DOI: 10.1002/ejoc.201000361

Pyrrole-2-carbohydrazides as Ligands for Cu-Catalyzed Amination of Aryl Halides with Amines in Pure Water

Jianwei Xie,[a] Xinhai Zhu,[a] Manna Huang,[a] Fei Meng,[a] Weiwei Chen,[a] and Yiqian Wan*[a]

Keywords: Pyrrole-2-carbohydrazides / Copper / Amination / Microwave chemistry / Water chemistry

Pyrrole-2-carbohydrazides were synthesized and found to be novel and efficient ligands for the Cu-catalyzed amination of aryl halides with amines in pure water with high yields. A variety of aryl bromides or iodides could be aminated, promoted by the CuI/*N*′-phenyl-1*H*-pyrrole-2-carbohydrazide (**L13**) system, under microwave irradiation or conventional heating without the protection by an inert gas.

Introduction

Arylamines are prevalent building blocks of numerous drugs, materials, and natural products, and their preparations have been attracted much attention.[1] The transition-metal-catalyzed C–N coupling reaction is one of the most important approaches. In the past decades, although significant improvements have been achieved in the copper-catalyzed Ullmann and Goldberg reactions and the palladium-catalyzed Buchwald–Hartwig reaction in organic media,[1a,2] there is still a need to develop a generally efficient and environmentally friendly catalytic system for this class of reactions.

Among the 12 principles of green chemistry, the desire for utilizing "safer solvents" and to "design for energy efficiency" can be considered two key principles of relevance to synthetic chemists.[3] Water, as the cheapest, non-toxic, non-flammable and environmentally benign solvent in the reaction steps, has been successfully employed for various organic synthesis,[3,4] of which the copper-catalyzed C–N bond formation in aqueous media – even in pure water – has been given much attention in recent years.[4b,5–8] However, some drawbacks of the catalytic systems, such as inert-gas protection, long reaction times, and narrow scope of substrates, limit their universal application. Moreover, to the best of our knowledge, there are only a few methods well established to effectively promote *N*-arylation of anilines in aqueous media.[7c,8a–8d] In addition, microwave heating, because of rapid and convenient superheating to high temperatures in combination with excellent reaction control and low-energy consumption,[8g] can accelerate a variety of synthetic transformations by time- and energy-saving protocols. The combination of these principles, "water" and "microwave", must therefore be considered to be a promising and enabling green alternative.

As part of our ongoing research interest in aqueous organic reactions,[8c,8d,9] we herein wish to report pyrrole-2-carbohydrazides as novel effective ligands for the copper-catalyzed C–N coupling reaction in water without the protection by an inert gas.

Results and Discussion

Initially, we examined **L2** as a ligand for promoting the Cu-catalyzed amination of 4-bromoanisole with aniline (Scheme 1 and Figure 1). Addition of 25 mol-% of **L2** resulted in the formation of the desired coupling product with moderate yield (50% GC yield) after 5 min under microwave irradiation at 130 °C in water. This encouraged us to synthesize a variety of pyrrole-2-carbohydrazides and to test their corresponding effects. As indicated in Figure 2, pyrrole-2-carboxamide and other heterocyclic 2-carbohydrazides exhibited lower conversions of the 4-bromoanisole for this transformation (Figure 2, **L1** and **L3**–**L5**), and this revealed that the hydrogen atom on the nitrogen atom of the pyrrole ring and the hydrogen atom of the non-amide nitrogen atom were both necessary for the corresponding pyrrole-2-carbohydrazides to be effective ligands. This can be further confirmed by replacing the related hydrogen atoms with methyl groups, which leads to a markedly decreased catalytic activity (Figure 2, **L8** and **L9**). Knowing that a monosubstituted non-amide nitrogen atom of pyrrole-2-carbohydrazide provided higher activities than a non- or disubstitute one (Figure 2, **L7** vs. **L2** and **L9**), we reasonable synthesized four different monosubstituted pyrrole-2-carbohydrazides, which contain electron-releasing or electron-withdrawing groups, to investigate their effects as

---

[a] School of Chemistry and Chemical Engineering, Sun Yat-Sen University,
Guangzhou 510275, P. R. of China
Fax: +86-20-84112245
E-mail: ceswyq@mail.sysu.edu.cn

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201000361.

