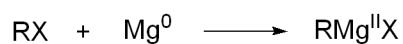


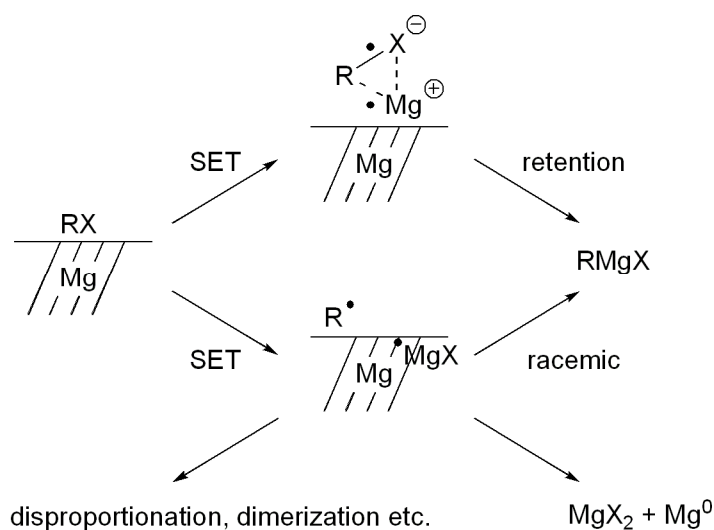
Metallation

1. Oxidative Addition

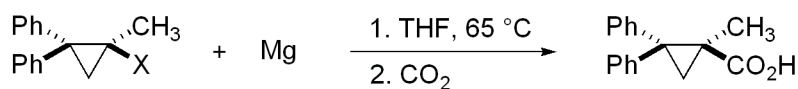
1.1. Grignard Reagents



Proposed Mechanism for Grignard Formation:



reaction occurs with partial retention, depending on halogen



R	yield [%]	ee [%]
Cl	81	27
Br	70	19
I	40	2

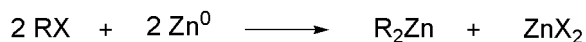
Bond energy and reduction potential of C-X bond



the weaker the bond, the greater the amount of loose radical pairs

Acc. Chem. Res. **1990**, *23*, 286.

1.2. Organozinc Reagents

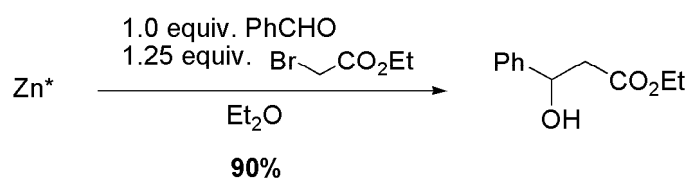


activation of Zn^0 -dust necessary:

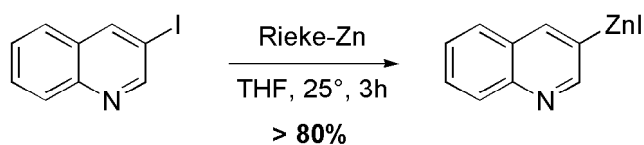
1. dilute HCl, TMSCl or TMSCl/dibromoethane
2. Rieke-zinc:



Examples:

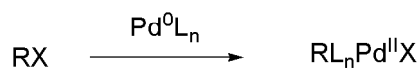


Organometallics **1986**, 5, 1257.



Krause, N. (Ed.) *Modern Organocopper Chemistry* **2002**, p. 56.

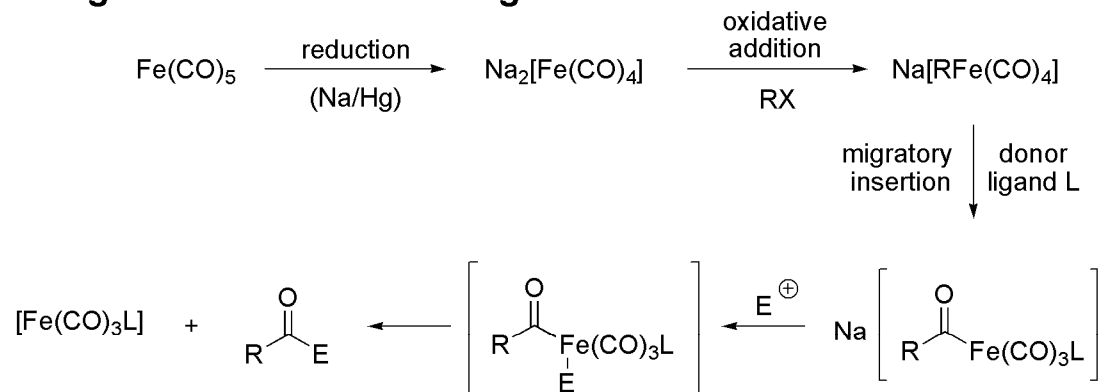
1.3. Organopalladium



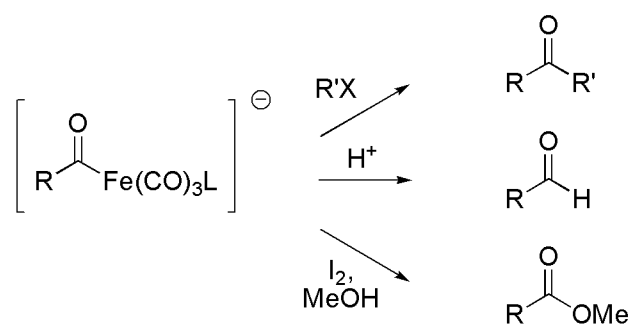
reactivity: I >> OTf > Br >>> Cl
 electron-deficient halides > electron-rich halides

