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Report

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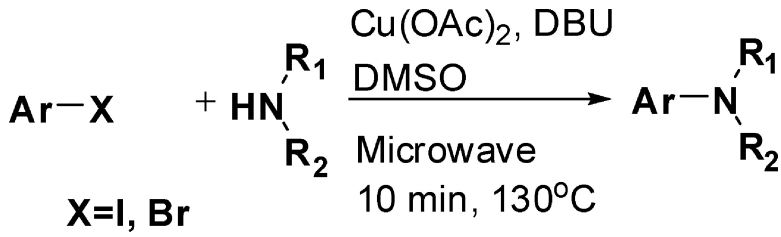

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Introduction

The significance of amination of aryl halides has been manifested by its wide applications in the synthesis of the organically and medicinally interesting building blocks containing the *N*-aryl moiety throughout pharmaceuticals, agrochemicals, natural products, and materials.[1] The state-of-the-art in the area includes the copper-mediated Ullmann coupling[2] and the Buchwald−Hartwig reaction[3] by utilizing the palladium-catalyzed arylation of amines. Although these methods are highly effective, there is still much room for improvement, for example, these methods usually require long reaction times and high reaction temperatures, and moreover some of them suffer from a relatively narrow scope of substrates. Microwave (MW)-assisted organic reactions have been demonstrated as a powerful means in significantly accelerating organic processes including aromatic nucleophilic substitution reactions.[4] Notably, Tu and Meciarova, respectively, reported the construction of arylamines using this technique.[5] Our group also have achieved success by using arylboronic acids and amines as the substrates.[6] However, the described methods are only limited to electron-rich aliphatic amines or imidazole. The electron-deficient nitrogen-containing aromatic heterocycles were found to be less reactive or unreactive.[7]

Herein, we wish to report a novel MW-assisted protocol for the efficient amination of aryl halides with various amines in the presence of $Cu(OAc)_2$. Several distinguished features of the process are deserved to be mentioned: (i) proceeding faster and generally giving good to excellent yields, (ii) using $Cu(OAc)_2$ without requiring any other additives, and more significantly, (iii) a much broader substrate scope: both aromatic and aliphatic amines and various substituted aryl halides can be applied.

Initially, we studied the MW-assisted amination of aryl halides using iodobenzene and imidazole as the model substrates for optimization of the reaction conditions, and the results are summarized in Table 1. No coupling occurred in the absence of the $Cu(OAc)_2$ (entry 1, Table 1), while the addition of 1.0 equiv of $Cu(OAc)_2$ resulted in the formation of the desired coupling product in 77% yield after 10 min of irradiation at 120 °C in the presence of DBU (entry 2, Table 1). Probing of the solvent effect revealed that DMSO was superior to dioxane or DMF (entries 2−4, Table 1). We next examined the effect of base on the coupling reaction. It was found that the nature of bases had a pronounced impact on the process. DBU turned out to be better than NEt_3, while the inorganic base NaOH was ineffective (entries 2, 5 and 6, Table 1). Finally, the increase of the reaction temperature to 130 °C in the presence of 1.0 equiv of $Cu(OAc)_2$ and 2.0 equiv of DBU led to better results (entry 12, Table 1). No gain was observed when the reaction temperature was further increased (entries 13, Table 1). When comparing microwave reactions with conventional preheated oil bath reaction, we observed a sharp decrease in yield (27%) under conventional thermal condition (entries 12, 14, Table 1).

With the optimized conditions in hand, we then examined the generality of the process. As shown in Tables 2 and 3, we were pleased to find that the method was applicable to a broad substrate scope on both aryl halides and amines.

First, the new process was applied to a variety of nitrogen-containing compounds, including aliphatic morpholine, isopropylamine, and aromatic amines imidazole, pyrazole, indole, pyrrole, benzimidazole, and substituted 1,2-dihydropyridin-2-one, with iodo- or bromobenzene. The desired amination products were obtained in moderate to excellent yields (Table 2). Both the aliphatic amines and nitrogen heterocycles were effective in the formation of C−N bond (entries 1−6, and 9−12, Table 2). This coupling reaction is sensitive to steric hindrance. Moderate yields were observed for 2-methylimidazole and 2-isopropylimidazole (entries 7 and 8, Table 2).

The scope of the process with respect to the variation of aryl halides was investigated next (Table 3). The coupling reaction of imidazole, which proved to be a difficult substrate with poor reaction yields,[5] with a vast array of aryl halides containing various electron-donating and -withdrawing substituents were also carried out under the optimal reaction conditions. As shown, the corresponding N-arylation products were obtained in moderate to excellent yields (entries 1−6

Table 1. Optimization of the Catalysis Conditions

entry	solvent	base (equiv)	$Cu(OAc)_2$ (equiv)	temp (°C)	yield (%)[a]
1	DMSO	DBU (1.0)	0.0	120	0
2	DMSO	DBU (1.0)	1.0	120	77
3	dioxane	DBU (1.0)	1.0	120	0
4	DMF	DBU (1.0)	1.0	120	67
5	DMSO	NaOH (1.0)	1.0	120	7
6	DMSO	NEt_3 (1.0)	1.0	120	16
7	DMSO	DBU (1.0)	0.5	120	81
8	DMSO	DBU (1.0)	2.0	120	79
9	DMSO	DBU (0.5)	1.0	120	76
10	DMSO	DBU (2.0)	1.0	120	87
11	DMSO	DBU (3.0)	1.0	120	83
12	DMSO	DBU (2.0)	1.0	130	92
13	DMSO	DBU (2.0)	1.0	140	90
14[b]	DMSO	DBU (2.0)	1.0	130	27

[a] Isolated yield. [b] Cross-coupling under conventional thermal condition.

