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Synthesis and application of atropisomeric dihydrobenzofuran-based bisphosphine (BICMAP)

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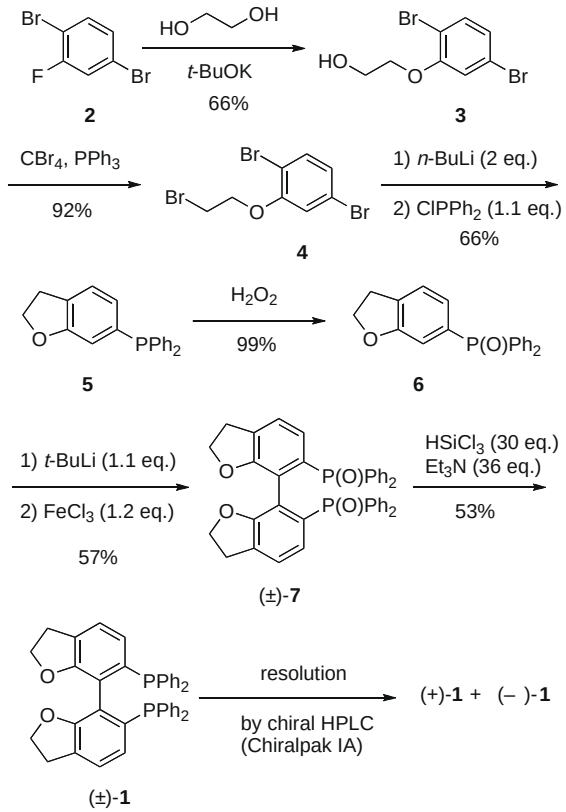
ABSTRACT

A new atropisomeric dihydrobenzofuran-based bisphosphine ligand **1** was easily prepared from 1,4-dibromo-2-fluorobenzene. This racemic bisphosphine (±)-**1** was used as a ligand for the palladium-catalyzed Suzuki–Miyaura reaction of aryl chloride with arylboronic acids and Hartwig–Buchwald amination of aryl bromides with aniline derivatives. The optical resolution of (±)-**1** was also carried out by HPLC with a chiral stationary phase column.

Chiral phosphines are important molecules that affect asymmetric inductions as ligands for transition metal catalysts.[1] Atropisomeric biaryls are also well established as one important class of ligands for asymmetric metal-catalyzed reactions by the discovery and the application of BINAP.[2] Recently many new chiral biarylphosphines have been reported, such as MeO-BIPHEP,[3] BIBFUP,[4] BIFAP,[5] BICAP,[6] SEGPHOS,[7] and SYNPHOS.[8] We herein report the synthesis of a new atropisomeric bisphosphine ligand bearing a dihydrobenzofuran (coumaran) core, hereafter named BICMAP ((±)-**1**), and its use in the palladium-catalyzed Suzuki–Miyaura reaction[9] and Hartwig–Buchwald amination.[10,11] The optical resolution of (±)-**1** was also carried out by use of HPLC with a chiral stationary phase column.

Dihydrobenzofuran-based bisphosphine ligand **1** was easily prepared from inexpensive reagent 1,4-dibromo-2-fluorobenzene (**2**) (~$1/g)[12] via 6-diphenylphosphino-2,3-dihydrobenzofuran (**5**) (Scheme 1). A nucleophilic aromatic substitution (S_NAr) reaction of 1,4-dibromo-2-fluorobenzene (**2**) and ethylene glycol with potassium *tert*-butoxide gave corresponding alcohol **3**[13] that was converted into bromide **4** using CBr_4–PPh_3 in good yield.[14] 6-Diphenylphosphino-2,3-dihydrobenzofuran (**5**) was prepared by intramolecular alkylation and phosphination with chlorodiphenylphosphine via double lithium–bromide exchange of **4** with two equivalents of *n*-butyllithium.[15] After oxidation of the phosphine atom by hydrogen peroxide in chloroform, ortholithiation of phosphine oxides **6**[16] and further oxidative coupling with anhydrous ferric chloride furnished bisphosphine oxide (±)-**7** in good yield.[17] This bisphosphine oxide (±)-**7** was converted into racemic bisphosphine ligand (±)-**1** using trichlorosilane-triethylamine in good yield.[18] We successfully conducted single-crystal X-ray diffraction analysis of (±)-**1**, and the ORTEP diagram of (±)-**1** is shown in Figure 1. The optical resolution of (±)-**1** was efficiently carried out by HPLC with a chiral stationary phase column (Chir-



Scheme 1. Preparation of diphosphine ligand **1**.

