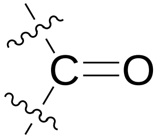
台灣大學開放式課程

有機化學乙

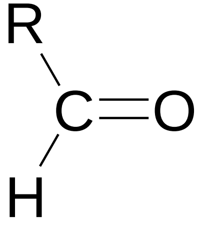
蔡蘊明　教授

Chapter 12
Alcohols from carbonyl compounds

※ Carbonyl compounds

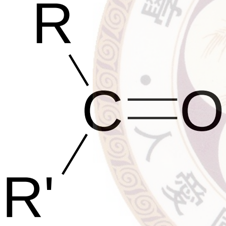


A carbonyl functional group (羰基)



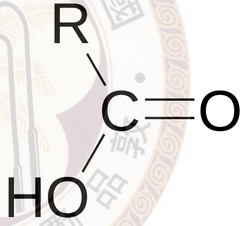
aldehyde

醛



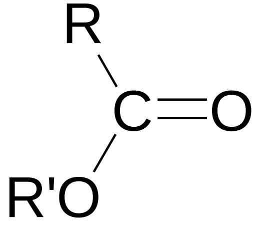
ketone

酮



carboxylic acid

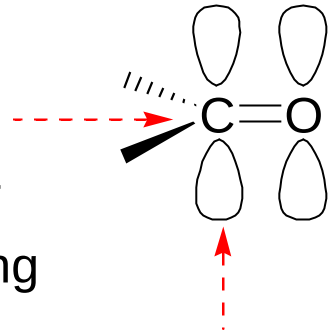
酸



ester

酯

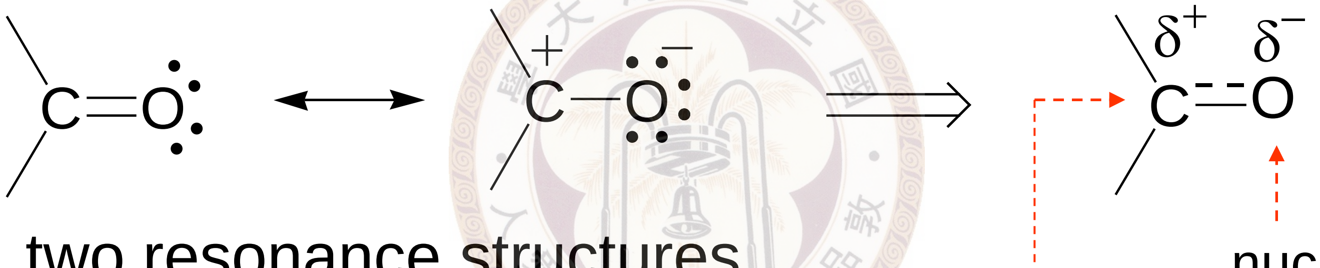
◎ Structure



sp^2 for σ bonding

planar

p for π bonding



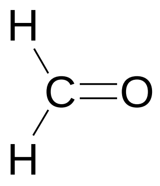
two resonance structures

electrophilic

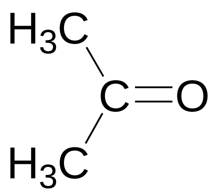
nucleophilc

Real structure:
hybrid of the two resonance structures

Polar in nature:

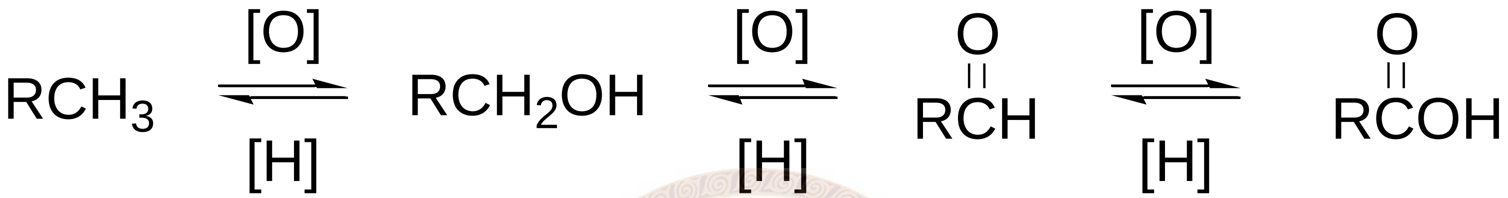


formaldehyde
μ = 2.27 D



acetone
μ = 2.88 D

※ Oxidation and reduction of organic compounds.



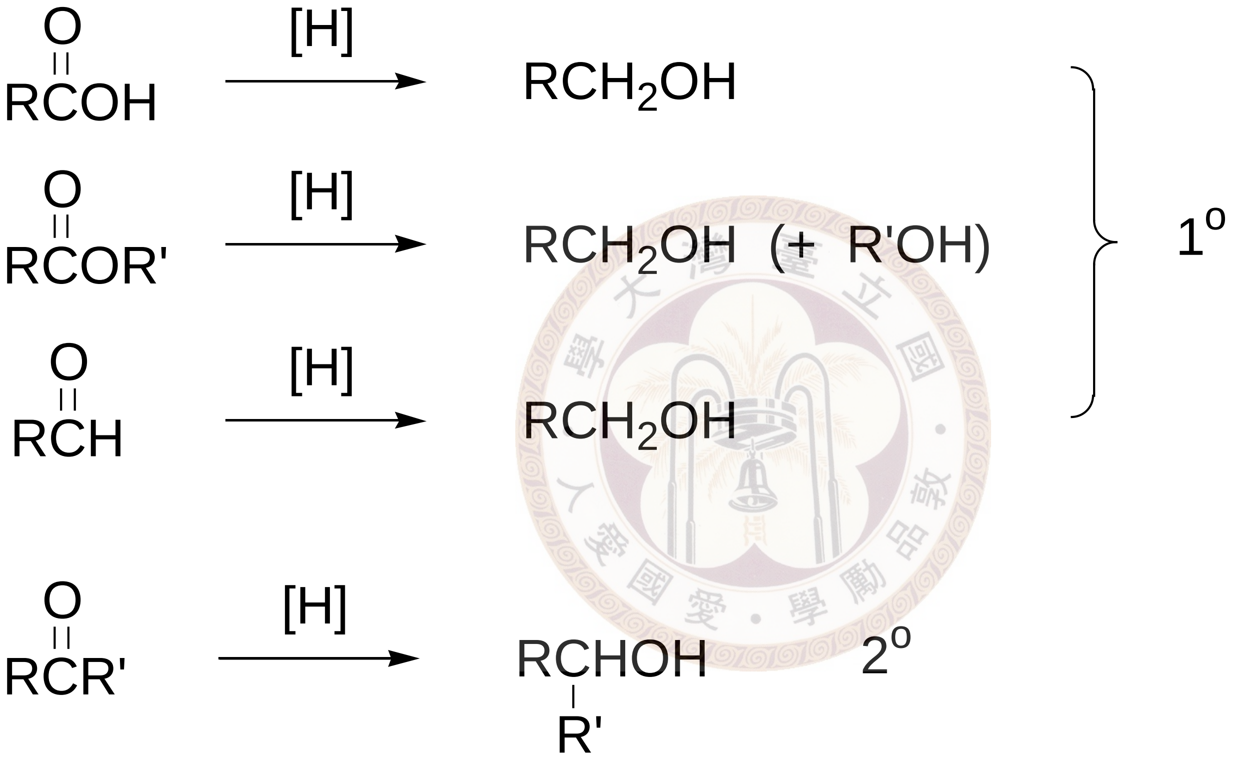
$$\mathrm{RCH_3} \underset{[H]}{\overset{[O]}{\rightleftharpoons}} \mathrm{RCH_2OH} \underset{[H]}{\overset{[O]}{\rightleftharpoons}} \mathrm{R}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{H} \underset{[H]}{\overset{[O]}{\rightleftharpoons}} \mathrm{R}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{OH}$$

A simple guideline:

