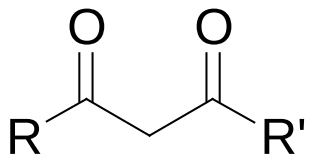
台灣大學開放式課程

有機化學乙

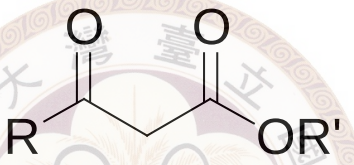
蔡蘊明　教授

Chapter 19
Condensation and conjugate addition reactions of carbonyl compounds

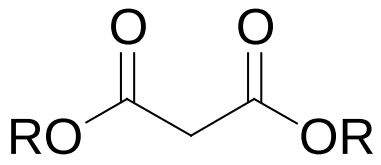
※ β-Dicarbonyl compounds



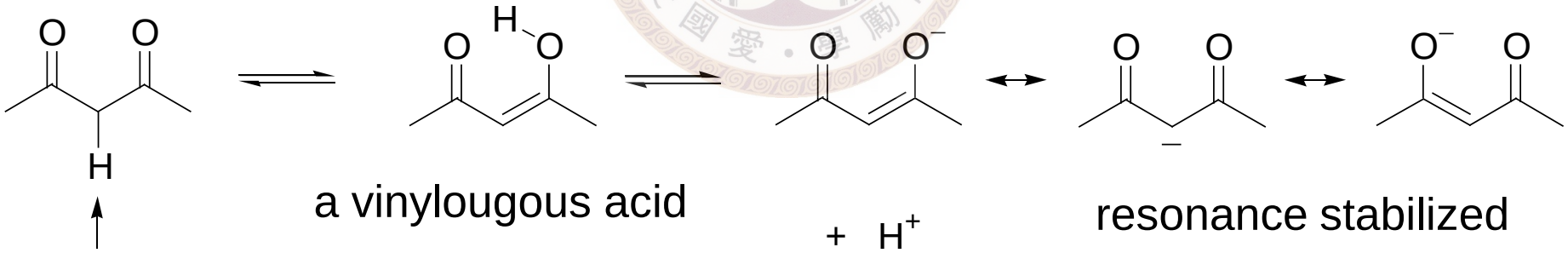
β-dicarbonyl system



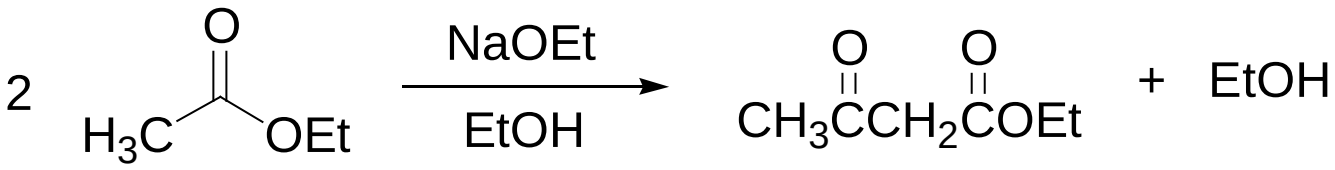
β-keto ester

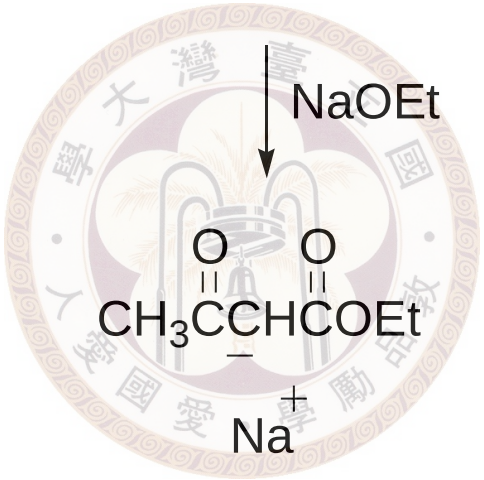


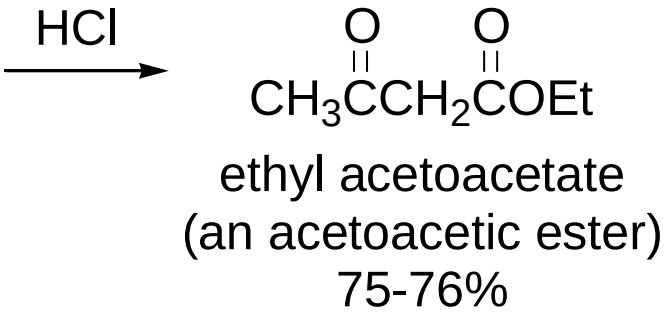
malonic ester



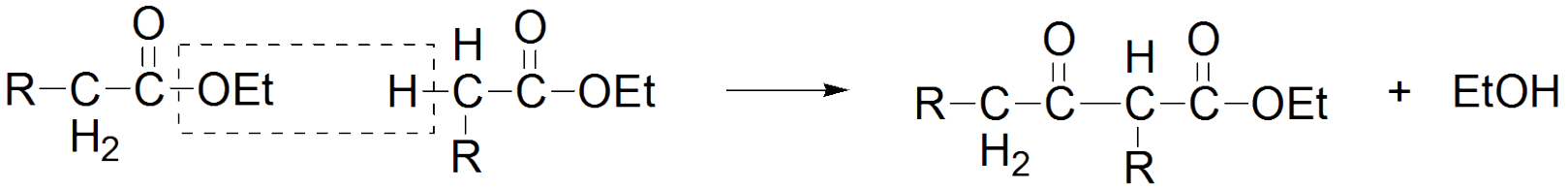
★ The Claisen condensation



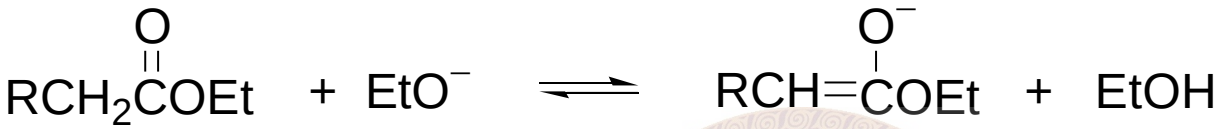


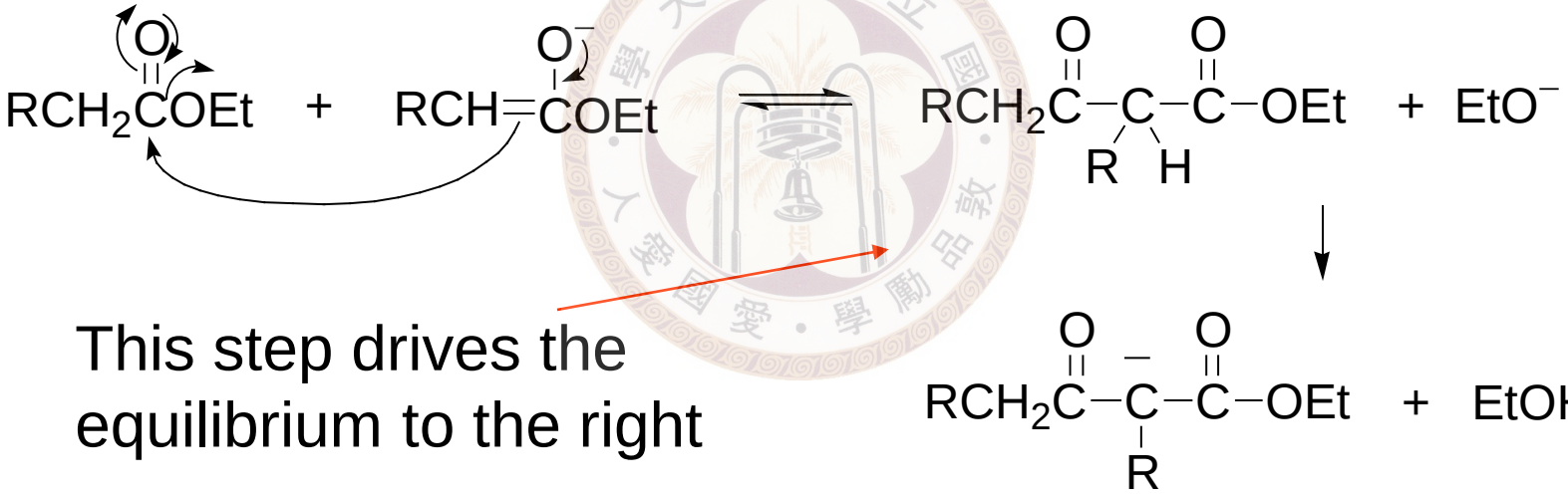


ethyl acetoacetate
(an acetoacetic ester)
75-76%

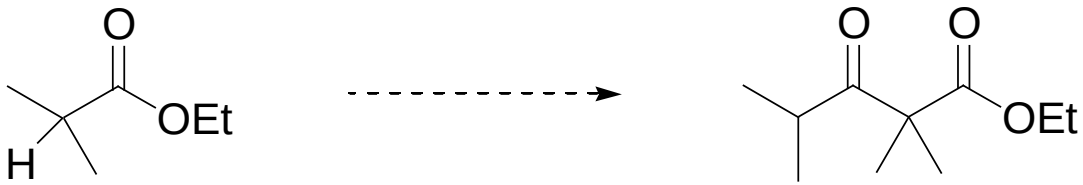


Mechanism:





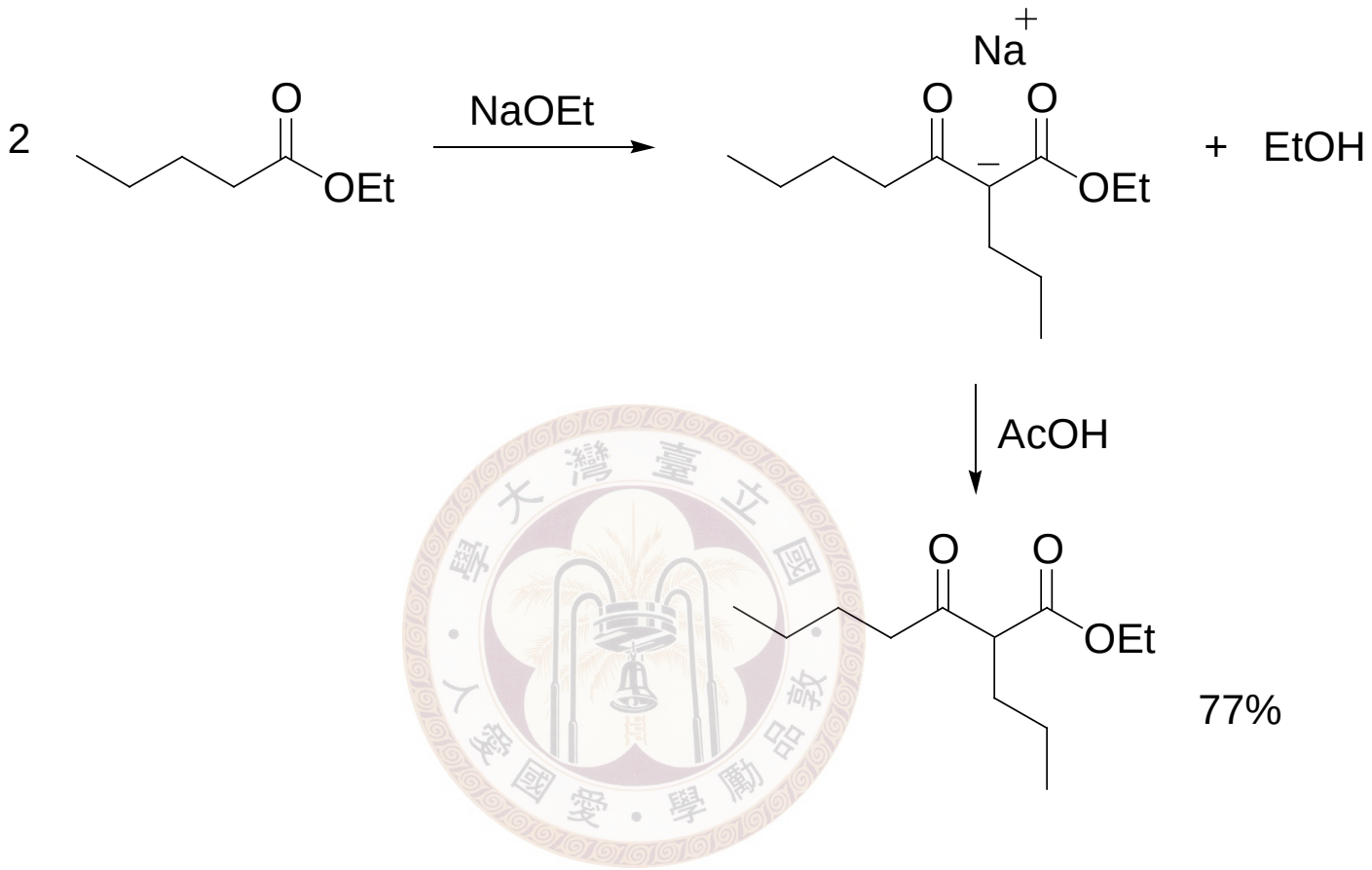
This step drives the equilibrium to the right



