Organic synthesis

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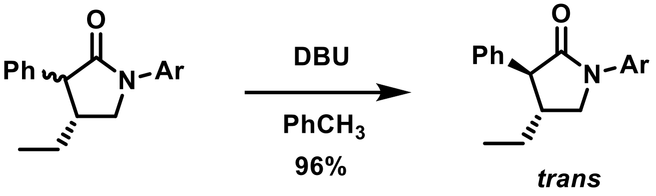
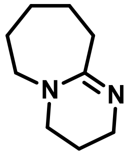
Masaryk University, Brno

epimerization of carbonyl compounds

- thermodynamic equilibration (deprotonation-protonation)





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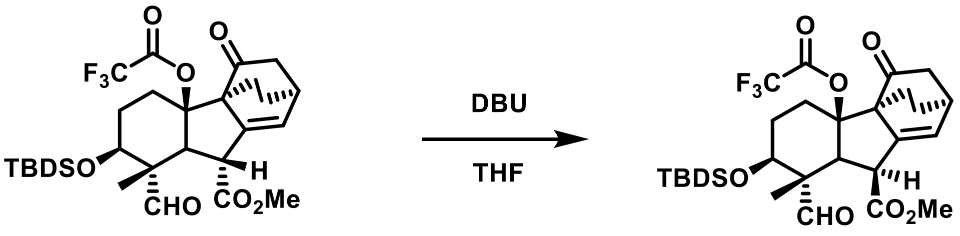
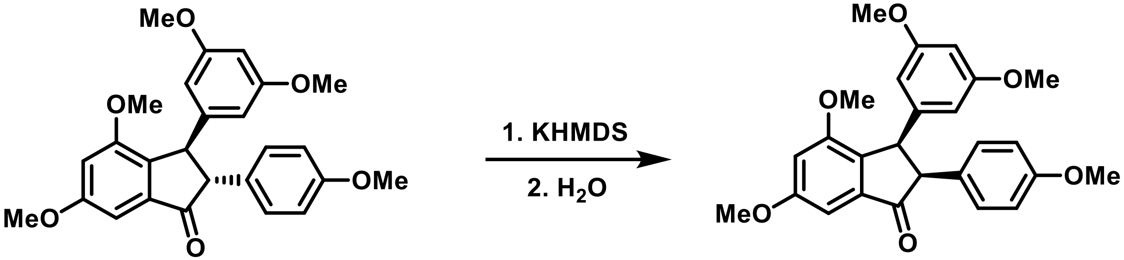


J. Am. Chem. Soc. **1985**, *107*, 5574.

- *kinetic* epimerization is also possible

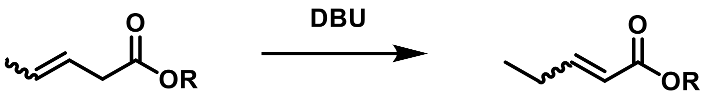


- C-protonation of enolate from less hindered site

J. Am. Chem. Soc. **2009**, *131*, 1753.

migration of double bond in carbonyl compounds

- deprotonation-protonation: anion is in conjugation with double bond



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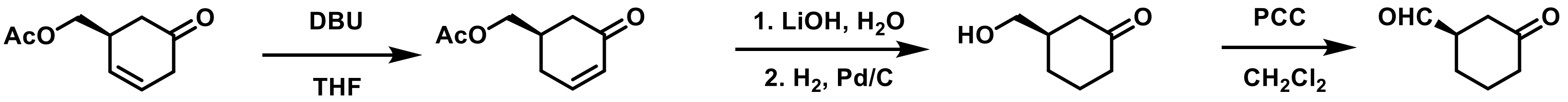
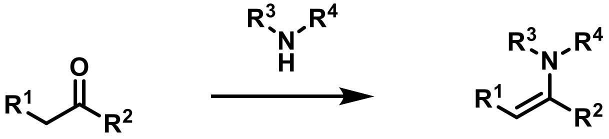
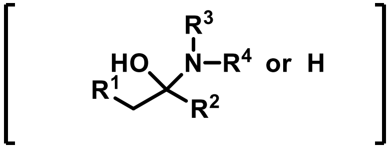


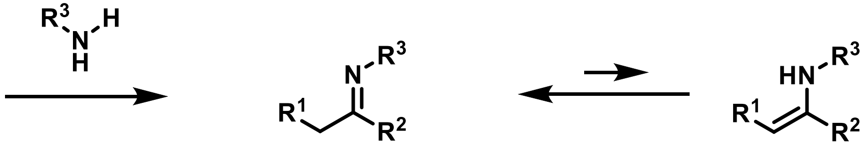
Tetrahedron Lett. **1983**, *24*, 4883.

