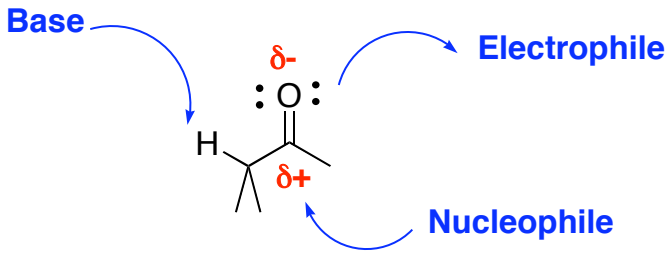
Chemistry of Carbonyl Compounds

- **Nucleophilic addition (1,2-add) / substitution**
- **Conjugate addition (1,4 add)**
- **Robinson annulation (McM 23.12)**

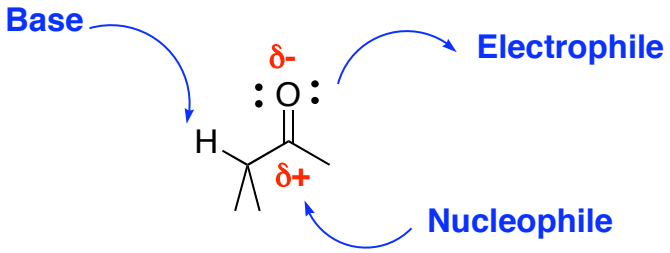
- **Alkylation of enolate anions**
- **Enamines as enolate equivs. (McM 23.11)**

- **Halogenation of enols / enolates**

- **Related react. in nature**



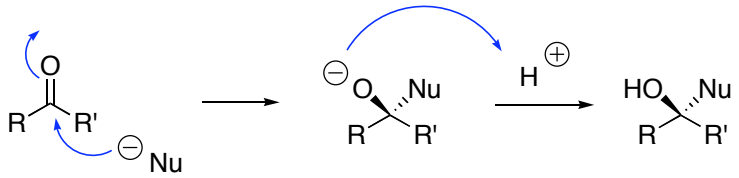
Chemistry of Carbonyl Compounds



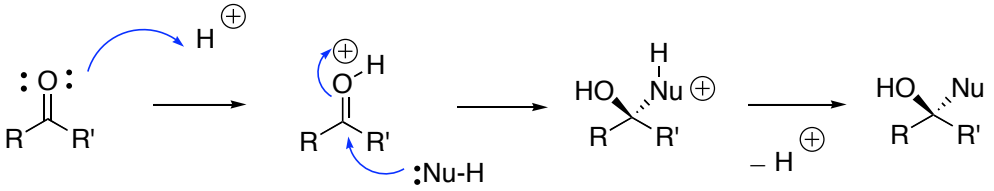
Nucleophilic addition / substitution

Aldehydes / Ketones

Addition reactions



Acid catalyzed

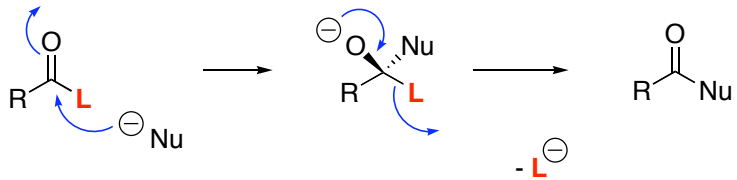


Better electrophile
Weaker nucleophile

R, R': H, alkyl, aryl - Not good leaving groups

Carboxylic acid derivatives

Substitution



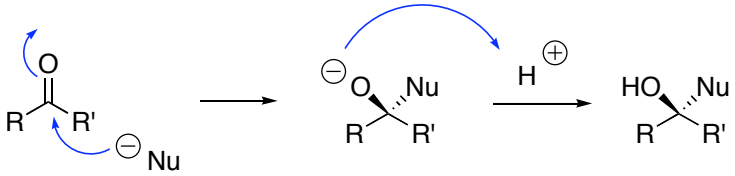
May also be acid cat.

L - Good leaving groups

-X > -OCOR > -OR > -NR_2
X: Halogen, R: H, alkyl, aryl

Aldehydes / Ketones

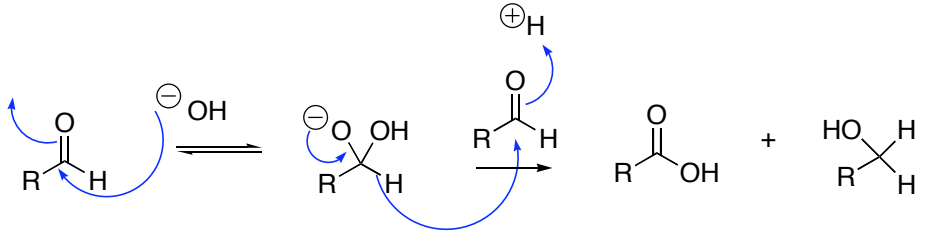
Addition reactions



R, R': H, alkyl, aryl - Not good leaving groups

The Cannizzarro reaction

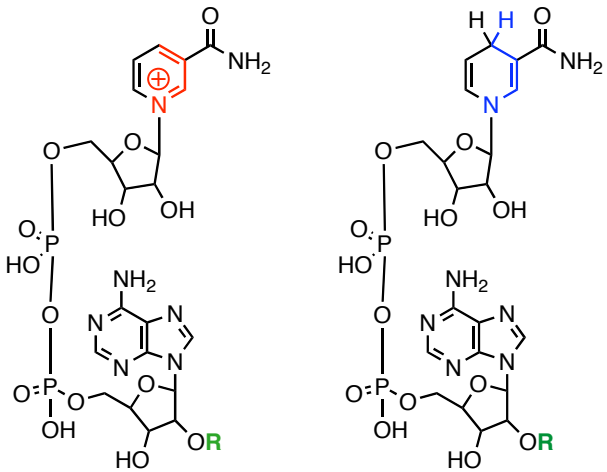
Hydride as leaving group!



R: No acidic α-H
ex -H, -Ph. -Bu^t

2 Aldehyde ⟶ Carboxylic acid + prim. alcohol

Nicotinamid adenine dinucleotide



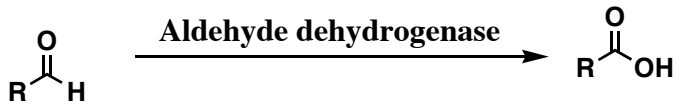
R=H NAD⊕ **NADH**

R=Phosphate: NADP$^+$, NADPH

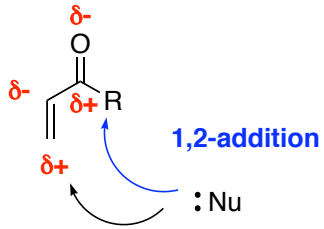
Alchohol dehydrogenase (NAD cont.)

