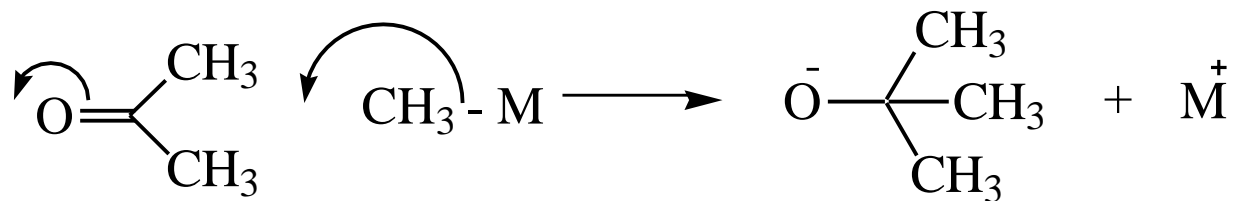
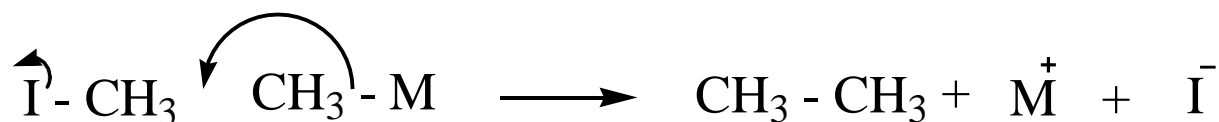
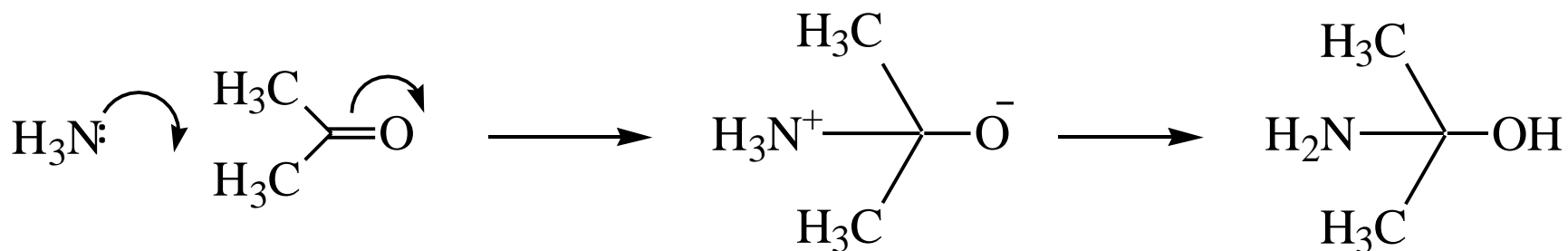
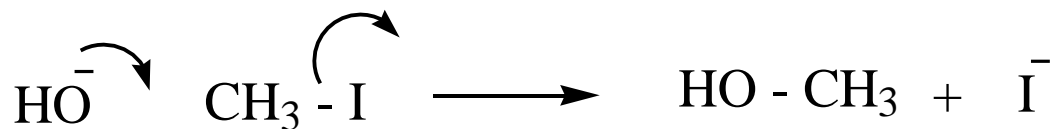


# Organomagnesium (Grignard) and organolithium reagents

# Different polarization of non-metallic and organometallic reagents

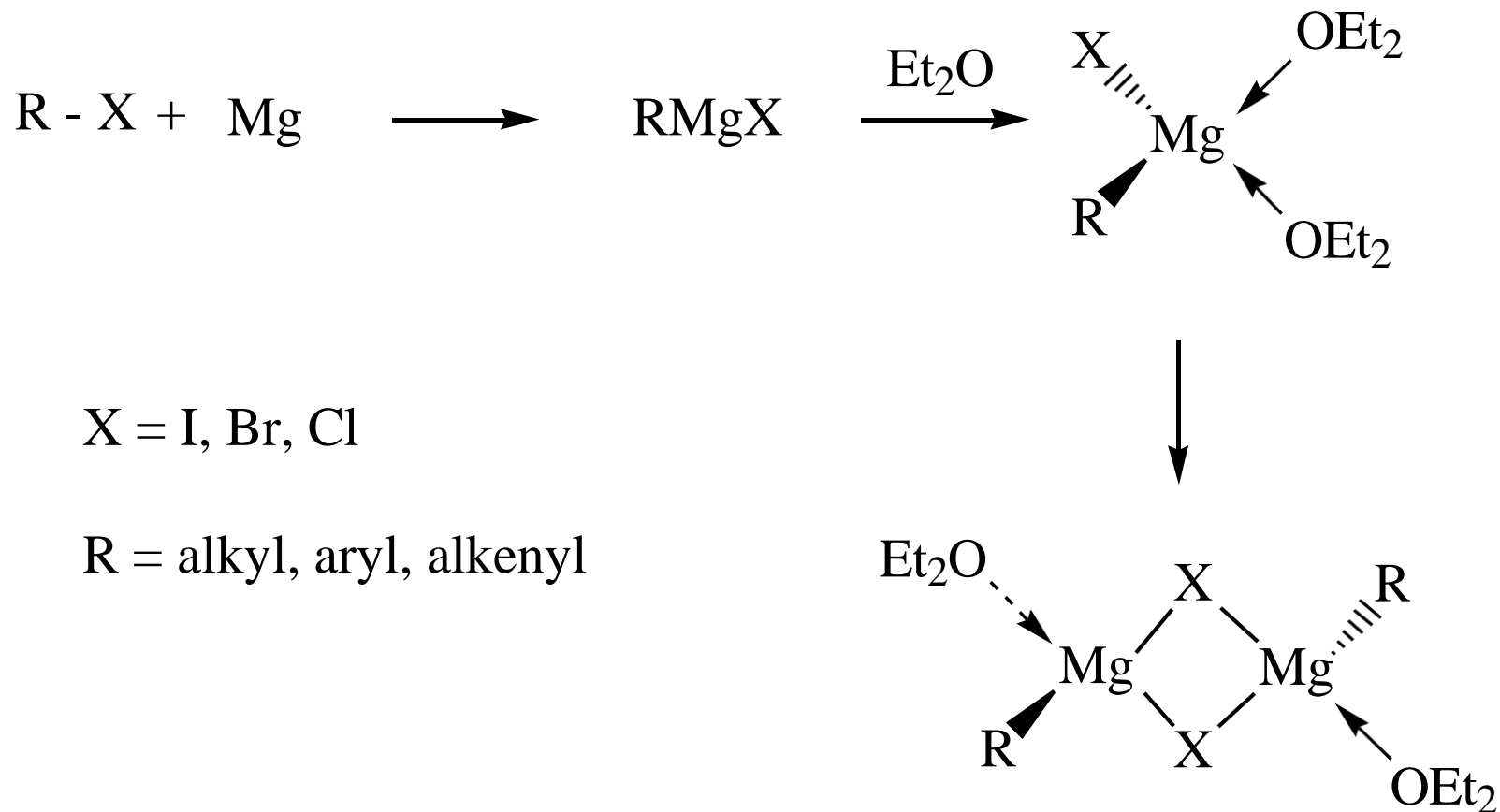


# Organometallic reagents (R-M) are not fully ionic

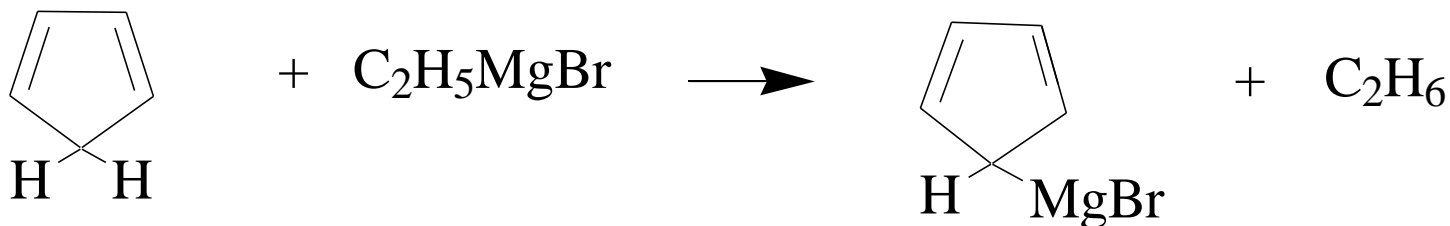
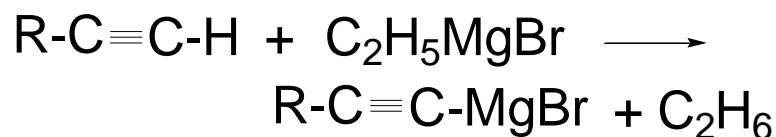
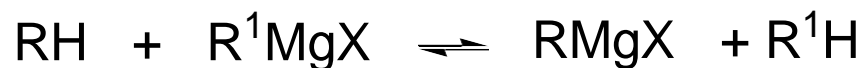
Metal	K	Na	Li	Mg
% Ionic Character	51	47	43	35

