

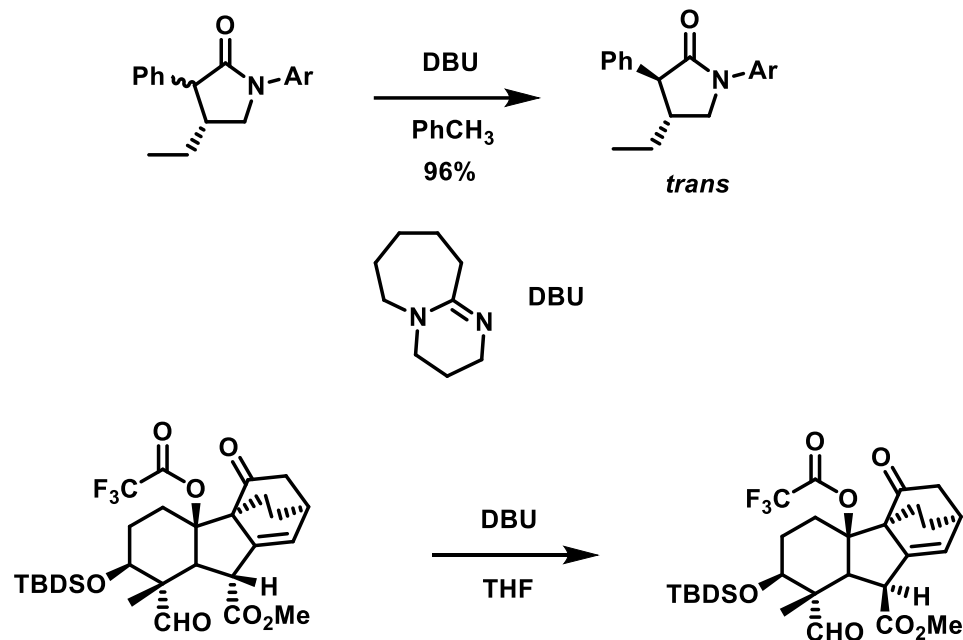
# **Organic synthesis**

**Kamil Paruch**

***Masaryk University, Brno***

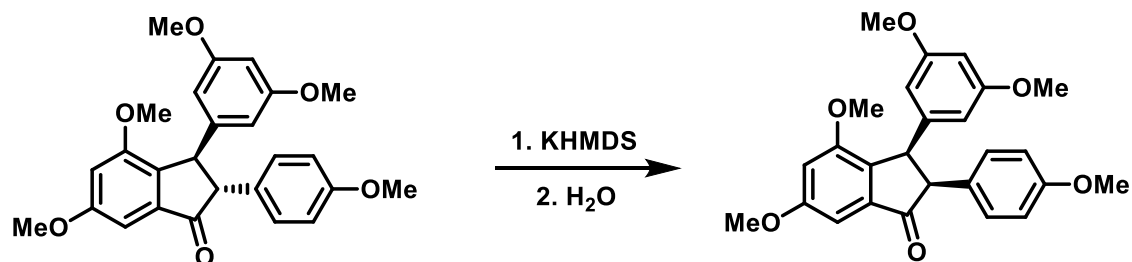
## epimerization of carbonyl compounds

- thermodynamic equilibration (deprotonation-protonation)



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

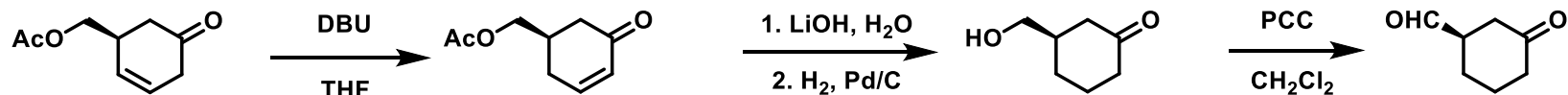
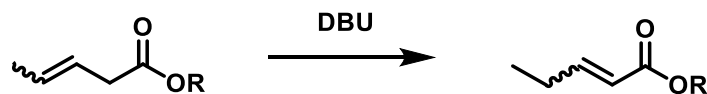
- kinetic* epimerization is also possible



