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pH-Dependent C−C Coupling Reactions Catalyzed by Water-Soluble Palladacyclic Aqua Catalysts in Water

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The series of water-soluble palladacyclic aqua complexes $[({}^t\text{Bu-SCS})\text{Pd}^{\text{II}}(\text{H}_2\text{O})]^+$ ($[\mathbf{1}]^+$, ^{t}Bu-SCS = C_6H_3-2,6-$(\text{CH}_2\text{S}{}^t\text{Bu})_2$), $[({}^i\text{Pr-SCS})\text{Pd}^{\text{II}}(\text{H}_2\text{O})]^+$ ($[\mathbf{2}]^+$, ^{i}Pr-SCS = C_6H_3-2,6-$(\text{CH}_2\text{S}{}^i\text{Pr})_2$), $[(\text{PCP})\text{Pd}^{\text{II}}(\text{H}_2\text{O})]^+$ ($[\mathbf{3}]^+$, PCP = C_6H_3-2,6-$(\text{OP}{}^i\text{Pr}_2)_2$), and $[(\text{PC})\text{Pd}^{\text{II}}(\text{H}_2\text{O})_2]^+$ ($[\mathbf{4}]^+$, PC = 4-MeC_6H_3-2-$(\text{OP}{}^i\text{Pr}_2)$) have been synthesized from the reaction of the corresponding palladacyclic chloro complexes with silver salts in water to optimize the catalytic activity for pH-dependent C−C coupling reactions in water by changing the supporting ligands from S-supporting (SCS) to P-supporting (PCP) ligands and also from tridentate (PCP) to bidentate (PC) ligands. It was confirmed that there was no precipitation of palladium black under the present reaction conditions. The PC palladacyclic aqua complex $[\mathbf{4}]^+$ exhibits the highest catalytic activity among the water-soluble palladacyclic aqua complexes $[\mathbf{1}]^+$−$[\mathbf{4}]^+$ for the pH-dependent Suzuki−Miyaura, Mizoroki−Heck, and Stille coupling reactions in water. This is one of the highest catalytic activities ever reported for coupling reactions with water-soluble palladium catalysts in water. The catalytic ability of the palladacyclic aqua catalysts is drastically dependent on the pH of the solution and the structures of supporting ligands. The structures of palladacyclic aqua and chloro complexes were unequivocally determined by X-ray analysis.

Introduction

Palladium-catalyzed C−C coupling by Suzuki−Miyaura,[1−7] Mizoroki−Heck,[8] and Stille[9] reactions is a versatile and well-established methodology in modern organic synthesis.[10,11] The coupling products provide a variety of valuable intermediates in the preparation of materials, natural products, and bioactive compounds.

The use of water as a solvent for palladium-catalyzed C−C coupling reactions has merited increasing attention, to decrease the use of volatile organic solvents and to simplify catalyst recovery.[12−15] Water, being cheap, readily available, nontoxic, and nonflammable, has clear advantages as a solvent for use in chemistry.[16−18] The C−C coupling reactions that can proceed in aqueous media have certainly been required to solve the

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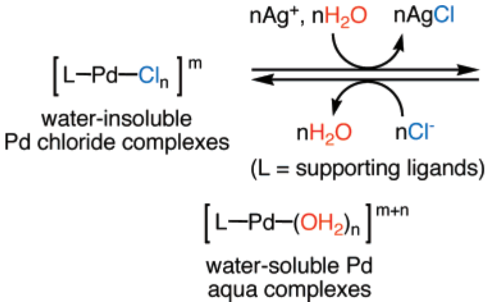
problems of solubility of substrates, which have to some extent been surmounted by the use of water-soluble palladium catalysts, amphiphilic polymer-supported palladium catalysts, and phase-transfer catalysts or the design of novel heterogeneous catalysts.[19−21] However, the activity of these systems remains too low to be industrially viable.[22]

The majority of these studies on Suzuki−Miyaura,[23−27] Mizoroki−Heck,[28−30] and Stille[31,32] coupling reactions in aqueous media have been carried out with water-soluble palladium catalysts containing water-soluble supporting ligands (e.g. TPPTS = meta-trisulfonated triphenylphosphine). Few have utilized palladium catalysts containing water molecules as ligands (i.e., palladium aqua complexes).[33] These palladium aqua complexes are readily synthesized from the reaction of the corresponding water-insoluble palladium chloro complexes with silver salts in water, as shown in eq 1. Since the aqua ligands of the palladium aqua complexes can be reversibly released, depending upon pH, to afford binding sites for substrates (e.g., Cl^-, as shown in the back-reaction of eq 1), the palladium aqua complexes are expected to be catalysts for pH-dependent C−C coupling reactions in water.



(1)

In this context, we have previously reported a pH-dependent Suzuki−Miyaura coupling reaction of organic bromides or iodides catalyzed by the water-soluble SCS palladacyclic aqua complex $[(^t\mathrm{Bu\text{-}SCS})\mathrm{Pd^{II}}(\mathrm{H_2O})]^+$ ($[\mathbf{1}]^+$, ^{t}Bu-SCS = $\mathrm{C_6H_3}$-2,6-($\mathrm{CH_2S}^t\mathrm{Bu})_2$; Chart 1), which was synthesized from the reaction of the corresponding water-insoluble palladacyclic chloro complex $[(^t\mathrm{Bu\text{-}SCS})\mathrm{Pd^{II}Cl}]$ (**5**) with $\mathrm{Ag_2SO_4}$ in water.[33] However, the SCS palladacyclic aqua complex $[\mathbf{1}]^+$ cannot be used as the catalyst for the Suzuki−Miyaura coupling reaction of organic chlorides and Mizoroki−Heck reaction of allyl bromides in water.[33] Development of water-soluble catalysts with increased activity toward organic chlorides and aryl bromides is certainly necessary for wider application of the C−C coupling reactions in water.

We report herein development of a new series of robust and active water-soluble palladacyclic aqua catalysts as shown in Chart 1: $[\mathbf{1}]^+$, $[(^i\mathrm{Pr\text{-}SCS})\mathrm{Pd^{II}}(\mathrm{H_2O})]^+$ ($[\mathbf{2}]^+$, ^{i}Pr-SCS = $\mathrm{C_6H_3}$-2,6-($\mathrm{CH_2S}^i\mathrm{Pr})_2$), $[(\mathrm{PCP})\mathrm{Pd^{II}}(\mathrm{H_2O})]^+$ ($[\mathbf{3}]^+$, PCP = $\mathrm{C_6H_3}$-2,6-($\mathrm{OP}^i\mathrm{Pr_2})_2$), and $[(\mathrm{PC})\mathrm{Pd^{II}}(\mathrm{H_2O})_2]^+$ ($[\mathbf{4}]^+$, PC = 4-Me$\mathrm{C_6H_3}$-2-($\mathrm{OP}^i\mathrm{Pr_2}$)). It is important to note that there is no formation of metallic palladium under the present reaction conditions.[34,35] The catalytic activity for C−C coupling reactions in water has been optimized by pH of the solution and by changing the supporting ligands, from S-supporting (SCS) to P-supporting (PCP) ligands and also from tridentate (PCP) to bidentate (PC) ligands. As a result, the water-soluble PC palladacyclic aqua complex $[(\mathrm{PC})\mathrm{Pd^{II}}(\mathrm{H_2O})_2]^+$ ($[\mathbf{4}]^+$) exhibited highly catalytic activity for a variety of C−C coupling reactions in water: the pH-dependent Suzuki−Miyaura coupling reaction (of organic chloride, bromide, and iodide), the Mizoroki−Heck reaction, and the Stille coupling reaction. The new water-soluble palladacyclic aqua catalysts $[\mathbf{2}]_2(\mathrm{SO_4})$, $[\mathbf{3}]_2(\mathrm{SO_4})$, and $[\mathbf{4}]_2(\mathrm{SO_4})$ were prepared from the reaction of $\mathrm{Ag_2SO_4}$ with the corresponding water-insoluble palladacyclic chloro complexes $[(^i\mathrm{Pr\text{-}SCS})\mathrm{Pd^{II}Cl}]$ (**6**), $[(\mathrm{PCP})\mathrm{Pd^{II}Cl}]$ (**7**), and $[(\mathrm{PC})\mathrm{Pd^{II}}(\mu\text{-}\mathrm{Cl})]_2$ (**8**), respectively. The structures of $[\mathbf{3}](\mathrm{PF_6})$, $[\mathbf{4}](\mathrm{BF_4})$, and **8** were unequivocally determined by X-ray analysis.

