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Facile preparation of chiral *P*,*N*-hydrazone ligands and their Pd-catalyzed asymmetric allylic alkylations

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Abstract

Chiral hydrazone ligands **2** are easily accessible in good yields by nucleophilic phosphanylation of corresponding *ortho*-fluorobenzaldehyde SAMP hydrazone derivatives with $KPPh_2$. Palladium-catalyzed asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate (**6**) with a dimethyl malonate–BSA–LiOAc system has been successfully carried out in the presence of chiral hydrazone ligands **2g** in high yields with high enantioselectivities.

Keywords: Enantioselective; Allylic alkylation; Palladium; Chiral hydrazone; Phosphanylation

1. Introduction

Palladium-catalyzed asymmetric allylic substitutions are one of the most effective methods for the enantioselective construction of carbon–carbon or carbon–heteroatom bonds [1–4]. Chiral 2-(phosphinoaryl)oxazoline can induce high enantiomeric excesses in palladium-catalyzed reactions of racemic and achiral allylic substrates with nucleophiles by Helmchen [5], Von Matt and Pfaltz [6], and Dawson et al. [7], independently. Following their pioneering studies, a number of *P*,*N*-chelate chiral ligands such as oxazolinophosphnes [8–10], aminophosphines [11–19], aminophosphinite [20], isoquinolinophosphines [21], pyrazolinophosphines [22], pyridinophosphines [23–26], iminophosphines [27–32] have been reported.

Recently, we reported the palladium-catalyzed asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate (**6**) in the presence of hydrazonophosphine type ligand such as 2-(diphenylphosphino)benzaldehyde SAMP hydrazone (DPPB-SAMP) (**1**) [33,34].

Polymer-supported catalysts [35] and fluorous biphasic catalysts [36] in catalytic asymmetric synthesis have the advantage of easy separation and potential recycling of expensive chiral catalysts. In these cases, a connecting part between ligand and polymer or fluorous alkane is required. As part of a project aimed at the development of these catalysts, here we report the easy synthetic procedure for new chiral hydrazone ligands, which have various substituents such as methyl, trifluoromethyl, and methoxyl at the aromatic ring of DPPB-SAMP (**1**), based on nucleophilic phosphanylation. Moreover, we report their application in palladium-catalyzed asymmetric allylic alkylation

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and examine the effect of various substituents on the ligands.

2. Experimental

2.1. General

Melting points were measured on a Shibata micromelting point apparatus. NMR spectra were recorded on a JEOL LA-400 system or a Bruker DPX-300 system using TMS as an internal standard. IR spectra were recorded on a JASCO FT-IR-230 spectrometer. Mass spectra were recorded on a JEOL JMS-HX110. Optical rotations were measured on a JASCO DIP-370. All aldehydes except **3d** were purchased from Aldrich and used without further purification. Aldehyde **3d** was prepared according to the literature method [37].

2.2. Preparation of *5*

A mixture of SAMP ((*S*)-1-amino-2-methoxymethylpyrrolidine) (**4**) (1.0 mmol, 0.16 ml), substituted 2-fluorobenzaldehyde (**3**) (1.0 mmol), and catalytic amount of trifluoroacetic acid in benzene (10 ml) was heated at 100 °C under an argon atmosphere for 24 h, and then cooled to room temperature. The reaction mixture was diluted with ether 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.

2.2.1. 2-Fluoro-3-trifluoromethylbenzaldehyde SAMP hydrazone (*5a*)

Ninety-two percent; $[\alpha]_D^{23} = -142$ (c 0.62, $CHCl_3$); yellow oil; ^{1}H NMR ($CDCl_3$) δ: 1.88–2.17 (m, 4H), 3.09–3.17 (m, 1H), 3.40 (s, 3H), 3.43–3.50 (m, 1H), 3.54 (dd, J = 8.1 and 6.7 Hz, 1H), 3.65 (dd, J = 9.4 and 3.7 Hz, 1H), 3.73–3.76 (m, 1H), 7.15 (t, J = 7.8 Hz, 1H), 7.27 (s, 1H), 7.38 (t, J = 6.9 Hz, 1H), 8.05 (t, J = 7.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 22.25, 26.91, 48.56, 59.32, 63.00, 74.42, 121.03, 121.80 (d, J_{cf} = 6.3 Hz), 123.66 (d, J_{cf} = 4.1 Hz), 124.26–124.64 (m), 126.78 (d, J_{cf} = 4.8 Hz), 128.84 (d, J_{cf} = 4.0 Hz), 153.00–158.00 (m); IR (neat): (CN) 1556 cm^{-1}; FAB-MS *m/z*: 305 ($M^+ + 1$, 37); HRMS *m/z* calcd for $C_{14}H_{16}F_4N_2O + H$ 305.1277, found 305.1273.

2.2.2. 2-Fluoro-4-trifluoromethylbenzaldehyde SAMP hydrazone (*5b*)

Ninety-eight percent; $[\alpha]_D^{23} = -158$ (c 0.86, $CHCl_3$); yellow oil; ^{1}H NMR ($CDCl_3$) δ: 1.90–2.11 (m, 4H), 3.14–3.16 (m, 1H), 3.40 (s, 3H), 3.43–3.48 (m, 1H), 3.54 (dd, J = 9.4 and 6.5 Hz, 1H), 3.65 (q, J = 9.5 Hz, 1H), 3.78–3.79 (m, 1H), 7.24 (t, J = 7.7 Hz, 1H), 7.24 (d, J = 13.5 Hz, 1H), 7.31 (d, J = 8.2 Hz, 1H); 7.95 (t, J = 3.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 22.28, 26.91, 48.43, 59.33, 63.00, 74.36, 112.75 (d, J_{cf} = 4.1 Hz) 113.00 (d, J_{cf} = 4.1 Hz), 120.83–120.91 (m), 121.52 (d, J_{cf} = 4.9 Hz), 128.82, 157.70, 160.21; IR (neat): (CN) 1545 cm^{-1}; FAB-MS *m/z*: 305 ($M^+ + 1$, 50); HRMS *m/z* calcd for $C_{14}H_{17}F_4N_2O + H$ 305.1277, found 305.1273.

