A General Copper-Promoted Coupling of Sulfoximines with Vinyl Bromides

Juan R. Dehli, Carsten Bolm*

Institut für Organische Chemie, Rheinisch-Westfälische Technische Hochschule Aachen, Professor-Pirlet-Strasse 1, 52056 Aachen, Germany
Fax: (+49)-241-809-2391, e-mail: carsten.bolm@oc.rwth-aachen.de

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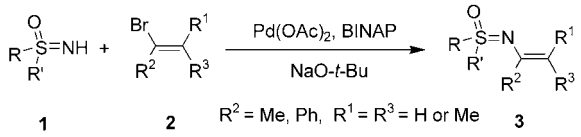
Abstract: Vinylsulfoximines have been prepared in high yields by copper-promoted coupling reactions starting from NH-sulfoximines and vinyl bromides.

Keywords: catalysis; copper; cross-coupling; sulfoximines; vinyl halides

The development of new methodologies to create C–N bonds has been an area of great interest in the last years.[1] In this context, metal-catalyzed or -mediated cross-coupling reactions of nitrogen nucleophiles (mainly amines and amides) with vinyl electrophiles (halides or triflates) has recently emerged as a powerful alternative for the synthesis of enamines and enamides.[2] The latter functional groups are very important for synthetic transformations[3] and are also present in natural products and biologically active compounds. For example, Porco and co-workers synthesized several antitumor macrolides[4] and antibiotics[5] by copper-mediated vinylic substitution, and Kozawa and Mori prepared a carbapenem derivative by intramolecular palladium-catalyzed coupling of a β-lactam with a vinyl bromide.[6]

On the other hand, we have been interested in the introduction of various carbon substituents (such as acyl,[7] alkyl[8] or aryl[9] groups) on the nitrogen atom of sulfoximines.[10] The resulting compounds can then, for instance, be used as benzothiazine building blocks[11] or incorporated (as pseudo-β-amino acids) in peptidic chains.[12] *N*-Arylsulfoximines (in which the nitrogen atom is directly bound to an sp^2 carbon) have been shown to be very successful ligands in copper-catalyzed asymmetric reactions.[13]

Considering the potential biological activity of the *N*-vinylsulfoximines **3**,[14] which can be regarded as enamide analogues, we focused our efforts on the development of a procedure that allowed the synthesis of these previously unavailable compounds. In this context, we very recently reported on a highly efficient palladium-catalyzed coupling reaction of *N*-unsubstituted sulfoximines **1** with vinyl bromides **2** or triflates (Scheme 1).[15] However, two major drawbacks hampered this methodology: first, the significant cost of palladium and the phosphine ligand, and second, the relatively limited substrate scope, as far as the vinyl bromide was concerned. Thus, only internal vinyl bromides could be used, and very bulky starting materials were not accepted.



Scheme 1. Synthesis of vinylsulfoximines by palladium catalysis.

Bearing the disadvantages of the palladium-catalyzed coupling reaction in mind, we turned our attention to copper reagents as possible catalysts or promoters of this reaction. In the last years, significant advances have been achieved in the use of this metal in cross-coupling reactions.[1e,16] With respect to the arylation of *N*-unsubstituted sulfoximines it proved to be complementary or superior to the palladium catalysis in several cases.[17] The copper-mediated sulfoximine/aryl coupling involves the use of CuI and a base (commonly Cs_2CO_3 or CsOAc), together with DMSO as solvent. The subsequent aqueous work-up, however, appeared to be inadequate for the preparation of *N*-vinylsulfoximines, since they were expected to be relatively sensitive towards hydrolysis. On that basis, the development of a new experimental protocol was considered to be essential for the success of the desired transformation.

As test reaction, the coupling between *S*-methyl-*S*-phenylsulfoximine (**1a**), which is readily available in multigram quantities, also in enantiomerically pure form,[18] and 2-bromo-3-methylbut-2-ene (**2a**), a sterically demanding substrate, was selected (Scheme 2).

