Supporting Information

Bifunctional spiro-type organocatalyst with high enantiocontrol: Application to the aza-Morita-Baylis-Hillman reactions

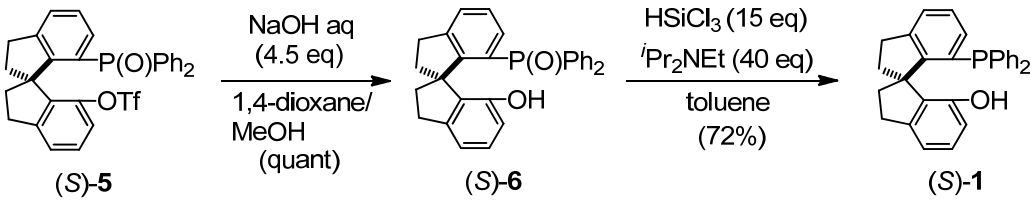
Shinobu Takizawa, Kimiko Kiriyama, Kenta Ieki, and Hiroaki Sasai*

The Institute of Scientific and Industrial Research (ISIR), Osaka University
8-1 Mihogaoka, Ibaraki-shi, Osaka 567-0047, Japan
Fax +81(6)68798469; E-mail sasai@sanken.osaka-u.ac.jp

General information:

^{1}H- and ^{13}C-NMR spectra were recorded with JEOL JMN LA-400 FT NMR (^{1}H-NMR – 400 MHz, ^{13}C-NMR – 100 MHz). ^{1}H NMR spectra are reported as follows: chemical shift in ppm (δ) relative to the chemical shift of $CDCl_3$ at 7.26 ppm, integration, multiplicities (s = singlet, d = doublet, q = quartet, t = triplet, m = multiplet), and coupling constants (Hz). ^{13}C-NMR spectra reported in ppm (δ) relative to the central line of triplet for $CDCl_3$ at 77 ppm. FTMS spectra were obtained with LTQ Orbitrap XL (Thermo Fisher Scientific). ESI mass spectra were obtained with JMS-T100LC (JEOL). Optical rotations were measured with JASCO P-1030 polarimeter. HPLC analyses were performed on a JASCO HPLC system (JASCO PU 980 pump and UV-975 UV/Vis detector) using a mixture of hexane and *i*-PrOH or EtOH as eluents. FT-IR spectra were recorded on a JASCO FT-IR system (FT/IR4100). Analytical TLC was performed on Merck silica gel plates with 60 F_{254} indicator. Visualization was accomplished with UV light. Column chromatography on SiO_2 was performed with Kanto Silica Gel 60 (40-100 μm). Commercially available organic and inorganic compounds were used without further purification except for the solvent, which was distilled from sodium/benzophenone or CaH_2.

Synthesis of acid-base organocatalyst (*S*)-1



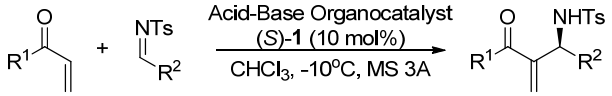
(*S*)-**5** (*S*)-**6** (*S*)-**1**

(*S*)-6: To a solution of (*S*)-**5**[1)] in 1,4-dioxane / MeOH (2:1) was added 3.0 M NaOH aq. (4.5 eq) at rt. After stirring for 24 h, the reaction was quenched with 1.0 M HCl aq. The organic phase was extracted with AcOEt, then washed with water and brine. The organic phase was concentrated *in*

vacuo. The residue was washed by hexane to afford (*S*)-**6** as a white solid. $[\alpha]_D^{21}$ – 140.0 (*c* 0.5, $CHCl_3$); IR (neat) υ 3118, 3076, 2950, 2861, 2842, 1590, 1466, 1437, 1301, 1176, 1100 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.52-7.28 (11H, m), 7.15 (1H, dt, *J* = 2.0, 7.6 Hz), 7.01 (1H, q, *J* = 7.6 Hz), 6.89 (1H, t, *J* = 8.0 Hz), 6.68 (1H, d, *J* = 7.6 Hz), 6.13 (1H, d, *J* = 8.0 Hz), 3.06-2.94 (2H, m), 2.87-2.72 (2H, m), 2.56-2.48 (1H, m), 2.36-2.27 (1H, m), 2.18-2.07 (2H, m); ^{13}C-NMR ($CDCl_3$) δ 152.1, 146.5, 131.7, 131.6, 131.5, 131.4, 131.2, 131.1, 129.0, 128.2, 128.1, 128.0, 127.9, 117.7, 116.5, 61.9, 39.2, 37.6, 31.0, 30.6; ^{31}P-NMR ($CDCl_3$) δ +31.19; HRMS (ESI) calcd for $C_{29}H_{25}O_2NaP$, m/z = 459.1490 $[(M+Na)^+]$; found, m/z = 459.1490.

