

Eco-friendly cross-coupling of diaryl diselenides with aryl and alkyl bromides catalyzed by CuO nanopowder in ionic liquid

Devender Singh,^a Eduardo E. Alberto,^a Oscar Endrigo Dorneles Rodrigues^{*a} and Antonio Luiz Braga^{*b}

Received 25th May 2009, Accepted 5th August 2009

First published as an Advance Article on the web 17th August 2009

DOI: 10.1039/b916266f

An eco-friendly cross-coupling reaction of aryl and alkyl bromides with diselenides using a catalytic amount of CuO nanopowder as a catalyst and an ionic liquid as a recyclable solvent is reported. The system shows high efficiency to catalyze this transformation, and in a green fashion due to the recyclable approach and the non-residual design protocol. This procedure has been utilized for the synthesis of a variety of diaryl selenides in good to excellent yields from the readily available aryl and alkyl bromides and diselenides.

Organoselenium compounds have become attractive synthetic targets. These compounds offer chemo-, regio-, and stereoselective reactions, and in life sciences selenium is known as a fundamental element.¹ In addition, organoselenium compounds are involved in a series of biological processes, they have an effective action against free radical species, and other important biological proprieties (e.g., antioxidant, antitumor, anti-inflammatory, and anti-infective activity).²

The preparation of aryl selenides involves a transition-metal-catalyzed reaction and a few protocols are reported in the literature.^{3–6,9} In earlier methods, for the formation of a C–Se bond, photochemical or harsh reaction conditions such as the use of polar and toxic solvents like HMPA and high reaction temperatures were required.⁷ Most of these metal-catalyzed reactions involve specially designed ligands or well-defined catalysts/reagents, which may increase the cost and limit the scope of applications. In this context, it is desirable to find novel catalytic procedures, especially in the absence of ligands, for an efficient route to such highly useful organic products.

On the other hand, nanotechnology has become an attractive new field for catalysis. Nanoscale heterogeneous catalysts offer higher surface area and low-coordinated sites, which are responsible for the higher catalytic activity.⁸ Due to this, the investigation of nanoparticles as catalysts in cross-coupling reactions has been of growing interest.

Organic reactions, catalyzed by copper nanostructures, are currently an area of intensive research, with many reports in the literature.^{9–14} Recently, a report concerning the synthesis of diaryl selenides using CuO nanoparticles was published.⁹ That protocol allowed the preparation of the desired products in good

yields, however, long reaction times and high temperatures limit the scope of the reaction to substrates that would withstand with these harsh reaction conditions. Moreover, the use of solvents such as DMSO is undesirable from an environmental point of view.

Ionic liquids have been used frequently in the last few years as an alternative reaction media for a broad range of different chemical transformations.^{15–21} Ionic liquids have been utilized as solvents in many transition-metal catalyzed C–C bond formation reactions: Heck reactions,^{22–29} Stille-coupling,³⁰ Negishi-coupling,³¹ Suzuki-coupling,³² Kumada-coupling,³³ Ullmann reaction³⁴ and Tsuji–Trost allylation.^{35,36} They present various interesting properties which alleviate some of the environmental issues, such as no effective vapour pressure, good solubilities for a wide range of compounds and they allow many combinations of anions and cations.

Therefore, the combination of nanotechnology and ionic liquids to perform chalcogen–carbon coupling could afford a new green methodology to synthesise this kind of compound. In this context, and in connection with our ongoing interest in synthesis and evaluation of organochalcogen derivatives as ligands in asymmetric transformations³⁷ we report herein an environmental friendly and efficient cross-coupling reaction of aryl and alkyl bromides with diaryl diselenides using a catalytic amount of commercially available CuO nanopowder as a catalyst and BMIM-BF₄ as a recyclable solvent.

We carried out the reaction employing 4-bromotoluene **1** as representative bromide and 0.5 equiv. of diphenyl diselenide **2** to get the diaryl selenide **3**, Table 1.

In a first set of experiments, we studied the influence of different ionic liquids, Table 1. It was possible to check that in all of them the desired product was obtained, with yields ranging from 74 to 82%. BMIM-BF₄ was a superior ionic liquid for this reaction (Table 1, entry 1).

