



UNIVERSITY OF  
**OXFORD**

First Year Organic Chemistry

# THE CHEMISTRY OF THE CARBONYL GROUP

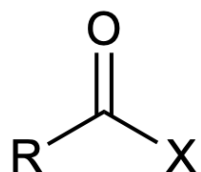
## CORE CARBONYL CHEMISTRY

Professor Jeremy Robertson

*8 lectures, HT, 2023*

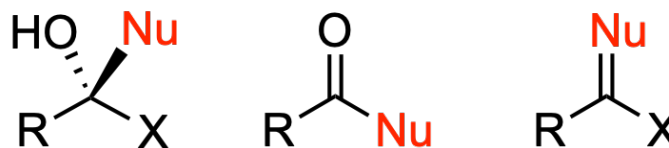
# Course structure

## General principles



- Origin of C=O reactivity
- Reactivity trends as electrophiles; nucleophiles and leaving groups

## Reactions of the carbonyl group



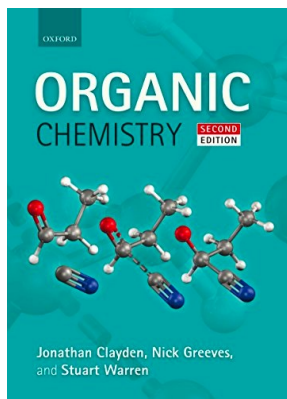
Carbonyl carbon as **electrophilic** centre

- Irreversible addition (reducing agents, organometallics)
- Reversible addition (hydrates, hemiacetals, acetals, imines)
- Addition/elimination (X = leaving group)
- Complete removal of C=O

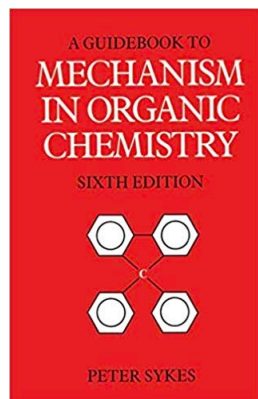
Carbonyl  $\alpha$ -carbon as **nucleophilic** centre

- Enol(ate)s and their equivalents

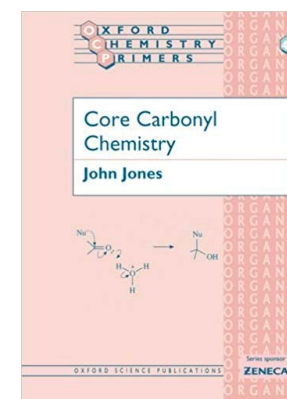
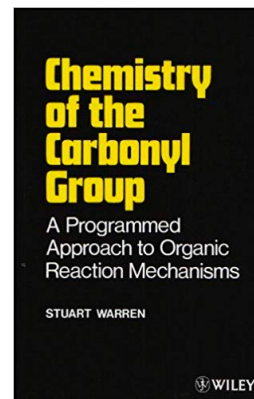
# Reference



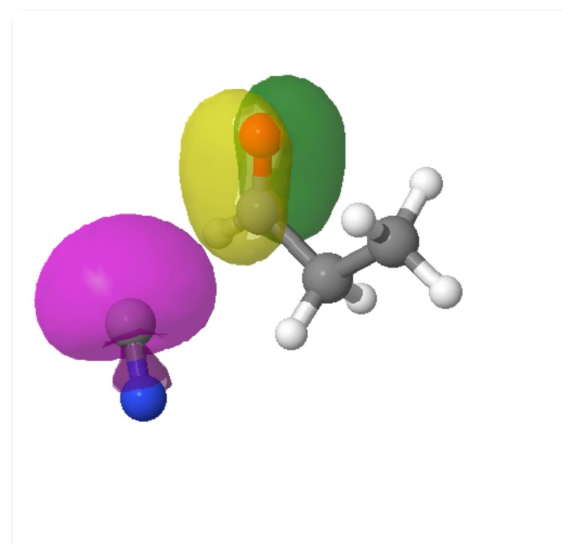
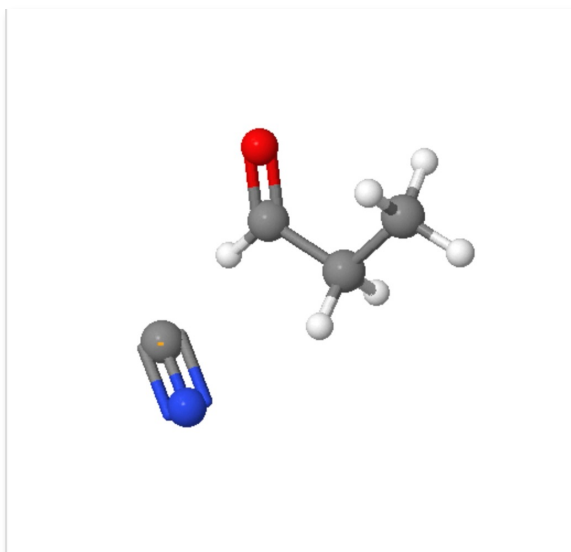
Chapters 6, 9, 10, 11, 22, 26



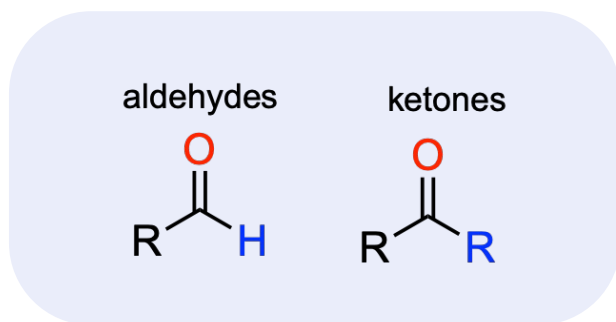
Chapter 8



<https://www.chemtube3d.com/>



# Structure



Pauling scale

$$0.7 < \chi_P < 4.0$$

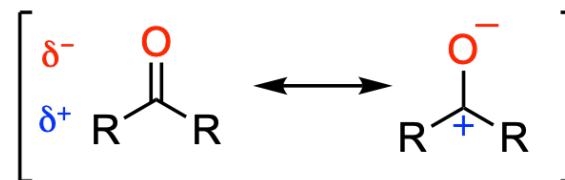
EN increases



C 2.6	N 3.0	O 3.4
	P 2.2	S 2.6

↑  
EN increases

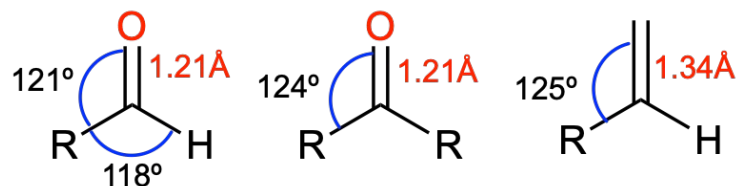
....the C=O bond has a dipole moment



C is electron deficient: **electrophilic centre**

# Structure

bond angle close to  $120^\circ$  (trigonal planar)



C=O,  $730\text{--}760\text{ kJ mol}^{-1}$

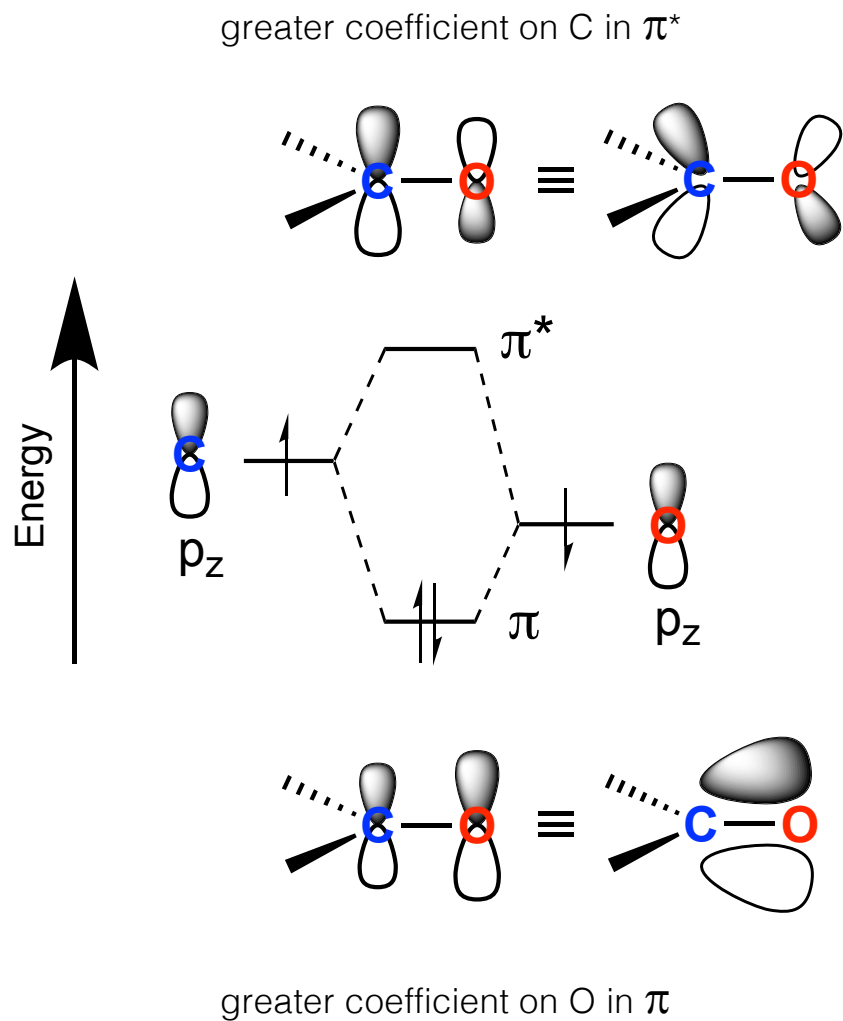
C=C,  $600\text{--}630\text{ kJ mol}^{-1}$

C-O,  $350\text{--}380\text{ kJ mol}^{-1}$

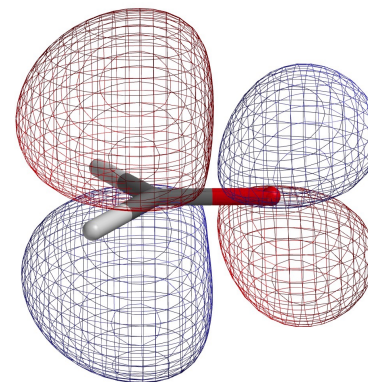
C-C,  $340\text{--}350\text{ kJ mol}^{-1}$

- C=O covalent and electrostatic character leads to a stronger bond than C=C
- Easier to break the C=O bond heterolytically than it is to break it homolytically (diradical)

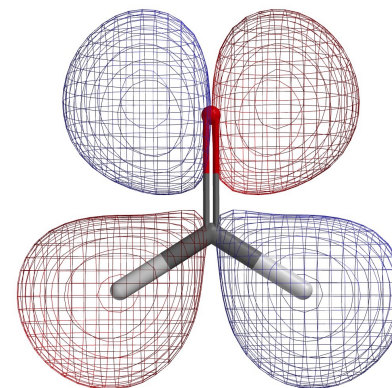
# Structure and Molecular Orbitals



- the LUMO  $\pi^*$  in formaldehyde,  $\text{H}_2\text{C}=\text{O}$

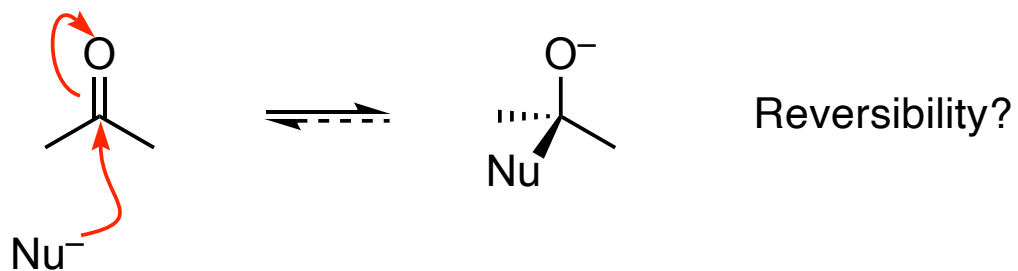


- the HOMO, however, is not the  $\text{C}=\text{O}$   $\pi$ -orbital, it's in-plane p-type; 'lone pair' on O
- lies between  $\pi$  and  $\pi^*$  in energy

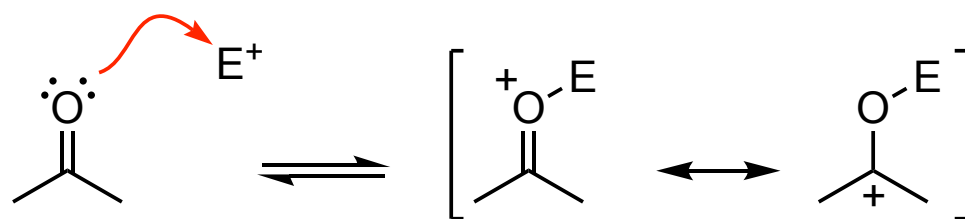


# Reactivity

## Nucleophilic addition



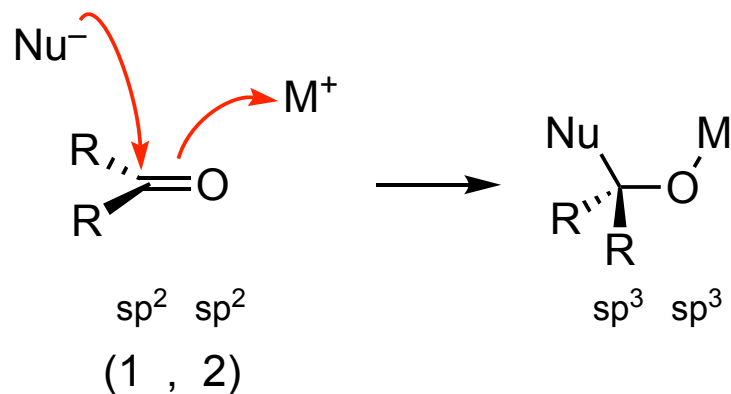
## Electrophilic activation by Lewis acids or Brønsted acids



Pay attention to the reaction conditions: acidic or basic

# Reactivity

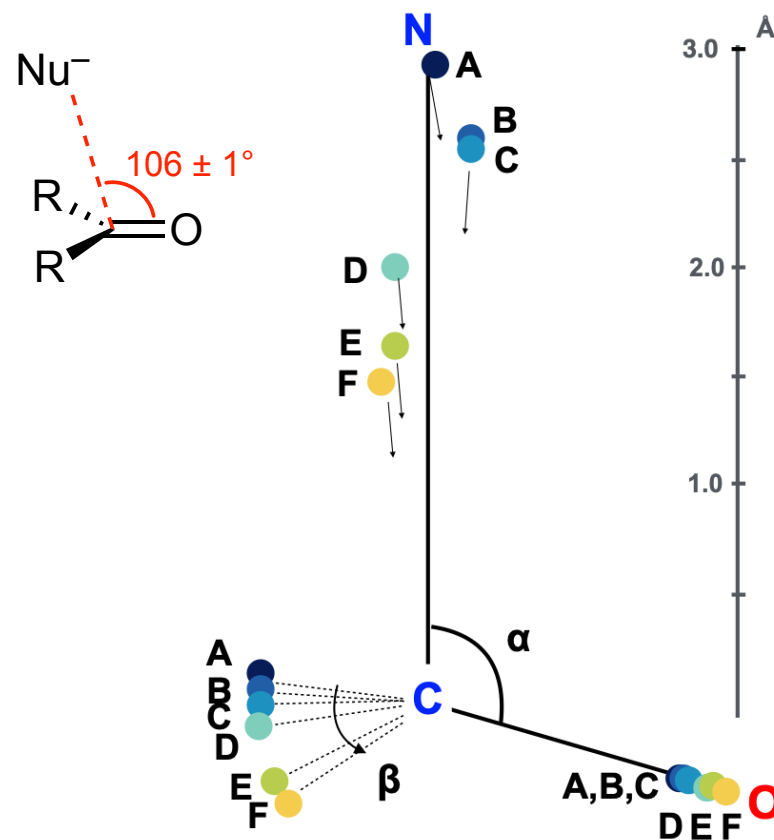
Irreversible 1,2-addition [Nu<sup>-</sup> interacts with π\*]



⇒ Size of R and Nu influence ease of reaction

⇒ Aldehydes generally more reactive than ketones

Bürgi–Dunitz angle

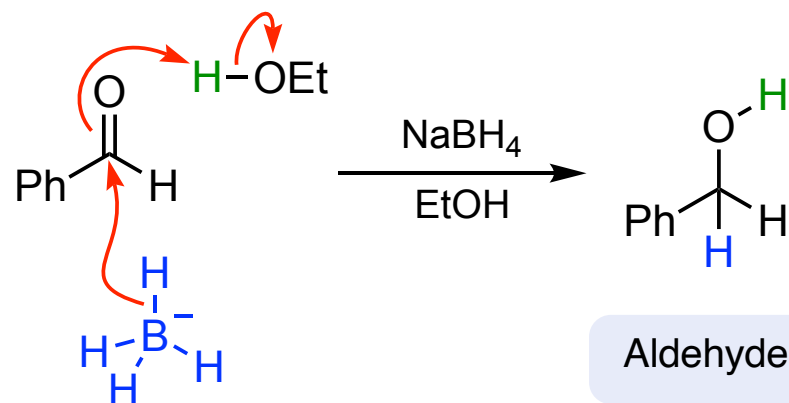


H. B. Bürgi, J. D. Dunitz,\* Eli Shefter<sup>14</sup>  
Laboratories for Inorganic and Organic Chemistry  
Federal Institute of Technology, Zürich, Switzerland  
Received April 30, 1973



# Irreversible 1,2-addition: Hydride reduction

Addition of "H<sup>-</sup>"; NaBH<sub>4</sub> and LiAlH<sub>4</sub>

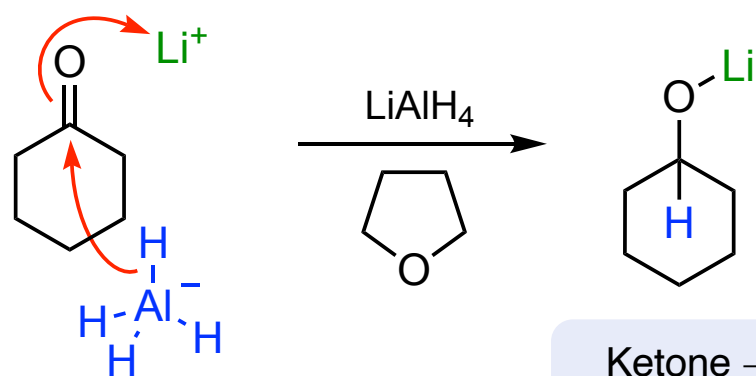


NaOEt adds to liberated BH<sub>3</sub>  
→ NaBH<sub>3</sub>OEt, a *stronger* reducing agent than NaBH<sub>4</sub>  
NaBH<sub>4</sub> can transfer *all four* hydrides

Aldehyde → RCH<sub>2</sub>OH (1°-alcohol)

LiAlH<sub>4</sub> is a (much) stronger reducing agent than NaBH<sub>4</sub>

Reacts rapidly with alcohols; therefore, use in ethereal solvents (Et<sub>2</sub>O or THF)

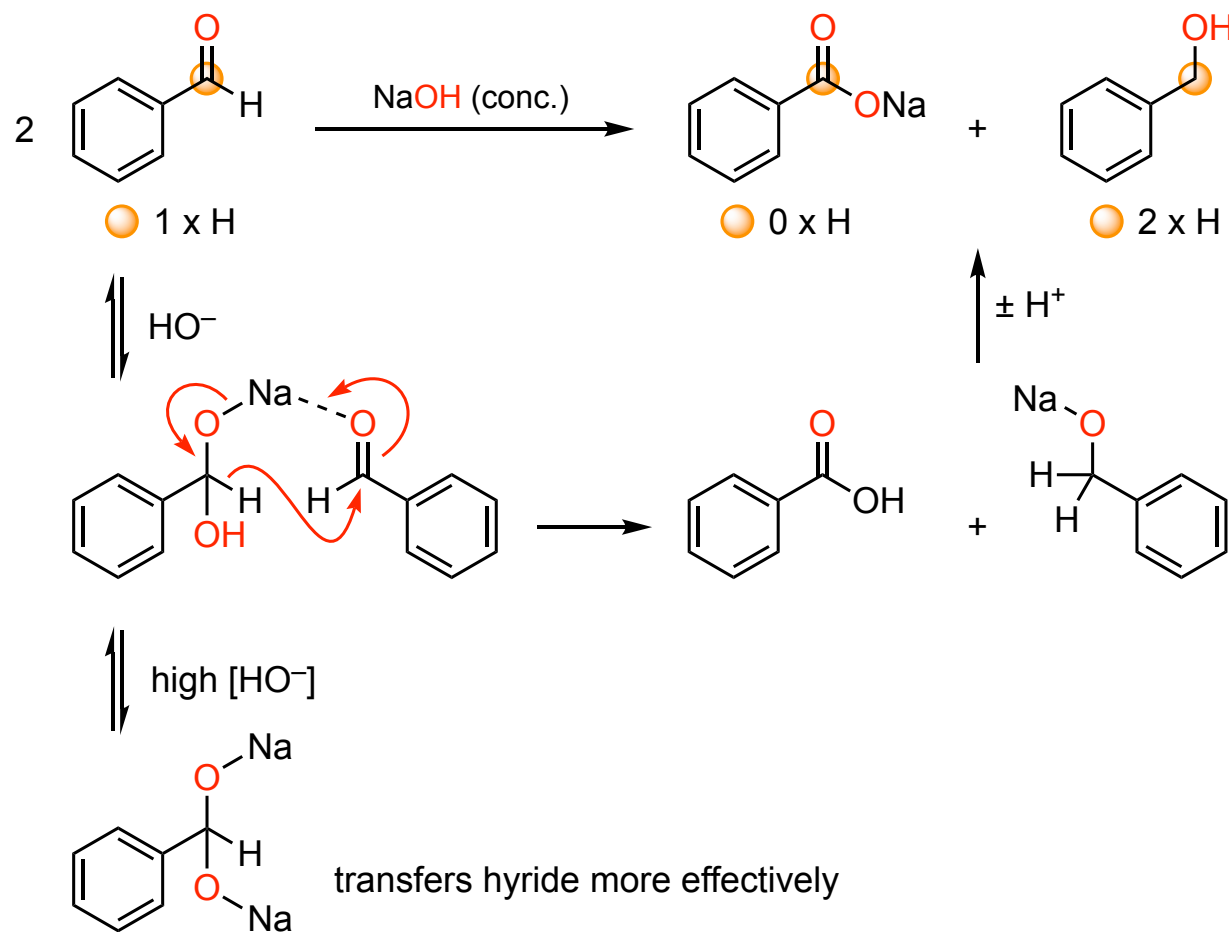


LiAl(OR)<sub>3</sub> is a *weaker* reducing agent than LiAlH<sub>4</sub>  
LiAlH<sub>4</sub> typically transfers *two or three* hydrides

Ketone → R<sub>2</sub>CHOH (2°-alcohol)

# Irreversible 1,2-addition: Other hydride transfer reactions

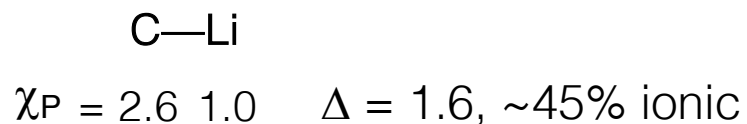
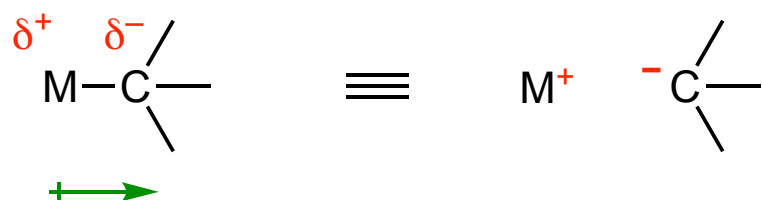
- Meerwein–Ponndorf–Verley reduction (OCP #47, pp 15–16)
- Cannizzaro reaction; a disproportionation



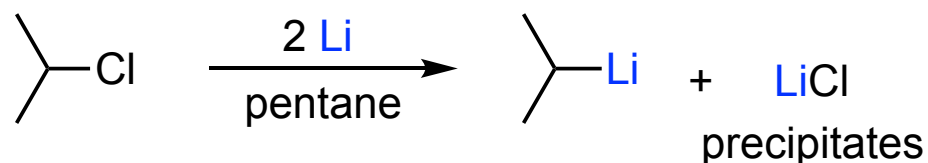
# Irreversible 1,2-addition: Addition of carbanions

R<sup>-</sup> equivalents; organometallics

M = Li, MgX most common

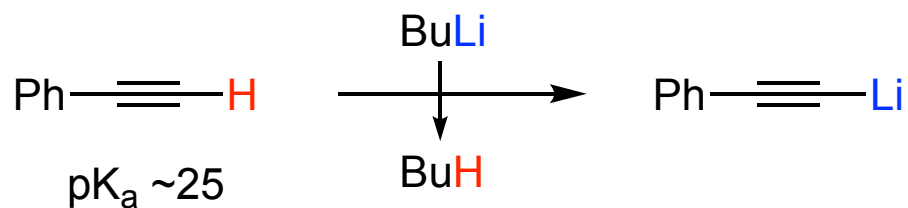


Organolithium reagents prepared by lithium-halogen exchange...



... or deprotonation with a strong base (pK<sub>a</sub> of conjugate acid >30)

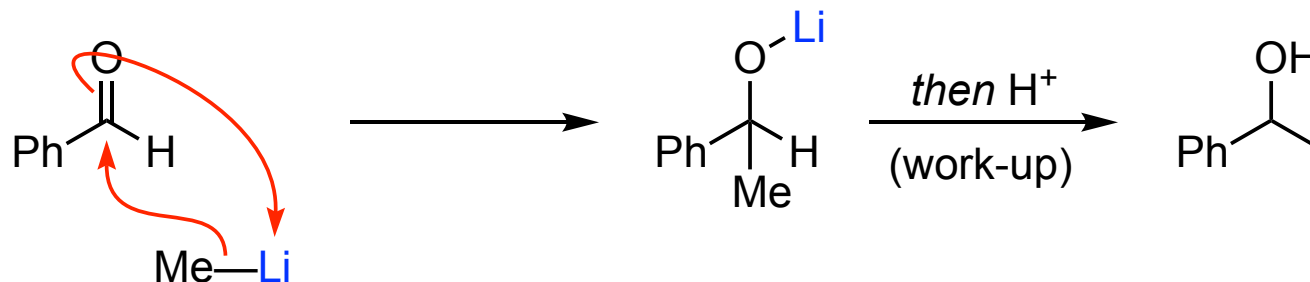
e.g. NaNH<sub>2</sub> (pK<sub>a</sub> of NH<sub>3</sub> ~33), LiN*i*-Pr<sub>2</sub> (LDA), BuLi (pK<sub>a</sub> of BuH >50)



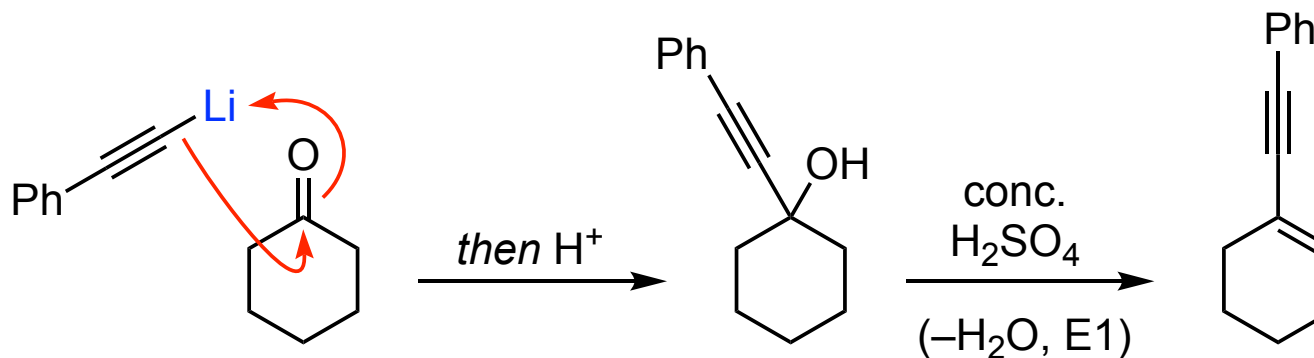
# Irreversible 1,2-addition: Addition of carbanions

Reactions; organolithium reagents are strongly basic and nucleophilic

Aldehydes give 2°-alcohols after 1,2-addition by an organometallic reagent



Ketones give 3°-alcohols

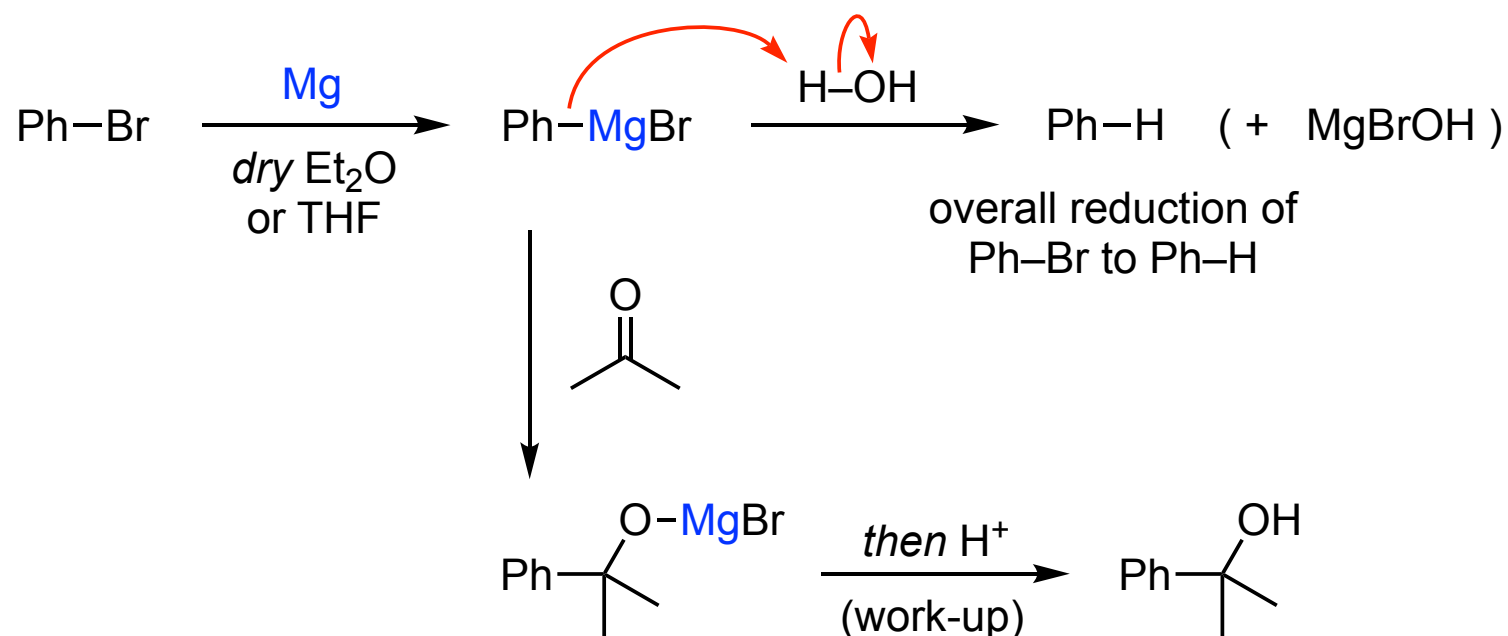


Carbon-carbon bond formation is crucial for *organic synthesis*

# Irreversible 1,2-addition: Addition of carbanions

Grignard reagents are equally important;  $R-MgX$  ( $R = \text{alkyl, aryl, vinyl, allyl, benzyl etc}$ ) prepared by insertion of  $Mg$  into  $R-X$  bond ( $X = Cl, Br, I$ )

Grignard and organolithium reagents react instantly with water or any other molecule that may be considered *protic* (i.e. containing at least one  $O-H$ ,  $N-H$ , or  $S-H$  bond)



# Irreversible 1,2-addition: Addition of carbanions

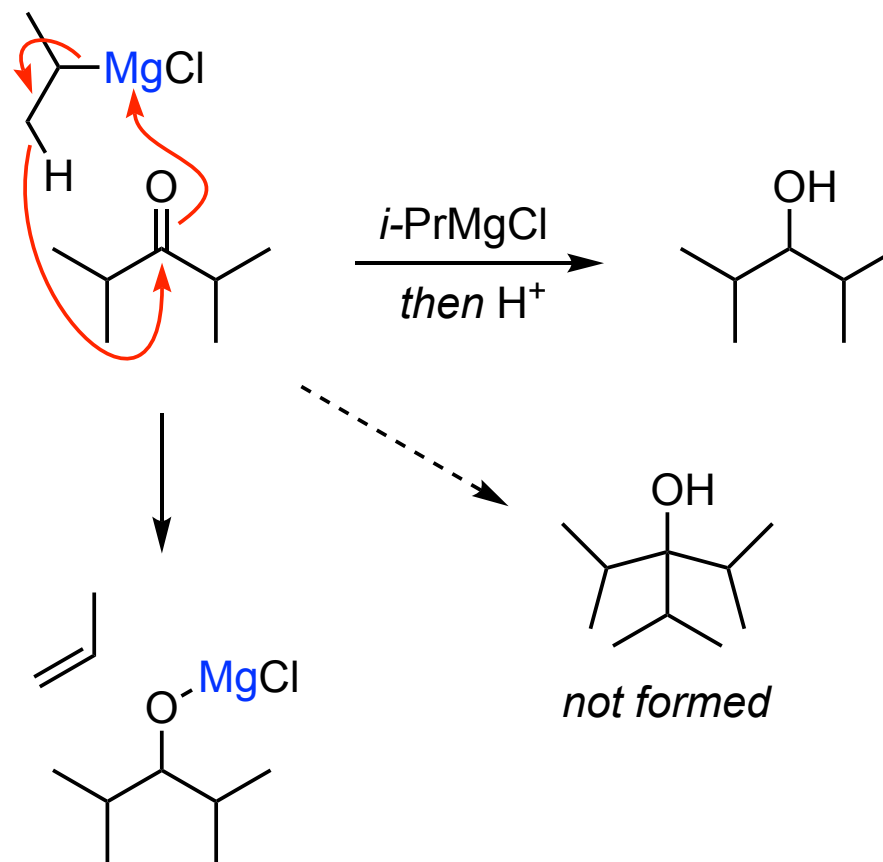
Grignard reagents: further aspects

(1) Lower reactivity than organolithium reagents (see later) but *Schlenk equilibrium* provides Lewis acid activation



not very  
reactive

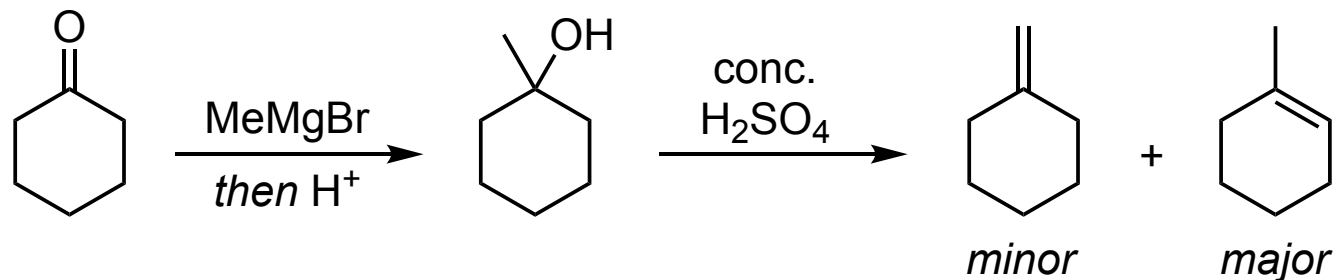
decent  
Lewis acid



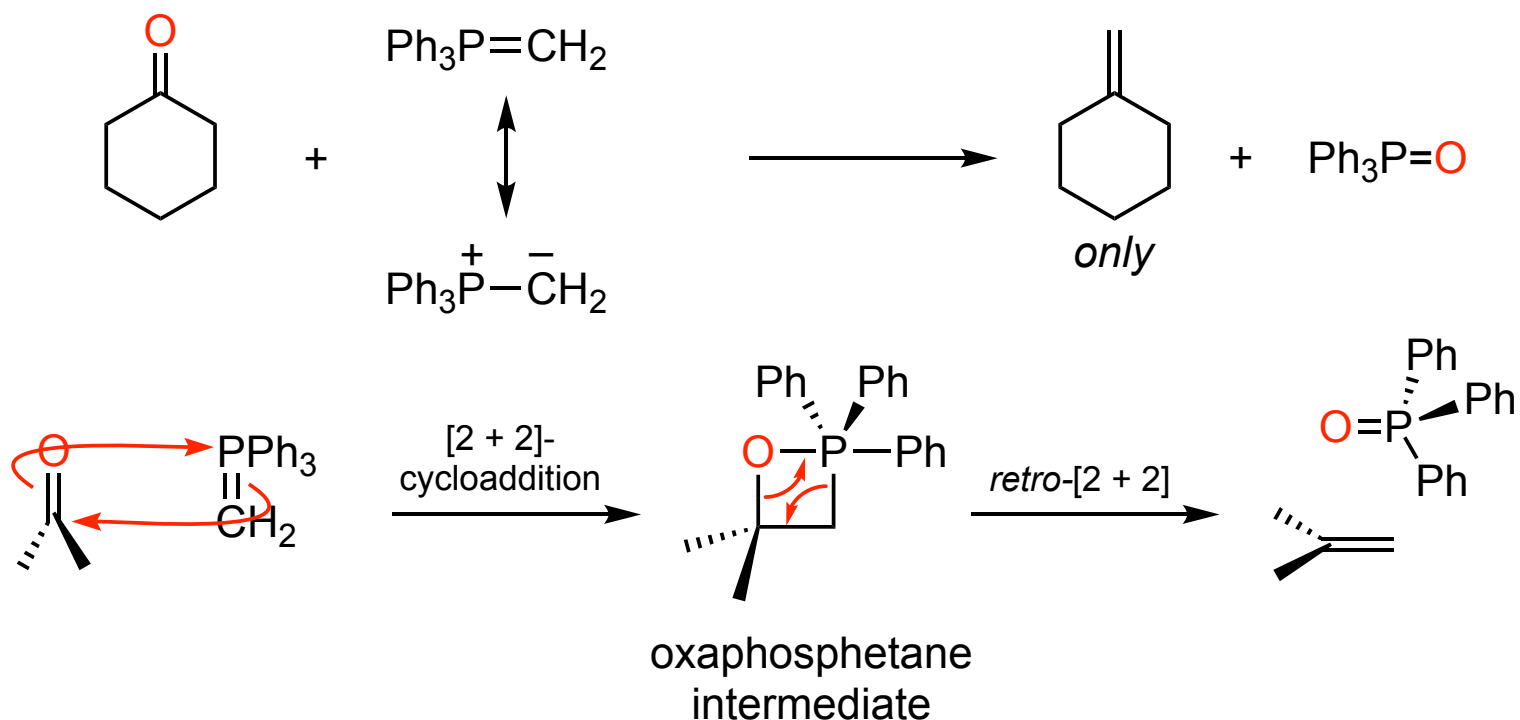
(2) Side reactions – such as reduction – compete if the carbonyl compound is hindered

# Irreversible 1,2-addition: Regiospecific alkene synthesis

How to convert C=O into C=C?



