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Amine-bridged bis(phenol) ligands for efficient Pd-catalyzed aqueous C-C coupling reactions

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The influence of ring size (5 or 6), chain length (1, 2 or 3) and bulkiness of *N*-aryl substituents in amine-bridged bis(phenol) ligands (1–3) on palladium-catalyzed aqueous C-C coupling reactions were revealed. The homocoupling of arylboronic acid can be completed in neat water with the aid of a catalytic amount of *p*-toluenesulfonyl chloride (TsCl) in a very short time under anaerobic or aerobic conditions. Interestingly, the same catalytic system was efficient for Suzuki–Miyaura reaction in aqueous acetone under aerobic conditions in the absence of TsCl. The crystal structures of ligand 1 and three unsymmetrical fluorine-substituted biaryl derivatives were also reported. Copyright © 2013 John Wiley & Sons, Ltd.

Supporting information may be found in the online version of this article.

Keywords: water; *N*,*O*-ligands; palladium; homocoupling; Suzuki reaction

Introduction

Water, being cheap, non-flammable, non-toxic and environmentally benign, has been recognized as perhaps the ultimate green solvent. To date, development of green chemistry through organic reactions conducted in water and aqueous solution has become one of the most exciting research endeavors in organic synthesis.[1–3] Palladium catalysts are critically important in numerous chemical processes including C-C bond formation reactions.[4–6] The symmetrical and unsymmetrical substituted biaryl motif is found in a range of pharmaceuticals, herbicides and natural products as well as in conducting polymers and liquid crystalline materials.[7–16] Among the developed reactions, the homocoupling reactions of arylboronic acid is a good method to obtain symmetrical substituted biaryls from just a single precursor since the first example in 1987 studied by Suzuki.[17,18] A striking advantage of this reaction is that the products are easily separated by simple filtration.[14,19] The Suzuki–Miyaura reaction is undoubtedly the most powerful tool to selectively generate unsymmetrical substituted biaryls,[5] and is an excellent example which has strongly benefited from aqueous chemistry.[20–33] Improvements in the activity, selectivity and scope of the catalysts could drastically reduce the environmental impact, and increase the sustainability of chemical reactions.[34] Recent advances in novel catalyst development have enabled this transformation to be applied with a broad substrate scope, a wide functional group tolerance, low catalyst loadings, etc.[6,35–41]

The development of amine-bridged bis(phenol) ligands that have a rigid framework with bulky *N*-aryl substituents on the ring nitrogen to restrict the rotation of the coordination group has rarely been explored.[42–44] The presence of the nitrogen atom on the amine bridge seems to have a significant effect on the catalytic activity of the corresponding ligands.[43,45,46] Previously, we also found that Pd/**2**- and Pd/**3**-catalyzed arylhalides with arylboronic acid in methanol aqueous afford good to excellent yield of coupling products.[47,48] Ligand structure defines the steric and electronic properties of the palladium catalyst and thus plays a crucial role in the efficiency of the Pd-catalyzed reaction. The amine-bridged bis(phenol) rigid ligands (Fig. 1, **1–3**), which contain a well-defined orientation of the *N*,*O*-chelate for metal coordination, have provided different steric and electronic properties through slight diversity of the amine bridge. It is of particular interest to explore the influence of ring size, chain length and bulkiness of *N*-aryl substituents in these ligands on the catalytic properties of palladium complexes in C-C coupling reactions.

In the continuation of our interest in the development of new ligands for Pd-catalyzed C-C bond formation reactions, here we report the catalytic activity of ligands **1–3** in Pd-catalyzed aqueous C-C coupling reactions. More specifically, the same catalytic system was efficient for Pd-catalyzed homocoupling of arylboronic acids in neat water and Suzuki–Miyaura reaction in aqueous acetone with or without TsCl (Fig. 2). Thus these results would be complementary to those known catalytic systems.

Experimental

General Considerations

All chemicals employed in the synthesis were analytical grade, obtained commercially, and used as received without further

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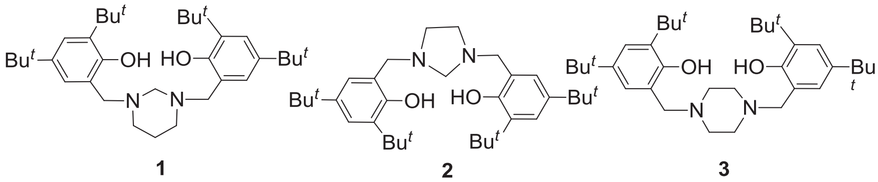


Figure 1. Amine-bridged bis(phenol) *N,O*-ligands **1**, **2** and **3**.

