Enantioselective Synthesis of Axially Chiral Anilides through Rhodium-Catalyzed [2+2+2] Cycloaddition of 1,6-Diynes with Trimethylsilylynamides

Ken Tanaka,* Kenzo Takeishi, and Keiichi Noguchi

Department of Applied Chemistry, Graduate School of Engineering, and Instrumentation Analysis Center, Tokyo University of Agriculture and Technology, Koganei, Tokyo 184-8588, Japan

I. General

Anhydrous CH_2Cl_2 (No. 27,099-7) was obtained from Aldrich and used as received. Modified-BINAP ligands (tol-BINAP, xyl-BINAP, H_8 -BINAP, xyl- H_8 -BINAP, and Segphos) were obtained from Takasago International Corporation. All other reagents were obtained from commercial sources and used as received. All reactions were carried out under an atmosphere of argon or nitrogen in oven-dried glassware with magnetic stirring. Diynes **1a**,¹ **1e**,² and **1f**³ were prepared according to literatures.

II. Synthesis of Ynamides

General Procedure. KHMDS (0.5 M in toluene, 0.62 mL, 0.310 mmol) was added to a solution of (37.7 mg, 0.178 mmol) in toluene (15 mL) under argon at $-30\text{ }^\circ\text{C}$. After the mixture was allowed to rt, phenyl(trimethylsilyl)ethynyl)iodonium triflate (159.0 mg, 0.353 mmol) was added in four portions. The resulting mixture was stirred for 15 h at rt and filtered through a plug of silica gel. Purification by silica gel column chromatography (hexane:EtOAc = 40:1) gave **2a** (43.0 mg, 0.140 mmol, 78% yield).

N-Benzyl-N-(trimethylsilyl)ethynyl)benzamide (2a).⁴

Yellow solid; Mp 38–39 $^\circ\text{C}$; ^1H NMR (CDCl_3 , 300 MHz) δ 7.78–7.88 (m, 2H), 7.28–7.56 (m, 8H), 4.86 (s, 2H), -0.03 (s, 9H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 170.4, 135.9, 133.3, 131.4, 128.88, 128.86, 128.4, 128.0, 127.5, 97.9, 75.5, 52.7, -0.3 .

N-Butyl-N-(trimethylsilyl)ethynyl)benzamide (2b).

Yellow oil; IR (neat); 2900, 2150, 1670, 1270, 840, 700 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 7.73–7.85 (m, 2H), 7.32–7.52 (m, 3H), 3.69 (t, $J = 7.2$ Hz, 2H), 1.75 (quintet, $J = 7.2$ Hz, 2H), 1.44 (sextet, $J = 7.2$ Hz, 2H), 0.98 (t, $J = 7.2$ Hz, 3H), 0.05 (s, 9H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 170.9, 133.8, 131.1, 128.7, 127.5, 98.0, 74.6, 48.5, 29.5, 19.7, 13.7, -0.2 ; HRMS (EI) calcd for $\text{C}_{16}\text{H}_{23}\text{NOSi}$ $[\text{M}]^+$ 273.1549, found 273.1552.

N-Isopropyl-N-(trimethylsilyl)ethynyl)benzamide (2c).

Yellow oil; IR (neat); 2925, 2150, 1660, 1290, 1240, 840, 690 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 7.72–7.84 (m, 2H), 7.31–7.51 (m, 3H), 4.73 (septet, J = 6.6 Hz, 1H), 1.30 (d, J = 6.6 Hz, 6H), 0.06 (s, 9H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 170.7, 134.2, 131.0, 128.7, 127.5, 94.7, 77.1, 47.1, 19.9, -0.2 ; HRMS (EI) calcd for $\text{C}_{15}\text{H}_{21}\text{NOSi}$ $[\text{M}]^+$ 259.1392, found 259.1396.

N-Phenyl-N-(trimethylsilanylethynyl)benzamide (2d).

Yellow solid; Mp 70–71 $^{\circ}\text{C}$; IR (neat); 2975, 2200, 1680, 1260, 840, 720 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 7.78–7.89 (m, 2H), 7.22–7.55 (m, 8H), 0.06 (s, 9H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 170.7, 139.5, 133.5, 131.6, 129.04, 129.02, 127.7, 127.2, 125.0, 97.2, 75.0, -0.3 ; HRMS (EI) calcd for $\text{C}_{18}\text{H}_{19}\text{NOSi}$ $[\text{M}-\text{CH}_3]^+$ 278.1001, found 278.0956.

