

A Highly Efficient Palladium/Copper Cocatalytic System for Direct Arylation of Heteroarenes: An Unexpected Effect of Cu(Xantphos)I

Jinkun Huang,* Johann Chan, Ying Chen, Christopher J. Borths, Kyle D. Baucom, Robert D. Larsen, and Margaret M. Faul

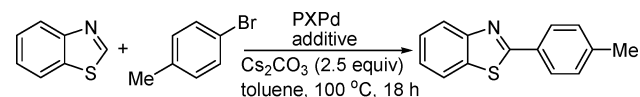
Chemical Process Research and Development, Amgen Inc., Thousand Oaks, California 91320

Received January 20, 2010; E-mail: jhuang@amgen.com

There is a continuing interest in the development of general methods for providing diverse scaffolds of pharmaceutically active compounds. Driven by the need for the synthesis of 2-aryl-substituted benzothiazoles, we became interested in the direct arylation of heteroarenes. While numerous methods to construct this motif have been reported in the literature,¹ transition-metal-catalyzed direct C–H arylation to effect this transformation has only recently been popularized.² However, its application remains challenging, in part because of the high catalyst loadings, use of strong bases, and drastic reaction conditions.³ Certain heteroarenes must be functionalized at the adjacent nitrogen.⁴ Herein we report our discovery of a highly efficient catalyst system utilizing a Pd/Cu cocatalyst that addresses these issues and enables a practical direct C–H arylation process.⁵

The optimization of the C–H arylation was first examined using benzothiazole and 4-tolyl bromide as coupling partners (Table 1). Low yields of the heteroarene coupling product were observed, except under conditions utilizing phosphorus or nitrogen ligands bound to copper(I). After extensive screening, we discovered that the commercially available, air-stable PXPd complex (**1**)⁶ in combination with Cu(Xantphos)I (**2**, Figure 1)⁷ forms an excellent cocatalyst system.⁸ Specifically, the combination of **1** (0.25 mol %) and **2** (1 mol %) gave 97% yield of the desired arylation product in 18 h (entry 11) at 100 °C. *At the same loading, neither 1 nor 2 individually can catalyze the C–H arylation reaction* (entries 4 and 12). Interestingly, the similar bidentate complex Cu(dppf)I is less effective in catalyzing the reaction (entry 10), and the bulky monodentate complex Cu(IPr)I⁹ shows no activity.

Table 1. Optimization of the Direct Arylation of Benzothiazole



Entry	PXPd ^a (mol %)	Additive	Cu(I) (mol %)	Yield ^b
1	2.5	none	0	30
2	1	none	0	16
3	1	Cu	4	32
4	0.25	none	0	<5
5	0.25	CuX ^c	1	<5
6	0.25	CuTc ^d	1	<5
7	0.25	CuI/Phen ^e	1	31
8	0.25	Cu(PPh ₃)(Phen)Br ^e	1	63
9	0.25	Cu(PPh ₃) ₃ Br	1	52
10	0.25	Cu(dppf)I	1	65
11	0.25	Cu(Xantphos)I^f	1	97
12	0	Cu(Xantphos)I ^f	1	0

^a PXPd = dichlorobis(chloro-di-*tert*-butylphosphine)palladium. ^b Yield determined by HPLC based on a purified standard. ^c X = I, Br, Cl, OTf. ^d CuTc = copper(I) thiophene-2-carboxylate. ^e Phen = 1,10-phenanthroline. ^f Xantphos = 9,9-dimethyl-4,5-bis(diphenylphosphine)xanthene.

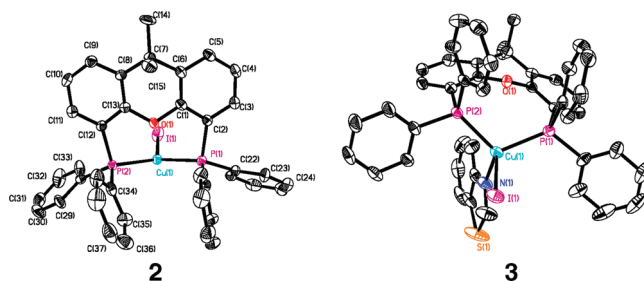


Figure 1. ORTEP views (50% probability) of the crystal structures of Cu(Xantphos)I (**2**) and Cu(Xantphos)(benzothiazole)I (**3**).