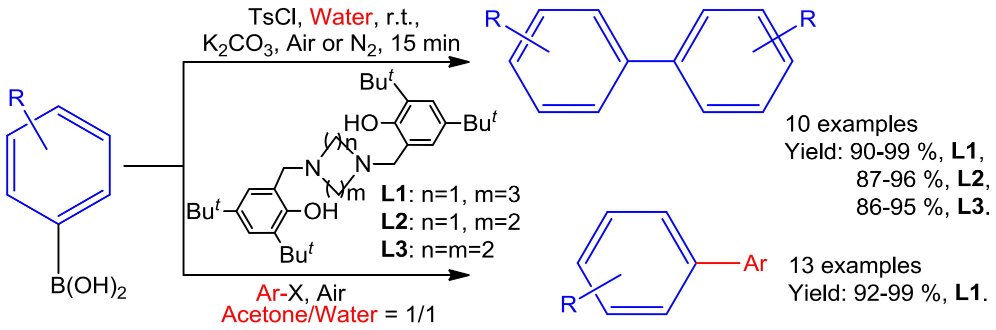


Figure 2. Pd-catalyzed aqueous C-C coupling reactions.

purification. Ligands **1**,[42] **2**[43] and **3**[44] were prepared as reported. NMR spectra were performed on a Bruker Avance III 400 MHz spectrometer (tetramethylsilane as internal standard) and coupling constants (*J* values) are given in hertz. Analyses by gas chromatography–mass spectrometry (GC-MS) were carried out on an Agilent 6890 gas chromatograph with 5973 mass spectral detector, using an AT.SE-30 column of 50 m length, 0.32 mm diameter and 0.5 µm film thickness.

Single-Crystal Structure Determination

Data collections for crystals were performed on a Bruker Smart Apex II CCD diffractometer equipped with graphite-monochromated Mo-Kα radiation ($\lambda = 0.71073$ Å). Intensity data were collected using φ and ω scans at 296 K. Datasets were corrected for Lorentz and polarization factors as well as for absorption by SADABS program.[49] Structures were solved by the direct method and refined by full-matrix least-squares fitting on F^2 by SHELX-97.[50,51] All non-hydrogen atoms were refined anisotropically except for the water molecules in **1**. All H atoms were refined using a riding model. Three F atoms on the -CF_3 group of **4** are disordered over two positions (F1/F1′, F2/F2′ and F3/F3′) with equal populations for each orientation. Experimental details of the X-ray analyses are provided in Table 1.

Table 1. Crystal data collection and structure refinements for compounds **1** and **4–6**

Compound	**1**	**4**	**5**	**6**
Formula	$C_{34}H_{55}N_2O_3$	$C_{15}H_{11}F_3O_1$	$C_{14}H_{10}F_2O_1$	$C_{14}H_9F_3O_1$
Formula weight	539.8	264.2	232.2	250.2
Crystal size (mm)	0.40 × 0.36 × 0.28	0.50 × 0.46 × 0.37	0.45 × 0.40 × 0.35	0.35 × 0.30 × 0.26
space group	*Pnma*	$P2_1/c$	$P2_1/c$	$P2_12_12_1$
a (Å)	8.8194(3)	11.431(5)	10.244	7.396(5)
b (Å)	37.3103(14)	11.431(5)	12.444	12.594(5)
c (Å)	10.2814(4)	13.715(5)	9.814	12.770(5)
α (°)	90.00	90.000(5)	90.00	90.000(5)
β (°)	90.00	105.968(5)	115.03	90.000(5)
γ (°)	90.00	90.000(5)	90.00	90.000(5)
V (Å^3)	3383.1(2)	1269.1(10)	1133.6	1189.5(10)
Z	8	4	4	4
R_{int}	0.0515	0.0231	0.0280	0.0116
$F(000)$	1188	544	480	512
Reflections collected	3893/2304	2996/2059	2520/1826	2691/1942
GOF on F^2	1.021	1.038	1.086	1.032
R_1 [$I > 2\sigma(I)$]	0.070	0.070	0.079	0.058
wR_2	0.245	0.137	0.189	0.111

Formula weight
Goodness-of-fit on F^2

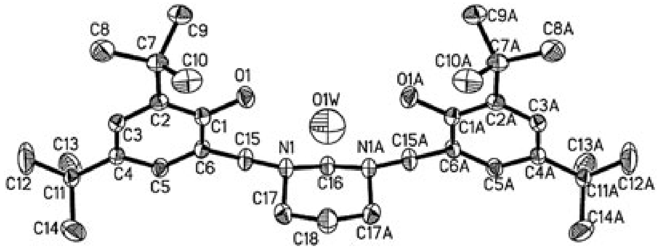


Figure 3. ORTEP view of molecular structure of ligand **1**.

