

# CuO-2,2'-Diamino-6,6'-Dimethylbiphenyl Catalyzed Suzuki–Miyaura Coupling Reactions of Arylboronic Acids with Aryl Iodides and Bromides

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**Abstract** CuO-catalyzed Suzuki–Miyaura cross-coupling reactions of arylboronic acids with aryl iodides and bromides using 2,2'-diamino-6,6'-dimethylbiphenyl as the ligand are described in the paper. Under suitable conditions, all reactions gave the desired coupling products in moderate to excellent yields.

**Keywords** Copper salt · 2,2'-Diamino-6,6'-dimethylbiphenyl · Suzuki–Miyaura coupling reaction · Synthetic methods

## 1 Introduction

Transition metal catalyzed cross-coupling reactions are versatile and efficient methods for carbon–carbon and carbon–heteroatom bonds formations because of their wide tolerance of a variety of organic functional groups [1–6]. Since its first discovery by Miyaura and Suzuki, the Suzuki–Miyaura coupling reaction [7–13], has become one of the most powerful methods for the formations of biaryl moiety, which can be found as subunits in natural products [14], pharmaceuticals [15], functional materials [16], etc. [17–20]. In the past years, the most widely used catalysts

for the Suzuki–Miyaura coupling reactions are palladium–phosphine complexes [21, 22]. However, the high cost of Pd catalysts, the common air-sensitive phosphine ligands, and the potential contamination of the products prevented the application of the Pd system, especially in the field of pharmaceutical chemistry. Therefore, there is also great requirement in developing economic and efficient catalytic systems. There has been increasing interest in the study of copper salts in the formation of carbon–carbon and carbon–heteroatom bonds in recent years [23–42]. During our investigations using non-phosphine-based ligands in the transition-metal catalyzed coupling reactions for C–C bonds formations, it was found that 2,2'-diamino-6,6'-dimethylbiphenyl (**L**) is a good ligand for CuO-catalyzed Suzuki–Miyaura coupling reactions of arylboronic acids with aryl iodides and bromides [43]. Herein, we wish to report these results in detail.

## 2 Results and Discussion

In preliminary studies, we used 20 mol% **L** as the ligand with 20 mol% CuO as the catalyst for the coupling reaction of 4-methoxyphenyl iodide (**1a**) with phenylboronic acid (**2a**) in DMF at 110 °C for 48 h to find out the best base. For the inorganic bases screened (Table 1, entries 1–6), K<sub>2</sub>CO<sub>3</sub> gave the best result and the corresponding product **3a** was obtained in 71% yield (Table 1, entry 2). The reaction conditions were further screened with several copper salts and temperatures to increase the efficiency of the coupling reaction. For other copper salts as CuCl, Cu<sub>2</sub>O, CuBr, CuI and CuBr<sub>2</sub>, all showed inferior results (Table 1, entries 7–11). With CuO as the copper source, when the reaction temperature was elevated to 130 and 160 °C, the yields were further increased to 86 and 87%,

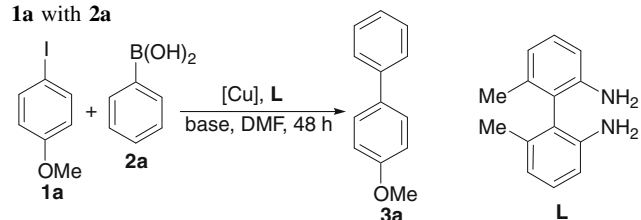
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respectively (Table 1, entries 12 and 13). Further studies showed that **L** played an important role in this reaction and it was found that no reaction occurred in the absence of **L** (Table 1, entry 14). So the optimal reaction conditions were established as using CuO (20 mol%) as the catalyst, **L** (20 mol%) as the ligand, K<sub>2</sub>CO<sub>3</sub> (2.0 equiv.) as the base and DMF (2.0 mL) as the solvent with the temperature of 130 °C (Table 1, entry 12).

