Efficient Copper-Catalyzed Sonogashira Couplings of Aryl Halides with Terminal Alkynes in Water

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Abstract: An efficient copper-catalyzed method has been developed for Sonogashira couplings of aryl halides with terminal alkynes in water. The protocol uses inexpensive CuBr as the catalyst, 1,10-phenanthroline as the ligand, tetrabutylammonium bromide (TBAB) as the phase-transfer catalyst, environmentally friendly water as the solvent, and various internal alkynes were synthesized in good to excellent yields.

Key words: copper, water, Sonogashira coupling, synthetic method, alkyne

Many antimycotics,[2] antibiotics,[3] liquid crystals, polymers, and optical or electronic materials[4] were synthesized from the internal alkyne intermediates via the Sonogashira reaction,[5] and the palladium/copper co-catalyzed coupling is a popular strategy for the construction of C(sp^2)–C(sp) bonds.[6] However, the drawbacks of the catalyst systems, such as air sensitivity, high cost, and toxicity, limit their applications for industrial processes, so it is highly desirable to develop readily available and inexpensive catalyst systems instead of palladium catalysts to promote the Sonogashira couplings. During the past more than ten years, several examples involving copper-,[7] iron-catalyzed,[8] and nickel/copper-,[9] iron/copper-cocatalyzed[10] Sonogashira reactions were reported. Although the previous methods are effective, the coupling reactions were performed in organic solvents. Therefore, it is necessary to search more convenient, practical, and environmentally benign approach to internal alkynes. It is well known to all that water is the most economical and environmentally friendly solvent in the world,[11] and the wide applications of internal alkynes found in many fields have stimulated researches into the development of new strategies for their synthesis in water. However, synthesis of organic molecules in water entails the additional challenges of water tolerance for the catalyst/ligand systems and the associated problems of substrate solubility and reactivity.[12] Recently, palladium-catalyzed[13a,b] or microwave-mediated[13c] Sonogashira couplings in water have been developed. Considering the readily availability and low toxicity of copper catalysts and their ligands, the development of a cheaper copper-catalyzed system enabling Sonogashira couplings has become an important goal. During the last decade, great progress on the copper-catalyzed Ullmann-type reaction has been made, which relied on the utilization of some special additives.[14] The copper-catalyzed Sonogashira couplings in water were recently reported,[15] unfortunately, toxic and readily oxidative Ph_3P was used as the ligand, which did not meet the environmentally benign conditions. We have developed copper-catalyzed cross-couplings in organic solvents[16] and in neatly aqueous medium.[17] Herein, we report a simple and highly efficient copper-catalyzed method for the synthesis of internal aromatic alkynes using environmentally benign water as the solvent.

As shown in Tables 1, 1-iodo-4-methylbenzene and phenylacetylene were firstly chosen as the model substrates to optimize reaction conditions including catalysts, ligands, bases, and temperature under nitrogen atmosphere. Six ligands were screened using 10 mol% of CuI as the catalyst, 20 mol% of tetrabutylammonium bromide as the phase-transfer catalyst (PTC) and 2 equivalents of NaOH as the base (relative to amount of 1-iodo-4-methylbenzene) in water at 110 °C (entries 1–6), and 1,10-phenanthroline (phen) provided the highest yield (entry 2). The target product was obtained in 31% yield in the absence of ligand (entry 7). Several bases were investigated (compare entries 2, 8–10), and NaOH showed best efficiency (entry 2). When reaction temperature was increased to 120 °C from 110 °C, higher yields were provided (compare entries 2 and 11). Various copper salts were tested (compare entries 11–14), and CuBr showed the highest reactivity (entry 12) with small amount of homocoupling product appearing. The coupling reaction afforded the target product in 63% yield in the absence of a phase-transfer catalyst. Therefore, the following catalyst system (10 mol% of CuBr, 20 mol% of phen, 20 mol% of tetrabutylammonium bromide, 2 equiv of NaOH) was optimal at a reaction temperature of 120 °C for the Sonogashira couplings of aryl halides with terminal alkynes in water.

