The Practical Synthesis of Double Axial Chiral Guanidines

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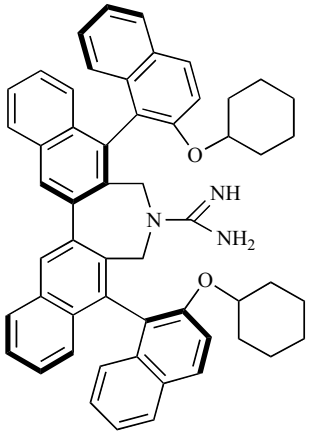
Abstract: Two novel double axial chiral guanidines were designed according to the concept of double axial chirality. The practical synthetic procedures from (*S*)-1,1'-binaphthol have been developed. The title compounds were fully characterized by NMR, MS, IR and elemental analysis or HRMS. The two chiral guanidines can be interesting catalysts for asymmetric catalysis and preliminary asymmetric catalytic activity was investigated in Henry reaction and conjugate addition.

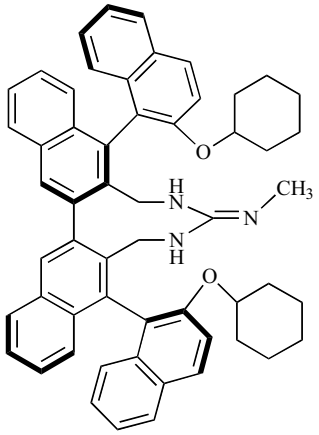
Keywords: Guanidine, chiral catalyst, organic base, synthesis.

As strong organic base catalysts, chiral guanidines have been used for many enantioselective transformations such as epoxidation [1], Michael addition reaction [2], silylation of secondary alcohols [3], Strecker reaction [4], Henry reaction [5] and Diels-Alder reaction [6]. Recently, highly efficient axial chiral guanidine catalysts were reported by Terada and co-workers [7]. The development of new chiral guanidines with novel backbones and the expansion of their application lysis. We assumed that if the substitutents at 3,3'-positions of BINOL possess a stable double axial chirality, better performance in organocatalysis may be achieved [8]. The target guanidines (*S*,*S*)-**1** and (*S*,*S*)-**2** have a larger chiral pocket than the former developed chiral guanidine catalysts [7].

The practical synthetic routes to chiral guanidines (*S,S*)-**1** and (*S,S*)-**2** were outlined in Scheme **1** and Scheme **2**, respectively. (*S*,*S*)-2,2'''-dicyclohexyloxy-1,1':3',3'':1'',1'''-



(*S,S*)-**1**



(*S,S*)-**2**

Fig. (1). New double axially chiral guanidines.

to other useful asymmetric organic transformations are still a great challenge for chemists. In this paper, the design, and synthesis of novel double axially chiral guanidines (*S*,*S*)-**1** and (*S*,*S*)-**2** (Fig. **1**) were reported.

The rationale for our design of novel chiral guanidine catalysts originated from the observation that the substitutents at 3,3'-positions of BINOL are very important in controlling the enantioselectivity in asymmetric organocata-

quaternaphthalene-2',2''-diol (*S,S*)-**3**, prepared from (*S*)-BINOL according to our previous procedure [8], reacted with Tf_2O in CH_2Cl_2 to afford its ditriflate, which was not purified and directly reacted with MeMgBr in Et_2O by the catalysis of $(Et_3P)_2NiCl_2$ to provide (*S*,*S*)-2,2'''-dicyclohexyloxy-2',2''-dimethyl-1,1':3',3'':1'',1'''-quaternaphthalene (*S,S*)-**4** in 87% yield for two steps. We also attempted $NiCl_2$(dppp) or $NiCl_2(PPh_3)_2$ as catalyst in this reaction, but none of the desired coupled product was obtained. (*S*,*S*)-2',2''-dibromomethyl-2,2'''- dicyclohexyloxy-1,1':3',3'':1'',1'''-quaternaphthalene (*S,S*)-**5** was then prepared in 78% yield by bromination of (*S,S*)-**4** with *N*-bromosuccinimide

