Cross-Coupling Reactions

Functionnalized Organometallic Reagents

C-N, C-O and C-S Bond Formation

Introduction to Organoboron Chemistry

Introduction to Organosilicon Chemistry

Carbometallation Reactions
Functionnalized Organometallic Reagents

Generalities

Organolithium Chemistry

Organomagnesium / Grignard Reagents

Organozinc Reagents

Organoalane Derivatives

Organoindium Chemistry

Organomanganese Reagents

Metallation with Sterically Hindered Bases
Functionnalized Organometallic Reagents

Generalities

Organometallic = C-M bond

Synthesis via

Deprotonation
Insertion
Exchange
Transmetallation

$R-M \xrightarrow{R'-X} R-R'$

$R-M \xrightarrow{R-X-R'} R'-X$

$R-X-M$

$R-M \xrightarrow{R-B(R')_2} R-X$

$R-Si(R')_3$

$R''-M \xrightarrow{R'-M} R-M$

$R-X \xrightarrow{R-M} R-X$

$R-M \xrightarrow{M^{(0)}} R-MX$

$R-X \xrightarrow{M'-X} R-M'$

$R-M \xrightarrow{-M-X} R-M'$
Functionnalized Organometallic Reagents

Organolithium Chemistry

Availability

- Li
- MeLi
- EtLi
- n-BuLi
- i-PrLi
- s-BuLi
- t-BuLi
- PhLi
Functionnalized Organometallic Reagents

Organolithium Chemistry

Preparation via Insertion

\[
\begin{align*}
R-\text{X} & \quad \text{R-M} \\
R-\text{Cl} & \quad \text{LiCl} \\
R-\text{Br} & \quad \text{LiBr} \\
R-\text{I} & \quad \text{LiI}
\end{align*}
\]

Primary Alkyl Lithium Reagents

\[
\begin{align*}
\text{Li} & \quad 80\% \text{ (from Cl, Br, I)} \\
\text{Li} & \quad 95\% \text{ (from Cl, Br)} \\
\text{Li} & \quad 90\% \text{ (from Cl)} \\
\text{Si-Li} & \quad 90\% \text{ (from Cl)} \quad \text{Solid at r.t.}
\end{align*}
\]

Solvent: \(\text{Et}_2\text{O, THF or PE}\)
**Functionnalized Organometallic Reagents**

Organolithium Chemistry

**Preparation via Insertion**

---

**Secondary Alkylithium Reagents**

- $\text{Li}$
  - 88% (from Br)

- $\text{Li}$
  - 70% (from Br)

- $\text{Li}$
  - 90% (from Br)

- $\text{Li}$
  - 50% (from Br)

**Tertiary Alkylithium Reagents**

- $\text{Li}$
  - 90% (from Br)

- $\text{Li}$
  - 51% (from Cl)

- $\text{Li}$
  - 82% (from Cl)
**Functionnalized Organometallic Reagents**

**Organolithium Chemistry**

*Preparation via Insertion*

**Alkenyllithium Reagents**

- \( \text{Li} \sim 80\% \text{ (from Cl)} \)
- \( \text{Li} \sim 75\% \text{ (from Br)} \)
- \( \text{Li} \sim 30\% \text{ (from Br)} \)
- \( \text{Li} \sim 40\% \text{ (from Cl)} \)

**Aryllithium Reagents**

- \( \text{Li} \sim 85\% \text{ (from Cl)} \)
- \( \text{Li} \sim 93\% \text{ (from Br)} \)
- \( \text{Li} \sim 87\% \text{ (from Br)} \)
- \( \text{Li} \sim 81\% \text{ (from Br)} \)
Functionnalized Organometallic Reagents

Organolithium Chemistry

Preparation via Insertion - Summary

- Usually working good on I / Br
- Cheaper but more difficult with Cl
- Alkenyl group are more difficult to react
- High degree of substitution leads to less reactivity
- Limited in group tolerance

\[
\begin{align*}
\text{R-M} & \quad \rightarrow \quad \text{R-R'} \\
\text{R'-X} & \\
\text{R-X-R'} & \quad \text{R-X-M} \\
\text{R-B(R')}_2 & \\
\text{R-Si(R')}_3 & \\
\text{R''-M} & \quad \text{R-} \quad \text{M} \\
\text{R} & \quad \text{R} & \quad \text{R'} \\
\text{NMe}_2 & \quad 0\% & \quad \text{Me}_2\text{N} & \quad 65\% \text{ (from Br)}
\end{align*}
\]
**Functionnalized Organometallic Reagents**

### Organolithium Chemistry

**Preparation via Permutation**

#### Missed discoveries

- **R-M** → **R-R'**
- **R'-X** → **R-M**
- **R-X-R'** → **R-X-M**
- **R-B(R')_2**
- **R-Si(R')_3**
- **R''-M** → **R-R'**

**Example 1**

![Chemical structure](image1)

\[ 	ext{Br} + n\text{-Bu-Li} \xrightarrow{\Delta} \text{Br} + n\text{-Bu-Li} + \text{LiBr} \]

76%

*C. S. Marvel et al. J. Am. Chem. Soc. 1927*

**Example 2**

![Chemical structure](image2)

\[ \text{Br} + R-Li \xrightarrow{r.t.} \text{R} + \text{LiBr} \]

*K. Ziegler et al. Liebig's Ann. Chem. 1929*
Functionnalized Organometallic Reagents