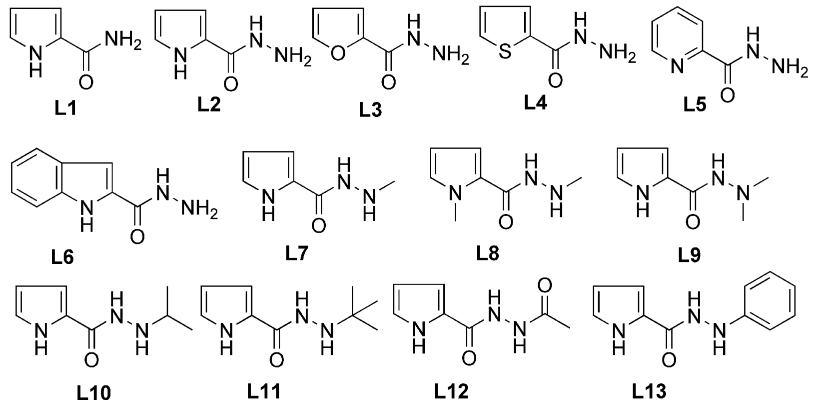
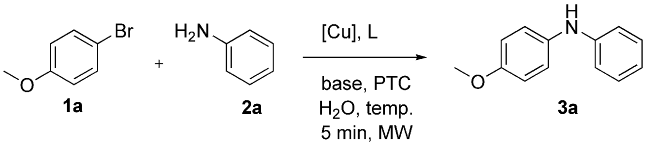


Figure 1. Ligands used in this work.

ligands for the model reaction (Figure 2. **L10**–**L13**). As expected, **L13** displayed the best activity for this process in pure water.



Scheme 1. Model reaction of the Cu-catalyzed C–N coupling.

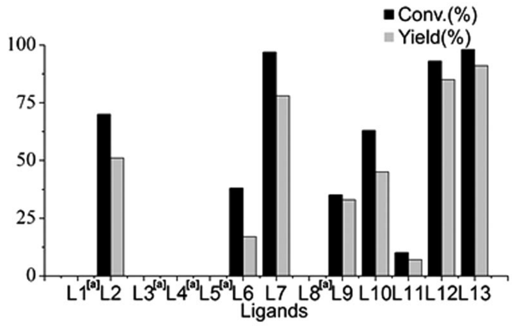


Figure 2. Effect of ligands on the coupling in the model reaction. Reaction conditions: 4-bromoanisole (0.5 mmol), aniline (2.5 mmol), CuO (0.025 mmol), **L** (0.125 mmol), KOH (1 mmol), TBAB (0.25 mmol), H_2O (1 mL), 130 °C, 5 min, microwaves (100 W). The yields were calculated by GC/MS. [a] No product was detected by TLC.

With the favourable ligand in hand, it was reasonable for us to test the effect of copper sources, and the preliminary results showed that most of Cu^I or Cu^{II} salts, in particular CuI, combined with **L13** afforded the *N*-arylated products in good to excellent yields, respectively, whereas Cu^0 resulted in lower yields of 57% (Table 1, Entries 2–7), and under copper-free conditions no reaction took place (Table 1, Entry 1). In addition, decreasing the loading of the catalyst from 5 mol-% to 3 mol-% led to a slight decrease of conversion (Table 1, Entries 7 and 8). Further optimization of the reaction conditions [e.g. bases, temperature, PTCs (phase-transfer catalysts), the proportions of reactants, and the ratio of **L13**/CuI] for the *N*-arylation process was carefully conducted. It should be noted that the relatively high molar ratio (5:1) of **L13**/CuI, which might be required because of decomposition of **L13**, was still a challenge in our experimental conditions.

