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Copper-Catalyzed C–N Cross-Coupling of Sulfondiimines with Boronic Acids

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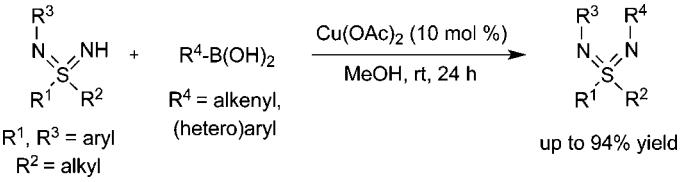
ABSTRACT



The copper-catalyzed C–N cross-coupling of sulfondiimines with boronic acids has been developed. The reaction proceeds at room temperature in good to excellent yields and provides access to a variety of *N,N*′-disubstituted sulfondiimines, including *N*-(hetero)aryl sulfondiimines and the first reported *N*-alkenylated sulfondiimine.

In the past decades, sulfoximines have attracted significant attention due to their biological activity. In particular, *N*-(hetero)aryl sulfoximines have been investigated as anticancer agents[1] or agrochemicals.[2] Replacement of the sulfoximine oxygen by nitrogen leads to a surprisingly unexplored class of tetracoordinated diaza analogues, namely the sulfondiimines. Despite possessing numerous intriguing properties, since their discovery in 1964[3] these high-valent sulfur compounds have been underrepresented in chemical literature, and to date, only a few applications exist.[4−6] Since our group reported the NCS-mediated oxidative imination of sulfiliminium salts,[7] a broad variety of *N*H-sulfondiimines are readily accessible, and further derivatization appeared desirable. In this context, we recently described the N-arylation of *N*H-sulfondiimines by palladium-catalyzed cross-coupling with aryl bromides.[8] Although this method provided access to a series of *N*,*N*′-disubstituted products, it suffered from several disadvantages, such as harsh reaction conditions including high reaction temperatures and the requirement of expensive palladium catalysts. Furthermore, the use of a glovebox was crucial, and the product scope was limited. As such, the development of a more experimentally simple and cost-efficient method for the synthesis of a more diverse library of sulfondiimines, in particular toward *N*-(hetero)aryl sulfondiimines, appeared desirable. We herein report an advancement in this area with the development of a copper-catalyzed C–N cross-coupling of sulfondiimines with boronic acids.

Inspired by a method previously developed in our group for the N-arylation of *N*H-sulfoximines,[9] the Chan–Lam type cross-coupling reaction of sulfondiimine **1a** with phenylboronic acid (**2a**) was initially investigated.[10,11] Early attempts were performed using 10 mol % of $Cu(OAc)_2$ in dry MeOH at room temperature with 2.3 equiv of the

(1) For *N*-(hetero)aryl sulfoximines showing anticancer activity, see: (a) Shetty, S. J.; Patel, G. D.; Lohray, B. B.; Lohray, V. B.; Chakrabarti, G.; Chatterjee, A.; Jain, M. R.; Patel, P. R. WO Patent 077574 (A2), 2007. (b) Lücking, U.; Siemeister, G.; Jautelat, R. WO Patent 099974 (A1), 2006.

(2) For *N*-(hetero)aryl sulfoximines as agrochemicals, see: Kajita, S.; Miyashita, Y.; Shibayama, K.; Tamai, T.; Tsukuda, K.; Yamada, S.; Yamaguchi, M. WO Patent 035737 (A1), 2008.

(3) Cogliano, J. A.; Braude, G. L. *J. Org. Chem.* **1964**, *29*, 1397.

(4) For sulfondiimines in heterocyclic chemistry, see: (a) Ried, W.; Jacobi, M. A. *Chem. Ber.* **1988**, *121*, 383. (b) Diederich, W. E.; Haake, M. *J. Org. Chem.* **2003**, *68*, 3817.

(5) For sulfondiimines in pseudopeptides, see: Dehli, J. R.; Bolm, C. *Synthesis* **2005**, 1058.

