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Novel bis(oxazole) pincer ligands for catalysis: Application in Suzuki-Miyaura cross coupling reactions under aerobic conditions

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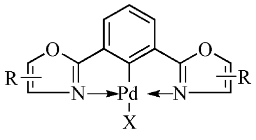
Abstract

Introducing bis(oxazole) ligands to catalysis: novel bis(oxazole) ligands could be readily synthesized from isophthaloyl dichlorides and ethyl glycinate hydrochlorides or 6-aminoacetophenone hydrochloride. Their corresponding pincer palladium complexes proved to be extremely robust catalysts for Suzuki-Miyaura cross coupling reactions, allowing the synthesis of biaryls under aerobic conditions with turn over numbers of up to 790,000 and turn over frequencies of up to 49,000 h^{-1}.

Keywords: Bis(oxazoles); Pincer ligands; Suzuki-Miyaura cross coupling; Palladium; Biaryls

1. Introduction

The oxazoline moiety has proved to be an excellent donor for metals, and especially bis(oxazolines) are recognized to be superior ligands for catalysis [1]. One drawback of oxazolines is their lability towards hydrolysis, especially at higher reaction temperatures and under acidic conditions. Based on our own interest in the development of bis(oxazoline) [2] and azabis(oxazoline) [3] ligands for catalysis, we wanted to explore bis(oxazoles) as an alternative, more stable ligand framework to form metal complexes, for which to the best of our knowledge no applications in catalysis have been reported [4]. As a starting point for bis(oxazoles) we chose pincer ligands of the NCN type since it was expected that especially stable palladium complexes **1** should be formed that would allow their detailed characterization.



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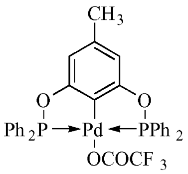

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Moreover, as a first benchmark application of these complexes in Suzuki-Miyaura cross coupling reactions were envisioned [5], for which PCP–palladium complexes such as **2** have been proved to give excellent results [6].

2. Experimental

2.1. Chemicals

Commercially available reagents were used as received. DMF, $ClCH_2CH_2Cl$ and CH_2Cl_2 were distilled over P_2O_5 and stored under N_2 over molecular sieves 3 Å. THF, 1,4-dioxane and benzene were dried with Na/benzophenone and stored over Na-wire under N_2. EtOAc, Et_2O, CH_2Cl_2 and hexanes for chromatographic separations were distilled before use. For column chromatography silica gel Geduran 60 (Merck, 0.063–0.200 mm) was used. TLC-analysis was done on silica gel 60 F_{254} (Merck) coated on aluminum sheets.

2.2. Synthesis of bis(oxazole) ligands

2.2.1. Bis(oxazole) 5a [7a]

Isophthaloyl dichloride **4a** (1.22 g, 6 mmol) and ethyl glycinate hydrochloride (2.51 g, 18 mmol) were suspended in 40 mL of dry CH_2Cl_2, and Et_3N (8.4 mL, 60 mmol) was added dropwise at 0 °C. After being stirred for 30 h with gradual warming to room temperature, the resultant mixture was diluted with