tautomerism imine-enamine



enamine



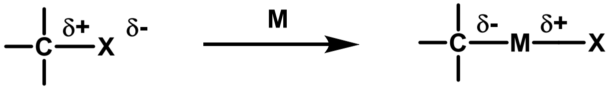


imine

enamine

(more stable tautomer)

Organometallic reagents (Li, Mg, Cu, Zn)



RLi (organolithium reagents)

preparation: **$$$**

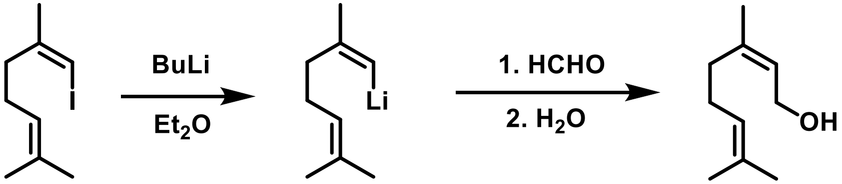
$$R{-}X \xrightarrow{Li} R{-}Li + LiX$$

X = Cl, Br

BuLi as a source of Li

- lithium-halogen exchange (typically fast even at low temperature)
- generated RLi is a weaker base than BuLi

basicity: $sp^3 > sp^2 > sp$

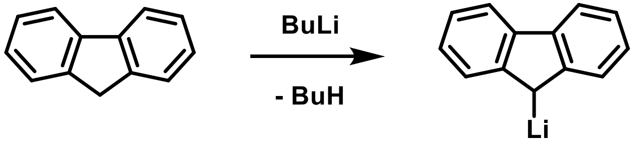


85%

Synthesis **1976**, 245.

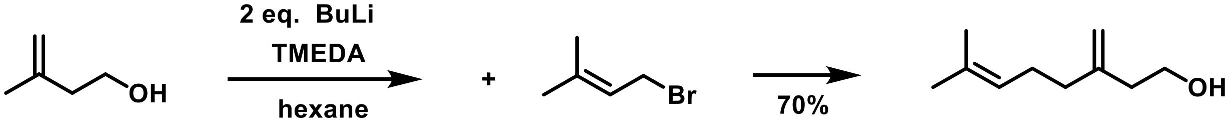
BuLi as a source of Li

- deprotonation of compounds that are more acidic than BuH

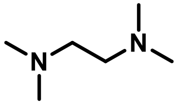


J. Med. Chem. **1992**, *35*, 3156.

?$_4$

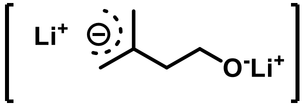


TMEDA



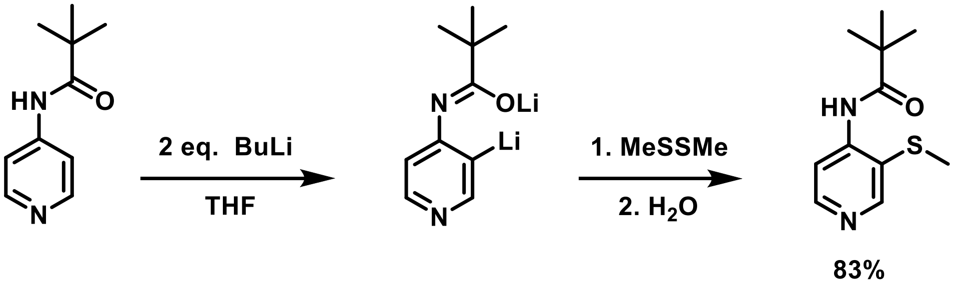
Tetrahedron Lett. **1973**, 4115.

- chelation of Li^+ -> higher polarity of C-Li bond; disruption of R-Li clusters

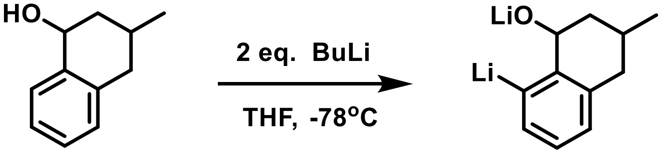


***ortho*-lithiation**

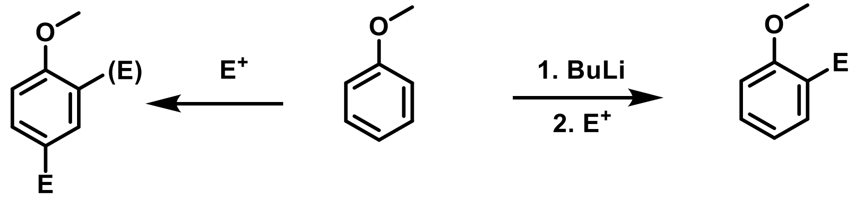
- regioselectivity of lithiation is directed by coordination of Li to the directing group (CONHR, CH_2OH, NHCOtBu, SO_2NHR, OMOM)

