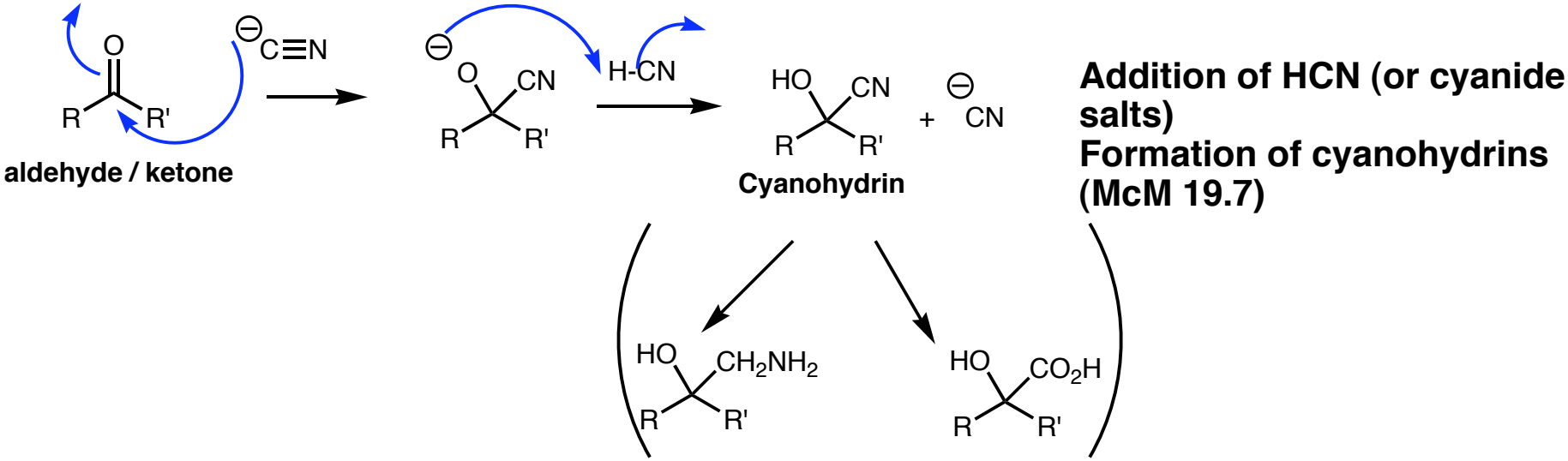
C-C bond forming reactions

Known C-C bond forming reactions
(New C-C bond forming reactions in KJM3200)

Organometallic coupling C-C bond forming reactions

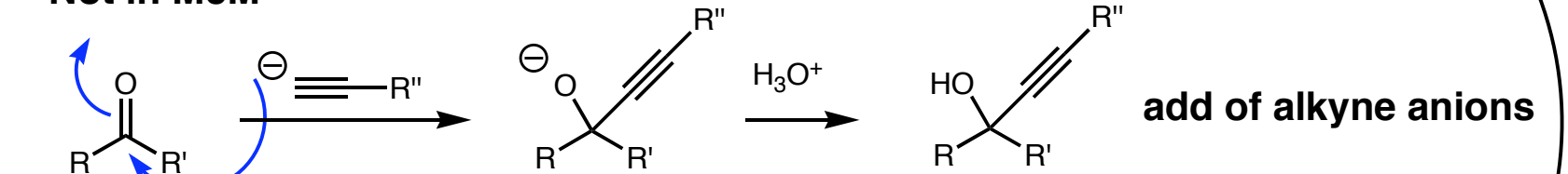
Protecting groups in organic synthesis

Addition to carbonyl groups

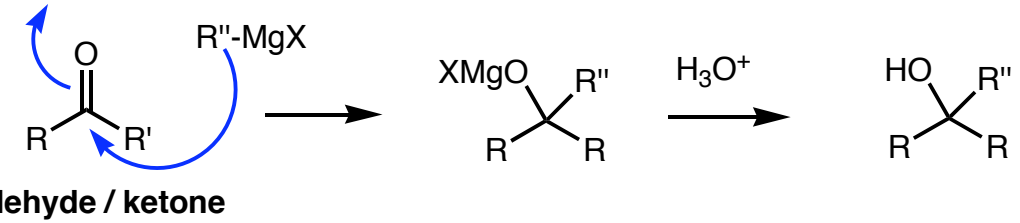


Addition of HCN (or cyanide salts)
Formation of cyanohydrins (McM 19.7)

Not in McM



add of alkyne anions

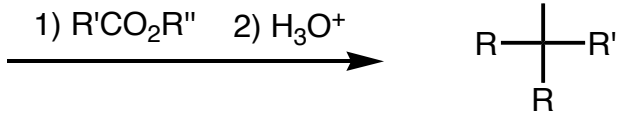


aldehyde / ketone

Addition of Grignard reagents (McM 19.8)
other organomet. reagents see, lab ex. 8)

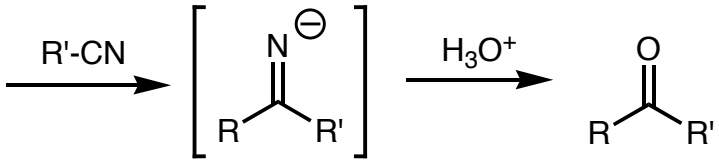
Other Grignard addition reactions

R-MgX
(2 equivs)



