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A Copper-Free Sonogashira Coupling Reaction in Ionic Liquids and Its Application to a Microflow System for Efficient Catalyst Recycling

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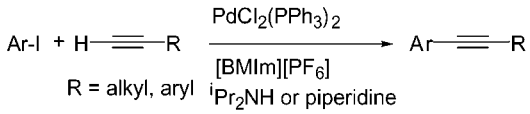
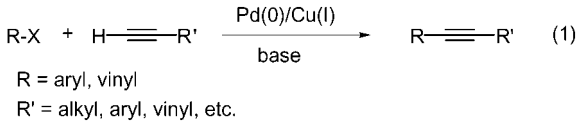
ABSTRACT



The $PdCl_2(PPh_3)_2$-catalyzed Sonogashira coupling reaction, in good to high yields, was performed in an ionic liquid ([BMIm][PF_6]) in the absence of a copper salt. The use of an ionic liquid allows for the facile separation and recycling of the catalyst. The application of the above reaction in a microflow system in conjunction with an IMM micromixer was also successful.

Of the variety of transition-metal catalyzed coupling reactions, Sonogashira coupling,[1] a palladium−copper catalyzed reaction of aryl halides and terminal alkyl or arylacetylenes, provides a useful tool for the preparation of alkyl, aryl-, and diaryl-substituted acetylenes (eq 1). The Sonogashira coupling reaction is frequently utilized as a key step in natural product synthesis.[2] Recent applications of this reaction include the synthesis of oligomeric, polymeric, and dendritic acetylene compounds, which are potentially useful in optical and electronic applications.[3] The Sonogashira coupling reaction is typically carried out in organic solvents, such as toluene, THF, and DMF, and a stoichiometric amount of base is required to trap the HX produced in the reaction. If the Sonogashira coupling could be carried out in ionic liquids,[4] the reaction would have a great advantage in terms of catalyst recycling, since the organic products could be readily



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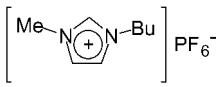
separated from the transition metal catalysts dissolved in the ionic liquids by simple extraction with a conventional organic solvent.[5]

We report herein on the Sonogashira coupling reaction in an ionic liquid, namely, 1-butyl-3-methylimidazolium hexafluorophosphate (**1**, [BMIm][PF_6]).[6] Interestingly, using $PdCl_2$-

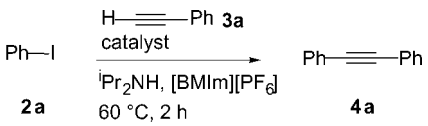


1 [BMIm][PF_6]

(PPh_3)$_2$ as catalyst and diisopropylamine or piperidine as base, the Sonogashira coupling reaction proceeded efficiently without using a copper cocatalyst. We also report on the successful execution of the Sonogashira reaction in a microflow reaction system, which demonstrates the first example of a homogeneous metal catalyzed reaction being conducted in a microreactor.[7]

Thus, when the reaction of iodobenzene (**2a**) with phenylacetylene (**3a**) was carried out in the presence of a catalytic amount of Pd(PPh_3)$_4$/CuI (5 mol %) and diisopropylamine (3.6 equiv) in **1** as a solvent at 60 °C for 2 h, the coupling product, diphenylacetylene (**4a**), was formed in 91% yield (Table 1, entry 1). The reaction, when conducted with Pd(PPh_3)$_4$ alone, resulted in the dramatic decrease in the yield of **4a** (entry 2). Interestingly, however, when $PdCl_2$(PPh_3)$_2$ was used as a catalyst, the coupling reaction occurred smoothly even in the absence of a copper cocatalyst, giving **4a** in 95% yield (entry 3).[8,9] For comparison, we tested a similar reaction with $PdCl_2$(PPh_3)$_2$ in organic solvents, but

Table 1. Palladium-Catalyzed Coupling Reaction of Iodobenzene and Phenylacetylene in [BMIm][PF_6][a]



entry	catalyst	yield[b] (%)
1	Pd(PPh_3)$_4$/CuI (5 mol %)	91
2	Pd(PPh_3)$_4$	13
3	$PdCl_2$(PPh_3)$_2$	96 (95)[c]
4[d]	$PdCl_2$(PPh_3)$_2$	96
5	Pd(OAc)$_2$/PPh_3 (10 mol %)	83
6	Pd(OAc)$_2$	61
7	$PdCl_2$	57
8	$PdCl_2$(NCPh)$_2$	63
9	$PdCl_2$(NCMe)$_2$	56
10[e]	$PdCl_2$(PPh_3)$_2$	83[c]
11[f]	$PdCl_2$(PPh_3)$_2$	80[c]