(*S*)-1: To a solution of (*S*)-**6** and diisopropyl ethyl anime (40 eq) in toluene was added trichlorosilane (15 eq) at 0 °C. After being stirred at 100 °C for 48 h, the mixture was cooled to rt, diluted with AcOEt and then quenched with small amount of water. The resulting suspension was filtrated and the solid was washed with AcOEt. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by short column chromatography (SiO_2, AcOEt only) to afford (*S*)-**1** as a white solid. $[\alpha]_D^{22}$ – 106.6 (*c* 0.5, $CHCl_3$); IR (neat) υ 3396, 3063, 3033, 3012, 2939, 2862, 1589, 1464, 1435, 1279, 1175 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.30 (1H, d, *J* = 7.2 Hz), 7.27-7.17 (7H, m), 7.10 (2H, dt, *J* = 1.6, 8.0 Hz), 7.06-6.97 (4H, m), 6.83 (1H, d, *J* = 7.2 Hz), 6.30 (1H, d, *J* = 8.0 Hz), 3.07-2.96 (4H, m), 2.34-2.21 (4H, m); ^{13}C-NMR ($CDCl_3$) δ 152.0, 145.1, 144.5, 133.7, 133.5, 133.4, 133.2, 128.6, 128.2, 128.1, 128.0, 127.9, 126.0, 117.0, 113.9, 60.8, 39.2, 38.2, 31.2, 30.8; ^{31}P-NMR ($CDCl_3$) δ -21.29; HRMS (ESI) calcd for $C_{29}H_{25}ONaP$, m/z = 443.1541 $[(M+Na)^+]$; found, m/z = 443.1534.

General procedure for the enantioselective aza-MBH reaction promoted by spiro-type organocatalyst (*S*)-1



2 **3** **4**

To a solution of organocatalyst (*S*)-**1** (4 mg, 0.01 mmol), imines (**3**, 0.1 mmol) and MS 3A in $CHCl_3$ (0.5 mL) was added enones (**2**, 0.3 mmol) at –10°C. The mixture was stirred until the reaction had reached completion by monitoring with TLC analysis. The mixture was directly purified by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 12/1 to 2/1) to afford the corresponding adducts **4**. The adducts **4a-e**,[2] **4f**,[3] **4i-l**[2] **4m**,[3] and **4n**[2] were identical in all respects with reported in the literature.

4a (R^1 = Me, R^2 = 4-Cl-C_6H_4-) 86% yield, 92% ee; ^{1}H-NMR ($CDCl_3$): δ 7.63 (2H, d, *J* = 8.4 Hz), 7.23 (2H, d, *J* = 8.4 Hz), 7.17 (2H, d, *J* = 8.4 Hz), 7.04 (2H, d, *J* = 8.4 Hz), 6.09 (1H, s), 6.06 (1H, s), 5.67 (1H, brs), 5.21 (1H, d, *J* = 8.8 Hz), 2.42 (3H, s), 2.16 (3H, s); DAICEL CHIRALPAK AS

column, detection at 254 nm, *i*-PrOH/*n*-hexane = 1/4, flow rate 0.7 mL/min, 18.4 min (major isomer, *S*) and 22.5 min (minor isomer, *R*).

4b (R^1 = Me, R^2 = 3-Cl-C_6H_4-) 86%, 93% ee; ^{1}H-NMR ($CDCl_3$) : δ 7.63 (2H, d, *J* = 8.0 Hz), 7.24 (2H, d, *J* = 8.0 Hz), 7.15-7.13 (2H, m), 7.02-7.00 (2H, m), 6.12 (1H, s), 6.07 (1H, s), 5.65 (1H, d, *J* = 8.0 Hz), 5.21 (2H, d, *J* = 8.0 Hz), 2.42 (3H, s), 2.17 (3H, s); DAICEL CHIRALPAK AD-H column, detection at 254 nm, Hex/*i*-PrOH = 4/1, flow rate 0.7 mL/min., 15.4 min (major isomer, *S*) and 19.0 min (minor isomer, *R*).

