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A Mild Negishi Cross-Coupling of 2-Heterocyclic Organozinc Reagents and Aryl Chlorides

Michael R. Luzung,* Jigar S. Patel, and Jingjun Yin*

Department of Process Research,
Merck Research Laboratories, P.O. Box 2000 Rahway,
New Jersey 07065, United States

michael_luzung@merck.com; jingjun_yin@merck.com

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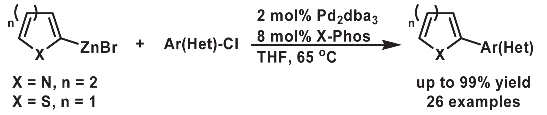
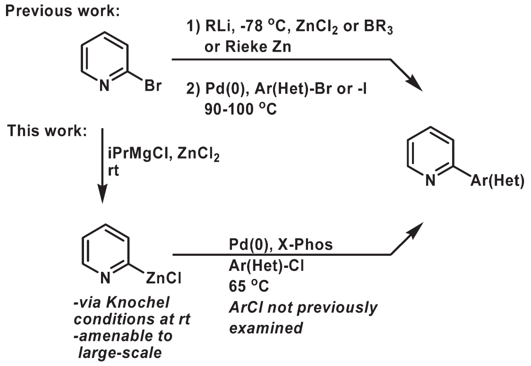


A mild Negishi cross-coupling of 2-heterocyclic organozinc reagents and aryl chlorides is described. The use of $Pd_2(dba)_3$ and X-Phos as a ligand provides high yields for many examples. An efficient method to generate the organozinc reagents at room temperature is also demonstrated.

The coupling of 2-heterocyclic organometallic reagents with aryl halides is a transformation used by many in the chemical community to produce coupled products prevalent in pharmaceuticals, ligands, and materials. Extensive research has focused on a variety of ways to form this C–C bond using Pd catalysis.[1] The Suzuki reaction has been the focus of many groups for this transformation (Scheme 1).[2] 2-Pyridyl couplings have been of particular interest to our drug discovery efforts.[2b,c] Commercially available 2-pyridylboronic esters can couple with aryl bromides and iodides using palladium phosphine oxide or chloride catalysts[2b] or utilizing CuCl[2c,d] to facilitate the transmetalation of these electron-deficient nucleophiles. While these methods show versatility in substrate scope, the reactions are performed at high temperatures in moderate yields, require stoichiometric Cu, or require substitution at the 6-position of the pyridyl reagent. Unactivated aryl chlorides have been relatively difficult to couple,[2g] as such research has mainly focused on aryl bromides, iodides, or activated chlorides. 2-Pyridyl borates can be synthesized, but they often require a cryogenic lithium–halogen exchange before subsequent trapping with a boron source, which is followed by alcohol metathesis at refluxing temperatures for isolation.[2f,3]

SCHEME 1. Cross-Coupling Reactions of 2-Heterocyclic Organometallic Reagents with Aryl Halides



An attractive alternative to the Suzuki reaction for this transformation is the Negishi cross-coupling, for which numerous reports have recently described using aryl bromides or iodides.[4] This note addresses the Negishi cross-coupling of 2-heterocyclic organozinc reagents with aryl and heteroaryl chlorides (Scheme 1). Aryl chlorides[5] may be more useful due to their low cost and higher availability relative to the corresponding bromides and iodides. Organozinc reagents have typically been synthesized using either lithium–halogen exchange[6a] or highly reactive Rieke zinc.[7] This note also addresses the synthesis of 2-heterocyclic organozinc reagents using Knochel conditions[8] at ambient temperature.

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(1) For a review on 2-pyridyl cross-couplings, see: Campeau, L.-C.; Fagnou, K. *Chem. Soc. Rev.* **2007**, *36*, 1058–1068.