[a] Reactions were carried out using 1 mmol of **2a**, 1.2 equiv of **3a**, 3.6 equiv of ^{i}Pr$_2$NH, and 5 mol % of palladium catalyst in 3 mL of **1** at 60 °C for 2 h. [b] GC yields. [c] Isolated yield. See footnote 8. [d] Reaction was conducted with 1 mol % of $PdCl_2$(PPh_3)$_2$ at 80 °C for 2 h. [e] Reaction was conducted in 1-butyl-3-methylimidazolium tetrafluoroborate. [f] Reaction was conducted in 1-ethyl-3-methylimidazolium tetrafluoroborate.

the results were less satisfactory (yield of **4a**: toluene (48%), THF (55%), and DMF (81%)[10]). A combination of palladium acetate and triphenylphosphine also gave good results (entry 5). A reaction using palladium catalysts which contain no phosphine ligands gave the coupling product in modest yields (entries 6−9).[11] Some other ionic liquids, such as 1-butyl-3-methylimidazolium tetrafluoroborate ([BMIm][BF_4]) and 1-ethyl-3-methylimidazolium tetrafluoroborate ([EMIm]-[BF_4]), also worked well, but the yields of **4a** were slightly inferior (entries 10 and 11).

The coupling of several aryl halides and terminal acetylenes was carried out in the presence of the $PdCl_2$(PPh_3)$_2$ catalyst (Table 2). All coupling products were easily separated from the catalyst and solvent by extraction with hexane or ether. The coupling reaction proceeded smoothly, irrespective of whether the substituents of the aryl iodides were electron-donating or electron-withdrawing, to give the corresponding disubstituted acetylenes in high yields (entries 1−4). Heteroaromatic compound such as 2-iodothiophene (**2f**) also reacted with **3a** to give phenyletynylthiophene (**4f**) in 85% yield (entry 5). The coupling reaction of vinyl bromide **2g** with **3a** gave the anticipated enyne **4g** in 86% yield (entry 6). When aliphatic acetylenes, such as 1-octyne (**3b**), were used, the reaction was sluggish without the use of copper cocatalysts. 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 (entry

(5) For examples of transition-metal catalyzed reactions using ionic liquids, see: (a) Calò, V.; Nacci, A.; Lopez, L. Mannarini, N. *Tetrahedron Lett*. **2000**, *41*, 8973. (b) Hagiwara, H.; Shimizu, Y.; Hoshi, T.; Suzuki, T.; Ando, M.; Ohkubo, K.; Yokoyama, C. *Tetrahedron Lett*. **2001**, *42*, 4349. (c) Mathews, C. J.; Smith, P. J.; Welton, T. *Chem. Commun*. **2000**, 1249. (d) Okazaki, H.; Kawanami, Y.; Yamamoto, K. *Chem. Lett*. **2001**, 650. (e) Bujisman, R. C.; Vuuren, E. V.; Sterrenburg, J. G. *Org. Lett*. **2001**, *3*, 3785. See also ref 4g and references therein.

(6) Huddleston, J. G.; Willauer, H. D.; Swatloski, R. P.; Visser, A. E.; Rogers, R. D. *Chem. Commun*. **1998**, 1765.

(7) Ehrfeld, W.; Hessel, V.; Löwe, H. In *Microreactors*; Wiley-VCH: Weinheim, 2000.

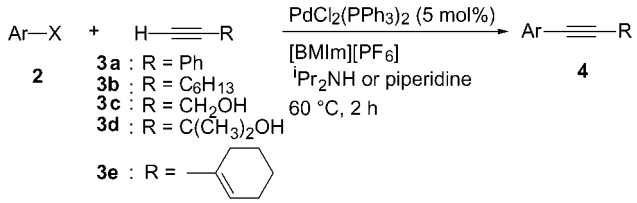
(8) **General Procedure for the Sonogashira Coupling Reaction in an Ionic Liquid.** In a 20 mL two-necked round-bottom flask, equipped with a magnetic stirrer bar and a reflux condenser, was placed 3 mL of **1**. The flask was then degassed under reduced pressure at room temperature for 1 h, and nitrogen gas was then introduced. To the ionic liquid was added $PdCl_2$(PPh_3)$_2$ (0.05 mmol, 35.1 mg), diisopropylamine (0.5 mL, 3.6 equiv), **2a** (1 mmol, 204 mg), and **3a** (1.2 mmol, 122 mg), and the resulting mixture was heated in an oil bath at 60 °C for 2 h under nitrogen. Product was extracted from the reaction mixture by the addition of hexane (5 mL), followed by decanting off a hexane solution of the products. This was repeated four additional times. After evaporation, the residue was purified by flash chromatography on silica gel using hexane as the eluant (R_f = 0.34) to give 169 mg of diphenylacetylene (**4a**) (95% yield).

