



An efficient and simple ligand from phthalandione for palladium-catalyzed Suzuki reaction in aqueous media



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ABSTRACT

An efficient and simple ligand derived from phthalandione was used for palladium catalyzed Suzuki coupling reaction in water/ethanol ($V/V = 2/1$) under aerobic conditions. The reaction exhibited a high catalytic efficiency even with lower Pd loading (0.002 mol %). In this work, the catalyst could be successfully used in coupling reaction between various aryl halides with phenylboronic acid in excellent yields with high turnover number (TON) (the maximal TON was up to 49,000 for the reaction of bromobenzene with phenylboronic acid). Moreover, this new ligand had been elucidated by ^1H NMR, ^{13}C NMR and X-ray crystal diffraction.

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Introduction

The palladium catalyzed Suzuki–Miyaura reaction is one of the most powerful and convenient approaches for the synthesis of biaryl derivatives that are structural elements of numerous natural products, agrochemicals, pharmaceuticals, and polymers.^{1–3} The most commonly used reaction protocol utilizes organic solvents in the presence of an inorganic base, a palladium catalyst precursor, and a ligand that coordinates to the palladium center to stabilize the catalyst. Among all the influencing factors, the ligand plays a pivotal role in the successful execution of the coupling reaction, because the activity and selectivity of the catalyst depend on the steric and electronic properties of the ligand attached to the Pd metal. In the traditional Suzuki–Miyaura reactions, the electron-rich phosphine ligands were generally employed to improve the catalytic performance.⁴ Since phosphine ligands are often water- and air-sensitive,^{5,6} catalysis under phosphine-free conditions is still a challenge of high importance. Then, a number of phosphine-free ligands for the Suzuki–Miyaura reaction had been reported, such as *N*-heterocyclic carbenes,^{7,8} diimines,^{9,10} diamines,^{11,12} and *N,O*-ligands.^{13–15} On the other hand, the classic Suzuki–Miyaura reaction was often carried out in organic media, such as DMF,^{16,17} THF,^{18,19} dioxane,²⁰ toluene,²¹ CH_3CN ,²² and methanol,^{16,23–25} which was contrary to the idea of green chemistry. From these standpoints, the development of efficient, stable, eco-

nomical, and environmentally friendly catalytic system remains a challenging task.

To the best of our knowledge, there are few papers about using amide as ligands for the Suzuki–Miyaura reaction.²⁶ Herein, we would like to report an efficient, convenient, and environmentally friendly protocol for the Suzuki–Miyaura reaction of aryl bromides with arylboronic acids in aqueous media. The synthetic route of the phthalandione derivative ligand (PDL) can be clearly seen in Scheme 1. The new ligand had been elucidated by ^1H NMR, ^{13}C NMR, and X-ray crystal diffraction (Scheme 2).

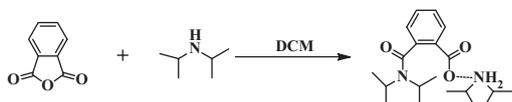
Results and discussion

We initially tested the reaction of phenylboronic acid with 4-bromo anisole in 3 mL aqueous media ($V_{\text{water}}/V_{\text{ethanol}}$, 2/1) as a model reaction under 80 °C in the presence of 0.1 mol % PdCl_2 and 2 equiv K_3PO_4 as a base in 2 h. The desired products were obtained in good yield (98%). Then, we enlarged the S/C up to 5000 (Pd loading = 0.02 mol %) to optimize the reaction conditions in the model reaction, including the effect of base, solvents, the reaction time, and Pd loadings.

As known, the base plays an important role in this reaction.²⁷ The effects of various inorganic and organic bases on the Suzuki–Miyaura reaction were investigated (Table 1). Among the bases screened for their influence on the yields of the model reaction, the use of stronger inorganic bases gave the desired product in high yield. Organic bases, such as Et_3N , Dicyclohexylamine, and DMAP, were also tested, but the results were not good (Table 1,

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Scheme 1. The synthetic route of PDL.

entries 10–12). Among the bases employed, KOH was found to be the best in the present protocol (Table 1, entry 2).

