

Iron-Catalyzed N-Arylation of Nitrogen Nucleophiles**

Arkaitz Correa and Carsten Bolm*

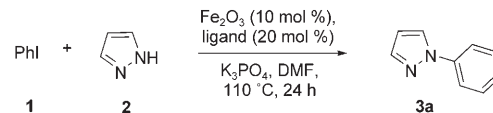
Transition-metal-catalyzed cross-coupling reactions for the formation of carbon–carbon and carbon–heteroatom bonds form the basis of essential and powerful strategies for the preparation of important compounds in biological, pharmaceutical, and materials sciences.^[1] Among C–N bond-forming processes, the N-arylation of nitrogen-containing heterocycles is of particular interest, as the resulting products contain important structural motifs of numerous natural products and biologically active compounds. Despite the significant progress made in the development of palladium- and copper-catalyzed coupling reactions of this type,^[2] there is still a need for new methods that involve cheap and environmentally friendly catalysts.

Since the pioneering work of Tamura and Kochi,^[3] iron salts have emerged as alternative and promising catalysts for many organic transformations, in particular for C–C bond-forming reactions.^[4–6] These methods are distinguished by the low cost, readily availability, and environmentally benign character of the iron salts used, in combination with the exceptionally high reaction rates observed and mild reaction conditions. Encouraged by these results, we envisaged the application of iron catalysts in the N-arylation of nitrogen nucleophiles with aryl halides.

Recently, Taillefer et al. reported efficient Fe/Cu cooperative catalysis in the assembly of *N*-aryl heterocycles by C–N bond formation,^[7] and Wakharkar and co-workers described the N-arylation of various amines with aryl halides in the presence of Cu–Fe hydrotalcite.^[8] Although these results are encouraging, a major drawback is the required presence of copper salts. Furthermore, a very high catalyst loading (30 mol % of [Fe(acac)₃] and 10 mol % of CuO) proved essential in the former procedure. Herein, we report the first genuinely iron-catalyzed N-arylation of N-nucleophiles in which simple aryl halides are used as electrophilic coupling partners. The catalyst system, which is obtained by combining readily available iron salts with chelating diamine derivatives,^[9] is widely applicable and promotes the N-arylation of both primary amides and a variety of N-heterocycles, such as pyrazole, pyrrolidin-2-one, indole, and 7-azaindole.

For initial optimization of the reaction conditions and the identification of the best iron source, ligand, base, and solvent, iodobenzene (**1**) and 1*H*-pyrazole (**2**) were chosen as model substrates. We tested amino acids, amino alcohols, 1,2-diamines, and phosphines as ligands in the presence of Fe₂O₃ (10 mol %) in DMF at 110 °C and found, to our delight, that the cross-coupling reaction was possible and provided the desired product **3a** in low but promising yields, when either L-proline (Table 1, entry 2) or diamine ligands (Table 1, entries 4 and 5) were employed. Control experiments confirmed that in the absence of either the ligand or the iron oxide no product was obtained.^[10] As dmeda proved to be the most effective ligand, further experiments were focused on its use as an iron chelator.

Table 1: Screening of ligands for the N-arylation of pyrazole (**2**).

		
Entry	Ligand ^[a]	Yield [%] ^[b]
1	none	0
2	L-proline	35
3	L-alaninol	0
4	<i>trans</i> -1,2-diaminocyclohexane	31
5	dmeda	52
6	tmeda	trace
7	<i>rac</i> -binap	0

[a] dmeda = *N,N'*-dimethylethylenediamine, tmeda = *N,N,N',N'*-tetramethylethylenediamine, binap = 2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl. [b] Yield of the isolated product after flash chromatography. DMF = *N,N*-dimethylformamide.

By screening a wide range of iron sources, we found that the *N*-arylated product **3a** could be obtained in yields ranging from 14 to 85 % with dmeda and a catalytic amount of an iron salt (10 mol %) in any oxidation state (0, II, or III; Table 2).^[11] The outcome of the reaction was dependent on the nature of the solvent and on the temperature. Thus, much better results were obtained when the reaction was carried out in toluene at 135 °C (Table 2, method B) than with DMF at 110 °C (Table 2, method A).^[12] Among the iron sources, Fe(ClO₄)₂ and FeCl₃ led to the best catalysts and afforded in both cases coupling product **3a** in 80 % yield (Table 2, entries 4 and 9, respectively). FeCl₃ was chosen for further investigations as it is less expensive and easier to handle than Fe(ClO₄)₂. With respect to the catalyst loading, 10 mol % of the iron salt was found to be optimal. When only 5 mol % of the iron salt were used, **3a** was formed in lower yield (56 %, Table 2, entry 10), and no significant improvement was observed with 20 mol % of the iron salt (85 %, Table 2, entry 11). In summary, the optimal