Experimental Section

Materials and Methods. All experiments were carried out under an air atmosphere. Sodium tetraphenylborate ($\mathrm{Ph_4BNa}$) was pur-

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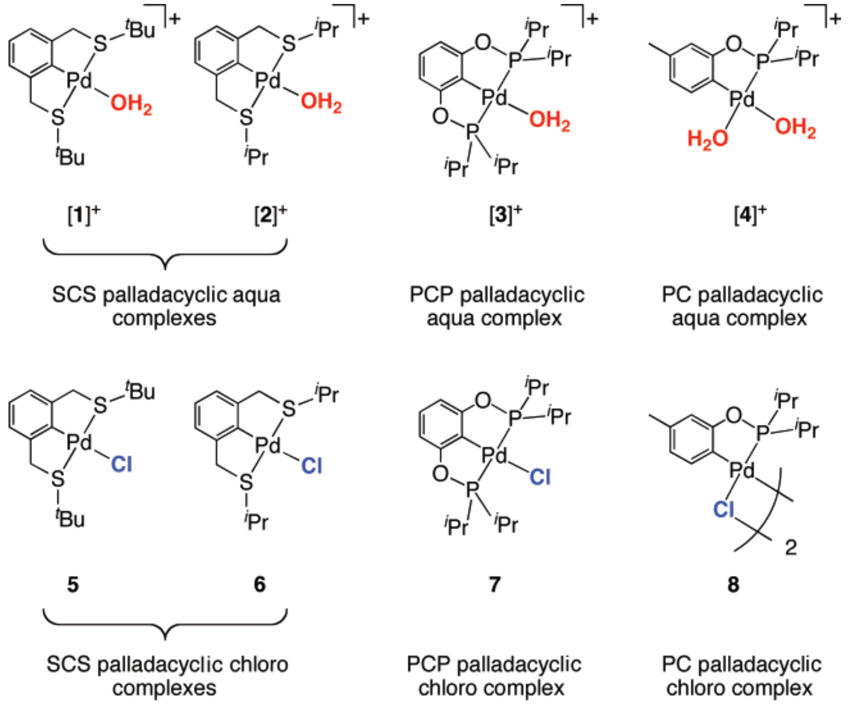
Chart 1



chased from Tokyo Kasei Kogyo Co. Ltd. and was used as received. Phenylboronic acid ($PhB(OH)_2$), 3-iodobenzoic acid (3-I-$C_6H_4CO_2H$), and other chemicals (highest purity available) were purchased from Aldrich Chemical Co. and used without further purification. The SCS(^{i}Pr) ligand (1,3-(^{i}PrSCH$_2$)$_2$C$_6$H$_4$) was prepared by the method described in the literature.[36] The SCS palladacyclic aqua complex [(^{t}Bu-SCS)Pd^{II}(H$_2$O)]$^+$ ([**1**]$^+$)[33] and the SCS and PCP palladacyclic chloro complexes [(^{t}Bu-SCS)Pd^{II}Cl] (**5**)[37] and [(PCP)Pd^{II}Cl] (**7**)[38] were prepared by the method described in the literature. Purification of water (18.2 MΩ cm) was performed with a Milli-Q system (Millipore; Milli-RO 5 plus and Milli-Q plus). The ^{1}H and ^{31}P NMR spectra were recorded on JEOL-JNM-AL300 and JEOL-JNM-ECP400 spectrometers at 25 °C. A Nissin magnetic stirrer (Model SW-R800) was used.

pH Adjustment. In the pH range of 6−13, pH values of the solutions were determined by a pH meter (TOA, HM-18E) equipped with a glass electrode (TOA; GS-5015C). During the reaction, a stainless steel-micro pH probe (IQ Scientific Instruments, Inc., PH15-SS) was dipped in the reaction mixture, and the pH of the solution was monitored by a pH meter (IQ Scientific Instruments, Inc., IQ200). To determine the exact pH values, the ^{1}H NMR experiments were performed by dissolving the samples in H$_2$O in an NMR tube (diameter 5.0 mm) with a sealed capillary tube (diameter 1.5 mm) containing 3-(trimethylsilyl)propionic-2,2,3,3-d_4 acid sodium salt (TSP, 500 mM, as the reference with the methyl proton resonance set at 0.00 ppm) dissolved in D$_2$O (for deuterium lock). Values of pD were corrected by adding 0.4 to the observed values.[39] In the experiments to determine the pK_a values of the palladacyclic aqua complexes by ^{1}H NMR, the pH of the solution was adjusted by using 0.01−0.1 M NaOD/D$_2$O without buffer for complex [**2**]$^+$, and the pH of the solution was adjusted by using mixture solvents of 0.01−0.1 M NaOD/D$_2$O (100 μL) and d_6-acetone (500 μL) without buffer for complexes [**3**]$^+$ and [**4**]$^+$. NaHCO$_3$/NaOH buffers prepared by 1 M NaHCO$_3$/H$_2$O and 5 M NaOH/H$_2$O were used to maintain the pH of the solution during the cross-coupling reactions.

PC Ligand (3-MeC$_6$H$_4$(OP^{i}Pr$_2$)). A solution of ClP^{i}Pr$_2$ (1.92 g, 12.6 mmol) in tetrahydrofuran (THF, 60 mL) was added to a solution of *m*-cresol (1.36 g, 12.6 mmol) and (dimethylamino)pyridine (DMAP, 1.61 g, 13.2 mmol) in THF (60 mL), with stirring at 0 °C. The resulting mixture was allowed to reach room temperature and stirred for an additional 6 h. Following removal of the solvent in vacuo, the solid residue was extracted with toluene (2 × 40 mL). The combined extracts were filtered through a short plug of Celite, and the toluene was removed in vacuo to give the product (yield 97% based on *m*-cresol) as a colorless oil. ^{1}H NMR (300 MHz, in CDCl$_3$, reference to TMS): δ 1.06−1.20 (m, 12H, CH(C*H*$_3$)$_2$), 1.84−1.99 (m, $^2J_{P,H}$ = 2.4 Hz, $^3J_{H,H}$ = 6.9 Hz, 2H, C*H*(CH$_3$)$_2$), 2.31 (s, 3H, C*H*$_3$), 6.70 (d, $^3J_{H,H}$ = 7.5 Hz, 1H, aromatic), 6.83 (d, $^3J_{H,H}$ = 7.5 Hz, 2H, aromatic), 7.05 (t, $^3J_{H,H}$ = 7.5 Hz, 1H, aromatic). ^{31}P NMR (121.5 MHz, in CDCl$_3$, referenced to 85% H$_3$PO$_4$): δ 148.9. Anal. Calcd for C$_{13}$H$_{21}$OP: C, 69.62; H, 9.44. Found: 69.57; H, 9.40.

