Diastereoselective Pyrrolidine Synthesis *via* Copper Promoted Intramolecular Aminooxygenation of Alkenes; Formal Synthesis of (+)-Monomorine

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Supporting Information 1

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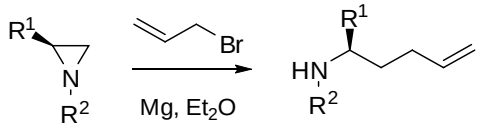
General Experimental Information: All reagents were used out of the bottle as purchased from the supplier without further purification unless otherwise specified. Solvents were purified using a commercial solvent filtration system. ^{1}H NMR spectra were recorded in $CDCl_3$ or C_6D_6 at 400 or 500 MHz. ^{13}C NMR spectra were recorded in $CDCl_3$ or C_6D_6 at 75 or 125.7 MHz. Spectra are reported in ppm relative to residual chloroform (7.26 ppm for ^{1}H NMRs and 77.0 ppm for ^{13}C NMRs) or benzene (7.16 ppm for ^{1}H NMRs and 128.0 ppm for ^{13}C NMRs). IR spectra were obtained neat using a Nicolet-Impact 420 FTIR. High resolution mass spectra were obtained at SUNY, Buffalo's mass spec. facility on a ThermoFinnigan MAT XL spectrometer. Optical rotations were obtained using a Rudolph Autopol 1 fitted with a micro cell with a 100 mm path length. Melting points are reported as uncorrected.

Procedure for the Synthesis of Substrates (1), (3), (5) and (7)



1, R^1 = *i*Pr, R^2 = PMBS
3, R^1 = Bn, R^2 = PMBS
5, R^1 = CH_2OTBDPS, R^2 = Ts
7, R^1 = *n*Bu, R^2 = Ts

Representative Procedure: (R)-4-Methoxy-N-(2-methylhept-6-en-3-yl)benzenesulfonamide (1)

Following the procedure that was previously reported,[1] magnesium metal (0.76 g, 31.2 mmol, 5 equiv) was stirred in dry Et_2O (10 mL) under Ar(g) in a 25 mL 2-neck flask equipped with a reflux condenser and magnetic stir bar. Freshly distilled allyl bromide (3.78 g, 31.2 mmol, 5 equiv) was added dropwise at r.t. After stirring the mixture for 2 h, a solution of the aziridine[2] (1.6 g, 6.25 mmol, 1 equiv) in Et_2O (5 mL) was added dropwise. The reaction mixture was stirred for an additional 16 h. The reaction was quenched with saturated NH_4Cl(aq) (15 mL) and extracted with ethyl acetate (3 x10 mL). The organic layers were separated, combined and washed with brine solution and dried over anhydrous Na_2SO_4. Evaporation of the organic layer *in vacuo* afforded 1.8 g of sulfonamide **1** (96% yield). The obtained sulfonamide **1** matched the reported ^{1}H NMR and ^{13}C NMR data:[1] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, J = 11 Hz, 2 H), 6.96 (d, J = 11 Hz, 2 H), 5.68 (m, 1 H), 4.92-4.87 (m, 2 H), 4.40 (d, J = 11 Hz, 1 H), 3.86 (s, 3 H), 3.11 (m, 1 H), 1.99 (m, 2 H), 1.84 (m, 1 H), 1.45 (m, 1 H), 1.36 (m, 1 H), 0.78 (d, J = 8.5 Hz, 3 H), 0.78 (d, J = 8.0, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6, 137.7, 133.2, 129.1, 115.0, 114.0, 58.7, 55.5, 31.0, 30.9, 29.8, 18.2, 17.6.

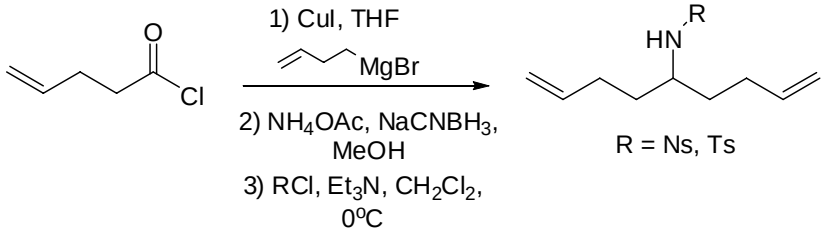
(R)-4-Methoxy-N-(1-phenylhex-5-en-2-yl)benzenesulfonamide (3)

The sulfonamide **3** was obtained as colorless oil in 96% yield. Data: $[\alpha]^{23}_{D}$ = -6.89 ^{o} (c = 1.18, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, J = 7.0 Hz, 2H), 7.23 (m, 3H), 7.01 (d, J = 8.0 Hz, 2H), 6.90 (d, J = 5.5 Hz, 2H), 5.70 (m, 1H), 4.89-4.92 (m, 2H), 4.36 (d, J = 8.0 Hz, 1H), 3.86 (s, 3H), 3.44 (m, 1H), 2.70 (m, 2H), 2.63 (m, 1H), 2.01 (m, 1H), 1.56

(m, 1H), 1.45 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.7, 137.5, 137.0, 132.4, 129.4, 129.0, 128.5, 126.6, 115.1, 114.1, 55.5, 54.4, 41.1, 33.6, 29.6; IR (neat, thin film) υ 3282, 3064, 3023, 2941, 2841, 2360, 2341, 1640, 1597, 1579, 1498, 1454, 1441, 1417, 1322, 1300, 1260, 1178, 1153, 1095, 1028, 972, 910, 833, 802, 746, 701, 668, 582, 559 cm^{-1}; HRMS (ESI) calcd for $[M+Na]^+$ $C_{19}H_{23}O_3N_1NaS$: 368.1291, found: 368.1292.

(R)-N-(1-(tert-Butyldiphenylsilyloxy)hex-5-en-2-yl)-4-methylbenzenesulfonamide (5)
The sulfonamide **5** was obtained as colorless oil in 98% yield. Data: $[\alpha]^{23}_D$ = -3.09 ^{o} (c = 0.59, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, J = 8.5 Hz, 2H), 7.54 (d, J = 7.0 Hz, 2H), 7.49 (d, J = 6.5 Hz, 2H), 7.43 (d, J = 5.5 Hz, 2H), 7.37 (dd, J = 5 Hz, 4.5 Hz, 4H), 7.22 (d, J = 8.0 Hz, 2H), 5.70 (m, 1H), 4.92 (d, J = 7.0 Hz, 1H), 4.90 (d, J = 14 Hz, 1H), 4.80 (d, J = 8.5 Hz, 1H), 3.44 (dd, J = 14 Hz, 3.5, 2H), 3.24 (m, 1H), 2.40 (s, 3H), 1.98 (m, 2H), 1.67 (m, 2H), 1.01 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ143.1, 138.1, 137.6, 135.5, 135.4, 132.8, 132.7, 129.8 (2C), 129.7, 129.6, 127.8, 127.7 (2C), 126.9, 115.1, 64.7, 54.5, 31.4, 29.6, 26.8, 21.4, 19.2; IR (neat, thin film) υ 3260, 3067, 2954, 2931, 2859, 2361, 1472, 1427, 1329, 1163, 1113, 1093, 997, 908, 814, 740, 702, 668, 551 cm^{-1}; HRMS (ESI) calcd for $[M+Na]^+$ $C_{29}H_{37}O_3N_1NaSSi$: 530.2156, found: 530.2155.

(R)-4-Methyl-N-(non-1-en-5-yl)benzenesulfonamide (7)
The sulfonamide **7** was obtained as colorless oil in 97% yield. Data: $[\alpha]^{23}_D$ = +8.87 ^{o} (c = 1.34, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J = 8.5 Hz, 2H), 7.29 (d, J = 8 Hz, 2H), 5.69 (m, 1H), 4.92 (dd, J = 12 Hz, 1.5 Hz, 1H), 4.42 (d, J = 8.5 Hz, 1H), 3.24 (m, 1H), 2.41 (s, 3H), 2.00 (m, 2H), 1.51 (m, 1H), 1.41 (m, 2H), 1.28 (m, 1H), 1.14 (m, 2H), 1.07 (m, 2H), 0.76 (t, J = 7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.1, 138.4, 137.7, 129.5, 127.0, 114.9, 53.6, 34.6, 34.2, 29.4, 27.3, 22.3, 21.4, 13.8; IR (neat, thin film) υ 3274, 3061, 2954, 2932, 2860, 2364, 1641, 1599, 1424, 1379, 1324, 1305, 1288, 1160, 1094, 1043, 909, 814, 666, 579, 551 cm^{-1}; HRMS (ESI) calcd for $[M+Na]^+$ $C_{16}H_{25}O_2NNaS_1$: 318.1498, found: 318.1505.