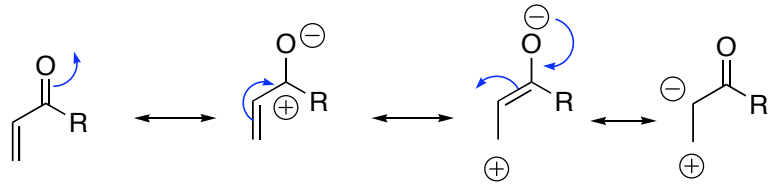
R-OH ⟷ **aldehyde / ketone**

prim or sec.



Conjugate Addition





1,4-addition
(conjugate addition / MIchael addition)

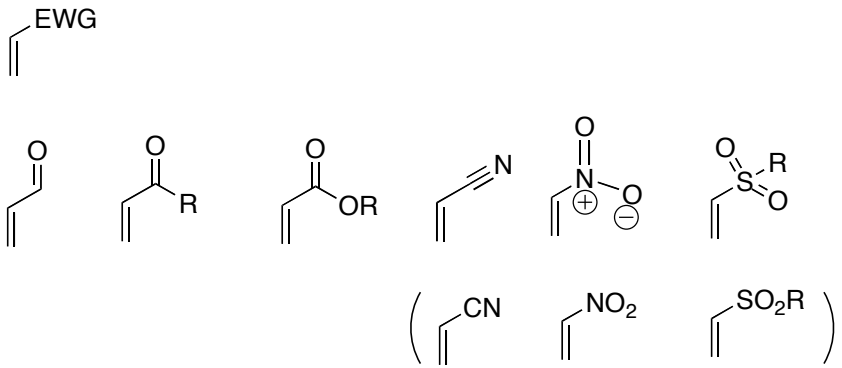
1,2-addition, Ex:
- **Alcohols**
- **Organolithium**

1,4-addition, Ex:
- **Amines**
- **Organocuprates**

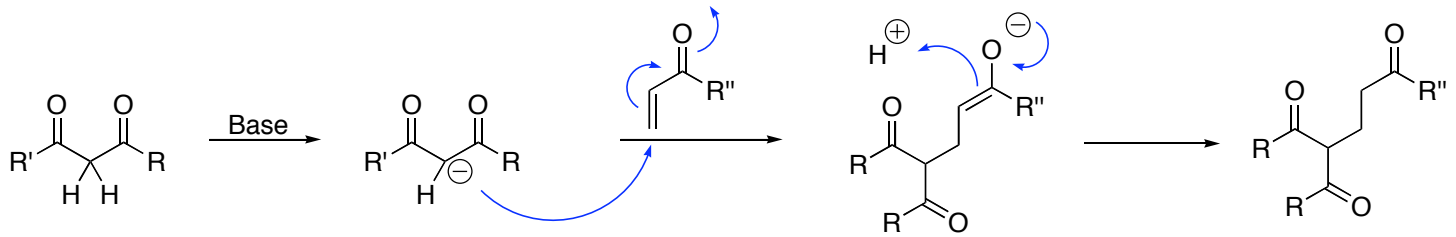
Identity of Nu
Sterical factors

Termodyn. prod,

Michael acceptor



Michael reaction



NB! resonance forms
Well stabilized enolate anion

HSAB theory (not in McM)

HSAB : Hard and soft acids and bases

Lewis bases / nucleophiles

Donor atom - hard bases:

- **high electroneg.**
- **low polarizability**
- **hard to oxidize**

Donor atom - soft bases:

- **low electroneg.**
- **high polarizability**
- **easy to oxidize**

Hardness

$F^- > Cl^- > Br^- > I^-$

$F^- > OH^- > NH_2^- > CH_3^-$

Lewis acids / electrophiles

Acceptor atom - hard acid

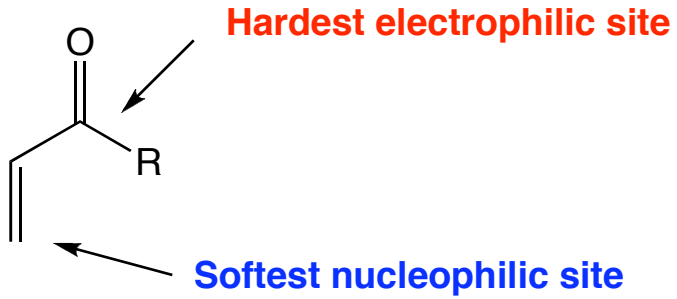
- **small**
- **high positive charge**
- **no unchared e- pair in valence shell**
- **high electroneg.**
- **low polarizability**

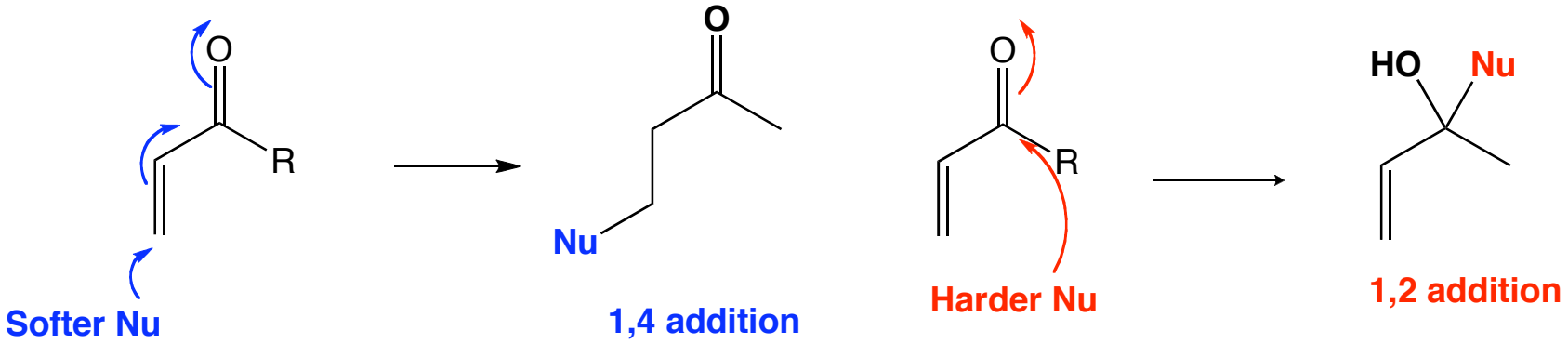
Acceptor atom - soft acid

- **large**
- **low positive charge**
- **unchared e- pair in valence shell**
- **low electroneg.**
- **high polarizability**

