Chapter 16

# Aldehydes & Ketones • More of Carbonyls

Aldehydes and ketones

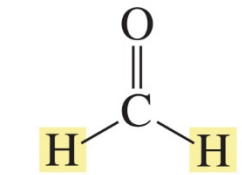
More reactions of RCOOH deriv's

$\alpha,\beta$-Unsat'd C=O comp'ds [C=C–C=O]

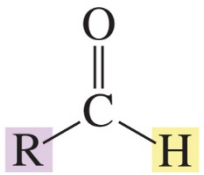
# Aldehydes and ketones



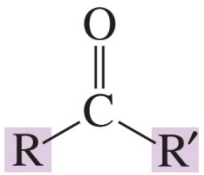
- the 2nd group of carbonyl family



formaldehyde

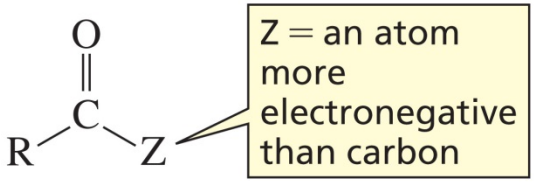


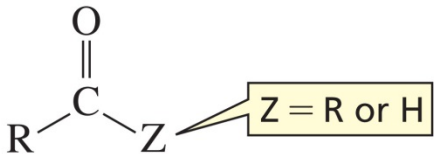
an aldehyde



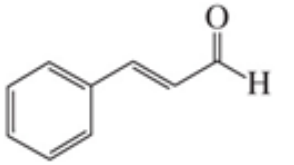
a ketone

III

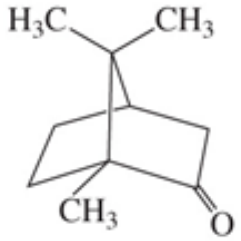


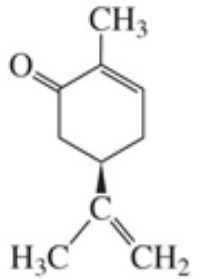

- occur in nature
  - pungent aldehydes; sweet ketones
    - <cf> alcohols, amines, acids
  - hormones



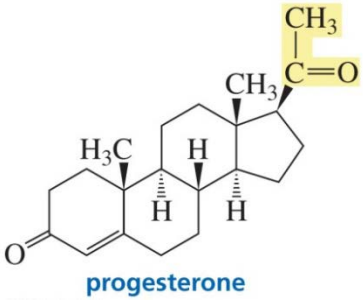
cinnamaldehyde
cinnamon flavoring



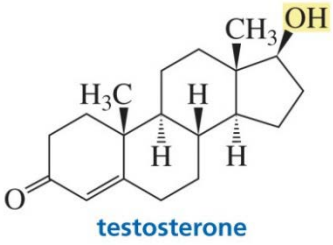
camphor



(*R*)-(–)-carvone
spearmint oil



progesterone

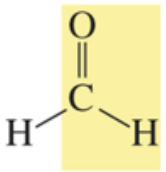


testosterone

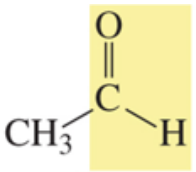
# Nomenclature



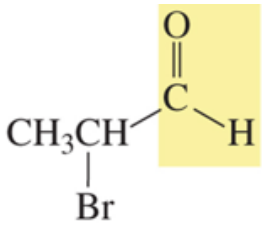
- aldehydes
  - alkanal; --aldehyde



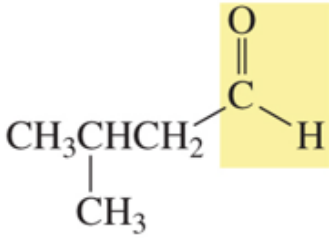
methanal
formaldehyde



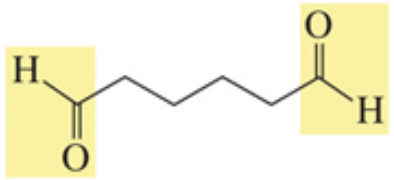
ethanal
acetaldehyde



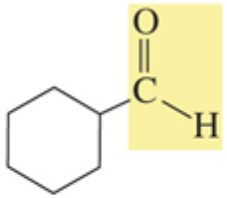
2-bromopropanal
α-bromopropionaldehyde



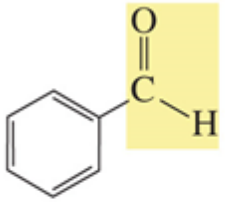
3-methylbutanal
isovaleraldehyde
β-methylbutyraldehyde



hexanedial

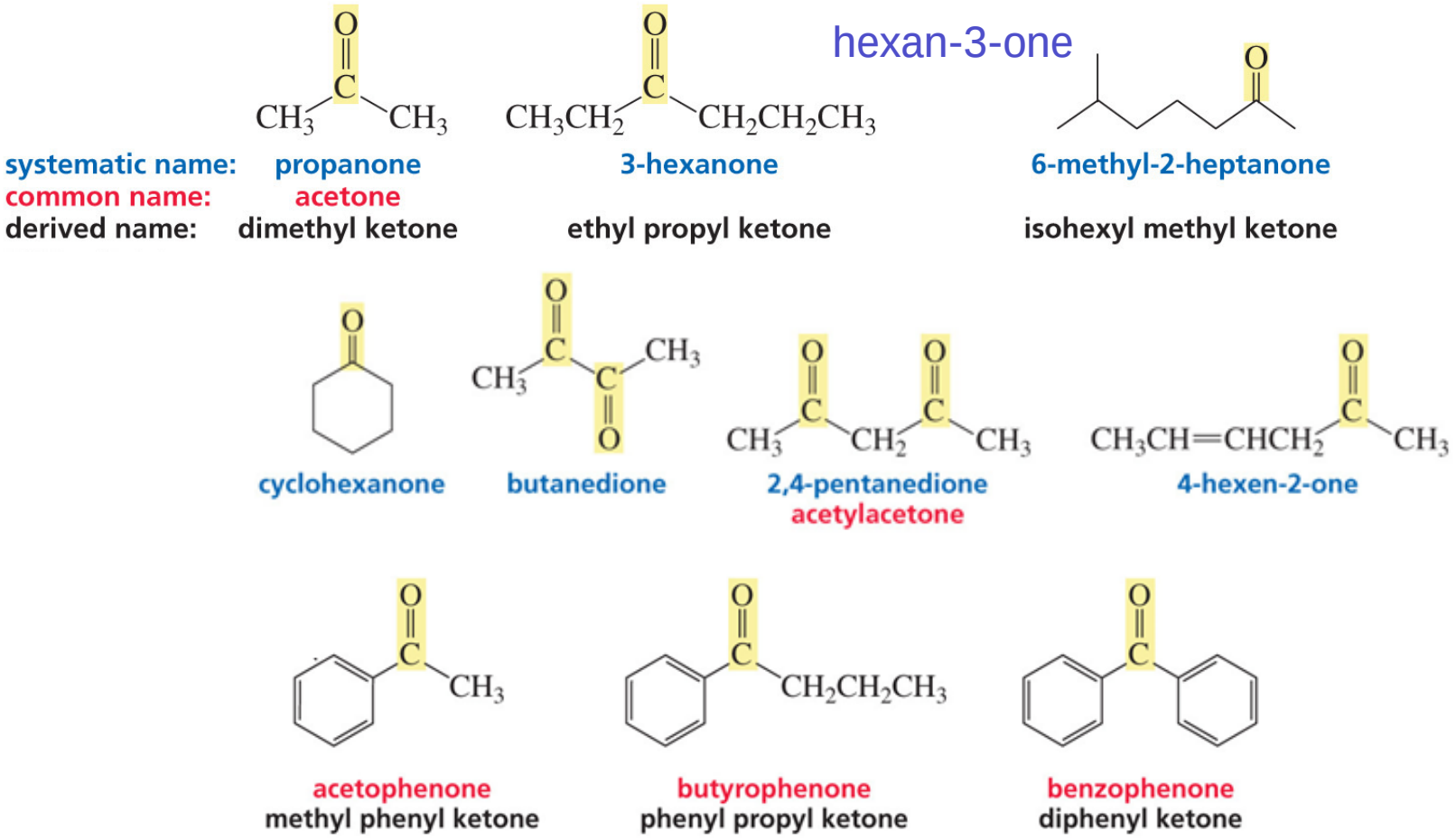


cyclohexanecarbaldehyde



benzenecarbaldehyde
benzaldehyde

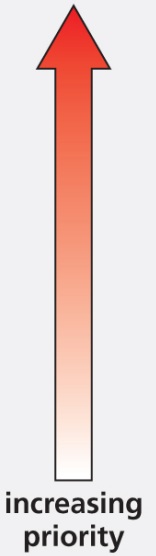
- ketones
  - alkanone; --yl --yl ketone; --acetone, --phenone