4-methyl-N-(nona-1,8-dien-5-yl)benzenesulfonamide (9)
The tosyl substrate **9** was synthesized according to the procedure reported by Hultzsch and co-workers.[4] Freshly distilled 4-bromo-1-butene (2.28 g, 16.9 mmol, 1 equiv) was added to magnesium filings (0.42 g, 17.2 mmol, 1.02 equiv) in 25 mL dry THF in an oven dried round bottom flask. The mixture was stirred for 2 h at r.t. after which it was taken up in a syringe and added dropwise to a solution of 4-pentenoyl chloride (2.0 g, 16.9 mmol, 1 equiv) and copper(I) iodide (0.16 g, 0.845 mmol, 0.05 equiv) in 20 mL dry THF cooled in an ice water bath. This mixture was stirred for 1 h and the solvent was removed. The resulting crude oil was diluted with CH_2Cl_2 (50 mL) and washed with 1N HCl (20 mL). The organic layer was separated, filtered, washed with saturated aqueous

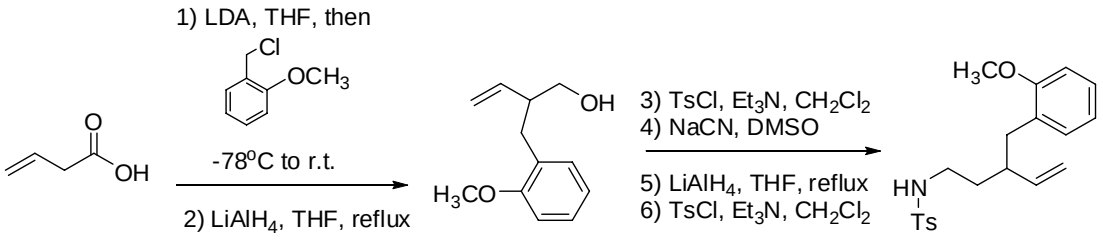
$NaHCO_3$ and dried over anhydrous Na_2SO_4. The solvent was concentrated *in vacuo* to afford 1,8-nonadien-5-one (2.0 g, 85% yield) which was then used without further purification.

1,8-Nonadien-5-one (1.8 g, 13.0 mmol, 1 equiv) and ammonium acetate (10 g, 130.0 mmol, 10 equiv) were dissolved in 43 mL MeOH. Sodium cyanoborohydride (0.57 g, 9 mmol, 0.7 equiv) was added at r.t. and was allowed to stir overnight. The solution was then brought to pH = 2 with conc. HCl. The solvent was removed *in vacuo*, and the residue was dissolved in H_2O and washed with ether. The aqueous layer was then made basic with solid KOH and was extracted with ether (3 x 50 mL). The organic layers were combined, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* which gave 0.70 g of 1,8-nonadien-5-amine (40% yield).

Triethylamine (1.75 g, 12.6 mmol, 2.5 equiv) and tosyl chloride (1.14 g, 6.0 mmol, 1.2 equiv) were added to a solution of 1,8-nonadien-5-amine (0.70 g, 5.0 mmol, 1 equiv) in 17 mL dry CH_2Cl_2. The mixture was allowed to stir at r.t. overnight. The mixture was then washed with 20 mL distilled H_2O. The organic layer was washed with brine solution and dried over Na_2SO_4. The solvent was then removed *in vacuo* and the crude oil was chromatographed on SiO_2 (10% EtOAc/hexanes) giving sulfonamide **9** as colorless oil (0.95 g, 65% yield). Data for **9**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, J = 8.5 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 5.61 (m, 2H), 5.05 (d, J = 8.5 Hz, 2H), 4.91 (dd, J = 11.5 Hz, 1.5 Hz, 4H), 3.28 (m, 1H), 2.42 (s, 3H), 2.01 (m, 4H), 1.54 (m, 2H), 1.43 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.0, 138.4, 137.6, 129.4, 126.9, 114.9, 53.1, 33.9, 29.3, 21.3; IR (neat, thin film) υ 3076, 2927, 2858, 1918, 1823, 1641, 1598, 1495, 1428, 1324, 1157, 1094, 993, 912, 815, 707, 666 cm^{-1}; HRMS (ESI) calcd for $[M]^+$ $C_{16}H_{23}O_2N_1S_1$: 293.1444, found: 293.1431.

4-Nitro-N-(nona-1,8-dien-5-yl)benzenesulfonamide (11)
The nosyl substrate **11** was obtained as colorless oil. Data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (d, J = 9.0 Hz, 2H), 8.06 (d, J = 8.5 Hz, 2H), 5.69 (m, 2H), 4.94 (d, J = 5.0 Hz, 2H), 4.93 (dd, J = 13.5 Hz, 1.5 Hz, 2H), 4.68 (d, J = 8.5 Hz, 1H), 3.39 (m, 1H), 1.99 (m, 4H), 1.57 (m, 2H), 1.43 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.9, 147.2, 137.0, 128.1, 124.2, 115.4, 53.8, 34.0, 29.3; IR (neat, thin film) υ 3287, 3101, 3078, 2976, 2925, 2854, 2361, 1641, 1606, 1532, 1428, 1353, 1308, 116, 1093, 994, 913, 854, 762, 747, 736, 686, 617, 566 cm^{-1}; HRMS (ESI) calcd for $[M]^+$ $C_{15}H_{20}O_4N_2S_1$: 324.1138, found: 324.1138.

Synthesis of Substrates (13) and (16)



13

Representative Procedure: N-(3-(2-Methoxybenzyl)pent-4-enyl)-4-methylbenzenesulfonamide (13)

Using a modified procedure,[3] diisopropyl amine (4.80 g, 47.0 mmol, 2.02 equiv) was stirred in 20 mL of dry THF in a single-neck round bottom flask equipped with a magnetic stir bar under Ar(g) conditions. The solution was cooled to -78^{o}C and *n*-butyl lithium (1.6 M in hexanes, 3.01 g, 47.0 mmol, 2.02 equiv) was added dropwise via syringe. After stirring the solution for 45 min, vinyl acetic acid (2.02 g, 23.0 mmol, 1 equiv) dissolved in 5 mL THF was added dropwise. The resulting solution was stirred for an additional 1 h. *O*-methoxybenzyl chloride (3.67 g, 23.0 mmol, 1.02 equiv) dissolved in 5 mL THF was added dropwise to the solution then the mixture was stirred at -78 to 0°C for 1 h. The mixture was then cooled to r.t., quenched with 5% $NaHCO_3$ and washed with EtOAc (15 mL). The basic aqueous layer was acidified with 4 N HCl to a pH of 2.5 and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine solution, dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. Purification of the crude product by column chromatography on silica gel (10% EtOAc in hexanes) afforded 1.07 g of colorless oil (23% yield).

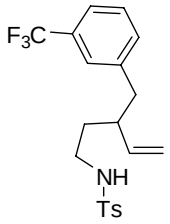
To a suspension of $LiAlH_4$ (0.55 g, 14.5 mmol, 3 equiv) in 20 mL dry THF was added dropwise a solution of the crude material obtained above (1.0 g, 4.85 mmol, 1 equiv) in 5 mL THF under Ar(g) at 0 °C. The mixture was heated under reflux for 1 h. Distilled H_2O (1.05 mL) was added upon cooling to r.t., followed by 1 N NaOH (1.05 mL) and of distilled H_2O (3.15 mL). The resulting mixture was filtered through celite and washed with EtOAc. The filtrate was concentrated *in vacuo* to afford 0.88 g of crude alcohol.

Under Ar(g) conditions, the crude alcohol (0.88 g, 4.58 mmol, 1 equiv) was dissolved in 9 mL dry CH_2Cl_2 at r.t. Triethylamine (0.56 g, 5.5 mmol, 1.2 equiv) was added followed by tosyl chloride (0.96 g, 5.04 mmol, 1.1 equiv). The mixture was allowed to stir for 24 h at r.t. which was then washed with distilled H_2O (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x10 mL) and the combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solution was concentrated *in vacuo* and the resulting crude product was used without further purification.

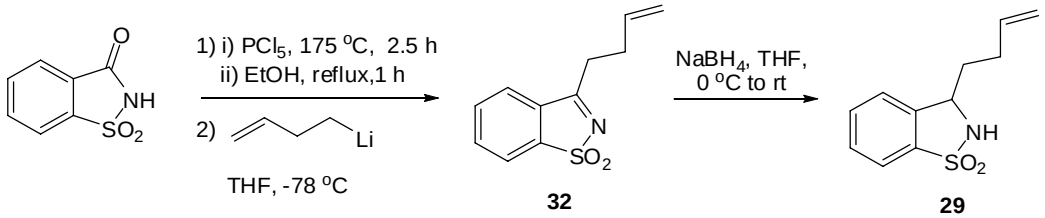
The crude product (1.6 g, 4.6 mmol, 1 equiv) was then dissolved in 23 mL DMSO. Sodium cyanide (0.45 g, 9.2 mmol, 2.0 equiv) was added at r.t. and the mixture was heated to 60^{o}C for 16 h. The mixture was then cooled to r.t, diluted with 30 mL of distilled H_2O and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine solution and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* to afford the crude nitrile.

A solution of the crude nitrile (0.89 g, 4.4 mmol, 1 equiv) in 10 mL dry THF was added dropwise to a suspension of $LiAlH_4$ (0.34 g, 9.3 mmol, 2.1 equiv) in 25 mL dry THF under Ar(g) at 0 °C. The mixture was heated under reflux for 1 h. The reaction mixture was cooled to r.t and H_2O (0.67 mL) was then added, followed by 1N NaOH(0.67 mL) and H_2O (2.02 mL). The mixture was filtered through celite and the solvent was removed *in vacuo* to afford the crude amine.

