Supporting Information for:

Sequential Enantiodivergent Organocatalysis: Reversibility in Enantioswitching Controlled by Conformationally Flexible Guanidine/Bisthiourea Organocatalyst

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1. Instrumentation

Flash chromatography was performed using silica gel 60 (spherical, particle size 0.040-0.100 mm; Kanto Co., Inc., Japan). Optical rotations were measured on a JASCO P-2200 polarimeter. ^{1}H and ^{13}C NMR spectra were recorded on JEOL EX300 and ECA/ECX400 instruments. Chemical shifts in chloroform-*d*, were reported in the scale relative to chloroform-*d* (7.26 ppm), for ^{1}H NMR respectively. For ^{13}C NMR, chemical shifts were reported in the scale relative to chloroform-*d* (77.0 ppm) as an internal reference. Mass spectra were recorded on JEOL JMS-T100LC and JEOL JMA-HX110 spectrometer.

2. Relationships between the *ee* of (*S*,*S*)-1 and that of 4aa

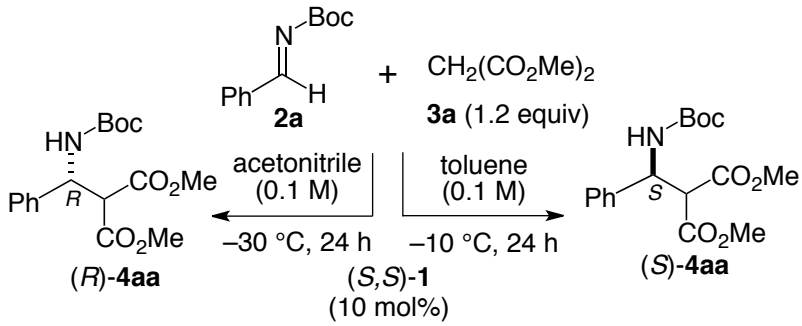


Table S-1 [a]

entry	*ee* of (*S*,*S*)-**1**(%)	(*S*)-**4aa** (%)[b]
1	100	88
2	80	73
3	60	58
4	40	32
5	20	16

Table S-2 [a]

entry	*ee* of (*S*,*S*)-**1**(%)	(*S*)-**4aa** (%)[b]
1	100	90
2	80	75
3	60	53
4	40	38
5	20	22

[a] Reactions were carried out on a 0.1 mmol scale in 1.0 mL of the solvent. [b] Determined by chiral HPLC analysis.[1]

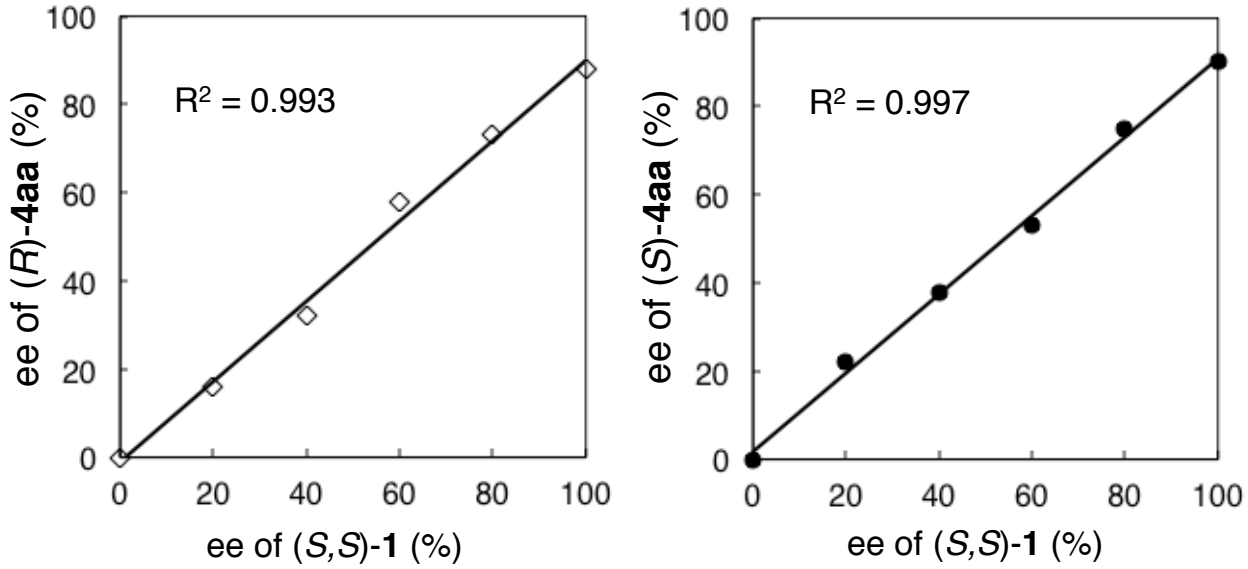
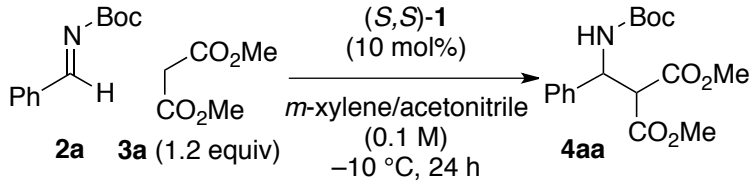


