

Highly efficient copper(0)-catalyzed Suzuki–Miyaura cross-coupling reactions in reusable PEG-400

Jincheng Mao*, Jun Guo, Fubing Fang, Shun-Jun Ji*

Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry and Chemical Engineering, Suzhou (Soochow) University, Suzhou 215123, PR China

Received 22 November 2007; received in revised form 17 February 2008; accepted 22 February 2008
Available online 4 March 2008

Abstract

Readily available copper powder with K_2CO_3 as the base was extremely effective catalyst for Suzuki–Miyaura coupling reaction performed in PEG-400, which afforded almost quantitative coupling products of aryl iodides. Using iodine as additive, coupling products of aryl bromides or chlorides could be obtained with moderate to good yields.

© 2008 Elsevier Ltd. All rights reserved.

1. Introduction

The Suzuki–Miyaura cross-coupling reaction has been considered as a very powerful, versatile, and popular tool for selective construction of carbon–carbon bonds in organic chemistry,¹ especially in the synthesis of biaryl compounds, which are important structural substructures in numerous polymers, agrochemicals, natural products, and pharmaceutical mediates.² During the past decades, numerous efforts have been made to develop efficient catalyst systems for Suzuki–Miyaura cross-coupling reaction.³ Among them, a palladium(0) complex together with (phosphorous) ligands is the most popular catalytic system. However, reuse of this type of catalysts is difficult since phosphorous ligands are sensitive to air and moisture.⁴ Furthermore, the drawbacks of the Pd-catalyst systems, such as high cost and toxicity, limit their massive applications for industrial scales. Therefore, the task of recycling and development of phosphine-free and palladium-free catalytic systems is a current important challenge in organic chemistry. In this way, the use of a cheaper metal instead of Pd provides another attractive route.⁵ Of these, copper-based alternatives are particularly attractive, due to their orders of magnitude lower cost and harmfulness to the

environment than any noble metal.⁶ Although copper catalysts have been used in many cross-coupling transformations, surprisingly, there are only few publications on the use of such reagents for the Suzuki–Miyaura cross-coupling reactions.^{7,8}

Recently, Rothenberg and co-workers firstly reported their findings about the effective copper-catalyzed coupling reactions of aryl halides with phenylboronic acid using mixed nanocluster catalysts.⁷ However, the nanocopper prepared by strict synthetic procedure could only catalyze the couplings of aryl iodides and existing additional metals (Pd and Ru) showed better efficiency. This result prompted us to study whether the Suzuki–Miyaura cross-coupling reaction could directly be catalyzed by more accessible copper catalyst and whether the catalytic system could also be reused. To meet the demands for recyclability and environmental concerns, a more facile way is to immobilize the catalyst on a liquid phase by dispersing it into a nonvolatile and low toxicity liquid, such as poly(ethylene)glycols (PEG),⁹ which has been used for biomedical applications, especially in the field of drug discovery.¹⁰ In this paper, we wish to report our finding that readily available copper powder, in combination with K_2CO_3 as the base, is an extremely effective catalyst for the Suzuki coupling reaction performed in PEG-400. Furthermore, we found that PEG-400 worked not only as the recycling solvent but could also accelerate the coupling reactions. In addition, molecular iodine was firstly employed as co-catalyst for

* Corresponding authors. Tel.: +86 512 65880403; fax: +86 512 65880089.
E-mail address: jcmiao@suda.edu.cn (J. Mao).

the coupling reactions of aryl bromide or chloride with arylboronic acids.¹¹

2. Results and discussion

In order to explore copper catalysts for the Suzuki–Miyaura coupling reactions, the coupling of 4-methylphenylboronic acid with iodobenzene was chosen as the model reaction to study the efficiency of different ligands (A–E), which have proved effective in other coupling reactions.¹² As shown in Figure 1, it can be seen that different ligands (A–E) provided poor yields of the coupling product while no ligand gave the best result (42% yield). Encouraged by this finding, we screened other copper salts for the coupling reaction (Table 1, entries 1–6). The results showed that copper powder could catalyze the coupling reaction with best yield of 72% (entry 6). Subsequently, several common solvents and bases were screened and the results showed that DMF was the best solvent (entries 7–12) and K₂CO₃ was the most effective base (entries 13–17). Then various phase transfer catalysts including TBAB (tetrabutyl ammonium bromide), 16-3-Br (cetyl trimethyl ammonium bromide) and 18-18-2-Br (dioctadecyl dimethyl ammonium bromide) were employed as additives. However, they had no positive effect on the catalytic reactions. Changes of the loading of copper powder could not lead to better results. In order to reuse the catalytic system, PEG-400 was chosen as the reaction medium. To our surprise,

