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Copper-Mediated *N*-Heteroarylation of Primary Sulfonamides: Synthesis of Mono-*N*-heteroaryl Sulfonamides

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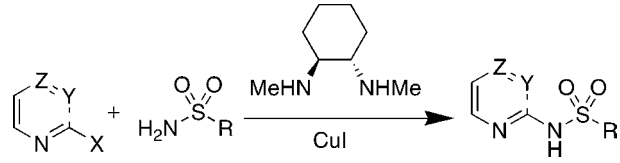
ABSTRACT



We describe the coupling of primary sulfonamides and various halogenated heterocyclic cores, with an emphasis on 2-heteroaryl halides, via copper catalysis. These studies enabled the synthesis of many new mono-*N*-heteroaryl sulfonamides. The electronic factors that influence the course of the reaction have also been investigated.

The sulfonamide functional group is a key feature in drug design. It is encountered in a multitude of marketed drugs and countless drug candidates.[1] During the course of a lead optimization process, we became interested in attenuating the pK_a of primary sulfonamides via *N*-heteroarylation (sulfonamides as carboxylic acid isosteres) (Figure 1). We sought a broad, practical, and predictable route to this class of targets based on the union of primary sulfonamides and heteroaryl halides (with an emphasis on 2-heteroaryl halides to accentuate electron withdrawing effects) via metal catalysis.

The challenges inherent to the catalytic reaction of basic heteroaromatic reagents have been outlined by Shen and Hartwig, who have introduced a route for their use in palladium-catalyzed *N*-heteroarylation reactions based on the precomplexation with triethyl borane.[2] The *N*-amidation of a series of unmasked heteroaryl donors with palladium as well as copper catalysts has also been described by the Buchwald group.[3] However, 2-heteroaryl halides, with the exception of 2-halo thiophenes, were not included in these studies. The mono-*N*-heteroarylation of primary sulfonamides using a small set of heteroaryl halides has been achieved under palladium-catalyzed conditions.[4] However, the results were highly variable, and differences in reactivity between

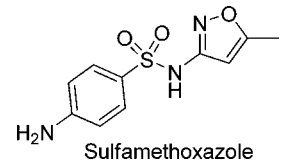


Figure 1. An example of an *N*-heteroaryl sulfonamide drug.

(1) See the table of sulfonamide drugs in: (a) Smith, D. A.; Jones, R. M. *Curr. Opin. Drug Discovery Dev.* **2008**, *11*, 72–79. (b) Also see ref 8 for other medicinal uses of sulfonamides.

(2) Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 7734–7735.

(3) Paladium catalyst: (a) Ikawa, T.; Barder, T. E.; Biscoe, M. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 13001–13007. (b) Fors, B. P.; Dooleweerdt, K.; Zeng, Q.; Buchwald, S. L. *Tetrahedron* **2006**, *62*, 6042–6049. (c) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727–7729. (d) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421–7428. (e) Enguehard-Gueiffier, C.; Thery, I.; Gueiffier, A.; Buchwald, S. L. *Tetrahedron* **2009**, *65*, 6576–6583.

(4) (a) Burton, G.; Cao, P.; Li, G.; Rivero, R. *Org, Lett.* **2003**, *23*, 4373–4376. (b) Steinhuebel, D.; Palucki, M.; Askin, D.; Dolling, U. *Tetrahedron Lett.* **2004**, *45*, 3305–3307. (c) Anjanappa, P.; Mullick, D.; Selvakumar, K.; Sivakumar, M. *Tetrahedron Lett.* **2008**, *49*, 4585–4587.

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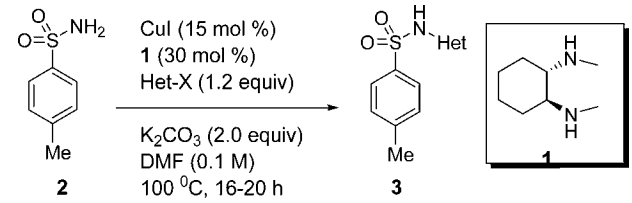
heterocyclic cores, the nature of the halide, and/or its position on the ring have been observed. The copper-catalyzed mono-*N*-arylation of primary sulfonamides is known;[5] however, the use of heteroaryl donors in these reactions still remains uncharted ground,[6] and the potential for product inhibition is a major concern.[7] Indeed, the conjugate base of the *N*-heteroarylation product, formed easily as a result of the increased acidity of the sulfonamide NH, may form a stable complex with the catalyst, thus impeding its turnover.[7b] In general, a *N*-heteroarylation procedure that covers a broad spectrum of heteroaryl halides (many have not been explored) is still needed.