Table 1. Effect of copper sources on the coupling in the model reaction by using **L13** as the ligand.[a]

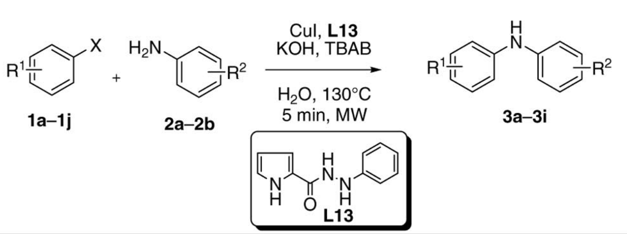
Entry	[Cu]	Conversion/yield [%][b]
1	–	0[c]
2	CuO	98/91
3	$CuSO_4$	97/91
4	$Cu(OAc)_2$	96/91
5	Cu_2O	91/82
6	Cu	63/57
7	CuI	99/95
8	CuI	98/91[d]

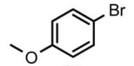
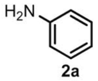
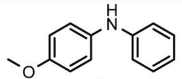
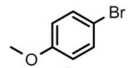
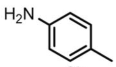
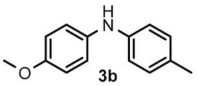
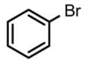
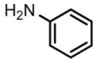
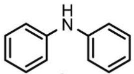
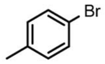
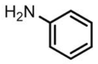
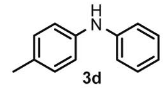
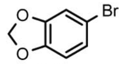
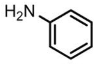
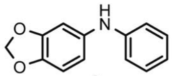
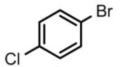
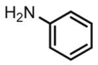
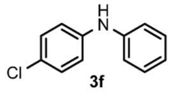
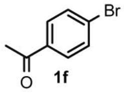
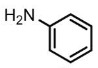
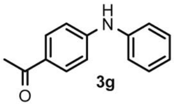
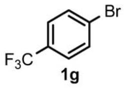
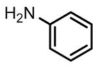
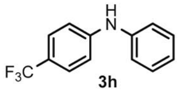
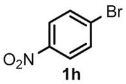
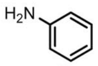
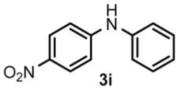
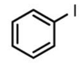
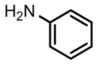
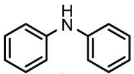
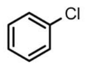
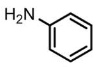
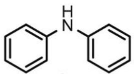
[a] Reaction conditions: 4-bromoanisole (0.5 mmol), aniline (2.5 mmol), [Cu] (0.025 mmol), **L13** (0.125 mmol), KOH (1 mmol), TBAB (0.25 mmol), H_2O (1 mL), 130 °C, 5 min, microwaves (100 W). [b] Calculated by GC/MS. [c] No product was dectected by TLC. [d] 0.015 mmol of CuI.

The reaction scope and limitations of this CuI/**L13** catalytic system was subsequently explored between typical aryl halides and anilines (Table 2), aliphatic amines, and nitrogen-containing heterocycles (Table 3) under the optimal conditions [5 mol-% of CuI, 25 mol-% of **L13**, KOH (2 equiv.) in water under microwave irradiation at 130 °C for 5 min].

As shown in Table 2, the *N*-arylation of anilines with most of electron-rich, electron-neutral, and electron-poor aryl bromides afforded the desired products with moderate to good isolated yields (Entries 1–7). It is intriguing that the reaction of 1-bromo-4-(trifluoromethyl)benzene with aniline gave only 47% isolated yield because of the lower conversion (62% conversion yield detected by GC analysis) (Entry 8). However, the arylation of aniline with 1-bromo-4-nitrobenzene provided a complex product mixture due to its high reactivity (Entry 9). Aryl iodides provided slightly higher yields than aryl bromides, but chlorobenzene, reacting with aniline, afforded only traces of product under the experimental conditions (Entries 10 and 11).