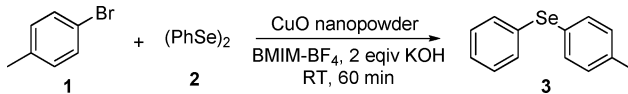
Table 1 CuO-nanoparticle catalyzed cross-coupling of 4-bromotoluene with diphenyl diselenide using different ionic liquids

| Entry ^a | Ionic liquid | Yield (%) ^b |
|--------------------|-----------------------|------------------------|
| 1 | BMIM-BF ₄ | 82 |
| 2 | BMIM-NTf ₂ | 78 |
| 3 | BMIM-PF ₆ | 74 |

^a CuO nanopowder was purchased from Aldrich®, with an average diameter of 30–40 nm, as shown in technical information. ^b GC yields.

^aDepartamento de Química, Universidade Federal de Santa Maria, Santa Maria, RS, 97105-900, Brazil. E-mail: rodriguesoed@smail.ufsm.br; Tel: +55-55 3220 8761

^bDepartamento de Química, Universidade Federal de Santa Catarina, Florianópolis, SC, 88040-900, Brazil. E-mail: albraga@qmc.ufsc.br; Tel: +55-48 3721 6844

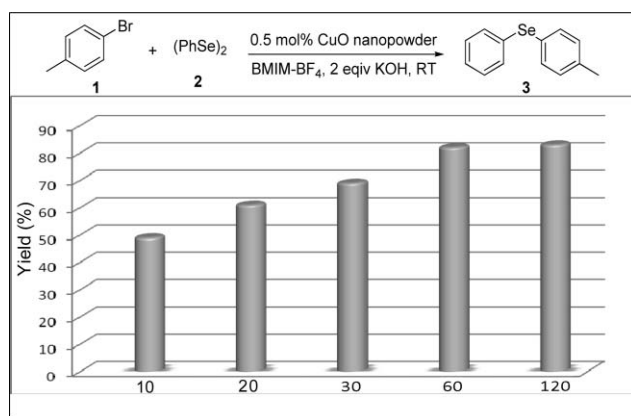
Table 2 CuO-nanopowder catalyzed cross-coupling of 4-bromotoluene **1** with diphenyl diselenide **2**


| Entry | CuO nano (mol%) | Yield ^a (%) |
|-------|-----------------|------------------------|
| 1 | 0.10 | 45 |
| 2 | 0.25 | 48 |
| 3 | 0.50 | 82 |
| 4 | 1.00 | 84 |

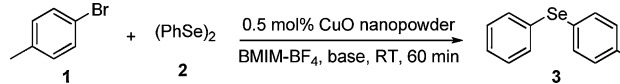
^a Yields were determined by GC.

To understand the influence of different variables in this reaction, several components were studied to optimize our procedure. Firstly, the amount of catalyst necessary to promote the reaction efficiently was examined, Table 2. We found that the variation of the CuO nanopowder amount had an effective influence. While 0.1 and 0.25 mol% afforded the desired product in moderate yields (entries 1 and 2), by using 0.5 mol%, the yield was improved to 82% (entry 3). When the amount of CuO nanopowder was increased to 1.0 mol%, the yield of compound **3** was not significantly modified, affording the desired product in 84% (entry 4).³⁸

With these results in hand, we selected 0.5 mol% of CuO nanopowder as the best amount of catalyst. The additional factors analyzed were the reaction time and the base. The variation in the reaction time from 10 to 120 minutes was studied. As shown in Fig. 1, the yield had a linear increase from 10 minutes to a maximum of 60 minutes. After this, longer reaction times did not have an influence on the product yield.

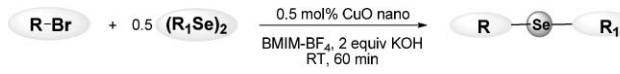
**Fig. 1** Time optimization in CuO nanocatalysis.

In terms of base, the influence of different bases was studied to perform a more efficient cleavage of diselenides affording the nucleophilic selenolate species. Thus, Cs₂CO₃ and KOH provided the diaryl selenides **3** in good yields (Table 3, entries 2 and 3), whereas other bases such as K₂CO₃ and Na₂CO₃ gave only moderate yields (Table 3, entries 1 and 4). The product was not observed in the absence of base, hence the necessity of that to perform the reaction (entry 5).

