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$Cu(OAc)_2$-Catalyzed N-Arylations of Sulfoximines with Aryl Boronic Acids

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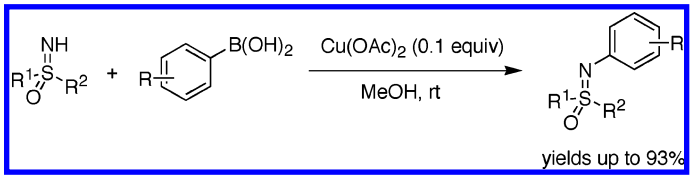
ABSTRACT



A simple and mild copper salt-catalyzed N-arylation of sulfoximines in high yields is reported. $Cu(OAc)_2$ activates aryl boronic acids for the reaction with NH-sulfoximines without additional base or heating. Furthermore, this new method allows the preparation of N-arylated sulfoximines, which have previously been more difficult to access.

In 1998, Chan,[1] Lam,[2] and Evans[3] reported on copper-mediated carbon−heteroatom cross-coupling reactions of boronic acids using a wide range of different nucleophiles such as amines, anilides, amides, imines, ureas, carbamates, and aromatic heterocycles. Very soon after, Collman and Zhong described a copper-catalyzed system for the N-arylation of imidazoles.[4] Since then, several new applications have been developed, which made this arylation method an important tool for sp^2-carbon−nitrogen bond formation.[5] For example, Lam recently showed that N-arylations of α-aminoesters with *p*-tolylboronic acid proceeded with almost complete retention of configuration (94−99% ee),[6] and Xie demonstrated the use of stoichiometric amounts of boronic acid for the N-arylation of imidazoles, amines, amides, imides, and sulfonamides in refluxing methanol without the need of an additional base.[7]

Our group has a long standing interest in N-arylation reactions of sulfoximines, since the resulting compounds have proven to be effective chiral ligands in various catalytic asymmetric reactions.[8] In particular for the synthesis of sulfoximines containing a rigid backbone, N-arylation reactions are often the key step to success.[8,9] For this purpose, two main methods based on palladium or copper catalysis have been developed.[10,11] Common characteristics of these reactions are the use of aryl halides[12] and the need for an external base such as Cs_2CO_3 or KO*t*-Bu at elevated

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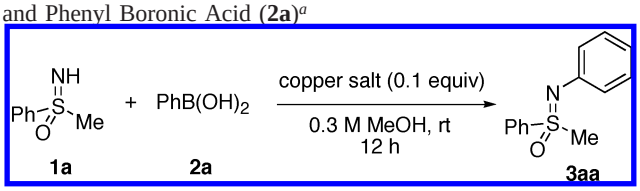
Table 1. Effect of Various Copper Salts on the Copper-Catalyzed Cross-Coupling Reaction of Sulfoximine **1a** and Phenyl Boronic Acid (**2a**)[a]



entry	copper salt	yield of **3aa** (%)
1	CuI	85
2	CuCl	55
3	$CuSO_4$	91
4	$Cu(OAc)_2 \cdot H_2O$	87
5	$Cu(OAc)_2$	93

[a] Reaction conditions: sulfoximine (1.0 equiv), $PhB(OH)_2$ (2.3 equiv), copper salt (0.1 equiv), in 0.3 M MeOH (with respect to **1a**) at room temperature, moisture excluded by a $CaCl_2$ drying tube.

temperatures.[13] We wondered if the scope of this important method could be extended by the application of other (formally *umgepolte*) aryl sources such as boronic acids. In this Letter, we present a simple and mild copper-catalyzed N-arylation of sulfoximines that utilizes such boron reagents under base free conditions.

Optimization experiments involved sulfoximine **1a** and phenyl boronic acid (**2a**) as test substrates and focused on determining the effect of the copper salt, the solvent, and the amount of boronic acid.[14] Table 1 shows the influence of various copper salts on this transformation.

