doi:10.1246/cl.2012.585

Magnetically Separable $CuFe_2O_4$ Nanoparticle Catalyzed C–Se Cross Coupling in Reusable PEG Medium

K. Harsha Vardhan Reddy, G. Satish, K. Ramesh, K. Karnakar, and Y. V. D. Nageswar*
Natural Product Chemistry, Indian Institute of Chemical Technology, Hyderabad-500 607, India

(Received February 13, 2012; CL-120121; E-mail: yvdnrao@iict.res.in)

A simple and efficient procedure for the synthesis of unsymmetrical diaryl selenides has been developed by magnetically separable $CuFe_2O_4$ nanoparticle catalyzed reactions of organoboranes with PhSeBr in recyclable PEG-400 medium at 80 °C and Cs_2CO_3 as base. Using this protocol, a variety of unsymmetrical selenides were obtained in good to excellent yields. The copper ferrite nanoparticles were magnetically separated, recycled, and reused up to four cycles.

Diaryl selenides act as versatile reagents and useful synthons in organic synthesis and catalysis. These are also known for their significant biological activities such as antioxidant, antitumor, antiinfective, enzyme inhibition, glutathione peroxidase mimicking, and immunomodulation.[1] In addition organic selenides are important products used in the formation of selenonium salts, selenium dihalides, selenoxides, and selenimines.[2,3]

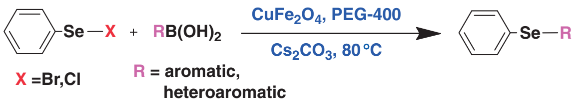
Traditional methods for the preparation of diaryl selenides involve the reaction of metal selenides or selenocyanates with aryl halides, formation of selenides via diazonium intermediates, cross coupling of aryl halides with aryl selenols[4] and conversion of aryl halides to diaryl selenides via the formation of aryllithium, arylmagnesium, or aryltin compounds.[5] Several of these methods include multiple steps, often requiring harsh reaction conditions, such as use of polar and toxic solvents such as HMPA (hexamethylphosphoric triamide) and high reaction temperatures.[6] To overcome these limitations various metal salts such as iron,[7] copper,[4,5,8] nickel,[9] palladium,[10] indium,[11] and lanthanum[12] based catalytic systems were studied to assess their efficacy in the synthesis of diaryl selenides.

Poly(ethylene glycol) (PEG) has emerged as a powerful phase-transfer catalyst and is utilized in many useful organic transformations under mild reaction conditions. Moreover, PEG is inexpensive, recyclable,[13] less flammable, less toxic, and miscible with wide variety of organic solvents, rendering the status of an eco-friendly alternative solvent for various organic transformations such as coupling,[14] substitution,[15] oxidation,[16] addition,[17] and reduction reactions.[18]

In recent years, heterogeneous catalysts have attracted the attention of researchers due to their economic and industrial significance, and published reports indicate that they score over homogeneous catalysts. Among these, nanoscale heterogeneous catalysts are highly preferred as they offer high surface area and low-coordinated sites, which are responsible for the higher catalytic activity,[19] having the advantage of easy product purification, and reusability of the catalyst.

However, recently very few methods have been developed using electrophilic substitution by $ArSe^+$ using milder nucleophiles like aryl boronic acids for the synthesis of diaryl selenides.[20] In continuation of our interest in the field of copper-catalyzed cross-coupling reactions,[21] we report herein magnetically separable $CuFe_2O_4$ nanoparticle catalyzed reactions of phenylboronic acids with phenylselenyl bromide forming unsymmetrical diphenyl selenides under ligand-free conditions in PEG, as a reusable solvent medium (Scheme 1).

