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Dppc$^+$PF$_6$$^-$–PdCl$_2$–[bmim][PF$_6$]–a copper-free recyclable catalytic system for Sonogashira coupling reaction

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An air-stable, copper-free and highly efficient Dppc$^+$PF$_6$$^-$–PdCl$_2$–[bmim][PF$_6$] catalytic system has been developed for the Sonogashira coupling reaction of aryl iodides with various aryl- and alkylacetylenes. The catalytic system allows for facile separation and can be recycled at least eight times with minimal loss of activity. Copyright © 2007 John Wiley & Sons, Ltd.

KEYWORDS: recyclable; copper-free; Dppc$^+$PF$_6$$^-$; catalytic system; the Sonogashira coupling reaction

INTRODUCTION

In the last few years various palladium-catalyzed cross-coupling reactions for C–C bond formation have evolved to powerful synthetic tools due to dramatic progress in the development of catalysts for such reactions.[1–5]The Sonogashira reaction (coupling of terminal alkynes with aryl and alkenyl halides catalyzed by palladium complexes in the presence of an amine and a small amount of CuI) is one of the most powerful and straightforward methods for the construction of sp^2–sp C–C bonds in organic synthesis.[6,7] This method has been widely used for the synthesis of natural products,[8,9] biologically active molecules,[10,11] nonlinear optical materials and molecular electronics,[12–14] dendrimeric and polymeric materials,[15,16] macrocycles with acetylene links,[17,18] and polyalkynylated molecules.[19–21] However, most of the above reactions were performed in organic homogeneous media. The major problems associated with the recovery of homogeneous catalysts and their separation from the reaction products and the difficulties associated with the recycling of the catalytic species have been addressed by immobilization on solid support such as polymers[22–25] or zeolite,[26,27] the use of aqueous media,[28,29] and the use of ionic liquid.[30–32] The development of the Sonogashira coupling reaction in ionic liquids has attracted increasing attention in recent years because industry seeks more environmentally friendly chemical manufacturing processes. Generally, the neutral phosphine ligands are used to complex the palladium species in ionic liquid, resulting in excellent results for the coupling reaction. However, the separation of the products with neutral phosphine ligands and palladium catalyst is difficult, and the catalyst can only be reused a few times because neutral phosphine ligands and catalyst easily dissolve in organic solvents. To overcome these problems, the use of a new catalyst system consisting of PdCl$_2$–ionic phosphine ligand–ionic liquid was suggested. Dppc$^+$PF$_6$$^-$ [1,1′-bis(diphenylphosphino)cobaltocenium hexafluorophosphate] (**1**), an underdeveloped ionic ligand,[33–35] proved to be a very suitable ligand for the biphasic hydroformylation and the Suzuki coupling reaction in ionic liquids, with high solubility in [bmim][PF$_6$] (1-butyl-3-methyl imidazolium hexafluorophosphate).[36] Herein we report that PdCl$_2$–Dppc$^+$PF$_6$$^-$, in combination with [bmim][PF$_6$] as solvent, is an air-stable, copper-free and recyclable catalysis system for the Sonogashira coupling reaction.

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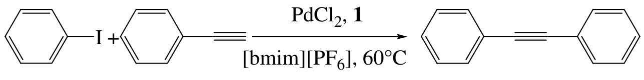
RESULTS AND DISCUSSION

In general, the Dppc$^+$PF$_6$$^-$, PdCl$_2$ and the base were mixed in [bmim][PF$_6$] and heated at 60 °C for about 1 h, resulting in the formation of a dark brown liquid. The liquid was active in the Sonogashira coupling reaction. We chose the cross-coupling of iodobenzene with phenyl acetylene as the model reaction to screen the catalyst and optimize the reaction conditions.

First, several different bases for the Sonogashira coupling reaction were tested. ^{i}PrNH was found to be the most effective, piperidine was less effective and Et$_3$N and inorganic bases such as Na$_2$CO$_3$ and Cs$_2$CO$_3$ were no longer effective in this catalyst system (entries 1–5, Table 1).

We have investigated the reactions using a veriety of aryl iodides, and a wide range of terminal alkynes as the substrates under the reaction conditions and the results are outlined in Table 2. As can be seen from Table 2, *meta*- or *para*-substituted electron-rich and electron-poor aryl iodides react with phenylacetylene very well to generate the corresponding cross-coupling products in excellent yields under the standard reaction conditions (entries 1–5, Table 2), while *ortho*-substituted aryl iodides also give the corresponding acetylenes in high yields for longer reaction times (entries 6 and 7, Table 2). Heteroaromatic compound such as 2-iodothiophene and 3-iodopyridine also reacted with phenyl acetylene to give acetylenes in high yields (entries 8 and 9, Table 2). The reactions of aryl iodides with aliphatic alkynes proceeded slowly under the standard reaction conditions and small amounts of homocoupling products were formed;[37] however, the use of piperidine as a base in place of diisopropylamine was found to be particularly useful in creating a copper-free reaction system (entries 10–13, Table 2).[32] In addition, the reaction of **2a** with propargyl alcohol (**3c**) and 1-ethynyl-1-cyclohexanol (**3d**) also gave the coupling products in high yields (entries 14 and 15, Table 2). These results indicated that a variety of important functional groups such as alcohol, ketone and heteroaromatic compounds were tolerated under the present conditions.