Both copper(I) and copper(II) salts were catalytically active in the coupling reaction even at room temperature. Among the tested copper salts, anhydrous copper(II) acetate was found to be the best catalyst, leading to 93% yield of **3aa** within 12 h at room temperature (Table 1, entry 4). Use of the hydrated form of this copper(II) salt gave **3aa** in 87% yield (entry 3). Interestingly, copper(I) iodide, which is known to promote the N-arylation of sulfoximines with aryl halides,[11] was also a good catalyst (entry 1), and the product was obtained with only a slightly reduced yield (85%). The best results were achieved with 10 mol % copper(II) acetate. Increasing the catalyst amount had only a minor effect on the product yield, and smaller quantities led to longer reaction

Table 2. Dependence of the Yield of **3aa** on the Amounts of $Cu(OAc)_2$ and Phenyl Boronic Acid (**2a**) Used in the N-Arylation of Sulfoximine **1a**[a]

entry	$Cu(OAc)_2$ (equiv)	**2a** (equiv)	yield of **3aa** (%)
1	0.1	1	33 (83[b])
2	1	1	58
3	0.1	2	86
4	0.1	2.3	93
5	1	2.3	93

[a] Reaction conditions: sulfoximine (1 equiv), boronic acid and copper salt in 0.3 M MeOH, rt, 24 h. [b] Based on recovered starting material.

times and incomplete conversions.[15] Also the use of solvents other than methanol (dried with 3 Å molecular sieves) resulted in lower conversions as well as reduced reaction rates.[16] The reaction worked best with vigorous stirring under anhydrous conditions.[17] Consistent with reports by Xie,[7] it was not necessary to add an external base, and no homocoupling of the boronic acid was detected during the course of the reaction. In some cases, the formation of small quantities (<10%) of the corresponding arylmethyl ether was observed.[18]

Table 2 shows that the amount of boronic acid was critical to the reaction outcome. Less than 2 equiv of the aryl source drastically reduced the yield of the N-arylated product. Even with 1 equiv of the copper salt (entries 2 and 5), the reaction of equimolar amounts of phenyl boronic acid and sulfoximine led to only 33% yield (57% conversion).

To evaluate the substrate scope of this new approach toward N-arylated sulfoximines, we investigated cross-couplings of various commercially available aryl boronic acids and a few other sulfoximines.[19] In all cases, the optimized conditions described above proved to be applicable. Good to excellent results were achieved with para-substituted boronic acids (Table 3, entries 3, 5, 7 and 9), irrespective of the electronic nature of the substituent of the boronic acid. Thus, couplings of **2c**, **2e**, and **2h** with sulfoximine **1a** gave almost identical yields of the corresponding arylated products **3ac**, **3ae**, and **3ah**, respectively. The same observation was made in reactions with ortho-substituted boronic acids **2b**, **2f**, and **2j**, albeit in these cases, the yields were slightly lower (Table 3, entries 2, 6, and 10).

The lower yields in most couplings of ortho-substituted aryl boronic acids indicated the importance of steric effects, and, indeed, whereas boronic acids with one ortho substituent were very suitable substrates for the cross-coupling reaction (entries 2, 4, 6 and 10), 2,4,6-trimethylphenyl boronic acid (**2k**) failed to give the corresponding N-arylated product **3ak**.

(10) (a) Bolm, C.; Hildebrand, J. P. *J. Org. Chem.* **2000**, *65*, 169. (b) Bolm. C.; Hildebrand, J. P. *Tetrahedron Lett.* **1998**, *39*, 5731. (c) Bolm, C.; Hildebrand, J. P.; Rudolph, J. *Synthesis* **2000**, 911. (d) Harmata, M.; Hong, X.; Ghosh, S. K. *Tetrahedron Lett.* **2004**, *45*, 5233.

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(12) In Pd-catalyzed arylations, aryl triflates and aryl nonaflates can also be applied. For details, see refs 10a−c.

(13) For intra- and intermolecular C-arylations of sulfoximines, see: (a) Bolm, C.; Martin, M.; Gibson, L. *Synlett* **2002**, 832. (b) Bolm, C.; Okamura, H.; Verrucci, M. *J. Organomet. Chem.* **2003**, *687*, 444. (c) Cho, G. Y.; Bolm, C. *Org. Lett.* **2005**, *7*, 1351.

(14) Generally, *racemic* **1a** was used in this study. However, it was also demonstrated that the coupling of enantiopure (*S*)-**1a** with **2a** to give **3aa** proceeded entirely stereospecifically. HPLC analysis of **3aa**: Chiralcel OD-H, 9:1 heptane−2-propanol, 0.5 mL/min; t_R = 53 min (*S*), t_R = 78 min (*R*).