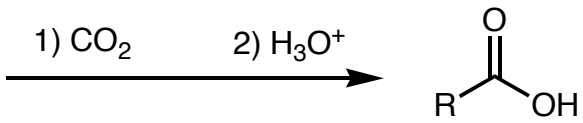
Add to esters, McM 21.6

R-MgX



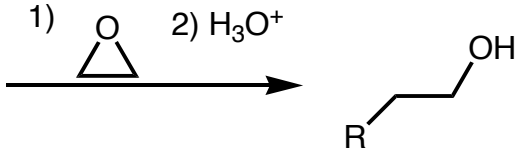
Add to nitrile. McM, 20.9

R-MgX

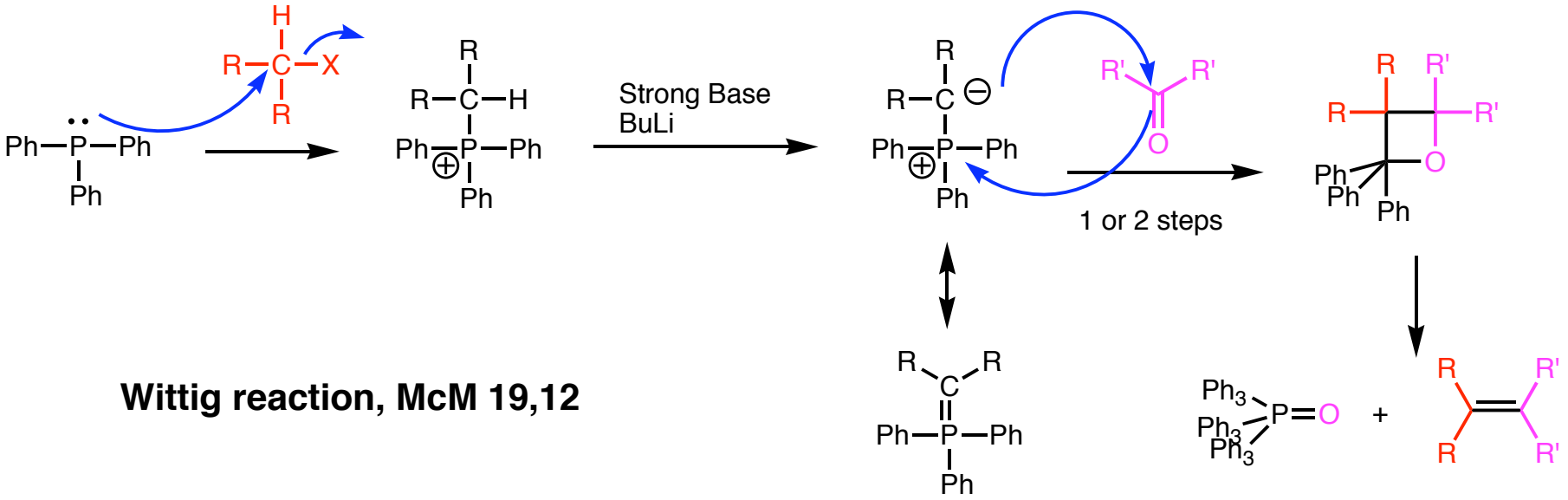


Add to CO_2, McM 20.6

R-MgX



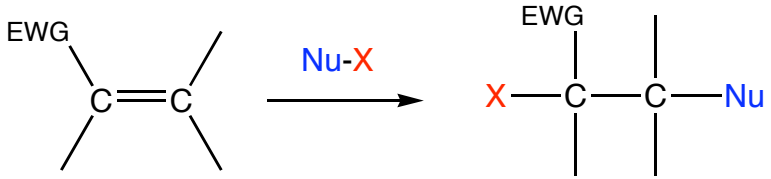
Add to epoxide, McC 18.8



Wittig reaction, McM 19,12

See also lab ex 6

Conjugate addition



Alkene

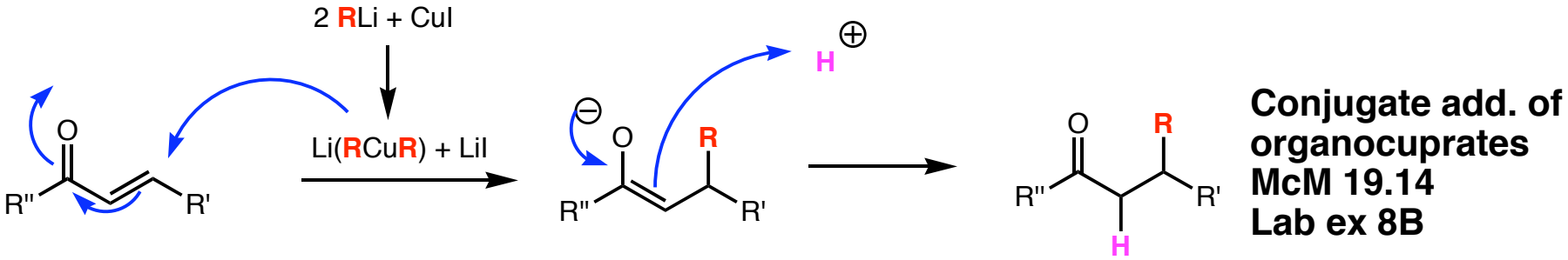
Funktionalized "alkane"

EWG: -COR, -CN, -NO_2 etc

Nucleophilic addition to alkenes

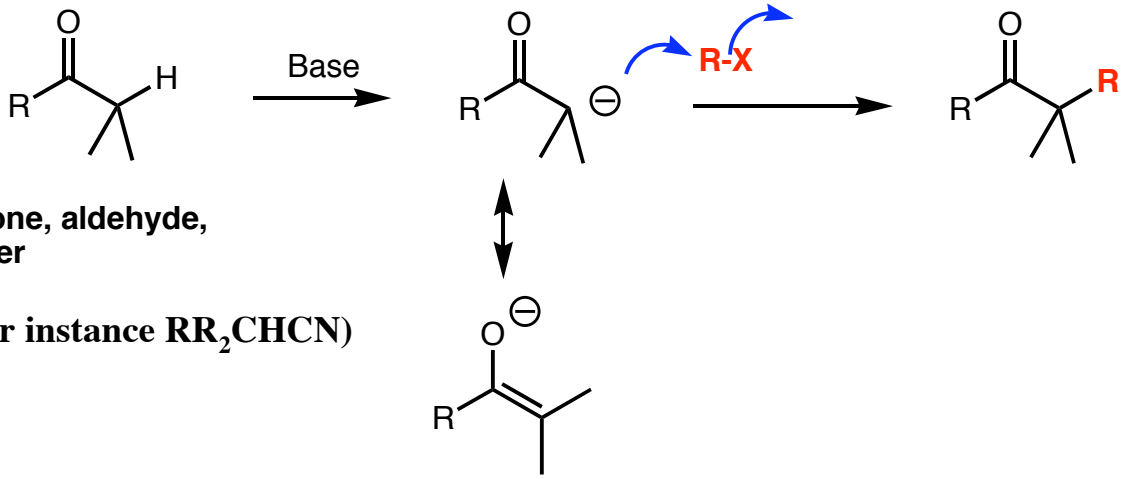
(chapt. 23)

Conjugate add., 1,4-add., Michael add.



