ORGANIC LETTERS

2010
Vol. 12, No. 6
1192−1195

Copper-Catalyzed Chlorination of Functionalized Arylboronic Acids[†]

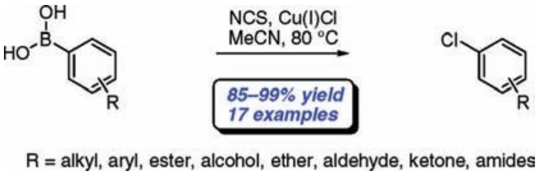
Hong Wu and John Hynes, Jr.*

Discovery Chemistry, Bristol-Myers Squibb Company, PO Box 4000,
Princeton New Jersey 08543

john.hynes@bms.com

Received December 21, 2009

ABSTRACT



A mild, efficient, Cu(I)-catalyzed method for the conversion of arylboronic acids to aryl chlorides is reported. This method is particularly useful for the conversion of electron-deficient arylboronic acids to aryl chlorides, a transformation that is inefficient in the absence of Cu catalysis.

Aryl chlorides have grown in utility as synthetic intermediates[1] and are essential components of many pharmaceutical compounds.[2] Classic methods for the synthesis of chlorinated arenes are via direct electrophilic aromatic substitution or the Sandmeyer reaction. More recently, boron−halogen exchange[3] has emerged as a means by which halogenated arenes can be generated. The majority of these transformations have been directed at the synthesis of aryl iodides, bromides,[4] and fluorides.[5]

Although aryl boron−bromide and boron−iodide exchange is efficient with NBS and NIS for some substrates, the analogous boron−chloride reaction with NCS fails or has limited scope, presumably due to the lower reactivity of NCS.[4c,f] Huffman showed that Cu(II) can mediate the bromination of arylboronates,[6] and Hartwig extended this to chlorides.[7] Unfortunately, this method relies on the use of excess Cu(II) halide salts (3.5 equiv) and, in the case of

---

[†] This manuscript is dedicated to Professor Ralph F. Hirschmann, 1922−2009.

(1) (a) Ikawa, T.; Barder, T. E.; Biscoe, M. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 13001. (b) Fu, G. C. *Acc. Chem. Res.* **2008**, *41*, 1555. (c) Shen, Q.; Ogata, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 6586. (d) Fors, B. P.; Watson, D. A.; Biscoe, M. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 13552. (e) Vo, G. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2009**, *131*, 11049.

(2) Of the top 15 selling medicines of 2008 in the U.S., three were aryl chlorides and two were aryl fluorides, accounting for a combined sales revenue of $22 billion. IMS Health Inc. 2008 U.S. Sales and Prescription Information. www.imshealth.com (accessed 12/10/09).

(3) For select references on the halodeboronation of alkenes, see: (a) Kunda, S. A.; Smith, T. L.; Hylarides, M. D.; Kabalka, G. W. *Tetrahedron Lett.* **1985**, *26*, 279. (b) Brown, H. C.; Subrahmanyam, C.; Hamaoka, T.; Ravindran, N.; Bowman, D. H.; Misumi, S.; Unni, M. K.; Somayaji, V.; Bhat, N. G. *J. Org. Chem.* **1989**, *54*, 6068. (c) Brown, H. C.; Hamaoka, T.; Ravindran, N.; Subrahmanyam, C.; Somayaji, V.; Bhat, N. G. *J. Org. Chem.* **1989**, *54*, 6075. (d) Brown, H. C.; Larock, R. C.; Gupta, S. K.; Rajagopalan, S.; Bhat, N. G. *J. Org. Chem.* **1989**, *54*, 6079. (e) Willis, D. A.; McGinnis, M. B.; Kabalka, G. W.; Pagni, R. M. *J. Organomet. Chem.* **1995**, *487*, 35. (f) Petasis, N. A.; Zavialov, I. A. *Tetrahedron Lett.* **1996**, *37*, 567. (g) Petasis, N. A.; Yudin, A. K.; Zavialov, I. A.; Prakash, G. K. S.; Olah, G. A. *Synlett* **1997**, 606. (h) Lightfoot, A. P.; Twiddle, S. J. R.; Whiting, A. *Tetrahedron Lett.* **2004**, 8557. (i) Hashmi, A. S. K.; Ramamurthi, T. D.; Rominger, F. *J. Organomet. Chem.* **2009**, *694*, 592.

