Overheads: - Outline

Recap Friday:

Addition of H⁻ and Grignards

To Ketones/Aldehydes:

H- : NaBH$_4$ or LiAlH$_4$
R- : R-MgBr or R-Li
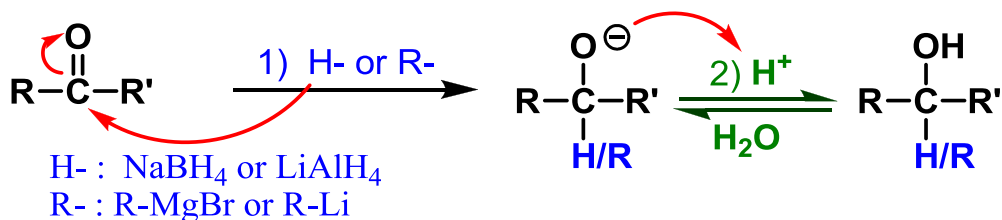
Reactions of R-C-LG with H⁻ + Grignards e.g. esters

1) LiAlH$_4$
2) H⁺ /H$_2$O

same as for ketone...   ...but LG can leave!

H⁻
(4 H's per LiAlH$_4$)

*NaBH$_4$ not strong enough
∴ need LiAlH$_4$

2) H⁺
H$_2$O
(when done)

ester ⟶ 1° alcohol

Grignards

1) CH$_3$MgBr
ether

1) 2 R'MgBr
2) H⁺ / H$_2$O

2) H⁺
H$_2$O
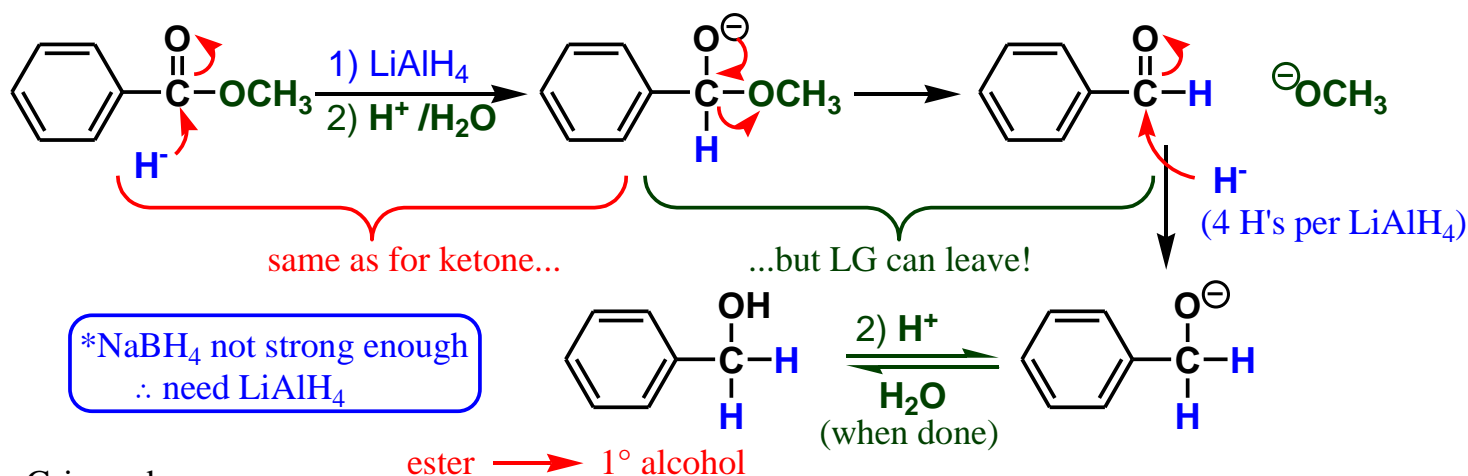
ester ⟶ 3° alcohol with 2 identical R groups
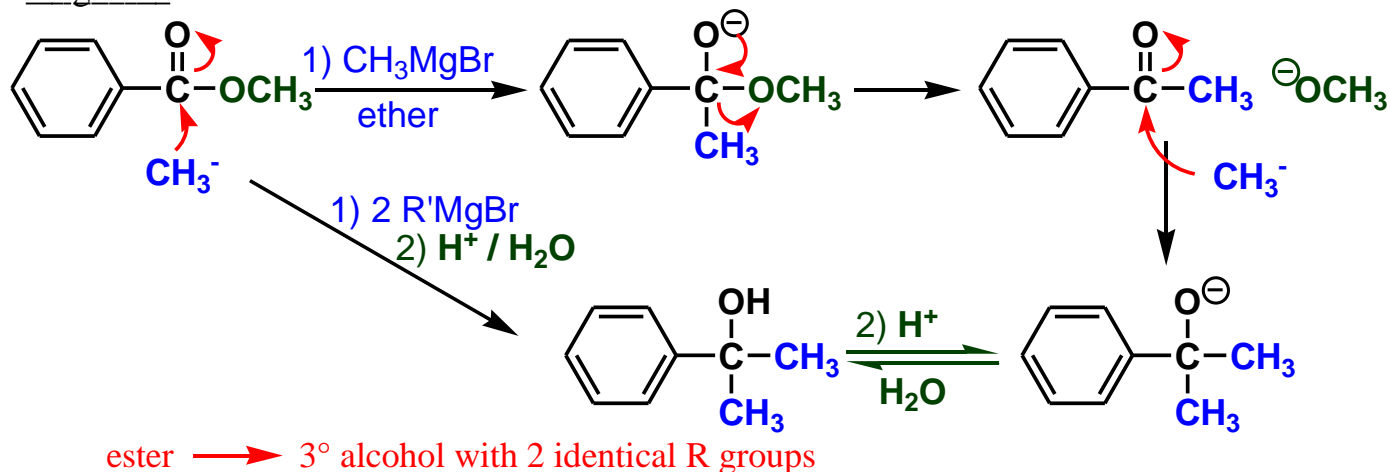
⟹ acyl halides and anhydrides give same products, but
usually use esters - less reactive, less dangerous