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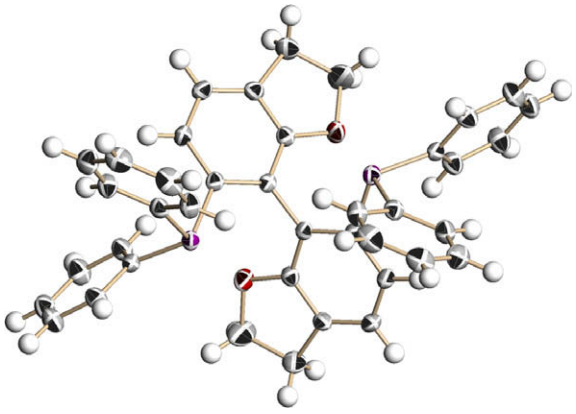


Figure 1. ORTEP diagram of (±)-**1**.

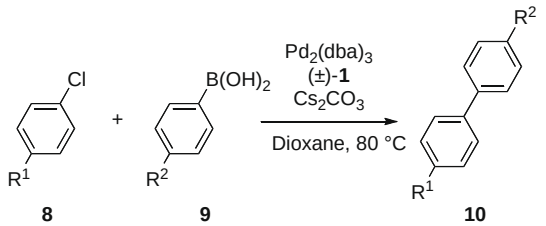
alpak IA) of a semi-preparative scale. Optically active (+)-**1** and (−)-**1** were obtained in an enantiomerically pure form.[19]

We investigated the ability of bisphosphine (±)-**1** as a ligand for the palladium-catalyzed Suzuki–Miyaura reaction of aryl chlorides **8** with arylboronic acids **9**. This reaction was carried out in the presence of 2.5 mol % of Pd_2dba_3, 7.5 mol % of (±)-**1**, and $CsCO_3$ as a base in dioxane (Table 1).[20] When the reaction was carried out using 1-chloro-4-nitrobenzene with phenylboronic acid, 4-nitrobiphenyl (**10a**) was obtained in good yield (Table 1, entry 1). The effect of various aryl chlorides and arylboronic acids in the Suzuki–Miyaura reaction was investigated (Table 2, entries 2–5). The reaction gave corresponding products **10b–e** in moderate to good yields.

We also investigated the ability of bisphosphine (±)-**1** as a ligand for the palladium-catalyzed Hartwig–Buchwald amination of aryl bromides **11** with aniline derivatives **12**. This reaction was carried out in the presence of 1 mol % of Pd_2dba_3, 2 mol % of (±)-**1**, and $CsCO_3$ as a base in PhMe (Table 2).[21] The reaction of various aryl bromides and aniline derivatives gave corresponding products **13a–d** with good yields. When (±)-BINAP was used instead of (±)-**1** as a ligand, the yield of **13a** was slightly decreased (Table 2, entry1 vs entry 2).

To investigate the nature of the catalyst structure of palladium complex with (±)-**1**, a single-crystal of palladium complex **14** was obtained from the reaction of (±)-**1** and $PdCl_2(MeCN)_2$.[22] The

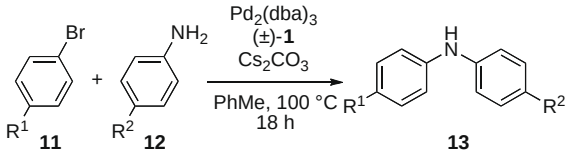
Table 1
Palladium-catalyzed Suzuki–Miyaura reaction using (±)-**1**[a]



