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Synthesis of Unsymmetrical Heterobiaryls using Palladium-Catalyzed Cross-coupling Reactions of Lithium Organozincates

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Abstract: Several unsymmetrical heterobiaryls have been synthesized through palladium-catalyzed cross-coupling reactions of lithium triorganozincates. The latter have been prepared by deprotonative lithiation followed by transmetalation using non hygroscopic ZnCl2·TMEDA (1/3 equiv).

Key words: cross-coupling, heterocycle, metatation, palladium, zinc

The importance of heterobiaryls in natural products and pharmaceutical intermediates, and their unique properties have stimulated tremendous efforts for the development of synthetic methods in the area of aryl-aryl bond formation.1 Like the Suzuki-Miyaura2 and Stille3 reactions, the Negishi4 cross-couplings of organozincs and aryl halides offer the advantage of stable starting materials and thus are known to tolerate a large range of functional groups. Nevertheless, the latter become more attractive when heteroaryl boronic acids cannot be prepared; in addition, they do not use highly toxic starting materials.

The organozincs are in general prepared by treating the corresponding lithium or magnesium compounds with zinc chloride.5 Alternative methods employ zinc dust or active Rieke zinc (direct insertion).5,6 Electrochemical methods have also been considered.7

A major drawback of the Negishi coupling procedure lies in obtaining dry zinc chloride or zinc bromide. Mutule and Suma described in 2005 a sequential microwave assisted Grignard formation-transmetalation-Negishi one pot reaction using the less hygroscopic TMEDA-chelated zinc chloride.8 Gauthier and co-workers developed an approach through lithium zinicates using only one third equivalent of zinc chloride for the synthesis of 5-aryl-2-furaldehydes from 5-lithio-2-furaldehyde diethyl acetal.9 Miller and Farrell reported the use of a catalytic amount of zinc chloride to perform nickel- or palladium-catalyzed cross-couplings of aryl Grignard reagents with aryl halides.10

Other authors completely avoided the use of zinc halide by generating lithium zinicates either by iodine-metal exchange11 or by deprotonation.12 Herein, we report palladium-catalyzed reactions for which the lithium zinicate intermediates are generated by transmetalation of the corresponding lithio compounds using ZnCl2·TMEDA.

We first optimized the procedure for the cross-coupling of zinc compounds obtained from 2-lithiobenzofuran. Benzo[8]furan (I) was lithiated using butyllithium in tetrahydrofuran (THF) at −15 °C.13 Transmetalation was performed using 1:1, 3:1 and 4:1 benzfuryllithium/ZnCl2·TMEDA stoichiometries in order to generate the corresponding organozinc, lithium triorganozincate and dilium tetraorganozincate, respectively.

Nickel-catalyzed cross-couplings of organozinc compounds have been described.14 However, the toxicity of nickel salts led us to explore alternative routes.15

In 2002 Figadère16 and Fürstner17 separately reported iron-catalyzed aryl-heteroaryl cross-coupling reactions starting from aryl Grignard reagents and heteroaryl chlorides. The reactions proceed in good yields when carried out in THF at −30 °C using iron(III) acetylacetonate (Fe(acac)3). A magnesium trialkylzincate, Et2ZnMgBr, also proved to react with methyl 4-chlorobenzoate when the reaction was conducted similarly.17 Attempts to perform the reaction between benzfurylzinc chloride and 2,4-dichloropyrimidine in the presence of Fe(acac)3 under the same reaction conditions failed.

We thus turned to palladium-catalyzed reactions (Scheme 1, Table 1).18 Cross-coupling reactions of all the benzfurylzincs performed with 2,4-dichloropyrimidine at 55 °C in THF with catalytic amounts of palladium(II) chloride and 1,1′-bis(diphenylphosphino)ferrocene (dpff)19 provided the expected benzfurylpyrimidine 2a.20 Whereas a lower 44% yield was obtained with the higher order zinicate,21 similar results were shown using the organozinc and lithium triorganozincate (62% and 56% yields respectively). Other ligands such as triphenylphosphine (53%), tri(cyclohexyl)phosphine (30%), 1,3-bis(diphenylphosphino)propane (< 20%), and 1,4-bis(diphenylphosphino)butane (< 10%) were tested for the palladium-catalyzed reaction involving lithium tri(2-benzofuryl)zincate, which was preferred for stoichiometry efficiency, but proved less efficient than dpff.22

Scheme 1: a Using PPh3 (4 mol.%) instead of dpff. b Using PCy3 (4 mol.%) instead of dpff.
The pyridylbenzofuran \(2b\) was similarly obtained in 61% yield from 2-chloropyridine (Table 1, entry 2).