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

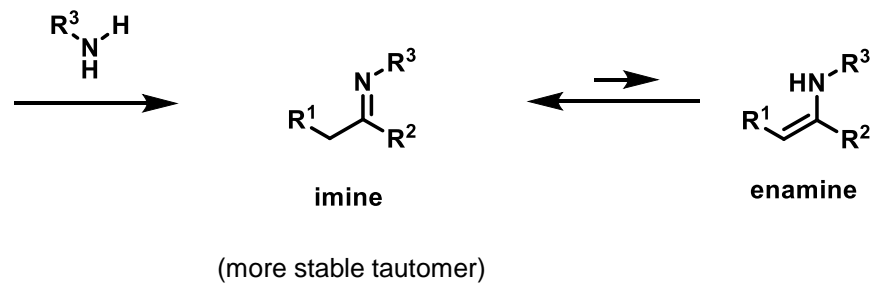
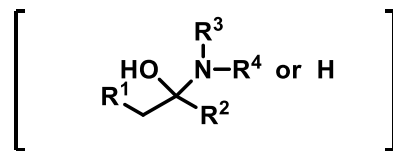
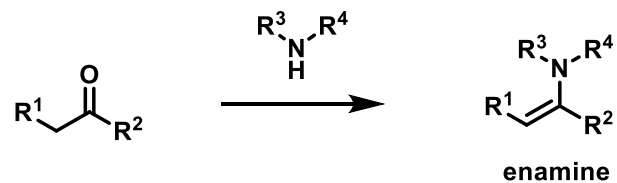
## migration of double bond in carbonyl compounds

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

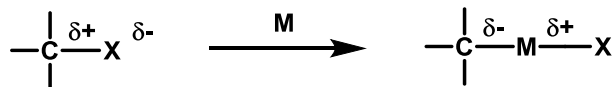


*Tetrahedron Lett.* **1983**, 24, 4883.

## tautomerism imine-enamine

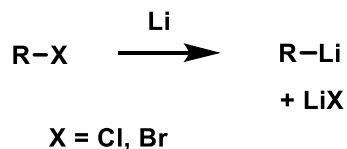


## Organometallic reagents (Li, Mg, Cu, Zn)



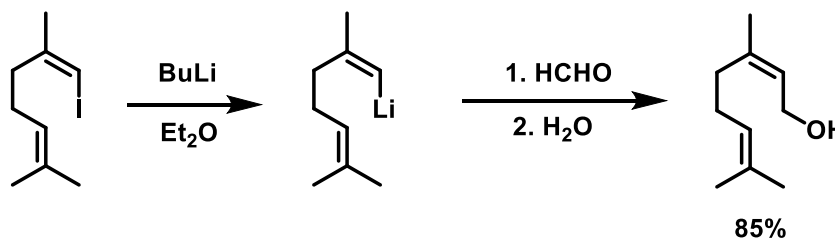
## RLi (organolithium reagents)

preparation: \$\$\$



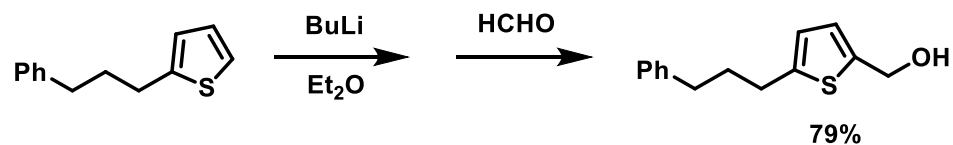
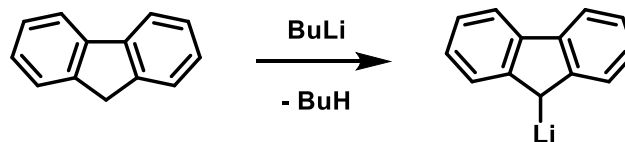
## BuLi as a source of Li