[*] Dr. A. Correa, Prof. Dr. C. Bolm
Institut für Organische Chemie
Rheinisch-Westfälische Technische Hochschule Aachen
Landoltweg 1, 52056 Aachen (Germany)
Fax: (+49) 241-809-2391
E-mail: carsten.bolm@oc.rwth-aachen.de

[**] We are grateful for financial support from the Fonds der Chemischen Industrie. A.C. thanks the Basque Government for support through the "Programa de Perfeccionamiento de Doctores en el extranjero del Departamento de Educación, Universidades e Investigación".

Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

Table 2: Screening of iron sources for the N-arylation of pyrazole (**2**).

$\text{PhI} + \text{2} \xrightarrow[\text{K}_3\text{PO}_4, \text{ solvent, temp., 24 h}]{[\text{Fe}] / \text{dmeda}} \text{3a}$			
Entry	Fe source (10 mol %)	Method ^[a]	Yield [%] ^[b]
1	none	A	0
		B	0
2	Fe	A	14
		B	50
3	FeCl ₂ ·4 H ₂ O	A	32
		B	61
4	Fe(ClO ₄) ₂	A	57
		B	80
5	[Fe(acac) ₂]	A	44
		B	48
6	Fe(oxalate) ₂ ·2 H ₂ O	A	44
		B	29
7	Fe ₂ O ₃	A	52
		B	70
8	[Fe(acac) ₃]	A	28
		B	62
9	FeCl ₃	A	32
		B	80
10	FeCl ₃	B ^[c]	56
11	FeCl ₃	B ^[d]	85

[a] Method A: **1** (1.5 equiv), **2** (1.0 equiv), dmeda (20 mol %), K₃PO₄ (2.0 equiv), DMF, 110°C; method B: as for method A but with toluene instead of DMF at 135°C. [b] Yield of the isolated product after flash chromatography. [c] FeCl₃: 5 mol %; dmeda: 10 mol %. [d] FeCl₃: 20 mol %; dmeda: 30 mol %. acac = acetylacetonate.

conditions for the iron-catalyzed N-arylation involved a combination of FeCl₃ (10 mol %), dmeda (20 mol %), K₃PO₄ (2 equiv), and toluene at 135°C (Table 2, entry 9).^[13] Furthermore, it is noteworthy that the cross-coupling process proved to be tolerant to water, as evidenced by the fact that product **3a** was obtained in a remarkable 70 % yield when the reaction was carried out in a mixture of toluene and water (1:1).

Encouraged by these results, we next investigated the scope of the process with respect to the aryl halide substrate. We tested a variety of substituted aryl iodides and bromides under the optimized reaction conditions with pyrazole (**2**) as the nucleophilic counterpart. In general, aryl iodides were more reactive than aryl bromides and gave the corresponding N-arylated products in higher yields (up to 87 %). With neither substrate type were side products observed. Furthermore, the coupling proceeded selectively at the carbon atom with the iodo substituent when chloro or fluoro substituents were also present (Table 3, entries 3, 5, 8, and 9). *Ortho* substituents hampered the reaction and led to the formation of the products in lower yields (Table 3, entries 2 and 3).

Other heterocycles, such as indole (Table 4, entry 1) and 7-azaindole, (Table 4, entries 2 and 3) were found to be effective N-nucleophiles. The corresponding N-phenyl derivatives **4** and **5a,b** were formed in good yields (up to 84 %) in the cross-coupling of aryl iodides with indole and 7-azaindole, respectively. Furthermore, both cyclic and acyclic amide derivatives (Table 4, entries 4–6 and 7–9, respectively) underwent the desired reaction to furnish the coupling products

Table 3: FeCl₃/dmeda-catalyzed N-arylation of pyrazole (**2**) with aryl iodides and bromides.

