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Synthesis and Properties of a New Chiral Diphosphine Ligand Bearing a Cyclodextrin-Based Molecular Recognition Site and Its Palladium(II) Complex

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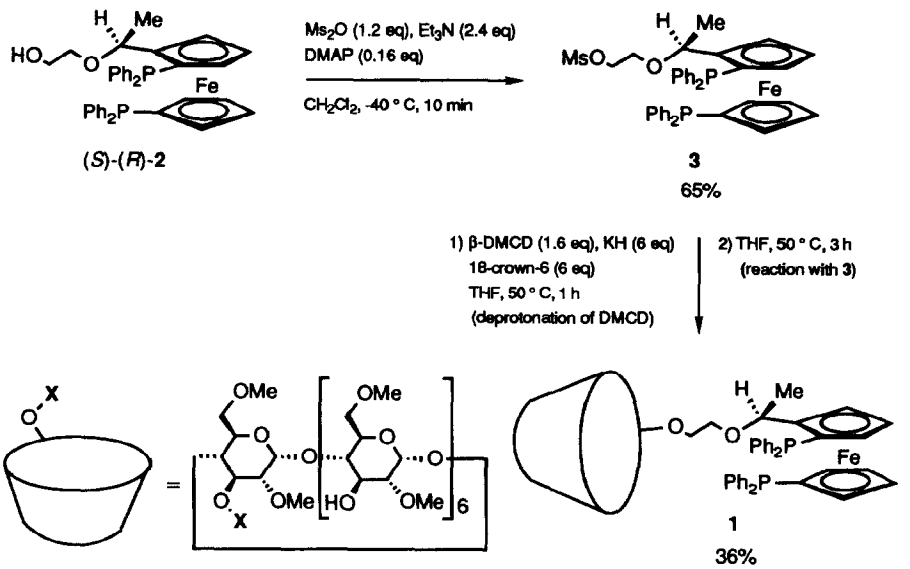
Abstract: A new chiral diphosphine tethered to heptakis(2,6-di-O-methyl)-β-cyclodextrin was synthesized and converted to a water soluble palladium(II) complex. Conductivity and dynamic light scattering measurements and UV-VIS spectra indicated that the palladium complex is aggregated in aqueous solution.

Cyclodextrins have attracted much attention as enzyme mimics owing to their ability to form inclusion complexes with hydrophobic substrates.[1] During the course of our studies on transition metal-catalyzed asymmetric synthesis by means of secondary interaction between chiral ligands and substrates,[2] we intended to prepare a chiral ferrocenylphosphine ligands bearing a cyclodextrin-based molecular recognition site.[3] We chose heptakis(2,6-di-O-methyl)-β-cyclodextrin (β-DMCD) as the cyclodextrin moiety because β-DMCD is soluble in not only water but also various organic solvents,[4] which enabled a coupling reaction to be performed with a quite hydrophobic ferrocenylphosphine moiety. Thus, the new ferrocenyldiphosphine ligand **1** tethered to β-DMCD was synthesized in a reasonable yield as outlined in Scheme 1. The terminal hydroxyl group of 2-hydroxyethoxy-substituted ferrocenylphosphine, (*S*)-(*R*)-**2**[5] was first mesylated with methanesulfonic anhydride to give **3** (65%) and reacted with 1.6 equiv of β-DMCD activated by potassium hydride in the presence of 18-crown-6 in THF. A chromatographic purification (silica gel, CH_2Cl_2/MeOH = 30/1) gave cyclodextrin-functionalized chiral ferrocenylphosphine **1** as an amorphous yellow solid (36% from **3**, 0.169 g), which was characterized by ^1H and $^{31}P\{^1H\}$ NMR ($CDCl_3$). To the best of our knowledge, this is the first example of phosphine-functionalized cyclodextrin.

