A reusable $FeCl_3·6H_2O$/cationic 2,2′-bipyridyl catalytic system for the coupling of aryl iodides with thiols in water under aerobic conditions†

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Received 20th November 2008, Accepted 14th January 2009
First published as an Advance Article on the web 22nd January 2009
DOI: 10.1039/b820790a

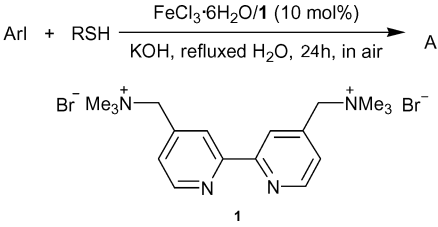
In this study, an $FeCl_3·6H_2O$/cationic 2,2′-bipyridyl system was employed as a catalyst in the coupling of aryl iodides with thiols to form an aryl–sulfur bond in refluxed water under aerobic conditions. The residual aqueous solution after extraction could be reused for several cycles without a significant decrease in activity.

Introduction

Transition-metal-catalyzed cross-coupling of aryl halides with thiols is a powerful method for the formation of carbon–sulfur bonds and is widely used in biological, pharmaceutical, and material science applications.[1] Since Migita and co-workers first reported the cross-coupling of aryl halides with thiols catalyzed by $Pd(PPh_3)_4$,[2] transition-metal-catalyzed formation of sulfur–carbon bonds has been widely employed by synthetic chemists. Several transition-metal catalysts, such as those based on palladium,[3] nickel,[4] copper,[5] and cobalt,[6] have been developed for use in this cross-coupling reaction. Recently, Bolm's group successfully developed a novel catalytic procedure for the S-arylation of aryl iodides with thiols, which uses anhydrous $FeCl_3$/DMEDA as a catalyst and NaO*t*Bu as a base in toluene under an Ar atmosphere.[7] The benefits of this procedure are that iron salt is inexpensive and is less toxic to people and the environment than other transition metals. However, moisture-sensitive NaO*t*Bu is employed as a base, so the use of a dried organic solvent under an inert atmosphere is required, leading to difficulties in recycling the catalyst.

On the other hand, the catalysis of organic reactions by water-soluble transition-metal complexes using water as a solvent has received much attention in recent years due to this green solvent being cheap, nontoxic, safe, and environmentally benign, as compared with organic solvents.[8] Furthermore, the easy separation of the catalyst-containing aqueous solution from the organic products enables reuse of the catalyst. Despite the reporting of iron-catalyzed S-arylation by Bolm's group, this cross-coupling reaction catalyzed by iron in water under air has yet to be developed, and the design of a greener and reusable iron-containing catalytic system for S-arylation is considered of high practical value.

We have recently prepared a water-soluble cationic 2,2′-bipyridyl ligand **1** and used it to bring palladium and rhodium complexes into aqueous phases in order to develop green and reusable catalytic systems for carbon–carbon bond-forming reactions[9] and phenylacetylene polymerizations in water.[10] Herein, we report that the combination of **1** and $FeCl_3·6H_2O$ was an efficient catalytic system for the cross-coupling of aryl iodides with thiols in neat water under air. This operationally-simple reaction enabled easy separation of the catalyst from the organic phase, and the residual aqueous solution could be reused for further reactions without any treatment (Scheme 1).