  
reactivity of organometallic reagents

# Ethers are the only solvents for organomagnesium (Grignard) reagents

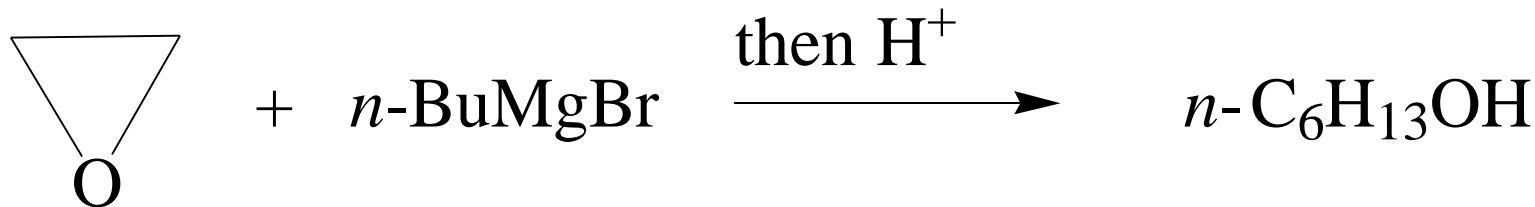


# Generation of Grignard reagents by metallation (hydrogen – metal exchange)

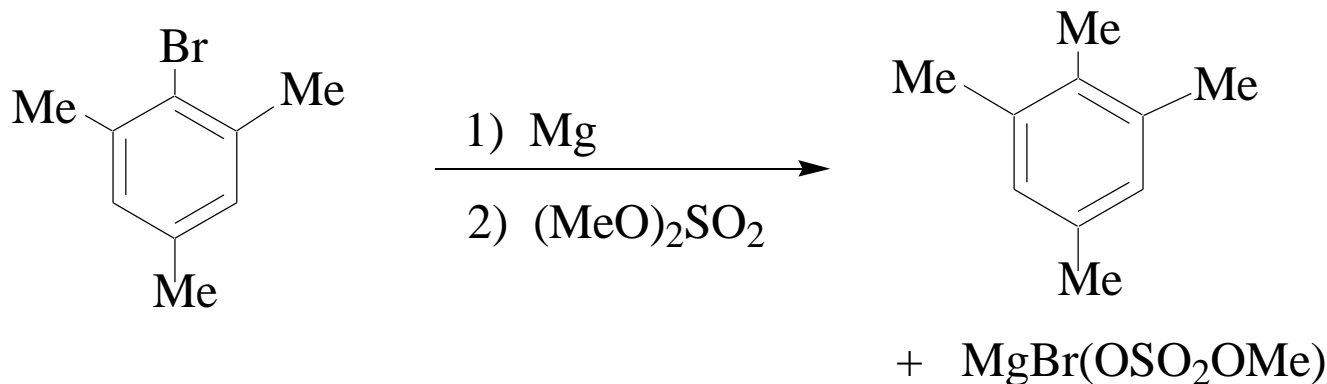
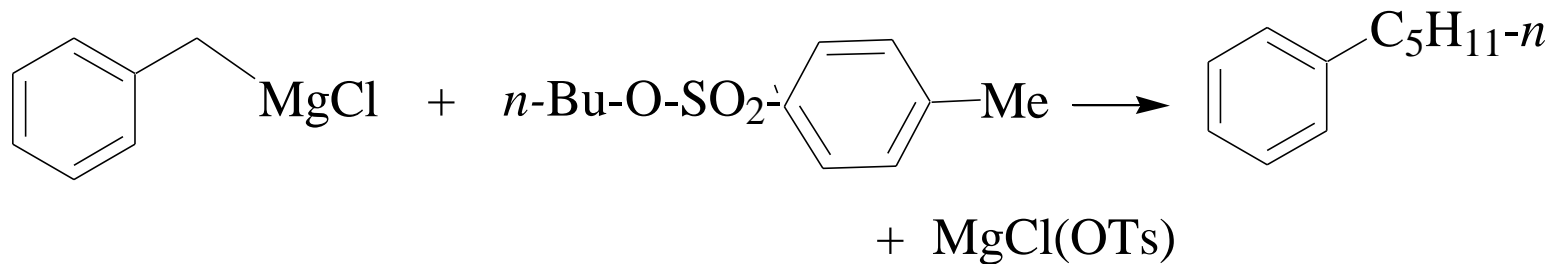
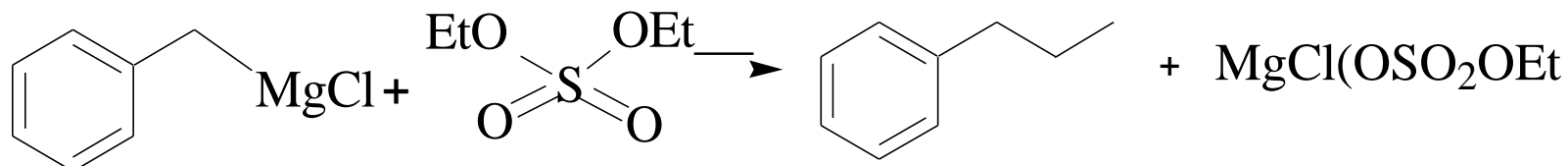
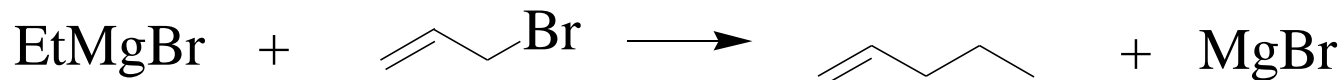


Reactivity: magnesium atom is transferred to a more electronegative atom, as in metallation

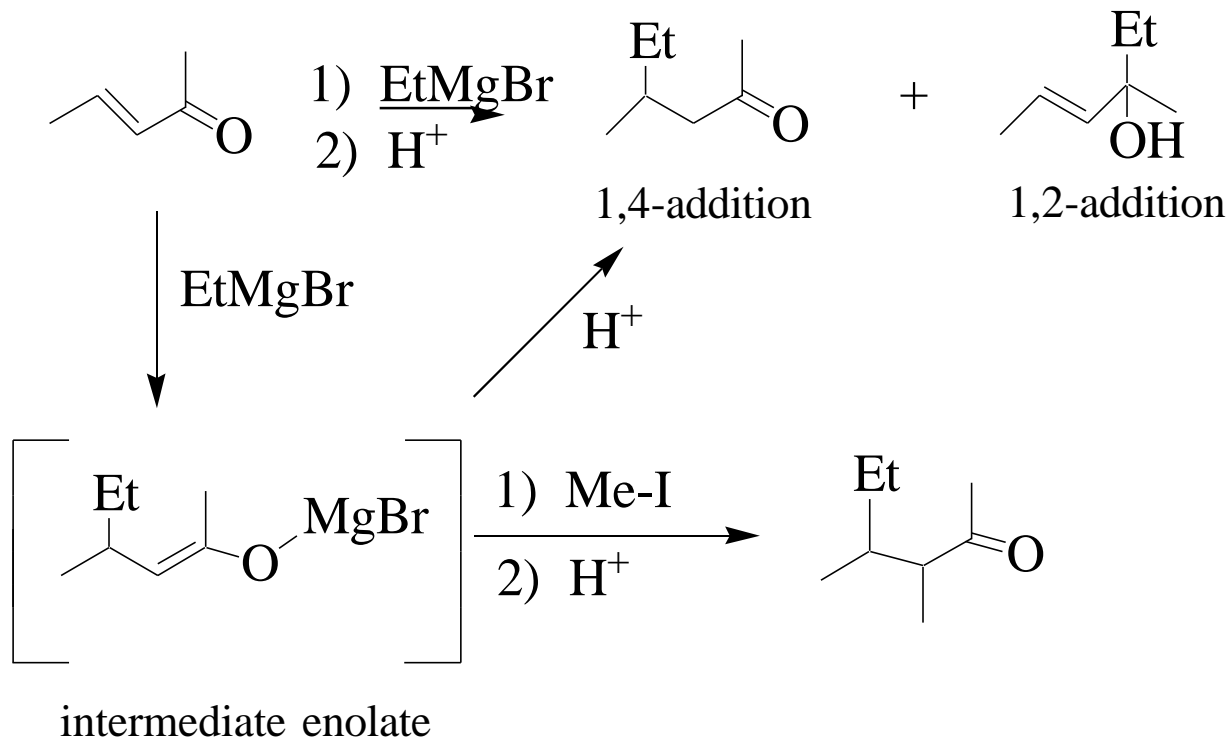
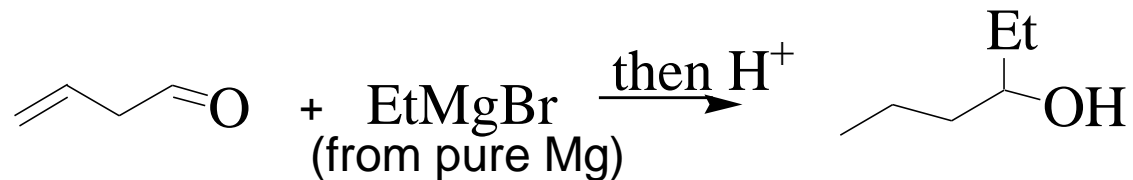
- $\text{ROH} + \text{R}^1\text{MgX} \rightarrow \text{RO-MgX} + \text{R}^1\text{H}$
- $\text{R}_2\text{NH} + \text{R}^1\text{MgX} \rightarrow \text{R}_2\text{N-MgX} + \text{R}^1\text{H}$
- $\text{R}_2\text{C=O} + \text{R}^1\text{MgX} \rightarrow \text{R}_2\text{R}^1\text{C-O-MgX}$



