

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

Ngoc Thang Tran,<sup>†</sup> Chan Sik Cho,<sup>†,\*</sup> Ho-Sang Sohn, and Sang Chul Shim<sup>†</sup>

Department of Materials Science and Metallurgical Engineering, Kyungpook National University, Daegu 702-701, Korea

<sup>†</sup>Department of Applied Chemistry, Kyungpook National University, Daegu 702-701, Korea. \*E-mail: cscho@knu.ac.kr

Received December 13, 2010, Accepted January 17, 2011

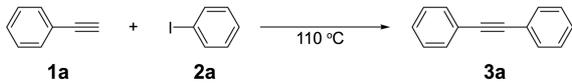
**Key Words** : Aryl iodides, Terminal alkynes, Iron powder, Carbon-carbon bond formation, Sonogashira coupling

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-ethynyl-naphthalene (**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 × 25 m, 0.25 μm 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>

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
	<b>2a</b>		95
<b>1b</b>	<b>2d</b>		95 <sup>b</sup>
<b>1b</b>	<b>2g</b>		99 <sup>b</sup>
$n-C_6H_{13}-C\equiv C-$ <b>1c</b>	<b>2a</b>		85 <sup>c</sup>
<b>1c</b>	<b>2d</b>		97 <sup>c</sup>
<b>1c</b>	<b>2f</b>		84 <sup>c</sup>
<b>1c</b>	<b>2g</b>		97 <sup>c</sup>
	<b>2a</b>		99
	<b>2a</b>		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.

**Acknowledgment.** This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2010-0007563).

### References

1. Sonogashira, K. *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., de Meijere, A., Eds.; Wiley-VCH: Weinheim, 2004; Vol. 1, pp 319-345.
2. Doucet, H.; Hierso, J. C. *Angew. Chem. Int. Ed.* **2007**, *46*, 834.
3. Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874.
4. Plenio, H. *Angew. Chem. Int. Ed.* **2008**, *47*, 6954.
5. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.
6. Saejueng, P.; Bates, C. G.; Venkataraman, D. *Synthesis* **2005**, 1706.
7. Tang, B. X.; Wang, F.; Li, J. H.; Xie, Y. X.; Zhang, M. B. *J. Org. Chem.* **2007**, *72*, 6294.
8. Biffis, A.; Scattolin, E.; Ravasio, N.; Zaccheria, F. *Tetrahedron Lett.* **2007**, *48*, 8761.
9. Wang, Z. L.; Wang, L.; Li, P. H. *Synthesis* **2008**, 1367.
10. Mao, J. C.; Guo, J.; Ji, S. J. *J. Mol. Cat. A: Chem.* **2008**, 284, 85.
11. Li, J. H.; Li, J. L.; Wang, D. P.; Pi, S. F.; Xie, Y. X.; Zhang, M. B.; Hu, X. C. *J. Org. Chem.* **2007**, *72*, 2053.
12. Deng, C. L.; Xie, Y. X.; Yin, D. L.; Li, J. H. *Synthesis* **2006**, 3370.
13. Liu, F.; Ma, D. *J. Org. Chem.* **2007**, *72*, 4844.
14. Cacchi, S.; Fabrizi, G.; Parisi, L. M. *Org. Lett.* **2003**, *5*, 3843.
15. Monnier, F.; Turtaut, F.; Duroure, L.; Taillefer, M. *Org. Lett.* **2008**, *10*, 3203.
16. Bolm, C.; Legros, J.; Paith, J. L.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217.
17. Taillefer, M.; Xia, N.; Ouali, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 934.
18. Correa, A.; Carril, M.; Bolm, C. *Angew. Chem. Int. Ed.* **2008**, *47*, 2880.
19. Volla, C. M. R.; Vogel, P. *Angew. Chem. Int. Ed.* **2008**, *47*, 1305.
20. Bézier, D.; Darcel, C. *Adv. Synth. Catal.* **2009**, *351*, 1732.
21. Mao, J.; Xie, G.; Wu, M.; Guo, J.; Ji, S. *Adv. Synth. Catal.* **2008**, *350*, 2477.
22. Volla, C. M. R.; Vogel, P. *Tetrahedron Lett.* **2008**, *49*, 5961.
23. Huang, H.; Jiang, H.; Chen, K.; Liu, H. *J. Org. Chem.* **2008**, *73*, 9061.
24. Carril, M.; Correa, A.; Bolm, C. *Angew. Chem. Int. Ed.* **2008**, *47*, 4862.
25. Sawant, D. J.; Tambade, P. J.; Wagh, Y. S.; Bhanage, B. M. *Tetrahedron Lett.* **2010**, *51*, 2758.
26. Cho, C. S.; Kim, B. T.; Kim, T.-J.; Shim, S. C. *J. Org. Chem.* **2001**, *66*, 9020.
27. Cho, C. S.; Kim, B. T.; Lee, M. J.; Kim, T.-J.; Shim, S. C. *Angew. Chem. Int. Ed.* **2001**, *40*, 958.
28. Cho, C. S.; Kim, B. T.; Kim, T.-J.; Shim, S. C. *Tetrahedron Lett.* **2002**, *43*, 7987.
29. Cho, C. S.; Kim, B. T.; Kim, H.-S.; Kim, T.-J.; Shim, S. C. *Organometallics* **2003**, *22*, 3608.
30. Cho, C. S.; Lim, D. K.; Heo, N. H.; Kim, T.-J.; Shim, S. C. *Chem. Commun.* **2004**, 104.
31. Cho, C. S. *J. Organomet. Chem.* **2005**, *690*, 4094.
32. Cho, C. S.; Shim, S. C. *J. Organomet. Chem.* **2006**, *691*, 4329.
33. Cho, C. S.; Patel, D. B. *Tetrahedron* **2006**, *62*, 6388.
34. Cho, C. S. *J. Mol. Cat. A: Chem.* **2007**, *267*, 49.
35. Cho, C. S. *Catal. Commun.* **2008**, *9*, 2261.
36. Cho, C. S.; Tran, N. T. *Catal. Commun.* **2009**, *11*, 191.
37. Guan, J. T.; Yu, G.-A.; Chen, L.; Weng, T. Q.; Yuan, J. J.; Liu, S. H. *Appl. Organomet. Chem.* **2009**, *23*, 75.