$\text{ArX} + \text{2} \xrightarrow[\text{K}_3\text{PO}_4, \text{ toluene, 135}^\circ\text{C, 24 h}]{\text{FeCl}_3 (10 \text{ mol \%}), \text{dmeda} (20 \text{ mol \%})} \text{3a-k}$			
Entry	ArX	Product	Yield [%] ^[a]
1			3a 80
2			3b 41
3			3c 18
4			3d 82
5			3e 87
6			3f 74
7			3g 87
8			3h 46
9			3i 56
10			3a 34
11			3j 39
12			3g 64
13			3k 37

[a] Yield of the isolated product after flash chromatography.

6a–c and **7a–c** in moderate to high yields (up to 97 %). Unfortunately, aromatic and alkyl amines proved to be unsuitable substrates and only trace amounts of the desired products were detected when the reaction was carried out under the standard conditions (Table 4, entries 10 and 11).

In summary, we have developed a novel and promising ligand-assisted iron-catalyzed N-arylation of nitrogen nucleophiles with differently substituted aryl iodides and bromides. The catalyst system consists of a mixture of the inexpensive and environmentally benign compound FeCl₃ and dmeda. This research has established a useful starting point for investigating future applications of iron-catalyzed N-arylation reactions, the efficiency and scope of which are the focus of continuing studies by our research group.

Table 4: FeCl₃/dmeda-catalyzed N-arylation of (aza)indole, pyrrolidin-2-one, and benzamide with aryl iodides.

$\text{R}-\text{C}_6\text{H}_4-\text{I} + \text{NuH} \xrightarrow[\text{K}_3\text{PO}_4, \text{toluene}, 135^\circ\text{C}, 24\text{ h}]{\text{FeCl}_3 (10\text{ mol } \%), \text{dmeda} (20\text{ mol } \%)} \text{R}-\text{C}_6\text{H}_4-\text{Nu} \quad \text{4-9}$					
Entry	NuH	Arl	Product		Yield [%] ^[a]
1				4	60
2				5 a	84
3				5 b	74
4				6 a	53
5				6 b	48
6				6 c	51
7				7 a	78
8				7 b	79
9				7 c	97
10				8	trace
11	BnNH ₂		BnNHPh	9	trace

[a] Yield of the isolated product after flash chromatography.

Experimental Section

Typical procedure: 1H-Pyrazole (**2**; 300 mg, 4.32 mmol), FeCl₃ (70 mg, 0.432 mmol), and K₃PO₄ (1.83 g, 8.64 mmol) were placed in an oven-dried tube, and phenyl iodide (**1**; 0.73 mL, 6.48 mmol) and dmeda (84 µL, 0.864 mmol) were added under an argon atmosphere, followed by dry toluene (4 mL). The tube was sealed under argon, and the mixture was heated to 135 °C and stirred at this temperature for 24 h. The heterogeneous mixture was then cooled to room temperature and diluted with dichloromethane. The resulting solution was filtered directly through a pad of silica gel and concentrated to yield the product, which was purified by chromatography on silica gel (pentane/ethyl acetate 1:1) to yield **3 a** (500 mg, 80 %) as a yellowish oil. The identity and purity of the product was confirmed by ¹H and

¹³C NMR spectroscopic analysis. See the Supporting Information for full details.

Received: July 23, 2007

Published online: October 17, 2007

Keywords: arylation · cross-coupling · diamine ligands · iron catalysis · nitrogen heterocycles

[1] a) A. R. Muci, S. L. Buchwald, *Top. Curr. Chem.* **2002**, 219, 131; b) *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: F. Diederich, A. de Meijere), Wiley-VCH, Weinheim, **2004**; c) J. F. Hartwig, *Synlett* **2006**, 1283.

[2] For reviews, see: a) K. Kunz, U. Scholz, D. Ganzer, *Synlett* **2003**, 2428; b) S. V. Ley, A. W. Thomas, *Angew. Chem.* **2003**, 115, 5558; *Angew. Chem. Int. Ed.* **2003**, 42, 5400; c) I. P. Beletskaya, A. V. Chepurkov, *Coord. Chem. Rev.* **2004**, 248, 2337; d) J.-P. Corbet, G. Mignani, *Chem. Rev.* **2006**, 106, 2651.

[3] a) M. Tamura, J. K. Kochi, *J. Am. Chem. Soc.* **1971**, 93, 1487; b) M. Tamura, J. K. Kochi, *Synthesis* **1971**, 303; c) M. Tamura, J. K. Kochi, *J. Organomet. Chem.* **1971**, 31, 289.