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

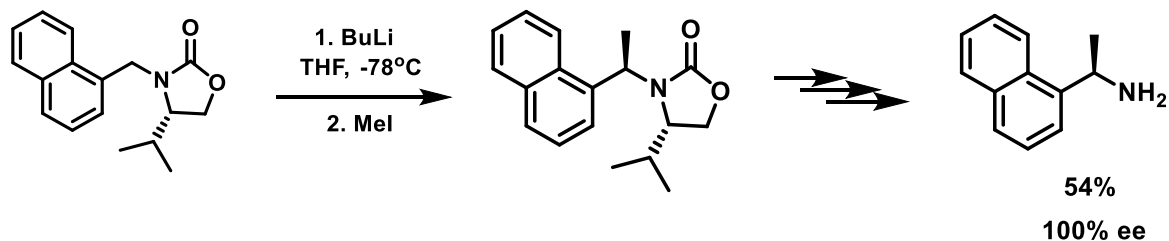
basicity:  $sp^3 > sp^2 > sp$ 

**BuLi as a source of Li**

- deprotonation of compounds that are more acidic than BuH



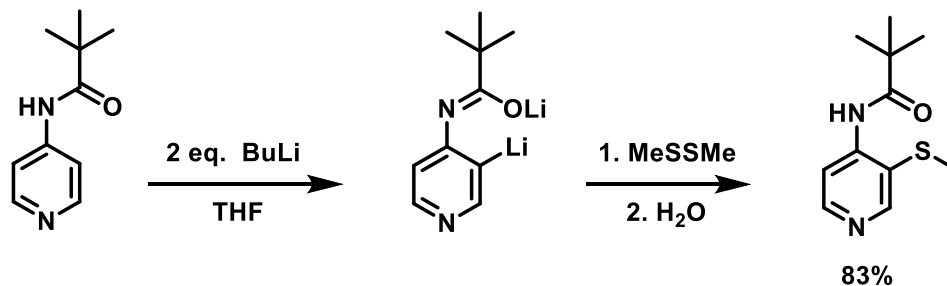
*J. Med. Chem.* **1992**, 35, 3156.



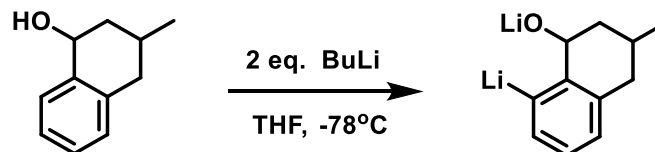
*J. Org. Chem.* **1989**, 54, 3002.

### ortho-lithiation

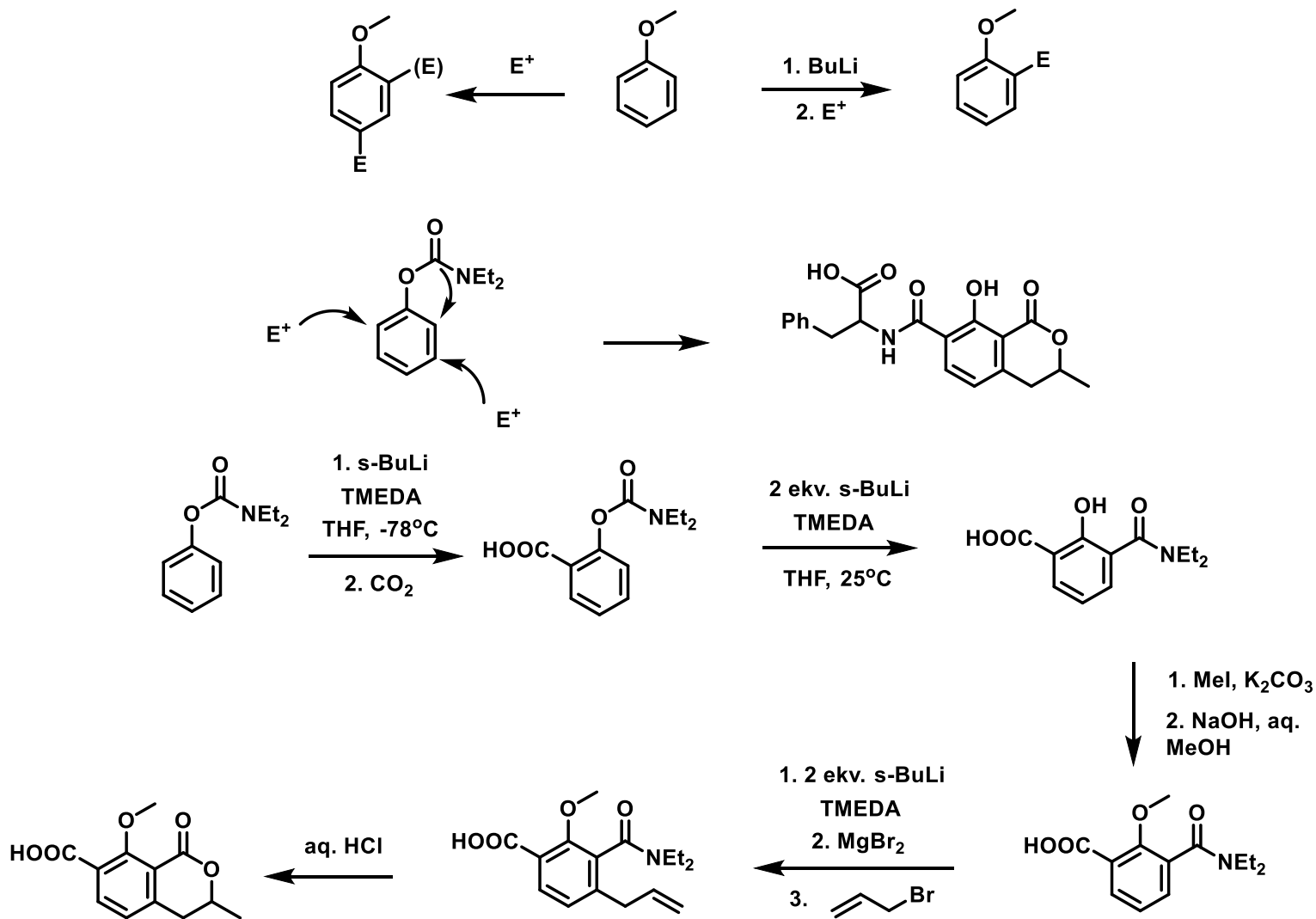
- regioselectivity of lithiation is directed by coordination of Li to the directing group (CONHR, CH<sub>2</sub>OH, NHCOtBu, SO<sub>2</sub>NHR, OMOM)



