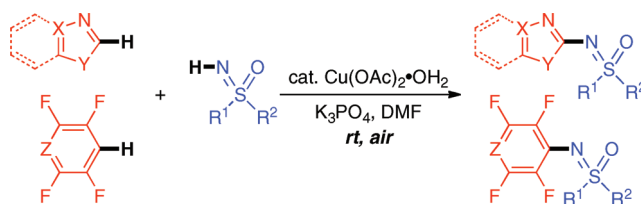


Copper-Catalyzed Direct Sulfoximation
of Azoles and Polyfluoroarenes under
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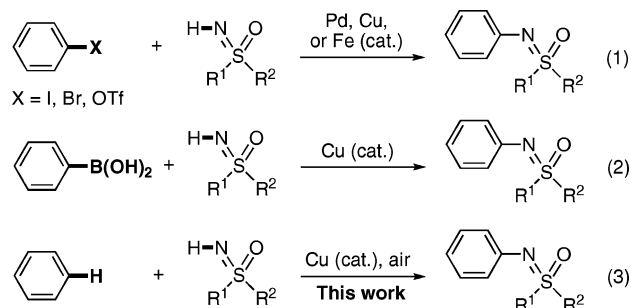
ABSTRACT



The direct dehydrogenative C–N coupling of azoles or polyfluoroarenes with N–H sulfoximines proceeds effectively in the presence of a copper catalyst at room temperature under air to afford the corresponding *N*-arylsulfoximines in good to high yields.

Sulfoximines have attracted attention in organic chemistry because of their successful use as chiral auxiliaries¹ and ligands² in asymmetric synthesis as well as pivotal motifs in biologically active compounds.³ In the latter context, *N*-(hetero)arylsulfoximines are of particular interest due to the fact that various derivatives showed anticancer activity⁴ or proved applicable as agrochemicals.⁵ Among the most effective and convergent approaches to the target structures

are metal-catalyzed *N*-arylations of N–H sulfoximines (Scheme 1). Various palladium, copper, and iron complexes

Scheme 1. Approaches to *N*-Arylsulfoximines

can be applied in catalytic reactions with aryl halides⁶ or arylboronic acids⁷ (eqs 1 and 2). While useful, all protocols have in common that a preactivation step such as halogenation or stoichiometric metalation of original arenes is

[†] Osaka University.[‡] RWTH Aachen University.(1) (a) Johnson, C. R. *Acc. Chem. Res.* **1973**, *6*, 341. (b) Pyne, S. *Sulfur Rep.* **1992**, *12*, 57. (c) Reggelin, M.; Zur, C. *Synthesis* **2000**, 1.(2) (a) Harmata, M. *Chemtracts* **2003**, *16*, 660. (b) Okamura, H.; Bolm, C. *Chem. Lett.* **2004**, *32*, 482.(3) (a) Kahraman, M.; Sinishtay, S.; Dolan, P. M.; Kensler, T. W.; Peleg, S.; Saha, U.; Chuang, S. S.; Bernstein, G.; Korczak, B.; Poser, G. H. *J. Med. Chem.* **2004**, *47*, 6854. (b) Worch, C.; Mayer, A. C.; Bolm, C. In *Organosulfur Chemistry in Asymmetric Synthesis*; Toru, T., Bolm, C., Eds.; Wiley-VCH: Weinheim, Germany, 2008; p 209 and references therein.(4) (a) Lücking, U.; Siemeister, G.; Jautelat, R. *PCT Int. Appl.* 2006, WO 2006/099974, A1 20060928 (CAN 145:377362). (b) Shetty, S. J.; Patel, G. D.; Lohray, B. B.; Lohray, V. B.; Chakrabarti, G.; Chatterjee, A.; Jain, M. R.; Patel, P. R. *PCT Int. Appl.* 2007, WO 2007077574, A2 20060928 (CAN 145:377362).(5) Tsukuda, K.; Yamada, S.; Yamaguchi, M. *PCT Int. Appl.* 2008, WO 2008/035737, A1 20080327 (CAN 148:403217).

inevitable to prepare the coupling reagents. Ultimately, the direct dehydrogenative C–N coupling between arenes and N–H sulfoximines is ideal from the viewpoint of step economy (eq 3). However, this type of coupling is, to the best of our knowledge, unprecedented.

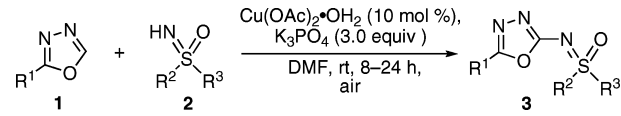
Recently, synthetic options by metal-catalyzed direct C–H functionalization have grown rapidly resulting in a large impact on synthetic organic chemistry.⁸ In this context, a few successful intermolecular C–N cross-couplings of arenes and nitrogen nucleophiles involving alkylamines, anilines, and amides have been developed.^{9,10} Herein, we report a catalytic direct sulfoximation of azoles and polyfluoroarenes for the synthesis of *N*-(hetero)arylsulfoximines. The reaction proceeds very smoothly under inexpensive copper catalysis at room temperature.