problem: β -H-elimination; traditionally only aryl or alkenyl substrates

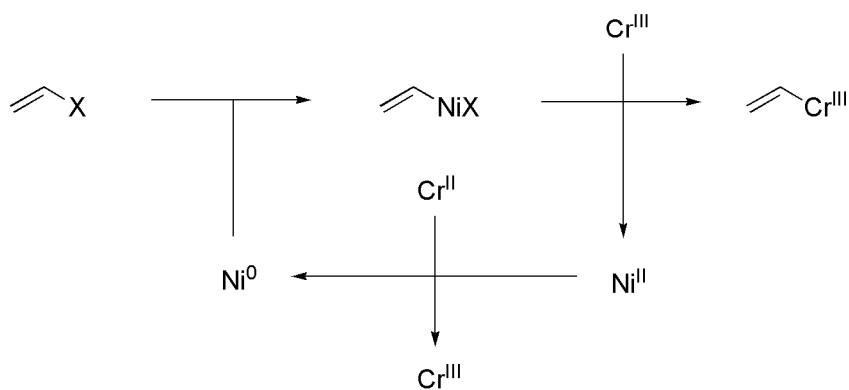
1.4. Organoiron: Collman-Reagent



Reactions:



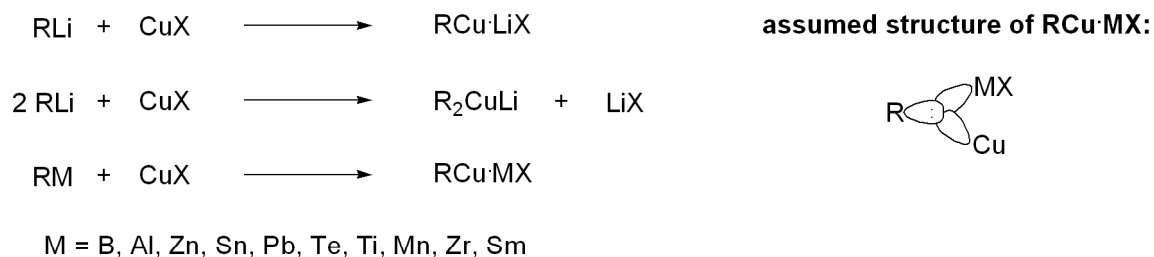
1.5. Organochromium: Nozaki-Hiyama-Kishi Reaction



2. Transmetalation

Transmetalation always proceeds in the direction of placing the more electropositive metal on the more electronegative (acidic) carbon!

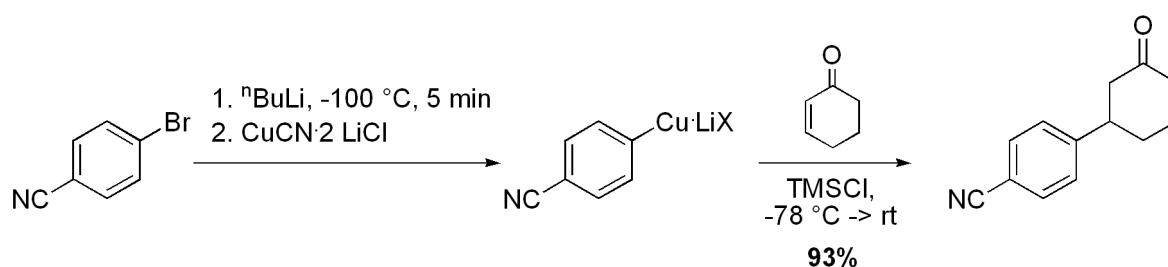
2.1. Cuprates



All organometallics in which the metal M is less electronegative than Cu, and all organometallic species of similar electronegativity but with weaker carbon-metal bonds, are potential candidates for transmetalation reactions.