Entry	R^1	R^2	Reaction time (h)	Product	Yield[b] (%)
1	NO_2	H	24	**10a**	91
2	NO_2	OMe	24	**10b**	88
3	Ac	H	24	**10c**	59
4	Ac	OMe	48	**10d**	80
5	CN	OMe	48	**10e**	94

[a] The reactions were carried out on 0.20 mmol scale of **8** with 1.5 equiv of **9** and 2.0 equiv of Cs_2CO_3 in the presence of $Pd_2(dba)_3$ (2.5 mol %) and ligand (±)-**1** (7.5 mol %) in dioxane (0.6 mL) at 80 °C under Ar.
[b] Isolated yields.

Table 2
Palladium-catalyzed Hartwig–Buchwald amination using (±)-**1**[a]



Entry	R^1	R^2	Product	Yield[b] (%)
1	NO_2	Me	**13a**	98
2[c]	NO_2	Me	**13b**	93
3	Ac	Me	**13c**	93
4	CN	Me	**13d**	92
5	NO_2	OMe	**13e**	91

[a] The reactions were carried out on 0.25 mmol scale of **11** with 1.2 equiv of **12** and 1.4 equiv of Cs_2CO_3 in the presence of $Pd_2(dba)_3$ (1 mol %) and ligand (±)-**1** (3 mol %) in PhMe (1.0 mL) at 100 °C for 18 h under Ar.
[b] Isolated yields.
[c] This reaction was carried out using (±)-BINAP instead of (±)-**1**.

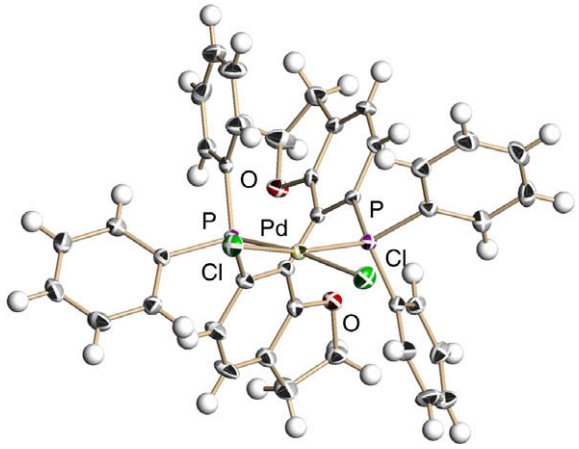


Figure 2. ORTEP diagram of palladium complex **14** (one molecule of chloroform omitted for clarity).

X-ray analysis of **14** showed that the two phosphine atoms are coordinated to palladium (Fig. 2), the bite angle of P–Pd–P is 92.5°, and the dihedral angle of the biaryl atropisomeric backbone is 62.5°. This dihedral angle is significantly narrower than that of BINAP-$PdCl_2$ complex (70.2°).[23]

In summary, a new atropisomeric dihydrobenzofuran-based bisphosphine ligand (±)-**1** was prepared, and the resolution of these isomers was achieved using HPLC with a chiral stationary phase column. We described the use of an efficient ligand for the palladium-catalyzed Suzuki–Miyaura reaction and Hartwig–Buchwald amination. Further studies to explore the scope of chiral ligand **1** in asymmetric catalytic reactions are currently underway.