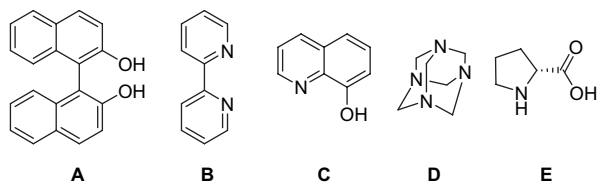
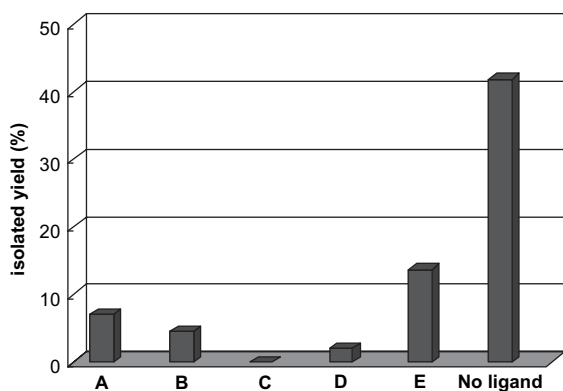
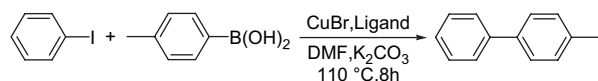


Figure 1. Suzuki reactions promoted by different ligands (the catalytic conditions: iodobenzene (1.0 equiv), 4-methylphenylboronic acid (1.3 equiv), CuBr (0.1 equiv), DMF (2.0 ml), K₂CO₃ (2.0 equiv); temperature: 110 °C; 8 h).

Table 1
Copper-catalyzed Suzuki–Miyaura coupling of iodobenzene and 4-methylphenylboronic acid^a

Entry	Cat.	Base	Solvent	Temp (°C)	Time (h)	Yield ^b (%)
1	CuI	K ₂ CO ₃	DMF	110	8	2
2	CuCl	K ₂ CO ₃	DMF	110	8	2
3	Cu ₂ O	K ₂ CO ₃	DMF	110	8	Trace
4	Cu(OAc) ₂ ·H ₂ O	K ₂ CO ₃	DMF	110	8	7
5	CuSO ₄	K ₂ CO ₃	DMF	110	8	Trace
6	Cu	K ₂ CO ₃	DMF	110	8	72
7	Cu	K ₂ CO ₃	DMSO	110	8	15
8	Cu	K ₂ CO ₃	Toluene	110	8	15
9	Cu	K ₂ CO ₃	IPOH	80	8	Trace
10	Cu	K ₂ CO ₃	Dioxane	100	8	18
11	Cu	K ₂ CO ₃	H ₂ O	80	8	14
12	Cu	K ₂ CO ₃	CH ₃ CN	80	8	9
13	Cu	Cs ₂ CO ₃	DMF	110	8	1
14	Cu	K ₃ PO ₄ ·H ₂ O	DMF	110	8	8
15	Cu	^t BuOK	DMF	110	8	Trace
16	Cu	KOH	DMF	110	8	20
17	Cu	KF	DMF	110	8	4
18	Cu	K ₂ CO ₃	PEG-400	110	8	84
19	Cu	K ₂ CO ₃	PEG-400	110	12	99
20 ^c	Cu	K ₂ CO ₃	PEG-400	110	12	32
21 ^d	Cu	K ₂ CO ₃	PEG-400	rt	18	Trace
22	Cu	K ₂ CO ₃	PEG-200	110	12	99
23	Cu	K ₂ CO ₃	Ethanediol	110	12	5
24	Cu	K ₂ CO ₃	Propanediol	110	12	77

^a Reaction conditions: iodobenzene (1.0 equiv), 4-methylphenylboronic acid (1.3 equiv), copper source (0.1 equiv), solvent (2.0 ml); base (2.0 equiv); temperature: 110 °C.

^b Isolated yield based on aryl halide.

^c The catalytic reaction was performed in air.

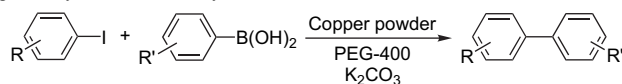
^d The catalytic reaction was performed at room temperature.

the yield of the coupling product was enhanced to 84% (entry 18). When the reaction was run for 12 h, almost quantitative coupling product was obtained (entry 19). The control experiments showed that the catalytic reactions performed in air afforded the product with 32% yield (entry 20) and at room temperature no product was obtained (entry 21). PEG-200 with lower molecular weight was also tested as solvent, providing the product with 99% yield (entry 22). In order to testify whether structure of polymeric alcohol was necessary, the smaller alcohols with different structures were employed in the coupling reactions, affording worse results (entries 23 and 24). The results showed that PEGs acted not only as recycling solvent but could also accelerate the coupling reactions.

Under the optimized condition, high yields were obtained in the coupling reactions of various aryl iodides and arylboronic acids. The results are summarized in Table 2. It can be seen that almost all of the coupling reactions could get complete conversions. In addition, we found that a catalytic amount (10%) of copper powder with 12 h at 110 °C could catalyze the coupling reactions of iodobenzene and sterically hindered arylboronic acids to give the corresponding products with moderate yields (Table 2, entries 5 and 8).