- comp'd with two functional groups ~ follow priority
  - only in systematic nomenclature

**Table 16.1** Functional Group Nomenclature

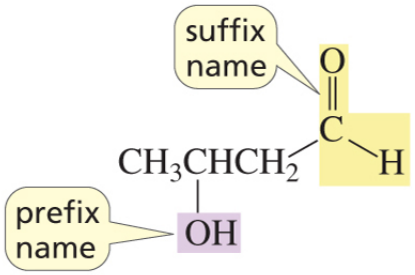
| Class | Suffix name | Prefix name |
|---|---|---|
| Carboxylic acid | -oic acid | Carboxy |
| Ester | -oate | Alkoxycarbonyl |
| Amide | -amide | Amido |
| Nitrile | -nitrile | Cyano |
| Aldehyde | -al | Oxo (=O) |
| Aldehyde | -al | Formyl (CH=O) |
| Ketone | -one | Oxo (=O) |
| Alcohol | -ol | Hydroxy |
| Amine | -amine | Amino |
| Alkene | -ene | Alkenyl |
| Alkyne | -yne | Alkynyl |
| Alkane | -ane | Alkyl |
| Ether | — | Alkoxy |
| Alkyl halide | — | Halo |



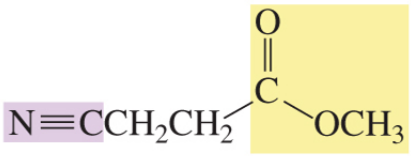

These are <u>not</u> ft'nal groups.

nitro

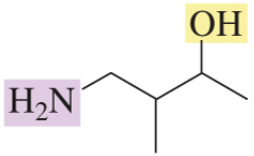
- with 2 ft'nal groups



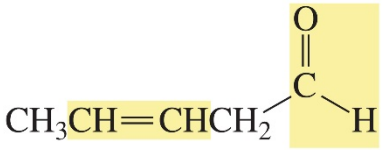

3-hydroxybutanal



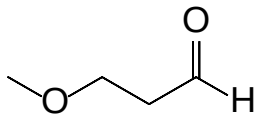

methyl 3-cyanopropanate



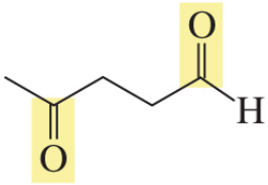

4-amino-3-methyl-2-butanol



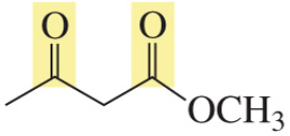

3-pentenal



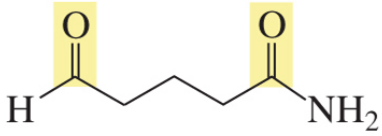

3-methoxypropanal




systematic name: 4-oxopentanal




methyl 3-oxobutanoate

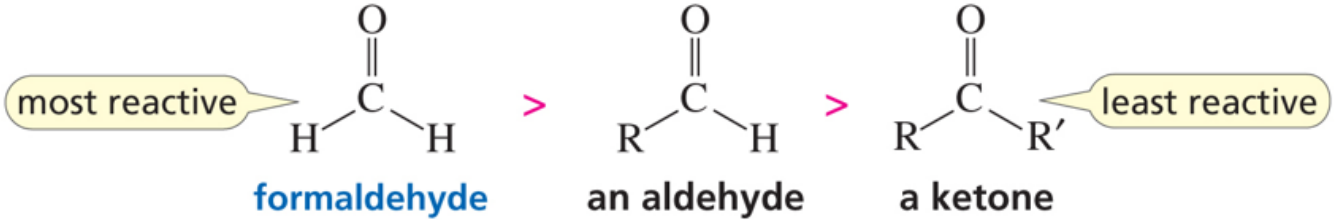


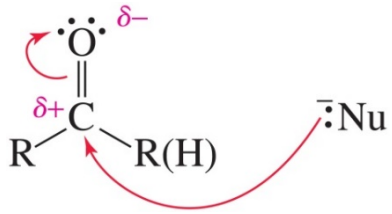

5-oxopentanamide

# Relative reactivity

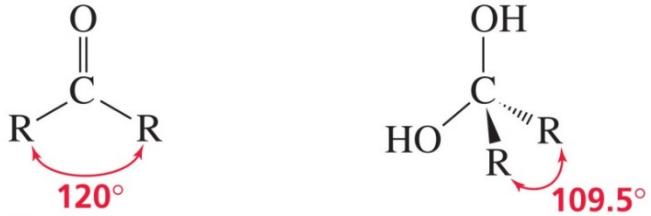


- to Nu:



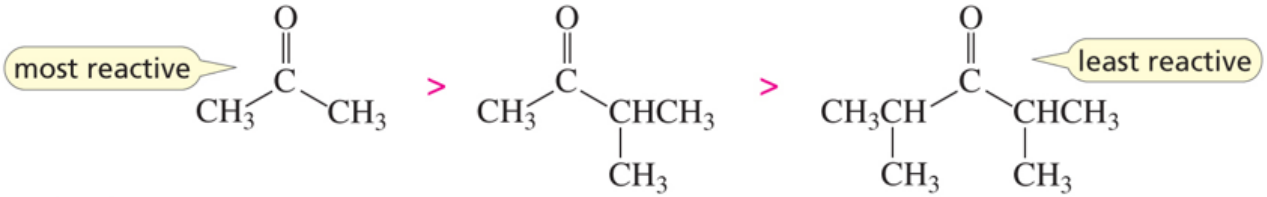




  - electronic [I/M] reason ~ R ED to C (more than H)
  - steric reason ~ R larger (than H)




also in TS/interm

    - betw ketones

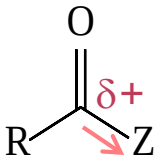


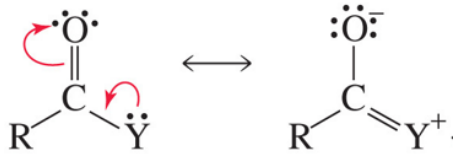
- compared with other carbonyls (to Nu:)

acyl halide > acid anhydride > aldehyde > ketone > ester ~ carboxylic acid > amide > carboxylate ion

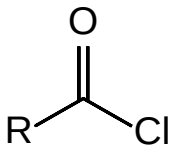
(most reactive … least reactive)

- why? inductive and resonance
  - EWG → C more δ+ ~ I↑
  - resonance → (+) delocalized ~ R↓

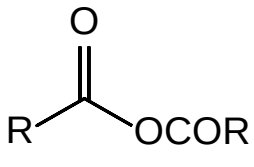


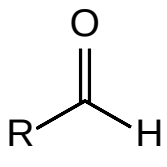

(+) localized



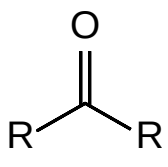

I↑>R↓



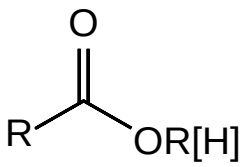

I↑>R↓



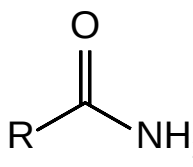

I0 & R0

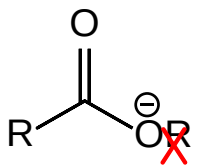



I↓>R0




I↑<R↓




I↑<R↓

# A&K: How to react 1



- nucleophilic addition rxn


  - when Z:⁻ is a **R:⁻** or **H:⁻**
    - C Nu: ~ RMgX, RC≡C:⁻, ⁻:C≡N
    - H Nu: ~ H:⁻
  - TI stable
  - irreversible
    - Z is too basic (compared with N: or O:) to leave.

# A&K: How to react 2



- nucleophilic addition-elimination rxn


  - when Z is of **N:** or **O:**
    - N Nu: ~ amines, $NH_3$
    - O Nu: ~ $H_2O$, ROH
  - and there is enough $H^+$ to protonate OH
  - elimination of water (of carbonyl O) by **:** of Z
  - reversible
    - Z can be eliminated.