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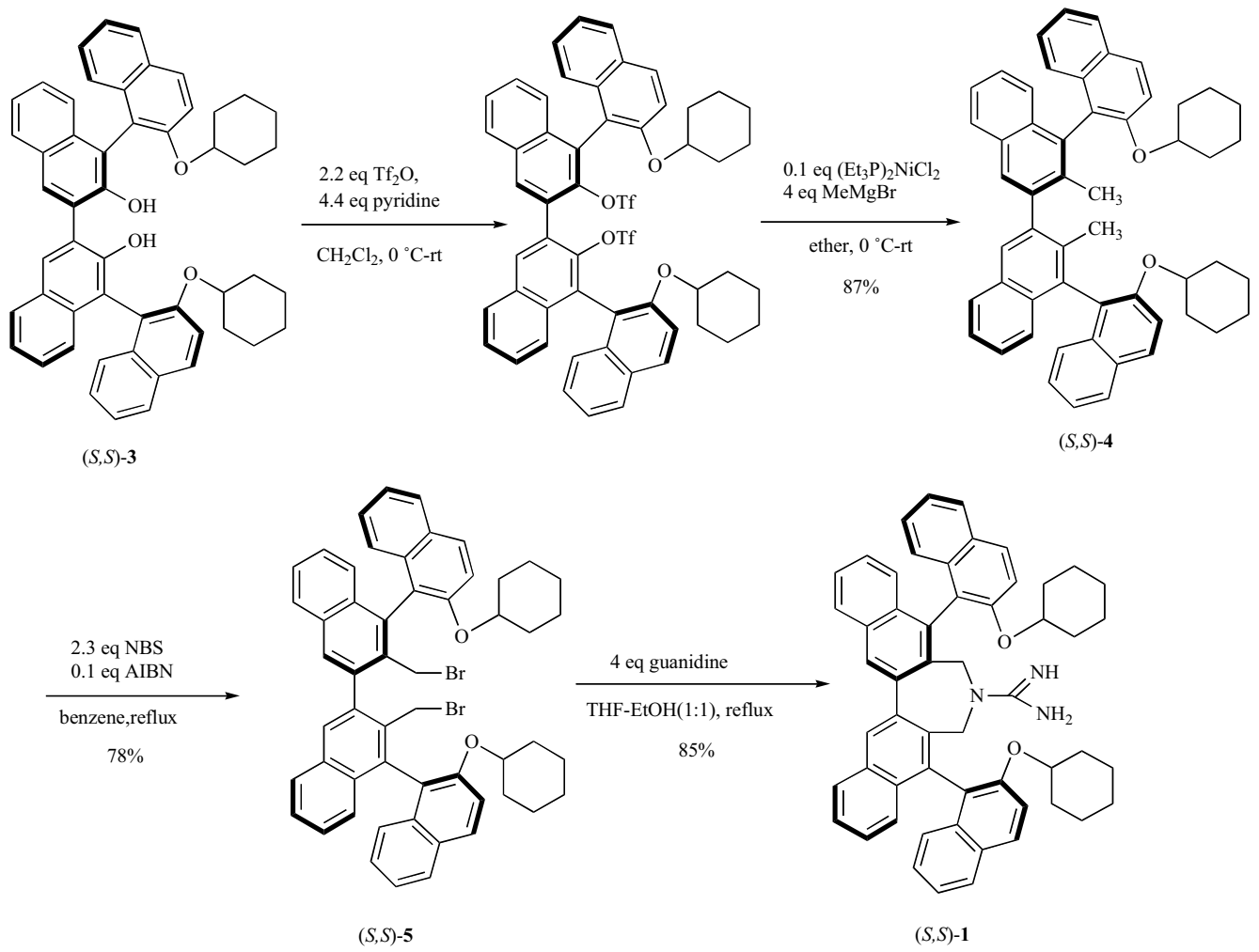


Scheme 1. The synthesis of double axial chiral guanidine (*S*,*S*)-**1**.