Figure S-1.

3. Relationships between ee of 4aa and *m*-xylene/acetonitrile content



2a **3a** (1.2 equiv) **4aa**

Table S-3 [a]

entry	acetonitrile content (%)	*ee* of (*R*)-**5a** (%)[b] run 1	run 2	run 3	average	SD
1	0	89	90	89	89	0.5
2	10	83	81	79	81	2
3	20	48	46	44	46	2
4	50	–24	–24	–20	–23	2.3
5	80	–61	–60	–61	–61	0.6
6	90	–67	–70	–73	–70	3.0
7	100	–79	–78	–79	–79	0.6

[a] Reactions were carried out on a 0.1 mmol scale in 1.0 mL of the solvent. [b] Determined by chiral HPLC analysis.[1]

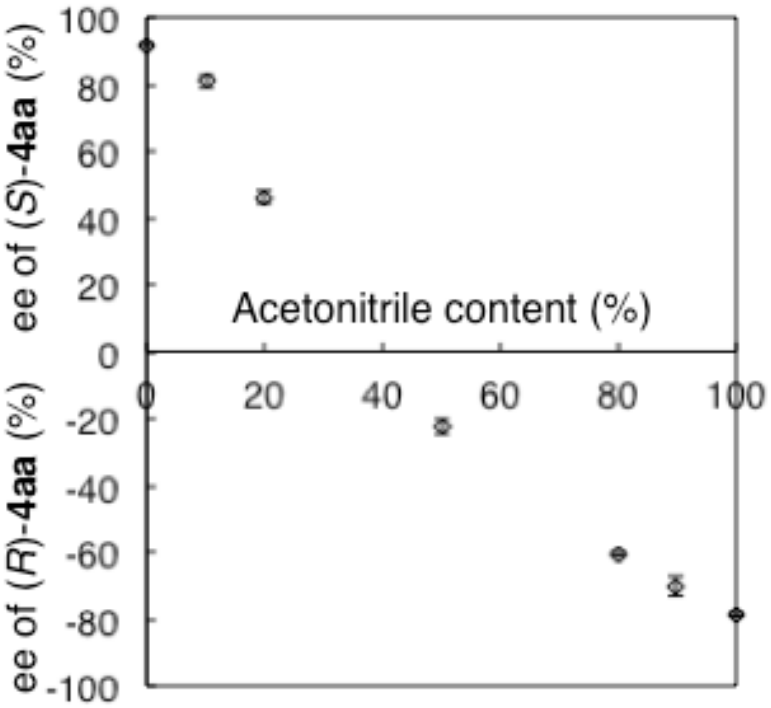
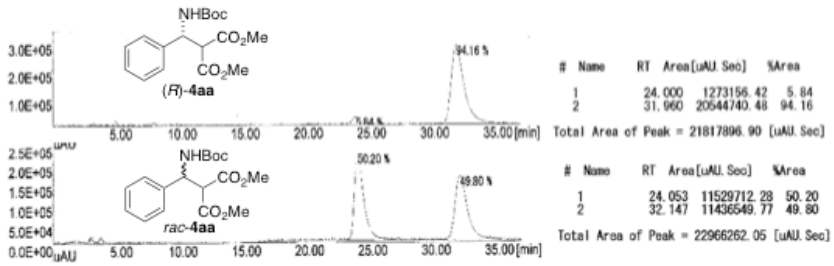


Figure S-2.