3) Addition of N Nucleophiles:
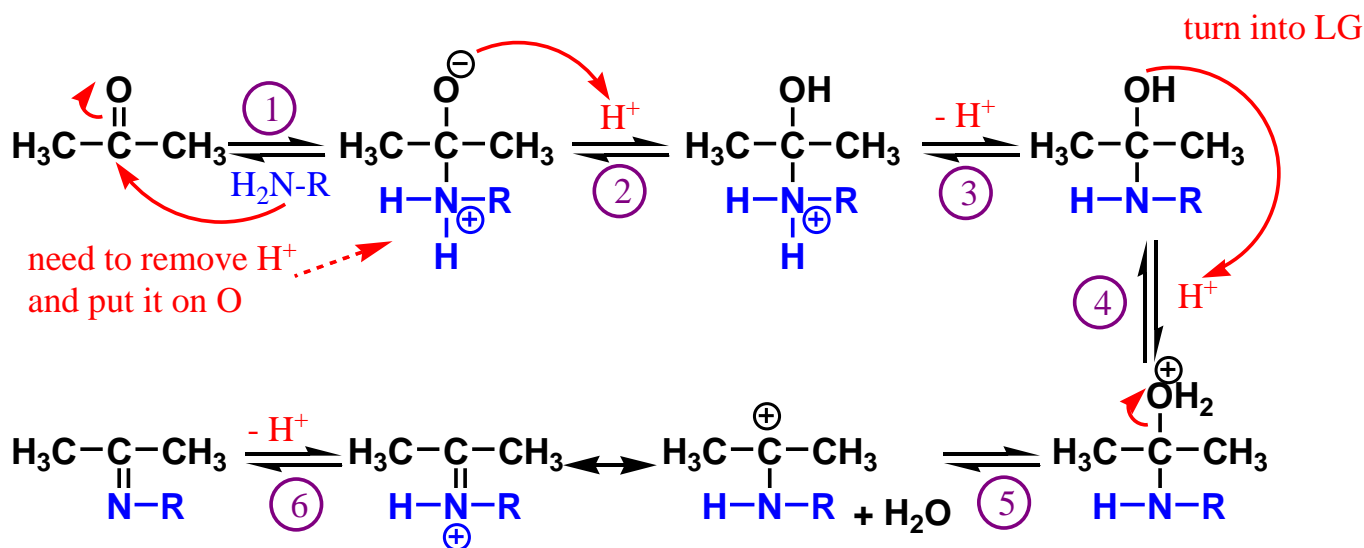- 1° amines (R-NH$_2$) add to ketones / aldehydes