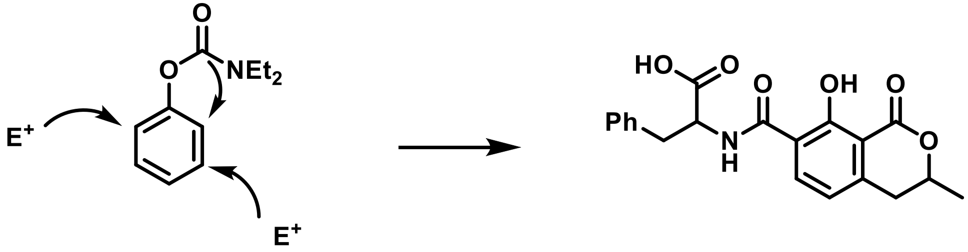


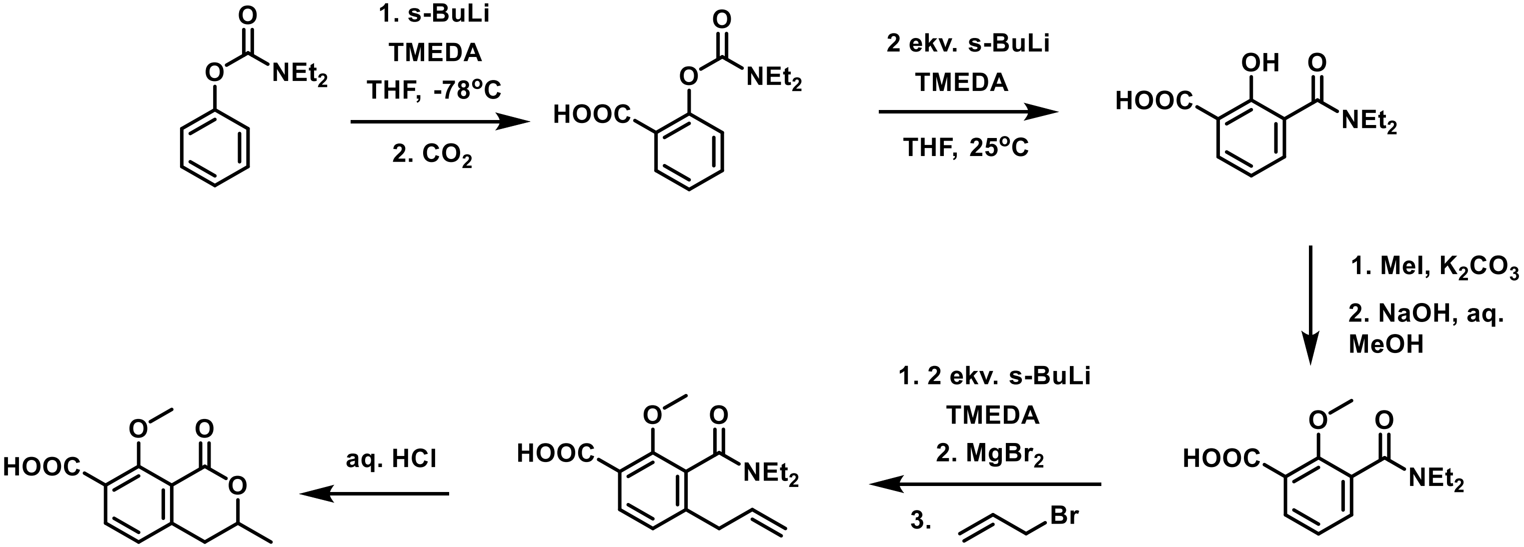
J. Org. Chem. **1983**, *48*, 3401.



Can. J. Chem. **1987**, *65*, 3165.

