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Bipyridinium Ionic Liquid-Promoted Cross-Coupling Reactions between Perfluoroalkyl or Pentafluorophenyl Halides and Aryl Iodides

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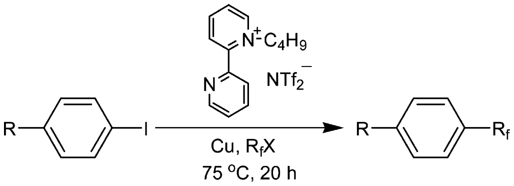
ABSTRACT



A new room-temperature ionic liquid has been synthesized from 2,2′-bipyridine. This liquid improved the copper-catalyzed cross-coupling reactions between perfluoroalkyl or pentafluorophenyl halides and aryl iodides. Good recyclability using this solvent system was observed.

It is becoming increasingly important to replace environmentally damaging volatile organic solvents in the chemical industry. Among the numerous alternatives such as polyfluoroalkyl-containing solvents, water, and supercritical fluids, a most promising option is room-temperature ionic liquids. These amazing liquids have essentially no vapor pressure and provide good solubility for a wide range of organic, inorganic, and organometallic compounds and, as a result, are suitable as reaction media. Since these liquids are salts, the cations and anions may interact with solutes and therefore have dramatic effects on any reactions attempted. Indeed, there are a number of reports citing great improvements in reaction yields and rates when ionic liquids are used as solvents.[1] One of the predominant research areas involving ionic liquids as solvents focuses on homogeneous catalysis since ionic liquids have been demonstrated to be ideal immobilizing agents for various classical transition metal catalyst precursors.[2] Since the coordinating abilities of ordinary ionic liquids are often very poor, the design of ionic liquids for use as solvents that can serve both for immobilization and as coordinating ligands for the catalyst in processes involving homogeneous catalysis is a worthwhile objective. To date, some efforts have been made to address this by synthesizing ionic liquids with functional groups that can complex the metal centers.[3]

We have recently described the synthesis of a 2,2′-biimidazolium-based ionic liquid from glyoxal and ammonium acetate and examined its coordination to transition metals. This monoquaternary 2,2′-biimidazolium ionic liquid

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[1] For recent reviews, see: (a) Knochel, P., Ed. *Topics in Current Chemistry*; Springer: New York, 1999; Vol. 206. (b) *Ionic Liquids as Green Solvents*; Rogers, R. D., Seddon, K. R., Eds.; ACS Symposium Series 856; American Chemical Society: Washington, DC, 2003. (c) *Ionic Liquids in Synthesis*; Wasserscheid, P., Welton, T., Eds.; Wiley-VCH: Weinheim, 2003.

[2] For recent reviews, see: (a) Welton, T. *Coord. Chem. Rev.* **2004**, *248*, 2459−2477. (b) Dupont, J.; de Souza, R. F.; Suarez, P. A. Z. *Chem. Rev.* **2002**, *102*, 3667−3692. (c) Rogers, S. *Chem. Commun.* **2001**, 2399−2407. (d) Wasserscheid, P.; Keim, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 3772−3789.

[3] For examples, see: (a) Zhao, D.; Fei, Z.; Geldbach, T. J.; Scopelliti, R.; Dyson, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 15876−15882. (b) Fei, Z.; Zhao, D.; Scopelliti, R.; Dyson, P. J. *Organometallics* **2004**, *23*, 1622−1628. (c) Zhao, D.; Fei, Z.; Scopelliti, R.; Dyson, P. J. *Inorg. Chem.* **2004**, *43*, 2197−2205. (d) Audic, N.; Clavëier, H.; Mauduit, M.; Guillemin, J.-C. *J. Am. Chem. Soc.* **2003**, *125*, 9248−9249. (e) Brauer, D. J.; Kottsieper, K.; Liek, C.; Stelzer, O.; Waffenschmidt, H.; Wasserscheid, P. *J. Organomet. Chem.* **2001**, *630*, 177−184. (f) Brasse, C. C.; Englert, U.; Salzer, A.; Waffenschmidt, H.; Wasserscheid, P. *Organometallics* **2000**, *19*, 3818−3823. (g) Wasserscheid, P.; Waffenschmidt, H.; Machnitzki, P.; Kottsieper, K. W.; Stelzer, O. *Chem. Commun.* **2001**, 451−452

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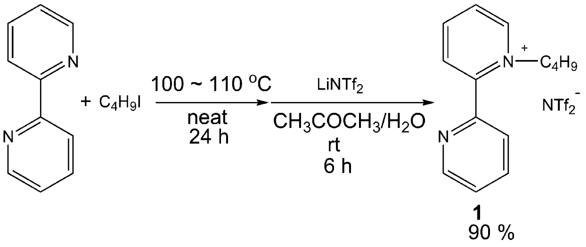
Scheme 1. Synthesis of IL **1**



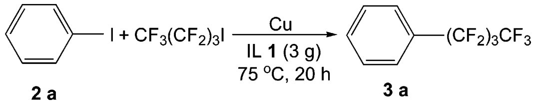
can be used as both a recyclable solvent and an efficient ligand for Heck and Suzuki reactions.[4] In our efforts to synthesize this kind of ionic liquid with multiple centers available for quaternization, we now have extended our research to 2,2′-bipyridine, which is commercially available, and have investigated its application in copper-catalyzed cross-coupling reactions between perfluoroalkyl or pentafluorophenyl halides and aryl iodides.