2.2.3. 2-Fluoro-4-methoxybenzaldehyde SAMP hydrazone (*5c*)

More than ninety-nine percent; $[\alpha]_D^{23} = -134$ (c 0.99, $CHCl_3$); brown oil; ^{1}H NMR ($CDCl_3$) δ: 1.86–2.04 (m, 4H), 3.02 (q, J = 9.13 Hz, 1H), 3.41 (s, 3H), 3.44–3.51 (m, 2H), 3.51–3.69 (m, 2H), 3.79 (s, 3H), 6.56 (dd, J = 12.5 and 2.5 Hz, 1H), 6.67 (dd, J = 8.8 and 2.4 Hz, 1H), 7.33 (s, 1H), 7.77 (t, J = 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 22.62, 27.25, 49.51, 55.95, 59.69, 63.58, 75.05, 101.39 (d, J_{cf} = 25.2 Hz), 111.00 (d, J_{cf} = 2.8 Hz), 118.13 (d, J_{cf} = 10.8 Hz), 126.14 (q, J_{cf} = 10.3 Hz), 159.41, 160.21 (d, J_{cf} = 10.9 Hz), 162.70; IR (neat): (CN) 1620 cm^{-1}; FAB-MS *m/z*: 266 (M^+, 88); HRMS *m/z* calcd for $C_{14}H_{19}FN_2O_2$ 266.1431, found 266.1420.

2.2.4. 2-Fluoro-4-methylbenzaldehyde SAMP hydrazone (*5d*)

Eighty-four percent; $[\alpha]_D^{23} = -172$ (c 1.01 $CHCl_3$); yellow oil; ^{1}H NMR ($CDCl_3$) δ: 1.86–2.05 (m, 4H), 2.32 (s, 3H), 3.05 (q, J = 8.1 Hz, 1H), 3.40 (s, 3H), 3.46–3.54 (m, 2H), 3.65–3.69 (m, 2H), 6.81 (d, J = 12.1 Hz, 1H), 6.89 (d, J = 8.0 Hz, 1H), 7.34 (s, 1H), 7.72 (t, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 21.00 (d, J_{cf} = 1.5 Hz), 22.10, 26.73, 48.77, 59.16, 62.95, 74.46, 115.65 (d, J_{cf} = 21.1 Hz), 121.95, 124.76–125.03 (m), 138.33 (d, J_{cf} = 7.9 Hz), 158.15, 161.43; IR (neat): (CN) 1585 cm^{-1}; FAB-MS *m/z*: 251

($M^+ + 1$, 68); HRMS *m/z* calcd for $C_{14}H_{19}FN_2O + H$ 251.1560, found 251.1548.

*2.2.5. 2-Fluoro-5-trifluoromethylbenzaldehyde SAMP hydrazone (**5e**)*

Ninety-nine percent; $[\alpha]_D^{23} = -136$ (c 0.54, $CHCl_3$); brown solid; mp 34.5–35.5 °C; ^{1}H NMR ($CDCl_3$) δ: 1.85–2.13 (m, 4H), 3.09–3.17 (m, 1H), 3.41 (s, 3H), 3.43–3.49 (m, 1H), 3.54 (dd, J = 9.5 and 6.6 Hz, 1H), 3.66 (dd, J = 9.5 and 3.7 Hz, 1H), 3.77–3.80 (m, 1H), 7.08 (t, J = 9.6 Hz, 1H), 7.25 (d, J = 7.4 Hz, 1H), 7.37 (m, 1H); 8.13 (dd, J = 6.8 and 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 22.67, 27.26, 48.98, 59.70, 63.38, 74.75, 116.33 (d, J_{cf} = 22.7 Hz), 122.03–122.94 (m), 124.48–124.66 (m), 126.23–127.33 (m), 159.82–163.17 (m); IR (neat): (CN) 1556 cm^{-1}; FAB-MS *m/z*: 305 ($M^+ + 1$, 50); HRMS *m/z* calcd for $C_{14}H_{17}F_4N_2O + H$ 305.1277, found 305.1268.

*2.2.6. 2-Fluoro-5-methoxybenzaldehyde SAMP hydrazone (**5f**)*

Ninety-seven percent; $[\alpha]_D^{23} = -150$ (c 1.12, $CHCl_3$); yellow oil; ^{1}H NMR ($CDCl_3$) δ: 1.88–2.09 (m, 4H), 3.04–3.13 (m, 1H), 3.41 (s, 3H), 3.43–3.51 (m, 2H), 3.65–3.75 (m, 2H), 3.81 (s, 3H), 6.65–6.71 (m, 1H), 6.91 (dd, J = 10.0 and 9.1 Hz, 1H), 7.29 (s, 1H), 7.35 (dd, J = 6.0 and 3.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 22.11, 26.76, 48.64, 55.62, 59.16, 62.86, 74.39, 108.22 (d, J_{cf} = 3.7 Hz), 113.84 (d, J_{cf} = 8.1 Hz), 115.82 (d, J_{cf} = 23.4 Hz), 124.11 (d, J_{cf} = 4.7 Hz), 125.30 (d, J_{cf} = 11.8 Hz), 153.02, 155.89 (d, J_{cf} = 47.9 Hz); IR (neat): (CN) 1554 cm^{-1}; FAB-MS *m/z*: 266 (M^+, 61); HRMS *m/z* calcd for $C_{14}H_{19}FN_2O_2 + H$ 267.1509, found 267.1510.

