

# Copper-Catalyzed Trifluoromethylation of Aryl and Vinyl Boronic Acids with An Electrophilic Trifluoromethylating Reagent

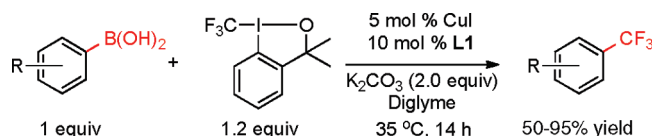
Tianfei Liu and Qilong Shen\*

Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, People's Republic of China

shenql@mail.sioc.ac.cn

Received March 5, 2011

## ABSTRACT

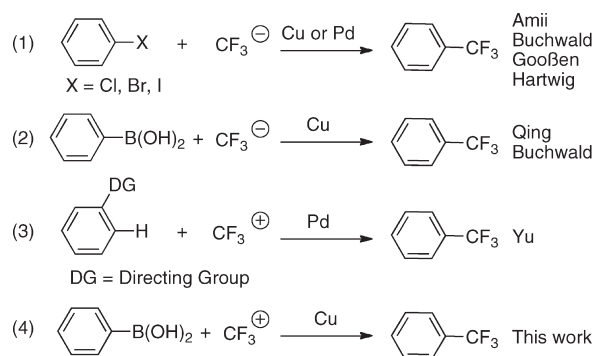


A copper-catalyzed trifluoromethylation of aryl- and alkenylboronic acids with Togni's reagent was described. The reaction proceeded in good to excellent yields for a range of different substrates including heteroarylboronic acids and substrates with a variety of functional groups under mild reaction conditions.

Trifluoromethyl-substituted arenes are prominent structural motifs found in pharmaceuticals, agrochemicals, and organic materials.<sup>1</sup> In particular, in medicinal chemistry, mainly due to the fact that introduction of the trifluoromethyl group often brings significant improvements in binding selectivity, lipophilicity, and metabolic stability, incorporation of the trifluoromethyl group into drug-like molecules has become a powerful and widely employed tactic in the process of drug design. Classic methods for the preparation of trifluoromethyl-substituted arenes have relied on two approaches: one involves C–F bond formation via a functional group transformation by a reactive fluorinating reagent such as SbF<sub>3</sub> or SF<sub>4</sub>,<sup>2</sup> and the other

includes C–C bond formation using a stoichiometric amount of [CuCF<sub>3</sub>] reagent.<sup>1c,3</sup> However, both of these methods suffer from either harsh reaction conditions and/or limited substrate scope. In the past three years, several strategies employing transition metal catalysts emerged for the preparation of trifluoromethyl-substituted arenes with a diversity of functional groups under relative mild

## Scheme 1. Methods for Preparation of Trifluoromethyl-Substituted Arenes



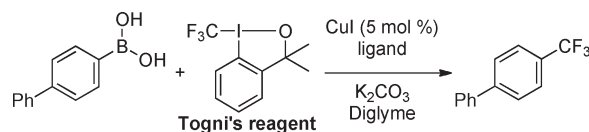
(1) (a) McClinton, M. A. *Tetrahedron* **1992**, 48, 6555. (b) Ma, J. A.; Cahard, D. *Chem. Rev.* **2008**, 108, PR1. (c) Clark, J. H.; Wails, D.; Bastock, T. W. *Aromatic Fluorination*; CRC Press: Boca Raton, FL, 1996. (d) Bégué, J. P.; Bonnet-Delpon, D. *Bioorganic and Medicinal Chemistry of Fluorine*; Wiley-Interscience: Hoboken, NJ, 2008. (e) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, 37, 320. (f) Kirk, K. L. *Org. Process Res. Dev.* **2008**, 12, 305. (g) Roy, S.; Gregg, B. T.; Gribble, G. W.; Le, V.; Roy, S. *Tetrahedron* **2011**, 67, 2161.

(2) (a) Swarts, F. *Bull. Acad. R. Belg.* **1892**, 24, 309. (b) Simons, J. H.; Lewis, C. J. *J. Am. Chem. Soc.* **1938**, 60, 492. (c) Henne, A. L.; Newman, M. S. *J. Am. Chem. Soc.*, 1938, 60, 1697. (d) Riera, J.; Castañer, J.; Carilla, J.; Robert, A. *Tetrahedron Lett.* **1989**, 30, 3825. (e) Castañer, J.; Riera, J.; Carilla, J.; Robert, A.; Molins, E.; Miravittles, C. *J. Org. Chem.* **1991**, 56, 103.