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14. *Preparation of 2-bromoethoxy-1,4-dibromobenzene* (**4**): To the mixture of **3** (6.33 g, 21.4 mmol), triphenylphosphine (6.18 g, 23.5 mmol) in acetonitrile (29.4 mL) was added carbon tetrabromide (7.82 g, 23.5 mmol) at room temperature. After stirring for 3.5 h, the mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography (elution with *n*-hexane/ethyl acetate = 8/1): 7.04 g, 19.6 mmol, 92%; white solid; mp 57–59 °C; ^{1}H NMR ($CDCl_3$) δ: 3.68 (t, J = 6.4 Hz, 2H), 4.32 (t, J = 6.4 Hz, 2H), 7.00–7.03 (m, 2H), 7.40 (d, J = 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 28.1, 69.2, 111.4, 117.2, 121.5, 125.7, 134.4, 155.2; EI-MS m/z (rel intensity) 358 (M^+, 19).
15. *Preparation of 6-diphenylphosphino-2,3-dihydrobenzofuran* (**5**): To the solution of bromide **4** (0.356 g, 1.00 mmol) in THF (2 mL) was added slowly *n*-BuLi in hexane (0.60 mL, 1.00 mmol, 1.66 M) at −80 °C for 10 min under an Ar atmosphere. After the mixture was stirred for 2 h, *n*-BuLi in hexane (0.60 mL, 1.00 mmol, 1.66 M) was added slowly at −80 °C for 10 min again. After the mixture was stirred for 1.5 h, chlorodiphenylphosphine (0.20 mL, 1.10 mmol) was added, and stirring was continued for 23 h at −80 °C. The mixture was quenched with satd NH_4Cl aq at 0 °C and diluted with ethyl acetate at room temperature. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (elution with *n*-hexane/ethyl acetate = 20/1): 0.201 g, 0.66 mmol, 66%; white solid; mp 76–78 °C; ^{1}H NMR ($CDCl_3$) δ: 3.20 (t, J = 8.7 Hz, 2H), 4.55 (t, J = 8.7 Hz, 2H), 6.69 (d, J = 7.1 Hz, 1H), 6.87 (ddd, J = 1.3, 7.6 and 8.7 Hz, 1H), 7.17 (dd, J = 0.8 and 7.5 Hz, 1H), 7.24–7.35 (m, 10H); ^{13}C NMR ($CDCl_3$) δ: 29.6, 71.1, 114.1 (d, J = 16.7 Hz), 124.9 (d, J = 16.7 Hz), 126.5 (d, J = 24.9 Hz), 128.1, 128.4 (d, J = 7.1 Hz, C × 4), 128.6 (s, C × 2), 133.6 (d, J = 19.5 Hz, C × 4), 137.0 (d, J = 10.8 Hz), 137.3 (d, J = 10.8 Hz, C × 2), 160.4 (d, J = 7.7 Hz); ^{31}P NMR ($CDCl_3$) δ: −4.1; EI-MS m/z (rel intensity): 304 (M^+, 100); HRMS (FAB-MS) m/z calcd for $C_{20}H_{17}OP$ 304.1017, found 304.0995.
16. *Preparation of 6-diphenylphosphinyl-2,3-dihydrobenzofuran* (**6**): To the solution of phosphine **5** (0.304 g, 1.00 mmol) in chloroform (5 mL) was added slowly 30% aqueous H_2O_2 (2.0 mL) then stirred for 2 h. After this, water was added to the mixture and the organic layer was separated. The organic layer was dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (elution with *n*-hexane/ethyl acetate = 1/3): 0.317 g, 0.99 mmol, 99%; white solid; mp 127–128 °C; ^{1}H NMR ($CDCl_3$) δ: 3.26 (t, J = 8.8 Hz, 2H), 4.59 (t, J = 8.8 Hz, 2H), 6.99 (d, J = 12.4 Hz, 1H), 7.18–7.32 (m, 2H), 7.41–7.57 (m, 6H), 