General Procedure for the Homocoupling of Arylboronic Acids

Appropriate amounts of ligand and metal precursor and 3.0 ml solvent were placed in a two-necked round-bottom flask with a magnetic stir bar at 0 °C. After stirring for 5 min, arylboronic acids (2.0 mmol) and base (2.0 mmol) were added to the flask. The reaction mixture was stirred under nitrogen or air atmosphere at ice-water temperature then at room temperature. The course of the reaction was monitored by GC-MS analysis and yields were calculated against *n*-dodecane. The solvent was removed under reduced pressure after the reaction was completed. The pure products were obtained through a short column chromatography using petroleum ether as eluent from any arylboronic acid. The organic solvent was evaporated under reduced pressure. Products were characterized by comparison of ^{1}H NMR spectroscopic data with those in the literature:

(1) biphenyl (Table 3, entry 1, Table 5, entry 7)[47]
(2) 4,4′-dichlorobiphenyl (Table 3, entry 2)[15]
(3) 4,4′-difluorobiphenyl (Table 3, entry 3)[16]
(4) 4,4′-dicyanobiphenyl (Table 3, entry 4)[16]
(5) 4,4′-dinitrobiphenyl (Table 3, entry 5)[16]
(6) 4,4′-dimethylbiphenyl (Table 3, entry 6)[12]
(7) 9,9′-biphenanthrene (Table 3, entry 8)[16]
(8) 3,3′-bipyridine (Table 3, entry 8)[16]
(9) 2,2′-bithiophene (Table 3, entry 9)[52]
(10) 4,4′-dimethoxybiphenyl (Table 3, entry 10)[52]

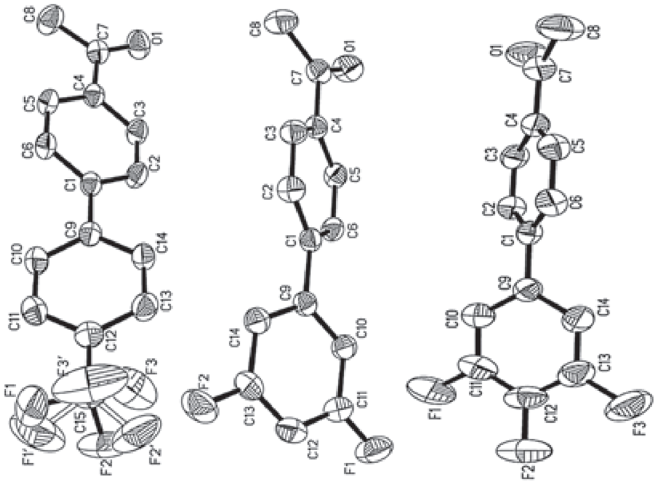
General Procedure for the Suzuki Reaction

The appropriate amounts of ligand **1** and metal precursor were added to the required solvent (3.0 ml). The mixture was stirred for 5 min, then the aryl halide (0.5 mmol), phenylboronic acid (0.75 mmol) and base (1.0 mmol) were added, and the mixture was stirred under air. The course of the reaction was monitored by GC-MS analysis, and yields were calculated against the aryl halides. On completion of the reaction, the solvent was removed under reduced pressure. The residue was dissolved with H_2O (3.0 ml) and Et_2O (3.0 ml), followed by extraction with Et_2O (2 × 3.0 ml). The organic fraction was dried over anhydrous $MgSO_4$, then filtered, and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography using 200-300 mesh silica gel and the purified products were characterized by comparing their NMR spectra (^{1}H or ^{1}H, ^{13}C or ^{1}H, ^{13}C and heteronuclear single quantum coherence (HSQC) with those found in the literature:

(1) 4-methyl-1,1′-biphenyl (Table 5, entries 1, 2 and 8)[43]
(2) 4-cyano-1,1′-biphenyl (Table 5, entry 3)[53]
(3) 4-methoxy-1,1′-biphenyl (Table 5, entry 4)[54]
(4) 4-acetyl-1,1′-biphenyl (Table 5, entry 5)[43]
(5) 2-methyl-1,1′-biphenyl (Table 5, entry 6)[55]
(6) 4-trifluoromethyl-1,1′-biphenyl (Table 5, entry 9)[47]
(7) 2-methoxy-1,1′-biphenyl (Table 5, entry 10)[56]
(8) 4-acetyl-3′,4′,5′-trifluoro-1,1′-biphenyl (Table 5, entry 11)[55]
(9) 4-acetyl-3′,5′-difluoro-1,1′-biphenyl (Table 5, entry 12)[56]
(10) 4-acetyl-4′-trifluoromethyl-1,1′-biphenyl (Table 5, entry 13)[57]