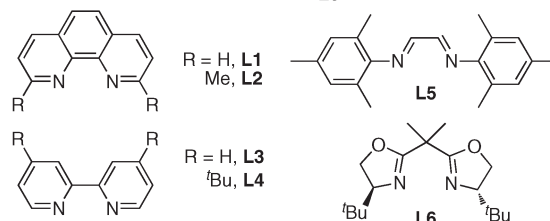
conditions. As illustrated in Scheme 1, these strategies can be classified into the following: (1) An aryl halide coupling with a nucleophilic “CF<sub>3</sub><sup>−</sup>” reagent with a catalytic amount of copper or palladium catalyst.<sup>5</sup> For example, Amii reported the first copper-catalyzed trifluoromethylation of electron-poor aryl iodides with Ruppert–Prakash’s reagent CF<sub>3</sub>SiEt<sub>3</sub> in the presence of CuI/1,10-phenanthroline.<sup>4,6</sup> In a landmark report, Buchwald reported a Pd-catalyzed trifluoromethylation of aryl chlorides by use of judiciously selected ancillary ligands.<sup>7</sup> (2) An arylboronic acid coupling with a nucleophilic “CF<sub>3</sub><sup>−</sup>” reagent in the presence of a stoichiometric amount of copper catalyst under oxidation conditions. Qing<sup>8</sup> and Buchwald<sup>9</sup> independently reported such a process using an oxidant such as Ag<sub>2</sub>CO<sub>3</sub> or O<sub>2</sub>, respectively. (3) An arene coupling with an electrophilic “CF<sub>3</sub><sup>+</sup>” reagent through C–H activation.<sup>10</sup> Yu reported a straightforward protocol for direct trifluoromethylation of arenes using Umemoto’s reagent in the presence of Pd(OAc)<sub>2</sub>.<sup>11</sup> Inspired by these studies, we envisioned an alternative strategy for the preparation of trifluoromethyl arenes by coupling of a nucleophilic [ArCu] species generated from arylboronic acid with a copper salt and an electrophilic [CF<sub>3</sub><sup>+</sup>] reagent (Scheme 1, eq 4).<sup>12</sup> Herein, we disclose the first copper-catalyzed trifluoromethylation

of aryl- and alkenylboronic acids in the presence of Togni’s reagent.

**Table 1.** CuI-Catalyzed Trifluoromethylation of 4-Biphenylboronic Acid with Togni’s Reagent in the Presence of Different Ligands<sup>a</sup>



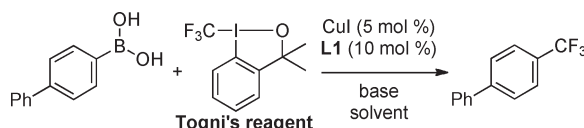
entry	CuX	ligand	yield (%) <sup>b</sup>
1	-	-	0
2	CuI	-	36
3	CuI	<b>L1</b>	90
4	CuI	<b>L1</b>	33 <sup>c</sup>
5	CuCl	<b>L1</b>	53
6	CuBr	<b>L1</b>	88
7	Cu(OAc) <sub>2</sub>	<b>L1</b>	41
8	Cu(OTf) <sub>2</sub>	<b>L1</b>	31
9	CuI	<b>L2</b>	7
10	CuI	<b>L3</b>	58
11	CuI	<b>L4</b>	20
12	CuI	<b>L5</b>	31
13	CuI	<b>L6</b>	10



<sup>a</sup> Reaction conditions: 4-biphenylboronic acid (0.2 mmol), Togni’s reagent (0.2 mmol), CuI (5 mol %), ligand (10 mol %), and K<sub>2</sub>CO<sub>3</sub> (0.4 mmol) in diglyme (1.0 mL) at 35 °C for 14 h. <sup>b</sup> Yields were determined by <sup>19</sup>F NMR analysis of the crude reaction mixture with an internal standard. <sup>c</sup> 5 mol % of **L1** was used.

