Strain-Release Trifluoromethoxylation and Pentafluorosulfanoxylation of [1.1.0]Bicyclobutanes: Expanded Access to Fluorinated Cyclobutane Hybrid Bioisosteres

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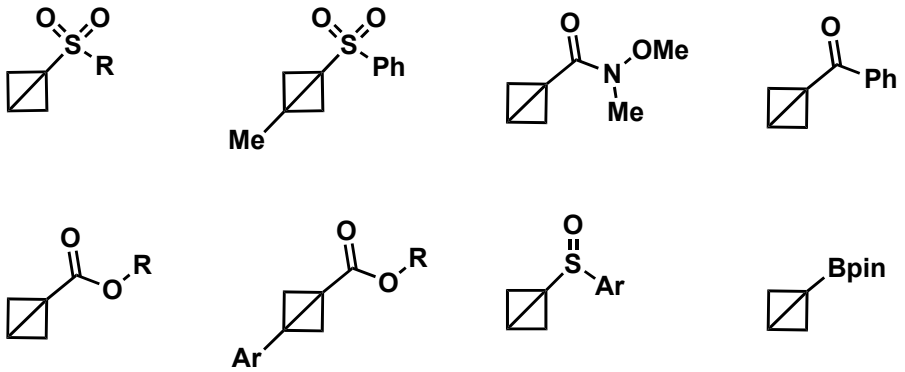
Table of Contents

General Information:

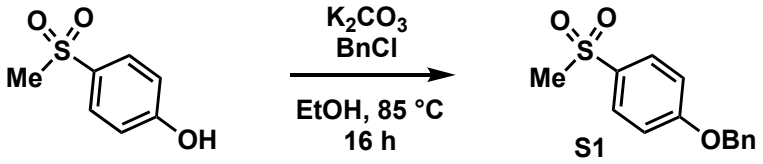
Unless otherwise stated, all reactions were carried out strictly under anhydrous conditions and under N_2 or Ar atmosphere and were stirred with Teflon-coated magnetic stir bars. Liquid reagents and solvents were transferred via syringe using standard Schlenk techniques. Dichloromethane (CH_2Cl_2), tetrahydrofuran (THF), diethyl ether (Et_2O) and toluene were obtained from a solvent purification system directly before use. Methanol (MeOH), acetonitrile (MeCN), *n*-pentane, dimethyl sulfoxide (DMSO), dimethylformamide (DMF), and ethyl acetate (EtOAc) were purchased in sealed bottles containing molecular sieves and were used as received. All other solvents were used as received unless otherwise stated. All NMR data were collected on either a 300, 400, or 800 MHz spectrometer. For ^{19}F NMR yield determination, α,α,α-trifluorotoluene (TFT) or fluorobenzene was introduced after each reaction as an internal standard, and the d1 relaxation delay was increased to 30 s during data collection. The ^{1}H, ^{13}C, and ^{19}F NMR chemical shifts are given in parts per million (δ) and calibrated to either residual solvent or TMS signal (^{1}H and ^{13}C), α,α,α-trifluorotoluene (TFT) (δ = – 62.61 ppm in $CDCl_3$), or fluorobenzene (δ = – 112.96 in $CDCl_3$).[1] NMR data are reported in the following fashion: chemical shift (multiplicity (s = singlet, d = doublet, q = quartet, p = pentet, sept = septet, dt = doublet of triplets, dd = doublet of doublets, tt = triplet of triplets, m = multiplet), integration, coupling constants (Hz)). Infrared spectroscopy (IR) data were collected on a Bruker Tensor 27 FT-IR spectrometer with ATR-IR attachment. IR signals are reported in reciprocal centimeters (cm^{-1}) and are rounded to the nearest 1 cm^{-1}. High-resolution mass spectrometry (HRMS) data was collected on a Thermo Q-Exactive HF. Melting point data was collected on a Stanford Research Systems MPA120EZ-Melt automated melting point system.

Synthesis of BCBs:

Sulfone-containing BCBs were synthesized following a one-pot procedure reported by Jung and Lindsay,[2] or by a stepwise route reported by Baran and co-workers.[3] 1-((3,5-difluorophenyl)sulfonyl) bicyclo[1.1.0]butane was purchased from Millipore-Sigma (SKU: ALD00558). All other BCBs were prepared according to literature procedures. Ester, ketone, and amide-substituted BCBs were synthesized following protocols reported by Procter, Studer, Glorius, and Malins.[4] The sulfoxide and Bpin-containing BCBs were synthesized according to procedures reported by Aggarwal and co-workers.[5] All NMR spectra were consistent with previously reported data.



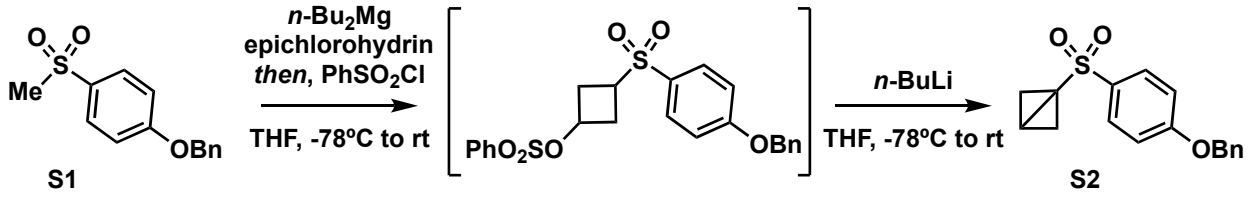
Scheme S1. Bicyclobutane starting materials.



A 500 mL round bottom flask equipped with a stir bar was charged with 4-hydroxyphenyl methyl sulfone (5.00 g, 29.0 mmol, 1.0 equiv., *purchased from Synthonix*) and dissolved in EtOH (150 mL). To the resulting mixture were added benzyl chloride (5.02 mL, 43.6 mmol, 1.5 equiv.) and potassium carbonate (6.02 g, 43.6 mmol, 1.5 equiv.); the flask was placed into a pre-heated oil bath set to 85 °C and stirred for 16 h. Upon completion, 300 mL H_2O was added to the reaction vessel and transferred to a 1 L separatory funnel. The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine (3 × 50 mL), dried over anhydrous Na_2SO_4, filtered through a pad of Celite, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography on silica gel, eluting with 20-40% EtOAc in hexanes (elution gradient). 1-(Benzyloxy)-4-(methylsulfonyl)benzene was obtained as a white, crystalline solid (6.9 g, 90%).

R_f: 0.40 (3:2 Hexanes:EtOAc), vis: UV (254 nm).
m.p.: 134.3 – 139.0 ºC.
^{1}H (300 MHz, $CDCl_3$): δ = 7.89-7.85 (m, 2H), 7.43-7.33 (m, 5H), 7.11-7.08 (m, 2H), 5.15 (s, 2H), 3.03 (s, 3H).
^{13}C{^{1}H} (201 MHz, $CDCl_3$): δ = 163.0, 135.9, 132.7, 129.7, 128.9, 128.6, 127.6, 115.5, 70.6, 45.0
ATR-IR (ν_{max}): 2951, 2921, 2852, 1591, 1574, 1497, 1391, 1310, 1293, 1249, 1138, 1092, 999, 965, 831, 770, 752, 701 cm^{-1}.

HRMS (*m/z*): (ESI) calc'd for $C_{14}H_{15}O_3S^+$ $[M-H]^+$ 263.0737, found 262.0725.



Synthesis of the [1.1.0]bicyclobutane was adapted from a known literature procedure.[2] An oven-dried 250 mL round bottom flask equipped with a magnetic stir bar was charged with 1-(benzyloxy)-4-(methylsulfonyl)benzene (6.00 g, 22.9 mmol, 1.0 equiv.), capped and flushed with Ar, anhydrous THF (115 mL) was added and the resulting solution was cooled to −78 °C. A solution of *n*-Bu_2Mg (23 mL,1.0 M in heptane, 22.9 mmol, 1.0 equiv.) was added dropwise and the reaction was stirred for 30 min at −78 °C. To the resulting mixture was added (±)-epichlorohydrin (1.79 mL, 22.9 mmol, 1.0 equiv) via syringe and the solution was slowly warmed to room temperature and stirred for 18 h. Then, the reaction was cooled to 0 °C in an ice bath and benzenesulfonyl chloride (3.79 mL, 29.7 mmol, 1.3 equiv.) was added dropwise via syringe and the mixture was stirred for 16 h at room temperature. The resulting solution was cooled to –78 °C, a solution of *n*-BuLi (11 mL, 27.5 mmol, 1.2 equiv) was added, and the reaction was slowly warmed to room temperature and stirred at the specified temperature for 2 h. The reaction was quenched by sequential addition of H_2O (45 mL) and aq. sat. NH_4Cl (45 mL), extracted three times with EtOAc, the combined organic fractions were dried over dried over Na_2SO_4 or $MgSO_4$ and concentrated under vacuum. The resulting crude 1-sulfonylbicyclo[1.1.0]butane was purified by flash column chromatography on silica gel, eluting with 10-20% EtOAc in hexanes (elution gradient). The final product was obtained as a white, crystalline solid (3.7 g, 54%).

R_f: 0.20 (4:1 Hexanes:EtOAc), vis: UV (254 nm).

m.p.: 125.1 – 130.0 ºC.

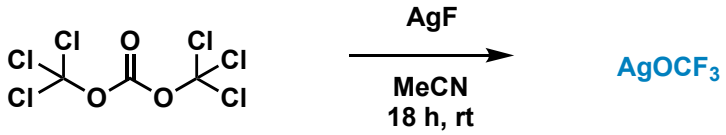
^{1}H (300 MHz, $CDCl_3$): δ= 7.88-7.84 (m, 2H), 7.45-7.33 (m, 5H), 7.11-7.07 (m, 2H), 5.15 (s, 2H), 2.51-2.47 (m, 3H), 1.37-1.34 (m, 2H).

^{13}C{^{1}H} (151 MHz, $CDCl_3$): δ= 162.5, 136.0, 133.9, 129.5, 128.9, 128.5, 127.6, 115.3, 70.5, 38.1, 23.6, 12.5

ATR-IR (ν_{max}): 3095, 2964, 2927, 1591, 1575, 1497, 1392, 1308, 1290, 1252, 1134, 1113, 1083, 1071, 1004, 818, 810, 768, 751, 701, 687, 625 cm^{-1}.

HRMS (*m/z*): (ESI) calc'd for $C_{17}H_{17}O_3S^+$ $[M-H]^+$ 301.0893, found 301.0878.

Synthesis of $AgOCF_3$:

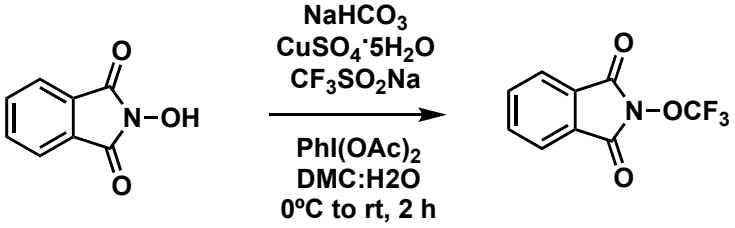


$AgOCF_3$ was prepared according to a known literature procedure.[6] To an oven-dried 20 mL microwave vial equipped with a stir bar were added triphosgene (594 mg, 2.0 mmol, 1.0 equiv.) and silver(I) fluoride (2.28 g, 18.0 mmol, 9.0 equiv.) under N_2 atmosphere in a glovebox. The vial was wrapped with aluminum foil, sealed with a Teflon-lined cap, and the MeCN (6.0 mL) was added via syringe. The suspension was stirred vigorously at room temperature overnight (note that there is an initial strong exotherm). Upon completion, the solution was filtered through a syringe filter (45 microns) into an oven-dried microwave vial which was wrapped with aluminum foil and sealed with a Teflon-lined cap. The solution was stored at –20 ºC in the

dark until it was ready to use. *Note: typically, the $AgOCF_3$ solution appeared colorless or very pale yellow. Occasionally, the stock solution would appear a dark yellow color, which always led to greatly diminished yields (20-40% drop). We observed that the quality of AgF is an important factor regarding the quality of the final $AgOCF_3$ solution. It is recommended to use a fresh batch of AgF to prepare the reagent. Additionally, the rate of stirring was in important factor in the success of the reaction - vigorous stirring is recommended.*

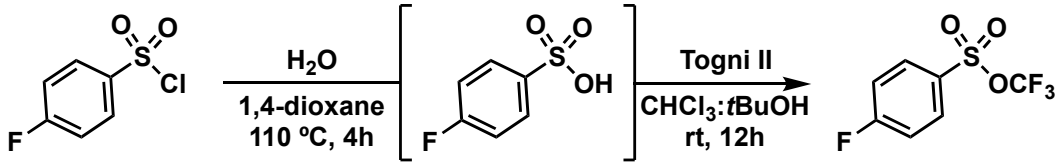
^{19}F (282 MHz, CD_3CN): δ = –27.11 (s, 3F).

Synthesis of other Nucleophilic–OCF_3 Sources:



2-(Trifluoromethoxy)isoindoline-1,3-dione was prepared according to a known literature procedure.[7] To a 100 mL round bottom flask were added $NaHCO_3$ (210 mg, 2.5 mmol, 0.5 equiv.), $CuSO_4{\cdot}5H_2O$ (62.5 mg, 5 mol %), and CF_3SO_2Na (1.56 g, 10.0 mmol, 2.0 equiv.). Dimethylcarbonate (16 mL) and DI H_2O (4.0 mL) were added *via* syringe, and the mixture was stirred until the solids dissolved. Then, *N*-hydroxyphthalimide (816 mg, 2.5 mmol, 1.0 equiv.) and $PhI(OAc)_2$ (3.22 g, 10.0 mmol, 2.0 equiv.) were added in quick succession, open to air. The reaction became dark green over the course of 5-10 minutes and colorless upon completion after stirring at rt for 2 h. The reaction mixture was quenched by the addition of sat. $NaHCO_3$ (10 mL) and was then diluted with EtOAc (10 mL) and transferred to a separatory funnel. The aqueous phase was extracted with EtOAc (2 × 5.0 mL) and the combined organic phases were washed with brine (1 × 5.0 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The resulting crude residue was purified by column chromatography on silica gel, eluting with 9:1 hexanes:EtOAc. The desired product was obtained as a white solid (0.386 g, 24%); all analyses matched previous literature reports. Note that the product elutes closely above an impurity.

^{1}H (300 MHz, $CDCl_3$): δ = 7.97-7.93 (m, 2H), 7.89-7.85 (m, 2H).
^{19}F (282 MHz, $CDCl_3$): δ = –65.14 (s, 3F).

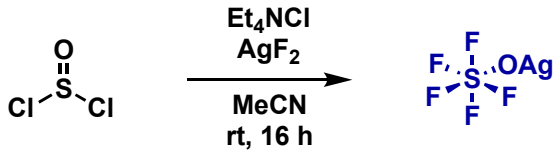


Trifluoromethyl 4-fluorobenzenesulfonate was prepared according to a known literature procedure.[8] To a 20 mL microwave vial equipped with a stir bar was added 4-fluorobenzenesulfonyl chloride (973 mg, 5.0 mmol, 1.0 equiv.) followed by 1,4-dioxane (2.5 mL) and DI H_2O (2.5 mL). The vial was tightly sealed with a crimper, and the mixture was stirred at 110 ºC for 4 h. Upon completion, the stir bar was removed, and the solvents were removed *in vacuo* (rotary evaporator). The resulting solid was azeotroped once with PhMe to ensure removal of water. Then, the stir bar was returned to vessel, and Togni's Reagent II was added (1.6 g, 5.0 mmol, 1.0 equiv.); the vial was sealed with a crimper, evacuated, and backfilled with Ar. Then,

$CHCl_3$ (5.5 mL) and *t*-BuOH (1.5 mL) were added *via* syringe, and the resulting mixture was stirred at rt for 12 h. Upon completion, the reaction was quenched by the addition of sat. $NaHCO_3$ (5.0 mL) and diluted with CH_2Cl_2 (5.0 mL). The aqueous phase was extracted with EtOAc (2 × 5.0 mL) and the combined organic phases were washed with brine (1 × 5.0 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel, eluting with 100:1 hexanes:EtOAc to give the desired product as a clear oil (0.323 g, 15%). *Note: the final product is volatile!*

^{1}H (300 MHz, $CDCl_3$): δ = 8.08-8.04 (m, 2H), 7.35-7.29 (m, 2H).
^{19}F (282 MHz, $CDCl_3$): δ = –53.96 (s, 3F), –99.08 (m, 1F).

Synthesis of $AgOSF_5$:



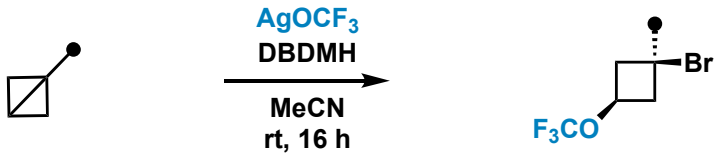
$AgOSF_5$ was synthesized according to a known literature procedure with some modifications.[9] To an oven-dried 20 mL microwave vial (vial **A**) was added Et_4NCl (0.33 g, 2.0 mmol, 2.0 equiv.). The vial was sealed, heated with a heat gun under vacuum, and refilled with Ar. This was repeated two times to remove residual moisture, then the vial was transported to a glovebox. Under N_2 atmosphere, a separate oven-dried 20 mL microwave vial (vial **B**) equipped with a stir bar was charged with AgF_2 (2.3 g, 16 mmol, 16 equiv.). Then, to vial **A** was added anhydrous MeCN (6.0 mL, 0.2 M) followed by thionyl chloride (73 μL, 1.0 mmol, 1.0 equiv.). This solution was then added slowly to vial **B** *via* syringe, and the resulting suspension was vigorously stirred at rt for 16 h. Upon completion, the resulting brown suspension was filtered through a syringe filter (occasionally, the filtrate would take on a light-pink color which disappeared after about 10 minutes). To the remaining solids was added 2.0 mL MeCN, which was then filtered and combined with the previous filtrate. A 0.3 mL aliquot was taken for ^{19}F NMR concentration determination with α,α,α-trifluorotoluene as internal standard. During data collection, 8 scans and 0 dummy scans were taken, the O1P was set to +30, and the d1 relaxation delay was extended to 30 s. *Note: to screen the effect of concentration on the reactivity of $AgOSF_5$ with BCBs, the stock solution could be concentrated in vacuo to about 1/5 the volume, typically yielding a 0.5 M solution.*

^{19}F (282 MHz, CD_3CN): δ = 134.84 (p, 1F, *J* = 159.9 Hz), 91.53 (d, 4F, *J* = 159.9 Hz).

Figure S1. *Left:* Appearance of the reaction mixture after approximately 5 min. *Right:* Appearance of the reaction mixture after completion (1.0 mmol scale).

General Procedures:

General Procedure A: Bromotrifluoromethoxylation of [1.1.0]Bicyclobutanes:



To an oven-dried microwave vial equipped with a stir bar was added the BCB substrate (0.2 mmol, 1.0 equiv.) and dibromodimethylhydantoin (DBDMH) (85 mg, 0.3 mmol, 1.5 equiv.). The vial was sealed with a crimper and then evacuated and backfilled with Ar three times. A solution of $AgOCF_3$ (0.6 mmol, 3.0 equiv.) was added via syringe and the mixture was allowed to stir at room temperature for 16 h. Upon completion, a 0.1 mL aliquot was taken for ^{19}F yield determination using a known amount of α,α,α-trifluorotoluene as an internal standard. The NMR sample was recombined with the crude reaction mixture and filtered through a pad of silica. The silica plug was rinsed with CH_2Cl_2, and the organic layer was concentrated *in vacuo*. The crude residue was then purified by column chromatography or preparative TLC (pTLC); see specific conditions for each substrate below.

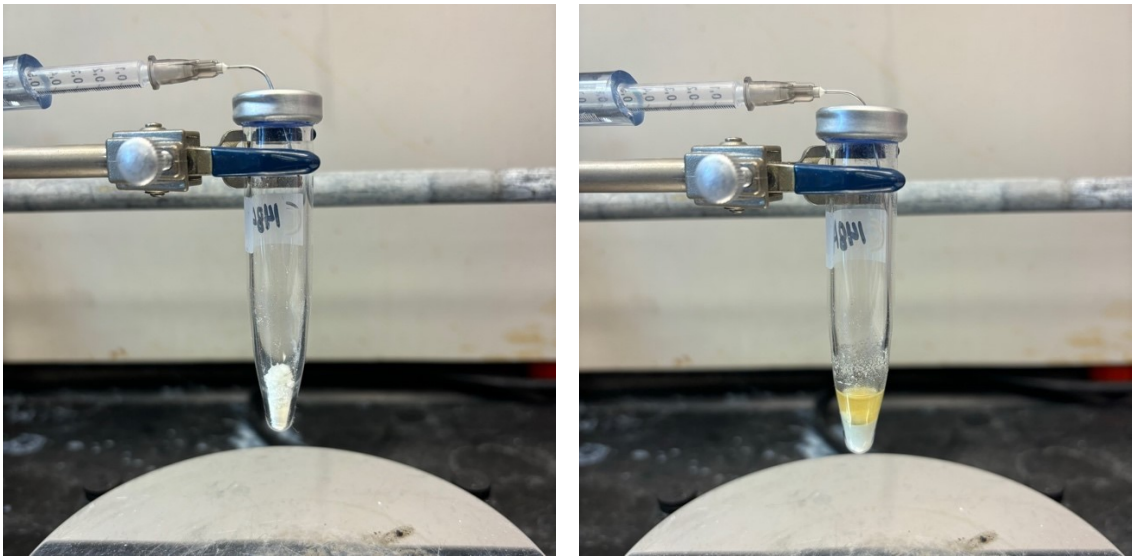
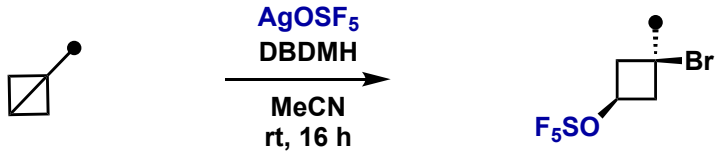


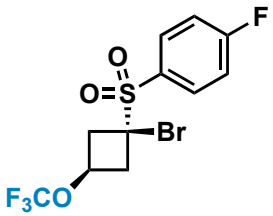
Figure S2. *Left:* Solid reagents added to an oven-dried microwave vial. *Right:* Appearance of reaction mixture after completion (0.1 mmol scale).

General Procedure B: Bromopentafluorosulfanoxylation of [1.1.0]Bicyclobutanes:



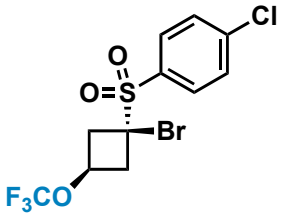
To an oven-dried microwave vial equipped with a stir bar was added the BCB substrate (0.4 mmol, 2.0 equiv.) and dibromodimethylhydantoin (DBDMH) (85 mg, 0.3 mmol, 1.5 equiv.). The vial was sealed with a crimper and then evacuated and backfilled with Ar three times. A solution of $AgOSF_5$ (0.2 mmol, 1.0 equiv.) in MeCN was added via syringe and the mixture was allowed to stir at 60 ºC for 16 h. Upon completion, a 0.1 mL aliquot was taken for ^{19}F yield determination using a known amount of α,α,α-trifluorotoluene as an internal standard. The NMR sample was recombined with the crude reaction mixture and filtered through a pad of silica. The silica plug was rinsed with CH_2Cl_2, and the organic layer was concentrated *in vacuo*. The crude residue was then purified by column chromatography or preparative TLC (pTLC); see specific conditions for each substrate below.

Characterization Data for 1-Bromo-3-Trifluoromethoxycyclobutanes:



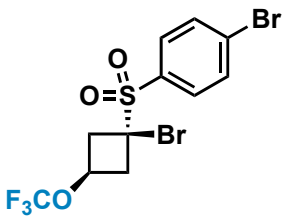
1-((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)-4-fluorobenzene (compound **1**) was synthesized from 1-((4-fluorophenyl)sulfonyl)bicyclo[1.1.0]butane following the **general procedure A**. The crude residue was purified by pTLC (preparative thin layer chromatography) eluting with 9:1 hexanes:EtOAc. The final product was obtained as a white, crystalline solid (41 mg, 54%).

R_f: 0.46 (9:1 Hexanes:EtOAc), vis: UV (254 nm).
m.p.: 82.0 – 84.5 ºC.
^{1}H (300 MHz, $CDCl_3$): δ = 8.07-8.01 (m, 2H), 7.32-7.24 (m, 2H), 5.05-4.96 (p, 1H, *J* = 6.9 Hz), 3.65-3.58 (m, 2H), 3.10-3.02 (m, 2H).
^{19}F (282 MHz, $CDCl_3$): δ = –59.94 (s, 3F), –100.99 (m, 1F).
^{13}C{^{1}H} (101 MHz, $CDCl_3$): δ = 168.6-165.1 (d, *J* = 258.7 Hz),134.3-134.1 (d, *J* = 9.8 Hz), 129.52-129.48 (d, *J* = 3.3 Hz), 126.3-116.1 (q, *J* = 257.9 Hz), 116.9-116.6 (d, *J* = 22.5 Hz), 66.6-66.5 (q, *J* = 3.6 Hz), 62.3, 44.5.
ATR-IR (ν_{max}): 3112, 1592, 1492, 1327, 1225, 1194, 1169, 1148, 1076, 847, 821, 723, 695 cm^{-1}.
HRMS (*m/z*): (ESI) calc'd for $C_{11}H_8BrF_4O_3S^-$ [M-H]$^-$ 374.9319, found 374.9330.



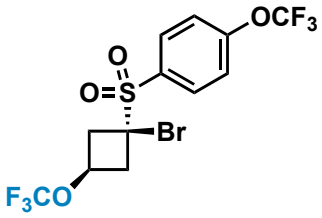
1-((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)-4-chlorobenzene (compound **2**) was synthesized from 1-((4-bromophenyl)sulfonyl) bicyclo[1.1.0]butane following the **general procedure A**. The crude residue was purified by pTLC eluting with 9:1 hexanes:EtOAc. The final product was obtained as a white solid (45 mg, 57%).

R_f: 0.44 (9:1 Hexanes:EtOAc), vis: UV (254 nm).
m.p.: 69.8 – 72.7 ºC.
^{1}H (300 MHz, $CDCl_3$): δ = 7.97-7.93 (d, 2H, *J* = 8.7 Hz), 7.60-7.56 (d, 2H, J = 8.7 Hz), 5.05-4.96 (p, 1H, J = 6.8 Hz), 3.66-3.58 (m, 2H), 3.10-3.03 (m, 2H).
^{19}F (282 MHz, $CDCl_3$): δ = –59.93 (s, 3F).
^{13}C{^{1}H} (101 MHz, $CDCl_3$): δ = 142.2, 132.6, 131.9, 129.6, 126.2-116.0 (q, *J* = 257.2 Hz), 66.6-66.4 (q, *J* = 3.4 Hz), 62.1, 44.4.
ATR-IR (ν_{max}): 3096, 1579, 1476, 1322, 1143, 1084, 827, 758, 714, 687 cm^{-1}.
HRMS (*m/z*): (ESI) calc'd for $C_{11}H_8BrClF_3O_3S^-$ [M-H]$^-$ 392.8999, found 392.9003.



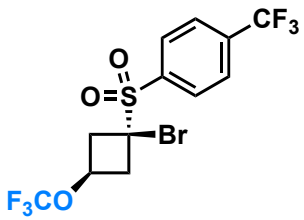
1-bromo-4-((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)benzene (compound **3**) was synthesized from 1-((4-bromophenyl)sulfonyl) bicyclo[1.1.0]butane following the **general procedure A**. The crude residue was purified by column chromatography on silica gel eluting with 9:1 hexanes:EtOAc. The final product was obtained as a white solid (62 mg, 71%).

R_f: 0.43 (9:1 Hexanes:EtOAc), vis: UV (254 nm).
m.p.: 65.3 – 66.6 ºC.
^{1}H (300 MHz, $CDCl_3$): δ = 7.88-7.85 (d, 2H, *J* = 8.6 Hz), 7.76-7.73 (d, 2H, *J* = 8.6 Hz), 5.04-4.95 (p, 1H, *J* = 6.8 Hz), 3.65-3.57 (m, 2H), 3.09-3.02 (m, 2H).
^{19}F (282 MHz, $CDCl_3$): δ = –59.90 (s, 3F).
^{13}C{^{1}H} (101 MHz, $CDCl_3$): δ = 132.51, 132.49, 132.38, 130.8, 126.1-115.9 (q, *J* = 256.9 Hz), 66.5-66.3 (q, *J* = 3.3 Hz), 62.0, 44.3.
ATR-IR (ν_{max}): 3089, 1573, 1321, 1144, 1083, 842, 744, 710 cm^{-1}.
HRMS (*m/z*): (ESI) calc'd for $C_{11}H_8Br_2F_3O_3S^-$ [M-H]$^-$ 434.8518, found 434.8538.



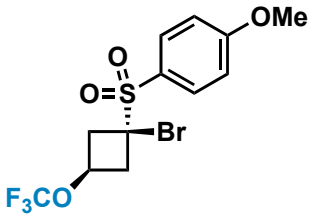
1-((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)-4-(trifluoromethoxy) benzene (compound **4**) was synthesized from 1-((4-(trifluoromethoxy) phenyl)sulfonyl)bicyclo[1.1.0]butane following the **general procedure A**. The crude residue was purified by pTLC (preparative thin-layer chromatography) eluting with 9:1 hexanes:EtOAc. The final product was obtained as a white solid (50 mg, 56%).

R_f: 0.59 (9:1 Hexanes:EtOAc), vis: UV (254 nm).
m.p.: 57.1 – 57.4 ºC.
^{1}H (300 MHz, $CDCl_3$): δ = 8.10-8.07 (d, 2H, *J* = 8.9 Hz), 7.44-7.42 (d, 2H, *J* = 8.9 Hz), 5.06-4.99 (p, 1H, *J* = 6.8 Hz), 3.67-3.61 (m, 2H), 3.11-3.06 (m, 2H).
^{19}F (282 MHz, $CDCl_3$): δ = –57.66 (s, 3F), –59.99 (s, 3F).
^{13}C{^{1}H} (101 MHz, $CDCl_3$): δ = 154.2-154.1 (q, *J* = 1.9 Hz), 133.6, 131.6, 125.0-117.3 (q, *J* = 257.7 Hz), 124.2-116.4 (q, *J* = 260.2 Hz), 66.5-66.4 (q, *J* = 3.3 Hz), 62.1, 44.5.
ATR-IR (ν_{max}): 3099, 2359, 1324, 1141, 839, 758, 715 cm^{-1}.
HRMS (*m/z*): (ESI) calc'd for $C_{12}H_8BrF_6O_4S^-$ [M-H]$^-$ 440.9236, found 440.9236.



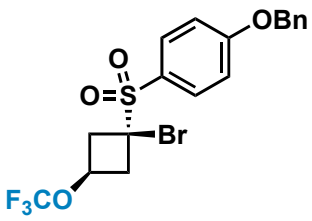
1-((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)-4-(trifluoromethyl)benzene (compound **4'**) was synthesized from 1-((4-(trifluoromethyl)phenyl)sulfonyl)bicyclo[1.1.0]butane following the **general procedure A** to further investigate the influence of electron-withdrawing groups on the outcome of the reaction. The crude residue was purified by pTLC (preparative thin-layer chromatography) eluting with 9:1 hexanes:EtOAc. The final product was obtained as a clear oil (57 mg, 59%).

R_f: 0.50 (9:1 Hexanes:EtOAc), vis: UV (254 nm).
^{1}H (300 MHz, $CDCl_3$): δ = 8.18-8.15 (d, 2H, *J* = 8.2 Hz), 7.90-7.87 (d, 2H, *J* = 8.2 Hz), 5.07-4.99 (p, 1H, *J* = 6.9 Hz), 3.69-3.61 (m, 2H), 3.13-3.06 (m, 2H).
^{19}F (282 MHz, $CDCl_3$): δ = –59.96 (s, 3F), –63.35 (s, 3F).
^{13}C{^{1}H} (101 MHz, $CDCl_3$): δ = 137.2, 136.8-136.7 (q, *J* = 33.3 Hz), 131.8, 126.3-126.2 (q, *J* = 3.8 Hz), 66.4-66.3 (q, *J* = 3.3 Hz), 61.8, 44.4.
ATR-IR (ν_{max}): 3098, 1323, 1264, 1154, 1062, 732, 704 cm^{-1}.
HRMS (*m/z*): (APCI) calc'd for $C_{11}H_8F_8O_3S_2$ [M-HBr] 404.98, not found.



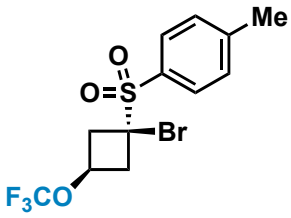
1-((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)-4-methoxybenzene (compound **5**) was synthesized from 1-((4-methoxyphenyl)sulfonyl) bicyclo[1.1.0]butane following the **general procedure A** with an additional 0.4 mL MeCN. The crude residue was purified by pTLC (preparative thin-layer chromatography) eluting with 9:1 hexanes:EtOAc. The final product was obtained as a white solid (29 mg, 37%).

R_f: 0.17 (4:1 Hexanes:EtOAc), vis: UV (254 nm).
m.p.: 73.4 – 76.1 ºC.
^{1}H (300 MHz, $CDCl_3$): δ = 7.96-7.91 (d, 2H, *J* = 9.0 Hz), 7.07-7.02 (d, 2H, *J* = 9.0 Hz), 5.04-4.95 (p, 1H, *J* = 6.8 Hz), 3.91 (s, 3H), 3.65-3.57 (m, 2H), 3.08-3.00 (m, 2H).
^{19}F (282 MHz, $CDCl_3$): δ = –59.88 (s, 3F).
^{13}C{^{1}H} (101 MHz, $CDCl_3$): δ = 164.9, 133.5, 124.6, 122.9-116.1 (q, *J* = 257.4 Hz), 114.5, 66.8-66.6 (q, *J* = 3.3 Hz), 62.7, 55.9, 44.5
ATR-IR (ν_{max}): 2920, 1596, 1498, 1325, 1143, 1081, 844, 724 698 cm^{-1}.
HRMS (*m/z*): (ESI) calc'd for $C_{12}H_{13}BrF_3O_3S^+$ $[M+H]^+$ 388.9665, found 388.9640.



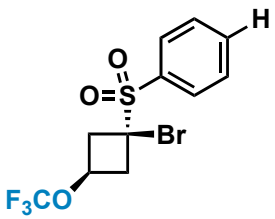
1-(benzyloxy)-4-((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)benzene (compound **6**) was synthesized from 1-((4-(benzyloxy)phenyl) sulfonyl)bicyclo[1.1.0]butane following the **general procedure A**. The crude residue was purified by pTLC (preparative thin-layer chromatography) eluting with 9:1 hexanes:EtOAc. The final product was obtained as a clear oil. The reaction was also repeated on 1.0 mmol scale to yield 309 mg of the desired product (55%).

R_f: 0.29 (9:1 Hexanes:EtOAc), vis: UV (254 nm).
^{1}H (300 MHz, $CDCl_3$): δ = 7.96-7.92 (d, 2H, *J* = 9.0 Hz), 7.44-7.34 (m, 5H), 7.14-7.11 (d, 2H, *J* = 9.0 Hz), 5.16 (s, 2H), 5.05-4.96 (p, 1H , *J* = 6.9 Hz), 3.65-3.58 (m, 2H), 3.09-3.01 (m, 2H).
^{19}F (282 MHz, $CDCl_3$): δ = –59.85 (s, 3F).
^{13}C{^{1}H} (101 MHz, $CDCl_3$): δ = 164.0, 135.5, 133.4, 128.9, 128.6, 127.6, 126.2-115.7 (q, *J* = 257.4 Hz), 124.7, 115.2, 70.6, 66.7-66.6 (q, J = 3.4 Hz), 62.6, 44.5.
ATR-IR (ν_{max}): 2931, 1592, 1259, 1230, 1143, 1080, 859, 741 cm^{-1}.
HRMS (*m/z*): (ESI) calc'd for $C_{18}H_{17}BrF_3O_4S^+$ [M+H$^+$] 464.9978, found 464.9960.



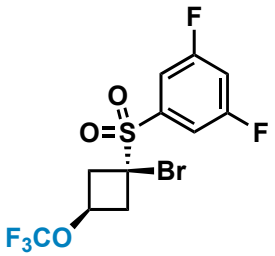
1-((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)-4-methylbenzene (compound **7**) was synthesized from 1-tosylbicyclo[1.1.0]butane following the **general procedure A** with an additional 0.4 mL MeCN. The crude residue was purified by pTLC (preparative thin-layer chromatography) eluting with 9:1 hexanes:EtOAc. The final product was obtained as a white solid (38 mg, 51%).

R_f: 0.33 (9:1 Hexanes:EtOAc), vis: UV (254 nm).
m.p.: 77.4 – 79.9 ºC.
^{1}H (300 MHz, $CDCl_3$): δ = 7.90-7.88 (d, 2H, *J* = 8.2 Hz), 7.41-7.38 (d, 2H, *J* = 8.2 Hz), 5.05-4.96 (p, 1H, *J* = 6.9 Hz), 3.67-3.59 (m, 2H), 3.08-3.01 (m, 2H), 2.48 (s, 3H).
^{19}F (282 MHz, $CDCl_3$): δ = –59.88 (s, 3F).
^{13}C{^{1}H} (101 MHz, $CDCl_3$): δ = 146.3, 131.1, 130.3, 129.7, 126.2-115.9 (q, *J* = 257.3 Hz), 66.6-66.5 (q, *J* = 3.4 H), 44.4, 21.8.
ATR-IR (ν_{max}): 2963, 2927, 1598, 1326, 1266, 1144, 1080, 860, 757, 715, 692 cm^{-1}.
HRMS (*m/z*): (ESI) calc'd for $C_{12}H_{13}BrF_3O_3S$+ [M+H$^+$] 372.9716, found 374.9692.



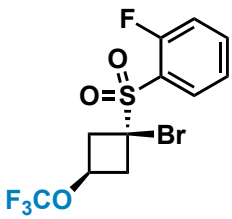
((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)benzene (compound **8**) was synthesized from 1-(phenylsulfonyl)bicyclo[1.1.0]butane following the **general procedure A**. The crude residue was purified by column chromatography eluting with 9:1 hexanes:EtOAc. The final product was obtained as a white solid (47 mg, 65%).

R_f: 0.41 (9:1 Hexanes:EtOAc), vis: UV (254 nm).
m.p.: 85.7 – 90.1 ºC.
^{1}H (300 MHz, $CDCl_3$): δ = 8.03-8.01 (m, 2H), 7.76-7.72 (m, 1H), 7.63-7.59 (m, 2H), 5.05-4.98 (p, 1H, *J* = 6.8 Hz), 3.67-3.62 (m, 2H), 3.09-3.03 (m, 2H).
^{19}F (282 MHz, $CDCl_3$): δ = –59.90 (s, 3F).
^{13}C{^{1}H} (101 MHz, $CDCl_3$): δ = 135.1, 133.5, 131.2, 129.2, 125.0-117.3 (q, J = 258.0 Hz), 66.62-66.59 (q, *J* = 3.4 Hz), 62.1, 44.5.
ATR-IR (ν_{max}): 1591, 1492, 1329, 1274, 1228, 1142, 840, 719 cm^{-1}.
HRMS (*m/z*): (ESI) calc'd for $C_{11}H_{11}BrF_3O_3S^+$ [M+H$^+$] 360.9539, found 360.9548.



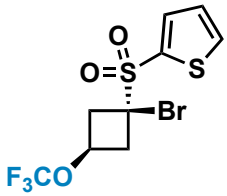
1-((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)-3,5-difluorobenzene (compound **9**) was synthesized from 1-((3,5-difluorophenyl)sulfonyl)bicyclo[1.1.0]butane following the **general procedure A**. The crude residue was purified by column chromatography eluting with 9:1 hexanes:EtOAc. The final product was obtained as a white solid (41 mg, 52%).

R_f: 0.42 (9:1 Hexanes:EtOAc), vis: UV (254 nm).
^{1}H (300 MHz, $CDCl_3$): δ = 7.58-7.55 (m, 2H), 7.24-7.17(m, 1H), 5.05-4.96 (p, 1H, *J* = 6.9 Hz), 3.68-3.60 (m, 2H), 3.14-3.06 (m, 2H).
^{19}F (282 MHz, $CDCl_3$): δ = –59.98 (s, 3F), –104.79 - –104.85 (m, 2F).
^{13}C{^{1}H} (101 MHz, $CDCl_3$): δ = 164.5-161.0 (m), 136.8-136.6 (t, *J* = 8.4 Hz), 126.2-116.0 (q, *J* = 258.1 Hz), 115.0-114.6 (m), 111.2-110.5 (t, *J* = 24.8 Hz), 66.4-66.2 (q, *J* = 3.5 Hz), 61.7, 44.5.
ATR-IR (ν_{max}): 3089, 2362, 1591, 1443,c1334, 1257, 1148, 1034, 870, 697 cm^{-1}.
HRMS (*m/z*): (ESI) calc'd for $C_{11}H_7BrF_3O_3S_2^-$ [M-H$^+$] 392.9224, found 392.9216.



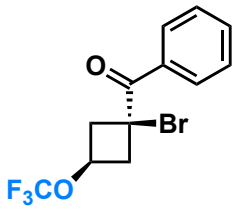
1-((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)-2-fluorobenzene (compound **10**) was synthesized from 1-((2-fluorophenyl)sulfonyl)bicyclo[1.1.0]butane following the **general procedure A**, but on a 0.1 mmol scale . The crude residue was purified by column chromatography eluting with 9:1 hexanes:EtOAc. The final product was obtained as a clear oil (15 mg, 40%).

R_f: 0.36 (9:1 Hexanes:EtOAc), vis: UV (254 nm).
^{1}H (300 MHz, $CDCl_3$): δ = 8.04-7.99 (m, 1H), 7.76-7.68 (m, 1H), 7.41-7.35 (m, 1H), 7.32-7.25 (m, 1H), 5.05-4.96 (p, 1H, *J* = 6.8 Hz), 3.89-3.82 (m, 2H), 3.14-3.07 (m, 2H).
^{19}F (282 MHz, $CDCl_3$): δ = –59.87 (s, 3F), –103.61 - –103.70 (m, 1F).
^{13}C{^{1}H} (101 MHz, $CDCl_3$): δ = 161.5-158.0 (d, *J* = 258.0 Hz), 137.5-137.4 (d, *J* = 8.9 Hz), 134.1, 126.2-116.0 (d, *J* = 257.3 Hz), 124.75-124.70 (d, *J* = 3.8 Hz), 122.6-122.4 (d, *J* = 13.9 Hz), 117.9-117.6 (d, *J* = 22.3 Hz) 66.7-66.5 (q, 3.5 Hz), 63.0, 44.22-44.17 (d, *J* = 4.1 Hz).
ATR-IR (ν_{max}): 3104, 2359, 1596, 1325, 1256, 1142, 1098, 828, 773, 721, 702, 664 cm^{-1}.
HRMS (*m/z*): (ESI) calc'd for $C_{11}H_8BrF_4O_3S^-$ $[M\text{-}H^+]^-$ 374.9319, found 374.9325.



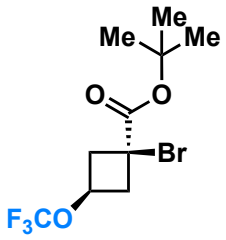
2-((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)thiophene (compound **11**) was synthesized from 2-(bicyclo[1.1.0]butan-1-ylsulfonyl)thiophene following the **general procedure A**. The crude residue was purified by column chromatography eluting with 9:1 hexanes:EtOAc. The final product was obtained as a clear oil (38 mg, 52%).

R_f: 0.47 (4:1 Hexanes:EtOAc), vis: UV (254 nm).
^{1}H (300 MHz, $CDCl_3$): δ = 7.61-7.59 (d, 1H, *J* = 4.1 Hz), 7.22-7.21 (d, 1H, *J* = 4.1 Hz), 5.02-4.93 (p, 1H, *J* = 6.9 Hz), 3.65-3.57 (m, 2H), 3.14- 3.06 (m, 2H).
^{19}F (282 MHz, $CDCl_3$): δ = –59.94 (m, 3F).
^{13}C{^{1}H} (101 MHz, $CDCl_3$): δ = 138.5, 133.6, 131.2, 126.2-116.0 (q, *J* = 257.6 Hz), 125.0, 66.5-66.4 (q, J = 3.6 Hz), 62.6, 44.3.
ATR-IR (ν_{max}): 3102, 1508, 1396, 1261, 1139, 1018, 805, 701, 663 cm^{-1}.
HRMS (*m/z*): (ESI) calc'd for $C_9H_7BrF_3O_3S_2^-$ $[M\text{-}H^+]$ 362.8978, found 362.8975.



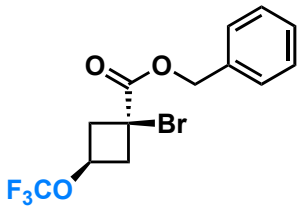
(1-bromo-3-(trifluoromethoxy)cyclobutyl)(phenyl)methanone (compound **12**) was synthesized from bicyclo[1.1.0]butan-1-yl(phenyl)methanone following the **general procedure A**. The crude residue was purified by pTLC eluting with 9:1 hexanes:EtOAc. The final product was obtained as a clear oil (33 mg, 41%).

R_f: 0.51 (4:1 Hexanes:EtOAc), vis: UV (254 nm).
^{1}H (300 MHz, $CDCl_3$): δ = 8.09-8.05 (m, 2H), 7.62-7.45 (m, 3H), 4.54-4.45 (p,1H, *J* = 6.9 Hz), 3.75-3.66 (m, 2H), 3.20-3.12 (m, 2H).
^{19}F (282 MHz, $CDCl_3$): δ = -59.72 (s, 3F).
^{13}C{^{1}H} (101 MHz, $CDCl_3$): δ = 192.9, 133.9, 131.6, 130.6, 128.6, 66.8-66.7 (*J* – 3.3 Hz), 48.1, 45.0.
ATR-IR (ν_{max}): 3020, 1680, 1272, 1215, 1152, 748, 675 cm^{-1}.
HRMS (*m/z*): (ESI) calc'd for $[M+H]^+$ 323.1092, not found.
HRMS (*m/z*): (APCI) calc'd for [M-HBr] 244.07, found 244.04.



tert-butyl 1-bromo-3-(trifluoromethoxy)cyclobutane-1-carboxylate (compound **13**) was synthesized from *tert*-butyl bicyclo[1.1.0]butane-1-carboxylate following the **general procedure A**. The crude residue was purified by column chromatography eluting with 9:1 hexanes:EtOAc. The final product was obtained as a clear oil (26 mg, 40%).

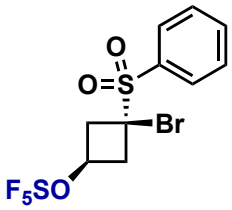
R_f: 0.59 (95:5 Hexanes:EtOAc), vis: UV (254 nm).
^{1}H (300 MHz, $CDCl_3$): δ = 4.64-4.55 (p, 1H, *J* = 6.9 Hz), 3.39-3.32 (m, 2H), 2.97-2.90 (m, 2H), 1.51 (s, 9H).
^{19}F (282 MHz, $CDCl_3$): δ = –59.90 (s, 3F).
^{13}C{^{1}H} (101 MHz, $CDCl_3$): δ = 169.5, 122.5-119.9 (q, J = 253.9 Hz), 83.4, 66.8-66.7 (q, *J* = 3.3 Hz), 45.8, 45.2, 27.7.
ATR-IR (ν_{max}): 2924, 1725, 1300, 1232, 1145, 749, 681 cm^{-1}.
HRMS (*m/z*): (ESI) calc'd for $[M+H]^+$ 318.0078, not found.
HRMS (*m/z*): (APCI) calc'd for [M-HBr] 240.09, found 240.14.



benzyl 1-bromo-3-(trifluoromethoxy)cyclobutane-1-carboxylate (compound **14**) was synthesized from benzyl bicyclo[1.1.0]butane-1-carboxylate following the **general procedure A**, on 0.5 mmol scale. The crude residue was purified by column chromatography eluting with 9:1 hexanes:EtOAc. The final product was obtained as a clear oil (134 mg, 76%). *Note: the desired product eluted very closely with a UV-active impurity, leading to mixed fractions.*

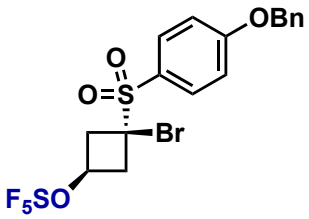
R_f: 0.67 (9:1 Hexanes:EtOAc), vis: UV (254 nm).
^{1}H (300 MHz, $CDCl_3$): δ = 7.41-7.39 (m, 5H), 5.25 (s, 2H), 4.68-4.59 (p, 1H, *J* = 7.0 Hz), 3.46-3.39 (m, 2H), 3.03-2.96 (m, 2H).
^{19}F (282 MHz, $CDCl_3$): δ =–59.92 (s, 3F).
^{13}C{^{1}H} (101 MHz, $CDCl_3$): δ = 170.4, 134.9, 128.8, 128.7, 128.1, 126.2-116.0 (q, *J* = 255.9 Hz), 68.4, 66.6-66.5 (q, *J* = 3.3 Hz), 45.8, 43.6.
ATR-IR (ν_{max}): 3036, 2961, 1733, 1456, 1377, 1263, 1141, 736, 696 cm^{-1}.
HRMS (*m/z*): (ESI) calc'd for$[M+H]^+$ 353.1352, not found.
HRMS (*m/z*): (APCI) calc'd for [M-HBr] 274.08, found 274.07.

Characterization Data for 1-Bromo-3-Pentafluorosulfanoxylcyclobutanes:



(3-bromo-3-(phenylsulfonyl)cyclobutoxy)pentafluoro-λ^6-sulfane (compound **15**) was prepared from 1-(phenylsulfonyl)bicyclo[1.1.0]butane following the **general procedure B**. The crude residue was purified by pTLC eluting with 1:1 hexanes:CH_2Cl_2, followed by 9:1 hexanes:EtOAc. The product was obtained as a white amorphous solid (11 mg, 13%)

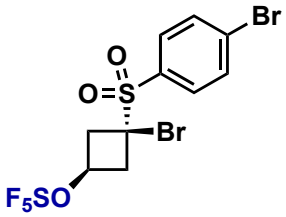
R_f: 0.43 (4:1 Hexanes:EtOAc), vis: UV (254 nm).
m.p.: not determined; decomposition observed above 100 ºC.
^{1}H (300 MHz, $CDCl_3$): δ = 8.04-8.01 (m, 2H), 7.78-7.72 (m, 1H), 7.64-7.59 (m, 2H), 5.42-5.33 (p, 1H, *J* = 6.9 Hz), 3.71-3.63 (m, 2H), 3.11-3.04 (m, 2H).
^{19}F (282 MHz, $CDCl_3$): δ = 76.61-74.38 (p, 1F, *J* = 153.8 Hz), 63.19-62.59 (m, 4F).
^{13}C{^{1}H} (201 MHz, $CDCl_3$): δ = 135.1, 133.4, 131.3, 129.2, 71.9-71.8 (p, *J* = 4.8 Hz), 61.5, 44.8.
ATR-IR (ν_{max}): 2924, 2360, 2339, 1446, 1208, 1153, 1078, 859, 763, 691 cm^{-1}.
HRMS (*m/z*): (ESI) calc'd for $C_{10}H_{11}BrF_5O_3S_2^+$ $[M+H]^+$ 416.9248, not found.
HRMS (*m/z*): (APCI) calc'd for [M-HBr] 338.00, found 338.00.
LRMS (*m/z*): (GC) calc'd for $C_{10}H_{10}F_5O_3S_2^+$ $[M-Br]^+$ 336.9, found 337.0, calc'd for $C_{10}H_{10}BrO_2S^+$ $[M-OSF_5]^+$ 277.0, found 276.9.



3-((4-(benzyloxy)phenyl)sulfonyl)-3-bromocyclobutoxy)pentafluoro-λ^6-sulfane (compound **16**) was prepared from 1-((4-(benzyloxy) phenyl) sulfonyl) bicyclo[1.1.0]butane following the **general procedure B**. The crude residue was purified by column chromatography on silica gel eluting with 9:1 hexanes:EtOAc, followed by pTLC eluting with 1:1 hexanes:CH_2Cl_2, followed by pTLC with 9:1 hexanes:EtOAc. The product was obtained as a white amorphous solid (17 mg, 11%)

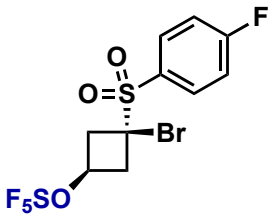
R_f: 0.36 (4:1 Hexanes:EtOAc), vis: UV (254 nm).
m.p.: not determined; decomposition observed above 105 ºC.
^{1}H (300 MHz, $CDCl_3$): δ = 7.95-7.92 (d, H, *J* = 9.0 Hz), 7.43-7.37 (m, 5H), 7.14-7.11(d, 2H, *J* = 9.0 Hz), 5.40-5.31 (p , 1H, *J* = 6.9 Hz), 5.16 (s, 2H), 3.67-3.59 (m, 2H), 3.10-3.02 (m, 2H).
^{19}F (282 MHz, $CDCl_3$): δ = 76.74-74.50 (p, 1F, J = 154.3 Hz), 63.21-62.61 (m, 4F).
^{13}C{^{1}H} (201 MHz, $CDCl_3$): δ = 164.1, 135.6, 133.5, 129.0, 128.7, 127.7, 124.7, 115.3, 72.0-71.9 (p, J = 4.8 Hz), 70.7, 62.0, 44.8.
ATR-IR (ν_{max}): 2923, 1445, 1210, 1150, 1079, 859, 761, 690 cm^{-1}.

HRMS (*m/z*): (ESI) calc'd for $C_{17}H_{17}BrF_5O_4S_2^+$ $[M+H]^+$ 522.9667, not found.
HRMS (*m/z*): (APCI) calc'd for [M-HBr] 444.05, found 443.99.
LRMS (*m/z*): (GC) calc'd for $C_{17}H_{17}BrF_5O_4S_2^+$ $[M+H]^+$ 523.0, not found.



(3-bromo-3-((4-bromophenyl)sulfonyl)cyclobutoxy)pentafluoro-λ^6-sulfane (compound **17**) was prepared according to the **general procedure B**. The crude residue was purified by column chromatography on silica gel eluting with 9:1 hexanes:EtOAc, followed by pTLC eluting with 4:1 hexanes:EtOAc. The product was obtained as a clear oil (12 mg, 12%)

R_f: 0.45 (9:1 Hexanes:EtOAc), vis: UV (254 nm).
^{1}H (300 MHz, $CDCl_3$): δ = 7.89-7.86 (d, 2H, *J* = 8.7 Hz), 7.77-7.74 (d, 2H, *J* = 8.7 Hz), 5.41-5.32 (p, 1H, *J* = 6.9 Hz), 3.68-3.60 (m, 2H), 3.12-3.04 (m, 2H).
^{19}F (282 MHz, $CDCl_3$): δ =76.48-74.24 (pent., 1F, *J* = 161.8 Hz), 63.18-62.59 (m, 4F).
^{13}C{^{1}H} (201 MHz, $CDCl_3$): δ = 132.58, 132.57, 132.4, 130.9, 71.7-71.5 (pent., 4.8 Hz), 61.4, 44.7.
ATR-IR (ν_{max}): 3102, 2360, 1574, 1471, 1388, 1152, 1073, 843, 777, 681 cm^{-1}.
HRMS (*m/z*): (ESI) calc'd for $C_{10}H_{10}Br_2F_5O_3S_2^+$ $[M+H]^+$ 494.8353, not found.
LRMS (*m/z*): (GC) calc'd $C_{10}H_{10}Br_2F_5O_3S_2^+$ $[M+H]^+$ 495.8, found 495.9.



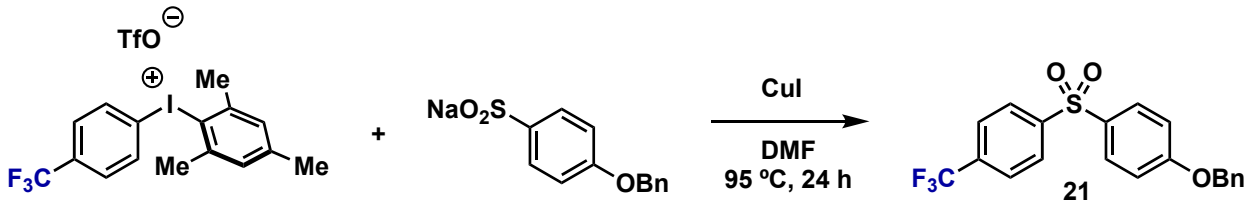
(3-bromo-3-((4-fluorophenyl)sulfonyl)cyclobutoxy)pentafluoro-λ^6-sulfane (compound **18**) was synthesized from 1-(phenylsulfonyl)bicyclo[1.1.0]butane, following the **general procedure B**. The crude residue was purified by pTLC eluting with 9:1 hexanes:EtOAc. The product was obtained as a white amorphous solid (13 mg, 15%). Melting point data was not obtained due to the small amount of material.

R_f: 0.41 (4:1 Hexanes:EtOAc), vis: UV (254 nm).
^{1}H (300 MHz, $CDCl_3$): δ = 8.08-8.01 (m, 2H), 7.32-7.27 (m, 2H), 5.42-5.32 (p, 1H, *J* = 6.8 Hz), 3.68-3.60 (m, 2H), 3.12-3.05 (m, 2H).
^{19}F (282 MHz, $CDCl_3$): δ = 76.51-74.27 (p, 1F, *J* = 155.0 Hz), 63.18-62.58 (m, 4F), –100.74- –100.83 (m, 1F).
^{13}C{^{1}H} (201 MHz, $CDCl_3$): δ = 167.5-166.2 (d, *J* = 259.2 Hz), 134.21-134.17 (d, *J* = 9.9 Hz), 129.39-129.37 (d, *J* = 3.8 Hz), 116.8-116.7 (d, *J* = 22.7 Hz), 71.7-71.6 (p, *J* = 4.6 Hz), 61.6, 44.8.
ATR-IR (ν_{max}): 3114, 2993, 1587, 1489, 1351, 1316, 1147, 1081, 840, 732, 694 cm^{-1}.
HRMS (*m/z*): (ESI) calc'd for $C_{10}H_{10}BrF_6O_3S_2^+$ $[M+H]^+$ 436.9154, not found.

LRMS (*m/z*): (GC) calc'd for $C_{10}H_{10}BrF_6O_3S_2^+$ $[M+H]^+$ 436.9, not found.

Glycine Reuptake Inhibitor Analogs:

N-methyl-*N*-(3-phenyl-3-(4-((4-(trifluoromethyl)phenyl)sulfonyl)phenoxy)propyl)glycine:

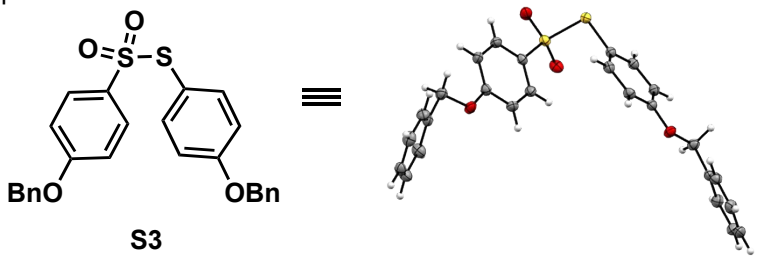


To an oven-dried 5 mL microwave vial equipped with a stir bar were added CuI (39 mg, 0.2 mmol, 0.2 equiv.), sodium 4-(benzyloxy)benzenesulfinate (270 mg, 1.0 mmol, 1.0 equiv.), and mesityl(4-(trifluoromethyl)phenyl) iodonium trifluoromethanesulfonate (594 mg, 1.1 mmol, 1.1 equiv.). The vial was sealed with a crimper and DMF (10 mL) was added *via* syringe. The vessel was transferred to a pre-heated oil bath (95 ºC) and allowed to stir for 24 h, during which a color change from light yellow to amber was observed. Upon reaction completion, the mixture was diluted with H_2O (15 mL) and EtOAc (5.0 mL) and transferred to a separatory funnel. The aqueous phase was extracted with EtOAc (3 × 5.0 mL) and the combined organic layer was washed with H_2O (1 × 10 mL) and brine (1 × 10 mL). The organic phase was dried over Na_2SO_4, concentrated *in vacuo*, and purified by column chromatography on silica gel eluting with hexanes:EtOAc, followed by another flash column eluting with hexanes/CH_2Cl_2. 1-(benzyloxy)-4-((4-(trifluoromethyl)phenyl)sulfonyl)benzene was obtained as a white solid (106 mg, 27%).

R_f: 0.20 (1:1 hexanes:CH_2Cl_2), vis: UV (254 nm).
m.p.: 139.6-141.8 ºC.
^{1}H (300 MHz, $CDCl_3$): δ = 8.06-8.03 (d, 2H, *J* = 8.3 Hz), 7.90-7.87 (d, 2H, *J* = 9.0 Hz), 7.76-7.73 (d, 2H, *J* = 8.3 Hz), 7.40-7.34 (m, 5H), 7.08-7.05 (d, 2H, *J* = 9.0 Hz), 5.11 (s, 2H).
^{19}F (282 MHz, $CDCl_3$): δ = –63.16 (s, 3F).
^{13}C{^{1}H} (201 MHz, $CDCl_3$): δ = 163.0, 146.0, 135.6, 135.2-133.9 (q, *J* = 32.8 Hz), 132.2, 130.3, 128.8, 128.5, 128.0, 127.5, 126.5-126.4 (q, *J* = 3.5 Hz), 115.7, 70.5.
ATR-IR (ν_{max}): 3058, 1593, 1497, 1324, 1256, 1176, 1156, 1137, 1108, 1062, 721, 669 cm^{-1}.
HRMS (*m/z*): (ESI) calc'd for $C_{20}H_{16}F_3O_3S^+$ $[M+H]^+$ 393.0767, not found.

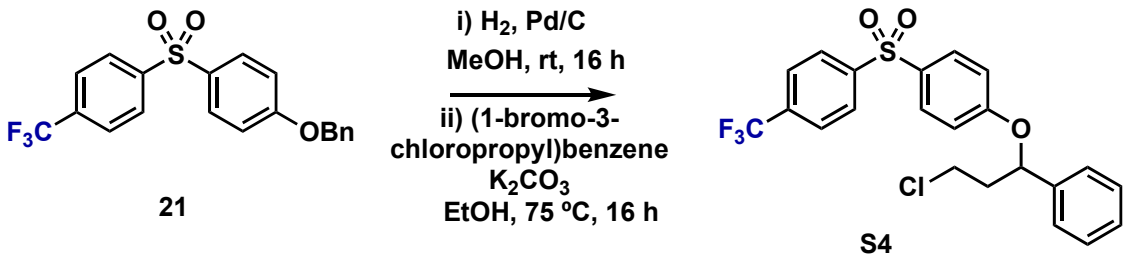
The desired benzyl-protected sulfone starting material elutes very closely with a sulfonothioate side-product impurity. Using a 4:1 hexanes:EtOAc solvent system as the mobile phase (left) results in this mixture appearing as a single spot by TLC. However, with 1:1 hexanes:CH_2Cl_2 mobile phase (right) separation is achievable. The identity of the impurity was serendipitously confirmed by SC-XRD when a single crystal of the sulfonothionate was picked from bulk material. The crystal was grown by slow solvent evaporation from EtOAc.

Figure S3. Separation of sulfonothionate impurity from desired sulfone starting material with varying mobile phases.



S3

R_f: 0.18 (1:1 hexanes:CH_2Cl_2), vis: UV (254 nm).
^{1}H (300 MHz, $CDCl_3$): δ = 7.53-7.50 d, 2H, *J* = 9.0 Hz), 7.45-7.37 (m, 10H), 7.30-7.27 (m, 4H), 6.97-6.91 (m, 4H), 5.14 (s, 2H), 5.10 (s, 2H).
^{13}C{^{1}H} (201 MHz, $CDCl_3$): δ = 162.8, 161.5, 138.6, 136.2, 135.8, 135.2, 130.3, 130.1, 128.91, 128.89, 128.6, 128.4, 127.6, 119.4, 115.9, 114.8, 70.5, 70.3.
ATR-IR (ν_{max}): 3056, 1591, 1492, 1455, 1323, 1230, 1264, 1174, 1139, 732, 702 cm^{-1}.
HRMS (*m/z*): (ESI) calc'd for $[M+H]^+$ 463.5855, not found.

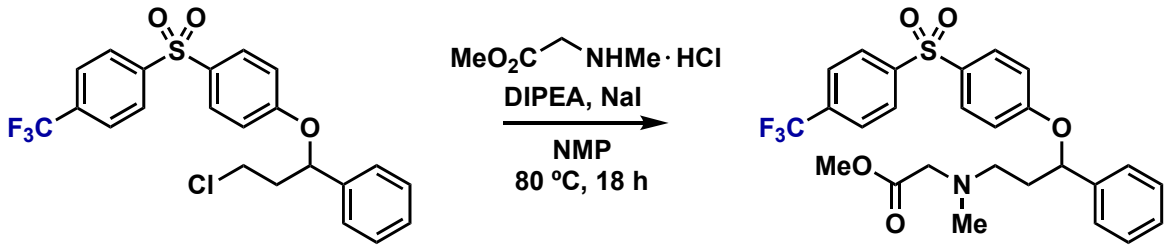


1-(benzyloxy)-4-((4-(trifluoromethyl)phenyl)sulfonyl)benzene (57 mg, 0.15 mmol, 1.0 equiv.) and Pd/C (10 mol %) were added to an oven-dried 2 mL microwave vial equipped with a stir bar. The vial was sealed, and MeOH (2.0 mL) was added. The vial was fitted with an H_2 balloon, and the reaction was vigorously stirred at rt for 16 h. After TLC indicated consumption of the starting material, the suspension was filtered over a pad of Celite and concentrated into a tared microwave vial. The resulting crude material was used without further purification.

R_f: 0.47 (3:2 Hexanes:EtOAc), vis: UV (254 nm).
^{1}H (300 MHz, $CDCl_3$): δ = 8.05-8.03 (d, 2H, *J* = 8.1 Hz), 7.87-7.85 (d, 2H, *J* = 8.8 Hz), 7.76-7.74 (d, 2H, *J* = 8.1 Hz), 6.95-6.92 (d, 2H, *J* = 8.8 Hz).
^{19}F (282 MHz, $CDCl_3$): δ = –63.19 (s, 3F).

To the vessel containing the crude phenol and a stir bar were added K_2CO_3 (40 mg, 0.3 mmol, 2.0 equiv.) and (1-bromo-3-chloropropyl)benzene (54 mg, 0.23 mmol, 1.5 equiv.) as a solution in EtOH (1.0 mL). The mixture was vigorously stirred at 75 ºC overnight (approx. 16 h) until TLC indicated consumption of the starting material. The mixture was diluted with H_2O (3.0 mL) and CH_2Cl_2 (2.0 mL) and transferred to a separatory funnel. The aqueous layer was extracted with CH_2Cl_2 (2 × 2.0 mL), the combined organic layers were dried over Na_2SO_4 and concentrate *in vacuo*. The resulting crude oil was purified by pTLC eluting with 4:1 hexanes/EtOAc to afford the desired 1-(3-chloro-1-phenylpropoxy)-4-((4-(trifluoromethyl)phenyl)sulfonyl)benzene as a clear oil (35 mg, 51% *over 2 steps*).

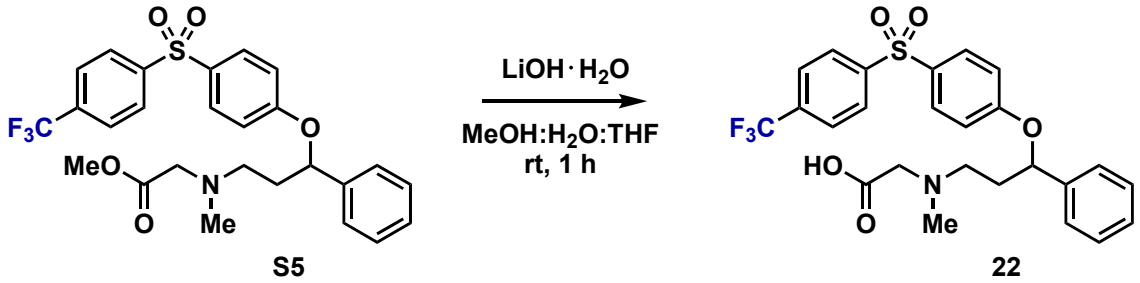
R_f: 0.45 (4:1 Hexanes:EtOAc), vis: UV (254 nm).
^{1}H (300 MHz, $CDCl_3$): δ = 8.01-7.98 (d, 2H, *J* = 8.2 Hz), 7.79-7.71 (m, 4H), 7.38-7.29 (m, 5H), 6.96-6.93 (d, 2H, *J* = 8.9 Hz), 5.46-5.42 (m, 1H), 3.79-3.71 (m, 1H), 3.60-3.53 (m, 1H), 2.56-2.42 (m, 1H), 2.27-2.16 (m,1H).
^{19}F (282 MHz, $CDCl_3$): δ = –63.18 (s, 3F).
^{13}C{^{1}H} (201 MHz, $CDCl_3$): δ = 162.3, 145.9, 139.5, 132.4, 130.2, 129.2, 128.9, 128.5, 128.0, 126.7, 126.5 (m), 125.9, 116.6, 77.4, 56.1, 41.2, 41.0, 24.6, 21.7, 13.6.
ATR-IR (ν_{max}): 3064, 2925, 1592, 1494, 1403, 1321, 1253, 1153, 1106, 1062, 836, 721 cm^{-1}.
HRMS (*m/z*): (ESI) calc'd for $C_{22}H_{19}ClF_3O_3S^+$ $[M+H]^+$ 455.0691, found 455.0670.



S4 **S5**

An 8 mL vial equipped with a stir bar was charged with 1-(3-chloro-1-phenylpropoxy)-4-((4-(trifluoromethyl)phenyl)sulfonyl)benzene (16 mg, 35 μmol, 1.0 equiv.), sodium iodide (5.2 mg, 35 μmol, 1.0 equiv.), and sarcosine methyl ester hydrochloride (9.6 mg, 70 μmol, 2.0 equiv.). NMP (0.4 mL) was added via syringe, followed by DIPEA (24 μL, 140 μmol, 4.0 equiv.). The reaction was heated to 70 ºC and progress was monitored by TLC. Upon consumption of the starting material (approx. 24 h), the mixture was diluted with EtOAc (2.0 mL) and H_2O (2.0 mL) and transferred to a separatory funnel. The aqueous layer was extracted with EtOAc (1 × 2.0 mL). The combined organic layers were washed with brine (1 × 2.0 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was purified by pTLC eluting with 3:2 hexanes:EtOAc to afford the desired methyl *N*-methyl-*N*-(3-phenyl-3-(4-((4-(trifluoromethyl)phenyl)sulfonyl) phenoxy)propyl)glycinate as a clear oil (10 mg, 55%).

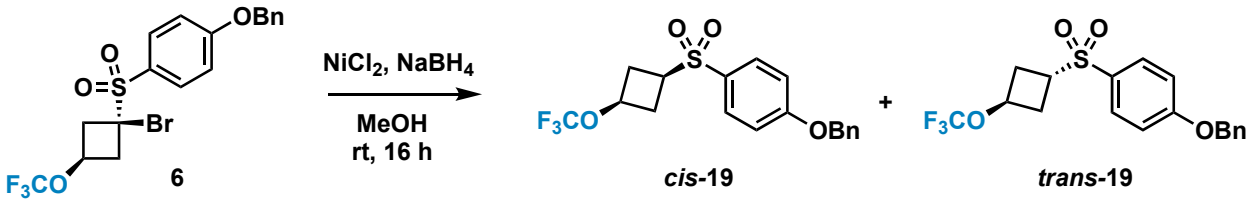
R_f: 0.31 (3:2 Hexanes:EtOAc), vis: UV (254 nm).
^{1}H (300 MHz, $CDCl_3$): δ = 8.00-7.98 (d, 2H, *J* = 8.2 Hz), 7.77-7.71 (m, 4H), 7.35-7.28 (m, 5H), 6.95-6.93 (d, 2H, *J* = 8.9 Hz), 5.34-5.31 (m, 1H), 3.64 (s, 3H), 3.24 (s, 2H), 2.69-2.55 (m, 2H), 2.37 (s, 3H), 2.22-2.13 (m,1H), 2.01-1.93 (m, 1H).
^{19}F (282 MHz, $CDCl_3$): δ = – 63.18 (s, 3F).
^{13}C{^{1}H} (201 MHz, $CDCl_3$): δ = 171.4, 162.6, 146.0, 140.6, 131.9, 130.1, 128.9, 128.1, 128.0, 126.5-126.3 (q, J = 3.7 Hz), 125.9, 116.5, 78.7, 58.6, 53.0, 51.6, 42.4, 36.7.
ATR-IR (ν_{max}): 2950, 2851, 1743, 1592, 1494, 1319, 1252, 1142, 1061, 702 cm^{-1}.
HRMS (*m/z*): (ESI) calc'd for $C_{26}H_{27}F_3NO_5S^+$ $[M+H]^+$ 522.1557, not found.