N-Benzyl-N-(trimethylsilanylethynyl)acetamide (2e).

Yellow oil; IR (neat); 2900, 2150, 1690, 1360, 1240, 840, 740, 690 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 7.27–7.39 (m, 5H), 4.64 (s, 2H), 2.33 (s, 3H), 0.14 (s, 9H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 171.7, 135.9, 128.8, 128.4, 127.9, 97.3, 75.7, 51.1, 22.3, -0.03 ; HRMS (EI) calcd for $\text{C}_{14}\text{H}_{19}\text{NOSi}$ $[\text{M}]^+$ 245.1236, found 245.1238.

Benzyl(trimethylsilanylethynyl)carbamic acid methyl ester (2f).

Yellow oil; IR (neat); 2900, 2175, 1720, 1460, 1360, 1250, 840, 760, 700 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 7.22–7.41 (m, 5H), 4.60 (s, 2H), 3.81 (s, 3H), 0.14 (s, 9H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 155.5, 135.7, 128.6, 128.4, 128.0, 95.6, 73.1, 54.1, 53.8, 0.07; HRMS (EI) calcd for $\text{C}_{14}\text{H}_{19}\text{NO}_2\text{Si}$ $[\text{M}-\text{OMe}]^+$ 230.1001, found 230.1059.

III. Synthesis of 1,6-Diynes.

5,5-Bis(methoxymethyl)nona-2,7-diyne (1b).⁵

To a stirred mixture of LiAlH_4 (182.3 mg, 4.80 mmol) in Et_2O (10 mL) at 0 $^{\circ}\text{C}$ was added a solution of diyne **1a**¹ (497.2 mg, 2.10 mmol) in Et_2O (5 mL). The resulting mixture was stirred at 0 $^{\circ}\text{C}$ for 30 min. The reaction was quenched by the addition of water (2.0 mL), followed by stirring at 0 $^{\circ}\text{C}$ for 10 min. The solution was dried over MgSO_4 , filtered through Celite, and concentrated to give a diol (120.3 mg, 0.67 mmol, 32% yield) as a colorless oil. To a stirred suspension of NaH (55% in paraffin liquid, 147.8 mg, 3.39 mmol) in THF (5 mL) was added a THF (5 mL) solution of the diol (218.4 mg, 1.21 mmol) at 0 $^{\circ}\text{C}$, and the resulting mixture was stirred at 0 $^{\circ}\text{C}$ for 10 min. MeI (0.30 mL, 4.82 mmol) was

added, and the resulting mixture was stirred at rt for 2 h. The reaction mixture was extracted with ether. The organic layer was washed with saturated aqueous NH_4Cl and brine, dried over Na_2SO_4 , and concentrated. The crude product was purified by silica gel column chromatography (hexane:EtOAc = 20:1) afforded 5,5-bis-methoxymethylnona-2,7-diyne (**1b**, 234.1 mg, 1.12 mmol, 93% yield) as a colorless oil. Colorless oil; ^1H NMR (CDCl_3 , 300 MHz) δ 3.34 (s, 6H), 3.32 (s, 4H), 2.24 (q, J = 2.4 Hz, 4H), 1.79 (t, J = 2.4 Hz, 6H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 77.4, 75.3, 73.9, 59.4, 42.0, 22.1, 3.6.

Di(2-pentynyl) ether (1c).⁶

To a stirred suspension of NaH (55% in paraffin liquid, 0.93 g, 21.3 mmol) in THF (20 ml) was added a THF (10 mL) solution of 2-pentyn-1-ol (0.80 g, 9.6 mmol) and 1-bromo-2-pentyne (1.68 g, 11.4 mmol) at rt, and the resulting mixture was stirred at rt for 2 h. The reaction mixture was extracted with ether. The organic layer was washed with brine, dried over Na_2SO_4 , and concentrated. The crude product was purified by silica gel column chromatography (hexane:EtOAc = 50:1) afforded di(2-pentynyl) ether (**1c**, 1.21 g, 8.04 mmol, 84% yield) as a colorless oil. Colorless oil; ^1H NMR (CDCl_3 , 300 MHz) δ 4.21 (t, J = 2.4 Hz, 4H), 2.23 (tq, J = 7.5 and 2.4 Hz, 4H), 1.15 (t, J = 7.5 Hz, 6H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 88.6, 74.6, 56.9, 13.7, 12.4.

4-Bromo-*N,N*-dibut-2-ynylbenzenesulfonamide (1d).