Organolithium Chemistry

Preparation via Permutation

Simultaneous Discovery


H. Gilman et al. J. Am. Chem. Soc. 1939
1. Aryl Fluorides DO NOT Undergo Exchange

2. Rates of Interchange Decrease from I > Br > Cl

3. Interchange is a Reversible Process that Leads to an Equilibrium Favoring the More Stable RLi
Functionnalized Organometallic Reagents

Organolithium Chemistry

Preparation via Permutation

Some Kinetics

<table>
<thead>
<tr>
<th>R</th>
<th>K_{obs}</th>
<th>pK_{a}</th>
<th>R</th>
<th>K_{obs}</th>
<th>pK_{a}</th>
<th>R</th>
<th>K_{obs}</th>
<th>pK_{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allyl Li</td>
<td>0.004</td>
<td>36.5</td>
<td>MeLi</td>
<td>3200</td>
<td>42</td>
<td>t-BuLi</td>
<td>3x10^5</td>
<td>42</td>
</tr>
<tr>
<td>PhLi</td>
<td>1.0</td>
<td>37</td>
<td>EtLi</td>
<td>7600</td>
<td>42</td>
<td>cyclohexylLi</td>
<td>1x10^6</td>
<td>43</td>
</tr>
<tr>
<td>BnLi</td>
<td>9.5</td>
<td>39</td>
<td>(H_3C)_2HCLi</td>
<td>4x10^4</td>
<td>42</td>
<td>cyclopentylLi</td>
<td>8x10^7</td>
<td>44</td>
</tr>
</tbody>
</table>
To summarize

1. Relative Stabilities of Carbanions:
   \( \text{sp} \gg \text{sp}^2 \gg \text{sp}^3 \)

2. The Less Hindered, the More Stable, the Less Reactive
Functionnalized Organometallic Reagents

Organolithium Chemistry

Preparation via Permutation

On the Mechanism – Still Being Discussed

Radical Process

$$\text{R-Li} \quad \text{SET} \quad \begin{array}{c} \text{R-Br} \text{R'-Li} \\ \text{R'-Br} \end{array} \leftrightarrow \begin{array}{c} \text{R', Br, R', Li} \\ \text{R', Li} \end{array} \rightarrow \text{R-Br} + \text{R'-Li}$$

Radical Ions  Caged Species

Ate-complex formation

$$\text{R-Li} + \begin{array}{c} \text{R-Br-R'} \text{Li} \\ \text{R'-Br} \end{array} \leftrightarrow \begin{array}{c} \text{R-Br} \text{R'-Li} \\ \text{R'-Li} \end{array}$$

Ate-complex
Functionnalized Organometallic Reagents

Organolithium Chemistry

Preparation via Permutation

On the Mechanism

\[
\begin{align*}
\left[ R, Br, R', Li^+ \right] \\
\text{competition} \\
\left[ R-Br-R' \right]^{\ominus} + \\
\left[ R-Br-R' \right]^{\ominus} + Li
\end{align*}
\]
**Functionnalized Organometallic Reagents**

**Organolithium Chemistry**

**Preparation via Permutation**

*Commonly Used Lithium Species for Li-X Exchange*

- t-BuLi
- s-BuLi
- n-BuLi
- MeLi

**General Rule**

\[ \text{Csp}^2-X + \text{Csp}^3-Li \rightleftharpoons \text{Csp}^2-Li + \text{Csp}^3-X \]
Functionnalized Organometallic Reagents

Organolithium Chemistry

Preparation via Permutation

Li-X Permutation of Alkyl-X Species

\[
\begin{align*}
\text{Br} & \quad \xrightarrow{\text{t-BuLi}} \quad \text{Li} & 91\% \\
\text{I} & \quad \xrightarrow{\text{t-BuLi}} \quad \text{Li} & 91\% \\
\text{I} & \quad \xrightarrow{\text{t-BuLi, -75°C}} \quad \text{Li} & 87\% \\
\text{n-hept} & \quad \xrightarrow{\text{t-BuLi, -50°C}} \quad \text{n-hept} & 91\% \\
\end{align*}
\]

Li-X Permutation of Alkenyl-X Species

\[
\begin{align*}
\text{Br} & \quad \xrightarrow{\text{t-BuLi, -115°C}} \quad \text{Li} & 74\% \\
\text{Br} & \quad \xrightarrow{\text{t-BuLi, 25°C}} \quad \text{Li} & 78\% \\
\text{n-hept} & \quad \xrightarrow{\text{t-BuLi, -75°C}} \quad \text{n-hept} & 83\% \\
\end{align*}
\]
Functionnalized Organometallic Reagents

Organolithium Chemistry

Li-X Permutation of Alkenyl-X Species

\[
\begin{align*}
R-M & \rightarrow R-R' \\
R'-X & \rightarrow R-M \\
R-X-R' & \rightarrow R-X-M \\
R-B(R')_2 & \rightarrow R-B(R')_2 \\
R-Si(R')_3 & \rightarrow R-Si(R')_3 \\
R''-M & \rightarrow R''-M
\end{align*}
\]

\[
\begin{align*}
\text{Li-X Permutation of Alkenyl-X Species} \\
& \text{Preparation via Permutation} \\
& \text{Retention of Configuration}
\end{align*}
\]

\[
\begin{align*}
\text{Li-X Permutation of Hetero-substituted Alkenyl-X Species} \\
& \text{Preparation via Permutation}
\end{align*}
\]

\[
\begin{align*}
\text{Retention of Configuration}
\end{align*}
\]
Functionnalized Organometallic Reagents

Organolithium Chemistry

\[ \text{Preparation via Permutation} \]

\[ R - \text{Li} \]