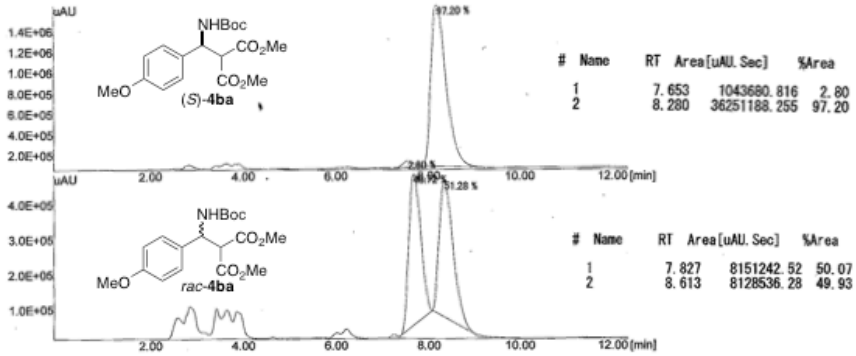
4. Copies of HPLC chart of (*R*)-4aa[1,2] and (*S*)-4ba[1] in the sequential enantiodivergent reactions.

4.1. Protocol a)

4aa

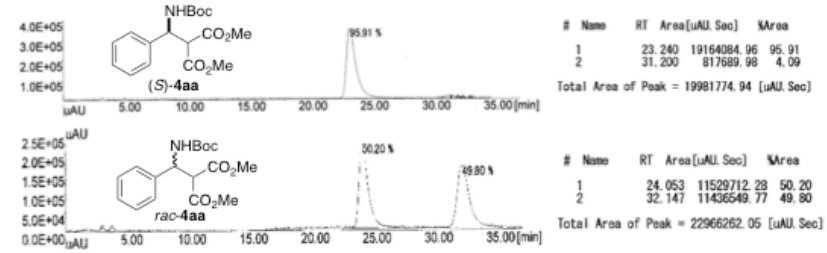


4ba

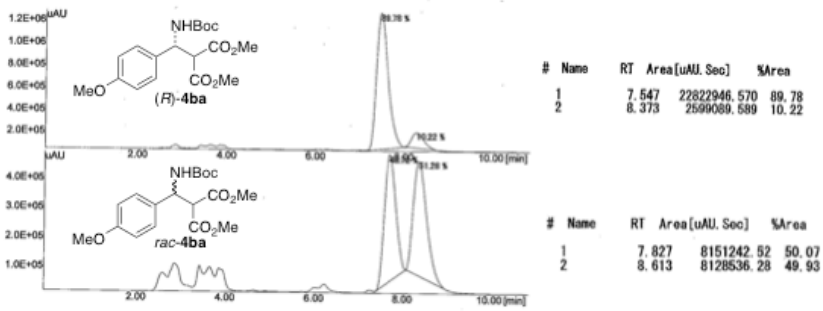