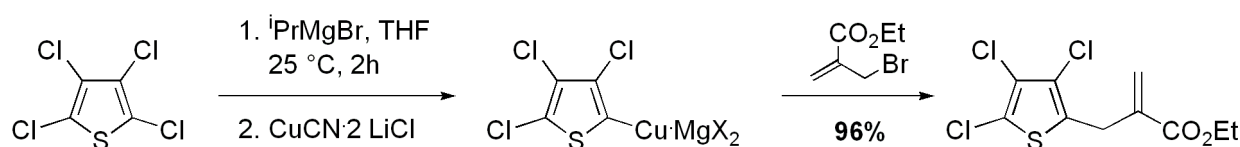
from organolithium reagents:

mainly alkenyl- and aryllithiums; not all functional groups tolerated (low temperature in certain cases)



from organomagnesium compounds:

they are less reactive, therefore more functional groups tolerated, especially for magnesium-halogen exchange

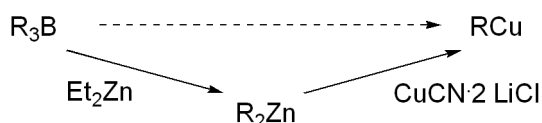


from organoboranes:

they have similar bond energies and electronegativities as cuprates;

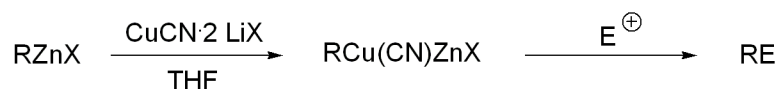
therefore limited to the formation of alkenyl- and unfunctionalized alkyl-copper compounds

sometimes better:



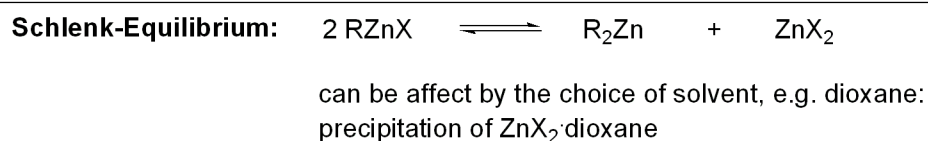
from organozinc compounds:

reagents undergo smooth transmetalations to a broad range of other metals and tolerate many functional groups as a consequence of their low-lying empty p-orbitals



exceptions: epoxides and alkyl halides do not react with RCu(CN)ZnX

two classes of reagents: RZnX and R₂Zn; reactivity of diorganozincs is slightly higher



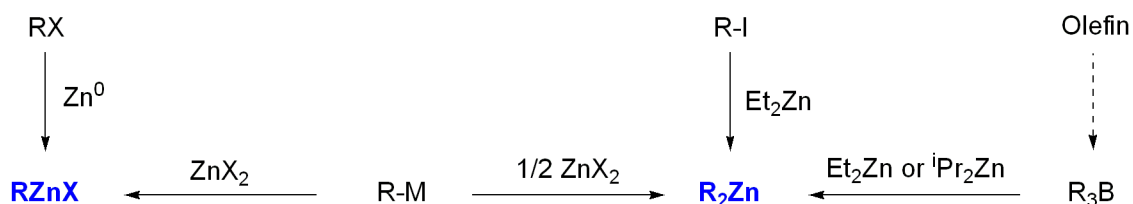
2.2. Organopalladium

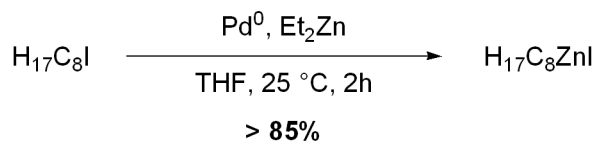
- transmetalations from Li, Mg, Zn, Zr, B, Al, Sn, Si, Ge, Hg, Tl, Cu, Ni have been reported
- transmetalation occurs with retention of configuration
- most important:

Sn	(Stille coupling)
B	(Suzuki coupling)
Zn	(Negishi coupling)
Mg	(Kumada)
Cu	(Sonogashira)

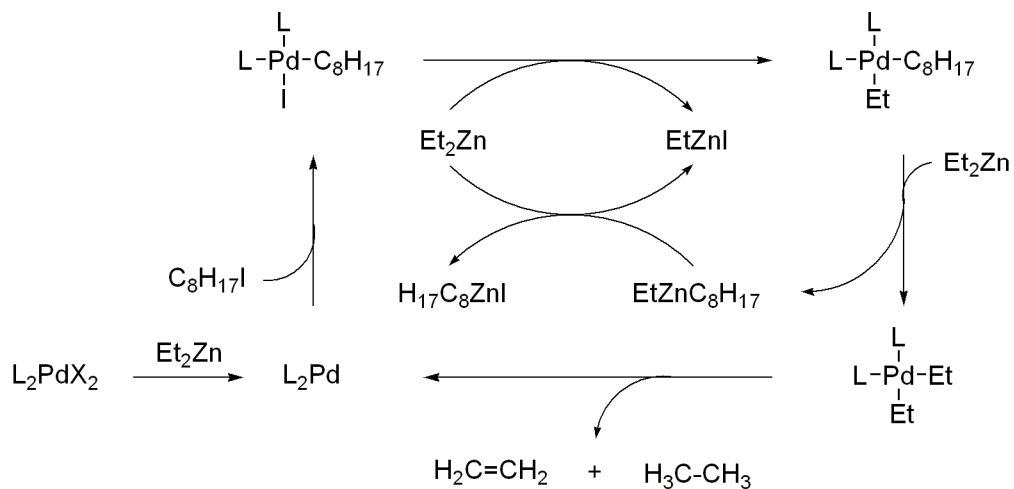
2.3. Organozinc

Preparation of organozinc reagents:

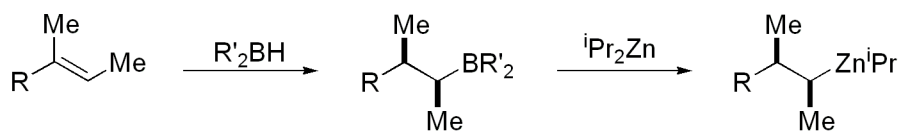




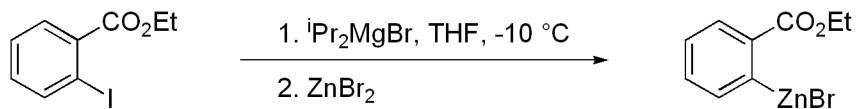
mechanism:



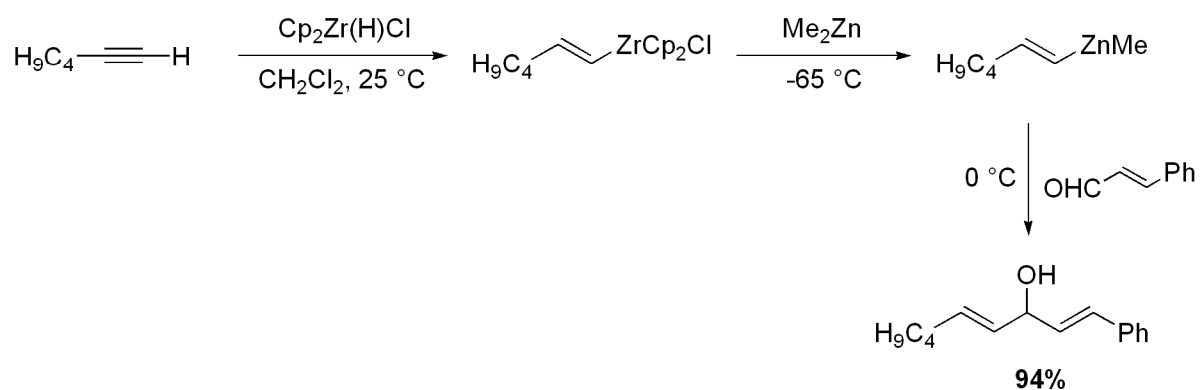
boron-zinc exchange occurs with retention of configuration:



from Grignard reagents:

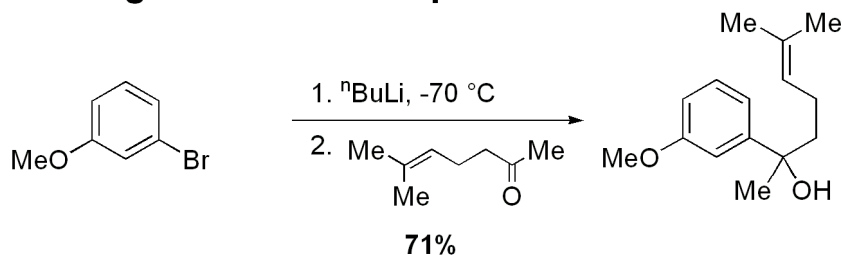


from organozirconium reagents:



3. Metal-Halogen-Exchange

3.1. Organolithium Compounds



J. Org. Chem. **1982**, 47, 331.

In general:



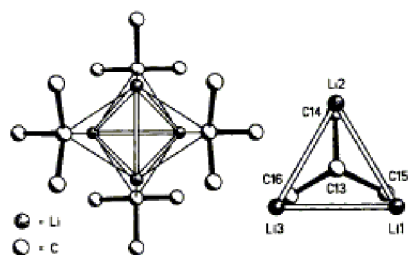
reactivity: ${}^t\text{BuLi} > {}^s\text{BuLi} > {}^n\text{BuLi}$

Note: 2 equiv of reagent are required

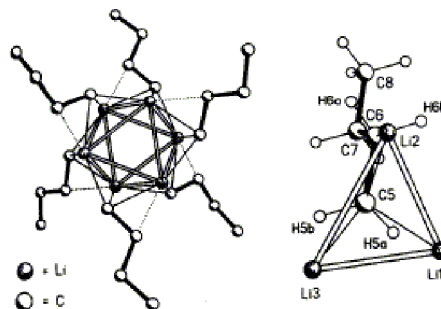


n -BuLi to n -BuBr: slower elimination, but such products may still compete with desired electrophile for reaction with the generated organolithium reagent.

organolithium compounds form aggregates:



crystal structure of ${}^t\text{BuLi}$ - tetramer



crystal structure of ${}^n\text{BuLi}$ - hexamer

Angew. Chem. Int. Ed. Engl. **1993**, 32, 580.

in solution:

RLi	solvent	association
MeLi	hydrocarbons THF, Et ₂ O TMEDA	hexamer tetramer monomer
${}^n\text{BuLi}$	cyclohexane Et ₂ O	hexamer tetramer
${}^t\text{BuLi}$	hydrocarbons	tetramer

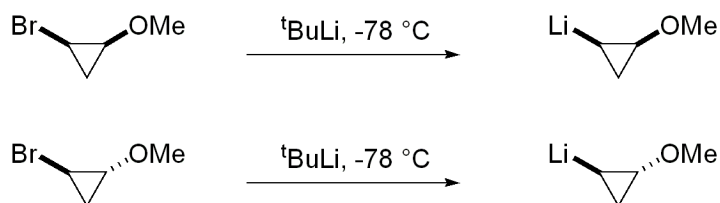
Organometallchemie,
Teubner
Studienbücher,
Stuttgart, **1993**, p.33.

Schlosser's base: extremely strong base



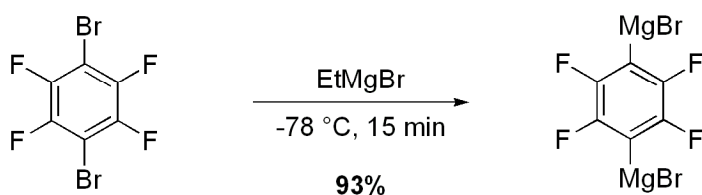
Tetrahedron Lett. **1991**, 32, 1483.

lithium-halogen exchange occurs under retention of configuration:



Tetrahedron Lett. **1975**, 16, 3685.

3.2. Organomagnesium Compounds



exchange rate enhanced by the presence of electronegative substituents

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

reactivity: $\text{ArI} > \text{ArBr} > \text{ArCl} > \text{ArF}$



can be affected by the choice of solvent:

$K = 480$ (Et_2O)

$K = 4$ (THF)

for dioxane, the equilibrium is completely on the left side due to precipitation of MgX_2

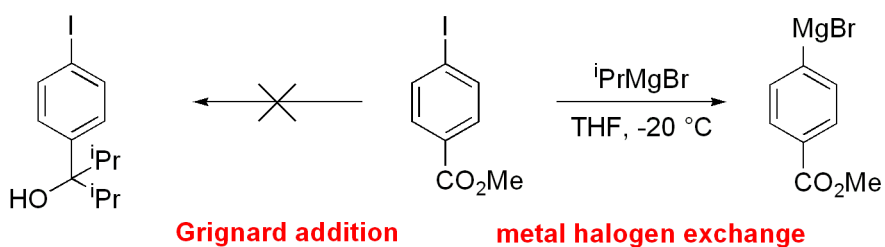
Tetrahedron **1967**, 23, 4215.

pK_a values in H_2O :



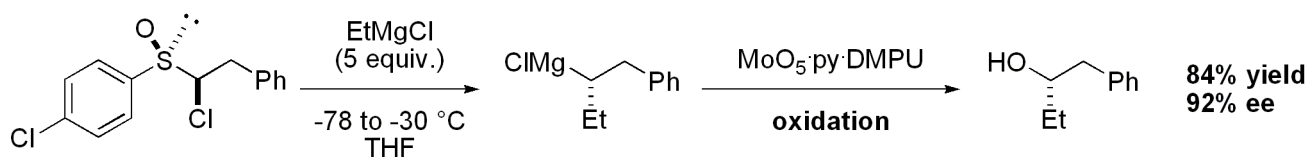
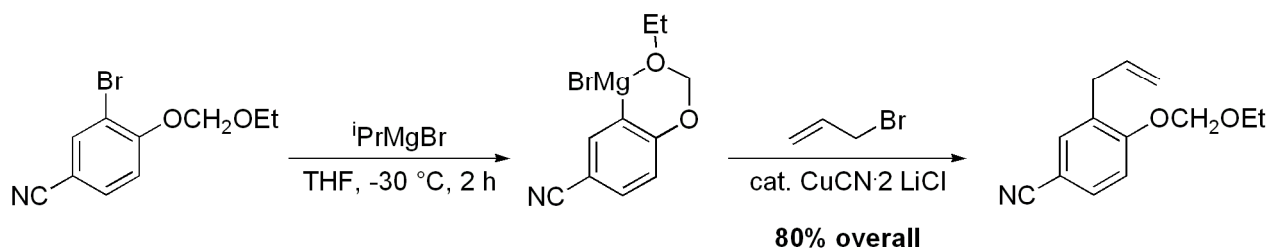
J. Am. Chem. Soc. **1962**, 84, 1684.