Generally speaking, a comp'd having $sp^3$ C bonded to two EN atoms is unstable.
p730, 781, 804

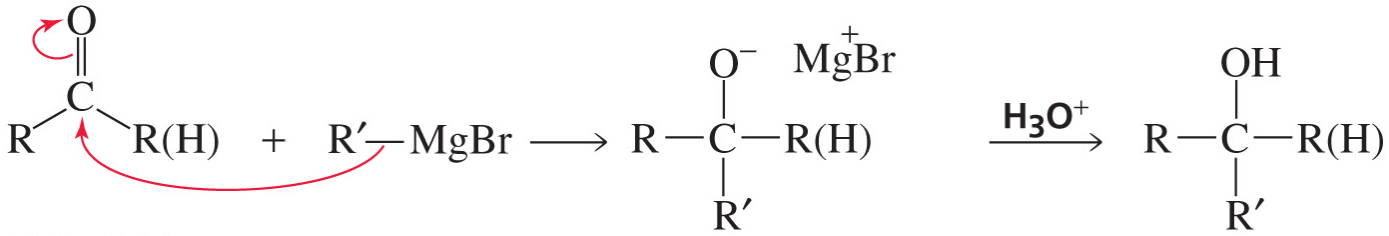
# Rxns with RMgX



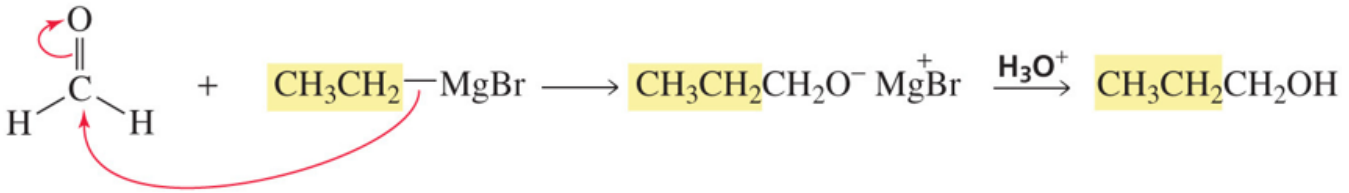
RMgX reacts like a carbanion [C:⁻, a C Nu:]

$CH_3CH_2MgBr$ reacts as if it were $CH_3\ddot{C}H_2\ \overset{+}{M}gBr$

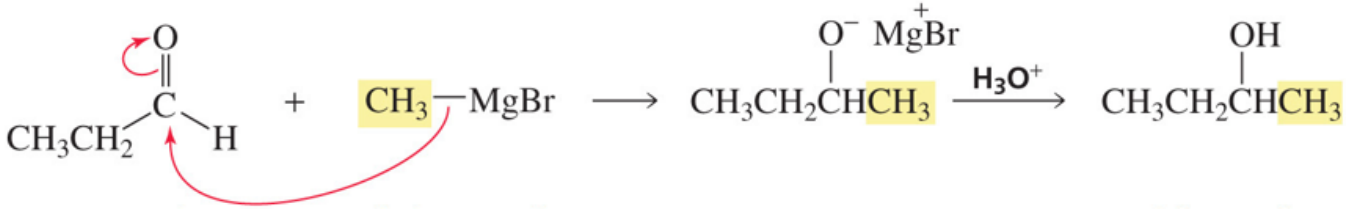
- A&K to alcohol



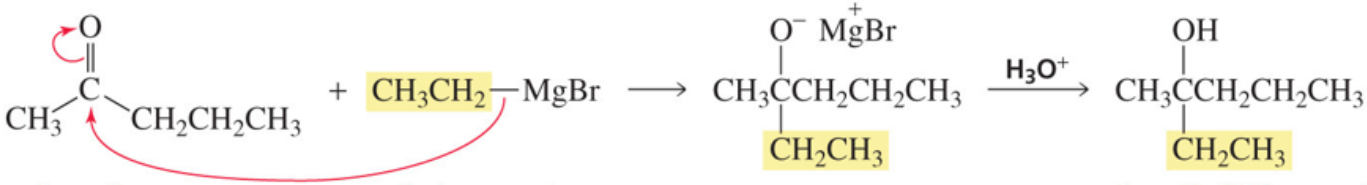

- HCHO → 1°



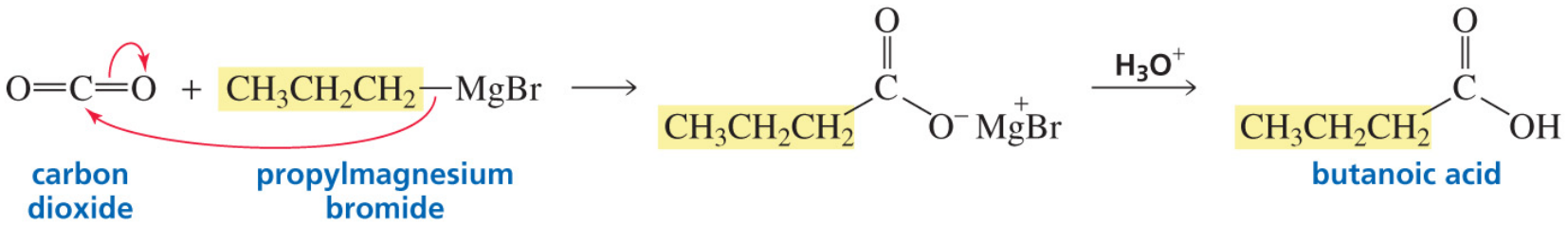

- RCHO → 2°



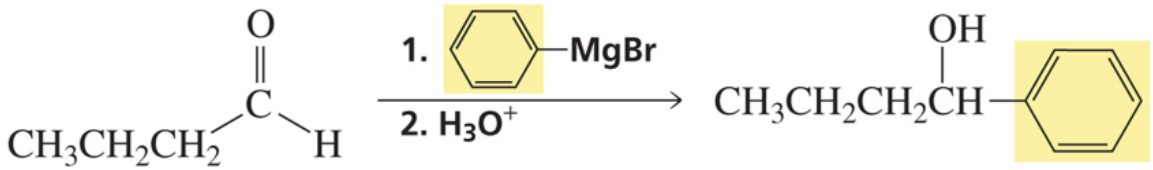

- RCOR' → 3°



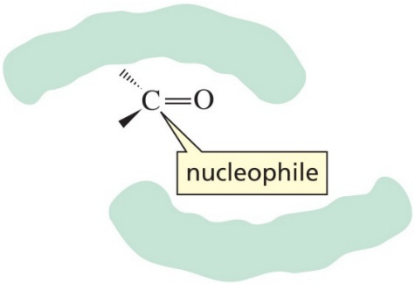
- $CO_2$ to RCOOH



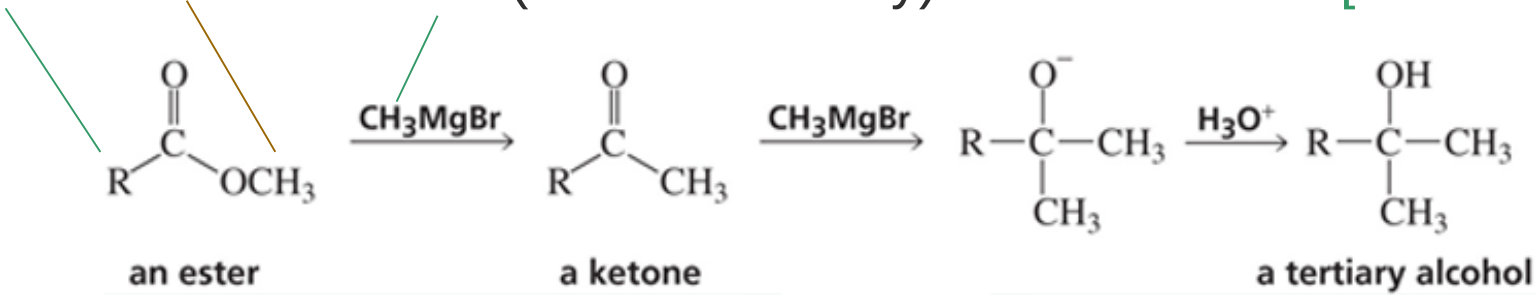

- stereochemistry
  - give racemates



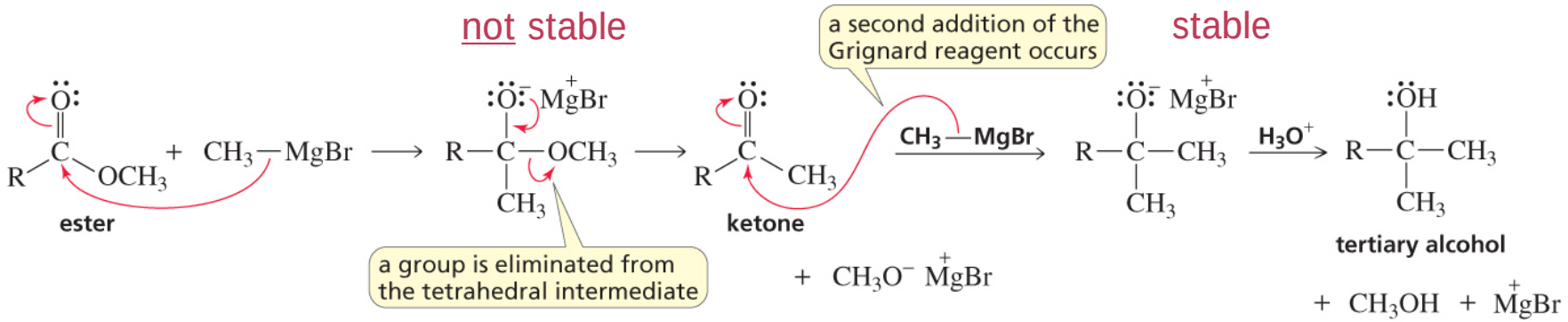

    - reactant and environment not chiral
  - give an enantiomer, if enzymatic
    - chiral environment