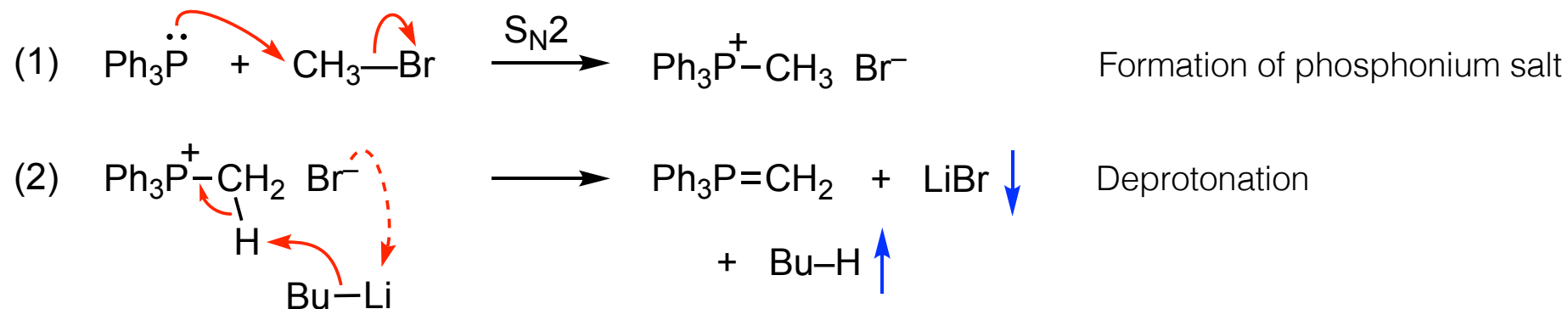
Solution: use the Wittig reaction: aldehyde/ketone + phosphorus ylid



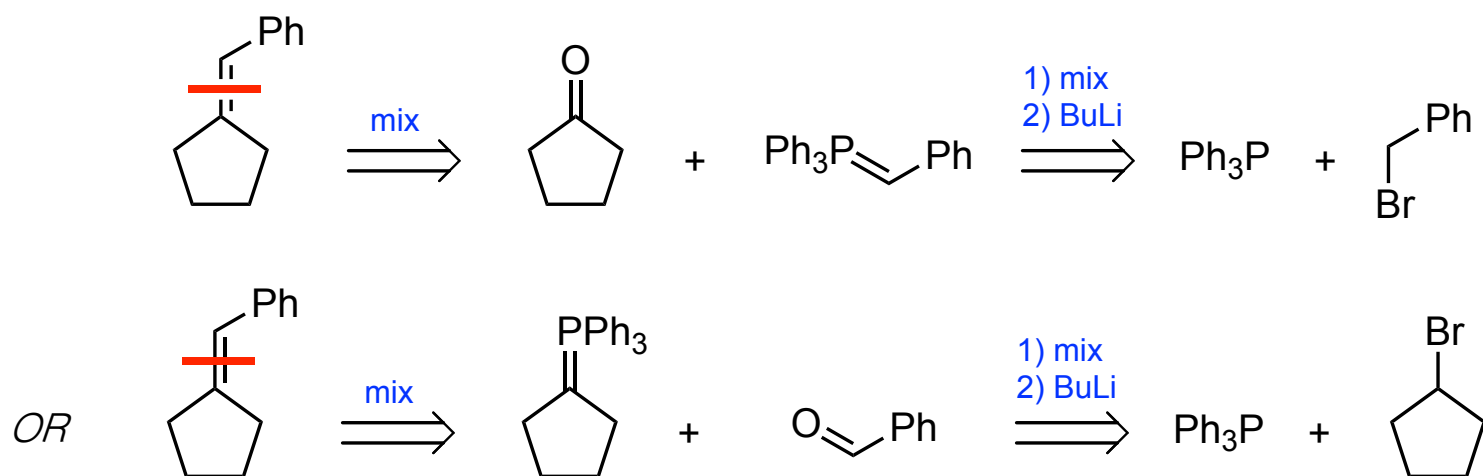
# Irreversible 1,2-addition: Regiospecific alkene synthesis

Wittig reaction is very general (not for tetrasubstituted alkenes,  $R_2C=CR_2$ )

Preparation of the ylid



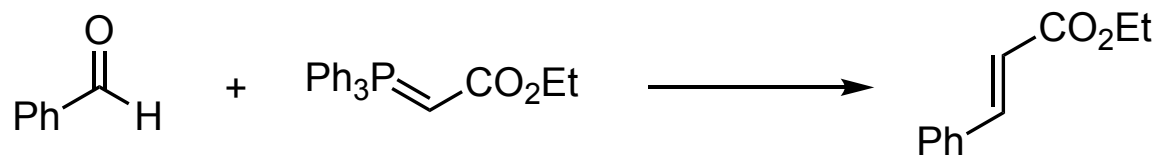
Use in synthesis (retrosynthesis: work backwards)





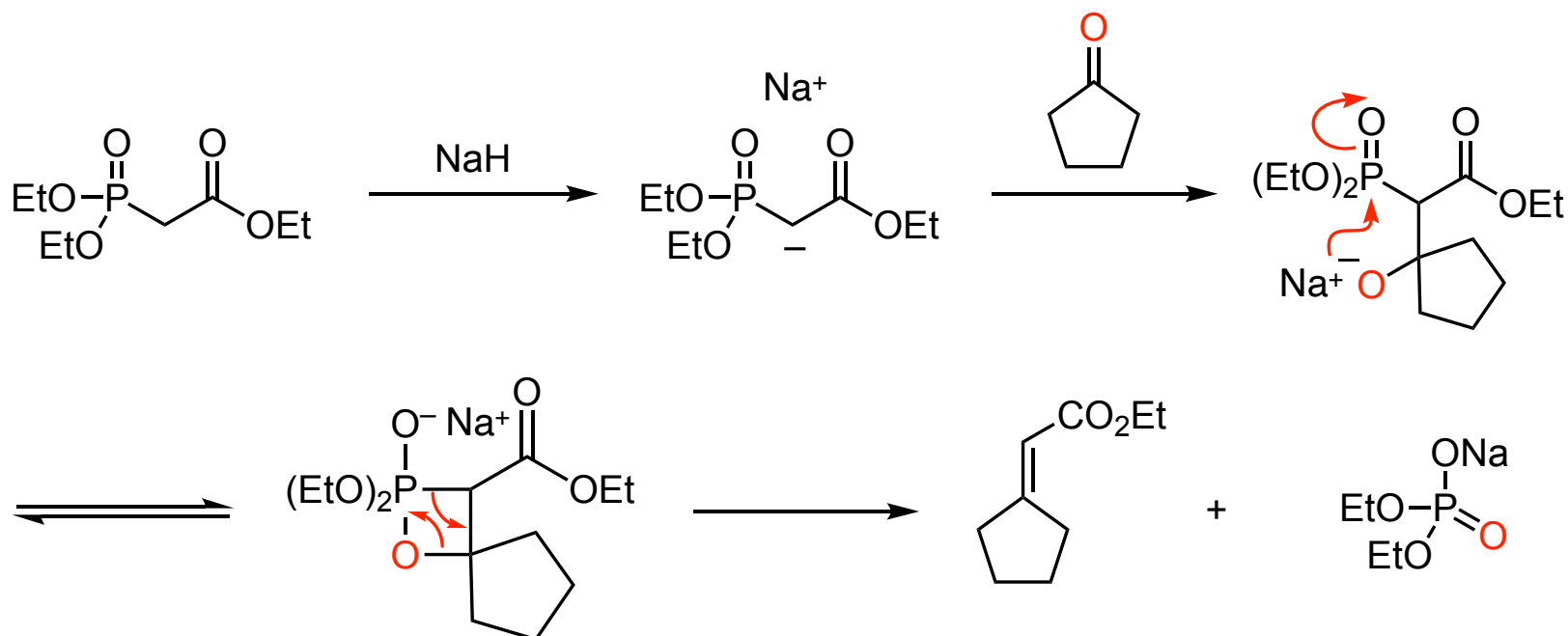
# Irreversible 1,2-addition: Regiospecific alkene synthesis

Wittig reaction also works with *stabilised ylids* (in effect: bearing conjugating EWGs)



Stabilised ylids react well with aldehydes, not so well with ketones

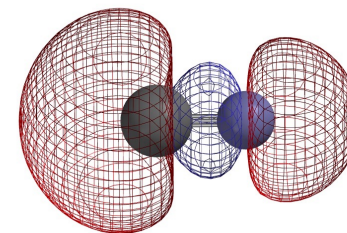
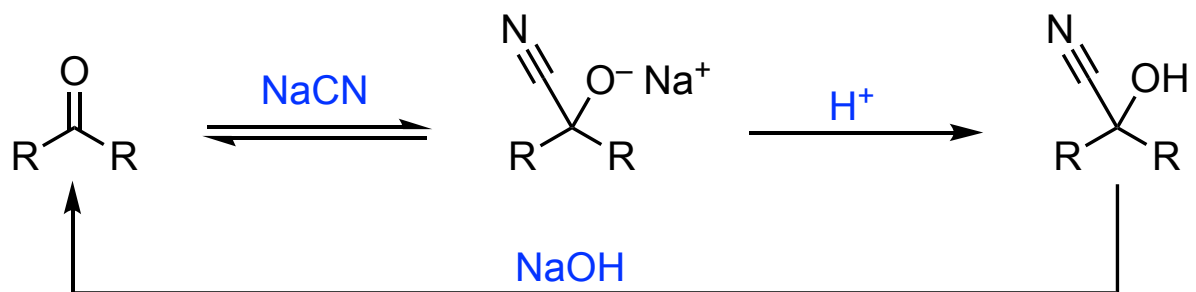
For ketones, use the Horner–Wadsworth–Emmons reaction



More nucleophilic phosphonate **anion**; water-soluble by-product

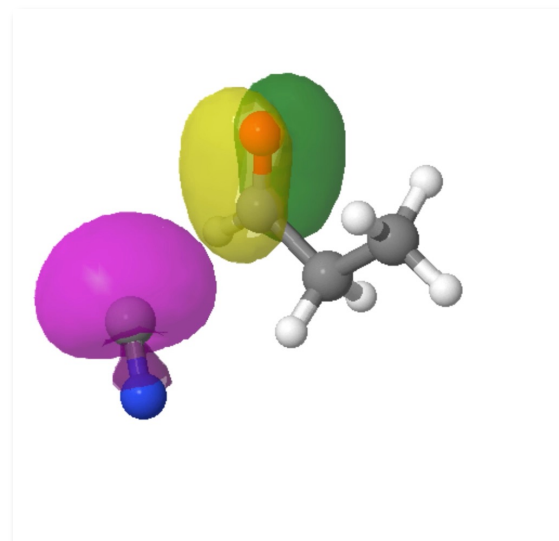
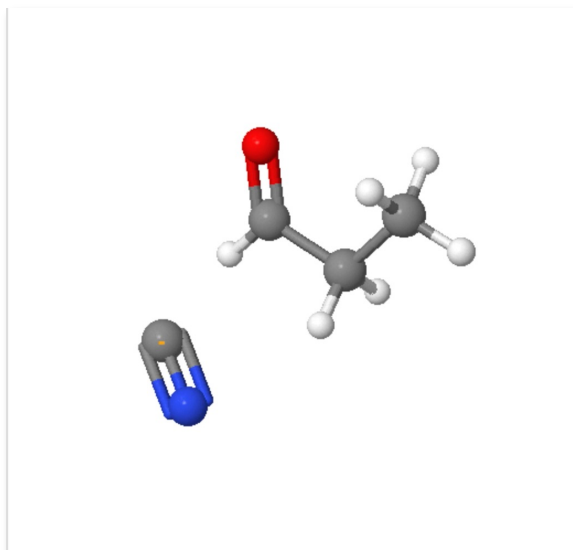
# Reversible 1,2-addition

Cyanohydrin formation; the position of the equilibrium depends on the carbonyl component



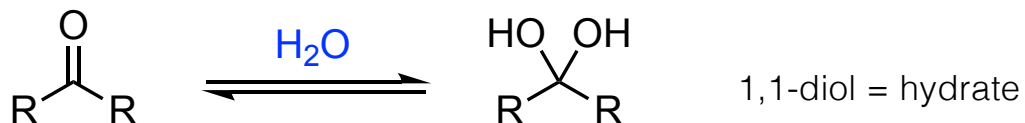
Larger HOMO coefficient on C

Usually productive with aldehydes and simple ketones;  
with  $ArCHO$ , the benzoin condensation can occur (see later)

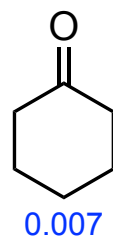
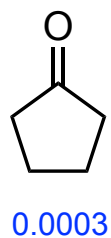
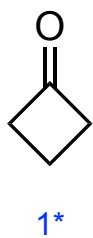
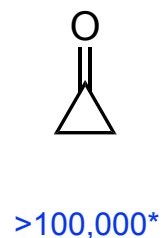
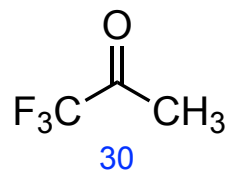
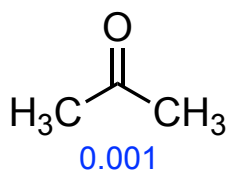
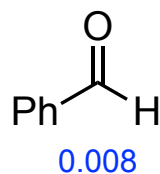
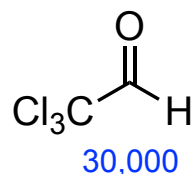
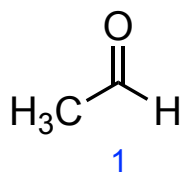
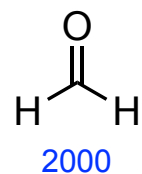


# Reversible 1,2-addition

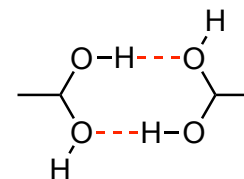
Hydrate formation; occurs naturally in aqueous solutions of aldehydes and ketones



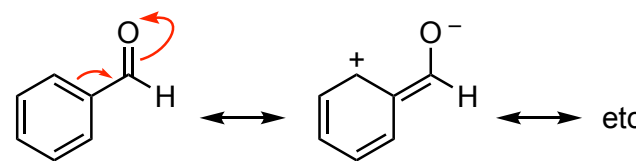
Indicative equilibrium ratios, [hydrate]/[carbonyl]



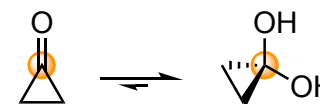
- Steric destabilisation of  $\text{sp}^3$  hydrate
- EWGs destabilise the carbonyl ( $\delta^+$ )
- Hydrogen bonding



- Conjugation stabilises the carbonyl (lost upon hydration)



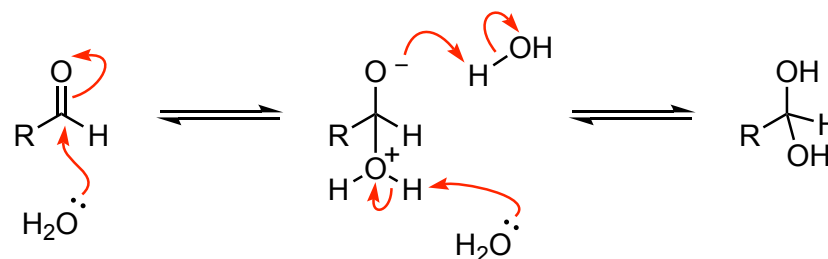
- Strain relief in small ring ketones



# Reversible 1,2-addition

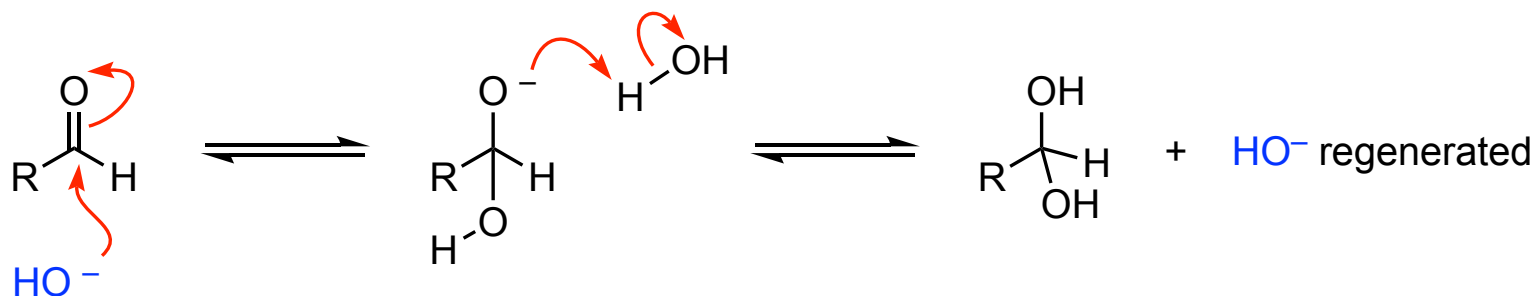
Hydrate formation; mechanisms

Neutral water



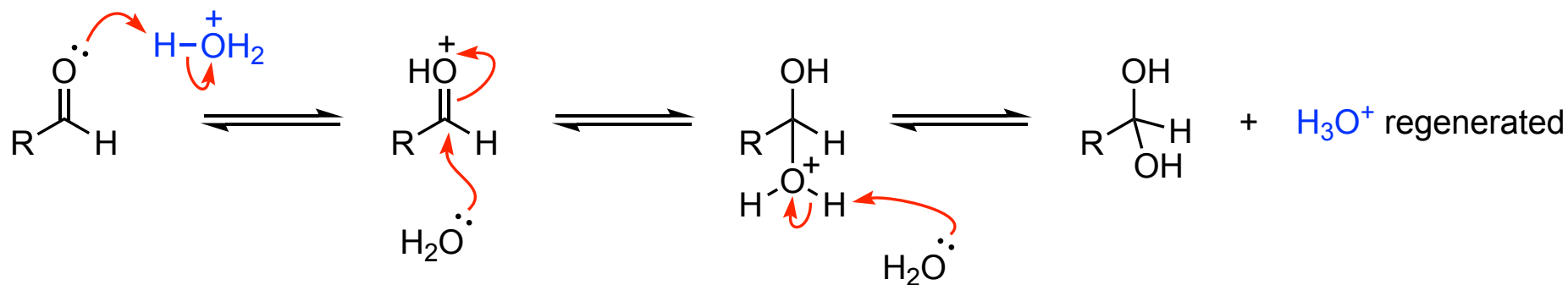
Base catalysed (HO<sup>-</sup>)

HO<sup>-</sup> is more nucleophilic than H<sub>2</sub>O; faster reaction



Acid catalysed (H<sub>3</sub>O<sup>+</sup>)

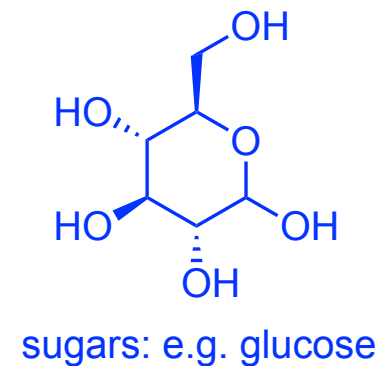
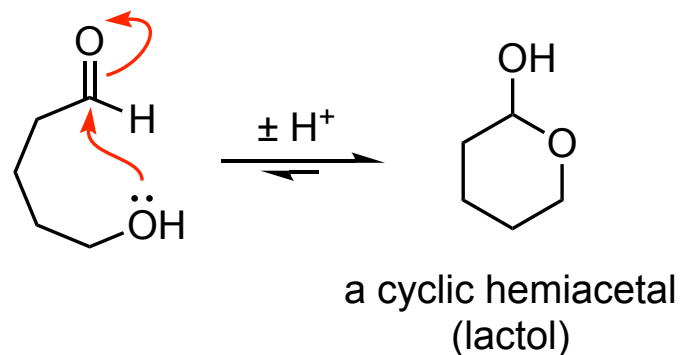
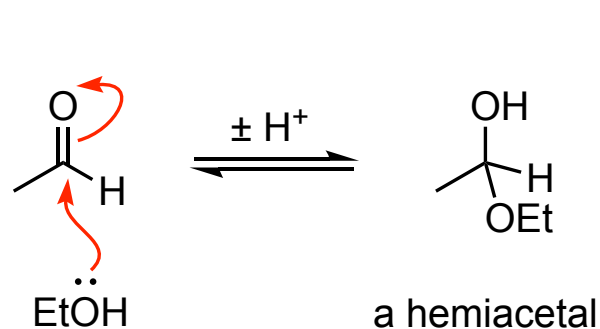
Protonated carbonyl is more electrophilic than carbonyl; faster reaction



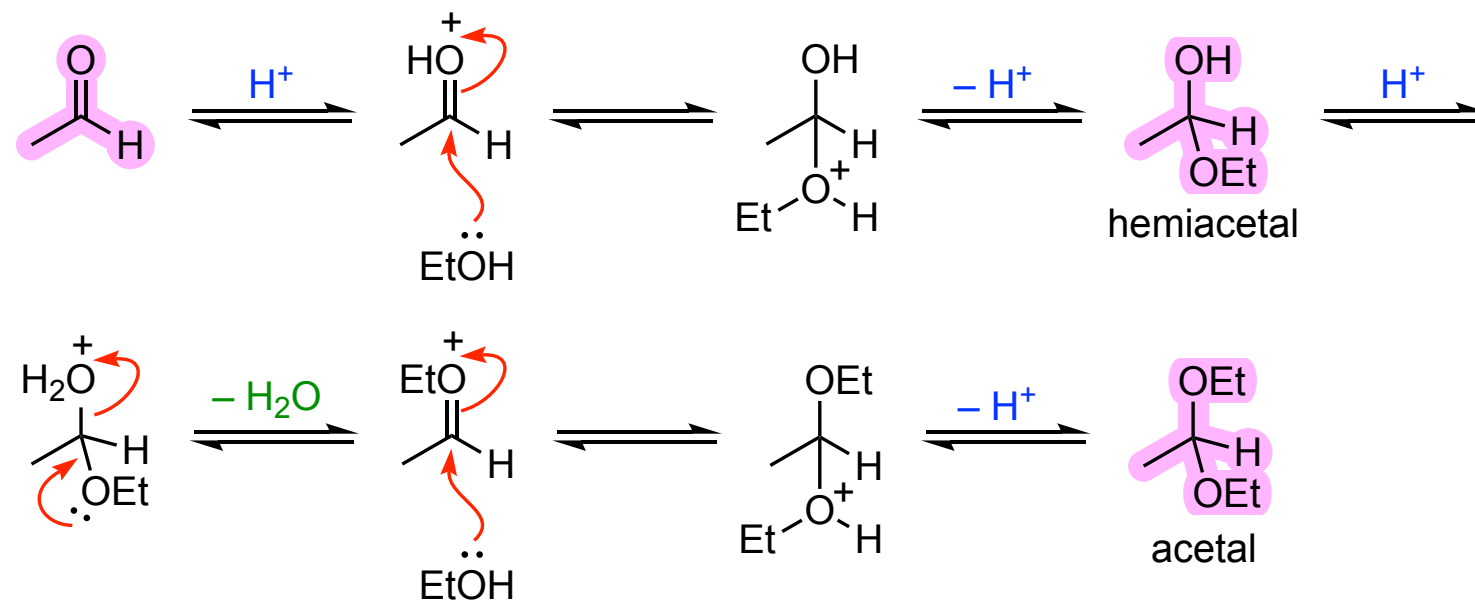
# Reversible 1,2-addition: 'condensation' reactions

Alcohols react similarly

Intramolecular: entropy tips the balance



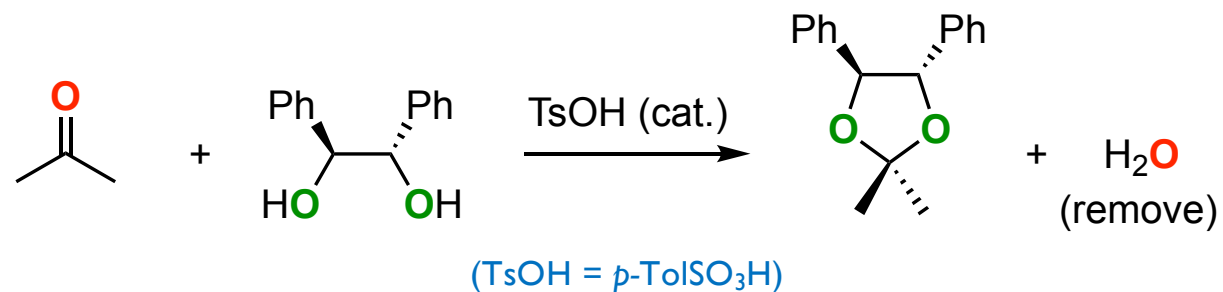
ROH as solvent, acid **catalysis** (rate  $\uparrow$ ), removal of **water** (equilibrium  $\rightarrow$ )



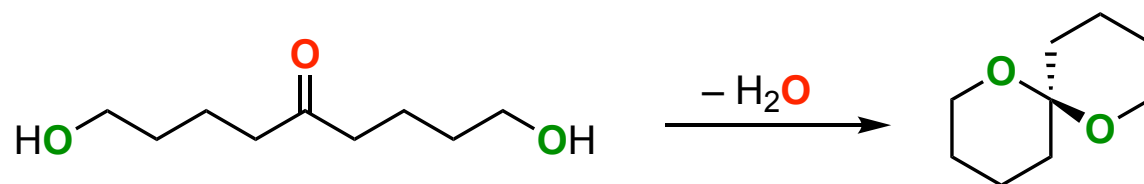
The reverse  
(acetal hydrolysis):  
add water +  $\text{H}^+$

# Reversible 1,2-addition

Diols lead to *cyclic acetals* (protecting group chemistry)



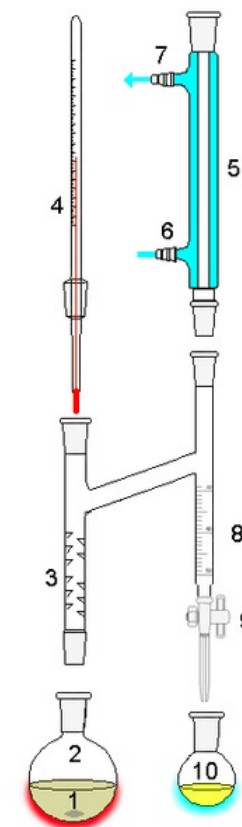
Can be intramolecular: 'spiroacetals', often spontaneous (entropy)



Olive fruit fly pheromone  
(*R*)-enantiomer attracts males  
and *vice versa*

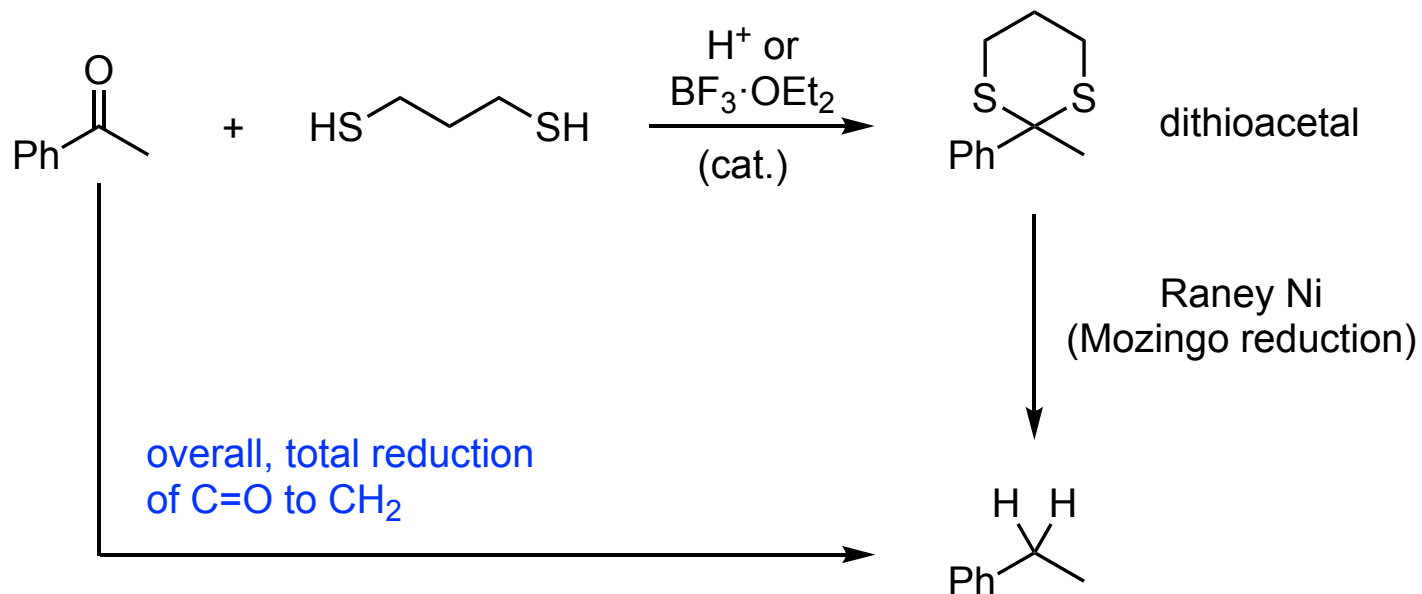


- $\text{MgSO}_4$
- $(\text{EtO})_3\text{CH}$
- Dean–Stark apparatus (toluene azeotrope)

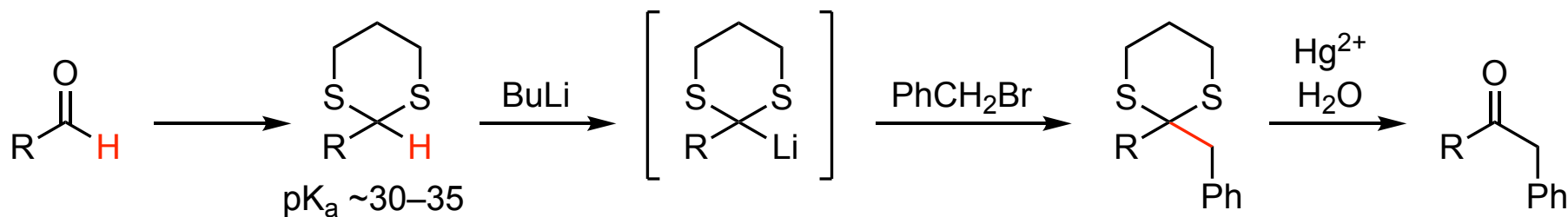


# Reversible 1,2-addition

Thiols react similarly but do not need a dehydrating agent



A second application; acyl anion equivalents (2<sup>nd</sup> year)



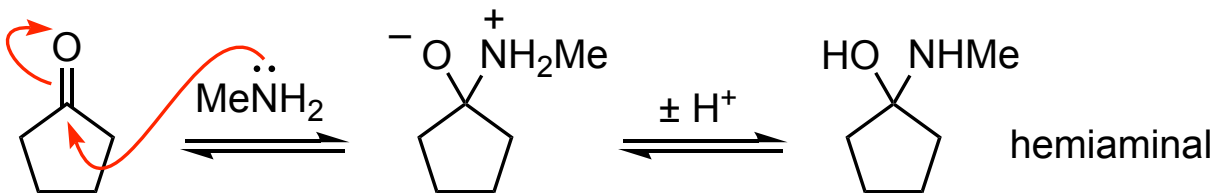
# Reversible 1,2-addition: Nitrogen nucleophiles

Nucleophilicity of nitrogen  $\Rightarrow$  neutral conditions; extra valence  $\Rightarrow$  alternative products

General mechanism applies for  $\sim$ all R-NH<sub>2</sub> nucleophiles; e.g. with **1°-amine  $\rightarrow$  imine**

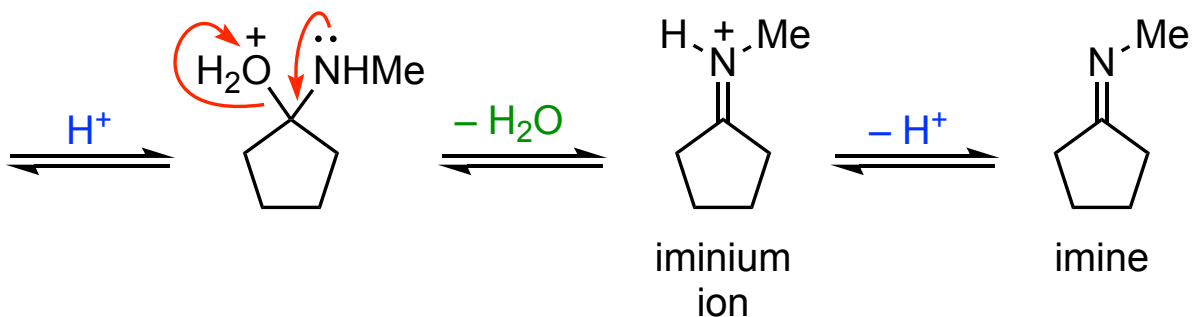
STAGE 1

(uncatalysed 1,2-addition)

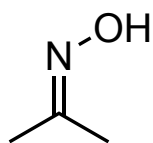


STAGE 2

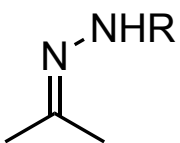
(acid-catalysed loss of water)



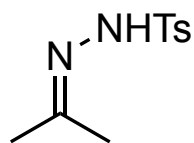
Derivative



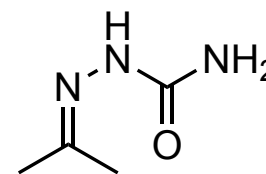
oxime



hydrazone

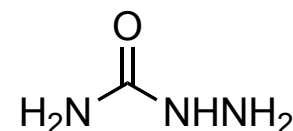


tosylhydrazone



semicarbazone

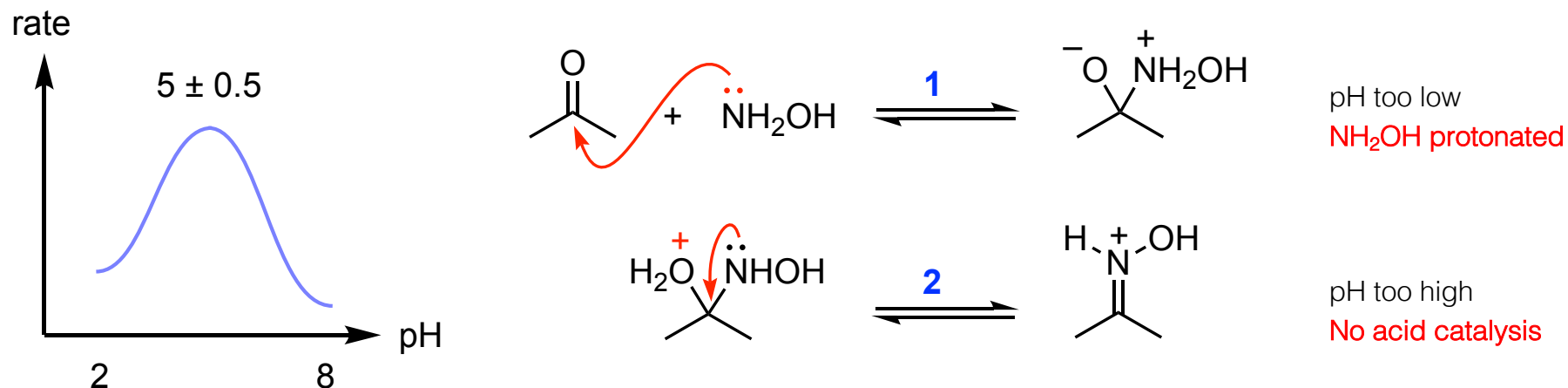
Reagent





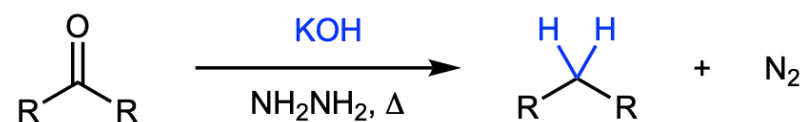
# Reversible 1,2-addition: Nitrogen nucleophiles

Support for the mechanism? pH–rate profile in oxime formation



Final aspect: the Wolff–Kishner reaction

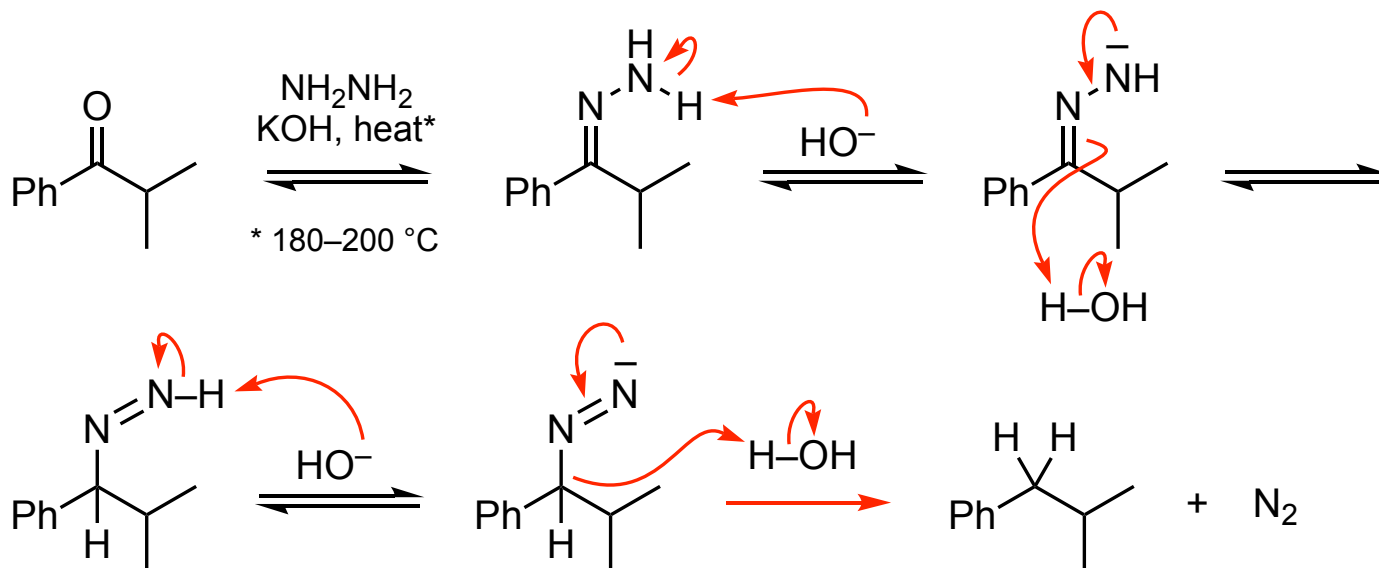
Another way to reduce aldehyde/ketone carbonyl all the way to the alkane



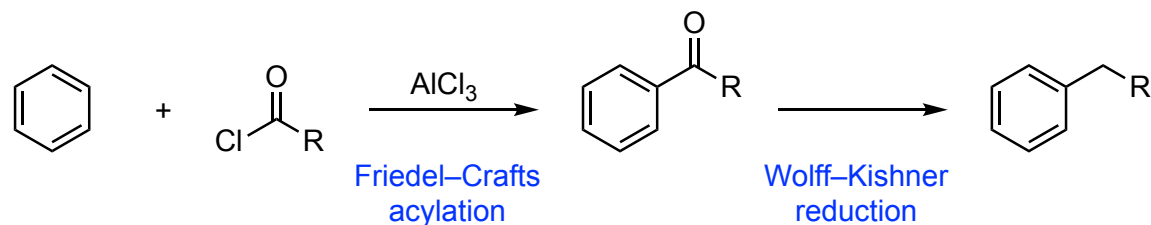
Huang-Minlon modification uses a high-boiling solvent (ethylene glycol) to improve yields

# Reversible 1,2-addition: Nitrogen nucleophiles

Wolff–Kishner mechanism; starts with hydrazone formation (see above); e.g.