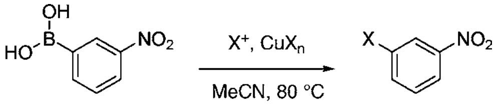
(4) For aryl iodo- and bromodeboronation reactions, see: (a) Kabalka, G. W.; Gooch, E. E.; Sastry, K. A. R. *J. Nucl. Med.* **1981**, *22*, 908. (b) Kabalka, G. W.; Sastry, K. A. R.; Pagni, P. G. *J. Radioanal. Chem.* **1982**, *74*, 315. (c) Thiebes, C.; Surya Prakash, G. K.; Petasis, N. A.; Olah, G. A. *Synlett* **1998**, 141. (d) Kabalka, G. W.; Akula, M. R.; Zhang, J. *Nucl. Med. Biol.* **2002**, *29*, 841. (e) Kabalka, G. W.; Mereddy, A. R. *Tetrahedron Lett.* **2004**, *45*, 343. (f) Szumigala, R. H.; Devine, P. N.; Gauthier, D. R., Jr.; Volante, R. P. *J. Org. Chem.* **2004**, *69*, 566. (g) Kabalka, G. W.; Mereddy, A. R. *Organometallics* **2004**, *23*, 4519. (h) See also ref 6a.

(5) (a) Clough, J. M.; Diorazio, L. J.; Widdowson, D. A. *Synlett* **1990**, 761. (b) Diorazio, L. J.; Widdowson, D. A.; Clough, J. M. *Tetrahedron* **1992**, *48*, 8073. (c) Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* **2008**, *130*, 10060. (d) Furuya, T.; Kaiser, H. M.; Ritter, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 5993. (e) Furuya, T.; Ritter, T. *Org. Lett.* **2009**, *11*, 2860. (f) Cazorla, C.; Metay, E.; Andrioletti, B.; Lemaire, M. *Tetrahedron Lett.* **2009**, *50*, 3936. (g) For an attractive conversion of aryl triflates to aryl fluorides, see: Watson, D. A.; Su, M.; Teverovskiy, G.; Zhang, Y.; Garcia-Fortanet, J.; Kinzel, T.; Buchwald, S. L. *Science* **2009**, *325*, 1661.

(6) (a) Thompson, A. L. S.; Kabalka, G. W.; Akula, M. R.; Huffman, J. W. *Synthesis* **2005**, 457. For a preliminary halodeboronation reaction of phenylboric acid with $CuBr_2$ and $CuCl_2$, see : (b) Ainley, A. D.; Challenger, F. *J. Chem. Soc.* **1930**, 2171.

10.1021/ol9029337

Table 1. Copper(I) and Electrophilic Halogen Source Survey



1a

2a, X = Cl
3a, X = Br
4a, X = I

entry	Cu salt (1 equiv)	X$^+$ (1 equiv)	reaction time, h	% yield[a]
1	CuCl	NCS	2	96
2		NCS	24	<1[b]
3	CuCl		24	30[b,c]
4		NBS	24	19[d]
5	CuBr	NBS	1	98
6		NIS	24	25[e]
7	CuI	NIS	2.5	87
8	CuCl	DCDMH[f]	2	98
9	CuOAc	NCS	2	64[g]
10	CuCl$_2$	NCS	2	>98[b]

[a] All yields are for isolated, pure products unless otherwise noted. [b] Yields were determined by analytical HPLC against commercial standards. [c] Two major byproducts corresponding to homodimerization and deboronation products were observed. [d] See ref 4c; in our hands a 21% yield was obtained. [e] See ref 4c; however, in our hands a 66% yield was obtained. [f] DCDMH = 1,3-dichloro-5,5-dimethylhydantion. [g] 4% 3-*O*-acetoxynitrobenzene was present in the isolated material, unoptimized.