(15) Use of 0.2 equiv of $Cu(OAc)_2$ → 94% of **3aa** after 10 h; 0.05 equiv of $Cu(OAc)_2$ → 86% of **3aa** after 24 h; 0.01 equiv of $Cu(OAc)_2$ → 52% of **3aa** after 40 h.

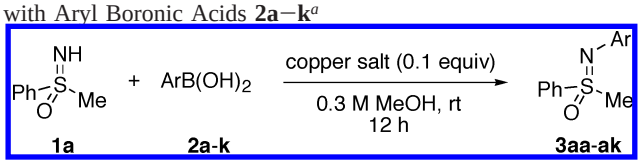
(16)) Yields of **3aa** after 24 h: 72% in DCM, 74% in DMSO, 66% in EtOH.

(17) Usually, the reactions were performed in 10 mL test tubes within a 250 mL flask under exclusion of atmospheric moisture.

(18) Quach, T. D.; Batey, R. A. *Org. Lett.* **2003**, *5*, 1381.

(19) No reaction was observed when methyl boronic acid was used instead of phenyl boronic acid.

Table 3. $Cu(OAc)_2$-Catalyzed N-Arylation of Sulfoximine **1a** with Aryl Boronic Acids **2a**−**k**[a]



entry	$ArB(OH)_2$	Ar	product	yield (%)
1	**2a**	C_6H_5−	**3aa**	93
2	**2b**	2-Me-C_6H_4−	**3ab**	75
3	**2c**	4-Me-C_6H_4−	**3ac**	92
4	**2d**	2-Cl-C_6H_4−	**3ad**	90
5	**2e**	4-Cl-C_6H_4−	**3ae**	93
6	**2f**	2-MeO-C_6H_4−	**3af**	73
7	**2g**	4-Br-C_6H_4−	**3ag**	71
8	**2h**	4-(t-$BuMe_2Si$)O-C_6H_4−	**3ah**	88
9	**2i**	4-Ph-C_6H_4−	**3ai**	74
10	**2j**	2-naphthyl−	**3aj**	62
11	**2k**	2,4,6-Me_3-C_6H_2−	**3ak**	

[a] Reaction conditions: sulfoximine **1a** (1 equiv), aryl boronic acid **2a**−**k** (2.3 equiv), $Cu(Oac)_2$ (0.1 equiv), 0.3 M MeOH, 12 h.

Sulfoximines **1b** and **1c** also reacted well with phenyl boronic acid (**2a**), and the corresponding N-phenylated products **3ba** and **3ca** were obtained with 86 and 81% yield, respectively (Figure 1). The chemoselective coupling of *S*-(4-bromo)-phenyl-*S*-methylsulfoximine (**1b**) is interesting for several reasons. First, it reveals that the N-coupling process is favorable over possible C-arylations (at both the aryl as well as the methyl group of the sulfoximine),[20] and second, it allows further functionalizations of the resulting N-arylated product, since the sulfoximine aryl group still bears a *p*-bromo substituent, which is accessible for further modifications.[21] The high yield in the coupling of **1c** demonstrates that steric bulk at the α-carbon of the sulfoximine moiety is tolerated, which further extends the scope of potential applications of the coupling process. In conclusion, we reported a novel copper-catalyzed N-arylation of sulfoximines using boronic acids as arylating agents. The cross-couplings proceed under mild reaction conditions at room temperature without additional external base. Considering the structural diversity and the huge number of boronic acid derivatives, we forsee that this new method will find broad application for the synthesis of a wide variety of sulfoximines with so far unknown properties.

(20) For interesting selectivities observed in metal-catalyzed N- and C-arylations of indazole derivatives with aryl boronic acids, see ref 5g.

(21) Cho, G. Y.; Okamura, H.; Bolm, C. *J. Org. Chem.* **2005**, *70*, 2346.

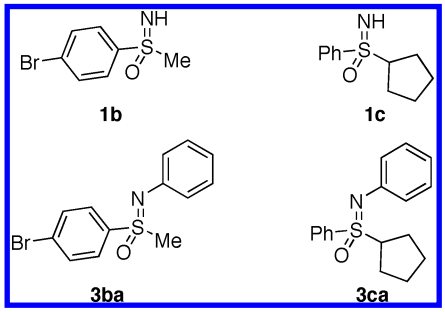


Figure 1.

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Supporting Information Available: Experimental procedures and full characterization (^1H and ^{13}C NMR data and spectra, MS, IR, and CHN analyses) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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