EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201301561

Low Catalyst Loadings for Ligand-Free Copper(I)-Oxide-Catalyzed *N*-Arylation of Methanesulfonamide in Water

Bryan Yong-Hao Tan,[a] Yong-Chua Teo,*[a] and Ai-Hua Seow[a]

Keywords: N-Arylation / Cross-coupling / Copper / Ligand-free reactions / Sulfonamides

A simple and practical protocol for the cross-coupling of methanesulfonamide and aryl iodides under ligand-free copper(I)-oxide-catalyzed conditions in water is reported. The method allows the preparation of a wide variety of synthetically useful *N*-arylated methanesulfonamides in good to excellent yields (up to 90 %) under the optimized conditions.

Introduction

N-Arylmethanesulfonamides are valuable compounds that are prevalent in pharmaceutical agents and natural products. In particular, they have been reported to have biological activities associated with TRPV1 antagonists,[1] matrix malloproteinase inhibitors,[2] non-nucleoside reverse-transcriptase inhibitors,[3] and antitumour[4] and class III antiarrhythmic agents.[5] The wide range of applications of these compounds has led to increased attention being given to the development of new and sustainable transition-metal-mediated *N*-arylation strategies for the assembly of their core structures. Of these strategies, the copper-mediated Goldberg-type reaction has emerged as a straightforward and inexpensive approach to the arylation process. However, these reactions have traditionally required harsh reaction conditions such as high temperatures and stoichiometric amounts of a copper catalyst, and this has limited their practicality.[6]

In recent years, the use of additional ligands in these procedures has made copper salts a more economically attractive option for the *N*-arylation of nitrogen heterocycles with aryl halides, and has led to a renaissance in the use of such salts.[7] Indeed, some ligands have been shown to significantly increase the yield and generality of the reaction. On the other hand, the use of ligands in these protocols adds to the overall operating costs.

Despite all these developments, the reported protocols for the *N*-arylation of methanesulfonamide remain limited. Ruble and co-workers reported the preparation of *N*-arylmethanesulfonamide by palladium-catalyzed cross-coupling using *t*BuXPhos as the assisting ligand.[8] Liu and Guo reported the use of glycine-derived ligands to facilitate the cross-coupling of sulfonamides with aryl halides using copper(I) iodide as the catalyst.[9] However, this protocol had a limited substrate scope and required additional steps to modify the amino acid into a suitable form. In both instances, the use of ligands was essential for the success of these protocols.

Organic reactions that use water as the solvent[10] have attracted a lot of attention, since water is sustainable, inexpensive, and benign to the environment.[11] However, the use of water could bring about additional challenges in catalytic systems, as the catalysts and substrates must be water tolerant and water soluble for the reaction to proceed.[12] Consequently, from an industrial and practical standpoint, the development of a sustainable and experimentally simple ligand-free catalytic system that operates at a low catalyst loading in an aqueous medium would represent a significant advance to the synthetic community.

Encouraged by our long-standing interest in ligand-free copper catalysis[13] and the development of more sustainable cross-coupling technologies, in this paper, we report a simple, practical, and efficient ligand-free Cu_2O-catalyzed *N*-arylation of methanesulfonamide using water as the solvent. This is an efficient protocol that gives excellent yields of the *N*-arylated derivatives (up to 90%) at low catalyst loadings (2–5%).

Results and Discussion

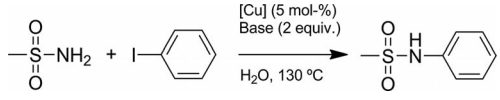
We started our investigations using iodobenzene (1 equiv.) and methanesulfonamide (1.5 equiv.) as model substrates for the *N*-arylation reaction. The reaction was carried out using CuI (5 mol-%) and Cs_2CO_3 (2 equiv.) in water at 130 °C for 24 h, and the desired *N*-arylmethanesulfonamide was formed in an excellent 89% yield (Table 1, entry 1). Inspired by this result, optimization studies were initiated to evaluate the efficacy of various Cu sources as well as the influence of different bases on the arylation process. The results of the optimization studies are shown in

[a] Natural Sciences and Science Education, National Institute of Education, Nanyang Technological University,
1 Nanyang Walk, 637616 Singapore
E-mail: yongchua.teo@nie.edu.sg
http://www.nie.edu.sg/profile/teo-yong-chua

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201301561.