Using the above mentioned optimized reaction conditions, we initiated our investigation into the scope of the combination of CuO-**L** catalyzed coupling reaction of aryl iodides with arylboronic acids and the results are summarized in Table 2. In most cases, aryl iodides **1** reacted with arylboronic acids **2** to give the corresponding products **3** in good to high yields (Table 2). Substituents on the *para*-position of aryl iodides dramatically affected on the yields. For instance, the reactions of 2-methylphenyl iodide (**1h**) with 4-methoxyphenylboronic acid (**2e**) and 2-methoxyphenyl iodide (**1i**) with phenylboronic acid (**2a**) only give

**Table 1** Optimization for the copper-catalyzed coupling reaction of **1a** with **2a**



Entry <sup>a</sup>	[Cu]	Base	Yield (%) <sup>b</sup>
1	CuO	Cs <sub>2</sub> CO <sub>3</sub>	21
2	CuO	K <sub>2</sub> CO <sub>3</sub>	71
3	CuO	KF·2H <sub>2</sub> O	58
4	CuO	Na <sub>3</sub> PO <sub>4</sub> ·12H <sub>2</sub> O	40
5	CuO	K <sub>3</sub> PO <sub>4</sub> ·3H <sub>2</sub> O	55
6	CuO	Na <sub>2</sub> CO <sub>3</sub>	30
7	CuCl	K <sub>2</sub> CO <sub>3</sub>	44
8	Cu <sub>2</sub> O	K <sub>2</sub> CO <sub>3</sub>	52
9	CuBr	K <sub>2</sub> CO <sub>3</sub>	44
10	CuI	K <sub>2</sub> CO <sub>3</sub>	35
11	CuBr <sub>2</sub>	K <sub>2</sub> CO <sub>3</sub>	32
12 <sup>c</sup>	CuO	K <sub>2</sub> CO <sub>3</sub>	86
13 <sup>d</sup>	CuO	K <sub>2</sub> CO <sub>3</sub>	87
14 <sup>e</sup>	CuO	K <sub>2</sub> CO <sub>3</sub>	NR

<sup>a</sup> Otherwise specified, all reactions were carried out using **1a** (0.5 mmol), **2a** (0.6 mmol), base (2.0 equiv.), CuO (20 mol%) and **L** (20 mol%) in DMF (2.0 mL) at 110 °C for 48 h

<sup>b</sup> Isolated yields

<sup>c</sup> The reaction was carried out at 130 °C

<sup>d</sup> The reaction was carried out at 160 °C

<sup>e</sup> The reaction was carried out at 130 °C in the absence of **L**

**Table 2** CuO-catalyzed Suzuki–Miyaura coupling of iodides **1** with boronic acids **2**


Entry <sup>a</sup>	<b>1</b> (R <sup>1</sup> )	<b>2</b> (R <sup>2</sup> )	Yields (%) <sup>b</sup>
1	<b>1a</b> (4-MeO/I)	<b>2b</b> (4-Me)	<b>3b</b> (82)
2	<b>1a</b>	<b>2c</b> (2-Me)	<b>3c</b> (99)
3	<b>1a</b>	<b>2d</b> (3,5-Me <sub>2</sub> )	<b>3d</b> (65)
4	<b>1b</b> (H)	<b>2e</b> (4-MeO)	<b>3a</b> (99)
5	<b>1c</b> (4-Cl)	<b>2e</b>	<b>3e</b> (95)
6	<b>1e</b> (4-Ac)	<b>2a</b> (H)	<b>3f</b> (70)
7	<b>1a</b>	<b>2e</b>	<b>3g</b> (90)
8	<b>1g</b> (4-F)	<b>2e</b>	<b>3h</b> (97)
9	<b>1h</b> (2-Me)	<b>2e</b>	<b>3c</b> (17)
10	<b>1i</b> (2-MeO)	<b>2a</b>	<b>3i</b> (17)
11	<b>1j</b> (4-NO <sub>2</sub> )	<b>2e</b>	<b>3j</b> (<5)
12	<b>1a</b>	<b>2f</b>	<b>3k</b> (77)

