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Palladium-Catalyzed Synthesis of Diarylbenzenes from Coupling Reactions between Equal Amount of Diiodoarenes and Arylboronic Acids[1]

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Abstract—We reported a highly effective Pd-catalytic system for the synthesis of diarylbenzenes through Suzuki-type reaction between equal amount of diiodoarenes and arylboronic acids. This preferential oxidative addition resulted in such high selectivity.

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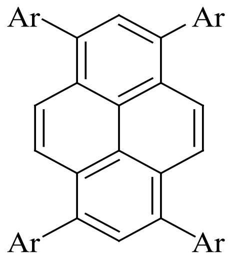
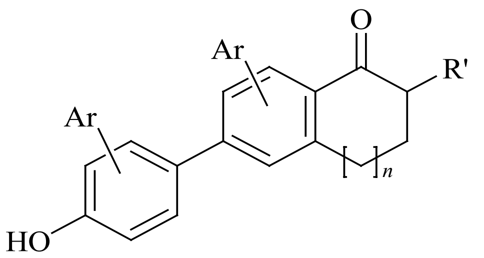
INTRODUCTION

The Suzuki reaction is a classical organic reaction of aryl- or vinylboronic acids with aryl- or vinyl halides catalyzed by a palladium complex [1, 2]. It is widely used to synthesize polyolefins, styrenes, and substituted biphenyls [3–7]. The 2010 Nobel Prize in chemistry was awarded in part to Suzuki for his discovery and development of this reaction. The Suzuki coupling products have widespread applications in fine chemical industries, photoelectric materials, synthesis of biologically active pharmaceuticals, as well as in the mushroom area of nanotechnology [8–19]. For example, as shown in Fig. 1, the indisposed tendency of $\mathbf{A_1}$–$\mathbf{A_3}$ toward crystallization and their moderate molecular dimensions permit exploitation as blue light emitting materials in OLEDs with respectable device performances [20]. Compound **B** is the most potent female sex hormone,



A1: Ar=2,4,6-trimethylphenyl
A2: Ar=2,3,5,6-tetramethylphenyl
A3: Ar=2,6-dimethyl-4-methoxyphenyl



B

Fig. 1. Transition-metal-catalyzed oxidative olefination.

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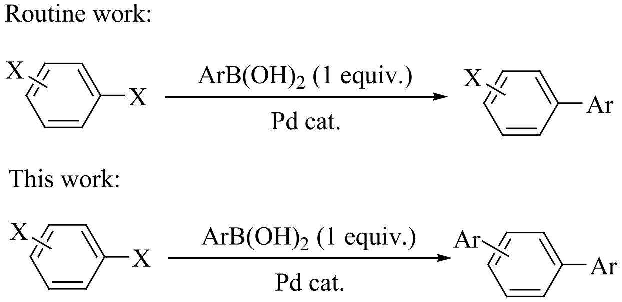
[1] The text was submitted by the authors in English.

Scheme 1. Coupling between equal amount of arylboronic acid and dihaloarylenes using different Pd catalysts.



which stimulates the growth of mammary tumors and endometriosis via activation of the estrogen receptor [21].

Normally, a molecule of dihalo reagent coupled with equal amount of phenylboronic acid gained monosubstituted product as shown in Scheme 1. Disubstituted product can be obtained only with a molecule of dihalo reagent coupled with two equiv. phenylboronic acid. How can a molecule of dihalo reagent coupled with equal amount of phenylboronic acid to gain disubstituted product? In the mechanism of the Suzuki reaction, Pd(0)-catalyst proceed via repeating the oxidative addition-transmetalation-reductive elimination catalytic cycle. If the regenerated Pd(0) catalyst could be oriented to undergo oxidative addition preferentially with its homogenously generated coupling product, then disubstituted product can be obtained smoothly. Hu and co-workers [22] found that the nature of the ligands has great influence on the oxidative addition rate of a Pd(0) catalyst. Differently, in the experiment we found that the solvent can also make the oxidative addition preferentially to process.

EXPERIMENTAL

All reactions were carried out in air. All halides and arylboronic acids were readily available. 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 400 NMR spectrometer with TMS as an internal reference. Products were characterized by comparison of ^{1}HNMR, ^{13}CNMR and TOF-MS data in the literature.