Table 1. Effect of base on the Sonogashira coupling reaction of iodobenzene with phenylacetylene in [bmim][PF$_6$]^a



2a **3a** **4a**

Entry	Base	Equiv (mol%)	Yield (%)^b
1	^{i}Pr$_2$NH	2.0	98
2	Et$_3$N	2.0	31
3	Piperidine	2.0	81
4	Na$_2$CO$_3$	2.0	40
5	Cs$_2$CO$_3$	2.0	43

^{a} All reactions were carried out using 1 mmol of iodobenzene, 1.2 equiv of phenylacetylene, 2 mol% of PdCl$_2$, 2 mol% **1** and 2.0 ml of [bmim][PF$_6$] at 60 °C for 2 h.
^{b} GC yields.

The recyclability of Dppc$^+$PF$_6$$^-$–PdCl$_2$–[bmim][PF$_6$] system was also surveyed in the coupling reaction of iodobenzene with phenyl acetylene. After carrying out the reaction, the products could be easily separated from the catalytic system by extraction with an organic solvent such as diethyl ether or hexane, and no apparent leaching of PdCl$_2$ and Dppc$^+$PF$_6$$^-$ was found in the organic extraction. The by-products were removed by washing with water. The resulting catalytic system could be reused successfully eight times with only a slight loss in its activity (Table 3), while the activity of the PdCl$_2$(PPh$_3$)$_2$–[bmim][PF$_6$] system declined quickly after three uses.[32] This is likely to be due to the ionic ligand Dppc$^+$PF$_6$$^-$ and PdCl$_2$ being tightly complexed with the ionic liquid and therefore not easily lost during extraction of the products.[38–40]

CONCLUSION

The Sonogashira coupling reaction of aryl iodides with terminal acetylenes, irrespective of their being aromatic or aliphatic, proceeded efficiently in an ionic liquid [bmim][PF$_6$], using PdCl$_2$–dppc$^+$PF$_6$$^-$ as the catalyst in the absence of a copper salt. The use of this system permitted the product to be easily separated from the catalyst and the recovered catalyst could be reused at least eight times without significant loss in activity. Study of further catalyst reuse in the Heck coupling reaction is underway.

EXPERIMENTAL SECTION

Materials

All commercially available solvents and reagents were used as supplied unless otherwise stated. dppc$^+$PF$_6$$^-$[36] and [bmim][PF$_6$][41] were prepared according to literature procedures.

Analysis

Product yields were calculated by GC, using a 6890N Network GC system (Agilent Technologies). GC-MS was obtained on an Autospec Q instrument under electron impact (EI) conditions at 70 eV. ^{1}H NMR was recorded on a Varian Mercury Plus 400 MHz instrument.

Typical procedure for the Sonogashira coupling reaction

In a 25.0 ml two-necked round-bottom flask was placed 2.0 ml of [bmim][PF$_6$] and the solvent was degassed under reduced pressure at room temperature for 0.5 h, and then nitrogen was introduced. To the solvent were added PdCl$_2$ (0.02 mmol, 3.54 mg), **1** (0.02 mmol, 14.04 mg), iodobenzene (1.0 mmol, 204 mg), phenylacetylene (1.2 mmol, 122 mg) and diisopropyl amine (2.0 mmol, 0.3 ml). The resulting mixture was heated

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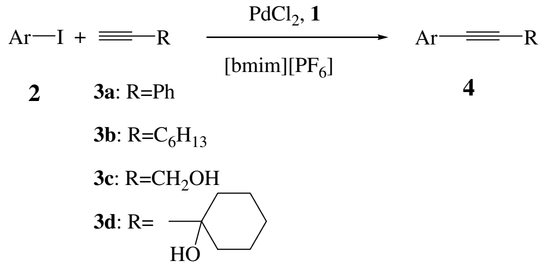
Table 2. Copper-free Sonogashira coupling reaction of aryl iodides with terminal alkynes catalyzed by PdCl$_2$–Dppc$^+$PF$_6$$^-$ in [bmim][PF$_6$]^a