Hard acids prefer to bind to hard bases

Soft acids prefer to bind to soft bases

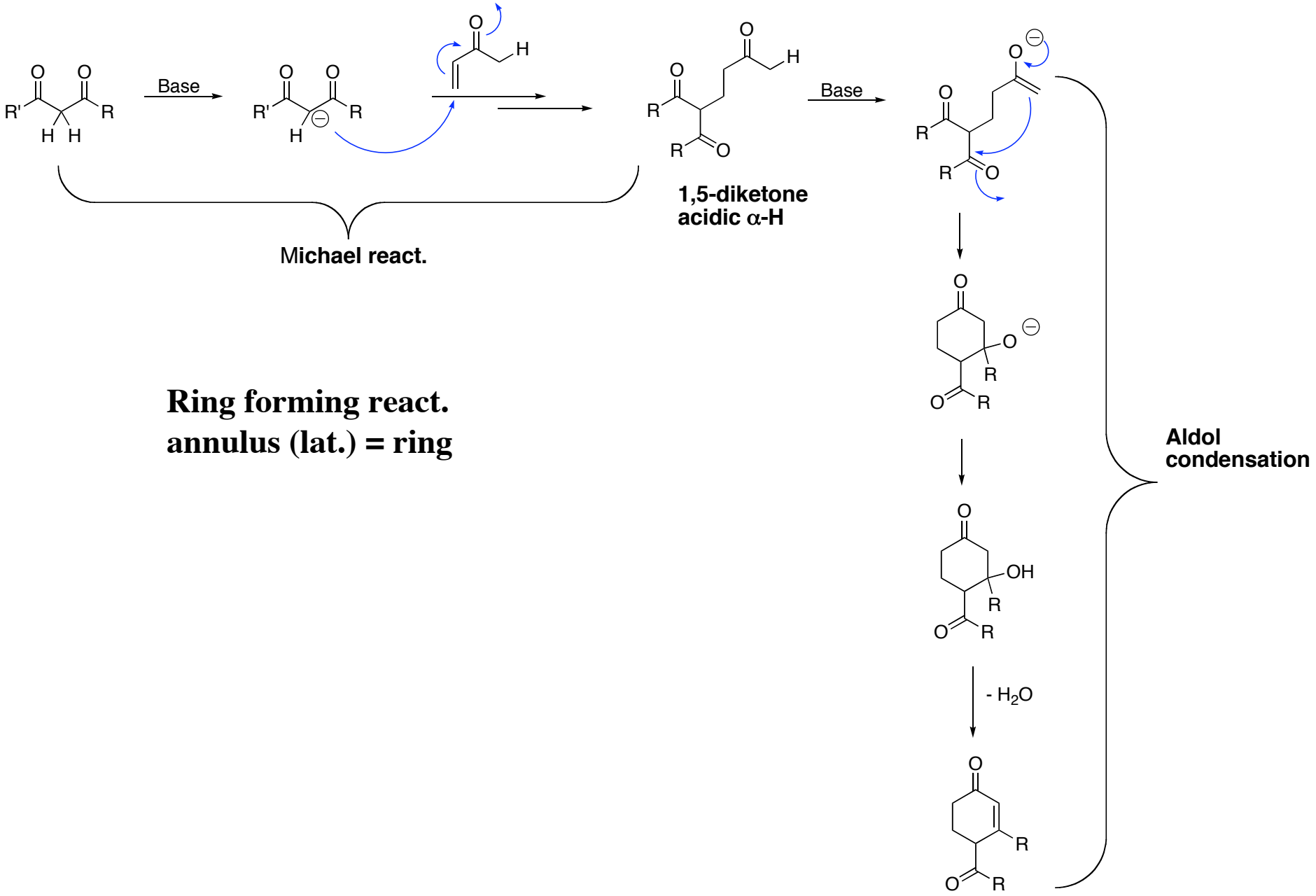




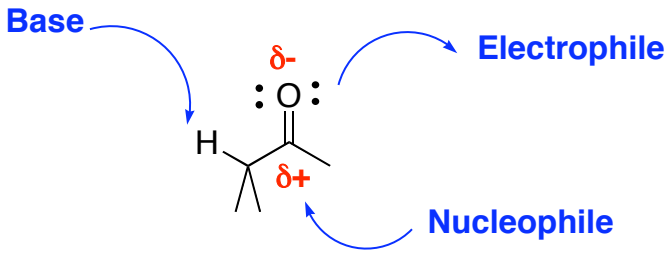
But also

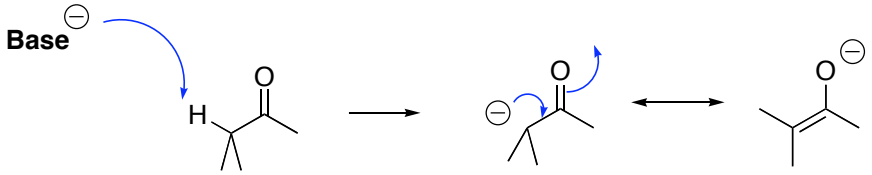
- **Kin. / termodyn. control**
- **Steric shielding**

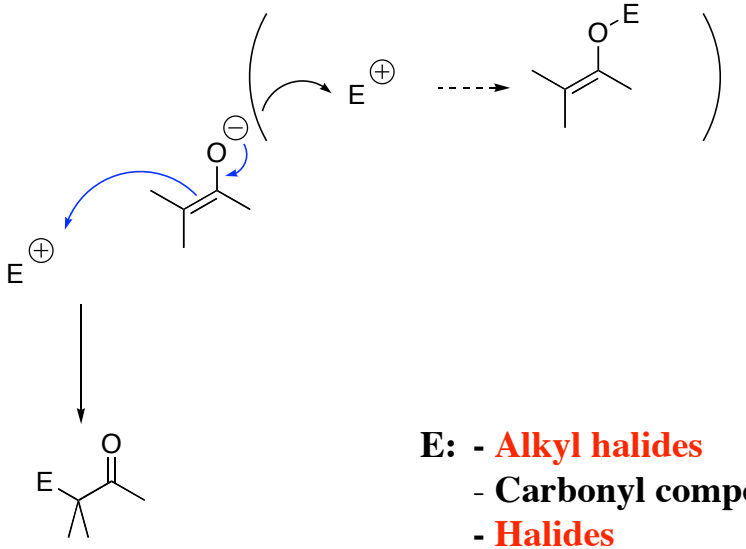
Robinson Annulation (McM 23.12)