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



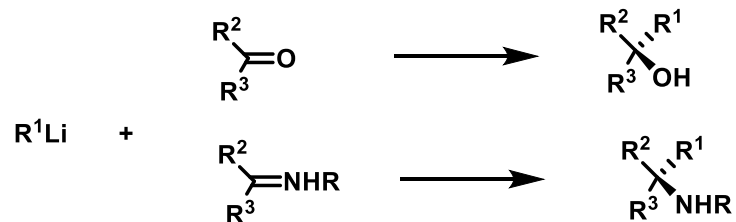
*Can. J. Chem.* **1987**, 65, 3165.



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

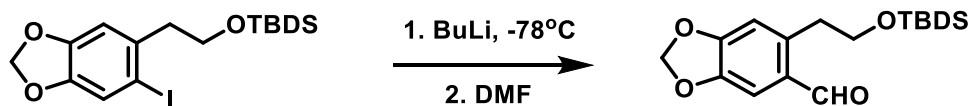
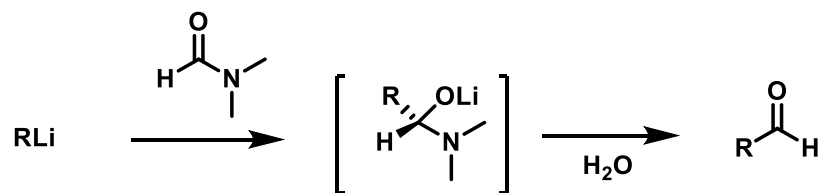


nucleophilic attack of C=O, C=N bonds



competition: deprotonation

formylation (with DMF)

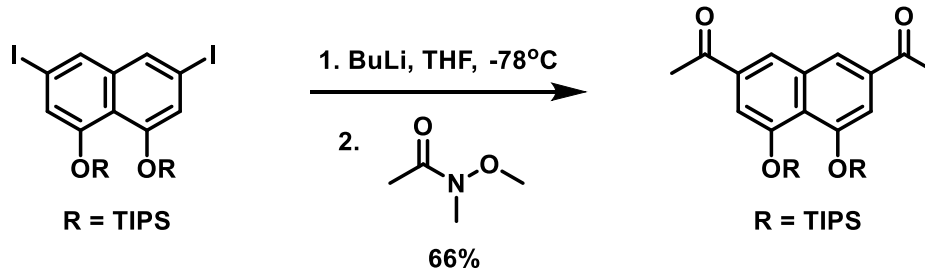
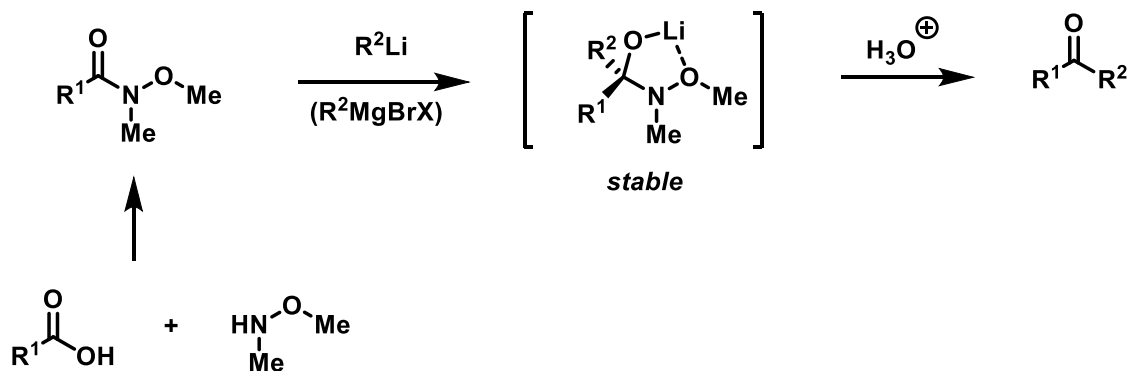


*J. Am. Chem. Soc.* **1994**, *116*, 9791.

