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One-Pot Synthesis of Functionalized Bis(trifluoromethylated) Benziodoxoles from Iodine(I) Precursors

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Supporting Information

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1. General Methods

Reagents: Solvents for HPLC and MS analysis such as acetonitrile and methanol were purchased from Sigma Aldrich in a purity of over 99% (HPLC-grade). Water was purified and deionized using a Milli-Q® water treatment system. Dry solvents, such as acetonitrile, dichloromethane, diethyl ether, tetrahydrofuran, and toluene were obtained from a dry solvent system using activated alumina columns under nitrogen atmosphere. Commercial materials and other solvents were purchased at the highest commercial quality from the providers Acros Organics, Alfa Aesar, Apollo Scientific, Carl Roth, Fluorochem, Merck, Sigma Aldrich, VWR, TCI Chemicals and Thermo Fisher Scientific. Air- and moisture-sensitive reactions were performed under nitrogen atmosphere using a Schlenk line. Before application, the flasks were repeatedly evacuated (external heating) and refilled with nitrogen.

NMR: ^{1}H and ^{19}F Nuclear Magnetic Resonance Spectra (NMR) was recorded on a Bruker DPX-400 MHz spectrometer at 298 K. ^{13}C and two-dimensional (2D) NMR measurements were performed on a Bruker Ascend 400 spectrometer at the same temperature. The chemical shifts are given in δ-values (ppm) and are calibrated on the residual peak of the deuterated solvent ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.0 ppm). The coupling constants *J* are given in Hertz [Hz]. Following abbreviations were used for the allocation of signal multiplicities: bs – broad signal, s – singlet, d – doublet, dd – doublet of doublets, dt – doublet of triplets, t – triplet, td – triplet of doublets, tq – triplet of quartets, q – quartet, qd – quartet of doublets, qq – quartet of quartets, p – pentet, h – heptet, m – multiplet. Quantitative NMR (qNMR) was performed by addition of internal standards (trifluorotoluene: δ_F = -63.7 ppm).

HPLC: HPLC-MS measurements were performed on an Agilent 1290 Infinity HPLC system with a G4226a 1290 Autosampler, a G4220A 1290 Bin Pump and a G4212A 1290 DAD detector, connected to a 6130 Quadrupole LC/MS, coupled with a Waters XBridge C18 column (250 x 4.6 mm, 5 µm). Water:MeCN 95:5 (solvent A) and water:MeCN 5:95 (solvent B), each containing 0.1% formic acid, were used as the mobile phase, at a flow rate of 0.6 mL.min-1 . The gradient was programmed as follows: 100% A to 100% B in 20 minutes then isocratic for 5 minutes. Preparative RP-HPLC were performed on an Agilent 1260 HPLC system with a G2260A 1260 Prep ALS Autosampler, a G1361a 1260 Prep Pump, a G1365C 1260 MWD detector and a G1364B 1260 FC-PS collector, coupled with a Waters XBridge semi-preparative C18 column (19 x 150 mm, 5 µm). Water (solvent A) and water:MeCN 5:95 (solvent B), each containing 0.1% formic acid, were used as the mobile phase at a flow rate of 20 $mL \cdot min^{-1}$.

MS: Mass spectra were recorded on a LTQ Orbitrap ELITE ETD (Thermo Fisher) equipped with different types of electrospray ionization (ESI, nanoESI, nanochip-ESI) combined with a

nanoUPLC 3000 system, or a Xevo® G2-S QTOF system including multi-ionization ESI-APCI and APPI sources.

IR: Infrared spectra were recorded on a JASCO FT-IR B4100 spectrophotometer with an ATR PRO410-S and a ZnSe prisma and are reported as cm^{-1} (w = weak, m = medium, s = strong, br = broad).

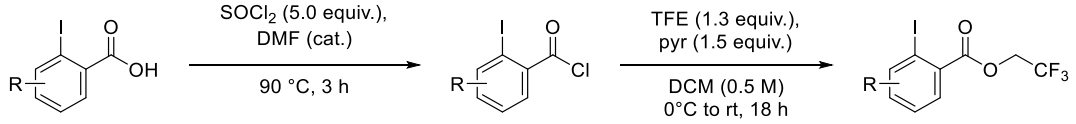
Chromatography: Thin-layer chromatography (TLC) was performed on precoated plates of silica gel F254 (Merck) with UV detection at 254 and 365 nm. Column chromatography was performed on silica gel SiliaFlash® P60 (40–63 µm, 230–400 mesh). For medium pressure liquid chromatography (MPLC) the BÜCHI Pure C-810 Flash system was used together with Reverleris® Reverse Phase (RP) C18 columns (Grace) using UV-detection at 220 nm, 254 nm, and 280 nm. The eluent system consisted of A = H_2O, B = MeCN. The purification method used the following elution gradient: 5% to 95% B, 0–25 min with a flow rate of 20 mL/min. Deviations from the gradient are shown in the corresponding procedures.

Melting point: Melting points were measured on a Büchi B-540 melting point apparatus using open glass capillaries, the data is uncorrected.

2. Chemical Procedures

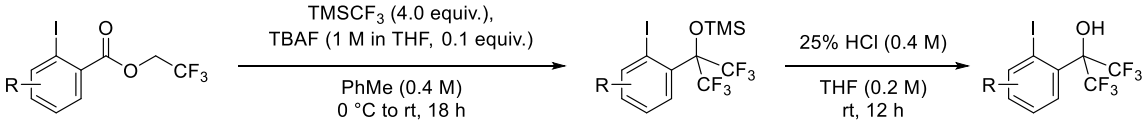
2.1. Synthesis of Iodinated Benzoic Acids

General Procedure for Synthesis of 2,2,2-Trifluoroethyl Benzoates (GP1)



Following a reported procedure for the brominated analogue,[1] 2-iodobenzoic acid (1.0 equiv.) or a corresponding analog was treated with thionyl chloride (5.0 equiv.) and a drop of DMF (cat.). The resulting suspension was heated under reflux (80-90 °C) for 3 h. The obtained slightly yellow clear solution was concentrated under reduced pressure. The remaining oil was dissolved in DCM (1.0 mL/mmol) and back-concentrated in vacuo. The crude benzoic chloride was used directly for next step without additional purification. A solution of the synthesized benzoic chloride in anhydrous DCM (1.0 M) was added to a pre-cooled (0 °C) solution of 2,2,2-trifluoroethanol (1.3 equiv.) and pyridine (1.5 equiv.) in anhydrous DCM (1.0 M, final concentration of benzoic chloride 0.5 M). The reaction mixture was allowed to warm up to room temperature and stirred for 18 h before being treated with water. The organic layer was separated from the aqueous layer followed by washing with 1 M HCl, water, and brine. The organic layer was dried over Na_2SO_4, filtered and submitted to a short path silica column (*n*-pentane/DCM = 1:1). The 2,2,2-trifluooethyl benzoates were obtained as colorless liquid or oil.

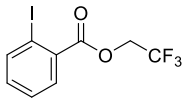
General Procedure for the Ester Reaction with $TMSCF_3$ (GP2)



Following a reported procedure for the brominated analogue[1], the corresponding 2,2,2-trifluoroethyl benzoate (1.0 equiv.) was diluted with anhydrous toluene (0.4 M) and $TMSCF_3$ (4.0 equiv.) was added. The reaction solution was cooled down to 0 °C and treated with a TBAF solution (1.0 M in THF, 0.1 equiv.). The reaction mixture was allowed to warm up to room temperature and stirred for 18 h. After addition of diethyl ether (same amount as PhMe) and 1 M HCl (same amount as PhMe), the layers were separated and the aqueous layer was extracted with Et_2O (2x, same amount as PhMe). The combined organic layers were washed with water, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The obtained residue was dissolved in THF (0.2 M) and treated with 25% HCl (0.4 M). The reaction mixture was stirred for 12 h at room temperature. Diethyl ether (same amount as PhMe) was added and the layers were separated. The aqueous phase was extracted with Et_2O (3x, same amount as PhMe). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by column chromatography to give the desired product as slightly yellow liquid, which solidified upon standing.

The color change of the reaction mixture from colorless to yellow (0 °C) and brown (room temperature) upon addition of TBAF is crucial for the reaction outcome. If no color change is observed, this is usually due to a low quality of the TBAF solution.

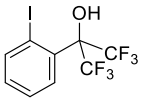
2,2,2-Trifluoroethyl 2-iodobenzoate (7a)



Following **GP1** on 48.4 mmol scale using 2-iodobenzoic acid (**1**, 12.0 g, 48.4 mmol, 1.0 equiv.). 2,2,2-Trifluoroethyl 2-iodobenzoate (**7a**, 15.2 g, 46.1 mmol, 95%) was obtained as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.05 (dd, *J* = 8.0, 1.2 Hz, 1 H, Ar*H*), 7.90 (dd, *J* = 7.8, 1.7 Hz, 1 H, Ar*H*), 7.45 (td, *J* = 7.6, 1.2 Hz, 1 H, Ar*H*), 7.21 (td, *J* = 7.7, 1.7 Hz, 1 H, Ar*H*), 4.70 (q, *J* = 8.4 Hz, 2 H, OC*H*$_2$CF$_3$). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 164.6, 142.0, 133.7, 133.0, 131.7, 128.2, 123.1 (q, *J* = 277.3 Hz), 94.8, 61.3 (q, *J* = 36.8 Hz). **^{19}F-NMR** (376 MHz, $CDCl_3$): δ = -73.3. **IR**: *v* 3678 (m), 2975 (s), 2899 (s), 1748 (m), 1588 (w), 1418 (m), 1284 (m), 1241 (s), 1169 (s), 1130 (m), 1102 (s), 1048 (s), 1022 (s), 961 (w), 896 (m), 739 (m). **HRMS** (ESI/LTQ) *m/z*: $[M+H]^+$ calcd for $C_9H_7F_3IO_2^+$ 330.9437, found 330.9447. Analytical data were in agreement with the literature.[2]

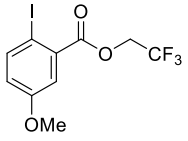
1,1,1,3,3,3-Hexafluoro-2-(2-iodophenyl)propan-2-ol (2a)



Following **GP2** on 45.5 mmol scale using 2,2,2-trifluoroethyl 2-iodoobenzoate (**7a**, 15.0 g, 45.5 mmol, 1.0 equiv.). 1,1,1,3,3,3-Hexafluoro-2-(2-iodophenyl)propan-2-ol (**2a**, 14.2 g, 38.4 mmol, 84%) was obtained as slightly yellow oil that solidified upon standing. Purification via column chromatography (*n*-pentane/DCM = 10:1 to 2:1).

TLC: R_f (*n*-pentane/DCM = 2:1) = 0.43. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 8.14 (dd, *J* = 8.0, 1.4 Hz, 1 H, Ar*H*), 7.63 (d, *J* = 8.2 Hz, 1 H, Ar*H*), 7.43 (ddd, *J* = 8.5, 7.3, 1.4 Hz, 1 H, Ar*H*), 7.10 (ddd, *J* = 8.1, 7.3, 1.6 Hz, 1 H, Ar*H*), 4.54 (bs, 1 H, O*H*). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 144.9, 131.6, 130.2–130.0 (m), 129.8, 128.1, 122.7 (q, *J* = 289.7 Hz), 90.8, 78.9 (p, *J* = 29.7 Hz). **^{19}F-NMR** (376 MHz, $CDCl_3$): δ = -73.4. **HRMS** (ESI/LTQ) *m/z*: $[M]^+$ calcd for $C_9H_5F_6IO^+$ 369.9284, found 369.9281. Analytical data were in agreement with the literature.[3]

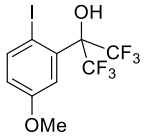
2,2,2-Trifluoroethyl 2-iodo-5-methoxybenzoate (7b)



Following **GP1** on 21.6 mmol scale using 2-iodo-5-methoxybenzoic acid (6.00 g, 21.6 mmol, 1.0 equiv.). 2,2,2-Trifluoroethyl 2-iodo-5-methoxybenzoate (**7b**, 6.95 g, 19.3 mmol, 89%) was obtained as red brown oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.88 (d, *J* = 8.7 Hz, 1 H, Ar*H*), 7.42 (d, *J* = 3.1 Hz, 1 H, Ar*H*), 6.81 (dd, *J* = 8.7, 3.1 Hz, 1 H, Ar*H*), 4.70 (q, *J* = 8.4 Hz, 2 H, OC*H*$_2$CF$_3$), 3.83 (s, 3 H ArOC*H*$_3$). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 164.4, 159.7, 142.5, 133.7, 123.1 (q, *J* = 277.3 Hz), 120.2, 117.4, 83.0, 61.3 (q, *J* = 36.9 Hz), 55.7. **^{19}F-NMR** (376 MHz, $CDCl_3$): δ = -73.3. **IR**: *v* 3382 (m), 2979 (m), 2910 (m), 1750 (m), 1656 (w), 1599 (w), 1566 (w), 1469 (m), 1415 (m), 1290 (m), 1245 (m), 1210 (m), 1163 (s), 1098 (s), 1054 (s), 974 (w), 881 (m), 817 (w), 770 (m). **HRMS** (ESI/QTOF) *m/z*: $[M+Na]^+$ calcd for $C_{10}H_8F_3INaO_3^+$ 382.9362, found 382.9366.

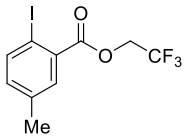
1,1,1,3,3,3-Hexafluoro-2-(2-iodo-5-methoxyphenyl)propan-2-ol (2b)



Following **GP2** on 19.2 mmol scale using 2,2,2-trifluoroethyl 2-iodo-5-methoxybenzoate (**7b**, 6.90 g, 19.2 mmol, 1.0 equiv.). 1,1,1,3,3,3-Hexafluoro-2-(2-iodo-5-methoxyphenyl)propan-2-ol (**2b**, 6.21 g, 15.5 mmol, 81%) was obtained as brown liquid that solidified upon standing. Purification via column chromatography (*n*-pentane/DCM = 4:1 to 2:1).

MP: 37–43 °C. **TLC**: R_f (*n*-pentane/DCM = 2:1) = 0.39. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 8.8 Hz, 1 H, Ar*H*), 7.20 (d, *J* = 2.8 Hz, 1 H, Ar*H*), 6.71 (dd, *J* = 8.8, 2.9 Hz, 1 H, Ar*H*), 4.36 (s, 1 H, O*H*), 3.81 (s, 3 H, ArOC*H*$_3$). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 159.4, 145.1, 130.6, 122.7 (q, *J* = 290.4 Hz), 117.3 (p, *J* = 3.2 Hz), 117.1, 78.7, 55.6. **^{19}F-NMR** (376 MHz, $CDCl_3$): δ = -73.5. **IR**: *v* 3354 (s), 2978 (m), 1657 (m), 1463 (w), 1393 (m), 1245 (m), 1190 (m), 1150 (w), 1083 (m), 1051 (s), 1015 (w), 957 (w), 871 (w), 734 (w). **HRMS** (Sicrit Plasma/LTQ) *m/z*: $[M]^+$ calcd for $C_{10}H_7F_6IO_2^+$ 399.9389, found 399.9390. One carbon signal was not resolved.

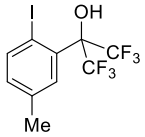
2,2,2-Trifluoroethyl 2-iodo-5-methylbenzoate (7c)



Following **GP1** on 20.2 mmol scale using 2-iodo-5-methylbenzoic acid (5.30 g, 20.2 mmol, 1.0 equiv.). 2,2,2-Trifluoroethyl 2-iodo-5-methylbenzoate (**7c**, 6.57 g, 19.1 mmol, 94%) was obtained as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 8.1 Hz, 1 H, Ar*H*), 7.69 (d, *J* = 2.3 Hz, 1 H, Ar*H*), 7.03 (ddd, *J* = 8.0, 2.3, 0.8 Hz, 1 H, Ar*H*), 4.70 (q, *J* = 8.4 Hz, 2 H, OC*H*$_2$CF$_3$), 2.36 (s, 3 H, ArC*H*$_3$). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 164.7, 141.7, 138.5, 134.8, 132.7, 132.4, 123.1 (q, *J* = 277.3 Hz), 90.7, 61.2 (q, *J* = 36.9 Hz), 21.0. **^{19}F-NMR** (376 MHz, $CDCl_3$): δ = -73.3. **IR**: *v* 3660 (w), 2979 (s), 2899 (m), 1750 (m), 1469 (m), 1444 (w), 1418 (m), 1393 (m), 1299 (s), 1277 (s), 1245 (s), 1199 (s), 1173 (s), 1108 (s), 1054 (s), 1008 (m), 975 (m), 900 (w), 820 (m), 770 (m). **HRMS** (ESI/QTOF) *m/z*: $[M+Na]^+$ calcd for $C_{10}H_8F_3INaO_2^+$ 366.9413, found 366.9412.

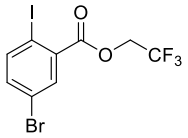
1,1,1,3,3,3-Hexafluoro-2-(2-iodo-5-methylphenyl)propan-2-ol (2c)



Following **GP2** on 16.0 mmol scale using 2,2,2-trifluoroethyl 2-iodo-5-methylbenzoate (**7c**, 5.50 g, 16.0 mmol, 1.0 equiv.). 1,1,1,3,3,3-Hexafluoro-2-(2-iodo-5-methylphenyl)propan-2-ol (**2c**, 5.22 g, 13.6 mmol, 85%) was obtained as slightly yellow oil that solidified upon standing. Purification via column chromatography (*n*-pentane/DCM = 10:1 to 2:1).

MP: 37–38 °C. **TLC**: R_f (*n*-pentane/DCM = 2:1) = 0.48. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 8.1 Hz, 1 H, Ar*H*), 7.42 (s, 1 H, Ar*H*), 6.93 (dt, *J* = 8.1, 1.3 Hz, 1 H, Ar*H*), 4.28 (bs, 1 H, O*H*), 2.35 (s, 3 H, ArCH_3). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 144.5, 138.4, 132.7, 130.9 (p, *J* = 3.1 Hz), 129.6, 122.7 (d, *J* = 289.8 Hz), 86.6, 78.9 (p, *J* = 29.9 Hz), 21.3. **^{19}F-NMR** (376 MHz, $CDCl_3$): δ = -73.4. **IR**: *v* 3668 (m), 2987 (s), 2908 (s), 1477 (m), 1455 (w), 1404 (m), 1210 (s), 1182 (s), 1151 (m), 1130 (m), 1058 (s), 1018 (m), 964 (m), 871 (w), 831 (w), 817 (m), 748 (m), 730 (m). **HRMS** (APPI/LTQ) *m/z*: $[M]^+$ calcd for $C_{10}H_7F_6IO^+$ 383.9440, found 383.9446.

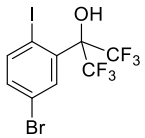
2,2,2-Trifluoroethyl 5-bromo-2-iodobenzoate (7d)



Following **GP1** on 18.8 mmol scale using 5-bromo-2-iodobenzoic acid (10.0 g, 30.6 mmol, 1.0 equiv.). 2,2,2-Trifluoroethyl 5-bromo-2-iodobenzoate (**7d**, 10.1 g, 24.6 mmol, 80%) was obtained as yellow liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 2.4 Hz, 1 H, Ar*H*), 7.88 (d, *J* = 8.4 Hz, 1 H, Ar*H*), 7.34 (dd, *J* = 8.4, 2.4 Hz, 1 H, Ar*H*), 4.71 (q, *J* = 8.3 Hz, 2 H, OCH_2CF_3). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 163.4, 143.2, 136.7, 134.6, 134.5, 122.9 (q, *J* = 277.3 Hz), 122.5, 92.8, 61.5 (q, *J* = 37.0 Hz). **^{19}F-NMR** (376 MHz, $CDCl_3$): δ = -73.2. **IR**: *v* 3653 (m), 3403 (m), 2972 (s), 2921 (m), 1743 (m), 1653 (w), 1465 (w), 1426 (w), 1381 (m), 1292 (s), 1269 (m), 1238 (m), 1181 (s), 1056 (s), 1000 (m), 979 (w), 885 (m), 819 (m), 777 (w), 733 (w). **HRMS** (Sicrit Plasma/LTQ) *m/z*: $[M]^+$ calcd for $C_9H_5BrF_3IO_2^+$ 407.8464, found 407.8465.

