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Copper-Mediated Cross-Coupling Reactions of N-Unsubstituted Sulfoximines and Aryl Halides

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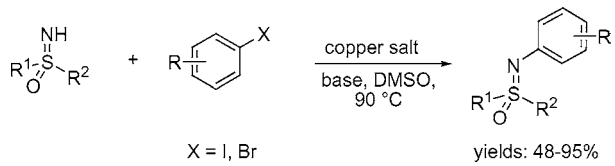
ABSTRACT



Copper-mediated cross-coupling reactions of sulfoximines with aryl iodides and aryl bromides provide N-arylated sulfoximines in high yields. The method is complementary to the known palladium-catalyzed N-arylation and allows the preparation of N-arylated sulfoximines, which have previously been inaccessible.

Due to their applicability as chiral auxiliaries,[1] ligands in asymmetric catalysis,[2] and building blocks in pseudopeptides,[3] sulfoximines have attracted much attention. Their preparation is well-established, and a number of synthetic approaches have been developed, which give access to a variety of derivatives in a relatively straightforward manner.[1] For N-arylations of sulfoximines we developed a stereospecific palladium-catalyzed cross-coupling reaction, in which aryl iodides, bromides, nonaflates, and triflates can be used.[4] This method has been extended by Harmata toward couplings of aryl chlorides[5] and was utilized in a number of syntheses to give new sulfoximines as ligands for catalysis,[2] benzothiazines,[6] and other cyclic derivatives.[7] Despite this success, some limitations of the palladium catalysis such as long reaction times, restricted substrate scope, and high metal/ligand (catalyst) cost motivated the search for an alternative cross-coupling protocol. Recently, copper-mediated or -catalyzed carbon−heteroatom bond formations (C−O, C−N, C−S)[8,9] have been developed by several groups after initial independent studies by Chan,[10] Evans,[11] and Lam.[12] They can be used in transformations of a wide range of

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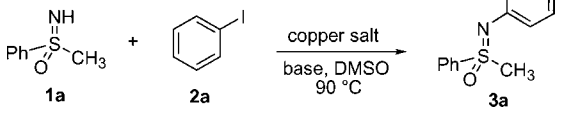
substrates under very mild reaction conditions, and, for large-scale applications, the low price of copper is a major advantage compared to the palladium methodology. Furthermore, differences in reactivity and regioselectivity between palladium and copper catalysts have been found that, for example, proved to be useful for the selective arylation of heterocycles such as 5-aryltetrazoles and 1,3-diarylindazoles.[13] In this Letter, we report the first copper-promoted cross-couplings to give N-arylated sulfoximines. The protocol starting from readily available educts is easy to perform; the products are obtained in high yields, and several derivatives can be prepared that were previously inaccessible.

As a test reaction, we chose the cross-coupling between sulfoximine **1a**[14] and phenyl iodide (**2a**). To establish the reaction conditions, the effect of base, solvent, and copper salt was evaluated. The results of this initial screening are summarized in Table 1.

Table 1. Effect of the Reaction Parameters on the Copper-Mediated Cross-Coupling of Sulfoximine **1a** and Phenyl Iodide (**2a**) to Give *N*-Phenyl Sulfoximine **3a**[a]



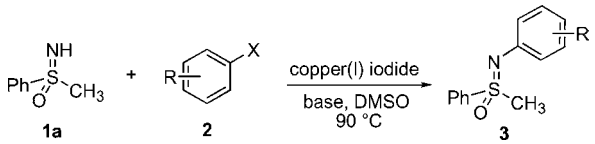
entry	copper salt	base	yield (%)
1	CuI	Cs_2CO_3	94
2	CuI	CsOAc	78
3	CuI	NaO*t*-Bu	91
4	CuI	K_3PO_3	39
5	CuBr	Cs_2CO_3	85
6	$CuSO_4$	Cs_2CO_3	46

[a] Reaction conditions: sulfoximine (1.0 equiv), phenyl iodide (2.0 equiv), base (2.5 equiv), copper salt (1.0 equiv), in DMSO (1 M with respect to **1a**) at 90 °C.

To our delight, several copper salts were found to promote the N-arylation giving *N*-phenyl sulfoximine **3a** in good to excellent yields. The best result was achieved with a combination of copper(I) iodide (1.0 equiv) and Cs_2CO_3 (2.5 equiv) in DMSO at 90 °C (Table 1, entry 1). Other copper salts such as copper(I) bromide or copper(II) sulfate also promoted the reaction; however, the yields were lower. Cs_2CO_3 proved to be superior to other bases. Use of solvents other than DMSO (such as DMF, THF, dichloroethane, or toluene) as well as lower amounts of metal salt, base, or aryl halide led to reduced yields of **3a**.[15] Exposure of the reaction mixture to oxygen diminished the product yield. The stereospecificity of the copper-promoted cross-coupling was shown by the conversion of enantiopure **1a** to give **3a** as a single enantiomer (HPLC analysis).[16]

Next, we investigated the substrate scope using various aryl iodides and bromides. The results are summarized in Table 2.