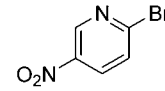
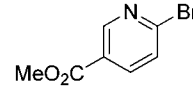
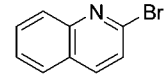
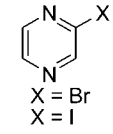
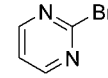
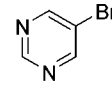
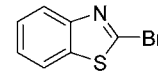
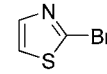
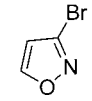
The recent mechanistic insights that enabled the Hiyama and Suzuki couplings of 2-pyridyl nucleophiles,[8] along with the *N*-amidation works reported in the literature,[3] gave us greater confidence that copper catalysts may be applied for the *N*-sulfonamidation of 2-heteroaryl halides.[9] We also believed that a solution to the coupling of this capricious subclass of heteroaryl donors may be broadly applicable to other systems. Herein, we detail the reduction of these hypotheses to practice.

We initiated our investigations by examining conditions under which 4-toluene sulfonamide and 2-bromopyridine can be coupled. We examined the effect of ligand, base, solvent, and copper salts.[10] The initial screening experiments were performed in dioxane with CuI (5 mol %), and cesium carbonate as base, and the best parameter was included in the next round of optimization. We observed

Table 1. Reaction Scope with Respect to Heteroaryl Halides



2 **3**

entry	Het-X	yield[a]
1		**4** 75%
2		**5** 72%
3		**6** 91%
4		**7** 65%
5		**8** 41% 50%
6		**9** 35%
7		**10** 60%
8		**11** 60%[b]
9		**12** 64%[c]
10		**13** 0%
11		**14** 0%

[a] Isolated yield after silica gel chromatography. [b] Reaction was heated to 130 °C. [c] Purified by tritutation.

that glycine,[11] *N*,*N*′-dimethylethane-1,2-diamine, and *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine[12] ligands afforded the desired product in 5%, 20%, and 26% yield, respectively. Phenanthroline,[13] 2-pyrrole carboxylic acid,[14] and (benzotriazol-1-yl)methanol[15] ligands did not afford any

(5) For the coupling between aryl boronic acids and sulfonamides see: (a) Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933–2936. (b) Combs, A. P.; Rafalski, M. *J. Comb. Chem.* **2000**, *2*, 29–32. (c) Lam, P. Y. S.; Vincent, G.; Clark, C. G.; Deudon, S.; Jadhav, P. K. *Tetrahedron Lett.* **2001**, *42*, 3415–3418. For the coupling of aryl halides and sulfonamides under the classic Goldberg reaction conditions see: (d) He, H.; Wu, Y.-J. *Tetrahedron Lett.* **2003**, *44*, 3385–3386. For examples of catalytic coupling of aryl halides and sulfonamides see: (e) Deng, W.; Wang, Y.-F.; Zou, Y.; Liu, L.; Guo, Q.-X. *Tetrahedron Lett.* **2004**, *45*, 2311–2315. (f) Deng, W.; Liu, L.; Zhang, C.; Liu, M.; Guo, Q.-X. *Tetrahedron Lett.* **2005**, *46*, 7295–7298.

(6) During the course of the preparation of this manuscript, the coupling of pyridine derivatives and sulfonamides was reported: Han, X. *Tetrahedron Lett.* **2010**, *51*, 360–362.

(7) For examples of use of 2-aminopyridine as ligands in copper catalysis, see: (a) Fagan, P. J.; Hauptman, E.; Shapiro, R.; Casalnuovo, A. *J. Am. Chem. Soc.* **2000**, *122*, 5043–505. For an example of product inhibition associated with the use of primary sulfonamides see: (b) Toto, P.; Gesquiere, J.-C.; Cousaert, N.; Deprez, B.; Willand, N. *Tetrahedron Lett.* **2006**, *47*, 4973–497. For an example of sulfonamide chromium ligand see: (c) Liu, X.; Henderson, J. A.; Sasaki, T.; Kishi, Y. *J. Am. Chem. Soc.* **2009**, *131*, 16678–16680.

(8) CuI as additives in the Hiyama and Suzuki cross-coupling of 2-borono and trimethylsilane pyridine, see: (a) Pierrat, P.; Gros, P.; Fort, Y. *Org. Lett.* **2005**, *7*, 697–700. (b) Jones, N. A.; Antoon, J. W.; Bowie, A. L., Jr.; Borak, J. B.; Stevens, E. P. *J. Heterocycl. Chem.* **2007**, *44*, 363–367. (c) Deng, J. Z.; Paone, D. V.; Ginetti, A. T.; Kurihara, H.; Dreher, S. D.; Weissman, S. A.; Stauffer, S. R.; Burgey, C. S. *Org. Lett.* **2009**, *11*, 345–347. (d) Gutz, C.; Lutzen, A. *Synthesis* **2010**, *1*, 85–90.

