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Iron-Catalyzed *N*-Arylations of Amides

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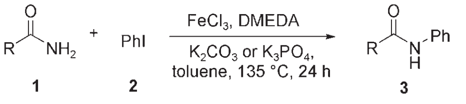
Transition metal-catalyzed *N*-arylation of amides constitutes a powerful C–N bond-forming process that has been extensively utilized in pharmaceutical and medicinal chemistry.[1] Despite remarkable advances in both palladium-[2] and copper-catalyzed[3] reactions of this type, the development of alternative catalysts involving more cost-efficient, nontoxic, and environmentally friendly metals to effect the target process remains an issue of scientific interest and paramount industrial significance. In this respect, iron poses as an ideal metal that offers significant advantages considering its low cost, ready availability, and environmentally benign character.[4]

Although iron-catalyzed C–C cross-coupling reactions have attracted particular attention,[5] the application of iron salts for the challenging carbon–heteroatom bond formation has remained largely undeveloped. Only recently, we found highly practical iron catalysts for the formation of C–N, C–O, and C–S linkages by means of arylation of nitrogen,[6] oxygen,[7] and sulfur nucleophiles,[8] respectively, with aryl halides. In connection with this work, we present herein a versatile, convenient, and experimentally simple iron-catalyzed *N*-arylation of primary amides (including aromatic, heterocyclic, and aliphatic substrates) and demonstrate its applicability to the synthesis of valuable *N*-heterocycles by intramolecular ring closures.

The key components for the presented catalyst system were 10 mol % of easy-to-handle $FeCl_3$ and 20 mol % of inexpensive *N,N'*-dimethylethylenediamine (DMEDA). In our initial studies,[6] we obtained promising results in conversions of amides, which encouraged us to investigate the scope of this synthetically valuable transformation. The couplings of differently substituted primary amides with phenyl iodide under the previously optimized conditions proceeded in moderate to excellent yields (43–96 %; Table 1). Screening studies revealed that the choice of the base and the solvent played a determining role. Thus, in most cases the use of K_2CO_3 led to higher yields than K_3PO_4 or Na*Ot*Bu, and the employment of toluene as solvent at 135 °C proved to be crucial for the success of the reaction. Benzamides bearing electron-donating substituents (entries 3 and 4, Table 1) afforded better results than those having electron-withdrawing groups (entry 2, Table 1). Also aliphatic amides provided the arylated products in moderate to good yields (entries 6–8, Table 1), with the exception of formamide (entry 5, Table 1), which was almost unreactive. Gratifyingly, important heterocyclic amides such as those bearing pyridinyl (entry 9, Table 1) and thiophenyl (entry 10, Table 1) moieties underwent coupling reactions providing the products in moderate to good yields under standard conditions. Conversely, secondary amides such as *N*-methylbenzamide and *N*-benzylbenzamide gave the corresponding *N*-arylated products in only trace amounts.

To determine the applicability of the iron-catalyzed *N*-arylation with respect to the aryl halides, the substrate scope

Table 1. Fe-catalyzed *N*-arylation of amides (**1**) with phenyl iodide (**2**).[a]



Entry	R	Yield of **3** [%][b]	
1	Ph	**3aa**	78[c]
2	4-Cl-Ph	**3ba**	65[d]
3	3-Me-Ph	**3ca**	96[d]
4	4-MeO-Ph	**3da**	73[d]
5	H	**3e**	traces
6	Me	**3fa**	43[d]
7	Et	**3ga**	63[c]
8	Pr	**3ha**	78[c]
9	3-Pyridinyl	**3ia**	45[d]
10	2-Thiophenyl	**3ja**	85[d]

[a] Reaction conditions: **1** (1.0 equiv), **2** (1.5 equiv), $FeCl_3$ (0.1 equiv), DMEDA (0.2 equiv), base (2.0 equiv), toluene (1 mL per mmol of **1**), 135 °C, 24 h. [b] Yield of isolated product after flash chromatography. [c] Use of K_3PO_4 as base. [d] Use of K_2CO_3 as base.