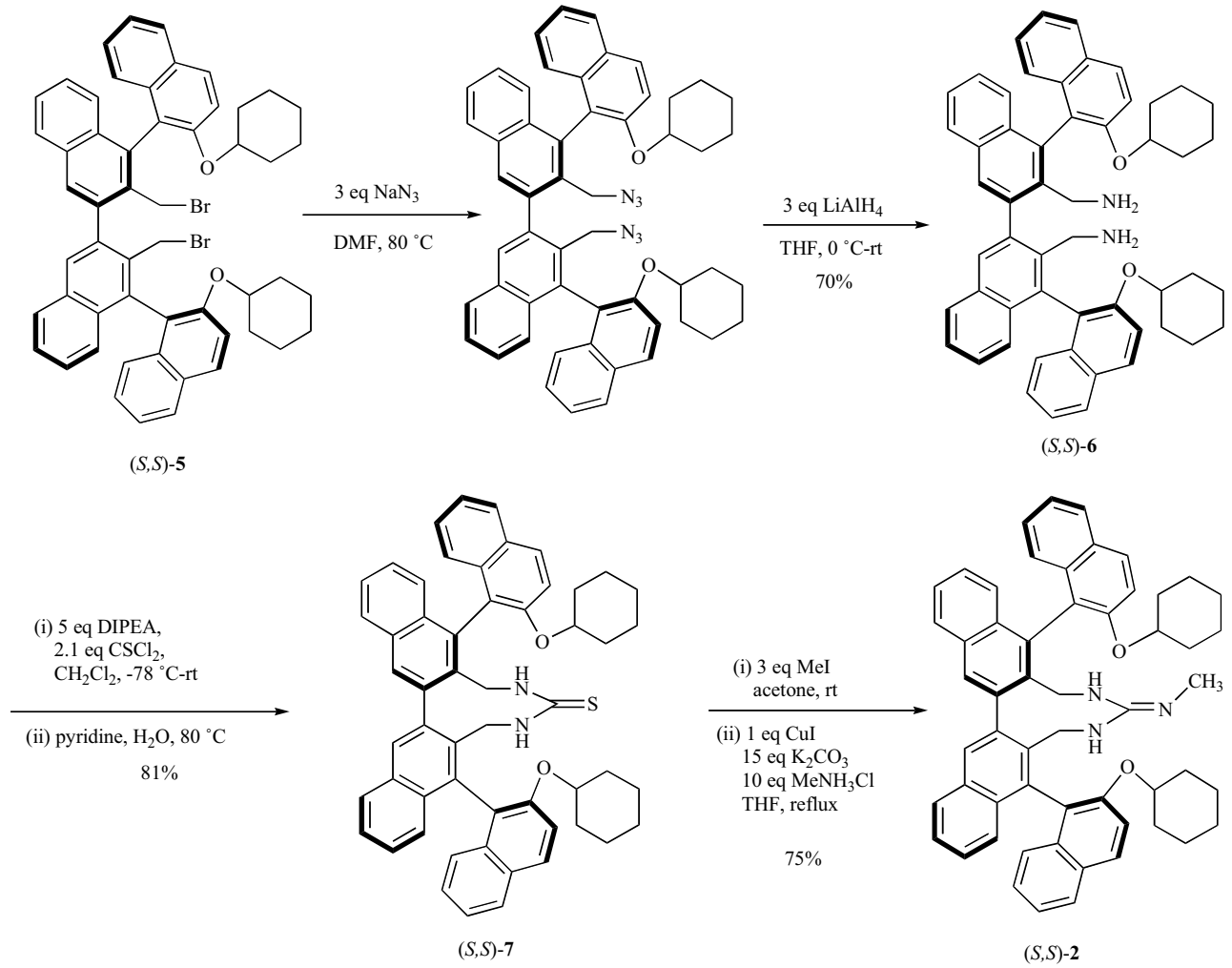
(NBS) in benzene. Finally, the compound (*S,S*)-**5** reacted with free guanidine in THF-EtOH to afford the new double axially chiral guanidine catalyst (*S*,*S*)-**1** in 85% yield.

Compound (*S,S*)-**5** reacted with NaN_3 in DMF to afford (*S*,*S*)-2',2''-diazidomethyl-2,2'''-dicyclohexyloxy-1,1':3',3'': 1'',1'''-quaternaphthalene, which was treated with $LiAlH_4$ in THF to produce (*S*,*S*)-2',2''-diaminomethyl-2,2'''-dicyclohexyloxy-1,1':3',3'':1'',1'''-quaternaphthalene (*S,S*)-**6** in 70% yield for two steps. (*S,S*)-**6** reacted with $CSCl_2$ in the presence of diisopropylethylamine in CH_2Cl_2 to afford (*S*,*S*)-2,2'''-dicyclohexyloxy-2',2''-diisothiocyanatomethyl- 1,1': 3',3'':1'',1'''-quaternaphthalene, which was treated with H_2O in pyridine at 80 °C to give the thiourea (*S,S*)-**7** in 81% yield [7a]. A CuI-catalyzed cross-coupling reaction of (*S,S*)-**7** with $MeNH_3Cl$ in the presence of K_2CO_3 provided chiral guanidine (*S,S*)-**2** in 75% yield.

