## Mild and General Conditions for Negishi Cross-Coupling Enabled by the Use of Palladacycle Precatalysts\*\*

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Biaryls, particularly those containing one or more heterocyclic components, are ubiquitous among pharmaceutically active compounds, natural products, and agrochemicals. For their preparation, palladium-catalyzed cross-coupling reactions have been extensively studied and practiced in both academic<sup>[1]</sup> and industrial<sup>[2]</sup> settings. Although various palladium-catalyzed cross-coupling methods to form Csp2-Csp2 bonds have been developed, the Negishi coupling is one of the most frequently utilized. The utility of Negishi couplings is partially due to the fact that organozinc reagents, despite their considerable basicity, are compatible with a large number of sensitive functional groups.<sup>[3]</sup> Equally important is that a wide array of highly functionalized organozinc reagents can be readily accessed.<sup>[4]</sup> Additionally, the recent development of solid salt-stabilized organozinc reagents, which are much less sensitive towards air and moisture,<sup>[5,6]</sup> has also rendered the Negishi coupling a more practical and user-friendly technique for synthetic organic chemists.

Numerous studies have been devoted to the development of more general and efficient catalyst systems for Negishi cross-coupling reactions (Scheme 1). In 2001, Fu and Dai described the first general protocol to effect the Negishi crosscoupling of aryl chlorides by using  $[Pd{P(tBu_3)}_2]$  (2 mol%) as the precatalyst in THF/NMP at 100°C.<sup>[7]</sup> In 2004, our research group reported a highly active catalyst based on dialkylbiarylphosphine **L1** (RuPhos), that permitted the efficient generation of a wide range of sterically hindered tri- and tetra*ortho*-substituted biaryls in THF at 70°C with low catalyst loadings.<sup>[8]</sup> In a series of publications, Knochel and co-workers demonstrated the utility of biarylphosphine **L2** (SPhos) as the supporting ligand for palladium-catalyzed Negishi coupling.<sup>[3,9]</sup> More recently, the group of Organ has also



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**Scheme 1.** Precatalysts and ligands employed for Negishi cross-coupling reactions.

developed a Pd-PEPPSI-IPent precatalyst capable of facilitating the reactions of a variety of extremely sterically hindered substrates to afford tetra-*ortho*-substituted biaryls under exceptionally mild reaction conditions with excellent yields.<sup>[10,11]</sup>

Despite these advances, significant challenges still remain. Notably, although simple aryl halides and aryl zinc reagents are easily transformed, couplings involving heteroaryl zinc reagents and heteroaryl halides are often less successful. This difficulty is due partly to the different electronic properties of heterocyclic compounds, as well as to the presence of heteroatoms capable of binding to the transition metal center, thus leading to catalyst deactivation and decomposition.<sup>[12]</sup> In particular, the transformation of five-membered heterocycles bearing more than one heteroatoms, such as pyrazoles and imidazoles, has proven to be challenging.<sup>[13,14]</sup> Thus, the development of a catalyst system capable of facilitating the coupling of a diverse range of heteroaryl and functionalized substrates under mild reaction conditions is still highly desirable. Herein, we report a general catalyst system based on a palladacycle precatalyst ligated by dialkylbiarylphosphine ligand L3 (XPhos) for the palladium-catalyzed Negishi cross-couplings at ambient temperature or with low catalyst loadings. With this system a myriad of heteroaryl coupling partners, many of which were previously unsuccessful substrates,<sup>[8]</sup> can now be effectively coupled. In addition, we report the success of this system for the Negishi coupling of polyfluoroaryl zinc reagents.

We recently reported the development of a new class of easily prepared, air- and moisture-stable aminobiphenylbased palladacycle precatalysts capable of rapidly and

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quantitatively generating the catalytically active  $L_1Pd^0$  species under basic conditions at room temperature.<sup>[15–18]</sup> Given their intrinsic basicity, we reasoned that organozinc reagents could readily activate these precatalysts in situ, and furthermore that the efficient and rapid formation of  $L_1Pd^0$  facilitated by these precatalysts would allow for Negishi cross-couplings under mild conditions and, potentially, with low catalyst loadings. Thus, palladacycle precatalyst **3c** was compared with other commonly used palladium sources in combination with **L3** for the Negishi cross-coupling of *p*-tolylzinc chloride (**4**) and 2-bromoanisole (**5**; Figure 1). Interestingly, the protocol