Table 3 CuO-nanopowder catalyzed cross-coupling of **1** with **2**


| Entry | Base | Amount (equiv.) | Yield (%) ^a |
|-------|---------------------------------|-----------------|------------------------|
| 1 | K ₂ CO ₃ | 2.0 | 41 |
| 2 | Cs ₂ CO ₃ | 2.0 | 78 |
| 3 | KOH | 2.0 | 82 |
| 4 | Na ₂ CO ₃ | 2.0 | 46 |
| 5 | none | — | 0 |

^a Yields were determined by GC.

Table 4 CuO nanopowder catalyzed cross-coupling of halides **1a–g** with diaryl diselenides **2a–d**


| Entry | R | R ₁ | Product | Yield (%) ^a |
|-------|---|----------------|---------|------------------------|
| 1 | | | | 82 |
| 2 | | | | 82 |
| 3 | | | | 80 |
| 4 | | | | 79 |
| 5 | | | | 70 |
| 6 | | | | 75 |
| 7 | | | | 76 |
| 8 | | | | 80 |
| 9 | | | | 76 |
| 10 | | | | 74 |

^a Yields referent of pure isolated products, characterized by ¹H and ¹³C NMR spectroscopic data.

After the optimizations, the reactions were carried with different alkyl and aryl bromides and substituted diselenides, Table 4.³⁹

In general, all reactions were very clean and selenides were obtained in excellent yields, as depicted in Table 4. We studied

the electronic and steric effects of attached groups in the aryl bromides and in the diselenide moiety. In terms of electronic effects, the reaction was not very sensitive to this influence, since the coupling of diphenyl diselenide with neutral, electron donating and electron withdrawing aryl bromides were efficiently achieved (entries 1–5). Comparing the coupling reaction between the aryl bromide **1c** and **1e**, the activated one (4-OMe group) **1c** showed a higher yield (entry 3 vs. 5). Despite this, the coupling was efficient and allowed the formation of diaryl selenides with good yields. Analyzing Table 4 (entries 3–4 and 8–10), it is possible to observe that in terms of steric and electronic effects, the reaction was not strongly influenced by these parameters. As described, the reaction was not hampered and the diaryl selenides were obtained in high yields. To extend the scope of our coupling protocol, alkyl bromides were also employed (entries 6 and 7). Using our methodology it was possible to prepare alkyl aryl selenides in reasonable yields, which are difficult to prepare according to the previous report.⁹

The quest for developing economic and environmental friendly methods is one of our prime concerns. It prompted us to evaluate the possibility of reusing the ionic liquid employed in our reactions. After the work-up, the catalyst CuO nanopowder was removed from BMIM-BF₄ by filtration and the recovered ionic liquid was used again for the next coupling reactions.⁴⁰ This operation was repeated for more three times without significant loss of efficiency, as shown in Fig. 2.

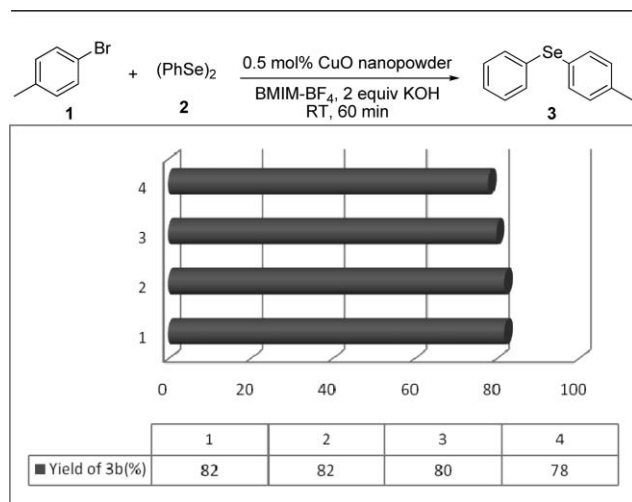


Fig. 2 Reuse of BMIM-BF₄.

In conclusion, we have developed a clean, eco-friendly, inexpensive and efficient methodology to obtain diaryl or alkyl aryl selenides from alkyl or aryl halides with diaryl diselenides using CuO nanopowder in ionic liquid as a recyclable solvent. Features of this method include the following: (i) easily accessible alkylating agents were used; (ii) very small amount of catalyst used; (iii) use of recyclable solvent.

Acknowledgements

The authors gratefully acknowledge, CNPq (INCT-Catalise, INCT-NANOBIOSESIMES, Jovem Pesquisador em Nanotec-

nologia) for financial support. Devender Singh thanks TWAS-CNPq for a Ph.D. fellowship.

