Cross-Coupling Reactions

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Iron-Catalyzed S-Arylation of Thiols with Aryl Iodides**

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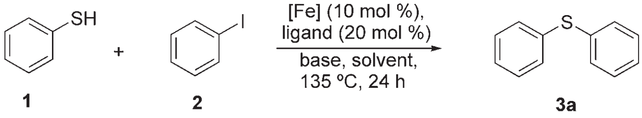
Transition-metal-catalyzed cross-coupling reactions of aryl halides with nitrogen, oxygen, and sulfur nucleophiles are powerful tools for the formation of C–N, C–O, and C–S bonds, respectively.[1] Although several palladium, nickel, and copper catalysts have proven to be highly effective in such coupling processes,[2] the development of new and cheap alternative catalysts for the aforementioned transformations is still desirable.

Among the various cross-coupling types, S-arylation is comparatively less studied.[3] Two factors make this process difficult: First, thiols are prone to undergo oxidative S–S coupling reactions, which result in the undesired formation of disulfides, and second, organic sulfur compounds can be effective metal binders, which leads to catalyst modification (or deactivation).[4] However, given the prevalence of C–S bonds in a wide range of pharmaceutically active compounds and polymeric materials,[5] it is desirable to find novel catalytic procedures that provide efficient access to such highly useful organic products. In this regard we envisaged the application of readily available, inexpensive, and environmentally friendly iron salts.[6] A particular challenge was seen in the required suppression of the known ability of iron to effect disulfide formation.[7]

Iron-catalyzed C–C coupling reactions have recently emerged as appealing synthetic methods, since easy-to-handle catalysts can be applied.[8] As part of our ongoing efforts devoted to the development of novel iron-catalyzed processes,[9] we introduced ligand-assisted $FeCl_3$-catalyzed N- and O-arylation reactions.[10,11] To our delight, we have now found that these iron-based catalysts can also be applied to arylations of sulfur nucleophiles. Thus, this novel and experimentally simple iron-catalyzed C–S bond-forming process provides ready access to valuable aryl sulfides.

Initially, the coupling of thiophenol (**1**) and phenyl iodide (**2**) was selected as a model system to optimize the reaction conditions. As shown in Table 1, the best conditions for the iron-catalyzed N-arylation[10a] provided promising results, and afforded thioether **3a** in 61% yield (Table 1, entry 1).

Table 1: Fe-catalyzed S-arylation of thiophenol (**1**) with phenyl iodide (**2**).[a]



Entry	Fe source	Ligand[b]	Base	Solvent	Yield of **3a** [%][c]
1	$FeCl_3$	DMEDA	K_3PO_4	toluene	61
2	$FeCl_3$	TMHD	Cs_2CO_3	DMF	28
3	$FeCl_3$	DMEDA	Cs_2CO_3	toluene	trace
4	$FeCl_3$	DMEDA	NaOH	toluene	trace
5	$FeCl_3$	DMEDA	K_2CO_3	toluene	51
6	$FeCl_3$	DMEDA	Na_2CO_3	toluene	trace
7	$FeCl_3$	DMEDA	NaOAc	toluene	trace
8	$FeCl_3$	DMEDA	KO*t*Bu	toluene	trace
9	**$FeCl_3$**	**DMEDA**	**NaO*t*Bu**	**toluene**	**91**
10	$FeCl_3$	DMEDA	NaO*t*Bu	toluene	75[d]
11	$Fe(ClO_4)_2$	DMEDA	NaO*t*Bu	toluene	trace
12	$[Fe(acac)_2]$	DMEDA	NaO*t*Bu	toluene	trace
13	Fe	DMEDA	NaO*t*Bu	toluene	trace
14	$FeCl_3$	DMEDA	NaO*t*Bu	toluene	trace[e]
15	$FeCl_3$	none	NaO*t*Bu	toluene	0

[a] Reaction conditions: **1** (1.0 equiv), **2** (1.5 equiv), [Fe] (0.1 equiv), ligand (0.2 equiv), base (2.0 equiv), solvent (1 mL mmol^{-1} of **1**), 135 °C, 24 h. [b] DMEDA = *N,N'*-dimethylethylenediamine; TMHD = 2,2,6,6-tetramethyl-3,5-heptadione. [c] Yield of isolated product after flash chromatography. [d] Use of 5 mol% of $FeCl_3$ and 10 mol% of DMEDA. [e] Phenyl disulfide was used as the substrate instead of thiophenol (**1**). acac = acetylacetonate.

