JOC*Note*

One-Pot Negishi Cross-Coupling Reactions of In Situ Generated Zinc Reagents with Aryl Chlorides, Bromides, and Triflates

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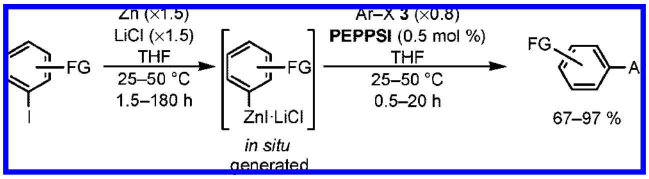
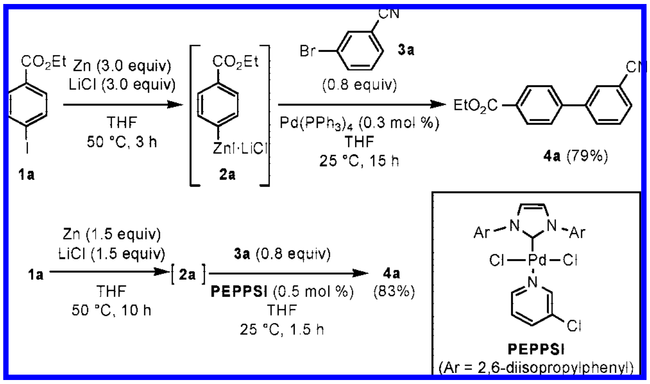


In situ generated aryl, heteroaryl, alkyl, or benzylic polyfunctional zinc reagents obtained by the addition of zinc and LiCl to the corresponding organic iodides undergo smooth Pd(0)-catalyzed cross-coupling reactions with aryl bromides, chlorides, and triflates in the presence of PEPPSI as a catalyst. This procedure avoids the manipulation of water and air-sensitive organozinc reagents and produces cross-coupling products in high yields.

Pd-catalyzed cross-coupling reactions have found numerous applications in research as well as in industry.[1] The Suzuki cross-coupling reaction especially has been used extensively due to the air and moisture stability of boronic acids and their derivatives.[2] Although this cross-coupling has a broad synthetic scope, it suffers from some limitations. Thus, the boronic derivatives often have to be prepared from the corresponding magnesium or lithium species, which limits the presence of functional groups.[3] Alternatively, organozinc reagents display in Pd-catalyzed cross-couplings (Negishi cross-coupling) much higher reactivity[4] and can readily be prepared in the presence of various functional groups. These environmentally friendly organometallics have, however, the drawback of being air- and moisture-sensitive. Recently, we have developed a very efficient LiCl-mediated direct insertion of zinc into unsaturated halides.[5] Using this method, we wish to report a one-pot protocol avoiding the handling of sensitive organozinc intermediates.

SCHEME 1. Preliminary Experiments of One-Pot Negishi Cross-Coupling Reaction



In preliminary experiments, we have treated ethyl 4-iodobenzoate (**1a**, 1.0 equiv) with zinc dust (3.0 equiv) and LiCl (3.0 equiv) in THF, resulting in the formation of the zinc reagent **2a** at 50 °C within 3 h (>98% conversion, Scheme 1). To this mixture, we have added 3-bromobenzonitrile (**3a**, 0.8 equiv) as well as $Pd(PPh_3)_4$ (0.3 mol %). After 15 h reaction time at 25 °C, we have obtained the desired cross-coupling product **4a** in 79% isolated yield. There was no need to remove the excess of zinc powder for performing the cross-coupling. We have improved these initial reaction conditions by reducing the zinc dust and LiCl amount (1.5 equiv) and by optimizing the Pd catalyst. In our hands, PEPPSI, introduced by Organ, displays the broader applicability.[6] Shorter reaction times and higher yields are generally obtained (Scheme 1 and Table 1).