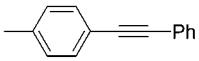
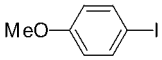
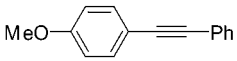
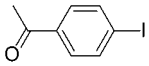
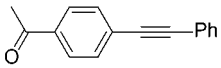
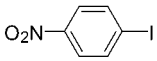
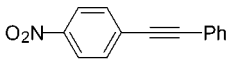
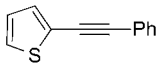
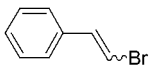
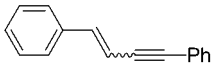
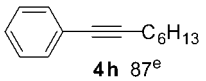
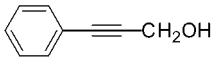
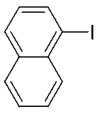
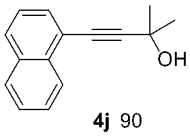
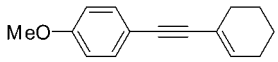
(9) Copper-free Sonogashira coupling reactions are not common. For the reaction with a strong base, such as $NaOCH_3$, see: (a) Cassar, L. *J. Organomet. Chem*. **1975**, *93*, 253. The use of amine as solvents: (b) Dieck, H. A.; Heck, F. R. *J. Organomet. Chem*. **1975**, *93*, 259. (c) Austin, W. B.; Bilow, N.; Kelleghan, W. J.; Lau, K. S. Y. *J. Org. Chem*. **1981**, *46*, 2280. (d) Alami, M.; Ferri, F.; Linstrumelle, G. *Tetrahedron Lett*. **1993**, *34*, 6403. Use of ammonium salts: (e) Nguefack, J.-F.; Bolitt, V.; Sinou, D. *Tetrahedron Lett*. **1996**, *37*, 5527. (f) Mori, A.; Kawashima, J.; Shimada, T.; Suguro, M.; Hirabayashi, K.; Nishihara, Y. *Org. Lett*. **2000**, *2*, 2935. Ligand manipulation: (g) Wagner, R. W.; Johnson, T. E.; Li, F.; Lindsey, J. S. *J. Org. Chem*. **1995**, *60*, 5266. (h) Böhm, V. P. W.; Herrmann, W. A. *Eur. J. Org. Chem*. **2000**, 3679.

(10) The result with DMF appeared reasonable as a copper-free process. However, the reaction with aliphatic acetylenes gave low yields of the coupling products.

(11) Nevertheless, these results obtained using **1** are noteworthy, since a similar reaction with Pd(OAc)$_2$ conducted in toluene gave a poor result (15%). For an example of a phosphine-free Sonogashira reaction, see ref 9d.

Table 2. Coupling Reaction of Aryl Halides **2** and Acetylenes **3** Catalyzed by $PdCl_2(PPh_3)_2$[a]



entry	aryl halide	acetylene	product yield[b] (%)
1	 **2b**	**3a**	 **4b** 95
2	 **2c**	**3a**	 **4c** 91
3	 **2d**	**3a**	 **4d** 91
4	 **2e**	**3a**	 **4e** 97
5	 **2f**	**3a**	 **4f** 85
6	 **2g** (*E*/*Z* = 86/14)[c]	**3a**	 **4g** 86 (*E*/*Z* = 93/7)[c]
7[d]	**2a**	**3b**	 **4h** 87[e]
8[d]	**2a**	**3c**	 **4i** 88
9[d]	 **2h**	**3d**	 **4j** 90
10[d]	**2c**	**3e**	 **4k** 97

[a] The reaction was carried out using 1 mmol of an aryl halide, 1.2 equiv of an acetylene, 3.6 equiv of $^{i}Pr_2NH$, and 5 mol % of $PdCl_2(PPh_3)_2$ in 3 mL of $[BMIm][PF_6]$ at 60 °C for 2 h. [b] Yields isolated by flash chromatography on SiO_2. [c] Ratio was determined by ^1H NMR. [d] Piperidine was used as a base. [e] Reaction was carried out at 80 °C.

7). Similarly, the reaction of **2a** with propargyl alcohol (**3c**) in the presence of piperidine gave the coupling product in 88% yield (entry 8). 1-Iodonaphthalene (**2h**) and 4-iodoanisole (**2c**) coupled with 2-methyl-3-butyn-2-ol (**3d**) and 1-ethynylcyclohexene (**3e**) respectively to afford the corresponding coupling products **4j** and **4k** in high yields (entries 9 and 10).

Catalyst recycling studies were also carried out. After extraction with hexane to separate the products from the catalyst, the resulting ionic liquid layer was washed with water to remove ammonium salts. The resulting ionic liquid containing the Pd catalyst could be reused successfully several times with only a slight loss in its activity (Table 3).

