N,N-Disubstituted Allylic Amine Type Aminophosphines with C(aryl)–N(amine) Bond Axial Chirality: Synthesis and Application to Palladium-Catalyzed Asymmetric Allylic Alkylation with Malonates

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Abstract: We designed and synthesized a series of N,N-disubstituted allylic amine type aminophosphines 2, 3 and 4, which are derivatives of chiral ligands 1. Aminophosphines 2–4 (except 2a) exist in C(aryl)–N(amine) bond axial chirality by chiral HPLC analysis. Both enantiomeric isomers of 4b were successfully obtained in an enantiomerically pure form. We demonstrated that 1a, 1b, and 4b can be used as effective chiral ligands for the palladium-catalyzed asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate with malonates in high enantioselectivities (up to 90% ee).

Key words: axial chirality, phosphine-olefin type chiral ligand, palladium, asymmetric allylic alkylation

1 INTRODUCTION

Chiral ligands are important molecules that affect asymmetric inductions for transition metal catalysts. One of the most important type of chiral ligands is P,P type ligands based on the discovery1 and application2,3 of BINAP. On the other hand, P,N hybrid type chiral ligands such as PHOX ligands are also useful in transition metal-catalyzed asymmetric reactions4–8. We also reported P,N hybrid type chiral ligands such as phosphine-hydrazone type9–13 and phosphine-amine type13–20 chiral ligands for palladium catalyzed asymmetric allylic alkylations. The P,S hybrid type chiral ligands were also reported for transition metal-catalyzed asymmetric reactions30. Recently, other type of hybrid ligands such as phosphine-olefin type chiral ligands31–40 have been developed and used successfully for transition metal-catalyzed asymmetric reactions. We also reported phosphine-olefin type chiral ligands 1 with N-1-adamantyl-N-cinnamylaniline moiety and C(aryl)–N(amine) bond axial chirality for the palladium catalyzed asymmetric allylic alkylation of indoles41.

Here we report the synthesis of various derivatives of chiral ligands 1, such as N-allylaniline type aminophosphines 2, N-tet-butyl type aminophosphines 3 and N-(3,5-dimethyl)-1-adamantyl type aminophosphines 4 (Fig. 1) and the applications to phosphine-olefin type chiral ligands for the palladium-catalyzed asymmetric allylic alkylation of malonates.
action mixture was filtered and evaporated under reduced pressure. The residue was purified by silica gel chromatography (hexane: EtOAc = 5: 1): 92% yield (0.221 g, 0.46 mmol) as a white solid; mp 160-162°C; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.47 (br-s, 6H), 1.89-1.92 (m, 9H), 2.47 (s, 3H), 3.43 (dd, $J$ = 4.2 and 15.4 Hz, 1H), 4.11 (dd, $J$ = 7.2 and 14.7 Hz, 1H), 4.54-4.55 (m, 1H), 4.77-4.89 (m, 2H), 6.89-7.02 (m, 2H), 7.32-7.57 (m, 9H), 7.67-7.74 (m, 2H); $^1$C NMR (75 MHz, CDCl$_3$) $\delta$ 22.4 (d, $J$$_{CP}$ = 1.4 Hz), 30.3, 36.5, 41.3, 53.1, 57.7, 112.9, 124.3 (d, $J$$_{CP}$ = 15.1 Hz), 128.1 × 2 (d, $J$$_{CP}$ = 11.3 Hz), 128.2 × 2 (d, $J$$_{CP}$ = 11.5 Hz), 130.89 (d, $J$$_{CP}$ = 3.2 Hz), 130.93 (d, $J$$_{CP}$ = 2.8 Hz), 131.1 × 2 (d, $J$$_{CP}$ = 9.4 Hz), 132.3 × 2 (d, $J$$_{CP}$ = 8.7 Hz), 133.4 (d, $J$$_{CP}$ = 14.0 Hz), 134.8 (d, $J$$_{CP}$ = 105.0 Hz), 134.9 (d, $J$$_{CP}$ = 102.1 Hz), 135.6 (d, $J$$_{CP}$ = 2.1 Hz), 136.0 (d, $J$$_{CP}$ = 106.1 Hz), 140.3, 142.2 (d, $J$$_{CP}$ = 8.3 Hz), 153.3 (d, $J$$_{CP}$ = 3.9 Hz); $^{31}$P NMR (121 MHz, CDCl$_3$) $\delta$ 28.9; HRMS (ESI-orbitrap) m/z calced for C$_{12}$H$_{16}$ONP + H, 482.2607 found 482.2592.