Scheme 1

Results and discussion

At the outset, 1-iodo-4-nitrobenzene and thiophenol were selected as representative reactants for optimization of the reaction conditions. The influence of bases, ligands, and the oxidation state of iron in the cross-coupling reaction was investigated, and the screening of reaction conditions is summarized in Table 1. The reaction gave the desired product, **4a**, in a 92% isolated yield when the reaction mixture, 1-iodo-4-nitrobenzene (3 mmol) and thiophenol (2 mmol), was stirred in refluxed water (5 mL) under aerobic conditions in the presence of $FeCl_3·6H_2O$/**1** (10 mol%) and 4 mmol KOH for 24 h (Entry 1). Although it is known that iron catalysts can promote the homocoupling of thiols to produce disulfides,[11] in this reaction, the formation of such by-products was diminished by using thiol as the limiting reagent. A ligand-free system afforded the cross-coupling reaction less successfully, the product being afforded in a 55% isolated yield (Entry 2). When $FeCl_2·4H_2O$ was used as the catalyst, 60 and 48% product yields were obtained in the presence and absence of ligand **1**, respectively, under the same conditions (Entries 3 and 4). We found that increasing the amount of ligand or KOH did not improve the yield for the formation of **4a** (Entries 5–7). Several common inorganic bases were employed in this reaction and their effects on the reaction studied: K_3PO_4 provided the arylated product in a 77% yield (Entry 8), whereas the other

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† Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic characterization data of cross-coupling products, and copies of ^1H and ^{13}C NMR of compound **4d**. See DOI: 10.1039/b820790a

Table 1 Optimization studies for the Fe-catalyzed coupling of 1-iodo-4-nitrobenzene (**2a**) with thiophenol (**3a**) in water[a]

Entry	Iron source	Base (mmol)	Yield (%)[b]
1	$FeCl_3·6H_2O$	KOH (4)	92
2[c]	$FeCl_3·6H_2O$	KOH (4)	55
3	$FeCl_2·4H_2O$	KOH (4)	60
4[c]	$FeCl_2·4H_2O$	KOH (4)	48
5[d]	$FeCl_3·6H_2O$	KOH (4)	81
6	$FeCl_3·6H_2O$	KOH (6)	48
7	$FeCl_3·6H_2O$	KOH (8)	40
8	$FeCl_3·6H_2O$	K_3PO_4 (4)	77
9	$FeCl_3·6H_2O$	K_2CO_3 (4)	41
10	$FeCl_3·6H_2O$	KF (4)	22
11	$FeCl_3·6H_2O$	CsF (4)	trace
12	$FeCl_3·6H_2O$	Cs_2CO_3 (4)	54
13	$FeCl_3·6H_2O$	KOAc (4)	trace

[a] Reaction conditions: **2a** (3 mmol), **3a** (2 mmol), [Fe] (10 mol%), **1** (10 mol%), base, H_2O (5 mL), refluxed for 24 h. [b] Isolated yields. [c] In the absence of **1**. [d] 20 mol% of **1** was used.

bases gave only trace amounts or moderate yields of the product (Entries 9–13).

The reusability of the aqueous catalytic system is very important from the practical and economic viewpoints. We chose the conditions of the presence and absence of ligand **1** for comparison (Table 1, Entry 1 and 2). For the reaction in the presence of **1**, after completion of the cross-coupling reaction of 1-iodo-4-nitrobenzene with thiophenol, the reaction mixture was extracted with hexane and the product was purified by column chromatography. The remaining aqueous solution was then charged with 1-iodo-4-nitrobenzene, thiophenol and base for the second-run reaction. As shown in Fig. 1, it was possible to use the catalyst-containing aqueous solution at least six times with only a slight decrease in activity. On the contrary, the activity of the iron catalyst was drastically decreased in each cycle and approached zero in the fifth cycle when the system lacked ligand **1**. Ligand **1** was therefore revealed to be important, not only through its stabilization of the iron salt in the aqueous phase, enabling the reuse of the catalytic system, but also because the ionic parts of the ligand may play a surfactant role and facilitate the reaction in neat water. It should be noted that the use of this water-soluble cationic 2,2′-bipyridyl/$FeCl_3·6H_2O$ catalytic system enabled easy separation of the catalyst from the organic phase and the use of a simple reaction procedure under air.