*2.2.7. 2-Fluoro-5-methylbenzaldehyde SAMP hydrazone (**5g**)*

Eighty-nine percent; $[\alpha]_D^{23} = -148$ (c 1.04, $CHCl_3$); brown oil; ^{1}H NMR ($CDCl_3$) δ: 1.87–2.05 (m, 4H), 2.30 (s, 3H), 3.06 (q, J = 8.1 Hz, 1H), 3.40 (s, 3H), 3.42–3.53 (m, 2H), 3.65–3.73 (m, 2H), 6.84–6.93 (m, 2H), 7.32 (s, 1H), 7.62 (d, J = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 20.79, 22.27, 26.91, 48.88, 53.31, 63.10, 74.64, 115.00 (d, J_{cf} = 21.4 Hz), 124.35–125.17 (m), 128.50 (d, J_{cf} = 8.0 Hz), 133.35 (d, J_{cf} = 3.4 Hz), 156.79, 160.03; IR (neat): (CN) 1558 cm^{-1}; FAB-MS *m/z*: 250 (M^+, 62); HRMS *m/z* calcd for $C_{14}H_{19}FN_2O + H$ 251.1560, found 251.1537.

*2.2.8. 2-Fluoro-6-trifluoromethylbenzaldehyde SAMP hydrazone (**5h**)*

Ninety-nine percent; $[\alpha]_D^{23} = -249$ (c 0.58, $CHCl_3$); yellow oil; ^{1}H NMR ($CDCl_3$) δ: 1.89–2.11 (m, 4H), 3.14–3.17 (m, 1H), 3.39 (s, 3H), 3.41–3.48 (m, 1H), 3.45 (dd, J = 9.5 and 6.6 Hz, 1H), 3.65 (dd, J = 9.5 and 3.6 Hz, 1H), 3.75–3.76 (m, 1H), 7.21–7.26 (m, 1H), 7.21–7.26 (m, 1H), 7.21–7.26 (m, 1H), 7.43–7.46 (m, 1H); ^{13}C NMR ($CDCl_3$) δ: 22.58, 27.21, 48.26, 59.61, 63.21, 74.53, 120.10 (d, J_{cf} = 23.0 Hz), 122.31 (d, J_{cf} = 9.4 Hz), 124.79, 126.06, 127.29, 159.06, 162.40; IR (neat): (CN) 1552 cm^{-1}; FAB-MS *m/z*: 305 ($M^+ + 1$, 58); HRMS *m/z* calcd for $C_{14}H_{17}F_4N_2O + H$ 305.1277, found 305.1269.

*2.2.9. 2-Fluoro-6-methoxybenzaldehyde SAMP hydrazone (**5i**)*

Eighty-four percent; $[\alpha]_D^{23} = -158$ (c 1.10, $CHCl_3$); brown oil; ^{1}H NMR ($CDCl_3$) δ: 1.87–2.10 (m, 4H), 3.10 (q, J = 7.66 Hz, 1H), 3.39 (s, 3H), 3.45–3.54 (m, 2H), 3.66–3.73 (m, 2H), 3.84 (s, 3H), 6.63–6.72 (m, 2H), 7.09 (dt, J = 8.3 and 6.2 Hz, 1H), 7.29 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 22.20, 26.83, 48.38, 56.09, 59.22, 62.92, 74.49, 106.39 (d, J_{cf} = 3.0 Hz), 108.89 (d, J_{cf} = 22.7 Hz), 114.50 (d, J_{cf} = 12.4 Hz), 124.45 (d, J_{cf} = 2.8 Hz), 127.44 (d, J_{cf} = 10.8 Hz), 158.04–158.78 (m), 162.11; IR (neat): (CN) 1608 cm^{-1}; EI-MS *m/z*: 266 (M^+, 23); HRMS *m/z* calcd for $C_{14}H_{19}FN_2O + H$ 267.1509, found 267.1523.

*2.3. Synthesis of ligand **2***

To a solution of $KPPh_2$ (1.2 mmol) in THF (2.4 ml) was added a solution of SAMP hydrazone **5** (1.0 mmol) in THF (5 ml). The resulting solution was heated at 60 °C under an argon atmosphere for 24 h, and then cooled to room temperature. The reaction mixture was diluted with degassed 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.

*2.3.1. 2-Diphenylphosphino-3-trifluoromethylbenzaldehyde SAMP hydrazone (**2a**)*

Twenty-five percent; $[\alpha]_D^{23} = -298$ (c 0.11, $CHCl_3$); yellow oil; ^{1}H NMR ($CDCl_3$) δ: 1.62–1.76 (m, 4H), 2.02–2.10 (m, 1H), 2.55–2.73 (m, 1H), 3.22–3.25 (m, 2H), 3.28 (s, 3H), 3.38–3.44 (m, 1H), 6.82 (s, 1H), 7.25–7.51 (m, 11H), 7.51–7.71 (m, 1H), 8.26 (d, $J = 7.9$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 21.87, 26.70, 48.47, 59.17, 62.32, 74.07, 124.50, 127.56, 127.71, 128.43 (d, $J_{cp} = 4.6$ Hz), 128.95, 129.36, 131.00–131.55 (m), 135.65, 135.88, 143.67 (d, $J_{cp} = 4.1$ Hz); ^{31}P NMR ($CDCl_3$) δ: −14.10 (q, $J_{fp} = 173.3$ Hz); IR (neat): (CN) 1541 cm^{-1}; FAB-MS *m*/*z*: 471 ($M^+ + 1$, 14); HRMS *m*/*z* calcd for $C_{26}H_{26}F_3N_2OP + H$ 471.1813, found 471.1804.