# SN<sub>2</sub>-type (coupling) reactions



# Transition metal ion (e.g. CuBr) mediated 1,4-addition to unsaturated carbonyl compounds





# Organolithium reagents

- Methyllithium  $\text{CH}_3\text{-Li}$  ( $\text{MeLi}$ )
- a strong base and a strong nucleophile
  
- *n*-Butyllithium  $n\text{-C}_4\text{H}_9\text{-Li}$  (*n*-BuLi)
- a strong base and a strong nucleophile
  
- *t*-Butyllithium  $\text{Me}_3\text{C-Li}$  (*t*-BuLi)
- a strong base and a strong nucleophile
  
- basicity increases in the following order:
- $\text{MeLi} < n\text{-BuLi} < t\text{-BuLi}$

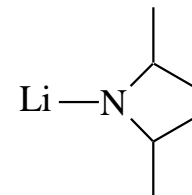
# Basicity vs. nucleophilicity

- A basic reagent has a strong affinity for proton (e.g. removal of proton from a C-H moiety)
- A nucleophilic reagent has a strong affinity for carbon in the molecule (e.g.  $S_N2$  reaction at the carbon atom)

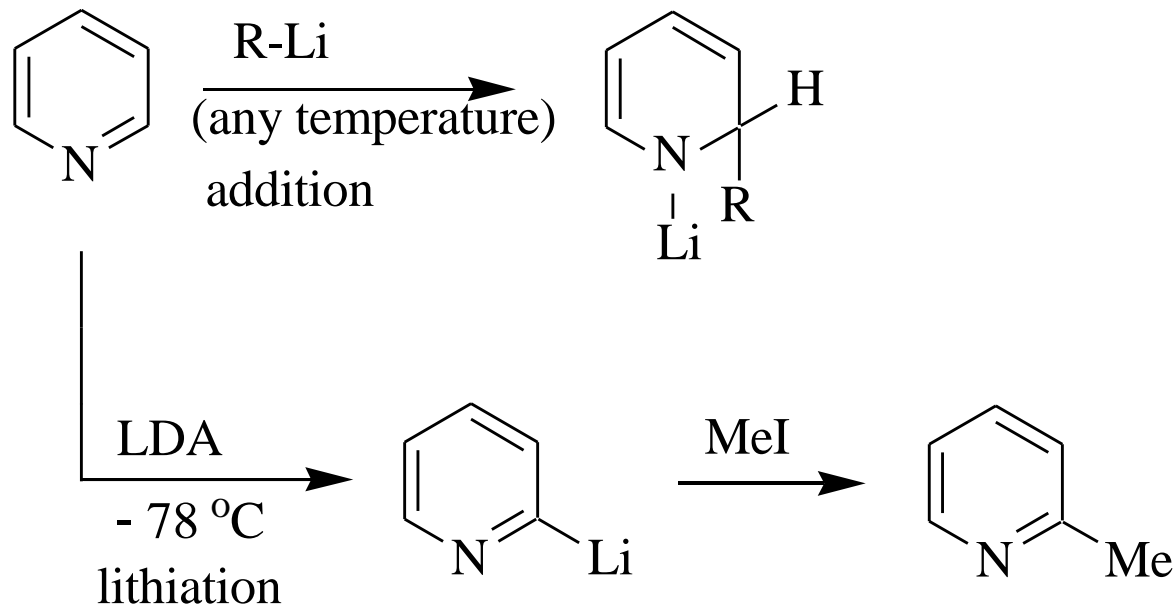
Phenyllithium  $C_6H_5-Li$  (PhLi)  
a strong base and a strong nucleophile

Lithium diisopropylamide  $iPr_2N-Li$  (LDA)  
a strong base and a relatively weak nucleophile

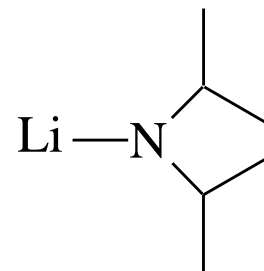
LDA: lithium diisopropylamide



Alkyl lithium and aryllithium reagents are strongly basic and strongly nucleophilic, while lithium amide reagents are strongly basic and relatively non-nucleophilic