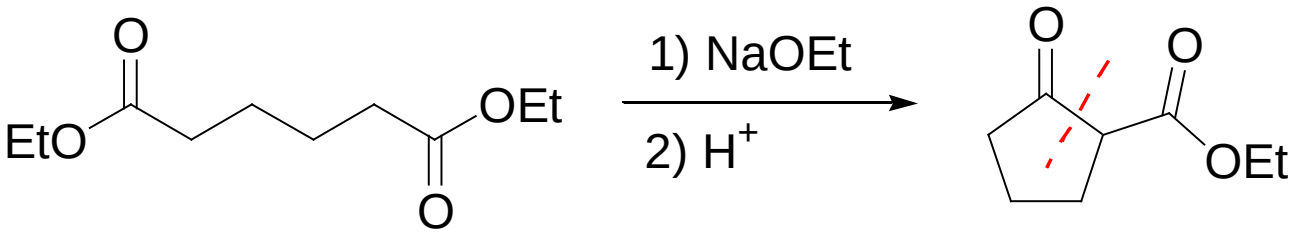
No Claisen condensation

No available acidic hydrogen

例



✓ Dieckmann condensation



diethyl haxanedioate
(diethyl adipate)

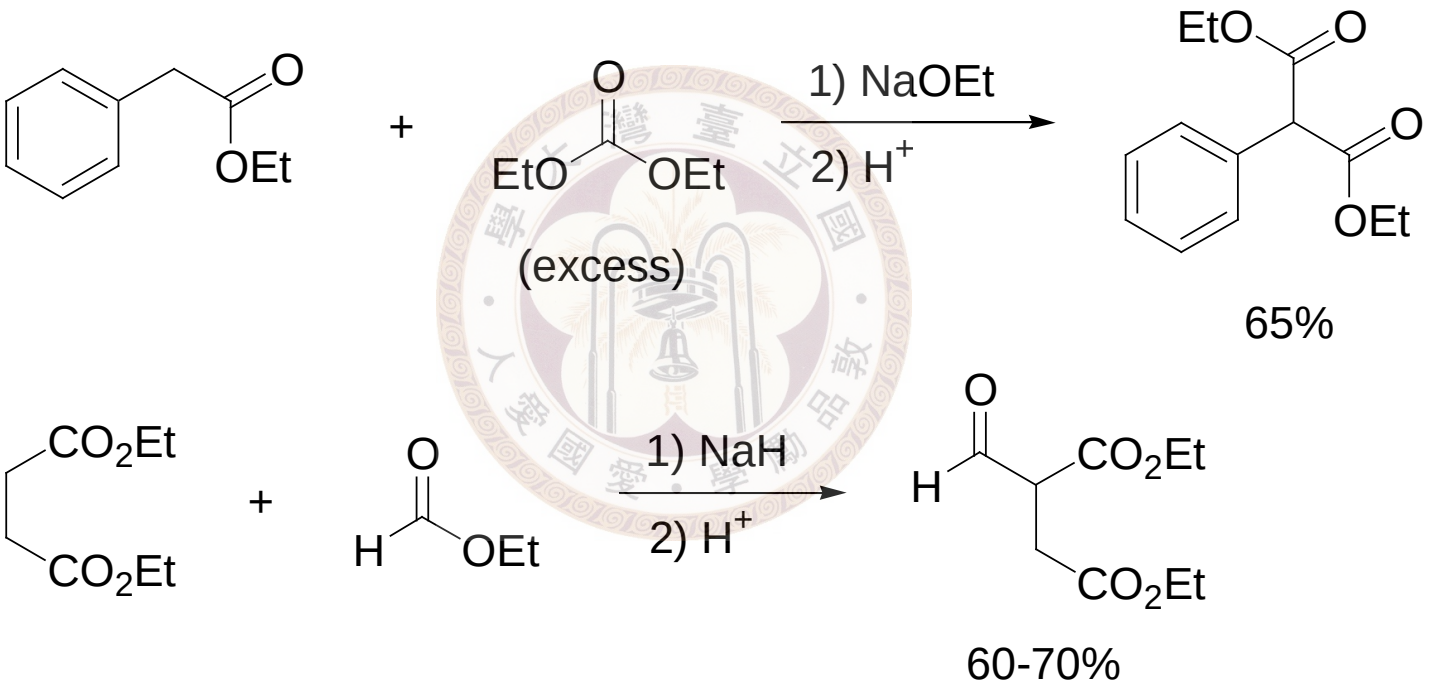
ethyl 2-oxocyclopentanecarboxylate

74-81%

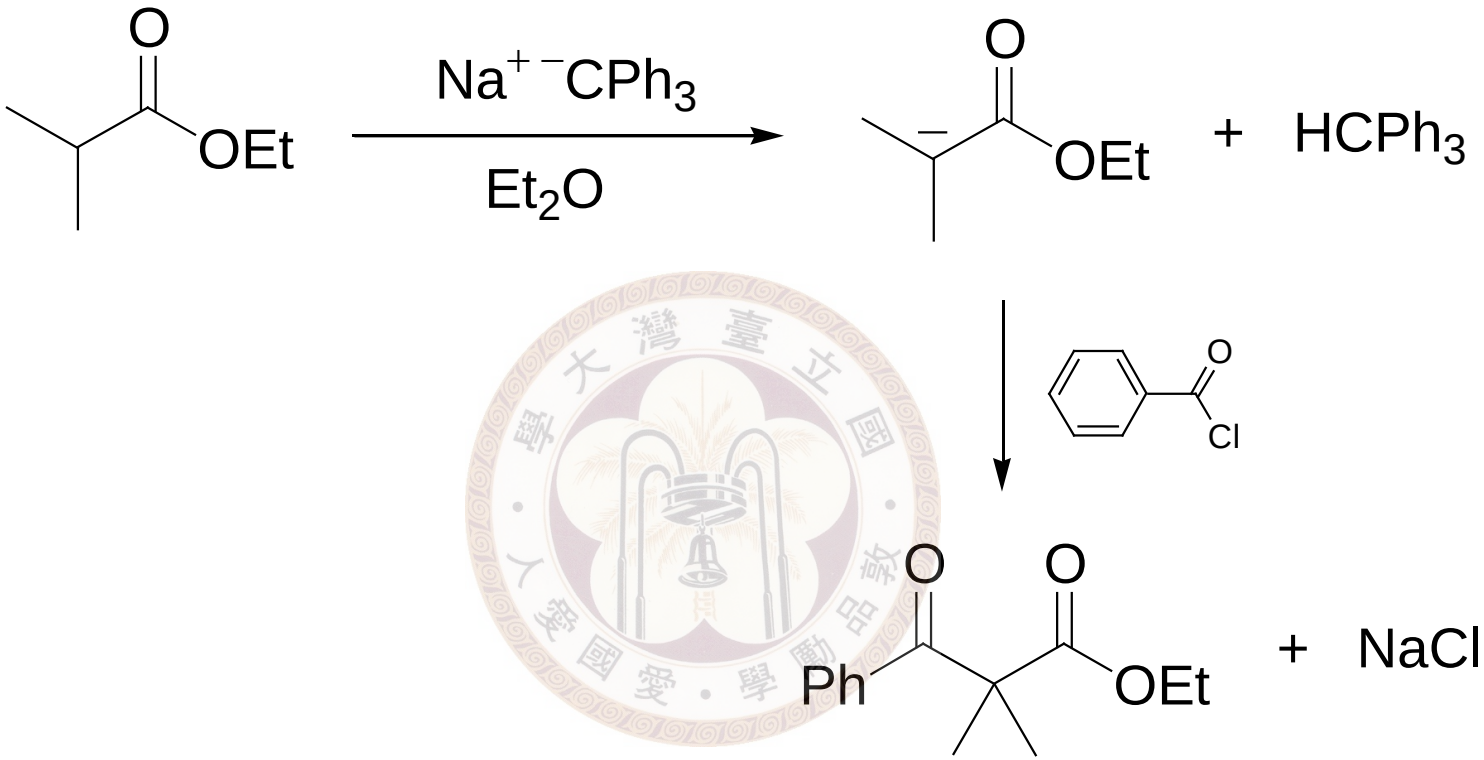
Basically, this is an intramolecular Claisen condensation

◎ Crossed Claisen condensation

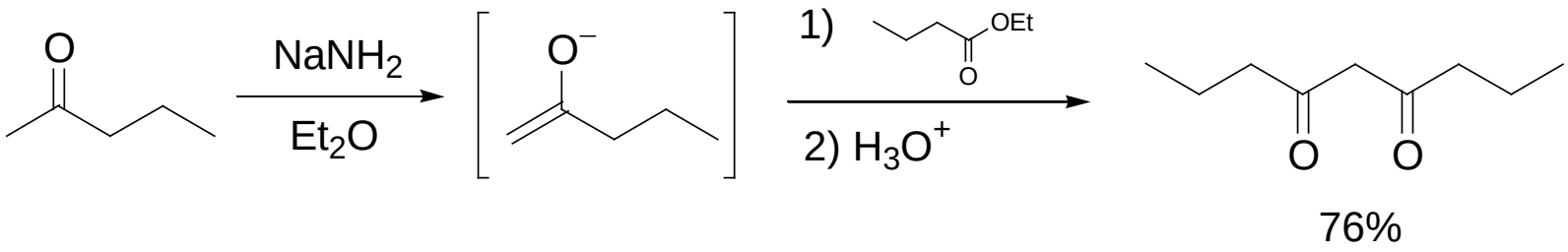
One component should have no α-hydrogen or be very reactive