Initially, phenylselenyl bromide and phenylboronic acid were used as model substrates to optimize the reaction conditions such as bases, solvents, and reaction temperature (Table 1). Among several bases screened, Cs_2CO_3 was found to be an excellent base (Table 1, Entry 5). Among other bases KOH also gave moderate yields (Table 1, Entry 1). In presence of bases such as K_2CO_3, Na_2CO_3, and K_3PO_4, lesser amount of the desired product was obtained (Table 1, Entries 2–4). The effect of solvents was also investigated and the highest yield was observed in PEG (Table 1, Entry 5), while reaction in solvents such as DMSO and THF also resulted in moderate yields (Table 1, Entries 7 and 8). A control experiment confirmed that the reaction did not occur in the absence of the base (Table 1, Entry 9). When the reaction was conducted at room temperature



Scheme 1. $CuFe_2O_4$ nanoparticle catalyzed synthesis of unsymmetrical diaryl selenides.

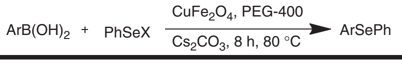
Table 1. Screening of $CuFe_2O_4$ nanoparticle catalyzed synthesis of unsymmetrical diaryl selenides[a]

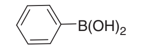
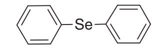
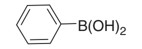
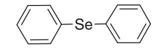
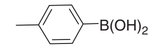
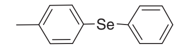
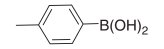
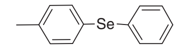
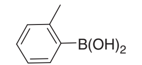
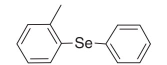
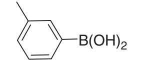
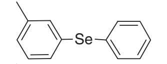
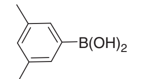
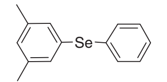
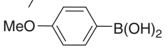
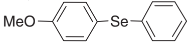
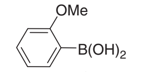
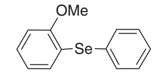
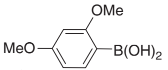
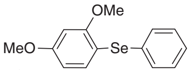
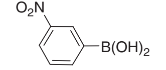
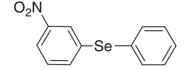
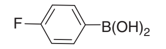
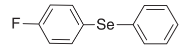
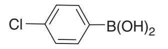
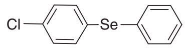
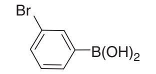
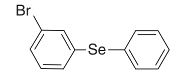
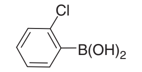
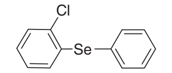
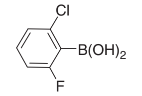
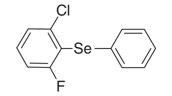
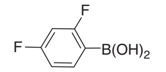
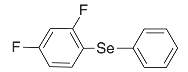
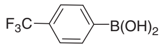
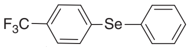
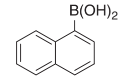
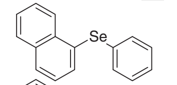
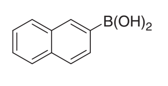
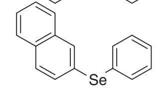
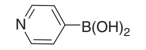
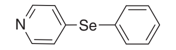
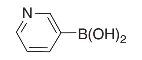
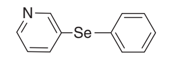
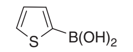
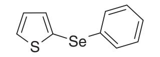
$$\text{PhSeBr} + \text{PhB(OH)}_2 \xrightarrow[\text{solvent, base}]{\text{CuFe}_2\text{O}_4\ (5.0\ \text{mol\%})} \text{PhSePh}$$

Entry	Catalyst	Base	Solvent	Temp/°C	Yield/%[b]
1	nano CuO	KOH	PEG	80	62
2	nano CuO	K_2CO_3	PEG	80	40
3	nano CuO	Na_2CO_3	PEG	80	20
4	nano CuO	K_3PO_4	PEG	80	34
5	**nano CuO**	**Cs_2CO_3**	**PEG**	**80**	**90**
6	nano CuO	Cs_2CO_3	PEG	rt	trace
7	nano CuO	Cs_2CO_3	DMSO	80	82
8	nano CuO	Cs_2CO_3	THF	80	50
9	nano CuO	—	PEG	80	0
10	nano Y_2O_3	Cs_2CO_3	PEG	80	15
11	nano NiO	Cs_2CO_3	PEG	80	trace
12	nano Co_3O_4	Cs_2CO_3	PEG	80	13
13	nano $NiFe_2O_4$	Cs_2CO_3	PEG	80	10
14	nano $CoFe_2O_4$	Cs_2CO_3	PEG	80	14