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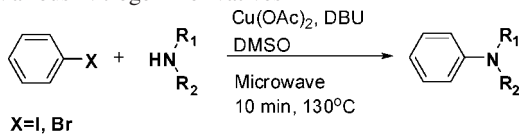
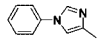
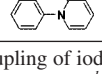
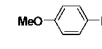
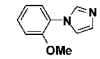
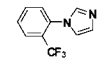
Table 2. Microwave-Assisted Cross-Coupling of Aryl Halides with Various Nitrogen Derivatives



Entry	Amines/ Amides	Product		Yield [%][a]
1			**1**	92[b] 93[c]
2			**2**	90[b] 89[c]
3			**3**	92[b] 91[c]
4			**4**	89[b] 86[c]
5			**5**	91[b] 90[c]
6			**6**	90[b] 91[c]
7			**7**	62[b,d] 53[c,d]
8			**8**	42[b,d] 34[c,d]
9			**9**	87[b] 82[c]
10			**10**	92[b] 93[c]
11			**11**	84[b] 81[c]
12			**12**	93[b,d] 88[c,d]

[a] Isolated yield. [b] Cross-coupling of iodobenzene with amides. [c] Cross-coupling of bromobenzene with amides. [d] Reacted at 150 °C.

Table 3. Microwave-Assisted Cross-Coupling of Imidazole with Different Substituted Aryl Halides

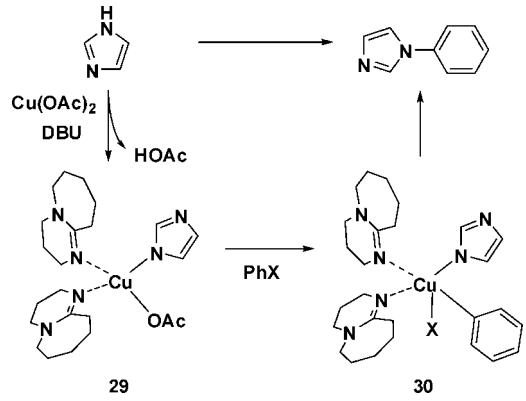
Entry	Aryl halides	Product		Yield [%][a]
1			**3**	92[b] 91[c]
2			**13**	92[b] 87[c]
3			**14**	90
4			**15**	54[d]
5			**16**	94[b] 92[c]
6			**17**	94
7			**18**	trace
8			**19**	91
9			**20**	89
10			**21**	94[b] 92[c]
11			**22**	89
12			**23**	63[e]
13			**24**	80[e]
14			**25**	89
15			**26**	90
16			**27**	92
17			**27**	85
18			**28**	89

[a] Isolated yield. [b] Cross-coupling of iodide with imidazole. [c] Cross-coupling of bromide with imidazole. [d] Reacted at 150 °C for 30 min. [e] Reacted at 150 °C for 10 min.

and 8−18, Table 3). Electronic effects on the reactions were limited. Both electron-rich and electron-poor substituted aryl halides were tolerated (entries 2, 5, 8, and 10, Table 3). However, steric effect is significant. Reactions of para- or meta-substituted aryl halides proceeded in high yields (entries 2, 3, 5, and 6, Table 3), while more steric ortho-substituted ones were not effective. Only a trace of the product was observed when 2-iodobenzotrifluoride was coupled with imidazole (entry 7, Table 3). However, prolonging the reaction time and elevating the reaction temperature led to a significant improvement in reaction yields (entry 4, Table 3). Encouraged by this result, we further investigated the coupling reaction of different heterocyclic halides with imidazole. It was found that pyridyl and pyrimidyl halides worked well, affording the corresponding product in good yields (entries 14 and 15, Table 3). The less-reactive thienyl halides gave rise to moderate yields (entries 12 and 13, Table 3). Coupling reactions of dihalogenated aryl halides with imidazole were also tested, and the chloride showed lower reactivity compared with bromides and iodides. The results indicate the reactivity order of aryl halides: iodides > bromides > chlorides (entries 16−18, Table 3). This selectivity in favor of the monosubstitution product thus allows an active halide site to be retained for further functionalization.

