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Water-soluble palladacycles containing hydroxymethyl groups: synthesis, crystal structures and use as catalysts for amination and Suzuki coupling of reactions

Xin Han[1] · Hong-Mei Li[2] · Chen Xu[2,3] · Zhi-Qiang Xiao[1] · Zhi-Qiang Wang[2] · Wei-Jun Fu[2] · Xin-Qi Hao[1] · Mao-Ping Song[1]

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Abstract Two water-soluble monophosphine [PPh_3 and 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl(Sphos)]-palladacycles containing hydroxymethyl groups **2**–**3** were prepared by cyclopalladation and chloride bridge-splitting reactions. The complexes were characterized by elemental analysis, ESI–MS and NMR. In addition, single-crystal X-ray analysis reveals that they have one-dimensional lamellar structures involving intermolecular hydrogen bonds and π–π interactions. The use of these palladacycles as catalysts for amination and Suzuki coupling of aryl chlorides in water was investigated. Complex **3** was found to be very efficient for these coupling reactions. Additionally, it was also successfully used in Suzuki coupling of (hydroxymethyl)phenylboronic acid for the synthesis of substituted 2-*N*-heterocyclic biarylmethanols.

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✉ Chen Xu
xubohan@163.com

✉ Xin-Qi Hao
xqhao@zzu.edu.cn

[1] College of Chemistry and Molecular Engineering, Zhengzhou University, Zhengzhou 450052, Henan, China

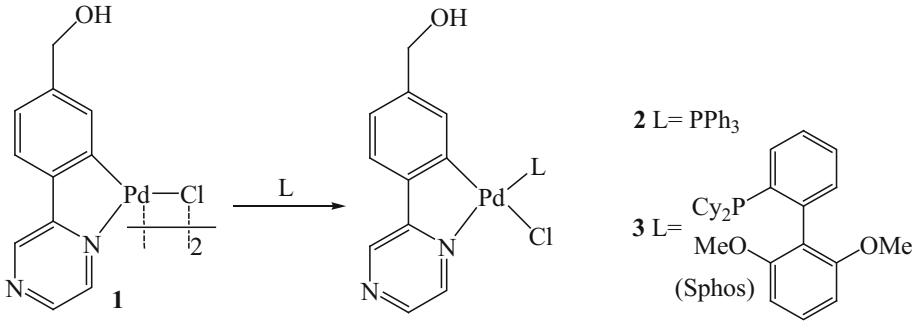
[2] College of Chemistry and Chemical Engineering, Luoyang Normal University, Luoyang 471022, Henan, China

[3] College of Food and Pharmacy, Luoyang Normal University, Luoyang 471022, Henan, China

Introduction

Palladium-catalyzed coupling reactions such as aminations and Suzuki couplings have become extremely powerful methods in organic synthesis for the formation of C–N or C–C bonds [1–3]. Among various Pd catalysts, palladacycles are one of the most efficient precatalysts for these coupling reactions [4, 5]. Key to the success of such couplings is the efficient generation of the active $Pd(0)L_n$ species (L = ligand) which participates in the catalytic cycle [6, 7]. Many such systems have been reported, including both phosphine and *N*-heterocyclic carbene (NHC)–palladacycles [4, 8, 9]. Recent progress in this field is focused on the use of water as a green solvent and on the use of the inexpensive and readily accessible aryl chlorides as starting materials. There are only a few examples of palladacycles containing water-soluble groups such as –OH or $–SO_3H$ being used in coupling reactions; furthermore, the coupling of aryl chlorides in water has been little reported [10–14].

In recent years, part of our research effort has focused on the synthesis and application of palladacycles [15, 16]. Generally, phosphine or NHC–palladacycles are far more active than the corresponding dimeric palladacycles. We have also developed palladacycle-catalyzed Suzuki reaction of aryl halides for the synthesis of substituted biarylmethanols in water [17, 18]. However, substrates are limited to aryl bromides and chlorides containing water-soluble hydroxymethyl groups. As a continuation of our interest in palladacycle-catalyzed coupling reactions, we prepared two water-soluble monophosphine-cyclopalladated arylpyrazine complexes **2** and **3** (Scheme 1) and examined their catalytic activities in water. Here, we report that complex **3** is an effective catalyst for amination and Suzuki coupling of aryl chlorides in water.



Scheme 1 Synthesis of complexes **2** and **3**

Experimental

All chemicals were commercially available expect for 4-(2-pyrazinyl)phenylmethanol [19] and its palladacyclic dimer **1** [20] which were prepared according to the published procedures. Elemental analyses were determined with a Carlo Erba 1160 Elemental Analyzer. Mass spectra were measured on an LC-MSD-Trap-XCT instrument. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX-400 spectrometer (400 and 100 MHz, respectively) in $CDCl_3$ with TMS as an internal standard.