To a stirred suspension of K_2CO_3 (1.74 g, 12.6 mmol) in CH_3CN (15 ml) was added 4-bromobenzenesulfoamide (0.60 g, 2.52 mmol) and 1-bromo-2-butyne (0.55 mL, 6.28 mmol), and the resulting mixture was refluxed for 2 h. The reaction mixture was extracted with ether. The organic layer was washed with brine, dried over Na_2SO_4 , and concentrated. The crude product was purified by silica gel column chromatography (hexane:EtOAc = 30:1) afforded 4-bromo-*N,N*-dibut-2-ynylbenzenesulfonamide (**1d**, 0.80 g, 2.35 mmol, 93% yield) as a pale yellow oil.

Pale yellow oil; IR (neat); 3300, 2900, 1570, 1425, 1330, 1150, 1090, 1060, 900, 750 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 7.60–7.74 (m, 4H), 4.08 (q, J = 2.4 Hz, 4H), 1.66 (t, J = 2.4 Hz, 6H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 137.5, 131.8, 129.5, 127.7, 82.0, 71.3, 36.7, 3.4; HRMS (EI) calcd for $\text{C}_{14}\text{H}_{14}\text{BrNO}_2\text{S}$ [$\text{M}-\text{CH}_3$] $^+$ 323.9694, found 323.9667.

IV. Rhodium-Catalyzed Enantioselective [2+2+2] Cycloaddition of 1,6-Diyne with Trimethylsilylynamides (Table 2 and eq 1)

General Procedure (Table 2, entry 1). Under an Ar atmosphere, (*S*)-xyl-BINAP (18.4 mg, 0.0250 mmol) and $[\text{Rh}(\text{cod})_2]\text{BF}_4$ (10.2 mg, 0.0250 mmol) were dissolved in CH_2Cl_2 (1.0 mL) and the mixture was stirred at rt for 5 min. H_2 was introduced to the resulting solution in a Schlenk tube. After stirring at rt for 1 h, the resulting solution was concentrated to dryness and dissolved in CH_2Cl_2 (1.0 mL). To this solution was added dropwise over 1 min a solution of diyne **1a** (59.1 mg, 0.250 mmol) and

trimethylsilylynamide **2a** (76.9 mg, 0.250 mmol) in CH₂Cl₂ (1.0 mL) at rt and washed remaining substrates away by using CH₂Cl₂ (3.0 mL). The mixture was stirred at rt for 38 h. The resulting solution was concentrated and purified by preparative TLC (hexane:EtOAc:Et₃N = 10:1:2), which furnished 5-(benzoylbenzylamino)-4,7-dimethyl-6-(trimethylsilyl)indan-2,2-dicarboxylic acid dimethyl ester (**3aa**, 38.9 mg, 0.072 mmol, 29% yield) as a colorless oil.

(+)-5-(Benzoylbenzylamino)-4,7-dimethyl-6-(trimethylsilyl)indan-2,2-dicarboxylic acid dimethyl ester (3aa, entry 1).

Colorless oil; $[\alpha]_D^{25} +101.0^\circ$ (*c* 0.845, CHCl₃, 97% ee); IR (neat); 2900, 1720, 1620, 1380, 1250, 1180, 840, 700 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.36–7.44 (m, 2H), 7.03–7.28 (m, 8H), 5.93 (d, *J* = 12.9 Hz, 1H), 3.85 (d, *J* = 12.9 Hz, 1H), 3.76 (s, 3H), 3.69 (s, 3H), 3.52 (s, 2H), 3.20 (d, *J* = 17.1 Hz, 1H), 3.07 (d, *J* = 17.1 Hz, 1H), 2.43 (s, 3H), 0.82 (s, 3H), 0.50 (s, 9H); ¹³C NMR (CDCl₃, 75 MHz) δ 172.2, 172.0, 168.3, 145.2, 141.1, 138.6, 135.7, 135.5, 134.7, 130.6, 130.4, 129.7, 129.4, 127.9, 127.7, 127.3, 58.9, 57.1, 53.0, 52.9, 40.4, 40.1, 20.5, 14.3, 2.4; HRMS (ESI) calcd for C₃₂H₃₇NO₅Si [M+Na]⁺ 566.2339, found 566.2350. CHIRALPAK AD, hexane:2-PrOH = 95:5, 1.0 mL/min, retention times: 21.0 min (major isomer) and 26.3 min (minor isomer).