Conjugate add. of organocuprates
McM 19.14
Lab ex 8B

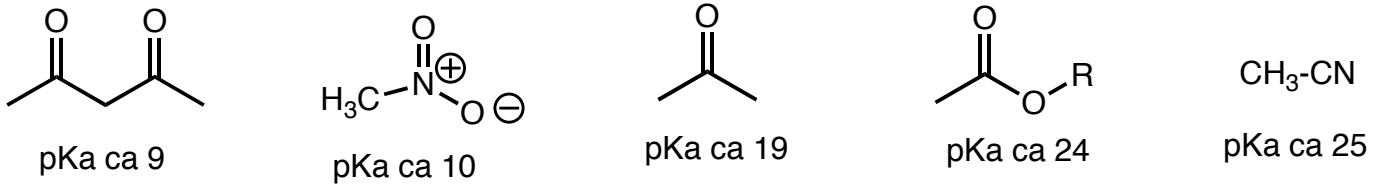
Alkylation α to C=O

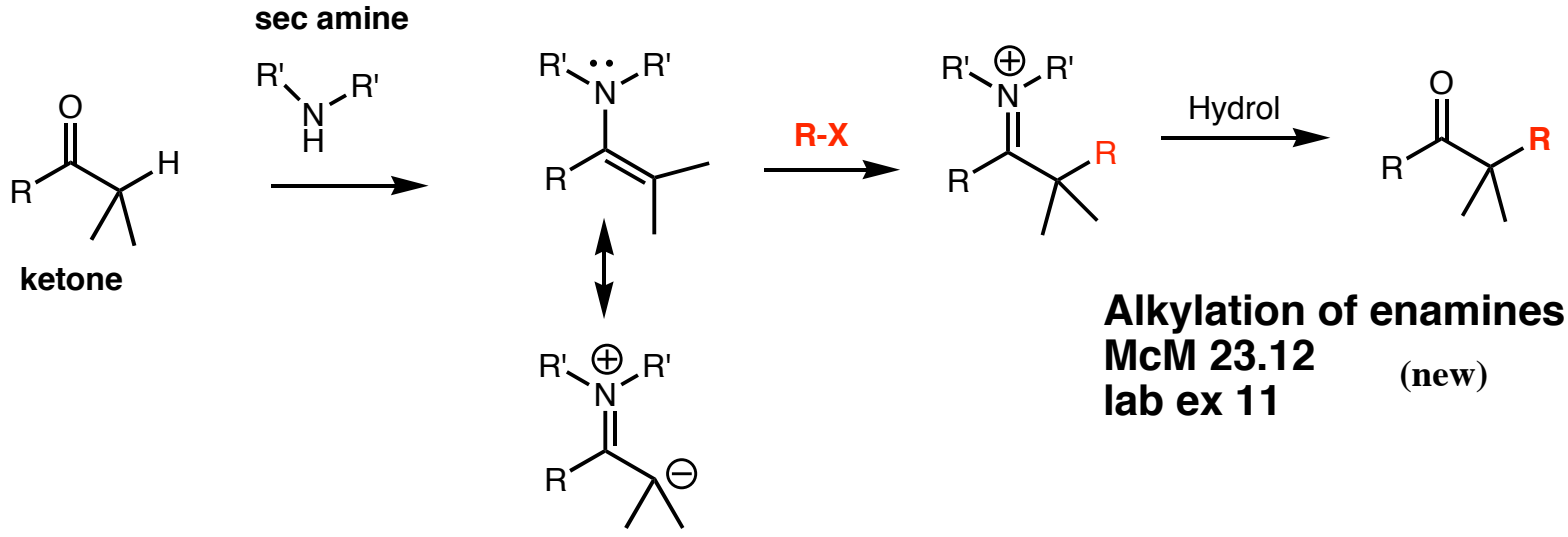


ketone, aldehyde, ester

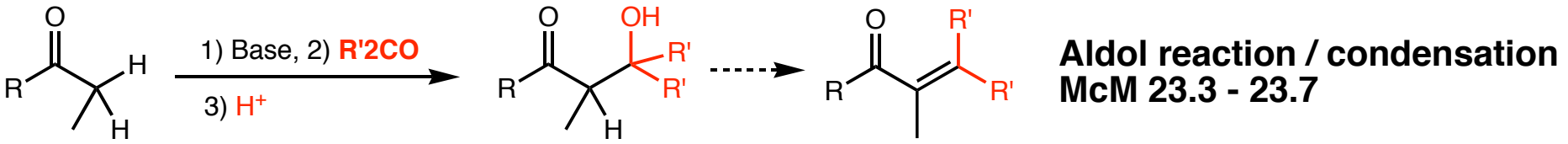
(also for instance RR_2CHCN)

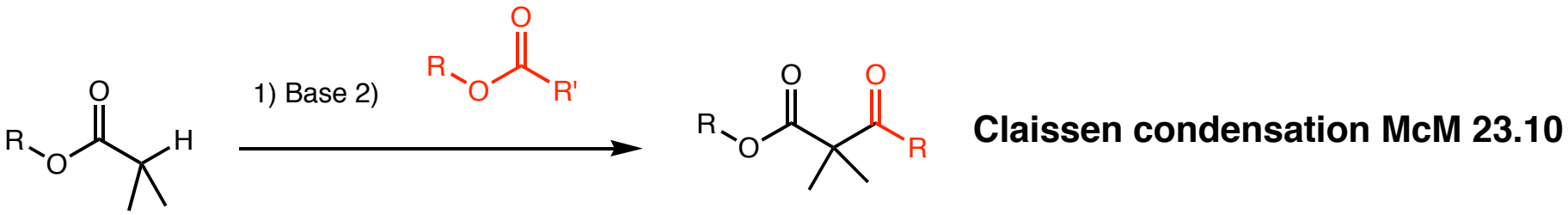
Alkylation of enolate anion
McM 22.8

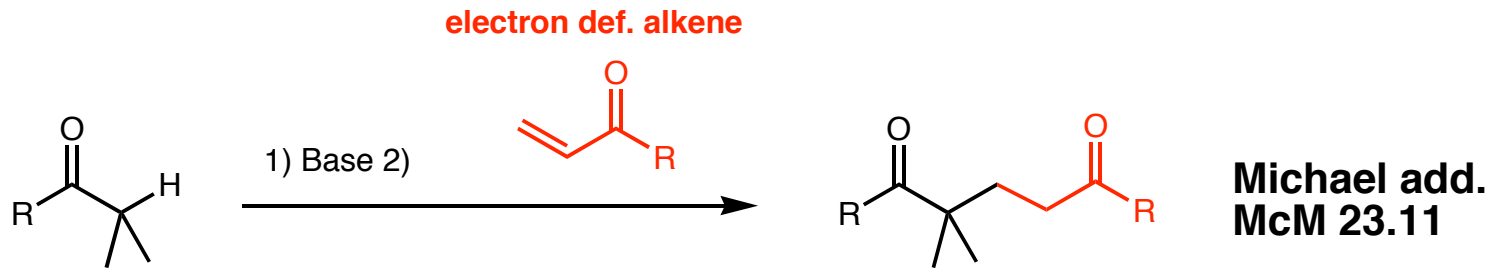




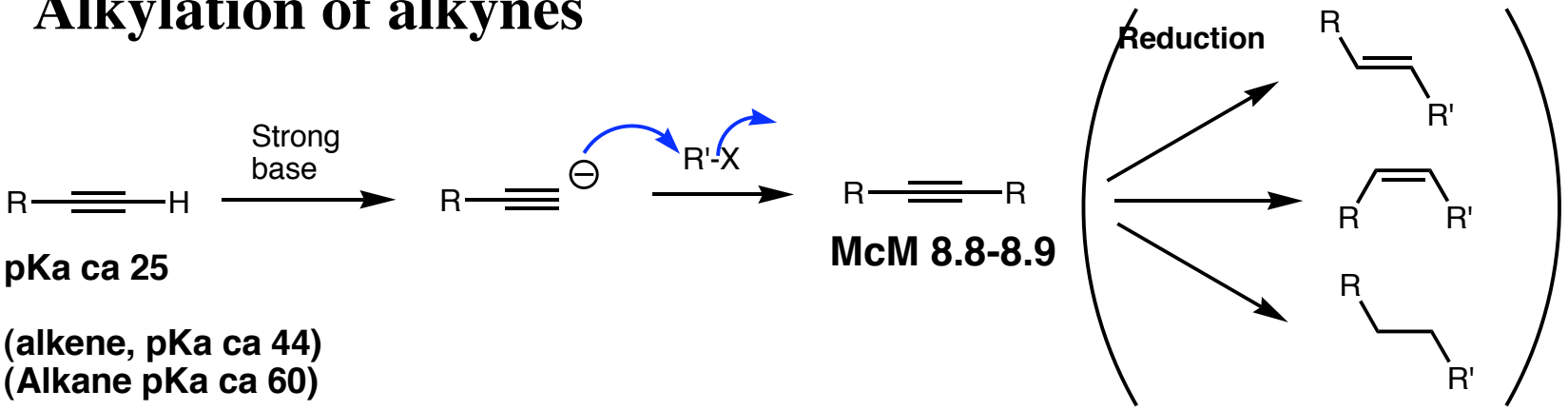
Alkylation of enamines
McM 23.12
lab ex 11
(new)


1) Base, 2) R'2CO
3) H+
Aldol reaction / condensation
McM 23.3 - 23.7


1) Base 2)
Claissen condensation McM 23.10


electron def. alkene
1) Base 2)
Michael add.
McM 23.11
Ketone, ester etc
precursor of stabilized enolate anion

Alkylation of alkynes

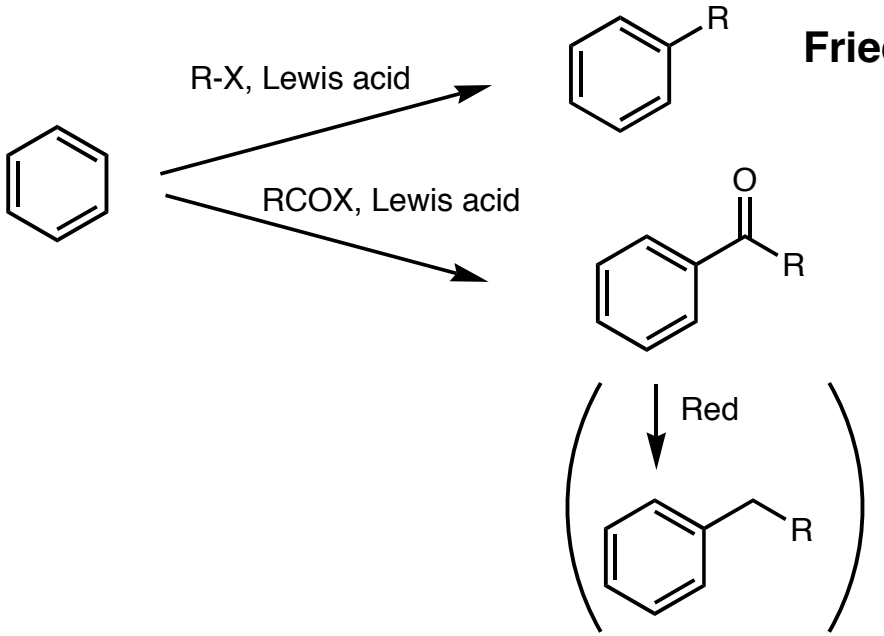


pKa ca 25

(alkene, pKa ca 44)
(Alkane pKa ca 60)