Table 1. The investigation into the use of different Cu salts indicated that Cu_2O was the optimum metal catalyst (Table 1, entry 4), giving an excellent yield of 93%. The results also showed that other Cu^I sources such as CuCl and CuBr were effective catalysts for the reaction, giving the products in yields of 86 and 87%, respectively (Table 1, entries 2 and 3). Moreover, the reaction using a Cu^{II} source (CuO) also gave the *N*-arylated product in a moderate yield of 61% (Table 1, entry 5). A control experiment indicated that only trace amounts of the product were formed in the absence of a Cu source (Table 1, entry 6). Next, we investigated the effect of different bases, such as K_3PO_4, K_2CO_3, and Na_2CO_3 on the arylation process (Table 1, entries 7–9). Of the bases tested, Cs_2CO_3 was the most suitable, while K_2CO_3 also proved to be an effective base for the reaction. Next, a series of commonly used organic solvents was screened to test the effect of the solvent on the coupling reaction. A good yield of 71% was obtained using DMSO as the solvent, and yields became progressively lower as the polarity of the solvent decreased (Table 1, entries 10–13). To increase the practicality of the protocol, we carried out the reaction at a lower operating temperature of 110 °C. However, the yield of the arylated product decreased significantly to 23% (Table 1, entry 14). Subsequently, the catalyst loading was reduced to 2 mol-% in an attempt to further improve the atom economy of the reaction, and under these conditions, the product was formed in an excellent yield of 90% (Table 1, entry 15). In summary, the *N*-arylation of methanesulfonamide in water was achieved by using a combination of Cu_2O (2 mol-%) and Cs_2CO_3 (2 equiv.), stirring the mixture at 130 °C in water for 24 h.

Table 1. Optimization studies on the ligand-free Cu-catalyzed cross-coupling of iodobenzene and methanesulfonamide.[a]



Entry	Catalyst	Base/solvent	Yield [%][b]
1	CuI	Cs_2CO_3	89
2	CuCl	Cs_2CO_3	86
3	CuBr	Cs_2CO_3	87
4	Cu_2O	Cs_2CO_3	93
5	CuO	Cs_2CO_3	61
6	–	Cs_2CO_3	trace
7	Cu_2O	K_3PO_4	trace
8	Cu_2O	K_2CO_3	79
9	Cu_2O	Na_2CO_3	15
10	Cu_2O	DMSO	71
11	Cu_2O	DMF	48
12	Cu_2O	THF	24
13	Cu_2O	toluene	20
14	Cu_2O	Cs_2CO_3	23[c]
15	Cu_2O	Cs_2CO_3	90[d]
16	Cu_2O	Cs_2CO_3	60[e]

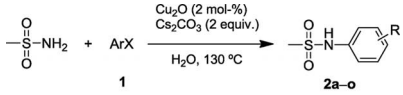
[a] Reaction conditions: iodobenzene (1.47 mmol), methanesulfonamide (2.21 mmol), base (2.94 mmol), Cu catalyst (5 mol-%), water (0.3 mL), 130 °C for 24 h. [b] Isolated yield. [c] The reaction temperature was 110 °C. [d] The catalyst loading was 2 mol-%. [e] The catalyst loading was 1 mol-%.

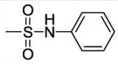
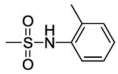
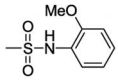
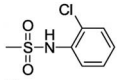
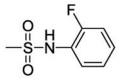
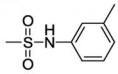
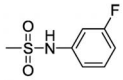
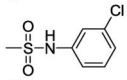
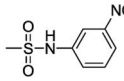
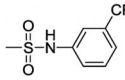
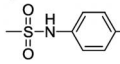
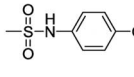
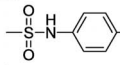
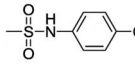
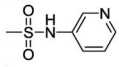
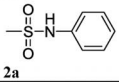
Having established this set of optimized conditions, we started to test the generality of this protocol using a variety of substituted aryl iodides with methanesulfonamide. The results are shown in Table 2. In most instances, good to excellent yields of the *N*-arylated derivatives were obtained using the optimized reaction conditions. *ortho*-Substituted aryl halides tended to give lower yields due to the steric hindrance of the substituent, which hampered the reaction. Consequently, a higher catalyst loading of 10 mol-% had to be used for the cross-coupling to proceed efficiently (Table 2, entries 2–4). Notably, a good yield of 80% was obtained when 2-fluoroiodobenzene was used with a 2 mol-% catalyst loading, possibly due to the inductive effect and less bulky nature of the fluoro group compared to the other *ortho* substituents tested (Table 2, entry 5). Aryl iodides bearing substituents with different electronic properties at the *meta* and *para* positions were tolerated by the protocol, and good yields were obtained for substrates with both electron-donating and electron-withdrawing substituents (Table 2, entries 6–14). Unfortunately, coupling reactions using heteroaryl iodides or aryl bromides as electrophilic partners could not be accomplished smoothly under our standard conditions, and only moderate yields of the products were obtained (Table 2, entries 15 and 16).