Li-X Permutation of Alkenyl-X Species - Selectivity

\[ \text{Minimisation of the Interaction} \]

Having a Coordinating Group

\[ \text{via} \]

\[ \left[ \begin{array}{c} \text{Br} \\ \text{Br} \\ \text{P(O)(OEt)}_2 \\ \text{Br} \\ \text{R} \\ \text{Li} \\ \text{P(O)(OEt)}_2 \\ \text{R} - \text{Li} \\ \end{array} \right] \]
**Functionnalized Organometallic Reagents**

Organolithium Chemistry

*Preparation via Permutation*

**Li-X Permutation of Aryl-X Species**

\[
\text{R-M} \rightarrow \text{R-R'}
\]

\[
\text{R-X-R'} \rightarrow \text{R-X-M}
\]

**Li-X Permutation of Heteroaryl-X Species**

\[
\text{Br-Cl} \rightarrow \text{Li} \quad \text{(80%)}
\]

\[
\text{Br-Cl} \rightarrow \text{Li} \quad \text{(54%)}
\]
Functionnalized Organometallic Reagents

Organolithium Chemistry

Preparation via Permutation

Li-X Permutation of Halogeno-Alkyl-X Species

\[
\begin{align*}
\text{I} & \quad \text{I} \\
\rightarrow & \quad n\text{-BuLi} \\
\quad & \quad \text{Li} \quad \text{I} \\
\quad & \quad -75^\circ\text{C} \\
\text{F} & \quad \text{F} \\
\text{CF}_3 & \quad \rightarrow \\
\quad & \quad n\text{-BuLi} \\
\quad & \quad \text{F} \quad \text{CF}_3 \\
\quad & \quad -40^\circ\text{C} \\
\text{I} & \quad \text{CBr}_3 \\
\rightarrow & \quad n\text{-BuLi} \\
\quad & \quad \text{Li} \quad \text{CBr}_3 \\
\quad & \quad -110^\circ\text{C} \\
\text{Cl} & \quad \text{Cl} \\
\text{Ph} & \quad \text{Ph} \\
\rightarrow & \quad n\text{-BuLi} \\
\quad & \quad \text{Ph} \quad \text{Ph} \\
\quad & \quad -100^\circ\text{C} \\
\text{Cl} & \quad \text{Cl}
\end{align*}
\]

Have Usually to Be Used in-situ at the Same Temperature

89%

54%

91%

75%
Functionnalized Organometallic Reagents

Organolithium Chemistry

Preparation via Deprotonation

Enolate Formation

Direct Deprotonation
**Functionnalized Organometallic Reagents**

**Organolithium Chemistry**

*Preparation via Deprotonation*

$\text{R-M} \rightarrow \text{R-R'}$

$\text{R'-X} \rightarrow \text{R-R'}$

$\text{R-M}$

$\text{R-X-R'}$

$\text{R-X-M}$

$\text{R-B(R')_2}$

$\text{R-Si(R')_3}$

$\text{R''-M}$

$\text{R-} \rightarrow \text{R'}$

$\text{R} \rightarrow \text{O}$

*To an oxygen ($\alpha-O$)*

**Tetrahedral System: Unfavoured**

$\text{R} \rightarrow \text{O} \rightarrow \text{R'}$

$\delta^+ \text{R} \rightarrow \text{O} \rightarrow \delta^- \text{R'}$

**The exception: Carbamates**

Stabilisation by Intramolecular Coordination

**Trigonal System: More Favoured**

$\text{R} \rightarrow \text{O} \rightarrow \text{R'}$

$\text{Li} \rightarrow \text{O} \rightarrow \text{R'}$

$n$-BuLi or $t$-BuLi

TMEDA
**Functionnalized Organometallic Reagents**

Organolithium Chemistry

Preparation via Deprotonation

\[ R - Li \]

\( \alpha \) to an oxygen (\( \alpha-O \))

\[
\begin{align*}
\text{OMe} & \quad \xrightarrow{t\text{-BuLi}} \\
\text{-65°C, THF} & \quad \xrightarrow{\text{OMe}} \\
\text{OMe} & \\
\text{O} & \\
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \xrightarrow{n\text{-BuLi}} \\
\text{0°C, Et}_2\text{O} & \quad \xrightarrow{\text{Li}} \\
\text{O} & \\
\text{Li} & \\
\end{align*}
\]

\[
\begin{align*}
\text{R}_3\text{SiO}_{\ldots} & \xrightarrow{t\text{-BuLi}} \\
\text{R}_3\text{SiO}_{\ldots} & \xrightarrow{\text{Li}} \\
\text{R}_3\text{SiO}_{\ldots} & \\
\end{align*}
\]

\[
\begin{align*}
\text{R}_3\text{SiO}_{\ldots} & \xrightarrow{\text{CO}_2} \\
\text{R}_3\text{SiO}_{\ldots} & \xrightarrow{\text{then H}^+} \\
\text{R}_3\text{SiO}_{\ldots} & \\
\end{align*}
\]

\[
\begin{align*}
\text{R}_3\text{SiO}_{\ldots} & \xrightarrow{\text{CO}_2} \\
\text{R}_3\text{SiO}_{\ldots} & \xrightarrow{\text{then H}^+} \\
\text{R}_3\text{SiO}_{\ldots} & \\
\end{align*}
\]
Functionnalized Organometallic Reagents

