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Preparation of *pseudo*-C_2-symmetric P,S-hybrid ferrocenyl ligand and its application to some asymmetric reactions

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Abstract

A solely planar chiral *pseudo*-C_2-symmetric ferrocene-based P,S-chelating **2** was prepared and applied to some asymmetric reactions. Although a poor enantioselectivity is obtained in the asymmetric allylic alkylation (AAA) of *rac*-**8** using the Pd complex bearing the P,S-hybrid ligand **2**, it is noteworthy that this result is superior to that obtained using the C_2-symmetric bisphosphine counterpart of **2**. The intermolecular asymmetric heck reaction (AHR) of **11** with aryl triflates catalyzed by another palladium complex containing **2** was also carried out. Although both relatively low reactivity and poor enantioselectivity were obtained, a high regioselectivy favoring the 2,5-dihydrofuran derivative (**14**) over the regioisomeric 2,3-dihydrofuran derivative (**15**) was observed in this study.

Keywords: Asymmetric catalysis; Ferrocene; P,S-ligand; Planar chirality; *Pseudo*-C_2 symmetry

1. Introduction

The incorporation of C_2 symmetry in ligand design is the most general strategy for restricting the numbers of diastereomeric transition states in metal-catalyzed enantioselective processes [1] since the cornerstone preparation of DIOP by Dang and Kagan in 1971 [2]. Thereafter, such a large number of C_2-symmetric homobidentate chiral ligands (e.g. bisphosphines and diamines) have been prepared and tested to achieve high reactivity as well as high selectivity in catalytic asymmetric synthesis [3].

In line with this approach, we have recently reported that a series of air-stable C_2-symmetric ferrocenylbisphosphines (R-FerroPHOS derivatives (**1**)) with dual planar chirality (*cylindrical chirality*)[1] [4] as their sole element of chirality is highly effective in the Rh-catalyzed asymmetric hydrogenation of dehydroamino acids [5], in the Rh-catalyzed asymmetric hydroboration of olefins [6], and in the Pd-catalyzed asymmetric allylic alkylation (AAA) of allyic acetates [7] with excellent yields and excellent enantioselectivities [8].

However, there would be certain situations where the two ligating atoms of the C_2-symmetric ligand need to be different from each other while still enjoying the topological value of C_2 symmetry at the same time. This is especially true when substrates in the pro-

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[1] Cylindrical molecular chirality is defined here as the virtual chirality derived from C_2 symmetricity of two identical planar chiralities in a given molecule.

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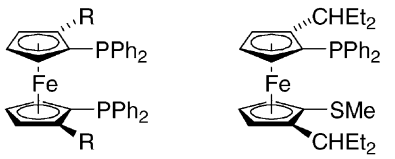


1: *R*-FerroPHOS **2**

Fig. 1. A new P,S-hybrid ligand **2** and its C_2-symmetric bisphosphine counterpart **1**.

jected reactions may well be of potentially multidentate nature in transition state. Thus, a C_2-symmetric ligand backbone equipped with strong and weak donor heteroatomic pairs (which breaks up the C_2 symmetry of the whole structure of the ligand) is needed [9].

The purpose of present study has been to compare the effectiveness of the new *pseudo*-C_2-symmetric ligand **2** with its C_2-symmetric bisphosphine counterpart (**1**) in some asymmetric reactions (Fig. 1). This differential ligation may be especially important when additional coordination sites on a metal for substrates and/or incoming reactants are needed. Most notably, to our best knowledge, our new chiral ligand **2** is the first example of *pseudo*-C_2-symmetric P,S-bidentate ligand that contains the planar chirality as the sole element of chirality (a solely planar chiral N,S-bidentate ferrocenyloxazoline has been reported in [10]).

2. Experimental

2.1. Materials

Chlorodiphenylphosphine was purchased from Aldrich, vacuum-distilled, and stored in a refrigerator under N_2 atmosphere. *n*-Butyl lithium (Aldrich) was assayed by titration with *N*-benzylbenzamide as an indicator in THF. Triethylaluminum in toluene (25 wt.%, Aldrich) was titrated by hydrolytic methods. bis(η^3-Allyl)di-μ-chloropalladium [11] and bis(dibenzylideneacetone)palladium [12] were prepared according to the literature procedures and stored in a refrigerator under N_2 atmosphere. *rac*-1,3-Diphenylprop-2-enyl acetate (**8**) was prepared from *trans*-chalcone through a conventional two-step procedure. Phenyl triflate and 2-(2-naphthyl) triflate were prepared from the reaction of the corresponding alcohol and trifluoroacetic anhydride.