The replacement of a hydrogen atom in aromatic compounds by a perfluoroalkyl group can bring about some remarkable changes in the physical properties, chemical reactivity, and biological activity of the derived fluorinated compounds. As a result, considerable effort has been devoted to the development of useful methods for efficient and selective introduction of a perfluoroalkyl group into organic compounds.[5] Among them, copper-catalyzed cross-coupling reactions between perfluoroalkyl halides and iodoaromatics are a direct and convenient method.[6] The main disadvantage of this process lies in the use of vigorous conditions, e.g., polar aprotic solvents such as DMSO, 110∼130 °C or even higher reaction temperature, and usually a large stoichiometric excess of copper employed to drive the reaction. However, the reaction proceeded at 70 °C with 2,2′-bipyridine as an additive, but a longer reaction time (>72 h) was still required.[7] Here, 2,2′-bipyridine assisted the reaction by acting as a ligand for the fluoroalkylcopper intermediate. Hence, polar aprotic solvents may be required to adequately immobilize this intermediate. Considering the high polarity of ionic liquids and the coordination ability of monoquaternary ionic liquids, it was of interest to synthesize a monoquaternary 2,2′-bipyridinium-based ionic liquid to use it as both the solvent and the ligand to promote such copper-catalyzed cross-coupling reactions.

The route to 1-butyl-2,2′-bipyridinium bis(trifluoromethanesulfonyl)amide (**1**) is depicted in Scheme 1. Initially, 2,2′-bipyridine was mixed with an excess of butyl iodide at 80 °C for 2 days with only a 15% conversion of 2,2′-bipyridine. However, when the neat mixture of 2,2′-bipyridine with 1.5 equiv of butyl iodide was heated at 100∼110 °C for 24 h, only the monoquaternary product was formed. No diquaternary salt was formed even upon the addition of more iodobutane with concomitant heating at higher temperature (140 °C). This is not surprising since the monoquaternary salt is insoluble in butyl iodide and thus is unavailable to be butylated further. Subsequent metathetical reaction with lithium bis(trifluoromethanesulfonyl)amide resulted in the formation of ionic liquid **1**. Excess butyl iodide was recovered by trapping at −195 °C in vacuo. Under these reaction conditions, a small trace of 2,2′-bipyridine remains, but **1** can be purified by removing the latter by sublimation. This method is particularly effective when the reaction scale is above 1 g of 2,2′-bipyridine. To our delight, the product can be classified as a room-temperature ionic liquid with a glass transition temperature of −58.79 °C and with high stability toward water and air. This ionic liquid containing the bis(trifluoromethanesulfonyl)amide as an anion was completely soluble in acetone, methylene chloride, and acetonitrile but insoluble in water and ether. In addition, it is thermally stable up to 308 °C (DSC).

Given the straightforward synthesis of the monoquaternary ionic liquid **1**, we began to investigate its efficacy as a solvent for copper-catalyzed cross-coupling perfluoroalkylation reactions. Activated copper (1 equiv), iodobenzene (1 equiv), and perfluorobutyl iodide (1 equiv) were added directly into 3 g of **1** under a dinitrogen atomosphere (Table 1). Initially, the reaction was carried out at room temperature. However, no reaction occurred after 24 h. Screening of various reaction conditions revealed that perfluorobutyl iodide was completely converted after heating at 75 °C for 20 h (checked by GC-MS). The reaction is remarkably clean, and no biphenyl, from Ullmann coupling, was observed. These are mild reaction conditions compared with those used previously.[6] Although it was not possible to isolate the pure complex, one explanation for these observations is that the highly polar ionic liquid **1** acts as both the solvent and the ligand for perfluorobutylcopper. It is likely that the ionic liquid-coordinated copper complex facilitated the cross-coupling reaction with iodobenzene. Importantly, the product, perfluorobutyl benzene, was easily separated by simple extrac-

Table 1. Copper-Catalyzed Perfluorobutylation in **1** and the Recycling of **1**[a]



cycle	1	2	3	4	5
yield (%) [b]	88	85	90	87	89

[a] All reactions were performed using a 1:1:1 mixture of iodobenzene, perfluorobutyl iodide, and copper. [b] Isolated yields after silica chromatography.