To an 8-mL vial equipped with a stir bar was added methyl *N*-methyl-*N*-(3-phenyl-3-(4-((4-(trifluoromethyl)phenyl)sulfonyl)phenoxy)propyl)glycinate (17 mg, 32 μmol, 1.0 equiv.), followed by MeOH (0.5 mL), THF (0.5 mL), and H_2O (0.5 mL). While stirring, lithium hydroxide monohydrate (6.6 mg, 0.16 mmol, 5.0 equiv.) was added in one portion. The reaction was stirred vigorously at room temperature until the starting material was consumed as indicated by TLC. The reaction was carefully acidified with 1 M HCl to approx. pH 4-5, and the aqueous layer was extracted with EtOAc (3 × 2.0 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The resulting crude solid was purified by pTLC eluting with 10% MeOH in CH_2Cl_2 to afford the desired *N*-methyl-*N*-(3-phenyl-3-(4-((4-(trifluoromethyl)phenyl)sulfonyl) phenoxy)propyl)glycine as a white solid (3 mg, 6%). All analytical data matched the previously reported literature. Due to the small amount of material obtained the ^{13}C chemical shifts were not fully resolved. Additionally, the final product was not fully soluble in $CDCl_3$ leading to peak broadening and loss of resolution. As the material needed to be prepared for *in vitro* testing, the purity of the material was estimated by integration of the ^1H NMR spectrum with an increased d1 relaxation delay.

R_f: 0.11 (9:1 CH_2Cl_2:MeOH), vis: UV (254 nm).
^{19}F (282 MHz, $CDCl_3$): δ = –63.15 (s, 3F).
HRMS (*m/z*): (ESI) calc'd for $C_{25}H_{24}F_3NO_5S^+$ $[M+H]^+$ 508.1406, found 508.1374.
HRMS (*m/z*): (APCI) calc'd for $C_{25}H_{23}F_3NO_5S^-$ $[M-H]^-$ 506.13, found 506.12.

N-methyl-*N*-(3-phenyl-3-(4-((-3-(trifluoromethoxy)cyclobutyl)sulfonyl)phenoxy) propyl) glycine



To an 8-mL vial equipped with a stir bar was added 1-(benzyloxy)-4-((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)benzene (81 mg, 0.17 mmol, 1.0 equiv.), followed by MeOH (1.0 mL). The mixture was stirred until all the starting material had dissolved and $NiCl_2$ (11 mg, 90 μmol, 0.5 equiv.) was added in one portion and $NaBH_4$ (32 mg, 0.85 mmol, 5.0 equiv.) in three portions. Strong bubbling was observed alongside the formation of a black precipitate. The reaction was allowed to stir for 16 h before 5.0 mL CH_2Cl_2 were added. The crude suspension was filtered through a Celite plug into a separatory funnel. The organic layer was washed with sat. NH_4Cl (2 × 2.0 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by pTLC, eluting with 7:3 hexanes:EtOAc. The *cis* and *trans* isomers were completely separable with careful loading. The desired 1-(benzyloxy)-4-((3-(trifluoromethoxy)

cyclobutyl)sulfonyl)benzene was obtained as a white solid (58 mg, 87%), only the *cis* isomer was carried forward.

R_f: 0.34 (4:1 Hexanes:EtOAc), vis: UV (254 nm).

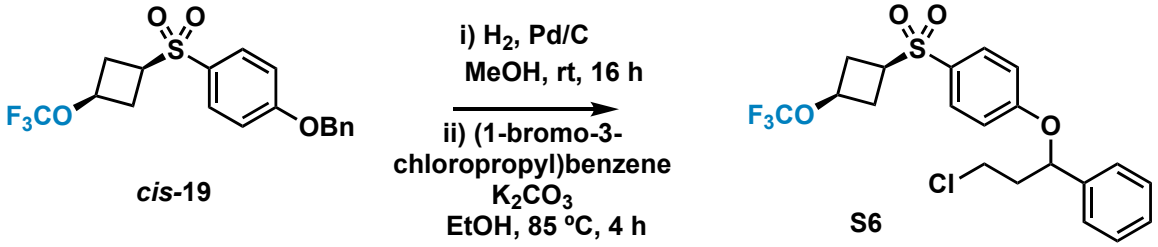
^{1}H (300 MHz, $CDCl_3$): δ = 7.81-7.77 (m, 2H), 7.45-7.33 (m, 5H), 7.12-7.08 (m, 2H), 5.14 (s, 2H), 4.57-4.47 (p, 1H, *J* = 7.5 Hz), 3.42-3.30 (m, 1H), 2.80-2.55 (m, 4H).

^{19}F (282 MHz, $CDCl_3$): δ = -59.66 (s, 3F).

^{13}C{^{1}H} (201 MHz, $CDCl_3$): δ = 163.3, 135.7, 130.6, 129.4, 128.9, 128.6, 127.6, 115.6, 70.6, 65.1-65.0 (q, *J* = 3.3 Hz), 49.0, 32.0.

ATR-IR (ν_{max}): 3060, 2987, 1737, 1592, 1496, 1228, 1177, 1136, 997, 848, 807, 744, 693 cm^{-1}.

HRMS (*m/z*): (ESI) calc'd for $[M+H]^+$ 387.0873, found 387.0873.



To an oven-dried 2 mL microwave vial equipped with a stir bar were added 1-(benzyloxy)-4-((3-(trifluoromethoxy)cyclobutyl)sulfonyl)benzene (32 mg, 83 μmol, 1.0 equiv.) and Pd/C (10 mol %). The vial was sealed with a crimper and MeOH (4.0 mL) was added *via* syringe. The vessel was purged with an H_2 balloon and allowed to stir vigorously overnight (approx. 16 h) at rt. After TLC indicated complete consumption of the starting material, the suspension was filtered over tightly packed Celite and the filtrate was concentrated *in vacuo*. The crude material was used in the next step without further purification.

R_f: 0.5 (1:1 Hexanes:EtOAc), vis: UV (254 nm).

^{1}H (300 MHz, $CDCl_3$): δ = 7.75-7.70 (m, 2H), 7.00-6.95 (m, 2H), 6.56 (s, 1H), 4.58-4.48 (p, 1H, *J* = 7.5Hz), 3.44-3.33 (m, 1H), 2.79-2.56 (m, 4H)

^{19}F (282 MHz, $CDCl_3$): δ = -59.79 (s, 3F)

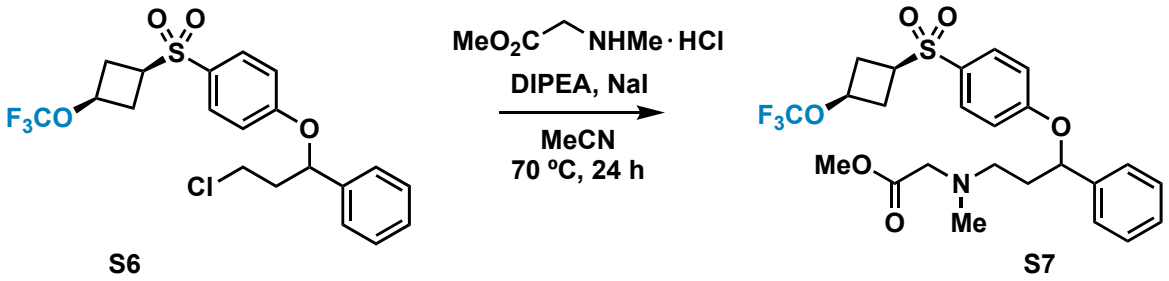
The crude 4-((3-(trifluoromethoxy)cyclobutyl)sulfonyl)phenol was concentrated into an 8 mL vial, dried under high vacuum, and stir bar was added. The crude oil was taken up in EtOH (0.5 mL), and (1-bromo-3-chloropropyl)benzene (42 mg, 0.18 mmol, 2.0 equiv.) was added as a solution in EtOH (0.5 mL). Potassium carbonate (23 mg, 0.18 mmol, 2.0 equiv.) was added in one portion and the mixture was stirred at 85 ºC overnight (approx. 16 h). After TLC indicated consumption of the starting material, the mixture was diluted with H_2O (3.0 mL) and EtOAc (2.0 mL). The layers were separated and the aqueous was extracted with EtOAc (1 × 2.0 mL). The combined organic layers were washed with brine (1 × 2.0 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was taken up in 0.2 mL CH_2Cl_2 and loaded directly onto a pTLC plate, eluting with 4:1 hexanes:EtOAc. The desired 1-(3-chloro-1-phenylpropoxy)-4-((3-(trifluoromethoxy)cyclobutyl)sulfonyl)benzene was obtained as a clear oil (20 mg, 54% over 2 steps).

R_f: 0.42 (4:1 Hexanes:EtOAc), vis: UV (254 nm).

^{1}H (300 MHz, $CDCl_3$): δ = 7.70-7.67 (m, 2H), 7.40-7.28 (m, 5H), 6.99-6.96 (m, 2H), 5.50-5.45 (m, 1H), 4.54-4.45 (p, 1H, *J* = 7.5 Hz), 3.82-3.74 (m, 1H), 3.63-3.56 (m, 1H), 3.36-3.24 (m, 1H), 2.77-2.69 (m, 2H), 2.60-2.46 (m, 3H), 2.31-2.19 (m, 1H).

^{19}F (282 MHz, $CDCl_3$): δ = -59.78 (s, 3F).

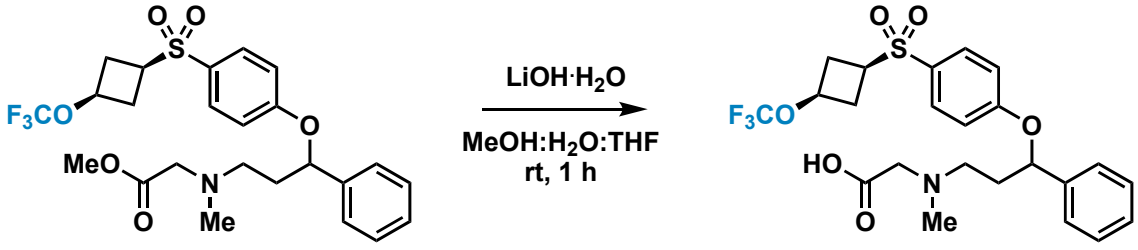
$^{13}C\{^1H\}$ (201 MHz, $CDCl_3$): δ = 162.5, 139.5, 130.5, 130.4, 129.6, 129.2, 128.6, 126.0, 123.7-118.6 (q, *J* = 256.5 Hz), 116.6, 77.5, 65.1-65.0 (q, *J* = 3.3 Hz), 49.0, 41.2-41.1 (d, *J* = 14.3 Hz), 32.0-31.9 (q, *J* = 7.7 Hz).
ATR-IR (ν_{max}): 3020, 1593, 1494, 1215, 1145, 1089, 835, 746, 697 cm^{-1}.
HRMS (*m/z*): (ESI) calc'd for $[M+H]^+$ 449.0796, found 449.0790.



S6 **S7**

To an 8-mL vial equipped with a stir bar was added 1-(3-chloro-1-phenylpropoxy)-4-((3-(trifluoromethoxy)cyclobutyl)sulfonyl)benzene (20 mg, 40 μmol, 1.0 equiv.), sodium iodide (11.0 mg, 70 μmol, 1.5 equiv.), and sarcosine methyl ester hydrochloride (10 mg, 70 μmol, 1.5 equiv.). MeCN (0.5 mL) was added *via* syringe, followed by DIPEA (30 μL, 0.12 mmol, 3.0 equiv.). The reaction was heated to 70 °C and progress was monitored by TLC. Upon consumption of the starting material (approx. 24 h), the mixture was diluted with EtOAc (2.0 mL) and H_2O (2.0 mL) and transferred to a separatory funnel. The aqueous layer was extracted with EtOAc (2 × 2.0 mL). The combined organic layers were washed with brine (1 × 2.0 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was purified by pTLC eluting with 3:2 hexanes:EtOAc. The desired methyl *N*-methyl-*N*-(3-phenyl-3-(4-((3-(trifluoromethoxy)cyclobutyl)sulfonyl)phenoxy)propyl)glycinate was obtained as a clear oil (8 mg, 40 %).

R_f: 0.35 (3:2 Hexanes:EtOAc), vis: UV (254 nm).
^1H (300 MHz, $CDCl_3$): δ = 7.67-7.64 (m, 2H), 7.38-7.25 (m, 5H), 6.99-6.96 (m, 2H), 5.39-5.34 (m, 1H), 4.54-4.44 (p, 1H, *J* = 7.5 Hz), 3.66 (s, 3H), 3.35-3.23 (m, 3H), 2.77-2.51 (m, 6H), 2.38 (s, 3H), 2.26-2.15 (m, 1H), 2.05-1.94 (m, 1H).
^{19}F (282 MHz, $CDCl_3$): δ = -59.78 (s, 3F).
$^{13}C\{^1H\}$ (201 MHz, $CDCl_3$): δ = 171.4, 162.9, 140.7, 130.4, 129.1, 129.0, 128.2, 122.0-120.3 (m), 116.6, 78.7, 65.1-65.0 (q, *J* = 3.3 Hz), 58.6, 53.1, 51.7, 49.0, 42.4, 36.7, 32.0-31.9 (d, *J* = 6.9 Hz), 31.1.
ATR-IR (ν_{max}): 3021, 1740, 1592, 1495, 1454, 1273, 1215, 1175, 1143, 835, 746, 682 cm^{-1}.
HRMS (*m/z*): (ESI) calc'd for $[M+H]^+$ 516.1663, found 516.1623.

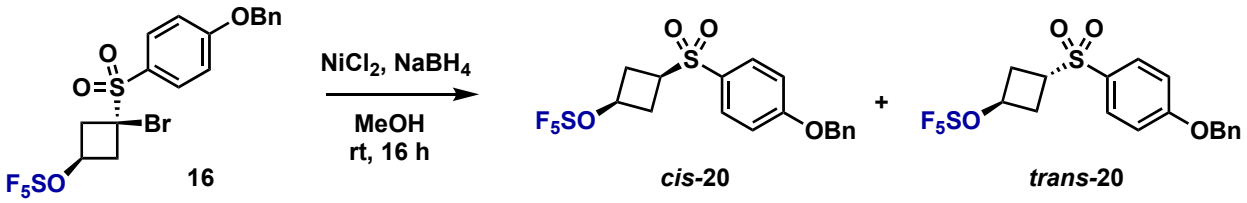


S7 **23**

To an 8-mL vial equipped with a stir bar was added methyl *N*-methyl-*N*-(3-phenyl-3-(4-((3-(trifluoromethoxy)cyclobutyl)sulfonyl)phenoxy)propyl)glycinate (40 mg, 78 μmol, 1.0 equiv.), followed by MeOH (1.0 mL), THF (1.0 mL), and H_2O (1.0 mL). While stirring, lithium hydroxide monohydrate (16 mg, 0.39 mmol, 5.0 equiv.) was added in one portion. The reaction was stirred vigorously at room temperature until the starting material was consumed as indicated by TLC. The reaction was carefully acidified with 1M HCl to approx. pH 4-5, and the aqueous layer was extracted with EtOAc (3 × 2.0 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The resulting crude solid was purified by pTLC eluting with 10% MeOH in CH_2Cl_2 to afford the desired *N*-methyl-*N*-(3-phenyl-3-(4-((3-(trifluoromethoxy)cyclobutyl) sulfonyl)phenoxy)propyl)glycine as a white solid (17 mg, 43 %).

R_f: 0.14 (99:1 CH_2Cl_2:MeOH), vis: UV (254 nm).
^{1}H (300 MHz, $CDCl_3$): δ = 7.63-7.60 (d, 2H, *J* = 8.7 Hz), 7.36-7.27 (m, 5H), 6.96-6.93 (d, 2H, *J* = 8.7 Hz), 5.42 (br s, 1H), 4.54-4.44 (p, 1H, *J* = 7.4 Hz), 3.38-3.16 (m, 5H), 2.72-2.49 (m, 7H), 2.34-2.25 (m, 2H).
^{19}F (282 MHz, $CDCl_3$): δ = –59.73 (s, 3F).
^{13}C{^{1}H} (201 MHz, $CDCl_3$): δ = 162.1, 139.4, 130.6, 129.7, 129.2, 128.6, 126.2-116.0 (q, *J* = 257.0 Hz), 125.9, 116.7, 78.2, 65.1-65.0 (q, *J* = 3.5 Hz), 48.8, 32.0, 31.9, 29.8.
ATR-IR (ν_{max}): 2992, 2562, 1712, 1562, 1380, 1142, 1088, 865, 800, 758, 654 cm^{-1}.
HRMS (*m/z*): (ESI) calc'd for $C_{23}H_{25}F_3NO_6S^-$ $[M-H]^-$ 500.1360, not found.
HRMS (*m/z*): (APCI) calc'd for $C_{23}H_{25}F_3NO_6S^-$ $[M-H]^-$ 500.14, found 500.14.
LRMS (*m/z*): (GC) calc'd for $C_{23}H_{25}F_3NO_6S^-$ $[M-H]^-$ 500.1, not found.

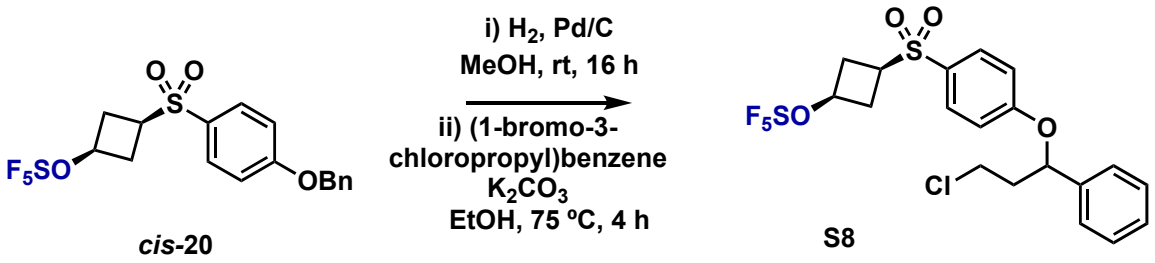
Attempts toward *N*-methyl-*N*-(3-(4-((-3-((pentafluoro-λ^6-sulfanyl)oxy)cyclobutyl)sulfonyl) phenoxy)-3-phenylpropyl)glycine



To an 8 mL vial equipped with a stir bar was added (3-((4-(benzyloxy)phenyl)sulfonyl)-3-bromocyclobutoxy)pentafluoro-λ^6-sulfane (31 mg, 60 μmol, 1.0 equiv.), followed by MeOH (1.0 mL). The mixture was stirred until all the starting material had dissolved and $NiCl_2$ (3.9 mg, 30 μmol, 0.5 equiv.) was added in one portion and $NaBH_4$ (11.3 mg, 0.3 mmol, 5.0 equiv.) in three portions. Strong bubbling was observed alongside the formation of a black precipitate. The reaction was allowed to stir for 16 h before 5.0 mL CH_2Cl_2 were added. The crude suspension was filtered through a Celite plug into a separatory funnel. The organic layer was washed with sat. NH_4Cl (2 × 2.0 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by pTLC, eluting with 3:2 hexanes:EtOAc. The *cis* and *trans* isomers were completely separable with careful loading. The desired (3-((4-(benzyloxy)phenyl)sulfonyl)cyclobutoxy)pentafluoro-λ^6-sulfane was obtained as a white solid (20 mg, 70%), only the *cis* isomer was carried forward.

R_f: 0.18 (*cis* isomer, 4:1 hexanes:EtOAc), vis: UV (254 nm).
^{1}H (300 MHz, $CDCl_3$): δ = 7.80-7.70 (d, 2H, *J* = 9.0 Hz), 7.42-7.36 (m, 5H), 7.12-7.07 (d, 2H, *J* = 9.0 Hz), 5.14 (s, 2H), 4.95-4.85 (p, 1H, *J* = 7.4 Hz), 3.39-3.27 (m, 1H), 2.83-2.73 (m, 2H), 2.67-2.58 (m, 2H).
^{19}F (282 MHz, $CDCl_3$): δ = 77.41-75.17 (p, 1F, *J* = 154.8 Hz), 63.12-62.53 (m, 4F).

$^{13}C\{^1H\}$ (201 MHz, $CDCl_3$): δ = 163.2, 135.6, 130.4, 129.3, 128.8, 128.5, 127.5, 115.6, 70.5, 70.4-70.2 (p, *J* = 4.7 Hz), 48.1, 32.4.
ATR-IR (ν_{max}): 2919, 1592, 1496, 1387, 1309, 1275, 1140, 1089, 995, 857, 747, 722 cm^{-1}.
HRMS (*m/z*): (ESI) calc'd for $C_{17}H_{18}F_5O_4S_2^+$ $[M+H]^+$ 445.0562, not found.
HRMS (*m/z*): (APCI) calc'd for $C_{17}H_{18}F_5O_4S_2^+$ $[M+H]^+$ 445.06, found 445.06.



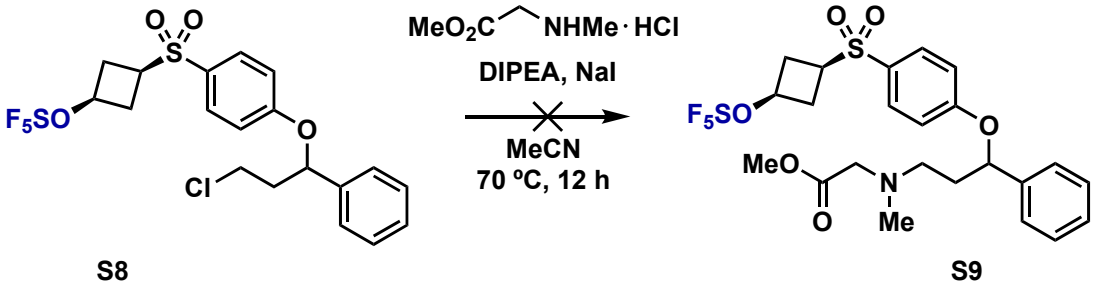
***cis*-20** **S8**

To an oven-dried 2-mL microwave vial equipped with a stir bar were added (3-((4-(benzyloxy)phenyl)sulfonyl)cyclobutoxy)pentafluoro-λ⁶-sulfane (20 mg, 45 μmol, 1.0 equiv.) and Pd/C (10 mol %). The vial was sealed with a crimper and MeOH (0.5 mL) was added *via* syringe. The vessel was purged with an H_2 balloon and allowed to stir vigorously overnight (approx. 16 h) at rt. After TLC indicated complete consumption of the starting material, the suspension was filtered over tightly packed Celite and the filtrate was concentrated *in vacuo*. The resulting crude material was used in the next step without further purification.

R_f: 0.25 (3:2 Hexanes:EtOAc), vis: UV (254 nm).
^1H (300 MHz, $CDCl_3$): δ = 7.72-7.70 (d, 2H, J = 8.7 Hz), 6.99-6.98 (d, 2H, *J* = 8.7 Hz), 4.94-4.87 (p, 1H, J = 7.4 Hz), 3.39-3.30 (m, 1H), 2.80-2.72 (m, 2H), 2.67-2.60 (m, 2H).
^{19}F (282 MHz, $CDCl_3$): δ = 77.00-75.30 (p, 1F, J = 155.6 Hz), 63.01-62.60 (m, 4F).

The crude 4-((3-((pentafluoro-λ⁶-sulfanyl)oxy)cyclobutyl)sulfonyl)phenol was concentrated into an 8 mL vial, dried under high vacuum, and stir bar was added. The crude oil was taken up in EtOH (0.25 mL), and (1-bromo-3-chloropropyl)benzene (13 mg, 54 μmol, 1.2 equiv.) was added as a solution in EtOH (0.25 mL). Potassium carbonate (11 mg, 90 μmol, 2.0 equiv.) was added in one portion and the mixture was stirred at 85 ºC overnight (approx. 16 h). After TLC indicated consumption of the starting material, the mixture was diluted with H_2O (3.0 mL) and EtOAc (2.0 mL). The layers were separated and the aqueous was extracted with EtOAc (1 × 2.0 mL). The combined organic layers were washed with brine (1 × 2.0 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was taken up in 0.2 mL CH_2Cl_2 and loaded directly onto a pTLC plate, eluting with 4:1 hexanes:EtOAc. The desired (3-((4-(3-chloro-1-phenylpropoxy)phenyl)sulfonyl)cyclobutoxy)pentafluoro-λ⁶-sulfane was obtained as a clear oil (12 mg, 53% over 2 steps).

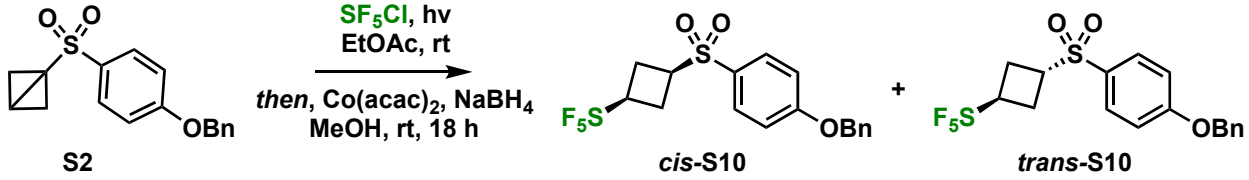
R_f: 0.41 (4:1 hexanes:EtOAc), vis: UV (254 nm).
^1H (300 MHz, $CDCl_3$): δ = 7.70-7.67 (d, 2H, *J* = 9.0 Hz), 7.37-7.30 (m, 5H), 7.00-6.97 (m, 2H, *J* = 9.0 Hz), 5.50-5.45 (m, 1H), 4.92-4.82 (p, 1H, *J* = 7.3 Hz), 3.82-3.74 (m, 1H), 3.62-3.55 (m, 1H), 3.33-3.22 (m, 1H), 2.80-2.69 (m, 2H), 2.64-2.45 (m, 3H), 2.30-2.19 (m, 1H).
^{19}F (282 MHz, $CDCl_3$): δ = 77.41-75.16 (p, 1F, *J* = 161.5 Hz), 63.11-62.52 (m, 4F).
$^{13}C\{^1H\}$ (201 MHz, $CDCl_3$): δ = 162.5, 139.5, 130.4, 129.5, 129.2, 128.6, 125.9, 116.6, 77.5, 70.5-703 (p, *J* = 4.7 Hz), 48.4, 41.2, 41.1, 32.5, 32.4.
HRMS (*m/z*): (ESI) calc'd for $C_{20}H_{23}ClF_5O_4S2^+$ $[M+H]^+$ 521.0641, not found.



S8 S9

To an 8-mL vial equipped with a stir bar was added (3-((4-(3-chloro-1-phenylpropoxy)phenyl)sulfonyl)cyclobutoxy)pentafluoro-λ^6-sulfane (20 mg, 39 μmol, 1.0 equiv.), sodium iodide (7.0 mg, 47 μmol, 1.2 equiv.), and sarcosine methyl ester hydrochloride (6.6 mg, 47 μmol, 1.2 equiv.). MeCN (0.2 mL) was added *via* syringe, followed by DIPEA (16 μL, 94 μmol, 2.4 equiv.). The reaction was heated to 70 ºC and progress was monitored by TLC. Upon consumption of the starting material (ca. 24 h), the mixture was diluted with EtOAc (2.0 mL) and H_2O (2.0 mL) and transferred to a separatory funnel. The aqueous layer was extracted with EtOAc (1 × 2.0 mL). The combined organic layers were washed with brine (1 × 2.0 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Analysis by ^1H and ^{19}F NMR indicated that a majority of the OSF_5-CB had decomposed under the designated reaction conditions (less than 5% OSF_5-CB could be accounted for by ^{19}F). We postulated that either 1) the starting material is sensitive to base, leading to OSF_5 elimination or 2) the OSF_5 group may act as a superior leaving group, and substitution occurred on the CB instead. Similar results were obtained when the reaction temperature was lowered to 50 ºC and when NMP was used in place of MeCN.

N-methyl-*N*-(3-(4-((3-(pentafluoro-λ^6-sulfanyl)cyclobutyl)sulfonyl)phenoxy)-3-phenyl propyl)glycine:



S2 *cis*-S10 *trans*-S10

An oven-dried microwave vial equipped with a stir bar was charged with 1-((4-(benzyloxy)phenyl)sulfonyl)bicyclo[1.1.0]butane (60 mg, 0.2 mmol, 1.0 equiv.). The vial was crimped, then evacuated and backfilled with Ar three times. Anhydrous EtOAc (2.0 mL) was added followed by a solution of SF_5Cl in *n*-pentane (0.24 mmol, 1.2 equiv.). The Ar line was removed, and the reaction was irradiated with white LEDs (Kessil A160WE Tuna Blue, maximum intensity) for 18 hours (the vial was placed ca. 5 cm away from the light source). Then, the solvent was removed *in vacuo* and MeOH (1.3 mL, 0.15 M) was added followed by $Co(acac)_2$ (77 mg, 0.3 mmol, 1.5 equiv.). $NaBH_4$ (38 mg, 1.0 mmol, 5.0 equiv.) was added slowly in three portions (vigorous bubbling and formation of a black precipitate was observed). The reaction mixture was stirred at room temperature (ca. 23 °C) for 16 h. Upon completion, the solution was diluted with CH_2Cl_2 (approx. 2.0 mL) and filtered through a Celite plug. The filtrate was then transferred to a separatory funnel and sat. NH_4Cl (5.0 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic fractions were washed with H_2O and brine (1 × 5 mL), dried over Na_2SO_4 or $MgSO_4$, concentrated *in vacuo*. The crude residue was purified by pTLC (preparative thin-layer chromatography) eluting with 4:1 hexanes:EtOAc. Followed by 100% CH_2Cl_2. 3-((4-(benzyloxy)phenyl)sulfonyl)cyclobutyl)pentafluoro-λ^6-sulfane was obtained as a white, crystalline solid (51

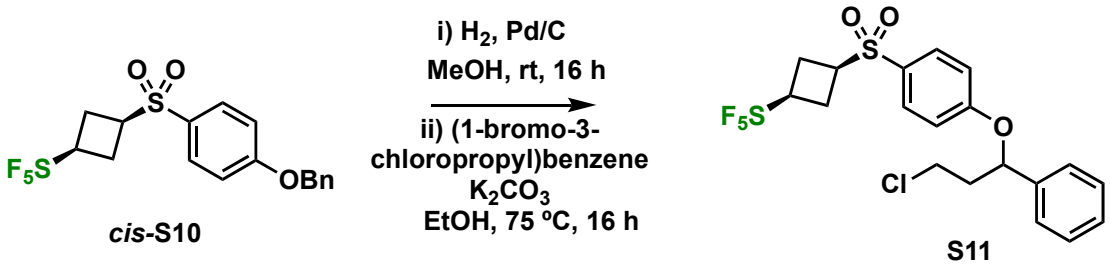
mg, 60%). Compound *trans*-**21** was isolated as a white solid (28 mg) and *cis*-**21** was isolated as a white solid (23 mg); the total isolated yield was 60%.

trans-3-((4-(benzyloxy)phenyl)sulfonyl)cyclobutyl)pentafluoro-λ^6-sulfane:

R_f: 0.32 (4:1 Hexanes:EtOAc), vis: UV (254 nm).
m.p.: 131.2 – 137.0 ºC.
^{1}H (300 MHz, $CDCl_3$): δ= 7.84-7.79 (m, 2H), 7.44-7.33 (m, 5H), 7.13-7.08 (m, 2H), 5.15 (s, 2H), 4.96-4.80 (m, 1H), 3.71-3.65 (m, 1H), 3.10-2.85 (m, 4H)
^{19}F (282 MHz, $CDCl_3$): δ = 84.00-81.95 (p, 1F, *J* = 143.2 Hz), 51.79-51.21 (dd, 4F, *J* = 143.2 Hz, *J* = 5.6 Hz).
^{13}C{^{1}H} (151 MHz, $CDCl_3$): δ= 163.5, 135.7, 130.8, 128.9, 128.7, 128.6, 127.6, 115.7, 73.5-72.6 (m), 53.3, 29.8-29.6 (m).
ATR-IR (ν_{max}): 2984, 2921, 2851, 1592, 1574, 1496, 1294, 1250, 1163, 1089, 848, 826, 794, 767, 748, 724, 696, 653 cm^{-1}.
HRMS (*m/z*): (ESI) calc'd for $C_{17}H_{18}F_5O_3S_2^+[M-H]^+$ 429.0613, found 429.0612

cis-3-((4-(benzyloxy)phenyl)sulfonyl)cyclobutyl)pentafluoro-λ^6-sulfane:

R_f: 0.16 (4:1 Hexanes:EtOAc), vis: UV (254 nm).
m.p.: 150.5 – 153.5 ºC.
^{1}H (300 MHz, $CDCl_3$): δ= 7.82-7.77 (m, 2H), 7.44-7.33 (m, 5H), 7.13-7.08 (m, 2H), 5.15 (s, 2H), 4.35-4.19 (m, 1H), 3.53-3.41 (m, 1H), 3.18-3.07 (m, 2H), 2.67-2.57 (m, 2H)
^{19}F (282 MHz, $CDCl_3$): δ = 82.78-80.72 (p, 1F, *J* = 143.2 Hz), 52.16-51.62 (dd, 4F, *J* = 143.2 Hz, *J* = 5.6 Hz).
^{13}C{^{1}H} (151 MHz, $CDCl_3$): δ= 163.5, 135.7, 130.8, 128.9, 128.9, 128.6, 127.6, 115.8, 70.6, 69.4-68.6 (m), 50.4, 30.7-30.4 (m).
ATR-IR (ν_{max}): 2952, 2921, 2852, 1592, 1578, 1498, 1281, 1260, 1247, 1142, 1115, 872, 840, 818, 783, 751, 734, 722, 695, 662, 637 cm^{-1}.
HRMS (*m/z*): (ESI) calc'd for $C_{17}H_{18}F_5O_3S_2^+[M-H]^+$ 429.0613, found 429.0595



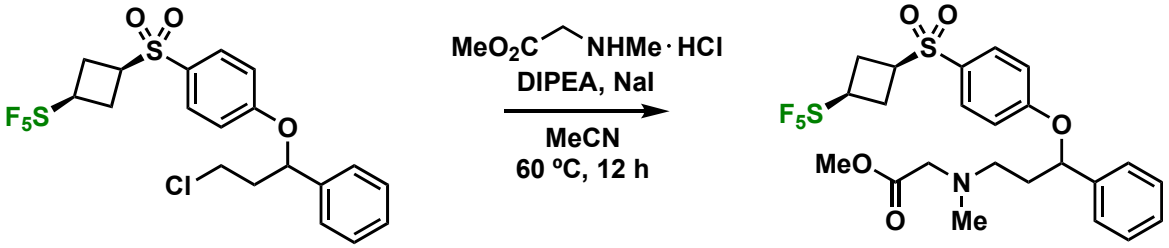
***cis*-S10** **S11**

To an oven-dried 2-mL microwave vial equipped with a stir bar were added *cis*-3-((4-(benzyloxy)phenyl)sulfonyl)cyclobutyl)pentafluoro-λ^6-sulfane (130 mg, 0.30 mmol, 1.0 equiv.) and Pd/C (10 mol %). The vial was sealed with a crimper, then MeOH (0.75 mL) and THF (0.75 mL) were added *via* syringe. The vessel was purged with an H_2 balloon and allowed to stir vigorously overnight (approx. 16 h) at rt. After TLC indicated complete consumption of the starting material, the suspension was filtered over tightly packed Celite and the filtrate was concentrated *in vacuo*. The resulting crude material was used in the next step without further purification.

R_f: 0.21 (3:2 Hexanes:EtOAc), vis: UV (254 nm).
^{1}H (300 MHz, $CDCl_3$): δ= 7.78-7.75 (m, 2H), 7.00-6.97 (m, 2H), 5.82 (s, 1H), 4.35-4.19 (m, 1H), 3.53-3.42 (m, 1H), 3.18-3.07 (m, 2H), 2.67-2.58 (m, 2H).

The crude 4-((3-(pentafluoro-λ^6-sulfaneyl)cyclobutyl)sulfonyl)phenol was concentrated into an 8-mL vial, dried under high vacuum, and stir bar was added. The crude oil was taken up in EtOH (2 mL), and (1-bromo-3-chloropropyl)benzene (140 mg, 0.60 mmol, 2.0 equiv.) was added as a solution in EtOH (1 mL). Potassium carbonate (83 mg, 0.60 mmol, 2.0 equiv.) was added in one portion and the mixture was stirred at 75 ºC overnight (approx. 16 h). After TLC indicated consumption of the starting material, the mixture was diluted with H_2O (3.0 mL) and EtOAc (2.0 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (1 × 2.0 mL). The combined organic layers were washed with brine (1 × 2.0 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was taken up in 0.2 mL CH_2Cl_2 and loaded directly onto a pTLC plate, eluting with 4:1 hexanes:EtOAc. 3-((4-(3-chloro-1-phenylpropoxy)phenyl)sulfonyl) cyclobutyl)pentafluoro-λ^6-sulfane was obtained as a clear oil (93 mg, 63% over 2 steps).

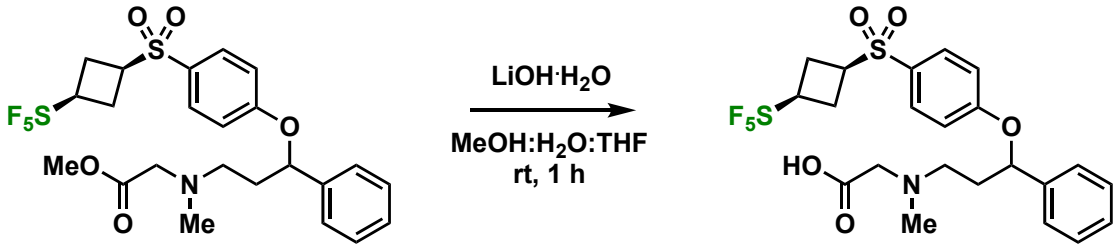
R_f: 0.14 (4:1 Hexanes:EtOAc), vis: UV (254 nm).
^{1}H (300 MHz, $CDCl_3$): δ= 7.71-7.66 (m, 2H), 7.40-7.27 (m, 5H), 7.01-6.97 (m, 2H), 5.50-5.46 (m, 1H), 4.32-4.16 (m, 1H), 3.82-3.74 (m, 1H), 3.63-3.55 (m, 1H), 3.47-3.36 (m, 1H), 3.15-3.03 (m, 2H), 2.63-2.45(m, 3H), 2.30-2.19 (m,1H).
^{19}F (282 MHz, $CDCl_3$): δ = 82.78-80.73 (p, 1F, *J* = 143.2 Hz), 52.15-51.61 (dd, 4F, J_F = 143.2 Hz, *J* = 5.6 Hz).
^{13}C{^{1}H} (151 MHz, $CDCl_3$): δ= 162.6, 139.4, 130.6, 129.2, 129.0, 128.6, 125.9, 116.6, 69.3-68.5 (m), 50.34, 41.14-41.07 (m), 30.6-30.4 (m).
ATR-IR (ν_{max}): 3066, 3032, 2966, 2928, 1592, 1494, 1320, 1300, 1280, 1251, 1167, 1142, 824, 785, 699, 635 cm^{-1}.
HRMS (*m/z*): (ESI) calc'd for $C_{19}H_{21}ClF_5O_3S_2^+$ [M-H]$^+$ 491.0536, found 491.0533.



S11 **S12**

To an 8-mL vial equipped with a stir bar was added (3-((4-(3-chloro-1-phenylpropoxy) phenyl)sulfonyl)cyclobutyl)pentafluoro-λ^6-sulfane (21.5 mg, 44 μmol, 1.0 equiv.), sodium iodide (7.9 mg, 53 μmol, 1.2 equiv.), and sarcosine methyl ester hydrochloride (7.4 mg, 53 μmol, 1.2 equiv.). MeCN (X mL) was added *via* syringe, followed by DIPEA (18.5 μL, 106 μmol, 2.4 equiv.). The reaction was heated to 70 ºC and progress was monitored by TLC. Upon consumption of the starting material (ca. 24 h), the mixture was diluted with EtOAc (2.0 mL) and H_2O (2.0 mL) and transferred to a separatory funnel. The aqueous layer was extracted with EtOAc (1 × 2.0 mL). The combined organic layers were washed with brine (1 × 2.0 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was purified by pTLC eluting with 3:2 hexanes/EtOAc to afford methyl *N*-methyl-*N*-(3-(4-(((1*s*,3*s*)-3-(pentafluoro-λ^6-sulfaneyl)cyclobutyl)sulfonyl)phenoxy)-3-phenylpropyl)glycinate as a clear oil (9.8 mg, 40%).

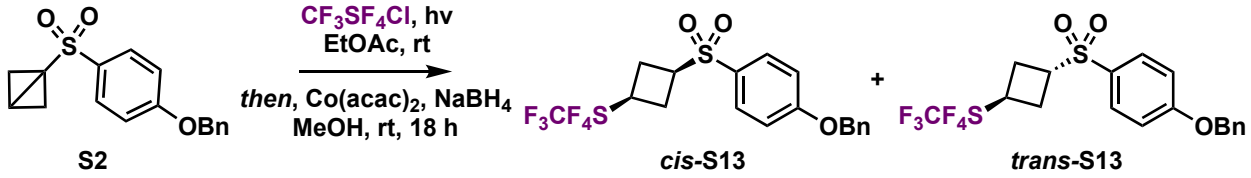
R_f: 0.10 (1:1 hexanes:EtOAc), vis: UV (254 nm).
^{1}H (300 MHz, $CDCl_3$): δ= 7.70-7.65 (m, 2H), 7.37-7.27 (m, 5H), 7.01-6.97 (m, 2H), 5.40-5.35 (m, 1H), 4.31-4.15 (m, 1H), 3.67 (s, 3H), 3.46-3.35 (m, 1H), 3.27 (s, 2H), 3.13-3.02 (m, 2H), 2.74-2.53 (m, 4H), 2.39 (s, 3H), 2.26-1.94 (m, 3H).
^{19}F (282 MHz, $CDCl_3$): δ = 82.78-80.72 (p, 1F, *J* = 143.2 Hz), 52.14-51.61 (dd, 4F, *J* = 143.2 Hz, *J* = 5.6 Hz).
^{13}C{^{1}H} (151 MHz, $CDCl_3$): δ= 171.4, 163.0, 140.6, 130.5, 129.0, 128.5, 128.2, 126.0, 116.7, 78.8, 69.2-68.8 (m), 58.6, 53.1, 51.7, 50.4, 42.4, 36.7, 30.6-30.5 (m).
ATR-IR (ν_{max}): 3032, 2953, 2847, 2808, 1743, 1592,1577, 1494, 1455, 1321, 1302, 1280, 1254, 1204, 1175, 1144, 1089, 830, 787 cm^{-1}.
HRMS (*m/z*): (ESI) calc'd for $C_{23}H_{29}F_5NO_5S_2^+$ $[M-H]^+$ 558.1402, found 558.1381.



To an 8-mL vial equipped with a stir bar was added methyl *N*-methyl-*N*-(3-(4-((3-(pentafluoro-λ^6-sulfaneyl)cyclobutyl)sulfonyl)phenoxy)-3-phenylpropyl)glycinate (7.8 mg, 0.014 mmol, 1.0 equiv.), followed by MeOH (0.1 mL), THF (0.1 mL), and H_2O (0.1 mL). While stirring, lithium hydroxide monohydrate (1 mg) was added in one portion. The reaction was stirred vigorously at room temperature until the starting material was consumed as indicated by TLC. The reaction was carefully acidified with 1 M HCl to ca. pH 4-5, and the aqueous layer was extracted with EtOAc (3 × 2.0 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The resulting crude solid was purified by pTLC eluting with 10% MeOH in CH_2Cl_2 to afford *N*-methyl-*N*-(3-(4-((3-(pentafluoro-λ^6-sulfanyl)cyclobutyl) sulfonyl)phenoxy)-3-phenylpropyl)glycine as a white solid (7.2 mg, 95 %).

R_f: 0.51 (4:1 DCM:MeOH), vis: UV (254 nm).
^{1}H (300 MHz, $CDCl_3$): δ= 7.73-7.70 (m, 2H), 7.43-7.26 (m, 5H), 7.14-7.11 (m, 2H), 5.61-5.56 (m, 1H), 4.78-4.69 (m, 1H), 3.85-3.74 (m, 2H), 3.27 (m, 2H), 2.86-2.73 (m, 4H), 2.66-2.56 (m, 2H), 2.48 (m, 2H), 2.26-1.99 (m, 2H).
^{19}F (282 MHz, $CDCl_3$): δ = 86.87-84.81 (p, 1F, *J* = 143.2 Hz), 52.92-52.39 (dd, 4F, *J* = 143.2 Hz, *J* = 5.6 Hz).
^{13}C{^{1}H} (151 MHz, $CDCl_3$): δ= 162.0, 140.3, 130.3, 128.7, 128.5, 128.0, 126.0, 116.5, 77.5, 69.8, 58.3, 52.5, 48.8, 41.5, 40.0, 34.5, 29.9
ATR-IR (ν_{max}): 3429, 3170, 2847, 1643, 1593, 1382, 1322, 1280, 1251, 1146, 870, 837, 790, 700, 663 cm^{-1}.
HRMS (*m/z*): (ESI) calc'd for $C_{22}H_{27}F_5NO_5S_2^+$ $[M-H]^+$ 544.1246, found 544.1257.

_N_-methyl-_N_-(3-phenyl-3-(4-(((1_s_,3_s_)-3-(tetrafluoro(trifluoromethyl)- λ⁶-sulfanyl)cyclobutyl) sulfonyl)phenoxy)propyl)glycine



S2 **_cis_-S13** **_trans_-S13**

To an oven-dried microwave vial equipped with a stir bar was added 1-((4-(benzyloxy)phenyl)sulfonyl)bicyclo[1.1.0]butane (60 mg, 0.2 mmol, 1.0 equiv.). The vial was crimped, then evacuated and backfilled with Ar three times. Anhydrous EtOAc (2.0 mL) was added followed by a solution of CF_3SF4Cl in *n*-pentane (0.24 mmol, 1.2 equiv.). The Ar line was removed, and the reaction was irradiated with white LEDs (Kessil A160WE Tuna Blue, maximum intensity) for 18 h (the vial was placed ca. 5 cm away from the light source). Then, the solvent was removed *in vacuo* and MeOH (1.3 mL, 0.15 M) was added followed by $Co(acac)_2$ (77 mg, 0.3 mmol, 1.5 equiv.). $NaBH_4$ (38 mg, 1.0 mmol, 5.0 equiv.) was added slowly in three portions (vigorous bubbling and formation of a black precipitate was observed). The reaction mixture was stirred at room temperature (ca. 23 °C) for 16 h. Upon completion, the solution was diluted with CH_2Cl_2 (approx. 2.0 mL) and filtered through a Celite plug. The filtrate was then transferred to a separatory funnel and sat. NH_4Cl (5.0 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic fractions were washed with H_2O and brine (1 × 5 mL), dried over Na_2SO_4 or $MgSO_4$, concentrated *in vacuo*. The crude residue was purified by pTLC (preparative thin layer chromatography) eluting with 4:1 hexanes:EtOAc. Followed by 100% CH_2Cl_2. 3-((4-(benzyloxy)phenyl)sulfonyl)cyclobutyl)pentafluoro-λ⁶-sulfane was obtained as a white, crystalline solid (39 mg, 64%). The *trans* isomer was isolated as a white solid (18 mg) and *cis* isomer was isolated as a white solid (21 mg); the total isolated yield was 54%.

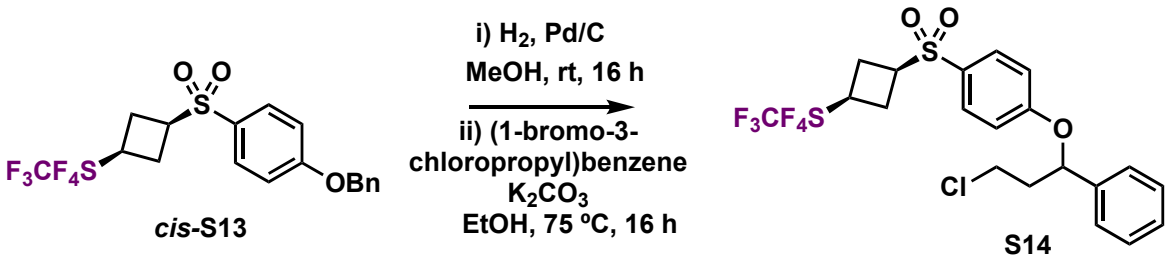
trans-3-((4-(benzyloxy)phenyl)sulfonyl)cyclobutyl)tetrafluoro(trifluoromethyl)- λ⁶-sulfane:

R_f: 0.39 (4:1 Hexanes:EtOAc), vis: UV (254 nm).
m.p.: 161.4-168.6 ºC.
^{1}H (300 MHz, $CDCl_3$): δ= 7.84-7.79 (m, 2H), 7.44-7.33 (m, 5H), 7.13-7.08 (m, 2H), 5.15 (s, 2H), 5.06-4.94 (m, 1H), 3.74-3.65 (m, 1H), 3.15-3.04 (m, 2H), 2.95-2.86 (m, 2H)
^{19}F (282 MHz, $CDCl_3$): δ = 28.31-28.02 (qd, 4F, $^3J_{F\text{-}F}$ = 25.6, $^3J_{F\text{-}H}$ = 5.8 Hz), –63.34 - –63.70 (dd, 4F, $^2J_{F\text{-}F}$ = 25.6 Hz).
^{13}C{^{1}H} (151 MHz, $CDCl_3$): δ= 163.46, 135.68, 130.98, 128.97, 128.77, 128.66, 127.65, 115.76, 75.75-75.01 (m), 70.64, 53.49, 30.12-29.83 (m)
ATR-IR (ν_{max}): 2960, 2920, 2851, 1592, 1574, 1494, 1273, 1236, 1219, 1138, 1088, 989, 802, 784, 774, 747, 724, 700, 664 cm^{-1}.
HRMS (*m/z*): (ESI) calc'd for $C_{18}H_{18}F_7O_3S_2^+$ $[M\text{-}H]^+$: calculated 479.0581, measured 479.0583

cis-3-((4-(benzyloxy)phenyl)sulfonyl)cyclobutyl)tetrafluoro(trifluoromethyl)- λ⁶-sulfane:

R_f: 0.15 (4:1 Hexanes:EtOAc), vis: UV (254 nm).
m.p.: 157.9-162.8 ºC.
^{1}H (300 MHz, $CDCl_3$): δ= 7.82-7.77 (m, 2H), 7.44-7.33 (m, 5H), 7.13-7.08 (m, 2H), 5.15 (s, 2H), 4.47-4.31 (m, 1H), 3.52-3.41 (m, 1H), 3.24-3.13 (m, 2H), 2.68-2.58 (m, 2H)

^{19}F (282 MHz, $CDCl_3$): δ = 28.91-28.62 (qd, 4F, $^3J_{F-F}$ = 25.6, $^3J_{F-H}$ = 5.8 Hz), –63.37 - –63.73 (dd, 4F, $^2J_{F-F}$ = 25.6 Hz).
^{13}C{^{1}H} (151 MHz, $CDCl_3$): δ= 163.44, 135.69, 130.73, 128.98, 128.94, 128.63, 127.63, 115.73, 71.47-70.63 (m), 50.49, 30.82-30.71 (m)
ATR-IR (ν_{max}): 3036, 2921, 1594, 1579, 1499, 1326, 1302, 1281, 1248, 1226, 1183, 1164, 1139, 1091, 1027, 993, 782, 768, 751, 724, 710, 690, 644, 627 cm^{-1}.
HRMS (*m/z*): (ESI) calc'd for $C_{18}H_{18}F_7O_3S_2^+$ $[M-H]^+$: calculated 479.0581, measured 479.0693.



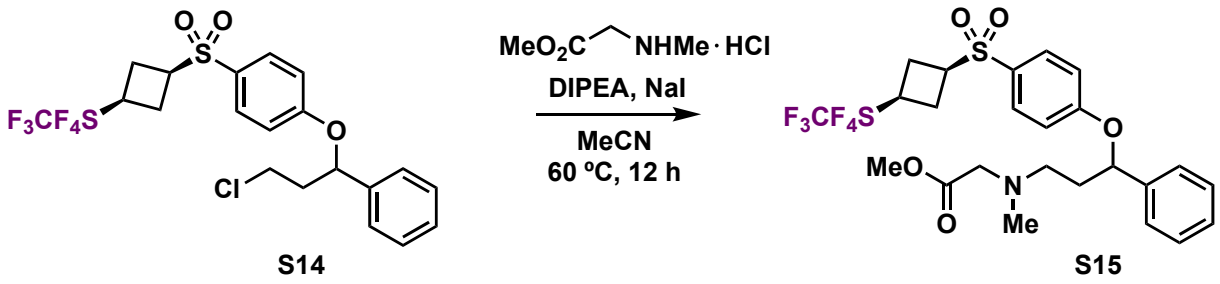
To an oven-dried 2 mL microwave vial equipped with a stir bar was added *cis*-3-((4-(3-chloro-1-phenylpropoxy)phenyl)sulfonyl)cyclobutyl)tetrafluoro(trifluoromethyl)-λ^6-sulfane (95 mg, 0.20 mmol, 1.0 equiv.) and Pd/C (10 mol %). The vial was sealed with a crimper, then MeOH (0.55 mL) and THF (0.55 mL) were added *via* syringe. The vessel was purged with an H_2 balloon and allowed to stir vigorously overnight (ca. 16 h) at rt. After TLC indicated complete consumption of the starting material, the suspension was filtered over tightly packed Celite and the filtrate was concentrated *in vacuo*. The resulting crude material was used in the next step without further purification.

R_f: 0.30 (3:2 Hexanes:EtOAc), vis: UV (254 nm).
^{1}H (300 MHz, $CDCl_3$): δ= 7.79-7.74 (m, 2H), 7.01-6.96 (m, 2H), 5.73 (s, 1H), 4.47-4.32 (m, 1H), 3.52-3.41 (m, 1H), 3.24-3.13 (m, 2H), 2.68-2.60 (m, 2H)

The crude 4-((-3-(tetrafluoro(trifluoromethyl)- λ^6-sulfanyl)cyclobutyl)sulfonyl)phenol was concentrated into an 8 mL vial, dried under high vacuum, and stir bar was added. The crude oil was taken up in EtOH (1.5 mL), and (1-bromo-3-chloropropyl)benzene (93 mg, 0.40 mmol, 2.0 equiv.) was added as a solution in EtOH (0.5 mL). Potassium carbonate (55 mg, 0.40 mmol, 2.0 equiv.) was added in one portion and the mixture was stirred at 75 ºC overnight (approx. 16 h). After TLC indicated consumption of the starting material, the mixture was diluted with H_2O (3.0 mL) and EtOAc (2.0 mL). The layers were separated and the aqueous was extracted with EtOAc (1 × 2.0 mL). The combined organic layers were washed with brine (1 × 2.0 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was taken up in 0.2 mL CH_2Cl_2 and loaded directly onto a pTLC plate, eluting with 4:1 hexanes:EtOAc. (3-((4-(3-chloro-1-phenylpropoxy)phenyl)sulfonyl)cyclobutyl)tetrafluoro(trifluoromethyl)-λ^6-sulfane was obtained as a clear oil (66 mg, 61% over 2 steps).

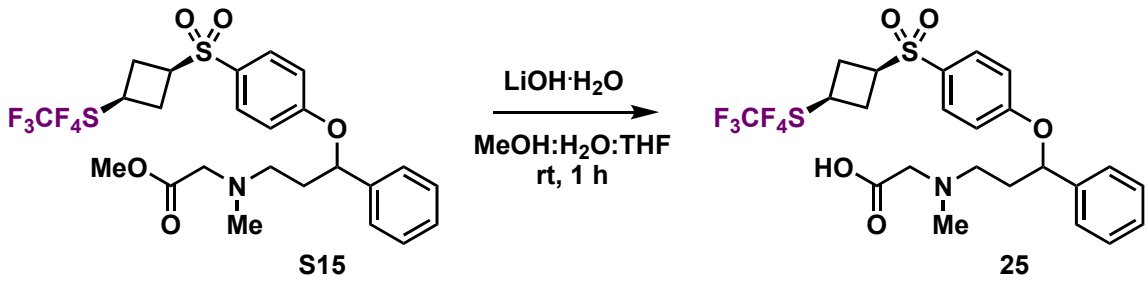
R_f: 0.16 (4:1 Hexanes:EtOAc), vis: UV (254 nm).
^{1}H (300 MHz, $CDCl_3$): δ= 7.72-7.66 (m, 2H), 7.40-7.27 (m, 5H), 7.01-6.95 (m, 2H), 5.50-5.46 (m, 1H), 4.44-4.28 (m, 1H), 3.82-3.74 (m, 1H), 3.63-3.55 (m, 1H), 3.47-3.35 (m, 1H), 3.20-3.09 (m, 2H), 2.64-2.45 (m, 3H), 2.30-2.17 (m,1H).
^{19}F (282 MHz, $CDCl_3$): δ = 28.89-28.60 (qd, 4F, $^3J_{F-F}$ = 25.6, $^3J_{F-H}$ = 5.8 Hz), –63.39 - –63.74 (dd, 4F, $^2J_{F-F}$ = 25.6 Hz).
^{13}C{^{1}H} (151 MHz, $CDCl_3$): δ= 162.6, 143.9, 139.5, 130.6, 129.2, 129.1, 128.8, 128.6, 128.1, 125.93, 125.90, 116.6, 71.5, 71.4-71.0 (m), 50.4, 41.9, 41.6, 41.2, 41.1, 30.8-30.7 (m)

ATR-IR (ν_{max}): 2969, 1592, 1493, 1321, 1301, 1280, 1231, 1143, 1089, 783, 721, 706, 639 cm^{-1}.
HRMS (*m/z*): (ESI) calc'd for $C_{20}H_{21}ClF_7O_3S_2^+$ $[M-H]^+$ 541.0504, found 541.0539



To an 8-mL vial equipped with a stir bar was added ((3-((4-(3-chloro-1-phenylpropoxy) phenyl) sulfonyl)cyclobutyl)tetrafluoro(trifluoromethyl)-λ^6-sulfane (33 mg, 61 μmol, 1.0 equiv.), sodium iodide (11 mg, 73 μmol, 1.2 equiv.), and sarcosine methyl ester hydrochloride (10 mg, 73 μmol, 1.2 equiv.). MeCN (0.7 mL) was added *via* syringe, followed by DIPEA (25 μL, 146 μmol, 2.4 equiv.). The reaction was heated to 70 ºC and progress was monitored by TLC. Upon consumption of the starting material (approx. 24 h), the mixture was diluted with EtOAc (2.0 mL) and H_2O (2.0 mL) and transferred to a separatory funnel. The aqueous layer was extracted with EtOAc (1 × 2.0 mL). The combined organic layers were washed with brine (1 × 2.0 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was purified by pTLC eluting with 3:2 hexanes/EtOAc to afford methyl *N*-methyl-*N*-(3-phenyl-3-(4-((-3-(tetrafluoro(trifluoromethyl)-λ^6-sulfanyl)cyclobutyl)sulfonyl)phenoxy)propyl)glycinate as a clear oil (12.7 mg, 34%).

R_f: 0.10 (1:1 Hexanes:EtOAc), vis: UV (254 nm).
^{1}H (300 MHz, $CDCl_3$): δ= 7.70-7.65 (m, 2H), 7.37-7.27 (m, 5H), 7.01-6.96 (m, 2H), 5.39-5.35 (m, 1H), 4.43-4.27 (m, 1H), 3.67 (s, 3H), 3.46-3.34 (m, 1H), 3.26 (s, 2H), 3.19-3.08 (m, 2H), 2.74-2.53 (m, 4H), 2.39 (s, 3H), 2.26-1.94 (m, 3H).
^{19}F (282 MHz, $CDCl_3$): δ = 28.89-28.60 (qd, 4F, $^3J_{F-F}$ = 25.6, $^3J_{F-H}$ = 5.8 Hz), –63.39 - –63.75 (dd, 4F, $^2J_{F-F}$ = 25.6 Hz).
^{13}C{^{1}H} (151 MHz, $CDCl_3$): δ= 171.4, 163.0, 140.6, 131.1, 130.5, 129.0, 128.6, 128.2, 126.0, 116.6, 116.15, 78.8, 71.3-71.1 (m), 58.6, 53.1, 51.7, 50.4, 42.4, 36.7, 30.8-30.7 (m).
ATR-IR (ν_{max}): 2952, 2864, 1748, 1592, 1577, 1494, 1456, 1321, 1302, 1281, 1233, 1175, 1144, 1089, 1056, 1033, 784, 707 cm^{-1}.
HRMS (*m/z*): (ESI) calc'd for $C_{24}H_{29}F_7NO_5S_2^+$ $[M-H]^+$ 608.1370, found 608.1343



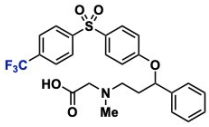
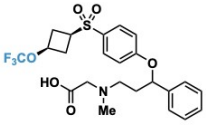
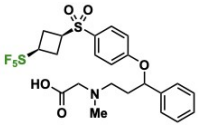
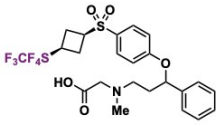
To an 8-mL vial equipped with a stir bar was added methyl *N*-methyl-*N*-(3-phenyl-3-(4-((-3-(tetrafluoro(trifluoromethyl)- λ^6-sulfaneyl)cyclobutyl)sulfonyl)phenoxy)propyl)glycinate (12.7 mg, 0.021

mmol, 1.0 equiv.), followed by MeOH (0.15 mL), THF (0.15 mL), and H_2O (0.15 mL). While stirring, lithium hydroxide monohydrate (1 mg) was added in one portion. The reaction was stirred vigorously at room temperature until the starting material was consumed as indicated by TLC. The reaction was carefully acidified with 1 M HCl to ca. pH 4-5, and the aqueous layer was extracted with EtOAc (3 × 2.0 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The resulting crude solid was purified by pTLC eluting with 10% MeOH in CH_2Cl_2 to afford the desired *N*-methyl-*N*-(3-phenyl-3-(4-((3-(tetrafluoro(trifluoromethyl)- λ^6-sulfanyl)cyclobutyl)sulfonyl)phenoxy)propyl)glycine as a white solid (11 mg, 86%).

R_f: 0.28 (4:1 DCM:MeOH), vis: UV (254 nm).
^{1}H (300 MHz, $CDCl_3$): δ= 7.73-7.70 (m, 2H), 7.42-7.25 (m, 5H), 7.14-7.11 (m, 2H), 5.60-5.56 (m, 1H), 4.92-4.77 (m, 1H), 3.84-3.73 (m, 1H), 3.27 (m, 1H), 2.88-2.78 (m, 4H), 2.67-2.57 (m, 2H), 2.47 (m, 2H), 2.26-1.98 (m, 2H).
^{19}F (282 MHz, $CDCl_3$): δ = 28.76-28.47 (qd, 4F, $^3J_{F\text{-}F}$ = 25.6, $^3J_{F\text{-}H}$ = 5.8 Hz), –63.20 - –63.55 (dd, 4F, $^2J_{F\text{-}F}$ = 25.6 Hz).
^{13}C{^{1}H} (151 MHz, $CDCl_3$): δ= 162.0, 140.3, 130.3, 128.7, 128.6, 128.0, 126.0, 116.5, 77.5, 72.3, 58.3, 52.5, 48.9, 41.5, 40.0, 34.4, 30.2
ATR-IR (ν_{max}): 3428, 3170, 2846, 1641, 1593, 1548, 1235, 1146, 788, 722, 708 cm^{-1}.
HRMS (*m/z*): (ESI) calc'd for $C_{23}H_{27}F_7NO_5S_2^+$ $[M\text{-}H]^+$ 594.1214, found 594.1221.

Summary of ADME Properties:

Table S1. Summary of ADME properties for compounds **22-25**.

Compound	 22	 23	 24	 25
Measured LogD / calc'd	2.10 / 2.36	1.10 / 1.44	1.30 / 1.69	2.10 / 2.74
HT Solubility pH = 6.8 (mM)[a]	0.266	0.504	0.259	0.498
LM CL_{int} m / r / h (µL/min/mg)[b]	<23 / 24 / <23	- / <23 / <23	32 / 26 / 27	17 / 14 / 24
CYP3A4 inhibition IC_{50} (µM)	-	-	>25	>25
HepG2 Cytotoxicity CC_{50} (µM)	-	-	>100	>100
LE-MDCK[c] $P_{appAtoB}$ ($cm \cdot 10^{-6}/s$) / Recovery	2.60 / 63%	0.30 / 66%	0.30 / 62%	1.00 / 75%

[a] HT = high throughput. [b] LM CL_{int} = liver microsomal intrinsic clearance in mouse, rat, and human, respectively. [c] Low efflux Madin–Darby canine kidney permeability.

Optimization of Bromotrifluoromethoxylation of [1.1.0]Bicyclobutanes:

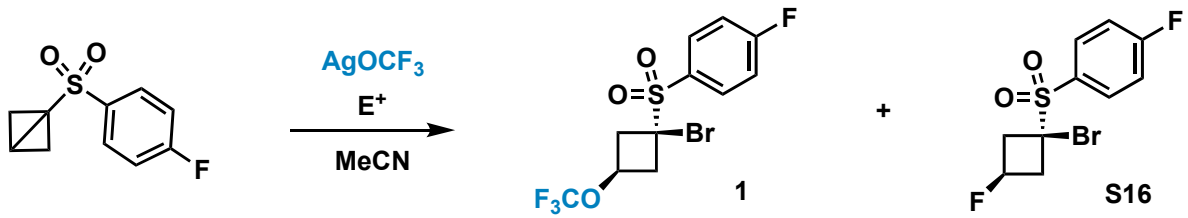
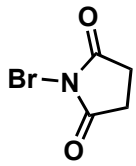


Table S2. Optimization of Bromotrifluoromethoxylation reaction conditions.

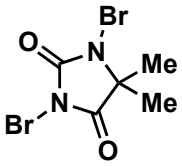
Entry	AgOCF$_3$ equiv.	Conc. (M)	Br source (equiv.)	Additive (equiv.)	Temp. (ºC)	Time (h)	% yield 1	% yield S16
1	1.5	0.2	Br_2 (0.5)	–	23	16	trace	n.d.
2	1.5	0.2	Br_2 (1.0)	–	23	16	7	<1
3	1.5	0.2	NBS (1.5)	–	23	16	14	2
4	1.5	0.2	DBDMH (1.5)	–	23	16	44	5
5	1.5	0.2	NBS (1.5)	–	60	16	10	4
6	1.5	0.2	DBDMH (1.5)	–	60	16	34	17
7	1.5	0.2	Br_2 (1.0)	–	60	16	4	<1
8	3.0	0.2	NBS (1.5)	–	23	16	29	<1
9	3.0	0.2	DBDMH (1.5)	–	23	16	54	7
10	3.0	0.2	NBr-Phth	–	23	16	52	<1
11	5.0	0.2	DBDMH (1.5)	–	23	16	53	4
12	3.0	0.2	NBS (1.5)	–	60	16	20	5
13	3.0	0.2	DBDMH (1.5)	–	60	16	22	<1
14	3.0	0.2	DBDMH (0.5)	–	23	16	34	0
15	3.0	0.2	DBDMH (1.0)	–	23	16	45	0
16	3.0	0.2	DBDMH (2.0)	–	23	16	52	0
17[b]	3.0	0.2	DBDMH (1.5)	–	23	16	54	0
18	3.0	0.2	DBDMH	–	23	1	6	n.d.

			(1.5)					
19	3.0	0.2	DBDMH (1.5)	–	23	2	12	<1
20	3.0	0.2	DBDMH (1.5)	–	23	6	25	<1
21	3.0	0.2	DBDMH (1.5)	CuCl (1.0)	23	16	3	4
22	3.0	0.2	DBDMH (1.5)	TBAB (1.0)	23	16	41	<1
23	3.0	0.2	DBDMH (1.5)	DB-18-c-6 (1.0)	23	16	45	2
24	3.0	0.33	DBDMH (1.5)	–	23	16	66	2
25	3.0	0.1	DBDMH (1.5)	–	23	16	32	2
26	3.0	0.2	DBDMH (1.5)	–	23	16	14	2
27	3.0	0.33	DBDMH (1.5)	–	0	16	40	n.d.
28	3.0	0.33	DBDMH (1.5)	–	-40	16	38	n.d.

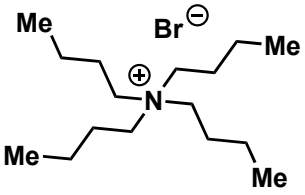
[a] Yields determined by ^{19}F NMR. [b] Reaction was conducted on a 0.2 mmol scale.



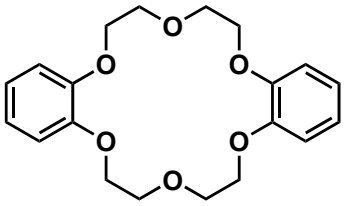
NBS



DBDMH



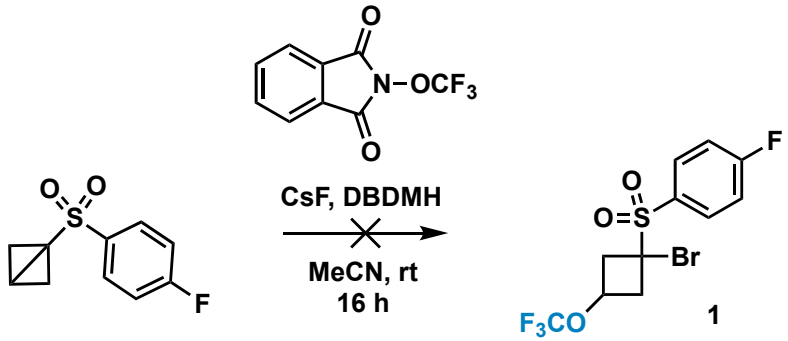
TBAB



DB-18-crown-6

Screening Attempts with other Nucleophilic–OCF_3 Sources and Electrophiles:

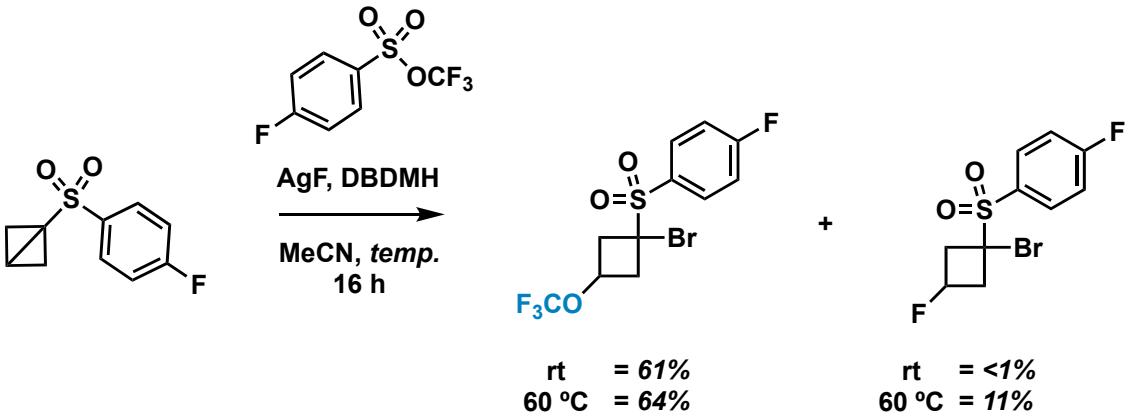
Several sources of "M–OCF_3" (*e.g.*, $AgOCF_3$ or $CsOCF_3$) are known in the literature and were investigated for their compatibility in the bromo-trifluoromethoxylation reaction. Specifically, 2-(trifluoromethoxy)isoindoline-1,3-dione and trifluoromethyl 4-fluorobenzenesulfonate were utilized as $CsOCF_3$ and $AgOCF_3$ sources, respectively:



Scheme S4. Attempted bromo-trifluoromethoxylation of **1** using 2-(trifluoromethoxy)isoindoline-1,3-dione.