4.2. Protocol b)

4aa

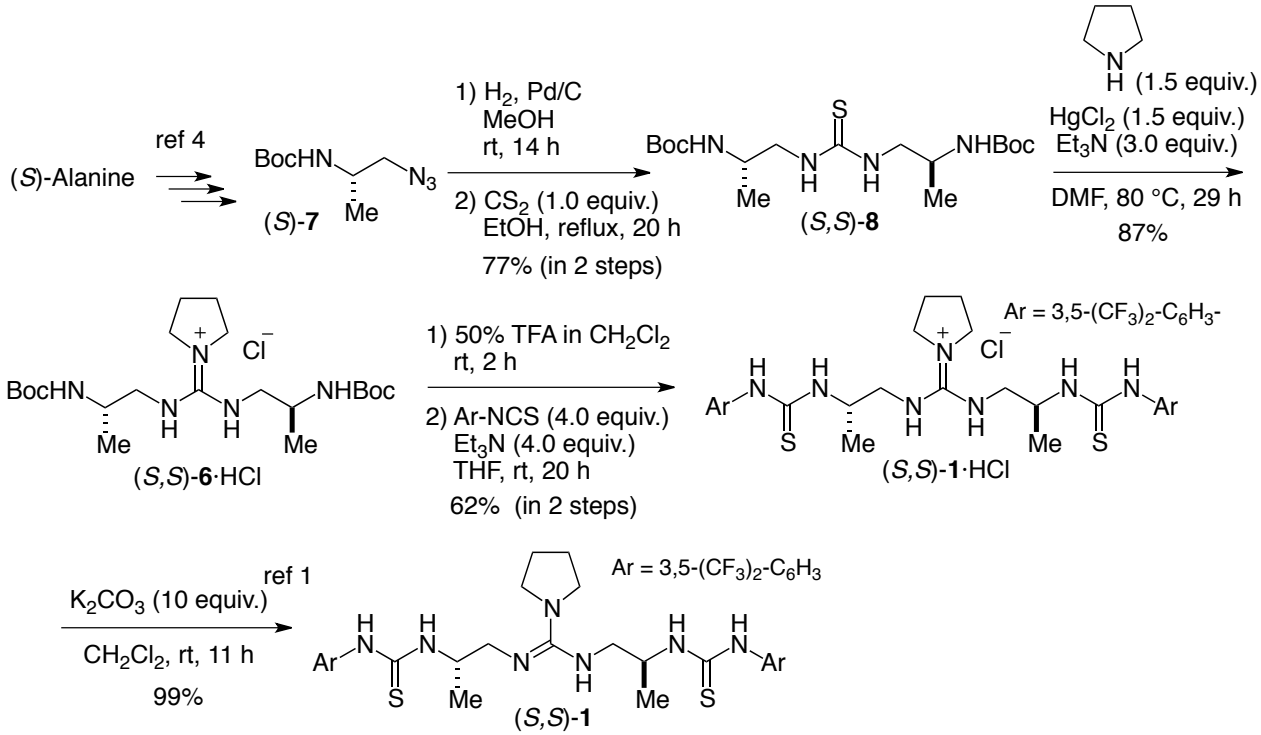


4ba



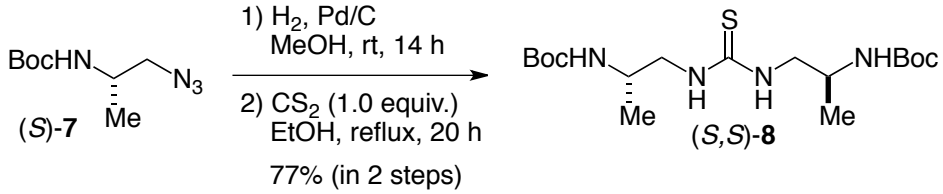
5. Synthesis of (*S*,*S*)-1

(*S*,*S*)-**1** was synthesized according to the previously developed synthetic procedure,[3] as shown in Scheme S-1.

