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# **Efficient Cross-Coupling Reactions of Nitrogen Nucleophiles with Aryl Halides in Water**

Yong-Chua Teo<sup>a,\*</sup>

<sup>a</sup> Natural Sciences and Science Education, National Institute of Education, Nanyang Technological University, 1 Nanyang Walk, Singapore 637616
 Fax: (+65)-6896-9414; phone: (+65)-6790-3846; e-mail: yongchua.teo@nie.edu.sg

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**Abstract:** A facile and practical strategy has been developed for the *N*-arylation of nitrogen nucleophiles with aryl halides catalyzed by a combination of iron(III) chloride [FeCl<sub>3</sub>] and dimethylethylenediamine (dmeda) in water. A variety of nitrogen nucleophiles including pyrazole, indole, 7-azaindole and benzamide afforded the *N*-arylated products in the presence of the catalytic system (in up to 88% yield).

**Keywords:** arylation; cross-coupling; heterogeneous catalysis; iron; water

The transition metal-catalyzed formation of carbon/ heteratom bonds has recently experienced a renaissance in chemical synthesis and emerged as a versatile tool for the synthesis of important intermediates in the pharmaceutical and fine chemical industries.<sup>[1]</sup> In particular, the N-arylation of nitrogen heterocycles with aryl halides has acquired a major role due to the versatility of the products, which are prevalent building blocks for the construction of many natural products and medicinal agents. The vast majority of the existing protocols for performing this type of transformation has been mediated by palladium and copper metal catalysts.<sup>[2]</sup> Recently, the use of iron salts to perform established transition metal-catalyzed coupling reactions has also emerged as an alternative and promising strategy<sup>[3,4]</sup> following the pioneering work by Tamura and Kochi.<sup>[5]</sup> Iron salts are inexpensive, relatively less toxic and, in consequence more environmentally benign in comparison to other transition metals.

Organic reactions in water have recently attracted much attention too, not only because unique reactivity is often observed in water but also due to its low cost, safety and environmentally benign nature which avoids the problems of pollution that are inherent with organic solvents.<sup>[6]</sup> The synthesis of organic molecules via reactions in water is an extensively investigated topic which entails the additional challenges of water tolerance for the catalyst<sup>[7]</sup> and the associated problem of substrate solubilities and reactivities. In this aspect, the development of direct metal-catalyzed coupling reactions that utilize less expensive and more sustainable catalysts in water remains an elusive goal in modern synthetic chemistry. The majority of recent strategies for the transition metal-mediated coupling reactions in aqueous media has been promoted either by palladium or copper metal catalysts.<sup>[8]</sup> To the best of our knowledge, the utilization of iron catalysts for coupling reactions in water has yet to be reported. In this paper, we disclose the first N-arylation of nitrogen heterocycles with aryl halides catalyzed by a combination of readily available FeCl<sub>3</sub> with chelating diamine derivatives in water.

The iron-catalyzed N-arylation of nitrogen nucleophiles attracted our attention because of our endeavours towards the development of environmentally friendly protocols and the need for a more versatile and operational simple catalytic system for this important process which avoids the use of organic solvents and stringent inert conditions for the reaction. In our initial study, the reaction between iodobenzene 1 and 1*H*-pyrazole **2** was chosen as model for the coupling reaction in water. A series of experiments was carried out to evaluate the ability of various ligands and iron sources for the N-arylation process. The standardized protocol was carried out using 1H-pyrazole (1 equiv.), iodobenzene (1.5 equiv.), iron source (20 mol%), ligand (40 mol%), tripotassium phosphate monohydrate K<sub>3</sub>PO<sub>4</sub>·H<sub>2</sub>O (2 equiv.) in water at 125°C for 24 h. The optimization results are shown in Table 1.

Investigation into the ligand system revealed that the reaction proceeded in a biphasic system with the best yield achieved when the reaction was carried out using a combination of FeCl<sub>3</sub> and N,N'-dimethylethy-

**Table 1.** Screening of various ligands and iron sources for the *N*-arylation of pyrazole 2 in water.<sup>[a]</sup>



<sup>[a]</sup> Unless otherwise noted, the reaction was carried out with 1*H*-pyrazole (2.16 mmol), iodobenzene (3.24 mmol), K<sub>3</sub>PO<sub>4</sub>·H<sub>2</sub>O (4.32 mmol), Fe source (20 mol%), ligand (40 mol%) in water (1.5 mL) at 125 °C for 24 h.

<sup>[b]</sup> Isolated yield after column chromatography.