The choice of solvent was also important in the Suzuki–Miyaura reaction. In order to investigate this effect, we screened different solvents with the model reaction. As was evidenced from Table 2, the reaction in pure water afforded 4-methylbiphenyl in a low yield after 2 h (entry 7). However, the addition of appropriate amounts of polar organic solvents (such as DMF, THF, Dioxane, MeOH, *i*-PrOH, and EtOH) into water led to an increase in the activity, and better yield was obtained. From the results in Table 2, it could be seen clearly that the mixture of water and ethanol (V/V, 2/1) was the best media for this catalyst system (Table 2, entry 9). These results suggested that the proper ratio of water and ethanol played the key role in the model reaction with the probable reason of the good solubility of two substrates in these mixed solvents.²⁸

Considering hydrolysis and ionization of PDL in alkaline solution to some extent, we illustrated the effect of diisopropylamine (DIPA, L-02) and phthalandione (L-03) to the process of the coupling reaction and carried out the related study in the model reaction. These results were shown in Table 3. It was found that L-02 had a little effect on response to the cross-coupling reaction with higher Pd-loading (0.1 mol %) while L-03 could promote the model reaction to some extent with the same Pd-loading. It was noteworthy that the catalytic reactions proceeded fast in the co-solvent solution containing active palladium species, which was stable without the formation of Pd-black (Table 3, entry 4), while Pd-black formed significantly within 4 h using L-02 or L-03 as ligand in the model reaction. It indicated that PDL could prevent the aggregation of Pd-nano particle to Pd-black and stabilize the Pd-nano particle more efficiently than L-02 and L-03. As can be seen from the results of Table 3 and the above discussion, PDL was proved to be an effective ligand in the palladium catalyzed Suzuki reaction.

Under the optimized reaction conditions (water/ethanol, KOH, 80 °C, 0.002 mol % catalyst), we subsequently investigated the coupling reaction using different aryl halides and hetero-aryl halides

Table 1
The effect of base on the Suzuki–Miyaura reaction^a

Entry	Base	Pd loading (mol %)	Yield ^b (%)
1	K ₃ PO ₃	0.02	92
2	KOH	0.02	99
3	KHCO ₃	0.02	82
4	K ₂ CO ₃	0.02	91
5	NaOH	0.02	93
6	NaHCO ₃	0.02	79
7	Na ₂ CO ₃	0.02	91
8	NaOAc	0.02	76
9	Cs ₂ CO ₃	0.02	95
10	Et ₃ N	0.02	46
11	DMAP	0.02	37
12	Dicyclohexylamine	0.02	18

^a Reaction conditions: 4-bromo anisole (0.5 mmol), phenylboronic acid (0.75 mmol), base (1.0 mmol), solvent (3.0 mL), 80 °C, 2 h, n (ligand)/n (Pd) = 2.

^b Isolated yield.

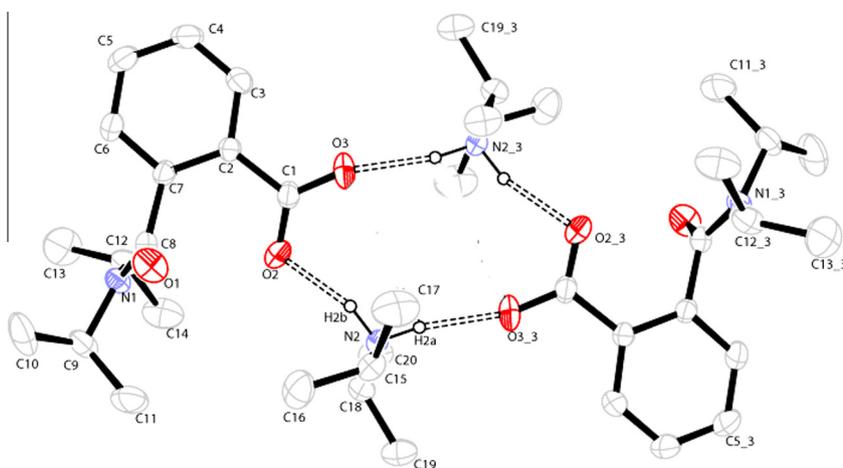
Table 2
Suzuki–Miyaura reaction employing various solvents^a