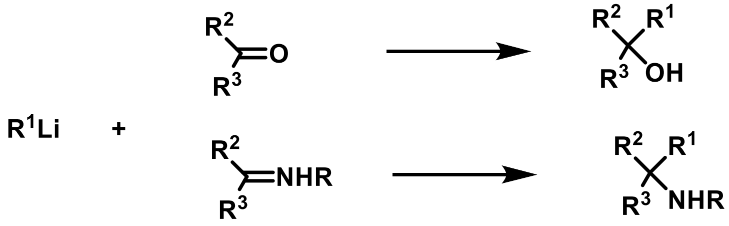






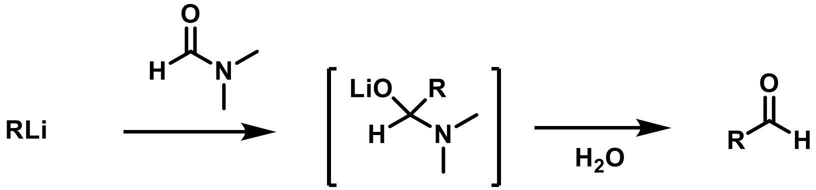
J. Am. Chem. Soc. **1985**, *107*, 6312.

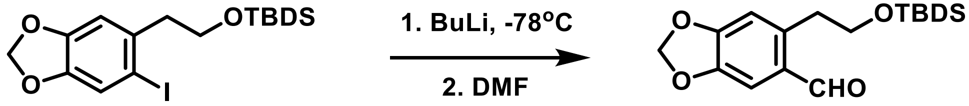
nucleophilic attack of C=O, C=N bonds



competition: deprotonation

formylation (with DMF)