[c] The reaction was performed with Fe source (10 mol%) and L4 (20 mol%) in water (1.5 mL) at 125 °C for 36 h.

lenediamine (dmeda) L4 (Table 1, entry 4). Moderate yield was also achieved when trans-1,2-diaminocyclohexane L3 (Table 1, entry 3) was employed as the assisting ligand. However, only a trace amount of the product was detected in both cases of L-proline L1 and N, N, N', N'-tetramethylethylene diamine (tmeda) L5 as ligands (Table 1, entries 1 and 5). It is worthy of note that the reaction was found to proceed with good yield when the amount of FeCl<sub>3</sub> was reduced to 10 mol% albeit with extended reaction times (Table 1, entry 6). Control experiments were also carried out to confirm that no product was obtained in the absence of either the ligand or iron source (Table 1, entries 7 and 8). With this encouraging result, we proceed to screen the efficiency of the various iron sources for the N-arylation process using 10 mol% iron catalyst loading and 20 mol% dmeda L4 in water. Among them, the reaction catalyzed by either FeCl<sub>3</sub> or  $Fe(ClO_4)_2$  in combination with L4 afforded the N-arylated products in good yields of 76% and 74%, respectively (Table 1, entries 6 and 9). Conversely, the employment of [Fe(acac)<sub>2</sub>], Fe(oxalate)·2H<sub>2</sub>O and Fe<sub>2</sub>O<sub>3</sub> as the iron source afforded the products in lower yields of 64%, 52% and 41%, respectively (Table 1, entries 11 and 12). In summary, the optimal conditions for the *N*-arylation process in water consist of the combination of FeCl<sub>3</sub> (10 mol%), dmeda **L4** (20 mol%) and K<sub>3</sub>PO<sub>4</sub>·H<sub>2</sub>O (2 equiv.) at 125 °C for 36 h.

With a set of optimized conditions in hand, a study was initiated to explore the scope of the aryl halides in the N-H arylation process. We carried out the reactions using 1*H*-pyrazole as the nitrogen nucleophile and a variety of substituted aryl iodides and bromides under the optimized reaction conditions. The results obtained are shown in Table 2.

In general, the reaction of 1*H*-pyrazole with aryl iodides provided much superior yields than those with aryl bromides employed as arylating agents. The steric effect of ortho-substituents on the aryl iodides was highly significant as the reactions led to lower yields of the arylated products regardless of the electronic nature of the substituents (Table 2, entries 2 and 3). In this context, the protocol was limited only to sterically unhindered aryl halides. The reaction was highly chemoselective, reacting only between the carbon atom and the iodine substituent even in the presence of other halogen substituents (Table 2, entries 3, 5, 7, 8 and 9). The reaction occurs only at the iodo substituent when 4-fluoro-, 4-chloro- and 4-bromoiodobenzene were used as the electrophilic counterparts. Moreover, the system was also efficient when substituted 3-methylpyrazole was used as the nucleophilic counterpart, affording the arylated product in a good yield of 73% (entry 13). It is worthy of note that the reaction was operationally simple and convenient to carry out in a screw-capped reaction vial, which precludes the need for stringent inert conditions and use of sealed apparatus as compared to previous reports on iron-catalyzed cross-coupling reactions. Moreover, the employment of water as the sole reaction media and FeCl<sub>3</sub> being an inexpensive and environmentally benign metal species (other iron salts are more expensive than FeCl<sub>3</sub>) greatly enhances the economical and environmentally friendly aspects of this catalytic system.

The scope of the arylation was tested with other heterocycles and both acyclic and cyclic amides. The results are shown in Table 3. Heterocycles such as indole and 7-azaindole were found to be effective nucleophilic counterparts for the coupling process, affording the respective *N*-phenyl derivatives (Table 3, entries 1–4) in good yields (up to 81%) although with a slightly higher catalyst loading. Moreover, the *N*-arylation of benzamide was also accomplished in moderate yields (Table 3, entries 5 and 6) under the influence of the catalytic system. However, the reactions

Table 2. N-Arylation of pyrazole 2 with aryl halides catalyzed by FeCl<sub>3</sub>/dmeda in water.<sup>[a]</sup>

ArX +	NH N	FeCl <sub>3</sub> (10 mol%) dmeda (20 mol%)	√N~_Ar
		K₃PO₄ •H₂O H₂O, 125 °C, 36 h	
	2		3a – i

Entry	ArX	Product		Yield [%] <sup>[b]</sup>
1		N.N.	3a	76
2	OMe		3b	45
3			3c	17
4	Me	N Me	3d	74
5		N CI	3e	75
6	MeO		3f	88
7	F	N.N.F	3g	80
8	CI	N. CI	3h	70
9	Br	N Br	3i	75
10	Br	N.N.	<b>3</b> a	23
11	MeO Br	N OMe	3j	32
12	MeO-	N OMe	3f	21
13		Me	3k	73 <sup>[c]</sup>

<sup>[a]</sup> Unless otherwise noted, the reaction was carried out with 1*H*-pyrazole (2.16 mmol), aryl halide (3.24 mmol), K<sub>3</sub>PO<sub>4</sub>·H<sub>2</sub>O (4.32 mmol), FeCl<sub>3</sub> (10 mol%), dmeda (20 mol%) in water (1.5 mL) at 125 °C for 36 h.