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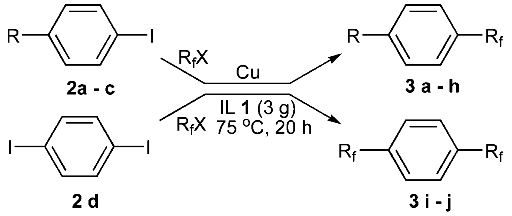
[4] (a) Xiao, J.-C.; Twamley, B.; Shreeve, J. M. *Org. Lett.* **2004**, *6*, 3845−3847. (b) Xiao, J.-C.; Shreeve, J. M. *J. Org. Chem.* **2005**, *70*, 3072−3078.

[5] (a) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123−3197. (b) *Organofluorine Chemistry: Principles and Commercial Applications*; Banks, R. E., Smart, B. E., Tatlow, J. C., Eds.; Plenum Press: New York, 1994. (c) Chambers, R. D. *Fluorine in Organic Chemistry*; CRC Press: Boca Raton, FL, 2004. (d) Kirsch, P. *Modern Fluoroorganic Chemistry*; Wiley-VCH: Weinheim, Germany, 2004.

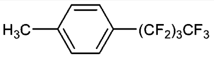
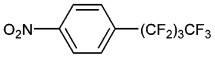
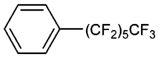
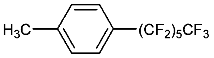
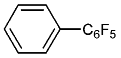
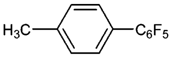
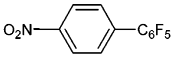
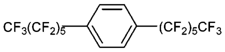
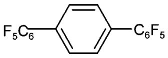
[6] Mcloughlin, V. C. R.; Thrower, J. *Tetrahedron* **1969**, *25*, 5921−5940.

[7] (a) Croxtall, B.; Fawcett, J.; Hope, E. G.; Stuart, A. M. *J. Chem. Soc., Dalton Trans.* **2002**, 491−499. (b) Wiedenfeld, D.; Niyogi, S.; Chakrabarti, D. *J. Fluorine Chem.* **2000**, *104*, 303−306.

Table 2. Couplings of Perfluoroalkyl or Pentafluorophenyl Halides with Aryl Iodides[a]



R = H, CH_3, NO_2
R_fX = $CF_3(CF_2)_3I$, $CF_3(CF_2)_5I$, C_6F_5Br
R_f = $CF_3(CF_2)_3$, $CF_3(CF_2)_5$, C_6F_5

entry	product		yield (%)[b]
1		**3b**	86
2		**3c**	87
3		**3d**	85
4		**3e**	90
5		**3f**	84
6		**3g**	88
7		**3h**	91
8		**3i**	90
9		**3j**	92

[a] Reactions were carried out using 1 mmol of perfluoroalkyl or pentafluorophenyl halides, 1 equiv of aryl iodides, and 1 equiv of copper in 3 g of ionic liquid at 75 °C for 20 h. [b] Isolated yields.

tion and decantation with ethyl ether. The desired product was isolated in 88% yield by column chromatography on silica gel using hexane as an eluent.

Reuse of ionic liquid **1** was examined. After extraction with ethyl ether, the resulting ionic liquid layer was mixed with methylene chloride. Filtration was employed to remove insoluble materials. The resulting methylene chloride layer was washed with pyridine solution (10 wt %) and then water. Removing the solvent and drying in vacuo at 80 °C for 4 h was sufficient to return the ionic liquid to its original state (determined by NMR). The recycled ionic liquid was then used for another four cycles of this coupling reaction. Similar high conversions were obtained, showing that the ionic liquid remained active (Table 1). Further, no significant loss (~5%) of the ionic liquid was observed after five cycles, which indicates that it could be recycled efficiently in this way.

Having established the recyclability and reuse of the ionic liquid, we tried perfluoroalkylation with other aryl iodides bearing a range of electron-donating and -withdrawing substituents (Table 2). Similar results were obtained for each substrate. The yields were not influenced by the substituents on the aryl group. This synthesis is applicable to bromopentafluorobenzene (Table 2, entries 5−7). After the reaction, a pentafluorophenyl group was introduced exclusively at the iodine site. Fluorine replacement did not occur in bromopentafluorobenzene. The reaction is also applicable to 1,4-diiodobenzene, affording 1,4-diperfluoroalkyl or 1,4-pentafluorophenyl benzene in high yields (Table 2, entries 8 and 9). In all cases, the ionic liquid was recovered and reused for the next substrate. Accordingly, the ionic liquid has been used 14 times without any decrease in activity.

In conclusion, a novel monoquaternary ionic liquid, 1-butyl-2,2′-bipyridinium bis(trifluoromethanesulfonyl) amide, has been synthesized in a straightforward manner from commercially available starting material and tested in copper-catalyzed cross-coupling reactions between perfluoroalkyl or pentafluorophenyl halides and aryl iodides. Better performance was obtained than under conventional reaction conditions. This procedure permits extensive recycling of the solvent without any loss in activity. On the basis of these current efforts, it is likely that a number of transition metal-catalyzed reactions could be performed equally well or perhaps even more effectively in this ionic liquid. Studies to determine applicability to other catalytic reactions are currently underway.

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Supporting Information Available: Experimental procedures, additional catalysis experiments, and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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