Synthesis of Benzyl Amines Via Copper-Catalyzed Enantioselective Aza-Friedel-Crafts Additions of Phenols to *N*-Sulfonyl Aldimines

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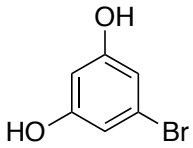
Supporting Information: Experimental Procedures and Characterization of New Compounds

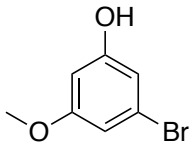
Table of Contents

General Experimental Information:

All reagents were used out of the bottle as purchased from the supplier without further purification unless otherwise noted. All reactions were carried out under an argon environment unless otherwise noted. 4,5-Dihydro-2-(2-(4,5-dihydrooxazol-2-yl)propan-2-yl)oxazole, (achiral bisoxazoline) or 1,10-phenanthroline were used to generate racemic samples for HPLC analysis. Achiral box was synthesized using our previously reported procedure[1]. 1,2-Dichloroethane was distilled from CaH_2 prior to use. ^1H NMR spectra were recorded in $CDCl_3$ (using 7.26 ppm for reference of $CHCl_3$) at 300, 400 or 500 MHz unless otherwise noted. ^{13}C NMR spectra were recorded in $CDCl_3$ (using 77.0 ppm as internal reference) at 75 or 100 MHz unless otherwise noted. Coupling constants (*J*) are in hertz. Abbreviations used are s = singlet, d = doublet, t = triplet, m = multiplet, q = quartet, ABq = AB quartet, AX = AX quartet and bs = broad singlet. IR spectra were taken neat using a Nicolet-Impact 420 FTIR. Wave numbers in cm^{-1} are reported for characteristic peaks. High-resolution mass spectra were obtained at SUNY Buffalo's mass spectrometry facility on a ThermoFinnigan MAT XL spectrometer. Flash column chromatography was carried out using 230 x 400 mesh silica gel under increased pressure. Melting points were obtained on an electro thermal melting point apparatus and are reported uncorrected. X-ray structures were obtained at the X-ray crystallographic facilities at the University of Rochester. Optical rotations were obtained using a Rudolph Autopol I Polarimeter fitted with a micro cell with a 1 dm path length. Enantiomeric excess was determined by high performance liquid chromatography (HPLC) using Chiralpak AD-RH or Regis (*S*, *S*)-Whelk chiral analytical column (UV detection at 254 nm).

Synthesis of Phenols





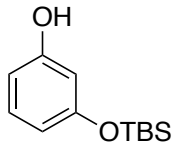
3-Bromo-5-methoxyphenol (1c) and 5-Bromobenzene-1,3-diol (1d)

Phenols **1c** and **1d** were synthesized in a procedure adapted from literature precedent.[2]

A 50 mL round bottom flask was charged with a magnetic stir bar, oven-dried, and cooled to room temperature under argon. The flask was charged with 1-bromo-3,5-dimethoxybenzene (1.0 g, 4.6 mmol), CH_2Cl_2 (20 mL), and cooled to -78˚ in a dry-ice/acetone bath. To this solution, BBr_3 (1M in CH_2Cl_2, 1.5 equiv., 6.9 mL, 6.9 mmol) was added slowly over 30 min. The solution was allowed to warm to room temperature and the reaction was stirred over night. The solution was poured into ice/water (20 mL) and extracted with EtOAc (3 x 20 mL). The organic layer washed with H_2O (2 x 20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude products were isolated by column chromatography 4:1 to 1:1 hexanes/EtOAc as the eluent to give 469 mg 5-bromobenzene-1,3-diol (54% yield) and 407 mg 3-bromo-5-methoxyphenol (44% yield).

3-Bromo-5-methoxyphenol (1c) ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.65 (d, J = 2.0 Hz, 1H), 6.61 (d, J = 1.6 Hz, 1H), 6.33 (t, J = 2.0 Hz, 1H), 4.81 (s, 1H), 3.77 (s, 3H).

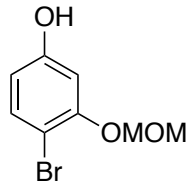
5-Bromobenzene-1,3-diol (1d) ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.60 (d, J = 2.4 Hz, 2H), 6.29 (t, J = 2.0 Hz, 1H), 5.19 (s, 2H).



3-((*tert*-Butyldimethylsilyl)oxy)phenol (1e)

Phenol **1e** was synthesized as previously reported.[3]

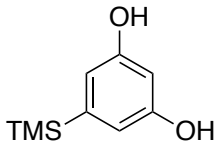
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (t, J = 8.0 Hz, 1H), 6.43 (dd, J = 8.4 Hz, 1.6 Hz, 2H), 6.35 (t, J = 2.4 Hz, 1H), 4.73 (s, 1H), 0.98 (s, 9H), 0.20 (s, 6H).

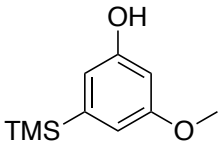


4-Bromo-3-(methoxymethoxy)phenol (1f)

Phenol **1f** was synthesized as previously reported.[4]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.4 Hz, 1H), 6.71 (d, *J* = 2.8 Hz, 1H), 6.40 (dd, *J* = 8.4 Hz, 2.8 Hz, 1H), 5.22 (s, 2H), 4.72 (bs, 1H), 3.52 (s, 3H).





5-(Trimethylsilyl)benzene-1,3-diol (1g) and 3-Methoxy-5-(trimethylsilyl)phenol (1h)

Synthesized in a procedure adapted from literature precedent.[5,6]

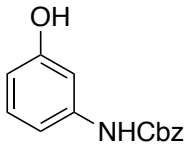
A 250 mL round bottom flask was charged with a magnetic stir bar, oven-dried, and cooled to room temperature under argon. The flask was charged with 5-bromo-1,3-dimethoxybenzene (3.0 g, 13.8 mmol), THF (90 mL), and cooled to -78 °C in a dry-ice/acetone bath. *sec*-Butyllithium (1.3 M in cyclohexane, 13.8 mL, 18.0 mmol, 1.3 equiv.) was added drop-wise and the solution was allowed to stir at -78 °C for 30 min. Trimethylsilyl chloride (2.1 mL, 16.6 mmol) was added drop-wise and the solution was allowed to warm to room temperature and stir overnight. The reaction was quenched with sat. NH_4Cl (aq) and extracted with EtOAc (3 x 50 mL). The organic layer was washed with H_2O (2 x 50 mL) and brine (1 x 50 mL). The organic layer was dried over anhydrous Mg_2SO_4, concentrated *in vacuo*, and the crude product purified by column chromatography 9:1 to 3:1 hexanes:EtOAc to yield 2.67 g (3,5-dimethoxyphenyl)trimethylsilane (92% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.65 (d, *J* = 2.0 Hz, 2H), 6.45 (t, *J* = 2.0 Hz, 1H), 3.81 (s, 3H), 0.26 (s, 9H).

A 250 mL round bottom flask was charged with a magnetic stir bar, oven-dried, and cooled to room temperature under argon. The flask was charged with (3,5-dimethoxyphenyl)trimethylsilane (2.67 g, 12.7 mmol), CH_2Cl_2 (60 mL), and cooled to -78 °C in a dry-ice/acetone bath. To this solution, boron tribromide (1M in CH_2Cl_2, 2

equiv., 25.4 mL, 25.4 mmol) was added slowly over 30 min. The solution was allowed to warm to room temperature and the reaction was stirred over night. The solution was poured into ice/water (20 mL) and extracted with EtOAc (3 x 20 mL). The organic layer washed with H_2O (2 x 20 mL), dried over anhydrous Mg_2SO_4, filtered, and concentrated *in vacuo*. The crude products were isolated by column chromatography (9:1 to 1:1 hexanes:EtOAc) to afford 5-(trimethylsilyl)benzene-1,3-diol as a white crystal and 3-methoxy-5-(trimethylsilyl)phenol as an orange oil.

5-(Trimethylsilyl)benzene-1,3-diol (1g) ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.55 (d, J = 2.4 Hz, 2H), 6.35 (t, J = 2.0 Hz, 1H), 5.19 (bs, 2H), 0.23 (s, 9H).

3-Methoxy-5-(trimethylsilyl)phenol (1h) ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.64 (d, J = 2.0 Hz, 1H), 6.56 (d, J = 2.4 Hz, 1H), 6.40 (t, J = 2.4 Hz, 1H), 4.70 (s, 1H), 3.80 (s, 3H), 0.29 (s, 9H).



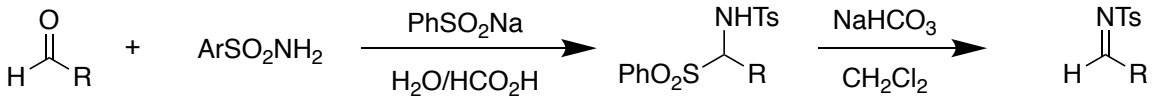
Benzyl (3-hydroxyphenyl)carbamate (1i)

Phenol **1i** was synthesized as previously reported.[7]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (m, 5H), 7.20 (s, 1H), 7.14 (t, J = 8.4 Hz, 1H), 7.44 (d, J = 7.6 Hz, 1H), 6.68 (s, 1H), 6.56 (dd, J = 8.4 Hz, 1.6 Hz, 1H), 5.48 (bs, 1H), 5.20 (s, 2H).

Synthesis of Alkyl Imines

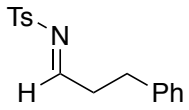
General procedure



A mixture of aldehyde (1 equiv.), sulfonamide (1 equiv.) and sodium benzenesulfinate (1.1 equiv.) in formic acid and H_2O (1:1) was stirred at room temperature overnight. The

resulting white precipitate was filtered off and washed with H_2O (2 x 15 mL), and hexanes (2 x 15 mL).

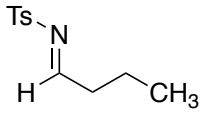
The white solid was dissolved in CH_2Cl_2 and treated with saturated $NaHCO_3$ (aq.) for 1 h at room temperature. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The organic layers were combined, dried over $NaSO_4$, filtered, and concentrated *in vacuo*. The purity of the imine was determined by crude ^1H NMR, and only if the imine was pure, it would be used in the copper-catalyzed *aza*-Friedel-Crafts reaction. No other purification techniques were used.



4-Methyl-*N*-(3-phenylpropylidene)benzenesulfonamide (2a)

Imine **2a** was synthesized as previously reported in agreement with literature data.[8]

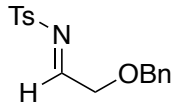
^1H NMR (400 MHz, $CDCl_3$) δ 8.63 (t, J = 4.0 Hz, 1H), 7.78 – 7.75 (m, 2H), 7.33 (d, J = 8.4 Hz, 2H), 7.27 – 7.17 (m, 3H), 7.12 (d, J = 6.8 Hz, 2H), 2.95 (t, J = 7.2 Hz, 2H), 2.89 – 2.81 (m, 2H), 2.45 (s, 3H).



***N*-Butylidene-4-methylbenzenesulfonamide (2b)**

Imine **2b** was synthesized as previously reported in agreement with literature data.[9]

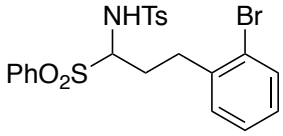
^1H NMR (400 MHz, $CDCl_3$): δ 8.60 (t, J = 4.8 Hz, 1H), 7.81 (d, J = 7.6 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 2.52 – 2.44 (m, 2H), 2.44 (s, 3H), 1.72 – 1.60 (m, 2H), 0.95 (t, J = 7.6 Hz, 3H).



***N*-(2-(Benzyloxy)ethylidene)-4-methylbenzenesulfonamide (2c)**

Imine **2c** was synthesized as previously reported in agreement with literature data.[10]

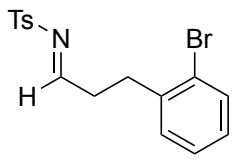
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (t, *J* = 2.8 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 2H), 7.40 – 7.23 (m, 7H), 4.60 (s, 2H), 4.35 (d, *J* = 2.8 Hz, 2H), 2.45 (s, 3H).



***N*-(3-(2-bromophenyl)-1-(phenylsulfonyl)propyl)-4-methylbenzenesulfonamide**

100 mg 3-(2-bromophenyl)propanal was converted to 166 mg sulfone (63% yield).

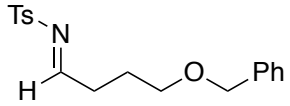
m.p. 111.1 - 111.8 ° C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, *J* = 7.2 Hz, 2H), 7.67 (t, *J* = 7.6 Hz, 1H), 7.58 – 7.47 (m, 5H), 7.29 – 7.20 (m, 4H), 7.10 – 7.06 (m, 1H), 5.08 (d, *J* = 10.0 Hz, 1H), 4.65 (td, *J* = 8.8 Hz, 4.4 Hz, 1H), 2.81 – 2.72 (m, 1H), 2.71 – 2.62 (m, 1H), 2.50 – 2.38 (m, 1H), 2.40 (s, 3H), 1.98 – 1.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0, 139.1, 137.5, 135.7, 134.3, 132.9, 130.4, 129.8, 129.7, 129.2, 128.3, 127.7, 126.7, 124.2, 73.1, 31.9, 28.8, 21.6; IR (neat): 3260, 1598, 1447, 1307, 1161, 1080, 1023, 963, 908, 814, 732, 687, 666 cm^{-1}.



***N*-(3-(2-Bromophenyl)propylidene)-4-methylbenzenesulfonamide (2d)**

Imine **2d** was synthesized following the procedure adapted from Chemla.[11]166 mg sulfone was converted to 102 mg (85% yield).

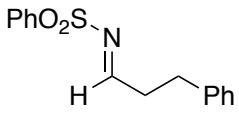
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (t, *J* = 4.0 Hz, 1H), 7.89 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.8 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.19 – 7.06 (m, 2H), 7.08 – 7.01 (m, 1H), 3.06 (t, *J* = 7.6 Hz, 2H), 2.89 – 2.83 (m, 2H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8, 144.7, 138.9, 134.3, 132.9, 130.5, 129.7, 128.2, 128.1, 127.6, 124.2, 35.7, 31.0, 21.6; IR (neat): 2921, 1627, 1596, 1471, 1440, 1321, 1260, 1185, 1157, 1090, 1019, 909, 812, 784, 732, 672 cm^{-1}; HRMS (ESI) for $C_{16}H_{16}BrNO_2S$: calculated $[M + H]^+$ *m/z* 366.0158, found 366.0160.



***N*-(4-(Benzyloxy)butylidene)-4-methylbenzenesulfonamide (2e)**

Imine **2e** was synthesized as previously reported. Its ^{1}H NMR is in agreement with literature data.[9]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (t, *J* = 4.4 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 2H), 7.37 – 7.26 (m, 7H), 4.44 (s, 2H), 3.78 (t, *J* = 6.0 Hz, 2H), 2.67 – 2.41 (m, 2H), 2.43 (s, 3H), 1.93 (m, 2H).

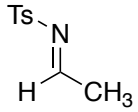


***N*-(3-Phenylpropylidene)benzenesulfonamide (2f)**

Imine **2f** was synthesized as previously reported. Its ^{1}H NMR is in agreement with

literature data.[12]

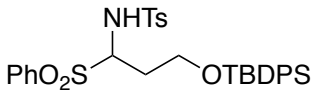
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (t, *J* = 5.1 Hz, 1H), 7.89 (d, *J* = 7.2 Hz, 2H), 7.64 (t, *J* = 7.2 Hz, 1H), 7.53 (t, *J* = 8.4 Hz, 2H), 7.26 – 7.17 (m, 2H), 7.12 (d, *J* = 6.9 Hz, 2H), 2.96 (t, *J* = 6.9 Hz, 2H), 2.92 – 2.81 (m, 2H).



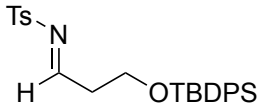
***N*-Ethylidene-4-methylbenzenesulfonamide (2g)**

Imine **2g** was synthesized as previously reported. Its ^{1}H NMR is in agreement with literature data.[11]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (q, *J* = 4.8 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 2.44 (s, 3H), 2.25 (d, *J* = 4.8 Hz, 3H).



***N*-(3-((*tert*-butyldiphenylsilyl)oxy)-1-(phenylsulfonyl)propyl)-4-methylbenzenesulfonamide**



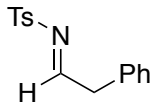
***N*-(3-((*tert*-Butyldiphenylsilyl)oxy)propylidene)-4-methylbenzenesulfonamide (2h)**

Imine **2h** was synthesized following the procedure from Chemla.[11]

A mixture of 3-((*tert*-butyldiphenylsilyl)oxy)propanal (300 mg, 0.96 mmol, 1 equiv), toluenesulfonamide (164 mg, 0.96 mmol, 1 equiv.), and sodium benzenesulfinate (173

mg, 1.06 mmol, 1.1 equiv.) in formic acid (3 mL) and H_2O (1.5 mL) was stirred for 12 h at room temperature. The resulting white precipitate was filtered off, washed with H_2O (2 x 15 mL) and hexanes (2 x 15 mL) to give 305 mg of a sulfone intermediate (78% yield). m.p. 97.8 – 98.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.0 Hz, 2H), 7.68 (t, *J* = 6.8 Hz, 1H), 7.59 – 7.38 (m, 14H), 7.11 (d, *J* = 8.0 Hz, 2H), 5.78 (d, *J* = 9.2 Hz, 1H), 3.91 – 3.81 (m, 1H), 3.66 – 3.58 (m, 1H), 2.37 (s, 3H), 2.29 – 2.16 (m, 1H), 1.97 – 1.86 (m, 1H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 137.7, 135.8, 135.4, 134.2, 132.9, 132.9, 129.8, 129.8, 129.6, 129.1, 127.8, 127.7, 126.7, 71.2, 59.5, 30.7, 26.7, 21.5, 19.0; IR (neat): 3258, 2931, 2858, 1598, 1448, 1428, 1342, 1307, 1239, 1161, 1111, 1079, 908, 815, 730, 703, 687, 666 cm^{-1}.

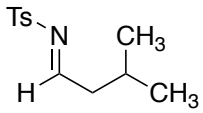
Of the sulfone intermediate, 90 mg was dissolved in CH_2Cl_2 (2 mL) and treated with saturated $NaHCO_3$ (2 mL) while stirring for 1 h. The organic phase was decanted and the aqueous phase extracted with CH_2Cl_2 (2 x 5 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford 46 mg of *N*-(3-((*tert*-butyldiphenylsilyl)oxy)propylidene)-4-methylbenzenesulfonamide (35% yield over two steps) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (t, *J* = 4.8 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 2H), 7.59 (d, *J* = 6.8 Hz, 4H), 7.47 – 7.34 (m, 6H), 7.31 (d, *J* = 8.0 Hz, 2H), 3.94 (t, *J* = 6.0 Hz, 2H), 2.72 (q, *J* = 5.6 Hz, 2H), 2.43 (s, 3H), 0.97 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 144.7, 135.5, 135.5, 134.4, 133.0, 129.8, 129.8, 128.3, 127.8, 127.7, 59.7, 38.8, 26.6, 21.6, 19.0, 1.0; IR (neat): 2961, 1632, 1472, 1428, 1327, 1259, 1162, 1089, 1018, 909, 799, 733, 702, 671 cm^{-1}; HRMS (ESI) for $C_{26}H_{31}NO_3SSi$: calculated $[M + H]^+$ *m/z* 466.1872, found 466.1878.



4-Methyl-*N*-(2-phenylethilidene)benzenesulfonamide (2i)

Imine **2i** was synthesized as previously reported. Its ^{1}H NMR is in agreement with literature data.[13]

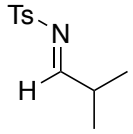
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (t, *J* = 5.2 Hz, 1H), 7.81 (d, *J* = 8.8 Hz, 2H), 7.38 – 7.26 (m, 5H), 7.18 (d, *J* = 6.8 Hz, 2H), 3.79 (d, *J* = 5.2 Hz, 2H), 2.45 (s, 3H).



4-Methyl-*N*-(3-methylbutylidene)benzenesulfonamide (2j)

Imine **2j** was synthesized as previously reported. Its ^{1}H NMR is in agreement with literature data.[11]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (t, *J* = 5.6 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 2.44 (s, 3H), 2.39 (t, *J* = 5.6 Hz, 2H), 2.12 – 2.03 (m, 1H), 0.96 (d, *J* = 6.8 Hz, 6H).



4-Methyl-*N*-(2-methylpropylidene)benzenesulfonamide (2k)

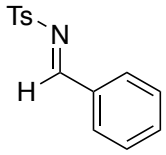
Imine **2k** was synthesized as previously reported. Its ^{1}H NMR is in agreement with literature data.[11]

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51 (d, *J* = 4.4 Hz, 1H), 7.81 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 2.76 – 2.62 (m, 1H), 2.45 (s, 3H), 1.16 (d, *J* = 6.8 Hz, 6H).

Synthesis of Aryl Imines

General Procedure for the synthesis of aryl aldimines

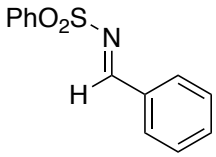
In a round bottomed flask charged with a magnetic stir bar was added sulfonamide (4.8 mmol), aryl aldehyde (4.8 mmol) and $Si(OEt)_4$ (5.4 mmol) and heated to 160 °C using a Dean-Stark apparatus. The mixture was then allowed to cool to room temperature, diluted with EtOAc, filtered, and recrystallized to give the aryl aldimine.



***N*-Benzylidene-4-methylbenzenesulfonamide (4a)**

Imine **4a** was synthesized as previously reported. Its ^{1}H NMR was in agreement with literature data.[14]

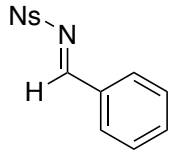
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.03 (s, 1H), 7.94 - 7.88 (m, 4H), 7.62 (t, J = 6.9 Hz, 1H), 7.49 (t, J = 7.5 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 2.44 (s, 3H).



***N*-Benzylidenebenzenesulfonamide (4b)**

Imine **4b** was synthesized as previously reported and its ^{1}H NMR is in agreement with literature data.[15]

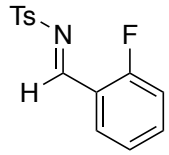
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.07 (s, 1H), 8.02 (d, J = 7.6 Hz, 2H), 7.94 (d, J = 7.2 Hz, 2H), 7.67 – 7.45 (m, 5H).



***N*-Benzylidene-4-nitrobenzenesulfonamide (4c)**

Imine **4c** was synthesized as previously reported and its ^{1}H NMR was in agreement with literature data.[16]

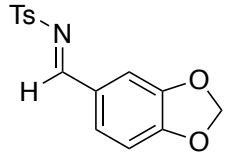
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (s, 1H), 8.40 (d, J = 8.4 Hz, 2H), 8.22 (d, J = 8.0 Hz, 2H), 7.96 (d, J = 8.4 Hz, 2H), 7.68 (t, J = 7.6 Hz, 1H), 7.51 (t, J = 8.0 Hz, 2H).



***N*-(2-Fluorobenzylidene)-4-benzenesulfonamide (4d)**

Imine **4d** was synthesized as previously reported and its ^{1}H NMR is in agreement with literature data.[17]

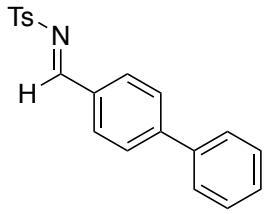
^{1}H NMR (400 MHz, $CDCl_3$) 9.36 (s, 1H), 8.10 − 8.06 (m, 1H), 7.90 (d, J = 8.0 Hz, 2H), 7.64 − 7.58 (m, 1H), 7.36 (d, J = 8.0 Hz, 2H), 7.25 − 7.22 (m, 1H), 7.19 − 7.15 (m, 1H), 2.45 (s, 3H).



***N*-(Benzo[*d*][1,3]dioxol-5-ylmethylene)-4-methylbenzenesulfonamide (4e)**

Imine **4e** was synthesized as previously reported and its ^{1}H NMR is in agreement with literature data precedent.[18]

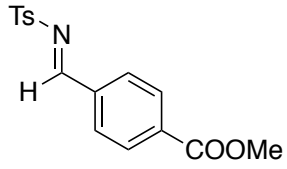
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.88 (s, 1H), 7.87 (dd, *J* = 6.3 Hz, 1.8 Hz, 2H), 7.45 (d, *J* = 1.8 Hz, 1H), 7.39 (dd, *J* = 5.4 Hz, 1.5 Hz, 1H), 7.34 (d, *J* = 8.1 Hz, 2H), 6.90 (d, *J* = 8.1 Hz, 1H), 6.07 (s, 2H), 2.43 (s, 3H).



***N*-([1,1'-Biphenyl]-4-ylmethylene)-4-methylbenzenesulfonamide (4f)**

Imine **4f** was synthesized as previously reported and its ^{1}H NMR is in agreement with literature data.[19]

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.07 (s, 1H), 7.99 (d, *J* = 8.4 Hz, 2H), 7.90 (d, *J* = 8.0 Hz, 2H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 8.0 Hz, 2H), 7.50-7.39 (m, 3H), 7.36 (d, J = 7.6 Hz, 2H), 2.45 (s, 3H).

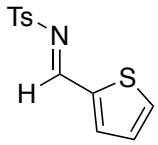


Methyl 4-((tosylimino)methyl)benzoate (4g)

Imine **4g** was synthesized as previously reported and its ^{1}H NMR is in agreement with literature data.[20]

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.07 (s, 3H), 8.13 (d, *J* = 8.4 Hz, 2H), 7.99 (d, *J* = 8.0 Hz,

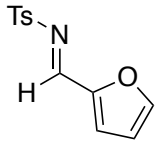
2H), 7.90 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 7.6 Hz, 2H), 3.95 (s, 3H), 2.45 (s, 3H).



4-Methyl-*N*-(thiophen-2-ylmethylene)benzenesulfonamide (4h)

Imine **4h** was synthesized as previously reported in and its ^{1}H NMR is in agreement with literature data.[20]

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (s, 1H), 7.87 (d, J = 8.8 Hz, 2H), 7.77 (d, J = 4.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.21 (t, J = 4.4 Hz, 1H), 2.43 (s, 3H).

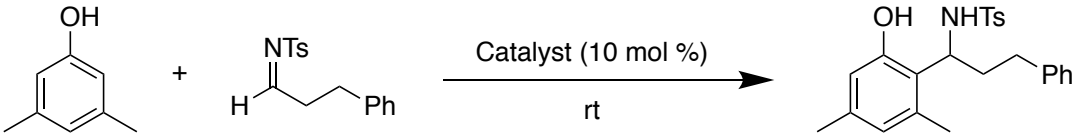


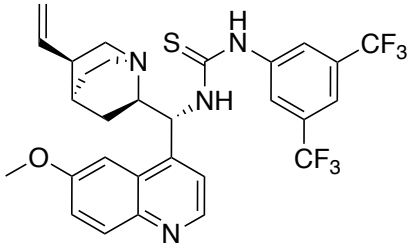
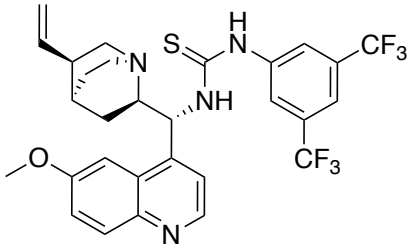
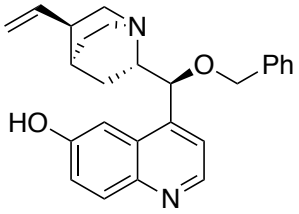
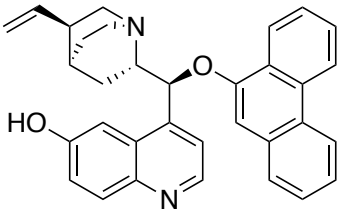
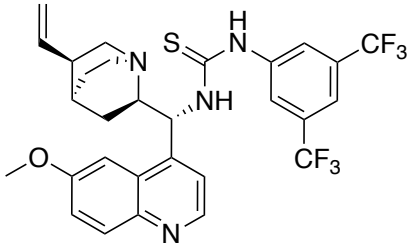
***N*-(Furan-2-ylmethylene)-4-methylbenzenesulfonamide (4i)**

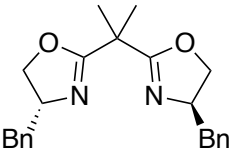
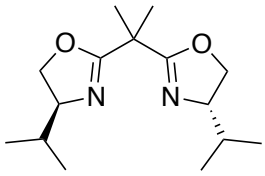
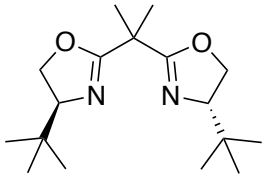
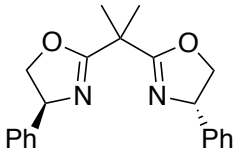
Imine **4i** was synthesized as previously reported and its ^{1}H NMR is in agreement with literature data.[14]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (s, 1H), 7.87 (d, J = 8.0 Hz, 2H), 7.74 (d, J = 0.4 Hz, 1H), 7.36 – 7.30 (m, 2H), 6.64 (dd, J = 3.6 Hz, 1.6 Hz, 1H), 2.43 (s, 3H).

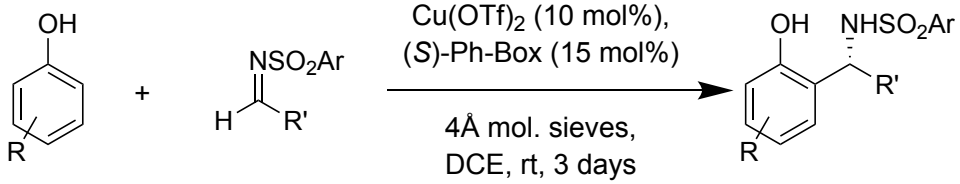
Aza-Friedel-Crafts Reaction Attempts Utilizing Alternate Catalysts



Entry	Solvent	Phenol equiv.	Time	Catalyst	Yield	*ee*
1	CH_2Cl_2	1.5	72 h		21%	18%
2	EtOAc	5	72 h		14%	8%
3	CH_2Cl_2	5	24 h		21%	27%
4	CH_2Cl_2	5	72 h		20%	4%
5	CH_2Cl_2	5	72 h		33%	20%

6	CH_2Cl_2	5	72 h	$Cu(OTf)_2$, 	19%	43%
7	CH_2Cl_2	5	72 h	$Cu(OTf)_2$, 	23%	69%
8	CH_2Cl_2	5	72 h	$Cu(OTf)_2$, 	5%	37%
9	**CH_2Cl_2**	**5**	**72 h**	**$Cu(OTf)_2$,** 	**53%**	**84%**

Representative Procedure for the $Cu(OTf)_2$-Catalyzed Enantioselective Phenol Addition to Alkyl Aldimines:



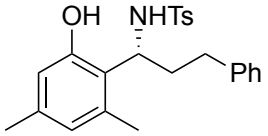
$Cu(OTf)_2$ (7.2 mg, 0.020 mmol, 10 mol %) was lightly flame dried in a vial charged with a magnetic stir bar. (*S*)-Ph-Box (10.1 mg, 0.030 mmol, 15 mol %) and 1,2-dichloroethane (1 mL) was added and the solution allowed to stir at room temperature for 2 h. Flame activated 4 Å mol. sieves (~20 mg) were added followed by solid imine (0.20 mmol, 1 equiv.) and phenol (0.30 mmol, 1.5 equiv.). The reaction was flushed with argon, sealed, and was stirred at room temperature for 72 h. The reaction was diluted with EtOAc (~3

mL) and filtered through a pad of silica gel (~5 cm) with EtOAc (3 x 50 mL). The combined filtrate was concentrated *in vacuo* and the crude product was purified by flash chromatography on silica gel.

Note: Reaction success is reliant on the purity of the imine and phenol starting materials.

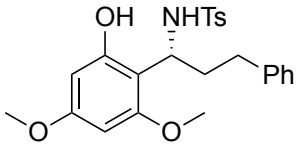
Characterization of Novel Alkyl Aldimine Addition Products

Alkyl Imines - Phenol Scope



(*R*)-*N*-(1-(2-hydroxy-4,6-dimethylphenyl)-3-phenylpropyl)-4-methylbenzenesulfonamide (3a)

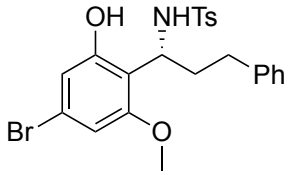
Imine **1a** (60 mg, 0.209 mmol) was converted to 45 mg **3a** (53% yield) using the procedure for alkyl imines. Mannich product **3a** was obtained as an off-white wax. $[\alpha]_D^{25}$ = 14.9 (c = 1.36 in $CHCl_3$); *ee* = 94%, determined by HPLC analysis [Regis (*S, S*)-Whelk, 90:10 hexanes/*i*PrOH, 0.35 mL/min, λ = 254 nm, t(major) = 38.2 min, t(minor) = 46.2 min]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.0 Hz, 2H), 7.24 (t, *J* = 7.5 Hz, 2H), 7.16 (t, *J* = 7.0 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 2H), 6.98 (d, *J* = 8.5 Hz, 2H), 6.30 – 6.23 (m, 2H), 6.16 (s, 1H), 6.08 (s, 1H), 4.54 – 4.49 (m, 1H), 2.80 – 2.73 (m, 1H), 2.62 – 2.54 (m, 1H), 2.33 – 2.24 (m, 1H), 2.28 (s, 3H), 2.07 (s, 3H), 1.99 – 1.92 (m, 1H), 1.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.0, 142.8, 141.5, 137.8, 137.2, 136.1, 128.9, 128.5, 128.3, 126.6, 125.8, 123.5, 121.9, 114.6, 52.8, 36.6, 32.4, 21.3, 20.6, 19.4; IR (neat): 3389, 3322, 2963, 2919, 1620, 1587, 1495, 1454, 1304, 1261, 1154, 1093, 1039, 838, 810, 740, 701, 673 cm^{-1}; HRMS (ESI) for $C_{24}H_{27}NO_3S$: calculated $[M + Na]^+$ *m/z* 432.1609, found 432.1604.

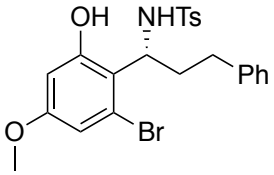


<u>Alternative procedure</u> for (*R*)-*N*-(1-(2-hydroxy-4,6-dimethoxyphenyl)-3-phenylpropyl)-4-methylbenzenesulfonamide (3b)

Note: With 3,5-dimethoxyphenol, an alternate procedure was needed in order to reduce a racemic background reaction.

