Air-stable P-Chiral Bidentate Phosphine Ligand with (1-Adamantyl)methylphosphino Group

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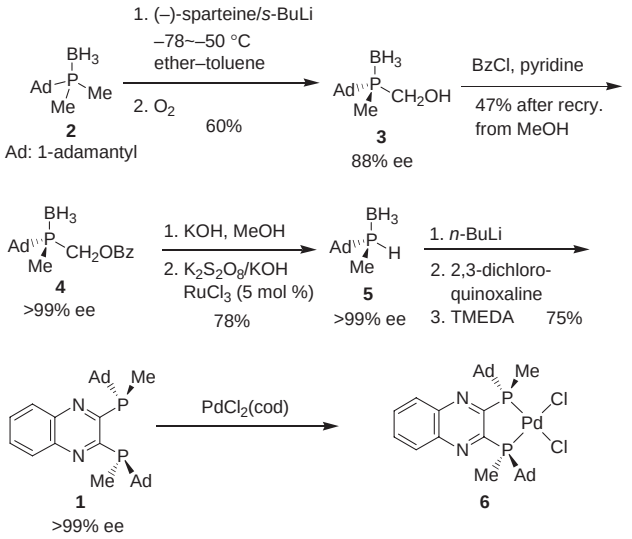
Air-stable diphosphine ligand, (*R*,*R*)-2,3-bis((1-adamantyl)-methylphosphino)quinoxaline, was prepared by the reaction of enantiomerically pure (*S*)-(1-adamantyl)methylphosphine–borane with 2,3-dichloroquinoxaline. The ligand exhibited excellent enantioselectivities in Rh-catalyzed asymmetric hydrogenation and Pd-catalyzed asymmetric ring-opening reaction.

Optically active phosphine ligands play an important role in transition-metal-catalyzed asymmetric reactions.[1] While numerous chiral phosphine ligands have been designed and synthesized for almost four decades, it is still necessary to develop new ones for the establishment of more efficient catalytic processes of various asymmetric reactions.[2] Previously, we reported new P-chiral phosphine ligands, BisP* and MiniPHOS, that possess a bulky alkyl group such as *tert*-butyl group and the smallest alkyl group (methyl group) on the same phosphorus atom, and demonstrated their exceedingly high enantioselectivity in rhodium-catalyzed asymmetric hydrogenation reactions.[3–5] However, the fact that these ligands are quite sensitive to air has hindered their widespread application in various asymmetric catalyses. In order to overcome this difficulty, we recently synthesized an air-stable P-chiral phosphine ligand, *t*-Bu-QuinoxP*.[6] This ligand exhibits very high to almost perfect enantioselectivities not only in rhodium-catalyzed asymmetric hydrogenation but also in rhodium- or palladium-catalyzed asymmetric reactions. We are interested in examining the catalytic activity of structurally analogous ligands possessing a bulkier alkyl group at the phosphorus atoms. Here, we report the synthesis of (*R*,*R*)-2,3-bis((1-adamantyl)methylphosphino)quinoxaline (**1**) (abbreviated as Ad-QuinoxP*) and its enantioselectivities in representative catalytic asymmetric reactions.

The synthesis of Ad-QuinoxP* (**1**) was carried out according to the procedure that uses phosphine–boranes as key intermediates (Scheme 1). 1-Adamantyl(dimethyl)phosphine–borane (**2**) was subjected to enantioselective deprotonation with (−)-sparteine/*sec*-BuLi at low temperature and the generated organolithium compound was treated with oxygen gas to give optically active hydroxy derivative **3** with 88% ee in 60% yield. In order to increase the ee of the alcohol, it was converted into benzoyl derivative **4**, which was recrystallized from methanol two times to afford an enantiomerically pure compound.[7] Hydrolysis of this ester and subsequent oxidative one-carbon degradation produced enantiomerically pure secondary phosphine–borane **5**.[8] Deprotonation with *n*-BuLi and subsequent substitution reaction with 2,3-dichloroquinoxaline, followed by treatment with tetramethylethylenediamine to remove the boranato groups, afforded the desired ligand **1** as an orange air-stable amorphous solid in 75% yield.[9] We expected to obtain this ligand as a crystalline solid similar to *t*-Bu-QuinoxP*. Unfortunately, however, numerous attempts at the crystallization of **1** have proved unsuccessful.