SCS Palladacyclic Aqua Complex [(^{i}Pr-SCS)Pd^{II}(H$_2$O)]$_2$SO$_4$ ([2]$_2$(SO$_4$)). The SCS palladacyclic aqua complex [**2**]$_2$(SO$_4$) was synthesized from the reaction of the SCS palladacyclic chloro complex **6** (277 mg, 0.7 mmol) with Ag$_2$SO$_4$ (110 mg, 0.35 mmol) in H$_2$O (50 mL) at pH 8 in H$_2$O under an air atmosphere. After the mixture was stirred for 24 h, the precipitating AgCl was removed by filtration. The solvent was evaporated to yield a yellow powder of [**2**]$_2$(SO$_4$), which was dried in vacuo (yield 84% based on **6**). ^{1}H NMR (300 MHz, in H$_2$SO$_4$/H$_2$O at pH 2.0, referenced to TSP, 30 °C): δ 1.32−1.35 (d, $^3J_{H,H}$ = 6.9 Hz, 12H, CH(C*H*$_3$)$_2$), 3.19−3.33 (sep, $^3J_{H,H}$ = 6.9 Hz, 2H, C*H*), 4.05 (br, 4H, C*H*$_2$), 6.82 (d, 2H, C*H* aromatic), 6.90 (t, 1H, C*H* aromatic). Anal. Calcd for C$_{28}$H$_{46}$O$_6$Pd$_2$S$_5$: C, 39.48; H, 5.44. Found: C, 39.12; H, 5.34.

PCP Palladacyclic Aqua Complex [(PCP)Pd^{II}(H$_2$O)]$_2$SO$_4$ ([3]$_2$(SO$_4$)). A reaction of the PCP palladacyclic chloro complex **7** (500 mg, 1.04 mmol) with Ag$_2$SO$_4$ (163 mg, 0.52 mmol) at pH 8 in H$_2$O at 25 °C for 24 h provides a colorless solution of the PCP palladacyclic aqua complex [**3**]$_2$SO$_4$. The precipitated AgCl was removed by filtration. The solvent was evaporated to yield a

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colorless powder of [**3**]$_2$(SO$_4$), which was dried in vacuo (yield 90% based on **7**). ^{1}H NMR (300 MHz, in D$_2$O, referenced to TMS; Figure S1 in the Supporting Information): δ 1.25−1.42 (m, 24H, CH(C*H*$_3$)$_2$), 2.52−2.64 (sep, $^3J_{H,H}$ = 7.2 Hz, 4H, C*H*(CH$_3$)$_2$), 6.46 (d, $^3J_{H,H}$ = 8.4 Hz, 2H, aromatic), 6.9 (t, $^3J_{H,H}$ = 7.8 Hz, 1H, aromatic). Anal. Calcd for $C_{18}H_{33}F_6O_3P_3Pd$: C, 35.52; H, 5.37. Found: C, 35.40; H, 5.45.

PC Palladacyclic Aqua Complex [(PC)Pd^{II}(H$_2$O)$_2$]$_2$SO$_4$ ([4]$_2$(SO$_4$)). A solution of the PC palladacyclic chloro complex **8** (365 mg, 0.50 mmol) and Ag$_2$SO$_4$ (0.78 mg, 2.5 mmol) in H$_2$O/MeOH (50 mL, H$_2$O:MeOH = 1:4) was stirred at ambient temperature for 24 h under an air atmosphere, and the precipitated AgCl was removed by filtration. The solvent was evaporated to yield a yellow powder of [**4**]$_2$(SO$_4$), which was dried in vacuo (yield 67% based on **8**). ^{1}H NMR (300 MHz, in D$_2$O, referenced to TSP; Figure S2 in the Supporting Information): δ 1.19−1.32 (m, 12H, CH(C*H*$_3$)$_2$), 2.19 (s, 3H, CH$_3$), 2.39−2.51 (m, $^3J_{H,H}$ = 6.9 Hz, 2H, C*H*(CH$_3$)$_2$), 6.70−6.72 (m, 2H, aromatic), 7.12 (t, 1H, aromatic). ^{31}P NMR (121.5 MHz, in D$_2$O, referenced to 85% H$_3$PO$_4$): δ 208.3. Anal. Calcd for $C_{26}H_{48}O_{10}P_2Pd_2S$: C, 37.73; H, 5.84. Found: C, 37.16; H, 5.21. The complex [**4**]$_2$SO$_4$ is hygroscopic.

SCS Palladacyclic Chloro Complex [(^{i}Pr-SCS)Pd^{II}Cl] (6). A mixture of sodium tetrachloropalladate(II) (0.26 g, 0.81 mmol), sodium acetate (0.07 g, 0.81 mmol), and 1,3-bis(isopropylthiomethyl)benzene (0.22 g, 0.85 mmol) in ethanol (20 mL) was heated under reflux with stirring over a period of 25 min, after which time it was very dark. The solvent was removed under reduced pressure and the product extracted into dichloromethane and treated with charcoal. It formed a yellow power of **6** (yield: 72% based on sodium tetrachloropalladate) from chloroform-hexane. ^{1}H NMR (300 MHz, in D$_2$O, referenced to TSP): δ 1.52−1.56 (d, $^3J_{H,H}$ = 6.9 Hz, 12H, CH(C*H*$_3$)$_2$), 3.44−3.58 (sep, $^3J_{H,H}$ = 6.6 Hz, 2H, C*H*(CH$_3$)$_2$), 4.11 (s, 2H, CH$_2$), 6.84−6.92 (m, 3H, aromatic). Anal. Calcd for $C_{14}H_{21}ClPdS_2$: C, 42.54; H, 5.35. Found: C, 42.63; H, 5.06.

PC Palladacyclic Chloro Complex [(PC)Pd^{II}(μ-Cl)]$_2$ (8). A toluene (50 mL) solution of 3-MeC$_6$H$_4$(OP^{i}Pr$_2$) (480 mg, 2.14 mmol) and PdCl$_2$(COD) (COD = 1,5-cyclooctadiene, 611 mg, 2.14 mmol) was refluxed for 4 h. After the toluene was removed in vacuo, a yellow powder was obtained. Following recrystallization from dichloromethane, a purified yellow product of **8** was obtained (yield 70% based on PdCl$_2$(COD)). ^{1}H NMR (300 MHz, CDCl$_3$, referenced to TMS): δ 1.25−1.50 (m, 12H, CH(C*H*$_3$)$_2$), 2.24 (s, 3H, CH$_3$), 2.29−2.49 (m, $^3J_{H,H}$ = 7.5 Hz, 2H, C*H*(CH$_3$)$_2$), 6.93 (d, $^3J_{H,H}$ = 7.8 Hz, 1H, aromatic), 7.22 (s, 1H, aromatic), 7.37 (d, $^3J_{H,H}$ = 7.8 Hz, 1H, aromatic). ^{31}P NMR (121.5 MHz, in CDCl$_3$, referenced to 85% H$_3$PO$_4$): δ 202.0. Anal. Calcd for $C_{26}H_{40}Cl_2O_2P_2Pd_2$: C, 42.76; H, 5.52. Found: C, 42.59; H, 5.36.