This new catalytic system has been found to be general for the coupling of a broad range of heteroarenes with a variety of aryl halides (Table 2). Electron-poor or -rich aryl bromides containing functionalities such as nitrile, trifluoromethyl, vinyl, ester, or aldehyde as well as pyridinyl rings are well-tolerated. Activated aryl chlorides (entries 3 and 9) are compatible, providing excellent conversion to the desired products. Phenyl triflate shows good reactivity, but the corresponding reaction with iodobenzene is sluggish, affording only a moderate yield (entry 1).¹⁰ Electron-rich benzothiazoles (entries 11 and 13) are more reactive than their electron-poor counterparts (entry 12; see below). Benzoxazole is an excellent coupling partner (entry 15), while *N*-methylbenzimidazole is much less reactive (entry 16).

While the unprecedented high efficiency of the current catalytic system is not well understood, it is believed to stem from the introduction of Cu(Xantphos)I (**2**). Accordingly, we focused our attention on elucidating its role in the reaction. To probe its function, an equimolar mixture of **2** and benzothiazole was dissolved in CH₂Cl₂ at room temperature, from which a 1:1 complex (**3**) was cleanly formed to afford X-ray-quality crystals (Figure 1).

The lone pair on the nitrogen atom in benzothiazole binds to the copper center to form tetrahedral complex **3**. This solid-state structure correlates well with ¹H NMR data, wherein the proton chemical shift of the 2-position shifts downfield from 9.00 ppm in benzothiazole to 9.19 ppm in **3**. We postulate that the effect of this coordination lowers the pK_a of the adjacent C–H bond, allowing for facile deprotonation.¹¹

On the basis of the experimental observations, we propose a mechanism in which the copper complex takes part in the critical transmetalation step in the Pd/Cu double-cocatalytic cycles (Scheme 1). Formation of **3** and its subsequent deprotonation¹²/rearrangement would afford **4**.¹³ Transmetalation of the 2-benzothiazole–copper species **4** to palladium(II) followed by reductive elimination would give the desired product and release both the copper and palladium catalysts.¹⁴ The presumed presence of such organo-copper intermediates is in agreement with the function of copper(I) reported recently in a Suzuki coupling¹⁵ and the well-known Sono-

Table 2. Scope of PXPd/Cu(Xantphos)I-Catalyzed C–H Arylation

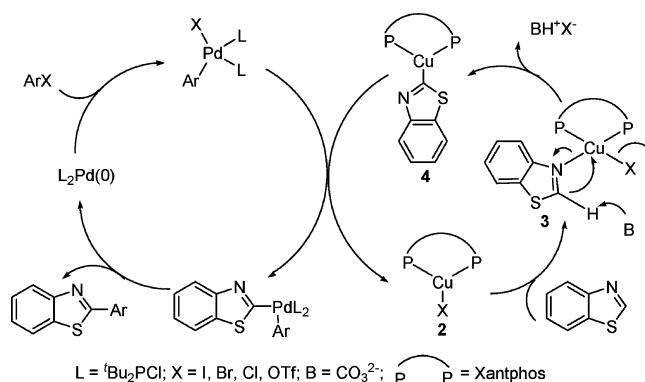
$\text{R} \begin{array}{c} \text{N} \\ \diagup \quad \diagdown \\ \text{C}=\text{H} \\ \text{Z} \end{array} + \text{ArX} \xrightarrow[\text{toluene, 100 } ^\circ\text{C}]{\text{PXPd (0.25 mol \%)} \\ \text{Cu(Xantphos)I (1 mol \%)} \\ \text{Cs}_2\text{CO}_3 \text{ (2.5 equiv)}} \text{R} \begin{array}{c} \text{N} \\ \diagup \quad \diagdown \\ \text{C}=\text{Ar} \\ \text{Z} \end{array}$ Z = O, S, NMe			
Entry	ArX	Product	Yield (%) ^a
1			X = Cl, 6 X = Br, 97 X = OTf, 88 X = I, 68
2			95
3			X = Br, 98 X = Cl, 90
4 ^b			68
5 ^b			84
6			96
7			73
8			91
9			X = Cl, 88 X = Br, 95
10			88
11			98
12			85
13			94
14			96
15			R' = H, 99 R' = 4-OMe, 95 R' = 4-CN, 88
16 ^b			R' = H, 62 R' = 3-OMe, 48 R' = 4-CF3, 56

^a Isolated yield. The reactions were monitored by LC–MS.^b Reaction conducted with 0.5 mol % **1** and 2 mol % **2**.

gashira reaction,¹⁶ but other mechanisms,^{1b} including aromatic electrophilic substitution as proposed by others,^{3c,g} cannot be excluded.

In summary, we have disclosed a mild and efficient catalytic system for direct arylation of heteroarenes. This new catalytic system has been demonstrated to be suitable for the couplings of a broad range of substrates. Notable features of this system include the unprecedented high efficiency achieved by very low metal loadings, which is attributed to the unique role of Cu(Xantphos)I. Further applications to other substrates as well additional data on the reaction mechanism will be reported in due course.