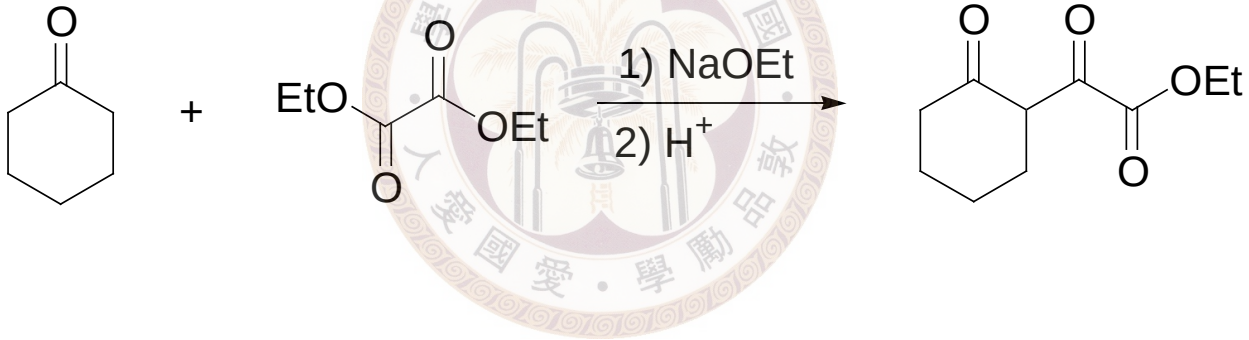


Others:

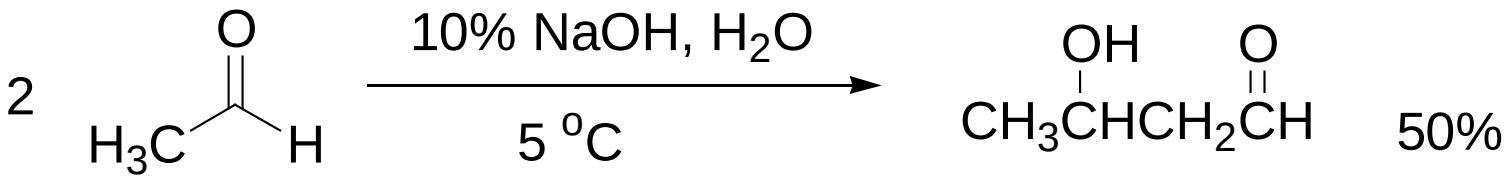


◎ Acylation of ketones





★ The aldol reaction

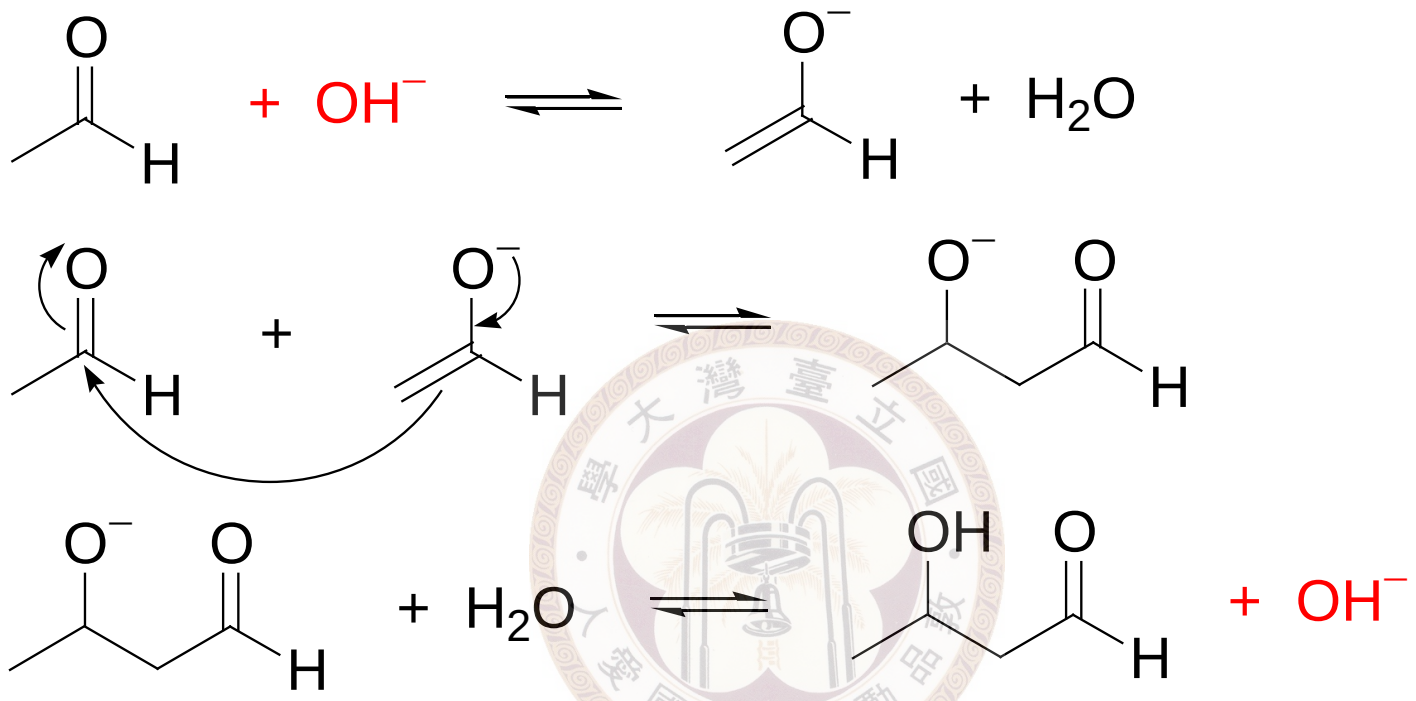


3-hydroxybutanal

an aldol product

*Also called an aldol addition product

Mechanism:

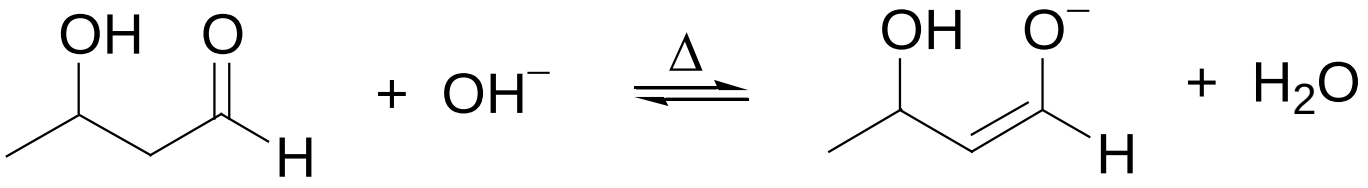


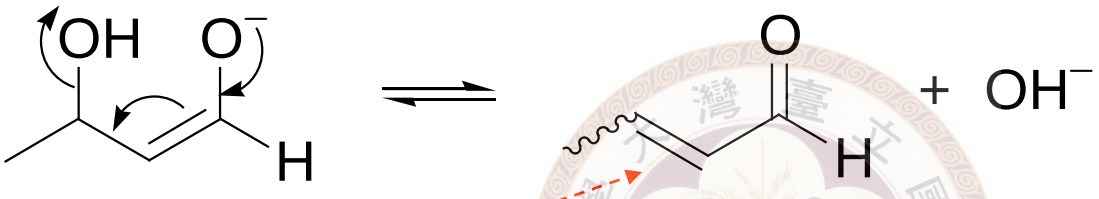
✓ The aldol reaction is reversible

✓ For aldehydes, the equilibrium favors the aldol products

*The reverse of aldol reaction is called retro-aldol reaction

◎ Dehydration of aldol addition product





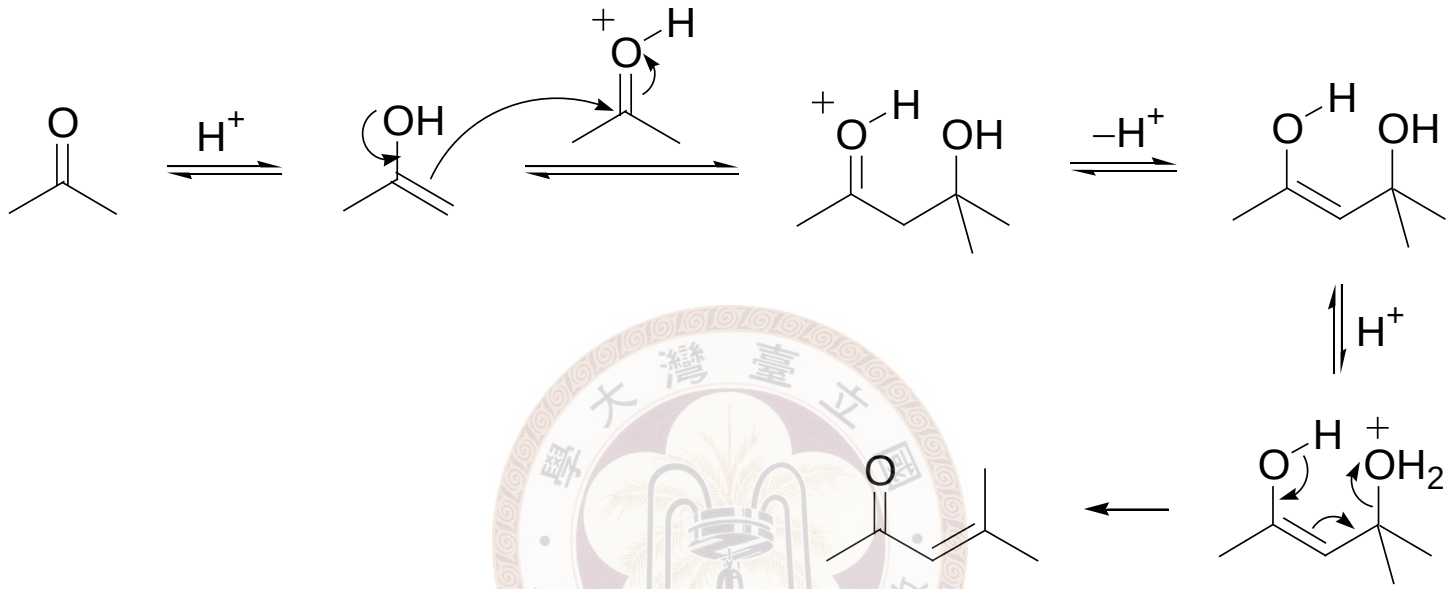
crotonaldehyde
(2-butenal)
an enal

an aldol condensation product

This double bond is more stable due to conjugation

✓ Aldol addition or condensation?
depend on the reaction condition and substrate structure