X-ray Crystallographic Analysis. Crystallographic data for the palladacyclic aqua complexes [**3**](PF$_6$) and [**4**](BF$_4$) and the palladacyclic chloro complex **8** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication Nos. CCDC-266121, 266122, and 266124, respectively. Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB21EZ, U.K. (fax, (+44)-1223-336-033; e-mail, deposit@ccdc.cam.ac.uk). Measurements were made on a Rigaku/MSC Mercury CCD diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.7107 Å). Data were collected and processed using the CrystalClear program (Rigaku). All calculations were performed using the teXsan crystallographic software package of Molecular Structure Corp.

Typical Procedure for the pH-Dependent C−C Bond Formation Reactions (E.g., Suzuki−Miyaura Coupling Reaction). The pH-dependent Suzuki−Miyaura coupling reaction catalyzed by the water-soluble palladacyclic aqua complexes in water were investigated at 25−100 °C. The reactions can be carried out under an air atmosphere, because the catalysts are not sensitive to O$_2$. Tetraphenylborate (25.1 mg 73.3 μmol) and 3-iodobenzoic acid (72.9 mg 294 μmol) were dissolved in NaHCO$_3$/NaOH buffers (6 mL, pH 10), to which 118 μM [**4**]$^+$/H$_2$O (0.50 mL, 5.88 × 10^{-2} μmol: 0.02 mol % of [**4**]$^+$) was added. The mixture was vigorously stirred for 20 min at 25 °C. It is important to note that there is no formation of metallic palladium under the present experimental conditions. To maintain the pH of the solution during the reaction, NaHCO$_3$/NaOH buffers were used. It was confirmed that the pH of the solution does not change in the course of the reaction. The TONs were determined by ^{1}H NMR analysis of the reaction mixture samples (based on the organic halides and the products).

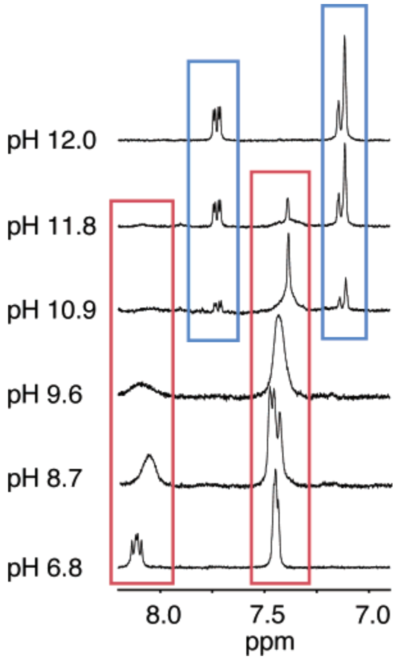


Figure 1. pH-dependent ^{1}H NMR spectra of [**4**]$_2$(SO$_4$) in a pH range of 6.8−12.0. Experiments were performed by dissolving [**4**]$_2$(SO$_4$) (0.5 μmol) in solvent mixtures of d_6-acetone (100 μL) and NaOD/D$_2$O (0.01 M-0.1 M, 500 μL) at 25 °C.

Results and Discussion

Synthesis and Characterization of Palladacyclic Aqua Complexes. The water-soluble palladacyclic aqua complexes [**1**]$_2$(SO$_4$), [**2**]$_2$(SO$_4$), [**3**]$_2$(SO$_4$), and [**4**]$_2$(SO$_4$) were prepared by the reactions of Ag$_2$SO$_4$ with the corresponding water-insoluble palladacyclic chloro complexes **5**−**8**, respectively. As shown in Figure 1, ^{1}H NMR titration experiments revealed that the pK_a value of the aqua complex [**4**]$^+$ was 10.9. At this pH, the aqua complex (indicated by red in Figure 1) was deprotonated to form the corresponding hydroxo complex (indicated by blue in Figure 1). Similarly, the pK_a values of [**1**]$^+$−[**3**]$^+$ were determined by ^{1}H NMR titration experiments as 10.7, 10.6, and 10.8, respectively. Solubilities of the palladacyclic aqua complexes [**1**]$^+$−[**4**]$^+$ in water at pH 7 at 25 °C are 40, 32, 2.4, and 2.1 mg/mL. The solubility is enough to utilize the palladacyclic aqua complexes as water-soluble catalysts (0.02 mol %) for the C−C coupling reactions in water. It was confirmed by ^{1}H NMR that the palladacyclic aqua complexes are stable in water during the reactions.[34]

Crystal Structures of the Palladacyclic Aqua and Chloro Complexes. NH$_4$PF$_6$ was added to the solution of the PCP palladacyclic aqua complex [**3**](PF$_6$) in water to give a powder of the palladacyclic aqua complex [**3**](PF$_6$), which was collected by filtration. Colorless crystals of [**3**](PF$_6$) used in the X-ray structure analysis were obtained from a CH$_2$Cl$_2$ solution of

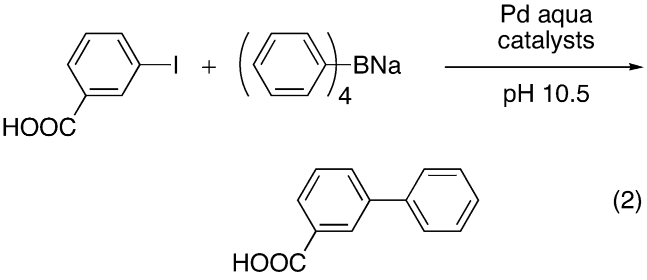
Table 1. Summary of Crystal Data, Data Collection Parameters, and Structure Refinement Details for [3](PF$_6$), [4](BF$_4$), and 8

	[**3**](PF$_6$)	[**4**](BF$_4$)	**8**
empirical formula	$C_{18}H_{33}F_6O_3P_3Pd$	$C_{26}H_{48}B_2F_8O_6P_2Pd_2$	$C_{26}H_{40}O_2P_2Pd_2Cl_2$
fw	610.77	905.02	730.25
cryst color	colorless	yellow	yellow
cryst dimens (mm)	0.30 × 0.20 × 0.20	0.20 × 0.20 × 0.20	0.20 × 0.10 × 0.10
cryst syst	triclinic	triclinic	monoclinic
a (Å)	8.821(1)	11.470(4)	14.202(6)
b (Å)	11.261(2)	13.402(5)	11.287(4)
c (Å)	13.800(2)	14.227(5)	19.757(8)
α (deg)	95.359(8)	70.71(1)	90
β (deg)	95.705(7)	76.78(1)	101.497(6)
γ (deg)	99.059(6)	74.00(1)	90
V (Å^3)	1338.7(3)	1961(1)	3103(2)
space group (No.)	$P\bar{1}$ (2)	$P\bar{1}$ (2)	$P2_1/n$ (14)
Z	2	2	4
D_{calcd} (g cm^{-3})	1.515	1.532	1.563
F_{000}	620	912	1472
μ(Mo Kα) (cm^{-1})	9.30	10.70	14.55
radiation (λ, Å)	0.7107	0.7107	0.7107
temp (°C)	−50	−50	−50
$2\theta_{max}$ (deg)	54.9	55	55
abs cor method	empirical	empirical	empirical
no. of rflns obsd (all, $2\theta < 54.97°$)	5684	8580	7095
no. of params	313	415	307
R^a	0.090	0.086	0.084
$R_w{}^b$	0.143	0.181	0.069
R1^c	0.050	0.064	0.044
S^d	1.15	1.15	0.85
max shift/error in final cycle	0.001	0.001	0.001
max peak in final diff map (e Å^{-3})	1.78	1.41	2.30
min peak in final diff map (e Å^{-3})	−0.55	−1.07	−2.07