Ring forming react.
annulus (lat.) = ring





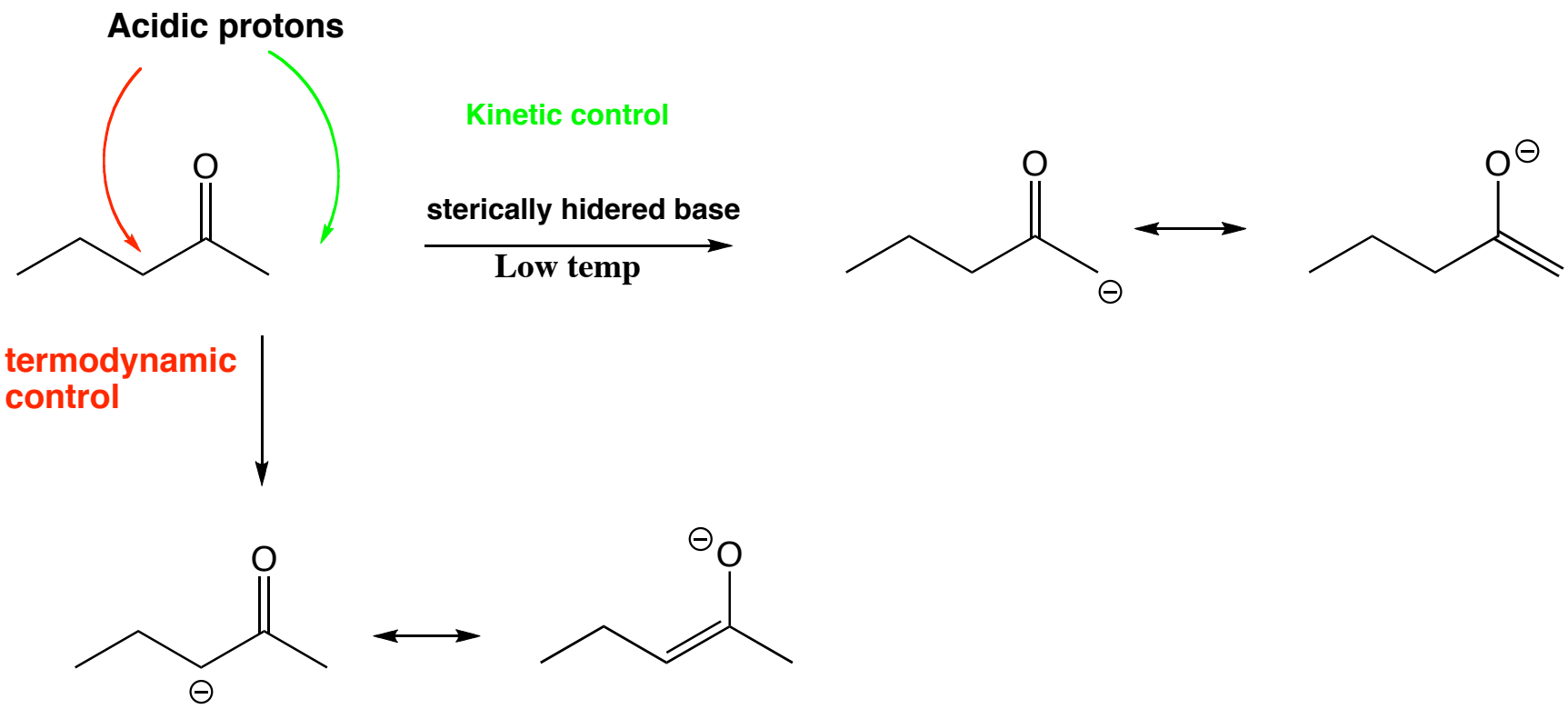


(React with hard E⁺)

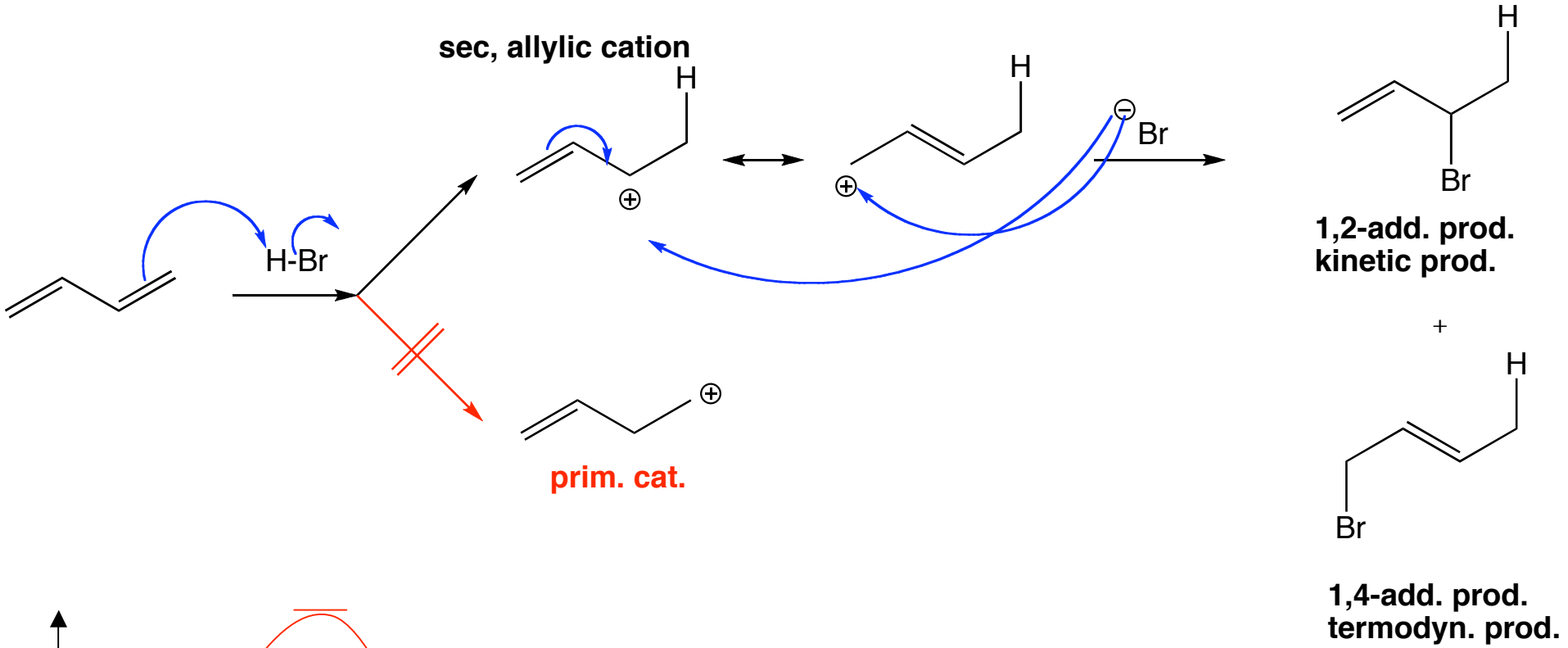
E: - **Alkyl halides**
- **Carbonyl compounds (Aldol, Claissen condens.)**
- **Halides**

