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The first use of porphyrins as catalysts in cross-coupling reactions: a water-soluble palladium complex with a porphyrin ligand as an efficient catalyst precursor for the Suzuki–Miyaura reaction in aqueous media under aerobic conditions

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Abstract—For the first time, a palladium complex with a porphyrin ligand is used as a catalyst precursor for cross-coupling reactions. The synthesis of a palladium complex with a phosphine-free and water-soluble potassium carboxylate salt of a porphyrin, and its evaluation in the Suzuki–Miyaura reaction of phenylboronic acid with aryl bromides (from electron-rich to electron-poor), in neat water, under aerobic conditions is described. Catalysis is performed at 100 °C for 4 h, using K_2CO_3 as base, and a substrate to catalyst molar ratio of 1000:1, leading to yields of coupling products in the range of 80–100%. The catalyst can be recycled and reused, but unfortunately, with a loss in activity.

1. Introduction

Homogeneous palladium catalysis has become an essential tool for synthetic organic chemists in carbon–carbon bond formation.[1] The coupling of aryl halides with organoboronic acids, the Suzuki–Miyaura reaction, is one of the most important palladium-catalyzed cross-coupling reactions.[1,2] The replacement of organic solvents by water in transition metal homogeneous catalysis has received remarkable attention, as water is inexpensive, non-toxic, non-flammable, environmentally sustainable, and allows simple separation and reuse of the catalyst.[3] For these reasons, intensive research efforts are being directed to perform the Suzuki–Miyaura coupling either via aqueous biphasic catalysis or in neat water.[4] Initially, water-soluble phosphines were used as ligands for the cross-coupling reactions in aqueous media,[5] but in recent years, other hydrophilic phosphine-free systems, such as CNC-pincer palladium complexes,[6] have also been found to be highly efficient catalysts for this transformation.

Palladium porphyrins are of great interest owing to their high yield of intersystem crossing and long lifetime of the resulting triplet state in diverse media.[7] Palladium porphyrins have found applications as luminescent markers,[8] oxygen sensors,[9] sensitizers for singlet oxygen formation,[10] and photo-induced protein cross-linking agents.[11] Additionally, bis-zinc(II) porphyrin building blocks have been used to assemble monodentate phosphorus ligands as an approach to prepare supramolecular bidentate chelating ligands for rhodium and palladium catalysis.[12] Our groups have contributed towards the synthesis of new metalloporphyrin derivatives,[13] mainly as biomimetic complexes, and have reported the application of new phosphines[14a] as well as air-stable phosphine-free ligands[14b–e] for palladium-catalyzed coupling reactions, having the advantage of performing the reactions under aerobic conditions. In

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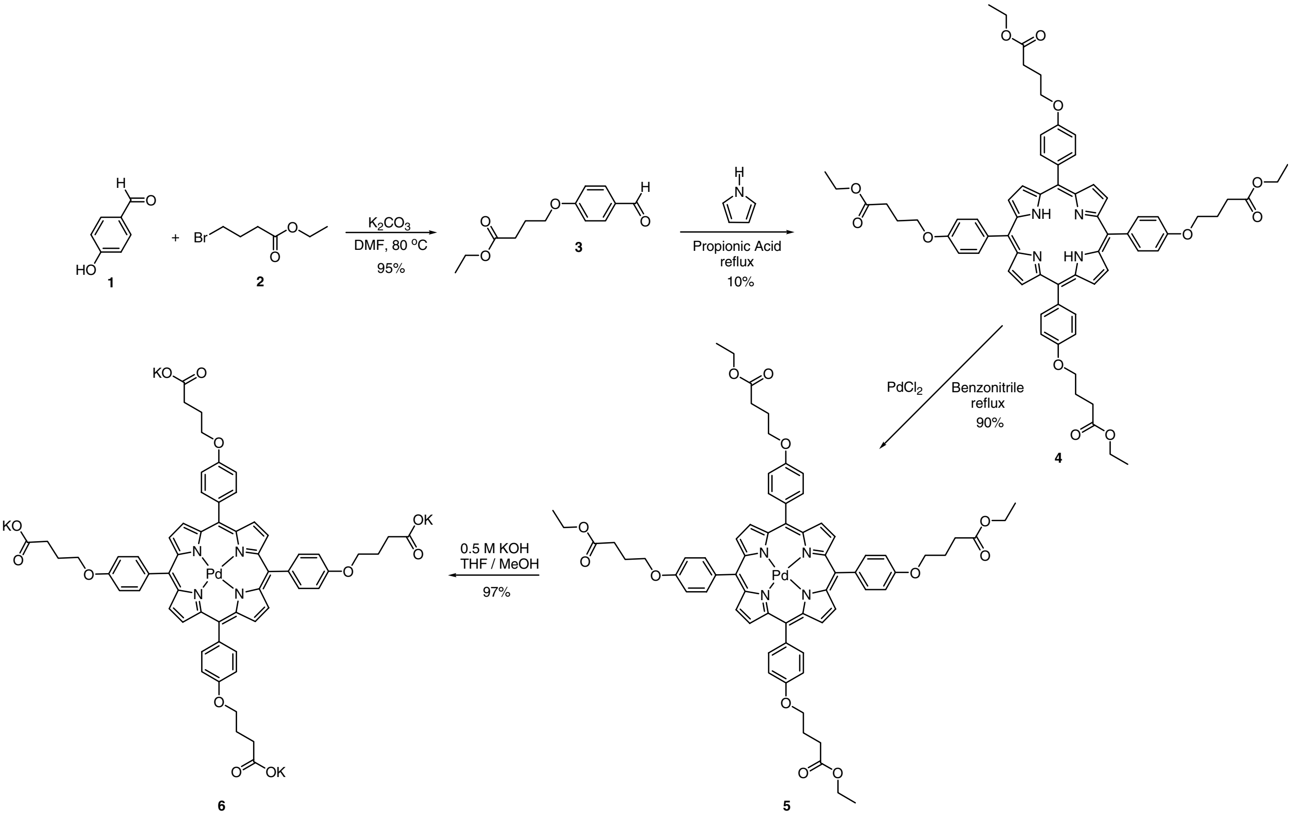
the present work, we report the synthesis of a palladium complex with a phosphine-free and water-soluble potassium carboxylate salt of a porphyrin, which was successfully applied in the Suzuki–Miyaura reaction of phenylboronic acid with aryl bromides, in neat water, under aerobic conditions. Although palladium-catalyzed coupling reactions have been used extensively for the synthesis of porphyrins,[15] this Letter represents the first study concerning the evaluation of a porphyrin ligand as a precatalyst in cross-coupling reactions.