This ligand was reacted with $PdCl_2$(cod) to afford complex



Scheme 1.

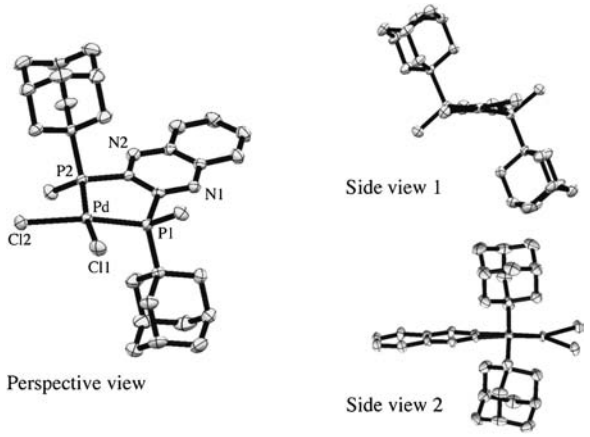
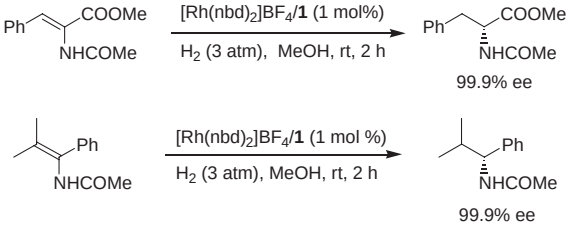


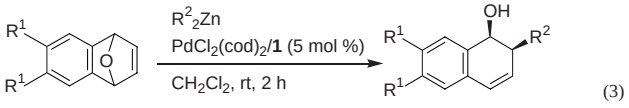
Figure 1. Molecular structure of $PdCl_2$(Ad-QuinoxP*)·$2CHCl_3$: The two chloroform molecules and hydrogen atoms are omitted for clarity.

6.[10] Its molecular structure was determined by single-crystal X-ray analysis.[11] As shown in Figure 1, the complex is rigid owing to the quinoxaline backbone, and the five-membered palladium chelate forms an almost flat plane. Also worth noting is that the two Pd–Cl bonds deviate by approximately 16° from the chelate plane due to steric repulsion between the chlorine atom and the bulky adamantyl group. Side views of the X-ray structure clearly show that the second and forth quadrants are effectively shielded by the adamantyl groups and the other diagonal quadrants are occupied by the methyl groups. This imposed asymmetric environment would lead to excellent enantioselectivity in asymmetric catalysis.

The enantioinduction ability of the ligand was examined in the typical Rh-catalyzed asymmetric hydrogenation. The hydrogenations of methyl (*Z*)-α-acetamidocinnamate and 1-acetylamino-1-phenyl-2-methylpropene afforded the corresponding reduction products both with 99.9% ee.[12] These results suggest the high utility of this ligand for the asymmetric hydrogenation of similar prochiral substrates.



This ligand was successfully used also in the palladium-catalyzed asymmetric ring-opening reaction.[13] Thus, reactions using a premixing catalyst with $PdCl_2$(cod) and **1** provided products with 96–98% ee in almost quantitative yields.[14] It is worthy to note that the ee's obtained in this study are about 1% higher than the ee's by the use of *t*-Bu-QuinoxP*.[6] The excellent enantioselectivities indicate the high utility of this ligand in this class of asymmetric catalyses.



R^1 = H, R^2 = Me: 86%, 96.4% ee
R^1 = H, R^2 = Et: 67%, 98.5% ee
R^1 = F, R^2 = Me: 69%, 95.2% ee

In summary, we have prepared a new air-stable P-chiral diphosphine ligand possessing adamantyl groups (Ad-QuinoxP*) and demonstrated extremely high enantioselectivity in rhodium-catalyzed hydrogenation and palladium-catalyzed ring-opening reaction.

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This paper is dedicated to Professor Teruaki Mukaiyama on the occasion of his 80th birthday.