As shown in Table 2, we investigated the coupling scope of various aryl halides with terminal alkynes in water under our standard conditions,[18] and the examined substrates provided the corresponding target products in good to excellent yields. For aryl halides, the substrates containing electron-withdrawing groups showed higher activity than ones containing electron-donating groups, and the reactivity order of the aryl halides was iodides > bromides. Aryl

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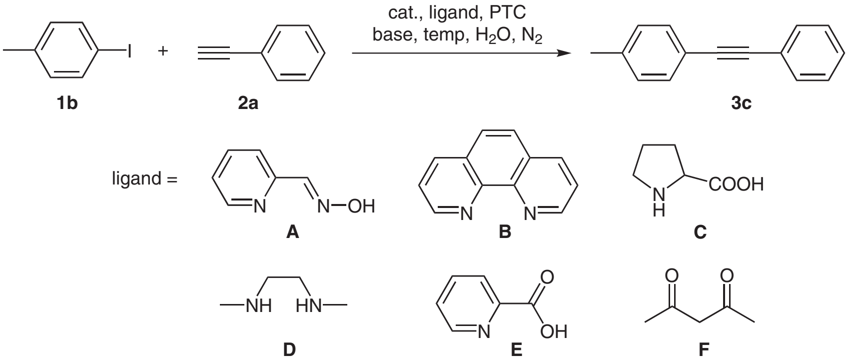
Table 1 Copper-Catalyzed Coupling of 1-Iodo-4-methylbenzene with Phenylacetylene: Optimization of Conditions[a]



Entry	Catalyst	Ligand	Base	Temp (°C)	Yield (%)[b]
1	CuI	**A**	NaOH	110	50
2	CuI	**B**	NaOH	110	72
3	CuI	**C**	NaOH	110	44
4	CuI	**D**	NaOH	110	60
5	CuI	**E**	NaOH	110	34
6	CuI	**F**	NaOH	110	25
7	CuI	–	NaOH	110	31
8	CuI	**B**	KOH	110	50
9	CuI	**B**	K_2CO_3	110	30
10	CuI	**B**	Cs_2CO_3	110	35
11	CuI	**B**	NaOH	120	77
12	CuBr	**B**	NaOH	120	83
13	CuCl	**B**	NaOH	120	66
14	$CuCl_2$	**B**	NaOH	120	74
15	CuBr	**B**	NaOH	120	63[c]

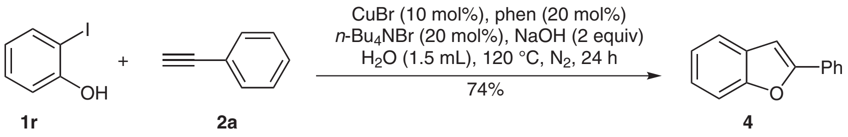
[a] Reaction conditions: 1-iodo-4-methylbenzene (**1b**, 1 mmol), phenylacetylene (**2a**, 2 mmol), catalyst (0.1 mmol), ligand (0.2 mmol), n-Bu_4NBr (0.2 mmol), base (2 mmol), H_2O (1.5 mL) in a sealed Schlenk tube under nitrogen atmosphere, 24 h.

[b] Isolated yield.

[c] In the absence of n-Bu_4NBr.

bromides could also provide the coupling products in moderate yields when 2 equivalents of KI and more TBAB were added to the reaction systems (see entries 21–24). For alkynes, aromatic ones showed higher reactivity. The Sonogashira couplings could tolerate various functional groups including ether (entry 10), C–Cl bond (entries 12–16 and 22), C–Br bond (entry 17), C–F bond (entries 5, 7, 14, 18, and 19), nitro (entries 20 and 23) in the substrates. We attempted reaction of 2-iodophenol (**1r**) with phenylacetylene (**2a**) under our standard conditions, and the cascade reaction provided 2-phenylbenzofuran (**4**) in 74% yield (Scheme 1).