2.1.2 Synthesis of aminophosphine oxide 6b

To the solution of phosphine oxide 5b (1.433 g, 3.0 mmol) in MeCN (30 mL) was added K$_2$CO$_3$ (4.147 g, 30 mmol) and allyl bromide (2.60 mL, 30 mmol) at room temperature. The reaction mixture was stirred for 67.5 h at 60°C. The reaction mixture was filtered and evaporated under reduced pressure. The residue was purified by silica gel chromatography (CHCl$_3$: hexane: Et$_2$O = 20: 1: 1): 51% yield (0.787 g, 1.52 mmol) as a yellow solid; mp 198-199°C; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.36-1.47 (m, 6H), 1.91-1.98 (m, 9H), 3.91 (dd, $J$ = 5.6 and 14.9 Hz, 1H), 4.39 (dd, $J$ = 7.4 and 15.1 Hz, 1H), 4.52 (d, $J$ = 10.3 Hz, 1H), 4.78 (dd, $J$ = 1.3 and 17.2 Hz, 1H), 5.32-5.45 (m, 1H), 7.13 (dd, $J$ = 8.6 and 13.5 Hz, 1H), 7.35-7.57 (m, 11H), 7.70-7.82 (m, 3H), 8.47-8.50 (m, 1H); $^1$C NMR (75 MHz, CDCl$_3$) $\delta$ 30.2, 36.4, 41.4, 53.7, 57.8, 113.6, 124.9 (d, $J$$_{CP}$ = 13.5 Hz), 125.7, 127.5, 128.0, 128.2, 128.3 × 4 (d, $J$$_{CP}$ = 11.8 Hz), 130.1 (d, $J$$_{CP}$ = 14.3 Hz), 130.7 (d, $J$$_{CP}$ = 102.8 Hz), 131.1 (d, $J$$_{CP}$ = 2.7 Hz), 131.2 (d, $J$$_{CP}$ = 2.6 Hz), 131.4 × 2 (d, $J$$_{CP}$ = 9.3 Hz), 132.3 × 2 (d, $J$$_{CP}$ = 8.9 Hz), 134.9 (d, $J$$_{CP}$ = 101.7 Hz), 136.1 (d, $J$$_{CP}$ = 105.0 Hz), 136.2 (d, $J$$_{CP}$ = 2.1 Hz), 137.6 (d, $J$$_{CP}$ = 9.3 Hz), 140.1, 154.1 (d, $J$$_{CP}$ = 3.3 Hz); $^{31}$P NMR (121 MHz, CDCl$_3$) $\delta$ 28.9; HRMS (ESI-orbitrap) m/z calced for C$_{16}$H$_{18}$ONP + H, 518.2607 found 518.2600.

Fig. 1 Phosphine-olefin type chiral ligands 1 and their derivatives 2-4.

To a mixture of phosphine oxide 6a (0.240 g, 0.50 mmol) and triethylamine (0.42 mL, 3.0 mmol) in m-xylene (10 mL) was added trichlorosilane (0.30 mL, 3.0 mmol) at 0°C under an Ar atmosphere. The reaction mixture was stirred at 120°C for 63 h. After being cooled to room temperature, the mixture was diluted with CHCl$_3$ and quenched with 2 M aqueous NaOH solution. The organic layer was washed with brine, dried over MgSO$_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane: EtOAc = 40: 1): 31% yield (72.0 mg, 0.15 mmol) as a light yellow solid; mp 131-132°C; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.43 (dd, $J$ = 11.7 and 36.5 Hz, 6H), 1.77-1.81 (m, 3H), 1.90-1.93 (m, 6H), 2.17 (s, 3H), 3.79 (dd, $J$ = 6.2 and 14.7 Hz, 1H), 4.00 (ddd, $J$ = 1.2, 7.5 and 14.7 Hz, 1H), 4.67 (dd, $J$ = 0.9 and 9.9 Hz, 1H), 4.76
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10.0 mL, ʣ Hz, 1H