**Figure 1.** Comparison of precatalyst **3 c** with several other palladium sources. Reaction conditions: *p*-tolylzinc chloride (0.65 mmol), 2-bromoanisole (0.5 mmol), Pd (0.1%, Pd/L=1:1), L=L**3**, THF, 75 °C, 20 min. Yields were determined by GC analysis of the crude reaction mixture.

employing palladacycle precatalyst **3**c facilitated the coupling in 92% yield after just 20 min, whereas the use of other palladium sources such as Pd(OAc)<sub>2</sub> and [Pd<sub>2</sub>dba<sub>3</sub>] resulted in product yields lower than 40% in the same amount of time. These results clearly indicate that palladacycle precatalyst **3** generates the catalytically active  $L_1Pd^0$  species most efficiently.

We next evaluated the ligand effects using palladacycle precatalysts of type **3**.<sup>[8]</sup> Given the success of bulky monophosphinobiaryl ligands  $L3^{[17,19]}$  and  $L5^{[20]}$  in facilitating Suzuki-Miyaura cross-couplings with high reactivity, we were interested in carefully evaluating their activity for Negishi cross-couplings. Differences in reaction rates for catalyst systems derived from ligands L1, L3, L4, and L5 were determined by monitoring the reaction progress using calorimetric analysis.<sup>[21a]</sup> As depicted by Figure 2, reaction rates for all of the catalyst systems derived from L1, L4, and L5 are significantly lower than that observed when L3 was used as the supporting ligand. While catalyst systems employing L3 and L4 both facilitated full conversion of 2-bromoanisole after approximately 30 min, the initial reaction rate for the catalyst generated from L4 was about 50% lower than the reaction rate for the catalyst derived from L3. This result illustrates the influence of the size of the substituents on the nonphosphorus-containing ring of the dialkylbiarylphosphine ligand on catalyst activity, in accordance with our previous findings.<sup>[21b,c]</sup> Further, the benefit of using a ligand with cyclohexyl rather than tert-butyl substituents on the phosphorous atom of the monophosphinobiaryl ligand is highlighted by the 10-fold difference in reaction rate between



Figure 2. Comparison of precatalysts with different dialkylbiarylphosphine ligands. Reaction conditions: *p*-tolylzinc chloride (0.65 mmol), 2-bromoanisole (0.5 mmol), 3 (0.1%), L = L2-5 (0.1%), THF, 75 °C.

catalysts based on **L4** and **L5**. Interestingly, a catalyst derived from **L1** furnished only 55% conversion at 0.1 mol% Pd loading, thus indicating that the catalyst based on **L1** is less effective at low palladium loadings than that generated from **L3**.<sup>[22]</sup> Taken together, these studies suggest that a catalyst system based on **L3** exhibits the highest activity for Negishi couplings.

In light of the importance of heterocyclic compounds in medicinal chemistry and materials chemistry,<sup>[23]</sup> we focused on the Negishi cross-coupling of heteroaryl zinc reagents with heterocyclic halides and pseudohalides (Scheme 2). We were interested in the Negishi coupling of five-membered 2heteroaromatic zinc chlorides (i.e., 2-furyl-, 2-thienyl-, 2benzofuranyl-, 2-benzothiophenyl-, and 2-indolylzinc chlorides) and 2-pyridylzinc chloride, because the corresponding organoboron reagents are difficult substrates for Suzuki-Miyaura coupling owing to the rapid protodeboronation.<sup>[17,24,25]</sup> We found that by using 0.25–4 mol% of 3c, these heteroaryl zinc reagents could be efficiently coupled at room temperature to furnish heterobiaryls (7a-7i) in excellent yield. Coupling reactions of 3-furyl-, 3-thienyl-, 3pyrroryl-, 3-indolyl-, and 3-pyridylzinc chlorides were equally effective under the current protocol (7k-7o). Azole coupling partners were also evaluated with the current catalyst system. 4-Iodo-1-tritylimidazole, and 2- and 4-bromothiazoles proved to be more-challenging substrates, requiring higher reaction temperatures to obtain appreciable amounts of coupled product (7p, 7q, and 7r, respectively). Benzo-fused azole and N-substituted pyrazole electrophiles were excellent substrates for this method and could be converted into the desired products (7s and 7t, respectively) in excellent yields at room temperature.<sup>[26]</sup> Products containing azoles such as pyrazolyl (7u, 7v, 7w, and 7z), 4-isoxazolyl (7x), 2-thiazolyl (7y) and 2-imidazolyl (7a') can also be synthesized from the cross-coupling of the respective zinc chlorides by using our protocol. Finally, different types of halides and pseudohalides can all be effectively coupled with organozinc reagents under our reaction conditions.