The trifluoromethylation of 4-biphenylboronic acid with Togni’s reagent<sup>13,14</sup> was chosen at the start of our investigation as a model reaction. We first examined CuI and 1,10-phenanthroline **L1** as a potential catalyst for reaction of 4-biphenyl boronic acid and Togni’s reagent in the presence of 2.0 equiv of K<sub>2</sub>CO<sub>3</sub> as the base in diglyme (Table 1). The reaction occurred smoothly to give the desired product in 90% yield as determined by <sup>19</sup>F NMR spectroscopy with an internal standard (Table 1, entry 3). Various copper precursors were evaluated to understand the effect of the precursor on the reaction. Copper catalyst was essential to the reaction efficiency as the reaction occurred in 36% yield in the presence of 5 mol % of CuI but no conversion was observed in the absence of CuI (Table 1, entries 1 and 2). Using other copper precursors such as CuCl, Cu(OAc)<sub>2</sub>, or Cu(OTf)<sub>2</sub> led to much lower yields (Table 1, entries 5, 7, and 8). Using CuBr resulted in comparable yield. The ratio of metal/ligand also influenced the conversion of the reaction. The best result was observed with a 1/2 ratio of CuI/**L1**, while a much lower 33% yield of the product was observed with a 1/1 ratio of CuI/**L1** (Table 1, entry 4). We then further investigated whether the yield could be improved by adding other chelating amine ligands. Reactions with hindered 2,9-dimethyl-1,

- (3) (a) Kobayashi, Y.; Kumadaki, I. *Tetrahedron Lett.* **1969**, 47, 4095. (b) McLaughlin, V. C. R.; Thrower, J. *Tetrahedron* **1969**, 25, 5921. (c) Wiemers, D. M.; Burton, D. J. *J. Am. Chem. Soc.* **1986**, 108, 832. (d) Carr, G. E.; Chambers, R. D.; Holmes, T. F.; Parker, D. G. *J. Chem. Soc., Perkin Trans. I* **1988**, 921. (e) Suzuki, H.; Yoshida, Y.; Osuka, A. *Chem. Lett.* **1982**, 135. (f) Urata, H.; Fuchikami, T. *Tetrahedron Lett.* **1991**, 32, 91. (g) Chen, Q.-Y.; Wu, S.-W. *Chem. Commun.* **1989**, 705. (h) Su, D.-B.; Duan, J.-X.; Chen, Q.-Y. *Tetrahedron Lett.* **1991**, 32, 7689. (i) Chen, Q.-Y.; Duan, J.-X. *Chem. Commun.* **1993**, 1389. (j) Dubinina, G. G.; Furutachi, H.; Vicio, D. A. *J. Am. Chem. Soc.* **2008**, 130, 8600. (k) Zhang, C.-P.; Wang, Z.-L.; Chen, Q.-Y.; Zhang, C.-T.; Gu, Y.-C.; Xiao, J.-C. *Angew. Chem., Int. Ed.* **2011**, 50, 1896. (l) Morimoto, H.; Tsubogo, T.; Litvinas, N. D.; Hartwig, J. F. *Angew. Chem., Int. Ed.* doi: 10.1002/anie.201100633. (4) Oishi, M.; Kondo, H.; Amii, H. *Chem. Commun.* **2009**, 1909. (5) Lundgren, R. J.; Stradiotto, M. *Angew. Chem., Int. Ed.* **2010**, 49, 9322. (6) Knauber, T.; Arian, F.; G., R.; Goossen, L. J. *Chem.—Eur. J.* **2011**, 17, 2689. (7) (a) Cho, E. J.; Senecal, T. D.; Kinzel, T.; Zhang, Y.; Watson, D. A.; Buchwald, S. L. *Science* **2010**, 328, 1679. (b) Grushin, V. V.; Marshall, W. J. *J. Am. Chem. Soc.* **2006**, 128, 4632. (c) Grushin, V. V.; Marshall, W. J. *J. Am. Chem. Soc.* **2006**, 128, 12644. (8) (a) Chu, L.; Qing, F.-L. *Org. Lett.* **2010**, 12, 5060. (b) Chu, L.; Qing, F.-L. *J. Am. Chem. Soc.* **2010**, 132, 7262. (9) Senecal, T. D.; Parsons, A. T.; Buchwald, S. L. *J. Org. Chem.* **2011**, 76, 1174. (10) Ball, N. D.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2010**, 132, 2878. (11) Wang, X.; Truesdale, L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, 132, 3648. (12) For selected metal-mediated functionalization of arylboronic acids, see: (a) Anbarasan, P.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2011**, 50, 519. (b) Liskey, C. W.; Liao, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, 132, 11389. (c) Murphy, J. M.; Liao, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, 129, 15434. (d) Kang, S.; Lee, H.; Jang, S.; Ho, P. *J. Org. Chem.* **1996**, 61, 4720. (e) Kang, S.; Yamaguchi, T.; Kim, T.; Ho, P. *J. Org. Chem.* **1996**, 61, 9082. (f) Kang, S.; Lee, H.; King, J.; Choi, S. *Tetrahedron Lett.* **1996**, 37, 3723. (13) For recent reviews on applications of hypervalent iodine see: (a) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, 109, 5299. (b) Brand, J. P.; González, D. F.; Nicolai, S.; Waser, J. *Chem. Commun.* **2011**, 47, 102. (14) (a) Eisenberger, P.; Gischig, S.; Togni, A. *Chem.—Eur. J.* **2006**, 12, 2579. (b) Niedermann, K.; Früh, N.; Vinogradova, E.; Wiehn, M. S.; Moreno, A.; Togni, A. *Angew. Chem., Int. Ed.* **2011**, 50, 1059. (c) Koller, R.; Stanek, K.; Stolz, D.; Aardoom, R.; Niedermann, K.; Togni, A. *Angew. Chem.* **2009**, 121, 4396.