Oxidation – # of O ↑, # of H ↓

Reduction – # of O ↓ , # of H ↑

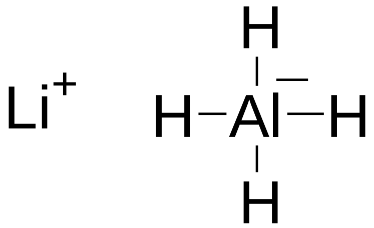
※ Preparation of alcohols from carbonyl compounds



$$\left.\begin{array}{lcl} \mathrm{R\overset{\overset{\displaystyle O}{\|}}{C}OH} & \xrightarrow{[H]} & \mathrm{RCH_2OH} \\[2ex] \mathrm{R\overset{\overset{\displaystyle O}{\|}}{C}OR'} & \xrightarrow{[H]} & \mathrm{RCH_2OH\ \ (+\ \ R'OH)} \\[2ex] \mathrm{R\overset{\overset{\displaystyle O}{\|}}{C}H} & \xrightarrow{[H]} & \mathrm{RCH_2OH} \end{array}\right\}\ 1^{o}$$

$$\mathrm{R\overset{\overset{\displaystyle O}{\|}}{C}R'} \xrightarrow{[H]} \mathrm{R\underset{\underset{\displaystyle R'}{|}}{C}HOH} \qquad 2^{o}$$

◎ Lithium aluminum hydride (LAH)



$$\mathrm{Li}^{+} \quad \mathrm{H{-}\overset{\displaystyle H}{\underset{\displaystyle H}{Al}}{}^{-}{-}H}$$

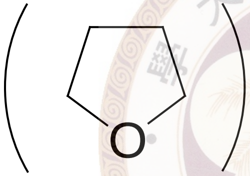
A highly reactive reducing agent

Reacts violently with H_2O and ROH

and releases H_2

Solvents often used:

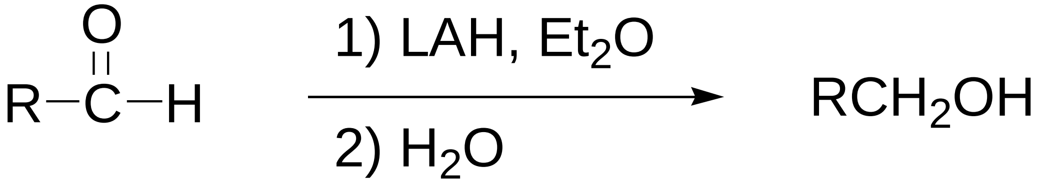
THF



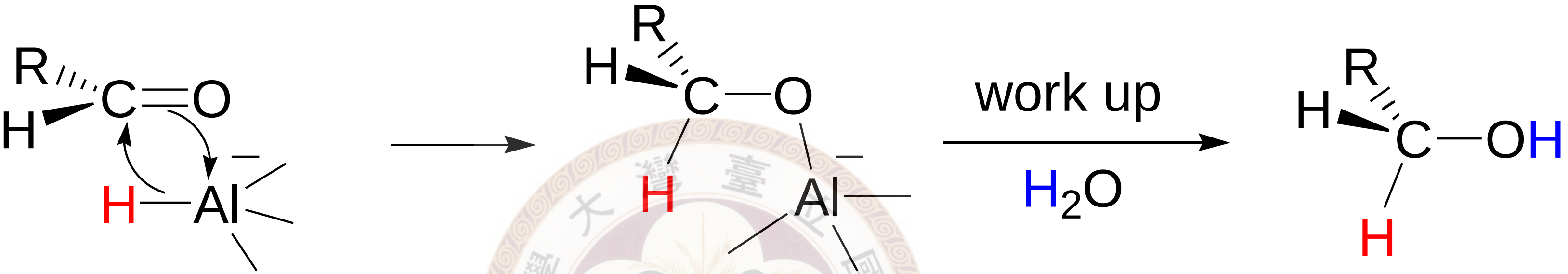
Diethyl ether

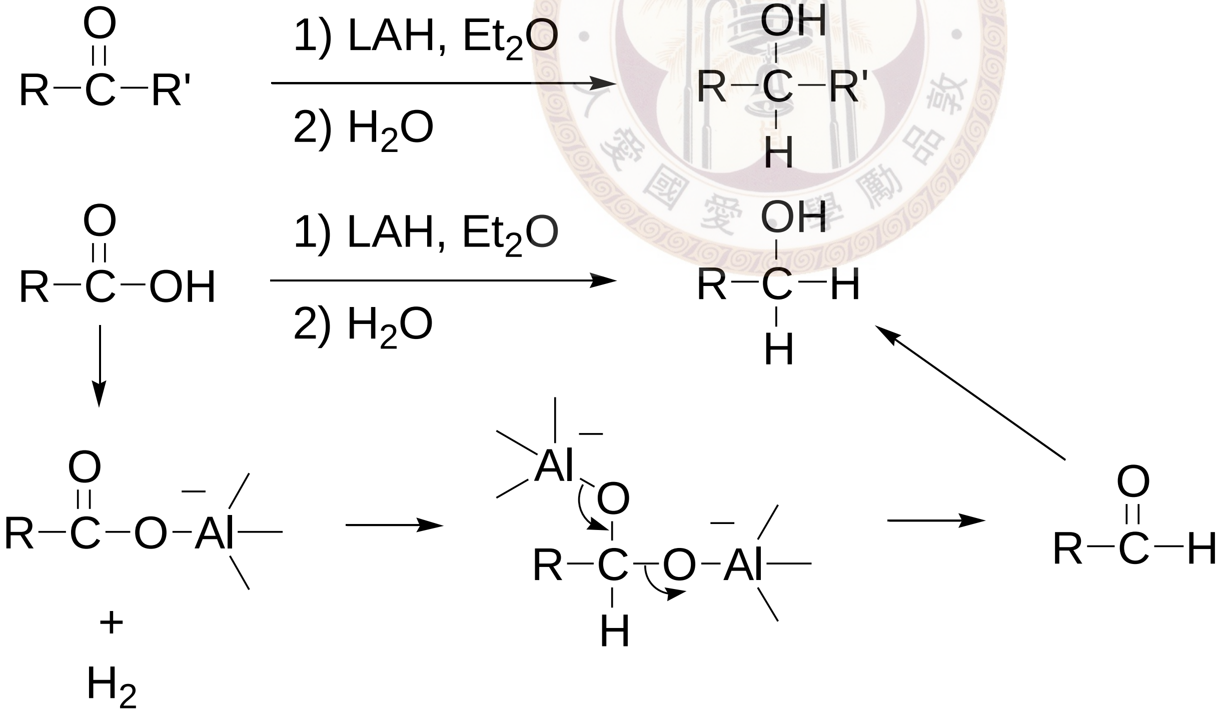
(Et_2O)

Good ligands for aluminum

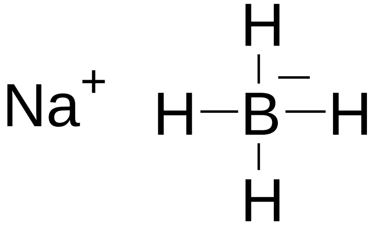

R–C(=O)–H
1) LAH, Et_2O
2) H_2O
RCH_2OH

Mechanism:


R
H
C
O
H
Al
–
work up
H_2O
OH
H

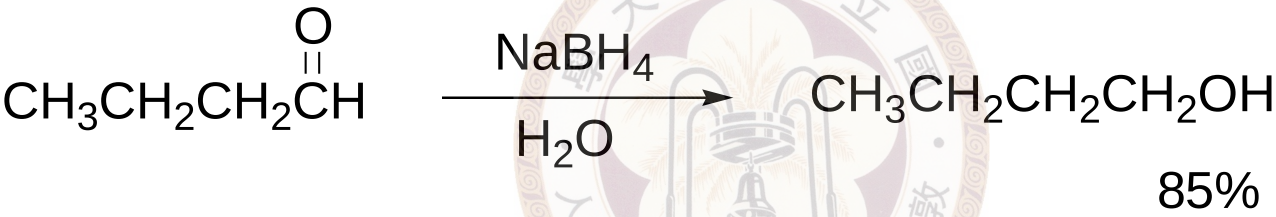

R–C(=O)–R'
1) LAH, Et_2O
2) H_2O
OH
R–C–R'
H
R–C(=O)–OH
1) LAH, Et_2O
2) H_2O
OH
R–C–H
H
R–C(=O)–O–Al
–
+
H_2
Al
O
R–C–O–Al
H
R–C(=O)–H