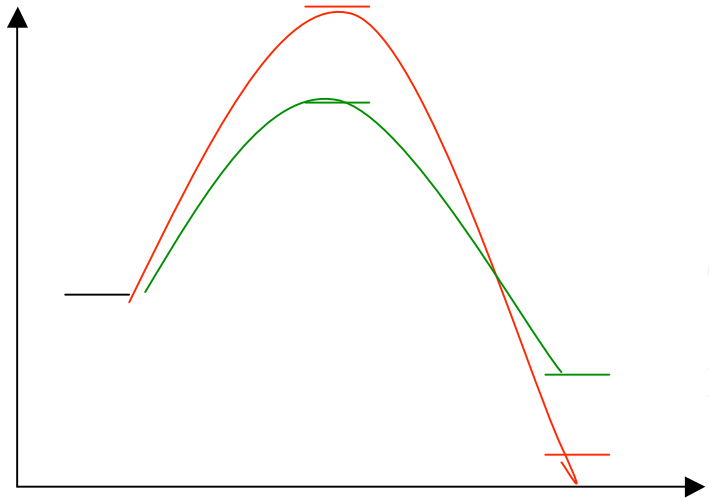
(React. with soft E⁺)

Regioselectivity in enolate anion formation (not in McM)



Electrophilic addition to conjugated dienes

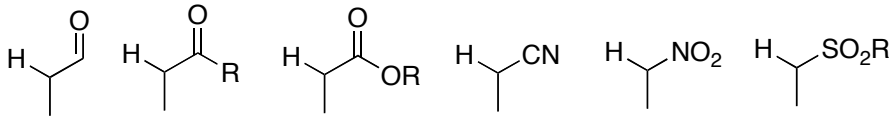




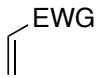
Termodyn prod: High activation barrier, most stable prod.
Vigorous cond. (high temp), reversible

Kinetic prod: Low activation barrier, less stable prod.
Mils cond, (low temp,) irreversible

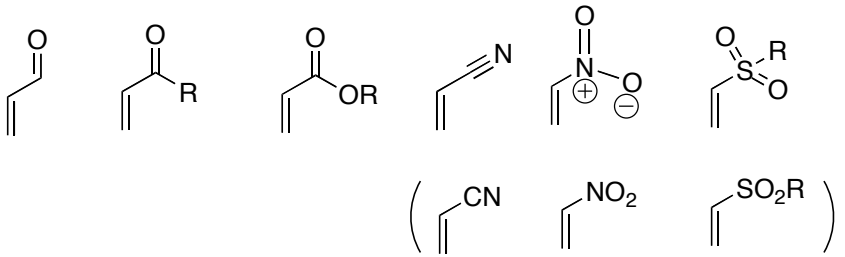
Enolizable



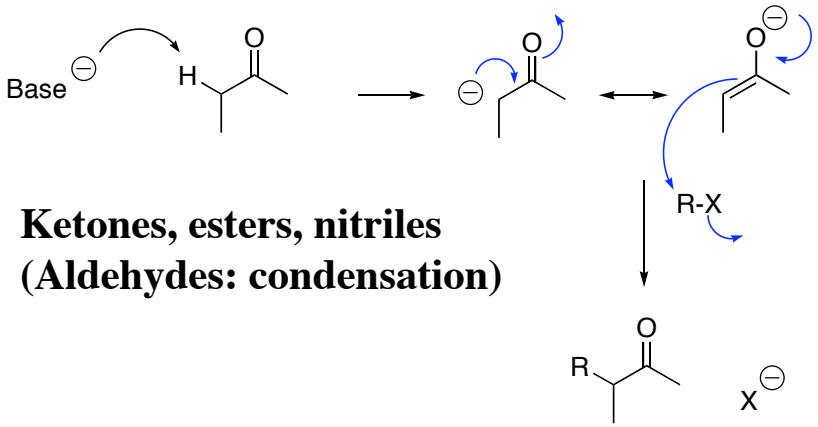
ca pKa: 17 19 25 25 10 30



Michael acceptor

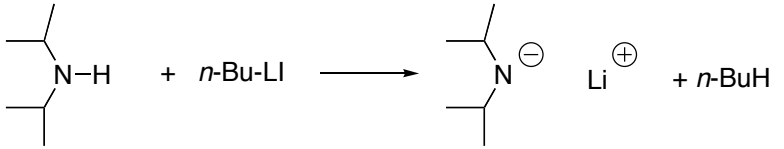


Alkylation of enolate anions



Ketones, esters, nitriles
(Aldehydes: condensation)