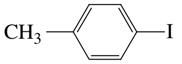
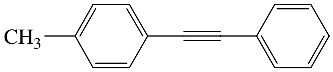
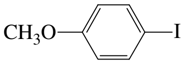
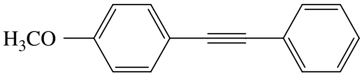
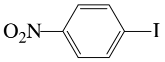
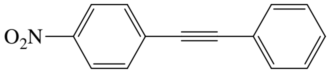
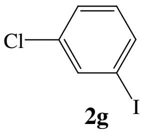
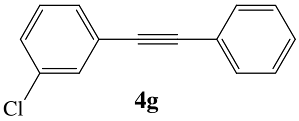
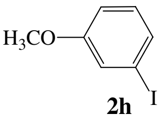
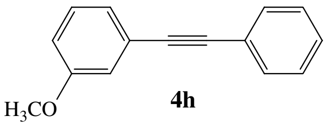
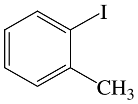
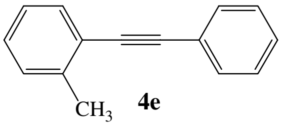
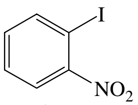
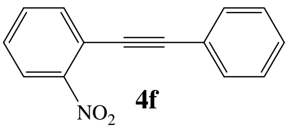
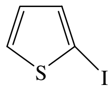
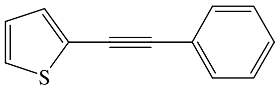
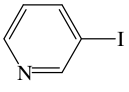
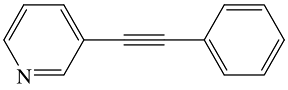
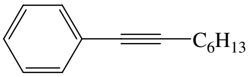
Entry	Aryl halide	Acetylene	Time (h)	Product	Yield (%)^b
1	 **2b**	**3a**	2.0	 **4b**	97
2	 **2c**	**3a**	2.0	 **4c**	95
3	 **2d**	**3a**	2.0	 **4d**	99
4	 **2g**	**3a**	2.0	 **4g**	97
5	 **2h**	**3a**	2.0	 **4h**	96
6	 **2e**	**3a**	8.5	 **4e**	91
7	 **2f**	**3a**	3.5	 **4f**	98
8	 **2i**	**3a**	2.0	 **4i**	98
9	 **2j**	**3a**	4.0	 **4j**	99
10	**2a**	**3b**	9.0	 **4k**	60(88^c)

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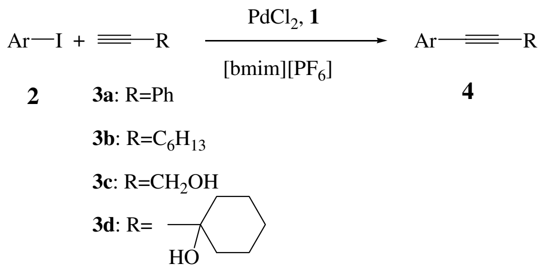
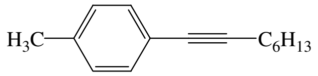
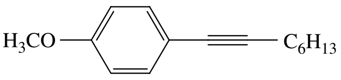
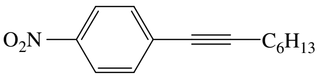
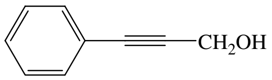
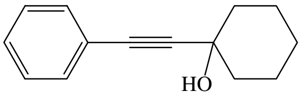
Table 2. (*Continued*)



Entry	Aryl halide	Acetylene	Time (h)	Product	Yield (%)^b
11	**2b**	**3b**	7.0	 **4l**	59(83^c)
12	**2c**	**3b**	6.5	 **4m**	26(74^c)
13	**2d**	**3b**	6.0	 **4n**	82(99^c)
14	**2a**	**3c**	6.0	 **4o**	88
15	**2a**	**3d**	6.0	 **4q**	91

[a] All reactions were carried out using 1 mmol of an aryl iodide, 1.2 equiv of an alkyne, 2.0 equiv of ^{i}Pr$_2$NH, 2 mol% of PdCl$_2$, 2 mol% **1** and 2.0 ml of [bmim][PF$_6$] at 60 °C.
[b] GC yields using hexadecane as internal standard.
[c] Reactions were carried out at 120 °C for 2 h, 1.5 equiv of piperidine was used as a base.

Table 3. Recycling experiments for the PdCl$_2$–Dppc$^+$PF$_6^-$ — [bmim][PF$_6$]-catalyzed Sonogashira coupling reaction[a]

Run	Time (h)	Yield (%)^b
1	1.0	98
2	1.0	99
3	1.0	97
4	1.0	97
5	1.0	95
6	1.0	91
7	1.5	91
8	1.5	92
9	2.0	67

[a] All reactions were carried out using 1 mmol of iodobenzene, 1.2 equiv of phenylacetylene, 2.0 equiv of ^{i}Pr$_2$NH, 2 mol% of PdCl$_2$, 2 mol% **1** and 2.0 ml of [bmim][PF$_6$] at 60 °C.
[b] GC yields.

to 60 °C (about 1 h) using an oil bath under vigorous stirring, and maintained for another 1 h. Then it was cooled and extracted with diethyl ether (4 × 5.0 ml). After evaporation under reduced pressure, the residue was purified by flash chromatography to give the product.

Typical procedure for the catalyst recycling of the Sonogashira coupling reaction

After the product was extracted with diethyl ether (4 × 5.0 ml), the ammonium salt remaining in the ionic liquid was removed by extraction with water (4 × 5.0 ml). Excess amount of diethyl ether and water was removed under reduced pressure. To the remaining ionic liquid containing Pd catalyst, iodobenzene (1.0 mmol), phenylacetylene (1.2 mmol) and diisopropyl amine (2.0 mmol, 0.3 ml) were added and heated at the required temperature with stirring for the proper time.

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