2.2. General method

All experiments involving moisture- and/or air-sensitive compounds were performed in oven- and/or flame-dried glassware with rubber septa under a positive pressure of nitrogen using standard Schlenk technique. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as a visualizing agent and *p*-anisaldehyde solution, and heat as developing agent. Flash chromatography was performed using E. Merck 230–400 mesh silica gel according to the procedure of Still et al. [13]. Neutral TLC plates were prepared by treating the normal TLC plates with a mixture of triethylamine and *n*-hexane (1:19 (v/v)). Melting points were determined using a Thomas–Hoover capillary melting point apparatus and are uncorrected. Optical rotations were obtained using a Rudolph Autopol III digital polarimeter and optical rotation data are reported as follows: $[\alpha]_D^T$ (concentration c = g/100 ml, solvent). HPLC separations were performed with chiral stationary columns purchased from Daicel using a Waters 486 tunable absorbance detector operating at 254 nm with a Waters 746 data module. GC analyses were performed using a CP-cyclodextrin-B-2,3,6-M-19 (25 m × 0.25 mm, 0.25 μm film thickness) capillary GC column purchased from Chrompack with Hewlett-Packard Model HP 5890 GC fitted with a HP3396A integrator. Infrared spectra were obtained on a Mattson Galaxy 2000 spectrometer. NMR spectra were obtained on Varian Mercury INOVA 500 (500 MHz ^{1}H, 125.7 MHz ^{13}C, and 202.4 MHz ^{31}P NMR) spectrometer or Gemini 300 (300 MHz ^{1}H and 75.5 MHz ^{13}C NMR) spectrometer. ^{1}H NMR spectra were referenced to tetramethylsilane (δ = 0.00 ppm) as an internal standard and are reported as follows: chemical shift, multiplicity (br: broad, s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet). ^{13}C NMR spectra were referenced to the residual $CDCl_3$ (δ = 77.0 ppm) and ^{31}P NMR spectra were referenced to external 85% H_3PO_4 (δ = 0.00 ppm). Mass spectra (VG Trio 2000, low resolution, EI) and microanalysis data (Carlo Erba EA 1180 elemental analyzer) were provided by the

Organic Chemistry Research Center at Sogang University.

2.3. Preparation of P,S-hybrid ligand

2.3.1. (R,R,$_p$S,$_p$S)-2,2′-bis(α-N,N-Dimethylamimopropyl)-1,1'-dibromoferrocene (4)

To a stirred solution of diamine (**3**) (2.14 g, 6.01 mmol) in dry diethyl ether (20 ml, 0.3 M) was added dropwise *n*-BuLi (2.30 M in hexanes, 10.4 ml, 24.0 mmol) over 15 min at room temperature. After several minutes, the color of the mixture changed from orange to red. After overnight, the reaction mixture was cooled in a dry ice–acetone bath and a solution of 1,2-dibromotetrachloroethane (8.80 g, 27.0 mmol) in dry THF (13.5 ml) was added dropwise via cannula over 15 min. The resulting dark brown suspension was allowed to warm to room temperature over 90 min, stirred at room temperature for 1 h, and then quenched with saturated $Na_2S_2O_3$ solution at 0 °C. The mixture was diluted with diethyl ether. The organic layer was separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated using a rotatory evaporator. The resulting residue was purified by column chromatography (2% EtOAc/*n*-hexane) on silica gel, which was pre-deactivated with 2% Et_3N/*n*-hexane, to afford the diastereomerically pure dibromide (**4**) (2.60 g, 84%) as a brown solid. TLC (neutral TLC, 5% EtOAc/*n*-hexane): R_f = 0.30; mp: 46–48 °C. $[\alpha]_D^{27}$ + 115 (c = 1.0, $CHCl_3$). IR (KBr): 2971, 2930, 2820, 2777, 1450, 1375, 1042, 990, 817, 774, 511 cm^{-1}. MS (EI, 70 eV) *m*/*z* (relative intensity): 513 (8.85), 468 (29.4), 425 (60.9), 397 (52.0), 346 (15.1), 228 (66.7), 134 (54.5), 104 (58.7), 86 (100). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 4.24 ppm (dd, J_{HH} = 2.5, 1.0 Hz, 2H, Cp), 4.13 ppm (t, J_{HH} = 2.5 Hz, 2H, Cp), 4.00 ppm (dd, J_{HH} = 2.5, 1.0 Hz, 2H, Cp), 3.50 ppm (dd, J_{HH} = 7.5, 11.2 Hz, 2H, $CHCH_2CH_3$), 2.07–1.97 ppm (m, 2H, $CHCH_2CH_3$), 2.04 ppm (s, 12H, NCH_3), 1.81–1.74 ppm (m, 2H, $CHCH_2CH_3$), 1.12 ppm (t, J_{HH} = 7.5 Hz, 6H, $CHCH_2CH_3$). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ = 86.48, 81.04, 75.93, 68.69, 67.73, 60.81, 40.71, 25.91, 12.15 ppm. Anal. Calcd. for $C_{20}H_{30}Br_2FeN_2$: C, 46.72; H, 5.88. Found: C, 46.97; H, 5.45.

2.3.2. (R,R,$_p$S,$_p$S)-2,2'-bis(α-Acetoxyethyl)-1,1′-dibromoferrocene (5)

A mixture of dibromodiamine (**4**) (1.10 g, 2.26 mmol) and acetic anhydride (7.39 g, 72.4 mmol) in a 25-ml Schlenk flask was thoroughly degassed and heated at 70 °C for 10 h. Then, volatiles were removed at 40 °C under vacuum (0.7 mmHg). The residue was purified by column chromatography (5% EtOAc/*n*-hexane) on silica gel, which was pre-deactivated with 5% Et_3N/*n*-hexane, to afford the diacetate (**5**) (999 mg, >85%) as an orange solid. TLC (neutral TLC, 10% EtOAc/*n*-hexane): R_f = 0.10; mp: 90–92 °C. $[\alpha]_D^{27}$ = −39.0 (c = 0.59, $CHCl_3$). IR (KBr): 3093, 2985, 2953, 2937, 1728, 1454, 1376, 1235, 1175, 1115, 1021, 957, 930, 841, 819, 721, 607, 490 cm^{-1}. MS (EI, 70 eV) *m*/*z* (relative intensity): 518 (M + 2, 1.10), 515 (3.33), 458 (1.39), 455 (3.28), 345 (6.10), 285 (20.8), 171 (100), 91 (24.7). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 5.93 ppm (q, J_{HH} = 6.5 Hz, 2H, $CHCH_3$), 4.39 ppm (dd, J_{HH} = 1.0, 2.5 Hz, 2H, Cp), 4.32 ppm (dd, J_{HH} = 1.0, 2.5 Hz, 2H, Cp), 4.18 ppm (t, J_{HH} = 2.5 Hz, Cp), 2.01 ppm (s, 6H, $C(O)CH_3$), 1.62 ppm (d, J_{HH} = 6.5 Hz, 6H, $CHCH_3$). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ = 170.0, 86.75, 80.61, 75.79, 69.84, 67.01, 66.75, 20.98, 18.78 ppm. Anal. Calcd. for $C_{18}H_{26}Br_2FeO_4$: C, 41.90; H, 3.91. Found: C, 41.91; H, 3.91.

