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Iron-Catalyzed C–N Cross-Coupling of Sulfoximines with Aryl Iodides

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Abstract: An inexpensive and experimentally simple, iron-catalyzed *N*-arylation reaction of *NH*-sulfoximines with aryl iodides is reported. This complementary method to the known palladium- and copper-catalyzed ones features the use of a combination of environmentally friendly $FeCl_3$ and *N,N′*-dimethylethylenediamine (DMEDA) as catalytic system and allows the efficient preparation of various *N*-arylsulfoximines in high yields.

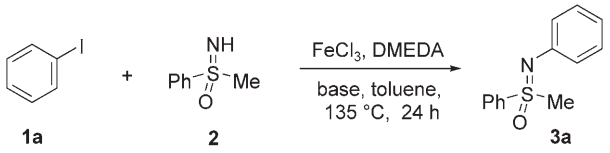
Keywords: *N*-arylation; C–N cross-coupling; homogeneous catalysis; iron; sulfoximines

The development of cost-efficient and environmentally friendly, metal-catalyzed C–N cross-coupling protocols for the preparation of valuable nitrogen compounds is one of the most pressing goals for modern chemistry and chemical industry.[1] So far, this field has been largely dominated by palladium-[2] and copper-based[3] methods and, despite their efficiency, the search for alternative and less expensive catalysts to accomplish such processes is a major focus of synthetic organic chemists. In this context, iron salts offer attractive advantages and, due to their sustainability, they are recognized as ideal catalysts mainly in the field of C–C cross-coupling reactions.[4,5] Along these lines, we have recently reported novel and highly practical ligand-assisted, iron-catalyzed C–N and C–O cross-couplings applying either nitrogen[6] and oxygen nucleophiles,[7] respectively, together with differently substituted aryl halides. In connection with our expertise in the field of sulfoximine chemistry and following with our ongoing research on the development of iron-based catalytic processes,[8] we report herein the development of an advantageous *N*-arylation reaction of *NH*-sulfoximines with aryl iodides. The success of latter protocol relies on the employment of a combination of catalytic amount of $FeCl_3$ and *N,N′*-dimethylethylenediamine (DMEDA) as chelating ligand.

Despite their applications as chiral auxiliaries and precursors for biologically relevant molecules,[9,10] sulfoximines have attracted a great deal of attention due to their effectiveness as versatile chiral ligands for asymmetric catalysis.[11] The construction of the *NH*-sulfoximine core is well-established,[9,12] and among the modifications on its four substituents, the arylation at the sulfoximine nitrogen atom is of particular interest, given the importance of the resulting *N*-aryl sulfoximine derivatives. Hence, we have extensively studied this transformation and several protocols utilizing either palladium or copper catalysts were described.[13] Pleasingly, we have now found that such a cross-coupling reaction can be catalyzed by inexpensive and easy-to-handle iron salts, and the experimental results are disclosed in this communication.

We initiated our study by selecting the coupling of phenyl iodide (**1a**) and (*rac*)-*S*-methyl-*S*-phenylsulfoximine (**2**) as a model reaction. The results of this preliminary screening are summarized in Table 1. When applying the previously reported conditions for the iron-catalyzed *N*-arylation of nitrogen heterocycles and amides (Table 1, entry 1),[6] the target *N*-phenylsulfoximine **3a** was obtained in low yield along with unreactive *NH*-sulfoximine **2**. The use of other bases (Cs_2CO_3, NaO-*t*-Bu and K_2CO_3) led to the desired arylated product in slightly better yields, but, unfortunately, full conversion was not achieved in those cases (Table 1, entries 2, 3 and 4, respectively). Notably, when performing the target coupling utilizing a weak base such as K_2CO_3 for prolonged reaction times, full conversion was observed and the *N*-phenylsulfoximine **3a** was obtained in good yield (83%, Table 1, entry 5). Interestingly, increasing the catalyst loading had a perceptibly beneficial effect on the reaction outcome and the desired product **3a** was obtained in yields ranging from 65 to 99% after 24 h (Table 1, entries 6, 7 and 8). We concluded thus that the optimal conditions for the *N*-arylation of sulfoximine **2** in-