In an attempt to expand the scope of the method, a series of aliphatic and alicyclic sulfonamide derivatives were tested. The results are shown in Table 3. We were pleased to discover that a range of alicyclic and aliphatic sulfonamides could be coupled to iodobenzene using low catalyst loadings of 2–5 mol-% to give the products in moderate to excellent yields (54–90%). It can be noted that as the length of the alkyl chain on the sulfonamide increased, the yields of the products decreased, possibly due to a decrease in the solubilities of the substrates (Table 3, entries 1–3). The C-N coupling was promising with a sterically hindered cyclopropyl substituent on the sulfonamide, and a moderate 54% yield of the product was obtained at 5 mol-% catalyst loading (Table 3, entry 4). Excellent yields of 90 and 82% were obtained for the *N*-arylation of five-membered and six–membered cyclic secondary sulfonamides, respectively (Table 3, entries 5 and 6). Phenyl methanesulfonamide, a substrate that contains α-acidic protons, was also tolerated under the reaction conditions, and gave the product in 57% yield (Table 3, entry 7).

Based on the reported literature, we propose that the catalytic cycle involves an active Cu^I catalytic species and a Cu^{III} intermediate. The three elementary steps of the mechanism are: coordination of the nitrogen of the sulfonamide to the Cu^I metal center, oxidative addition of the aryl halide to form the Cu^{III} intermediate, and finally reductive elimination of the *N*-arylated product to regenerate the active catalytic Cu^I species. At this point, the role of water in enhancing the rate of the cross-coupling reaction remains uncertain. Clearly, more mechanistic studies need to be initiated to elucidate the detail of the catalytic cycle, and to deduce the role of water in this cross-coupling reaction.

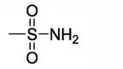
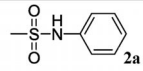
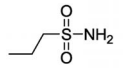
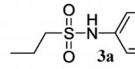
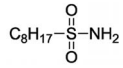
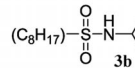
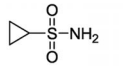
Table 2. *N*-arylation of methanesulfonamide with various aryl halides.[a]



Entry	ArX	Product	Yield (%)[b]
1		 **2a**	90
2		 **2b**	66[c]
3		 **2c**	84[c]
4		 **2d**	52[c]
5		 **2e**	80
6		 **2f**	80[d]
7		 **2g**	82
8		 **2h**	77
9		 **2i**	76
10		 **2j**	80
11		 **2k**	75[d]
12		 **2l**	63
13		 **2m**	82
14		 **2n**	66
15		 **2o**	50[d]
16		 **2a**	36[d]

[a] Unless otherwise stated, the reaction was carried out with aryl halide (1.47 mmol), methanesulfonamide (2.21 mmol), Cs_2CO_3 (2.94 mmol), Cu_2O (2 mol-%), and water (0.3 mL) at 130 °C for 24 h. [b] Isolated yield. [c] The reaction was carried out using 10 mol-% Cu_2O. [d] The reaction was carried out using 5 mol-% Cu_2O.

Table 3. *N*-arylation of various aliphatic and cyclic sulfonamides with iodobenzene.[a]

Entry	Sulfoamide	Product	Yield (%)[b]
1		 **2a**	90
2		 **3a**	65[c]
3		 **3b**	60[c]
4		**3c**	54[c]
5		**3d**	90
6		**3e**	82
7		**3f**	57

[a] Unless otherwise stated, the reaction was carried out with iodobenzene (1.47 mmol), sulfonamide (2.21 mmol), Cs_2CO_3 (2.94 mmol), Cu_2O (2 mol-%), and water (0.3 mL) at 130 °C for 24 h. [b] Isolated yield. [c] The reaction was carried out using 5 mol-% Cu_2O.

Conclusions

In conclusion, we have developed a practical and convenient protocol for the direct cross-coupling of methanesulfonamide with differently substituted aryl iodides using an inexpensive Cu_2O catalyst under ligand-free conditions. A wide variety of *N*-arylated aliphatic and alicyclic sulfonamides were obtained in moderate to excellent yields (up to 90%). The commercial availability and experimental simplicity of this catalytic system is expected to be particularly useful in industrial applications. Further studies to expand the substrate scope are currently ongoing in our laboratories.

