Recyclable Iron/Graphite Catalyst for C–S Cross Coupling of Thiols with Aryl Halides under Ligand-Free Conditions

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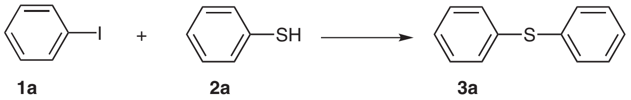
Abstract: A recyclable iron/graphite (Fe/Cg) catalyst for the efficient C–S cross-coupling of various iodoarenes with aromatic/aliphatic thiols has been developed under ligand-free conditions (26 examples, up to 99% yield). The catalyst can be easily recovered and recycled up to seven cycles without loss of activity.

Key words: arylhalides, cross-coupling, recyclable catalyst, iron, thiols

Organosulfur compounds have wide applications in medicinal and material chemistry. Their preparations are a bit challenging owing to the deactivation of metal by sulfur due to its strong co-ordinating properties. Various Metals viz. Pd,[1] Cu,[2] Ni,[3] Co,[4] La,[5] etc. are all well explored for C–S bond formation and the very recent development of iron-catalyzed sustainable reactions has drawn the attention of the scientific community.[6] Though C–S cross-coupling of aryl halides with thiols employing iron catalysts are reported,[7] none of these are recyclable and apart from this the recent ones using phosphine ligands [8] makes these methods more expensive from the economic point of view. Considering the above limitations, a recyclable protocol employing iron is highly desirable. Therefore in continuation to our sustainable method development program[9] we present herein our recently innovated Fe/Cg[10] catalyst for the C–S cross coupling of various iodoarenes with aromatic/aliphatic thiols under ligand-free conditions. Metals dispersed on graphite, viz. M–graphite (M = K, Zn, Sn, Fe, Ti, Pd),[11] are reported for organic transformations, but their tedious preparation procedures limit their usage as catalysts. However, our iron–graphite catalyst was prepared via simple easy-to-handle procedure in which, Fe(III)(acac)$_3$ was dispersed on graphite simply by stirring in THF solution under nitrogen atmosphere. The amount of iron was found to be 4.3% on graphite by ICP-AES analysis.[12] The catalytic performance of Fe/Cg along with various iron catalysts like Fe/C, nano Fe_3O_4, and nano Fe_2O_3 was screened for the thioetherification of iodobenzene and thiophenol as model reaction, in combination with various bases like Na_2CO_3, K_2CO_3, K_3PO_4, etc. and solvents toluene, 1,4-dioxane, DMSO, DMF, etc. for the catalyst, base, and solvent optimization (as summarized in Table 1). The best combination turned out to be DMSO as solvent and KOH as the base for the optimum yields obtained (Figure 1). However, the reaction in the presence of Fe(III)(acac)$_3$ or graphite alone gave very low yields of the product (Table 1). The bromo/chloro benzenes were also screened using the same combination of solvent and base. Of all the iron catalysts employed with various bases, solvents, and aryl halides, Fe/Cg-catalyzed reaction of iodobenzene with thiophenol using DMSO–KOH gave the best results (Figure 1).

Table 1 Optimization of Fe/Cg-Ccatalyzed Iodobenzene Reaction with Thiophenol[a]



Entry	Fe catalyst	Base	Solvent	Temp (°C)	Yield (%)
1	Fe/Cg	Cs_2CO_3	DMSO	125	52
2	Fe/Cg	K_3PO_4	DMSO	125	56
3	Fe/Cg	K_2CO_3	DMSO	125	traces
4	Fe/Cg	KO*t*-Bu	DMSO	125	44
5	Fe/Cg	Na_2CO_3	DMSO	125	traces
6	Fe/Cg	NaOH	DMSO	125	86
7	Fe/Cg	KOH	DMSO	125	99
8	Fe/C	KOH	DMSO	125	69
9	nanoFe_2O_3	KOH	DMSO	125	72
10	nanoFe_3O_4	KOH	DMF	125	51
11	Fe/Cg	KOH	toluene	125	60
12	Fe/Cg	KOH	dioxane	125	24
13	Fe/Cl_3	KOH	DMSO	125	traces
14	Fe/Cl_2	KOH	DMSO	125	traces
15	Fe(acac)$_3$	KOH	DMSO	125	8
16	graphite	KOH	DMSO	125	5

[a] Reaction conditions: Fe/Cg (7 wt%, 162 mg), iodobenzene (1.2 mmol), thiophenol (1.0 mmol), solvent (1.5 mL), base (2.0 mmol), under N_2 atmosphere for 24 h.

