Electronic Supporting Information of the Manuscript “Enantioselective Organocatalytic Oxidation of Functionalized Sterically Hindered Disulfides”

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General Methods.

All reactions were run under an atmosphere of dry argon using oven-dried glassware and freshly distilled dried solvents. THF and diethyl ether were distilled from sodium benzophenone ketyl. Dichloromethane was distilled from calcium hydride. TLC was performed on Silica Gel GF₂₅₄ (Merck) with detection by charring with phosphomolybdic acid/EtOH. For flash chromatography, silica Gel (Merck 230-400 mesh) was used. Columns were eluted with positive air pressure. Chromatographic eluents are given as volume to volume ratios (v/v). NMR spectra were recorded with a Bruker Avance DPX300 (¹H, 300 MHz) and Bruker Avance DRX500 (¹H, 500 MHz) spectrometers. Chemical shifts are reported in ppm, and coupling constants are reported in Hz. Routine spectra were referenced to the residual proton or carbon signals of the solvent. High-resolution mass spectra were recorded on a Kratos MS-80RFA 241-MC apparatus. Optical rotations were determined with a Perkin-Elmer 341 polarimeter. Elemental analyses were recorded on a leco CHNS-932 apparatus. The organic extracts were dried over anhydrous sodium sulfate and concentrated in vacuo.

Ligand **1** is obtained from (1*R*, 2*S*)-(+)-*cis*-1-aminoindan-2-ol and 3,5-di-*tert*-butylsalicylaldehyde. Ligand **2** is obtained from benzyl 2-amino-4,6-benzylidene-2-deoxy- α -D-glucopyranoside and 3,5-di-*tert*-butylsalicylaldehyde.¹ The syntheses of both ligands have been done following the procedure reported for the synthesis of **1**.²

Ketones **3** and **4** have been obtained following published procedures.³

General procedure for the synthesis of disulfide dialdehyde.⁴

To a solution of aldehyde (0.198mmoles) in 20 mL of dry CCl₄ was added dropwise S₂Cl₂ (13.4g, 7.99mL, 0.099mmoles), and the temperature was kept at 50 - 55°C. After a short time, evolution of gas started (HCl). The reaction mixture was stirred for 2h at 60 - 65°C and then for 16h at 50°C. The remaining HCl was then eliminated by bubbling dry nitrogen into the solution (2h). After, the solvent was evaporated under reduced pressure and the white solid product was washed from cold hexane.

2,2,5,5-tetraethyl-3,4-dithiahexane-1,6-dial (8**)**

(77% yield); *R_f* 0.65 (Hexane : AcOEt, 4:1); ¹H NMR (500 MHz, CDCl₃) δ 9.10 (s, 2H), 1.79-1.62 (m, 8H), 0.88 (t, *J* = 5Hz, 12H); ¹³C NMR (125 MHz, CDCl₃) δ 194.9, 65.6, 21.8, 8.1. HRMS *m/e* calcd. for C₁₂H₂₂O₂S₂ (M)⁺: 262.1061, found: 262.1059.

2,5-dicyclohexyl-3,4-dithiahexane-1,6-dial (9**)**

(70% yield); *R_f* 0.64 (Hexane : AcOEt, 2:1); ¹H NMR (500 MHz, CDCl₃) δ 8.96 (s, 2H), 1.70-1.49 (m, 16H), 1.31- 1.29 (m, 4H); ¹³C NMR (75 MHz, CDCl₃): δ 194.3, 60.9, 30.3, 25.1, 23.1; HRMS *m/e* calcd. for C₁₄H₂₂O₂S₂ (M)⁺: 286.1061, found: 286.1058.

Typical procedure for the chemoselective reduction of disulfide dialdehydes.

A solution of dialdehyde (3.82mmol) in 12mL of absolute ethanol was cooled to 0°C, and NaBH₄ (0.58g, 15.28mmol) was added portionwise. After 30 min of stirring, the mixture was carefully treated with cooled 6N HCl aqueous solution and then poured into 20 mL of ice-cold water. After extraction with Et₂O (3x20 mL), the combined extracts were washed with saturated NaCl aqueous solution, dried over Na₂SO₄ and the solvent was evaporated under reduced pressure to give the corresponding diol.

2,2,5,5-tetraethyl-3,4-dithiahexane-1,6-diol (10**).⁴**

(97% yield); mp 54-55°C; *R_f* 0.22 (Hexane : AcOEt, 4:1); ¹H NMR (300 MHz, CDCl₃): δ 3.49 (s, 4H), 1.60 - 1.43 (m, 8H), 1.17 (s, 2H), 0.89 (t, *J* = 7.5 Hz, 12H); ¹³C NMR (75 MHz, CDCl₃): δ 76.0, 60.5, 25.0, 8.7.