- RCOOR' to RCOR" (and successively) to 3° alcohol [RR"R"OH]

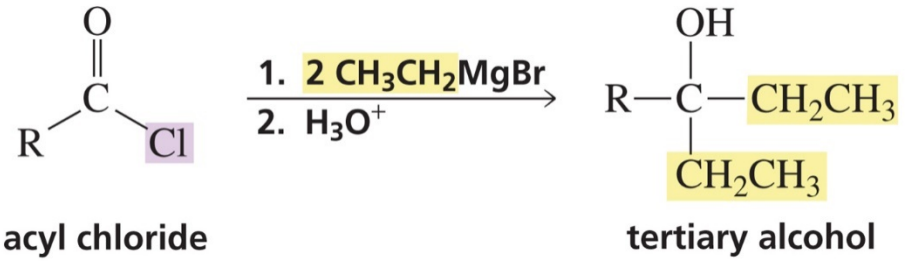



  - add'n-elim'n followed by (2nd) add'n

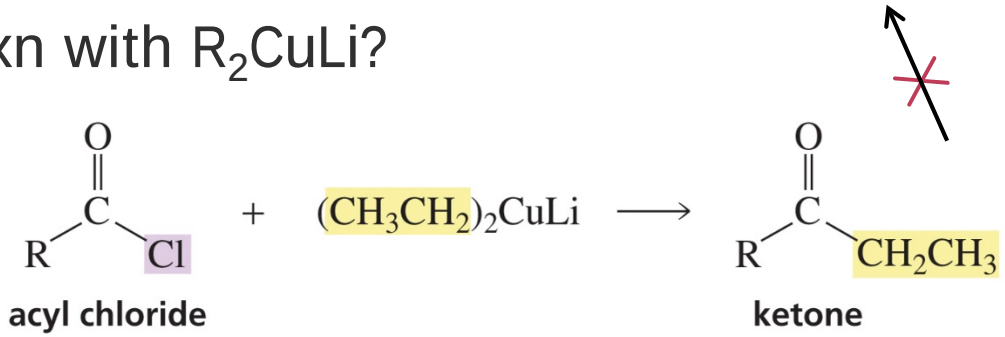



  - 2° alcohol from formate [R"CH(OH)R"]

- RCOCl and RCOOCOR' also (to ketone to alcohol)




  - rxn with $R_2CuLi$?

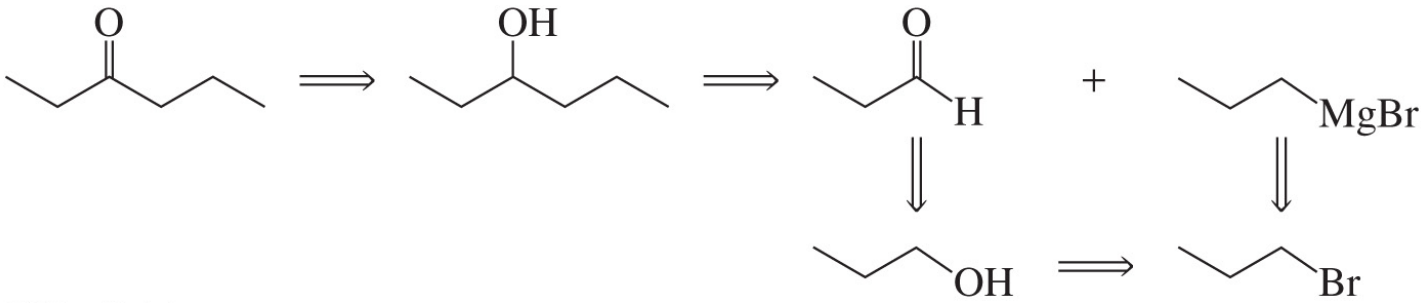


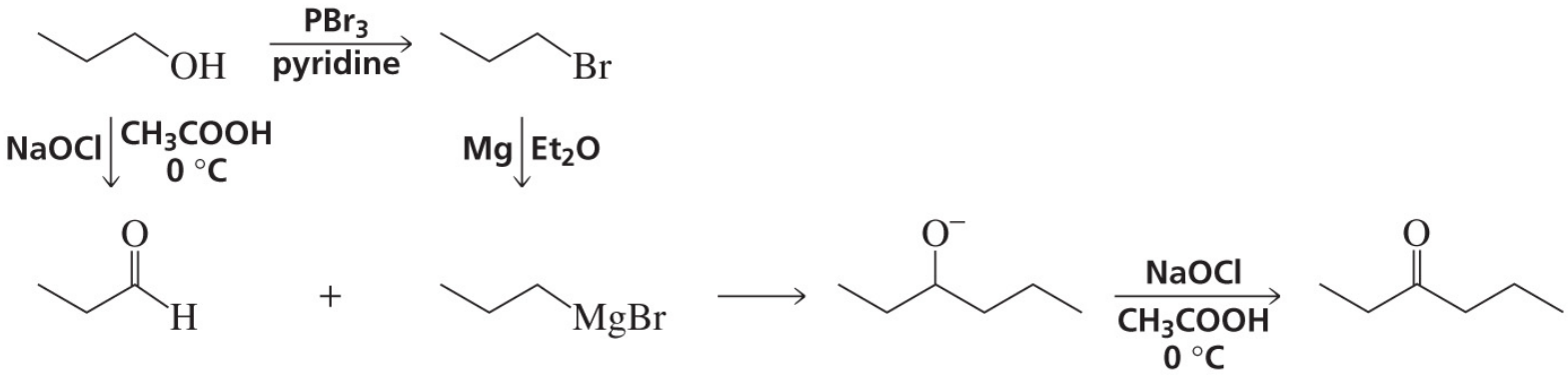

Is R of Gilman reagent a Nu:? maybe yes and maybe no. See Chapt 11

- RCOOH or $RCONH_2$ also? No. Problem 11
  - due to leaving propensity of $^-OH$ and $^-NH_2$?

- RMgX for C-C bond formation [adding C's]

<ex> 3-hexanone from 1-propanol and no C-containing comp'd



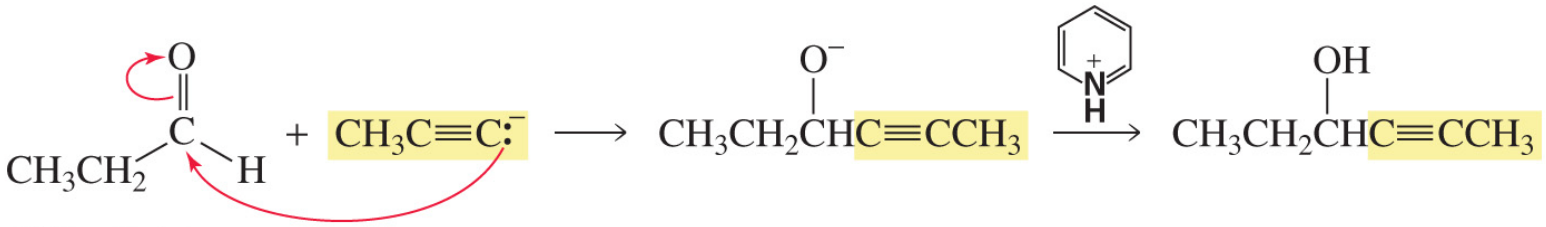



# Rxn with acetylide ion



- acetylide ~ $CH{\equiv}C:^-$ or $RC{\equiv}C:^-$ ~ also a C Nu:


- A&K to alcohol



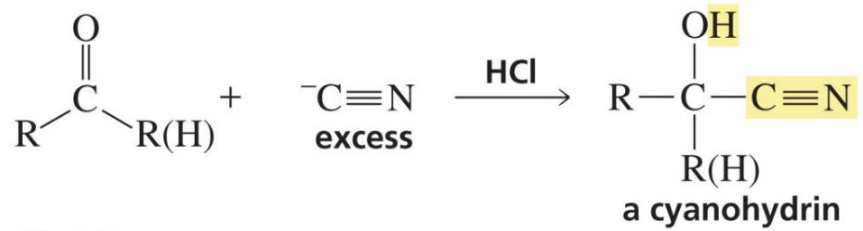

  - need weak acid (in the 2nd step [work-up])
    - to protonate $O^-$, but <u>not</u> to add to ≡
    - like $C_5H_5NH^+$ ($pK_a \approx 5$) ~ $H_3O^+$ too strong ($H_2O$ too weak)
- other carbonyls?
  - to ketone to alcohol (like RMgX) sl #13
  - e.g. ester Problem 14

# Rxn with cyanide ion



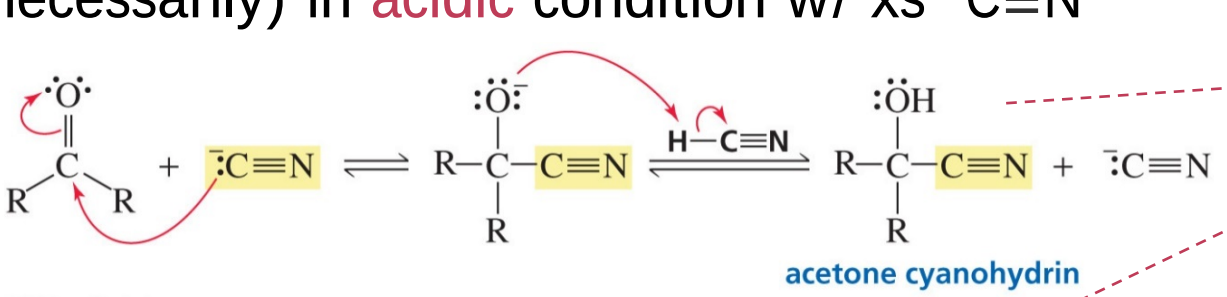
- cyanide ~ another C Nu: ~ weaker than the former
- A&K to cyanohydrin

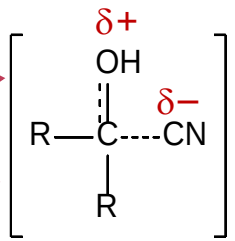
$pK_a(HCN) \approx 9$




⁻CN in acidic condition?
Use xs ⁻CN [NaCN] over HCl.
HCl protonate ⁻CN → HCN
⁻CN left is the Nu:.
HCN protonate O⁻.
More ⁻CN produced.
See Problem 15 - 17

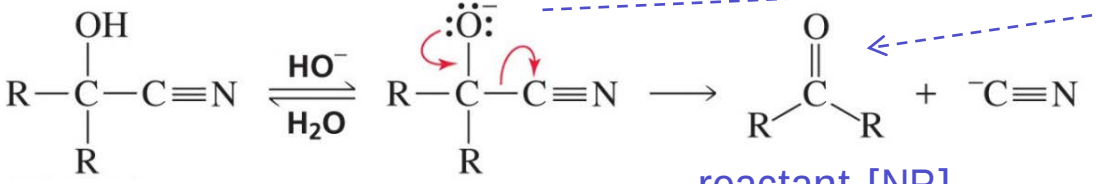
- (necessarily) in acidic condition w/ xs ⁻C≡N



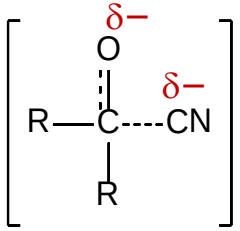




high E TS

- If in basic (or neutral), ⁻C≡N leaves.

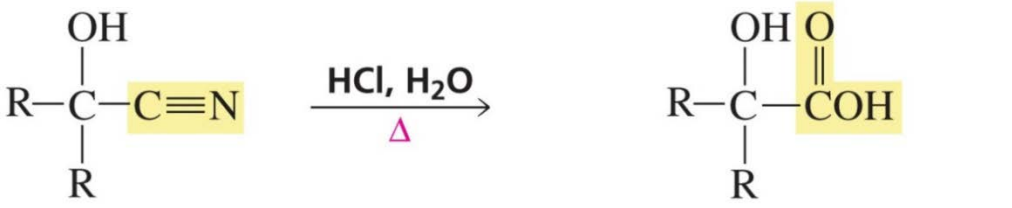



reactant [NR]



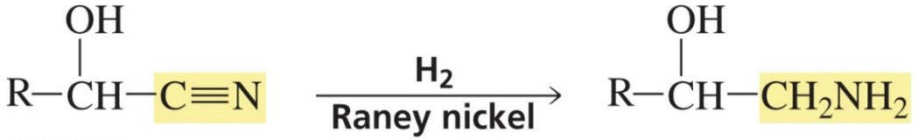

low E TS

- synthesis using cyanohydrin §15.15
  - RCOOH with OH




a cyanohydrin — an $\alpha$-hydroxycarboxylic acid

  - amine with OH




- cyanide react w/ other carbonyls?
  - yes with RCOCl, RCOOCOR
  - no with others ← cyanide weaker Nu:

$pK_a(HCN) \approx 9$

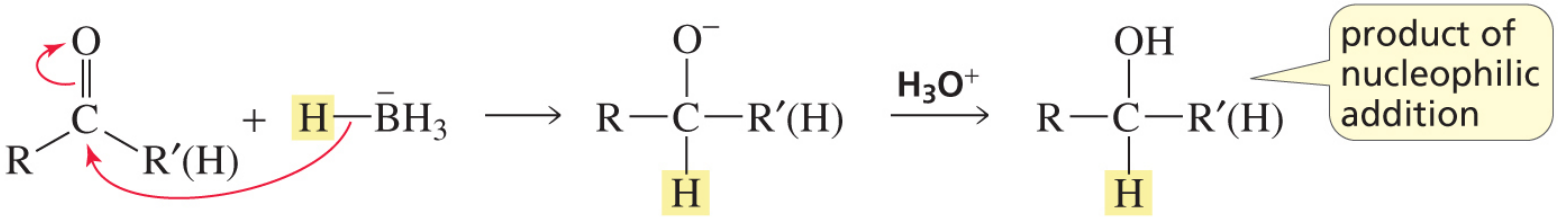
# Rxn with hydride ion

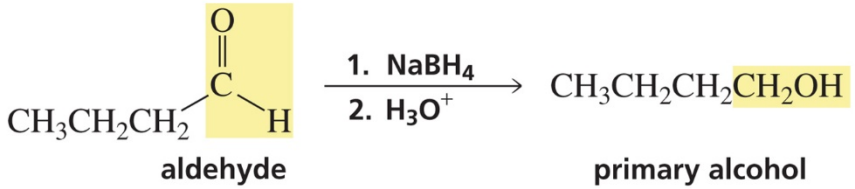


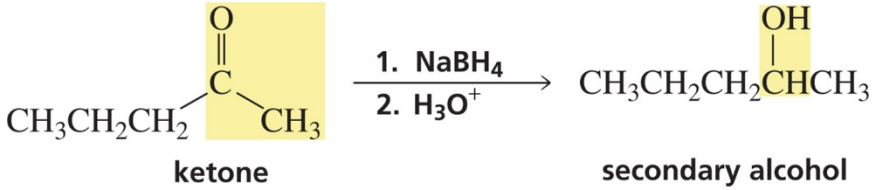
- hydride ion [H:⁻] ~ strong B:, good Nu: $pK_a(H_2) \approx 35$
  - $NaBH_4$ and $LiAlH_4$ are common sources [reducing agents].
    - $LiAlH_4$ stronger than $NaBH_4$