Notes and references

- (a) D. L. Klayman, and H. H. Günter, *Organoselenium Compounds: Their Chemistry and Biology*, Wiley-Interscience, New York, 1973; (b) J. T. Rotruck, A. L. Pope, H. E. Ganther, A. B. Swanson, D. G. Hafeman and W. G. Hoekstra, *Science*, 1973, **179**, 588; (c) L. Flohé, E. A. Günzler and H. H. Schock, *FEBS Lett.*, 1973, **32**, 132; (d) R. J. Shamberger, *Biochemistry of Selenium*, Plenum Press, New York, 1983; (e) L. Flohé, J. R. Andreesen, R. Brigelius-Flohé, M. Maiorino and F. Ursini, *IUBMB Life*, 2000, **49**, 411; (f) C. Jacob, G. I. Giles, N. M. Giles and H. Sies, *Angew. Chem., Int. Ed.*, 2003, **42**, 4742.
- (a) G. Mughesh and H. Singh, *Chem. Soc. Rev.*, 2000, **29**, 347; (b) G. Mughesh, W. W. Du Mont and H. Sies, *Chem. Rev.*, 2001, **101**, 2125; (c) C. W. Nogueira, G. Zeni and J. B. T. Rocha, *Chem. Rev.*, 2004, **104**, 6255; (d) B. K. Sarma and G. Mughesh, *Org. Biomol. Chem.*, 2008, **6**, 965.
- (a) T. Nishino, M. Okada, T. Kuroki, T. Watanabe, Y. Nishiyama and N. Sonoda, *J. Org. Chem.*, 2002, **67**, 8696; (b) N. Taniguchi and T. Onami, *J. Org. Chem.*, 2004, **69**, 915; (c) S. Kumar and L. Engman, *J. Org. Chem.*, 2006, **71**, 5400; (d) N. Taniguchi, *J. Org. Chem.*, 2007, **72**, 1241; (e) I. P. Beletskaya, A. S. Sigeev, A. S. Peregudov and P. V. Petrovskii, *J. Organomet. Chem.*, 2000, **605**, 96; (f) Y. Nishiyama, K. Tokunaga and N. Sonoda, *Org. Lett.*, 1999, **1**, 1725; (g) C. Millois and P. Diaz, *Org. Lett.*, 2000, **2**, 1705; (h) K. Ajiki, M. Hirano and K. Tanaka, *Org. Lett.*, 2005, **7**, 4193.
- For a review on an aryl-chalcogen bond formation, see: *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon Press, Ltd., New York, 1991, Vol. 6.
- For selected examples of an aryl-heteroatom bond formation, see: (a) B. H. Yang and S. L. Buchwald, *J. Organomet. Chem.*, 1999, **576**, 125; (b) J.-F. Marcoux, S. Doye and S. L. Buchwald, *J. Am. Chem. Soc.*, 1997, **119**, 10539; (c) F. Hartwig and G. Mann, *J. Org. Chem.*, 1997, **62**, 5413; (d) M. Palucki, J. P. Wolfe and S. L. Buchwald, *J. Am. Chem. Soc.*, 1997, **119**, 3395.