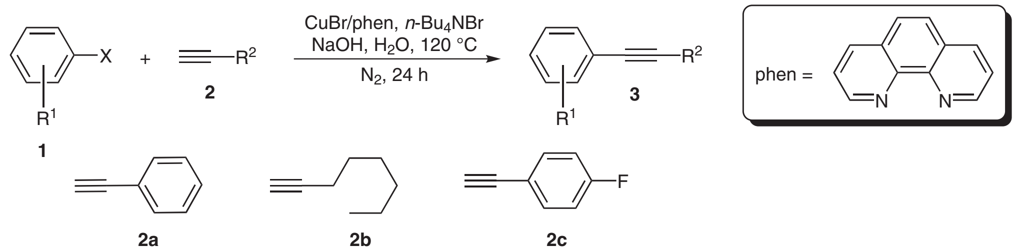
In summary, we have developed an efficient copper-catalyzed method for the synthesis of internal alkynes via



Scheme 1 Cascade reaction of 2-iodophenol (**1r**) with phenylacetylene (**2a**) to provide 2-phenylbenzofuran (**4**)

Sonogashira couplings of aryl halides with terminal alkynes in water. The method is of good tolerance towards various functional groups in the substrates, and it will attract much attention in industrial and academic researches.

Table 2 Copper-Catalyzed Sonogashira Couplings of Aryl Halides with Terminal Alkynes in Water[a]



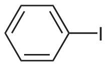
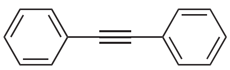
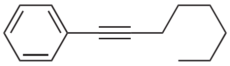
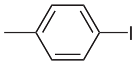
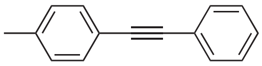
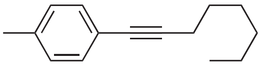
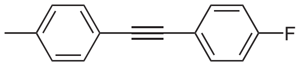
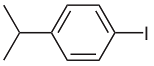
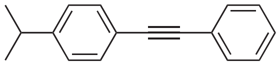
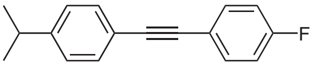
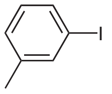
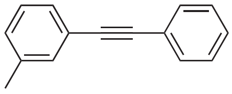
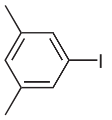
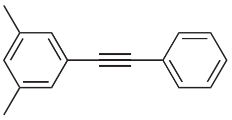
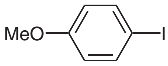
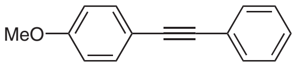
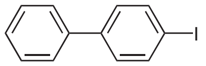
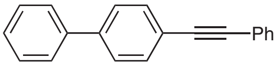
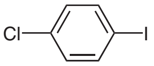
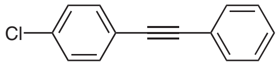
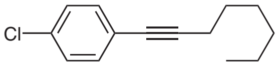
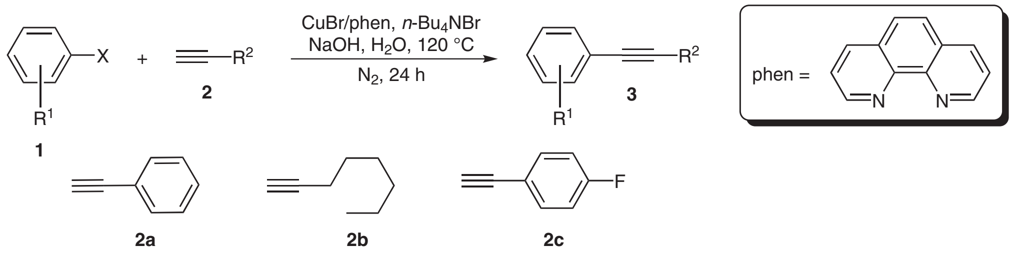
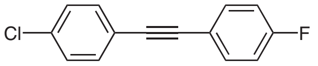
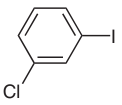
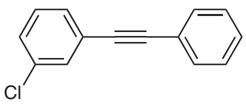
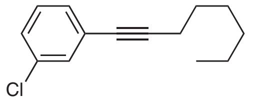
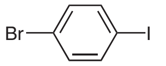
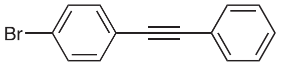
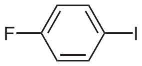
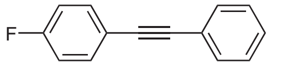
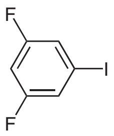
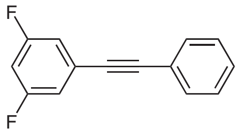
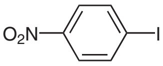
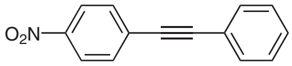
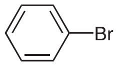
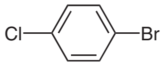
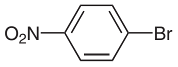
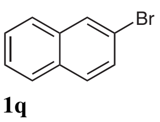
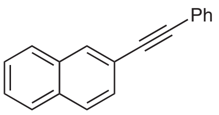
Entry	1	2	3	Yield (%)[b]
1	 **1a**	**2a**	 **3a**	80
2	**1a**	**2b**	 **3b**	53
3	 **1b**	**2a**	 **3c**	83
4	**1b**	**2b**	 **3d**	75
5	**1b**	**2c**	 **3e**	78
6	 **1c**	**2a**	 **3f**	80
7	**1c**	**2c**	 **3g**	75
8	 **1d**	**2a**	 **3h**	81
9	 **1e**	**2a**	 **3i**	80
10	 **1f**	**2a**	 **3j**	72[c]
11	 **1g**	**2a**	 **3k**	65
12	 **1h**	**2a**	 **3l**	85
13	**1h**	**2b**	 **3m**	76