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200 mL of EtOAc and washed with water (2× 50 mL), the water phase was extracted with 150 mL of EtOAc. The combined organic phase was washed with 10% aqueous HCl, water, and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and then filtered and concentrated under reduced pressure to yield *N*,*N*′-bis(2-oxo-2-ethoxyethyl)isophthalamide (**A**) (2.0 g, 99% yield) as a colorless oil which slowly solidified. The compound could be used in the next step without purification. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.20$ (t, $J = 1.6$ Hz, 1H), 7.92 (dd, $J = 1.8$, 7.8 Hz, 2H), 7.46 (t, $J = 7.7$ Hz, 1H), 7.09 (t, $J = 5.1$ Hz, 2H), 4.26 (q, $J = 7.1$ Hz, 4H), 4.23 (d, $J = 5.2$ Hz, 4H), 1.32 (t, $J = 7.1$ Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.2$, 166.7, 133.9, 130.5, 129.0, 125.4, 61.8, 41.9, and 14.2. A mixture of **B** (338 mg, 1 mmol) and P_2O_5 (2.8 g, 20 mmol) in 40 mL of dry $ClCH_2CH_2Cl$ was stirred for 14 h at 90 °C. The reaction mixture was cooled to room temperature, diluted with 30 mL of Et_2O, and then carefully neutralized with 10% cold KOH aqueous solution (*ca.* 35 mL) followed by extraction with EtOAc (three portions of 50 mL). The combined organic phase was washed with water and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and then filtered and concentrated to dryness. The crude product was purified by column chromatography (silica, hexanes:EtOAc 1:1 as eluent) to afford 39 mg of **5a** as a pale white solid. Yield 13%. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.42$ (t, $J = 1.5$ Hz, 1H), 7.92 (dd, $J = 1.8$, 7.8 Hz, 2H), 7.46 (t, $J = 7.8$ Hz, 1H), 6.22 (s, 2H), 4.19 (q, $J = 7.0$ Hz, 4H), 1.45 (t, $J = 7.1$ Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 159.9$, 151.9, 129.2, 128.2, 126.1, 122.1, 101.1, 68.2, 14.6.

2.2.2. *Bis(oxazole)* **5b**

2-Bromoisophthaloyl dichloride **4b** [7b] (1.73 g, 6 mmol) and ethyl glycinate hydrochloride (2.51 g, 18 mmol) were suspended in 40 mL of dry CH_2Cl_2, and Et_3N (8.4 mL, 60 mmol) was added dropwise at 0 °C. After being stirred for 30 h with gradual warming to room temperature, the resultant mixture was concentrated, diluted with 70 mL of H_2O, and then extracted with CH_2Cl_2 (four portions of 150 mL each). The combined organic phase was washed with 10% aqueous HCl, water, and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and then filtered and concentrated under reduced pressure to yield 2-bromo-*N*,*N*′-bis(2-oxo-2-ethoxyethyl)isophthalamide (**B**) (2.10 g, 84% yield) as a white solid. The compound could be used in the next step without purification. mp 191–192 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.54$ (dd, $J = 7.1$, 8.0 Hz, 2H), 7.42 (dd, $J = 6.9$, 8.2 Hz, 1H), 6.48 (t, $J = 4.8$ Hz, 2H), 4.27 (q, $J = 7.1$ Hz, 4H), 4.25 (d, $J = 5.0$ Hz, 4H), 1.32 (t, $J = 7.1$ Hz, 6H). A mixture of **B** (1.66 g, 4 mmol) and P_2O_5 (7.5 g, 52.8 mmol) in 80 mL of dry $ClCH_2CH_2Cl$ was heated for 30 min at 60 °C, and then stirred for 14 h at 90 °C. The reaction mixture was cooled to room temperature, diluted with 50 mL of Et_2O, and then carefully neutralized with 10% cold NaOH (*ca.* 55 mL) followed by extraction with EtOAc (3× 150 mL each). The combined organic phase was washed with water and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and then filtered and concentrated. The crude product was purified by column chromatography (silica, hexanes:EtOAc 1:1 as eluent) to afford **5b** (880 mg, 58% yield) as a light yellow solid. mp 56–57 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.80$ (d, $J = 8.0$ Hz, 2H), 7.43 (t, $J = 7.8$ Hz, 1H), 6.31 (s, 2H), 4.22 (q, $J = 7.1$ Hz, 4H), 1.47 (t, $J = 7.1$ Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 160.1$, 150.9, 132.1, 130.9, 127.3, 120.0, 100.9, 68.3, 14.6. MS (EI-MS): *m*/*z* (%) = 380.1 (56), 378.1 (57) [M^+], 296.1 (98), 294.0 (100), 268.0 (44), 266.0 (46). Elemental analysis for $C_{16}H_{15}BrN_2O_4$: found C 50.99, H 4.21, N 7.14, Br 20.51; calcd. C 50.68, H 3.99, N 7.39, Br 21.07.