4c (R^1 = Me, R^2 = 2-Cl-C_6H_4-) 72%, 95% ee; ^{1}H-NMR ($CDCl_3$) : δ 7.62 (2H, d, *J* = 8.0 Hz), 7.32-7.30 (1H, m), 7.23-7.20 (1H, m), 7.17 (2H, d, *J* = 8.0 Hz), 7.13-7.06 (2H, m), 6.15 (2H, s), 5.79 (1H, d, *J* = 8.8 Hz), 5.68 (2H, d, *J* = 8.8 Hz), 2.37 (3H, s), 2.21 (3H, s); DAICEL CHIRALPAK AD-H column, detection at 254 nm, Hex/*i*-PrOH = 4/1, flow rate 0.7 mL/min., 19.8 min (major isomer, *S*) and 22.2 min (minor isomer, *R*).

4d (R^1 = Me, R^2 = 4-Br-C_6H_4-) 83%, 94% ee; ^{1}H-NMR ($CDCl_3$) : δ 7.63 (2H, d, *J* = 8.4 Hz), 7.32 (2H, d, *J* = 8.4 Hz), 7.23 (2H, d, *J* = 8.0 Hz), 6.98 (2H, d, *J* = 8.0 Hz), 6.10 (1H, s), 6.06 (1H, s), 5.65 (1H, d, *J* = 8.8 Hz), 5.19 (1H, d, *J* = 8.8 Hz), 2.42 (3H, s), 2.16 (3H, s); DAICEL CHIRALPAK AD-H column, detection at 254 nm, Hex/*i*-PrOH = 4/1, flow rate 0.7 mL/min., 18.3 min (major isomer, *S*) and 20.9 min (minor isomer, *R*).

4e (R^1 = Me, R^2 = 4-F-C_6H_4-) 79%, 87% ee; ^{1}H-NMR ($CDCl_3$) : δ 7.64 (2H, d, *J* = 8.0 Hz), 7.24 (2H, d, *J* = 8.0 Hz), 7.09-7.06 (2H, m), 6.91-6.87 (2H, m), 6.09 (1H, s), 6.06 (1H, s), 5.62 (1H, d, *J* = 8.8 Hz), 5.23 (1H, d, *J* = 8.8 Hz), 2.41 (3H, s), 2.16 (3H, s); DAICEL CHIRALPAK AD-H column, detection at 254 nm, Hex/*i*-PrOH = 4/1, flow rate 0.7 mL/min., 15.7 min (major isomer, *S*) and 17.3 min (minor isomer, *R*).

4f (R^1 = Me, R^2 = 4-CN-C_6H_4-) 99%, 90% ee; ^{1}H-NMR ($CDCl_3$) : δ 7.64 (2H, d, *J* = 8.4 Hz), 7.49 (2H, dd, *J* = 2.0, 8.4 Hz), 7.28 (2H, d, *J* = 8.0 Hz), 7.23 (2H, d, *J* = 8.0 Hz), 6.11 (1H, s), 6.05 (1H, s), 5.90 (1H, t, *J* = 9.2 Hz), 5.28 (1H, d, *J* = 9.2 Hz), 2.42 (3H, s), 2.15 (3H, s); DAICEL CHIRALPAK AD-H column, detection at 254 nm, Hex/*i*-PrOH = 4/1, flow rate 0.7 mL/min., 30.6 min (major isomer, *S*) and 36.0 min (minor isomer, *R*).