(9) For recent reviews on copper catalysis, see: (a) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954–6971. (b) Carril, M.; SanMartin, R.; Dominguez, E. *Chem. Soc. Rev.* **2008**, *37*, 639–647. (c) Ma, D. W.; Cai, Q. *Acc. Chem. Res.* **2008**, *41*, 1450–1460. (d) Kienle, M.; Dubbaka, S. R.; Brade, K.; Knochel, P. *Eur. J. Org. Chem.* **2007**, 4166–4176. (e) Frlan, R.; Kikelj, D. *Synthesis* **2006**, 2271–2285. Corbet, J.-P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651–2710. (f) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337–2364. (g) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400–5449. (h) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428–2439.

(10) The screening results are summarized in Table 1 in the SI.

(11) Ma, D. W.; Cai, Q.; Zhang, H. *Org. Lett.* **2003**, *5*, 2453–2455.

(12) Antilla, J. C.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 11684–11688.

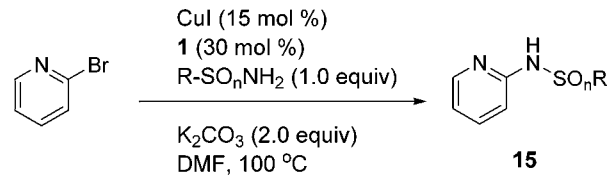
(13) (a) Kiyomori, A.; Marcoux, J.-F.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, *40*, 2657–2660. (b) Goodbrand, H. B.; Hu, N.-X. *J. Org. Chem.* **1999**, *64*, 670–674.

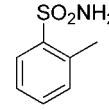
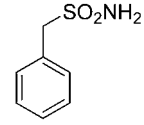
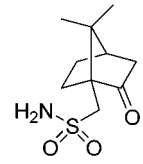
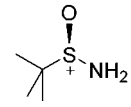
(14) Altman, R. A.; Anderson, K. W.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 5167–5169.

products. Many bases including K_3PO_4 (24%), Cs_2CO_3 (26%), NaH (19%), KOH (22%), Et_3N (15%), and LiHMDS (16%) can be used in the reaction; the best result was obtained with K_2CO_3 (38%). A variety of copper salts can effect this transformation ($Cu(OAc)_2$, CuBr, $Cu(CF_3SO_3)_2$, CuO, afforded the desired product in 21%, 24%, 33%, and 34% yield, respectively), but CuI (38%) was selected for the subsequent optimization studies. Finally, the reaction can be performed in dioxane (21%), DMSO (23%), DMA (19%), and toluene (17%). Superior results were observed with DMF (43%). Further optimization of the reaction parameters (stoichiometry of reagents, concentration, temperature, time, *data not shown*) resulted in marginal improvement, and ultimately increasing catalyst loading to 15 mol % was essential to achieve complete conversion. This optimal procedure closely mirrors the copper-catalyzed *N*-arylation conditions previously described in the literature.[3c−e]

With these successful conditions in hand,[16] we explored the generality of this copper coupling process. The results are summarized in Table 1. 2-Bromopyridine was coupled to 4-toluene sulfonamide in 75% yield (entry 1). This reaction can also be performed under microwave conditions, although we noted a slight decrease in the yield (data not shown). To increase the acidity of the newly formed sulfonamide in this series, electron-withdrawing groups (EWGs) were attached to the pyridine ring. 2-Bromo-5-nitropyridine yielded product **5** in 72% yield (entry 2). Similarly, product **6** was obtained in 91% yield when methyl 6-bromonicotinate was used as the aryl donor (entry 3). The latter result represents a clear improvement over the use of 2-bromopyridine (entry 1), and indicates that the modulation of the pK_a of the NH (product) through the use of EWGs does not negatively impact the performance of the catalyst. Next, we explored the use of more electron deficient heteroarene cores starting with 2-bromoquinoline, which afforded the corresponding product **7** in 65% yield (entry 4). 2-Bromopyrazine also underwent coupling with 4-toluene sulfonamide to afford the expected product **8** in 41% yield (entry 5). Switching to 2-iodopyrazine resulted in a marginal improvement of the yield of the reaction (50%, entry 5). In both cases, the halide starting materials were completely consumed. We also confirmed that the low coupling yield was not due to product stability issues (**8** was quantitatively recovered upon heating under the reaction conditions for 20 h). Taken together, these results suggest that product inhibition was not significantly operative. Thus, the lower yield of the reaction may be attributed to the instability of the heteroaryl-metal catalytic intermediates.[17] The origin of this instability appears to be of electronic nature; the more electron deficient the heteroarene, the higher the instability (entry 1 versus entry 5). This experimental observation may be applied predictively. For instance, the yield of the coupling process declined further when 2-bromopyrimidine was employed as aryl donor (35%, entry 6). In contrast, 5-bromopyrimidine afforded the coupling product in 60% yield (entry 7). Thus, for heteroarenes that are less electron deficient than pyrazine and pyrimidine, copper may prove a judicious choice of catalyst. In the 5-membered azole series, 4-bromo-1-methylpyrazole afforded 60% yield of the coupling product **11** (entry 8). In this instance, the reaction was perfomed at 130 °C to ensure complete conversion of the bromide starting material. Benzothiazole derivatives, represented by 2-bromobenzothiazole, are tolerated under the reaction conditions (64%, entry 9). The product of this reaction was purified by trituration to circumvent potential issues of