◎ Sodium borohydride ($NaBH_4$)



$$Na^+ \; \left[H-\underset{H}{\overset{H}{B}}-H \right]^-$$

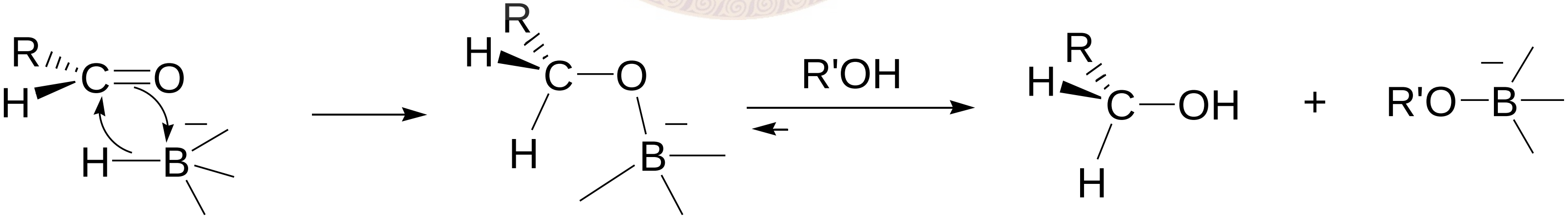
- Less reactive than LAH
- Reacts slowly with H_2O
- Alcohols or H_2O are often used as solv.
- Does not reduce acid or ester

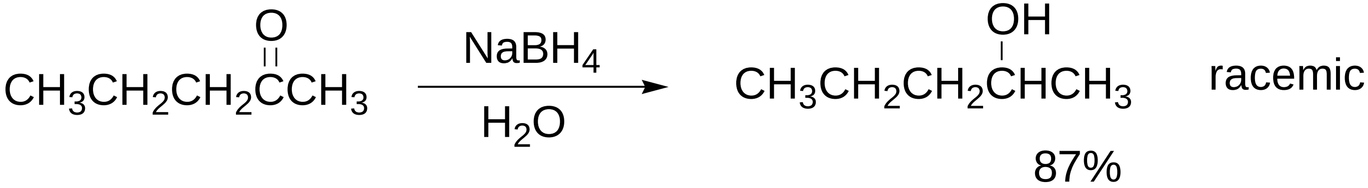


$$CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}H \xrightarrow[H_2O]{NaBH_4} CH_3CH_2CH_2CH_2OH$$

85%

Mechanism:

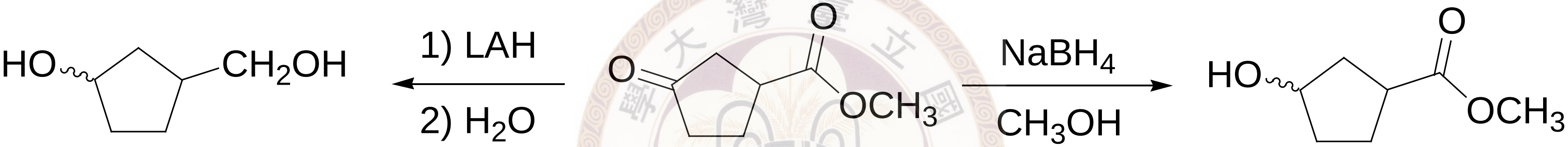




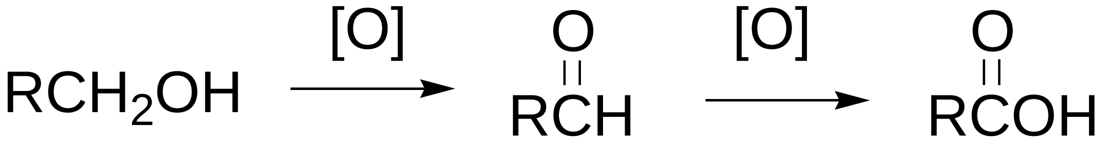
$$CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}CH_3 \xrightarrow[H_2O]{NaBH_4} CH_3CH_2CH_2\overset{OH}{\overset{|}{C}}HCH_3$$

racemic

87%

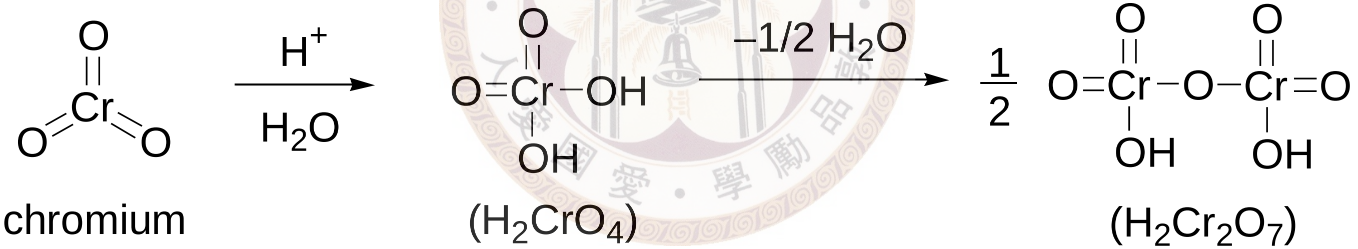


※ Oxidation of alcohols



$$RCH_2OH \xrightarrow{[O]} \overset{O}{\overset{\|}{R C H}} \xrightarrow{[O]} \overset{O}{\overset{\|}{R C O H}}$$

◎ Jones reagent: CrO_3/aq. H_2SO_4/acetone



chromium trioxide

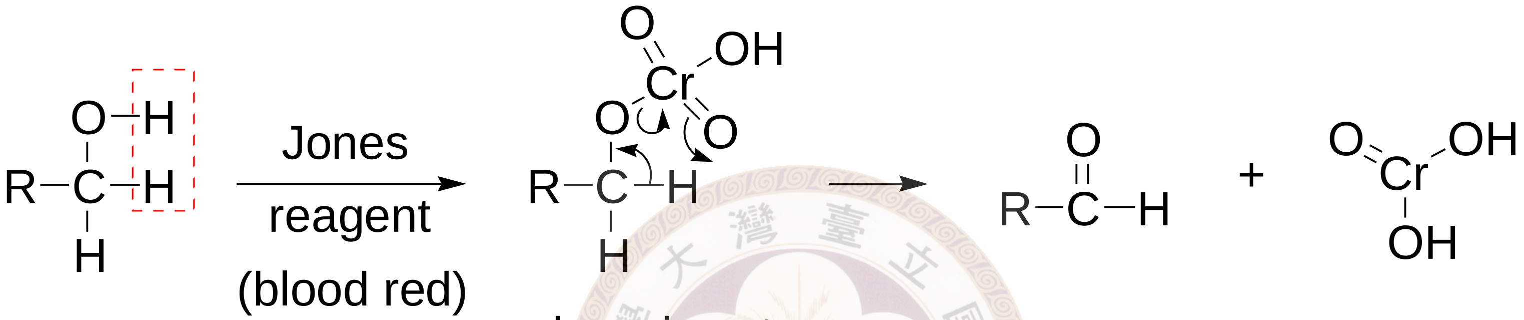
(H_2CrO_4) chromic acid

($H_2Cr_2O_7$) dichromic acid

All are Cr(VI)

$$RCH_2OH \xrightarrow{\text{Jones reagent}} RCOOH$$

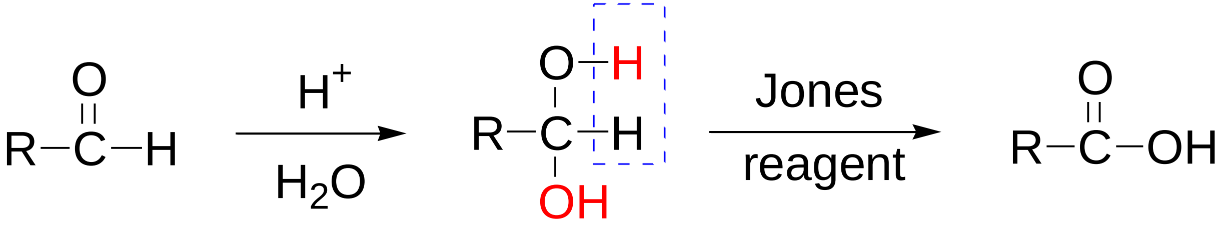
Mechanism:



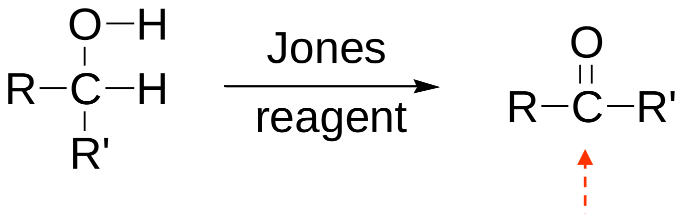
a chromic ester

$$\begin{tikzcd} Cr(VI) \arrow[r, "\text{2 e}^- \text{ oxidation}"'] & Cr(IV) \arrow[d] \arrow[d] \\ & Cr(III) \end{tikzcd}$$

green

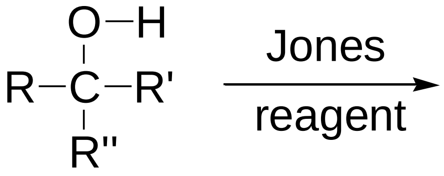


a carbonyl hydrate



2^o alcohol

No removable H, can not be oxidized further



NR (no reaction)

3^o alcohol

✓ Chemical test:

1^o, 2^o alcohol + CrO_3 / aq. H_2SO_4 → Cr^{3+}

orange red greenish opaque

3^o alcohol + CrO_3/aq. H_2SO_4 → no change

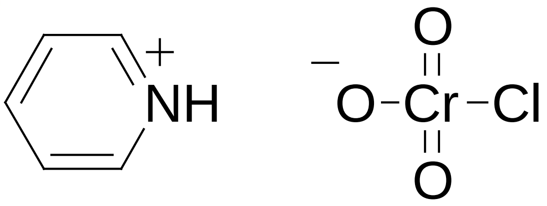
Q: Can we stop at aldehyde?

Solution 1: remove aldehyde as is formed by distillation
(aldehyde has lower bp than alcohol)

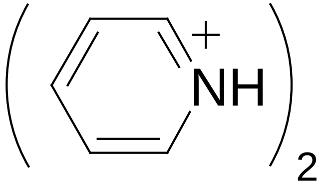
Limitation: aldehyde must have lower bp (<100 °C)
for practical reason

Solution 2: use PCC or PDC

PCC: pyridinium chlorochromate



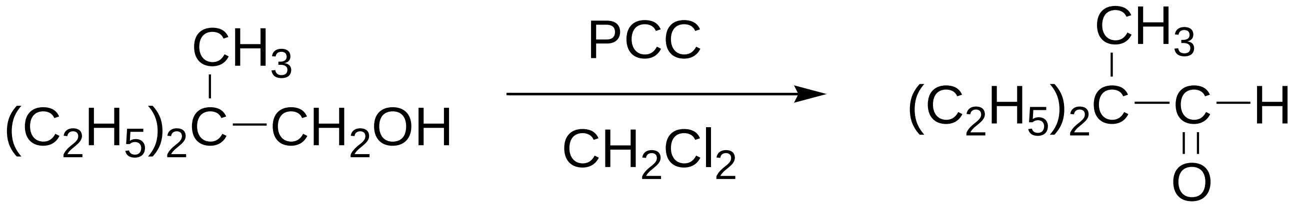
PDC: pyridinium dichromate



$Cr_2O_7^{2-}$

*They are soluble in CH_2Cl_2 and weakly acidic

例



$$(C_2H_5)_2\overset{CH_3}{\overset{|}{C}}-CH_2OH \xrightarrow[CH_2Cl_2]{PCC} (C_2H_5)_2\overset{CH_3}{\overset{|}{C}}-\underset{O}{\underset{\|}{C}}-H$$

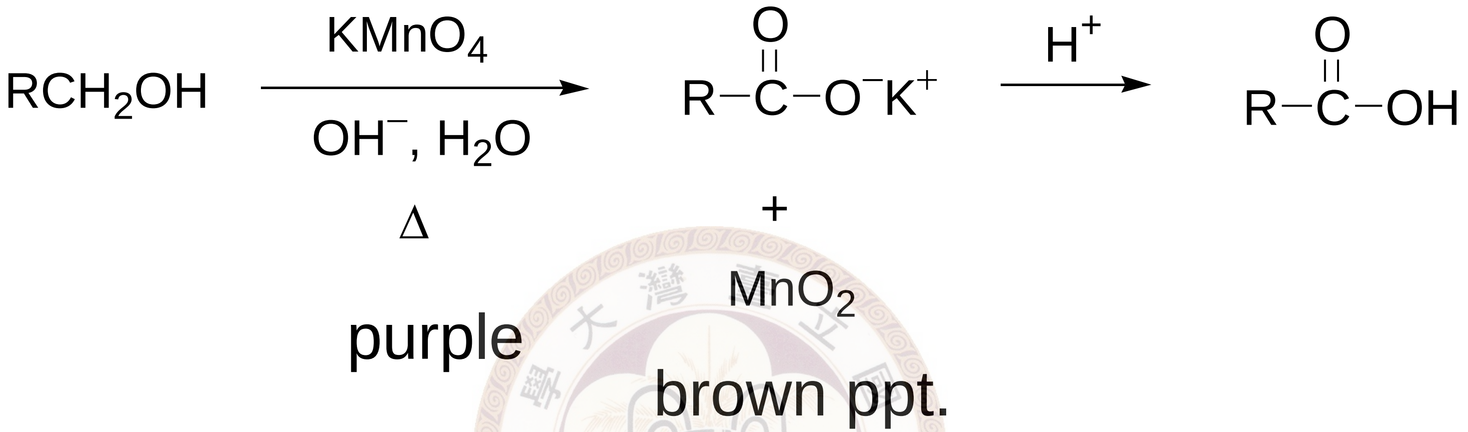
Reason for the success:

non-aqueous condition is used

→ no carbonyl hydrate formation (no H_2O)

→ no further oxidation

◎ $KMnO_4$



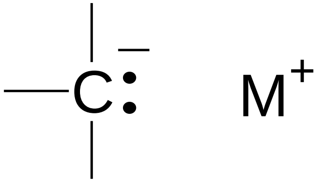
$$RCH_2OH \xrightarrow[OH^-,\ H_2O,\ \Delta]{KMnO_4} R-\overset{O}{\overset{\|}{C}}-O^-K^+ \xrightarrow{H^+} R-\overset{O}{\overset{\|}{C}}-OH$$

$+ MnO_2$

purple

brown ppt.

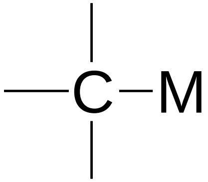
※ Organometallic compounds



$M^+ = Na^+, K^+$

ionic

very polar



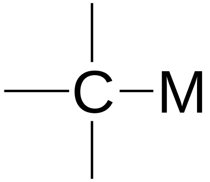
M = Li, Mg

in between

例 butyllithium

$CH_3CH_2CH_2CH_2Li$

soluble in hexane
but still a very strong base
(water sensitive)



M = Pd, Pb, Sn, Hg....

covalent

weakly basic
(water insensitive)

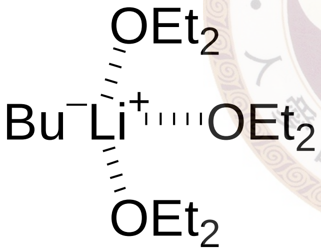
◎ Organolithium compounds

$$CH_3CH_2CH_2CH_2Br + 2\ Li \xrightarrow[Et_2O]{-10\ ^{o}C} CH_3CH_2CH_2CH_2Li + LiBr$$