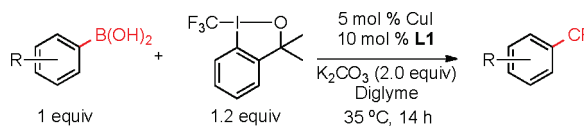
**Table 2.** Optimization of the CuI/**L1**-Catalyzed Trifluoromethylation of 4-Biphenylboronic Acid with Togni's Reagent<sup>a</sup>


entry	base	solvent	yield (%) <sup>b</sup>
1	K <sub>2</sub> CO <sub>3</sub>	DME	79
2	K <sub>2</sub> CO <sub>3</sub>	THF	52
3	K <sub>2</sub> CO <sub>3</sub>	Et <sub>2</sub> O	0
4	K <sub>2</sub> CO <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub>	16
5	K <sub>2</sub> CO <sub>3</sub>	DMF	23
6	K <sub>2</sub> CO <sub>3</sub>	DMSO	28
7	K <sub>2</sub> CO <sub>3</sub>	1,4-dioxane	37
8	K <sub>2</sub> CO <sub>3</sub>	toluene	9
9	K <sub>2</sub> CO <sub>3</sub>	CH <sub>3</sub> CN	34
10	K <sub>2</sub> CO <sub>3</sub>	NMP	19
11 <sup>c</sup>	K <sub>2</sub> CO <sub>3</sub>	DME/H <sub>2</sub> O	63
12	K <sub>2</sub> CO <sub>3</sub>	diglyme	90
13 <sup>d</sup>	K <sub>2</sub> CO <sub>3</sub>	diglyme	97
14	Na <sub>2</sub> CO <sub>3</sub>	diglyme	21
15	Cs <sub>2</sub> CO <sub>3</sub>	diglyme	3
16	K <sub>3</sub> PO <sub>4</sub>	diglyme	21
17	CsOH·H <sub>2</sub> O	diglyme	17
18	KOH	diglyme	trace

<sup>a</sup> Reaction conditions: 4-biphenylboronic acid (0.2 mmol), Togni's reagent (0.2 mmol), CuI (5 mol %), ligand (10 mol %), and K<sub>2</sub>CO<sub>3</sub> (0.4 mmol) in diglyme (1.0 mL) at 35 °C for 14 h. <sup>b</sup> Yields were determined by <sup>19</sup>F NMR analysis of the crude reaction mixture with an internal standard. <sup>c</sup> The ratio of DME/H<sub>2</sub>O is 9:1. <sup>d</sup> Reaction was conducted with a 1/1.2 ratio of 4-biphenylboronic acid/Togni's reagent.

10-phenanthroline **L2**, however, occurred in a negligible 7% yield (Table 1, entry 9). Reactions with other dinitrogen ligands such as 2,2'-bipyridone **L3** and its derivatives **L4** or ligands **L5**–**L6** were less effective (Table 1, entries 10–13).

