Organolithium reagents as cross-coupling reaction partners

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Literature presentation
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Cross-coupling reactions

- Formation of new C-C bonds by combining two molecular fragments (electrophile-nucleophile)
  
  \[
  \text{RML} + \text{R'}-\text{X} \xrightarrow{\text{cat.}} \text{R-R'} + \text{MLX}
  \]

  \(\text{R}=\text{alkyl, aryl, vinyl}\)
  \(\text{R'}=\text{alkyl, aryl, vinyl}\)
  \(\text{M}=\text{B, Al, Zn, Sn, Si, Mg, Li}\)
  \(\text{cat.}=\text{Pd, Ni, Cu, Fe}\)
  \(\text{X}=\text{halide, triflate, tosylate, phosphonate, sulfonate}\)
  \(\text{L}=\text{halide, oxygen, organic ligand}\)

- Often catalysed by transition metals (Pd, Ni, Cu, Fe...), Pd most common:
  - Can promote reaction of less reactive partners (Ar-Cl)
  - Provides high turnover numbers (TONs) – suitable for large scale
  - Allows low T reactions

- Reaction optimisation:
  - Expand substrate scope
  - Lower catalyst loading
  - Functional group tolerance
  - Organocatalysis -(easier purification)
  - Green solvents

Cross-coupling reactions

• C-C bond formation key in the synthesis of natural products, pharmaceuticals, agrochemicals...

• Development of organic synthesis over the last three decades allowing access to complex structures

• Wide range of organic halides and organometallic reagents used but...

• ... organolithium reagents not used directly in cross-coupling due to:
  - High reactivity
  - Poor selectivity

Giannerini, M.; Fañanás-Mastral, M.; Feringa, B.L. *Nature*, **2013**, *5*, 667-672
Organometallic reagents

- B, Sn, Zn, Si, Mg...

- Organoboron and organotin compounds usually made from organolithium...

  ...Organolithium could be directly used instead!

- RLi:

<table>
<thead>
<tr>
<th>pros</th>
<th>cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Cheap</td>
<td>- Highly reactive</td>
</tr>
<tr>
<td>- Easy to access</td>
<td>- Homocoupled byproducts</td>
</tr>
<tr>
<td>(commercially or via X-Li</td>
<td>(X-Li exchange &gt;&gt; Pd-cat C-C formation)</td>
</tr>
<tr>
<td>exchange)</td>
<td></td>
</tr>
</tbody>
</table>

Giannerini, M.; Fañanás-Mastral, M.; Feringa, B.L. *Nature*, 2013, 5, 667-672
Selective cross-coupling with organolithium reagents

• Precedents
  - Murahashi and coworkers – high T, reflux

    \[
    \begin{align*}
    \text{R}_1 \text{C} &= \text{C} \quad 1 \text{ eq } \text{RLi} \\
    \text{R}_2 \text{X} \quad 10\% \text{ Pd (0)} & \rightarrow \quad \text{R}_1 \text{C} &= \text{C} \\
    & \quad \text{R}_2 \text{R}_3 \\
    \end{align*}
    \]

  - Yoshida and coworkers – flow microreactor

    \[
    \begin{align*}
    \text{Ar}_1 \text{X} \quad \text{BuLi} & \rightarrow \quad \text{Ar}_1 \text{Li} \\
    & \rightarrow \quad \text{Ar}_2 \text{X} \\
    & \rightarrow \quad \text{Ar}_1 \text{Ar}_2
    \end{align*}
    \]

• **2013** - First efficient catalytic cross-coupling of RLi reported by Feringa *et al.*


Giannerini, M.; Fañanás-Mastral, M.; Feringa, B.L. *Nature*, **2013**, 5, 667-672
Selective cross-coupling with organolithium reagents

\[ R^1-X + R^2-M \xrightarrow{\text{Transition metal catalyst}} R^1-R^2 \]

\( X = \text{halide or sulfonate} \)

Stille (M = Sn); Negishi (M = Zn); Suzuki-Miyaura (M = B);
Hiyama-Denmark (M = Si); Kumada (M = Mg).

\[ R^1-\text{Br} + R^2-\text{Li} \xrightarrow{\text{Pd catalyst}} R^1-R^2 \]

1 h
Room temperature
Selectivity >95%
High yield

\( R^1 = \text{alkenyl, aryl, heteroaryl} \)
\( R^2 = \text{alkyl, aryl, heteroaryl} \)

Selective cross-coupling with organolithium reagents

- Key: overcome fast Br-Li exchange
  - Pd catalyst design: promote OA, transmetallation and RE
  - Control reactivity of RLi: solvent choice
Selective cross-coupling with alkyllithium reagents

- Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd complex</th>
<th>Ligand</th>
<th>Reaction time (h)</th>
<th>Conversion (%)</th>
<th>2a:3:4:2x</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd$_2$(dba)$_3$, 2.5 mol%</td>
<td>XPhos, 10 mol %</td>
<td>3</td>
<td>Full</td>
<td>80:5:10:5</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>-</td>
<td>3</td>
<td>25</td>
<td>-:&gt;95:-:-</td>
</tr>
<tr>
<td>3</td>
<td>Pd$_2$(dba)$_3$, 2.5 mol%</td>
<td>-</td>
<td>3</td>
<td>22</td>
<td>23:48:29:-</td>
</tr>
<tr>
<td>4</td>
<td>Pd$_2$(dba)$_3$, 2.5 mol%</td>
<td>SPhos, 10 mol %</td>
<td>1</td>
<td>Full</td>
<td>89:5:6:-</td>
</tr>
<tr>
<td>5</td>
<td>Pd$_2$(dba)$_3$, 2.5 mol%</td>
<td>PdP(t-Bu)$_3$, 6 mol %</td>
<td>1</td>
<td>Full</td>
<td>90:6:4:-</td>
</tr>
<tr>
<td>6</td>
<td>Pd[P(t-Bu)$_3$]$_2$, 5 mol%</td>
<td>-</td>
<td>1</td>
<td>Full</td>
<td>96:4:-:-</td>
</tr>
<tr>
<td>7</td>
<td>Pd[P(t-Bu)$_3$]$_2$, 1 mol%</td>
<td>-</td>
<td>1</td>
<td>Full</td>
<td>95:4:1:-</td>
</tr>
</tbody>
</table>

Conditions: 1.2 equiv. n-BuLi (1.6 M solution in hexane diluted with toluene to a final concentration of 0.36 M) was added to a solution of 4-methoxy-bromobenzene (3 mmol) in toluene (2 ml).

Giannerini, M.; Fañanás-Mastral, M.; Feringa, B.L. *Nature*, **2013**, *5*, 667-672
Selective cross-coupling with alkyllithium reagents

- **Scope**

\[
\begin{align*}
\text{Ar–Br} & + \text{RLi} & \xrightarrow{\text{Pd}[\text{P}^3(\text{Bu})_3]_2 \ 5 \text{ mol}\%} & \text{Ar–R} \\
1 & & & 2
\end{align*}
\]

Toluene, r.t.

- 2a, 80%
- 2b, 88%
- 2c, 84%
- 2d, 92%
- 2e, 87%
- 2f, 83%
- 2g, 88%
- 2h, 90%
- 2i, 88%
- 2j, 94%
- 2k, 95%
- 2l, 93%
- 2m, 97%
- 2n, 93%
- 2o, 87%
- 2p, 91%
- 2q, 89%
- 2r, 99%
- 2s, 92%
- 2t, 61%
- 2u, 43%
- 2v, 75%
- 2w, 78%
- 2x, 89%
- 2y, 79%

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Selective cross-coupling with aryllithium reagents

- Conditions

1. Conditions: Pd[P(′Bu)₃]₂ 5 mol%, Pd₂(dba)₃ 2.5 mol%, P(′Bu)₃ 7.5 mol%
2. Conversion: 70%, Full
3. Ratio: 90:10, 98:2

Selective cross-coupling with aryllithium reagents

• Scope

\[
\text{Ar–Br} + \text{Ar}^\prime \text{Li} \xrightarrow{\text{Toluene, r.t.}} \text{Ar–Ar}^\prime
\]

1. Commercial

- 5a, 84% (93\%)\(^+\)
- 5b, 80%
- 5c, 85%
- 5d, 83%
- 5e, 89%

2. Halogen-lithium exchange

- 5f, 81\%\(^+\)
- 5g, 88\%\(^+\)
- 5h, 81\%\(^+\)
- 5i, 99\%\(^+\)
- 5j, 84%

3. Directed metatation

- 5k, 90%
- 5l, 75%
- 5m, 71%
- 5n, 80%

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Application of selective cross-coupling with organolithium reagents

- Aryl-alkyl coupling

- Aryl-aryl coupling

<table>
<thead>
<tr>
<th>Reported method</th>
<th>Feringa et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>M: SnBu₃ Pd(PPh₃)₄, 3 mol%, DMF, 90°C, 24h 73% yield</td>
<td>M: Li Pd₂(dba)₃, 2.5 mol%, P(‘Bu)₃, 7.5 mol% TMEDA (1.2 eq.), toluene, 40°C, 1h 85% yield</td>
</tr>
</tbody>
</table>

Shorter reaction times and milder conditions
No need to generate B, Sn reagents

Catalytic cross-coupling between organolithium reagents and aryl chlorides

- RLi and Ar-Cl coupling is challenging. Ar-Cl cheap, commercially available but have low reactivity
- Sterically hindered phosphines and NHCs most commonly used ligands for cross-coupling of Ar-Cl
- Feringa et al: new cross-coupling between Ar-Li and Ar-Cl reagents (RT: 40min-4h).

Summary

• Until now organolithium reagents have been unexplored as cross coupling partners due to their high reactivity and poor selectivity, with common side products (homocoupling, dehalogenation...)

• First fast, selective method for catalytic cross-coupling of alkyl, aryl and heteroaryl-lithium reagents with aryl bromides has been reported

• Direct cross-coupling between aryl chlorides and aryl, heteroaryl-lithium reagents has also been reported

• Wide functional group tolerance (RBr-RLi coupling: not nitriles and ketones but esters)

• Great applicability for C-C bond formation in medicinal chemistry and organic materials