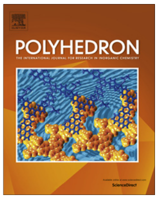
Polyhedron 70 (2014) 39–46

Contents lists available at ScienceDirect

Polyhedron

journal homepage: www.elsevier.com/locate/poly



Palladium–bis(oxazoline) complexes with inherent chirality: Synthesis, crystal structures and applications in Suzuki, Heck and Sonogashira coupling reactions

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ARTICLE INFO

Article history:
Received 4 October 2013
Accepted 22 December 2013
Available online 30 December 2013

Keywords:
Palladium
Bis(oxazoline)
Inherent chirality
Coupling reactions

ABSTRACT

New palladium–bis(oxazoline) (Pd–BOX) complexes were synthesized and characterized. The X-ray crystal structures of the two complexes showed that the palladium ion is bound to the nitrogen atoms of the two heterocycles of the bidentate ligand and two chloride ions in a distorted square planar geometry. The coordination to the palladium ion allows these non C_2-symmetric bis(oxazoline) ligand-based complexes to acquire a rigid backbone curvature generating an inherent chirality. The catalytic activities were evaluated in Suzuki–Miyaura, Mizoroki–Heck and Sonogashira coupling reactions. The complexes showed high catalytic activities towards numerous C–C coupling reactions with various aryl halides, aryl boronic acids, alkenes and alkynes. The reactions were optimized for the most suitable temperature, solvent, and base system.

1. Introduction

Palladium-catalyzed C–C bond coupling reactions have been established as a powerful tool for the production of monomers for polymers, agrochemicals, pharmaceuticals, flavors and fragrances [1]. During the last decades, the Suzuki–Miyaura [2], Mizoroki–Heck [3], and Sonogashira [4] coupling reactions have been playing key roles in organometallic chemistry and recent organic synthesis. Particularly, these reactions are involved in the majority of methods used to construct biaryl compounds [5] for the total synthesis of natural products, material science and supramolecular chemistry [6]. Recently the scope and practical use of such coupling reactions have significantly enhanced and the design and synthesis of new ligands to facilitate these coupling reactions have great contributions to this progress [7]. A good number of reports deal with catalytic species based on transition metals and phosphine ligands to catalyze the coupling reactions [8]. However, there are limited number of reports that describes the use of nitrogen as a donor atom with palladium complexes [7,9]. In addition, phosphine ligands are in general air and moisture sensitive. Thus, rather than the catalytic species generated in situ, the development of new catalysts that are well defined, efficient, inexpensive, insensitive to air and moisture, and less toxic is highly desirable. An alternative would be nitrogen-based ligands which are generally non-toxic, stable to air/moisture, modular, and less expensive than phosphine ligands [9]. Therefore, the current research is more focused on the synthesis of ligands containing nitrogen as a donor atom such as oxime-based palladacycle [10], amine [11], bis *N*-heterocyclic carbene [12], and *N*-heterocyclic carbene-oxazoline [13]. In this context, dinitrogenated bis(oxazoline) ligands [14–16] and particularly their C_2-symmetric chiral molecules have been extensively used with different metal ions in asymmetric catalysis [17]. However, only few examples that describe the applications of palladium-bis(oxazoline) complexes in C–C bond coupling reactions have been reported so far [18]. In this paper, we report on the synthesis and characterization of two new bis(oxazoline) (BOX) ligands and their corresponding chloridobis(oxazoline)palladium(II) (Pd–BOX) complexes. The results of the catalytic applications to C–C bond cross coupling reactions such as Suzuki–Miyaura, Mizoroki–Heck, and Sonogashira reactions are presented.

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http://dx.doi.org/10.1016/j.poly.2013.12.023

2. Experimental

2.1. Materials and instrumentation

2.1.1. Materials

Starting material for the synthesis of ligands and complexes was purchased from Sigma Aldrich and used without further purification. Chlorobenzene (anhydrous) was purchased from Sigma Aldrich and used as received. Other solvents used in the synthesis were of reagent grade (Merck) and were distilled before use. Purification of the products was carried out using flash column chromatography. The column was packed with Silica gel 60 F from Fluka Chemie AG (Buchs, Switzerland). Palladium compounds were purchased from Strem Company.