McM 8.8-8.9

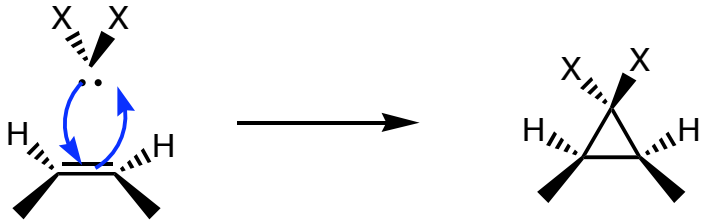
Electrophilic aromatic substitution



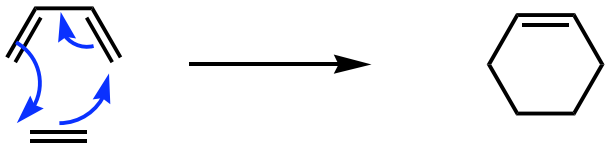
Friedel Craft alkylation (McM 16.3)

Friedel Craft acylation (McM 16.4)

Cycloadditions



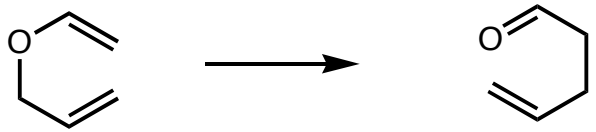
Add of carbenes / carbenoids(McM 7.6)
Cyclopropanes



Diels Alder (McM 14.5. 30)
6-membered rings

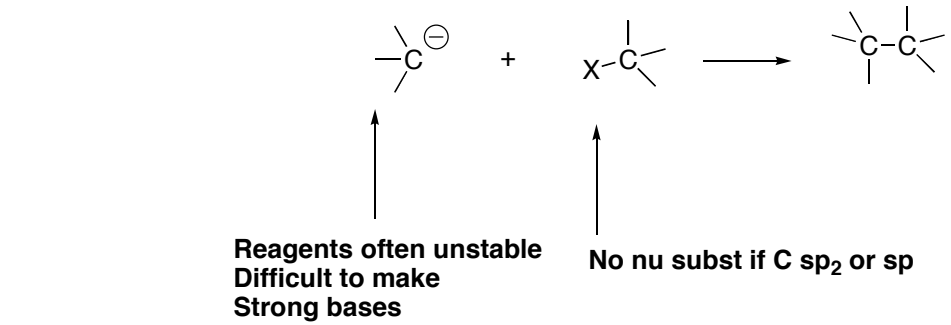
(chapt. 30, in the end of this course)

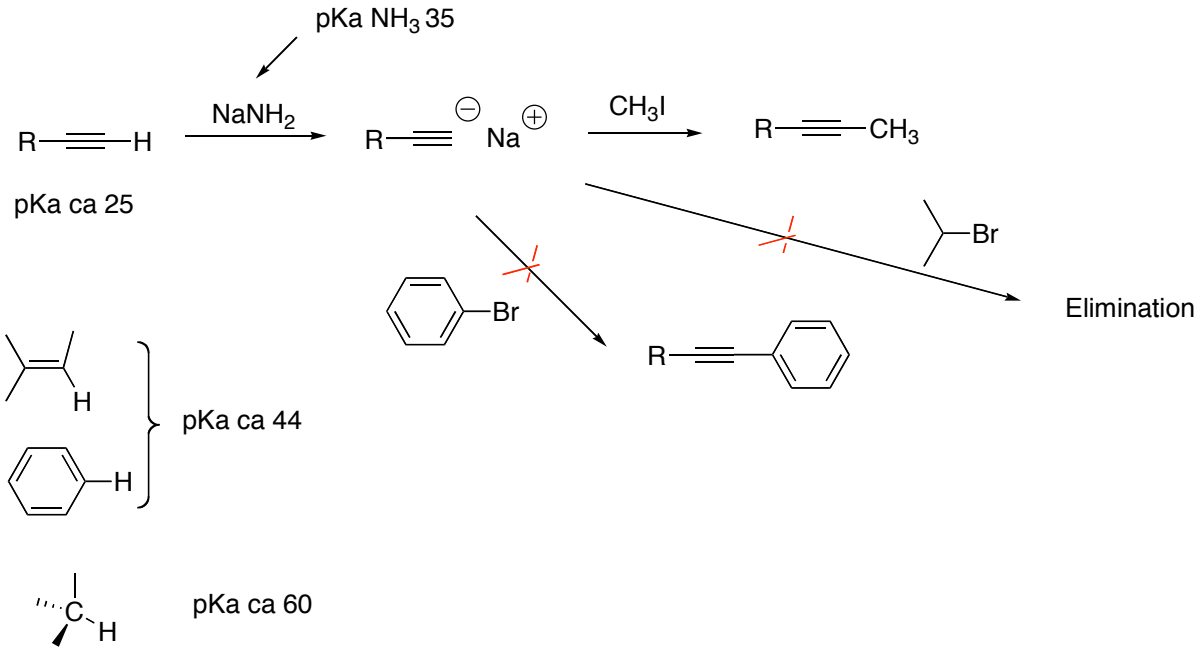
Rearrangements



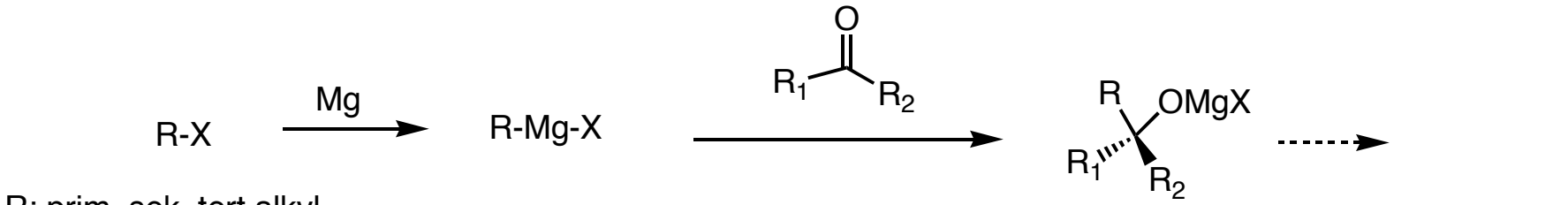
Sigmatrophic rearrangements
for instance Claissen rearrangement
(McM 30)

C-C Bond Formation - Organometallic Coupling Reactions (McM 10.9, Lab ex 10)





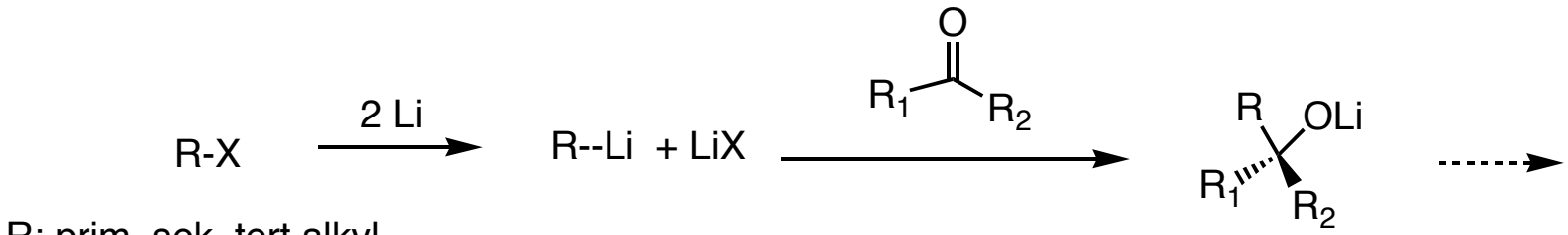
Grignard reagents and Organolithium reagents



