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Copper-Facilitated Suzuki Reactions: Application to 2-Heterocyclic Boronates

James Z. Deng,[*,†] Daniel V. Paone,[*,†] Anthony T. Ginnetti,[†] Hideki Kurihara,[‡] Spencer D. Dreher,[‡] Steven A. Weissman,[‡] Shaun R. Stauffer,[†] and Christopher S. Burgey[†]

*Department of Medicinal Chemistry, Merck Research Laboratories,
P.O. Box 4, West Point, Pennsylvania 19486, and Department of Process Research,
Merck Research Laboratories, P.O. Box 2000, Rahway, New Jersey 07065*

james_deng@merck.com; daniel_paone@merck.com

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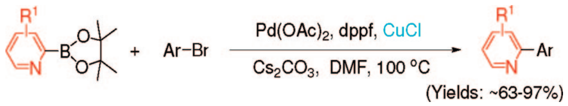
ABSTRACT



The palladium-catalyzed Suzuki−Miyaura reaction has been utilized as one of the most powerful methods for C−C bond formation. However, Suzuki reactions of electron-deficient 2-heterocyclic boronates generally give low conversions and remain challenging. The successful copper(I) facilitated Suzuki coupling of 2-heterocyclic boronates that is broad in scope is reported. Use of this methodology affords greatly enhanced yields of these notoriously difficult couplings. Furthermore, mechanistic investigations suggest a possible role of copper in the catalytic cycle.

Since the discovery of the palladium-catalyzed Suzuki−Miyaura reaction, organoboronates have been developed as powerful reagents for carbon−carbon bond formation due to their stability, nontoxicity, and functional group compatibility.[1] Although numerous ligand systems have been developed for a wide array of coupling partners, reaction of electron-deficient boronates such as 2-pyridyl remains challenging[2] and of high interest to the synthetic community, particularly the pharmaceutical industry. For example, coupling of 2-pyridylboronic acid was unsuccessful under a very general Suzuki coupling system.[2b]

It is hypothesized that transmetalation from boron to palladium of electron-deficient 2-heterocyclic boronates is slow relative to protodeboronation, leading to poor conversions.[3] To address this, recent efforts have focused on formation of more stable or activated boronates.[4] While these methods perform well for certain substrates, highly electron-deficient boronates remain problematic.[4c] Additionally, the lithium borate salts utilized demonstrate limited stability and require preparation through metalations which limit functional group tolerance. The use of pinacol boronates is attractive due to their commercial availability and relative stability toward air and moisture; however, no general solution for the direct coupling of 2-pyridylpinacol boronates has been reported.

We sought to generate in situ a more reactive organometal species from the corresponding 2-heterocyclic boronic esters, which could subsequently participate in the palladium-catalyzed cross-coupling. While copper(I) halides have been used extensively in Stille reactions,[5] there are few reports about their use in the Suzuki couplings, and the role of copper

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[†] Department of Medicinal Chemistry.

[‡] Department of Process Research.

(1) Suzuki reviews: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483. (b) Miyaura, N. *J. Organomet. Chem.* **2002**, *653*, 54–57.

(2) For Suzuki reactions with heterocyclic boronates, see: (a) Campeau, L.-C.; Fagnou, K. *Chem. Soc. Rev.* **2007**, *36*, 1058–1068. (b) Billingsley, K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3358–3366. (c) Bouillon, A.; Lancelot, J.-C.; Sopkova de Oliveira Santos, J.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2003**, *59*, 10043–10049.

(3) (a) Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302–4314. (b) Fischer, F. C.; Havinga, E. *Recl. Trav. Chim. Pays-Bas* **1974**, *93*, 21–24. (c) Ishiyama, T; Isahida, K.; Miyaura, N. *Tetrahedron* **2001**, *57*, 9813–9816.

(4) (a) Hodgson, P. B.; Salingue, F. H. *Tetrahedron Lett.* **2004**, *45*, 685–687. (b) Yamamoto, Y.; Takizawa, M.; Yu, X.; Miyaura, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 928–931. (c) Billingsley, K.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 4695–4698.

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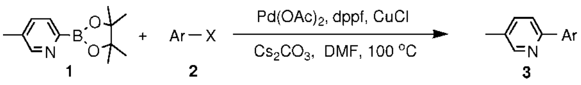
has not been defined.[6,4a,b] We report herein the successful copper(I)-facilitated Suzuki coupling of 2-heterocyclic boronates that is broad in scope; furthermore, mechanistic investigations suggest a possible role of copper in the catalytic cycle.

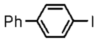
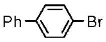
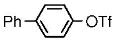
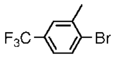
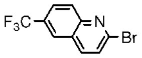
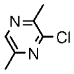
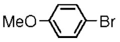
Initial survey reactions of 2-pyridyl boronates with Pd(dppf)Cl_2 gave much higher conversions with CuI additive relative to the noncopper conditions. Encouraged by these results, we sought to optimize the reaction conditions using parallel microscale high-throughput experimentation techniques.[7] We rapidly evaluated various parameters including copper source, ligand, base, and solvent. It was found that the reactivity of copper salt followed the order CuCl > CuBr, Cu_2O > CuI and that the amount of bipyridyl formation was minimized with CuCl or Cu_2O. Dppf was found to be the optimal ligand, with DMF and Cs_2CO_3 as preferred solvent and base. In addition, we used microscale design of experiments (DOE)[8] to determine the optimal temperature (100 °C) and equivalencies of reagents (2:1 of boronate to aryl halide) and also discovered that the most robust reactions were acheived when dppf was used as a 2:1 ratio to palladium.