Entry	Solvent	Pd loading (mol %)	Time	Yield ^b (%)
1	DMF	0.02	4	81
2	THF	0.02	4	62
3	Dioxane	0.02	4	86
4	<i>i</i> -PrOH	0.02	4	71
5	MeOH	0.02	4	89
6	EtOH	0.02	4	82
7	H ₂ O	0.02	4	46
8	H ₂ O/MeOH (2:1)	0.02	2	91
9	H ₂ O/EtOH (2:1)	0.02	2	99
10	H ₂ O/ <i>i</i> -PrOH (2:1)	0.02	2	87
11	H ₂ O/Dioxane (2:1)	0.02	2	94
12	H ₂ O/THF (2:1)	0.02	2	79
13	H ₂ O/DMF (2:1)	0.02	2	92

^a Reaction conditions: 4-bromo anisole (0.5 mmol), phenylboronic acid (0.75 mmol), base (1.0 mmol), solvent (3.0 mL), 80 °C, 2 h, n (ligand)/n (Pd) = 2.

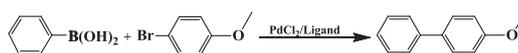
^b Isolated yield.

with phenylboronic acid and the data were collected in Table 4. In particular, high catalytic activity was observed in the reaction



Scheme 2. ORTEP drawing for two PDL units with 30% probability ellipsoids, showing the atomic numbering scheme. Symmetry transformation for N1₃, N2₃, O2₃, O3₃, C5₃, C11₃, C12₃, C13₃: $-x, -y, -z$. The two PDL units are linked by hydrogen bonds labeled using dashed lines.

Table 3
The effect of phthalandione and diisopropylamine on the Suzuki reaction^a



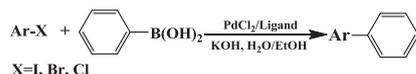
Entry	Ligand	Pd loading (mol %)	Temp(°C)/Time(h)	Yield ^b (%)	TON	Pd-black formation ^c
1	No ligand	0.1	80/4	34	340	Yes
2		0.1	80/4	52	520	Yes
3		0.1	80/4	71	710	Yes
4		0.002	80/0.5	98	49,000	No

^a Reaction conditions: 4-bromo anisole (0.5 mmol), phenylboronic acid (0.75 mmol), KOH (1.0 mmol), solvent (3.0 mL, $V_{\text{water}}/V_{\text{ethanol}} = 2/1$), 80 °C, n (ligand)/n (Pd) = 2.

^b Isolated yield.

^c After 2 h, Pd black appeared (yes or no).

Table 4
Suzuki–Miyaura reaction^a of phenylboronic acid and various aryl halides in water/ethanol



Entry	Ar-X	Pd loading (mol %)	Time(h)	Yield ^{b,c} (%)
1		0.002	0.5	98
2		0.002	0.5	98
3		0.002	0.5	98
4		0.002	0.5	98
5		0.002	0.5	95
6		0.002	0.5	98
7		0.002	1	89
8		0.002	0.5	98
9		0.002	0.5	98
10		0.002	1	91
11		0.002	0.5	97
12		0.002	0.5	96
13		0.002	0.5	97
14		0.002	0.5	97
15		0.002	2	79

Table 4 (continued)

Entry	Ar-X	Pd loading (mol %)	Time(h)	Yield ^{b,c} (%)
16		0.002	2	88
17		0.002	4	92 ^d
18		0.01	4	91
19		0.01	4	94
20		0.01	4	96
21		0.05	4	84
22		0.1	10	23 ^e

^a Reaction conditions: aryl halide (0.5 mmol), phenylboronic acid (0.75 mmol), KOH (1.0 mmol), solvent (3.0 mL, $V_{\text{water}}/V_{\text{ethanol}} = 2/1$), 80 °C, n (ligand)/n (Pd) = 2.

^b Isolated yield.

^c Yields were of average of two runs.

^d The product is 1,4-terphenyl.

^e Time = 10 h, 100 °C, Pd black appeared.

of substituted bromobenzenes with phenylboronic acid. Considering the model reaction of phenylboronic acid with 4-bromoanisole, for example, when 0.002 mol % Pd loading was used, the yield of desired products was up to 98% (Table 4, entry 4). To the best of our knowledge, this is a good result in the system using phosphine-free ligands in the presence of 0.002 mol % catalyst in mixed solvents.²⁹ In our system, the reaction was found to afford good to excellent yield for the desired product with different electron-withdrawing and electron-donating aryl bromides. Due to the steric hindrance of 2-BrC₆H₄Me, 2-bromo-*m*-xylene, and 2-bromo-*p*-xylene, the desired products were obtained in medium yield (entries 7, 15, and 16). We also investigated the reaction of heteroaryl bromides and aryl chlorides. The target products of aryl-heteroaryl were also obtained in good yields (Table 4, entries 18–21) when we extended the reaction time. Unfortunately, the coupling of aryl chlorides with phenylboronic acid did not perform as well as aryl bromides, even we when raised the Pd loading up to 0.1 mol % and prolonged the reaction time to 10 h (entry 22).