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10.0 mL, ʣ Hz, 1H

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10.0 mL, ʣ Hz, 1H

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10.0 mL, ʣ Hz, 1H

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133.9 × 2 (d, J<sub>CP</sub> = 19.9 Hz), 134.1, 137.6, 139.0 (d, J<sub>CP</sub> = 15.8 Hz), 139.9 (d, J<sub>CP</sub> = 15.2 Hz), 140.9 (d, J<sub>CP</sub> = 3.9 Hz), 141.4 (d, J<sub>CP</sub> = 6.6 Hz), 153.1 (d, J<sub>CP</sub> = 25.4 Hz); 13<sup>C</sup>NMR (121.54 M Hz, CDCl<sub>3</sub>) 8 - 13.9; HRMS (ESI-orbitrap) m/z calc'd for C<sub>9</sub>H<sub>12</sub>N<sub>8</sub>OP + H<sub>2</sub> 464.2498 found 464.2498; HPLC (Daicel CHIRALCEL® OD, 0.46 × 25 cm + Daicel CHIRALCEL® OD-H, 0.46 × 25 cm, UV 220 nm, Hexane = 100, 0.3 mL/min) t<sub>R</sub> = 54.5 min (CD: λ<sub>ext</sub> (Δε) 254 (-)), t<sub>R</sub> = 60.5 min (CD: λ<sub>ext</sub> (Δε) 254 (+)).

2.1.8 Synthesis of aminophosphine (±)-3b

To a mixture of phosphine oxide 8b (0.515 g, 1.0 mmol) and triethylamine (8.4 mL, 60 mmol) in m-xylene (30.0 mL) was added trichlorosilane (2.0 mL, 20.0 mmol) at 0°C under an Ar atmosphere. The reaction mixture was stirred at 120°C for 24 h. After being cooled to room temperature, the mixture was diluted with CHCl<sub>3</sub> and quenched with 2 M aqueous NaOH solution. The organic layer was washed with brine, dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane: EtO<sub>2</sub> = 60: 1): 15% yield (73.8 mg, 0.15 mmol) as a white solid; mp 50-52°C; 1<sup>H</sup>NMR (300 MHz, CDCl<sub>3</sub>) δ 1.26 (s, 9H), 4.13 (dd, J<sub>CP</sub> = 5.45 and 15.4 Hz, 1H), 4.33-4.40 (m, 1H), 6.02 (d, J<sub>CP</sub> = 15.0 Hz, 1H), 6.13 (dd, J<sub>CP</sub> = 6.00 and 16.0 Hz, 1H), 7.07-7.36 (m, 16H), 7.45-7.58 (m, 3H), 7.76-7.79 (m, 1H), 8.39 (d, J<sub>CP</sub> = 8.14 Hz, 1H); 1<sup>3</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 29.9 (d, J<sub>CP</sub> = 5.1 Hz), 53.7 (d, J<sub>CP</sub> = 8.2 Hz), 56.7, 125.5, 126.0, 126.2 × 2, 126.4, 126.6, 126.1 (d, J<sub>CP</sub> = 2.2 Hz), 127.7, 128.0, 128.1 × 2, 128.16 × 2, 128.22, 128.4 × 2 (d, J<sub>CP</sub> = 6.2 Hz), 129.2, 131.6, 132.1 (d, J<sub>CP</sub> = 1.9 Hz), 133.0 × 2 (d, J<sub>CP</sub> = 18.8 Hz), 133.8 × 2 (d, J<sub>CP</sub> = 19.4 Hz), 135.1, 136.6 (d, J<sub>CP</sub> = 5.0 Hz), 137.46, 137.48 (d, J<sub>CP</sub> = 7.7 Hz), 138.8 (d, J<sub>CP</sub> = 15.9 Hz), 139.8 (d, J<sub>CP</sub> = 15.4 Hz), 152.9 (d, J<sub>CP</sub> = 26.7 Hz); 31<sup>P</sup>NMR (121 MHz, CDCl<sub>3</sub>) δ 14.7; HRMS (ESI-orbitrap) m/z calc'd for C<sub>9</sub>H<sub>12</sub>N<sub>8</sub>OP + H<sub>2</sub> 499.2429 found 499.2443; HPLC (Daicel CHIRALCEL® OJ, 0.46 × 25 cm, UV 220 nm, Hexane:EtOH = 94: 6, 0.2 mL/min) t<sub>R</sub> = 43.1 min (CD: λ<sub>ext</sub> (Δε) 254 (-)), t<sub>R</sub> = 53.9 min (CD: λ<sub>ext</sub> (Δε) 254 (+)).