[a] $R = \Sigma(F_o{}^2 - F_c{}^2)/\Sigma F_o{}^2$. [b] $R_w = [\Sigma w(F_o{}^2 - F_c{}^2)^2/\Sigma w(F_o{}^2)^2]^{1/2}$. [c] $R1 = \Sigma||F_o{}^2| - |F_c||/\Sigma|F_o|$ for $I > 2.0\sigma(I)$ data. [d] Goodness of fit indicator $S = [\Sigma w(|F_o| - |F_c|)^2/(N_o - N_v)]^{1/2}$ (N_o = number of observations, N_v = number of variables).

[**3**](PF$_6$). Yellow crystals of the PC palladacyclic aqua complex [**4**](BF$_4$) used in the X-ray structure analysis was obtained from a 4% HBF$_4$ solution of [**4**]$^+$. Yellow crystals of the PC palladacyclic chloro complex **8** used in the X-ray structure analysis were obtained by layering a CH_2Cl_2 solution of **8** with hexane. Crystal data, data collection parameters, and structure refinement details for [**3**](PF$_6$), [**4**](BF$_4$), and **8** are given in Table 1. Selected bond lengths and angles for [**3**](PF$_6$), [**4**](BF$_4$), and **8** are given in Table 2. The palladacyclic aqua complexes [**3**](PF$_6$) and [**4**](BF$_4$) adopt distorted-square-planar coordination with H_2O ligands. ORTEP drawings of [**3**](PF$_6$), [**4**](BF$_4$), and **8** are shown in Figures 2−4, respectively.

Suzuki−Miyaura Coupling Reactions Catalyzed by Water-Soluble Palladacyclic Aqua Complexes in Water. Now that a series of water-soluble palladacyclic aqua complexes have been structurally characterized, the catalytic reactivities are compared in Suzuki−Miyaura coupling reaction of a water-soluble substrate, 3-I-$C_6H_4CO_2H$, with Ph_4BNa catalyzed by [**1**]$^+$, [**2**]$^+$, [**3**]$^+$, or [**4**]$^+$ under the same experimental conditions (eq 2). The results are summarized in Table 3. The reaction of the water-soluble organic bromide 3-Br-$C_6H_4CO_2H$ and organic chloride 3-Cl-$C_6H_4CO_2H$ with the organoboron compounds also affords the corresponding products under the present experimental conditions, although the reactivity of 3-X-$C_6H_4CO_2H$ decreases in the order X = I > Br ≫ Cl. Only 0.02−0.0002 mol % of catalyst [**4**]$^+$ exhibits the catalytic activity. A remarkable TON (290 000) was attained using [**4**]$^+$ as a catalyst at a higher temperature (100 °C) after 12 h, as shown in Table 3. It was confirmed that no decomposition of [**4**]$^+$ and no precipitation of palladium black was observed during the reactions (Figure S3 in the Supporting Information).



(2)

TONs of the Suzuki−Miyaura coupling reaction with [**1**]$^+$, [**2**]$^+$, [**3**]$^+$, or [**4**]$^+$ were compared under the same experimental conditions, as shown in Figure 5. The ^{i}Pr-SCS palladacyclic aqua complex [**2**]$^+$ shows higher catalytic reactivity compared with the ^{t}Bu-SCS palladacyclic aqua complex [**1**]$^+$, which indicates that the release of the steric demand in palladacyclic aqua complexes is important to obtain the highly catalytic activity. The higher catalytic reactivity of the PCP palladacyclic aqua complex [**3**]$^+$ as compared with the SCS palladacyclic aqua complex [**2**]$^+$, which also contains one H_2O ligand, may be rationalized by comparing the difference in the structure of the supporting ligands between [**3**]$^+$ (P-supporting ligand) and [**2**]$^+$ (S-supporting ligand). Among the water-soluble palladacyclic aqua complexes [**1**]$^+$−[**4**]$^+$, the PC palladacyclic aqua complex [**4**]$^+$ exhibits the highest catalytic activity. This is one of the highest catalytic activities ever reported for the Suzuki−Miyaura coupling reaction of aryl bromide and aryl chloride in water.[15,19a,24b,40−42] Such a high catalytic activity of [**4**]$^+$ may result from the introduction of an additional two water molecules as ligands, which can act as the catalytically active sites, as compared with [**3**]$^+$, which contains only one H_2O ligand. This indicates that the introduction of two H_2O ligands as active sites is an important factor to attain the high catalytic activity in water.

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Table 2. Selected Bond Lengths (*l*/Å) and Angles (*ϕ*/deg) for [3](PF_6), [4](BF_4), and 8

[**3**](PF_6)		[**4**](BF_4)		**8**	
Pd1−C1	1.975(4)	Pd1−C1	1.981(6)	Pd1−C1	1.989(5)
Pd1−O1	2.158(3)	Pd1−O1	2.172(6)	Pd1−Cl1	2.423(1)
Pd1−P1	2.2948(8)	Pd1−O2	2.166(4)	Pd1−Cl2	2.427(2)
Pd1−P2	2.2977(8)	Pd1−P1	2.183(2)	Pd1−P1	2.175(2)
C1−C2	1.399(5)	C1−C2	1.388(9)	C1−C2	1.396(7)
C1−C6	1.391(5)	C1−C6	1.396(8)	C1−C6	1.421(7)
C2−O3	1.381(4)	C6−O3	1.428(7)	C6−O1	1.405(6)
C6−O2	1.391(4)	O3−P1	1.622(5)	O1−P1	1.633(4)
O2−P1	1.639(3)				
O3−P2	1.645(3)				
Pd1−C1−C2	121.5(3)	Pd1−C1−C2	123.9(5)	Pd1−C1−C2	126.2(4)
Pd1−C1−C6	121.4(3)	Pd1−C1−C6	121.5(4)	Pd1−C1−C6	119.8(4)
Pd1−P1−O2	104.5(1)	Pd1−P1−O3	107.8(2)	Pd1−P1−O1	107.4(1)
Pd1−P2−O3	104.3(1)	C1−Pd1−O1	179.4(2)	C1−Pd1−Cl1	96.7(2)
C1−Pd1−O1	175.2(1)	C1−Pd1−O2	93.0(2)	C1−Pd1−Cl2	176.4(2)
C1−Pd1−P1	80.2(1)	C1−Pd1−P1	80.8(2)	C1−Pd1−P1	80.2(2)
C1−Pd1−P2	80.1(1)	O1−Pd1−O2	87.4(2)	Cl1−Pd1−P1	176.86(6)
O1−Pd1−P1	101.71(9)	O1−Pd1−P1	98.8(1)	Cl1−Pd1−Cl2	86.48(5)
O1−Pd1−P2	98.53(9)	O2−Pd1−P1	173.6(1)	Cl2−Pd1−P1	96.64(6)
P1−Pd1−P2	158.98(4)	C1−C6−O3	116.3(5)	C1−C6−O1	117.1(5)
C1−C2−O3	119.0(3)	C6−O3−P1	113.4(4)	C6−O1−P1	111.7(3)
C1−C6−O2	119.2(3)				
C2−O3−P2	114.6(2)				
C6−O2−P1	114.3(2)				

