

## Iron Powder-CuI Cooperative Catalytic System in Sonogashira Cross-Coupling Reaction

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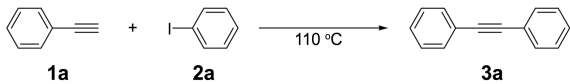
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The transition metal-catalyzed sp-carbon-sp<sup>2</sup>-carbon bond forming reaction by the cross-coupling of terminal alkynes with aryl and vinyl halides (or triflates) is well known as Sonogashira cross-coupling reaction.<sup>1-4</sup> This protocol has been widely used as a powerful synthetic tool for the synthesis of prevalent and valuable intermediates for pharmaceuticals and organic materials.<sup>1-4</sup> Since the coupling intrinsically catalyzed by Pd(PPh<sub>3</sub>)<sub>4</sub> and CuI was discovered in 1975,<sup>5</sup> many elegant catalytic systems which facilitate such a coupling under the milder and cheaper conditions have been developed by the tuning of a ligand combined with the kind of palladium catalysts.<sup>1-4</sup> Furthermore, besides such palladium based systems, several catalytic systems which are inexpensive and benign to the environment have been developed for both an academic viewpoint and a large scale industrial application. For example, many copper salts combined with appropriate ligands have been used as an alternative to palladium based systems for Sonogashira cross-coupling reaction.<sup>6-15</sup> In connection with this report, iron salts have recently had an upsurge as a promising catalyst in carbon-carbon bond forming reactions due to their natural abundance, low cost and environmental friendliness.<sup>16-20</sup> Thus, a number of iron catalysts have also been applied to Sonogashira coupling. For representative examples, Mao and Vogel groups have reported that terminal alkynes are readily cross-coupled with aryl iodides in the presence of Fe(acac)<sub>3</sub> in combination with CuI without an additional ligand.<sup>21-22</sup> It was also disclosed by Liu group that Fe<sub>2</sub>O<sub>3</sub>/N,N,N',N'-tetramethylethylenediamine catalytic system can be used for such a coupling by the assistance of Cu(acac)<sub>2</sub> cocatalyst.<sup>23</sup> It is also worthy to note that terminal alkynes were found to be cross-coupled with aryl iodides in the presence of FeCl<sub>3</sub> combined with N,N'-dimethylethylenediamine or PPh<sub>3</sub> without further addition of a copper ancillary.<sup>24,25</sup> Under these circumstances, during the course of our ongoing studies on transition metal-catalyzed carbon-carbon and carbon-nitrogen bond forming reactions,<sup>26-36</sup> herein this report describes an efficient iron powder/CuI/PPh<sub>3</sub>-catalyzed cross-coupling reaction between terminal alkynes and aryl iodides leading to coupled alkynes.

Phenylacetylene (**1a**) and iodobenzene (**2a**) were chosen as the model reactants for optimizing reaction conditions.

Several attempted representative results under various conditions are listed in Table 1. Treatment of **1a** with 1.2 equiv of **2a** in DMF in the presence of a catalytic amount of iron powder (10 mol % based on **1a**), PPh<sub>3</sub> (10 mol % based on **1a**) and CuI (10 mol % based on **1a**) along with K<sub>2</sub>CO<sub>3</sub> for 10 h afforded diphenylacetylene (**3a**) in 95% isolated yield with complete conversion of **1a** and concomitant formation of a trace amount of 1,4-diphenylbuta-1,3-diyne by the homo-coupling of **1a** on GLC (run 1). Lower reaction rate and yield were observed in the absence of either PPh<sub>3</sub>, or Fe powder, or CuI (runs 2-4). Even though the reaction proceeds in the absence of iron powder, the yield of **3a** was lower than that of the reaction by the addition of iron powder (run 3). It is known that CuI/PPh<sub>3</sub> catalytic system catalyzes cross-coupling of terminal alkynes and aryl iodides in H<sub>2</sub>O at a higher temperature in a pressure tube.<sup>37</sup> It is worthwhile to note that the reaction proceeds even in the absence of CuI (run 4). These results indicate that the coexistence of Fe powder, PPh<sub>3</sub> and CuI is necessary for the effective

