

Efficient Iron/Copper Cocatalyzed S-Arylations of Thiols with Aryl Halides

Xin Ku, He Huang, Hualiang Jiang, and Hong Liu*

Drug Discovery and Design Centre, State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Shanghai Institutes for Biological Sciences, and Graduate School, Chinese Academy of Sciences, 555 Zuchongzhi Road, Shanghai 201203, China

Received November 12, 2008

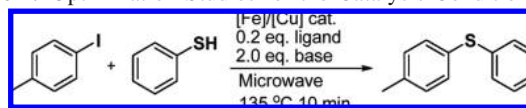
The formation of aryl–sulfur bonds has emerged as a powerful means for the synthesis of many molecules that are of biological, pharmaceutical, and materials interest.¹ However, transition-metal-catalyzed cross-coupling reactions of aryl halides with thiols suffer from many limitations which make it a relatively less studied transformation.² Basically there are two reasons for this: First, thiols can act as catalyst poisons and deactivate metal-based catalysts via strong coordination, often making the catalytic systems totally ineffective.³ Second, thiols are air-sensitive and prone to form undesired disulfides, so most of the C–S cross coupling reactions were performed under inert conditions. To overcome these difficulties, increasing improvements have been made and various catalytic systems have burst onto the scene.^{4–7} Migita et al. first reported cross coupling reactions of aryl halides with thiols in the presence of Pd(PPh₃)₄ in their seminal work in 1980.^{4a} Recently, the application of other metals in the catalytic C–S bond formation resulted in synthetic protocols based on nickel,⁵ cobalt,⁶ and copper.⁷ Iron complexes, which are environmentally benign, inexpensive, and easy-to-handle for industrial applications, used only or in combination with other metals, have recently emerged as appealing catalysts for cross coupling reactions.⁸ Very recently, Bolm et al. has achieved significant success in C–S cross coupling by utilizing catalytic amount of FeCl₃ in combination with *N,N'*-dimethylethylenediamine (DMEDA).^{8c} Although these methods are effective, there is considerable room for improvement. For example, the above-mentioned methods are limited in terms of the substrates for which they can be used; in particular, they are ineffective for aryl chloride, aryl bromides, heterocyclic halides, and aliphatic thiols. It usually requires long reaction times and harsh reaction conditions et al. These disadvantages reduce their ability to construct libraries rapidly and form expected sulfides in a practical fashion. Consequently, it is a highly challenging and desired endeavor to find a readily available, inexpensive and environmentally friendly catalytic system for C–S cross-coupling reactions.

As part of our continuing effort devoted to the development of iron and copper catalyzed cross coupling reactions involving C–C and C–N formation,⁹ we reported here the

first iron/copper cocatalyzed C–S cross coupling reaction in the presence of a catalytic amount of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) under microwave (MW) irradiation. These conditions have been employed in a wide range of substrates including aliphatic thiols, heterocyclic thiols, various substituted aryl thiols, and aryl halides or heterocyclic halides.

Initially, we choose 4-iodotoluene and thiophenol as model substrates to screen the catalysts and optimize the reaction conditions. As shown in Table 1, the preliminary investigation was carried out in *N,N*-dimethylformamide (DMF) under microwave irradiation at 135 °C for 10 min. No desired product was observed in the absence of copper source (Table 1, entries 1–3). Nevertheless, the application of catalytic amounts of FeCl₃ and Cu(acac)₂ provided promising result (61% yield; Table 1, entry 4; acac = acetylacetonate), highlighting the indispensability of the copper catalyst in this process. Combined with Cu(acac)₂ as cocatalyst, Fe₂O₃ outperformed both Fe(acac)₃ and FeCl₃ in higher yields (Table 1, entries 4–6). To our desire, switching Cu(acac)₂ to Cu(OAc)₂ promoted the yield to 94% (Table 1, entry 7), while CuCl₂ was not able to increase the production (Table 1, entry 8). However, catalytic amount of Cu(OAc)₂ or Cu(acac)₂ alone afforded a moderate yield of cross coupling product (Table 1, entries 9 and 10). The more effective base that we have surveyed is Cs₂CO₃ (Table 1, entries 7, 11, and 12). Furthermore, the application of a catalytic amount of simple and inexpensive ligand (TMEDA) impacted pronouncedly on the reaction yields (Table 1, entries 7 and