Synthesis of complexes 2 and 3

A solution of dimer **1** (0.1 mmol) and PPh_3 or Sphos (0.2 mmol) in acetone (10 mL) was stirred at room temperature for 30 min. The product was separated by passing through a short silica gel column with CH_2Cl_2 as eluent. Complex **2**: Yield 82 %. Anal. Calcd. for $C_{29}H_{24}ClN_2OPPd$: C, 59.1; H, 4.1; N, 4.8. Found: C, 59.5; H, 3.8; N, 5.0 %. MS–ESI$^+$ [*m/z*]: 553.1 $(M–Cl)^+$. ^{1}H NMR (400 MHz, $CDCl_3$): ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.27 (s, 1H), 8.89 (d, $J = 1.6$ Hz, 1H), 8.65 (d, $J = 1.6$ Hz, 1H), 8.12 (d, $J = 8.0$ Hz, 1H), 7.73–7.80 (m, 8H), 7.39–7.43 (m, 9H), 4.81 (s, 2H), 2.13 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.3, 141.2, 139.1, 138.4, 134.7, 132.5, 131.8, 130.3, 130.7, 128.9, 123.6, 119.1, 104.4, 103.2, 65.1. Complex **3**: Yield 90 %. Anal. Calcd. for $C_{37}H_{44}ClN_2O_3PPd$: C, 60.3; H, 6.0; N, 3.8. Found: C, 60.6; H, 5.8; N, 4.1 %. MS–ESI$^+$ [*m/z*]: 701.2 $(M–Cl)^+$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.32 (s, 1H), 8.91 (d, $J = 1.6$ Hz, 1H), 8.69 (d, $J = 1.6$ Hz, 1H), 8.14 (d, $J = 8.0$ Hz, 1H), 7.85 (m, 1H), 7.79 (s, 1H), 7.19–7.25 (m, 3H), 6.53–6.68 (m, 4H), 4.83 (s, 2H), 3.46 (s, 6H), 2.72 (m, 2H), 1.36–1.69 (m, 20H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.2, 158.6, 146.5, 145.4, 143.7, 141.8, 139.4, 139.2, 135.9, 135.7, 134.7, 132.1, 131.3, 129.5, 129.1, 125.3, 124.1, 119.5, 109.7, 109.5, 104.6, 103.6, 65.3, 55.2, 32.5, 29.1, 27.8, 26.6.

General procedure for Buchwald–Hartwig amination

In a Schlenk tube, a mixture of the required amount of catalyst, plus the aryl chloride (1.0 mmol), amine (1.2 mmol), KOH (3.0 mmol) and ^{t}BuOH (4 mmol) in water (3.0 mL) was evacuated and charged with nitrogen. The reaction mixture was then heated at 100 °C for 12 h. After cooling, the mixture was extracted three times with CH_2Cl_2. The combined organic layers were washed with water, dried and evaporated to dryness. The products were isolated by flash chromatography on silica gel using a mixture of CH_2Cl_2/ethyl acetate (5/1) as eluent and characterized by comparison of data with those in the literature [15, 21].

General procedure for Suzuki coupling

In a Schlenk tube, a mixture of the required amount of catalyst, plus the aryl chloride (1.0 mmol), aryl boronic acid (1.5 mmol) and the selected base (2.0 mmol) in water was evacuated and charged with nitrogen. The reaction mixture was heated at 100 °C for 12 h. After cooling, the mixture was extracted with CH_2Cl_2 and the extract was evaporated. The resulting residue was purified by flash chromatography on silica gel using a mixture of CH_2Cl_2/ethyl acetate (5/1) as eluent. The known products **5**, **6a** [17, 18], **6b** [22], **6c** [23], **6e** [24], **6g** [19], **6h** [25] and **7a** [26] were characterized by comparison of data with those in the literature. The products **6d**, **6f** and **7b–h** were new compounds and characterized by elemental analysis, MS, ^{1}H and ^{13}C NMR.

4-(6-Methoxy-2-pyridinyl)phenylmethanol **6d**. Anal. Calcd. for $C_{13}H_{13}NO_2$: C, 72.5; H, 6.1; N, 6.5. Found: C, 72.9; H, 5.8; N, 6.7 %. MS–ESI$^+$ [*m/z*]: 216.1 $(M + H)^+$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, $J = 6.4$ Hz, 2H), 7.65 (t, $J = 6.0$ Hz, 1H), 7.47 (d, $J = 6.0$ Hz, 2H), 7.36 (d, $J = 6.0$ Hz, 1H), 6.72 (d, $J = 6.4$ Hz, 1H), 4.77 (s, 2H), 4.06 (s, 3H), 1.88 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$):

163.7, 154.3, 141.5, 139.2, 138.5, 127.2, 126.9, 112.8, 109.3, 65.1, 53.3.

4-(5-Acetyl-2-pyridinyl)phenylmethanol **6f**. Anal. Calcd. for $C_{14}H_{13}NO_2$: C, 74.0; H, 5.8; N, 6.2. Found: C, 74.3; H, 5.5; N, 6.6 %. MS–ESI$^+$ [*m/z*]: 228.1 $(M + H)^+$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.22 (d, $J = 1.2$ Hz, 1H), 8.30 (d, $J = 6.4$ Hz, 1H), 8.05 (d, $J = 6.4$ Hz, 2H), 7.85 (d, $J = 6.8$ Hz, 1H), 7.50 (d, $J = 6.4$ Hz, 2H), 4.79 (s, 2H), 2.68 (s, 3H), 2.29 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 196.6, 160.7, 150.1, 143.1, 137.3, 136.5, 130.6, 127.6, 127.3, 120.2, 64.8, 26.8.

2-(5-Methyl-2-pyridinyl)phenylmethanol **7b**. Anal. Calcd. for $C_{13}H_{13}NO$: C, 78.4; H, 6.6; N, 7.0. Found: C, 78.8; H, 6.3; N, 7.2 %. MS–ESI$^+$ [*m/z*]: 200.1 $(M + H)^+$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.48 (s, 1H), 7.66 (d, $J = 6.0$ Hz, 1H), 7.42–7.53 (m, 5H), 6.52 (br, 1H), 4.48 (s, 2H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 156.4, 148.4, 140.3, 139.9, 138.2, 131.9, 131.1, 129.9, 128.1, 123.7, 121.7, 64.7, 18.2.