$Cu(OTf)_2$ (7.6 mg, 0.021 mmol, 10 mol %) was lightly flame dried in a vial charged with a magnetic stir bar. (*S*)-Ph-Box (10.5 mg, 0.0313 mmol, 15 mol %) and 1,2-dichloroethane (1 mL) were added and the solution was stirred at room temperature for 2 h. Flame activated 4 Å mol. sieves (~20 mg) were added followed by 4-methyl-*N*-(3-phenylpropylidene)benzenesulfonamide (**1a**) (60 mg, 0.209 mmol, 1 equiv.) and 3,5-dimethoxyphenol (48.3 mg, 0.313 mmol, 1.5 equiv.). The reaction was flushed with argon, sealed, and stirred at room temperature for 72 h. The reaction was then diluted with EtOAc (~3 mL) and filtered through a pad of silica (~5 cm) and flushed with EtOAc (100 mL) and the combined filtrate concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford 91 mg product (99% yield) as an orange viscous oil. $[\alpha]_D^{26}$ = -4.5 (c = 0.65 in $CHCl_3$); *ee* = 82%, determined by HPLC analysis [Chiralpak AD-RH, 95:5 hexanes/*i*PrOH, 1.00 mL/min, λ = 254 nm, t(minor) = 25.3 min, t(major) = 29.0 min]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.0 Hz, 2H), 7.22 (t, *J* = 7.6 Hz, 2H), 7.16 - 7.08 (m, 3H), 7.01 (d, *J* = 8.0 Hz, 2H), 6.06 (bs, 1H), 5.97 (d, *J* = 10.4 Hz, 1H), 5.82 (d, *J* = 1.6 Hz, 1H), 5.76 (d, *J* = 2.0 Hz, 1H), 4.95 - 4.81 (m, 1H), 3.65 (s, 3H), 3.61 (s, 3H), 2.79 - 2.70 (m, 1H), 2.52 - 2.40 (m, 1H), 2.28 (s, 3H), 2.19 - 2.07 (m, 1H), 2.02 - 1.92 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 158.0, 154.3, 142.7, 141.9, 137.2, 128.8, 128.4, 128.2, 126.7, 125.6, 107.5, 93.8, 91.1, 55.3, 55.2, 49.8, 37.1, 32.6, 21.3; IR (neat): 3328, 2939, 1598, 1495, 1454, 1328, 1202, 1151, 1095, 895, 812, 752, 700, 666 cm^{-1}; HRMS (ESI) for $C_{24}H_{27}NO_5S$: calculated $[M + Na]^+$ *m/z* 464.1508, found 464.1521.





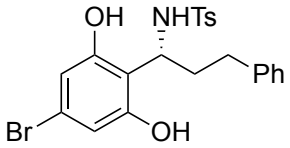
(*R*)-*N*-(1-(4-bromo-2-hydroxy-6-methoxyphenyl)-3-phenylpropyl)-4-methylbenzenesulfonamide ($3c_1$) and (*R*)-*N*-(1-(2-bromo-6-hydroxy-4-methoxyphenyl)-3-phenylpropyl)-4-methylbenzenesulfonamide ($3c_2$)

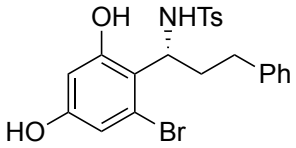
Imine **1a** (60 mg, 0.209 mmol) was converted to 63 mg of **$3c_1$** (61% yield) and 35 mg of **$3c_2$** (34% yield) using the procedure for alkyl imines. Mannich products **$3c_1$** and **$3c_2$** were obtained as an off-white waxy solid and a clear viscous oil, respectively.

Data for **$3c_1$**: $[\alpha]_D^{28}$ = +6.4 (c = 1.50 in $CHCl_3$), *ee* = 99%, determined by HPLC analysis [Chiralpak AD-RH, 95:5 hexanes/*i*PrOH, 0.60 mL/min, λ = 254 nm, t(major) = 28.9 min, t(minor) = 34.5 min]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, *J* = 8.4 Hz, 2H), 7.26 - 7.20 (m, 2H), 7.19 - 7.08 (m, 3H), 7.02 (d, *J* = 8.0 Hz, 2H), 6.41 (d, *J* = 1.2 Hz, 1H), 6.29 (d, *J* = 1.2 Hz, 1H), 6.45 (bs, 1H), 5.88 (d, *J* = 6.9 Hz, 1H), 4.95 - 4.85 (m, 1H), 3.64 (s, 3H), 2.82 - 2.75 (m, 1H), 2.55 - 2.44 (m, 1H), 2.33 (s, 3H), 2.19 - 2.04 (m, 1H), 1.99 - 1.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.3, 141.5, 136.8, 128.9, 128.4, 128.2, 126.6, 125.8, 121.7, 113.9, 112.2, 107.0, 55.7, 49.6, 36.4, 32.4, 21.4; IR (neat): 3328, 2924, 2854, 1586, 1495, 1453, 1415, 1334, 1215, 1151, 1091, 968, 908, 864, 848, 811, 732, 700, 671 cm^{-1}; HRMS (ESI) for $C_{23}H_{24}BrNO_4S$: calculated $[M + Na]^+$ *m/z* 512.0507, found 512.0510.

Data for **$3c_2$**: $[\alpha]_D^{27}$ = -6.6 (c = 1.20 in $CHCl_3$); *ee* = 88%, determined by HPLC analysis [Chiralpak AD-RH, 95:5 Hexanes/*i*PrOH, 0.60 mL/min, λ = 254 nm, t(minor) = 26.2 min, t(major) = 31.1 min]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.1 Hz, 2H), 7.26 - 7.03 (m, 7H), 6.43 (d, *J* = 1.8 Hz, 1H), 6.26 (d, *J* = 10.5 Hz, 1H), 6.16 (s, 1H), 4.96 - 4.78 (m, 1H), 3.61 (s, 3H), 2.90 - 2.76 (m, 1H), 2.59 - 2.42 (m, 1H), 2.29 (s, 3H), 2.22 - 2.04 (m, 1H), 2.03 - 1.84 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 154.6, 143.3, 141.3, 136.3, 129.2, 128.4, 128.3, 126.9, 125.8, 124.3, 118.5, 110.4, 102.1, 56.5, 55.4, 36.5, 32.3, 21.3; IR (neat): 3319, 2927, 1606, 1578, 1495, 1454, 1420, 1288, 1238, 1207, 1150, 1121,

1092, 1041, 974, 908, 811, 731, 699, 669 cm^{-1}; HRMS (ESI) for $C_{23}H_{24}NO_4S$: calculated $[M + Na]^+$ *m/z* 512.0507, found 512.0505.





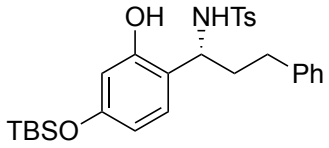
(*R*)-*N*-(1-(4-bromo-2,6-dihydroxyphenyl)-3-phenylpropyl)-4-methylbenzenesulfonamide ($3d_1$) and (*R*)-*N*-(1-(2-bromo-4,6-dihydroxyphenyl)-3-phenylpropyl)-4-methylbenzenesulfonamide ($3d_2$)

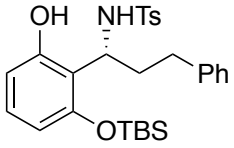
Imine **1a** (60 mg, 0.209 mmol) was converted to 44 mg $\mathbf{3d_1}$ (44% yield) and 43 mg $\mathbf{3d_2}$ (43% yield) using the procedure for alkyl imines. Mannich product $\mathbf{3d_1}$ and $\mathbf{3d_2}$ were obtained as an off-white solid and a white waxy solid, respectively.

Data for $\mathbf{3d_1}$: m.p. decomposes; $[\alpha]_D^{28}$ = -15.2 (c = 0.45 in EtOH); *ee* = 98%, determined by HPLC analysis [Chiralpak AD-RH, 91:9 hexanes/iPrOH, 0.50 mL/min, λ = 254 nm, t(minor) = 20.9 min, t(major) = 23.3 min]; ^{1}H NMR (400 MHz, CD_3OD) δ 7.47 (d, *J* = 8.4 Hz, 2H), 7.21 (t, *J* = 7.6 Hz, 2H), 7.16 – 7.08 (m, 3H), 7.02 (d, *J* = 8.0 Hz, 2H), 6.16 (s, 2H), 4.95 – 4.80 (m, 1H), 2.80 – 2.71 (m, 1H), 2.57 – 2.44 (m, 1H), 2.32 (s, 3H), 2.17 – 2.02 (m, 1H), 1.96 – 1.84 (m, 1H); ^{13}C NMR (100 MHz, CD_3COD) δ 144.3, 143.4, 138.6, 129.9, 129.4, 129.3, 127.7, 126.7, 121.4, 113.8, 110.9, 51.1, 38.1, 37.6, 21.5; IR (neat): 3328, 1599, 1496, 1421, 1304, 1151, 1084, 1031, 873, 811, 700, 670 cm^{-1}; HRMS (ESI) for $C_{22}H_{22}BrNO_4S$: calculated $[M + Na]^+$ *m/z* 498.0351, found 498.0335.

Data for $\mathbf{3d_2}$: $[\alpha]_D^{27}$ = -1.0 (c = 0.85 in $CHCl_3$); *ee* = 67%, determined by HPLC analysis [Chiralpak AD-RH, 91:1 hexanes/*i*PrOH, 0.50 mL/min, λ = 254 nm, t(minor) = 33.7 min, t(major) = 40.8 min]; ^{1}H NMR (300 MHz, CD_3COD): δ 7.49 (d, *J* = 7.5 Hz, 2H), 7.25 - 7.09 (m, 5H), 7.05 (d, *J* = 7.8 Hz, 2H), 6.25 (d, *J* = 1.8 Hz, 1H), 5.92 (d, *J* = 1.2 Hz, 1H), 4.87 (s, 3H), 4.90 - 4.75 (m, 1H), 2.88 - 2.73 (m, 1H), 2.61 - 2.50 (m, 1H), 2.29 (s, 3H), 2.21 - 2.04 (m, 1H), 1.95 - 1.81 (m, 1H); ^{13}C NMR (75 MHz, CD_3COD): 159.0, 157.4, 144.1, 143.1, 138.7, 130.0, 129.6, 129.3, 127.7, 126.7, 125.1, 118.3, 111.7, 103.7, 57.6,

38.0, 33.6, 21.4; IR (neat): 3322, 1703, 1611, 1592, 1495, 1446, 1287, 1150, 1124, 1093, 1045, 1005, 832, 812, 732, 700, 671 cm^{-1}; HRMS (ESI) for $C_{22}H_{22}BrNO_4S$: calculated $[M + Na]^+$ *m/z* 498.0351, found 498.0349.





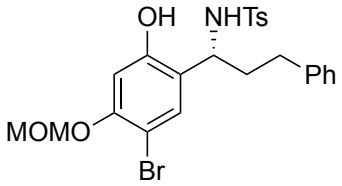
(*R*)-*N*-(1-(4-((*tert*-butyldimethylsilyl)oxy)-2-hydroxyphenyl)-3-phenylpropyl)-4-methylbenzenesulfonamide ($3e_1$) and (*R*)-*N*-(1-(2-((*tert*-butyldimethylsilyl)oxy)-6-hydroxyphenyl)-3-phenylpropyl)-4-methylbenzenesulfonamide ($3e_2$)

Imine **1a** (60 mg, 0.209 mmol) was converted to 81 mg $\mathbf{3e_1}$ (76% yield) and 16 mg $\mathbf{3e_2}$ (15% yield) using the procedure for alkyl imines. Mannich products $\mathbf{3e_1}$ and $\mathbf{3e_2}$ were obtained as an orange oil and a crystalline white solid, respectively.

Data for $\mathbf{3e_1}$: $[\alpha]_D^{27}$ = +19.1 (c = 3.10 in $CHCl_3$); *ee* = 92%, determined by HPLC analysis [Chiralpak AD-RH, 90:10 hexanes/*i*PrOH, 0.50 mL/min, λ = 254 nm, t(major) = 9.7 min, t(minor) = 12.1 min]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.4 Hz, 2H), 7.26 - 7.12 (m, 3H), 7.08 (d, *J* = 7.2 Hz, 2H), 7.03 (d, *J* = 8.4 Hz, 2H), 6.55 (d, *J* = 8.1 Hz, 1H), 6.51 (s, 1H), 6.16 (s, 1H), 6.13 (d, *J* = 8.4 Hz, 1H), 5.94 (d, *J* = 9.3 Hz, 1H), 4.31 - 4.20 (m, 1H), 2.74 - 2.41 (m, 2H), 2.30 (s, 3H), 2.23 - 2.01 (m, 2H), 0.96 (s, 9H), 0.15 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.8, 153.9, 142.9, 141.3, 137.1, 129.4, 129.1, 128.4, 128.2, 126.8, 125.7, 119.0, 111.7, 108.1, 56.7, 37.2, 32.5, 25.5, 21.3, 18.0, -4.6; IR (neat): 3332, 2930, 2858, 1613, 1516, 1496, 1430, 1296, 1254, 1177, 1153, 1094, 989, 908, 871, 838, 810, 781, 731, 699, 670 cm^{-1}; HRMS (ESI) for $C_{28}H_{37}NO_4SSi$: calculated $[M + Na]^+$ *m/z* 534.2110, found 534.2129.

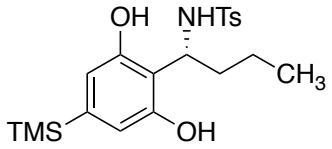
Data for $\mathbf{3e_2}$: m.p. 168.9 – 169.8 ˚C; *ee* not determined due to inseparability of enantiomers; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 (d, *J* = 7.5 Hz, 2H), 7.26 – 7.01 (m, 7H), 6.68 (d, *J* = 7.8 Hz, 1H), 6.20 – 6.10 (m, 2H), 5.36 (d, *J* = 9.3 Hz, 1H), 4.95 (s, 1H), 4.98 – 4.86 (m, 1H), 2.74 – 2.60 (m, 1H), 2.54 – 2.41 (m, 1H), 2.31 (s, 3H), 2.02 – 1.86

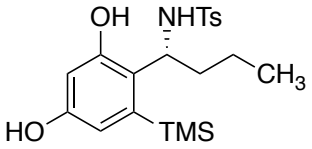
(m, 2H), 1.00 (s, 9H), 0.25 (d, J = 9.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.6, 153.5, 142.8, 141.4, 137.6, 129.2, 129.1, 128.3, 126.9, 125.8, 122.9, 107.6, 105.6, 55.3, 38.3, 32.5, 25.9, 21.4, 18.2, -3.9, -4.3; IR (neat): 3282, 2929, 2858, 1598, 1507, 1454, 1304, 1256, 1151, 1113, 1094, 993, 909, 841, 810, 781, 732, 700, 666 cm^{-1}; HRMS (ESI) for $C_{28}H_{37}NO_4SSi$: calculated $[M + Na]^+$ *m/z* 534.2110, found 534.2103.



(*R*)-*N*-(1-(5-bromo-2-hydroxy-4-(methoxymethoxy)phenyl)-3-phenylpropyl)-4-methylbenzenesulfonamide (3f)

Imine **1a** (60 mg, 0.209 mmol) was converted to 96 mg **3f** (77% yield) using the procedure for alkyl imines. Mannich product **3f** was obtained as a clear viscous oil. $[\alpha]_D^{27}$ = +6.1 (c = 2.90 in $CHCl_3$); *ee* = 96%, determined by HPLC analysis [Chiralpak AD-RH, 95:5 hexanes/*i*PrOH, 1.00 mL/min, λ = 254 nm, t(major) = 22.8 min, t(minor) = 33.0 min]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 8.4 Hz, 2H), 7.26 - 7.20 (m, 2H), 7.18 - 7.14 (m, 1H), 7.05 (d, J = 6.8 Hz, 4H), 6.56 (s, 1H), 6.68 (s, 1H), 6.49 (s, 1H), 5.79 (d, J = 9.6 Hz, 1H), 5.08 (s, 2H), 4.21 - 4.13 (m, 1H), 3.46 (s, 3H), 2.64 - 2.56 (m, 1H), 2.52 - 2.43 (m, 1H), 2.32 (s, 3H), 2.19 - 1.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 153.3, 143.4, 140.9, 136.6, 132.7, 129.3, 128.3, 126.9, 125.9, 121.2, 104.7, 102.5, 95.0, 56.3, 56.0, 36.6, 32.4, 21.4; IR (neat): 3327, 2926, 1610, 1497, 1420, 1324, 1287, 1216, 1150, 1088, 1015, 960, 909, 812, 730, 700, 670 cm^{-1}; HRMS (ESI) for $C_{24}H_{26}BrNO_5S$: calculated $[M + Na]^+$ *m/z* 542.0613, found 542.0602.



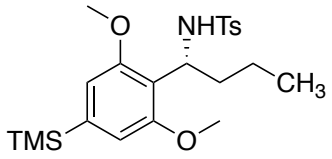


(*R*)-*N*-(1-(2,6-dihydroxy-4-(trimethylsilyl)phenyl)butyl)-4-methylbenzenesulfonamide ($3g_1$) and (*R*)-*N*-(1-(2,4-dihydroxy-6-(trimethylsilyl)phenyl)butyl)-4-methylbenzenesulfonamide ($3g_2$)

Imine **1b** (45 mg, 0.200 mmol) was converted to 47 mg **$3g_1$** (58% yield) and 12 mg **$3g_2$** (14% yield) using the procedure for alkyl imines. Mannich products **$3g_1$** and **$3g_2$** were obtained as light yellow and light orange solids, respectively.

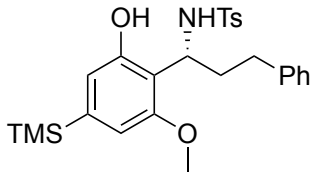
Data for **$3g_1$**: m.p. 145 – 146 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 8.8 Hz, 2H), 6.98 (d, J = 8.4 Hz, 2H), 6.22 (s, 2H), 5.94 (d, J = 9.6 Hz, 1H), 5.35 (bs, 2H), 4.90 – 4.83 (m, 1H), 2.27 (s, 3H), 1.90 – 1.79 (m, 1H), 1.76 – 1.64 (m, 1H), 1.49 – 1.36 (m, 1H), 1.31 – 1.18 (m 1H), 0.87 (t, J = 7.6 Hz, 3H), 0.15 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.3, 142.5, 141.4, 137.2, 128.8, 126.8, 114.6, 112.7, 50.0, 37.1, 21.4, 19.3, 13.6, -1.3; IR (neat): 3403, 2957, 1707, 1613, 1578, 1399, 1304, 1247, 1185, 1153, 1111, 1090, 1020, 919, 893, 830, 810, 755, 669 cm^{-1}; HRMS (ESI) for $C_{20}H_{29}NO_4SSi$: calculated $[M + Na]^+$ *m/z* 430.1484, found 430.1477.

Data for **$3g_2$**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 8.4 Hz, 2H), 7.04 (d, J = 8.0 Hz, 2H), 6.41 (d, J = 2.4 Hz, 1H), 6.20 (s, 1H), 6.12 (d, J = 9.2 Hz, 1H), 6.06 (d, J = 2.4 Hz, 1H), 5.07 (s, 1H), 4.51 (td, J = 9.6, 4.8 Hz, 1H), 2.31 (s, 3H), 2.05 – 1.82 (m, 1H), 1.57 – 1.46 (m, 2H), 1.38 – 1.25 (m, 1H), 0.88 (t, J = 7.2 Hz, 3H), 0.26 (s, 9H) ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.8, 154.2, 142.8, 140.8, 137.8, 129.0, 126.7, 125.0, 113.9, 104.6, 57.3, 38.1, 21.4, 19.8, 13.9, 0.8; IR (neat): 3331, 2958, 1598, 1402, 1304, 1251, 1140, 1091, 1022, 1004, 886, 838, 759, 671 cm^{-1}; HRMS (ESI) for $C_{20}H_{29}NO_4SSi$: calculated $[M + Na]^+$ *m/z* 430.1484, found 430.1498.



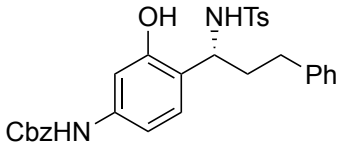
N-(1-(2,6-dimethoxy-4-(trimethylsilyl)phenyl)butyl)-4-methylbenzenesulfonamide ($3g_1$)

Phenol $\mathbf{3g_1}$ (47 mg, 0.12 mmol, 1 equiv.) was dissolved in a suspension of anhydrous K_2CO_3 (65 mg, 0.47 mmol, 4.1 equiv.) in DMF (0.2 mL) and cooled to 0 °C. MeI (36 μL, 0.58 mmol, 5 equiv.) was added slowly and the reaction was allowed to warm to room temperature and vigorously stirred overnight. The reaction was quenched with 50% saturated NH_4Cl (5 mL) and diluted with ether (5 mL). The aqueous phase was extracted with diethyl ether (3 x 5 mL) and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography using 9:1 hexanes/EtOAc to 5:2 hexanes/EtOAc to give 40 mg (*R*)-*N*-(1-(2,6-dimethoxy-4-(trimethylsilyl)phenyl)butyl)-4-methylbenzenesulfonamide as a white crystalline solid (80% yield); m.p. 128.6 – 130.3 ˚C; $[\alpha]_D^{28}$ = +5.8 (c = 0.95 in $CHCl_3$; *ee* = 70%, determined by HPLC analysis [Regis (*S, S*)-Whelk, 90:10 hexanes/*i*PrOH, 0.80 mL/min, λ = 254 nm, t(major) = 34.2 min, t(minor) = 40.9 min]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.1 Hz, 2H), 6.88 (d, *J* = 8.1 Hz, 2H), 6.34 (s, 2H), 5.92 (d, *J* = 10.5 Hz, 1H), 4.98 – 4.85 (m, 1H), 3.71 (s, 6H), 2.23 (s, 3H), 1.85 – 1.72 (m, 1H), 1.65 – 1.36 (m, 2H), 1.33 – 1.16 (m, 1H), 0.87 (t, *J* = 7.2 Hz, 3H), 0.21 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) 141.9, 140.8, 137.6, 128.3, 126.7, 117.4, 107.8, 55.4, 49.4, 37.3, 21.4, 19.4, 13.7, -1.1; IR (neat): 2957, 2867, 1595, 1562, 1456, 1394, 1332, 1287, 1239, 1183, 1162, 1127, 1093, 1042, 901, 886, 826, 755, 732, 669 cm^{-1}; HRMS (ESI) for $C_{22}H_{33}NO_4SSi$: calculated $[M + K]^+$ *m/z* 474.1537, found 474.1532.



(*R*)-*N*-(1-(2-hydroxy-6-methoxy-4-(trimethylsilyl)phenyl)-3-phenylpropyl)-4-methylbenzenesulfonamide (3h)

Imine **1a** (60 mg, 0.209 mmol) of imine was converted to 76 mg **3h** (76% yield) using the procedure for alkyl imines. Mannich product **3h** was obtained as an orange oil; $[\alpha]_D^{26}$ = +3.5 (c = 1.02 in $CHCl_3$); *ee* >99%, determined by HPLC analysis [Chiralpak AD-RH, 57:43 EtOH/H_2O (with 0.1% formic acid), 0.60 mL/min, λ = 210 nm, t(minor) = 27.3 min, t(major) = 31.4 min]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.0 Hz, 2H), 7.25 - 7.20 (m, 2H), 7.16 - 7.11 (m, 3H), 6.93 (d, *J* = 8.0 Hz, 2H), 6.29 (s, 1H), 6.25 (s, 1H), 6.02 (d, *J* = 11.2 Hz, 1H), 5.27 (bs, 1H), 4.99 - 4.90 (m, 1H), 3.66 (s, 3H), 2.86 - 2.78 (m, 1H), 2.59 - 2.48 (m, 1H), 2.22 (s, 3H), 2.20 (m, 1H), 2.01 - 1.92 (m, 1H), 0.18 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 153.1, 142.4, 141.9, 141.3, 137.0, 128.6, 128.4, 128.3, 128.2, 126.7, 125.6, 115.3, 113.3, 106.9, 55.3, 49.9, 36.7, 32.5, 21.4, -1.2; IR (neat): 3326, 2953, 1602, 1573, 1496, 1395, 1287, 1247, 1153, 1091, 900, 827, 755, 699, 671, 565 cm^{-1}; HRMS (ESI) for $C_{26}H_{33}NO_4SSi$: calculated $[M + Na]^+$ *m/z* 506.1797, found 506.1799.

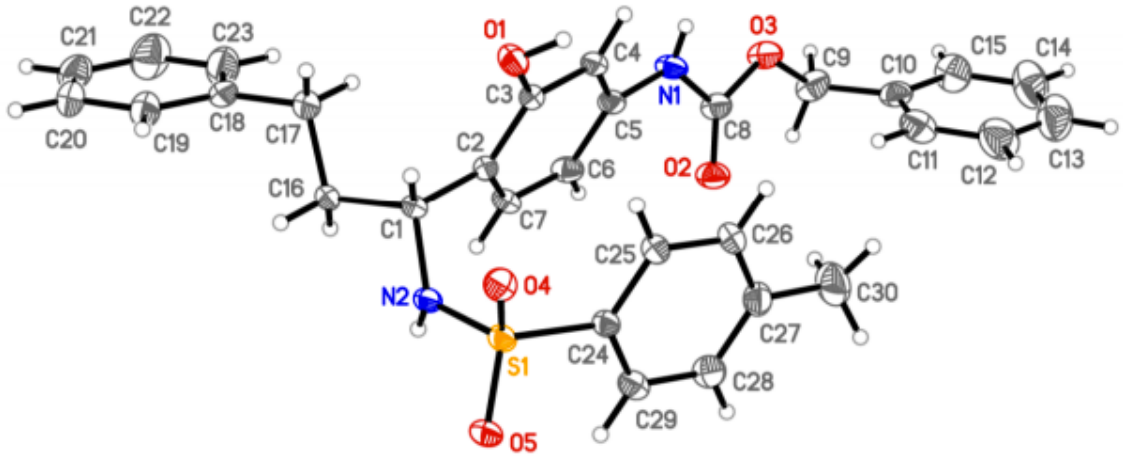


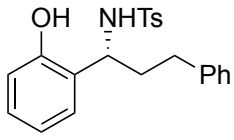
Benzyl (*R*)-(3-hydroxy-4-(1-((4-methylphenyl)sulfonamido)-3-phenylpropyl)phenyl)carbamate (3i)

Imine **1a** (60 mg, 0.209 mmol) was converted to 72 mg of **3i** (65% yield) using the procedure for alkyl imines. Mannich product **3i** was obtained as a white crystalline solid;

m.p. 165-168 ˚C; $[\alpha]_D^{28}$ = +14.2 (c = 1.35 in EtOH); *ee* = 97%, determined by HPLC analysis [Chiralpak AD-RH, 80:20 hexanes/*i*PrOH, 1.00 mL/min, λ = 254 nm, t(major) = 24.9 min, t(minor) = 29.8]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.4 Hz, 2H), 7.41 - 7.32 (m, 5H), 7.21 (t, *J* = 7.2 Hz, 2H), 7.16 - 6.95 (m, 6H), 6.90 (s, 1H), 6.76 (s, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 6.40 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H), 5.70 (d, *J* = 9.6 Hz, 1H), 5.18 (s, 2H), 4.34 - 4.21 (m, 1H), 2.61 - 2.53 (m, 1H), 2.50 - 2.41 (m, 1H), 2.26 (s, 3H), 2.17 - 1.97 (m, H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 142.9, 141.2, 137.8, 137.3, 135.6, 129.3, 129.1, 128.7, 128.5, 128.4, 128.3, 128.1, 126.9, 126.8, 121.7, 67.3, 56.4, 36.9, 32.5, 21.3; IR (neat): 3318, 2926, 1702, 1609, 1539, 1496, 1430, 1304, 1223, 1152, 1120, 1062, 963, 909, 856, 810, 735, 697, 668 cm^{-1}; HRMS (ESI) for $C_{30}H_{30}N_2O_5S$: calculated $[M + Na]^+$ *m/z* 553.1773, found 553.1791.

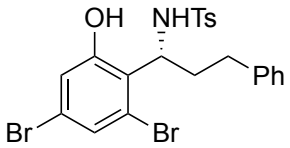
The X-ray crystal structure of **3i** (CCDC 1588079) was used to establish the absolute configuration of the stereocarbon (C1 below). The structure was obtained by William W. Brennessel at the Crystallographic Facility at the University of Rochester.





(*R*)-*N*-(1-(2-hydroxyphenyl)-3-phenylpropyl)-4-methylbenzenesulfonamide (3j)

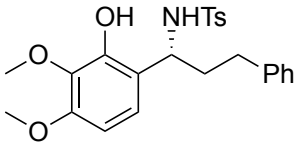
Imine **1a** (60 mg, 0.209 mmol) was converted to 24 mg **3j** (30% yield) using the procedure for alkyl imines. Mannich product **3j** was obtained as a white waxy solid; *ee* = 96%, determined by HPLC analysis [Regis (*S, S*)-Whelk, 90:10 hexanes/*i*PrOH, 0.35 mL/min, λ = 254 nm, t(major) = 51.6 min, t(minor) = 63.9 min]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.5 Hz, 2H), 7.24 (t, *J* = 7.5 Hz, 2H), 7.16 (t, *J* = 7.5 Hz, 1H), 7.07 (d, *J* = 7.0 Hz, 2H), 7.02 (d, *J* = 8.5 Hz, 2H), 6.98 (t, *J* = 7.5 Hz, 1H), 6.75 (d, *J* = 7.5 Hz, 1H), 6.67 (t, *J* = 7.5 Hz, 1H), 6.56 (d, *J* = 8.5 Hz, 1H), 5.97 (s, 1H), 5.75 (d, *J* = 14.5 Hz, 1H), 4.37 – 4.28 (m, 1H), 2.65 – 2.60 (m, 1H), 2.54 – 2.49 (m, 1H), 2.30 (s, 3H), 2.20 – 2.03 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.9, 143.0, 141.1, 137.1, 129.2, 129.0, 128.5, 128.4, 128.3, 126.9, 126.1, 125.9, 120.5, 116.2, 57.0, 37.0, 32.5, 21.4; IR (neat): 3317, 3028, 2924, 2856, 1598, 1496, 1456, 1420, 1316, 1154, 1093, 1064, 968, 911, 812, 753, 700, 670, 605 cm^{-1}; HRMS (ESI) for $C_{22}H_{23}NO_3S$ calculated $[M + Na]^+$ *m/z* 404.1296, found 404.1287.



(*R*)-*N*-(1-(2,4-dibromo-6-hydroxyphenyl)-3-phenylpropyl)-4-methylbenzenesulfonamide (3k)

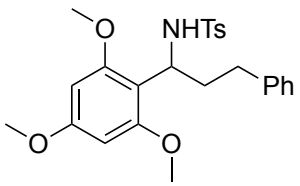
Imine **1a** (60 mg, 0.209 mmol) was converted to 29 mg **3k** (26% yield) using the procedure for alkyl imines. Mannich product **3k** was obtained as a clear oil; $[\alpha]_D^{26}$ = -2.3 (c = 0.70 in $CHCl_3$); *ee* = 86%, determined by HPLC analysis [Regis (*S, S*)-Whelk, 95:5 hexanes/*i*PrOH, 0.75 mL/min, λ = 254 nm, t(major) = 27.0 min, t(minor) = 34.0 min]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.5 Hz, 2H), 7.26 - 7.00 (m, 9H), 6.64 (s, 1H), 6.18 (d, *J* = 9.9 Hz, 1H), 4.92 - 4.80 (m, 1H), 2.90-2.75 (m, 1H), 2.60 - 2.47 (m, 1H), 2.32 (s, 3H), 2.28 - 2.10 (m, 1H), 2.01 - 1.95 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 143.9, 140.9, 136.0, 129.3, 128.5, 128.4, 127.3, 126.8, 126.0, 125.1, 124.5, 121.2, 118.7, 56.5, 35.8, 32.2, 21.5; IR (neat): 3319, 2924, 1580, 1495, 1405, 1335, 1257, 1151, 1092, 963, 913, 837, 812, 733, 699, 668 cm^{-1}; HRMS (ESI) for $C_{22}H_{21}Br_2NO_3S$

calculated $[M + Na]^+$ *m/z* 559.9507, found 559.9478.



(*R*)-*N*-(1-(2-hydroxy-3,4-dimethoxyphenyl)-3-phenylpropyl)-4-methylbenzenesulfonamide (3l)

Imine **1a** (60 mg, 0.209 mmol) was converted to 52 mg **3l** (56% yield) using the procedure for alkyl imines. Mannich product **3l** was obtained as a pale yellow solid; m.p. 147-148 ˚C; $[\alpha]_D^{24}$ = -1.2 (c = 0.70 in $CHCl_3$); *ee* = 33%, determined by HPLC analysis [Regis (*S, S*)-Whelk, 90:10 hexanes/*i*PrOH, 0.80 mL/min, λ = 254 nm, t(minor) = 38.1 min, t(major) = 42.3 min]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.4 Hz, 2H), 7.28 - 7.21 (m, 2H), 7.19 - 7.08 (m, 3H), 7.01 (d, *J* = 7.8 Hz, 2H), 6.45 (d, *J* = 8.7 Hz, 1H), 6.20 (d, *J* = 8.7 Hz, 1H), 6.12 (s, 1H), 5.56 (d, *J* = 10.2 Hz, 1H), 4.35 - 4.22 (m, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 2.72 - 2.61 (m, 1H), 2.59 - 2.44 (m, 1H), 2.23 (s, 3H), 2.22 - 1.98 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.5, 146.1, 142.4, 141.4, 137.8, 128.8, 128.4, 128.3, 126.9, 125.8, 125.8, 123.6, 119.1, 103.3, 60.7, 57.0, 55.8, 37.2, 32.5, 21.3; IR (neat): 3326, 2932, 1617, 1506, 1466, 1431, 1321, 1288, 1216, 1154, 1095, 976, 881, 813, 796, 751, 699, 669 cm^{-1}; HRMS (EI) for $C_{24}H_{27}NO_5S$: calculated $[M]^+$ *m/z* 441.1610, found 441.1610.

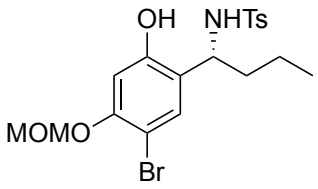


4-Methyl-*N*-(3-phenyl-1-(2,4,6-trimethoxyphenyl)propyl)benzenesulfonamide (3m)

Imine **1a** (60 mg, 0.209 mmol) was converted to 24 mg **3m** (25% yield) using the

procedure for alkyl imines. Mannich product **3m** was obtained as a white solid. ^{1}H NMR data matched that previously reported by Kim[21]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.1 Hz, 2H), 7.26 - 7.21 (m, 2H), 7.17 - 7.11 (m, 3H), 6.96 (d, *J* = 8.4 Hz, 2H), 5.85 (d, *J* = 11.4 Hz, 1H), 5.82 (s, 2H), 4.94 - 4.85 (m, 1H), 3.71 (s, 3H), 3.66 (s, 6H), 2.82 - 2.73 (m, 1H), 2.54 - 2.44 (m, 1H), 2.28 (s, 3H), 2.21 - 2.04 (m, 1H), 1.96 - 1.81 (m, 1H); *ee* < 5%, determined by HPLC analysis [Regis (*S, S*)-Whelk, 93:7 hexanes/*i*PrOH, 0.65 mL/min, λ = 254 nm, t_1 = 88.1 min, t_2 = 97.5 min].