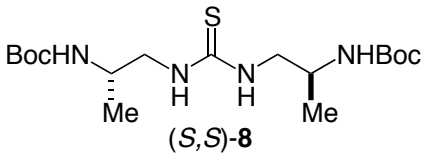


Scheme S-1. Synthesis of (*S*,*S*)-**1**

Typical procedure for preparation of (*S*,*S*)-8

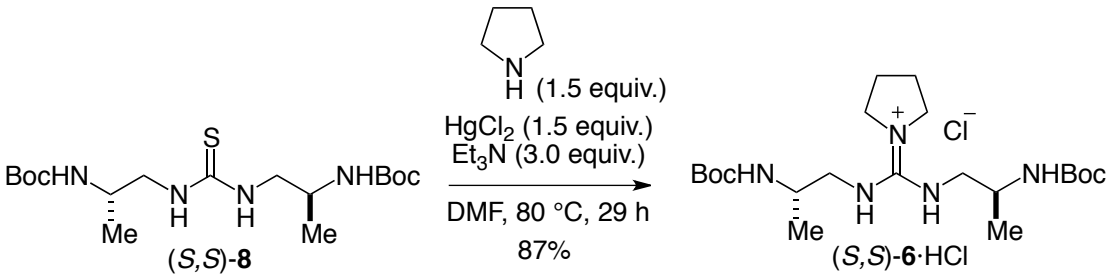


A mixture of azide (*S*)-**7** (7.88 g, 39.4 mmol)[4] and Pd/C (10%, 80.0 mg) in MeOH (80 mL) was stirred under 1 atm of hydrogen at room temperature for 14 h. The mixture was filtrated through a pad of Celite, and the filtrate was concentrated under reduced pressure. To a solution of the resulting amine in EtOH (150 mL) was added CS_2 (2.3 mL, 39.4 mmol) at room temperature, and the resulting mixture was heated to reflux and stirred for 20 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (Hexane/EtOAc, 1:2) to give thiourea (*S*,*S*)-**8** (5.91 g, 77% in 2steps)

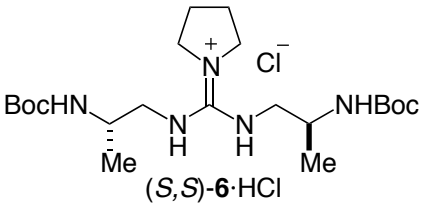


$[\alpha]_D^{23} = -8.0°$ (*c* 1.5, CH_3OH). IR (neat) 3310, 2977, 2929, 1692, 1516, 1454, 1391, 1366, 1251, 1169 cm^{-1}. ^1H NMR (500 MHz, CD_3OD) δ 3.90-3.44 (br, 6H), 1.43 (s, 18H), 1.12 (d, J = 6.4 Hz, 6H). ^{13}C NMR (125 MHz, CD_3OD) δ 183.8, 158.2, 79.5, 50.3 (br), 47.8 (br), 29.0, 18.7. HRMS (FAB, M+H) calcd for $C_{17}H_{35}N_4O_4S$ 391.2379, found 391.2359.

Typical procedure for preparation of (*S*,*S*)-6·HCl

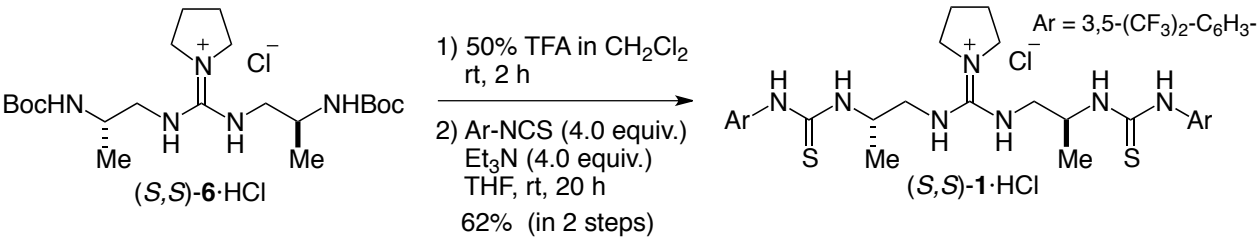


To a mixture of (*S*,*S*)-**8** (2.00 g, 5.12 mmol), pyrrolidine (0.64 mL, 7.68 mmol) and triethylamine (2.16 mL, 15.4 mmol) in DMF (15 mL) was added $HgCl_2$ (2.09 g, 7.68 mmol) at room temperature, and the resulting mixture was stirred for 29 h at 80 °C. The resulting mixture was diluted with EtOAc, and filtered though a pad of Celite. The filtrate was poured into water. The aqueous layer was extracted with EtOAc (x 3) and the combined organic layer was washed with brine (x 3). The organic layer was dried over $MgSO_4$. After removing the solvent under reduced pressure, the residue was purified by flash column chromatography (chloroform/methanol, 25:1 to 5:1) to give (*S*,*S*)-**6**·HCl (2.06 g, 87%)