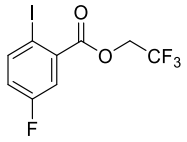
1,1,1,3,3,3-Hexafluoro-2-(5-bromo-2-iodophenyl)propan-2-ol (2d)



Following **GP2** on 24.5 mmol scale using 2,2,2-trifluoroethyl 5-bromo-2-iodobenzoate (**7d**, 10.0 g, 24.5 mmol, 1.0 equiv.). 1,1,1,3,3,3-Hexafluoro-2-(5-bromo-2-iodophenyl)propan-2-ol (**2d**, 4.80 g, 10.7 mmol, 44%) was obtained as yellow liquid that solidified upon standing. Purification via column chromatography (*n*-pentane/DCM = 2:1).

MP: 43–44 °C. **TLC**: R_f (*n*-pentane/DCM = 2:1) = 0.23. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 8.5 Hz, 1 H, Ar*H*), 7.72 (s, 1 H, Ar*H*), 7.24 (dd, *J* = 8.5, 2.3 Hz, 1 H, Ar*H*), 4.14 (s, 1 H, O*H*). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 146.0, 134.8, 133.0 (p, *J* = 3.1 Hz), 131.7, 122.7, 122.5 (q, *J* = 290.0 Hz), 88.7, 78.5 (p, *J* = 30.1 Hz). **^{19}F-NMR** (376 MHz, $CDCl_3$): δ = -73.5. **IR**: *v* 3401 (s), 2971 (s), 2903 (s), 1638 (m), 1466 (w), 1393 (m), 1249 (m), 1199 (m), 1066 (s), 1058 (s), 1033 (m), 954 (w), 875 (w), 828 (w), 730 (w). **HRMS** (APPI/LTQ) *m/z*: $[M]^+$ calcd for $C_9H_4BrF_6IO^+$ 447.8389, found 447.8388.

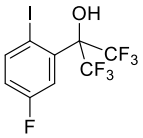
2,2,2-Trifluoroethyl 5-fluoro-2-iodobenzoate (7e)



Following **GP1** on 25.0 mmol scale using 5-fluoro-2-iodobenzoic acid (6.65 g, 25.0 mmol, 1.0 equiv.). 2,2,2-Trifluoroethyl 5-fluoro-2-iodobenzoate (**7e**, 8.29 g, 23.8 mmol, 95%) was obtained as yellow liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.99 (dd, *J* = 8.8, 5.4 Hz, 1H, Ar*H*), 7.62 (dd, *J* = 8.9, 3.0 Hz, 1H, Ar*H*), 6.99 (ddd, *J* = 8.8, 7.6, 3.0 Hz, 1H, Ar*H*), 4.71 (q, *J* = 8.3 Hz, 2H, O*C*$H_2$$CF_3$). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 163.5 (d, *J* = 2.7 Hz), 162.5 (d, *J* = 249.9 Hz), 143.4 (d, *J* = 7.2 Hz), 134.4 (d, *J* = 7.2 Hz), 123.0 (q, *J* = 277.4 Hz), 121.4 (d, *J* = 21.5 Hz), 119.2 (d, *J* = 24.4 Hz), 87.9 (d, *J* = 3.4 Hz), 61.5 (q, *J* = 37.0 Hz). **^{19}F-NMR** (376 MHz, $CDCl_3$): δ -73.3 (t, *J* = 8.3 Hz, CF_3), -112.5 – -112.6 (m, Ar*F*). **IR**: *v* 2218 (w), 1492 (w), 1460 (m), 1285 (m), 1261 (s), 1212 (m), 1174 (s), 1160 (s), 1007 (m), 959 (s), 911 (w), 885 (w), 811 (w), 755 (m), 729 (s). **HRMS** (APPI/LTQ) *m/z*: $[M+H]^+$ calcd for $C_9H_6F_4IO_2^+$ 348.9343, found 348.9350.

1,1,1,3,3,3-Hexafluoro-2-(5-fluoro-2-iodophenyl)propan-2-ol (2e)

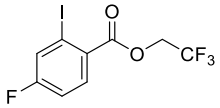


Following **GP2** on 19.2 mmol scale using 2,2,2-trifluoroethyl 5-fluoro-2-iodobenzoate (**7e**, 8.29 g, 23.8 mmol, 1.0 equiv.). 1,1,1,3,3,3-Hexafluoro-2-(5-fluoro-2-iodophenyl)propan-2-ol (**2e**, 6.50 g, 14.8 mmol, 62%) was obtained as orange liquid that solidified upon standing. Purification via column chromatography (*n*-pentane/DCM = 100% to 70:30).

MP: 35–36 °C. **TLC**: R_f (*n*-pentane/DCM = 2:1) = 0.23. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 8.08 (dd, *J* = 8.8, 6.0 Hz, 1 H, Ar*H*), 7.38 (d, *J* = 13.9 Hz, 1 H, Ar*H*), 6.98–6.83 (m, 1 H, Ar*H*), 4.21 (bs, 1 H, O*H*). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 162.2 (d, *J* = 249.6 Hz), 146.0 (d, *J* = 7.5 Hz), 131.6 (d, *J* = 6.9 Hz), 122.5 (q, *J* = 289.7 Hz), 119.3 (d, *J* = 21.0 Hz), 118.4–118.0 (m), 83.6 (d, *J* = 2.8 Hz), 78.9–78.3 (m). **^{19}F-NMR** (376 MHz, $CDCl_3$): δ = -73.6 (CF_3), -111.7 (Ar*F*). **IR**: *v* 3459 (w), 1602 (w), 1580 (w), 1474 (m), 1390 (m), 1259 (s), 1229 (s), 1173 (m), 1154 (m), 1019 (m), 984 (m), 964

(m), 877 (m), 848 (m), 820 (m), 751 (m), 749 (m), 732 (m). **HRMS** (APPI/LTQ) *m/z*: $[M]^+$ calcd for $C_9H_4F_7IO^+$ 387.9190, found 387.9191.

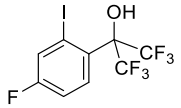
2,2,2-Trifluoroethyl 4-fluoro-2-iodobenzoate (7f)



Following **GP1** on 18.8 mmol scale using 4-fluoro-2-iodobenzoic acid (5.00 g, 18.8 mmol, 1.0 equiv.). 2,2,2-Trifluoroethyl 4-fluoro-2-iodobenzoate (**7f**, 6.09 g, 17.5 mmol, 93%) was obtained as yellow liquid in 94% purity (based on ^{19}F signals: δ = -73.4, -73.8).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.96 (dd, *J* = 8.8, 5.8 Hz, 1 H, Ar*H*), 7.78 (dd, *J* = 8.1, 2.5 Hz, 1 H, Ar*H*), 7.16 (ddd, *J* = 8.8, 7.6, 2.6 Hz, 1 H, Ar*H*), 4.69 (q, *J* = 8.3 Hz, 2 H, O*CH*$_2$CF$_3$). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 164.1 (d, *J* = 259.9 Hz), 163.5, 133.6 (d, *J* = 9.2 Hz), 129.4 (d, *J* = 24.0 Hz), 128.7 (d, *J* = 3.3 Hz), 123.1 (q, *J* = 277.3 Hz), 115.6 (d, *J* = 21.4 Hz), 95.6 (d, *J* = 8.7 Hz), 61.3 (q, *J* = 36.9 Hz). **^{19}F-NMR** (376 MHz, $CDCl_3$): δ = -73.4 (C*F*$_3$), -104.5 (Ar*F*). **IR**: *v* 3685 (w), 3364 (w), 2973 (s), 2888 (s), 1912 (w), 1768 (w), 1662 (w), 1595 (w), 1490 (w), 1451 (w), 1407 (m), 1382 (m), 1307 (w), 1256 (m), 1170 (m), 1065 (s), 975 (w), 875 (m), 766 (w). **HRMS** (Sicrit Plasma/LTQ) *m/z*: $[M]^+$ calcd for $C_9H_5F_4IO_2^+$ 347.9265, found 347.9266.

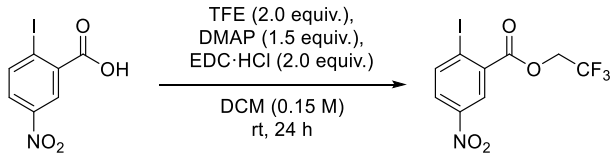
1,1,1,3,3,3-Hexafluoro-2-(4-fluoro-2-iodophenyl)propan-2-ol (2f)



Following **GP2** on 17.2 mmol scale using 2,2,2-trifluoroethyl 4-fluoro-2-iodobenzoate (**7f**, 6.00 g, 17.2 mmol, 1.0 equiv.). 1,1,1,3,3,3-Hexafluoro-2-(4-fluoro-2-iodophenyl)propan-2-ol (**2f**, 3.55 g, 9.15 mmol, 53%) was obtained as yellow liquid. Purification via column chromatography (*n*-pentane/DCM = 2:1).

TLC: R_f (*n*-pentane/DCM = 2:1) = 0.22. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.87 (dd, *J* = 8.1, 2.8 Hz, 1 H, Ar*H*), 7.58 (dd, *J* = 9.2, 5.6 Hz, 1 H, Ar*H*), 7.16 (ddd, *J* = 9.2, 7.0, 2.8 Hz, 1 H, Ar*H*), 4.03 (s, 1 H, O*H*). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 162.2 (d, *J* = 256.9 Hz), 131.9 (d, *J* = 23.8 Hz), 131.0 (dq, *J* = 8.8, 3.2 Hz), 125.9 (d, *J* = 3.8 Hz), 122.6 (q, *J* = 289.7 Hz), 115.4 (d, *J* = 21.1 Hz), 90.7 (d, *J* = 7.6 Hz), 78.7 (p, *J* = 30.0 Hz). **^{19}F-NMR** (376 MHz, $CDCl_3$): δ = -73.7 (C*F*$_3$), -109.7 (Ar*F*). **IR**: *v* 3361 (m), 2978 (s), 2907 (s), 1597 (m), 1580 (m), 1489 (m), 1452 (m), 1407 (m), 1386 (m), 1253 (s), 1224 (s), 1213 (s), 1189 (m), 1152 (m), 1087 (s), 1051 (s), 964 (m), 936 (m), 867 (m), 813 (w), 751 (w), 748 (w), 737 (w), 700 (w). **HRMS** (APPI/LTQ) *m/z*: $[M]^+$ calcd for $C_9H_4F_7IO^+$ 387.9190, found 387.9193.

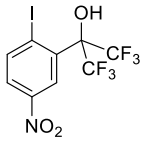
2,2,2-Trifluoroethyl 2-iodo-5-nitrobenzoate (7g)



2-Iodo-5-nitrobenzoic acid (5.00 g, 17.1 mmol, 1.0 equiv.), DMAP (3.13 g, 25.6 mmol, 1.5 equiv.) and EDC·HCl (6.54 g, 34.1 mmol, 2.0 equiv.) were added into an oven-dried 250 mL flask. The flask was evacuated and flushed with nitrogen three times before dry DCM (113 mL, 0.15 M) and TFE (2.58 mL, 3.41 g, 34.1 mmol, 2.0 equiv.) were added. The reaction mixture was stirred at room temperature for 24 h. A saturated $NaHCO_3$ solution (50 mL) was added and the layers were separated. The organic layer was washed with water (50 mL) and brine (25 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The obtained residue was purified by column chromatography (*n*-pentane/EtOAc = 4:1) to give the desired ester **7g** (3.18 g, 8.47 mmol, 50%) as yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.66 (d, *J* = 2.6 Hz, 1 H, Ar*H*), 8.27 (d, *J* = 8.6 Hz, 1 H, Ar*H*), 8.04 (dd, *J* = 8.6, 2.7 Hz, 1 H, Ar*H*), 4.77 (q, *J* = 8.2 Hz, 2 H, OCH_2CF_3). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 163.0, 147.9, 143.4, 134.6, 127.3, 126.1, 122.8 (q, *J* = 277.4 Hz), 103.1, 61.8 (q, *J* = 37.3 Hz). **^{19}F-NMR** (376 MHz, $CDCl_3$): δ -73.2. **IR**: *v* 2992 (s), 2912 (s), 1753 (m), 1609 (m), 1530 (m), 1406 (m), 1367 (m), 1304 (m), 1263 (m), 1241 (s), 1184 (m), 1123 (m), 1079 (s), 1036 (m), 896 (m), 867 (m), 737 (m). **HRMS** (ESI/QTOF) *m/z*: $[M+H]^+$ calcd for $C_9H_6F_3INO_4^+$ 375.9288, found 375.9286.

1,1,1,3,3,3-Hexafluoro-2-(2-iodo-5-nitrophenyl)propan-2-ol (2g)



Following **GP2** on 19.2 mmol scale using 2,2,2-trifluoroethyl 2-iodo-5-nitrobenzoate (**7g**, 3.00 g, 8.00 mmol, 1.0 equiv.). 1,1,1,3,3,3-Hexafluoro-2-(2-iodo-5-nitrophenyl)propan-2-ol (**2g**, 1.35 g, 3.25 mmol, 41%) was obtained as a yellow solid. Purification via column chromatography (*n*-pentane/DCM = 1:1).

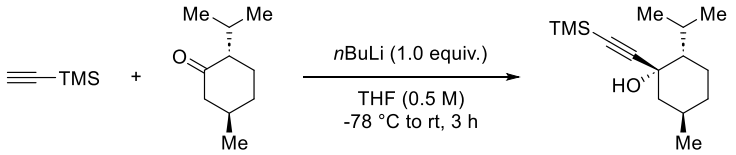
MP: 48–50 °C. **TLC**: R_f (*n*-pentane/DCM = 1:1) = 0.16. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 8.49–8.43 (m, 1 H, Ar*H*), 8.39 (d, *J* = 8.7 Hz, 1 H, Ar*H*), 7.94 (dd, *J* = 8.7, 2.5 Hz, 1 H, Ar*H*), 3.95 (s, 1 H, O*H*). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 147.6, 146.5, 131.7, 125.4, 124.8–124.4 (m), 122.3 (d, *J* = 289.7 Hz), 99.3, 78.6 (p, *J* = 30.3 Hz). **^{19}F-NMR** (376 MHz, $CDCl_3$): δ = -73.6. **IR**: *v* 1608 (w), 1577 (w), 1530 (m), 1463 (w), 1343 (m), 1261 (s), 1223 (s), 1182 (s), 1152 (s), 1112 (m), 1065 (m), 1019 (m), 968 (m), 908 (m), 861 (s), 838 (m), 769 (w), 737 (m), 730 (m). **HRMS** (nanochip-ESI/LTQ) *m/z*: $[M+Na]^+$ calcd for $C_9H_4F_6INNaO_3^+$ 437.9032, found 437.9017; (ESI-QTOF) *m/z*: $[M-H]^-$ calcd for $C_9H_3F_6INO_3^-$ 413.9067, found 413.9072.

2.2. Synthesis of Alkynes

The following TMS protected alkynes or vinyl boronic acids were commercially available: trimethyl(phenylethynyl)silane (for **8a**), ((4-fluorophenyl)ethynyl)trimethylsilane (for **8b**), ((4-methoxyphenyl)ethynyl)trimethylsilane (for **8c**), trimethyl(prop-1-yn-1-yl)silane (for **8d**), trimethyl(pent-1-yn-1-yl)silane (for **8e**), (*E*)-styrylboronic acid (for **8g**), (3-bromoprop-1-yn-1-yl)trimethylsilane (for **8h**).

Triisopropyl((trimethylsilyl)ethynyl)silane (for **8f**) was synthesized as reported previously.[4] Diisopropyl (phenylethynyl)boronate and 4,4,5,5-tetramethyl-2-(phenylethynyl)-1,3,2-dioxaborolane (for optimization) were synthesized following a reported procedure.[5,6]

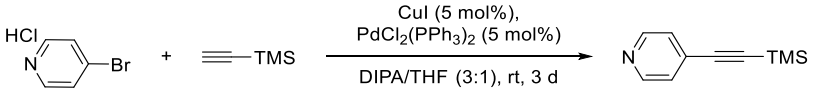
(1*S*,2*S*,5*R*)-2-Isopropyl-5-methyl-1-((trimethylsilyl)ethynyl)cyclohexan-1-ol (S1)



Ethynyl(trimethyl)silane (7.25 mL, 5.00 g, 50.9 mmol, 1.0 equiv.) was dissolved in dry THF (0.5 M, 100 mL) and the mixture was cooled down to -78 °C. 2.5 M *n*BuLi in hexane (20.4 mL, 50.9 mmol, 1.0 equiv.) was added dropwise. After being stirred at -78 °C for 1 h, (-)-menthone (10.6 mL, 9.42 g, 61.1 mmol, 1.2 eq.) was added and the reaction mixture was warmed up to room temperature, stirred for 2 h, and quenched with a saturated NH_4Cl solution (20 mL). The aqueous layer was separated from the organic layer, followed by extraction with EtOAc (3x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The obtained residue was purified by MPLC (t_R = 18.7–20.7 min, gradient: 5–95% in 28 min) to give the desired product **S1** (1.72 g, 6.81 mmol, 13%) as a colorless liquid and a mixture of diastereomers (*dr* = 6:1, determined between carbon signals δ_C 110.95 and δ_C 111.80). The mixture of diastereomers was used for the next without any further purification.

ORD: $[\alpha]_D^{20}$ = -55.1 (c = 0.59, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 2.37 (pd, *J* = 7.0, 2.2 Hz, 1 H, C*H*), 1.98–1.89 (m, 1 H, CH_2), 1.78–1.67 (m, 2H, C*H*, CH_2), 1.53–1.45 (m, 2 H, CH_2), 1.44–1.32 (m, 2 H, C*H*, CH_2), 1.29 (ddd, *J* = 12.3, 4.0, 2.2 Hz, 1 H, C*H*), 0.97 (d, *J* = 7.0 Hz, 3 H, CH_3), 0.92 (d, *J* = 6.9 Hz, 3 H, CH_3), 0.87 (d, *J* = 6.4 Hz, 3 H, CH_3), 0.16 (s, 9 H, TMS). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 111.0, 87.5, 72.2, 50.5, 50.1, 35.0, 28.4, 27.4, 24.1, 22.1, 20.9, 19.0, 0.2. **IR**: *v* 3675 (m), 2965 (s), 2899 (s), 1966 (w), 1642 (w), 1444 (w), 1407 (m), 1393 (m), 1242 (m), 1058 (s), 896 (w), 867 (m), 844 (w). **HRMS** (HESI/LTQ) *m/z*: $[M+Na]^+$ calcd for $C_{15}H_{28}NaOSi^+$ 275.1802, found 275.1802.

