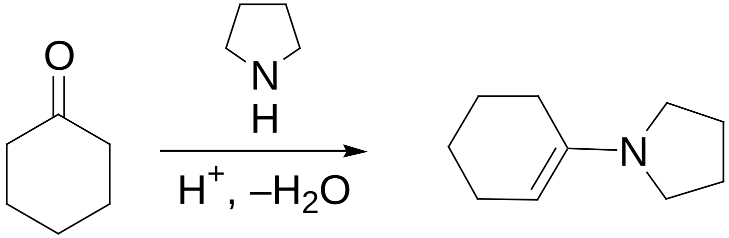
an enamine

Removal of water can drive the equilibrium to the right



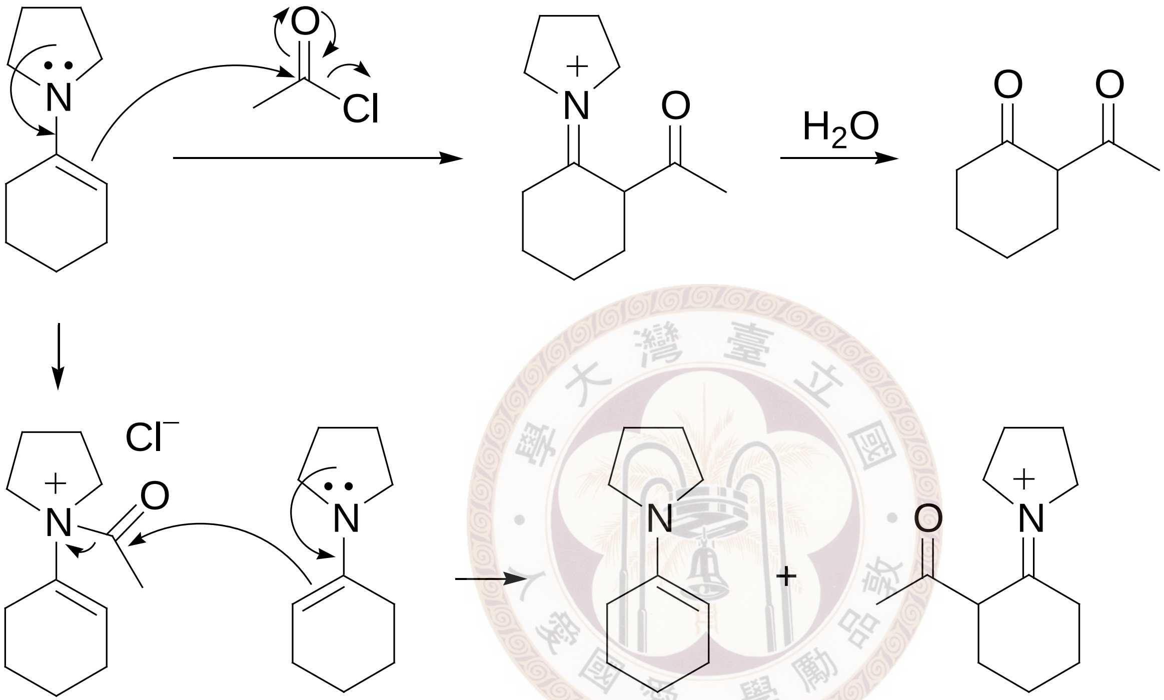
Ambident nucleophile

例

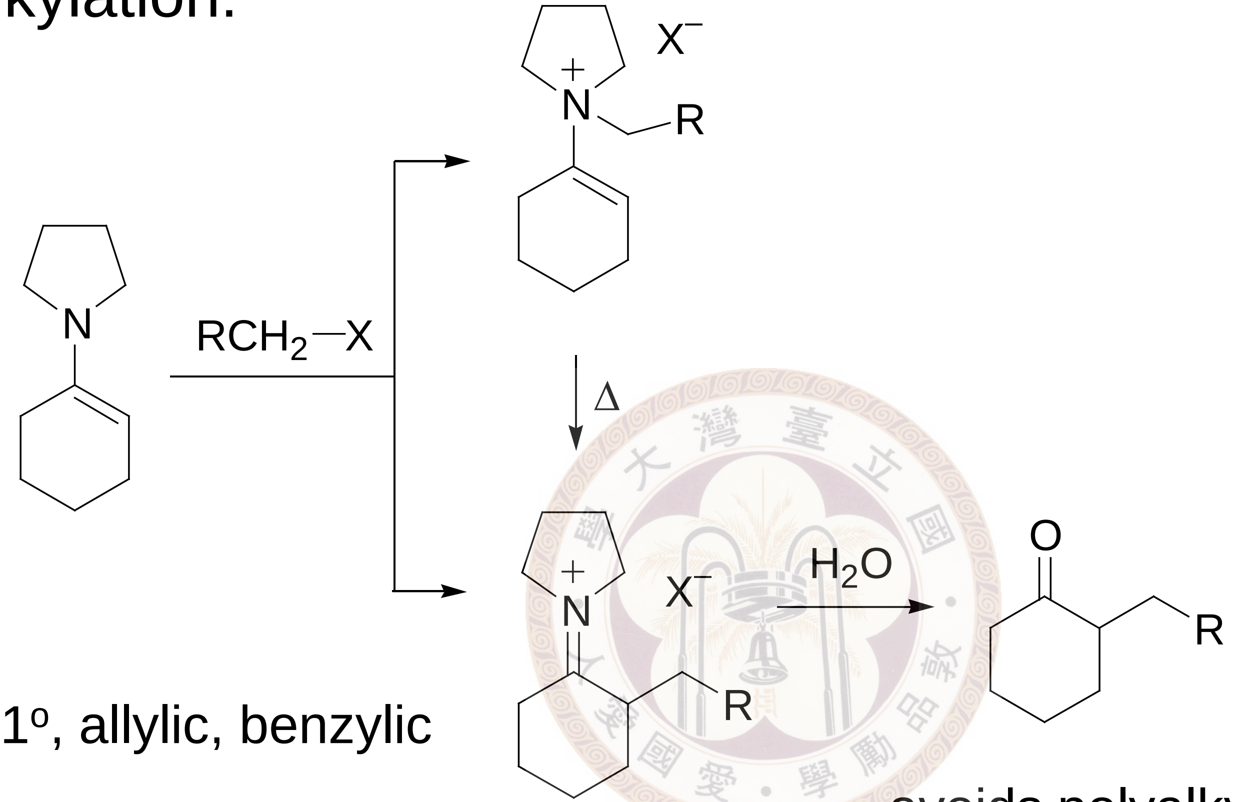


N-(1-cyclohexenyl)pyrrolidine

Acylation:



Alkylation:



For 1º, allylic, benzylic

avoids polyalkylation

例