*2.3.2. 2-Diphenylphosphino-4-trifluoromethylbenzaldehyde SAMP hydrazone (**2b**)*

Fourteen percent; $[\alpha]_D^{23} = -80$ (c 0.15, $CHCl_3$); yellow oil; ^{1}H NMR ($CDCl_3$) δ: 1.88–1.99 (m, 4H), 2.86–2.88 (m, 1H), 3.31 (s, 3H), 3.23–3.28 (m, 1H), 3.33–3.39 (m, 1H), 3.46 (dd, $J = 9.4$ and 3.6 Hz, 1H), 3.61–3.62 (m, 1H), 7.00 (d, $J = 3.9$ Hz, 1H), 7.51 (s, 1H), 7.25–7.36 (m, 10H), 7.48–7.53 (m, 1H), 7.92–7.96 (m, 1H); ^{13}C NMR ($CDCl_3$) δ: 22.14, 26.76, 48.55, 59.21, 62.75, 74.04, 124.73 (d, $J_{cp} = 4.1$ Hz), 125.23, 128.22–129.06 (m), 129.95, 133.89 (d, $J_{cp} = 17.2$ Hz), 134.09 (d, $J_{cp} = 17.2$ Hz), 135.92, 136.05, 143.73 (d, $J_{cp} = 21.3$ Hz); ^{31}P NMR ($CDCl_3$) δ: −11.65; IR (neat): (CN) 1539 cm^{-1}; FAB-MS *m*/*z*: 471 ($M^+ + 1$, 11); HRMS *m*/*z* calcd for $C_{26}H_{26}F_3N_2OP + H$ 471.1813, found 471.1791.

*2.3.3. 2-Diphenylphosphino-4-methoxybenzaldehyde SAMP hydrazone (**2c**)*

More than ninety-nine percent; $[\alpha]_D^{23} = -105$ (c 1.00, $CHCl_3$); white solid; mp 81.5–82.5 °C; ^{1}H NMR ($CDCl_3$) δ: 1.76–1.97 (m, 4H), 2.76 (q, $J = 8.0$ Hz, 1H), 3.26–3.33 (m, 2H), 3.32 (s, 3H), 3.40–3.48 (m, 2H), 3.58 (s, 3H), 6.31 (dd, $J = 4.9$ and 2.7 Hz, 1H), 6.86 (dd, $J = 8.7$ and 2.7 Hz, 1H), 7.20–7.31 (m, 10H), 7.63 (d, $J = 4.1$ Hz, 1H), 7.79 (dd, $J = 8.7$ and 4.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 22.11, 26.70, 49.21, 54.96, 59.17, 62.93, 74.35, 114.52, 118.53, 126.55 (d, $J_{cp} = 5.1$ Hz), 128.42–128.70 (m), 135.05, 135.28, 136.80 (d, $J_{cp} = 6.7$ Hz), 136.93 (d, $J_{cp} = 6.0$ Hz), 158.37; ^{31}P NMR ($CDCl_3$) δ: −11.42; IR (neat): (CN) 1593 cm^{-1}; FAB-MS *m*/*z*: 433 ($M^+ + 1$, 15); HRMS *m*/*z* calcd for $C_{26}H_{29}N_2O_2P + H$ 433.2045, found 433.2051.

*2.3.4. 2-Diphenylphosphino-4-methylbenzaldehyde SAMP hydrazone (**2d**)*

Fifty-eight percent; $[\alpha]_D^{23} = -76$ (c 1.08, $CHCl_3$); yellow oil; ^{1}H NMR ($CDCl_3$) δ: 1.58–1.93 (m, 4H), 2.16 (s, 3H), 2.74–2.83 (m, 1H), 3.25–3.34 (m, 2H), 3.32 (s, 3H), 3.45–3.53 (m, 2H), 6.59 (d, $J = 4.1$ Hz, 1H), 7.12 (d, $J = 7.8$ Hz, 1H), 7.25–7.34 (m, 10H), 7.66 (d, $J = 4.3$ Hz, 1H), 7.75 (dd, $J = 8.0$ and 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 21.21, 21.99, 26.59, 48.89, 59.05, 62.71, 74.18, 124.90, 128.23–128.40 (m), 129.60, 131.28, 133.65–136.27 (m), 163.80; ^{31}P NMR ($CDCl_3$) δ: −12.12; IR (neat): (CN) 1568 cm^{-1}; FAB-MS *m*/*z*: 417 ($M^+ + 1$, 12); HRMS *m*/*z* calcd for $C_{26}H_{29}N_2OP + H$ 417.2096, found 417.2099.

