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Recyclable Sonogashira coupling reactions in an ionic liquid, effected in the absence of both a copper salt and a phosphine†

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(Bisimidazole)Pd(Me)Cl catalyzes an efficient and recyclable Sonogashira coupling reaction without copper salts or bulky phosphine ligands, in an ionic liquid.

Typically, cross-coupling reactions involve vinyl or aryl substituents attached to a secondary unsaturated moiety. Among them, the Sonogashira-(Hagihara) palladium-catalyzed coupling reaction is recognized as a powerful and reliable synthetic method for the formation of substituted or nonsubstituted acetylenes.[1] The unique properties of acetylenic arrays continue to attract considerable interest with research in nonlinear optical electronic devices[2] and in natural product synthesis.[3]

Typical literature procedures for the Sonogashira coupling reaction use a palladium catalyst with a metal co-catalyst and base. The most widely employed co-catalysts are copper salts, which can also induce Glaser-type homocoupling of the alkynes. To avoid this drawback, copper-free coupling reactions have been developed using strong base or an amine as the solvent.[4] It is also noteworthy that alkynyl aluminates[5] or alkynyl borates[6] can be used for alkynyl counterparts, resulting in excellent chemoselectivity and high yields in the absence of copper salts. The reactivity of the palladium catalyst has been markedly enhanced by using bulky, electron-rich phosphine ligands such as P^tBu_3.[7] Despite these fine results, there still is a need for a general protocol that would be applicable to a wide range of Sonogashira coupling reactions. We became interested in the use of ionic liquids[8] as reaction media due to significant economical and environmental reasons for developing recyclable catalytic reactions from both academic and industrial perspectives. In this manuscript, we disclose the results of recyclable Sonogashira coupling reactions in an ionic liquid without copper salts[9] or a phosphine. In accordance with our research program on recyclable catalytic reactions,[10] we recently found an efficient and recyclable [bisimidazole]Pd(II) catalyst which is valuable for the Heck reaction under phosphane-free conditions.[11] The catalyst can be recycled five times without any loss of catalytic activity in an ionic liquid. These results encouraged us to examine the Sonogashira coupling reaction with a novel palladium catalyst.

The catalytic activity of [(bisimidazole)PdClMe] (**1**) was examined for the Sonogashira coupling reaction of iodobenzene and phenylacetylene (Table 1).

Using 2 mol% of **1** and 2 mL of [bmim]PF_6 as the solvent, we found amine bases (*i.e.*, TEA, DIEA or piperidine) were effective for the reaction but inorganic bases (*i.e.*, K_2CO_3, Cs_2CO_3) were sluggish in this system, perhaps due to solubility problems. Fortunately, all of these amine bases furnished high yields of products in short reaction times. We were also gratified to observe that the catalyst could be recycled four times in high yield using these amine bases (Table 1). This means that the palladium catalyst is very efficient for the Sonogashira coupling reaction. It is noteworthy that the coupling reaction occurred smoothly even *in the absence of a copper co-catalyst and bulky phosphine ligands*. A more versatile and practical test of the recyclability of the catalyst was examined with various iodoarene substrates. Reactions containing electron-poor, electron-rich or heteroaromatic substrates with phenylacetylene were run under optimized conditions, and the results are described in Table 2. All of the coupling reactions proceeded smoothly to give the corresponding products, with reuse of the catalyst. We confirmed that small amounts (less than 5%) of Glaser-type homocoupling products were formed in this reaction.

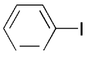
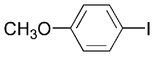
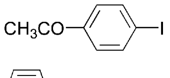
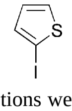
It is well-known that the relative reactivity of the aryl halides is Ar–I > > Ar–Br > Ar–Cl. This factor is significant for aryl halides or acetylenes containing electron withdrawing substituents in which case the rate of coupling is faster than the reoxidation of Pd^0. With electron rich substrates, the corresponding coupling reactions proceeds more slowly. In addition, the Sonogashira coupling reaction is influenced by steric factors as well. The results in Table 3 illustrate these points.