aryl bromides, is accompanied by variable yields 24−96%.[6a] Regardless, previous methods of boron−halogen exchange suffer from poor reactivity with electron-deficient substrates. We have developed an efficient and mild boron−chloride exchange (chlorodeboronation) reaction. Importantly, this method is copper catalyzed, is effective for both electron-rich and electron-deficient substrates, requires low metal loading, and further demonstrates the remarkable ability of Cu(I) to mediate heteroatom couplings with boronic acids.[8]

The exceptionally low yield (3.7%) for the conversion of 3-nitrobenzene boronic acid (**1a**) to 3-chloronitrobenzene (**2a**) with NCS/cat. NaOMe provided a starting point for our initial investigations.[9] We speculated that Cu(I) would favorably modulate the reactivity of **1a** with NCS.[10] Gratifyingly, the addition of 1 equiv of CuCl to the reaction mixture provided **2a** in 96% isolated yield (Table 1, entry 1).[11] CuBr/NBS and CuI/NIS combinations were also found to give excellent yields of the corresponding bromo (**3a**) and iodo (**4a**) analogues, respectively (entries 5 and 7). In contrast, Cu(II) alone is an inefficient promoter as the yield of **3a** from a boronate ester using CuBr$_2$ is 28%.[6a] We are not aware of any iododeboronation procedures using CuI$_2$. Control experiments confirmed the mediator role of Cu(I) in this reaction (entries 2, 4, and 6). Moderate reactivity was observed with CuCl alone (entry 3). Our Cu(I) conditions also promote the chlorination with 1,3-dichloro-5,5-dimethylhydantion (DCDMH) (entry 8) and appear superior to previous methods that use this reagent.[9] Under these stoichiometric conditions, alternative copper sources, including CuOAc (entry 9) and CuCl$_2$ (entry 10), provided moderate to high yields of **2a**. Additionally, potassium 3-nitrotrifluoroborate underwent rapid conversion to **2a** (97% yield, 2 h),[12] whereas the corresponding pinacol ester was less reactive (20% conversion at 24 h, data not shown). Temperature influences rate but not efficiency. Reactions of **1a** proceed to 95% conversion in 24 h at rt and >99% in 2 h at 80 °C. Moreover, reaction temperatures of 120 °C, obtained in a microwave reactor, reduced reaction times to 30 min or less (data not shown). For the determination of the scope of this process, all reactions reported in this study were performed at 80 °C in MeCN.

Given the limited reports of aryl chlordeboronation, we focused our efforts on this problem. The functionalized boronic acids shown in Table 2 were used to demonstrate the scope of this reaction. In all cases, chlorination proved highly efficient (85−99% isolated yield). Electron-rich (entries 1−5) and electron-deficient (entries 6−12) aryl chlorides were obtained by this method from the corresponding boronic acids.[13] Functional group tolerance is excellent. In addition to ester (entry 6), nitrile (entry 7), and amide (entry 9) groups, ketone, aldehyde, acid, and alcohol (entries 10−13) groups were well tolerated. This method also accommodates sterically congested boronic acids (entries 14−16) including biphenyl-2-boronic acid (96% yield) and 2,6-dimethylboronic acid (94% yield).

Having demonstrated the broad applicability of the stoichiometric Cu(I)-mediated process, we hoped to gain further insight into the reaction mechanism with catalytic levels of the Cu(I) halide. Our initial experiments with reduced Cu(I) loading (0.5 and 0.2 equiv, data not shown) revealed that a catalytic process is operative. Table 3 demonstrates the effectiveness of this process using catalytic Cu(I): 0.1 equiv of CuCl and 1 equiv of NCS in MeCN (0.25−0.5M) at 80 °C. Comparable yields for the catalytic CuCl relative to stoichiometric conditions were obtained for all compounds tested. Slightly longer reaction times were required for the catalytic reactions. Several advantages to this method are that the reactions proceed with high efficiency and virtually no side

---

(7) Murphy, J. C.; Liao, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 15434.

(8) Chan, D. M. T.; Lam, P. Y. S. In *Boronic Acids*; Hall, D. G., Ed.; John Wiley & Sons: Weinheim, 2005; pp 205−240.

(9) This reaction was optimized to 43% yield (HPLC) with the use of DCDMH instead of NCS. See ref 4f.