[a]Reaction conditions: Phenylselenyl bromide (1.0 mmol), phenylboronic acid (1.0 mmol), $CuFe_2O_4$ (5.0 mol %), base (2.0 equiv), solvent (3.0 mL), 80 °C, 8 h. [b]Isolated yield.

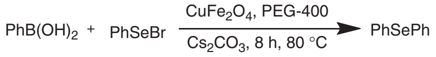
Table 2. C–Se cross coupling of organoboranes with phenylselenyl bromide[a]



Entry	Boronic acid	X	Product	Yield[b]/%
1		Br		90
2		Cl		87[c]
3		Br		84
4		Cl		81[c]
5		Br		84
6		Br		87
7		Br		85
8		Br		83
9		Br		80
10		Br		78
11		Br		80
12		Br		79
13		Br		80
14		Br		82
15		Br		75
16		Br		74
17		Br		71
18		Br		78
19		Br		89
20		Br		91
21		Br		79
22		Br		76
23		Br		78

[a]Reaction conditions: Phenylselenyl bromide (1.0 mmol), phenylboronic acid (1.0 mmol), $CuFe_2O_4$ (5.0 mol %), Cs_2CO_3 (2.0 equiv), PEG-400 (3.0 mL), 80 °C, 8 h. See ref. 23 for details. [b]Isolate yield. [c]After 10 h.

Table 3. Recycling of $CuFe_2O_4$ nanoparticles[a]



Recycles	Yield[b]/%	Catalyst recovery/%
Native	90	97
1	88	95
2	85	92
3	82	89

[a]Reaction conditions: Phenylselenyl bromide (1.0 mmol), phenylboronic acid (1.0 mmol), $CuFe_2O_4$ (5.0 mol %), Cs_2CO_3 (2.0 equiv), PEG-400 (3.0 mL), 80 °C, 8 h. [b]Isolated yield.

lower yields were obtained (Table 1, Entry 6). Ideal temperature for the reaction was found to be 80 °C. To study the fate of the reaction, we have screened various nanocatalytic systems such as Y_2O_3, NiO, Co_3O_4, $NiFe_2O_4$, and $CoFe_2O_4$. However, unfortunately we got poor yields of the corresponding products (Table 1, Entries 10–14). Later the influence of the amount of catalyst on the yield of the product was evaluated and it was observed that 5.0 mol % of $CuFe_2O_4$ was ideal. The best result was obtained when the reaction was pursued at 80 °C using 5.0 mol % of the $CuFe_2O_4$ nanoparticles in the presence of Cs_2CO_3 (2.0 equiv) and PEG (3.0 mL).

While exploring the scope of this novel transformation, we examined the cross coupling of various phenylboronic acids with phenylselenyl bromide. In general, all the reactions were clean, and the unsymmetrical aryl selenides were obtained in high yields under the optimized conditions. Electron-donating groups (e.g., Me, Et, and OMe, Table 2, Entries 3–9) on boronic acid produced the corresponding products in good yields, whereas electron-withdrawing groups (e.g., NO_2, F, Cl, and CF_3 Table 2, Entries 11–18) on boronic acid decreased yields of the corresponding products. Consequently, cross-coupling reactions with halo-substituted aryl boronic acids exhibited an interesting chemoselectivity (Table 2, Entries 12–17). Utilizing these reaction conditions, various heteroaromatic boronic acids were also allowed to react with phenylselenyl bromide to obtain the corresponding diaryl selenides in encouraging yields (Table 2, Entries 21–23).