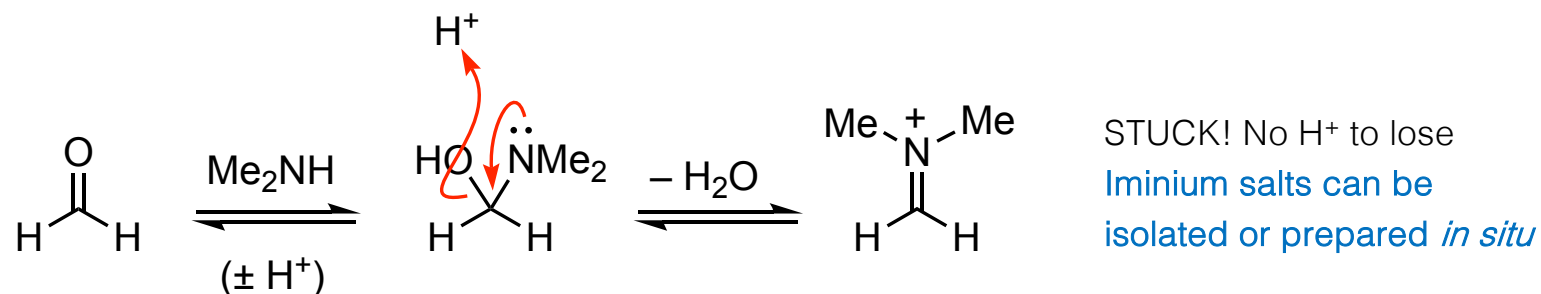
In combination with acylation, this reaction gives a route to efficient overall alkylation of benzene derivatives (separate lecture course)



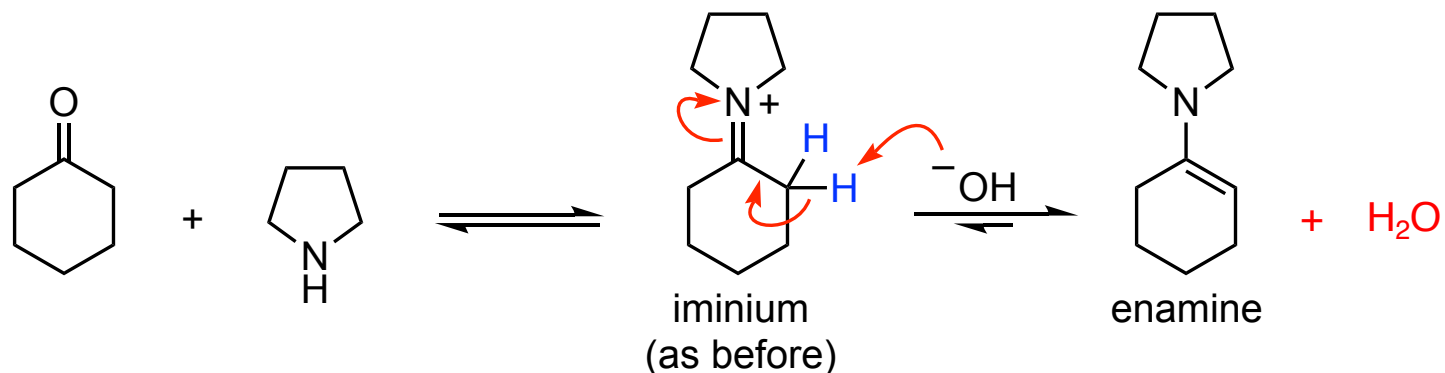
# Reversible 1,2-addition: Nitrogen nucleophiles

Imine formation with **2°-amines**?

(a) First case: the carbonyl component bears no adjacent protons; e.g. PhCHO, HCHO



(b) Second case: the carbonyl component has  $\geq 1$  adjacent proton; e.g.

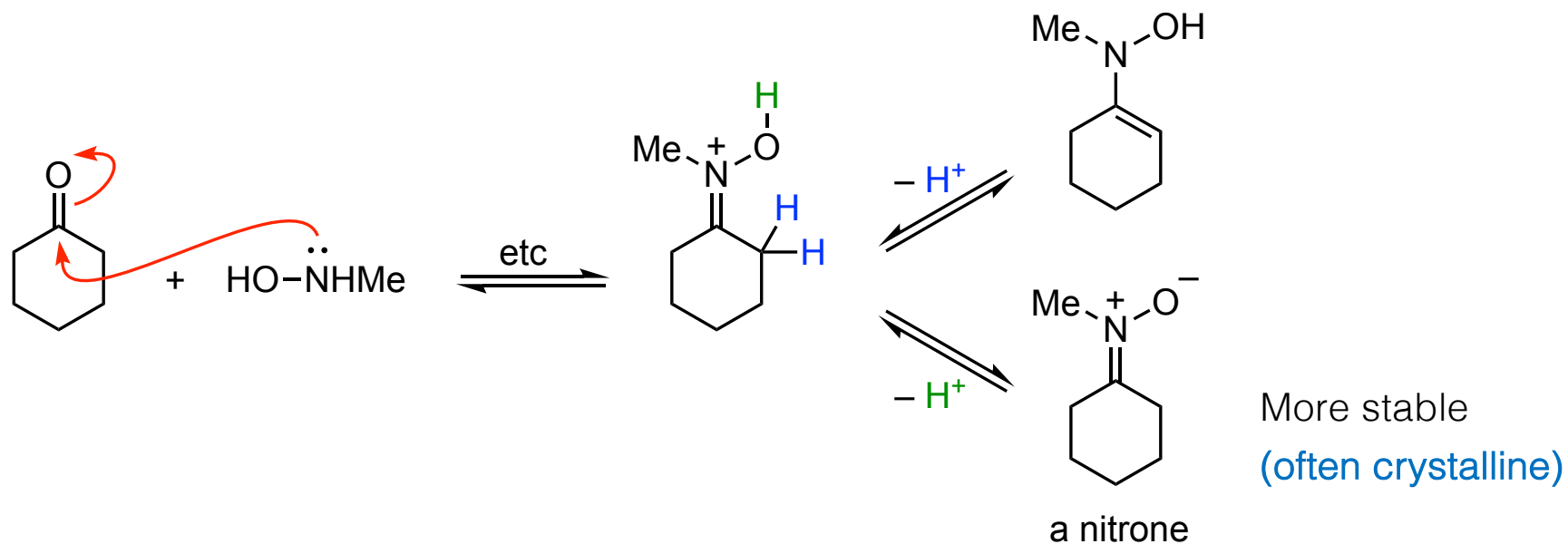


We'll review the chemistry of enamines later...

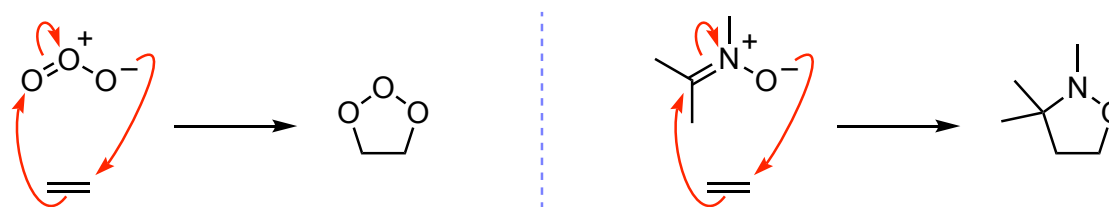
# Reversible 1,2-addition: Nitrogen nucleophiles

Special case: *N*-alkyl hydroxylamine

Reaction proceeds as with  $\text{NH}_2\text{OH}$  up to the iminium but then...



Reactions of nitronium in 3<sup>rd</sup> year; parallels with  $\text{O}_3$  in first step of ozonolysis

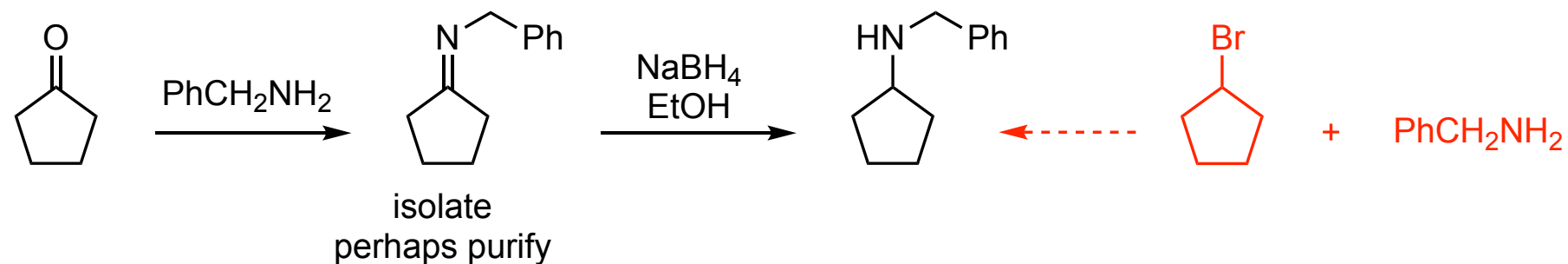


# Reversible 1,2-addition: Nitrogen nucleophiles

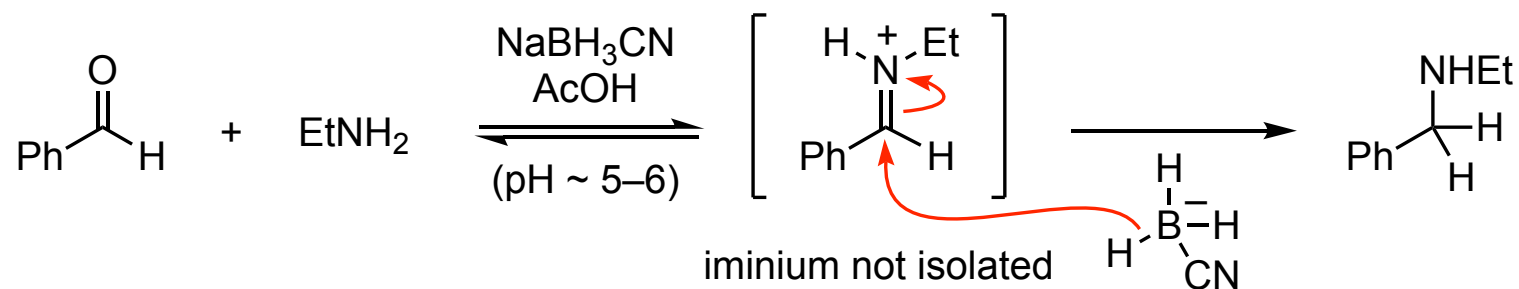
## Iminium ions in synthesis

Reductive amination; imine formation then reduction; better than  $S_N2$ -type alkylation (why?)

(a) Stepwise



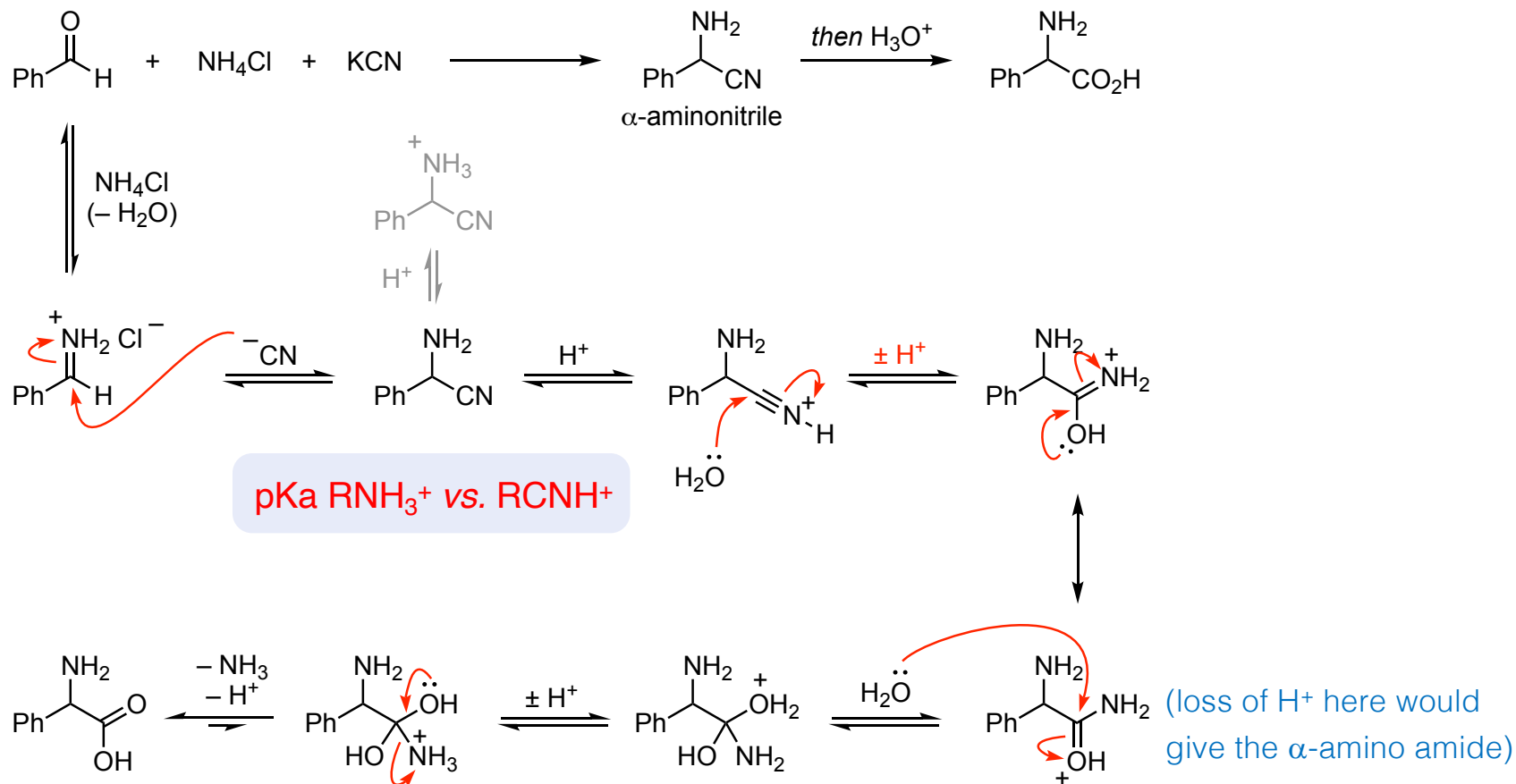
(b) 'One-pot'; reduction of the iminium ion *in situ*;  $\text{NaBH}_3\text{CN}$  as a milder reducing agent



# Reversible 1,2-addition: Nitrogen nucleophiles

Iminium ions in synthesis: Strecker synthesis of  $\alpha$ -amino acids (see also Trinity Term course)

Reaction comprises: (1) iminium formation, (2) addition of cyanide, (3) nitrile hydrolysis



Mannich reaction later...



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First Year Organic Chemistry

THE CHEMISTRY OF THE CARBONYL GROUP  
CORE CARBONYL CHEMISTRY (2)

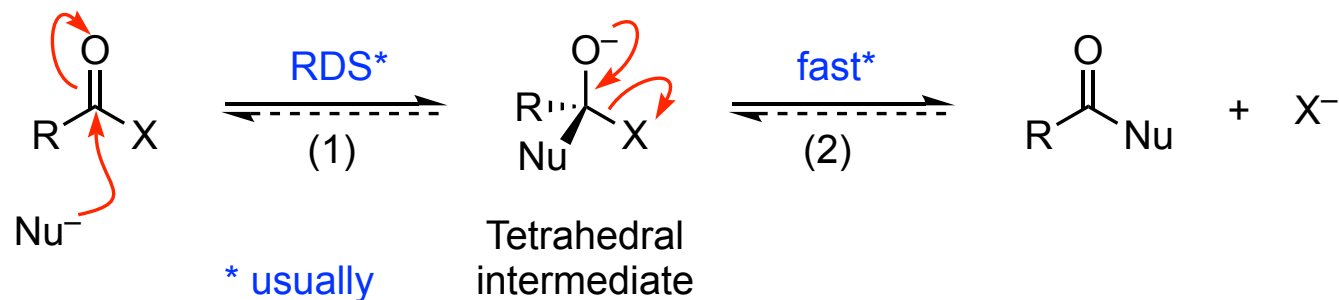
Professor Jeremy Robertson

*8 lectures, HT, 2023*

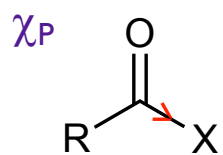
# Carboxylic acid derivatives

Moving up an oxidation level; replace H or R with a heteroatom (O, N, halogen etc)

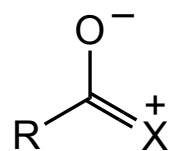
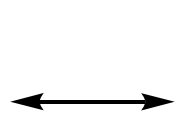
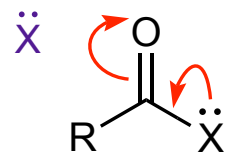
Substitution by (1) addition then (2) elimination



Step 1 not reversible when  $\text{Nu}^- = \text{carbanion or H}^-$

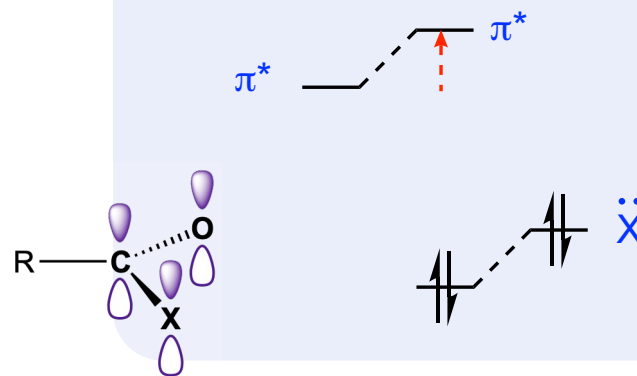


Inductive effect:  
increase  $\delta^+$ , lower  $\pi^*$   
 $\Rightarrow$  faster reaction



Conjugation effect:  
reduce  $\delta^+$ , raise  $\pi^*$   
 $\Rightarrow$  slower reaction

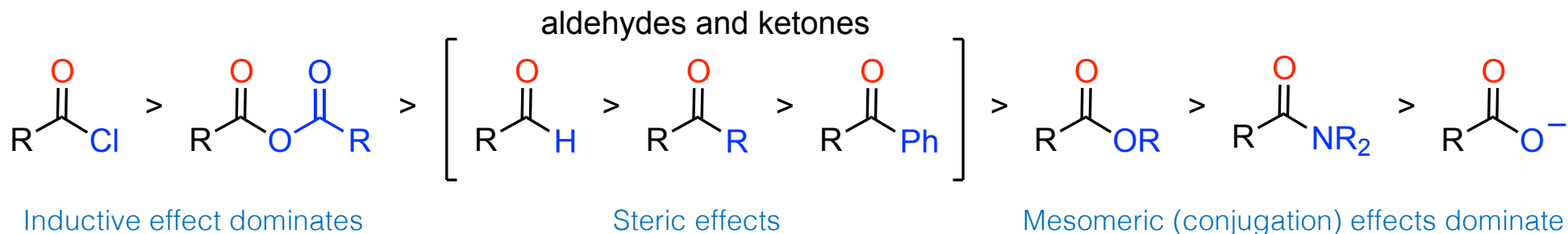
Lone pair/ $\pi^*$  mixing *stabilises* the molecule,  
*raises* the energy of the  $\pi^*$ ,  
*increases* HOMO ( $\text{Nu}^-$ ) – LUMO ( $\pi^*$ ) gap





# Carboxylic acid derivatives

Inductive and conjugation effects combine to give a reactivity (electrophilicity) order



Step 2 rarely reversible in synthetically meaningful reactions

rate depends on leaving group ability of  $\text{X}^-$ ; correlates with  $\text{pK}_a$  of  $\text{XH}$

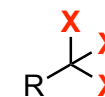
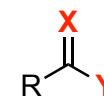
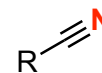
X	CH <sub>3</sub>	H	NH <sub>2</sub>	OEt	OH	CN	OAc	Cl	Br
pK <sub>a</sub> (XH)	50	36	33	16	15.5	9	4.5	-8	-9
	Poor leaving groups (almost) never ejected			Increasingly good leaving groups rapidly ejected from the T <sub>d</sub> intermediate					

**Aside:** IR spectroscopy is important for identifying C=O groups; probes electronic features, see 2<sup>nd</sup> year

# Carboxylic acid derivatives

## Preparation of carboxylic acids

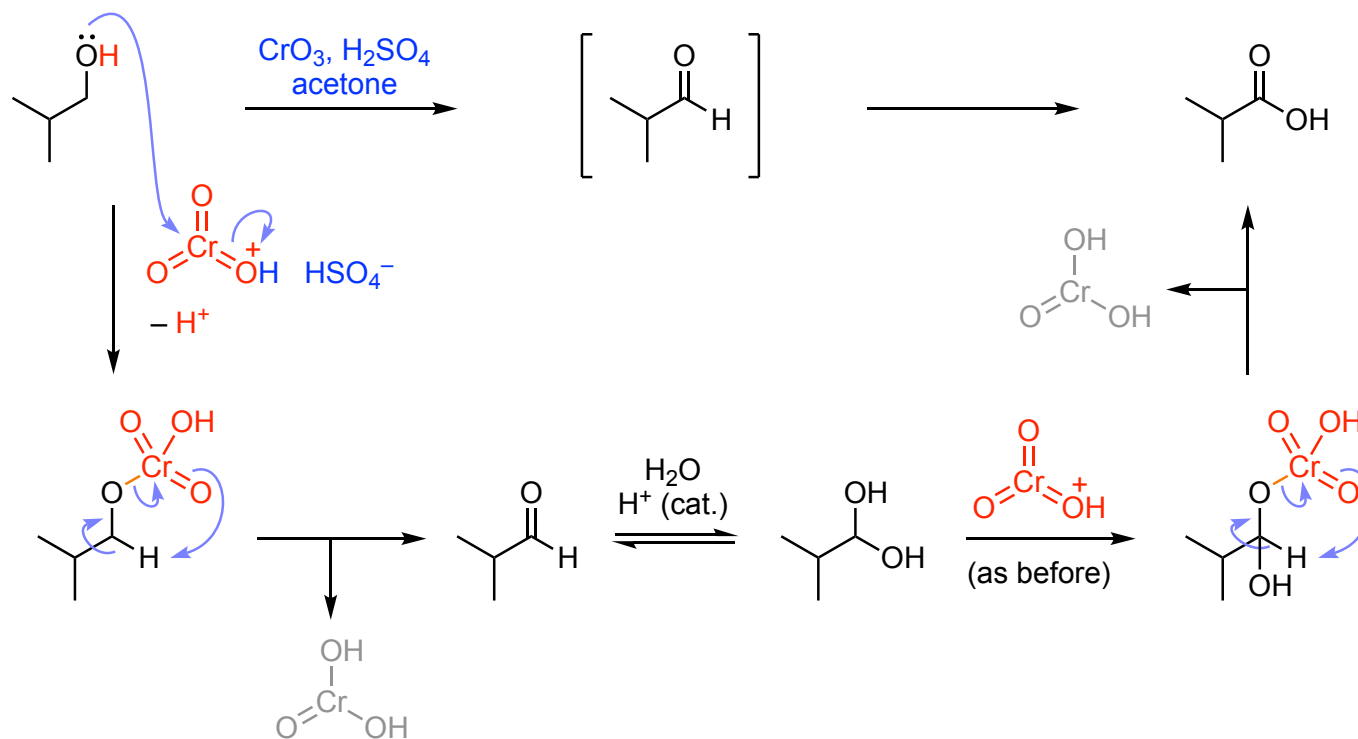
(1) Hydrolysis of molecules at the same oxidation level;  
e.g. final step of Strecker amino acid synthesis (above)



X = N, O  
Y = N, O, Hal

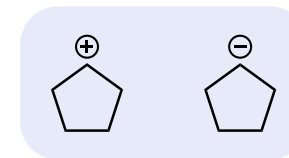
X = N, O, Hal

(2) Oxidation of 1°-alcohols via aldehydes; Jones' reagent



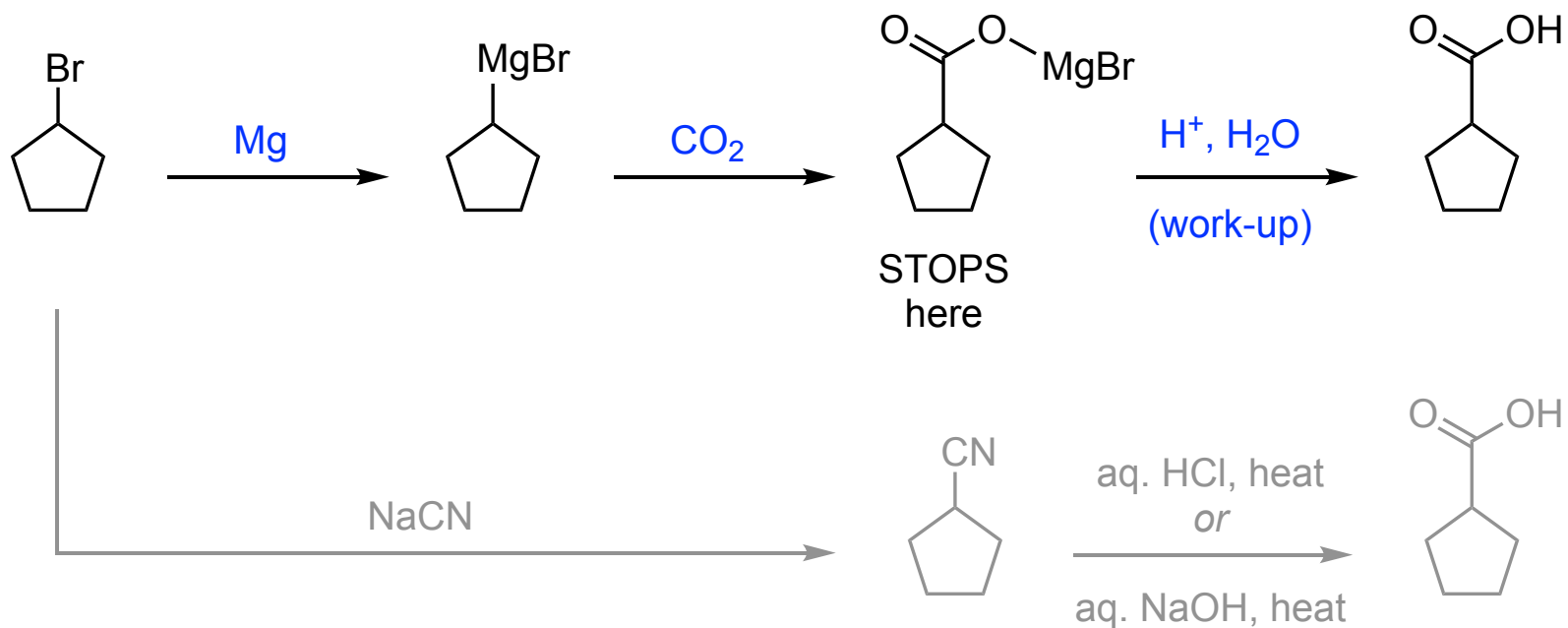
**Orange/red Cr(VI)** → Cr(IV);  
the Cr(IV) species react with  
Cr(VI) to give Cr(V) which  
can also oxidise the  
substrate giving **green Cr(III)**

# Carboxylic acid derivatives



## Preparation of carboxylic acids

(3) Carboxylation of Grignard reagents [Q. organolithium reagents?]

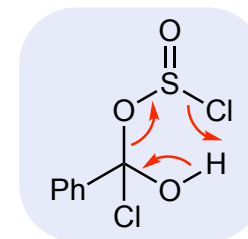
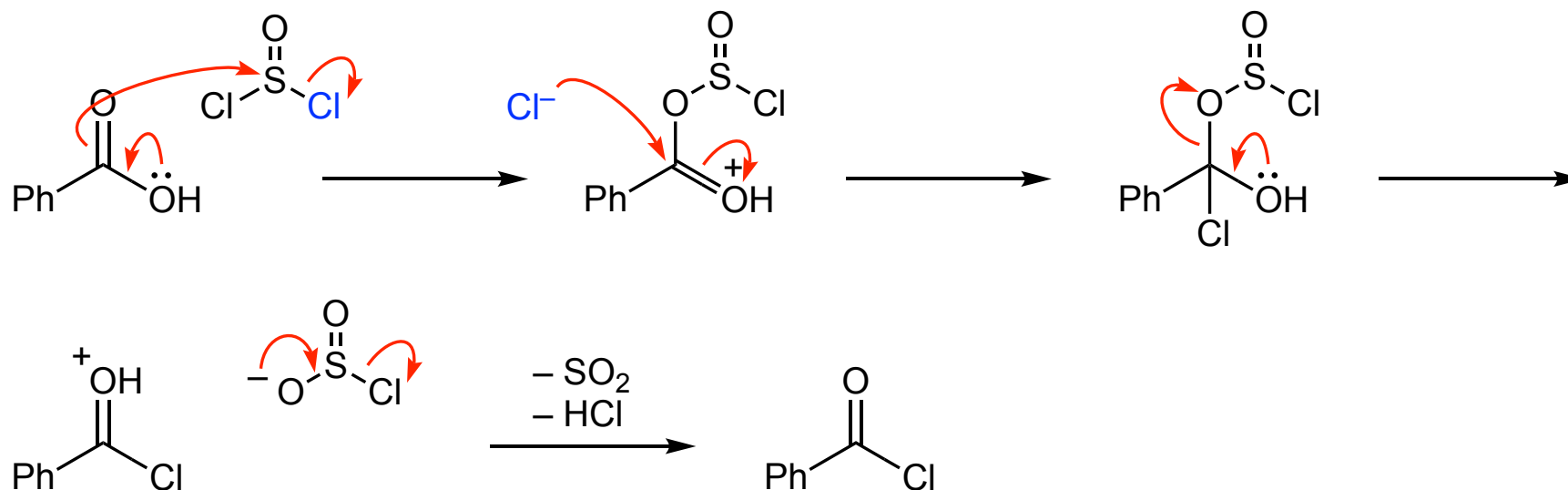


The carboxylic acid is a good starting point for preparing all the other derivatives, either directly or via the [acid chloride](#)

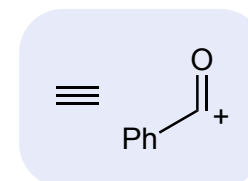
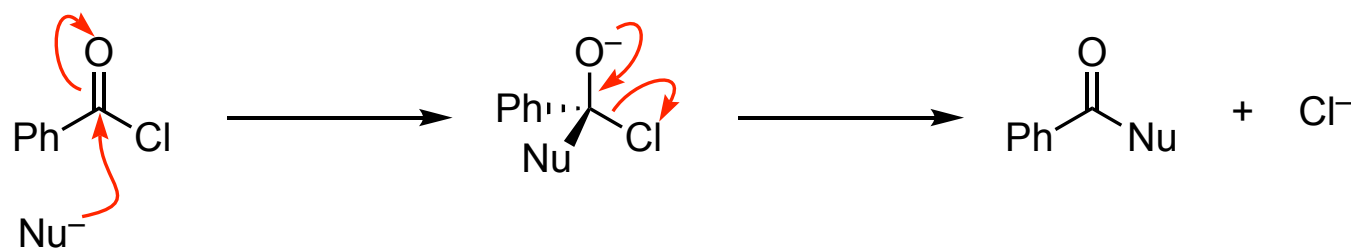
# Carboxylic acid derivatives

Preparation of carboxylic acid chlorides (many methods)

Thionyl chloride,  $\text{SOCl}_2$

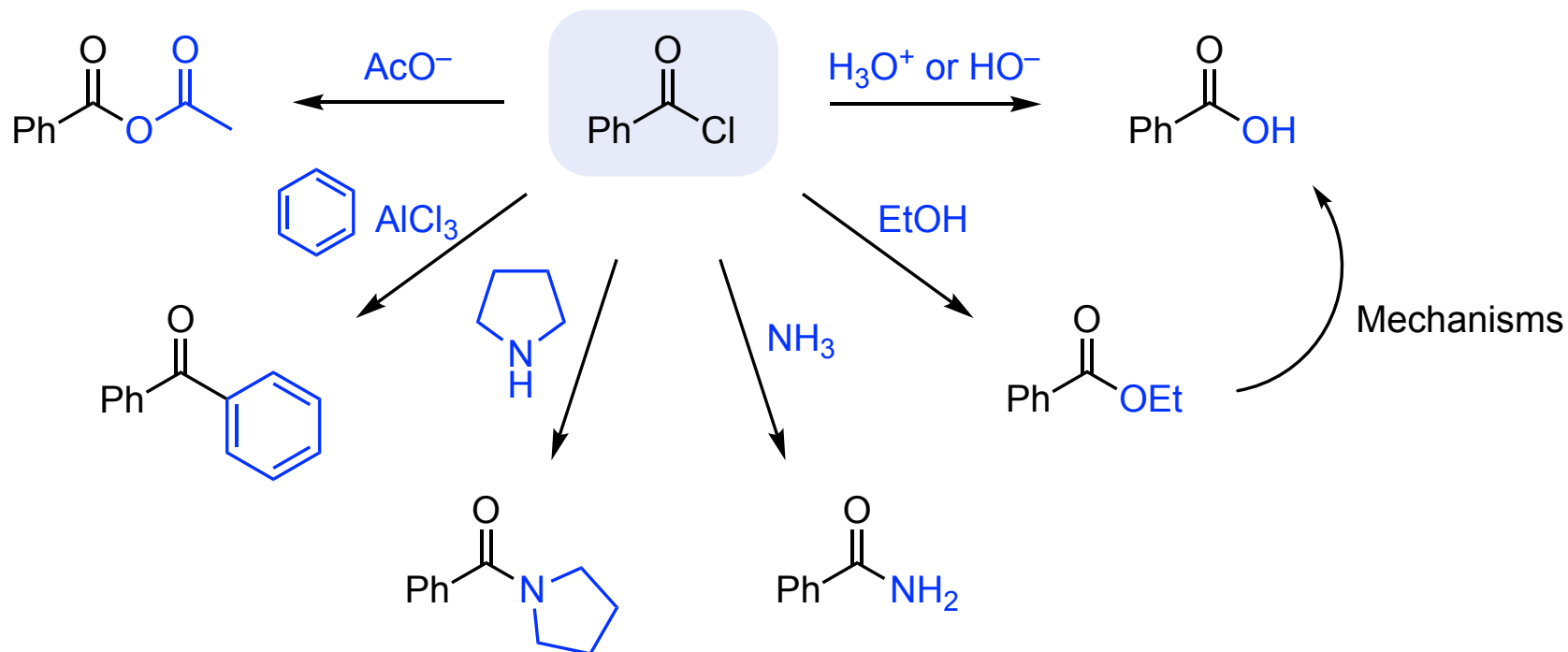


Acid chlorides are *acylating agents*

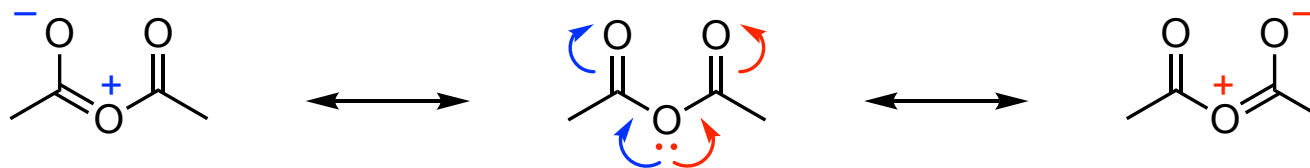


# Carboxylic acid derivatives

Reactions of carboxylic acid chlorides – follow the general addition/elimination mechanism



Anhydrides behave similarly



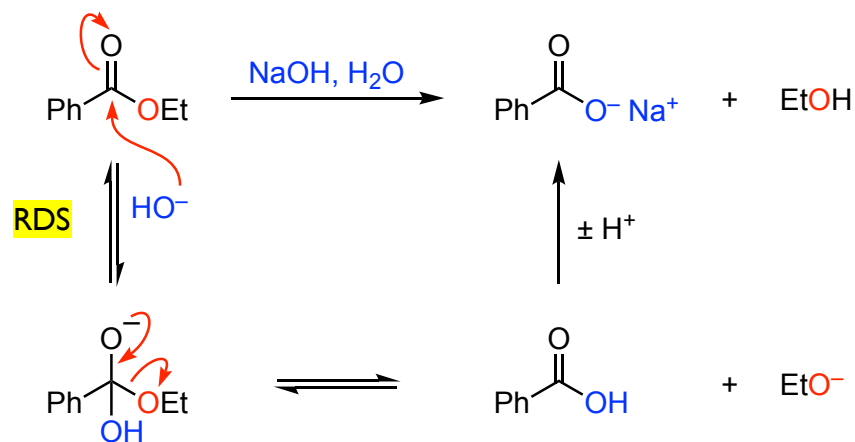
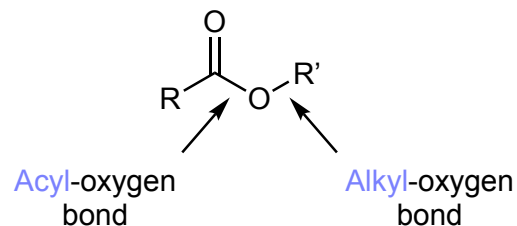
# Carboxylic acid derivatives

Mechanisms of ester hydrolysis: Ingold classification, 8 possibilities, see March [labelling studies]

Conditions: Acidic or Basic?