Thus, we have prepared in situ a variety of arylzinc reagents bearing an ester group (derived from **1a** or **1b**; entries 1 and 2) or a nitrile (derived from **1c** or **1d**; entries 3−5). In all cases, the Negishi cross-coupling reaction occurs smoothly using 0.8 equiv of an aromatic bromide or chloride, affording the desired cross-coupling products **4b−f** in 80−91% yields. An *ortho*-substituted aryl iodide such as 2-trifluoromethyl-1-iodobenzene (**1e**) is readily converted to the intermediate zinc reagent and undergoes the expected cross-coupling reaction with 4-cyano-1-bromobenzene (**3g**) at 25 °C within 15 h, providing the biaryl **4g** in 97% yield (entry 6). Aromatic iodides bearing electron-donating groups are also good substrates, although the zinc insertion is slower (48−180 h; entries 7 and 8). The subsequent cross-coupling with an unsaturated halide furnishes the desired products **4h** (92%; entry 7) and **4i** (67%; entry 8). In addition,

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(1) (a) Tsuji, J. *Palladium Reagents and Catalysts, Innovations in Organic Synthesis*; Wiley: New York, 1995. (b) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998.

(2) (a) Song, Q. B.; Lin, R. X.; Teng, M. Y.; Zhang, J.; Ma, C. A. *Synthesis* **2006**, 123. (b) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, 2419. (c) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633. (d) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. (e) Miyaura, N. *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI: London, 1998; Vol. 6, p 187. (f) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(3) (a) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544. (b) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176. (c) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (d) Knochel, P. *Handbook of Functionalized Organometallics*; Wiley-VCH: Weinheim, Germany, 2005.

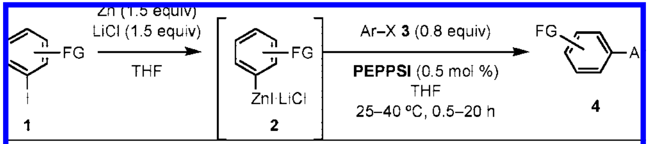
(4) (a) Negishi, E.-i. In *Metal-Catalyzed Cross-Coupling Reactions*: Diederich, F.; Stang, P. J., Eds.; Wiley: New York, 1998; Chapter 1. (b) Erdik, E. *Tetrahedron* **1992**, *48*, 9577.

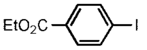
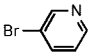
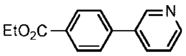
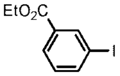
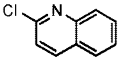
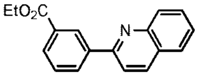
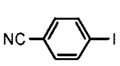
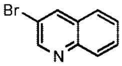
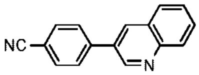
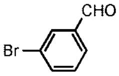
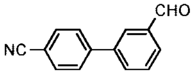
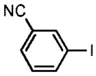
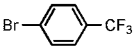
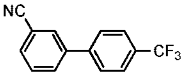
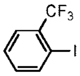
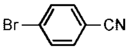
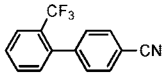
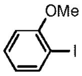
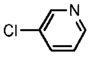
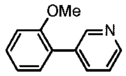
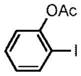
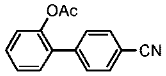
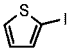
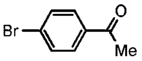
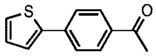
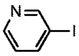
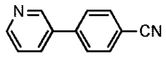
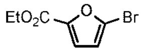
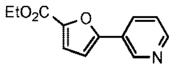
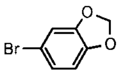
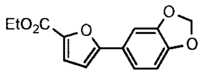
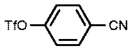
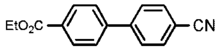
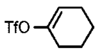
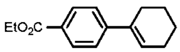
(5) Krasovskiy, A.; Malakhov, V.; Gavryushin, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 6040.

(6) (a) O'Brien, C. J.; Kantchev, E. A. B.; Valente, C.; Hadei, N.; Chass, G. A.; Lough, A.; Hopkinson, A. C.; Organ, M. G. *Chem.—Eur. J.* **2006**, *12*, 4743. (b) Organ, M. G.; Avola, S.; Dubovyk, I.; Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Valente, C. *Eur. J. Chem.* **2006**, *12*, 4749.