Recyclability of the catalyst[22] was checked using coupling reaction of phenylselenyl bromide with phenylboronic acid as the model reaction. After each cycle, the nanoparticles were magnetically separated, washed with ethyl acetate, and acetone and then dried in vacuo. The recovered nano $CuFe_2O_4$ was used directly in the next cycle. The recycling results are listed in Table 3, indicating the yields of diaryl selenides up to four cycles.

In summary, we have developed a facile copper ferrite nanoparticle catalyzed cross coupling of phenylselenyl bromide with various organoboranes to give the corresponding unsymmetrical diaryl selenides under ligand-free conditions in poly(ethylene glycol) as a convenient, nontoxic, thermally stable, inexpensive, and recyclable reaction medium for coupling reaction, substituting the volatile organic solvents.

We are grateful to CSIR, New Delhi, for research fellowships to K.H.V.R, G.S, and K.K and to the UGC, New Delhi, for fellowship to K.R.

References and Notes

1 a) G. Mugesh, H. B. Singh, *Chem. Soc. Rev.* **2000**, *29*, 347. b) G. Mugesh, W.-W. du Mont, H. Sies, *Chem. Rev.* **2001**, *101*, 2125. c) C. W. Nogueira, G. Zeni, J. B. T. Rocha, *Chem. Rev.* **2004**, *104*, 6255.

2 a) *Organic Selenium Compounds: Their Chemistry and Biology*, ed. by D. L. Klayman, W. H. H. Gunther, John Wiley & Sons, Inc., New York, NY, **1973**. b) A. Krief, L. Hevesi, in *Organoselenium Chemistry I: Functional Group Transformations*, Springer, Berlin, **1988**. c) *Comprehensive Organometallic Chemistry II*, ed. by E. W. Abel, F. G. A. Stone, G. Wilkinson, Pergamon, New York, NY, **1995**. d) *Organoselenium Chemistry: Modern Developments in Organic Synthesis* in *Topics in Current Chemistry*, ed. by T. Wirth, Springer-Verlag, Berlin, **2000**, Vol. 208. doi:10.1007/3-540-48171-0.

3 a) N. N. Magdesieva, *Russ. Chem. Rev.* **1988**, *57*, 161. b) D. M. Freudendahl, S. A. Shahzad, T. Wirth, *Eur. J. Org. Chem.* **2009**, 1649.

4 R. K. Gujadhur, D. Venkataraman, *Tetrahedron Lett.* **2003**, *44*, 81.

5 I. P. Beletskaya, A. S. Sigeev, A. S. Peregudov, P. V. Petrovskii, *Tetrahedron Lett.* **2003**, *44*, 7039.

6 a) H. Suzuki, H. Abe, A. Osuka, *Chem. Lett.* **1981**, 151. b) A. Osuka, N. Ohmasa, H. Suzuki, *Synthesis* **1982**, 857. c) C.-M. Andersson, A. Hallberg, M. Linden, R. Brattsand, P. Moldéus, I. Cotgreave, *Free Radical Biol. Med.* **1994**, *16*, 17. d) C.-M. Andersson, A. Hallberg, T. Högberg, *Adv. Drug Res.* **1996**, *28*, 65.

7 M. Wang, K. Ren, L. Wang, *Adv. Synth. Catal.* **2009**, *351*, 1586.

8 a) S. Bhadra, A. Saha, B. C. Ranu, *J. Org. Chem.* **2010**, *75*, 4864. b) D. Singh, E. E. Alberto, O. E. D. Rodrigues, A. L. Braga, *Green Chem.* **2009**, *11*, 1521. c) D. Alves, C. G. Santos, M. W. Paixão, L. C. Soares, D. de Souza, O. E. D. Rodrigues, A. L. Braga, *Tetrahedron Lett.* **2009**, *50*, 6635. d) A. Saha, D. Saha, B. C. Ranu, *Org. Biomol. Chem.* **2009**, *7*, 1652. e) N. Taniguchi, T. Onami, *J. Org. Chem.* **2004**, *69*, 915. f) S. Kumar, L. Engman, *J. Org. Chem.* **2006**, *71*, 5400. g) N. Taniguchi, *J. Org. Chem.* **2007**, *72*, 1241. h) L. Wang, M. Wang, F. Huang, *Synlett* **2005**, 2007. i) D. Chang, W. Bao, *Synlett* **2006**, 1786. j) N. Taniguchi, T. Onami, *Synlett* **2003**, 829. k) N. Taniguchi, *Synlett* **2005**, 1687. l) V. P. Reddy, A. V. Kumar, K. R. Rao, *J. Org. Chem.* **2010**, *75*, 8720.