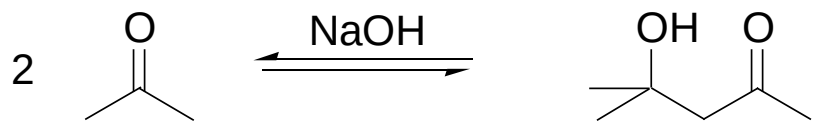
◎ Acid-catalyzed aldol condensation



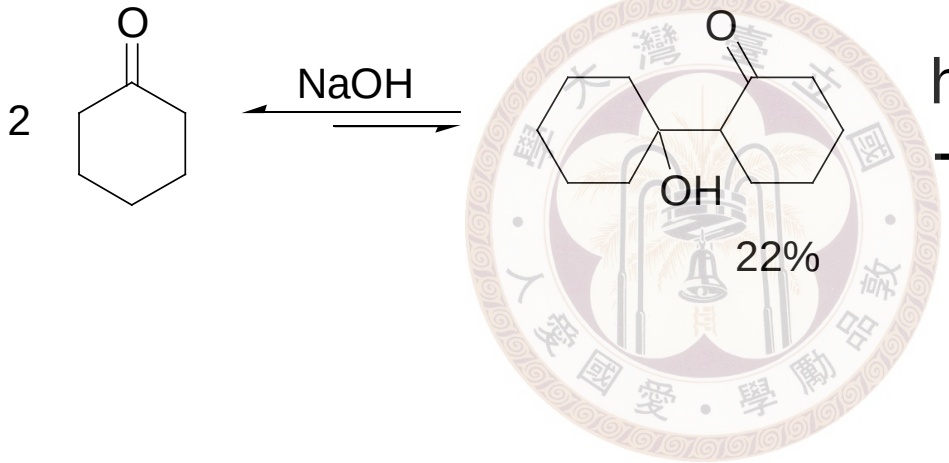
Dehydration is easier under acidic condition

◎ Aldol reaction of ketones

equilibrium favors starting materials



55%

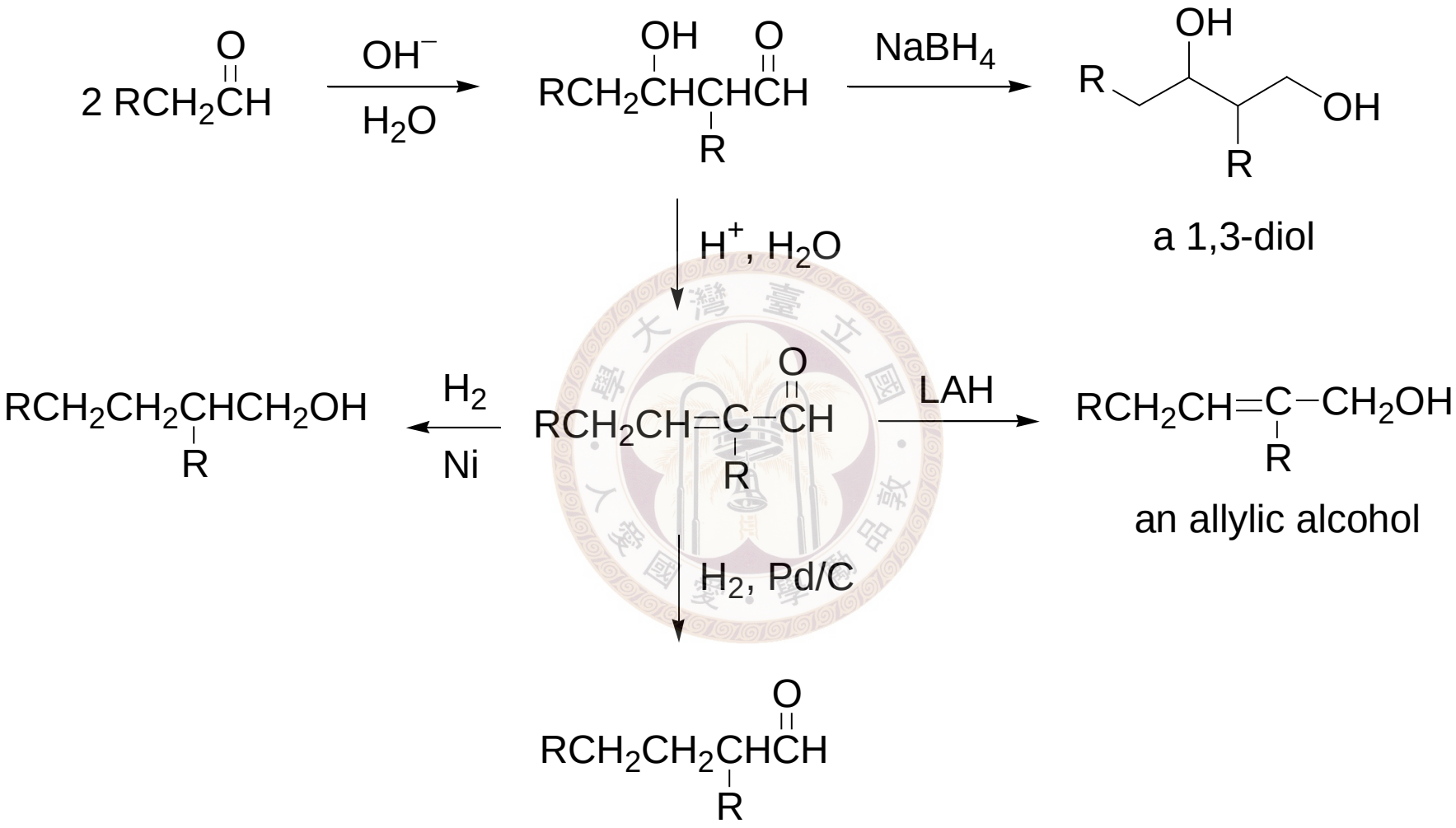


22%

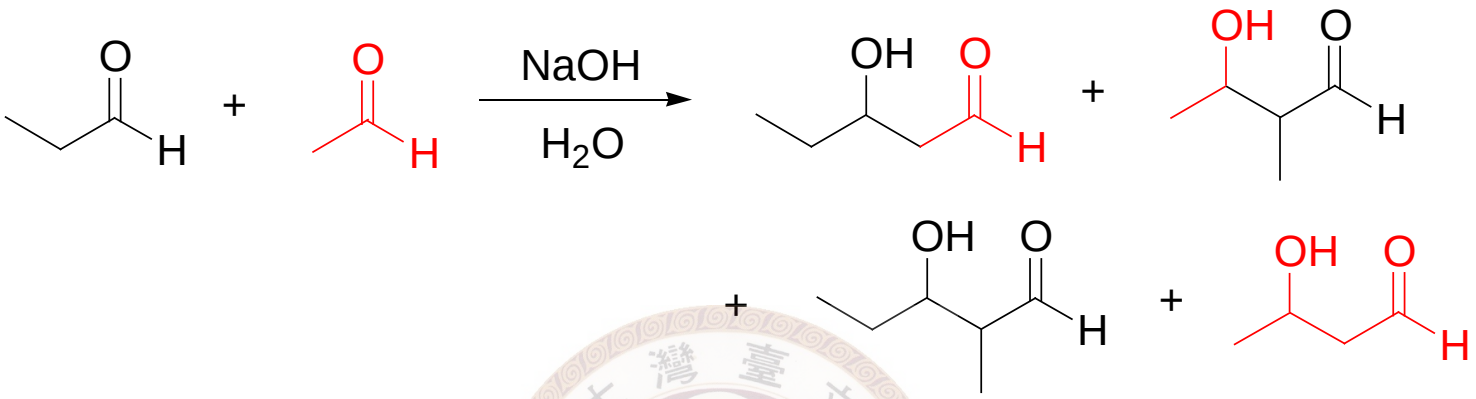
higher steric effect

→ lower yield

◎ Synthetic application

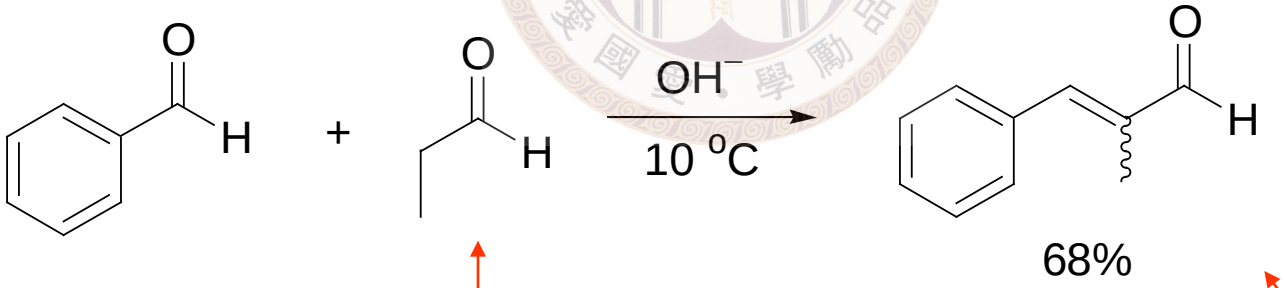


◎ Crossed aldol reaction



A mixture is obtained

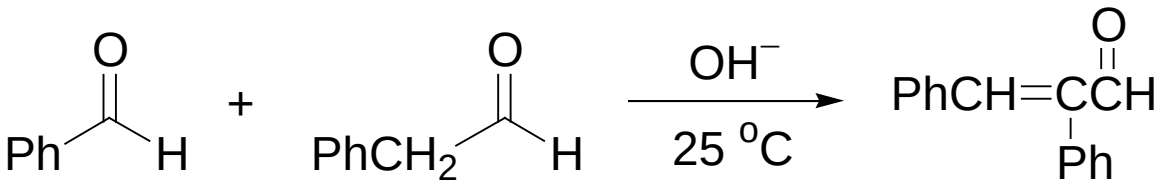
Solutions:

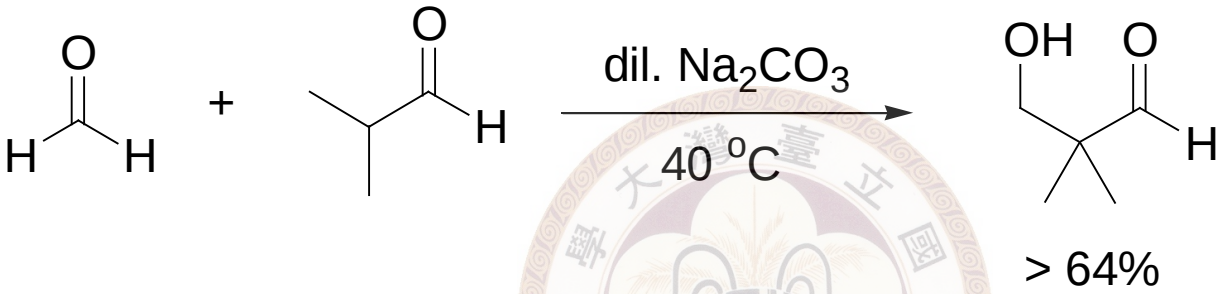


has no α-hydrogen (non-enolizable)

adds slowly to avoid self condensation

an extended conjugate system: dehydrates very easily

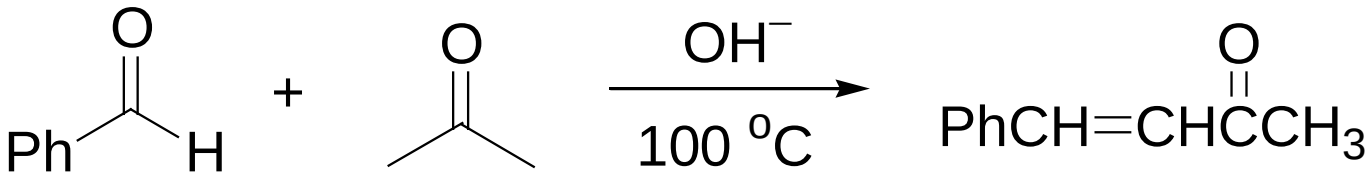




> 64%

◎ The Claisen-Schmidt reactions

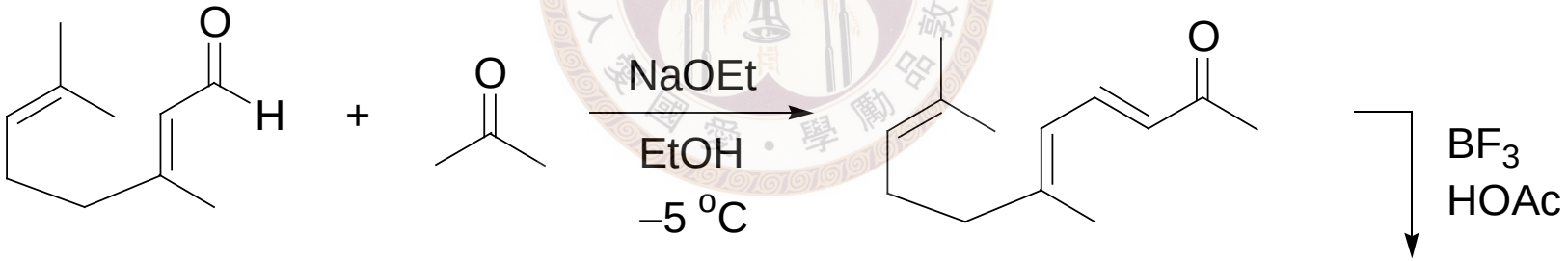
condensation of non-enolizable aldehyde with ketone