With these results in hand, we surveyed the scope of the electrophile using boronate ester **1** (Table 1).[9] Reaction of aryl iodides proceeded in high yield with CuCl (89%, entry 1) relative to the standard Suzuki conditions without CuCl (22%). This yield enhancement is even more pronounced when moving to the less reactive bromide and triflate electrophiles (entries 2 and 3), where almost no conversion is observed without the use of CuCl, and high yields (88% and 76%, respectively) are maintained with CuCl. Ortho substitution is tolerated (entry 4), as are heteroaryl halides (entries 5 and 6), but the yield is lower for the electron-rich 4-methoxyphenyl bromide in entry 7.

Next, various 2-heterocyclic boronates were examined (Table 2). Unsubstituted and substituted 2-pyridyl substrates bearing electron-withdrawing substituents performed well under these reaction conditions (entries 1−5) with yields ranging from 70 to 97%. Once again, control reactions without CuCl gave negligible conversions. Notably, the highly electron-deficient cyano boronate (entry 6) affords a 63% yield.[4c] While moderate conversions are observed for 2-pyrazinyl and 2-pyrrolo boronates (entries 7 and 8) without CuCl, higher yields are achieved with CuCl. Interestingly, 6-substituted 2-pyridyl boronates gave high isolated yields both with and without CuCl (entries 9 and 10), regardless of the electronic properties of the 6-substituents.[10]

Table 1. Scope of the Electrophile[a]



entry	Ar−X	yield (%) [b]	conversion (%) without CuCl
1		89	22 [c]
2		88	<5
3		76	0
4		76	<5
5		77	<5
6		78	0
7		46	<5

[a] Reaction conditions: 1.0 equiv of halide, 2.0−2.5 equiv of 2-pyridyl boronate, 2.0 equiv of Cs_2CO_3, 5 mol % of Pd$(OAc)_2$, 10 mol % of dppf, 100 mol % of CuCl, 0.1 M DMF, 100 °C, 16 h. [b] Yields are based on purification after silica gel chromatography. Conversions are based on LC/MS. [c] Isolated yield.

We hypothesize that the reaction primarily operates through the basic Suzuki catalytic cycle (Figure 1). Direct transmetalation from electron-deficient heterocyclic boronates to palladium (path A) is relatively slow in comparison with deboronation (path B). Alternatively, transmetalation to form a 2-pyridyl copper species (path C) and a second transmetalation to a palladium complex (path D) may provide a more efficient process, allowing conversion to cross-coupled product after reductive elimination. The major competing reaction is the reductive homocoupling of the 2-pyridyl copper species resulting in 2,2′-pyridine dimer, thus necessitating the use of excess boronate for complete conversions.[11]

We sought to provide mechanistic support for the proposed initial transmetalation from boron to copper (path C) by treating pyridyl boronate **7** with 1 equivt of CuCl at 80 °C (Scheme 1). After 90 min, homocoupled dimer **8** was obtained as the major product, characteristic of an intermediary 2-pyridylcopper species.[12a] No conversion to **8** was observed in the control reaction without CuCl, providing indirect evidence for path C.

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(5) (a) Farina, V.; Kapadia, S.; Krishman, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905–5911. (b) Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600–7605. (c) Mee, S. P. H.; Lee, V.; Baldwin, J. E. *Angew. Chem., Int. Ed.* **2004**, *43*, 1132–1136.

(6) (a) Savarin, C.; Liebeskind, L. S. *Org. Lett.* **2001**, *3*, 2149–2152. (b) Li, J.-H.; Li, J.-L.; Wang, D.-P.; Pi, S.-F.; Xie, Y.-X.; Zhang, Y.-X.; Zhang, M.-B.; Hu, X.-C. *J. Org. Chem.* **2007**, *72*, 2053–2057. (c) Thathagar, M. B.; Beckers, J.; Rothenberg, G. *J. Am. Chem. Soc.* **2002**, *124*, 11858–11859.

(7) Details of similar high-throughput experiments are found in: Dreher, S. D.; Dormer, P. G.; Sandrock, D. L.; Molander, G. A. *J. Am. Chem. Soc.* **2008**, *130*, 9257–9259.

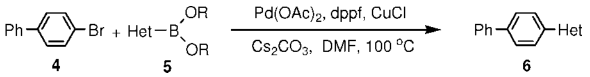
(8) For a recent example of DOE applied to a Pd-catalyzed reaction, see: Denmark, S. E.; Butler, C. R. *J. Am. Chem. Soc.* **2008**, *130*, 3690–3704.