Table 1 Coupling Reactions of Lithium Triarylzincates with Heteroaryl Chlorides

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Base, conditions</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{BuLi, }-15 ^\circ\text{C, 1 h})</td>
<td>BuLi, THF, conditions</td>
<td>2a</td>
<td>56</td>
</tr>
<tr>
<td>2</td>
<td>(\text{BuLi, }-15 ^\circ\text{C, 1 h})</td>
<td>BuLi, THF, conditions</td>
<td>2b</td>
<td>61, 76*</td>
</tr>
<tr>
<td>3</td>
<td>(\text{BuLi, }-15 ^\circ\text{C, 1 h})</td>
<td>BuLi, THF, conditions</td>
<td>2c</td>
<td>61</td>
</tr>
<tr>
<td>4</td>
<td>(\text{BuLi, }-75 ^\circ\text{C, 1 h})</td>
<td>BuLi, THF, conditions</td>
<td>2d</td>
<td>61</td>
</tr>
<tr>
<td>5</td>
<td>(\text{BuLi, }-75 ^\circ\text{C, 1 h})</td>
<td>BuLi, THF, conditions</td>
<td>2e</td>
<td>81</td>
</tr>
<tr>
<td>6</td>
<td>(\text{BuLi, }-15 ^\circ\text{C, 1 h})</td>
<td>BuLi, THF, conditions</td>
<td>2f</td>
<td>56</td>
</tr>
<tr>
<td>7</td>
<td>(\text{BuLi, }-75 ^\circ\text{C, 1 h})</td>
<td>BuLi, THF, conditions</td>
<td>2g</td>
<td>85</td>
</tr>
<tr>
<td>8</td>
<td>(\text{LiTMP, }-75 ^\circ\text{C, 1 h})</td>
<td>BuLi, THF, conditions</td>
<td>2h</td>
<td>61</td>
</tr>
<tr>
<td>9</td>
<td>(\text{BuLi, }25 ^\circ\text{C, 2 h})</td>
<td>BuLi, THF, conditions</td>
<td>2i</td>
<td>64</td>
</tr>
<tr>
<td>10</td>
<td>(\text{LiTMP, }-75 ^\circ\text{C, 1 h})</td>
<td>BuLi, THF, conditions</td>
<td>2j</td>
<td>62</td>
</tr>
</tbody>
</table>

*Coupling step performed in the presence of DME (5 equiv). *Since 2,4-dichloropyrimidine rapidly reacts with air damp, lower yields can be partly attributed to the presence of pyrimidinone in the starting heteroaryl chloride.

Having optimized the conditions, various aromatic substrates were used in the deprotonation-transmetalation-coupling sequence using 2,4-dichloropyrimidine and/or 2-chloropyridine.

Furan (3) was similarly lithiated, subsequent transmetalation using ZnCl₂·TMEDA (1/3 equiv) and coupling with 2,4-dichloropyrimidine afforded the expected furylpyrimidine \(4\) (entry 3). Benzo[b]thiophene (5), thiophene (6) and 2-chlorothiophene (7), which were lithiated using butyllithium in THF at \(-75, -15\) and \(-75 ^\circ\text{C}\), respectively, gave the bis-heterocycles \(8a, 8b, 9a, 9b\) and \(10\) (entries 4-7). N-Boc pyrrole (11) was deprotonated upon treatment with lithium 2,2,6,6-tetramethylpiperidide (LiTMP) in THF at \(-75 ^\circ\text{C}\) to give the 2-pyridyl derivative \(12\) (entry 8) after subsequent transmetalation-coupling reactions. Anisole (13) was similarly ortho-functionalized\(^{35}\) to afford the 2-pyridyl derivative \(14\) (entry 9). The reaction also proved convenient for the functionalization of a \(\pi\)-deficient substrate, 2-fluoropyridine (15), which was converted to the bipyridine \(16\) (entry 10) after lithiation using LiTMP in THF at \(-75 ^\circ\text{C}\), followed by transmetalation and cross-coupling steps.