The crude amine (0.4 g, 2.0 mmol, 1 equiv) was dissolved in 7 mL CH_2Cl_2 under Ar(g). Triethylamine (0.42 g, 4.2 mmol, 2.1 equiv) was added to the solution followed by tosyl chloride (0.46 g, 2.4 mmol, 1.2 equiv). The mixture was stirred at r.t. for 16 h which was then washed with distilled H_2O (10 mL). The organic layer was washed with brine solution and dried over anhydrous Na_2SO_4. Purification by column chromatography on silica (10 % EtOAc in hexanes) afforded the sulfonamide **13** as colorless oil (0.65 g, 41% yield over 4 steps). Data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J = 8 Hz, 2H), 7.31 (d, J = 8.5 Hz, 2H), 7.19 (t, J = 7.5 Hz, 1H), 7.01 (d, J = 7.0 Hz, 1H), 6.89 (t, J = 7.5 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H), 5.59 (m, 1H), 4.92 (d, J = 10.0 Hz, 1H), 4.82 (d, J = 17.5 Hz, 1H), 4.49 (br.s., 1H), 3.83 (s, 3H), 3.03 (m, 2H), 2.66 (dd, J = 7.0 Hz, 6.5 Hz, 1H), 2.53 (dd, J = 7.5 Hz, 5.5 Hz, 1H), 2.44 (s, 3H), 2.33 (m, 1H), 1.53 (m. 1H), 1.44 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ157.4, 143.2, 141.4, 137.0, 130.9, 129.6, 128.1, 127.3, 127.0, 120.1, 115.2, 110.3, 55.2, 41.6, 41.3, 35.5, 33.5, 21.4; IR (neat, thin film) υ 3292, 3064, 2922, 2857, 2363, 2343, 1599, 1558, 1494, 1464, 1326, 1243, 1159, 1094, 1049, 1029, 917, 814, 754, 668, 551 cm^{-1}; HRMS (ESI) calcd for $[M+Na]^+$ $C_{20}H_{25}O_3N_1NaS_1$: 382.1447, found: 382.1432.



4-Methyl-N-(3-(3-(trifluoromethyl)benzyl)pent-4-enyl)benzenesulfonamide (16)
The sulfonamide **16** was obtained as colorless oil. Data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J = 7.5 Hz, 2H), 7.45 (d, J = 7.5 Hz, 1H), 7.37 (m, 5H), 5.50 (m, 1H), 4.95 (d, J = 9.0 Hz, 1H), 4.84 (d, J = 17.5 Hz, 1H), 3.02 (m, 1H), 2.98 (m, 1H), 2.68 (m, 2H), 2.43 (s, 3H), 2.36 (m, 1H), 1.64 (m, 1H), 1.46 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ143.3, 140.5, 140.0, 136.8, 132.5, 129.6, 128.4, 127.0, 125.7 (q, J_{C-F} = 3.37 Hz), 122.8 (q, J_{C-F} = 3.97 Hz), 116.5, 42.9, 41.3, 41.1, 33.8, 21.3; IR (neat, thin film) υ 3073, 2928, 2860, 1641, 1598, 1494, 1450, 1421, 1329, 1202, 1160, 1124, 1094, 1074, 1019, 1001, 919, 815, 750, 704, 661, 571, 551 cm^{-1}; HRMS (ESI) calcd for $[M]^+$ $C_{20}H_{22}O_2N_1F_3S_1$: 397.1318, found: 397.1318.



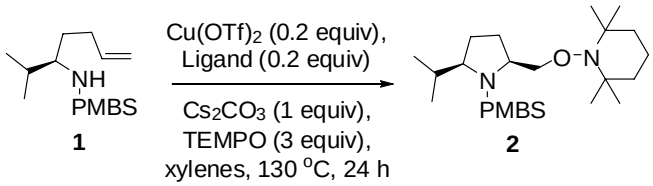
3-(3-Butenyl)-1,2-benzisothiazoline 1,1-dioxide (29)
Modifying the procedures reported by Engberts[5] and Gosciniak,[6] saccharin (5 g, 27.3 mmol, 1 equiv) and PCl_5 (8.5 g, 40.9 mmol, 1.5 equiv) were placed in an oven-dried 500

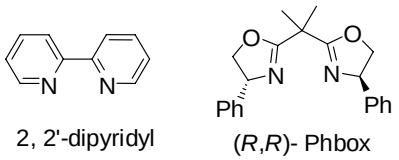
mL round-bottom flask equipped with magnetic stir bar and air condenser. The reaction mixture was gently heated until the reaction had subsided, after which the temperature was raised to 175 ^{o}C for an additional 1.5 h. The $POC1_3$ was removed by suction, which was treated with 400 mL of absolute ethanol. The reaction mixture was then heated under reflux for 1 h. After cooling the solution to r.t., the solution was filtered. Cooling the filtrate in an ice bath afforded the white crystals (1.5 g, 26% yield), pseudosaccharin chloride which was collected by filtration and were used for the next step.

3-Butenyl lithium was synthesized following the reported procedure.[7] *Tert*-butyllithium (1.7 M in pentane, 12.2 mL, 40.0 mmol, 2.1 equiv) was added to a solution of 4-iodo-1-butene[8] (1.79 g, 9.84 mmol, 1 equiv) in Et_2O (42 mL) upon cooling in a dry ice-acetone bath. The solution was stirred for 1 h at -78 ^{o}C, then warmed to r.t. and was added to a stirred solution of psuedosaccharin chloride (6.2 mmol, 1 equiv) in 100 mL dry THF via syringe. The reaction mixture was cooled to -78 ^{o}C in a dry ice-acetone bath and was stirred for 4 h. After the reaction mixture was warmed to r.t., it was then quenched with aqueous saturated NH_4Cl solution and extracted with ethyl ether (3 x 50 mL). The organic solution was washed with brine solution and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum gave **32** (1.18 g, 86% yield). Data: mp 79-82 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (dd, J = 3.0 Hz , 2.0 Hz, 1H), 7.74 (m, 2H) 7.69 (dd, J = 3.5 Hz, 2.5 Hz, 1H), 5.95 (m, 1H), 5.16 (dd, J = 16.5 Hz, 1 Hz, 1H), 5.09 (d, J = 10.5 Hz, 1H), 3.06 (t, J = 7.5 Hz, 2H), 2.67 (q, J = 7.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.4, 139.7, 135.7, 133.8, 133.5, 131.1, 123.8, 122.4, 116.5, 30.4, 29.0; IR (neat, thin film) υ 3085, 2998, 2980, 2916, 2358, 2342, 1843, 1640, 1604, 1560, 1451, 1393, 1325, 1310, 1286, 1225, 1180, 1168, 1129, 998, 922, 852, 771, 765, 596, 537 cm^{-1}; HRMS (ESI) calcd for $[M+Na]^+$ $C_{11}H_{11}O_2N_1Na_1S_1$: 244.0403, found: 244.0407.

Sodium borohydride (0.81 g, 21.3 mol, 4 equiv) was added in small portions to a solution of **32** (1.18 g, 5.3 mmol, 1 equiv) in 29 mL dry THF at 0 ^{o}C. The reaction mixture was stirred for 24 h at r.t. then water (20 mL) was added under cooling. The solvent was evaporated *in vacuo* and 4 N HCl was added until pH 4. The aqueous layer was extracted with $CHCl_3$ (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated. Purification of the crude product by column chromatography on silica (30% EtOAc in hexanes) gave **29** as colorless oil (0.55 g, 47% yield). Data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, J = 7.5 Hz, 1H), 7.62 (t, J = 7.0 Hz, 1H), 7.52 (t, J = 7.5 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 5.84 (m, 1H), 5.12 (d, J = 4.5 Hz, 1H), 5.10 (dd, J = 16.0 Hz, 1.5 Hz, 1H), 5.04 (d, J = 10.0 Hz, 1H), 4.73 (m, 1H), 2.27 (m, 2H), 2.08 (m, 1H), 1.89 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.3, 136.8, 135.5, 133.0, 129.2, 124.0, 121.2, 116.1, 116.0, 57.2, 34.9, 29.9; IR (neat, thin film) υ 3274, 3074, 2953, 2925, 2847, 2359, 2341, 1640, 1471, 1453, 1388, 1284, 1194, 1167, 1131, 1061, 917, 798, 758, 720, 648, 581, 535 cm^{-1}; HRMS (ESI) calcd for $[M+Na]^+$ $C_{11}H_{13}O_2N_1Na_1S_1$: 246.0559, found: 246.0561.