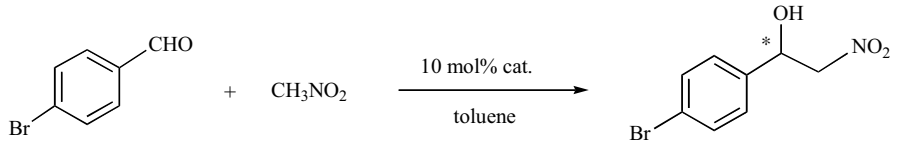
With these new guanidines in hand, the asymmetric catalytic activity in a series of organic reactions was investigated. We initially studied the Henry reaction [9] of *p*-bromobenzaldehyde with nitromethane by the catalysis of 10 mol % of new guanidines **1** or **2** in toluene at room temperature. These guanidines can catalyze the Henry reaction efficiently and the corresponding Henry reaction product was obtained in 100% and 97% yield, respectively. But the enantioselectivity is low, only 7% ee was obtained with guanidine **2** as catalyst. No improvement in results was obtained during the optimization of reaction conditions such as with lower temperature and change solvents.

The asymmetric conjugate addition of naphthoquinone to nitroalkenes is another important reaction because it produces chiral nitroalkylated compounds, which are precursors of a variety of other functionalized bioactive compounds [10]. We then investigated the addition reaction of 2-hydroxynaphthoquinone to nitrostyrene catalyzed by 10 mol % of new guanidines **1** or **2** in toluene at room temperature. The guanidines can catalyze the conjugate addition reaction efficiently and the corresponding product was obtained in 98% and 97% yield, respectively. But the enantioselectivity is low, only 10% ee was obtained with guanidine **2** as catalyst under optimized conditions. Currently, we do not know why the results obtained with each of the two catalysts so different.

In summary, a practical method for the preparation of sterically hindered double axially chiral guanidines (*S,S*)-**1** and (*S,S*)-**2** has been developed. In the first step, $(Et_3P)_2NiCl_2$ was first used by us to catalyze the cross-coupling reaction between the ditriflate of (*S,S*)-**3** and MeMgBr. Guanidines (*S*,*S*)-**1** and (*S*,*S*)-**2** have a larger chiral

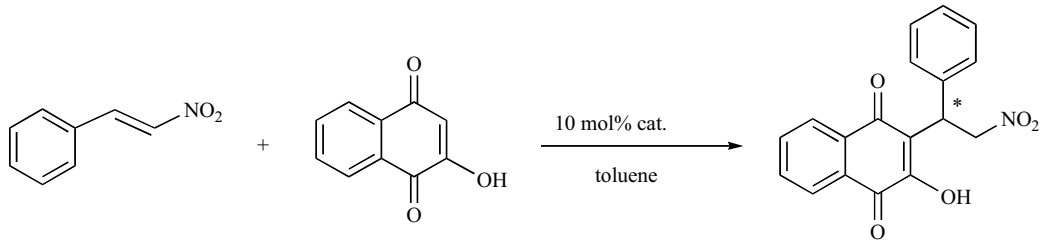


Scheme 2. The synthesis of double axial chiral guanidine (*S*,*S*)-**2**.



cat. **1**: >99% yield, 0% ee
2: 97% yield, 7% ee

Scheme 3. Asymmetric Henry reaction.



cat. **1**: 98% yield, 0% ee
2: 97% yield, 10% ee

Scheme 4. Asymmetric conjugate addition.

pocket than the formerly developed chiral guanidine catalysts, and have potential as good organocatalysts. The preliminary results in asymmetric reaction demonstrate their high catalytic reactivity as strong brønsted base although with low enantioselectivity. We are currently seeking to investigate the application of the two chiral guanidines in other asymmetric catalysis in our group.