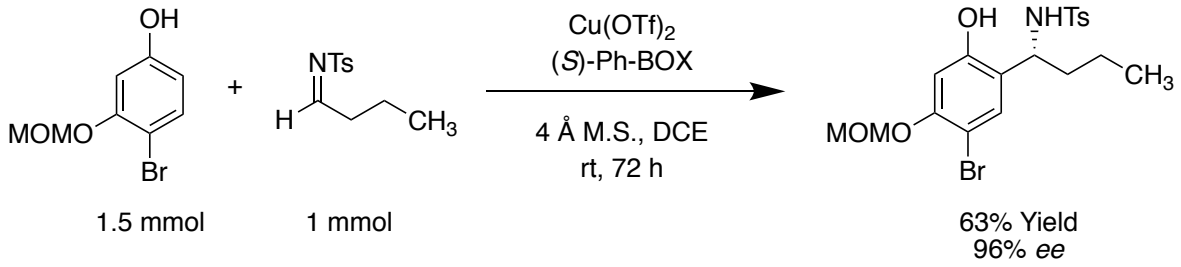
Alkyl Imine Scope



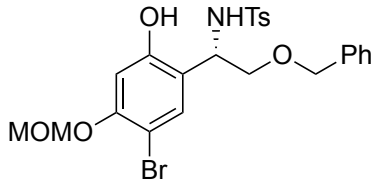
(*R*)-*N*-(1-(5-bromo-2-hydroxy-4-(methoxymethoxy)phenyl)butyl)-4-methylbenzenesulfonamide (3n)

Imine **1b** (46 mg, 0.204 mmol) was converted to 80 mg **3n** (85% yield) using the procedure for alkyl imines. Mannich product **3n** was obtained as a clear viscous oil; $[\alpha]_D^{26}$ = +15.2 (c = 0.60 in $CHCl_3$); *ee* = 91%, determined by HPLC analysis [Chiralpak AD-RH, 90:10 hexanes/*i*PrOH, 1.00 mL/min, λ = 254 nm, t(major) = 6.9 min, t(minor) = 9.2 min]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.4 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 6.80 (s, 1H), 6.52 (bs, 1H), 6.46 (s, 1H), 5.55 (d, *J* = 9.2 Hz, 1H), 5.08 (m, 2H), 4.20 - 4.10 (m, 1H), 3.47 (s, 3H), 2.34 (s, 3H), 1.81 (m, 2H), 1.37 - 1.09 (m, 2H), 0.83 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.3, 153.3, 143.4, 136.8, 13.5, 129.2, 127.0, 121.7, 104.5, 102.6, 95.0, 56.3, 55.9, 37.3, 21.5, 19.4, 13.5; IR (neat): 3331, 2959, 1610, 1500, 1420, 1325, 1153, 1090, 1017, 925, 812, 671 cm^{-1}; HRMS (ESI) for $C_{19}H_{24}BrNO_5S$: calculated $[M + Na]^+$ *m/z* 480.0456, found 480.0435.

1 mmol Scale Synthesis of 3n



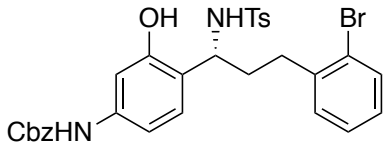
$Cu(OTf)_2$ (36 mg, 0.10 mmol, 10 mol %) was lightly flame dried in a 20 mL vial charged with a magnetic stir bar. (*S*)-Ph-Box (50 mg, 0.150 mmol, 15 mol %) and 1,2-dichloroethane (5 mL) were added and the solution allowed to stir at room temperature for 2 h. Flame activated 4 Å mol. sieves (~100 mg) were added followed by *N*-butylidene-4-methylbenzenesulfonamide (225 mg, 1.0 mmol, 1 equiv.) and 4-bromo-3-(methoxymethoxy)phenol (350 mg, 1.5 mmol, 1.5 equiv.). The reaction was flushed with argon, sealed, and was stirred at room temperature for 72 h. The reaction was diluted with EtOAc (10 mL) and filtered through a pad of silica gel (~5 cm) with EtOAc (200 mL). The combined filtrate was concentrated *in vacuo* and the crude product was purified by flash chromatography on silica gel (30% to 60% EtOAc in hexanes) to afford 289 mg of (*R*)-*N*-(1-(5-bromo-2-hydroxy-4-(methoxymethoxy)phenyl)butyl)-4-methylbenzenesulfonamide **3n** (63% yield, 96% *ee*).



(*S*)-*N*-(2-(benzyloxy)-1-(5-bromo-2-hydroxy-4-(methoxymethoxy)phenyl)ethyl)-4-methylbenzenesulfonamide (3o)

Imine **1c** (61 mg, 0.201 mmol) was converted to 83 mg of **3o** (77% yield) using the procedure for alkyl imines. Mannich product **3o** was obtained as a white waxy solid; $[\alpha]_D^{25}$ = +27.2 (c = 1.45 in $CHCl_3$); *ee* = 90%, determined by HPLC analysis [Chiralpak

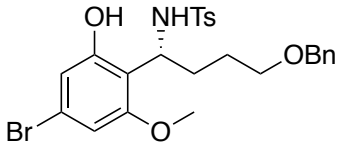
AD-RH, 95:5 hexanes/*i*PrOH, 1.00 mL/min, λ = 254 nm, t(minor) = 52.0 min, t(major) = 58.0 min]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.38-7.29 (m, 3H), 7.27-7.05 (m, 2H), 7.10 (d, *J* = 8.4 Hz, 2H), 6.87 (s, 1H), 6.50 (s, 1H), 5.62 (d, *J* = 7.6 Hz, 1H, 5.10, (s, 2H), 4.52 (ABq, J_{AB} = 11.8 Hz, Δν = 7.2 Hz, 2H), 4.46-4.39 (m, 1H), 3.77 (ABXq, J_{AB} = 9.6 Hz, J_{AX} = 4.4 Hz, J_{BX} = 4.4 Hz, 2H), 3.48 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 154.2, 143.4, 136.4, 133.4, 129.3, 128.7, 128.4, 128.0, 127.0, 119.3, 105.9, 102.6, 94.9, 73.9, 73.0, 56.3, 55.8, 21.5; IR (neat); 3276, 2969, 1610, 1497, 1419, 1328, 1287, 1215, 1151, 1086, 1014, 948, 813, 737, 698, 668 cm^{-1}; HRMS (ESI) for $C_{24}H_{26}BrNO_6S$: calculated $[M + Na]^+$ *m/z* 558.0562, found 558.0551.

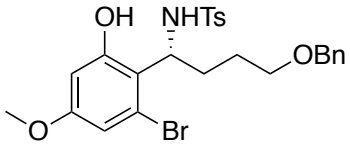


Benzyl (*R*)-(4-(3-(2-bromophenyl)-1-((4-methylphenyl)sulfonamido)propyl)-3-hydroxyphenyl)carbamate (3p)

Imine **1d** (75 mg, 0.205 mmol) was converted to 89 mg of **3p** (71% yield) using the procedure for alkyl imines. Mannich product **3p** was obtained as a white solid; m.p. = 183 – 185 ˚C; $[\alpha]_D^{28}$ = +18.2 (c = 1.30 in EtOH); *ee* = 90%, determined by HPLC analysis [Chiralpak AD-RH, 80:20 hexanes/*i*PrOH, 1.00 mL/min, λ = 254 nm, t(major) = 19.9 min, t(minor) = 28.8 min]; ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 8.55 (d, *J* = 14.0 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.43 – 7.30 (m, 4H), 7.26 (d, *J* = 4.4 Hz, 2H), 7.17 – 7.04 (m, 4H), 6.99 (d, *J* = 8.0 Hz, 1H), 6.79 (d, *J* = 7.6 Hz, 1H), 6.66 (d, *J* = 8.8 Hz, 1H), 5.15 (s, 2H), 4.70 – 4.62 (m, 1H), 2.85 – 2.78 (m, 1H), 2.66 – 2.56 (m, 1H), 2.28 (s, 3H), 2.05 – 1.98 (m, 2H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 206.3, 155.1, 154.2, 143.2, 142.1, 140.0, 140.0, 138.0, 133.5, 131.4, 129.9, 129.3, 129.2, 128.9, 128.9, 128.7, 128.6, 127.7, 124.8, 122.9, 110.4, 106.3, 66.8, 54.7, 37.3, 33.7, 30.5, 30.3, 30.1, 29.9, 29.7, 29.5, 29.3, 21.4; IR (neat); 3327, 1701, 1611, 1544, 1430, 1319, 1223, 1155, 1063, 1025, 969, 859, 811, 746, 698, 669 cm^{-1}; HRMS (ESI) for $C_{30}H_{29}BrN_2O_5S$:

calculated $[M + Na]^+$ *m/z* 631.0878, found 631.0900.



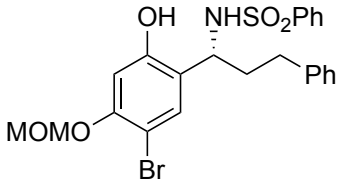


(*R*)-*N*-(4-(benzyloxy)-1-(4-bromo-2-hydroxy-6-methoxyphenyl)butyl)-4-methylbenzenesulfonamide ($3q_1$) and (*R*)-*N*-(4-(benzyloxy)-1-(2-bromo-6-hydroxy-4-methoxyphenyl)butyl)-4-methylbenzenesulfonamide ($3q_2$)

Imine **1e** (67 mg, 0.202 mmol) was converted to 48 mg of $\mathbf{3q_1}$ (44% yield) and 35 mg of $\mathbf{3q_2}$ (32% yield) using the procedure for alkyl imines. Mannich products $\mathbf{3q_1}$ and $\mathbf{3q_2}$ were both obtained as clear viscous oils.

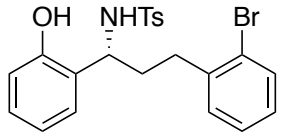
Data for $\mathbf{3q_1}$: $[\alpha]_D^{27}$ = -11.2 (c = 1.70 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.4 Hz, 2H), 7.40 – 7.24 (m, 5H), 7.19 (s, 1H), 6.98 (d, *J* = 8.0 Hz, 2H), 6.34 (s, 1H), 6.23 (d, *J* = 1.2 Hz, 1H), 5.94 (bs, 1H), 4.90 – 4.78 (m, 1H), 4.52 (s, 2H), 3.63 (s, 3H), 3.51 (t, *J* = 7.6 Hz, 2H), 2.31 (s, 3H), 1.93 – 1.81 (m, 2H), 1.65 – 1.44 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 143.1, 136.8, 128.8, 128.5, 128.0, 127.9, 126.5, 121.1, 106.6, 73.2, 70.6, 55.7, 49.9, 25.9, 21.4; IR (neat): 3326, 2925, 1736, 1585, 1495, 1453, 1415, 1333, 1215, 1184, 1155, 1087, 910, 858, 842, 810, 733, 698, 670 cm^{-1}; HRMS (ESI) for $C_{25}H_{28}BrNO_5S$: calculated $[M + Na]^+$ *m/z* 556.0769, found 556.0782.

Data for $\mathbf{3q_2}$: $[\alpha]_D^{27}$ = -2.5 (c = 1.85 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (m, 3H), 7.37 – 7.25 (m, 4H), 7.04 (d, *J* = 8.0 Hz, 2H), 6.41 (d, *J* = 1.6 Hz, 1H), 6.21 (d, *J* = 7.2 Hz, 1H), 6.04 (d, *J* = 1.6 Hz, 1H), 4.79 – 4.69 (m 1H), 4.49 (s, 2H), 3.60 (s, 3H), 3.48 (t, *J* = 5.6 Hz, 2H), 2.28 (s, 3H), 1.93 – 1.66 (m, 3H), 1.61 – 1.49 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 154.9, 143.1, 137.8, 136.3, 129.1, 128.4, 127.9, 127.8, 126.9, 124.1, 118.4, 110.2, 102.0, 73.0, 69.9, 56.7, 55.3, 31.5, 26.2, 21.3; IR (neat): 3322, 2859, 1605, 1578, 1495, 1454, 1421, 1289, 1208, 1153, 1126, 1090, 1044, 976, 924, 811, 737, 698, 669 cm^{-1}; HRMS (ESI) for $C_{25}H_{28}BrNO_5S$: calculated $[M + Na]^+$ *m/z* 556.0769, found 556.0769.



(*R*)-*N*-(1-(5-bromo-2-hydroxy-4-(methoxymethoxy)phenyl)-3-phenylpropyl)benzenesulfonamide (3r)

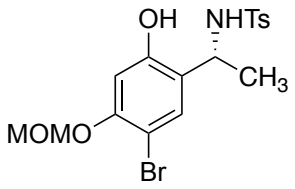
Imine **1f** (55 mg, 0.201 mmol) was converted to 57 mg of **3r** (56% yield) using the procedure for alkyl imines. Mannich product **3r** was obtained as a white solid; m.p. = decomposition at 155 ˚C; $[\alpha]_D^{27}$ = -0.9 (c = 1.05 in $CHCl_3$); *ee* = 95%, determined by HPLC analysis [Chiralpak AD-RH, 90:10 hexanes/*i*PrOH, 0.75 mL/min, λ = 254 nm, t(major) = 14.0 min, t(minor) = 16.6 min]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.8 Hz, 2H), 7.40 (t, *J* = 7.2 Hz, 1H), 7.32 - 7.12 (m, 5H), 7.05 (d, *J* = 7.2 Hz, 2H), 6.84 (s, 1H), 6.43 (s, 1H), 6.32 (s, 1H), 5.71 (d, *J* = 9.3 Hz, 1H), 5.07 (s, 2H), 4.27 - 4.16 (m, 1H), 3.46 (s, 3H), 2.65 - 2.42 (m, 2H), 2.20 - 1.98 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.4, 153.2, 140.8, 138.8, 132.7, 132.4, 128.6, 128.4, 128.4, 126.9, 126.0, 121.2, 104.8, 102.7, 94.9, 56.3, 55.9, 36.6, 32.4; IR (neat): 3321, 1609, 1498, 1447, 1421, 1326, 1216, 1153, 1091, 1016, 961, 752, 723, 688 cm^{-1}; HRMS (ESI) for $C_{23}H_{24}BrNO_5S$: calculated $[M + Na]^+$ *m/z* 528.0456, found 528.0446.



(*R*)-*N*-(3-(2-bromophenyl)-1-(2-hydroxyphenyl)propyl)-4-methylbenzenesulfonamide (3s)

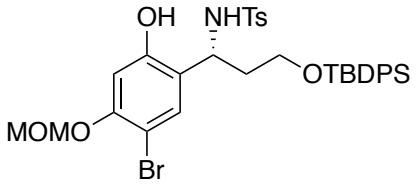
Imine **1d** (75 mg, 0.205 mmol) was converted to 48 mg of **3s** (51% yield) using the procedure for alkyl imines. Mannich product **3s** was obtained as a clear oil; $[\alpha]_D^{26}$ = +18.2 (c = 0.90 in $CHCl_3$); *ee* = 96%, determined by HPLC analysis [Chiralpak AD-RH,

92:8 hexanes/*i*PrOH, 1.00 mL/min, λ = 254 nm, t(major) = 23.3 min, t(minor) = 26.8 min]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.2 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.19 (t, *J* = 7.2 Hz, 1H), 7.14 (d, *J* = 7.2 Hz, 1H), 7.08 – 6.97 (m, 4H), 6.85 (d, *J* = 7.6 Hz, 1H), 6.71 (t, *J* = 7.6 Hz, 1H), 6.58 (d, *J* = 7.6 Hz, 1H), 5.58 (s, 2H), 4.42 – 4.35 (m, 1H), 2.80 – 2.73 (m, 1H), 2.62 – 2.54 (m, 1H), 2.31 (s, 3H), 2.18 – 2.00 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9, 132.8, 130.4, 129.2, 128.9, 128.6, 127.7, 127.5, 126.9, 126.1, 120.8, 116.3, 56.6, 35.4, 33.1, 21.4; IR (neat): 3283, 2925, 1702, 1597, 1505, 1456, 1420, 1317, 1229, 1185, 1153, 1093, 1065, 1022, 968, 854, 812, 752, 705, 668 cm^{-1}; HRMS (ESI) for $C_{22}H_{22}BrNO_3S$: calculated $[M + Na]^+$ *m/z* 482.0401, found 482.0418.



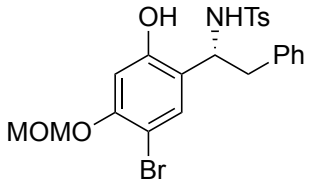
(*R*)-*N*-(1-(5-bromo-2-hydroxy-4-(methoxymethoxy)phenyl)ethyl)-4-methylbenzenesulfonamide (3t)

Imine **1g** (40 mg, 0.203 mmol) was converted to 44 mg of **3t** (50% yield) using the procedure for alkyl imines. Mannich product **3t** was obtained as a yellow waxy solid; $[\alpha]_D^{27}$ = +39.3 (c = 1.10 in $CHCl_3$); *ee* = 86%, determined by HPLC analysis [Chiralpak AD-RH, 90:10 hexanes/*i*PrOH, 0.50 mL/min, λ = 254 nm, t(major) = 22.1 min, t(minor) = 27.6 min]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.6 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 6.93 (s, 1H), 6.69 (bs, 1H), 6.53 (s, 1H), 5.52 (d, *J* = 5.2 Hz, 1H), 5.10 (s, 2H), 4.48 - 4.37 (m, 1H), 3.47 (s, 3H), 2.36 (s, 3H), 1.37 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 153.5, 143.6, 136.6, 131.6, 129.4, 127.0, 122.6, 105.0, 102.6, 95.0, 56.3, 51.0, 21.5, 21.5; IR (neat): 3329, 1500, 1420, 1326, 1153, 1088, 1013, 671 cm^{-1}; HRMS (ESI) for $C_{17}H_{20}BrNO_5S$: calculated $[M + Na]^+$ *m/z* 452.0143, found 452.0135.



(*R*)-*N*-(1-(5-bromo-2-hydroxy-4-(methoxymethoxy)phenyl)-3-((*tert*-butyldiphenylsilyl)oxy)propyl)-4-methylbenzenesulfonamide (3u)

Imine **1h** (95 mg, 0.204 mmol) was converted to 58 mg of **3u** (41% yield) using the procedure for alkyl imines. Mannich product **3u** was obtained as a white solid; m.p. = Decomposition at 172 ˚C; $[\alpha]_D^{26}$ = +21.6 (c = 0.89 in $CHCl_3$); *ee* = 97%, determined by HPLC analysis [Chiralpak AD-RH, 88:12 hexanes/*i*PrOH, 0.05 mL/min, λ = 254 nm, t(major) = 69.4 min, t(minor) = 74.9 min]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.55 (m, 6H); 7.45 – 7.35 (m, 6H), 7.12 (d, *J* = 7.6 Hz, 2H), 7.03 (s, 1H), 6.83 (s, 1H), 6.52 (s, 1H), 6.16 (d, *J* = 7.2 Hz, 1H), 5.10 (s, 2H), 4.70 – 4.62 (m, 1H), 3.63 – 3.58 (m, 1H), 3.48 (s, 3H), 3.45 – 3.40 (m, 1H), 2.36 (s, 3H), 2.02 – 1.96 (m, 1H), 1.87 – 1.79 (m, 1H), 1.09 (9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 153.4, 143.4, 136.7, 135.5, 135.4, 132.8, 132.7, 132.4, 129.8, 129.8, 129.4, 127.8, 127.8, 127.1, 121.0, 104.9, 102.6, 95.0, 61.1, 56.3, 53.4, 37.0, 26.8, 21.5, 19.0; IR (neat): 3337, 2930, 1589, 1499, 1472, 1427, 1393, 1331, 1215, 1152, 1110, 1087, 1015, 964, 909, 813, 733, 702, 670 cm^{-1}; HRMS (ESI) for $C_{34}H_{40}BrNO_6SSi$: calculated $[M + Na]^+$ *m/z* 720.1427, found 720.1456.

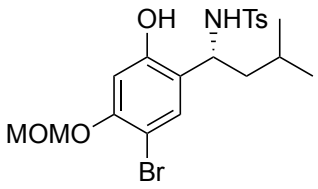


(*R*)-*N*-(1-(5-bromo-2-hydroxy-4-(methoxymethoxy)phenyl)-2-phenylethyl)-4-methylbenzenesulfonamide (3v)

Note: (*S*)-*i*Pr-Box was used in this reaction instead of (*S*)-Ph-Box as ligand.

Imine **1i** (55 mg, 0.201 mmol) was converted to 40 mg of **3v** (39% yield) using the

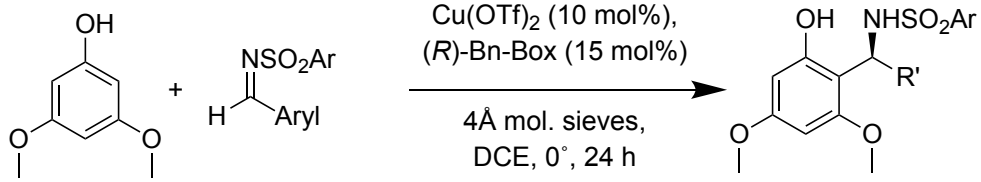
procedure for alkyl imines. Mannich product **3v** was obtained as a clear viscous oil white waxy solid; $[\alpha]_D^{27}$ = +1.6 (c = 1.10 in $CHCl_3$); *ee* = 94%, determined by HPLC analysis [Chiralpak AD-RH, 90:10 hexanes/*i*PrOH, 1.00 mL/min, λ = 254 nm, t(major) = 10.2 min, t(minor) = 13.7 min]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.0 Hz, 2H), 7.18 (t, *J* = 2.8 Hz, 3H), 7.07 (d, *J* = 8.0 Hz, 2H), 7.01 - 6.94 (m, 2H), 6.85 (s, 1H), 6.51 (s, 1H), 6.39 (m, 1H), 5.37 (bs, 1H), 5.10 (s, 2H), 4.50 - 4.41 (m, 1H), 3.48 (s, 3H), 3.10 - 2.92 (m, 2H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 153.3, 143.4, 136.7, 136.2, 132.6, 129.3, 129.1, 128.6, 127.0, 126.8, 121.2, 104.8, 102.7, 95.0, 57.0, 56.3, 41.6, 21.5; IR (neat): 3323, 1609, 1498, 1420, 1327, 1154, 1091, 1016, 947, 812, 701, 670 cm^{-1}; HRMS (ESI) for $C_{23}H_{24}BrNO_5S$: calculated [M + Na]+ *m/z* 528.0456, found 528.0437.



(*R*)-*N*-(1-(5-bromo-2-hydroxy-4-(methoxymethoxy)phenyl)-3-methylbutyl)-4-methylbenzenesulfonamide (3w)

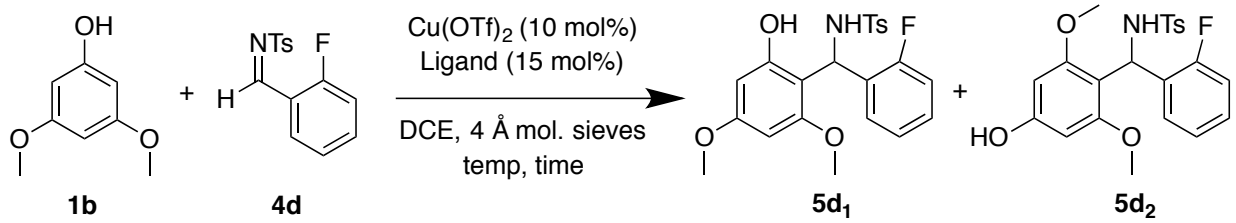
Imine **1j** (50 mg, 0.209 mmol) was converted to 12 mg of **3w** (12% yield) using the procedure for alkyl imines. Mannich product **3w** was obtained as a clear viscous oil; $[\alpha]_D^{27}$ = +8.3 (c = 0.30 in $CHCl_3$); *ee* = 94%, determined by HPLC analysis [Chiralpak AD-RH, 90:10 hexanes/*i*PrOH, 0.50 mL/min, λ = 254 nm, t(major) = 11.3 min, t(minor) = 14.7 min]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 8.4 Hz, 2H), 6.86 (s, 1H), 6.47 (s, 1H), 5.93 (s, 1H), 5.23 (d, *J* = 8.4 Hz, 1H), 5.10 (ABq, J_{AB} = 7.0 Hz, Δν = 3.4 Hz, 2H), 4.35 - 4.22 (m, 1H), 3.49 (s, 3H), 2.35 (s, 3H), 1.68-1.43 (m, 3H), 0.84 (ABq, J_{AB} = 6.4 Hz, Δν = 8.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 153.2, 143.3, 136.9, 132.4, 129.2, 127.0, 121.9, 105.0, 102.9, 95.1, 56.3, 53.9, 44.3, 30.9, 24.6, 22.4, 22.1, 21.5; IR (neat): 3321, 2957, 1610, 1500, 1420, 1328, 1216, 1153, 1091, 1017, 966, 924, 812, 671 cm^{-1}; HRMS (ESI) for $C_{20}H_{26}BrNO_5S$: calculated $[M + Na]^+$ *m/z* 494.0613, found 494.0612.

General Procedure for the $Cu(OTf)_2$-Catalyzed Enantioselective Phenol Addition to Aryl Aldimines:



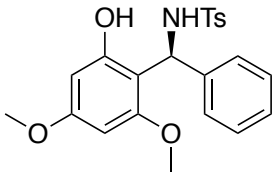
$Cu(OTf)_2$ (7.2 mg, 0.020 mmol, 10 mol %) was lightly flame dried in a vial charged with a magnetic stirbar. (*R*)-Bn-Box (10.1 mg, 0.030 mmol, 15 mol %) and 1, 2-dichloroethane (1 mL) was added and the solution allowed to stir at room temperature for 2 h. Flame activated 4Å mol. sieves (~20 mg) were added followed by imine (0.20 mmol, 1 equiv.) and phenol (0.30 mmol, 1.5 equiv.). The reaction was cooled to 0 °C, flushed with argon, sealed, and allowed to stir at 0 °C for 24 h. The reaction was then diluted with EtOAc (~3 mL) and flushed through a pad of silica (~5 cm) and rinsed with EtOAc (100 mL) and the combined filtrate concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel.

Optimization of Aza-Friedel-Crafts with Aryl Imines



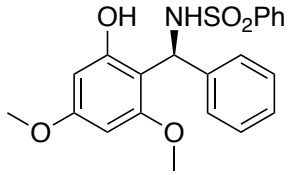
Entry	Ligand	Time (h)	Temp (°C)	Yield (%) **5d$_1$**	ee (%) **5d$_1$**	Yield (%) **5d$_2$**	ee (%) **5d$_2$**
1	(*S*)-Ph-Box	72	23	33	42	36	<5
2	(*S*)-Ph-Box	24	0	62	11	37	n.d.
3	(*R*)-Bn-Box	24	0	99	88	—	—
4	(*S*)-*i*Pr-Box	24	0	99	70	—	—

Aryl Imine Products



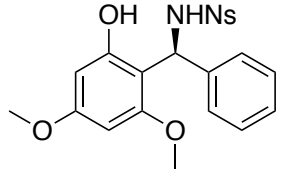
(*S*)-*N*-((2-hydroxy-4,6-dimethoxyphenyl)(phenyl)methyl)-4-methylbenzenesulfonamide (5a)

Imine **4a** (52 mg, 0.201 mmol) was converted to 83 mg of **5a** (100% yield) using the procedure for aryl imines. Mannich product **5a** was obtained as a white solid. ^{1}H NMR data matched that previously reported by Qu and optical rotation is consistent with the opposite enantiomer.[22] $[\alpha]_D^{27}$ = -19.4 (c = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.0 Hz, 2H), 7.28-7.26 (m, 2H), 7.23-7.15 (m, 3H), 7.01 (d, *J* = 8.0 Hz, 2H), 6.37 (d, *J* = 10.4 Hz, 1H), 6.31 (bs, 1H), 6.08 (d, *J* = 10.4 Hz, 1H), 5.87 (d, *J* = 1.6 Hz, 1H), 5.80 (d, *J* = 1.6 Hz, 1H), 3.64 (s, 3H), 3.57 (s, 3H), 2.29 (s, 3H); *ee* = 89%, determined by HPLC analysis [Chiralpak AD-RH, 95:5 hexanes/*i*PrOH, 1.00 mL/min, λ = 254 nm, t(major) = 38.6 min, t(minor) = 43.1 min].



(*S*)-*N*-((2-hydroxy-4,6-dimethoxyphenyl)(phenyl)methyl)benzenesulfonamide (5b)

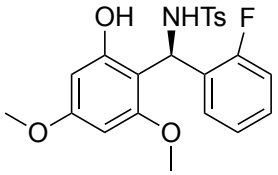
Imine **4b** (50 mg, 0.204 mmol) was converted to 77 mg **5b** (95% yield) using the procedure for aryl imines. Mannich product **5b** was obtained as a white waxy solid. $[\alpha]_D^{27}$ = -18.4 (c = 1.35 in $CHCl_3$); *ee* = 85%, determined by HPLC analysis [Chiralpak AD-RH, 95:5 hexanes/*i*PrOH, 1.00 mL/min, λ = 254 nm, t(major) = 31.8 min, t(minor) = 39.9 min]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.6 Hz, 2H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.27 (t, *J* = 6.4 Hz, 2H), 7.24 - 7.14 (m, 4H), 6.48 (d, *J* = 10.4 Hz, 1H), 6.38 (s, 1H), 6.12 (d, *J* = 10.4 Hz, 1H), 5.87 (d, *J* = 2.4 Hz, 1H), 5.78 (d, *J* = 2.0 Hz, 1H), 3.63 (s, 3H), 3.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 157.9, 154.5, 140.8, 139.9, 132.1, 128.3, 128.0, 126.8, 126.8, 126.5, 107.1, 93.8, 91.3, 55.5, 55.2, 52.0; IR (neat): 3326, 2940, 1598, 1511, 1493, 1447, 1424, 1323, 1201, 1147, 1090, 1047, 1028, 908, 814, 722, 697, 687 cm^{-1}; HRMS (ESI) for $C_{21}H_{21}NO_5S$: calculated $[M + Na]^+$ *m/z* 422.1038, found 422.1045.



(*S*)-*N*-((2-hydroxy-4,6-dimethoxyphenyl)(phenyl)methyl)-4-nitrobenzenesulfonamide (5c)

Imine **4c** (60 mg, 0.207 mmol) was converted to 90 mg of **5c** (98% yield) using the procedure for aryl imines. Mannich product **5c** was obtained as a yellow waxy solid. $[\alpha]_D^{27}$ = -16.4 (c = 2.90 in $CHCl_3$); *ee* = 93%, determined by HPLC analysis [Chiralpak AD-RH, 95:5 hexanes/*i*PrOH, 1.00 mL/min, λ = 254 nm, t(major) = 37.7 min, t(minor) = 42.6 min]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.7 Hz, 2H), 7.81 (d, *J* = 8.7 Hz,

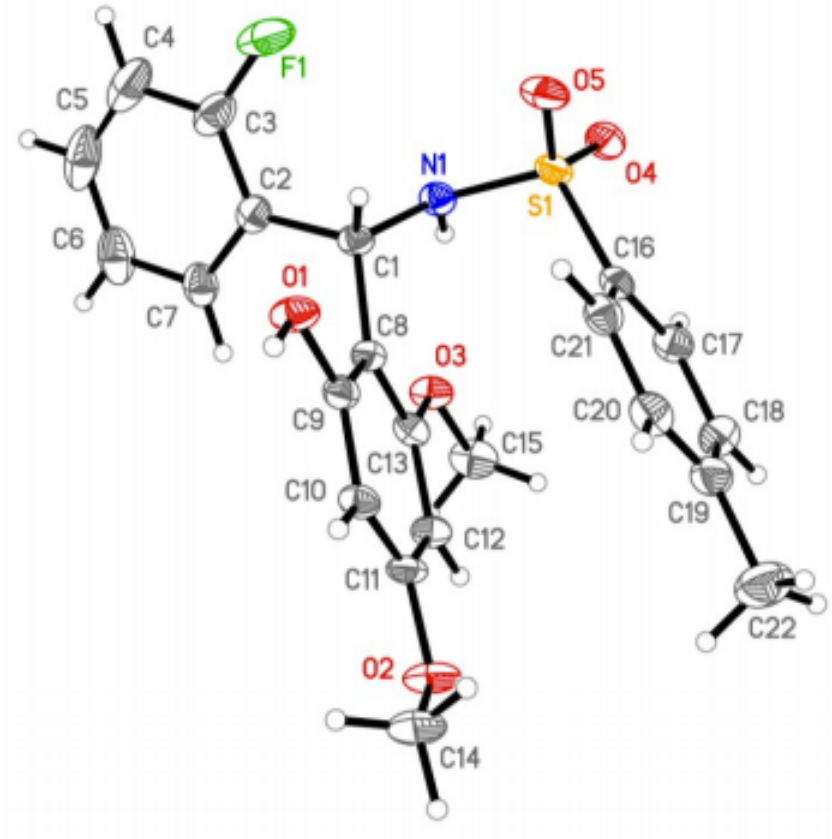
2H), 7.29-7.19 (m, 5H), 6.64 (d, J = 11.1 Hz, 1H), 6.14 (m, 2H), 5.79 (m, 2H), 3.61 (s, 3H), 3.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9, 158.0, 154.2, 149.5, 145.6, 140.0, 128.2, 128.0, 127.1, 126.4, 123.4, 106.5, 93.9, 91.1, 55.6, 55.2, 52.3; IR (neat) 3316, 2941, 1599, 1528, 1494, 1454, 1425, 1347, 1311, 1202, 1148, 1090, 1050, 1028, 909, 854, 815, 734, 698, 684 cm^{-1}; HRMS (ESI) for $C_{21}H_{20}N_2O_7S$: calculated $[M - H]^-$ *m/z* 443.0918, found 443.0917.

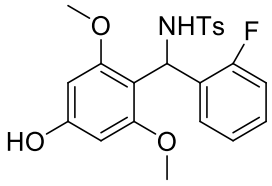


(*R*)-*N*-((2-fluorophenyl)(2-hydroxy-4,6-dimethoxyphenyl)methyl)-4-methylbenzenesulfonamide ($5d_1$)

Imine **4d** (56 mg, 0.202 mmol) was converted to 86 mg of **$5d_1$** (99% yield) using the procedure for aryl imines. Mannich product **$5d_1$** was obtained as an off-white crystalline solid. ^{1}H NMR data matched that previously reported by Qu and optical rotation was consistent with their opposite enantiomer.[22] $[\alpha]_D^{27}$ = -3.1 (c = 0.50 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 8.4 Hz, 2H), 7.34 (td, J = 7.6, 1.2 Hz, 1H), 7.14 (m, 1H), 7.07 (d, J = 8.0 Hz, 2H), 6.98 - 6.88 (m, 2H), 6.43 (s, 1H), 6.32 (d, J = 9.2 Hz, 1H), 6.25 (d, J = 9.6 Hz, 1H), 5.90 (d, J = 2.0 Hz, 1H), 5.84 (d, J = 2.4 Hz, 1H), 3.65, (s, 3H), 3.63 (s, 3H), 2.32 (s, 3H); *ee* = 88%, determined by HPLC analysis [Chiralpak AD-RH, 90:10 Hexanes/*i*PrOH, 1.00 mL/min, λ = 254 nm, t(major) = 17.3 min, t(minor) = 20.0 min].

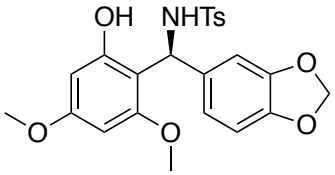
The X-ray crystal structure of **$5d_1$** (CCDC 1588080) was used to establish the absolute configuration of the stereocarbon (C1 below). The structure was obtained by William W. Brennessel at the Crystallographic Facility at the University of Rochester.





N-((2-fluorophenyl)(4-hydroxy-2,6-dimethoxyphenyl)methyl)-4-methylbenzenesulfonamide ($5d_2$)

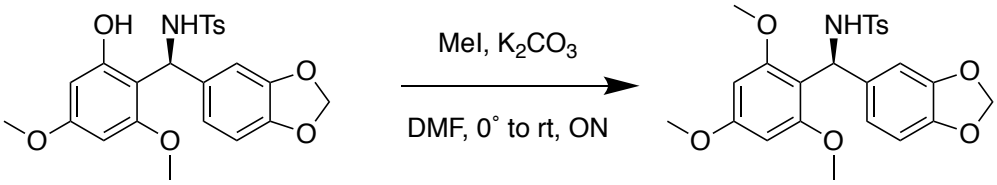
^{1}H NMR (300 MHz, d-acetone) δ 8.37 (s, 1H), 7.58 – 7.49 (m, 3H), 7.23 – 7.11 (m, 3H), 7.10 – 6.90 (m, 2H), 6.74 (d, J = 10.8 Hz, 1H), 6.39 (d, J = 10.5 Hz, 1H), 5.92 (s, 2H), 3.65 (s, 6H), 2.32 (s, 3H); ^{13}C NMR (75 MHz, d-acetone) δ 162.4, 159.8, 159.1, 159.0, 143.2, 139.5, 130.4, 130.3, 130.2, 130.0, 129.5, 129.2, 129.1, 127.5, 124.1, 124.1, 115.8, 115.5, 107.3, 92.6, 55.8, 47.4, 47.4, 21.3; IR (neat): 3316, 1600, 1477, 1330, 1148, 1123, 1045, 998, 811, 758, 674 cm^{-1}; HRMS (ESI) for $C_{22}H_{22}FNO_5S$: calculated $[M + Na]^+$ m/z 454.1095, found 454.1114.