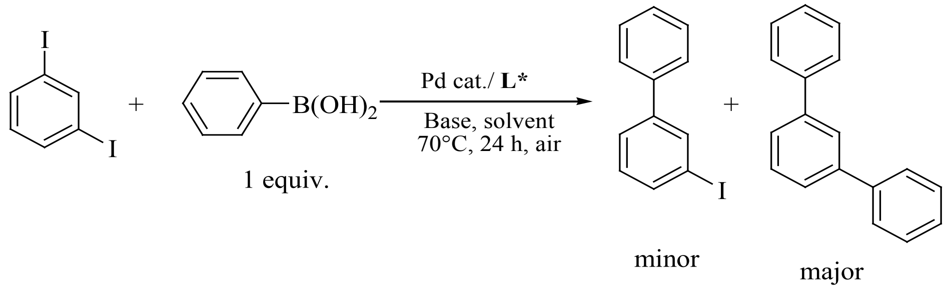
General procedure for Pd-catalyzed coupling between equal amount of dihaloarene and arylboronic acid. A mixture of dihaloarene (0.4 mmol), arylboronic acid (0.4 mmol), K_2CO_3 (0.8 mmol), $PdCl_2$ (7 mol %), PPh_3 (15 mol %), and PEG-400 (2 mL) in a sealed tube was stirred in air at 70°C for the desired time until complete consumption of starting material as monitored by TLC. After that the mixture was poured into ethyl acetate, then washed with water, extracted with ethyl acetate, dried by anhydrous Na_2SO_4, then filtered and evaporated under vacuum, the residue was purified by flash column chromatography (petroleum ether or petroleum ether/ethyl acetate) to afford the corresponding coupling products.

RESULTS AND DISCUSSION

In a pilot experiment, we carried out the reaction of equal amount of 1,3-diiodoarene and arylboronic acid as the model reaction to screen the reaction conditions and the results are depicted in Table 1. It could be seen that PEG-400 played the key role compared to other solvents in the process of preferential oxidative addition, and 75% yield of the desired product can be obtained (Table 1, entries 1–7). Screening various bases including organic bases and inorganic bases (Table 1, entries 8–13), K_2CO_3 was proved the best (Table 1, entry 9). Despite this, KOH and Cs_2CO_3 gave the moderate yields. PPh_3 showed higher efficiency as the reaction ligand than all other employed ligands, such as PCy_3, dppe, $P(NEt)_3$ and $P(OPh)_3$ (Table 1, entries 14–17). We were pleased to find that $PdCl_2$ showed higher catalytic activity than other palladium sources (Table 1, entries 18–20). In order to improve the yield, we screened temperature and reaction time (Table 1, entries 21–24), 70° and 24 h proved to be best. In addition, we tried to reduce the amount of catalyst and ligand but failed (Table 1, entries 25–26). However, when changing the amount of base to 2 equiv, 97% yield of the desired product was obtained (Table 1, entry 27).

With the optimized reaction conditions in hand, we next applied the coupling of 1, 3-diiodoarene and a wide range of arylboronic acids bearing either electron-donating or electron-withdrawing groups as summarized in Table 2. To our delight, excellent yields (79–88%) were achieved in the coupling of *o,m,p*-methoxy-substituted arylboronic acid (Table 2, entries 2–4). Unfortunately, aldehyde-substituted arylboronic acids gave moderate yields (34–53%) in the coupling with 1, 3-diiodoarene (Table 2, entries 5–7). We speculated that electron-withdrawing inductive effects of aldehyde substituent reduced the electron density of benzene ring. In addition, methyl, fluoro, chloro, *tert*-butyl-

Table 1. Screening catalytic conditions in coupling between equal amount of diiodobenzene and phenylboronic acid[a]