Procedure for Catalytic Diastereoselective Aminooxygenation Reaction

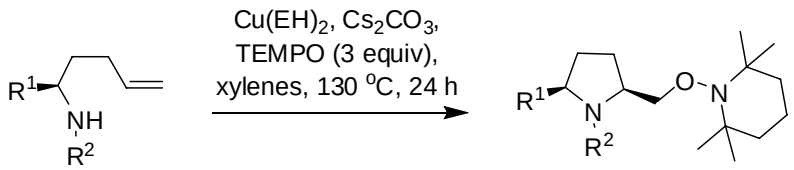




Representative Procedure: 1-(((2S,5R)-5-Isopropyl-1-(4-methoxyphenylsulfonyl)pyrrolidin-2-yl)methoxy)-2,2,6,6-tetramethylpiperidine (2)
$Cu(OTf)_2$ (0.020 mmol, 0.2 equiv), (*R*,*R*)-phenylbis-oxazoline (0.020 mmol, 0.2 equiv) and xylenes (1.01 mL) were combined in a 100 mL round bottom flask equipped with a magnetic stir bar. The mixture was stirred at 50 °C for 2 h. The solution was cooled to r.t. and treated with the sulfonamide **1** (0.101 mmol, 1 equiv), TEMPO (0.303 mmol, 3 equiv) and K_2CO_3 (0.101 mmol, 1 equiv). The reaction mixture was heated to 130 °C for 24 h under O_2 (1 atm balloon). Filtration of the cooled solution through a SiO_2 plug and removal of the solvent *in vacuo* afforded the crude product. Purification via flash chromatography on SiO_2 (10-30% EtOAc in hexanes gradient) gave pyrrolidine **2** in 60% yield and 14% of the starting olefin **1**.

Procedure for Stoichiometric Diastereoselective Aminooxygenation Reaction

A. α-Substituted 4-pentenyl sulfonamides



2, R^1 = *i*Pr, R^2 = PMBS
4, R^1 = Bn, R^2 = PMBS
6, R^1 = $CH_2OTBDPS$, R^2 = Ts
8, R^1 = *n*Bu, R^2 = Ts
10, R^1 = 3-butenyl, R^2 = Ts
12, R^1 = 3-butenyl, R^2 = Ns

Representative Procedure: 1-(((2S,5R)-5-Isopropyl-1-(4-methoxyphenylsulfonyl)pyrrolidin-2-yl)methoxy)-2,2,6,6-tetramethylpiperidine (2)
The sulfonamide **1** (30.0 mg, 0.101 mmol, 1 equiv), $Cu(EH)_2$ (53.0 mg, 0.151 mmol, 1.5 equiv), Cs_2CO_3 (32.9 mg, 0.101 mmol, 1 equiv), TEMPO (47.3 mg, 0.303 mmol, 3 equiv) and xylenes (1.01 mL) were combined in an oven-dried pressure tube equipped

with magnetic stir bar. The reaction mixture was heated in an oil bath to 130 ^{o}C for 24 h. It was then cooled to room temperature, diluted with ether and filtered through a SiO_2 plug. Removal of the solvent *in vacuo* afforded the crude product. Purification by flash chromatography on SiO_2 (10% ethyl acetate in hexanes) gave the disubstituted pyrrolidine **2** in 94% yield (42.8 mg). The *cis* configuration of **2** was determined by X-ray crystallographic analysis (Figure 1).

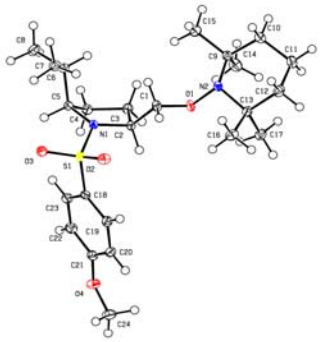
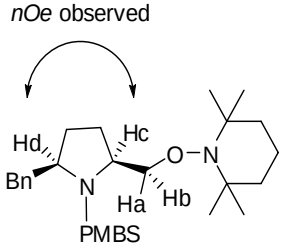


Figure **1**. Crystal structure of **2**.

Data for **2**: mp 124-129 ^{o}C; $[\alpha]^{23}_{D}$ = -49.3 ^{o} (c = 0.50, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, J = 9.0 Hz, 2H), 6.98 (d, J = 8.5 Hz, 2H), 3.92 (dd, J = 5.0 Hz, 3.5 Hz, 1H), 3.87 (s, 3H), 3.75 (t, J = 8.5, 1H), 3.69 (m, 1H), 3.42 (m, 1H), 2.10 (m, 1H), 1.88 (m, 1H), 1.67 (m, 1H), 1.54-1.43 (m, 6H), 1.37-1.22 (m, 4H), 1.15 (s, 6H), 1.08 (s, 6H), 0.98 (d, J = 6.5 Hz, 3H), 0.89 (d, J = 6.5, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.7, 129.8, 129.7, 114.0, 78.1, 67.1, 59.8 (2C), 59.5, 55.5, 39.5, 33.0, 32.8, 30.9, 27.1, 25.3, 20.2, 20.1, 17.2, 17.0; IR (neat, thin film) υ 2969, 2934, 2874, 1597, 1498, 1467, 1413, 1345, 1305, 1261, 1210, 1158, 1096, 1056, 1027, 994, 971, 918, 836, 804, 768, 733, 671, 587, 566, 443, 434 cm^{-1}; HRMS (ESI) calcd for $[M+H]^+$ $C_{24}H_{41}O_4N_2S$: 453.2782, found: 453.2794.

1-(((2S,5R)-5-Benzyl-1-(4-methoxyphenylsulfonyl)pyrrolidin-2-yl)methoxy)-2,2,6,6-tetramethylpiperidine (4)



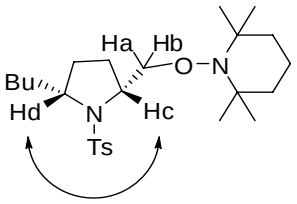
The disubstituted pyrrolidine **4** was obtained as colorless oil in 97% yield. The *cis* stereochemistry of **4** was determined by *nOe* experiment which showed a strong signal between Hc and Hd. Data for **4**: $[\alpha]^{23}_{D}$ = +16.2 ^{o} (c = 0.71, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, J = 9.0 Hz, 2H), 7.29 (t, J = 7.5 Hz, 2H), 7.29 (t, J = 9.0 Hz, 1H), 7.22 (d, J = 6.5 Hz, 2H), 6.99 (d, J = 9.0 Hz, 2H), 3.91 (dd, J = 5.5 Hz, 3.0 Hz, 1H), 3.86 (s, 3H), 3.78 (t, J = 7.5 Hz, 2H), 3.72 (m, 1H), 3.36 (dd, J = 10.0 Hz, 3 Hz, 1H), 2.82 (dd, J =

10.0 Hz, 3.0 Hz, 1H), 1.89 (m, 1H), 1.67 (m, 1H), 1.50-1.40 (m, 6H), 1.33 (m, 1H), 1.30 (m, 1H), 1.17 (s, 6H), 1.11 (s, 6H); ^{13}C NMR (125 MHz, C_6D_6) δ 162.9, 138.9, 130.5, 130.0(2C), 128.6, 128.2, 126.6, 114.2, 79.1, 63.3, 60.4, 60.1, 59.9, 54.9, 43.1, 40.0, 39.9, 33.4, 33.3, 29.2, 27.5, 20.4, 17.4; IR (neat, thin film) υ 3062, 2972, 2932, 2864, 2833, 2359, 2341, 1596, 1577, 1497, 1470, 1453, 1413, 1373, 1346, 1305, 1260, 1208, 1178, 1157, 1132, 1094, 1029, 988, 971, 910, 874, 834, 803, 761, 742, 701, 669, 629, 612, 595, 562, 510 cm-1; HRMS (ESI) calcd for $[M+H]^+$ $C_{28}H_{41}O_4N_2S$: 501.2782, found:501.2778.

1-(((2S,5R)-5-((tert-Butyldiphenylsilyloxy)methyl)-1-tosylpyrrolidin-2-yl)methoxy)-2,2,6,6-tetramethylpiperidine (6)

The disubstituted pyrrolidine **6** was obtained as colorless oil in 96% yield. The *cis* configuration of **6** was assigned by analogy to **2** and **4**. Data: $[\alpha]^{23}_D$ = +3.77 ^{o} (c = 0.96, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (t, J = 7.0 Hz, 4H), 7.64 (d, J = 8.0 Hz, 2H), 7.42 (t, J = 7.5 Hz, 6H), 7.30 (d, J = 8.0 Hz, 2H), 4.01 (d, J = 5.5 Hz, 1H) 3.92 (dd, J = 6.0 Hz, 3.0 Hz, 1H), 3.80 (t, J = 8.0 Hz, 1H), 3.67 (d, J = 5.5 Hz, 2H), 3.64 (m, 1H), 2.44 (s, 3H), 1.97 (m, 1H), 1.89 (m, 1H), 1.55 (m, 2H), 1.42 (m, 4H), 1.31 (m, 2H), 1.15 (s, 3H), 1.12 (s, 3H), 1.09 (s, 9H), 1.05 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.2, 135.5, 134.7, 133.6, 133.5, 129.6, 129.5, 127.6(2C), 78.2, 66.3, 62.0, 60.0, 59.8, 39.6, 33.1, 32.9, 27.3, 27.0, 26.9, 21.4, 20.2, 19.2, 17.0; IR (neat, thin film) υ 2965, 2931, 2882, 2360, 2342, 1428, 1350, 1305, 1207, 1163, 1112, 1051, 997, 962, 817, 739, 701, 665, 618, 588, 555 cm^{-1}; HRMS (ESI) calcd for $[M+Na]^+$ $C_{38}H_{54}O_4N_2NaSSi$: 685.3466, found: 685.3476.