Solvent: Et_2O or THF or hexane

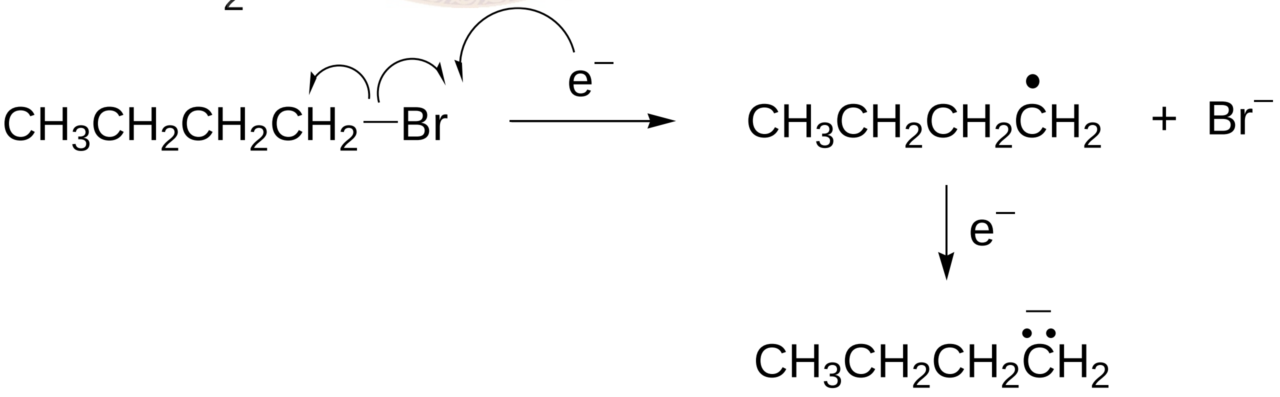
Reactivity: RI > RBr > RCl

Ethereal solvent: coordinates with BuLi



$Bu^{-}Li^{+}\cdots(OEt_2)_3$ helps formation and more stable

Mechanism:



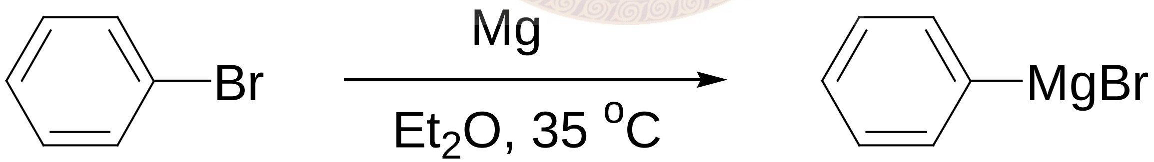
$$CH_3CH_2CH_2CH_2{-}Br \xrightarrow{e^-} CH_3CH_2CH_2\dot{C}H_2 + Br^- \xrightarrow{e^-} CH_3CH_2CH_2\overset{-}{\ddot{C}}H_2$$

◎ Grignard reagents

$$\left.\begin{array}{l} R\text{-}X + Mg \xrightarrow[\text{or THF}]{Et_2O} R\text{-}MgX \\[2em] Ar\text{-}X + Mg \xrightarrow[\text{or THF}]{Et_2O} Ar\text{-}MgX \end{array}\right\} \text{Grignard reagents}$$

(also for vinyl halides)

例



phenylmagnesium bromide

*Ethereal solvent complexes with Grignard reagent

★ Reactions with acids

RMgX and RLi are strong bases
reacts with H_2O, ROH, R-C≡C-H

例 $$R\text{-}MgX + H\text{-}OR' \longrightarrow R\text{-}H + R'OMgBr$$

$$RLi + D_2O \longrightarrow R\text{-}D + LiOD$$

Overall reduction of halides:

$$\begin{tikzcd} R\text{-}X + Mg \arrow[r] \arrow[rr, dashed, bend right] & R\text{-}MgX \arrow[r, "H_2O"] & R\text{-}H \end{tikzcd}$$

Preparation of acetylides:

$$R\!-\!\!\equiv\!\!-\!H \; + \; \underset{(R'Li)}{R'MgX} \longrightarrow \underset{\left(R\!-\!\!\equiv\!\!-\!Li\right)}{R\!-\!\!\equiv\!\!-\!MgX} \; + \; R'H$$

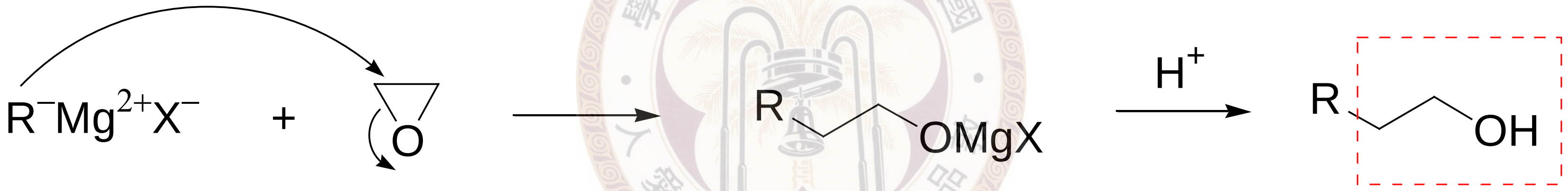
◎ Reactions of Grignard reagents

*R-MgX is more covalent and less basic than R-Li

→ R-MgX used more often as nucleophile

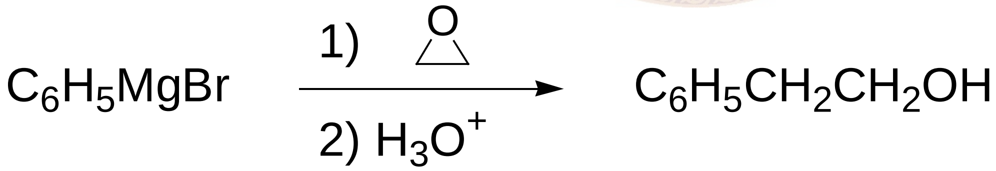
R-Li used more often as base

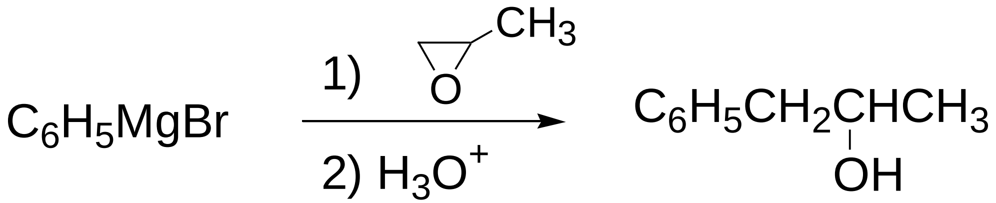
✓ Opening of epoxides



another way to
prepare alcohols

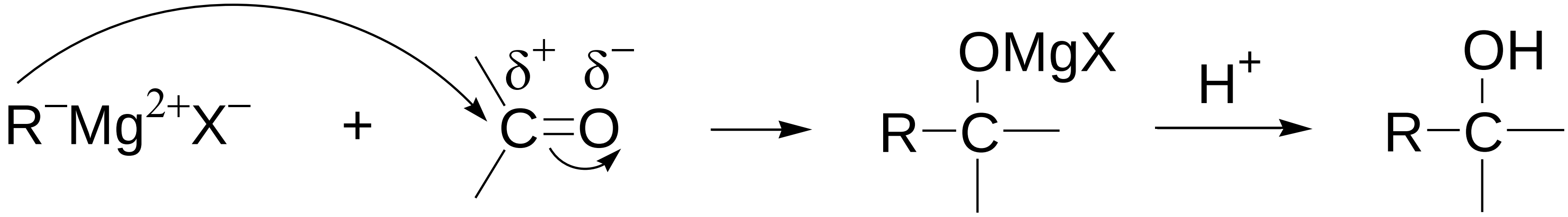
例



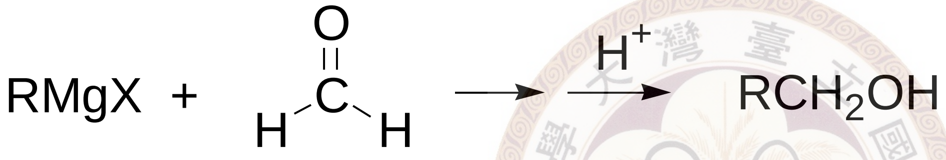


attack less
hindered carbon

◎ Reaction with carbonyl compounds

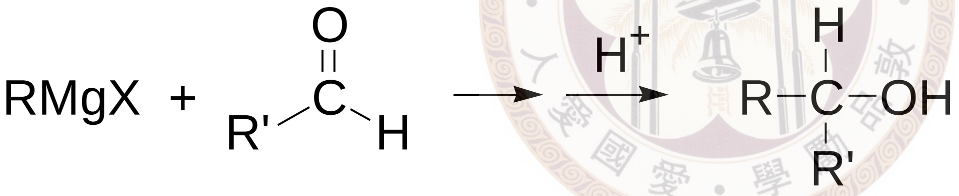


$$R^{-}Mg^{2+}X^{-} + \overset{\delta^{+}}{C}=\overset{\delta^{-}}{O} \longrightarrow R-\overset{OMgX}{\underset{|}{\overset{|}{C}}}- \xrightarrow{H^{+}} R-\overset{OH}{\underset{|}{\overset{|}{C}}}-$$