9 H. J. Cristau, B. Chabaud, R. Labaudiniere, H. Christol, *Organometallics* **1985**, *4*, 657.

10 Y. Nishiyama, K. Tokunaga, N. Sonoda, *Org. Lett.* **1999**, *1*, 1725.

11 K. Ren, M. Wang, L. Wang, *Org. Biomol. Chem.* **2009**, *7*, 4858.

12 S. N. Murthy, B. Madhav, V. P. Reddy, Y. V. D. Nageswar, *Eur. J. Org. Chem.* **2009**, 5902.

13 A. Kamal, D. R. Reddy, Rajendar, *Tetrahedron Lett.* **2005**, *46*, 7951.

14 a) J. Mao, J. Guo, F. Fang, S.-J. Ji, *Tetrahedron* **2008**, *64*, 3905. b) S. Chandrasekhar, Ch. Narsihmulu, S. S. Sultana, N. R. Reddy, *Org. Lett.* **2002**, *4*, 4399. c) L. Xu, W. Chen, J. Ross, J. Xiao, *Org. Lett.* **2001**, *3*, 295. d) W. Mai, L. Gao, *Synlett* **2006**, 2553. e) L. Wang, Y. Zhang, L. Liu, Y. Wang, *J. Org. Chem.* **2006**, *71*, 1284. f) W.-J. Zhou, K.-H. Wang, J.-X. Wang, *Adv. Synth. Catal.* **2009**, *351*, 1378. g) Z. Duan, S. Ranjit, P. Zhang, X. Liu, *Chem.—Eur. J.* **2009**, *15*, 3666. h) J.-H. Li, W.-J. Liu, Y.-X. Xie, *J. Org. Chem.* **2005**, *70*, 5409. i) E. Colacino, L. Villebrun, J. Martinez, F. Lamaty, *Tetrahedron* **2010**, *66*, 3730. j) C. S. Cho, *Catal. Commun.* **2008**, *9*, 2261. k) W. Han, C. Liu, Z.-L. Jin, *Org. Lett.* **2007**, *9*, 4005. l) D. Srimani, A. Bej, A. Sarkar, *J. Org. Chem.* **2010**, *75*, 4296.

15 V. V. Namboodiri, R. S. Varma, *Green Chem.* **2001**, *3*, 146.

16 a) Z. Hou, N. Theyssen, W. Leitner, *Green Chem.* **2007**, *9*, 127. b) A. Haimov, R. Neumann, *Chem. Commun.* **2002**, 876. c) G. Jenzer, D. Sueur, T. Mallat, A. Baiker, *Chem. Commun.* **2000**, 2247.

17 P. C. Andrews, A. C. Peatt, C. L. Raston, *Green Chem.* **2004**, *6*, 119.

18 a) D. J. Cole-Hamilton, *Science* **2003**, *299*, 1702. b) W. Leitner, *Nature* **2003**, *423*, 930. c) K. H. Lam, L. Xu, L. Feng, Q.-H. Fan, F. L. Lam, W.-h. Lo, A. S. C. Chan, *Adv. Synth. Catal.* **2005**, *347*, 1755. d) W.-B. Wang, S.-M. Lu, P.-Y. Yang, X.-W. Han, Y.-G. Zhou, *J. Am. Chem. Soc.* **2003**, *125*, 10536.