10.1021/jo801063c CCC: $40.75

TABLE 1. One-Pot Negishi Reaction for Functionalized Aryl Compound Synthesis

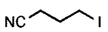
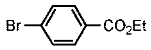
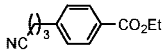
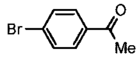
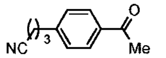
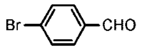
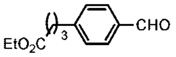
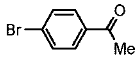
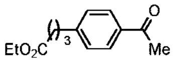
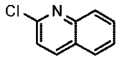
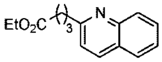
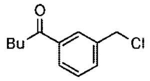
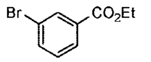
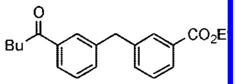
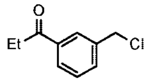
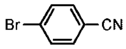
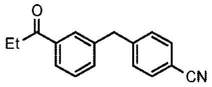
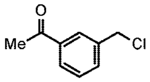
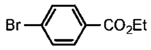
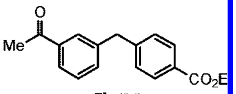
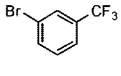
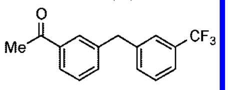
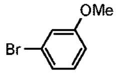
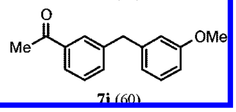


entry	aryl iodide	ArX 3	functionalized aryls, yield (%)[a]
1	 **1a** (50 °C, 10 h)[b]	 **3b** (50 °C, 3 h)[c]	 **4b** (86)
2	 **1b** (50 °C, 12 h)[b]	 **3c** (40 °C, 20 h)[c]	 **4c** (85)
3	 **1c** (50 °C, 8 h)[b]	 **3d** (25 °C, 5 h)[c]	 **4d** (91)
4	**1c**	 **3e** (25 °C, 2 h)[c]	 **4e** (80)
5	 **1d** (50 °C, 10 h)[b]	 **3f** (25 °C, 4.5 h)[c]	 **4f** (83)
6	 **1e** (25 °C, 48 h)[b]	 **3g** (25 °C, 15 h)[c]	 **4g** (97)
7	 **1f** (25 °C, 180 h)[b]	 **3h** (25 °C, 2 h)[c]	 **4h** (92)
8	 **1g** (25 °C, 48 h)[b]	**3g** (25 °C, 0.5 h)[c]	 **4i** (67)
9	 **1h** (25 °C, 1.5 h)[b]	 **3i** (25 °C, 1 h)[c]	 **4j** (82)
10	 **1i** (50 °C, 12 h)[d]	**3g** (50 °C, 5 h)[c]	 **4k** (75)
11	 **1j** (30 °C, 3 h)[b]	**3b** (50 °C, 5 h)[c]	 **4l** (86)
12	**1j**	 **3j** (50 °C, 20 h)[c]	 **4m** (91)
13	**1a**	 **3k** (25 °C, 4h)	 **4n** (78%)
14	**1a**	 **3l** (25 °C, 4h)	 **4o** (75%)

[a] Isolated yields of analytical pure product. [b] Reaction conditions for the zinc insertion reaction. [c] Reaction conditions for the Pd catalyzed cross-coupling reaction. [d] 3.0 equiv of Zn and LiCl was used for the zinc insertion.

TABLE 2. One-Pot Negishi Reactions Using Alkyl and Benzylic Zinc Intermediates

$$\underset{\mathbf{5}}{\text{R–X}} \xrightarrow[\text{THF}\ (\text{X = Cl, Br, I})]{\text{Zn (1.5 equiv)},\ \text{LiCl (1.5 equiv)}} \left[\underset{\mathbf{6}}{\text{R–ZnX·LiCl}}\right] \xrightarrow[\text{THF},\ 25\text{–}50\ ^\circ\text{C},\ 1\text{–}15\ \text{h}]{\text{Ar–X}\ \mathbf{3},\ \mathbf{PEPPSI}\ (0.25\text{–}0.5\ \text{mol \%})} \underset{\mathbf{7}}{\text{R–Ar}}$$

entry	halides	ArX 3	7, yield (%)[a]
1[b]	 **5a** (25 °C, 2 h)[c]	 **3m**[d] (25 °C, 2 h)[e]	 **7a** (86)
2	**5a**	 **3i**[d] (25 °C, 2 h)[e]	 **7b** (70)
3	 **5b** (50 °C, 12 h)[c]	 **3n**[d] (25 °C, 1 h)[e]	 **7c** (87)
4	**5b**	 **3i**[d] (25 °C, 2 h)[e]	 **7d** (83)
5	**5b**	 **3c**[d] (50 °C, 15 h)[e]	 **7e** (73)
6	 **5c** (25 °C, 4 h)[c]	 **3o**[f,g] (25 °C, 2 h)[e]	 **7f** (92)
7	 **5d** (25 °C, 4 h)[c]	 **3g**[f,g] (25 °C, 2 h)[e]	 **7g** (79)
8	 **5e** (25 °C, 3 h)[c]	 **3m**[f,g] (25 °C, 2 h)[e]	 **7h** (94)
9	**5e**	 **3p**[f,g] (25 °C, 5 h)[e]	 **7i** (86)
10	**5e**	 **3q**[f,g] (25 °C, 5 h)[e]	 **7j** (60)