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Table 2 Fe/Cg-Catalyzed Coupling of Iodoarenes with Thiols[a]

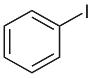
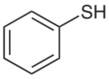
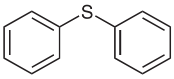
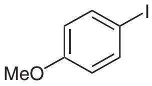
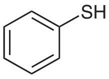
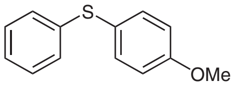
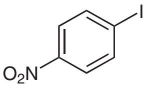
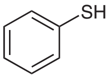
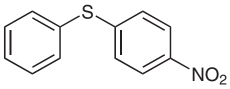
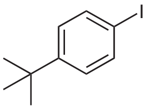
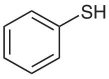
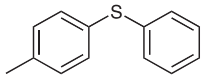
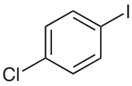
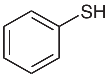
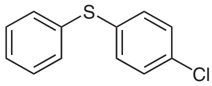
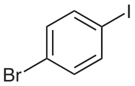
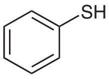
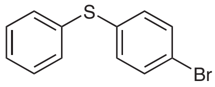
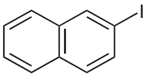
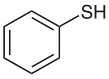
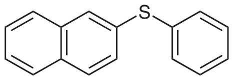
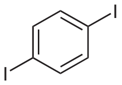
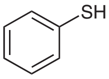
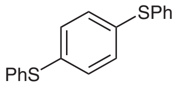
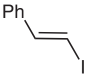
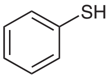
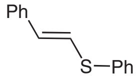
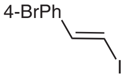
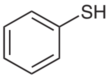
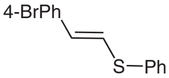
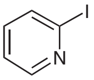
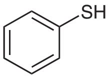
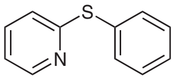
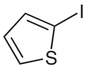
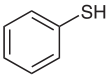
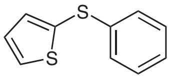
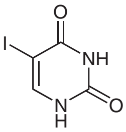
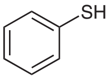
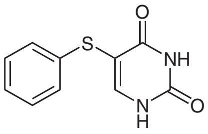
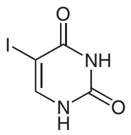
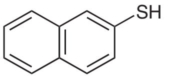
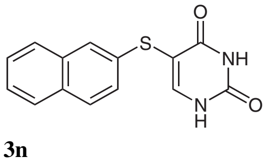
Entry	Iodoarene **1**	Thiol **2**	Product **3**	Yield (%)[b]
1			 **3a**	98
2			 **3b**	67
3			 **3c**	89
4			 **3d**	90
5			 **3e**	71
6			 **3f**	86
7			 **3g**	85
8			 **3h**	82[c]
9			 **3i**	97
10			 **3j**	92
11			 **3k**	91
12			 **3l**	95
13			 **3m**	78

Table 2 Fe/Cg-Catalyzed Coupling of Iodoarenes with Thiols[a] (continued)

Entry	Iodoarene **1**	Thiol **2**	Product **3**	Yield (%)[b]
14			 **3n**	72

[a] Reaction conditions: Fe/Cg (7 wt%, 162 mg), iodoarene (1.2 mmol), thiol (1.0 mmol), DMSO (1.5 mL), KOH (2.0 mmol), 125 °C under nitrogen atmosphere were stirred for 24 h.

[b] Isolated yield.

[c] Conditions: 2 equiv thiophenol.