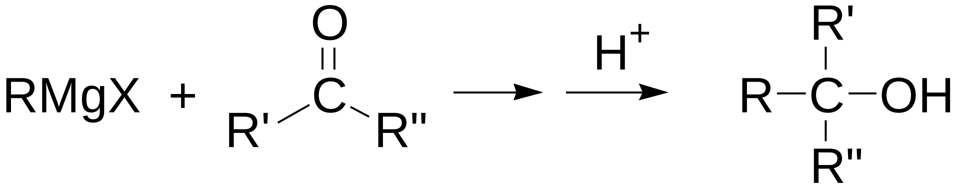
$$RMgX + H_2C=O \longrightarrow \xrightarrow{H^{+}} RCH_2OH$$

1° alcohol



$$RMgX + R'CHO \longrightarrow \xrightarrow{H^{+}} R-\overset{H}{\underset{R'}{C}}-OH$$

2° alcohol

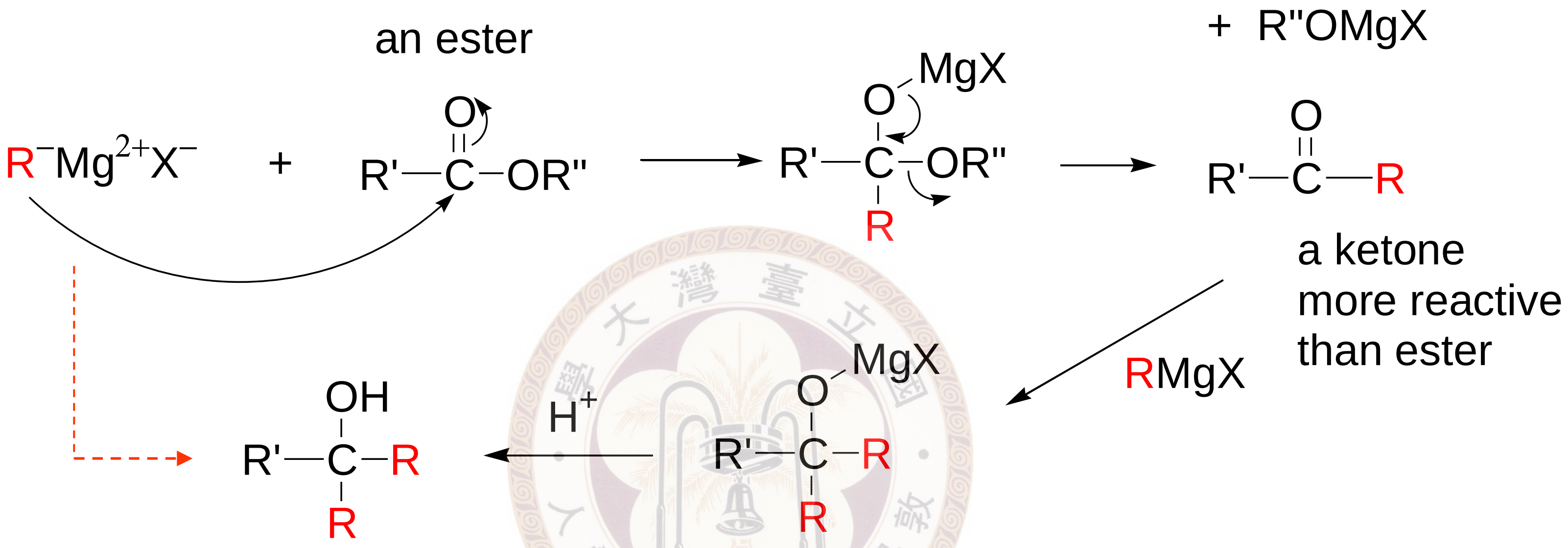


$$RMgX + R'COR'' \longrightarrow \xrightarrow{H^{+}} R-\overset{R'}{\underset{R''}{C}}-OH$$

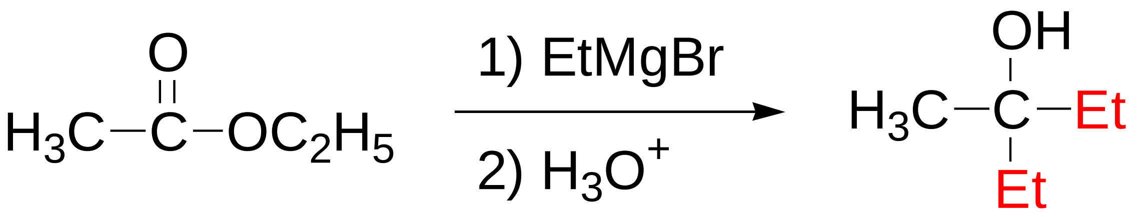
3° alcohol

★ This is a very useful way to prepare alcohols

✓ Reaction with esters



例

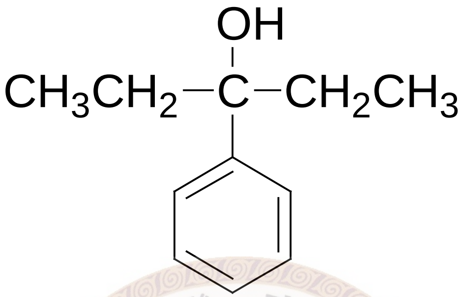


$$H_3C-\overset{\overset{\displaystyle O}{\|}}{C}-OC_2H_5 \xrightarrow[\text{2) } H_3O^+]{\text{1) EtMgBr}} H_3C-\underset{\underset{\displaystyle Et}{|}}{\overset{\overset{\displaystyle OH}{|}}{C}}-Et$$