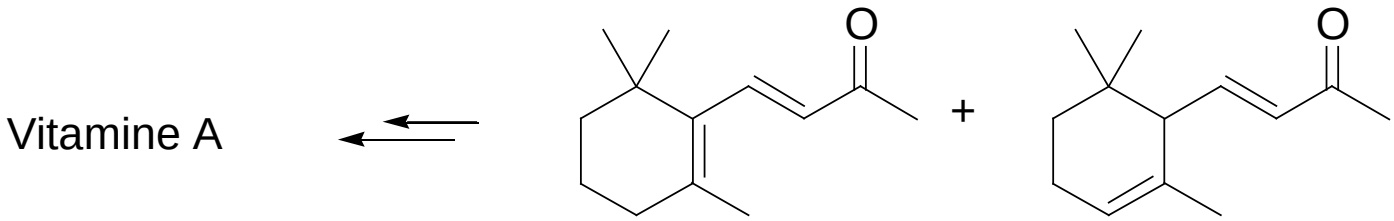


70%

slow addition not necessary

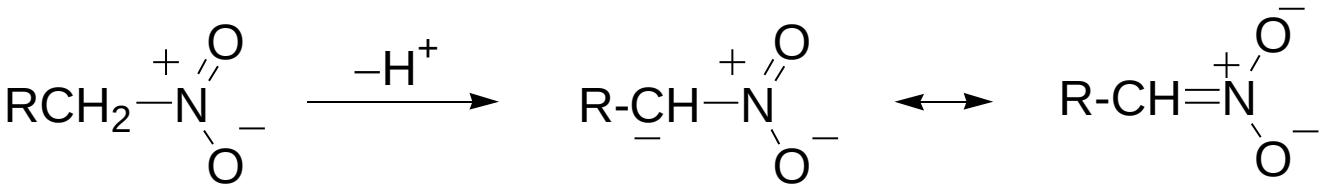
self condensation is slow





β-ionone

◎ Condensation with nitroalkanes



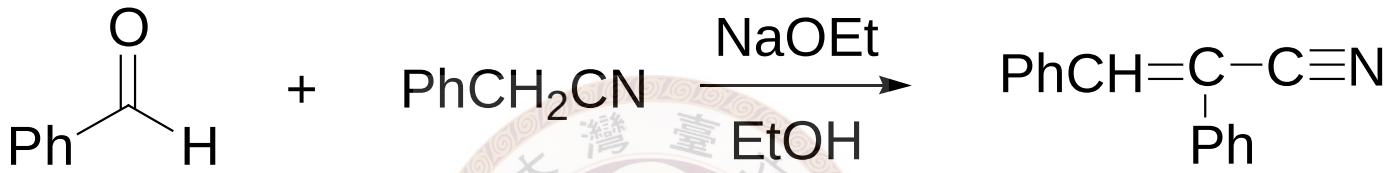
nitroalkane

resonance stabilized

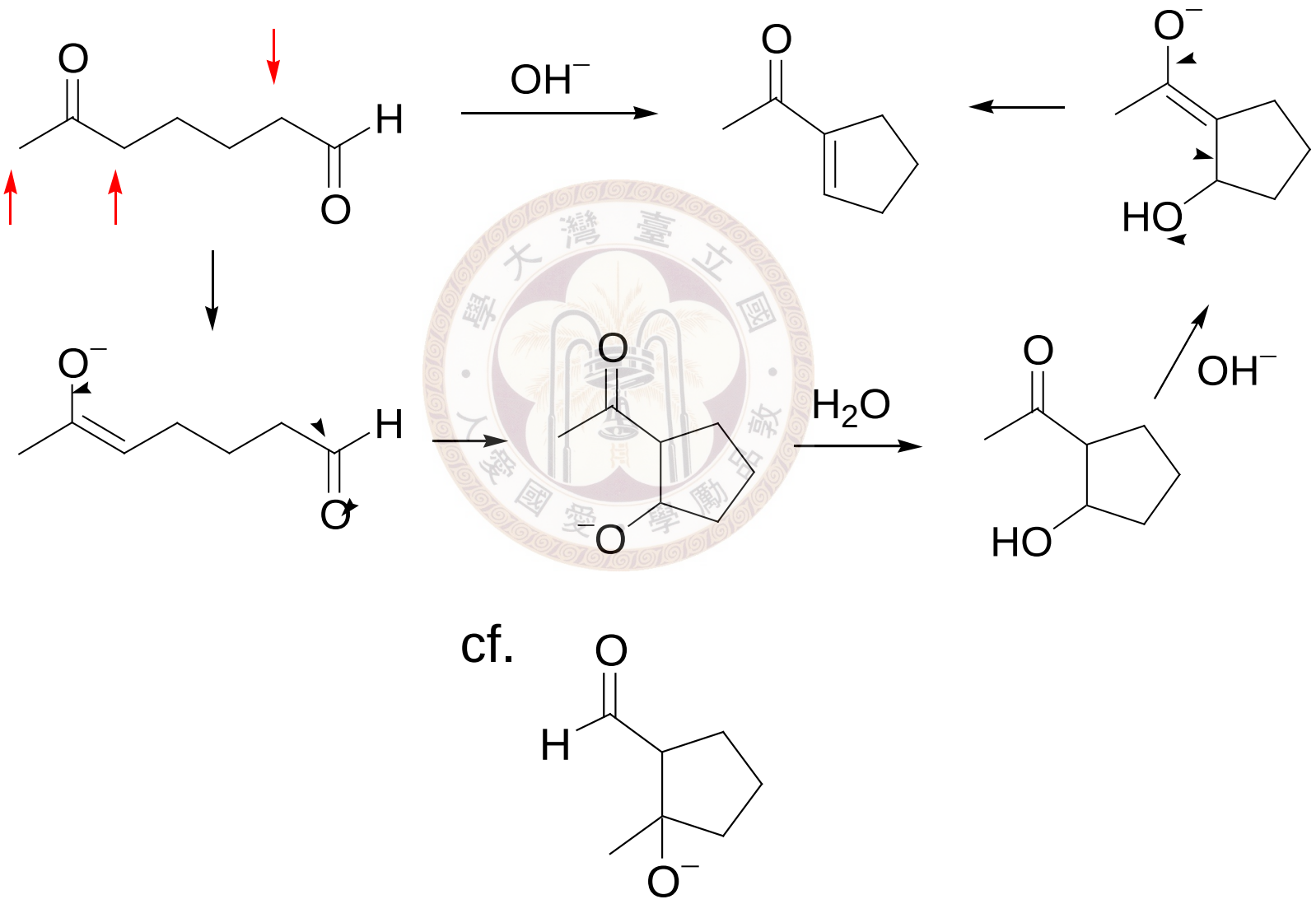
pK_a ~ 10

◎ With nitriles

CH_3CN $pK_a \sim 25$

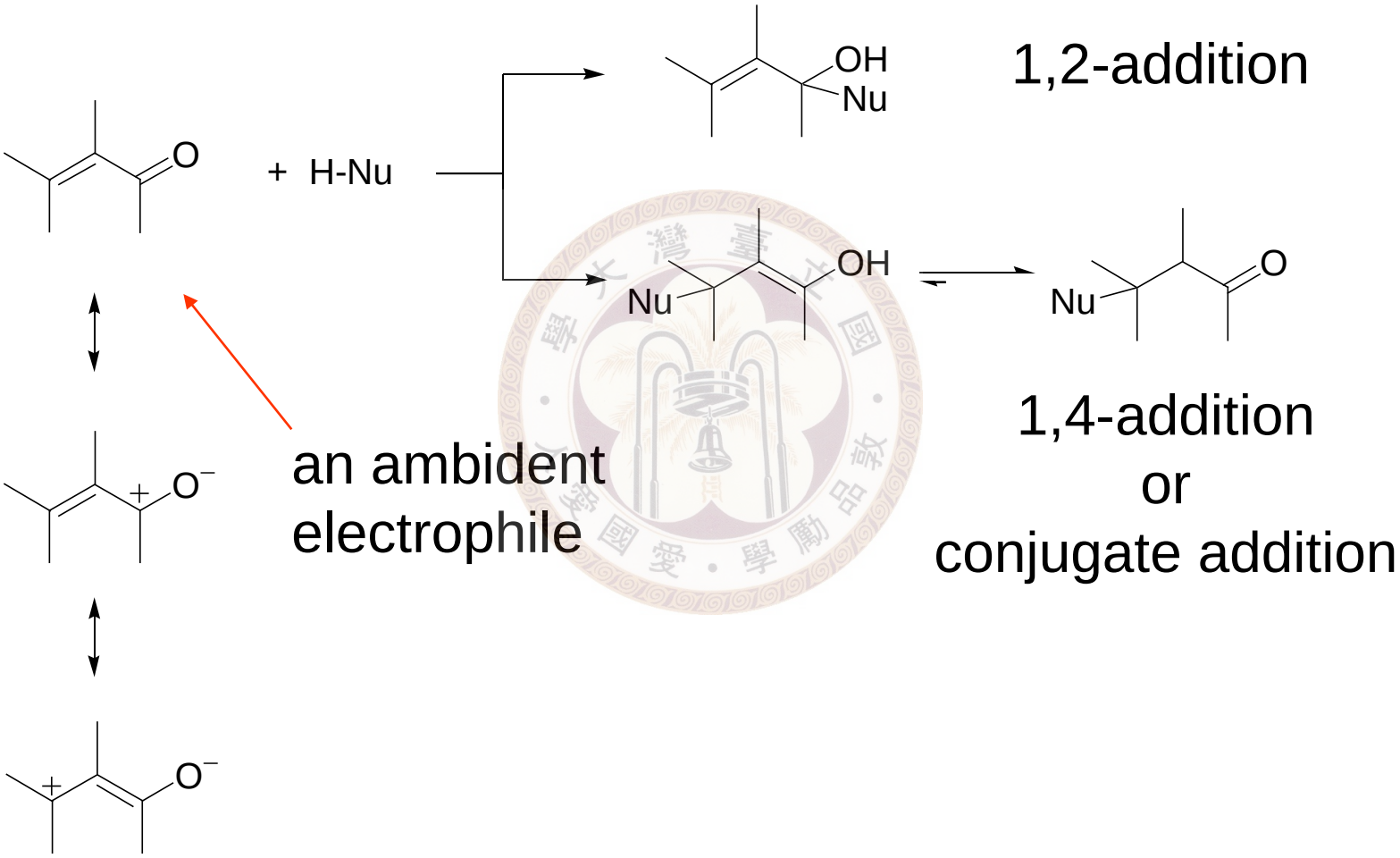


◎ Application of aldol reaction: ring formation

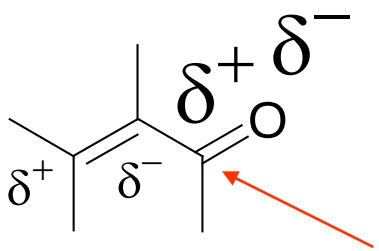


cf.