Experimental Section

General Procedure for the *N*-Arylation of Methanesulfonamides: Cu_2O (Sigma–Aldrich, 99.99% purity; 0.0294 mmol), methanesulfonamide (2.21 mmol), Cs_2CO_3 (2.94 mmol), distilled water (0.3 mL), and aryl halide (1.47 mmol) were added to a reaction vial, and a screw cap was fitted to it. The reaction mixture was stirred under air in a closed system at 130 °C for 24 h, and then the heterogeneous mixture was allowed to cool to room temperature and diluted with methanol. The combined organic extracts were dried with anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was loaded onto a column using minimal amounts of dichloromethane and methanol, and it was purified by silica-gel column chromatography to give the *N*-arylated product. The identity and purity of the products were confirmed by ^1H and ^{13}C NMR spectroscopic analysis.

***N*-Phenylmethanesulfonamide (2a):**[9] Following the general procedure using methanesulfonamide (0.210 g, 2.205 mmol) and iodo-

benzene (0.165 mL, 1.47 mmol), the coupled product (226 mg, 90%) was obtained as a pale brown solid after purification by flash chromatography (hexane/ethyl acetate, 80:20). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.41 (m, 2 H), 7.19–7.28 (m, 3 H), 6.76 (br. s, 1 H), 3.03 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.8, 129.7, 125.4, 120.8, 39.2 ppm. HRMS: calcd. for $[M]^-$ 171.0354; found 171.0392.

***N*-*o*-Tolylmethanesulfonamide (2b):**[8] Following the general procedure with methanesulfonamide (0.210 g, 2.205 mmol) and 2-iodotoluene (0.187 mL, 1.47 mmol), but using copper(I) oxide (0.021 g, 10 mol-%), the coupled product (180 mg, 66%) was obtained as a pale brown solid after purification by flash chromatography (hexane/ethyl acetate, 80:20). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (d, J = 7.9 Hz, 1 H), 7.12–7.23 (m, 3 H), 6.74 (br. s, 1 H), 3.01 (s, 3 H), 2.34 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.8, 131.2, 131.0, 127.2, 126.2, 123.3, 39.8, 18.0 ppm. HRMS: calcd. for $[M]^-$ 185.0510; found 185.0587.

***N*-(2-Methoxyphenyl)methanesulfonamide (2c):**[8] Following the general procedure with methanesulfonamide (0.210 g, 2.205 mmol) and 2-iodoanisole (0.191 mL, 1.47 mmol), but using copper(I) oxide (0.021 g, 10 mol-%), the coupled product (248 mg, 84%) was obtained as a white solid after purification by flash chromatography (hexane/ethyl acetate, 80:20). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52 (d, J = 7.9 Hz, 1 H), 7.13 (dt, J = 1.2, 8.3 Hz, 1 H), 6.91–6.99 (m, 2 H), 6.81 (br. s, 1 H), 3.88 (s, 3 H), 2.95 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.5, 126.1, 125.6, 121.4, 120.9, 110.7, 55.8, 39.0 ppm. HRMS: calcd. for $[M]^-$ 201.0460; found 201.0518.

***N*-(2-Chlorophenyl)methanesulfonamide (2d):**[14] Following the general procedure with methanesulfonamide (0.210 g, 2.205 mmol) and 1-chloro-2-iodobenzene (0.179 mL, 1.47 mmol), but using copper(I) oxide (0.021 g, 10 mol-%), the coupled product (157 mg, 52%) was obtained as a white solid after purification by flash chromatography (hexane/ethyl acetate, 80:20). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65–7.67 (dd, J = 1.52, 8.80 Hz, 1 H), 7.42–7.44 (dd, J = 2.04, 8.08 Hz, 1 H), 7.29–7.33 (td, J = 1.52 Hz, 8.08 Hz, 1 H), 7.13–7.17 (td, J = 1.52 Hz, 7.8 Hz 1 H), 3.11 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.6, 129.7, 128.3, 126.3, 125.1, 122.5, 39.8 ppm. HRMS: calcd. for $[M]^-$ 204.9964; found 204.9899.