1-(((2R,5R)-5-Butyl-1-tosylpyrrolidin-2-yl)methoxy)-2,2,6,6-tetramethylpiperidine (8)



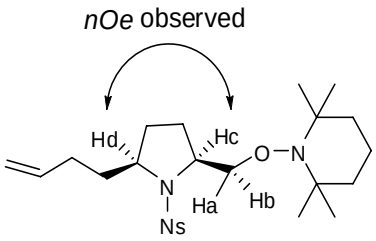
nOe observed

The disubstituted pyrrolidine **8** was obtained as colorless oil in 94% yield. The *cis* stereochemistry of **8** was determined by *nOe* experiment which showed a strong signal between Hc and Hd and no signal between Ha and Hd. Data for **8**: $[\alpha]^{23}_D$ = +22.7 ^{o} (c = 0.70, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J = 8.5 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 3.92 (dd, J = 5.0 Hz, 4.0 Hz, 1H), 3.82 (t, J = 7.5 Hz, 1H), 3.72 (m, 1H), 3.57 (m, 1H), 2.42 (s, 3H), 1.92 (m, 2H), 1.48 (m, 8H), 1.33 (m, 6H), 1.18 (s, 3H), 1.15 (s, 3H), 1.08 (s, 6H), 0.90 (t, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.1, 135.0, 129.5, 127.6, 78.5, 61.8, 59.9, 59.8, 59.6, 39.6, 36.3, 33.0, 32.9, 29.9, 28.4, 27.3, 22.6, 21.4, 20.2, 17.0, 14.0; IR (neat, thin film) υ 2963, 2928, 2870, 2360, 1598, 1494, 1456, 1373, 1348, 1261, 1244, 1207, 1183, 1161, 1133, 1093, 1047, 992, 815, 709, 664, 588, 555 cm^{-1}; HRMS (ESI) calcd for $[M+H]^+$ $C_{25}H_{43}O_3N_2S$: 451.2989, found: 451.2995.

1-(((2S,5S)-5-(but-3-enyl)-1-tosylpyrrolidin-2-yl)methoxy)-2,2,6,6-tetramethylpiperidine (10)

Pyrrolidine **10** was obtained as colorless oil in 97% yield. The *cis* configuration of **10** was assigned by analogy to **12**. Data for **10**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 5.86 (m, 1H), 5.06 (dd, J = 16.0, 1.5 Hz, 1H), 4.98 (d, J = 13.5 Hz, 1H), 3.92 (m, 1H), 3.83 (t, J = 7.5 Hz, 1H), 3.71 (m, 1H), 3.60 (m, 1H), 2.42 (s, 3H), 2.13 (m, 3H), 1.91 (m, 1H), 1.43-1.59 (m, 10H), 1.18 (m, 3H), 1.15 (s, 3H), 1.09 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.7, 136.6, 133.5, 128.1, 126.1, 113.2, 59.7, 58.3, 38.1, 34.0, 31.5, 28.9, 28.5, 25.8, 20.0, 18.8, 15.5; IR (neat, thin film) υ 3074, 2979, 2930, 2371, 2258, 1733, 1638, 1598, 1494, 1470, 1451, 1376, 1348, 1303, 1262, 1207, 1161, 1131, 1093, 1045, 992, 911, 815, 709, 665 cm^{-1}; HRMS (ESI) calcd for $[M+H]^+$ $C_{25}H_{41}O_3N_2S$: 449.2832, found: 449.2842.

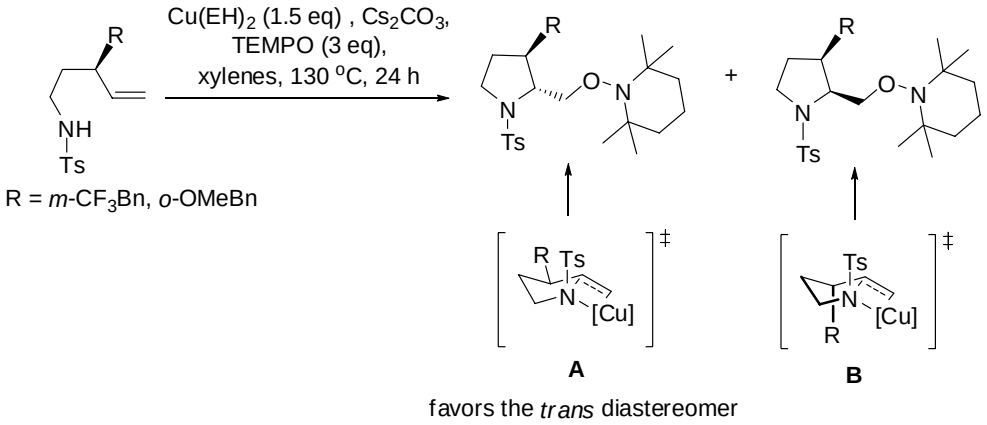
(±)-1-(((2S,5S)-5-(But-3-enyl)-1-(4-nitrophenylsulfonyl)pyrrolidin-2-yl)methoxy)-2,2,6,6-tetramethylpiperidine (12)



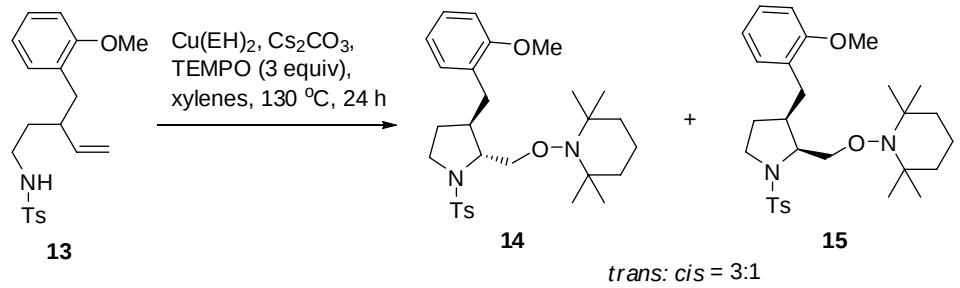
The disubstituted pyrrolidine **12** was obtained as white solid in 76% yield. The *cis* stereochemistry of **12** was determined by *nOe* experiment which showed a strong signal between Hc and Hd. Data for **12**: mp 115-119 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (d, J = 9.0 Hz, 2H), 8.02 (d, J = 9.0 Hz, 2H), 5.85 (m, 1H), 5.07 (dd, J = 16.0 Hz, J = 1.0 Hz, 1H), 5.01 (d, J = 10.5 Hz, 1H), 3.93 (m, 2H), 3.71 (m, 1H), 3.60 (m, 1H), 2.16-2.05 (m, 3H), 1.99 (m, 1H), 1.65-1.53 (m, 6H), 1.43 (m, 4H), 1.17 (s, 3H), 1.16 (s, 3H), 1.09 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.0, 143.8, 137.6, 128.7, 124.2, 115.1, 78.1, 61.7, 60.2, 60.0, 39.6, 35.4, 32.9, 30.3, 30.0, 27.3, 20.3, 17.0; IR (neat, thin film) υ 2973, 2932, 2871, 2360, 2340, 1640, 1605, 1531, 1471, 1453, 1400, 1373, 1350, 1307, 1208, 1166, 1133, 1091, 1048, 992, 910, 854, 734, 688, 617, 575 cm^{-1}; HRMS (ESI) calcd for $[M]^+$ $C_{24}H_{37}O_5N_3S_1$: 479.2448, found: 479.2446.

B. γ-Substituted Substrates

The diastereoselective aminooxygenation reaction of γ-substituted substrates (e.g. substrates **13** and **16**) favors the formation of the *trans* pyrrolidine with 3:1 and 2:1 selectivity for **13** and **16** respectively. The proposed major transition state favors the positioning of the R group in the equatorial position (**A**) over the axial position (**B**) thereby favoring the formation of the *trans* adduct (Scheme 1).

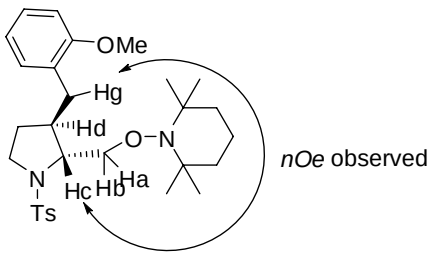


Scheme 1. Diastereoselective aminooxygenation reaction of γ-substituted substrates.