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7 Colorless crystals: mp 98–99 °C, $[\alpha]^{22}_D = -25.1$ (*c* 1.07, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.0–0.9 (br q, 3H), 1.33 (d, $J_{HP} = 9.9$ Hz, 3H), 1.7–2.1 (m, 15H), 4.69 (dd, $J = 14.0$ Hz, $^2J_{HP} = 1.0$ Hz, 1H), 4.76 (dd, $J = 14.0$ Hz, $^2J_{HP} = 2.2$ Hz, 1H), 7.46–7.50 (m, 2H), 7.63–7.59 (m, 1H), 8.04 (d, $J = 7.7$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 1.8 (d, $J_{CP} = 18.0$ Hz), 27.5 (d, $^3J_{CP} = 7.2$ Hz), 30.5 (d, $J_{CP} = 25.6$ Hz), 36.2, 36.3, 57.0 (d, $J_{CP} = 28.8$ Hz), 128.6, 129.0, 129.7, 133.5, 165.8; IR (KBr) 3070, 2915, 2365, 1720, 1450, 1320, 1245, 1110, 1065, 710 cm^{-1}; HRMS (FAB) calcd for $C_{19}H_{27}BO_2P$ ($[M-1]^+$) 329.1842, found 329.1845. The ee of this product was 99% (Chiralcel OJ–H, hexane/2-propanol = 90:10, flow rate = 0.5 mL/min, wavelength = 254 nm, Retention times: 17.6 min ((S) enantiomer, 22.0 min ((R) enantiomer)).

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9 Ad-QuinoxP*: orange amorphous solid, $[\alpha]^{27}_D = -248$ (*c* 0.33, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.39–1.41 (m, 6H), 1.53–1.85 (m, 30H), 7.73 (dd, $J = 6.3$ Hz, 4.4 Hz, 2H), 8.11 (dd, $J = 6.3$ Hz, 4.4 Hz, 2H). IR (KBr) 3060, 2900, 2845, 1450, 1300, 1075, 1005, 870, 760 cm^{-1}; HRMS (FAB): calcd for $C_{30}H_{40}N_2P_2$ (M^+) 490.2667, found. 490.2643. The ee of this product was >99.9% (Chiralcel OD–H, pentane, flow rate = 0.2 mL/min, wavelength = 254 nm, Retention times: 26.4 min [(S,S) enantiomer], 32.0 min [(R,R) enantiomer], 33.9 min [meso isomer]). This compound was neither oxidized nor epimerized at the P-stereogenic phosphorus atoms on standing in air at room temperature for more than 6 months.

10 Mp > 300 °C (decomp.). $[\alpha]^{24}_D = -121$ (*c* 0.99, $CHCl_3$).

11 Single crystals of **6** suitable for X-ray crystallographic analysis were grown from $CHCl_3$/pentane. Crystal data for **6** ($C_{32}H_{42}Cl_8N_2P_2Pd$ (**6**•2$CHCl_3$): $M_r = 906.62$, $T = 173$ K, triclinic space group *P*1, $a = 9.4461(10)$ Å, $b = 10.4572(11)$ Å, $c = 11.0933(11)$ Å, $\alpha = 68.6450(10)°$, $\beta = 75.9880(10)°$, $\gamma = 67.1510(10)°$, $V = 933.98(17)$ A^3, $Z = 1$, $\rho_{calcd} = 1.612$ g cm^{-3}, 5281 reflections collected, $R_1 = 0.022$ for $I > 2\sigma(I)$, $R_w = 0.061$ for all data, GOF = 1.176, CCDC-633549.

12 Conditions for the determination of the ee's by HPLC analysis. *N*-Acetylphenylalanine methyl ester: Chiralcel OJ, hexane/2-propanol = 9:1, 0.5 mL/min, wavelength = 254 nm, retention times: 22.3 min (R), 31.7 min (S); 1-phenyl-1-acetylamino-2-methylpropane: Chiralcel AD, hexane/2-propanol = 9:1, 0.5 mL/min, wavelength = 254 nm, retention times: 9.7 min (S), 11.9 min (R).

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14 Conditions for the determination of the ee's by HPLC analysis. R^1 = H, R^2 = Me: Chiralcel OD–H, hexane/2-propanol = 199:1, 1 mL/min, wavelength = 254 nm, retention times: 28.5 min (minor), 30.6 min (major); R^1 = H, R^2 = Et: Chiralcel OD–H, hexane/2-propanol = 199:1, 1 mL/min, wavelength = 254 nm, retention times: 26.0 min (minor), 29.6 min (major); R^1 = F, R^2 = Me: Chiralcel OD–H (two columns), hexane/2-propanol = 199:1, 0.5 mL/min, wavelength = 254 nm, retention times: 126.5 min (major), 132.6 min (minor).

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