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Efficient Iron-Catalyzed N-Arylation of Aryl Halides with Amines

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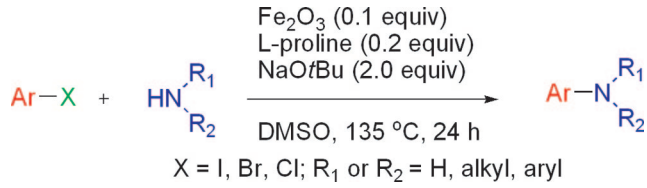
ABSTRACT



A practical and promising protocol was developed for N-arylations of various amines with differently substituted aryl halides. The processes are efficiently promoted by the catalyst system involving the environmentally benign Fe_2O_3 and the universal ligand L-proline. The versatility, convenient operation, low cost, and environmental friendliness, in combination with the high yields, render this method viable for use in both laboratory research and larger industrial scales.

Transition-metal-catalyzed amination of aryl halides is considered to be an important strategy that finds wide applications in the synthesis of many substances such as drugs, materials, natural products, agrochemicals, and optical devices.[1] Typically, C−N bonds are formed by copper-mediated[2] Ullmann reaction and palladium-catalyzed[3] Buchwald−Hartwig reaction. Although significant progress has been made with regard to C−N bond formation, there continues to be an increasing demand for low-cost and environment-friendly catalysts. In the past decade, efforts have been made to develop catalytic systems that are inexpensive and environmentally safe. Taillefer and co-workers reported an economically competitive system that enabled N-arylation reactions by iron−copper cooperative catalysis.[4] Recently, Bolm et al. reported the first genuine iron-catalyzed N-arylation of N-nucleophiles.[5] Although these results are encouraging, there is considerable room for improvement. For example, the above-mentioned methods

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(1) For general reviews, see: (a) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337. (b) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318. (c) Corbert; J. P.; Mignani, G. *Chem. Rev* **2006**, *106*, 2651. (d) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400.

(2) For representative papers on the copper mediated C−N cross coupling reactions, see: (a) Zhang, H.; Cai, Q.; Ma, D. W. *J. Org. Chem.* **2005**, *70*, 5165. (b) Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581. (c) Quach, T. D.; Batey, R. A. *Org. Lett.* **2003**, *5*, 4397. (d) Jiang, D. S.; Fu, H.; Jiang, Y. Y.; Zhao, Y. F. *J. Org. Chem.* **2007**, *72*, 672. (e) Cristau, H. J.; Cellier, P. P.; Spindler, J. F.; Taillefer, M. *Chem.−Eur. J.* **2004**, *10*, 5607. (f) Taillefer, M.; Ouali, A.; Renard, B.; Spindler, J. F. *Chem.−Eur. J.* **2006**, *12*, 5301. (g) Martin, R.; Larsen, C. H.; Cuenca, A.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 3379.

(3) For representative papers on the palladium-catalyzed C−N cross coupling reactions, see: (a) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046. (b) Barluenga, J.; Aznar, F.; Valés, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 343. (c) Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 7240. (d) Buchwald, S. L.; Mauger, C.; Mignani, G.; Scholz, U. *Adv. Synth. Catal.* **2006**, *348*, 23. (e) Anderson, K. W.; Tundel, R. E.; Ikawa, T.; Altman, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed* **2006**, *45*, 6523. (f) Shen, Q. L.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 7734.

(4) Taillefer, M.; Xia, N.; Oualli, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 934.

(5) (a) Correa, A.; Bolm, C. *Angew. Chem., Int. Ed.* **2007**, *46*, 8862. (b) Correa, A.; Elmore, S.; Bolm, C. *Chem.−Eur. J.* **2008**, *14*, 3527.