***N*-(2-Fluorophenyl)methanesulfonamide (2e):** Following the general procedure using methanesulfonamide (0.210 g, 2.205 mmol) and 2-fluoroiodobenzene (0.172 mL, 1.47 mmol), the coupled product (222 mg, 80%) was obtained as a white solid after purification by flash chromatography (hexane/ethyl acetate, 80:20). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54–7.58 (m, 1 H), 7.10–7.18 (m, 3 H), 6.84 (br. s, 1 H), 3.03 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.2, 126.6, 125.1, 124.7, 123.7, 115.8, 39.7 ppm. HRMS: calcd. for $[M]^-$ 189.0260; found 189.0222. M.p. 75.6–76.5 °C.

***N*-*m*-Tolylmethanesulfonamide (2f):**[15] Following the general procedure with methanesulfonamide (0.210 g, 2.205 mmol) and 3-iodotoluene (0.189 mL, 1.47 mmol), but using copper(I) oxide (0.011 g, 5 mol-%), the coupled product (218 mg, 80%) was obtained as a pale brown solid after purification by flash chromatography (hexane/ethyl acetate, 80:20). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (t, J = 7.6 Hz, 1 H), 6.99–7.05 (m, 3 H), 6.90 (br. s, 1 H), 3.01 (s, 3 H), 2.35 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.8, 136.7, 129.5, 126.2, 121.4, 117.8, 39.2, 21.4 ppm. HRMS: calcd. for $[M]^-$ 185.0510; found 185.0477.

***N*-(3-Fluorophenyl)methanesulfonamide (2g):** Following the general procedure using methanesulfonamide (0.210 g, 2.205 mmol) and 3-fluoroiodobenzene (0.173 mL, 1.47 mmol), the coupled product (228 mg, 82%) was obtained as a white solid after purification by flash chromatography (hexane/ethyl acetate, 80:20). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (br. s, 1 H), 7.26–7.32 (m, 1 H), 6.98–7.02 (m, 2 H), 6.84–6.88 (m, 1 H), 3.06 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.3, 138.5, 130.5, 115.7, 112.0, 107.6, 39.4 ppm. HRMS: calcd. for $[M]^-$ 189.0260; found 189.0231. M.p. 76.3–77.1 °C.

***N*-(3-Chlorophenyl)methanesulfonamide (2h):**[16] Following the general procedure using methanesulfonamide (0.210 g, 2.205 mmol) and 3-chloroiodobenzene (0.182 mL, 1.47 mmol), the coupled product (232 mg, 77%) was obtained as a pale brown solid after purification by flash chromatography (hexane/ethyl acetate, 80:20). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.30 (m, 2 H), 7.11–7.17 (m, 2 H), 6.99 (br. s, 1 H), 3.05 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.0, 135.4, 130.7, 125.4, 120.3, 118.3, 39.6 ppm. HRMS: calcd. for $[M]^-$ 204.9964; found 204.9987.

***N*-(3-Nitrophenyl)methanesulfonamide (2i):**[14] Following the general procedure using methanesulfonamide (0.210 g, 2.205 mmol) and 3-nitroiodobenzene (0.366 g, 1.47 mmol), the coupled product (241 mg, 76%) was obtained as a yellow solid after purification by flash chromatography (hexane/ethyl acetate, 80:20). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03–8.05 (m, 2 H), 7.53–7.59 (m, 2 H), 3.11 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.2, 141.2, 131.8, 126.6, 119.7, 115.0, 40.3 ppm. HRMS: calcd. for $[M]^-$ 216.0205; found 216.0274.

***N*-(3-(Trifluoromethyl)phenyl)methanesulfonamide (2j):** Following the general procedure using methanesulfonamide (0.210 g, 2.205 mmol) and 3-iodobenzotrifluoride (0.212 mL, 1.47 mmol), the coupled product (281 mg, 80%) was obtained as a white solid after purification by flash chromatography (hexane/ethyl acetate, 80:20); m.p. 68.8–69.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.51 (m, 4 H), 7.13 (br. s, 1 H), 3.07 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.5, 132.2, 130.4, 123.4, 123.5, 121.9, 117.0, 39.7 ppm. $C_8H_8F_3NO_2S$ (239.21) calcd. C, 40.17; H, 3.37; N, 5.86; S, 13.40; found C, 40.02; H, 3.32; N, 5.88; S, 13.33.

