

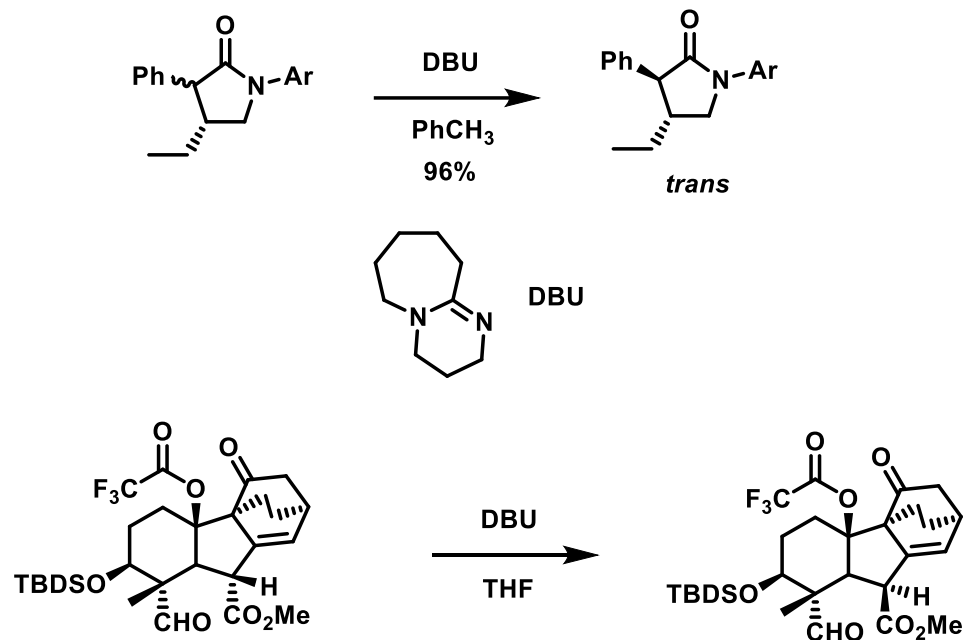
Organic synthesis

Kamil Paruch

Masaryk University, Brno

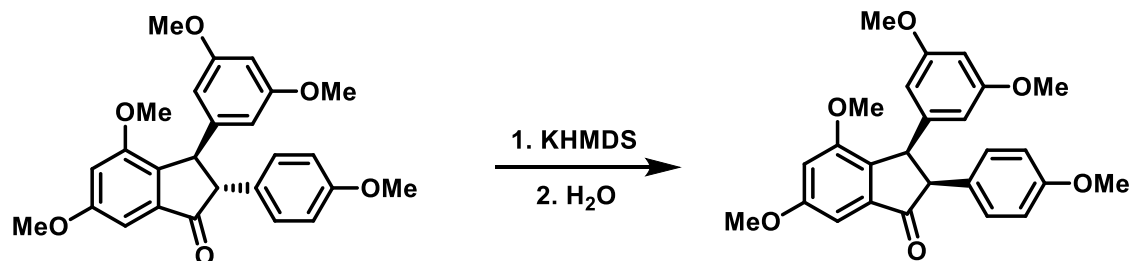
epimerization of carbonyl compounds

- thermodynamic equilibration (deprotonation-protonation)



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

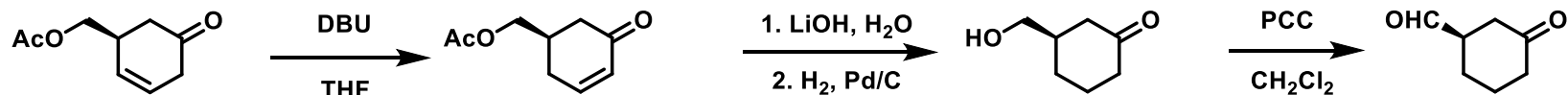
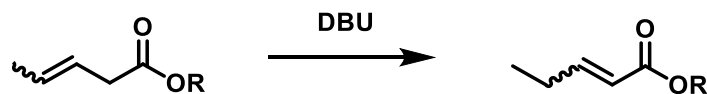
- kinetic* epimerization is also possible



• C-protonation of enolate from less hindered site *J. Am. Chem. Soc.* **2009**, 131, 1753.

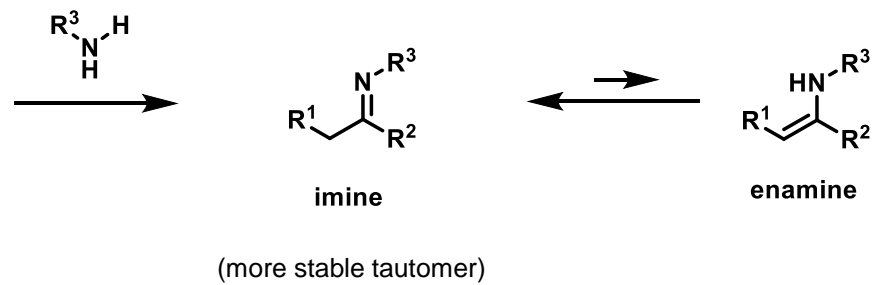
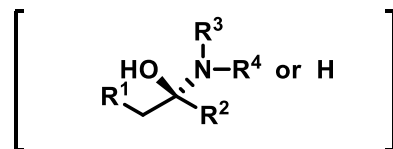
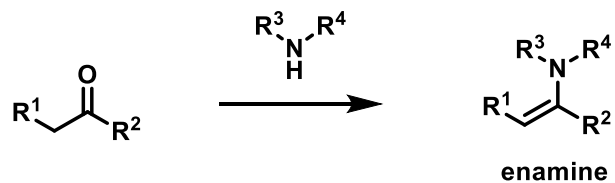
migration of double bond in carbonyl compounds

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

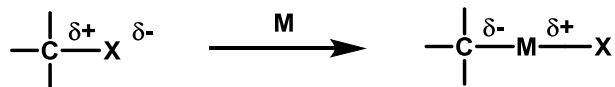


Tetrahedron Lett. **1983**, 24, 4883.

