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Copper-catalyzed cross-coupling of sulfonamides with aryl iodides and bromides facilitated by amino acid ligands

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Abstract—A highly general, convenient, and inexpensive catalyst system was developed for the *N*-arylation of sulfonamides with aryl iodides or bromides by using 5–20 mol % of CuI as catalyst, 20 mol % of *N*-methylglycine (for aryl iodides) or *N*,*N*-dimethylglycine (for aryl bromides) as ligand, and K_3PO_4 as base.

Transition metal catalyzed cross-coupling of sulfonamides with aryl halides provides a straightforward route to *N*-arylsulfonamides. This reaction has recently received considerable attention because a large number of pharmaceutically active compounds (e.g., class III antiarrhythmic agents, non-nucleotide reverse transcriptase inhibitors, non-peptidic vasopressin V1a receptor antagonists, and HIV-1 protease inhibitors) contain an aryl sulfonamide.[1] Up to now catalysts based on two transition metals have been examined for the *N*-arylation of sulfonamides. The first one is Pd, which often requires the use of expensive, unstable, and poisonous phosphine ligands.[2] The second one is Cu, which is more likely to be used for large scale synthesis because Cu catalysts can often work with relatively cheap nitrogen-centered ligands.[3,4]

In 2003, He and Wu systematically studied the CuI-catalyzed *N*-arylation of sulfonamides with a number of aryl bromides and iodides for the first time.[5] No ligand was utilized in their study but the synthesis required the use of microwave heating. Although the arylation can be finished relatively rapidly in the microwave oven (2–4 h), the yields of the couplings are mostly modest (54–90%). Later Steinhuebel et al. reported the Cu_2O-catalyzed *N*-arylation of sulfonamides under normal heating conditions.[6] *N*-Methyl-2-pyrrolidone was used as solvent and 2,2′-bipyridine was utilized as the ligand. The yields of their couplings ranged from 35% to 93%. Furthermore, in a related work, Lam et al. reported the synthesis of *N*-arylsulfonamides through the copper-catalyzed *N*-arylation of sulfonamides with arylboronic acids.[7]

Ma et al.[8] and we[9] have recently found that simple amino acids can serve as ligands for Cu(I)-catalyzed cross-couplings between aryl halides and diverse nucleophiles. These catalytic reactions are advantageous not only because of their high yields, but also because of the following desirable properties of amino acids. (1) Amino acid is cheap and safe to use. (2) The amino acid ligand is easy to remove after the reaction because it is highly soluble in water. (3) Amino acid waste is relatively environmentally benign. (4) There are a large number of different amino acids. Most of them are chiral and we may use them as ligands in the synthesis of atropisomeric coupling products. To date the Cu(I)/amino acid catalysts have been successfully utilized for the cross-coupling of aryl halides with amides, carbamates, amines, amino acids, *N*-heterocycles, sulfinic acids, alkynes, and azides.[8,9] To expand the scope of the Cu(I)/amino acid-catalyzed reactions, herein we report our recent application of amino acid ligands to Cu-catalyzed *N*-arylation of sulfonamides.

During the course of our study, we have screened many different combinations of amino acid ligands, bases, solvents, and reaction temperatures in order to maximize the cross-coupling yield. The best ligand turns out to be *N*-methylglycine, which is a non-expensive and readily available compound. The most suitable base is K_3PO_4 and the best solvent is DMF.[9] In order to test the applicability of the new procedure, we have

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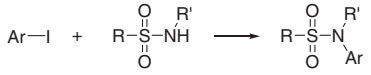
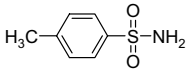
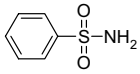
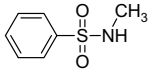
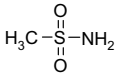
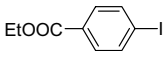
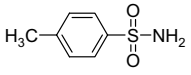
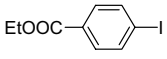
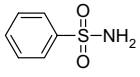
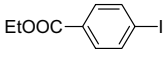
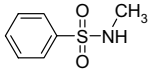
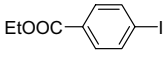
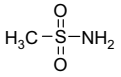
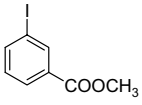
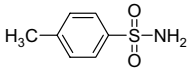
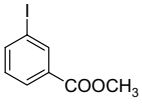
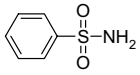
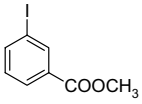
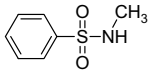
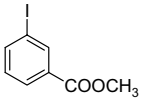
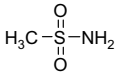
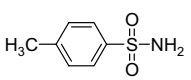
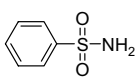
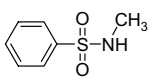
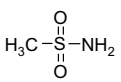
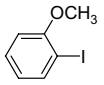
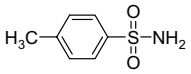
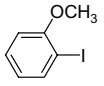
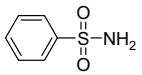
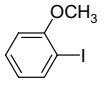
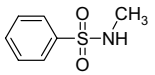
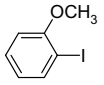
Table 1. Yields of the CuI/*N*-methylglycine-catalyzed coupling reactions between aryl iodides and sulfonamides[10]