2.1.2. Instrumentation

^1H and ^{13}C NMR spectra were recorded on 500 MHz Joel 1500 NMR machine. Chemical shifts (δ) were reported in ppm relative to tetramethyl silane (TMS) using $CDCl_3$. IR spectra were recorded on Perkin-Elmer 16F PC FT-IR spectrometer and reported in wave numbers (cm^{-1}), or by Nicolet™ 6700 FT-IR spectrometer. Gas chromatography (GC) analyses were realized on Agilent GC 6890. The products of the reactions were also analyzed on GC–MS Varian Saturn 2000 equipped with 30 m capillary column (HP-5). Thin-layer chromatography (TLC) analyses were performed on silica gel Merck 60 F_{254} plates (250 μm layer thickness).

2.2. Synthesis of the ligands **1** and **2**

We have adopted a synthetic route by analogy to other bis(oxazoline) ligands [19,20]. A 100-mL two-necked round bottom flask fixed with a reflux condenser was charged substituted dicyanobenzene (500 mg, 3.50 mmol), zinc triflate (5 mol%, 0.18 mmol, 0.060 g), and dry chlorobenzene (20.0 mL) under free-oxygen and free-water conditions. The mixture was stirred for 5 min and then a solution of achiral 2-aminoalcohol (8.80 mmol) in dry chlorobenzene (5.0 mL) was added slowly. The reaction mixture was heated and refluxed at 135 °C for 24 h. The solvent was removed under reduced pressure to give an oily residue which was dissolved in 25 mL of dichloromethane. The solution was extracted twice with 15 mL of water and the aqueous phase was washed with 15.0 mL of dichloromethane. The combined organic layers were dried with sodium sulfate and the solvent was removed under vacuum to give the crude oil. Further purification of the ligands was done by silica gel column chromatography (ether/dichloromethane 1/4).

2.2.1. 2,2′-(4-Phenoxy-1,2-phenylene)bis(4,4-dimethyl-4,5-dihydrooxazole) (**1**)

Greenish oil; isolated yield = 94%; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.64 (d, J = 8.5 Hz, 1H), 7.28–7.24 (m, 3H), 7.06 (t, J = 7.9 Hz, 1H), 6.98–6.92 (m, 3H), 3.97 (s, 4H, OCH_2 × 2), 1.29 (s, 12H, $NC(CH_3)_2$ × 2); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm); 28.0 ($NC(CH_3)_2$ × 2), 67.7 ($NC(CH_3)_2$), 67.9 ($NC(CH_3)_2$), 79.3 (OCH_2), 79.4 (OCH_2), 119.4, 119.6, 123.0, 124.0, 129.8, 130.6, 131.5, 156.0, 158.8, 161.6, 161.7; IR ν (cm^{-1}) 2969, 1656, 1488, 1354, 1233, 1078, 974, 737; GC–MS m/z 365 (M^{+1}); *Anal.* Calc. for $C_{22}H_{24}N_2O_3$ (364.44): C, 72.51; H, 6.64; N, 7.69. Found: C, 72.44; H, 6.52; N, 7.87%.

2.2.2. 2,2′-(4-Phenoxy-1,2-phenylene)bis(4-isopropyl-4,5-dihydrooxazole) (**2**)

Colorless oil; isolated yield = 86%; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.71 (d, J = 8.9 Hz, 1H), 7.30–7.34 (m, 3H), 7.13 (t, J = 7.3 Hz, 1H), 6.08–7.04 (m, 3H), 4.35 (t, J = 17.3 Hz, 2H, NCH × 2), 4.00–4.08 (m, 4H, OCH_2 × 2), 1.84 (m, 2H, isopropyl CH × 2), 1.01 (d, J = 6.1 Hz, 6H, isopropyl CH_3 × 2), 0.92 (d, J = 6.7 Hz, 6H, isopropyl CH_3 × 2); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 18.1 (isopropyl CH_3 × 2), 19.0 (isopropyl CH_3 × 2), 32.5 (isopropyl CH), 32.6 (isopropyl CH), 70.4 (OCH_2), 70.6 (OCH_2), 72.9 (NCH), 73.0 (NCH), 119.4, 119.5, 119.6, 122.9, 124.0, 129.9, 130.5, 130.6, 131.6, 131.7, 156.0, 158.9, 163.0, 163.1; IR ν (cm^{-1}) 2959, 2926, 1653, 1589, 1489, 1355, 1224, 1090, 736; GC–MS m/z 393 (M^{+1}); *Anal.* Calc. for $C_{24}H_{28}N_2O_3$ (392.50): C, 73.44; H, 7.19; N, 7.14. Found: C, 73.54; H, 7.04; N, 7.37%.