Table 2. CuI-catalyzed C–N coupling reaction of aryl halides with anilines in water.[a]



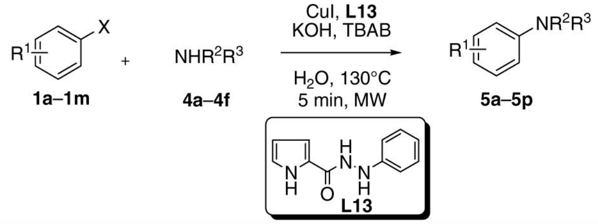
Entry	ArX	Amine	Product	Yield [%][b]
1	 1a	 2a	 3a	78 83[c]
2	 1a	 2b	 3b	75
3	 1b	 2a	 3c	79
4	 1c	 2a	 3d	74
5	 1d	 2a	 3e	80
6	 1e	 2a	 3f	66
7	 1f	 2a	 3g	75
8	 1g	 2a	 3h	47
9	 1h	 2a	 3i	53
10	 1i	 2a	 3c	81
11	 1j	 2a	 3c	trace

[a] Reaction conditions: **1** (1.0 mmol), **2** (4 mmol), CuI (0.05 mmol), **L13** (0.25 mmol), KOH (2 mmol), TBAB (0.50 mmol), H_2O (2 mL), 130 °C, 5 min, microwaves (100 W). [b] Isolated yields. [c] With a sealed tube in an oil bath at 130 °C for 5 min.

The *N*-arylation of aliphatic amines and nitrogen-containing heterocycles was also successfully carried out by using the CuI/**L13** catalyst system in water (Table 3). The results indicated that all the aryl halides reacted with benzylamine in a way similar to the arylation of anilines. Besides, linear and cyclic aliphatic primary amines were also smoothly *N*-arylated under the optimum conditions (Entries 12 and 13). It is worth noting that the sterically hindered *o*-bromotoluene or cyclic secondary amines reacted also effectively under the experimental conditions (Entries 4, and 14–15). In addition, the *N*-arylation of pyrazole was also performed under the presented conditions. Aryl iodides reacted with pyrazole to give moderate to good yields, although the *N*-arylation of pyrazole with aryl bromides under these conditions was still a challenge (Entries 16–19).

In comparison to microwave heating, the amination of 4-bromoanisole was performed with a sealed tube in a preheated oil bath at 130 °C for 5 min, and afforded yields similar to those under microwave-assisted conditions, which indicated the microwave irradiation was not prerequistite (Table 2, Entry 1; Table 3, Entries 1, and 12–13). These results are of great interest for large-scale industrial applications.

Table 3. CuI-catalyzed C–N coupling reaction of aryl halides with aliphatic amines in water.[a]



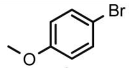
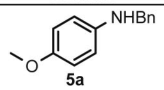
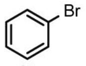
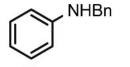
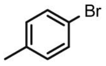
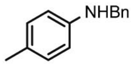
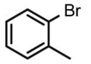
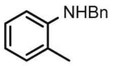
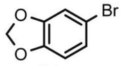
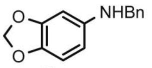
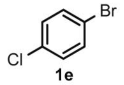
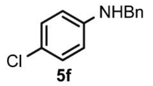
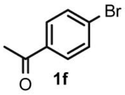
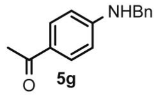
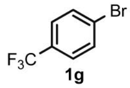
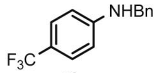
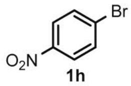
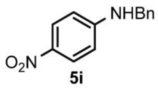
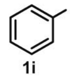
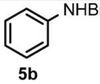
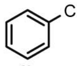
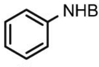
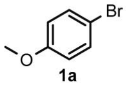
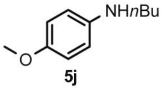
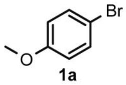
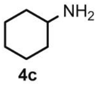
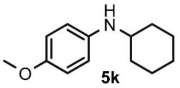
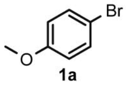
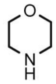
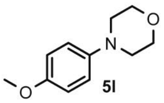
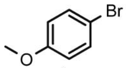
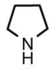
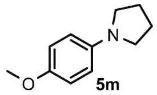
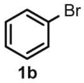
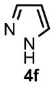
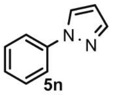
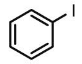
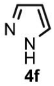
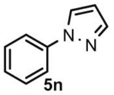
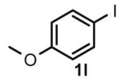
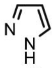
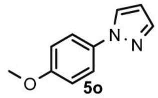
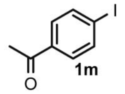
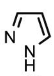
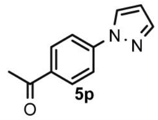
Entry	ArX	Amine	Product	Yield [%][b]
1	 1a	$BnNH_2$ **4a**	 5a	81 77[c]
2	 1b	$BnNH_2$ **4a**	 5b	76
3	 1c	$BnNH_2$ **4a**	 5c	78
4	 1k	$BnNH_2$ **4a**	 5d	67
5	 1d	$BnNH_2$ **4a**	 5e	80
6	 1e	$BnNH_2$ **4a**	 5f	85
7	 1f	$BnNH_2$ **4a**	 5g	82
8	 1g	$BnNH_2$ **4a**	 5h	72
9	 1h	$BnNH_2$ **4a**	 5i	61