7.62–7.72 (m, 4H); ^{13}C NMR ($CDCl_3$) δ: 29.6, 71.3, 112.4 (d, J = 12.2 Hz), 124.8 (d, J = 10.1 Hz), 125.1 (d, J = 14.7 Hz), 128.4 (d, J = 12.0 Hz, C × 4), 131.7 (d, J = 2.6 Hz), 131.8 (d, J = 2.8 Hz, C × 2), 132.0 (d, J = 10.0 Hz, C × 4), 133.1, 133.3 (s, C × 2), 160.1, (d, J = 17.2 Hz); ^{31}P NMR ($CDCl_3$) δ: 30.0; EI-MS m/z (rel intensity): 320 (M^+, 54); HRMS (FAB-MS) m/z calcd for $C_{20}H_{17}O_2P$+H 321.1044, found 321.1039.
17. *Preparation of 2,2′-diphenylphosphinyl-1,1′-bi-5,6-dihydrobenzofuran* ((±)-**7**): To the solution of phosphine oxide **6** (0.961 g, 3.00 mmol) in THF (24 mL) was added slowly *t*-BuLi in pentane (2.1 mL, 3.34 mmol, 1.59 M) at −80 °C for 10 min under an Ar atmosphere. After the mixture was stirred for 3 h, ferric chloride ($FeCl_3$) (0.593 g, 3.60 mmol) in THF (2 mL) was added. After the mixture was stirred for 13 h at room temperature, it was concentrated under reduced pressure. The residue was added to 6 M HCl aq (10 mL) and chloroform. The organic layer was washed with 6 M NaOH aq (10 mL) and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (elution with chloroform/methanol = 40/1): 0.549 g, 0.86 mmol, 57%; white solid; mp 156–158 °C; ^{1}H NMR ($CDCl_3$) δ: 2.92–3.18 (m, 4H), 3.78 (dd, J = 8.7 and 18.7 Hz, 2H), 4.17–4.28 (m, 2H), 6.76 (dd, J = 7.6 and 13.8 Hz, 2H), 7.03 (dd, J = 2.6 and 7.7 Hz, 2H), 7.23–7.31 (m, 4H), 7.32–7.51 (m, 8H), 7.57–7.66 (m, 4H), 7.68–7.76 (m, 4H); ^{13}C NMR ($CDCl_3$) δ: 29.8 (s, C × 2), 70.5 (s, C × 2), 121.6 (d, J = 3.2 Hz, C × 2), 123.8 (d, J = 15.8 Hz, C × 2), 126.4 (d, J = 12.7 Hz, C × 2), 127.8 (d, J = 12.2 Hz, C × 8), 130.2 (d J = 105.2 Hz, C × 2), 130.3 (d, J = 2.6 Hz, C × 2), 130.9 (d, J = 9.7 Hz, C × 4), 132.2 (d, J = 9.7 Hz, C × 4), 132.3 (d, J = 10.0 Hz, C × 4), 133.9 (d, J = 35.5 Hz, C × 2), 135.3 (d, J = 36.2 Hz, C × 2), 158.7 (d, J = 15.2 Hz, C × 2); ^{31}P NMR ($CDCl_3$) δ: 29.9; FAB-MS m/z (rel intensity): 639 (M^++1, 14); HRMS (FAB-MS) m/z calcd for $C_{40}H_{32}O_4P_2$+H 639.1854, found 639.1886.
18. *Preparation of (±)-2,2′-diphenylphosphino-1,1′-bi-5,6-dihydrobenzofuran* ((±)-BICMAP, (±)-**1**): To a mixture of phosphine oxide (±)-**7** (232.5 mg, 0.364 mmol) and triethylamine (1.82 mL, 13.1 mmol) in *m*-xylene (4.9 mL) was added trichlorosilane (1.10 mL, 10.9 mmol) at 0 °C under an Ar atmosphere. The reaction mixture was stirred for 6 h at 110 °C. After being cooled to room temperature, the mixture was quenched with 6 M NaOH aq (10 mL) and diluted with chloroform and water. The organic layer was dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (elution with *n*-hexane/ethyl acetate = 10/1): 116.7 mg, 0.192 mmol, 53%; white solid; mp 229–231 °C; ^{1}H NMR ($CDCl_3$) δ: 2.90–3.04 (m, 2H), 3.06–3.22 (m, 2H), 