(6) For sulfondiimines in methods development, see: (a) Georg, G. I.; Pfeifer, S. A.; Haake, M. *Tetrahedron Lett.* **1985**, *26*, 2739. (b) Yoshimura, T.; Fujie, T.; Fujii, T. *Tetrahedron Lett.* **2007**, *48*, 427.

(7) Candy, M.; Guyon, C.; Mersmann, S.; Chen, J.-R.; Bolm, C. *Angew. Chem., Int. Ed.* **2012**, *51*, 4440.

(8) Candy, M.; Bohmann, R. A.; Bolm, C. *Adv. Synth. Catal.* **2012**, *354*, 2928.

(9) Moessner, C.; Bolm, C. *Org. Lett.* **2005**, *7*, 2667.

(10) For other Chan–Lam reactions and the proposed mechanism, see: (a) Qiao, J. X.; Lam, P. Y. S. *Synthesis* **2011**, 829 and references therein. (b) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400 and references therein.

(11) For more details on the synthesis of the starting materials, see ref 7.

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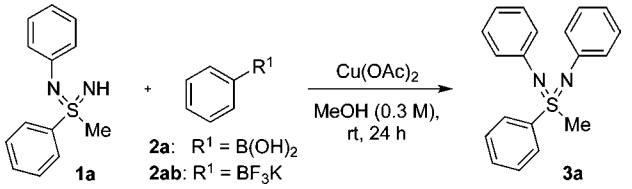
phenylboronic acid affording the *N*-phenylated product **3a** in 85% yield (Table 1, entry 1).

To further explore this reaction process, alternate copper salts [both Cu(I) and Cu(II)] and solvents were evaluated. Results showed that copper salts other than anhydrous $Cu(OAc)_2$ and solvents other than anhydrous methanol led to lower yields and reactivity. As reported for literature-known reactions,[10] the amount of oxygen and water present in the reaction flask proved to have a significant impact on the transformation. While incomplete conversions and low yields were observed in an argon atmosphere (64%; Table 1, entry 2), exclusion of moisture by a $CaCl_2$-drying tube afforded sulfondiimine **3a** in the best yield (85%; Table 1, entry 1). Other reactions performed in an oxygen atmosphere or with the addition of molecular sieves led to lower yields of the desired product **3a** (both 82%; Table 1, entries 3–4).

Table 1. Optimization of the Reaction Conditions



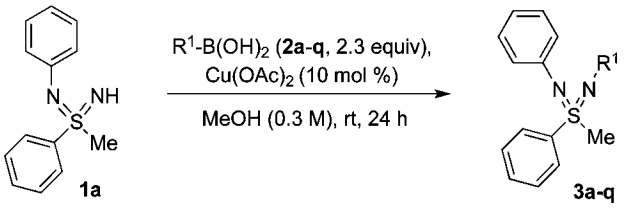
entry	$Cu(OAc)_2$ (mol %)	**2** (equiv)	**3a**, yield[a] (%)
1	10	**2a** (2.3)	85
2	10	**2a** (2.3)	64[b]
3	10	**2a** (2.3)	82[c]
4	10	**2a** (2.3)	82[d]
5	10	**2a** (1.0)	50
6	10	**2a** (2.0)	79
7	5	**2a** (2.3)	79
8	10	**2ab** (2.3)	37[e]

[a] Yields after column chromatography; moisture excluded by $CaCl_2$-drying tube. [b] Under argon atmosphere. [c] Under oxygen atmosphere. [d] Addition of molecular sieves. [e] Reaction performed for 40 h at 40 °C.

Reducing the amount of boronic acid or the catalyst loading resulted in lower yields and incomplete conversion to the product **3a** (Table 1, entries 5–7). Additional investigations indicated that the use of potassium trifluoroborate salts was also possible, but resulted in lower yields of **3a** (37%; Table 1, entry 8) than when the boronic acid was employed.