**Table 1.** Optimization of conditions for the reaction of phenylacetylene (**1a**) with phenyl iodide (**2a**)<sup>a</sup>

					
Run	Catalytic systems	Bases	Solvents	Time (h)	Yield (%)
1	Fe powder/CuI/PPh <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	DMF	10	95
2	Fe powder/CuI	K <sub>2</sub> CO <sub>3</sub>	DMF	10	82
3	CuI/PPh <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	DMF	10	80
4	Fe powder/PPh <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	DMF	10	76
5	Fe powder/CuI/PPh <sub>3</sub>	—	DMF	10	6
6	Fe powder/CuI/PPh <sub>3</sub>	K <sub>3</sub> PO <sub>4</sub>	DMF	10	99
7	Fe powder/CuI/PPh <sub>3</sub>	Cs <sub>2</sub> CO <sub>3</sub>	Toluene	1	73
8	Fe powder/CuI/PPh <sub>3</sub>	Cs <sub>2</sub> CO <sub>3</sub>	Dioxane	1	64
9	Fe powder/CuI/PPh <sub>3</sub>	Cs <sub>2</sub> CO <sub>3</sub>	PEG-400	1	19
10	Fe powder/CuI/PPh <sub>3</sub>	Cs <sub>2</sub> CO <sub>3</sub>	DMF	1	99
11	CuI/PPh <sub>3</sub>	Cs <sub>2</sub> CO <sub>3</sub>	DMF	10	77

<sup>a</sup>Reaction conditions: **1a** (1 mmol), **2a** (1.2 mmol), Fe powder (0.1 mmol), CuI (0.1 mmol), PPh<sub>3</sub> (0.1 mmol), base (2 mmol), solvent (2 mL), at 110 °C, under N<sub>2</sub>.

formation of **3a** (runs 1-4). However, when the reaction was carried out in the absence of base under the employed conditions, **3a** was produced in only 6% yield with incomplete conversion of both substrates (run 5). Replacing  $K_2CO_3$  by  $K_3PO_4$  under the same reaction conditions resulted in quantitative yield of **3a** (run 6). As a result, after further elaborated tuning with base, reaction time and solvent, the best result in terms of both product **3a** yield and complete conversion of **1a** is best accomplished by the standard set of reaction conditions shown in run 10 of Table 1 (runs 7-11).

On the other hand, the certificate of analysis of commercial Fe powder (99.9%, Strem Chemicals, Inc.) shows several elements such as As (< 3 ppm), Pb (< 4 ppm) and

Hg (< 2 ppm) along with insoluble materials in aqueous acid (0.05%). We also confirmed that no Pd contaminant in Fe powder was observed by ICP-AES (inductively coupled plasma-atomic emission spectroscopy). However, even though Cu was detected in 9 ppm by ICP-AES, similar treatment of **1a** with **2a** under the catalytic system of CuI (1500 ppm based on **1a**)/ $PPh_3$ / $CS_2CO_3$ /DMF afforded **3a** in only 6% yield.

For investigating the reaction scope, the optimized condition was subjected to the reaction of various terminal alkynes **1** with aryl iodides **2** and several representative results are summarized in Table 2. Phenylacetylene (**1a**) reacted with an array of aryl iodides (**2a-g**) having electron-donating and -withdrawing substituents on the aromatic ring to afford the corresponding coupled alkynes (**3a-g**) in quantitative isolated yields. The product yield was considerably affected by the position of the substituent on **2**, whereas the electronic nature of that had no relevance to the product yield. With *ortho*-substituted aryl iodide **2b**, the coupled product yield was lower than that when *meta*- and *para*-substituted aryl iodides (**2c-g**) were used. Thus, a longer reaction time was actually needed for the satisfactory coupling with **2b**. In the reaction of vinyl alkyne, 1-ethynylcyclohex-1-ene (**1b**) with several aryl iodides, the corresponding coupled alkynes were also obtained in quantitative yields. Here again, lower reaction rate was observed with **2d** and **2g**. Lower reaction rate and yield were observed with alkyl alkyne **1c** when compared with those of aryl and vinyl alkynes. The coupling of **1c** with several aryl iodides afforded coupled alkynes (**3k-n**) in the range of 84-97% yields for a longer reaction time. From the reaction between 2-ethynynaphthalene (**1d**) and **2a**, the corresponding coupled alkyne **3o** was also produced in quantitative yield. Heteroaryl alkyne, 2-ethynylpyridine (**1e**) was also cross-coupled with **2a** to give 2-(2-phenylethynyl)pyridine (**3p**) in 76% yield for 10 h.