2-(6-Methyl-2-pyridinyl)phenylmethanol **7c**. Anal. Calcd. for $C_{13}H_{13}NO$: C, 78.4; H, 6.6; N, 7.0. Found: C, 78.7; H, 6.2; N, 7.3 %. MS–ESI$^+$ [*m/z*]: 200.1 $(M + H)^+$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (t, $J = 6.0$ Hz, 1H), 7.55–7.59 (m, 1H), 7.51–7.54 (m, 1H), 7.44–7.49 (m, 3H), 7.21 (d, $J = 6.4$ Hz, 1H), 6.64 (br, 1H), 4.49 (s, 2H), 2.65 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 158.6, 157.0, 140.4, 140.2, 137.7, 131.1, 130.1, 129.2, 128.1, 121.9, 120.8, 64.7, 24.3.

2-(6-Methoxy-2-pyridinyl)phenylmethanol **7d**. Anal. Calcd. for $C_{13}H_{13}NO_2$: C, 72.5; H, 6.1; N, 6.5. Found: C, 72.8; H, 5.9; N, 6.9 %. MS–ESI$^+$ [*m/z*]: 216.1 $(M + H)^+$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (t, $J = 6.4$ Hz, 1H), 7.50–7.52 (m, 2H), 7.42–7.48 (m, 2H), 7.15 (d, $J = 6.4$ Hz, 1H), 6.81 (d, $J = 8.4$ Hz, 1H), 5.44 (br, 1H), 4.55 (s, 2H), 4.00 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 163.3, 157.4, 139.9, 139.8, 139.7, 130.6, 130.4, 129.2, 128.2, 117.1, 109.7, 64.5, 53.8.

2-(5-Trifluoromethyl-2-pyridinyl)phenylmethanol **7e**. Anal. Calcd. for $C_{13}H_{10}F_3NO$: C, 61.7; H, 4.0; N, 5.5. Found: C, 61.9; H, 3.7; N, 5.3 %. MS–ESI$^+$ [*m/z*]: 254.1 $(M + H)^+$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.85 (d, $J = 4.0$ Hz, 1H), 7.87 (s, 1H), 7.48–7.58 (m, 5H), 5.66 (br, 1H), 4.50 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 160.6, 149.3, 140.3, 139.5, 139.7, 138.5, 131.5, 130.1, 128.5, 126.9, 123.8, 121.6, 119.6, 117.8, 64.4.

2-(5-Acetyl-2-pyridinyl)phenylmethanol **7f**. Calcd. for $C_{14}H_{13}NO_2$: C, 74.0; H, 5.8; N, 6.2. Found: C, 74.4; H, 5.6; N, 6.5 %. MS–ESI$^+$ [*m/z*]: 228.1 $(M + H)^+$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.21 (d, $J = 1.2$ Hz, 1H), 8.40 (d, $J = 6.4$ Hz, 1H), 7.76 (d, $J = 6.4$ Hz, 1H), 7.59 (d, $J = 6.0$ Hz, 1H), 7.53 (d, $J = 6.0$ Hz, 1H), 7.43–7.51 (m, 2H), 5.90 (br, 1H), 4.50 (s, 2H), 2.71 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 196.0, 162.9, 148.6, 140.5, 138.8, 137.0, 131.5, 130.6, 130.3, 130.2, 128.4, 123.8, 64.5, 26.8.

2-(2-Pyrazinyl)phenylmethanol **7g**. Anal. Calcd. for $C_{11}H_{10}N_2O$: C, 70.9; H, 5.4; N, 15.0. Found: C, 71.3; H, 5.2; N, 15.3 %. MS–ESI$^+$ [*m/z*]: 187.1 $(M + H)^+$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.97 (d, $J = 1.0$ Hz, 1H), 8.56 (d, $J = 1.0$ Hz, 2H), 7.62 (d, $J = 6.4$ Hz, 1H), 7.56 (d, $J = 6.0$ Hz, 1H), 7.50–7.53 (m, 2H), 5.25 (br, 1H), 4.51 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 154.4, 145.2, 143.2, 142.4, 140.7, 136.3, 131.6, 130.3, 129.7, 128.1, 127.6, 64.3.

2-(2-Pyrimidinyl)phenylmethanol **7h**. Anal. Calcd. for $C_{11}H_{10}N_2O$: C, 70.9; H, 5.4; N, 15.0. Found: C, 71.2; H, 5.1; N, 15.3 %. MS–ESI$^+$ [*m/z*]: 187.1 $(M + H)^+$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.90 (d, $J = 4.0$ Hz, 2H), 8.20–8.23 (m, 1H), 7.50–7.53 (m, 3H), 7.32–7.35 (m, 1H), 5.92 (br, 1H), 4.62 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 156.1, 157.1, 140.7, 137.5, 131.5, 131.3, 130.9, 128.3, 119.0, 64.8.

Crystal structure determination

Crystallographic data for complexes **2** and **3** were collected on an Xcalibur Eos Gemini diffractometer with Cu–Ka radiation ($\lambda = 0.71073$ Å) at ambient temperature. The data were corrected for Lorentz-polarization factors as well as for absorption. Structures were solved by direct methods and refined by full-matrix least-squares methods on F^2 with the SHELXL-97 program [27]. The hydroxymethyl group in **2** was disordered over two positions with occupancies of 0.567(7):0.433(7); it is also refined isotropically. Crystal data, as well as details of data collection and refinements, are summarized in Table 1. The CCDC deposition numbers are 14,44,953 and 14,44,954 for **2** and **3**, respectively. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/datarequest/cif.