Initial attempts to prepare **3a** by copper-mediated cross-couplings failed. For example, use of toluene as

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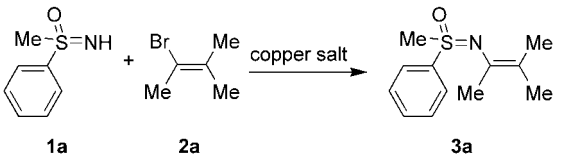
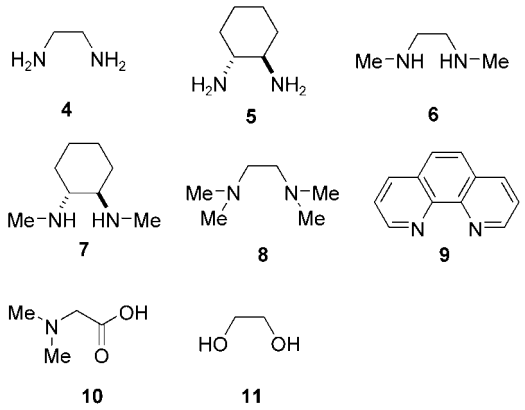


Scheme 2. Test reaction for the copper-promoted cross-coupling reaction.

solvent, in combination with CuI (1 equiv.) and K_2CO_3 (1.5 equivs.) did not lead to the expected product at all. Stimulated by Buchwald's observation that 1,2-diamines were suitable ligands in copper-promoted C–N couplings,[16] the effect of such chelates on the sulfoximine/vinyl cross-coupling reaction was next evaluated. To our delight, the presence of such ligands affected the transformation significantly. Thus, addition of even the simplest 1,2-diamine, ethylenediamine (**4**), resulted in the formation of **3a**, although the conversion of **1a** was only moderate at this stage (61%). With *trans*-cyclohexane-1,2-diamine (**5**), a mixture of products (including the expected one) was obtained. Gratifyingly, the use of secondary diamines, such as *N*,*N*′-dimethylethylenediamine (**6**) or *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine (**7**), gave complete conversion of the sulfoximine. The tertiary diamine TMEDA (**8**) as well as previously reported ligands for similar carbon-heteroatom cross-coupling reactions, such as 1,10-phenantroline (**9**),[19] *N*,*N*-dimethylglycine (**10**),[20] or glycol (**11**),[21] failed to lead to **3a**.



Next, the effect of other metal sources including those with copper in another oxidation state was examined in the test reaction, using *N*,*N*′-dimethylethylenediamine (**6**) as ligand, K_2CO_3 as base and toluene as solvent. Use of CuBr, CuCl, $CuSO_4$, $CuCl_2$ or $Cu(acac)_2$ gave only traces of **3a**. As expected, when the reaction was carried out in the absence of the copper salt, the coupling did not take place. With catalytic quantities of CuI (5 mol %, in combination with 10 mol % of diamine **6**) the conversion of **1a** was only 8%.

The applicability of other bases and solvents was also evaluated (Table 1). Clearly, K_2CO_3 and Cs_2CO_3 proved to be superior to Na_2CO_3 and K_3PO_4 (entries 1–4). The stronger base NaO-*t*-Bu yielded only a trace of the product (entry 5). This result was surprising, since this base was the one of choice in the palladium-catalyzed sulfoximine/vinyl coupling.[15]

The reaction also showed a strong solvent dependence. Besides toluene, dioxane was applicable, whereas use of THF and, in particular, CH_2Cl_2 proved to be inappropiate (Table 1, entries 6–8). It should be noted, however, that the lower temperature (70 and 40 °C for THF and CH_2Cl_2, respectively, compared to 110 °C for toluene) could also be responsible for these poorer results.

On the basis of these results, the optimal conditions involved the following parameters: CuI as copper salt (in stoichiometric quantity), K_2CO_3 as a base (being more economical that Cs_2CO_3), *N*,*N*′-dimethylethylenediamine (**6**) as a ligand, and toluene as solvent. Under these optimized conditions, a study on the substrate scope was carried out, and the results are summarized in the Table 2.

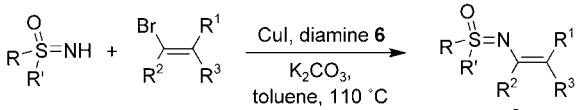
First, various sulfoximines were coupled with 2-bromo-3-methylbut-2-ene (**2a**). As in the palladium-catalyzed process, both alkyl aryl and cyclic sulfoximines proved suitable substrates, and the corresponding products were formed in excellent yields (Table 2, entries 1–4). In the palladium catalysis, only a narrow range of vinyl bromides coupled well, and the possible structural variations were rather limited. To our delight we found that this was not the case for the copper-mediated couplings. In fact, 1-bromo-2-methylpropene, a terminal vinyl bromide which had been a problematic substrate before, was an excellent coupling partner now giving vinylsulfoximine **3f** in 95% yield (Table 2, entry 6). Furthermore, β-bromostyrene was accepted as substrate (entry 7), and its coupling proceeded with complete retention of configuration (as confirmed by NMR spec-