※ α,β-Unsaturated aldehydes and ketones

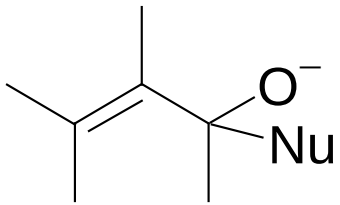


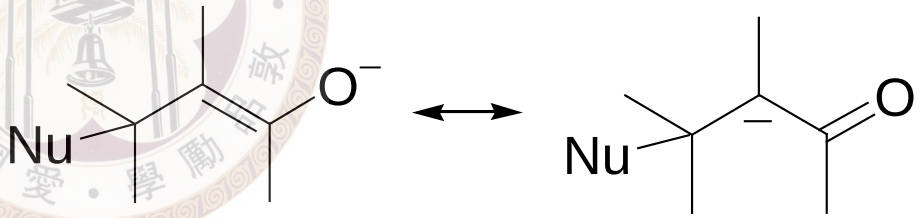
✓ 1,2-Addition is kinetic product



more positive: reacts faster

✓ 1,4-Addition is thermodynamically controlled





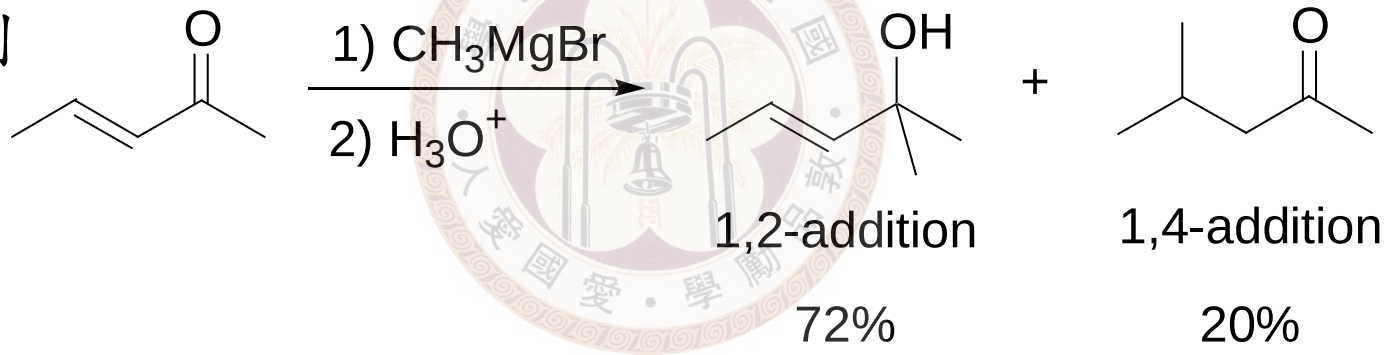
Resonance stabilized
→ More stable

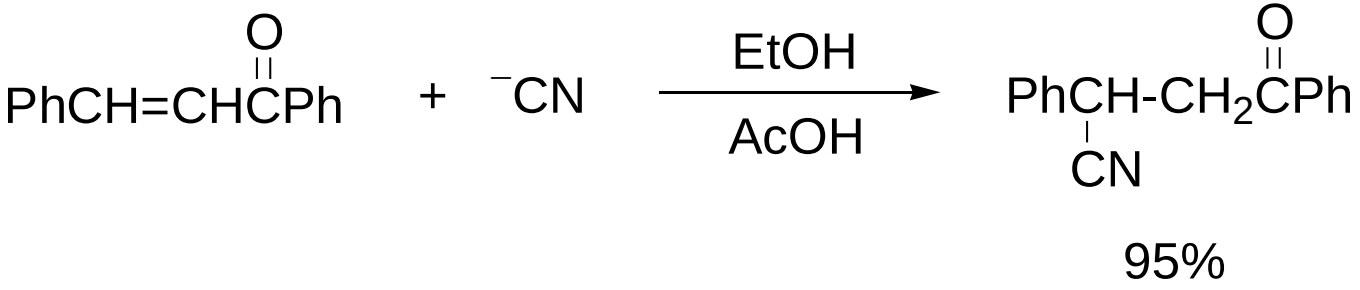
✓ In general:

highly reactive nucleophiles such as RLi, RMgBr
→ 1,2-addition
moderately reactive nucleophiles
→ 1,4 addition

Ex: RO^-, ROH, RNH_2, ^-CN

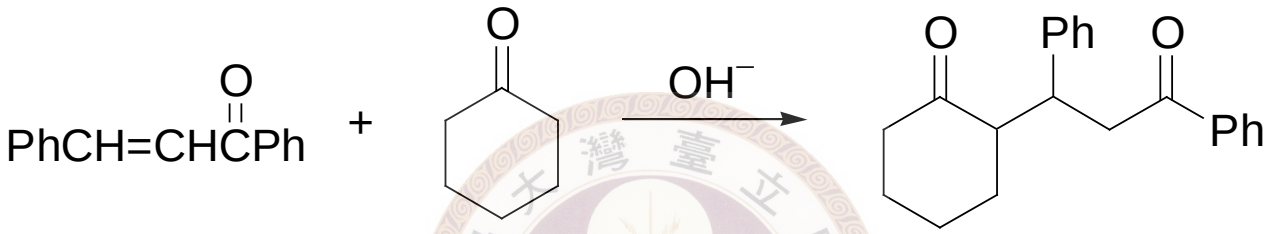
例



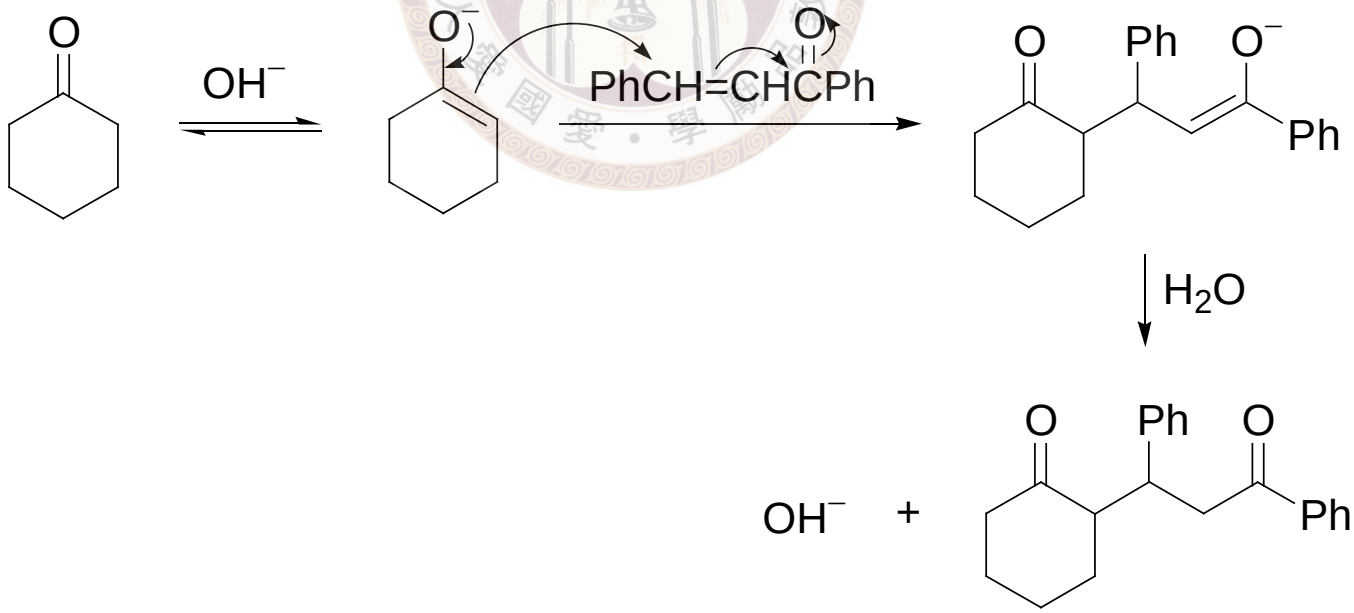


★ Michael addition

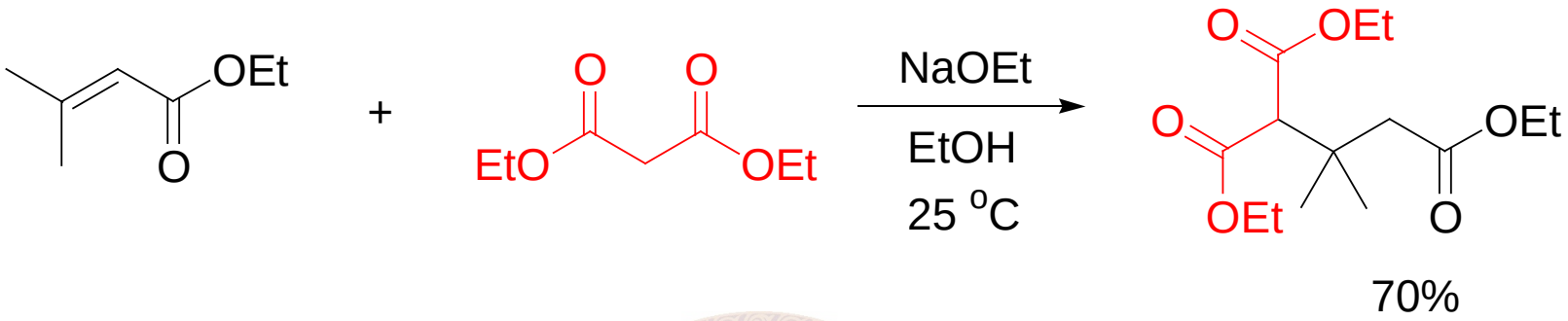
Addition of enolate to α,β-unsaturated carbonyl compounds