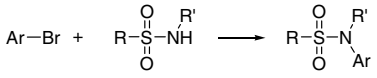
Entry	Aryl iodide	Sulfonamide	Isolated yield (%)
1			95
2			94
3			82
4			99
5			99
6			99
7			98
8			95
9			99
10			99
11			99
12			99
13			50
14			56
15			Trace
16			80
17			76
18			55
19			Trace
20			60

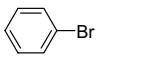
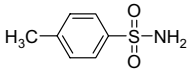
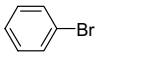
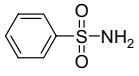
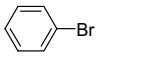
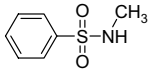
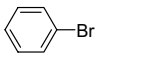
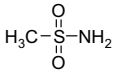
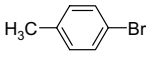
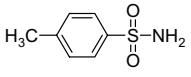
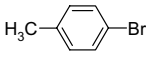
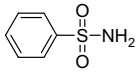
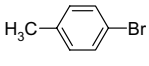
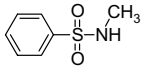
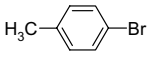
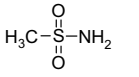
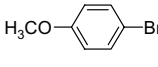
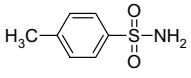
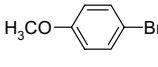
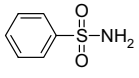
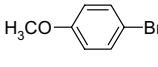
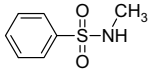
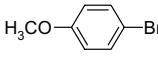
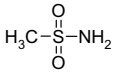
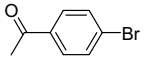
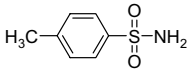
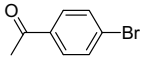
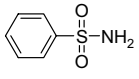
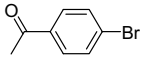
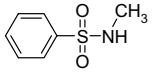
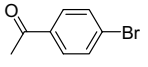
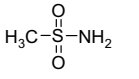
examined a few different combinations of aryl iodides and sulfonamides (see Table 1). It is found that when iodobenzene, ethyl 4-iodobenzoate and methyl 3-iodobenzoate are used as aryl iodide, the yields of the cross-coupling reactions range from 82% to 99% (entries 1–12). Compared to the previous catalytic systems (where yields = 54–90% or 35–93%),[5,6] the present catalytic system is clearly advantageous because it gives significantly higher reaction yields. Nonetheless, we found that when 2-iodotoluene or 2-iodoanisole is used as aryl iodide, the yields of the cross-couplings become much lower (entries 13–20), due to steric hindrance of the 2-methyl or 2-methoxy group. Furthermore, in the cross-coupling of 2-iodotoluene or 2-iodoanisole with *N*-methylbenzenesulfonamide (entries 15 and 19), only trace amount of product was obtained.

Having successfully dealt with aryl iodides, we next try to optimize a procedure for the cross-coupling between sulfonamides and aryl bromides. Again, we have screened different combinations of amino acid ligands, bases, solvents, and reaction temperatures in order to maximize the cross-coupling yield. Interestingly, we found that *N*,*N*-dimethylglycine is a more suitable ligand than *N*-methylglycine for aryl bromide.[11] Using the optimized procedure, we have examined the cross-coupling between a number of different sulfomides and aryl bromides (see Table 2). We found that the yields of the cross-couplings mostly range from 80% to 99%. The cross-coupling reaction proceeds well with aryl bromides with both electron-withdrawing groups (e.g., 4-bromoacetophenone) and electron-donating groups (e.g., 4-bromoanisole). The lowest yield (68%) is obtained for the cross-coupling between 4-bromoanisole and *N*-methylbenzenesulfonamide (entry 11), where the steric hindrance of the *N*-methyl group may exert significant negative effects.