(+)-5-(Benzoylbutylamino)-4,7-dimethyl-6-(trimethylsilyl)indan-2,2-dicarboxylic acid dimethyl ester (3ab, entry 2, reaction time: 18 h).

Pale yellow oil; $[\alpha]_D^{25} +125.6^\circ$ (*c* 0.800, CHCl₃, 97% ee); IR (neat); 2900, 1730, 1620, 1400, 1240, 840, 700 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.29–7.40 (m, 2H), 7.17–7.29 (m, 1H), 7.05–7.17 (m, 2H), 4.44 (dt, *J* = 12.3 and 4.5 Hz, 1H), 3.76 (s, 3H), 3.73 (s, 3H), 3.53 (s, 2H), 3.44 (d, *J* = 16.8 Hz, 1H), 3.28 (d, *J* = 16.8 Hz, 1H), 2.99 (dt, *J* = 12.3 and 4.5 Hz, 1H), 2.36 (s, 3H), 1.73 (s, 3H), 1.57–1.76 (m, 1H), 1.13–1.43 (m, 3H), 0.89 (t, *J* = 7.2 Hz, 3H), 0.40 (s, 9H); ¹³C NMR (CDCl₃, 75 MHz) δ 172.1, 168.4, 145.7, 141.1, 138.6, 138.5, 135.9, 135.3, 129.6, 129.23, 129.16, 127.3, 58.8, 53.9, 53.1, 53.0, 40.5, 40.3, 28.0, 20.6, 20.4, 15.6, 13.8, 2.2; HRMS (ESI) calcd for C₂₉H₃₉NO₅Si [M+Na]⁺ 532.2495, found 532.2511. CHIRALPAK AD-H, hexane:2-PrOH = 90:10, 1.0 mL/min, retention times: 15.2 min (minor isomer) and 17.4 min (major isomer).

(–)-5-(Benzoylisopropylamino)-4,7-dimethyl-6-(trimethylsilyl)indan-2,2-dicarboxylic acid dimethyl ester (3ac, entry 3, reaction time: 15 h).

Colorless oil; $[\alpha]_D^{25} -1.20^\circ$ (*c* 1.255, CHCl_3 , 87% ee); IR (neat); 2900, 1720, 1620, 1340, 1240, 1160, 840, 700 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 7.13–7.25 (m, 3H), 7.01–7.13 (m, 2H), 4.67 (septet, $J = 6.6$ Hz, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.53 (s, 2H), 3.52 (d, $J = 16.8$ Hz, 1H), 3.44 (d, $J = 16.8$ Hz, 1H), 2.27 (s, 3H), 2.06 (s, 3H), 1.45 (d, $J = 6.6$ Hz, 3H), 0.84 (d, $J = 6.6$ Hz, 3H), 0.25 (s, 9H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 172.20, 172.16, 168.6, 142.6, 141.1, 139.0, 138.7, 137.4, 136.7, 130.5, 129.2, 128.9, 127.2, 58.8, 53.1, 53.0, 51.0, 40.5, 40.4, 22.1, 20.6, 20.3, 17.2, 2.3; HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{37}\text{NO}_5\text{Si}$ $[\text{M}+\text{Na}]^+$ 518.2339, found 518.2346. CHIRALPAK AD-H, hexane:2-PrOH = 90:10, 1.0 mL/min, retention times: 7.8 min (minor isomer) and 14.7 min (major isomer).

(-)-5-(Benzoylphenylamino)-4,7-dimethyl-6-(trimethylsilyl)indan-2,2-dicarboxylic acid dimethyl ester (3ad, entry 4, *cis:trans* = 60:40, reaction time: 42 h).

The ratio of *cis:trans* was determined by ^1H NMR chemical shift of Me singlet adjacent to amide group. The highfield Me singlet of the anilide was assigned to the *cis*-rotamer. Colorless oil; $[\alpha]_D^{25} -32.6^\circ$ (*c* 1.140, CHCl_3 , 97% ee); IR (neat); 2900, 1720, 1640, 1430, 1230, 840, 710 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 6.91–7.58 (m, 10H, *cis*; 8H, *trans*), 6.56–6.68 (m, 2H, *trans*), 3.70–3.84 (m, 6H, *cis* and *trans*), 3.38–3.70 (m, 4H, *cis* and *trans*), 2.32 (s, 3H, *trans*), 2.25 (s, 3H, *cis*), 2.18 (s, 3H, *trans*), 1.95 (s, 3H, *cis*), 0.22 (s, 9H, *trans*), 0.16 (s, 9H, *cis*); ^{13}C NMR (CDCl_3 , 75 MHz) δ 172.6, 172.1, 172.0, 169.8, 169.0, 146.3, 145.3, 143.1, 142.9, 141.6, 141.5, 139.5, 139.0, 138.8, 138.2, 137.7, 136.6, 136.1, 135.6, 130.3, 130.0, 129.8, 129.3, 129.0, 128.2, 128.0, 127.9, 127.4, 125.0, 124.4, 124.3, 123.9, 58.9, 53.1, 40.7, 40.5, 40.2, 21.0, 20.3, 15.3, 15.1, 2.2; HRMS (ESI) calcd for $\text{C}_{31}\text{H}_{35}\text{NO}_5\text{Si}$ $[\text{M}+\text{Na}]^+$ 552.2182, found 552.2241. CHIRALPAK AD, hexane:2-PrOH = 80:20, 1.0 mL/min, retention times: 11.8 min (minor isomer) and 23.9 min (major isomer).