<sup>a</sup> All reactions were carried out using **1** (0.5 mmol), **2** (0.6 mmol), K<sub>2</sub>CO<sub>3</sub> (2.0 equiv.), CuO (20 mol%) and **L** (20 mol%) in DMF (2.0 mL) at 130 °C for 48 h

<sup>b</sup> Isolated yields

the corresponding coupling products in very low yields, respectively (Table 2, entries 9 and 10). For the reaction of strongly electron-withdrawing group substituted 4-nitrophenyl iodide (**1j**) with 4-methoxyphenylboronic acid (**2e**), almost no coupling product was obtained (Table 2, entry 11). For the reaction of 4-methoxyphenyl iodide (**1a**) with 3-furylboronic acid (**2f**), the corresponding coupling product **3k** also was formed in 77% yield (Table 2, entry 12).

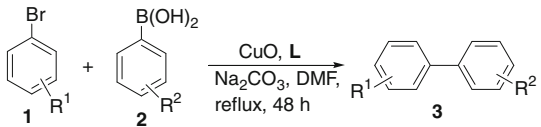
Though under the optimal conditions for the reactions of iodides with boronic acids, aryl bromides showed almost no reactivity, however, when the reactions were carried out under reflux in DMF using Na<sub>2</sub>CO<sub>3</sub> as the base, the coupling products **3** could be also obtained in acceptable to high yields (Tables 3 and 4). Substituents on the arylboronic acids have some effect on the reaction. For instance, arylboronic acids with hindered groups gave inferior result (Table 4, entry 2). Meanwhile, arylboronic acids with electron-poor group as Cl atom gave the corresponding product in relatively lower yield (Table 4, entry 4). For the reaction of 4-formylphenyl bromide **1q** with phenylboronic acid **2a**, the reaction became disordered and only 27% yield of the coupling product **3n** was achieved (Table 4, entry 9). It should be noted here that though the combination of CuO-**L** is a good catalyst for the coupling

**Table 3** Optimization for the reaction of **1k** with **2a**


Entry <sup>a</sup>	Base	T (°C)	Yield (%) <sup>b</sup>
1	NaOH	135	Trace
2	KOH	135	Trace
3	Cs <sub>2</sub> CO <sub>3</sub>	135	Trace
4	Na <sub>2</sub> CO <sub>3</sub>	135	40
5	K <sub>3</sub> PO <sub>4</sub> ·3H <sub>2</sub> O	135	16
6	NaHCO <sub>3</sub>	135	33
7	KHCO <sub>3</sub>	135	20
8	CH <sub>3</sub> COOK	135	Trace
9	KF·2H <sub>2</sub> O	135	Trace
10	K <sub>2</sub> CO <sub>3</sub>	135	Trace
11	Na <sub>2</sub> CO <sub>3</sub>	Reflux	84

<sup>a</sup> All reactions were carried out using **1k** (0.5 mmol), **2a** (0.6 mmol), base (2.0 equiv.), CuO (20 mol%) and **L** (20 mol%) in DMF (2.0 mL) at the listed temperature for 48 h

<sup>b</sup> Isolated yields

**Table 4** CuO-catalyzed Suzuki–Miyaura coupling of bromides **1** with boronic acids **2**


Entry <sup>a</sup>	<b>1</b> (R <sup>1</sup> )	<b>2</b> (R <sup>2</sup> )	Yields (%) <sup>b</sup>
1	<b>1k</b> (4-MeO)	<b>2b</b> (4-Me)	<b>3b</b> (97)
2	<b>1k</b>	<b>2d</b> (3,5-Me <sub>2</sub> )	<b>3d</b> (43)
3	<b>1l</b> (3-MeO)	<b>2a</b> (H)	<b>3l</b> (83)
4	<b>1l</b>	<b>2g</b> (4-Cl)	<b>3m</b> (50)
5	<b>1m</b> (4-F)	<b>2e</b> (4-MeO)	<b>3h</b> (95)
6	<b>1n</b> (H)	<b>2e</b>	<b>3a</b> (76)
7	<b>1o</b> (4-Cl)	<b>2e</b>	<b>3e</b> (84)
8	<b>1p</b> (4-Me)	<b>2e</b>	<b>3b</b> (78)
9	<b>1q</b> (4-CHO)	<b>2a</b>	<b>3n</b> (27)
10	<b>1r</b> (4-Ac)	<b>2a</b>	<b>3f</b> (84)
11	<b>1k</b>	<b>2e</b>	<b>3g</b> (80)
12	<b>1l</b>	<b>2b</b>	<b>3o</b> (69)