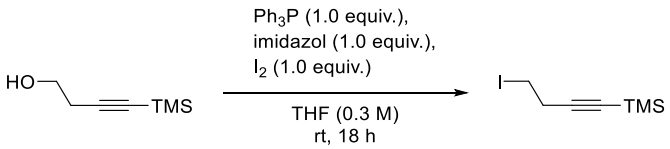
4-((Trimethylsilyl)ethynyl)pyridine (S2)



Following a reported procedure[7]: In a one-neck round bottom flask, $PdCl_2(PPh_3)_2$ (176 mg, 0.250 mmol, 5 mol%), CuI (47.6 mg, 0.250 mmol, 5 mol%) and 4-bromopyridine hydrochloride (972 mg, 5.00 mmol, 1.0 equiv.) were added followed by a 3:1 mixture of dry THF/diisopropylamine (60 mL). Finally, trimethylsilylacetylene (830 µL, 589 mg, 6.00 mmol, 1.2 equiv.) was charged and the reaction mixture was stirred under N_2 atmosphere at room temperature for 3 days. After this time, the mixture was filtered through a short pad of celite and rinsed with DCM (100 mL). The solvent was removed, and the crude was purified by column chromatography (100 % *n*-pentane to 50:50 *n*-pentane/EtOAc, affording compound **S2** as a yellow oil (522 mg, 3.00 mmol, 60% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.57–8.56 (m, 2 H, Ar*H*), 7.31–7.29 (m, 2 H, Ar*H*), 0.26 (bs, 9 H, TMS). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 149.9, 131.3, 126.0, 102.1, 100.1, -0.2. Analytical data were in agreement with the literature.[7]

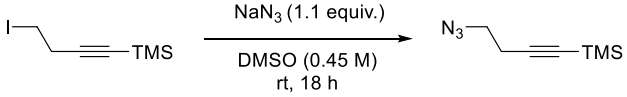
4-Iodanylbut-1-ynyl(trimethyl)silane (S3)



Following a reported procedure[8], 4-(trimethylsilyl)but-3-yn-1-ol (11.7 mL, 10.0 g, 70.3 mmol, 1.0 equiv.) was dissolved in dry THF and cooled down to 0 °C. Triphenylphosphine (18.4 g, 70.3 mmol, 1.0 equiv.), imidazole (4.79 g, 70.3 mmol, 1.0 equiv.) and iodine (17.8 g, 70.3 mmol, 1.0 equiv.) were added and the reaction was allowed to warm up to room temperature. The reaction mixture was stirred for 18 h at room temperature before diethyl ether (100 mL) and a 10% sodium thiosulfate solution (100 mL) were added. The layers were separated and the aqueous layer was extracted with diethyl ether (2x 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The obtained residue was purified through a silica plug (*n*-pentane) to obtain the desired product **S3** (14.7 g, 58.2 mmol, 83%) as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 3.22 (t, *J* = 7.5 Hz, 2 H, C*H*$_2$I), 2.79 (t, *J* = 7.5 Hz, 2 H, C*H*$_2$CH$_2$I), 0.16 (s, 9 H, TMS). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 105.2, 86.9, 25.2, 1.2, 0.1. **MS** (ESI/QTOF) m/z: 504.1 $[2M+H]^+$. Analytical data were in agreement with the literature.[8]

4-Azidobut-1-ynyl(trimethyl)silane (S4)

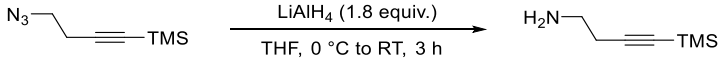


Following a reported procedure[8], sodium azide (4.16 g, 64.0 mmol, 1.1 equiv.) was dissolved in DMSO (127 mL). 4-Iodanylbut-1-ynyl(trimethyl)silane (**S3**, 14.7 g, 58.2 mmol, 1.0 equiv.)

was added and the reaction was stirred for 18 h at room temperature. The reaction mixture was poured into ice-cold water (200 mL) and the aqueous layer was extracted with diethyl ether (3x 100 mL) and the combined organic layers were washed with water (2x 100 mL), brine (50 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The product **S4** (8.22 g, 49.2 mmol, 85%) was obtained as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 3.37 (t, *J* = 6.9 Hz, 2 H, C*H*$_2$N$_3$), 2.52 (t, *J* = 6.9 Hz, 2 H, C*H*$_2$CH$_2$N$_3$), 0.16 (s, 9 H, TMS). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 102.7, 87.4, 49.9, 21.1, 0.0. **HRMS** (ESI/QTOF) m/z: $[M+Ag]^+$ calcd for $C_7H_{13}AgN_3Si^+$ 273.9924, found 273.9922. Analytical data were in agreement with the literature.[8]

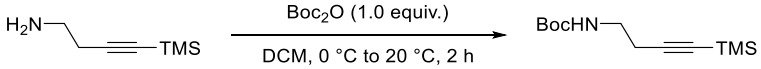
4-(Trimethylsilyl)but-3-yn-1-amine (S5)



Following a reported procedure[9], a solution of **S4** (4.00 g, 23.9 mmol, 1.0 equiv) in dry THF (44 mL) was added to a cooled (0° C) solution of $LiAlH_4$ in THF (2.4 M, 18 mL, 1.8 mmol) under N_2 atmosphere. After 15 min, the reaction mixture was allowed to reach room temperature and stirred for another 3 h. The reaction mixture was carefully quenched with H_2O and extracted with EtOAc (3x 15 mL) followed by filtration over Celite plug. Finally, the solvent was concentrated under reduced pressure to yield product **S5** as a colorless oil which was used without further purification (1.60 g, 9.56 mmol, 40% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.81 (t, *J* = 6.3 Hz, 2 H, H$_2$NC*H*$_2$), 2.35 (t, *J* = 6.3 Hz, 2 H, H$_2$NCH$_2$C*H*$_2$), 1.39 (bs, 2 H, N*H*$_2$), 0.14 (s, 9 H, TMS). Analytical data were in agreement with the literature.[9]

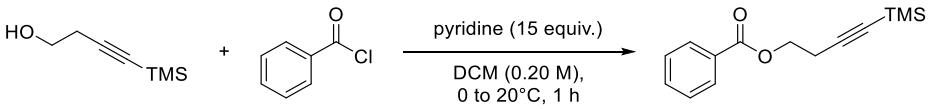
***Tert*-butyl (4-(trimethylsilyl)but-3-yn-1-yl)carbamate (S6)**



Following a reported procedure[10]: A solution of di-*tert*-butylcarbonate (2.50 g, 11.2 mmol, 1.0 equiv.) in dry DCM (5 mL) was added to a solution of 4-trimethylsilylbut-3-yn-1-amine (**S5**, 1.60 g, 11.2 mmol, 1.0 equiv.) in DCM (5 mL) at 0 °C during 30 min. After the addition, the reaction mixture was allowed to reach room temperature and stirred for another 2 h. Finally, the solvent was removed under reduced pressure and the resulting residue was triturated with pentane (15 mL, aprox), affording compound **S6** as a white solid (2.45 g, 10.2 mmol, 90% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 4.80 (bs, 1 H, N*H*), 3.25 (q, *J* = 6.4 Hz, 2 H, NHC*H*$_2$), 2.40 (t, *J* = 6.6 Hz, 2 H, CH$_2$C*H*$_2$C), 1.44 (s, 9 H, Boc), 0.14 (s, 9 H, TMS). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 155.8, 104.3, 86.5, 79.5, 60.5, 39.5, 28.3, 0.2. **HRMS** (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{12}H_{23}NNaO_2Si^+$ 264.1390; Found 264.1393.Analytical data were in agreement with the literature.[10]

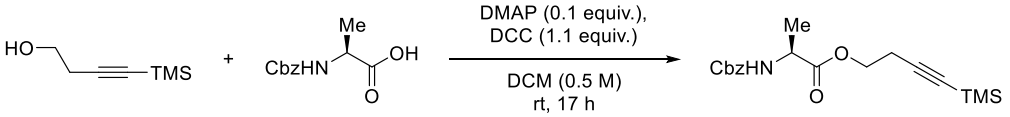
4-(Trimethylsilyl)but-3-yn-1-yl benzoate (S7)



Following a reported procedure[11]: In one-neck round bottom flask a solution of 4-trimethylsilylbut-3-yn-1-ol (1.70 mL, 1.40 g, 10.0 mmol, 1.0 equiv.) and benzoyl chloride (1.40 mL, 1.70 g, 1.20 mmol, 1.0 equiv.) in dry DCM (20 mL) was prepared. Then, the reaction mixture was cooled down to 0 °followed by the addition of dry pyridine (1.20 mL, 150 mmol, 15 equiv.). The reaction mixture was allowed to reach room temperature and stirred for 1 h. After this time, the mixture was quenched with HCl (1 M, 40 mL) and stirred for another 15 min followed by separation of the layers. The aqueous layer was extracted with DCM (3x 60 mL) and the organic layers were recombined and washed with H_2O (2x 20 mL), brine (10 mL), dried over $MgSO_4$ and filtered and concentrated under reduced pressure yielding a residue which was purified by column chromatography (100% *n*-pentane to 90:10 *n*-pentane/EtOAc). Compound **S7** was obtained as a pale-yellow oil (2.35 g, 9.60 mmol, 95% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.08–8.05 (m, 2 H, Ar*H*), 7.60–7.52 (m, 1 H, Ar*H*), 7.47–7.42 (m, 2 H, Ar*H*), 4.41 (t, *J* = 7.0 Hz, 2 H, COOCH_2CH$_2$), 2.70 (t, *J* = 7.0 Hz, 2 H, CH$_2$CH_2C), 0.15 (s, 9 H, TMS). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 166.5, 134.7, 133.2, 129.8, 128.5, 102.4, 86.8, 62.8, 20.6, 0.12. **IR** *v* 2961 (m), 2182 (m), 1723 (s), 1274 (s), 1249 (s), 1216 (m), 1112 (s), 1069 (m), 1027 (m), 843 (s), 760 (s), 711 (s). **HRMS** (APCI/QTOF) m/z: $[M+H]^+$ calcd for $C_{14}H_{19}O_2Si^+$ 247.1149, found 247.1147.

4-(Trimethylsilyl)but-3-yn-1-yl ((benzyloxy)carbonyl)-L-alaninate (S8)

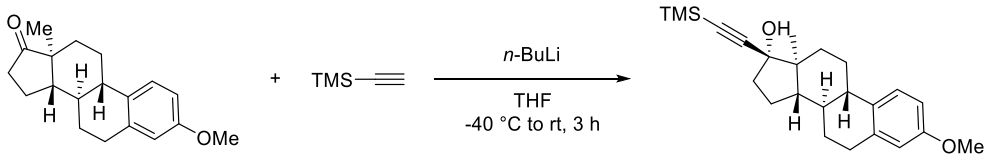


4-Trimethylsilylbut-3-yn-1ol (3.33 mL, 2.85 g, 20.0 mmol, 1.0 equiv.) was diluted with anhydrous DCM (40 mL, 0.5 M). *N*,*N*-dimethylpyridin-4-amine (DMAP, 244 mg, 2.00 mmol, 0.1 equiv.) and *N*,*N*'-dicyclohexylcarbodiimide (DCC, 4.54 g, 22.0 mmol, 1.1 equiv.) was added. After addition of (2*S*)-2-(phenylmethoxycarbonylamino)propanoic acid (4.69 g, 21.0 mmol, 1.05 equiv.), the reaction mixture was stirred for 17 h at room temperature. The suspension was filtered through a plug of silica and the product was eluted with *n*-pentane/EtOAc = 1:1 (100 mL). The desired product **S8** (6.94 g, 20.0 mmol, 99%) was obtained as colorless oil in quantitative yield.

ORD: $[\alpha]_D^{20}$ = -40.9 (c = 2.94, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.38–7.29 (m, 5 H, Ar*H*), 5.32 (d, *J* = 7.8 Hz, 1 H, N*H*), 5.11 (d, *J* = 2.1 Hz, 2 H, PhCH_2O), 4.41 (p, *J* = 7.3 Hz, 1 H, NHC*H*CH$_3$), 4.31–4.15 (m, 2 H, OCH_2), 2.57 (t, *J* = 6.9 Hz, 2 H, CH_2C≡C), 1.43 (d, *J* = 7.2 Hz, 3 H, CH_3), 0.14 (s, 9 H, TMS). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 172.8, 155.7, 136.4, 128.7, 128.3, 128.3, 101.9, 86.9, 67.1, 63.2, 49.8, 20.4, 19.0, 0.1. **IR**: *v* 3400 (m), 2972 (s), 2910 (m), 1736 (m), 1532 (w),

1458 (w), 1405 (m), 1339 (w), 1246 (m), 1209 (m), 1181 (m), 1044 (s), 885 (w), 838 (s), 752 (m). **HRMS** (ESI/QTOF) *m/z*: $[M+Na]^+$ calcd for $C_{18}H_{25}NNaO_4Si^+$ 370.1445, found 370.1432.

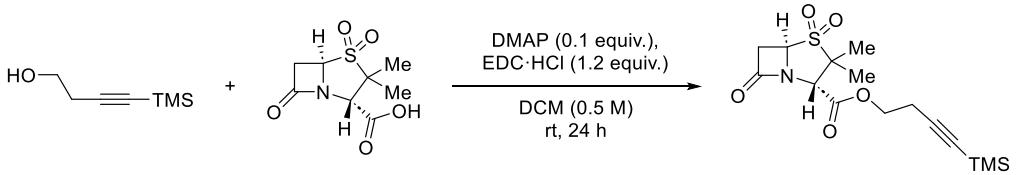
(8R,9S,13S,14S,17S)-3-Methoxy-13-methyl-17-((trimethylsilyl)ethynyl)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[a]phenanthren-17-ol (S9)



Following a reported procedure[12]: In a round bottom flask, to solution of trimethylsilylacetylene (1.10 mL, 737 mg, 7.50 mmol, 3.0 equiv.) in dry THF (3.5 mL) was added *n*-BuLi (2.5 M in *n*-hexane, 3.00 mL, 7.50 mmol, 3.0 equiv.) at -40 °C under N_2 atmosphere. After the addition, the reaction mixture was allowed to reach – 20 °C and stirred for another 2 h. Then, a solution of estone (816 mg, 2.50 mmol, 1.0 equiv.) in dry THF (3.5 mL) was added dropwise at -40 °C and the reaction mixture was allowed to reach room temperature and stirred for 3 h. The mixture was quenched by adding HCl (3 M, until neutralization) and H_2O (15 mL) and then, extracted with DCM (3 x 50 mL). Organics were recombined, washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced presure, yielding compound **S9** as a white solid (500 mg, 1.31 mmol, 52% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, *J* = 7.6 Hz, 1 H, Ar*H*), 6.72 (dd, *J* = 8.6, 2.9 Hz, 1 H, Ar*H*), 6.63 (d, *J* = 2.9 Hz, 1 H, Ar*H*), 3.78 (s, 3 H, OCH_3), 2.86 (bs, 1 H, O*H*), 2.40–1.63 (m, 11 H, aliphatic), 1.35–1.21 (m, 4 H, aliphatic), 0.87 (s, 3 H, CH_3), 0.18 (s, 9 H, TMS). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 157.6, 138.1, 132.7, 126.5, 114.0, 111.7, 109.7, 90.2, 80.3, 55.3, 49.8, 47.4, 43.4, 39.6, 39.1, 34.3, 33.0, 30.0, 27.5, 26.6, 23.0, 22.5, 14.2, 0.2. Analytical data were in agreement with the literature.[12]

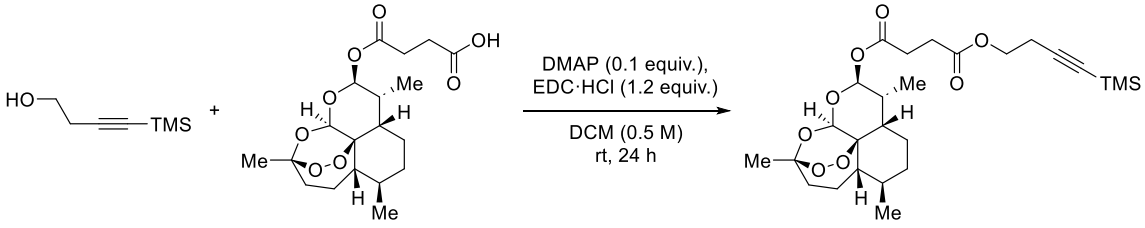
4-(Trimethylsilyl)but-3-yn-1-yl (2*S*,5*R*)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate 4,4-dioxide (S10)



DMAP (105 mg, 0.858 mmol, 0.1 equiv.) and EDC·HCl (1.97 g, 10.3 mmol, 1.2 equiv.) was added to a solution of sulbactam (2.00 g, 8.58 mmol, 1.0 equiv.) and 4-trimethylsilylbut-3-yn-1-ol (1.71 mL, 1.46 g, 10.3 mmol, 1.2 equiv.) in dry DCM (43 mL, 0.2 M). The reaction mixture was stirred at room temperature for 24 h before being filtered through a silica plug. The filtrate was concentrated in vacuo and the obtained residue was purified by column chromatography (*n*-pentane/EtOAc = 6:1). The desired product **S10** (1.61 g, 4.52 mmol, 53%) was obtained as yellow oil.

TLC: R_f (*n*-pentane/EtOAc = 6:1) = 0.10 ($KMnO_4$ stain). **ORD**: $[\alpha]_D^{20}$ = +390.6 (c = 0.72, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 4.62 (dd, *J* = 4.1, 2.3 Hz, 1 H, C*H*SO_2), 4.42–4.34 (m, 2 H, OC*H*$_2$, NC*H*CO_2), 4.20 (dt, *J* = 10.6, 6.0 Hz, 1 H, OC*H*$_2$), 3.47 (dd, *J* = 6.6, 3.2 Hz, 2 H, NCOC*H*$_2$), 2.63 (t, *J* = 6.5 Hz, 2 H, C*H*$_2$C≡C), 1.66 (s, 3 H, C*H*$_3$), 1.46 (s, 3 H, C*H*$_3$), 0.14 (s, 9 H, TMS). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 170.9, 166.9, 102.0, 87.3, 64.4, 63.3, 62.9, 61.2, 38.4, 20.5, 20.3, 18.6, 0.1. **IR**: *v* 2964 (m), 2178 (m), 1804 (s), 1757 (s), 1458 (w), 1394 (m), 1332 (m), 1289 (m), 1271 (m), 1256 (m), 1220 (m), 1191 (s), 1162 (m), 1122 (s), 1086 (m), 1072 (m), 1027 (m), 1011 (m), 957 (m), 906 (m), 841 (s), 791 (w), 760 (m), 737 (w), 709 (m). **HRMS** (APCI/QTOF) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{24}NO_5SSi^+$ 358.1139, found 358.1132.

(3*R*,5*aS*,6*R*,8*aS*,9*R*,10*S*,12*R*,12*aR*)-3,6,9-Trimethyldecahydro-12*H*-3,12-epoxy[1,2]dioxepino[4,3-*i*]isochromen-10-yl (4-(trimethylsilyl)but-3-yn-1-yl) succinate (S11)



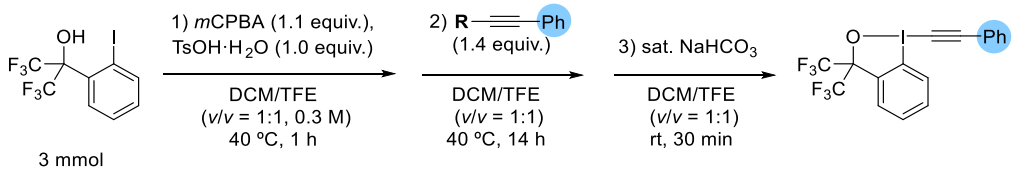
DMAP (63.6 mg, 0.520 mmol, 0.1 equiv.) and EDC·HCl (1.20 g, 6.24 mmol, 1.2 equiv.) was added to a solution of artesunate (2.00 g, 5.20 mmol, 1.0 equiv.) and 4-trimethylsilylbut-3-yn-1-ol (1.04 mL, 888 mg, 6.24 mmol, 1.2 equiv.) in dry DCM (25 mL, 0.2 M). The reaction mixture was stirred at room temperature for 24 h before being filtered through a silica plug. The filtrate was concentrated in vacuo and the obtained residue was purified by column chromatography (*n*-pentane/EtOAc = 6:1). The desired product **S11** (1.34 g, 2.64 mmol, 51%) was obtained as colorless oil.

TLC: R_f (*n*-pentane/EtOAc = 6:1) = 0.14 ($KMnO_4$ stain). **ORD**: $[\alpha]_D^{20}$ = +142.5 (c = 1.25, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 5.78 (d, *J* = 9.8 Hz, 1 H, OC*H*OCO), 5.42 (s, 1 H, OC*H*O), 4.17 (t, *J* = 7.1 Hz, 2 H, OC*H*$_2$), 3.47 (q, *J* = 7.0 Hz, 1 H, C*H*$_2$OCO), 2.77–2.58 (m, 4 H, C*H*$_2$OCO, C*H*$_2$), 2.55 (t, *J* = 7.2 Hz, 3 H, C*H*$_2$C≡C, C*H*), 2.36 (ddd, *J* = 14.6, 13.4, 4.0 Hz, 1 H, C*H*), 2.05–1.97 (m, 1 H, C*H*), 1.93–1.84 (m, 1 H, C*H*), 1.79–1.64 (m, 3 H, C*H*, C*H*$_2$), 1.61 (dt, *J* = 13.9, 4.5 Hz, 1 H, C*H*), 1.52–1.44 (m, 1 H, C*H*), 1.39–1.22 (m, 4 H, C*H*, C*H*$_3$), 1.06–0.97 (m, 1 H, C*H*$_2$), 0.95 (d, *J* = 5.9 Hz, 3 H, C*H*$_3$), 0.84 (d, *J* = 7.1 Hz, 3 H, C*H*$_3$), 0.14 (s, 9 H, TMS). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 171.9, 171.2, 104.6, 102.2, 92.3, 91.6, 86.7, 80.2, 62.6, 51.7, 45.4, 37.4, 36.3, 34.2, 31.9, 29.3, 28.9, 26.1, 24.7, 22.1, 20.4, 20.3, 12.2, 0.1. **IR**: *v* 2975 (s), 2179 (w), 1814 (w), 1746 (m), 1454 (m), 1407 (m), 1394 (m), 1328 (m), 1245 (m), 1228 (m), 1220 (m), 1162 (m), 1145 (m), 1101 (m), 1051 (s), 1026 (s), 931 (w), 891 (m), 849 (s), 766 (w), 737 (w). **HRMS** (APCI/QTOF) *m/z*: $[M+Na]^+$ calcd for $C_{26}H_{40}NaO_8Si^+$ 531.2385, found 531.2392.