(+)-5-(Acetylbenzylamino)-4,7-dimethyl-6-(trimethylsilyl)indan-2,2-dicarboxylic acid dimethyl ester (3ae, entry 5, reaction time: 16 h).

Colorless oil; $[\alpha]_D^{25} +35.9^\circ$ (*c* 1.235, CHCl_3 , 90% ee); IR (neat); 2900, 1720, 1640,

1390, 1240, 1180, 840, 700 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 7.11–7.31 (m, 3H), 7.00–7.11 (m, 2H), 5.66 (d, J = 12.9 Hz, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 3.66 (d, J = 12.9 Hz, 1H), 3.56 (s, 2H), 3.36 (s, 2H), 2.38 (s, 3H), 1.79 (s, 3H), 1.19 (s, 3H), 0.36 (s, 9H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 172.2, 170.5, 144.8, 141.3, 138.9, 138.7, 135.9, 134.7, 130.5, 130.4, 128.1, 127.6, 58.9, 54.7, 53.1, 40.5, 40.2, 22.8, 20.5, 14.2, 2.3; HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{35}\text{NO}_5\text{Si}$ $[\text{M}+\text{Na}]^+$ 504.2182, found 504.2200. CHIRALPAK AD-H, hexane:2-PrOH = 96:4, 1.0 mL/min, retention times: 13.3 min (major isomer) and 15.2 min (minor isomer).

(–)-Benzyl[2-(4-bromobenzenesulfonyl)-4,7-dimethyl-6-(trimethylsilyl)-2,3-dihydro-1H-indol-5-yl]carbamate (3df, entry 6, *cis:trans* = 86:14, reaction time: 15 h).

The ratio of *cis:trans* was determined by ^1H NMR chemical shift of MeO singlet. The highfield MeO singlet of the anilide was assigned to the *cis*-rotamer. Pale yellow oil; $[\alpha]_D^{25}$ -20.3° (c 5.810, CHCl_3 , 98% ee); IR (neat); 2900, 1680, 1570, 1320, 1150, 1100, 1060, 820, 730, 690 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 7.64–7.78, 7.13–7.30, and 6.93–7.06 (m, 9H, *cis* and *trans*), 5.27 (d, J = 13.8 Hz, 1H, *cis*), 5.14 (d, J = 13.8 Hz, 1H, *trans*), 4.40–4.52 (m, 2H, *cis* and *trans*), 4.32 (dd, J = 12.3 and 3.0 Hz, 1H, *cis* and *trans*), 3.92 (d, J = 13.8 Hz, 1H, *trans*), 3.86 (d, J = 13.8 Hz, 1H, *cis*), 3.85 (dd, J = 12.3 and 3.0 Hz, 1H, *cis* and *trans*), 3.85 (s, 3H, *trans*), 3.63 (s, 3H, *cis*), 2.31 (s, 3H, *cis*), 2.29 (s, 3H, *trans*), 1.21 (s, 3H, *trans*), 1.18 (s, 3H, *cis*), 0.34 (s, 9H, *trans*), 0.33 (s, 9H, *cis*); ^{13}C NMR (CDCl_3 , 75 MHz) δ 155.9, 144.4, 137.3, 136.8, 136.5, 135.8, 135.7, 134.6, 132.5, 130.0, 129.6, 128.9, 128.2, 127.94, 127.88, 56.5, 54.0, 53.7, 53.0, 20.1, 13.9, 1.9; HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{33}\text{BrN}_2\text{O}_4\text{SSi}$ $[\text{M}+\text{Na}]^+$ 623.1011, found 623.1044. CHIRALPAK AD, hexane:2-PrOH = 85:15, 1.0 mL/min, retention times: 8.6 min (minor isomer) and 17.2 min (major isomer).