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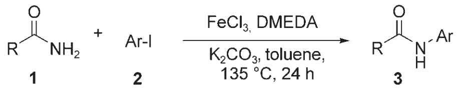
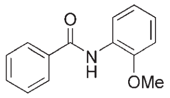
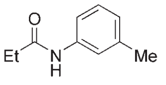
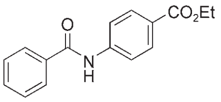
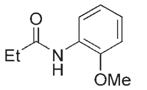
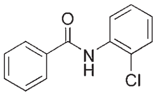
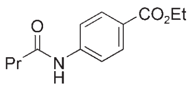
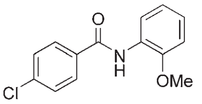
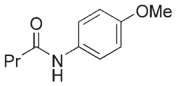
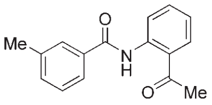
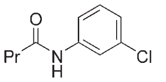
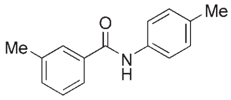
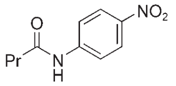
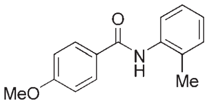
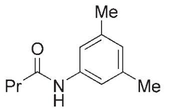
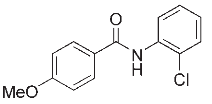
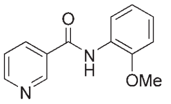
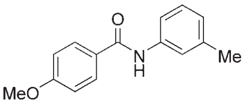
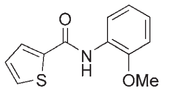
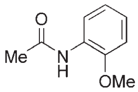
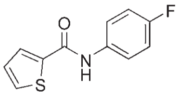
was further investigated. The use of differently substituted aryl iodides (R = F, Cl, OMe, Me, COMe, CO_2Et, NO_2) had a beneficial effect on the reaction outcome, and in most cases the corresponding *N*-arylated compounds **3** were obtained in good to excellent yields (40–91 %; Table 2). Noteworthy, steric hindrance at the aryl iodide was tolerated, and neither electron-donating nor electron-withdrawing *ortho* substituents hampered the target coupling.[9] Unfortunately, attempts to apply aryl bromides as arylating agents provided the target cross-coupling products in only very low yields.[10]

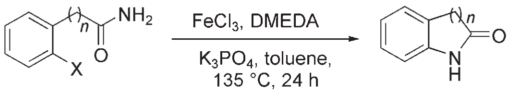
Table 2. Fe-catalyzed *N*-arylation of amides (**1**) with aryl iodides (**2**).[a]



Product	Yield of **3** [%][b]	Product	Yield of **3**[%][b]
	**3ab**(79)[c]		**3gb**(70)[c]
	**3ac**(72)[c]		**3gc**(57)[c]
	**3ad**(66)[c]		**3hb**(78)
	**3bb**(80)		**3hc**(71)
	**3cb**(86)		**3hd**(72)
	**3cc**(89)		**3he**(66)
	**3 db**(67)		**3hf**(67)
	**3dc**(91)		**3ib**(40)
	**3dd**(88)		**3jb**(85)
	**3 fb**(46)		**3jc**(80)

[a] Reaction conditions: **1** (1.0 equiv), **2** (1.5 equiv), $FeCl_3$ (0.1 equiv), DMEDA (0.2 equiv), base (2.0 equiv), toluene (1 mL per mmol of **1**), 135 °C, 24 h. [b] Yield of isolated product after flash chromatography. [c] Use of K_3PO_4 as base.

Next, an intramolecular version of the *N*-arylation protocol was tested. To our delight, iodo-substituted arenes with primary amide functions cyclized well, affording oxindole **4a** and quinolinone **4b** in 72 and 73 % yield, respectively (Scheme 1). Considering that these cyclizations are the first examples of iron-catalyzed intramolecular arylation reactions, we regard them as promising starting points for the development of syntheses of other nitrogen-containing heterocycles with iron-based catalysts. Consistent with the observations made in the intermolecular cross-couplings, only trace amounts of the desired oxindole were observed in attempted five-membered-ring formations starting from aryl bromides.



4a: *n* = 1; with X = I (72%)
with X = Br (0%)
4b: *n* = 2; with X = I (73%)

Scheme 1. Iron-catalyzed intramolecular *N*-arylation: Reaction conditions: substrate (1.0 equiv), $FeCl_3$ (0.1 equiv), DMEDA (0.2 equiv), K_3PO_4 (2.0 equiv), toluene (1 mL per mmol of substrate), 135 °C, 24 h; for **4b** use of K_2CO_3 as base and reaction time of 30 h.

In summary, we have developed an iron-based catalyst system for efficient *N*-arylations of primary amides with aryl iodides, which represents an excellent complement to the previously established palladium- and copper-catalyzed *N*-arylation protocols. Due to its manipulation ease, low-cost, and benign character, the new iron catalyst system described appears promising for large-scale applications. Studies to improve the catalyst performance and to expand the substrate scope of the method are currently in progress in our laboratories.

Experimental Section

General procedure for *N*-arylation of amides: A sealable tube equipped with a magnetic stir bar was charged with amide (1.0 equiv), K_3PO_4 or K_2CO_3 (2.0 equiv), and $FeCl_3$ (0.10 equiv). The aperture of the tube was then covered with a rubber septum, and an argon atmosphere was established. Aryl halide (1.5 equiv), *N,N'*-dimethylethylendiamine (0.20 equiv) and toluene (1 mL per mmol of amide) were added by using a syringe. The septum was then replaced by a teflon-coated screw cap, and the reaction vessel was placed in an oil bath at 135 °C. After the mixture had been stirred at this temperature for 24 h, it was cooled to room temperature and diluted with dichloromethane. The resulting solution was directly filtered through a pad of silica and concentrated to yield the *N*-aryl amide **3**, which was purified by silica gel chromatography. The identity and purity of the known products was confirmed by ^1H and ^{13}C NMR spectroscopic analysis, and the new products were fully characterized (see the Supporting Information).

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Keywords: amides • arylation • cross-coupling • heterogeneous catalysis • iron • sustainable chemistry

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