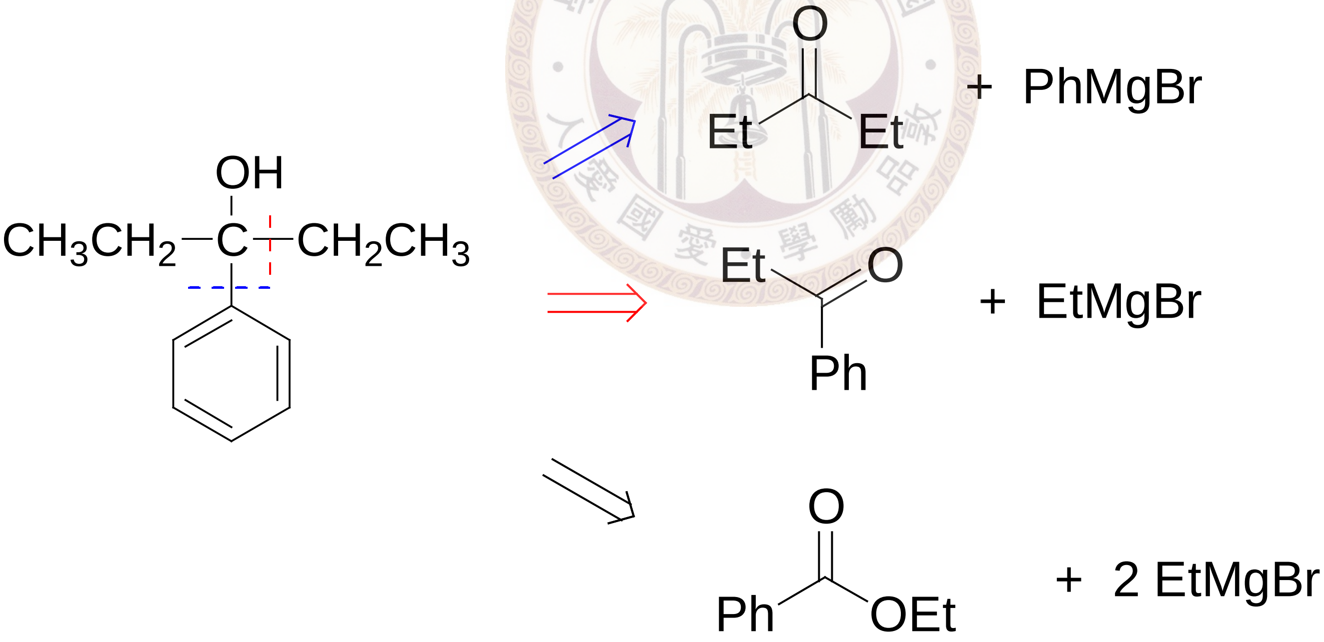
67%

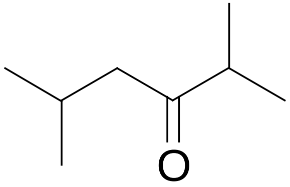
◎ Planning a Grignard synthesis

Q: Synthesis of

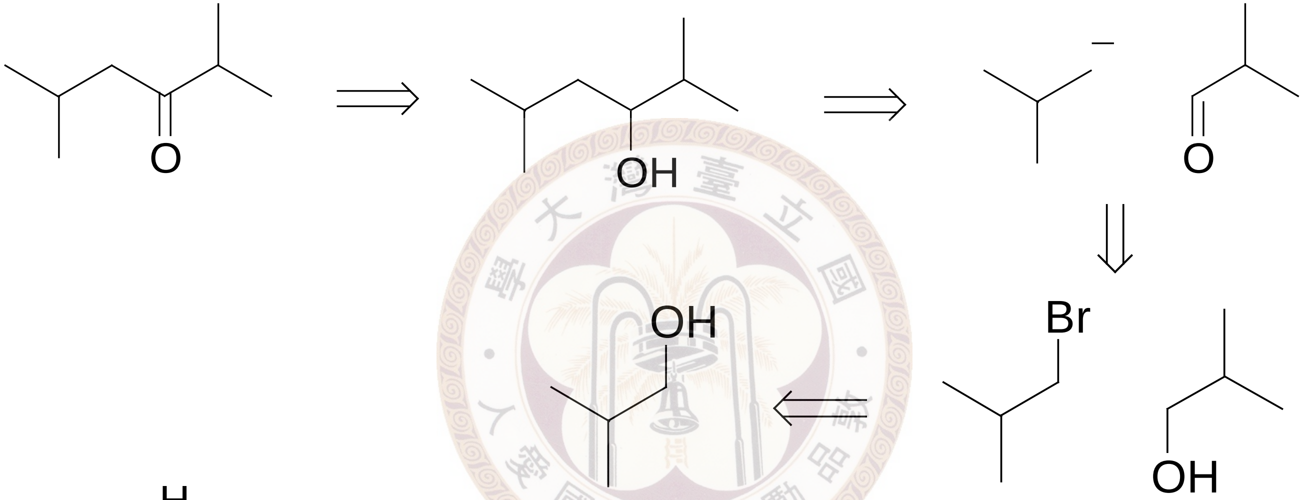


Retrosynthetic analysis:

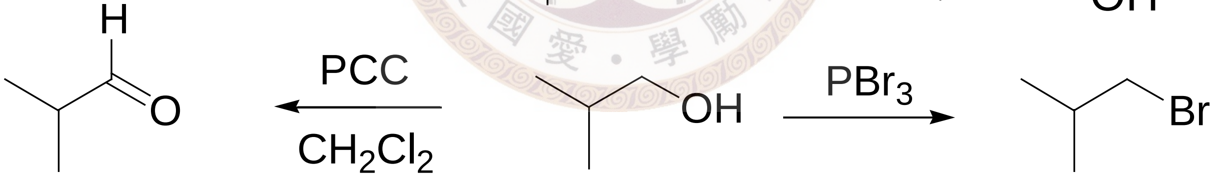


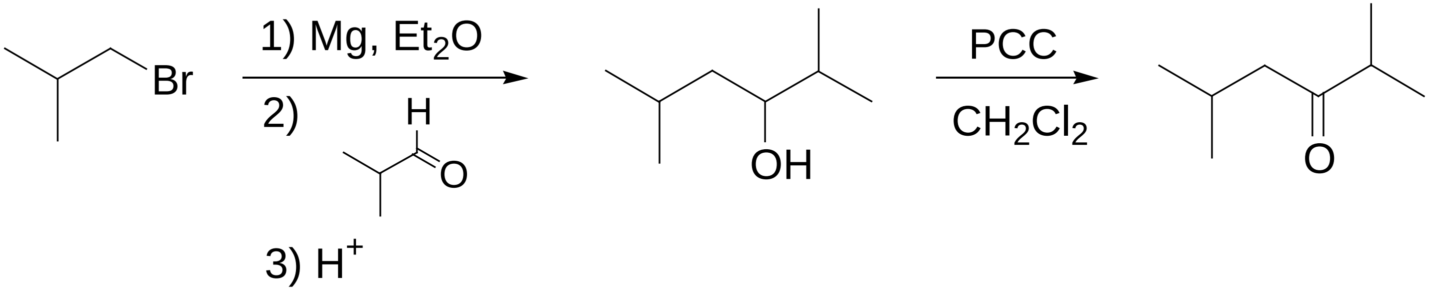
Q: Synthesis of  using alcohols with less than 4 carbons

Retrosynthetic analysis:

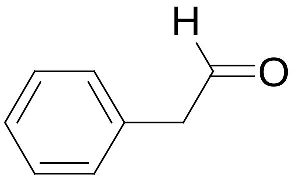


Ans:

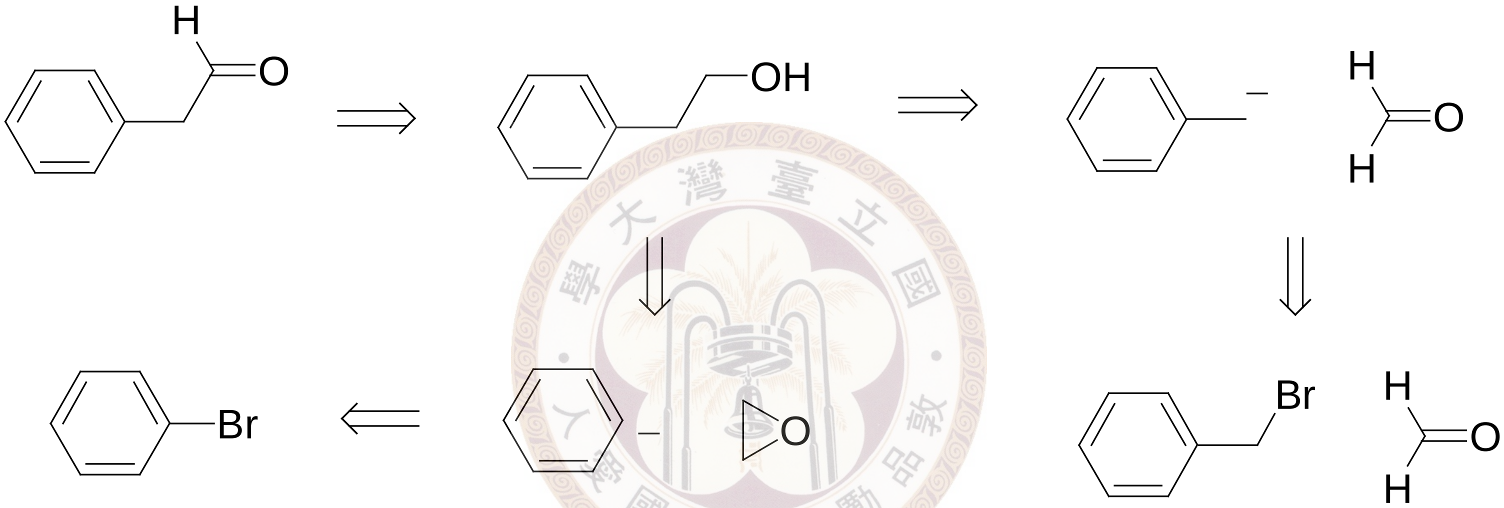




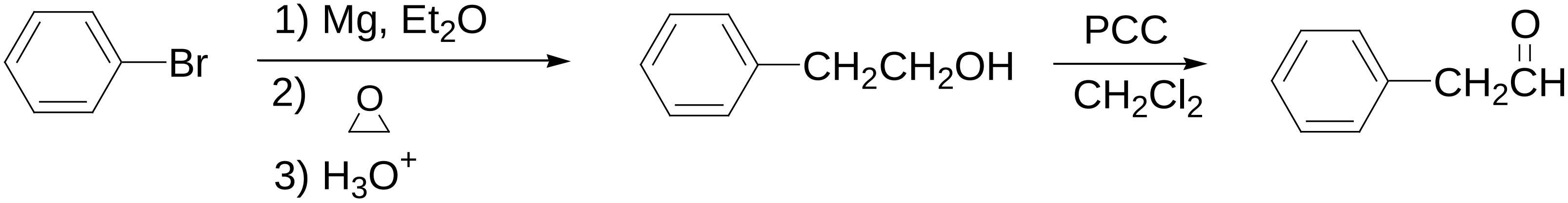
Q: Synthesis of



Rretrosynthetic analysis:



Ans:



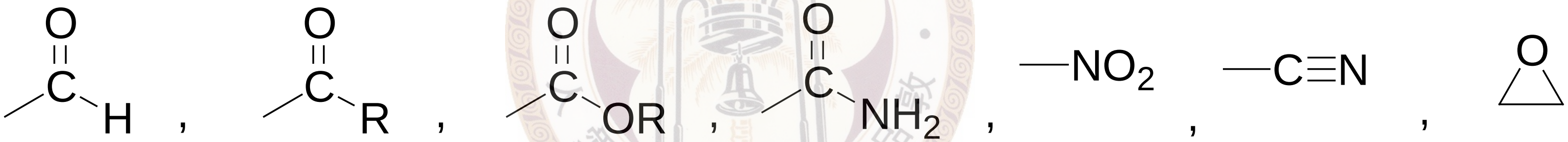
★ Limitations

✓ RMgX is still a strong base

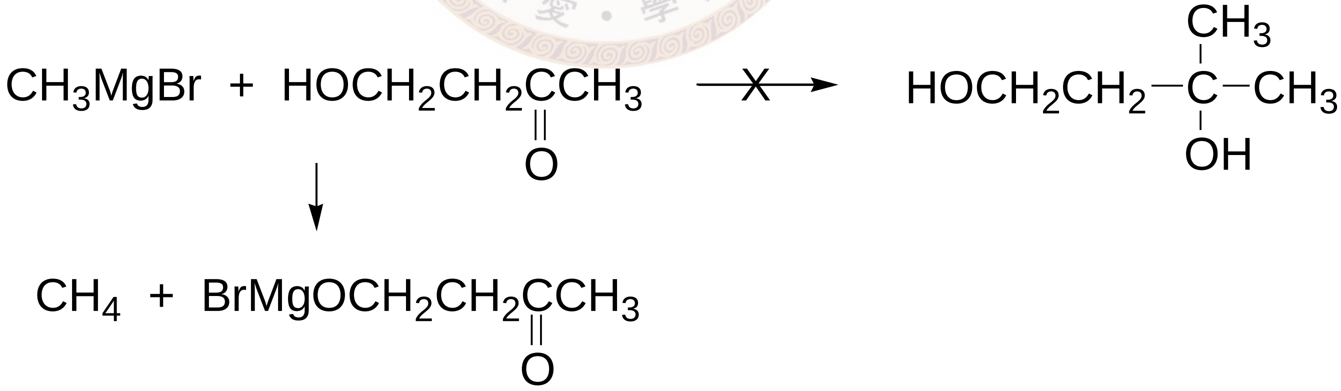
can not tolerate the presence of:

-OH, $-NH_2$, -NHR, $-CO_2H$, $-SO_3H$, -SH, -C≡C-H

✓ Reactive FGs can not coexist:



例

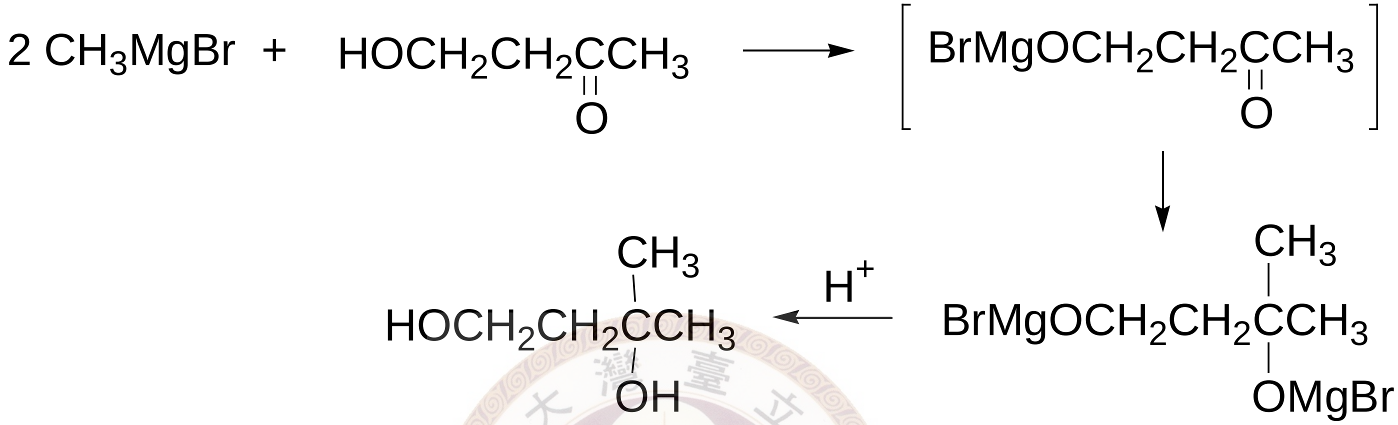


$$CH_3MgBr + HOCH_2CH_2\underset{\overset{\|}{O}}{C}CH_3 \xrightarrow{\times} HOCH_2CH_2-\underset{OH}{\overset{CH_3}{C}}-CH_3$$

$$\downarrow$$

$$CH_4 + BrMgOCH_2CH_2\underset{\overset{\|}{O}}{C}CH_3$$

A solution:

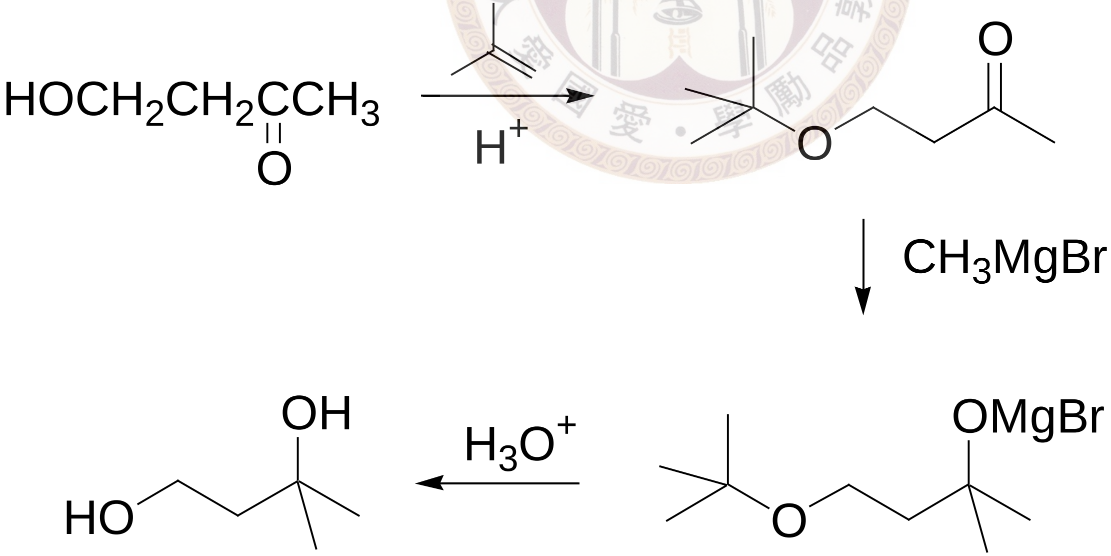


$$2\ CH_3MgBr + HOCH_2CH_2\underset{O}{\underset{\|}{C}}CH_3 \longrightarrow \left[BrMgOCH_2CH_2\underset{O}{\underset{\|}{C}}CH_3 \right]$$

$$\downarrow$$

$$HOCH_2CH_2\underset{OH}{\underset{|}{\overset{CH_3}{\overset{|}{C}}}}CH_3 \xleftarrow{H^+} BrMgOCH_2CH_2\underset{OMgBr}{\underset{|}{\overset{CH_3}{\overset{|}{C}}}}CH_3$$

Other strategy: protect -OH



$$HOCH_2CH_2\underset{O}{\underset{\|}{C}}CH_3$$

◎ The use of alkyllithium

Similar to Grignard reagents
More reactive but more basic
→ More side-reaction

◎ Sodium alkynide