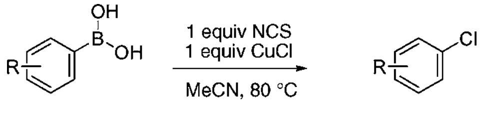
(10) (a) Savarin, C.; Srogl, J.; Liebeskind, L. L. *Org. Lett.* **2002**, *4*, 4309. (b) See also: Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400.

(11) Representative Procedure: To a solution of arylboronic acid (1 equiv) in acetonitrile (0.25−0.5 M) were added CuCl (1 equiv) and NCS (1 equiv). The reaction was heated at 80 °C until completion of the reaction was confirmed by HPLC (typically 1−18 h). The reaction was then cooled to room temperature and diluted with ether. The ether layer was washed with 1 N HCl, 1 N NaOH, and brine. The ether layer was dried over MgSO$_4$, filtered, and concentrated in vacuo. Typically, the material obtained was sufficient in purity. Trace impurities could be removed via column chromatography on silica gel using ether/pentane or EtOAc/heptane as an eluent. Solvent alternatives to MeCN have not been thoroughly investigated.

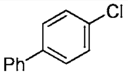
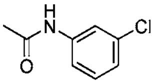
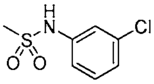
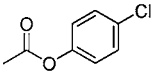
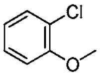
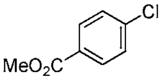
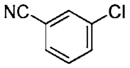
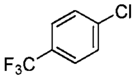
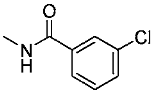
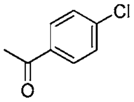
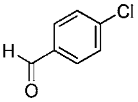
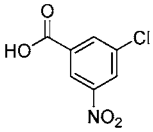
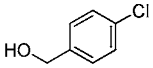
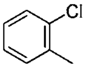
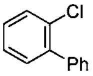
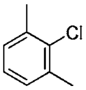
(12) The reported yield for the synthesis of **4a** from a potassium trifluoroborate is 64%; see ref 4e.

(13) Additional control studies testing the reactivity of various boronic acids with NCS alone wer performed on select substrates. The percent conversion by HPLC under identical conditions in the absence of CuCl are as follows: **1b**, 60%; **1c**, 0%; **1k**, 29%; **1m**, 0%. In the absence of CuCl, significant impurities were observed during the reaction of **1c** with NCS.

Table 2. Substrate Scope for Copper(I)-Mediated Boronic Acid to Chloride Conversion

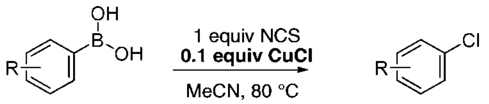


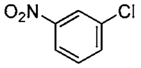
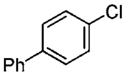
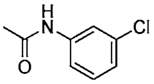
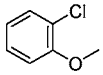
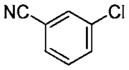
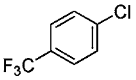
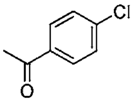
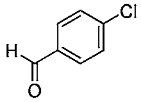
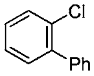
1b–1q → **2b–2q**

entry	acid	halide product		reaction time, h	% yield[a]
1	**1b**		**2b**	12	98
2	**1c**		**2c**	2	96
3	**1d**		**2d**	2	93
4	**1e**		**2e**	3	93
5	**1f**		**2f**	18	97
6	**1g**		**2g**	5	95
7	**1h**		**2h**	1	98
8	**1i**		**2i**	12	98[b]
9	**1j**		**2j**	2	96
10	**1k**		**2k**	4	98
11	**1l**		**2l**	1	85
12	**1m**		**2m**	18	95
13	**1n**		**2n**	12	94
14	**1o**		**2o**	2	98[b]
15	**1p**		**2p**	4	96
16	**1q**		**2q**	7	94

[a] All yields are for isolated, spectroscopically pure products unless otherwise noted. [b] Yield for this entry was determined by analytical HPLC due to product volatility.