Table 3. *(Continued)*

Entry	ArX	Amine	Product	Yield [%][b]
10	 **1i**	BnNH$_2$ **4a**	 **5b**	82
11	 **1j**	BnNH$_2$ **4a**	 **5b**	trace
12	 **1a**	*n*BuNH$_2$ **4b**	 **5j**	73 80[c]
13	 **1a**	 **4c**	 **5k**	63 76[c]
14	 **1a**	 **4d**	 **5l**	54
15	 **1a**	 **4e**	 **5m**	62
16	 **1b**	 **4f**	 **5n**	trace
17	 **1i**	 **4f**	 **5n**	63
18	 **1l**	 **4f**	 **5o**	78
19	 **1m**	 **4f**	 **5p**	54

[a] Reaction conditions: **1** (1 mmol), **4** (4 mmol), CuI (0.05 mmol), **L13** (0.25 mmol), KOH (2 mmol), TBAB (0.50 mmol), H_2O (2 mL), 130 °C, 5 min, microwaves (100 W). [b] Isolated yield. [c] With a sealed tube in an oil bath at 130 °C for 5 min.

Conclusions

We established for the first time pyrrole-2-carbohydrazides as novel ligands for Cu-catalyzed Ullmann C–N coupling reactions in pure water. A variety of aryl bromides or iodides could be aminated, promoted by the CuI/**L13** system, under microwave irradiation and conventional heating without the protection of an inert gas. In addition, the low catalyst loading, the application of a broad range of copper salts, and the short reaction times of the process presented herein, may be beneficial for the development of green chemistry.

Experimental Section

Typical Procedure for the C–N Coupling Reaction under Microwave Irradiation: Into a 10 mL of microwave vessel were added CuI (9.5 mg, 0.05 mmol), **L13** (50.3 mg, 0.25 mmol), 4-bromoanisole (186 mg, 1 mmol), aniline (372 mg, 4 mmol), KOH (112 mg, 2.0 mmol), TBAB (161 mg, 0.5 mmol), H_2O (2.0 mL) and a magnetic stir bar. The vessel was sealed with a septum and placed into the microwave cavity. The temperature of the mixture was ramped from room temperature to 130 °C under microwave irradiation, which took 30–60 s. Once 130 °C was reached, the reaction mixture was kept at this temperature for 5 min. After allowing the mixture to cool to room temperature, the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (3× 30 mL). The combined organic phases were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatograph on silica gel (ethyl acetate/petroleum ether, 1:20) to afford the target product 4-methoxy-*N*-phenylaniline (**3a**) (156 mg, 78% yield). The purity of the compound was confirmed by ^1H NMR, ^{13}C NMR, and MS data.

Typical Procedure for the C–N Coupling Reaction in an Oil Bath: Into a 10 mL tube were added CuI (9.5 mg, 0.05 mmol), **L13** (50.3 mg, 0.25 mmol), 4-bromoanisole (186 mg, 1 mmol), aniline (372 mg, 4 mmol), KOH (112 mg, 2.0 mmol), TBAB (161 mg, 0.5 mmol), H_2O (5 mL) and a magnetic stir bar, and the tube was sealed. The reaction mixture was stirred at 130 °C in a preheated oil bath for 5 min, then cooled to room temp. and extracted with ethyl acetate (3× 30 mL). The combined organic phases were washed with water and brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatograph on silica gel to afford the target product (165 mg, 83% yield).