(2) For selected heterocyclic Suzuki reactions, see: (a) Guetz, G.; Luetzen, A. *Synthesis* **2010**, *1*, 85–90. (b) Yang, D. X.; Colletti, S. L.; Wu, K.; Song, M.; Li, G. Y.; Shen, H. C. *Org. Lett.* **2009**, *11*, 381–384. (c) Deng, J. Z.; Paone, D. V.; Ginnetti, A. T.; Kurihara, H.; Dreher, S. D.; Weissman, S. A.; Stauffer, S. R.; Burgey, C. S. *Org. Lett.* **2009**, *11*, 345–347. (d) Knapp, D. M.; Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2009**, *131*, 6961–6963. (e) Ackermann, L.; Potukuchi, H. K. *Synlett* **2009**, *17*, 2852–2856. (f) Billingsley, K. L.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 4695–4698. (g) Billingsley, K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3358–3366. (h) Hodgson, P. B.; Salingue, F. H. *Tetrahedron Lett.* **2004**, *45*, 685–687. (i) Bouillon, A.; Lancelot, J.-C.; Sopkova de Oliveira Santos, J.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2003**, *59*, 10043–10049. (j) Deshayes, K.; Broene, R. D.; Chao, I.; Knobler, C. B.; Diederich, F. *J. Org. Chem.* **1991**, *56*, 6787–6795.

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(5) (a) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176–4211. (b) For two examples of microwave-assisted Ni-catalyzed Negishi cross-coupling of 2-pyridylzinc chloride, see: Walla, P.; Kappe, C. O. *Chem. Commun.* **2004**, 564–565.

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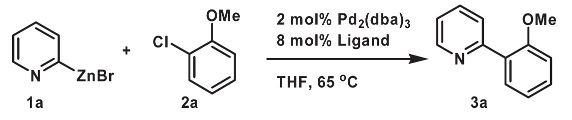
TABLE 1. Ligand Screen.[a]



ligand (conversion, %)	ligand (conversion, %)
dppe (< 3%)	S-Phos (~20%)
dppf (< 3%)	tBu-X-Phos (~30%)
1,1′-(tBu$_2$P)-ferrocene (< 3%)	JohnPhos (~50%)
Cy$_3$P-HBF$_4$ (< 3%)	RuPhos (~50%)
tBu$_3$P-HBF$_4$ (10%)	X-Phos (100%)

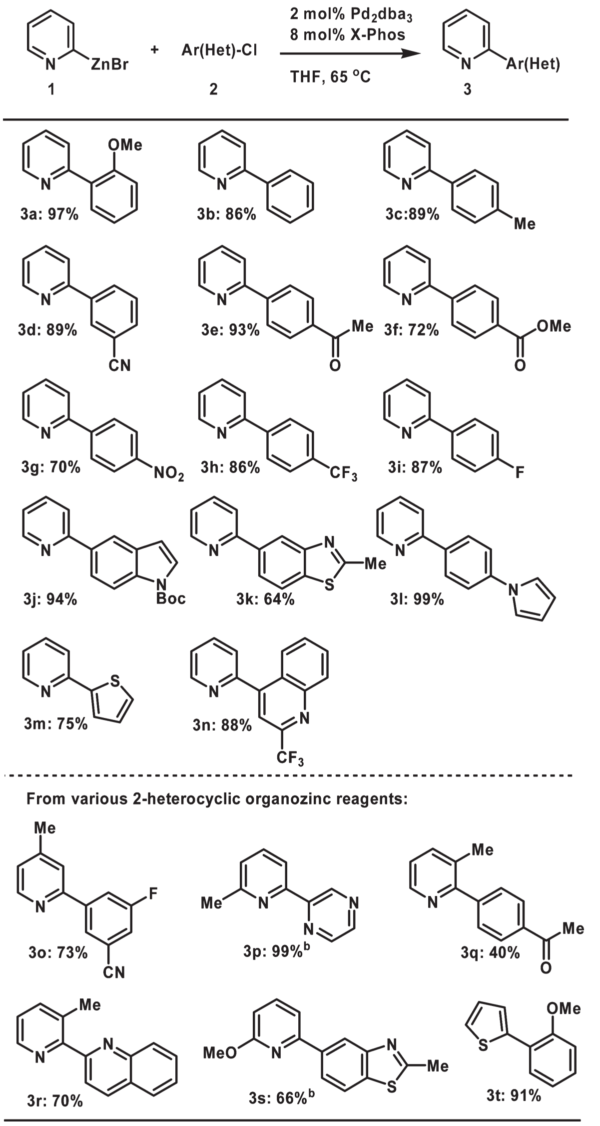
[a] Conversion monitored by HPLC with an internal standard (biphenyl).