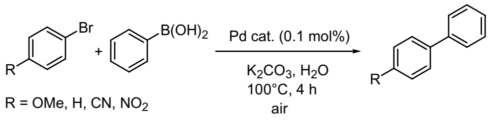
2. Results and discussion

The synthesis of the water-soluble palladium porphyrin **6** is outlined in Scheme 1. Functionalized benzaldehyde **3** was obtained in 95% yield by the alkylation of 4-hydroxybenzaldehyde (**1**) with ethyl 4-bromobutyrate (**2**) in the presence of K_2CO_3, in DMF at 80 °C. Porphyrin **4** was prepared in 10% yield following the classical method of Adler and Longo,[16] via the reaction of the aldehyde **3** with pyrrole in refluxing propionic acid. Palladium insertion was carried out by the addition of palladium chloride to the free base **4** in refluxing benzonitrile,[17] leading to porphyrin **5** in 90% yield. Metal insertion was confirmed by the characteristic changes in the UV–vis spectrum of the metallated porphyrin **5** compared to **4**, and by ^{1}H NMR spectroscopy. The visible absorption spectra of porphyrin **4** had a Soret band at 422 nm and four Q-bands (519, 555, 589 and 651 nm). In the metallated compound **5**, the Soret shift occurred at 420 nm and the Q-bands were reduced to two (525 and 559 nm). These features are characteristic of palladium insertion in a porphyrin system. Moreover, the absence of negative chemical shifts in the ^{1}H NMR spectrum of porphyrin **5** was also an indicative that porphyrin **5** had been metallated. Finally, complex **6** was obtained, almost quantitatively, by saponification using a large excess of KOH in THF/MeOH mixture. Complex **6**, as the potassium carboxylate salt displayed complete solubility in water.

Palladium-porphyrin complex **6**, as a stock solution in water (1 mM), was used as catalyst in the Suzuki–Miyaura reaction of phenylboronic acid with representative aryl bromides (electron-rich and electron-poor) at 100 °C, using K_2CO_3 as base, and a substrate to catalyst molar ratio of 1000:1 (Scheme 2, Table 1). All the reactions were performed in air, and water was the only solvent used. As expected, the catalytic activity depended on the halide, while electron-withdrawing groups on the aryl ring increased the reaction rate. After 4 h reaction time, the GC yield of the coupling product was found to be 80% for deactivated 4-bromoanisole (entry 1), 83% for non-activated bromobenzene (entry 2), and 100% for activated 4-bromobenzonitrile (entry 3). For activated substrates, the yield was very high even after 1–2 h (entries 4 and 5). The feasibility of recycling and reusing the catalyst was also examined taking the coupling of phenylboronic acid with 4-bromobenzonitrile as a model (entry 3; cycles 1–3). After the first cycle, extraction with hexane allowed a simple separation of the coupling product from the water-soluble catalyst **6**. The resulting aqueous phase was reused, simply by the



Scheme 1.