Results and Discussion

The colorless crystals of **1**, suitable for X-ray diffraction analysis, were grown by the slow evaporation of methanol at room temperature. A perspective view of the molecular structure of compound **1** with atom numbering scheme is shown in Fig. 3. In the asymmetric unit of **1**, there is only half a ligand molecule. The C16 and C18 atoms reside on a mirror plane with half a population so that another symmetry-related half is generated. In the molecular structure of **1** the amine bridge moiety possesses a stable chair conformation. The chair conformation of **1** was due to the weak hydrogen bonding between the tertiary nitrogen atom and hydrogen atom of the phenoxy groups; the bond distance of H1O-N is 1.888(4) Å. The C-N bond distances of **1** are 1.473(3) Å (N-C15), 1.451(2) Å (N-C16) and 1.465(4) Å (N-C17), whereas the bond length of



4 **5** **6**

Figure 4. ORTEP view of unsymmetrical fluorine-substituted biaryl derivative.

Table 2. Investigation of homocoupling reaction of phenylboronic acid conditions[a]

Entry	Pd	Pd/**L**	Base	Solvent	Conditions	Time (h)	Yield (%)[b]
1	$PdCl_2$	Pd/**1** = 1	K_2CO_3	Acetone/H_2O (3/1)	N_2	2	96
2	$PdCl_2$	Pd/**1** = 1	Na_2CO_3	Acetone/H_2O (3/1)	N_2	3	95
3	$PdCl_2$	Pd/**1** = 1	NaOH	Acetone/H_2O (3/1)	N_2	3	65
4	$PdCl_2$	Pd/**1** = 1	Cs_2CO_3	Acetone/H_2O (3/1)	N_2	2	98
5	$PdCl_2$	Pd/**1** = 1	KOH	Acetone/H_2O (3/1)	N_2	3	96
6	$PdCl_2$	Pd/**1** = 1	$NaHCO_3$	Acetone/H_2O (3/1)	N_2	24	75
7	$PdCl_2$	Pd/**1** = 1	NaOAc	Acetone/H_2O (3/1)	N_2	24	32
8	$PdCl_2$	Pd/**1** = 1	K_2CO_3	Acetone/H_2O (3/1)	Air	24	55
9	$PdCl_2$	Pd/**1** = 1	K_2CO_3	Acetone	Air	3	75
10	$PdCl_2$	Pd/**1** = 1	None	Acetone/H_2O (3/1)	Air	3	50
11	$PdCl_2$	Pd/**1** = 1	K_2CO_3	Ethanol	N_2	3	98
12	$PdCl_2$	Pd/**1** = 1	K_2CO_3	Ethanol (95%)	N_2	3	98
13	$PdCl_2$	Pd/**1** = 1	K_2CO_3	Methanol	N_2	1	98
14	$PdCl_2$	Pd/**1** = 1	K_2CO_3	Water	N_2	1	98
15	$PdCl_2$	Pd/**1** = 1	K_2CO_3	Toluene	N_2	1	67
16	$PdCl_2$	Pd/**1** = 1	K_2CO_3	Acetone/H_2O (1/1)	N_2	3	99
17	$PdCl_2$	Pd/**1** = 1	K_2CO_3	Acetone/H_2O (3/1)	N_2	1	99
18	$Pd(OAc)_2$	Pd/**1** = 1	K_2CO_3	H_2O	N_2	0.25	99
19	$Pd(CF_3COO)_2$	Pd/**1** = 1	K_2CO_3	H_2O	N_2	0.5	99
20	$Pd(PPh_3)_4$	-	K_2CO_3	H_2O	N_2	0.25	99
21	$Pd_2(dba)_3$	Pd/**1** = 1	K_2CO_3	H_2O	N_2	0.5	99
22	$Pd(OAc)_2$	Pd/**1** = 2	K_2CO_3	H_2O	N_2	0.25	90
23	$Pd(OAc)_2$	Pd/**1** = 1.5	K_2CO_3	H_2O	N_2	0.25	98
24	$Pd(OAc)_2$	Pd/**1** = 1:2	K_2CO_3	H_2O	N_2	0.25	90
25	$Pd(OAc)_2$	Pd/**1** = 1:3	K_2CO_3	H_2O	N_2	0.25	80
26	$Pd(OAc)_2$	Pd/**1** = 1	K_2CO_3	H_2O	Air	0.25	99
27	$Pd(OAc)_2$	Pd/**1** = 1	none	H_2O	Air	3	53
28	$Pd(OAc)_2$	Pd/**1** = 1	K_2CO_3	H_2O	Air	0.25	99[c]
29	$Pd(OAc)_2$	Pd/**1** = 1	K_2CO_3	H_2O	Air	0.25	99[d]
30	$Pd(OAc)_2$	Pd/**1** = 1	K_2CO_3	H_2O	Air	3	90[e]
31	None	Pd/**1** = 1	K_2CO_3	H_2O	Air	24	Trace
32	$Pd(OAc)_2$	Pd/**1** = 1	K_2CO_3	H_2O	Air	1	71[f]
33	$Pd(OAc)_2$	Pd/**1** = 1	K_2CO_3	H_2O	Air	3	Trace[g]
34	$Pd(OAc)_2$	Pd/**2** = 1	K_2CO_3	H_2O	Air	3	96
35	$Pd(OAc)_2$	Pd/**3** = 1	K_2CO_3	H_2O	Air	3	95
36	$Pd(OAc)_2$	No ligand	K_2CO_3	H_2O	Air	24	55