Entry	Cat. (mol %)	**L*** (mol %)	Solvent	Base	Yield, %[b]
1	$Pd(OAc)_2$ (7)	PPh_3 (15)	H_2O	K_3PO_4	37
2	$Pd(OAc)_2$ (7)	PPh_3 (15)	DMF	K_3PO_4	31
3	$Pd(OAc)_2$ (7)	PPh_3 (15)	DMSO	K_3PO_4	32
4	$Pd(OAc)_2$ (7)	PPh_3 (15)	Toluene	K_3PO_4	29
5	$Pd(OAc)_2$ (7)	PPh_3 (15)	glycol	K_3PO_4	48
6	$Pd(OAc)_2$ (7)	PPh_3 (15)	CH_3CN	K_3PO_4	32
7	$Pd(OAc)_2$ (7)	PPh_3 (15)	PEG-400	K_3PO_4	75
8	$Pd(OAc)_2$ (7)	PPh_3 (15)	PEG-400	*t*-BuOK	56
9	$Pd(OAc)_2$ (7)	PPh_3 (15)	PEG-400	K_2CO_3	87
10	$Pd(OAc)_2$ (7)	PPh_3 (15)	PEG-400	KOH	68
11	$Pd(OAc)_2$ (7)	PPh_3 (15)	PEG-400	Et_3N	36
12	$Pd(OAc)_2$ (7)	PPh_3 (15)	PEG-400	Na_2CO_3	64
13	$Pd(OAc)_2$ (7)	PPh_3 (15)	PEG-400	Cs_2CO_3	68
14	$Pd(OAc)_2$ (7)	PCy_3 (15)	PEG-400	K_2CO_3	72
15	$Pd(OAc)_2$ (7)	dppe (15)	PEG-400	K_2CO_3	86
16	$Pd(OAc)_2$ (7)	$P(NEt)_3$ (15)	PEG-400	K_2CO_3	69
17	$Pd(OAc)_2$ (7)	$P(OPh)_3$ (15)	PEG-400	K_2CO_3	53
18	$PdCl_2$ (7)	PPh_3 (15)	PEG-400	K_2CO_3	90
19	$Pd(dba)_2$ (7)	PPh_3 (15)	PEG-400	K_2CO_3	74
20	$PdCl_2(PPh_3)_2$	PPh_3 (15)	PEG-400	K_2CO_3	66
21[c]	$PdCl_2$ (7)	PPh_3 (15)	PEG-400	K_2CO_3	78
22[d]	$PdCl_2$ (7)	PPh_3 (15)	PEG-400	K_2CO_3	74
23[e]	$PdCl_2$ (7)	PPh_3 (15)	PEG-400	K_2CO_3	89
24[f]	$PdCl_2$ (7)	PPh_3 (15)	PEG-400	K_2CO_3	90
25	$PdCl_2$ (2)	PPh_3 (5)	PEG-400	K_2CO_3	74
26	$PdCl_2$ (5)	PPh_3 (10)	PEG-400	K_2CO_3	82
27[g]	$PdCl_2$ (7)	PPh_3 (15)	PEG-400	K_2CO_3	97

[a] Catalytic conditions: 1,3-diiodobenzene (0.4 mmol), phenylboronic acid (0.4 mmol), base (0.4 mmol), 70°C, 24 h, in air.

[b] Isolated yield of diphenylbenzene.

[c] 50°C.

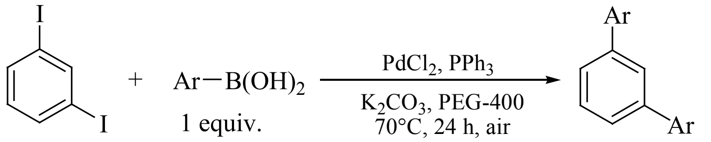
[d] 90°C.

[e] 5 h.

[f] 36 h.

[g] 0. 8 mmol of K_2CO_3.

Table 2. Pd-catalyzed cross-coupling between diiodobenzene and arylboronic acid[a]