- (a) A. Krief, *Comprehensive Organometallic Chemistry II*, ed. E. W. Abel, F. G. A. Stone and G. Wilkinson, Pergamon Press Ltd, New York, 1995, vol. 11, ch. 13; (b) *Organoselenium Chemistry: Topics in Current Chemistry 208*, ed. T. Wirth, Springer-Verlag, Heidelberg, 2000; (c) C. Paulmier, *Selenium Reagents and Intermediates in Organic Synthesis*, Pergamon Press Ltd., Oxford, 1986; (d) *Organic Chemistry Series 4*, ed. J. E. Baldwin, Pergamon Press Ltd., Oxford, 1986.
- (a) H. Suzuki, H. Abe and A. Osuka, *Chem. Lett.*, 1981, 151; (b) R. K. Gujadhur and D. Venkataruman, *Tetrahedron Lett.*, 2003, **44**, 81; (c) W. R. Bowman, H. Heaney and P. H. G. Smith, *Tetrahedron Lett.*, 1984, **25**, 5821; (d) H. Suzuki, H. Abe and A. Osuka, *Chem. Lett.*, 1980, 1363; (e) F. Y. Kwong and S. L. Buchwald, *Org. Lett.*, 2002, **4**, 3517.
- (a) M. Kosugi, T. Shimizu and T. Migita, *Chem. Lett.*, 1978, 13; (b) T. Migita, T. Shimizu, Y. Asami, J.-i. Shiobara, Y. Kato and M. Kosugi, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 1385; (c) H.n J. Cristau, B. Chabaud and C. H. Christol, *Synthesis*, 1981, 892; (d) N. Zheng, J. C. McWilliams, F. J. Fleitz, J. D. III Armstrong and R. P. Volante, *J. Org. Chem.*, 1998, **63**, 9606; (e) P. G. Ciattini, E. Morera and G. Ortar, *Tetrahedron Lett.*, 1995, **36**, 4133.
- V. P. Reddy, A. V. K. Kokkiralra Swapna and K. R. Rao, *Org. Lett.*, 2009, **11**, 951.
- (a) V. Polshettiwar, B. Baruwati and R. S. Varma, *Chem. Commun.*, 2009, 1837; (b) V. Polshettiwar and R. S. Varma, *Org. Biomol. Chem.*, 2009, **7**, 37; (c) V. Polshettiwar, B. Baruwati and R. S. Varma, *Green Chem.*, 2009, **11**, 127.
- V. Polshettiwar and R. S. Varma, *Chem.-Eur. J.*, 2009, **15**, 1582.
- A. Saha, D. Saha and B. C. Ranu, *Org. Biomol. Chem.*, 2009, **7**, 1652.
- M. Shibasaki and M. Kanai, *Chem. Rev.*, 2008, **108**, 2853.
- M. Meldal and C. W. Tornøe, *Chem. Rev.*, 2008, **108**, 2952.
- J. D. Holbrey and K. R. Seddon, *Clean Prod. Process.*, 1999, **1**, 233.
- K. R. Seddon, *J. Chem. Technol. Biotechnol.*, 1997, **68**, 351.
- T. Welton, *Chem. Rev.*, 1999, **99**, 2071.
- P. Wasserscheid and W. Keim, *Angew. Chem.*, 2000, **39**, 3772.
- R. Sheldon, *Chem. Commun.*, 2001, 2399.