Table 1 Sonogashira coupling of iodobenzene with phenylacetylene in [bmin][PF] without copper salt or phosphine[a]

Entry	Base/equiv.	Temp./ °C	Cycle no. (time/h)[b]			
1	Et_3N (2)	60	1 (2) 85	2 (2) 90	3 (2) 85	4 (2) 72
2	$^iPr_2NH$ (3.6)	60	1 (2) 98	2 (2) 92	3 (2) 55	4 (3) 60
3	Piperidine (1.5)	120	1 (1) 90	2 (1) 73	3 (2) 79	4 (2) 70
4[c]	Et_3N (2)	60	1 (2) 91	2 (2) 71	3 (2) 71	4 (4) 33
5	K_2CO_3 (1.5)	60	(4) 11			
6	Cs_2CO_3 (1.5)	120	(2) 17			

[a] All reactions were carried out using 1 mmol of iodobenzene, 1.25 equiv. of phenylacetylene, 2 mol% of **1** and 2 mL of the ionic liquid. [b] Values given for each cycle are GC yields (%). [c] 4-Iodoanisole was used.

Table 2 Recyclable Sonogashira coupling of iodobenzene with phenylacetylene in [bmin][PF] without copper salt or phosphine[a]

Entry	Substrates	Cycle no. (time/h)[a]			
1		1 (1) 90	2 (1) 73	3 (2) 79	4 (2) 70
2		1 (1) 95	2 (1) 89	3 (2) 90	4 (2) 68
3		1 (1) 95	2 (1) 90	3 (2) 88	4 (2) 69
4		1 (1) 75	2 (1) 68	3 (2) 73	4 (2) 79

[a] All reactions were carried out using 1 mmol of iodobenzene, 1.25 equiv. of phenylacetylene, 2 mol% of **1**, 1.5 equiv of piperidine and 2 mL of the ionic liquid at 120 °C. [b] Values are given for each cycle based on GC yields (%).

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† Electronic supplementary information (ESI) available: experimental details. See http://www.rsc.org/suppdata/cc/b4/b402477j/

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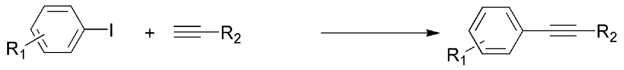
The Sonogashira coupling of iodoarenes with 1-alkynes has been previously employed, without CuI (necessary when the reaction is performed in organic solvents) and with the palladium catalyst, $PdCl_2(PPh_3)_2$, in an ionic liquid.[9] We have now demonstrated that the novel complex, [(bisimidazole)PdClMe], is an efficient and versatile catalyst for the Sonogashira reaction, enabling a wide range of couplings with recyclability of the catalyst, in the absence of copper co-catalyst and extra phosphine ligands.

In a typical reaction procedure for recycle of the catalyst (entry 1, Table 2), iodobenzene (204 mg, 1 mmol) and phenylacetylene (128 mg, 1.2 mmol) were added to the Pd(II) catalyst,**1**, (6.4 mg, 0.02 mmol), piperidine (128 mg, 1,25 mmol) and 2 mL of $[bmim]PF_6$. The reaction mixture was stirred at 120 °C until completion of the reaction (indicated by disappearance of the starting material (TLC)). After extraction with ethyl ether to separate the products from the catalyst, the resulting ionic liquid layer was washed with water to remove the amine salt. The recovered ionic liquid layer was reused without any pretreatment.

Table 3 Copper-free Sonogashira coupling of various iodoarenes with aryl or alkyl acetylenes in [bmin][PF][a]



Entry	R_1	R_2	Yield (isolated, %)
1	2-Me	Ph	42
2[b]	2-^{i}Pr	Ph	32
3	2-NO_2	Ph	74
4	3-OMe	Ph	58
5	3-Cl	Ph	94
6	4-Me	Ph	98
7	4-NO_2	Ph	83
8	4-CF_3	Ph	94
9[c]	4-OMe	Ph	trace
10	4-COMe	CH_2OH	40
11	4-COMe	CH(Me)OH	43
12	4-COMe	CH(Ph)(Me)OH	58
13	4-COMe	$CO_2{}^nBu$	54
14	4-COMe	C_6H_{13}	28
15	4-COMe	CH_2NMe_2	0

[a] All reactions were carried out using 1 mmol of iodobenzene, 1.25 equiv. of acetylene, 2 mol% of **1**, 1.5 equiv of piperidine and 2 mL of the ionic liquid at 120 °C for 1 h.. [b] Reaction time: 2 h. [c] 4-Iodoanisole was used. Reaction time: 4 h.

In conclusion, we have developed an efficient and recyclable palladium-mediated Sonogashira coupling reaction in the absence of a copper salt or a bulky phosphine using an ionic liquid.

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