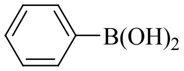
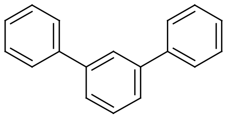
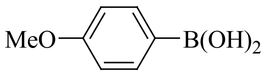
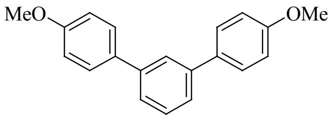
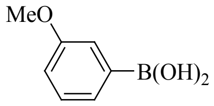
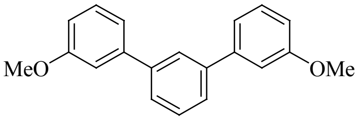
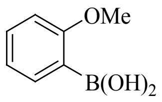
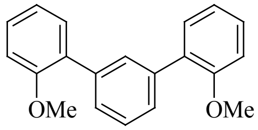
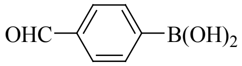
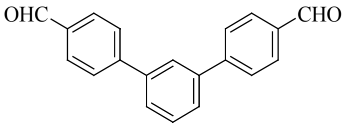
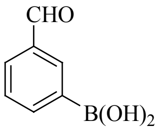
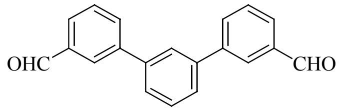
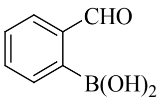
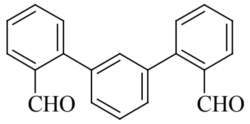
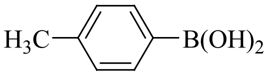
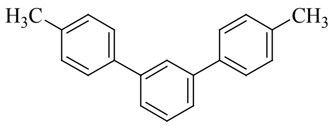
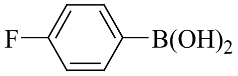
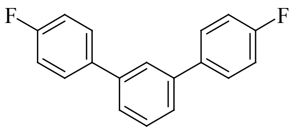
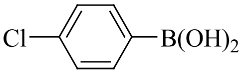
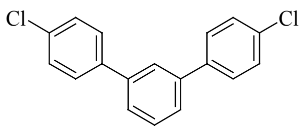
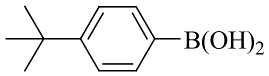
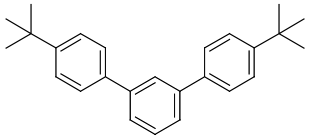
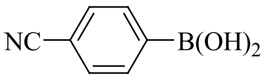
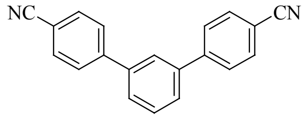
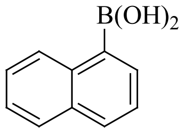
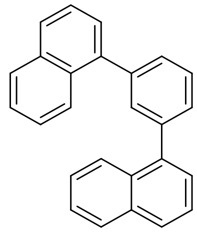
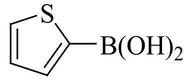
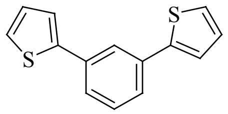
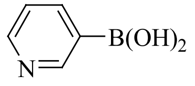
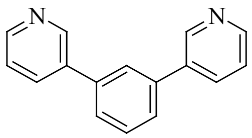
Entry	Arylboronic acid	Product	Yield, %[b]
1			97
2			89
3			88
4			80
5			47
6			42
7			34
8			84
9			82
10			72
11			70

Table 2. (Contd.)

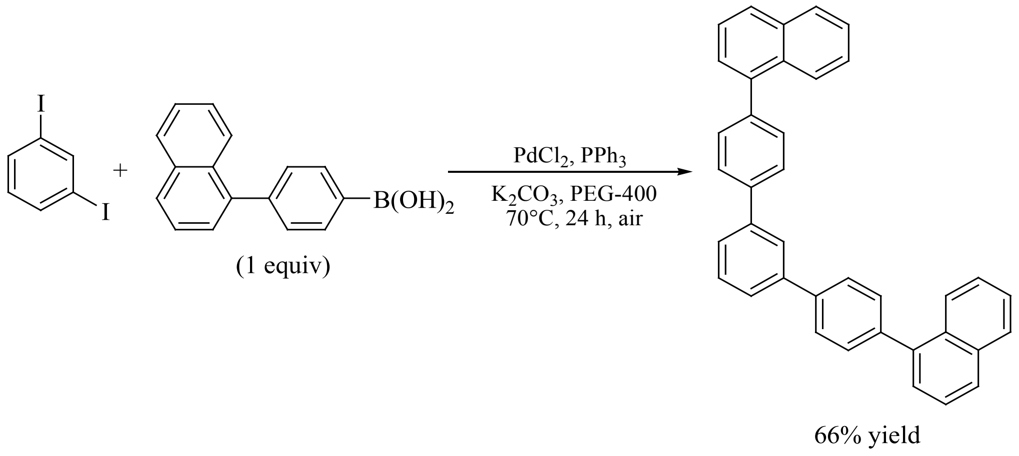
Entry	Arylboronic acid	Product	Yield, %[b]
12			51
13			53
14			58
15			82

[a] Reaction conditions: 1,3-diiodobenzene (0.4 mmol), phenylboronic acid (0.4 mmol), $PdCl_2$ (7 mol%), PPh_3 (15 mol %), K_2CO_3 (0.8 mmol), PEG-400 (2 mL), in air, 24 h.