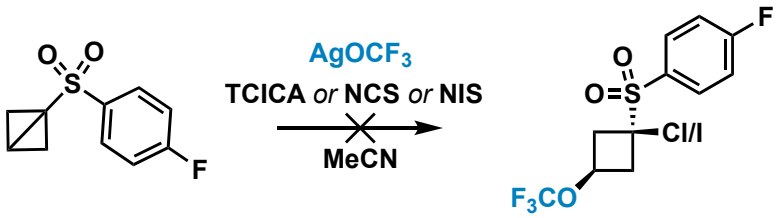
To an oven-dried 2 mL microwave vial equipped with a stir bar were added CsF (0.3 mmol, 3.0 equiv.), 2-(trifluoromethoxy)isoindoline-1,3-dione (0.3 mmol, 3.0 equiv.), 1-((4-fluorophenyl)sulfonyl)bicyclo[1.1.0] butane (0.1 mmol, 1.0 equiv.), and DBDMH (0.15 mmol, 1.5 equiv.). The vial was sealed with a crimper, then evacuated and backfilled with Ar three times. Anhydrous MeCN (0.3 mL) was added *via* syringe and the reaction was stirred at rt for 16 h. Upon completion, an aliquot was taken for ^{19}F NMR yield determination. No desired product was detected; however, complete decomposition of the starting material was observed.

The reaction was then repeated at 60 ºC to investigate the effect of temperature on the reaction. Similarly, no desired product was observed, only decomposition of the BCB.



Scheme S5. Bromo-trifluoromethoxylation of **1** using trifluoromethyl 4-fluorobenzenesulfonate.

To an oven-dried 2 mL microwave vial equipped with a stir bar were added AgF (0.3 mmol, 3.0 equiv.), trifluoromethyl 4-fluorobenzenesulfonate (0.3 mmol, 3.0 equiv.), 1-((4-fluorophenyl)sulfonyl)bicyclo[1.1.0] butane (0.1 mmol, 1.0 equiv.), and DBDMH (0.15 mmol, 1.5 equiv.). The vial was sealed with a crimper, then evacuated and backfilled with Ar three times. Anhydrous MeCN (0.3 mL) was added *via* syringe and the reaction was stirred at rt or 60 ºC for 16 h. Upon completion, an aliquot was taken for ^{19}F NMR yield determination. The ^{19}F NMR shift and R_f values of the desired product were the same as a standard of **1** obtained from the general procedure.



Scheme S6. Attempts at chloro- and iodo-trifluoromethoxylation.

In addition to screening for bromo-trifluoromethoxylation, analogous chloro- and iodo-trifluoromethoxylation reactions were attempted using the reagents specified above. In the case of iodo-trifluoromethoxylation, the corresponding iodo-trifluoromethoxy cyclobutane was formed in <20 % by ^{19}F NMR; however, competitive diiodination was observed. Attempts at chloro-trifluoromethoxylation did not generate any of the desired product, as determined by ^{19}F NMR analysis. When TCICA was utilized, rapid formation of a white precipitate was observed.

Optimization of Bromo-Pentafluorosulfanoxylation of [1.1.0]Bicyclobutanes:

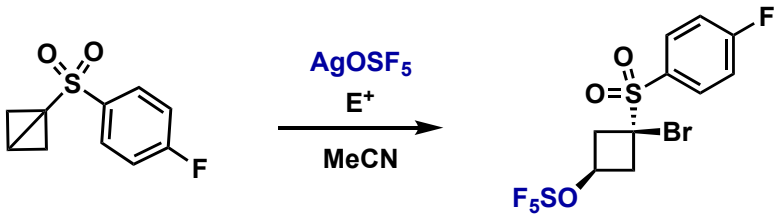


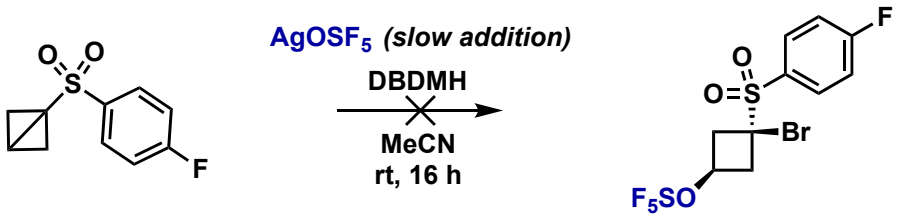
Table S3. Optimization of bromo-oxypentafluorosulfanylation of BCBs.

Entry	Equiv. BCB	Equiv. $AgOSF_5$	Electrophile (equiv.)	Additive (equiv.)	Temp. (ºC)	Time (h)	% yield[a]
1	2.0	1.0	Br_2 (0.5)	–	-40	16	6
2	2.0	1.0	Br_2 (0.5)	–	0	16	4
3	2.0	1.0	Br_2 (0.5)	–	23	16	5
4	2.0	1.0	NBS (1.5)	–	23	16	15
5	2.0	1.0	DBDMH (1.5)	–	23	16	24

6	1.0	1.0	DBDMH (1.5)	–	23	16	21
7	2.0	1.0	DBDMH (1.5)	–	23	48	20
8	2.0	1.0	DBDMH (1.5)	2,2'-bipy (1.0)	23	16	8
9	2.0	1.0	DBDMH (1.5)	dtbbpy (1.0)	23	16	7
10	2.0	1.0	DBDMH (1.5)	PPh_3 (1.0)	23	16	5
11[b]	2.0	1.0	DBDMH (1.5)	–	60	16	30
12	2.0	1.0	DBDMH (1.5)	2,2'-bipy (1.0)	60	16	16
13	2.0	1.0	DBDMH (1.5)	CuCl (1.0)	60	16	0
14	2.0	1.0	DBDMH (1.5)	K_3PO_4 (1.0)	60	16	5
15	2.0	1.0	DBDMH (1.5)	DB-18-c-6 (1.0)	60	16	6
16	1.0	1.0	DBDMH (1.5)	–	60	16	20
17	1.0	2.0	DBDMH (1.5)	–	60	8	7
18	1.0	3.0	DBDMH (1.5)	–	60	8	6
19	1.0	2.0	DBDMH (1.5)	–	60	16	8
20	1.0	3.0	DBDMH (1.5)	–	60	16	6
21	1.0	3.0	DBDMH (1.5)	styrene (0.5)	60	16	5

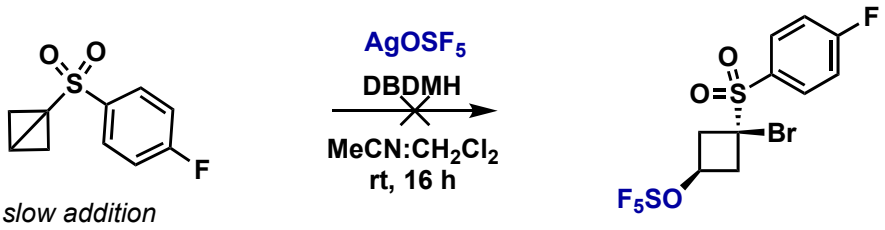
[a] Yields determined by ^{19}F NMR. [b] The ^{19}F NMR yields of the major side products **S16** & **S18** were determined to be 13% and <2%, respectively, under optimized conditions.

Other reactions attempted during optimization campaign:



Scheme S7. Other reaction conditions screened during optimization campaign.

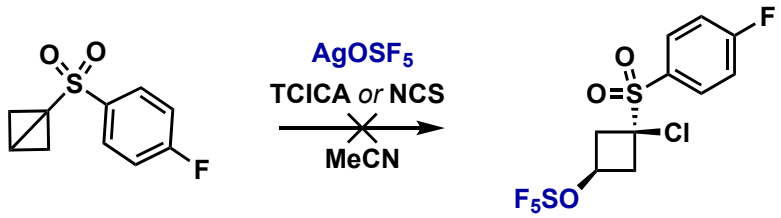
The BCB and DBDMH were dissolved in 0.5 mL MeCN and the $AgOSF_5$ stock solution was added dropwise over the course of 1 hour at room temperature. No desired product was observed by ^{19}F NMR analysis.



Scheme S8. Other reaction conditions screened during optimization campaign.

To the $AgOSF_5$ and DBDMH mixture was added a 0.1 M solution of the BCB in CH_2Cl_2 dropwise over the course of an hour. No desired product was observed by ^{19}F NMR analysis.

Chloro-Pentafluorosulfanoxylation Attempts:



In addition to screening for bromo-pentafluorosulfanoxylation, electrophilic chlorination reagents were screened for an analogous chloro-pentafluorosulfanoxylation reaction. Attempts at chloro-pentafluorosulfanoxylation using the reagents specified above resulted in no desired product formation. In addition, the *syn* dichloride was not detected in the crude reaction mixture by ^{19}F NMR analysis.

Iodo-Pentafluorosulfanoxylation Attempts:

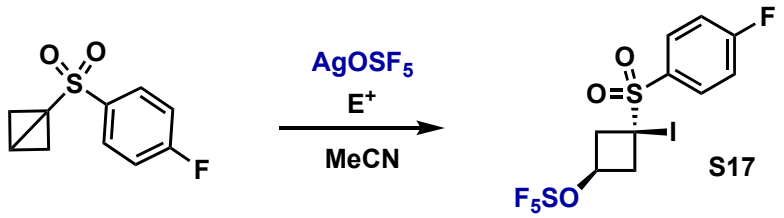
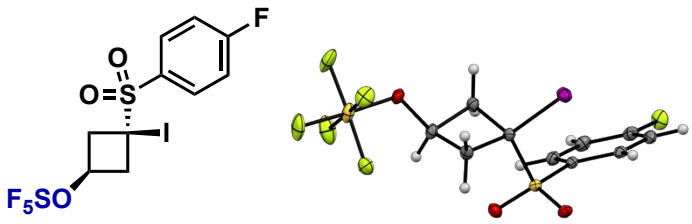


Table S4. Attempted reactions for iodo-oxypentafluorosulfanylation of BCBs.

Entry	Equiv. BCB	Electrophile (equiv.)	Additive (equiv.)	Temperature (ºC)	% yield[a] S17
1	1.0	I_2 (0.5)	–	23	<3
2	2.0	I_2 (0.5)	–	23	5
3	2.0	I_2 (0.5)	–	60	12
4[b]	2.0	I_2 (0.5)	–	60	9
5	2.0	NIS (1.0)	CuI (1.0)	23	0
6	2.0	NIS (1.0)	$CuCl_2$ (1.0)	23	0
7[c]	2.0	NIS (1.0)	CuCl (1.0)	23	8
8[c]	2.0	NIS (1.0)	$NiCl_2$ (1.0)	23	6
9	2.0	DIDMH[d] (1.0)	–	60	18
10	2.0	ICH_2CH_2I (1.0)	–	60	<1
11	2.0	$(CH_3)_2CH_2I$ (1.0)	–	60	n.d.
12	2.0	CHI_3 (1.0)	–	60	n.d.
13	2.0	CI_4 (1.0)	–	60	n.d.

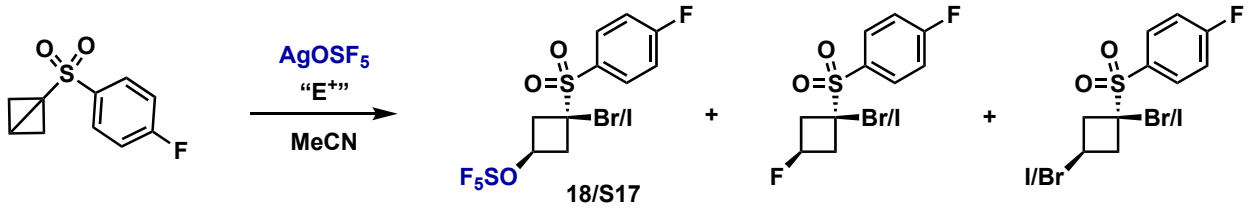
[a] Yields determined by ^{19}F NMR. [b] $AgOSF_5$ and BCB were stirred at 60 ºC for 1 h before the addition of I_2. [c] Residual $AgOSF_5$ was observed in the ^{19}F NMR aliquot. [d] DIDMH = 1,3-Diiodo-5,5-dimethylhydantoin.



Pentafluoro(3-((4-fluorophenyl)sulfonyl)-3-iodocyclobutoxy)-λ⁶-sulfane (compound **S17**) was prepared from 1-(phenylsulfonyl)bicyclo[1.1.0]butane using *N*-iodosuccinimide or I_2. The crude residue was purified by pTLC eluting with 9:1 hexanes:EtOAc. The product was obtained as a white amorphous solid; several reaction mixtures were combined to obtain enough material for crystal growth. Crystals suitable for SC-XRD were grown by slow solvent evaporation from toluene.

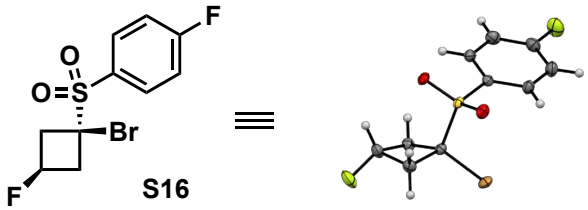
R_f: 0.5 (4:1 Hexanes:EtOAc), vis: UV (254 nm).
^{1}H (300 MHz, $CDCl_3$): δ = 8.11-8.06 (m, 2H), 7.32-7.27 (m, 2H), 5.57-5.51 (app. t, 1H, *J* = 6.9 Hz), 3.75-3.69 (m, 2H), 3.17-3.12 (m, 2H).
^{19}F (282 MHz, $CDCl_3$): δ = 76.66-74.42 (p, 1F , *J* = 160.7 Hz), 63.20-62.60 (m, 4F), –100.91 (m, 1F).
^{13}C{^{1}H} (101 MHz, $CDCl_3$): δ = 167.9-165.3 (d, *J* = 258.7 Hz), 134.4-134.3 (d, *J* = 9.9 Hz), 129.79-129.76 (d, *J* = 3.3 Hz), 116.6-116.4 (d, *J* = 22.8 Hz), 73.6-73.5 (p, J = 4.9 Hz), 46.7, 34.2.

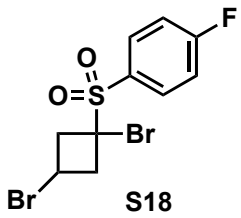
Side-Products Observed during Pentafluorosulfanoxylation Reactions:



Scheme S9. Side products observed during pentafluorosulfanoxylation optimization campaign.

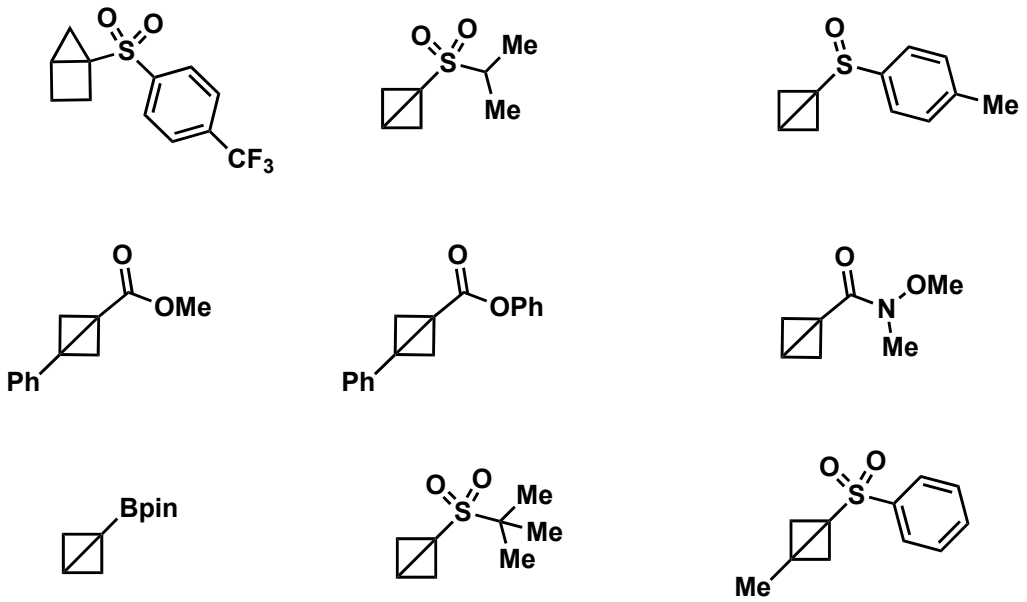
We found two major unproductive pathways compete with OSF_5-cyclobutane formation. First, we observed the formation of **S16** under nearly all conditions screened during reaction optimization. We managed to isolate and confirm the stereochemistry of this side product during the synthesis of **18** (see X-ray Crystallography section). Second, the formation of a dibrominated or diiodinated cyclobutane was observed when employing DBDMH or NIS/I_2, respectively. The formation of these side products is consistent with the known reactivity of molecular halogens in the presence of sulfonyl-containing BCBs.[10]





R_f: 0.47 (4:1 Hexanes:EtOAc), vis: UV (254 nm).
^{1}H (300 MHz, $CDCl_3$): δ = 8.05-8.00 (m, 2H), 7.31-7.25 (m, 2H), 4.75-4.64 (m, 1H), 3.89-3.81 (m, 2H), 3.28-3.20 (m, 2H).
^{19}F (282 MHz, $CDCl_3$): δ = – 101.06 (m, 3F).
^{13}C{^{1}H} (101 MHz, $CDCl_3$): δ = 168.5-165.1 (d, *J* = 258.4 Hz), 134.2-134.1 (d, *J* = 9.8 Hz), 129.64-129.59 (d, *J* = 3.2 Hz), 116.8-116.5 (d, *J* = 22.6 Hz), 65.1, 48.1, 33.1.
ATR-IR (ν_{max}): 3096, 1923, 1580, 1476, 1323, 1262, 1231, 1177, 1084, 827, 758, 687 cm^{-1}.
HRMS (*m/z*): (APCI) calc'd for $C_{10}H_9BrFO_2S$ [M-HBr] 290.9485, not found.

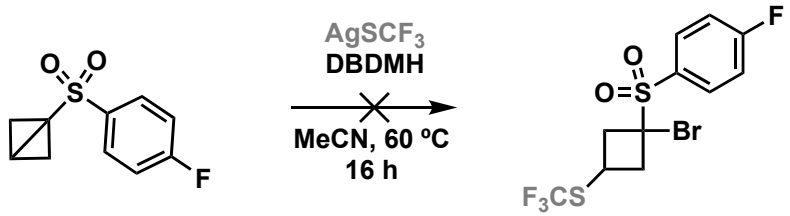
Bromo-Trifluoromethoxylation Scope Limitations:



Scheme S10. Failed substrates leading to trace or no desired product in bromo-trifluoromethoxylation reaction.

Note that, in the case of the Bpin- and amide-containing BCB substrates, a black precipitate formed immediately after the addition of the $AgOCF_3$ solution; no product formation was observed by ^{19}F NMR analysis of the crude reaction mixture. In the case of the sulfoxide-containing BCB, ^{19}F NMR analysis of the crude reaction mixture revealed an intractable mixture of products formed in low yields, which could tentatively be attributed to OCF_3-containing species. We postulate that oxidation of the sulfoxide is one likely side reaction in the presence of DBDMH. Lastly, reactions attempted with 3-substituted BCBs and alkyl-sulfonyl BCBs similarly gave rise to intractable product mixtures.

Attempted Reactions Using $AgSCF_3$:



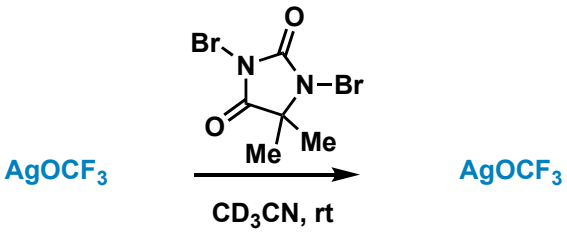
Scheme S11. Attempted bromo-trifluoromethylthiolation reaction.

Following the general procedure A, trifluoromethylthiolation of 1-((4-fluorophenyl) sulfonyl)bicyclo[1.1.0]butane was attempted using DBDMH or allyl chloride as electrophiles. Employing DBDMH resulted in trace C-SCF_3 signals detected in the crude ^{19}F NMR spectrum, but majority decomposition. Using allyl chloride resulted in no reaction – only $AgSCF_3$ was detected in the crude ^{19}F NMR spectrum and the BCB was identified by TLC.

Preliminary Mechanistic Studies:

Control Reactions:

The control reaction between $AgOCF_3$ and DBDMH revealed that no reaction occurs. In contrast, treating $AgSCF_3$ with DBDMH leads to rapid and unselective decomposition of the reagent. These deleterious side reactions are likely the reason for the low yields observed in the bromo-trifluoromethylthiolation reaction described above.



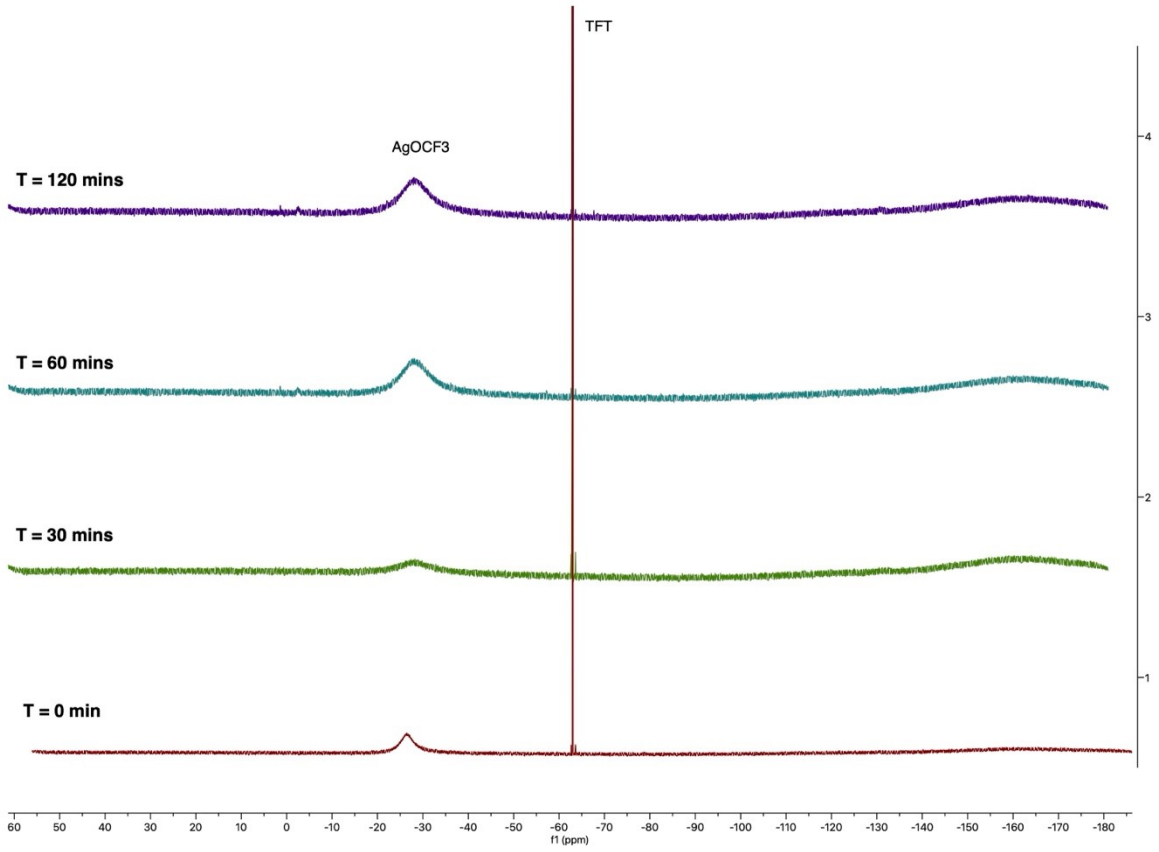
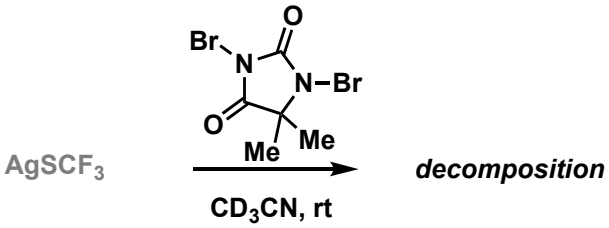


Figure S4. Tracking a mixture of $AgOCF_3$ and DBDMH (1:1) in CD_3CN over time.



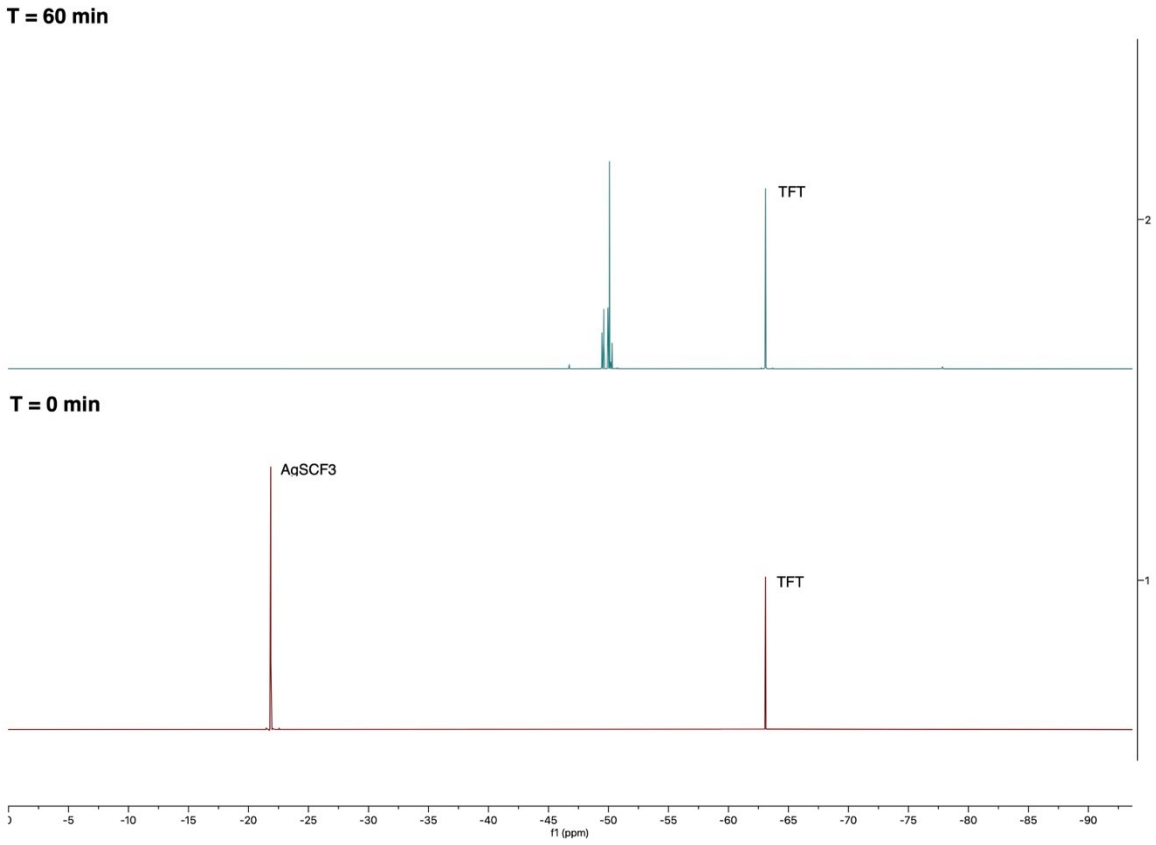


Figure S5. Decomposition of $AgSCF_3$ in the presence of DBDMH in CD_3CN.

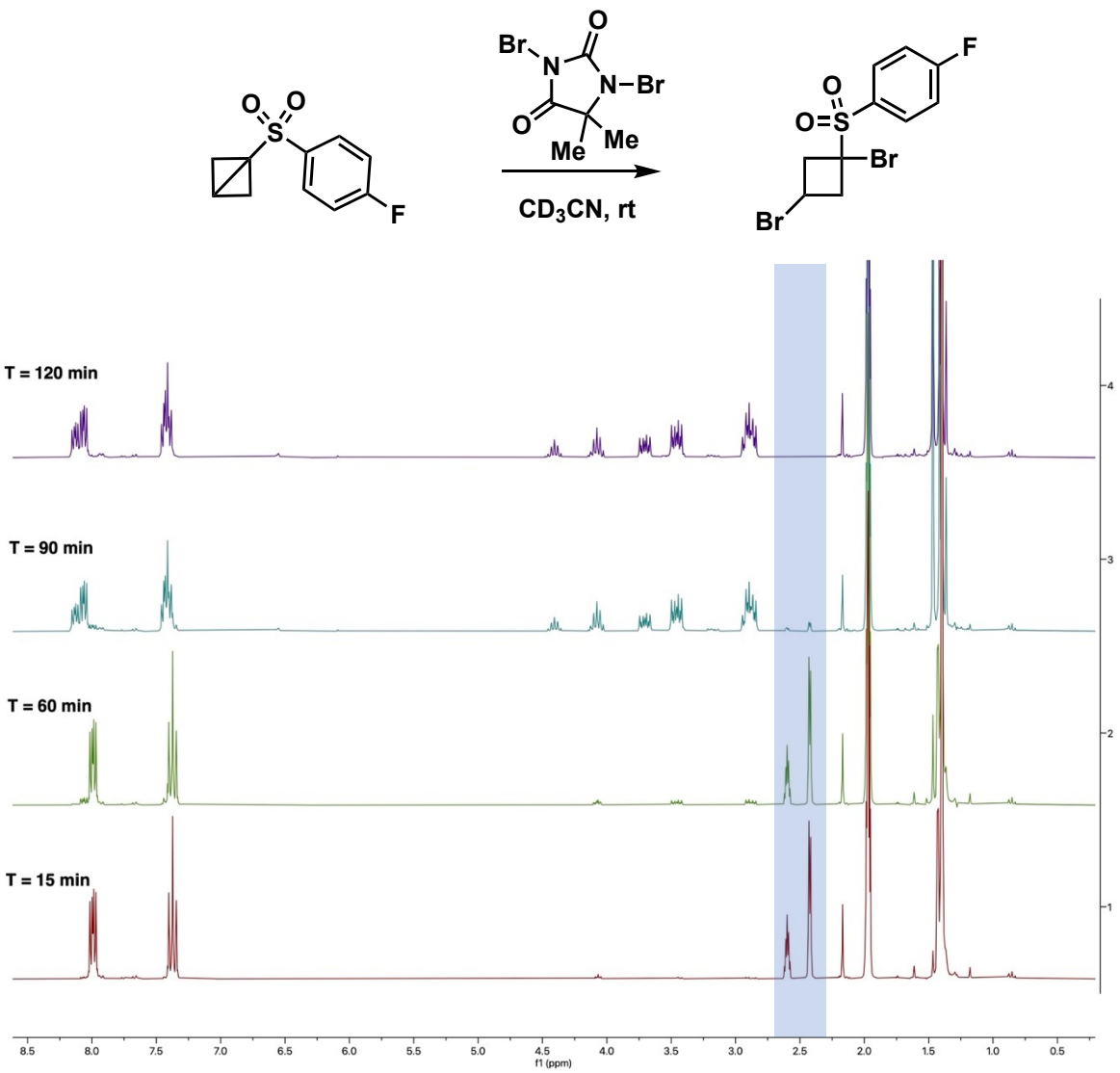


Figure S6. Tracking a mixture of BCB and DBDMH in CD_3CN over time. The blue bar indicates signals corresponding to the BCB.

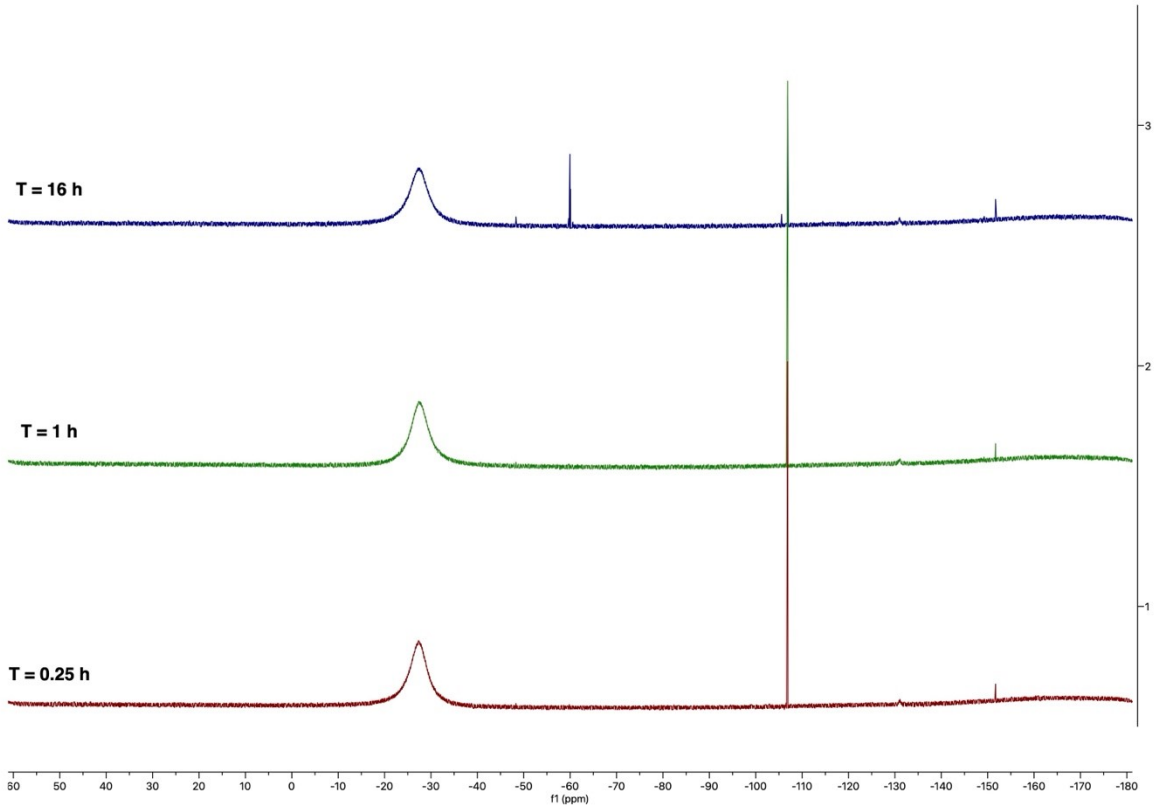
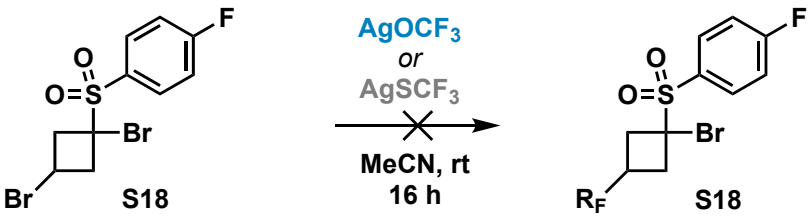


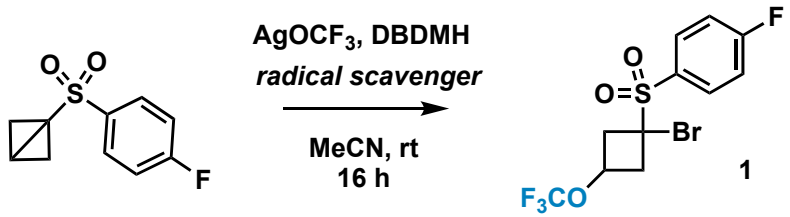
Figure S7. Tracking a mixture of BCB and $AgOCF_3$ in CD_3CN over time.



Scheme S12. Attempted fluorination of dibrominated cyclobutane.

Finally, we ruled out the possibility of the dibrominated cyclobutane **S18** acting as an intermediate in trifluoromethoxy-cyclobutane formation. Mixing **S18** with an excess of either $AgOCF_3$ or $AgSCF_3$ did not result in the formation of the desired product. In both cases the starting materials remained unreacted.

Radical Scavengers:



Scheme S13. Addition of radical scavengers to optimized reaction conditions.

The **general procedure A** was followed with the addition of 1.0 equiv. of the specified radical scavenger (or with the addition of an O_2 balloon instead of Ar). Upon reaction completion, an aliquot was taken for ^{19}F NMR yield determination. Note that the product yield decreased in the presence of TEMPO, BHT, and hydroquinone, but this alone is not sufficient evidence to indicate a radical mechanism (i.e., these reagents could be inhibiting the reaction in other ways). On the other hand, flooding the reaction mixture with O_2 gas resulted in 56% product yield and seems to be more suggestive of a polar pathway than a radical pathway.

Table S5. Effect of radical scavengers on the bromo-trifluoromethoxylation.

Entry	Additive (1.0 equiv.)	% yield 1
1	TEMPO	11
2	BHT	16
3	hydroquinone	3
4	O_2 (1 atm)	56

Additionally, the reaction was conducted open to air to investigate the tolerance of the reaction to the presence of O_2 and moisture. The yield determined by ^{19}F NMR was 40%, indicating the exclusion of moisture is important.

NMR Spectra:

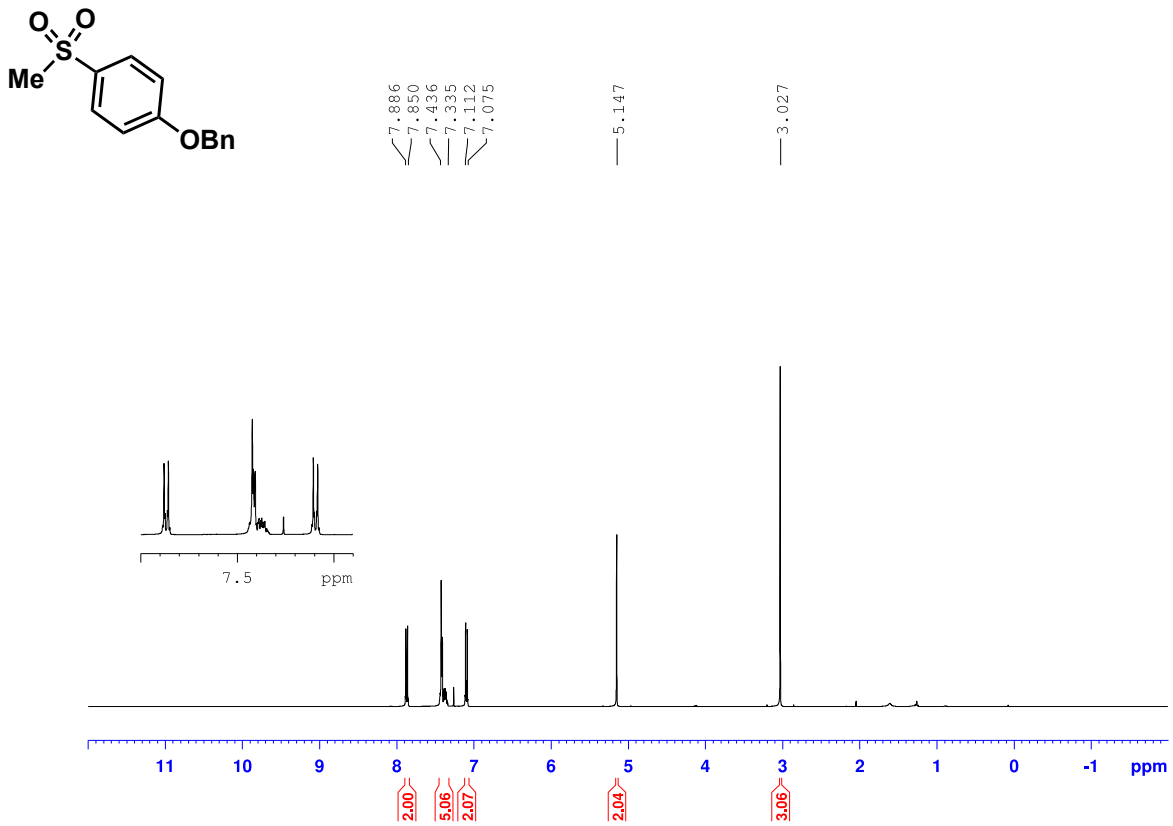


Figure S8. ^{1}H NMR spectrum of 1-(benzyloxy)-4-(methylsulfonyl)benzene (compound **S1**) in $CDCl_3$.

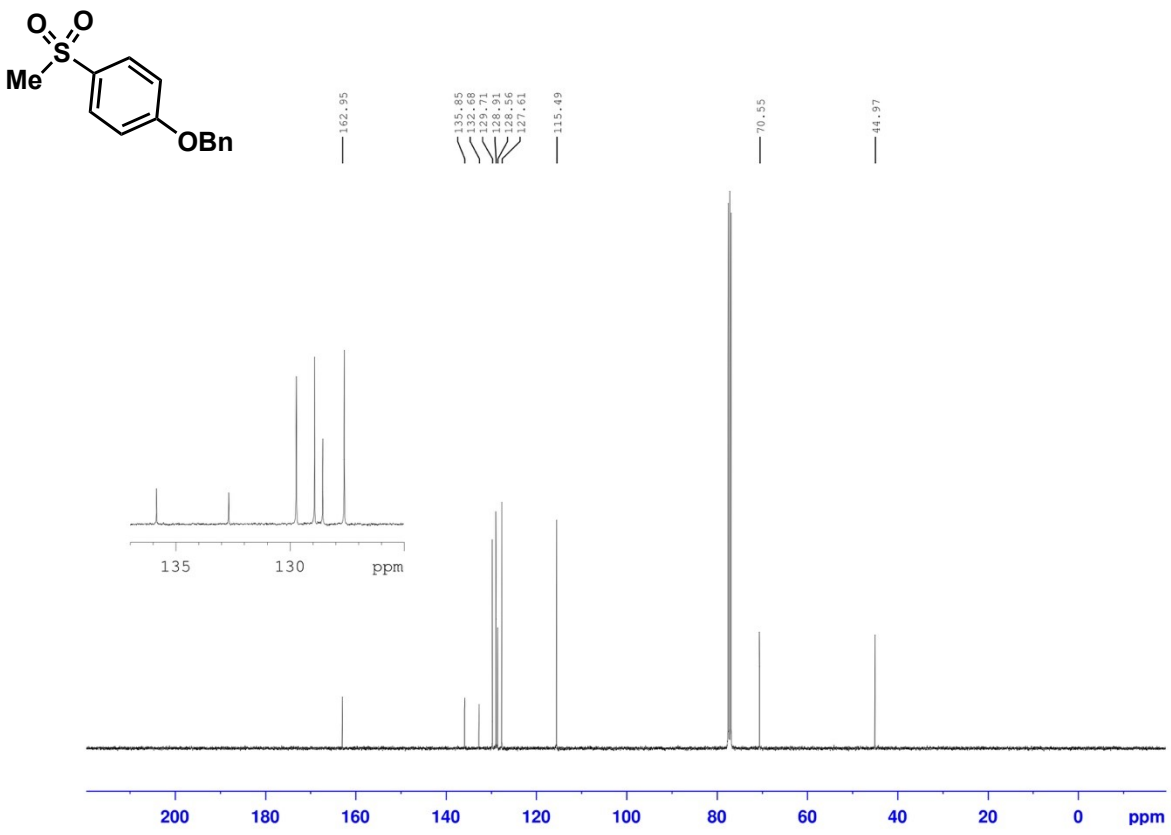


Figure S9. ^{13}C NMR spectrum of 1-(benzyloxy)-4-(methylsulfonyl)benzene (compound **S1**) in $CDCl_3$.

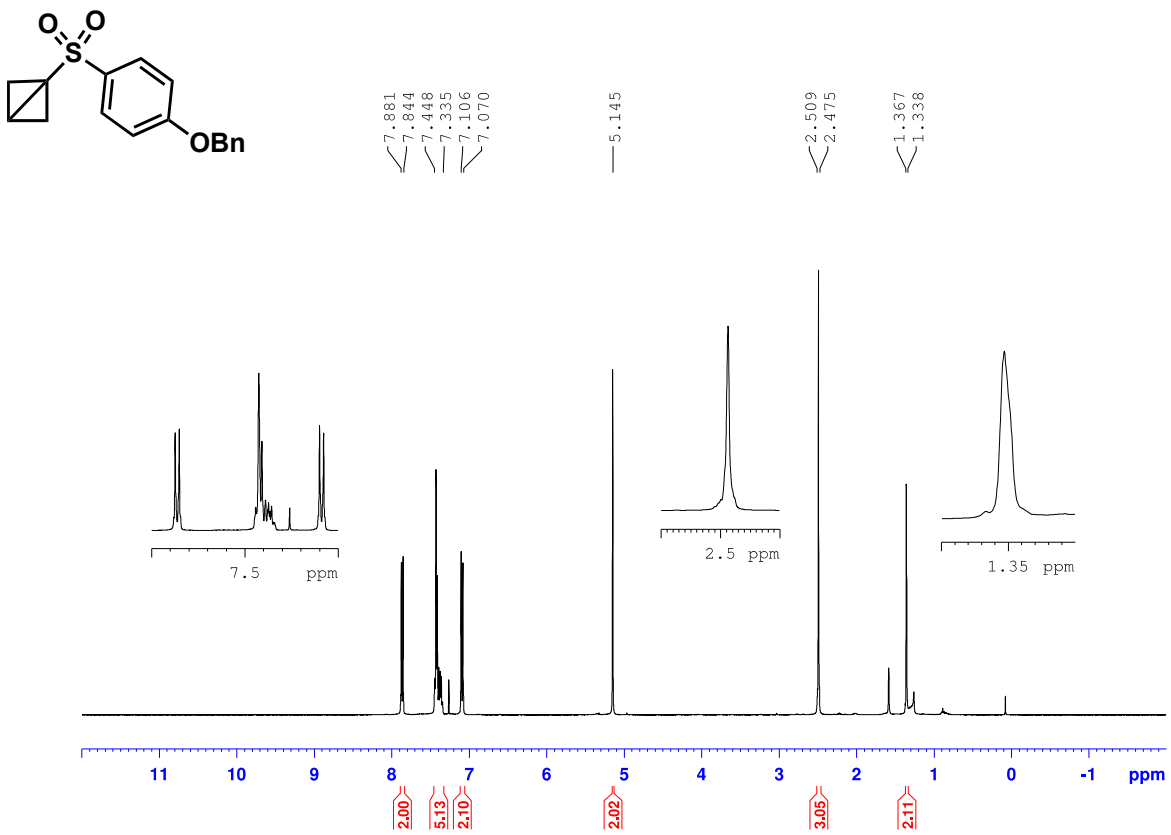


Figure S10. ^{1}H NMR spectrum of 1-((4-(benzyloxy)phenyl)sulfonyl)bicyclo[1.1.0]butane (compound **S2**) in $CDCl_3$.

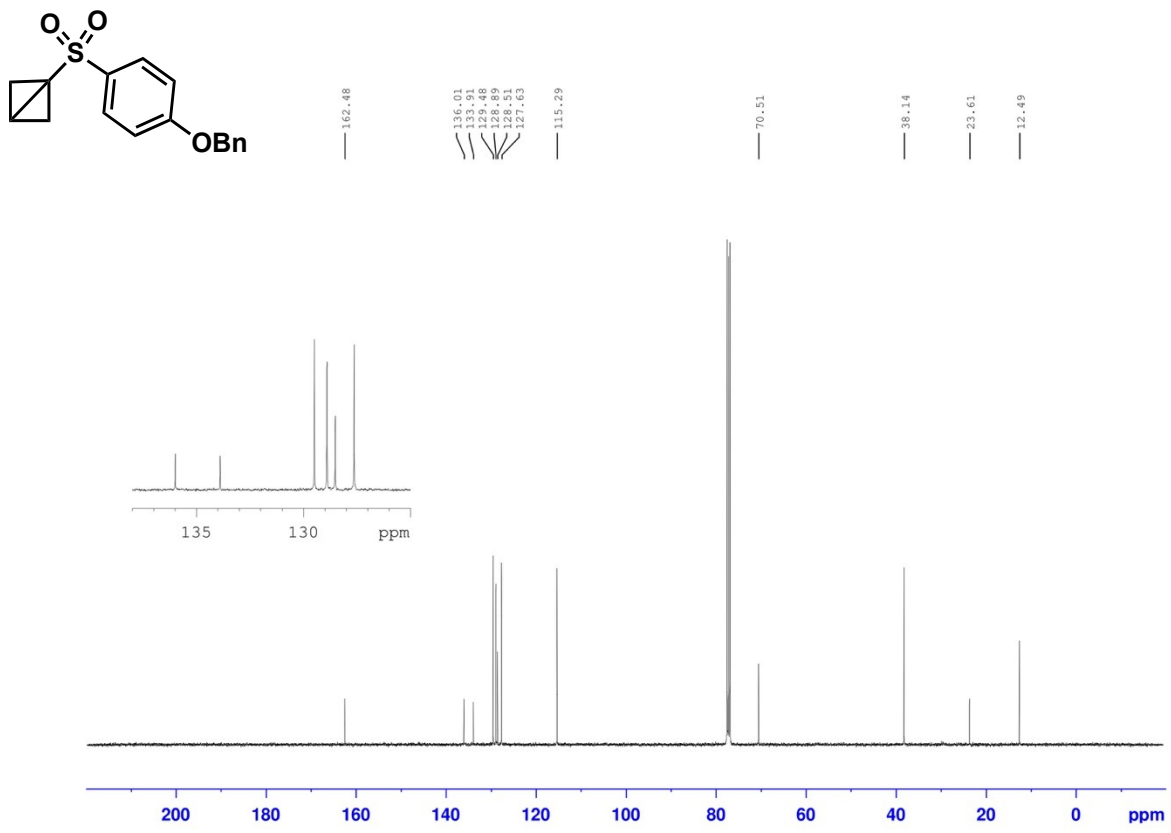


Figure S11. $^{13}C\{^{1}H\}$ NMR spectrum of 1-((4-(benzyloxy)phenyl)sulfonyl)bicyclo[1.1.0]butane (compound **S2**) in $CDCl_3$.

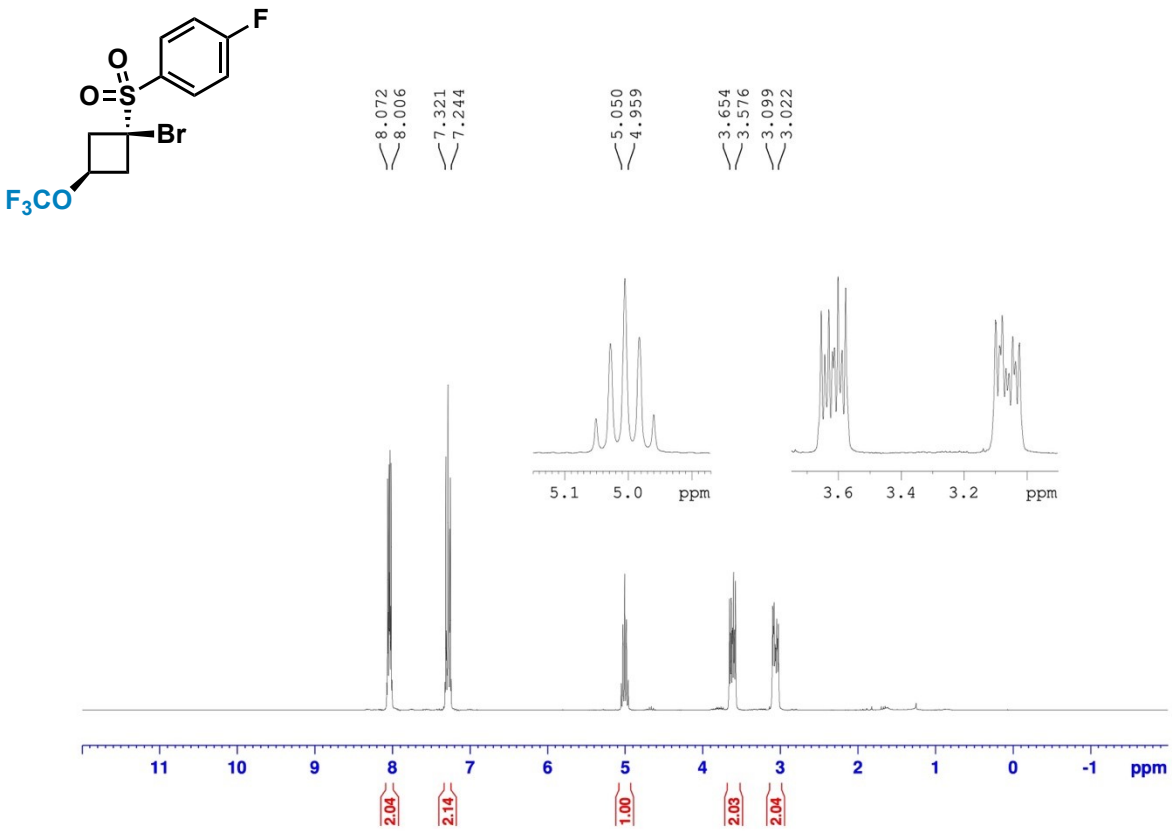


Figure S12. ^{1}H NMR spectrum of 1-((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)-4-fluorobenzene (compound **1**, *syn* isomer) in $CDCl_3$.

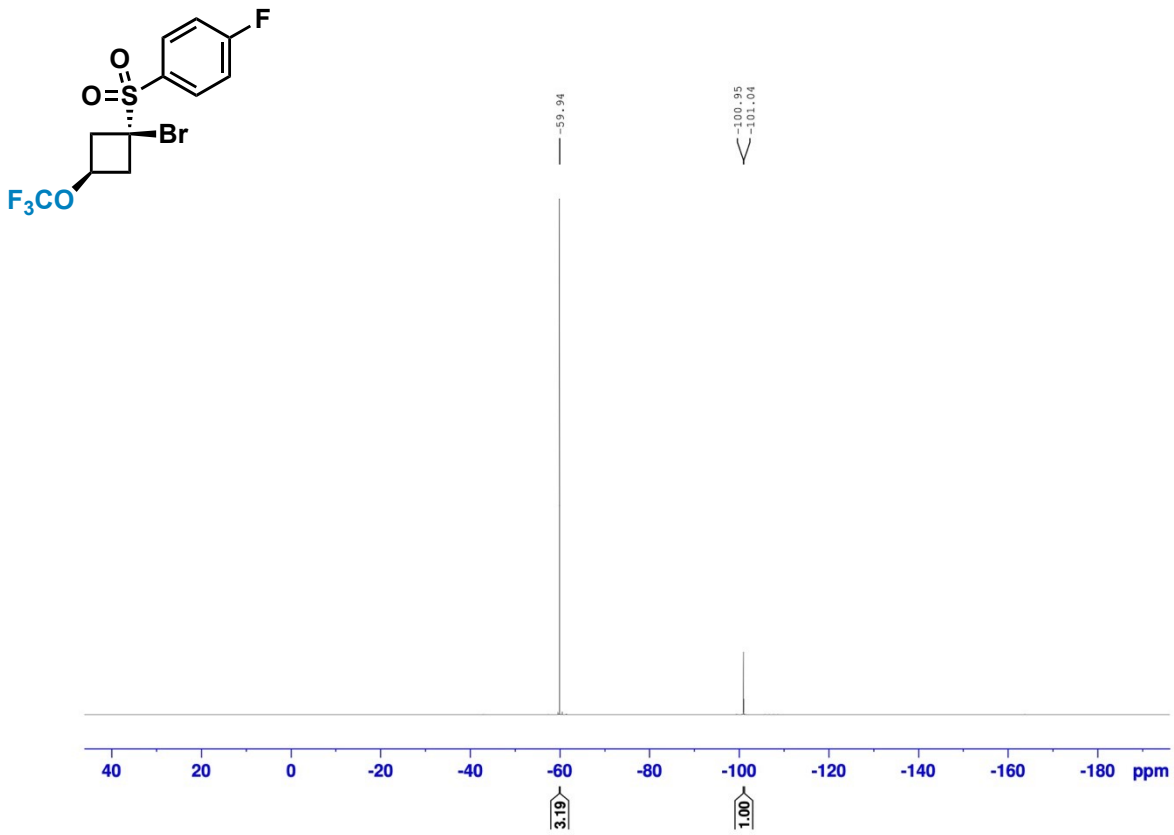


Figure S13. ^{19}F NMR spectrum of 1-((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)-4-fluorobenzene (compound **1**, *syn* isomer) in $CDCl_3$.

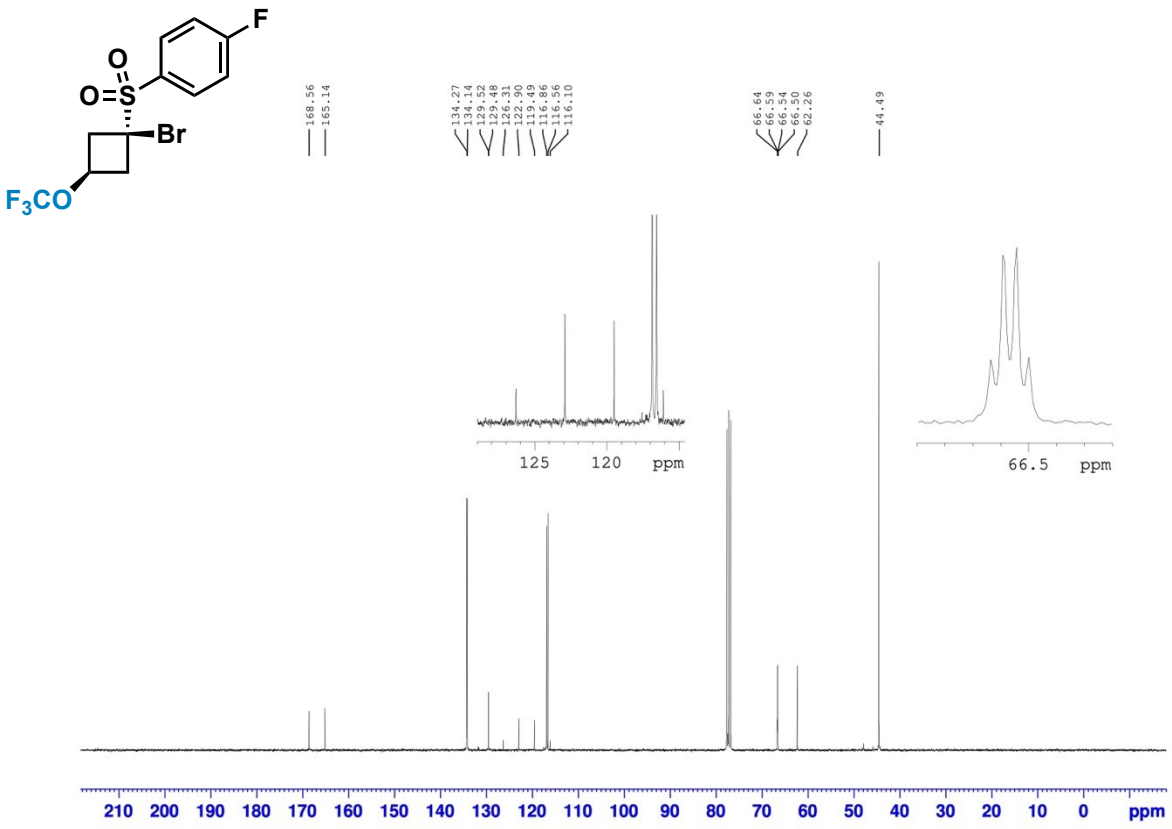


Figure S14. $^{13}C\{^{1}H\}$ NMR spectrum of 1-((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)-4-fluorobenzene (compound **1**, *syn* isomer) in $CDCl_3$.

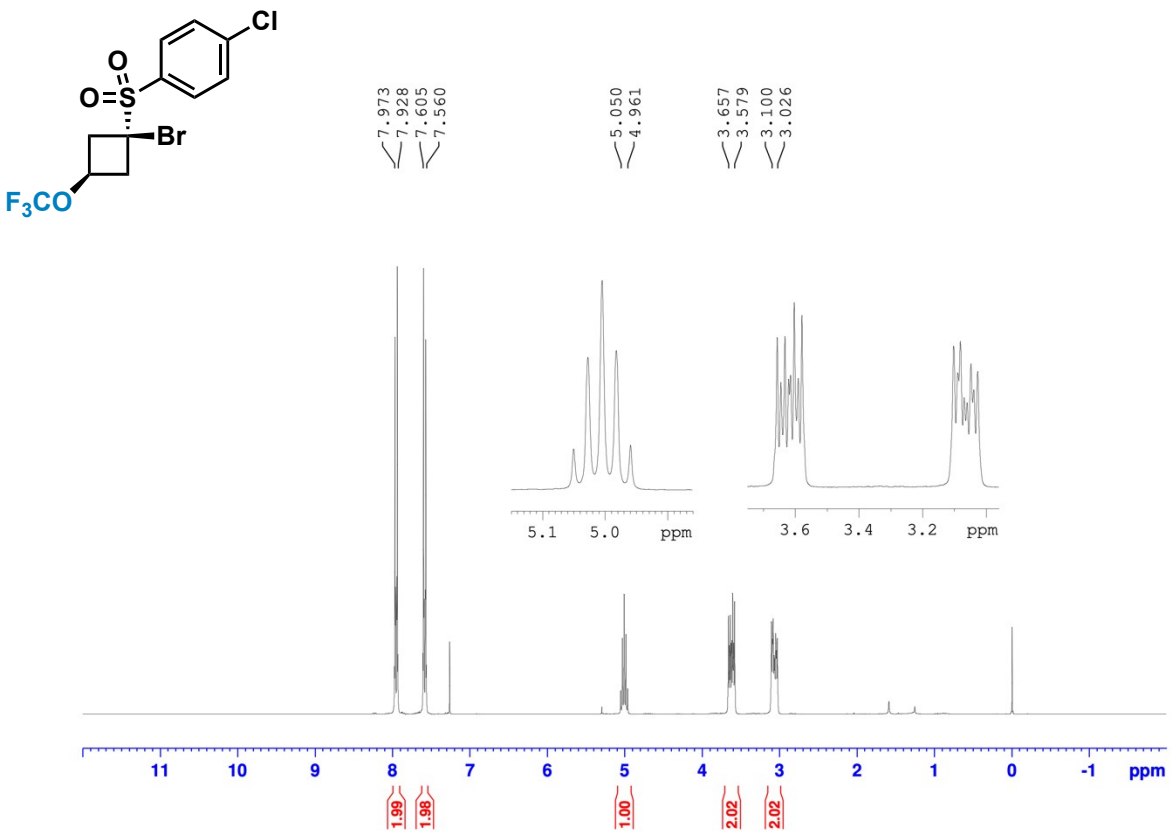


Figure S15. ^{1}H NMR spectrum of 1-(((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)-4-chlorobenzene (compound **2**, *syn* isomer) in $CDCl_3$.

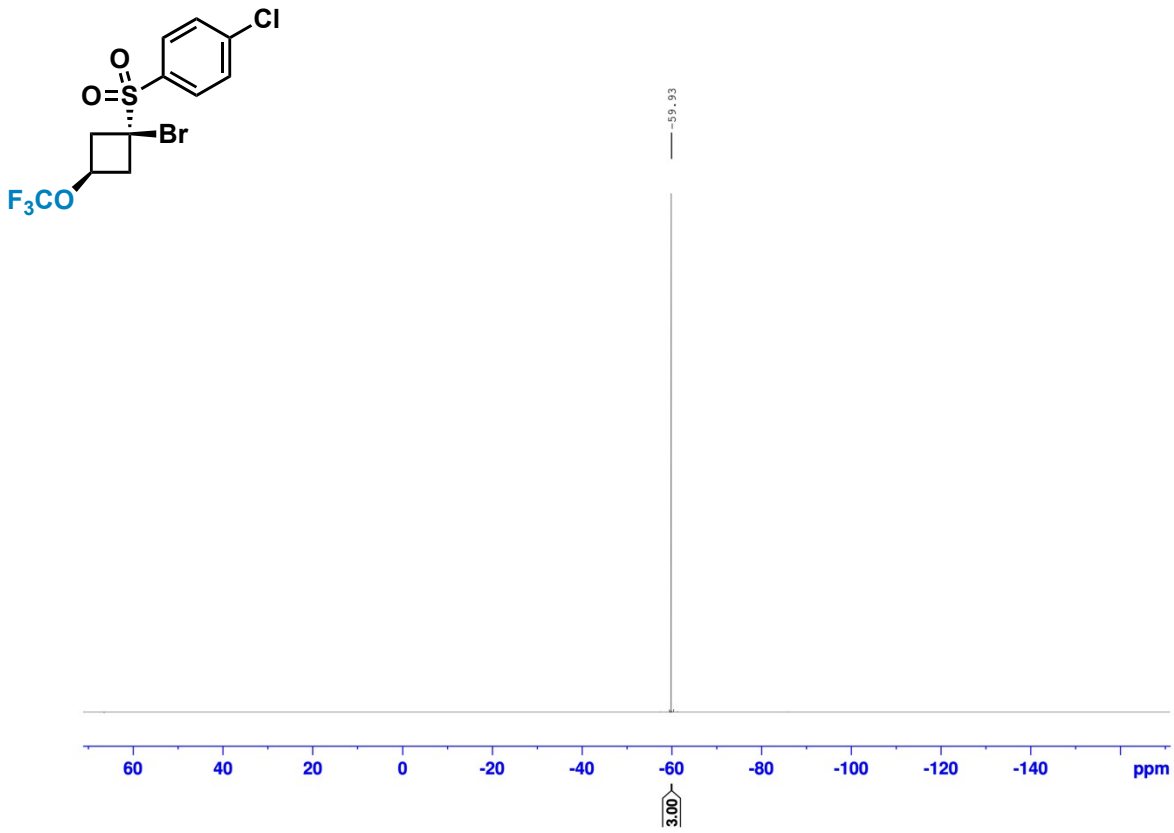


Figure S16. ^{19}F NMR spectrum of 1-(((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)-4-chlorobenzene (compound **2**, *syn* isomer) in $CDCl_3$.

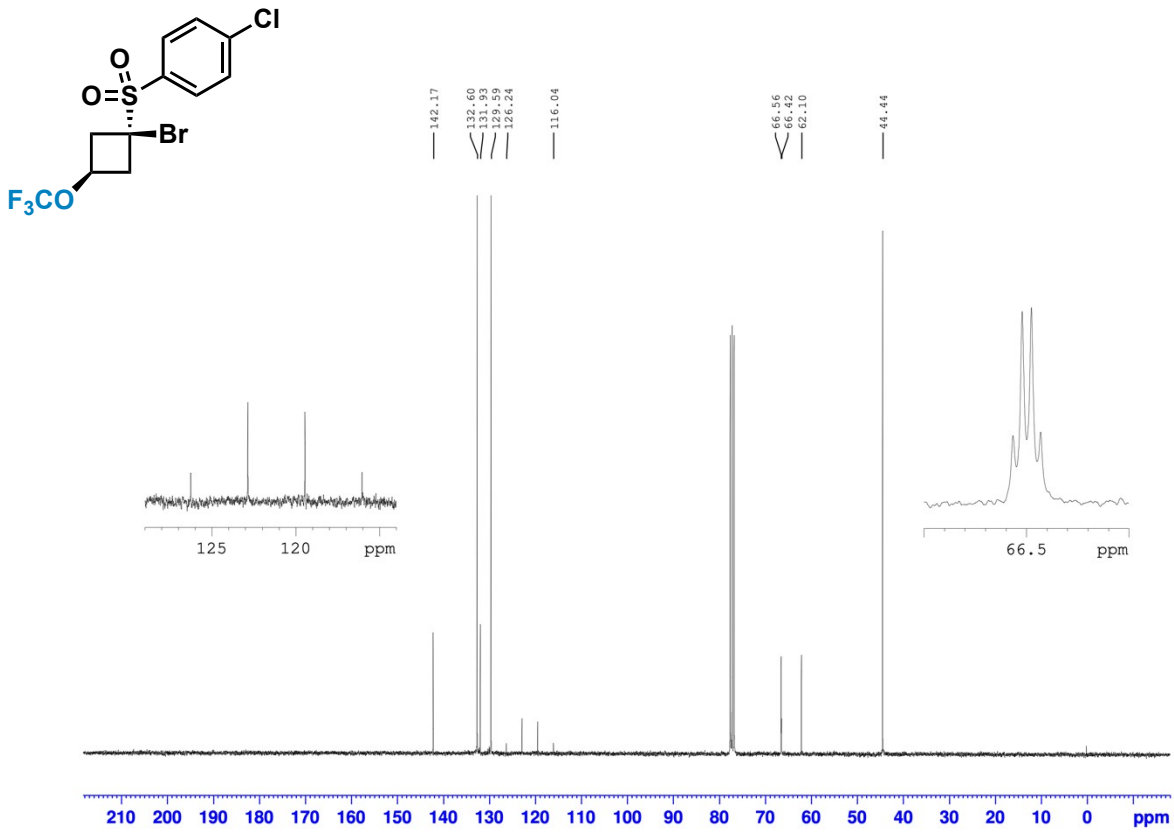


Figure S17. $^{13}C\{^{1}H\}$ NMR spectrum of 1-(((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)-4-chlorobenzene (compound **2**, *syn* isomer) in $CDCl_3$.

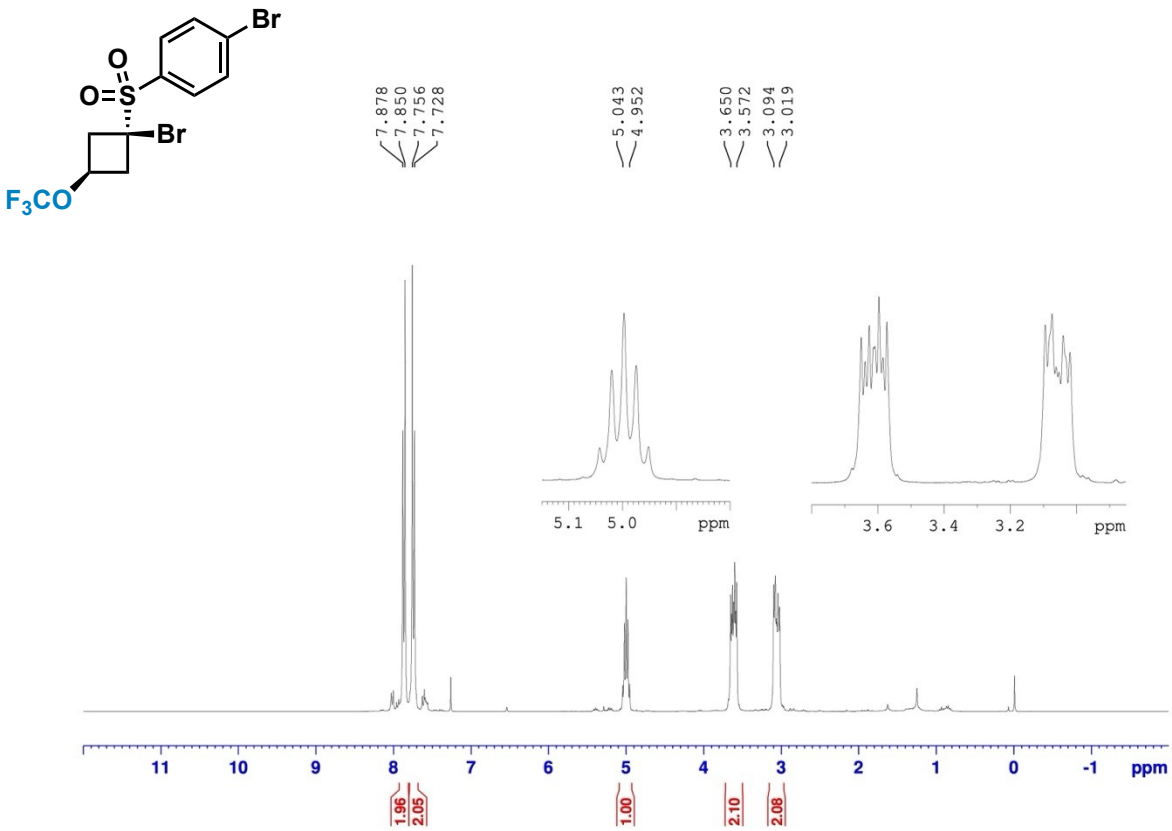


Figure S18. ^{1}H NMR spectrum of 1-bromo-4-((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)benzene (compound **3**, *syn* isomer) in $CDCl_3$.