(*S*)-*N*-(benzo[*d*][1,3]dioxol-5-yl(2-hydroxy-4,6-dimethoxyphenyl)methyl)-4-methylbenzenesulfonamide (5e)

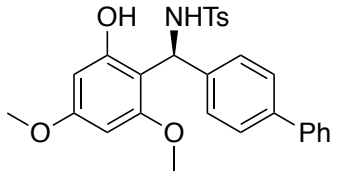
Imine **4e** (61 mg, 0.201 mmol) was converted to 72 mg of **5e** (78% yield) using the procedure for aryl imines. Mannich product **5e** was obtained as a clear oil. $[\alpha]_D^{27}$ = -27.1 (c = 0.20 in $CHCl_3$); *ee* = 92%, determined by HPLC analysis of the derivatized product *via O*-methylation; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.4 Hz, 2H), 7.03 (d, *J* = 7.6 Hz, 2H), 6.78-6.24 (m, 2H), 6.64 (d, *J* = 8.4 Hz, 1H), 6.24 (d, *J* = 9.6 Hz, 1H), 5.96 (m, 2H), 5.88 (m, 2H), 5.85 (d, *J* = 2.4 Hz, 1H), 5.82 (d, *J* = 2.4 Hz, 1H), 3.67 (s, 3H), 3.60 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 158.0, 154.3, `47.5, 146.4, 142.8, 137.1, 134.9, 128.9, 126.9, 119.8, 107.8, 107.5, 100.9, 94.0, 91.4, 55.5, 55.3, 51.9, 21.4; IR (neat): 3330, 2925, 1598, 1488, 1453, 1329, 1236, 1202, 1151, 1091, 1039, 930, 811, 735, 695 cm^{-1}; HRMS (ESI) for $C_{23}H_{23}NO_7S$: calculated $[M + Na]^+$ *m/z* 480.1093, found 480.1074.

Conversion of (*S*)-*N*-(benzo[*d*][1,3]dioxol-5-yl(2-hydroxy-4,6-dimethoxyphenyl)methyl)-4-methylbenzenesulfonamide (5e) to (*S*)-*N*-(benzo[*d*][1,3]dioxol-5-yl(2,4,6-trimethoxyphenyl)methyl)-4-methylbenzenesulfonamide (S-1) *via O*-methylation to determine enantiomeric excess



Phenol **5e** (54 mg, 0.118 mmol, 1 equiv.) was dissolved in a suspension of anhydrous

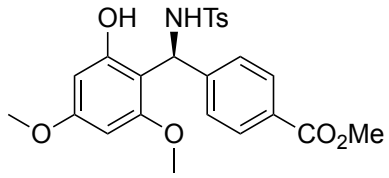
K_2CO_3 (33 mg, 0.236 mmol, 2 equiv.) in DMF (0.2 mL) and cooled to 0 ˚C. Methyl iodide (42 mg, 18 μL, 0.295 mmol, 2.5 equiv.) was added slowly and the reaction was allowed to warm to room temperature and vigorously stirred overnight. The reaction was then quenched with 50% saturated NH_4Cl (5 mL) and the diluted with diethyl ether (5 mL). The aqueous phase was extracted with diethyl ether (3 x 5 mL) and the combined organic layers were dried over anhydrous sodium sulfate, filter, and concentrated *in vacuo*. The crude residue was purified by flash chromatography 9:1 hexanes/EtOAc to 5:2 Hexanes/EtOAc to give 53 mg of **S-1** as an off-white solid (96% yield); m.p. = 124 – 127˚C; $[\alpha]_D^{27}$ = -8.3 (c = 0.80 in $CHCl_3$; *ee* = 97%, determined by HPLC analysis [Chiralpak AD-RH, 90:10 hexanes/*i*PrOH, 1.00 mL/min, λ = 254 nm, t(minor) = 30.0 min, t(major) = 36.0 min]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.5 Hz, 2H), 7.00 (d, *J* = 8.1 Hz, 2H), 6.76 (s, 1H), 6.71 (d, *J* = 8.7 Hz, 1H), 6.64 (d, *J* = 8.4 Hz, 1H), 6.21 (d, *J* = 10.5 Hz, 1H), 5.99 (d, *J* = 10.5 Hz, 1H), 5.88 (s, 4H), 3.74 (s, 3H), 3.64 (s, 6H), 2.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9, 157.8, 147.4, 146.2, 142.4, 137.5, 135.4, 128.6, 128.8, 119.6, 108.7, 107.6, 107.4, 100.8, 90.6, 55.6, 55.3, 51.4, 21.3; IR (neat): 3310, 2940, 1593, 1488, 1455, 1437, 1418, 1331, 1289, 1224, 1205, 1150, 1119, 1092, 1037, 929, 912, 868, 811, 733, 706, 675 cm^{-1}; HRMS (ESI) for $C_{24}H_{25}NO_7S$: calculated $[M + Na]^+$ *m/z* 494.1249, found 494.1247.



(*S*)-*N*-([1,1'-biphenyl]-4-yl(2-hydroxy-4,6-dimethoxyphenyl)methyl)-4-methylbenzenesulfonamide (5f)

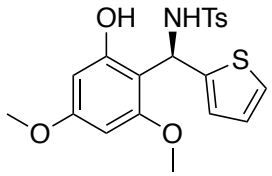
Imine **4f** (70 mg, 0.209 mmol) was converted to 99 mg of **5f** (97% yield) using the procedure for aryl imines. Mannich product **5f** was obtained as a white waxy solid. $[\alpha]_D^{27}$ = -0.5 (c = 1.80 in $CHCl_3$); *ee* = 85%, determined by HPLC analysis [Chiralpax AD-RH, 90:10 hexanes/*i*PrOH, 1.00 mL/min, λ = 254 nm, t(minor) = 17.4 min, t(major) = 20.8

min]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.0 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.44-7.7.29 (m, 7H), 7.01 (d, *J* = 8.4 Hz, 2H), 6.45 (d, *J* = 10.0 Hz, 1H), 6.40 (s, 1H), 6.13 (d, *J* = 10.4 Hz, 1H), 5.91 (d, *J* = 2.0 Hz, 1H), 5.83 (d, *J* = 2.0 Hz, 1H), 3.66 (s, 3H), 3.60 (s, 3H), 2.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 158.0, 154.5, 142.9, 140.8, 140.0, 139.7, 136.9, 128.9, 128.7, 127.1, 127.0, 126.9, 126.8, 107.2, 93.9, 91.3, 55.5, 55.3, 51.8, 21.3; IR (neat) 3328, 2938, 1598, 1511, 1487, 1455, 1426, 1327, 1202, 1148, 1091, 1047, 1008, 910, 812, 762, 730, 673 cm^{-1}; HRMS (ESI) for $C_{28}H_{27}NO_5S$: calculated $[M + Na]^+$ *m/z* 512.1508, found 512.1512.



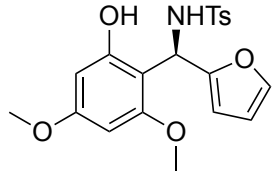
Methyl (*S*)-4-((2-hydroxy-4,6-dimethoxyphenyl)((4-methylphenyl)sulfonamido)methyl)benzoate (5g)

Imine **4g** (65 mg, 0.205 mmol) was converted to 97 mg of **5g** (100% yield) using the procedure for aryl imines. Mannich product **5g** was obtained as a pale yellow solid. ^{1}H NMR data matched that previously reported by Qu.[22] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 6.99 (d, *J* = 8.0 Hz, 2H), 6.99 (s, 1H), 6.45 (d, *J* = 10.4 Hz, 1H), 6.11 (d, *J* = 10.0 Hz, 1H), 5.91 (d, *J* = 1.6 Hz, 1H), 5.78 (d, *J* = 1.6 Hz, 1H), 3.87 (s, 3H), 3.62 (s, 3H), 3.57 (s, 3H), 2.27 (s, 3H); $[\alpha]_D^{27}$ = -23.8 (c = 1.80 in $CHCl_3$); *ee* = 94%, determined by HPLC analysis [Chiralpak AD-RH, 85:15 hexanes/*i*PrOH, 1.00 mL/min, λ = 254 nm, t(minor) = 11.6 min, t(major) = 14.3 min].



(*R*)-*N*-((2-hydroxy-4,6-dimethoxyphenyl)(thiophen-2-yl)methyl)-4-methylbenzenesulfonamide (5h)

Imine **4h** (55 mg, 0.207 mmol) was converted to 77 mg of **5h** (89% yield) using the procedure for aryl imines. Mannich product **5h** was obtained as a clear viscous oil. $[\alpha]_D^{27}$ = -10.0 (c = 1.70 in $CHCl_3$); *ee* = 92%, determined by HPLC analysis [Chiralpak AD-RH, 70:30 H_2O/MeCN, 0.20 mL/min, λ = 254 nm, t(major) = 275.5 min, t(minor) = 334.2 min]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 5.2 Hz, 1H), 6.81 (dd, *J* = 5.2 Hz, 3.6 Hz, 1H), 6.72 (d, *J* = 3.2 Hz, 1H), 6.42 (d, *J* = 10.4 Hz, 1H), 6.24 (d, *J* = 9.6 Hz, 1H), 6.13 (s, 1H), 5.87 (d, *J* = 2.0 Hz, 1H), 5.83 (d, *J* = 2.0 Hz, 1H), 3.67 (s, 3H), 3.63 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 158.0, 154.4, 145.7, 143.0, 136.9, 129.0, 126.9, 126.5, 124.6, 124.5, 107.3, 93.9, 91.4, 55.6, 55.3, 49.1, 21.4; IR (neat) 3324, 2939, 1598, 1511, 1455, 1423, 1326, 1288, 1201, 1147, 1089, 1032, 940, 910, 811, 729, 703, 669 cm^{-1}; HRMS (ESI) for $C_{20}H_{21}NO_5S_2$: calculated $[M + Na]^+$ *m/z* 442.0759, found 442.0766.



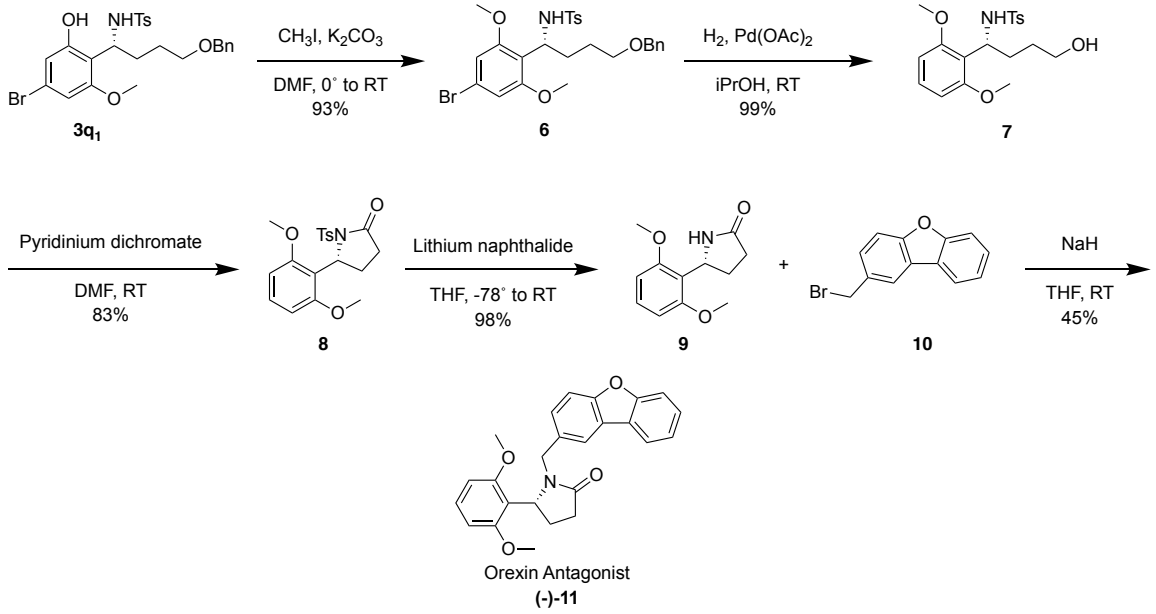
(*R*)-*N*-(furan-2-yl(2-hydroxy-4,6-dimethoxyphenyl)methyl)-4-methylbenzenesulfonamide (5i)

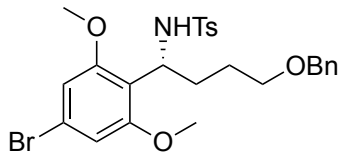
Imine **4i** (50 mg, 0.201 mmol) was converted to 77 mg of **5i** (96% yield) using the procedure for aryl imines. Mannich product **5i** was obtained as a white solid. ^{1}H NMR

data matched that previously reported by Qu.[22] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.4 Hz, 2H), 7.24 (s, 1H), 7.09 (d, *J* = 8.4 Hz, 2H), 6.21 (dd, *J* = 4.0, 2.0 Hz, 1H), 6.12-6.00 (m, 3H), 5.91-5.82 (m, 3H), 3.69 (s, 3H), 3.66 (s, 3H), 2.34 (s, 3H); $[\alpha]_D^{27}$ = -22.9 (c = 0.30 in $CHCl_3$); *ee* = 91%, determined by HPLC analysis [Chiralpak AD-RH, 60:40 EtOH/H_2O (with 0.1% formic acid), 0.60 mL/min, λ = 254 nm, t(major) = 5.2 min, t(minor) = 6.2 min].

Synthetic Schemes

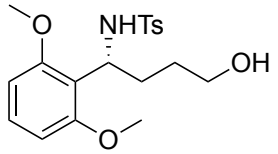
Dual Orexin Antagonist





(*R*)-*N*-(4-(benzyloxy)-1-(4-bromo-2,6-dimethoxyphenyl)butyl)-4-methylbenzenesulfonamide (6)

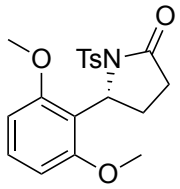
To a solution of 100 mg of phenol **3q$_1$** (0.187 mmol, 1 equiv.) in DMF (1 mL) was added K_2CO_3 (65 mg, 0.468 mmol, 2.5 equiv.). The suspension was cooled to 0 °C and methyl iodide (17.5 μL, 40 mg, 0.281 mmol, 1.5 equiv.) was added slowly. The reaction was allowed to warm to room temperature and was stirred overnight. After, the reaction was quenched with saturated aqueous ammonium chloride (15 mL) and diluted with Et_2O (10 mL). The organic phase was separated and the aqueous layer extracted with Et_2O (3 x 15 mL). The combined organic layers we dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude reaction was subject to silica gel column chromatography (9:1 to 7:3 hexanes/EtOAc) to afford 93 mg of (*R*)-*N*-(4-(benzyloxy)-1-(4-bromo-2,6-dimethoxyphenyl)butyl)-4-methylbenzenesulfonamide (**6**) as a dull yellow oil (93% yield); $[\alpha]_D^{23}$ = -9.2 (c = 0.93 in $CHCl_3$); *ee* = 84%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, *J* = 8.0 Hz, 2H), 7.37 – 7.23 (m, 5H), 6.96 (d, *J* = 8.0 Hz, 2H), 6.37 (s, 2H), 5.74 (d, *J* = 10.4 Hz, 1H), 4.92 – 4.82 (m, 1H), 4.45 (s, 2H), 3.67 (s, 6H), 3.50 – 3.38 (m, 2H), 2.31 (s, 3H), 1.91 – 1.82 (m, 1H), 1.80 – 1.65 (m, 2H), 1.57 – 1.45 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.8, 138.6, 137.3, 128.5, 128.3, 127.5, 127.4, 126.5, 121.4, 115.2, 107.4, 72.8, 69.8, 55.8, 49.2, 31.4, 26.3, 21.4; IR (neat): 2939, 2857, 1583, 1495, 1453, 1407, 1337, 1223, 1161, 1126, 1093, 909, 852, 837, 811, 732, 698, 669 cm^{-1}; HRMS (ESI) for $C_{26}H_{30}BrNO_5S$: calculated $[M + Na]^+$ *m/z* 570.0926, found 570.0941.



(*R*)-*N*-(1-(2,6-dimethoxyphenyl)-4-hydroxybutyl)-4-methylbenzenesulfonamide (7)

To a solution of benzyl ether **6** (74 mg, 0.135 mmol, 1 equiv.) in *i*PrOH was added $Pd(OAc)_2$ (32 mg, 0.0541 mmol, 0.40 equiv.) and a stir bar. The atmosphere was exchanged for a hydrogen gas (1 atm) atmosphere and the reaction was allowed to stir at room temperature for 2 h. The reaction was then flushed through a pad of silica gel (5 cm). The silica pad was flushed thoroughly with EtOAc (100 mL). The solvent was concentrated and the crude reaction was subject to silica gel column chromatography (9:1 to 2.5:1 CH_2Cl_2:EtOAc) to afford 50.7 mg *des*-bromo alcohol product (*R*)-*N*-(1-(2,6-

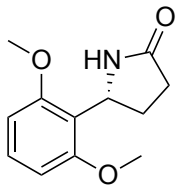
dimethoxyphenyl)-4-hydroxybutyl)-4-methylbenzenesulfonamide (**7**) as a dull yellow oil (99% yield); $[\alpha]_D^{25}$ = -16.1 (c = 0.56 in $CHCl_3$; *ee* = 84%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.0 Hz, 2H), 6.94 (t, *J* = 8.0 Hz, 1H), 6.91 (d, *J* = 8.4 Hz, 2H), 6.23 (d, *J* = 8.0 Hz, 2H), 5.98 (d, *J* = 10.4 Hz, 1H), 4.80 – 4.25 (m, 1H), 3.67 (s, 6H), 3.60 (t, *J* = 5.6 Hz, 2H), 2.23 (s, 3H), 1.95 – 1.84 (m, 1H), 1.77 – 1.61 (m, 3H (OH overlap)), 1.56 – 1.44 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.3, 137.3, 128.4, 128.2, 126.5, 116.1, 103.6, 62.4, 55.4, 49.2, 31.4, 29.3, 21.2; IR (neat): 3308, 2938, 1595, 1475, 1437, 1332, 1270, 1245, 1158, 1111, 1048, 917, 813, 781, 729, 707, 667 cm^{-1}; HRMS (ESI) for $C_{19}H_{25}NO_5$: calculated $[M + Na]^+$ *m/z* 402.1351, found 402.1345.



(*R*)-5-(2,6-dimethoxyphenyl)-1-tosylpyrrolidin-2-one (8)

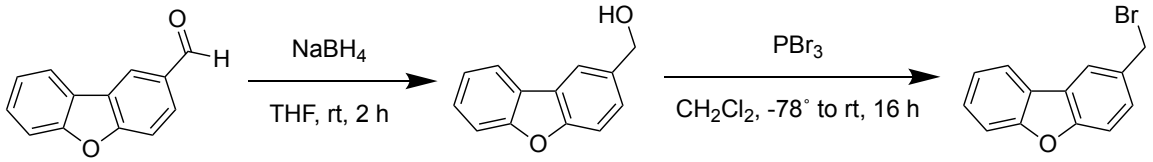
To a solution of amino alcohol **7** (50.7 mg, 0.134 mmol, 1 equiv.) in DMF (1 mL) was added pyridinium dichromate (252 mg, 0.670 mmol, 5 equiv.) and the reaction was allowed to stir for 16 h at room temperature. After, water was added (15 mL) and the reaction diluted with EtOAc (20 mL). The organic phase was separated and the aqueous phase extracted with EtOAc (3 x 15 mL). The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude reaction mixture was subject to silica gel column chromatography (4:1 to 1:1 hexanes/EtOAc) to afford 41.7 mg amide product (*R*)-5-(2,6-dimethoxyphenyl)-1-tosylpyrrolidin-2-one (**8**) as a white crystalline solid (83% yield); $[\alpha]_D^{24}$ = +30.9 (c = 0.99 in $CHCl_3$); *ee* = 84%; ^{1}H NMR (400 MHz, 25˚, $CDCl_3$) δ 7.33 (d, *J* = 8.0 Hz, 2H), 7.18 (t, *J* = 8.4 Hz, 1H), 7.04 (d, *J* = 8.4 Hz, 2H), 6.58 (bs, 1H), 6.16 (bs, 1H), 6.11 (dd, *J* = 10.0 Hz, 3.2 Hz, 1H), 3.90 (bs, 3H), 3.06 (bs, 3H), 2.69 – 2.46 (m, 3H), 2.34 (s, 3H), 1.91 – 1.84 (m, 1H); ^{13}C NMR (100 MHz, 25˚, $CDCl_3$): δ 174.9, 158.1, 143.7, 135.7, 129.3, 128.6, 128.2, 116.4, 104.1. 53.0, 32.3, 24.0, 21.5; ^{1}H NMR (400 MHz, 50˚, $CDCl_3$) δ 7.35 (d, *J* = 8.0 Hz, 2H), 7.17 (t, *J* = 8.4 Hz, 1H), 7.04 (d, *J* = 8.0 Hz, 2H), 6.38 (bs, 2H), 6.10 (dd, *J* = 10.0 Hz, 3.2 Hz, 1H), 3.47 (bs, 6H), 2.65 (m, 3H), 2.33 (s, 3H), 1.90 – 1.83 (m, 1H); ^{13}C NMR (100 MHz, 25˚, $CDCl_3$) δ 174.7, 158.3,

143.6, 136.1, 129.3, 128.6, 128.3, 116.9, 104.2, 53.1, 32.3, 24.1, 21.4; IR (neat): 2940, 2841, 1729, 1595, 1476, 1358, 1330, 1251, 1187, 1167, 1101, 1036, 1019, 966, 937, 910, 844, 814, 783, 729, 705, 670.0 cm^{-1}; HRMS (ESI) for $C_{19}H_{21}NO_5S$: calculated $[M + H]^+$ *m/z* 376.1213, found 376.1216.



(*R*)-5-(2,6-dimethoxyphenyl)pyrrolidin-2-one (9)

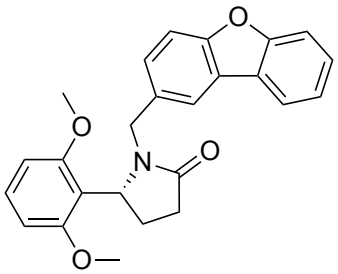
Naphthalene (600 mg, 4.67 mmol) was dissolved in degassed THF (10 mL). Lithium (33 mg, 4.67 mmol) was added, and the mixture was sonicated for 30 min and then stirred at room temperature for 2 h in order to obtain a 0.5 M dark green Li-naphthalenide solution. *N*-Tosyl lactam **8** (0.33 mg, 0.0879 mmol) was dissolved in THF (1.5 mL), and the resulting solution was cooled to −78 °C. The Li-naphthalenide was then added drop-wise until the reaction mixture stayed permanently dark green (ca. 10 mL). The mixture was stirred at −78 °C for 30 min and at room temperature for 30 min before quenching with 1.0 M $NaHCO_3$ (ca. 10 mL). The aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography afforded 19 mg amide product 5-(2,6-dimethoxyphenyl)pyrrolidin-2-one (**9**) as a dull yellow waxy solid (98 % yield). $[\alpha]_D^{26}$ = -51.5 (c = 0.90 in $CHCl_3$); *ee* = 84%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (t, *J* = 8.4 Hz, 1H), 6.55 (d, *J* = 8.8 Hz, 2H), 5.48 (s, 1H), 5.44 – 5.40 (m, 1H), 3.80 (s, 6H), 2.60 – 2.35 (m, 3H), 2.23 – 2.15 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.0, 158.6, 129.1, 117.7, 104.1, 55.8, 47.8, 30.6, 26.3; IR (neat): 3219, 2934, 2840, 1681, 1593, 1475, 1437, 1383, 1278, 1251, 1194, 1150, 1105, 1024, 909, 784, 728 cm^{-1}; HRMS (ESI) for $C_{12}H_{15}NO_3$: calculated $[M + H]^+$ *m/z* 222.1125, found 222.1120.



2-(Bromomethyl)dibenzo[*b*,*d*]furan (10)

Arylbromide **10** was synthesized as previously reported and its ^{1}H NMR is in agreement with literature data.[23]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 1.6 Hz, 1H), 7.95 (d, *J* = 7.6 Hz, 1H), 7.59 – 7.43 (m, 4H), 7.38 (t, *J* = 6.8 Hz, 1H), 4.70 (s, 2H).

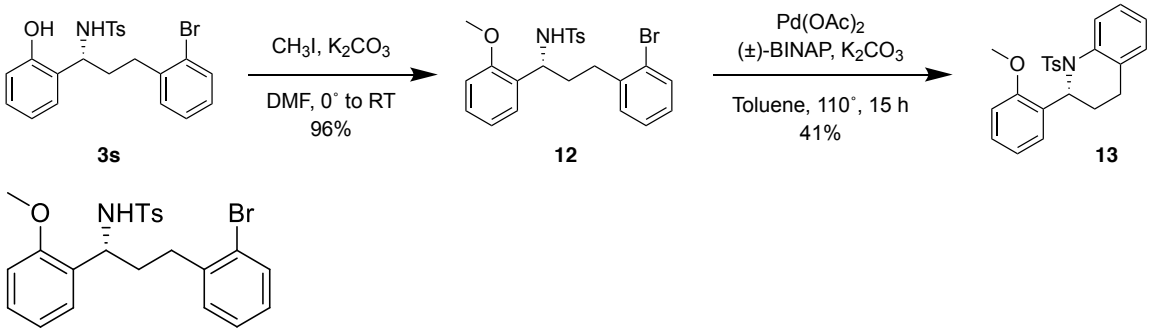


(*R*)-1-(dibenzo[b,d]furan-2-ylmethyl)-5-(2,6-dimethoxyphenyl)pyrrolidin-2-one (11)

Amide **9** (18 mg, 0.081 mmol) was dissolved in a 1:1 mixture of solvents THF/DMF (2.5 mL) and cooled to 0 °C. This solution was treated with 2-(bromomethyl)dibenzo[*b*,*d*]furan (**10**, 27 mg, 0.102 mmol, 1.25 equiv.) and NaH (5 mg, 0.203 mmol, 2.5 equiv.). The ice bath was removed and the reaction allowed to stir at room temperature overnight. The mixture was then filtered, evaporated, and purified by column chromatography to afford 15 mg of (*R*)-1-(dibenzo[*b*,*d*]furan-2-ylmethyl)-5-(2,6-dimethoxyphenyl)pyrrolidin-2-one (**11**) as a white solid (45% yield), 50% conversion based on recovered starting material (9 mg); m. p. = 125 – 126°; $[\alpha]_D^{24}$ = -70.5 (c = 0.50 in $CHCl_3$); *ee* = 84%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.6 Hz, 2H), 7.59 (s, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 1H), 7.39 (d, *J* = 8.8 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.21 – 7.15 (m, 2H), 6.55 – 6.42 (m, 2H), 5.27 (dd, *J* = 9.6, 4.4 Hz, 1H), 4.32 (ABq, J_{AB} = 14.4 Hz, Δν = 461.8 Hz, 2H), 3.72 (s, 3H), 3.59 (s, 3H), 2.77 – 2.63 (m, 1H), 2.59 – 2.48 (m, 1H), 2.34 – 2.21 (m, 1H), 2.10 – 2.00 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 131.9, 129.4, 128.2, 127.0, 124.1, 122.7, 121.1, 120.6, 115.7, 111.6,

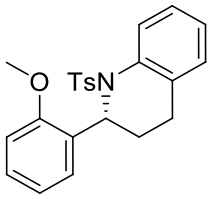
110.9, 55.6, 51.7, 44.7, 31.3, 29.7, 23.3; IR (neat): 2934, 2838, 1668, 1594, 1475, 1448, 1434, 1417, 1374, 1325, 1279, 1250, 1194, 1150, 1106, 1023, 925, 841, 804, 783, 769, 751, 729, 693 cm^{-1}; HRMS (ESI) for $C_{25}H_{23}NO_4$: calculated $[M + H]^+$ *m/z* 402.1700, found 402.1713.

Enantioselective Tetrahydroquinoline Synthesis



***R*)-*N*-(3-(2-bromophenyl)-1-(2-methoxyphenyl)propyl)-4-methylbenzenesulfonamide (12)**

To a solution of phenol **3s** (155 mg, 0.337 mmol) in DMF (1.5 mL) was added K_2CO_3 (116 mg, 0.842 mmol, 2.5 equiv.). The reaction was cooled to 0 °C and methyl iodide (26 μL, 60 mg, 0.421 mmol, 1.5 equiv.) was added slowly. The reaction was allowed to warm to room temperature and stir overnight. Saturated aqueous NH_4Cl was added (15 mL) and the reaction diluted with Et_2O (20 mL). The organic phase was separate and the aqueous layer was then extracted with Et_2O (2 x 15 mL). The organic phases were combined, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude reaction mixture was purified by column chromatography to afford methyl ether **12** as a clear oil (96% yield); $[\alpha]_D^{26}$ = +8.3 (c = 0.10 in $CHCl_3$); *ee* = 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.41 (m, 3H), 7.21 – 7.17 (m, 2H), 7.10 – 7.00 (m, 2H), 6.98 (d, J = 7.6 Hz, 2H), 6.84 (dd, J = 7.6, 1.6 Hz, 1H), 6.70 (td, J = 7.6, 0.8 Hz, 1H), 6.58 (d, J = 7.6 Hz, 1H), 5.71 (d, J = 9.6 Hz, 1H), 4.44 – 4.35 (m, 1H), 3.70 (s, 3H), 2.88 – 2.77 (m, 1H), 2.64 – 2.53 (m, 1H), 2.28 (s, 3H), 2.19 – 1.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 142.5, 140.8, 137.5, 132.7, 130.4, 129.1, 128.9, 128.4, 127.6, 127.4, 126.8, 124.3, 120.5, 110.6, 57.4, 55.0, 35.7, 33.2, 21.3; IR (neat): 3278, 2936, 1600, 1494, 1464, 1439, 1322, 1243, 1184, 1156, 1094, 1068, 1024, 967, 908, 812, 751, 706, 667 cm^{-1}; HRMS (ESI) for $C_{23}H_{24}BrNO_3S$ calculated $[M + H]^+$ *m/z* 474.0733, found 474.0755.



(*R*)-2-(2-methoxyphenyl)-1-tosyl-1,2,3,4-tetrahydroquinoline (13)

Amino bromide **12** (47 mg, 0.099 mmol), $Pd(OAc)_2$ (12 mg, 0.020 mmol, 20 mol%), (±)-BINAP (25 mg, 0.040 mmol, 40 mol%), and K_2CO_3 (34 mg, 0.25 mmol, 2.5 equiv.) were added to a pressure tube previously charged with a magnetic stir bar. Toluene (1 mL) was added, the tube sealed, and the reaction was heated to 110 °C for 18 h while stirring. The reaction was then filtered, concentrated, and purified by column chromatography (hexanes/EtOAc 9:1 to 1:1) to afford 16 mg cross coupled product **13** as a white solid (41% yield); m. p. = decomposition at 130˚; $[\alpha]_D^{26}$ = +9.9 (c = 0.17 in $CHCl_3$); *ee* = 90%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, J = 8.0 Hz, 1H), 7.42 (d, J = 8.4 Hz, 2H), 7.33 – 7.27 (m, 2H), 7.21 – 7.15 (m, 3H), 7.11 (t, J = 7.6 Hz, 1H), 6.97 (d, J = 11.6 Hz, 1H), 6.90 – 6.82 (m, 2H), 5.59 (dd, J = 9.2, 6.4 Hz, 1H), 3.84 (s, 3H), 2.38 (s, 3H), 2.38 – 2.20 (m, 2H), 1.72 (td, J = 14.4, 3.2 Hz, 1H), 1.62 – 1.52 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6, 143.3, 136.9, 136.1, 135.2, 132.0, 129.3, 127.9, 127.5, 127.2, 127.0, 126.7, 125.4, 120.7, 110.5, 55.9, 55.4, 31.6, 26.2, 21.5; IR (neat): 2924, 1600, 1488, 1456, 1351, 1286, 1244, 1163, 1106, 1090, 1025, 970, 857, 814, 793, 753, 713, 660 cm^{-1}; HRMS (ESI) for $C_{23}H_{23}NO_3S$ calculated $[M + H]^+$ *m/z* 393.1471, found 394.1469.