Table 1. Optimization Studies for the Catalysis Conditions^a



entry	Fe source	Cu source	base	ligand	temp [°C]	time [min]	yield [%] ^b
1	FeCl ₃		Cs ₂ CO ₃	TMEDA	135	10	0
2	Fe(acac) ₃		Cs ₂ CO ₃	TMEDA	135	10	0
3	Fe ₂ O ₃		Cs ₂ CO ₃	TMEDA	135	10	0
4	FeCl ₃	Cu(acac) ₂	Cs ₂ CO ₃	TMEDA	135	10	61
5	Fe(acac) ₃	Cu(acac) ₂	Cs ₂ CO ₃	TMEDA	135	10	70
6	Fe ₂ O ₃	Cu(acac) ₂	Cs ₂ CO ₃	TMEDA	135	10	79
7	Fe ₂ O ₃	Cu(OAc) ₂	Cs ₂ CO ₃	TMEDA	135	10	94
8	Fe ₂ O ₃	CuCl ₂	Cs ₂ CO ₃	TMEDA	135	10	50
9		Cu(acac) ₂	Cs ₂ CO ₃	TMEDA	135	10	70
10		Cu(OAc) ₂	Cs ₂ CO ₃	TMEDA	135	10	69
11	Fe ₂ O ₃	Cu(OAc) ₂	<i>t</i> -BuONa	TMEDA	135	10	81
12	Fe ₂ O ₃	Cu(OAc) ₂	K ₂ CO ₃	TMEDA	135	10	66
13	Fe ₂ O ₃	Cu(OAc) ₂	K ₂ CO ₃	DMEDA	135	10	87
14	Fe ₂ O ₃	Cu(OAc) ₂	Cs ₂ CO ₃	L-proline	135	10	30
15	Fe ₂ O ₃	Cu(OAc) ₂	Cs ₂ CO ₃		135	10	53
16	Fe ₂ O ₃	Cu(OAc) ₂	Cs ₂ CO ₃	TMEDA	150	10	90
17	Fe ₂ O ₃	Cu(OAc) ₂	Cs ₂ CO ₃	TMEDA	120	10	79
18	Fe ₂ O ₃	Cu(OAc) ₂	Cs ₂ CO ₃	TMEDA	135	5	57
19	Fe ₂ O ₃	Cu(OAc) ₂	Cs ₂ CO ₃	TMEDA	135	20	86
20 ^c	Fe ₂ O ₃	Cu(OAc) ₂	Cs ₂ CO ₃	TMEDA	135	10	69
21 ^d	Fe ₂ O ₃	Cu(OAc) ₂	Cs ₂ CO ₃	TMEDA	135	10	88
22 ^e	Fe ₂ O ₃	Cu(OAc) ₂	Cs ₂ CO ₃	TMEDA	135	1200	55

^a Reaction conditions: 4-iodotoluene (1.2 equiv), thiophenol (1.0 equiv), base (2.0 equiv), ligand (0.2 equiv), [Fe] (0.2 equiv), [Cu] (0.1 equiv), DMF, microwave, 135 °C, 10 min. ^b Isolated yield. ^c Water was used as solvent. ^d Dimethyl sulfoxide (DMSO) was used as solvent. ^e Cross-coupling under conventional thermal condition.

* To whom correspondence should be addressed. E-mail: hliu@mail.shnc.ac.cn.

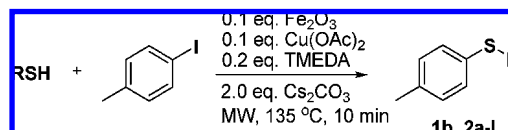
Table 2. Microwave-Assisted Iron/Copper Cocatalyzed S-Arylation of Thiophenol with Different Aryl Halides

entry	aryl halides	product	yield [%]
1			95 (X = I)
			70 (X = Br)
			48 (X = Cl)
2			94 (X = I)
			69 (X = Br)
3			94 (X = I)
			45 (X = Cl)
4			90
5			85
6			95
7			90 (X = I)
			66 (X = Cl)
8			92
9			93
10			82 (X = I)
			72 (X = Br)
11			54 (X = Br) 26 (X = Cl)

13–15). The optimum combination of irradiation time and reaction temperature is 10 min/135 °C (Table 1, entries 16–19). Although the reaction can be performed in water with an acceptable yield, DMF was finalized as the most appropriate solvent with a superior product yield (Table 1, entries 7, 20, and 21). Comparing the microwave-assisted reaction conditions with conventional thermal conditions, apparently the former manifested a significant boost in terms of shorter reaction time and higher yields (Table 1, entries 7 and 22). Remarkably, all the experiments were performed in a mild and practical fashion (air and moisture tolerant), and no undesired disulfide was detected as byproduct.