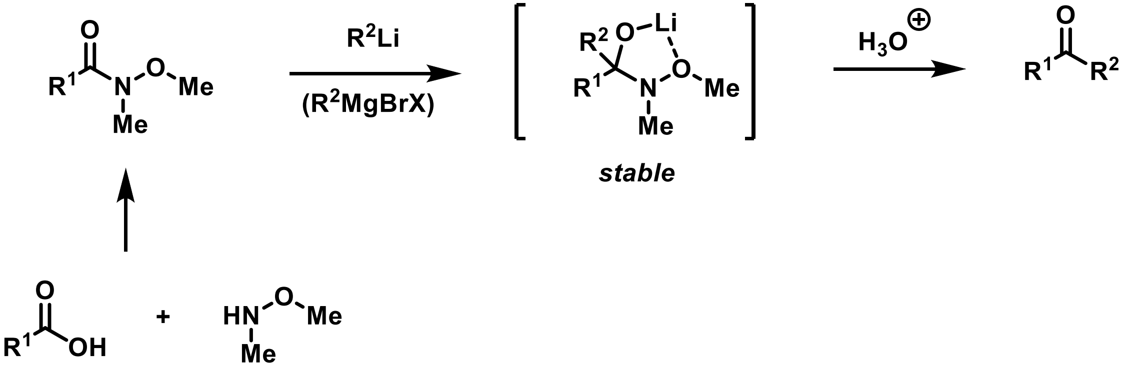


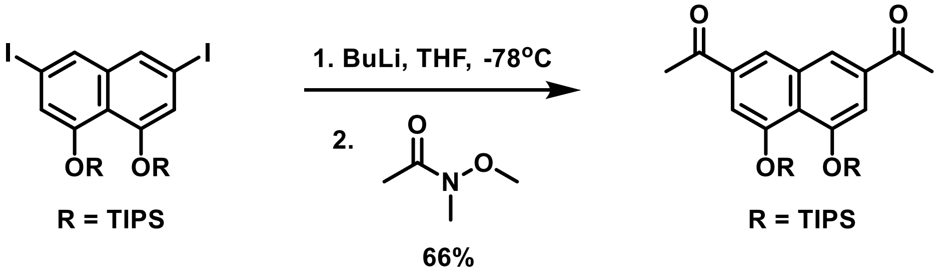


J. Am. Chem. Soc. **1994**, *116*, 9791.

Weinreb amides

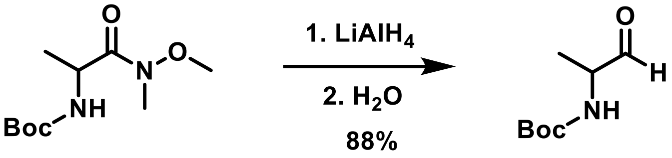
- reliable preparation of ketones





J. Org. Chem. **2000**, *65*, 8774.

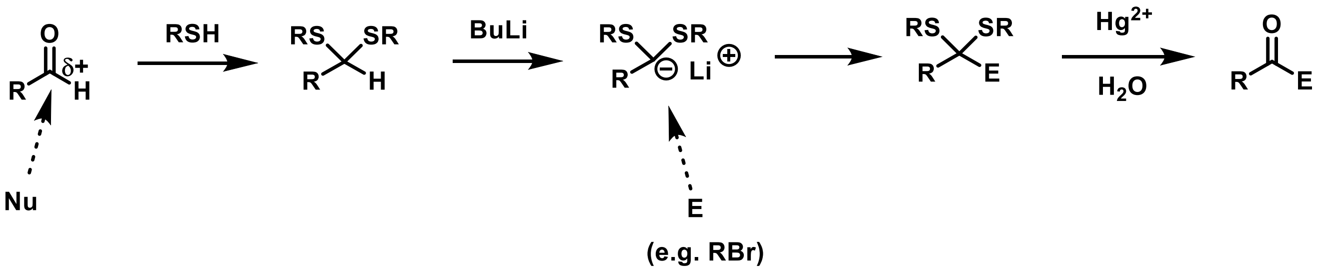
- similarly: reduction to aldehydes

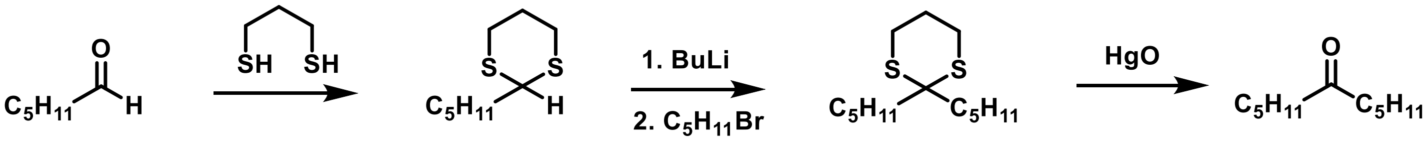


J. Med. Chem. **1985**, *28*, 1874.

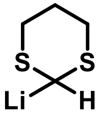
deprotonation of 1,3-dithianes

- generation of *nucleophilic* acyl equivalents

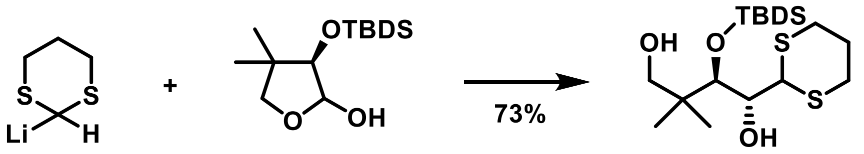


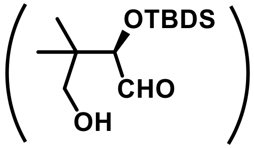


J. Org. Chem. **1975**, *40*, 231.



nucleophilic equivalent of CHO





Can. J. Chem. **1991**, *69*, 62.

RMgX (Grignard reagents)

preparation: **$$$**

$$\mathrm{R{-}X} \xrightarrow[\mathrm{Et_2O}\ \ \mathrm{THF}]{\mathrm{Mg}} \mathrm{R{-}Mg{-}X}$$

X = Br, I

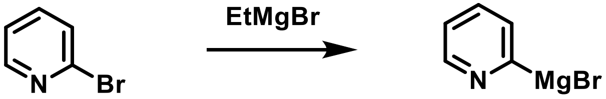
activation of Mg: I_2, $Br(CH_2)_2Br$

Rieke metals:

$$\mathrm{MCl_n} + \mathrm{K} \xrightarrow[\text{refl. THF}]{} \mathrm{M^*}$$

M = Mg, Cu, Zn

from more basic RMgX:



transmetalation:

$$\mathrm{R{-}Li} \xrightarrow{\mathrm{MgBr_2}} \mathrm{R{-}Mg{-}Br}$$

+ LiBr

formation of C-C bonds

reactions with s alkyl halides typically do not give good yields

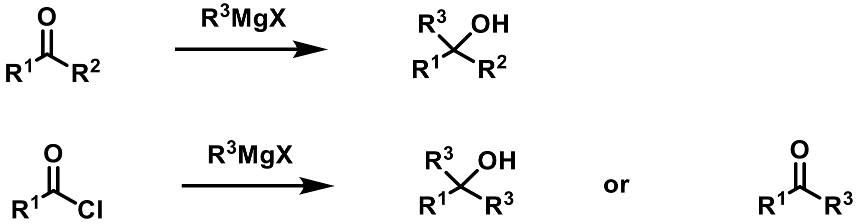
exception:

reactive RMgX (e.g. $CH_2=CH-CH_2MgX$) + reactive RX (e.g. MeI, BnBr, allylBr)