2,5-dicyclohexyl-3,4-dithiahexane-1,6-diol (11)

(Quantitative yield); R_f 0.23 (Hexane : AcOEt,2:1); ^1H NMR (300 MHz, CDCl_3) δ 3.51 (s, 4H), 2.25 (s, 2H), 1.69–1.49 (m, 16H), 1.35–1.25 (m, 4H). ^{13}C NMR (75 MHz, CDCl_3): δ 68.2, 56.43, 32.52, 26.01, 21.98. HRMS m/e calcd. for $\text{C}_{14}\text{H}_{26}\text{O}_2\text{S}_2\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 313.1272, found: 313.1282.

General procedure for the acetylation of diols 10 and 11.

To a solution of the corresponding diol (3.75 mmol) in of pyridine (5 mL) was added a catalytic amount of DMAP and acetic anhydride (5mL) at 0°C. The reaction mixture was stirred for 48h at room temperature and then poured into 20 mL of ice-cold water, extracted with CH_2Cl_2 (3x20mL), washed with 2M H_2SO_4 aqueous solution (3x10mL), saturated NaHCO_3 aqueous solution (2x10mL) and saturated NaCl aqueous solution (10mL) and dried over Na_2SO_4 . The solvent was evaporated under reduced pressure and the residue purified by flash chromatography (silica gel, hexane: ethyl acetate, 8:1).

2,2,5,5-tetraethyl-3,4-dithiahexane-1,6-diacetate, (12)

(80% yield); R_f 0.47 (Hexane : EtOAc 2:1); ^1H NMR (300 MHz, CDCl_3) δ 4.08 (s, 4H), 2.06 (s, 6H), 1.50 (q, $J = 7.5$ Hz, 8H), 0.96 (t, $J = 7.5$ Hz, 12H); ^{13}C NMR (125 MHz, CDCl_3) δ 170.7, 66.4, 55.7, 25.7, 20.8, 8.0; HRMS m/e calcd. for $\text{C}_{16}\text{H}_{30}\text{O}_4\text{S}_2\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 373.1483, found: 373.1501.

2,5-dicyclohexyl-3,4-dithiahexane-1,6-diacetate (13)

(91% yield); R_f 0.43 (Hexane : EtOAc 4:1); ^1H NMR (500 MHz, CDCl_3) δ 4.08 (s, 4H), 2.07 (s, 6H), 1.67-1.48 (m, 16H), 1.28-1.26 (m, 4H). ^{13}C NMR (125 MHz, CDCl_3) δ 170.9, 69.2, 52.5, 32.3, 25.5, 21.7, 20.9. HRMS m/e calcd. for $\text{C}_{18}\text{H}_{30}\text{O}_4\text{S}_2\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 397.1483, found: 397.1484.

2,2,5,5-tetraethyl-3,4-dithiahexane-1,6-dibenzoatete, (14)

To a solution of **10** (1g, 3.7 mmol) in pyridine (5 mL) was added a catalytic amount of DMAP and benzoylchloride (1.71mL, 14.8mmol) at 0°C. The reaction mixture was stirred for 48h at

room temperature (monitored by TLC) and then poured into 20 mL of ice-cold water, extracted with CH₂Cl₂ (3x20mL), washed with 2M H₂SO₄ aqueous solution (3x10mL), saturated NaHCO₃ aqueous solution (2x10mL), saturated NaCl aqueous solution (10mL) and dried over Na₂SO₄. The solvent was evaporated under reduced pressure and the residue purified by flash chromatography (silica gel, hexane:ethyl acetate, 9:1) to give **14**.

(77% yield); *R_f* 0.71 (hexane : EtOAc, 2:1); ¹H NMR (500 MHz, CDCl₃) δ 8.10-8.05 (d, *J* = 7.5 Hz, 4H), 7.55-7.54 (t, *J* = 7.5 Hz, 2H), 7.44 (t, *J* = 7.5 Hz, 4H), 4.32 (s, 4H), 1.73 - 1.64 (m, 8H), 0.96 (t, *J* = 7.5 Hz, 12H); ¹³C NMR (125 MHz, CDCl₃) δ 170.6, 133.0, 130.1, 129.7, 128.4, 67.2, 56.2, 26.0, 8.18; HRMS *m/e* calcd. for C₂₆H₃₄O₄S₂Na (M+Na)⁺: 497.1796, found: 497.1800.