## Weinreb amides

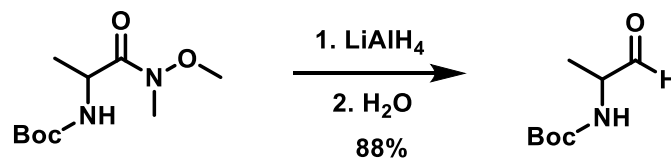
- reliable preparation of ketones

R<sup>1</sup> can be also H (formylation): *Tetrahedron Lett.* **1999**, 40, 7889.



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

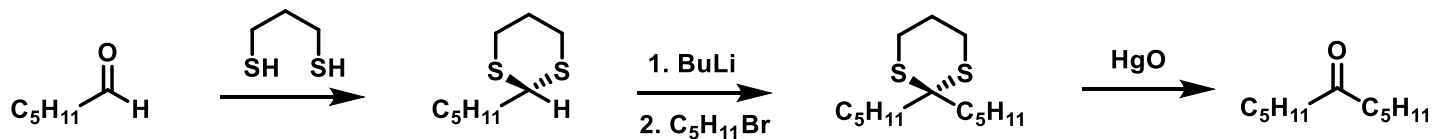
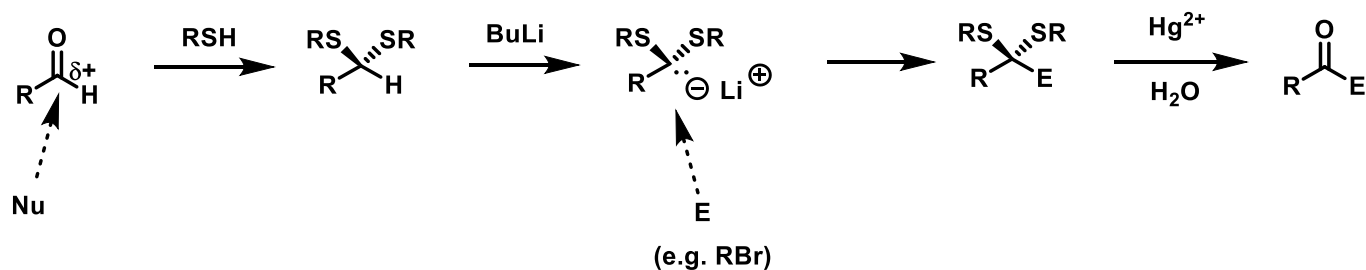
- similarly: reduction to aldehydes



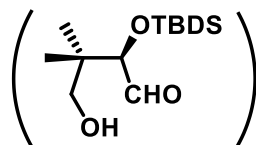
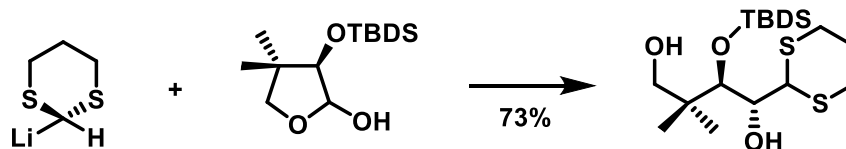
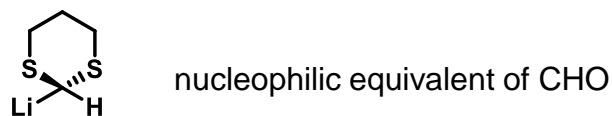
*J. Med. Chem.* **1985**, 28, 1874.

## deprotonation of 1,3-dithianes

- generation of *nucleophilic acyl* equivalents



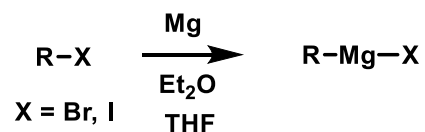
*J. Org. Chem.* **1975**, *40*, 231.