Since the addition of 1,2-dimethoxyethane (DME) to the reaction mixture proved to improve yields of Negishi cross-coupling products\(^{37}\), the palladium-catalyzed reaction between lithium tri(2-thienyl)zincate and 2-chloropyridine was performed in the presence of five equivalents of this cosolvent to give the pyridylbenzofuran \(2b\) in a slightly higher yield (76%, entry 2).

Nevertheless, even using these improved conditions, the coupling between the N,N-diethylbenzamide lithium zincate and 2-chloropyridine failed, a result probably due to the size of the diethylamide group.

In addition, when heteroaryl chlorides were replaced by phenyl chlorides the reactions also failed, even in the presence of electron-withdrawing groups at the phenyl 4-position. We therefore turned to the corresponding bromides\(^{38}\) which have lower carbon-halogen bond dissociation energies\(^{39}\) and investigated the access to functionalized 2-phenylthiophenes (Scheme 2).

The reaction of lithium tri(2-thienyl)zincate with 4-bromoanisole afforded the expected coupling product \(9b\) but in a poor 10% yield due to the competitive formation of 2,2′-bithiophene (40-50% yield). With bromobenzenes containing electron-withdrawing groups at the 4-position, such as 2-bromo-4-nitrobenzene, methyl 4-bromobenzoate and 4-bromobenzonitrile, the expected derivatives \(9c, 9d, 9e\) were obtained.
9d\textsuperscript{42} and 9e\textsuperscript{43} were isolated in yields ranging from 38 to 79%.

Since 2-chloropyridine and, above all, 2,4-dichloropyrimidine are \(\pi\)-deficient chloro substrates, a reaction mechanism involving a nucleophile aromatic substitution by an aryl group was suspected (Scheme 3, left). However, this was discarded since the reaction between lithium tri(2-benzofuryl)zincate and 2,4-dichloropyrimidine performed without catalyst did not allow the cross-coupling product 2a to be formed. A mechanism involving an addition-elimination of an organopalladate as first step can be proposed alternatively (Scheme 3, right) though this is unlikely if one considers the poor reactivity of 2,4-dichloropyrimidine towards an arylzincate.\textsuperscript{44}

A more classical pathway is an oxidative addition of 2,4-dichloropyrimidine to a Pd(0) complex followed by transmetalation by the nucleophile (Scheme 4, right). However, the oxidative addition could take place either at the 2- or 4- position. To test the regioselectivity of the oxidative addition, the reaction of 2,4-dichloropyrimidine (0.01 mmol) with Pd(PPh\textsubscript{3})\textsubscript{4} (0.01 mmol) was followed by \(^1\)H NMR (250 MHz, TMS) and \(^{31}\)P NMR (101 MHz, \(\text{H}_2\text{PO}_4\)) in CD\textsubscript{2}Cl\textsubscript{2} at 27 °C. Two \(^1\)H signals of equal magnitude at 6.73 ppm (dt, \(J_{HH} = 5.1\) Hz, \(J_{PH} = 1.2\) Hz, \(H_2\)) and 6.58 ppm (d, \(J_{HH} = 5.1\) Hz, \(H_3\)) associated to a \(^{31}\)P singlet at 22.0 ppm characterized the formation of complex 17 by oxidative addition at the 4-position, in agreement with the regioselectivity observed in the catalytic reactions. It should be noted that the presence of a lithium zincate could also allow the formation of an arylpalladate ArPd(0)L\textsubscript{2},\textsuperscript{45} which could regioselectively react with 2,4-dichloropyrimidine by oxidative addition as depicted in Scheme 4 (left).

\begin{center}
\textbf{Scheme 3} Ligands are omitted for clarity.
\end{center}

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\end{center}

In conclusion, we have described the synthesis of unsymmetrical heterobiaryls using palladium-catalyzed cross-coupling reactions of lithium triorganozincates, which have been prepared through one pot deprotonative lithiation-transmetalation using non hygroscopic ZnCl\textsubscript{2}·TMEDA.