2.3. Optimization

An oven-dried MW vial was charged with *para*-toluene sulfonic acid monohydrate (*p*TsOH·H_2O, 1.0 equiv.) and *meta*-chloroperoxy-benzoic acid (*m*CPBA, 1.1 equiv.). The flask was evacuated (0.5 mbar) and backfilled with nitrogen three times. The solvent mixture consisting of DCM and 2,2,2-trifluoroethanol (*v*/*v* = 1:1, [M]) was added, followed by 1,1,1,3,3,3-hexafluoro-2-(2-iodophenyl)propan-2-ol (1.11 g, 3.00 mmol, 1.0 equiv.). The reaction mixture was stirred for 1 h at 40 °C before being cooled down to the desired temperature. The corresponding TMS-protected alkyne (X equiv.) was added at the desired temperature and the reaction mixture was stirred for the indicated time at the desired temperature. After the desired time, the reaction mixture was treated with a sat. $NaHCO_3$ solution (same amount as organic solvent) and allowed to warm up to room temperature. After at least 30 min of vigorously stirring, the layers were separated and the aqueous layer was extracted with additional portions of dichloromethane (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The obtained residue was purified by column chromatography.

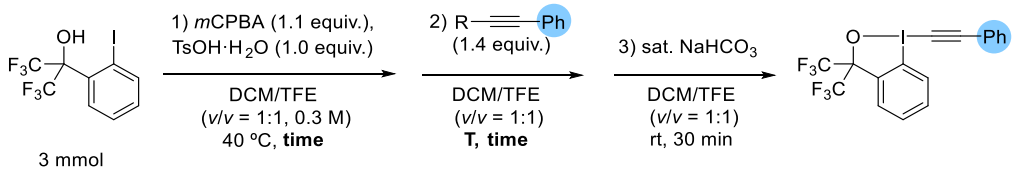
Table S1 Screening of the alkyne transfer reagent



Entry	R	^{19}F-NMR yield[a] [%]
1	**TMS**	**40**
2	B(O*i*Pr)$_3$	36
3	Bpin	36

a) ^{19}F-NMR yield determined by ^{19}F-NMR using $PhCF_3$ (1 equiv.) as internal standard.

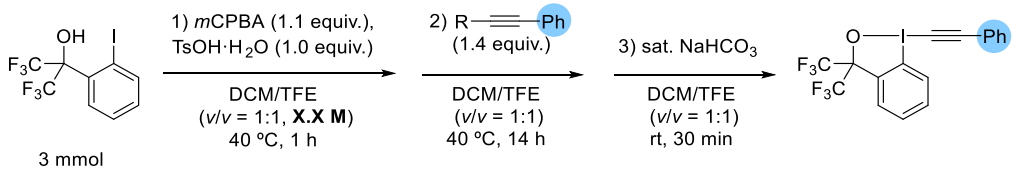
Table S2 Screening of the temperature and reaction time



Entry	Activation Time [h]	Temperature (T) [°C]	Time [h]	^{19}F-NMR yield[a] [%]
1	1	40	14	40
2[b]	1	rt	6	30
3	0.5	rt	14	34
4	1	0	6	82
5	**1**	**0**	**15**	**95**
6	0.5	0	6	75
7	0.5	0	4	60
8	0.5	-10	6	80

a) ^{19}F-NMR yield determined by ^{19}F-NMR using $PhCF_3$ (1 equiv.) as internal standard. b) Activation step was performed at room temperature (rt).

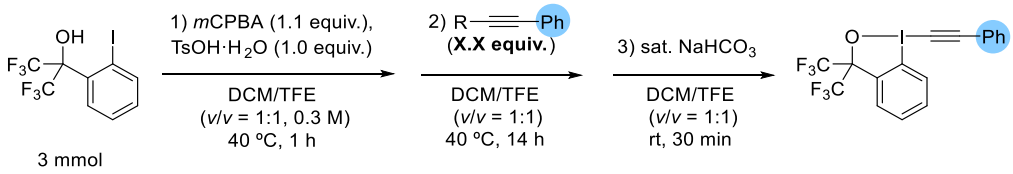
Table S3 Screening of the Concentration



Entry	Concentration [M]	^{19}F-NMR yield[a] [%]
1	**0.3**	**95**
2	0.5	70
3[b]	0.5	77
4[b]	0.05	77
5[c]	0.3	80
6[d]	0.3	80

a) ^{19}F-NMR yield determined by ^{19}FNMR using $PhCF_3$ (1 equiv.) as internal standard. b) Activation step was performed at room temperature (rt). c) Activation step time was 30 min and $B(OiPr)_3$ instead of TMS alkyne was used. d) Bpin instead of TMS alkyne was used.

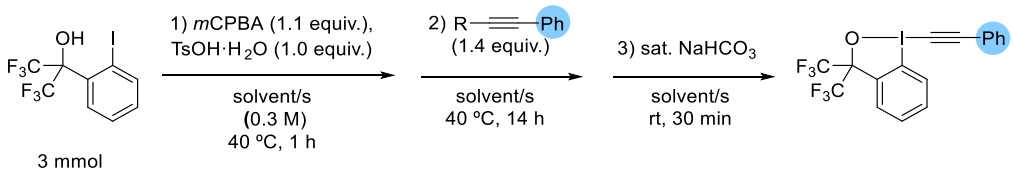
Table S4 Screening of the equivalents of TMS alkyne



Entry	Equivalents	^{19}F-NMR yield[a] [%]
1	**1.4**	**95**
2	1.1	75
3[b]	2.0	45
4	2.0	62

a) ^{19}F-NMR yield determined by ^{19}F-NMR using $PhCF_3$ (1 equiv.) as internal standard. b) Activation step was performed at room temperature (rt).

Table S5 Screening of Solvents

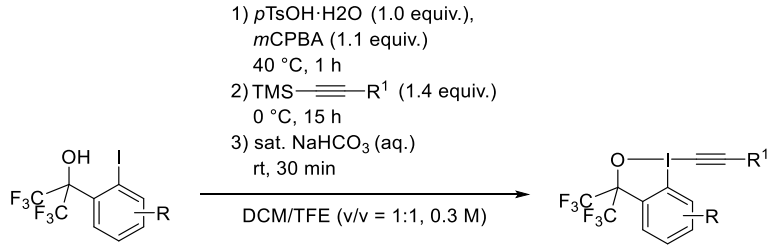


Entry	Solvent/s	^{19}F-NMR yield[a] [%]
1	**DCM/TFE (*v*/*v* = 1:1)**	**95**
2	DCM	11
3	MeCN/TFE (*v*/*v* = 1:1)	44
4	THF/TFE (*v*/*v* = 1:1)	47
5	PhMe/TFE (*v*/*v* = 1:1)	31
6	1,4-dioxane/TFE (*v*/*v* = 1:1)	35

a) ^{19}F-NMR yield determined by ^{19}F-NMR using $PhCF_3$ (1 equiv.) as internal standard.

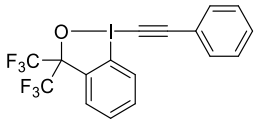
2.4. Scope

General Procedure for the Synthesis of Bis(trifluoromethylated) Ethynylbenziodoxoles (GP3)



A round bottom flask (25 or 50 mL) was charged with *para*-toluene sulfonic acid monohydrate (*p*TsOH·H_2O, 1.0 equiv.) and *meta*-chloroperoxy-benzoic acid (*m*CPBA, 77%, 1.1 equiv.). The flask was evacuated (0.5 mbar) and backfilled with nitrogen three times. The solvent mixture consisting of DCM and 2,2,2-trifluoroethanol (*v*/*v* = 1:1, 0.3 M) was added, followed by the corresponding 1,1,1,3,3,3-hexafluoro-2-(2-iodophenyl)propan-2-ol derivative (1.0 equiv.). The reaction mixture was stirred for 1 h at 40 °C before being cooled down using an ice bath. The corresponding TMS-protected alkyne (1.4 equiv.) was added at 0 °C and the reaction mixture was stirred for 15 h at 0 °C (large dewar bowl with crushed ice, covered with aluminum foil). After 15 h, the reaction mixture was treated with a sat. $NaHCO_3$ solution (same amount as organic solvent) and allowed to warm up to room temperature. After at least 30 min of vigorously stirring, the layers were separated and the aqueous layer was extracted with additional portions of dichloromethane (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The obtained residue was purified by recrystallization, column chromatography or washing with *n*-pentane.

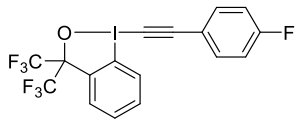
1-(Phenylethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (8a)



Following **GP3** on 8.00 mmol scale using 1,1,1,3,3,3-hexafluoro-2-(2-iodophenyl)propan-2-ol (**2a**, 2.96 g, 8.00 mmol, 1.0 equiv.) and trimethyl(2-phenylethynyl)silane (2.20 mL, 1.95 g, 11.2 mmol, 1.4 equiv.). 1-(Phenylethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo-[*d*][1,2]iodaoxole (3.20 g, 6.80 mmol, 85%) was obtained as white solid. Purification via column chromatography (10% EtOAc in *n*-pentane). The reaction was also upscaled to 32.0 mmol, allowing the formation of the product **8a** (11.9 g, 25.4 mmol) in 79% yield.

TLC: R_f (*n*-pentane/DCM = 2:1) = 0.18. **^{1}H-NMR** (400 MHz, $CDCl_3$): = 8.32–8.25 (m, 1 H, Ar*H*), 7.88–7.82 (m, 1 H, Ar*H*), 7.74–7.65 (m, 2 H, Ar*H*), 7.56 (dd, *J* = 8.1, 1.7 Hz, 2 H, Ar*H*), 7.46–7.36 (m, 3 H, Ar*H*). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 133.1, 132.8, 131.4, 130.3, 130.1, 130.1–130.0 (m), 128.8, 128.5, 123.7 (q, *J* = 290.3 Hz), 121.4, 111.6, 105.4, 82.5–81.1 (m), 54.5. **^{19}F-NMR** (376 MHz, $CDCl_3$): δ = -76.2. **HRMS** (ESI/QTOF) *m/z*: $[M+H]^+$ calcd for $C_{17}H_{10}F_6IO^+$ 470.9675, found 470.9683. Analytical data were in agreement with the literature.[13]

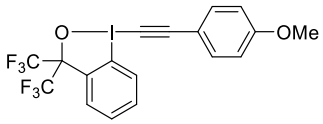
1-((4-Fluorophenyl)ethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (8b)



Following **GP3** on 3.00 mmol scale using 1,1,1,3,3,3-hexafluoro-2-(2-iodophenyl)propan-2-ol (**2a**, 1.11 g, 3.00 mmol, 1.0 equiv.) and 2-(4-fluorophenyl)ethynyl-trimethylsilane (910 µL, 860 mg, 4.20 mmol, 1.4 equiv.). 1-((4-Fluorophenyl)ethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (**8b**, 940 mg, 1.92 mmol, 64%) was obtained as white solid. Purification via column chromatography (*n*-pentane/EtOAc = 95:5).

MP: 135–140 °C (dec.). **TLC**: R_f (*n*-pentane/EtOAc = 97:3) = 0.30. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 8.28–8.24 (m, 1H, Ar*H*), 7.90–7.82 (m, 1H, Ar*H*), 7.75–7.66 (m, 2H, Ar*H*), 7.58–7.53 (m, 2H, Ar*H*), 7.13–7.07 (m, 2H, Ar*H*). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 163.7 (d, *J* = 252.5 Hz), 134.9 (d, *J* = 8.4 Hz), 133.1, 131.4, 130.1, 130.12–130.05 (m), 128.5, 123.7 (q, *J* = 291.1 Hz) 117.6 (d, *J* = 3.8 Hz), 116.3 (d, *J* = 22.5 Hz), 111.5, 104.2, 82.1–81.2 (p, *J* = 29.6 Hz), 54.6. **^{19}F-NMR** (376 MHz, $CDCl_3$): δ = -76.2 (s, ArC*F*$_3$), -107.2 – -107.2 (m, Ar*F*). **HRMS** (ESI/QTOF) m/z: $[M+Na]^+$ Calcd for $C_{17}H_8F_7INaO^+$ 510.9400, found 510.9410. Analytical data were in agreement with the literature.[13]

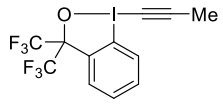
1-((4-Methoxyphenyl)ethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (8c)



Following **GP3** on 3.00 mmol scale using 1,1,1,3,3,3-hexafluoro-2-(2-iodophenyl)propan-2-ol (**2a**, 1.11 g, 3.00 mmol, 1.0 equiv.) and 2-(4-methoxyphenyl)ethynyl-trimethylsilane (900 µL, 860 mg, 4.20 mmol, 1.4 equiv.). 1-((4-Methoxyphenyl)ethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (**8c**, 920 mg, 1.84 mmol, 61%) was obtained as white solid. Purification via column chromatography (*n*-pentane/EtOAc = 95:5).

MP: 114–117 °C (dec.). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 8.31–8.22 (m, 1 H, Ar*H*), 7.88–7.80 (m, 1 H, Ar*H*), 7.72–7.62 (m, 2 H, Ar*H*), 7.50 (d, *J* = 8.9 Hz, 2 H, Ar*H*), 6.91 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 3.85 (s, 3 H, OC*H*$_3$). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 161.2, 134.5, 133.0, 131.3, 130.2, 130.1–129.9 (m), 128.4, 123.8 (q, *J* = 290.4 Hz), 114.4, 113.3, 111.7, 106.0, 82.8–80.4 (m), 55.6, 52.8. **^{19}F-NMR** (376 MHz, $CDCl_3$): δ = -76.2. **HRMS** (ESI/QTOF) *m/z*: $[M+H]^+$ calcd for $C_{18}H_{12}F_6IO_2^+$ 500.9781, found 500.9793. Analytical data were in agreement with the literature.[13]

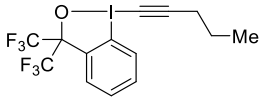
1-(Prop-1-yn-1-yl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ³-benzo[*d*][1,2]iodaoxole (8d)



Following **GP3** on 8.00 mmol scale using 1,1,1,3,3,3-hexafluoro-2-(2-iodophenyl)propan-2-ol (**2a**, 2.96 g, 8.00 mmol, 1.0 equiv.) and trimethyl(prop-1-ynyl)silane (1.66 mL, 1.26 g, 11.2 mmol, 1.4 equiv.). 1-(Prop-1-yn-1-yl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ³-benzo[*d*][1,2]iodaoxole (**8d**, 2.31 g, 5.65 mmol, 71%) was obtained as a white amorphous solid. Purification via column chromatography (*n*-pentane/EtOAc = 95:5).

MP: 165–168 °C (dec.). **TLC**: R_f (*n*-pentane/EtOAc = 97:3) = 0.25. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 8.25–8.20 (m, 1 H, Ar*H*), 7.86–7.80 (m, 1 H, Ar*H*), 7.71–7.65 (m, 2 H, Ar*H*), 2.19 (s, 3 H, CH_3). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 132.9, 131.2, 130.2, 129.9 (p, *J* = 2.7 Hz), 128.4, 123.8 (q, *J* = 290.4 Hz), 111.0, 103.3, 82.0–81.3 (m), 43.1, 5.5. **^{19}F-NMR** (376 MHz, $CDCl_3$): δ = -76.2. **HRMS** (Sicrit Plasma/LTQ) *m/z*: $[M+H]^+$ calcd for $C_{12}H_8F_6IO^+$ 408.9519, found 408.9520 . Analytical data were in agreement with the literature.[13]

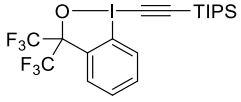
1-(Pent-1-yn-1-yl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ³-benzo[*d*][1,2]iodaoxole (8e)



Following **GP3** on 8.00 mmol scale using 1,1,1,3,3,3-hexafluoro-2-(2-iodophenyl)propan-2-ol (**2a**, 2.96 g, 8.00 mmol, 1.0 equiv.) and trimethyl(pent-1-ynyl)silane (2.05 mL, 1.57 g, 11.2 mmol, 1.4 equiv.). (Pent-1-yn-1-yl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ³-benzo[*d*][1,2]iodaoxole (**8e**, 3.12 g, 7.15 mmol, 89%) was obtained as white solid. Purification via washing with *n*-pentane (2x 10 mL).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.26–8.20 (m, 1 H, Ar*H*), 7.86–7.79 (m, 1 H, Ar*H*), 7.71–7.64 (m, 2 H, Ar*H*), 2.50 (t, *J* = 7.0 Hz, 2 H, C≡CCH_2), 1.65 (h, *J* = 7.2 Hz, 2 H, C≡CCH_2CH_2), 1.06 (t, *J* = 7.4 Hz, 3 H, C≡C$CH_2CH_2CH_3$). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 132.9, 131.2, 130.2, 129.9 (p, *J* = 2.7 Hz), 128.3, 123.8 (q, *J* = 290.6 Hz), 111.0, 107.9, 81.7 (p, *J* = 29.6 Hz), 43.6, 22.4, 22.1, 13.7. **^{19}F-NMR** (376 MHz, $CDCl_3$): δ = -76.2. **HRMS** (Sicrit Plasma/LTQ) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{12}F_6IO^+$ 436.9832, found 436.9832. Analytical data were in agreement with the literature.[14]

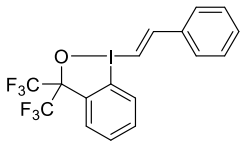
((3,3-Bis(trifluoromethyl)-1λ³-benzo[d][1,2]iodaoxol-1(3H)-yl)ethynyl)triisopropylsilane (8f)



Following **GP3** on 4.00 mmol scale using 1,1,1,3,3,3-hexafluoro-2-(2-iodophenyl)propan-2-ol (**2a**, 1.48 g, 4.00 mmol, 1.0 equiv.) and trimethyl-[2-tri(propan-2-yl)silylethynyl]silane (1.43 g, 5.60 mmol, 1.4 equiv.). (Pent-1-yn-1-yl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ³-benzo-[*d*][1,2]iodaoxole (**8f**, 1.61 g, 2.92 mmol, 73%) was obtained as white amorphous solid. Purification via column chromatography (*n*-pentane/EtOAc = 97:3).

MP: 125–130 °C (dec.). **TLC**: R_f (*n*-pentane/EtOAc = 97:3) = 0.23. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 8.36 (dd, *J* = 8.0, 1.5 Hz, 1 H, Ar*H*), 7.84 (d, *J* = 7.5 Hz, 1 H, Ar*H*), 7.72–7.64 (m, 2 H, Ar*H*), 1.15–1.14 (m, 21 H, TIPS).**^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 132.9, 131.3, 130.13, 130.13–130.10 (m), 128.3, 123.8 (q, *J* = 292.7 Hz), 112.3, 111.0, 81.6 (p, *J* = 29.3 Hz), 69.9, 18.7, 11.1.**^{19}F-NMR** (376 MHz, $CDCl_3$): δ = -76.2. **HRMS** (ESI/QTOF) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{26}F_6IOSi^+$ 551.0696, found 551.0701. Analytical data were in agreement with the literature.[15]

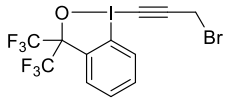
(*E*)-1-Styryl-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (8g)



Following **GP3** on 8.00 mmol scale using 1,1,1,3,3,3-hexafluoro-2-(2-iodophenyl)propan-2-ol (**2a**, 2.96 g, 8.00 mmol, 1.0 equiv.) and (*E*)-2-phenylethenylboronic acid (1.66 g, 11.2 mmol, 1.4 equiv.). (*E*)-1-Styryl-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (**8g**, 3.36 g, 7.13 mmol, 89%) was obtained as white solid (96% purity). Purification via column chromatography (*n*-pentane/EtOAc = 3:1).

TLC: R_f (*n*-pentane/EtOAc = 1:1) = 0.51. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.99–7.91 (m, 1 H, Ar*H*), 7.70–7.64 (m, 2 H, Ar*H,* C*H*=CHPh), 7.62–7.55 (m, 4 H, Ar*H*), 7.54–7.49 (m, 3 H, Ar*H*), 7.31 (d, *J* = 11.0 Hz, 1 H*,* CH=C*H*Ph). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 152.2, 135.5, 132.2, 131.1, 130.8, 130.63, 130.60, 129.3, 127.48, 127.46, 124.2 (q, *J* = 291.4 Hz), 111.2, 104.6, 81.4 (p, *J* = 29.1 Hz). **^{19}F-NMR** (376 MHz, $CDCl_3$): δ = -76.1. **HRMS** (Sicrit Plasma/LTQ) *m/z*: $[M+H]^+$ calcd for $C_{17}H_{12}F_6IO^+$ 472.9832, found 472.9822. Analytical data were in agreement with the literature.[3]

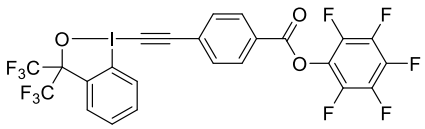
1-(3-Bromoprop-1-yn-1-yl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (8h)



Following **GP3** on 4.00 mmol scale using 1,1,1,3,3,3-hexafluoro-2-(2-iodophenyl)propan-2-ol (**2a**, 1.48 g, 4.00 mmol, 1.0 equiv.) and 3-bromoprop-1-ynyl(trimethyl)silane (915 µL, 1.07 g, 5.60 mmol, 1.4 equiv.). 1-(3-Bromoprop-1-yn-1-yl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]ioda-oxole (**8h**, 858 mg, 1.76 mmol, 44%) was obtained as a white solid. Purification via MPLC (t_R = 16.3–18.6 min, gradient: 5–95% in 28 min).