Which bond is cleaved: Acyl or Alkyl?

RDS: unimolecular (1) or bimolecular (2)?

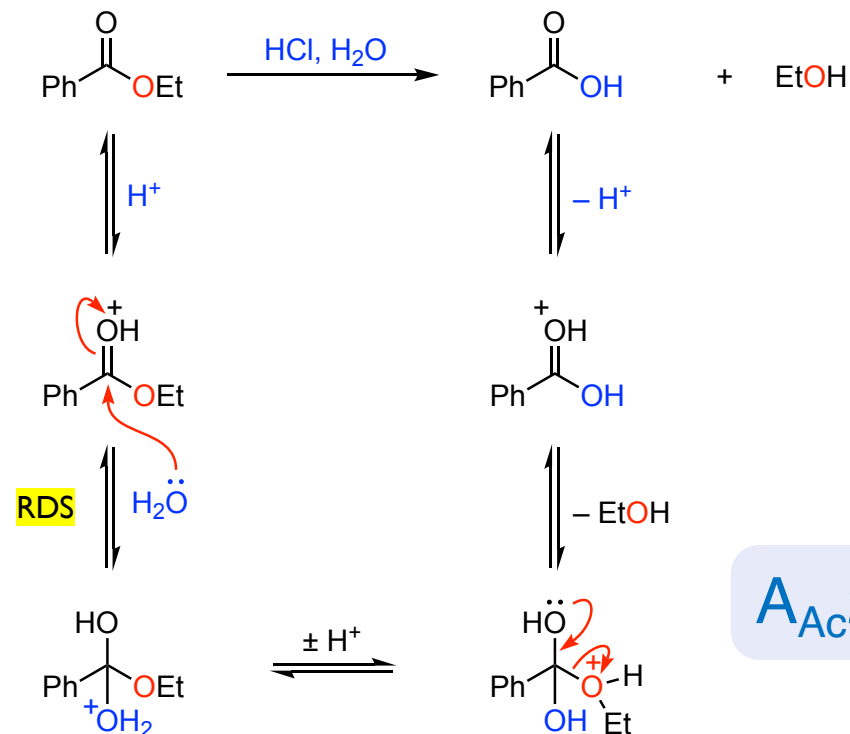


Basic

Acyl bond cleaved

RDS: bimolecular (2)

**B<sub>Ac2</sub>**

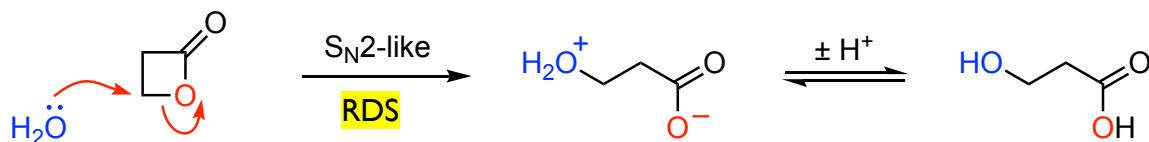


**A<sub>Ac2</sub>**

# Carboxylic acid derivatives

$B_{AC}2$  and  $A_{AC}2$  are the *standard mechanisms* for 'normal' esters

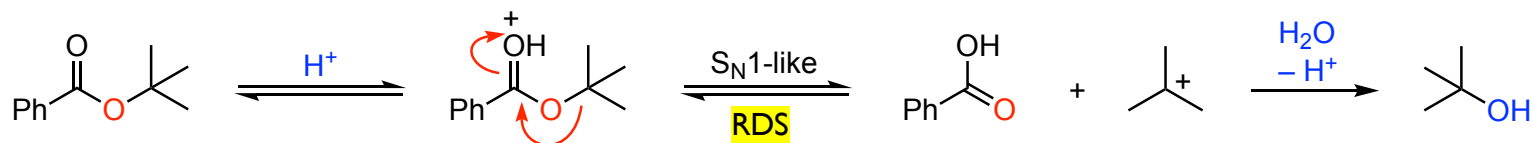
Special cases: small-ring lactones (3- or 4-membered cyclic esters) under **neutral** conditions ( $B_{AC}2$  using aq. NaOH)



$B_{AL}2$

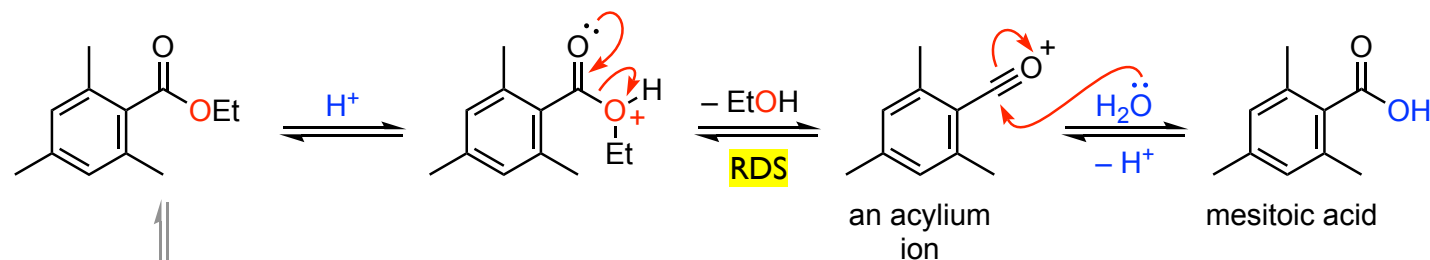
Also for  $RSO_3R'$

*tert*-Butyl esters under **acidic** conditions

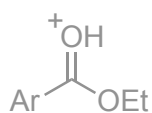


$A_{AL}1$

Mesityl esters under **acidic** conditions



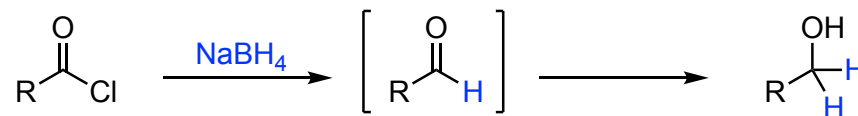
$A_{AC}1$



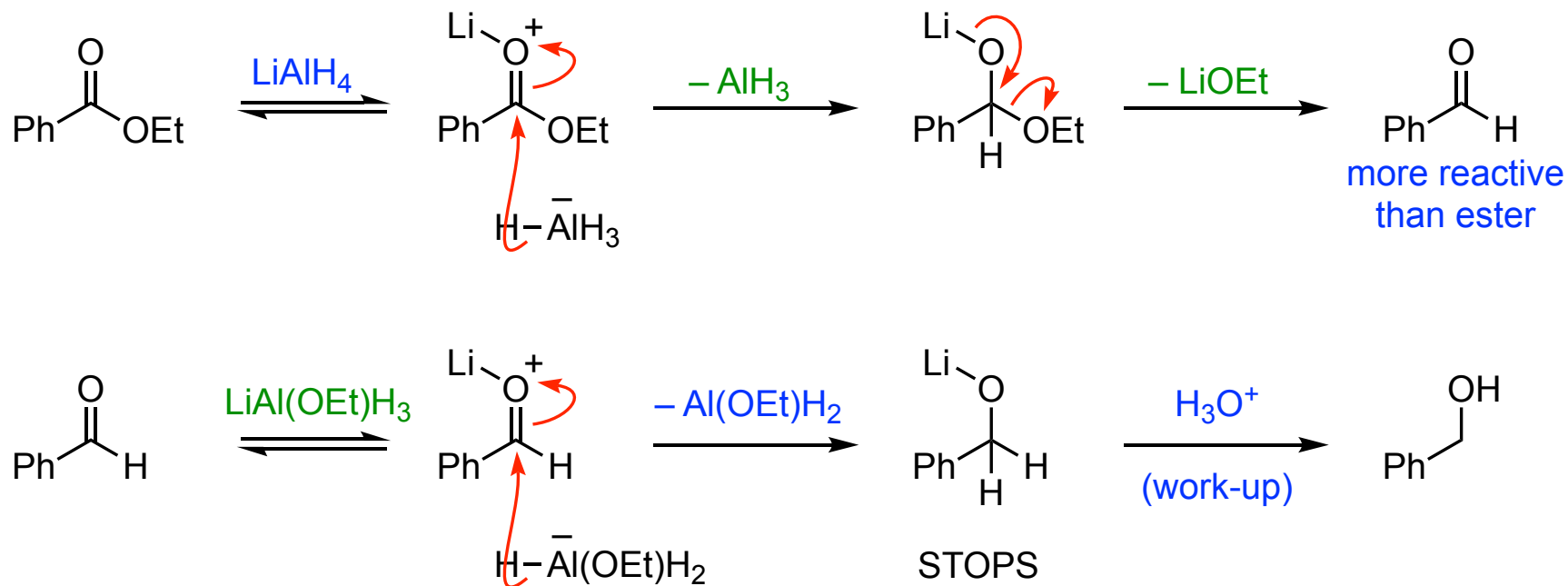
# Carboxylic acid derivatives

Reactions with hydride donors and organometallics: irreversible reactions

(1)  $\text{NaBH}_4$ : only acid chlorides & anhydrides are sufficiently reactive under normal conditions



(2)  $\text{LiAlH}_4$ : powerful reducing agent, reduces all carboxylic acid derivatives

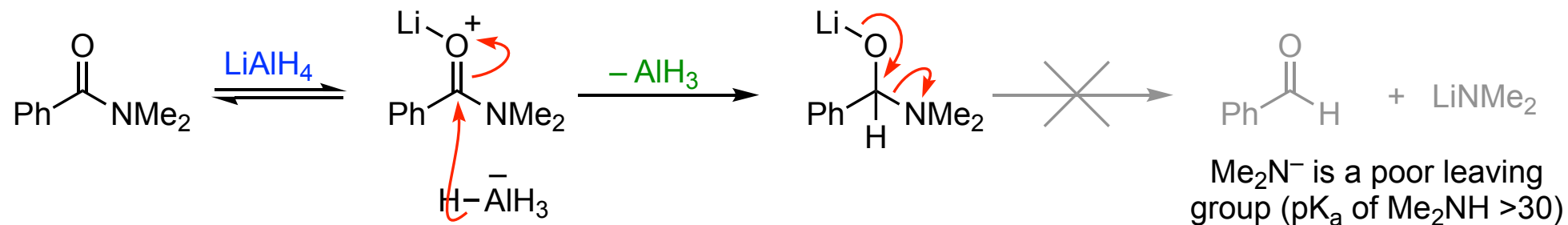


That is: ester  $\rightarrow$  1°-alcohol

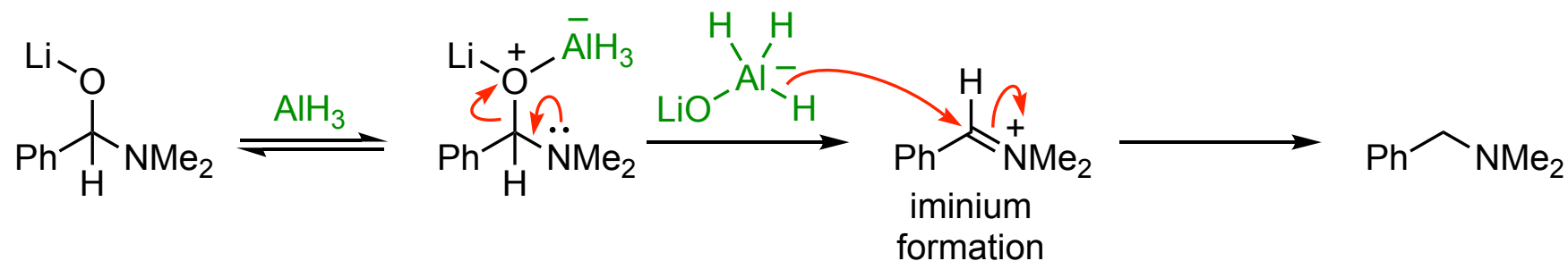


# Carboxylic acid derivatives

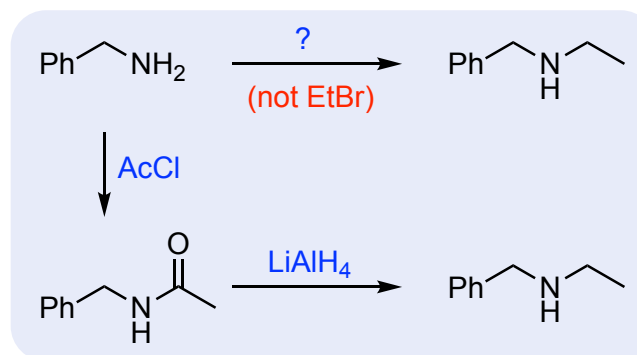
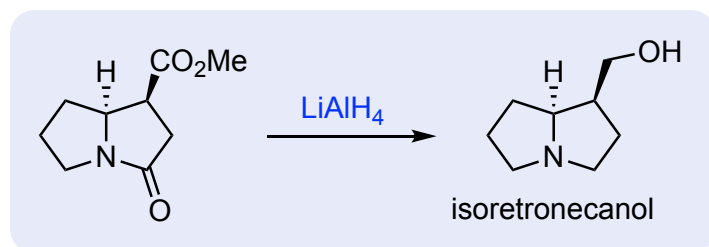
(3) Amides take an unexpected course



Instead:



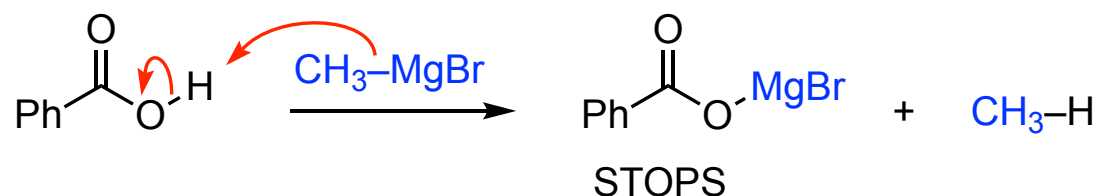
That is: **amide** → **amine**



# Carboxylic acid derivatives

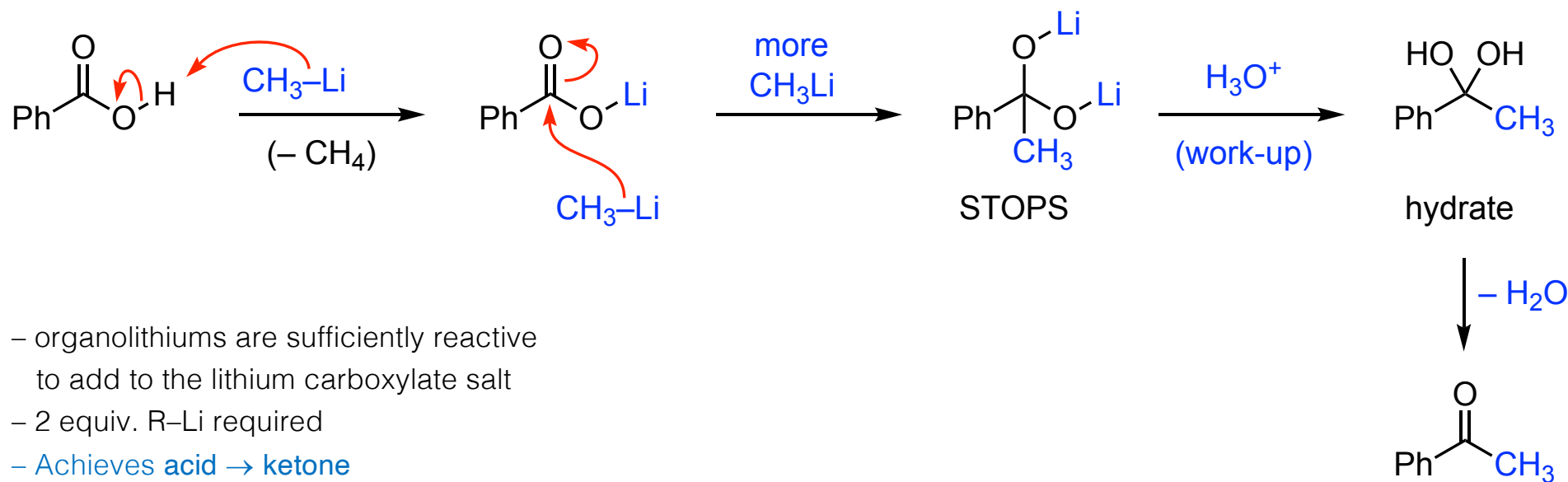
## Reactions with organometallic reagents

Carboxylic acids + Grignard reagents (*cf.* slide #35)



- Grignards are strongly basic
- Grignards are insufficiently reactive to add to the magnesium carboxylate salt
- Unproductive reaction

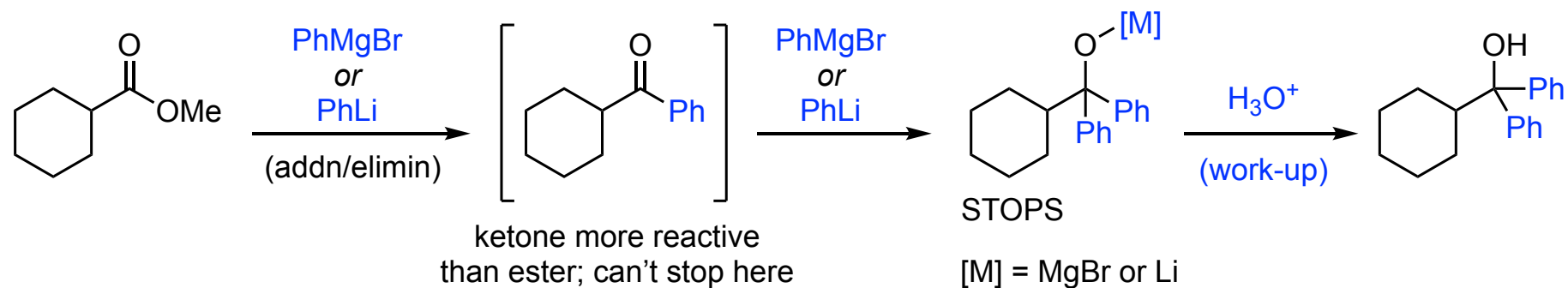
Carboxylic acids + organolithium reagents



- organolithiums are sufficiently reactive to add to the lithium carboxylate salt
- 2 equiv. R-Li required
- Achieves acid  $\rightarrow$  ketone

# Carboxylic acid derivatives

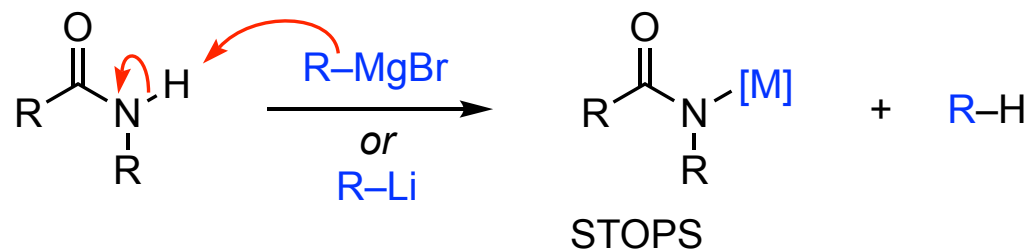
Esters + RMgX or RLi



That is: ester  $\rightarrow$  3°-alcohol

What about **amides** + RMgX or RLi?

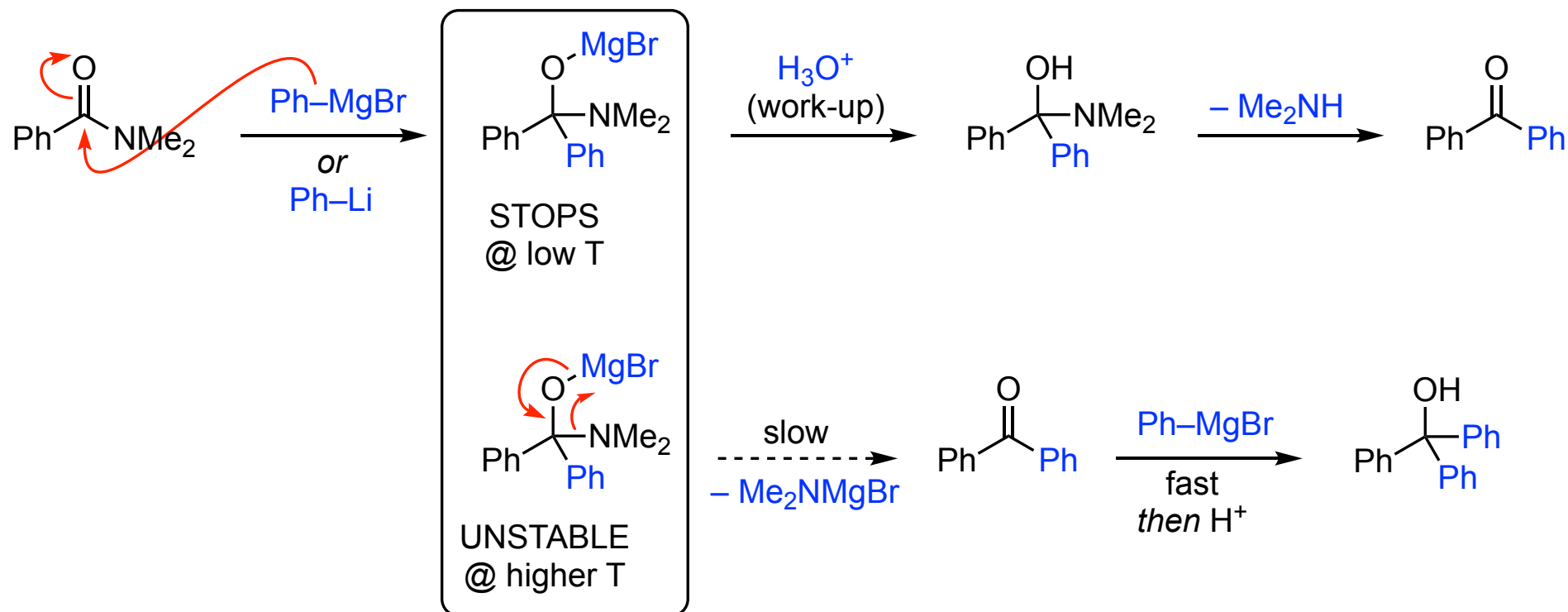
Unproductive when nitrogen is NH<sub>2</sub> or NHR



- Amide pKa  $\sim$  17 so deprotonated by R-[M]
- Neither Grignards nor organolithiums can react with the amide salt

# Carboxylic acid derivatives

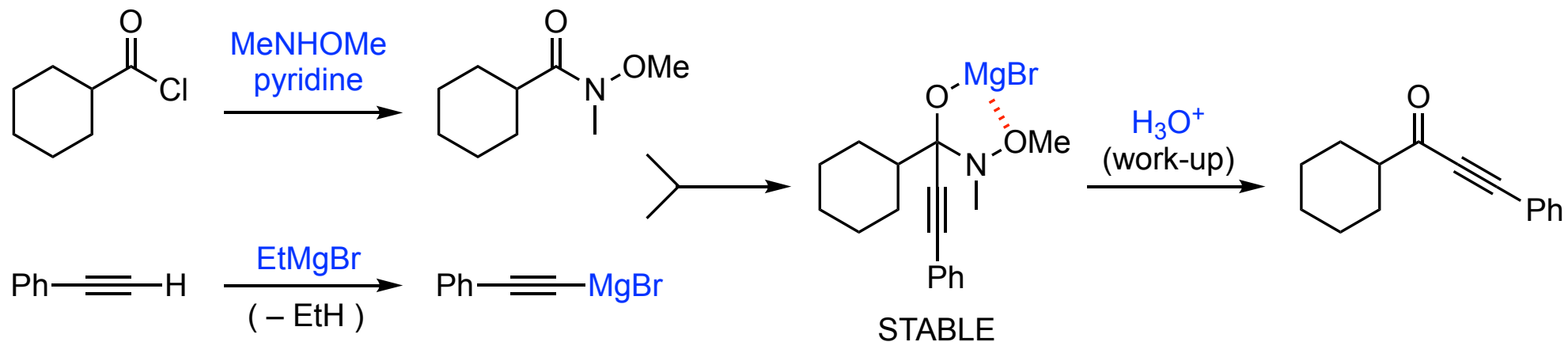
3°-Amides + RMgX or RLi can achieve **amide** → **ketone** although not 100% reliable



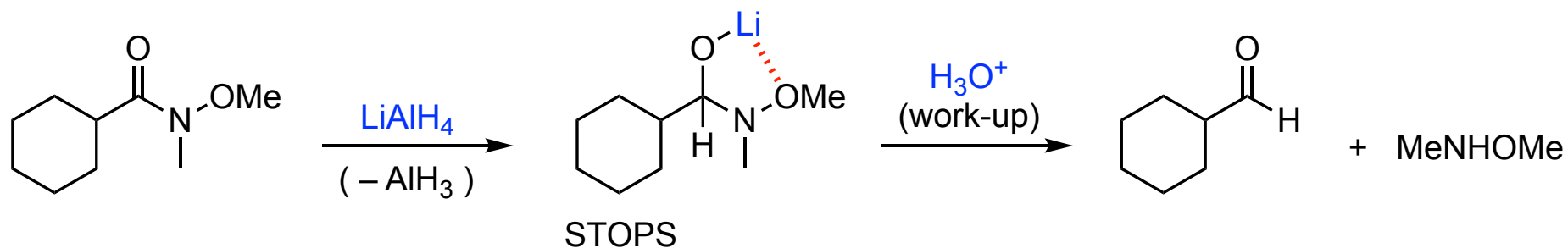
Weinreb amides are more predictable...

# Carboxylic acid derivatives

## Formation and reaction of Weinreb amides



Weinreb amides can also be used to prepare aldehydes (*cf.*  $\text{RCONMe}_2 \rightarrow \text{RCH}_2\text{NMe}_2$ )

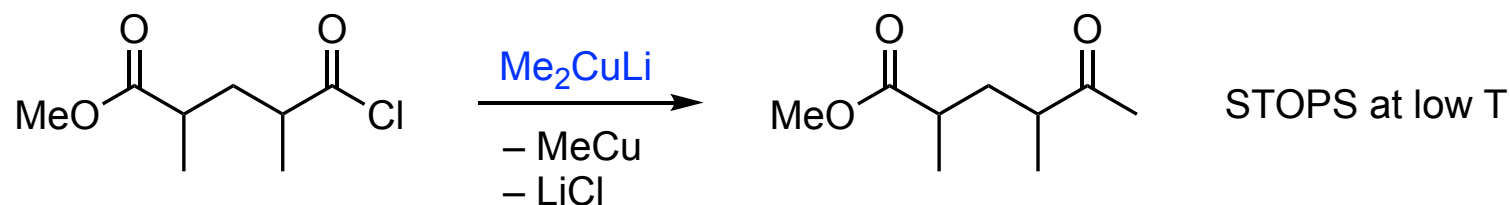
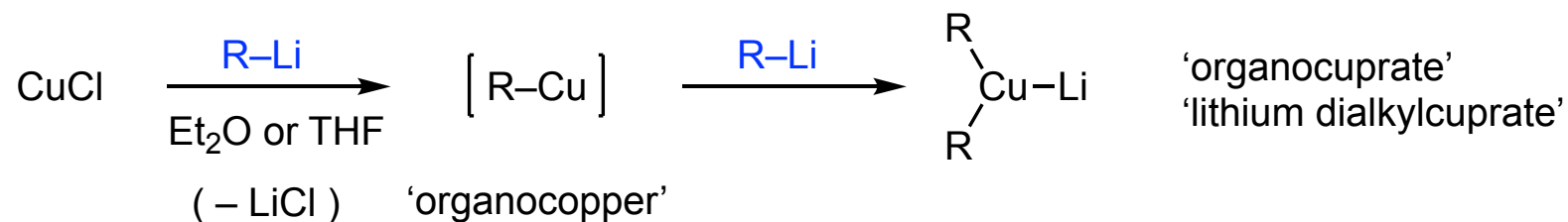


# Carboxylic acid derivatives

Three further methods to prepare ketones from carboxyl derivatives

(1) From carboxylic acids with 2 equiv. of an organolithium reagent, see p42

(2) From carboxylic acid chlorides + **cuprate** reagents (*mechanism...*)

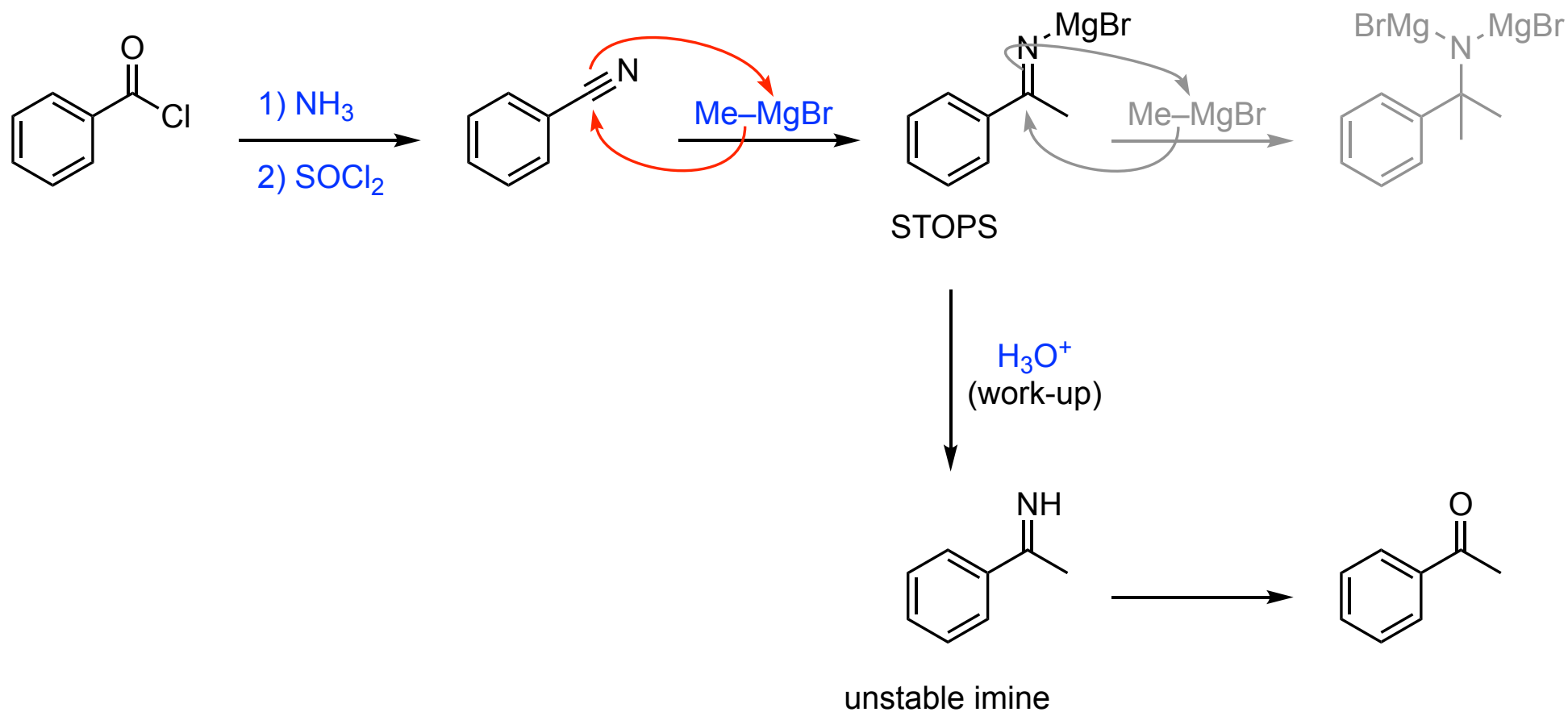


Cuprate reagents usually react slowly with ketones when  $T < -30\text{ }^\circ\text{C}$

# Carboxylic acid derivatives

## (3) Nitriles + Grignard (or organolithium) reagents

Nitriles are at the same oxidation level as carboxylic acids (and can be made from them)





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First Year Organic Chemistry

THE CHEMISTRY OF THE CARBONYL GROUP  
CORE CARBONYL CHEMISTRY (3)

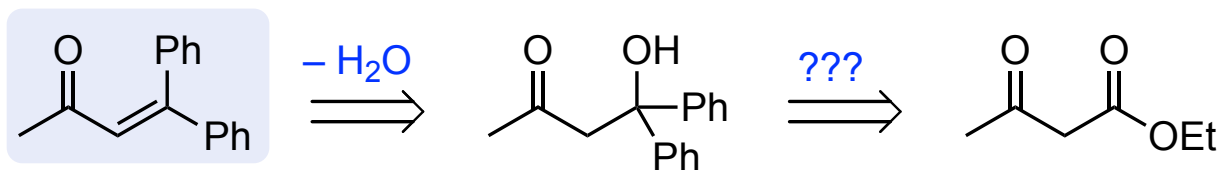
Professor Jeremy Robertson

*8 lectures, HT, 2023*



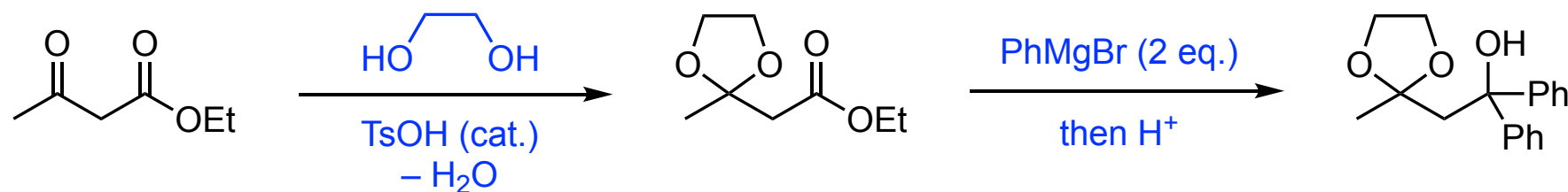
# Addendum: protecting groups (acetals)

Teaching lab (S213) – synthesis of an enone ( $\alpha,\beta$ -unsaturated ketone)

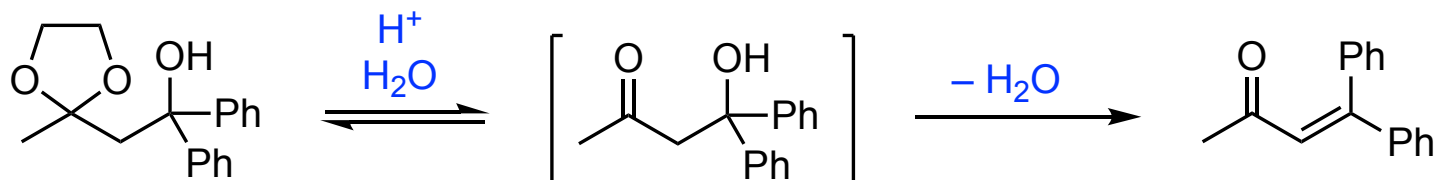


Organometallic addition to an ester in the presence of a (more reactive) ketone?