2.3.3. ($_p$S,$_p$S)-1,1′-Dibromo-2,2′-di(3-pentyl) ferrocene (6)

To a stirred solution of diacetoxyferrocene (**5**) (1.04 g, 1.86 mmol) in dry dichloromethane (18.6 ml, 0.1 M) was added dropwise triethylaluminum (1.90 M solution in toluene, 4.89 ml, 9.28 mmol) at −78 °C. The reaction mixture was stirred for 60 min at −78 °C. The reaction mixture was warmed to room temperature and stirred for additional 20 min at that temperature. The mixture was transferred into the aqueous saturated $NaHCO_3$ solution (10 ml) at 0 °C via cannula and saturated sodium potassium tartrate solution (10 ml) was then added. The solvent was removed using a rotatory evaporator and the residue was dissolved in dry diethyl ether (15 ml). The resulting suspension was stirred vigorously for 15 min and then acidified with 1 N HCl (10 ml). The organic layer was separated and the aqueous layer was extracted with diethyl ether. The com-

bined organic extracts were washed successively with saturated $NaHCO_3$ solution, water, and brine. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated using a rotatory evaporator. Purification by column chromatography (2% EtOAc/*n*-hexane) on silica gel afforded the dibromoferrocene (**6**) (893 mg, 99%) as an orange solid. TLC (5% EtOAc/*n*-hexane): $R_f = 0.78$; mp: 36–37 °C. $[\alpha]_D^{27} = +83$ ($c = 1.0$, $CHCl_3$). IR (KBr): 2961, 2932, 2872, 1460, 1376, 958, 809, 498 cm^{-1}. MS (EI, 70 eV) *m*/*z* (relative intensity): 483 (M^+, 100), 404 (11.5), 374 (18.8), 324 (4.84), 239 (4.25), 180 (16.7), 153 (29.4), 134 (19.5), 104 (25.2), 78 (11.4). ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 4.20$ ppm (t, $J_{HH} = 2.0$ Hz, 2H, Cp), 4.01 ppm (t, $J_{HH} = 2.5$ Hz, 2H, Cp), 3.98 ppm (m, 2H, Cp), 2.48–2.44 ppm (m, 2H, $CHCH_2CH_3$), 1.95–1.87 ppm (m, 2H, $CHCH_2CH_3$), 1.64–1.53 ppm (m, 4H, $CHCH_2CH_3$), 1.52–1.43 ppm (m, 2H, $CHCH_2CH_3$), 1.04 ppm (t, $J_{HH} = 7.5$ Hz, 6H, $CHCH_2CH_3$), 0.624 ppm (t, $J_{HH} = 7.5$ Hz, 6H, $CHCH_2CH_3$). ^{13}C NMR ($CDCl_3$, 125.7 MHz): $\delta = 93.84$, 80.66, 74.11, 67.93, 66.58, 37.40, 25.13, 24.88, 12.35, 8.932 ppm. Anal. Calcd. for $C_{20}H_{28}Br_2Fe$: C, 49.6; H, 5.83. Found: C, 49.8; H, 5.76.

2.3.4. ($_pS$,$_pS$)-1-Bromo-1′-diphenylphosphino-2,2′-di(3-penty)ferrocene (7)