tautomerism imine-enamine

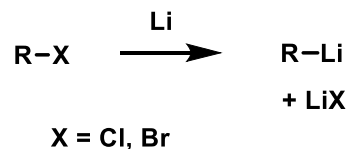


Organometallic reagents (Li, Mg, Cu, Zn)



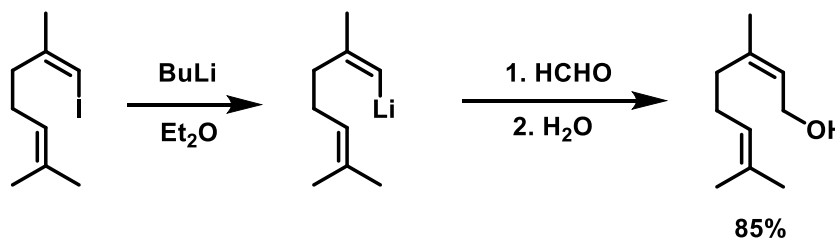
RLi (organolithium reagents)

preparation: \$\$\$



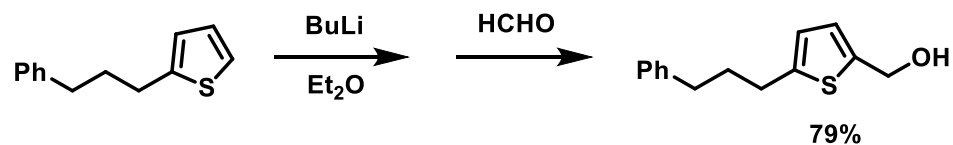
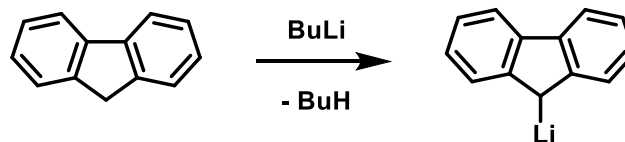
BuLi as a source of Li

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

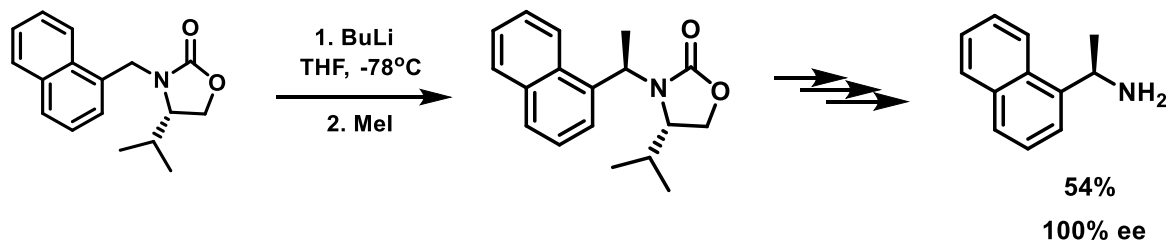
basicity: $sp^3 > sp^2 > sp$ 

BuLi as a source of Li

- deprotonation of compounds that are more acidic than BuH



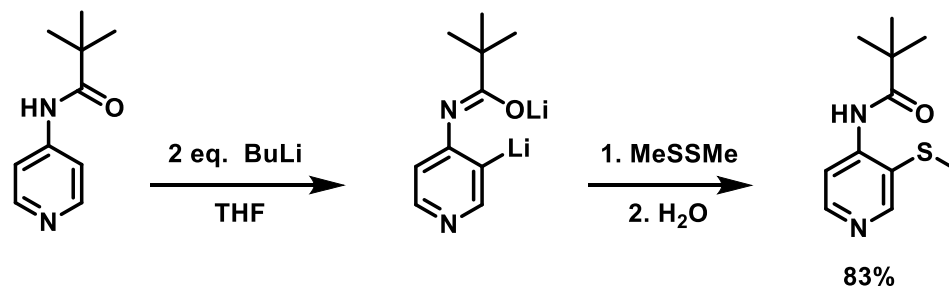
J. Med. Chem. **1992**, 35, 3156.



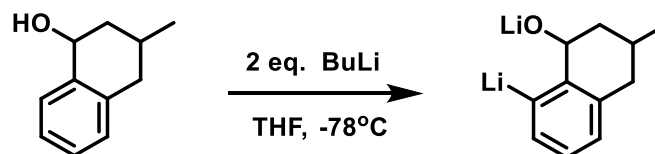
J. Org. Chem. **1989**, *54*, 3002.