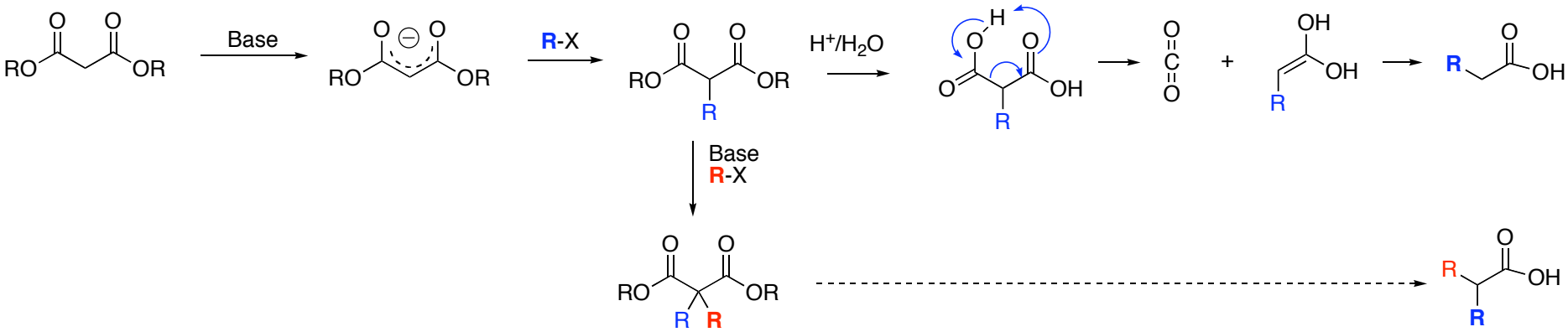
Base: Strong, sterical hindrance

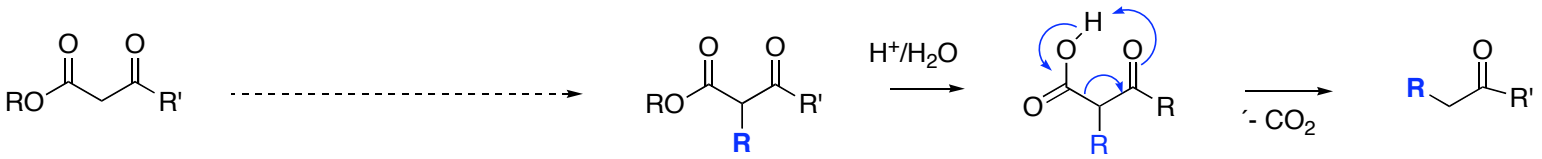


pKa ca 40

Litium Diisopropyl Amide

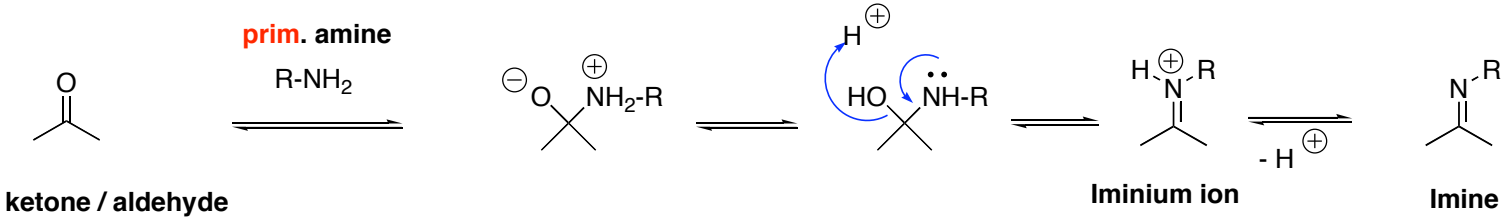
Alkylation of 1,3-dicarbonyl compounds followed by decarboxylation

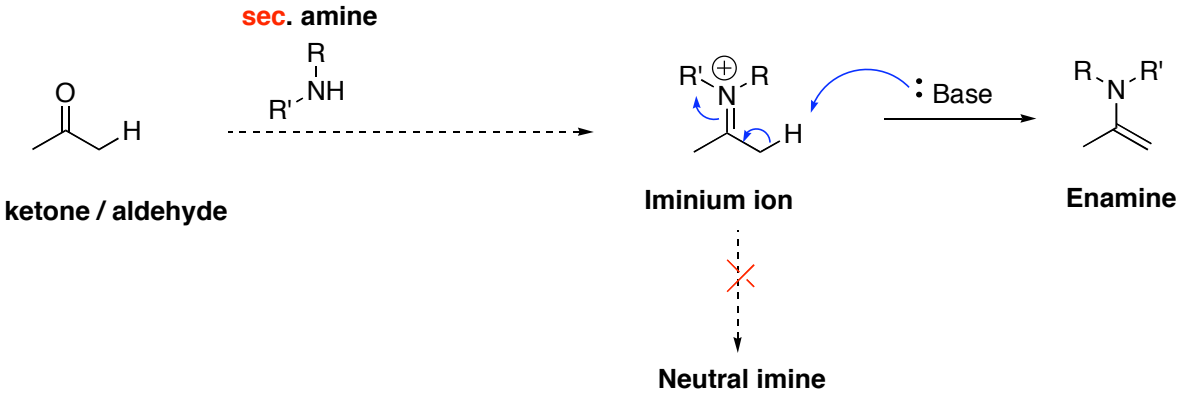




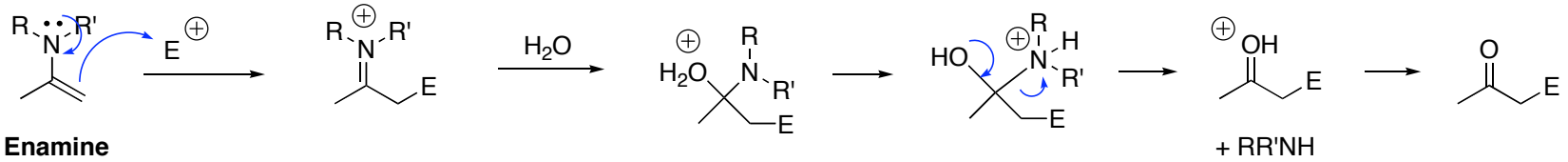
Enamines as enolate equivalents (McM 23.11, Lab ex. 11)