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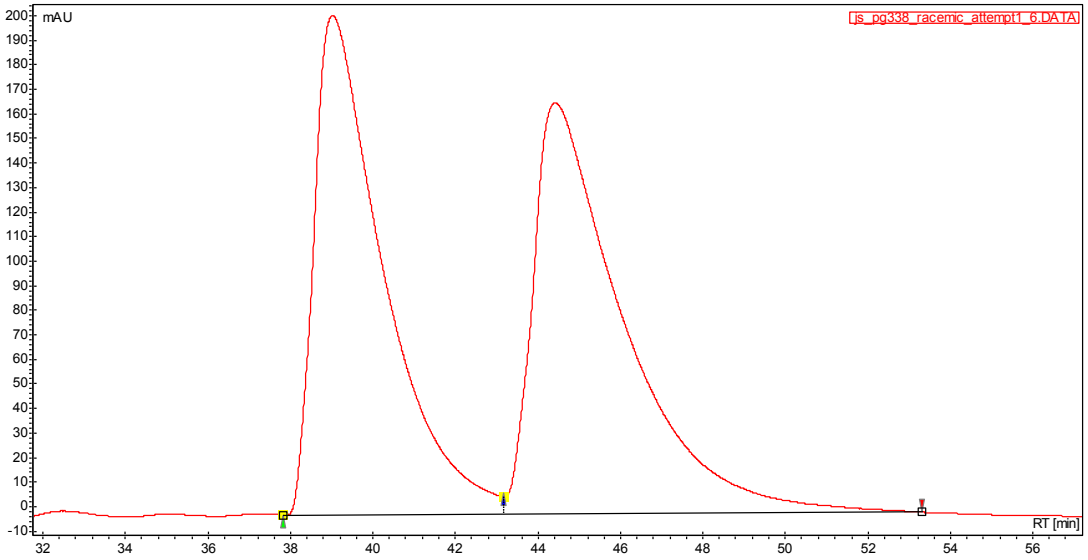
HPLC Traces:



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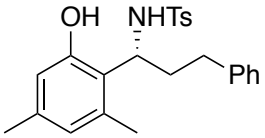

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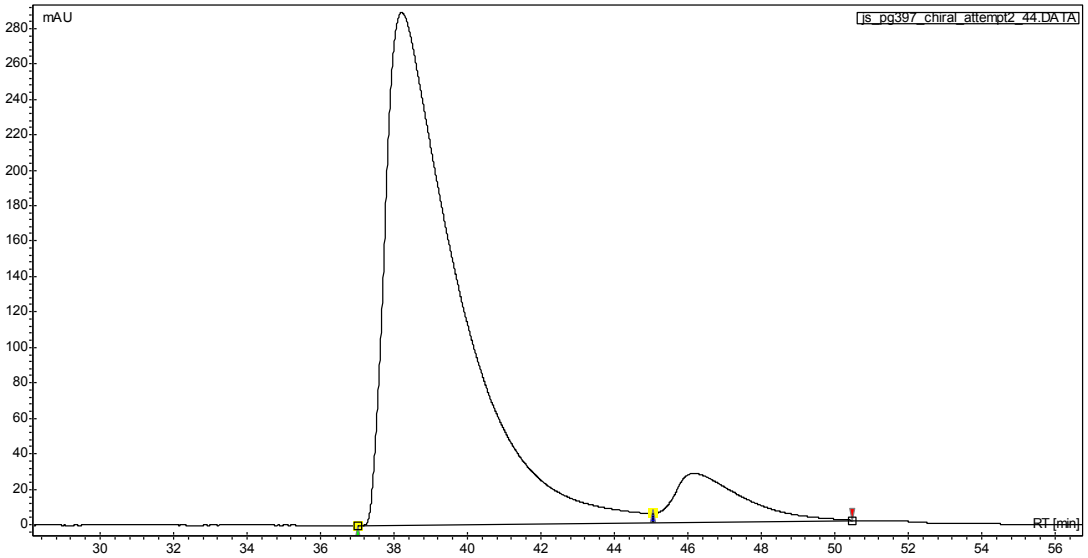

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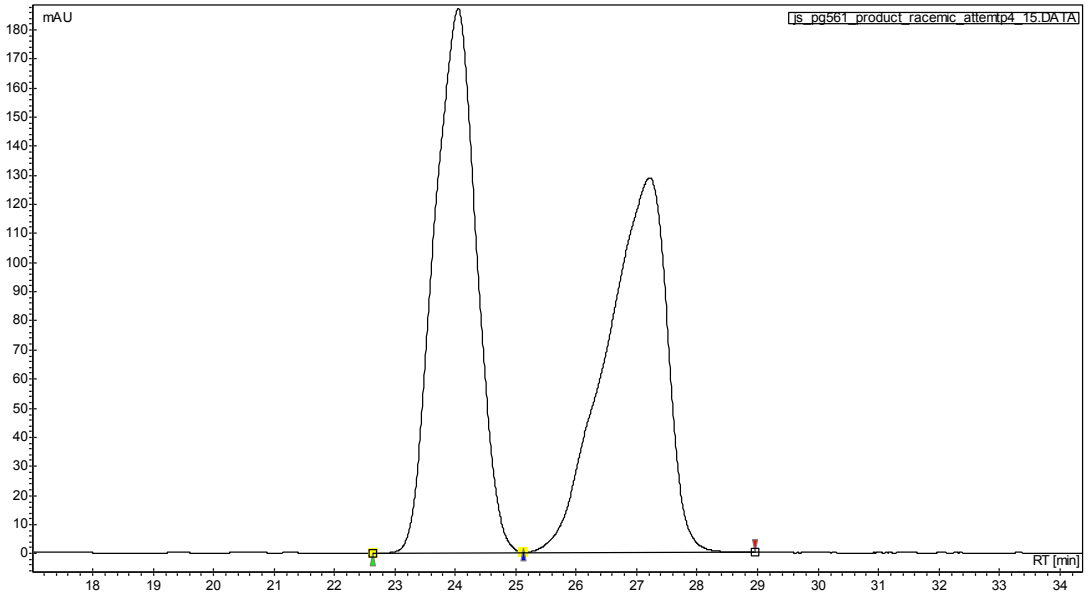

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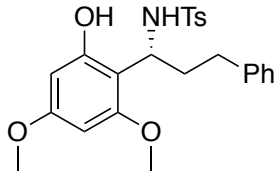

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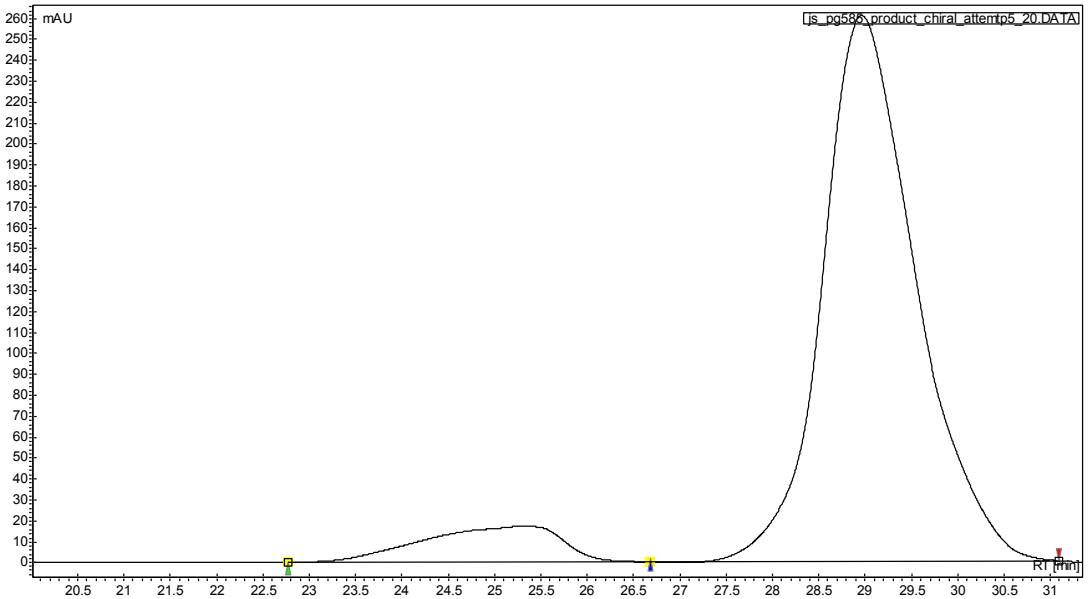

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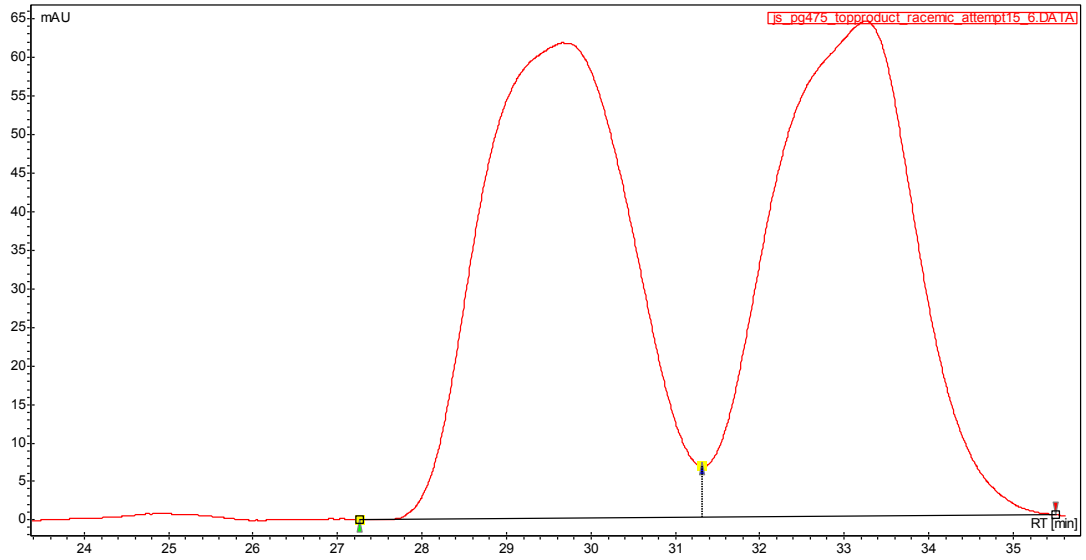

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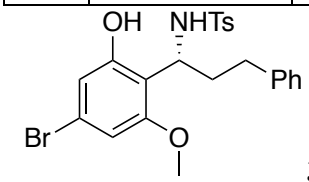

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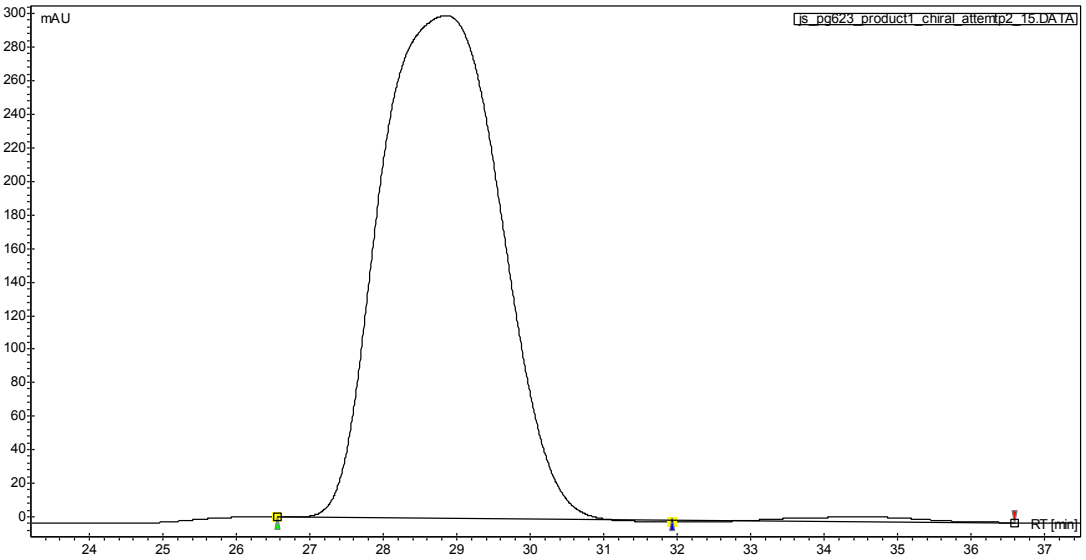

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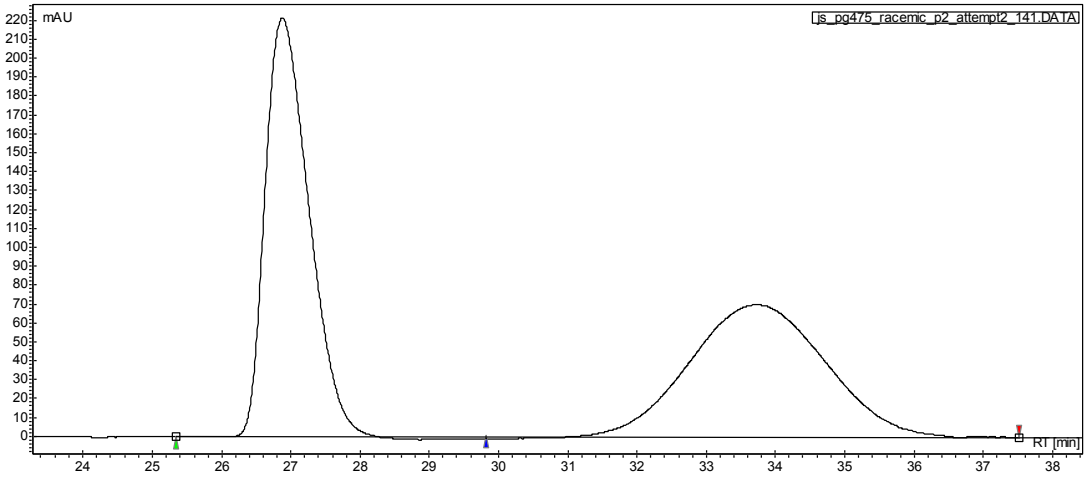

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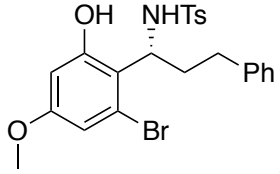

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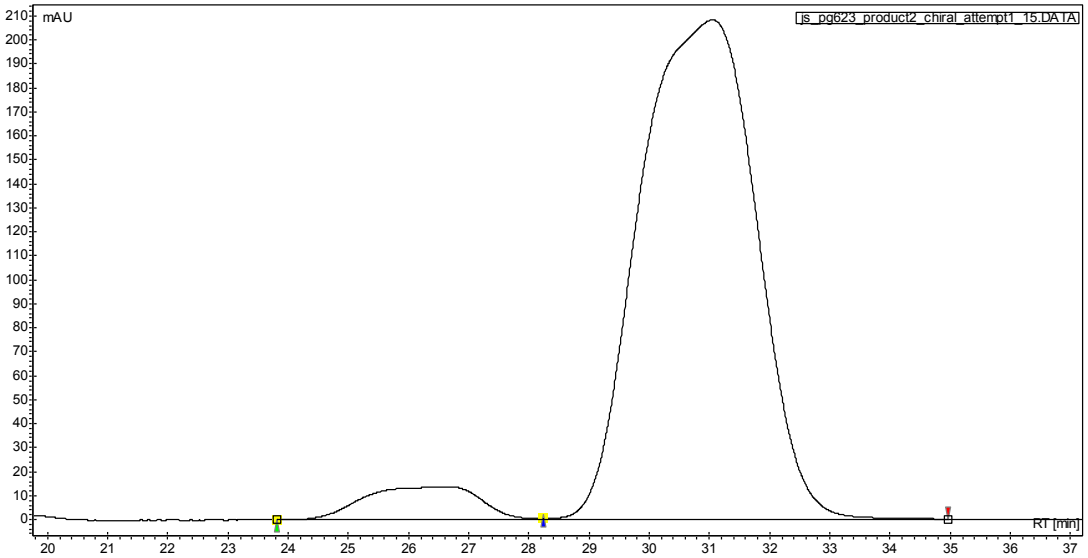

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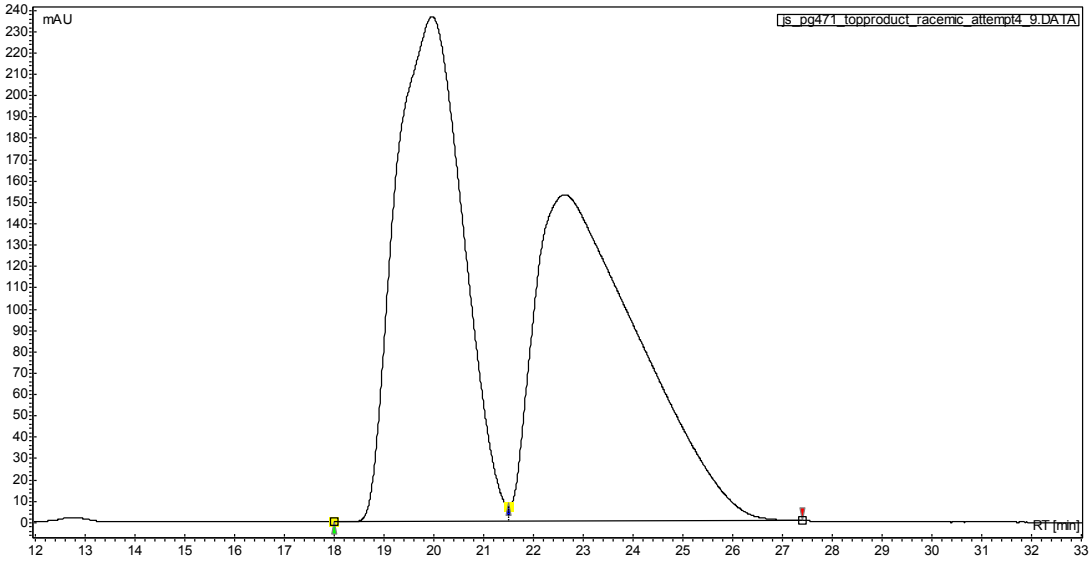

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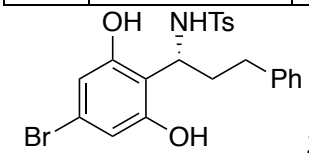

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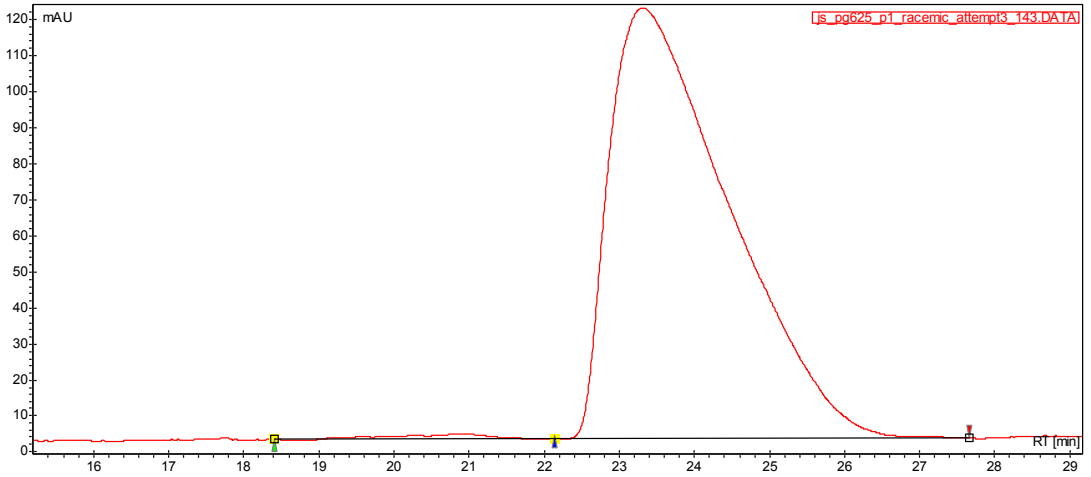

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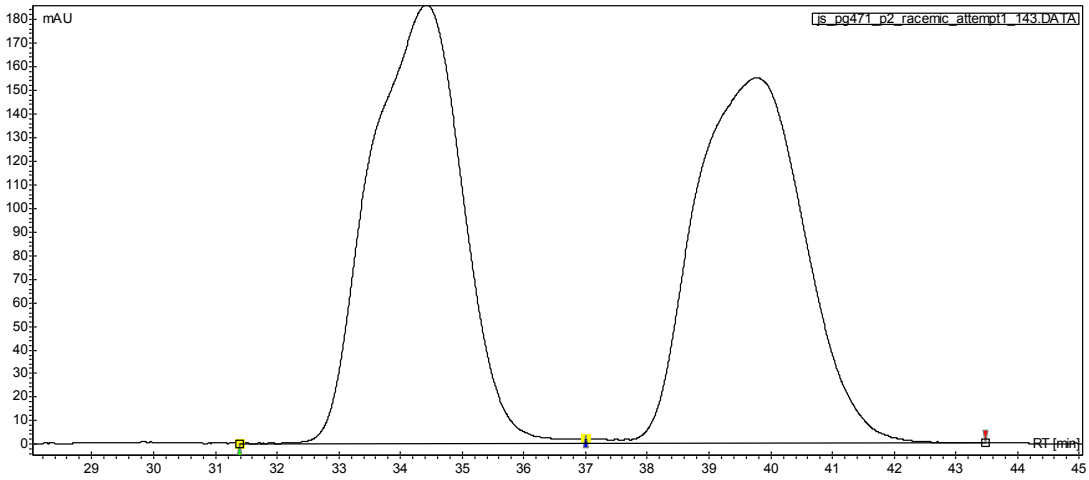

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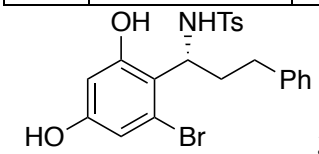

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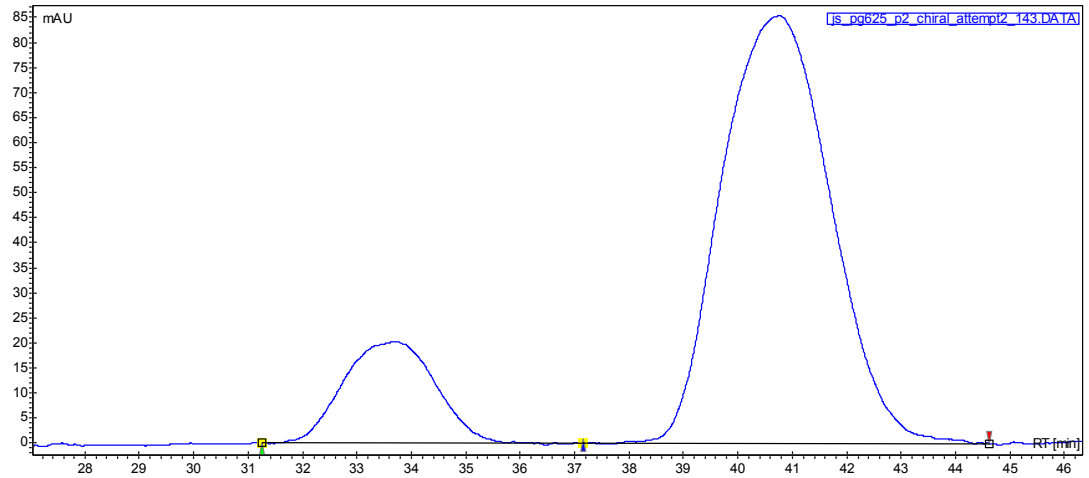

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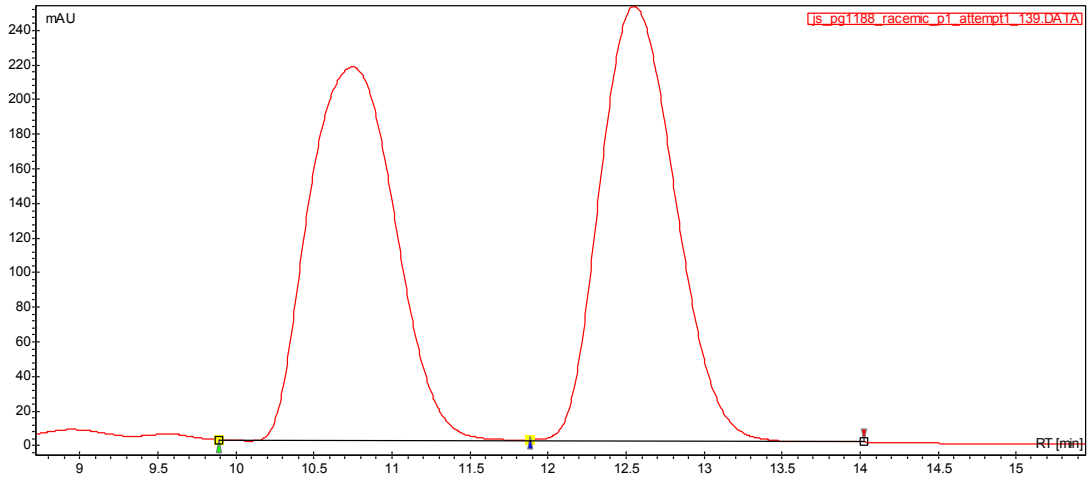

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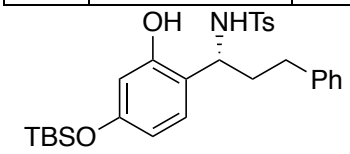

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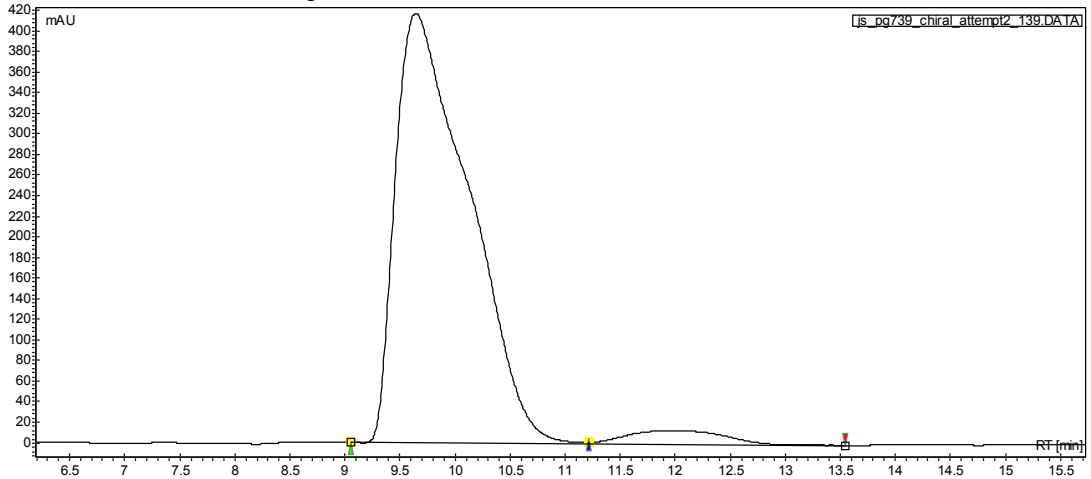

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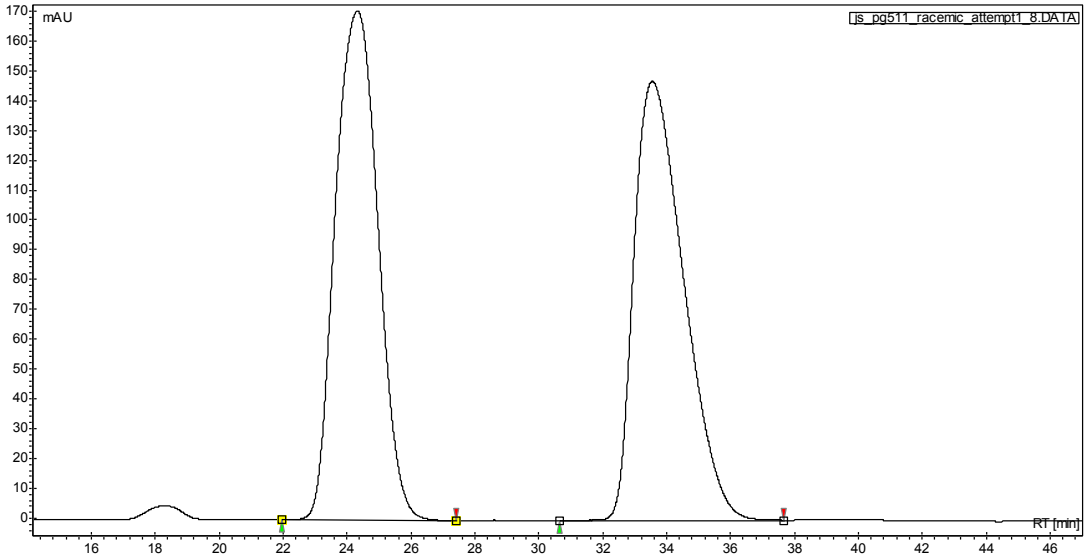

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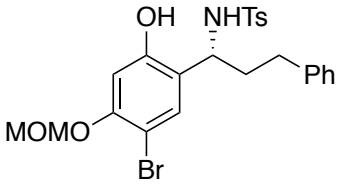

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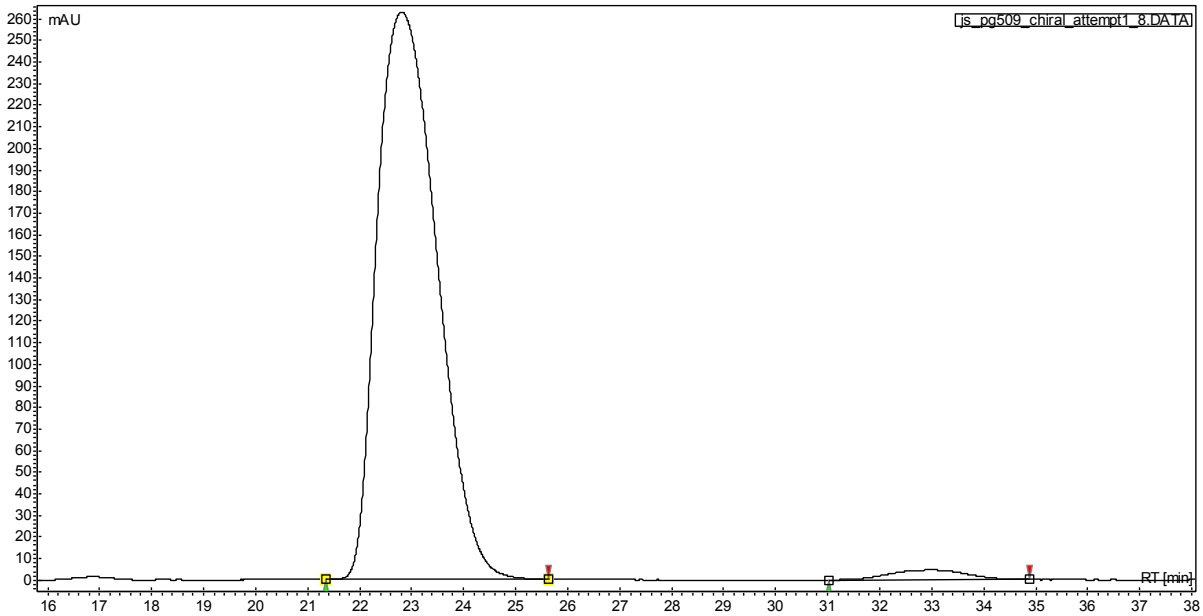

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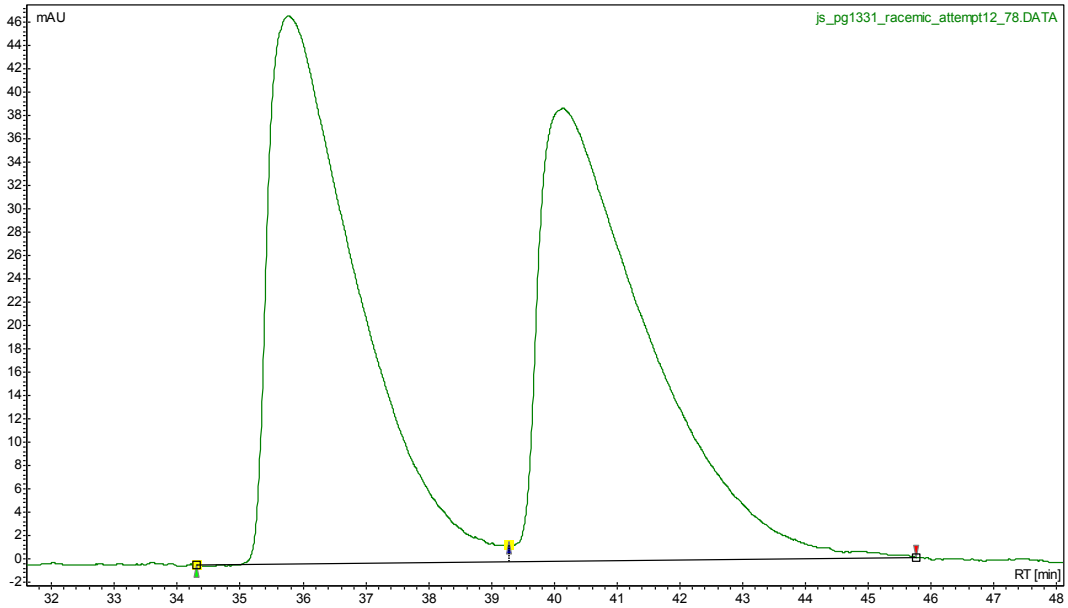

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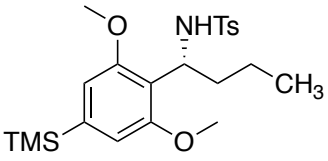
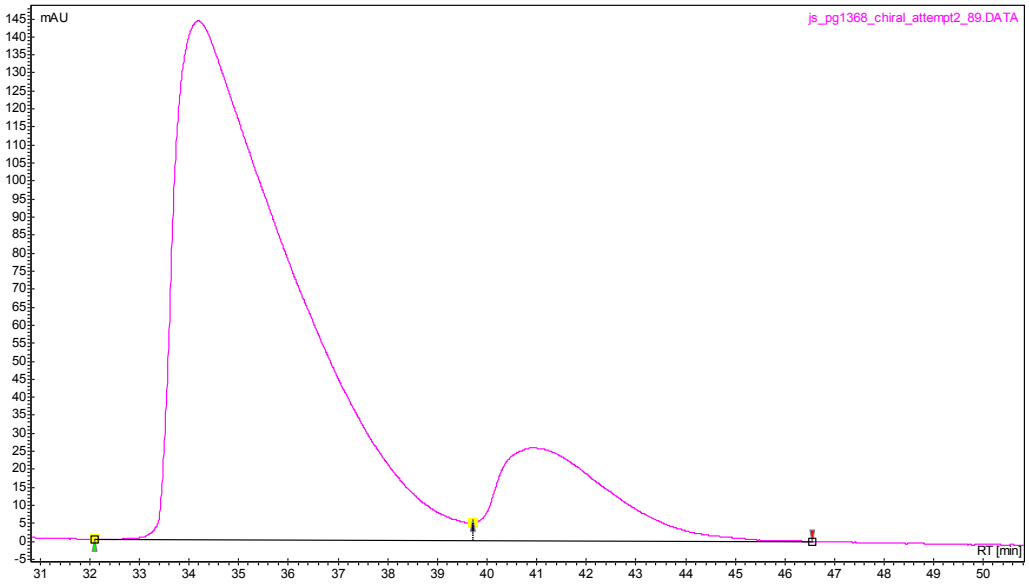


Derivative of **3g$_1$**



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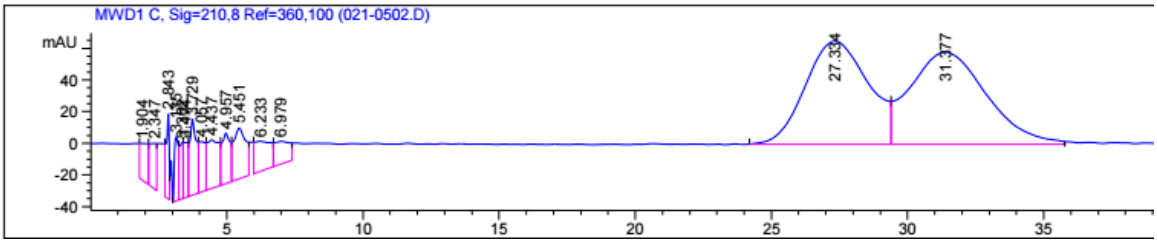
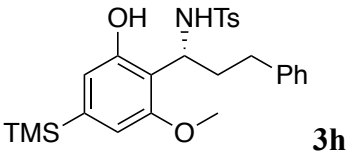
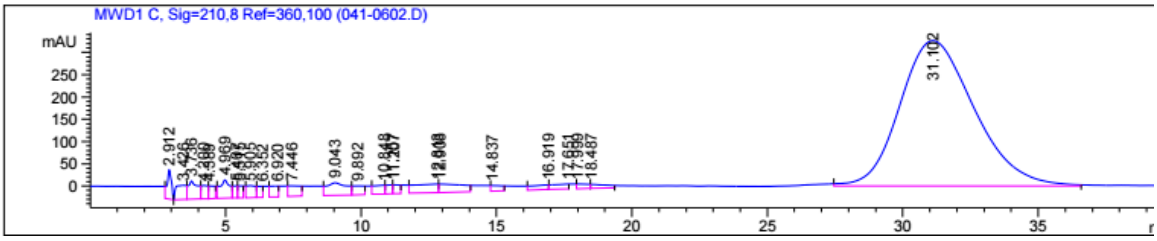