ortho-lithiation

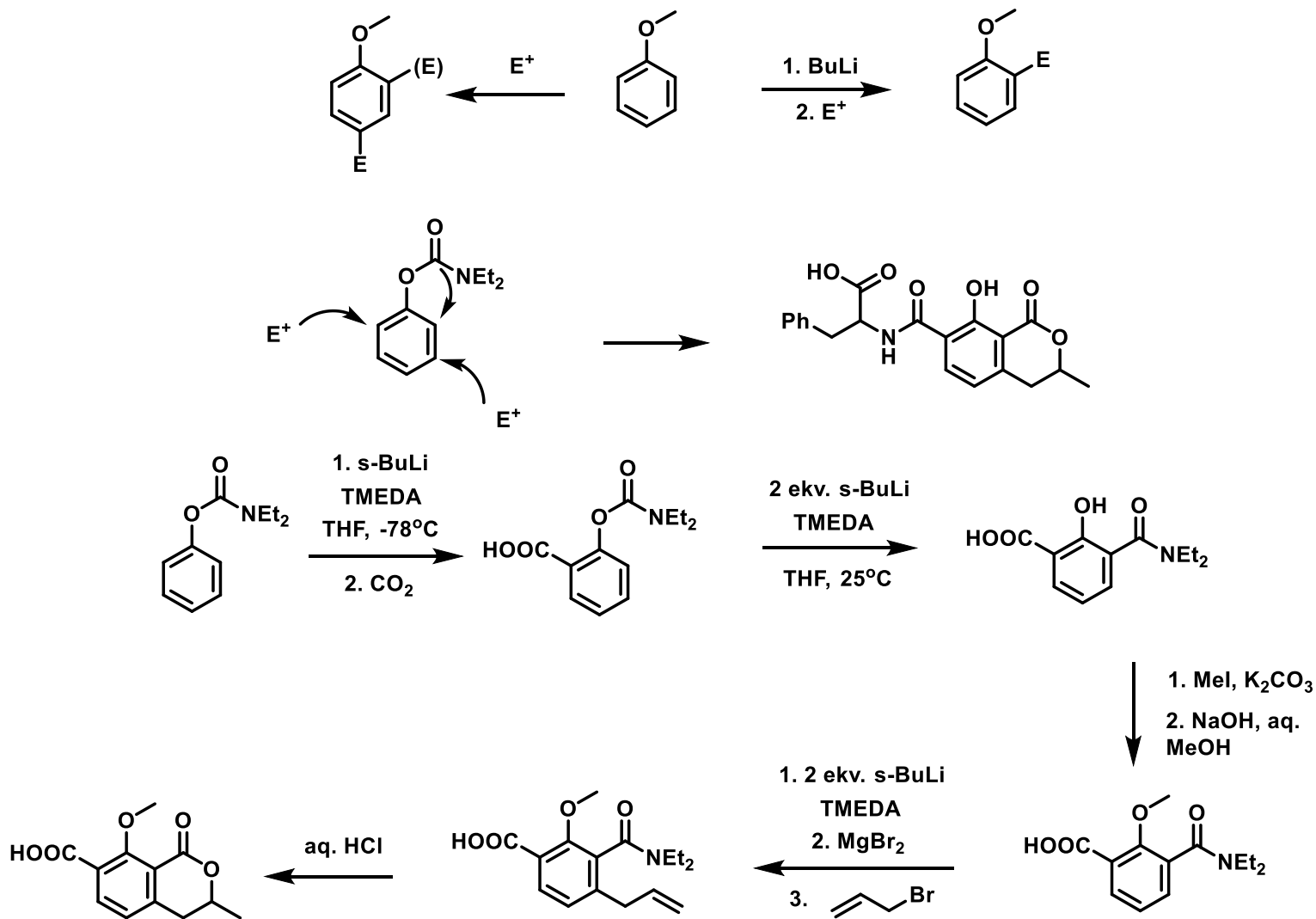
- regioselectivity of lithiation is directed by coordination of Li to the directing group (CONHR, CH₂OH, NHCOtBu, SO₂NHR, OMOM)



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

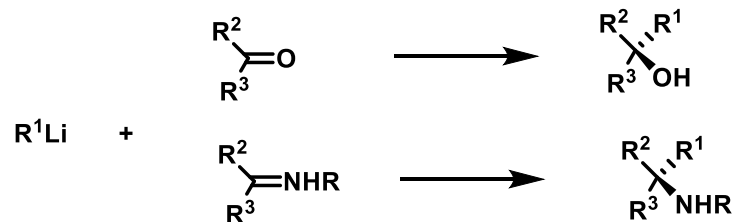


Can. J. Chem. **1987**, *65*, 3165.



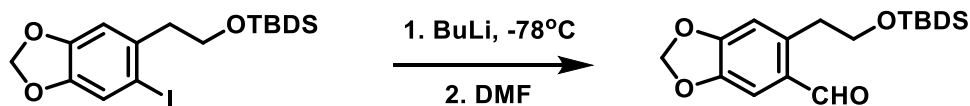
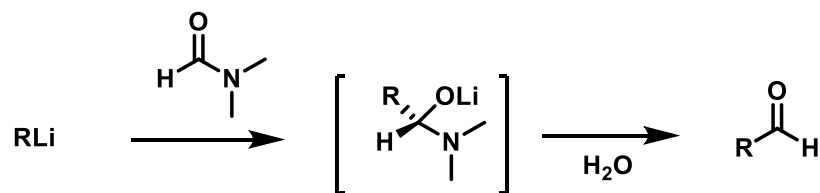
J. Am. Chem. Soc. **1985**, *107*, 6312.

nucleophilic attack of C=O, C=N bonds



competition: deprotonation

formylation (with DMF)

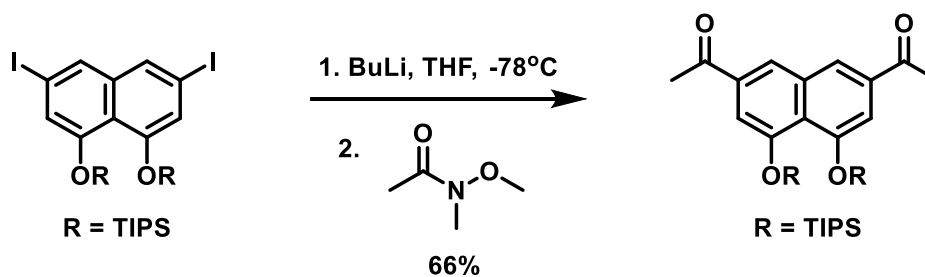
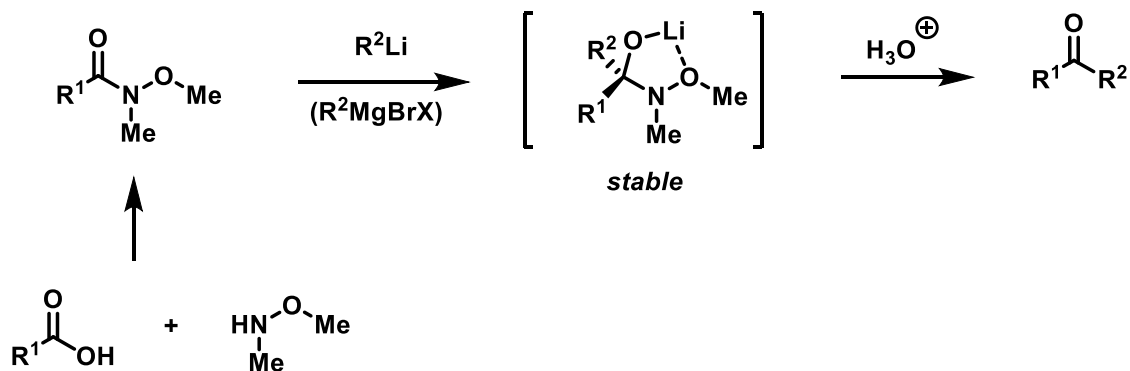


J. Am. Chem. Soc. **1994**, *116*, 9791.

Weinreb amides

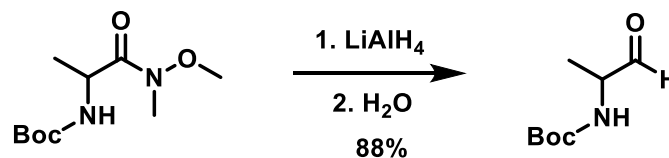
- reliable preparation of ketones

R¹ can be also H (formylation): *Tetrahedron Lett.* **1999**, 40, 7889.