Organolithium Chemistry

Preparation via Deprotonation

$\alpha$ to an oxygen ($\alpha-O$) – Stabilization by Delocalization

$R-M \rightarrow R-R'$

$R'-X \rightarrow R-X-R'$

$R-X-M$

$R-B(R''_2)$

$R-Si(R''_3)$

$R''-M$

$R \rightarrow \rightarrow R'$

$R-M$

$n$-BuLi

$O$
Functionnalized Organometallic Reagents

Organolithium Chemistry

Preparation via Deprotonation

α to an oxygen (α-O) – Stabilization by Delocalization
Functionnalized Organometallic Reagents

Organolithium Chemistry

Preparation via Deprotonation

$\alpha$ to an oxygen ($\alpha$-O)- Stabilization by Coordination

(Zimmermann-Traxler)
Functionnalized Organometallic Reagents

Organolithium Chemistry

Preparation via Deprotonation

α to an oxygen (α-O)- Stabilization by Coordination

\[ R - M \rightarrow R - R' \]
\[ R' - X \rightarrow R - R' \]
\[ R - M \]
\[ R - X - R' \]
\[ R - X - M \]
\[ R - B(R')_2 \]
\[ R - Si(R')_3 \]
\[ R'' - M \]

\[ \text{s-BuLi, TMEDA, -95°C, THF} \]

\[ \text{D}_2\text{O} \]

\[ \text{Metallic Electrophile} \]
**Functionnalized Organometallic Reagents**

Organolithium Chemistry

**Preparation via Deprotonation**

α to an oxygen (α-O) – Case of Cyclic Ethers

\[ \text{O} \quad \overset{\text{R'-Li}}{\longrightarrow} \quad \text{O} - \text{Li} \quad \text{usually decomposition} \]

\[ \text{O} \quad \overset{s-\text{BuLi, (-)-spartein}}{\longrightarrow} \quad \text{O} - \text{Li} \]

\[ \text{R} - \text{Li} \quad \text{D}_{2}\text{O} \quad 70\% \]

\[ \text{R} - \text{Li} \quad \text{Me}_{3}\text{SiCl} \quad \text{SiMe}_{3} \]
**Functionnalized Organometallic Reagents**

**Organolithium Chemistry**

\[ R-M \rightarrow R-R' \]
\[ R'-X \rightarrow R-X-R' \]
\[ R-X-M \]
\[ R-B(R')_2 \]
\[ R-Si(R')_3 \]
\[ R''-M \rightarrow R-R' \]

**Preparation via Deprotonation**

\[ R-Li \]

\[ \alpha \text{ to a nitrogen (} \alpha-N \text{)} \]

**Destabilising Effect – Worse than Oxygen**

**Stabilising Effect**

**Dipole-Stabilised Carbanions**
**Functionnalized Organometallic Reagents**

**Organolithium Chemistry**

*Preparation via Deprotonation*

\[ R-M \rightarrow R-Li \]

\[ R'-X \rightarrow R-R' \]

\[ R-\text{B}(R')_2 \]

\[ R-\text{Si}(R')_3 \]

\[ R''-M \rightarrow R-R' \]

\[ \alpha \text{ to a nitrogen (}\alpha-N\text{)} – Case of Amides \]

\[ R-\text{Si}(R')_3 \rightarrow n-\text{BuLi} \rightarrow \text{Ar-CHO} \rightarrow \]

**Azetine Core**

**Pyrrolidine Core**

**Oxazolidine Core**
Functionnalized Organometallic Reagents

Organolithium Chemistry

Preparation via Deprotonation

α to a nitrogen (α-N) – Case of Amides

Primary Alkyl-lithium More Stable than Secondary Alkyl-lithium

Benzylic Position = More Easy to Deprotonate
Functionnalized Organometallic Reagents

Organolithium Chemistry

Preparation via Deprotonation

$\alpha$ to a nitrogen ($\alpha$-N) – Case of Secondary Amides

\[ \text{R-M} \quad \rightarrow \quad \text{R-R'} \]

\[ \text{R'-X} \quad \rightarrow \quad \text{R-R'} \]

\[ \text{R-M} \]

\[ \text{R-X-R'} \quad \rightarrow \quad \text{R-R'} \]

\[ \text{R-X-M} \]

\[ \text{R-B(R')}_2 \]

\[ \text{R-Si(R')}_3 \]

\[ \text{R''-M} \quad \rightarrow \quad \text{R-R'} \]

\[ \text{R} \quad \text{Li} \]

\[ \text{Preparation via Deprotonation} \]

\[ \text{2 x LDA} \quad -78^\circ \text{C} \]

\[ \text{Bul} \]

\[ 95\% \]

\[ 77\% \]
**Functionnalized Organometallic Reagents**

**Organolithium Chemistry**

*Preparation via Deprotonation*

$R-M \rightarrow R-R'$

$R'-X \rightarrow R-X-R'$

$R-X-R'$

$R-X-M$

$R-B(R')_2$

$R-Si(R')_3$

$R''-M$

$R \equiv R'$

*α to a nitrogen (α-N)*

$n$-BuLi

-78°C

*α-lithiation at benzylic sites outpaces enolisation*
**Functionnalized Organometallic Reagents**

**Organolithium Chemistry**

**Preparation via Deprotonation**

1. $t$-BuLi

2. $\text{Br}$

$\alpha$ to a nitrogen ($\alpha$-N)