*2.3.5. 2-Diphenylphosphino-5-trifluoromethylbenzaldehyde SAMP hydrazone (**2e**)*

Twenty-six percent; $[\alpha]_D^{23} = -55$ (c 0.37, $CHCl_3$); yellow oil; ^{1}H NMR ($CDCl_3$) δ: 1.81–2.05 (m, 4H), 2.80–2.89 (m, 1H), 3.33 (s, 3H), 3.22–3.36 (m, 2H), 3.46 (dd, $J = 9.4$ and 3.6 Hz, 1H), 3.56–3.64 (m, 1H), 6.86 (dd, $J = 8.0$ and 4.3 Hz, 1H), 6.88–7.52 (m, 1H), 6.88–7.52 (m, 10H), 7.53 (d, $J = 4.1$ Hz, 1H), 8.09 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 22.17, 26.76, 48.70, 59.19, 62.75, 74.08, 121.32–121.37 (m), 122.35, 126.05, 128.42–129.01 (m), 130.44, 130.86, 133.70–134.30 (m), 136.03 (q, $J_{cf} = 26.6$ Hz), 137.37, 137.62, 140.98, 141.23; ^{31}P NMR ($CDCl_3$) δ: −11.88; IR (neat): (CN) 1549 cm^{-1}; FAB-MS *m*/*z*: 471 ($M^+ + 1$, 12); HRMS *m*/*z* calcd for $C_{26}H_{26}F_3N_2OP + H$ 471.1813, found 471.1791.

*2.3.6. 2-Diphenylphosphino-5-methoxybenzaldehyde SAMP hydrazone (**2f**)*

Fourty-nine percent; $[\alpha]_D^{23} = -71$ (c 1.11, $CHCl_3$); yellow oil; ^{1}H NMR ($CDCl_3$) δ: 1.79–2.00 (m, 4H), 2.87 (q, $J = 7.4$ Hz, 1H), 3.28–3.41 (m, 2H), 3.33 (s, 3H), 3.50 (dd, $J = 9.3$ and 3.6 Hz, 1H,), 3.55–3.59 (m, 1H), 3.84 (s, 3H), 6.66 (dd, $J = 8.5$ and 2.7 Hz, 1H), 6.75 (dd, $J = 8.5$ and 4.6 Hz, 1H), 7.24–7.32 (m, 10H), 7.44 (d, $J = 4.8$ Hz, 1H), 7.71 (d, $J = 3.1$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 22.02, 26.65, 48.81, 55.06, 59.06, 62.66, 74.16, 108.83 (d, $J_{cp} = 5.4$ Hz), 113.51, 124.50, 128.23–133.83 (m), 135.21, 137.43, 142.30 (d, $J_{cp} = 20.0$ Hz), 160.12; ^{31}P NMR

($CDCl_3$) δ: −14.80; IR (neat): (CN) 1591 cm^{-1}; FAB-MS *m/z*: 433 ($M^+ + 1$, 19), HRMS *m/z* calcd for $C_{26}H_{29}N_2O_2P$ + H 433.2045, found 433.2048.

*2.3.7. 2-Diphenylphosphino-5-methylbenzaldehyde SAMP hydrazone (**2g**)*

Fifty-five percent; $[\alpha]_D^{23} = -70$ (c 1.08, $CHCl_3$); white solid; mp 80.5–81.5 °C; ^{1}H NMR ($CDCl_3$) δ: 1.78–1.96 (m, 4H), 2.34 (s, 3H), 2.83 (dd, J = 22.0 and 12.9 Hz, 1H), 3.27–3.34 (m, 2H), 3.32 (s, 3H), 3.48 (dd, J = 9.3 and 3.6 Hz, 1H), 3.75 (sept, J = 3.4 Hz, 1H), 6.69 (dd, J = 7.8 and 4.9 Hz, 1H), 6.90 (d, J = 7.7 Hz, 1H), 7.24–7.32 (m, 10H), 7.66–7.68 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 21.33, 22.18, 26.79, 49.04, 59.21, 62.87, 74.35, 125.51 (d, J_{cp} = 4.8 Hz), 127.89 (d, J_{cp} = 1.0 Hz), 128.44 (d, J_{cp} = 6.8 Hz), 130.09 (d, J_{cp} = 14.9 Hz), 131.36 (d, J_{cp} = 22.2 Hz), 133.73–134.15 (m), 137.32 (d, J_{cp} = 5.3 Hz), 137.45 (d, J_{cp} = 4.7 Hz), 138.71, 140.56 (d, J_{cp} = 18.9 Hz); ^{31}P NMR ($CDCl_3$) δ: −13.24; IR (neat): (CN) 1556 cm^{-1}; EI-MS *m/z*: 417 ($M^+ + 1$, 19); HRMS *m/z* calcd for $C_{26}H_{29}N_2OP$ + H 417.2096, found 417.2095.

*2.3.8. 2-Diphenylphosphino-6-trifluoromethylbenzaldehyde SAMP hydrazone (**2h**)*

Twenty-five percent; $[\alpha]_D^{23} = -70$ (c 0.26, $CHCl_3$); yellow solid; mp 67.0–68.0 °C; ^{1}H NMR ($CDCl_3$) δ: 1.75–2.00 (m, 4H), 2.78–2.90 (m, 1H), 3.14 (s, 3H), 2.78–2.90 (m, 1H), 3.06 (q, J = 17.0 Hz, 1H), 3.35–3.43 (m, 1H), 3.35–3.43 (m, 1H), 7.03–7.11 (m, 1H), 7.03–7.11 (m, 1H), 7.18–7.32 (m, 10H), 7.52 (s, 1H), 7.63 (d, J = 6.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 22.07, 26.49, 48.48, 58.84, 62.44, 73.49, 124.97, 126.01–126.24 (m), 127.98–128.37 (m), 133.44, 133.74 (d, J_{cp} = 24.3 Hz), 134.04, 138.84, 139.89 (d, J_{cp} = 7.5 Hz), 140.04; ^{31}P NMR ($CDCl_3$) δ: −6.14; IR (neat): (CN) 1543 cm^{-1}; FAB-MS *m/z*: 471 ($M^+ + 1$, 12); HRMS *m/z* calcd for $C_{26}H_{26}F_3N_2OP$ + H 471.1813, found 471.1791.