***N*-*p*-Tolylmethanesulfonamide (2k):**[8] Following the general procedure with methanesulfonamide (0.210 g, 2.205 mmol) and 4-iodotoluene (0.321 g, 1.47 mmol), but with copper(I) oxide (0.011 g, 5 mol-%), the coupled product (204 mg, 75%) was obtained as a pale brown solid after purification by flash chromatography (hexane/ethyl acetate, 80:20). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17–7.28 (m, 4 H), 7.14 (br. s, 1 H), 3.00 (s, 3 H), 2.35 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.5, 134.2, 130.2, 121.7, 38.9, 20.8 ppm. HRMS: calcd. for $[M]^-$ 185.0510; found 185.0540.

***N*-(4-Methoxyphenyl)methanesulfonamide (2l):**[8] Following the general procedure using methanesulfonamide (0.210 g, 2.205 mmol) and 4-iodoansiole (0.344 g, 1.47 mmol), the coupled product (186 mg, 63%) was obtained as a white solid after purification by flash chromatography (hexane/ethyl acetate, 80:20). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20 (d, J = 8.9 Hz, 2 H), 6.89 (d, J = 8.9 Hz, 2 H), 6.55 (br. s, 1 H), 3.80 (s, 3 H), 2.95 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.2, 129.0, 124.8, 114.8, 55.5, 38.9 ppm. HRMS: calcd. for $[M]^-$ 201.0460; found 201.0422.

***N*-(4-Fluorophenyl)methanesulfonamide (2m):**[17] Following the general procedure using methanesulfonamide (0.210 g, 2.205 mmol) and 4-fluoroiodobenzene (0.170 mL, 1.47 mmol), the coupled product (228 mg, 82%) was obtained as a white solid after purification by flash chromatography (hexane/ethyl acetate, 80:20). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22–7.27 (m, 2 H), 7.06 (t, J = 8.5 Hz, 2 H), 6.71 (br. s, 1 H), 3.01 (s, 3 H) ppm. ^{13}C NMR

(100 MHz, $CDCl_3$): δ = 160.8, 132.4, 123.9, 116.5, 39.2 ppm. HRMS: calcd. for $[M]^-$ 189.0260; found 189.0321.

***N*-(4-Chlorophenyl)methanesulfonamide (2n):**[8] Following the general procedure using methanesulfonamide (0.210 g, 2.205 mmol) and 1-chloro-4-iodobenzene (0.351 g, 1.47 mmol), the coupled product (199 mg, 66%) was obtained as a white solid after purification by flash chromatography (hexane/ethyl acetate, 80:20). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (d, J = 8.8 Hz, 2 H), 7.17 (d, J = 8.8 Hz, 2 H), 6.50 (br. s, 1 H), 3.03 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.2, 131.1, 129.8, 122.2, 39.5 ppm. HRMS: calcd. for $[M]^-$ 204.9964; found 204.9922.

***N*-(Pyridin-3-yl)methanesulfonamide (2o):**[18] Following the general procedure using methanesulfonamide (0.210 g, 2.205 mmol) and 3-iodopyridine (0.301 g, 1.47 mmol), the coupled product (132 mg, 52%) was obtained as a yellow solid after purification by flash chromatography (hexane/ethyl acetate, 60:40). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49 (d, J = 11.0 Hz, 1 H), 7.76 (d, J = 10.0 Hz, 1 H), 7.33–7.36 (m, 1 H), 4.97 (br. s, 1 H), 3.06 (s, 3 H) ppm. ^{13}C NMR (100 MHz, MeOD): δ = 145.3, 141.8, 136.6, 128.9, 125.2, 39.4 ppm. HRMS: calcd. for $[M]^-$ 172.0306; found 172.0502.

***N*-Phenylpropane-1-sulfonamide (3a):** Following the general procedure using propanesulfonamide (0.272 g, 2.205 mmol) and iodobenzene (0.165 mL, 1.47 mmol), the coupled product (190 mg, 65%) was obtained as a yellow liquid after purification by flash chromatography (hexane/ethyl acetate, 80:20). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (t, J = 7.3 Hz, 2 H), 7.25 (d, J = 8.1 Hz, 2 H), 7.16 (t, J = 7.3 Hz, 1 H), 6.94 (br. s, 1 H), 3.06–3.10 (m, 2 H), 1.81–1.90 (m, 2 H), 1.01 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.9, 129.7, 125.1, 120.4, 53.3, 17.2, 12.9 ppm. HRMS: calcd. for $[M]^-$ 199.0667; found 199.0642.