The pH dependence of the TOF of the Suzuki−Miyaura coupling reaction was also examined using the best catalyst [**4**]$^+$, as shown in Figure 6. The TOF decreases drastically with increasing pH to exhibit no catalytic reactivity at pH 13. Such a drastic decrease in the catalytic reactivity at a high pH comes from the deprotonation of the H_2O ligand of [**4**]$^+$. At a pH higher than about 11, the aqua complex [**4**]$^+$ is deprotonated to form the hydroxo complex, which shows no catalytic reactivity. This was confirmed by the ^{1}H NMR spectra of [**4**]$^+$ at different pH values (Figure 1). From the pH titration, the pK_a value of [**4**]$^+$ is determined as 10.9 (vide supra). The retarded catalytic reactivity of the hydroxo complex may come from the strong binding of OH, which precludes the oxidative addition of 3-X-$C_6H_4CO_2H$ (X = I, Br, Cl) in the catalytic cycle of Suzuki−Miyaura coupling or the Mizoroki−Heck reaction.[43]

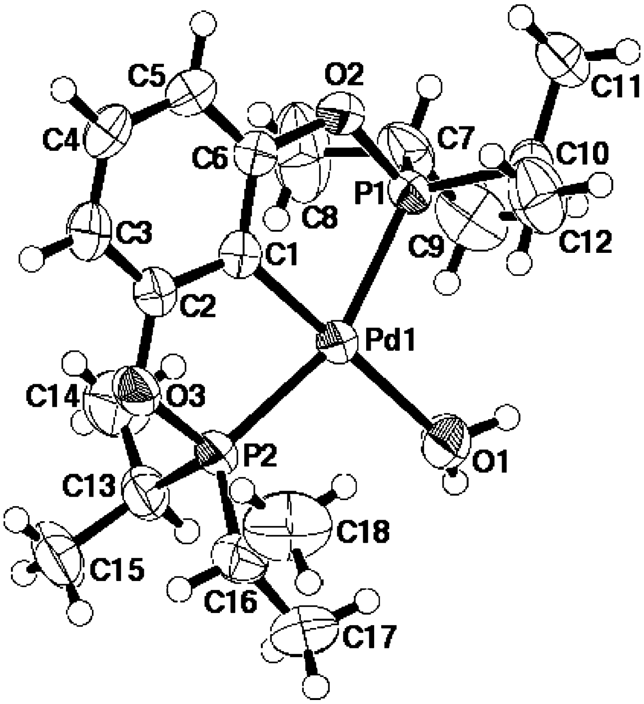
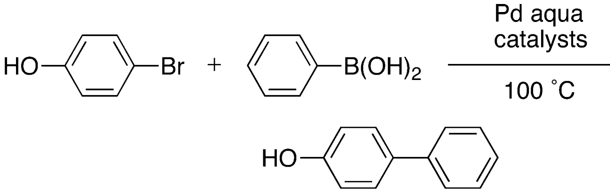


Figure 2. ORTEP drawing of [**3**](PF_6). The anion (PF_6) is omitted for clarity.

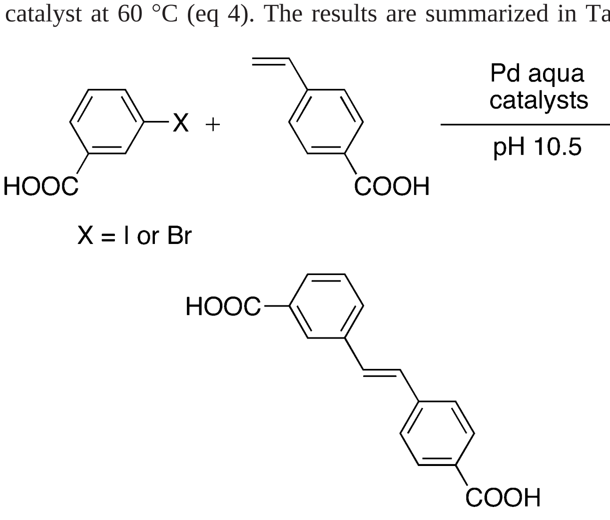
The catalyst [**4**]$^+$ is also highly effective for *p*-bromophenol with $C_6H_5B(OH)_2$ to yield *p*-hydroxybiphenyl (eq 3). Recently,



(3)

Nájera et al. have reported that the palladium−dipyridylmethylamine complex **9**[15] exhibits much higher catalytic reactivity in this reaction (eq 3) than the highly active oxime-derived palladacyclic catalyst (**10**)[26a] among the previously reported systems (Chart 2). Our catalyst [**4**]$^+$ exhibits even higher catalytic activity than **9** under similar experimental conditions, as reported in the literature (Table 4).[15]

Mizoroki−Heck Reaction Catalyzed by Water-Soluble Palladacyclic Aqua Complexes in Water. The Mizoroki−Heck reactions of 3-X-$C_6H_4CO_2H$ (X = I, Br) with 4-CH_2=CH-(C_6H_4)CO_2H in water was also investigated using [**4**]$^+$ as a catalyst at 60 °C (eq 4). The results are summarized in Table 5. The reactions of the water-soluble organic iodides with 4-vinylbenzoic acid afford the corresponding stilbene derivatives



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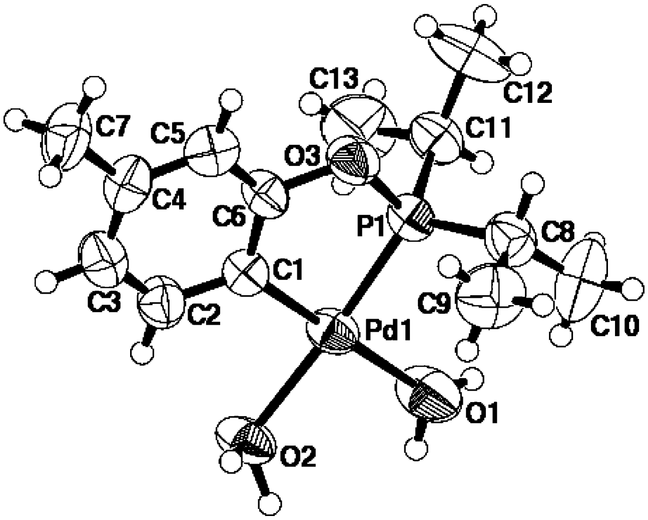


Figure 3. ORTEP drawing of [**4**](BF_4). The anion (BF_4) is omitted for clarity.