(–)-N-[2,2-Dimethoxymethyl-4,7-dimethyl-6-(trimethylsilyl)indan-5-yl]-N-phenylbenzamide (3bd, entry 7, *cis:trans* = 59:41, reaction time: 16 h).

The ratio of *cis:trans* was determined by ^1H NMR chemical shift of Me singlet adjacent to amide group. The highfield Me singlet of the anilide was assigned to the *cis*-rotamer. Pale yellow oil; $[\alpha]_D^{25}$ -17.5° (c 2.065, CHCl_3 , 98% ee); IR (neat); 2850, 1640, 1300, 1100, 840,

740, 690 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 6.90–7.55 (m, 10H, *cis*; 8H, *trans*), 6.56–6.70 (m, 2H, *trans*), 3.21–3.51 (m, 10H, *cis* and *trans*), 2.62–2.94 (m, 4H, *cis* and *trans*), 2.28 (s, 3H, *trans*), 2.21 (s, 3H, *cis*), 2.15 (s, 3H, *trans*), 1.91 (s, 3H, *cis*), 0.22 (s, 9H, *trans*), 0.16 (s, 9H, *cis*); ^{13}C NMR (CDCl_3 , 75 MHz) δ 169.9, 169.1, 145.7, 144.6, 143.8, 143.6, 143.2, 143.1, 141.7, 141.1, 139.4, 138.6, 136.9, 136.6, 136.3, 134.5, 132.2, 130.4, 130.1, 129.7, 129.6, 128.9, 128.1, 128.0, 127.9, 127.2, 125.0, 124.24, 124.19, 123.9, 76.3, 76.24, 76.16, 59.3, 59.2, 46.8, 46.5, 39.0, 38.7, 38.5, 21.0, 20.3, 15.3, 15.0, 2.2; HRMS (ESI) calcd for $\text{C}_{31}\text{H}_{39}\text{NO}_3\text{Si}$ $[\text{M}+\text{Na}]^+$ 524.2597, found 524.2623. CHIRALPAK AD-H, hexane:2-PrOH = 80:20, 1.0 mL/min, retention times: 6.0 min (minor isomer) and 7.6 min (major isomer).

(-)-*N*-[4,7-Diethyl-6-(trimethylsilyl)-1,3-dihydroisobenzofuran-5-yl]-*N*-phenylbenzamide (3cd, entry 8, *cis:trans* = 73:27, reaction time: 16 h).

The ratio of *cis:trans* was determined by ^1H NMR chemical shift of Et triplet adjacent to amide group. The hghfield Et triplet of the anilide was assigned to the *cis*-rotamer. Yellow oil; $[\alpha]_D^{25} -178.2^\circ$ (*c* 3.495, CHCl_3 , 96% ee); IR (neat); 2850, 1640, 1580, 1280, 1050, 840, 740, 690 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 6.93–7.57 (m, 10H, *cis*; 8H, *trans*), 6.62–6.70 (m, 2H, *trans*), 5.20 (s, 2H, *trans*), 5.17 (s, 2H, *trans*), 5.13 (s, 2H, *cis*), 5.10 (s, 2H, *cis*), 2.24–2.88 (m, 4H, *cis* and *trans*), 1.15 (t, $J = 7.5$ Hz, 3H, *trans*), 0.94 (t, $J = 7.5$ Hz, 3H, *trans*), 0.84 (t, $J = 7.5$ Hz, 3H, *cis*), 0.49 (t, $J = 7.5$ Hz, 3H, *cis*), 0.27 (s, 9H, *trans*), 0.15 (s, 9H, *cis*); ^{13}C NMR (CDCl_3 , 75 MHz) δ 170.4, 168.8, 145.8, 145.3, 144.0, 143.44, 143.38, 143.0, 141.7, 141.5, 138.61, 138.57, 138.4, 136.4, 136.0, 133.0, 130.4, 129.7, 129.1, 129.0, 128.3, 128.0, 127.9, 127.3, 125.0, 124.7, 124.5, 124.2, 73.4, 73.1, 72.8, 27.2, 26.8, 23.2, 23.0, 14.9, 14.8, 12.7, 11.7, 3.0, 2.8; HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{33}\text{NO}_2\text{Si}$ $[\text{M}+\text{Na}]^+$ 466.2178, found 466.2200. CHIRALPAK AD-H, hexane:2-PrOH = 70:30, 1.0 mL/min, retention times: 7.5 min (minor isomer) and 20.5 min (major isomer).