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

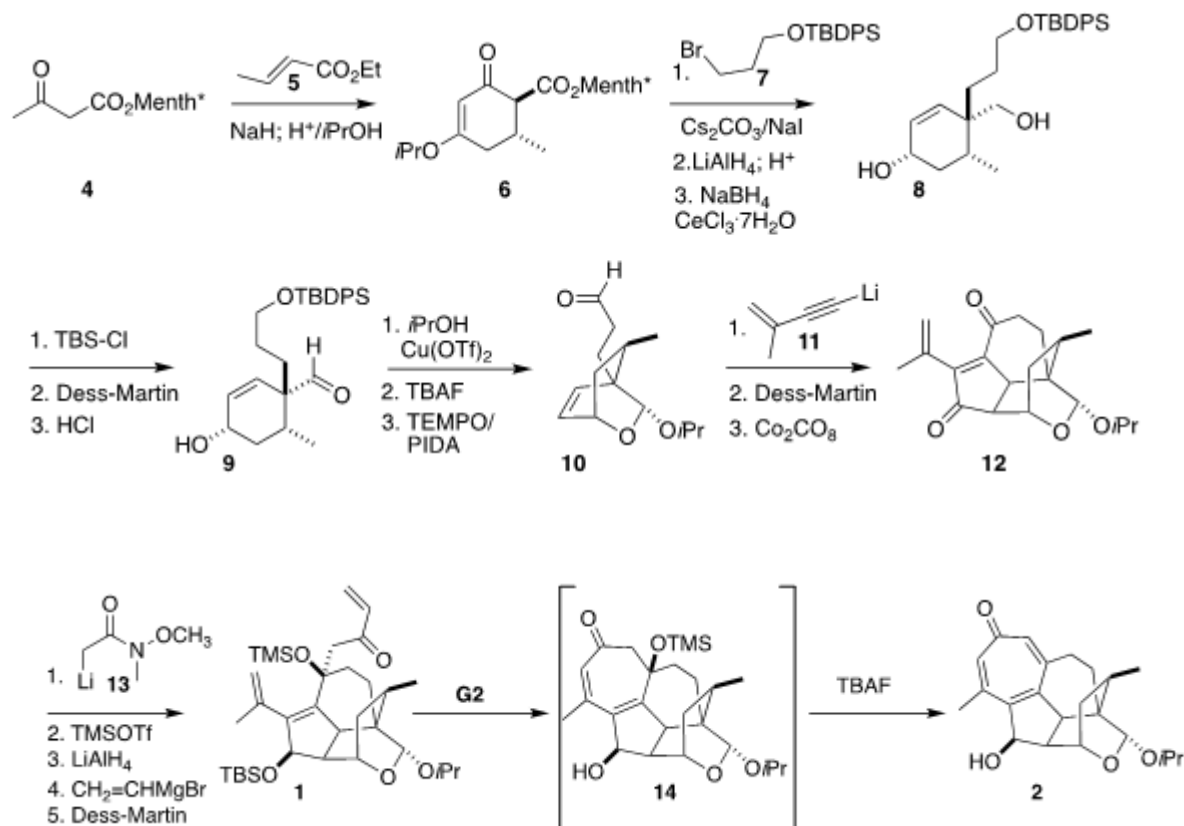
- similarly: reduction to aldehydes



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

Weinreb amides

- can be part of organometallic reagent (e.g. reagent **13**)

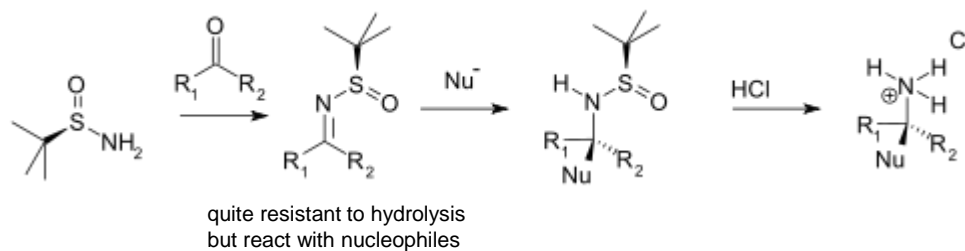


Angew. Chem. Int. Ed. **2021**, *60*, 18572.
Eur. J. Org. Chem. **2022**, e202101430.

Ellman's reagent (sulfinamide)

- both enantiomeric forms are commercially available
- used in asymmetric synthesis as chiral auxiliaries, often as chiral ammonia equivalents for the synthesis of amines