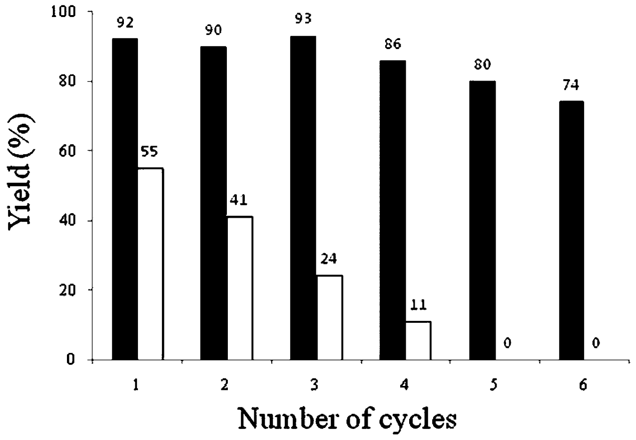


Fig. 1 Recyclability of $FeCl_3·6H_2O$/**1** (■) *versus* $FeCl_3·6H_2O$ (□) for the coupling of 1-iodo-4-nitrobenzene with thiophenol. *Reaction conditions*: 1-iodo-4-nitrobenzene (3 mmol), thiophenol (2 mmol), KOH (4 mmol), and catalyst (10 mol%) under refluxed H_2O (5 mL) for 24 h for each cycle.

In order to clarify whether the gradual loss of activity from the fourth cycle onwards in the presence of **1** was due to the successive extraction or deactivation of the catalyst, a successive addition experiment was performed. After completion of the first run (24 h), a fresh portion of 1-iodo-4-nitrobenzene, thiophenol, KOH, and water was added directly to the unseparated reaction mixture and the second cycle was executed under conditions identical to those of the first run; this procedure was repeated until the completion of the sixth cycle. We found that the overall isolated yield of **4a** was 558%, corresponding to an average of 93% yield for each cycle. This result excludes the possibility of deactivation of the catalyst during the reactions and indicates that the successive extraction in the previous recycling studies led to the decrease in the catalyst concentration in each cycle.

To explore the scope of this cross-coupling reaction catalyzed by our system, the reactions of a variety of aryl iodides and thiols were examined and the amount of disulfides formed was also analyzed (Table 2). 1-Iodo-4-nitrobenzene coupled with various aryl thiols efficiently to give the corresponding products **4b–d** in high yields (Entries 1–3), and the employment of 1-iodo-3-nitrobenzene resulted in the formation of **4e–h** in good yields. Although a slower cross-coupling rate led to the formation of a small amount of disulfide, it could be separated easily upon purification (Entries 4–7). Cross-coupling reactions with 1-chloro-4-iodobenzene proceeded exclusively at the C–I group, affording chloro-substituted thioethers (Entries 8–10). Entries 11–19 illustrate that iodobenzene and electron-rich iodotoluene were also effectively coupled with thiols, affording the corresponding thioethers in 64–96% yields. When 4-iodobenzonitrile and ethyl-4-iodobenzoate were used as the substrates, the hydrolyzed product **4r** was the sole cross-coupling product, obtained in high yields under such reaction conditions (Entries 20 and 21). Contrary to the first reported iron-catalyzed S-arylation system,[7] aliphatic thiols such as benzyl mercaptan coupled with aryl iodides in our system to give **4s** and **4t** in 25 and 22% yields along with 11 and 12% of disulfides, respectively (Entries 22 and 23).

Experimental

General procedure for the iron-catalyzed carbon–sulfur bond formation reaction

A 20 mL reactor equipped with a condenser was charged with $FeCl_3·6H_2O$ (54 mg, 0.2 mmol), ligand **1** (92 mg, 0.2 mmol) and H_2O (5 mL). After stirring at 50 °C for 0.5 h, aryl iodide **2** (3.0 mmol), thiol **3** (2.0 mmol) and KOH (4.0 mmol) were added to the solution, and the reaction mixture was then stirred under reflux conditions in air for 24 h. After cooling of the reaction mixture to room temperature, the aqueous solution was extracted with hexane; the organic layer was dried over $MgSO_4$ and the solvent was then removed under vacuum. Column chromatography on silica gel afforded the desired product.