Protect the ketone first

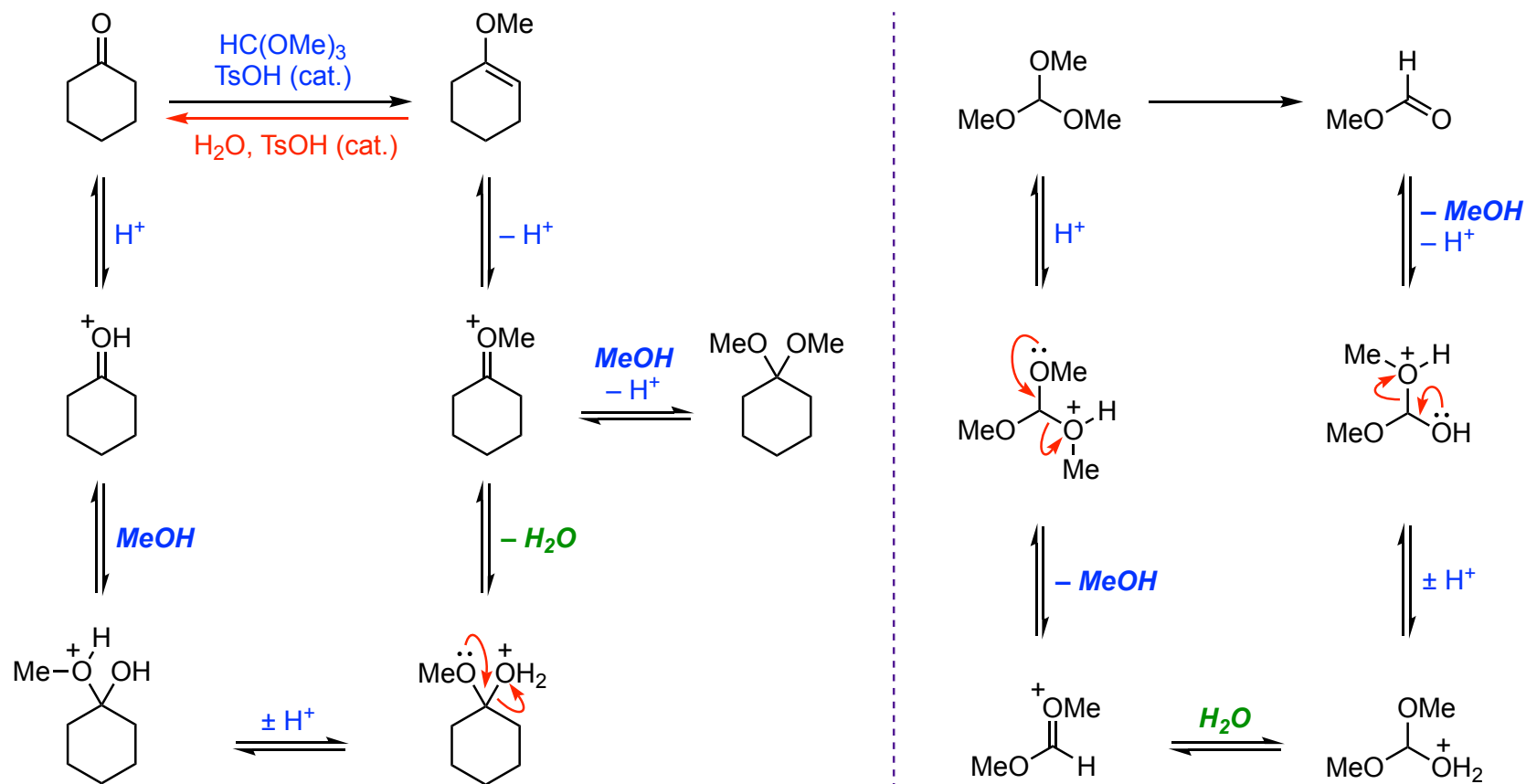


Then deprotect the acetal; elimination takes place under the reaction conditions



# Addendum: protecting groups (enol ethers)

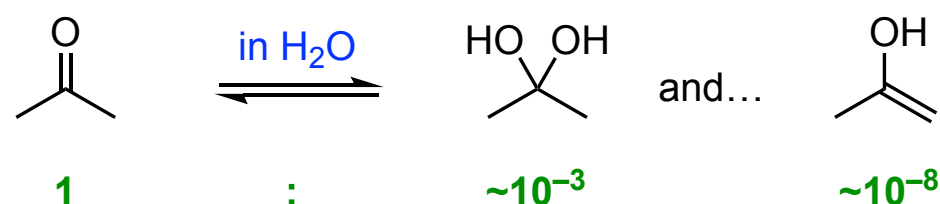
Enol ethers, like acetals, may be considered as a protected or latent form of a carbonyl group



Carbonyl / enol ether / acetal 'equivalence'; reaction conditions  $\Rightarrow$  major component

# Enolisation and its consequences

Acetone in aqueous solution

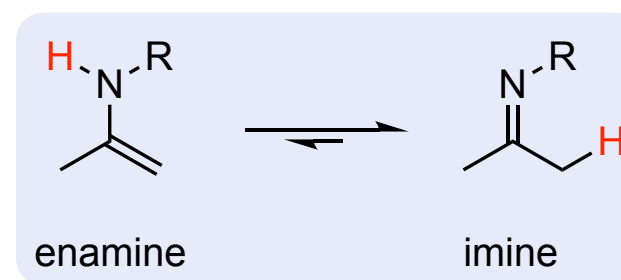
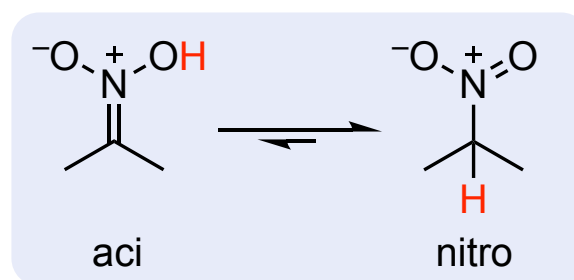
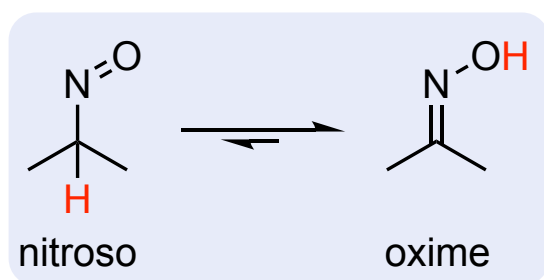


## Tautomers

- Constitutional isomers
- Related by a proton transfer...
- and a switch in X=Y position to an adjacent site

Called **keto-enol tautomerism**

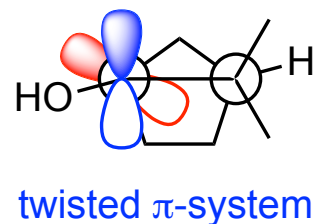
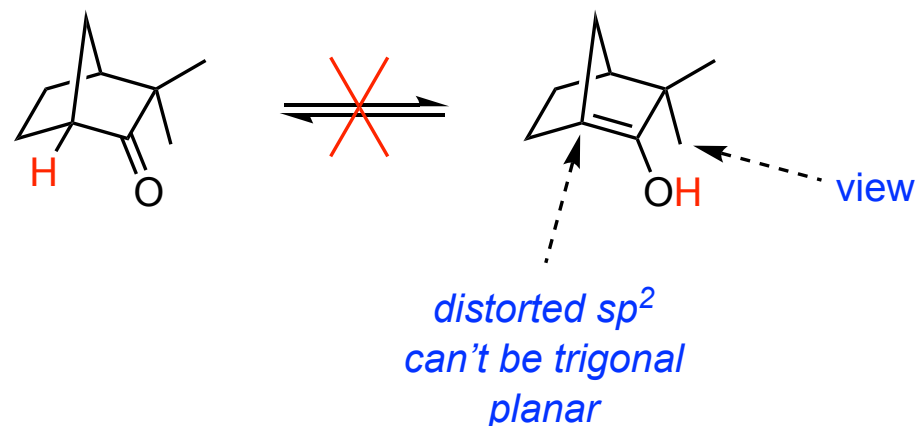
Simple RCHO, R<sub>2</sub>CO contain  $\sim 10^{-8}$ – $10^{-4}$  of enol form; must possess  $\geq 1$  adjacent ( $\alpha$ -) proton



Also ring-chain tautomerism (e.g. lactols) and valence tautomerism (e.g. benzene oxide)

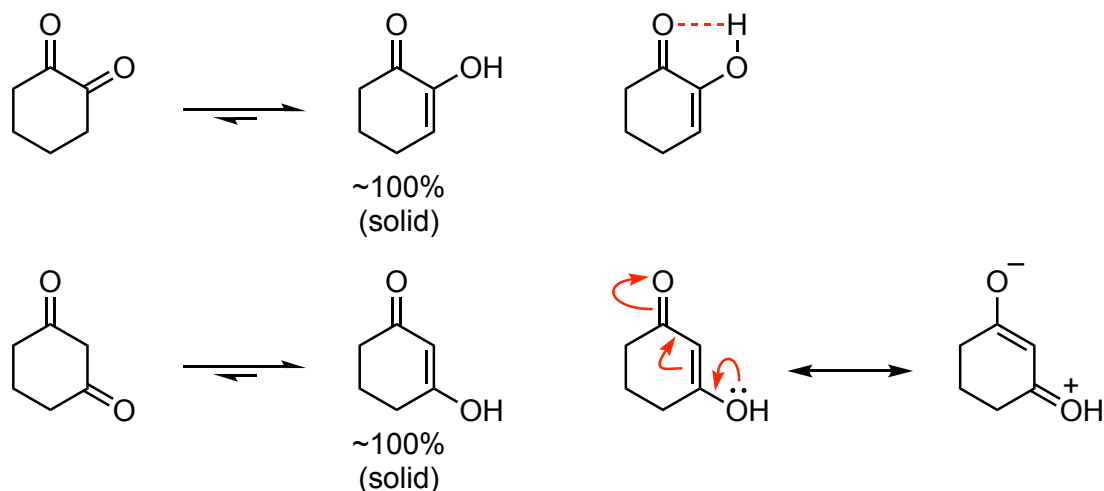
# Enolisation and its consequences

Some compounds with  $\alpha$ -protons cannot form enols

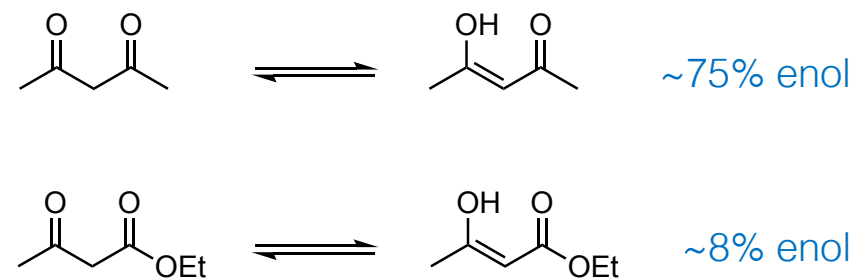


**Bredt's rule:** no bridgehead  
C=C in bridged rings  
(OK if ring  $\geq 8$  members)

In some, the enol form may be preferred  
(**H-bonding, delocalisation**)



Or the enol form may be significant

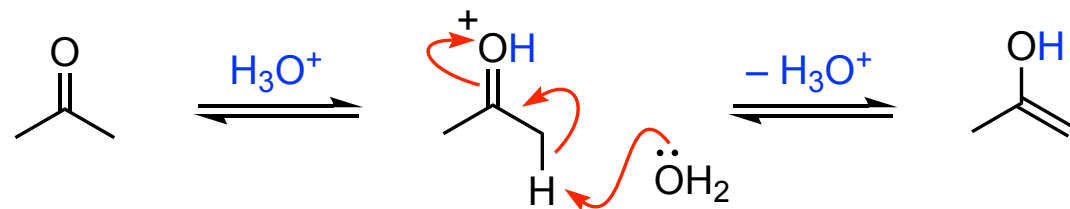


*Solvent-dependent*

# Enolisation and its consequences

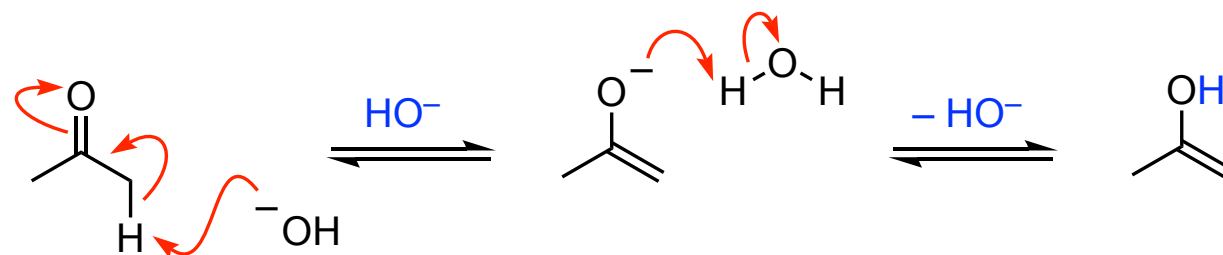
Enolisation can be **acid**- or **base**-catalysed

Acid



O-Protonation speeds up proton removal by water

Base

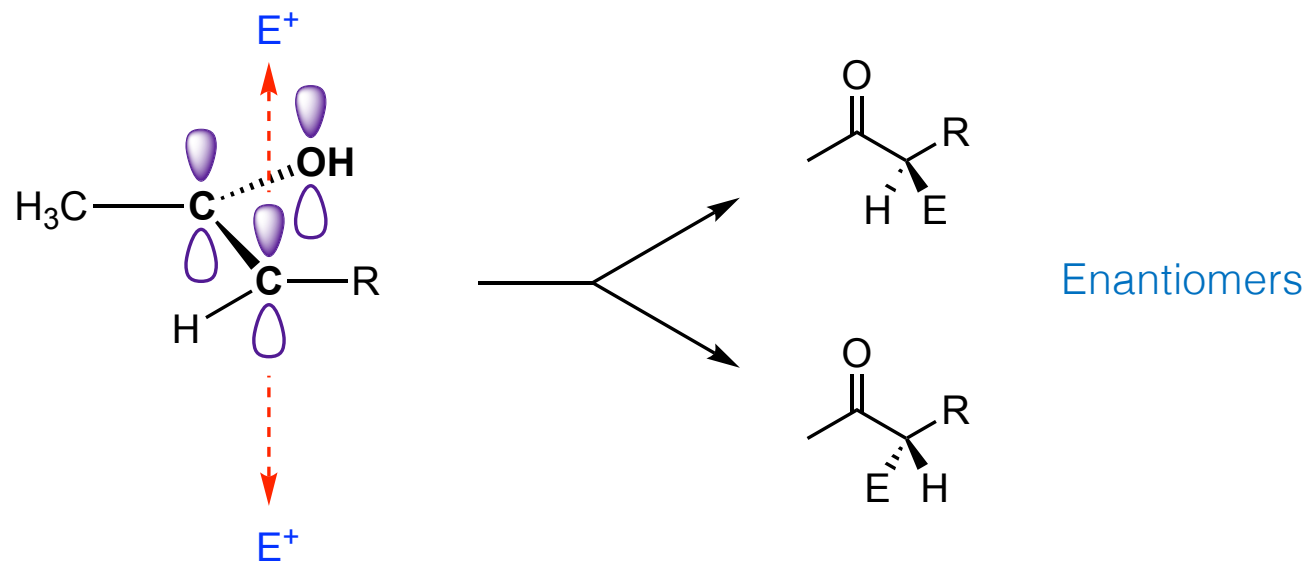
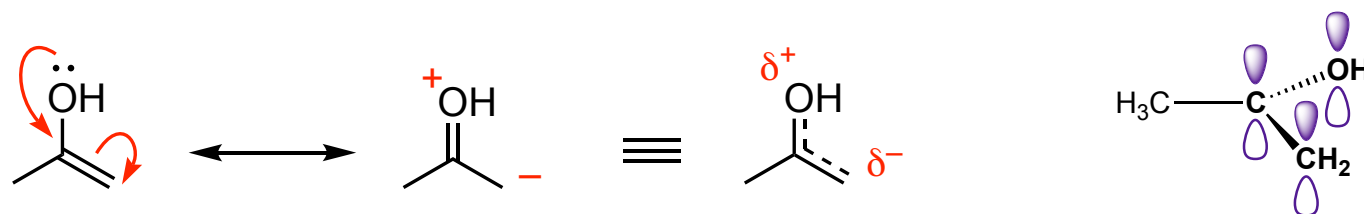


Hydroxide ion removes a proton more effectively (*cf.* in neutral water)

# Enolisation and its consequences

Enols are ambident nucleophiles but reaction through carbon is preferred

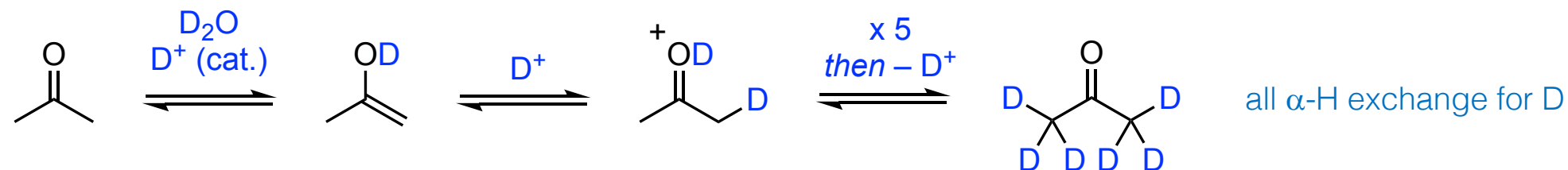
Enols are also mildly *acidic*; the pKa in water of the enol of acetone ~10–11



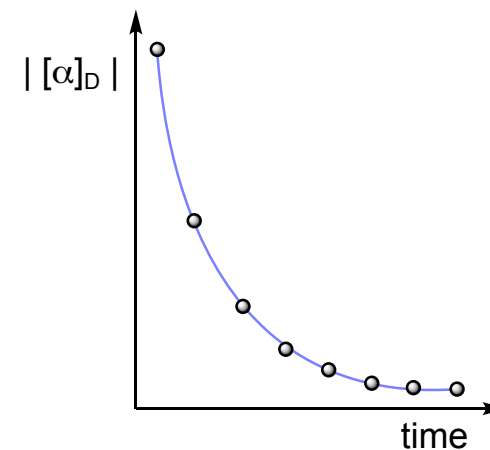
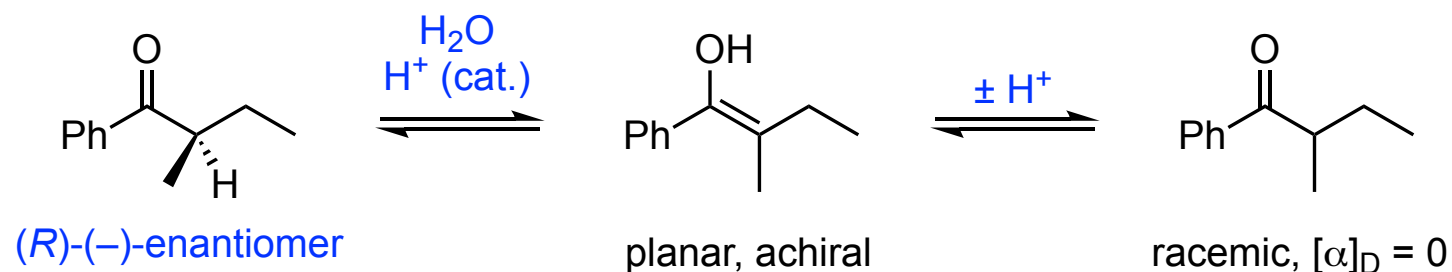
# Enolisation and its consequences

Consequences of enolisation (apply equally to base-catalysed conditions; see later)

(a) H/D exchange in  $D_2O/D^+$



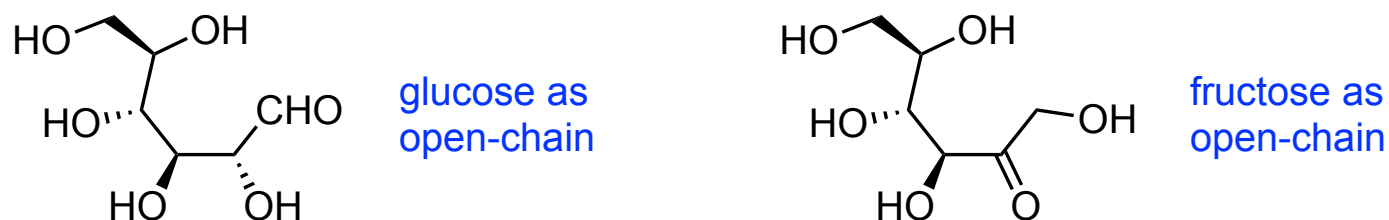
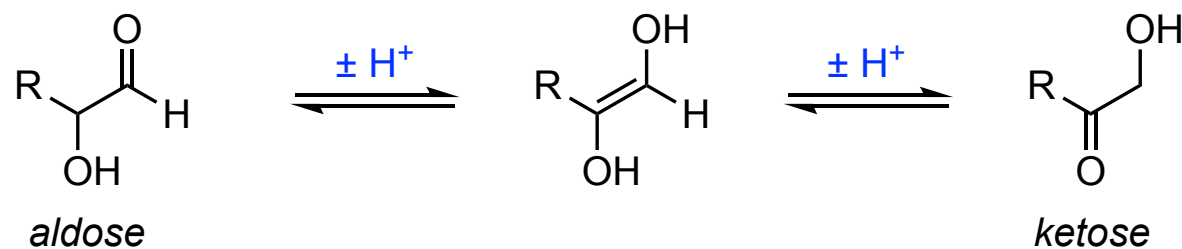
(b) Racemisation (epimerisation) of  $\alpha$ -centre



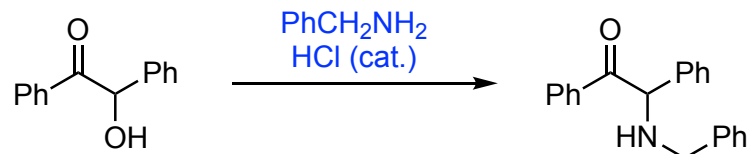
# Enolisation and its consequences

## (c) Rearrangement of $\alpha$ -hydroxy carbonyl compounds

Lobry de Bruyn–Alberda van Ekenstein (!) reaction;\* importance in [sugar chemistry](#)



**Homework:** Amadori rearrangement is closely related; suggest a mechanism for the following

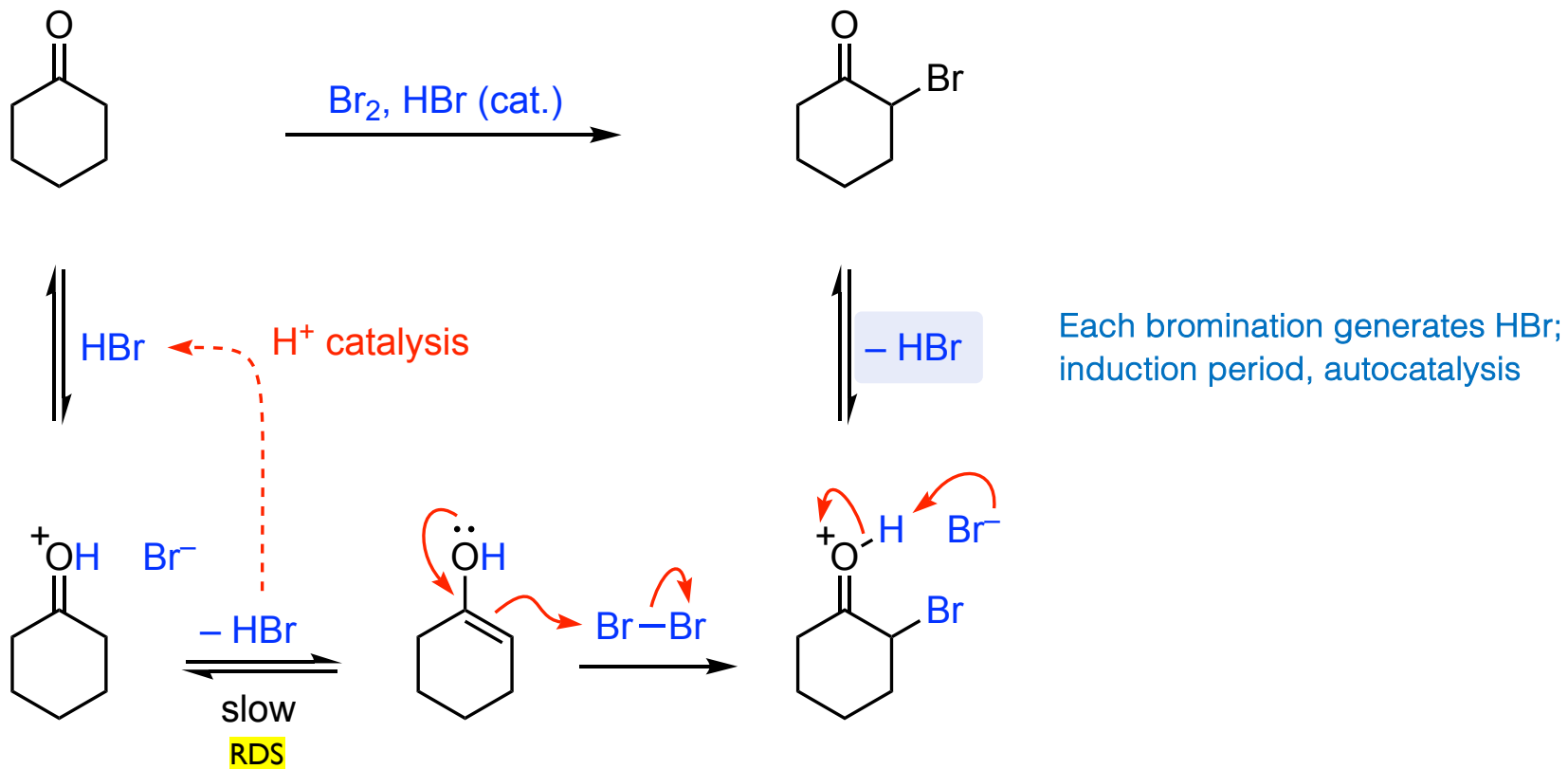


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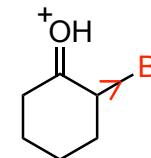
# Enolisation and its consequences

(d) Halogenation: **monobromination** under acidic conditions



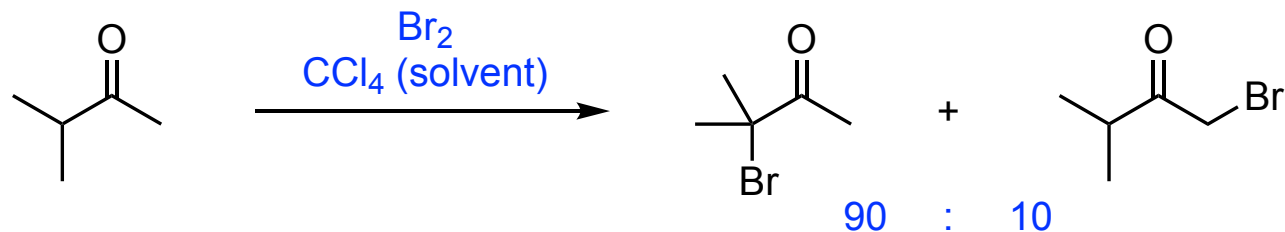
Rate  $\propto$  [cyclohexanone][HBr] that is, it's independent of the [Br<sub>2</sub>]

Low rate of subsequent bromination; lower [R<sub>2</sub>C=OH<sup>+</sup>] when R contains Br

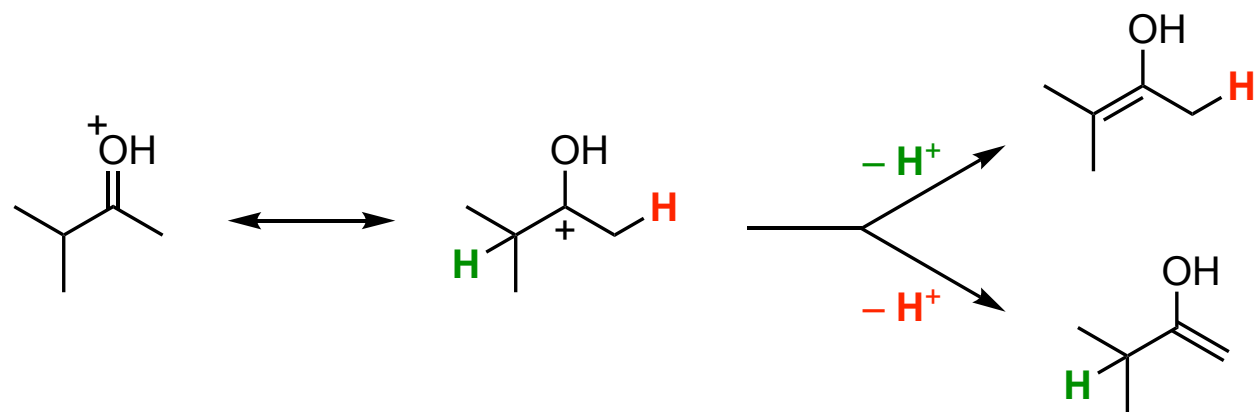


# Enolisation and its consequences

Regioselectivity (reaction takes place at a preferred site)



Relate to Saytzeff\* orientation in E1 elimination



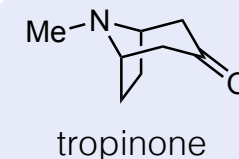
The alkene regioisomer with the more substituted C=C is usually the more stable

... as is the transition state leading to it

$(C-H)\sigma - (C=C)\pi^*$

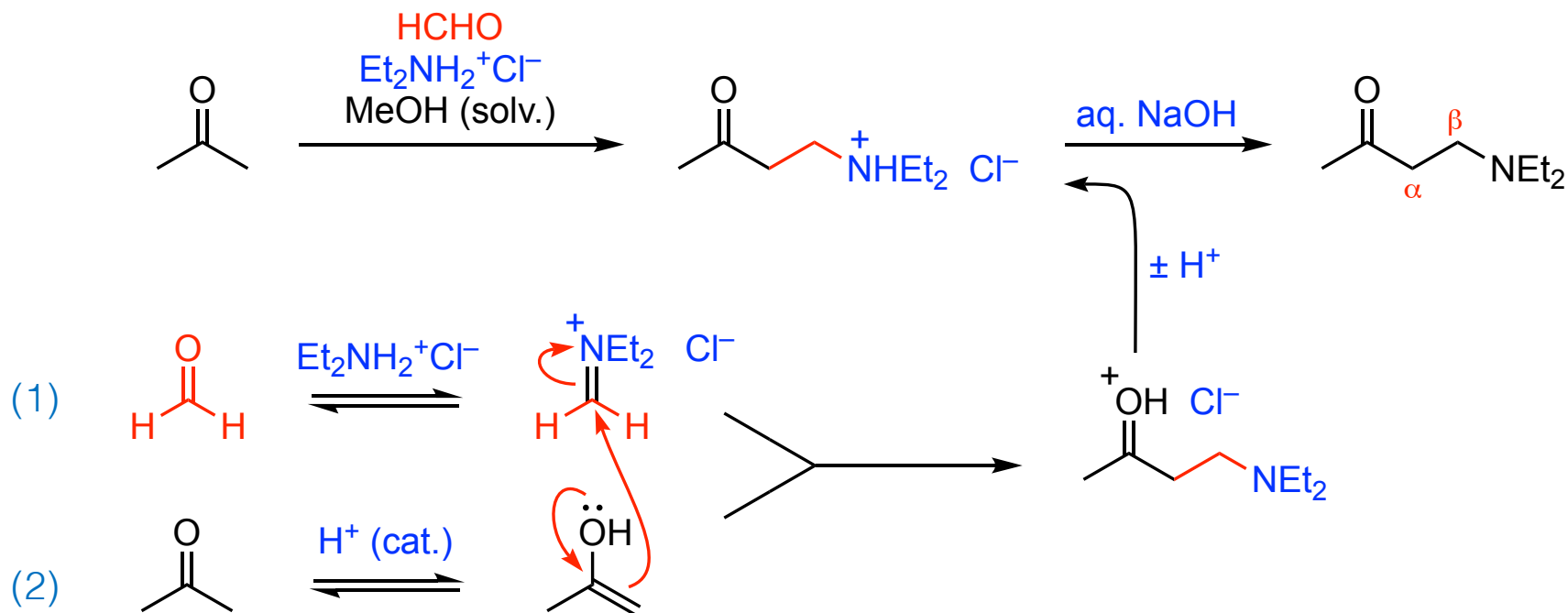
The more substituted alkene: more electron rich; reacts more rapidly with electrophiles

# Enolisation and its consequences

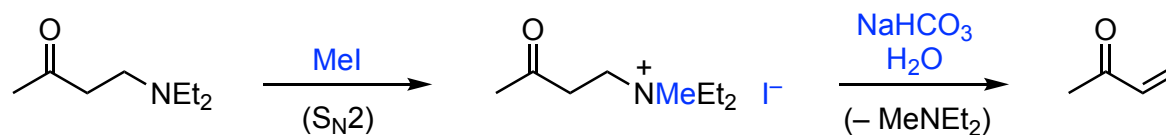


The Mannich reaction; another transformation involving enols

Achieves **ketone**  $\rightarrow$   **$\beta$ -amino ketone** *en route* to enones; (1) iminium formation & (2) enolisation



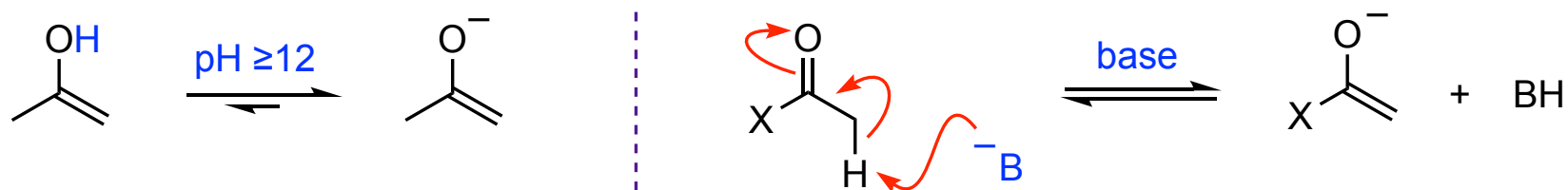
An optional further step activates the dialkylamino group as a leaving group for  $E1_{CB}$  elimination



# Enolisation and its consequences: enolates

Enols:  $pK_a \sim 10-12$ ; what happens if we raise the  $pK_a$  to  $>12$ ?