Synthesis of enamines

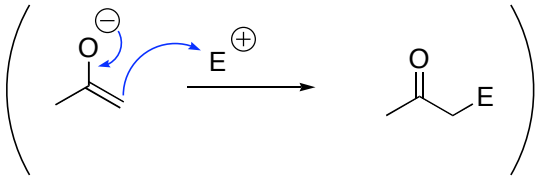




Reactivity of enamines



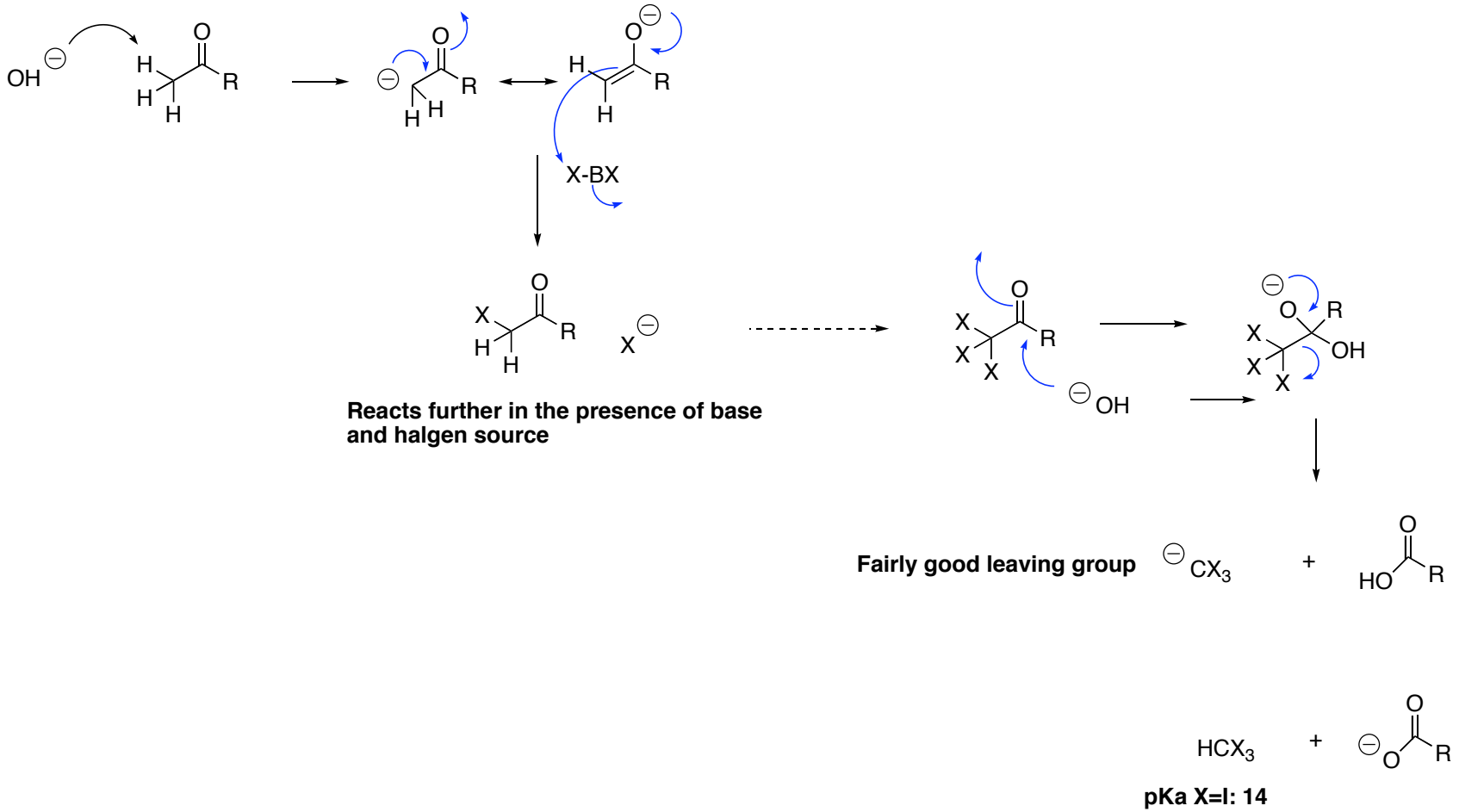
Enamine



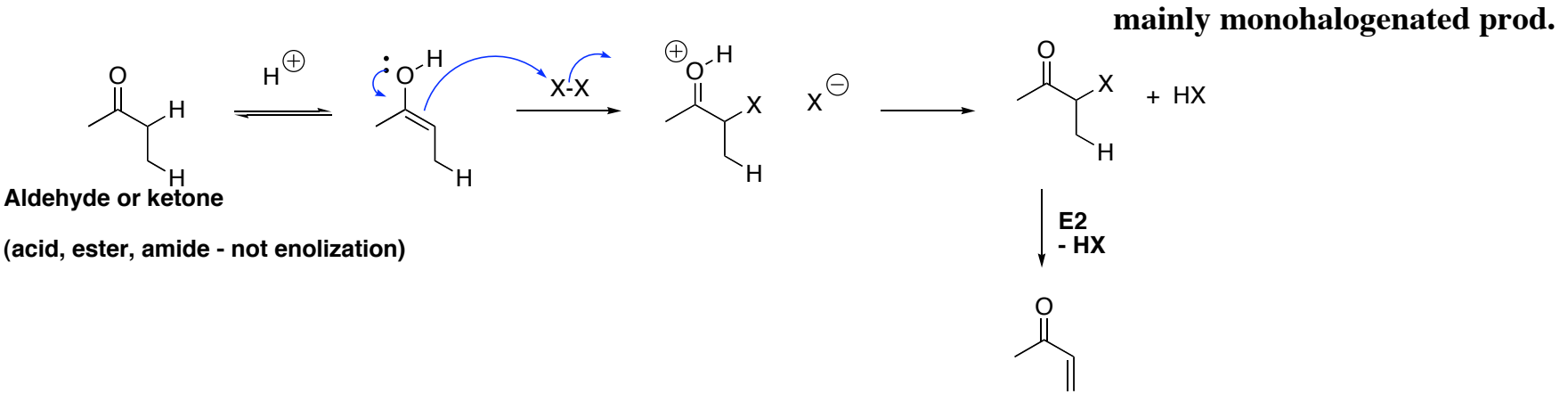
- **Alkylation (alkyl halides)**
- **Conjugate addition (Michael acceptors)**
- **Acylation (acid halides)**