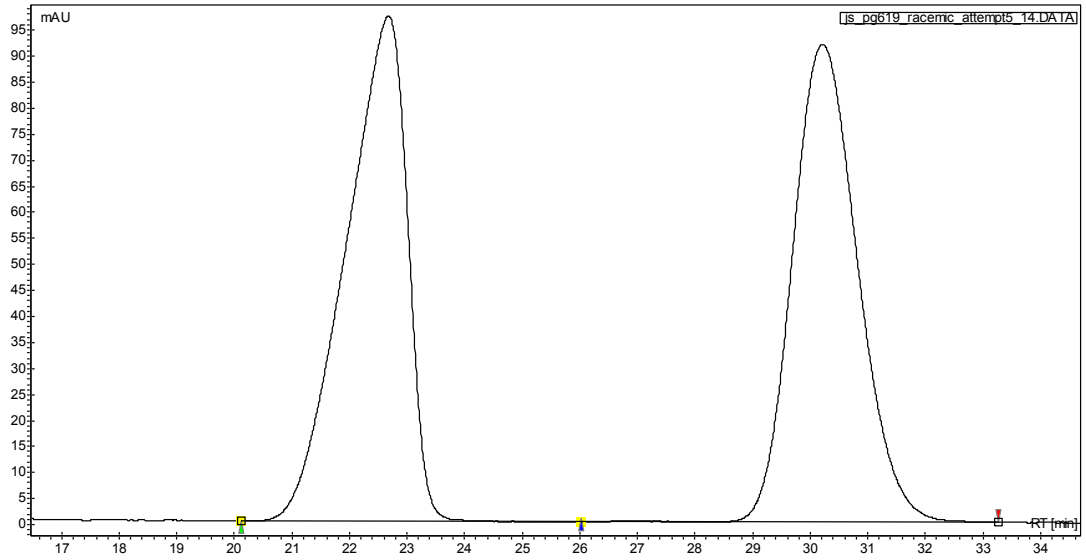
#	Time [min]	Area [%]
1	27.3	48.1
2	31.4	51.9



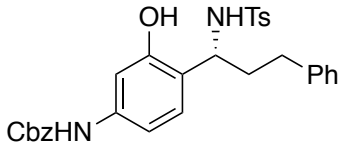
3h



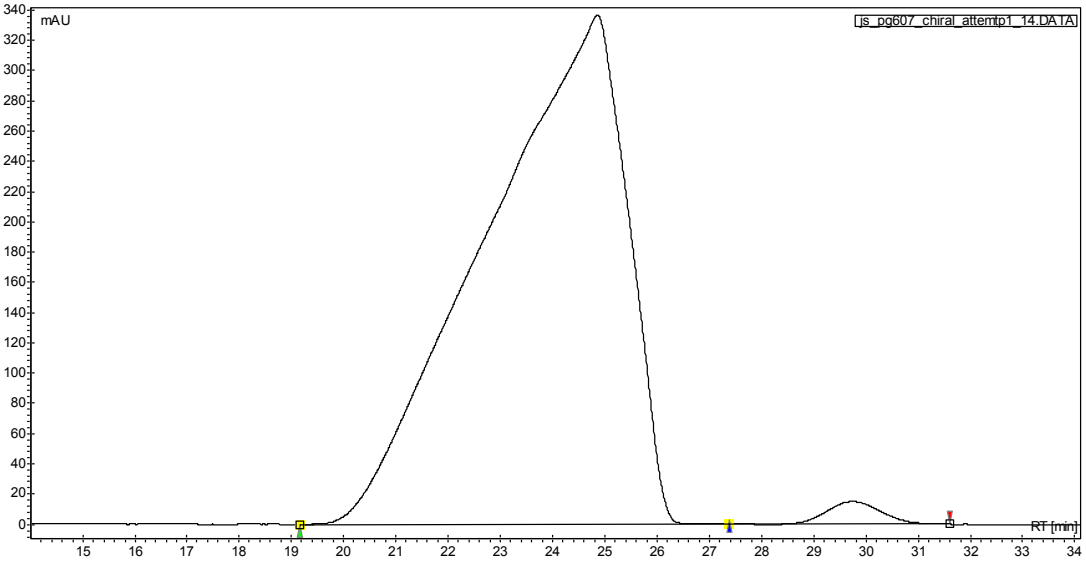
#	Time [min]	Area [%]
1	27.3	-
2	31.1	>99



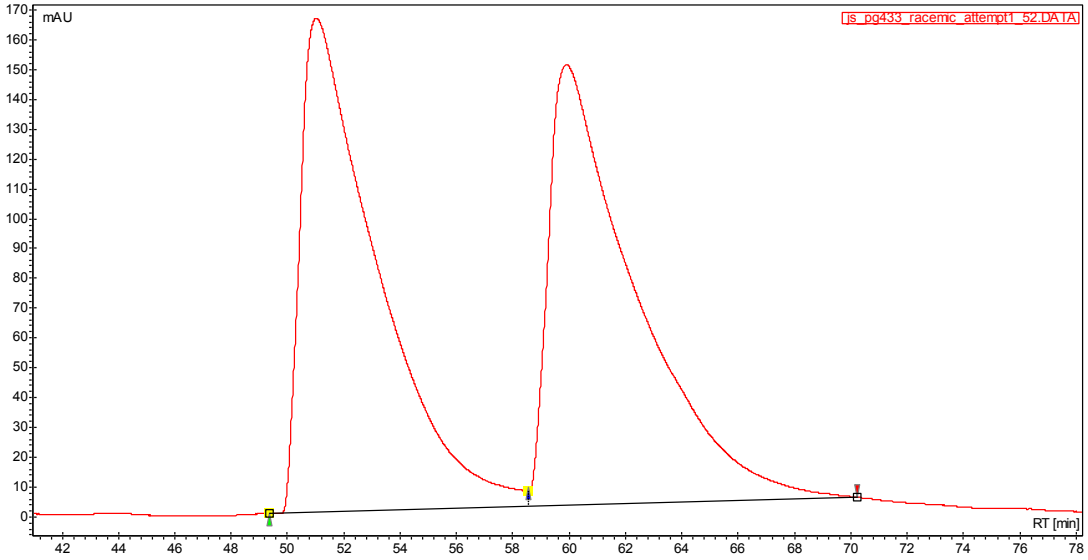
#	Time [min]	Area [%]
1	22.7	49.9
2	30.2	50.1



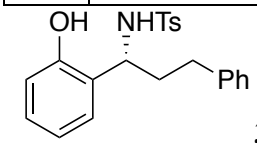
3i



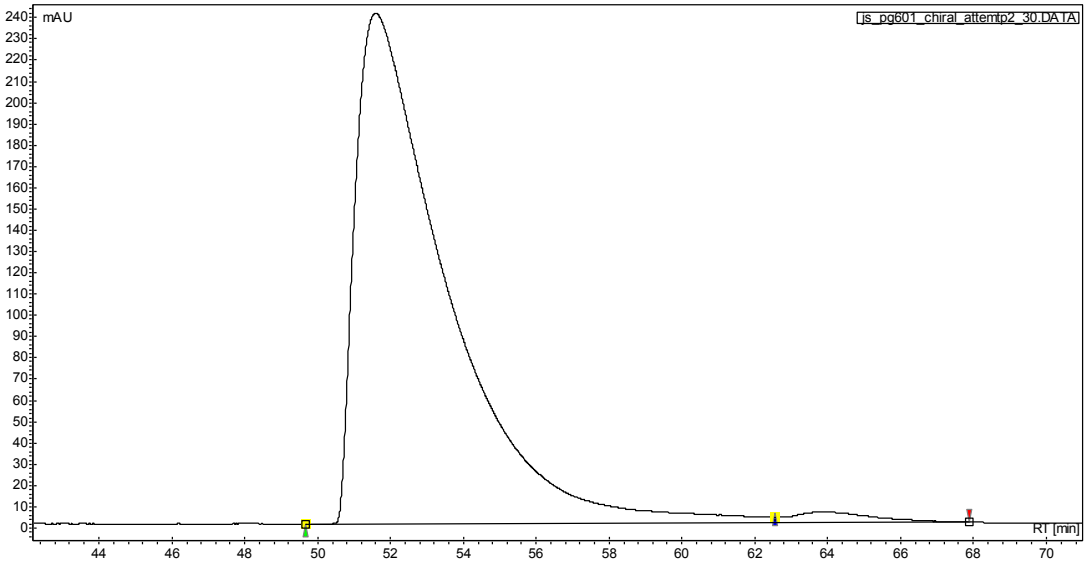
#	Time [min]	Area [%]
1	24.9	98.3
2	29.8	1.7



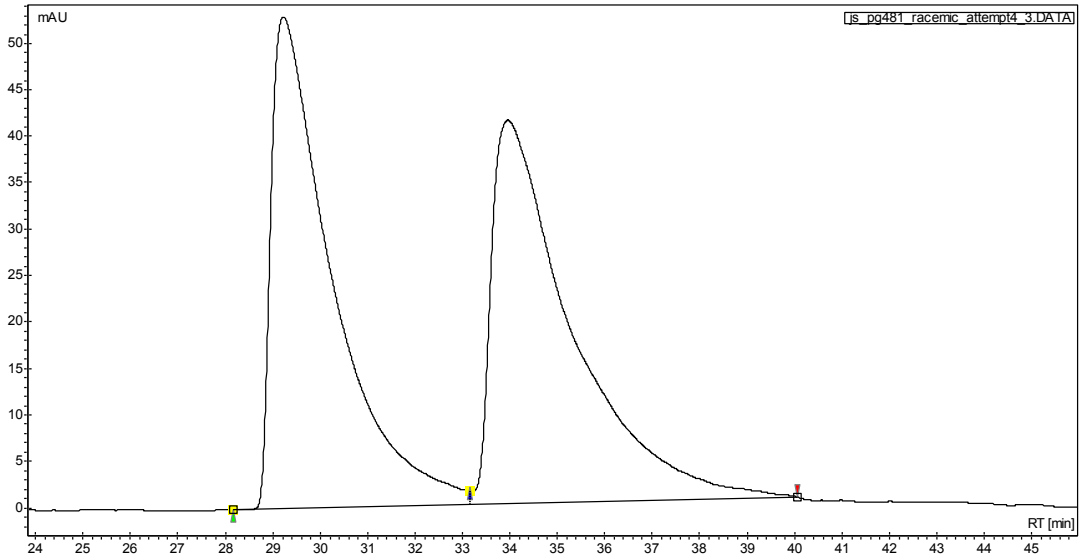
#	Time [min]	Area [%]
1	51.0	49.8
2	59.9	50.2



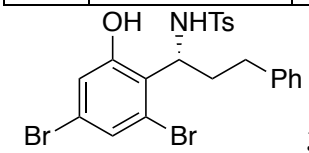
3j



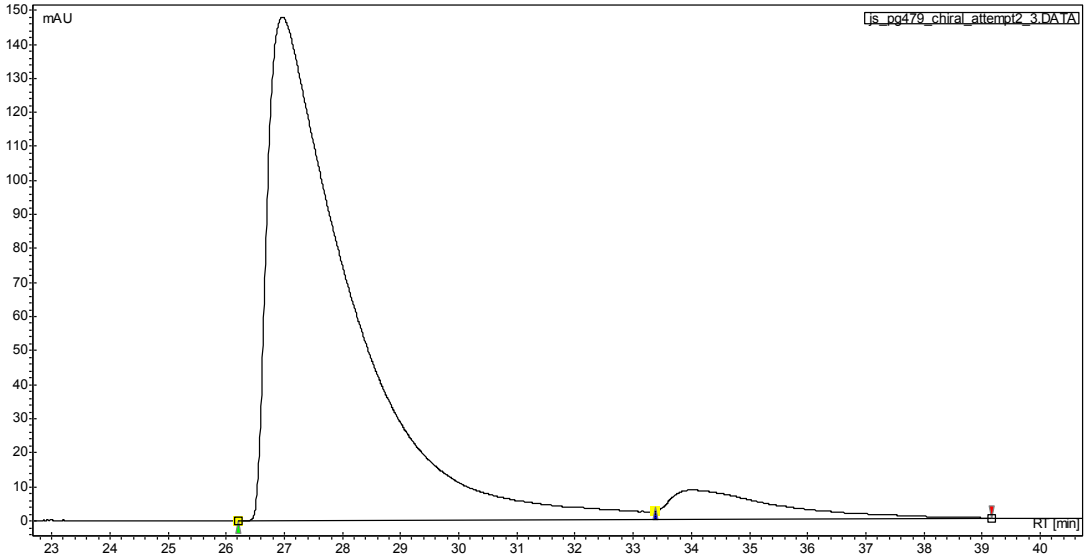
#	Time [min]	Area [%]
1	51.6	98.2
2	63.9	1.8



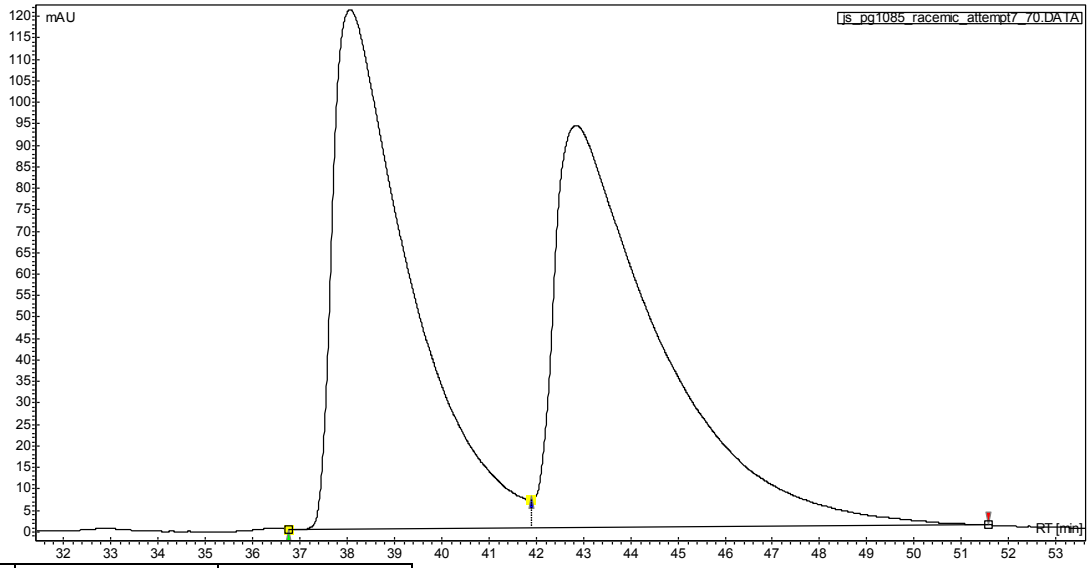
#	Time [min]	Area [%]
1	29.2	49.4
2	34.0	50.6



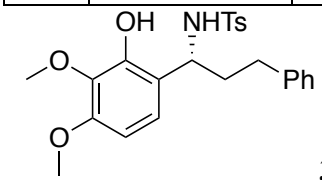
3k



#	Time [min]	Area [%]
1	27.0	92.9
2	34.0	7.1



#	Time [min]	Area [%]
1	38.1	48.6
2	42.9	51.4



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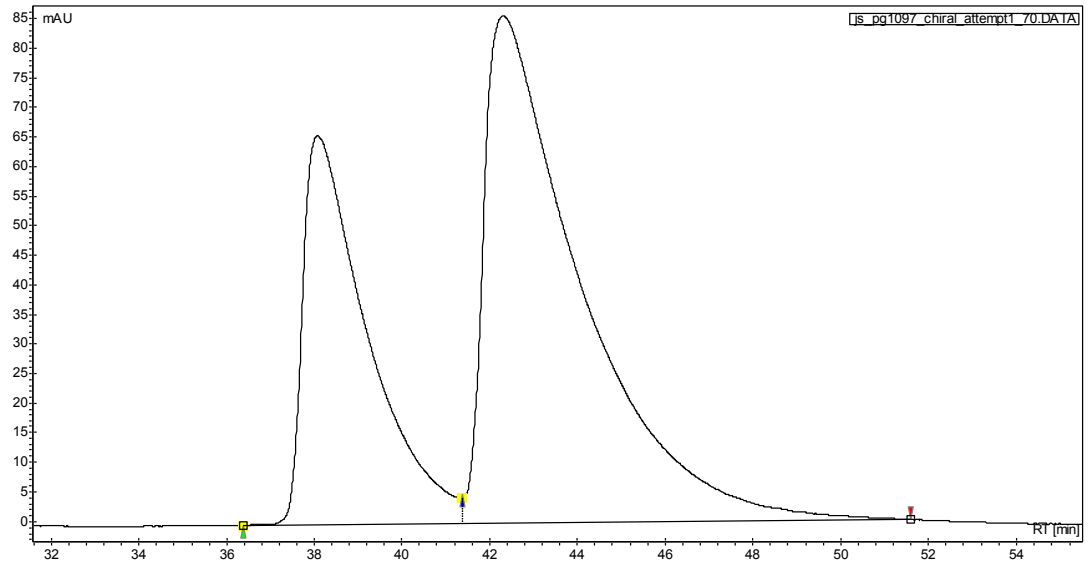
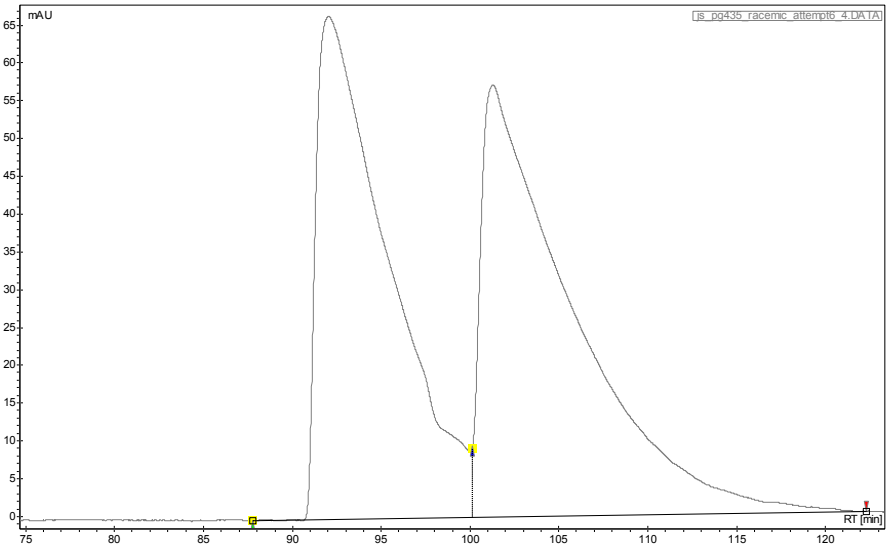
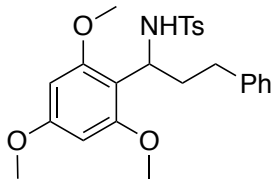


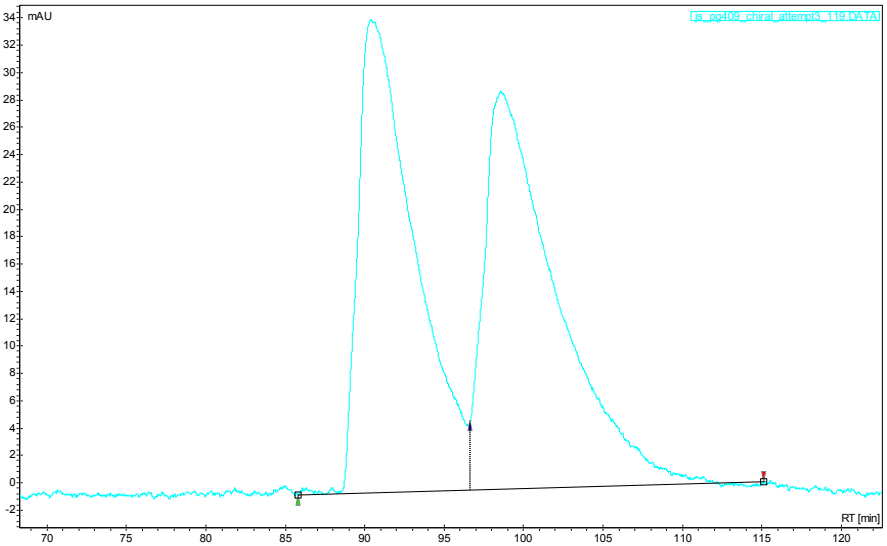
#	Time [min]	Area [%]
1	38.1	33.7
2	42.3	66.3



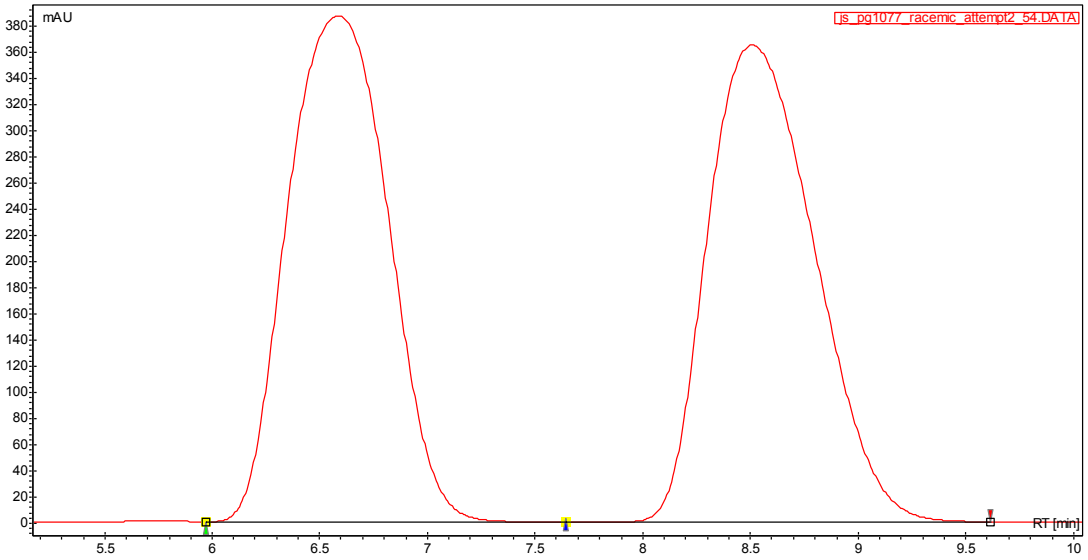
#	Time [min]	Area [%]
1	92.1	47.7
2	101.3	52.3



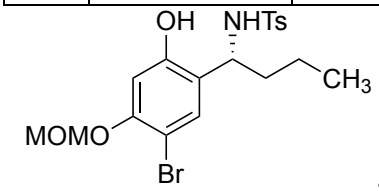
3m



#	Time [min]	Area [%]
1	90.4	48.2
2	98.7	51.8



#	Time [min]	Area [%]
1	6.6	50.0
2	8.5	50.0



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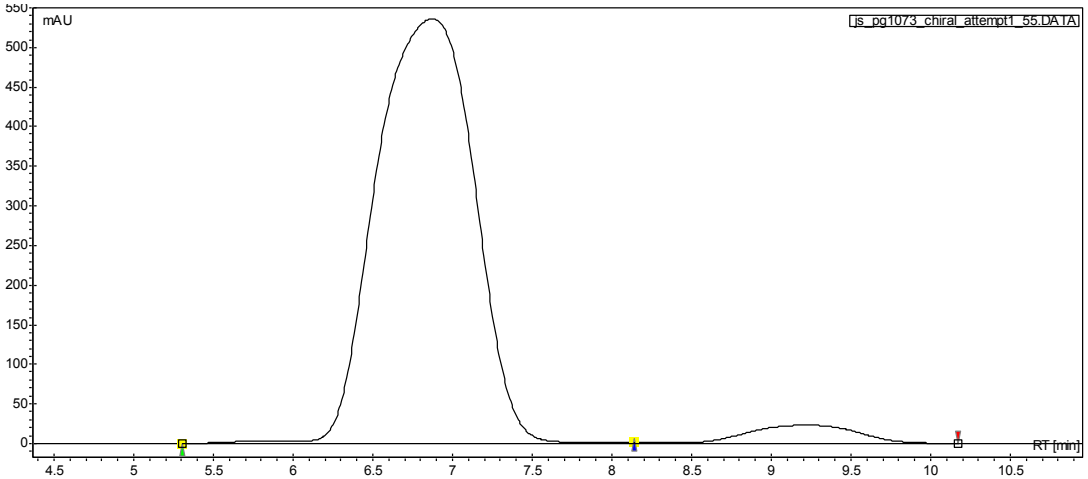
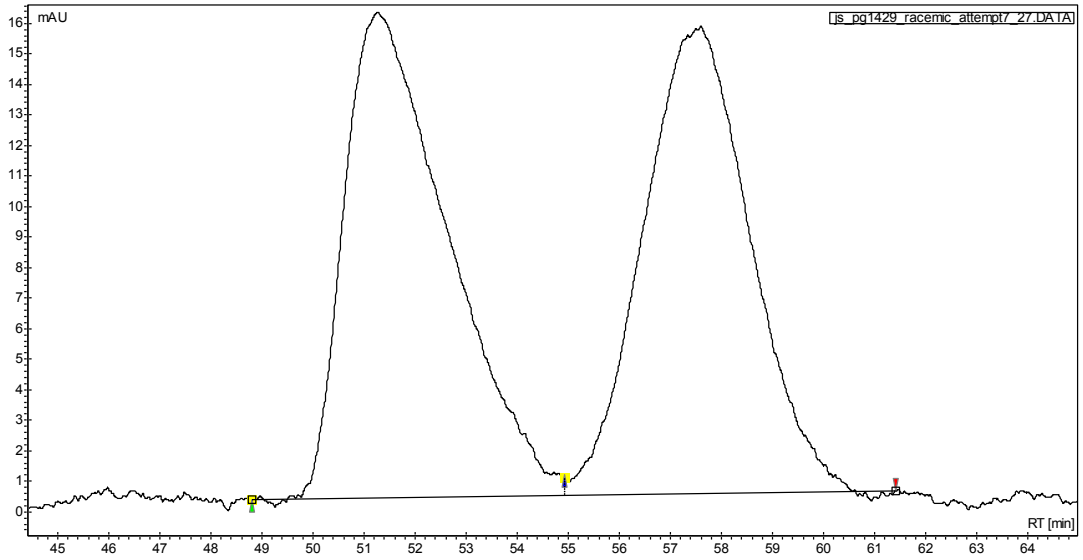
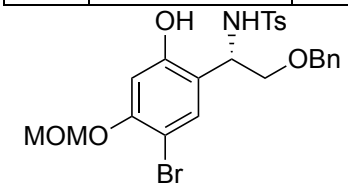


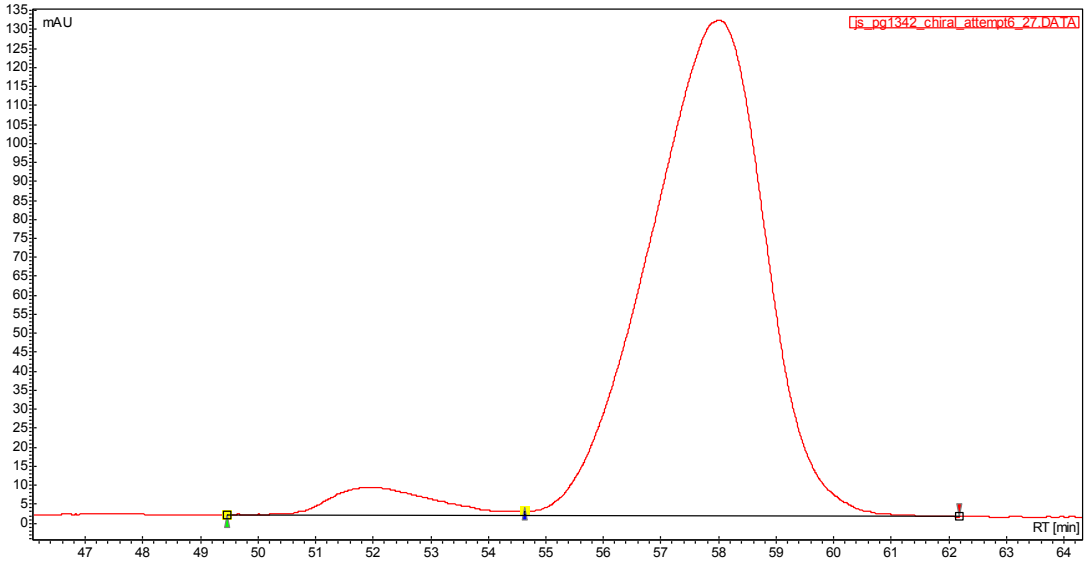
#	Time [min]	Area [%]
1	6.9	95.5
2	9.2	4.5



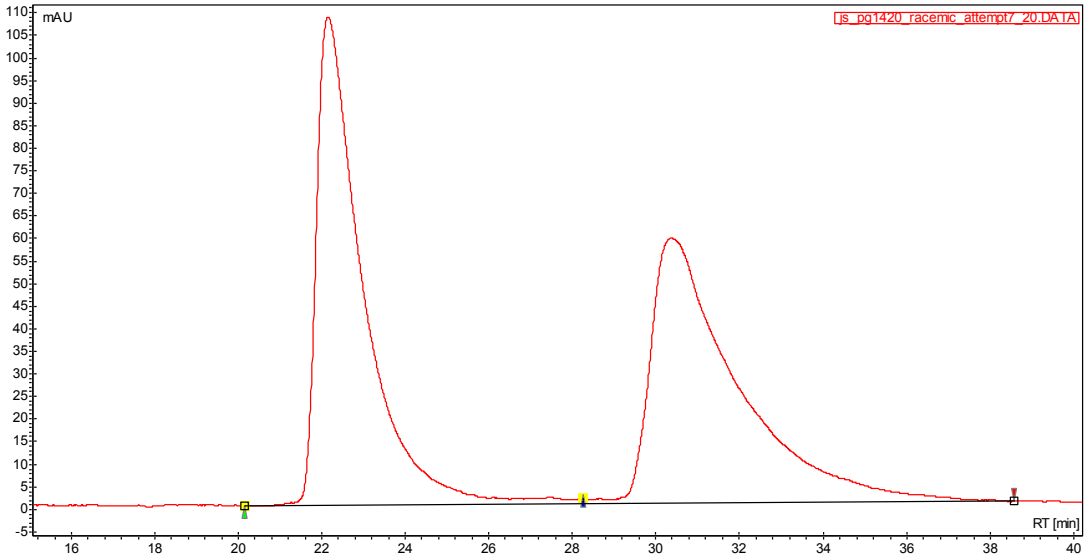
#	Time [min]	Area [%]
1	51.3	50.3
2	57.6	49.7



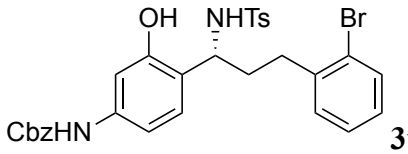
3o



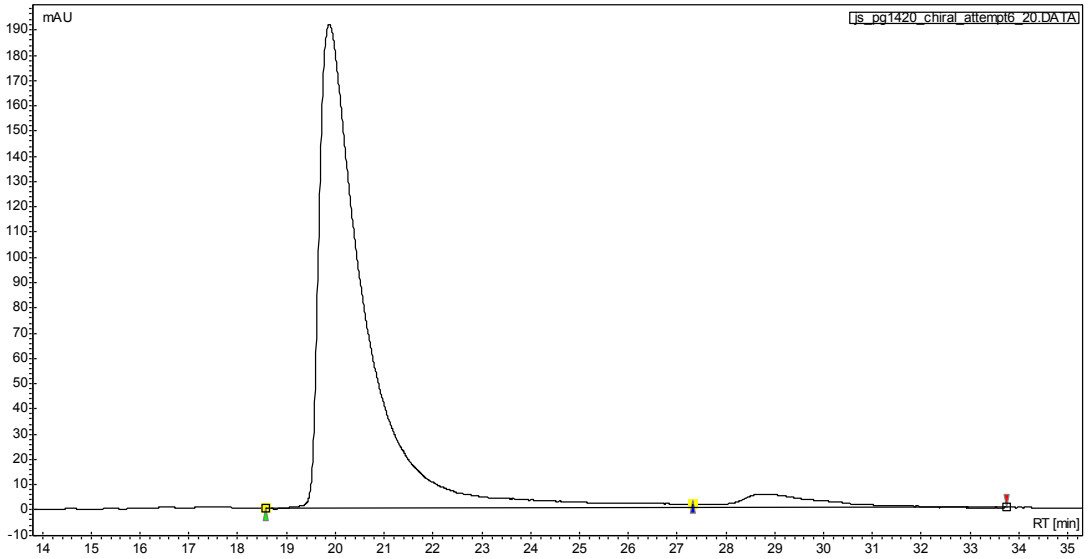
#	Time [min]	Area [%]
1	52.0	5.1
2	58.0	94.9



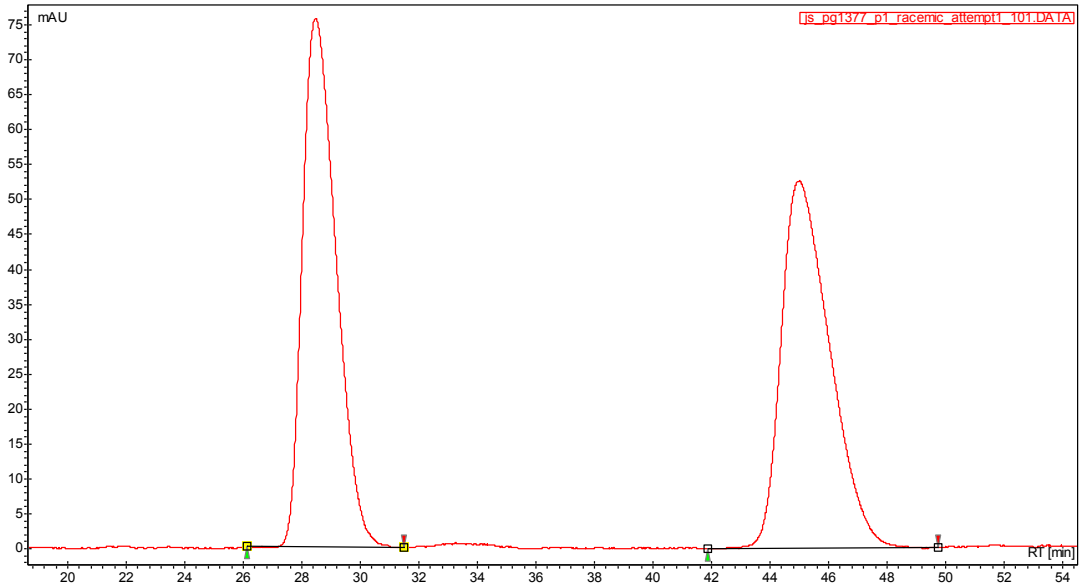
#	Time [min]	Area [%]
1	22.2	49.9
2	30.4	50.1



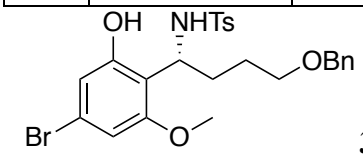
3p



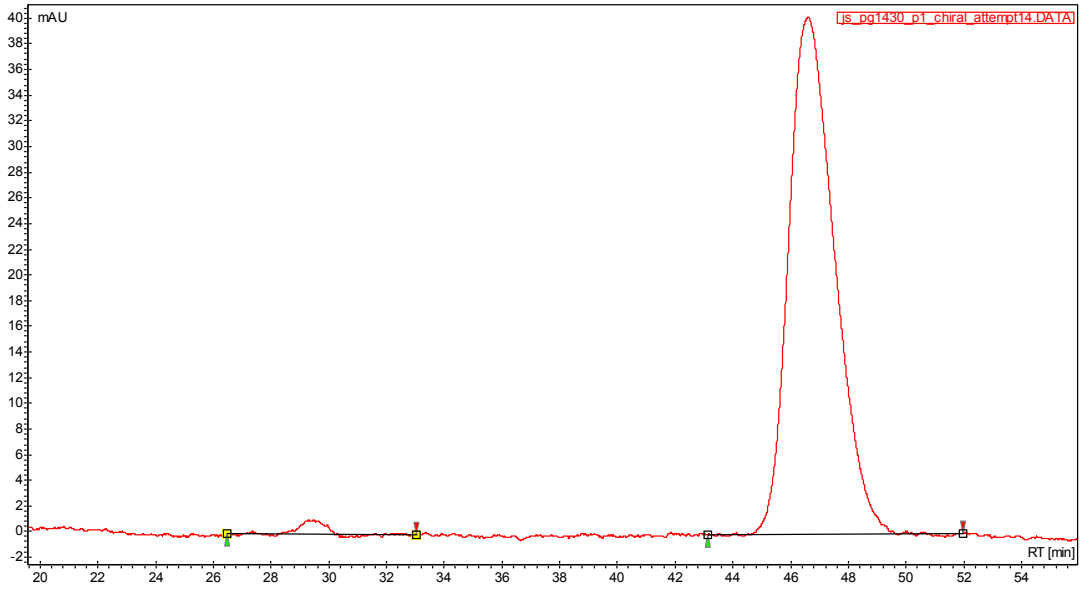
#	Time [min]	Area [%]
1	19.9	95.0
2	28.8	5.0