4g (R^1 = Me, R^2 = 3-CN-C_6H_4-) 97%, 93% ee; $[\alpha]_D^{18}$ – 6.2 (*c* 1.1, CH_2Cl_2); IR (neat) υ 3254, 3067, 2962, 2926, 2372, 2230, 1919, 1672, 1591, 1442, 1327, 1265, 1154 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.62 (2H, d, *J* = 8.4 Hz), 7.45 (2H, t, *J* = 7.2 Hz), 7.33 (2H, t, *J* = 8.0 Hz), 7.24 (2H, d, *J* = 8.0 Hz), 6.14 (1H, s), 6.07 (1H, s), 5.87 (1H, d, *J* = 9.2 Hz), 5.26 (1H, d, *J* = 9.2 Hz), 2.42 (3H, s), 2.16 (3H, s); ^{13}C-NMR ($CDCl_3$) δ 198.6, 145.4, 143.8, 140.5, 137.3, 131.1, 130.8, 129.9, 129.6, 129.4, 129.2, 127.1, 118.3, 112.5, 58.6, 26.1, 21.4; HRMS (APCI) calcd for $C_{19}H_{18}N_2O_3S$, m/z = 355.1116 [$(M+H)^+$]; found, m/z = 355.1108; DAICEL CHIRALPAK AD-H column, detection at 222 nm, Hex/*i*-PrOH = 65/35, flow rate 0.5 mL/min., 11.0 min (major isomer, *S*) and 14.2 min (minor isomer, *R*).

4h (R^1 = Me, R^2 = 2-CN-C_6H_4-) 92%, 97% ee; $[\alpha]_D^{18}$ - 29.9 (*c* 0.7, CH_2Cl_2); IR (neat) υ 3236, 3055,

2962, 2926, 2373, 1924, 1682, 1600, 1529, 1448, 1343, 1263, 1159 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.74 (1H, dd, *J* = 1.6, 8.4 Hz), 7.66 (2H, d, *J* = 8.4 Hz), 7.63 (1H, dd, *J* = 1.2, 8.0 Hz), 7.48 (1H, t, *J* = 7.6 Hz), 7.35 (1H, dt, *J* = 1.6, 8.4 Hz), 7.22 (2H, d, *J* = 8.0 Hz), 6.07 (1H, s), 5.97 (2H, brs), 5.94 (1H, s), 2.39 (3H, s), 2.16 (3H, s); ^{13}C-NMR ($CDCl_3$) δ 198.5, 148.0, 144.9, 143.5, 137.0, 133.2, 132.9, 130.4, 129.5, 129.3, 128.5, 129.2, 127.2, 124.7, 54.6, 26.2, 21.4; HRMS (APCI) calcd for $C_{19}H_{18}N_2O_3NaS$, m/z = 377.0936 [$(M+Na)^+$]; found, m/z = 377.0961; DAICEL CHIRALPAK AD-H column, detection at 222 nm, Hex/*i*-PrOH = 65/35, flow rate 0.5 mL/min., 17.5 min (major isomer, *S*) and 21.6 min (minor isomer, *R*).

4i (R^1 = Me, R^2 = 4-NO_2-C_6H_4-) 97%, 96% ee; ^{1}H-NMR ($CDCl_3$) : δ 8.08 (2H, d, *J* = 8.8 Hz), 7.64 (2H, d, *J* = 8.0 Hz), 7.34 (2H, d, *J* = 8.8 Hz), 7.25 (2H, d, *J* = 8.0 Hz), 6.13 (1H, s), 6.07 (1H, s), 5.82 (1H, d, *J* = 9.6 Hz), 5.30 (1H, d, *J* = 9.6 Hz), 2.42 (3H, s), 2.16 (3H, s); DAICEL CHIRALPAK AD-H column, detection at 254 nm, Hex/*i*-PrOH = 4/1, flow rate 0.7 mL/min., 41.1 min (major isomer, *S*) and 54.5 min (minor isomer, *R*).

4j (R^1 = Me, R^2 = 3-NO_2-C_6H_4-) 94%, 94% ee; ^{1}H-NMR ($CDCl_3$) : δ 7.62 (2H, d, *J* = 8.0 Hz), 7.45 (2H, dt, *J* = 1.2, 6.4 Hz), 7.33 (1H, t, *J* = 7.6 Hz), 7.24 (1H, d, *J* = 8.4 Hz), 6.14 (1H, s), 6.08 (1H, s), 5.91 (1H, d, *J* = 9.6 Hz), 5.26 (1H, d, *J* = 9.6 Hz), 2.42 (3H, s), 2.16 (3H, s); DAICEL CHIRALPAK AD-H column, detection at 222 nm, Hex/*i*-PrOH = 65/35, flow rate 0.5 mL/min., 12.4 min (major isomer, *S*) and 14.9 min (minor isomer, *R*).