(±)-cis/trans-1-((3-(2-Methoxybenzyl)-1-tosylpyrrolidin-2-yl)methoxy)-2,2,6,6-tetramethylpiperidine (14) and (15)

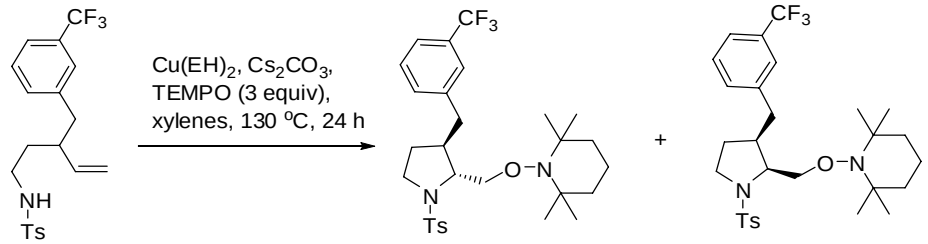
The procedure for the diastereoselective aminooxygenation of **13** was the same as for the conversion of **1** to **2**. The 3:1 ratio of **14** and **15** was determined from the analysis of the crude ^{1}H NMR spectrum. The crude product was purified by column chromatography (10% ethyl acetate: hexanes) which gave a mixture of **14** and **15** in 80% yield. The diastereomers were separated by HPLC (5-20% ethyl acetate in hexanes, gradient). The *trans* stereoisomer in which the relative stereochemistry was assigned by *nOe* experiment eluted first followed by the *cis* stereoisomer.



The *trans* stereochemistry of **14** was determined by *nOe* experiment which showed a strong signal between Hc and Hg. Data for *trans* isomer **14**: ^{1}H NMR (500 MHz, C_6D_6) δ 7.71 (d, J = 8.5 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 7.17 (t, J = 8.5 Hz, 1H), 7.01 (d, J = 7.5 Hz, 1H), 6.85 (t, J = 7.5 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H), 4.16 (dd, J = 5.5 Hz, 4.5 Hz, 1H), 4.07 (dd, J = 7.5 Hz, 2.5 Hz, 1H), 3.78 (m, 1H), 3.71 (s, 3H), 3.53 (t, J = 9.5 Hz,

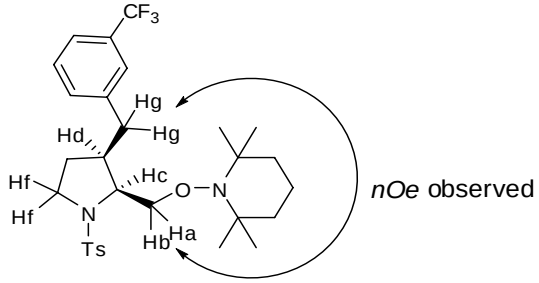
1H), 3.02 (q, J = 7.5 Hz, 1H), 2.91 (dd, J = 9.0 Hz, 4.5 Hz, 1H), 2.75 (dd, J = 10.5 Hz, 3.0 Hz, 1H), 1.97 (m, 1H), 1.86 (m, 1H), 1.56 – 1.46 (m, 6H), 1.33 (s, 3H), 1.24 (s, 3H), 1.18 (s, 3H), 1.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.4, 143.2, 134.9, 130.4, 129.5, 127.9, 127.6, 127.4, 120.1, 110.0, 78.5, 65.8, 63.6, 59.9, 59.8, 54.9, 47.7, 41.1, 39.5, 33.8, 33.0, 32.8, 29.3, 21.5, 20.1, 17.0, 15.2; IR (neat, thin film) υ 2999, 2970, 2927, 2888, 2360, 2342, 1599, 1494, 1457, 1439, 1373, 1346, 1304, 1290, 1244, 1209, 1161, 1132, 1095, 1051, 1030, 994, 815, 753, 669, 589, 550 cm^{-1}; HRMS (ESI) calcd for $[M+H]^+$ $C_{29}H_{43}O_4N_2S_1$: 515.2938, found: 515.2947.

Data for *cis* isomer **15**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, J = 8.5 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 7.17 (t, J = 8.5 Hz, 1H), 7.01 (d, J = 7.5 Hz, 1H), 6.85 (t, J = 7.5 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H), 4.16 (dd, J = 5.5 Hz, 4.5 Hz, 1H), 4.07 (dd, J = 7.5 Hz, = 2.5 Hz, 1H), 3.78 (m,1H), 3.71 (s, 3H), 3.55 (t, J = 9.5 Hz, 1H), 3.02 (m, 1H), 2.91 (dd, J = 9.0 Hz, 4.5 Hz, 1H), 2.42 (s, 3H), 1.97 (m, 1H), 1.86 (m. 1H), 1.46-1.59 (m, 7H), 1.33 (s, 3H), 1.24 (s, 3H), 1.18 (s, 3H), 1.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ157.3, 143.0, 134.8, 129.8, 129.5, 128.9, 127.5, 127.3, 120.2, 110.2, 77.6, 62.1, 60.1, 59.7, 54.9, 47.7, 42.2, 39.9, 33.2, 32.7, 30.1, 29.6, 21.4, 20.4, 17.1; IR (neat, thin film) υ 2927, 2877, 2360, 2340, 1599, 1494, 1464, 1345, 1290, 1244, 1163, 1129, 1093, 1029, 816, 752, 682, 668, 656, 594, 548 cm^{-1}; HRMS (ESI) calcd for $[M+H]^+$ $C_{29}H_{43}O_4N_2S_1$: 515.2938, found: 515.2943.

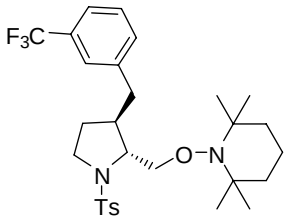


(±)-cis/trans-2,2,6,6-Tetramethyl-1-((1-tosyl-3-(3-(trifluoromethyl)benzyl)pyrrolidin-2-yl)methoxy)piperidine (17) and (18)

The procedure for the diastereoselective aminooxygenation of **16** was the same as for the conversion of **1** to **2**. The 2:1 ratio of **17** and **18** was determined from the analysis of the crude ^{1}H NMR spectrum. The crude product was purified by column chromatography (10% ethyl acetate: hexanes) which gave a mixture of **17** and **18** in 88% yield. The diastereomers were separated by HPLC (5-20% ethyl acetate in hexanes, gradient). The *cis* stereoisomer was eluted first followed by the *trans* stereoisomer.



The *cis* isomer **18** was assigned by *nOe* experiment. Data for *cis* isomer **18**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 7.5 Hz, 1H), 7.38 (t, J = 7.5 Hz, 1H), 7.31 (m, 4H), 4.14 (dd, J = 5.5 Hz, 5 Hz, 1H), 4.01 (dd, J = 7.5 Hz, 2.5 Hz, 1H), 3.76 (m, 1H), 3.58 (t, J = 8.5 Hz, 1H), 3.07 (q, J = 7.0 Hz, 1H), 2.97 (dd, J = 8.5 Hz, 6.0 Hz, 1H), 2.81 (dd, J = 9.5 Hz, 4.5 Hz, 1H), 2.43 (s, 3H), 1.96 (m, 1H), 1.82 (m, 1H), 1.67 (m, 1H), 1.47 (m, 6H), 1.32 (s, 3H), 1.25 (s. 3H), 1.15 (s, 3H), 1.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.4, 141.3, 134.4, 131.9, 129.7, 128.8, 127.4, 124.8 (q, J_{C-F} = 3.97 Hz), 123.1 (q, J_{C-F} = 3.37 Hz), 77.6, 61.5, 60.1, 59.7, 47.5, 43.3, 39.8, 35.2, 33.4, 32.8, 30.0, 29.9, 21.4, 20.4, 17.0; IR (neat, thin film) υ 2974, 1933, 1873, 2363, 2344, 1739, 1598, 1493, 1450, 1374, 1333, 1263, 1242, 1200, 1163, 1125, 1096, 1073, 1046, 1030, 1015, 991, 955, 910, 876, 815, 734, 704, 689, 663, 656, 594, 547 cm^{-1}; HRMS (ESI) calcd for $[M+H]^+$ $C_{29}H_{40}O_3N_2F_3S_1$: 553.2706, found: 553.2723.



The *trans* isomer **17** was obtained as yellow solid and the relative stereochemistry was determined by X-ray crystallography (Figure 2).

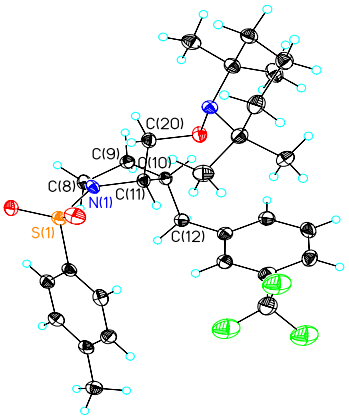
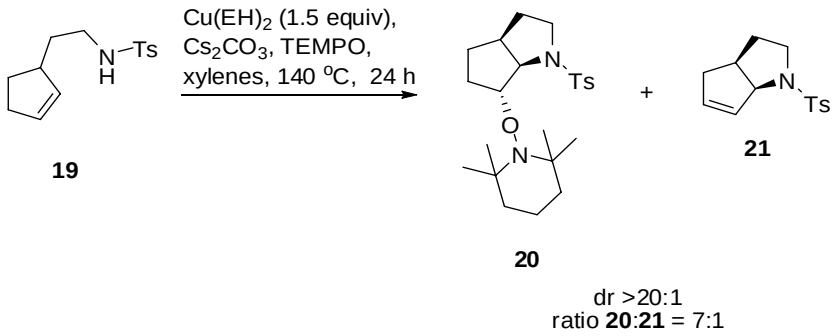


Figure **2**. Crystal structure of **17**.