In summary, we have successfully developed a palladium catalyzed Suzuki–Miyaura reaction using amide derived from phthalidione as a ligand in aqueous media under aerobic conditions. The low-cost ligand and the environment friendly procedure make it potential for the application.

Experimental

All aryl halides and arylboronic acids were purchased from energy chemical. Other chemicals were purchased from commercial sources without any process. NMR spectroscopy was performed on a Bruker advance II 400 spectrometer operating at 400 MHz (^1H NMR) and 100 MHz (^{13}C NMR) with CDCl_3 as the solvent and TMS as internal standard. Melting points were determined on a Thomas–Hoover capillary melting point apparatus. The isolation of pure products was carried out via column (Silica gel 200–300 mesh).

Synthesis of PDL

592.5 mg (4 mmol) of *o*-phthalic anhydride was dissolved in 40 mL CH_2Cl_2 , and 2.2 mL diisopropylamine (16 mmol) was added dropwise under ice-water bath. After the end of addition, the mixture was stirred at room temperature for 8 h. The solvent was removed under reduced pressure and the residue was purified by recrystallization ($\text{EtOAc}/\text{Cyclohexane} = 1:1$). Finally, a white crystal (1.28 g) was obtained, yield: 91%. mp: 183–184 °C. ^1H NMR (400 MHz, CDCl_3): δ 0.92 (d, $J = 6.54$ Hz, 3H, CH_3), 1.09 (d, $J = 6.53$ Hz, 3H, CH_3), 1.19 (d, $J = 6.48$ Hz, 12H, CH_3), 1.47 (m, 6H, CH_3), 3.24 (m, 2H, CH), 3.45 (m, 1H, CH), 3.64 (m, 1H, CH), 7.06 (m, 1H, ArH), 7.32 (m, 2H, ArH), 7.86 (d, $J = 7.00$ Hz, 1H, ArH) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 18.18 (4C, CH_3), 19.09 (1C, CH_3), 19.39 (1C, CH_3), 19.45 (1C, CH_3), 19.67 (1C, CH_3), 124.67 (1C, Ar), 126.26 (1C, Ar), 128.34 (1C, Ar), 128.66 (1C, Ar), 134.86 (1C, Ar), 138.38 (1C, Ar), 170.63 (1C, $-\text{CO}-$), 170.71 (1C, $-\text{CO}-$).

X-ray crystallography

A single crystal of complex (0.39 × 0.36 × 0.24 mm) was examined by X-ray crystallography performed on an Xcalibur E diffractometer equipped with Mo-K α radiation ($\lambda = 0.7107 \text{ \AA}$) using ω -scan technique at 294(2)K. Empirical absorption correction was applied using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.³⁰ The structure was solved by the direct method and refined by a full-matrix, least-squares technique based on F^2 by the use of SHELXL-97 program.³¹ All the non-hydrogen atoms were located from successive Fourier syntheses. The positions of H atoms were generated geometrically and refined isotropically. Anisotropic refinement including all non-H atoms converged to agreement factors $R = 0.0793$ and $R_w = 0.1270$, where $w = 1/[\sigma^2(F_o^2) + (0.0741P)^2]$, $s = \sin(\theta)/\lambda$, and $P = (F_o^2 + 2F_c^2)/3$. Atomic scattering factors were taken from International Tables for X-ray crystallography.³²

Crystallographic data reported in this Letter have been deposited with Cambridge Crystallographic Data Centre as supplementary publication No. CCDC-(945352). Copies of the data can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk. Selected crystallographic data and structure determination parameters for the complex are shown in supporting information.

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Supplementary data

Supplementary data (including general experiment details, NMR and X-ray crystal diffraction data of PDL, and ^1H NMR spectra of all products listed in Table 4) associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2013.11.039>.

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