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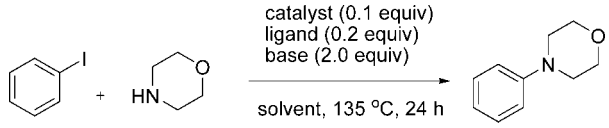
Table 1. Optimization of the Catalysis Conditions



entry	catalyst	ligand	base	solvent	yield (%)
1	–	–	NaO*t*Bu	DMSO	53
2	–	L-proline	NaO*t*Bu	DMSO	52
3	$FeCl_3$	L-proline	NaO*t*Bu	DMSO	77
4	$Fe(ClO_4)_2{\cdot}6H_2O$	L-proline	NaO*t*Bu	DMSO	67
5	Fe_2O_3	L-proline	NaO*t*Bu	DMSO	85
6	Fe_2O_3	DMEDA	NaO*t*Bu	DMSO	52
7	Fe_2O_3	TMEDA	NaO*t*Bu	DMSO	66
8	Fe_2O_3	TMHD	NaO*t*Bu	DMSO	75
9	Fe_2O_3	L-proline	NaO*t*Bu	DMF	trace
10	Fe_2O_3	L-proline	NaO*t*Bu	toluene	0
11	Fe_2O_3	L-proline	NaO*t*Bu	dioxane	0
12	Fe_2O_3	L-proline	Cs_2CO_3	DMSO	0
13	Fe_2O_3	L-proline	K_3PO_4	DMSO	trace
14	Fe_2O_3	L-proline	DBU	DMSO	0
15	Fe_2O_3	L-proline	KOH	DMSO	0
16[a]	Fe_2O_3	L-proline	NaO*t*Bu	DMSO	51

[a] Performed under microwave, 160 °C, 30 min.

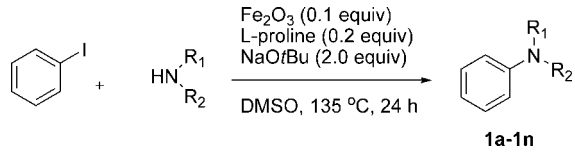
are limited in terms of the substrates for which they can be used; in particular, they are ineffective for aniline and alkylamine derivatives. Therefore, iron-catalyzed C−N cross-coupling reactions need to be modified to expand the scope of these methods and to employ more universal ligands. In this study, we wish to report efficient Fe_2O_3-catalyzed N-arylation of aryl halides with various amines using L-proline as the ligand. In comparison to currently existing methods of the C−N bond formation, our proposed approach has several distinguishing features that are worth mentioning: (i) the approach employs an environment-friendly and economically competitive catalytic system that is a combination of readily available iron salts and an universal ligand; (ii) the approach offers experimental simplicity and can be performed without the need for protection from air or moisture; (iii) in this approach, a broader scope of substrates, both aliphatic and aromatic amines and various substituted aryl halides, can be applied.

Initially, we carried out a set of experiments using iodobenzene (1.5 equiv) and morpholine (1.0 equiv) as model substrates for optimizing the reaction conditions, and the results are summarized in Table 1. Only a moderate amount of the expected product was formed without the iron source (Table 1, entries 1 and 2). However, the product was obtained in 77% yield when $FeCl_3$ and L-proline were used as the catalyst and ligand in DMSO, respectively, at 135 °C. Next, we screened the iron sources, and preliminary results showed that iron salts such as Fe_2O_3 and $Fe(ClO_4)_2{\cdot}6H_2O$ were also effective when L-proline was used as the ligand (Table 1, entries 4 and 5). The most efficient and air-stable Fe_2O_3 was selected to examine the effect of the ligands. Attempts to use DMEDA (*N*,*N*′-dimethylethylenediamine), TMEDA (*N*,*N*,*N*′,*N*′-tetramethylethylenediamine), and TMHD (2,2,6,6-tetramethyl-3,5-heptanedione) resulted in low yields (Table 1, entries 6−8). Next, we probed the solvent effect and found that DMSO was considerably superior to dioxane, toluene, or DMF (Table 1, entries 9−11). Finally, we found that the nature of the bases had a pronounced impact on the process. Cs_2CO_3, K_3PO_4, DBU, and KOH were all ineffective (Table 1, entries 12−15). We compared the conventional preheated oil bath reaction with microwave reactions, and we found that the yield decreased in the latter case (Table 1, entries 5 and 16). In summary, the optimum results were obtained when amine (1.0 equiv) and aryl halide (1.5 equiv) were allowed to react with Fe_2O_3 (0.1 equiv), L-proline (0.2 equiv), and NaO*t*Bu (2.0 equiv) stirred in DMSO at 135 °C for 24 h.