To a stirred solution of dibromoferrocene (**6**) (690 mg, 1.42 mmol) in dry THF (5.6 ml, 0.25 M) was added dropwise *n*-BuLi (2.12 M solution in hexanes, 0.670 ml, 1.42 mmol) at −78 °C. After the reaction mixture was kept at this temperature for 1 h, chlorodiphenylphosphine (345 mg, 1.56 mmol) was then added at −78 °C. The reaction mixture was warmed to room temperature over a period of 1 h, stirred at room temperature for 1 h, and then quenched with saturated $NaHCO_3$ solution. The mixture was extracted with diethyl ether, washed with brine, dried over $MgSO_4$, and filtered. After removing the solvent, the crude product was purified by column chromatography on silica gel (2% EtOAc/*n*-hexane) to afford the pure bromophosphine (**7**) (812 mg, 97%) as a yellow solid. TLC (5% EtOAc/*n*-hexane): $R_f = 0.47$; mp: 52–55 °C. $[\alpha]_D^{28} = -179$ ($c = 1.0$, $CHCl_3$). IR (KBr): 2964, 2934, 2874, 1463, 1438, 1378, 1168, 828, 748, 698, 513, 488 cm^{-1}. MS (EI, 70 eV) *m*/*z* (relative intensity): 591 ($M + 2$, 18.6), 589 (M^+, 100), 560 (21.4), 510 (29.9), 424 (0.900), 375 (15.3), 291 (30.8), 183 (58.8). ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 7.62$–7.59 ppm (m, 2H, C_6H_5), 7.38–7.36 ppm (m, 3H, C_6H_5), 7.22–7.13 ppm (m, 5H, C_6H_5), 4.30 ppm (d, $J_{HH} = 1.5$ Hz, 1H, Cp), 4.13 ppm (t, $J_{HH} = 2.5$ Hz, 1H, Cp), 3.93 ppm (t, $J_{HH} = 2.5$ Hz, 1H, Cp), 3.86–3.85 ppm (m, 1H, Cp), 3.83–3.82 ppm (m, 1H, Cp), 3.76–3.75 ppm (m, 1H, Cp), 2.71–2.66 ppm (m, 1H, $CHCH_2CH_3$), 2.34–2.29 ppm (m, 1H, $CHCH_2CH_3$), 1.97–1.92 ppm (m, 1H, $CHCH_2CH_3$), 1.82–1.78 ppm (m, 1H, $CHCH_2CH_3$), 1.59–1.50 ppm (m, 3H, $CHCH_2CH_3$), 1.46–1.38 ppm (m, 3H, $CHCH_2CH_3$), 1.01 ppm (t, $J_{HH} = 7.5$ Hz, 3H, $CHCH_2CH_3$), 0.95 ppm (t, $J_{HH} = 7.5$ Hz, 3H, $CHCH_2CH_3$), 0.55 ppm (t, $J_{HH} = 7.5$ Hz, 3H, $CHCH_2CH_3$), 0.42 ppm (t, $J_{HH} = 7.5$ Hz, 3H, $CHCH_2CH_3$). ^{13}C NMR ($CDCl_3$, 125.7 MHz): $\delta = 140.8$ ppm (d, $J_{PC} = 8.5$ Hz), 137.8 ppm (d, $J_{PC} = 7.3$ Hz), 135.7 ppm (d, $J_{PC} = 22$ Hz), 132.2 ppm (d, $J_{PC} = 18.4$ Hz), 129.3, 128.2 ppm (d, $J_{PC} = 8.5$ Hz), 127.8 ppm (d, $J_{PC} = 6.2$ Hz), 101.0 ppm (d, $J_{PC} = 25.6$ Hz), 93.11, 75.30 ppm (d, $J_{PC} = 3.6$ Hz), 73.68, 73.38 ppm (d, $J_{PC} = 3.6$ Hz), 71.23, 67.29 ppm (d, $J_{PC} = 31.8$ Hz), 38.36, 38.28, 30.92, 25.71 ppm (d, $J_{PC} = 3.6$ Hz), 25.38, 24.94 ppm (d, $J_{PC} = 2.4$ Hz), 12.42 ppm (d, $J_{PC} = 4.9$ Hz), 9.00, 8.06 ppm. ^{31}P NMR ($CDCl_3$, 202.4 MHz): $\delta = -24.81$ ppm. Anal. Calcd. for $C_{32}H_{38}BrFeP$: C, 65.44; H, 6.50. Found: C, 65.83; H, 6.40.

2.3.5. ($_pS$,$_pS$)-1′-Methylthio-1-diphenylphosphino-2,2′-di(3-pentyl)ferrocene (2)

To a stirred solution of bromophosphine (**7**) (568 mg, 0.964 mmol) in dry THF (3.9 ml, 0.25 M) was added dropwise *n*-BuLi (2.23 M solution in hexanes, 0.454 ml, 1.01 mmol) at −78 °C. After the reaction mixture was kept at this temperature for 1 h, dimethyl disulfide (99.9 mg, 1.06 mmol) was then added at −78 °C. The reaction was slowly warmed to room temperature over 1 h, and stirred further 1 h at this temperature. The reaction was quenched with water. The mixture was extracted with diethyl ether, washed with brine, dried over $MgSO_4$, and filtered. After removing the solvent, the crude product was purified by column chromatography (1% EtOAc/*n*-hexane) on silica gel to afford the P,S-hybrid ligand **2** (432 mg, 80%) as an orange oil. TLC (5% EtOAc/*n*-hexane): $R_f = 0.58$. $[\alpha]_D^{28} =$

−355 (c = 0.6, $CHCl_3$). IR (KBr): 3075, 3050, 2964, 2929, 2874, 1463, 1433, 1378, 828, 743, 698, 428 cm^{-1}. MS (EI, 70 eV) m/z (relative intensity): 556 (M^+, 100), 528 (19.7), 342 (13.7), 295 (6.07), 266 (8.53), 183 (20.4), 107 (8.49), 77 (4.59). ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.64–7.61 ppm (m, 2H, C_6H_5), 7.39–7.37 ppm (m, 3H, C_6H_5), 7.22–7.14 ppm (m, 5H, C_6H_5), 4.26 ppm (dd, J_{HH} = 1.5, 3.5 Hz, 1H, Cp), 4.13 ppm (t, J_{HH} = 2.5 Hz, 1H, Cp), 4.07 ppm (t, J_{HH} = 2.5 Hz, 1H, Cp), 3.95–3.93 ppm (m, 2H, Cp), 3.55 ppm (dd, J_{HH} = 1.0, 2.5 Hz, 1H, Cp), 2.67–2.66 ppm (m, 1H, $CHCH_2CH_3$), 2.44–2.38 ppm (m, 1H, $CHCH_2CH_3$), 1.98–1.92 ppm (m, 1H, $CHCH_2CH_3$), 1.90–1.86 ppm (m, 1H, $CHCH_2CH_3$), 1.87 (s, 3H, SCH_3), 1.62–155 ppm (m, 3H, $CHCH_2CH_3$), 1.50–1.43 ppm (m, 1H, $CHCH_2CH_3$), 1.01 ppm (t, J_{HH} = 7.5 Hz, 3H, $CHCH_2CH_3$), 0.97 ppm (t, J_{HH} = 7.5 Hz, 3H, $CHCH_2CH_3$), 0.585 ppm (t, J_{HH} = 7.5 Hz, 3H, $CHCH_2CH_3$), 0.451 ppm (t, J_{HH} = 7.5 Hz, 3H, $CHCH_2CH_3$). ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ = 140.9 ppm (d, J_{PC} = 8.5 Hz),138.1 ppm (d, J_{PC} = 8.5 Hz), 135.6 ppm (d, J_{PC} = 23.3 Hz), 132.2 ppm (d, J_{PC} = 18.4 Hz), 129.1, 128.1 ppm (d, J_{PC} = 7.4 Hz), 127.8 ppm (d, J_{PC} = 4.9 Hz), 127.5, 100.9 ppm (d, J_{PC} = 25.6 Hz), 95.79, 83.17, 73.19 ppm (d, J_{PC} = 4.8 Hz), 72.38 ppm (d, J_{PC} = 4.8 Hz), 72.15, 71.03, 69.67, 67.92, 38.44 ppm (d, J_{PC} = 8.5 Hz), 38.06, 30.90, 25.85 ppm (d, J_{PC} = 3.6 Hz), 25.03 ppm (d, J_{PC} = 23.3 Hz), 19.03, 12.44 ppm (d, J_{PC} = 2.5 Hz), 9.11, 8.18 ppm. ^{31}P NMR ($CDCl_3$, 202.4 MHz): δ = −24.42 ppm. Anal. Calcd. for $C_{33}H_{41}FePS$: C, 71.21; H, 7.43. Found: C, 71.44; H, 7.39.