2.1.9 Synthesis of aminophosphine oxide 10a

To the solution of memantine (5.38 g, 30 mmol) in THF (70 mL) at -80°C was added slowly n-BuLi in hexane (20.6 mL, 33 mmol, 1.60 M). The reaction mixture was stirred for 60 min at -80°C. After phosphine oxide 9a (3.22 g, 10 mmol) was added at room temperature, the stirring was continued for 16 h at room temperature. The mixture was diluted with ether and quenched with sat. NH<sub>4</sub>Cl aq. The organic layer was washed with brine, dried over MgSO<sub>4</sub>, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane: EtOAc = 8: 1: 1): 45% yield (0.132 g, 0.23 mmol) as white solid; mp 51-53°C; 1<sup>H</sup>NMR (300 MHz, CDCl<sub>3</sub>) δ 0.67 (s, 3H), 0.68 (s, 3H), 0.76 (d, J = 12.6 Hz, 1H), 0.89 (d, J = 12.6 Hz, 1H), 1.06 (s, 4H), 1.34-1.43 (m, 2H), 1.49-1.55 (m, 2H), 1.70 (s, 2H), 1.94-1.96 (m, 1H), 2.47 (s, 3H), 3.72 (dd, J = 15, 5.7 and 14.7 Hz, 1H), 4.31 (dd, J = 7.9 and 15.0 Hz, 1H), 5.65-5.75 (m, 1H), 6.16 (d, J = 15.9 Hz, 1H), 6.85-7.01 (m, 2H), 7.14-7.18 (m, 3H), 7.23-7.28 (m, 2H), 7.31-7.54 (m, 9H), 7.67-7.74 (m, 2H); 13<sup>C</sup>NMR (75 MHz, CDCl<sub>3</sub>) δ
To a mixture of phosphine oxide 10b (0.621 g, 1.0 mmol) and triethylamine (1.53 mL, 11.0 mmol) in m-xylene (40 mL) was added trichlorosilane (1.01 mL, 10.0 mmol) at 0°C under an Ar atmosphere. The reaction mixture was stirred at 120°C for 42 h. After being cooled to room temperature, the mixture was diluted with CHCl₃ and quenched with 2 M aqueous NaOH solution. The organic layer was washed with brine, dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane: EtOAc = 4:1) to give 11b (0.60 g, 78%).

**2.1.12 Synthesis of aminophosphines (±)-4a**

To a mixture of triethylamine (1.53 mL, 11.0 mmol) in m-xylene (40 mL) was added trichlorosilane (1.01 mL, 10.0 mmol) at 0°C under an Ar atmosphere. The reaction mixture was stirred at 120°C for 42 h. After being cooled to room temperature, the mixture was diluted with CHCl₃ and quenched with 2 M aqueous NaOH solution. The organic layer was washed with brine, dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane: EtOAc = 4:1) to give 11b (0.60 g, 78%).

**2.1.13 Synthesis of aminophosphines (±)-4a**

To a mixture of triethylamine (1.53 mL, 11.0 mmol) in m-xylene (40 mL) was added trichlorosilane (1.01 mL, 10.0 mmol) at 0°C under an Ar atmosphere. The reaction mixture was stirred at 120°C for 42 h. After being cooled to room temperature, the mixture was diluted with CHCl₃ and quenched with 2 M aqueous NaOH solution. The organic layer was washed with brine, dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane: EtOAc = 4:1) to give 11b (0.60 g, 78%).

**2.1.14 Synthesis of aminophosphines (±)-4b**

To a mixture of triethylamine (1.53 mL, 11.0 mmol) in m-xylene (40 mL) was added trichlorosilane (1.01 mL, 10.0 mmol) at 0°C under an Ar atmosphere. The reaction mixture was stirred at 120°C for 42 h. After being cooled to room temperature, the mixture was diluted with CHCl₃ and quenched with 2 M aqueous NaOH solution. The organic layer was washed with brine, dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane: EtOAc = 4:1) to give 11b (0.60 g, 78%).