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



1a 2 3a

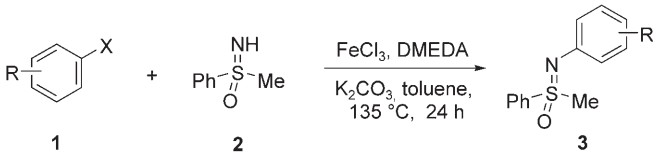
Entry	$FeCl_3$ (equivs.)	DMEDA (equivs.)	Base	Yield of **3a** [%][b]
1	0.10	0.20	K_3PO_4	24
2	0.10	0.20	Cs_2CO_3	16
3	0.10	0.20	NaO-*t*-Bu	43
4	0.10	0.20	K_2CO_3	40
5	0.10	0.20	K_2CO_3	82[c]
6	0.15	0.30	K_2CO_3	65
7	**0.20**	**0.40**	**K_2CO_3**	**96**
8	0.30	0.40	K_2CO_3	99
9	0.20	0	K_2CO_3	trace
10	0	0.40	K_2CO_3	trace

[a] *Reaction conditions:* **1a** (1.5 equivs.), **2** (1.0 equiv.), $FeCl_3$, DMEDA, base (2.0 equivs.), toluene (1 mL mmol^{-1} of **2**), 135 °C, 24 h, argon atmosphere.
[b] Yield of isolated product after flash chromatography.
[c] Reaction time: 72 h.

volved the use of a combination of 20 mol% of $FeCl_3$ and 40 mol% of DMEDA in the presence of K_2CO_3 as base in toluene at 135 °C.[14] Note that variable yields were observed according to the purity and commercial origin of the required $FeCl_3$.[15] Test reactions in the absence of either ligand (Table 1, entry 9) or iron source (Table 1, entry 10) verified the crucial role that both species played in the described coupling process.[16] When the latter reaction was performed in the presence of air and moisture the target product was obtained in a remarkable 82% yield. Additionally, the coupling of enantiopure sulfoximine (*S*)-**2** and phenyl iodide (**1a**) provided the sulfoximine **3a** as a single enantiomer.[17] Therefore, the present iron catalyst can indeed be a practical alternative to effect the target C–N cross-coupling and appears suitable for industrial-scale synthesis, when financial, operational and environmental issues are of concern.

The scope of the iron-catalyzed arylation of *NH*-sulfoximines was subsequently explored, and the influence of differently substituted aryl halides was evaluated. Both electron-rich (R = Me, OMe) and electron-poor (R = Cl, I, F, NO_2, CO_2Et) aryl iodides coupled with sulfoximine **2** in excellent yields (73–96%, Table 2, entries 1–12). Furthermore, it is remarkable that *ortho* substituents did not hamper the *N*-arylation process. Unfortunately, aryl bromides were less reactive and furnished the corresponding *N*-arylsulfoximines **3** in much lower yields (Table 2, entries 13–16).

Table 2. Fe-catalyzed *N*-arylation of sulfoximine **2** with aryl halides **1**.[a]



1 2 3

Entry	Aryl halide	X	R	Product	Yield [%][b]
1	**1a**	I	H	**3a**	96
2	**1b**	I	2-OMe	**3b**	73
3	**1c**	I	2-Cl	**3c**	74
4	**1d**	I	2-I	**3d**	76
5	**1e**	I	2-Me	**3e**	78
6	**1f**	I	3-Me	**3f**	95
7	**1g**	I	3,5-Me_2	**3g**	84
8	**1h**	I	4-OMe	**3h**	78
9	**1i**	I	4-F	**3i**	86
10	**1j**	I	4-NO_2	**3j**	78
11	**1k**	I	4-Me	**3k**	88
12	**1l**	I	4-CO_2Et	**3l**	83
13	**1m**	Br	H	**3a**	9
14	**1n**	Br	4-CF_3	**3n**	12
15	**1o**	Br	4-OMe	**3h**	trace
16	**1p**	Br	3-NO_2	**3p**	10

[a] *Reaction conditions:* **1** (1.5 equivs.), **2** (1.0 equiv.), $FeCl_3$ (0.20 equivs.), DMEDA (0.40 equivs.), K_2CO_3 (2.0 equivs.), toluene (1 mL mmol^{-1} of **2**), 135 °C, 24 h, argon atmosphere.
[b] Yield of isolated product after flash chromatography.