$$R,R'C=O \; + \; H_2N-R'' \rightleftharpoons R,R'C=N-R'' \; + \; H_2O$$

an imine

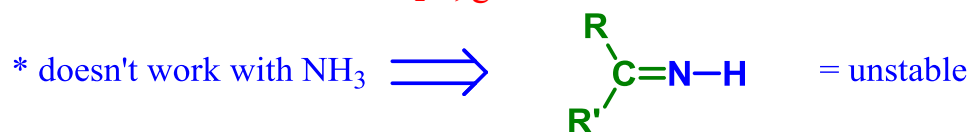R'' = R, Ar, OH, NH$_2$ etc
- eg amino acid

Mechanism: another 6 easy steps!
- But no LG – so instead turn the O into a LG (eventually)
- R-NH$_2$ good Nu⁻ (stronger base than H$_2$O) so do not need H⁺ catalyst

turn into LG

H$_3$C-C(=O)-CH$_3$ $\xrightarrow[H_2N-R]{1}$ H$_3$C-C(O⁻)(CH$_3$)-N(H)(⊕)(H)-R $\xrightarrow[2]{H^+}$ H$_3$C-C(OH)(CH$_3$)-N(H)(⊕)(H)-R $\xrightarrow[3]{-H^+}$ H$_3$C-C(OH)(CH$_3$)-N(H)-R

need to remove H⁺
and put it on O

$\boxed{4}$ H⁺

H$_3$C-C(=N-R)-CH$_3$ $\xrightarrow[6]{-H^+}$ H$_3$C-C(N(H)(⊕)-R)-CH$_3$ ⟷ H$_3$C-C(⊕)(N(H)-R)-CH$_3$ + H$_2$O $\xleftarrow[5]{}$ H$_3$C-C(OH$_2$⊕)(CH$_3$)-N(H)-R

- If remove H$_2$O, eq'm shifts to right →
- if react imine with H$_2$O, get reverse reaction ←

* doesn't work with NH$_3$ ⟹ R,R'C=N-H   = unstable

* 2° amines (H-N(R)-R) can't make R,R'C=N-R

⟹ in step 6, no H⁺ on N to remove!

eg
H$_3$C-C(=O)-CH$_3$ + H$_3$C-N(H)-CH$_3$ ⇌ [5 easy steps] H$_3$C-C(⊕)(N(CH$_3$)CH$_3$)-C(H)(H)-H base ⟷ H$_3$C-C(=N(⊕)(CH$_3$)CH$_3$)-CH$_3$

step 6-alt!