Under the optimized reaction conditions (0.1 equiv Fe_2O_3 , 0.1 equiv $[\text{Cu}(\text{OAc})_2]$, 0.2 equiv TMEDA, 2.0 equiv Cs_2CO_3 , and DMF, 135 °C, 10 min), we evaluated the scope of this novel transformation among a wide range of electronically and structurally diverse aryl halides.

In general, all the reactions were very clean, and the desired products were obtained in good to excellent yields.

Table 3. Microwave-Assisted Iron/Copper Cocatalyzed S-Arylation of Phenyl Iodide with Various Thiols

entry	thiol	product	yield [%]
1			94
2			90
3			78
4			90
5			93
6			90
7			73
8			70
9			51
10			81
11			88
12			75
13			81

The coupling of thiophenol with aryl halides was quite successful (Table 2). This protocol is tolerant to both electron-withdrawing and electron-donating functional groups (Table 2, entries 2–9), excellent yields were obtained even in the presence of a strongly electron-donating functional group (Table 2, entry 5). In addition, the catalytic system was tolerant of aryl halides bearing cyano and nitro groups (Table 2, entries 6 and 7). Remarkably, sterically demanding ortho-substituents also coupled without any difficulty (Table 2, entry 4). Although aryl bromides and chlorides were proved to be “unreactive” and only limited success had been achieved,^{4f,6} relatively good yield of the desired product was obtained in the presence of our catalytic system (Table 2, entries 2, 7, 10, and 11). Coupling reactions of dihalogenated aryl halides with thiophenol were also tested, and the iodides

showed the highest reactivity (Table 2, entries 8 and 9). This selectivity in favor of the monosubstituted products allows retaining an active halide site for further functionalization. It is noteworthy that the catalytic system was also proved efficient in cross-coupling reactions with more challenging heterocyclic halides, thus allowing easy access to heterocyclic sulfide derivatives which are present in numerous appealing compounds (Table 2, entries 10 and 11).

Studies on the scope of the coupling reactions with respect to a wide array of electronically and structurally diverse thiols were summarized in Table 3. As expected, the tolerance of the catalytic system on thiol counterpart was remarkable. Substrates with electron-withdrawing groups were more reactive than those with electron-donating groups (Table 3, entries 2–5). Highly sterically hindered 2,6-dimethylthiophenol was found to afford excellent yields of the corresponding thioether (Table 3, entry 6). We managed to obtain the desired coupling product of aliphatic thiols with aryl iodide in good yields, consequently provided a new practical protocol for the synthesis of phenyl alkyl sulfide (Table 3, entries 7–9). We also extended the scope of thiol substrates to heterocyclic thiols, and desired coupling products were also successfully obtained in high yields (Table 3, entries 11–13).

In summary, we have developed a highly efficient iron/copper cocatalyzed cross coupling reaction of both aryl and alkyl thiols with aryl halides. To the best of our knowledge, this is the first report of aryl–sulfur bond formation using iron/copper cocatalyst. The reactions were readily facilitated to afford desired thioethers under mild conditions in good to excellent yields. The versatility, air-stability, operational simplicity, low cost and environmental friendliness of this method, in addition to higher yields and shorter reaction time it provides, highlight the potential of using this method in large scale library synthesis involving carbon–heteroatom and C–C bond formation.

Acknowledgment. We gratefully acknowledge financial support from the State Key Program of Basic Research of China (Grant 2006BAI01B02), the National Natural Science Foundation of China (Grants 20721003 and 20872153), the Basic Research Project for Talent Research Group from the Shanghai Science and Technology Commission, and the 863 Hi-Tech Program of China (Grants 2006AA020602).