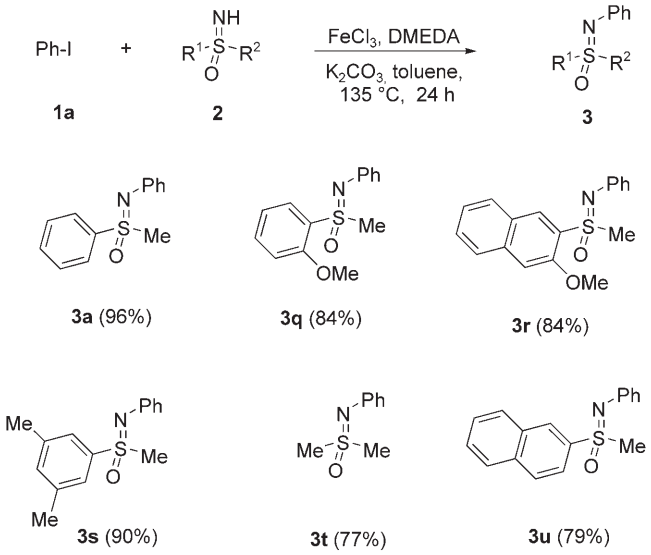
This valuable protocol was not restricted to the employment of *S*-methyl-*S*-phenylsulfoximine (**2**) as nucleophile and proved also applicable for the efficient *N*-arylation of other *NH*-sulfoximines with phenyl iodide as reacting partner. Particularly noteworthy is that even sulfoximines bearing bulky substituents at the α-carbon were reactive and that their coupling proceeded well too (Scheme 1).

In summary, we have developed an efficient and experimentally simple ligand-assisted iron-catalyzed *N*-arylation of various *NH*-sulfoximines with differently substituted aryl iodides. The key finding for this protocol is the catalytic effect of a combination of readily available and inexpensive $FeCl_3$ and DMEDA. Our results expand the application of iron salts as promising cost-efficient catalysts in organic synthesis, and hence further investigation to improve the catalyst performance as well as mechanistic studies are in progress in our laboratories.

Experimental Section

General Procedure for *N*-Arylation of Sulfoximines

A sealable tube equipped with a magnetic stir bar was charged with *NH*-sulfoximine (1.0 equiv.), anhydrous $FeCl_3$



Scheme 1. Fe-catalyzed *N*-arylation of sulfoximines **2** with phenyl iodide (**1a**). *Reaction conditions:* **1a** (1.5 equivs.), **2** (1.0 equiv.), $FeCl_3$ (20 mol%), DMEDA (40 mol%), K_2CO_3 (2.0 equivs.), toluene (1 mL mmol^{-1} of **2**), 135 °C, 24 h (for **3r** and **3s**: 30 h), argon atmosphere.

(0.20 equivs.) and K_2CO_3 (2.0 equivs.). The aperture of the tube was then covered with a rubber septum, and an argon atmosphere was established. The aryl halide (1.5 equivs.), DMEDA (0.40 equivs.) and toluene (1 mL/mmol of sulfoximine) were added *via* syringe. The septum was then replaced by a teflon-coated screw cap, and the reaction vessel was placed in a 135 °C oil bath. After stirring at this temperature for 24 h, the heterogeneous mixture was cooled to room temperature and diluted with dichloromethane. The resulting solution was directly filtered through a pad of silica and concentrated to deliver the product, which was purified by silica gel chromatography to yield the *N*-arylated product. The identity and purity of the known products was confirmed by ^{1}H and ^{13}C NMR spectroscopic analysis and the new products were fully characterized. See Supporting Information for full details.

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[17] HPLC analysis of *N*-phenylsulfoximine **3a**: Chiralcel OD-H. 9:1 heptane/2-propanol, 0.5 mL min^{-1}; t_R = 41 min (*S*), t_R = 62 min (*R*).