Data for *trans* isomer **17**: mp 143-146 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 8.0 Hz, 1H), 7.35 (m, 3H), 7.17 (d, J = 8.0 Hz, 1H), 7.07 (s, 1H), 3.93 (dd, J = 5.5 Hz, 3.5 Hz, 1H), 3.81 (t, J = 8.5 Hz, 1H), 3.48 (m, 1H), 3.38 (m, 2H), 2.58 (m, 1H), 2.46 (s, 3H), 2.26 (m, 1H), 2.04 (m, 1H), 1.49-124 (m, 6H), 1.16 (s, 3H), 1.09 (s. 3H), 1.05 (s, 3H), 0.924 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5, 140.3, 134.7, 132.0, 129.7, 128.8, 127.6, 125.6 (q, J_{C-F} = 3.45 Hz), 123.1 (q, J_{C-F} = 3.97 Hz), 78.6, 62.3, 59.8, 47.6, 43.0, 39.5, 38.7, 33.1, 32.8, 29.7, 21.4, 20.3, 20.0, 17.0; IR (neat, thin film) υ 2973, 2929, 2873, 2356, 1597, 1493, 1451, 1373, 1347, 1334, 1261, 1244,

1201, 1161, 1125, 1096, 1055, 1002, 905, 877, 816, 752, 735, 704, 663, 598, 590, 551, 512 cm-[1]; HRMS (ESI) calcd for $[M]^+$ $C_{29}H_{39}O_3N_2F_3S_1$: 552.2628, found: 552.2641.



(3aS,6aS)-6-(2,2,6,6-Tetramethylpiperidin-1-yloxy)-1-tosyloctahydrocyclopenta[b]pyrrole (20)

Substrate **19** was synthesized according to the reported procedure.[9] The procedure for the aminooxygenation reaction of substrate **19** is the same as in the conversion of **1** to **2** except that the reaction was heated to 140 °C for 36 h. Based on the ^{1}H NMR spectrum of the crude product, the aminooxygenation product **20** and elimination product **21** was obtained in 7:1 ratio. Purification of the crude product by column chromatography (10% EtOAC in hexanes) in silica gel gave **20** as a white solid in 57% yield. The stereochemistry of **20** was determined by X-ray crystallography (Figure 3).

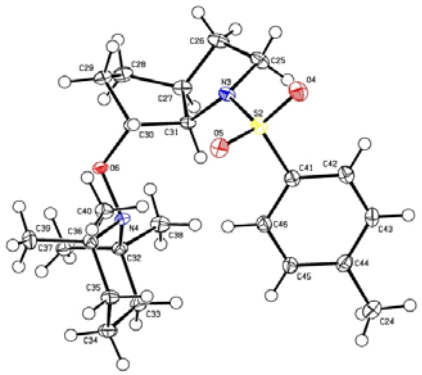
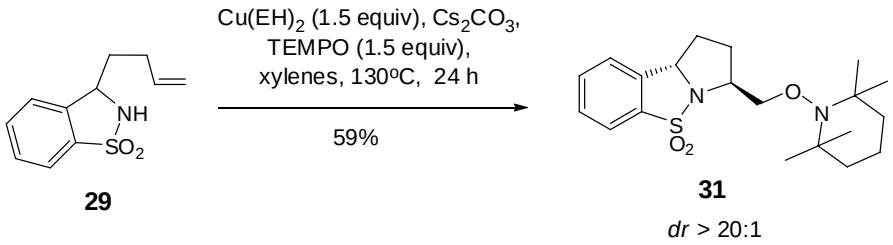


Figure **3**. Crystal structure of **20**.

Data for **20**: mp = 103-109 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, J = 8.5 Hz, 2H), 7.32 (d, J = 8.0 Hz, 1H), 4.62 (t, J = 2.0 Hz, 1H), 3.91 (d, J = 8.0 Hz, 1H), 3.38 (m, 1H), 3.19 (m, 1H), 2.57 (m, 1H), 2.43 (s, 3H), 1.94 (m, 2H), 1.75 (m, 1H), 1.50-1.57 (m, 7H), 1.43 (m, 2H), 1.12-1.31 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.2, 134.0, 129.4, 128.0, 88.7, 68.4, 59.9, 49.6, 41.8, 40.4, 34.3 (br peak), 31.2, 30.0, 29.8, 21.5, 20.4, 17.2; IR (neat, thin film) υ 3061, 2930, 2869, 2852, 2252, 1733, 1660, 1598, 1494, 1454, 1376, 1349, 1306, 1288, 1256, 1240, 1164, 1128, 1092, 1029, 965, 837, 816, 731, 710, 669, 659, 586, 549 cm^{-1}; HRMS (ESI) calcd for $[M]^+$ $C_{23}H_{36}O_3N_2S_1$: 420.2441, found: 420.2447.

The elimination product **21** matches the ^{1}H NMR spectrum of the previously reported data:[1] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 5.81 – 5.74 (d, 2H), 4.56 (d, 1H), 3.36 (m, 1H), 3.08 (m, 1H), 2.52 (m, 1H), 2.43 (s, 3H), 2.17 – 2.12 (m, 1H), 1.85 (m, 1H), 1.55 – 1.50 (m, 2H).



29 **31**

dr > 20:1

(±)-3-(2,2,6,6-Tetramethyl-piperidin-1-yloxymethyl)-1,2,3,9b-tetrahydro[*d*]pyrrolo[1,2-*b*]isothiazole 5-5-dioxide (31)

The procedure for the aminooxygenation reaction of **29** was the same as for the conversion of **1** to **2** except that 1.5 equiv of TEMPO was used. Using more equivalent of TEMPO leads to low yield of the desired product presumably due to decomposition of starting material. Purification of the crude product by flash chromatography on silica gel (5-20% EtOAc in hexanes gradient) gave a white solid (49.5 mg) in 59% yield. The *trans* stereochemistry of **31** was determined by X-ray crystallography (Figure 4).

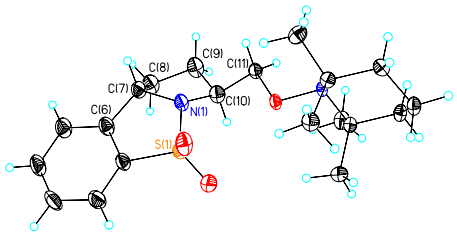
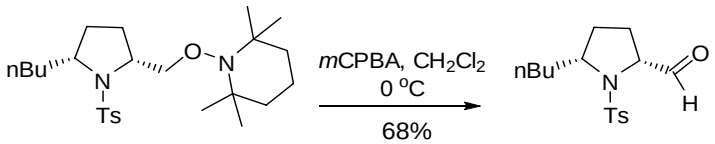


Figure **4**. Crystal structure of **31**.

Data for **31**: mp 103-106 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, J = 7.5 Hz, 1H), 7.60 (t, J = 7.5 Hz, 1H), 7.51 (t, J = 7.5 Hz, 1H), 7.34 (d, J = 7.5 Hz, 1H), 5.04 (t, J = 7.0 Hz, 1H), 4.25 (m, 1H), 3.97 (m, 2H), 2.54 (m, 1H), 2.11 (m, 1H), 2.03 (M, 1H), 1.86 (m, 1H), 1.60 (m, 2H), 1.45 (m, 4H), 1.21 (s, 3H), 1.21 (m, 3H), 1.16 (s, 3H), 1,14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.4, 136.1, 132.9, 129.3, 123.7, 121.6, 79.3, 65.7, 60.0, 58.7, 39.6, 33.0, 32.3, 29.6, 20.2, 17.0; IR (neat, thin film) υ 2969, 2933, 2870, 2360, 2341, 1734, 1705, 1469, 1452, 1374, 1359, 1312, 1258, 1171, 1133, 1091, 1059, 972, 759, 742, 579 cm^{-1}; HRMS (ESI) calcd for $[M+H]^+$ $C_{20}H_{31}O_3N_2S_1$: 379.2050, found: 379.2049.