With optimal conditions in hand, further investigations into the substrate scope of this reaction process were performed. Sulfondiimine **1a** was coupled with a variety of commercially available boronic acids to afford the corresponding *N*,*N*′-disubstituted sulfondiimines **3** in good to excellent yields (Table 2). Both electron-donating and -withdrawing groups on the aromatic ring of the arylboronic acid were well-tolerated. To this end, methoxy- and thiomethyl-substituted products **3b** and **3c** were synthesized (72% and 67% yield, respectively), and acetyl- and trifluoromethylboronic acid afforded products **3d** and **3e** in yields of 90% and 89% (Table 2, entries 2–5). In addition, 4-biphenyl- and 2-naphthylboronic acid reacted well affording the products **3f** and **3g** in 84% and 94% yield (Table 2, entries 6 and 7).

Table 2. Cross-Coupling of Sulfondiimine **1a** with Boronic Acids **2a**–**q**



entry	R^1-, boronic acid **2**	product, yield (%)[a]
1	C_6H_5- (**2a**)	**3a**, 85
2	4-MeO-C_6H_4- (**2b**)	**3b**, 72
3	4-MeS-C_6H_4- (**2c**)	**3c**, 67
4	4-Ac-C_6H_4- (**2d**)	**3d**, 90
5	3-F_3C-C_6H_4- (**2e**)	**3e**, 89
6	4-biphenyl- (**2f**)	**3f**, 84
7	2-naphthyl- (**2g**)	**3g**, 94
8	2-Br-C_6H_4- (**2h**)	**3h**, 94
9	2-Cl-C_6H_4- (**2i**)	**3i**, 85
10	4-Me-C_6H_4- (**2j**)	**3j**, 87
11	3-Me-C_6H_4- (**2k**)	**3k**, 85
12	2-Me-C_6H_4- (**2l**)	**3l**, 51
13	2,4,6-Me_3-C_6H_4- (**2m**)	–
14	6-Cl-pyridin-3-yl- (**2n**)	**3n**, 84
15	thiophen-3-yl- (**2o**)	**3o**, 82
16	5-indolyl- (**2p**)	**3p**, 61[b]
17	benzo[*b*]thien-3-yl- (**2q**)	**3q**, 41[b]

[a] After column chromatography, moisture excluded by $CaCl_2$-drying tube. [b] Reaction performed for 40 h.

Notably, in contrast to the previously reported procedure,[8] this method facilitated the preparation of bromo- and chloro-substituted products **3h** and **3i** (94% and 85%, respectively; Table 2, entries 8 and 9). Of particular interest, the carbon–halogen bond was preserved during the reaction process and remains amenable to further transformation by classical cross-coupling reactions. Steric factors notably affected the reactivity, as illustrated in the case of methylphenylboronic acid: while *para*- and *meta*-substituted derivatives **2j** and **2k** reacted well (87% and 85% yield, respectively), the corresponding *ortho*-substituted boronic acid **2l** (51% yield) resulted in a significant decrease in yield, and the sterically hindered 2,4,6-trimethylphenyl derivative **2m** did not react at all (Table 2, entries 10–13). Of note, the cross-coupling reaction of sulfondiimine **1a** with heteroaromatic substrates was also successful (Table 2, entries 14–17). To this end, chloro-pyridinyl and thiophenyl derivatives **3n** and **3o** were synthesized in good yields (84% and 82%, respectively) and indolyl (**3p**, 61% yield) and

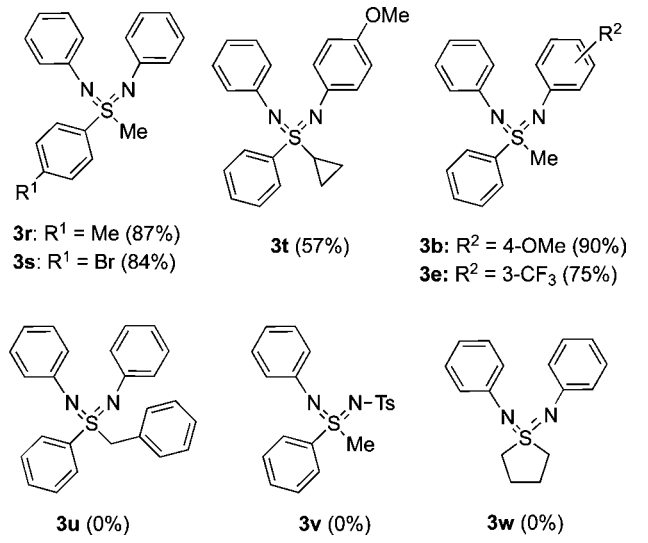


Figure 1. Various *N*H-sulfondiimines stemming from reactions with phenylboronic acid (**2a**).