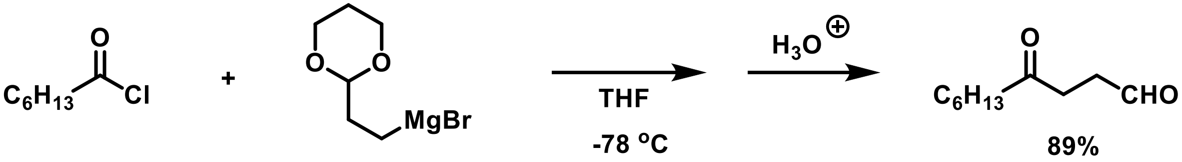
or:

J. Am. Chem. Soc. **1971**, *93*, 1483.

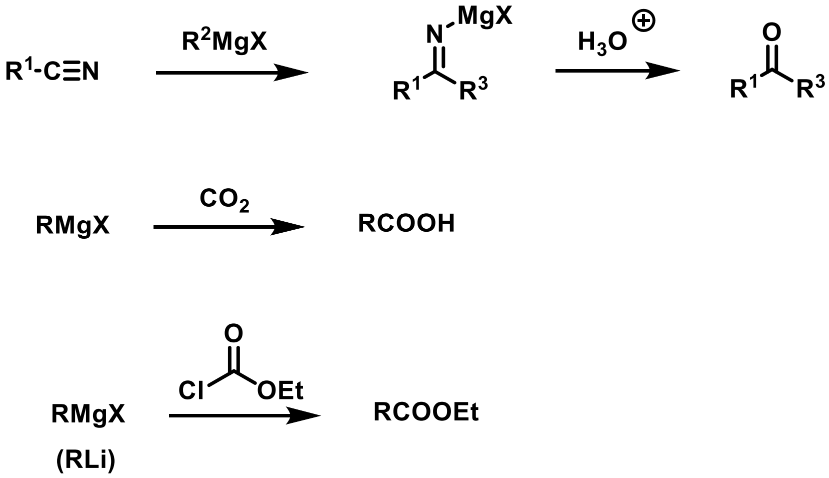
nucleophilic attack on C=O bond

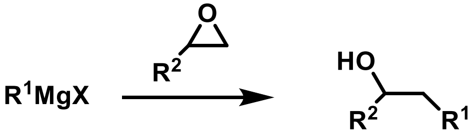


(low temp. and or cat. $FeCl_3$)

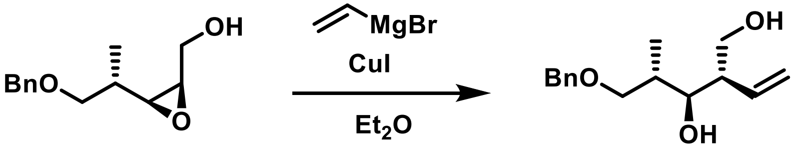


J. Org. Chem. **1976**, *41*, 560.



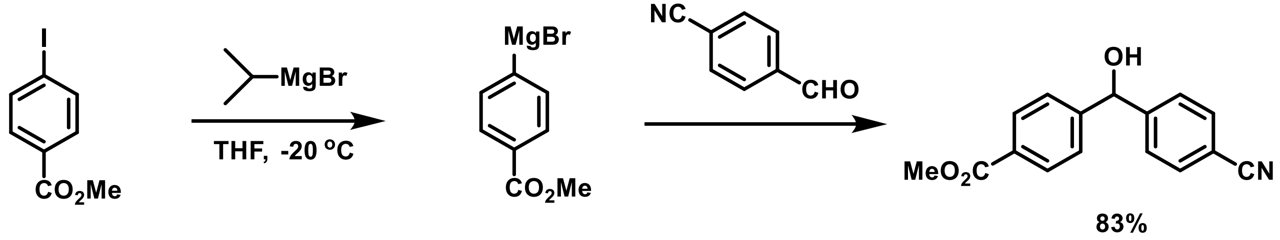


directed attack on epoxide



Tetrahedron Lett. **1979**, 4343.

under proper conditions, in situ prepared RMgX reagents can be compatible with reactive functional groups



Angew. Chem. Int. Ed. **2003**, *42*, 4302.