Pyridinone Core
Functionnalized Organometallic Reagents

Organolithium Chemistry

Preparation via Deprotonation

$\alpha$ to a nitrogen ($\alpha$-N) – 5-membered N-Heterocycles

\[ R - M \rightarrow R - R' \]

\[ R' - X \rightarrow R - R' \]

\[ R - M \]

\[ R - X - R' \]

\[ R - X - M \]

\[ R - B(R')_2 \]

\[ R - Si(R')_3 \]

\[ R'' - M \]

\[ R - \cdots - R' \]

\[ n\text{-BuLi} \]

\[ -78^\circ C \]

\[ \text{Ph} \]

\[ \text{OH} \]

78%

\[ R' - OR \]

\[ n\text{-BuLi} \]

\[ -78^\circ C \]

\[ E^+ \]

\[ \text{HCl} \]

\[ \text{O} \]

\[ R' - \text{E} \]
Functionnalized Organometallic Reagents

Organolithium Chemistry

Preparation via Deprotonation

α to a nitrogen (α-N) – Lithiation of Formamidines

Stabilising Effect

Dipole-Stabilised Carbanions

MeOH, H⁺
or N₂H₄

NaBH₄
Functionnalized Organometallic Reagents

Organolithium Chemistry

Preparation via Deprotonation

α to a nitrogen (α-N) – Lithiation of Formamidines
Functionnalized Organometallic Reagents

Organolithium Chemistry

Preparation via Deprotonation

\[ \alpha \text{ to a nitrogen (} \alpha\text{-N)} \] – Lithiation of Nitrosoamines

\[ R-M \rightarrow R-R' \]

\[ R-X-R' \]

\[ R-X-M \]

\[ R-B(R')_2 \]

\[ R-Si(R')_3 \]

\[ R''-M \]

\[ R \rightarrow R' \]

\[ n-\text{BuLi} \]

\[ E^+ \]

\[ \text{Ni-Raney} \]

\[ R-NH_2 \]
Functionnalized Organometallic Reagents

Organolithium Chemistry

Preparation via Deprotonation

α to a nitrogen (α-N) – Lithiation of Nitrosoamines
Functionnalized Organometallic Reagents

Organolithium Chemistry

Preparation via Deprotonation

α to a nitrogen (α-N) – Lithiation of Imines and Hydrazones
Functionnalized Organometallic Reagents

Organolithium Chemistry

Preparation via Deprotonation

α to a nitrogen (α-N) – Lithiation of N-Oxides and Amine-Boron Complexes
**Functionnalized Organometallic Reagents**

- **Organolithium Chemistry**
  - Preparation via Deprotonation
  - α to a sulfur (α-S)

**Dithiane Chemistry**

- Stabilising Effect
  - Interaction with C-S σ*

**Examples**:
- R-M → R-R'
- R'-X
- R-X-R'
- R-X-M
- R-B(R')₂
- R-Si(R')₃
- R''—M
- R—R'
**Functionnalized Organometallic Reagents**

**Organolithium Chemistry**

*Preparation via Deprotonation*

α to a sulfur (α-S) – Lithiation of Thioethers

\[
\begin{align*}
\text{R-M} & \rightarrow \text{R-R'} \\
\text{R'-X} & \rightarrow \text{R-M} \\
\text{R-X-R'} & \rightarrow \text{R-X-M} \\
\text{R-B(R')}_2 & \rightarrow \text{R'-X} \\
\text{R-Si(R')}_3 & \rightarrow \text{R-M} \\
\text{R''-M} & \rightarrow \text{R-R'}
\end{align*}
\]

\[
\text{\textbf{R-Li}}
\]

\[
\begin{align*}
\text{Ph-S} & \rightarrow n-BuLi \\
\text{DABCO} & \rightarrow \text{THF} \\
0^\circ \text{C} & \rightarrow 97\%
\end{align*}
\]

\[
\begin{align*}
\text{O} & \text{O} \\
\text{SPh} & \rightarrow n-BuLi \\
\text{Li} & \rightarrow E^+ \\
\text{O} & \text{O} \\
\text{SPh} & \rightarrow \text{E}
\end{align*}
\]
Functionnalized Organometallic Reagents

Organolithium Chemistry

 Preparation via Deprotonation

$\alpha$ to a sulfur ($\alpha$-S) – Lithiation of Allyl Sulfides

$\text{PhS} = \text{Li} \rightarrow \text{PhS} = \text{E} \text{R^1}$

Retention of Configuration

Double Stabilisation
**Functionnalized Organometallic Reagents**

**Organolithium Chemistry**

**Preparation via Deprotonation**

α to a sulfur (α-S) – Synthesis of Thiiranes

\[
R - M \rightarrow R - R' \\
R' - X \rightarrow R - X - R' \\
R - X - M \\
R - B(R')_2 \\
R - Si(R')_3 \\
R'' - M \\
R - R' \\
R - Li
\]

\[
\begin{align*}
\text{O} & \quad \text{N} \\
\text{S} & \quad \text{Li}
\end{align*}
\]

\[n-\text{BuLi}\]

\[\text{PhCHO}\]

\[\text{Thiiran}\]

\[\text{Thiiranone}\]

\[\text{Thiirane}\]
**Functionnalized Organometallic Reagents**

**Organolithium Chemistry**

**Preparation via Deprotonation**

\[ R-M \rightarrow R-Li \]

\[ R-X-R' \rightarrow R-X-M \]

\[ R-B(R')_2 \]

\[ R-Si(R')_3 \]

\[ R''-M \rightarrow R-R' \]

\[ \alpha \text{ to a sulfur (}\alpha-S\text{)} – Lithiation of Thiophenes \]