Nitriles, esters, imines, and amids are tolerated (low temperature!):



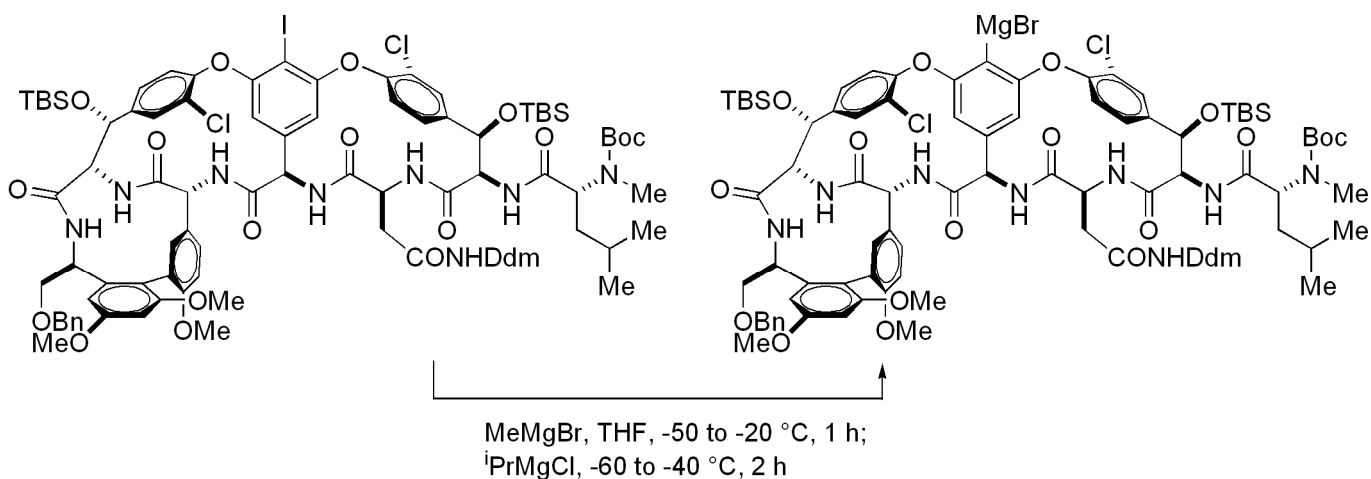
but: aldehyde-containing aryl iodides undergo preferentially Grignard addition

chelating groups in *ortho*-position facilitate exchange:



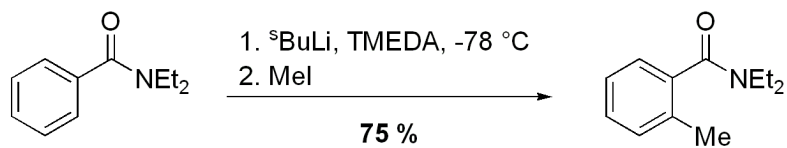
Angew. Chem. Int. Ed. **2000**, *39*, 3072.

from Nicolaou's synthesis of Vancomycin:

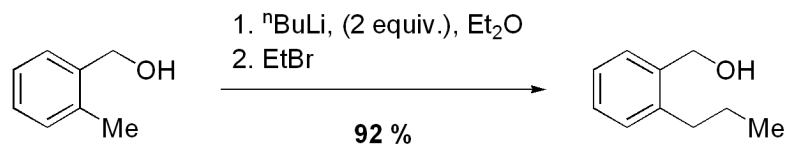


Angew. Chem. Int. Ed. **1998**, *37*, 2717.

4. Directed Metallation

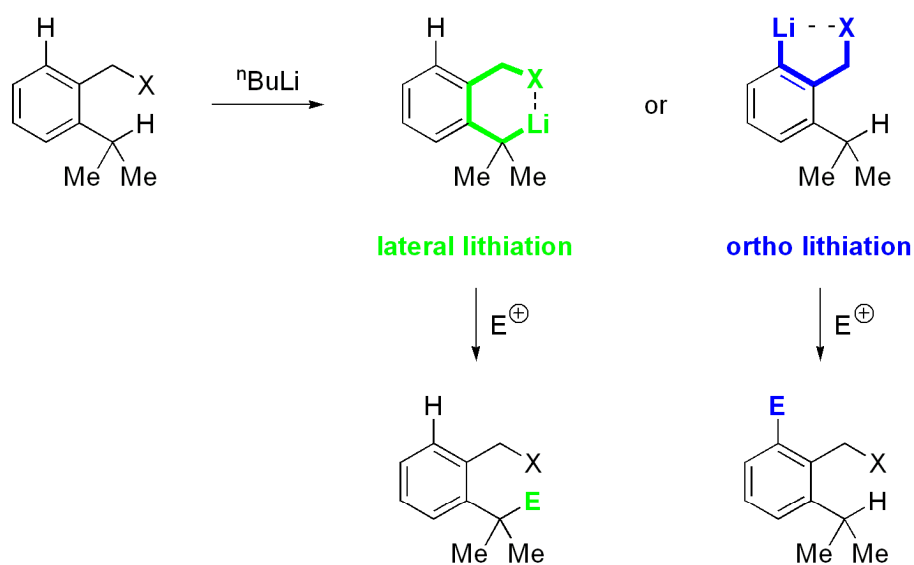


Org. React., Vol. 26, 1979, 1.