Scheme 2.

Table 1. Suzuki–Miyaura cross-coupling in water, catalyzed by palladium-porphyrin complex **6** under aerobic conditions

Entry	R	Time (h)	GC yield[a] (%)
1	OMe	4	80
2	H	4	83
3	CN	4	Cycle-1: 100 Cycle-2: 76 Cycle-3: 53
4	CN	2	99
5	NO_2	1	93

Reagents and conditions: ArBr (1.0 mmol), $PhB(OH)_2$ (1.5 mmol), K_2CO_3 (2.0 mmol), Pd complex **6** in H_2O (1 mM, 1 mL), 100 °C.

[a] Yield of coupled product R–C_6H_4–Ph, based on aryl bromide (GC).

addition of the substrate and base. The reaction was repeated at 100 °C for 4 h, for up to three cycles, but unfortunately, the catalyst exhibited a loss in activity, perhaps due to the decreased stability of complex **6** under the reaction conditions. Palladium leaching from the aqueous phase can be excluded due to the negligible catalytic activity of the organic phase after the extraction of the coupling products. In order to investigate this, the organic extracts derived from the reaction of phenylboronic acid with 4-bromoanisole were evaporated to dryness, water (2 mL) was added, and the mixture was filtered. The aqueous phase was mixed with 4-bromobenzonitrile, phenylboronic acid and K_2CO_3 using the same molar ratio as in the previous experiments, and refluxed in air. Even after 24 h, no coupling product was detected, indicating that no leaching had occurred.

3. Conclusions

In summary, we have synthesized a palladium complex of a phosphine-free and water-soluble potassium carboxylate salt of a porphyrin, which can serve as an efficient precatalyst for the Suzuki–Miyaura cross-coupling of aryl bromides with phenylboronic acid under mild reaction conditions, in neat water, in air. The catalyst could be easily recycled and reused, but unfortunately, with a loss in activity. This first study of the application of porphyrins to cross-coupling reactions provides important information on the catalytic activity of these systems. The development of analogous water-soluble porphyrins displaying higher stability under the reaction conditions for palladium-catalyzed reactions is currently in progress.

4. Experimental

4.1. Aldehyde 3

A mixture of 4-hydroxybenzaldehyde (4.00 g, 33 mmol) and K_2CO_3 (5.40 g, 39 mmol) was stirred in anhydrous DMF (15 mL). Ethyl 4-bromobutyrate (7.62 g, 39 mmol) was added dropwise and the mixture was heated at 80 °C for 2 h. After cooling, the salts were filtered. DMF was evaporated to dryness, and the reaction mixture was re-dissolved in CH_2C1_2 (100 mL) and washed with 4 × 50 mL distilled water. Drying over sodium sulfate, filtration and evaporation of the solvent afforded benzaldehyde **3** as a pale yellow oil (7.09 g, 95%). The reaction product was used without any further purification. ^1H NMR (500 MHz, $CDCl_3$): δ 9.86 (s, 1H, CHO), 7.81 (d, $J = 8.5$ Hz, 2H, Ar), 6.98 (d, $J = 8.5$ Hz, 2H, Ar), 4.13 (q, $J = 7.0$ Hz, 2H, CH_2), 4.09 (t, $J = 6.5$ Hz, 2H, CH_2), 2.51 (t, $J = 7.0$ Hz, 2H, CH_2), 2.14 (sextet, $J = 6.5$ Hz, 2H, CH_2), 1.24 (t, $J = 7.0$ Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.2 (CO), 173.4 (CO), 164.3 (C), 132.4 (Ar), 130.4 (C), 115.1 (Ar), 67.5 (CH_2), 60.9 (CH_2), 31.0 (CH_2), 24.8 (CH_2), 14.6 (CH_3). HRMS (ES^+) Calcd for $C_{13}H_{16}O_4$ $(M)^+$: 236.1049. Found: 236.1042.

