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

2004 Vol. 6, No. 19 3293–3296

ORGANIC LETTERS

Gae Young Cho, Pauline Rémy, Jenny Jansson, Christian Moessner, and Carsten $\operatorname{Bolm}^{\!*}$

Institute of Organic Chemistry, RWTH Aachen University, Professor-Pirlet-Str. 1, D-52056 Aachen, Germany

carsten.bolm@oc.rwth-aachen.de

Received June 23, 2004

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 chlorides⁵ 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

Reviews: (a) Johnson, C. R. Acc. Chem. Res. 1973, 6, 341. (b) Pyne,
 S. G. Sulfur Rep. 1999, 21, 281. (c) Reggelin, M.; Zur, C. Synthesis 2000,
 1.

⁽²⁾ For recent examples, see: (a) Bolm, C.; Simic, O. J. Am. Chem. Soc. 2001, 123, 3830. (b) Bolm, C.; Simic, O.; Martin, M. Synlett 2001, 1878. (c) Harmata, M.; Ghosh, S. K. Org. Lett. 2001, 3, 3321. (d) Bolm, C.; Martin, M.; Simic, O.; Verrucci, M. Org. Lett. 2003, 5, 427. (e) Bolm, C.; Verrucci, M.; Simic, O.; Cozzi, P. G.; Raabe, G.; Okamura, H. Chem. Commun. 2003, 2826. (f) Bolm, C.; Martin, M.; Gescheidt, G.; Palivan, C.; Neshchadin, D.; Bertagnolli, H.; Feth, M.; Schweiger, A.; Mitrikas, G.; Harmer, J. J. Am. Chem. Soc. 2003, 125, 6222. Reviews: (g) Harmata, M. Chemtracts 2003, 16, 660. (h) Okamura, H.; Bolm, C. Chem. Lett. 2004, 33, 482 and references therein.

^{(3) (}a) Bolm, C.; Kahmann, J. D.; Moll, G. *Tetrahedron Lett.* **1997**, *38*, 1169. (b) Bolm, C.; Moll, G.; Kahmann, J. D. *Chem. Eur. J.* **2001**, *7*, 1118. (c) Tye, H.; Skinner, C. L. *Helv. Chim. Acta* **2002**, *85*, 3272. (d) Bolm, C.; Müller, D.; Hackenberger, C. P. R. Org. Lett. **2002**, *4*, 893. (e) Bolm, C.; Müller, D.; Dalhoff, C.; Hackenberger, C. P. R.; Weinhold, E. Bioorg. Med. Chem. Lett. **2003**, *13*, 3207.

^{(4) (}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.

⁽⁵⁾ Harmata, M.; Hong, X.; Ghosh, S. K. Tetrahedron Lett. 2004, 45, 5223.

⁽⁶⁾ Harmata, M.; Pavri, N. Angew. Chem., Int. Ed. 1999, 38, 2419.

^{(7) (}a) Bolm, C.; Martin, M.; Gibson, L. Synlett **2002**, 832. (b) Bolm, C.; Okamura, H.; Verrucci, M. J. Organomet. Chem. **2003**, 687, 444.

⁽⁸⁾ For a review, see: Ley, S. V.; Thomas, A. W. Angew. Chem., Int. Ed. 2003, 42, 5400.

⁽⁹⁾ For recent examples of Cu-promoted C-N couplings, see: (a) Okano, K.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2003**, *5*, 4987. (b) Xu, G.; Wang, Y.-G. *Org. Lett.* **2004**, *6*, 985.

substrates under very mild reaction conditions, and, for largescale 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 theCopper-Mediated Cross-Coupling of Sulfoximine 1a and PhenylIodide (2a) to Give N-Phenyl Sulfoximine $3a^a$

+)	copper salt base, DMSO 90 ℃	Ph ^S _{CH3} 3a	
copper salt	base	yield (%)	
CuI	Cs ₂ CO ₃	94	
CuI	CsOAc	78	
CuI	NaO <i>t</i> -Bu	91	
CuI	K ₃ PO ₃	39	
CuBr	Cs_2CO_3	85	
CuSO ₄	Cs_2CO_3	46	
	+ 2a 2a copper salt CuI CuI CuI CuI CuI CuI CuI CuI	+ 2a copper salt base, DMSO 90 °C 90 °C Solution Copper salt base Cui Cs ₂ CO ₃ Cui CsOAc Cui CsOAc Cui NaO <i>t</i> -Bu Cui K ₃ PO ₃ CuBr Cs ₂ CO ₃ CuSO ₄ Cs ₂ CO ₃	

^{*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}

۹ Ph 0 1	NH ^S `CH₃ a	+	R L Copper	r(I) iodide , DMSO F 00 °C	N´ ⊓ O 3	CH ₃
entry	2	X	R	method ^a	3	yield (%)
1	b	Ι	2-Me	А	b	84
2	С	Ι	2-Br	Α	с	68
3	d	Ι	$2-NO_2$	А	d	83
4	е	Ι	2-OMe	А	е	72
5	f	Ι	$2-P(O)Ph_2$	В	f	71
6	g	Ι	3-CN	Α	g	94
7	h	Ι	4-Me	А	h	93
8	i	Ι	4-CHO	С	i	85
9	j	Ι	4-CO ₂ Et	Α	j	88
10	k	Ι	$4-NO_2$	Α	k	82
11	1	Ι	2-NO ₂ ,4-F	В	1	95
12	m	Ι	2-NO ₂ ,4-OMe	В	m	80
13	n	Ι	$2, 4, 6-Cl_3$	В	n	60
14	0	Br	$2-NO_2$	В	0	78
15	р	Br	$2-NO_{2,}4-CF_{3}$	В	р	83
16	q	Br	2-NHAc,5-NO ₂	С	q	65
17	r	Br	2-NHAc, 3-NO ₂	С	r	48

^{*a*} Method A: sulfoximine (1.0 equiv), aryl halide (2.0 equiv), CuI (1.0 equiv), Cs₂CO₃ (2.5 equiv) in DMSO at 90 °C. Method B: same as A except CsOAc (2.5 equiv) was used instead of Cs₂CO₃. 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 crosscoupling 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 Cs₂CO₃ (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 Cs₂CO₃ as a base, many byproducts were detected. In contrast, with CsOAc a very smooth conversion led to the corresponding arylated

⁽¹⁰⁾ Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. Tetrahedron Lett. 1998, 39, 2933.

⁽¹¹⁾ Evans, D. A.; Katz, J. L.; West, T. R. *Tetrahedron Lett.* **1998**, *39*, 2937.

⁽¹²⁾ Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan. D. M. T.; Combs, A. *Tetrahedron Lett.* **1998**, *39*, 2941.

^{(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 $\rm Cs_2\rm CO_3$ 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; $t_R = 30 \text{ min } (S)$, $t_R = 44 \text{ min } (R)$.

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 20 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 Cs₂CO₃ 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



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 2g 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



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

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



^{*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 eightmembered 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 coppermediated 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 crosscoupling reactions, investigating the use of the new bissulfoximines as ligands in asymmetric catalysis, and studying copper-catalyzed C-arylation reactions.

Acknowledgment. The Deutsche Forschungsgemeinschaft within the SFB 380 and the GRK 440 as well as the Fonds der Chemischen Industrie are gratefully acknowledged for financial support. J.J. thanks Uppsala University for supporting her stay as an exchange student at RWTH Aachen University.

Supporting Information Available: Experimental procedures and full characterization (¹H, ¹³C, and ³¹P 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.

OL048806H