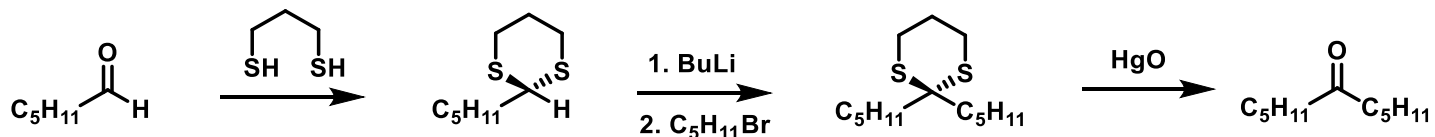
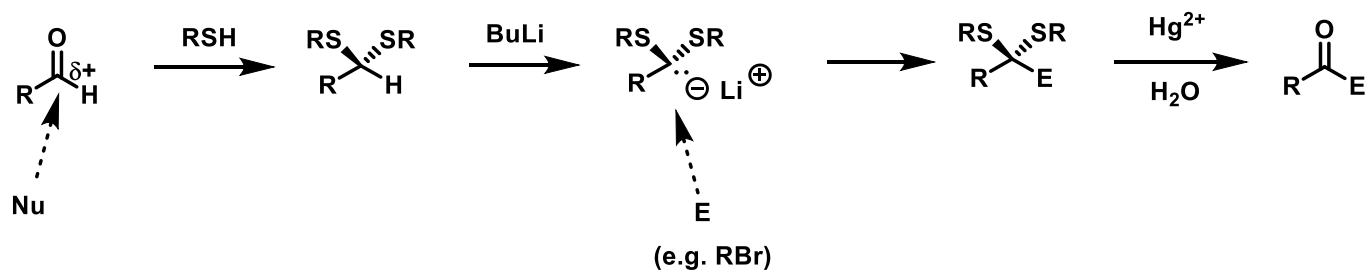
Chem. Rev. **2010**, *110*, 3600.



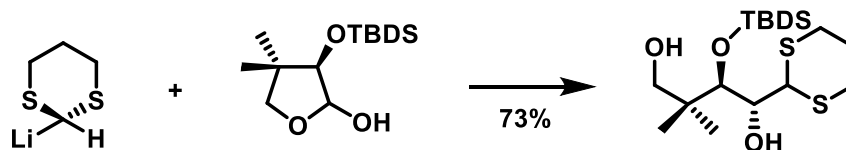
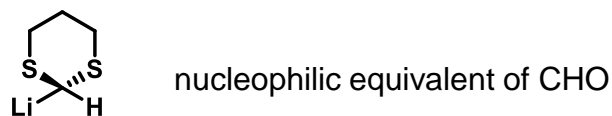
- typical nucleophiles: RMgX, RZnX, RLi, enolates

deprotonation of 1,3-dithianes

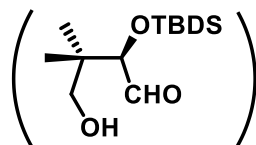
- generation of *nucleophilic acyl* equivalents



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

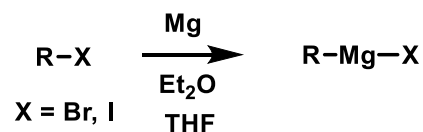


Can. J. Chem. **1991**, *69*, 62.

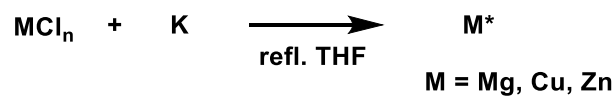


RMgX (Grignard reagents)

preparation: \$\$\$

activation of Mg: I₂, Br(CH₂)₂Br

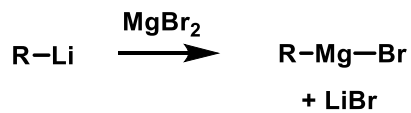
Rieke metals:

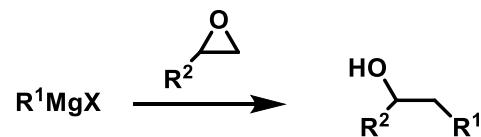
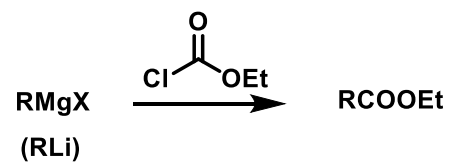
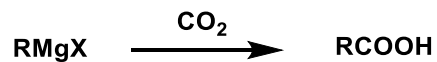
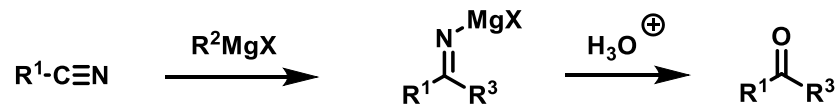


from more basic RMgX:

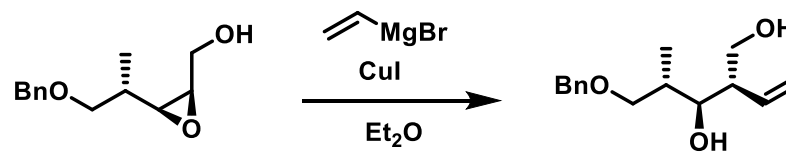


transmetalation:



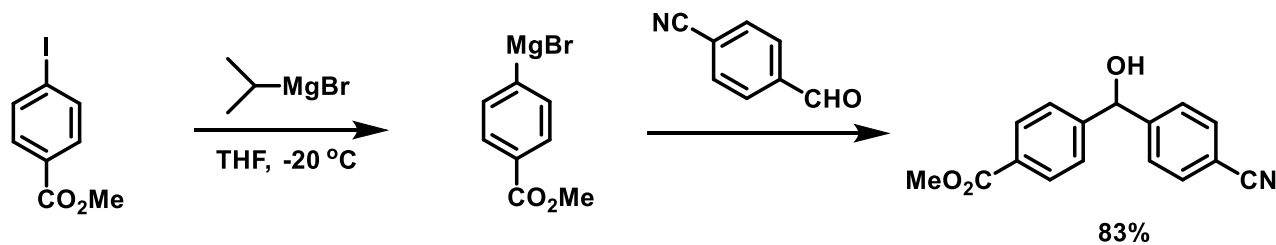


directed attack on epoxide



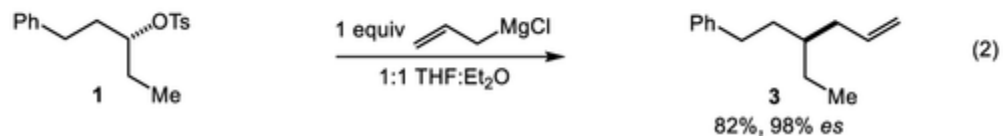
Tetrahedron Lett. **1979**, 4343.