In summary, we have demonstrated that the cross-coupling of aryl, vinyl, alkyl substituted terminal alkynes with aryl iodides was catalyzed by Fe powder/ $PPh_3$ /CuI. The present reaction provides a cheaper cooperative catalytic system in Sonogashira cross-coupling reaction and further study for a catalytic role of iron powder is currently under investigation.

## Experimental Section

Melting points were determined on a Stanford Research Inc. MPA100 automated melting point apparatus. GLC analyses were carried out with a Shimadzu GC-17A instrument equipped with a CBP10-S25-050 column (Shimadzu, fused silica capillary column, 0.33 mm  $\times$  25 m, 0.25  $\mu$ m film thickness) using nitrogen as carrier gas. The isolation of pure products was carried out *via* column (silica gel 60, 70-230 mesh, Merck) or thin layer (silica gel 60 GF<sub>254</sub>, Merck) chromatography. Iron powder (99.9%) was purchased from Strem Chemicals Inc. Commercially available organic and inorganic compounds were used without further purification except for solvents, which were distilled prior to use.

**Table 2.** Fe powder/ $PPh_3$ /CuI-catalyzed Sonogashira cross-coupling of terminal alkynes **1** with aryl iodides **2**<sup>a</sup>

$R-C\equiv C + I-Ar \xrightarrow[DMF]{Fe\ powder/CuI/PPh_3, Cs_2CO_3} R-C\equiv C-Ar$ (R = aryl, heteroaryl, vinyl, alkyl)			
Terminal alkynes <b>1</b>	Aryl iodides <b>2</b>	Coupled alkynes <b>3</b>	Yield (%)
			99
<b>1a</b>			85 <sup>b</sup>
<b>1a</b>			96
<b>1a</b>			97
<b>1a</b>			99
<b>1a</b>			95
<b>1a</b>			99
			95
<b>1b</b>			95 <sup>b</sup>
<b>1b</b>			99 <sup>b</sup>
$n-C_6H_{13}-C\equiv C$ <b>1c</b>			85 <sup>c</sup>
<b>1c</b>			97 <sup>c</sup>
<b>1c</b>			84 <sup>c</sup>
<b>1c</b>			97 <sup>c</sup>
			99
			76 <sup>b</sup>

<sup>a</sup>Reaction conditions: **1** (1 mmol), **2** (1.2 mmol), Fe powder (0.1 mmol),  $PPh_3$  (0.1 mmol), CuI (0.1 mmol),  $CS_2CO_3$  (2 mmol), DMF (2 mL), at 110 °C, for 1 h, under  $N_2$ . <sup>b</sup>For 10 h. <sup>c</sup>For 20 h.

**General Procedure for Fe Powder/PPh<sub>3</sub>/CuI-Catalyzed Cross-Coupling Reaction of Terminal Alkynes with Aryl Iodides.** A mixture of alkyne (1 mmol), aryl iodide (1.2 mmol), iron powder (0.0056 g, 0.1 mmol), PPh<sub>3</sub> (0.026 g, 0.1 mmol), CuI (0.019 g, 0.1 mmol), Cs<sub>2</sub>CO<sub>3</sub> (0.652 g, 2 mmol) and DMF (2 mL) was placed in a sealable reactor with Teflon cap (Radleys Discovery Technologies). After the system was flushed with N<sub>2</sub>, the mixture was stirred at 110 °C for a required time. After the reaction mixture was cooled down to room temperature, it was filtered through a short silica gel column (ethyl acetate as eluent) to eliminate inorganic salts. Removal of the solvent left a crude mixture, which was separated by column or thin layer chromatography (silica gel, ethyl acetate-hexane mixture) to give coupled alkynes **3**. All coupled alkynes prepared by the above procedure were characterized by GLC and melting point comparison with authentic samples synthesized by known methods and purchased from chemical companies.

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