*2.3.9. 2-Diphenylphosphino-6-methoxybenzaldehyde SAMP hydrazone (**2i**)*

Sixty percent; $[\alpha]_D^{23} = -41$ (c 1.06, $CHCl_3$); yellow solid; mp 48.0–49.0 °C; ^{1}H NMR ($CDCl_3$) δ: 1.77–1.92 (m, 4H), 2.79–2.85 (m, 2H), 2.98–3.01 (m, 1H), 3.14 (s, 3H), 3.35–3.41 (m, 2H), 3.87 (s, 3H), 6.42 (dd, J = 3.9 and 3.7 Hz, 1H), 6.86 (d, J = 8.1 Hz, 1H), 7.02 (t, J = 15.9 Hz, 1H), 7.18–7.30 (m, 10H), 7.64 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 22.14, 26.46, 48.80, 55.66, 58.83, 62.61, 73.76, 110.35, 126.59–128.17 (m), 133.48, 133.85 (d, J_{cp} = 17.6 Hz), 140.46 (d, J_{cp} = 9.5 Hz), 140.59 (d, J_{cp} = 5.5 Hz), 157.06 (d, J_{cp} = 6.7 Hz); ^{31}P NMR ($CDCl_3$) δ: −6.43; IR (neat): (CN) 1576 cm^{-1}; FAB-MS *m/z*: 433 ($M^+ + 1$, 10); HRMS *m/z* calcd for $C_{26}H_{29}N_2O_2P$ + H 433.2045, found 433.2010.

2.4. General procedure for the palladium-catalyzed asymmetric allylic alkylation

To mixture of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.01 mmol, 0.004 g), chiral phosphine-hydrazone ligand **2** (0.02 mmol), and LiOAc (0.01 mmol) in a solvent (1 ml) was added BSA (1.5 mmol, 0.37 ml), and racemic allylic ester **6** (0.5 mmol) at room temperature under an Ar atmosphere. After 30 min, nucleophile **7** (1.5 mmol) was added, and stirring was continued for the time indicated in Table 3 at the desired temperature. The reaction mixture was diluted with ether 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.

3. Results and discussion

3.1. Preparation of chiral phosphine-hydrazones

Chiral hydrazones **2** as ligands were easily prepared from corresponding 2-fluorobenzaldehyde **3** in two steps. 2-Fluorobenzaldehyde SAMP hydrazone derivatives **5** were prepared from corresponding 2-fluorobenzaldehyde **3** and (*S*)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP) (**4**). SAMP hydrazones **5** were converted into the desired chiral hydrazone ligands **2** by nucleophilic phosphanylation with $KPPh_2$ [38–42] in THF (Table 1; Scheme 1).

3.2. Palladium-catalyzed asymmetric allylic alkylation

The palladium-catalyzed asymmetric allylic alkylation of racemic 1,3-diphenyl-2-propenyl acetate (**6**) was carried out in the presence of 2 mol% of

Table 1
Preparation of hydrazone ligands **2**

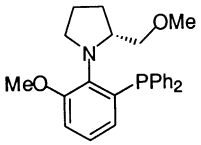
	R	Yield of **5** (%)[a]	Yield of **2** (%)[a]
a	3-CF_3	92	25
b	4-CF_3	98	14
c	4-OMe	>99	>99
d	4-Me	84	58
e	5-CF_3	99	26
f	5-OMe	93	49
g	5-Me	89	55
h	6-CF_3	93	25
i	6-OMe	84	60

[a] Isolated yield.

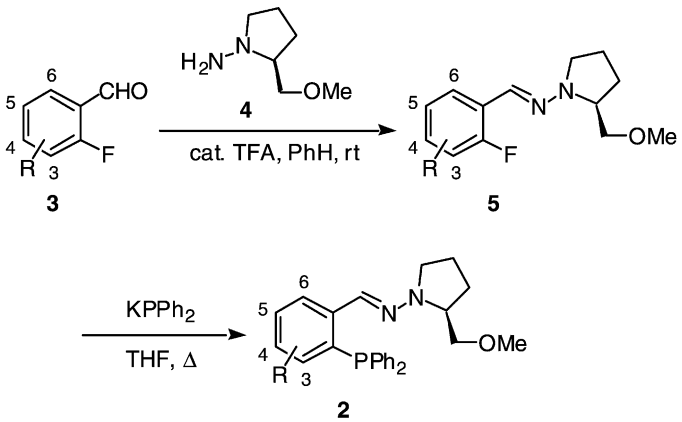
$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 4 mol% of ligand **2**, 2 mol% of LiOAc, and BSA in THF at room temperature for 24 h. The effects of the ligands **2** were examined by using dimethyl malonate (**7a**) as a nucleophile. These results are summarized in (Scheme 2) Table 2.