- **Monoalkylation**
- **No strong base**

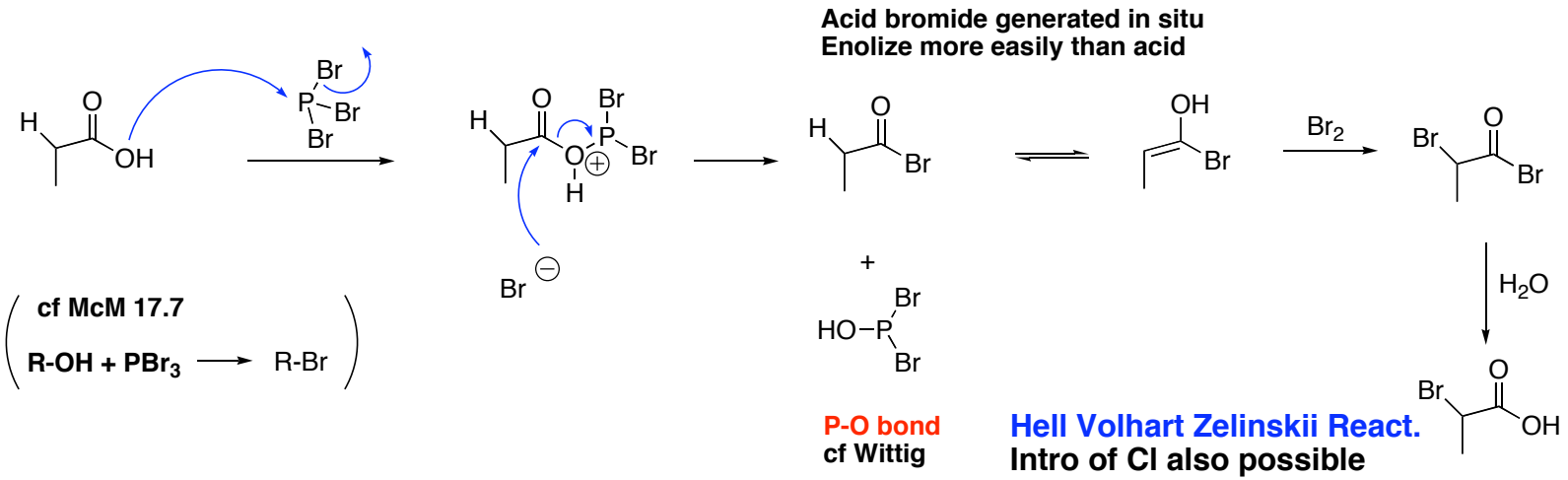
Halogenation of enolate anions



Halogenation of neutral enols



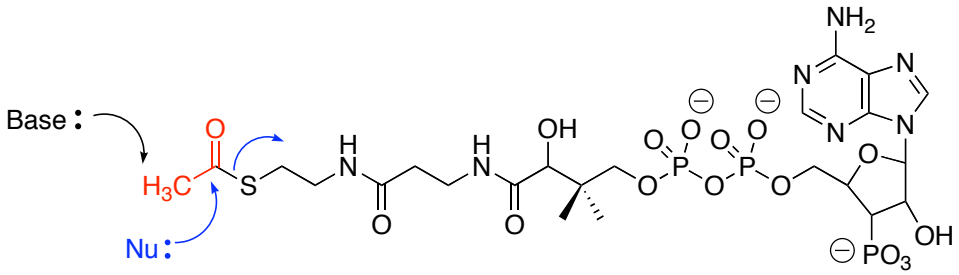
α-Bromination of acids



Carbonyl condensations in nature

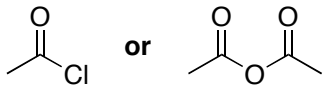
Acyl-CoA

Acetyl-CoA (Acetyl co-enzyme A)

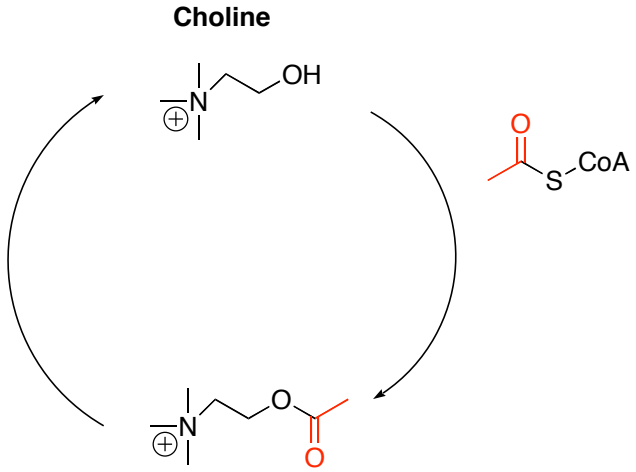


Acetyl-CoA

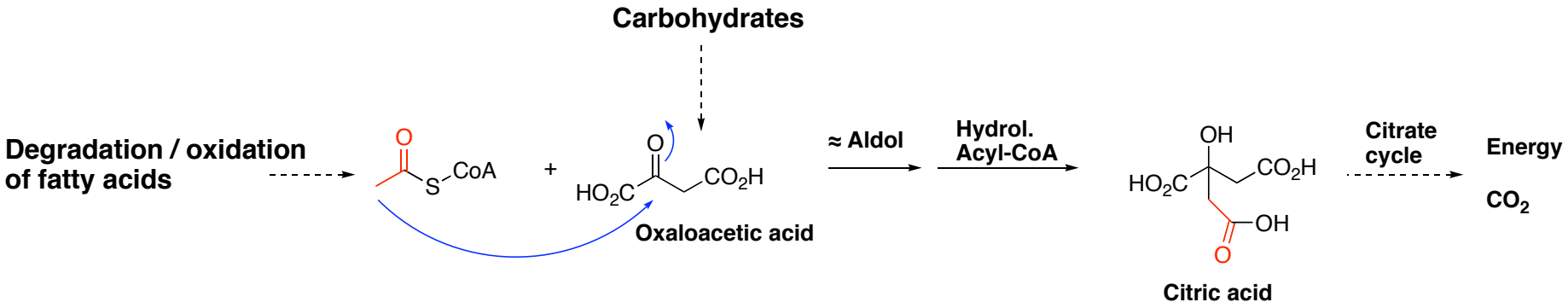
Nature's

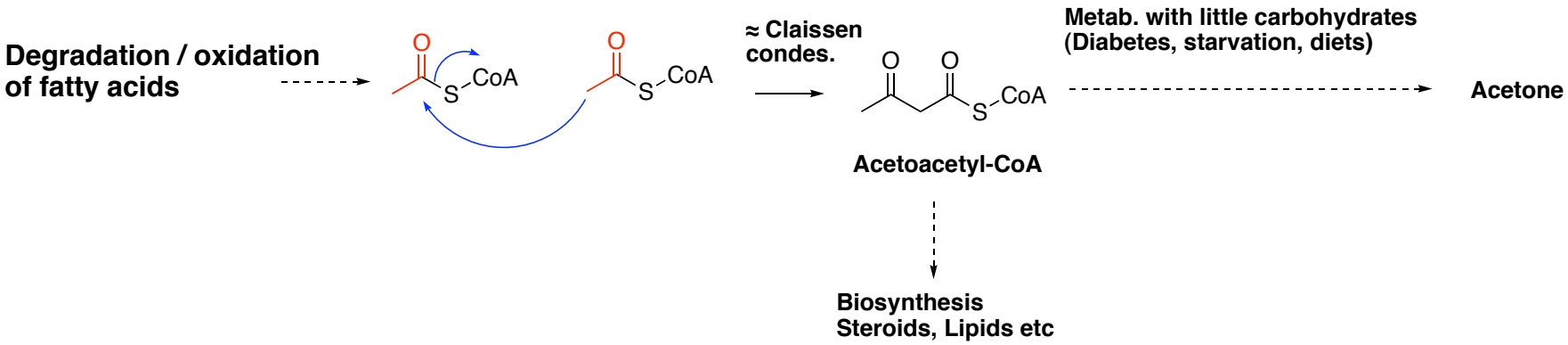


Synthesis of Acetylcholine (neurotransmittor)



Acetylcholine


Carbohydrates
Degradation / oxidation of fatty acids
CoA
+
Oxaloacetic acid
≈ Aldol
Hydrol. Acyl-CoA
Citrate cycle
Energy
CO2
Citric acid


Degradation / oxidation of fatty acids
CoA
≈ Claissen condes.
Acetoacetyl-CoA
Metab. with little carbohydrates (Diabetes, starvation, diets)
Acetone
Biosynthesis
Steroids, Lipids etc

* +