[4] For general reviews, see: a) C. Bolm, J. Legros, J. Le Pailh, L. Zani, *Chem. Rev.* **2004**, 104, 6217; b) A. Fürstner, R. Martin, *Chem. Lett.* **2005**, 34, 624.

[5] For recent contributions on iron catalysis, see: a) A. Fürstner, A. Leitner, M. Méndez, H. Krause, *J. Am. Chem. Soc.* **2002**, 124, 13856; b) A. Fürstner, A. Leitner, *Angew. Chem.* **2002**, 114, 632; *Angew. Chem. Int. Ed.* **2002**, 41, 609; c) B. Scheiper, M. Bonnekessel, H. Krause, A. Fürstner, *J. Org. Chem.* **2004**, 69, 3943; d) R. Martin, A. Fürstner, *Angew. Chem.* **2004**, 116, 4045; *Angew. Chem. Int. Ed.* **2004**, 43, 3955; e) I.

Sapountzis, W. Lin, C. C. Kofink, C. Despotopoulou, P. Knochel, *Angew. Chem.* **2005**, 117, 1682; *Angew. Chem. Int. Ed.* **2005**, 44, 1654; f) C. C. Kofink, B. Blank, S. Pagano, N. Götz, P. Knochel, *Chem. Commun.* **2007**, 1954; g) G. Anilkumar, B. Bitterlich, F. G. Gelalcha, M. K. Tse, M. Beller, *Chem. Commun.* **2007**, 289; h) K. Komeyama, T. Morimoto, K. Takaki, *Angew. Chem.* **2006**, 118, 3004; *Angew. Chem. Int. Ed.* **2006**, 45, 2938; i) K. Komeyama, Y. Mieno, S. Yukawa, T. Morimoto, K. Takaki, *Chem. Lett.* **2007**, 36, 752; j) B. Plietker, *Angew. Chem.* **2006**, 118, 6200; *Angew. Chem. Int. Ed.* **2006**, 45, 6053; k) J. Kischel, I. Jovel, K. Metins, A. Zapf, M. Beller, *Org. Lett.* **2006**, 8, 19; l) H. Egami, T. Katsuki, *J. Am. Chem. Soc.* **2007**, 129, 8940.

[6] For selected iron-catalyzed reactions reported by our research group, see: a) J. Legros, C. Bolm, *Angew. Chem.* **2003**, 115, 5645;

- Angew. Chem. Int. Ed.* **2003**, *42*, 5487; b) J. Legros, C. Bolm, *Angew. Chem.* **2004**, *116*, 4321; *Angew. Chem. Int. Ed.* **2004**, *43*, 4225; c) J. Legros, C. Bolm, *Chem. Eur. J.* **2005**, *11*, 1086; d) O. G. Mancheño, C. Bolm, *Org. Lett.* **2006**, *8*, 2349; e) M. Nakanishi, C. Bolm, *Adv. Synth. Catal.* **2007**, *349*, 861.
- [7] M. Taillefer, N. Xia, A. Oualli, *Angew. Chem.* **2007**, *119*, 952; *Angew. Chem. Int. Ed.* **2007**, *46*, 934.
- [8] V. H. Jadhav, D. K. Dumbre, V. B. Phapale, H. B. Borate, R. D. Wakharkar, *Catal. Commun.* **2007**, *8*, 65.
- [9] For an Fe-catalyzed asymmetric epoxidation of aromatic alkenes in which a related catalyst system formed by combining $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$, a chiral diamine, and pyridine-2,6-dicarboxylic acid was used, see: F. G. Gelalcha, B. Bitterlich, G. Anilkumar, M. K. Tse, M. Beller, *Angew. Chem.* **2007**, *119*, 7431; *Angew. Chem. Int. Ed.* **2007**, *46*, 7293.
- [10] Product **3a** was not detected in the absence of a ligand even when a stoichiometric amount of Fe_2O_3 was used.
- [11] The use of other iron sources, such as $\text{Fe}(\text{ClO}_4)_3$, $\text{Fe}(\text{OTf})_2$, or FeCl_2 , led to only trace amounts of *N*-phenyl pyrazole (**3a**).
- [12] An increase in the temperature from 110 to 135 °C in method A resulted in lower yields of **3a** than those observed with method B.
- [13] When other bases (NaOtBu , Cs_2CO_3 , K_2CO_3) were used, or when dioxane was used as the solvent, the *N*-phenyl derivative was obtained in lower yields. All the experiments were carried out with anhydrous FeCl_3 (purity > 98%) provided by Merck.