If $\alpha$-S Lithiation is possible, Lithiation Reaction $\alpha$ to Se Remains Impossible

\[
\begin{align*}
\text{Thiophene} & \xrightarrow{n\text{-BuLi}} \text{Thiophene-Li} \quad \text{O} \\
\text{Thiophene-Li} & \rightarrow \text{Thiophene-OH}
\end{align*}
\]
Functionnalized Organometallic Reagents

Organolithium Chemistry

Preparation via Deprotonation

\[ \text{R-M} \rightarrow \text{R-R'} \]

\[ \text{R-X-R'} \rightarrow \text{R-X-M} \]

\[ \text{R-B(R')}_2 \]

\[ \text{R-Si(R')}_3 \]

\[ \text{R''-M} \rightarrow \text{R-R'} \]

\[ n-\text{BuLi} \quad \text{TMEDA} \]

\[ n-\text{BuLi} \quad \text{HMPA} \]

\[ \text{Me}_2\text{N} \quad \text{NMe}_2 \quad \text{TMEDA} \]

\[ \text{Me}_2\text{N-P} \quad \text{NMe}_2 \quad \text{HMPA} \]

\[ \text{Si} \quad \downarrow \quad \text{Li} \quad \text{Li} \]

\[ \alpha \text{ to a Silicon (\(\alpha\)-Si)} \]
Functionnalized Organometallic Reagents

Organolithium Chemistry

\[ R-M \rightarrow R-R' \]

Ortholithiation

Preparation via Deprotonation

\[ R-Li \]

\[ R-X-R' \]

\[ R-X-M \]

\[ R-B(R')_2 \]

\[ R-Si(R')_3 \]

Basic works

What Will Affect the Selectivity?

\[ \text{Benzene} \quad n-\text{BuLi}\quad \text{TMEDA, 25°C} \quad \text{Li} \]

92%
Functionnalized Organometallic Reagents

Organolithium Chemistry

Preparation via Deprotonation

Ortholithiation - A Comparison

Softer Bases

Stronger Base

Electronically Stabilised

Ortholithiation
**Functionnalized Organometallic Reagents**

**Organolithium Chemistry**

**Preparation via Deprotonation**

**Ortholithiation**

\[ R-M \rightarrow R-R' \]

\[ R'-X \rightarrow R-M \]

\[ R-X-R' \]

\[ R-X-M \]

\[ R-B(R')_2 \]

\[ R-Si(R')_3 \]

\[ R''-M \rightarrow R \rightarrow R' \]

\[ n-BuLi \rightarrow O \]

\[ 0^\circ C \]

**Chemical Structures:**

- Benzyl Alcohol
- Benzylamine

**Equations:**

\[ \text{Benzyl Alcohol} \rightarrow \text{Benzyl Lithium} \]

\[ \text{Benzylamine} \rightarrow \text{Benzyl Lithium} \]
**Functionnialized Organometallic Reagents**

Organolithium Chemistry

**Preparation via Deprotonation**

\[
R - M \quad R' - X \quad R - R' \\
R - M \\
R - X - R' \\
R - X - M \\
R - B(R')_2 \\
R - Si(R')_3 \\
R'' - M \\
R \quad R' \\
\]

more electronegative than N

more acidic

less acidic

less Lewis-acidic, decreased coordination effect

more Lewis-basic than O

\[
\text{less Lewis-acidic, decreased coordination effect} \\
\]

\[
n\text{-Bu-Li.TMEDA} \\
n\text{-Bu-Li coordination to the best Lewis-base} \\
\]

\[
\text{n-Bu-Li} \\
\text{n-BuLi.TMEDA} \\
\]

\[
R - Li \\
\]

\[
O \quad n\text{-BuLi} \quad n\text{-BuLi.TMEDA} \\
\]

\[
\text{Li} \\
\]
Functionnalized Organometallic Reagents

Organolithium Chemistry

Preparation via Deprotonation

Ortholithiation – Classes of Ortho-Directing Group

**Oxazolines**

\[
\text{Oxazolines} \quad \xrightarrow{n-\text{BuLi}} \quad \text{Oxazolines-Li}
\]

\[
\begin{align*}
\text{Oxazolines} & \quad \text{Oxazolines-Li} \\
\text{at } -50^\circ \text{C} & \\
\end{align*}
\]

**Sulfonamides**

\[
\text{Sulfonamides} \quad \xrightarrow{n-\text{BuLi}} \quad \text{Sulfonamides-Li}
\]

\[
\begin{align*}
\text{Sulfonamides} & \quad \text{Sulfonamides-Li} \\
\text{at } -50^\circ \text{C} & \\
\end{align*}
\]
Functionnalized Organometallic Reagents

Organolithium Chemistry

Preparation via Deprotonation

Ortholithiation – Classes of Ortho-Directing Group

- 3\textsuperscript{ν} amides
- sulfones
- sulfonamides
- oxazolines
- MOM-ether
- ether
- halogen
- alkoxide
- 2\textsuperscript{ν} amides
- sulfoxides
- 2\textsuperscript{ν} sulfonamides
- imines
- N-carbamates
- anilines
- trifluoromethyl
- amines
Functionnalized Organometallic Reagents

Organolithium Chemistry

Preparation via Deprotonation

Ortholithiation – All there is to know

\[ R-M \rightarrow R-R' \]

\[ R'-X \rightarrow R-M \]

\[ R-X-R' \]

\[ R-X-M \]

\[ R-B(R')_2 \]

\[ R-Si(R')_3 \]

\[ R''-M \]

\[ R-R' \]

\[ R-Li \]
Functionnalized Organometallic Reagents

Organolithium Chemistry

Preparation via Deprotonation

Ortholithiation - Exemples

1. B(OMe)_3
2. H_2O_2
3. TBDMS-Cl

1. n-BuLi
2. TMEDA
THF, -100°C

O
Li

75%

n-BuLi
TMEDA
Et_2O, -100°C

90%
Functionnalized Organometallic Reagents

Organolithium Chemistry

Preparation via Deprotonation

Ortholithiation - Exemples

R-M → R-R'