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

## RMgX (Grignard reagents)

preparation: \$\$\$

activation of Mg: I<sub>2</sub>, Br(CH<sub>2</sub>)<sub>2</sub>Br

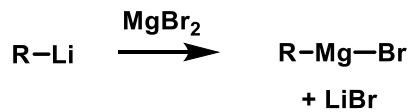
Rieke metals:



from more basic RMgX:



transmetalation:

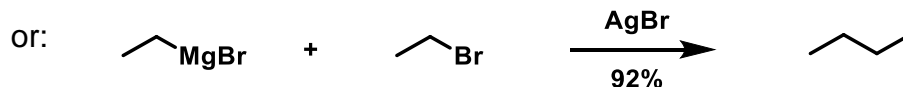


## formation of C-C bonds

reactions with s alkyl halides typically do not give good yields

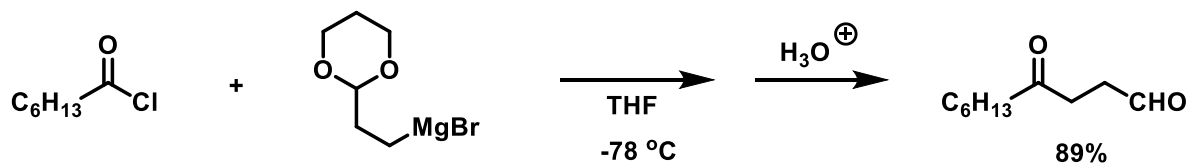
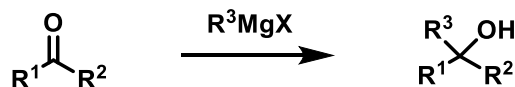
*exception:*

reactive RMgX (e.g.  $\text{CH}_2=\text{CH}-\text{CH}_2\text{MgX}$ ) + reactive RX (e.g. MeI, BnBr, allylBr)

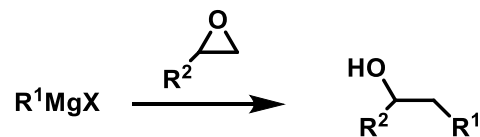
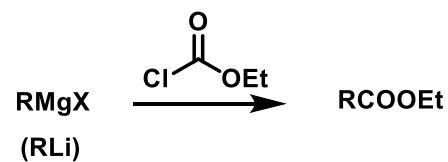
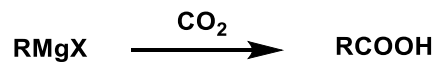
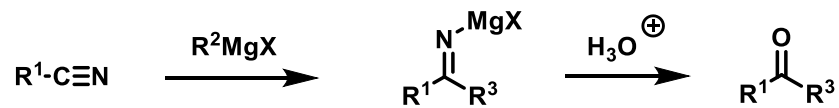


*J. Am. Chem. Soc.* **1971**, 93, 1483.

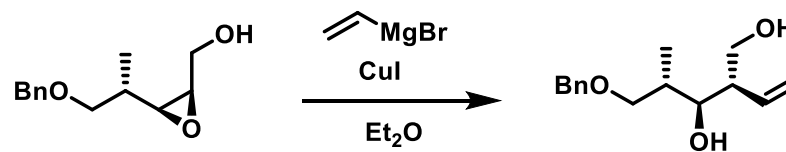
## nucleophilic attack on C=O bond



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

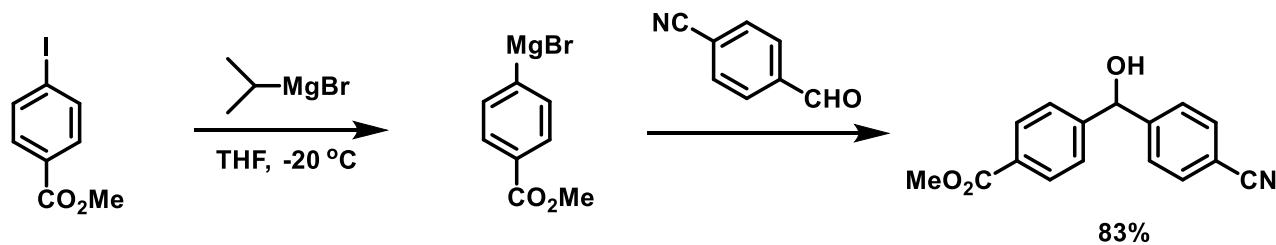


directed attack on epoxide



*Tetrahedron Lett.* **1979**, 4343.

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



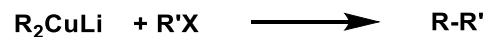
*Angew. Chem. Int. Ed.* **2003**, 42, 4302.