(+)-*N*-[2-(4-Bromobenzenesulfonyl)-4,7-dimethyl-6-(trimethylsilyl)-2,3-dihydro-1*H*-isoindol-5-yl]-*N*-phenylbenzamide (3dd, entry 9, *cis:trans* = 45:55, reaction time: 40 h).

The ratio of *cis:trans* was determined by ^1H NMR chemical shift of Me singlet adjacent to amide group. The hghfield Me singlet of the anilide was assigned to the *cis*-rotamer. Yellow oil; $[\alpha]_D^{25} +5.07^\circ$ (*c* 5.790, CHCl_3 , 84% ee); IR (neat); 2900, 1640, 1570, 1300,

1160, 830, 730, 690 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 7.62–7.87 (m, 4H, *cis* and *trans*), 6.93–7.50 (m, 10H, *cis*; 8H, *trans*), 6.53–6.68 (m, 2H, *trans*), 4.32–4.84 (m, 4H, *cis* and *trans*), 2.27 (s, 3H, *trans*), 2.19 (s, 3H, *cis*), 2.10 (s, 3H, *trans*), 1.89 (s, 3H, *cis*), 0.22 (s, 9H, *trans*), 0.17 (s, 9H, *cis*); ^{13}C NMR (CDCl_3 , 75 MHz) δ 169.8, 168.8, 147.0, 146.1, 142.8, 142.4, 139.5, 137.8, 137.6, 137.5, 137.4, 137.2, 136.2, 135.9, 135.7, 135.6, 135.5, 135.1, 132.5, 132.4, 131.7, 130.5, 130.0, 129.7, 128.93, 128.85, 128.8, 128.3, 128.2, 128.04, 127.97, 127.9, 127.8, 127.5, 124.8, 124.6, 123.8, 54.2, 54.1, 53.9, 53.6, 20.5, 19.9, 15.2, 15.0, 2.0; HRMS (ESI) calcd for $\text{C}_{32}\text{H}_{33}\text{BrN}_2\text{O}_3\text{SSi}$ $[\text{M}+\text{Na}]^+$ 655.1062, found 655.1105. CHIRALPAK AD-H, hexane:2-PrOH = 60:40, 0.9 mL/min, retention times: 42.1 min (minor isomer) and 74.8 min (major isomer).

(S)-(+)-N-Benzyl-N-[4,7-dimethyl-2-(toluene-4-sulfonyl)-6-(trimethylsilanyl)-2,3-dihydro-1H-isoindol-5-yl]benzamide (3ea, entry 10, reaction time: 15 h).

Colorless solid; Mp 210–211 $^{\circ}\text{C}$; $[\alpha]_{\text{D}}^{25} +87.6^{\circ}$ (*c* 0.920, CHCl_3 , 79% ee); IR (neat); 2900, 1620, 1380, 1330, 1250, 1160, 1100, 840, 700, 660 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 7.69–7.79 (m, 2H), 7.02–7.41 (m, 12H), 5.93 (d, *J* = 12.9 Hz, 1H), 4.58 (d, *J* = 13.5 Hz, 1H), 4.51 (d, *J* = 13.5 Hz, 1H), 4.21 (d, *J* = 13.5 Hz, 1H), 4.09 (d, *J* = 13.5 Hz, 1H), 3.79 (d, *J* = 12.9 Hz, 1H), 2.43 (s, 3H), 2.37 (s, 3H), 0.77 (s, 3H), 0.51 (s, 9H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 168.3, 145.9, 143.6, 137.6, 137.4, 136.4, 135.5, 135.3, 135.1, 134.2, 130.4, 129.9, 129.8, 129.3, 129.2, 128.1, 127.9, 127.5, 127.4, 57.1, 53.8, 53.4, 21.5, 20.1, 14.1, 2.2; HRMS (ESI) calcd for $\text{C}_{34}\text{H}_{38}\text{N}_2\text{O}_3\text{SSi}$ $[\text{M}+\text{Na}]^+$ 605.2270, found 605.2289. CHIRALPAK AD, hexane:2-PrOH = 75:25, 1.0 mL/min, retention times: 29.7 min (major isomer) and 34.6 min (minor isomer). The absolute configuration of (+)-**3ea** was determined to be *S* by anomalous dispersion method. The single crystals which are suitable for X-ray crystallographic analysis were obtained by recrystallization from acetone/pentane.