R: prim, sek, tert alkyl
alkenyl
aryl

Nucleophile
Strong base

Reacts with carbonyls
Strong bases



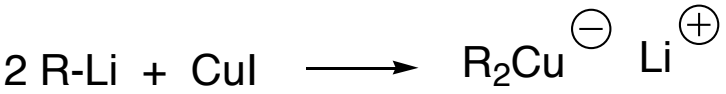
R: prim, sek, tert alkyl
alkenyl
aryl

Nucleophile
Strong base

BuLi used a lot as **strong** base

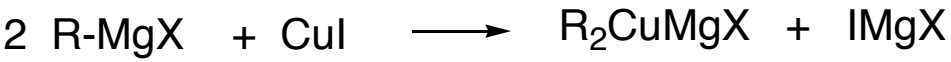
RMgX or RLi does not react well with alkyl halides in substitutions

Organocuprates (McM 10.9)

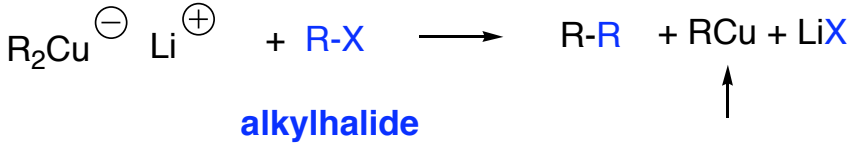


Gilman reagent
Dialkylcuprate

(R: alkyl, alkenyl, alkynyl, aryl)



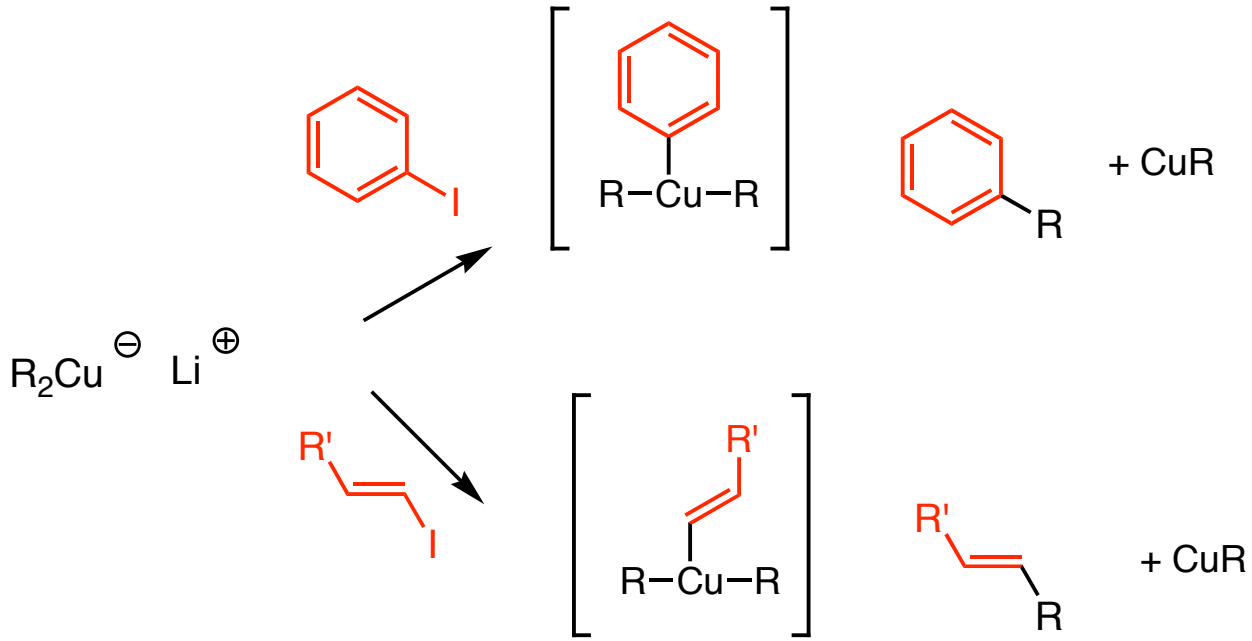
Participate in substitution with alkylhalides (Cl, Br, I)



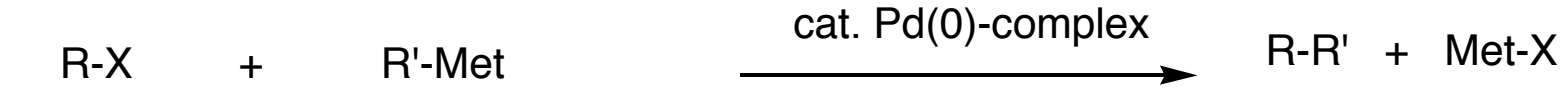
Mech. see next slide

Not S_N1 or S_N2

Also reaction with alkenyl halides and arylhalides (sp^2)



Palladium catalyzed coupling reactions (Lab ex. 10)



-aryl halide
-alkenyl halide
-alkynyl halide

R': alkynyl, alkenyl, aryl, alkyl
-Met; (-MgX), -ZnX, -SnR_3,- -$B(OR)_2$,

R'-Met:

R'ZnX - Negishi coupling

- Esp. good for <u>R' = alkyl,</u> R'ZnX generated in situ

R'$SnBu_3$ / R'$SnMe_3$ - Stille coupling

-R' (alkynyl) aryl, alkenyl, organotin comp. tox R'$SnBu_3$ / R'$SnMe_3$ stable

R'$B(OH)_2$ / R'$B(OR)_2$ - Suzuki coupling

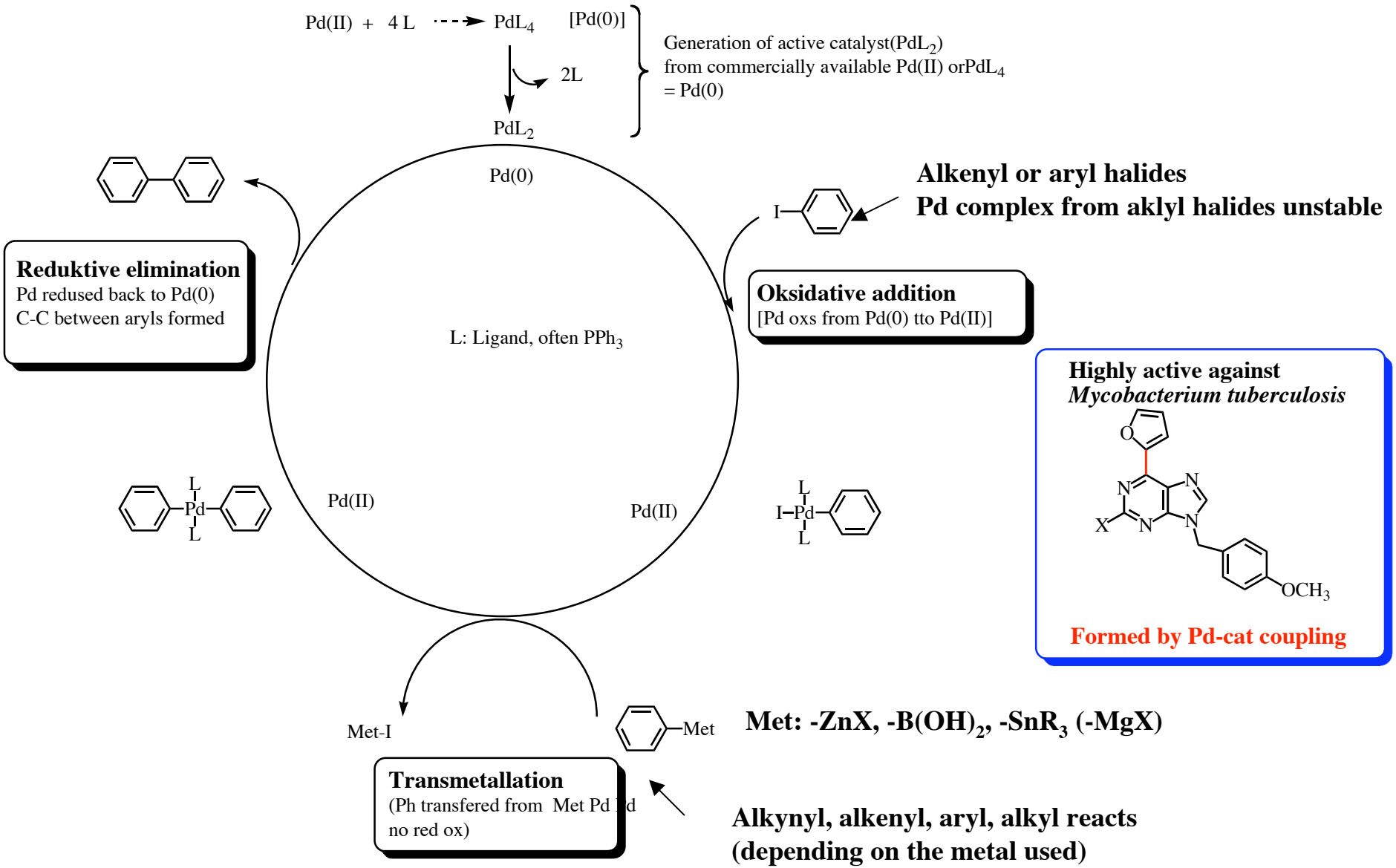
- R' (alkynyl) aryl, alkenyl, Green react. R'$B(OH)_2$ / R'$B(OR)_2$ relatively stable