Entries 1–9 were the results of these ligands **2a**–**2i** with various substitutents on the aryl ring. Using ligand **2a** (3-CF_3) in this reaction, the reactivity and the

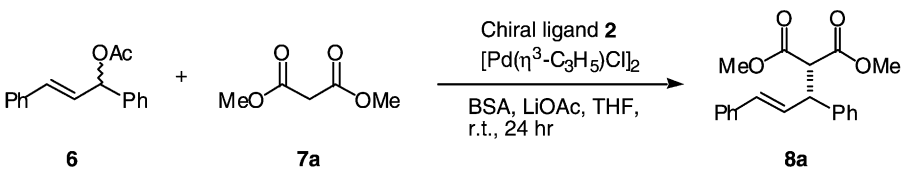
Table 2
Palladium-catalyzed asymmetric allylic alkylation

Entry	Ligand	Yield of **8a** (%)[a]	Ee of **8a** (%)[b]
1	**2a**	37	48
2	**2b**	26	78
3	**2c**	98	74
4	**2d**	96	85
5	**2e**	63	90
6	**2f**	>99	84
7	**2g**	93	91
8	**2h**	87	90
9	**2I**	>99	88
10 [33,34]	**1**	96	92
11 [18][c]	 **9**	97	85

[a] Isolated yield.
[b] The ee values were determined by HPLC analysis using a chiral column (Chiralcel OD-H (hexane:*i*-PrOH = 99:1)).
[c] Toluene was used instead of THF as a solvent.



Scheme 1. Preparation of hydrazone ligands **2**.



Scheme 2. Palladium-catalyzed allylic alkylation using hydrazone ligands **2**.

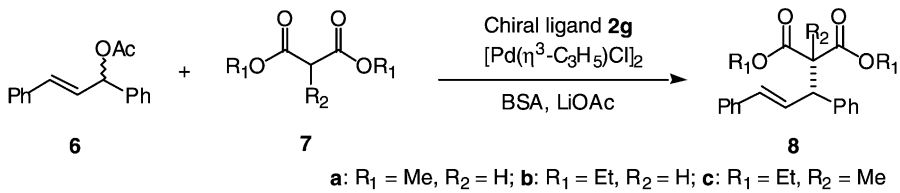
Table 3
Palladium-catalyzed asymmetric allylic alkylation

Entry	Nucleophile	Solvent	Temperature (°C)	Time (h)	Yield of **8** (%)[a]	ee of **8** (%)[b]
1	**7a**	THF	RT	24	93	91
2	**7a**	PhMe	RT	3	99	92
3	**7a**	DCM	RT	24	99	92
4	**7a**	PhMe	−20	168	95	94
5	**7b**	PhMe	RT	24	98	91[c]
6	**7c**	PhMe	RT	24	74	83[d]

[a] Isolated yield.
[b] The ee values were determined by HPLC analysis using a chiral column (Chiralcel OD-H (hexane:*i*-PrOH = 99:1)).
[c] The ee value was determined by HPLC analysis using a chiral column (Chiralcel OJ (hexane:*i*-PrOH = 95:5)).
[d] The ee value was determined by HPLC analysis using a chiral column (Chiralcel OD-H + OD (hexane:*i*-PrOH = 199:1)).

enantioselectivity were low (37% yield, 48% ee) (entry 1, Table 1). In this case, it is difficult to make a favorable complex of Pd and *P*,*N*-bidentate ligand **2a** by the effect of a substitution such as trifluoromethyl at the *ortho*-position of the PPh_2. Substituent effects indicated the ligands with electron-donating substituents (OMe or Me) tended to give higher activities than ligands with electron-withdrawing ones (CF_3). The ligands with slightly electron-donating substitutents such as a methyl group gave higher enantioselectivities than the ligands with electron-donating or electron-withdrawing ones. The effects of the position of the substituent on the aryl ring of ligands on this reaction were examined. The ligands that have various substitutents at the *ortho*- and *meta*- position of the hydrazone gave higher enantioselectivities than the ligands that have various substitutents at the *ortho*- and *meta*-position of the PPh_2. Using ligand **2g** (5-Me) which has a methyl group at the *meta*-position of the hydrazone, the reactivity and enantioselectivity were almost same as DPPA-SAMP ligand **1** [33,34] (entry 7 versus entry 10). The absolute configuration of the product **8a** in these reactions was proved to be *R* as determined from the sign of the optical rotation. When aminophosphine (*R*)-**9** was used as a ligand instead of (*S*)-**2i**, the palladium-catalyzed asymmetric allylic alkylation gave (*R*)-**8a** (entry 11) [18]. Therefore, we have shown that the palladium-catalyzed asymmetric allylic alkylation may provide either enantiomer of product (**8a**) using chiral ligands prepared from one chiral source such as chiral 1-(methoxymethyl)pyrrolidine.

In order to improve the reactivity and enantioselectivity, we further examined the effect of solvent using ligand **2g**. When the reaction was carried out in toluene, the reaction was almost finished within 3 h, and the enantioselectivity obtained was slightly higher than in the case of THF (entry 1 versus entry 2, Table 3). The enantioselectivity and yield were dependent on the reaction temperature (entry 2 versus entry 4), the highest enantioselectivity (94% ee) was obtained at −20 °C (entry 4). Next we examined the influence of the size of the nucleophile. The reaction with diethyl malonate instead of dimethyl malonate gave the corresponding product in good yield (98%) with 91% ee (entry 5). When the reaction was carried out with diethyl methylmalonate, the reaction was slow (74%), and the enantioselectivity was decreased (83% ee) (Scheme 3) (entry 6, Table 3).



Scheme 3. Palladium-catalyzed allylic alkylation using hydrazone ligands **2g**.

4. Conclusions

In conclusion, we have prepared the chiral hydrazone ligands **2** easily from corresponding fluorobenzaldehyde in two steps. The hydrazone **2g** can be used as ligand in palladium-catalyzed asymmetric allylic substitution with high enantiomeric excess (up to 94% ee).