4k (R^1 = Me, R^2 = 2-NO_2-C_6H_4-) 91%, 93% ee; ^{1}H-NMR ($CDCl_3$) : δ 7.74 (1H, d, *J* = 8.4 Hz), 7.67 (2H, d, *J* = 7.2 Hz), 7.64 (1H, d, *J* = 7.6 Hz), 7.50 (1H, t, *J* = 7.6 Hz), 7.36 (1H, t, *J* = 7.6 Hz), 7.23 (2H, d, *J* = 7.6 Hz), 6.07 (1H, s), 5.97 (1H, brs), 5.95 (1H, d, *J* = 7.2 Hz), 5.86 (1H, d, *J* = 8.8 Hz), 2.40 (3H, s), 2.16 (3H, s); DAICEL CHIRALPAK AS column, detection at 222 nm, Hex/*i*-PrOH = 65/35, flow rate 0.8 mL/min., 32.7 min (major isomer, *S*) and 72.2 min (minor isomer, *R*).

4l (R^1 = Me, R^2 = C_6H_5-) 93%, 88% ee ; ^{1}H-NMR ($CDCl_3$) : δ 7.65 (2H, d, *J* = 8.4 Hz), 7.25-7.19 (5H, m), 7.10-7.08 (2H, m), 6.10 (1H, s), 6.09 (1H, s), 5.62 (1H, d, *J* = 8.4 Hz), 5.26 (1H, d, *J* = 8.8 Hz), 2.41 (3H, s), 2.16 (3H, s); DAICEL CHIRALPAK AD-H column, detection at 254 nm, Hex/*i*-PrOH = 4/1, flow rate 0.7 mL/min., 15.4 min (minor isomer, *S*) and 17.5 min (major isomer, *R*).

4m (R^1 = Me, R^2 = 2-$C_{10}H_7$-) 94%, 85% ee; ^{1}H-NMR ($CDCl_3$) : δ 7.76-7.74 (1H, m), 7.69-7.65 (4H, m), 7.50 (1H, s), 7.46-7.41 (2H, m), 7.20-7.17 (3H, m), 6.17 (1H, s), 6.16 (1H, s), 5.72 (1H, d, *J* = 8.8 Hz), 5.43 (1H, d, *J* = 8.8 Hz), 2.35 (3H, s), 2.18 (3H, s); DAICEL CHIRALPAK AD-H column, detection at 254 nm, Hex/*i*-PrOH = 4/1, flow rate 0.7 mL/min., 21.8 min (minor isomer, *S*) and 23.5 min (major isomer, *R*).

4n (R^1 = Et, R^2 = 4-NO_2-C_6H_4-) 73%, 98% ee; ^{1}H-NMR ($CDCl_3$) : δ 8.07 (2H, d, *J* = 8.8 Hz), 7.64 (2H, d, *J* = 8.0 Hz), 7.35 (2H, d, *J* = 8.8 Hz), 7.24 (2H, d, *J* = 8.0 Hz), 6.12 (1H, s), 6.03 (1H, s), 5.88 (1H, d, *J* = 8.8 Hz), 5.31 (1H, d, *J* = 8.8 Hz), 2.50 (2H, q, *J* = 7.2 Hz), 2.41 (3H, s), 0.94 (3H, t, *J* = 7.2 Hz); DAICEL CHIRALPAK AD-H column, detection at 254 nm, Hex/*i*-PrOH = 4/1, flow rate

0.7 mL/min. , 41.3 min (major isomer, *S*) and 46.1 min (minor isomer, *R*).

References

1) J.-H. Xie, L.-X. Wang, Y. Fu, S.-F. Zhu, B.-M. Fan, H.-F. Duan and Q.-L. Zhou, *J. Am. Chem. Soc.* **2003**, *125*, 4404.

2) (a) M. Shi and Y.-M. Xu, *Angew. Chem. Int. Ed.* **2002**, *41*, 4507; (b) M. Shi and L.-H. Chen, *Chem. Commun.* **2003**, 1310; (c) Y.-M. Xu and M. Shi, *J. Org. Chem.* **2004**, *69*, 417.

3) (*a*) K. Matsui, S. Takizawa and H. Sasai, *J. Am. Chem. Soc.* **2005**, *127*, 3680; (*b*) K. Matsui, K. Tanaka, A. Horii, S. Takizawa and H. Sasai, *Tetrahedron*: *Asymmetry* **2006**, *17*, 578.