In alkaline solution the equilibrium shifts from the enol to the *enolate*



The RH equilibrium position depends on the relative  $pK_a$  of the carbonyl component and BH

Carbonyl	$pK_a^*$	Base (B)	BH	$pK_a^*$
CH <sub>3</sub> COCl	16	HO <sup>-</sup>	H <sub>2</sub> O	15.7
CH <sub>3</sub> CHO	17	EtO <sup>-</sup>	EtOH	16
CH <sub>3</sub> COCH <sub>3</sub>	19	<i>t</i> -BuO <sup>-</sup>	<i>t</i> -BuOH	17
CH <sub>3</sub> CO <sub>2</sub> Et	24	H <sup>-</sup>	H <sub>2</sub>	36
CH <sub>3</sub> CN	25	H <sub>2</sub> N <sup>-</sup>	NH <sub>3</sub>	38**
CH <sub>3</sub> CONMe <sub>2</sub>	30	<i>i</i> -Pr <sub>2</sub> N <sup>-</sup>	<i>i</i> -Pr <sub>2</sub> NH	36

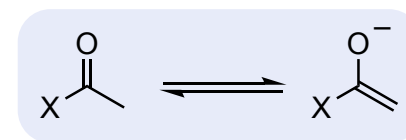
\* Indicative values, relative to those measured in aqueous solution

\*\* 33 in liq. NH<sub>3</sub>

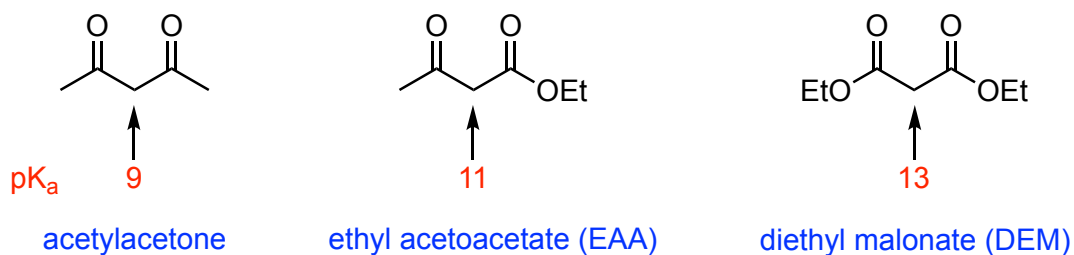
# Enolates

Trends in carbonyl  $\alpha$ -acidity parallel electrophilicity (slides 32–33)

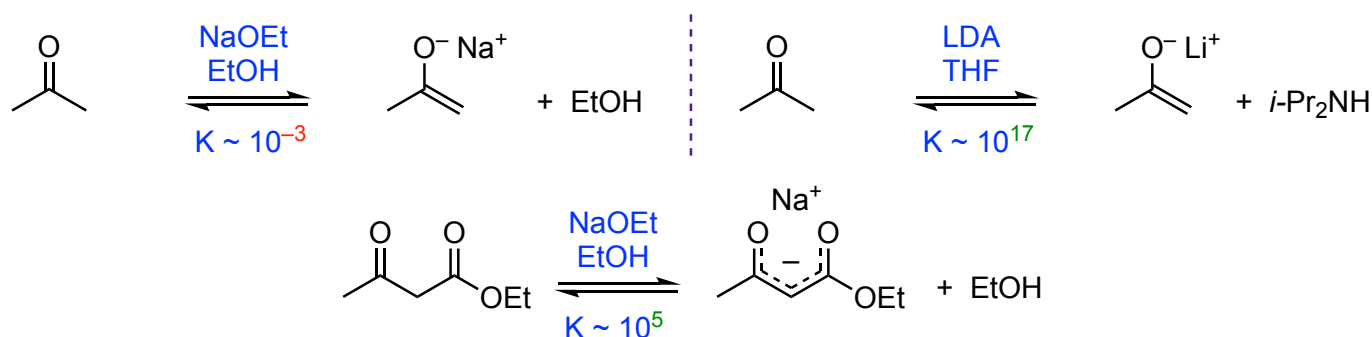
X	+I (alkyl)	reduces acidity	+M (RO, R <sub>2</sub> N)	reduces acidity
	-I (Cl)	increases acidity	-M (C=O)	<i>increases acidity</i>



$\pm$  I,M groups at the  $\alpha$ -position  $\Rightarrow$  the same trends; an important case of -M: 1,3-dicarbonyls



Use all this to approximate equilibria for carbonyl and base combinations (ignores solvent effects)

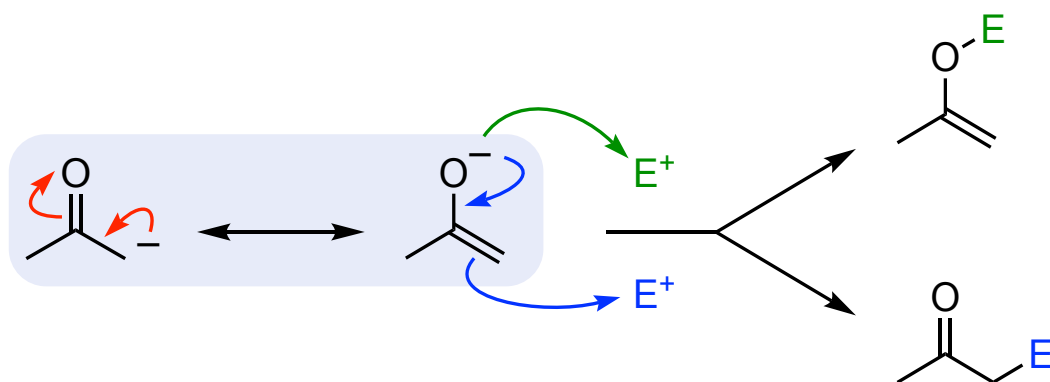
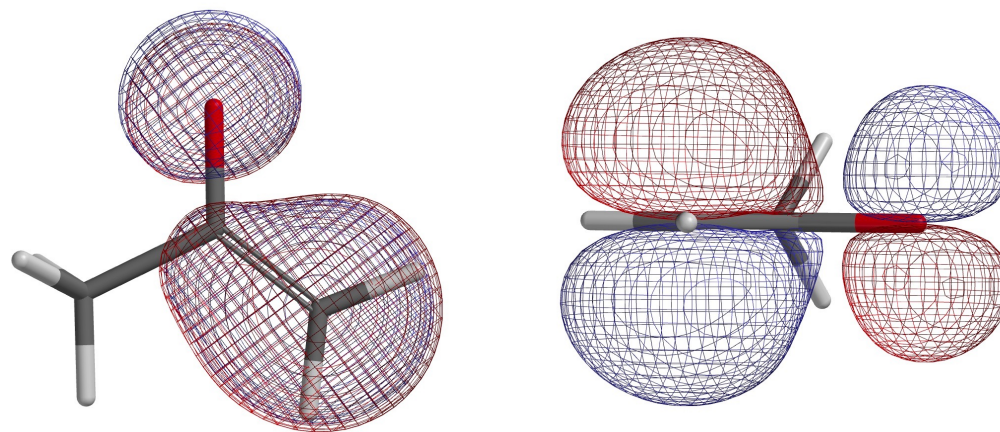


# Enolates

Enolates carry a negative charge

⇒ more nucleophilic than enols

Ambident nucleophiles: *O*- vs. *C*-reactivity



Via *O*- : electrostatic control

$H^+$ ,  $M^+$ ,  $RCOCl$ ,  $RSO_2Cl$ ,  $Me_3SiCl$

Via *C*- : FMO (HOMO/LUMO) control

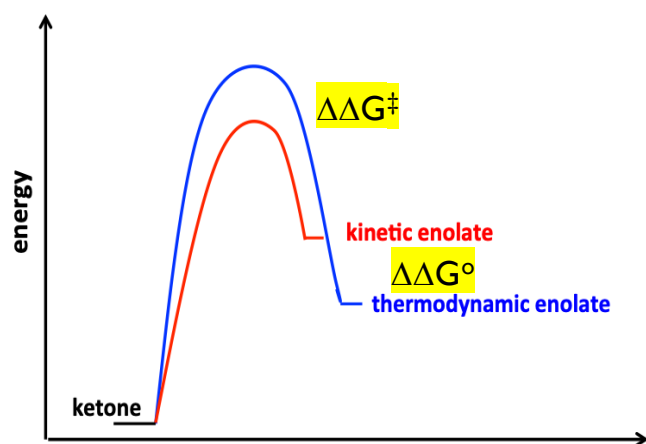
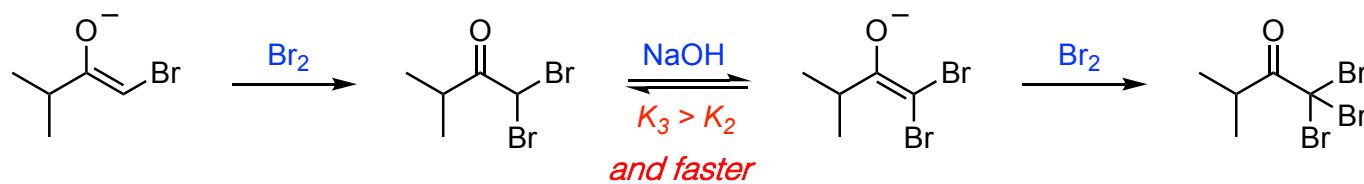
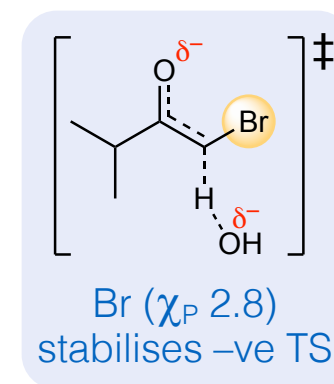
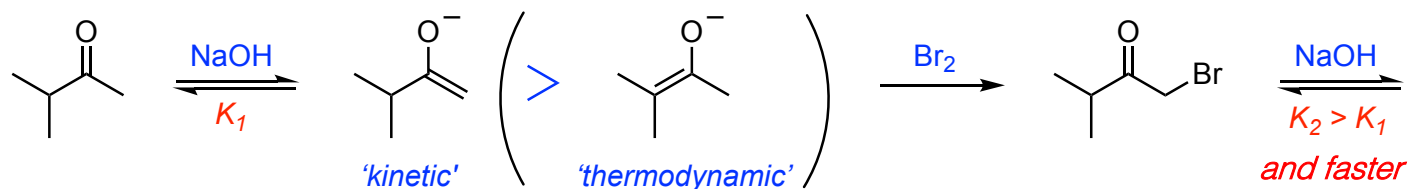
$Br_2$ ,  $I_2$ ,  $R-Br$ ,  $R-I$ ,  $RCHO$ ,  $RCO_2R$ ,  
 $C=C-C=O$

Electronegative oxygen carries more of the charge but more tightly;  
there's a higher orbital coefficient in the enolate HOMO on carbon

*BUT* solvents and counterions play a large part (2<sup>nd</sup> year)

# Enolates

Halogenation under basic conditions; halogens increase the  $\alpha$ -acidity  $\Rightarrow$  **multiple halogenation**



**Kinetic enolate** –  $\Delta\Delta G^\ddagger$  important

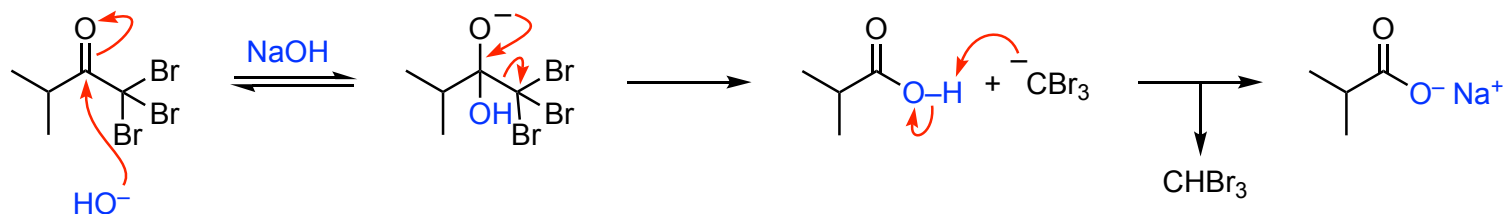
- $\text{H}^+$  removed from less hindered position
- less stable
- favoured by an excess of a strong, hindered base, low temperature, short reaction time

**Thermodynamic enolate** –  $\Delta\Delta G^\circ$  important

- more substituted
- more stable
- favoured by excess ketone, high temperature, long reaction time

# Enolates

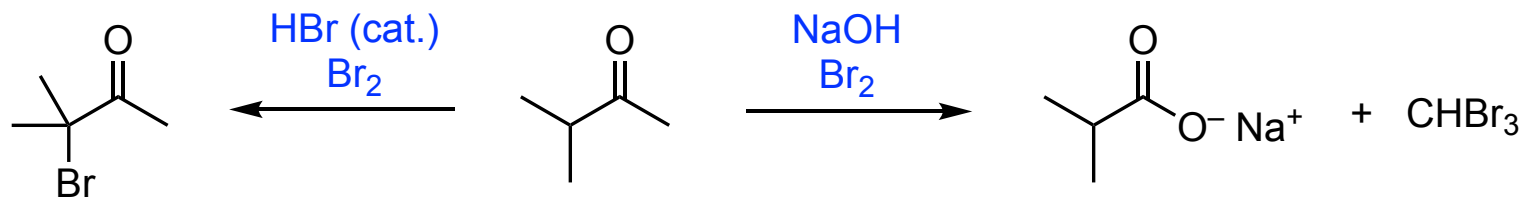
In this example, and other methyl ketones, the reaction does not stop here...



- $\text{CHBr}_3$  – bromoform – has  $\text{pK}_a = 13.5$  so  $\text{Br}_3\text{C}^-$  can leave
- addition of  $\text{HO}^-$  can occur at any other point in the sequence
  - $\text{H}_3\text{C}^-$ ,  $\text{BrH}_2\text{C}^-$ , and  $\text{Br}_2\text{HC}^-$  are insufficiently stable to leave
  - those additions are therefore reversible and unproductive

‘Bromoform test’ and ‘iodoform test’ (with  $\text{I}_2$ ) for methyl ketones; solid  $\text{CHBr}_3$  &  $\text{CHI}_3$  precipitate out

Compare the bromination outcomes under *acidic* and *basic* conditions

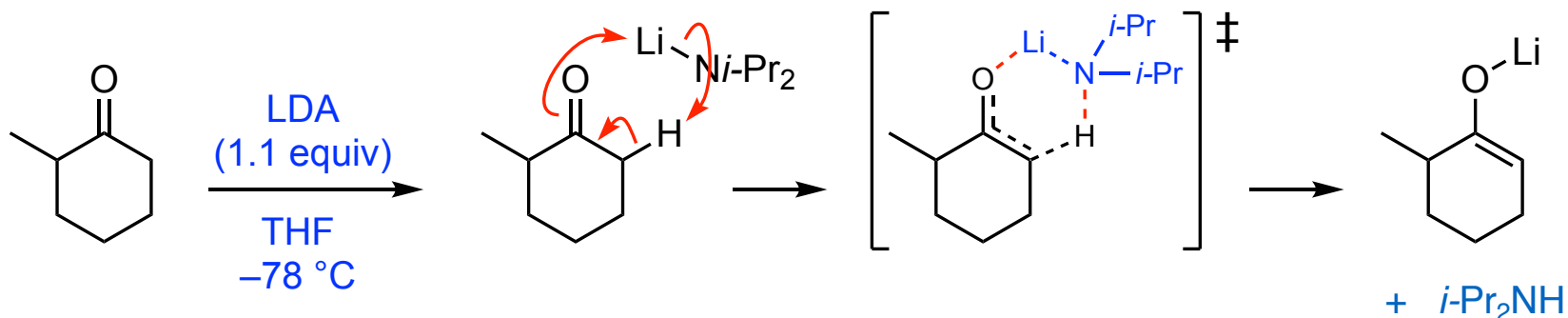




# Enolates

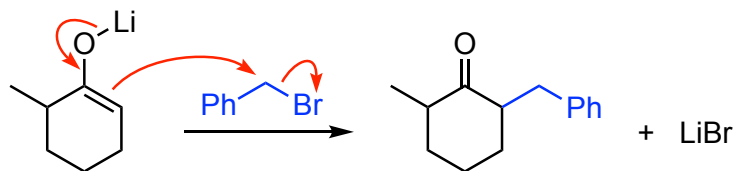
So far... equilibrium enolate formation; how about 'irreversible' enolate formation?

Use a sufficiently strong base to 'completely' deprotonate the carbonyl; e.g. LDA



- LDA formed from  $i\text{-Pr}_2\text{NH}$  + BuLi (in *dry* THF)
- LDA used in slight excess to ensure no ketone remains
- Low temperature  $\Rightarrow$  maximise regioselectivity
- Bulky isopropyl groups  $\Rightarrow$  deprotonate less hindered side  
 $\Rightarrow$  no addition to C=O

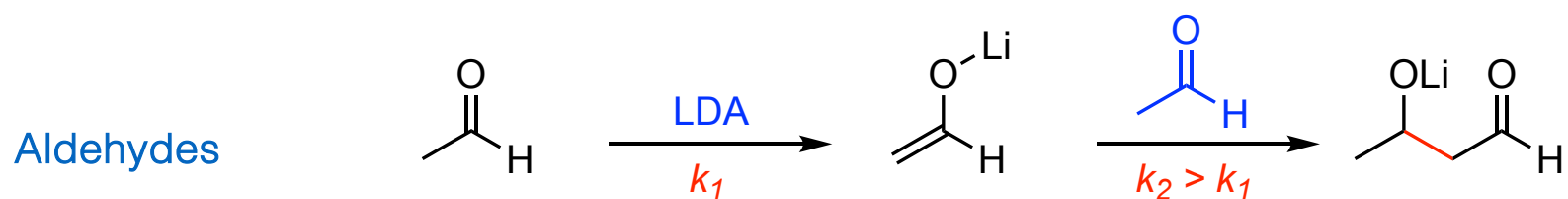
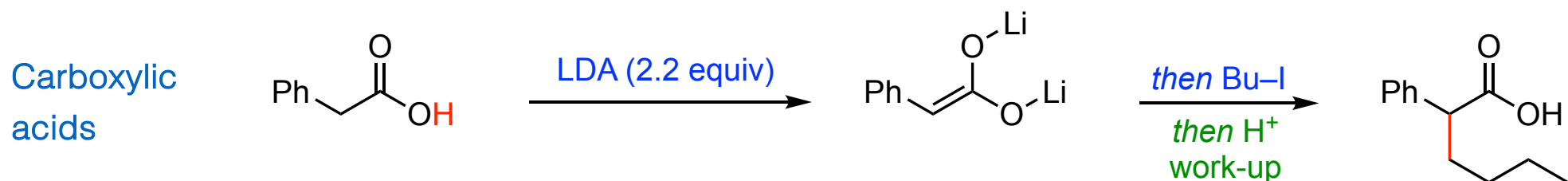
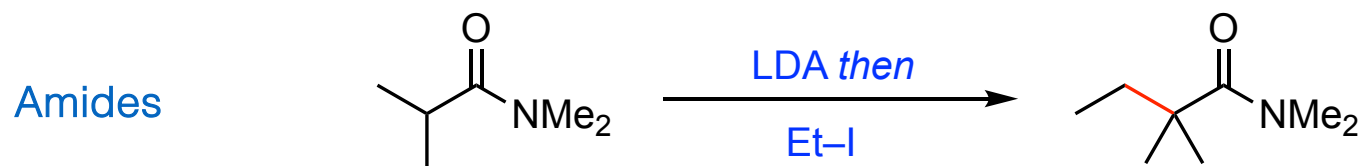
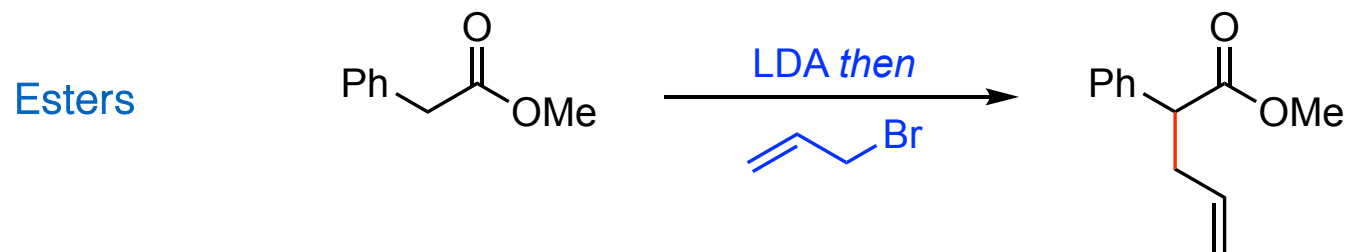
Enolate is alkylated by *SN2-reactive* alkyl halides ( $\text{CH}_3\text{I}$ ,  $\text{RCH}_2\text{I}$ ,  $\text{PhCH}_2\text{Br}$ ,  $\text{CH}_2=\text{CHCH}_2\text{Br}$ )



- The sterically-hindered N in  $i\text{-Pr}_2\text{NH}$  does not get alkylated by the alkyl halide under the reaction conditions

# Enolates

LDA is a sufficiently strong base to fully deprotonate most carbonyl compounds

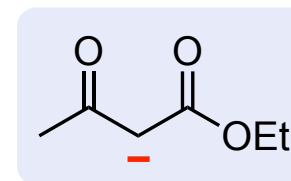
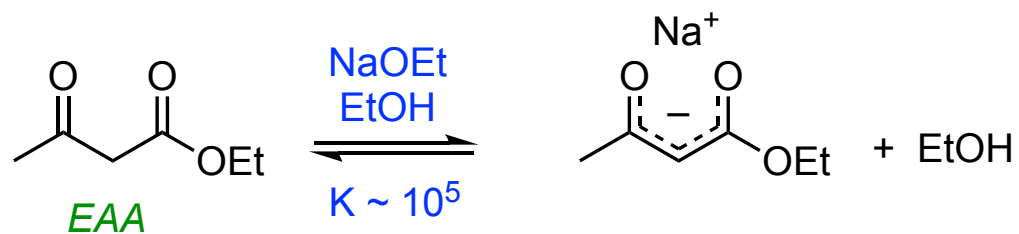


Aldehydes are so electrophilic they react with the enolate as it's formed; see later

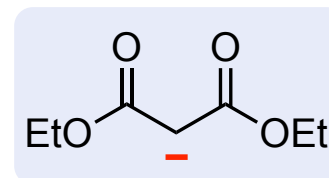
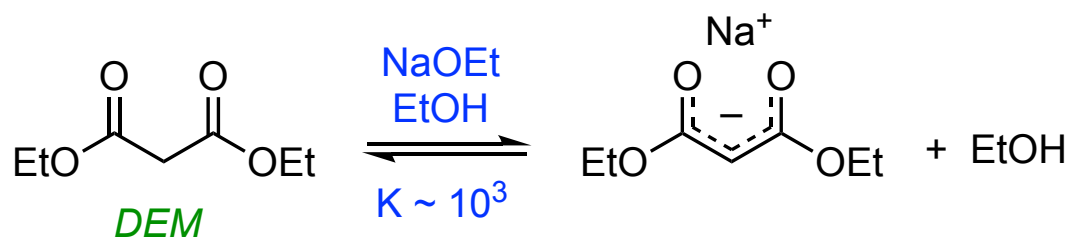
# Enolates

Practical alternatives? 1,3-Dicarbonyls have higher acidity  $\Rightarrow$  milder base, room temperature etc

*Cf. slide 61*



Less reactive enolate  
 $\text{RCOCH}_3$  synthesis



More reactive enolate  
 $\text{RCO}_2\text{H}$  synthesis

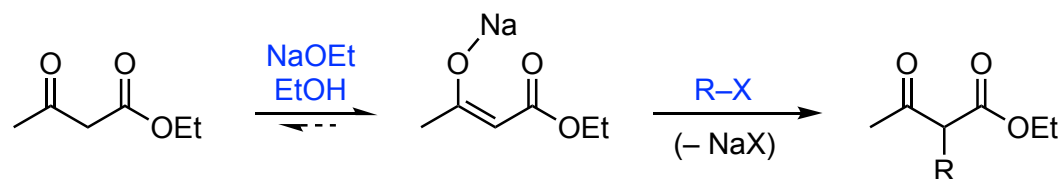
NaOEt used so that any addition to the ester results in the same ester

In practice: select EtOH as the solvent and add Na (*carefully*)

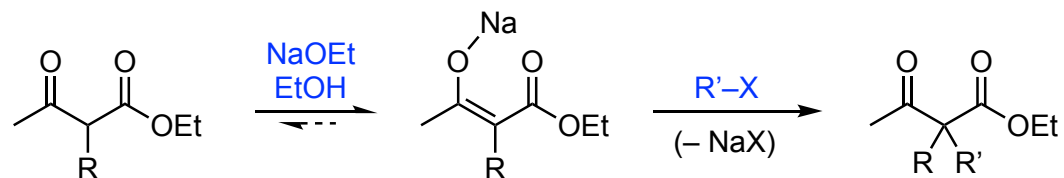
# Enolates

## General scheme for the application of EAA enolate

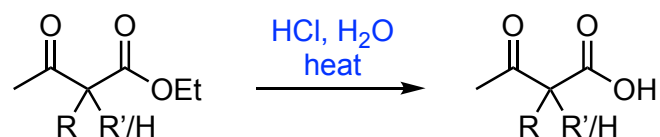
(1) Deprotonate and alkylate



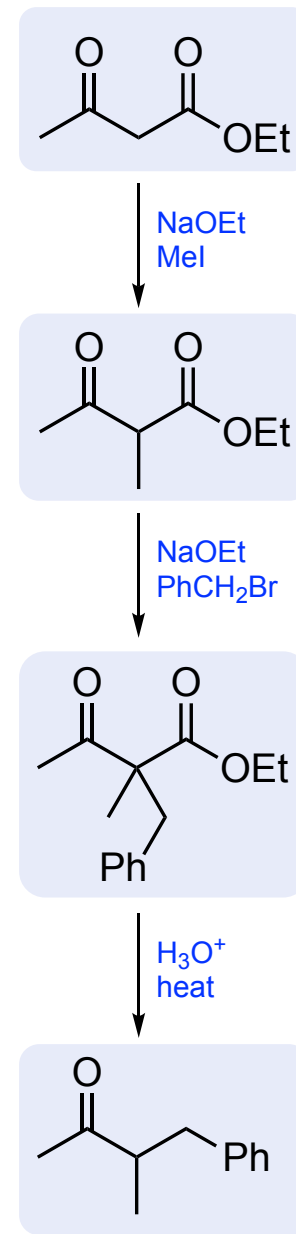
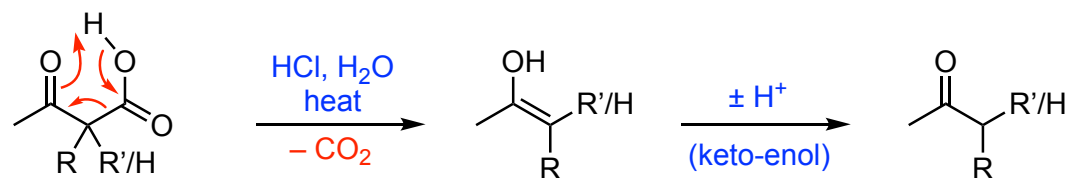
(2) **Optional:** deprotonate and alkylate again with the same or a different alkyl halide



(3) Following alkylation (1) or (2), hydrolyse the ester under *acidic* conditions:  $A_{Ac}2$  mechanism



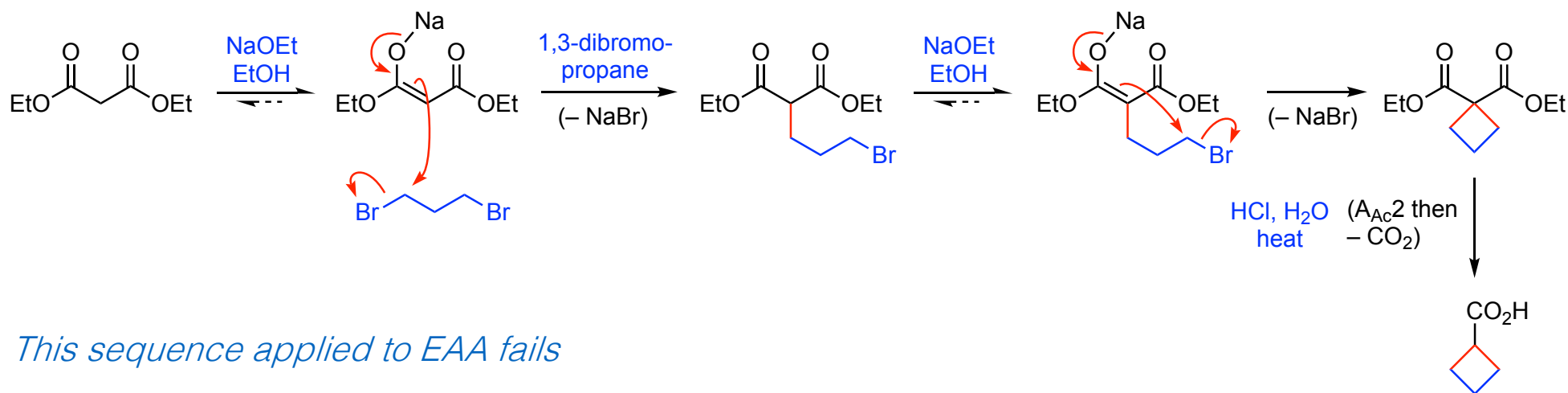
(4) The  $\beta$ -keto acid decarboxylates under the reaction conditions, leaving a methyl ketone



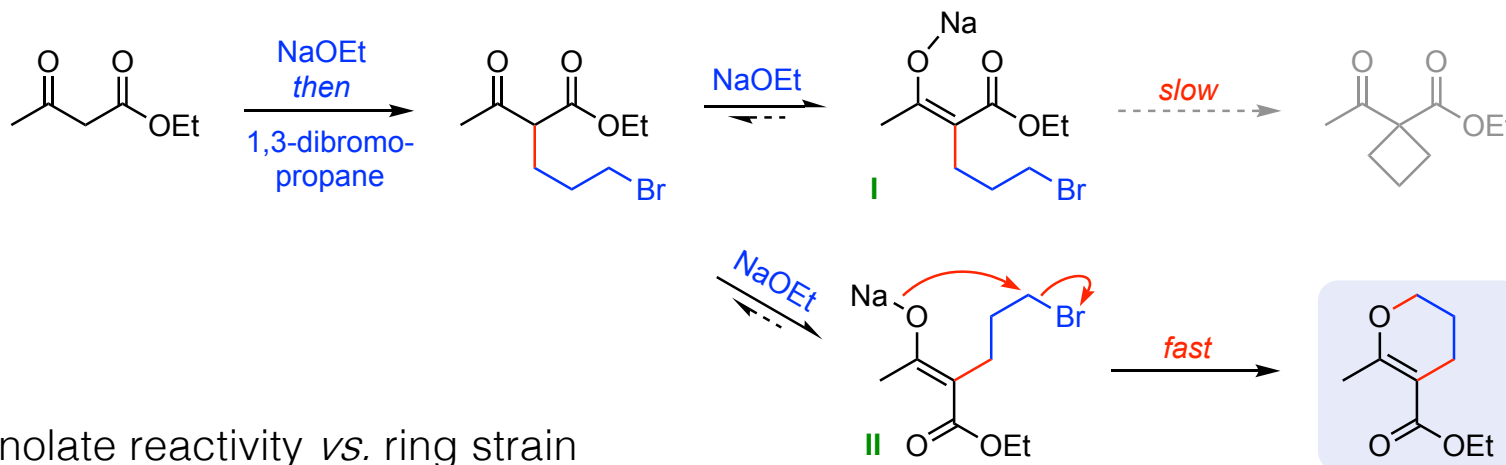
# Enolates

DEM reacts similarly; produces alkylated carboxylic acids; advantages in ring synthesis

In this example, the two alkyl halides are connected, resulting in a ring



*This sequence applied to EAA fails*

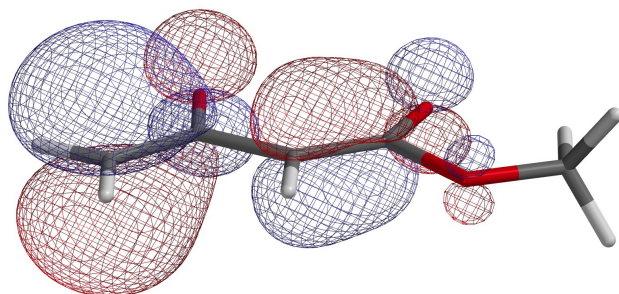
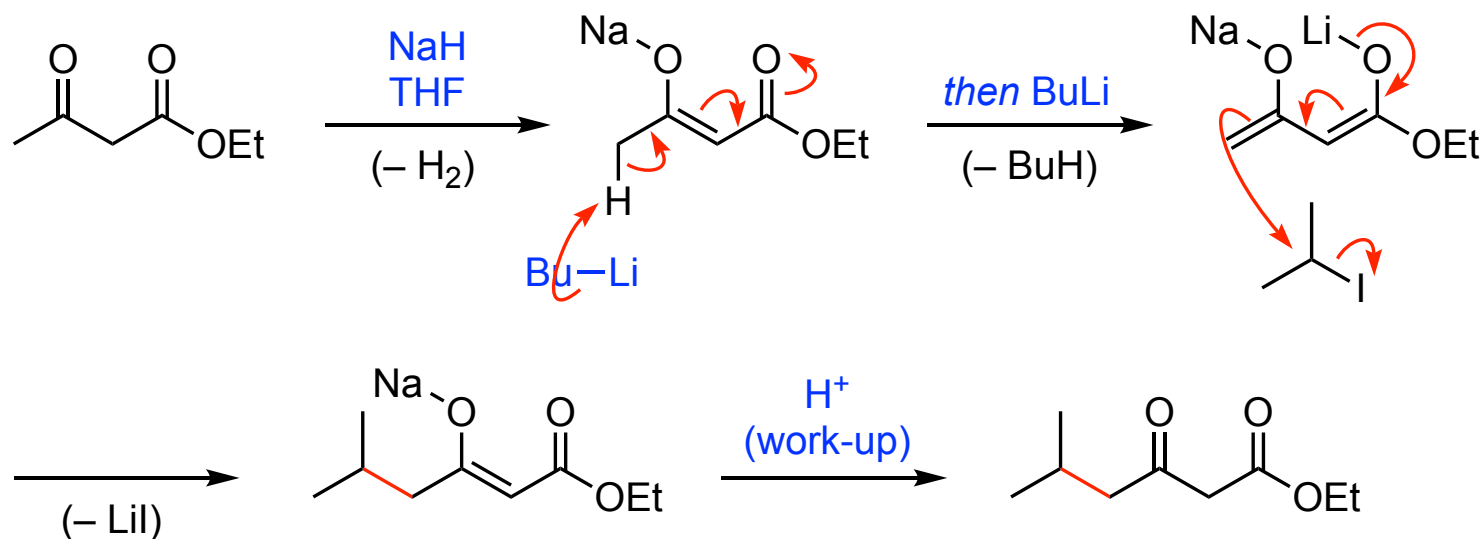


Enolate reactivity vs. ring strain

# Enolates

EAA has the advantage that it can be deprotonated twice to make a reactive *dienolate*

Usually NaH (1 equiv) then BuLi (1 equiv); can use LDA (2 equiv)



The HOMO of this dienolate has its largest coefficient on the terminal carbon

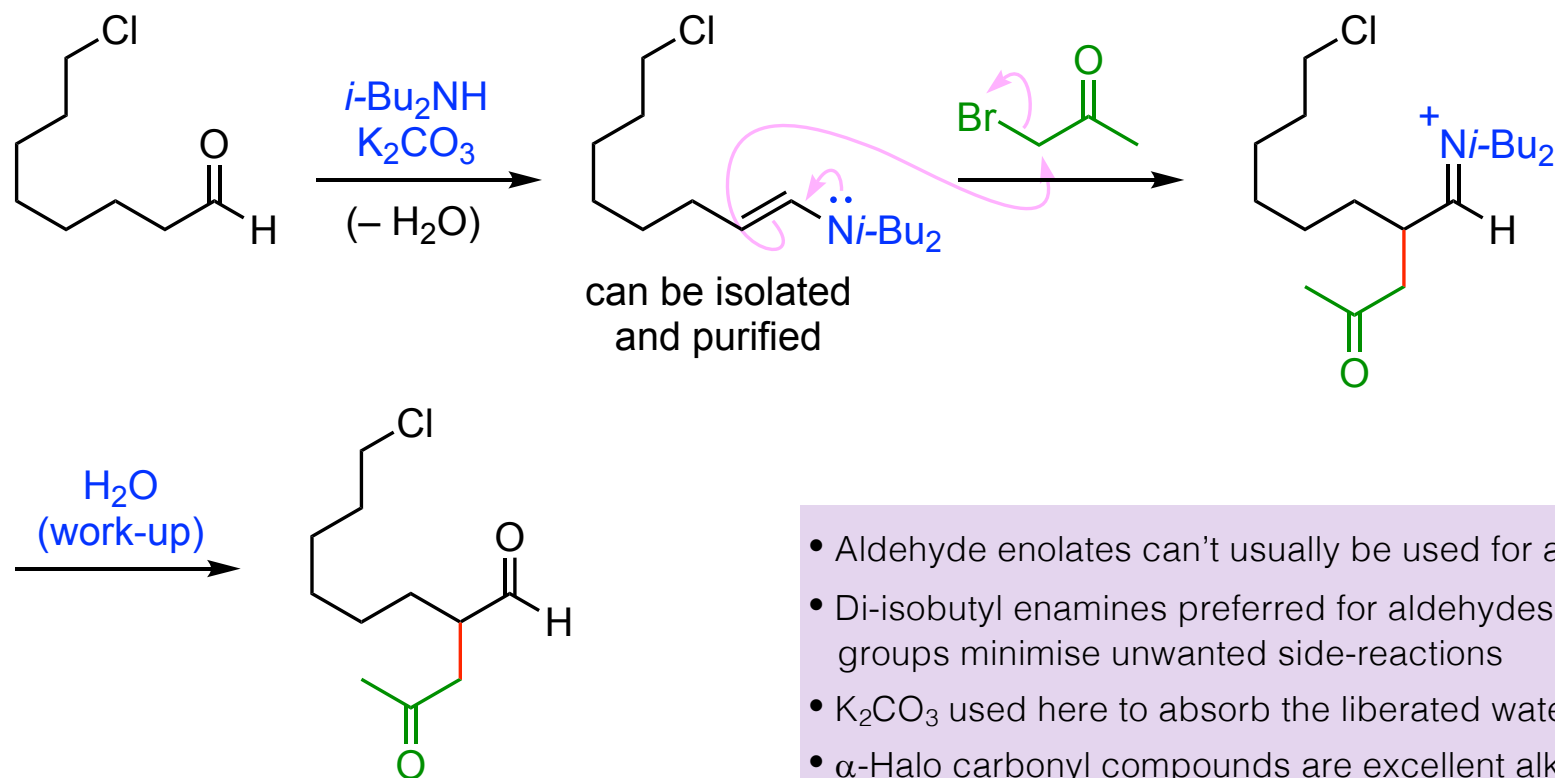
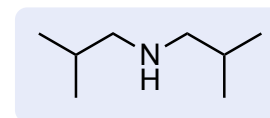
The new product can be further alkylated etc as for EAA (slide 68)

# Enamines

Enamines have the character of enol(ate)s; more reactive than enols, less reactive than enolates

Prepared from aldehydes/ketones + 2° amine; see slide 27

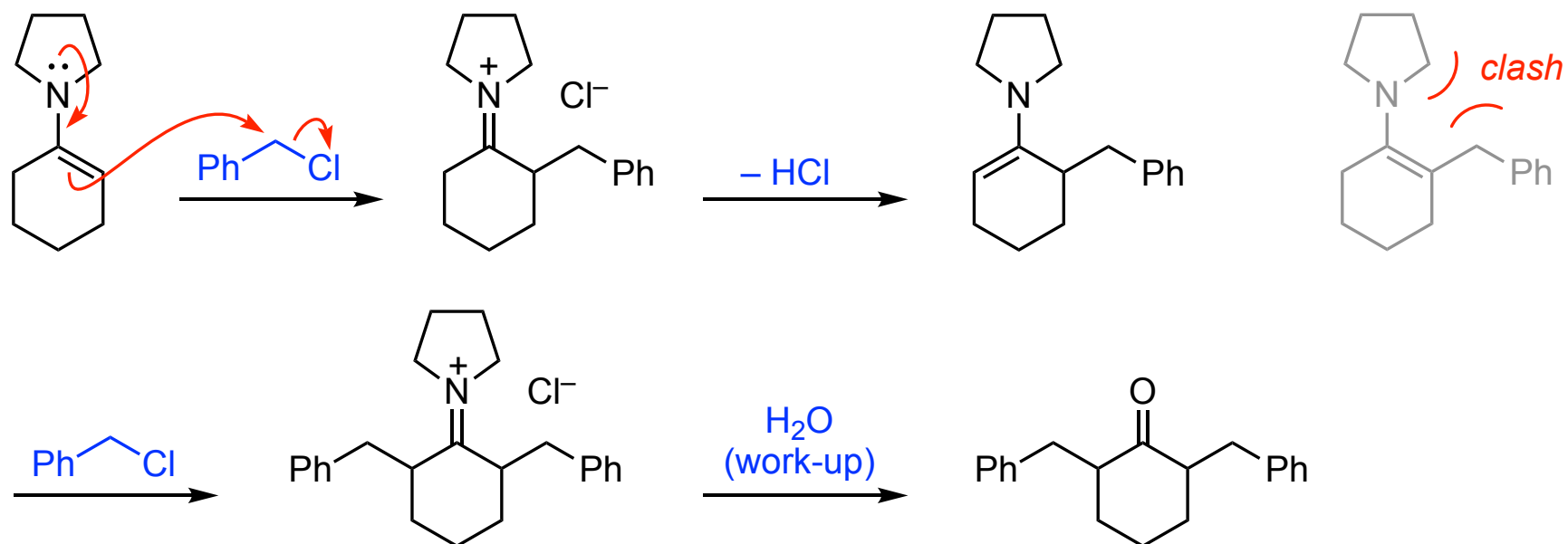
Good for monoalkylation with reactive alkyl halides and other electrophiles



- Aldehyde enolates can't usually be used for alkylation (slide 66)
- Di-isobutyl enamines preferred for aldehydes; the large alkyl groups minimise unwanted side-reactions
- $K_2CO_3$  used here to absorb the liberated water
- $\alpha$ -Halo carbonyl compounds are excellent alkylating agents (and are lachrymators 😭)

# Enamines

Enamines allow di-alkylation either side of a ketone carbonyl; use excess R-X



Many applications in reactions with other carbonyl compounds including  $\alpha,\beta$ -unsaturated ketones and esters