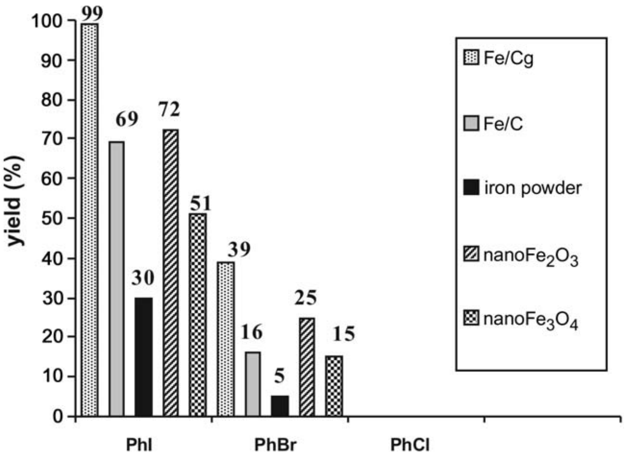
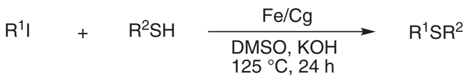


Figure 1



$$R^1I \quad + \quad R^2SH \xrightarrow[\text{DMSO, KOH}\ 125\ °C,\ 24\ h]{\text{Fe/Cg}} R^1SR^2$$

Scheme 1 Fe/Cg-catalyzed cross-coupling

Thus the optimized reaction conditions for the desired C–S cross-coupling were found to be 7 wt% (162 mg) [13] of Fe/Cg, 2.0 equiv of KOH, 125 °C with DMSO (1.5 mL) as solvent. The yields were higher with DMSO when compared to other solvents such as DMF, toluene, and dioxane. The most probable explanation for the strong dependence of the reaction on the solvent system, especially DMSO, may be due to the formation of dimsyl ion in the presence of KOH forming an equilibrium by proton exchange with RSH, leading to the formation of RS^- thus accelerating the reaction. The formation of dimsyl ion with KOH and similar type of equilibrium with ROH is already well established.[14] A variety of bases were screened in which NaOH and KOH provided the product in good to excellent yields with KOH giving the maximum yield (Table 1, entries 6 and 7), whereas the yields were moderate with bases like Cs_2O_3, K_3PO_4, and KO*t*-Bu. With the optimized conditions on hand, we have put a variety of iodobenzenes to test viz. substituted iodoarenes, iodouracils, vinyl iodides, heteroiodoarenes for thioetherification. It can be seen from Table 2 that the reaction of these iodobenzenes afforded aryl sulfides in excellent to good yields. The reaction of thiophenol with electron-withdrawing, electron-releasing *para*-substituted iodoarenes afforded good yields of coupled partners (entries 2–6, Table 2). The heteroarenes, iodouracils, and vinyl iodides successfully cross-coupled in good to excellent yields (entries 9–12) exemplifying the catalyst's efficiency. We have further put many aliphatic thiols to test the efficiency of the catalyst in converting the aryl halides to coupled products. This was summarized in Table 3 where many aliphatic thiols were successfully coupled to afford thioethers in moderate to excellent yields. This reaction might be proceeding by the activation of aryl halide by iron in the layers of graphite which further reacts with the mercapto nucleophile as proposed by Nagai et al. in the case of alkylation of phenols.[15] Next, we studied recyclability of the catalyst. The catalyst was easily separated by centrifugation and washed with ethyl acetate followed by acetone, then dried in a hot air oven at 80 °C and employed for the next reaction. It was observed to be recyclable up to seven cycles without loss of activity (Figure 2). To check whether any iron has leached into the solution during the reaction, the supernatant after the reaction was subjected to ICP-AES analysis and we found that 0.005% of iron has leached into the reaction mixture. The XPS[16] and IR spectral studies confirmed that $Fe(acac)_3$ on graphite is intact even after the seventh cycle.[17] To rule out the possibility that the reaction was catalyzed by traces of copper impurities,[18] we analyzed iron/graphite carefully by XPS, EDX, and ICP analysis. The spectral analysis has shown no signature of copper (934.5 eV binding-energy curve in XPS was absent).