To further demonstrate the utility of our method, we sought to extend the scope of our catalyst system to reactions of polyfluorophenyl zinc reagents (Scheme 3). We were particularly intrigued by the coupling of fluorinated aryl



Scheme 2. Cross-coupling of heteroaryl zinc reagents and heteroaryl halides. Reaction conditions: ArZnCl (1.3 mmol), ArX (1.0 mmol), 3c (0.25–2 mol%), L3 (0.25–2 mol%), THF, RT, 12 h. Yields are of the isolated products, and an average of two runs. [a] ArZnCl (1.2 mmol) was used. [b] ArZnCl (2.3 mmol), ArX (1.0 mmol), 3c (1 mol%), L3 (1 mol%), THF, RT, 12 h. [c] 3b and L1 instead of 3c and L3; [d] ArZnCl (1.3 mmol), ArX (1.0 mmol), 3c (2–4 mol%), L3 (2–4 mol%), THF, 80°C, 12 h.



**Scheme 3.** Cross-coupling of polyfluoroaryl zinc reagents and heteroaryl halides at room temperature. Yields are of the isolated products, and an average of two runs. Reaction conditions: ArZnCl (1.3 mmol), ArX (1.0 mmol), **3c** (1–2 mol%), **L3** (1–2 mol%), THF, RT, 12 h. [a] ArZnCl (2.3 mmol), ArX (1.0 mmol), **3c** (1–2 mol%), **L3** (1–2 mol%), **L4** (1.2 mol%), **L3** (1–2 mol%), **L4** (1.2 mol%), **L4** (1.2 mol%), **L3** (1–2 mol%), **L4** (1.2 mol%), **L4** (1.2 mol%), **L5** (1.2 mol%), **L3** (1–2 mol%), **L4** (1.2 mol%), **L4** (1.2 mol%), **L3** (1–2 mol%), **L4** (1.2 mol%), **L5** (1.2 mol%),

zinc reagents because methods for the preparation of polyfluorinated biaryls remain underdeveloped. The corresponding polyfluorophenyl boronic acids constitute a challenging family of nucleophiles for Suzuki-Miyaura coupling owing to rapid protodeboronation.<sup>[17]</sup> For example, the halflife time of 2,3,6-trifluorophenylboronic acid under our most recently developed reaction conditions for Suzuki-Miyaura coupling is only 2 min,<sup>[17]</sup> thus rendering the Suzuki–Miyaura coupling of this boronic acid a formidable task. We therefore reasoned that Negishi coupling could serve as an important alternative to achieve this type of transformation.<sup>[27]</sup> Subjecting various types of polyfluorophenyl zinc reagents to the current protocol furnished coupling products in uniformly good yields (8a-8j). Moreover, when the reaction temperature was increased to 40 °C, perfluoro-4-pyridylzinc chloride reacted well with an aryl triflate derived from estrone to give 8 k.<sup>[28,29]</sup>

Encouraged by the high level of reactivity of our catalyst system, we set out to examine the scope of this system at extremely low levels of catalyst loading (Scheme 4). The reaction proceeded with lower catalyst loadings of 0.025– 0.05 mol % (turnover number = 2000–4000) and a variety of functional groups, including an acetal (**9e**), a tertiary amine (**9f**), an amide (**9f**), and heterocycles (**9c** and **9d**), were tolerated. These results clearly demonstrate the ability of our catalyst to operate at low concentrations of catalyst for a range of functionalized substrates. However, we note that with the current catalyst system, substrates bearing an *ortho* coordinating substituent such as an ester or a ketone usually

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**Scheme 4.** Cross-coupling of aryl zinc chlorides and aryl halides at low catalyst loadings. Reaction conditions: ArZnCl (1.3 mmol), ArX (1.0 mmol), **3c** (0.025–0.05 mol%), **L3** (0.025–0.05 mol%), THF, 75 °C, 12 h. Yields are of the isolated products, and an average of two runs.

require catalyst loadings higher than  $0.1 \mod \%$  to achieve full conversion.

In summary, through the use of our recently developed palladacycle precatalysts, we have identified a highly active catalyst system based on **L3** for the Negishi cross-coupling of heteroaryl zinc reagents and polyfluoroaryl zinc reagents under mild reaction conditions. Our method is effective with a broad scope of heteroaryl halides, pseudohalides and other types of challenging substrates, thus delivering a wide range of heterobiaryls that represent structural motifs frequently found in biologically active compounds.

