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Copper-free $PdCl_2/PPh_3$-catalyzed Sonogashira coupling reaction of aryl bromides with terminal alkynes in water

Jin Tao Guan, Tan Qing Weng, Guang-Ao Yu and Sheng Hua Liu*

Key Laboratory of Pesticide & Chemical Biology, Ministry of Education, College of Chemistry, Central China Normal University, Wuhan 430079, China

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Abstract—A simple, copper-free and efficient catalytic system for the Sonogashira coupling reaction of aryl bromides with terminal alkynes in pure water has been developed. The use of $PdCl_2/PPh_3$ in the presence of pyrrolidine allows the coupling reaction to proceed at 120 °C in moderate to excellent yields.

As an important method for the synthesis of substituted alkynes, the cross-coupling of aryl halides with terminal alkynes has received much attention in recent years.[1] It has been widely employed in the synthesis of natural products,[2] biologically active molecules[3] and materials science.[4] In recent years, a variety of modifications have been reported for this reaction and great progress has been made.[5] The most important modification is the elimination of the copper salt,[6] which was used as co-catalyst since it could induce a Glaser-type homocoupling reaction of the terminal alkynes to diynes in the presence of oxidative agents or air.[7] However, in most of the catalytic processes, organic solvents are usually employed as the reaction media, often creating a great deal of safety, health and environmental issues due to their flammability, toxicity and volatility. From an economic and environmental standpoint, it is desirable to avoid any use of hazardous and expensive organic solvents. The use of water or aqueous solution represents one of the most economically and environmentally viable alternatives to organic solvents for metal-catalyzed reactions.[8] Several examples of Pd-catalyzed Sonogashira reactions in aqueous media have been reported; however, many of these reactions are carried out in an aqueous-organic and in some case, special phosphine ligands and copper salts are required in order to reach high reaction efficiency.[9] Recently, a copper-free $PdCl_2$-catalyzed Sonogashira coupling reaction of aryl iodides with terminal acetylenes is carried out in pure water.[10] As part of our ongoing project on palladium-catalyzed reactions,[11,12] we report herein the Sonogashira reaction of aryl bromides with terminal alkynes catalyzed by air-stable and readily available $PdCl_2/PPh_3$ in pure water without adding any organic co-solvent and copper salt.

For the optimization of the reaction conditions, we chose the cross-coupling of bromobenzene (**1a**) with phenyl acetylene (**2a**) as the model reaction, and the effects of the base and catalyst on the reaction were examined. First, several bases were screened for the Sonogashira coupling reaction in the presence of catalytic amount of $PdCl_2/PPh_3$. As shown in Table 1, the reaction is significantly influenced by the base employed. The reaction works very well when organic bases, such as Et_3N, $(i\text{-}Pr)_2NH$, piperidine, and pyrrolidine, are used (entries 4–7 in Table 1), with the best result obtained in the case of pyrrolidine as the base (entry 6 in Table 1). Inorganic bases could be used in this particular reaction; however, they were inferior to organic ones (entries 1–3 in Table 1). Accordingly, the activities of some catalysts were evaluated using pyrrolidine as the base (Table 2). Initial catalyst screening indicated that the use of palladium(0) or palladium(II) complexes with added phosphine ligands displayed excellent catalytic activity toward the formation of **3a** (entries 1–3 in Table 2). In particular, the use of 2 mol % $PdCl_2$ with 4 mol % PPh_3 was the most effective catalyst system for this Sonogashira coupling (entry 2 in Table 2). However,

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Keywords: Water; Copper-free; Aryl bromides; Sonogashira coupling reaction.

* Corresponding author. E-mail: chshliu@mail.ccnu.edu.cn

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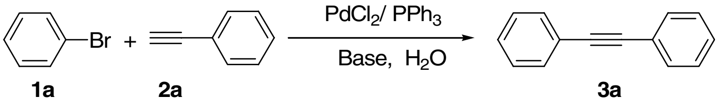
Table 1. Effect of base on the Sonogashira coupling of bromobenzene with phenylacetylene in water[a]

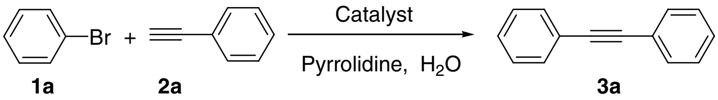


Entry	Base	Yield[b] (%)
1	K_3PO_4	83
2	NaOAc	21
3	K_2CO_3	43
4	Piperidine	90
5	(*i*-Pr)$_2$NH	89
6	Pyrrolidine	93
7	Et_3N	83

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), base (2 equiv), $PdCl_2$ (2 mol %), PPh_3 (4 mol %), degassed water (1 mL) at 120 °C for 100 min in a sealed tube.