***N*-Phenyloctane-1-sulfonamide (3b):** Following the general procedure using octanesulfonamide (0.426 g, 2.205 mmol) and iodobenzene (0.165 mL, 1.47 mmol), the coupled product (237 mg, 60%) was obtained as a pale brown solid after purification by flash chromatography (hexane/ethyl acetate, 80:20); m.p. 41.5–42.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (t, J = 8.3 Hz, 2 H), 7.22 (d, J = 7.6 Hz, 2 H), 7.16 (t, J = 7.3 Hz, 1 H), 6.76 (br. s, 1 H), 3.09 (t, J = 8.3 Hz, 2 H), 1.77–1.85 (m, 2 H), 1.22–1.37 (m, 10 H), 0.84–0.94 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.8, 129.7, 125.2, 120.4, 51.6, 31.7, 29.0, 28.9, 28.2, 23.5, 22.6, 14.1 ppm. HRMS: calcd. for $[M]^-$ 269.1449; found 269.1455.

***N*-Phenylcyclopropanesulfonamide (3c):** Following the general procedure using cyclopropanesulfonamide (0.267 g, 2.205 mmol) and iodobenzene (0.165 mL, 1.47 mmol), the coupled product was obtained (156 mg, 54%) as a pale brown solid after purification by flash chromatography (hexane/ethyl acetate, 80:20); m.p. 80.5–81.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (t, J = 7.8 Hz, 2 H), 7.27 (d, J = 7.6 Hz, 2 H), 7.19 (t, J = 7.3 Hz, 1 H), 6.70 (br. s, 1 H), 2.46–2.52 (m, 1 H), 1.15–1.19 (m, 2 H), 0.93–0.98 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.8, 129.5, 125.5, 121.8, 29.8, 5.6 ppm. HRMS: calcd. for $[M]^-$ 197.0510; found 197.0582.

2-Phenylisothiazolidine 1,1-Dioxide (3d):[19] Following the general procedure using isothiazolidine 1,1-dioxide (0.267 g, 2.205 mmol) and iodobenzene (0.165 mL, 1.47 mmol), the coupled product (261 mg, 90%) was obtained as a white solid after purification by flash chromatography (hexane/ethyl acetate, 80:20). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (t, J = 7.8 Hz, 2 H), 7.27 (d, J = 7.2 Hz, 2 H), 7.15 (t, J = 7.2 Hz, 1 H), 3.79 (t, J = 6.4 Hz, 2 H), 3.39 (t, J = 7.0 Hz, 2 H), 2.50–2.58 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.6, 129.4, 124.6, 119.5, 48.3, 46.8, 18.8 ppm. $C_9H_{11}NO_2S$ (197.26) calcd. C, 54.80; H, 5.62; N, 7.10; S, 16.26; found C, 55.01; H, 5.47; N, 7.02; S, 16.55.

2-Phenyl-1,2-thiazinane 1,1-Dioxide (3e):[19] Following the general procedure using 1,2-thiazinane 1,1-dioxide (0.298 g, 2.205 mmol) and iodobenzene (0.165 mL, 1.47 mmol), the coupled product (254 mg, 82%) was obtained as a pale brown solid after purification by flash chromatography (hexane/ethyl acetate, 80:20). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.37 (m, 3 H), 7.28–7.30 (m, 2 H), 3.74 (t, J = 5.5 Hz, 2 H), 3.21 (t, J = 6.0 Hz, 2 H), 2.31–2.37 (m, 2 H), 1.88–1.94 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.5, 129.1, 127.4, 126.0, 53.5, 50.7, 24.6, 24.3 ppm. $C_{10}H_{13}NO_2S$ (211.28) calcd. C, 56.85; H, 6.20; N, 6.63; S, 15.18; found C, 56.45; H, 6.00; N, 6.91; S, 15.08.

***N*,1-Diphenylmethanesulfonamide (3f):**[20] Following the general procedure using phenylmethanesulfonamide (0.378 g, 2.205 mmol) and iodobenzene (0.165 mL, 1.47 mmol), the coupled product (207 mg, 57%) was obtained as a pale brown solid after purification by flash chromatography (hexane/ethyl acetate, 80:20). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.33 (m, 5 H), 7.27–7.28 (m, 2 H), 7.13–7.20 (m, 3 H), 6.20 (br. s, 1 H), 4.34 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.9, 130.9, 129.7, 129.0, 128.9, 128.6, 125.0, 120.0, 57.4 ppm. HRMS: calcd. for $[M]^-$ 247.0667; found 247.0699.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra of all newly synthesized compounds.

Acknowledgments

The authors would like to thank the National Institute of Education, Singapore and Nanyang Technological University for funding this work.