In order to extend the range of substrates, we intended to apply our methodology to a wide range of difficult halides,

Table 2
Copper-catalyzed Suzuki–Miyaura couplings of aryl iodides and arylboronic acids^a



Entry	ArX	Arylboronic acid	Product	Yield ^b (%)
1				99
2				99
3				99
4				90
5				85
6				99
7				94
8				77
9				99
10				97
11				99
12				99
13				99

^a Reaction conditions: aryl iodide (1.0 equiv); arylboronic acid (1.3 equiv); copper powder (0.1 equiv); solvent as PEG-400 (2.0 ml); base: K_2CO_3 (2.0 equiv); temperature: 110 °C; 12 h.

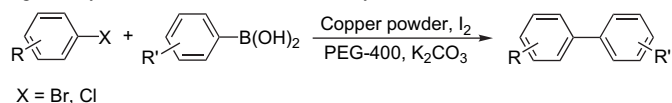
^b Isolated yield based on aryl halide.

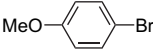
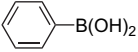
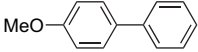

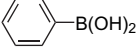
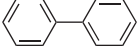

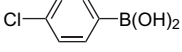
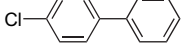
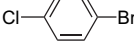
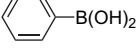
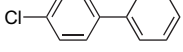
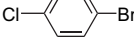
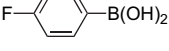
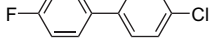
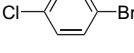
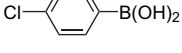
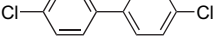
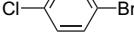
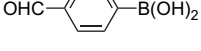
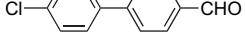
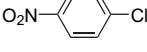
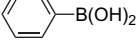
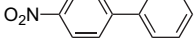
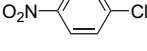
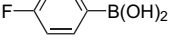
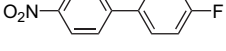
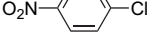
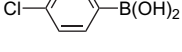
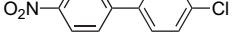
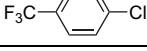
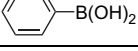
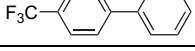
such as aryl bromides or chlorides. To our surprise, we could not get the coupling products, even at elevated temperature (140 °C) and extended time (36 h). As is well known that molecular iodine is regarded as an effective catalyst or additive in many organic syntheses,¹³ iodine (20 mol %) was added into this catalyst system in hope of good efficiency. Luckily, the coupling products of aryl bromides or chlorides were obtained. After heating for extended periods of time, the corresponding coupling products were obtained with good yields. In order to verify the unique catalytic properties of molecular iodine,

other iodides such as potassium iodide or copper iodide were used which showed poor reactivity. Since our novel catalytic system contains copper and iodine at the same time, copper iodide alone was used instead of copper powder in the coupling reaction. Under these conditions, no coupling product was afforded.

Varying the loading of iodine, we found that 0.2 equiv of iodine was enough to avoid getting large amount of the homocoupling product. Therefore, with the improvement of our protocol using $Cu/I_2/K_2CO_3/PEG-400$, the results listed in Table 3

Table 3

Copper-catalyzed Suzuki–Miyaura couplings of aryl bromides or chlorides and arylboronic acids mediated with iodine as the additive^a

Entry	ArX	Arylboronic acid	Product	Yield ^b (%)
1				81
2				91
3				78
4				86
5				84
6				71
7				75
8				51
9				43
10				23
11				38

^a Reaction condition: aryl bromide or chloride (1.0 equiv) arylboronic acid (1.3 equiv), copper powder (0.1 equiv), solvent as PEG-400 (2.0 ml); base: K₂CO₃ (2.0 equiv); I₂ (0.2 equiv); temperature: 140 °C; 36 h.

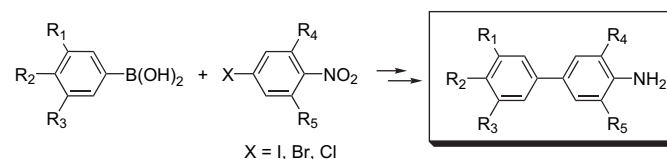
^b Isolated yield based on aryl halide.

were obtained. It is found that the coupling products of aryl bromides were obtained with good yields (Table 3, entries 1–7) and the coupling reactions of aryl chlorides were conducted with moderate results due to their poor reactivity (entries 8–11), which is attributed to the strength of the C–Cl bond.¹⁴

In order to show the versatility of our methodology, several commercially available sources of copper powder have been tested in our catalytic system, affording similar results. In addition, the feasibility of recycling the catalytic system was also tested. In the view that the various biphenylamines are used as intermediates in the synthesis of numerous organic compounds including the azo dyes and as antioxidants in consumer goods including most rubber products,¹⁵ the model coupling reaction between phenylboronic acid and 4-nitro-iodobenzene was chosen and studied, since its products are the precursors for

biphenylamines (Scheme 1). Notably, the way to recover the catalytic system was very simple, only by adding diethyl ether to the reaction and decanting the upper layer. It was found that at the same temperature and similar reaction time our catalytic system with low cost could be conveniently reused (up to five cycles) with good catalytic activity for the process, which is potentially useful for large-scale processes (Table 4).

