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N-Arylations of Sulfoximines with 2-Arylpyridines by Copper-Mediated Dual N−H/C−H Activation

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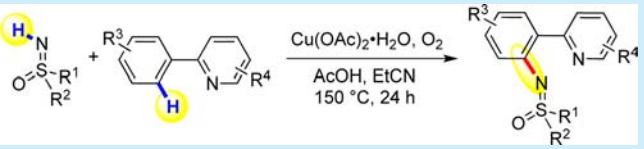
Supporting Information

ABSTRACT: A high-yielding method providing rapid access to new *N*-arylated sulfoximines has been developed. A stoichiometric amount of copper facilitates the C−H activation of 2-arylpyridines which then undergo oxidative C−N cross-couplings with various sulfoximine derivatives.



Due to their unique properties sulfoximines have found a number of applications in medicinal and agricultural chemistry.[1] Since 1992, we have been involved in this area,[2] mainly focusing on the use of sulfoximines as chiral ligands for asymmetric metal catalysis.[3] The most effective compounds of this type identifed for this purpose were all arylated at the sulfoximine nitrogen as exemplified by sulfoximines **1**−**3** (Figure 1), which all led to products with >90% ee in the respective catalyses.[4,5]

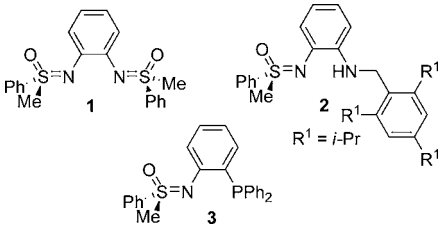
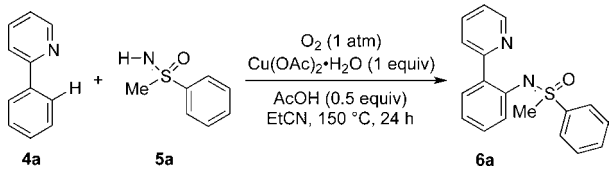


Figure 1. Effective sulfoximine-based chiral ligands for asymmetric metal catalysis.

For the preparation of *N*-arylated sulfoximines various methods have been previously described, predominantly involving the use of aryl halides, triflates, and boronic acids. Those functionalized arenes are then coupled with *NH*-sulfoximines by palladium or copper catalysis.[6] More recently, we found in collaboration with Miura and co-workers that *N*-arylations could also be achieved by copper-catalyzed dual C−H/N−H activation provided that the arene was sufficiently activated to allow a base-assisted cupration.[7,8] We herein report that such couplings can now also be performed through directed metalations of 2-arylpyridines leading to new *N*-arylated sulfoximine derivatives which are difficult to prepare by other means.[9] It is also noteworthy that the substrate activation was achieved with simple hydrated copper acetate and dioxygen was applied as the terminal oxidant.[10,11]

During the reactivity search and the optimization process, 2-phenylpyridine (**4a**) and *S*-methyl-*S*-phenylsulfoximine (**5a**) were selected as starting materials. The latter substrate was used in a 2-fold excess to maximize conversions. The role of several reaction parameters including the metal, solvent, oxidant, additive, and reaction temperature was explored. Using air as oxidant and acetonitrile as solvent only $Cu(OAc)_2 \cdot H_2O$ was found to promote the coupling (at 130 °C) providing product **6a** in 26% yield. Other metal salts such as $CuBr_2$, $CuCl_2$, and $Pd(OAc)_2$ proved inactive.[12] A solvent screening revealed that the use of an organonitrile was critical. (For further details, see the Supporting Information.) Subsequently, the yield of **6a** was increased to 38% when dioxygen was used as oxidant instead of air. Applying the higher boiling propionitrile as solvent and increasing the reaction temperature to 130 °C led to an additional improvement providing **6a** in 55% yield. Finally, an additive screening (see the Supporting Information) showed that the presence of acetic acid (0.5 equiv) had a positive effect,[13] affording the *N*-arylated sulfoximine derivative **6a** in 80% yield after 24 h (Scheme 1).[14]

Scheme 1. Optimized Conditions for the Coupling Reaction



Having established the optimized reaction conditions, an investigation into the versatility and functional group tolerance of this reaction process was performed (Figure 2).

First, the sulfoximine component was varied, and couplings with 2-phenylpyridine (**4a**) were investigated. To our delight, all reactions proceeded well, and the resulting products (**6a**−**g**) were obtained in good yields. Compared to the reaction of *S*-methyl-containing sulfoximine **4a**, the *N*-arylation of the analogous *S*-ethyl derivative led to the corresponding product in a slightly lower yield (80% for **6a** versus 72% for **6b**). This was also comparable to the result observed for the formation of *S*,*S*-diphenylsulfoximine **6c** (69% yield). Other *S*-methyl-

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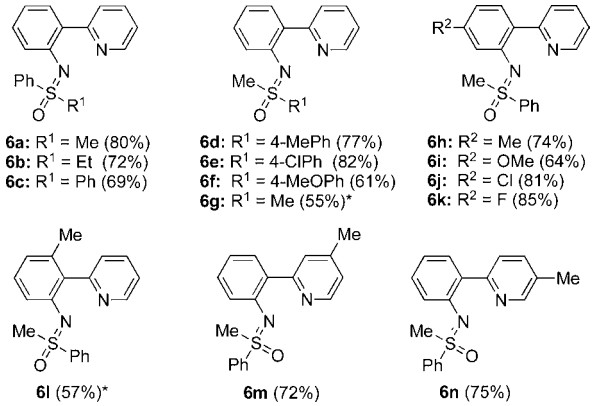


Figure 2. Substrate scope of the copper-mediated oxidative coupling. *Use of 2-nitrobenzoic acid (0.5 equiv) instead of AcOH.

containing starting materials with substituted *S*-aryl groups afforded the corresponding products (**6d**–**f**) in yields ranging from 61% to 82%. In the reaction of *S*,*S*-dimethylsulfoximine, 2-nitrobenzoic acid had to be used as additive instead of acetic acid to avoid the acetylation of the sulfoximine, which occurred as a side reaction. Accordingly, **6g** was obtained in 55% yield.