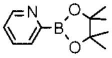
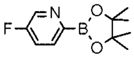
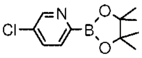
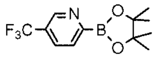
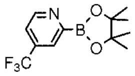
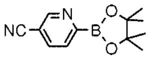
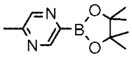
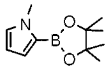
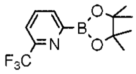
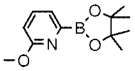
(9) Though several substrates gave complete conversion within 1 h, reactions were continued to 16 h as a general protocol. Alternatively, reactions could be conducted using mircowave irradiation at 160 °C and were typically complete in 20 min.

(10) A similar phenomenon with C−H insertions was reported: Lewis, J. C.; Bergman, R. G.; Ellman, J. A *J. Am. Chem. Soc.* **2007**, *129*, 5332–5333.

(11) This homocoupling is also associated with loss of Cu(I) from the catalytic cycle. Use of Cu_2O minimizes homocoupling and enables a catalytic copper reaction, as 87% yield is achieved in entry 1, Table 1 with 10 mol % Cu_2O. Conversions are substrate dependent, and efforts to develop more robust catalytic copper conditions are ongoing.

Table 2. Scope of Heterocyclic Boronates



entry	boronate	yield (%)[a]	conversion (%) without CuCl
1		97	15
2		77	<5
3		70	<5
4		87	10
5		94	15
6		63	0
7		42	20
8		80	45
9		95	91[b]
10		75	76[b]

[a] Reaction conditions as in Table 1. [b] Isolated yield.

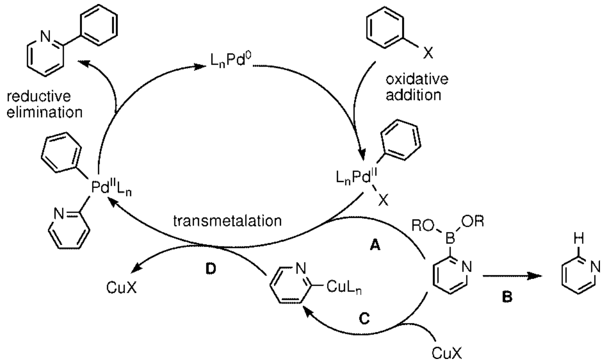
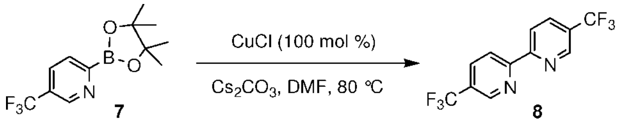
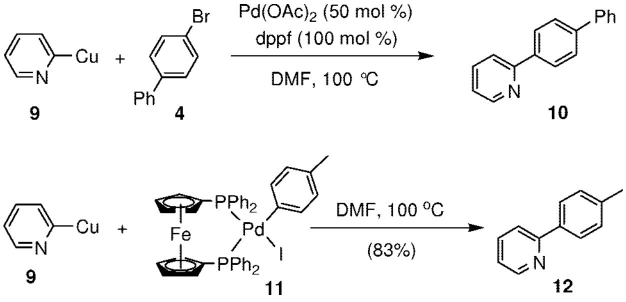


Figure 1. Possible mechanism.

Scheme 1



Scheme 2



To further support the existence of a 2-pyridylcopper species in the productive path of the proposed catalytic cycle, 2-pyridylcopper **9**[12] was independently prepared and reacted with bromide **4** (Scheme 2). Using 50 mol % of palladium,[13] complete conversion of bromide to **10** was observed. To specifically address the feasibility of the proposed second transmetalation from copper to palladium (path D), **9** was reacted with the preformed Pd(dppf)−aryl iodide oxidative addition complex **11**.[14] After heating in DMF at 100 °C for 60 min, cross-coupled product **12** was obtained in 83% yield. This reaction also proceeded cleanly at ambient temperature, though at a much slower rate.

In summary, we have developed a general solution for the Suzuki coupling of 2-heterocyclic boronates employing CuCl, with wide scope in both the boronate and electrophile. Mechanistic studies suggest that the role of copper is to facilitate the transmetalation of boronates to the palladium complex. This method may also find utility in other transformations where transmetalation from boron is problematic.

Acknowledgment. We thank Professor David MacMillan of Princeton University for helpful discussions concerning possible reaction mechanisms.

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

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[12] (a) Malmberg, H.; Nilsson, M. *Tetrahedron* **1986**, *42*, 3981–3986. (b) Malmberg, H.; Nilsson, M. *Tetrahedron* **1982**, *38*, 1509–1510.

[13] It was necessary to increase the concentration of $Pd(OAc)_2$ and dppf due to competing homocoupling of the preformed 2-pyridylcopper species.

[14] (a) Driver, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 8232–8245. (b) Negishi, E.; Takahashi, T.; Baba, S.; Van Horn, D. E.; Okukado, N. *J. Am. Chem. Soc.* **1987**, *109*, 2393–2401. (c) Fitton, P.; Johnson, M. P.; McKeon, J. E. *J. Chem. Soc., Chem. Commun.* **1968**, 6–7.