EN(Al) = 1.5; EN(B) = 2.0

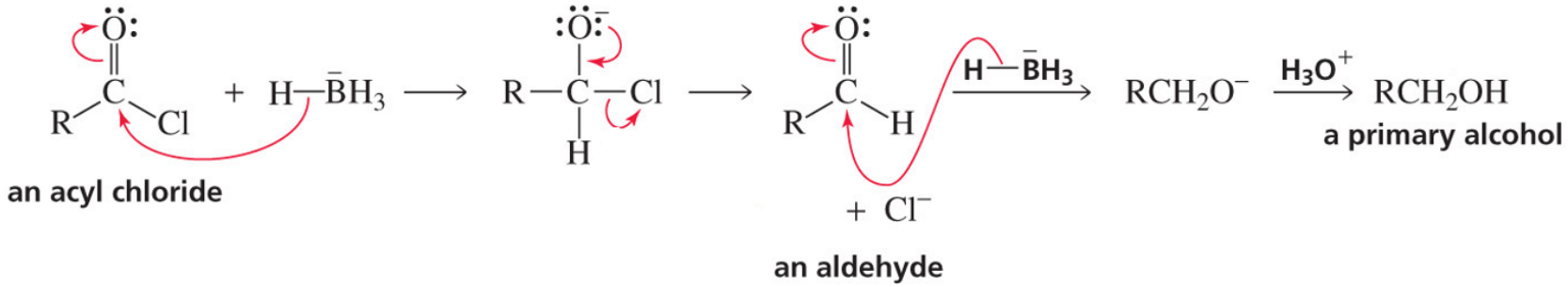
- A&K
  - to alcohol

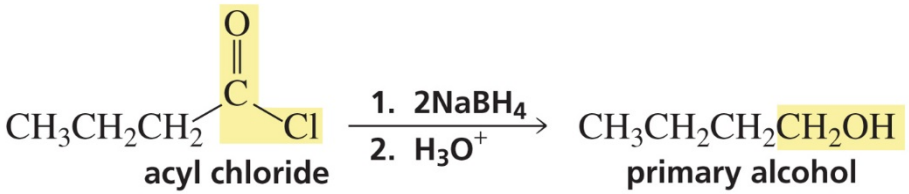


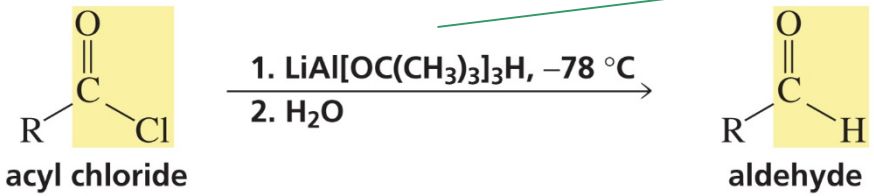



- RCOX
  - to aldehyde to alcohol
  - add'n-elim'n followed by (2nd) addition [reduction]

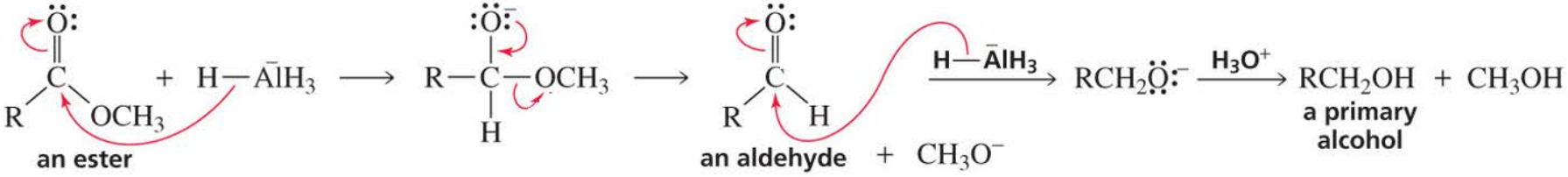


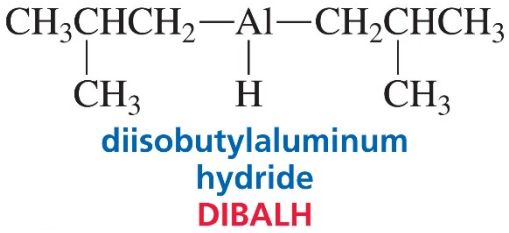

$Al(OR)_3H$, weaker than $LiAlH_4$ or $NaBH_4$, reduce only to RCHO

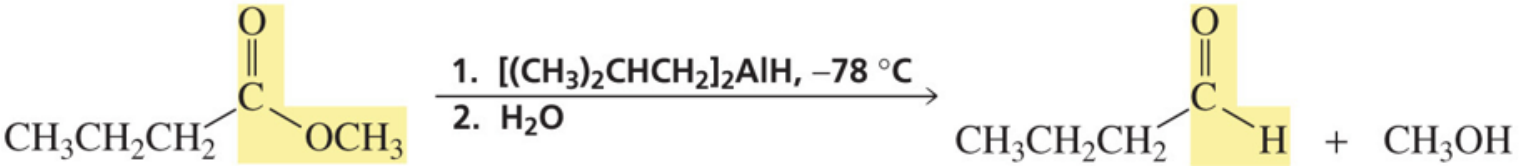
- RCOOR'
  - $LiAlH_4$ has to be used,
    - explosive!! with H ~ $LiAlH_4$ + ROH → $Li(OR)_4$ + $2H_2\uparrow$
    - must be used with dry aprotic solvent like ether
  - since RCOOR' is less reactive (than RCOX, AA, and A&K)
  - RCOOR' → two alcohols [$RCH_2OH$ + R'OH]



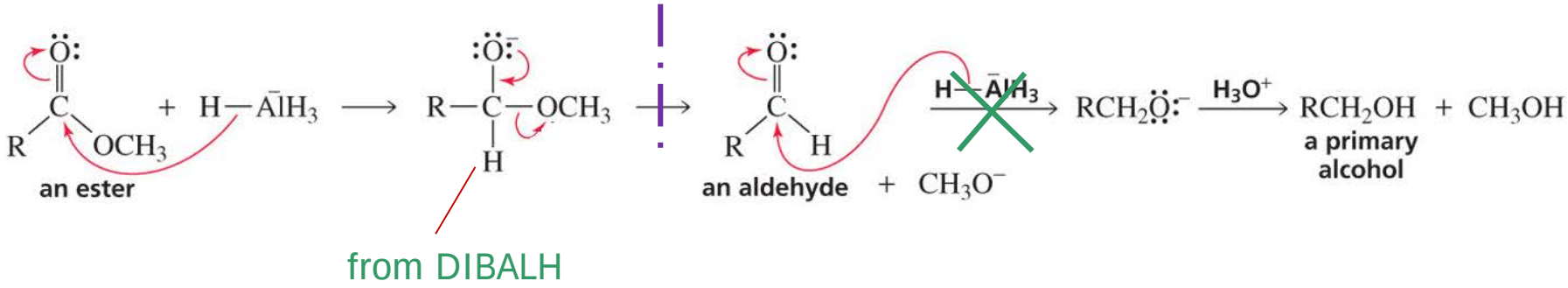

    - cannot be stopped at aldehyde (more reactive than ester)

- RCOOR' (cont'd)
  - still want aldehyde from ester?
    - use less reactive DIBALH
    - at low Temp