Table 2. Copper-Mediated Cross-Coupling of Sulfoximine **1a** and Aryl Iodides (**2a**−**n**) or Aryl Bromides (**2p**−**r**) to Give N-Arylated Sulfoximines **3**[a]



entry	**2**	X	R	method[a]	**3**	yield (%)
1	**b**	I	2-Me	A	**b**	84
2	**c**	I	2-Br	A	**c**	68
3	**d**	I	2-NO_2	A	**d**	83
4	**e**	I	2-OMe	A	**e**	72
5	**f**	I	2-P(O)Ph_2	B	**f**	71
6	**g**	I	3-CN	A	**g**	94
7	**h**	I	4-Me	A	**h**	93
8	**i**	I	4-CHO	C	**i**	85
9	**j**	I	4-CO_2Et	A	**j**	88
10	**k**	I	4-NO_2	A	**k**	82
11	**l**	I	2-NO_2,4-F	B	**l**	95
12	**m**	I	2-NO_2,4-OMe	B	**m**	80
13	**n**	I	2,4,6-Cl_3	B	**n**	60
14	**o**	Br	2-NO_2	B	**o**	78
15	**p**	Br	2-NO_2,4-CF_3	B	**p**	83
16	**q**	Br	2-NHAc,5-NO_2	C	**q**	65
17	**r**	Br	2-NHAc, 3-NO_2	C	**r**	48

[a] Method A: sulfoximine (1.0 equiv), aryl halide (2.0 equiv), CuI (1.0 equiv), Cs_2CO_3 (2.5 equiv) in DMSO at 90 °C. Method B: same as A except CsOAc (2.5 equiv) was used instead of Cs_2CO_3. Method C: sulfoximine (2.0 equiv), aryl halide (1.0 equiv), CuI (1.0 equiv), CsOAc (2.5 equiv) in DMSO at 90 °C. [b] Enantiopure (*S*)-**1a** was used.

For most substrates the conditions optimized for the cross-coupling of **1a** with phenyl iodide (**2a**) (method A) proved to be applicable, and generally the corresponding arylated sulfoximines **3** were obtained in high yields. In some cases, the use of CsOAc instead of Cs_2CO_3 (method B) or the application of an excess of sulfoximine (method C) led to an improved yield. For example, when 4-iodobenzaldehyde (**2i**) was applied in the coupling using Cs_2CO_3 as a base, many byproducts were detected. In contrast, with CsOAc a very smooth conversion led to the corresponding arylated

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(13) (a) Beletskaya, I. P.; Davydov, D. V.; Gorovoy, M. S. *Tetrahedron Lett.* **2002**, *43*, 6221. (b) Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron Lett.* **2000**, *41*, 9053.
(14) In this study, racemic **1a** was mostly used. For the preparation of enantiomerically pure **1a**, see: (a) Fusco, R.; Tericoni, F. *Chim. Ind. (Milan)* **1965**, *47*, 61. (b) Johnson, C. R.; Schroeck, C. W. *J. Am. Chem. Soc.* **1973**, *95*, 7418. (c) Brandt, J.; Gais, H.-J. *Tetrahedron: Asymmetry* **1997**, *8*, 909. (d) For alternative approaches, see: Okamura, H.; Bolm, C. *Org. Lett.* **2004**, *6*, 1305 and references therein.
(15) For example, with 1.0 equiv of Cs_2CO_3 and 1.2 equiv of phenyl iodide the yield of **2** was only 24%.
(16) HPLC analysis of **3a**: Chiralcel OD-H, 9:1 heptane/2-propanol, 0.5 mL/min; t_R = 30 min (*S*), t_R = 44 min (*R*).

sulfoximine **3i** in 85% yield (Table 1, entry 8). In general, electronic effects played a minor role and high conversions were achieved no matter if the substituents were electron withdrawing or donating. Ortho substituents did not hamper the coupling reactions. Both aryl iodides as well as aryl bromides (Table 1, entries 1−13 and 14−17, respectively) could be used. A direct comparison using aryl iodide **2d** and aryl bromide **2o** in the coupling with **1a** to give **3d** in each case (Table 1, entries 3 and 14) revealed that both aryl halides react equally well. A reactivity difference, however, was indicated in the conversion of 2-bromophenyl iodide (**2c**), which selectively gave *N*-2-bromoaryl sulfoximine **3c** in 68% yield (Table 2, entry 2). Interestingly, the chemoselectivity (iodide preferred over bromide) was base dependent, and switching from Cs_2CO_3 to CsOAc gave a mixture of both possible monocoupled products.