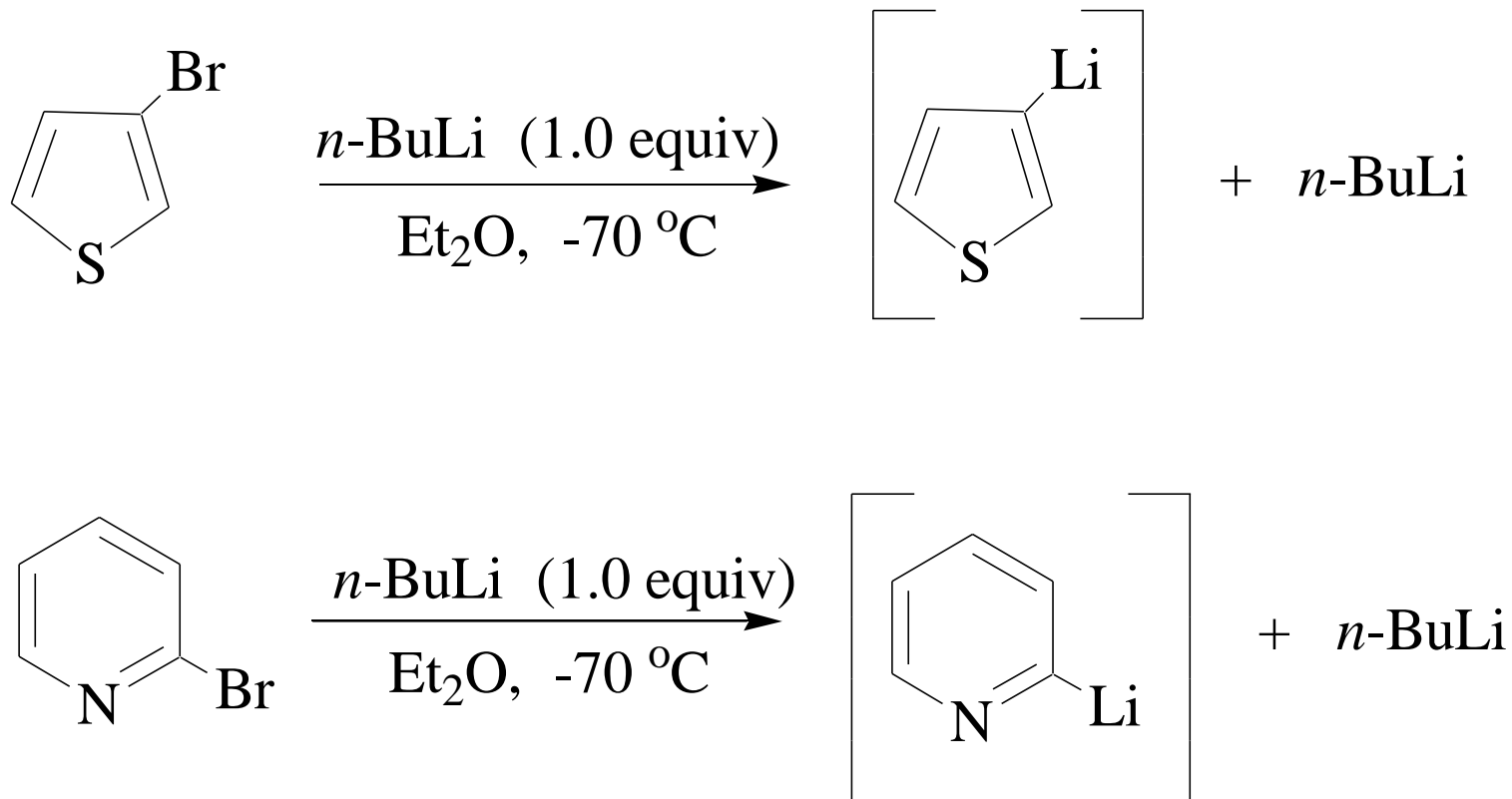
LDA: lithium diisopropylamide



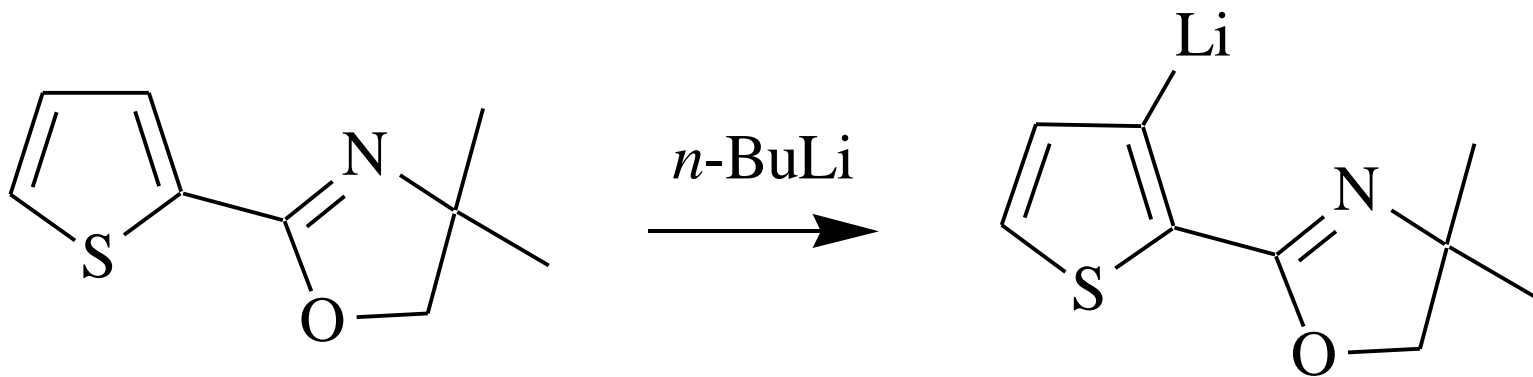
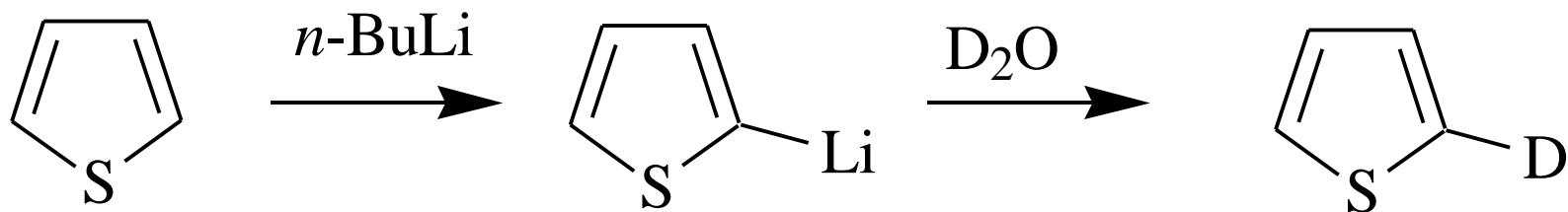
# Generation of organolithium reagents

- $\text{RCl} + 2\text{Li} \longrightarrow \text{RLi} + \text{LiCl}$   
the reaction of alkyl halides with lithium metal
- $\text{RLi} + \text{R}^1\text{X} \longrightarrow \text{R}^1\text{Li} + \text{RX}$   
lithium – halogen exchange in the reaction of an alkyllithium reagent and an alkyl halide,  
 $\text{X} = \text{I}$  or  $\text{Br}$
- $\text{RLi} + \text{R}^1\text{H} \longrightarrow \text{RH} + \text{R}^1\text{Li}$   
lithium – hydrogen exchange in the reaction of an organolithium reagent with a relatively acidic hydrocarbon portion of a molecule (lithiation)