Acknowledgment. This work is dedicated to the memory of Prof. Keith Fagnou. We also thank Drs. Xiang Wang, Anthony O.

Scheme 1. Proposed Mechanism for the Direct C–H Arylation

King, and Jerry A. Murry and Prof. Steve L. Buchwald for their insightful suggestions. We are grateful to Drs. Tsang-Lin Hwang, Bo Shen, and Richard Staples for structural analysis assistance.

Supporting Information Available: Detailed experimental procedures, analytical data for compounds, and CIF files for **2** and **3**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (1) (a) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998. (b) *Modern Arylation Methods*; Ackermann, L., Ed.; Wiley-VCH: Weinheim, Germany, 2009.
- (2) Reviews: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (b) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (c) Bellina, F.; Rossi, R. *Tetrahedron* **2009**, *65*, 10269.
- (3) Selected examples: Pd (or with Cu): (a) Ackermann, L.; Althammer, A.; Fenner, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 201. (b) Do, H.-Q.; Kashif Khan, R. M.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 15185. (c) Chiong, H. A.; Daugulis, O. *Org. Lett.* **2007**, *9*, 1449. (d) Nandurkar, N. S.; Bhanushali, M. J.; Bhor, M. D.; Bhanage, B. M. *Tetrahedron Lett.* **2008**, *49*, 1045. (e) Bellina, F.; Calandri, C.; Cauteruccio, S.; Rossi, R. *Tetrahedron* **2007**, *63*, 1970. (f) Yokooji, A.; Okazawa, T.; Tetsuya, S.; Miura, M.; Nomura, M. *Tetrahedron* **2003**, *59*, 5685. (g) Pivsa-Art, S.; Satoh, Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467. Rh: (h) Wang, X.; Lane, B. S.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 4996. (i) Lewis, L. C.; Wu, J. Y.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 2493. Cu: (j) Zhao, D.; Wang, W.; Yang, F.; Lan, J.; Yang, L.; Gao, G.; You, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 3296. (k) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 12404. (l) Ackermann, L.; Potukuchi, H. K.; Landsberg, D.; Vincente, R. *Org. Lett.* **2008**, *10*, 3081. Ni: (m) Hachiya, H.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 1737. (n) Canivet, J.; Yamaguchi, J.; Ban, I.; Itami, K. *Org. Lett.* **2009**, *11*, 1733.
- (4) (a) Campeau, L.-C.; Stuart, D. R.; Leclerc, J.-P.; Bertrand-Laperle, M.; Villermure, E.; Sun, H.-Y.; Lasserre, S.; Guimond, N.; Lecavallier, M.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 3291. (b) Larivee, A.; Mousseau, J. J.; Charette, A. B. *J. Am. Chem. Soc.* **2008**, *130*, 52.
- (5) A multikilogram process based on this system was run successfully.
- (6) **1** is commercially available from Combiphos. For examples in coupling reactions, see: Li, G. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 1513. Other ligands such as P^tBu₃, Xantphos, and some biphenyl phosphines with [Pd(allyl)Cl]₂ are competent palladium catalyst partners.
- (7) **2** is an air-stable white solid that can be conveniently prepared in quantitative yield from an equimolar ratio of CuI and Xantphos in CH₂Cl₂ or CH₃CN.
- (8) The coupling experiment using 0.25 mol % Pd and Xantphos in the absence of **1** gave <5% product.
- (9) IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene.
- (10) Similar controversial poor reactivity of aryl iodides in C–H arylation has recently been observed: Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581.
- (11) The electron-rich 6-piperidinylbenzothiazole (Table 2, entry 13) is a superior substrate in comparison with its 6-nitrile analogue (<5% conversion). ¹H NMR studies showed strong binding of **2** with the former to form the corresponding complex, but the analogous interaction was not observed with the latter. A similar explanation has been proposed in N-oxide C–H arylations. See: Goresky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848.
- (12) The isotope effect (*k_H/k_D* = 1.3) indicates that deprotonation is unlikely to be the rate-determining step.
- (13) The Xantphos bite angle may play a crucial role: Kamer, P. C.; Van Leeuwen, P. W. N. M.; Reek, J. N. H. *Acc. Chem. Res.* **2001**, *34*, 895.
- (14) A similar mechanism was proposed in Pd/Cu-catalyzed decarboxylative coupling: Goossen, L. J.; Deng, G.; Levy, L. M. *Science* **2006**, *313*, 662.
- (15) 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.
- (16) Osakada, K.; Sakata, R.; Yamamoto, T. *Organometallics* **1997**, *16*, 5354.

JA100354J