**Typical Procedure: Preparation of 2-(2-benzoyl[b]thiophenyl)pyridine (8b).** To a stirred and cooled (-75 °C) solution of benzo[b]thiophene (5, 0.54 g, 4.0 mmol) in dry THF (5 mL) under argon was added BuLi (about 1.6 M hexanes solution, 4.0 mmol) and, 1 h later, ZnCl\textsubscript{2}·TMEDA\textsuperscript{46} (0.33 g, 1.3 mmol). The mixture was slowly warmed to room temperature (1 h) before addition of 2-chloropyridine (0.45 g, 4.0 mmol), PdCl\textsubscript{2} (14 mg, 80 mmol) and dpdf (44 mg, 80 mmol). The mixture was cooled before addition of water (0.5 mL) and EtOAc (50 mL), dried over MgSO\textsubscript{4}, and the solvents were removed under reduced pressure. Compound 8b was isolated by chromatographic purification on silica gel column (eluents: heptane/CH\textsubscript{2}Cl\textsubscript{2} 50/50 to 30/70) as a white powder (1.0 g, 81%).\textsuperscript{28}

**Acknowledgment**

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the coupling of organozinc reagents, see: Hayashi, T.;
Konishi, M.; Kobri, Y.; Kumada, M.; Higuchi, T.; Hirotsu,

Compound 2a: pale yellow powder; mp 186 °C. The spectral data were found identical to those previously described:
Strekowski, L.; Harden, M. J.; Grubb, W. B.; III; Patterson, S. E.; Czarny, A.; Mokrosz, M. J.; Cegla, M. T.;

Compound 2b: white powder; mp 88 °C. The spectral data were found identical to those previously described:


Compound 4: white powder; mp 88 °C. The spectral data were found identical to those previously described:

Compound 8a: pale yellow powder; mp 198 °C. The spectral data were found identical to those previously described:

Compound 8b: white powder; mp 126 °C. The physical and spectral data were found identical to those of a commercial sample (Aldrich).

Compound 9a: white powder; mp 124 °C. The physical data were found identical to those previously described:
Brown, D. J.; Cowden, W. B.; Strekowski, L. Aust. J. Chem. 1982, 35, 1209–1214. 1H NMR (CDCl₃): δ 7.17 (dd, J = 7.5 and 5.7 Hz, 1H), 7.46 (d, J = 7.8 Hz, 1H), 7.59 (dd, J = 7.5 and 1.5 Hz, 1H), 7.82 (dd, J = 5.7 and 1.5 Hz, 1H), 8.53 (d, J = 8.1 Hz, 1H). 13C NMR (CDCl₃): δ 113.7, 128.8, 129.2, 131.8, 140.5, 159.5, 161.7, 162.0.

Compound 10: pale yellow powder; mp 67 °C. The spectral data were found identical to those previously described: (a) Constable, E. C.; Sousa, L. R. J. Organomet. Chem. 1992,


(35) Compound 16: beige powder; mp < 50 °C; ¹H NMR (CDCl₃): δ 7.25–7.37 (m, 2H), 7.72–7.91 (m, 2H), 8.25 (d, J = 3.2 Hz, 1H), 8.47–8.58 (m, 1H), 8.72 (d, J = 4.8 Hz, 1H); ¹³C NMR (CDCl₃): δ 122.1 (d, J = 4.3 Hz), 122.6, 123.2, 124.3 (d, J = 10.4 Hz), 136.8, 141.6 (d, J = 3.8 Hz), 147.7 (d, J = 15.1 Hz), 150.0, 151.4 (d, J = 6.8 Hz), 160.9 (d, J = 241 Hz); HRMS: calcd for C₁₀H₁₇F₂N⁺ (M⁺) 174.0593, found 174.0595.


(41) Compound 9c: yellow powder; mp 135 °C. The spectral data were found identical to those previously described: Li, J.-H.; Zhu, Q.-M.; Xie, Y.-X. *Tetrahedron* 2006, 62, 10888–10895.

(42) Compound 9d: white powder; mp 134 °C. The spectral data were found identical to those previously described: Sieber, F.; Wentworth, P., Jr.; Janda, K. D. *J. Comb. Chem.* 1999, 1, 540–546.

(43) Compound 9e: white solid; mp 88 °C. The spectral data were found identical to those previously described: Denmark, S. E.; Baird, J. D. *Org. Lett.* 2006, 8, 793–795.


1) BuLi or LiTMP
2) ZnCl$_2$:TMEDA (1/3 equiv)
3) PdCl$_2$ (2%), dppf (2%)
55 °C, 12 h
4) hydrolysis

(X = CH, N)