# Lithium – halogen exchange

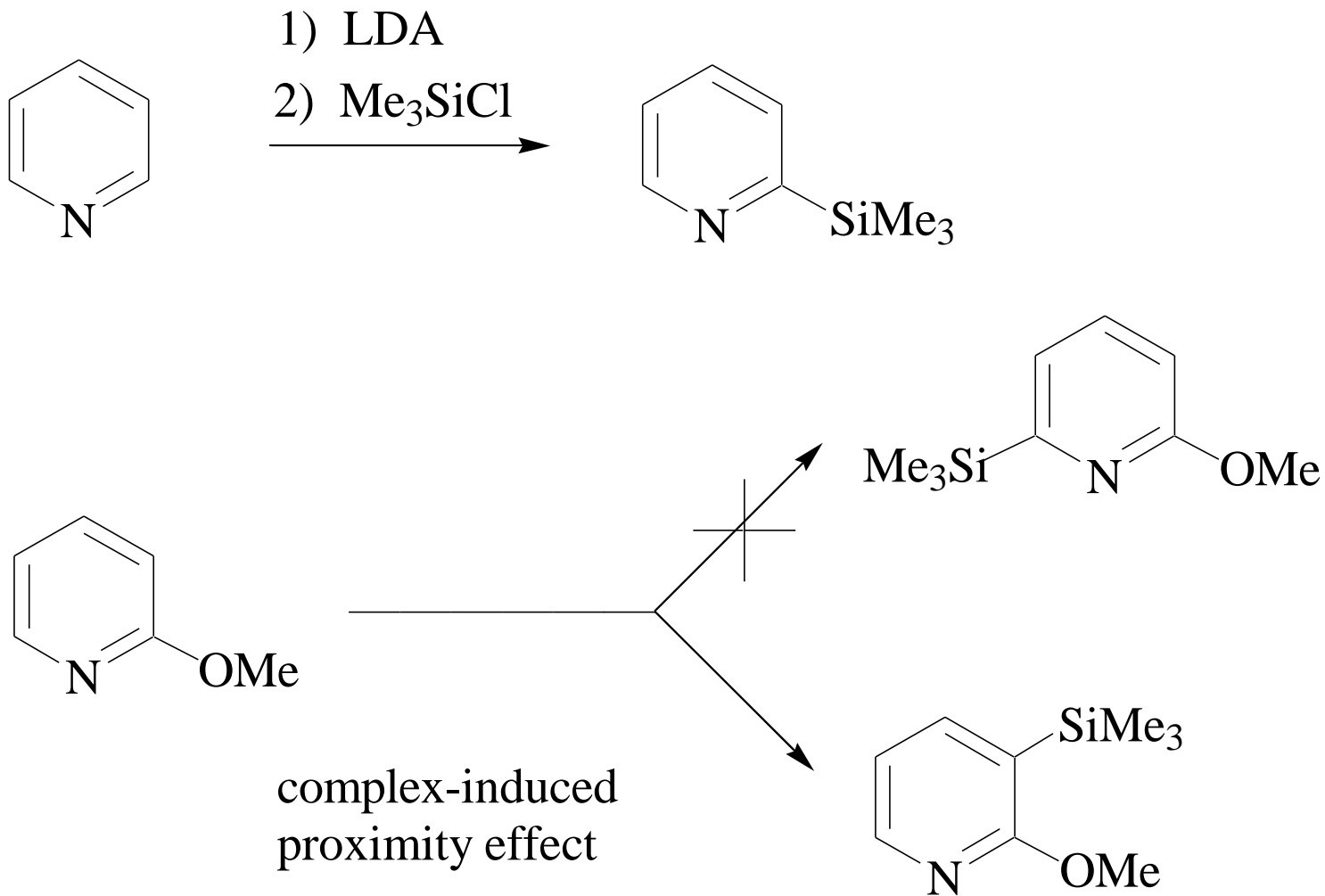


# Lithiation and complex – induced proximity effect (CIPE)

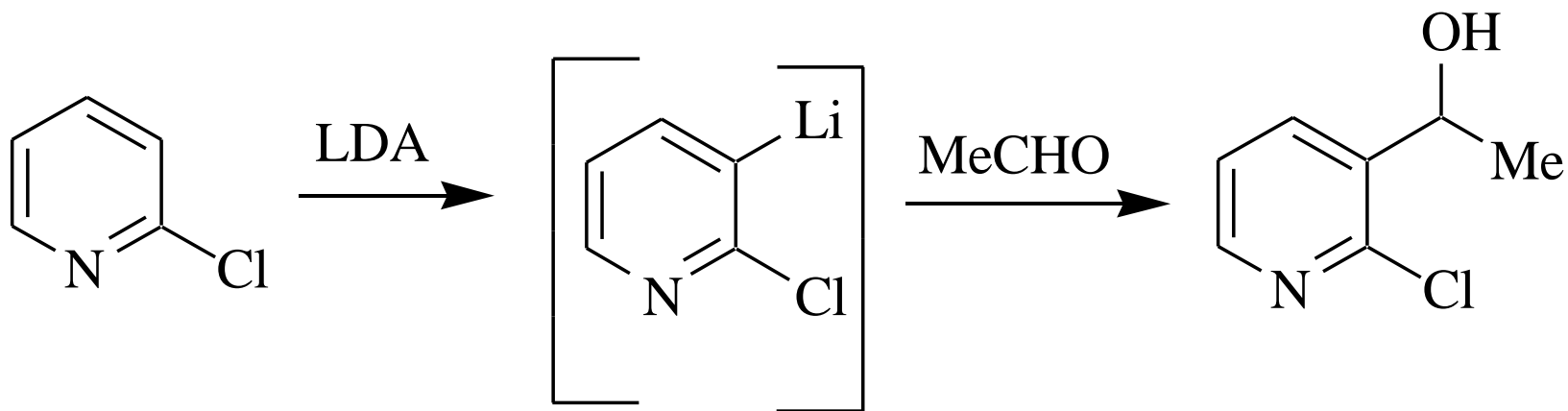


complex-induced proximity effect

# Lithiation and CIPE (contd.)



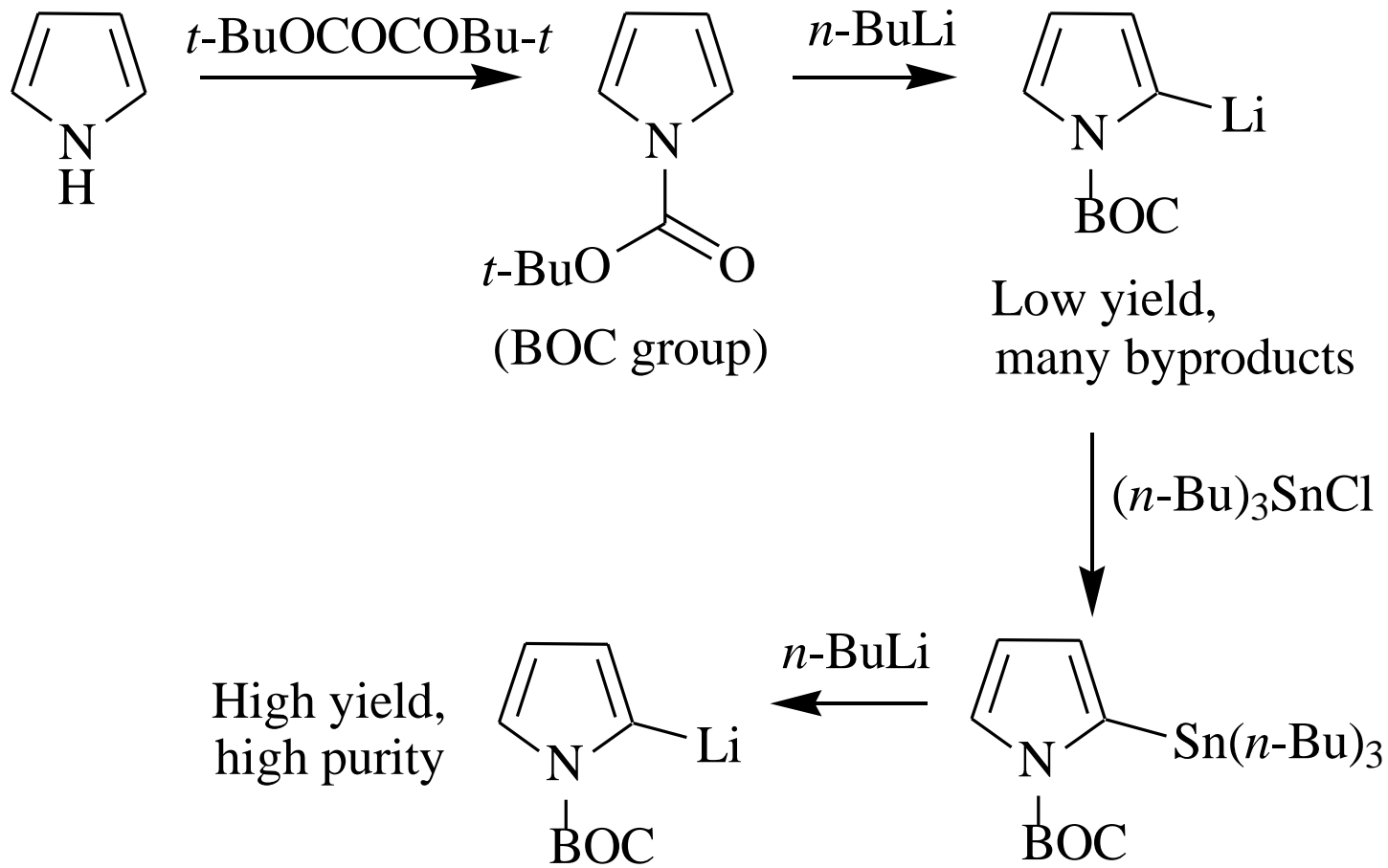
## CIPE (contd.)