2.3. Synthesis of the palladium-bis(oxazoline) complexes **A** and **B**

A 25-mL round-bottom flask flushed with argon was charged with Bis(benzonitrile)palladium(II) chloride (0.400 mmol, 0.153 g) and **1** (0.400 mmol) in CH_2Cl_2 (5.0 mL) at room temperature and stirred for 4 h. The reaction was monitored by TLC until no free **1** was observed. The organic phase was separated and filtered and the solvent was removed under reduced pressure. The resulting solid was dissolved in a minimum amount of CH_2Cl_2 and layered with hexane. After 24 h, the crystals started to develop. The crystals were separated and washed with Et_2O and characterized with different spectroscopic techniques including ^1H NMR, ^{13}C NMR, FT-IR, elemental analysis in addition to X-ray single-crystal diffraction analysis.

2.3.1. Dichlorido(2,2′-(4-phenoxy-1,2-phenylene)bis(4,4-dimethyl-4,5-dihydrooxazole)-N,N’)palladium(II) (**A**)

Yellow solid; mp 242–243 °C; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.74 (d, J = 8.8 Hz, 1H), 7.46 (t, J = 8.2 Hz, 2H), 7.30 (d, J = 2.4 Hz, 1H), 7.27 (t, J = 7.6 Hz, 1H), 7.22 (d, J = 2.4 Hz, 1H), 7.15 (d, J = 7.6 Hz, 2H), 4.30–4.19 (m, 4H, OCH_2 × 2), 1.75 (s, 3H, $NC(CH_3)$), 1.73 (s, 3H, $NC(CH_3)$), 1.61 (s, 3H, $NC(CH_3)$), 1.58 (s, 3H, $NC(CH_3)$); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm); 28.2 ($NC(CH_3)$), 28.3 ($NC(CH_3)$), 29.0 ($NC(CH_3)$), 29.1 ($NC(CH_3)$), 71.2 ($NC(CH_3)_2$), 71.5 ($NC(CH_3)_2$), 80.8 (OCH_2), 80.9 (OCH_2), 118.7, 119.2, 120.7, 125.7, 127.8, 130.5, 132.6, 154.3, 161.5, 163.7, 164.0; IR ν (cm^{-1}) 2972, 1637, 1582, 1486, 1372, 1236, 1063, 961, 729; UV–Vis spectrum (CH_2Cl_2) λ_{max}, 301 nm (ε = 1003 M^{-1} cm^{-1}); *Anal.* Calc. for $C_{22}H_{24}Cl_2N_2O_3Pd$ (541.77): C, 48.77; H, 4.47; N, 5.17. Found: C, 48.83; H, 4.66; N, 5.29%.

2.3.2. Dichlorido(2,2′-(4-phenoxy-1,2-phenylene)bis(4-isopropyl-4,5-dihydrooxazole)-N,N′)palladium(II) (B)

Orange solid; mp 235–236 °C; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.90 (d, J = 8.6 Hz, 1H), 7.50–7.45 (m, 3H), 7.31–7.27 (m, 2H), 7.18–7.14 (m, 2H), 4.96–4.92 (m, 2H, NCH × 2), 4.62–4.54 (m, 2H, OCH_2 × 2), 4.42–4.35 (m, 2H, OCH_2 × 2), 2.69 (m, 2H, isopropyl CH × 2), 1.31 (d, J = 7.0 Hz, 6H, isopropyl CH_3 × 2), 0.91 (d, J = 6.7 Hz, 6H, isopropyl CH_3 × 2); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 16.1 (isopropyl CH_3 × 2), 20.3 (isopropyl CH_3 × 2), 30.7 (isopropyl CH × 2), 69.4 (OCH_2 x 2), 71.0 (NCH), 71.3 (NCH), 117.7, 120.4, 120.5, 120.7, 121.0, 125.6, 126.4, 130.5, 133.1, 134.6, 154.2, 161.7, 164.5, 164.8; IR ν (cm^{-1}) 3063, 2963, 1640, 1585, 1484, 1380, 1228, 1064, 692; UV–Vis spectrum (CH_2Cl_2) λ_{max}, 299 nm (ε = 2157 M^{-1} cm^{-1}); *Anal.* Calc. for $C_{24}H_{28}Cl_2N_2O_3Pd$ (569.82): C, 50.59; H, 4.95; N, 4.92. Found: C, 50.28; H, 4.88; N, 5.11%.

2.4. General procedure for the Suzuki–Miyaura coupling reaction

The reaction was conducted in a 15 mL round bottom flask. Aryl halide (0.50 mmol), phenylboronic acid (0.60 mmol), Pd–BOX complex (0.010 mmol), K_2CO_3 (2.0 mmol), DMF (5.0 mL) was stirred for 6 h at 70 °C under argon. After completion of the reaction, the mixture was cooled down to room temperature, filtered and