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Copper-Catalyzed Direct Sulfoximination of Azoles and Polyfluoroarenes under Ambient Conditions

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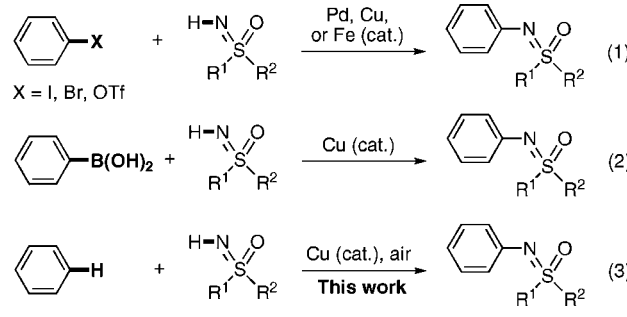
ABSTRACT

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 auxiliaries[1] and ligands[2] 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 activity[4] 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 halides[6] or arylboronic acids[7] (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

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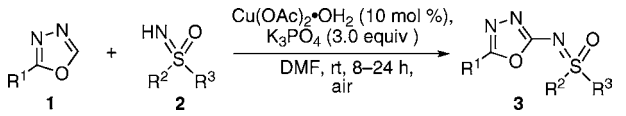
inevitable to prepare the coupling reagents. Ultimately, the direct dehydrogenative C−N coupling between arenes and N−H sulfoximines is ideal from the viewpoint of step economy (eq 3). However, this type of coupling is, to the best of our knowledge, unprecedented.

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 sulfoximination 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 $Cu(OAc)_2{\cdot}OH_2$ and 3.0 equiv of K_3PO_4 in DMF under ambient conditions for 8 h afforded the directly iminated product **3aa** in 92% yield (96% GC) (Table 1, entry 1). Several observations concerning optimization studies are to be noted: the use of other copper salts, $Cu(OTf)_2$, CuI, and $CuCl_2$, 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 K_3PO_4 and DMF was essential for full conversion, and other reaction systems using K_2CO_3, KOAc, *o*-xylene, DMSO, THF, or CH_2Cl_2 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).

Table 1. Copper-Catalyzed Direct Sulfoximination of 1,3,4-Oxadiazoles **1** with Sulfoximines **2**[a]



1 **2** **3**

entry	R^1 **1**	R^2, R^3 **2**	**3**, yield (%)[b]
1	Ph (**1a**)	Ph, Me (**2a**)	**3aa**, 92 (96)
2	4-MeC_6H_4 (**1b**)	**2a**	**3ba**, 86
3	4-$MeOC_6H_4$ (**1c**)	**2a**	**3ca**, 95
4	4-$CF_3C_6H_4$ (**1d**)	**2a**	**3da**, 89
5	4-ClC_6H_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_6H_4, Me (**2e**)	**3ae**, 70

[a] A mixture of **1** (0.60 mmol), **2** (0.40 mmol), $Cu(OAc)_2{\cdot}OH_2$ (0.040 mmol), and K_3PO_4 (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.

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

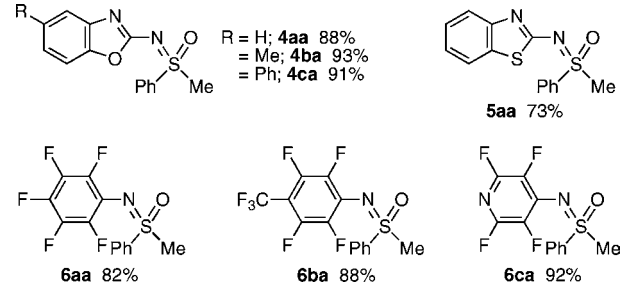


Figure 1. Products of Copper-Catalyzed Direct Sulfoximination of Azoles and Polyfluoroarenes.

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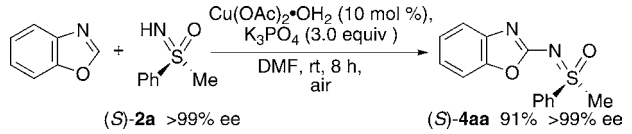
(11) Attempts to apply benzimidazole, benzothiophene, or benzofuran remained unsuccessful.

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 arene[13] leading to the corresponding (aryl)(sulfoximidoyl)copper intermediate [ArCuN═S(═O)R^1R^2] and (ii) oxygen-promoted reductive elimination[14] 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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(14) Even with 1.0 equiv of $Cu(OAc)_2$•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.

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