2.4. General procedure for the asymmetric allylic alkylation of 1,3-diphenylprop-2-enyl acetate (*8*)

A mixture of P,S-hybrid ligand **2** (12.2 mg, 22.0 μmol) and $[Pd(\pi\text{-allyl})Cl]_2$ (3.66 mg, 10.0 μmol) in dry dichloromethane (1.00 ml) was stirred at room temperature under N_2 for 30 min, and the resulting red solution was added to a mixture of 1,3-diphenylprop-2-enyl acetate (**8**) (252 mg, 1.00 mmol) and potassium acetate (2.00 mg, 20.0 μmol) in dry dichloromethane (1.00 ml) via cannula, followed by the addition of dimethyl malonate (396 mg, 3.00 mmol) and BSA (613 mg, 3.00 mmol). The reaction was carried out at room temperature and monitored by TLC for the disappearance of **8**. When **8** disappeared completely (ca. 20 min), the solvent was evaporated using a rotatory evaporator and the resulting mixture was extracted with ether. The extract was washed twice with ice-cold saturated NH_4Cl solution, dried over anhydrous $MgSO_4$, filtered, and concentrated using a rotatory evaporator. The resulting residue was purified by column chromatography (15% EtOAc/*n*-hexane) on silica gel to give (–)-(*S*)-dimethyl (1,3-diphenylprop-2-enyl)malonate (**9**) (318 mg, >99%) as a white solid. The absolute configuration was confirmed definitely by comparison of the optical rotation with a literature value [14]. The enantiomeric excess was determined to be 38.5% by HPLC analysis of the product **9** with a chiral stationary phase column (Daicel Chiralpak AD column, 2-propanol/*n*-hexane = 1:9, flow rate: 0.8 ml/min, (*R*)-isomer: 14.8 min, (*S*)-isomer: 20.2 min).

2.5. General procedure for the asymmetric Heck reaction of 2,3-dihydrofuran (*11*)

A mixture of P,S-hybrid ligand **2** (33.4 mg, 60.0 μmol) and $Pd(dba)_2$ (17.2 mg, 30.0 μmol) in dry solvent (0.62 ml) was stirred at 70 °C under N_2 atmosphere for 1 h, and then aryl triflate (1.00 mmol), 2,3-dihydrofuran (**11**) (350 mg, 5.00 mmol), and amine (3.00 mmol) were added successively. The mixture was then heated at the appropriate temperature with vigorous stirring. After cooling to room temperature, the crude mixture was extracted with diethyl ether, washed with brine, dried over anhydrous $MgSO_4$, and concentrated using a rotatory evaporator. The resulting residue was purified by column chromatography (2% EtOAc/*n*-hexane) on silica gel to afford (*R*)-2-aryl-2,5-dihydrofuran as a pale yellow oil. The absolute configuration was confirmed definitely by comparison of the optical rotation with a literature value [15,16]. The enantiomeric excess was determined by HPLC analysis of the product with a chiral stationary phase column (2-phenyl-2,5-dihydrofuran (**14**): Daicel Chiralcel OD column, *n*-hexane, flow rate: 1.0 ml/min, (*R*)-isomer: 56.0 min, (*S*)-isomer: 71.26 min; 2-(2-naphthyl)-2,5-dihydrofuran (**16**): Daicel Chiralcel OD-H column, 2-propanol/*n*-hexane = 1:9, flow rate: 0.5 ml/min, (*R*)-isomer: 19.8 min, (*S*)-isomer: 21.36 min).