[a] Reaction conditions: phenylboronic acid (2.0 mmol), base (2.0 mmol), solvent (3.0 ml), catalyst Pd/**1** = 1:1 (0.5 mol%), 0–25 °C, TsCl (0.5 mmol).
[b] Determined by GC-MS; average of two runs.
[c] Catalyst 0.1 mol%;
[d] Catalyst 0.05 mol%;
[e] Catalyst 0.01 mol%; [f] TsCl (0.3 mmol);
[g] Catalyst TsCl (0 mmol).

C1-O1 is 1.374(4) Å, which is slightly longer compared with the piperazine moiety.[43] The bond angles around the nitrogen atom vary from 110.15(1)° (C16-N-C17) to 110.95(1)° (C15-N-C16). The bond angle around C15-N-C17 is 112.33(2)°, which is slightly larger compared with the literature value.[43]

Three unsymmetrical fluorine-substituted biaryl derivatives (Fig. 4, compounds **4**, **5** and **6**) all gave yellow crystals by the slow evaporation of dichloromethane and petroleum ether mixture at room temperature. Further, their molecular structures were confirmed by single-crystal X-ray diffraction study in addition to ^{1}H, ^{13}C and HSQC spectra. A perspective view of these single crystals with atom numbering scheme is shown in Fig. 4.

As fluorine is a small, highly polar and almost non-polarizable atom, it is more accurate at close interatomic distances ri and also the charge on the substituent atom (e.g. F) will vary depending on the chemical environment of the substituent as opposed to a fixed C-F dipole. In particular the charge on a fluorine atom decreases in the order $CH_2F > CHF_2 > CF_3$; thus the electric field contribution will decrease in this order also. Their C1-C9 bond distances are 1.490(2) Å (**4**), 1.490(2) Å (**5**) and 1.479(2) Å (**6**) respectively, whereas the bond length of compound **6** is slightly longer compared with the others. The C-F bond lengths for these compounds were 1.288(4) Å (**4**, C15-F1), 1.271(6) Å (**4**, C15-F2), 1.245(6) Å (**4**, C15-F3), 1.311 (2) Å (**5**, C11-F1), 1.312(2) Å (**5**, C11-F2), 1.351(3) Å (**6**, C11-F1), 1.360(2) Å (**6**, C11-F2), 1.351(3) Å (**6**, C11-F3), which were slightly less than the experimental values (cf. fluoroethane 1.372 vs. 1.397 Å).[58] The bond angle around C6-C1-C2 is 117.45(1)°, 121.25(2)°, 120.57(2)°, and the bond angle around C6-C1-C9 is 121.23(1)°, 120.79(2)°, 121.40(2)° respectively. More details of the crystallographic data are given in the X-ray crystallographic files in CIF format (supporting information).

One area of research interest has been in the use of water and aqueous solution as a solvent for many organic reactions over the past decade.[31,59] The homocoupling of phenylboronic acid in the presence of catalyst ($PdCl_2$/**1**) was studied to identify suitable bases and solvents. In acetone/water solvent, the bases K_2CO_3, Cs_2CO_3, KOH, and Na_2CO_3 were found to be the best (Table 2, entries 1, 2, 4 and 5). The synthesis of unsymmetrical diaryl sulfones using the $PdCl_2$-catalyzed coupling of aryl boronic acids with TsCl has been developed by Bandgar,[60] herein, just the product of homocoupling of phenylboronic acid was found. A considerable improvement in the yield was obtained when the reaction was carried out in protic solvents. The solvents methanol, ethanol, ethanol (95%) and water were found to be suitable (Table 2, entries 11–17). We found that neat water can promote the reaction, and resulted in excellent yield (Table 2, entry 14). When attempts were made to carry out reactions in the absence of nitrogen atmosphere, the homocoupling reactions proceeded smoothly. The reaction mixture maintained a yellow under anaerobic or aerobic conditions.