**3.**

Aminophosphines with C(aryl)–N(amine) Bond Axial Chirality

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To a mixture of phosphine oxide 10b (0.621 g, 1.0 mmol) and triethylamine (1.53 mL, 11.0 mmol) in m-xylene (40 mL) was added trichlorosilane (1.01 mL, 10.0 mmol) at 0°C under an Ar atmosphere. The reaction mixture was stirred at 120°C for 42 h. After being cooled to room temperature, the mixture was diluted with CHCl₃ and quenched with 2 M aqueous NaOH solution. The organic layer was washed with brine, dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane: EtOAc = 4:1) to give 11b (0.60 g, 78%).

**4.**

Aminophosphines with C(aryl)–N(amine) Bond Axial Chirality

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To a mixture of phosphine oxide 10b (0.621 g, 1.0 mmol) and triethylamine (1.53 mL, 11.0 mmol) in m-xylene (40 mL) was added trichlorosilane (1.01 mL, 10.0 mmol) at 0°C under an Ar atmosphere. The reaction mixture was stirred at 120°C for 42 h. After being cooled to room temperature, the mixture was diluted with CHCl₃ and quenched with 2 M aqueous NaOH solution. The organic layer was washed with brine, dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane: EtOAc = 4:1) to give 11b (0.60 g, 78%).
2.2 Optical resolution

2.2.1 Optical resolution of (±)-4b

HPLC resolution of (±)-4b (88.0 mg, 0.145 mmol) dissolved in hexane (3.5 mL) was carried out by successive injections of 1 mL on a Daicel CHIRALCEL® OD (1.0 φ × 25 cm) + CHIRALCEL® OD-H (1.0 φ × 25 cm). A solution of hexane: EtOH = 1000: 1 was used as the eluent working at a flow rate of 1.2 mL/min and with UV monitoring at 220 nm. (+)-4b and (−)-4b were obtained by evaporation of fractions respectively.

(+)-4b: 32% yield (28.3 mg, 0.047 mmol) as a white solid, 99% ee; [α]D 20 = +74.0 (c 1.04, CHCl₃); 1H NMR (300 MHz, CDCl₃) δ 0.61 (s, 3H), 0.67 (s, 3H), 0.75 (d, J = 12.1 Hz, 1H), 0.90 (d, J = 12.1 Hz, 1H), 1.01-0.8 (m, 4H), 1.41-1.59 (m, 4H), 1.72 (d, J = 11.9 Hz, 1H), 1.88 (d, J = 11.7 Hz, 1H), 1.98 (s, 1H), 4.18 (dd, J = 7.1 and 14.9 Hz, 1H), 4.45 (dd, J = 7.1 and 14.8 Hz, 1H), 6.07 (d, J = 15.9 Hz, 1H), 6.28-6.35 (m, 6H), 9.66-7.02 (m, 11H), 7.34-7.35 (m, 3H), 7.41-7.58 (m, 5H), 7.78 (d, J = 7.3 Hz, 1H), 8.44 (d, J = 8.2 Hz, 1H); 13C NMR (75 MHz, CDCl₃) δ 30.4 (d, JCP = 2.8 Hz), 30.6, 32.6 (d, JCP = 4.4 Hz), 40.4 (d, JCP = 4.4 Hz), 42.5, 47.7 (d, JCP = 4.4 Hz), 47.9 (d, JCP = 3.9 Hz), 50.4, 51.7 (m, 3H); 19F NMR (121 MHz, CDCl₃) δ -14.5; EI-MS m/z (rel intensity) 605 (M⁺, 6); HRMS (ESI-orbitrap) m/z calc for C₃₀H₃₄N⁺ + H 606.3284 found 606.3275; HPLC (Daicel CHIRALCEL® OD, 0.46 × 25 cm + Daicel CHIRALCEL® OD-H, 0.46 × 25 cm, UV 254 nm, Hexane = 100, 0.5 mL/min; tR = 30.8 min (minor), tR = 33.6 min (major).

2.3 General procedure for the palladium-catalyzed allylic alkylation

To a mixture of [Pd(η⁵-C₅H₅)Cl]₂ (3.63 mg, 10 μmol), chiral aminophosphine ligand 1a (10.8 mg, 20 μmol), and NaOAc 1.65 mg, 20 μmol) in a PhMe (0.4 mL) was added BSA (0.15 mL, 0.60 mmol) and 1,3-diphenyl-2-propenyl acetate (50.5 mg, 0.20 mmol) at room temperature under an Ar atmosphere. The mixture was stirred for 10 min. After malonate (0.60 mmol) was added, the stirring was continued for 24 h at room temperature. The reaction mixture was diluted with ether and water. The organic layer was washed with water and dried over MgSO₄. The filtrate was concentrated with a rotary evaporator and the residue was purified by column chromatography.