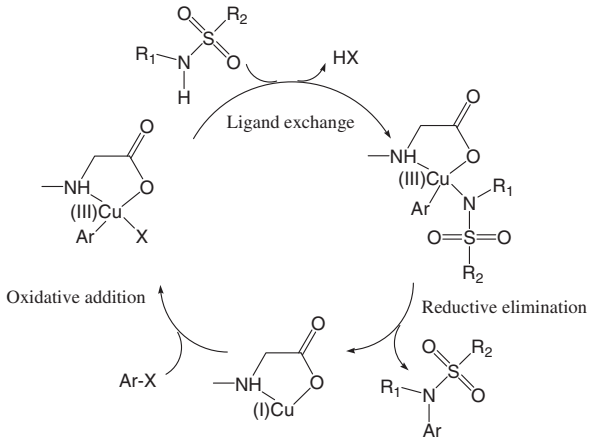
At present the mechanism of the Cu(I)-catalyzed cross-coupling reaction is not completely clear yet.[12] Nonetheless, the results from the present study are consistent with the mechanism in which a four-coordinated Cu(III) intermediate is involved (Scheme 1).[12] According to the mechanism, the role of the amino acid ligand in the reac-

Table 2. Yields of the CuI/*N*,*N*-dimethylglycine-catalyzed coupling reactions between aryl bromides and sulfonamides



Entry	Aryl bromide	Sulfonamide	Isolated yield (%)
1			99
2			95
3			82
4			99
5			91
6			96
7			99
8			89
9			85
10			75
11			68
12			80
13			95
14			91
15			90
16			96

tion is either to promote the oxidative addition of aryl halide to the Cu(I) species or to stabilize the Cu(III) intermediate. The mechanism also explains why it is not the amino group of amino acid ligand (e.g., the N–H group of *N*-methylglycine) but the sulfonamide



Scheme 1.

nitrogen that participates in the coupling, because in the Cu(III) complex sulfonamide nitrogen is anionic (therefore more reactive) whereas the NH group of the amino acid ligand is neutral.

In summary, we reported a novel Cu(I)-catalyzed *N*-arylation reaction of sulfonamides with aryl bromides and iodides facilitated by amino acid ligands. Compared to the previous results,[2,5,6] the present coupling reaction gives significantly higher yields and, at the same time, it is considerably less expensive and more environmentally benign. The present study provides further evidence that Cu(I)/amino acid is a powerful catalyst system for C-heteroatom cross-coupling reactions.[8,9] We wish that the cross-coupling reaction reported here would find application for the preparation of pharmaceutically important *N*-aryl sulfonamides.

Acknowledgments

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References and notes

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10. Typical procedures for the CuI/amino acid-catalyzed sulfonamide arylation reactions of aryl iodides are as follows. An oven-dried, three-necked flask is charged with CuI (47.6 mg, 0.25 mmol, 5.0 mol %), sulfonamides (6.0 mmol), *N*-methylglycine ligand (1.0 mmol, 20 mol %), and K_3PO_4 (2.65 g, 12.5 mmol). The flask is evacuated and backfilled with nitrogen. Then aryl iodide (5.0 mmol) and DMF (10.0 ml) are added under nitrogen. The reaction mixture is stirred under 100 °C for 24 h. The resulting suspension is cooled to room temperature and the solvent was removed. The residue is filtered through a 2–3 cm pad of silica gel with the help of 100 ml of ethyl acetate. The filtrate is concentrated and the residue is purified by chromatography to afford pure product.
11. Typical procedures for the CuI/amino acid-catalyzed sulfonamide arylation reactions of aryl bromides are as follows. An oven-dried, three-necked flask is charged with CuI (190.4 mg, 1.00 mmol, 20.0 mol %), sulfonamides (6.0 mmol), *N*,*N*-dimethylglycine (1.0 mmol, 20 mol %), and K_3PO_4 (2.65 g, 12.5 mmol). The flask is evacuated and backfilled with nitrogen. Then aryl iodide (5.0 mmol) and DMF (10.0 ml) are added under nitrogen. The reaction mixture is refluxed for 48 h. The resulting suspension is cooled to room temperature and the solvent was removed. The residue is filtered through a 2–3 cm pad of silica gel with the help of 100 ml of ethyl acetate. The filtrate is concentrated and the residue is purified by chromatography to afford pure product.
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