Conversely, the conditions for the iron-catalyzed O-arylation[11] proved rather ineffective, and **3a** was obtained in very low yield (Table 1, entry 2). Moreover, the control experiment of the latter reaction in the absence of catalyst showed that under those conditions the product could also result from a classical aromatic nucleophilic substitution reaction.

Further experiments revealed a significant dependence of the S-arylation of **1** with **2** on the nature of the base. Thus, whereas K_3PO_4, K_2CO_3, and NaO*t*Bu provided the arylated compound in moderate to excellent yield (Table 1, entries 1, 5, and 9), other bases such as Na_2CO_3, Cs_2CO_3, NaOH, NaOAc, and KO*t*Bu only gave trace amounts of **3a** (Table 1, entries 3, 4, and 6–8). It is noteworthy that in all the reactions the undesired phenyl disulfide, which arises from an iron-catalyzed oxidation reaction of **1**, was detected as a by-product. Unfortunately, the use of less-oxidizing iron species (Table 1, entries 11–13), degassed solvents, or other diamine-type ligands such as *N,N,N',N'*-tetramethylethylenediamine or *trans*-1,2-diaminocyclohexane did not prevent such competitive oxidation processes. To determine if **3a** was obtained by direct S-arylation of **1** or, alternatively, a two-step procedure involving oxidation of the thiophenol and subsequent aryla-

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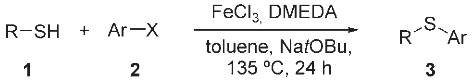
tion of the resulting corresponding disulfide, thiophenol (**1**) was replaced by diphenyl sulfide as the starting material. The absence of any arylated product in this reaction (Table 1, entry 14) ruled out the latter reaction path.

The importance of the ligand was revealed by a reaction carried out in its absence: In this case, the C−S coupling product was not observed at all, and diphenyl disulfide was the only product (Table 1, entry 15). Thus, the chemoselectivity of the iron-catalyzed S-arylation can be entirely controlled by the addition of a simple diamine ligand (Table 1, compare entries 9 and 15). The optimal reaction conditions for the S-arylation of thiophenol with phenyl iodide involved the use of 10 mol% of $FeCl_3$, 20 mol% of DMEDA, and 2 equivalents of NaO*t*Bu in toluene at 135 °C.[12] The use of 5 mol% of the iron source furnished **3a**, although in good but lower yield (Table 1, entry 10).

Next, the scope of this novel transformation in coupling reactions of other thiols with differently substituted aryl halides was evaluated (Table 2). In general, all reactions were very clean, and the thioethers **3** were obtained in high yields under the previously optimized conditions. In a few cases, trace amounts of the undesired disulfide were detected, but those could be separated during the purification by column chromatography. The current iron-catalyst system efficiently coupled thiols with electron-rich, electron-neutral, and electron-deficient aryl iodides (32–98% yield, Table 2, entries 1–18). Furthermore, sterically demanding *ortho* substituents did not hamper the arylation reaction and the corresponding thioethers **3** were obtained in good yields (Table 2, entries 4, 11, 13, 16, and 17). Neither aryl bromides nor aryl chlorides were reactive under the standard conditions (Table 2, entry 1). Consequently, cross-coupling reactions with chloro-substituted aryl iodides proceeded exclusively at the iodo group

Table 2: Fe-catalyzed S-arylation of thiols with aryl halides.[a]