Oxidation of TEMPO Adduct/Formal Synthesis of (+)-Monomorine



8 **27**

(2*R*,5*R*)-2-(Formyl)-5-butyl-*N*-(*p*-tosyl)-pyrrolidine (27)
Using a modified procedure,[10] a solution of the TEMPO adduct **8** (40 mg, 0.089 mmol, 1 equiv) in 1 mL dry CH_2Cl_2 was stirred in a 5 mL round bottom flask equipped with magnetic stir bar. After the addition of *m*-CPBA (22.9 mg, 0.133 mmol, 1.5 equiv), the reaction mixture was stirred and kept at 0 ^oC for 2 h. Stirring the solution for more than 2 h leads to undesired product. It was then quenched with cold aq. $Na_2S_2O_3$ (3 mL), extracted with CH_2Cl_2 (4 mL), then with EtOAc (2 x 4 mL). The combined organic extracts were washed with aq. $NaHCO_3$, followed by brine solution, dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification was done by flash chromatography (10% EtOAc: hexanes) to afford **27**, a white solid in 68% yield (18.6 mg). The data matched those of the literature values.[11] $[\alpha]^{23}_D = +17.2$ ^{o} (c = 0.60, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.63 (d, J = 2.0 Hz, 1H), 7.72 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 3.87 (dt, J = 5.5 Hz, 2.5 Hz, 1H), 3.67 (m, 1H), 2.44 (s, 3H), 2.00 (m, 1H), 1.90 (m, 1H), 1.86 (m, 1H), 1.25-1.56 (m, 7H), 0.92 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.4, 144.0, 134.0, 129.9, 127.6, 67.7, 62.0, 35.9, 29.8, 28.2, 25.5, 22.5, 21.5, 14.0; IR (neat, thin film) υ 2954, 2934, 2868, 2361, 1734, 1597, 1457, 1347, 1206, 1161, 1092, 1035, 1010, 816, 708, 666, 596, 551 cm^{-1}; HRMS (ESI) calcd for $[M+H]^+$ $C_{16}H_{24}O_3N_1S_1$: 310.1471, found: 310.1470.

Crystallographic Data for Compounds 2, 17, 20 and 31

X-ray diffraction data for compounds **2**, **17, 20** and **31** were collected at 90(1) K using a Bruker SMART APEX2 CCD diffractometer installed at a rotating anode source (MoKα radiation, λ=0.71073Å), and equipped with an Oxford Cryosystems nitrogen gas-flow apparatus. The data were collected by the rotation method with 0.5^o frame-width (ω scan) and 30 sec. exposure time per frame. Five sets of data (360 frames in each set) were collected, nominally covering complete reciprocal space. The data were integrated, scaled, sorted and averaged using the APEXII software package.[12] The structure was solved by direct methods using SHELXS.[13] The structure was refined by full-matrix least squares against F^2 using SHELXL.[13]

All non-hydrogen atoms were refined anisotropically. X-H distances were set to idealized values and not refined. Hydrogen atoms were refined with the "riding" model with U_{iso}=1.5 U_{eq} for CH_3 and U_{iso}=1.2 U_{eq} for the remaining hydrogens.

Crystal data and data collection information are summarized in Tables 1-4.

Table 1. Crystal data and data collection information for compound **2** (CCDC 696031).

Chemical formula	$C_{24}\ H_{40}\ N_2\ O_4\ S$
Stoichiometric formula	$C_{24}\ H_{40}\ N_2\ O_4\ S$
Formula weight	452.64
Crystal system, space group	Orthorhombic, $P2_12_12_1$
Unit cell dimensions:	a = 8.1083(5) [Å]
	b = 10.8440(6) [Å]
	c = 27.2736(16) [Å]
	α = 90 [°]
	β = 90 [°]
	γ = 90 [°]
Volume	2398.1(2) [$Å^{-3}$]
Z, Calculated density	4, 1.254 [Mg/m^3]
Radiation	MoKα
Wavelength	λ = 0.71073 [Å]
θ-range for data collection	1.49 to 28.19 [°]
$\sin\theta/\lambda$ max	0.66 [$Å^{-1}$]
Absorption coefficient	μ = 0.167 [mm^{-1}]
Temperature	90(1) [K]
F(000)	984
Crystal size	0.25 x 0.15 x 0.04 [mm]
Crystal shape	Prism
Crystal color	Colorless
Data Collection	
Diffractometer	APEXII CCD area detector diffractometer
Measurement method	ϖ-scan
Absorption correction	Multi-scan (SADABS 2004/1; Sheldrick, 2004)
Max. and min. transmission	T_{max}= 0.998, T_{min}= 0.959
Reflections collected / unique / R_{int}	46282 / 5894 / 0.0359
Completeness to θ = 27.54°	99.9 [%]
Limiting indices	h = -10 $\rightarrow$ 10
	k = -14$\rightarrow$ 14
	l = -36 $\rightarrow$ 36
Refinement	
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5894 / 0 / 286
R [I>2sigma(I)]	R1 = 0.0255 / wR2 = 0.0618
R (all data)	R1 = 0.0305 / wR2 = 0.0649
Goodness-of-fit on F^2 = S	1.084
$\Delta\rho_{max}$	0.279 [e $Å^{-3}$]
$\Delta\rho_{min}$	-0.232 [e $Å^{-3}$]
Flack parameter	-0.02(4)

Table 2. Crystal data and data collection information for **17** (CCDC 711960).

Chemical formula	$C_{29}H_{39}F_3N_2O_3S$
M_r	552.68
Cell setting, space group	Monoclinic, *C*2/*c*
Temperature (K)	90 (2)
a, *b*, *c* (Å)	36.619 (6), 7.7648 (12), 20.354 (3)
β (°)	101.835 (3)
V (Å^3)	5664.4 (15)
Z	8
D_x (Mg m^{-3})	1.296
Radiation type	Mo *K*α
μ (mm^{-1})	0.17
Crystal form, colour	Block, colorless
Crystal size (mm)	0.48 × 0.28 × 0.14
Data collection	
Diffractometer	Bruker SMART APEX2
Data collection method	ωandφ–scans
Absorption correction	Multi-scan (based on symmetry-related measurements)
T_{min}	0.924
T_{max}	0.977
No. of measured, independent and observed reflections	22109, 5555, 4207
Criterion for observed reflections	$I > 2\sigma(I)$
R_{int}	0.051
θ_{max} (°)	26.0
Refinement	
Refinement on	F^2
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.058, 0.161, 1.05
No. of relections	5555 reflections
No. of parameters	347
H-atom treatment	Constrained to parent site
Weighting scheme	Calculated $w = 1/[\sigma^2(F_o^2) + (0.0592P)^2 + 3.2247P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$	<0.0001
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.82, –0.72

Table 3. Crystal data and data collection information for **20** (CCDC 714177).

Chemical formula	$C_{46}H_{72}N_4O_6S_2$
Formula weight	841.20
Temperature	363(2) K
Wavelength	0.71073 Å
Crystal system	orthorhombic
Space group	P n a 21
Unit cell dimensions	a = 16.017(3) Å α = 90°
	b = 8.7090(17) Å β = 90°
	c = 31.460(6) Å γ = 90°
Volume	4388.4(15) $Å^3$
Z	4
Density (calculated)	1.273 Mg/cm^3
Absorption coefficient	0.174 mm^{-1}
F(000)	1824
Theta range for data collection	1.29 to 30.57°
Index ranges	-22<=h<=22, -12<=k<=12, -45<=l<=45
Reflections collected	95952
Independent reflections	13467 [R(int) = 0.0602]
Structure solution technique	direct methods
Structure solution program	SHELXS-97 (Sheldrick, 2008)
Refinement method	Full-matrix least-squares on F^2
Refinement program	SHELXL-97 (Sheldrick, 2008)
Function minimized	$\Sigma\, w(F_o^2 - F_c^2)^2$
Data / restraints / parameters	13467 / 1 / 533
Goodness-of-fit on F^2	1.057
Δ/σ_{max}	0.002
Final R indices	11229 data; I>2σ(I) R1 = 0.0365, wR2 = 0.0871
	all data R1 = 0.0544, wR2 = 0.0983
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0466P)^2+1.1249P]$ where $P=(F_o^2+2F_c^2)/3$
Absolute structure parameter	0.4(1)
Largest diff. peak and hole	0.481 and -0.348 $eÅ^{-3}$
R.M.S. deviation from mean	0.053 $eÅ^{-3}$

Table 4. Crystal data and data collection information for **31** (CCDC 704323).

Chemical formula	$C_{20}H_{30}N_2O_3S$
M_r	378.52
Cell setting, space group	Monoclinic, $P2_1/c$
Temperature (K)	90 (2)
a, b, c (Å)	15.0345 (11), 8.1634 (6), 16.5707 (14)
β (°)	98.427 (2)
V (Å^3)	2011.8 (3)
Z	4
D_x (Mg m^{-3})	1.250
Radiation type	Mo $K\alpha$
μ (mm^{-1})	0.18
Crystal form, colour	Block, colorless
Crystal size (mm)	0.48 × 0.40 × 0.22
Data collection	
Diffractometer	Bruker SMART APEX2
Data collection method	ωandϕ–scans
Absorption correction	Multi-scan (based on symmetry-related measurements)
T_{min}	0.917
T_{max}	0.961
No. of measured, independent and observed reflections	28293, 4459, 3713
Criterion for observed reflections	$I > 2\sigma(I)$
R_{int}	0.037
θ_{max} (°)	27.2
Refinement	
Refinement on	F^2
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.053, 0.139, 1.08
No. of relections	4459 reflections
No. of parameters	239
H-atom treatment	Constrained to parent site
Weighting scheme	Calculated $w = 1/[\sigma^2(F_o^2) + (0.0544P)^2 + 2.7105P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$	<0.0001
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.78, –0.45

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