The coupling of 2-pyridylzinc bromide with 2-chloroanisole was attempted for the ligand screen using Pd$_2$(dba)$_3$ as the Pd source in THF at 65 °C (Table 1). While bidentate ligands[9] were unsuccessful for the Negishi cross-coupling, it was found that more electron-rich Buchwald-type ligands[6,10] were the key to higher conversion. Surprisingly, RuPhos,[6a] which was previously reported to give excellent yields for Ar−Ar Negishi cross-couplings with aryl chlorides, gave only ~50% conversion to the desired coupled product. An extensive ligand survey revealed that X-Phos[10] gave complete conversion for this transformation.

With these conditions in hand, 2 mol % of Pd$_2$(dba)$_3$ and 8 mol % of X-Phos in THF at 65 °C, we attempted to understand the scope of this reaction using several aryl and heteroaryl chlorides and commercially available 2-pyridyl- and 2-thienylzinc reagents (Table 2). Aryl chlorides with varying substituents on the phenyl ring ranging from electron rich to electron poor were successfully coupled (**3a−i,o,q,t**). Functional handles such as nitrile, ketone, ester, and nitro (**3d−g,o,q**) were well tolerated under the reaction conditions. Fluorinated substrates (**3h−i,n−o**) also gave excellent yields. Heteroaryl chlorides such as indole, benzothiazole, pyrrole, thiophene, and quinoline survived these conditions with no major side reactions observed (**3j−n,p,r−s**).

While there are very useful methods of organozinc generation for 2-heterocyclic substrates, we wanted to apply conditions that would not require cryogenic temperatures or highly reactive metals which may be a safety issue on large scale. In order to generate these reagents on large scale in a safe and easy manner, we applied Knochel conditions (Table 3).[8] 2-Pyridyl and 2-thienyl bromides were treated with isopropylmagnesium chloride for metal−halogen exchange at room temperature. The organozinc reagent was then synthesized in situ by treating the Grignard with a solution of zinc chloride at ambient temperature to undergo transmetalation. These mixtures were then further utilized for subsequent Negishi cross-coupling with heteroaryl chlorides.

TABLE 2. Pd-Catalyzed Negishi Cross-Coupling of 2-Pyridylorganozinc Reagents and Aryl Chlorides with X-Phos[a]



[a] Reaction conditions: 1.5 equiv of **1**, 1 equiv of ArCl **2** (1 mmol), 2 mol % of Pd$_2$(dba)$_3$, 8 mol % of X-Phos, THF (0.3−0.4M), 65 °C, 2−12 h. All isolated yields. [b] 3.5 equiv of RZnX used.

Table 3 shows coupling with a variety of heterocycles in excellent yields. In particular, compound **6c**, which contains a hydroxyl group as an additional functional handle, can be formed in good yield. The Negishi cross-coupling can also be applied to more complicated molecules, showing the potential for late-stage coupling. The parent compound to entry **6f** is hydroquinine 4-chlorobenzoate, which is a well-known ligand used in asymmetric catalysis.[11] It contains a tertiary amine, an ester, and a quinoline, all of which can potentially undergo side reactions. Under the optimized two-step sequence, compound **6f** is obtained in 97% yield.