Based on our understanding about copper-catalyzed cross-coupling reactions,^{6–8} the possible mechanism of copper



Scheme 1. A useful route to obtain biphenylamines.

Table 4
Recycling data for copper powder-catalyzed Suzuki–Miyaura coupling of 4-nitro-iodobenzene and phenylboronic acid performed in PEG-400^a

Run	Time (h)	Yield ^b (%)
0	12	99
1	12	95
2 ^c	12	88
3	16	79
4	18	69
5	18	66

^a Reaction conditions: 4-nitro-iodobenzene (1.0 equiv), phenylboronic acid (1.3 equiv), copper powder (0.1 equiv), solvent as PEG-400 (2.0 ml); base: K_2CO_3 (4.0 equiv); temperature: 110 °C.

^b Isolated yield based on aryl halide.

^c Additional 2.0 ml of PEG-400 and 1.5 equiv K_2CO_3 were added into the system.

powder-catalyzed ligand-free Suzuki–Miyaura coupling reaction performed in PEG-400 was proposed in Figure 2. It is presumed that PEG-400 works not only as the recycled medium but also as a ligand. In addition, iodine in the system could possibly make aryl bromides or chlorides transform into aryl iodides in the presence of K_2CO_3 as the base, which makes the coupling of difficult substrates facile to be performed. The related experiments were under way in our laboratory to prove the mechanism.

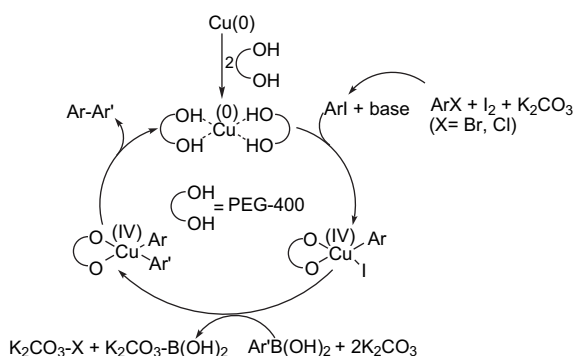


Figure 2. The proposed mechanism of copper powder-promoted ligand-free Suzuki–Miyaura coupling reaction in PEG-400.

3. Conclusion

In summary, we have developed an effective catalytic system for copper-catalyzed Suzuki–Miyaura coupling reaction: $Cu/K_2CO_3/PEG-400$. It could afford almost quantitative coupling products of aryl iodides. Using molecular iodine as additive, we could get moderate to good yields of coupling products of aryl bromides or chlorides. With simple workup, we could reuse our catalytic system several times. All these characteristics of our protocol make the reaction quite suitable for scale-up and commercialization. Further work is in progress in this laboratory with the aim of expanding this catalytic system to other processes and studying on the mechanism of this copper-catalyzed Suzuki–Miyaura coupling reaction.

4. Experimental

4.1. General experimental

All reactions were carried out under an argon atmosphere condition. Solvents were dried and degassed by standard methods, and all arylboronic acids and aryl halides were purchased from Aldrich and Alfa. Flash column chromatography was performed using silica gel (300–400 mesh). Analytical thin-layer chromatography was performed using glass plates pre-coated with 200–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). NMR spectra were measured in $CDCl_3$ on a Varian Inova-400 NMR spectrometer (400 MHz or 300 MHz) with TMS as an internal reference. Products were characterized by comparison of 1H and ^{13}C NMR data with that in the literatures.

4.2. General procedure for Suzuki–Miyaura coupling reactions of arylboronic acid and aryl iodides

A schlenk tube (evacuated and back-filled with argon) was charged with copper powder (0.1 equiv), potassium carbonate (2.0 equiv), arylboronic acid (1.0 equiv), and any remaining solids (aryl iodide) in the solvent of PEG-400 (2 ml) and then aryl iodide (1.3 equiv) was added under argon. The tube was sealed under argon, and the mixture was heated to 110 °C and stirred for 12 h. After cooling to room temperature, the mixture was diluted with water, and the combined aqueous phases were extracted three times with ethyl acetate. The organic layers were combined, dried over Na_2SO_4 , and concentrated to yield the crude product, which was further purified by silica gel chromatography, using petroleum ether as eluent to provide the desired product.