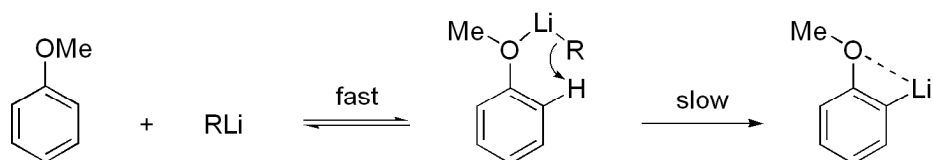


Org. React., Vol. 47, 1995, 1.

in general:



mechanism:

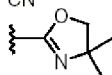


1. acceleration of deprotonation by Lewis-base coordination
2. strong bases used, like ⁿBuLi, ^sBuLi, ^tBuLi, LDA
3. often additives used (TMEDA, DABCO e. g.) to break up aggregates

directing groups:

carbon based

Strong: CON⁻R
 CSN⁻R
 CONR₂
 CON(R)CH(Z)TMS, Z = H, TMS
 CH=NR
 (CH₂)_nNR₂, n = 1,2
 CH(OH)CH₂NR₂
 CN

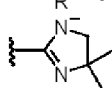
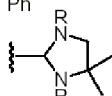


Moderate:



Weak:

C(OTMS)=CH₂
 CH(OR)₂
 C≡C⁻
 Ph



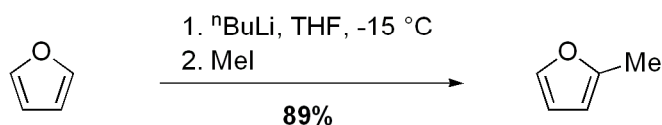
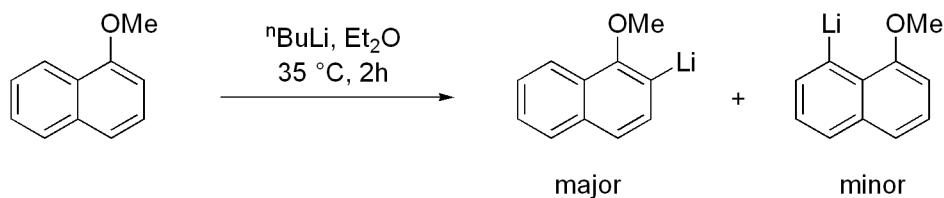
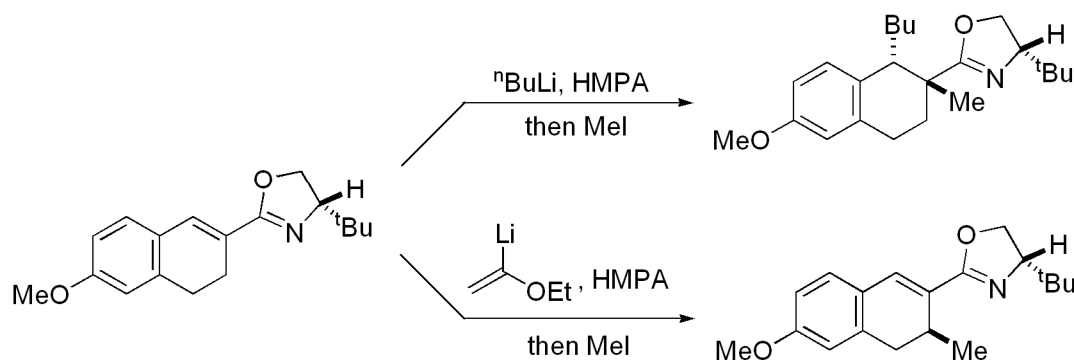
heteroatom based

Strong: N⁻COR
 N⁻CO₂R
 OCONR₂
 OPO(NR)₂
 OCH₂OMe
 OTHP
 OPh
 SO₃R
 SO₂N⁻R
 SO₂NR
 SO₃⁻
 SO₂^tBu
 SO^tBu

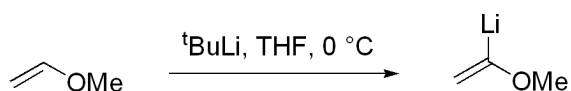
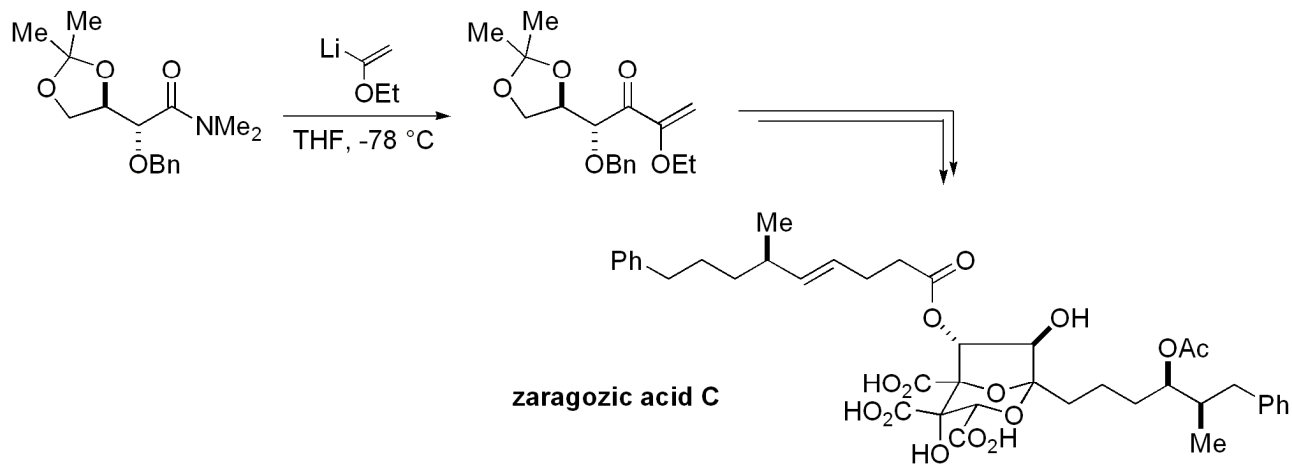
Moderate: NR₂
 N=C
 OMe
 OCH=CH₂
 OPO(OR)₂
 O(CH₂)₂X, X = OMe, NR₂
 F
 Cl
 PO(NR)₂
 PS(Ph)NR₂