3. Results and discussion

3.1. Preparation of chiral ligand

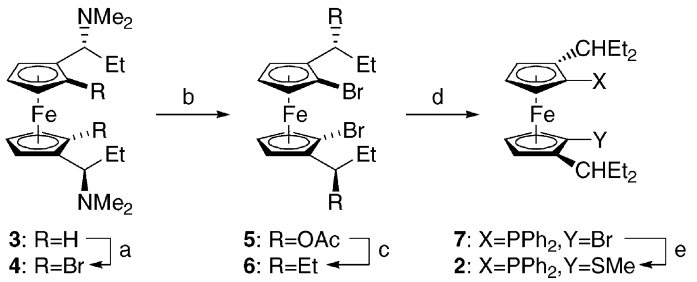
Our synthesis started from the nearly enantiomerically pure (>99% e.e.) C_2-symmetric diamine (**3**), which was prepared in two steps from 1,1′-ferrocenedicarboxaldehyde in excellent overall yield [5,6,8], utilizing thiazincolidine-catalyzed asymmetric Et_2Zn addition developed in our laboratory [17]. In the actual event, the diamine (**3**) was conventionally dilithiated with *n*-BuLi in diethyl ether and subsequently reacted with 1,2-dibromotetrachloroethane to furnish the C_2-symmetrical dibromoferrocene (**4**) in 84% yield as a single diastereomer after simple column chromatography (Scheme 1).

After heating a mixture of **4** and excess Ac_2O at 70 °C for 10 h, the resulting diacetoxyferrocene (**5**) was isolated in a good yield with complete retention of configuration on the *pseudo*-benzylic position [18]. Subsequently, the diacetoxyferrocene (**5**) was reacted with triethylaluminum [5,6,8] at −78 °C to afford the cylindrically chiral dibromoferrocene (**6**) in a quantitative yield after column chromatography on silica gel. A single lithium–bromine exchange of **6** (for a similar strategy using 1,1′-bis(tri-*n*-butylstannyl)ferrocene see [19]) by treating with 1.00 eq. of *n*-BuLi at −78 °C for 60 min followed by reaction with chlorodiphenylphosphine yielded 1-bromo-1′-diphenylphosphino-2,2′-di(3-pentyl)ferrocene (**7**) in an excellent yield. Finally, the novel P,S-chelating ligand **2** was obtained in a good yield as a red oil from the reaction of **7** with 1.1 eq. of *n*-BuLi at −78 °C for 60 min followed by trapping the derived monolithio species with dimethyl disulfide.

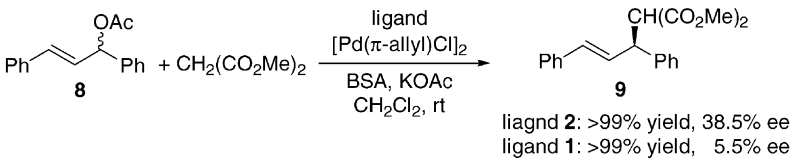
3.2. Asymmetric allylic alkylation

Up to now, few mixed thioether-containing ligands have been applied to enantioselective allylic alkylation reactions [20]. While the coordinating ability of thioether donors in late transition metal complexes is well precedented (for a review see [21]), the stereogenic center formed at sulfur upon coordination may be flexible by its low inversion barrier (15–20 kcal/mol) [22]. Therefore, any attempt to incorporate a thioether donor into a chiral ligand must consider potential erosion of enantioselectivities as a result of sulfur inversion. With this intrinsic limitation in mind, we wished to compare the efficiency of the *pseudo*-C_2-symmetric ligand **2** with its C_2-symmetric bisphosphine counterpart **1** in the asymmetric catalysis. At first, we tested **2** briefly in the Pd-catalyzed asymmetric allylic alkylation of *rac*-1,3-diphenylprop-2-enyl acetate (**8**), since this reaction is not only one of the best understood catalytic asymmetric transformations but good results also can often be obtained using nonsymmetrical heterobidentate ligands (for a recent review see [23]).

As depicted in Scheme 2, using a new palladium complex derived from 1.0 mol% of $[Pd(\pi\text{-allyl})Cl]_2$ and 2.2 mol% of **2**, we carried out the allylic alkylation of *rac*-**8** with dimethyl malonate under a set of conditions (CH_2Cl_2 (0.5 M), 3 eq of BSA with 5 mol% KOAc, room temperature). After 20 min, the reaction was complete giving the (*S*)-**9** in a quantitative yield with only 38.5% e.e. Although the enantioselectivity of 38.5% is low, it is noteworthy that this result is superior to that (5.5% e.e.) obtained using the C_2-symmetric bisphosphine counterpart (3-Pt-FerroPHOS (**1**), R = 3-pentyl) [7]. In this



Scheme 1. Reagents and conditions: (a) (i) *n*-BuLi, ether, RT, 12 h, (ii) $(BrCCl_2)_2$, THF, −78 °C to RT, 84%; (b) Ac_2O, 70 °C, 10 h, >85%; (c) Et_3Al, CH_2Cl_2, −78 °C to RT, 99%; (d) (i) *n*-BuLi, THF, −78 °C, 1 h, (ii) $ClPPh_2$, −78 °C to RT, 97%; (e) (i) *n*-BuLi, THF, −78 °C, 1 h, (ii) $(MeS)_2$, −78 °C to RT, 80%.



Scheme 2. Palladium-catalyzed asymmetric allylic alkylation of *rac*-**8** using the P,S-hybrid ligand **2**.

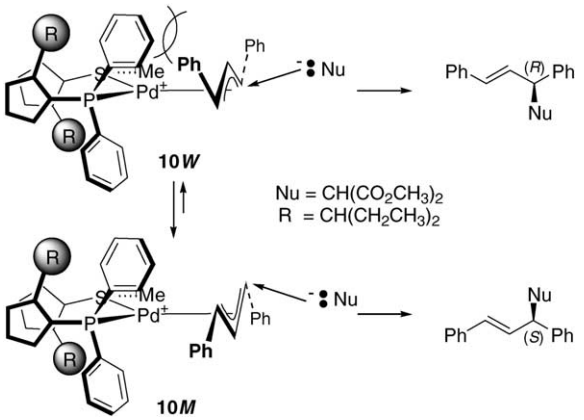


Fig. 2. A hypothetical working model predicting the major enantiomer.

case, a sterically more demanding bisphosphine **1** (MME-FerroPHOS, R = (1-methoxy-1-methyl)ethyl) was shown to be an excellent ligand [7].