Table 2 Copper-Catalyzed Sonogashira Couplings of Aryl Halides with Terminal Alkynes in Water[a] (continued)



Entry	1	2	3	Yield (%)[b]
14	**1h**	**2c**	 **3n**	80
15	 **1i**	**2a**	 **3o**	83
16	**1i**	**2b**	 **3p**	75
17	 **1j**	**2a**	 **3q**	84
18	 **1k**	**2a**	 **3r**	88
19	 **1l**	**2a**	 **3s**	84
20	 **1m**	**2a**	 **3t**	92[c]
21	 **1n**	**2a**	**3a**	58[d]
22	 **1o**	**2a**	**3l**	72[d]
23	 **1p**	**2a**	**3t**	52[d,e]
24	 **1q**	**2a**	 **3u**	48[c,d]

[a] Reaction condition: aryl halide **1** (1 mmol), alkyne **2** (2 mmol), CuBr (0.1 mmol), 1,10-phenanthroline (0.1 mmol), *n*-Bu$_4$NBr (0.2 mmol), NaOH (2 mmol), H$_2$O (1.5 mL), 120 °C under nitrogen atmosphere, 24 h.

[b] Isolated yield.

[c] Addition of 0.8 mmol of *n*-Bu$_4$NBr.

[d] Addition of 2 mmol of KI.

[e] Addition of 1 mmol of *n*-Bu$_4$NBr.

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(1) These two authors contributed equally to this work.

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(18) **General Procedure for the Synthesis of Compounds 3a–u**
A 10 mL Schlenk tube equipped with a magnetic stirring bar was charged with CuBr (0.1 mmol, 15 mg), NaOH (2 mmol, 80 mg), 1,10-phenanthroline (0.2 mmol, 36 mg), TBAB [0.2–1 mmol, see Table 2 for the details; note: an additional KI (2 mmol) should be added for aryl bromide]. The tube was evacuated and back-filled with nitrogen, and this procedure was repeated three times. Aryl halide (1.0 mmol), alkyne (2 mmol), and H_2O (1.5 mL) were sequentially added to the tube at r.t. under a stream of nitrogen, and the tube was sealed and put into a pre-heated oil bath at 120 °C for 24 h under nitrogen atmosphere. After the resulting solution was cooled to r.t., and the solution was extracted with EtOAc (3 × 3 mL). The combined organic phase was concentrated, and the remained residue was purified by column chromatography on silica gel to provide the desired product.