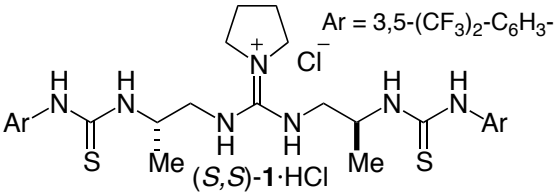


$[\alpha]_D^{14} = -5.0$ (*c* 1.6, CH_3OH). ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (br s, 2H), 5.57 (br s, 2H), 3.75 (br, 2H), 3.49 (br, 4H), 3.30, (br, 4H), 1.89 (br, 1H), 1.82 (br, 1H), 1.30 (s, 18H), 1.15 (d, J = 4.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 156.0, 79.3, 77.2, 49.4, 46.3, 28.1, 25.1, 18.2. HRMS (ESI, M-Cl) calcd for $C_{21}H_{42}N_5O_4$ 428.3237, found 428.3224.

Typical procedure for preparation of (*S*,*S*)-1·HCl

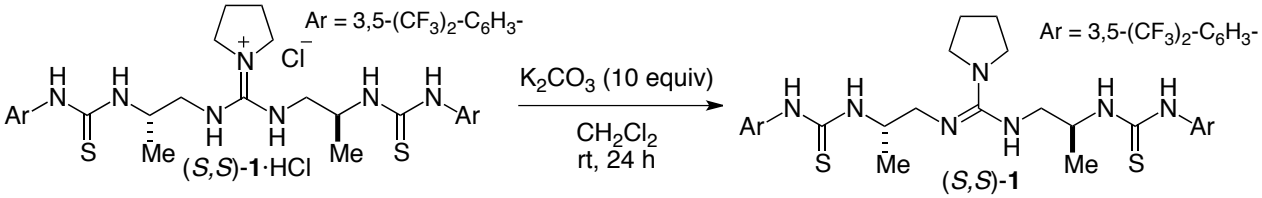


To a solution of (*S*,*S*)-**6**·HCl (315 mg, 0.679 mmol) in CH_2Cl_2 (5.0 mL) was added TFA (2.5 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2 h, and the resulting mixture was concentrated under reduced pressure to give the corresponding diamine. To a solution of diamine and triethylamine (0.38 mL, 2.72 mmol) in THF (10 mL) was added 3,5-bis(trifluoromethyl)phenyl isothiocyanate (0.49 mL, 2.72 mmol) and the mixture was stirred at room temperature for 20 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH, 100/1 to 50:1) to give the bisthiourea. The counter anion of the catalyst was exchanged into chloride by treatment with saturated NH_4Claq of EtOAc solution of (*S*,*S*)-**1**·HCl (339 mg, 62% in 2 steps).

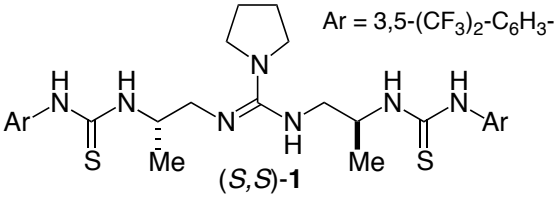


$[\alpha]_D^{25} = -166.7$ (*c* 1.9, $CHCl_3$). ^1H NMR (400 MHz, CD_3OD) δ 8.22 (s, 4H), 7.62 (s, 2H), 4.86 (br, 2H), 3.53-3.42 (m, 8H), 1.97 (m, 4H), 1.28 (d, J = 6.9 Hz, 6H). ^{13}C NMR (100 MHz, CD_3OD) δ 182.8, 157.7, 142.9, 132.6 (q, J_{CF} = 32.5 Hz), 129.3, 128.7, 124.7 (d, J_{CF} = 271.3 Hz), 123.8 (br), 120.6, 119.0, 118.0 (br), 50.7, 50.4, 26.4, 18.0. HRMS (ESI, M-Cl) calcd for $C_{29}H_{32}F_{12}N_7S_2$ 770.1969, found 770.1945.