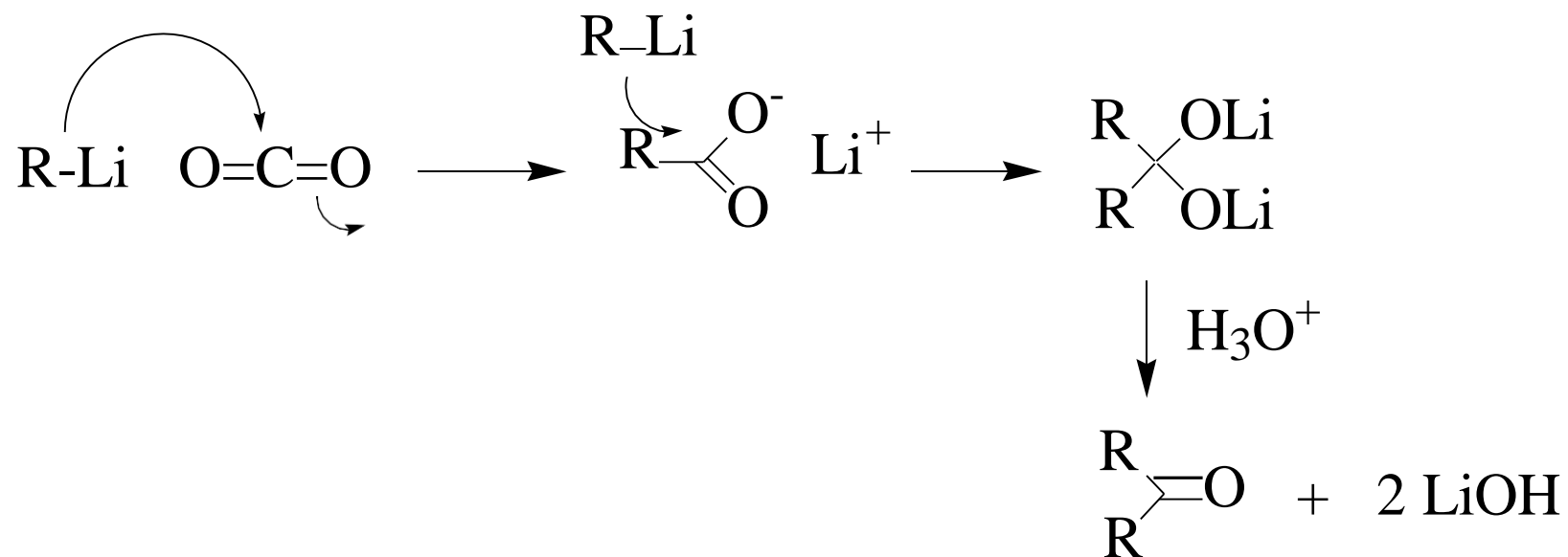
complex-induced proximity effect



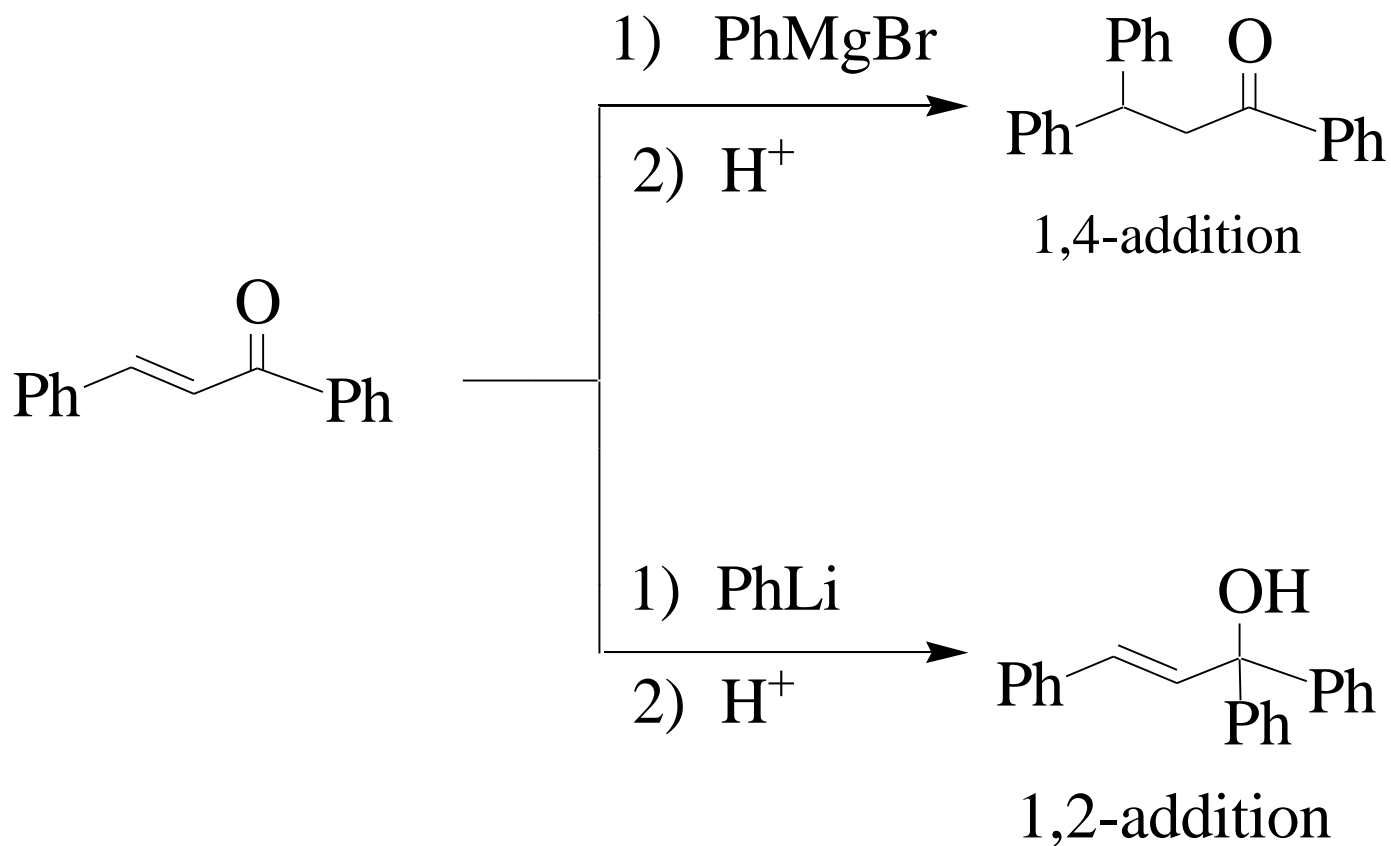
# CIPE and transmetalation



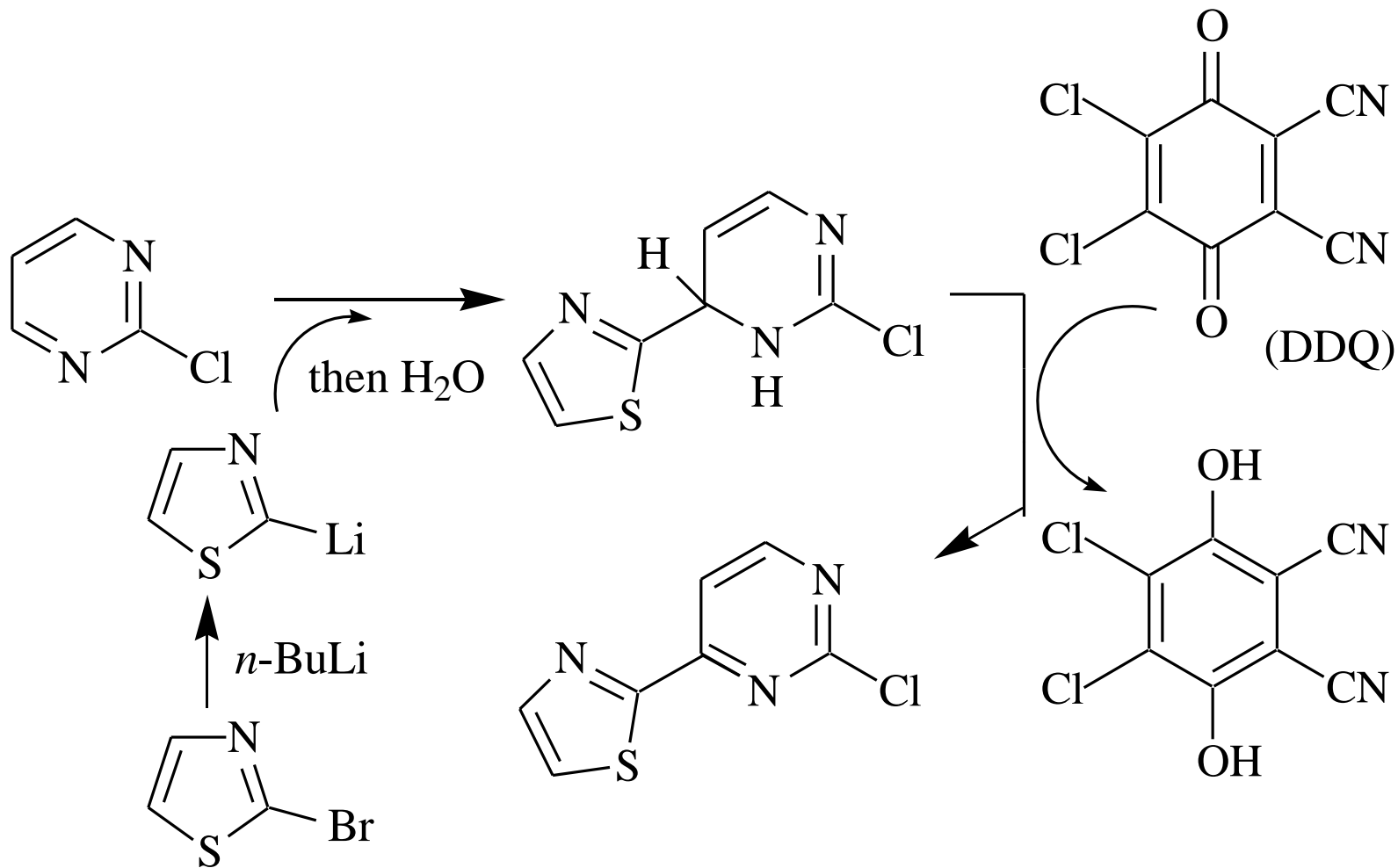
# Synthesis of ketones



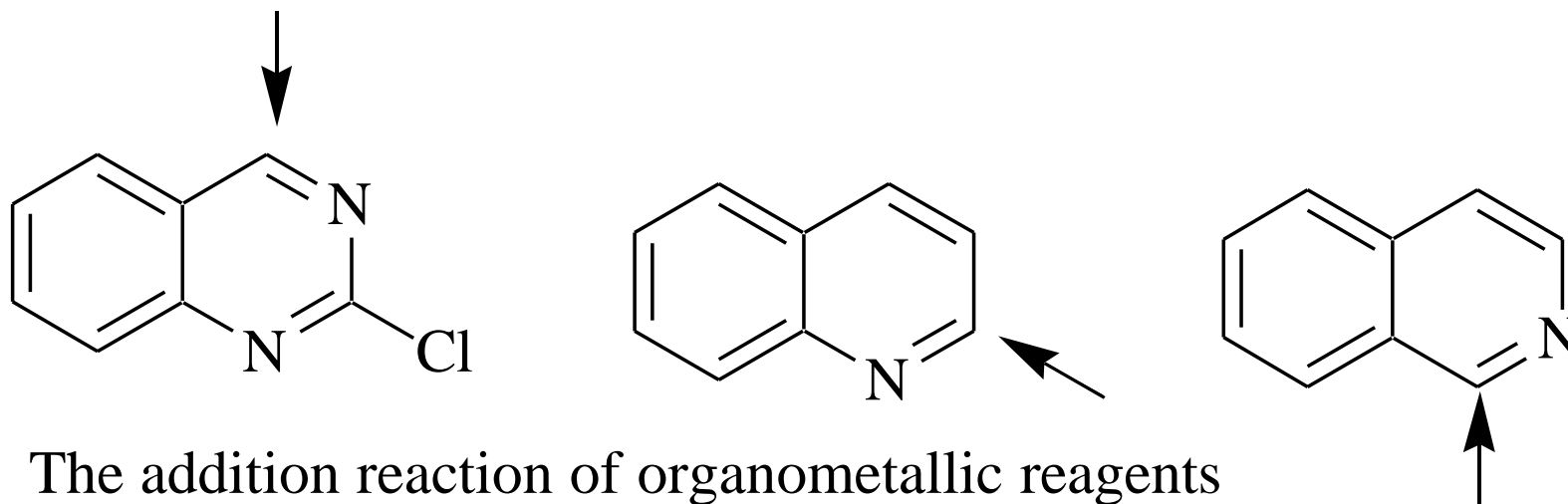
# Reaction with unsaturated carbonyl compounds