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- a) A. de Meijere, F. Diederich in *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed., Wiley-VCH, Weinheim, 2004;
   b) E.-i. Negishi in *Handbook of Organopalladium Chemistry for Organic Synthesis*, Wiley-Interscience, New York, 2002.
- [2] a) J. Magano, J. R. Donetz, *Chem. Rev.* 2011, 111, 2177-2250;
   b) J. P. Corbet, G. Mignani, *Chem. Rev.* 2006, 106, 2651-2710.
- [3] a) G. Manolikakes, C. M. Hernandez, M. A. Schade, A. Metzger, P. Knochel, J. Org. Chem. 2008, 73, 8422–8436; b) G. Manolikakes, M. A. Schade, C. M. Hernandez, H. Mayer, P. Knochel, Org. Lett. 2008, 10, 2765–2768; c) G. Manolikakes, Z. Dong, H. Mayr, J. Li, P. Knochel, Chem. Eur. J. 2009, 15, 1324–1328.
- [4] a) P. Knochel, P. Jones in Organozinc Reagents, A Practical Approach, Oxford University Press, New York, 1999; b) P. Knochel, R. D. Singer, Chem. Rev. 1993, 93, 2117–2188; c) B. Haag, M. Mosrin, H. Ila, V. Malakhov, P. Knochel, Angew. Chem. 2011, 123, 9968–9999; Angew. Chem. Int. Ed. 2011, 50, 9794–9824.

- [5] S. Bernhardt, G. Manolikakes, T. Kunz, P. Knochel, Angew. Chem. 2011, 123, 9372–9376; Angew. Chem. Int. Ed. 2011, 50, 9205–9209.
- [6] C. I. Stathakis, S. Bernhardt, V. Quint, P. Knochel, Angew. Chem. 2012, 124, 9563–9567; Angew. Chem. Int. Ed. 2012, 51, 9428– 9432.
- [7] C. Dai, G. C. Fu, J. Am. Chem. Soc. 2001, 123, 2719-2724.
- [8] J. E. Milne, S. L. Buchwald, J. Am. Chem. Soc. 2004, 126, 13028– 13032.
- [9] L. Melzig, A. Metzger, P. Knochel, *Chem. Eur. J.* 2011, 17, 2948– 2956.
- [10] S. Çalimsiz, M. Sayah, D. Mallik, M. G. Organ, Angew. Chem. 2010, 122, 2058–2061; Angew. Chem. Int. Ed. 2010, 49, 2014– 2017.
- [11] For recent reviews, see: a) C. Valente, M. E. Belowich, N. Hadei, M. G. Organ, *Eur. J. Org. Chem.* 2010, 4343-4354; b) C. Valente, S. Çalimsiz, K. H. Hoi, D. Mallik, M. Sayah, M. G. Organ, *Angew. Chem.* 2012, *124*, 3370-3388; *Angew. Chem. Int. Ed.* 2012, *51*, 3314-3332.
- [12] Q. Shen, S. Shekhar, J. P. Stambuli, J. F. Hartwig, Angew. Chem. 2005, 117, 1395–1399; Angew. Chem. Int. Ed. 2005, 44, 1371– 1375.
- [13] M. Su, S. L. Buchwald, Angew. Chem. 2012, 124, 4788–4791; Angew. Chem. Int. Ed. 2012, 51, 4710–4713.
- [14] For a recent review, see: M. Schnürch, R. Flasik, A. F. Khan, M. Spina, M. D. Mihovilovic, P. Stanetty, *Eur. J. Org. Chem.* 2006, 3283–3307.
- [15] N. C. Bruno, M. T. Tudge, S. L. Buchwald, *Chem. Sci.* 2012, DOI: 10.1039/C2SC20903A.
- [16] M. R. Biscoe, B. P. Fors, S. L. Buchwald, J. Am. Chem. Soc. 2008, 130, 6686-6687.
- [17] T. Kinzel, Y. Zhang, S. L. Buchwald, J. Am. Chem. Soc. 2010, 132, 14073-14075.
- [18] For a recent review on the development of preformed palladium precatalysts, see: H. Li, C. C. C. J. Seechurn, T. J. Colacot, ACS Catal. 2012, 2, 1147–1164.
- [19] a) K. L. Billingsley, K. W. Anderson, S. L. Buchwald, Angew. Chem. 2006, 118, 3564–3568; Angew. Chem. Int. Ed. 2006, 45, 3484–3488; b) K. L. Billingsley, S. L. Buchwald, J. Am. Chem. Soc. 2007, 129, 3358–3366; c) M. A. Oberli, S. L. Buchwald, Org. Lett. 2012, 14, 4606–4609.
- [20] a) J. P. Wolfe, S. L. Buchwald, Angew. Chem. 1999, 111, 2570–2573; Angew. Chem. Int. Ed. 1999, 38, 2413–2416; b) J. P. Wolfe, R. A. Singer, B. H. Yang, S. L. Buchwald, J. Am. Chem. Soc. 1999, 121, 9550–9561.
- [21] a) D. G. Blackmond, Angew. Chem. 2005, 117, 4374-4393; Angew. Chem. Int. Ed. 2005, 44, 4302-4320; b) E. R. Strieter, D. G. Blackmond, S. L. Buchwald, J. Am. Chem. Soc. 2003, 125, 13978-13980; c) E. R. Strieter, D. G. Blackmond, S. L. Buchwald, Angew. Chem. 2006, 118, 939-942; Angew. Chem. Int. Ed. 2006, 45, 925-928.
- [22] The use of an SPhos-based palladacycle gave similar results as observed with RuPhos.
- [23] a) J. A. Joule, K. Mills, in *Heterocyclic Chemistry*, 5th ed., Wiley, Chichester, **2010**; b) R. Leurs, R. A. Bakker, H. Timmerman, I. J. P. de Esch, *Nat. Rev. Drug Discovery* **2005**, *4*, 107–120.
- [24] For Suzuki–Miyaura coupling of 2-pyridyl boronates, see:
  a) K. L. Billingsley, S. L. Buchwald, Angew. Chem. 2008, 120, 4773–4776; Angew. Chem. Int. Ed. 2008, 47, 4695–4698;
  b) D. X. Yang, S. L. Colletti, K. Wu, M. Song, G. Y. Li, H. C. Shen, Org. Lett. 2009, 11, 381–384; for improved palladium-catalyzed processes that occur in high yield, see: c) J. Z. Deng, D. V. Paone, A. T. Ginnetti, H. Kurihara, S. D. Dreher, S. A. Weissman, S. R. Stauffer, C. S. Burgey, Org. Lett. 2009, 11, 345–347; d) D. M. Knapp, E. P. Gillis, M. D. Burke, J. Am. Chem. Soc. 2009, 131, 6961–6963; e) G. R. Dick, E. M. Woerly, M. D. Burke,