4.3. General procedure for Suzuki–Miyaura coupling reactions of arylboronic acid and aryl bromides or chlorides

A schlenk tube (evacuated and back-filled with argon) was charged with copper powder (0.1 equiv), potassium carbonate (2.0 equiv), iodine (0.2 equiv), arylboronic acid (1.0 equiv), and any remaining solids (aryl bromide or chloride) in the solvent of PEG-400 (2 ml) and then aryl bromide or chloride (1.3 equiv) was added under argon. The tube was sealed under argon, and the mixture was heated to 140 °C and stirred for 36 h. After cooling to room temperature, the mixture was diluted with water and the combined aqueous phases were extracted three times with ethyl acetate. The organic layers were combined, dried over Na_2SO_4 , and concentrated to yield the crude product, which was further purified by silica gel chromatography, using petroleum ether as eluent to provide the desired product.

4.4. General procedure for recycled Suzuki–Miyaura coupling reactions of phenylboronic acid and 4-nitro-iodobenzene

A schlenk tube (evacuated and back-filled with argon) was charged with copper powder (0.1 equiv), potassium carbonate (4.0 equiv), phenylboronic acid (1.0 equiv), and 4-nitro-iodobenzene (1.3 equiv) in the solvent of PEG-400

(2 ml). The tube was sealed under argon, and the mixture was heated to 110 °C and stirred for 12 h. After cooling to room temperature, the mixture was directly extracted three times with diethyl ether. The upper layers were decanted, combined, and concentrated to yield the crude product, which was further purified by silica gel chromatography, using petroleum ether and ethyl acetate (10:1) as eluent to provide the desired product. The mixture of copper powder, potassium carbonate, and PEG-400 was solidified (cooled) and subjected to a second run of the Suzuki–Miyaura coupling reaction by charging with the same substrates (phenylboronic acid and 4-iodo-nitrobenzene). Then the system was evacuated and back-filled with argon for three times. The following procedure is the same as above.

4.4.1. 4-Methylbiphenyl¹⁶

Mp 46–47 °C, ¹H NMR (CDCl₃, 300 Hz) (δ, ppm) 2.37 (s, 3H, CH₃), 7.22 (d, *J*=7.5 Hz, 2H, ArH), 7.30 (t, *J*=7.2 Hz, 1H, ArH), 7.40 (t, *J*=7.5 Hz, 2H, ArH), 7.48 (d, *J*=7.8 Hz, 2H, ArH), 7.56 (d, *J*=7.5 Hz, 2H, ArH); ¹³C NMR (75 MHz, CDCl₃) (δ, ppm) 141.59, 138.79, 137.44, 129.93, 129.16, 127.44, 127.42, 21.56.

4.4.2. Biphenyl¹⁷

¹H NMR (400 MHz, CDCl₃) (δ, ppm) 7.36 (d, *J*=7.2 Hz, 2H, ArH), 7.45 (t, *J*=7.2 Hz, 4H, ArH), 7.60 (t, *J*=7.2 Hz, 4H, ArH); ¹³C NMR (100 MHz, CDCl₃) (δ, ppm) 141.67, 129.22, 127.72, 127.64.

4.4.3. 4-Fluorobiphenyl¹⁸

¹H NMR (CDCl₃, 300 Hz) (δ, ppm) 7.12 (t, *J*=8.7 Hz, 2H, ArH), 7.34 (t, *J*=7.1 Hz, 1H, ArH), 7.43 (t, *J*=7.2 Hz, 2H, ArH), 7.51–7.56 (m, 4H, ArH); ¹³C NMR (100 MHz, CDCl₃) (δ, ppm) 164.15, 161.70, 140.71, 137.80, 137.77, 129.29, 129.19, 129.11, 127.72, 127.48, 116.18, 115.97.

4.4.4. 4-Methoxybiphenyl-4'-carbaldehyde¹⁹

¹H NMR (CDCl₃, 300 Hz) (δ, ppm) 3.87 (s, 3H, CH₃O), 7.01 (d, *J*=6.3 Hz, 2H, ArH), 7.60 (d, *J*=6.6 Hz, 2H, ArH), 7.71 (d, *J*=6.0 Hz, 2H, ArH), 7.93 (d, *J*=6.0 Hz, 2H, ArH), 10.04 (s, 1H, CHO); ¹³C NMR (CDCl₃, 75 Hz) (δ, ppm) 192.39, 130.80, 128.98, 127.63, 119.38, 114.94, 55.88.

4.4.5. 2-Methoxybiphenyl²⁰

¹H NMR (CDCl₃, 300 Hz) (δ, ppm) 3.70 (s, 3H, CH₃O), 6.987–6.96 (m, 2H, ArH), 7.21 (t, *J*=6.3 Hz, 3H, ArH), 7.31 (t, *J*=7.2 Hz, 2H, ArH), 7.44 (d, *J*=7.5 Hz, 2H, ArH); ¹³C NMR (100 MHz, CDCl₃) (δ, ppm) 156.84, 138.93, 131.30, 129.95, 129.02, 128.39, 127.32, 121.22, 111.60, 55.94.