2,2,5,5-tetraethyl-1,6-di-(4-methoxy-benzyloxy)-3,4-dithiahexane (15)

To a solution of NaH (60% dispersion in mineral oil) (330mg, 3.769mmol) in anhydrous DMF (10mL) under dry argon was added dropwise a solution of diol **10** (1g, 3.442mmol) in anhydrous DMF (5mL) at 0°C. After stirring for 15 min, *p*-methoxybenzylchloride (1.4mL, 10.38 mmol) was added and the reaction mixture was stirred for 24h at room temperature (monitored by TLC). Then, methanol (2 mL) was added at 0°C and the solvent was evaporated under reduced pressure. The residue was extracted with (1:1) ether:hexane mixture, the organic phase was washed with saturated NH₄Cl aqueous solution and dried over Na₂SO₄. The solvent was evaporated under reduced pressure and the residue purified by flash chromatography (silica gel, hexane:EtOAc, 6:1) to give pure **15**.

(71% yield); *R_f* 0.47 (Hexane:EtOAc, 4:1); ¹H NMR (300 MHz, CDCl₃) δ 7.23 (d, *J* = 8.4 Hz, 4H), 6.85 (d, *J* = 8.4 Hz, 4H), 4.40 (s, 4H), 3.78 (s, 6H), 3.31 (s, 4H), 1.62-1.46 (m, 8H), 0.86-0.81 (t, *J* = 7.2 Hz, 12 H); ¹³C NMR (100 MHz, CDCl₃) δ 159.4, 129.6, 129.4, 113.9, 73.1, 72.9, 57.2, 55.5, 26.6, 8.5; HRMS *m/e* calc. for C₂₈H₄₂O₄NaS₂ (M+Na)⁺: 529.2422, found: 529.2440.

Typical Procedure for the Synthesis of Racemic Thiosulfinates (21-23).

To a solution of disulfide (1.44mmol) in acetic acid (1.44 mL) was added H₂O₂ (1.59mmol) with stirring at 0°C and then poured into 20 mL of ice-cold water. The reaction mixture was extracted with CH₂Cl₂ (3x20mL), washed with saturated NaHCO₃ aqueous solution and dried over Na₂SO₄. The solvent was evaporated under reduced pressure and the residue purified by flash chromatography.

General Procedure for the enantioselective oxidation of disulfides.⁵

An alkaline buffer solution (pH=9.3) (10mL) of a catalytic amount of tetrabutylammonium hydrogen sulfate (15 mg, 0.04mmol) and ketone **7** (77mg, 0.3mmol) were added to a solution of the corresponding disulfide (1mmol) in CH₃CN/DMM (1:2) (15 mL) under stirring at 0°C. A mixture of Oxone (0.85g, 1.38mmol) in Na₂(EDTA) solution (6.5mL) and K₂CO₃ (0.8g, 5.8mmol) in distilled water (6.5mL) were added dropwise separately and slowly for 1h. Upon stirring for additional 12h at 0°C, the resulting mixture was diluted with water, and extracted with ether, dried over Na₂SO₄. The solvent was evaporated under reduced pressure and the residue purified by flash chromatography to give the corresponding thiosulfinate.

2,2,5,5-Tetraethyl-3,4-dithiahexane-3-oxide-1,6-diol (**17**)

(80% yield) *R_f* 0.19 (Hexane : EtOAc 1 :1), [α]_D²⁵ = -67.00 (c. 1.0, CHCl₃) for 72% ee; ¹H NMR (300 MHz, CDCl₃) δ 4.14 (dd, *J* = 6 Hz, 10 Hz, 1H), 4.01 (dd, *J* = 6 Hz, 10 Hz, 1H), 3.82- 3.67 (m, 2H, 2H), 3.13 (d, *J* = 6 Hz, 2H), 2.02-1.58 (m, 8H), 1.03-0.86 (m, 12H). ¹³C NMR (75 MHz, CDCl₃) δ 69.5, 67.6, 64.6, 63.9, 26.8, 26.4, 22.8, 8.1, 8.0, 7.9. HRMS *m/e* calcd. for C₁₂H₂₆O₃S₂Na (M+Na)⁺: 305.1221, found: 305.1227.

The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chiralpak AD column), 95:5 hexane/isopropanol ; 1mL/min, 254 nm ; *r_t*(major isomer) = 23.02min ; *r_t*(minor isomer) = 27.99min

2,2,5,5-tetraethyl-1,6-diacetate-3,4-dithiahexane-3-oxide (**19**).