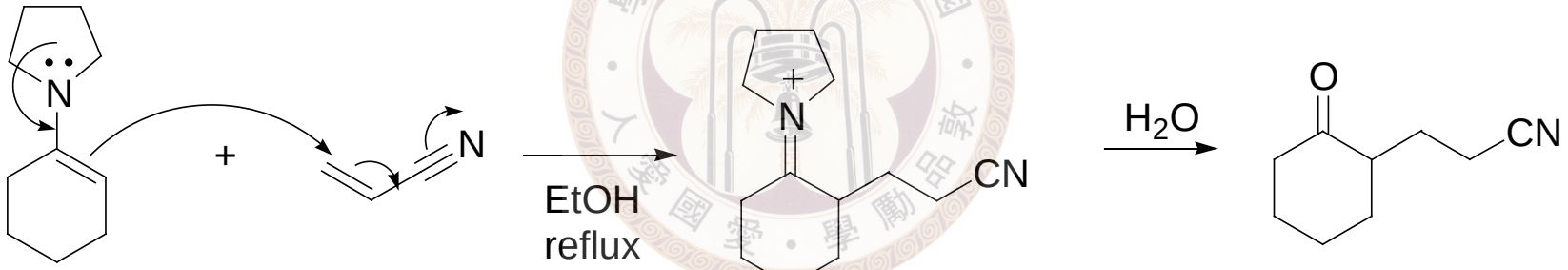
Mechanism



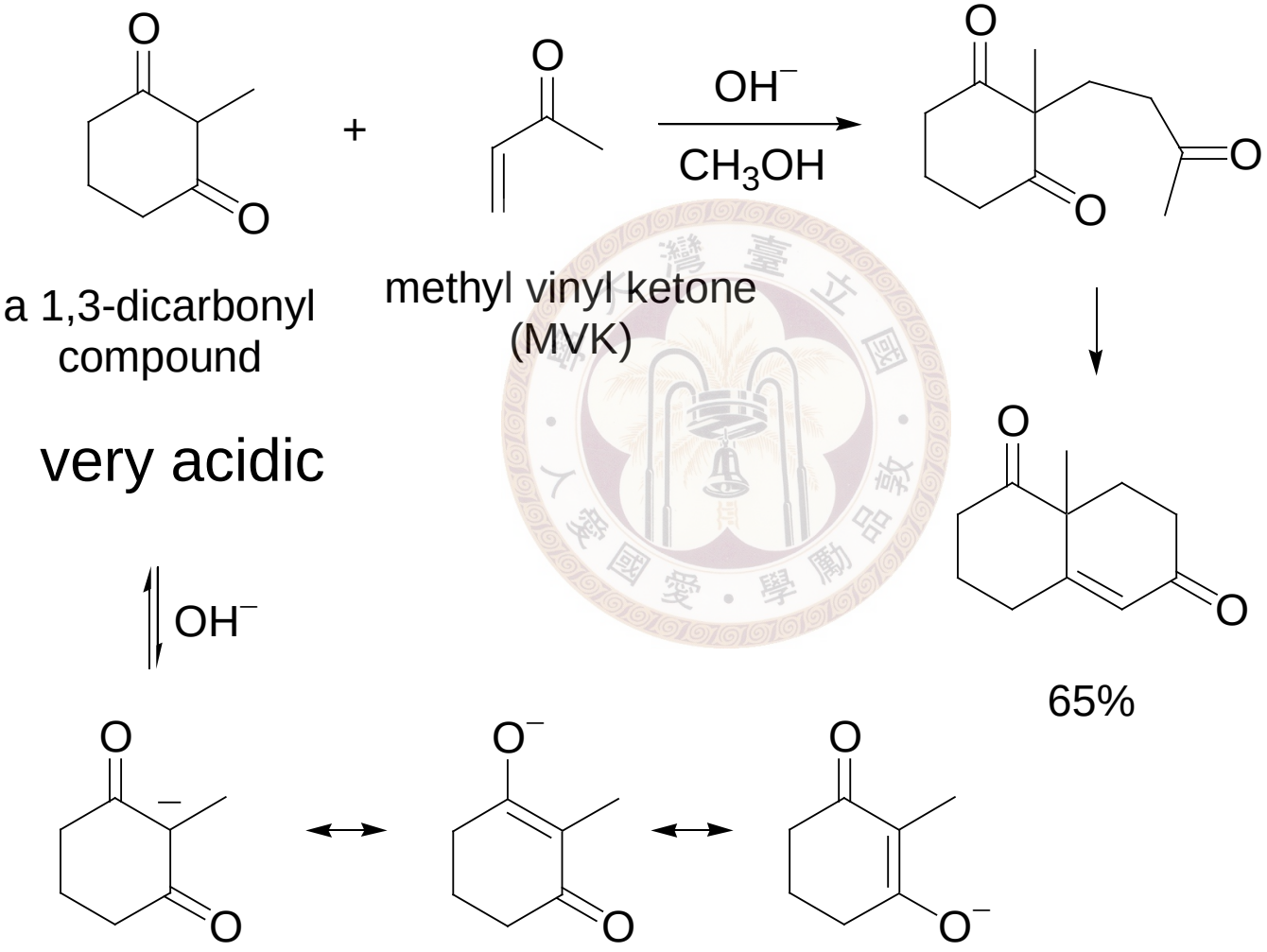
例


OEt
O
+
O
O
EtO
OEt
NaOEt
EtOH
25 °C
O
OEt
O
OEt
OEt
O

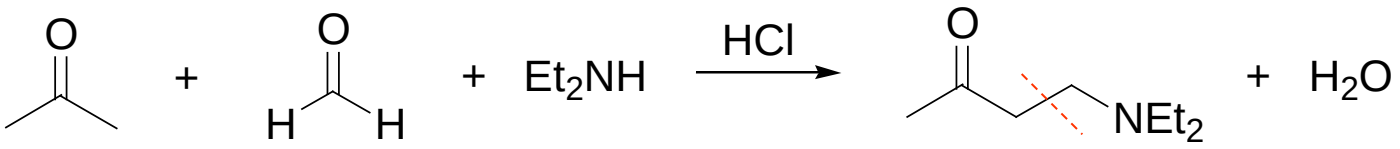
70%


N
+
N
EtOH
reflux
N
CN
H2O
O
CN

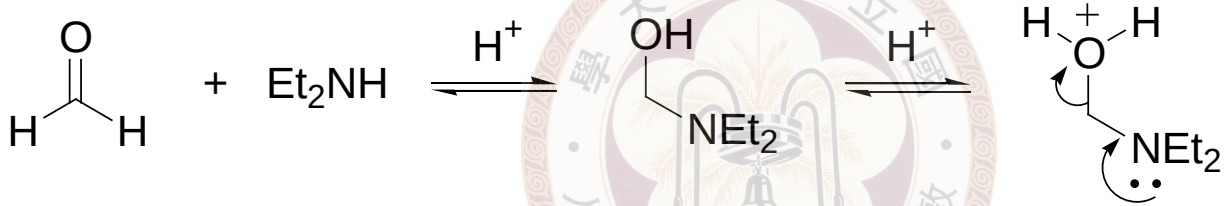
※ Robinson annulation



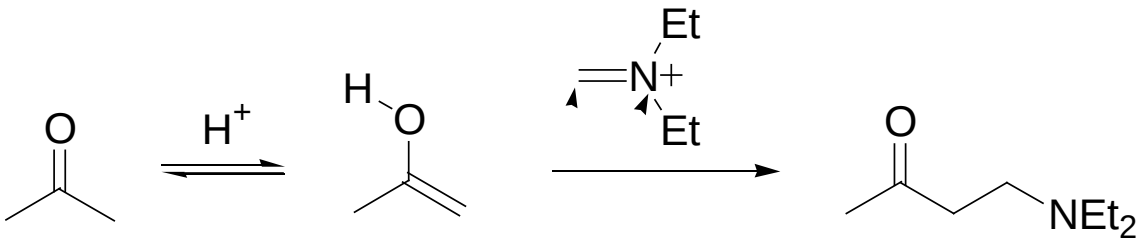
※ The Mannich reaction



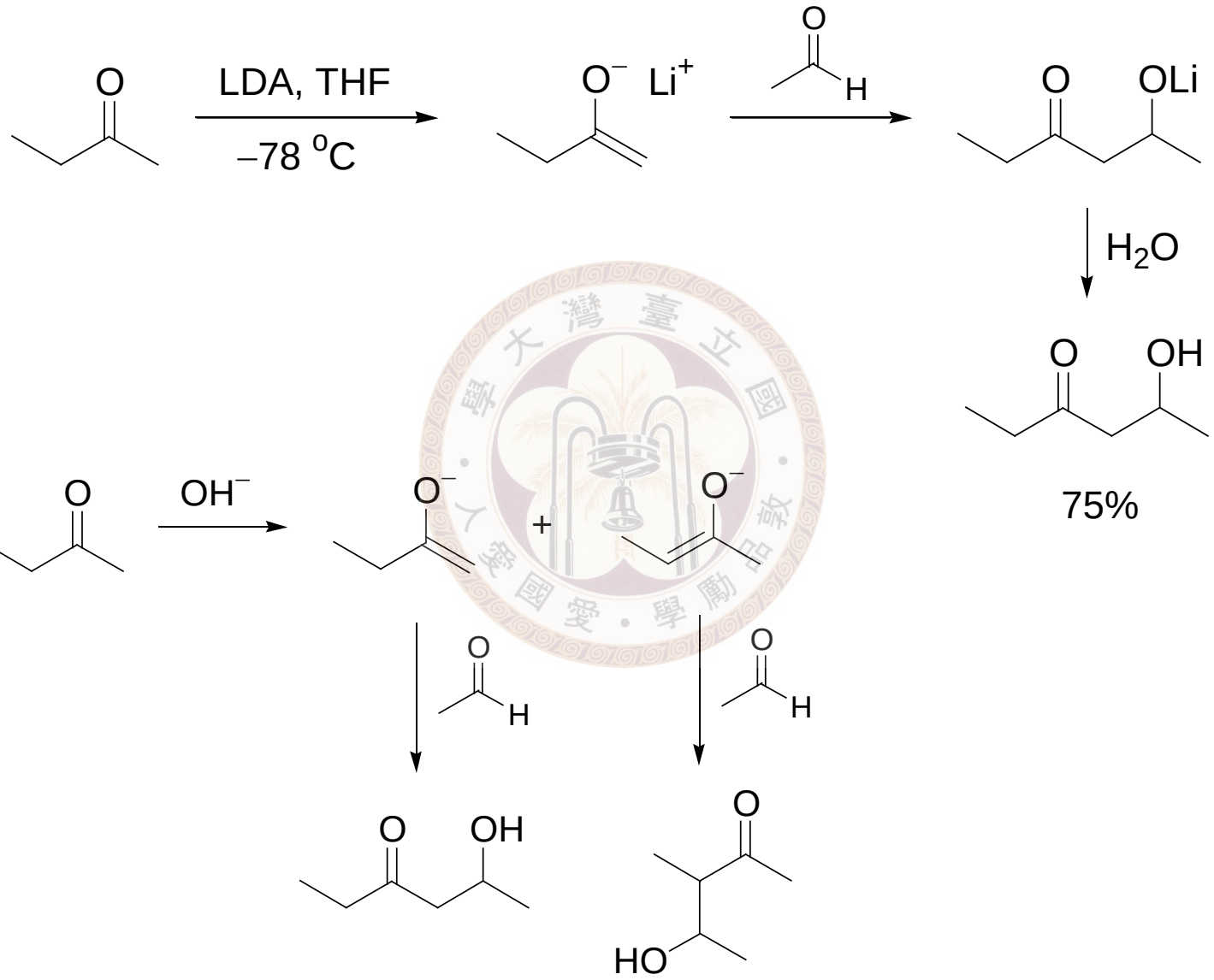
Mechanism:



An imminium ion
(very reactive)