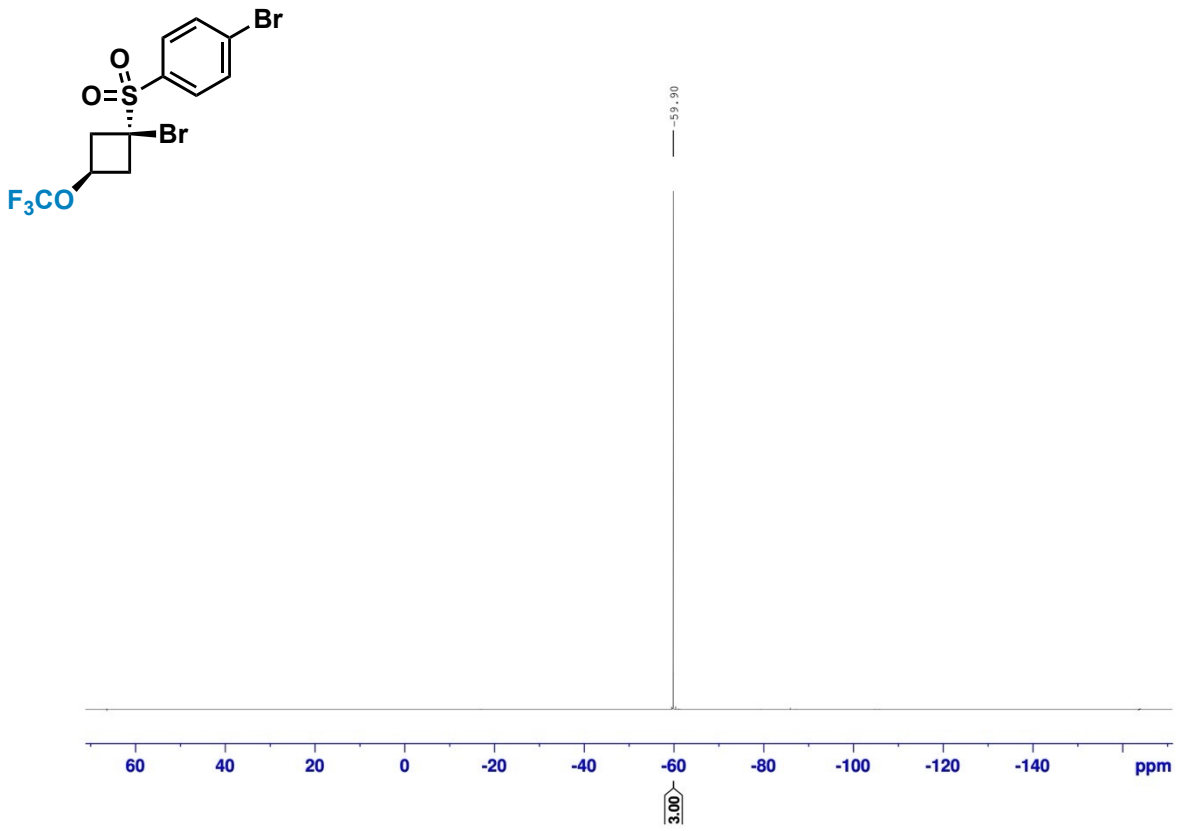


Figure S19. ^{19}F NMR spectrum of 1-bromo-4-((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)benzene (compound **3**, *syn* isomer) in $CDCl_3$.

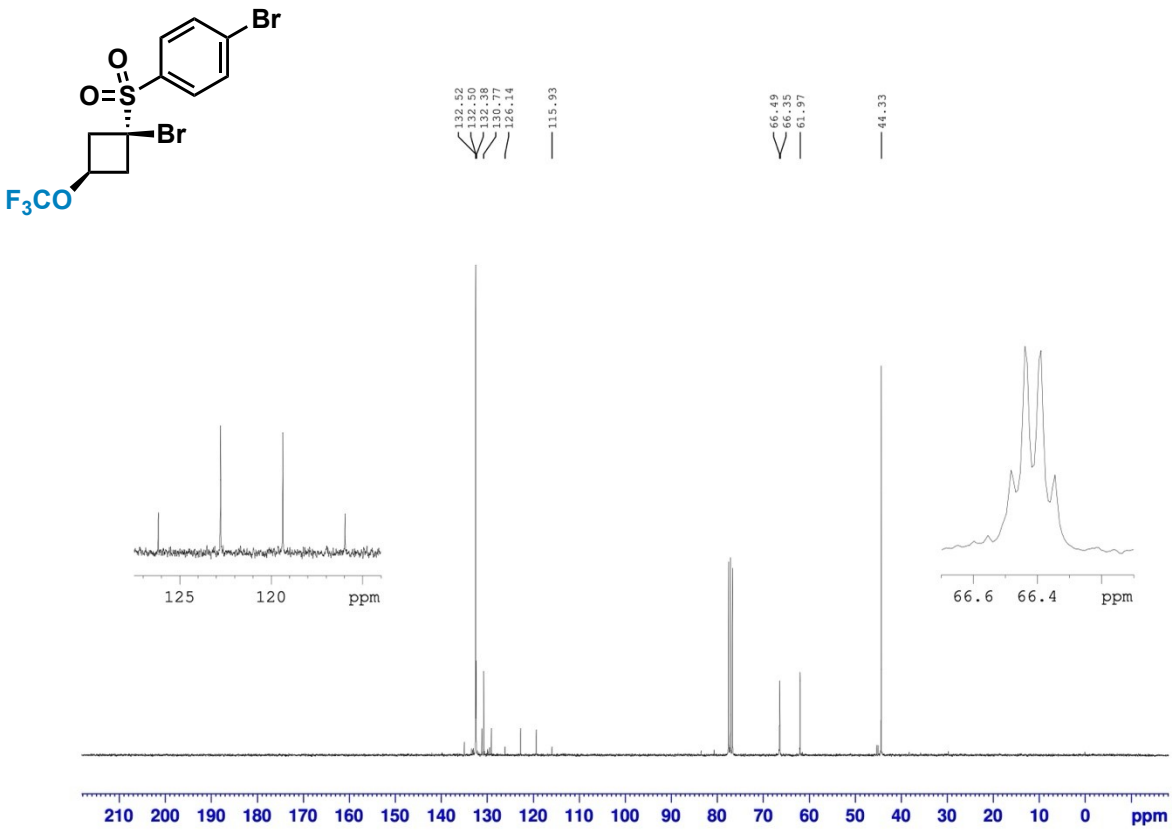


Figure S20. $^{13}C\{^{1}H\}$ NMR spectrum of 1-bromo-4-((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)-benzene (compound **3**, *syn* isomer) in $CDCl_3$.

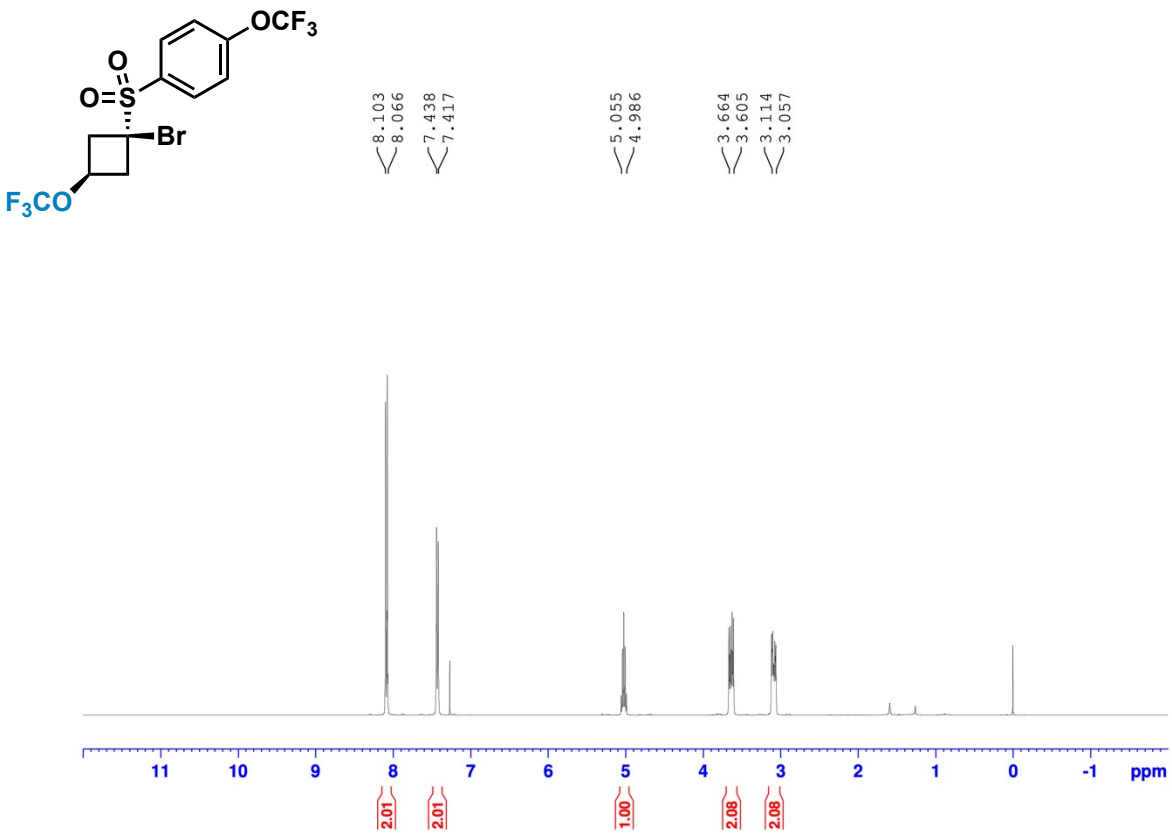


Figure S21. ^{1}H NMR spectrum of 1-((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)-4-(trifluoro methoxy)benzene (compound **4**, *syn* isomer) in $CDCl_3$.

Figure S22. ^{19}F NMR spectrum of 1-((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)-4-(trifluoromethoxy benzene (compound **4**, *syn* isomer) in $CDCl_3$.

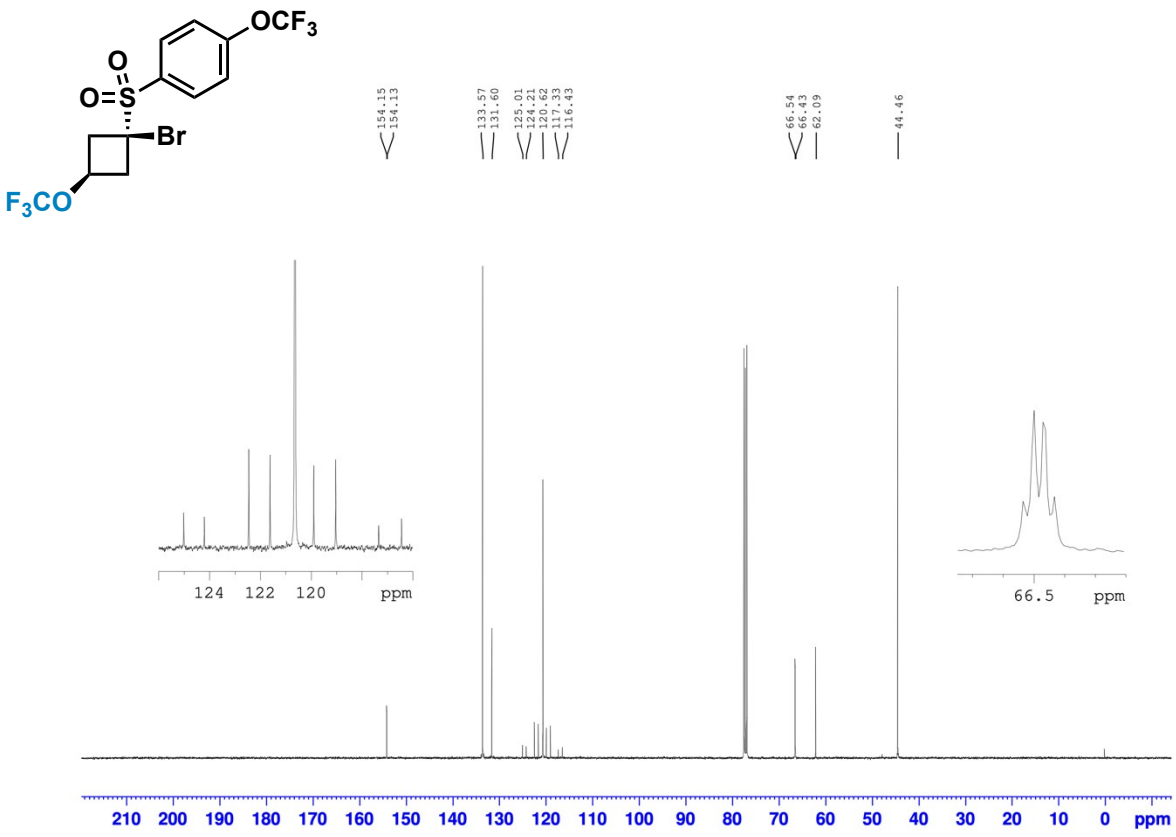


Figure S23. $^{13}C\{^{1}H\}$ NMR spectrum of 1-((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)-4(trifluoro methoxy)benzene (compound **4**, *syn* isomer) in $CDCl_3$.

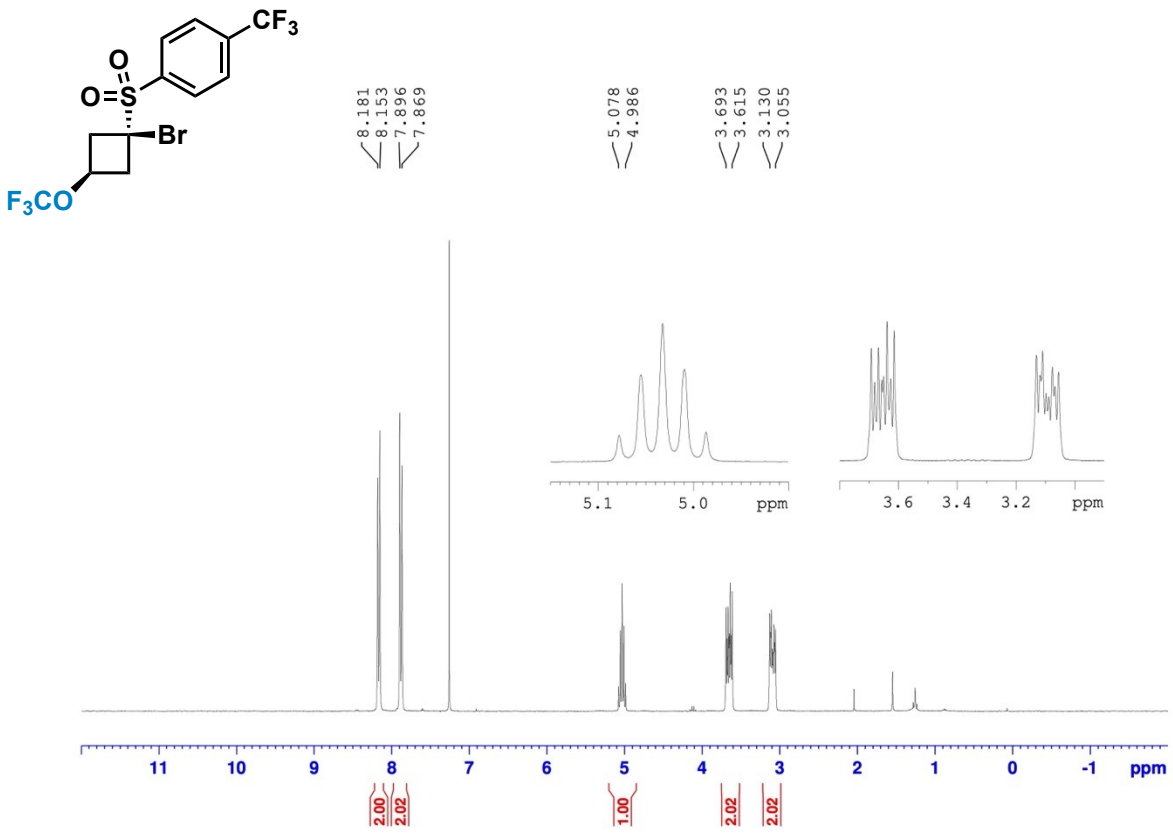


Figure S24. ^{1}H NMR spectrum of 1-((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)-4-(trifluoromethyl)benzene (compound **4'**, *syn* isomer) in $CDCl_3$.

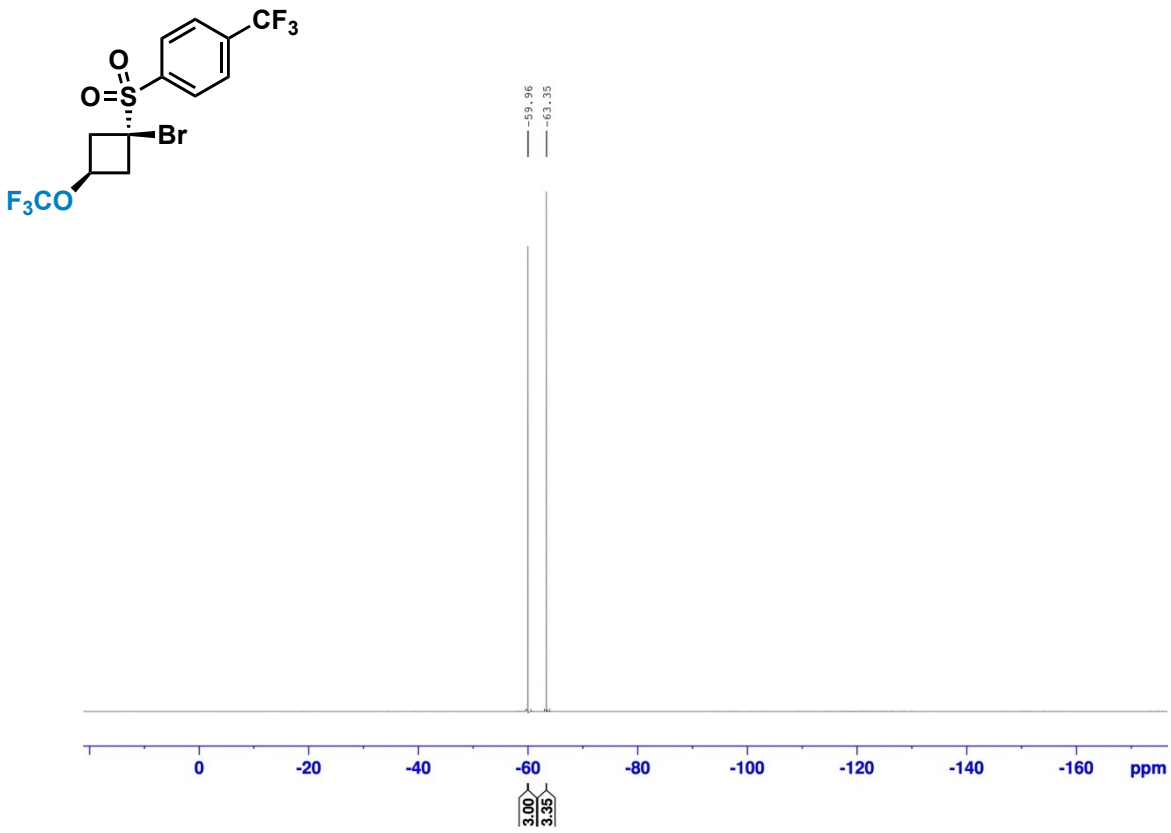


Figure S25. ^{19}F NMR spectrum of 1-((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)-4-(trifluoromethyl)benzene (compound **4'**, *syn* isomer) in $CDCl_3$.

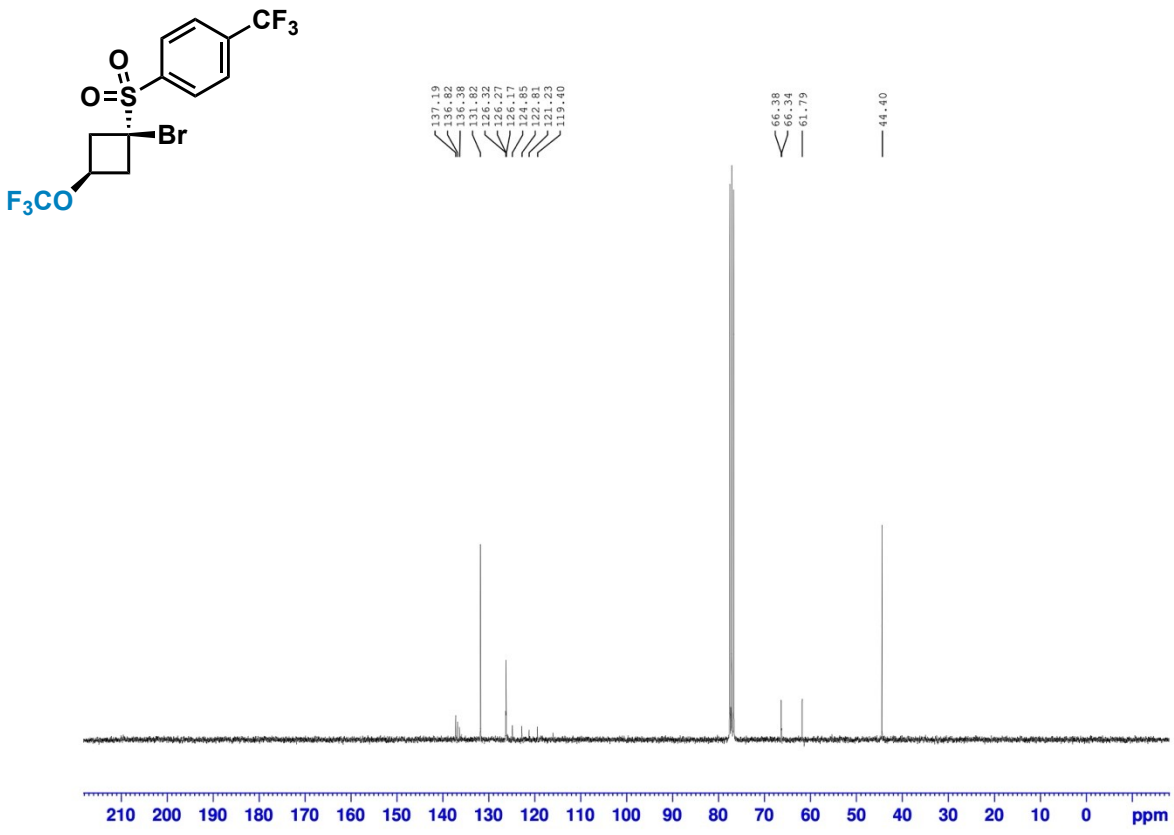


Figure S26. $^{13}C\{^{1}H\}$ NMR spectrum of 1-((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)-4-(trifluoromethyl)benzene (compound **4'**, *syn* isomer) in $CDCl_3$.

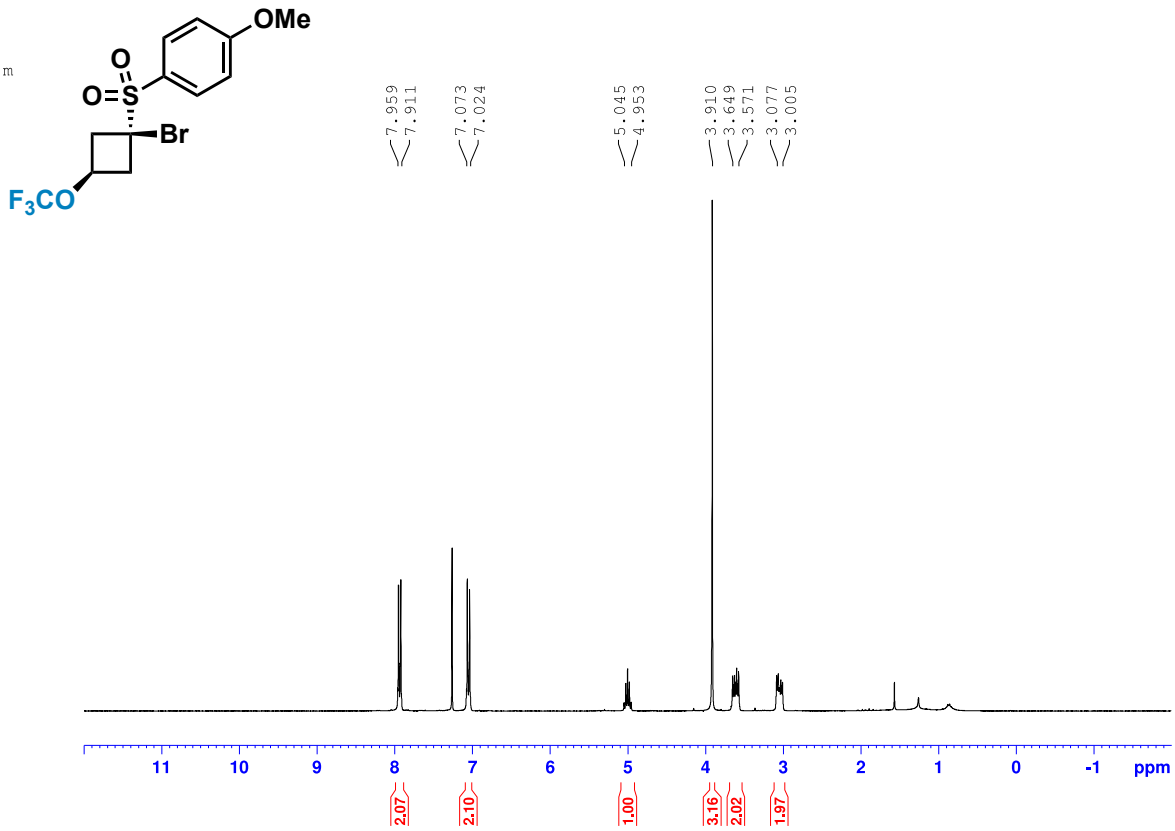


Figure S27. ^{1}H NMR spectrum of 1-((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)-4-methoxybenzene (compound **5**, *syn* isomer) in $CDCl_3$.

Figure S28. ^{19}F NMR spectrum of 1-((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)-4methoxybenzene (compound **5**, *syn* isomer) in $CDCl_3$.

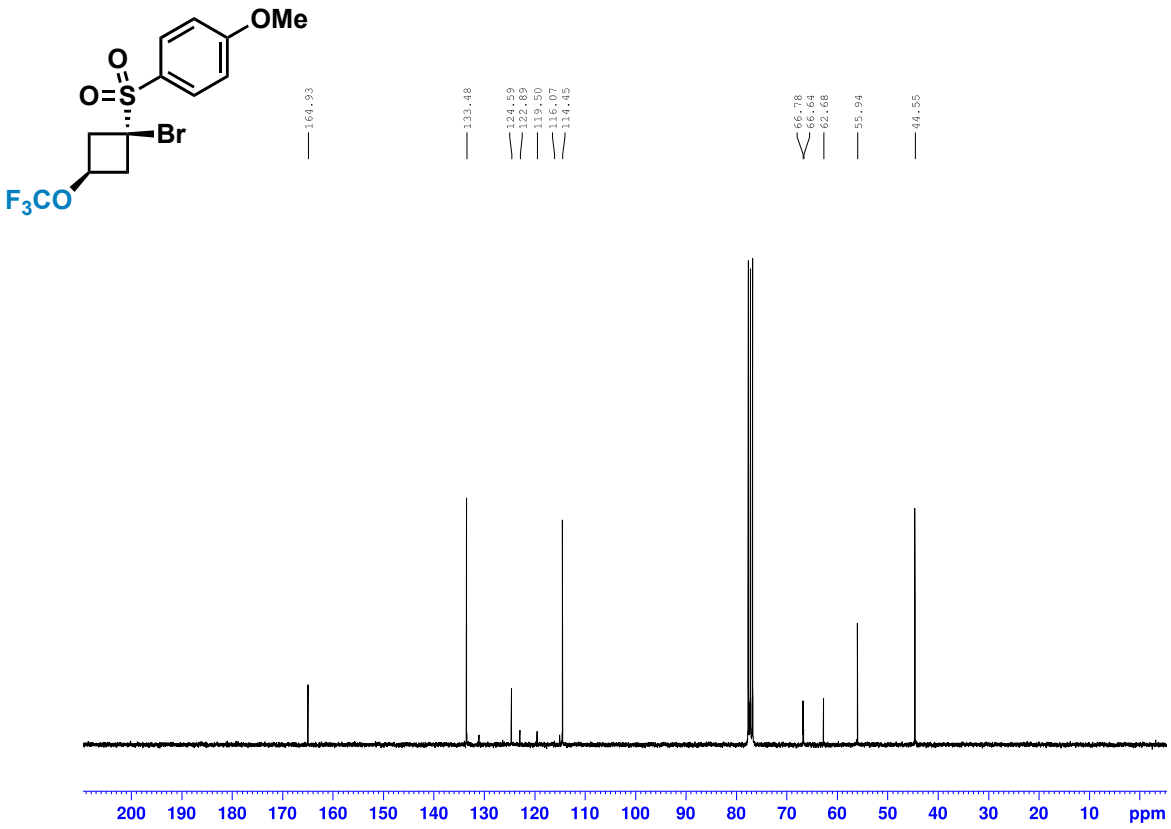


Figure S29. $^{13}C\{^{1}H\}$ NMR spectrum of 1-((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)-4-methoxybenzene (compound **5**, *syn* isomer) in $CDCl_3$.

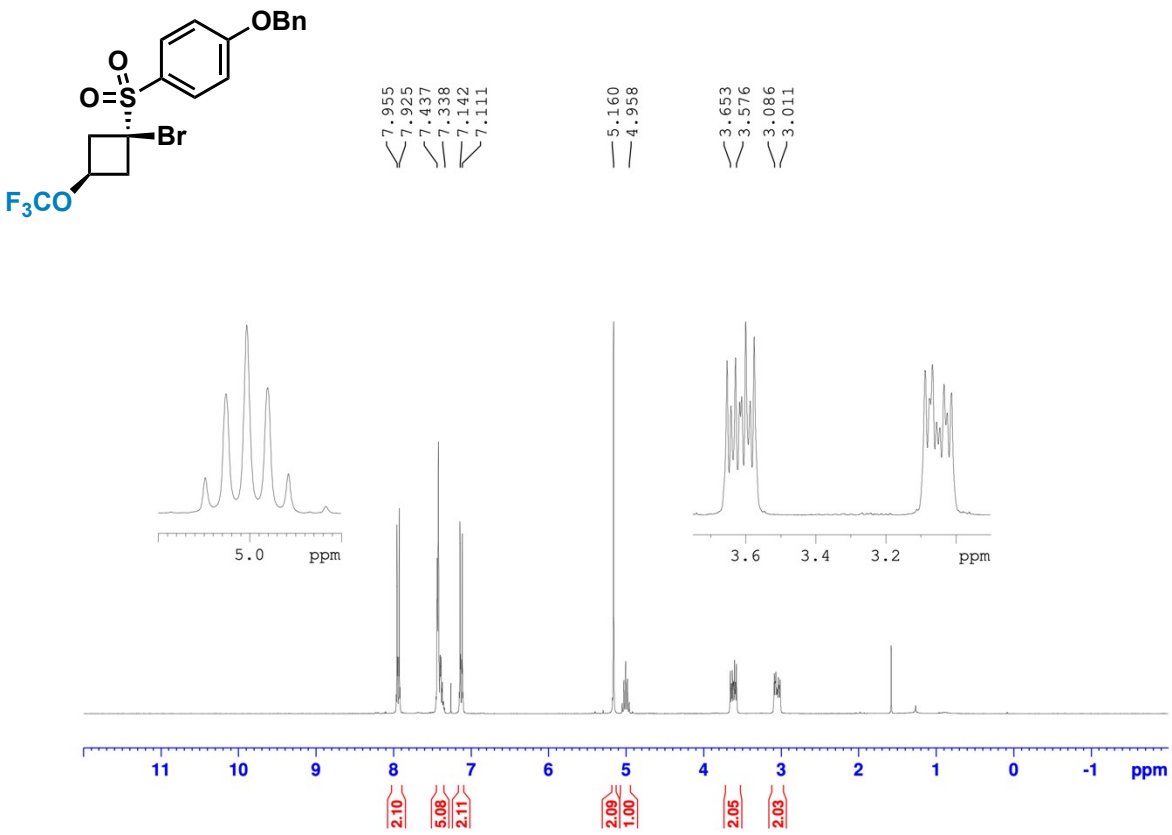


Figure S30. ^{1}H NMR spectrum of 1-(benzyloxy)-4-((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl) benzene (compound **6**, *syn* isomer) in $CDCl_3$.

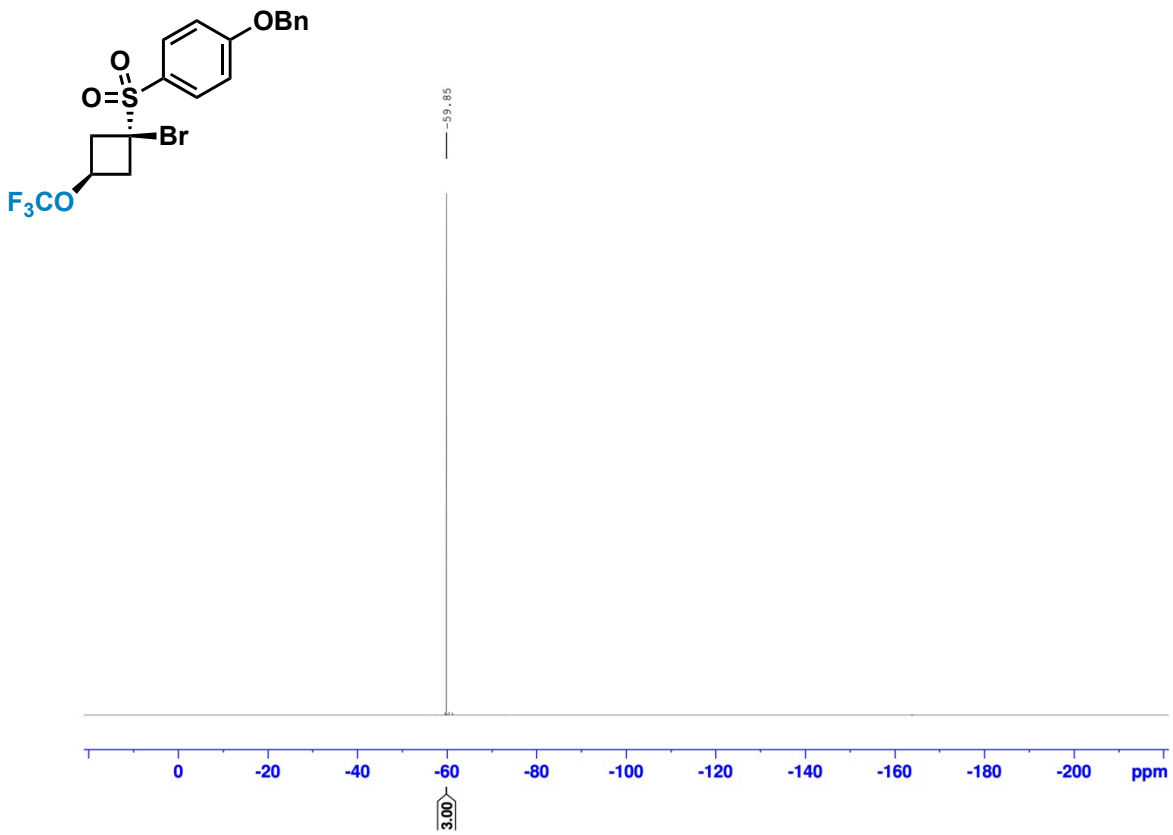


Figure S31. ^{19}F NMR spectrum of 1-(benzyloxy)-4-((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl) benzene (compound **6**, *syn* isomer) in $CDCl_3$.

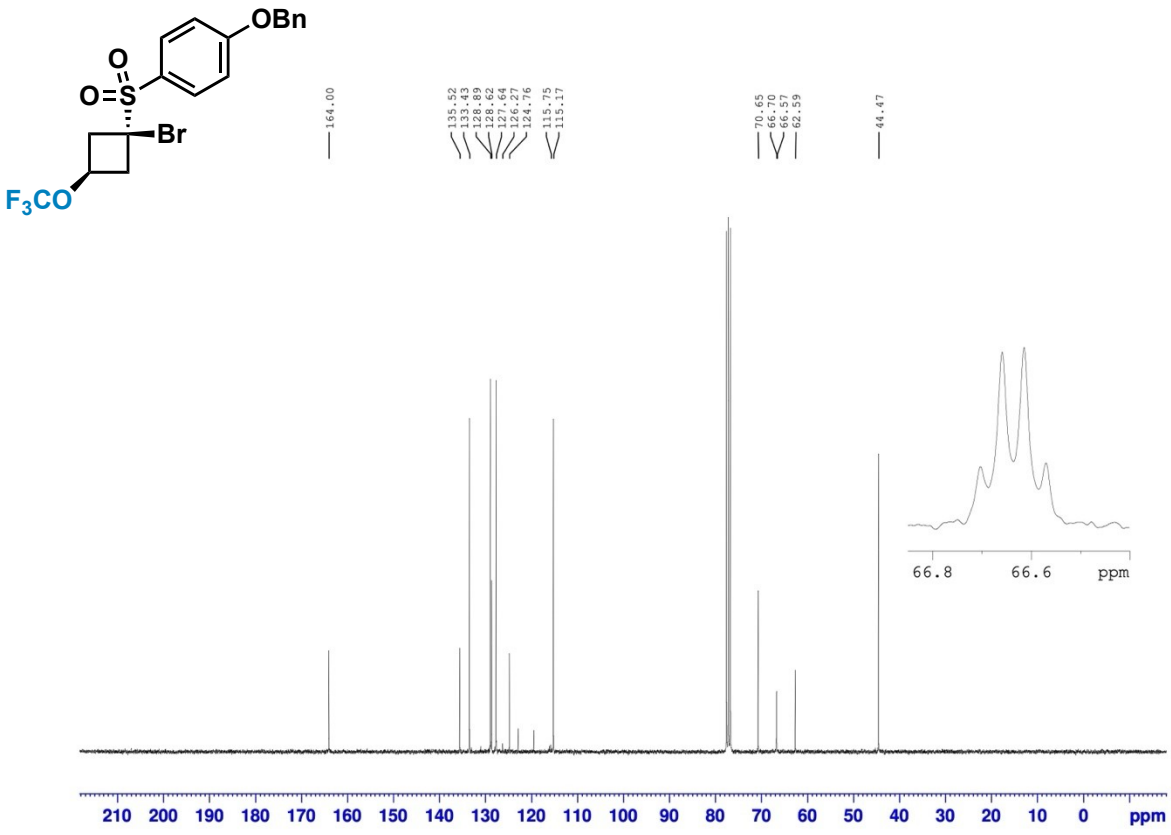


Figure S32. $^{13}C\{^{1}H\}$ NMR spectrum of 1-(benzyloxy)-4-((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl) benzene (compound **6**, *syn* isomer) in $CDCl_3$.

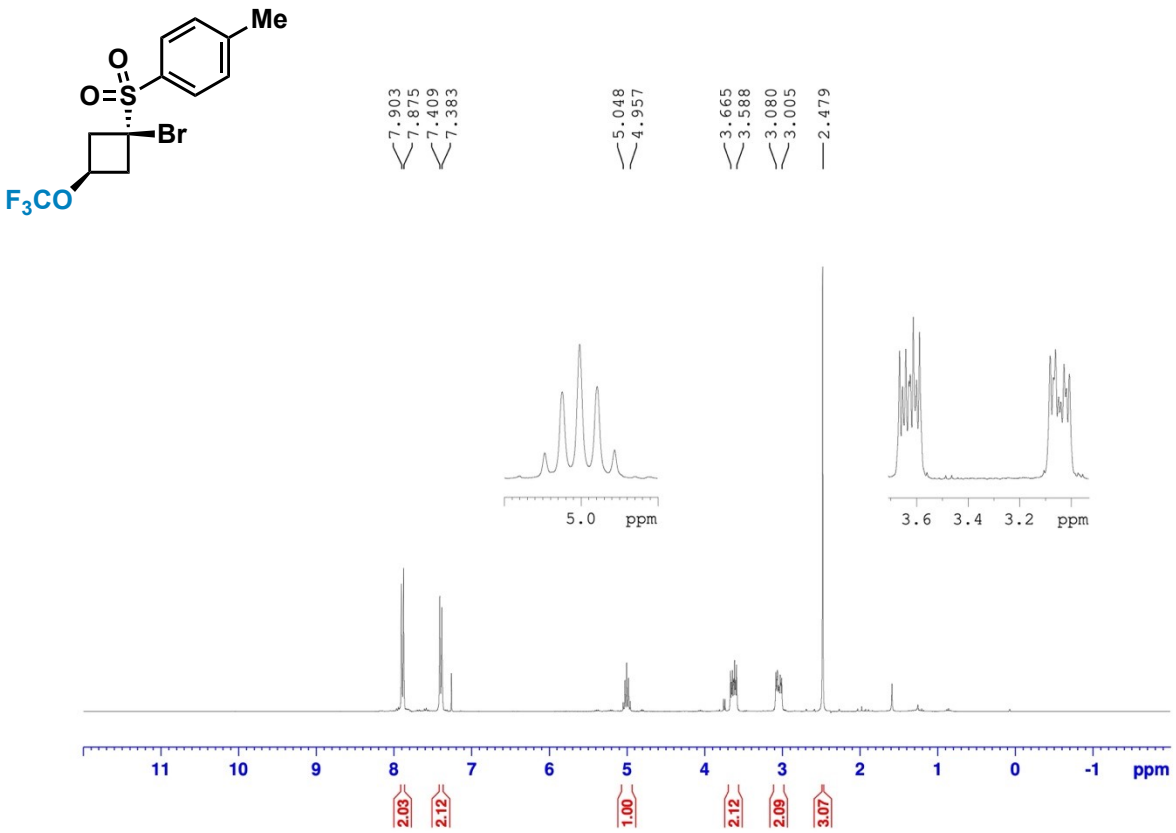


Figure S33. ^{1}H NMR spectrum of 1-((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)-4-methylbenzene (compound **7**, *syn* isomer) in $CDCl_3$.

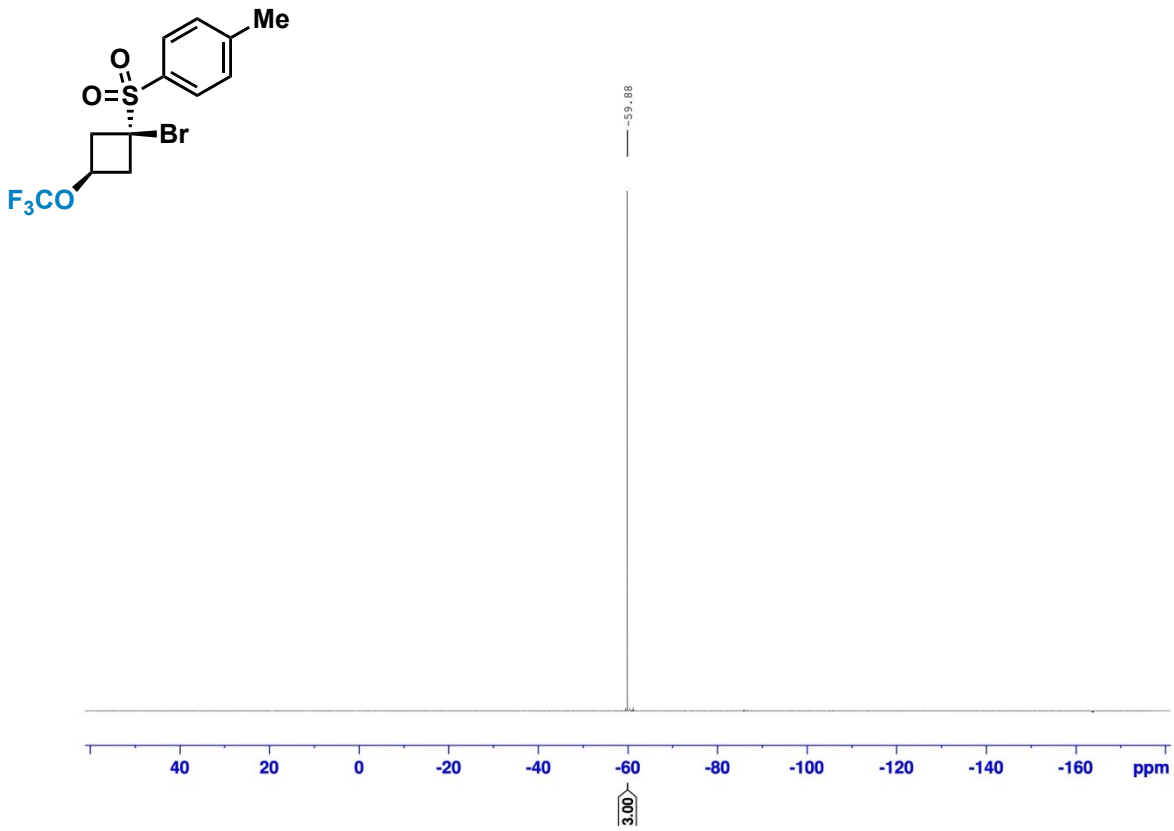


Figure S34. ^{19}F NMR spectrum of 1-((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)-4-methylbenzene (compound **7**, *syn* isomer) in $CDCl_3$.

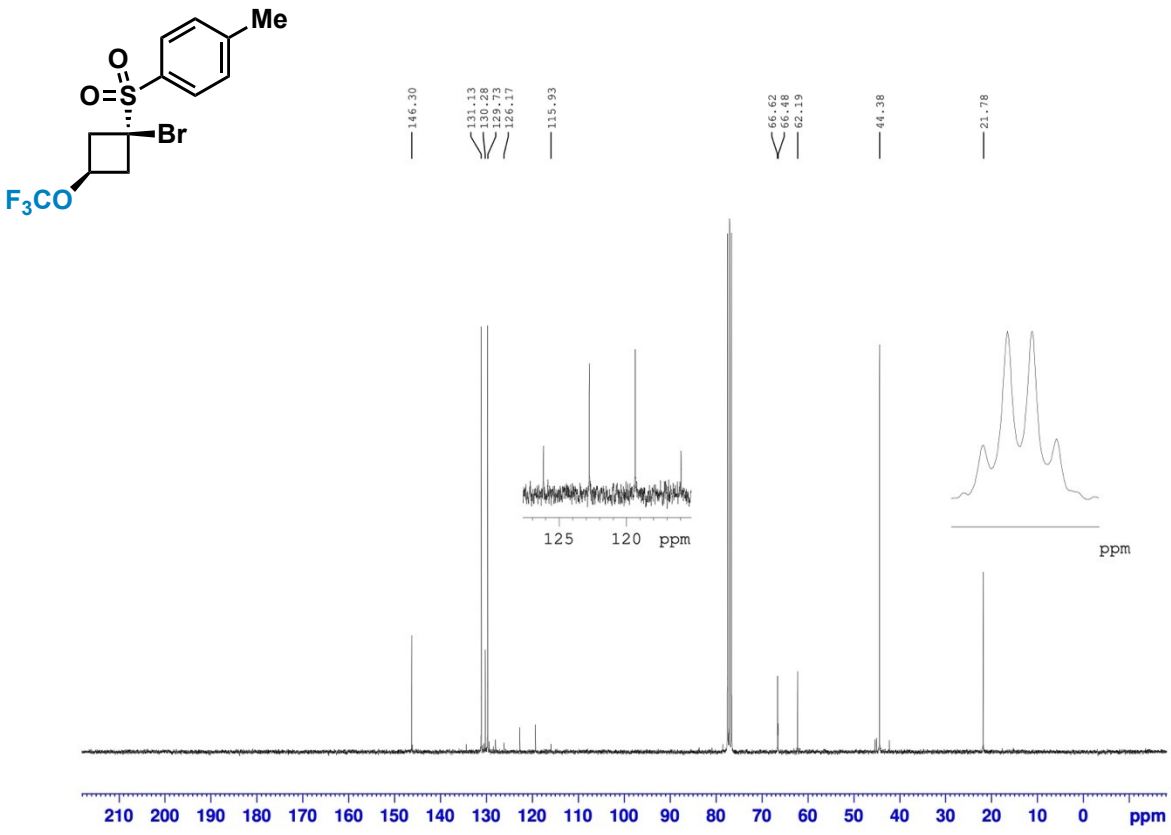


Figure S35. $^{13}C\{^{1}H\}$ NMR spectrum of 1-((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)-4-methylbenzene (compound **7**, *syn* isomer) in $CDCl_3$.

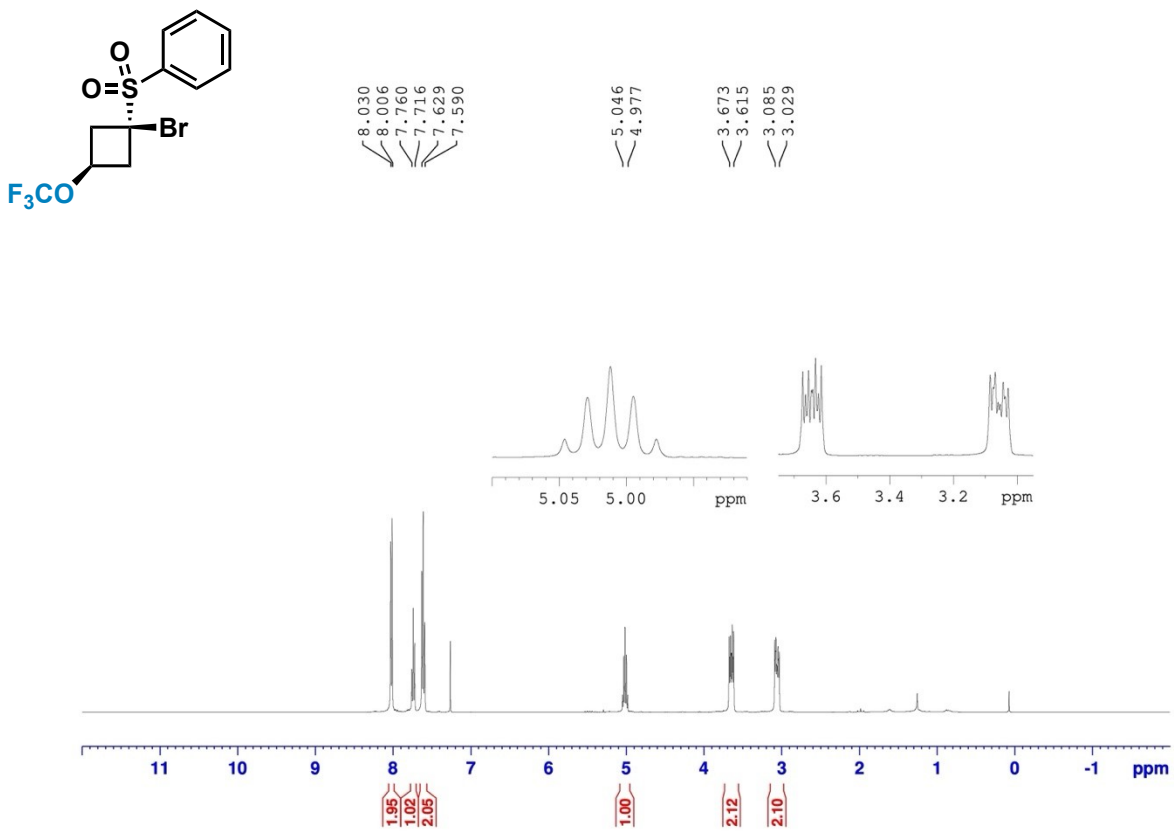


Figure S36. ^{1}H NMR spectrum of ((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)benzene (compound **8**, *syn* isomer) in $CDCl_3$.

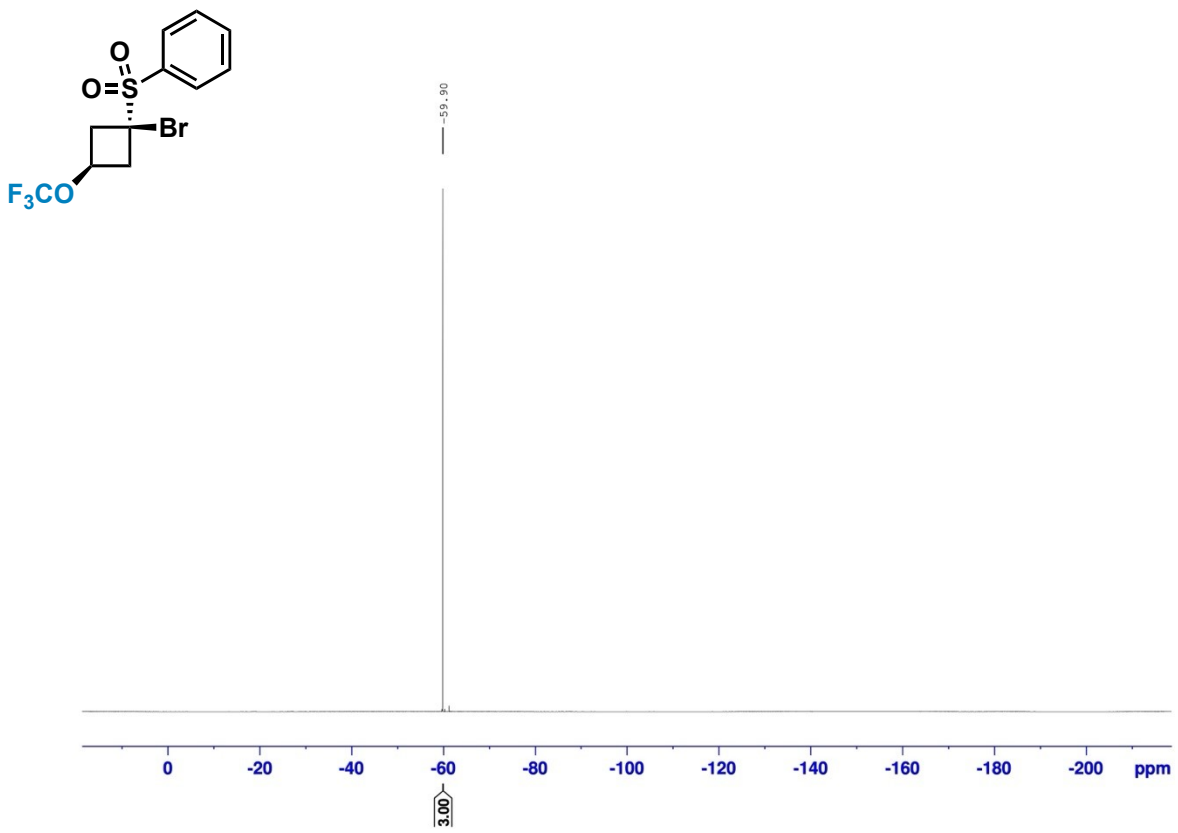


Figure S37. ^{19}F NMR spectrum of ((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)benzene (compound **8**, *syn* isomer) in $CDCl_3$.

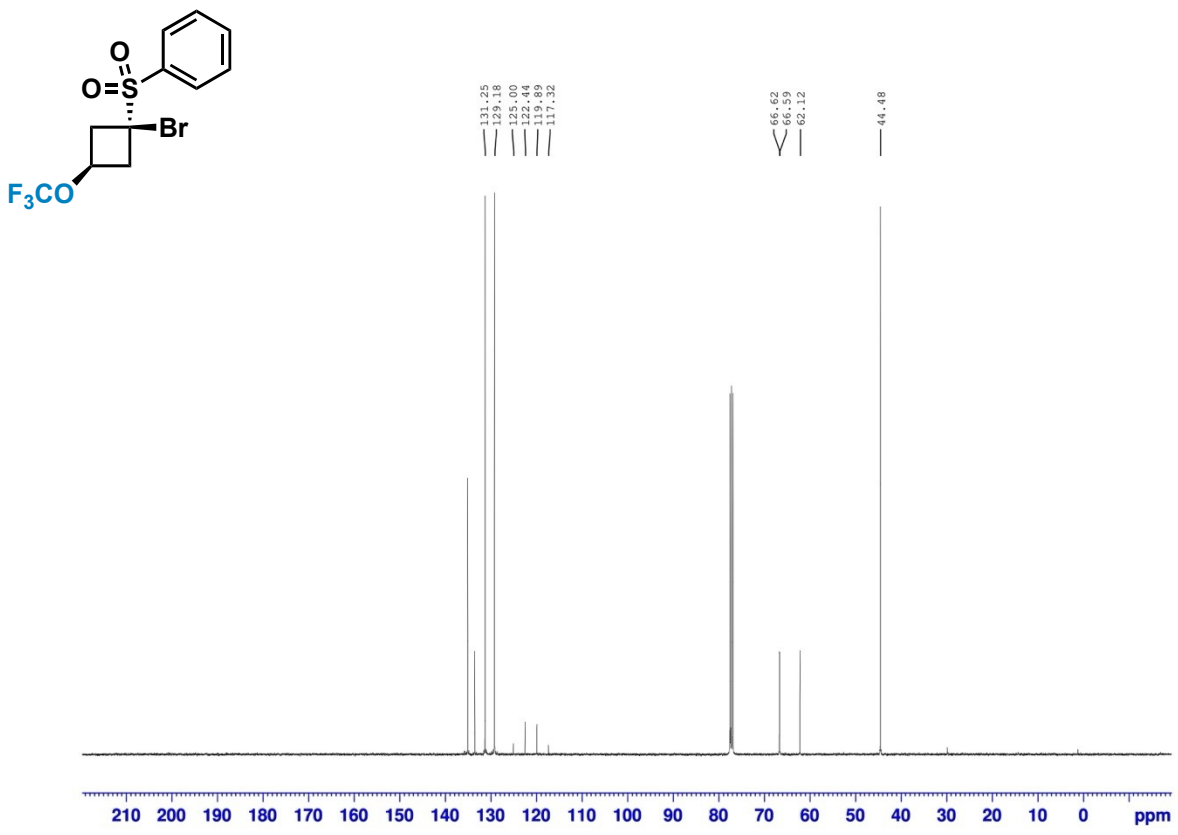


Figure S38. $^{13}C\{^{1}H\}$ NMR spectrum of ((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)benzene (compound **8**, *syn* isomer) in $CDCl_3$.

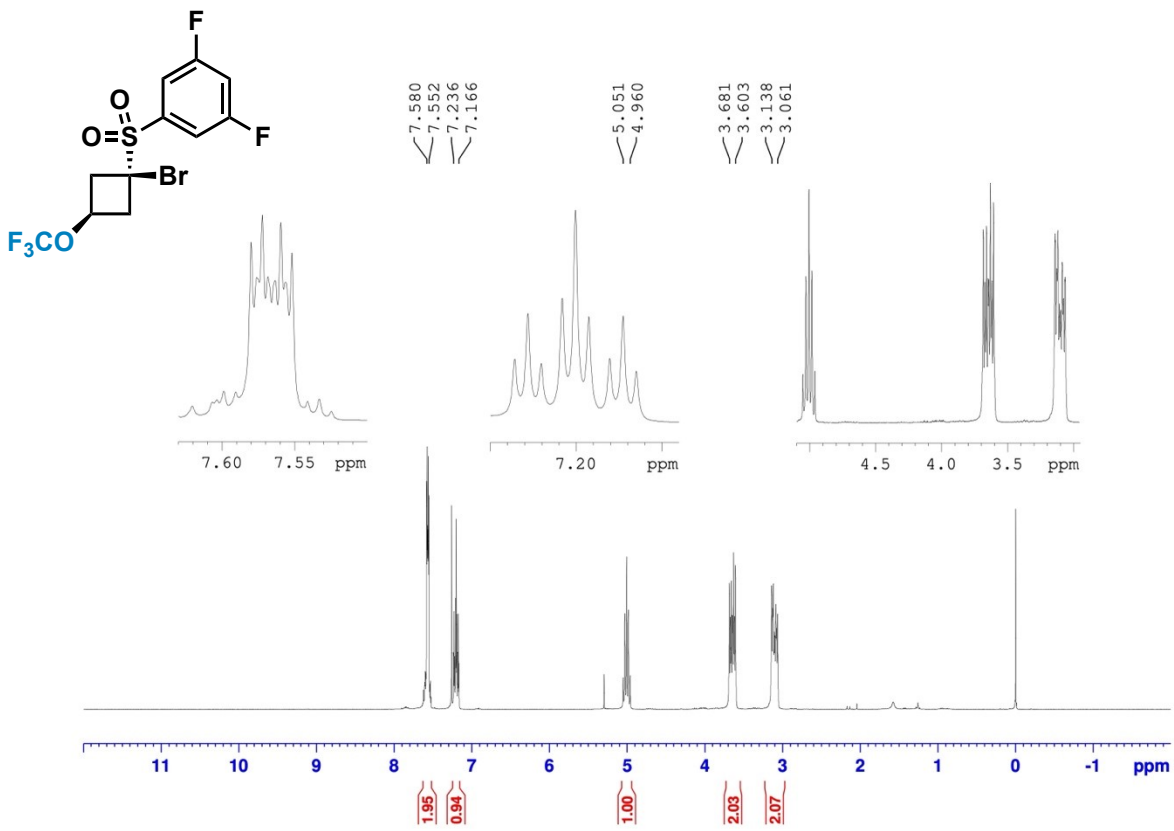


Figure S39. ^{1}H NMR spectrum of 1-((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)-3,5-difluorobenzene (compound **9**, *syn* isomer) in $CDCl_3$.

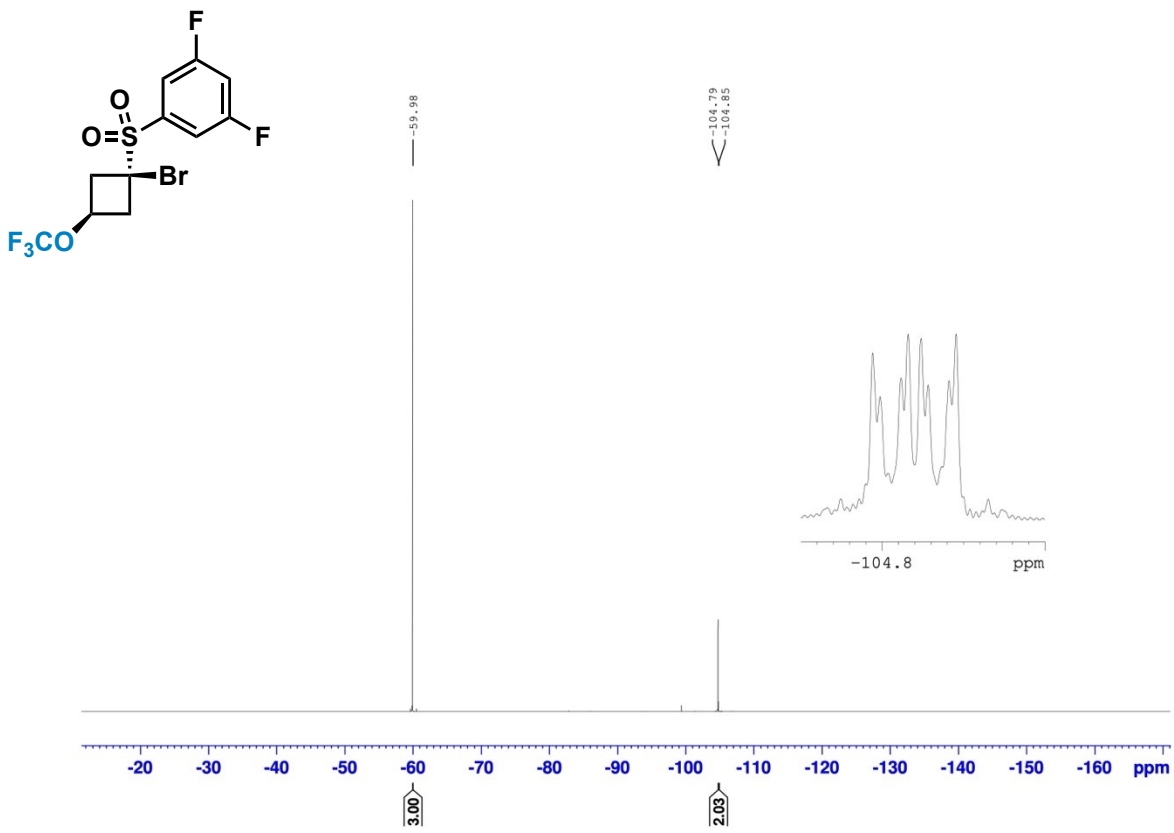


Figure S40. ^{19}F NMR spectrum of 1-((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)-3,5-difluorobenzene (compound **9**, *syn* isomer) in $CDCl_3$.

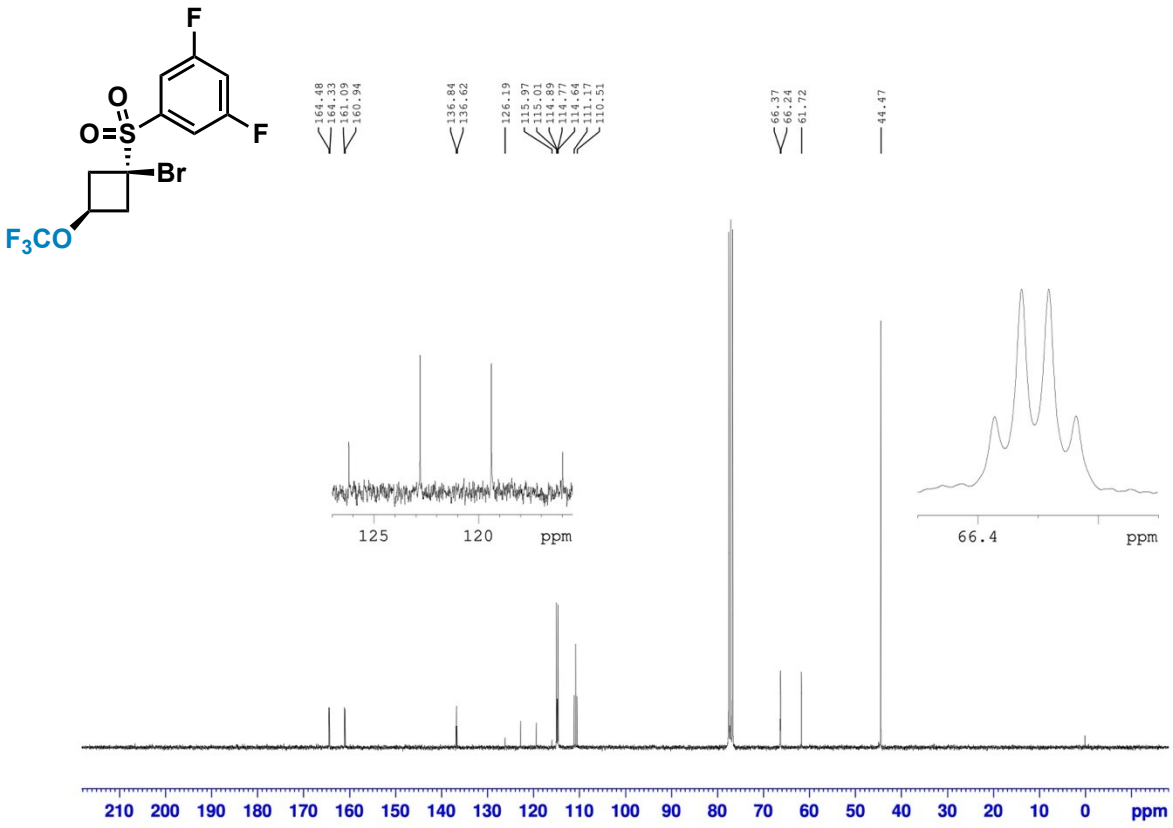


Figure S41. $^{13}C\{^{1}H\}$ NMR spectrum of 1-((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)-3,5-difluoro benzene (compound **9**, *syn* isomer) in $CDCl_3$.

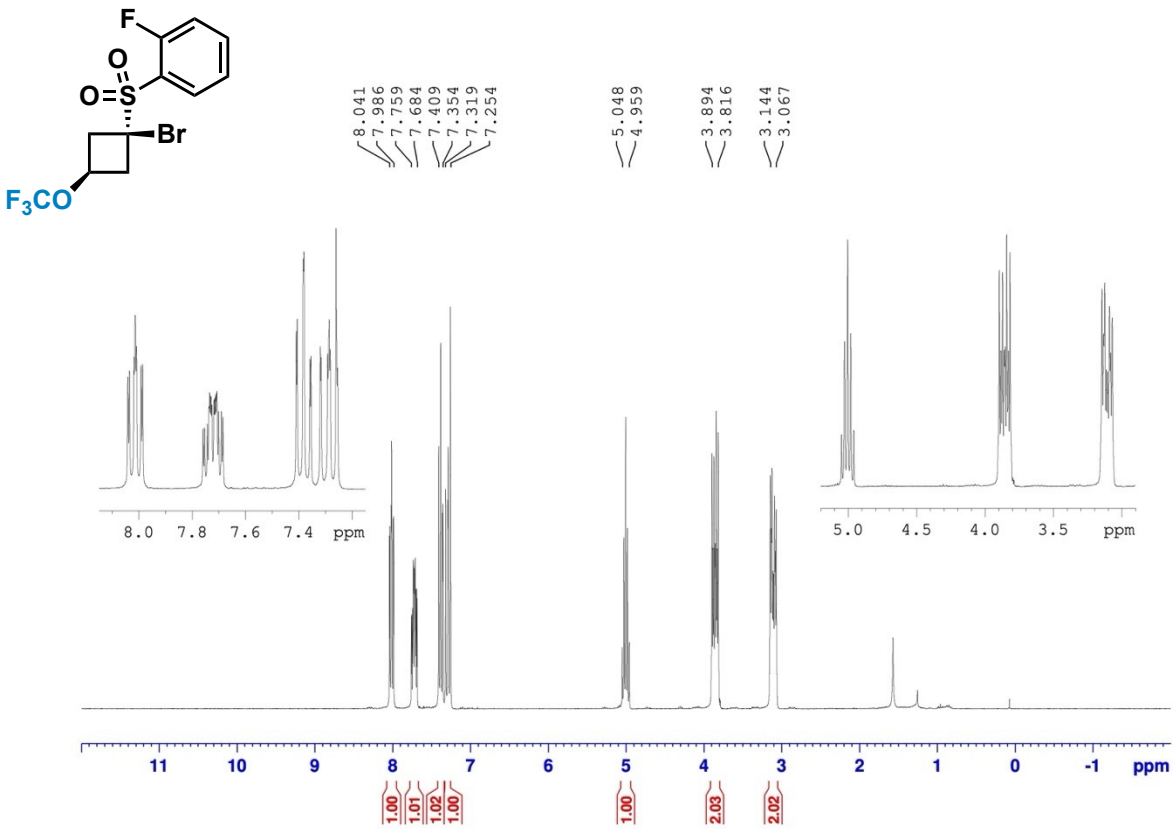


Figure S42. ^{1}H NMR spectrum of 1-((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)-2-fluorobenzene (compound **10**, *syn* isomer) in $CDCl_3$.

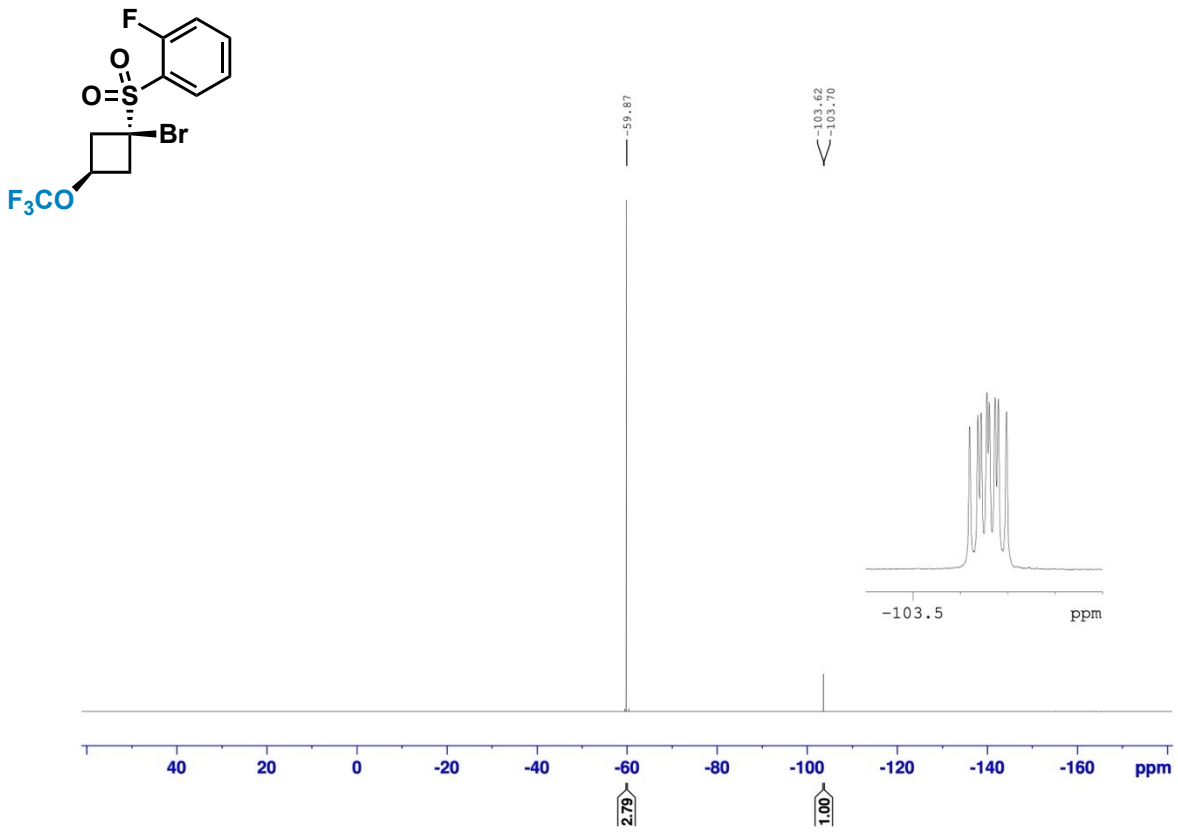


Figure S43. ^{19}F NMR spectrum of 1-((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)-2-fluorobenzene (compound **10**, *syn* isomer) in $CDCl_3$.