R'-X

R-M

R-X-R'

R-X-M

R-B(R')₂

R-Si(R')₃

R''-M

R-→-R'

MeO-Br 1. n-BuLi 2. ClPPh₂ 3. H₂O₂

MeO-Li 1. n-BuLi 2. ClPPh₂ 3. H₂O₂

MeO-PPh₂

MeO-PPh₂

induction effect

coordination effect
Functionnalized Organometallic Reagents

Organolithium Chemistry

Preparation via Deprotonation

Ortholithiation - Exemples

Lithium-sulfoxide Exchange
Functionnalized Organometallic Reagents

Organolithium Chemistry

Preparation via Deprotonation

Ortholithiation - Exemples

R-M → R-R'

R'-X → R-R'

R-X-R'

R-X-M

R-B(R')_2

R-Si(R')_3

R''-M

R-R'

R-M

R-M → R-R'

R'-X → R-R'

R-X-R'

R-X-M

R-B(R')_2

R-Si(R')_3

R''-M

R-R'

Ortholithiation - Exemples

LDA

THF

-75°C

RCHO

OH

R

LDA

THF

-75°C

LDA

THF

-75°C

80%
Functionnalized Organometallic Reagents

Organolithium Chemistry

Preparation via Deprotonation

Ortholithiation - Examples

R-M → R-R'
R'-X → R-X-R'
R-X-M → R-B(R')₂
R-Si(R')₃ → R-Si(R')₃
R''-M → R-''-R'

1. s-BuLi
   -78°C
2. RCHO

MeSO₃H
MeOH
5 min, Δ

n-BuLi

Me₃SiCl

98%

1. n-BuLi
   2. Me

95%
Functionnalized Organometallic Reagents

Organolithium Chemistry

Preparation via Deprotonation

Ortholithiation - Exemples
Functionnalized Organometallic Reagents

Organolithium Chemistry

Preparation via Deprotonation

Ortholithiation - Exemples

R-M → R-R'
R'-X → R-R'
R-M

R-X-R'
R-X-M

R-B(R')₂

R-Si(R')₃

R''—M

R—M

n-BuLi

16%

14%

n-BuLi

n-BuLi

Ph

Ph

70%
Functionnalized Organometallic Reagents

Organolithium Chemistry

Preparation via Deprotonation

Lateral Lithiation

Ortholithiation VS Lateral Lithiation

- Coordination Effect
- Inductive Electron Withdrawal

- Coordination Effect
- Conjugation
Functionnalized Organometallic Reagents

Organolithium Chemistry

Preparation via Deprotonation

Lateral Lithiation

Can be Seen as an Extended Enolisable System
Functionnalized Organometallic Reagents

Organolithium Chemistry

Preparation via Deprotonation

R - Li

Lateral Lithiation

Amides

R-M

R'-X

R-M

R-X-R'

R-X-M

R-B(R')₂

R-Si(R')₃

Nitriles

R''-M

R-R'
**Functionnalized Organometallic Reagents**

**Organolithium Chemistry**

*Preparation via Deprotonation*

**Lateral Lithiation**

**Carboxylates**

\[ \text{R-M \rightarrow R-R'} \]

\[ \text{R'-X \rightarrow R-R'} \]

\[ \text{R-M} \]

\[ \text{R-X-R'} \]

\[ \text{R-X-M} \]

\[ \text{R-B(R')}_2 \]

\[ \text{R-Si(R')}_3 \]

\[ \text{R''-M} \]

\[ \text{R-\( \equiv \)-R'} \]

**Esters**

\[ \text{R-M} \]

\[ \text{R-X-R'} \]

\[ \text{R-X-M} \]

\[ \text{R-B(R')}_2 \]

\[ \text{R-Si(R')}_3 \]

\[ \text{R''-M} \]

\[ \text{R-\( \equiv \)-R'} \]
Functionnalized Organometallic Reagents

Organolithium Chemistry

Preparation via Deprotonation

\[ R-M \rightarrow R-R' \]

\[ R'-X \rightarrow R-M \]

\[ R-X-R' \]

\[ R-X-M \]

\[ R-B(R')_2 \]

\[ R-Si(R')_3 \]

\[ R''-M \rightarrow R-R' \]

Lateral Lithiation

Enolisable Ketones

Non-Enolisable Ketones

\[ \text{Enolisable Ketones} \]

\[ \text{Non-Enolisable Ketones} \]

\[ \text{Preparation via Deprotonation via Deprotonation} \]

\[ 2 \times n-\text{BuLi} \quad \text{TMEDA} \]

\[ \text{LDA} \quad \text{THF, } -78^\circ \text{C} \]

\[ \text{Me}_3\text{SiCl} \]

\[ 85\% \]

\[ 94\% \]
Functionnalized Organometallic Reagents

Organolithium Chemistry

Preparation via Deprotonation

Lateral Lithiation

Remote Amine

Methoxy

Only Possibility
Functionnalized Organometallic Reagents

Organolithium Chemistry

Preparation via Deprotonation

Schlosser’s Base – « Superbase »