2.3.1 (S)-12a (Table 1, entry 11)¹⁵

99% yield (64.9 mg, 0.20 mmol), 99% ee; [α]D 20 = -17.2 (c 0.53, CHCl₃); 1H NMR (300 MHz, CDCl₃) δ 3.52 (s, 3H), 3.71 (s, 3H), 3.96 (d, J = 10.9 Hz, 1H), 4.27 (d, J = 8.5 and 10.9 Hz, 1H), 6.33 (dd, J = 8.5 and 15.7 Hz, 1H), 6.48 (d, J = 15.8 Hz, 1H), 7.20–7.33 (m, 10H); 13C NMR (75 MHz, CDCl₃) δ 49.2, 52.5, 52.6, 57.6, 126.3, 127.1, 127.5, 128.4, 128.7, 129.0, 131.8, 136.7, 140.1, 167.8, 168.2; EI-MS m/z (rel intensity) 324 (M⁺, 18); HPLC (Daicel CHIRALPAK® AD-H, 0.46 φ × 25 cm, UV 254 nm), hexane : 2-propanol = 90 : 10, 0.5 mL/min; tR = 24.4 min (minor) and 31.3 min (major).

2.3.2 (S)-12b (Table 1, entry 12)¹⁵

94% yield (66.2 mg, 0.188 mmol), 90% ee; mp 48-50°C; [α]D 20 = -14.8 (c 0.53, CHCl₃); 1H NMR (300 MHz, CDCl₃) δ 1.01 (q, J = 7.2 Hz, 3H), 1.21 (q, J = 7.1 Hz, 3H), 3.90-4.02 (m, 3H), 4.17 (q, J = 7.2 Hz, 2H), 4.26 (dd, J = 8.4 and 11.0 Hz, 1H), 6.33 (dd, J = 8.4 and 15.7 Hz, 1H), 6.48 (d, J = 15.8 Hz, 1H), 7.17–7.32 (m, 10H); 13C NMR (75 MHz, CDCl₃) δ 13.7, 14.1, 49.2, 55.7, 61.4, 61.6, 126.3, 127.1, 127.5, 127.9, 128.4, 128.6, 129.3, 131.6, 136.8, 140.2, 167.4, 167.8; EI-MS m/z (rel intensity) 352 (M⁺, 20); HPLC (Daicel CHIRALPAK® AD-H, 0.46 φ × 25 cm, UV 254 nm), hexane : 2-propanol = 85 : 15, 1.0 mL/min; tR = 9.4 min (minor) and 12.8 min (major).

2.3.3 (S)-12c (Table 1, entry 13)¹⁵

86% yield (70.3 mg, 0.172 mmol), 87% ee; mp 64-66°C; [α]D 20 = -10.2 (c 0.53, CHCl₃); 1H NMR (300 MHz, CDCl₃) δ 1.22 (s, 3H), 1.42 (s, 3H), 3.73 (d, J = 10.9 Hz, 1H), 4.16 (dd, J = 8.1 and 11.0 Hz, 1H), 6.33 (dd, J = 8.1 and 15.8 Hz, 1H), 6.45 (d, J = 15.8 Hz, 1H), 7.18–7.30 (m, 10H); 13C NMR (75 MHz, CDCl₃) δ 27.5, 27.9, 49.0, 59.3, 81.5, 81.8, 126.3, 126.8, 127.3, 128.2, 128.4, 128.5, 130.1, 131.2, 137.0, 140.7, 1194

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3 RESULTS AND DISCUSSION

3.1 Synthesis

Racemic N-allylaniline type aminophosphines (±)-2 were easily prepared in two steps from phosphine oxides 5\textsuperscript{17}. The N-alkylation of 5 with allyl bromide occurred in the presence of \( \text{K}_2\text{CO}_3 \). These aminophosphine oxides 6 were converted into desired racemic compounds (±)-2 using trichlorosilane-triethylamine (Scheme 1).