4.4.6. 1-Phenylnaphthalene²¹

¹H NMR (CDCl₃, 300 Hz) (δ, ppm) 7.45–7.49 (m, 6H, ArH), 7.82–7.84 (m, 6H, ArH); ¹³C NMR (CDCl₃, 75 Hz) (δ, ppm) 133.82, 130.46, 129.86, 128.64, 128.26, 126.20.

4.4.7. 2-Methylbiphenyl²²

¹H NMR (CDCl₃, 300 Hz) (δ, ppm) 2.19 (s, 3H, CH₃), 7.15–7.32 (m, 9H, ArH).

4.4.8. 3-Methoxybiphenyl²³

¹H NMR (CDCl₃, 300 Hz) (δ, ppm) 3.76 (s, 3H, CH₃O), 6.80 (d, *J*=7.8 Hz, 1H, ArH), 7.08 (t, *J*=9.3 Hz, 6H, ArH), 7.23–7.36 (m, 2H, ArH), 7.50 (d, *J*=7.5 Hz, 2H, ArH); ¹³C NMR (100 MHz, CDCl₃) (δ, ppm) 160.37, 143.20, 141.53, 130.20, 129.18, 127.86, 127.64, 120.11, 113.33, 113.10, 55.71.

4.4.9. 4-Methoxybiphenyl²⁴

¹H NMR (CDCl₃, 300 Hz) (δ, ppm) 3.86 (s, 3H, CH₃O), 6.96–7.00 (m, 2H, ArH), 7.26 (s, 1H, ArH), 7.40–7.44 (m, 2H, ArH), 7.52–7.57 (m, 4H, ArH); ¹³C NMR (CDCl₃, 100 Hz) (δ, ppm) 129.19, 128.63, 127.21, 127.13, 114.66, 55.8.

4.4.10. 4-Chloro-4'-nitrobiphenyl^{3h}

Mp 112–113 °C; ¹H NMR (CDCl₃, 400 Hz) (δ, ppm), 7.47 (d, *J*=8.4 Hz, 2H, ArH), 7.56 (d, *J*=8.4 Hz, 2H, ArH), 7.71 (d, *J*=8.8 Hz, 2H, ArH), 8.30 (d, *J*=8.8 Hz, 2H, ArH); ¹³C NMR (CDCl₃, 100 Hz) (δ, ppm) 147.67, 146.76, 137.62, 135.70, 129.83, 129.08, 128.13, 124.67.

4.4.11. 4-Fluoro-4'-nitrobiphenyl²⁵

¹H NMR (CDCl₃, 400 Hz) (δ, ppm) 7.17–7.21 (m, 2H, ArH), 7.59–7.62 (m, 2H, ArH), 7.69–7.71 (m, 2H, ArH), 8.29–8.31 (m, 2H, ArH); ¹³C NMR (CDCl₃, 100 Hz) (δ, ppm) 165.06, 147.03, 138.20, 135.39, 129.66, 129.58, 128.18, 128.12, 124.66, 116.78, 116.56.

4.4.12. 4-Chloro-4'-fluorobiphenyl

¹H NMR (CDCl₃, 400 Hz) (δ, ppm) 7.12 (t, *J*=8.8 Hz, 2H, ArH), 7.38–7.51 (m, 6H, ArH); ¹³C NMR (CDCl₃, 100 Hz) (δ, ppm) 164.27, 161.82, 139.13, 136.57, 136.54, 133.85, 129.42, 128.70, 116.34, 116.13.

4.4.13. 4-Chloro-biphenyl-4'-carbaldehyde²⁶

¹H NMR (CDCl₃, 400 Hz) (δ, ppm) 7.44 (d, *J*=8.4 Hz, 2H, ArH), 7.55 (d, *J*=8.4 Hz, 2H, ArH), 7.70 (d, *J*=8.0 Hz, 2H, ArH), 7.94 (d, *J*=8.0 Hz, 2H, ArH), 10.05 (s, 1H, CHO).

4.4.14. Biphenyl-4-carbaldehyde²⁷

¹H NMR (CDCl₃, 400 Hz) (δ, ppm) 7.42–7.51 (m, 2H, ArH), 7.64 (d, *J*=7.6 Hz, 2H, ArH), 7.76 (d, *J*=8.0 Hz, 2H, ArH), 7.96 (d, *J*=8.0 Hz, 2H, ArH), 10.06 (s, 1H, CHO); ¹³C NMR (CDCl₃, 100 Hz) (δ, ppm) 192.41, 147.64, 140.15, 135.62, 130.73, 129.47, 128.93, 128.13, 127.81.

