Cross-Coupling

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Iron-Catalyzed C–O Cross-Couplings of Phenols with Aryl Iodides**

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Diaryl ethers constitute an important class of organic compounds that are of paramount importance throughout the polymer and life-sciences industries.[1] Indeed, many natural cyclopeptides bearing a diaryl ether bridge, such as the antibiotic vancomycin[2] and the anti-HIV agents chloropeptins[3], exhibit remarkable physiological activities. Consequently, the development of any new and practical method for assembling the target compounds can be of great synthetic significance. Likewise, owing to the numerous appealing applications of diaryl ethers, much effort has been devoted to providing direct and efficient processes for their preparation.

Diaryl ethers are primarily synthesized using transition-metal-catalyzed cross-coupling reactions, and palladium[4] and copper[5] catalysts have so far been the metals of choice for such purposes. However, despite the efficiency of the latter protocols,[6] the development of less expensive and environmentally more benign catalysts is a major goal for organic synthesis. In this respect, iron-catalyzed reactions offer attractive industrial prospects in terms of sustainable chemistry and hence constitute a challenging research area.[7] Whereas iron, a practically ideal transition metal because of its low price and environmentally benign features, has been extensively investigated as an alternative catalyst in the field of cross-coupling reactions,[8,9] the projected iron-catalyzed O-arylation posed a challenge.

We recently reported an efficient and practical iron-catalyzed N-arylation of nitrogen nucleophiles that allows the easy preparation of a wide range of *N*-aryl derivatives.[10] The key finding for this reaction was the catalytic effect of a combination of $FeCl_3$ and *N*,*N*′-dimethylethylenediamine (DMEDA). In connection with this previous work, we report herein on the development of a novel iron-catalyzed O-arylation reaction, which features the synthesis of diaryl ethers in high yields using readily available aryl halides as arylating agents. In this case, the success of the process relies on the employment of a catalytic amount of $FeCl_3$ together with 2,2,6,6-tetramethyl-3,5-heptanedione (TMHD) as the chelating ligand.

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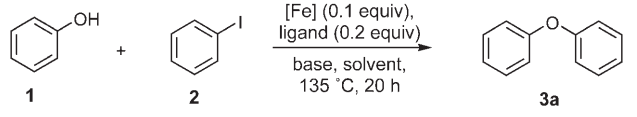
As a model study for the optimization of the reaction conditions, we first chose the coupling of phenol (**1**) and phenyl iodide (**2**) to give diphenyl ether (**3a**). In contrast to our expectations, **3a** was not formed at all when applying the previously reported conditions for the iron-catalyzed N-arylation process[10] (Table 1, entry 1). Apparently, the interplay between ligand, base, and solvent strongly depended on the substrate, and these parameters played a determinant role in the reaction outcome. Consequently, the influence of different bases, solvents, and ligands in the projected cross-coupling was investigated.

The screening summarized in Table 1 shows that the desired diphenyl ether (**3a**) could be obtained in yields ranging from 10–85% when DMEDA (L1, Table 1, entry 2), *N*,*N*-dimethylglycine (L2, Table 1, entries 3–5) or TMHD (L3, Table 1, entries 6–7) was employed. The best results were achieved when the reaction was performed in the presence of L2 or L3, furnishing ether **3a** in 72% yield (Table 1, entry 5)

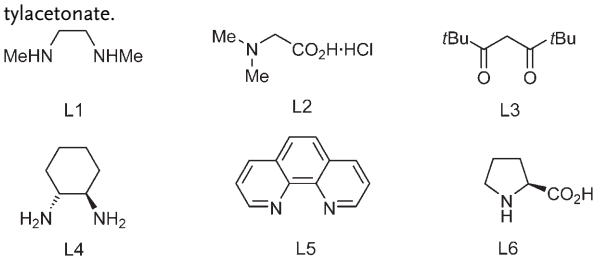
Table 1: Iron-catalyzed O-arylation of phenol (**1**) with phenyl iodide (**2**).[a]



1 + **2** → **3a**

Entry	Fe source	Ligand	Base	Solvent	Yield of **3a** [%][b]
1	$FeCl_3$	L1	K_3PO_4	toluene	0
2	$FeCl_3$	L1	Cs_2CO_3	DMF	18
3	$FeCl_3$	L2	K_3PO_4	toluene	10
4	$FeCl_3$	L2	Cs_2CO_3	toluene	64
5	$FeCl_3$	L2	Cs_2CO_3	DMF	72
6	**$FeCl_3$**	**L3**	**Cs_2CO_3**	**DMF**	**85**
7	$FeCl_3$	L3	Cs_2CO_3	toluene	17
8	$FeCl_3$	L3	NaO*t*Bu	DMF	0
9	$FeCl_3$	L3	K_3PO_4	DMF	traces
10	$FeCl_3$	–	Cs_2CO_3	DMF	11
11	–	L3	Cs_2CO_3	DMF	0
12	$FeCl_3$	L4	Cs_2CO_3	DMF	traces
13	$FeCl_3$	L5	Cs_2CO_3	DMF	traces
14	$FeCl_3$	L6	Cs_2CO_3	DMF	traces
15	$FeCl_3 \cdot 6H_2O$	L3	Cs_2CO_3	DMF	43
16	$[Fe(acac)_3]$[c]	–	Cs_2CO_3	DMF	35