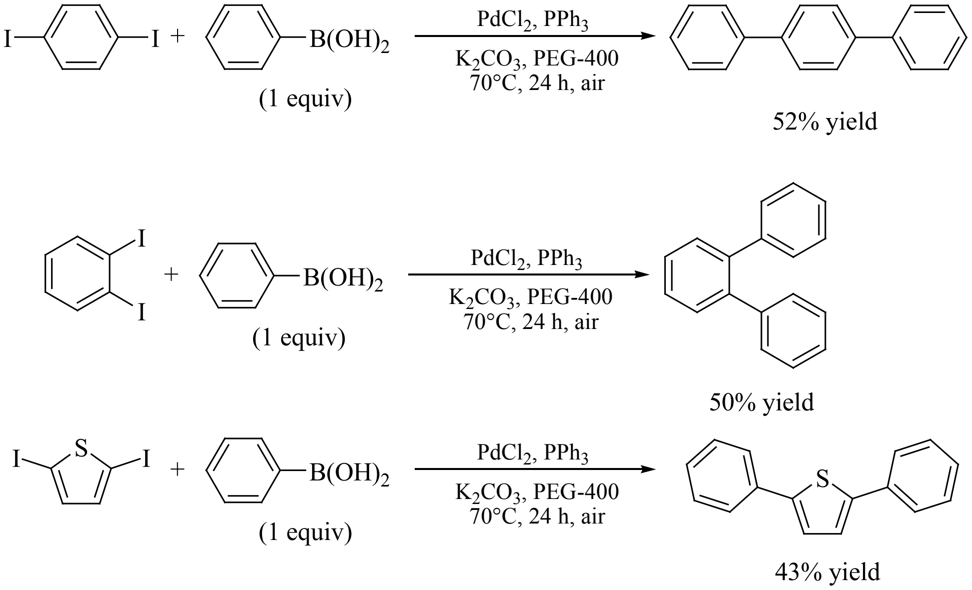
[b] Isolated yield of diarylarenes.

substituted arylboronic acids reacted well with 1,3-diiodoarene (70–84%) (Table 2, entries 8–11). It is noteworthy that cyano-substituted arylboronic acid gave 51% yield of the desired product (Table 2, entry 12). Besides, 53% yield of the desired product was obtained when 1-naphthylboric acid coupled with 1, 3-diiodoarene (Table 2, entry 13). When heterocyclic boronic acids such as 2-thienylboric acid and 3-pyridylboric acid were used, satisfactory yields were obtained (58% and 82%) (Table 2, entries 14 and 15). Thus demonstrating the tolerance of the present scaffold.

Scheme 2. Pd-catalyzed coupling between equal equivalent of 1,4-diiodobenzene and 4-(naphthalen-1-yl)phenylboronic acid.



Scheme 3. Pd-catalyzed coupling between equal equivalent of 1,4-diiodobenzene and 4-(naphthalen-1-yl)phenylboronic acid.



To further explore the scope and generality of this approach, we examined conjugated arylboronic acid coupling with 1, 3-diiodoarene, and the target product was obtained in 66% yield, which was shown in Scheme 2.

Afterwards, 1, 4-diiodoarene, 1, 2-diiodoarene were used to coupling with phenylboronic acid, 52% and 50% yield of desired products were gained respectively. In addition, halogenated heterocyclic reagent 2,5-diiodothiophene coupled with phenylboronic acid smoothly and gave moderate yield (Scheme 3).

In summary, we have developed an effective way to prepare diarylbenzene between only equal amount of diiodoarenes and arylboronic acids and the corresponding target products were obtained in moderate to good yields. It is really an economic way for the potential large-scale application. This simple PdCl$_2$/PPh$_3$/PEG-400 was identified as a powerful catalyst system. The characteristic of this communication is that solvent has significant influence on the reaction selectivity. Further work in this direction is in progress.

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