4.4.15. Biphenyl-3-carbaldehyde²⁸

¹H NMR (CDCl₃, 400 Hz) (δ, ppm) 7.40 (s, 1H, ArH), 7.41–7.49 (m, 3H, ArH), 7.62 (t, *J*=6.8 Hz, 3H, ArH), 7.86 (d, *J*=7.2 Hz, 2H, ArH), 8.10 (s, 1H, ArH), 10.09 (s, 1H, CHO); ¹³C NMR (CDCl₃, 100 Hz) (δ, ppm) 192.85, 142.66, 140.18, 137.39, 133.56, 129.99, 129.49, 129.12, 128.69, 128.50, 127.64.

4.4.16. 4,4'-Dichlorobiphenyl²⁹

¹H NMR (300 MHz, CDCl₃) (δ, ppm) 7.40 (d, *J*=8.1 Hz, 4H, ArH), 7.33 (d, *J*=8.4 Hz, 4H, ArH); ¹³C NMR (75 MHz, CDCl₃) (δ, ppm) 138.88, 134.02, 129.52, 128.70.

4.4.17. 4-Nitrobiphenyl³⁰

¹H NMR (400 MHz, CDCl₃) (δ, ppm) 7.49–7.56 (m, 3H, ArH), 7.67 (d, *J*=7.6 Hz, 2H, ArH), 7.78 (d, *J*=8.4 Hz, 2H, ArH), 8.34 (d, *J*=8.4 Hz, 2H, ArH); ¹³C NMR (100 MHz, CDCl₃) (δ, ppm) 147.85, 138.98, 129.38, 129.14, 128.02, 127.61, 125.11, 124.38.

4.4.18. 4-Chlorobiphenyl³¹

¹H NMR (400 MHz, CDCl₃) (δ, ppm) 7.33–7.45 (m, 5H, ArH), 7.49–7.55 (m, 4H, ArH); ¹³C NMR (75 MHz, CDCl₃) (δ, ppm) 140.43, 140.11, 133.82, 129.50, 129.43, 129.37, 129.35, 128.85, 128.05, 127.44, 110.20.

4.4.19. 4-Trifluoromethylbiphenyl³²

Mp 69–70 °C; ¹H NMR (400 MHz, CDCl₃) (δ, ppm) 7.35 (t, *J*=7.6 Hz, 1H, ArH), 7.40–7.49 (m, 3H, ArH), 7.60 (d, *J*=7.2 Hz, 3H, ArH), 7.69 (s, 2H, ArH); ¹³C NMR (100 MHz, CDCl₃) (δ, ppm) 129.48, 129.24, 128.67, 127.91, 127.74, 127.65, 126.17.

Acknowledgements

The authors would like to thank the Natural Science Foundation of Education Committee of Jiangsu Province (06KJB150099, 05KJB150116), Natural Science Foundation of Jiangsu Province (BK2006048), Natural Science Foundation of China (20472062, 20672079), China Postdoctoral Science Foundation, and Key Laboratory of Organic Synthesis of Jiangsu Province for financial support.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.02.068.