Supporting Information Available. Detailed experimental procedures and characterization data for all products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References and Notes

- (1) (a) DeMartino, G.; Edler, M. C.; LaRegina, G.; Coluccia, A.; Barbera, M. C.; Barrow, D.; Nicholson, R. I.; Chiosis, G.; Brancale, A.; Hamel, E.; Artico, M.; Silvestri, R. *J. Med. Chem.* **2006**, *49*, 947–954. (b) Gangjee, A.; Zeng, Y.; Talreja, T.; McGuire, J. J.; Kisliuk, R. L.; Queener, S. F. *J. Med. Chem.* **2007**, *50*, 3046–3053. (c) Liu, G.; Huth, J. R.; Olejniczak, E. T.; Mendoza, R.; DeVries, P.; Leitza, S.; Reilly, E. B.; Okasinski, G. F.; Fesik, S. W.; von Geldern, T. W. *J. Med. Chem.* **2001**, *44*, 1202–1210.
- (2) For general reviews, see: (a) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400–5449. (b) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217–6254. (c) Correa, A.; Garcia Mancheno, O.; Bolm, C. *Chem. Soc. Rev.* **2008**, *37*, 1108–1117. (d) Corbet, J. P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651–2710.
- (3) Kondo, T.; Mitsudo, T. *Chem. Rev.* **2000**, *100*, 3205–3220.
- (4) For representative papers on palladium-catalyzed C–S cross coupling reactions, see: (a) Kosugi, M.; Ogata, T.; Terada, M.; Sano, H.; Migita, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3657–3658. (b) Li, G. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 1513–1516. (c) Fernandez-Rodriguez, M. A.; Shen, Q.; Hartwig, J. F. *Chem.–Eur. J.* **2006**, *12*, 7782–7796. (d) Fernandez-Rodriguez, M. A.; Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 2180–2181. (e) Li, G. Y.; Zheng, G.; Noonan, A. F. *J. Org. Chem.* **2001**, *66*, 8677–8681. (f) Itoh, T.; Mase, T. *Org. Lett.* **2004**, *6*, 4587–4590.
- (5) (a) Zhang, Y.; Ngeow, K. C.; Ying, J. Y. *Org. Lett.* **2007**, *9*, 3495–3498. (b) Jammi, S.; Barua, P.; Rout, L.; Saha, P.; Punniyamurthy, T. *Tetrahedron Lett.* **2008**, *49*, 1484–1487.
- (6) Wong, Y. C.; Jayanth, T. T.; Cheng, C. H. *Org. Lett.* **2006**, *8*, 5613–5616.
- (7) For representative papers on copper catalyzed C–S cross coupling reactions, see: (a) Rout, L.; Sen, T. K.; Punniyamurthy, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 5583–5586. (b) Sperotto, E.; van Klink, G. P.; de Vries, J. G.; van Koten, G. J. *Org. Chem.* **2008**, *73*, 5625–5628. (c) Bates, C. G.; Gujadhur, R. K.; Venkataraman, D. *Org. Lett.* **2002**, *4*, 2803–2806. (d) Chen, Y. J.; Chen, H. H. *Org. Lett.* **2006**, *8*, 5609–5612. (e) Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 3517–3520. (f) Ranu, B. C.; Saha, A.; Jana, R. *Adv. Synth. Catal.* **2007**, *349*, 2690–2696.
- (8) For recently representative papers on iron- or iron/copper-catalyzed coupling reactions, see: (a) Bistri, O.; Correa, A.; Bolm, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 586–588. (b) Carril, M.; Correa, A.; Bolm, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 4862–4865. (c) Correa, A.; Carril, M.; Bolm, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 2880–2883. (d) Rao Volla, C. M.; Vogel, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 1305–1307. (e) Correa, A.; Elmore, S.; Bolm, C. *Chem.–Eur. J.* **2008**, *14*, 3527–3529. (f) Bonnamour, J.; Bolm, C. *Org. Lett.* **2008**, *10*, 2665–2667. (g) Taillefer, M.; Xia, N.; Ouali, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 934–936.
- (9) (a) Guo, D.; Huang, H.; Xu, J.; Jiang, H.; Liu, H. *Org. Lett.* **2008**, *10*, 4513–4516. (b) Huang, H.; Jiang, H. L.; Chen, K. X.; Liu, H. *J. Org. Chem.* **2008**, *73*, 9601–9604.

CC800182Q