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Efficient Copper-Catalyzed N-Arylation of Sulfoximines with Aryl Iodides and Aryl Bromides

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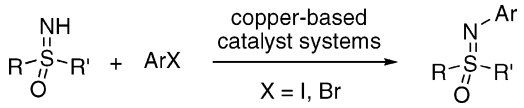

Two simple and inexpensive systems for copper-catalyed N-arylations of sulfoximines with aryl bromides and aryl iodides have been developed. Using 10 mol % of a copper(I) salt in combination with 20 mol % of a 1,2-diamine and Cs_2CO_3 provides N-arylated sulfoximines in high yields. Various functional groups and heteroatoms are tolarated. The method is complementary to the known protocols for N-arylations of sulfoximines, which require stoichiometric quantities of copper salts or cost-intensive palladium/BINAP catalysts.

During the past decades, sulfoximines have attracted significant attention due to their successful use as chiral auxiliaries in asymmetric synthesis[1] and ligands in enantioselective metal catalysis.[2] Furthermore, they have been applied as structural units in pseudopeptides[3] and other pharmaceutically interesting molecules.[4] In general, the preparation of sulfoximines is well-documented, and several approaches toward synthetically useful derivatives have been established.[1] For the N-arylation of sulfoximines by cross-coupling with aryl bromides, iodides, or triflates, we have recently introduced two strategies utilizing either palladium catalysts[5] or stoichiometric amounts of copper salts.[6,7] Given the metal and ligand cost in the first case and taking into account the high metal loading in the second, we initiated a search for other catalyst systems involving simple metal salts and easy to perform reaction conditions. Here we report on the development of highly efficient cross-coupling reactions between *NH*-sulfoximines and aryl iodides or bromides with catalytic quantities of copper(I) salts.[8,9]

Results and Discussion

In the optimizing process, sulfoximine **1** and phenyl iodide (**2a**) were used as starting materials, and the effect of solvent, base, copper source, ligand, and temperature

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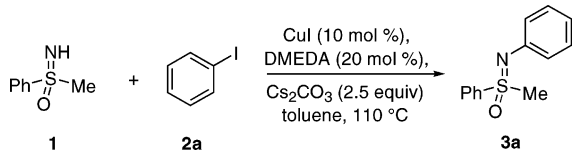
SCHEME 1



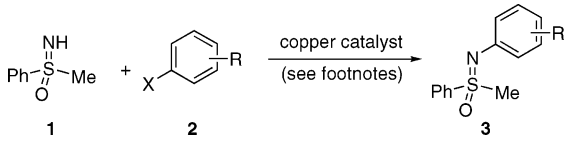
was investigated.[10] The following observations were made: (1) As solvent, toluene is superior to DMSO and dioxane. (2) Cesium carbonate is a much more efficient base than $Cs(OAc)_2$, K_2CO_3, K_3PO_4, KOH, or NaH. (3) Copper(I) iodide is a better copper source than $Cu(OAc)_2$, $Cu(CF_3SO_3)_2$, Cu_2O, $[Cu(phen)(PPh_3)_2]NO_3$, and CuBr. (4) As ligand, *N*,*N*′-dimethylethyldiamine (DMEDA) is superior to TMEDA, proline, and 1,10-phenanthroline. (5) The best conversions are achieved at 110 °C. From those data a set of optimized parameters was deduced (method A), and the best results were achieved using a combination of sulfoximine **1** (1.0 equiv), aryl iodide **2a** (2.0 equiv), Cs_2CO_3 (2.5 equiv), CuI (0.1 equiv), and DMEDA (0.2 equiv) in toluene at 110 °C (Scheme 1). With lower amounts of base, ligand, or aryl halide, the yield of **3a** was reduced. Use of only 5 mol % of the copper salt doubled the reaction time. As expected, no coupling took place when the reaction was carried out in the absence of the metal catalyst.

Under the optimized conditions, a variety of aryl iodides reacted well, affording the corresponding N-arylated sulfoximines in very good to excellent yield (Table 1, entries 1−10). Electronic effects of the substituents on the arene were of minor importance as revealed by the conversions of nitro- and methoxy-substituted aryl iodides, which all led to products in >92% yield. Steric hindrance appears to have an impact, but even aryl iodide **2j** having a rather bulky phosphorus substituent in the ortho-position afforded the corresponding sulfoximine with 86% yield (entry 10).