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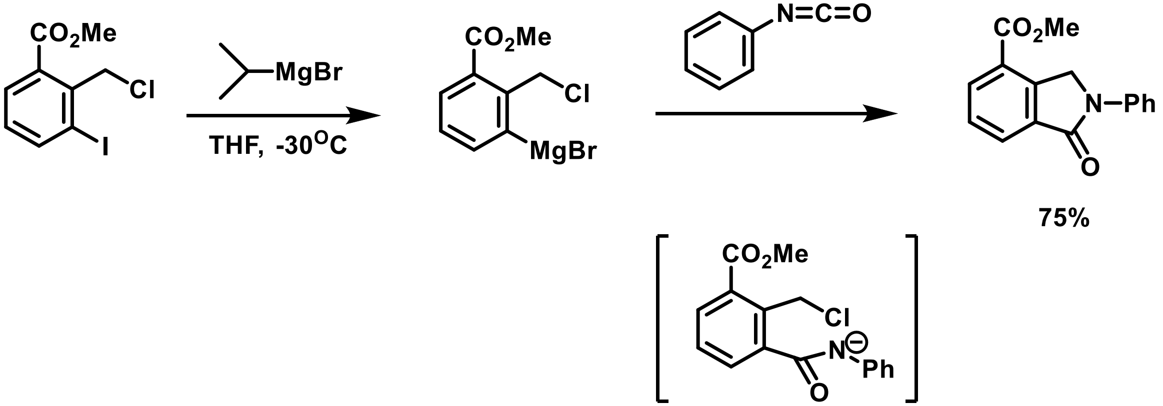


Organocuprates: RCu; R_2CuLi; R_3CuLi_2; RCuCNLi

nucleophilic R (& much less basic than Li and Mg analogs)

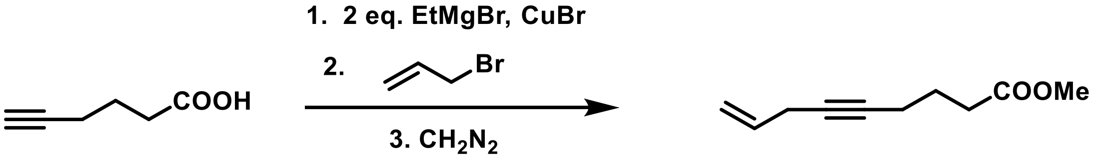
$$2\ RLi + CuI \longrightarrow R_2CuLi + LiI$$

$$RLi + CuCN \longrightarrow RCuCNLi$$

nucleophilic attack on RX

$$R_2CuLi + R'X \longrightarrow R\text{-}R'$$

R' : alkyl, alkenyl, alkynyl, aryl



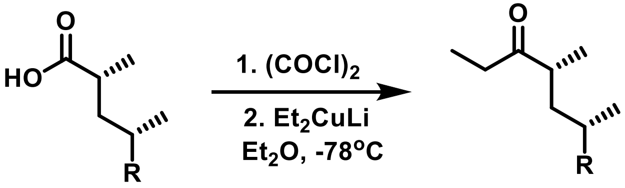
Tetrahedron Lett. **1984**, *25*, 5119.

regioselective nucleophilic opening of epoxides

- Nu attack at less substituted C

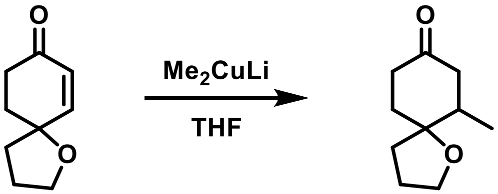
Tetrahedron Lett. **1977**, 3407.

preparation of ketones from acid chlorides



J. Am. Chem. Soc. **1981**, *103*, 1568.

1,4-addition to α,β-unsaturated carbonyl compounds



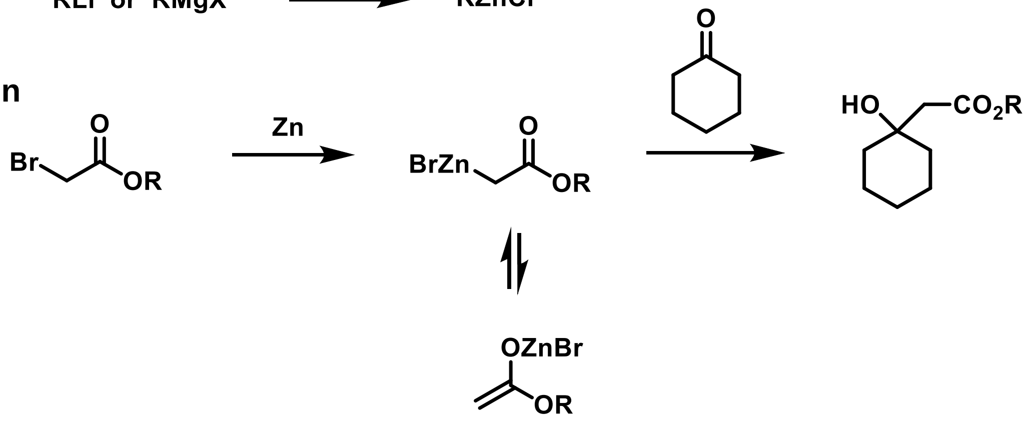
Tetrahedron Lett. **1985**, *26*, 6015.