Table 2. Reaction Scope with Respect to Sulfonamides



entry	R-SO$_n$NH$_2$		yield[a]
1		**16**	65%
2		**17**	74%
3	MeSO$_2$NH$_2$	**18**	62%
4		**19**	82%
5		**20**	>90[b]

[a] Isolated yield after silica gel chromatography. [b] Percent conversion as determined by HPLC.

(15) Verrna, A. K.; Kesharwani, T.; Singh, J.; Tandon, V.; Larock, R. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 1138–1143.

(16) **Typical experimental procedure:** A dry vial was cooled to rt under nitrogen, and was charged with copper(I) iodide (43.0 mg, 0.23 mmol), potassium carbonate (415 mg, 3.0 mmol), and *p*-toluene sulfonamide (257 mg, 1.50 mmol). Dry DMF (10 mL) was added, followed by ligand **1** (0.071 mL, 0.45 mmol) and 2-bromopyridine (286 mg, 1.80 mmol). The resulting blue suspension was stirred at rt for 5 min, then heated to 100 °C for 16 h. The reaction mixture was then cooled to rt, diluted with ethyl acetate (75 mL), then transferred to a separatory funnel and washed with 10% aqueous ammonium chloride. The aqueous phase was extracted with ethyl acetate (3 times 60 mL). The combined organic phases were washed with water (3 times 75 mL) and brine then dried over magnesium sulfate. All the volatiles were evaporated, and the resulting residue was purified by silica gel chromatography with a DCM/MeOH gradient.

(17) Recent experimental and theoretical studies have indicated that the rate-determining step of the arylation of amides with copper is the oxidative addition. We assumed that a similar reaction mechanism is operative: (a) Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4120–4125. (b) Zhang, S.-L.; Liu, L.; Fu, Y.; Guo, Q.-X. *Organometallics* **2007**, *26*, 4546–4554. (c) Strieter, E. R.; Bhayana, B.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 16720–16734.

tautomerization.[18] Thiazole and oxazole derivatives failed under the reaction conditions (entries 10 and 11).

We also explored the generality of the reaction with respect to the sulfonamide component. As shown in Table 2, 2-tolyl sulfonamide, a sterically hindered substrate, is tolerated under the reaction conditions (65%, entry 1). Phenyl methanesulfonamide, bearing α-acidic protons, also performed well (74%, entry 2). The smaller aliphatic methylsulfonamide underwent coupling with 2-bromopyridine in moderate yield (62%, entry 3). Camphor sulfonamide can also be employed in the reaction without the need to protect the ketone functionality (84%, entry 4). In this instance, the bis-arylation biproduct was also isolated in 9% yield. Finally, we also observed that aliphatic sulfinamides, exemplified by Ellman's auxiliary,[19] can be used under the reaction conditions. This exciting preliminary result opens the door to the rapid synthesis of many aryl and heteroaryl amines from their halide precursors by exploiting the relative lability of the Ellman's auxiliary after the coupling process (Ellman's auxiliary as ammonia surrogate). Additionally, this offers an alternative strategy for further fine-tuning the pK_a of the sulfonamide NH while allowing for chiral discrimination.

(18) Forlani, L. *Gazz. Chim. Ital.* **1981**, *111*, 159–162.
(19) Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913–9914.

In summary, we have investigated the coupling of primary sulfonamides and 2-heteroaryl halides. The procedure is broadly applicable to other heterocyclic systems, and allowed access to many novel *N*-heteroaryl sulfonamides that will be difficult to access otherwise. The predictability of this method is a significant advantage over the reported palladium-catalyzed protocols. However, the limitations of this methodology are also apparent (oxazole and thiazoles derivatives failed, while the highly electron deficient heteroarenes are low yielding). The effective *N*-sulfonamidation of these heteroarenes may require the development of even milder reaction conditions.

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Supporting Information Available: Detailed experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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