19 a) G. Pacchioni, *Surf. Rev. Lett.* **2000**, *7*, 277. b) W. D. Knight, K. Clemenger, W. A. de Heer, W. A. Saunders, M. Y. Chou, M. L. Cohen, *Phys. Rev. Lett.* **1984**, *52*, 2141. c) A. Kaldor, D. M. Cox, M. R. Zakin, *Molecular Surface Chemistry: Reactions of Gas-Phase Metal Clusters* in *Advances in Chemical Physics: Evolution of Size Effects in Chemical Dynamics*, ed. by I. Prigogine, S. A. Rice, **1988**, Vol. 70, Part 2, p. 211. doi:10.1002/9780470122693.ch6.

20 a) G. W. Kabalka, B. Venkataiah, *Tetrahedron Lett.* **2002**, *43*, 3703. b) C. S. Freitas, A. M. Barcellos, V. G. Ricordi, J. M. Pena, G. Perin, R. G. Jacob, E. J. Lenardão, D. Alves, *Green Chem.* **2011**, *13*, 2931.

21 a) V. P. Reddy, K. Swapna, A. V. Kumar, K. R. Rao, *J. Org. Chem.* **2009**, *74*, 3189. b) K. Swapna, A. V. Kumar, V. P. Reddy, K. R. Rao, *J. Org. Chem.* **2009**, *74*, 7514. c) V. P. Reddy, A. V. Kumar, K. Swapna, K. R. Rao, *Org. Lett.* **2009**, *11*, 951. d) V. P. Reddy, A. V. Kumar, K. Swapna, K. R. Rao, *Org. Lett.* **2009**, *11*, 1697. e) V. P. Reddy, K. Swapna, A. V. Kumar, K. R. Rao, *Synlett* **2009**, 2783. f) V. P. Reddy, A. V. Kumar, K. R. Rao, *Chem. Lett.* **2010**, *39*, 212. g) V. P. Reddy, A. V. Kumar, K. R. Rao, *Tetrahedron Lett.* **2010**, *51*, 3181. h) K. Swapna, S. N. Murthy, Y. V. D. Nageswar, *Eur. J. Org. Chem.* **2010**, 6678. i) K. H. V. Reddy, V. P. Reddy, J. Shankar, B. Madhav, B. S. P. A. Kumar, Y. V. D. Nageswar, *Tetrahedron Lett.* **2011**, *52*, 2679. j) K. H. V. Reddy, V. P. Reddy, B. Madhav, J. Shankar, Y. V. D. Nageswar, *Synlett* **2011**, 1268. k) K. H. V. Reddy, V. P. Reddy, A. A. Kumar, G. Kranthi, Y. V. D. Nageswar, *Beilstein J. Org. Chem.* **2011**, *7*, 886. l) K. Swapna, S. N. Murthy, M. T. Jyothi, Y. V. D. Nageswar, *Org. Biomol. Chem.* **2011**, *9*, 5989.

22 a) N. Panda, A. K. Jena, S. Mohapatra, *Chem. Lett.* **2011**, *40*, 956. b) R. Zhang, J. Liu, S. Wang, J. Niu, C. Xia, W. Sun, *ChemCatChem* **2011**, *3*, 146. c) N. Panda, A. K. Jena, S. Mohapatra, S. R. Rout, *Tetrahedron Lett.* **2011**, *52*, 1924.

23 **General experimental procedure for the synthesis of unsymmetrical diphenyl selenides**: To a stirred solution of phenylselenyl bromide (236 mg, 1 mmol) and phenylboronic acid (122 mg, 1 mmol) in PEG-400 (3 mL) was added nano-CuFe$_2$O$_4$ powder (5 mol %, 12 mg) and Cs$_2$CO$_3$ (2.0 equiv). The reaction mixture was heated at 80 °C for 8 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was extracted with ethyl acetate. The combined organic layers were dried with anhydrous Na$_2$SO$_4$. The solvent was evaporated under vacuum to give the crude product, which was purified by column chromatography (hexane) to yield the expected product (90%). The purity of the product was confirmed by ^{1}H NMR and ^{13}C NMR and MS.[24]

24 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.