EXPERIMENTAL

All air- and moisture-sensitive manipulations were carried out with standard Schlenk techniques under nitrogen or under argon. Unless otherwise indicated, all commercially available compounds were used without further purification. THF was either distilled over benzophenone ketyl under nitrogen or purified by passing through a neutral alumina column under nitrogen. Et_2O was purified by passing through a neutral alumina column under nitrogen. CH_2Cl_2 was distilled over CaH_2 under nitrogen. DMF was distilled over CaH_2 under vacuum. Melting points were measured on an XT-4 melting point apparatus and uncorrected. The ^1H NMR spectra were recorded on Varian Mercury Plus (200 MHz). ^{13}C NMR spectra were recorded on Varian Mercury Plus spectrometer (50 MHz). Infrared spectra were obtained on a Nicolet AVATAR 330 FT-IR spectrometer. Mass spectra were obtained on a VGZAB-HS mass spectrometer, a Thermo Finnigan LCQ Decaxp PLUS LC/MS spectrometer (ESI) and a Bruker Apex IV FTMS spectrometer. Elemental analyses were carried out on an Elementar VARIO EL instrument. Optical rotations were measured on a Perkin-Elmer 341 LC spectrometer.

Synthesis of (*S*,*S*)-2,2'''-Dicyclohexyloxy-2',2''-dimethyl-1,1':3',3'':1'',1'''- quaternaphthalene [(*S*,*S*)-4]

To a solution of (*S*,*S*)-2,2'''-dicyclohexyloxy-1,1':3',3'': 1'',1'''- quarternaphthalene-2',2''-diol (10.29 g, 14 mmol) and pyridine (5.0 mL, 62 mmol) in CH_2Cl_2 (100 mL) was added Tf_2O (5.87 mL, 31.3 mmol) dropwise at 0 °C. The solution was allowed to warm to room temperature and stirred overnight. Evaporation of the solvents and the residue was redissolved in AcOEt (150 mL) and washed with 1 N HCl (50 mL), saturated $NaHCO_3$ solution (50 mL) and saturated brine (30 mL). The organic phase were dried over Na_2SO_4 and concentrated to give the crude bis-trifluoromethanesulfonic acid ester, which was directly used for the following reaction without any further purification.

To a solution of the crude bis-trifluoromethanesulfonic acid ester and $(Et_3P)_2NiCl_2$ (0.512 g, 1.4 mmol) in Et_2O (200 mL) was slowly added MeMgBr (3.0 M in Et_2O, 19 mL, 57 mmol) at 0 °C. The solution was allowed to warm to room temperature and stirred for 100 h. The reaction was quenched by 2 N HCl (30 mL), the whole mixture was filtered to remove the catalyst. The filtrate was extracted with AcOEt (2 × 100 mL). The organic extracts were washed with saturated brine (100 mL) and dried over Na_2SO_4. Evaporation of solvents and purification of the residue by column chromatography on silica gel with PE(60-90 °C)-AcOEt-DCM (50:1:4) as eluent to afford the product (*S,S*)-**4** (8.9 g, 87% yield) as colorless solid. m.p.123-126 ℃. $[\alpha]_D^{25}$ = -85.9 (*c* 1.0, $CHCl_3$). IR (FT-IR, film): 3055, 2932, 2857, 1620, 1591, 1508, 1466, 1328, 1264, 1235, 1146, 809, 747 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.82-1.65 (m, 20H), 1.92 (s, 6H), 4.08-4.25 (m, 2H), 7.13-7.43 (m, 14H), 7.81-7.95 (m, 8H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 17.7, 22.8, 23.0, 25.2, 31.6, 32.0, 75.9, 117.2, 123.7, 124.3, 125.0, 125.39, 125.45, 126.2, 126.4, 127.6, 127.7, 127.9, 128.9, 129.2, 132.0, 132.7, 133.3, 134.0, 134.6, 141.3, 153.0. HRMS (ESI): *m/z* calcd for $C_{54}H_{51}O_2$ ($[M+H]^+$) 731.3889. Found 731.3884. Anal. calcd for $C_{54}H_{50}O_2$: C, 88.73; H, 6.89; found: C, 88.63; H, 7.44.