MP: 143–145 °C (dec.). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 8.24–8.13 (m, 1 H, Ar*H*), 7.87–7.79 (m, 1 H, Ar*H*), 7.74–7.67 (m, 2 H, Ar*H*), 4.13 (s, 2H, C≡C*C*H_2Br). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 133.3, 131.5, 130.1 (p, *J* = 2.5 Hz), 130.0, 128.5, 123.6 (q, *J* = 290.3 Hz), 111.2, 99.7, 81.8 (p, *J* = 29.9 Hz), 53.3, 13.8. **^{19}F-NMR** (376 MHz, $CDCl_3$): δ = -76.2. **IR**: *v* 3668 (m), 2986 (s), 2896 (s), 1723 (w), 1415 (m), 1375 (m), 1307 (w), 1256 (s), 1227 (m), 1173 (m), 1155 (m), 1075 (s), 1053 (s), 1008 (m), 950 (m), 880 (w), 849 (w), 769 (w), 727 (w). **HRMS** (APPI/LTQ) *m/z*: $[M+H]^+$ calcd for $C_{12}H_7BrF_6IO^+$ 486.8624, found 486.8641.

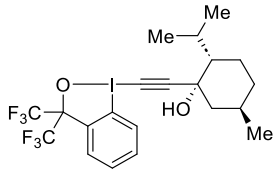
Perfluorophenyl 4-((3,3-bis(trifluoromethyl)-1λ³-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)benzoate (8i)



Following **GP3** on 4.00 mmol scale using 1,1,1,3,3,3-hexafluoro-2-(2-iodophenyl)propan-2-ol (**2a**, 1.48 g, 4.00 mmol, 1.0 equiv.) and perfluorophenyl 4-((trimethylsilyl)ethynyl)benzoate (2.15 g, 5.60 mmol, 1.4 equiv.). The reaction was performed at room temperature for 4 h instead of 0 °C. Perfluorophenyl 4-((3,3-bis(trifluoromethyl)-1λ³-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethyn-yl)benzoate (**8i**, 1.28 g, 1.88 mmol, 47%) was obtained as a white solid. Purification via column chromatography (*n*-pentane/EtOAc = 50:1 to 5:1).

MP: 181–184 °C. **^{1}H-NMR** (500 MHz, $CDCl_3$): δ = 8.28–8.25 (m, 1 H, Ar*H*), 8.23 (d, *J* = 8.4 Hz, 2 H, Ar*H*), 7.88 (d, *J* = 7.8 Hz, 1 H, Ar*H*), 7.76–7.73 (m, 2 H, Ar*H*), 7.71 (d, *J* = 8.4 Hz, 2 H, Ar*H*). **^{13}C-NMR** (126 MHz, $CDCl_3$): δ = 161.9, 141.5 (dm, *J* = 239.6 Hz), 138.1 (dm, *J* = 253.5 Hz), 138.1 (dm, *J* = 253.5 Hz), 133.3, 133.0, 131.6, 131.0, 130.2, 130.1, 128.5, 127.92, 127.86, 125.4–125.0 (m), 123.6 (q, *J* = 288.5 Hz), 111.4, 103.3, 82.4–81.4 (m), 60.1. **^{19}F-NMR** (376 MHz, $CDCl_3$): δ = -76.1, -152.4 (d, *J* = 16.8 Hz), -157.3 (t, *J* = 21.6 Hz), -161.8 – -162.1 (m). **IR**: *v* 2978 (w), 2931 (m), 2902 (w), 1401 (m), 1241 (m), 1071 (w). **HRMS** (ESI/LTQ) *m/z*: $[M+H]^+$ calcd for $C_{24}H_9F_{11}IO_3^+$ 680.9415, found 680.9393.

(1*S*,2*S*,5*R*)-1-((3,3-Bis(trifluoromethyl)-1λ³-benzo[*d*][1,2]iodaoxol-1(3H)-yl)ethynyl)-2-isopropyl-5-methylcyclohexan-1-ol (8j)

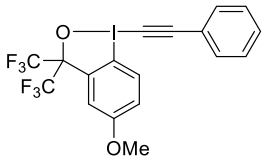


Following **GP3** on 4.00 mmol scale using 1,1,1,3,3,3-hexafluoro-2-(2-iodophenyl)propan-2-ol (**2a**, 1.48 g, 4.00 mmol, 1.0 equiv.) and (1*S*,2*S*,5*R*)-2-isopropyl-5-methyl-1-((trimethylsilyl)ethynyl)cyclohexan-1-ol (**S2**, 1.41 g, 5.60 mmol, 1.4 equiv.). The desired product **8j** (1.23 g, 2.24 mmol, 56%) was obtained as white solid. Purification via MPLC (t_R = 23.1–26.1 min, gradient: 5–95% in 28 min).

MP: 118–120 °C (dec.). **ORD**: $[\alpha]_D^{20}$ = -2.5 (c = 1.33, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 8.20 (dd, *J* = 7.7, 1.7 Hz, 1 H, Ar*H*), 7.86–7.79 (m, 1 H, Ar*H*), 7.73–7.64 (m, 2 H, Ar*H*), 2.41 (pd, *J* = 7.0, 1.8 Hz, 1 H, C*H*), 2.05 (dt, *J* = 13.6, 3.2 Hz, 1 H, CH_2), 1.85–1.71 (m, 3 H, C*H*, CH_2), 1.63–1.36 (m, 4 H, C*H*, CH_2), 1.03 (d, *J* = 7.0 Hz, 3 H, CH_3), 0.99 (d, *J* = 6.5 Hz, 3 H, CH_3), 0.92 (d, *J* = 6.4 Hz, 3 H, CH_3). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 133.0, 131.3, 130.1, 130.1–130.0 (m), 128.3, 123.7 (q, *J* = 290.6 Hz), 111.2, 111.1, 81.7 (p, *J* = 29.4 Hz), 73.5, 50.7, 50.1, 48.3, 34.7, 29.1, 27.4, 24.0, 22.0, 20.5, 18.8. **^{19}F-NMR** (376 MHz, $CDCl_3$): δ = -76.2. **IR**: *v* 3335 (m), 2945 (m), 2872 (w), 2145 (w), 1639 (w), 1443 (w), 1379 (w), 1296 (m), 1260 (m), 1224 (m), 1187 (s), 1159

(m), 1087 (w), 1051 (m),1019 (m), 965 (m), 952 (s), 885 (w), 846 (w), 755 (m), 730 (s). **HRMS** (Sicrit Plasma/LTQ) *m/z*: $[M+H]^+$ calcd for $C_{21}H_{24}F_6IO_2^+$ 549.0720, found 549.0713.

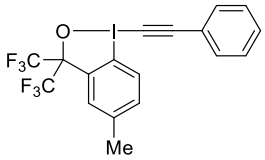
5-Methoxy-(1-phenylethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ³-benzo[*d*][1,2]iodaoxole (8k)



Following **GP3** on 4.00 mmol scale using 1,1,1,3,3,3-hexafluoro-2-(2-iodo-5-methoxyphenyl)propan-2-ol (**2b**, 1.60 g, 4.00 mmol, 1.0 equiv.) and trimethyl(2-phenylethynyl)silane (1.20 mL, 976 mg, 5.60 mmol, 1.4 equiv.). 5-Methoxy-(1-phenylethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ³-benzo-[*d*][1,2]iodaoxole (**8k**, 1.51 g, 3.02 mmol, 75%) was obtained as a white solid. Purification via recrystallization in EtOH (4.0 mL).

MP: 135–139 °C (dec.). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 9.1 Hz, 1 H, Ar*H*), 7.55 (dd, *J* = 8.0, 1.7 Hz, 2 H, Ar*H*), 7.46–7.37 (m, 3 H, Ar*H*), 7.37–7.33 (m, 1 H, Ar*H*), 7.21 (dd, *J* = 9.1, 2.8 Hz, 1 H, Ar*H*), 3.90 (s, 3 H, ArOC*H*$_3$). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 162.6, 132.7, 131.6, 130.2, 129.0, 128.8, 123.7 (q, *J* = 291.2 Hz), 121.5, 119.1, 115.9–115.6 (m), 105.0, 99.7, 81.5 (p, *J* = 29.4 Hz), 56.2, 54.3. **^{19}F-NMR** (376 MHz, $CDCl_3$): δ = -76.1. **IR**: *v* 3358 (m), 2989 (m), 2903 (m), 1660 (w), 1453 (w), 1407 (m), 1276 (w), 1076 (s), 1026 (m), 878 (m). **HRMS** (Sicrit Plasma/LTQ) *m/z*: $[M+H]^+$ calcd for $C_{18}H_{12}F_6IO_2^+$ 500.9781, found 500.9780.

5-Methyl-(1-phenylethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ³-benzo[*d*][1,2]iodaoxole (8l)

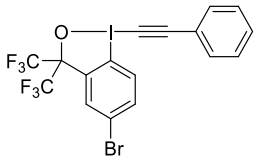


Following **GP3** on 4.00 mmol scale using 1,1,1,3,3,3-hexafluoro-2-(2-iodo-5-methylphenyl)propan-2-ol (**2c**, 1.54 g, 4.00 mmol, 1.0 equiv.) and trimethyl(2-phenylethynyl)silane (1.20 mL, 976 mg, 5.60 mmol, 1.4 equiv.). 5-Methyl-(1-phenylethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ³-benzo-[*d*][1,2]iodaoxole (**8l**, 1.44 g, 2.96 mmol, 74%) was obtained as white solid in 96% purity. Purification via MPLC (t_R = 18.0–19.9 min, gradient: 5–95% in 28 min).

MP: 183–185 °C (dec.). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 8.5 Hz, 1 H, Ar*H*), 7.63 (s, 1 H, Ar*H*), 7.55 (dd, *J* = 8.0, 1.7 Hz, 2 H, Ar*H*), 7.49 (ddd, *J* = 8.5, 2.0, 0.8 Hz, 1 H, Ar*H*), 7.45–7.36 (m, 3 H, Ar*H*), 2.50 (s, 3 H, ArC*H*$_3$). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 142.2, 134.1, 132.7, 130.9 –130.5 (m), 130.2, 130.1, 128.8, 128.1, 123.7 (d, *J* = 290.4 Hz), 121.5, 107.9, 105.0, 82.5–80.8 (m), 54.5, 21.2. **^{19}F-NMR** (376 MHz, $CDCl_3$): δ = -76.1. **IR**: *v* 3667 (m), 2996 (s), 2910 (s),

1663 (w), 1455 (w), 1407 (m), 1382 (m), 1249 (m), 1242 (m), 1066 (s), 1044 (s), 1033 (m), 892 (w), 870 (w). **HRMS** (APPI/LTQ) *m/z*: $[M+H]^+$ calcd for $C_{18}H_{12}F_6IO^+$ 484.9832, found 484.9831.

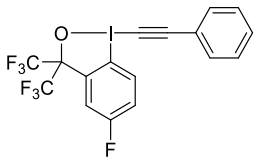
5-Bromo-(1-phenylethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ³-benzo[*d*][1,2]ioda-oxole (8m)



Following **GP3** on 4.00 mmol scale using 1,1,1,3,3,3-hexafluoro-2-(5-bromo-2-iodophenyl)propan-2-ol (**2d**, 1.80 g, 4.00 mmol, 1.0 equiv.) and trimethyl(2-phenylethynyl)silane (1.20 mL, 976 mg, 5.60 mmol, 1.4 equiv.). 5-Bromo-(1-phenylethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ³-benzo[*d*][1,2]ioda-oxole (**8m**, 1.18 g, 2.15 mmol, 54%) was obtained as colorless needles. Purification via recrystallization in MeCN (5.0 mL).

MP: 184–186 °C (dec.). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 8.8 Hz, 1 H, Ar*H*), 7.94 (bs, *J* = 1.4 Hz, 1 H, Ar*H*), 7.79 (dd, *J* = 8.8, 2.1 Hz, 1 H, Ar*H*), 7.55 (dd, *J* = 8.2, 1.6 Hz, 2 H, Ar*H*), 7.48–7.38 (m, 3 H, Ar*H*). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 136.2, 133.0 (p, *J* = 2.8 Hz), 132.8, 132.3, 130.5, 129.8, 128.8, 126.5, 123.5 (q, *J* = 290.7 Hz), 121.1, 110.2, 106.1, 81.4 (p, *J* = 29.9 Hz), 54.0. **^{19}F-NMR** (376 MHz, $CDCl_3$): δ = -76.1. **IR**: *v* 2942 (w), 2149 (w), 1713 (w), 1648 (w), 1569 (w), 1488 (w), 1447 (w), 1386 (w), 1292 (s), 1263 (s), 1213 (m), 1193 (s), 1184 (s), 1162 (m), 1119 (m), 1068 (m), 1014 (w), 968 (s), 888 (w), 820 (w), 769 (w), 730 (m). **HRMS** (APPI/LTQ) *m/z*: $[M+H]^+$ calcd for $C_{17}H_9BrF_6IO^+$ 548.8780, found 548.8777.

5-Fluoro-(1-phenylethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ³-benzo[*d*][1,2]ioda-oxole (8n)

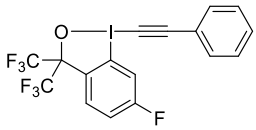


Following **GP3** on 4.00 mmol scale using 1,1,1,3,3,3-hexafluoro-2-(5-fluoro-2-iodophenyl)propan-2-ol (**2e**, 1.80 g, 4.00 mmol, 1.0 equiv.) and trimethyl(2-phenylethynyl)silane (1.20 mL, 976 mg, 5.60 mmol, 1.4 equiv.). 5-Fluoro-(1-phenylethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ³-benzo[*d*][1,2]ioda-oxole (**8n**, 1.36 g, 2.79 mmol, 70%) was obtained as white solid. Purification via recrystallization in MeOH (3.0 mL).

MP: 152–155 °C (dec.). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 8.22 (dd, *J* = 9.1, 4.7 Hz, 1 H, Ar*H*), 7.59–7.51 (m, 3 H, Ar*H*), 7.48–7.33 (m, 4 H, Ar*H*). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 165.0 (d, *J* = 253.1 Hz), 132.8, 132.7 (d, *J* = 7.8 Hz), 130.5, 129.9 (d, *J* = 8.8 Hz), 128.8, 123.5 (q, *J* = 290.4 Hz), 121.2, 120.6 (d, *J* = 23.6 Hz), 118.1–117.4 (m), 105.9, 104.5, 81.8–80.9 (m), 54.0. **^{19}F-NMR** (376 MHz, $CDCl_3$): δ = -76.2 (C*F*$_3$), -109.7 (Ar*F*). **IR**: *v* 3366 (m), 2982 (m), 2902 (m), 1645 (w), 1465 (w), 1409 (w), 1386 (m), 1270 (w), 1241 (w), 1198 (w), 1180 (w), 1155 (w), 1088 (m), 1047 (s), 987

(w), 962 (w), 885 (m), 755 (w), 727 (w). **HRMS** (Sicrit plasma/LTQ) *m/z*: $[M+H]^+$ calcd for $C_{17}H_9F_7IO^+$ 488.9581, found 488.9581.

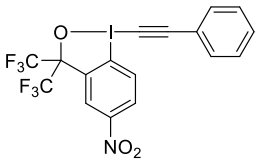
6-Fluoro-(1-phenylethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ³-benzo[*d*][1,2]ioda-oxole (8o)



Following **GP3** on 4.00 mmol scale using 1,1,1,3,3,3-hexafluoro-2-(4-fluoro-2-iodophenyl)propan-2-ol (**2f**, 1.55 g, 4.00 mmol, 1.0 equiv.) and trimethyl(2-phenylethynyl)silane (1.20 mL, 976 mg, 5.60 mmol, 1.4 equiv.). 6-Fluoro-(1-phenylethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ³-benzo[*d*][1,2]ioda-oxole (**8o**, 1.38 g, 2.83 mmol, 71%) was obtained as colorless needles. Purification via recrystallization in EtOH (2.0 mL).

MP: 138–141 °C. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 8.02 (dd, *J* = 7.8, 2.4 Hz, 1 H, Ar*H*), 7.78 (ddq, *J* = 6.2, 3.7, 1.2 Hz, 1 H, Ar*H*), 7.58–7.53 (m, 2 H, Ar*H*), 7.49–7.36 (m, 4 H, Ar*H*). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 165.5 (d, *J* = 256.9 Hz), 132.8, 130.6 (dq, *J* = 8.5, 3.1 Hz), 130.5, 128.9, 125.8 (d, *J* = 3.1 Hz), 123.6 (q, *J* = 290.3 Hz), 121.1, 118.9 (d, *J* = 22.3 Hz), 116.3 (d, *J* = 28.0 Hz), 113.3 (d, *J* = 8.7 Hz), 106.1, 81.5 (p, *J* = 29.8 Hz), 54.6. **^{19}F-NMR** (376 MHz, $CDCl_3$): δ = -76.1 (C*F*$_3$), -106.4 (Ar*F*). **IR**: *v* 3069 (w), 2975 (w), 2147 (m), 1724 (w), 1602 (m), 1580 (m), 1485 (s), 1443 (m), 1393 (w), 1301 (m), 1278 (s), 1263 (s), 1211 (s), 1184 (s), 1149 (s), 1128 (s), 1068 (m), 1026 (m), 961 (s), 945 (s), 863 (m), 850 (m), 822 (m), 805 (m), 791 (w), 766 (w), 751 (s), 729 (m). **HRMS** (ESI/QTOF) *m/z*: $[M+Na]^+$ calcd for $C_{17}H_8F_7INaO^+$ 510.9400, found 510.9401.

5-Nitro-(1-phenylethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ³-benzo[*d*][1,2]ioda-oxole (8p)

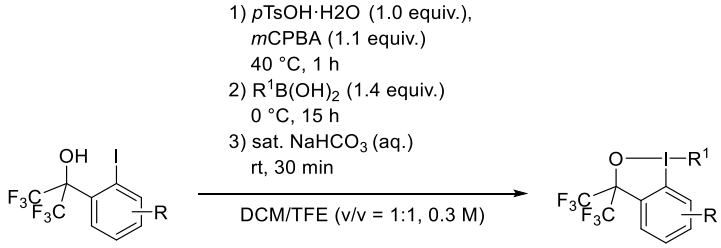


Following **GP3** on 3.00 mmol scale using 1,1,1,3,3,3-hexafluoro-2-(2-iodo-5-nitrophenyl)propan-2-ol (**2g**, 1.25 g, 3.00 mmol, 1.0 equiv.) and trimethyl(2-phenylethynyl)silane (826 µL, 732 mg, 4.20 mmol, 1.4 equiv.). 5-Nitro-(1-phenylethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ³-benzo[*d*][1,2]ioda-oxole (**8p**, 776 mg, 1.51 mmol, 50%) was obtained as white solid. Purification via recrystallization in MeOH (8.0 mL).

MP: 178–181 °C. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 8.63 (s, 1 H, Ar*H*), 8.52 (d, *J* = 1.3 Hz, 2 H, Ar*H*), 7.60–7.52 (m, 2 H, Ar*H*), 7.51–7.37 (m, 3 H, Ar*H*). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 150.9, 132.9, 132.6, 130.8, 129.8, 128.9, 127.7, 124.7–124.5 (m), 123.3 (q, *J* = 290.5 Hz), 120.8, 118.3, 107.1, 81.6 (p, *J* = 30.1 Hz), 54.1. **^{19}F-NMR** (376 MHz, $CDCl_3$): δ = -76.0. **IR**: *v* 3384 (m), 2992 (m), 2910 (m), 2149 (w), 1613 (w), 1580 (w), 1544 (m), 1490 (w), 1454 (m), 1352 (m), 1292 (m), 1260 (s), 1220 (m), 1184 (s), 1152 (s), 1090 (m), 1047 (s), 1014 (m), 978 (m), 964 (s), 907 (m), 881 (w),

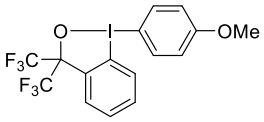
863 (m), 759 (m), 741 (w), 727 (s)**. HRMS** (ESI/QTOF) *m/z*: $[M+H]^+$ calcd for $C_{17}H_9F_6INO_3^+$ 515.9526, found 515.9531.