<sup>a</sup> All reactions were carried out using **1** (0.5 mmol), **2** (0.6 mmol), Na<sub>2</sub>CO<sub>3</sub> (2.0 equiv.), CuO (20 mol%) and **L** (20 mol%) in DMF (2.0 mL) under reflux for 48 h

<sup>b</sup> Isolated yields

reactions of aryl iodides and bromides with arylboronic acids, there is no reactivity for this combination in the coupling reactions of aryl chlorides.

### 3 Experimental

#### 3.1 Materials

<sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Bruker Avance-300 or 500 MHz Spectrometer for solution in CDCl<sub>3</sub> with tetramethylsilane (TMS) as an internal standard; *J* values are in Hertz. DMF was distilled from CaH<sub>2</sub> under reduced pressure. Commercially obtained reagents were used without further purification. Flash column chromatography was carried out using Huanghai 300–400 mesh silica gel at increased pressure.

#### 3.2 Experimental Procedures

General procedure for the CuO-**L** catalyzed coupling reactions of aryl iodides with arylboronic acids:

(If aryl iodide is a liquid) under N<sub>2</sub> atmosphere, arylboronic acid **2** (0.6 mmol), CuO (20 mol%), ligand **L** (20 mol%), K<sub>2</sub>CO<sub>3</sub> (2.0 equiv.) and degassed DMF (2.0 mL) were added into a Schlenk reaction tube, then aryl iodide (0.5 mmol) was added. The mixture was stirred at 130 °C for 48 h. Then the solvent was diluted with EtOAc, washed with saturated brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and purified by a flash column chromatography (SiO<sub>2</sub>) to give product **3**.

(If aryl iodide is a solid) under N<sub>2</sub> atmosphere, aryl iodide (0.5 mmol), arylboronic acid **2** (0.6 mmol), CuO (20 mol%), ligand **L** (20 mol%), K<sub>2</sub>CO<sub>3</sub> (2.0 equiv.) and degassed DMF (2.0 mL) were added into a Schlenk reaction tube. The mixture was stirred at 130 °C for 48 h. Then the solvent was diluted with EtOAc, washed with saturated brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and purified by a flash column chromatography (SiO<sub>2</sub>) to give product **3**.

General procedure for the CuO-**L** catalyzed coupling reactions of aryl bromides with arylboronic acids: Under N<sub>2</sub> atmosphere, arylboronic acid **2** (0.6 mmol), CuO (20 mol%), **L** (20 mol%), Na<sub>2</sub>CO<sub>3</sub> (2.0 equiv.) and degassed DMF (2.0 mL) were added into a Schlenk reaction tube, then aryl bromide **1** (0.5 mmol) was added. The mixture was stirred at reflux for 48 h. Then the solvent was diluted with EtOAc, washed with saturated brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and purified by a flash column chromatography (SiO<sub>2</sub>) to give product **3**.

### 4 Conclusions

In conclusion, 2,2'-diamino-6,6'-dimethylbiphenyl (**L**) was found to be a good ligand in the CuO-catalyzed Suzuki–Miyaura coupling reactions of various arylboronic acids with aryl iodides and bromides under the appropriate reaction

conditions. The ligand is air-stable and the reactions are easily to operate. The reactions can also tolerate a wide range of groups on both aryl halides and arylboronic acids.

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