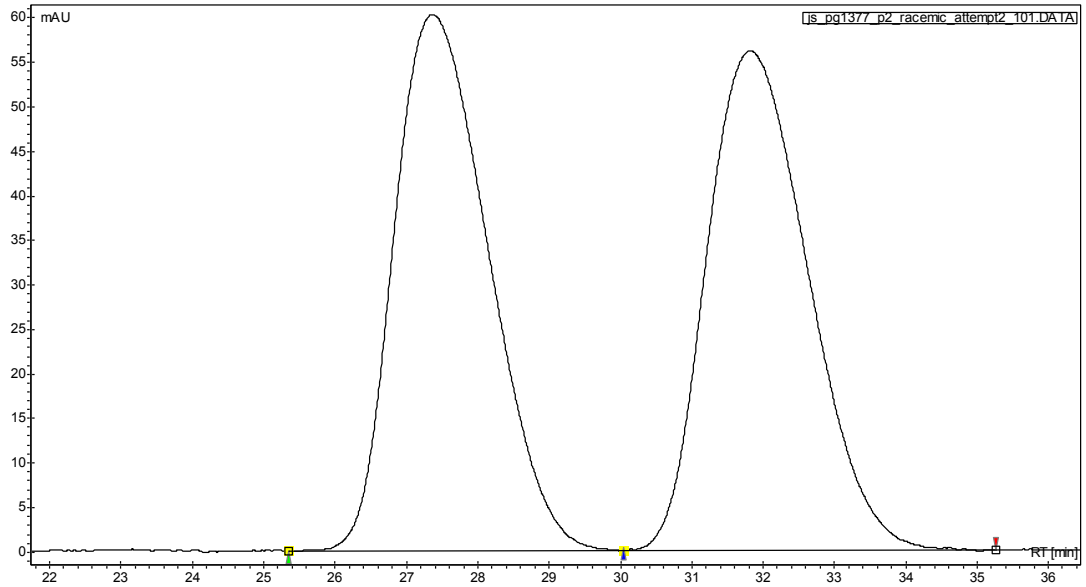
#	Time [min]	Area [%]
1	28.5	49.8
2	45.0	50.2



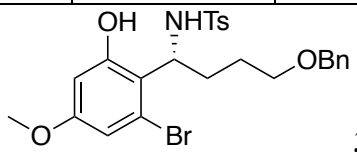
3q$_1$



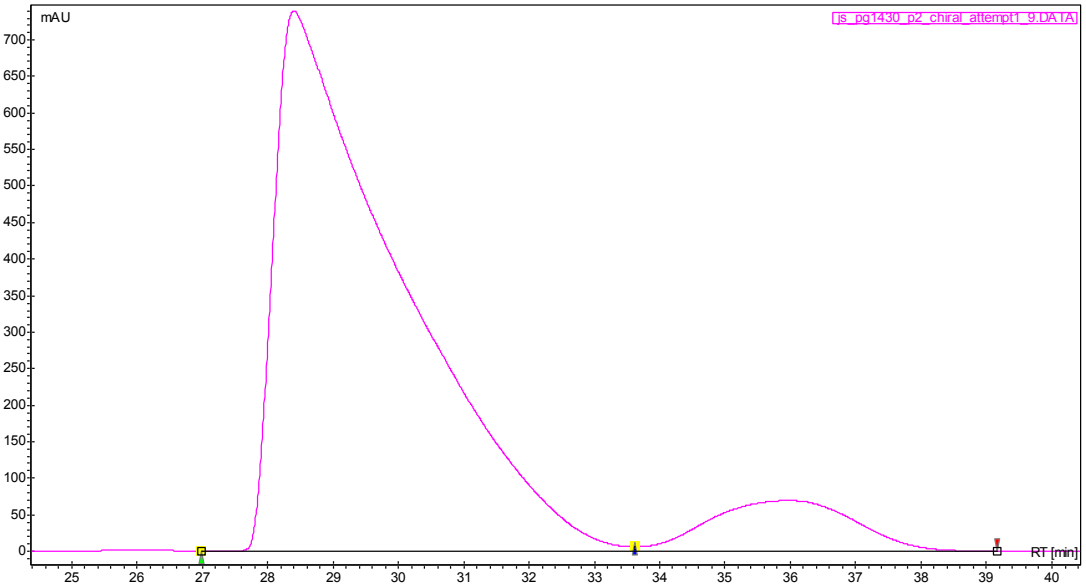
#	Time [min]	Area [%]
1	29.5	1.2
2	46.6	98.8



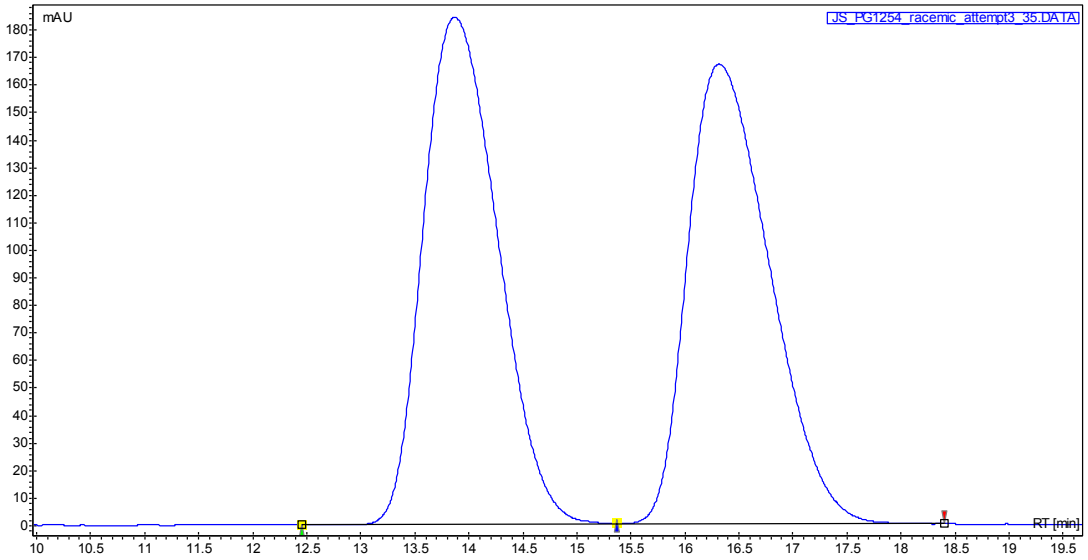
#	Time [min]	Area [%]
1	27.4	50.0
2	31.8	50.0



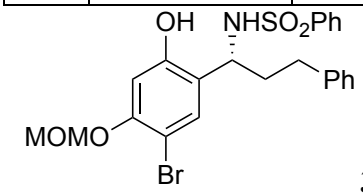
3q₂



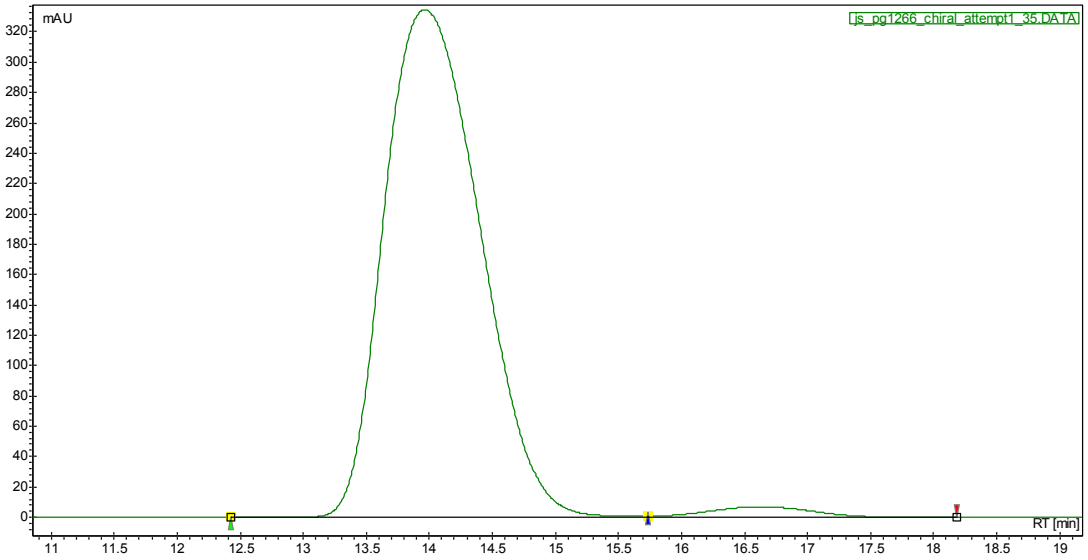
#	Time [min]	Area [%]
1	28.4	90.2
2	36.0	9.8



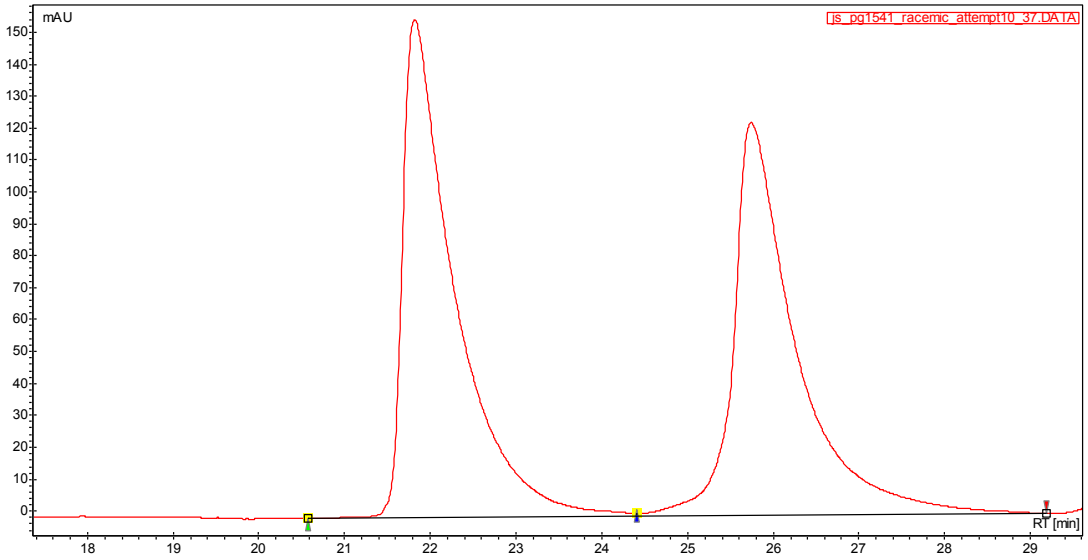
#	Time [min]	Area [%]
1	13.9	50.1
2	16.3	49.9



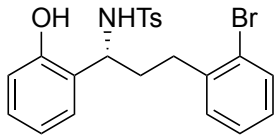
3r



#	Time [min]	Area [%]
1	14.0	97.7
2	16.6	2.3



#	Time [min]	Area [%]
1	21.8	51.3
2	25.8	48.7



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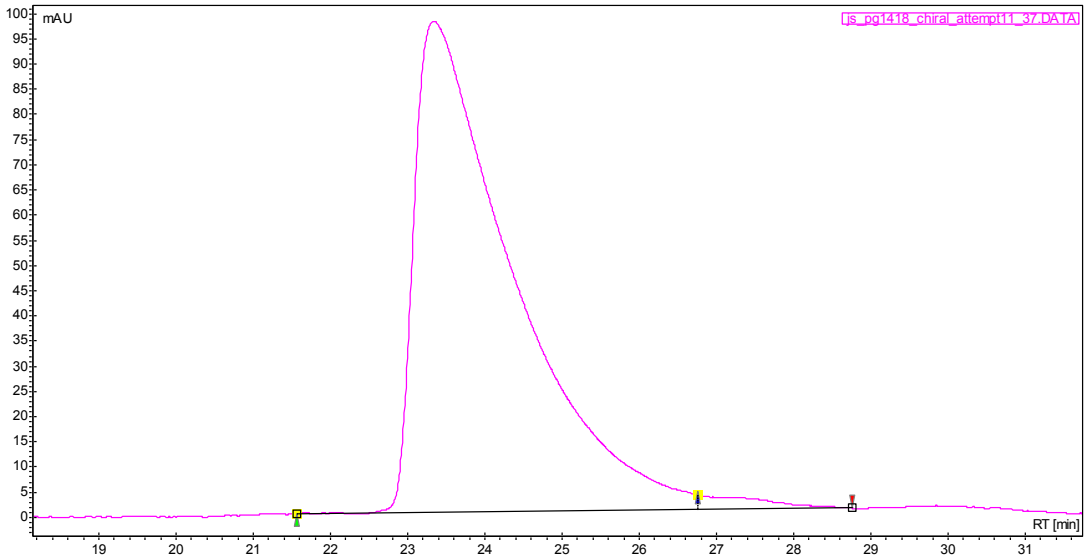
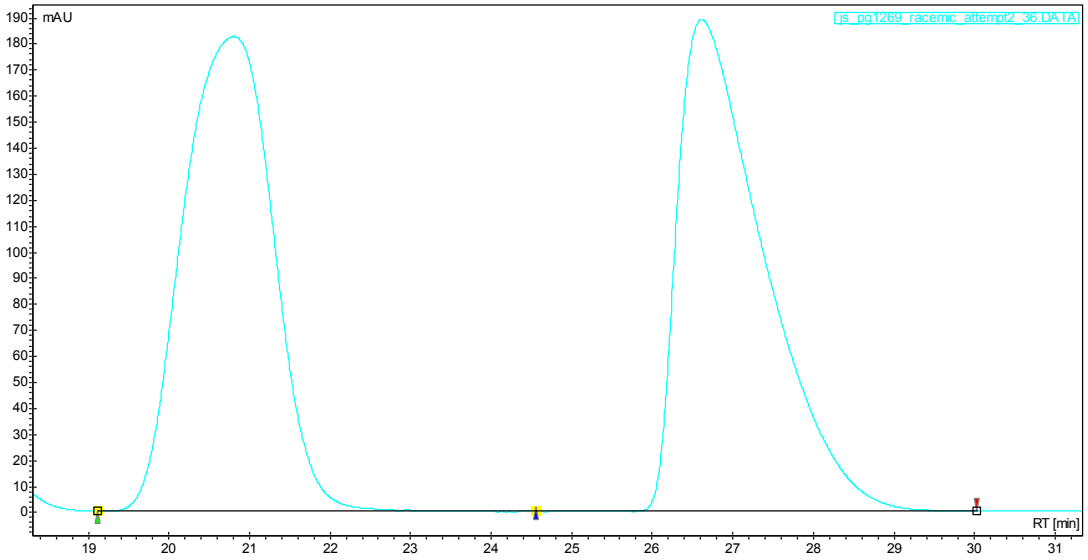
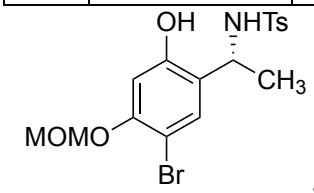


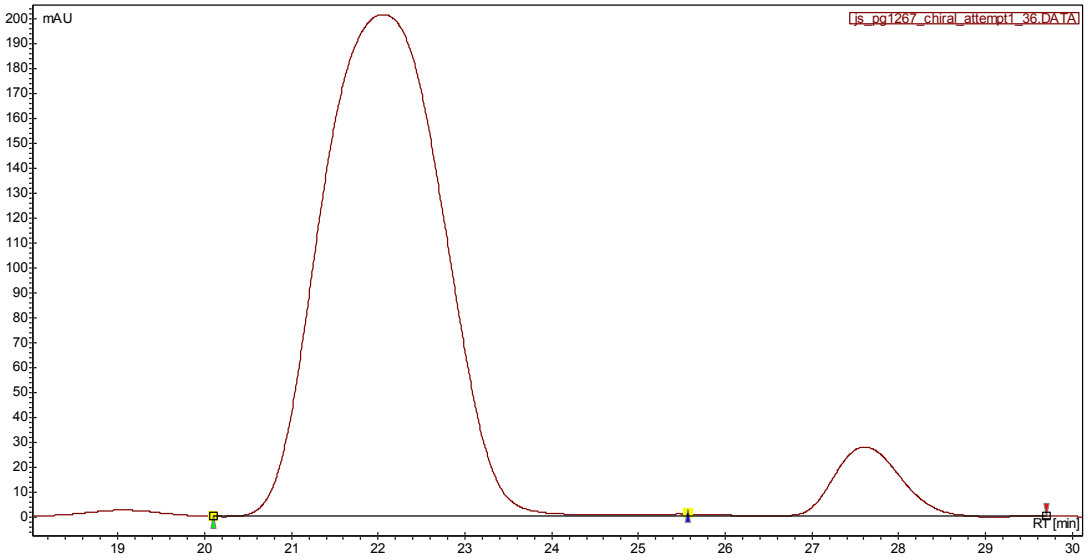
#	Time [min]	Area [%]
1	23.3	98.1
2	26.8	1.9



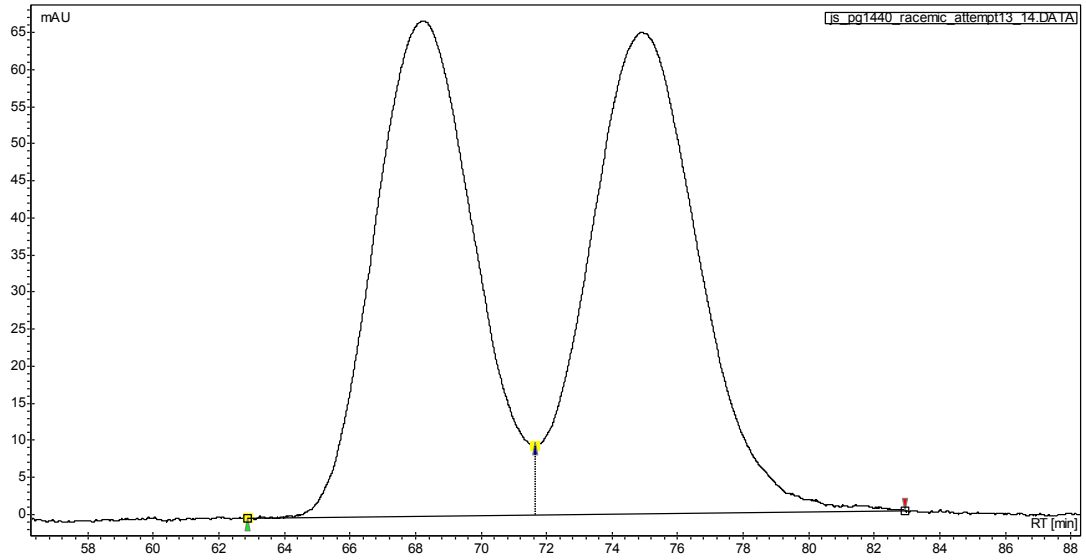
#	Time [min]	Area [%]
1	20.8	50.2
2	26.6	49.8



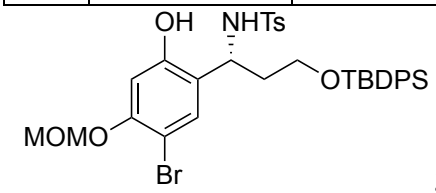
3t



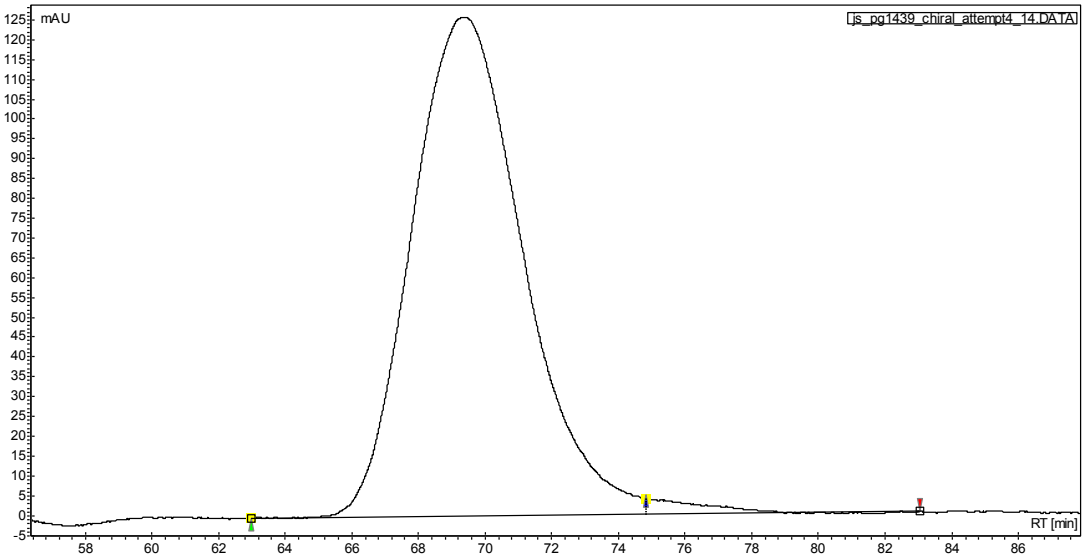
#	Time [min]	Area [%]
1	22.1	93.1
2	27.6	6.9



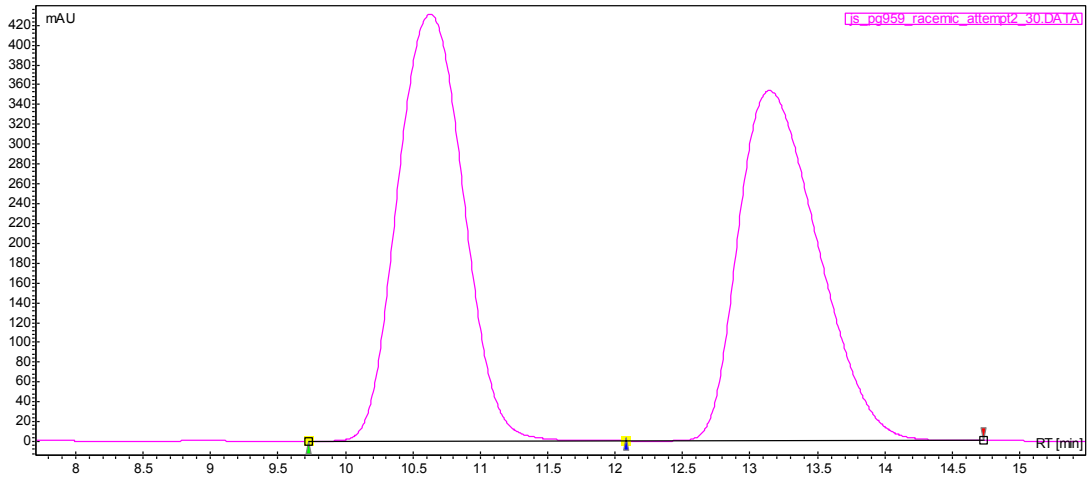
#	Time [min]	Area [%]
1	68.2	48.4
2	74.9	51.6



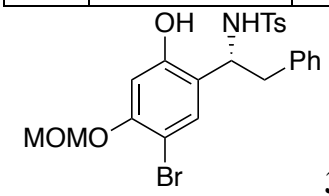
3u



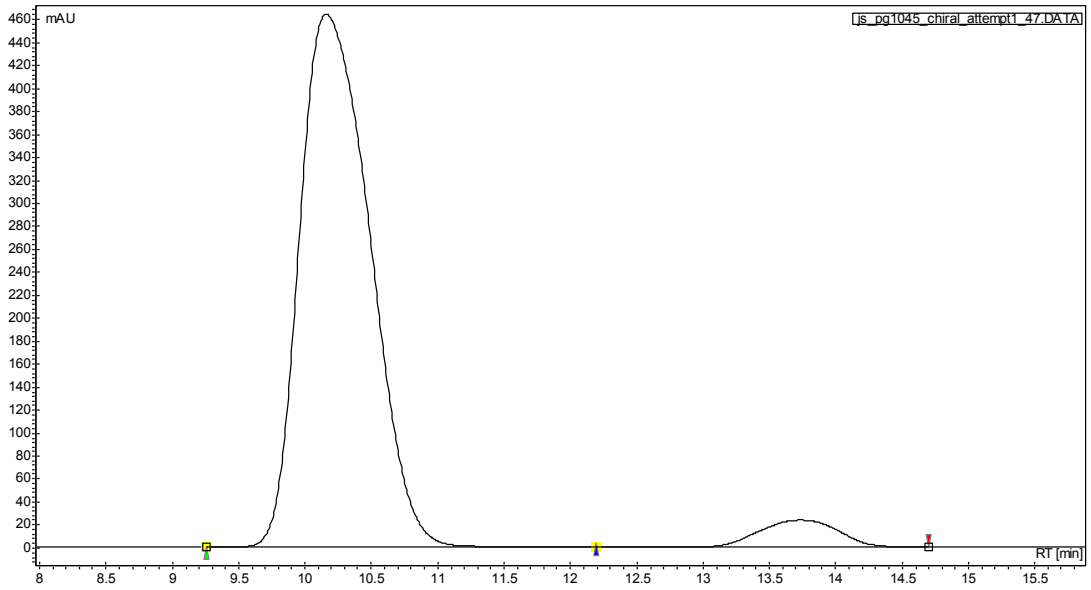
#	Time [min]	Area [%]
1	69.4	98.6
2	74.9	1.4



#	Time [min]	Area [%]
1	10.6	50.2
2	13.2	49.8

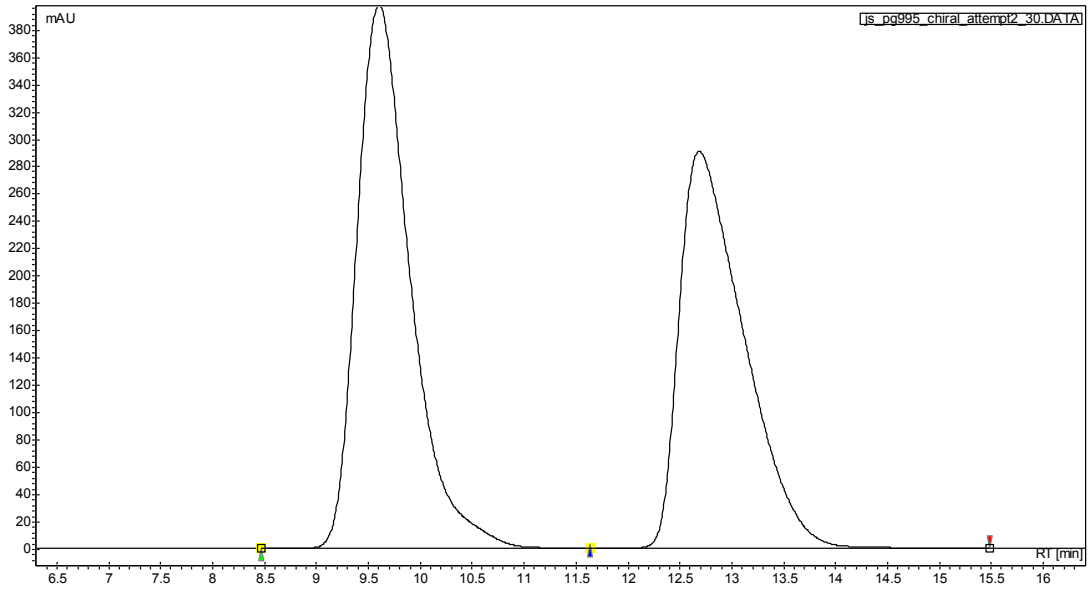


3v using (*S*)-*i*Pr-BOX

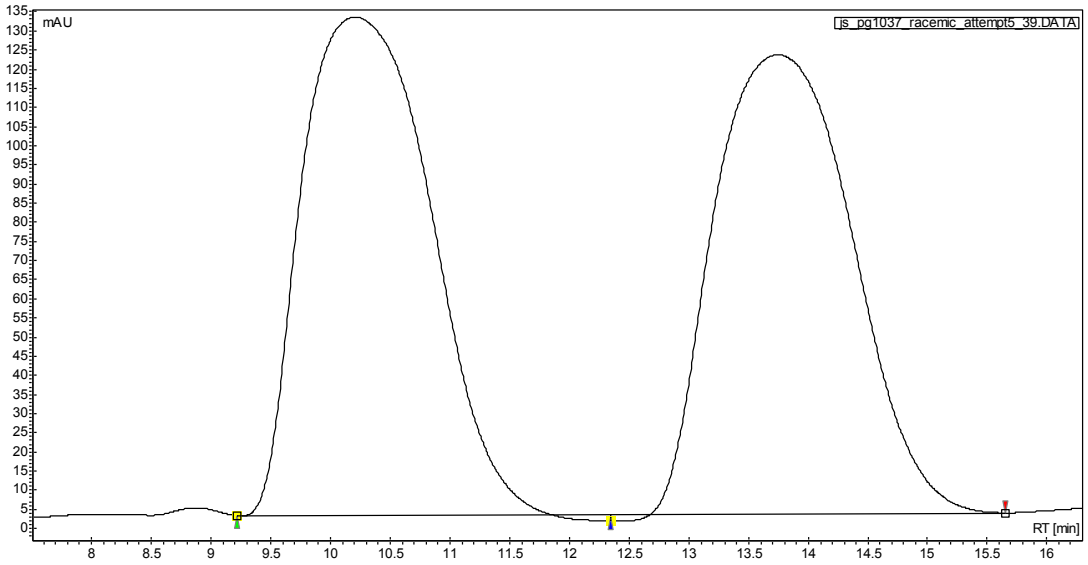


#	Time [min]	Area [%]
1	10.2	94.6
2	13.7	5.4

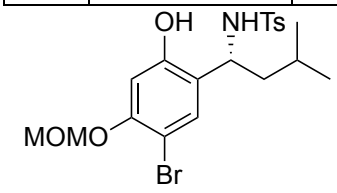
3v using (*S*)-Ph-BOX



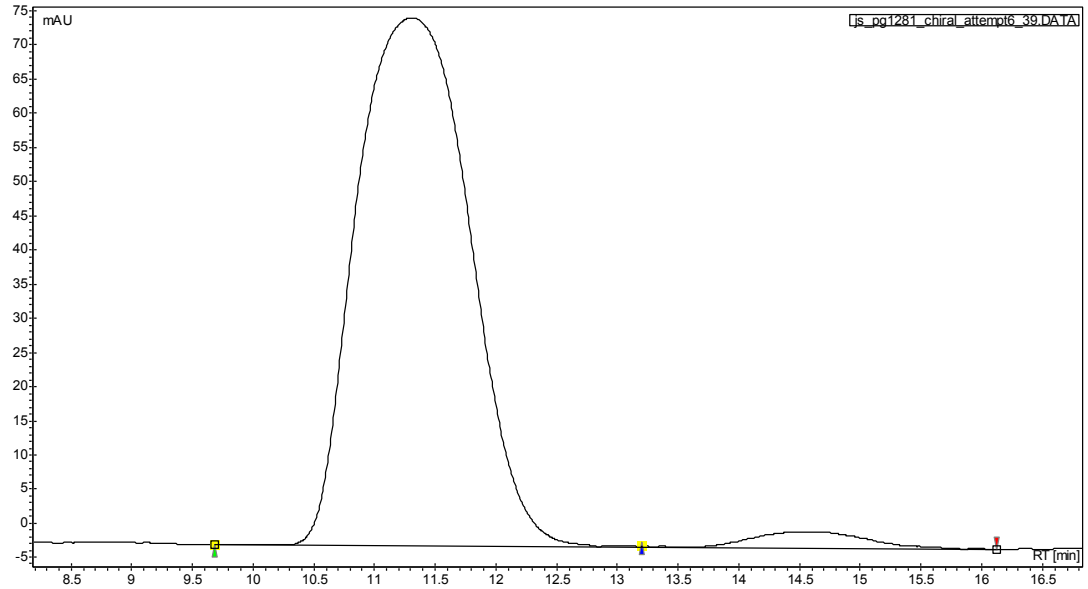
#	Time [min]	Area [%]
1	9.6	53.2
2	12.7	46.8



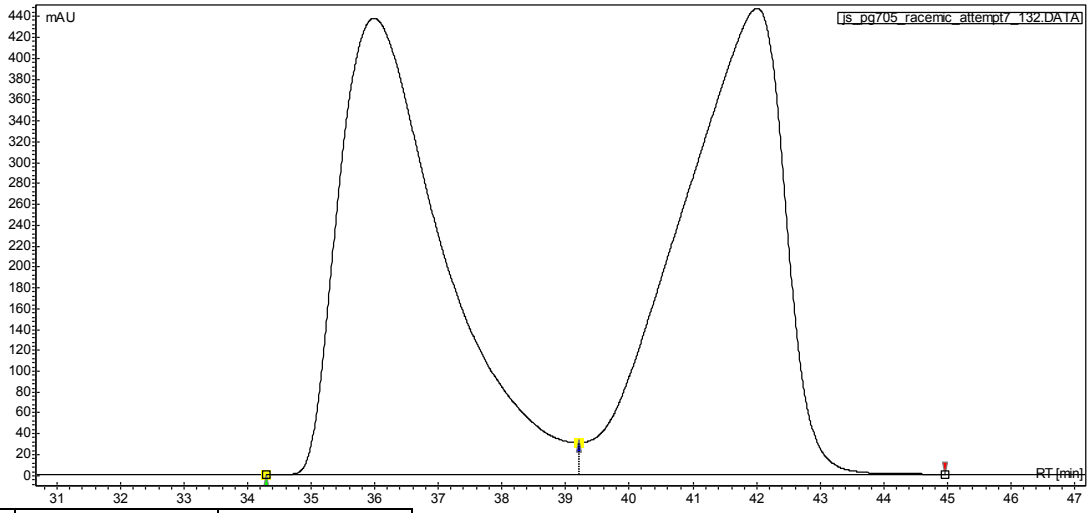
#	Time [min]	Area [%]
1	10.2	50.2
2	13.8	49.8



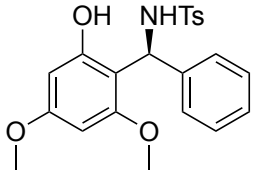
3w



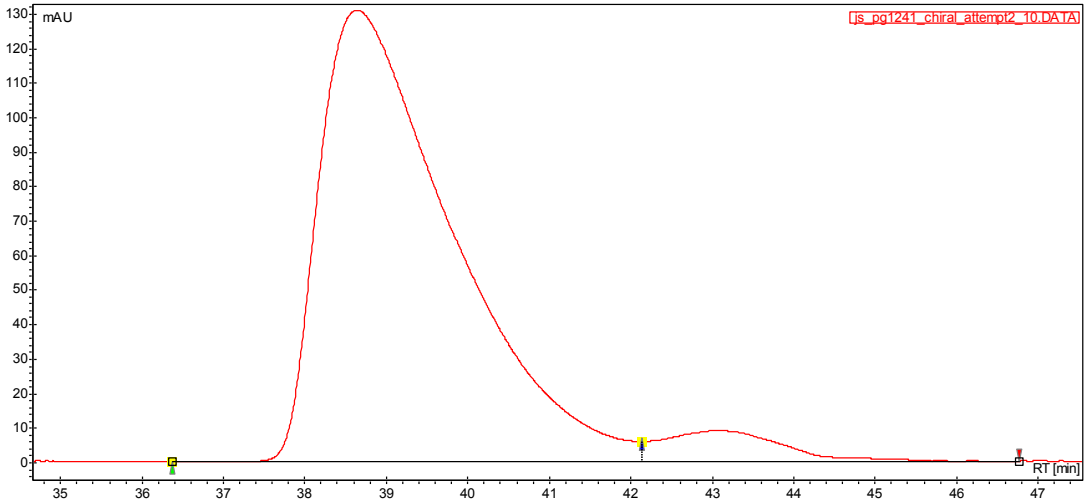
#	Time [min]	Area [%]
1	11.3	97.0
2	14.7	3.0