Results and discussion

Synthesis and structures of complexes 2 and 3

The water-soluble palladacycles **2** and **3** were easily prepared via the bridge-splitting reactions of dimer **1** with PPh_3 or Sphos (Scheme 1). They were characterized by elemental analysis, MS, ^{1}H and ^{13}C NMR. The NMR spectra of these complexes are consistent with the proposed structures. In the mass spectra of **2**–**3**, the most intense peak was attributed to [M–Cl]. In addition, the structures of both complexes have been determined by X-ray single-crystal diffraction.

Both palladacycles adopt a *trans*-geometry in the solid state. The molecules are shown in Figs. 1 and 2. The Pd

Table 1 Crystallographic data for complexes **2** and **3**

Empirical formula	$C_{29}H_{24}ClN_2OPPd$ **2**	$C_{37}H_{44}ClN_2O_3PPd$ **3**
Fw	589.32	737.56
Crystal system	Triclinic	Monoclinic
Space group	P-1	$P2_1/n$
a (Å)	10.1923(6)	9.5974(4)
b (Å)	10.5975(6)	19.3574(8)
c (Å)	13.6470(7)	18.9165(7)
α (°)	87.800(4)	90
β (°)	68.259(5)	100.308(4)
γ (°)	66.385(6)	90
Volume ($Å^3$)	1244.39(14)	3457.6(2)
Z	2	4
D_c (g/cm^3)	1.573	1.417
GOF	1.037	1.025
F(000)	596.0	1528.0
Reflections	9004	14,404
Independent reflections	4441	7051
Final *R* indices [$I > 2$ sigma(I)]	$R1 = 0.0356$, $wR2 = 0.0928$	$R1 = 0.0428$, $wR2 = 0.0860$
R indices (all data)	$R1 = 0.0418$, $wR2 = 0.0966$	$R1 = 0.0665$, $wR2 = 0.0957$

atom in each complex is in a slightly distorted square-planar environment, being coordinated by a Cl atom, the P atom and the C and N atoms of the arylpyrazine ligand. The Pd–N (2.101(3) Å) and Pd–P (2.2953(9) Å) bond lengths of **3** are similar to those of related Sphos-palladacycles (2.124(3)–2.126(4) Å and 2.2786(9)–2.2848(12) Å) [20, 28, 29], while they are longer than those of the PPh_3-palladacycle **2** (2.091(3) Å and 2.2531(9) Å) possibly due to the steric bulk of the Sphos ligand. The crystal of **2** shows intermolecular C–H···Cl (Cl···H = 2.828 Å) and C–H···N (N···H = 2.711 Å) hydrogen bonds. In addition, there are also intermolecular π–π interactions with ca. 3.813 and 3.676 Å face–face separations, which link the molecules into a 1D lamellar structure (Fig. 3). Like **2**, complex **3** also has a one-dimensional lamellar structure involving different O–H···Cl (Cl···H = 2.390 Å) hydrogen bonds and π–π interactions between the neighboring benzene and pyrazine rings (the interplane distance is 3.669 Å) (Fig. 4). However, no obvious C–H···N hydrogen bonds can be found in **3**.

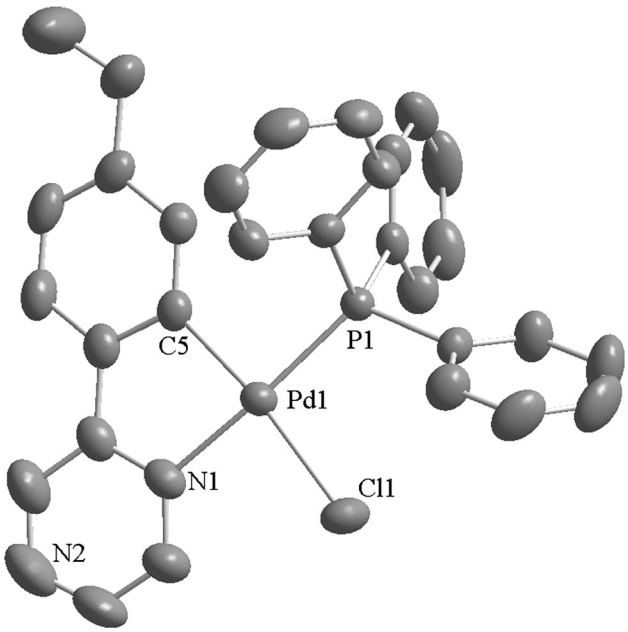


Fig. 1 Molecular structure of complex **2**. H atoms are omitted for clarity. Selected bond lengths (Å) and angles (°) are as follows: Pd(1)–C(5) 2.021(4), Pd(1)–P(1) 2.2531(9), Pd(1)–N(1) 2.091(3), Pd(1)–Cl(1) 2.3690(11), and C(5)–Pd(1)–N(1) 81.10(15), C(5)–Pd(1)–P(1) 94.63(11), N(1)–Pd(1)–Cl(1) 91.11(108), P(1)–Pd(1)–Cl(1) 93.09(4)

Buchwald–Hartwig amination reactions

The palladium-catalyzed coupling of amines with aryl halides, commonly referred to as Buchwald–Hartwig amination [2, 30, 31], is usually carried out in an organic solvent in the presence of a strong base such as ^{t}BuOK. We have found that phosphane–palladacycles are very efficient for the amination of aryl chlorides in water [21]. Considering that complexes **2** and **3** are water-soluble phosphane–palladacycles by virtue of hydroxymethyl groups, we were interested to see whether catalytic activity was observed in amination (Scheme 2). Based on our previous experiments [21], we chose the coupling of *o*-chlorotoluene with *p*-toluidine to evaluate the effectiveness of these palladacycles with a catalytic loading of 0.5 mol% and shortening

