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Suzuki−Miyaura Coupling of Aryl Carbamates, Carbonates, and Sulfamates

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Transition-metal-catalyzed cross-coupling reactions continue to play a vital role in modern synthetic chemistry.[1] Although cross-couplings of aryl halides and triflates are most common, recent studies have demonstrated the successful cross-coupling of simple and affordable phenolic derivatives. In 2008, notable achievements in this area include the Suzuki−Miyaura coupling of electron-deficient aryl methyl ethers by Chatani,[2] and the Suzuki−Miyaura coupling of aryl pivalates,[3] which was reported simultaneously by our group[4a] and the group of Shi.[4b] A conceptual advantage of these technologies in comparison with methodologies involving halides and sulfonates is the potential to direct the installation of other functional groups onto an aromatic ring prior to cross-coupling (Figure 1). In practice, however, the ability to use methyl ethers (R = Me) and pivalates [R = −C(O)CMe$_3$] in this sense is somewhat limited.[5] In view of the importance of polyfunctionalized aromatics in medicine, ligands for catalysis, and materials chemistry, we sought to address this problem. In this communication, we describe the first Suzuki−Miyaura couplings of aryl carbamates, carbonates, and sulfamates. Moreover, we disclose a concise synthesis of the anti-inflammatory drug flurbiprofen (**1**)[6] using this methodology.

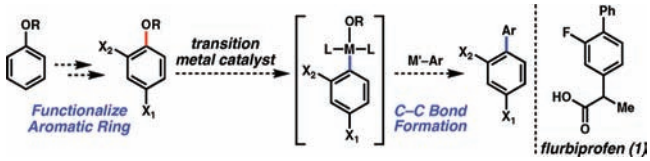
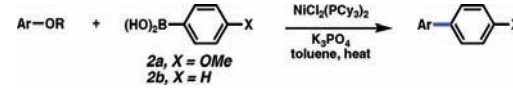


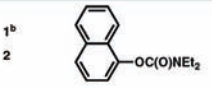
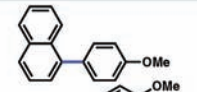
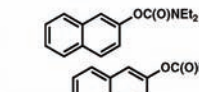
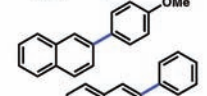
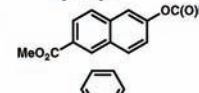
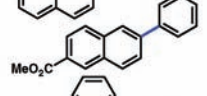
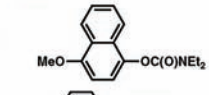
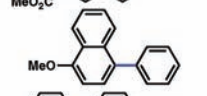
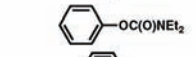
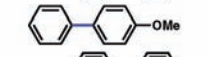
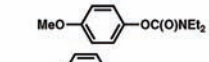
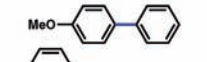
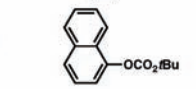
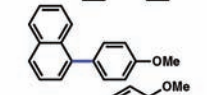
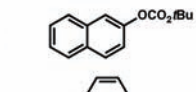
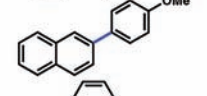
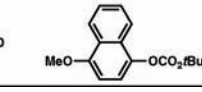
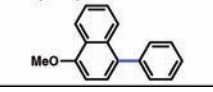
Figure 1. Approach to polysubstituted aromatics such as flurbiprofen.

Of the potential phenolic derivatives to be studied, aryl carbamates and sulfamates were considered ideal because of their ready availability and pronounced stability under a variety of reaction conditions. Furthermore, these substrates can be used to direct the installation of functional groups at both the ortho and para positions (via ortho lithiation chemistry pioneered by Snieckus[7] and electrophilic aromatic substitution,[8] respectively). Although Ni-catalyzed Kumada couplings of these substrates have been documented,[7b,9] cross-coupling under milder, more attractive Suzuki−Miyaura conditions has not been reported. Notably, the oxidative addition of a metal into the aryl C−O bond of an aryl carbamate or sulfamate presents a considerable challenge.