[a] Isolated yields of analytical pure product. [b] One-pot cross-coupling reaction had been done in THF/DMI = 2/1. [c] Reaction conditions for the zinc insertion. [d] 0.8 equiv of the reagent was used. [e] Reaction conditions for the Pd-catalyzed cross-coupling reaction. [f] 0.5 equiv of the reagent was used. [g] 0.25 mol % of PEPPSI was used.

we have applied this one-pot protocol to heteroaromatic compounds, such as 2-iodothiophene (**1h**), 3-iodopyridine (**1i**), and 2-bromo-5-(carbethoxy)furan (**1j**), affording the expected cross-coupling products **4j−m** in 75−91% yields (entries 9−12). The cross-coupling could be further extended to other organic electrophiles such as aryl and vinyl triflates (**3k** and **3l**) in 75−78% yield (entries 13 and 14). In the case of 3-iodopyridine (**1i**), the amount of zinc and LiCl should be increased to 3.0 equiv to achieve full conversion to the corresponding organozinc intermediate.

Alkylzinc halides bearing an ester or a nitrile (**5a** and **5b**) were generated in situ in a similar way. After the addition of an unsaturated bromide or chloride in the presence of PEPPSI, the desired cross-coupling products **7a−e** are obtained in 70−87% yield (entries 1−5 of Table 2). The addition of 1,3-dimethyl-2-imidazolidinone (DMI) as cosolvent facilitates the reaction.

Remarkably, polyfunctional benzylic zinc reagents bearing a keto group can be generated in situ starting from the corresponding benzylic chlorides **5c**−**e**.[7] A smooth cross-coupling occurs with 0.5 equiv of various aromatic bromides, furnishing polyfunctional diarylmethanes **7f**−**j** in 60−94% yield (entries 6−10 of Table 2).

In summary, we have reported a practical in situ generation of polyfunctional zinc reagents using commercially available zinc dust in the presence of LiCl and found general reaction conditions using PEPPSI for a subsequent cross-coupling with various aryl and heteroaryl bromides, chlorides, or triflates. This procedure avoids the handling of air- and water-sensitive zinc reagents and would be suited for large-scale industrial applications.

Experimental Section

General Procedure. Anhydrous LiCl (1.5−3.0 equiv) was placed in an argon-flushed flask and dried using a heat gun under high vacuum. Zinc dust (<10 μm, Aldrich, 98+%, 1.5−3.0 equiv) was added under argon, and the heterogeneous mixture of Zn and LiCl was dried again on high vacuum. The reaction flask was flushed with argon, and then THF (ca. 0.8 M) was added. Zn was activated by $BrCH_2CH_2Br$ (5 mol %; heating to ebullition for 15 s) and Me_3SiCl (1 mol %, heating to ebullition for 15 s). The aryl iodide (1.0 mmol) was added at 25 °C, and the resulting reaction mixture was stirred at the indicated temperature. When capillary GC analysis of a hydrolyzed aliquot containing an internal standard showed a conversion of >98%, the aryl halide (**3**, 0.5−0.8 equiv) in THF (0.5−0.8 mL) was added at the indicated temperature followed by the addition of PEPPSI (0.20 mL of 20 mmol/L solution in THF, 0.004 mmol). After completion of the cross-coupling reaction (as determined by GC analysis), the reaction mixture was quenched with saturated aqueous NH_4Cl solution (5 mL) and extracted with ether (3 × 5 mL), and the combined organic phase was washed with brine and dried over $MgSO_4$. Evaporation of the solvent in vacuo and purification by column chromatography afforded the expected cross-coupling products.

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Supporting Information Available: Experimental procedures and full characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Metzger, A.; Schade, M. A.; Knochel, P. *Org. Lett.* **2008**, *10*, 1107.