Supporting Information (see footnote on the first page of this article): Experimental procedures, characterization data, and copies of the ^1H NMR, ^{13}C NMR, and mass spectra of all compounds.

Acknowledgments

We acknowledge the National Natural Science Foundation of China (20872182, 20802095) and the National High Technology Research and Development Program of China (863 Program) (No. 2006AA09Z446) for their financial support. We also thank the CEM Corporation for providing the microwave equipment Discover.

---

[1] For a selected review and some recent examples, see: a) G. Evano, N. Blanchard, M. Toumi, *Chem. Rev.* **2008**, *108*, 3054–3131; b) A. W. Czarnik, *Acc. Chem. Res.* **1996**, *29*, 112–113; c) T. Wiglenda, R. Gust, *J. Med. Chem.* **2007**, *50*, 1475–1484; d) A. Grauer, A. Späth, D. Ma, B. König, *Chem. Asian J.* **2009**, *4*, 1134–1140.

[2] For recent reviews and books on copper- or palladium-catalyzed C–N bond formation, see: a) S. V. Ley, A. W. Thomas, *Angew. Chem. Int. Ed.* **2003**, *42*, 5400–5449; b) K. Kunz, U. Scholz, D. Ganzer, *Synlett* **2003**, 2428–2439; c) I. P. Beletskaya, A. V. Cheprakov, *Coord. Chem. Rev.* **2004**, *248*, 2337–2364; d) D. Ma, Q. Cai, *Acc. Chem. Res.* **2008**, *41*, 1450–1460; e) F. Monnier, M. Taillefer, *Angew. Chem. Int. Ed.* **2009**, *48*, 6954–6971; f) J. F. Hartwig, *Synlett* **2006**, 1283–1294; g) M. Kienle, S. R. Dubbaka, K. Brade, P. Knochel, *Eur. J. Org. Chem.* **2007**, 4166–4176; h) J. F. Hartwig, *Acc. Chem. Res.* **2008**, *41*, 1534–1544; i) F. Monnier, M. Taillefer, *Angew. Chem. Int. Ed.* **2008**, *47*, 3096–3099; j) D. S. Surry, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2008**, *47*, 6338–6361; k) S. L. Buchwald, C. Mauger, G. Mignani, U. Scholz, *Adv. Synth. Catal.* **2006**, *348*, 23–39; l) L. Jiang, S. L. Buchwald, *Palladium-Catalyzed Aromatic Carbon-Nitrogen Bond Formation in Metal-Catalyzed Cross-Coupling Reaction*, 2nd ed., Wiley-VCH, Weinheim, **2004**; m) J. F. Hartwig, *Palladium-Catalyzed Amination of Aryl Halides and Related Reactions*, John Wiley & Sons, New York, **2002**.

[3] D. Dallinger, C. O. Kappe, *Chem. Rev.* **2007**, *107*, 2563–2591.

[4] a) U. M. Lindström, *Chem. Rev.* **2002**, *102*, 2751–2772; b) C. J. Li, L. Chen, *Chem. Soc. Rev.* **2006**, *35*, 68–82; c) C. J. Li, *Chem. Rev.* **2005**, *105*, 3095–3165; d) C. Li, T. Chan, *Comprehensive Organic Reactions in Aqueous Media*, 2nd ed., John Wiley & Sons, New Jersey, **2007**; e) M. Carril, R. SanMartin, E. Domínguez, *Chem. Soc. Rev.* **2008**, *37*, 639–647; f) C. I. Herrerías, X. Yao, Z. Li, C. J. Li, *Chem. Rev.* **2007**, *107*, 2546–2562.