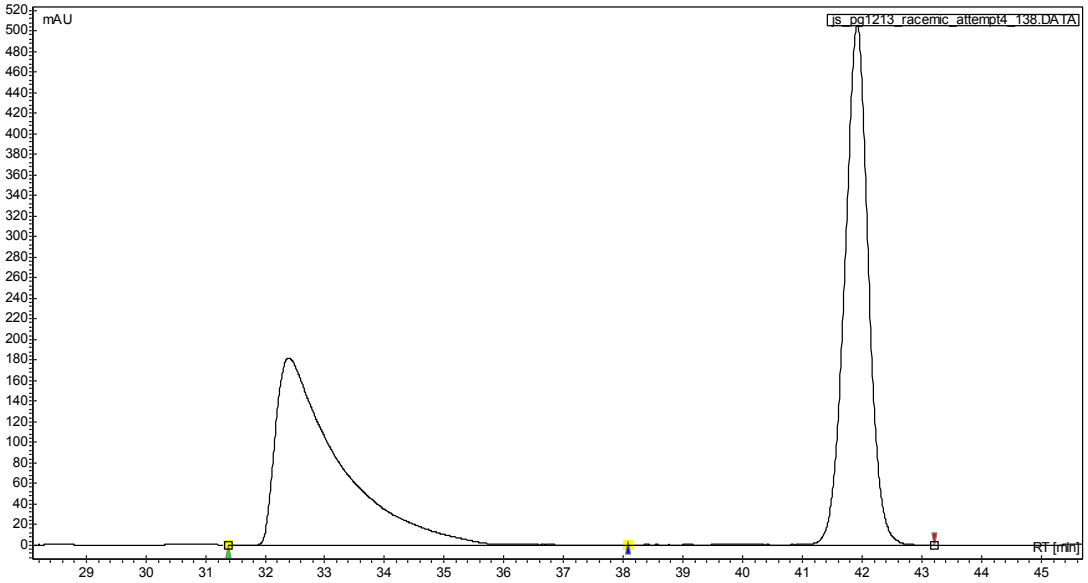
#	Time [min]	Area [%]
1	36.0	49.6
2	42.0	50.4



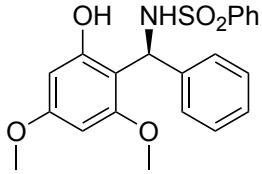
5a



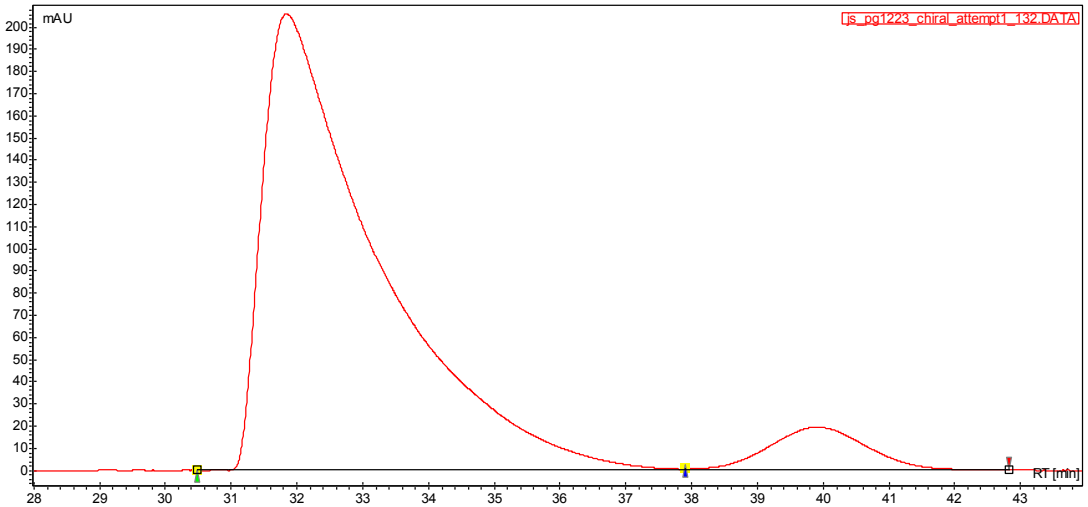
#	Time [min]	Area [%]
1	38.6	94.3
2	43.1	5.7



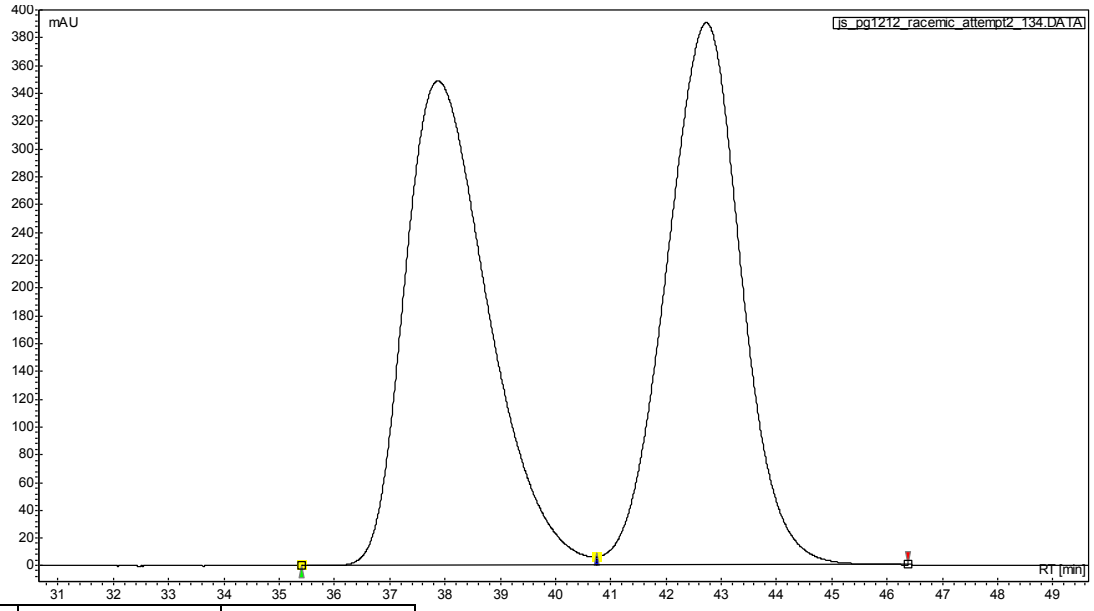
#	Time [min]	Area [%]
1	32.4	48.7
2	41.9	51.3



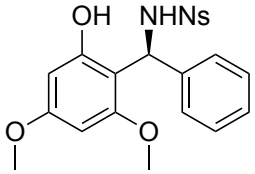
5b



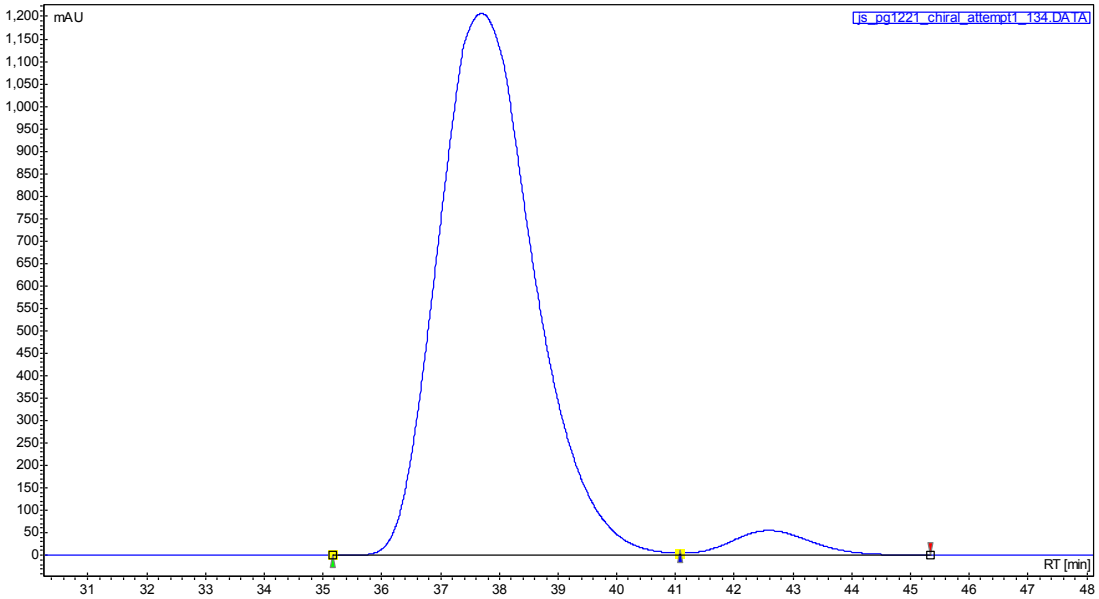
#	Time [min]	Area [%]
1	31.8	92.6
2	39.9	7.4



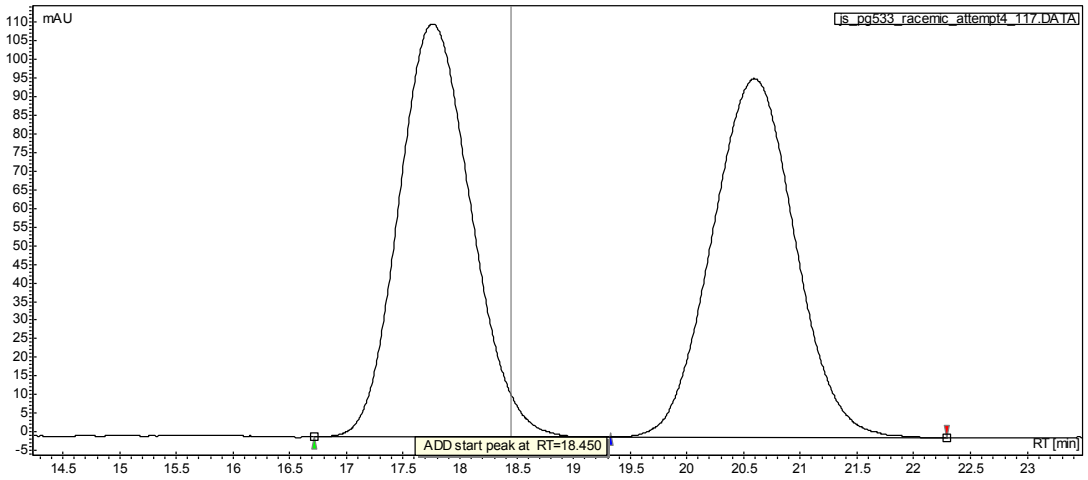
#	Time [min]	Area [%]
1	37.9	49.9
2	42.7	50.1



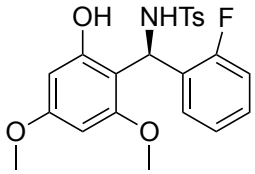
5c



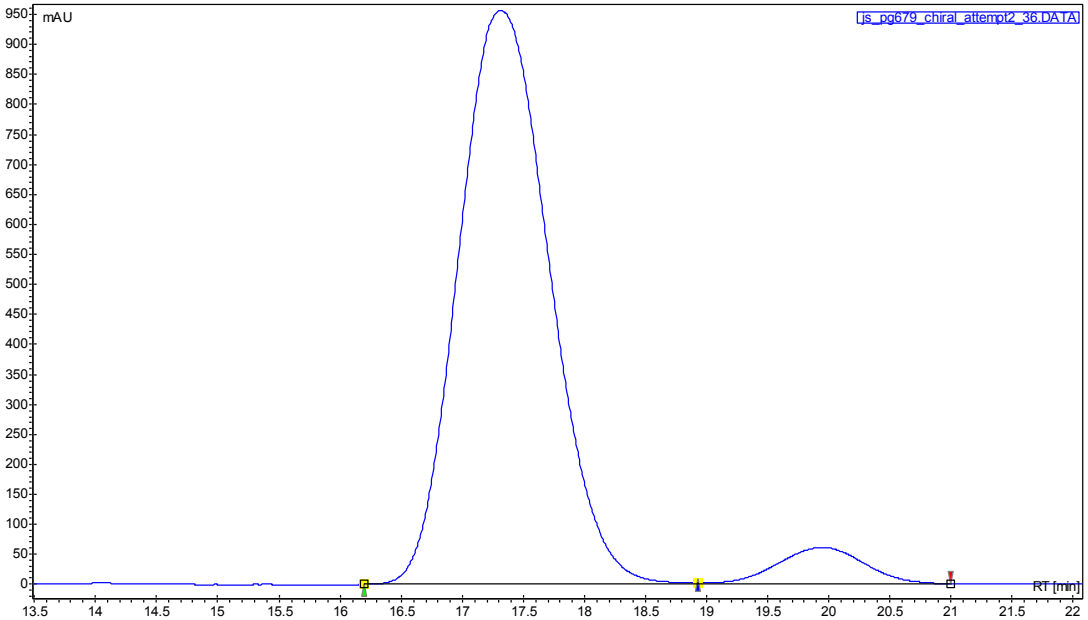
#	Time [min]	Area [%]
1	37.7	96.3
2	42.6	3.7



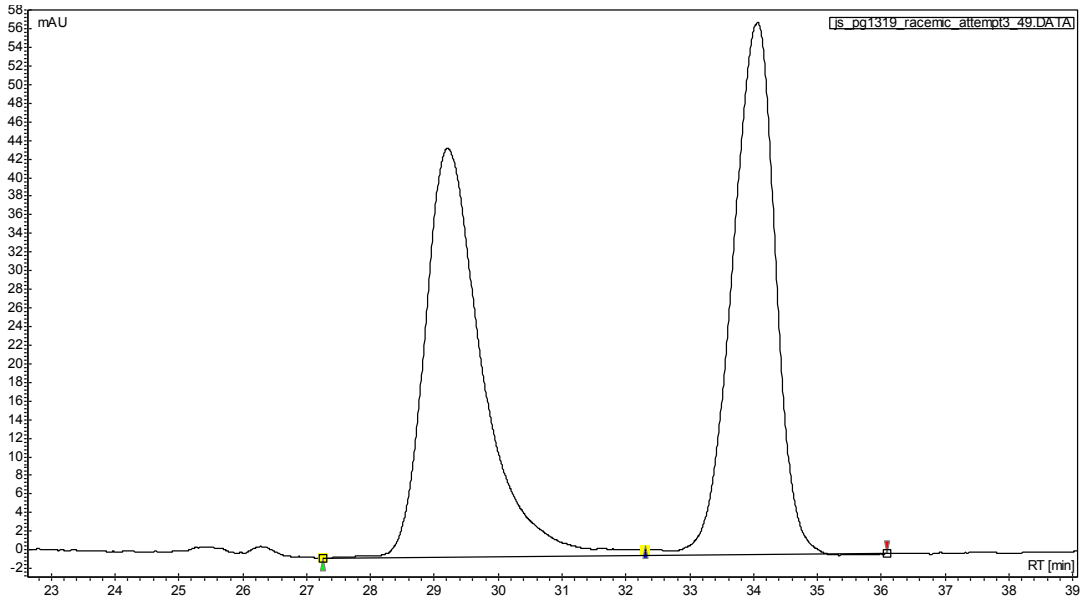
#	Time [min]	Area [%]
1	17.8	50.1
2	20.6	49.9



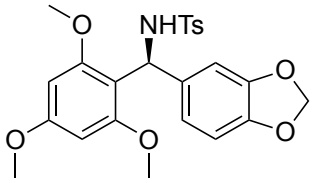
5d



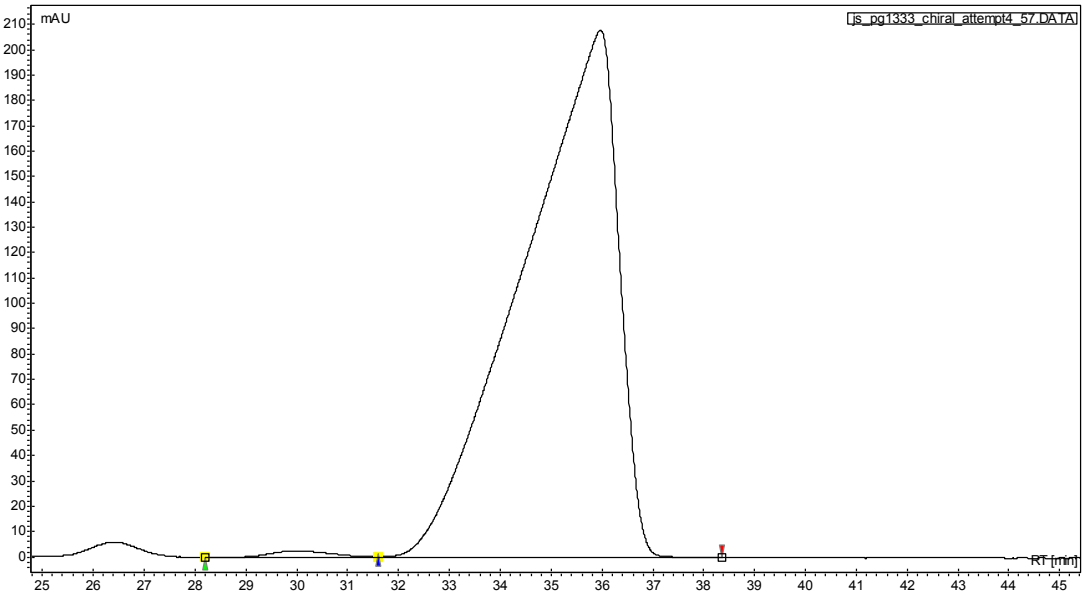
#	Time [min]	Area [%]
1	17.3	94.2
2	20.0	5.8



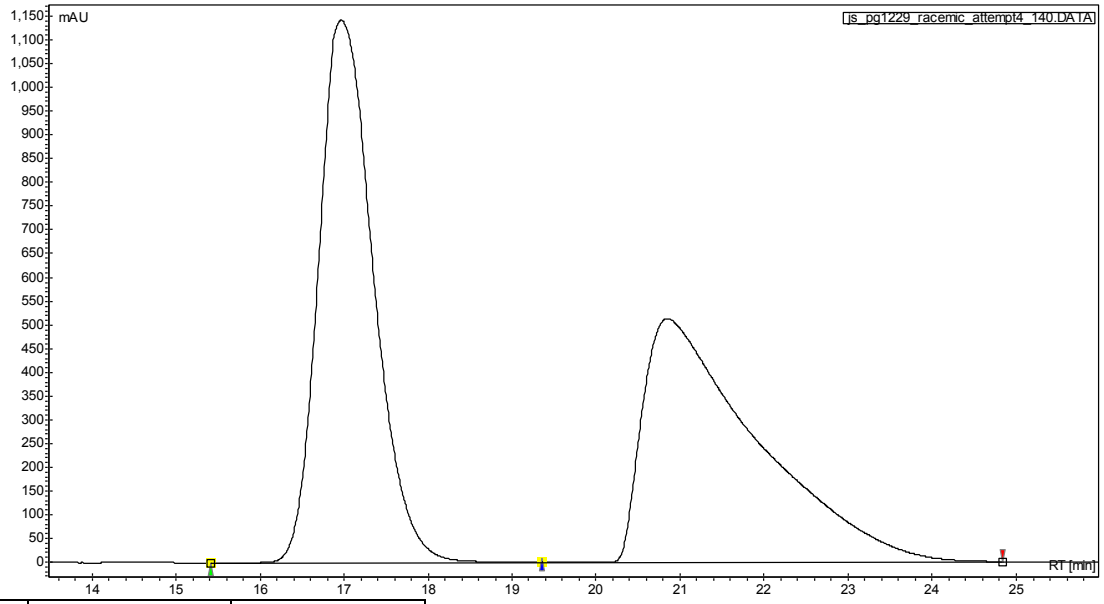
#	Time [min]	Area [%]
1	29.2	50.5
2	34.1	49.5



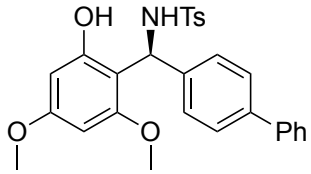
Derivative of **5e**



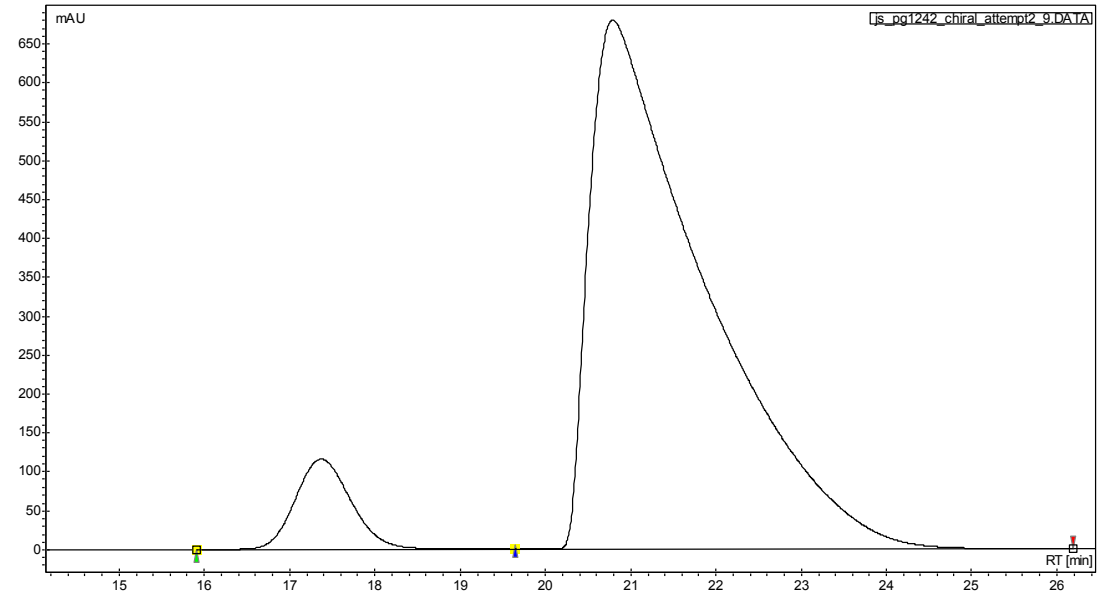
#	Time [min]	Area [%]
1	30.0	0.9
2	36.0	99.1



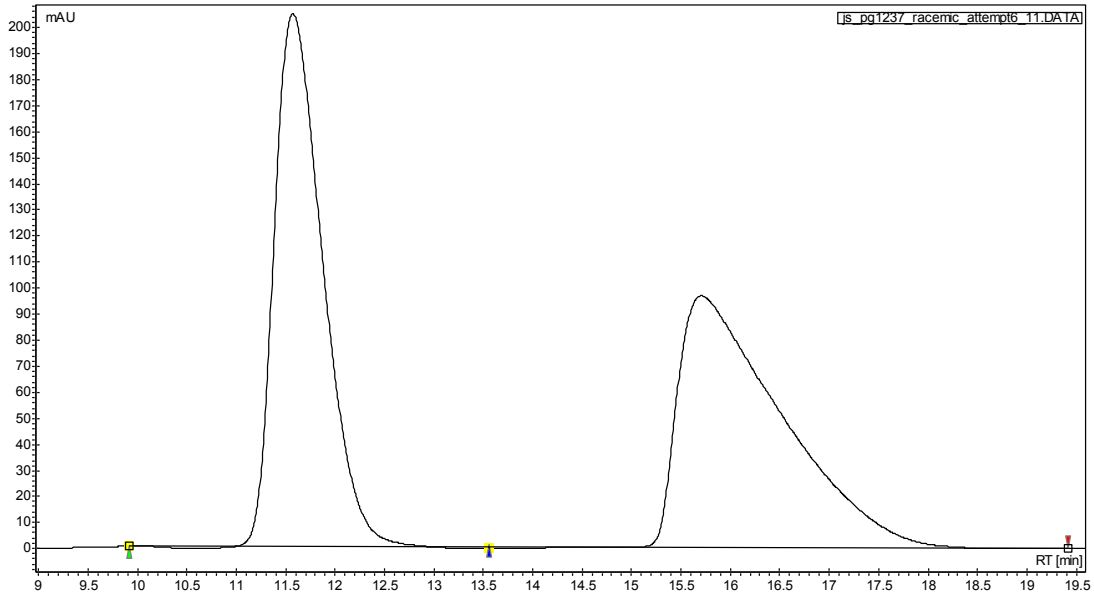
#	Time [min]	Area [%]
1	17.0	51.7
2	20.9	48.3



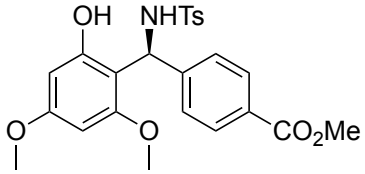
5f



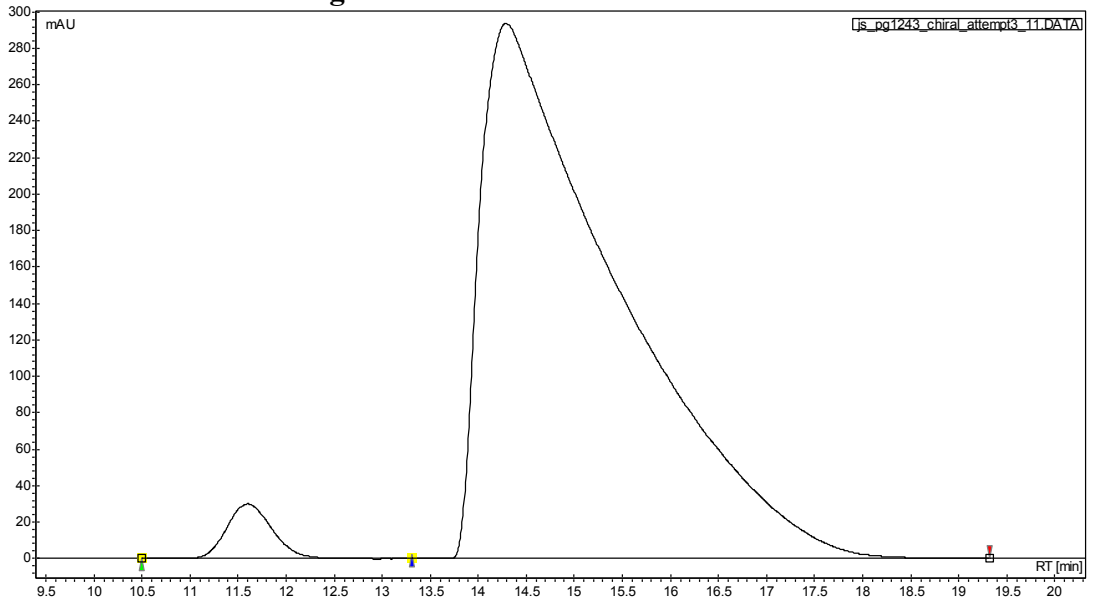
#	Time [min]	Area [%]
1	17.4	7.6
2	20.8	92.4



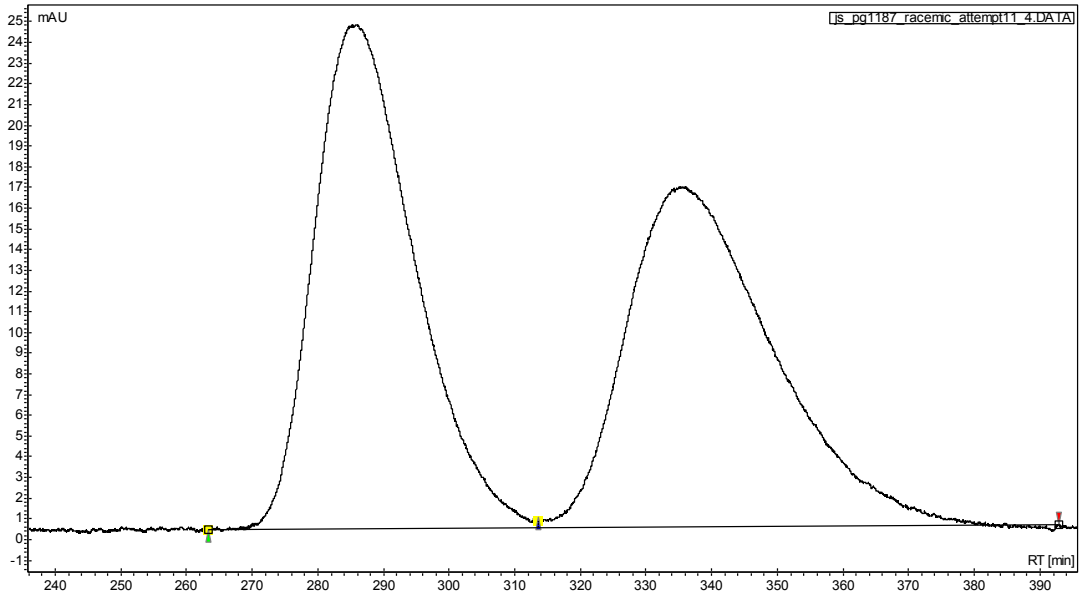
#	Time [min]	Area [%]
1	11.6	49.8
2	15.7	50.2



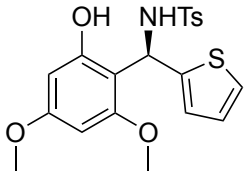
5g



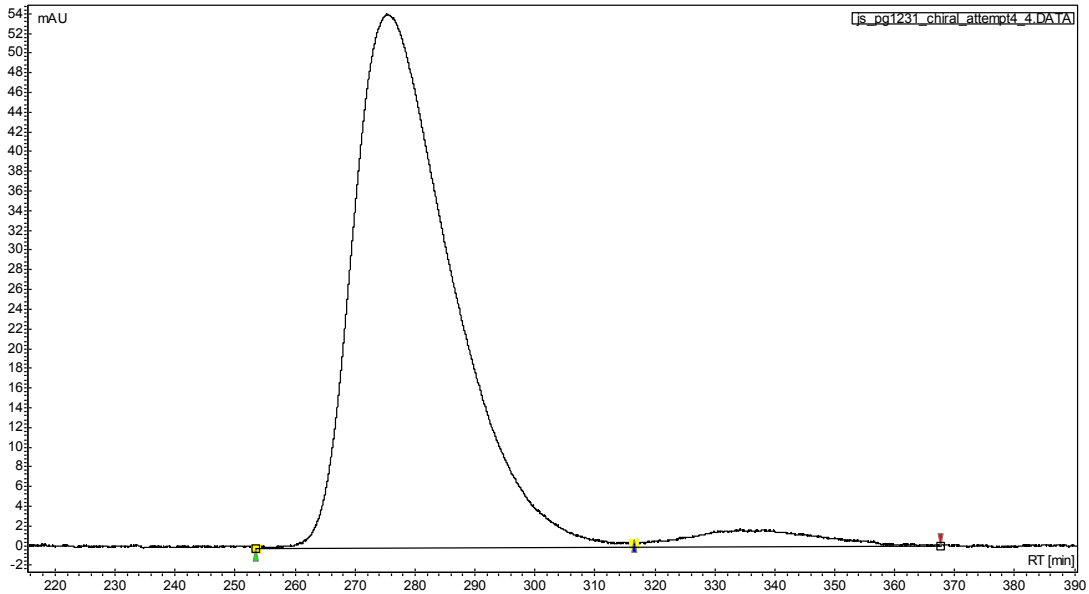
#	Time [min]	Area [%]
1	11.6	3.2
2	14.3	96.8



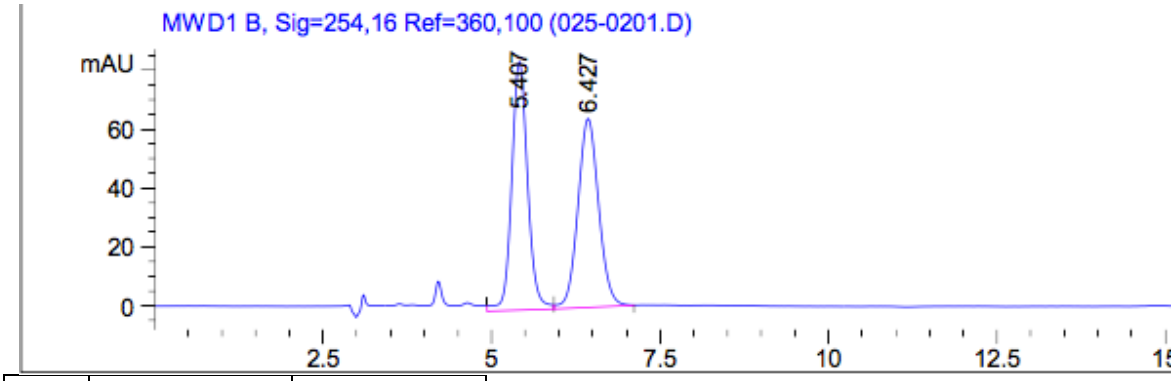
#	Time [min]	Area [%]
1	285.8	50.5
2	336.0	49.5



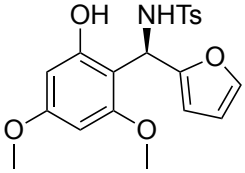
5h



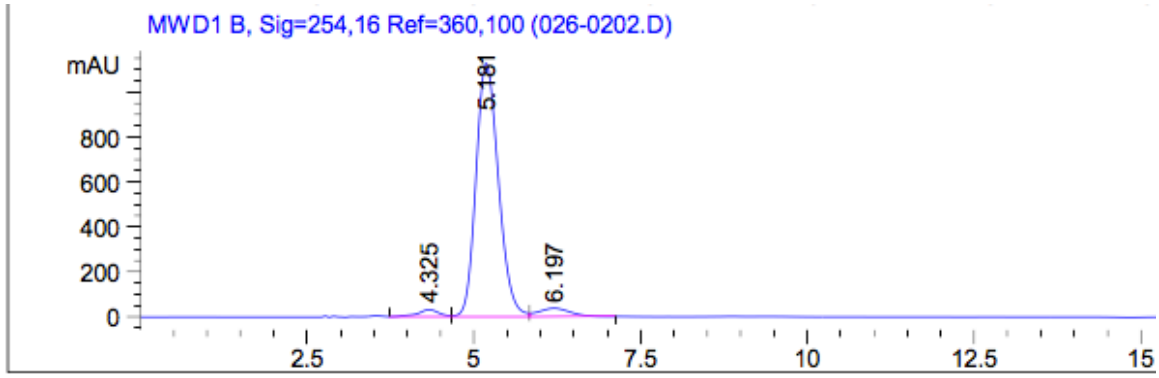
#	Time [min]	Area [%]
1	275.5	96.1
2	334.2	3.9



#	Time [min]	Area [%]
1	5.4	50.1
2	6.4	49.9



5i



#	Time [min]	Area [%]
1	5.2	95.6
2	6.2	4.4