In a typical experiment, treatment of 2-phenyl-1,3,4-oxadiazole (**1a**) with *S*-methyl-*S*-phenylsulfoximine (**2a**) in the presence of 10 mol % of Cu(OAc)₂·OH₂ and 3.0 equiv of K₃PO₄ in DMF under ambient conditions for 8 h afforded the directly iminated product **3aa** in 92% yield (96% GC) (Table 1, entry

conversion, and other reaction systems using K₂CO₃, KOAc, *o*-xylene, DMSO, THF, or CH₂Cl₂ largely diminished the yields (0–54% GC yields). By using the copper-based catalyst, a variety of 2-substituted 1,3,4-oxadiazoles efficiently coupled with **2a**. Electron-donating as well as electron-withdrawing groups on the benzene ring were compatible toward the reaction (entries 2–5). A bulky naphthalene substituent did not interfere (entry 6). Moreover, alkyl-substituted **1g** coupled (entry 7). The generality of sulfoximines was also good (entries 8–11). Noteworthy is the fact that the carbon bromide moiety of **2e** was left intact, which could be useful for further manipulation by a conventional cross-coupling methodology (entry 11).

Among other azoles tested, benzoxazoles and benzothiazole were found to undergo direct coupling without any difficulties (Figure 1).¹¹ The corresponding 2-iminoazoles

Table 1. Copper-Catalyzed Direct Sulfoximation of 1,3,4-Oxadiazoles **1** with Sulfoximines **2**^a



entry	R ¹ 1	R ² , R ³ 2	3 , yield (%) ^b
1	Ph (1a)	Ph, Me (2a)	3aa , 92 (96)
2	4-MeC ₆ H ₄ (1b)	2a	3ba , 86
3	4-MeOC ₆ H ₄ (1c)	2a	3ca , 95
4	4-CF ₃ C ₆ H ₄ (1d)	2a	3da , 89
5	4-ClC ₆ H ₄ (1e)	2a	3ea , 90
6	1-naphthyl (1f)	2a	3fa , 92
7	Ph(CH ₂) ₂ (1g)	2a	3ga , 85
8	1a	Ph, Ph (2b)	3ab , 79
9	1a	Me, Me (2c)	3ac , 60
10	1a	2-naphthyl, Me (2d)	3ad , 87
11	1a	4-BrC ₆ H ₄ , Me (2e)	3ae , 70

^a A mixture of **1** (0.60 mmol), **2** (0.40 mmol), Cu(OAc)₂·OH₂ (0.040 mmol), and K₃PO₄ (1.2 mmol) was stirred in DMF (1.0 mL) for 8–24 h at room temperature under air. ^b In parentheses, yield determined by GC method.

1). Several observations concerning optimization studies are to be noted: the use of other copper salts, Cu(OTf)₂, CuI, and CuCl₂, resulted in comparable or somewhat lower yields of 93, 95, and 72% (GC), respectively; the addition of ligands such as 1,10-phenanthroline, 2,2′-bipyridine, and *N,N,N′,N′*-tetramethylethylenediamine decreased the yield of **3aa** by ca. 30–40%; a combination of K₃PO₄ and DMF was essential for full

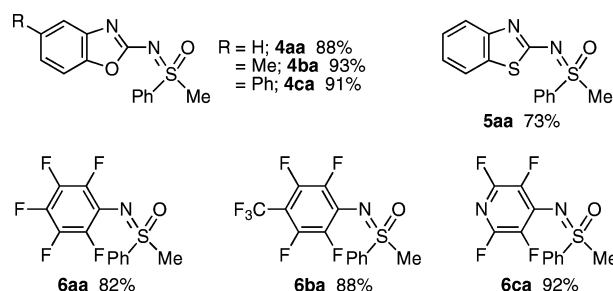


Figure 1. Products of Copper-Catalyzed Direct Sulfoximation of Azoles and Polyfluoroarenes.

4aa–ca and **5aa** were obtained in good to high yields. Given that (hetero)arenes containing a relatively acidic C–H bond showed good efficiency, polyfluoroarenes were also antici-

(8) Recent reviews: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (b) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200. (c) Campeau, L. C.; Stuart, D. R.; Fagnou, K. *Aldrichchim. Acta* **2007**, *40*, 35. (d) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (e) Park, Y. J.; Park, J.-W.; Jun, C.-H. *Acc. Chem. Res.* **2008**, *41*, 222. (f) Lewis, L. C.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013. (g) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013. (h) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074. (i) Kulkarni, A. A.; Daugulis, O. *Synthesis* **2009**, 4087. (j) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (k) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. (l) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, *46*, 677. (m) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (n) Dudnik, A. S.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2010**, *49*, 2096. (o) Satoh, T.; Miura, M. *Chem.–Eur. J.* **2010**, *16*, 11212. (p) Satoh, T.; Miura, M. *Synthesis* **2010**, 3395.