react. requires base

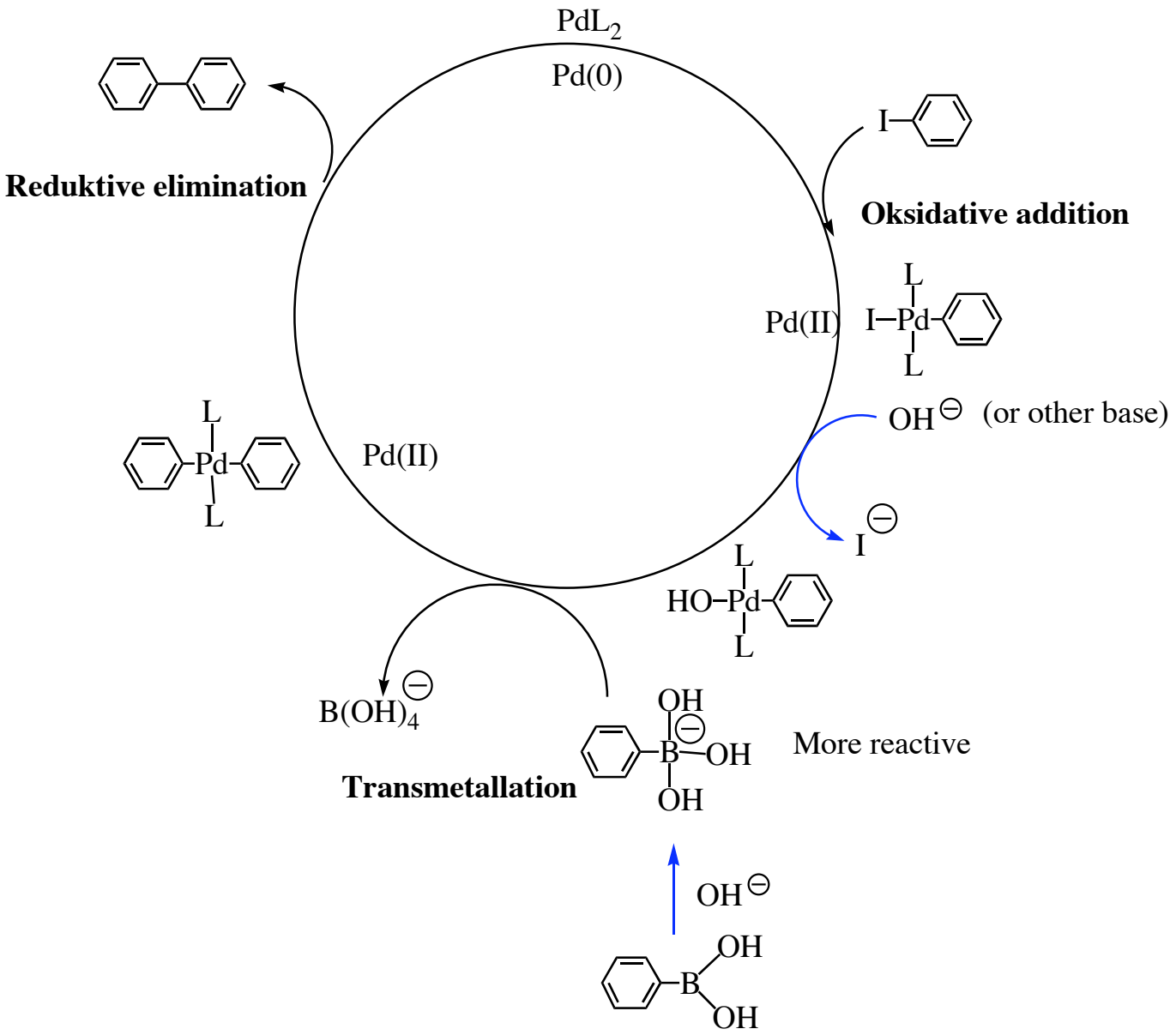
R'MgX - Kumada coupling

Less reactive, often Ni-cat. (less stable than Pd-cat)