4.2. Porphyrin 4

A solution of benzaldehyde **3** (3.00 g, 13 mmol) in propionic acid (150 mL) was heated to 100 °C and pyrrole (0.97 mL, 14 mmol) was added dropwise. The mixture was refluxed for 2 h, and then the crude product was evaporated to dryness under vacuum. Filtration through a silica gel pad with CH_2Cl_2/MeOH (95:5, v/v) as eluent was performed to remove the tar. The resulting crude product was purified by chromatography on silica gel, and the product was eluted with CH_2Cl_2/EtOH 97:3 to give compound **4** as a purple solid (0.37 g, 10%). ^1H NMR (500 MHz, $CDCl_3$): δ 8.87 (s, 8H, Ar), 8.12 (d, $J = 8$ Hz, 8H, Ar), 7.26 (d, $J = 8.5$ Hz, 8H, Ar), 4.30 (t, $J = 6.0$ Hz, 8H, CH_2), 4.26 (q, $J = 7.0$ Hz, 8H, CH_2), 2.70 (t, $J = 7.0$ Hz, 8H, CH_2), 2.32 (m, 8H, CH_2), 1.36 (t, $J = 7$ Hz, 12H, CH_3), −2.73 (s, 2H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.7 (CO), 159.1 (C), 136.0 (Ar), 135.2 (C), 131.4 (Ar), 120.2 (C), 113.2 (Ar), 67.5 (CH_2), 61.0 (CH_2), 31.5 (CH_2), 25.3 (CH_2), 14.8 (CH_3). UV–vis: λ_{abs} (CH_2Cl_2) (ε, $mM^{-1}\,cm^{-1}$) 422 (389.4), 519 (16.5), 555 (12.2), 589 (6.0), 651 (7.8). HRMS (ES^+) Calcd for $C_{68}H_{71}N_4O_{12}$ $(M+H)^+$: 1135.5068. Found: 1135.4997.

4.3. Porphyrin 5

Porphyrin **4** (65 mg, 0.057 mmol) was dissolved in benzonitrile (70 mL) and $PdCl_2$ (20.4 mg, 0.115 mmol) was added. The solution was refluxed for 3 h, cooled, and then reduced to dryness under vacuum. Then, CH_2Cl_2 (40 mL) was added, and the mixture was washed with aqueous NaCl (2 × 30 mL). The organic layer was dried over sodium sulfate, filtered, concentrated, and the residue was chromatographed on a silica gel column (CH_2Cl_2/MeOH, 97:3) to obtain **5** as an orange solid (63 mg, 90%). ^1H NMR (500 MHz, $CDCl_3$): δ 8.83 (s, 8H, Ar), 8.03 (d, $J = 8.5$ Hz, 8H, Ar), 7.20 (d, $J = 8.5$ Hz, 8H, Ar), 4.24 (m, 16H, CH_2), 2.67 (t, $J = 7.0$ Hz, 8H, CH_2), 2.28 (q, $J = 6.5$ Hz, 8H, CH_2), 1.35 (t, $J = 7.0$ Hz, 12H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.7 (CO), 159.1 (C), 142.3 (C), 135.5 (Ar), 134.7 (C), 131.3 (Ar), 121.8 (C), 113.2 (Ar), 67.5

(CH_2), 61.0 (CH_2), 31.4 (CH_2), 25.3 (CH_2), 14.7 (CH_3). UV–vis: λ_{abs} (CH_2Cl_2) (ε, $mM^{-1}\,cm^{-1}$) 420 (402.3), 525 (29.2), 559 (3.5). HRMS (ES^+) Calcd for $C_{68}H_{69}N_4O_{12}Pd$ $(M+H)^+$: 1239.3947. Found: 1239.3864.

4.4. Porphyrin 6

Palladium porphyrin **5** (29 mg, 23 μmol) was dissolved in a solution of THF (45 mL), methanol (18 mL) and 0.5 M KOH (19 mL). The reaction was monitored by thin layer chromatography (CH_2Cl_2/MeOH, 9:1). After stirring at room temperature for 24 h, the solution was evaporated to dryness to afford compound **6** as a dark red solid (28 mg, 97%). UV–vis: λ_{abs} (MeOH) (ε, $mM^{-1}\,cm^{-1}$) 417 (395.2), 524 (33.3), 558 (5.0).

4.5. General experimental procedure for the Suzuki–Miyaura coupling

A round bottom flask equipped with a reflux condenser, was charged in air with aryl bromide (1.0 mmol), phenylboronic acid (0.183 g, 1.5 mmol), K_2CO_3 (0.276 g, 2.0 mmol), and a stock solution of complex **6** in H_2O (1 mM, 1 mL, 0.001 mmol). The mixture was stirred in a preheated 100 °C oil bath for 4 h, and then allowed to cool to room temperature. After the addition of water (1 mL) and extraction with hexane (4×10 mL), the organic phase was dried over Na_2SO_4, filtered, passed through Celite and analyzed by GC and GC–MS. For the reuse of the catalyst, the flask, containing the aqueous solution of the complex, was charged with aryl bromide (1.0 mmol), phenylboronic acid (0.183 g, 1.5 mmol), and K_2CO_3 (0.276 g, 2.0 mmol), and the mixture was stirred at 100 °C for 4 h. On each occasion, after cooling and extraction with hexane, the combined organic extracts were dried over Na_2SO_4, filtered, passed through Celite and analyzed by GC and GC–MS. Dichloromethane was used as the extracting solvent for the coupling product of 1-bromo-4-nitrobenzene with phenylboronic acid. All the biaryls prepared are known compounds.[14c]

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