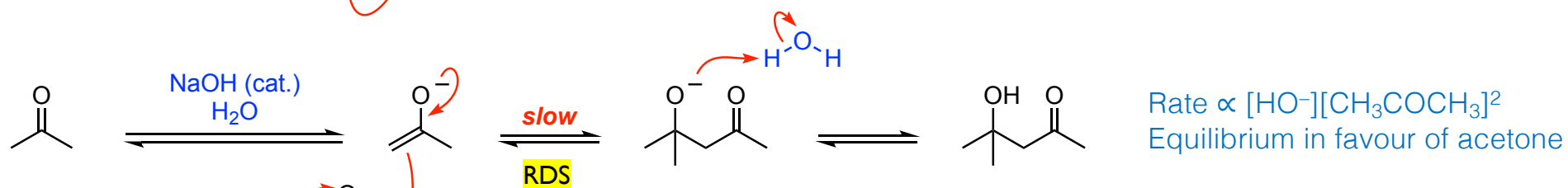
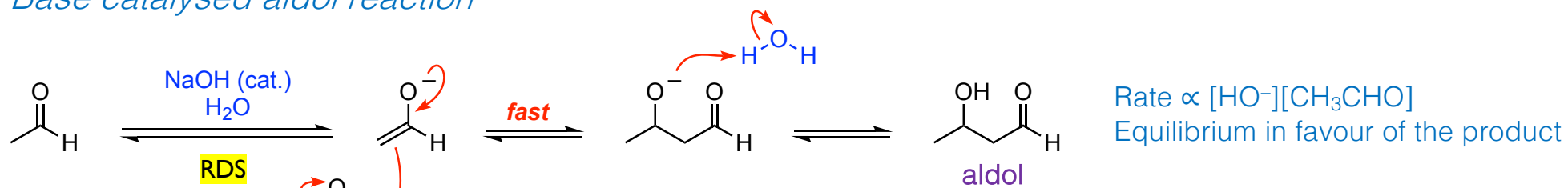


# Enol(ate) reactions with carbonyl compounds

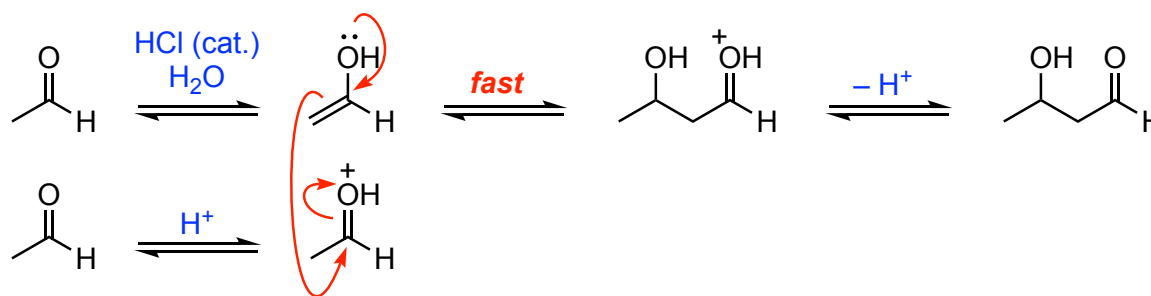
Usually take place under reversible conditions; thermodynamic control; driven by product stability

Recall (slide 66) that aldehyde enolates react with the parent aldehyde ~instantly

## Base catalysed aldol reaction



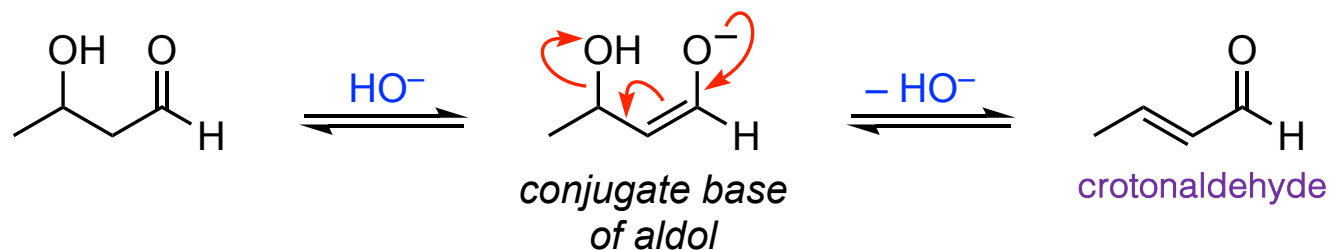
## Acid catalysed aldol reaction



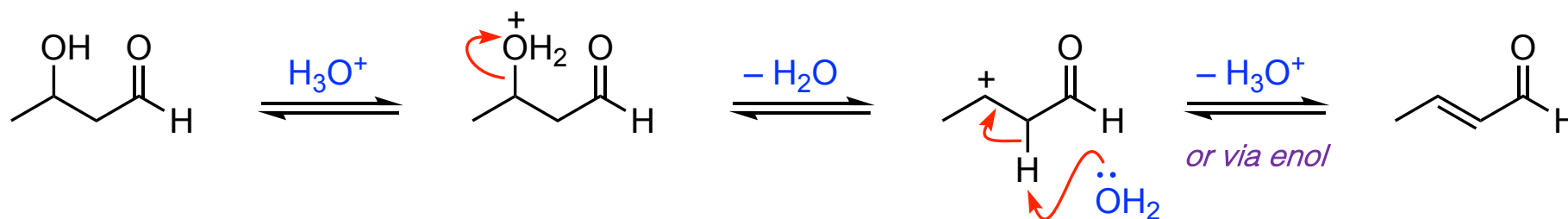
# Enol(ate) reactions with carbonyl compounds

Subsequent elimination  $\rightarrow$   $\alpha,\beta$ -unsaturated aldehyde can take place especially when heated

Loss of  $\text{HO}^-$  under basic conditions:  $\text{E1}_{\text{CB}}$  mechanism



Loss of  $\text{H}_2\text{O}$  under acidic conditions:  $\text{E1}$  mechanism



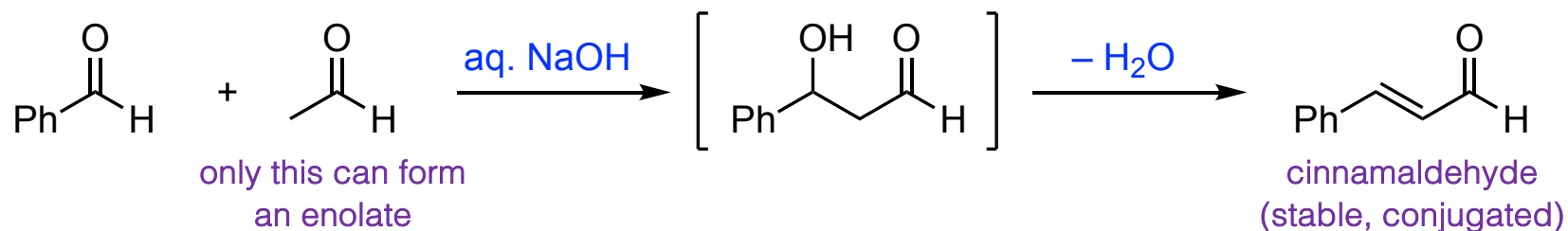
Overall: 5% aq.  $\text{NaOH}$  @  $0^\circ\text{C}$   $\rightarrow$  aldol adduct; heat with acid or base  $\rightarrow$  enone

Elimination can be spontaneous if further conjugation present

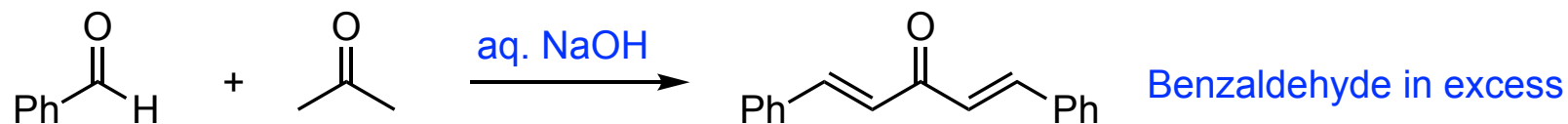
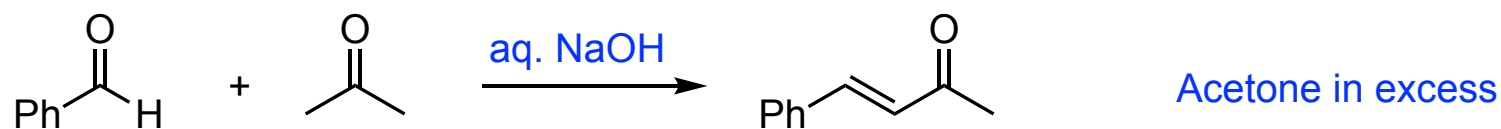
# Enol(ate) reactions with carbonyl compounds

Crossed aldol reactions under reversible conditions?

Only useful if one component has no  $\alpha$ -hydrogens [with ArCHO 'Claisen-Schmidt']

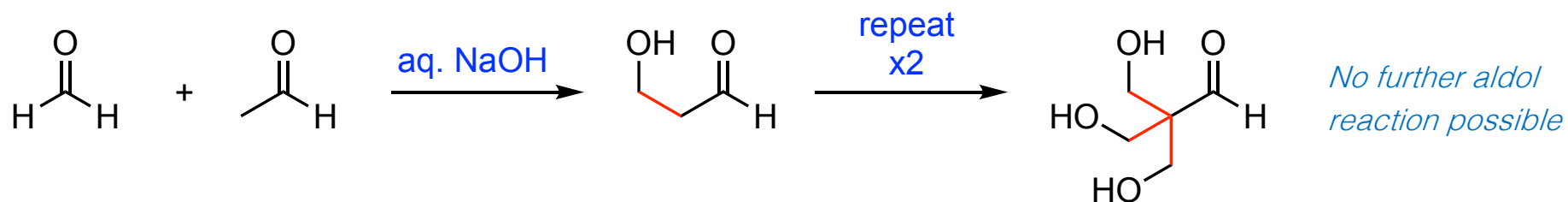


Ketones react similarly and the obtained product is dictated by the ratio of reactants

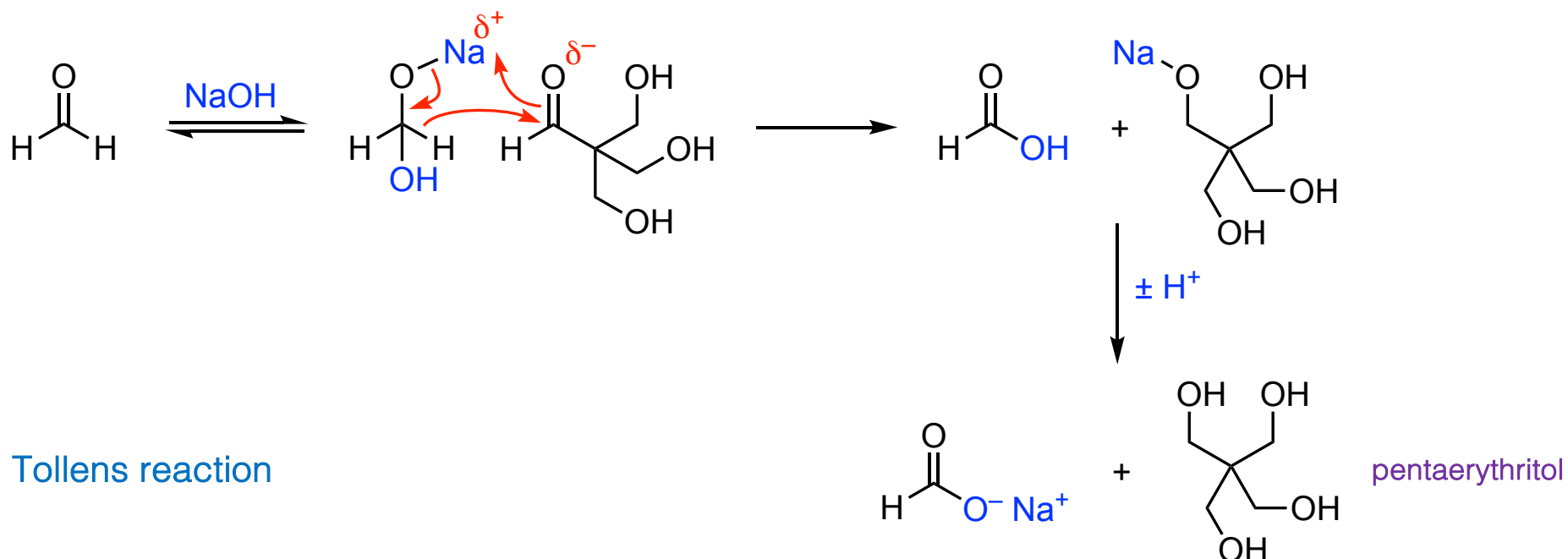


# Enol(ate) reactions with carbonyl compounds

Reactions with excess formaldehyde (more electrophilic) proceed exhaustively

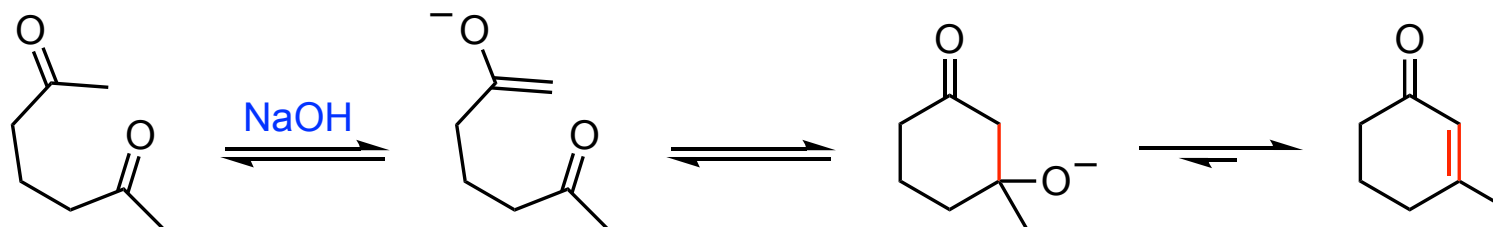


Reaction doesn't stop here; terminates with a crossed-Cannizzaro reaction

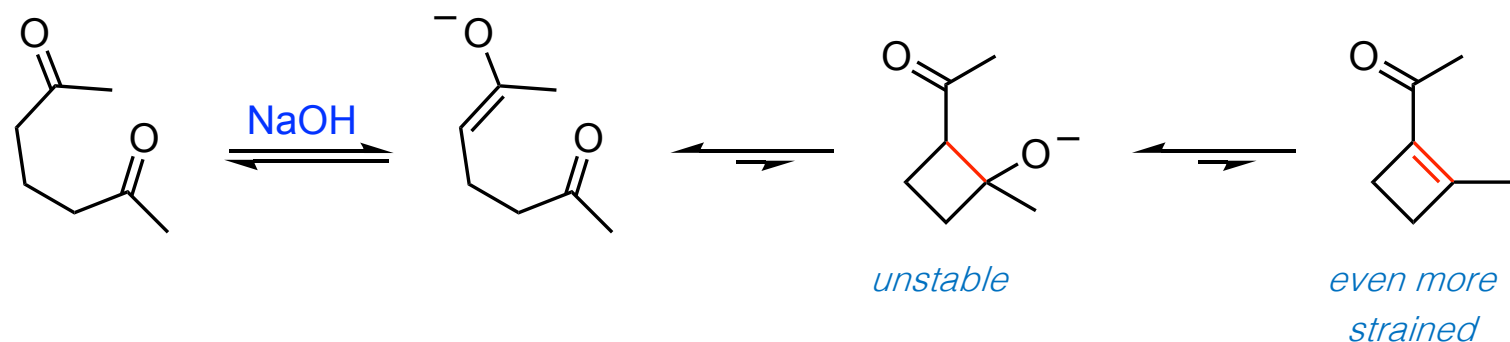


# Enol(ate) reactions with carbonyl compounds

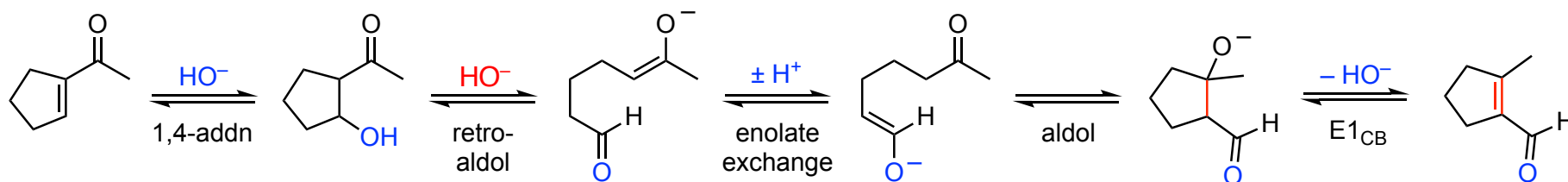
Aldol reactions can be intramolecular – synthesis of **cyclic enones**



No productive alternative aldol reactions...



Aldol reactions are reversible; retro-aldol/aldol equilibrates to a more stable enone





UNIVERSITY OF  
**OXFORD**

First Year Organic Chemistry

THE CHEMISTRY OF THE CARBONYL GROUP  
CORE CARBONYL CHEMISTRY (4)

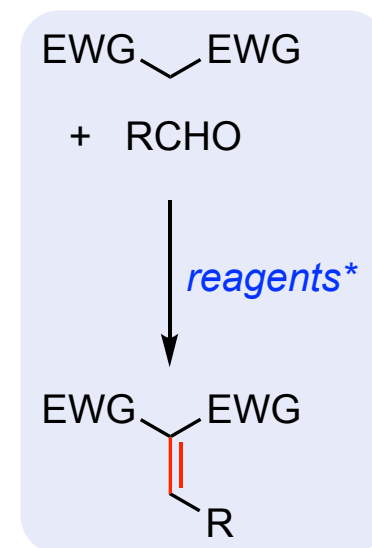
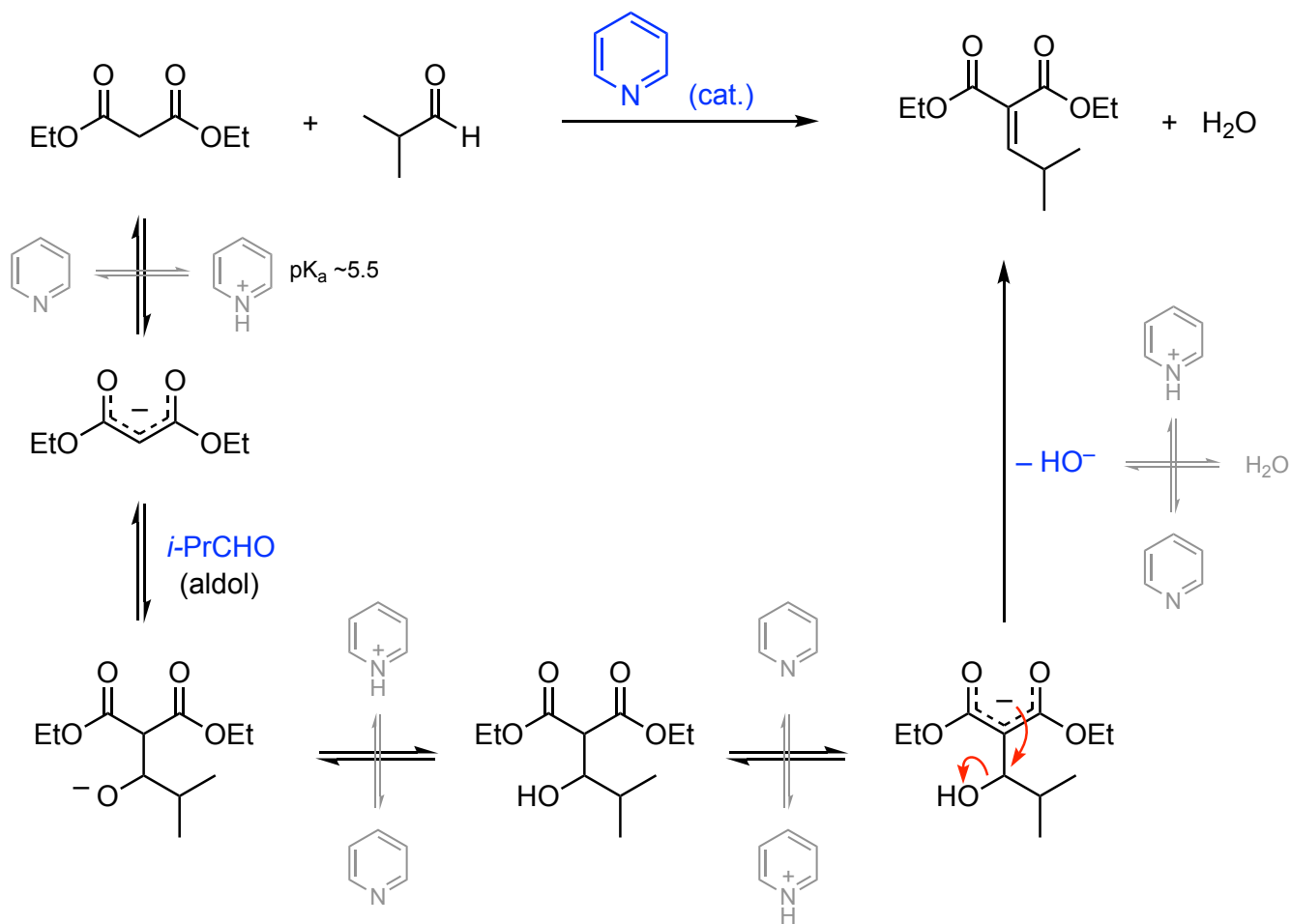
Professor Jeremy Robertson

*8 lectures, HT, 2023*

# More aldol-type reactions

Aldol variants; mechanistically very similar; differ in the nature of the enolate

(a) **Knoevenagel condensation**: the enolate derives from [EWG]-CH<sub>2</sub>-[EWG]

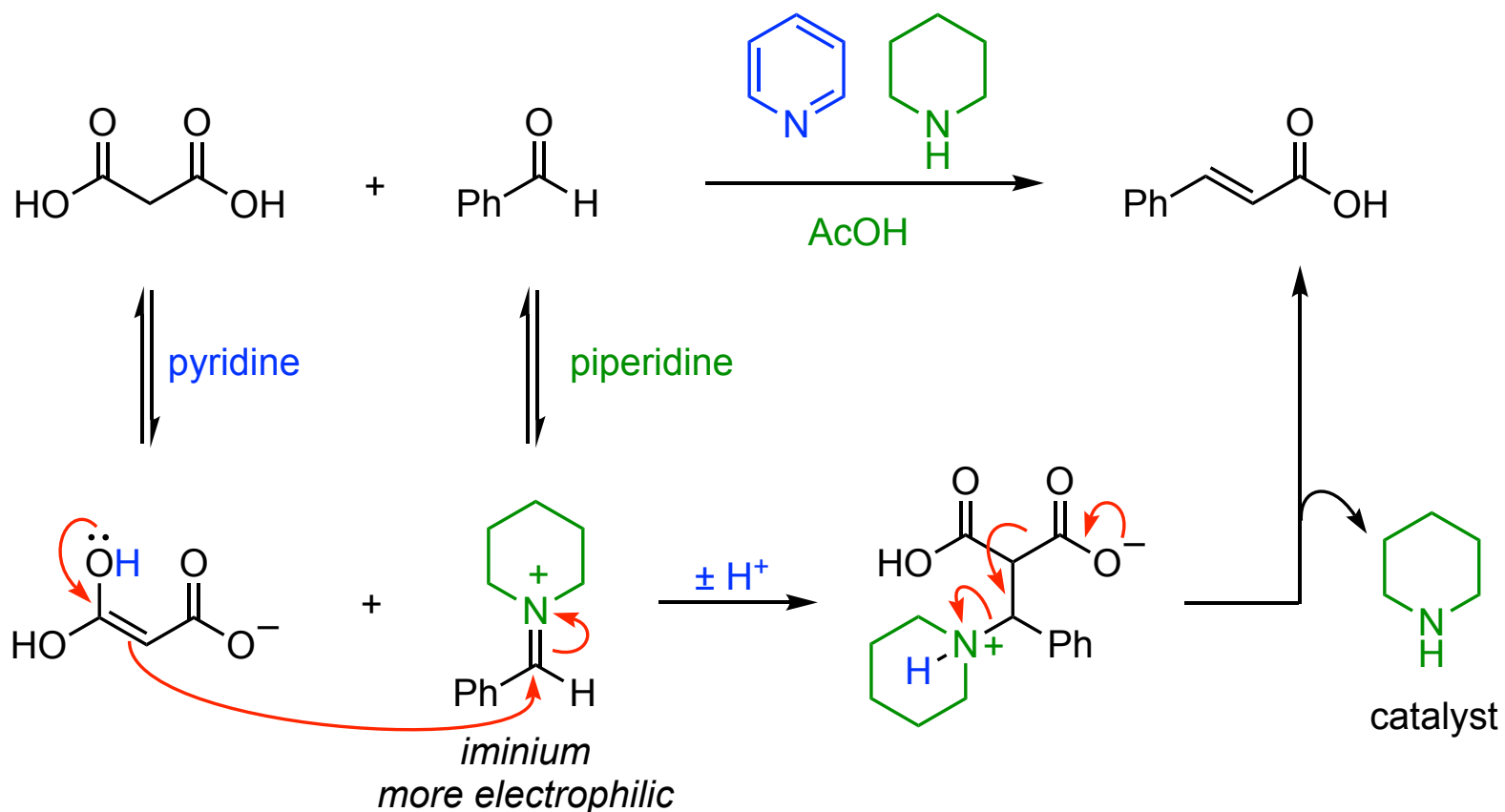


EWG  
-CO<sub>2</sub>R, -CN, -SO<sub>2</sub>R etc  
\* Reagents  
pyridine (+ piperidine, AcOH)

# More aldol-type reactions

With malonic acid, decarboxylation accompanies elimination – synthesis of  $\alpha,\beta$ -unsaturated acids

In this example, piperidine and AcOH are added to speed the reaction: *organocatalysis* (3<sup>rd</sup> year)



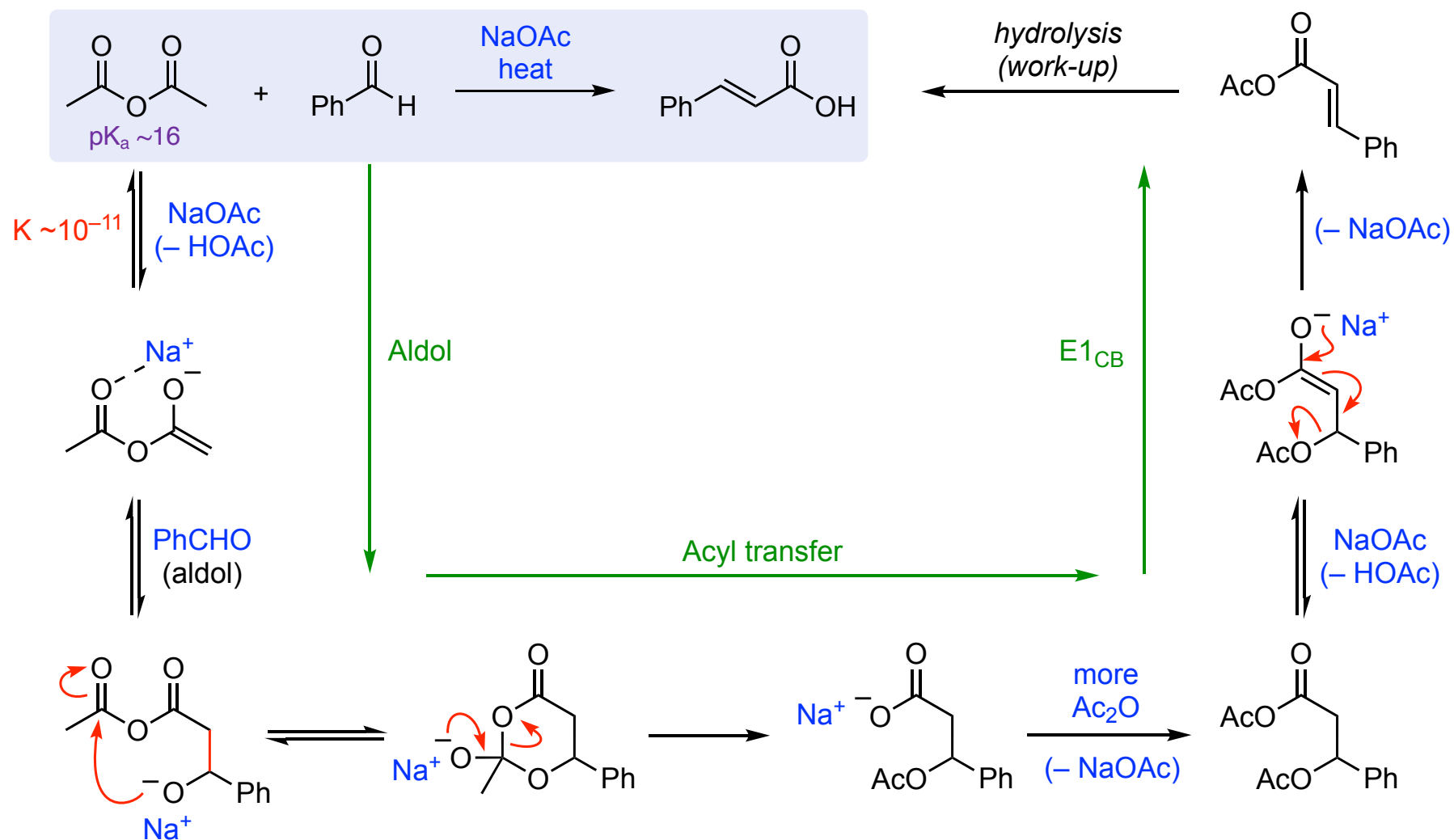
You can write the mechanism without the piperidine but if piperidine's present the reaction is faster

Recall (slide 59): enol + iminium = Mannich reaction



# More aldol-type reactions

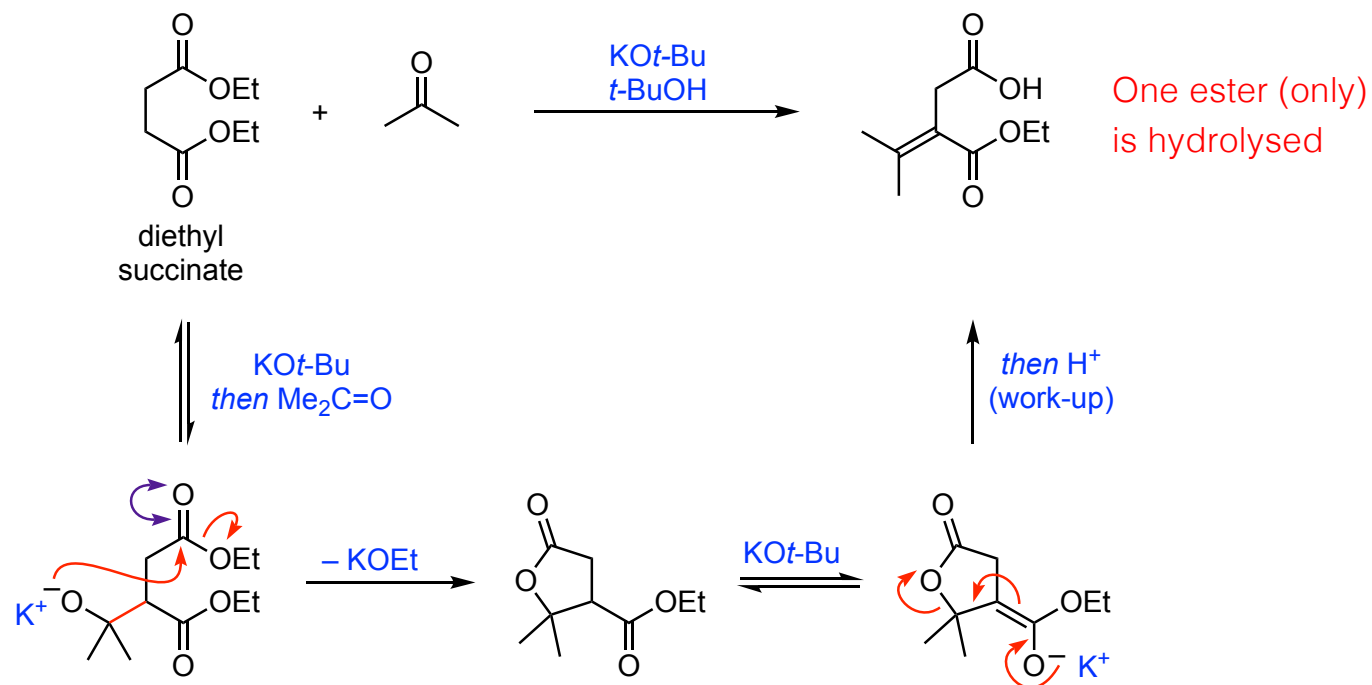
(b) **Perkin reaction**: the enolate derives from acetic anhydride – synthesis of  $\alpha,\beta$ -unsaturated acids



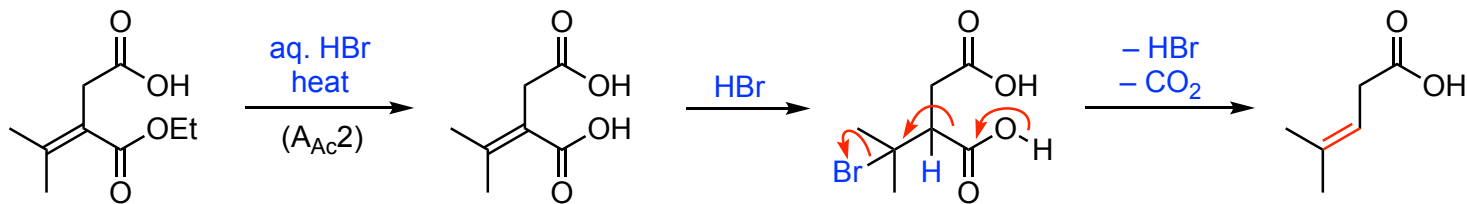
# More aldol-type reactions

(c) **Stobbe reaction**: the enolate derives from a 1,4-diester ('succinate') –  $\beta,\gamma$ -unsaturated acids

(i) Aldol-type enone of succinate monoester



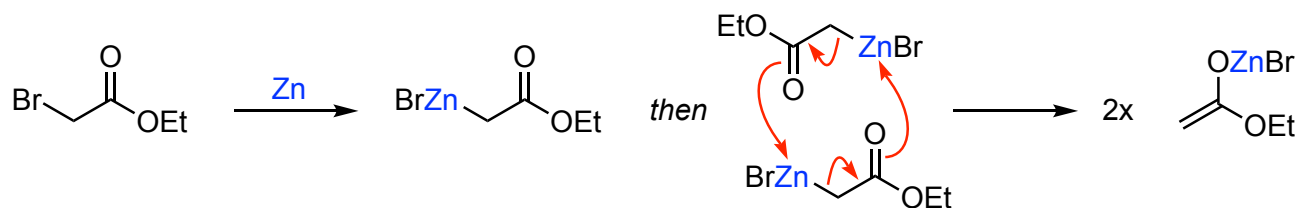
(ii) **Optional** decarboxylation under acidic conditions



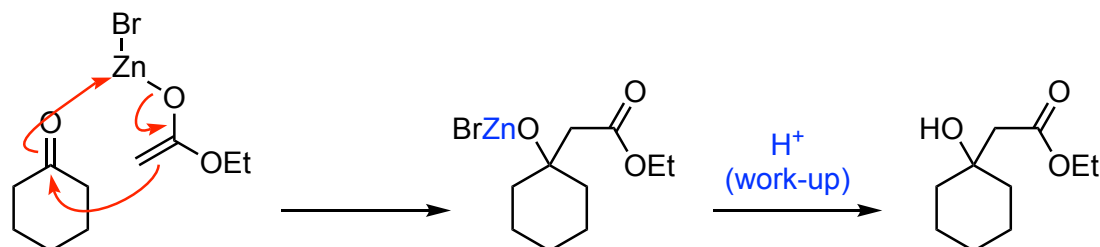
# More aldol-type reactions

(d) **Reformatsky reaction**: zinc enolate from  $\alpha$ -bromoacetate esters –  $\beta$ -hydroxy esters

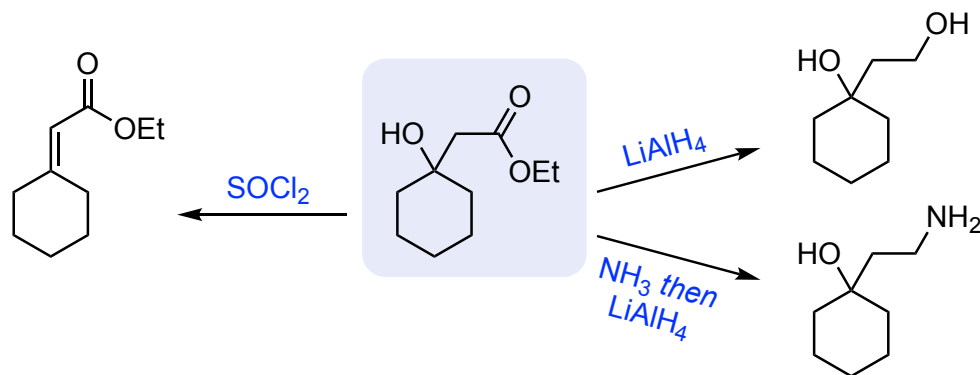
(i) Preparation of the zinc enolate (organozinc reagents react very slowly with esters)



(ii) Aldol-type reaction with an aldehyde or ketone (and  $H^+$  work-up)