# Addition reaction to the formal C=N bond of heteroaromatic compounds



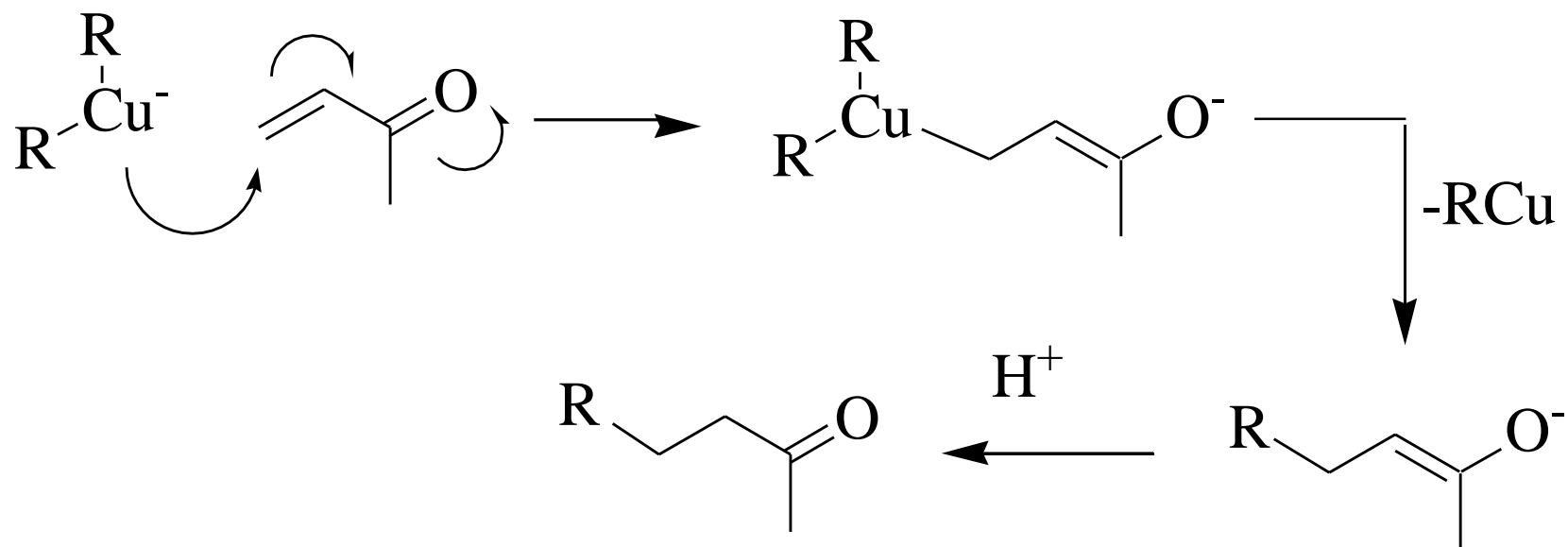
# Addition to heteroaromatic compounds (contd.)



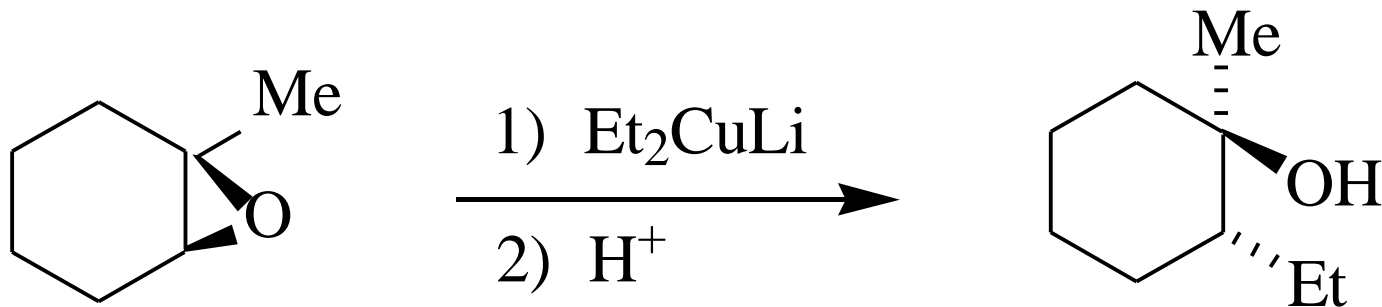
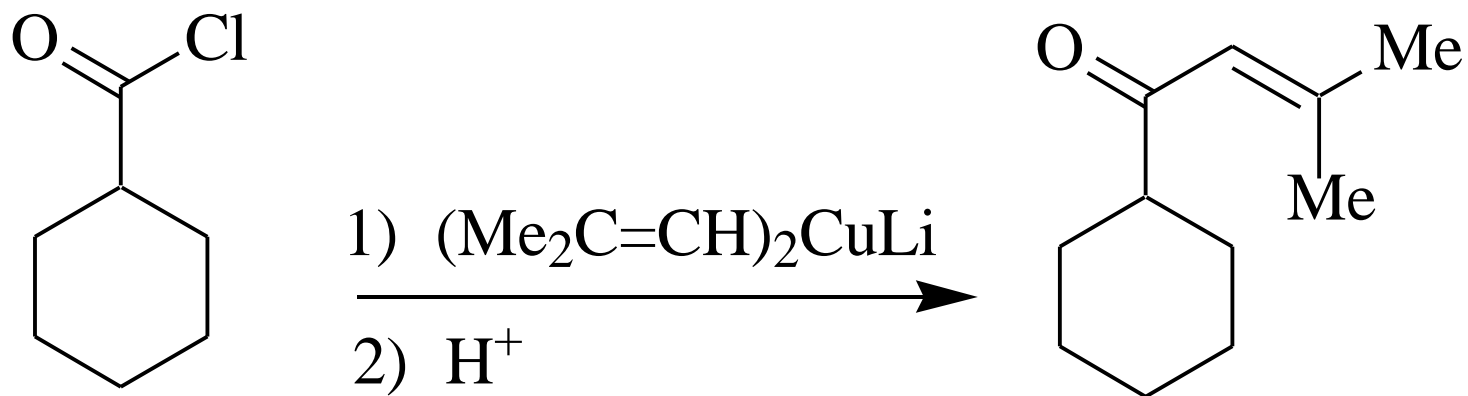
# Organocopper (RCu) and lithium organocuprates (R<sub>2</sub>CuLi)

- MeLi + CuI → MeCu + LiI  
colorless                                      yellow
  
- MeLi + MeCu → Me<sub>2</sub>CuLi  
colorless

# 1,4-addition reaction of $R_2CuLi$ (not reactive enough for a 1,2-addition)

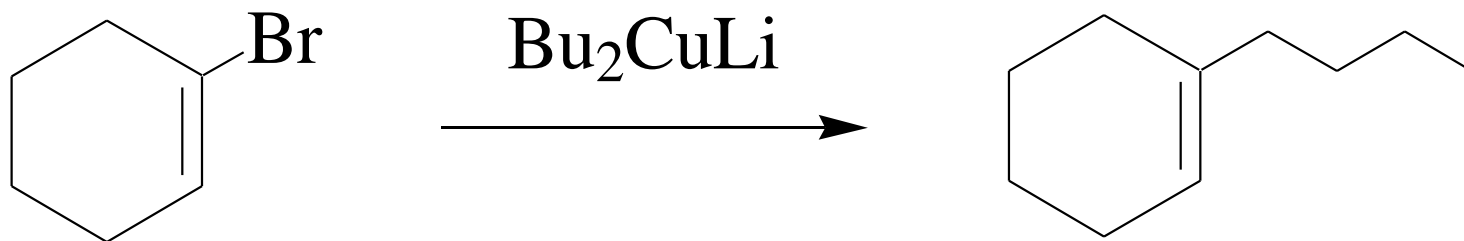
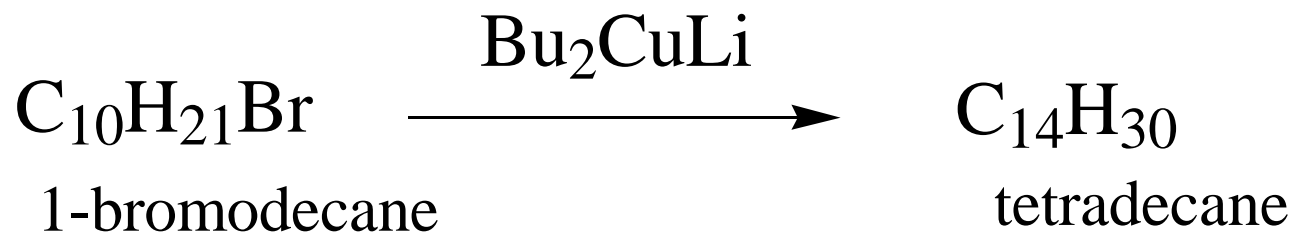


# $R_2CuLi$ : reactions with acid chlorides and epoxides



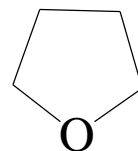


# $R_2CuLi$ : coupling reactions

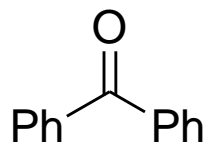


# Drying of diethyl ether (ether or Et<sub>2</sub>O) and tetrahydrofuran (THF) for organolithium reactions

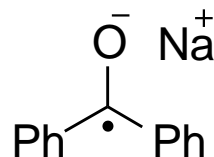
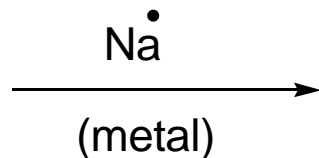
EtOEt  
diethyl ether



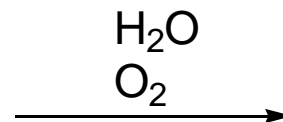
tetrahydrofuran



benzophenone  
(colorless)