[a] Reaction conditions: **1** (1.0 equiv), **2** (1.5 equiv), [Fe] (0.1 equiv), L (0.2 equiv), base (2.0 equiv), solvent (1 mL mmol^{-1} of **1**), 135 °C, 20 h. [b] Yield of isolated product after flash chromatography. [c] acac = acetylacetonate.

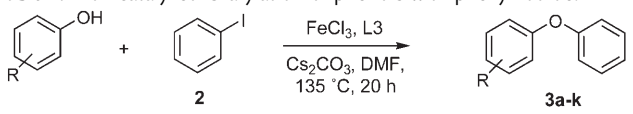


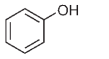
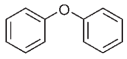
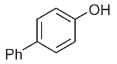
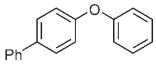
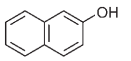
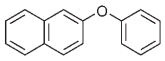
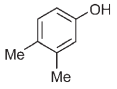
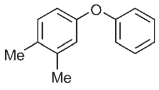
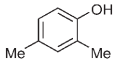
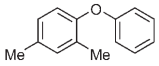
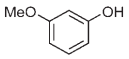
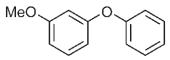
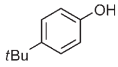
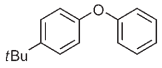
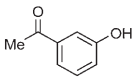
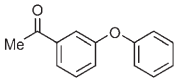
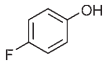
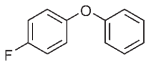
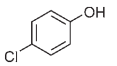
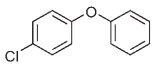
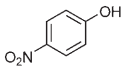
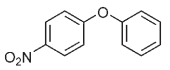
and 85% yield (Table 1, entry 6), respectively. Related ligands (Table 1, L4–L6) only provided traces of the desired coupling product (Table 1, entries 12–14). Noteworthy is also that the choice of Cs_2CO_3 as the base and DMF as the solvent was crucial for the O-arylation.[11] Indeed, when other bases (NaO*t*Bu, K_3PO_4, K_2CO_3, $NaHCO_3$, KOAc, and Na_2CO_3) and solvents (toluene, acetonitrile, and dioxane) were tested, diphenyl ether (**3a**) was obtained in much lower yields. Hence, the optimal conditions for the O-arylation process consist of the combination of $FeCl_3$ (10 mol%), L3 (20 mol%), Cs_2CO_3 (2 equiv), and DMF at 135°C (Table 1, entry 6).[12,13] Control experiments in the absence of either ligand (Table 1, entry 10) or iron source (Table 1, entry 11) confirmed the crucial role that both species play in the described cross-coupling reaction. The employment of $FeCl_3 \cdot 6H_2O$ provided **3a** in lower yields (Table 1, entry 15). Interestingly, the related iron species [Fe(acac)$_3$] was not as efficient as the combination of $FeCl_3$ and diketone L3 (Table 1, entry 16).

Encouraged by the efficiency of the cross-coupling protocol described above, the substrate scope was investigated next. A variety of substituted phenols were tested under the optimized conditions using phenyl iodide as the arylating agent. Gratifyingly, several electron-rich phenols were suitable substrates for the iron-catalyzed O-arylation, affording the corresponding diaryl ethers **3a–g** in excellent yields (85–99%, Table 2, entries 1–7). Electron-deficient phenols provided the coupling products in slightly lower yields (74–87%, Table 2, entries 8–10), and when the phenol incorporated strongly electron-withdrawing moieties such as a nitro group (Table 2, entry 11), the reaction did not occur.[14]

Next, the scope of the process with respect to the aryl halides was examined. Consistent with the previous studies, phenyl bromide was found to be less efficient than phenyl iodide, furnishing **3a** in 69% yield only after 70 h (Table 3, entry 1).[15] Chlorobenzene proved unreactive (Table 3, entry 1). Most of the substituted aryl iodides tested afforded the corresponding diaryl ethers **3** in very high yield (up to 90%, Table 3, entries 1, 4–11). The reaction conditions were compatible with a variety of functionalized aryl iodides, including those bearing ether, nitro, and ester groups (Table 3, entries 6, 10, and 11, respectively). The coupling reaction of sterically hindered aryl iodides was slightly disfavored.