Table 2 Results of $FeCl_3 \cdot 6H_2O$/**1**-catalyzed coupling of aryl iodides (**2**) with thiols (**3**) in water[a]

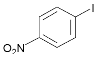
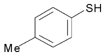
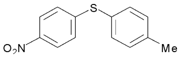
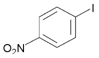
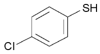
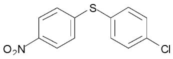
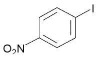
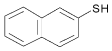
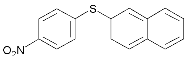
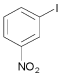
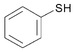
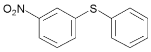
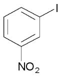
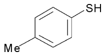
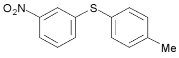
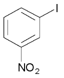
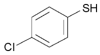
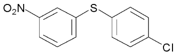
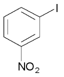
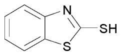
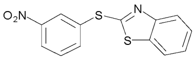
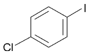
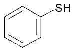
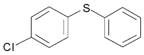
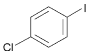
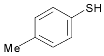
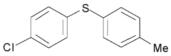
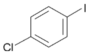
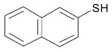
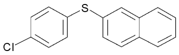
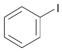
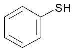
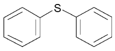
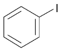
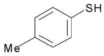
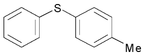
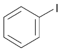
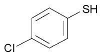
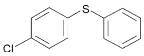
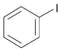
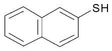
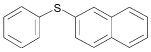
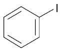
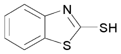
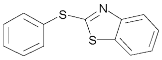
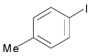
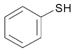
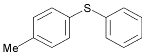
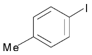
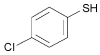
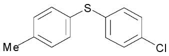
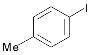
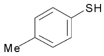
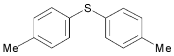
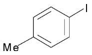
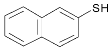
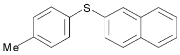
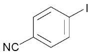
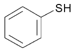
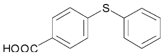
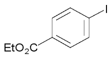
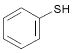
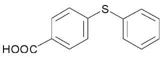
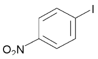
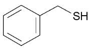
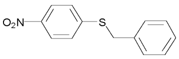
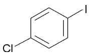
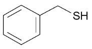
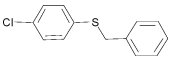
			Yield (%)[b]	
Entry	Aryl iodide (**2**)	Thiol (**3**)	ArSR (**4**)	RSSR (**5**)
1			 **4b**, 80	0
2			 **4c**, 99	0
3			 **4d**, 86	0
4			 **4e**, 68	10
5			 **4f**, 56	15
6			 **4g**, 77	8
7			 **4h**, 83	0
8			 **4i**, 99	0
9			 **4j**, 81	0
10			 **4k**, 87	0
11			 **4l**, 89	0
12			 **4m**, 96	0
13			 **4i**, 94	0
14			 **4n**, 70	13
15			 **4o**, 92	0
16			 **4m**, 82	0
17			 **4j**, 74	9
18			 **4p**, 87	0
19			 **4q**, 64	12
20			 **4r**, 92	0

Table 2 *(Contd.)*

Entry	Aryl iodide (**2**)	Thiol (**3**)	Yield (%)[b] ArSR (**4**)	 RSSR (**5**)
21			 **4r**, 87	0
22			 **4s**, 25	11
23			 **4t**, 22	12

[a] Reaction conditions: **2** (3 mmol), **3** (2 mmol), $FeCl_3 \cdot 6H_2O$ (10 mol%), **1** (10 mol%), KOH (4 mmol), H_2O (5 mL), refluxed for 24 h. [b] Isolated yields.