(+)-N-Benzyl-N-[4,7-dimethyl-2-(toluene-4-sulfonyl)-6-(trimethylsilanyl)-2,3-dihydro-1H-isoindol-5-yl]acetamide (3ee, entry 11, reaction time: 16 h).

Pale yellow oil; $[\alpha]_{\text{D}}^{25} +47.6^{\circ}$ (*c* 1.950, CHCl_3 , 88% ee); IR (neat); 2900, 1630, 1390, 1330, 1160, 1100, 830, 740, 660 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 7.72–7.87 (m, 2H), 6.97–7.41 (m, 7H), 5.67 (d, *J* = 13.2 Hz, 1H), 4.64 (d, *J* = 13.5 Hz, 1H), 4.52 (d, *J* = 13.5 Hz, 1H), 4.42 (d, *J* = 13.8 Hz, 1H), 4.33 (d, *J* = 13.8 Hz, 1H), 3.61 (d, *J* = 13.2 Hz, 1H), 2.43 (s, 3H), 2.32 (s, 3H), 1.74 (s, 3H), 1.13 (s, 3H), 0.36 (s, 9H); ^{13}C NMR (CDCl_3 , 75

MHz) δ 170.1, 145.4, 143.7, 137.7, 137.6, 136.4, 135.7, 135.5, 133.9, 130.4, 129.8, 129.4, 128.2, 127.8, 127.5, 54.8, 53.8, 53.5, 22.7, 21.5, 20.0, 13.9, 2.1; HRMS (ESI) calcd for $C_{29}H_{36}N_2O_3SSi$ $[M+Na]^+$ 543.2114, found 543.2126. CHIRALPAK AD, hexane:2-PrOH = 75:25, 1.0 mL/min, retention times: 7.9 min (major isomer) and 14.2 min (minor isomer).

(+)-5-(Benzoylbenzylamino)-7-methyl-6-(trimethylsilanyl)-1,3-dihydroisobenzofuran-4-carboxylic acid methyl ester (3fa, eq 1).

Colorless oil; $[\alpha]_D^{25} +53.5^\circ$ (c 0.695, $CHCl_3$, 50% ee); IR (neat); 2900, 1700, 1630, 1380, 1260, 840, 700 cm^{-1} ; 1H NMR ($CDCl_3$, 300 MHz) δ 7.36–7.47 (m, 2H), 7.03–7.32 (m, 8H), 5.79 (d, J = 13.5 Hz, 1H), 5.18 (d, J = 14.7 Hz, 1H), 5.09 (s, 2H), 4.95 (d, J = 14.7 Hz, 1H), 3.98 (d, J = 13.5 Hz, 1H), 3.20 (s, 3H), 2.43 (s, 3H), 0.41 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.7, 165.0, 146.7, 143.4, 143.0, 139.7, 139.1, 136.1, 135.5, 130.9, 129.7, 129.5, 128.0, 127.7, 127.3, 122.8, 75.6, 73.2, 57.4, 51.5, 20.8, 2.2; HRMS (ESI) calcd for $C_{28}H_{31}NO_4Si$ $[M+Na]^+$ 496.1920, found 496.1923. CHIRALPAK AD-H, hexane:2-PrOH = 90:10, 1.0 mL/min, retention times: 23.8 min (minor isomer) and 27.1 min (major isomer). The structure of **3fa** was confirmed by NOE experiments.

V. References

- 1) Duong, H. A.; Cross, M. J.; Louie, J. *J. Am. Chem. Soc.* **2004**, *126*, 11438–11439.
- 2) Atkinson, R. S.; Grimshire, M. J. *J. Chem. Soc., Perkin Trans. I* **1986**, *7*, 1215–1224.
- 3) Yamamoto, Y.; Nagata, A.; Ando, Y.; Arikawa, Y.; Tatsumi, K.; Itoh, K. *Chem. Eur. J.* **2003**, *9*, 2469–2483.
- 4) Witulski, B.; Stengel, T. *Angew. Chem., Int. Ed.* **1998**, *37*, 489–492.
- 5) Nishikawa, T.; Kakiya, H.; Shinokubo, H.; Oshima, K. *J. Am. Chem. Soc.* **2001**, *123*, 4629–4630.
- 6) Tsukada, N.; Sugawara, S.; Nakaoka, K.; Inoue, Y. *J. Org. Chem.* **2003**, *68*, 5961–5966.

2c

1d

S26

3fa