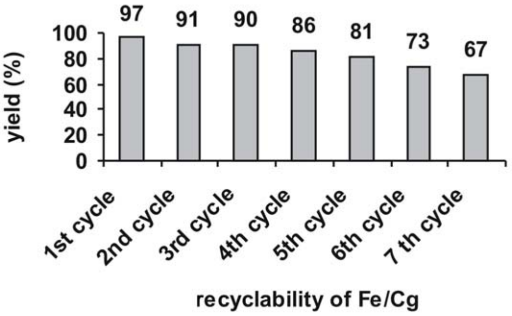
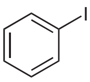
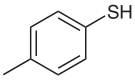
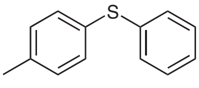
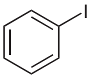
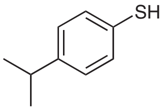
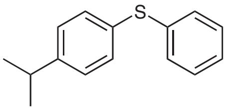
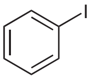
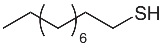
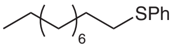
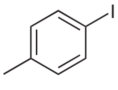
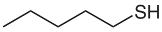
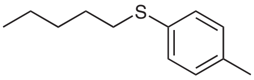
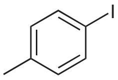
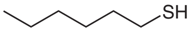
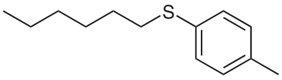
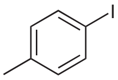
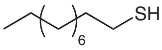
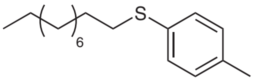
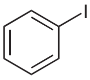
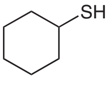
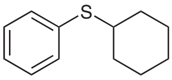
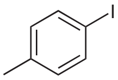
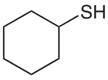
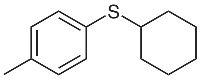
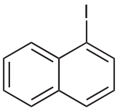
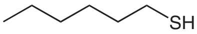
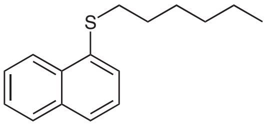
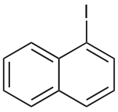
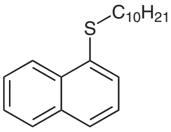
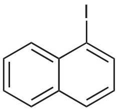
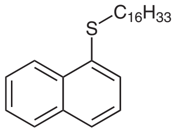
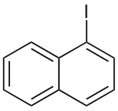
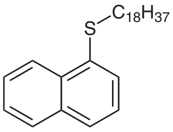


Figure 2 Recyclability of Fe/Cg catalyst

Table 3 Fe/Cg-Catalyzed Coupling of Iodoarenes with Thiols[a]

Entry	Iodoarene **1**	Thiol **2**	Product **3**	Yield (%)[b]
1			 **3o**	91
2			 **3p**	84
3			 **3q**	68
4			 **3r**	81
5			 **3s**	75
6			 **3t**	73
7			 **3u**	92
8			 **3v**	83
9			 **3w**	76
10		*n*-$C_{10}H_{21}$	 **3x**	68
11		*n*-$C_{16}H_{33}$	 **3y**	61
12		*n*-$C_{18}H_{37}$	 **3z**	58

[a] Reaction conditions: Fe/Cg (7 wt%, 162 mg), iodoarene (1.2 mmol), thiol (1.0 mmol), DMSO (1.5 mL), KOH (2.0 mmol), 125 °C under nitrogen atmosphere were stirred for 24 h.

[b] Isolated yield.

ICP-AES and EDX analysis also showed no traces of Cu, thus ruling out the possibility of traces of copper catalyzing the reaction.

In conclusion we have developed a novel catalytic system employing heterogeneous iron catalyst, which can be easily prepared from the readily available raw materials and can be recycled up to seven cycles without loss of activity for thioetherification reaction.[19]

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(19) **Typical Procedure for C–S Cross-Coupling**
Fe/Cg (7 wt%, 162 mg) was added to a 25 mL flask, which was previously charged with iodoarene (1.2 mmol), thiol (1 mmol) and KOH (2.0 equiv). Dry DMSO (1.5 mL) was added while purging the flask with nitrogen. The round-bottom flask was purged once again and back filled with nitrogen and heated in an oil bath at 125 °C for a period of 24 h after which the flask was removed from the oil bath and allowed to come to r.t. Fe/Cg was removed by ultracentrifugation at 8000 rpm. After which the reaction mixture was poured into H_2O (5 mL), and the aqueous layer was extracted with EtOAc (3 × 10 mL).