General mechanism

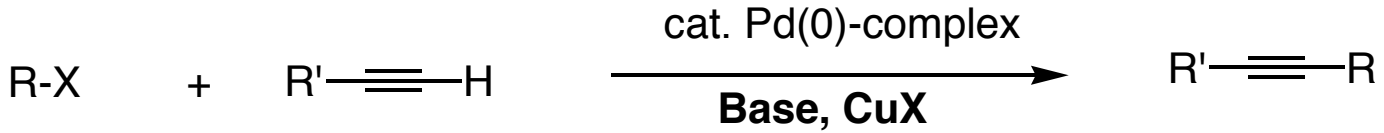


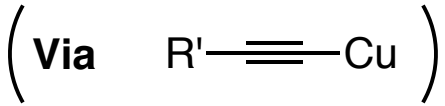
The Suzuki reaction



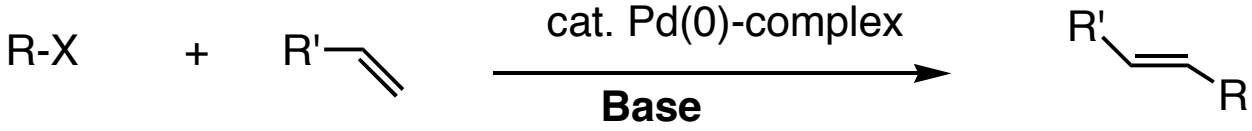
Special cases - No preformed R'Met

Coupling on alkynes - Sonogashira coupling

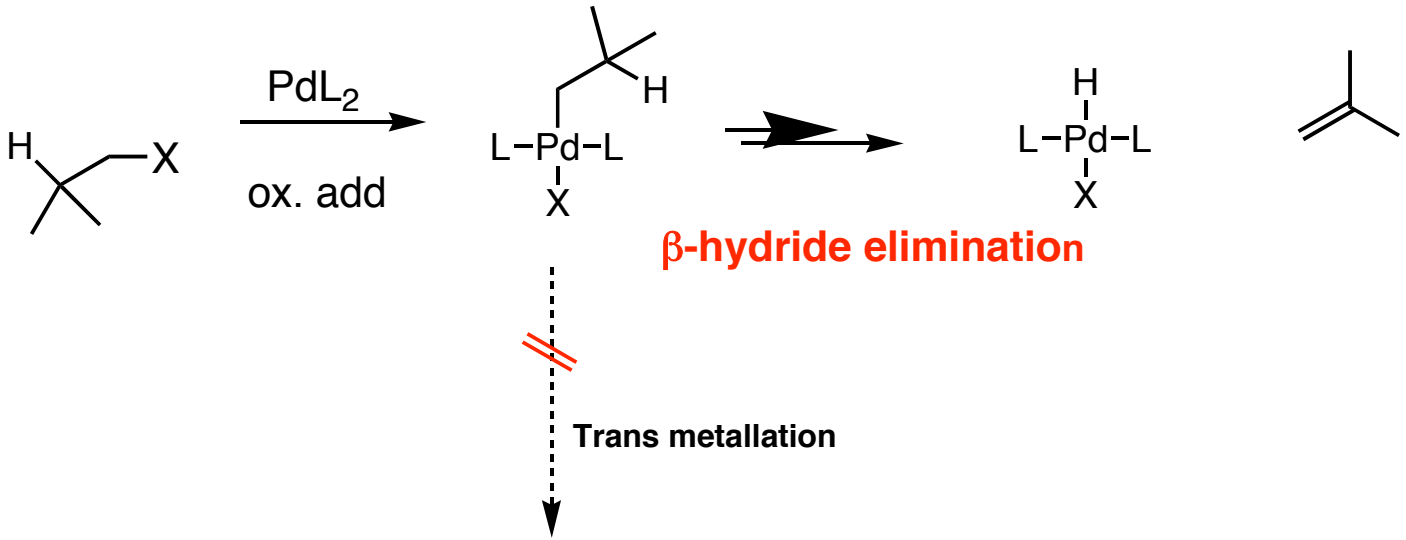




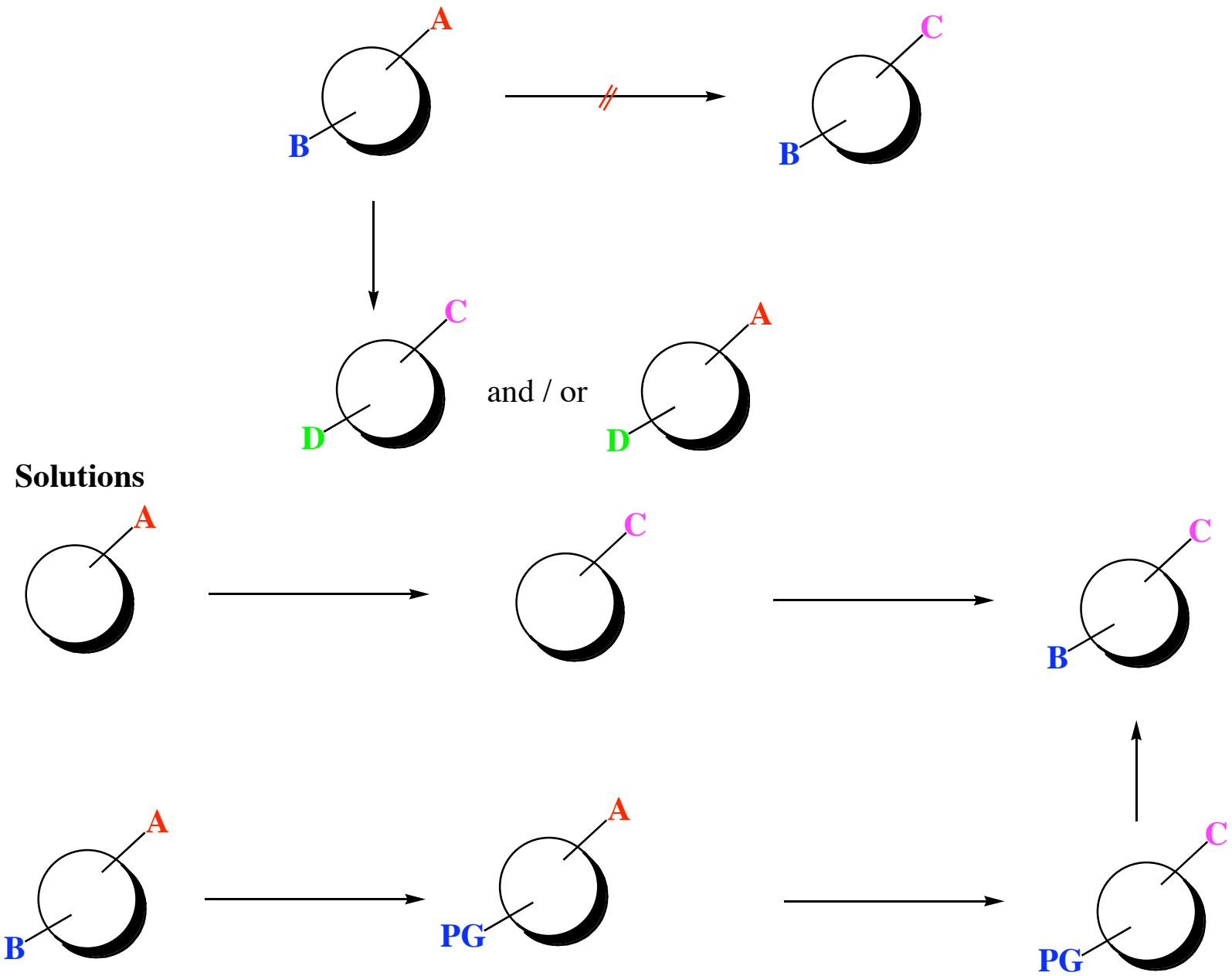
Coupling on alkenes - Heck coupling (Somewhat diff. mech.)