Synthesis of (*S*,*S*)- 2',2''-dibromomethyl-2,2'''-dicyclohexyloxy-1,1':3',3'':1'',1'''- quaternaphthalene [(*S*,*S*)-5]

To a solution of (*S*,*S*)-2',2''-dimethyl-2,2'''-dicyclohexyloxy-1,1':3',3'':1'',1'''- quaternaphthalene (2.19 g, 3.0 mmol) in benzene (20 mL) was added N-bromosuccinimide (NBS) (1.26 g, 7.0 mmol) and 2,2'-azobis(isobutyronitrile) (AIBN) (0.05 g, 0.3 mmol). The mixture was heated and refluxed for 8 h. After being cooled to room temperature, the mixture was washed with water (20 mL) and dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography with PE(60-90 °C)-AcOEt-DCM (10:1:2) as eluent to give the product (*S,S*)-**5** (2.1 g, 78% yield) as colorless solid. m.p. 135 °C (decomp.). $[\alpha]_D^{25}$ = -123.1 (*c* 1.0, $CHCl_3$). IR (FT-IR, film): 3056, 2933, 2856, 1621, 1590, 1507, 1465, 1330, 1264, 1236, 1146, 810, 736 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.80-1.79 (m, 20H), 4.20 (d, *J* = 6.4 Hz, 2H), 4.21 (br, 2H), 4.37 (d, *J* = 6.4 Hz, 2H), 7.05-7.50 (m, 14H), 7.86 -8.03 (m, 6H), 8.18 (s, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.1, 23.5, 25.2, 31.3, 31.6, 32.3, 76.4, 116.4, 122.0, 123.8, 126.1, 126.2, 126.5, 126.8, 127.6, 128.1, 129.0, 129.8, 130.3, 132.8, 133.0, 133.3, 134.1, 135.7, 137.7, 152.6. HRMS (ESI): *m/z* calcd for $C_{54}H_{48}Br_2O_2$ ($[M]^+$) 886.2021. found 886.2016. Anal. calcd for $C_{54}H_{48}Br_2O_2$: C, 72.98; H, 5.44; found: C, 72.57; H, 6.08.

Synthesis of Chiral Guanidine [(*S*,*S*)-1]

To a solution of (*S*,*S*)-2',2''-dibromomethyl-2,2'''-dicyclohexyloxy-1,1':3',3'':1'',1'''- quaternaphthalene (600 mg, 0.67 mmol) in THF-EtOH(1:1) (20 mL) was added free guanidine (159 mg, 2.7 mmol). The mixture was refluxed for 10 h and cooled to room temperature. The reaction was quenched by 1 N HCl (30 mL) and extracted with CH_2Cl_2 (50 mL), The extracts were washed with 2N KOH solution (30 mL), saturated brine (20 mL) and dried over anhydrous Na_2SO_4. Evaporation of solvents gave the chiral guanidine product (*S,S*)-**1** (450 mg, 85% yield) as pale yellow solid. m.p. 231-235 °C (decomp.). $[\alpha]_D^{25}$ = -79.6 (*c* 1.0, $CHCl_3$). IR (FT-IR, film): 3056, 2931, 2855, 2357, 1621, 1591, 1466, 1446, 1330, 1264, 1236, 810, 735 cm^{-1}. ^1H NMR (200 MHz, DMSO): δ 0.87-1.73 (m, 20H), 3.58-3.85 (m, 2H), 4.22 (br, 2H), 4.36 (br, 2H), 6.12 (br, 2H), 6.76-7.69 (m, 14H), 7.96-8.33 (m, 6H), 8.50 (s, 2H). ^{13}C NMR (50 MHz, DMSO): δ 28.8, 30.7, 31.1, 32.6, 33.7, 34.5, 74.7, 111.4, 114.3, 116.2, 120.6, 126.2, 127.0, 127.8, 128.7, 129.3, 129.9, 130.9, 131.6, 133.0, 135.5, 138.2, 142.1, 143.4, 144.8, 151.1, 155.7. HRMS (ESI): *m/z* calcd for $C_{55}H_{52}N_3O_2$ ($[M+H]^+$) 786.4060; found 786.4054.