### Organocuprates: $\text{RCu}$ ; $\text{R}_2\text{CuLi}$ ; $\text{R}_3\text{CuLi}_2$ ; $\text{RCuCNLi}$

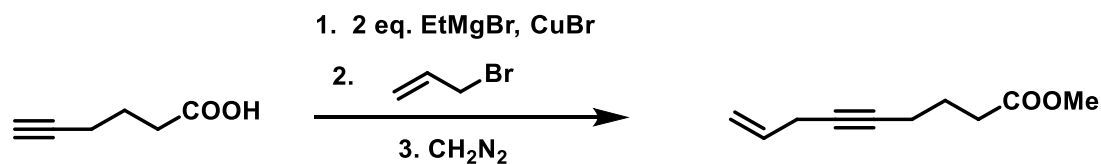
nucleophilic R (& much less basic than Li and Mg analogs)



### nucleophilic attack on RX



$\text{R}'$  : alkyl, alkenyl, alkynyl, aryl



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

### regioselective nucleophilic opening of epoxides

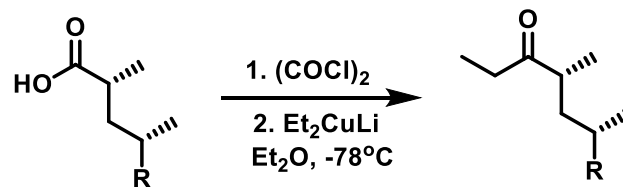
- Nu attack at less substituted C



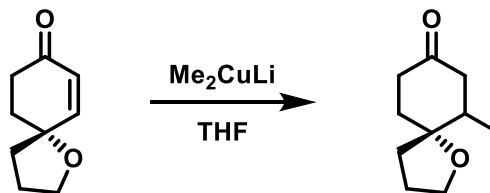
*Tetrahedron Lett.* **1977**, 3407.



## preparation of ketones from acid chlorides



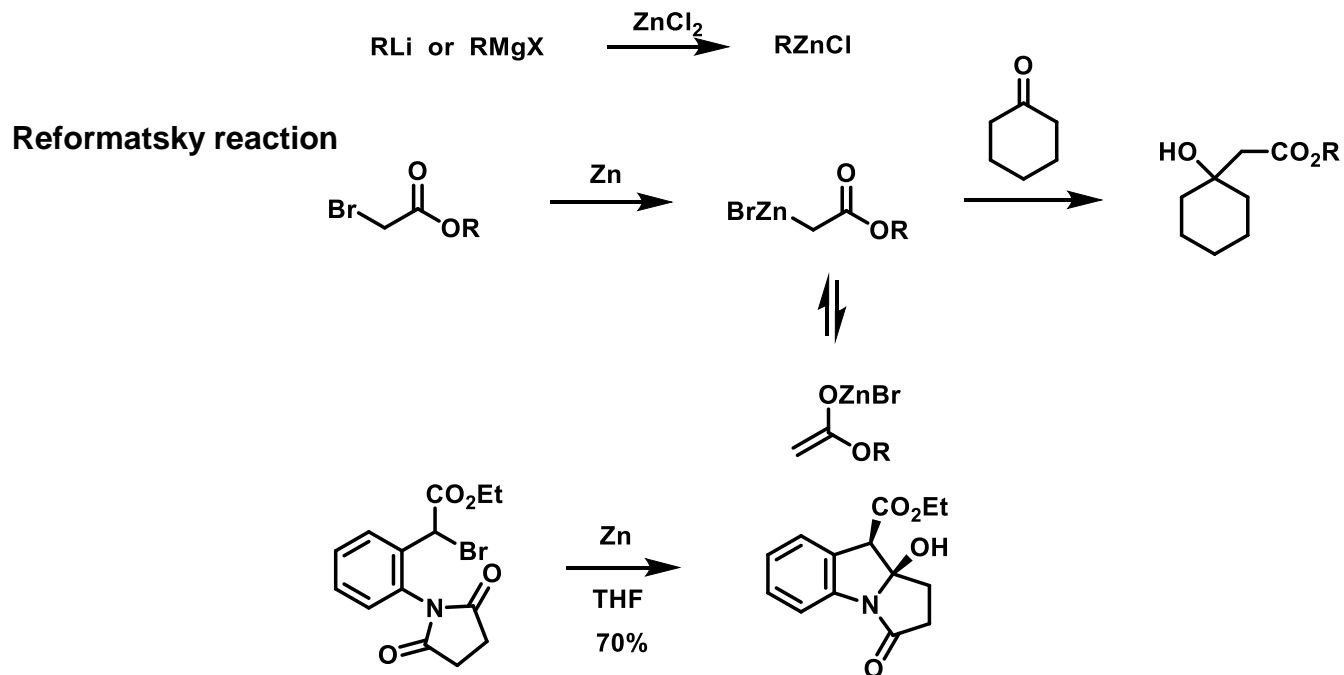
*J. Am. Chem. Soc.* **1981**, 103, 1568.