3.74 (dd, J = 8.8 and 18.7 Hz, 2H), 4.24–4.36 (m, 2H), 6.60 (dt, J = 1.7 and 7.6 Hz, 2H), 7.08 (d, J = 7.6 Hz, 2H), 7.13–7.34 (m, 20H); ^{13}C NMR ($CDCl_3$) δ: 29.8 (s, C × 2), 70.7 (s, C × 2), 124.0 (t, J = 2.2 Hz, C × 4), 124.7 (s, C × 2), 126.7 (s, C × 2), 127.8 (d, J = 1.2 Hz, C × 2), 127.9 (t, J = 3.5 Hz, C × 4), 128.0 (s, C × 2), 128.1 (t, J = 3.1 Hz, C × 4), 133.3 (t, J = 10.3 Hz, C × 4), 134.0 (t, J = 10.5 Hz, C × 4), 137.3 (dd, J = 3.6, 4.6 Hz, C × 2), 137.7 (dd, J = 5.4 and 6.9 Hz, C × 2), 138.6 (dd, J = 6.2 and 7.3 Hz, C × 2), 158.6 (t, J = 6.4 Hz, C × 2); ^{31}P NMR ($CDCl_3$) δ: −13.0; EI-MS m/z (rel intensity): 606 (M^+, 0.08); HRMS (FAB-MS) m/z calcd for $C_{40}H_{32}O_2P_2$+H 607.1956, found 607.1953; HPLC: Daicel CHIRALPAK® IA (0.46 ϕ × 25 cm, UV 254 nm, hexane/ethanol = 97: 3, 0.3 mL/min), t_R = 22.3 (CD: λ_{ext} ($\Delta\varepsilon$) 254 (−)) and 25.9 min (CD: λ_{ext} ($\Delta\varepsilon$) 254 (+)); X-ray diffraction analysis data of (±)-**1**. Colorless prismatic crystals from hexane/$CHCl_3$, orthorhombic space group *Pnc*2, a = 12.1145(12) Å, b = 14.5546(15) Å, c = 8.9488(9) Å, α = 90°, β = 90°, γ = 90°, V = 1577.9(3) Å^3, Z = 4, ρ = 1.277 g/cm^3, μ (Mo Kα) = 1.73 cm^{-1}. The structure was solved by the direct method of full-matrix least-squares, where the final R and Rw were 0.0338 and 0.0863 for 2118 reflections.
19. *Optical resolution of (±)-BICMAP* ((±)-**1**): Chiral HPLC was carried out with a Daicel CHIRALPAK® IA column (10 mm f × 250 mm) with hexane/ethanol = 98:2 eluent. A solution of 2.9 mg of (±)-**1** in 2 mL of hexane was injected for each batch with flow rate of 0.8 mL/min. Enantiomers were eluted at 45.5 and 51.0 min: (+)-**1**; 0.79 mg, 27%; >99% ee; $[\alpha]_D^{20}$ +38 (c 0.0275, EtOH); HPLC (Daicel CHIRALPAK® IA, 0.46 ϕ × 25 cm, UV 254 nm), t_R = 21.0 min (hexane/ethanol = 97:3, 0.3 mL/min) (CD: λ_{ext} ($\Delta\varepsilon$) 254 (−)); (−)-**1**: 0.87 mg, 30%; 98.6% ee; $[\alpha]_D^{20}$ −37 (c 0.0230, EtOH); HPLC (Daicel CHIRALPAK® IA, 0.46 ϕ × 25 cm, UV 254 nm), t_R = 23.5 min (hexane/ethanol = 97:3, 0.3 mL/min) (CD: λ_{ext} ($\Delta\varepsilon$) 254 (+)).
20. *General procedure for the palladium-catalyzed Suzuki–Miyaura reaction*: To a test tube, arylchloride **8** (0.20 mmol), arylboronic acid **9** (0.30 mmol), $Pd_2(dba)_3$ (0.005 mmol, 4.6 mg), ligand (±)-**1** (0.015 mmol, 9.1 mg), Cs_2CO_3 (0.40 mmol, 130.3 mg) and dioxane (0.60 mL) were added under an Ar atmosphere. The mixture was stirred at 80 °C. After 24 or 48 h, the reaction mixture was diluted with ethyl acetate and water. The organic layer was washed with brine and dried over $MgSO_4$. The filtrate was concentrated with a rotary evaporator and the residue was purified by column chromatography (elution with *n*-hexane/ethyl acetate = 100–20/1). All prepared compounds **10** were known and identified by ^{1}H NMR, ^{13}C NMR, and MS.