Attempts to utilize aryl bromides as aryl sources under the conditions optimized for the coupling with aryl iodides remained unsuccessful, and the conversions were low. A solution of the problem was envisaged by making use of Buchwald's aromatic Finkelstein reaction.[11] Consequently, a (one-pot−two-steps) protocol was developed that involved two sequential copper catalyses. First, the bromide on the arene was substituted by an iodide, and then, second, the *NH*-sulfoximine was N-arylated to give **3** as described above (Scheme 2).

Since the aromatic Finkelstein reaction did not tolerate the presence of Cs_2CO_3 and the sulfoximine, the transformation had to be performed sequentially (method B). For the halide exchange reactions, the best results were achieved by keeping mixtures of the aryl bromides, CuI (10 mol %), DMEDA (20 mol %), and NaI (4 equiv) in dioxane at 110 °C for 20 h. Then, the base and the sulfoximine were added, and stirring was continued at 110 °C for an additional 20 h. The results obtained in couplings of sulfoximine **1** with various aryl bromides are summarized in Table 1 (entries 11−16).

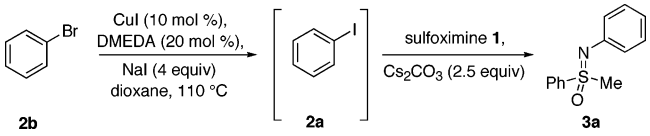
TABLE 1. Copper-Catalyzed N-Arylation Reactions of Sulfoximine 1 with Aryl Halides



entry	aryl halide	X	R	method[a]	product	yield (%)
1	**2a**	I	H	A	**3a**	95
2	**2b**	I	2-NO_2	A	**3b**	93
3	**2c**	I	3-NO_2	A	**3c**	98
4	**2d**	I	4-NO_2	A	**3d**	92
5	**2e**	I	2-OMe	A	**3e**	99
6	**2f**	I	4-Me	A	**3f**	95
7	**2g**	I	3-CN	A	**3g**	99
8	**2h**	I	4-CO_2Et	A	**3h**	92
9	**2i**	I	2,4,6-Cl_3	A	**3i**	93
10	**2j**	I	2-P(O)Ph_2	A	**3j**	86
11	**2k**	Br	H	B	**3a**	93
12	**2l**	Br	4-OMe	B	**3l**	84
13	**2m**	Br	3,5-Me_2	B	**3m**	82
14	**2n**	Br	2-Me	B	**3n**	93
15	**2o**	Br	2-OMe	B	**3e**	97
16	**2p**	Br	2-F	B	**3p**	86

[a] Method A: sulfoximine **1** (1.0 equiv), aryl iodide (2.0 equiv), CuI (10 mol %), Cs_2CO_3 (2.5 equiv), and DMEDA (20 mol %) in toluene at 110 °C for 18−22 h. Method B: aryl bromide (2.0 equiv), CuI (10 mol %), DMEDA (20 mol %), and NaI (4.0 equiv) in dioxane at 110 °C for 20 h, then addition of sulfoximine **1** (1.0 equiv) and Cs_2CO_3 (2.5 equiv) followed by further stirring at 110 °C for 20 h.

SCHEME 2



As evidenced by the data presented in Table 1, both steps (the aromatic Finkelstein reaction as well as the N-arylation) proceeded well, and independent of the substitution pattern of the aryl bromides, the N-arylated sulfoximines were obtained in high yields (82−97%). Steric effects played no (or at least a very minor) role as indicated by the excellent yields achieved in the couplings of ortho-substituted aryl bromides **2n** and **2o** (entries 14 and 15). Compared to the reactions with the aryl iodides (Table 1, entries 1−10), the yields in the transformations of the aryl bromides (entries 11−16) appeared to be slightly lower, which could be a result of two factors. First, the latter process involved a two-step reaction sequence, whereas the former only consisted of a single step. Second, for the Finkelstein reaction the use of dioxane as solvent was required, which was known to be a less effective solvent for N-arylation reactions.

To expand the substrate scope, cross-couplings between **1** and heterocyclic aryl bromides were also briefly investigated. To our delight, we found that all transformations proceeded well, giving the corresponding sulfoximines **3q−s** with very high to excellent yields. Even potentially coordinating 2-bromo pyridines **2r** and **2s** reacted well,

(10) In this study, only *racemic* **1** was used. For the preparation of enantiomerically pure **1**, 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. For alternative approaches, see: (d) Okamura, H.; Bolm, C. *Org. Lett.* **2004**, *6*, 1305 and references therein. Furthermore, there is no indication that other sulfoximines behave differently, and thus, we consider the copper-catalyzed protocol reported here to be a general approach for the synthesis of N-arylated sulfoximines.