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Angew. Chem. 2012, 124, 2721–2726; Angew. Chem. Int. Ed. 2012, 51, 2667–2672.

- [25] a) G. A. Molander, B. Biolatto, J. Org. Chem. 2003, 68, 4302–4314; b) T. Ishiyama, K. Isahida, N. Miyaura, *Tetrahedron* 2001, 57, 9813–9816.
- [26] Our attempts to couple 5-bromoimidazoles, 3-bromoimidazo-[1,2-a]pyridine, 3-bromoimidazo[1,2-a]pyrazine, and 6chloroimidazo[2,1-b]thiazole were unsuccessful.
- [27] M. Abarbri, F. Dehmel, P. Knochel, *Tetrahedron Lett.* **1999**, *40*, 7449–7453.
- [28] At an early stage of this study, freshly prepared solutions of ZnCl<sub>2</sub> in THF were utilized in our procedure. In an effort to

develop a method of enhanced operational simplicity, we evaluated the effectiveness of commercially available  $ZnCl_2$  solutions, and the 2-MeTHF solution of  $ZnCl_2$  was identified as the optimal choice to furnish consistent results, completely excluding the use of a glovebox. 2-MeTHF solution of  $ZnCl_2$  was used for the syntheses of **71**, **7m**, **7n**, **7p**, **7q**, **7r**, **7w**, and **7a'** (Scheme 3) as well as **8k** (Scheme 4).

[29] For alternative strategies to prepare polyfluorinated biaryls, see: a) M. Lafrance, C. N. Rowley, T. K. Woo, K. Fagnou, J. Am. Chem. Soc. 2006, 128, 8754–8756; b) H.-Q. Do, O. Daugulis, J. Am. Chem. Soc. 2008, 130, 1128–1129; c) Y. Nakamura, N. Yoshikai, L. Ilies, E. Nakamura, Org. Lett. 2012, 14, 3316–3319.