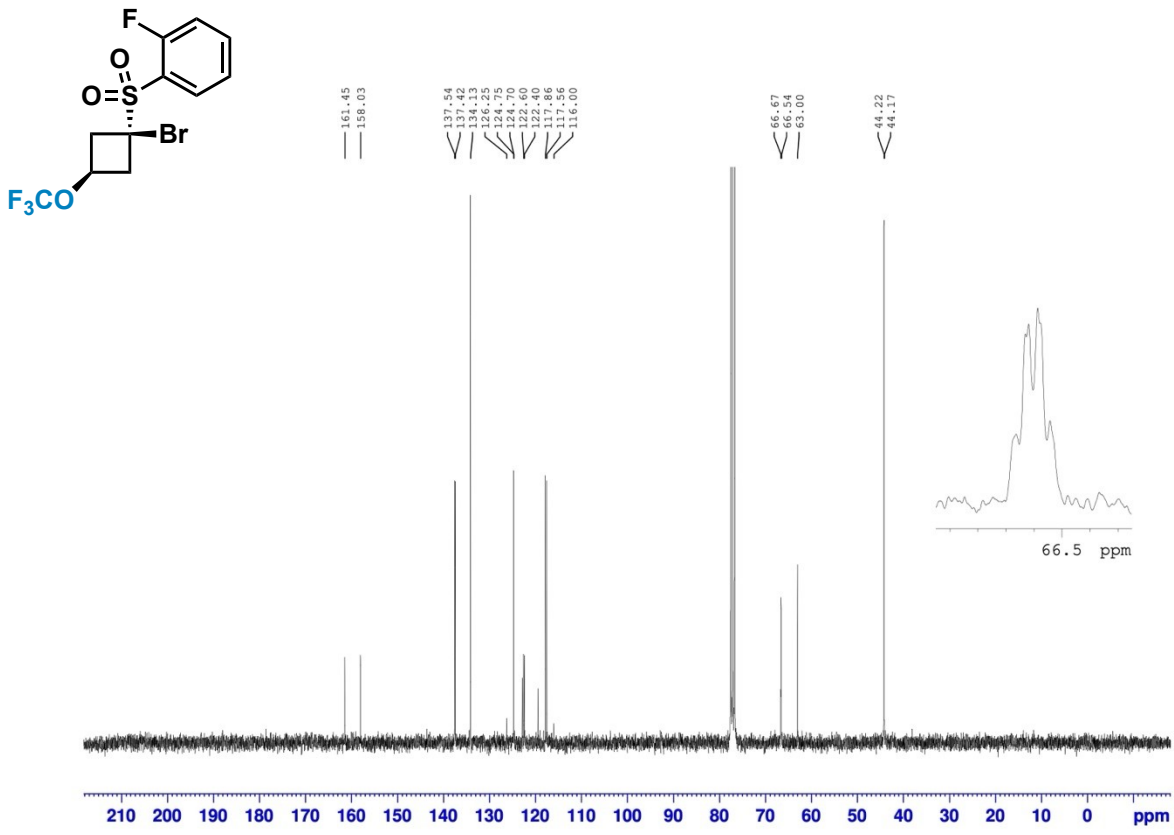


Figure S44. $^{13}C\{^{1}H\}$ NMR spectrum of 1-((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)-2-fluorobenzene (compound **10**, *syn* isomer) in $CDCl_3$.

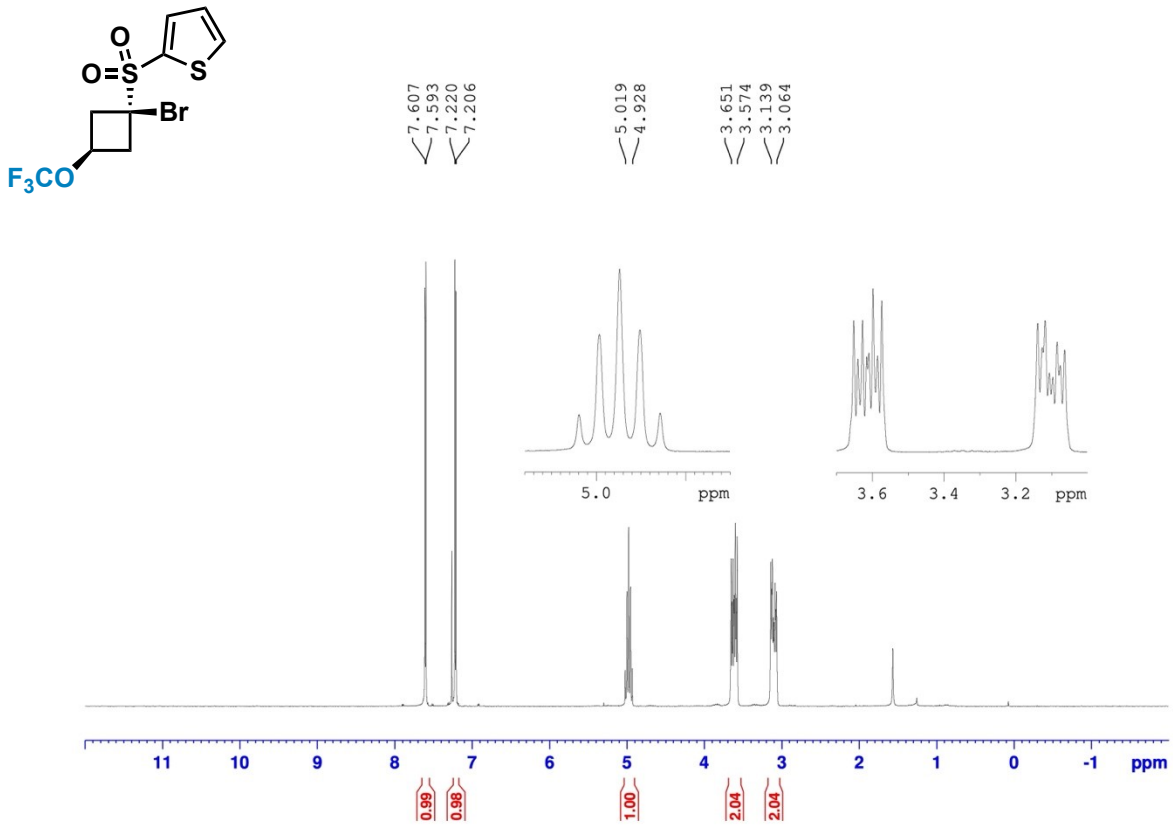


Figure S45. ^{1}H NMR spectrum of 2-((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)thiophene (compound **11**, *syn* isomer) in $CDCl_3$.

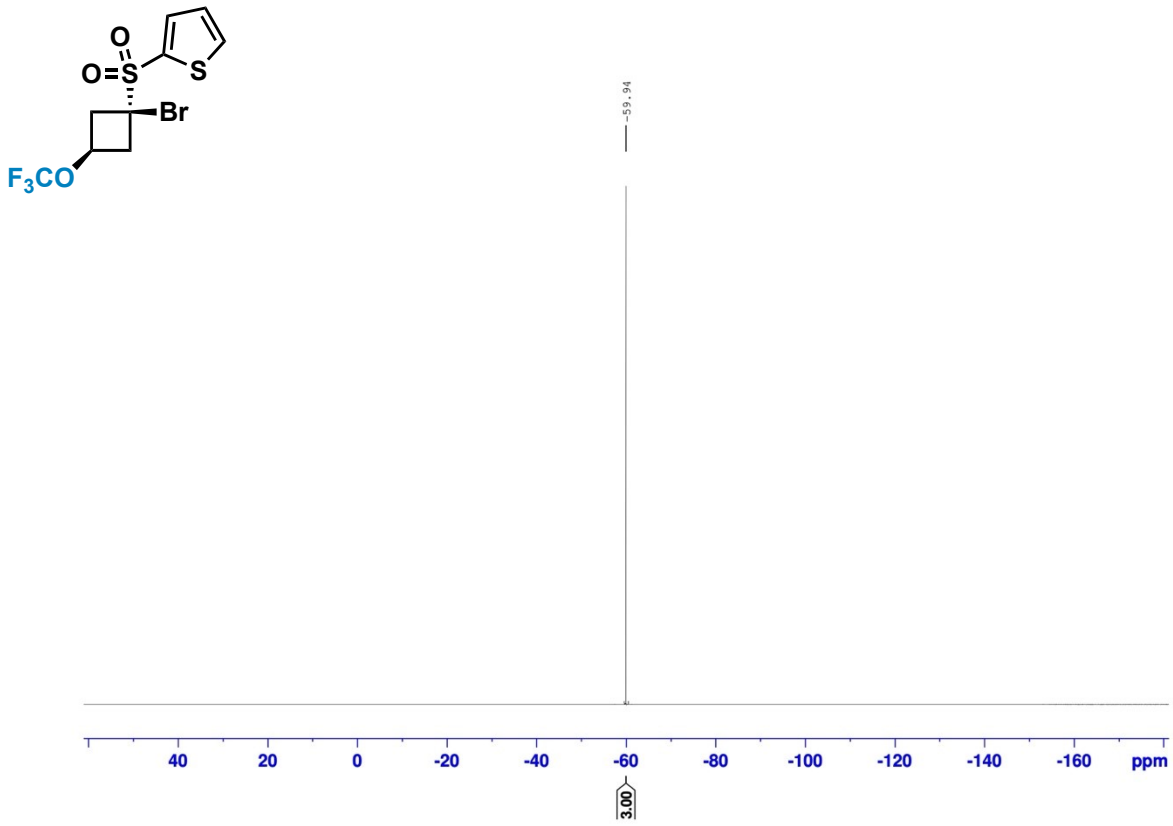


Figure S46. ^{19}F NMR spectrum of 2-((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)thiophene (compound **11**, *syn* isomer) in $CDCl_3$.

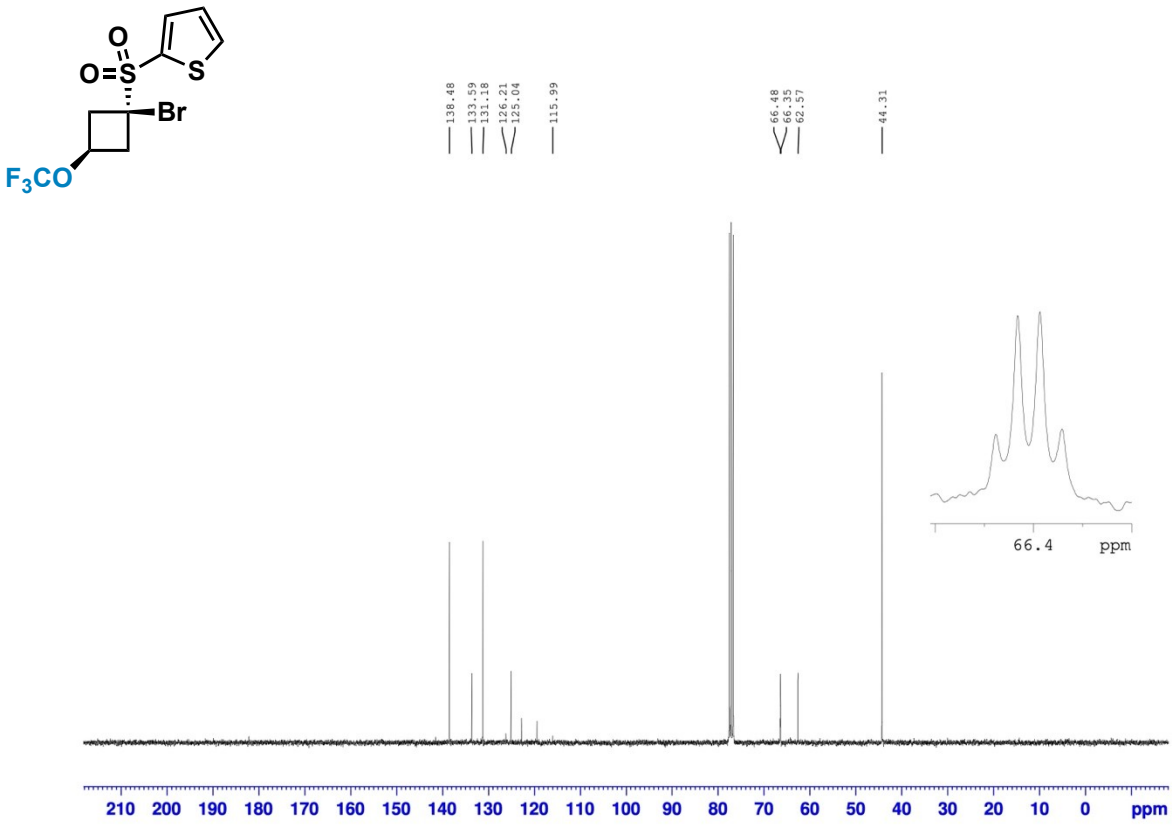


Figure S47. $^{13}C\{^{1}H\}$ NMR spectrum of 2-((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)thiophene (compound **11**, *syn* isomer) in $CDCl_3$.

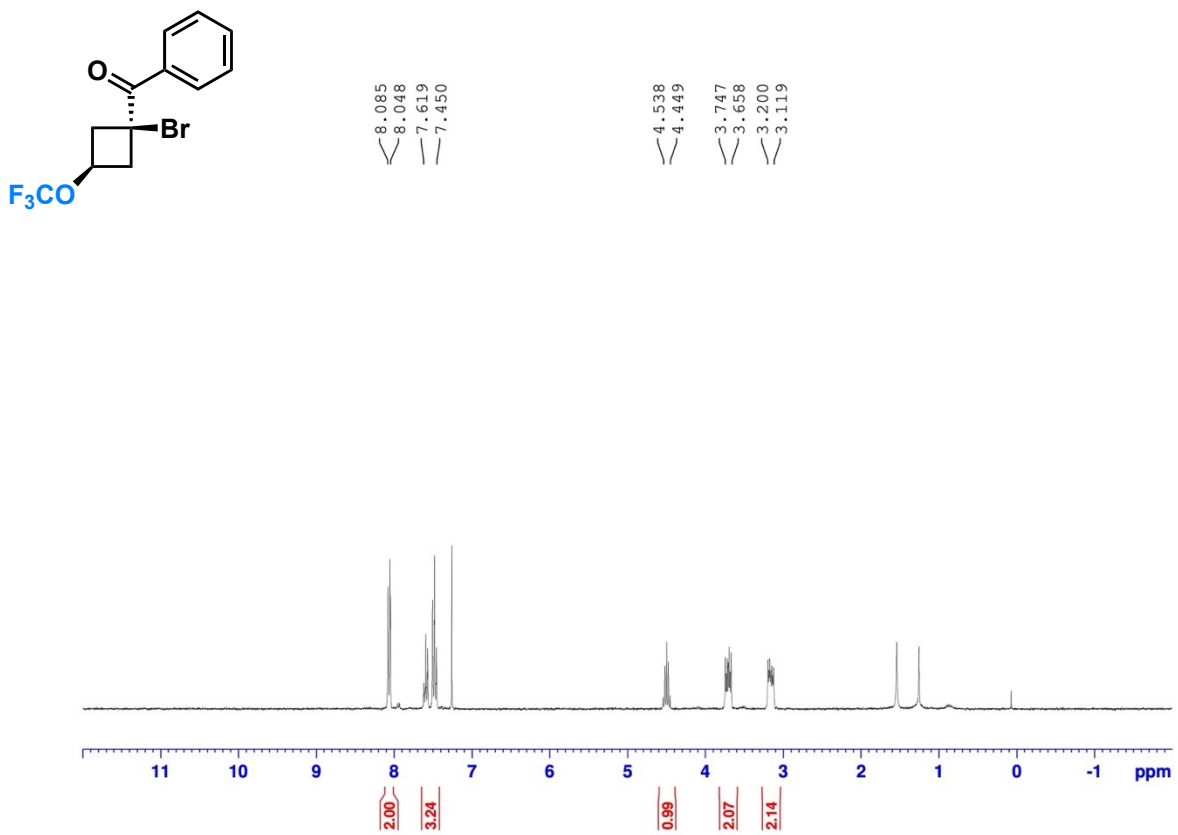


Figure S48. ^{1}H NMR spectrum of (1-bromo-3-(trifluoromethoxy)cyclobutyl)(phenyl)methanone (compound **12**, *syn* isomer) in $CDCl_3$.

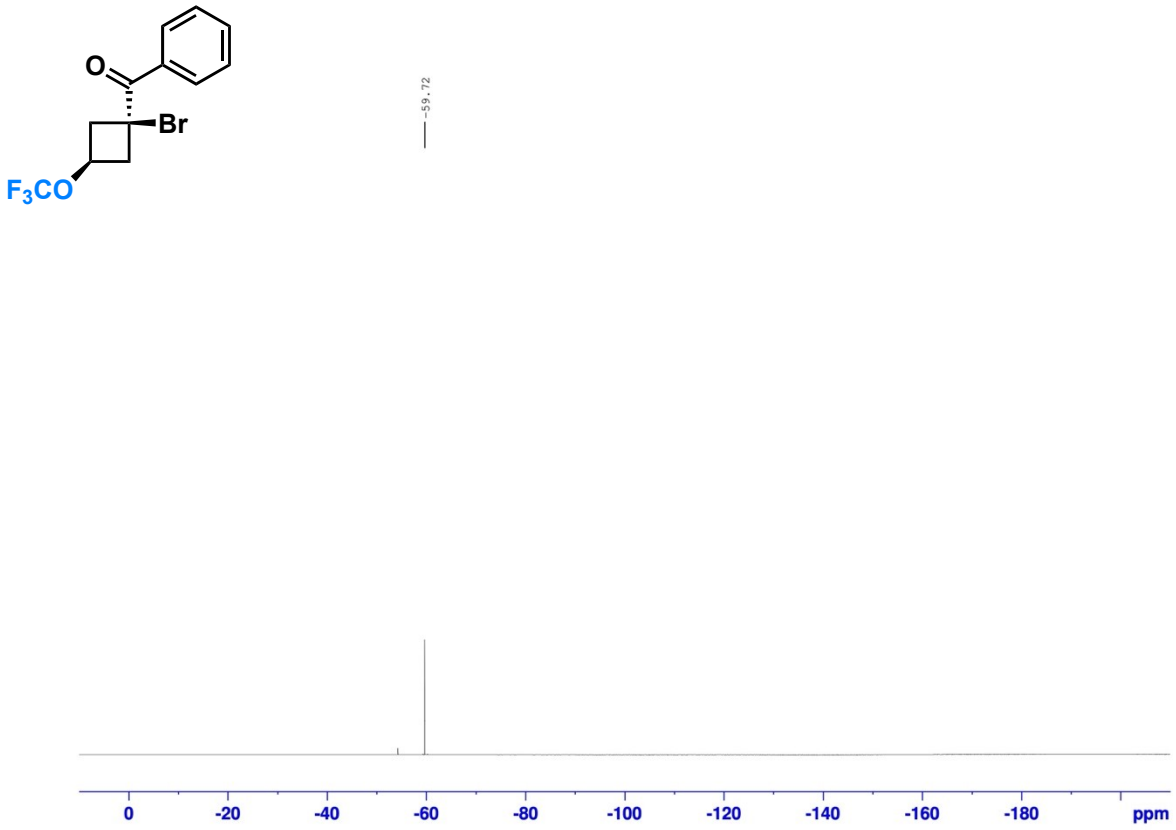


Figure S49. ^{19}F NMR spectrum of (1-bromo-3-(trifluoromethoxy)cyclobutyl)(phenyl)methanone (compound **12**, *syn* isomer) in $CDCl_3$.

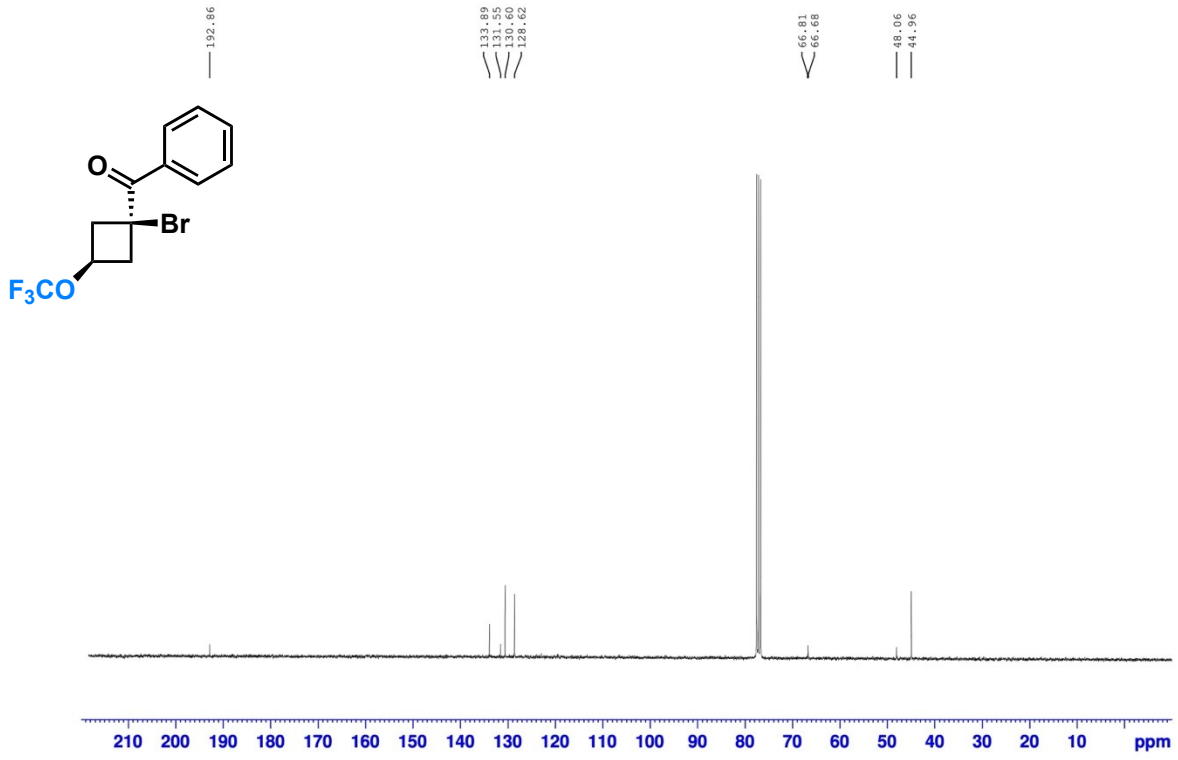


Figure S50. $^{13}C\{^{1}H\}$ NMR spectrum of (1-bromo-3-(trifluoromethoxy)cyclobutyl)(phenyl)methanone (compound **12**, *syn* isomer) in $CDCl_3$.

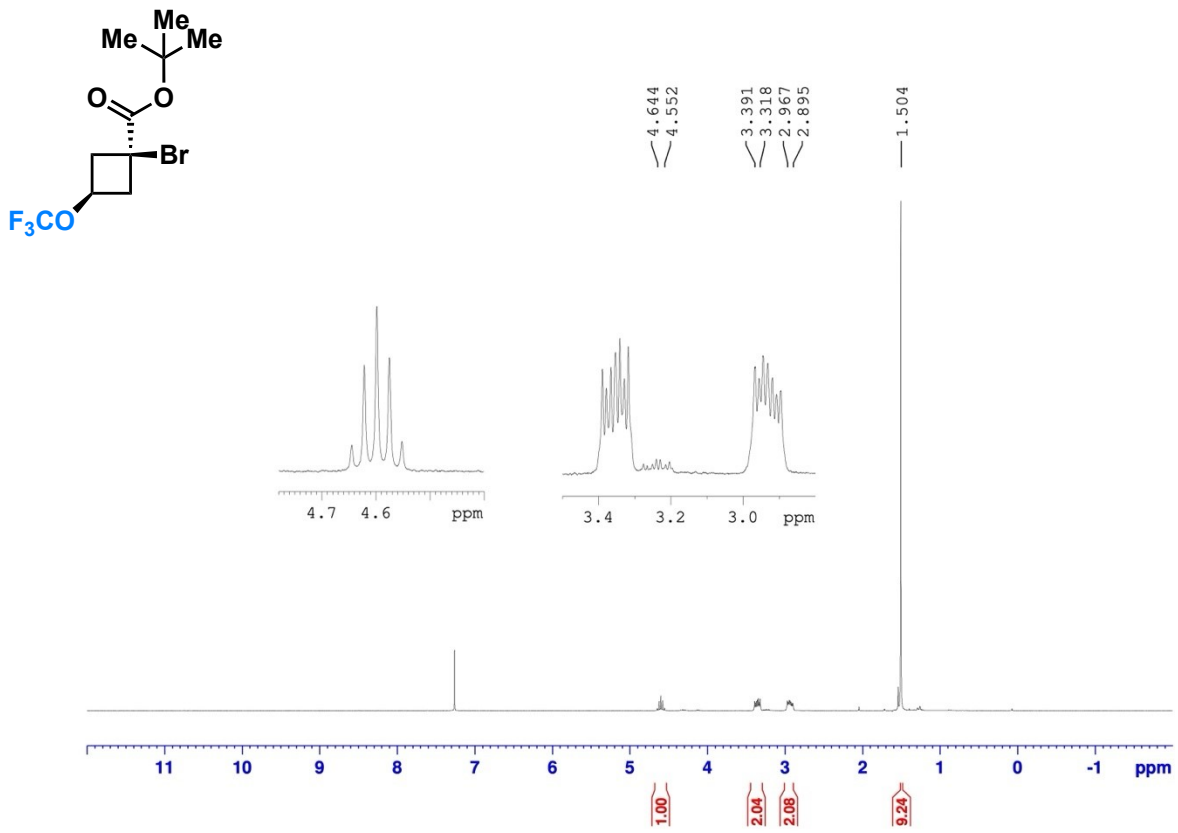


Figure S51. ^{1}H NMR spectrum of *tert*-butyl 1-bromo-3-(trifluoromethoxy)cyclobutane-1-carboxylate (compound **13**, *syn* isomer) in $CDCl_3$.

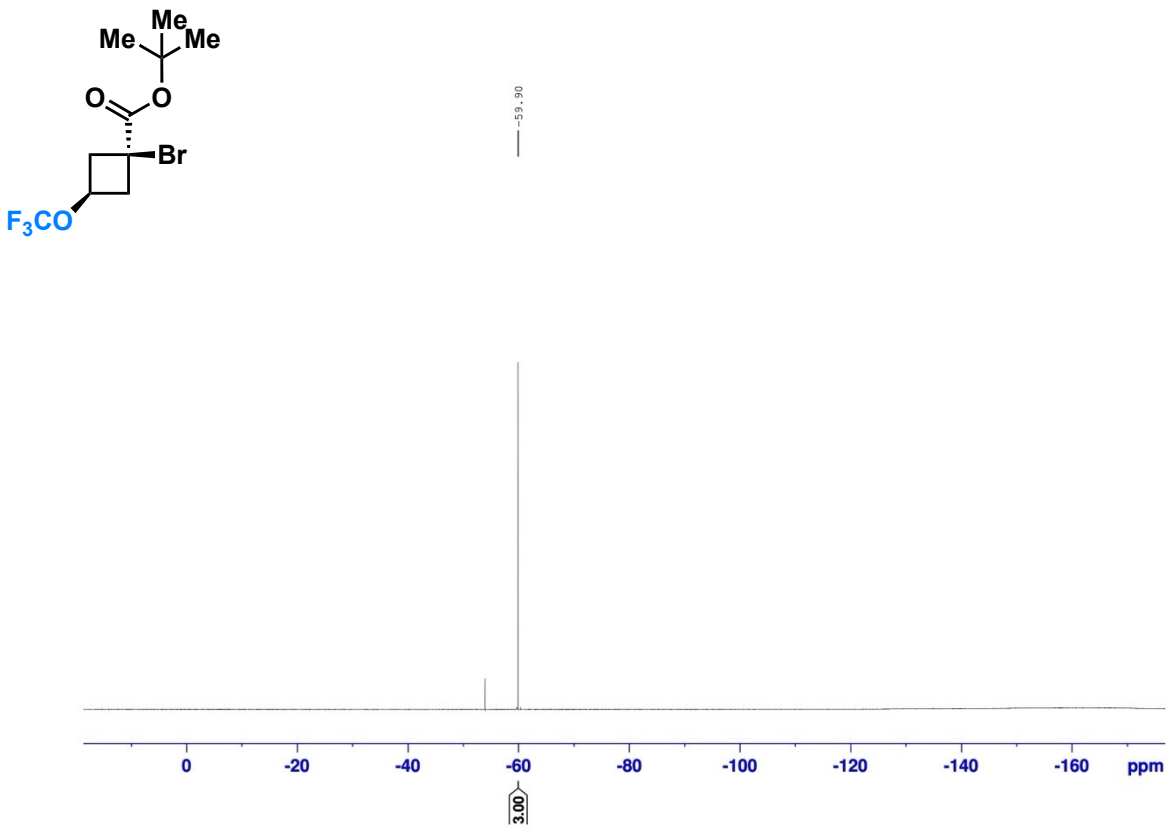


Figure S52. ^{19}F NMR spectrum of *tert*-butyl 1-bromo-3-(trifluoromethoxy)cyclobutane-1-carboxylate (compound **13**, *syn* isomer) in $CDCl_3$.

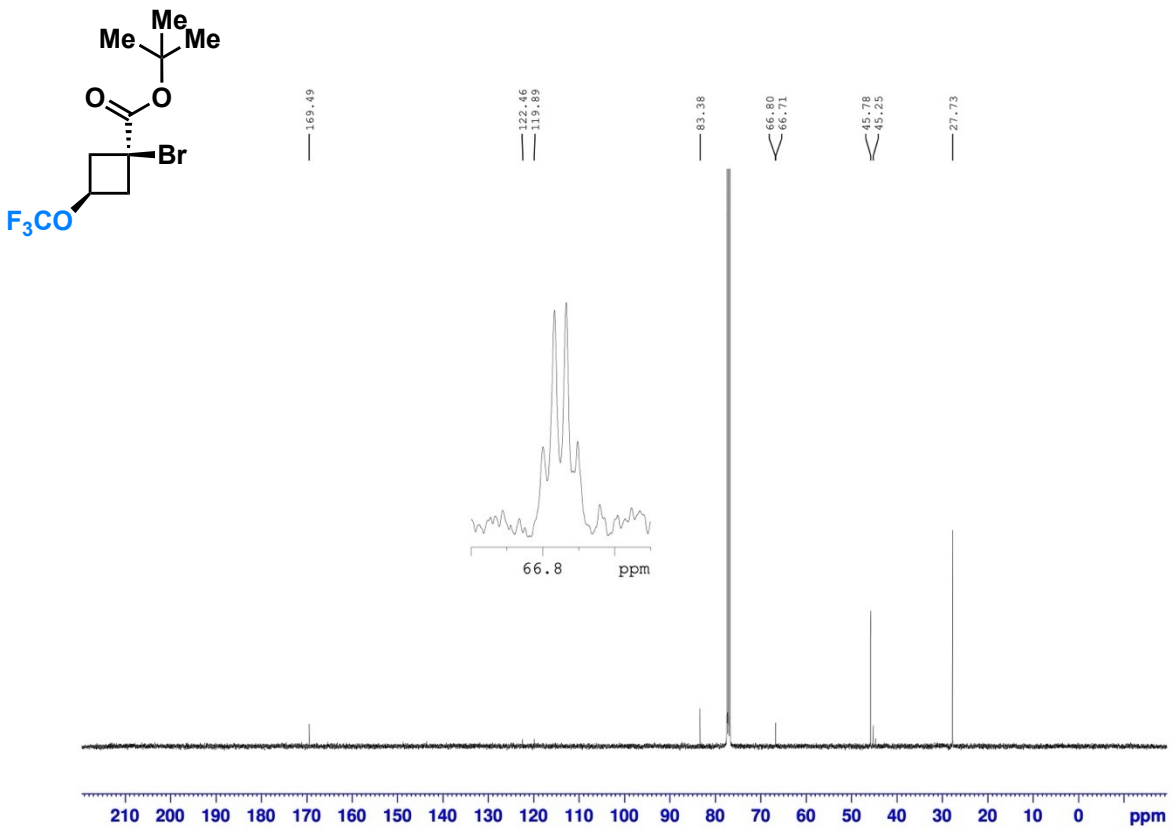


Figure S53. $^{13}C\{^{1}H\}$ NMR spectrum of *tert*-butyl 1-bromo-3-(trifluoromethoxy)cyclobutane-1-carboxylate (compound **13**, *syn* isomer) in $CDCl_3$.

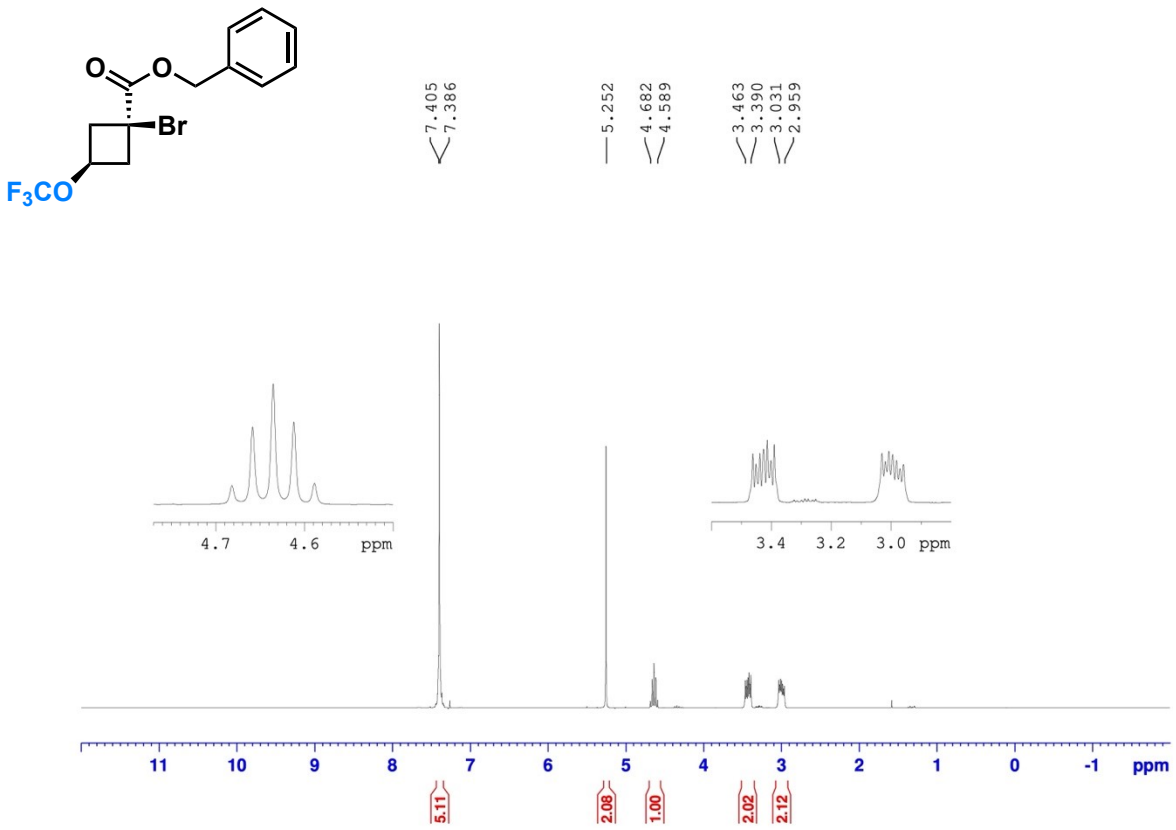


Figure S54. ^{1}H NMR spectrum of benzyl 1-bromo-3-(trifluoromethoxy)cyclobutane-1-carboxylate (compound **14**, *syn* isomer) in $CDCl_3$.

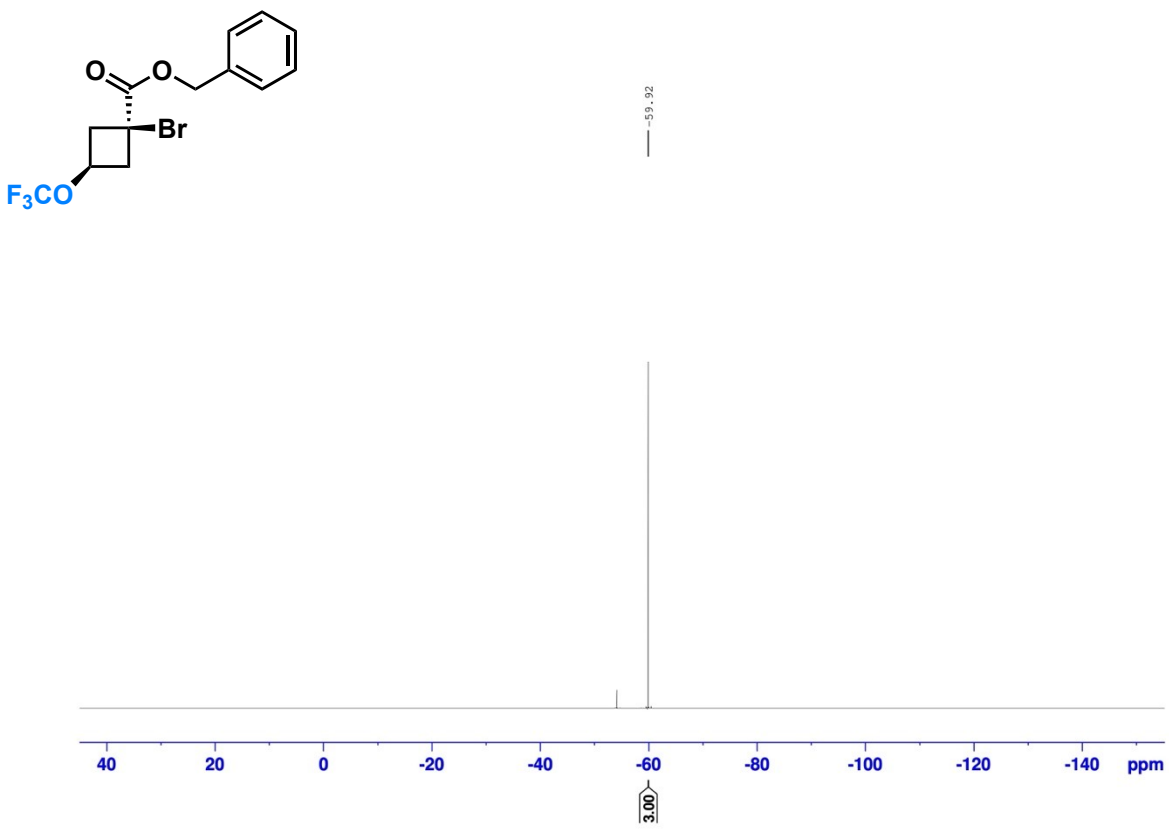


Figure S55. ^{19}F NMR spectrum of benzyl 1-bromo-3-(trifluoromethoxy)cyclobutane-1-carboxylate (compound **14**, *syn* isomer) in $CDCl_3$.

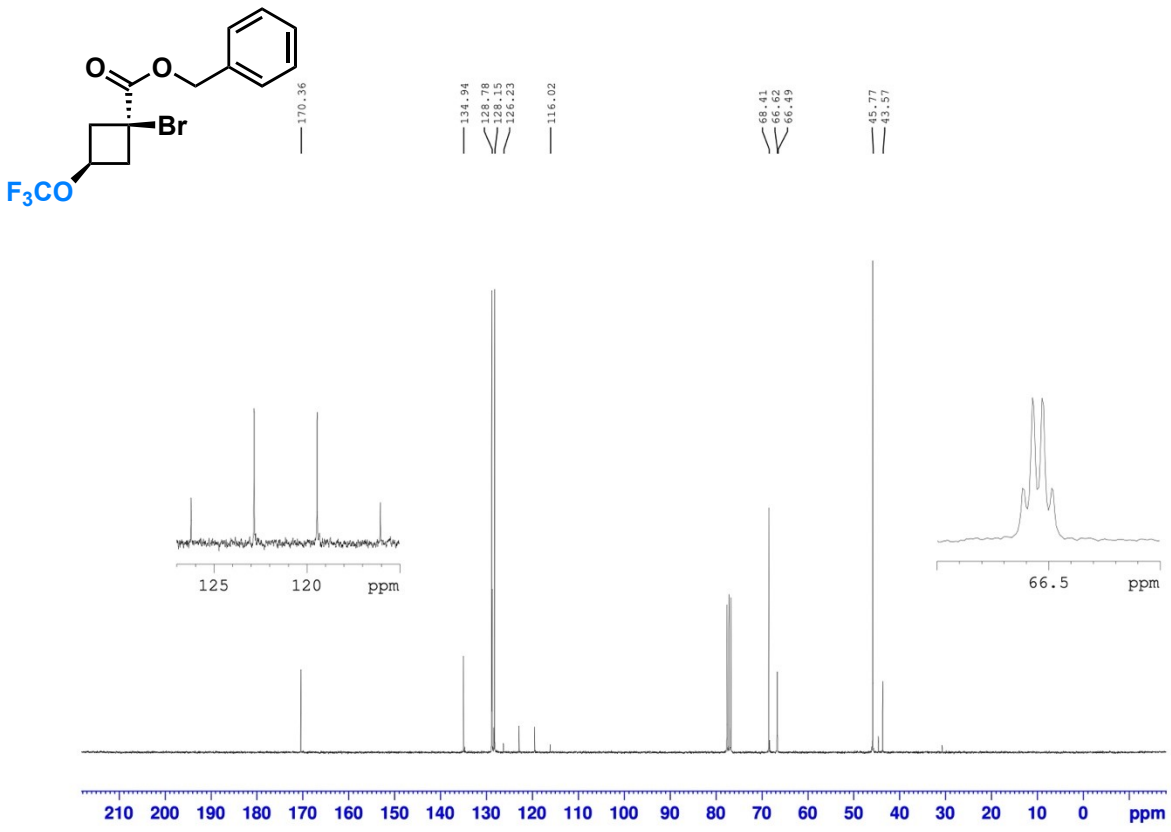


Figure S56. $^{13}C\{^{1}H\}$ NMR spectrum of benzyl 1-bromo-3-(trifluoromethoxy)cyclobutane-1-carboxylate (compound **14**, *syn* isomer) in $CDCl_3$.

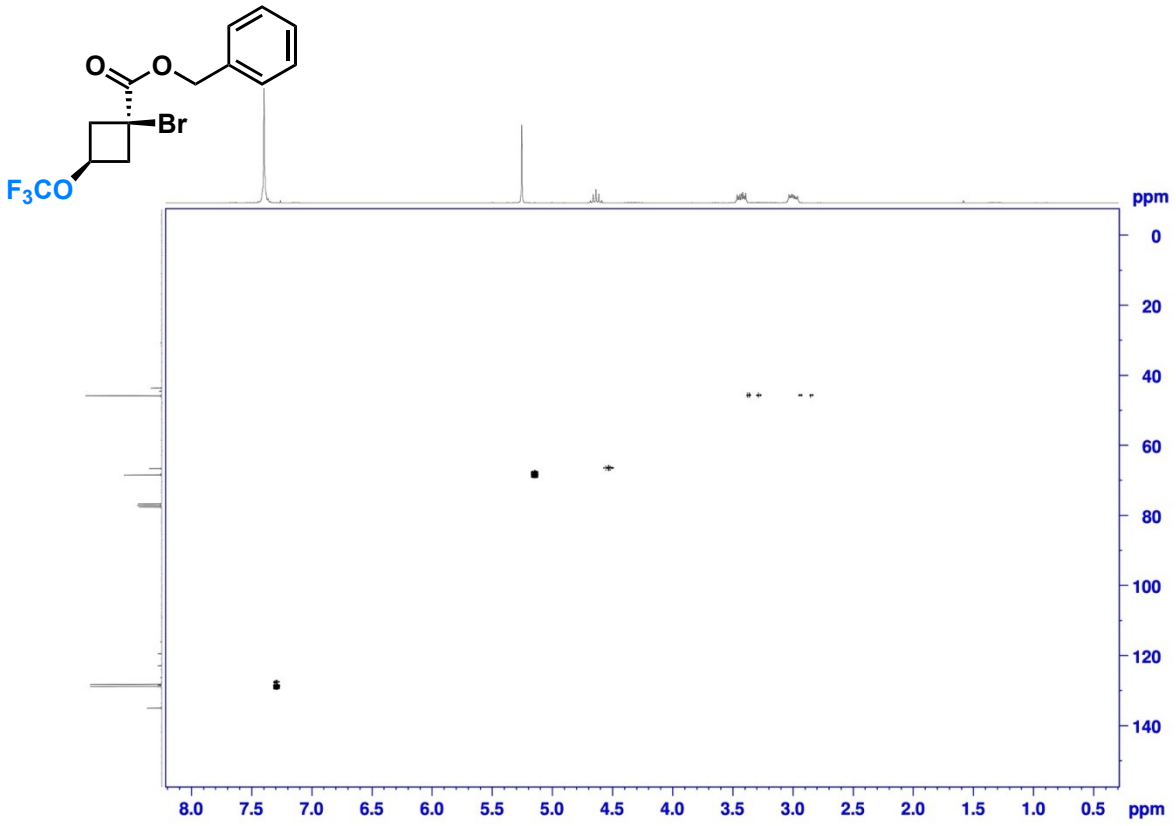


Figure S57. ^{1}H-^{13}C HSQC NMR spectrum of benzyl 1-bromo-3-(trifluoromethoxy)cyclobutane-1-carboxylate (compound **14**, *syn* isomer) in $CDCl_3$.

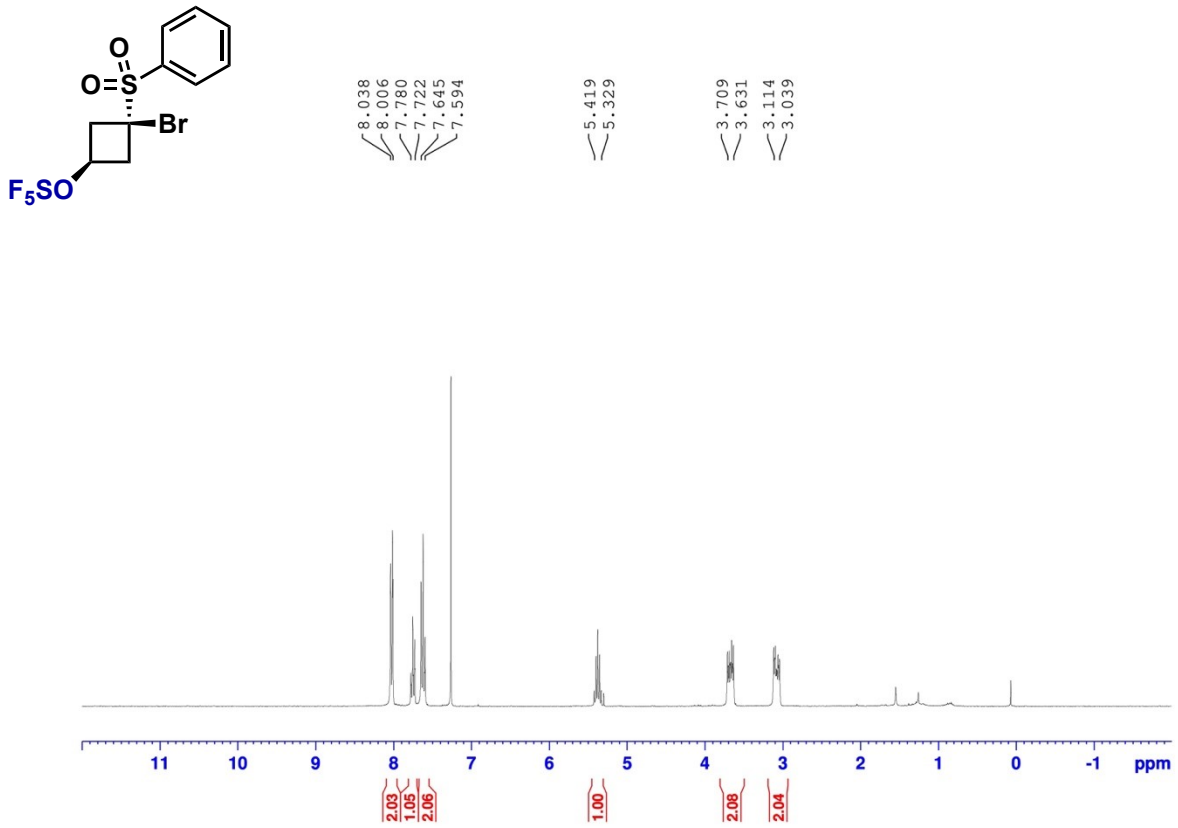


Figure S58. ^{1}H NMR spectrum of (3-bromo-3-(phenylsulfonyl)cyclobutoxy)pentafluoro-λ^{6}-sulfane (compound **15**, *syn* isomer) in $CDCl_3$.

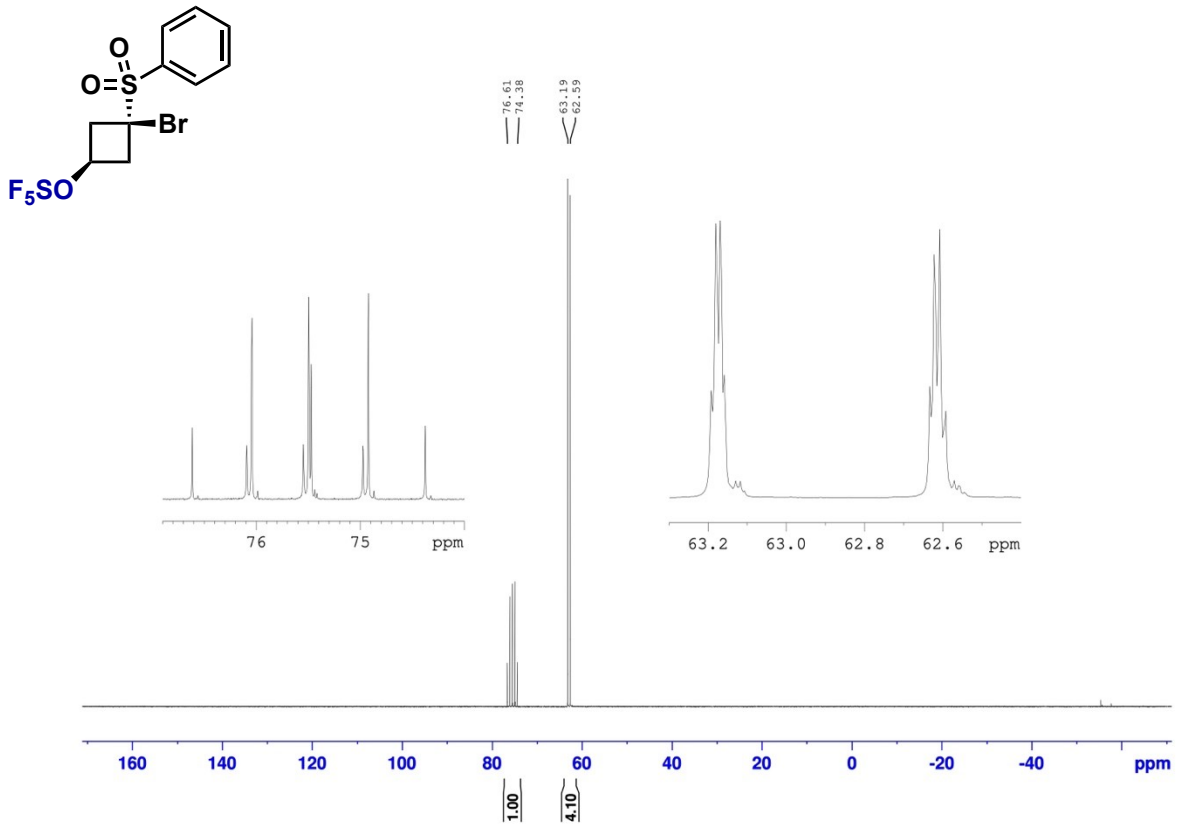


Figure S59. ^{19}F NMR spectrum of (3-bromo-3-(phenylsulfonyl)cyclobutoxy)pentafluoro-λ^6-sulfane (compound **15**, *syn* isomer) in $CDCl_3$.

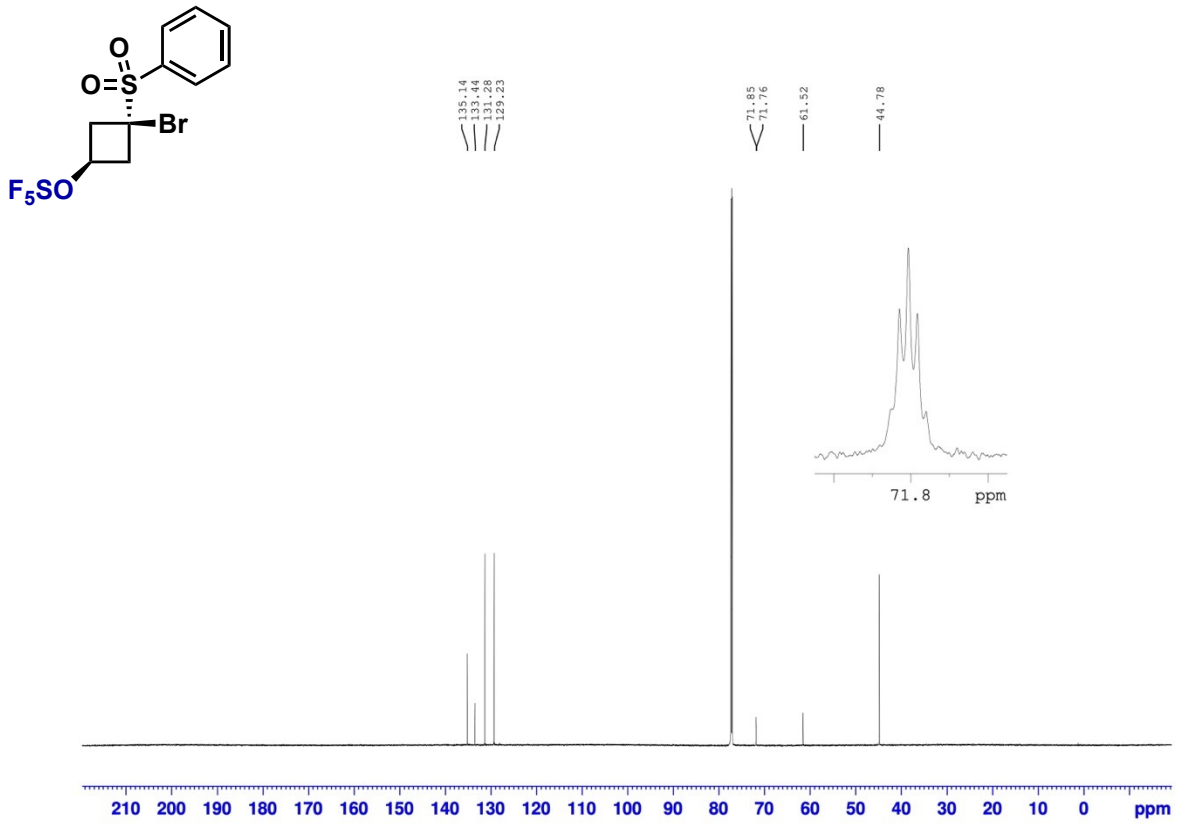


Figure S60. $^{13}C\{^{1}H\}$ NMR spectrum of (3-bromo-3-(phenylsulfonyl)cyclobutoxy)pentafluoro-λ^6-sulfane (compound **15**, *syn* isomer) in $CDCl_3$.

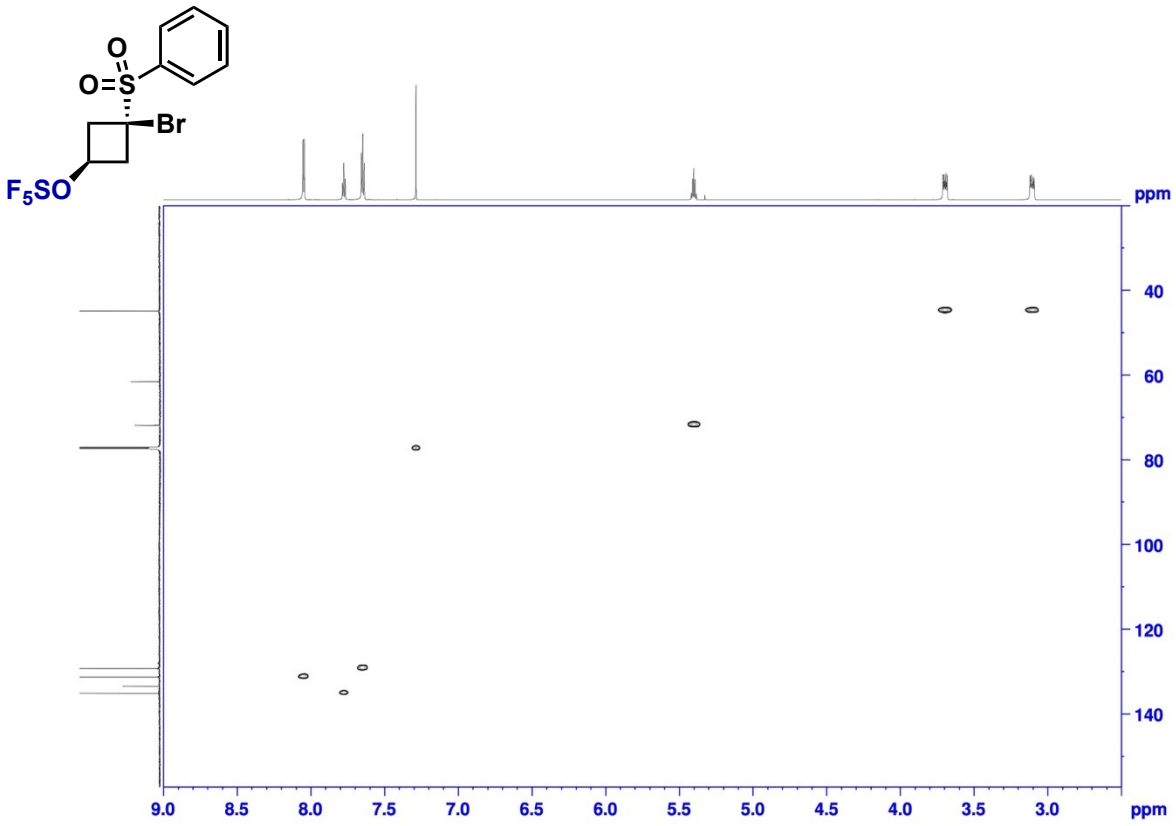


Figure S61. ^{1}H-^{13}C HSQC NMR spectrum of (3-bromo-3-(phenylsulfonyl)cyclobutoxy)pentafluoro-λ^{6}-sulfane (compound **15**, *syn* isomer) in $CDCl_3$.

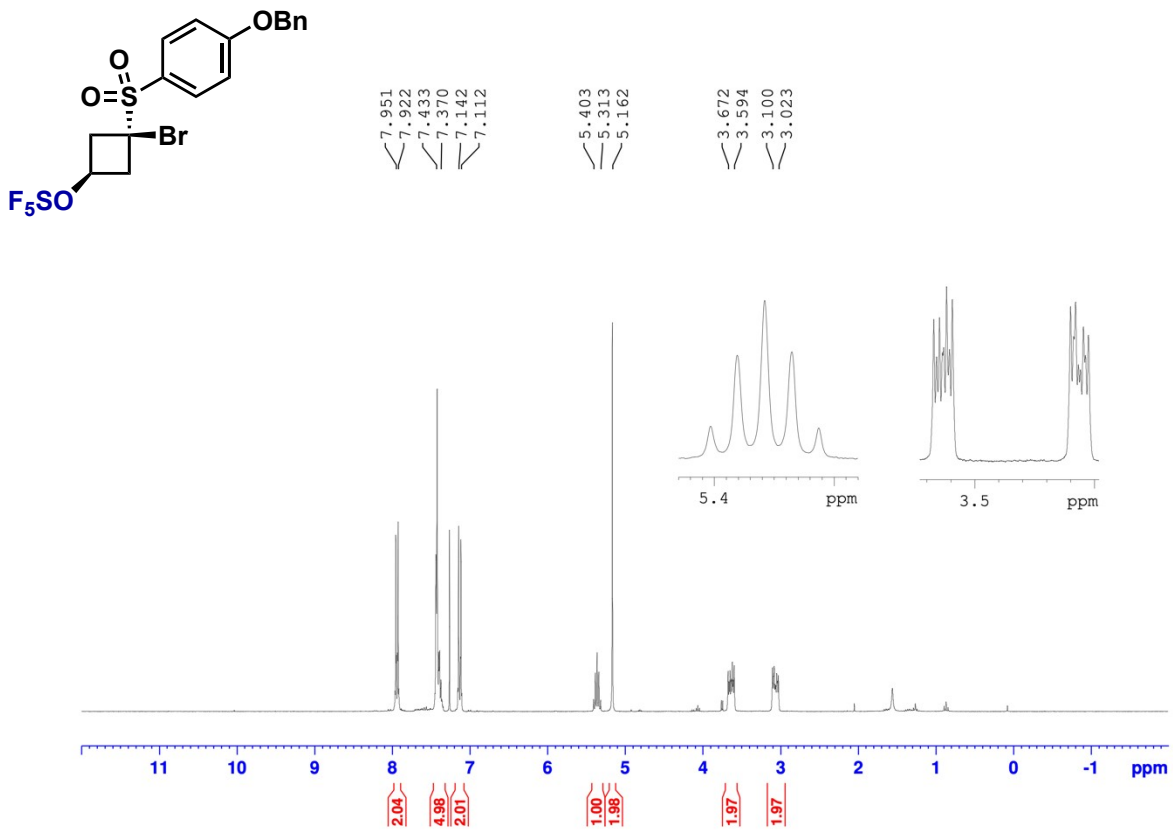


Figure S62. ^{1}H NMR spectrum of (3-((4-(benzyloxy)phenyl)sulfonyl)-3-bromocyclobutoxy)pentafluoro-λ^{6}-sulfane (compound **16**, *syn* isomer) in $CDCl_3$.

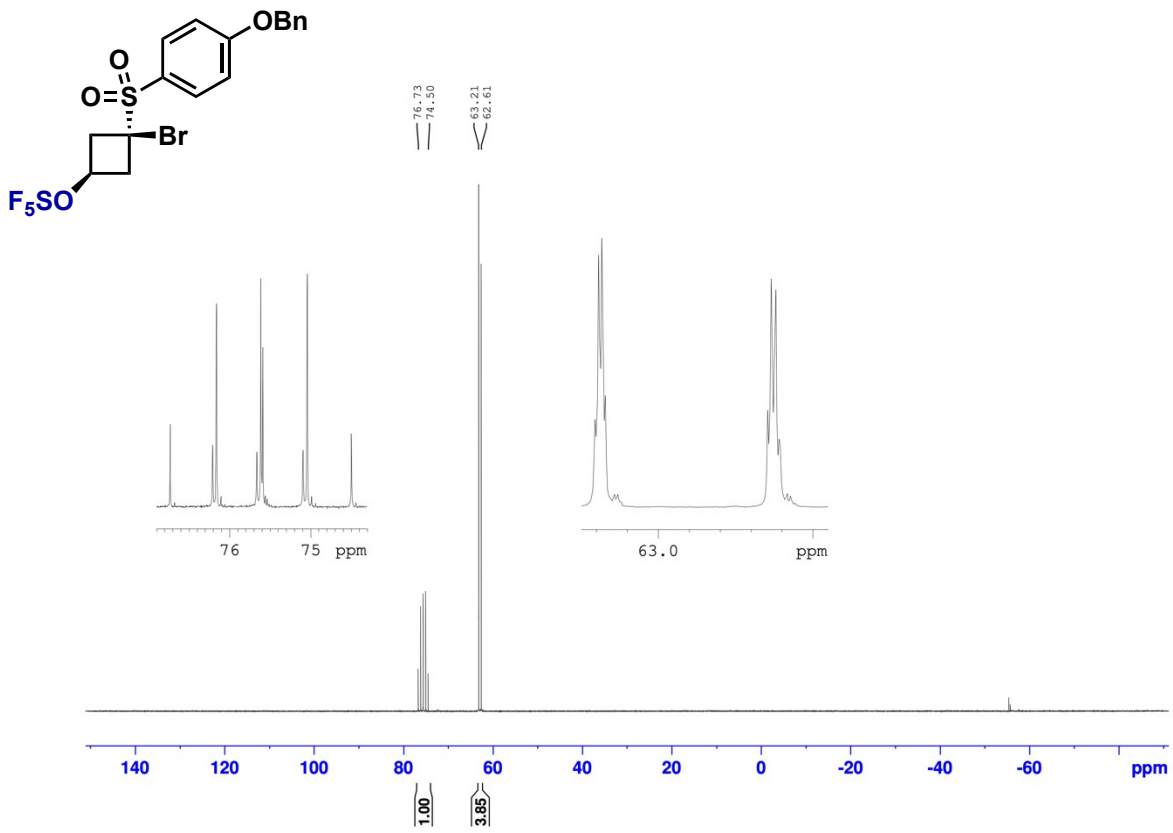


Figure S63. ^{19}F NMR spectrum of (3-((4-(benzyloxy)phenyl)sulfonyl)-3-bromocyclobutoxy)pentafluoro-λ^6-sulfane (compound **16**, *syn* isomer) in $CDCl_3$.

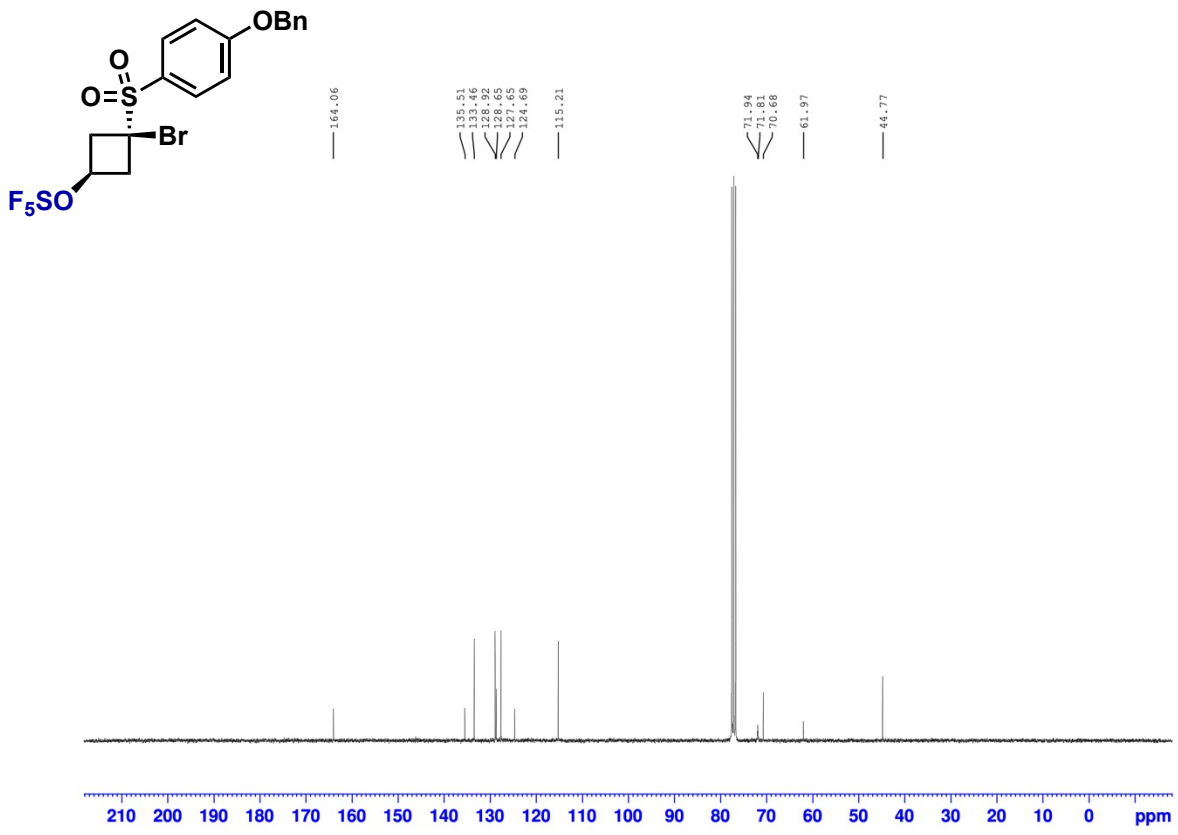


Figure S64. $^{13}C\{^{1}H\}$ NMR spectrum of (3-((4-(benzyloxy)phenyl)sulfonyl)-3-bromocyclobutoxy)pentafluoro-λ^6-sulfane (compound **16**, *syn* isomer) in $CDCl_3$.

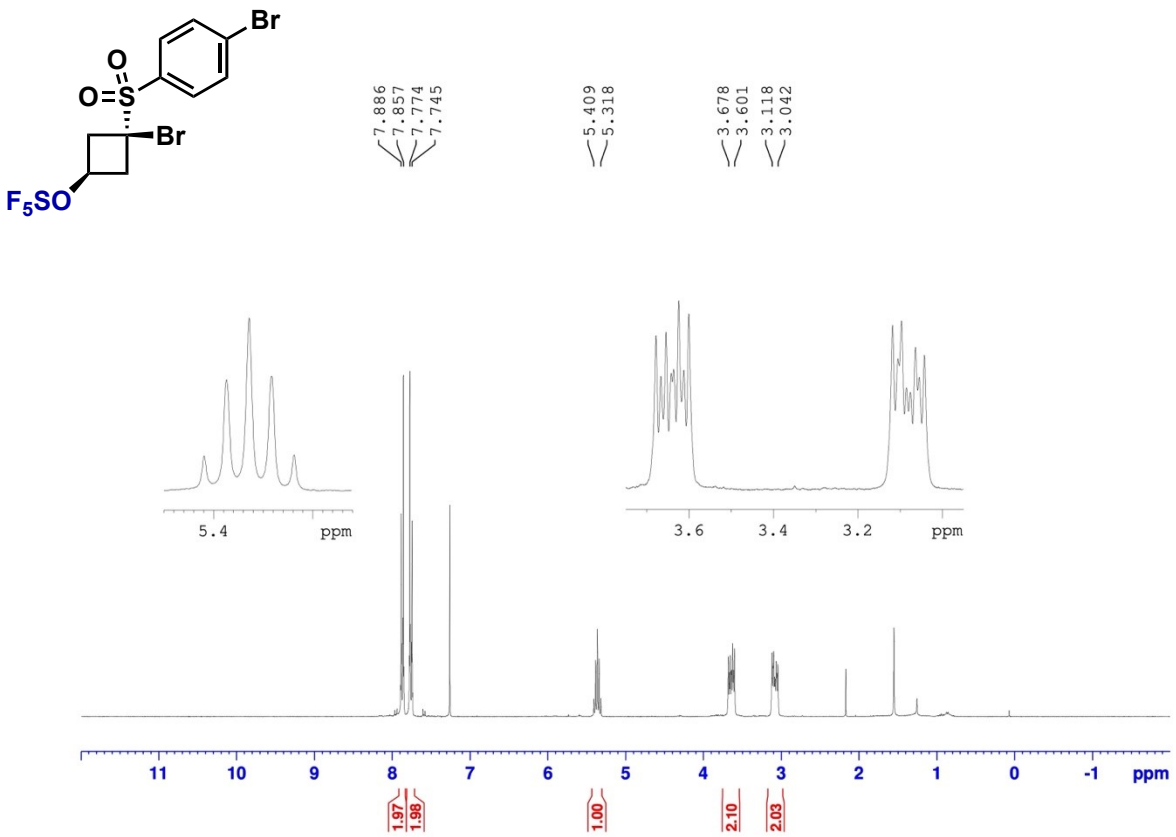


Figure S65. ^{1}H NMR spectrum of 3-bromo-3-((4-bromophenyl)sulfonyl)cyclobutoxy)pentafluoro-λ^{6}-sulfane (compound **17**, *syn* isomer) in $CDCl_3$.