We also prepared racemic N-\textit{t-}butyl type aminophosphines (±)-3 in the same manner as (±)-2 from phosphine oxides 7\textsuperscript{17} via N-alkylation with cinnamyl bromide and reduction using trichlorosilane-triethylamine (Scheme 2).

We also prepared racemic N-(3,5-dimethyl)-1-adamantyl type aminophosphines (±)-4 from phosphine oxides 9\textsuperscript{17,20} via S\textsubscript{N}Ar reaction with memantine (3,5-dimethyl-1-adamantanamine), N-alkylation with cinnamyl bromide and reduction using trichlorosilane-triethylamine (Scheme 3).

To investigate whether C(aryl)–N(amine) bond axial chirality exists in phosphine-olefin type aminophosphines 2–4, we analytically separated these isomers (except 2a) using HPLC with a chiral stationary phase column and obtained a pair of clear positive (+) and negative (−) CD trace signals of HPLC run. Although we thought that aminophosphine 2a exist in C(aryl)–N(amine) bond axial chirality, we could not found that analytic conditions about the separation of enantiomeric isomers of 2a by using...
3.2 Optical resolution of 4b

We next attempted the optical resolution of these amino-phosphines. We only successfully obtained $(+)-4b$ and $(-)-4b$ by the optical resolution of $(\pm)-4b$ using a semi-preparative chiral HPLC (Scheme 4). The optical purities of each of the enantiomers were 99% ee from the chiral HPLC analysis. On the other hand, we could not obtain enantiopure compounds 2b, 3a, 3b, and 4a by optical resolution using chiral palladium resolving agents\cite{20} and/or a semi-preparative chiral HPLC method unfortunately.

3.3 Palladium-catalyzed allylic alkylation

Finally, we investigated the ability of compound 4b and the already prepared compounds 1a and 1b as chiral ligands for palladium-catalyzed asymmetric allylic alkylation with malonates. The reaction of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate was performed in the presence of $[\text{Pd}(\eta^3-C_3H_5)\text{Cl}]_2$ and chiral ligand (Pd/ligand = 1/1) as a model reaction (Table 1). The reaction with 4 mol% of $(+)-4b/Pd$ as a catalyst and 10 mol% of LiOAc as a base in PhMe at room temperature for 24 h gave corresponding product $(S)$-12a in a 86% yield with moderate enantioselectivity (62% ee) (entry 1). We also tested $(aR)$-
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We next investigated the effects of various solvents using (aR)-(−)-1a as a chiral ligand (entries 2, and 4-8). Using THF and ether as a solvent, the enantioselectivity of the product dramatically decreased. When the reaction was carried out in dichloromethane, hexane, and benzotrifluoride, the enantioselectivity also slightly decreased. We next changed the base for the reaction in PhMe (entries 2, 9, and 10). Using NaOAc as a base, the enantioselectivity increased to 83% ee. When the reaction was carried out using 10 mol % of (−)-1a/Pd as a catalyst, corresponding product (S)-12a was obtained in high enantioselectivity (90% ee) with a high yield (entry 11). When the reaction was carried out with 1,3-diphenyl-2-propenyl pivalate instead of 1,3-diphenyl-2-propenyl acetate, the enantioselectivity slightly decreased to 86% ee (entries 12). The reaction of 1,3-diphenyl-2-propenyl acetate with diethyl malonate instead of dimethyl malonate gave corresponding product 12b in similar levels of enantioselectivity (entry 11 vs entry 13). On the other hand, the reaction using di-tert-butyl malonate gave corresponding product 12c in 87% ee (entry 14).

4 CONCLUSIONS
We found that C(aryl)−N(amine) bond axial chirality exists in N-allylaniline type amorphine phosphines 2b, N-tert-butyl type amorphines 3, and N-(3,5-dimethyl)-1-adamantyl type amorphines 4. We successfully achieved optical resolution of (±)-4b using a semi-preparative chiral HPLC. We also found that a palladium-catalyzed asymmetric allylic alkylation of malonates using a N-1-adamantyl-N-cinnamylaniline derivative 1a with a C(aryl)−N(amine) bond axial chirality as a phosphine-olefin type chiral ligand in PhMe gave desired products (S)-12 with high enantioselectivities (up to 90% ee). We believe this methodology is useful for the field of oil science including the synthesis of optically active compounds from the essential oils.

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