The reaction mechanism may be similar to that postulated for N-arylation with aryl siloxanes or arylboronic acids[8] (Scheme 1). The first step involves the rapid coordination and dissolution of copper (II) acetate by heterocycles, such as imidazole, to form a four-coordination copper complex (intermediate **29**). The second step involves the oxidative addition of the aryl halides to form a five-coordination copper complex (intermediate **30**). Complex **30** can undergo reduc-

Scheme 1. Possible Mechanism of N-Arylation Promoted by Copper(II) Acetate (X = Br, I)



tive elimination to give the C−N cross coupled products. Quantum chemical calculations at the level of B3LYP/LANL2DZ[9] indicate that these two intermediates may stably exist. The detailed results of calculations are presented in the Supporting Information (Tables S1 and S2 and Figures S2 and S3).

In summary, motivated by the deficiency and limitations of the current N-arylation reactions, we have developed a practical, convenient strategy for the preparation of arylamines. The processes are efficiently promoted by readily available $Cu(OAc)_2$ in the presence of DBU in MW irradiation. A variety of amines and aryl halides can participate in the process with good yields. The short reaction times and simple reaction conditions, coupled with a broad substrate scope, render this method particularly attractive for the efficient preparation of biologically and medicinally interesting molecules, and the versatility of this methodology is suitable for library synthesis in drug discovery efforts.

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Supporting Information Available. Detailed experimental procedures and compound characterization data for all products, and quantum chemistry calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) (a) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (b) Chegaev, K.; Lazzarato, L.; Tosco, P.; Cena, C.; Marini, E.; Rolando, B.; Carrupt, P. A.; Fruttero, R.; Gasco, A. *J. Med. Chem.* **2007**, *50*, 1449. (c) Wiglenda, T.; Gust, R. *J. Med. Chem.* **2007**, *50*, 1475.

(2) (a) Rao, H.-H.; Jin, Y.; Fu, H.; Jiang, Y.-Y.; Zhao, Y.-F. *Chem.—Eur. J.* **2006**, *12*, 3636. (b) Altman, R. A.; Buchwald, S. L. *Org. Lett.* **2006**, *8*, 2779. (c) Taillefer, M.; Xia, N.; Ouali, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 934. (d) Correa, A.; Bolm, C. *Angew. Chem., Int. Ed.* **2007**, *46*, 8862.

(3) (a) Klapars, A.; Huang, X.-H.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421. (b) Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2002**, 581. (c) Shen, Q.-L.; Shekhar, S.; Stambuli, J. P.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2005**, *44*, 1371. (d) Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4120. (e) Anderson, K. W.; Tundel, R. E.; Ikawa, T.; Altman, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 6523. (f) Shafir, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 8742. (g) Shen, Q.-L.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 7734. (h) Surry, D. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 10354.

(4) (a) Shore, G.; Morin, S.; Organ, M. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2761. (b) Santra, S.; Andreana, P. R. *Org. Lett.* **2007**, *9*, 5035. (c) Fustero, S.; Jimenez, D.; Sanchez-Rosello, M.; Del Pozo, C. *J. Am. Chem. Soc.* **2007**, *129*, 6700. (d) Huang, H.; Liu, H.; Chen, K.-X.; Jiang, H.-L. *J. Comb. Chem.* **2007**, *9*, 197.

(5) (a) Meciarova, M.; Podlesna, J.; Toma, S. *Monatsh. Chem.* **2004**, *135*, 419. (b) Shi, L.; Wang, M.; Fan, C.-A.; Zhang, F.-M.; Tu, Y.-Q. *Org. Lett.* **2003**, *5*, 3515.

(6) Chen, S.-Y.; Huang, H.; Liu, X.-J.; Shen, J.-K.; Jiang, H.-L.; Liu, H. *J. Comb. Chem*. **2008**, *10*, 358.

(7) For recent progress in Cu-catalyzed *N*-arylation of nitrogen-containing heterocycles with aryl halides, please see: (a) Huang, Y.-Z.; Gao, J.; Ma, H.; Miao, H.; Xu, J. *Tetrahedron Lett.* **2008**, *49*, 948. (b) Zhu, L.-B.; Guo, P.; Li, G. C.; Lan, J.-B.; Xie, R.-G.; You, J.-S. *J. Org. Chem.* **2007**, *72*, 8535. (c) Verma, A. K.; Singh, J.; Sankar, V. K.; Chaudhary, R.; Chandra, R. *Tetrahedron Lett.* **2007**, *48*, 4207. (d) Zhu, L.-B.; Cheng, L.; Zhang, Y.-X.; Xie, R.-G.; You, J.-S. *J. Org. Chem.* **2007**, *72*, 2737. (e) Chang, J. W. W.; Xu, X.-H.; Chan, P. W. H. *Tetrahedron Lett.* **2007**, *48*, 245. (f) Kantam, M. L.; Rao, B. P. C.; Choudary, B. M.; Reddy, R. S. *Synlett* **2006**, *14*, 2195.

(8) (a) Lam, P. Y. S.; Deudon, S.; Averill, K. M.; Li, R.; He, M.; DeShong, P.; Clark, C. G. *J. Am. Chem. Soc.* **2000**, *122*, 31–7600. (b) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Averill, K.; Chan, D. M. T.; Combs, A. P. *Synlett* **2000**, 674.

(9) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B.* **1988**, *37*, 785.

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