<sup>[b]</sup> Isolated yield after column chromatography.

<sup>[c]</sup> 3-Methylpyrazole was used as the nucleophilic counterpart in the reaction.

were less satisfactory in the case of cyclic amides (Table 3, entries 7 and 8) and only trace amounts of the desired products were detected when imidazole (Table 3, entry 9), aromatic (Table 3, entry 10) and alkyl amines (Table 3, entry 11) were employed.

**Table 3.** *N*-Arylation of indole, 7-azaindole, benzamide and pyrrolidin-2-one with aryl halides catalyzed by  $FeCl_3/dmeda$  in water.<sup>[a]</sup>

R	+	NuH	[Fe] (20 mol dmeda (40 mo K <sub>3</sub> PO <sub>4</sub> •H <sub>2</sub> 0 H <sub>2</sub> O, 125 °C,	%) ol%) ———— O 36 h	R Nu
R = H or Me					<b>4</b> – <b>9</b>



 <sup>&</sup>lt;sup>[a]</sup> Unless otherwise noted, the reaction was carried out with nitrogen nucleophile (2.16 mmol), aryl halide (3.24 mmol), K<sub>3</sub>PO<sub>4</sub>·H<sub>2</sub>O (4.32 mmol), FeCl<sub>3</sub> (20 mol%), dmeda (40 mol%) in water (1.5 mL) at 125 °C for 36 h.

<sup>[b]</sup> Isolated yield after column chromatography.

Based on literature reports, a possible mechanism of the iron-catalyzed cross-coupling is proposed in Scheme 1. The mechanism involves three elementary steps: coordination of the nitrogen nucleophile to the iron(II)-dmeda complex, oxidative addition of the aryl halide, and reductive elimination of the coupling product, thereby regenerating the active catalytic spe-



**Scheme 1.** Proposed mechanism of the iron-catalyzed *N*-arylation of nitrogen nucleophiles.

cies. In this mechanism, we have assumed that the active catalytic species are monomeric and oxidative addition takes place *via* a single metal center. However, a dinuclear oxidative addition process can also occur. Moreover, we are also uncertain as to whether the coordination step precedes or follows the oxidative step. Clearly, more experimental data need to be accumulated to confirm and elucidate the actual mechanism and active iron catalytic species.

In summary, we have developed a very practical and efficient protocol for the N-arylation of nitrogen nucleophiles with substituted aryl iodides and bromides promoted by a ligand-assisted iron catalyst in water. Noteworthy features include (i) the N-arylation of various nitrogen nucleophiles with substituted aryl halides proceeded efficiently in water, (ii) the procedure is experimentally simple to perform and precludes the need for stringent inert conditions, (iii) the catalytic system can be easily generated using a mixture of the inexpensive FeCl<sub>3</sub> and dmeda, and (iv) the protocol is economical and environmentally friendly. Further investigation to elucidate the active catalytic species and to broaden the scope of this catalytic system to other coupling reactions is currently ongoing in our laboratory.

# **Experimental Section**

#### **General Procedure**

A reaction vial was charged with the N nucleophile (2.16 mmol), anhydrous FeCl<sub>3</sub> (Riedel-de-Haen, 98% purity, Lot 70600, 0.216 mmol),  $K_3PO_4$ ·H<sub>2</sub>O (4.32 mmol), aryl halide (3.24 mmol), dimethylethylenediamine (dmeda) (0.432 mmol) and water (1.5 mL). The reaction vial was then screw capped and the reaction mixture stirred under air in a closed system at 125 °C. After being stirred at this temperature for 36 h, the heterogeneous mixture was cooled to room temperature and diluted with dichloromethane. The

resulting solution was directly filtered through a pad of celite and washed with saturated NaCl. The combined organic extracts were dried with anhydrous MgSO<sub>4</sub> and the solvent removed under reduced pressure. The crude product was purified by silica-gel column chromatography to afford the *N*-arylated product. The identity and purity of known products was confirmed by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopic analysis. See the supporting information for full details.

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