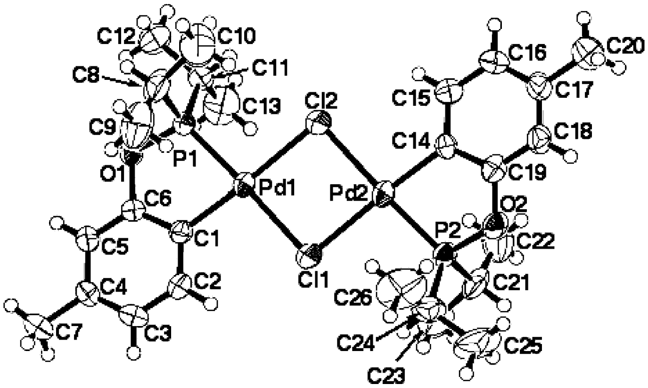


Figure 4. ORTEP drawing of **8**.

Table 3. Suzuki−Miyaura Coupling Reaction in Water[a]

entry	X of 3-X-C_6H_4-CO_2H	cat.	amt of cat. (mol %)	*T* (°C)	*t* (min)	yield (%)	TON[b]	TOF[c]
1	I	[**4**]$^+$	0.02	25	20	21	1 100	3 200
2	I	[**4**]$^+$	0.02	60	20	72	3 200	12 800
3	I	[**4**]$^+$	0.02	100	20	99	5 000	15 000
4	I	[**4**]$^+$	0.001	100	720	100	100 000	8 300
5	I	[**4**]$^+$	0.0002	100	720	57	290 000	16 000
6	Br	[**4**]$^+$	0.02	100	20	99	4 900	15 000
7	Br	[**4**]$^+$	0.001	100	720	70	70 000	5 800
8	Cl	[**4**]$^+$	0.02	100	720	50	2 500	830
9	I	[**3**]$^+$	0.001	100	720	72	72 000	6000
10	I	[**3**]$^+$	0.0002	100	720	25	123 000	13 000
11	Br	[**3**]$^+$	0.001	100	720	23	23 000	1 700
12	I	[**2**]$^+$	0.001	100	720	96	96 000	8 000
13	Br	[**2**]$^+$	0.001	100	720	0	0	0
14	I	[**1**]$^+$	0.001	100	720	85	85 000	7 100
15	Br	[**1**]$^+$	0.001	100	720	0	0	0

[a] Conditions: organic halide (294 μmol), Ph_4BNa (73.3 μmol), and $NaHCO_3$/NaOH buffer (6 mL, pH 10.5) prepared by 1 M $NaHCO_3$/H_2O and 5 M NaOH/H_2O. [b] TON: turnover number ((mol of product)/(mol of catalyst)), determined by ^1H NMR analysis of the reaction mixture samples (based on the organic halides and the product). [c] TOF: turnover frequency ((mol of product)/(mol of catalyst))/h.

under the present experimental conditions. Only 0.02−0.002 mol % of catalyst [**4**]$^+$ exhibits the high catalytic activity.[13,15,28−31] The highest TON was obtained using 0.002 mol % of catalyst [**4**]$^+$: 22 000 at 100 °C after 12 h.

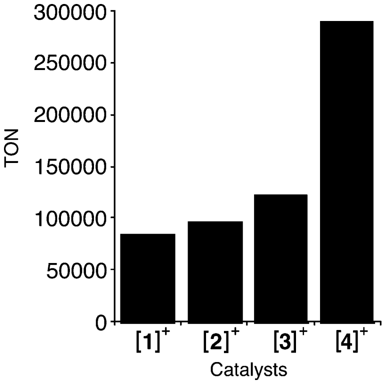


Figure 5. TONs of the Suzuki−Miyaura coupling reaction with [**1**]$^+$−[**4**]$^+$ in $NaHCO_3$/NaOH buffer (6 mL, pH 10.5) containing 3-I-$C_6H_4CO_2H$ (294 μmol) and Ph_4BNa (73.3 μmol) at 100 °C for 12 h in water.

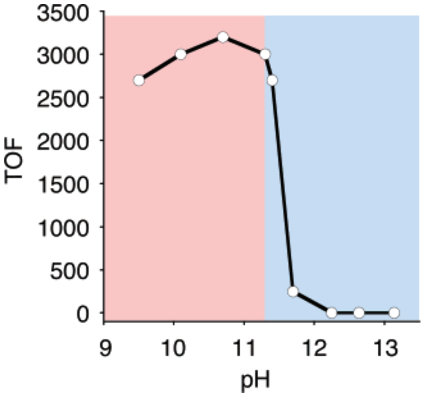
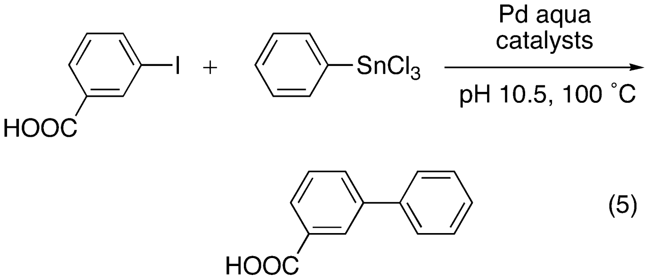


Figure 6. Typical pH-dependence profile of Suzuki−Miyaura coupling reactions of 3-I-$C_6H_4CO_2H$ with Ph_4BNa. Conditions: [**4**]$^+$ (0.02 mol %), 3-I-$C_6H_4CO_2H$ (294 μmol), Ph_4BNa (72.9 μmol), $NaHCO_3$/NaOH buffers (6 mL) prepared from 1 M $NaHCO_3$/H_2O and 5 M NaOH/H_2O, room temperature, 20 min.

The Mizoroki-Heck reaction catalyzed by [**4**]$^+$ shows a bell-shaped pH dependency, as shown in Figure 7. The decrease in the catalytic reactivity at pH >11.5 results from the deprotonation of the H_2O ligand of [**4**]$^+$, as in the case of the Suzuki−Miyaura coupling reaction (Figure 6). An increase in the catalytic reactivity in the region of pH 9.0−11.5 is ascribed to the requirement of the deprotonation step in the catalytic cycle of the Mizoroki−Heck reaction.[30] Thus, the optimum pH for the catalytic reactivity is obtained at pH 11.5. It was confirmed that no decomposition of the complexes and no precipitation of palladium black was observed (Figure S3 in the Supporting Information).

Stille Coupling Reaction Catalyzed by Water-Soluble Palladacyclic Aqua Complexes in Water. The Stille coupling reaction of 3-I-$C_6H_4CO_2H$ (294 μmol) with $PhSnCl_3$ (294 μmol) also proceeds efficiently using [**4**]$^+$ as a catalyst (0.002 mol %) in water at pH 10.5 at 100 °C (eq 5). As shown in Table 6,



(5)

the yield of the product (3-Ph-$C_6H_4CO_2H$) was 100% for 12 h

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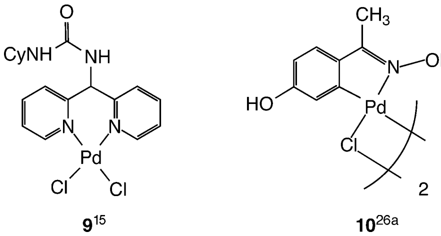
(43) At present, however, the catalytic mechanism has yet to be clarified in detail.