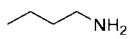
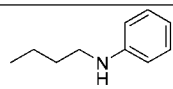
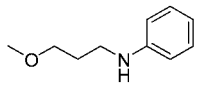
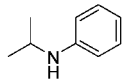
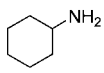
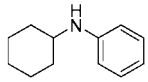
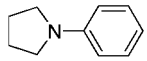
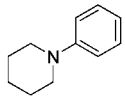
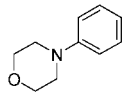
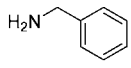
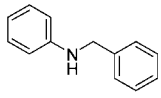
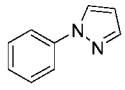
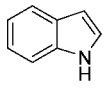
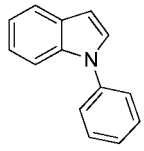
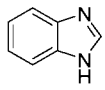
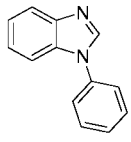
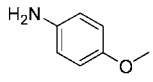
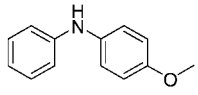
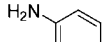
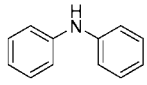
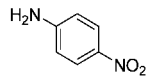
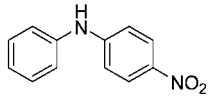
Having determined the optimized conditions, we examined the scope of the process with respect to amine substrates. We applied the new process to a variety of nitrogen-containing compounds including aliphatic primary amines, aliphatic secondary amines, benzylamine, anilines, and nitrogen heterocycles with iodobenzene. The desired amination products were obtained in moderate to good yields (Table 2). We noticed that all primary amines worked well, affording the corresponding coupling product in good yields (Table 2, entries 1−4). The steric hindrance of the secondary amines often makes them more sluggish than primary amines toward coupling with aryl halides. Remarkably, we found that aliphatic secondary amines also worked well (Table 2, entries 5−7). Although satisfactory results were obtained in the case of primary amines, poor coupling yields were obtained for benzylamine (Table 2, entry 8). Moderate yields were observed for nitrogen heterocycles such as pyrazole, indole, and benzoimidazole (Table 2, entries 9−11). As shown, anilines containing an electron-withdrawing group typically afforded lower yields than anilines and those containing an electron-donating group (Table 2, entries 12−14).

We then investigated the scope of the process with respect to aryl halides (Table 3). We tested a variety of substituted aryl halides under the optimized reaction conditions with morpholine as the model amine. As expected, the corresponding N-arylation products were obtained in moderate to excellent yields. Aryl iodides and aryl bromides were more reactive than aryl chlorides and gave the corresponding N-arylated products in higher yields. The coupling reactions of dihalogenated aryl halides with morpholine were also tested, and the chlorides showed lower reactivity as compared with the bromides and iodides. The results indicate the reactivity order of aryl halides: iodides > bromides ≫ chlorides (Table 3; entries 1, 10, and 11). In general, no significant electronic effects were observed for the electron-rich and electron-poor substituted aryl halides (Table 3; entries 2, 5, 8, and 10). However, the steric effect was significant. The reactions of *para*- or *meta*-substituted aryl halides afforded higher yields (Table 3; entries 2, 3, 5, 6, and 9), while more steric *ortho*-substituted aryl halides were less reactive. Only a trace of the product was observed when 2-iodobenzotrifluoride was coupled with morpholine (Table 3; entries 4 and 7). Furthermore, we investigated the coupling

Table 2. Fe_2O_3/L-Proline-Catalyzed N-Arylation of Aryl Iodide with Various Nitrogen Derivatives

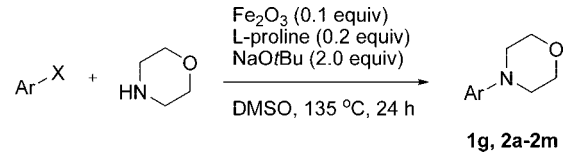


1a-1n

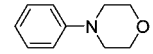
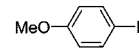
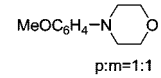
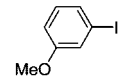
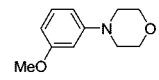
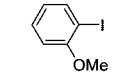
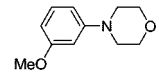
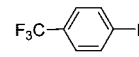
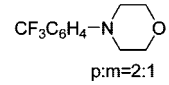
entry	amines	product		yield [%]
1			**1a**	72 41[a]
2			**1b**	70
3			**1c**	83
4			**1d**	86
5			**1e**	90 59[a]
6			**1f**	75
7			**1g**	85
8			**1h**	51
9			**1i**	67 39[a]
10			**1j**	55
11			**1k**	49
12			**1l**	54 18[a]
13			**1m**	33
14			**1n**	trace

[a] Performed without Fe_2O_3 and L-proline.