[b] GC yields.

Table 2. Effect of catalyst on the Sonogashira coupling of bromobenzene with phenylacetylene in water[a]



Entry	Catalyst	Yield[b] (%)
1	Pd(dba)$_2$/PPh_3 (4 mol %)	90
2	$PdCl_2$/PPh_3 (4 mol %)	93
3	$PdCl_2(PPh_3)_2$	87
4	$PdCl_2$	19
5	$PdCl_2$/PPh_3 (6 mol %)	88
6	$PdCl_2$/PPh_3 (8 mol %)	87

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), pyrrolidine (2 equiv), 2 mol % of palladium catalyst, and degassed water (1 mL) at 120 °C for 100 min.

[b] GC yields.

$PdCl_2$ itself without added phosphine ligands was much less effective for this transformation (entry 4 in Table 2). In addition, increasing the amount of PPh_3 to 6 or 8 mol % did not benefit the reaction (entries 5 and 6 in Table 2).

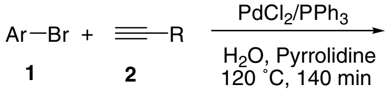
The Sonogashira coupling reactions of a variety of aryl bromides and terminal alkynes were studied under the optimal conditions. As shown in Table 3, the aryl bromide with electron-withdrawing groups or methyl group reacted with **2a** to give the desired products in excellent yields under the reaction conditions (entries 1–11), while the methoxyl-substituted aryl bromide (**1e**) reacted with **2a** to give **3e** in slightly lower yield (entry 5). For *ortho*-substituted aryl bromides, relatively lower yields were obtained compared to similar aryl bromides (entries 12–14). Heteroaromatic compounds such as 2-bromothiophene (**1q**) and 2-bromopyridine (**1r**) also reacted with **2a** to give cross-coupling products (**3q**) and (**3r**) in 93% and 95% yields (entries 15 and 16), respectively. Moderate yields were obtained when aliphatic acetylenes were used as coupling partners. For example, **1a** coupled with 1-octyne (**2b**) and propargyl alcohol (**2c**) gave the corresponding coupling products (**3s**) and (**3t**) in 82% and 70% yields (entries 17 and 18), respectively. Similarly, the reaction of **1a** with 1-ethynyl-1-cyclohexanol (**2d**) gave the desired product (**3u**) in 43% yield (entry 19). These results indicated that a variety of important functional groups could be tolerated under the reaction conditions.

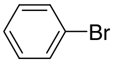
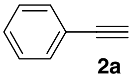
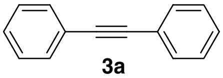
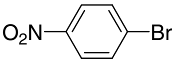
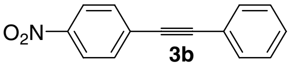
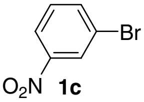
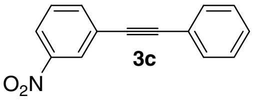
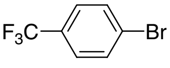
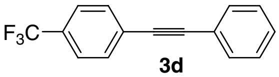
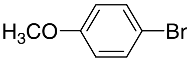
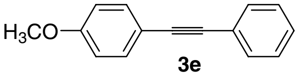
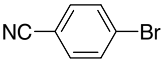
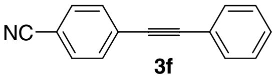
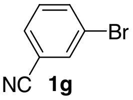
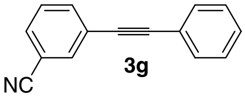
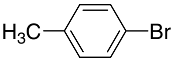
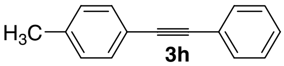
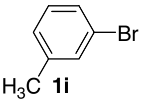
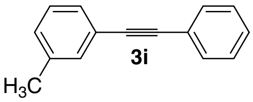
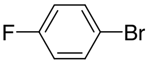
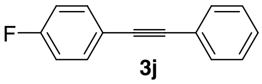
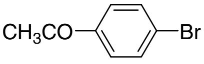
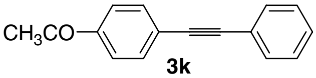
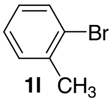
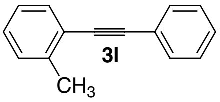
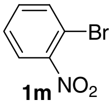
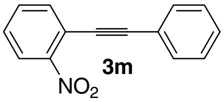
In summary, we have demonstrated a practical and efficient $PdCl_2$/PPh_3-catalyzed copper-free Sonogashira reaction of aryl bromides with terminal alkynes in water in the presence of pyrrolidine. The highlights of this catalytic system include the copper-free, ready availability of catalyst, high catalytic activity and water as the sole solvent.