Chart 2



9[15] **10**[26a]

Table 4. Catalytic Reactivity of [4]$^+$ on Suzuki−Miyaura Coupling Reactions Compared with the Prominent Catalytic Reactivity of Previously Reported Water-Soluble Palladacyclic Chloro Catalysts 9 and 10 under Experimental Conditions Similar to Those Reported in the Literature[15,26a]

entry	X of 3-X-C_6H_4-OH	cat.	amt of cat. (mol %)	*T* (°C)	*t* (min)	yield (%)	TON[a]	TOF[b]
1	Br	[**4**]$^+$	0.0005	100	120	67	134 000	67 000
2	Br	**9**[c]	0.00076	100	120	95	125 000	62 500
3	Br	**10**[d]	0.005	100	15	88	17 600	70 400

[a] TON: turnover number ((mol of product)/(mol of catalyst)), determined by ^1H NMR analysis of the reaction mixture samples (based on the organic halides and the product). [b] TOF: turnover frequency ((mol of product)/(mol of catalyst))/h. [c] Reference 15. [d] Reference 26a.

Table 5. Mizoroki−Heck Reaction in Water[a]

entry	X of 3-X-$C_6H_4CO_2H$	cat.	amt of cat. (mol %)	*T* (°C)	*t* (min)	yield (%)	TON[b]	TOF[c]
1	I	[**4**]$^+$	0.02	60	20	20	1 000	3 000
2	I	[**4**]$^+$	0.02	80	20	43	2 200	66 00
3	I	[**4**]$^+$	0.02	100	20	70	3 500	11 000
4	I	[**4**]$^+$	0.002	100	720	43	22 000	1 800
5	Br	[**4**]$^+$	0.02	60	180	20	1 000	330
6	Br	[**4**]$^+$	0.02	100	180	51	2 600	870
7	I	[**3**]$^+$	0.02	100	20	16	790	2400
8	Br	[**3**]$^+$	0.02	100	20	0	0	0
9	I	[**2**]$^+$	0.02	100	20	0	0	0
10	I	[**1**]$^+$	0.02	100	20	0	0	0

[a] Conditions: 3-X-$C_6H_4CO_2H$ (294 μmol), 4-CH_2=CH-$C_6H_4CO_2H$ (294 μmol), $NaHCO_3$/NaOH buffer (6 mL, pH 10.5) prepared by 1 M $NaHCO_3/H_2O$ and 5 M $NaOH/H_2O$. [b] TON: turnover number ((mol of product)/(mol of catalyst)), determined by ^1H NMR analysis of the reaction mixture samples (based on the 4-CH_2=CH-$C_6H_4CO_2H$ and the product). [c] TOF: turnover frequency ((mol of product)/(mol of catalyst))/h.

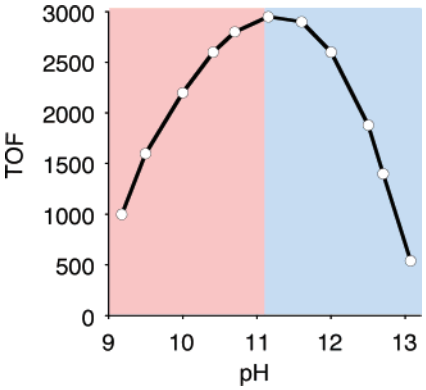


Figure 7. Typical pH-dependence profile of the Mizoroki−Heck reaction of 3-I-$C_6H_4CO_2H$ with 4-CH_2=CH-$C_6H_4CO_2H$. Conditions: [**4**]$^+$ (0.02 mol %), 3-I-$C_6H_4CO_2H$ (294 μmol), 4-CH_2=CH-$C_6H_4CO_2H$ (294 μmol), $NaHCO_3$/NaOH buffers (6 mL) prepared from 1 M $NaHCO_3/H_2O$ and 5 M $NaOH/H_2O$, 60 °C, 20 min.

with a high TON of 50 000. Thus, the catalyst [**4**]$^+$ can also be used as an effective catalyst for the Stille coupling reaction in water for practical use.

Table 6. Stille Coupling Reaction in Water[a]

entry	X of 3-X-C_6H_4-CO_2H	cat.	amt of cat. (mol %)	*T* (°C)	*t* (min)	yield (%)	TON[b]	TOF[c]
1	I	[**4**]$^+$	0.002	100	720	100	50 000	4 200
2	I	[**4**]$^+$	0.02	100	20	99	5 000	15 000
3	I	[**3**]$^+$	0.02	100	20	42	2 100	6 300
4	I	[**2**]$^+$	0.02	100	20	0	0	0
5	I	[**1**]$^+$	0.02	100	20	0	0	0

[a] Conditions: 3-X-$C_6H_4CO_2H$ (294 μmol), $PhSnCl_3$ (294 μmol), $NaHCO_3$/NaOH buffer (6 mL, pH 10.5) prepared by 1 M $NaHCO_3/H_2O$ and 5 M $NaOH/H_2O$. [b] TON: turnover number ((mol of product)/(mol of catalyst)), determined by ^1H NMR analysis of the reaction mixture samples (based on 3-X-$C_6H_4CO_2H$ and the product). [c] TOF: turnover frequency ((mol of product)/(mol of catalyst))/h.

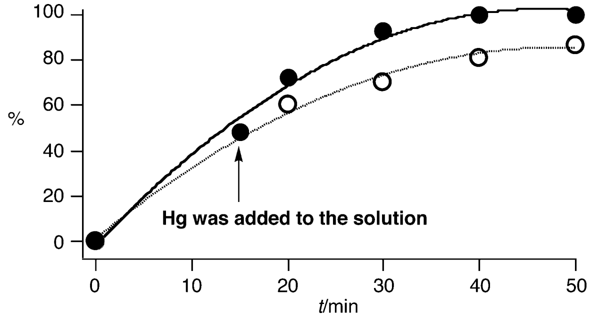


Figure 8. (●) Time course of the yields of the Suzuki−Miyaura coupling reaction of [**4**]$^+$ (0.02 mol %) with 3-I-$C_6H_4CO_2H$ (294 μmol) and Ph_4BNa (72.9 μmol) in water (3 mL) at pH 10.2 at 70 °C. (○) Time course of the yields of the Suzuki−Miyaura coupling reaction after addition of Hg(0) (300 equiv) to the reaction solution.

Mercury Drop Test. It has been reported that Hg(0) will not affect a homogeneous catalyst but form an amalgam with a heterogeneous catalyst, thereby poisoning it.[34] The Hg(0)-poisoning experiment is easy to perform but is not definitive by itself and is not universally applicable. Figure 8 shows the time course of the yields of the Suzuki−Miyaura coupling reaction after addition of 300 equiv of Hg(0) (relative to the catalyst [**4**]$_2SO_4$, at t = 15 min) to the reaction solution. The result indicates that there is no heterogeneous metal particles in the reaction solution under the present reaction conditions.

In conclusion, the water-soluble PC palladacyclic aqua complex $[(PC)Pd^{II}(H_2O)_2]^+$ ([**4**]$^+$) exhibits high catalytic activity for a variety of C−C coupling reactions in water: the pH-dependent Suzuki−Miyaura coupling reaction (of organic chloride, bromide, and iodide), the Mizoroki−Heck reaction, and the Stille coupling reaction. The catalytic ability of the palladacyclic aqua catalyst is drastically dependent on the pH of the solution and the structures of supporting ligands.

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Supporting Information Available: Crystallographic data (CIF files) for [**3**](PF_6), [**4**](BF_4), and **8** and Figures S1−S3, giving ^1H NMR spectra for [**3**]$_2(SO_4)$ and [**4**]$_2(SO_4)$ and pictures of reaction solutions of the Suzuki−Miyaura and Mizoroki−Heck reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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