- 20 For a comprehensive review about ionic liquids see: (a) J. Dupont, R. F. Souza and P. A. Z. Suarez, *Chem. Rev.*, 2002, **102**, 3667; (b) C. C. Cassol, G. Ebeling, B. Ferrera and J. Dupont, *Adv. Synth. Catal.*, 2006, **348**, 243; (c) J. Ranke, S. Stolte, R. Störmann, J. Arning and B. Jastorff, *Chem. Rev.*, 2007, **107**, 2183; (d) P. Hapiot and C. Lagrost, *Chem. Rev.*, 2008, **108**, 2238.
- 21 C. M. Gordon, *Appl. Catal., A*, 2001, **222**, 101.
- 22 D. E. Kaufmann, M. Nouroozian and H. Henze, *Synlett*, 1996, 1091.
- 23 W. A. Herrmann and V. P. W. Böhm, *J. Organomet. Chem.*, 1999, **572**, 141.
- 24 A. J. Carmichael, M. J. Earle, J. D. Holbrey, P. B. MacCormac and K. R. Seddon, *Org. Lett.*, 1999, **1**, 997.
- 25 V. Calò, A. Narci, L. Lopez and N. Mannarini, *Tetrahedron Lett.*, 2000, **41**, 8973.
- 26 V. P. W. Böhm and W. A. Herrmann, *Chem.–Eur. J.*, 2000, **6**, 1017.
- 27 L. Xu, W. Chen, J. Ross and J. Xiao, *Org. Lett.*, 2001, **3**, 295.
- 28 S. Bouquillon, B. Ganchev, B. Estrine, F. Henin and J. Muzart, *J. Organomet. Chem.*, 2001, **634**, 153.
- 29 R. R. Deshmukh, R. Rajagopal and K. V. Srinivasan, *Chem. Commun.*, 2001, 1544.
- 30 S. T. Handy and X. Zhang, *Org. Lett.*, 2001, **3**, 233.
- 31 J. Sirieix, M. Ossberger, B. Berzmeier and P. Knochel, *Synlett*, 2000, 1623.
- 32 C. J. Mathews, P. J. Smith and T. Welton, *Chem. Commun.*, 2000, 1249.
- 33 V. P. W. Böhm, T. Weskamp, W. K. Getottmayr and W. A. Herrmann, *Angew. Chem., Int. Ed.*, 2000, **39**, 1602.
- 34 J. Horwath, P. James and J. Dai, *Tetrahedron Lett.*, 2000, **41**, 10319.
- 35 S. Toma, B. Gotov, I. Kmentová and E. Solcániová, *Green Chem.*, 2000, **2**, 149.
- 36 I. Kmentová, B. Gotov, E. Solcániová and S. Toma, *Green Chem.*, 2002, **4**, 103.
- 37 For selected examples see: (a) A. L. Braga, S. J. N. Silva, D. S. Lüdtkke, R. L. Drekenner, C. C. Silveira, J. B. T. Rocha and L. A. Wessjohann, *Tetrahedron Lett.*, 2002, **43**, 7329; (b) A. L. Braga, D. S. Lüdtkke, M. W. Paixão and O. E. D. Rodrigues, *Org. Lett.*, 2003, **5**, 2635; (c) A. L. Braga, D. S. Lüdtkke, E. E. Alberto and J. A. Sehnem, *Tetrahedron*, 2005, **61**, 11664; (d) A. L. Braga, J. A. Sehnem, F. Vargas and R. C. Braga, *J. Org. Chem.*, 2005, **70**, 9021; (e) A. L. Braga, D. S. Lüdtkke, M. W. Paixão, E. E. Alberto, H. A. Stefani and L. Juliano, *Eur. J. Org. Chem.*, 2005, 4260; (f) A. L. Braga, D. S. Lüdtkke and E. E. Alberto, *J. Braz. Chem. Soc.*, 2006, **17**, 11; (g) R. S. Schwab, F. Z. Galetto, J. B. Azeredo, A. L. Braga, D. S. Lüdtkke and M. W. Paixão, *Tetrahedron Lett.*, 2008, **49**, 5094; (h) G. Marin, A. L. Braga, A. S. Rosa, F. Z. Galetto, R. A. Burrow, H. Gallardo and M. W. Paixão, *Tetrahedron*, 2009, **65**, 4614; (i) A. L. Braga, E. E. Alberto, L. C. Soares, J. B. T. Rocha, J. H. Sudati and D. H. Ross, *Org. Biomol. Chem.*, 2009, **7**, 43; (j) A. L. Braga, R. S. Schwab, E. E. Alberto, S. M. Salman, J. Vargas and J. B. Azeredo, *Tetrahedron Lett.*, 2009, **50**, 2309; (k) A. L. Braga, W. A. S. Filho, R. S. Schwab, O. E. D. Rodrigues, L. Dornelles, H. C. Braga and D. S. Lüdtkke, *Tetrahedron Lett.*, 2009, **50**, 3005; (l) E. E. Alberto, L. C. Soares, J. H. Sudati, A. C. A. Borges, J. B. T. Rocha and A. L. Braga, *Eur. J. Org. Chem.*, 2009, DOI: 10.1002/ejoc.200900485.
- 38 During the preparation of this manuscript, a similar cross-coupling reaction was published. The methodology employed 2 mol% of catalyst in DMSO, with similar yields as obtained in our protocol (see ref 9).
- 39 General procedure to the synthesis of selenides **3a–j**: in a Schlenk tube under nitrogen atmosphere and at room temperature CuO nanoparticles (0.006 mmol, 0.5 mol%) followed by diphenyl diselenide **2a** (0.5 mmol) and KOH (1.0 mmol, 2.0 equiv) were added to a solution of bromo toluene **1b** (1.1 mmol) in BMIM-BF₄ (1.0 mL). The progress of the reaction was monitored by TLC. After, the reaction was complete, the product was extracted by successive washing with diethyl ether (5 × 5 mL) and drying over MgSO₄. The solvent and volatiles were completely removed under vacuum to give the crude product. The compounds were purified by column chromatography over silica gel.
- 40 After work-up, BMIM-BF₄ was treated with DCM and filtered over Celite to remove the CuO residue. The solution was dried over MgSO₄ and the volatiles were removed under vacuum. The recovered ionic liquid was reused for the next reaction.