Typical experimental procedure for cross-coupling of bromobenzene (**1a**) *with phenylacetylene* (**2a**) *to afford diphenylacetylene* (**3a**) (*Table 3, entry 1*)

A mixture of bromobenzene (**1a**) (53.0 μL, 0.5 mmol), phenylacetylene (66.0 μL, 0.6 mmol), pyrrolidine (85.0 μL, 1.0 mmol), $PdCl_2$ (1.8 mg, 0.01 mmol), PPh_3 (5.3 mg, 0.02 mmol), and degassed water (1.0 mL) under nitrogen in a sealed tube was heated at 120 °C for 140 min. It was then cooled and extracted with diethyl ether (4 × 5 mL). After evaporation under reduced pressure, the residue was purified by flash chromatography to give the pure product.

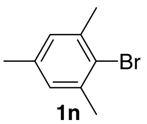
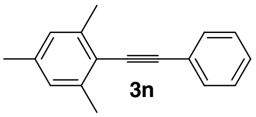
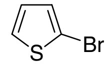
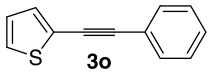
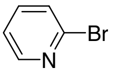
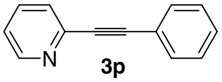
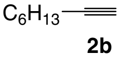
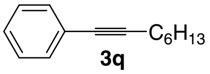
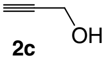
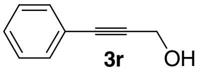
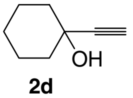
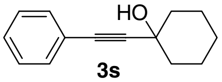
Table 3. $PdCl_2/PPh_3$-catalyzed Sonogashira coupling reaction of aryl halides (**1**) with terminal alkynes (**2**)[a]



Entry	Aryl bromide	Alkyne	Product	Yield[b] (%)
1	 **1a**	 **2a**	 **3a**	86
2	 **1b**	**2a**	 **3b**	97
3	 **1c**	**2a**	 **3c**	91
4	 **1d**	**2a**	 **3d**	95
5	 **1e**	**2a**	 **3e**	71
6	 **1f**	**2a**	 **3f**	93
7	 **1g**	**2a**	 **3g**	87
8	 **1h**	**2a**	 **3h**	93
9	 **1i**	**2a**	 **3i**	91
10	 **1j**	**2a**	 **3j**	90
11	 **1k**	**2a**	 **3k**	92
12	 **1l**	**2a**	 **3l**	57
13	 **1m**	**2a**	 **3m**	60

(*continued on next page*)

Table 3 (*continued*)

Entry	Aryl bromide	Alkyne	Product	Yield[b] (%)
14	 **1n**	**2a**	 **3n**	44
15	 **1o**	**2a**	 **3o**	93
16	 **1p**	**2a**	 **3p**	95
17	**1a**	 **2b**	 **3q**	82
18	**1a**	 **2c**	 **3r**	70
19	**1a**	 **2d**	 **3s**	43

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol), pyrrolidine (2 equiv), $PdCl_2$ (2 mol %), PPh_3 (4 mol %), degassed water (1 mL) at 120 °C for 140 min in a sealed tube.

[b] Yield of isolated product (average of two runs).

Acknowledgments

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