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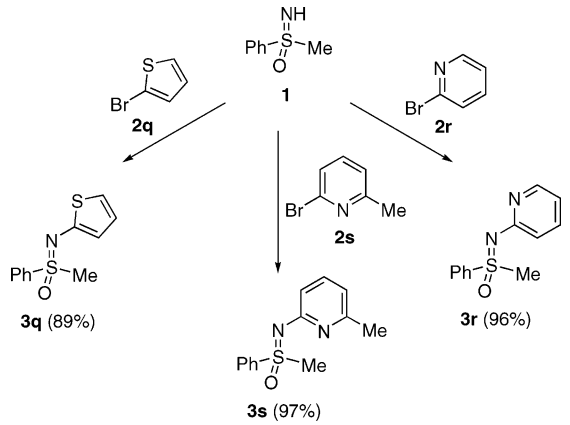
SCHEME 3[a]



[a] Coupling conditions: Ar−Br (1 equiv), CuI (10 mol %), DMEDA (20 mol %), NaI (4 equiv), and dioxane, 110 °C, 20 h; then **1** (1 equiv), Cs_2CO_3 (2.5 equiv), 110 °C, 20 h.

affording **3r** and **3s** in 96 and 97% yield, respectively (Scheme 3).

In summary, we have developed a copper-catalyzed cross-coupling reaction for the synthesis of N-arylated sulfoximines leading to products in excellent yields. In comparison with the established copper-mediated and palladium-catalyzed reactions reported by us earlier,[5,6] this novel protocol requires a less cost-intensive ligand/metal salt combination and provides the products in higher yields.

Experimental Section

General Procedure for N-Arylations of Sulfoximines (Method A). Under an argon atmosphere, a dry Schlenk tube was charged with sulfoximine **1** (1.0 equiv), aryl iodide (2.0 equiv), CuI (0.1 equiv), DMEDA (0.2 equiv), Cs_2CO_3 (2.5 equiv), and degassed toluene (1 M). After being heated to 110 °C for 18−22 h, the heterogeneous mixture was cooled to room temperature and neutralized with aqueous HCl. The aqueous layer was extracted three times with dichloromethane. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel afforded the N-arylated sulfoximines.

Method B. Under an argon atmosphere, a dry Schlenk tube was charged with the aryl bromide (2.0 equiv), CuI (0.1 equiv), DMEDA (0.2 equiv), and NaI (4.0 equiv). Then, degassed dioxane (1 M) was added, and the resulting heterogeneous mixture was heated to 110 °C for 18−22 h. Then, sulfoximine **1** (1.0 equiv) and Cs_2CO_3 (2.5 equiv) were added, and the mixture was kept at 110 °C for an additional 20 h. Subsequently, the mixture was cooled to room temperature and extracted sequentially with dichloromethane and an aqueous ammonia solution. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel afforded the N-arylated sulfoximines.

***N*-(Phenyl)-*S*-methyl-*S*-phenylsulfoximine (3a).** Following method A using *rac*-*S*-methyl-*S*-phenylsulfoximine (**1**, 143 mg, 0.922 mmol) and iodobenzene (**2a**, 206 μL, 1.844 mmol) gave 200 mg (95%) of **3a** as a light brown solid. According to method B using *rac*-*S*-methyl-*S*-phenylsulfoximine (**1**, 83 mg, 0.538 mmol) and bromobenzene (**2k**, 105 μL, 1.00 mmol) 116 mg (93%) of **3a** was obtained as a light brown solid: mp 100−101 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 7.95−7.99 (m, 2H), 7.54−7.58 (m, 1H), 7.47−7.53 (m, 2H), 7.08−7.14 (m, 2H), 6.99−7.03 (m, 2H), 6.83−6.88 (m, 1H), 3.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 144.9 (C), 139.4 (C), 133.2 (CH), 129.5 (2 × CH), 129.0 (2 x CH), 128.6 (2 × CH), 123.3 (2 × CH), 121.7, (CH), 46.1 (CH_3); MS [EI, *m/z* (relative intensity)]: 231 [M^+ (100%)]. All spectral data correspond to those given in the literature.[6]

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Supporting Information Available: General synthetic procedures, characterization data of all products, and copies of ^{1}H and ^{13}C NMR spectra of compounds **3a**−**s**. This material is available free of charge via the Internet at http://pubs.acs.org.

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