[5] Cu-catalyzed formation of aromatic amines in aqueous media or pure water, see: a) Z. Guo, J. Guo, Y. Song, L. Wang, G. Zou, *Appl. Organomet. Chem.* **2009**, *23*, 150–153; b) J. Kim, S. Chang, *Chem. Commun.* **2008**, 3052–3054; c) F. Lang, D. Zewge, I. N. Houpis, R. P. Volante, *Tetrahedron Lett.* **2001**, *42*, 3251–3254; d) N. Xia, M. Taillefer, *Angew. Chem. Int. Ed.* **2009**, *48*, 337–339; e) D. Wang, Q. Cai, K. Ding, *Adv. Synth. Catal.* **2009**, *351*, 1722–1726; f) H. Xu, C. Wolf, *Chem. Commun.* **2009**, 3035–3037; g) L. Jiang, X. Lu, H. Zhang, Y. Jiang, D. Ma, *J. Org. Chem.* **2009**, *74*, 4542–4546; h) Z. Wu, Z. Jiang, D. Wu, H. Xiang, X. Zhou, *Eur. J. Org. Chem.* **2010**, 1854–1857.

[6] Cu-catalyzed *N*-arylation of nitrogen-containing heterocycles in aqueous media or pure water, see: a) L. Liu, M. Frohn, N. Xi, C. Dominguez, R. Hungate, P. J. Reider, *J. Org. Chem.* **2005**, *70*, 10135–10138; b) G. V. Oshovsky, A. Ouali, N. Xia, M. Zablocka, R. T. Boeré, C. Duhayon, M. Taillefer, J. P. Majoral, *Organometallics* **2008**, *27*, 5733–5736; c) J. P. Collman, M. Zhong, L. Zeng, S. Costanzo, *J. Org. Chem.* **2001**, *66*, 1528–1531; d) Y. Wang, Z. Wu, L. Wang, Z. Li, X. Zhou, *Chem. Eur. J.* **2009**, *15*, 8971–8974; e) L. Liang, Z. Li, X. Zhou, *Org. Lett.* **2009**, *11*, 3294–3297.

[7] Cu-catalyzed C–N intramolecular coupling in aqueous media or pure water, see: a) N. Barbero, M. Carril, R. SanMartin, E. Domínguez, *Tetrahedron* **2008**, *64*, 7283–7288; b) M. Carril, R. SanMartin, E. Domínguez, I. Tellitu, *Green Chem.* **2007**, *9*, 219–220; c) L. D. S. Yadav, B. S. Yadav, V. K. Rai, *Synthesis* **2006**, 1868–1872.

[8] Cu-catalyzed *N*-arylation of other amines in aqueous media or pure water, see: a) R. F. Pellón, R. Carrasco, L. Rodés, *Synth. Commun.* **1993**, *23*, 1447–1453; b) H. Rao, H. Fu, Y. Jiang, Y. Zhao, *J. Org. Chem.* **2005**, *70*, 8107–8109; c) X. Zhu, Y. Ma, L. Su, H. Song, G. Chen, D. Liang, Y. Wan, *Synthesis* **2006**, 3955–3962; d) X. Zhu, L. Su, L. Huang, G. Chen, J. Wang, H. Song, Y. Wan, *Eur. J. Org. Chem.* **2009**, 635–642; e) R. F. Pellón, A. Estévez-Braun, M. L. Docampo, A. Martín, A. G. Ravelo, *Synlett* **2005**, 1606–1608; f) Z. Lu, R. J. Twieg, S. D. Huang, *Tetrahedron Lett.* **2003**, *44*, 6289–6292; g) S. Röttger, P. J. R. Sjöberg, M. Larhed, *J. Comb. Chem.* **2007**, *9*, 204–209; h) G. E. Job, S. L. Buchwald, *Org. Lett.* **2002**, *4*, 3703–3706; i) D. Ma, C. Xia, *Org. Lett.* **2001**, *3*, 2583–2586; j) H. Xu, F. Zheng, Y. Liang, Z. Cai, Y. Feng, D. Che, *Tetrahedron Lett.* **2010**, *51*, 669–671; k) Z. Lu, R. J. Twieg, *Tetrahedron Lett.* **2005**, *46*, 2997–3001; l) A. Klapars, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 7421–7428.

[9] a) G. Chen, X. Zhu, J. Cai, Y. Wan, *Synth. Commun.* **2007**, *37*, 1355–1361; b) G. Chen, J. Weng, Z. Zheng, X. Zhu, Y. Cai, J. Cai, Y. Wan, *Eur. J. Org. Chem.* **2008**, 3524–3528.

Received: March 17, 2010