(9) (a) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790. (b) Uemura, T.; Imoto, S.; Chatani, N. *Chem. Lett.* **2006**, *35*, 842. (c) Monguchi, D.; Fujiwara, T.; Furukawa, H.; Mori, A. *Org. Lett.* **2009**, *11*, 1607. (d) Wang, Q.; Schreiber, S. L. *Org. Lett.* **2009**, *11*, 5178. (e) Cho, S. H.; Kim, J. Y.; Lee, S. Y.; Chang, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 9127. (f) Shuai, Q.; Deng, G.; Chua, Z.; Bohle, D. S.; Li, C.-J. *Adv. Synth. Catal.* **2010**, *352*, 632. (g) Zhao, H.; Wang, M.; Su, W.; Hong, M. *Adv. Synth. Catal.* **2010**, *352*, 1301.

(10) Intramolecular fashion: (a) Tsang, W. C. P.; Zheng, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560. (b) Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2006**, *128*, 9048. (c) Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14058. (d) Jordan-Hore, A. A.; Johansson, C. C. C.; Gulias, M.; Beck, E. M.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 16184. (e) Mei, T.-S.; Wang, X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 10806.

(11) Attempts to apply benzimidazole, benzothiophene, or benzofuran remained unsuccessful.

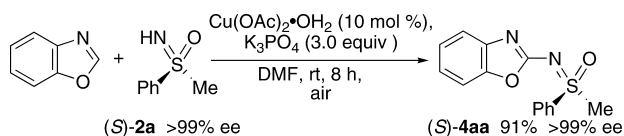
(6) (a) Bolm, C.; Hildebrand, J. P. *Tetrahedron Lett.* **1998**, *39*, 5731. (b) Bolm, C.; Hildebrand, J. P. *J. Org. Chem.* **2000**, *65*, 169. (c) Bolm, C.; Hildebrand, J. P.; Rudolph, J. *Synthesis* **2000**, 911. (d) Bolm, C.; Cho, G. Y.; Rémy, P.; Jansson, J.; Moessner, C. *Org. Lett.* **2004**, *6*, 3293. (e) Correa, A.; Bolm, C. *Adv. Synth. Catal.* **2008**, *350*, 391.

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

pated to work well as arene coupling partners.¹² As hypothesized, pentafluorobenzene reacted with **2a** under identical conditions to provide **6aa** in 82% yield. The reactions with 2,3,5,6-tetrafluoro-substituted benzotrifluoride and pyridine were also possible (**6ba** and **6ca**). However, 1,2,4,5-tetrafluorobenzene itself coupled with **2a** sluggishly (not shown, ca. 20% GC yield).

Owing to the mildness of the reaction conditions, the enantiopure sulfoximine (*S*)-**2a** could be transformed into the *N*-benzoxazolylsulfoximine (*S*)-**4aa** without affecting the enantiomeric excess (Scheme 2).

Scheme 2



Although further efforts on the clarification of the reaction mechanism are required, one possibility involves (i) the sequential base-assisted cupration of sulfoximine and arene¹³ leading to the corresponding (aryl)(sulfoximidoyl)copper intermediate $[\text{ArCuN}=\text{S}(=\text{O})\text{R}^1\text{R}^2]$ and (ii) oxygen-promoted reductive elimination¹⁴ along with the regeneration of a catalytically active copper species.¹⁵

In summary, we have described an effective copper catalysis for the direct coupling of azoles or polyfluoroarenes

with sulfoximines at room temperature. The reaction enables the rapid and concise construction of *N*-heteroaryl or -polyfluoroarylsulfoximines of substantial interest in medicinal and pharmaceutical chemistry.

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

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(13) Base-assisted cupration of arenes: (a) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 12404. (b) Yoshizumi, T.; Tsurugi, H.; Satoh, T.; Miura, M. *Tetrahedron Lett.* **2008**, *49*, 1598. (c) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 1128. (d) Zhao, D.; Wang, W.; Yang, F.; Lan, J.; Yang, L.; Gao, G.; You, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 3296. (e) Kawano, T.; Yoshizumi, T.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 3072. (f) Besselièvre, F.; Piguel, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 9553. (g) Ackermann, L.; Potukuchi, H. K. *Org. Biomol. Chem.* **2010**, *8*, 4503. (h) Kawano, T.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2010**, *132*, 6900, and references therein.

(14) Even with 1.0 equiv of $\text{Cu}(\text{OAc})_2 \cdot \text{OH}_2$, only a trace amount of **3aa** was detected under N_2 conditions (vs Table 1, entry 1). The outcome suggests that molecular oxygen may work as not only an oxidant to Cu but also the crucial accelerator in the reaction.

(15) Relevant reaction mechanism: (a) Hamada, T.; Ye, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 833. (b) Kitahara, M.; Hirano, K.; Tsurugi, H.; Satoh, T.; Miura, M. *Chem.—Eur. J.* **2010**, *16*, 1772. (c) Wei, Y.; Zhao, H.; Kan, J.; Su, W.; Hong, M. *J. Am. Chem. Soc.* **2010**, *132*, 2522, and ref 9c,d, and 9g.

(12) Shen, K.; Fu, Y.; Li, J.-N.; Liu, L.; Guo, Q.-X. *Tetrahedron* **2007**, *63*, 1568.