21. *General procedure for the palladium-catalyzed Hartwig–Buchwald amination*: To a test tube, arylbromide **11** (0.25 mmol), aniline **12** (0.3 mmol), $Pd_2(dba)_3$ (0.0025 mmol, 2.3 mg), ligand (±)-**1** (0.0075 mmol, 4.6 mg), Cs_2CO_3 (0.35 mmol, 114.1 mg) and PhMe (1.0 mL) were added under an Ar atmosphere. The mixture was stirred at 100 °C. After 18 h, the reaction mixture was diluted with ethyl acetate and water. The organic layer was washed with brine and dried over $MgSO_4$. The filtrate was concentrated with a rotary evaporator and the residue was purified by column chromatography (elution with *n*-hexane/ethyl acetate = 6:1). All prepared compounds **13** were known and identified by ^{1}H NMR, ^{13}C NMR, and MS.
22. *Preparation of palladium complex* (±)-**14**. To a solution of $PdCl_2(MeCN)_2$ (7.78 mg, 0.03 mmol) in a $CHCl_3$ (2.0 mL) was added (±)-**1** (18.2 g, 0.03 mmol) in a $CHCl_3$ (2.0 mL) at room temperature and stirred for 2 h. The reaction mixture was evaporated under reduced pressure. The residue was purified by silica gel chromatography (elution with $CHCl_3$/MeOH = 20:1): 25.5 mg, 0.0282 mmol, 94%; yellow solid; mp 258–259 °C; ^{1}H NMR ($CDCl_3$) δ: 2.71–2. 87(m, 2H), 2.93–3.09 (m, 2H), 4.31–4.51 (m, 4H), 6.45 (dd, J = 7.8 and 11.9 Hz, 2H), 6.72 (dd, J = 1.9 and 7.8 Hz, 2H), 7.27–7.48 (m, 12H), 7.63–7.75 (m, 4H), 7.87–8.08 (m, 4H); ^{13}C NMR ($CDCl_3$) δ: 29.4 (s, C × 2), 71.2 (s, C × 2), 118.6 (dd, J = 4.0, 10.4 Hz, C × 4), 124.6 (d, J = 53.9, C × 2), 124.9 (d, J = 12.3 Hz, C × 2), 126.6 (d, J = 4.4 Hz, C × 2), 127.8 (dd, J = 11.7, 29.3 Hz, C × 8), 128.6 (d, J = 5.4 Hz, C × 2), 129.9 (d, J = 62.1 Hz, C × 2), 130.8 (d, J = 2.9 Hz, C × 2), 131.2 (d, J = 2.1 Hz, C × 2), 135.0 (d, J = 10.4 Hz, C × 4), 135.6 (s, C × 2), 135.8 (s, C × 2), 158.6 (dd, J = 1.0 and 12.3 Hz, C × 2); ^{31}P NMR ($CDCl_3$) δ: 26.9; FAB-MS m/z (rel intensity) 747([M−Cl]$^+$, 5); HRMS (FAB-MS) m/z calcd for $C_{40}H_{32}O_2ClP_2Pd$ 747.0601, found 747.0557; X-ray diffraction analysis data of **14** (Fig. 2): Yellow plate crystals from hexane/$CHCl_3$, $C_{40}H_{32}O_2Cl_2P_2Pd{\cdot}CHCl_3$, monoclinic space group $P2_1/n$, a = 11.5010(7) Å, b = 19.5208(12) Å, c = 16.6287(10) Å, α = 90°, β = 92.8320(10)°, γ = 90°, V = 3728.7(4) Å^3, Z = 4, ρ = 1.609 g/cm^3, μ (Mo Kα) = 9.79 cm^{-1}. The structure was solved by the direct method of full-matrix least-squares, where the final R and Rw were 0.0367 and 0.0837 for 8391 reflections.
23. Mikami, K.; Aikawa, K.; Kainuma, S.; Kawakami, Y.; Saito, T.; Sayo, N.; Kumonayashi, H. *Tetrahedron: Asymmetry* **2004**, *15*, 3885.