Despite this difficulty, we have found that Suzuki−Miyaura coupling of aryl carbamates with arylboronic acids proceeds in the presence of $NiCl_2(PCy_3)_2$, K_3PO_4, and heat, with toluene as the solvent (Table 1). The fact that $NiCl_2(PCy_3)_2$ could be used to facilitate the desired transformation is advantageous,[10] as this readily available complex shows marked stability toward air and water and can be used on the benchtop rather than in a glovebox.[11] The carbamate derivative of 1-naphthol could be converted to the desired biaryl product at 110 °C with 5 mol % Ni complex (entry 1). However, the yield improved substantially when the reaction was carried out at higher temperatures with increased catalyst loading (entry 2). 2-Naphthol derivatives could also be coupled under these conditions (entries 3 and 4). In addition, the reaction was tolerant of an electron-withdrawing group (−CO_2Me, entry 4) and an electron-donating group (−OMe, entry 5) on the

Table 1. Cross-Coupling of Aryl Carbamates and Carbonates with Arylboronic Acid **2a** or **2b**[a]



entry	Ar–OR	(HO)$_2$B–Ar	product	yield[c]
1[b]		2a		51%
2				86%
3		2a		47%
4		2b		54%
5		2b		77%
6		2a		52%
7		2b		41%
8		2a		72%
9		2a		85%
10		2b		65%

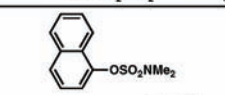
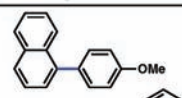
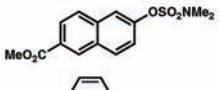
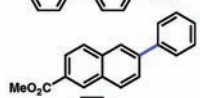
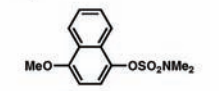
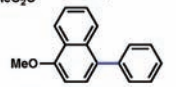
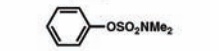
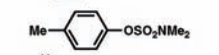
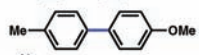
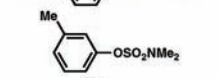
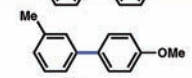
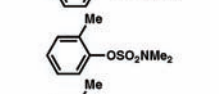
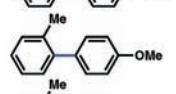
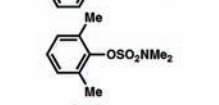
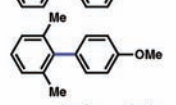
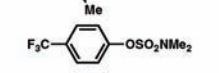
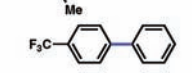
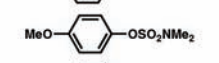
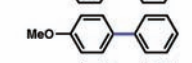
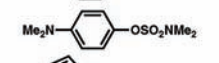
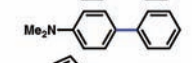
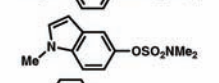
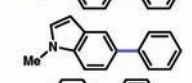
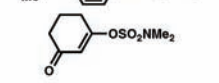
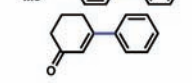
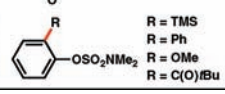
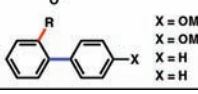
[a] Conditions: $NiCl_2(PCy_3)_2$ (10 mol %), $ArB(OH)_2$ (4 equiv), K_3PO_4 (7.2 equiv), toluene (0.3 M), 130 °C, 24 h. [b] Conditions: $NiCl_2(PCy_3)_2$ (5 mol %), $ArB(OH)_2$ (2.5 equiv), K_3PO_4 (4.5 equiv), toluene (0.3 M), 110 °C, 24 h. [c] Isolated yields.

naphthyl ring. The corresponding reactions of nonfused aryl carbamates proved to be more challenging. Nonetheless, carbamates derived from phenol and *p*-methoxyphenol could be converted to the corresponding cross-coupled products, albeit in modest yields (entries 6 and 7). Aryl *tert*-butylcarbonates were also deemed to be suitable cross-coupling partners (entries 8−10). Interestingly, the carbonate congener of 2-naphthol delivered the cross-coupled product in significantly higher yield than the corresponding carbamate (entry 9 vs entry 3).