Known as LiKOR

Li-C + K-OR

Mixture of

\[ n\text{-BuLi} + \text{OK} \]

\[ \text{R-B(R')}_2 \]

\[ \text{R-Si(R')}_3 \]

\[ \text{R'' - M} \]

\[ \text{R - R'} \]

\[ \text{R' - X} \]

\[ \text{R-M} \]

\[ \text{R-X-R'} \]

\[ \text{R-X-M} \]

\[ \text{R-M} \rightarrow \text{R-R'} \]

\[ \text{R-Li} \]
Functionnalized Organometallic Reagents

Organolithium Chemistry

Preparation via Deprotonation

Schlosser’s Base – « Superbase »

\[ \text{R-M} \rightarrow \text{R-R'} \]

\[ \text{R-X-R'} \]

\[ \text{R-X-M} \]

\[ \text{R-B(R')_2} \]

\[ \text{R-Si(R')_3} \]

\[ \text{R''-M} \]

\[ \text{R} \]

\[ \text{F} \]

\[ n-\text{BuLi} \]

\[ \text{KOT-Bu} \]

\[ \text{F} \text{Li/K} \]

\[ \text{CF}_3 \]

\[ n-\text{BuLi} \]

\[ \text{KOT-Bu} \]

\[ \text{CF}_3 \text{Li/K} \]
Functionnalized Organometallic Reagents

Organolithium Chemistry

Preparation via Deprotonation

Schlosser’s Base – « Superbase »

Metallates Preferentially Next to Powerful Electron-Withdrawing Groups
**Functionnalized Organometallic Reagents**

Organolithium Chemistry

*Preparation via Deprotonation*

**Schlosser’s Base – « Superbase »**

\[ R-M \rightarrow R-R' \]

\[ R-X-R' \]

\[ R-X-M \]

\[ R-B(R')_2 \]

\[ R-Si(R')_3 \]

\[ R''-M \]

\[ R-R' \]

\[ n-C_9H_{19} \quad \text{t-BuLi, \ KOT-Bu} \quad \rightarrow \quad n-C_9H_{19} \quad \text{Li/K} \]

1. FB(OMe)_2
2. H_2O_2

\[ \rightarrow \quad n-C_9H_{19} \quad \text{OH} \quad 57\% \]

\[ \quad \quad \text{Li/K} \quad \quad \text{CO}_2 \quad \rightarrow \quad \quad \text{COOH} \quad 78\% \]
Functionnalized Organometallic Reagents

Organolithium Chemistry

Preparation via Deprotonation

Schlosser’s Base – « Superbase »
Functionnalized Organometallic Reagents

Organolithium Chemistry

Preparation via Deprotonation

Schlosser’s Base – « Superbase »

R-M → R-R'

R-X-R'

R-X-M

R-B(R')_2

R-Si(R')_3

R''-M

R- Li

t-BuLi KOt-Bu → t-BuLi KOt-Bu

KOT-Bu

Mel

Me

Me

Me

Me

i-Pr

CO₂H

i-Pr
Functionnalized Organometallic Reagents
Organolithium Chemistry

Preparation via Deprotonation

Schlosser's Base – « Superbase »
Functionnalized Organometallic Reagents

Organolithium Chemistry

Preparation via Deprotonation

Stereoselective Formation of Organolithiums – Without Coordinating Group

99% ee

Fast racemisation

-70°C, 2 min

0°C, 20 min

20% ee

raccemic

Complete Retention
Even at 0°C
**Functionnalized Organometallic Reagents**

**Organolithium Chemistry**

*Preparation via Deprotonation*

**Stereoselective Formation of Organolithiums – Without Coordinating Group**

**Diagram:**

- **R-M → R-R'**
- **R-X-R' → R-X-M**
- **R-B(R')₂**
- **R-Si(R')₃**
- **R''-M → R-R'**

**Reagents:**

- OTBDMS
- t-BuLi
- Bu₂S₂

**Examples:**

- **OTBDMS:**
  - Syn / anti 96 : 4
  - -100°C 5 min

- **OTBDMS:**
  - Syn / anti 95 : 5

- **OTBDMS:**
  - Syn / anti 96 : 4
  - -100°C 10 sec.
**Functionnalized Organometallic Reagents**

**Organolithium Chemistry**

**Preparation via Deprotonation**

**Stereoselective Formation of Organolithiums – With Stabilising Effect**

\[ \text{R-M} \rightarrow \text{R-R'} \]

\[ \text{R'-X} \rightarrow \text{R-R'} \]

\[ \text{R-M} \]

\[ \text{R-X-R'} \]

\[ \text{R-X-M} \]

\[ \text{R-B(R')}_2 \]

\[ \text{R-Si(R')}_3 \]

\[ \text{R''-M} \]

\[ \text{R-R'} \]

\[ \text{SnBu}_3 \]

\[ n-\text{BuLi} \]

\[ \text{TMEDA} \]

\[ -78^\circ \text{C} \]

\[ \text{Me} \]

\[ 96\% \text{ ee} \]

\[ \text{Me} \]

\[ 96\% \text{ ee} \]

**Stable for 2.5 h**

\[ \text{Stable for 1.5 h} \]
Functionnalized Organometallic Reagents

Organolithium Chemistry

Preparation via Deprotonation

Stereoselective Formation of Organolithiums – With Stabilising Effect

R-M → R-R'

R-X-R' → R-X-M

R-B(R')_2

R-Si(R')_3

R''-M → R-R'

R-M

R-X-R'

R-X-M

R-B(R')_2

R-Si(R')_3

R''-M → R-R'

Stable for 2.5 h

96% ee

Stable for 1.5 h

96% ee