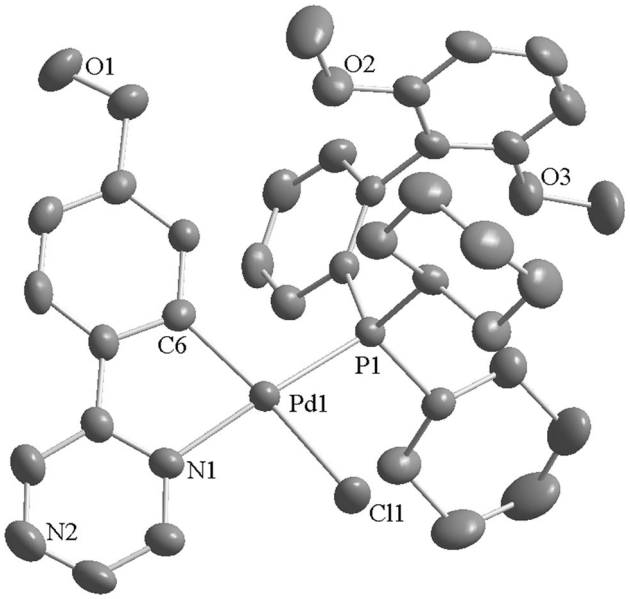


Fig. 2 Molecular structure of complex **3**. H atoms are omitted for clarity. Selected bond lengths (Å) and angles (°): Pd(1)–C(6) 2.024(3), Pd(1)–P(1) 2.2953(9), Pd(1)–N(1) 2.101(3), Pd(1)–Cl(1) 2.3993(9), and C(6)–Pd(1)–N(1) 80.65(11), C(6)–Pd(1)–P(1) 100.36(9), N(1)–Pd(1)–Cl(1) 91.09(7), P(1)–Pd(1)–Cl(1) 89.26(3)

the reaction time from 24 to 12 h. The palladacycle **3** was found to be slightly more active than the related phosphane–palladacycle (yield of **4a** is 87 %) [21], producing the product **4a** in a 96 % yield. However, complex **2** was inactive. Similar to the result with *o*-chlorotoluene, *o*-chloroanisole afforded the desired products **4d–h** in excellent yields. It is noteworthy that the present catalytic system also showed high efficiency for the coupling of aliphatic or secondary amines. Electron-deficient aryl chlorides such as 4-chloroacetophenone and 3-chloronitrobenzene could be coupled very efficiently with a catalytic loading as low as 0.2 mol%. Even the very sterically hindered 2-chloromxylene yielded the corresponding arylamines **4k–n** in good yields.

Suzuki coupling reactions

Biarylalcohols are important building blocks for the construction of biologically active compounds [22, 32, 33]. We have previously reported aqueous-phase catalysis of Suzuki coupling of aryl bromides and chlorides containing water-soluble hydroxymethyl groups by palladacycles [17, 18]. To develop a general and efficient catalyst system for the synthesis of substituted biarylmethanols, the Suzuki couplings of common aryl chlorides were studied in water. Initially, the coupling of *o*-chlorotoluene with 4-(hydroxymethyl)phenylboronic acid was investigated with various bases plus 0.2 mol% of complex **3** at 100 °C for 12 h. The results are summarized in Table 2. Cs_2CO_3 was found to be the most effective base; $K_3PO_4{\cdot}3H_2O$ and K_2CO_3 also gave good yields (entries 2–4). The relative activities of several catalyst systems for the model reaction were then investigated. The dimer **1** as well as complex **2** and $Pd(OAc)_2$/Sphos were almost inactive under the same conditions