Table 1. Effect of base and solvent in the copper-mediated cross-coupling of sulfoximine **1a** with vinyl bromide **2a**.[a]

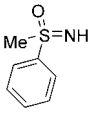
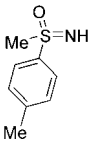
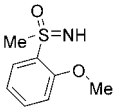
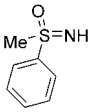
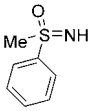
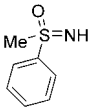
Entry	Base	Solvent	Conversion [%]
1	K_2CO_3	toluene	>98
2	Na_2CO_3	toluene	16
3	Cs_2CO_3	toluene	>98
4	K_3PO_4	toluene	44
5	NaO-*t*-Bu	toluene	<3
6	K_2CO_3	THF	64[b]
7	K_2CO_3	dioxane	>98
8	K_2CO_3	CH_2Cl_2	0[c]

[a] Reaction conditions: CuI (1.0 mmol), diamine **6** (2.0 mmol), base (2.0 mmol), sulfoximine **1a** (1.0 mmol) und vinyl bromide **2a** (1.5 mmol) in toluene (5 mL) at 110 °C for 20 h.
[b] Reaction carried out at 70 °C.
[c] Reaction carried out at 40 °C.

Table 2. Copper-promoted cross-coupling of sulfoximines with vinyl bromides.[a]



1 **2** **3**

Entry	Sulfoximine	Vinyl Bromide	Product	Yield [%][b]
1			**3a**	94
2			**3b**	92
3			**3c**	93
4			**3d**	91
5			**3e**	97
6			**3f**	95
7			**3g**	90[c]
8			**3h**	78[d]

[a] Reaction conditions: CuI (1.0 mmol), *N*,*N*′-dimethylethylenediamine (**6**, 2.0 mmol), K_2CO_3 (2.0 mmol), sulfoximine (1.0 mmol), vinyl bromide (1.5 mmol) in toluene (5 mL) at 110 °C for 24 h.
[b] Based on the amount of essentially pure crude product.
[c] Isomer *cis*:*trans* ratio of substrate and product = 1:5.5.
[d] After column chromatography (SiO_2; only 1 mmol of vinyl bromide was used).

troscopy). The successful vinylation of sulfoximine **1a** with 1,2,2-triphenylvinyl bromide further highlights the broadened substrate scope (entry 8). In this case, the full substitution of the resulting vinylsulfoximine increased its stability allowing purification by common silica gel column chromatography.

In summary, a copper-mediated methodology for the coupling of vinyl bromides with *N*-unsubstituted sulfoximines has been described. Compared with the recently reported palladium-catalyzed process it has several advantages, such as lower reagent (metal and ligand) cost and broader substrate scope. Current efforts in our laboratories are directed towards the development of a catalytic version of this reaction, as well as the application of this procedure for the synthesis of chiral ligands and analogues of biologically active compounds.

Experimental Section

All vinyl bromides were purchased from commercial suppliers and used without further purification. *N*-Unsubstituted sulfoximines were prepared according to a procedure recently described in the literature.[22] Toluene was distilled from sodium benzophenone ketyl radical and stored under argon.

Representative Procedure for the Coupling of Sulfoximines with Vinyl Bromides

A Schlenk flask equipped with a magnetic stirbar was charged with CuI (190 mg, 1.0 mmol), K_2CO_3 (276 mg, 2.0 mmol) and the sulfoximine (1.0 mmol) and purged with argon. Then, toluene (5.0 mL) was added, followed by *N*,*N*′-dimethylethylenediamine (213 μL, 2.0 mmol) and the vinyl bromide (1.5 mmol). After heating the mixture at 110 °C under stirring during 24 h, it was allowed to cool to room temperature, diluted with diethyl ether, and filtered through a thin pad of celite. The solvents were then removed under vacuum, yielding the essentially pure *N*-vinylsulfoximine.

Characterization data for sulfoximines **3a**–**h** are contained in the Supporting Information (3 pages).

Acknowledgements

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