Table 3. Chloride Formation with Catalytic CuCl

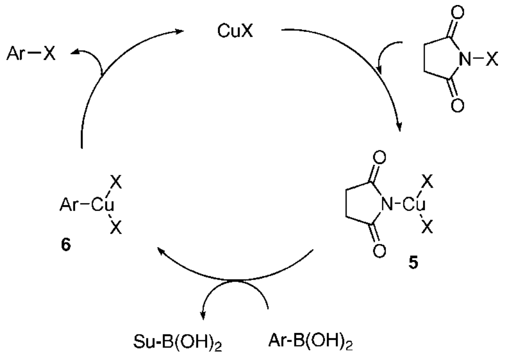


entry	acid	halide product	reaction time, h	%yield[a]
1	**1a**		12	98
2	**1b**		20	98
3	**1c**		18	96
4	**1f**		24	79
5	**1h**		18	98
6	**1i**		18	98[b]
7	**1k**		18	93
8	**1l**		20	95
9	**1p**		18	83

[a] Isolated yields unless otherwise noted. [b] Yield for this entry determined by analytical HPLC due to product volatility.

products or significant impurities. Products are usually isolated in high purity following a standard workup. In most instances, chromatographic purification can be avoided and solvent waste minimized. The reactions are conveniently monitored by HPLC, and the percent conversion is an excellent predictor of isolated yields (see the Supporting Information).

Scheme 1. Proposed Mechanism



A plausible mechanism for this transformation follows that of Liebskind et al. for the Cu(I)-catalyzed coupling of arylboronic acids with *N*-thio-substituted imides (Scheme 1).[10a] Oxidative addition of the Cu(I) halide with the corresponding *N*-halosuccinimide would generate a Cu(III) complex (e.g., **5**). Transmetalation with boron would generate a Ar−Cu(X)$_2$ species (**6**).[14] Reductive elimination would afford the aryl halide. The recent isolation of a stable Pd^{IV} oxidative addition product with NCS supports intermediates such as **5**.[15] While the proposed mechanism is plausible, alternative mechanistic frameworks cannot be ruled out given the complex nature of copper chemistry. For example, NCS could oxidize Cu(I)Cl to Cu(II)Cl$_2$ providing a direct route to intermediate **6**.[16] Preliminary investigations in our laboratories indicate boronic acids react as well as boronate esters using stoichiometric CuCl$_2$.[17] While not advanced in the literature, the halodeboronation of boronate esters with stoichiometric Cu(II) halide salts may occur via this pathway.

In conclusion, we have described the first transition-metal-catalyzed aryl chlorodeboronation reaction. This protocol offers several advantages over previous methods. The conditions are mild, and catalyst loading is low. The substrate scope is broad and functional group tolerance is high. This robust synthetic pathway to chlorinated arenes is also applicable to electron-rich and electron-deficient arylboronic acids, the latter of which are inefficient substrates for chlorodeboronation reactions.

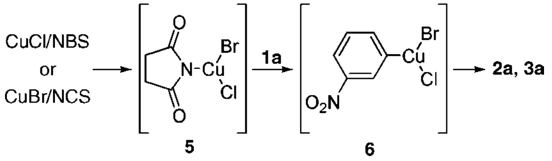
Acknowledgment. We thank Murali Dhar (BMS), Percy Carter (BMS), and Lawrence Williams (Rutgers University) for critical review of this manuscript.

Supporting Information Available: Spectroscopic data for isolated compounds and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

OL9029337

---

[14] Preliminary studies indicate the potential intermediacy of compound **6**. In the absence of significant competing side reactions, a combination using equimolar amounts of CuCl/NBS or CuBr/NCS should proceed through the copper(III) species **5**. Subsequent reaction with **1a** would provide a mixture of **2a** and **3a** via intermediate **6**. If this pathway is valid, both combinations should provide identical ratios of products favoring the faster reductive elimination pathway. Indeed, when these mixed combinations were independently reacted with **1a**, **3a** formation was favored over **2a** by 2−3-fold as confirmed by ^{1}H NMR analysis.



[15] See: Whitfield, S. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 15142.

[16] King, A. E.; Brunold, T. C.; Stahl, S. S. *J. Am. Chem. Soc.* **2009**, *131*, 5044.

[17] The reaction of **1a** with 1 equiv of CuCl$_2$ in MeCN at 80 °C for 18 h provided >95% conversion to **2a**.