Conclusions

In this paper, we have developed a green and reusable catalytic system for the coupling of aryl iodides with thiols using environmentally-friendly and cheap $FeCl_3 \cdot 6H_2O$ as a catalyst in the greenest solvent, water. This method avoids the use of air-sensitive reagents and the reaction can therefore be performed under air, rendering the experimental procedure very simple. In addition, the catalytic system can be reused at least six times with only a slight decrease in activity, indicating its potential for use in industrial applications. Further mechanistic studies on this reaction and the applicability of this green system in other organic syntheses are now under investigation in our group.

Acknowledgements

This research was financially supported by the National Science Council of Taiwan (NSC96-2113-M-027-003-MY2).

Notes and references

1 D. J. Procter, *J. Chem. Soc., Perkin Trans. 1*, 2001, 335; G. Liu, J. R. Huth, E. T. Olejniczak, R. Mendoza, P. DeVries, S. Leitza, E. B. Reilly, G. F. Okasinski, S. W. Fesik and T. W. Von Geldern, *J. Med. Chem.*, 2001, **44**, 1202; J. Hassan, M. Sevignon, C. Gozzi, E. Schulz and M. Lemaire, *Chem. Rev.*, 2002, **102**, 1359; S. V. Ley and A. W. Thomas, *Angew. Chem., Int. Ed.*, 2003, **42**, 5400; I. P. Beletskaya and A. V. Cheprakov, *Coord. Chem. Rev.*, 2004, **248**, 2337; G. De Martino, M. C. Edler, G. La Regina, A. Coluccia, M. C. Barbera, D. Barrow, R. I. Nicholson, G. Chiosis, A. Brancale, E. Hamel, M. Artico and R. Silvestri, *J. Med. Chem.*, 2006, **49**, 947; J.-P. Corbet and G. Mignani, *Chem. Rev.*, 2006, **106**, 2651; I.-P. Beletskaya and V. P. Ananikov, *Eur. J. Org. Chem.*, 2007, 3431; A. Gangjee, Y. Zeng, T. Talreja, J. J. McGuire, R. L. Kisliuk and S. F. Queener, *J. Med. Chem.*, 2007, **50**, 3046.

2 T. Migita, T. Shimizu, Y. Asami, J. Shiobara, Y. Kato and M. Kosugi, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 1385; M. Kosugi, T. Ogata, M. Terada, H. Sano and T. Migita, *Bull. Chem. Soc. Jpn.*, 1985, **58**, 3657.

3 G. Y. Li, *Angew. Chem., Int. Ed.*, 2001, **40**, 1513; U. Schopfer and A. Schlapbach, *Tetrahedron*, 2001, **57**, 3069; M. Murata and S. L. Buchwald, *Tetrahedron*, 2004, **60**, 7397; T. Itoh and T. Mase, *Org. Lett.*, 2004, **6**, 4587; C. Mispelaere-Canivet, J.-F. Spindler, S. Perrio and P. Beslin, *Tetrahedron*, 2005, **61**, 5253; M. A. Fernández-Rodríguez, Q. Shen and J. F. Hartwig, *J. Am. Chem. Soc.*, 2006, **128**, 2180.

4 H. J. Cristau, B. Chabaud, A. Chêne and H. Christol, *Synthesis*, 1981, 892; K. Takagi, *Chem. Lett.*, 1987, 2221; V. Percec, J.-Y. Bae and D. H. Hill, *J. Org. Chem.*, 1995, **60**, 6895; C. Millois and P. Diaz, *Org. Lett.*, 2000, **2**, 1705.