Weak: O⁻
S⁻Snieckus *Chem. Rev.* **1990**, *90*, 879.

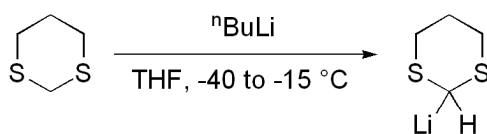
examples:

*Helv. Chim. Acta* **1977**, *60*, 2085.*J. Org. Chem.* **1996**, *31*, 1221.Meyers
Tetrahedron Lett. **1997**, *38*, 5415.

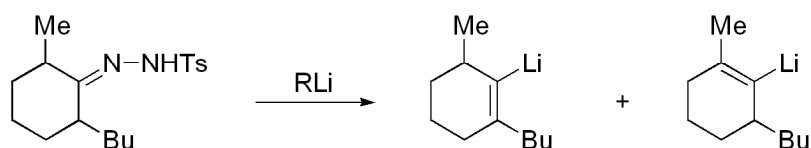
directed metallation of non-aromatic substrates

Baldwin *J. Am. Chem. Soc.* **1974**, *96*, 7125.

zaragozic acid C

Carreira *J. Am. Chem. Soc.* **1995**, *117*, 8106.Corey-Seebach method *J. Org. Chem.* **1975**, *40*, 231.

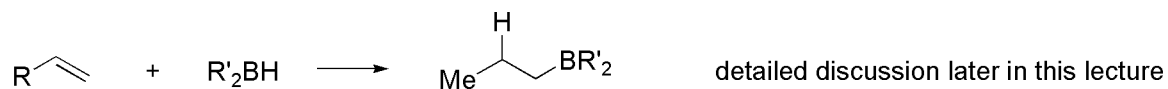
5. Lithiation via the Shapiro Reaction

*J. Org. Chem.* **1981**, *46*, 1315.

for more references, see: *J. Chem. Soc.* **1952**, 4735.
Org. React., Vol 23, **1976**, 405.
Org. React., Vol. 39, **1990**, 1.

6. Hydrometallation

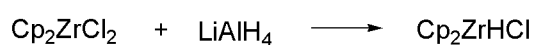
6.1. Hydroboration



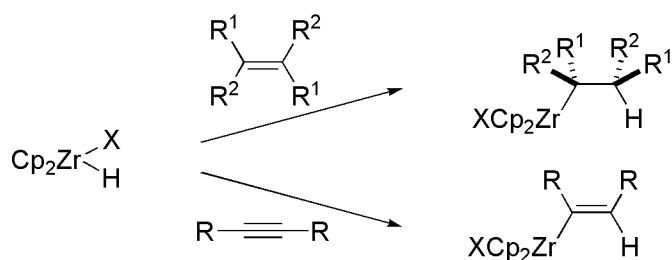
6.2. Hydrozirconation

most commonly used reagent: Cp_2ZrHCl (**Schwartz's reagent**)

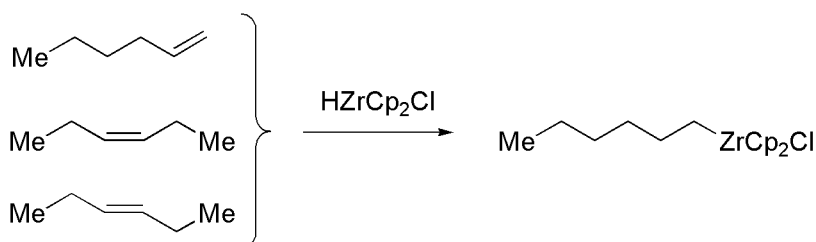
preparation:



addition occurs in a *syn*-fashion:



Zr migrates along alkyl chains to the terminal position:



for alkynes: no migration away from sp^2 -carbons observed
terminal addition is preferred