Acknowledgements

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References

[1] B.M. Trost, D.L. Van Vranken, Chem. Rev. 96 (1996) 395.
[2] J.M.J. Williams, Synlett (1996) 705.
[3] G. Helmchen, J. Oraganomet. Chem. 576 (1999) 203.
[4] B.M. Trost, Chem. Pharm. Bull. 50 (2002) 1.
[5] J. Sprinz, G. Helmchen, Tetrahedron Lett. 34 (1993) 1769.
[6] P. Von Matt, A. Pfaltz, Angew. Chem. Int. Ed. Engl. 32 (1993) 566.
[7] J.G. Dawson, C.G. Frost, J.M.J. Williams, S.J. Coote, Tetrahedron Lett. 34 (1993) 3149.
[8] S.R. Gilbertosn, D. Xie, Z. Fu, J. Org. Chem. 66 (2001) 7240.
[9] W.-P. Deng, S.-L. You, X.-L. Hou, L.-X. Dai, Y.-H. Yu, W. Xia, J. Sun, J. Am. Chem. Soc. 123 (2001) 6508.
[10] S. Lee, J.H. Koh, J. Park, J. Oraganomet. Chem. 637–639 (2001) 99.
[11] M. Bourghida, M. Widhalm, Tetrahedron: Asymmetry 9 (1998) 1073.
[12] M. Widhalm, K. Mereiter, M. Bourghida, Tetrahedron: Asymmetry 9 (1998) 2983.
[13] J.P. Cahill, P.J. Guiry, Tetrahedron: Asymmetry 9 (1998) 4301.
[14] J.C. Anderson, R.J. Cubbon, J.D. Harling, Tetrahedron: Asymmetry 10 (1999) 2829.
[15] Y. Wang, H. Guo, K. Ding, Tetrahedron: Asymmetry 11 (2000) 4153.
[16] T. Mino, Y. Tanaka, M. Sakamoto, T. Fujita, Heterocycles 57 (2000) 1485.
[17] T. Mino, Y. Tanaka, K. Akita, K. Anada, M. Sakamoto, T. Fujita, Tetrahedron: Asymmetry 12 (2001) 1677.
[18] T. Mino, Y. Tanaka, M. Sakamoto, T. Fujita, Tetrahedron: Asymmetry 12 (2001) 2435.
[19] R. Stranne, J.-L. Vasse, C. Moberg, Org. Lett. 3 (2001) 2525.
[20] G. Chen, X. Li, H. Zhang, L. Gong, A. Mi, X. Cui, Y. Jiang, M.C.K. Choi, A.S.C. Chan, Tetrahedron: Asymmetry 13 (2002) 809.
[21] J.M. Brown, D.I. Hulmes, P.J. Guiry, Tetrahedron 50 (1994) 4493.
[22] A. Togni, U. Burckhardt, V. Gramlich, P.S. Pregosin, R. Salzmann, J. Am. Chem. Soc. 118 (1996) 1031.
[23] T. Constantieux, J.-M. Brunel, A. Labande, G. Buono, Synlett (1998) 49.
[24] K. Ito, R. Kashiwagi, K. Iwasaki, T. Katsuki, Synlett (1999) 1563.
[25] J.W. Han, H.-Y. Jang, Y.K. Chung, Tetrahedron: Asymmetry 10 (1999) 2853.
[26] K. Ito, R. Kashiwagi, S. Hayashi, T. Uchida, T. Katsuki, Synlett (2001) 284.
[27] A. Saitoh, K. Achiwa, K. Tanaka, T. Morimoto, J. Org. Chem. 65 (2000) 4227.
[28] H.-L. Kwong, L.-S. Cheng, W.-S. Lee, J. Mol. Catal. A: Chem. 150 (1999) 23.
[29] Y. Suzuki, Y. Ogata, K. Hiroi, Tetrahedron: Asymmetry 10 (1999) 1219.
[30] T. Kohara, Y. Hashimoto, K. Saigo, Synlett (2000) 517.
[31] H.-Y. Jang, H. Seo, J.W. Han, Y.K. Chung, Tetrahedron Lett. 41 (2000) 5083.
[32] T. Fukuda, A. Takehara, M. Iwao, Tetrahedron: Asymmetry 12 (2001) 2793.
[33] T. Mino, W. Imiya, M. Yamashita, Synlett (1997) 583.
[34] T. Mino, M. Shiotsuki, N. Yamamoto, T. Suenaga, M. Sakamoto, T. Fujita, M. Yamashita, J. Org. Chem. 66 (2001) 1795.
[35] H.-J. Park, J.-H. Han, H. Seo, H.-Y. Jang, Y.-K. Chung, J. Suh, J. Mol. Catal. A: Chem. 174 (2001) 151.
[36] M. Cavazzini, G. Pozzi, S. Quici, D. Maillard, D. Sinou, Chem. Commun. (2001) 1220.
[37] T. Neugebauer, A. Marhold, Jpn. Kokai Tokkyo Koho, 2001-002601; Chem. Abstract, 134 (2001) 41974z.
[38] H. Christina, E. McFarlane, W. McFarlane, Polyhedron 7 (1988) 1875.
[39] S.J. Coote, G.J. Dawson, C.G. Frost, J.M.J. Williams, Synlett (1993) 509.
[40] J.V. Allen, G.J. Dawson, C.G. Frost, J.M.J. Williams, S.J. Coote, Tetrahedron 50 (1994) 799.
[41] M. Hingst, M. Tepper, O. Stelzer, Eur. J. Inorg. Chem. 1 (1998) 73.
[42] M.W. Haenel, S. Oevers, J. Bruckmann, J. Kuhnigk, C. Krueger, Synlett (1998) 301.