H$_3$C-C(N(CH$_3$)CH$_3$)=C(H)-H

enamine
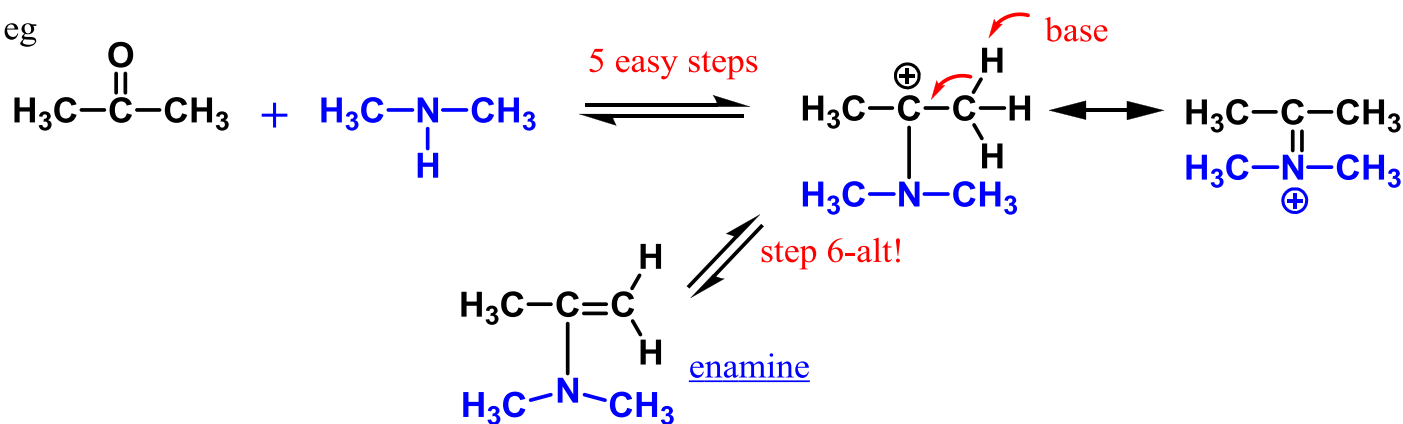
4) Addition of O Nucleophiles:
- seen addition of OH^-
- can also be acid-catalyzed:

$$H_3C-\overset{O}{\underset{}{C}}-CH_3 \underset{H_2O}{\overset{H^+}{\rightleftharpoons}} H_3C-\overset{\overset{\oplus}{O}-H}{\underset{}{C}}-CH_3 \rightleftharpoons H_3C-\overset{OH}{\underset{\underset{\oplus}{H-O-H}}{C}}-CH_3 \overset{-H^+}{\rightleftharpoons} H_3C-\overset{OH}{\underset{OH}{C}}-CH_3$$

hydrate
K_{eq} very small
for ketones
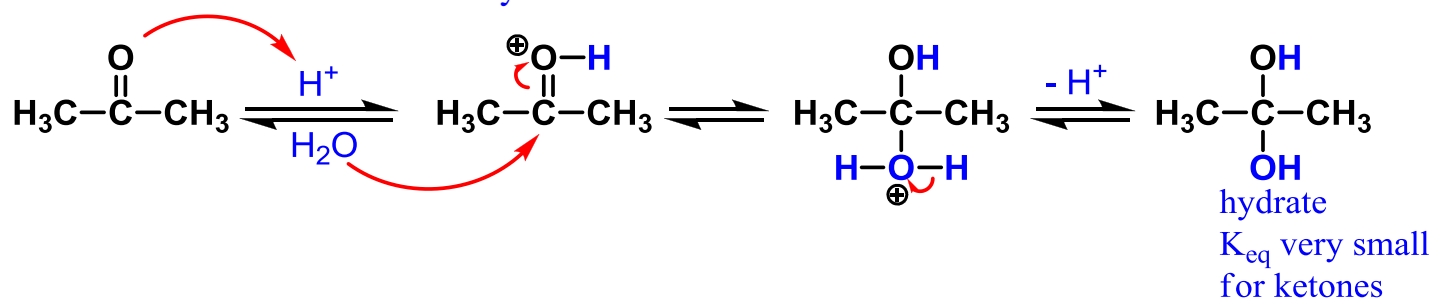
Addition of Alcohols (ROH)

$$H_3C-\overset{O}{\underset{}{C}}-CH_3 \underset{2\ ROH}{\overset{H^+}{\rightleftharpoons}} H_3C-\overset{OR}{\underset{OR}{C}}-CH_3 \quad +\ H_2O$$