General Procedure for the Synthesis of Bis(trifluoromethylated) Arylbenziodoxoles (GP4)



A microwave vial (10 mL) was charged with *para*-toluene sulfonic acid monohydrate (*p*TsOH·H_2O, 1.0 equiv.) and *meta*-chloroperoxy-benzoic acid (*m*CPBA, 1.1 equiv.). The flask was evacuated (0.5 mbar) and backfilled with nitrogen three times. The solvent mixture consisting of DCM and 2,2,2-trifluoroethanol (*v*/*v* = 1:1, 0.3 M) was added, followed by the 1,1,1,3,3,3-hexafluoro-2-(2-iodophenyl)propan-2-ol (370 mg, 1.00 mmol, 1.0 equiv.). The reaction mixture was stirred for 1 h at 40 °C before being cooled down using an ice bath. The corresponding aryl boronic acid (1.4 equiv.) was added at 0 °C and the reaction mixture was stirred for 15 h at 0 °C (dewar bowl with crushed ice, covered with aluminum foil). After 15 h, the reaction mixture was treated with sat. $NaHCO_3$ solution (same amount as organic solvent) and allowed to warm up to room temperature. After at least 30 min of vigorously stirring, the layers were separated and the aqueous layer was extracted with additional portions of dichloromethane (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The obtained residue was purified by column chromatography.

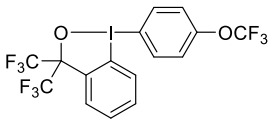
1-(4-Methoxyphenyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (9a)



Following **GP4** on 1.00 mmol scale using 1,1,1,3,3,3-hexafluoro-2-(2-iodophenyl)propan-2-ol (**2a**, 370 mg, 1.00 mmol, 1.0 equiv.) and (4-methoxyphenyl)boronic acid (213 mg, 1.40 mmol, 1.0 equiv.). 1-(4-Methoxyphenyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (**9a**, 370 mg, 0.780 mmol, 78%) was obtained as white solid. Purification via column chromatography (*n*-pentane/EtOAc = 50:1 to 4:1).

MP: 190–200 °C (dec.). **TLC**: R_f (*n*-pentane/EtOAc = 80:20) = 0.20. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 7.7 Hz, 1 H, Ar*H*), 7.77 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 7.57–7.52 (m, 1 H, Ar*H*), 7.35 (ddd, *J* = 8.6, 7.2, 1.5 Hz, 1 H, Ar*H*), 7.00 (d, *J* = 8.9 Hz, 2 H, Ar*H*), 6.81 (d, *J* = 9.4 Hz, 1 H, Ar*H*). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 162.6, 138.8, 132.1, 131.2, 130.5–130.4 (m), 130.35, 127.5, 124.3 (q, *J* = 291.6 Hz), 117.2, 112.0, 108.3, 81.8–81.2 (m), 55.7. **^{19}F-NMR** (376 MHz, $CDCl_3$): δ = -76.1. **HRMS** (APPI/LTQ-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{16}H_{12}F_6IO_2^+$ 476.9781, found 476.9783. Analytical data were in agreement with the literature.[16]

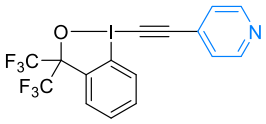
1-(4-(Trifluoromethoxy)phenyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (9b)



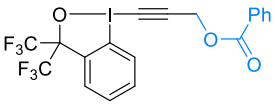
Following **GP4** on 1.00 mmol scale using 1,1,1,3,3,3-hexafluoro-2-(2-iodophenyl)propan-2-ol (**2a**, 370 mg, 1.00 mmol, 1.0 equiv.) and 4-(trifluoromethoxy)phenyl]boronic acid (288 mg, 1.40 mmol, 1.0 equiv.). 1-(4-(Trifluoromethoxy)phenyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (**9b**, 476 mg, 0.900 mmol, 90%) was obtained as pale-yellow solid. Purification via column chromatography (*n*-pentane/EtOAc = 50:1 to 4:1).

MP: 185–195 °C (dec.). **TLC**: R_f (*n*-pentane/EtOAc = 80:20) = 0.18. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 8.7 Hz, 3 H, Ar*H*), 7.61–7.54 (m, 1 H, Ar*H*), 7.42–7.36 (m, 1 H, Ar*H*), 7.33 (d, *J* = 7.7 Hz, 2 H, Ar*H*), 6.78 (dd, *J* = 8.5, 1.1 Hz, 1 H, Ar*H*). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 152.1 (q, *J* = 1.9 Hz), 139.0, 132.5, 131.0, 130.7, 130.6–130.5 (m), 127.7, 125.1 (q, *J* = 291.8 Hz), 123.4, 120.4 (q, *J* = 258.2 Hz), 120.0 (bs), 111.1, 81.2 (p, *J* = 28.6 Hz). **^{19}F-NMR** (376 MHz, $CDCl_3$): δ = -57.8 (ArOC*F*$_3$), -75.9 (C*F*$_3$). **IR**: *v* 2360 (m), 1560 (s), 1250 (s), 1207 (s), 1200 (s), 1171 (s), 1157 (s), 969 (s), 951 (s), 904 (s), 760 (s), 731 (s)**.** **HRMS** (ESI/QTOF) m/z: $[M+H]^+$ calcd for $C_{16}H_9F_9IO_2^+$ 530.9498, found 530.9509.

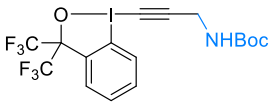
2.5. Unsuccessful Substrates



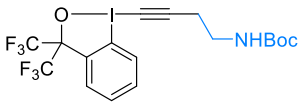
no reaction
(even at 40 °C instead of 0 °C)



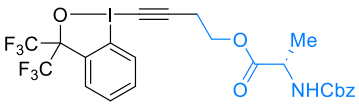
no reaction



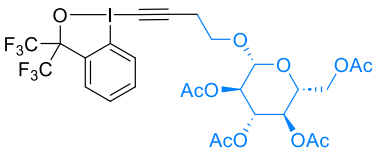
no reaction



no reaction



no reaction
(even at 40 °C instead of 0 °C)



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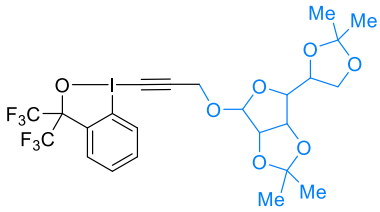
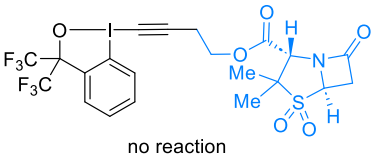
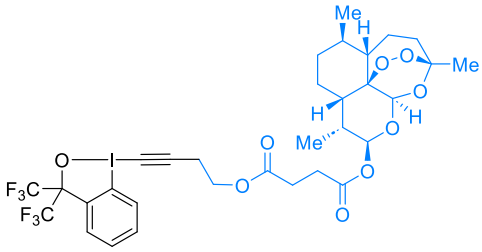


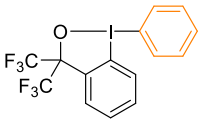
no reaction



no reaction



no reaction
(even at 40 °C instead of 0 °C)



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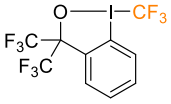
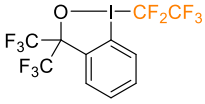
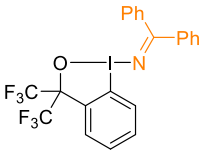


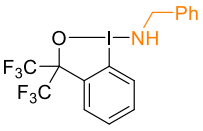
no reaction



no reaction



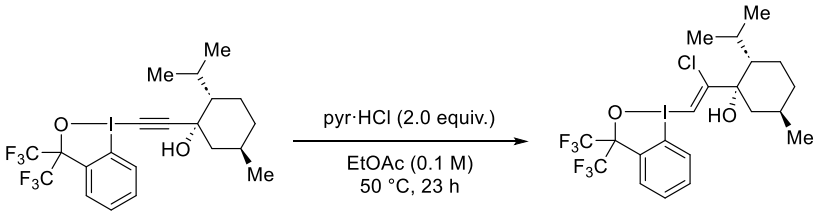
no reaction



no reaction
(even at 40 °C
instead of 0 °C)

2.6. Product Modifications

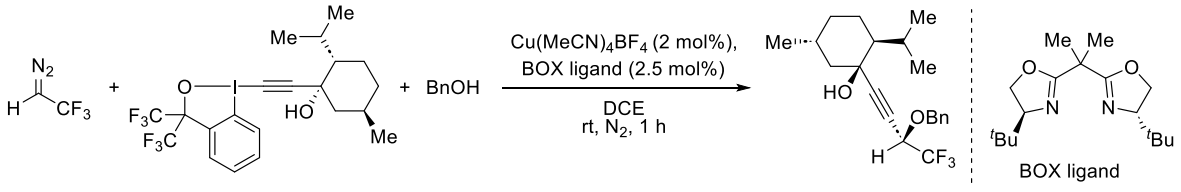
(1*S*,2*S*,5*R*)-1-((*Z*)-2-(3,3-Bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)-1-chloro-vinyl)-2-isopropyl-5-methylcyclohexan-1-ol (10)



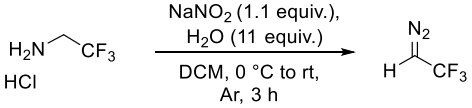
Following a reported procedure by Yoshikai[17], EBX **8j** (274 mg, 0.500 mmol, 1.0 equiv.) and pyridine hydrochloride (116 mg, 1.00 mmol, 2.0 equiv.) were added into a 25 mL microwave vial. Ethyl acetate (5.0 mL, 0.1 M) was added and the reaction was stirred for 23 h at 50 °C. The reaction was diluted with Et_2O (25 mL). The organic layer was washed with 1 M HCl solution (3x 10 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The obtained residue was submitted to MPLC (t_R = 14.1–17.9 min, gradient: 5–95% in 25 min) to give the desired product **10** (94.0 mg, 0.161 mmol, 32%) as a white solid.

MP: 189–192 °C. **ORD**: $[\alpha]_D^{20}$ = -15.1 (c = 3.0, MeOH). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.87 (d, J = 7.7 Hz, 1 H, Ar*H*), 7.62 (ddd, J = 7.8, 7.0, 1.2 Hz, 1 H, Ar*H*), 7.57–7.49 (m, 1 H, Ar*H*), 7.46 (dd, J = 8.3, 1.1 Hz, 1 H, Ar*H*), 7.32 (s, 1 H, C=C*H*), 1.90 (s, 1 H, C*H*), 1.88 – 1.70 (m, 5 H, C*H*, CH_2), 1.66 (dq, *J* = 13.5, 3.4 Hz, 1 H, CH_2), 1.54 (dd, J = 9.8, 2.2 Hz, 1 H, C*H*), 1.46 (qd, J = 13.1, 3.3 Hz, 1 H, CH_2), 1.00–0.89 (m, 9 H, CH_3). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 159.7, 132.2, 131.3, 130.8–130.7 (m), 130.6, 127.3, 124.1 (q, *J* = 291.8 Hz), 110.6, 104.6, 82.8, 81.4 (p, *J* = 28.9 Hz), 46.8, 46.4, 34.6, 28.3, 27.8, 23.6, 22.1, 20.6, 18.2. **^{19}F-NMR** (376 MHz, $CDCl_3$): δ = -76.0 – -76.1. **IR**: *v* 3342 (w), 2955 (m), 1563 (w), 1509 (w), 1469 (w), 1439 (w), 1387 (w), 1368 (w), 1332 (w), 1292 (w), 1264 (s), 1216 (m), 1184 (s), 1155 (s), 1133 (m), 1126 (m), 1069 (w), 1025 (w), 964 (m), 949 (m), 899 (w), 874 (w), 856 (w), 791 (w), 755 (m), 730 (s). **HRMS** (ESI/QTOF) *m/z*: $[M+H]^+$ calcd for $C_{21}H_{25}ClF_6IO_2^+$ 585.0487, found 585.0494.

(1*S*,2*S*,5*R*)-1-((*S*)-3-(Benzyloxy)-4,4,4-trifluorobut-1-yn-1-yl)-2-isopropyl-5-methylcyclohexan-1-ol (11)



The following reported procedure was taken directly from our previous publication.[18]
Synthesis of diazo compound:

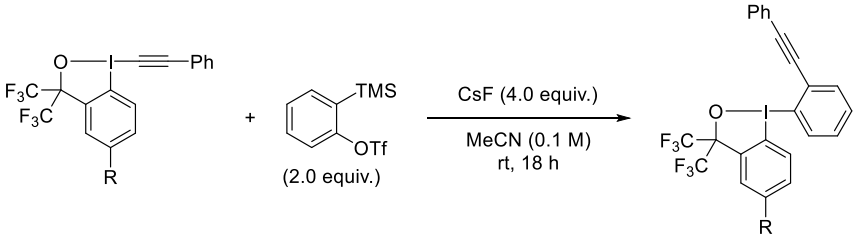


Under argon, 2,2,2-trifluoroethanamine hydrochloride (0.678 g, 5.00 mmol, 1.0 equiv.) and sodium nitrite (0.379 g, 5.50 mmol, 1.1 equiv.) were dissolved in degassed DCM (10 mL). Degassed water (1.00 mL, 55.5 mmol, 11 equiv.) was added slowly at 0 °C. The solution was stirred for 2 h at 0 °C and 1 h at room temperature. Layers were separated and the organic layer was dried over $MgSO_4$, transferred into a vial, sealed, and stored at −18 °C. The concentration of the obtained solution was determined to be 0.33-0.40 M by ^{19}F NMR analysis (according to an internal reference, $PhCF_3$). **^{19}F NMR** (377 MHz, DCM-d_2) δ −55.6. The values of the NMR spectra are in accordance with reported literature data.

Stock solution of the catalyst (to avoid problems of complexation, the catalytic solution was preparing triplicating the amount of each component): In an oven-dried microwave vial, $Cu(MeCN)_4BF_4$ (4.8 mg, 1.50 µmol, 0.06 equiv.) and BOX ligand (5.5 mg, 1.90 µmol, 0.075 equiv.) were charged and the vial was capped with a septum. Then, the system was evacuated and backfilled with 3 cycles of vacuum-N_2. Finally, dry DCE (5 mL) was added into the vial and the resulting colourlesss solution was stirring (430 rpm) at room temperature during 1 h.
Procedure: In an oven-dried microwave vial, compound **8j** (137.1 mg, 0.250 mmol, 1.0 equiv.) and the vial was capped with a septum. Then, the system was evacuated and backfilled with 3 cycles of vacuum-N2, followed by the addition of 2-diazo-1,1,1-trifluoroethane (1.4 mL, 0.50 mmol, 0.33-0.40 M in DCM, 2.00 equiv.) and benzyl alcohol (52 µL, 0.50 mmol, 2.00 equiv.). The resulting reaction mixture was stirred at RT under N_2 atmosphere and the catalytic solution (1.50 mL) was added dropwise. After 1 h of reaction, the mixture was filtered through a short pad of celite and rinsed up with EtOAc (15 mL). The solvent was removed under reduced pressure and the resulting residue was purified MPLC (t_R = 24.8–26.6 min, gradient: 5–95% in 28 min). (1*S*,2*S*,5*R*)-1-((*S*)-3-(Benzyloxy)-4,4,4-trifluorobut-1-yn-1-yl)-2-isopropyl-5-methylcyclohexan-1-ol (**11**) was obtained as a pale yellow oil as 9:1 mixture of diastereoisomers (48.0 mg, 0.126 mmol, 50%). The absolute configuration was assumed in analogy to the reported reaction. The dr was measured by ^{19}F-NMR of the crude reaction mixture (δ_F -76.74, δ_F -76.68).[18]

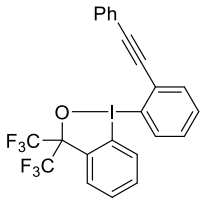
TLC: R_f (*n*-pentane) = 0.15. **^{1}H-NMR** (400 MHz, $CDCl_3$, *mixture of diastereoisomers*): δ 7.40–7.31 (m, 5 H, Ar*H*), 4.85 (d, *J* = 12.0 Hz, 1 H, C*H*$_2$OPh), 4.69 (d, *J* = 11.9 Hz, 1 H, C*H*$_2$OPh), 4.53 (q, *J* = 5.8 Hz, 1 H, *H*CF_3), 2.38–2.31 (m, 1 H, C*H*(OH)), 2.01–1.95 (m, 1 H, aliphatic menthol), 1.82–1.72 (m, 2 H, aliphatic menthol), 1.65 (bs, 1 H, O*H*) 1.58–1.31 (m, 5 H, aliphatic menthol), 0.99 (d, *J* = 7.0 Hz, 3 H, C*H*$_3$), 0.96 (d, *J* = 7.0 Hz, 3 H, C*H*$_3$), 0.90 (d, *J* = 6.5 Hz, 3 H, C*H*$_3$). **^{13}C-NMR** (101 MHz, $CDCl_3$, *mixture of diastereoisomers*): δ 136.2, 128.8, 128.5, 128.3, 122.6 (q, *J* = 281.4 Hz), 94.2, 73.7 (q, *J* = 2.2 Hz), 72.0, 71.3, 67.7 (q, *J* = 35.2 Hz), 50.5, 49.8, 34.8, 28.8, 27.3, 23.9, 22.0, 20.7, 18.9. **^{19}F-NMR** (376 MHz, $CDCl_3$): δ = -76.67 (d, *J* = 6.2 Hz, *minor diastereoisomer*), -76.73 (d, *J* = 6.2 Hz, *major diastereoisomer*). **IR**: *v* 2959 (s), 2357 (s), 2332 (s), 1366 (s), 1272 (s), 1179 (s), 1150 (s), 1096 (s), 1078 (s), 944 (s), 912 (s), 743 (s). **HRMS** (nanochip-ESI/LTQ-Orbitrap) m/z: $[M+H]^+$ Calcd for $C_{22}H_{30}F_3O_2^+$ 383.2192, found 383.2182.

General Procedure for Carboiodanation of Arenes (GP5)



Following a reported procedure[19], **8** (0.25 mmol, 1.0 equiv.) and dry CsF (152 mg 1.00 mmol, 4.0 equiv.) were added into an oven-dried microwave vial equiped with a stirring bar. Then, the vial was capped, evacuated and backfilled with N_2 (3 cycles) followed by the addition of dry MeCN (2.5 mL). Finally, (2-trimethylsilylphenyl) trifluoromethanesulfonate (0.128 mL, 157 mg, 2.0 equiv.) was added and the resulting reaction mixture was stirred at room temperature under N_2 atmosphere during 18 h. After this time, an aliquot was taken and the reaction was monitored by TLC (*n*-pentane/EtOAc, 95:5) until observing full conversion of the EBX derivative. The reaction mixture was filtered through a short pad of celite and rinsed up with EtOAc (3 x 10 mL). The solvent was removed and the residue was purified by preparative TLC (*n*-pentane/EtOAc, 80:20) (Note: the content was distributed in 2 plates to allow a better separation).

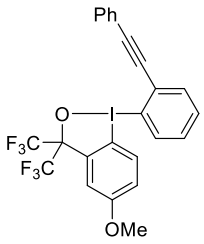
1-(2-(Phenylethynyl)phenyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (12a)



Following **GP5** on 0.250 mmol scale using **8a** (118 mg, 0.250 mmol, 1.0 equiv.). 1-(2-(Phenylethynyl)phenyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1 λ^3-benzo[*d*][1,2]iodaoxole (**12a**, 95.0 mg, 0.174 mmol, 70%) was obtained as white amorphous solid. Purification via preparative TLC (*n*-pentane/EtOAc, 80:20).