(89% yield) *R_f* 0.46 (Hexane : EtOAc, 3:1), [α]_D²⁰ = -71.68 (c. 1.1, CHCl₃) for 89% ee, ¹H NMR (300 MHz, CDCl₃) δ 4.24-4.09 (m, 4H), 1.98 (s, 3H), 1.97 (s, 3H), 1.89-1.60 (m, 8H), 0.95-0.82 (m, 12H); ¹³C NMR (75 MHz, CDCl₃) δ 170.4, 170.1, 68.7, 67.8, 63.1, 58.5, 28.2, 27.7, 23.4, 23.1, 20.8, 20.7, 8.2, 8.0, 7.9, 7.8; HRMS *m/e* calcd. for C₁₆H₃₀O₅S₂Na (M+Na)⁺: 389.1432, found: 389.1432.

The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chiralpak AD column), 98 :2 hexane/isopropanol ; 1mL/min, 254 nm ; *r_t*(major isomer) = 23.94min ; *r_t*(minor isomer) = 26.93min.

2,2,5,5-tetraethyl-1,6-dibenzoate-3,4-dithiahexane-3-oxide (**22**)

(89% yield) R_f 0.33 (Hexane : EtOAc, 3: 1); $[\alpha]_D^{25} = -76.14$ (c. 1.0, CHCl_3) for 93% ee, ^1H NMR (500 MHz, CDCl_3) δ 8.09-8.05 (m, 4H), 7.58-7.56 (m, 2H), 7.45-7.39 (m, 4H), 4.62-4.45 (m, 4H), 2.05-1.65 (m, 8H), 1.12-0.92 (m, 12H); ^{13}C NMR (125 MHz, CDCl_3) δ 166.0, 133.2, 133.1, 129.9, 129.8, 129.7, 128.5, 128.4, 69.3, 68.3, 63.6, 59.0, 28.6, 28.2, 23.6, 23.0, 8.3, 8.1, 8.0; HRMS m/e calcd. for $\text{C}_{26}\text{H}_{34}\text{O}_5\text{S}_2\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 513.1745, found: 513.1728.

The ee was determined by chiral HPLC analysis (Daicel Chiralpak AD column), 95 :5 hexane/isopropanol ; 1mL/min, 254 nm ; r_t (major isomer) = 28.99min ; r_t (minor isomer) = 32.93min.

2,2,5,5-tetraethyl-1,6-di-*p*-methoxybenzyloxy-3,4-dithiahexane-3-oxide (22)

(20,3% yield) R_f 0.42 (Hexane:EtOAc, 6:1); $[\alpha]_D^{20} = -43.22$ (c. 1.0, CHCl_3) for 90% ee; ^1H NMR (300 MHz, CDCl_3) δ 7.26-7.22 (m, 4H), 6.84 (d, $J = 7.8$ Hz, 4H), 4.45 (s, 4H), 3.78 (s, 6H), 3.68-3.55 (m, 4H), 2.02-1.66 (m, 8H), 0.99-0.86 (m, 12H), ^{13}C NMR (75 MHz, CDCl_3): δ 159.4, 130.7, 130.4, 129.5, 114.0, 74.3, 73.4, 73.2, 70.2, 69.3, 59.9, 55.5, 28.7, 28.6, 24.0, 23.6, 8.9, 8.6, 8.4. HRMS m/e calcd. for $\text{C}_{28}\text{H}_{43}\text{O}_5\text{S}_2$ ($\text{M}+\text{H}$) $^+$: 523.2552, found: 523.2579.

The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chiralpak AD column), 95 :5 hexane/isopropanol ; 0.7mL/min, 254 nm ; r_t (minor isomer) = 20.80min ; r_t (major isomer) = 22.24min.

2,5-dicyclohexyl-3,4-dithiahexane-1,6-diol-3-oxide (18)

(82% yield) R_f 0.2 (Hexane : EtOAc, 2:1); $[\alpha]_D^{25} = -74.79$ (c. 1.0, CHCl_3) for 70% ee; ^1H NMR (400 MHz, CDCl_3) δ 4.30 (d, $J=16$ Hz, 1H), 4.20-4.0 (m, 2H), 3.85-3.51 (m, 2H), 3.1 (bs, 2H), 2.10-1.20 (m, 20H); ^{13}C NMR (125 MHz, CDCl_3) δ 71.0, 67.2, 64.1, 59.9, 34.4, 33.3, 28.3, 27.7, 25.8, 25.2, 22.1, 21.9, 21.7, 21.6; HRMS m/e calcd. for $\text{C}_{14}\text{H}_{26}\text{O}_3\text{S}_2\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 329.1221, found: 329.1216.