acetal

use ROH as
solvent to make
acetal

7 easy steps
add 2 Nu⁻ ∴ 1 extra step

use H_2O as solvent to
"hydrolyze" acetal back
to ketone
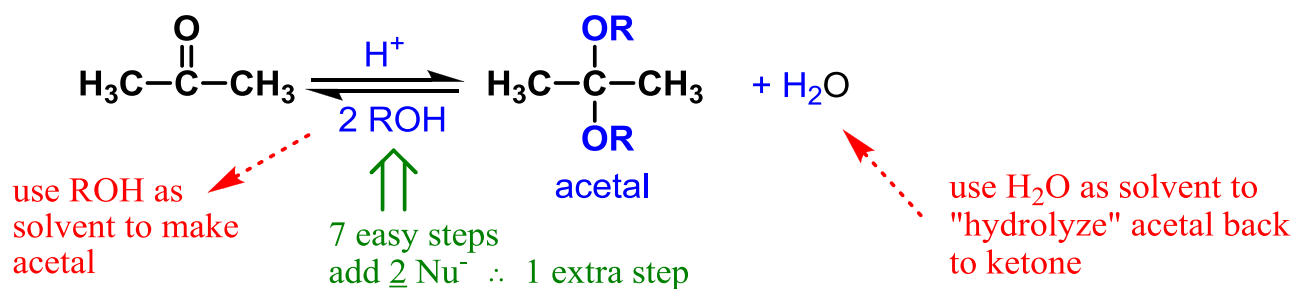
Mechanism similar to hydrate, but in 2 "stages"

$$H_3C-\overset{O}{\underset{}{C}}-CH_3 \underset{ROH}{\overset{H^+}{\rightleftharpoons}} \left[H_3C-\overset{OH}{\underset{OR}{C}}-CH_3 \right] \underset{ROH}{\overset{H^+}{\rightleftharpoons}} H_3C-\overset{OR}{\underset{OR}{C}}-CH_3$$

hemiacetal
(hemi=half)

acetal

same 3 steps as
hydrate

another 4
steps

except in rare cases = unstable
⟶ get either ketone or acetal @ eq'm
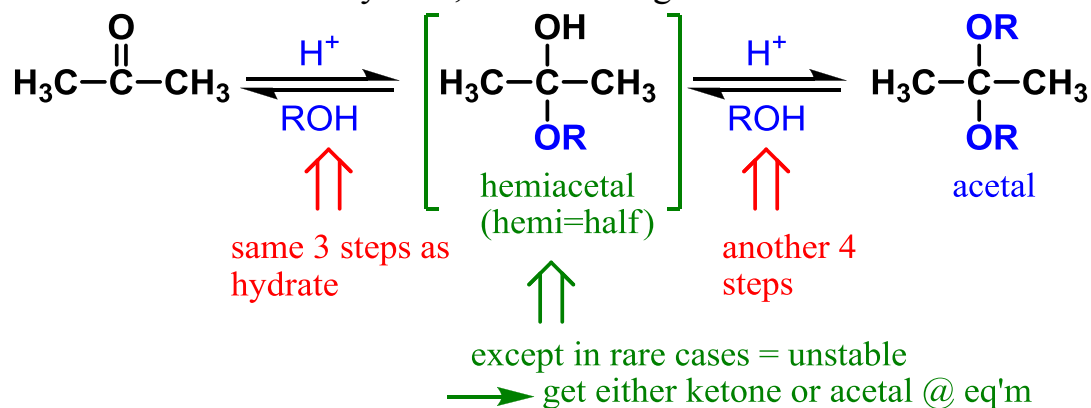
Full Mechanism: in 7 easy steps
- Add ROH (twice!)
- Remove H_2O
- Transfer $+H^+$ / $-H^+$ / $+H^+$ / $-H^+$

hemiacetal

$H_3C-C-CH_3$ H^+ $H_3C-C-CH_3$ ② $H_3C-C-CH_3$ $-H^+$ $H_3C-C-CH_3$

①   ROH $H-O-R$ ③ $O-R$

④ H^+

$\overset{\oplus}{O}H_2$

acetal

$H_3C-C-CH_3$ $-H^+$ $H_3C-C-CH_3$ ROH $H_3C-C-CH_3$ $H_3C-C-CH_3$

⑦ $O-R$ ⑥ $O-R$ ⑤ $O-R$

(+ H₂O)

$H_3C-C-CH_3$

$\oplus O-R$