Reactions of sulfoximine **5a** with *para*-substituted 2-arylpyridines led to products **6h**–**k** in yields between 64% and 85%. In this series, the halo-containing derivatives **6j** and **6k** were obtained with the highest yields (81% and 85%, respectively). In addition, 2-(*o*-tolyl)pyridine reacted well with **5a** (giving **6l** in 57% yield) provided that 2-nitrobenzoic acid was again used as additive in place of acetic acid to avoid acetylation of the sulfoximine.

Finally it was demonstrated that substituents on the pyridine moiety were tolerated. Thus, compounds with methyl groups in the 4 or 5 position reacted with **5a** to give **6m** and **6n** in 72% and 75% yield, respectively.

With a focus on the stereochemistry of the starting material, 2-phenylpyridine (**4a**) was reacted with enantiopure (*S*)-**5a**. Analysis of the er of **6a** by chiral HPLC confirmed our assumption that the coupling was stereospecific.

Attempts to couple sulfoximine **5a** under the optimized conditions with benzaldehyde *O*-methyl oxime (**7**), *N*-methoxybenzamide (**8**), or other aryl-substituted nitrogen-containing heterocycles [phenyl pyrimide (**9**), 2-phenyl-1,3,4-oxadiazole (**10**), and 7,8-benzoquinoline (**11**)] remained unsuccessful (Figure 3).[15]

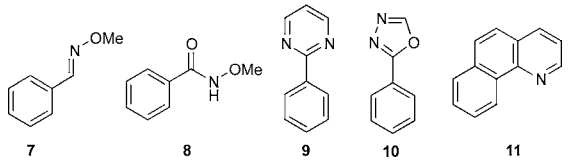


Figure 3. Potential reaction partners of **5a** that did not react.

With the goal of gaining insight into the reaction details and with the intention to detect relevant intermediates in the conversion of **4a** and **5a** to give **6a**, ESI-MS studies of the crude reaction mixture were performed. This analysis revealed three major species (Figure 4). In addition to protonated **6a**, two copper complexes {[**6a**·Cu(OAc)]$^+$ and [(**6a**)$_2$·Cu(OAc)]$^+$} were identified having one or two product molecules attached to a cationic copper acetate fragment. Attempts to isolate such

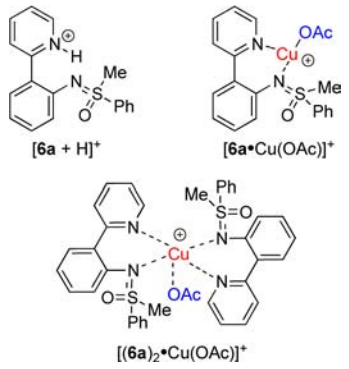
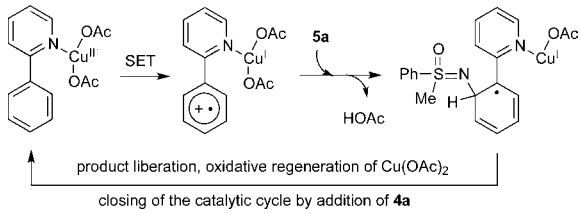


Figure 4. Major species identified by ESI-MS analysis of the reaction mixture.

species as single crystals remained unsuccessful. The strength of the metal coordination was indicated by the fact that liberation of product **6a** from the metal required treatment of the reaction mixture with Na_2S.[16] If such metal–ligand coordination complexes can lead to effective catalysts still requires additional investigation.[17]

Based on all findings, we assume a mechanism that is analogous to the one proposed by Yu and co-workers in related C–H functionalizations of 2-phenylpyridine.[11e] In that scenario, single-electron-transfer processes, coordinated copper intermediates, and radical cations play significant roles (Scheme 2).

Scheme 2. Proposed Mechanism



In conclusion, a new method for the *N*-arylations of sulfoximines by dual C–H/N–H activation has been discovered. Pyridine nitrogens serve as directing elements allowing the remote positions of connected arenes to be derivatized. The combined use of simple hydrated copper diactetate as activator and dioxygen as oxidant are crucial for the success of this reaction process. The resulting products are capable of being *N*,*N*′-chelating ligands which might prove useful for applications in catalysis, material sciences, and biorelated areas. Studies along such lines are now ongoing in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, analytical data, and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(14) The attempt to reduce the metal salt loading from 1 equiv to 20 mol % significantly affected the yield of **6a** (22%). That effect is probably due to the chelating ability of the product to complex the activating metal, which inhibits turnover.

(15) In addition, biphenyl did not react with sulfoximine **5a** (20 h reaction time; analysis by TLC and ^{1}H NMR).

(16) For details, see the Supporting Information

(17) In contrast to the copper complexes detected here, where the metal and the *N*,*N*′-chelating ligand form 6-membered rings, most of the successfully applied copper sulfoximine complexes appear to involve 5-membered chelates. For relevant work on asymmetric catalysis with such complexes, see ref 3 and articles cited therein. An X-ray crystal structure of a related copper sulfoximine complex can be found in: Bolm, C.; Verrucci, M.; Simic, O.; Cozzi, P. G.; Raabe, G.; Okamura, H. *Chem. Commun.* **2003**, 2816.