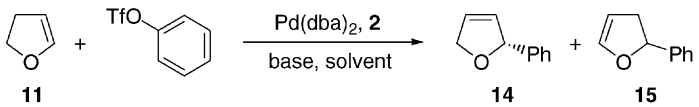
The stereochemical outcome can be rationalized with a hypothetical working model (Fig. 2). The enantiodifferentiation step in Pd-catalyzed allylic alkylation is the substitution of Pd(π-allyl) complexes with incoming nucleophiles, and nucleophilic attack occurs predominantly at the allyl terminus from *trans* to the better π-acceptor (P ≫ S) [24]. Since the (*S*)-isomer was obtained as the major enantiomer, the reaction probably proceeds through a M-type intermediate '10M' rather than a W-type intermediate '10W'.

3.3. Asymmetric Heck reaction (AHR)

Our *pseudo*-C_2-symmetric P,S-hybrid ligand **2** was also employed in the Pd-catalyzed AHR of 2,3-dihydrofuran (**11**) with aryl triflates. Initially, to evaluate the catalytic efficiency of **2** in intermolecular AHR (for a recent review see [25]), phenyl triflate was reacted with 5.0 eq. of **11** in the presence of 6.0 mol% of a palladium catalyst derived from mixing **2** and catalyst precursor (Scheme 3).

Although various reaction parameters including base, solvent, catalyst precursor, and reaction temperature, which have been known to affect strongly on the enantioselectivity as well as the catalytic activity, were screened extensively, all the reactions tested gave disappointing results and some of them are depicted in Table 1. Thus, the reaction with $Pd(dba)_2$ (dba: dibenzylideneacetone) as catalyst precursor (With $Pd(OAc)_2$ as catalyst precursor and **2**, the reaction did not proceed at all regardless of conditions) did proceed at 70 °C in the presence of 3.0 eq. of *N*,*N*-diisopropylethylamine as base to afford (*R*)-2-phenyl-2,5-dihydrofuran (**14**) in 37% yield with 11% e.e. accompanied with a trace amount of the isomerized product **15** (entry 1). The best enantioselectivity (34% e.e.) was obtained when the reaction was carried out in THF using triethylamine as base albeit the yield of **14** was still low (entry 4).

It is the most noteworthy that the major product of every run (Table 1) was the 2,5-dihydrofuran deriva-



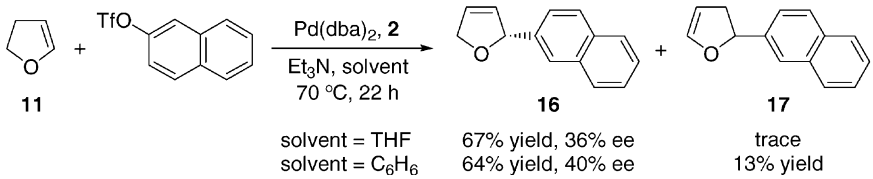
Scheme 3. Asymmetric Heck reaction of **11** with PhOTf using the P,S-hybrid ligand **2**.

Table 1
Asymmetric Heck reaction of **11** with PhOTf using the P,S-hybrid ligand **2**[a]

Entry	Base	Solvent	Temperature (°C)	Time (h)	**14** (yield % (e.e. (%), configuration)[b])	**15** (yield %)
1	*i*-Pr_2NEt	Benzene	70	22	37 (11, R)	trace
2	Et_3N	Benzene	70	22	32 (25, R)	trace
3	Proton sponge	Benzene	60	72	11 (11, R)	–
4	Et_3N	THF	70	22	34 (34, R)	trace
5	*i*-Pr_2NEt	THF	70	24	34 (32, R)	–
6	2,6-Lutidine	THF	70	24	34 (24, R)	–

[a] All reactions were carried out in 1.0 M solution using 5.0 mmol of **11**, 1.0 mmol of PhOTf, and 3.0 mmol of base under N_2 atmosphere, in the presence of 3.0 mol% of Pd-catalyst derived from mixing 6.0 mol% of **6** with 3.0 mol% of $Pd(dba)_2$, unless otherwise stated. Yields were based on PhOTf employed.

[b] Enantiomeric excesses were determined by HPLC analysis using a chiral stationary column (Daicel Chiralcel OD-H column). And absolute configurations were confirmed by comparison of the optical rotation with a literature value [15].



Scheme 4. Asymmetric Heck reaction of **11** with 2-naphthyl triflate using the P,S-hybrid ligand **2**.

tive **14,** although the results showed that the e.e. value and the chemical yield were not strongly dependent on the base and the solvent used. The corresponding 2,3-dihydrofuran derivative **15**, which is the major product in the Pd(BINAP)-catalyzed reaction (BINAP: 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) [26,27], was not detected or was formed in only a negligible amount.

The asymmetric Heck reaction between **11** and 2-naphthyl triflate was also carried out as shown in Scheme 4. Switching to the sterically more bulky 2-(2-naphthyl) triflate showed a positive effect on the chemical yield of the 2-ary-2,5-dihydrofuran derivative **16** but little effect on the enantioselectivity of the reaction. Thus, the reaction of 2,3-dihydrofuran (**11**) with 2-naphthyl triflate in THF or benzene at 70 °C in the presence of a base such as Et_3N or 2,6-lutidine gave (*R*)-2-(2-naphthyl)-2,5-dihydrofuran (**16**) in 50–64% yield with 36–40% e.e. Somewhat high e.e. of 40% was obtained when the reaction was performed in benzene although an appreciable amount of the isomerized product **17** was accompanied in this solvent.