N-Arylations of sulfoximines **1b** and **1c**[17] with phenyl iodide (**2a**) as an aryl source and Cs_2CO_3 as a base to give **3s** and **3t** in 63 and 53% yield, respectively, confirmed that the protocol was not limited to conversions of **1a** (Figure 1). Particularly noteworthy are the results that highlight the

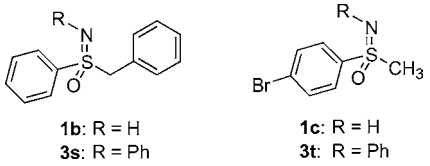
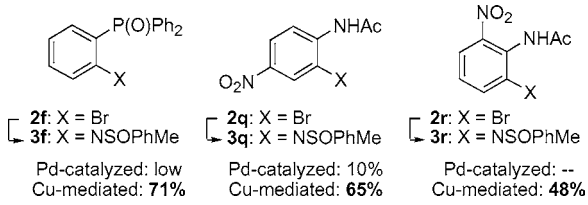


Figure 1.

differences between the copper- and the palladium-promoted cross-coupling. For example, we previously reported, that transformations of aryl iodides under palladium catalysis were difficult, even in the presence of additives such as lithium and silver salts.[4] In the copper-mediated reactions described here, those substrates behave perfectly well, giving products in high yields. Furthermore, we found that in several cases even for aryl bromides the copper-based protocol was superior to the palladium-based one. For example, attempts to cross-couple multiply substituted aryl bromide **2q** under palladium catalysis for 2 days gave **3q** in only 10% yield. In contrast, the novel copper-mediated transformation afforded the desired product in 65% yield after only 12 h (Table 1, entry 16). Moreover, N-arylated sulfoximine **3r** could only be obtained by the copper-mediated route, whereas no product was observed under palladium catalysis.

The synthesis of **3f** was improved by using copper for a different reason. There, the N-arylated sulfoximine was formed (albeit in low quantities) in the palladium-catalyzed coupling, but isolation of the product proved to be cumbersome due to the presence of inseparable impurities. Fortunately, the copper methodology allowed the preparation of the desired product in a very straightforward manner, giving

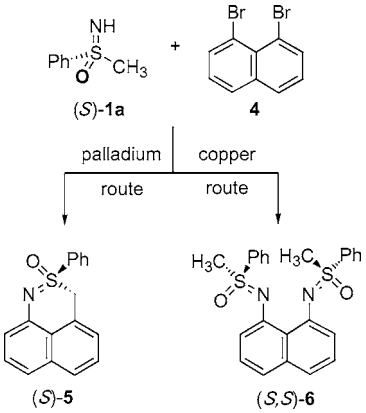
Scheme 1



pure **3f** in 71% yield after simple purification by column chromatography.

The most interesting difference between the palladium- and copper-mediated routes is shown in Scheme 2. Recently,

Scheme 2[a]



[a] Key: Palladium route: $Pd(OAc)_2$, BINAP, NaO*t*-Bu, toluene, reflux, 48 h. Copper route: CuI, CsOAc, DMSO, 90 °C, 12 h.

we have reported that the palladium-catalyzed coupling of dibromoarenes and sulfoximines affords six- to eight-membered heterocycles in excellent yields.[7a] For example, 1,8-dibromonaphthalene (**4**) gives **5** in 90% yield by a sequence of intermolecular N-arylation followed by intramolecular ring closure. Interestingly, the copper-mediated reaction of the same substrates gives an entirely different product. Thus, C_2-symmetric bissulfoximine **6** is formed (56% yield), which results from a double cross-coupling reaction lacking the intramolecular cyclization through C−C bond formation.[18] In this context, it should be noted that related C_2-symmetric bissulfoximines have been successfully applied as ligands in asymmetric catalysis, leading to excellent enantioselectivities in hetero-Diels−Alder reactions,[2a] other cycloadditions,[2c,d] and nucleophilic allylic substitutions.[2b]

In summary, we have developed ligand-free copper-mediated cross-coupling reactions for the synthesis of various N-arylated sulfoximines in high yields. The novel protocol has been proven to be a powerful complement to the previously described palladium catalysis. Shorter reaction

(17) For the preparation and synthetic application of **1c**, see: Cho, G.-Y.; Okamura, H.; Bolm, C. Manuscript in preparation.

(18) As indicated in Scheme 2, the coupling was performed with enantiopure sulfoximine **1a**. Only a single diastereomer of **6** was obtained (after column chromatography).

times, higher reactivity, and economical practicality are advantages of the copper methodology. We are currently searching for catalytic versions of copper-mediated cross-coupling reactions, investigating the use of the new bis-sulfoximines as ligands in asymmetric catalysis, and studying copper-catalyzed C-arylation reactions.

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Supporting Information Available: Experimental procedures and full characterization (^{1}H, ^{13}C, and ^{31}P NMR data and spectra and 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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