Typical procedure for preparation of (*S*,*S*)-1[1]

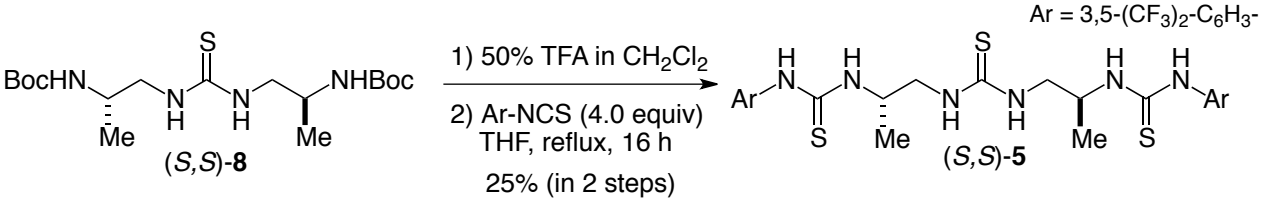


To a solution of (*S*,*S*)-**1a**·HCl (71.0 mg, 0.0881 mmol) in CH_2Cl_2 (2.0 mL) was added K_2CO_3 (122 mg, 0.881 mmol) and stirred vigorously at room temperature for 11 h. The resulting mixture was diluted with CH_2Cl_2, and filtered though a pad of Celite. The filtrates were concentrated *in vacuo* to give (*S*,*S*)-**1** (67.8 mg, 99%). The catalyst was used for the asymmetric reaction without further purification, and was stored under air at room temperature.

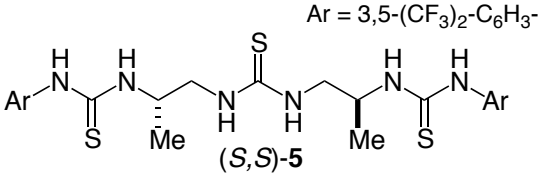


$[\alpha]_D^{22} = -154.1$ (*c* 0.67, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (br s, 4H), 7.39 (br s, 2H), 5.01 (br s, 2H), 3.60-2.90 (br, 8H), 1.88 (br s, 4H), 1.30-1.00 (br s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.6, 156.1, 141.3, 131.1 (J_{CF} = 32.6 Hz), 123.2 (J_{CF} = 272.2 Hz), 122.3, 116.9, 51.5, 49.9, 48.5, 25.2, 17.9. HRMS (ESI, M+H) calcd for $C_{29}H_{32}F_{12}N_7S_2$ 770.1969, found 770.1964.

6. Synthesis of (*S*,*S*)-5



To a solution of (*S*,*S*)-**8** (300 mg, 0.76 mmol) in CH_2Cl_2 (5.0 mL) was added TFA (2.5 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 h, and the resulting mixture was concentrated under reduced pressure to give diamine. To a solution of diamine in THF (8 mL) was added 3,5-bis(trifluoromethyl)phenyl isothiocyanate (0.56 mL, 3.04 mmol) and the mixture was stirred under reflux for 16 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH, 50/1) to give the (*S*,*S*)-**5** (140 mg, 25% in 2 steps)



$[\alpha]_D^{14} = -28.7$ (*c* 1.1, CH_3OH). ^{1}H NMR (300 MHz, CD_3OD) δ 8.12 (s, 4H), 7.57 (s, 2H), 4.52 (br, 2H), 3.84 (br, 4H), 1.25 (d, *J* = 5.6 Hz, 6H). ^{13}C NMR (100 MHz, CD_3OD) δ 182.3, 142.8, 132.5 (J_{CF} = 33.6 Hz), 127.6 (J_{CF} = 273.3 Hz), 123.8, 121.4, 119.1, 117.9, 58.3, 18.3. HRMS (ESI, M+Na) calcd for $C_{25}H_{24}F_{12}N_6Na_1S_3$ 755.0931, found 755.0946.

7. References

1) Y. Sohtome, S. Tanaka, K. Takada, T. Yamaguchi and K. Nagasawa, *Angew. Chem. Int. Ed.*, 2010, **49**, 9254.

2) A. L. Tillman, J. Ye and D. J. Dixon, *Chem. Commun.* 2006, 1191.

3) Y. Sohtome, Y. Hashimoto, K. Nagasawa, *Adv. Synth. Catal.* 2005, **347**, 1643.

4) A recent example, see: A. K. Medda, C. M. Park, A. Jeon, H. Kim, J.-H. Sohn, H.-S. Lee, *Org. Lett.* 2011, **13**, 3486.