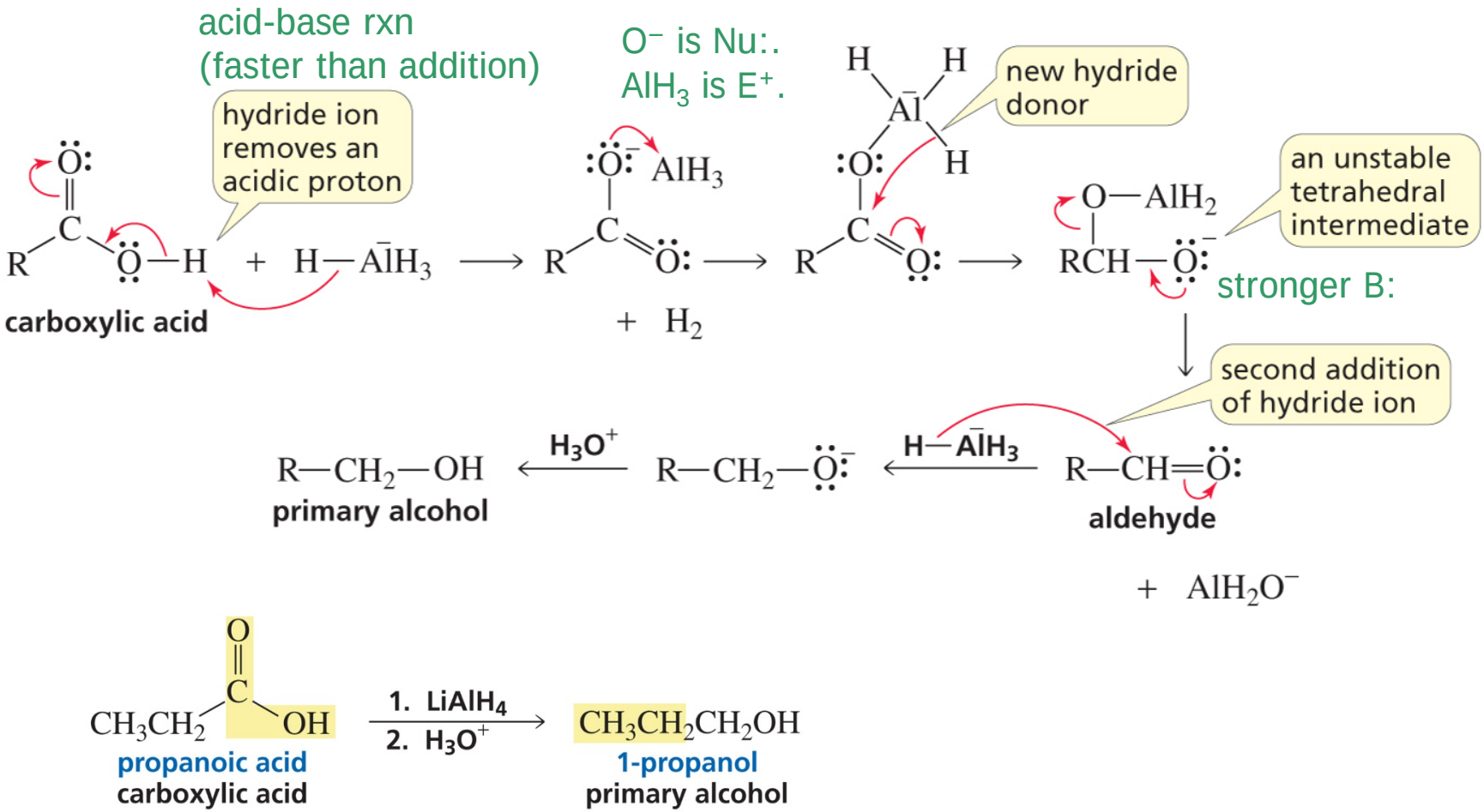


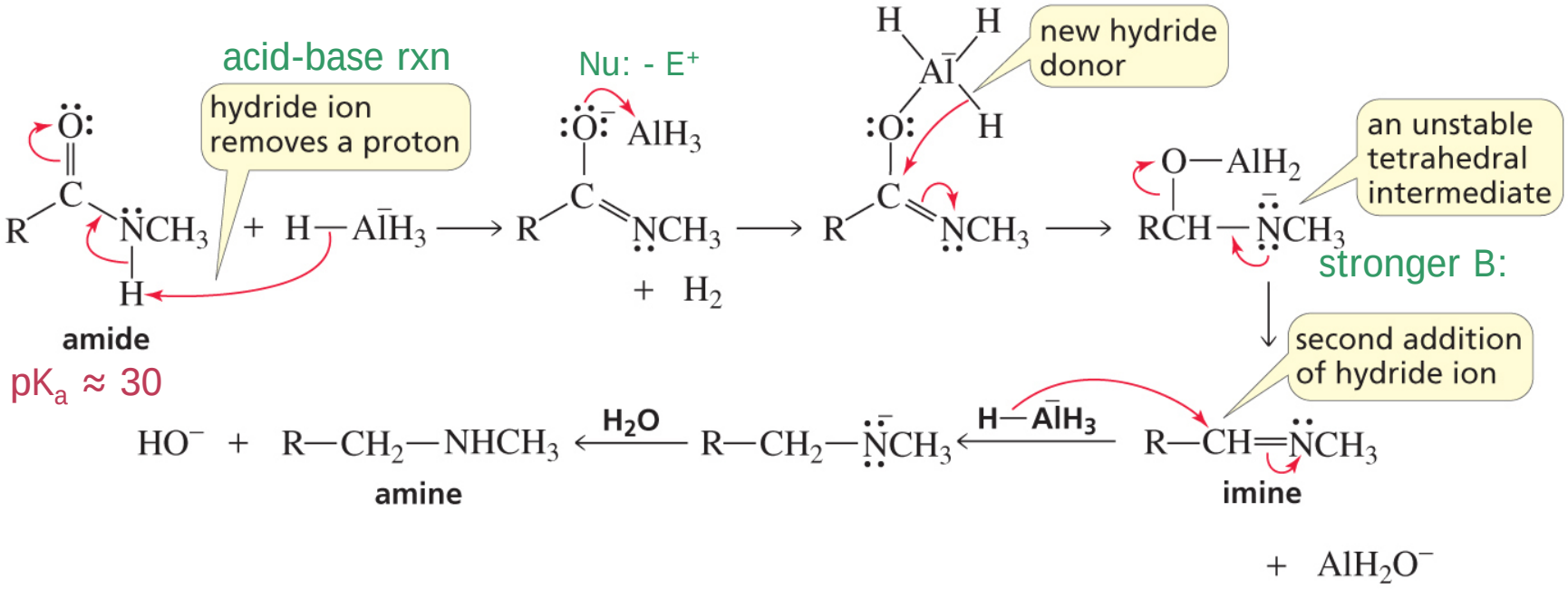

    - The intermediate (hemiacetal) is stable at low Temp.
      - remove residual DIBALH, and warm up



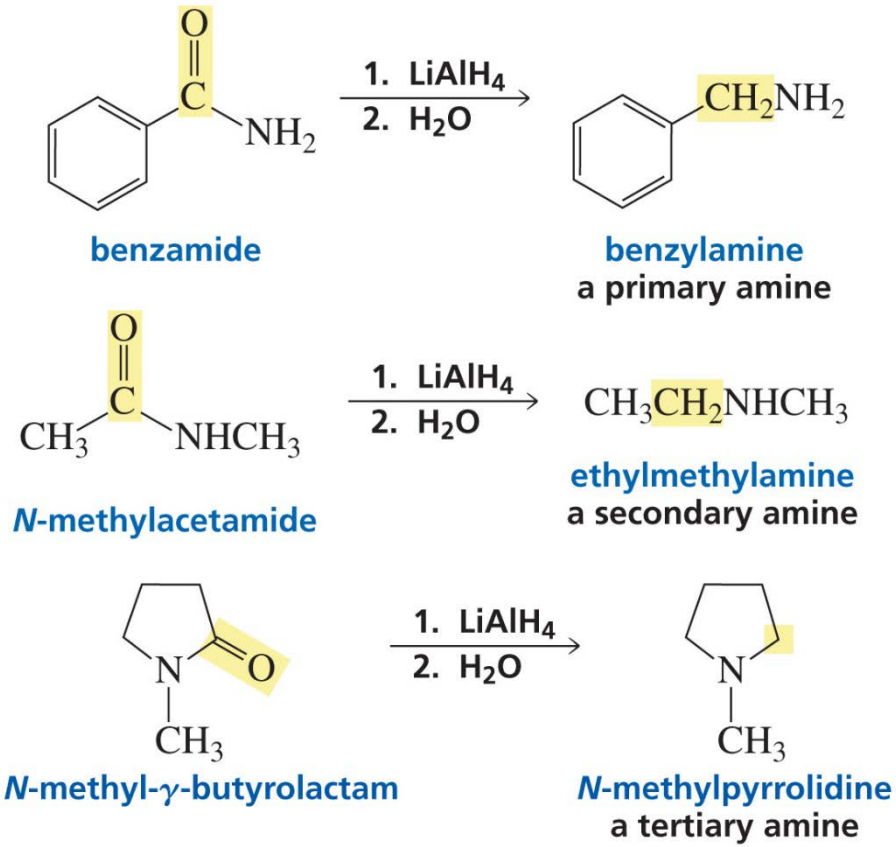
- RCOOH
  - to 1° alcohol through aldehyde (by different mechanism)



- amides
  - producing amine through imine
  - the same mechanism as for RCOOH



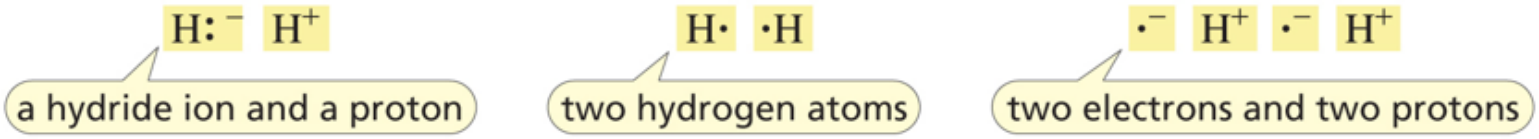
- amides (cont'd)
  - 1°, 2°, and 3° amines from amide with unsubstit'd, monosubstit'd, and disubstit'd N, respectively