MP: 180–185 °C (dec.). **TLC**: R_f (*n*-pentane/EtOAc = 80:20) = 0.15. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 8.02 (dd, *J* = 7.6, 1.4 Hz, 1 H, Ar*H*), 7.88 (d, *J* = 6.4 Hz, 1 H, Ar*H*), 7.78 (dd, *J* = 7.8, 1.5 Hz, 1 H, Ar*H*), 7.66 (td, *J* = 7.6, 1.4 Hz, 1 H, Ar*H*), 7.60–7.53 (m, 1 H, Ar*H*), 7.46–7.34 (m, 2 H, Ar*H*), 7.24–7.20 (m, 5 H, Ar*H*), 6.91 (dd, *J* = 8.3, 1.1 Hz, 1 H, Ar*H*). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 137.8, 132.8, 132.3, 132.2, 131.7, 131.0, 130.6, 130.5, 130.4, 129.4, 128.5, 127.8, 124.4, 124.2 (q, *J* = 291.2 Hz), 121.7, 110.9, 95.8, 88.4, 81.8–81.2 (m). One carbon is not resolved. **^{19}F-NMR** (376 MHz, $CDCl_3$): δ = -76.1. **IR**: *v* 2218 (w), 1492 (w), 1460 (m), 1440 (w), 1286 (m), 1263 (s), 1213 (m), 1177 (s), 1156 (s), 963 (s), 946 (s), 755 (s), 731 (s). **HRMS** (ESI/QTOF) m/z: $[M+H]^+$ calcd for $C_{23}H_{14}F_6IO^+$ 546.9988, found 546.9994.

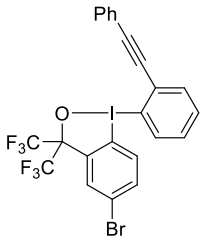
5-Methoxy-1-(2-(phenylethynyl)phenyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (12b)



Following **GP5** on 0.250 mmol scale using **8k** (125 mg, 0.250 mmol, 1.0 equiv.). 5-Methoxy-1-(2-(phenylethynyl)phenyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (**12b**, 87.0 mg, 0.151 mmol, 60%) was obtained as white amorphous solid. Purification via preparative TLC (*n*-pentane/EtOAc, 80:20).

MP: 195–205 °C (dec.). **TLC**: R_f (*n*-pentane/EtOAc = 80:20) = 0.18. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 8.00 (dd, *J* = 7.8, 1.3 Hz, 1 H, Ar*H*), 7.76 (dd, *J* = 7.8, 1.5 Hz, 1 H, Ar*H*), 7.64 (td, *J* = 7.6, 1.3 Hz, 1 H, Ar*H*), 7.42–7.35 (m, 2 H, Ar*H*), 7.33–7.21 (m, 5 H, Ar*H*), 6.90 (dd, *J* = 9.1, 2.8 Hz, 1 H, Ar*H*), 6.70 (d, *J* = 9.0 Hz, 1 H, Ar*H*), 3.80 (s, 3 H, OCH_3). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 161.8, 137.8, 132.7, 132.5, 132.1, 131.8, 130.5, 130.3, 129.3, 128.5, 128.3, 124.2 (q, *J* = 291.2 Hz), 124.1, 121.7, 118.3, 116.14–116.11 (m), 99.3, 95.6, 88.5, 81.6–80.7 (m), 55.9. **^{19}F-NMR** (376 MHz, $CDCl_3$): δ = -76.0. **IR**: *v* 2218 (w), 1493 (w), 1460 (m), 1440 (w), 1288 (m), 1263 (s), 1213 (m), 1176 (s), 1156 (s), 963 (m), 949 (s), 755 (s), 729 (m). **HRMS** (ESI/QTOF) m/z: $[M+H]^+$ calcd for $C_{24}H_{16}F_6IO_2^+$ 577.0094, found 577.0108.

5-Bromo-1-(2-(phenylethynyl)phenyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (12c)

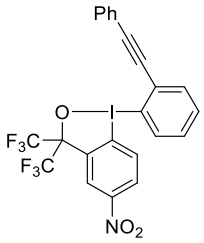


Following **GP5** on 0.250 mmol scale using **8m** (137 mg, 0.250mmol, 1.0 equiv.). 5-Bromo-1-(2-(phenylethynyl)phenyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (**12c**, 97.0 mg, 0.155 mmol, 62%) was obtained as white amorphous solid. Purification via preparative TLC (*n*-pentane/EtOAc, 80:20).

MP: 205-210°C (dec.). **TLC**: R_f (*n*-pentane/EtOAc = 80:20) = 0.20. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = = 8.01 (dd, *J* = 7.7, 1.3 Hz, 1H, Ar *H*), 7.97–7.96 (m, 1 H, Ar*H*), 7.79 (dd, *J* = 7.8, 1.5 Hz, 1 H, Ar*H*), 7.67 (td, *J* = 7.6, 1.3 Hz, 1 H, Ar*H*), 7.47 (dd, *J* = 8.8, 2.1 Hz, 1 H, Ar*H*), 7.42 (td, *J* = 7.6, 1.4 Hz, 1 H, Ar*H*), 7.35–7.21 (m, 5 H), 6.71 (d, *J* = 8.8 Hz, 1 H, Ar*H*). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 137.8, 135.4, 133.5–133.4 (m), 133.3, 132.9, 132.5, 131.7, 130.6, 130.5, 129.5, 129.0, 128.6, 125.6, 124.0, 123.2 (q, *J* = 245 Hz), 121.5, 109.5, 96.1, 88.2. One carbon is not resolved. **^{19}F-NMR** (376 MHz, $CDCl_3$): δ = -79.0. **IR**: *v* 2218 (w), 1490 (w), 1460 (m), 1284 (m), 1259 (s), 1212

(m), 1173 (s), 1160 (s), 1007 (m), 960 (s), 911 (w), 757 (s), 730 (s). **HRMS** (ESI/QTOF) *m/z*: $[M+H]^+$ calcd for $C_{23}H_{13}BrF_6IO^+$ 624.9093, found 624.9084.

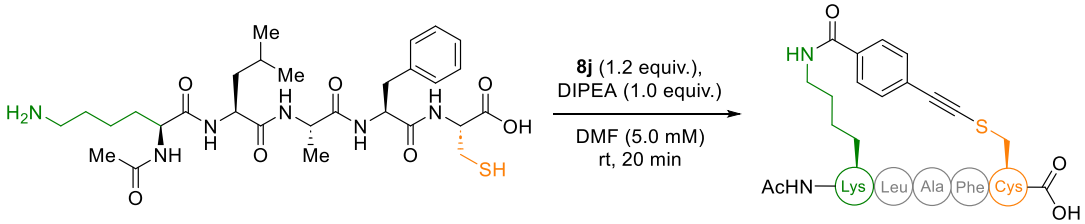
5-Nitro-1-(2-(phenylethynyl)phenyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (12d)



Following **GP5** on 0.250 mmol scale using **8p** (129 mg, 0.250 mmol, 1.0 equiv.). 5-Nitro-1-(2-(phenylethynyl)phenyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (**12d**, 86.0 mg, 0.146 mmol, 58%) was obtained as orange amorphous solid. Purification via preparative TLC (*n*-pentane/EtOAc, 70:30).

MP: 175–178 °C (dec.). **TLC**: R_f (*n*-pentane/EtOAc = 70:30) = 0.25. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 8.67–8.62 (m, 1 H, Ar*H*), 8.20 (dd, *J* = 8.9, 2.4 Hz, 1 H, Ar*H*), 8.05 (dd, *J* = 7.8, 1.2 Hz, 1 H, Ar*H*), 7.83 (dd, *J* = 7.8, 1.4 Hz, 1 H, Ar*H*), 7.72 (td, *J* = 7.6, 1.3 Hz, 1 H, Ar*H*), 7.47 (td, *J* = 7.6, 1.5 Hz, 1 H, Ar*H*), 7.36–7.28 (m, 1 H, Ar*H*), 7.28–7.23 (m, 4 H, Ar*H*), 7.09 (d, *J* = 9.0 Hz, 1 H, Ar*H*). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 150.1, 137.7, 133.5, 133.2, 132.9, 131.7, 130.8, 130.6, 129.7, 128.9, 128.6, 126.8, 124.9–124.8 (m), 124.2, 123.4 (q, *J* = 291.4 Hz), 121.2, 117.5, 96.4, 88.0, 81.4 (p, *J* = 29.8 Hz). **^{19}F-NMR** (376 MHz, $CDCl_3$): δ = -76.0. **IR**: *v* 3112 (w), 2214 (w), 1611 (w), 1573 (w), 1537 (m), 1493 (w), 1457 (w), 1351 (s), 1281 (m), 1260 (s), 1212 (m), 1180 (s), 1162 (s), 1102 (m), 1010 (w), 978 (m), 972 (m), 964 (m), 909 (m), 863 (m), 758 (s), 733 (s), 729 (s), 722 (m). **HRMS** (ESI/QTOF) m/z: $[M+H]^+$ calcd for $C_{23}H_{13}F_6INO_3^+$ 591.9839, found 591.9847.

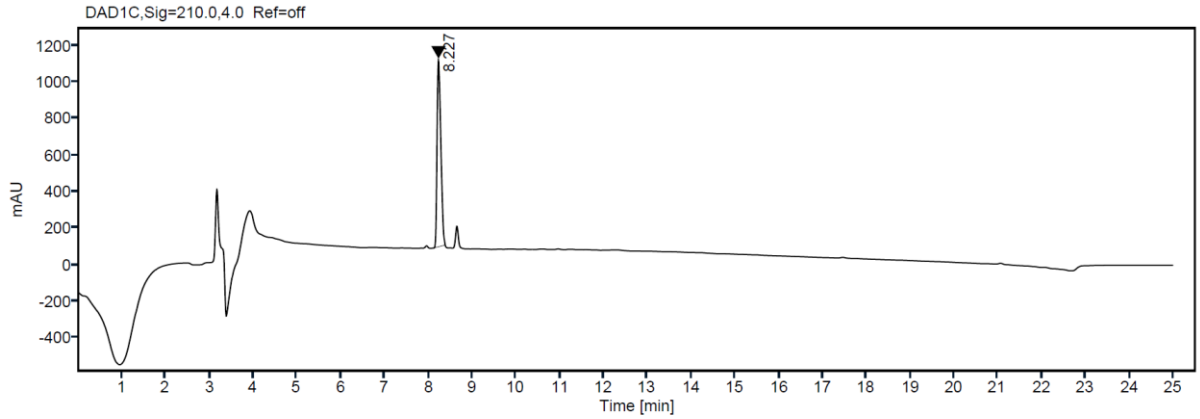
Peptide Stapling (13)



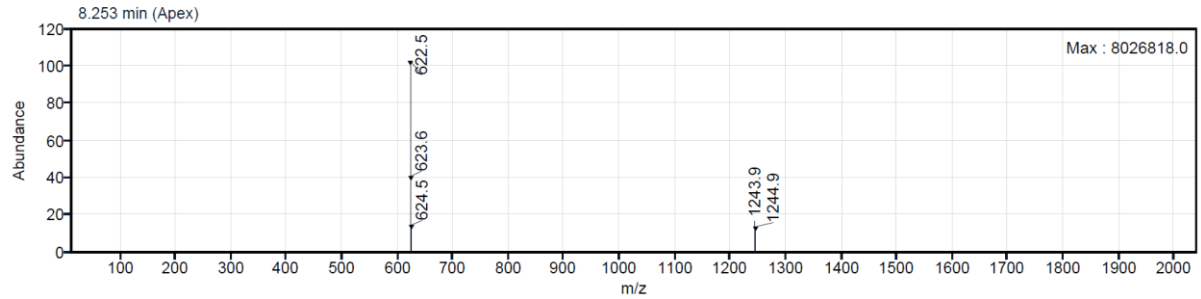
The starting peptide was synthesized by solid phase peptide synthesis as described previously.[20] To a solution of the peptide (6.22 mg, 10.0 µmol, 1.0 equiv.) in DMF (2.0 mL) was added the bifunctional EBX reagent **8j** (8.16 mg, 12.0 µmol, 1.2 equiv.) and DIPEA (2.0 µL, 1.29 mg, 10.0 µmol, 1.0 equiv.). The mixture was stirred for 20 min at room temperature without inert gas or light protection. For isolation, the crude mixture was submitted to preparative HPLC (water/acetonitrile, method: 5 to 95% MeCN over 25 min) and the product fraction was concentrated with lyophilization. The product **13** (4.60 mg, 6.14 µmol, 61%) was isolated as awhite solid.

HPLC: t_R = 10.68 min (5–95% MeCN in 20 min). **^{1}H-NMR** (400 MHz, DMSO-d_6): δ = 8.65 (d, *J* = 8.0 Hz, 1 H, N*H*), 8.11 (t, *J* = 5.1 Hz, 1 H, N*H*), 8.07 (d, *J* = 7.8 Hz, 1 H, N*H*), 7.98 (d, *J* = 7.1 Hz, 1 H, N*H*), 7.91 (d, *J* = 7.8 Hz, 1 H, N*H*), 7.77 (d, *J* = 8.4 Hz, 2 H, Ar*H*), 7.39 (d, *J* = 8.3 Hz, 2 H, Ar*H*), 7.24–7.18 (m, 5 H, Ar*H*), 4.72 – 4.60 (m, 2 H, CH_α), 4.33–4.26 (m, 1 H, CH_α), 4.21–4.14 (m, 1 H, CH_α), 4.04 (p, *J* = 7.1 Hz, 1 H, CH_α), 3.10–2.99 (m, 2 H, CH_2), 2.82 (dd, *J* = 13.8, 7.5 Hz, 1 H, CH_2), 1.81 (s, 3 H, C(O)CH_3), 1.68–1.43 (m, 6 H, CH_2), 1.40–1.27 (m, 4 H, CH_2), 0.92 (d, *J* = 7.0 Hz, 3 H, CH_3), 0.83 (d, *J* = 6.6 Hz, 4 H, CH_3, C*H*), 0.78 (d, *J* = 6.5 Hz, 3 H, CH_3). One CH signal is overlapping with the solvent signal. **HRMS** (ESI/LTQ) m/z: $[M+H]^+$ calcd for $C_{38}H_{50}N_7O_7S^+$ 748.3487, found 748.3485.

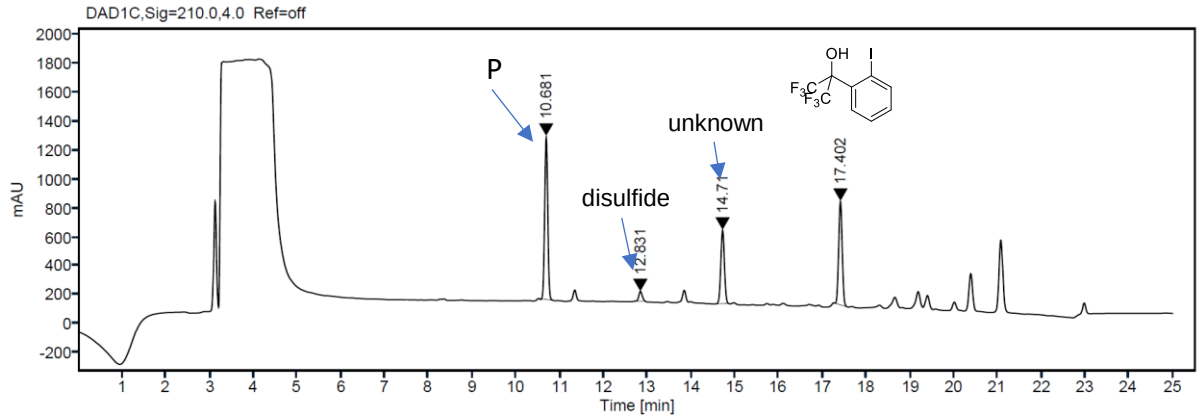
HPLC-UV 210 nm of peptide AcKLAFC



Retention time: 8.253 min **Area Percent:** 100%

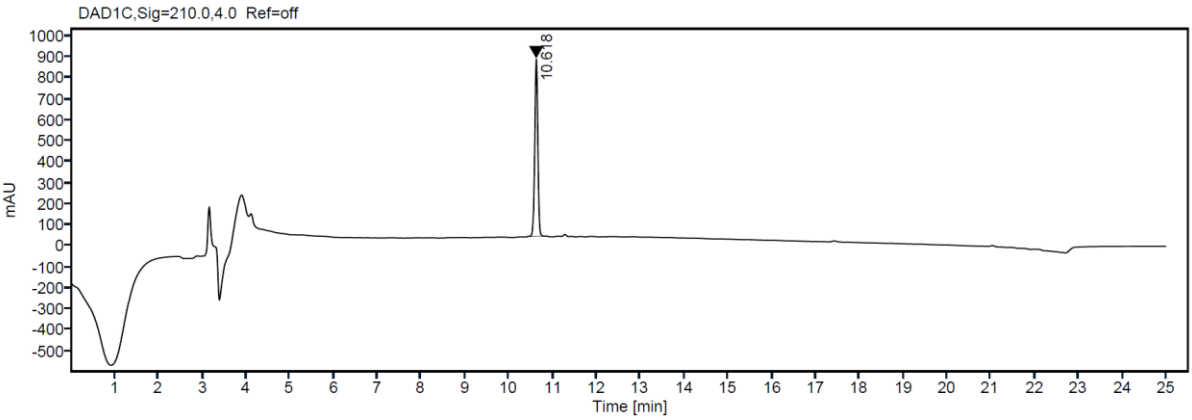


HPLC-UV 210 nm of reaction crude

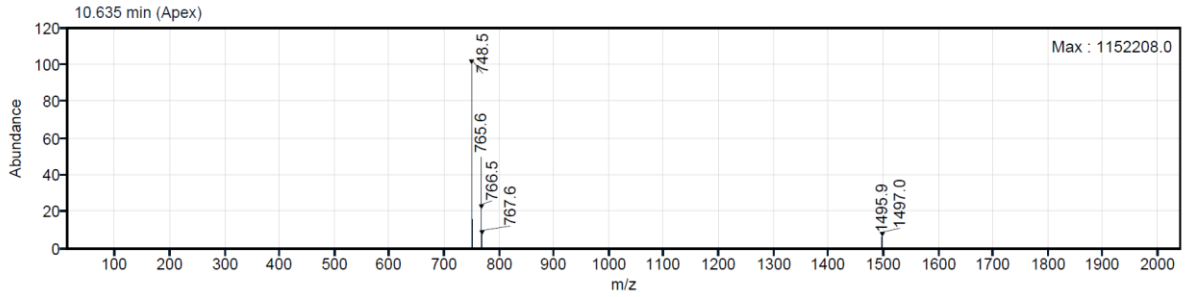


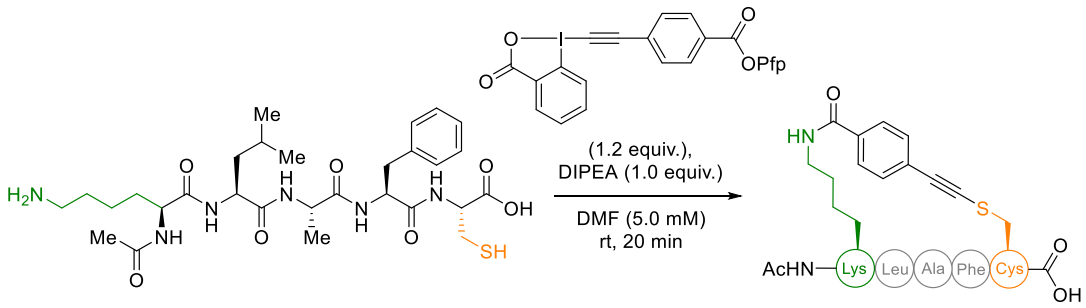
HPLC-UV ratio: **P**: **Disulfide**: **Unknown peptide related peaks** = 62:4:28

HPLC-UV 210 nm of product



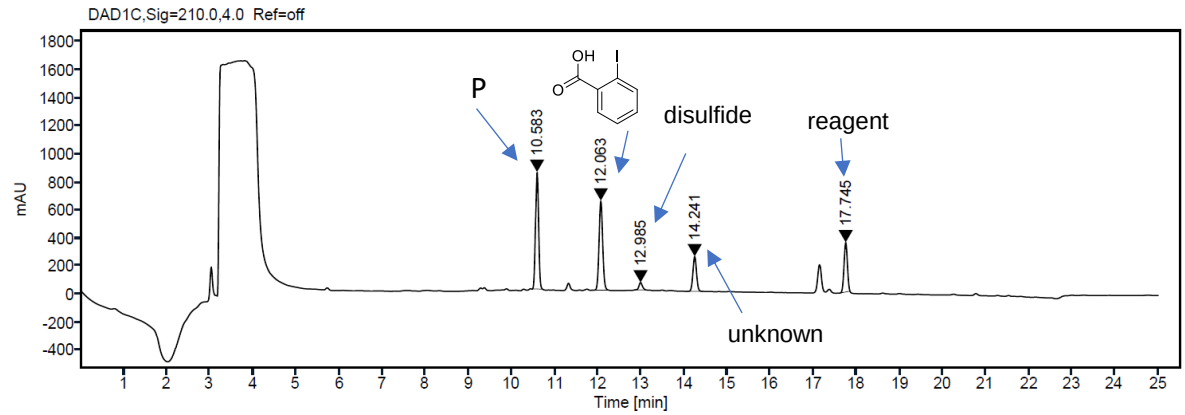
Retention time: 10.635 min **Area Percent:** 100%