Scheme 1



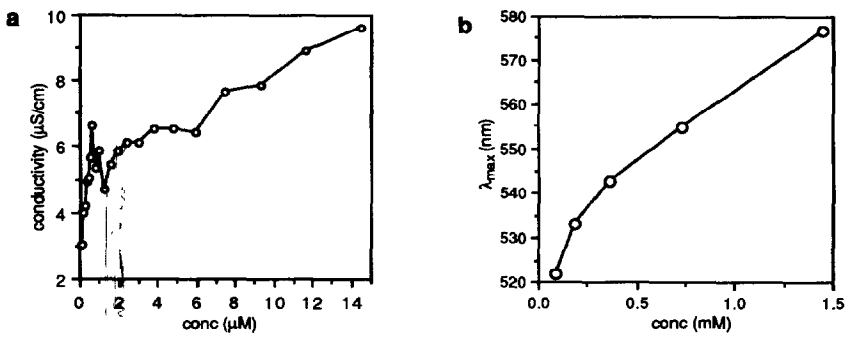


Figure 1. (a) Determination of critical micelle concentration for $PdCl_2$·**1** in water at ambient temperature. The palladium complex was dissolved in distilled water, and diluted by incremental addition of water while the conductivity of the solution was monitored. (b) Effect of concentration of $PdCl_2$·**1** in water on λ_{max} in the visible-light region. Molar absorptivity ε_{max} was almost constant around a value of 600.

Palladium complex $PdCl_2$·**1** (reddish-brown solid) was prepared by treating **1** with equimolar amount of $PdCl_2(MeCN)_2$ in CH_2Cl_2. The ^{31}P NMR ($CDCl_3$, δ 30.1 and 36.6, J_{P-P} = 21.4 Hz) indicats that two phosphorous atoms are in coordination with the palladium atom in cis-chelation manner. Although free ligand **1** is almost insoluble in water, the palladium complex showed high solubility in water (> 4 mM). Conductivity data of the aqueous solution shown in Figure 1a indicated that the palladium complex ionized and formed a certain aggregate (critical micelle concentration = 1.2 μM). Dynamic light scattering experiments afforded a value of hydrodynamic radius of 4 nm at a concentration of 3 mM.[6] Interestingly, the color of the aqueous solution changed from its usual red to an unusual green color (> ca 0.7 mM) as the concentration was increased. The dependance of λ_{max} in the visible light region on the concentration of the palladium complex is shown in Figure 1b. The aggregation is probably responsible for the change in λ_{max} with concentration, although the structure of aggregate and the detailed mechanism of the concentration-chromism have not been clear yet.

Currently, our efforts are being made to explore new catalytic asymmetric reactions in aqueous solutions, where the catalysis of transition metal complex and the hydrophobic binding of substrate into the cyclodextrin cavity might be cooperative for the enantioselection.

Experimental Section

General. ^1H and $^{31}P\{^1H\}$ NMR spectra were measured with a Varian VXR-200 spectrometer. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. Conductivity measurements were recorded on a YANAGIMOTO MY-8 conductivity meter. Dynamic light scattering experiments were performed on a OTSUKA ELECTRONICS DLS-700 dynamic light scattering spectrometer. Aqueous solution of $PdCl_2$·**1** was filtered through a 0.5-μm membrane filter. UV-VIS spectra were recorded on a JASCO MHT-344 UV-VIS spectrophotometer.

Materials. Heptakis(2,6-di-O-methyl)-β-cyclodextrin purchased from Wako Pure Chemical Industries Ltd. was recrystallized from methanol. Its purity was confirmed by $^{13}C\{^1H\}$ NMR (D_2O/dioxane).[4e] (*S*)-(*R*)-**2** was synthesized according to the literature procedure.[5]

(*S*)-(*R*)-3. To a solution of (*S*)-(*R*)-**2** (1.5 g, 2.4 mmol), DMAP (47 mg, 0.38 mmol), and Et_3N (0.8 mL, 5.7 mmol) in CH_2Cl_2 (15 mL) was slowly added a solution of methanesulfonic anhydride (0.52 g, 3.0 mmol) in CH_2Cl_2 (10 mL) at -40 °C. After the stirring for a few minutes, 20 mL of water was slowly added. The mixture was separated, extracted with 30 mL of CH_2Cl_2, and dried over magnesium sulfate. A chromatographic purification (silica gel, hexane/AcOEt =4/1) afforded **3** (65%): ^1H NMR (200 MHz, TMS, $CDCl_3$) δ 1.46 (d, J = 6.3 Hz, 3 H), 2.77 (s, 3 H), 3.27-3.60 (m, 4 H), 3.62 (m, 1 H), 3.66 (m, 1 H), 4.01 (m, 1 H), 4.09 (m, 1 H), 4.13 (m, 1 H), 4.37 (m, 1 H), 4.45 (m, 1 H), 4.75 (dq, JP-H = 2.0 Hz, JH-H = 6.3 Hz, 1 H), 7.10-7.40 (m, 18 H), 7.40-7.55 (m, 2 H).