Synthesis of (*S,S*)-2',2''-diaminomethyl-2,2'''-dicyclohexyloxy-1,1':3',3'':1'',1'''- quaternaphthalene [(*S,S*)-6]

A mixture of (*S*,*S*)-2',2''-dibromomethyl-2,2'''-dicyclohexyloxy-1,1':3',3'':1'',1'''- quaternaphthalene (620 mg, 0.7 mmol) and NaN_3 (135 mg, 2.1 mmol) in DMF (15 mL) was stirred at 80 °C for 10 h. The reaction mixture was cooled to room temperature and diluted with water (30 mL) and extracted with AcOEt (60 mL). The organic extracts were dried over anhydrous Na_2SO_4 and concentrated. The crude diazide obtained was used for subsequent reaction without further purification.

To a suspension of $LiAlH_4$ (80 mg, 2.1 mmol) in THF (20 mL) was added the solution of the above crude diazide in THF (20 mL) at 0 °C. The reaction mixture was gradually warmed to room temperature and stirred for 14 h. The reaction was quenched with water (2 mL) and Na_2SO_4 (10 g) was added. The mixture was filtered through a pad of Celite and the filtrate was concentrated. Evaporation of solvents gave the diamine product (*S*,*S*)- 2',2''-diaminomethyl-2,2'''-dicyclohexyloxy-1,1':3',3'':1'',1'''-quaternaphthalene (*S,S*)-**6** (370 mg, 70% yield) as yellow oil. $[\alpha]_D^{25} = -132.6$ (*c* 1.0, $CHCl_3$). IR (FT-IR, film): 3058, 2932, 2856, 1620, 1591, 1508, 1465, 1330, 1264, 1235, 1146, 809, 749 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.78–1.78 (m, 20H), 2.79 (s, 1H), 2.84 (s, 1H), 3.27–3.59 (m, 4H), 4.12-4.29 (m, 2H), 6.97–7.40 (m, 14H), 7.72–7.94 (m, 8H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.1, 23.4, 25.1, 29.6, 31.5, 32.3, 76.4, 122.9, 123.9, 125.2, 125.9, 126.7, 126.9, 127.8, 128.1, 129.2, 129.5, 132.3, 132.4, 132.9, 133.1, 133.5, 134.5, 139.0, 139.1, 139.7, 153.0. HRMS (ESI): *m/z* calcd for $C_{54}H_{53}N_2O_2$ ($[M+H]^+$) 761.4107; found 761.4102. Anal. Calcd for $C_{54}H_{52}N_2O_2 \cdot 1.5H_2O$: C, 82.31; H, 7.03; N, 3.55; found: C, 82.10; H, 7.05; N, 3.46.

Synthesis of Chiral Thiourea [(*S,S*)-7]

To a solution of (*S*,*S*)-2',2''-diaminemethyl-2,2'''-dicyclohexyloxy-1,1':3',3'':1'',1'''- quaternaphthalene (457 mg, 0.6 mmol) and diisopropylethylamine (522 μL, 3 mmol) in CH_2Cl_2 (20 mL) was added thiophosgene ($CSCl_2$) (87 μL, 1.25 mmol) in CH_2Cl_2 (10 mL) at -78 °C. The mixture was allowed to warm to room temperature and stirred for 8 h. The reaction was quenched by 1N $NaHSO_4$ solution (30 mL) and extracted with CH_2Cl_2 (2 × 20 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The crude diisothiocyanate obtained was used for subsequent reaction without further purification.

To a solution of the crude diisothiocyanate in pyridine (20 mL) was added water (3 mL) and stirred for 20 h at 80 °C. After removel of solvents, the residue was purified by column chromatorgraphy with PE (60-90 °C)-AcOEt (4:1) as eluent to afford the thiourea product (390 mg, 81% yield) as pale yellow solid. m.p. 159-163 ℃. $[\alpha]_D^{25} = -96.5$ (*c* 1.0, $CHCl_3$). IR (FT-IR, film): 3051, 2933, 2856, 1620, 1590, 1523, 1508, 1339, 1247, 1237, 1146, 827, 734 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.79-1.71 (m, 20H), 3.82 (dd, *J* = 15.6, 7.8 Hz, 2H), 4.33-4.45 (m, 4H), 5.49 (t, *J* = 7.2 Hz, 2H), 6.98 (d, *J* = 8.2 Hz, 2H), 7.19-7.55 (m, 12H), 7.88 (d, *J* = 7.8 Hz, 2H), 8.00 (d, *J* = 8.2 Hz, 4H), 8.17 (s, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.9, 23.1, 25.2, 31.5, 32.3, 47.3, 74.9, 114.3, 116.0, 120.2, 123.62, 123.64, 126.2, 126.3, 126.6, 127.2, 127.9, 128.4, 128.8, 129.6, 130.6, 132.8, 133.0, 133.3, 134.0, 136.0, 138.6, 154.2. HRMS (ESI): *m/z* calcd for $C_{55}H_{51}N_2O_2S$ ($[M+H]^+$) 803.3671; found 803.3666. Anal. calcd for $C_{55}H_{50}N_2O_2S \cdot H_2O$: C, 80.46; H, 6.38; N, 3.41; found: C, 80.84; H, 6.46; N, 3.43.