Table 3. Fe_2O_3/L-Proline-Catalyzed N-Arylation of Morpholine with Different Substituted Aryl Halides



1g, 2a-2m

entry	aryl halides	product		yield [%]
1			**1g**	85 (X=I) 82 (X=Br) 51 (X=Cl)
2		 p:m=1:1	**2a (p)** **2b (m)**	73 45[a]
3			**2b**	75 43[a]
4			**2b**	33
5		 p:m=2:1	**2c (p)** **2d (m)**	84
6			**2d**	59
7			**2e**	Trace
8		m:p=1:1	**2f (p)** **2g (m)**	66
9		m:p=4:1	**2f (p)** **2g (m)**	72
10		p:m=2:1	**2h (p)** **2i (m)**	83 49[a]
11		p:m=2:1	**2h (p)** **2i (m)**	81
12		(3-):(4-)=1:1	**2j (3-)** **2k(4-)**	70
13			**2l**	93（X=I） 92（X=Br）
14			**2m**	81 48[a]

[a] Performed without Fe_2O_3 and L-proline.

reaction of heterocyclic halides with morpholine. We found that pyridyl halides worked well, affording the amination products in excellent yields (Table 3; entries 12−14). In addition, we performed several experiments to determine whether the yields were due to background reaction or Fe catalysis. The results of key examples showed that the

catalyst system involving Fe_2O_3 and L-proline was effective. Without the Fe catalyst and ligand, these reactions afford products only in moderate or low yields (Table 2; entries 1, 5, 9, and 12; Table 3; entries 2, 3, 10, and 14).

As shown in Table 3, the cine substitution[6] effects were obvious. The *para*-substituted aryl halides with a group such as OMe, CF_3, Me, or Cl provided a mixture of *meta*- and *para*-amination products via a benzyne intermediate (Table 3; entries 2, 5, and 8−11). Further, *ortho*-methoxy phenyl iodide only yielded the *meta*-amination product, possibly because the steric effects of the methoxy group of the benzyne intermediate resulted in a less sterically hindered *meta*-attack of the nucleophilic amines[6b] (Table 3, entry 4). However, in the case of *meta*-substituted aryl halides, we found that the cine substitution effects on the reactions were limited (Table 3; entries 3, 6, and 9). Moreover, 3-iodopyridine also afforded 3- and 4-substituted amination products (Table 3, entry 12). However, all the 2-substituted pyridyl halides afforded only the corresponding amination products (Table 3, entries 13 and 14).

(6) For representative papers on the cine substitution effects, see: (a) Chapman, O. L.; Mattes, K.; McIntosh, C. L.; Pacansky, J.; Calder, G. V.; Orr, G. *J. Am. Chem. Soc.* **1973**, *95*, 6134. (b) Shi, L.; Wang, M.; Fan, C.-A.; Zhang, F.-M.; Tu, Y.-Q *Org. Lett.* **2003**, *5*, 3515. (c) Fujita, M.; Kim, W. H.; Sakanishi, Y.; Fujiwara, K.; Hirayama, S.; Okuyama, T.; Ohki, Y.; Tatsumi, K.; Yoshioka, Y. *J. Am. Chem. Soc.* **2004**, *126*, 7548.

In summary, we developed a practical and promising protocol for the N-arylation of various amines with differently substituted aryl halides. The processes are efficiently promoted by a catalyst system that is a combination of a cheap and environment-friendly Fe_2O_3 and the universal ligand L-proline. The versatility, convenient operation, low cost, and environmental friendliness of this method, in addition to the high yields it provides, make it viable for use both in laboratory research and in larger industrial scales. Currently, we are exploring the scope and application of the proposed iron-catalyzed N-arylation with regard to the synthesis of pharmaceutical molecules.

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Supporting Information Available: Full experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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