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

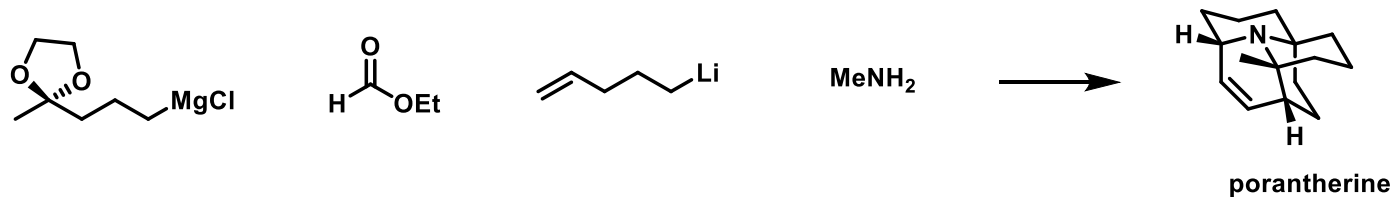


Angew. Chem. Int. Ed. **2003**, 42, 4302.

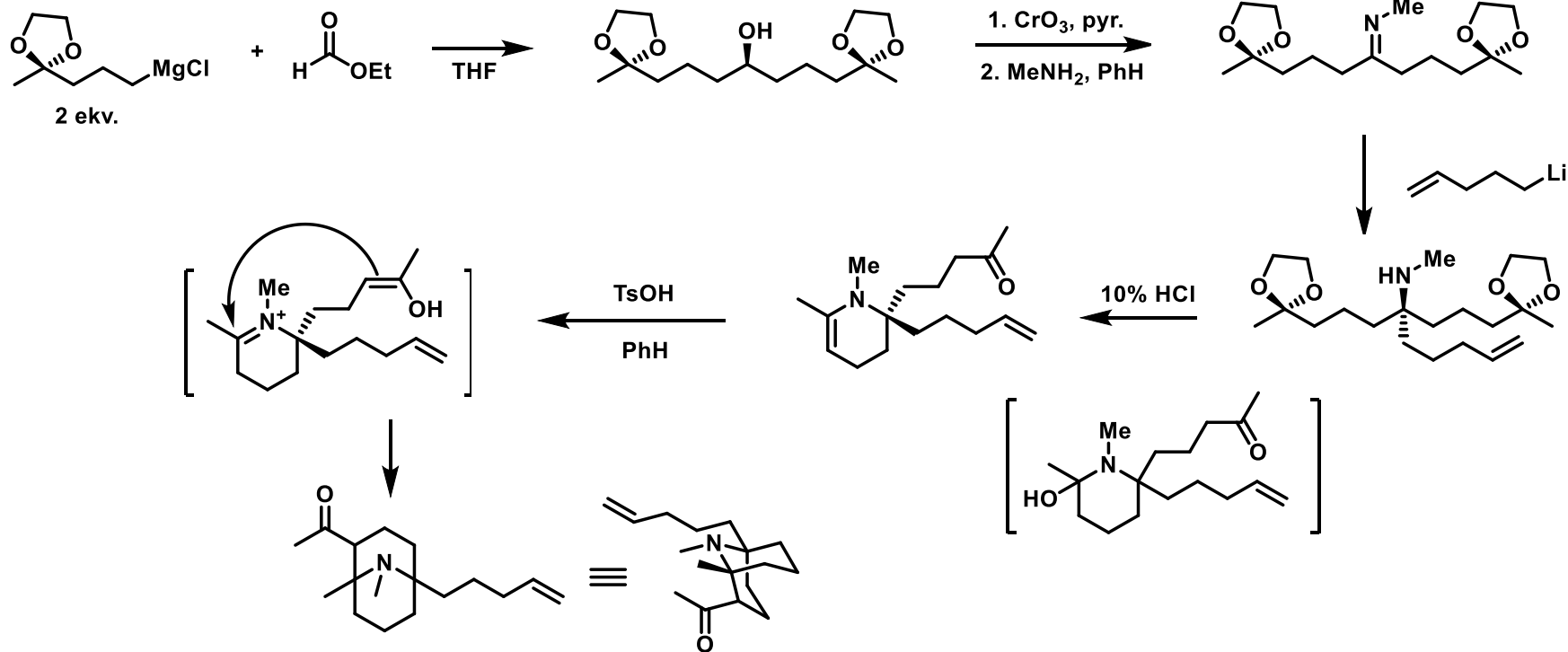
- allyl magnesium chloride can undergo nucleophilic substitution with tosylates:



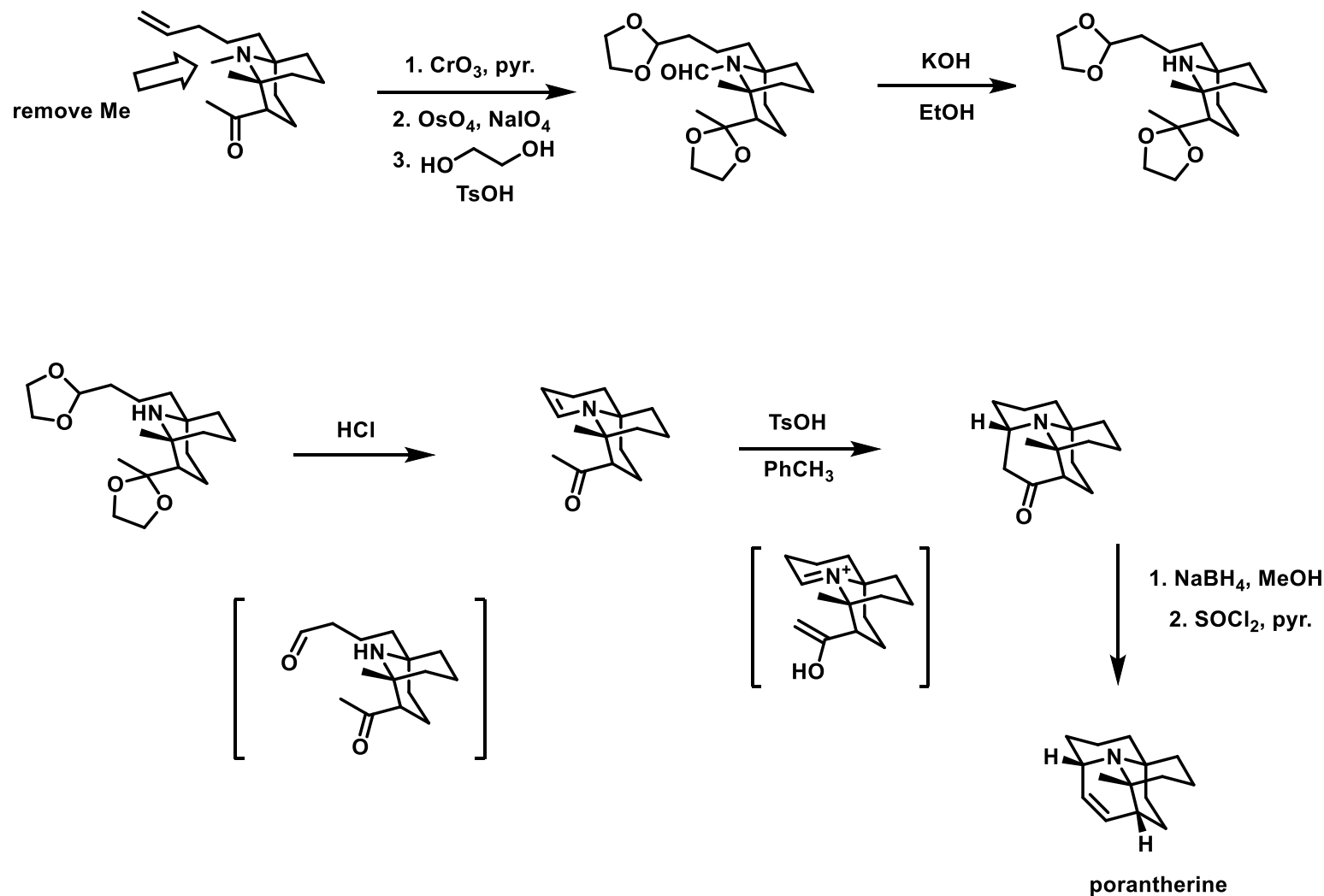
Org. Lett. **2021**, *23*, 7215.



J. Am. Chem. Soc. **1974**, *96*, 6516.



1st step: oxidation of N-Me to N-CHO



Organocuprates: RCu ; R_2CuLi ; R_3CuLi_2 ; RCuCNLi

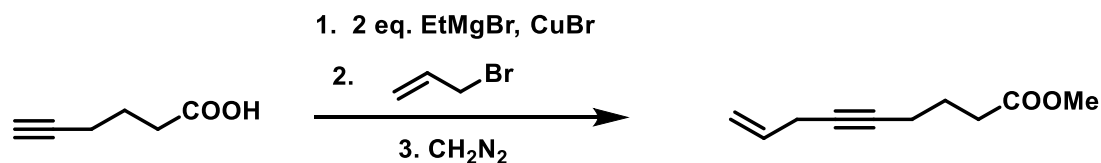
nucleophilic R (& much less basic than Li and Mg analogs)



nucleophilic attack on RX



R' : alkyl, alkenyl, alkynyl, aryl



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

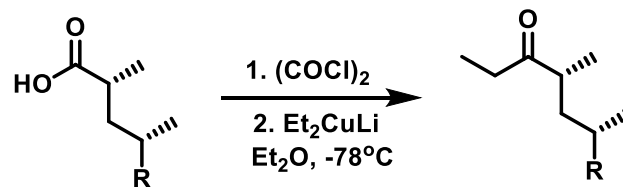
regioselective nucleophilic opening of epoxides

- Nu attack at less substituted C

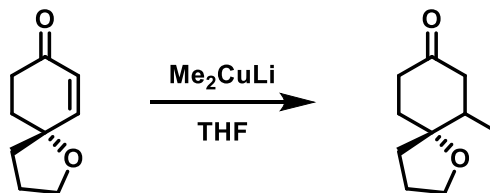


Tetrahedron Lett. **1977**, 3407.

preparation of ketones from acid chlorides



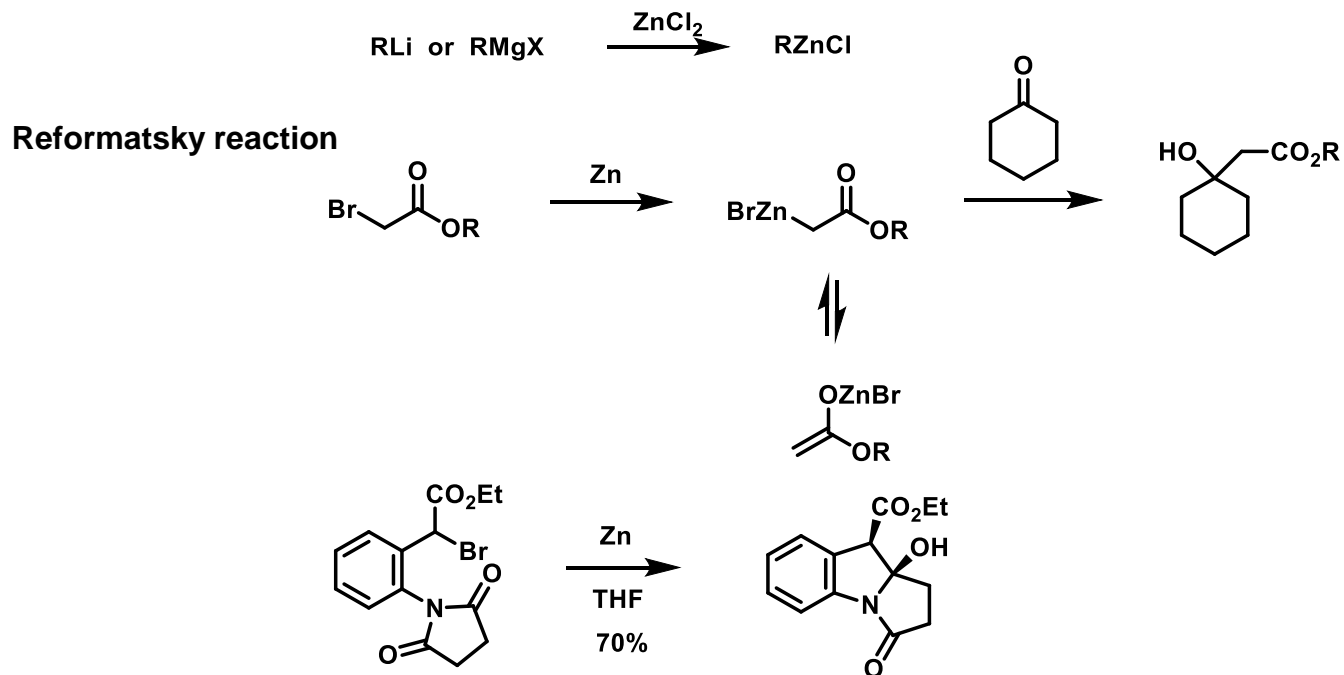
J. Am. Chem. Soc. **1981**, 103, 1568.