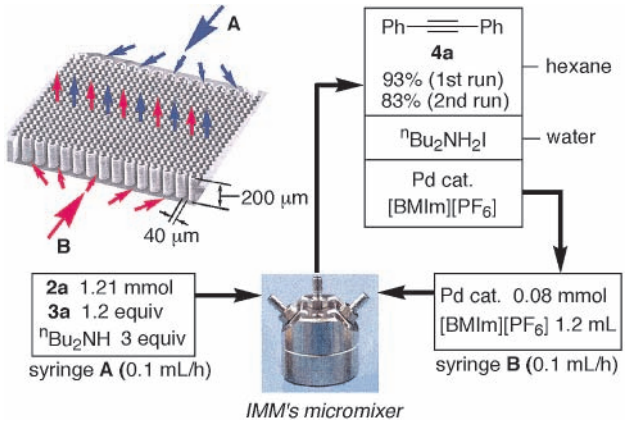
Table 3. Recycling Studies for the Coupling Reaction of **2a** with **3a**[a]

number of cycles	yield[b] (%)
1	96
2	80
3	78
4	63 (75)[c]

[a] Reactions were carried out using 1 mmol of **2a**, 1.2 equiv of **3a**, 3.6 equiv of $^{i}Pr_2NH$, and 5 mol % of $PdCl_2(PPh_3)_2$ in 3 mL of **1** at 60 °C for 2 h. [b] GC yields. [c] Reaction was carried out for 3 h.

Recently microreaction technology has attracted considerable attention in terms of achieving high thermal efficiency, high-speed mixing, and high surface/volume ratios.[7] Applications of microreactors to heterogeneous catalytic reactions constitute a topic of interest.[12] However, we believed that a high-speed micromixing system might also be useful in the case of a homogeneous catalyst system which does not use conventional organic solvents. This led us to examine the present reaction in a microflow system,[13] using a micromixer having 2 × 15 interdigitated channels (40 μm width and 200 μm depth) which is commercially available from IMM. If such reactions could be conducted under these conditions, it would permit the development of a new catalyst recycling system to ensure the continuous production of acetylenic compounds. Thus, a mixture of **2a**, **3a**, and $^{n}Bu_2NH$ (syringe A) was introduced at one inlet of the micromixer and Pd catalyst[14] in $[BMIm][PF_6]$ (syringe B) was introduced at the other inlet, by means of a syringe pump (flow rate, 0.1 mL/h; bath temperature, 110 °C) (Scheme 1). The

Scheme 1. Sonogashira Reaction in a Microflow System



reagents were mixed in the micromixer, and the reaction mixture was continuously removed from the outlet with ca. 10 min of the resident time in the mixer. The coupling product **4a** was formed and was easily isolated from the mixture by extraction with hexane/water (93% GC yield).[15]

In the second run, with the recovered catalyst solution, **4a** was obtained in 83% yield. We are currently in the process of constructing an automated recycling system for the catalyst for the continuous production of coupling products.

In conclusion, the Sonogashira coupling reaction of aryl iodides with terminal acetylenes, irrespective of being aromatic or aliphatic, proceeds efficiently in an ionic liquid, [BMIm][PF_6], using $PdCl_2(PPh_3)_2$ as the catalyst in the absence of a copper salt. The use of an ionic liquid permitted the product to be easily separated from the catalyst. The recovered catalyst could then be reused, and the execution of the coupling reaction using a microflow system was also successful.

Acknowledgment. The authors thank Mr. Jun Kanazawa at Nippon Soda Co., Ltd. for useful discussions. This research was supported by a Grant-in-Aid for Scientific Research on Priority Areas (A) Exploitation of Multi-Element Cyclic Molecules from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: Experimental procedure and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) For recent examples of synthesis using microflow systems, see: (a) Salimi-Moosavi, H.; Tang, T.; Harrison, D. J. *J. Am. Chem. Soc*. **1997**, *119*, 8716. (b) Chambers, R. D.; Spink, R. C. H. *Chem. Commun*. **1999**, 883. (c) Bellefon, C.; Tanchoux, N.; Caravieihes, S. Grenouillet, P.; Hessel, V. *Angew. Chem., Int. Ed.* **2000**, *39*, 3442. (d) Suga, S.; Okajima, M.; Fujiwara, K.; Yoshida, J. *J. Am. Chem. Soc*. **2001**, *123*, 7941.

(14) A recycled palladium catalyst was used for this study using micromixer, since $PdCl_2(PPh_3)_2$, which shows a low solubility in a [BMIm]-[PF_6] at the initial stage of the reaction, could clog the microchannels.

(15) We confirmed that a miniflow reactor (T-shaped tubular glass reactor, 0.2 cm i.d., 4 cm length) resulted in a low conversion of substrates, which supports highly efficient mixing as the key to the observed smooth reaction with a micromixer.