Cyclodextrin-functinalized ferrocenylphosphine 1. To a suspension of potassium hydride (1.4 mmol) (24% KH in oil was washed with hexane) in THF (5.5 mL) was added β-DMCD (0.499 g, 0.38 mmol) and 18-crown-6 (0.40 g, 1.5 mmol) at room temperature. After the mixture was stirred at 50 °C for 1 h, a solution of **3** (0.170 g, 0.24 mmol) in THF was added at room temperature. The mixture was stirred at 50 °C for 3 h, quenched with saturated aquaous NH_4Cl (30 mL) at room temperature, extracted with $CHCl_3$ (25 mL x3), and dried over sodium sulfate. A chromatographic purification (silica gel, CH_2Cl_2/MeOH = 30/1) afforded **1** (36%) as an amorphous yellow solid: mp 148-153 °C; $[\alpha]^{25}_D$ +171 (*c* 1.1, $CHCl_3$); ^1H NMR (200 MHz,

TMS, $CDCl_3$) δ 1.51 (d, J = 6.4 Hz, 3 H), 3.0-3.2 (m, 4 H), 3.20-3.33 (m, 7 H), 3.33-3.86 (m, 70 H), 3.86-4.40 (m, 7 H), 4.08 (m, 1 H), 4.11 (m, 1 H), 4.37 (m, 1 H), 4.47 (m, 1 H), 4.62-4.82 (m, 1 H), 4.88 (m, 1 H), 4.93-5.07 (m, 7 H), 5.08 (s, 1 H), 5.13 (s, 1 H), 5.16 (s, 1 H), 5.22 (s, 1 H), 7.09-7.40 (m, 18 H), 7.40-7.58 (m, 2 H); $^{31}P\{^1H\}$ NMR (81 MHz, 85% H_3PO_4, $CDCl_3$) δ -17.0 (s), -23.1 (s).

$PdCl_2$·1. To a solution of **1** (0.130 g, 0.070 mmol) in CH_2Cl_2 (2 mL) was added $PdCl_2(MeCN)_2$ (18 mg, 0.068 mmol) at room temperature, and stirred overnight. An insoluble material was filtered off and washed with CH_2Cl_2. The combined filtrate was concentrated to a volume of 2 mL. The addition of ether (20 mL) to the solution, filtration, washing with ether, and drying in vacuo gave $PdCl_2$·**1** (82%) as an reddish-brown solid: ^1H NMR (200 MHz, TMS, $CDCl_3$) δ 1.66 (d, J = 6.0 Hz, 3 H), 3.0-3.23 (m, 4 H), 3.24-3.34 (m, 7 H), 3.34-3.90 (m, 70 H), 3.90-4.09 (m, 7 H), 4.23 (m, 2 H), 4.32 (m, 1 H), 4.47 (m, 1 H), 4.80 (m, 1 H), 4.88 (m, 1 H), 4.92-5.08 (m, 8 H), 5.09 (s, 1 H), 5.23 (s, 1 H), 5.25 (s, 1 H), 6.06-6.22 (m, 1 H), 7.05-7.20 (m, 2 H), 7.2-7.7 (m, 12 H), 7.8-8.2 (m, 4 H), 8.30-8.45 (m, 2 H); $^{31}P\{^1H\}$ NMR (81 MHz, 85% H_3PO_4, $CDCl_3$) δ 30.1 (d, J = 21.4 Hz), 36.6 (d, J = 21.4 Hz).

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