1,4-addition to  $\alpha,\beta$ -unsaturated carbonyl compounds

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

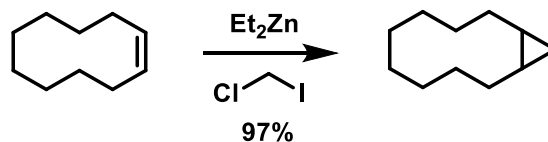
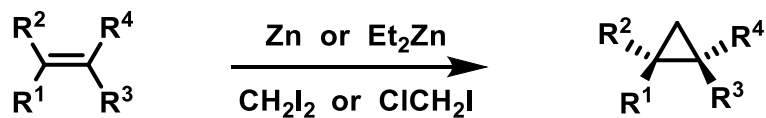
## Organozinc reagents: $RZnX$ ; $R_2Zn$

- also much less basic than Li and Mg analogs



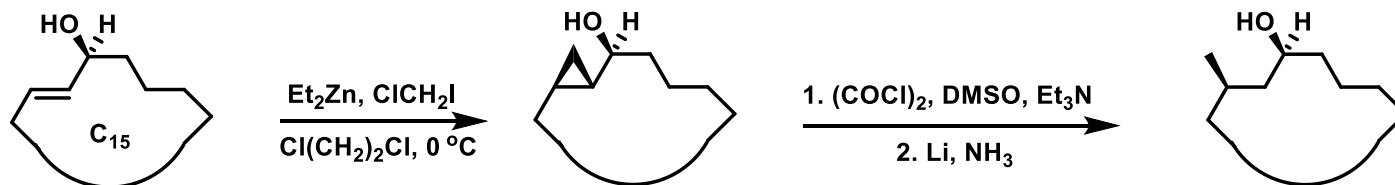
## Cyclopropanation (Simmons-Smith rxn)

stereoselective: syn-addition (cyclic transition state)



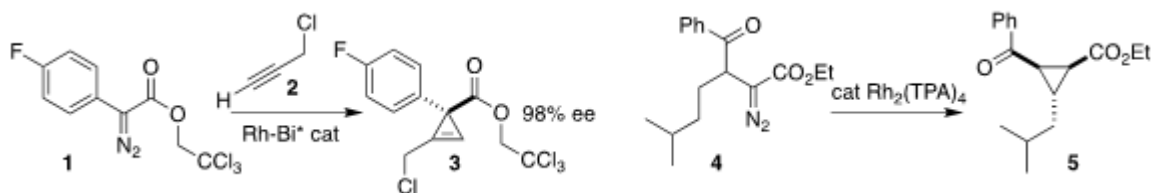
*J. Org. Chem.* **1988**, *53*, 1331.

- 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.

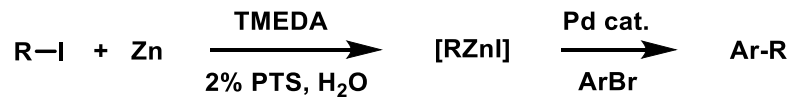
**alternative cyclopropanation:** generation of carbene from diazo compounds



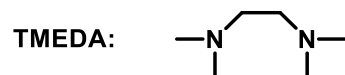
*J. Am. Chem. Soc.* **2021**, *143*, 5666.

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

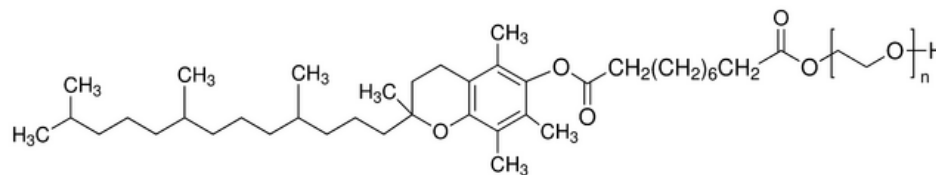
## Generation and use of organozinc reagents in water



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



PTS: polyoxyethanyl- $\alpha$ -tocopheryl sebacate



- micellar catalysis
- „nanoreactors“ from PTS in water