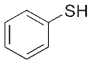
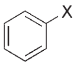
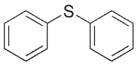
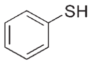
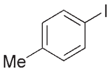
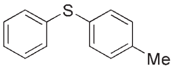
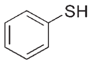
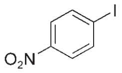
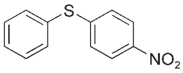
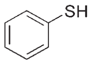
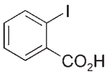
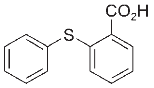
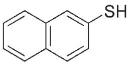
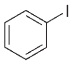
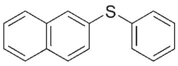
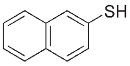
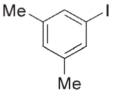
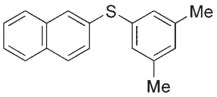
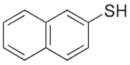
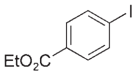
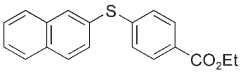
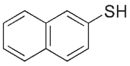
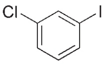
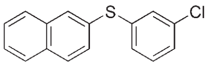
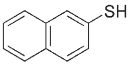
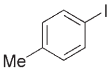
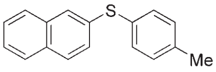
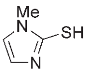
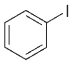
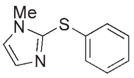
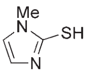
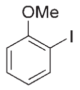
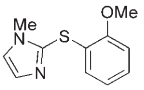
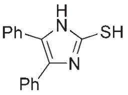
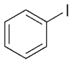
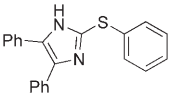
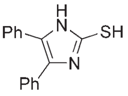
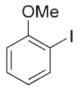
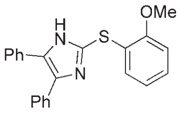
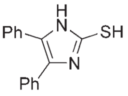
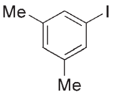
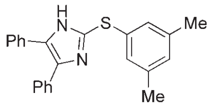
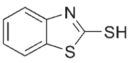
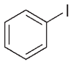
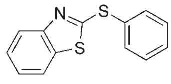
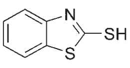
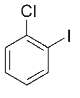
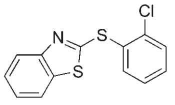
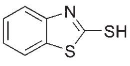
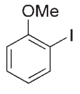
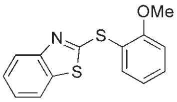
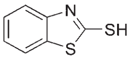
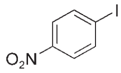
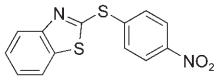
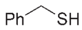
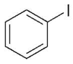
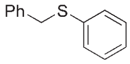
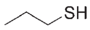
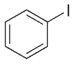
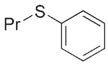
Entry	R-SH	Ar-X	Product		Yield [%][b]
1		 X = I, Br, Cl		**3a**	X = I, 91 X = Br, 0 X = Cl, 0
2				**3b**	98
3				**3c**	88[c]
4				**3d**	90[c]
5				**3e**	85
6				**3f**	84
7				**3g**	81
8				**3h**	85
9				**3i**	91
10				**3j**	52[d]
11				**3k**	71[d]
12				**3l**	61
13				**3m**	33[e]
14				**3n**	32
15				**3o**	91
16				**3p**	80
17				**3q**	91

Table 2: (Continued)

Entry	R-SH	Ar-X	Product		Yield [%][b]
18				**3r**	80
19				**3s**	0
20				**3t**	0

[a] Reaction conditions: R-SH (1.0 equiv), Ar-X (1.5 equiv), $FeCl_3$ (0.1 equiv), DMEDA (0.2 equiv), NaO*t*Bu (2.0 equiv), toluene (1 mL mmol^{-1} of R-SH), 135 °C, 24 h. [b] Yield of isolated product after flash chromatography. [c] Use of R-SH (1.6 equiv) and Ar-X (1.0 equiv). [d] Use of Cs_2CO_3 as base. [e] Use of K_3PO_4 as base.

(Table 2, entries 8 and 16). Importantly, the iron catalyst also proved efficient in coupling reactions of more challenging thiols bearing heterocycles such as benzisothiazole and imidazole, thus allowing access to heterocyclic sulfide derivatives which are present in numerous appealing compounds.[13] Unfortunately, all attempts to couple aliphatic thiols (Table 2, entries 19 and 20) with aryl halides failed. The tolerance of potentially reactive functional groups such as carboxylic acids and esters to the described protocol is remarkable (Table 2, entries 4 and 7, respectively).

In summary, we have developed an efficient iron-catalyzed S-arylation protocol of aromatic and heteroaromatic thiol derivatives, which involves an inexpensive catalyst system formed by combining $FeCl_3$ and DMEDA. This method avoids the use of expensive and/or air-sensitive ligands and provides in most cases the desired sulfide in high yields. At the present stage, the success of the protocol is restricted to the use of aryl iodides as the electrophilic counterpart. This limitation is balanced by the fact that certain synthetically attractive heterocyclic thiols can be used as starting materials, which have not been utilized so far in these kinds of reactions. Overall the novel iron-catalyzed S-arylation reported here constitutes a promising C–S bond-forming process of potential industrial significance because of its operational simplicity and environmental and economic advantages. Its increased efficiency and enlargement of the substrate scope are currently under investigation by our research group.

Experimental Section

General procedure for S-arylation of thiols: A sealable tube equipped with a magnetic stir bar was charged with thiophenol (**1**, 1.0 equiv), NaO*t*Bu (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. Phenyl iodide (**2**, 1.5 equiv), *N*,*N'*-dimethylethylendiamine (0.20 equiv), and toluene (1 mL mmol^{-1} of **1**) 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 stirring the heterogeneous mixture 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 afford the product, which was purified by chromatography on silica gel to yield thioether **3**. 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 the Supporting Information for full details.

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