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

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

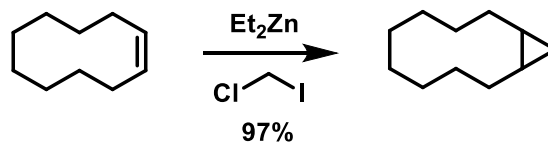
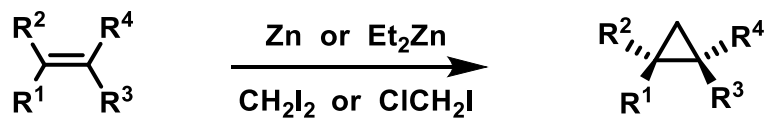
Organozinc reagents: $RZnX$; R_2Zn

- also much less basic than Li and Mg analogs



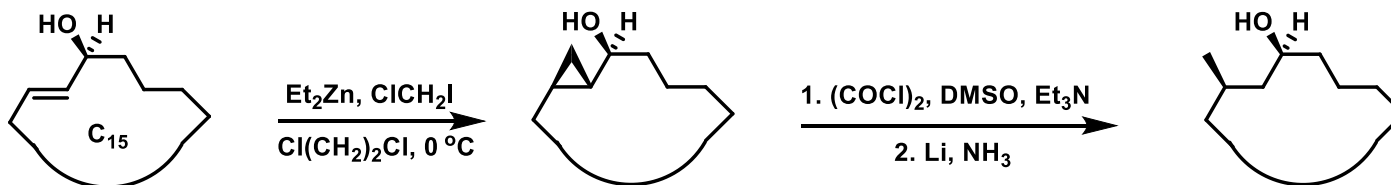
Cyclopropanation (Simmons-Smith rxn)

stereoselective: syn-addition (cyclic transition state)



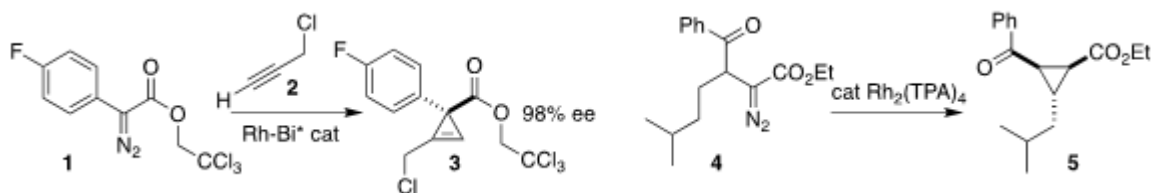
J. Org. Chem. **1988**, *53*, 1331.

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



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

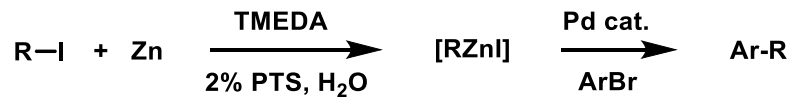
alternative cyclopropanation: generation of carbene from diazo compounds



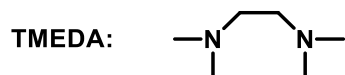
J. Am. Chem. Soc. **2021**, *143*, 5666.

Angew. Chem. Int. Ed. **2021**, *60*, 6177.

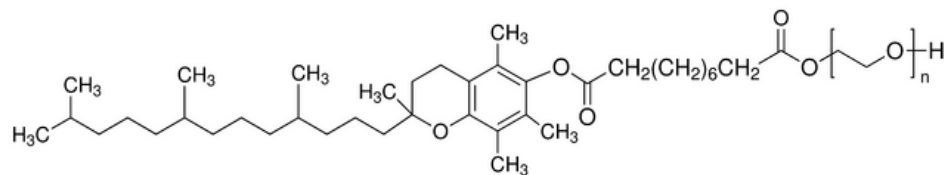
Generation and use of organozinc reagents in water



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



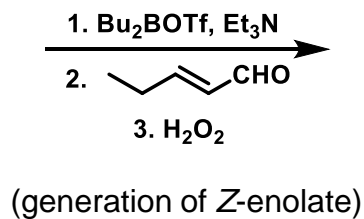
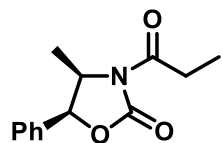
PTS: polyoxyethanyl- α -tocopheryl sebacate



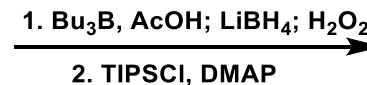
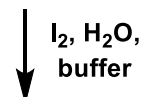
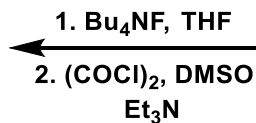
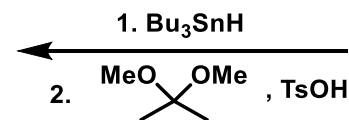
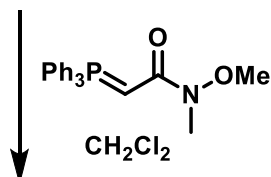
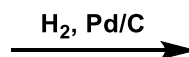
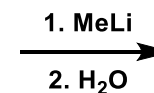
- micellar catalysis
- „nanoreactors“ from PTS in water



(cleavage of oxazolidinone + reduction of COOH)



A
syn-aldol

**B****E****D****C****F****G****H**