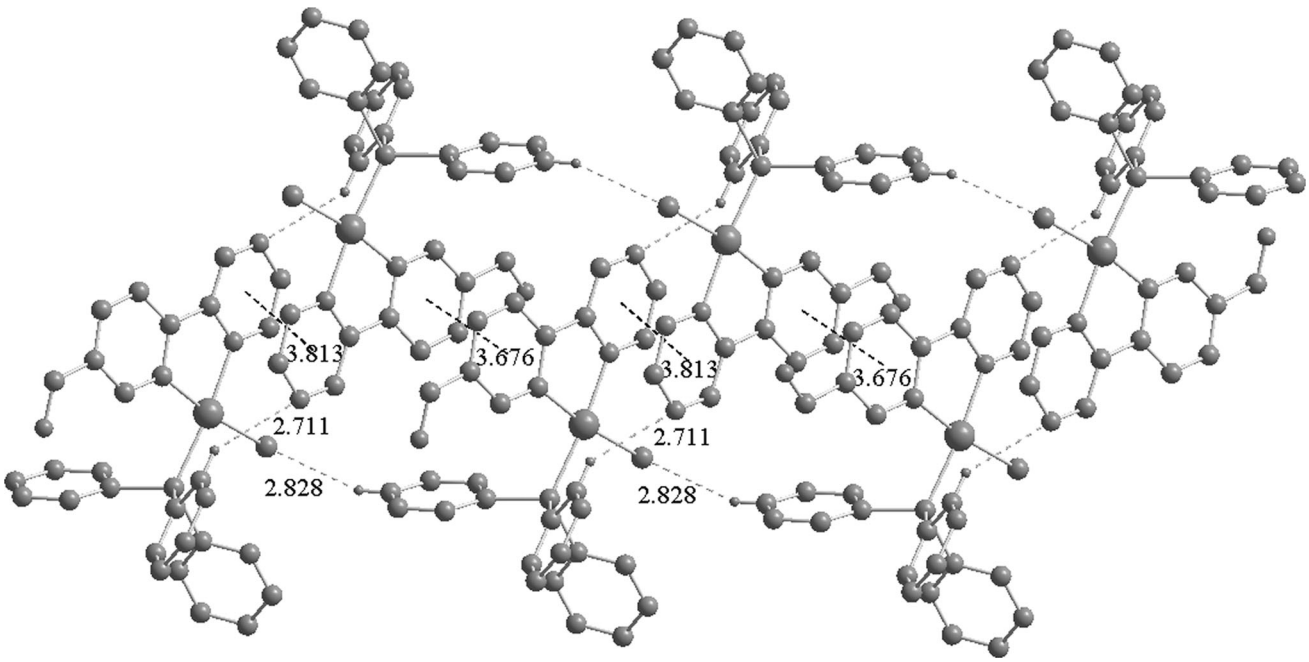


Fig. 3 One-dimensional lamellar structure of complex **2** formed by C–H···Cl(N) hydrogen bonds and π–π interactions. Non-hydrogen bonding H atoms are omitted for clarity

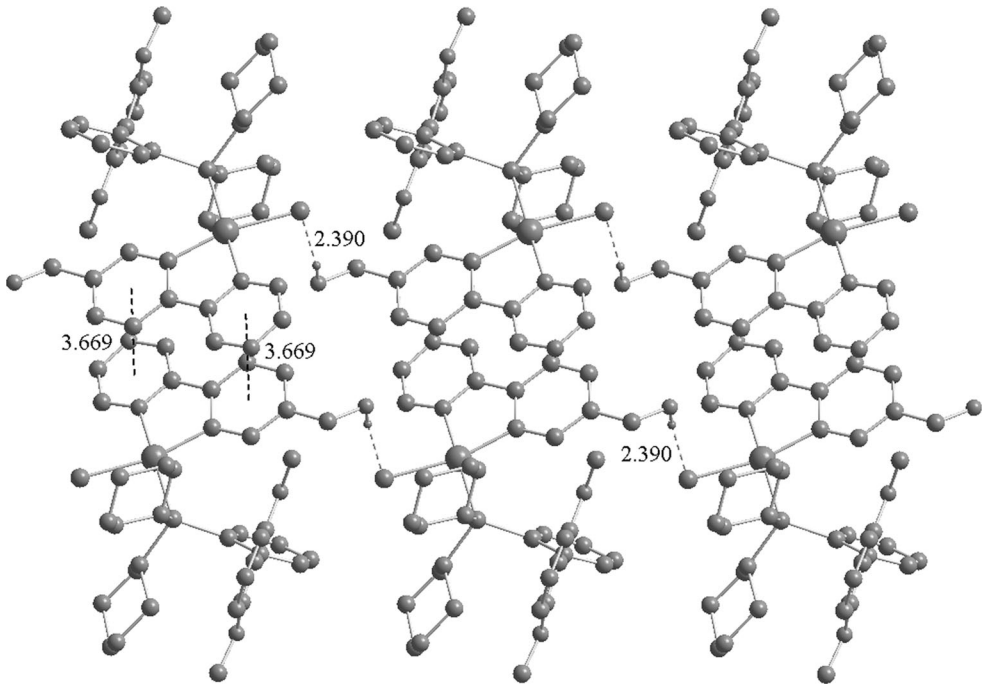
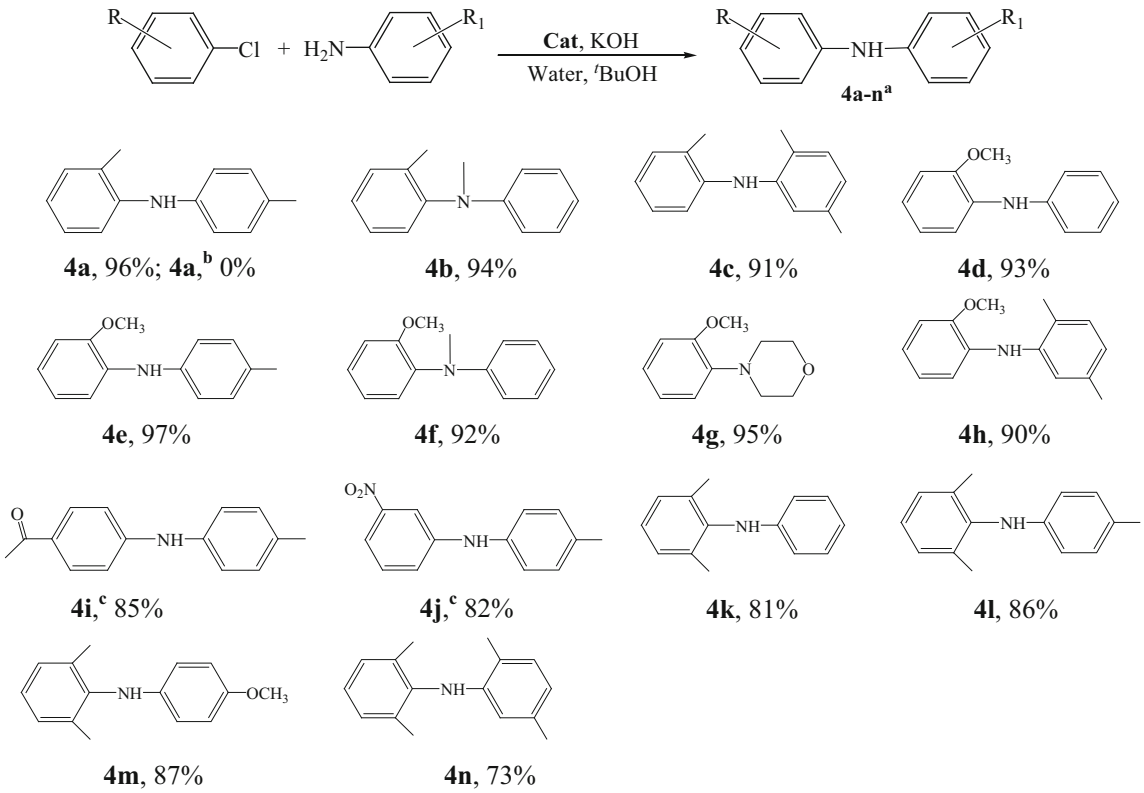
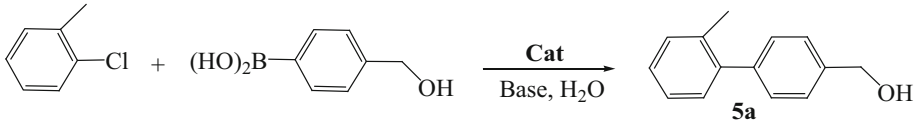