4. Conclusion

As described above, we have prepared a new solely planar chiral ferrocenyl P,S-bidentate ligand **2** in good overall yield (ca. 55% for five steps) using a predictable asymmetric methodology. The chiral ligand **2** is the first example of P,S-chelating ligand that contains two different planar chiralities as the sole chiral element. The palladium complex bearing **2** is such a highly active catalyst for allylic alkylation that the reaction of *rac*-**8** with dimethyl malonate gives the alkylation product **9** in a nearly quantitative yield only after 20 min at room temperature. Although the enantioselectivity of (*S*)-**9** attained in this reaction is quite low, it is somewhat superior to that obtained using the C_2-symmetric counterpart of **2**. The stereochemical outcome of the reaction can be easily explained by a conventional transition state model (Fig. 2). The intermolecular asymmetric Heck reaction of 2,3-dihydrofuran (**11**) with aryl triflates catalyzed by another palladium complex containing **2** was also carried out. Unfortunately, both relatively low reactivity and poor enantioselectivity were obtained in this study.

However, noteworthy is that the high regioselectivy favoring the 2,5-dihydrofuran derivative **14** over the regioisomeric 2,3-dihydrofuran derivative **15** is observed. Application of our new chiral ligand **2** to other transition-metal-catalyzed asymmetric reactions and further investigation with new *pseudo*-C_2-symmetric ligands are now in active progress in our laboratory.

Acknowledgements

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References

[1] J.K. Whitesell, Chem. Rev. 89 (1989) 1581.
[2] T.P. Dang, H.B. Kagan, J. Am. Chem. Soc. 94 (1972) 6429.
[3] R. Noyori, Asymmetric Catalyst in Organic Synthesis, Wiley, New York, 1994.
[4] E.L. Eliel, S.H. Wilen, N.N. Mander, Stereochemistry of Organic Compounds, Wiley, New York, 1994.
[5] J. Kang, J.H. Lee, S.H. Ahn, J.S. Choi, Tetrahedron Lett. 39 (1998) 5523.
[6] J. Kang, J.H. Lee, J.B. Kim, G.J. Kim, Chirality 12 (2000) 378.
[7] J. Kang, J.H. Lee, J.S. Choi, Tetrahedron: Asym. 12 (2001) 33.
[8] J.H. Lee, Ph.D. Thesis, Sogang University, 2000.
[9] R. Stranne, J.-L. Vasse, C. Moberg, Org. Lett. 3 (2001) 2525.
[10] S.-L. You, Y.-G. Zhou, X.-L. Hou, L.-X. Dai, Chem. Commun. (1998) 2765.
[11] Y. Tatsuno, T. Yoshida, Seiotsuka, Inorg. Synth. 19 (1979) 220.
[12] T. Ukai, H. Kawazawa, Y. Ishii, J.J. Bonnett, J.A. Ibers, J. Organomet. Chem. 65 (1974) 253.
[13] W.C. Still, M. Kahn, A. Mita, J. Org. Chem. 43 (1978) 2923.
[14] P. von Matt, A, Pfaltz, Angew. Chem., Int. Ed. Engl. 32 (1993) 566.
[15] A. Pfaltz, O. Loiseleur, M. Hayashi, N. Schmees, Synthesis (1997) 1338.
[16] F. Ozawa, A. Kubo, T. Hayashi, Tetrahedron Lett. 33 (1992) 1485.
[17] J. Kang, J.W. Kim, J.W. Lee, D.S. Kim, J.I. Kim, Bull. Korean Chem. Soc. 17 (1996) 1135 (and references therein).
[18] G. Gokel, P. Hoffmann, H. Klusacek, D. Marquarding, E. Ruch, I. Ugi, Angew. Chem., Int. Ed. Engl. 9 (1970) 64.
[19] W. Zhang, Y.-I. Yoneda, T. Kida, Y. Nakatsuji, I. Ikeda, Tetrahedron: Asym. 9 (1998) 3371.
[20] D.A. Evans, K.R. Campos, J.S. Tedrow, F.E. Michael, M.R. Gagne, J. Am. Chem. Soc. 122 (2000) 7905 (and references therein).
[21] S. Murray, F. Hartley, Chem. Rev. 81 (1981) 365.
[22] E. Abel, S.K. Bhargava, K.G. Orrell, Prog. Inorg. Chem. 32 (1984) 1.
[23] A. Pfaltz, M. Lautens, in: E.N. Jacobsen, A. Pfaltz, H. Yamammoto (Eds.), Comprehensive Asymmetric Catalysis, vol. II, Springer, New York, 1999, Chapter 24, p. 833.
[24] B. Akermark, B. Krakenberg, S. Hansson, A. Vitagliano, Organometallics 6 (1987) 620.
[25] M. Shibasaki, E.M. Vogl, in: E.N. Jacobsen, A. Pfaltz, H. Yamammoto (Eds.), Comprehensive Asymmetric Catalysis, vol. I, Springer, New York, 1999, Chapter 14, p. 457.
[26] F. Ozawa, A. Kubo, T. Hayashi, J. Am. Chem. Soc. 113 (1991) 1417.
[27] A. Miyashita, A. Yasuda, H. Takaya, K. Toriumi, T. Ito, T. Souchi, R. Noyori, J. Am. Chem. Soc. 102 (1980) 7932.