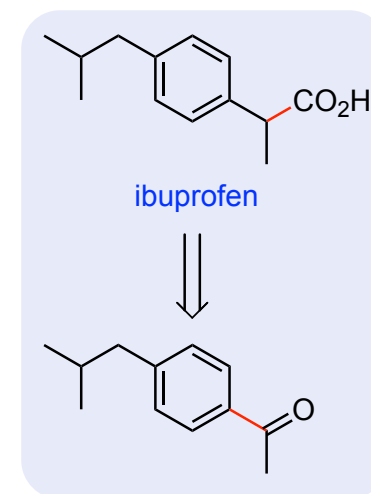
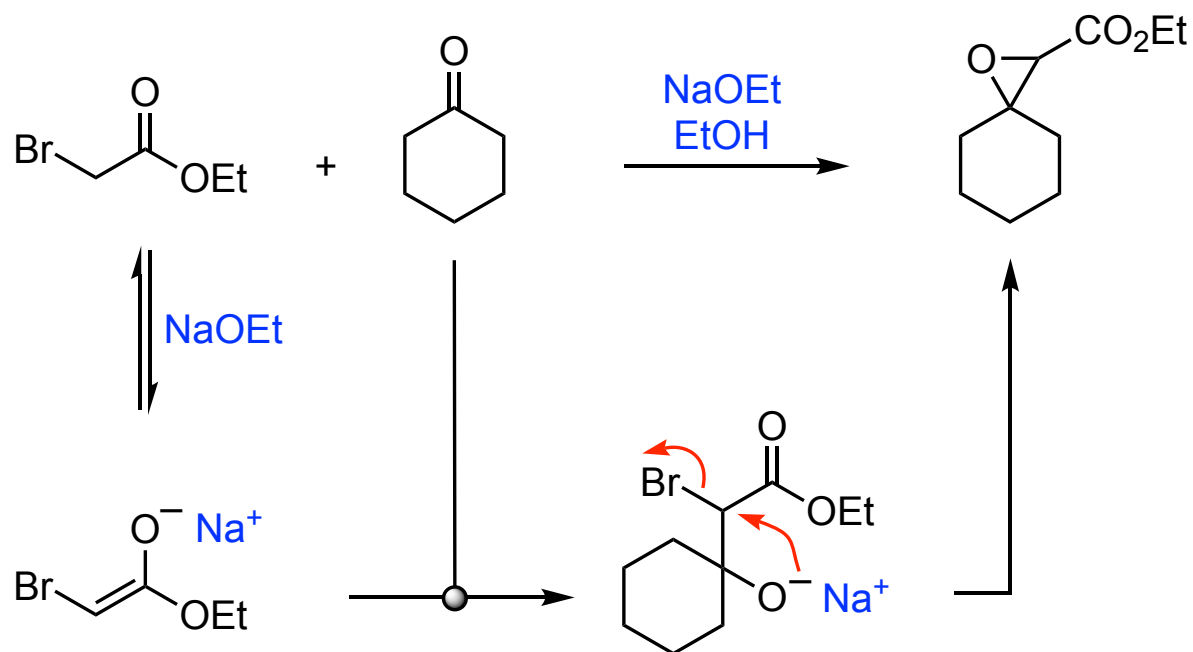
(iii) **Optional** transformations of the product



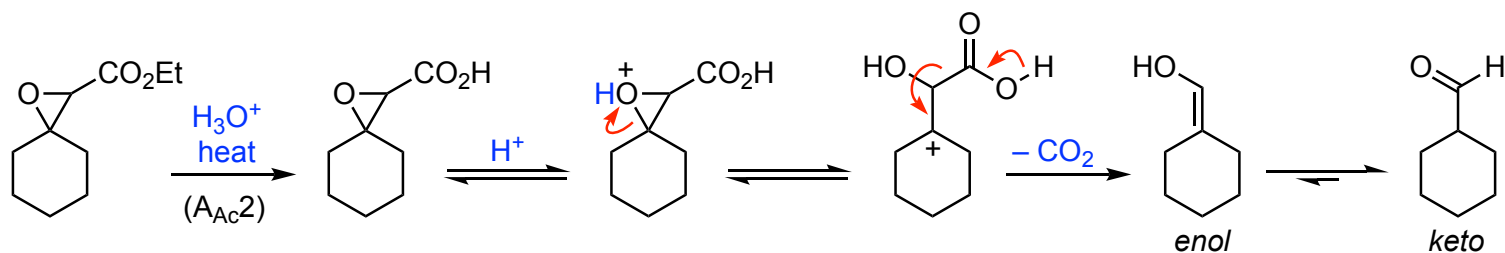
# More aldol-type reactions

(e) **Darzens reaction**: enolate of  $\alpha$ -bromoacetate esters – **glycidic esters**

(i) Glycidic ester formation. Glycidic acids are  $\alpha,\beta$ -epoxy acids



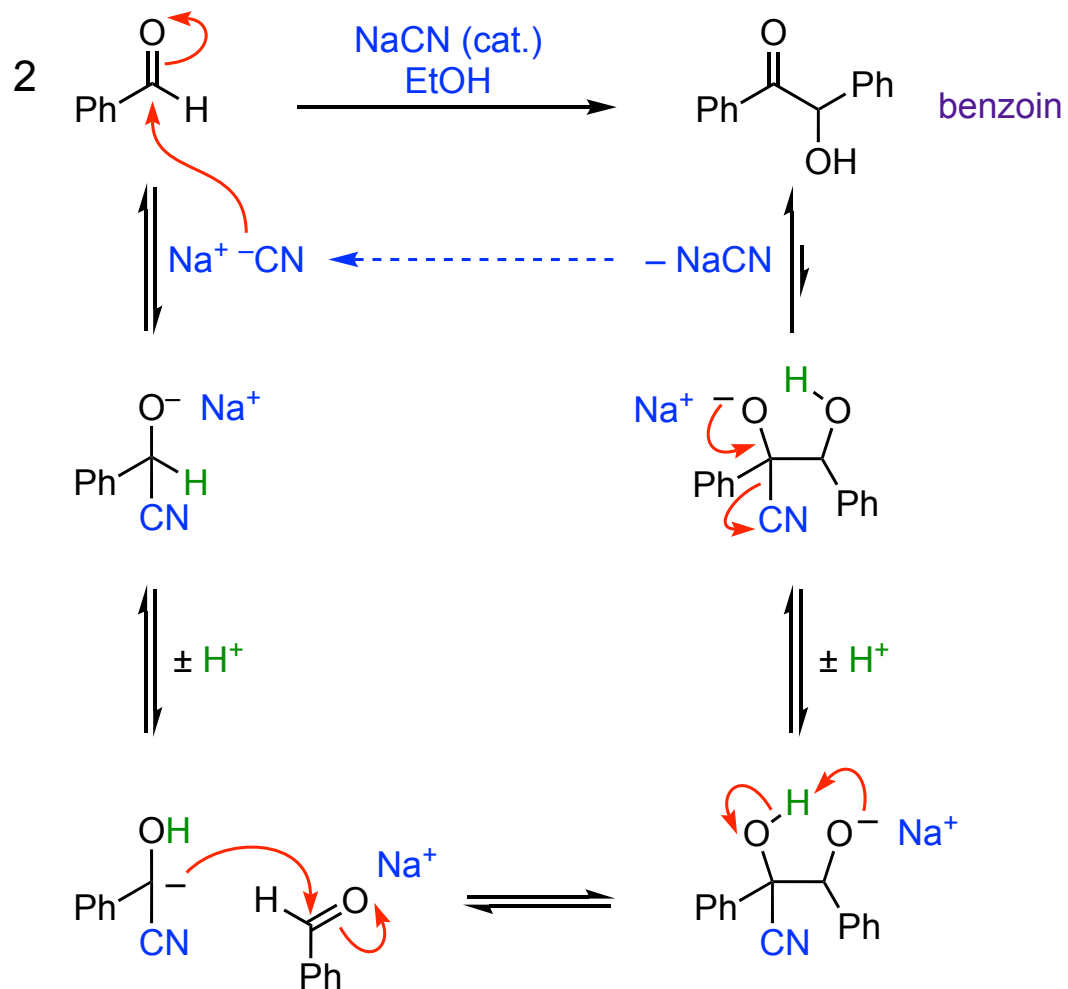
(ii) **Optional** hydrolysis and decarboxylation results in overall *homologation*



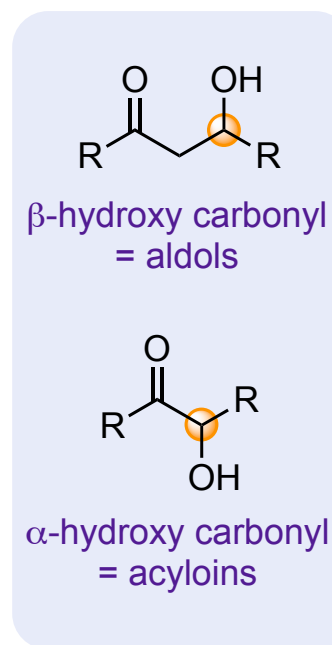
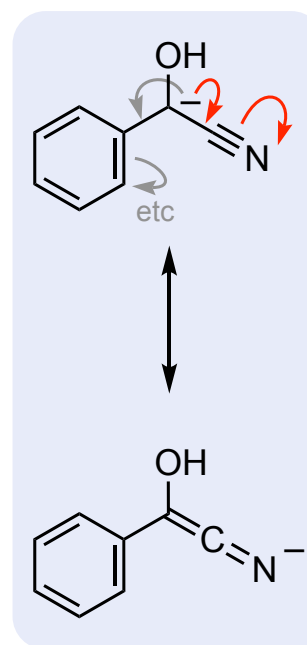
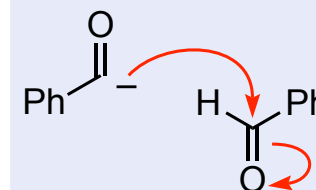
# More aldol-type reactions

(f) **Benzoin reaction**: special reaction of a nitrile 'enolate'; example of the **umpolung** concept

*Cf.* slide 18, (slide 23: another example of umpolung)



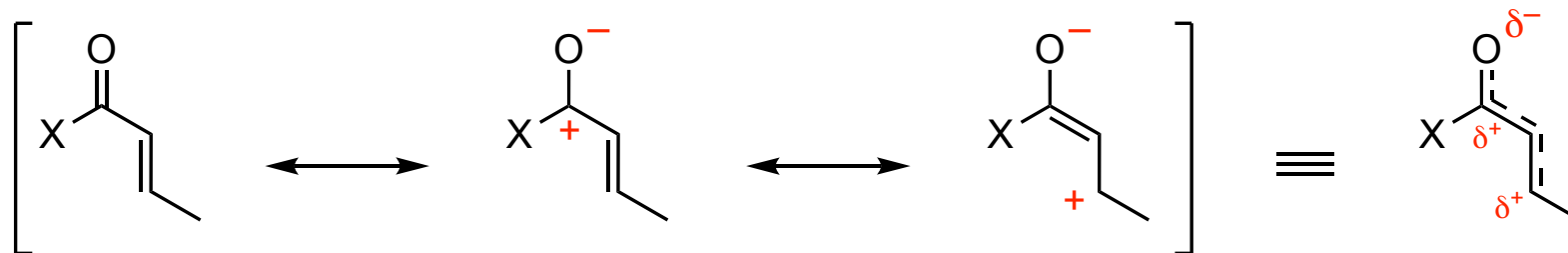
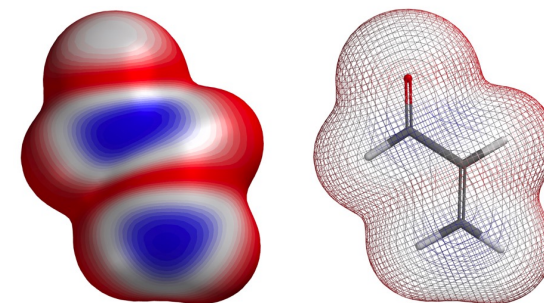
It's as if:



# Addition to $\alpha,\beta$ -unsaturated carbonyls

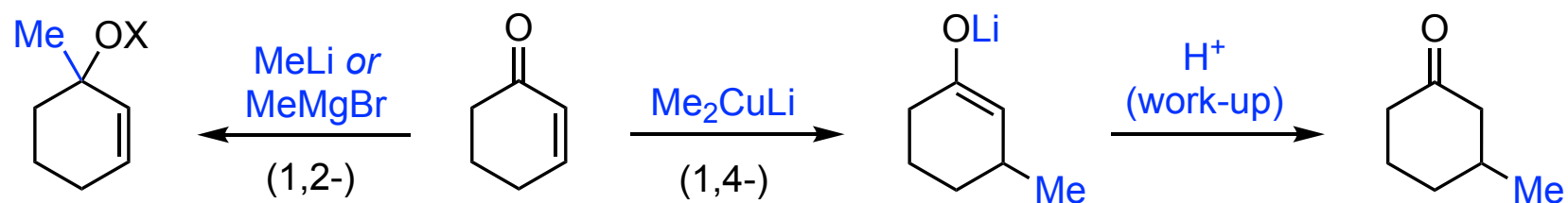
Enal, enone, and enoate ( $\alpha,\beta$ -unsaturated carbonyl) reactivity

Graphic shows |LUMO| map onto electron density (blue = electrophilic)



X = H, alkyl, OR

⇒ Both 1,2- and 1,4- (conjugate) addition;  
nature of nucleophile? reversibility?



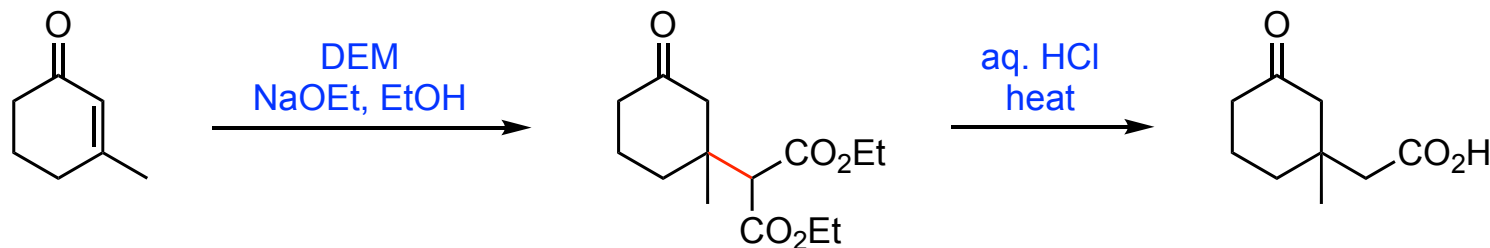
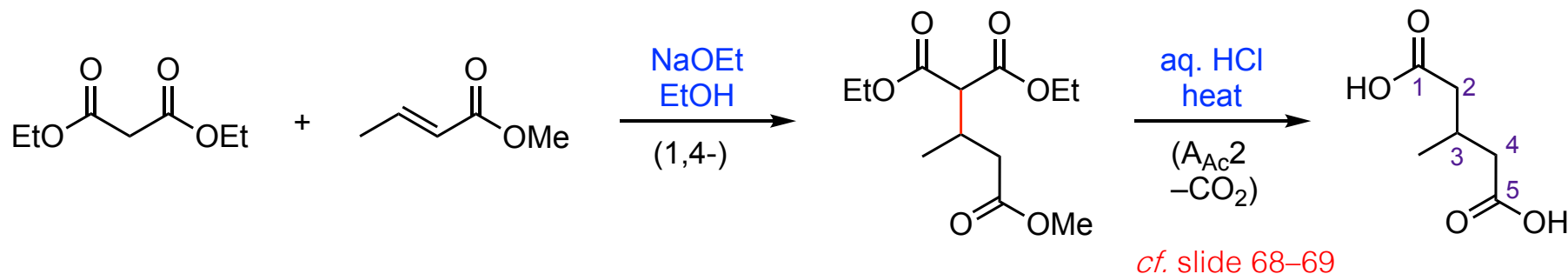
X = Li / MgBr  
X = H ← H<sup>+</sup> (work-up)

# Enolate addition to $\alpha,\beta$ -unsaturated carbonyls

**Michael reaction:** enolate +  $\alpha,\beta$ -unsaturated carbonyl  $\rightarrow$  1,5-dicarbonyl

Classically involves DEM + enone/enoate

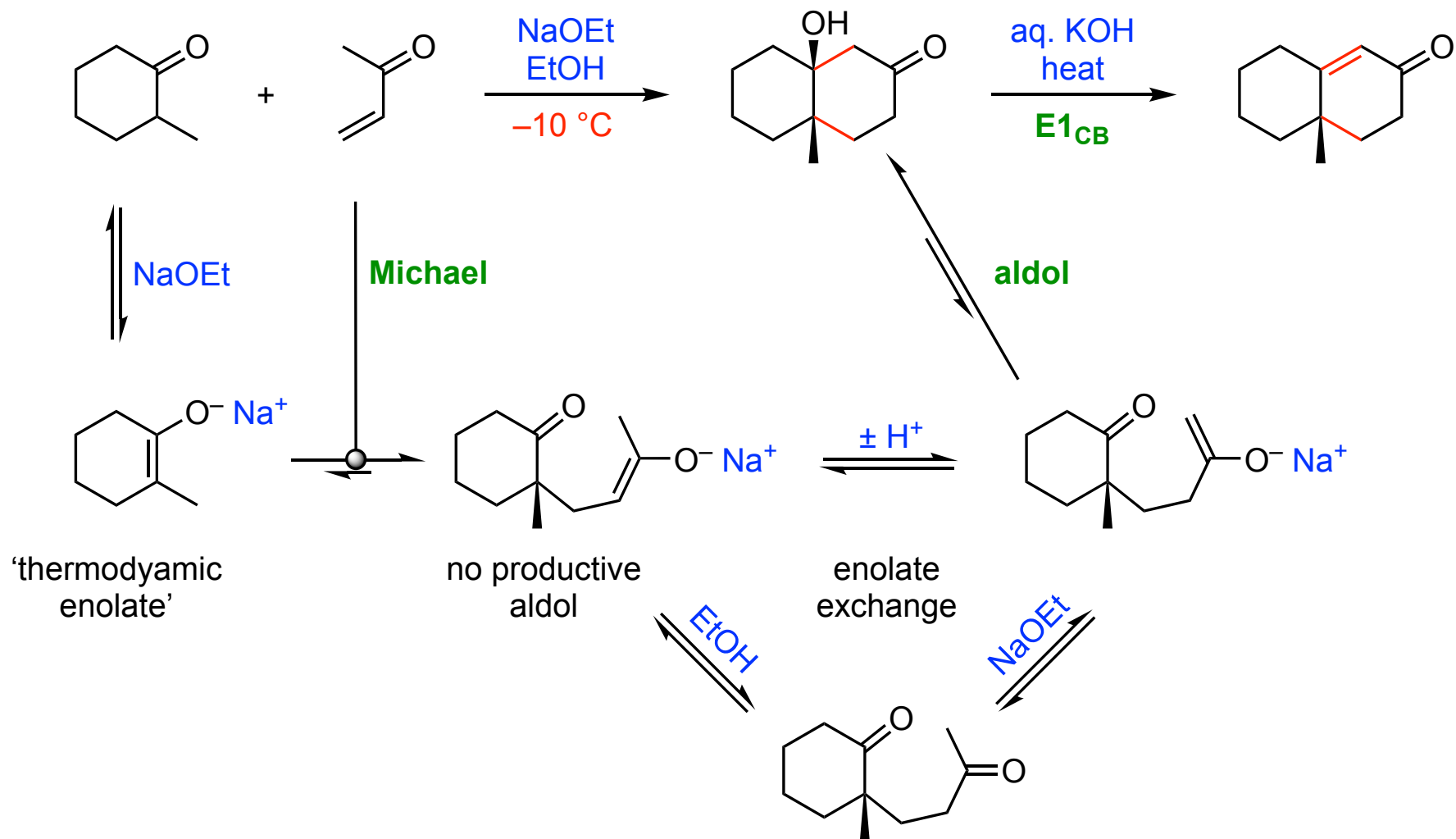
Driven here by creation of new (C–C) $\sigma$  ( $\sim 350$  kJ mol $^{-1}$ ) vs. breaking (C–C) $\pi$  ( $\sim 250$  kJ mol $^{-1}$ )



# Enolate addition to $\alpha,\beta$ -unsaturated carbonyls

**Robinson annulation:** Michael reaction then aldol reaction  $\rightarrow$  cyclohexenones

The 1935 reaction used  $\text{NaNH}_2$  as base; many variants subsequently\*

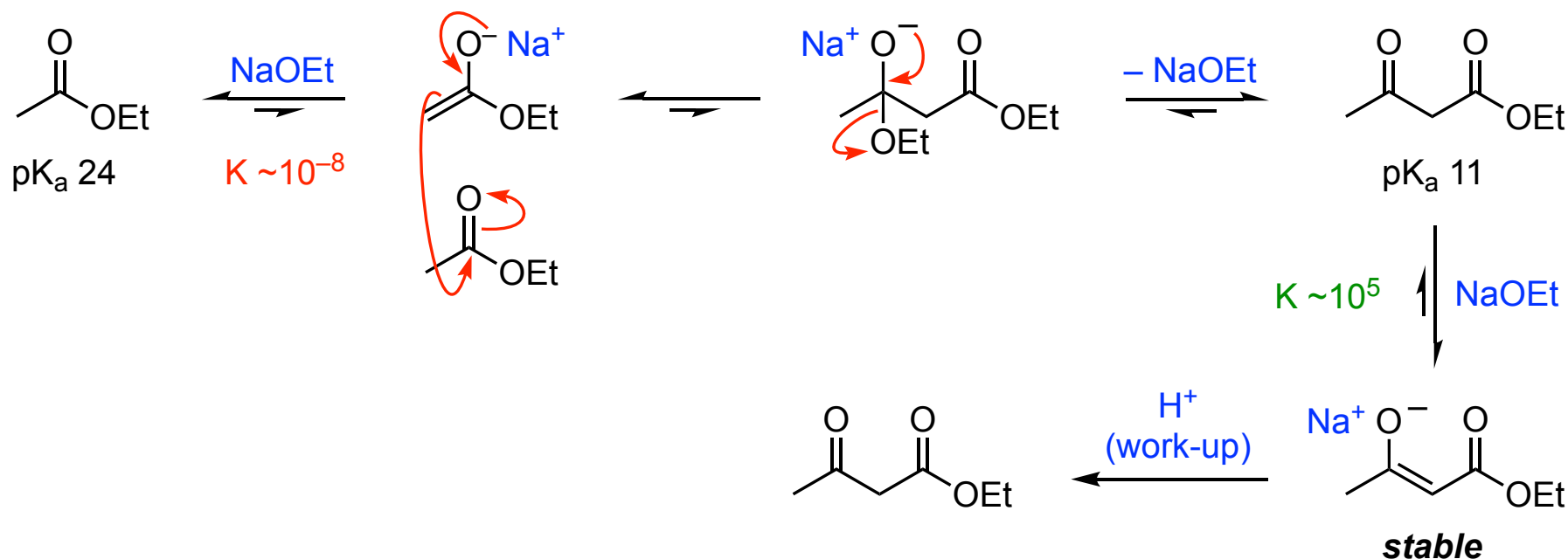




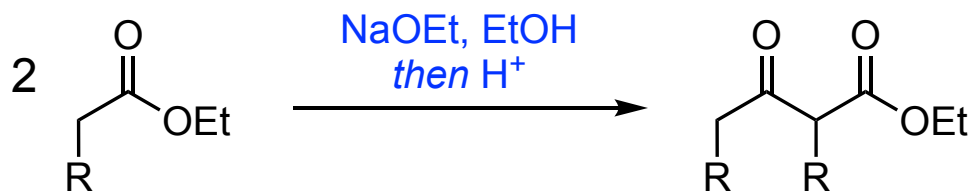
# Ester-ester condensation reactions

Q. What happens if an ester is deprotonated in the absence of an aldehyde or ketone?

A. It adds to itself; this can be a productive route to  **$\beta$ -ketoesters** like EAA [CTL: expt. S104]



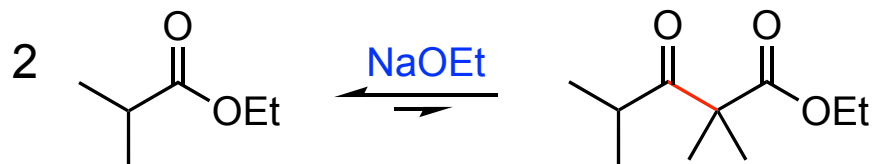
Known as the **Claisen condensation**; overall:



- The starting ester should have  $\alpha\text{-CH}_2$  ...
- ... so that the product can form a stable enolate
- Crossed Claisen condensations work well if one component cannot enolise

# Ester-ester condensation reactions

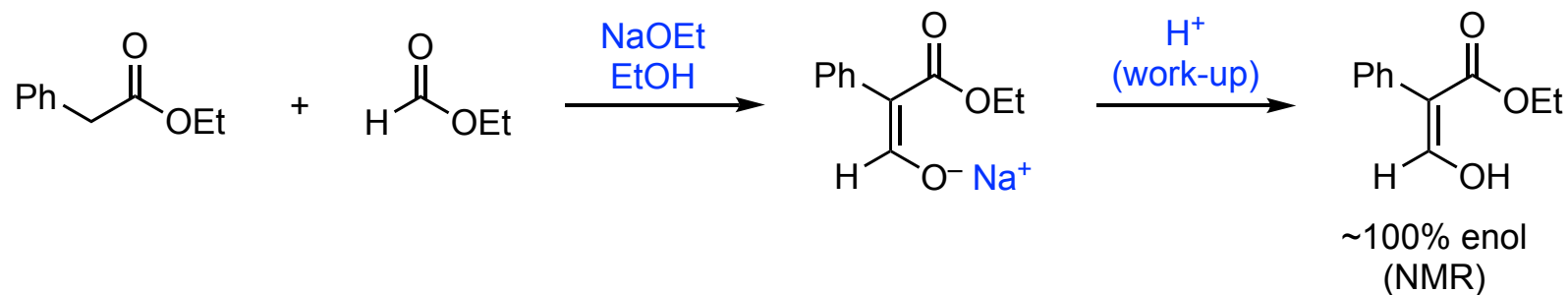
## An unsuccessful Claisen condensation



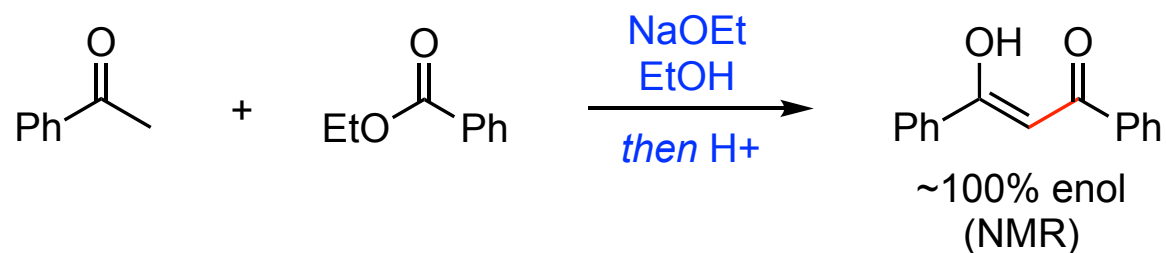
- The position between the two carbonyls bears no protons and cannot therefore form a stable enolate

## Crossed Claisen reactions with one non-enolisable component

### (i) Two esters



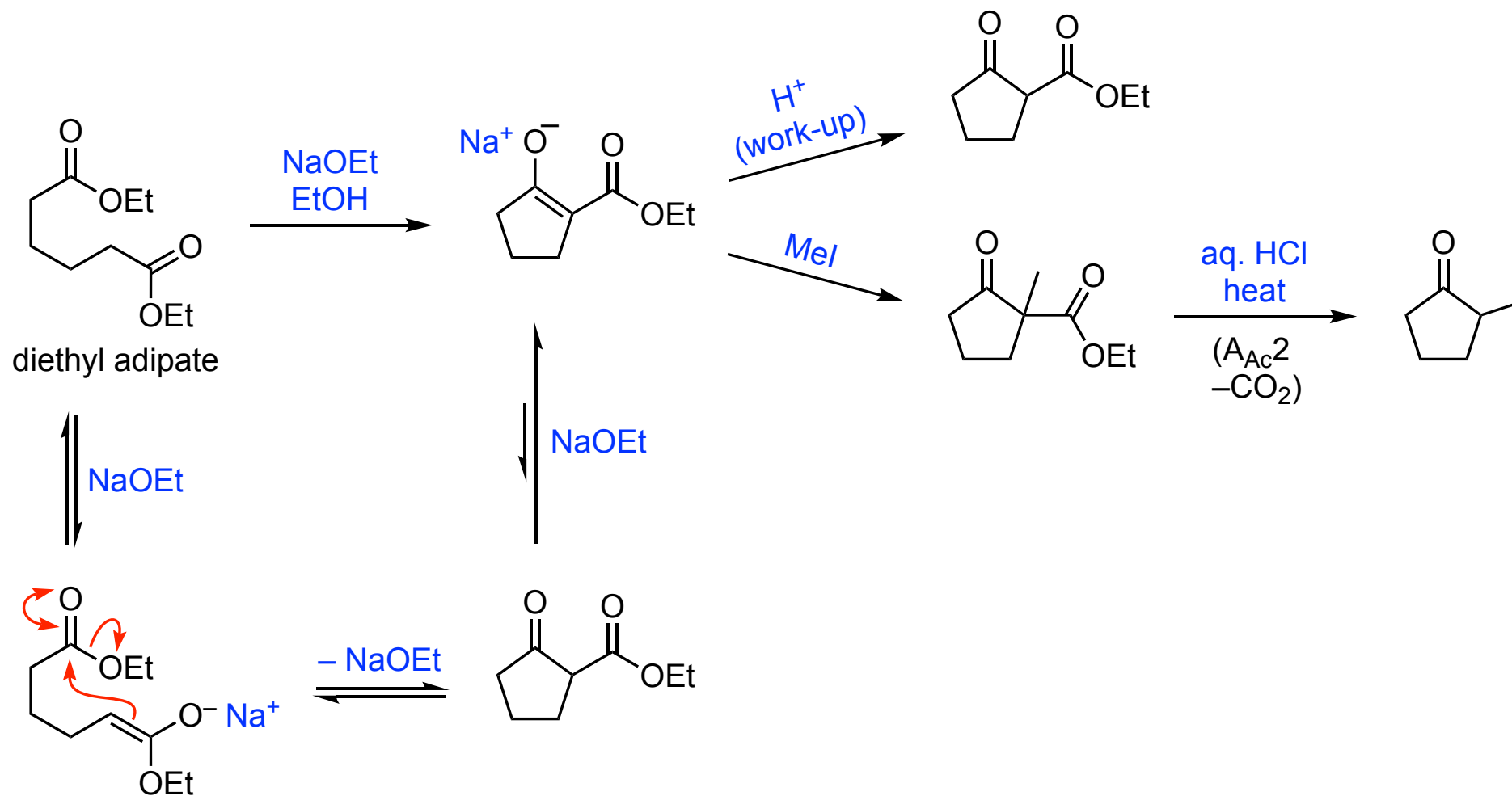
### (ii) Ester + ketone $\rightarrow$ $\beta$ -diketone



# Ester-ester condensation reactions

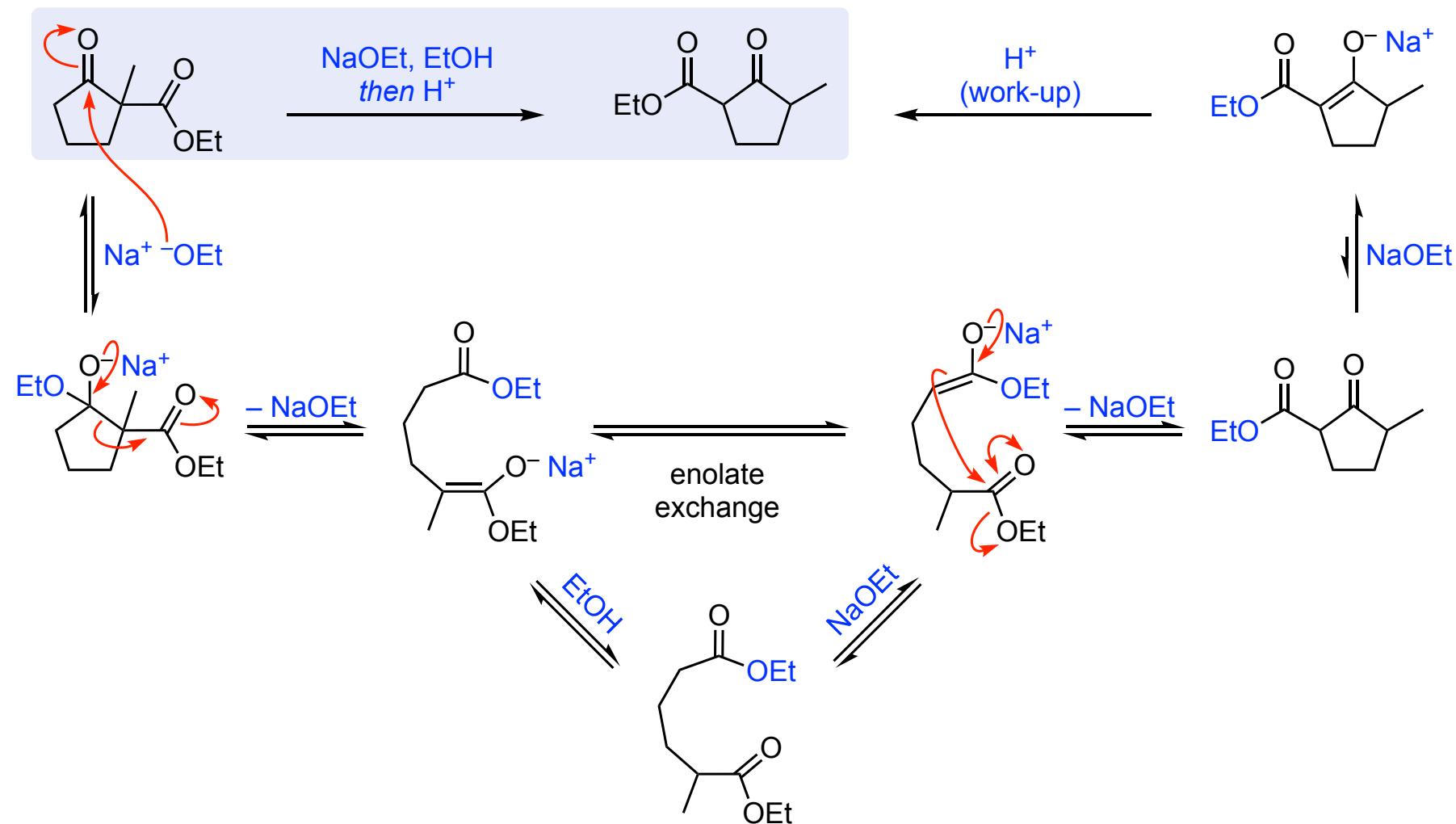
Intramolecular Claisen condensations: **Dieckmann cyclisation**

Classic example *en route* to (monoalkylated) cyclopentanones



# Ester-ester condensation reactions

Claisen and Dieckmann: reversibility...



# Prelims (Section A) carbonyl chemistry questions

Year	Question
2022J	Q1.III, Q2, Q5.II parts, Q7 most parts
2022S	Q2, Q7 (a), (e), (f)
2021J	Q2.II(b), Q4.I, Q5 (f)–(h), Q6, Q7.II(b)
2021S	Q1.II(c), Q2.II(c), Q4.I(b)–(e), Q5
2020J	Q1.III, Q2.II(c)–(e), Q6
2020S	no paper set
2019J	Q1.II, Q2 (a)–(e), Q7 most parts
2019S	Q2, Q4 (b)–(d), (f)
2018J	Q1, Q2 parts, Q4 (c) parts, Q6, Q7 (b) parts
2018S	Q2

## From June 2003

### 3. Answer Parts I and II.

#### Part I.

For EACH of the following compounds, indicate what products [if any] would be formed by treatment with NaOH in H<sub>2</sub>O. Give a mechanism for each of the reactions. [10]

- |                             |                           |
|-----------------------------|---------------------------|
| a) PhCHO                    | b) MeCOOMe                |
| c) MeCOCH <sub>2</sub> COMe | d) MeCH(OMe) <sub>2</sub> |

#### Part II.

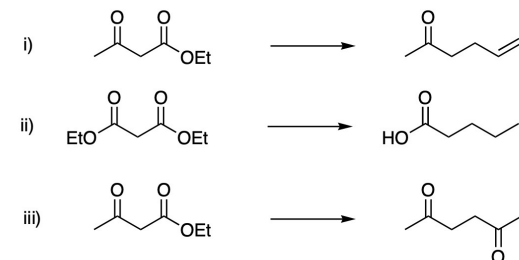
For EACH of the following compounds, indicate what products [if any] would be formed by treatment with H<sub>2</sub>SO<sub>4</sub> in H<sub>2</sub>O. Give a mechanism for each of the reactions. [10]

- |                          |                           |
|--------------------------|---------------------------|
| a) PhCOOCMe <sub>3</sub> | b) MeCOOMe                |
| c) MeOCH=CH <sub>2</sub> | d) MeCH(OMe) <sub>2</sub> |

### 4. Answer Parts I and II.

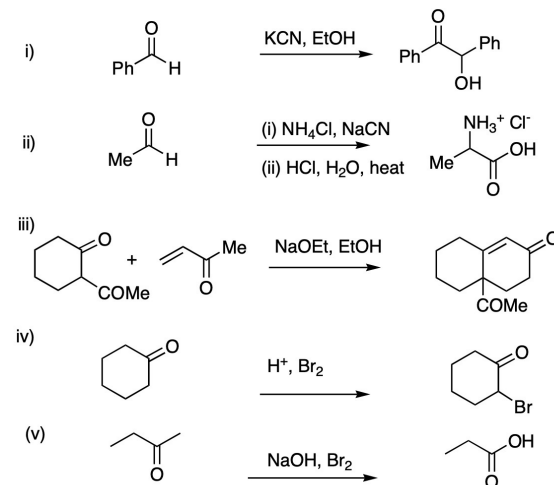
#### Part I.

Propose reagents for **two** of the following synthetic transformations. Give a mechanism for each of the reactions you propose. [2 x 4]



#### Part II.

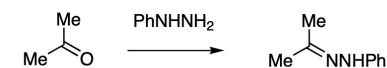
Suggest a mechanism for **four** of the following reactions: [4 x 3]



### 6. Answer Parts I and II.

#### Part I.

- i) Draw a mechanism for the formation of the hydrazone in the following reaction and explain why one of the steps is acid catalysed: [4]



- ii) Discuss how rate of the reaction varies as the pH is changed from 0 to 14. [3]
- iii) What product(s) would be formed from the reaction of phenyl hydrazine (PhNHNH<sub>2</sub>) with MeCOOMe? [3]