Only trace products were detected by GC-MS in air without TsCl (Table 2, entry 33); our results showed that a relatively strong oxidizing agent was essential for this homocoupling reaction, even in the presence of oxygen. Unlike the traditional protocols during our experiments, a single product was obtained by running the reaction directly in air or nitrogen under ice/water, then at room temperature with the aid of TsCl. In this way, we can further verify the developed mechanism of this reaction.[13–15]

Several palladium sources were tested, and the best results were obtained for $Pd(OAc)_2$ (Table 2, entries 14, 18–21); when $Pd(PPh_3)_4$ was used as catalyst without addition of any other ligands, the catalytic activity was similar to $Pd(OAc)_2$/**1** (Table 2, entry 20).

The catalytic activity of the $Pd(OAc)_2$ was investigated with respect to loadings. After many studies on the homocoupling reaction, we found that the best Pd/**L** molar ratio was 1:1 (Table 2, entries 22–35), and when less than 0.05 mol% $Pd(OAc)_2$ was applied, this resulted in slower speed or lower yield (Table 2, entries 28–30).

To evaluate the scope and limitations of this procedure, the reactions of a wide variety of arylboronic acids were examined in the presence of 0.05 mol% Pd/**L** (**L** = **1**, **2** or **3**) under optimal conditions in neat water (Table 3). Arylboronic acids with either electron-withdrawing or electron-donating substituents all gave excellent yields (86–99%). The homocoupling of heteroarylboronic acids (3-pypridylboronic acid, 2-thienylboronic acid) gave corresponding products in good isolated yields (88–92%) (Table 3, entries 8 and 9). In concluded, the homocoupling reaction of aryl boronic acids can accelerate by Pd/**L** system with the aid of a catalytic amount of TsCl in neat water under anaerobic or aerobic conditions. The present procedure involved mild reaction conditions within just 15 min compared with Zhang (0.5–3.0 mol% Pd)[14] or Smith (5.0 mol % Pd),[8] who obtained only moderate yields, even when prolonging the reaction time to 24 h.

The effectiveness of ligand **1** observed in the homocoupling of arylboronic acids encouraged us to study its catalytic activity in the Suzuki reaction. The reaction parameters were investigated in detail, as illustrated in Table 4. Ligand **1** is capable of catalyzing the coupling of 4-bromotoluene with phenylboronic acids to form unsymmetrical biaryl products in excellent yields in acetone aqueous (acetone/water = 1/1) under air within just 1 h (0.1 mol% Pd/**1**). Investigation of reaction temperature revealed that room temperature (r.t.) was not an efficient temperature (Table 4, entries 1–5), and the reaction can proceed smoothly under reflux. A similar study was undertaken to determine whether solvent polarity played a significant role in the reaction outcome

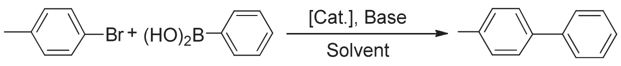
Table 3. Pd-catalyzed homocoupling of various arylboronic acids[a]

$$2\ \mathrm{Ar{-}B(OH)_2} \xrightarrow[\mathrm{TsCl, H_2O,\ K_2CO_3,\ air,\ r.t.}]{\mathrm{0.05\ mol\%,\ Pd(AcO)_2/\mathbf{1\text{-}3}}} \mathrm{Ar{-}Ar}$$

Entry	Product	Yield (%)[b]		
		L1	**L2**	**L3**
1	Ph–Ph	99	93	93
2	*p*-Cl–Ph–Ph–Cl-*p*	94	95	92
3	*p*-F–Ph–Ph–F-*p*	95	93	92
4	*p*-CN–Ph–Ph–CN-*p*	90	88	90
5	*p*-NO_2–Ph–Ph–NO_2-*p*	97	96	95
6	*p*-Me–Ph–Ph–Me-*p*	96	94	90
7	9,9′-Biphenanthrene	90	87	86
8	3,3′-Bipyridine	91	89	90
9	2,2′-Bithiophene	92	90	88
10	*p*-MeO–Ph–Ph–OMe-*p*	98	96	94

[a] Reaction conditions: arylboronic acids (1.0 mmol), K_2CO_3 (2.0 mmol), water (3.0 ml), catalyst $Pd(OAc)_2$/**L** = 1:1 (0.05 mol%), TsCl (0.5 mmol), r.t., 15 min.
[b] Isolated yields.