2.2.3. *Bis(oxazole)* **5c**

To a stirred mixture of isophthaloyl dichloride (**4a**) (1.01 g, 5.0 mmol, 1.0 equiv.) in 12 mL of dry pyridine was added in portions α-aminoacetophenone hydrochloride (1.88 g, 11 mmol, 2.2 equiv.). The reaction was refluxed for 30 min. Then the mixture was allowed to cool and diluted with water. The precipitate was filtered and dissolved in hot ethyl acetate. The organic solution was concentrated to a smaller volume and diethyl ether was added. White to beige product commences to crystallize out. Filtration afforded the crude product (0.99 g, 2.47 mmol, 49%), which was used without further purification. ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 9.02$ (t, 2H, $J = 5.5$ Hz), 8.48–8.42 (m, 1H), 8.12–8.00 (m, 6H), 7.74–7.52 (m, 7H), 4.83 (d, 4H, $J = 5.5$ Hz); ^{13}C NMR (75.5 MHz, DMSO-d_6): $\delta = 195.1$, 166.0, 135.0, 134.1, 133.5, 129.9, 128.8, 128.5, 127.8, 126.4, 46.4; MS (PI-EIMS): *m*/*z* (%) = 400.2 (14) [M^+], 295.2 (11) [$M^+ - PhCO$], 266.1 (84) [$M^+ - PhCOCH_2NH$], 105.1 (100) [$PhCO^+$], 77.1 (25) [Ph^+]. A mixture of *N*,*N*′-bis-(2-oxo-2-phenyl-ethyl)isophthalamide (1.03 g, 2.57 mmol, 1.0 equiv.) in 40 mL phosphorus oxychloride was refluxed for 16 h. Most of the phosphorus oxychloride was distilled in vacuum into a cold trap from the reaction mixture, and the residue was slowly added to water contained in a 250 mL beaker. The solid was filtered, washed with water and dried (crude product). Recrystallization from pyridine afforded 0.49 g (1.34 mmol, 52%) of **5c** as a white to beige solid. mp 177 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.85$–8.79 (m, 1H), 8.21 (dd, 2H, $J = 7.8$, 1.6 Hz), 7.81–7.74 (m, 4H), 7.61 (t, 1H, $J = 7.8$ Hz), 7.55–7.43 (m, 6H), 7.41–7.33 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 160.4$, 151.8, 129.5, 129.0, 128.7, 128.2, 128.0, 127.8, 124.4, 123.8, 123.5; IR (KBr): 3110, 3060, 1600, 1580, 1565, 1530, 1480, 1470, 1445, 1420, 1135, 1075, 1060, 1030, 965, 950, 940, 910, 860, 825, 800, 760, 710, 680 cm^{-1}; MS (PI-EIMS): *m*/*z* (%) = 364.2 (100) [M^+]; $C_{24}H_{16}N_2O_2$ (364.40): calcd. C 79.11, H 4.43, N 7.69; found C 78.42, H 3.77, N 7.49.

2.2.4. *Bis(oxazole)* **5d**

To a stirred mixture of 2-bromo-1,3-benzenedicarbonyl dichloride (**4b**) (1.50 g, 5.32 mmol, 1.0 equiv.) in 15 mL of dry pyridine was added in portions α-aminoacetophenone hydrochloride (2.00 g, 11.71 mmol, 2.2 equiv.). The reaction was refluxed for 15 min—the mixture got red, then yellow. The reaction was allowed to cool and diluted with water. The resulting precipitate was filtered, washed with diethyl ether and dried. This crude product was stirred in 20 mL of ethyl acetate. Filtration of the cold (0 °C) mixture afforded the product as beige solid (1.76 g, 3.67 mmol, 69%). ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 8.87$ (t, 2H, $J = 5.6$ Hz), 8.10–8.01 (m, 4H), 7.74–7.65 (m, 2H), 7.63–7.44 (m, 7H), 4.78 (d, 4H,