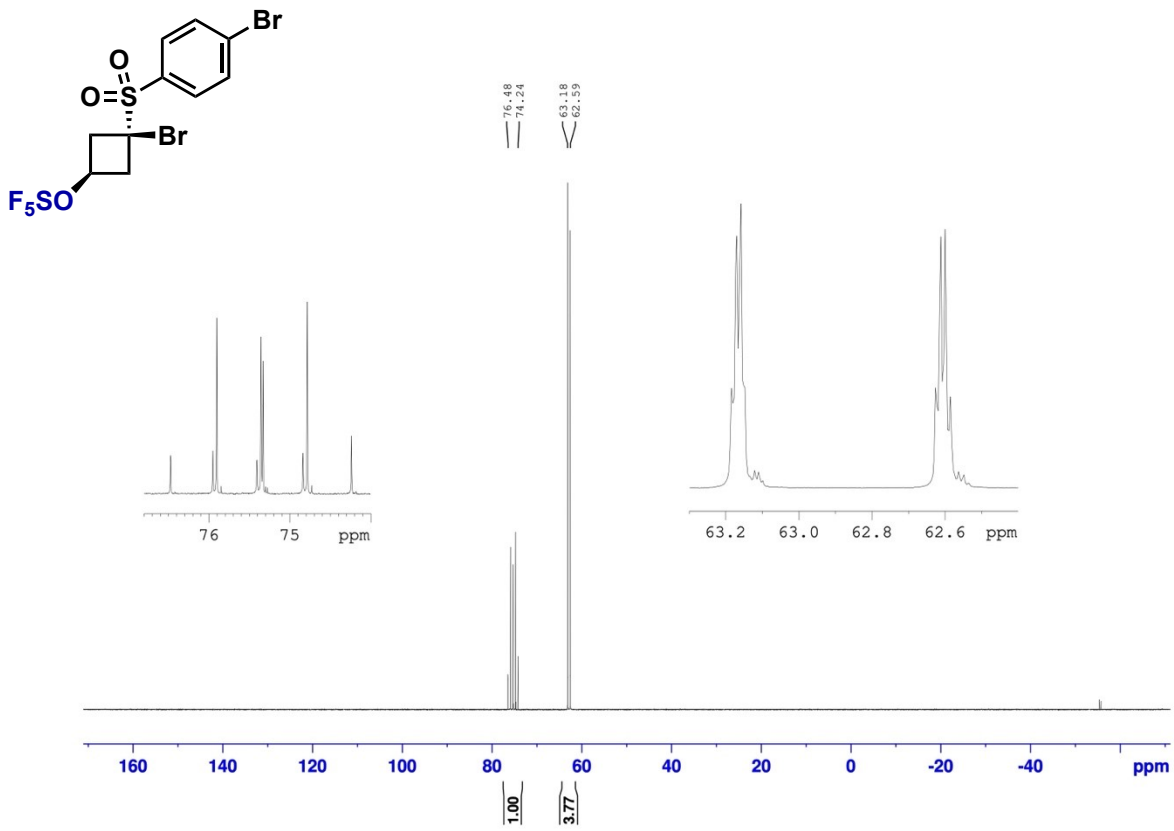


Figure S66. ^{19}F NMR spectrum of 3-bromo-3-((4-bromophenyl)sulfonyl)cyclobutoxy)pentafluoro-λ^6-sulfane (compound **17**, *syn* isomer) in $CDCl_3$.

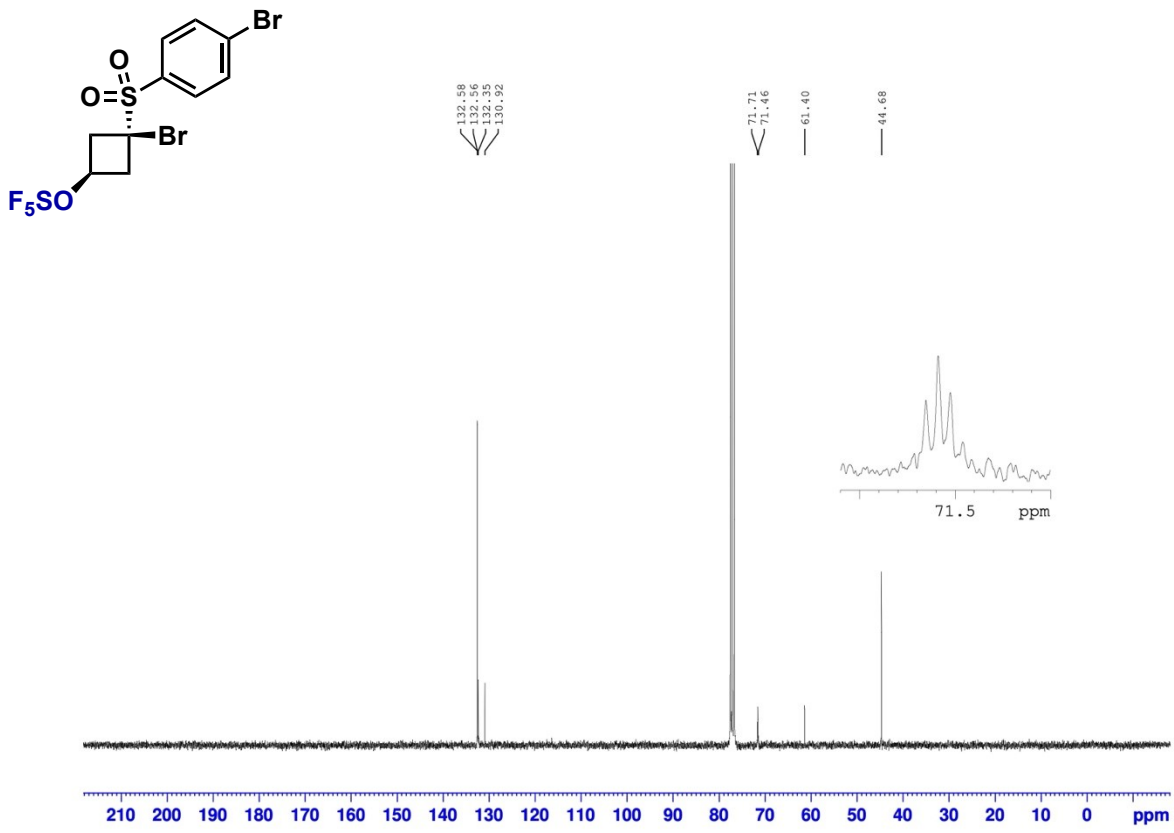


Figure S67. $^{13}C\{^{1}H\}$ NMR spectrum of 3-bromo-3-((4-bromophenyl)sulfonyl)cyclobutoxy)pentafluoro-λ^{6}-sulfane (compound **17**, *syn* isomer) in $CDCl_3$.

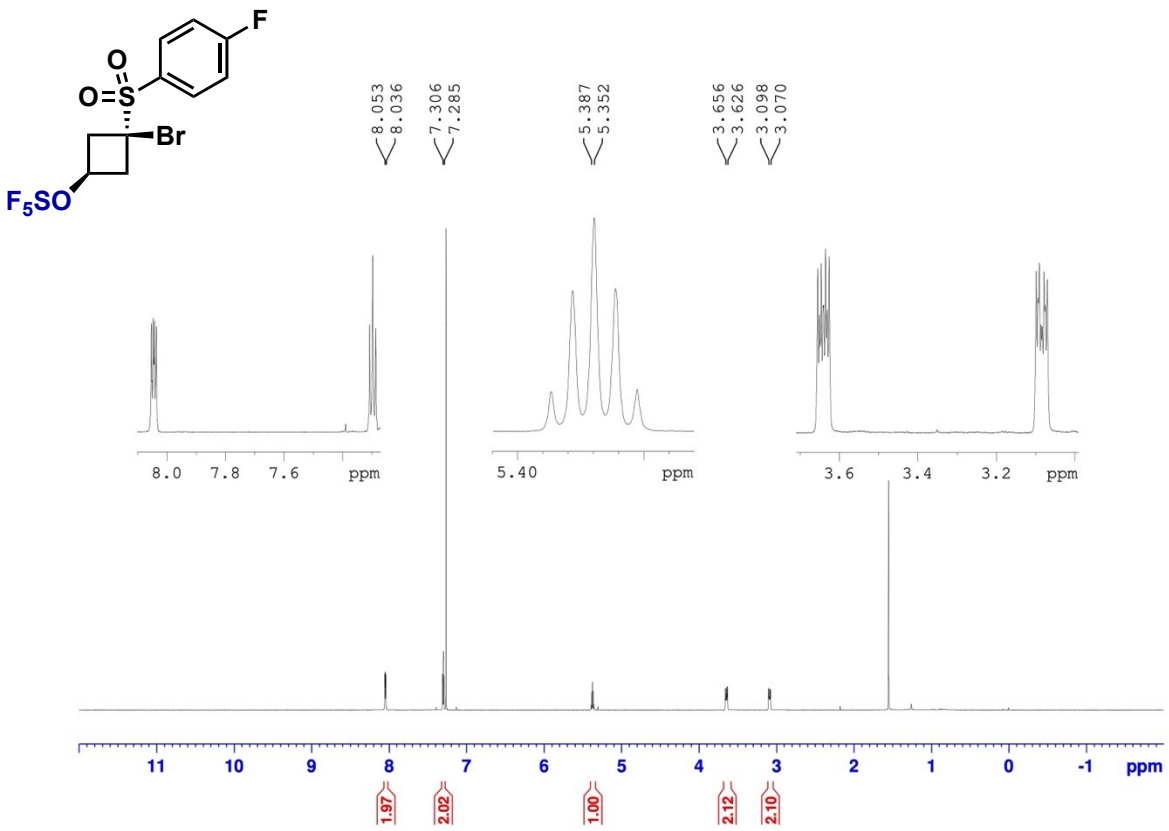


Figure S68. ^{1}H NMR spectrum of 3-bromo-3-((4-fluorophenyl)sulfonyl)cyclobutoxy)pentafluoro-λ^{6}-sulfane (compound **18**, *syn* isomer) in $CDCl_3$.

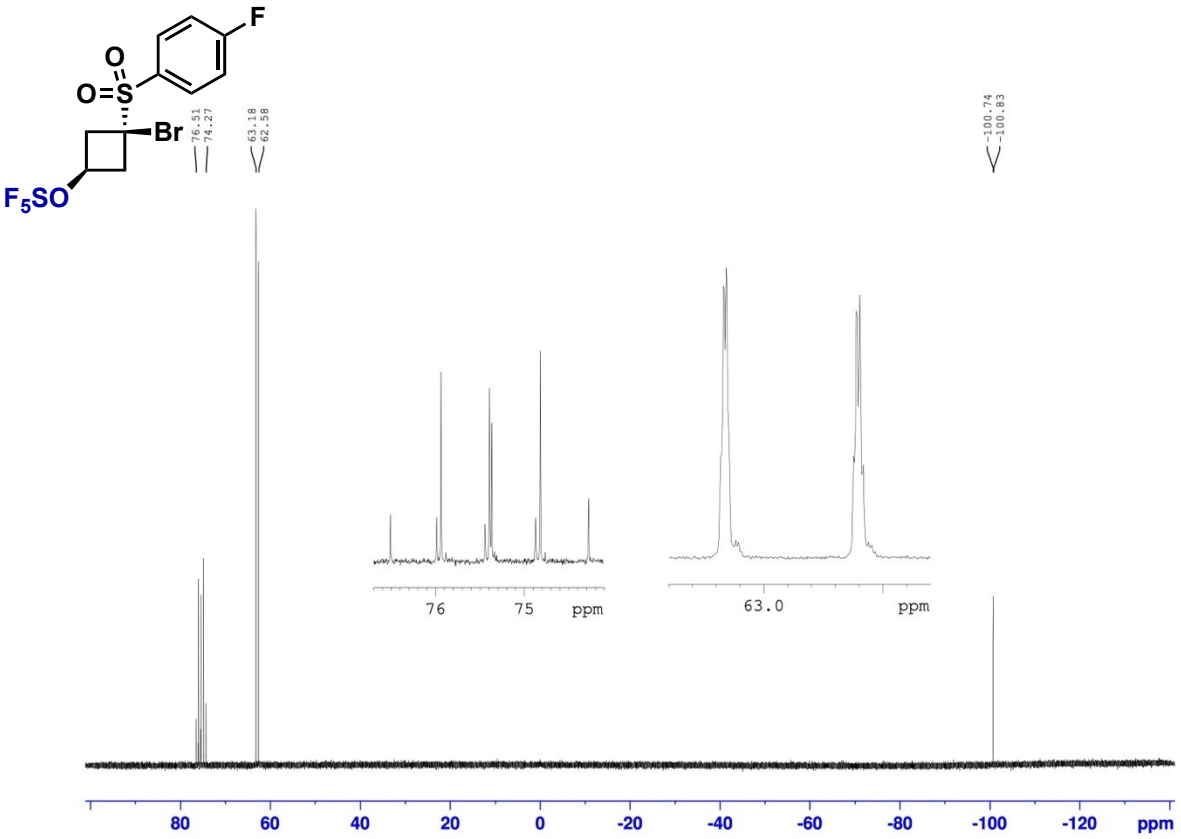


Figure S69. ^{19}F NMR spectrum of 3-bromo-3-((4-fluorophenyl)sulfonyl)cyclobutoxy)pentafluoro-λ^6-sulfane (compound **18**, *syn* isomer) in $CDCl_3$.

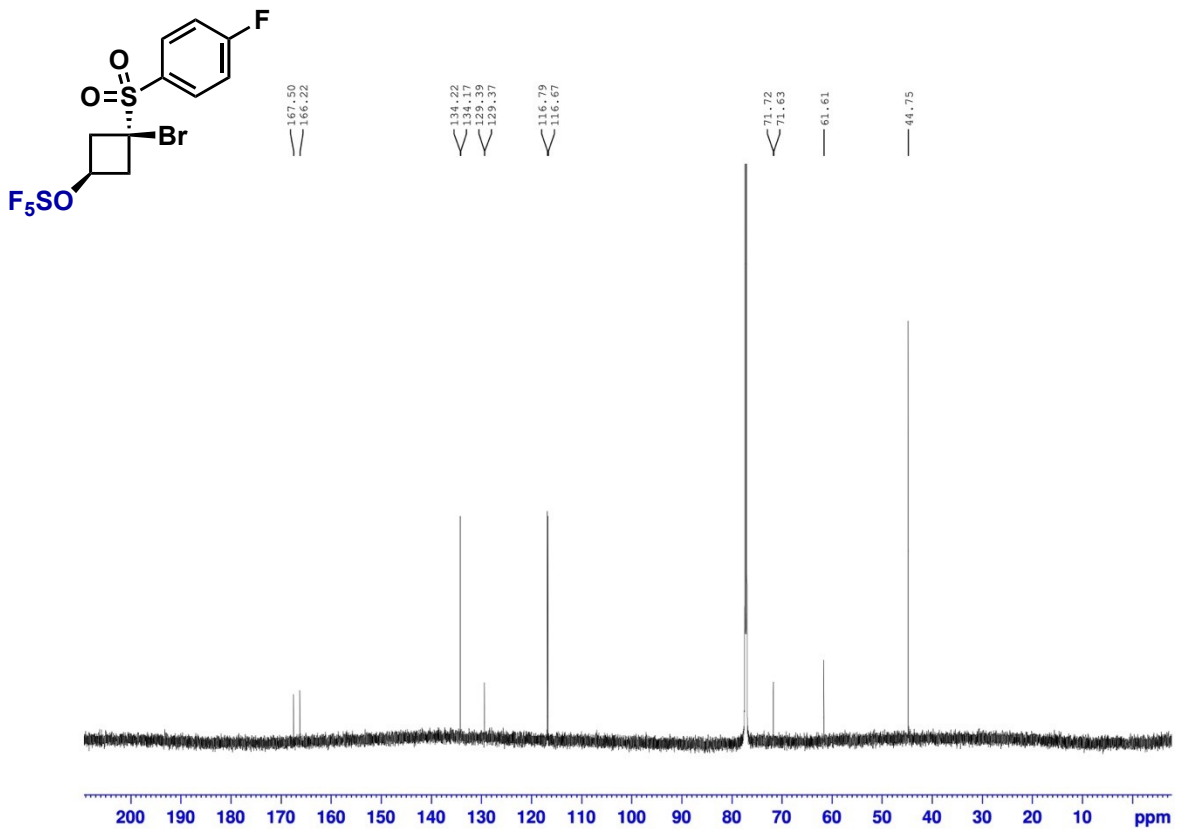


Figure S70. $^{13}C\{^{1}H\}$ NMR spectrum of 3-bromo-3-((4-fluorophenyl)sulfonyl)cyclobutoxy)pentafluoro-λ^{6}-sulfane (compound **18**, *syn* isomer) in $CDCl_3$.

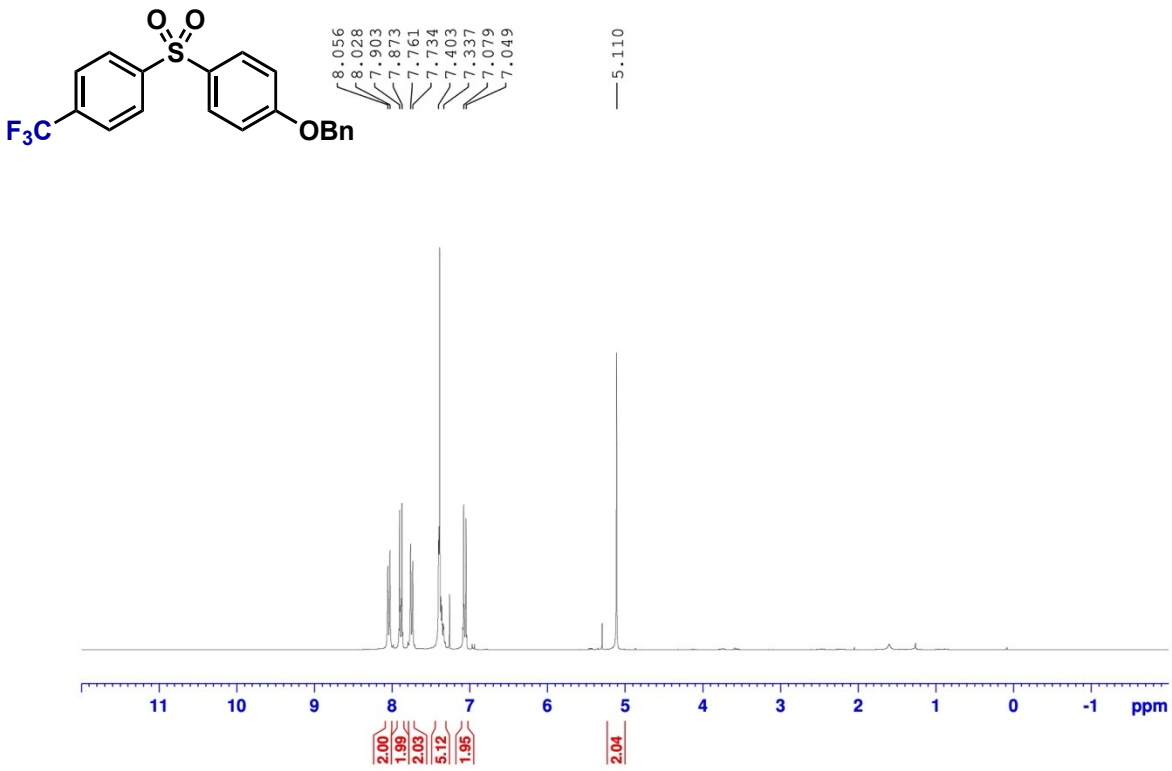


Figure S71. ^{1}H NMR spectrum of 1-(benzyloxy)-4-((4-(trifluoromethyl)phenyl)sulfonyl)benzene (compound **21**) in $CDCl_3$.

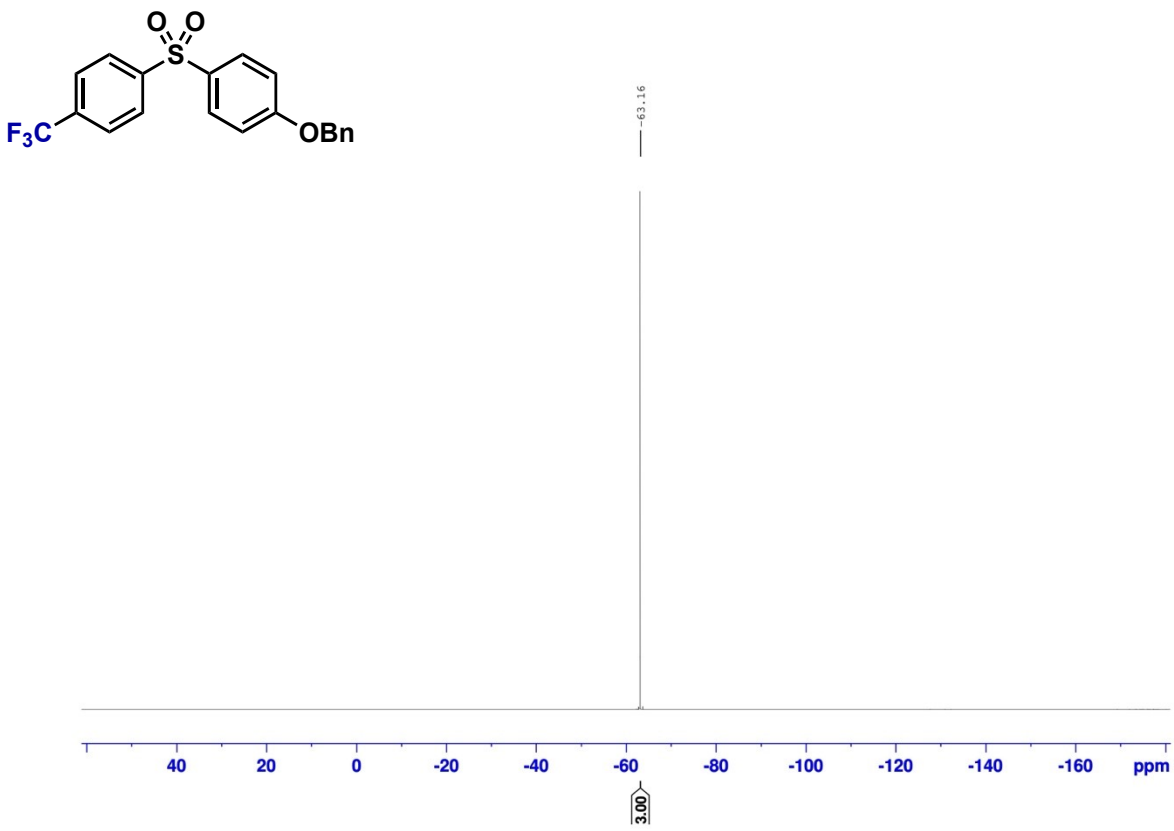


Figure S72. ^{19}F NMR spectrum of 1-(benzyloxy)-4-((4-(trifluoromethyl)phenyl)sulfonyl)benzene (compound **21**) in $CDCl_3$.

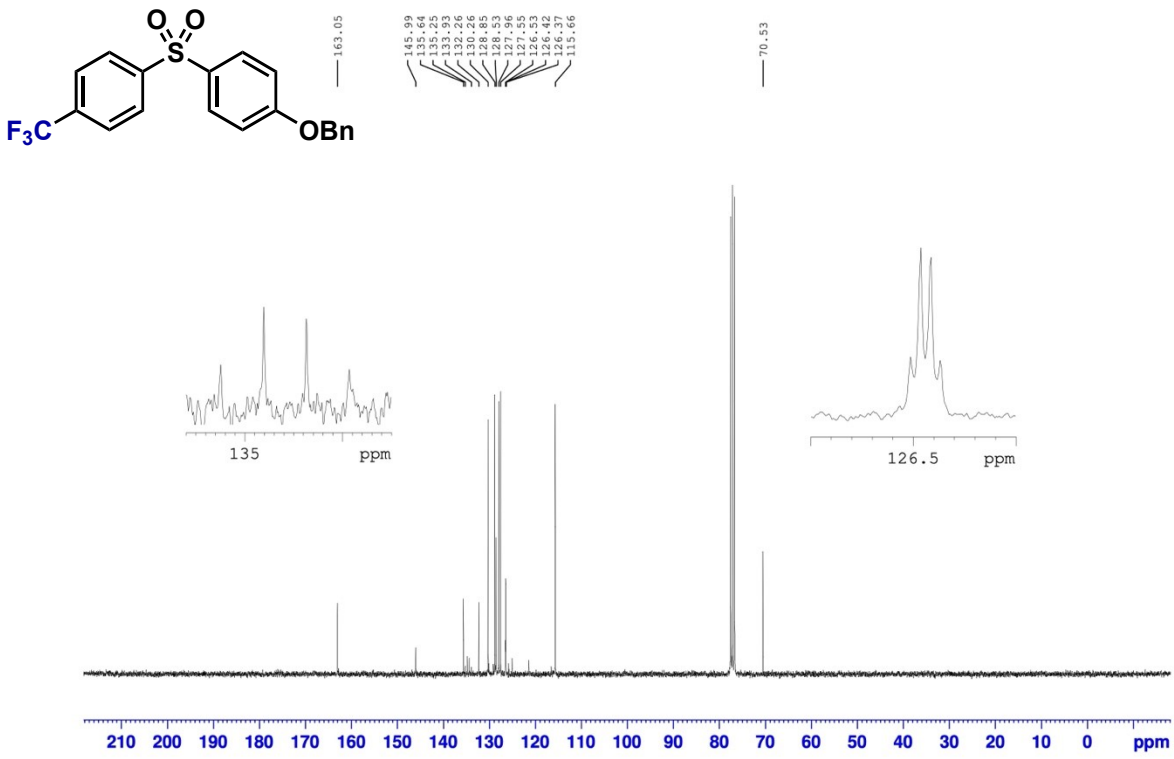


Figure S73. $^{13}C\{^{1}H\}$ NMR spectrum of 1-(benzyloxy)-4-((4-(trifluoromethyl)phenyl)sulfonyl)benzene (compound **21**) in $CDCl_3$.

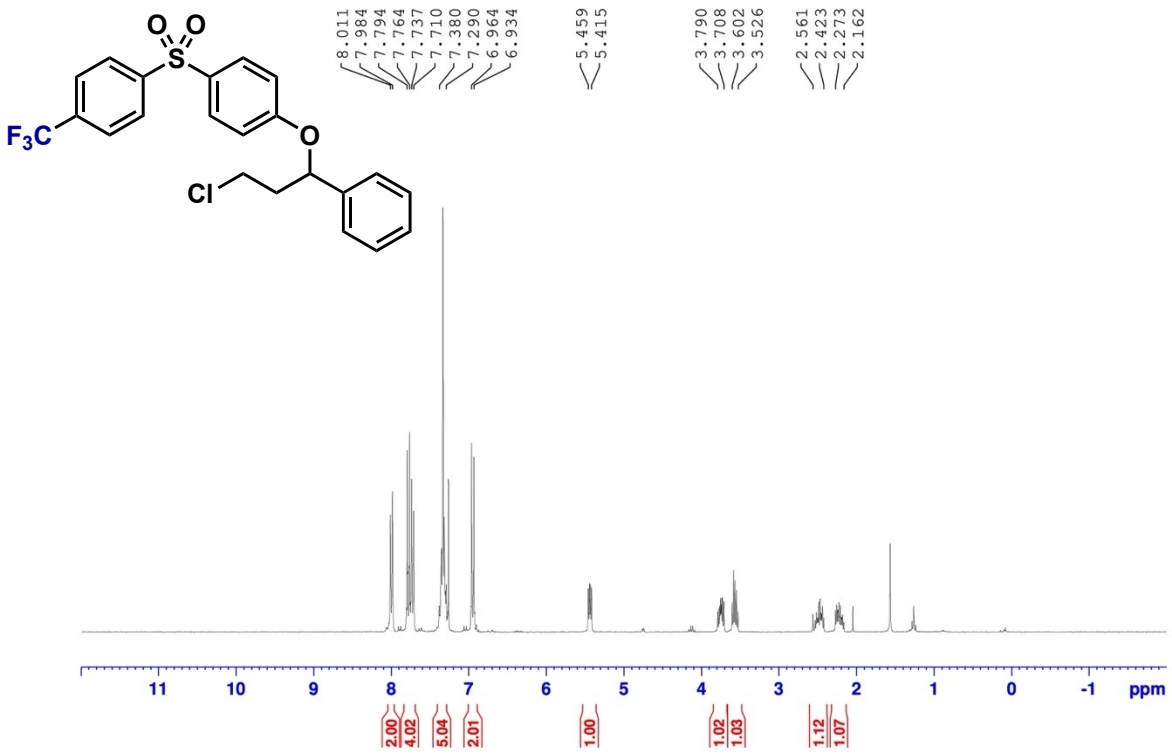


Figure S74. ^{1}H NMR spectrum of 1-(3-chloro-1-phenylpropoxy)-4-((4-(trifluoromethyl)phenyl)sulfonyl) benzene (compound **S4**) in $CDCl_3$.

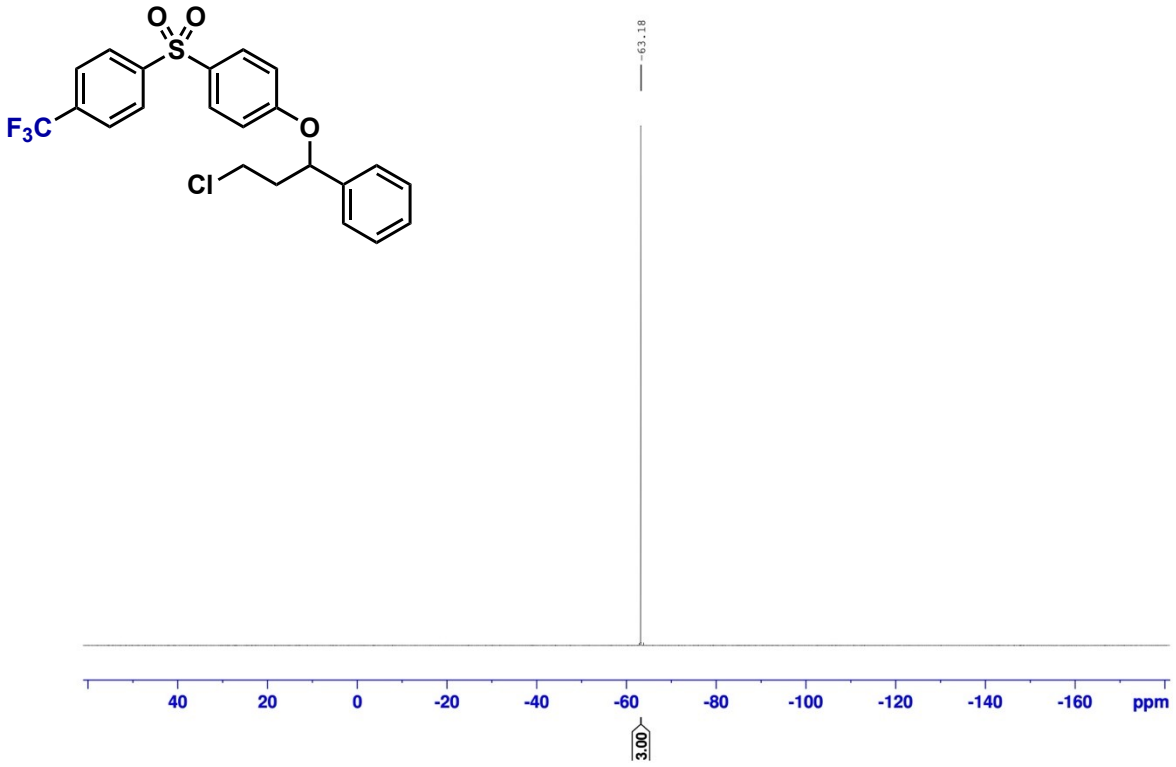


Figure S75. ^{19}F NMR spectrum of 1-(3-chloro-1-phenylpropoxy)-4-((4-(trifluoromethyl)phenyl)sulfonyl) benzene (compound **S4**) in $CDCl_3$.

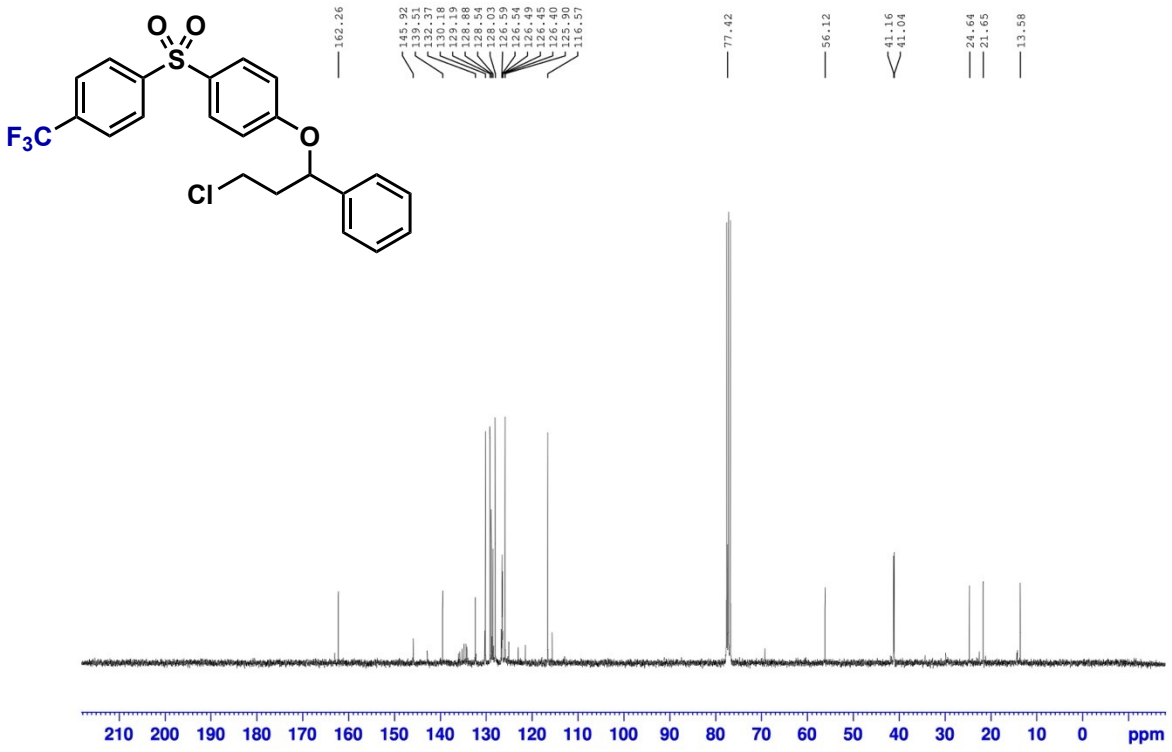


Figure S76. $^{13}C\{^{1}H\}$ NMR spectrum of 1-(3-chloro-1-phenylpropoxy)-4-((4-(trifluoromethyl)phenyl) sulfonyl)benzene (compound **S4**) in $CDCl_3$.

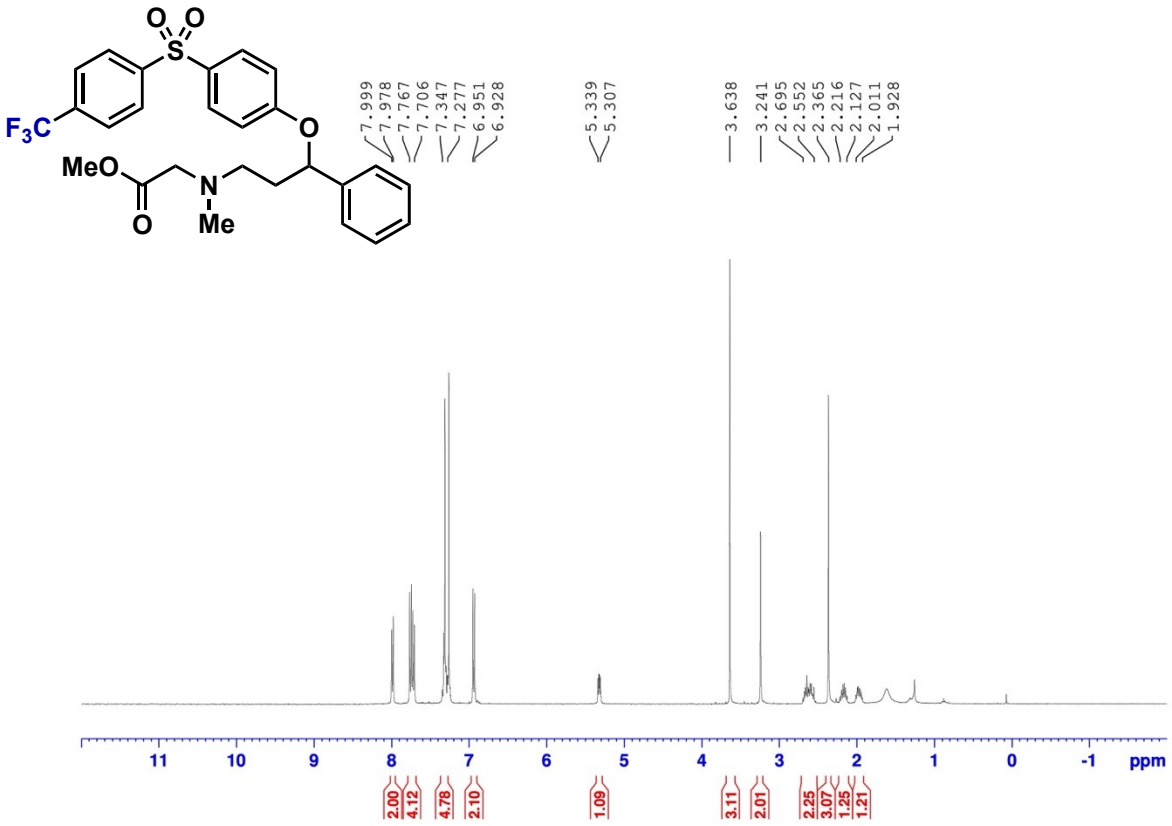


Figure S77. ^{1}H NMR spectrum of methyl *N*-methyl-*N*-(3-phenyl-3-(4-((4-(trifluoromethyl)phenyl)sulfonyl) phenoxy)propyl)glycinate (compound **S5**) in $CDCl_3$.

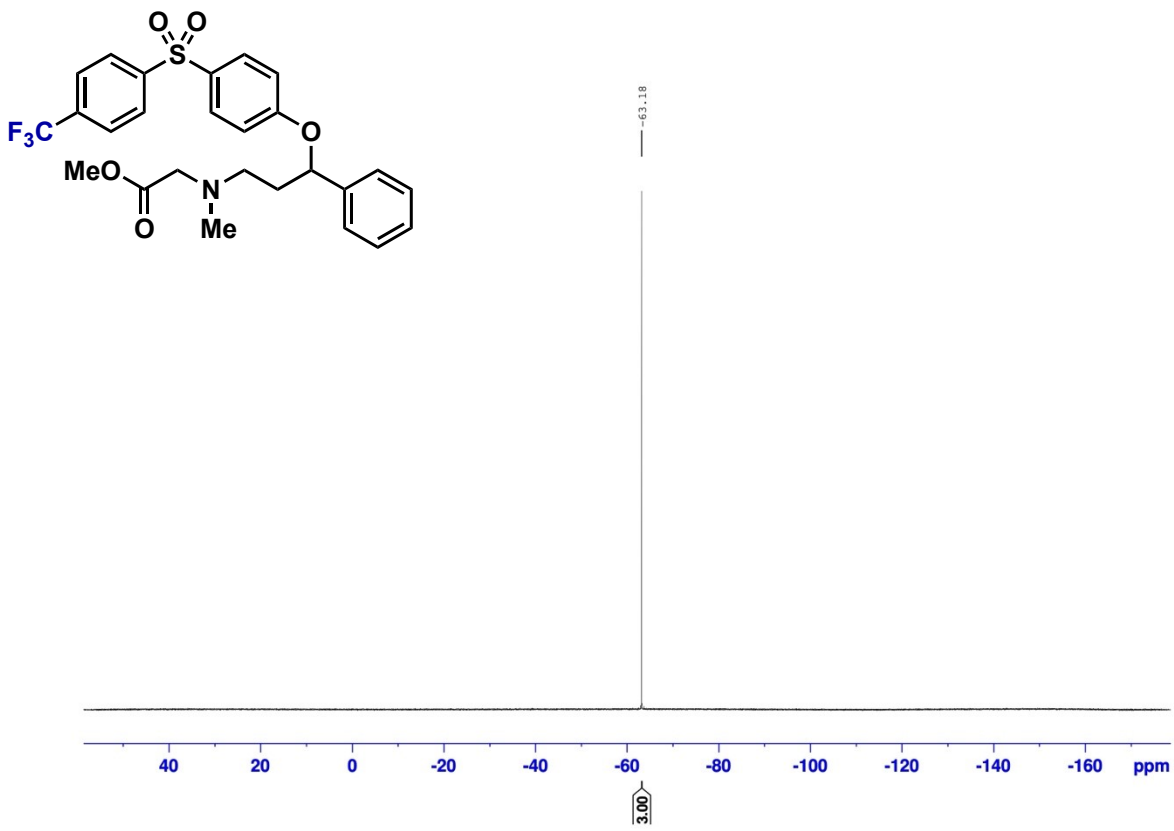


Figure S78. ^{19}F NMR spectrum of methyl *N*-methyl-*N*-(3-phenyl-3-(4-((4-(trifluoromethyl)phenyl)sulfonyl) phenoxy)propyl)glycinate (compound **S5**) in $CDCl_3$.

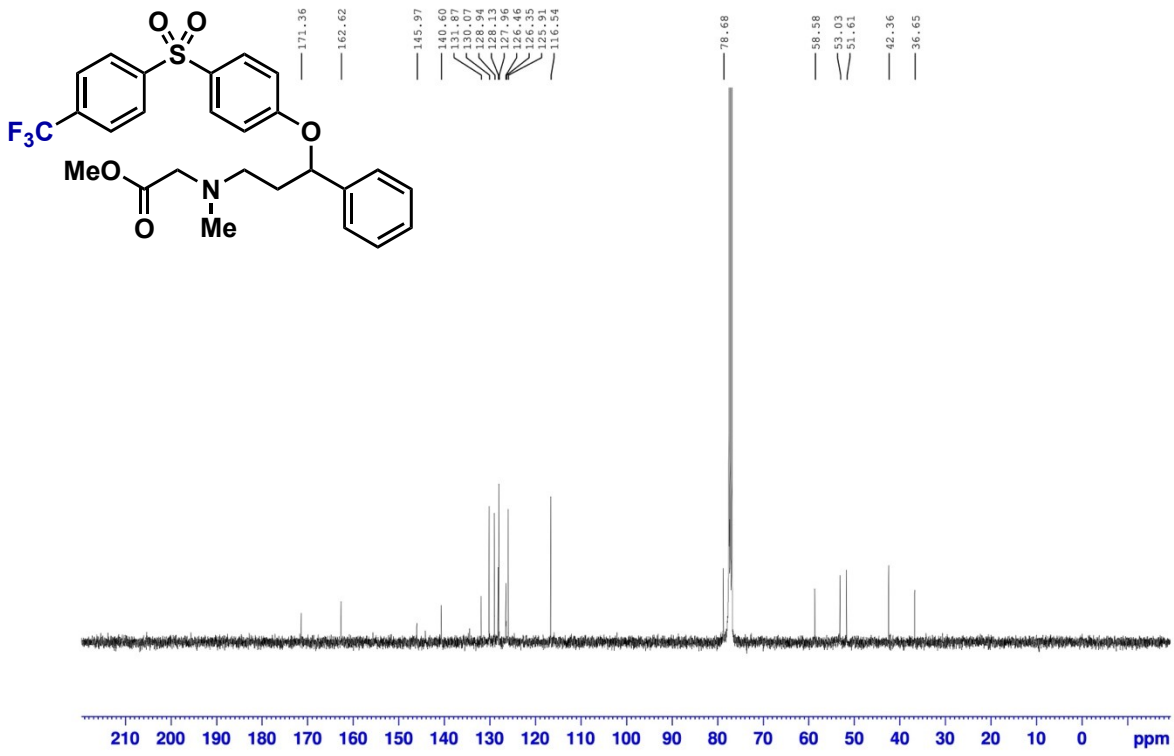


Figure S79. $^{13}C\{^{1}H\}$ NMR spectrum of methyl *N*-methyl-*N*-(3-phenyl-3-(4-((4-(trifluoromethyl)phenyl)sulfonyl) phenoxy)propyl)glycinate (compound **S5**) in $CDCl_3$.

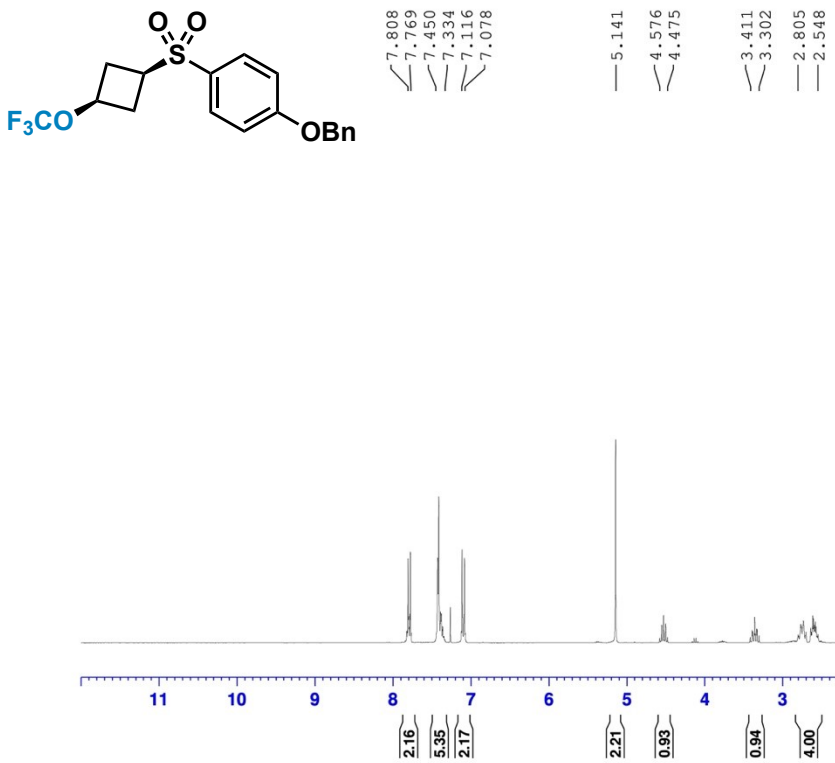


Figure S80. ^{1}H NMR spectrum of 1-(benzyloxy)-4-((3-(trifluoromethoxy)cyclobutyl)sulfonyl)benzene (compound ***cis*-19**) in $CDCl_3$.

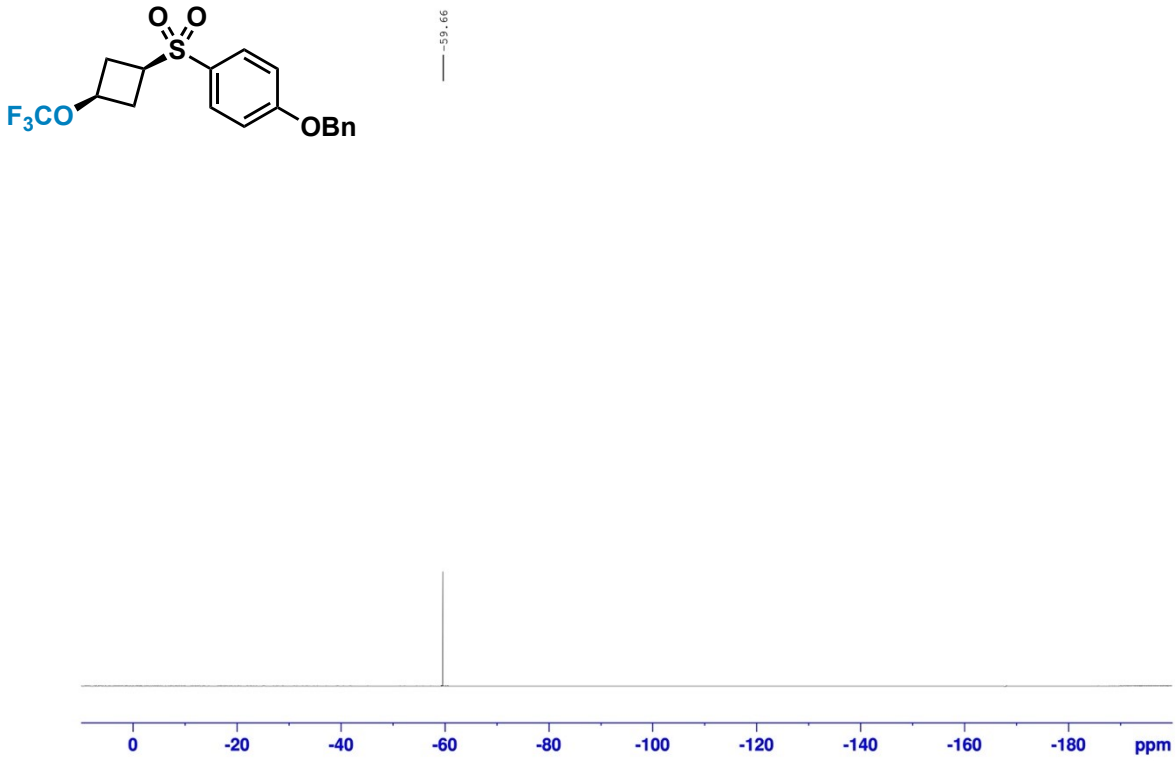


Figure S81. ^{19}F NMR spectrum of 1-(benzyloxy)-4-((3-(trifluoromethoxy)cyclobutyl)sulfonyl)benzene (compound ***cis*-19**) in $CDCl_3$.

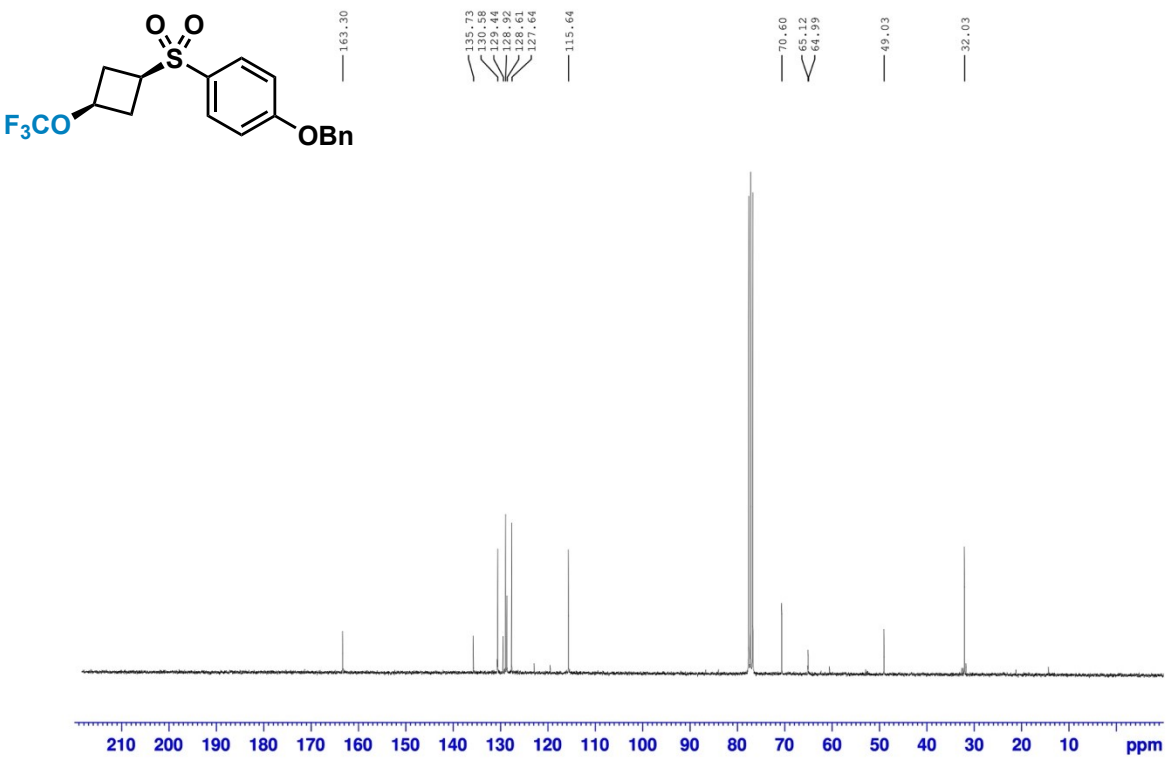


Figure S82. $^{13}C\{^{1}H\}$ NMR spectrum of 1-(benzyloxy)-4-((3-(trifluoromethoxy)cyclobutyl)sulfonyl)benzene (compound ***cis*-19**) in $CDCl_3$.

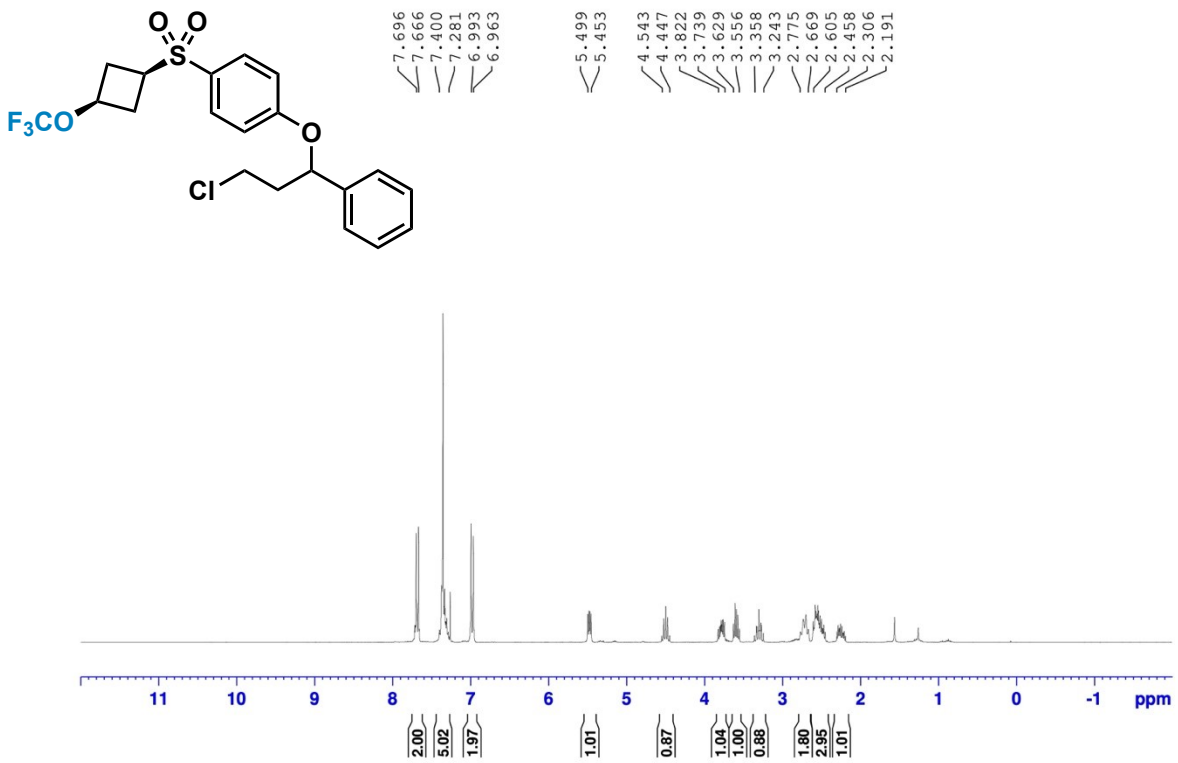


Figure S83. ^{1}H NMR spectrum of 1-(3-chloro-1-phenylpropoxy)-4-((3-(trifluoromethoxy)cyclobutyl) sulfonyl)benzene (compound **S6**) in $CDCl_3$.

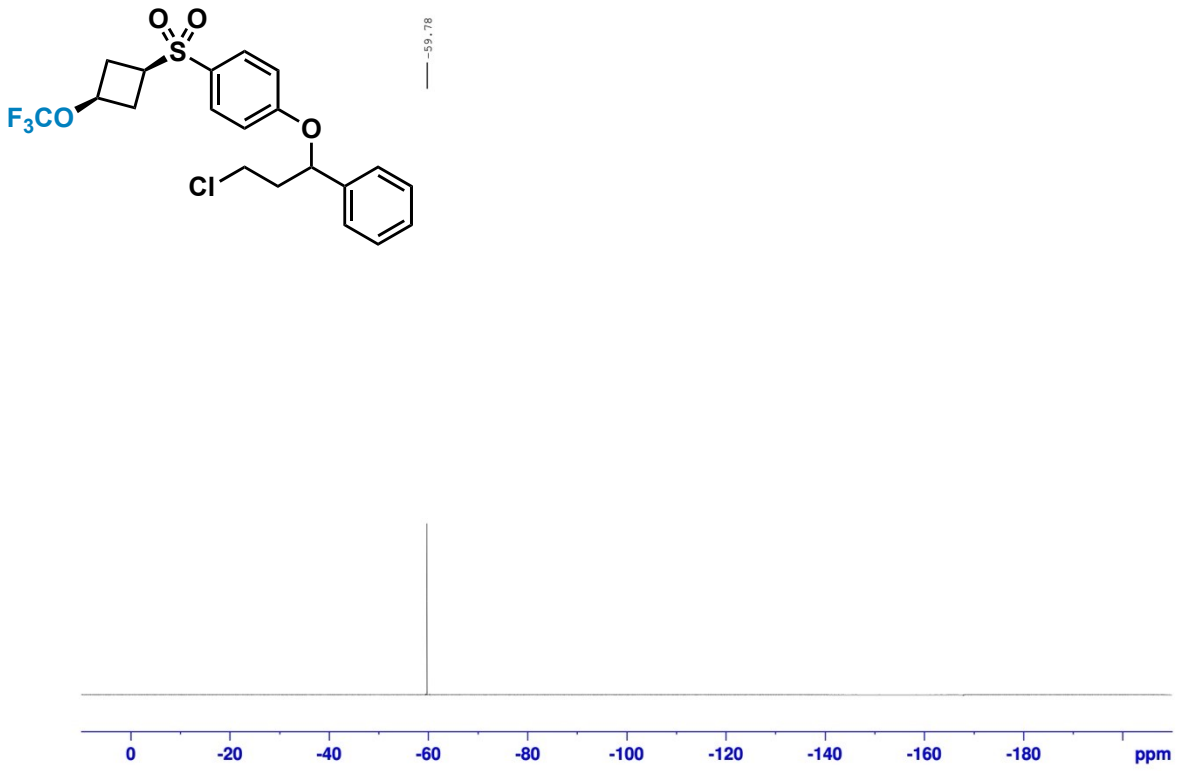


Figure S84. ^{19}F NMR spectrum of 1-(3-chloro-1-phenylpropoxy)-4-((3-(trifluoromethoxy)cyclobutyl) sulfonyl)benzene (compound **S6**) in $CDCl_3$.

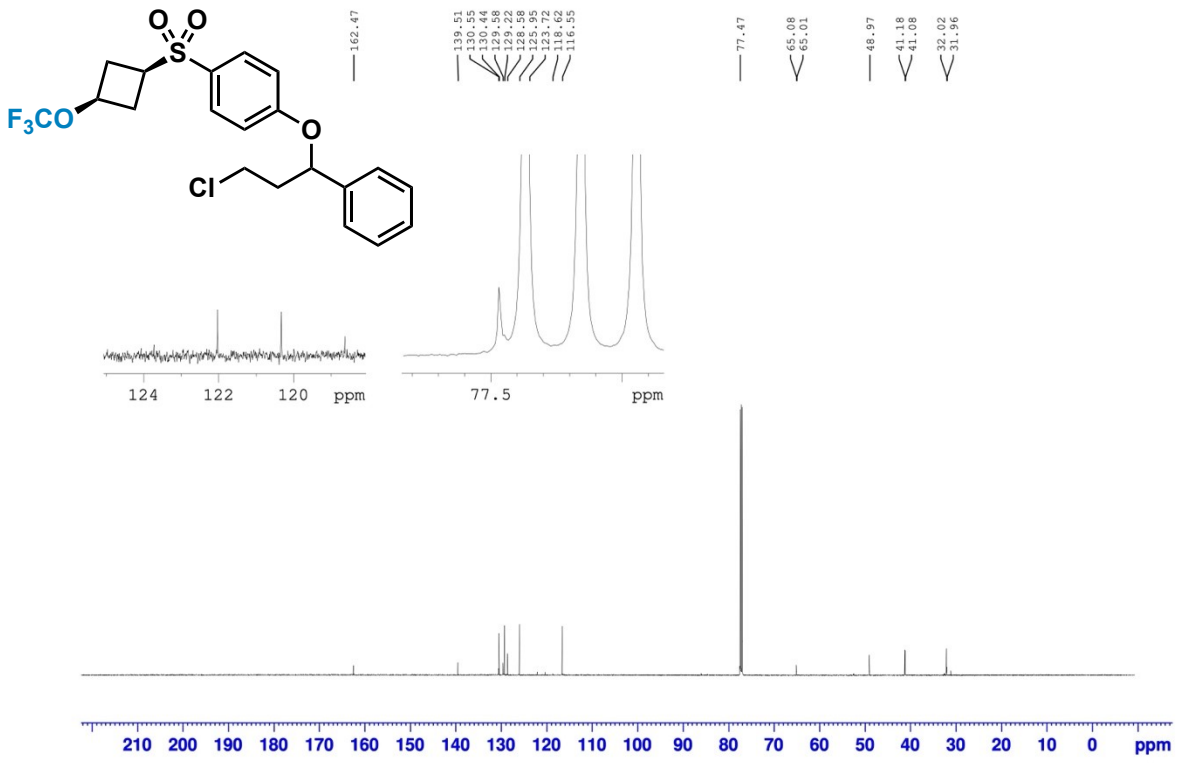


Figure S85. $^{13}C\{^{1}H\}$ NMR spectrum of 1-(3-chloro-1-phenylpropoxy)-4-((3-(trifluoromethoxy)cyclobutyl) sulfonyl)benzene (compound **S6**) in $CDCl_3$.

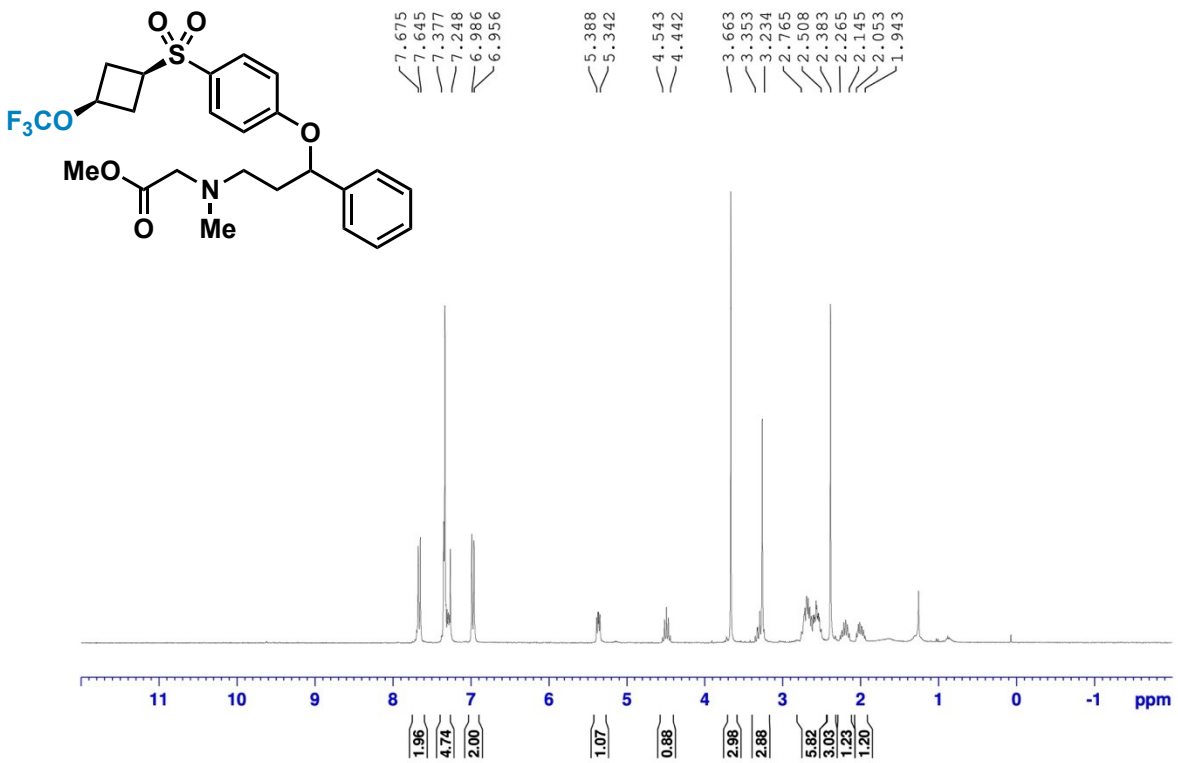


Figure S86. ^{1}H NMR spectrum of methyl *N*-methyl-*N*-(3-phenyl-3-(4-((3-(trifluoromethoxy)cyclobutyl) sulfonyl)phenoxy)propyl)glycinate (compound **S7**) in $CDCl_3$.

Figure S87. ^{19}F NMR spectrum of methyl *N*-methyl-*N*-(3-phenyl-3-(4-((3-(trifluoromethoxy)cyclobutyl) sulfonyl)phenoxy)propyl)glycinate (compound **S7**) in $CDCl_3$.

Figure S88. $^{13}C\{^{1}H\}$ NMR spectrum of methyl *N*-methyl-*N*-(3-phenyl-3-(4-((3-(trifluoromethoxy)cyclobutyl) sulfonyl)phenoxy)propyl)glycinate (compound **S7**) in $CDCl_3$.

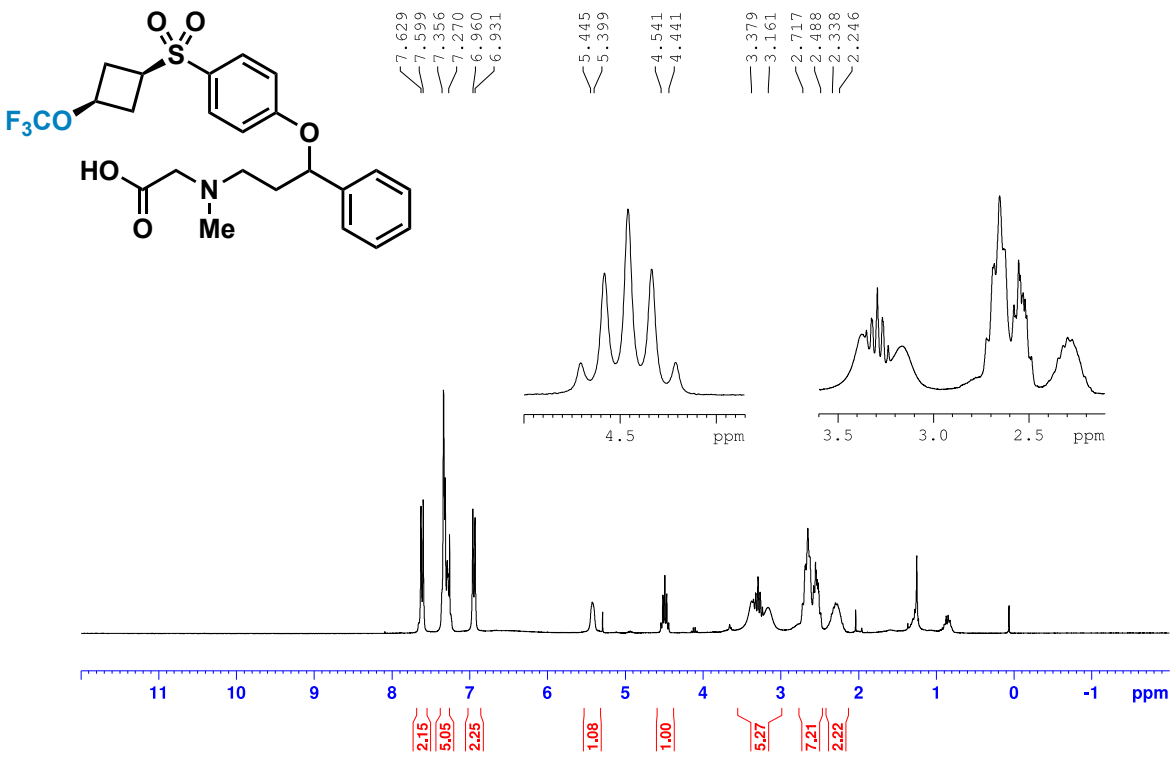


Figure S89. ^{1}H NMR spectrum of *N*-methyl-*N*-(3-phenyl-3-(4-((3-(trifluoromethoxy)cyclobutyl)sulfonyl) phenoxy)propyl)glycine (compound **23**) in $CDCl_3$.

Figure S90. ^{19}F NMR spectrum of *N*-methyl-*N*-(3-phenyl-3-(4-((3-(trifluoromethoxy)cyclobutyl)sulfonyl) phenoxy)propyl)glycine (compound **23**) in $CDCl_3$.

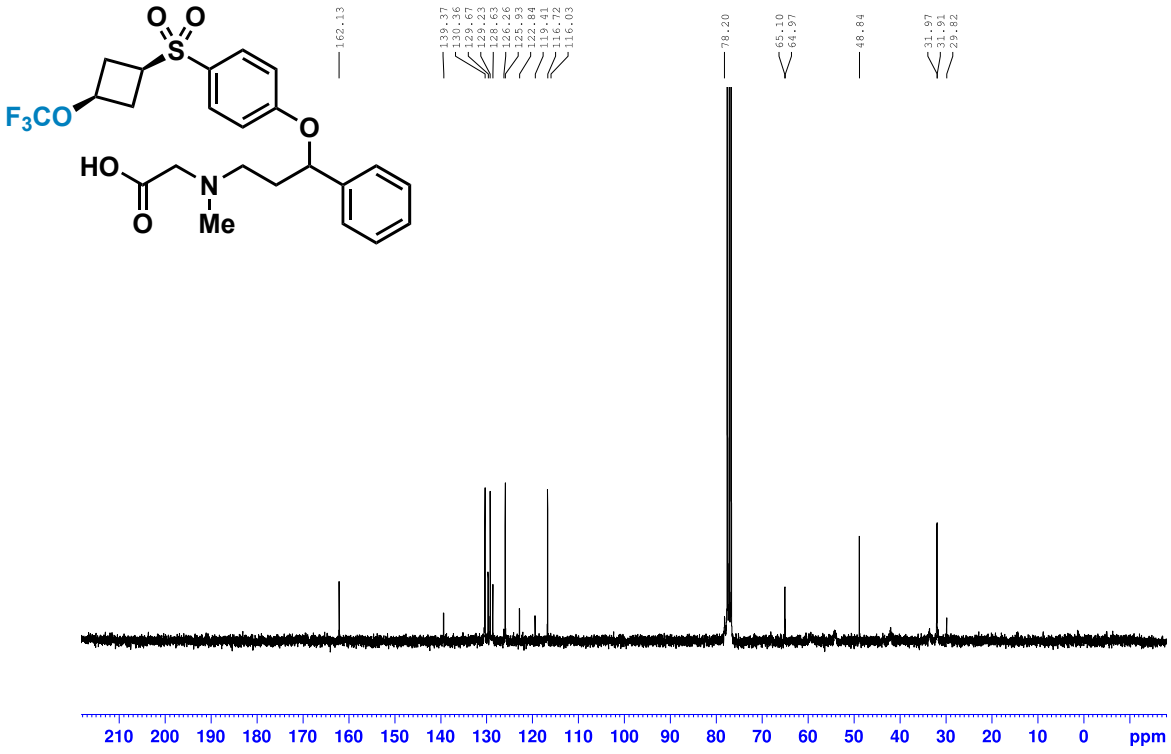


Figure S91. $^{13}C\{^{1}H\}$ NMR spectrum of *N*-methyl-*N*-(3-phenyl-3-(4-((3-(trifluoromethoxy)cyclobutyl)sulfonyl) phenoxy)propyl)glycine (compound **23**) in $CDCl_3$.