Fig. 4 One-dimensional lamellar structure of complex **3** formed by O–H···Cl hydrogen bonds and π–π interactions. Non-hydrogen bonding H atoms are omitted for clarity



Scheme 2 Amination of various aryl chlorides catalyzed by palladacycles. Reaction conditions: aryl chlorides (1.0 mmol), amine (1.2 mmol), **3** (0.5 mol %), KOH (3.0 mmol), ^{t}BuOH (4.0 mmol), H_2O (3 mL), 100 °C, 12 h. [a]Isolated yield. [b]Catalyst **2** (0.5 mol %). [c]Catalyst **3** (0.2 mol %)

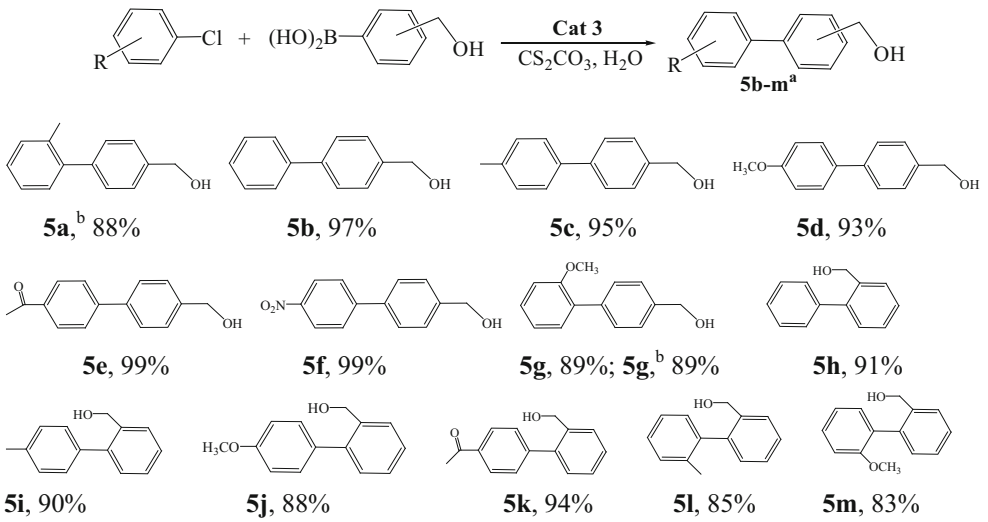
Table 2 Optimization of reaction conditions for the coupling of *o*-chlorotoluene with 4-(hydroxymethyl)phenylboronic acid



Entry	Base	Solvent	Catalyst (mol%)	Yield (%)[a]
1	Na_2CO_3	H_2O	**3**(0.2)	52
2	K_2CO_3	H_2O	**3**(0.2)	78
3	Cs_2CO_3	H_2O	**3**(0.2)	90
4	$K_3PO_4{\cdot}3H_2O$	H_2O	**3**(0.2)	81
5	KOAc	H_2O	**3**(0.2)	46
6	Cs_2CO_3	H_2O	**1**(0.1)	0
7	Cs_2CO_3	H_2O	**2**(0.2)	0
8	Cs_2CO_3	H_2O	$Pd(OAc)_2$/Sphos (0.2/0.3)	Trace
9	Cs_2CO_3	H_2O	**1**/Sphos (0.1/0.3)	75

Reaction conditions: *o*-chlorotoluene (1.0 mmol), 4-$HOCH_2$-$PhB(OH)_2$ (1.5 mmol), base (2.0 mmol), H_2O (3 mL), 100 °C, 12 h

[a] Isolated yield

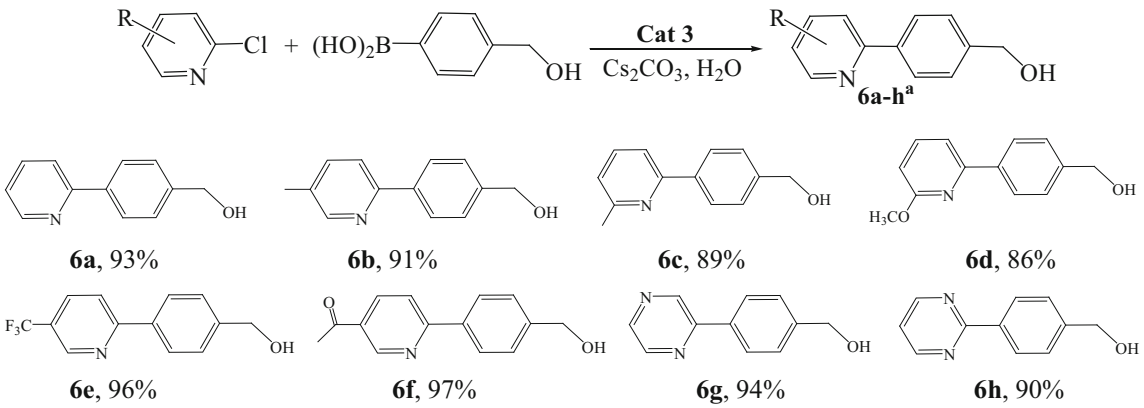


Scheme 3 Coupling of aryl chlorides with (hydroxymethyl)phenylboronic acids catalyzed by **3**. Reaction conditions: aryl chlorides (1.0 mmol), $HOCH_2$-$PhB(OH)_2$ (1.5 mmol), **3** (0.2 mol %), Cs_2CO_3 (2.0 mmol), H_2O (3 mL), 100 °C, 12 h. [a]Isolated yield. [b]Using 4-chlorophenylmethanol