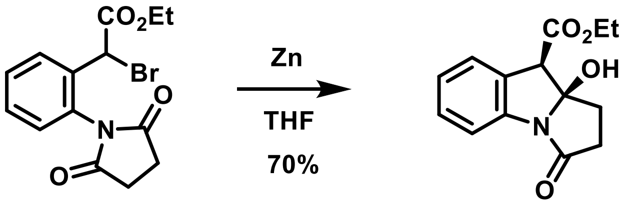
Organozinc reagents: RZnX; R_2Zn

- also much less basic than Li and Mg analogs

$$\mathrm{RLi\ or\ RMgX} \xrightarrow{\mathrm{ZnCl_2}} \mathrm{RZnCl}$$

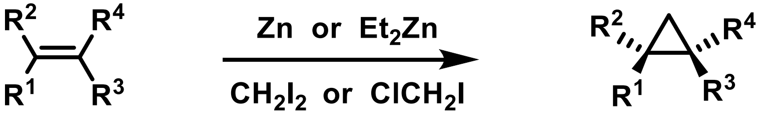
Reformatsky reaction

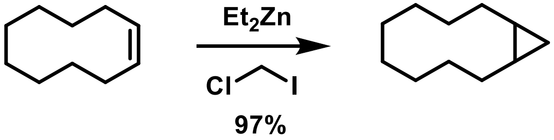




Cyclopropanation (Simmons-Smith rxn)

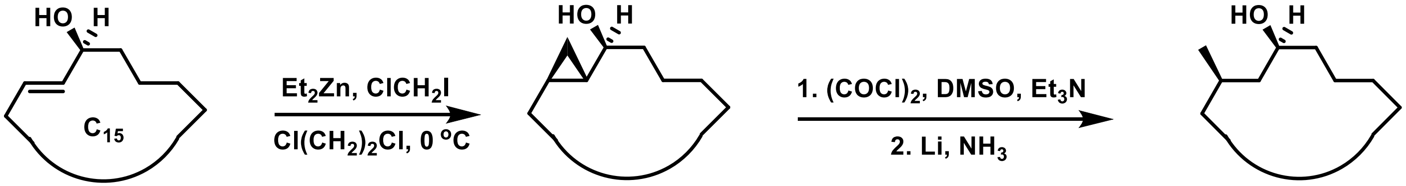
stereoselective: syn-addition (cyclic transition state)





J. Org. Chem. **1988**, *53*, 1331.

- **cyclopropanation can be stereoselectively directed using neighboring OH group**
- **cyclopropane ring is reactive and can udergo subsequent transformations**



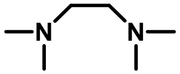
J. Am. Chem. Soc. **1993**, *115*, 1593.

Generation and use of organozinc reagents in water

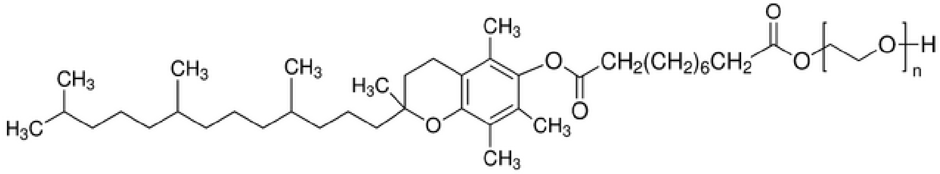
$$\mathrm{R{-}I} + \mathrm{Zn} \xrightarrow[\text{2\% PTS, } H_2O]{\text{TMEDA}} [\mathrm{RZnI}] \xrightarrow[\text{ArBr}]{\text{Pd cat.}} \mathrm{Ar{-}R}$$

J. Am. Chem. Soc. **2009**, *131*, 15592.

TMEDA:



PTS: polyoxyethanyl-α-tocopheryl sebacate



- micelar catalysis
- „nanoreactors“ from PTS in water