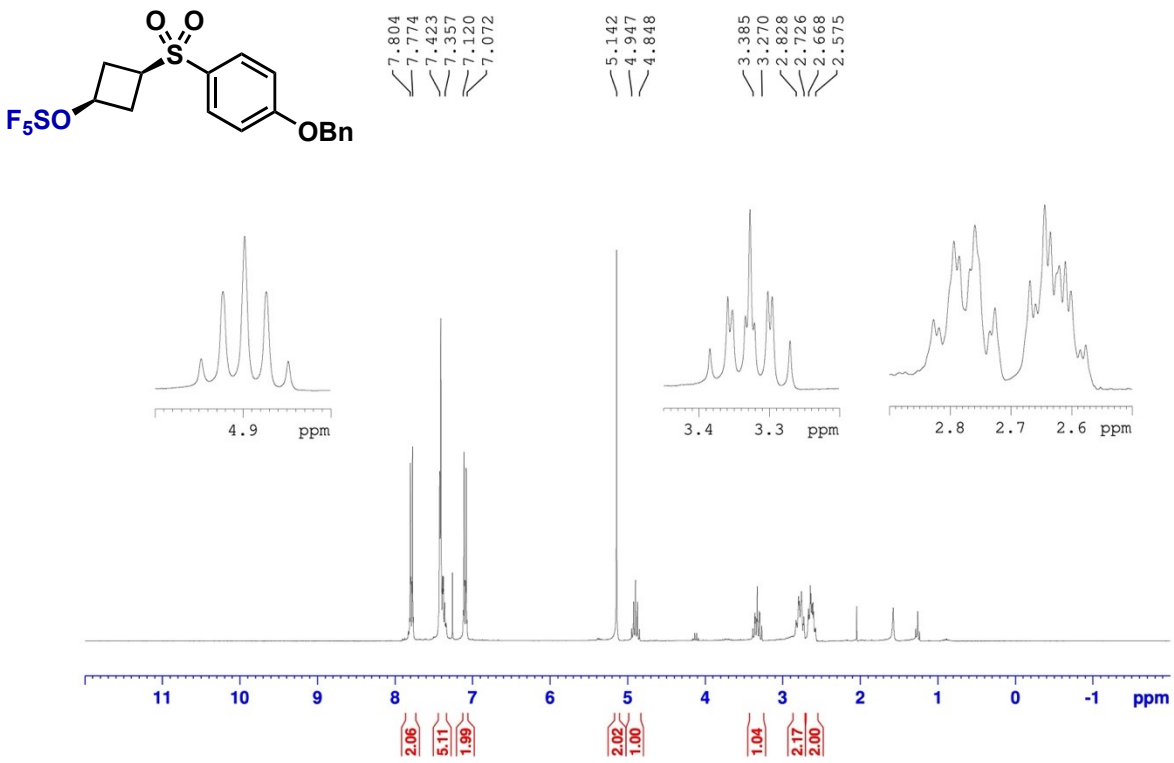


Figure S92. ^{1}H NMR spectrum of (3-((4-(benzyloxy)phenyl)sulfonyl)cyclobutoxy)pentafluoro-λ^{6}-sulfane (compound ***cis*-20)** in $CDCl_3$.

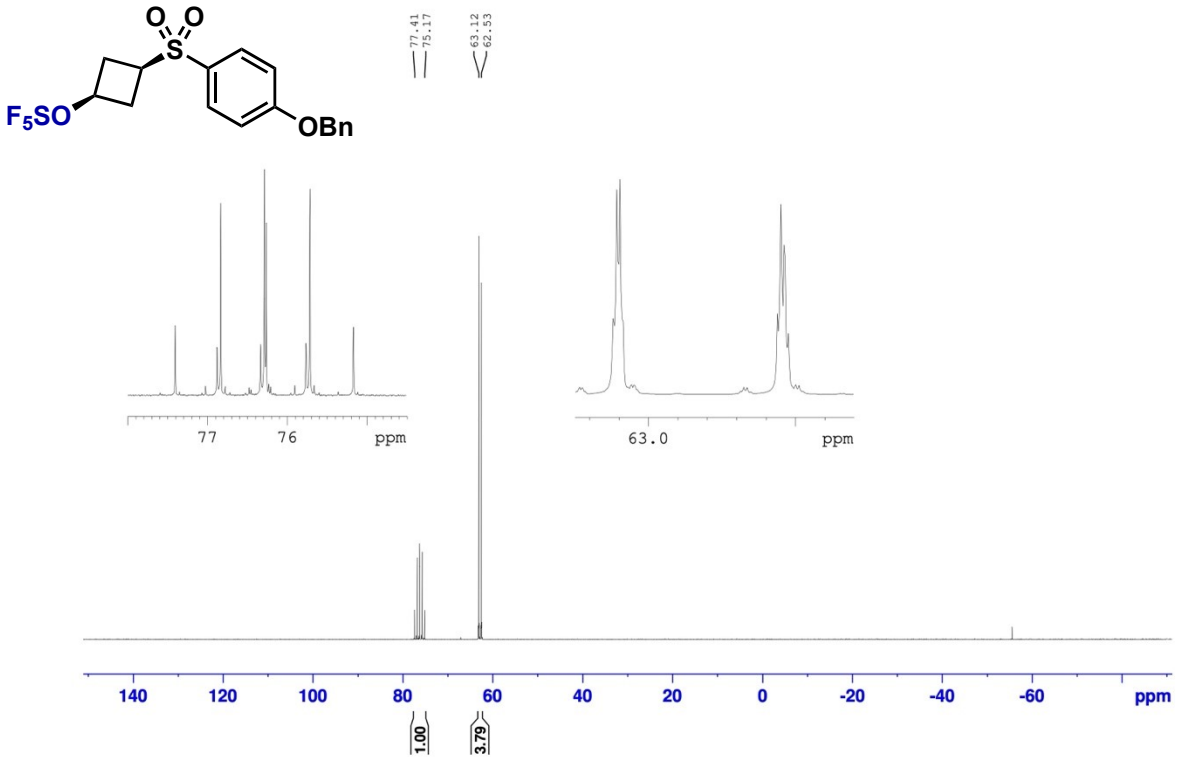


Figure S93. ^{19}F NMR spectrum of (3-((4-(benzyloxy)phenyl)sulfonyl)cyclobutoxy)pentafluoro-λ^6-sulfane (compound ***cis*-20** in $CDCl_3$.

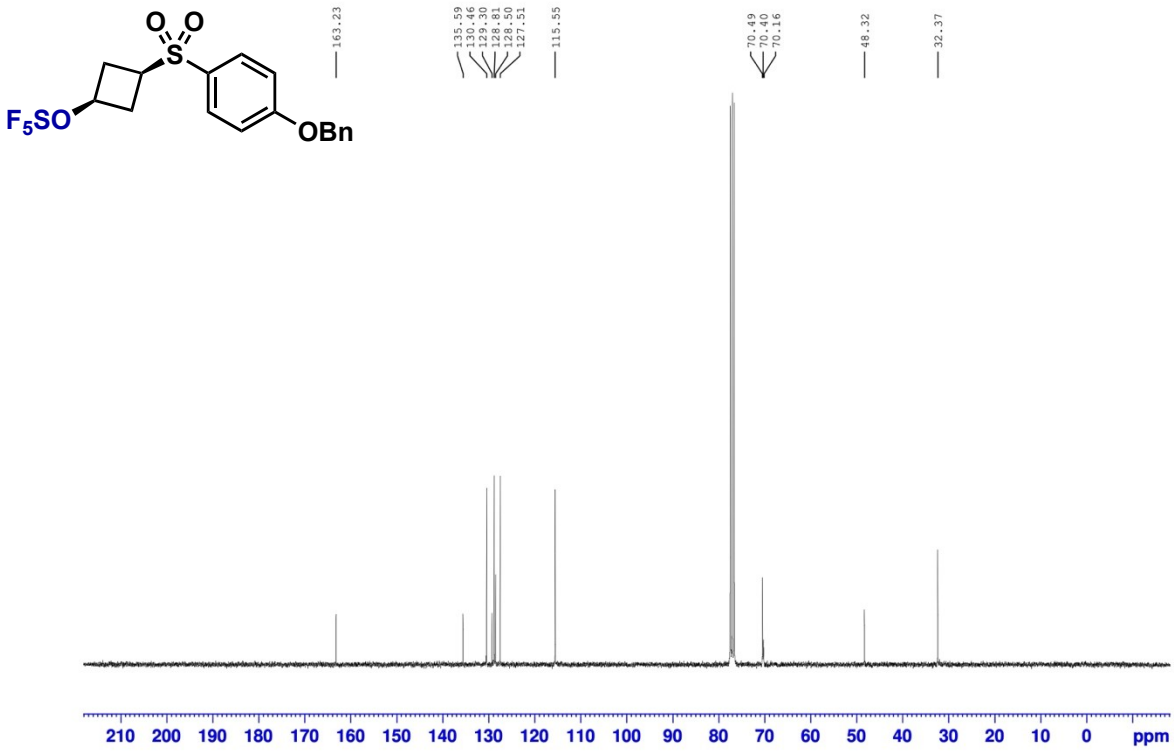


Figure S94. $^{13}C\{^{1}H\}$ NMR spectrum of (3-((4-(benzyloxy)phenyl)sulfonyl)cyclobutoxy)pentafluoro-λ^6-sulfane (compound ***cis*-20**) in $CDCl_3$.

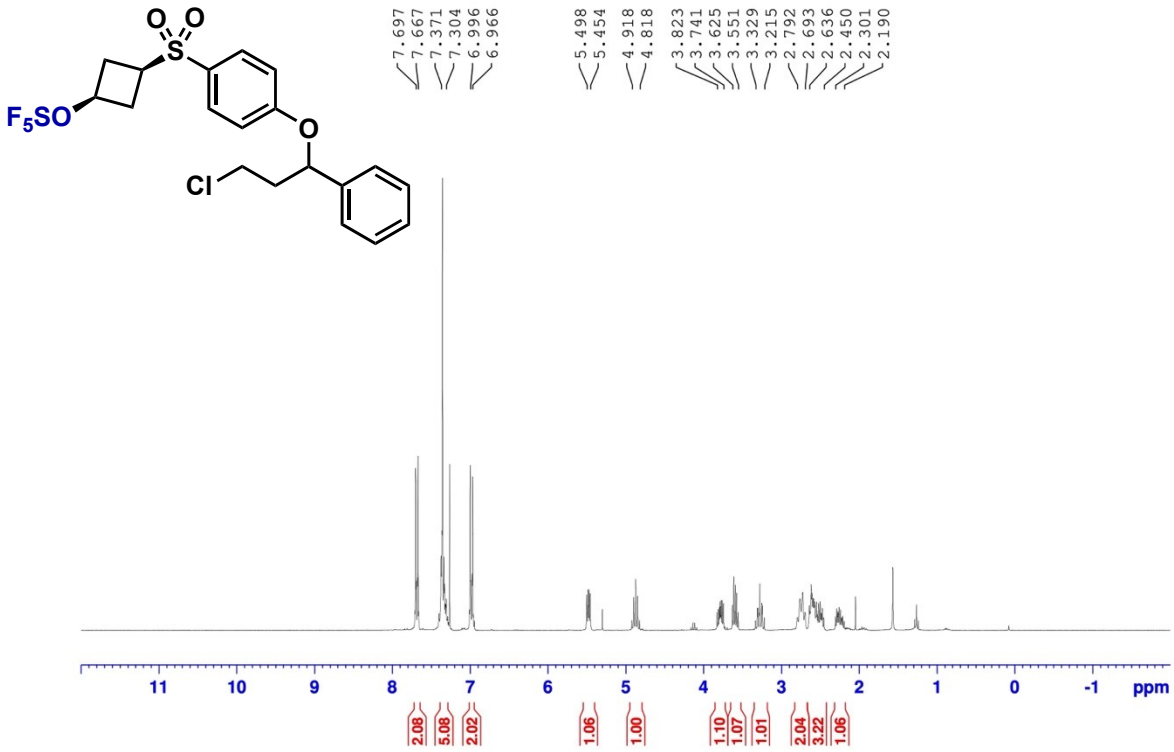


Figure S95. ^{1}H NMR spectrum of (3-((4-(3-chloro-1-phenylpropoxy)phenyl)sulfonyl)cyclobutoxy) pentafluoro-λ^{6}-sulfane (compound **S8**) in $CDCl_3$.

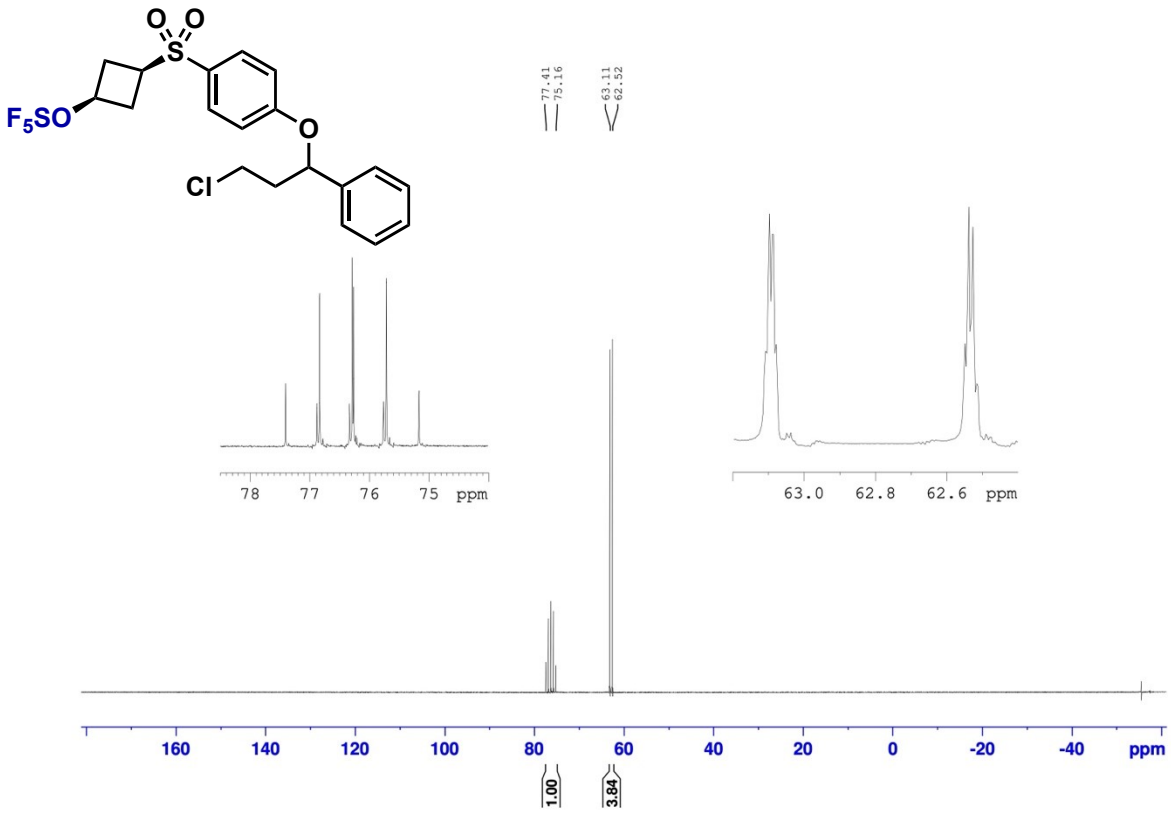


Figure S96. ^{19}F NMR spectrum of (3-((4-(3-chloro-1-phenylpropoxy)phenyl)sulfonyl)cyclobutoxy) pentafluoro-λ^6-sulfane (compound **S8**) in $CDCl_3$.

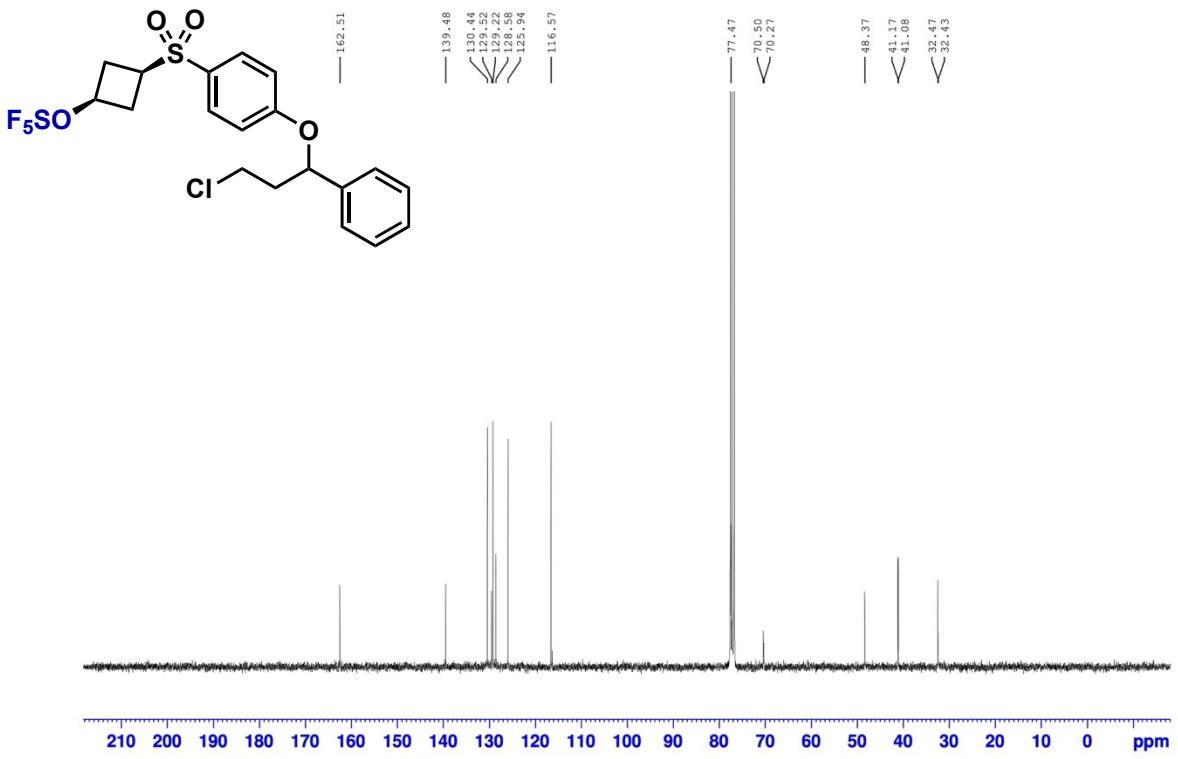


Figure S97. $^{13}C\{^{1}H\}$ NMR spectrum of (3-((4-(3-chloro-1-phenylpropoxy)phenyl)sulfonyl)cyclobutoxy) pentafluoro-λ^6-sulfane (compound **S8**) in $CDCl_3$.

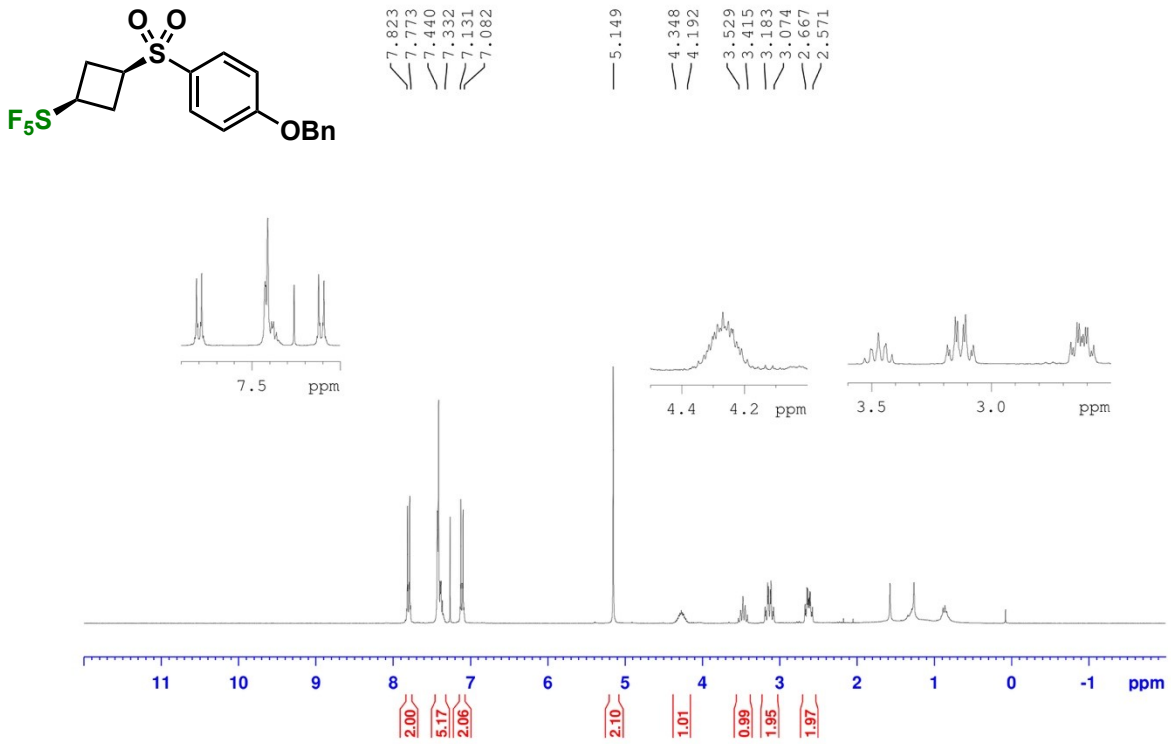


Figure S98. ^{1}H NMR spectrum of 3-((4-(benzyloxy)phenyl)sulfonyl)cyclobutyl)pentafluoro-λ^{6}-sulfane (compound ***cis*-S10**) in $CDCl_3$.

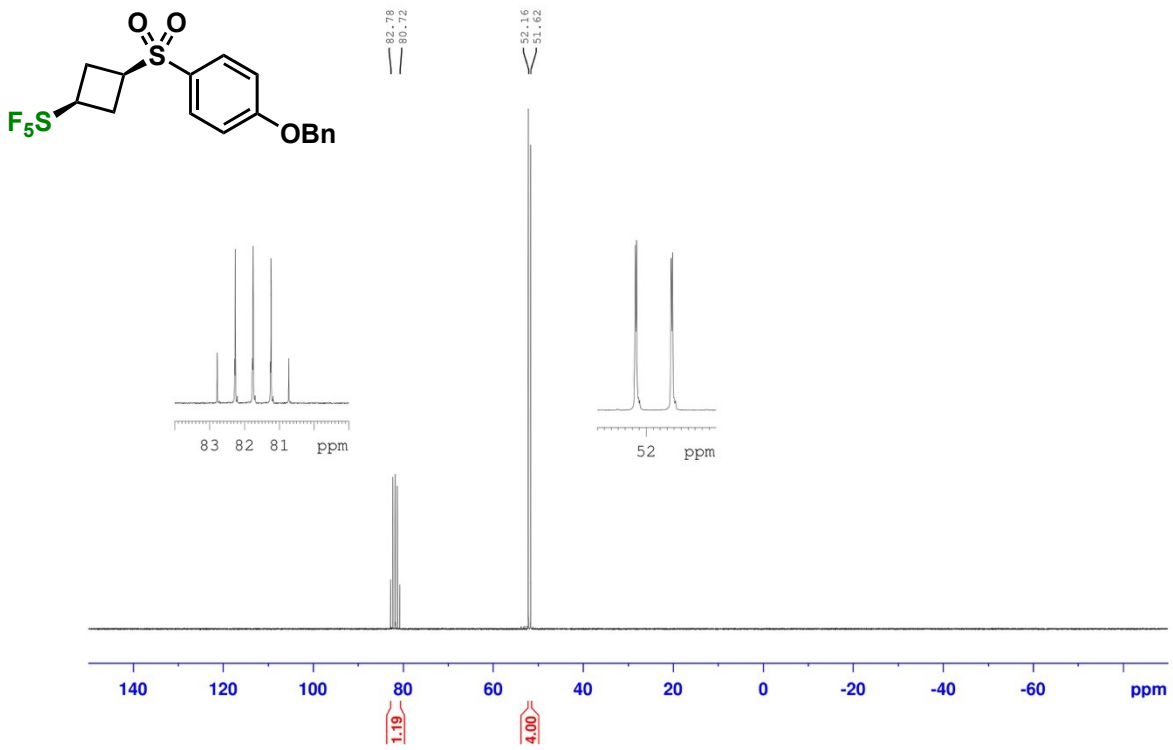


Figure S99. ^{19}F NMR spectrum of 3-((4-(benzyloxy)phenyl)sulfonyl)cyclobutyl)pentafluoro-λ^6-sulfane (compound ***cis*-S10**) in $CDCl_3$.

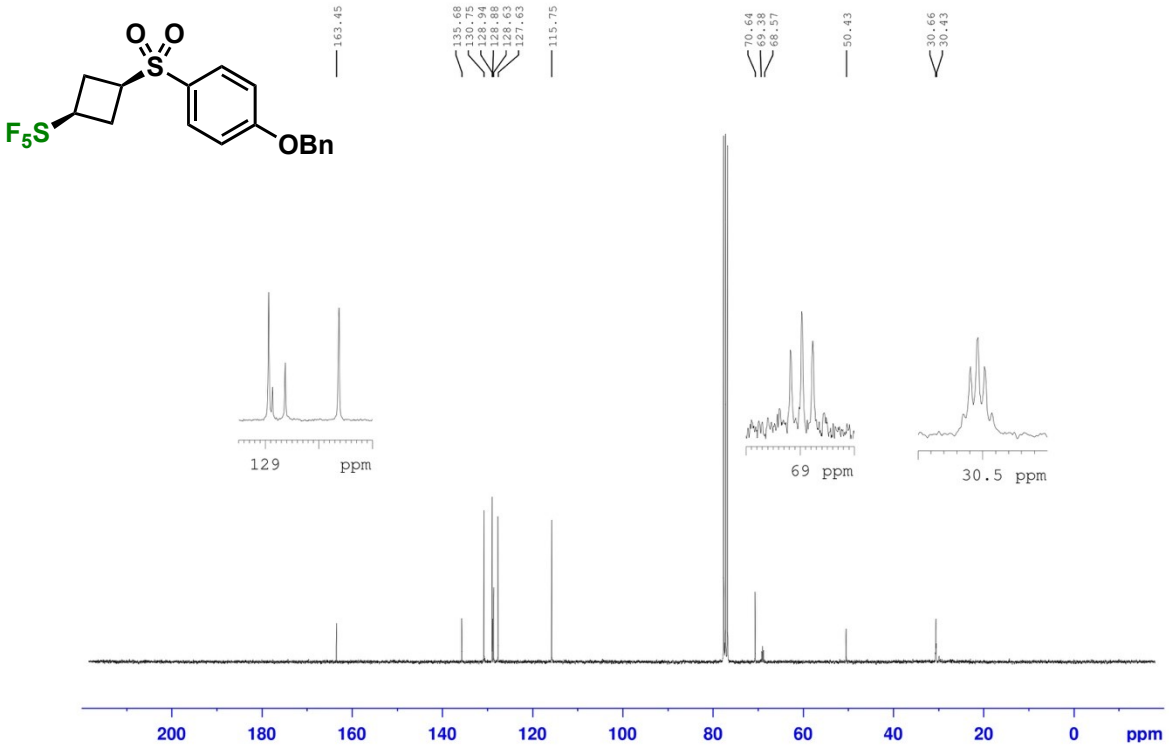


Figure S100. $^{13}C\{^{1}H\}$ NMR spectrum of 3-((4-(benzyloxy)phenyl)sulfonyl)cyclobutyl)pentafluoro-λ^6-sulfane (compound ***cis*-S10**) in $CDCl_3$.

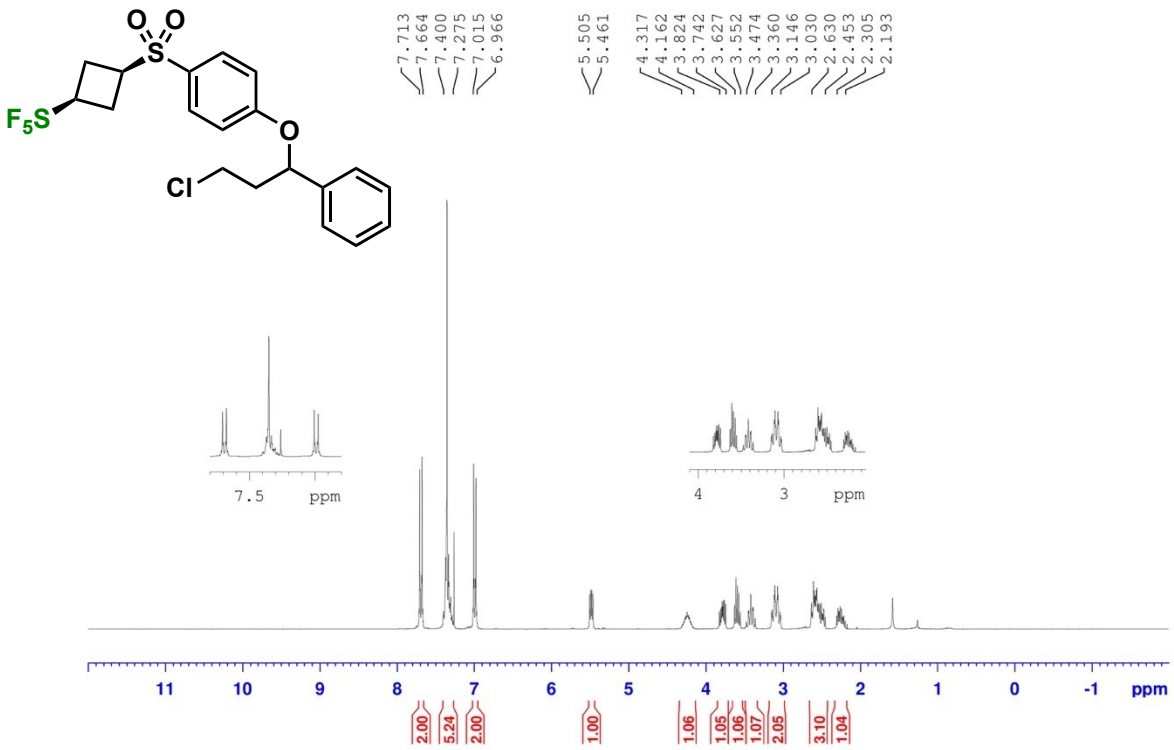


Figure S101. ^{1}H NMR spectrum (3-((4-(3-chloro-1-phenylpropoxy)phenyl)sulfonyl)cyclobutyl)pentafluoro-λ^{6}-sulfane (compound **S11**) in $CDCl_3$.

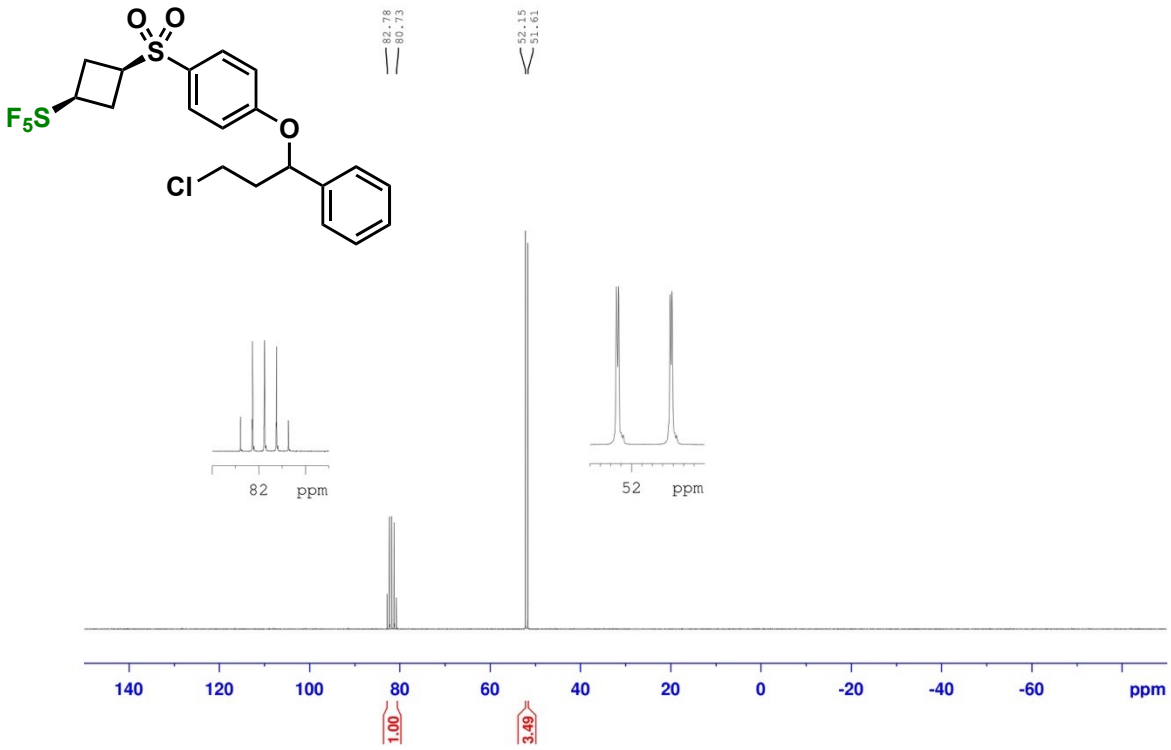


Figure S102. ^{19}F NMR spectrum (3-((4-(3-chloro-1-phenylpropoxy)phenyl)sulfonyl)cyclobutyl)pentafluoro-λ^6-sulfane (compound **S11**) in $CDCl_3$.

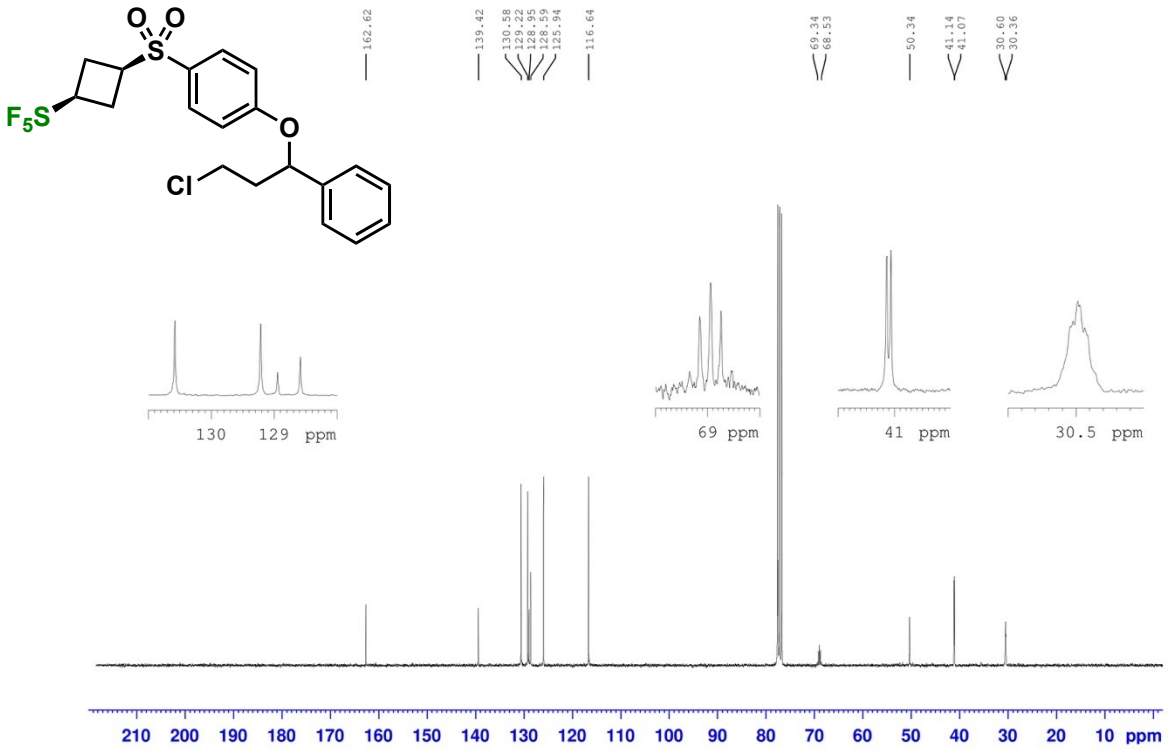


Figure S103. $^{13}C\{^{1}H\}$ NMR spectrum (3-((4-(3-chloro-1-phenylpropoxy)phenyl)sulfonyl)-cyclobutyl)pentafluoro-λ^6-sulfane (compound **S11**) in $CDCl_3$.

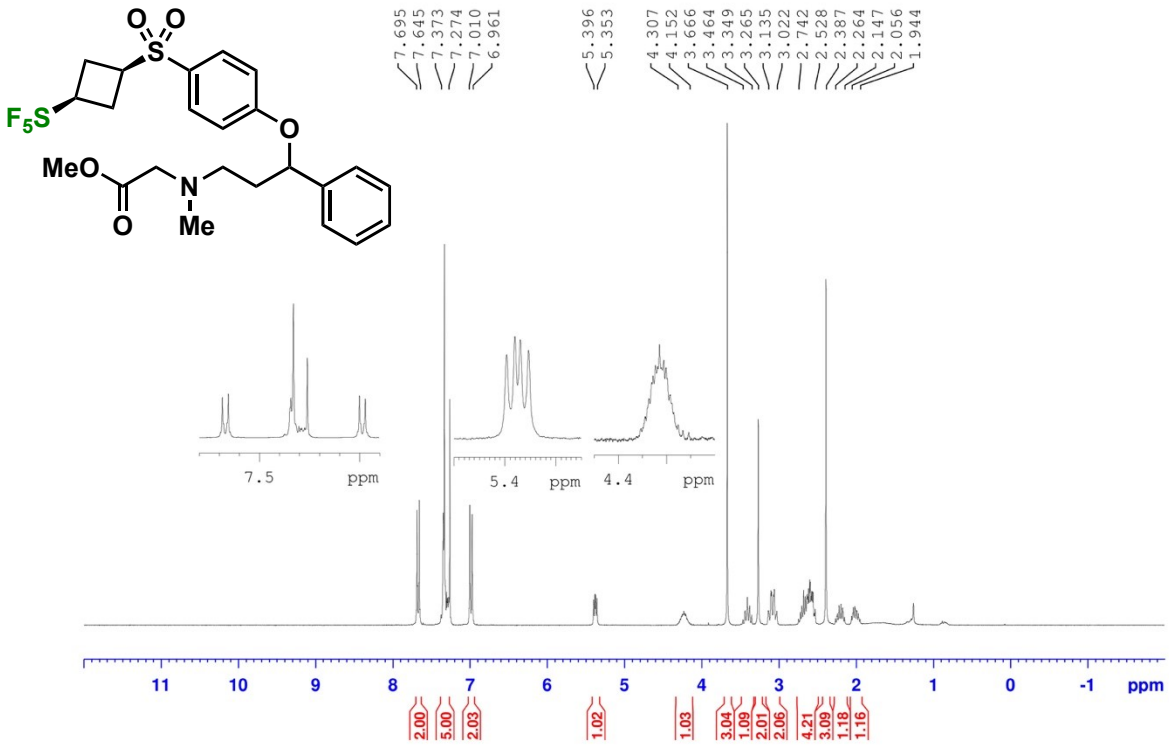


Figure S104. ^{1}H NMR spectrum methyl *N*-methyl-*N*-(3-(4-((3-(pentafluoro-λ^{6}-sulfaneyl)cyclobutyl)sulfonyl) phenoxy)-3-phenylpropyl)glycinate (compound **S12**) in $CDCl_3$.

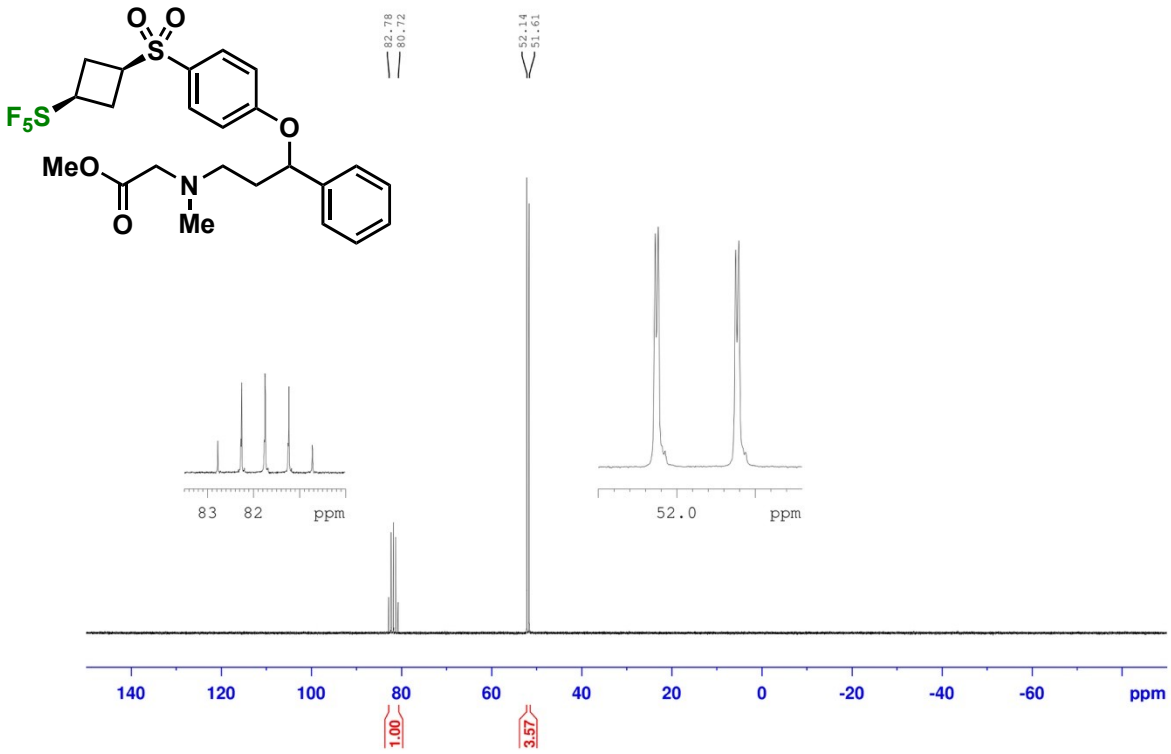


Figure S105. ^{19}F NMR spectrum methyl *N*-methyl-*N*-(3-(4-((3-(pentafluoro-λ^6-sulfaneyl)cyclobutyl)sulfonyl) phenoxy)-3-phenylpropyl)glycinate (compound **S12**) in $CDCl_3$.

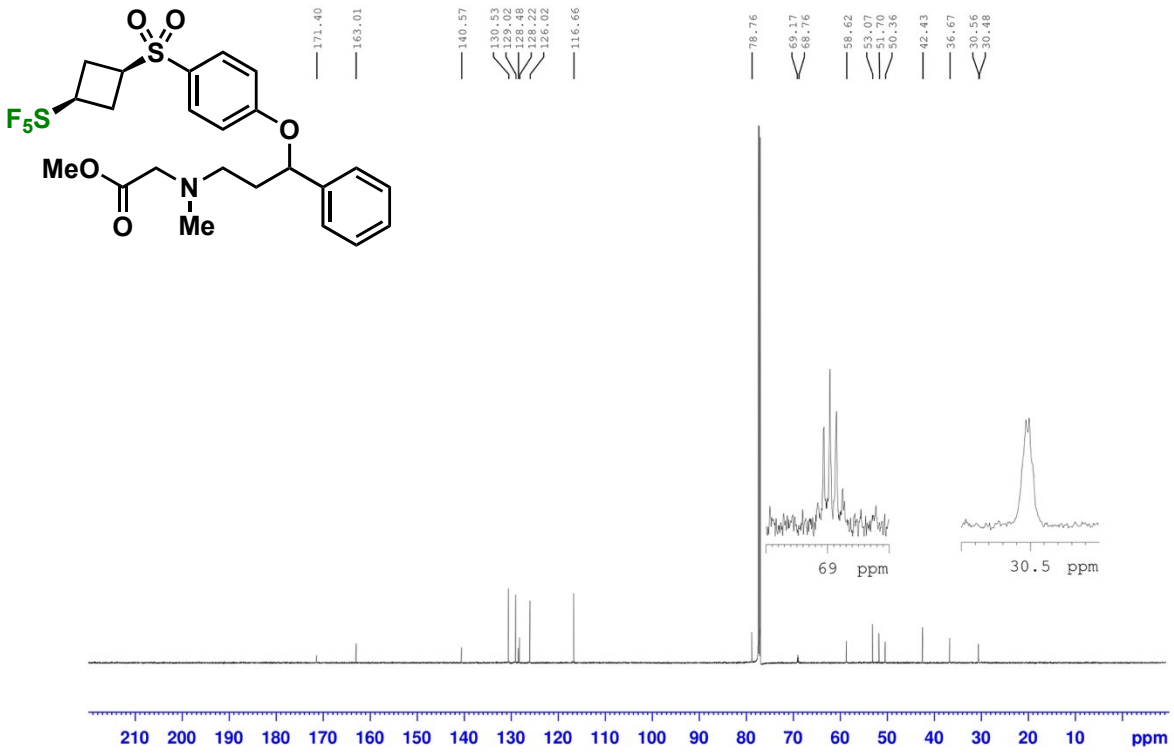


Figure S106. $^{13}C\{^{1}H\}$ NMR spectrum methyl *N*-methyl-*N*-(3-(4-((3-(pentafluoro-λ^6-sulfaneyl)cyclobutyl)sulfonyl) phenoxy)-3-phenylpropyl)glycinate (compound **S12**) in $CDCl_3$.

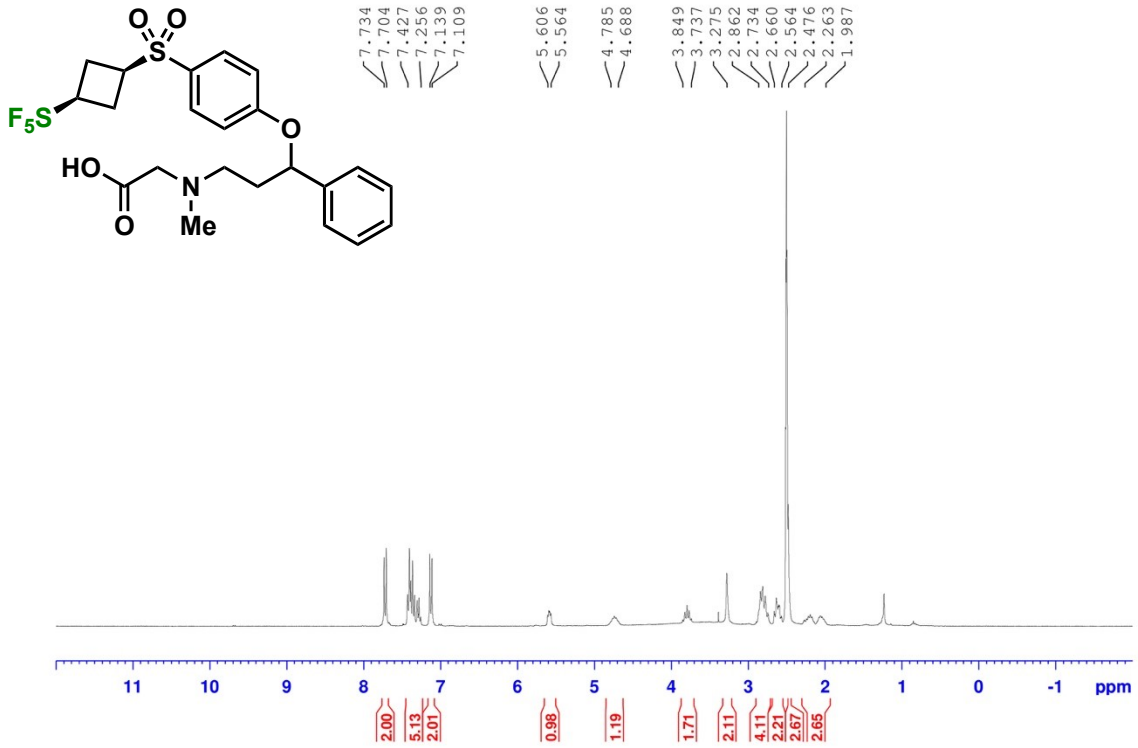


Figure S107. ^{1}H NMR spectrum of *N*-methyl-*N*-(3-(4-((-3-(pentafluoro-λ^{6}-sulfaneyl) cyclobutyl) sulfonyl) phenoxy)-3-phenylpropyl)glycine (compound **24**) in DMSO-d_6.

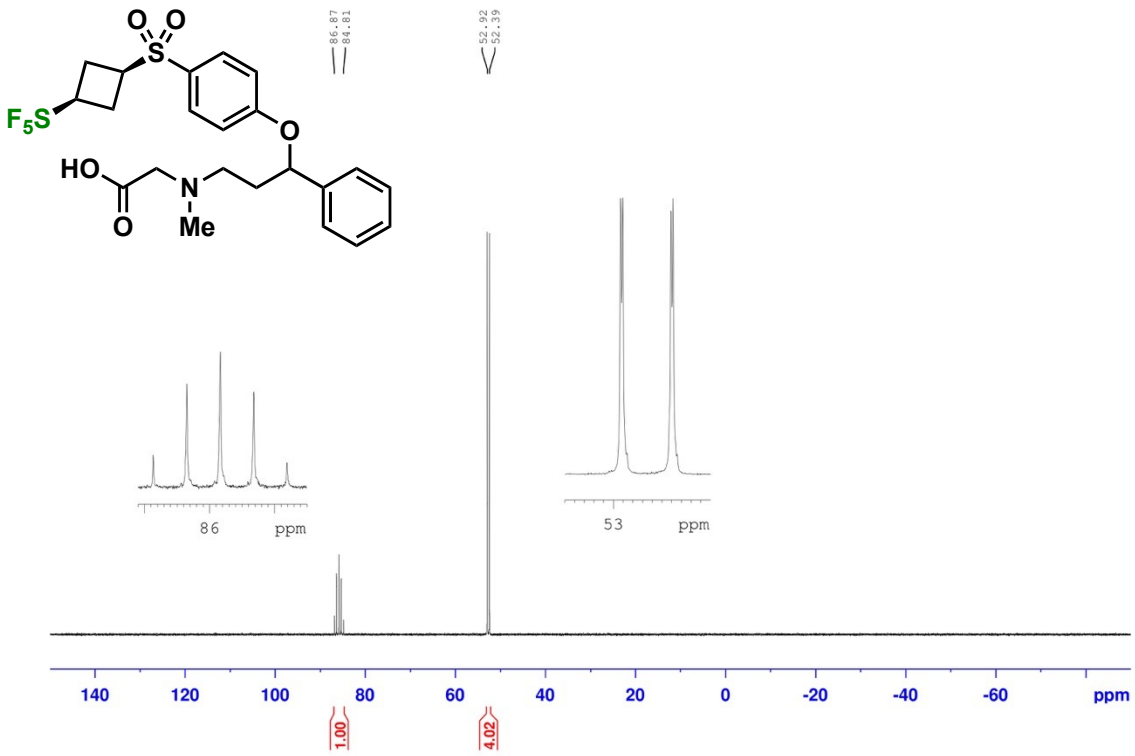


Figure S108. ^{19}F NMR spectrum of *N*-methyl-*N*-(3-(4-((-3-(pentafluoro-λ^6-sulfaneyl) cyclobutyl) sulfonyl) phenoxy)-3-phenylpropyl)glycine (compound **24**) in DMSO-d_6.

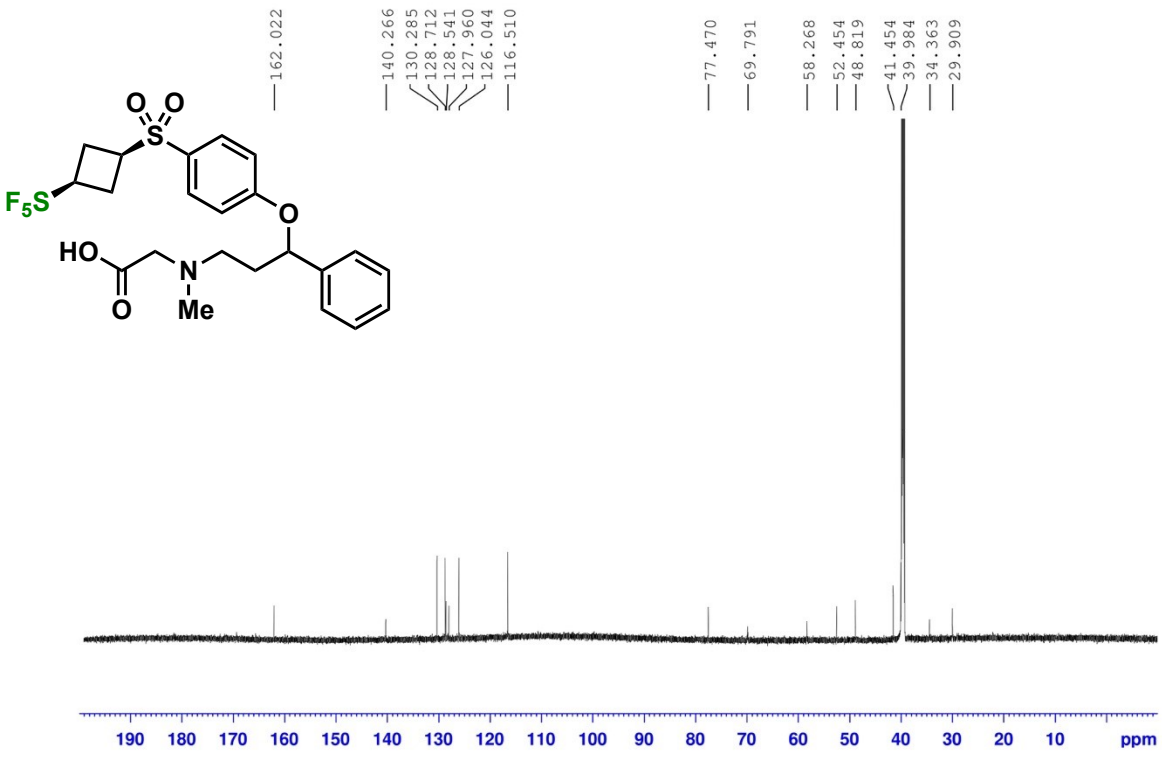


Figure S109. $^{13}C\{^{1}H\}$ NMR spectrum of *N*-methyl-*N*-(3-(4-((-3-(pentafluoro-λ^6-sulfaneyl) cyclobutyl) sulfonyl) phenoxy)-3-phenylpropyl)glycine (compound **24**) in DMSO-d_6.

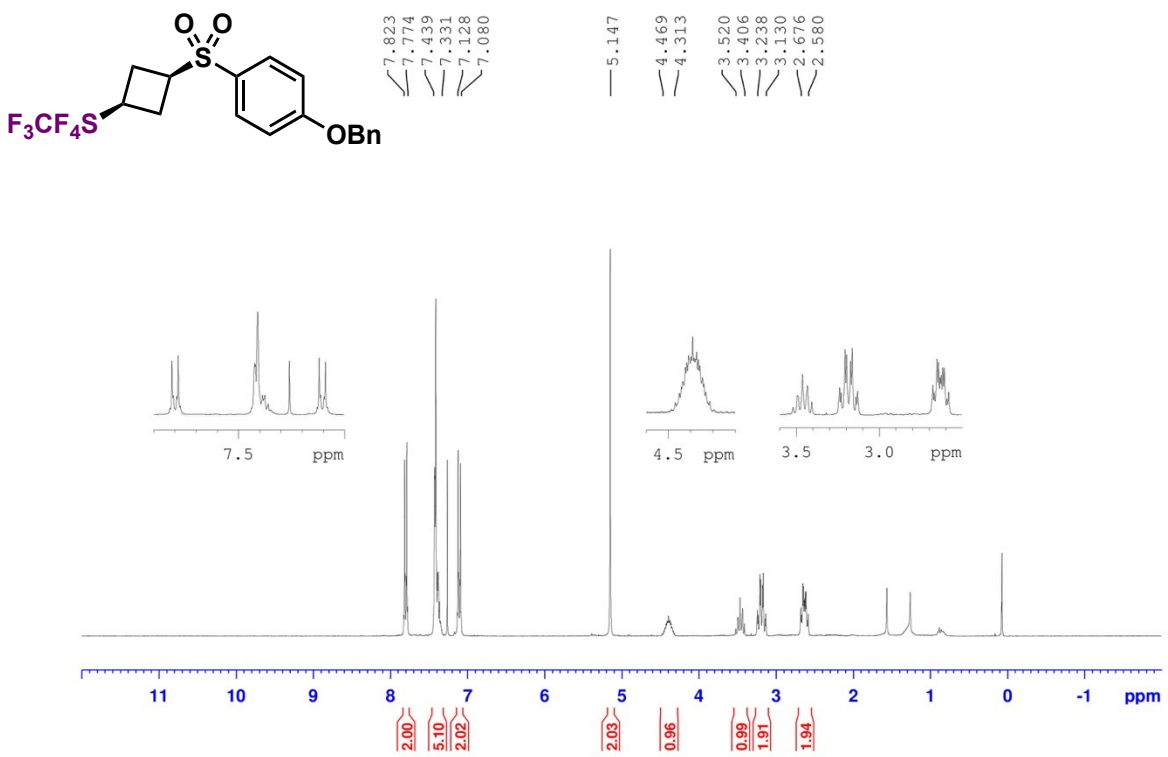


Figure S110. ^{1}H NMR spectrum of 3-((4-(benzyloxy)phenyl)sulfonyl)cyclobutyl)tetrafluoro(trifluoromethyl)-λ^{6}-sulfane (compound ***cis*-S13**) in $CDCl_3$.

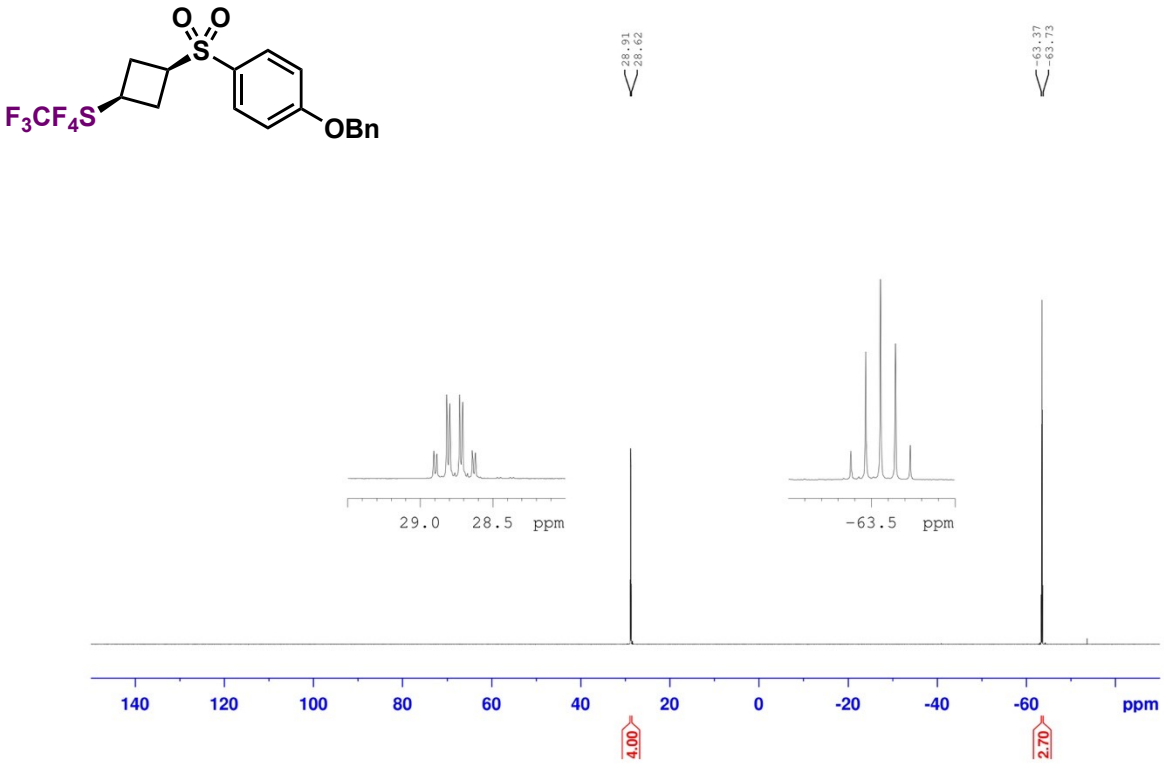


Figure S111. ^{19}F NMR spectrum of 3-((4-(benzyloxy)phenyl)sulfonyl)cyclobutyl)tetrafluoro (trifluoromethyl)-λ^6-sulfane (compound ***cis*-S13**) in $CDCl_3$.

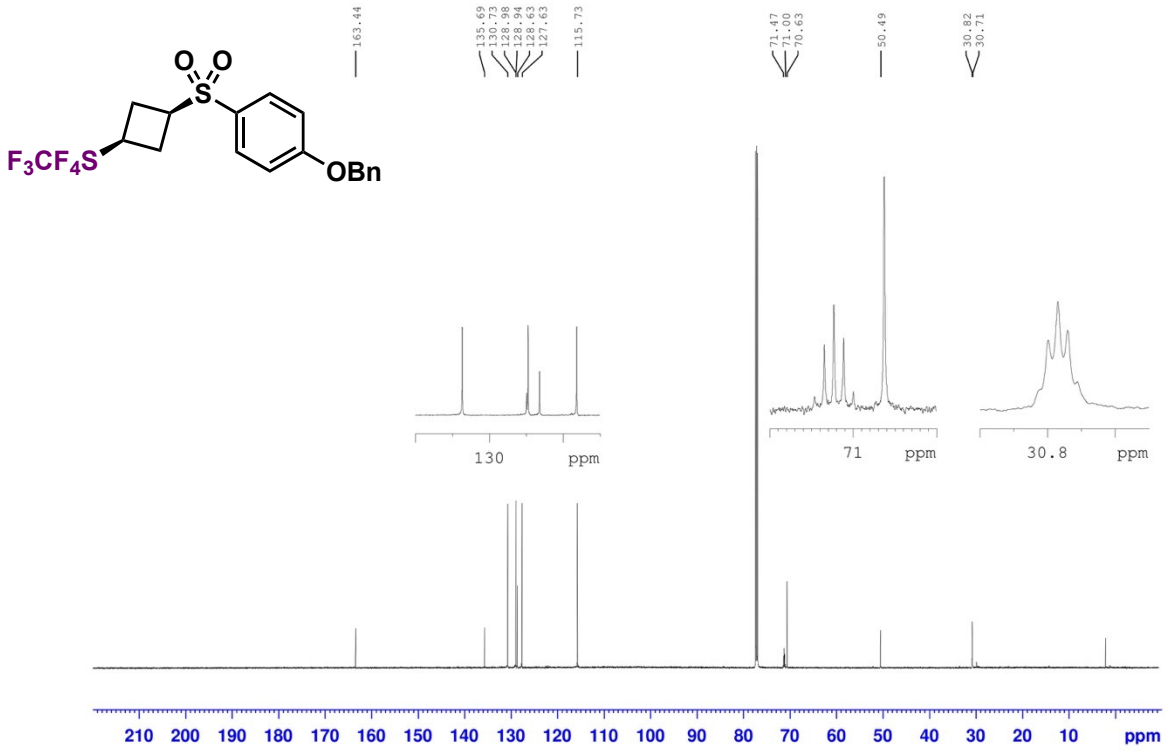


Figure S112. $^{13}C\{^{1}H\}$ NMR spectrum of 3-((4-(benzyloxy)phenyl)sulfonyl)cyclobutyl)tetrafluoro-(trifluoromethyl) -λ^6-sulfane (compound ***cis*-S13**) in $CDCl_3$.

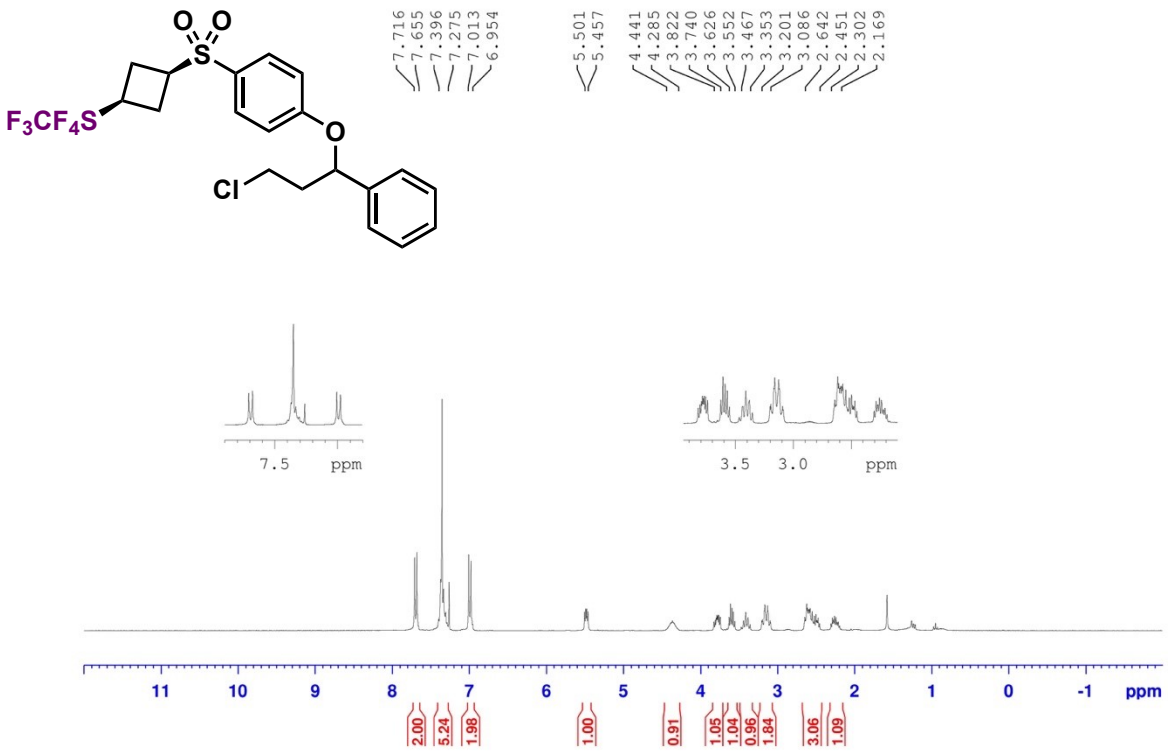


Figure S113. ^{1}H NMR spectrum (3-((4-(3-chloro-1-phenylpropoxy)phenyl)sulfonyl)cyclobutyl)tetrafluoro (trifluoromethyl)-λ^{6}-sulfane (compound **S14**) in $CDCl_3$.

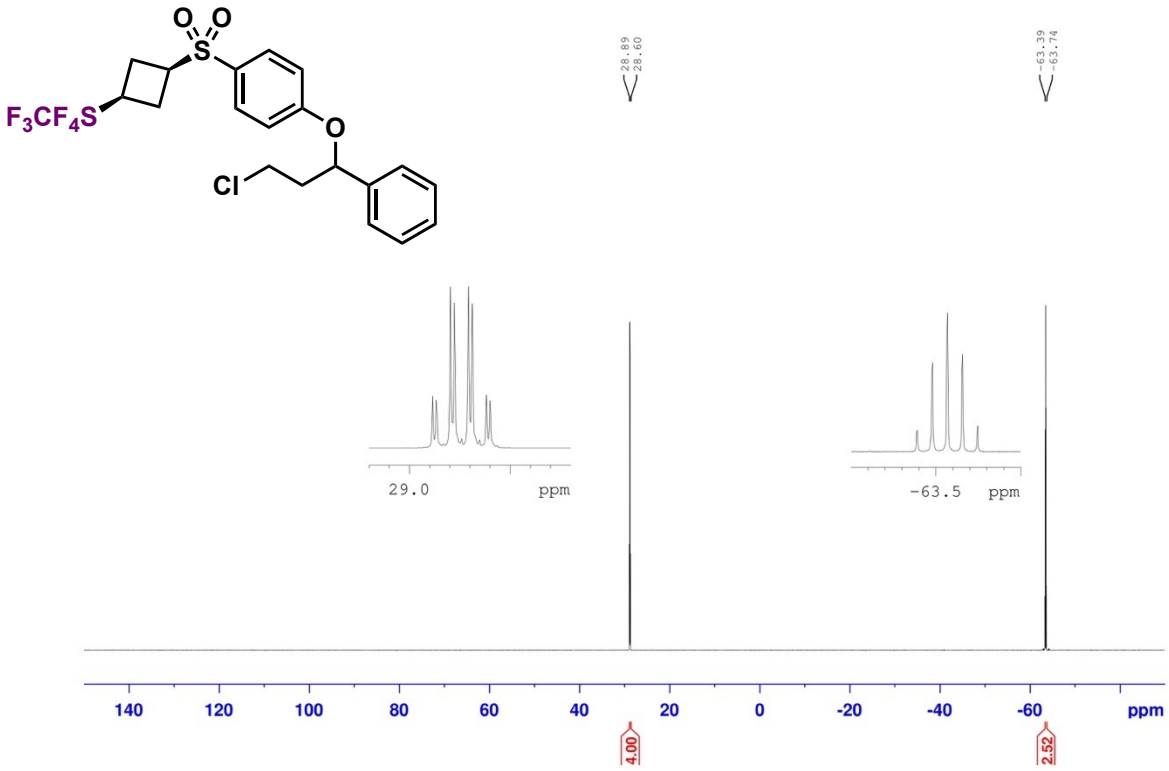


Figure S114. ^{19}F NMR spectrum (3-((4-(3-chloro-1-phenylpropoxy)phenyl)sulfonyl)cyclobutyl)tetrafluoro (trifluoromethyl)-λ^6-sulfane (compound **S14**) in $CDCl_3$.

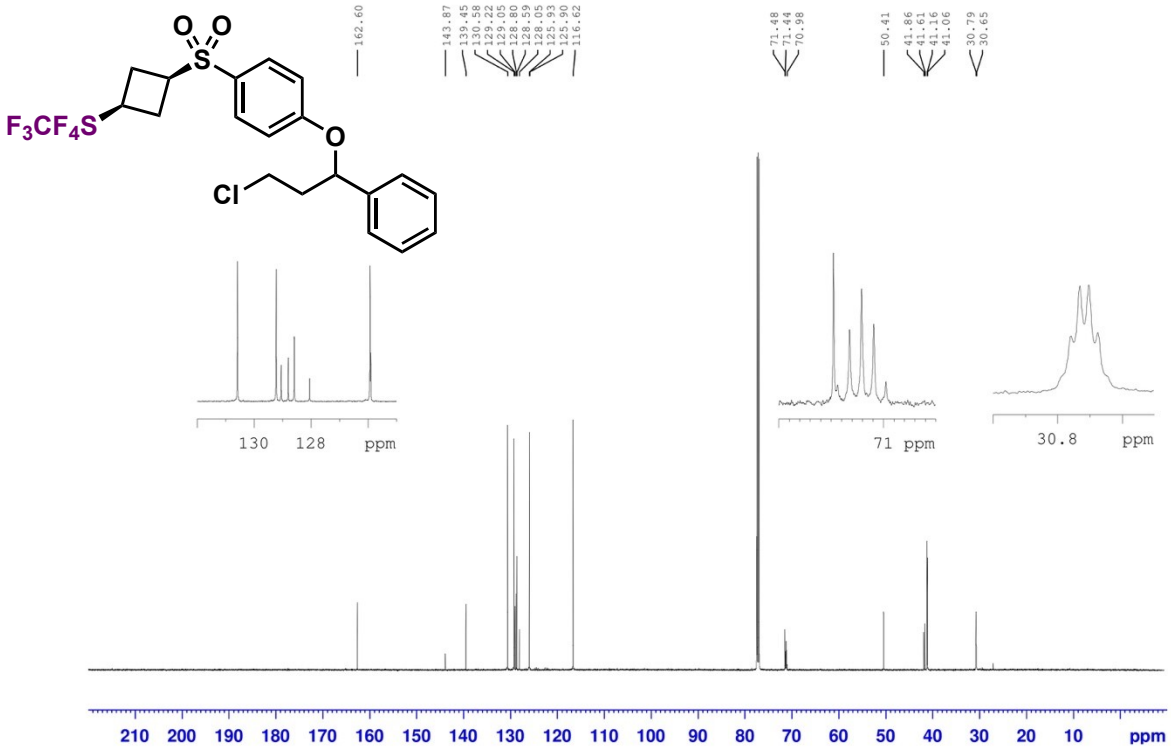


Figure S115. $^{13}C\{^{1}H\}$ NMR spectrum (3-((4-(3-chloro-1-phenylpropoxy)phenyl)sulfonyl)cyclobutyl)-tetrafluoro(trifluoromethyl)-λ^6-sulfane (compound **S14**) in $CDCl_3$.