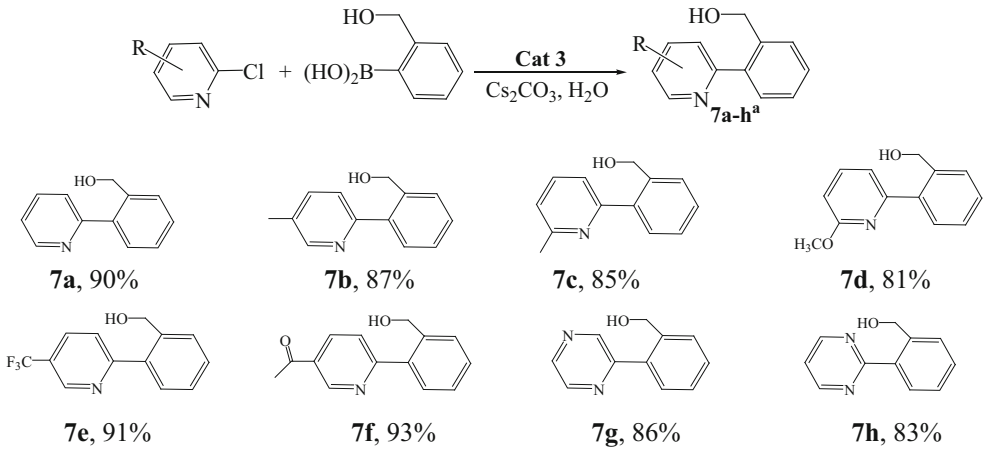
(entries 6–8). However, **1**/Sphos generated the product **5a** in a 75 % yield, suggesting that the dimer **1** can act as a good palladium source for Suzuki coupling in water (entry 9).

In subsequent experiments, the coupling of a variety of aryl chlorides with (hydroxymethyl)phenylboronic acids was investigated (Scheme 3). Both electron-poor and electron-rich aryl chlorides reacted with 4-(hydroxymethyl)phenylboronic acid to provide the products **5b–g** in excellent yields under the optimized reaction conditions. We then studied the reaction of 2-(hydroxymethyl)phenylboronic acid. The yields were slightly lower than those of the corresponding 4-substituted boronic acid, presumably due to steric factors, but still were very respectable. Reactions with *ortho*-aryl chlorides also proceeded efficiently to form the products **5l** and **5m** in good yields.

The scope of the Suzuki reaction was further investigated by varying the arylboronic acid. The couplings of 4-chlorophenylmethanol with 2-methylphenylboronic acid



Scheme 4 Coupling of *N*-heteroaryl chlorides with 4-(hydroxymethyl)phenylboronic acid catalyzed by **3**. Reaction conditions: *N*-heteroaryl chlorides (1.0 mmol), 4-$HOCH_2$-PhB$(OH)_2$ (1.5 mmol), **3** (0.2 mol %), Cs_2CO_3 (2.0 mmol), H_2O (3 mL), 100 °C, 12 h. [a]Isolated yield



Scheme 5 Coupling of *N*-heteroaryl chlorides with 2-(hydroxymethyl)phenylboronic acid catalyzed by **3**. Reaction conditions: *N*-heteroaryl chlorides (1.0 mmol), 2-$HOCH_2$-PhB$(OH)_2$ (1.5 mmol), **3** (0.2 mol %), Cs_2CO_3 (2.0 mmol), H_2O (3 mL), 100 °C, 12 h. [a]Isolated yield

and 2-methoxy-phenylboronic acid afforded the products **5a** and **5g** in good yields under the same conditions (Scheme 3). Suzuki coupling of heteroarylboronic acids is an important method for the synthesis of biologically active compounds [34, 35]. However, 2-pyridine-derived boronic acids are a particularly difficult class of substrate for the Suzuki reaction [36, 37]. Therefore, the coupling of 2-*N*-heteroaryl chlorides with arylboronic acids provides a valuable synthesis of the corresponding 2-*N*-heterocyclic biarylmethanols. In the present study, we investigated the Suzuki coupling of a variety of 2-*N*-heteroaryl chlorides with (hydroxymethyl)-phenylboronic acids. As expected, the catalyst was very effective for the coupling of 2-*N*-heteroaryl chlorides with 4-(hydroxymethyl)phenylboronic acid, giving the products **6a–h** in excellent yields (Scheme 4). This protocol was also found to proceed successfully with 2-(hydroxymethyl)phenylboronic acid, again furnishing good yields (Scheme 5).

Conclusion

Two water-soluble PPh_3 and Sphos-palladacycles containing hydroxymethyl groups have been synthesized and characterized. Complex **3** proved to be an efficient catalyst for both amination and Suzuki coupling reactions of aryl chlorides in water. Hence, this work provides a practical methodology for the synthesis of arylamines and substituted biarylmethanols.

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