As shown in Table 2, aryl sulfamates serve as superior coupling partners in the Ni-catalyzed Suzuki−Miyaura reaction. Both naphthyl and nonfused aromatic substrates could be converted to biaryl products in excellent yield (entries 1−11 and 14−17). Electron-withdrawing (entries 2 and 9) and electron-donating groups were tolerated (entries 3, 10, and 11). In addition to substrates with methyl substituents at the para, meta, and ortho positions (entries 5−7), a sterically congested 2,6-disubstituted substrate also participated in the desired cross-coupling process (entry 8). A heteroaromatic sulfamate (entry 12) and a vinyl sulfamate (entry 13) proved to be competent substrates. Finally, a range of ortho-substituted sulfamates, prepared by ortho lithiation/function-

10.1021/ja906477r CCC: $40.75

Table 2. Cross-Coupling of Aryl Sulfamates[a]

entry	R–OSO_2NMe_2	$(HO)_2B$–Ar	product	yield[b]
1		*2a*		95%
2		*2b*		72%
3		*2b*		92%
4		*2a*		87%
5		*2a*		89%
6		*2a*		91%
7		*2a*		92%
8		*2a*		63%
9		*2b*		81%
10		*2b*		80%
11		*2b*		76%
12		*2b*		75%
13		*2b*		75%
14[c]	 R = TMS	*2a*	 X = OMe	92%
15	R = Ph	*2a*	X = OMe	93%
16	R = OMe	*2b*	X = H	90%
17[c]	R = C(O)tBu	*2b*	X = H	85%

[a] Conditions: $NiCl_2(PCy_3)_2$ (5 mol %), $ArB(OH)_2$ (2.5 equiv), K_3PO_4 (4.5 equiv), toluene (0.3 M), 110 °C, 24 h. [b] Isolated yields. [c] Conditions: $NiCl_2(PCy_3)_2$ (10 mol %), $ArB(OH)_2$ (4 equiv), K_3PO_4 (7.2 equiv), toluene (0.3 M), 130 °C, 24 h.

alization of phenyl dimethylsulfamate,[12] underwent smooth cross-coupling in excellent yields (entries 14−17).

To further probe the scope and utility of the sulfamate cross-coupling methodology, a synthesis of the anti-inflammatory drug flurbiprofen[6] was performed (Figure 2). Boronic acid **3**, derived from ortho lithiation/borylation of phenyl dimethylsulfamate,[12] was fluorinated using the conditions described by Furuya and Ritter[13] to provide fluorosulfamate **4**. Selective iodination of **4** para to the sulfamate furnished **5** in 64% yield. Notably, both the fluoride and sulfamate of **5** were deemed unreactive toward Pd(0). As the aryl iodide displayed orthogonal reactivity, we carried out a site-selective enolate coupling to install the necessary propionate side chain. Whereas enolate coupling of aryl iodide **5** under Buchwald's Pd-based conditions was feasible,[14] higher yields of **6** were obtained using a Ni-catalyzed variant.[15] Although the sulfamate was not disturbed in this process, exposure of **6** to our Ni-catalyzed Suzuki−Miyaura conditions facilitated the key sulfamate cross-coupling. Acid-mediated hydrolysis furnished flurbiprofen (**1**) in 84% yield over the two steps. It should be emphasized that the aryl fluoride of **6** was chemically inert under our Ni-catalyzed cross-coupling conditions.[16]

In summary, we have discovered the first Suzuki−Miyaura coupling reactions of aryl carbamates, carbonates, and sulfamates. The method relies on the use of a readily available, air-stable Ni(II) complex to facilitate the desired transformations. Furthermore, the technology presented herein allows for the installation of multiple functional groups onto an aromatic ring prior to the cross-coupling event, as demonstrated by a concise synthesis of the anti-inflammatory drug flurbiprofen.

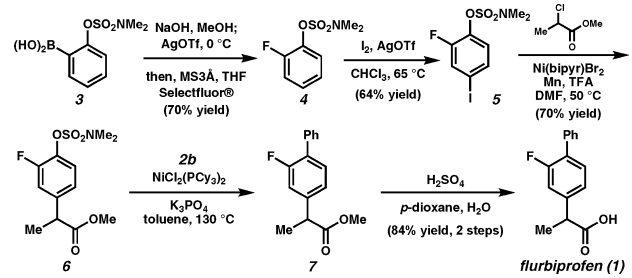


Figure 2. Synthesis of flurbiprofen using orthogonal cross-couplings.