References and notes

- (a) Suzuki, A. *Pure Appl. Chem.* **1991**, *63*, 419–422; (b) Oh-e, T.; Miyaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201–2208.
- For reviews, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483; (b) Diederich, F.; Stang, P. J. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, 1998; (c) Yong, B. S.; Nolan, S. P. *Chemtracts: Org. Chem.* **2003**, 205–227; (d) De Meijere, A.; Diederich, F. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, 2004; (e) Phan, N. T. S.; Van Der Sluys, M.; Jones, C. W. *Adv. Synth. Catal.* **2006**, *348*, 609–679.
- For selected papers on the palladium-catalyzed Suzuki–Miyaura cross-coupling reaction, see: (a) Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 3690–3693; (b) Eckhardt, M.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 13642–13643; (c) Willis, M. C.; Powell, L. H.; Claverie, C. K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1249–1251; (d) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871–1876; (e) Son, S. U.; Jang, Y.; Park, J.; Na, H. B.; Park, H. M.; Yun, H. J.; Lee, J.; Hyeon, T. *J. Am. Chem. Soc.* **2004**, *126*, 5026–5027; (f) Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. *J. Am. Chem. Soc.* **2004**, *126*, 15195–15201; (g) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685–4696; (h) Dai, M.; Liang, B.; Wang, C.; Chen, J.; Yang, Z. *Org. Lett.* **2004**, *6*, 221–224; (i) Li, J.-H.; Liu, W.-J. *Org. Lett.* **2004**, *6*, 2809–2811; (j) Anderson, K. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 6173–6177; (k) Liu, D.; Gao, W.; Dai, Q.; Zhang, X. *Org. Lett.* **2005**, *7*, 4907–4910; (l) Lebel, H.; Janes, M. K.; Charette, A. B.; Nolan, S. P. *J. Am. Chem. Soc.* **2004**, *126*, 5046–5047; (m) Schweizer, S.; Becht, J.-M.; DrianLe, C. *Adv. Synth. Catal.* **2007**, *349*, 1150–1158 and references cited therein.
- Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science: Mill Valley, CA, 1987.
- (a) Saito, S.; Ohtani, S.; Miyaura, N. *J. Org. Chem.* **1997**, *62*, 8024–8030; (b) Zim, D.; Lando, V. R.; Dupont, J.; Monteiro, A. L. *Org. Lett.* **2001**, *3*, 3049–3051.
- For special reviews on copper-catalyzed cross-couplings, see: (a) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2632–2657; (b) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359–1470; (c) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400–5449; (d) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337–2364.
- (a) Thathagar, M. B.; Beckers, J.; Rothenberg, G. *J. Am. Chem. Soc.* **2002**, *124*, 11858–11859; (b) Thathagar, M. B.; Beckers, J.; Rothenberg, G. *Adv. Synth. Catal.* **2003**, *345*, 979–985.
- (a) Li, J.-H.; Wang, D.-P. *Eur. J. Org. Chem.* **2006**, 2063–2066; (b) 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*, 2053–2057; (c) Li, J.-H.; Li, J.-L.; Xie, Y.-X. *Synthesis* **2007**, *7*, 984–988.
- Using PEG as solvent in coupling reactions, see: (a) Liu, L.; Zhang, Y.; Wang, Y. *J. Org. Chem.* **2005**, *70*, 6122–6125; (b) van der Heiden, M.; Plenio, H. *Chem.—Eur. J.* **2004**, *10*, 1789–1797; (c) Glegola, K.; Framery, E.; Pietrusiewicz, K. M.; Sinou, D. *Adv. Synth. Catal.* **2006**, *348*, 1728–1733.
- Poly(ethylene glycol): Chemistry and Biological Applications*; Harris, J. M., Zalipsky, S., Eds.; American Chemical Society: Washington, 1997.
- Copper-catalyzed halogen exchange in aryl halides: Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 4844–4845.
- (a) Jiang, D.; Fu, H.; Jiang, Y.; Zhao, Y. *J. Org. Chem.* **2007**, *72*, 672–674; (b) Wu, G. G.; Wong, Y. S.; Poirier, M. *Org. Lett.* **1999**, *1*, 745–747; (c) Fagan, P. J.; Hauptman, E.; Shapiro, R.; Casalnuovo, A. *J. Am. Chem. Soc.* **2000**, *122*, 5043–5051; (d) Cai, J.; Zhou, Z.; Zhao, G.; Tang, C. *Org. Lett.* **2004**, *4*, 4723–4725; (e) Zhu, W.; Ma, D. *Chem. Commun.* **2004**, 888–889.
- Togo, H.; Iido, S. *Synlett* **2006**, 2159–2175.
- For a review in palladium-catalyzed coupling reactions of aryl chlorides: Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176–4211.
- Radomski, J. L. *Annu. Rev. Pharmacol. Toxicol.* **1979**, *19*, 129–157.
- Zapf, A.; Ehrentraut, A.; Beller, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4153–4155.
- Creed, T.; Leardini, R.; McNab, H.; Nanni, D.; Nicolson, I. S.; Reed, D. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1079–1085.
- Lemo, J.; Heuze, K.; Astruc, D. *Org. Lett.* **2005**, *7*, 2253–2256.
- Mutule, L.; Suna, E. *Tetrahedron* **2005**, *61*, 11168–11176.
- Mowery, M. E.; DeShong, P. J. *Org. Chem.* **1999**, *64*, 3266–3270.
- Mino, T.; Shirae, Y.; Sakamoto, M.; Fujita, T. *J. Org. Chem.* **2005**, *70*, 2191–2194.
- Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550–9561.
- Nielsen, S. F.; Peters, D.; Axelsson, O. *Synth. Commun.* **2000**, *30*, 3501–3509.
- Schneider, S.; Bannwarth, W. *Helv. Chim. Acta* **2001**, *84*, 735–742.
- Enokido, T.; Fugami, K.; Endo, M.; Kameyama, M.; Kosugi, M. *Adv. Synth. Catal.* **2004**, *346*, 1685–1688.
- Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553–5566.
- Dupuis, C.; Adiey, K.; Charruault, L.; Michelet, V.; Savignac, M.; Genet, J.-P. *Tetrahedron Lett.* **2001**, *42*, 6523–6526.
- Tao, B.; Boykin, D. W. *J. Org. Chem.* **2004**, *69*, 4330–4335.
- Wang, L.; Zhang, Y.; Liu, L.; Wang, Y. *J. Org. Chem.* **2006**, *71*, 1284–1287.
- Zapf, A.; Beller, M. *Chem.—Eur. J.* **2000**, *6*, 1830–1833.
- Molander, G. A.; Biolatto, B. *Org. Lett.* **2002**, *4*, 1867–1870.
- Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2005**, *7*, 2229–2231.