Table 4. Investigation of Suzuki reaction of 4-bromotoluene and phenylboronic acid[a]



Entry	Pd source	Base	Solvent	Conditions	Time (h)	Yield (%)[b]
1	$Pd(OAc)_2$	K_2CO_3	Ethanol	r.t. N_2	1	40
2	$Pd(OAc)_2$	K_2CO_3	Methanol	r.t. N_2	1	40
3	$Pd(OAc)_2$	K_2CO_3	Water	r.t. air	24	40
4	$Pd(OAc)_2$	K_2CO_3	Acetone	r.t. air	3	Trace
5	$Pd(OAc)_2$	K_2CO_3	Toluene	r.t. air	3	65
6	$Pd(OAc)_2$	K_2CO_3	Methanol	Reflux air	1	90
7	$Pd(OAc)_2$	K_2CO_3	Toluene	Reflux air	1	85
8	$Pd(OAc)_2$	K_2CO_3	Acetone	Reflux air	1	80
9	$Pd(OAc)_2$	K_2CO_3	Water	Reflux air	2	85
10	$Pd(OAc)_2$	K_2CO_3	Acetone/water (1/3)	Reflux air	1	93
11	$Pd(OAc)_2$	K_2CO_3	Acetone/water (3/1)	Reflux air	1	55
12	$Pd(OAc)_2$	K_2CO_3	Acetone/water (1/1)	Reflux air	1	99
13	$Pd(OAc)_2$	NaOH	Acetone/water (1/1)	Reflux air	1	70
14	$Pd(OAc)_2$	KOH	Acetone/water (1/1)	Reflux air	1	85
15	$Pd(OAc)_2$	Cs_2CO_3,	Acetone/water (1/1)	Reflux air	1	97
16	$Pd(OAc)_2$	$NaHCO_3$	Acetone/water (1/1)	Reflux air	1	70
17	$Pd(OAc)_2$	Na_2CO_3	Acetone/water (1/1)	Reflux air	1	95
18	$Pd(OAc)_2$	K_3PO_4	Acetone/water (1/1)	Reflux air	1	96
19	$Pd(OAc)_2$	TMEDA	Acetone/water (1/1)	Reflux air	1	Trace
20	$Pd(OAc)_2$	TEA	Acetone/water (1/1)	Reflux air	1	42
21	$Pd(OAc)_2$	None	Acetone/water (1/1)	Reflux air	1	Trace
22	$PdCl_2$	K_2CO_3	Acetone/water (1/1)	Reflux air	3	97
23	$Pd(CF_3COO)_2$	K_2CO_3	Acetone/water (1/1)	Reflux air	3	95
24	$Pd(PPh_3)_4$	K_2CO_3	Acetone/water (1/1)	Reflux air	1	85[c]
25	$Pd_2(dba)_3$	K_2CO_3	Acetone/water (1/1)	Reflux air	3	99
26	$Pd(COD)Cl_2$	K_2CO_3	Acetone/water (1/1)	Reflux air	1	96
27	None	K_2CO_3	Acetone/water (1/1)	Reflux air	24	Trace
28	$Pd(OAc)_2$	K_2CO_3	Acetone/water (1/1)	Reflux air	1	85[d]
29	$Pd(OAc)_2$	K_2CO_3	Acetone/water (1/1)	Reflux air	1	95[e]
30	$Pd(OAc)_2$	K_2CO_3	Acetone/water (1/1)	Reflux air	1	60[f]
31	$Pd(OAc)_2$	K_2CO_3	Acetone/water (1/1)	Reflux air	1	70[g]
32	$Pd(OAc)_2$	K_2CO_3	Acetone/water (1/1)	Reflux air	1	75[h]
33	$Pd(OAc)_2$	K_2CO_3	Acetone/water (1/1)	Reflux air	1	45[i]

[a] Reaction conditions: 4-bromotoluene (1.0 mmol), phenylboronic acid (1.25 mmol), base (2.0 mmol), solvent (3.0 ml), catalyst Pd/**1** = 1:1 (0.1 mol%).
[b] Determined by GC-MS.
[c] $Pd(PPh_3)_4$ (0.1 mol%).
[d] Pd/**1** = 1:3; [e] Pd/**1** = 1:2; [f] Pd/**1** = 1:1.5; [g] Pd/**1** = 1:0.5.
[h] Catalyst 0.05 mol%.
[i] Without ligand.