In conclusion, we have described a mild Negishi cross-coupling of 2-heterocyclic organozinc reagents with aryl and heteroaryl chlorides, demonstrated with 26 examples total. This method complements current reactions for the coupling of 2-heterocyclic organometallic reagents and is expected to show utility in future drug discovery and development efforts. The organozinc reagents can be generated in situ using Knochel conditions at room temperature. These combined

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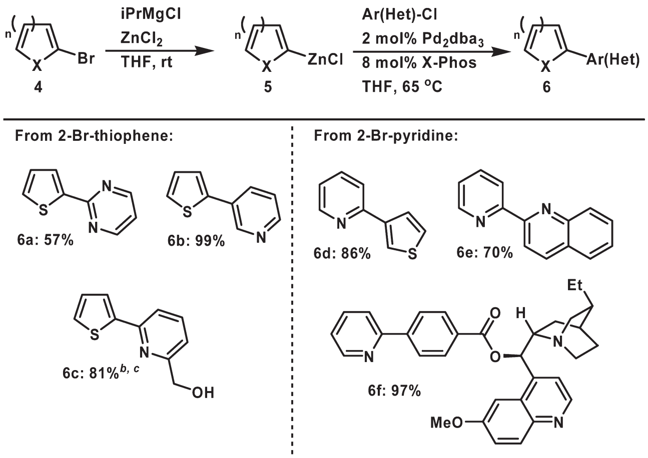
TABLE 3. Sequential Organozinc Synthesis and Negishi Cross-Coupling[a]



[a] Reaction conditions: 1.5 equiv of **5**, 1 equif of ArCl (1 mmol), 2 mol % of $Pd_2(dba)_3$, 8 mol % of X-Phos, THF (0.3−0.4 M), 65 °C, 2−12 h. All isolated yields. [b] 3.5 equiv of RZnX used. [c] 2-Bromo-6-(hydroxymethyl)-pyridine was used.

transformations can be applied to large-scale synthesis without further temperature or safety precautions. This method is currently being examined on more complex 2-heterocyclic organozinc reagents and the results will be reported in due course.

Experimental Section

Representative Procedure for the Synthesis of 2-Pyridyl and 2-Thienylzinc Chloride. A three-neck round-bottom flask with a stirbar was charged with isopropylmagnesium chloride (2.0 M, 2.75 mL, 5.5 mmol, 1.1 equiv). To this mixture was added neat 2-bromopyridine (0.476 mL, 5.0 mmol, 1.0 equiv) or 2-bromothiophene (0.479 mL, 5.0 mmol, 1.0 equiv) dropwise with the temperature not exceeding 30 °C. After 3−4 h, zinc chloride (0.5 M, 12 mL, 6.0 mmol, 1.2 equiv) was added dropwise with the temperature not exceeding 30 °C. After 1 h at room temperature, the mixture was used as is for subsequent cross-coupling.

Representative Procedure for the Negishi Cross-Coupling. A solution of $Pd_2(dba)_3$ (18.3 mg, 0.02 mmol, 2 mol %) and X-Phos (38.1 mg, 0.08 mmol, 8 mol %) in 2.7 mL of THF under nitrogen was stirred and heated at 65 °C for 10 min. To this solution was added an aryl chloride substrate (1 mmol). After the mixture was stirred for 15 min, an organozinc reagent (1.5 mmol) was added dropwise. The reaction was monitored by HPLC and/or TLC and upon completion was cooled to room temperature. The reaction was then quenched with 3 mL of $NaHCO_3$ and 3 mL of H_2O. After separation, the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with H_2O, dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. The crude product was purified by column chromatography on silica gel with a gradient of EtOAc in hexanes. Experimental data for **3a**: reaction time 2 h; yellow oil, purified by column chromatography on silica gel (182.6 mg, 97% yield); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.71 (d, 1H, J = 4.6 Hz), 7.82 (d, 1H, J = 8.0 Hz), 7.78 (dd, 1H, J = 7.6, 1.6 Hz), 7.71 (td, 1 H, J = 7.8, 1.7 Hz), 7.40−7.36 (m, 1H), 7.27−7.19 (m, 1H), 7.09 (t, 1H, J = 7.5 Hz), 7.01 (d, 1H, J = 8.3 Hz), 3.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.0, 156.2, 149.4, 135.6, 131.2, 129.9, 129.2, 125.1, 121.7, 121.1, 111.4, 55.6; HRMS calcd for $C_{12}H_{11}NOH^+$ 186.0913, found 186.0919.

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Supporting Information Available: Experimental procedures, full characterization, and copies of ^{1}H and ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.