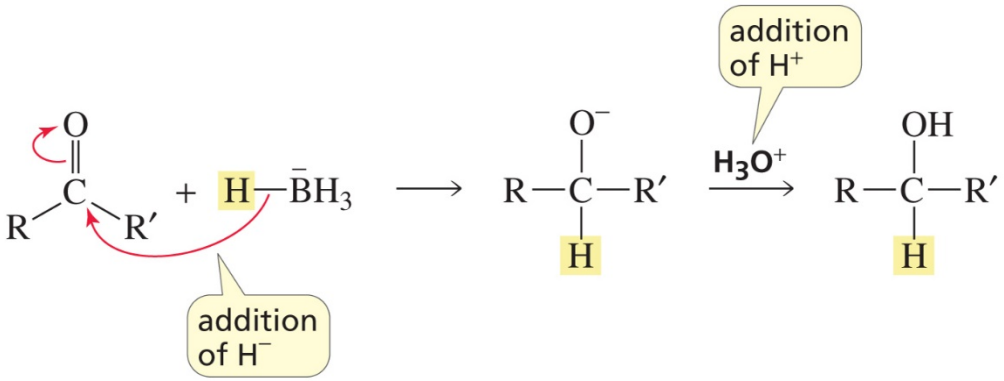
# Types of reduction



- reduction = addition of H; formation of more C-H bonds
- 3 types of $H_2$ [H:H] in reduction




## 1. H:⁻ and H⁺




$RCH{=}NCH_3 \xrightarrow[2.\ H_2O]{1.\ NaBH_4} RCH_2NHCH_3$

$RCH{=}CH_2 \xrightarrow{NaBH_4}$ no reaction

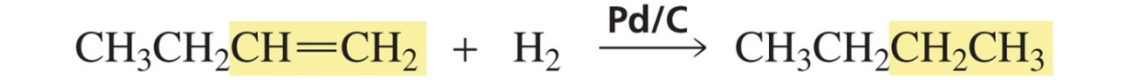
$RC{\equiv}N \xrightarrow[2.\ H_2O]{1.\ NaBH_4} RCH_2NH_2$

$RC{\equiv}CR \xrightarrow{NaBH_4}$ no reaction

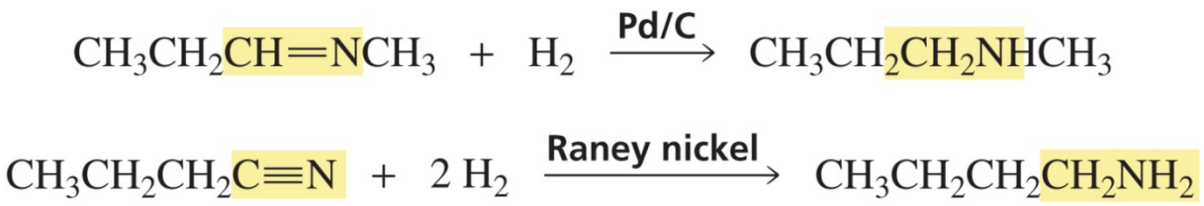
C electrophilic

=, ≡ nucleophilic

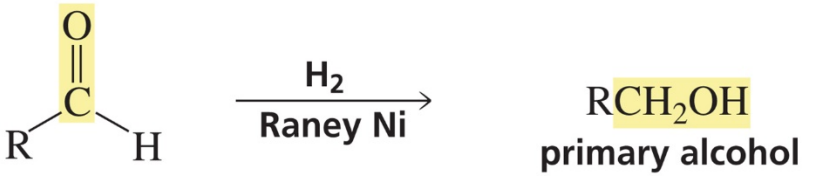
## 2. two H atoms ~ catalytic hydrogenation



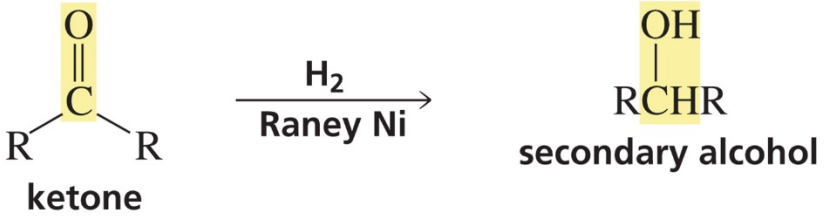

§5.9 and §7.9




§15.15 and sl#18

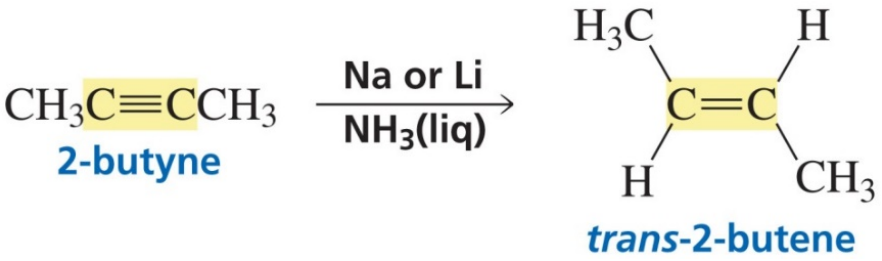



C=C < C=N < C=O




- not by Pd/C (less effective)
- not for esters, acids, or amides (less reactive)

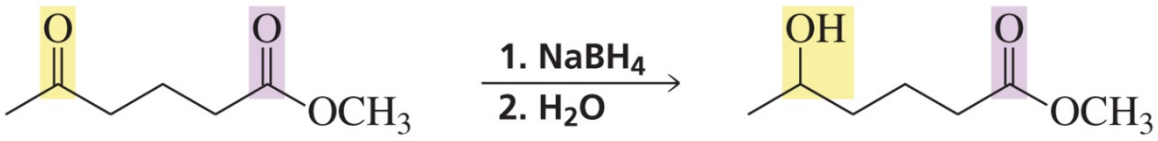
## 3. two e⁻'s and two H⁺'s ~ dissolving metal reduction §7.9



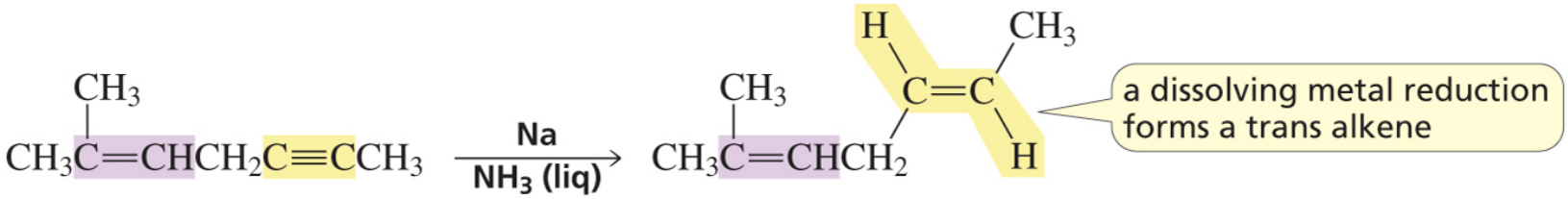
# Chemoselective reactions



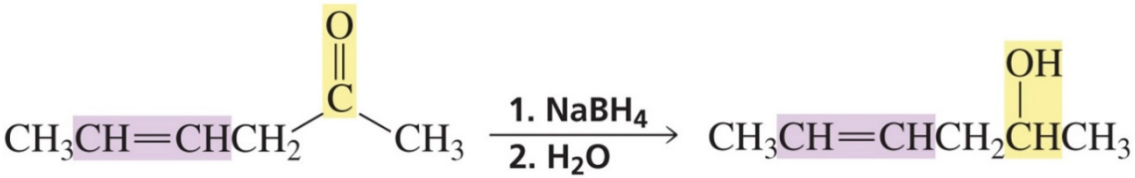
- One ft'nal group is reacted in preference to another.




  - ketone not ester (less reactive)




  - #3 not #2 ~ different mechanism




  - #1 not #2 ~ different mechanism

# Summary: Addition rxns



- C Nu:
  - RMgX > acetylide > cyanide
  - A&K to alcohol
  - other carbonyls ~ alcohol thru ketone dep on reactivity
- H Nu:
  - $LiAlH_4$ > $NaBH_4$ > $LiAl(OR)_3H$, DIBALH
  - A&K to alcohol
  - RCOX, RCOOR' ~ alcohol thru aldehyde
  - RCOOH, amide ~ different mechanism
- reduction mechanisms
  - of polar vs non-polar $\pi$ bond