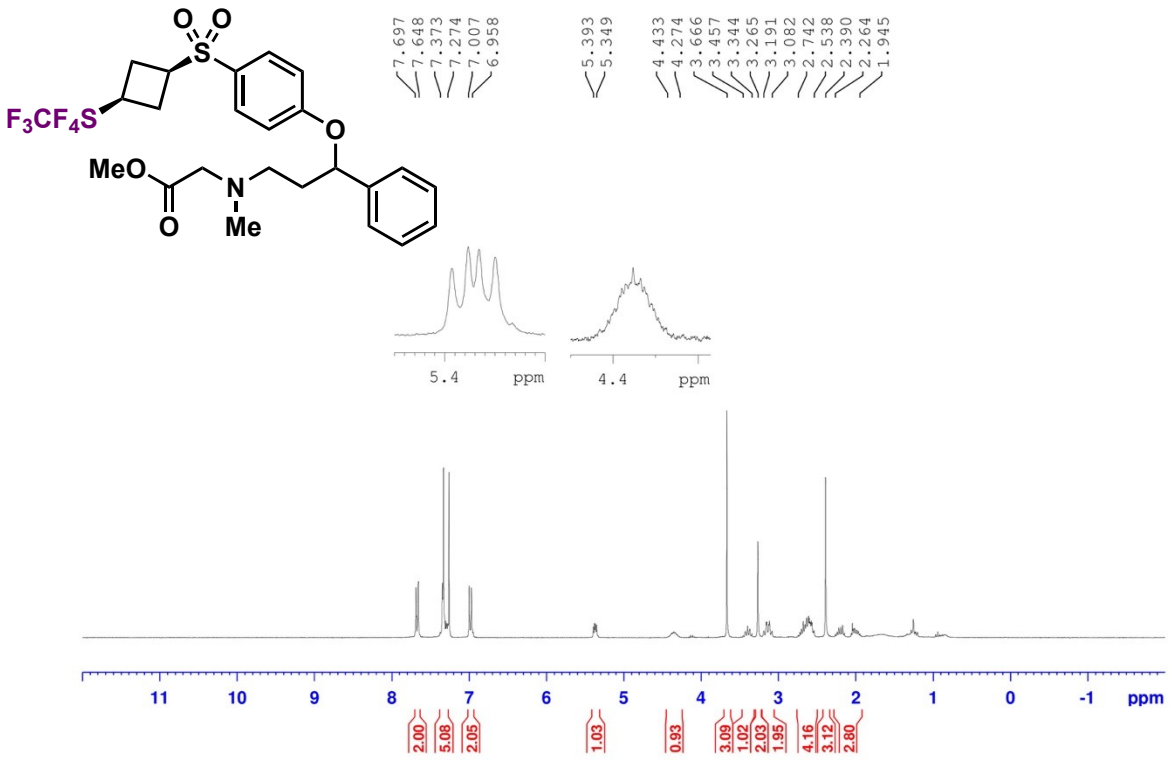


Figure S116. ^{1}H NMR spectrum methyl *N*-methyl-*N*-(3-phenyl-3-(4-((3-(tetrafluoro((trifluoromethyl)-λ^{6}-sulfanyl)cyclobutyl)sulfonyl)phenoxy)propyl)glycinate (compound **S14**) in $CDCl_3$.

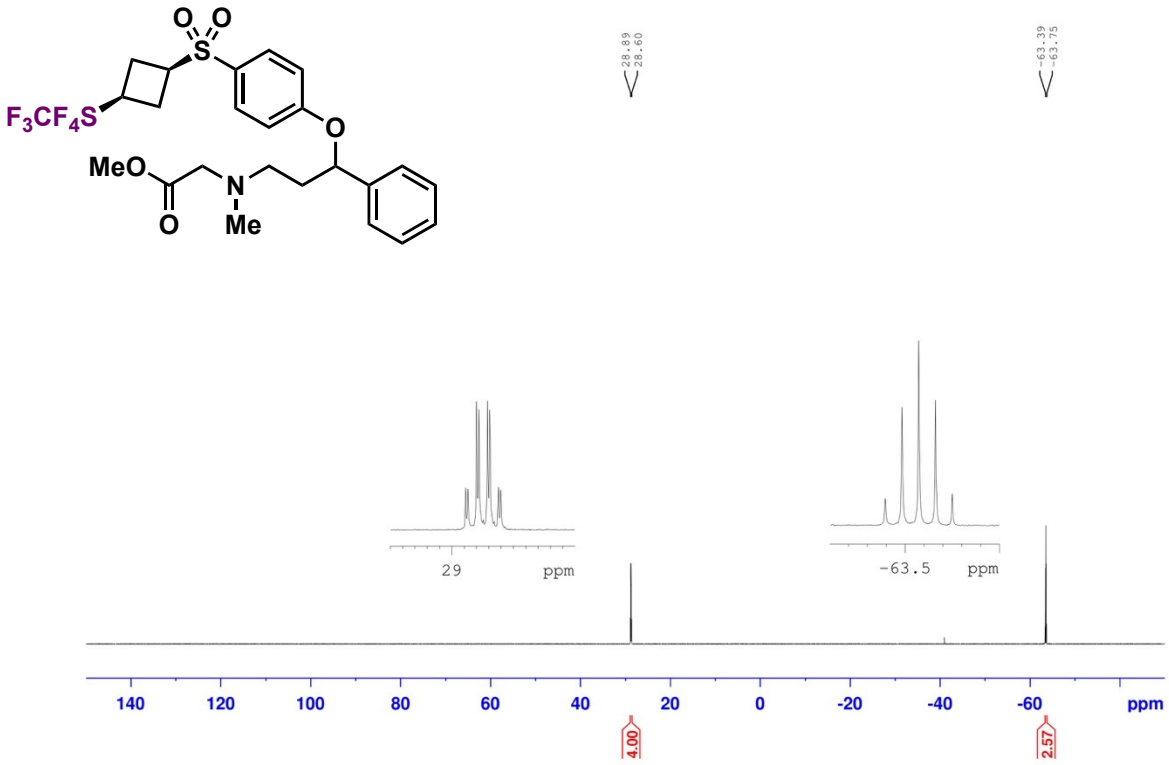


Figure S117. ^{19}F NMR spectrum methyl *N*-methyl-*N*-(3-phenyl-3-(4-((3-(tetrafluoro((trifluoromethyl)-λ^6-sulfanyl)cyclobutyl)sulfonyl)phenoxy)propyl)glycinate (compound **S14**) in $CDCl_3$.

Figure S118. $^{13}C\{^{1}H\}$ NMR spectrum methyl *N*-methyl-*N*-(3-phenyl-3-(4-((3-(tetrafluoro((trifluoromethyl)-λ^6-sulfanyl)cyclobutyl)sulfonyl)phenoxy)propyl)glycinate (compound **S14**) in $CDCl_3$.

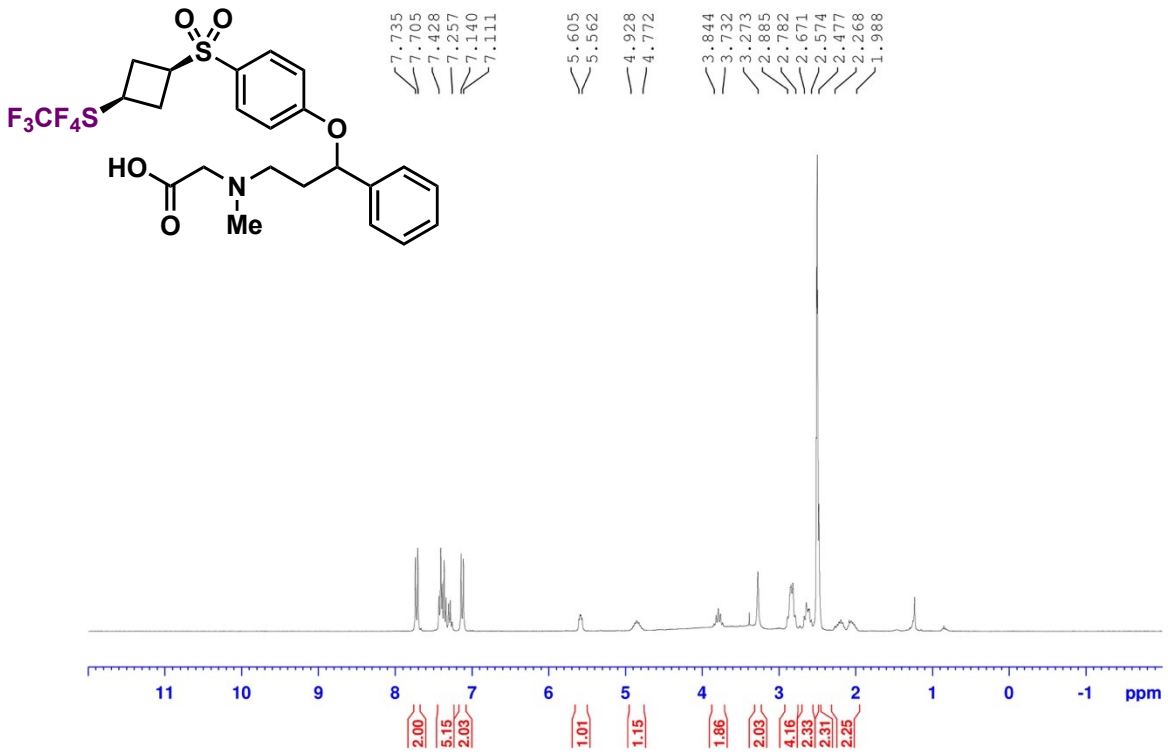


Figure S119. ^{1}H NMR spectrum of *N*-methyl-*N*-(3-phenyl-3-(4-((3-(tetrafluoro(trifluoromethyl)- λ^{6}-sulfanyl)cyclobutyl)sulfonyl)phenoxy)propyl)glycine (compound **25**) in DMSO-d_6.

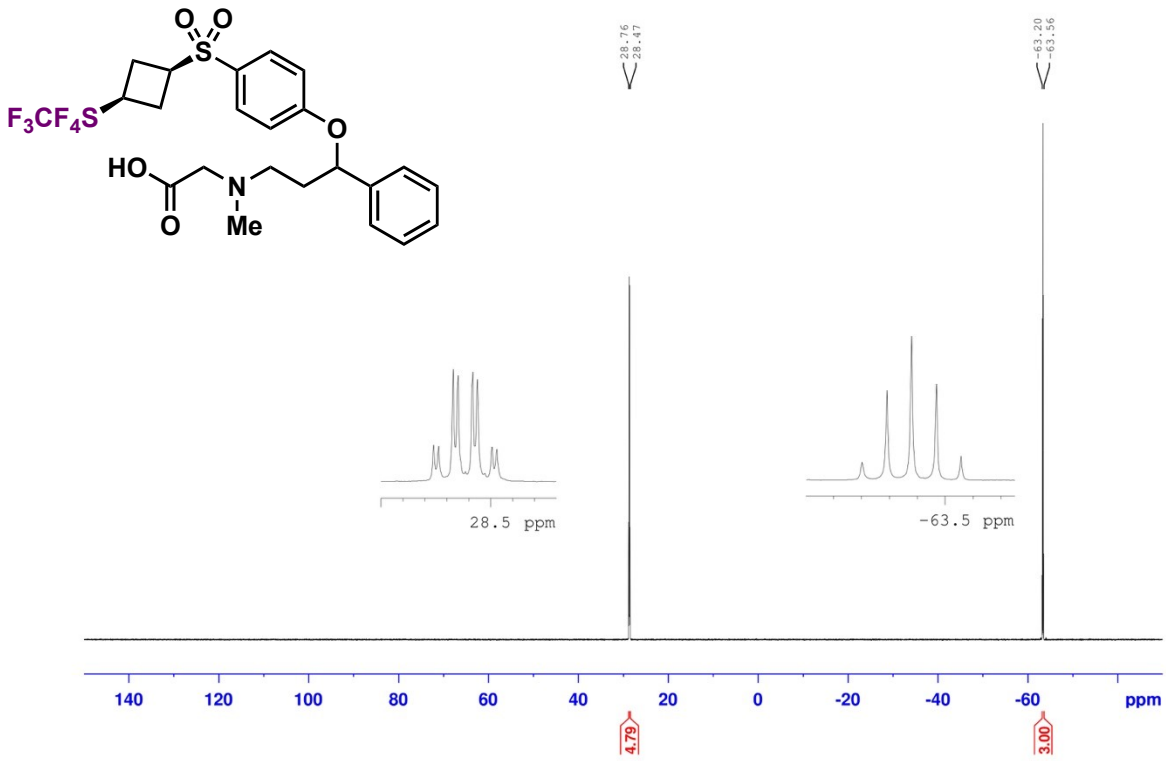


Figure S120. ^{19}F NMR spectrum of *N*-methyl-*N*-(3-phenyl-3-(4-((3-(tetrafluoro(trifluoromethyl)- λ^6-sulfanyl)cyclobutyl)sulfonyl)phenoxy)propyl)glycine (compound **25**) in DMSO-d_6.

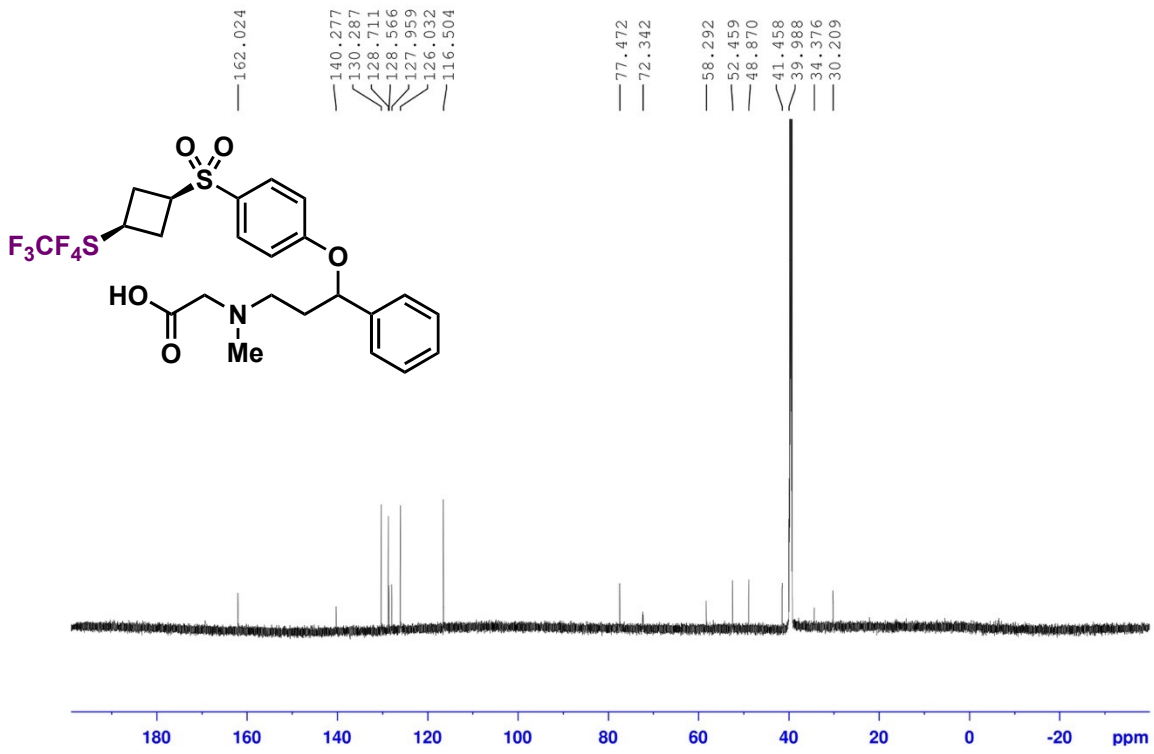


Figure S121. $^{13}C\{^{1}H\}$ NMR spectrum of *N*-methyl-*N*-(3-phenyl-3-(4-((3-(tetrafluoro(trifluoromethyl)- λ^6-sulfanyl)cyclobutyl)sulfonyl)phenoxy)propyl)glycine (compound **25**) in DMSO-d_6.

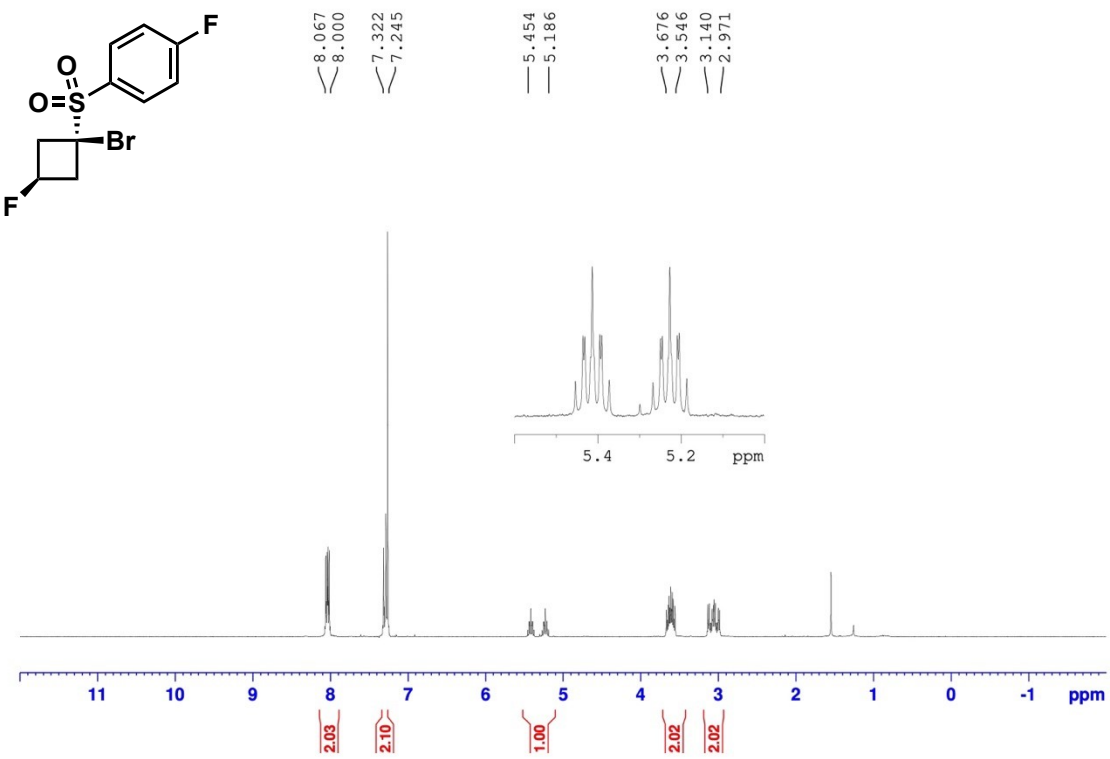


Figure S122. ^{1}H NMR spectrum of 1-((1-bromo-3-fluorocyclobutyl)sulfonyl)-4-fluorobenzene (compound **S16**) in $CDCl_3$.

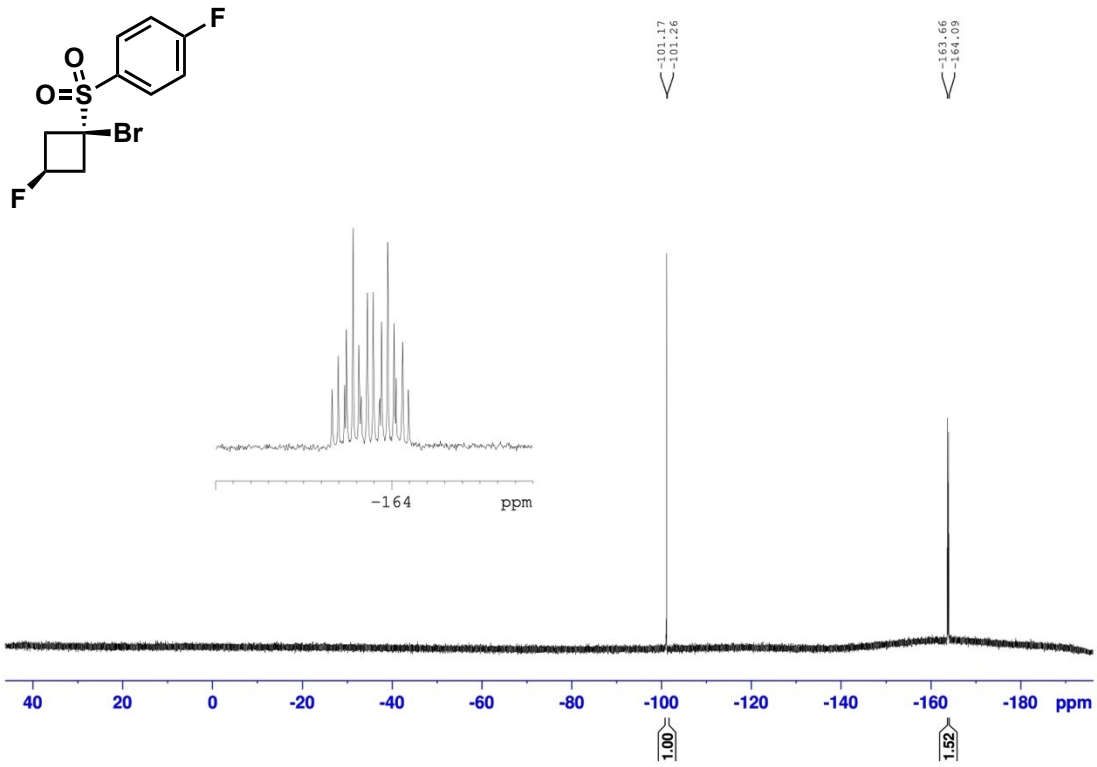


Figure S123. ^{19}F NMR spectrum of 1-((1-bromo-3-fluorocyclobutyl)sulfonyl)-4-fluorobenzene (compound **S16**) in $CDCl_3$.

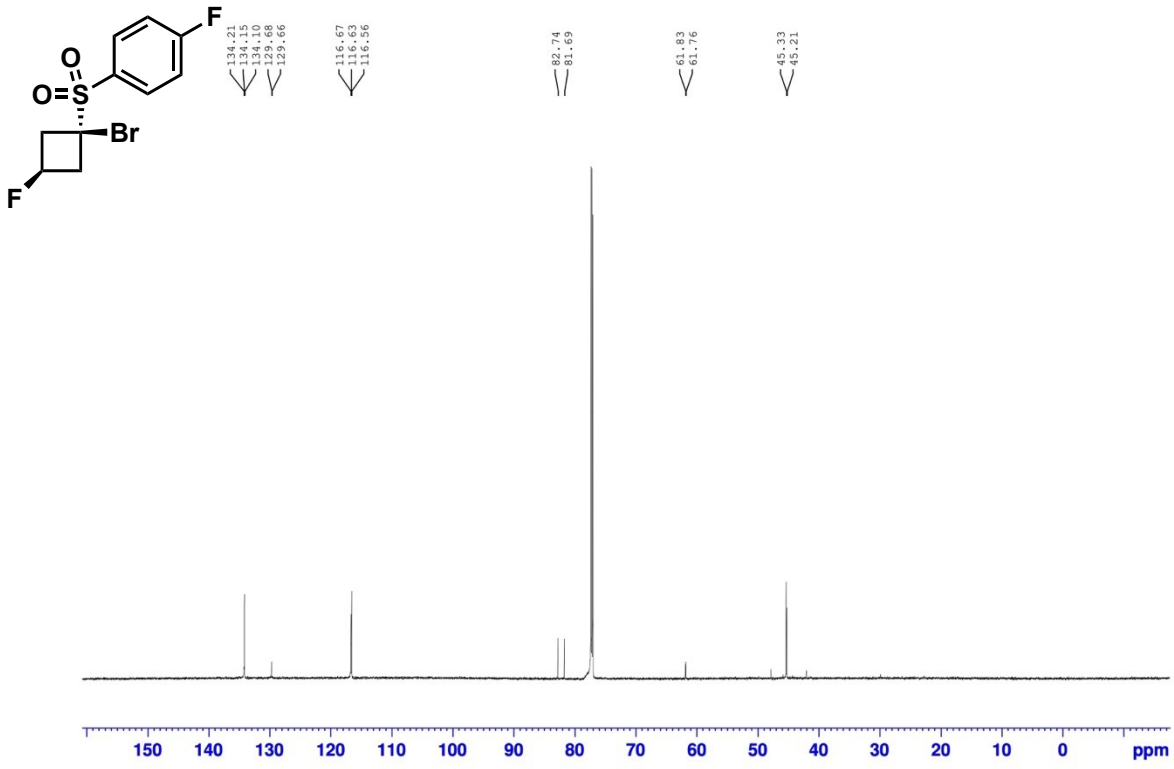


Figure S124. $^{13}C\{^{1}H\}$ NMR spectrum of 1-((1-bromo-3-fluorocyclobutyl)sulfonyl)-4-fluorobenzene (compound **S16**) in $CDCl_3$.

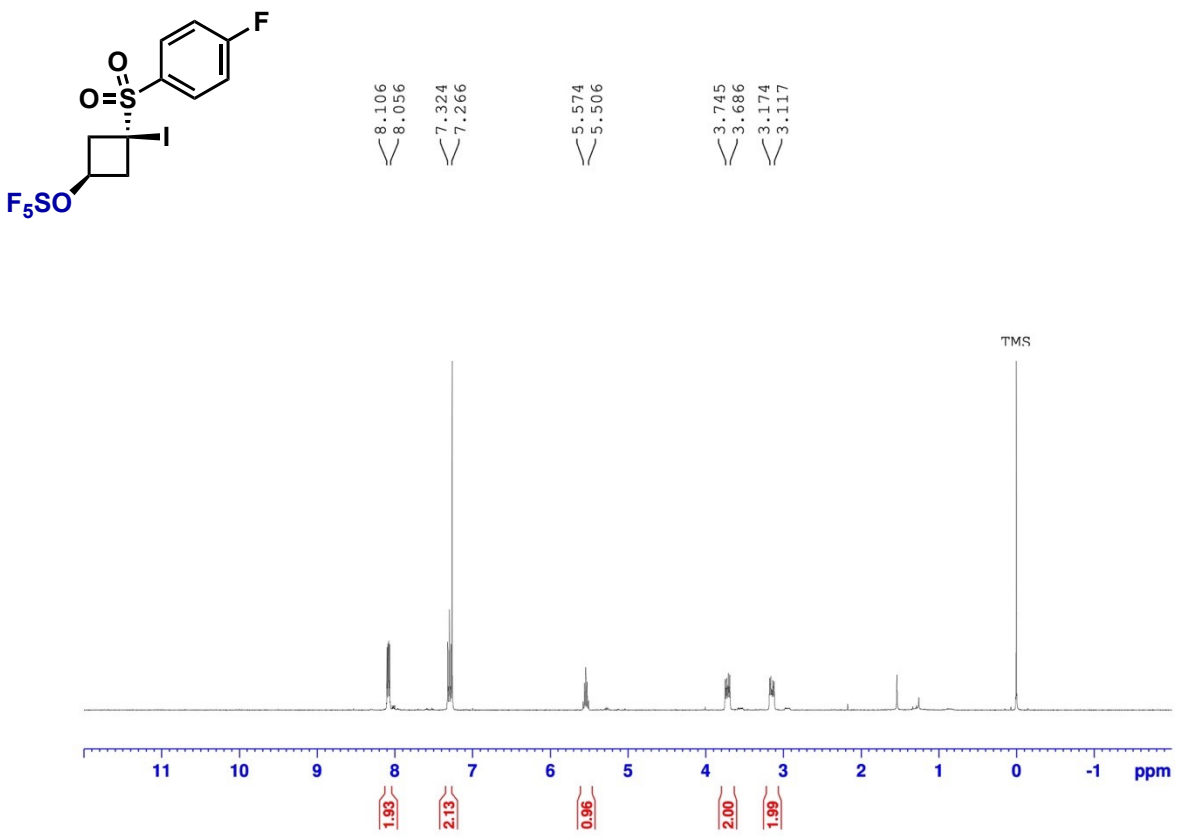


Figure S125. ^{1}H NMR spectrum of pentafluoro(3-((4-fluorophenyl)sulfonyl)-3-iodocyclobutoxy)-λ^{6}-sulfane (compound **S17**) in $CDCl_3$.

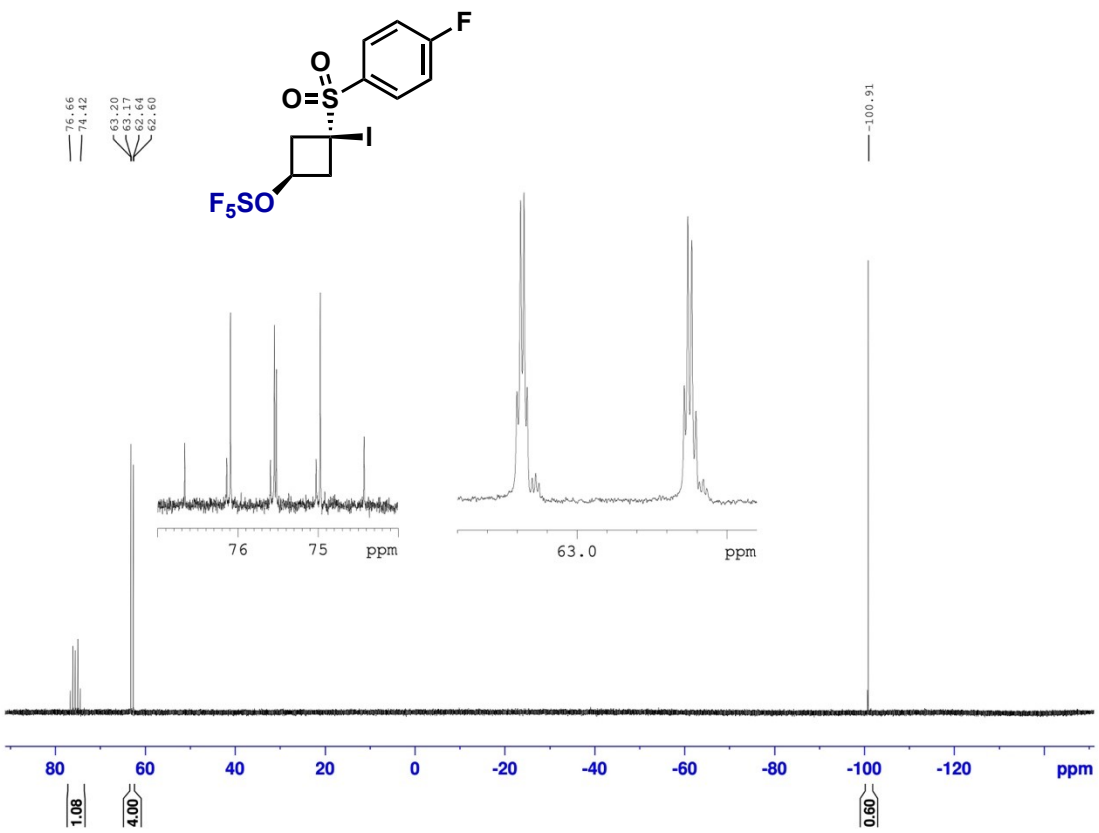


Figure S126. $^{19}F\{^{1}H\}$ NMR spectrum of pentafluoro(3-((4-fluorophenyl)sulfonyl)-3-iodocyclobutoxy)-λ^{6}-sulfane (compound **S17**) in $CDCl_3$.

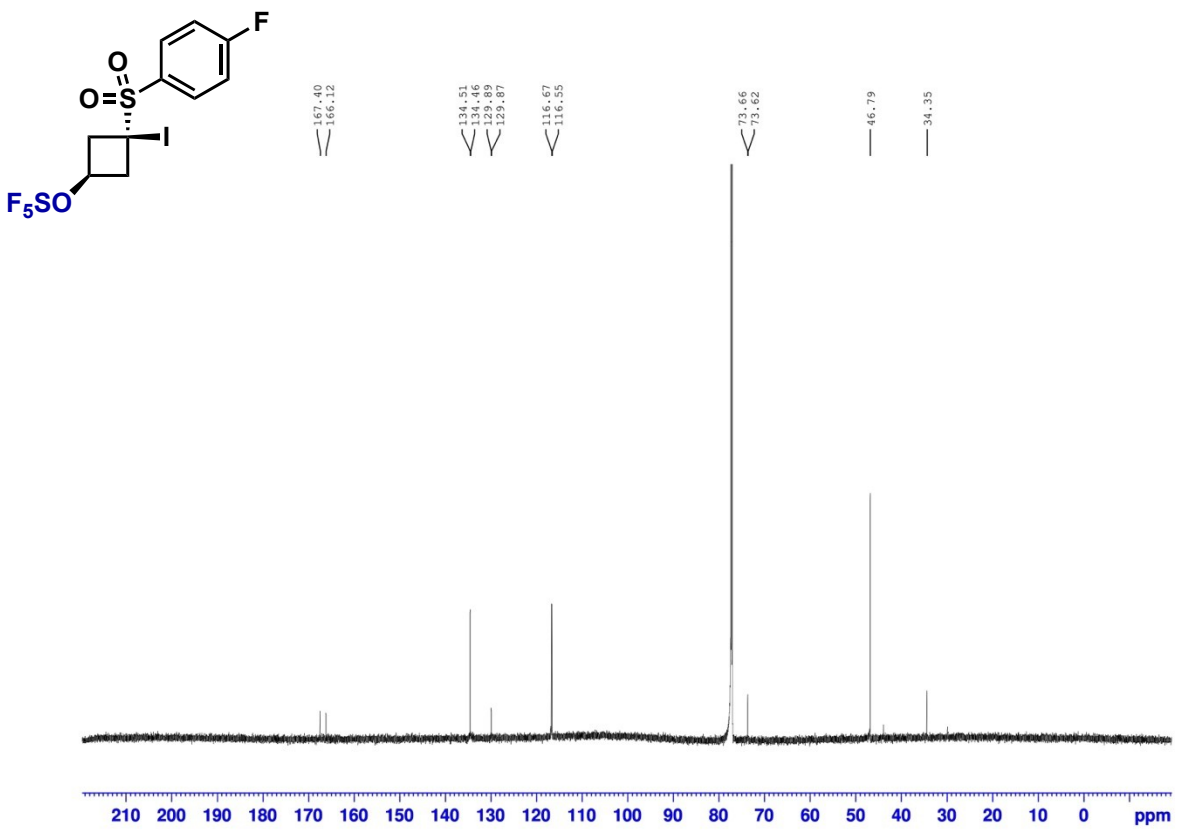


Figure S127. $^{13}C\{^{1}H\}$ NMR spectrum of pentafluoro(3-((4-fluorophenyl)sulfonyl)-3-iodocyclobutoxy)-λ^{6}-sulfane (compound **S17**) in $CDCl_3$.

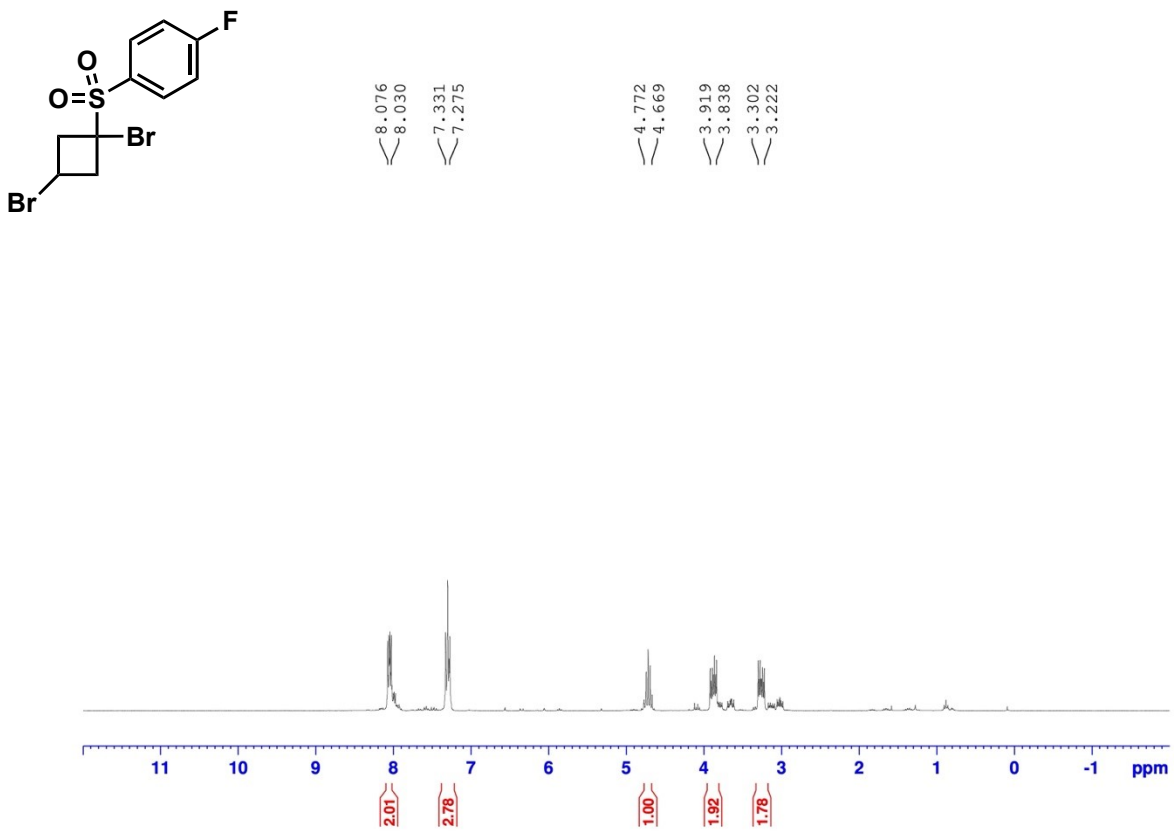


Figure S128. ^{1}H NMR spectrum of 1-((1,3-dibromocyclobutyl)sulfonyl)-4-fluorobenzene (compound **S18**) in $CDCl_3$ (mixture of isomers).

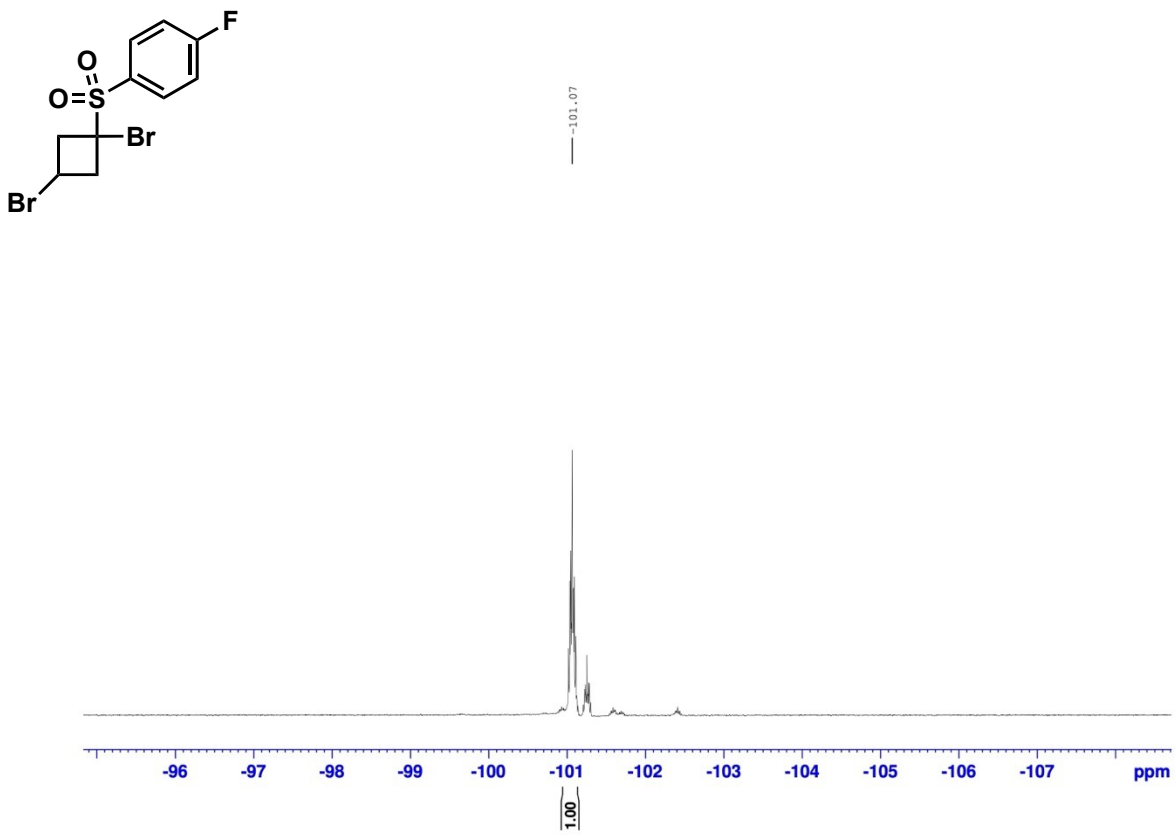


Figure S129. ^{19}F NMR spectrum of 1-((1,3-dibromocyclobutyl)sulfonyl)-4-fluorobenzene (compound **S18**) in $CDCl_3$ (mixture of isomers).

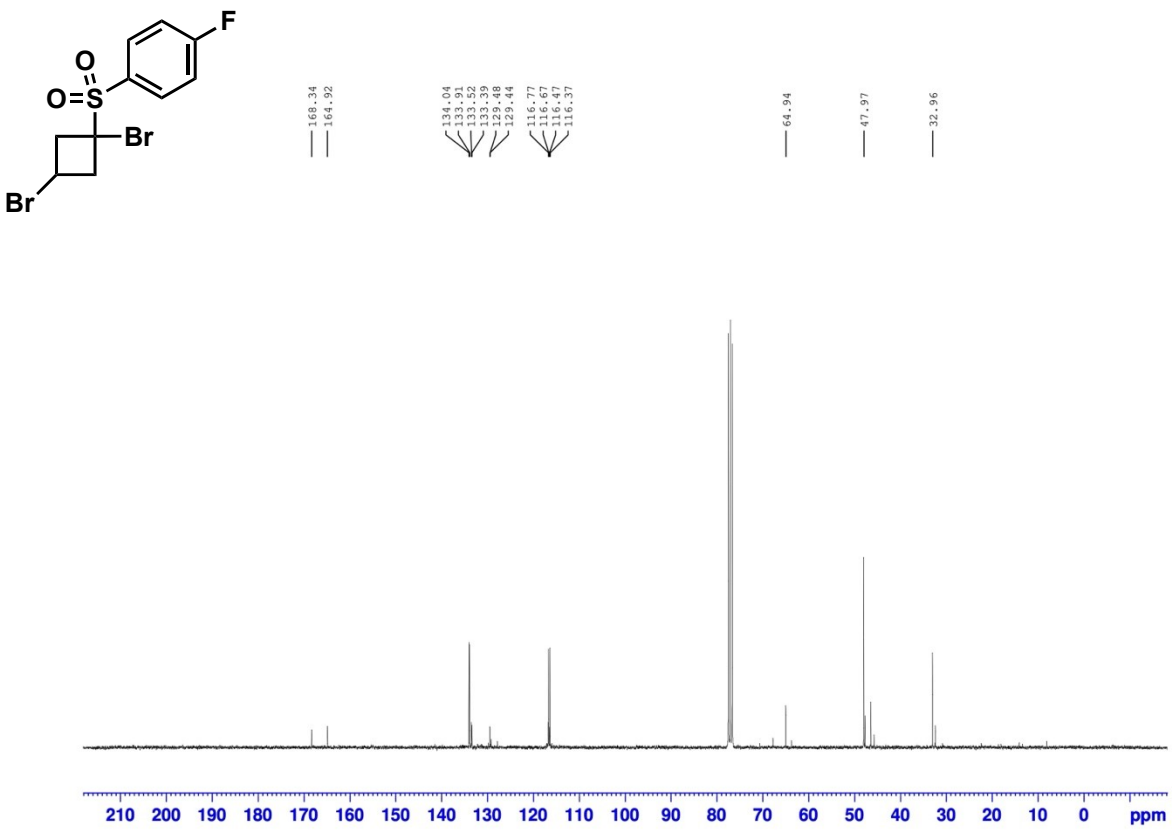


Figure S130. $^{13}C\{^{1}H\}$ NMR spectrum of 1-((1,3-dibromocyclobutyl)sulfonyl)-4-fluorobenzene (compound **S18**) in $CDCl_3$ (mixture of isomers).

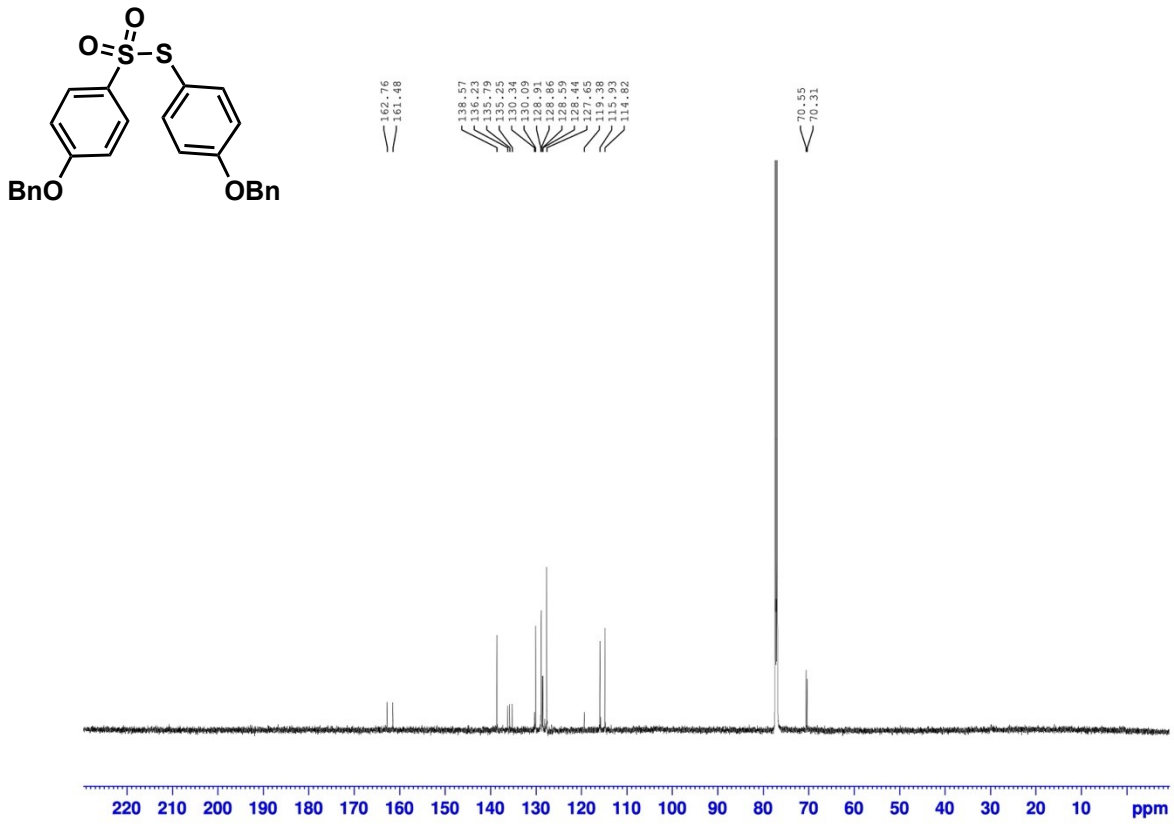


Figure S131. $^{13}C\{^{1}H\}$ NMR spectrum of *S*-(4-(benzyloxy)phenyl) 4-(benzyloxy)benzenesulfonothioate (compound **S3**) in $CDCl_3$.

X-ray Crystallography:

Experimental Crystallographic Tables:

Table S4.

	Compound S17	**Compound S13**	**Compound 15**
CCDC number	2355474	2388015	2356231
Empirical formula	$C_{10}H_9F_6IO_3S_2$	$C_{18}H_{17}F_7O_3S_2$	$C_{10}H_{10}BrF_5O_3S_2$
Formula weight	482.19	478.43	417.217
Temperature [K]	100(2)	133.00	90.15
Crystal system	monoclinic	monoclinic	monoclinic
Space group (number)	$P2_1/c$ (14)	$P2_1/n$ (14)	$P2_1/c$ (14)
a [Å]	11.4528(12)	17.3628(4)	15.2423(19)
b [Å]	9.0531(9)	5.49420(10)	8.1807(10)
c [Å]	14.0965(14)	21.4770(5)	12.1223(15)
α [°]	90	90	90
β [°]	92.756(2)	108.7710(10)	113.086(2)
γ [°]	90	90	90
Volume [Å^3]	1459.9(3)	1939.82(7)	1390.5(3)
Z	4	4	4
ρ_{calc} [gcm^{-3}]	2.194	1.638	1.993
μ [mm^{-1}]	2.554	3.293	3.319
F(000)	928	976	824.876
Crystal size [mm^3]	0.241×0.103×0.031	0.239×0.089×0.034	0.439×0.177×0.108
Crystal colour	colourless	colourless	colourless
Crystal shape	Rectangular	Rectangular	Rectangular
Radiation	MoK_α (λ=0.71073 Å)	CuK_α (λ=1.54178 Å)	Mo K_α (λ=0.71073 Å)
2Θ range [°]	5.35 to 54.96 (0.77 Å)	5.72 to 144.26 (0.81 Å)	5.76 to 55.00 (0.77 Å)
Index ranges	-14 ≤ h ≤ 14 -11 ≤ k ≤ 11 -18 ≤ l ≤ 18	-21 ≤ h ≤ 21 -6 ≤ k ≤ 6 -26 ≤ l ≤ 26	-19 ≤ h ≤ 19 -10 ≤ k ≤ 10 -15 ≤ l ≤ 15
Reflections collected	12715	40894	12254
Independent reflections	3344 R_{int} = 0.0186 R_{sigma} = 0.0159	3825 R_{int} = 0.0461 R_{sigma} = 0.0228	3193 R_{int} = 0.0340 R_{sigma} = 0.0285
Completeness	99.9 %	100.0 %	100.0 %
Data / Restraints / Parameters	3344/0/199	3825/129/299	3193/0/190
Goodness-of-fit on F^2	1.092	1.046	1.0320
Final *R* indexes [$I \geq 2\sigma(I)$]	R_1 = 0.0254 wR_2 = 0.0634	R_1 = 0.0388 wR_2 = 0.1055	R_1 = 0.0248 wR_2 = 0.0534
Final *R* indexes [all data]	R_1 = 0.0270 wR_2 = 0.0645	R_1 = 0.0432 wR_2 = 0.1096	R_1 = 0.0320 wR_2 = 0.0561
Largest peak/hole [eÅ^{-3}]	1.20/-0.78	0.63/-0.43	0.60/-0.44

	Compound 8	**Compound *cis*-19**	**Compound S3**
CCDC number	2388014	2388016	2388017
Empirical formula	$C_{11}H_{10}BrF_3O_3S$	$C_{18}H_{17}F_3O_4S$	$C_{26}H_{22}O_{3.99}S_2$
Formula weight	359.16	386.38	462.47
Temperature [K]	90(2)	133.00	133.00
Crystal system	orthorhombic	monoclinic	monoclinic
Space group (number)	$P2_12_12_1$ (19)	$P2_1/c$ (14)	$P2_1/c$ (14)
a [Å]	6.0803(3)	18.4827(6)	17.9146(4)
b [Å]	14.0712(8)	8.7216(3)	9.8344(2)
c [Å]	15.4400(9)	11.2089(4)	12.7724(3)
α [°]	90	90	90
β [°]	90	104.3180(10)	99.3640(10)
γ [°]	90	90	90
Volume [Å^3]	1321.00(13)	1750.74(10)	2220.25(9)
Z	4	4	4
ρ_{calc} [gcm^{-3}]	1.806	1.466	1.384
μ [mm^{-1}]	3.306	0.236	2.433
F(000)	712	800	968
Crystal size [mm^3]	0.495×0.280×0.068	0.222×0.148×0.109	0.211×0.183×0.075
Crystal colour	Colorless	colourless	colourless
Crystal shape	Plate	Irregular	rectangular
Radiation	MoK_α (λ=0.71073 Å)	MoK_α (λ=0.71073 Å)	CuK_α (λ=1.54178 Å)
2Θ range [°]	3.92 to 55.07 (0.77 Å)	4.55 to 50.74 (0.83 Å)	5.00 to 136.55 (0.83 Å)
Index ranges	-7 ≤ h ≤ 7 -18 ≤ k ≤ 18 -20 ≤ l ≤ 20	-22 ≤ h ≤ 22 -10 ≤ k ≤ 10 -13 ≤ l ≤ 13	-21 ≤ h ≤ 21 -11 ≤ k ≤ 11 -15 ≤ l ≤ 15
Reflections collected	9164	26827	27924
Independent reflections	3037 R_{int} = 0.0499 R_{sigma} = 0.0549	3207 R_{int} = 0.0723 R_{sigma} = 0.0381	4051 R_{int} = 0.0492 R_{sigma} = 0.0273
Completeness	99.9 %	99.9 %	99.9 %
Data / Restraints / Parameters	3037/102/245	3207/167/286	4051/0/292
Goodness-of-fit on F^2	1.052	1.052	1.075
Final *R* indexes [$I \geq 2\sigma(I)$]	R_1 = 0.0378 wR_2 = 0.0750	R_1 = 0.0598 wR_2 = 0.1392	R_1 = 0.0327 wR_2 = 0.0753
Final *R* indexes [all data]	R_1 = 0.0558 wR_2 = 0.0803	R_1 = 0.0797 wR_2 = 0.1552	R_1 = 0.0399 wR_2 = 0.0805
Largest peak/hole [eÅ^{-3}]	0.60/-0.68	0.76/-0.74	0.37/-0.37
Flack X parameter	-0.010(6)	–	–
Extinction coefficient	–	0.0053(13)	0.00052(8)

	Compound 21	**Compound *cis*-20**	**Compound S16**
CCDC number	2388018	2388019	2403288
Empirical formula	$C_{20}H_{15}F_3O_3S$	$C_{17}H_{17}F_5O_4S_2$	$C_{10}H_9BrF_2O_2S$
Formula weight	392.38	444.42	311.14
Temperature [K]	133.00	150.00	90.15
Crystal system	orthorhombic	monoclinic	monoclinic
Space group (number)	$P2_12_12_1$ (19)	$P2_1/c$ (14)	$P2_1/n$ (14)
a [Å]	8.04840(10)	19.244(2)	10.0400(11)
b [Å]	8.56770(10)	8.8045(10)	8.6290(10)
c [Å]	25.6907(4)	11.2480(12)	14.2763(16)
α [°]	90	90	90
β [°]	90	103.108(3)	109.979(2)
γ [°]	90	90	90
Volume [Å^3]	1771.54(4)	1856.1(4)	1162.4(2)
Z	4	4	4
ρ_{calc} [gcm^{-3}]	1.471	1.590	1.778
μ [mm^{-1}]	2.074	0.357	3.724
F(000)	808	912	616
Crystal size [mm^3]	0.245×0.09×0.03	0.384×0.225×0.214	0.582×0.484×0.252
Crystal colour	colourless	colourless	colourless
Crystal shape	rectangular	block	rectangular
Radiation	CuK_α (λ=1.54178 Å)	MoK_α (λ=0.71073 Å)	MoK_α (λ=0.71073 Å)
2Θ range [°]	6.88 to 144.30 (0.81 Å)	5.11 to 60.13 (0.71 Å)	4.35 to 61.12 (0.70 Å)
Index ranges	-9 ≤ h ≤ 9 -10 ≤ k ≤ 9 -31 ≤ l ≤ 31	-27 ≤ h ≤ 27 -12 ≤ k ≤ 12 -15 ≤ l ≤ 15	-13 ≤ h ≤ 14 -12 ≤ k ≤ 12 -20 ≤ l ≤ 20
Reflections collected	29384	40786	16237
Independent reflections	3492 R_{int} = 0.0452 R_{sigma} = 0.0246	5435 R_{int} = 0.0438 R_{sigma} = 0.0233	3553 R_{int} = 0.0330 R_{sigma} = 0.0273
Completeness	100.0 %	99.9 %	100.0 %
Data / Restraints / Parameters	3492/93/273	5435/283/321	3553/0/145
Goodness-of-fit on F^2	1.104	1.055	1.049
Final *R* indexes [$I \geq 2\sigma(I)$]	R_1 = 0.0292 wR_2 = 0.0655	R_1 = 0.0487 wR_2 = 0.1375	R_1 = 0.0256 wR_2 = 0.0662
Final *R* indexes [all data]	R_1 = 0.0330 wR_2 = 0.0678	R_1 = 0.0562 wR_2 = 0.1447	R_1 = 0.0315 wR_2 = 0.0688
Largest peak/hole [eÅ^{-3}]	0.16/-0.23	0.61/-0.42	0.80/-0.50
Flack X parameter	0.031(7)	–	–
Extinction coefficient	0.00070(15)	–	–

Comparative Structural Analyses of Fluorinated Cyclobutanes:

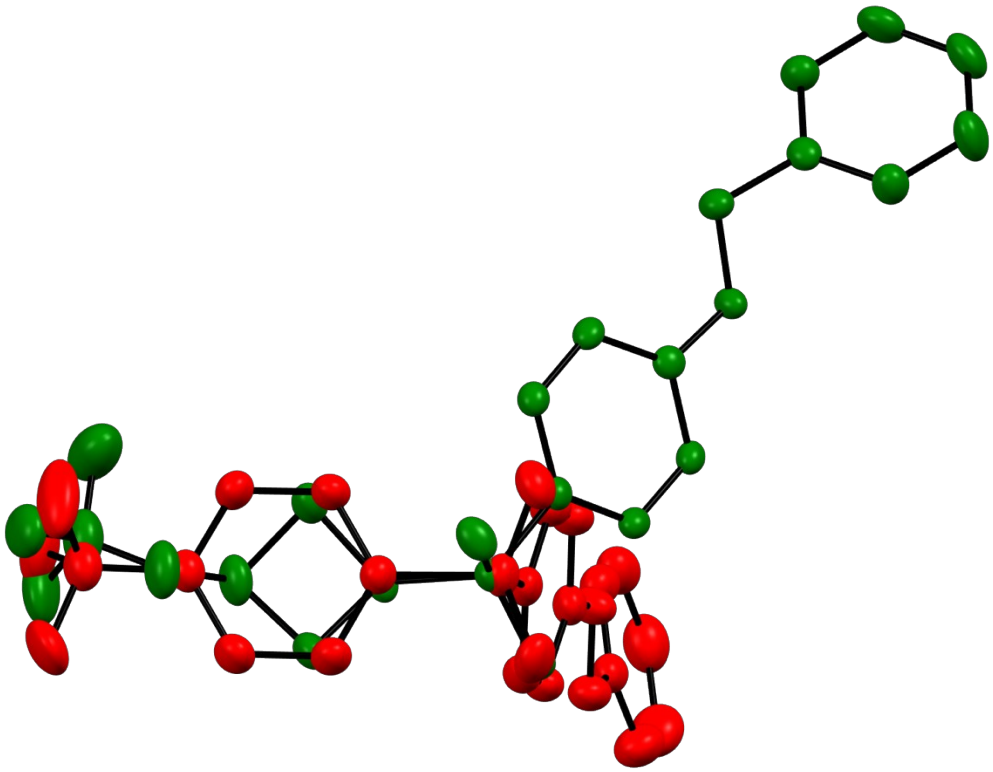


Figure S132. Overlay of **19** (green) and **21** (red).

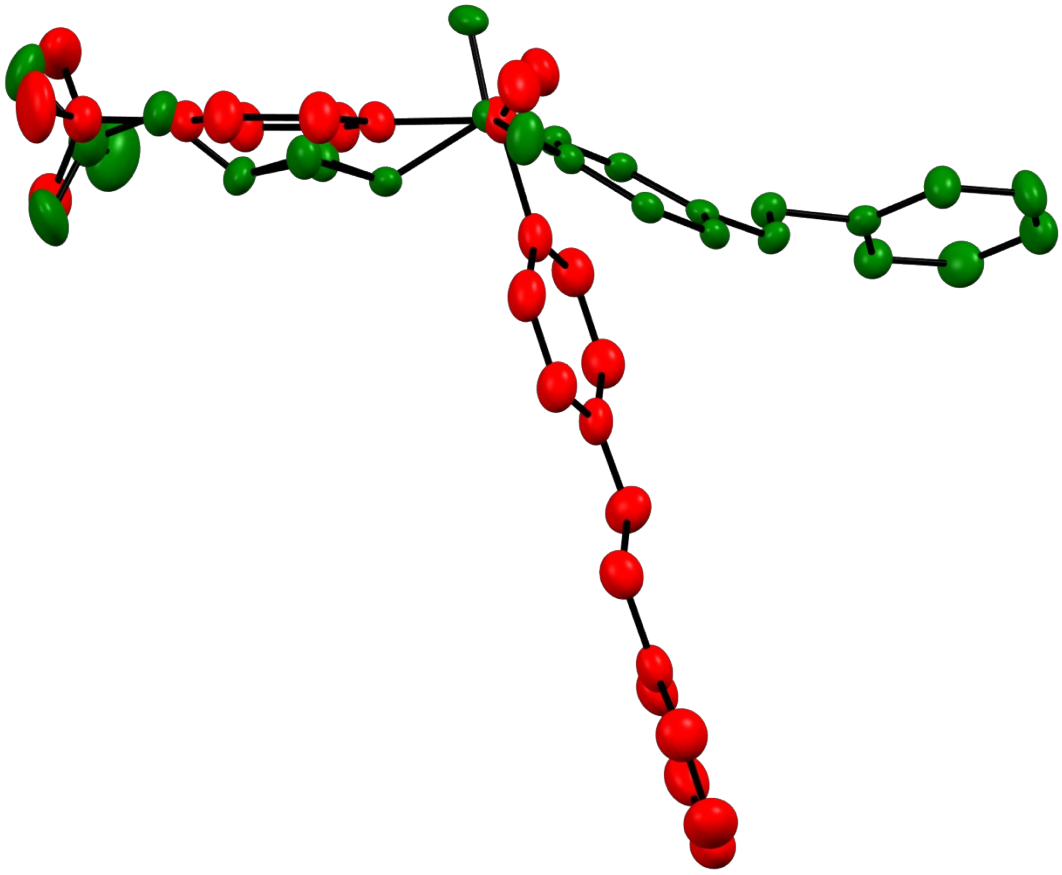


Figure S133. Overlay of **19** (green) and **21** (red).

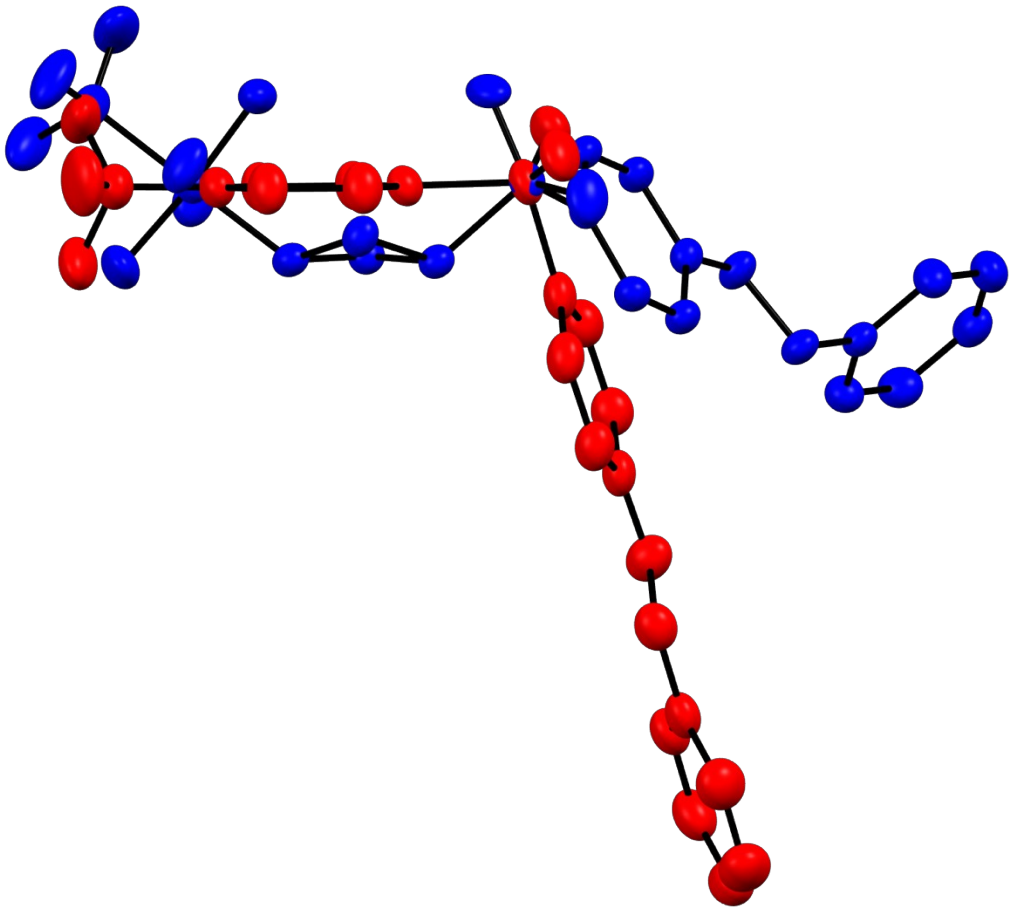


Figure S134. Overlay of *cis*-CB-SF_4CF_3 (blue) and **21** (red).

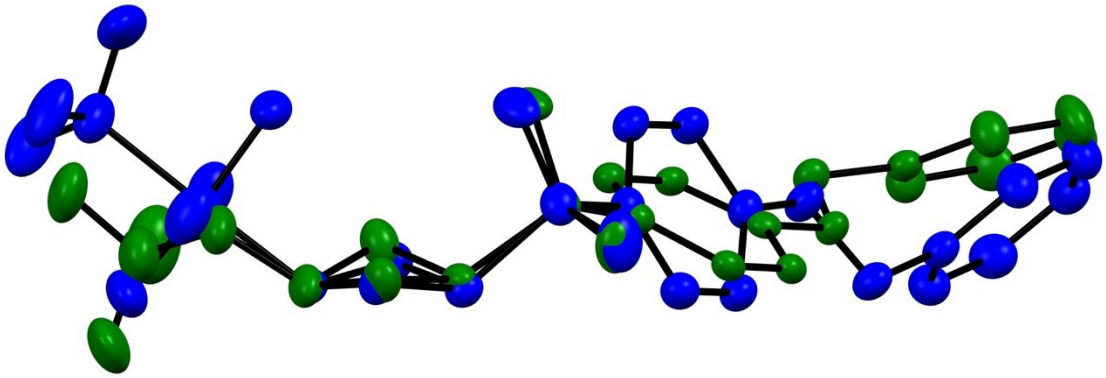
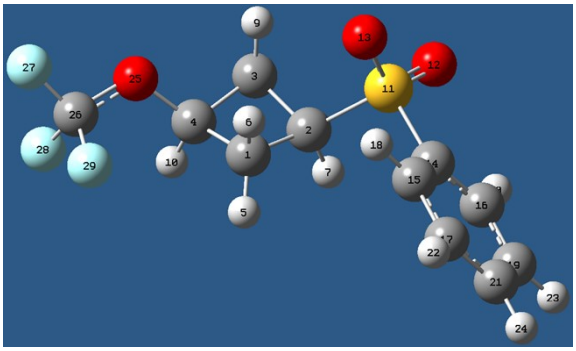


Figure S135. Overlay of *cis*-CB-SF_4CF_3 (blue) and **19** (green).

Computational Methods

The Gaussian 09, Revision E.01[11] and Gaussian 16, Revision A.03[12] suites were used for all calculations. Geometry optimizations and subsequent vibrational analyses were performed at ωB97XD/6-311++G**. The ωB97XD functional was used to account for long-range and dispersion interactions.[13] Polarization functions were applied to account for effects from ring strain. Minima were confirmed by means of vibrational analysis using the same functional/basis set combination: no imaginary frequencies were found.

((3-(trifluoromethoxy)cyclobutyl)sulfonyl)benzene (*cis* isomer)



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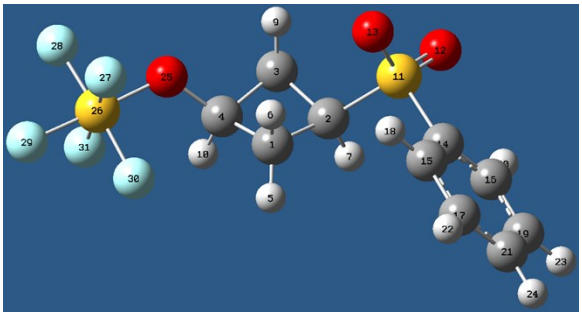
opt freq wb97xd/6-311++g(d,p) geom=connectivity

Center Number	Atomic Number	Forces (Hartrees/Bohr) X	Y	Z
1	6	-0.000005890	-0.000012764	-0.000001056
2	6	-0.000015462	0.000021060	-0.000025313
3	6	-0.000006796	-0.000003360	0.000001406
4	6	-0.000012841	0.000012944	0.000002342
5	1	-0.000007485	0.000003938	0.000006268
6	1	0.000005471	0.000002826	0.000005166
7	1	-0.000005019	-0.000001932	-0.000003577
8	1	-0.000008707	0.000007388	-0.000018559
9	1	0.000003221	0.000001821	-0.000014294
10	1	-0.000015003	0.000003402	-0.000002933
11	16	0.000010279	-0.000004382	-0.000007374
12	8	0.000005375	0.000004823	-0.000013162
13	8	0.000010924	-0.000005198	-0.000007227
14	6	0.000007835	-0.000008882	-0.000002392
15	6	0.000012083	0.000001217	0.000008362
16	6	0.000001229	0.000000458	-0.000001369
17	6	0.000011828	-0.000011584	0.000011076
18	1	0.000015021	-0.000005150	0.000005928
19	6	0.000011702	-0.000002628	-0.000000232
20	1	0.000004907	-0.000001096	-0.000009623
21	6	0.000010360	-0.000001575	0.000011862
22	1	0.000013863	-0.000007634	0.000017638
23	1	0.000004592	-0.000003558	0.000002364
24	1	0.000010677	-0.000007196	0.000014350
25	8	-0.000007401	0.000003590	-0.000006142
26	6	-0.000030208	-0.000000503	0.000013888
27	9	-0.000006283	0.000009412	0.000007514
28	9	-0.000015138	0.000005598	-0.000008543
29	9	-0.000003133	-0.000001035	0.000013633

pentafluoro(3-(phenylsulfonyl)cyclobutoxy)-λ⁶-sulfane (*cis* isomer)



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opt freq wb97xd/6-311++g(d,p) geom=connectivity

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1	6	0.000002014	0.000005176	-0.000007346
2	6	-0.000008171	-0.000006516	0.000019131
3	6	0.000006802	0.000004879	-0.000010324
4	6	0.000018227	-0.000007416	0.000017533
5	1	-0.000003316	-0.000001504	-0.000003949
6	1	-0.000000669	0.000002448	-0.000000315
7	1	0.000002068	-0.000002534	0.000001869
8	1	0.000004486	-0.000002186	0.000012184
9	1	0.000007299	0.000008640	0.000010248
10	1	-0.000005298	-0.000001762	-0.000008227
11	16	0.000005165	-0.000006390	-0.000000250
12	8	0.000009532	0.000003770	0.000014679
13	8	0.000004836	0.000006489	0.000004048
14	6	0.000003608	0.000000968	0.000006522
15	6	-0.000002775	-0.000001578	0.000001078
16	6	-0.000001276	-0.000009162	0.000004794
17	6	-0.000004911	-0.000004145	-0.000005045
18	1	0.000002283	0.000002125	-0.000003362
19	6	-0.000001698	-0.000016232	0.000002328
20	1	0.000001278	-0.000011154	0.000009482
21	6	-0.000003584	-0.000007728	0.000001017
22	1	-0.000004377	-0.000001773	-0.000006080
23	1	-0.000003392	-0.000015676	0.000005426
24	1	-0.000006250	-0.000011858	-0.000002217
25	8	-0.000026253	-0.000001085	-0.000005528
26	16	0.000009911	0.000013626	-0.000038100
27	9	0.000000044	0.000022558	0.000001018
28	9	-0.000003125	0.000009384	-0.000000221
29	9	-0.000001431	0.000016764	-0.000008861
30	9	-0.000000977	0.000005600	-0.000004559
31	9	-0.000000050	0.000006270	-0.000006974

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