Why difficult to couple alkyl halides

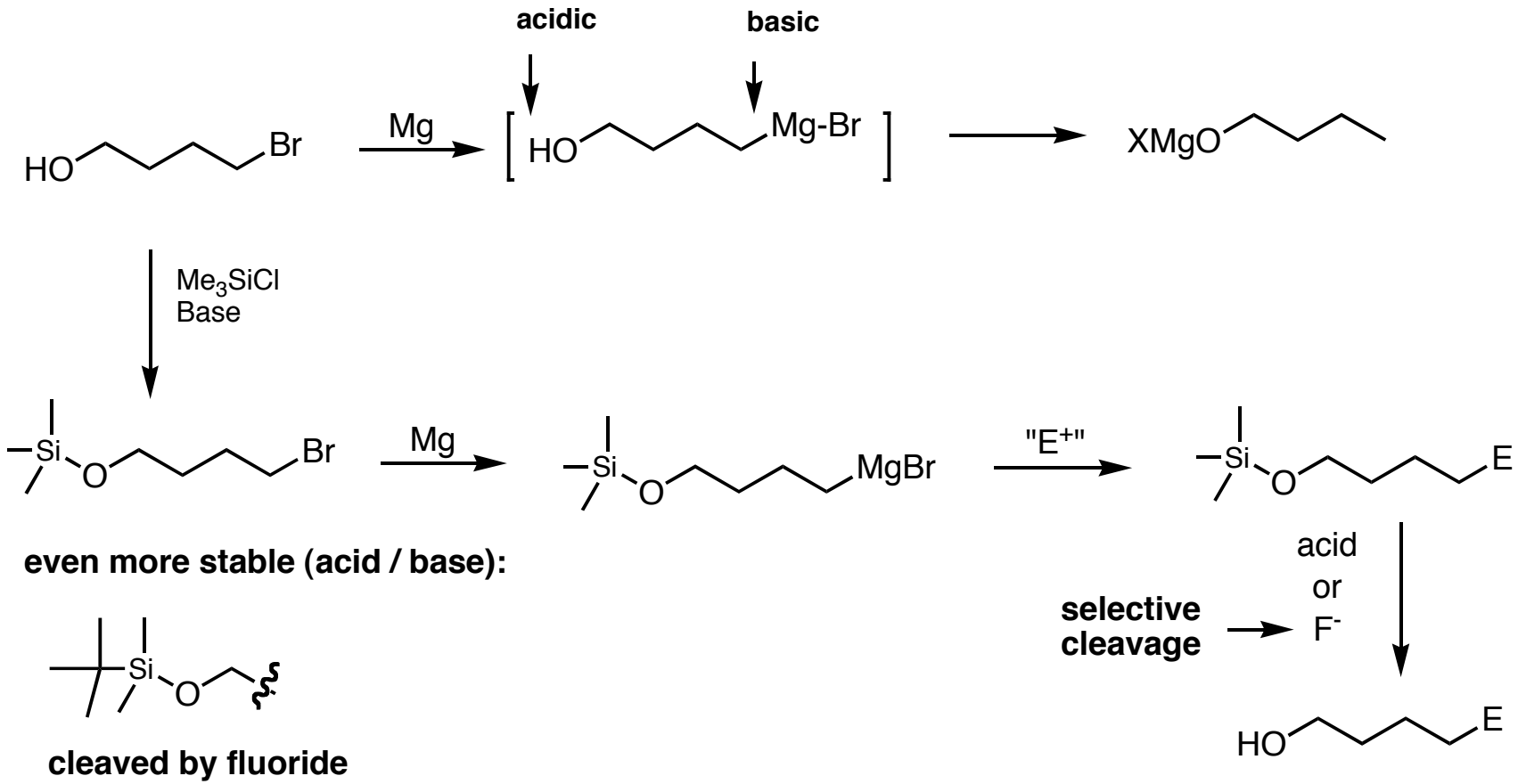


Protecting groups (PG) in organic synthesis (McM 17.9)

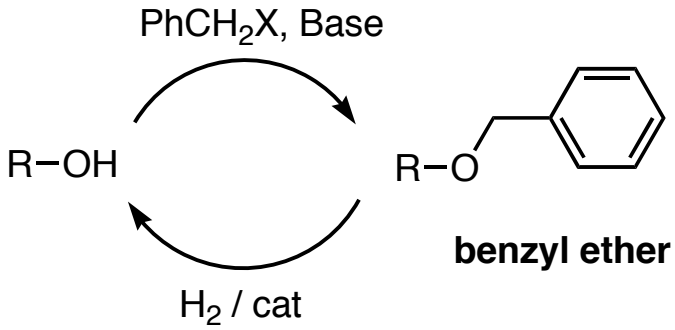


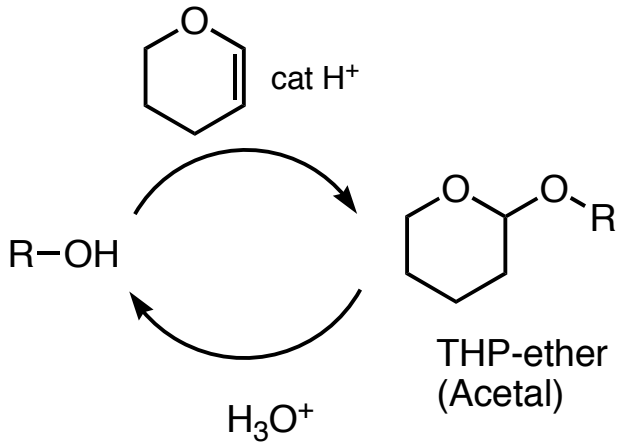
Examples

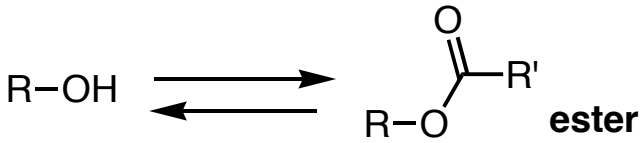
Protection of ROH (McM 17.9)



Other ex. of ROH protecting groups (not mentioned in McM)

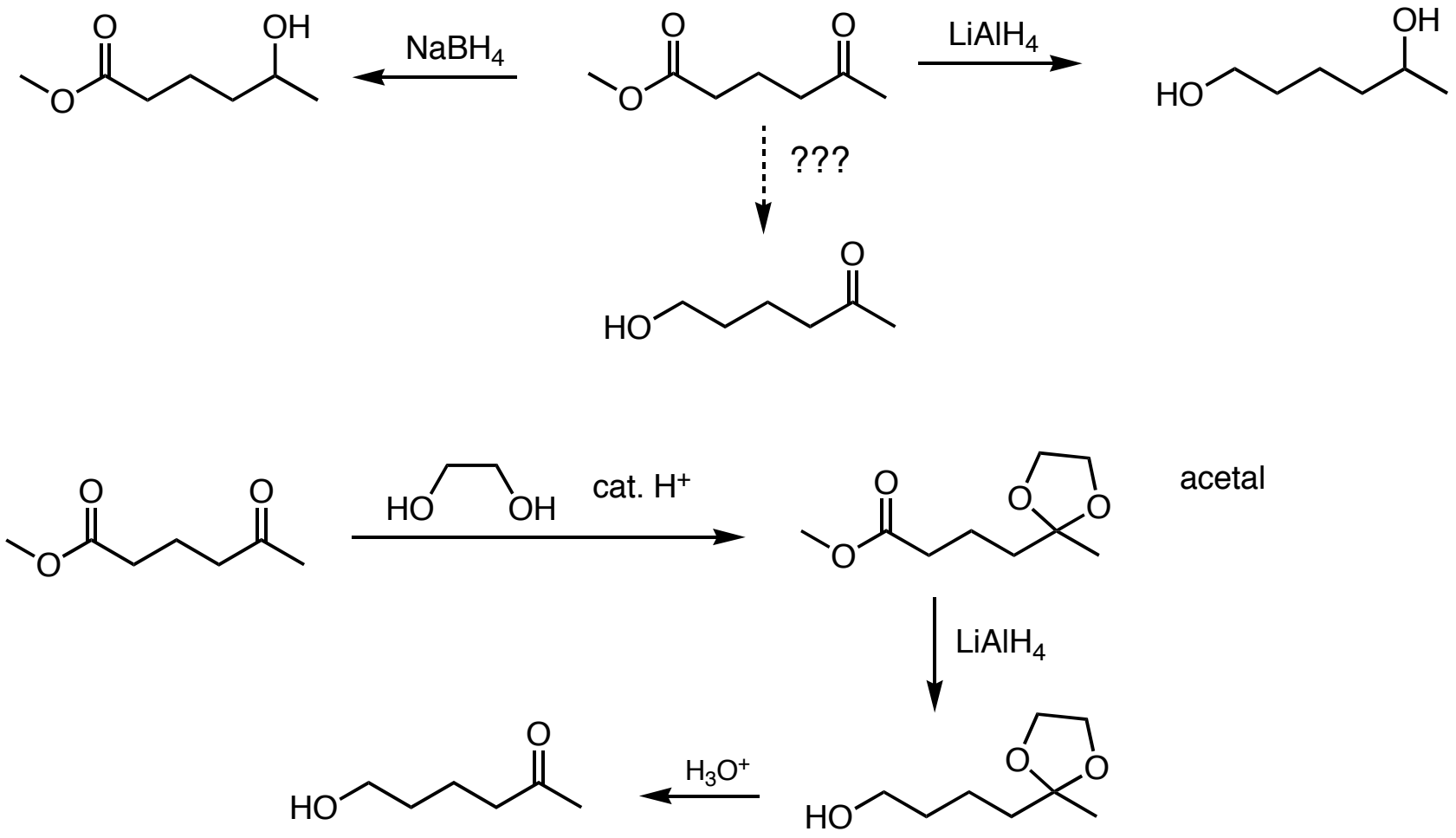






esters also for prot. of acids

Protection of aldehydes / ketones (McM 19.11)



- Two extra steps
- The protecting group curse