After indentifying an appropriate catalyst, we further optimized other critical reaction parameters such as solvent and base, as summarized in Table 2. Reactions in strong, polar, aprotic solvents such as DMF, DMSO, or NMP occurred in low yields (Table 2, entries 5–6 and 10), while reactions in the nonpolar solvent toluene gave the product in 9% yield (Table 2, entry 8). It was further found that reactions in coordinating ether-type solvents such as DME or diglyme occurred to full conversion after 14 h at 35 °C to give the desired product in good yield (Table 2, entries 1 and 12), while reactions in Et<sub>2</sub>O or 1,4-dioxane occurred in much lower yields (Table 2, entries 3 and 7). Interestingly, the reaction was not sensitive to water. Reactions in DME/H<sub>2</sub>O (9:1) occurred in slightly lower yields than those in DME (Table 2, entry 11). The yield of the product was further improved when a 1/1.2 ratio of boronic acid/Togni's reagent was used (Table 2, entry 12). The reaction was sensitive to the base. Using bases such as Na<sub>2</sub>CO<sub>3</sub>, Cs<sub>2</sub>CO<sub>3</sub>, K<sub>3</sub>PO<sub>4</sub>, CsOH·H<sub>2</sub>O, or KOH led to much lower yields or no detectable product (Table, entries 14–18).

**Table 3.** CuI/**L1**-Catalyzed Trifluoromethylation of 4-Biphenylboronic Acid with Togni's Reagent<sup>a</sup>


entry	product	yield (%) <sup>b</sup>	entry	product	yield (%) <sup>b</sup>
1		80	10		53
2		90	11		85
3		90	12		90
4		90	13		80 <sup>c</sup>
5		90	14		70
6		85	15		75 <sup>d</sup>
7		95	16		50 <sup>d</sup>
8		76	17		55 <sup>d</sup>
9		73	18		70 <sup>d</sup>

<sup>a</sup> Reaction conditions: 4-biphenyl boronic acid (0.5 mmol), Togni's reagent (0.6 mmol), CuI (5 mol %), ligand (10 mol %), and K<sub>2</sub>CO<sub>3</sub> (1.0 mmol) in diglyme (2.5 mL) at 35 °C for 14 h. <sup>b</sup> Isolated yields. <sup>c</sup> DME as solvent. <sup>d</sup> Reactions for 24 h.

With the optimized conditions (entry 13 in Table 2), we have investigated the scope of the copper/**L1**-catalyzed trifluoromethylation of aryl- and alkenylboronic acids. The results are summarized in Table 3. Reactions of simple arylboronic acids gave the corresponding trifluoromethyl-substituted arenes in good to excellent yields (Table 3, entries 1–7). Pharmaceutically interesting trifluoromethyl-substituted heteroarenes were synthesized in good yields (Table 3, entries 8–10). Challenging functionalized arylboronic acids were compatible with the reaction conditions. Reactions of arylboronic acids with functional groups such as enolizable ketones, esters, carbamates, amides, and chlorides occurred in good yields (Table 3, entries 11–14 and 18). It is interesting to note that alkenylboronic acids also converted effectively into trifluoromethyl-substituted olefins in reasonable yields (Table 3, entries 15–18). The resulting trifluoromethyl-substituted alkenes were partially isomerized, although the mechanism of the isomerization remains elusive.

In conclusion, we have demonstrated the first copper-catalyzed trifluoromethylation of aryl- and alkenylboronic acids with Togni's reagent. The reaction proceeded well for a range of different substrates including heteroarylboronic acids and substrates with a variety of functional groups under mild reaction conditions.<sup>15</sup> Mechanistic studies and synthetic applications of these transformations are ongoing in our laboratory.

**Acknowledgment.** The authors gratefully acknowledge Professor Long Lu and Professor Fengling Qing of Shanghai

---

(15) After our submission, Liu et al. reported a Cu-catalyzed method for trifluoromethylation with Umemoto's reagent: Xu, J.; Luo, D.-F.; Xiao, B.; Liu, J.; Gong, T.-J.; Fu, Y.; Liu, L. *Chem. Commun.* **2011**, 47, 4300.

Institute of Organic Chemistry, Chinese Academy of Sciences for insightful discussion of using Togni' reagent. We thank Ms. Xiangqing Jia of Chinese Pharmaceutical University for conducting some experiments. We also thank the financial support from the Key Program of National Natural Science Foundation of China (Grant No. 21032006), SIOC startup fund and the Key Program of National Natural Science Foundation of China (20632070), and National Basic Research Program of China (2010CB126103) for financial support.

**Supporting Information Available.** All experimental procedures and spectroscopic data of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.