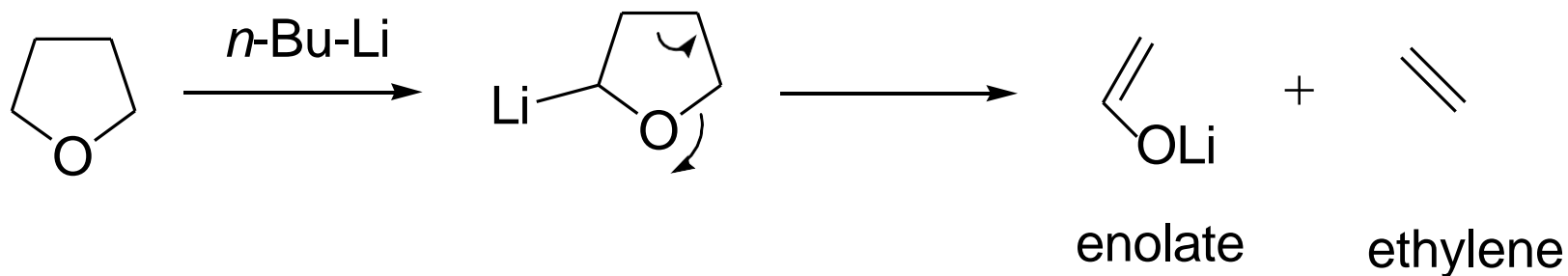
sodium benzophenone  
ketyl radical  
(intensively violet)



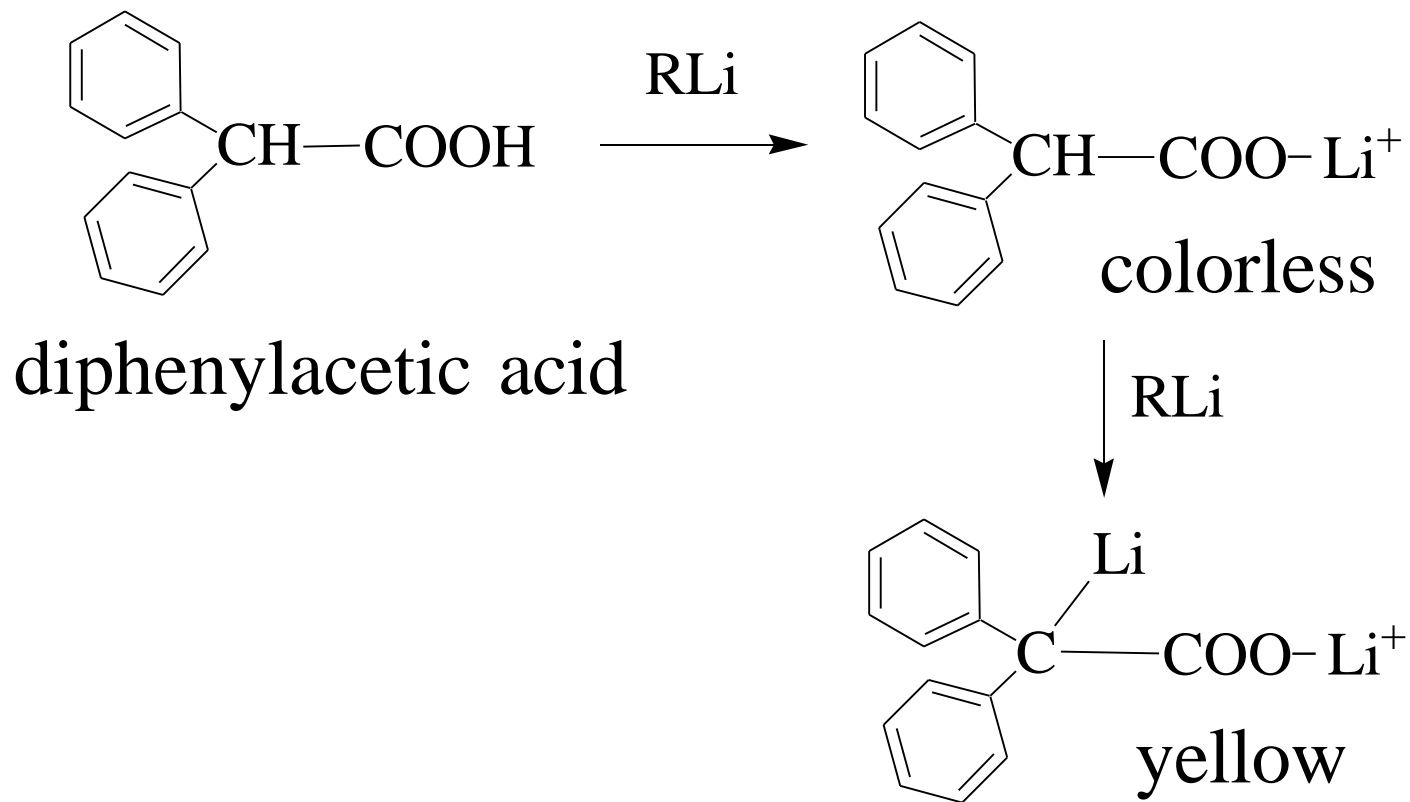
Brown mixture

# The use of THF

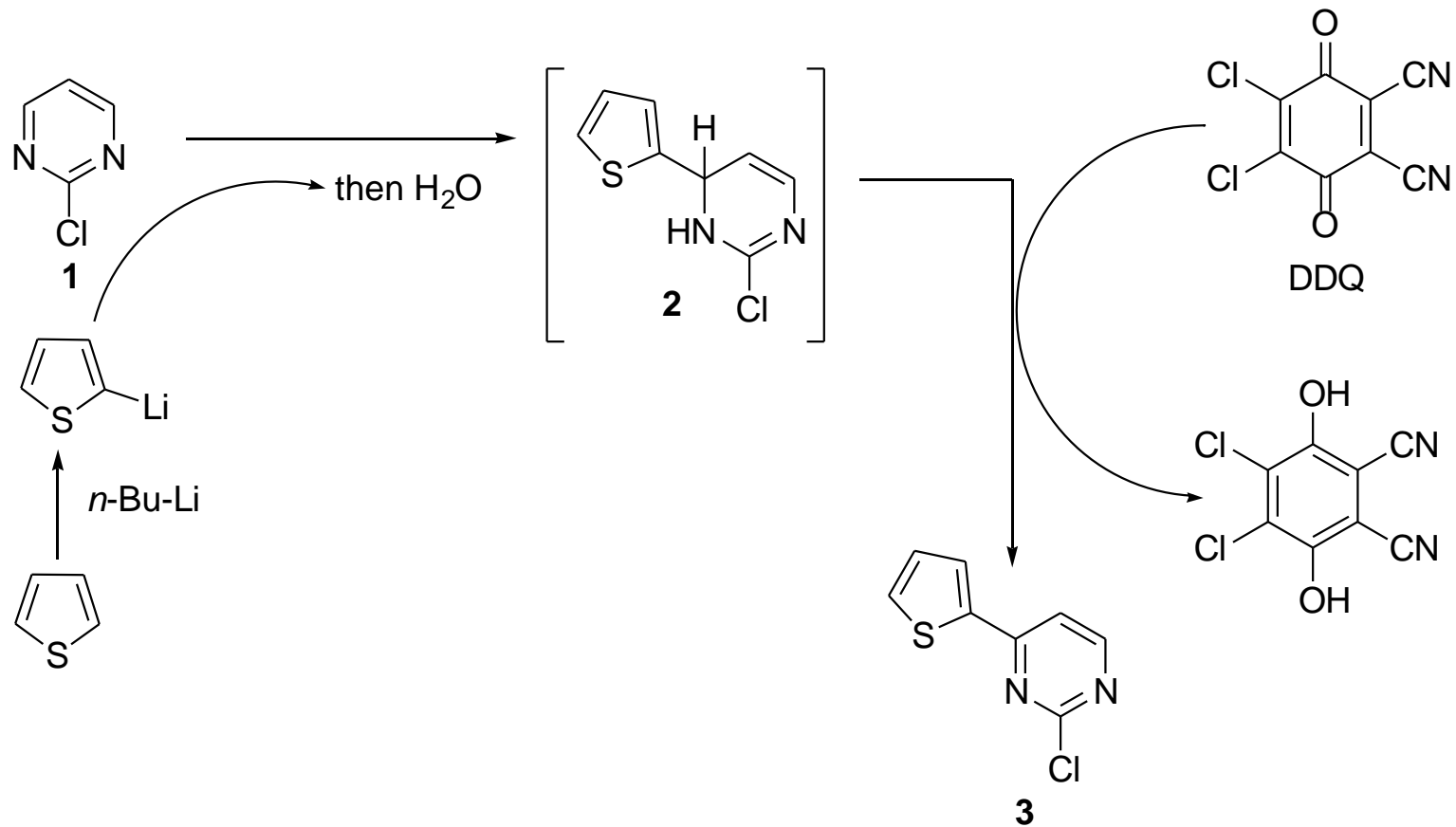
THF must be used below 0 °C. The following reaction occurs if the temperature is above °C:



# Titration of organolithium reagents



# Synthesis of 2-chloro-4-(2-thienyl)pyrimidine



# Synthesis of 3-butylcyclohexanone