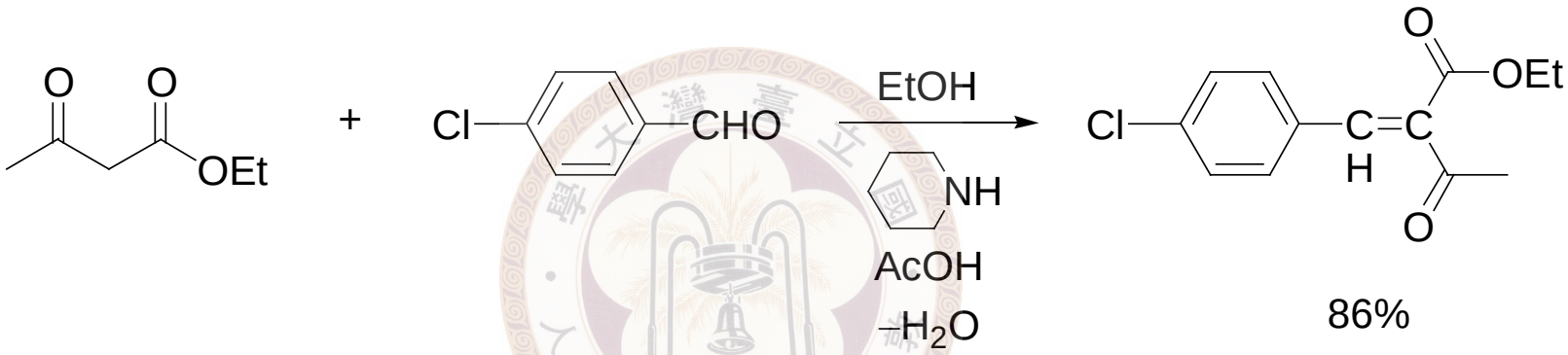


◎ Directed aldol reaction

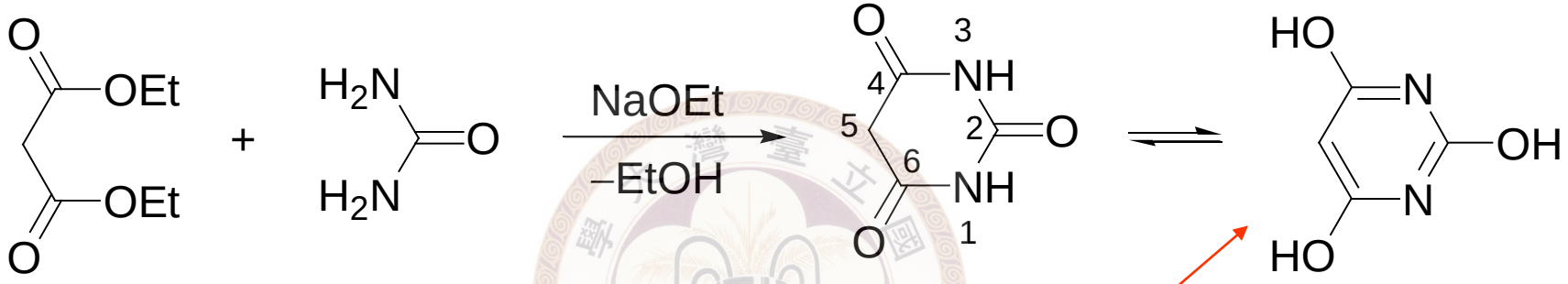


※ The Knovenagel condensation

Condensation of active methylene compound with aldehyde or ketone



※ Barbiturates (von Baeyer, 1863)

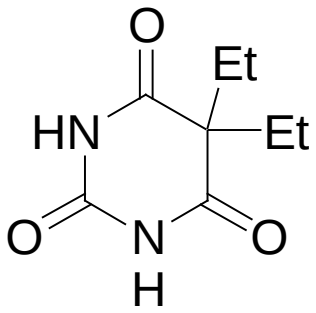


Contains a pyrimidine ring

barbituric acid

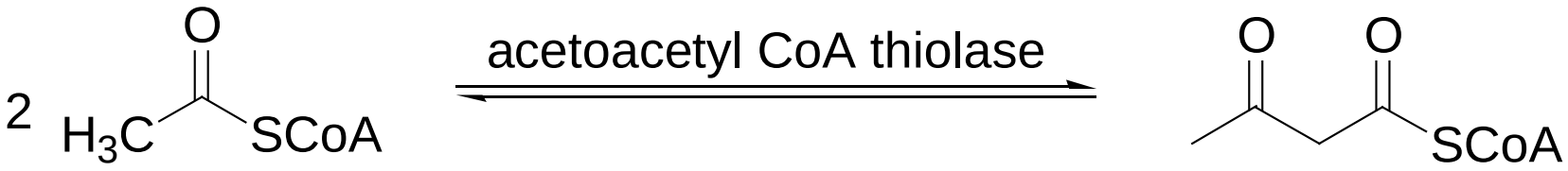
Stronger acid than acetic acid

安眠藥用



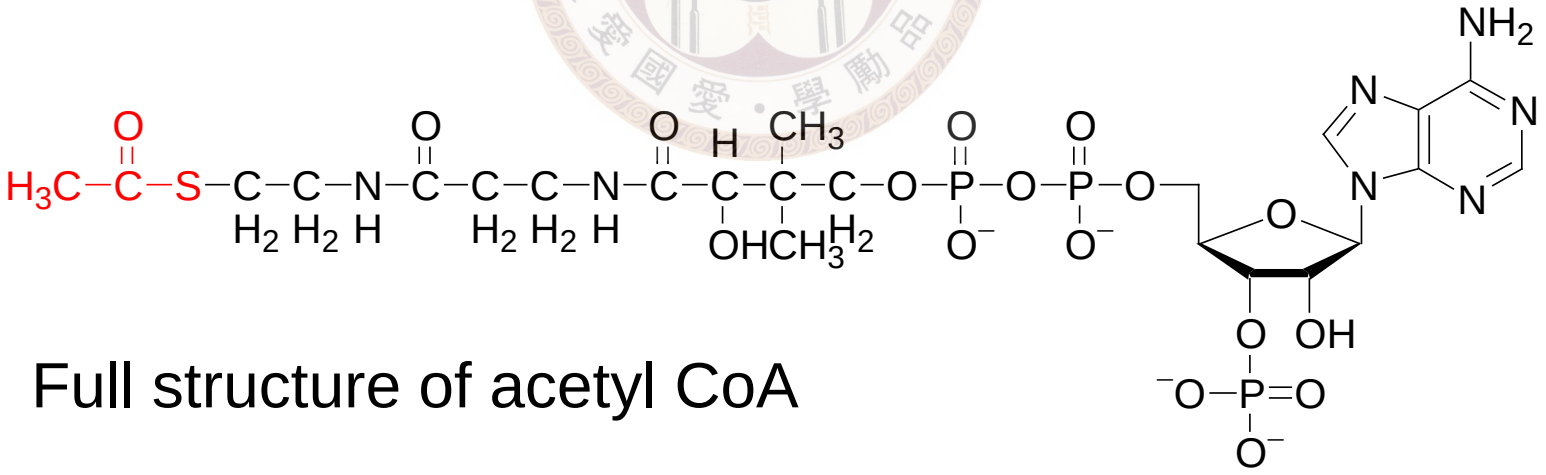
Veronal
(5,5-diethylbarbituric acid)
pK_a = 7.4

※ Biological chemistry

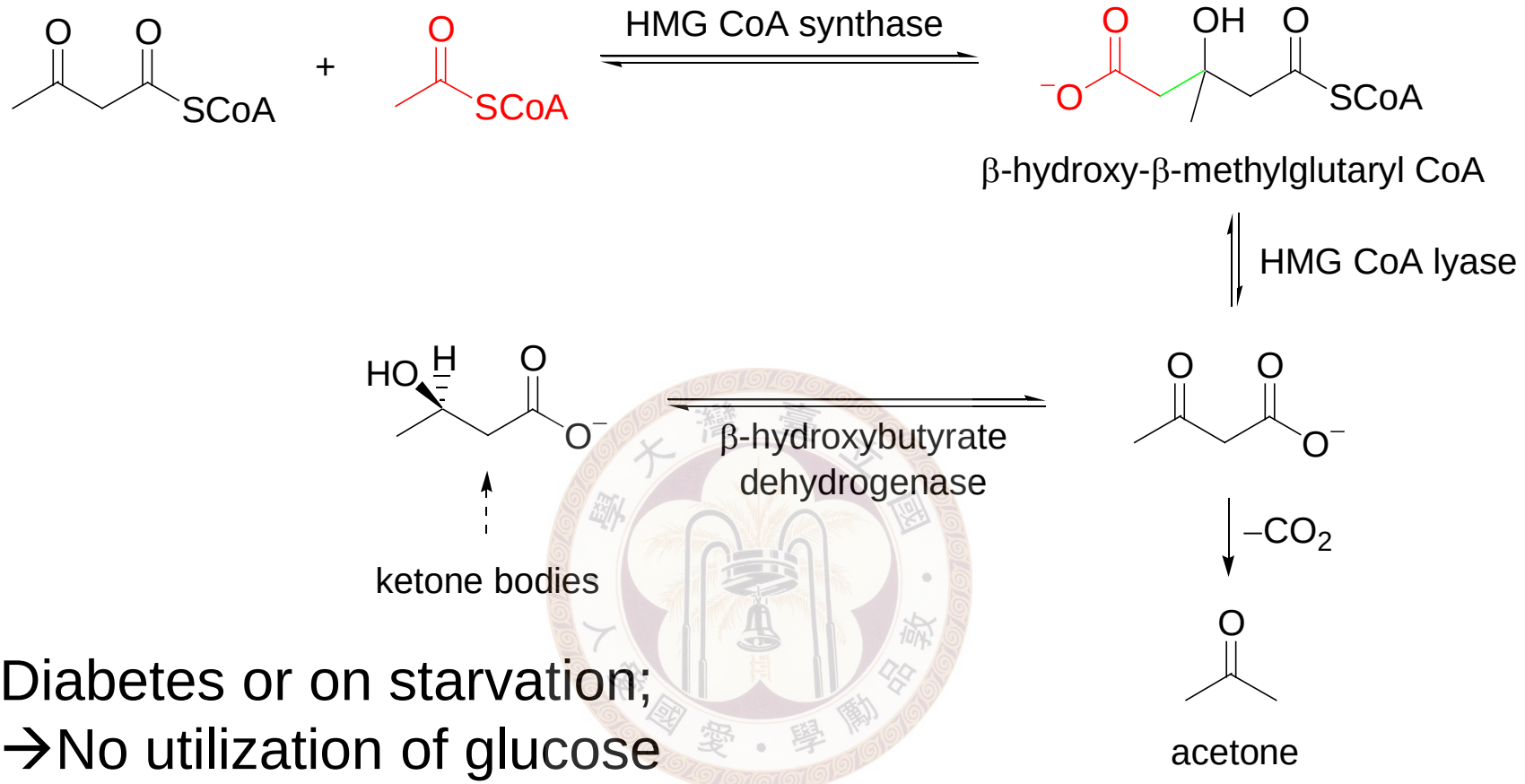


acetyl CoA

More acidic than ester



Full structure of acetyl CoA



Diabetes or on starvation;

→No utilization of glucose

→Fat metabolism for energy

→Produce too much acetyl CoA

→Excess acetone is formed

→Ketosis

Normal 3 mg/100 mL blood of ketone bodies

Ketosis can be as high as 90 mg/100mL