benzo[*b*]thienyl (**3q**, 41% yield) derivatives were accessible,[12] while the N−H moiety of indole remains available for further transformation.

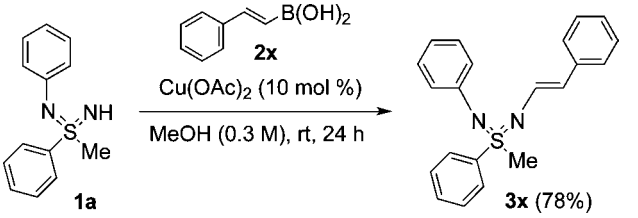
The previously optimized reaction conditions proved applicable to alternatively substituted *N*H-sulfondiimines (Figure 1). In general, *S*-aryl-*S*-alkyl sulfondiimines reacted readily with phenylboronic acid affording *N*-phenylated products **3r** (87%), **3s** (84%), and cyclopropyl derivative **3t** (57%) in good yields. Interestingly, the alternate synthetic pathway toward sulfondiimine **3b** by phenylation of a *N*-(4-methoxyphenyl)-substituted *N*H-sulfondiimine gave the product in a significantly higher yield (90%) than the previously mentioned transformation of sulfondiimine **1a** with 4-methoxyphenylboronic acid (72%; Table 2, entry 2). Unfortunately, sulfondiimines with an electron-withdrawing group on the nitrogen (here: *N*-tosyl), a *S*-benzyl substituent, or two aliphatic groups (here: tetrahydrothiophene) led to degradation of the *N*H-sulfondiimine, and products **3u**−**w** could not be obtained.

(12) The cross-coupling of sulfondiimine **1a** with furan-3-yl- or pyridin-3-ylboronic acid proved unsuccessful.

(13) Column chromatography with basic alumina was crucial. Use of silica gel led to partial hydrolysis. For an analogous behavior observed for *N*-alkynylated sulfoximines, see: Wang, L.; Huang, H.; Priebbenow, D. L.; Pan, F.-F.; Bolm, C. *Angew. Chem., Int. Ed.* **2013**, *52*, 3478.

To further extend the application of this reaction process, use of an alkenyl-substituted boronic acid was investigated. The cross-coupling of sulfondiimine **1a** with (*E*)-styrylboronic acid (**2x**) afforded (*E*)-*N*-alkenylated product **3x** in 78% yield (Scheme 1). This transformation represents, to the best of our knowledge, the first *N*-alkenylation of a sulfondiimine.[13] This result presents significant potential for the preparation of an entirely new class of *N*,*N*′-disubstituted sulfondiimines.

Scheme 1. The First N-Alkenylation of a Sulfondiimine



In conclusion, we have developed a new synthetic pathway toward *N*,*N*′-disubstituted sulfondiimines through the copper-catalyzed C−N cross-coupling with boronic acids. The reaction proceeds under mild and base-free conditions at room temperature using a simple copper catalyst and takes advantage of the *umpolung* reactivity of a variety of commercially available boronic acids. This protocol allows the preparation of several previously unreported *N*,*N*′-disubstituted sulfondiimines, including *N*-(hetero)-aryl sulfondiimines, in good to excellent yields. In addition, the synthesis of a previously unknown N-alkenylated sulfondiimine is presented.

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Supporting Information Available. Experimental procedures, full characterization of new products, and copies of ^{1}H, ^{13}C, and ^{19}F NMR spectra can be found in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.