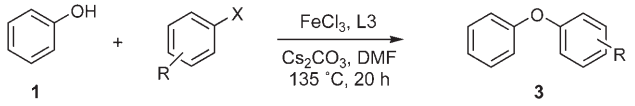
Table 2: Iron-catalyzed O-arylation of phenols with phenyl iodide.[a]

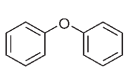
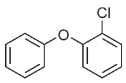
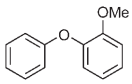
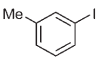
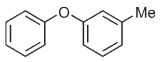
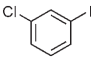
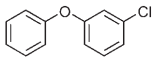
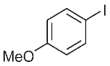
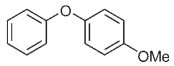
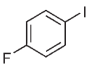
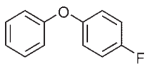
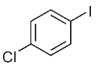
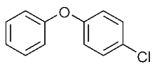


Entry	ArOH	Product		Yield of **3** [%][b]
1			**3a**	85
2			**3b**	95
3			**3c**	92
4			**3d**	92
5			**3e**	95
6			**3f**	99
7			**3g**	95
8			**3h**	74
9			**3i**	84
10			**3j**	87
11			**3k**	0

[a] Reaction conditions: ArOH (1.0 equiv), **2** (1.5 equiv), $FeCl_3$ (0.1 equiv), L3 (0.2 equiv), Cs_2CO_3 (2.0 equiv), DMF (1 mL mmol^{-1} of ArOH), 135°C, 20 h. [b] Yield of isolated product after flash chromatography.

Table 3: Iron-catalyzed O-arylation of phenol with different aryl halides.[a]



Entry	ArX	Product		Yield of **3** [%][b]
1			**3a**	0 (X = Cl) 69 (X = Br)[c] 85 (X = I)
2			**3l**	50
3			**3m**	0
4			**3n**	90
5			**3o**	87
6			**3p**	78
7			**3i**	78
8			**3j**	90
9			**3q**	87
10			**3k**	80
11			**3r**	78

[a] Reaction conditions: **1** (1.0 equiv), ArX (1.5 equiv), $FeCl_3$ (0.1 equiv), L3 (0.2 equiv), Cs_2CO_3 (2.0 equiv), DMF (1 mL mmol^{-1} of PhOH), 135°C, 20 h. [b] Yield of isolated product after flash chromatography. [c] The reaction was carried out at 135°C for 70 h.

Hence, when employing 1-chloro-2-iodobenzene, the reaction occurred with a lower yield than with less hindered substrates (Table 3, entry 2 vs. entries 5 and 8), and when 2-iodoanisole was used, the cross-coupling did not even occur (Table 3, entry 3).

In summary, we have demonstrated that the cheap and environmentally friendly catalyst system composed of $FeCl_3$ and diketone ligand TMHD is highly effective for the synthesis of diaryl ethers. This novel process constitutes a powerful and practical O-arylation protocol that appears promising for large-scale applications. Its scope is currently under investigation in our research group.

Experimental Section

General procedure for O-arylation of phenols: A sealable tube equipped with a magnetic stir bar was charged with phenol (**1**, 100 mg, 1.1 mmol), Cs_2CO_3 (700 mg, 2.2 mmol), and anhydrous $FeCl_3$ (17 mg, 0.11 mmol). The aperture of the tube was then covered with a rubber septum, and an argon atmosphere was established. Phenyl iodide (**2**, 0.18 mL, 1.65 mmol), 2,2,6,6-tetramethyl-3,5-heptanedione (TMHD, L3, 0.22 mmol, 46 μL), and DMF (1.7 mL) were added by 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 being stirred at this temperature for 20 h, the heterogeneous mixture was cooled to room temperature and diluted with dichloromethane. The resulting suspension was directly filtered through a pad of celite and the filtrate was concentrated to yield the product, which was purified by silica gel chromatography (pentane) to yield diphenyl ether **3a** as a colorless oil (154 mg, 85 % yield). The identity and purity of the product was confirmed by ^1H and ^{13}C NMR spectroscopic analysis. See the Supporting Information for full details.

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[14] 4-Nitrophenol has been shown to be unreactive in several copper-catalyzed O-arylation reactions with aryl halides. See reference [5g] and references cited therein.

[15] When using higher catalyst loading (20 mol % $FeCl_3$ and 40 mol % L3), no significant improvement was achieved, and the corresponding O-arylated product was obtained in 59 % yield after 20 h.