Synthesis of Chiral Guanidine [(*S,S*)-2]

To a solution of thiourea (241 mg, 0.3 mmol) in acetone (10 mL) was added MeI (38 μL, 0.9 mmol) and the solution was stirred for 2 h at room temperature. After removal of solvents, crude isothiourea was obtained. To a solution of crude isothiourea in THF (15 mL) was added CuI (58 mg, 0.3 mmol), K_2CO_3 (620 mg, 4.5 mmol) and $MeNH_3Cl$ (203 mg, 3 mmol). The reaction mixture was refluxed for 20 h. After cooling to room temperature, the reaction was quenched by 1N HCl (30 mL) and extracted with AcOEt (2 × 20 mL). The extracts were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography with PE(60-90 °C) -AcOEt (4:1) as eluent to give guanidinium salt. The obtained guanidinium salt was redissolved in CH_2Cl_2 (30 mL) and neutralized by 2N KOH (20 mL). The organic phase was separated and dried over anhydrous Na_2SO_4. Evaporation of solvents gave guanidine (*S,S*)-**2** (180 mg, 75% yield) as colorless solid. m.p.212 ℃ (decomp.). $[\alpha]_D^{25} = -135.5$ (*c* 1.0, $CHCl_3$).

^1H NMR (200 MHz, $CDCl_3$): δ 0.87-1.76 (m, 20H), 2.35 (s, 3H), 3.62-3.87 (m, 4H), 4.03-4.51 (m, 4H), 7.11-7.61 (m, 14H), 7.85-8.14 (m, 8H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.8, 23.2, 25.3, 25.9, 31.6, 32.2, 76.4, 115.3, 119.5, 120.5, 126.1, 126.7, 128.0, 129.2, 130.1, 130.5, 132.4, 133.2, 134.2, 134.8, 136.0, 139.1, 139.9, 141.1, 146.5, 149.8, 155.6. IR (FT-IR, film): 2933, 2857, 1641, 1591, 1507, 1466, 1332, 1264, 1235, 1147, 809, 735 cm^{-1}. MS (EI): *m/z* = 799 (M+, 3), 768 (5), 728 (6), 562 (20). HRMS (ESI): *m/z* calcd for $C_{56}H_{54}N_3O_2$ ($[M+H]^+$) 800.4216; found 800.4211.

General Procedure for the Henry Reaction

To a glass vial with magnetic stir bar was added *p*-bromobenzaldehyde (18.5 mg), chiral gunidine **2** (8 mg, 10 mol%), and THF (3 mL). To this solution was added $MeNO_2$ (61 mg) and the reaction mixture was stirred for 72 h at room temperature. The solvent was evaporated in vacuo, and the residue was purified by silica gel column chromatography with petroleum ether-ethyl acetate (5:1) as eluent to provide 77 mg product (97% yield). The enantiomeric excess was analyzed by chiral HPLC.

General Procedure for the Conjugate Addition to Nitrostyrene

To a glass vial with magnetic stir bar was added 2-hydroxy-1,4-naphthoquinone (17.4 mg, 0.1 mmol), nitrostyrene (14.9 mg, 0.1 mmol), guanidine **2** (8 mg, 10 mol%), and toluene (3 mL). After being stirred at room temperature for 48 h, the solvent was evaporated in vacuo, and the residue was purified by silica gel column chromatography with petroleum ether-ethyl acetate (2:1) as eluent. The nitroalkylated naphthoquinone was afforded, and the enantiomeric excess was analyzed by chiral HPLC.

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