5 P. S. Herradura, K. A. Pendola and R. K. Guy, *Org. Lett.*, 2000, **2**, 2019; C. Palomo, M. Oiarbide, R. Lopez and E. Gomez-Bengoa, *Tetrahedron Lett.*, 2000, **41**, 1283; C. G. Bates, R. K. Gujadhur and D. Venkataraman, *Org. Lett.*, 2002, **4**, 2803; F. Y. Kwong and S. L. Buchwald, *Org. Lett.*, 2002, **4**, 3517; C. Savarin, J. Srogl and L. S. Liebeskind, *Org. Lett.*, 2002, **4**, 4309; Y.-J. Wu and H. He, *Synlett*, 2003, 1789; C. G. Bates, P. Saejueng, M. Q. Doherty and D. Venkataraman, *Org. Lett.*, 2004, **6**, 5005; W. Deng, Y. Zou, Y.-F. Wang, L. Liu and Q.-X. Guo, *Synlett*, 2004, 1254; Y.-J. Chen and H.-H. Chen, *Org. Lett.*, 2006, **8**, 5609; D. Zhu, L. Xu, F. Wu and B. Wan, *Tetrahedron Lett.*, 2006, **47**, 5781; L. Rout, T. K. Sen and T. Punniyamurthy, *Angew. Chem., Int. Ed.*, 2007, **46**, 5583; X. Lu and W. Bao, *J. Org. Chem.*, 2007, **72**, 3863; H. Zhang, W. Cao and D. Ma, *Synth. Commun.*, 2007, **37**, 25; M. Carril, R. SanMartin, E. Dominguez and I. Tellitu, *Chem.–Eur. J.*, 2007, **13**, 5100; L. Rout, P. Saha, S. Jammi and T. Punniyamurthy, *Eur. J. Org. Chem.*, 2008, 640.

6 Y.-C. Wong, T. T. Jayanth and C.-H. Cheng, *Org. Lett.*, 2006, **8**, 5613.

7 A. Correa, M. Carril and C. Bolm, *Angew. Chem., Int. Ed.*, 2008, **47**, 2880.

8 For reviews see: C. J. Li, *Chem. Rev.*, 1993, **93**, 2023; G. Papadogianakis and R. A. Sheldon, *New J. Chem.*, 1996, **20**, 175; B. Cornils, *J. Mol. Catal. A: Chem.*, 1999, **143**, 1; J. P. Genet and M. Savignac, *J. Organomet. Chem.*, 1999, **576**, 305; *Synthesis Methods in Organometallic and Inorganic Chemistry*, ed. W. A. Herrmann, Enke, Stuttgart, 2000; *Aqueous-Phase Organometallic Catalysis*, ed. B. Cornils and W. A. Herrmann, Wiley-VCH, Weinhein, Germany, 2004; C.-J. Li, and T.-H. Chan, *Organic Reactions in Aqueous Media*, John Wiley & Sons, New York, 1997; *Organic Synthesis in Water*, ed. P. A. Grieco, Blackie Academic and Professional, London, 1998; N. E. Leadbeater, *Chem. Commun.*, 2005, 2881; C. J. Li, *Chem. Rev.*, 2005, **105**, 3095; C. J. Li and L. Chen, *Chem. Soc. Rev.*, 2006, **35**, 68; I. T. Horvath and P. T. Anastas, *Chem. Rev.*, 2007, **107**, 2167; D. Dallinger and C. O. Kappe, *Chem. Rev.*, 2007, **107**, 2563.

9 W.-Y. Wu, S.-N. Chen and F.-Y. Tsai, *Tetrahedron Lett.*, 2006, **47**, 9267; S.-N. Chen, W.-Y. Wu and F.-Y. Tsai, *Tetrahedron*, 2008, **64**, 8164.

10 Y.-H. Wang and F.-Y. Tsai, *Chem. Lett.*, 2007, 1492.

11 H. M. Meshram and R. Kache, *Synth. Commun.*, 1997, **27**, 2403; N. Iranpoor and B. Zeynizadeh, *Synthesis*, 1999, 49.