[1] J. Lee, S.-U. Kang, M.-J. Kil, M. Shin, J.-O. Lim, H.-K. Choi, M.-K. Jin, S.-E. Kim, Y.-S. Lee, K.-H. Min, Y.-H. Kim, H.-J. Ha, R. Tran, J. Welter, Y. Wang, T. Szabo, L. Pearce, D. Lundberg, A. Toth, V. Pavlyukovets, M. Morgan, P. Blumberg, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4136–4142.
[2] M. K. Khera, V. P. Palle, V. Sattigeri, J. Sattigeri, A. Soni, A. R. A. Rauf, R. Sivakumar, R. R. Reddy, A. Musib, I. A. Cliffe, P. K. Bhatnagar, A. Ray, P. Srivastava, S. G. Dastidar (Ranbaxy Laboratories Limited, India), WIPO Patent WO/2012/038944A1, **2012**.
[3] W. W. Freimuth, *Adv. Exp. Med. Biol.* **1996**, *394*, 279.
[4] J. Henichart, *Hoppe-Seyler's Z. Physiol. Chem.* **1982**, *363*, 835.
[5] H. Liu, M. Ji, H. Jiang, L. Liu, W. Hua, K. Chen, R. Ji, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2153–2157.
[6] K. Kunz, U. Scholz, D. Ganzer, *Synlett* **2003**, 2428–2439.
[7] For representative papers on ligand-assisted C-N coupling, see: a) S. V. Ley, A. W. Thomas, *Angew. Chem.* **2003**, *115*, 5558–5607; *Angew. Chem. Int. Ed.* **2003**, *42*, 5400–5449; b) D. S. Surry, S. L. Buchwald, *Chem. Sci.* **2010**, *1*, 13–31; c) F. Y. Kwong, S. L. Buchwald, *Org. Lett.* **2002**, *4*, 3517–3520; d) X. Gao, H. Fu, R. Qiao, Y. Jiang, Y. Zhao, *J. Org. Chem.* **2008**, *73*, 6864–6866.
[8] B. R. Rosen, J. C. Ruble, T. J. Beauchamp, A. Navarro, *Org. Lett.* **2011**, *13*, 2564–2567.
[9] W. Deng, L. Liu, C. Zhang, M. Liu, Q.-X. Guo, *Tetrahedron Lett.* **2005**, *46*, 7295–7298.
[10] For representative papers on C–N coupling in water, see: a) X. Sun, X. Tu, C. Dai, X. Zhang, B. Zhang, Q. Zeng, *J. Org. Chem.* **2012**, *77*, 4454–4459; b) Y.-C. Teo, G.-L. Chua, *Chem. Eur. J.* **2009**, *15*, 3072–3075; c) W.-B. Wu, J.-M. Huang, *Org. Lett.* **2012**, *14*, 5832–5835.
[11] C.-J. Li, B. M. Trost, *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 13197–13202.
[12] D. Sinou, *Adv. Synth. Catal.* **2002**, *344*, 221–237.
[13] For representative papers on our copper(I)-catalyzed C–N cross-coupling, see: a) F.-F. Yong, Y.-C. Teo, S.-H. Tay, B. Y.-

H. Tan, K.-H. Lim, *Tetrahedron Lett.* **2011**, *52*, 1161–1164; b) F.-F. Yong, Y.-C. Teo, G.-L. Chua, G. S. Lim, Y. Lin, *Tetrahedron Lett.* **2011**, *52*, 1169–1172; c) F.-F. Yong, Y.-C. Teo, *Synlett* **2010**, 3068–3072.

[14] A. Greenfield, C. Grosanu, *Tetrahedron Lett.* **2008**, *49*, 6300–6303.

[15] U. Zoller, P. Rona, *Tetrahedron Lett.* **1985**, *26*, 2813–2814.

[16] H. Wu, J. Hynes, *Org. Lett.* **2010**, *12*, 1192–1195.

[17] R. Sridhar, B. Sridhar, V. P. Srinivas, M. Kumar, K. R. Narender, R. Rao, Sridhar, *Adv. Synth. Catal.* **2007**, *349*, 1873–1876.

[18] X. Han, *Tetrahedron Lett.* **2010**, *51*, 360–362.

[19] C. Valente, R. Guedes, R. Moreira, J. Iley, J. Gut, P. Rosenthal, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4115–4119.

[20] B. Hill, Y. Liu, S. D. Taylor, *Org. Lett.* **2004**, *6*, 4285–4288.

Received: October 16, 2013
Published Online: December 18, 2013