The ee was determined by chiral HPLC analysis (Daicel Chiralpak AD column), 97:3 hexane/isopropanol ; 1mL/min, 254 nm ; r_t (minor isomer) = 86.05 min ; r_t (major isomer)= 97.67 min.

2,5-dicyclohexyl-1,6- diacetate-3,4-dithiahexane-3-oxide (20)

(97% yield) R_f 0.58 (Hexane:EtOAc, 2:1); $[\alpha]_D^{20} = -81.67$ [c. 1.0, CHCl_3] for 96% ee; ^1H NMR (500 MHz, CDCl_3) δ 4.47 (d, $J=12$ Hz, 1H), 4.35 (d, $J=12$ Hz, 1H), 4.20-4.10 (m, 2H), 2.00(s, 3H), 1.99 (s, 3H), 1.96- 1.10 (m, 20H); ^{13}C NMR (125 MHz, CDCl_3) δ 170.6, 170.4,

70.9, 66.4, 62.6, 55.3, 53.5, 33.9, 33.6, 27.7, 27.0, 25.3, 24.9, 22.1, 22.0, 21.5, 21.2; HRMS *m/e* calcd. for C₁₈H₃₁O₅S₂ (M+H)⁺: 391.1613, found: 391.1618.

The ee was determined by chiral HPLC analysis (Daicel Chiralpak AD column), 97:3 hexane/isopropanol ; 1mL/min, 254 nm ; r_t (major isomer) = 59.39 min ; r_t (minor isomer) = 64.13 min.

(S)-(-)-tert-Butyl tert-Butanethiosulfinate, (23).

(97% yield) *R_f* 0.48 (Hexane : EtOAc, 1:1) ; [α]_D²⁰ = -105.4 (c. 0.5, CHCl₃) for 84% ee [lit.⁶ (*R*)-(+)-23: [α]_D²⁰ = +150 (c. 0.55, CH₂Cl₂)] ; ¹H NMR (300 MHz, CDCl₃) δ 1.35 (s, 9H), 1.54 (s, 9H) ; ¹³C NMR (125 MHz, CDCl₃) δ 24.00, 32.10, 48.50, 59.00; HRMS *m/e* calcd. for C₈H₁₈OS₂Na (M+Na)⁺: 217.0696, found: 217.0684.

The ee was determined by chiral HPLC analysis (Daicel OJ column), 99.8 : 0.2 hexane/isopropanol; 0.3mL/min, 254 nm. r_t(*R* isomer): 45.4 min; r_t(*S* isomer): 50.6 min.

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13C RMN #75MHZ
CDCl3

RMN 300MHZ
CDCl3

pic 9

RMN 75MHz
CDCl₃

Retention Time (min)	Purity1 Angle	Purity1 Threshold	PDA Match1 Spect. Name	PDA Match1 Angle	PDA Match1 Threshold	PDA Match1 Lib. Name	Area ($\mu\text{V}\cdot\text{sec}$)	% Area	Height (μV)
28.999							13908795	96.53	200318
32.932							499676	3.47	7043

228.5
228.5

Retention Time (min)	Purity1 Angle	Purity1 Threshold	PDA Match1 Spect. Name	PDA Match1 Angle	PDA Match1 Threshold	PDA Match1 Lib. Name	Area ($\mu\text{V}\cdot\text{sec}$)	% Area	Height (μV)
28.343							12715406	50.57	183608
32.033							12426657	49.43	158653

Retention Time (min)	Purity1 Angle	Purity1 Threshold	PDA Match1 Spect. Name	PDA Match1 Angle	PDA Match1 Threshold	PDA Match1 Lib. Name	Area ($\mu\text{V}\cdot\text{sec}$)	% Area	Height (μV)	Int Type	Amo
59.365							3211282	49.52	25688	bb	
63.978							3272885	50.48	23255	bb

Retention Time (min)	Purity1 Angle	Purity1 Threshold	PDA Match1 Spect. Name	PDA Match1 Angle	PDA Match1 Threshold	PDA Match1 Lib. Name	Area ($\mu\text{V}\cdot\text{sec}$)	% Area	Height (μV)	Int Type	Amc
59.394							4577792	98.28	33746	bb	
64.135							80076	1.72	878	bb