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Supporting Information Available: Detailed experimental procedures and compound characterization data. 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., Meijere, A., Eds.; Wiley-VCH: Weinheim, Germany, 2004. (b) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (c) *Cross-Coupling Reactions: A Practical Guide*; Miyaura, N., Ed.; Topics in Current Chemistry, Vol. 219; Springer-Verlag: Berlin, 2002. (d) Corbet, J.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651. (e) Negishi, E. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 233.
(2) Tobisu, M.; Shimasaki, T.; Chatani, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4866.
(3) For reviews, see: (a) Tobisu, M.; Chatani, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 3565. (b) Goossen, L. J.; Goossen, K.; Stanciu, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 3569. (c) Knochel, P.; Gavryushin, A. *Synfacts* **2009**, 200.
(4) (a) Quasdorf, K. W.; Tian, X.; Garg, N. K. *J. Am. Chem. Soc.* **2008**, *130*, 14422. (b) Guan, B.-T.; Wang, Y.; Li, B.-J.; Yu, D.-G.; Shi, Z.-J. *J. Am. Chem. Soc.* **2008**, *130*, 14468.
(5) The ortho-directing ability of methyl ethers is modest (see ref 7a and references therein), whereas ortho substitution of aryl pivalates presents a considerable challenge.
(6) For pertinent reviews, see: (a) Richy, F.; Rabehnda, V.; Mawet, A.; Reginster, J.-Y. *Int. J. Clin. Pract.* **2007**, *61*, 1396. (b) Kumar, P.; Pathak, P. K.; Gupta, V. K.; Srivastava, B. K.; Kushwaha, B. S. *Asian J. Chem.* **2004**, *16*, 558.
(7) (a) For a review, see: Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (b) For the use of sulfamates in directed metallation reactions and Kumada couplings, see: Macklin, T. K.; Snieckus, V. *Org. Lett.* **2005**, *7*, 2519.
(8) Arenes that possess an −OC(O)R substituent are well-known to undergo electrophilic aromatic substitution to predominantly afford para-substituted products. See: Smith, M. B.; March, J. *March's Advanced Organic Chemistry*, 6th ed.; Wiley: Hoboken, NJ, 2007; p 668.
(9) (a) Sengupta, S.; Leite, M.; Raslan, D. S.; Quesnelle, C.; Snieckus, V. *J. Org. Chem.* **1992**, *57*, 4066. (b) Dallaire, C.; Kolber, I.; Gingras, M. *Org. Synth.* **2002**, *78*, 42. (c) Yoshikai, N.; Matsuda, H.; Nakamura, E. *J. Am. Chem. Soc.* **2009**, *131*, 9590. (d) Wehn, P. M.; Du Bois, J. *Org. Lett.* **2005**, *7*, 4685.
(10) $NiCl_2(PCy_3)_2$ is now commercially available from Strem Chemicals Inc. (cat. no. 28-0091) and can be prepared in multigram quantities following a simple one-step protocol. See: (a) Stone, P. J.; Dori, Z. *Inorg. Chim. Acta* **1971**, *5*, 434. (b) Barnett, K. W. *J. Chem. Educ.* **1974**, *51*, 422.
(11) In the presence of excess arylboronic acid, $NiCl_2(PCy_3)_2$ is thought to undergo reduction to an active Ni(0) catalyst.
(12) See the Supporting Information for details.
(13) Furuya, T.; Ritter, T. *Org. Lett.* **2009**, *11*, 2860.
(14) Moradi, W. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7996.
(15) Durandetti, M.; Gosmini, C.; Périchon, J. *Tetrahedron* **2007**, *63*, 1146.
(16) For Ni-catalyzed Kumada and Suzuki−Miyaura couplings of aryl fluorides, see: (a) Yoshikai, N.; Mashima, H.; Nakamura, E. *J. Am. Chem. Soc.* **2005**, *127*, 17978. (b) Dankwardt, J. W. *J. Organomet. Chem.* **2005**, *690*, 932. (c) Schaub, T.; Backes, M.; Radius, U. *J. Am. Chem. Soc.* **2006**, *128*, 15964.

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