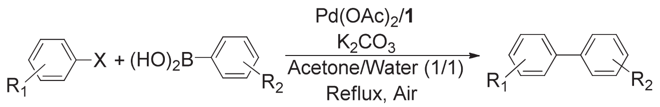
(Table 4, entries 1–12). We were pleased to observe that the reaction could be efficiently conducted in a number of solvents, and acetone/water (v/v = 1/1) was chosen as the best solvent.

Without the use of base as additive, only trace amount of product was obtained (Table 4, entry 21). Therefore, a range of bases including Cs_2CO_3, K_2CO_3, K_3PO_4, KOH, Na_2CO_3, NaOH and $NaHCO_3$ were screened (Table 4, entries 12–18); K_2CO_3 was found to be the most suitable and gave the desired product in 99% yield. The use of organic bases such as tetramethylethylenediamine (TMEDA) and triethylamine led to much decreased yields, and only trace and 42% yields were obtained, respectively (Table 4, entries 19 and 20).

Next, we examined the range of catalysts that could be employed by evaluating different palladium sources as well as ligand stoichiometry (Table 4, entries 22–26 and 28–30). Rewardingly, only a minor difference was observed when comparing reference conditions (Table 4, entry 12); the catalytic activity of Pd/**1** was higher than commercially available palladium catalyst $Pd(PPh_3)_4$.

Maintaining the same Pd/**L** ratio but decreasing $Pd(OAc)_2$ loading to 0.05 mol% was less effective, providing lower conversion within 1 h (Table 4, entry 32). Interestingly, maintaining the same Pd loading but increasing the ligand **1** level to 0.12–0.3 mol%, as described in an earlier report, led to lower conversion within the same reaction time (Table 4, entries 28–30). Higher concentration

Table 5. Suzuki reactions of various aryl halides with arylboronic acids[a]



Entry	Aryl halides	Product	Time (h)	Yield (%)[b]
1	*p*-Me–Ph–I	*p*-Me–Ph–Ph	0.5	99
2	*p*-Me–Ph–Br	*p*-Me–Ph–Ph	1	99
3	*p*-MeO–Ph–Br	*p*-MeO–Ph–Ph	3	99
4	*p*-CN–Ph–Br	*p*-CN–Ph–Ph	3	98
5	*p*-MeCO–Ph–Br	*p*-MeCO–Ph–Ph	3	99
6	*o*-Me–Ph–Br	*o*-Me–Ph–Ph	3	92
7	Ph–Br	Ph–Ph	1	99
8	*o*-MeO–Ph–Br	*o*-MeO–Ph–Ph	3	95
9	*p*-CF$_3$–Ph–Cl	*p*-CF$_3$–Ph–Ph	12	96
10	*p*-Me-Ph-Cl	*p*-Me–Ph–Ph	24	60[c]
11	*p*-MeCO–Ph–Br	*p*-MeCO–Ph–Ph–3F-*m,m′,p*	1	98
12	*p*-MeCO–Ph–Br	*p*-MeCO–Ph–Ph–2F-*m,m′*	1	96
13	*p*-MeCO–Ph–Br	*p*-MeCO–Ph–Ph–CF$_3$-*p*	1	98

[a] Reaction conditions: aryl halide (1.0 mmol), arylboronic acid (1.25 mmol), K$_2$CO$_3$ (1.0 mmol), acetone/water (v/v = 1/1, 3.0 ml), Pd(OAc)$_2$/**1** (0.1 mol %), reflux, in air.

[b] Isolated yields.

[c] 0.75 mmol TBAB.

of ligand **1** appears to either retard decomposition of the catalyst or provide a less reactive coordinate complex. Decreasing the ligand **1** level to 0.05 mol% also afforded lower conversion (Table 4, entry 31).

In order to assess the scope of the aryl halide coupling partner, we undertook a systematic study employing several arylboronic acids to evaluate coupling with various aryl halides (Table 5). Iodides, bromides, as well as activated chlorides were all found to give the desired product in excellent yields (Table 5, entries 1–9). The reaction was tolerant to substituents present on the aryl ring, affording the desired product in good to excellent yields.

Conclusions

A highly efficient green protocol for Pd-catalyzed aqueous C-C coupling reaction under mild conditions has been developed. In the homocoupling of arylboronic acid, Pd/**1** was higher efficient, with a catalytic amount of TsCl in neat water under anaerobic or aerobic conditions. The same catalytic system was more efficient for Suzuki–Miyaura reaction in aqueous acetone under air compared with Pd/**2** and Pd/**3** in the absence of TsCl. In conclusion, the steric hindrance of amine-bridged bis(phenol) ligands plays a role in the coupling reaction.

Supporting information

Supporting information may be found in the online version of this article.

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