Using carboxyl backbone reagent for the stapling reaction:

HPLC-UV 210 nm of reaction crude

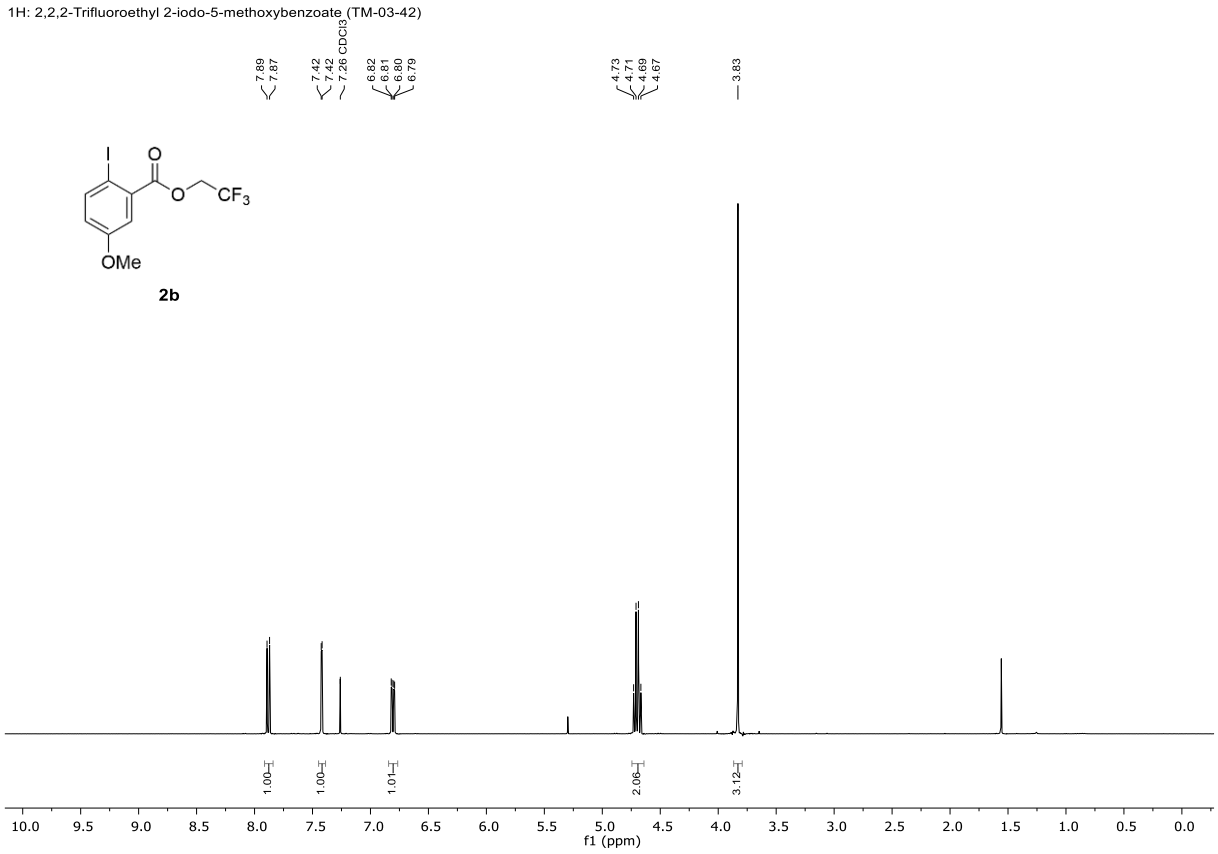


HPLC-UV ratio: **P**: **Disulfide**: **Unknown peptide related peaks** = 69:5:25

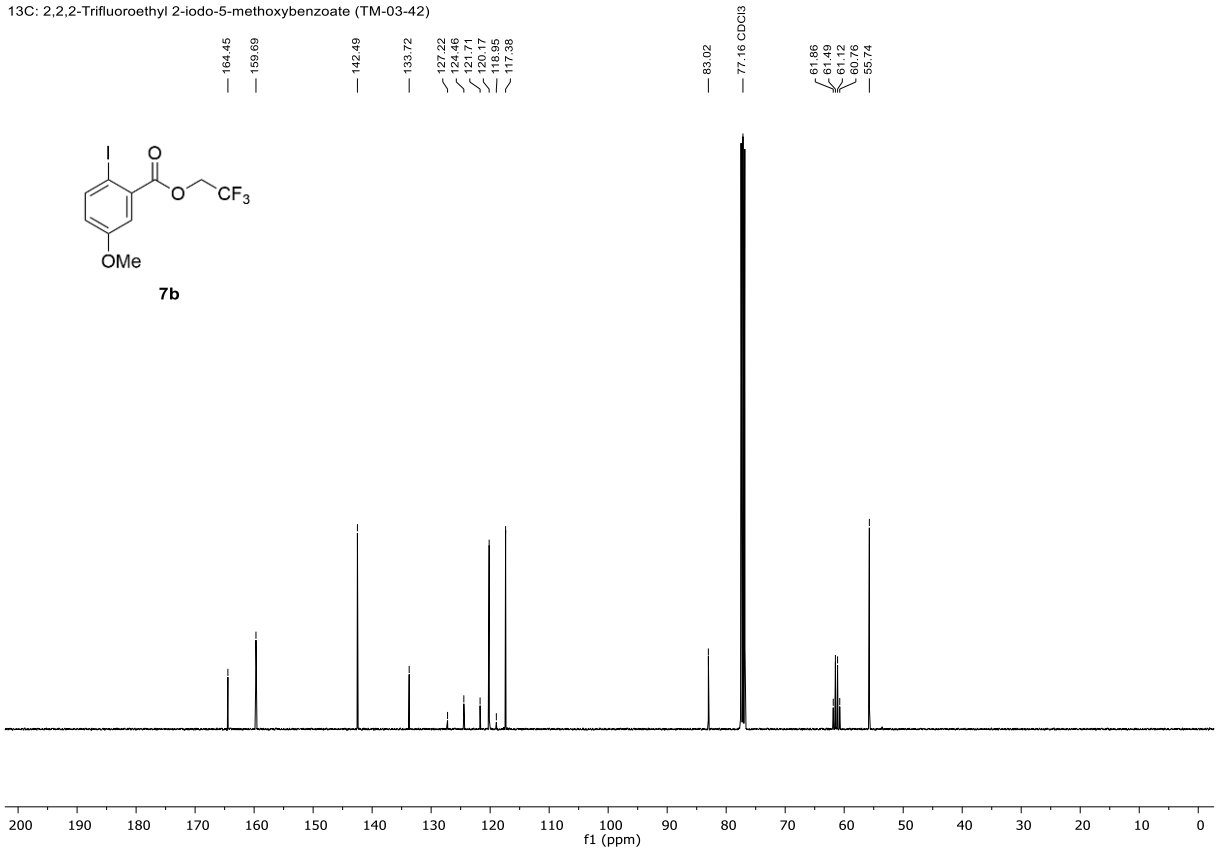
3. NMR Data

2,2,2-Trifluoroethyl 2-iodo-5-methoxybenzoate (7b)

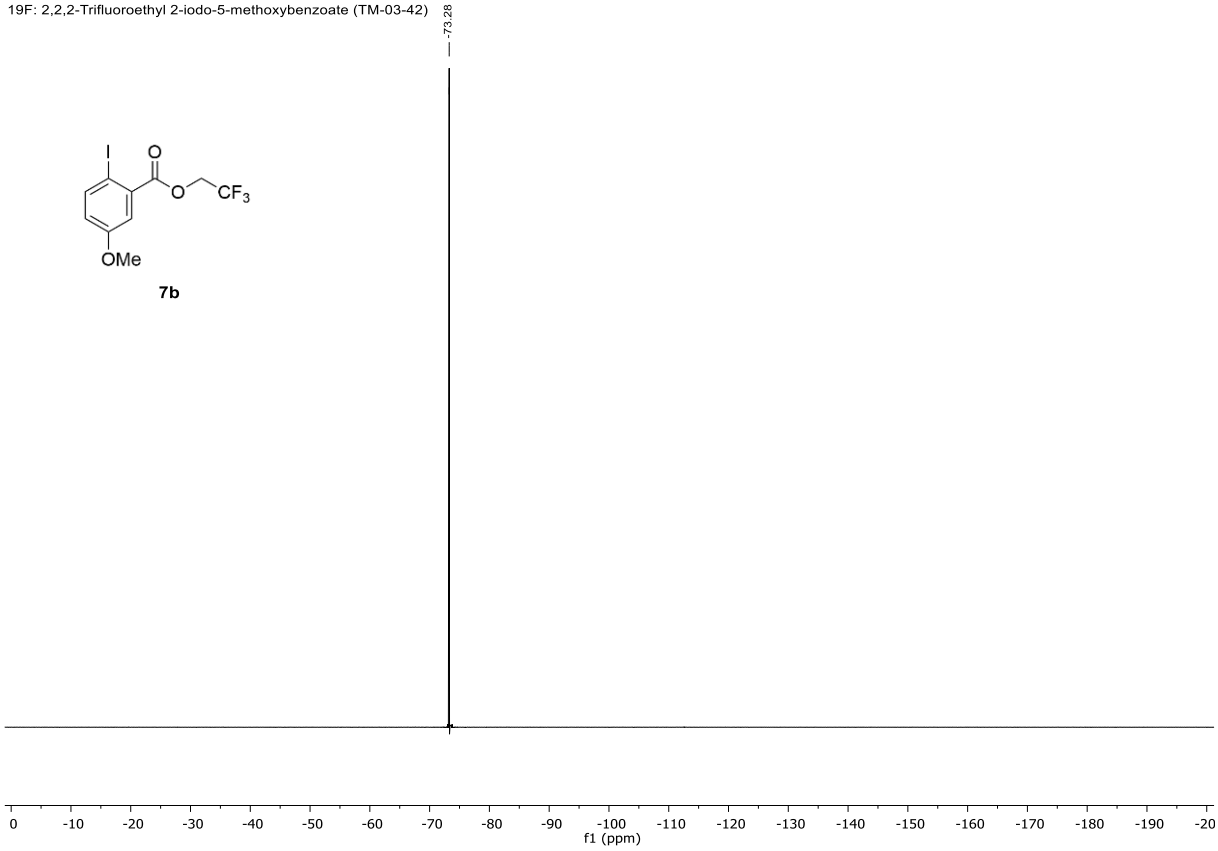
^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)



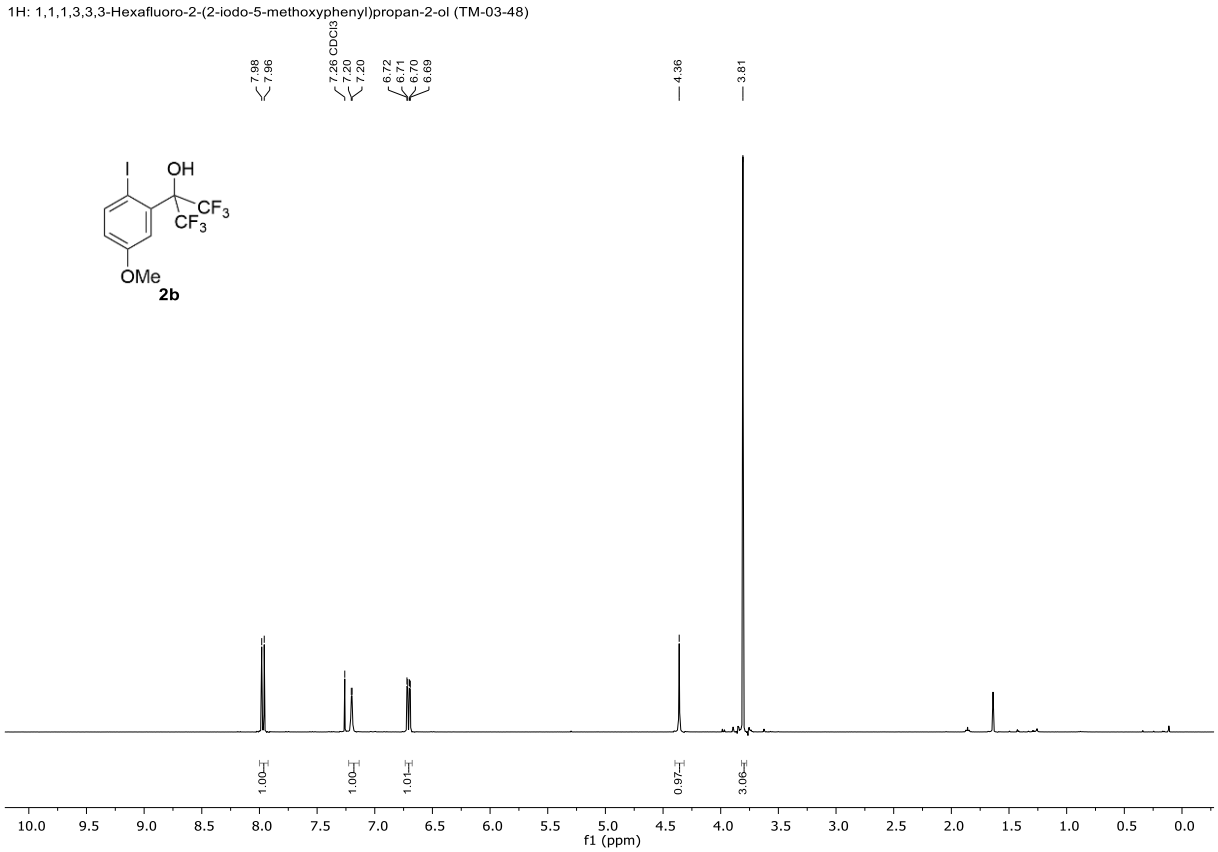
^{19}F-NMR (376 MHz, $CDCl_3$)



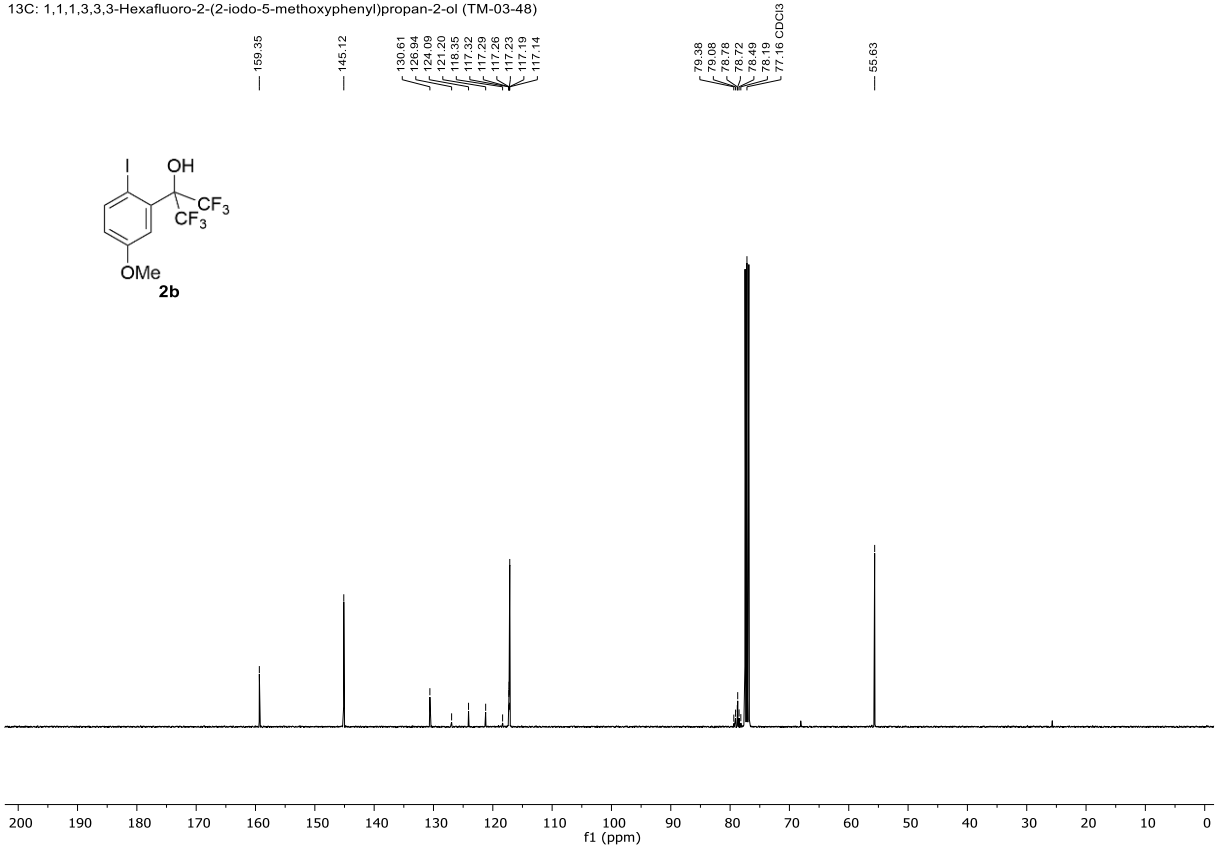
7b

1,1,1,3,3,3-Hexafluoro-2-(2-iodo-5-methoxyphenyl)propan-2-ol (2b)

^{1}H-NMR (400 MHz, $CDCl_3$)

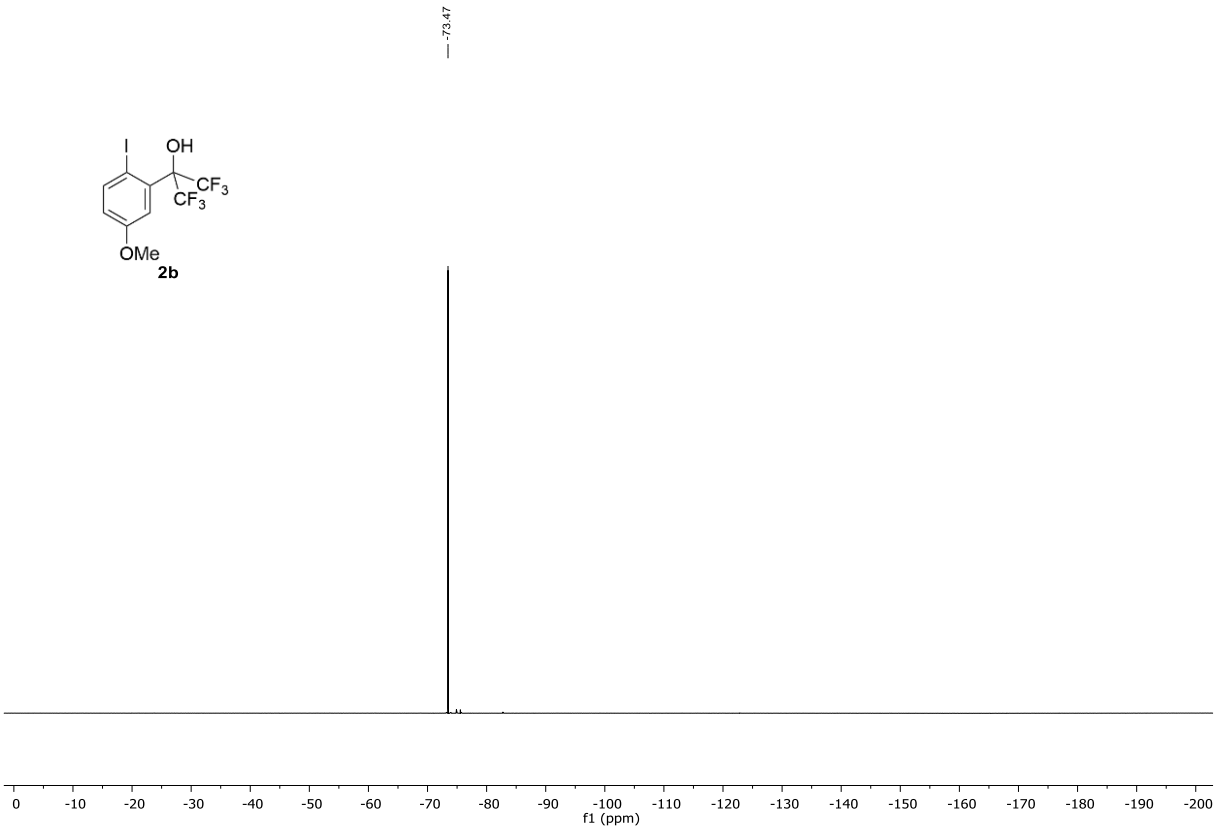


^{13}C-NMR (101 MHz, $CDCl_3$)



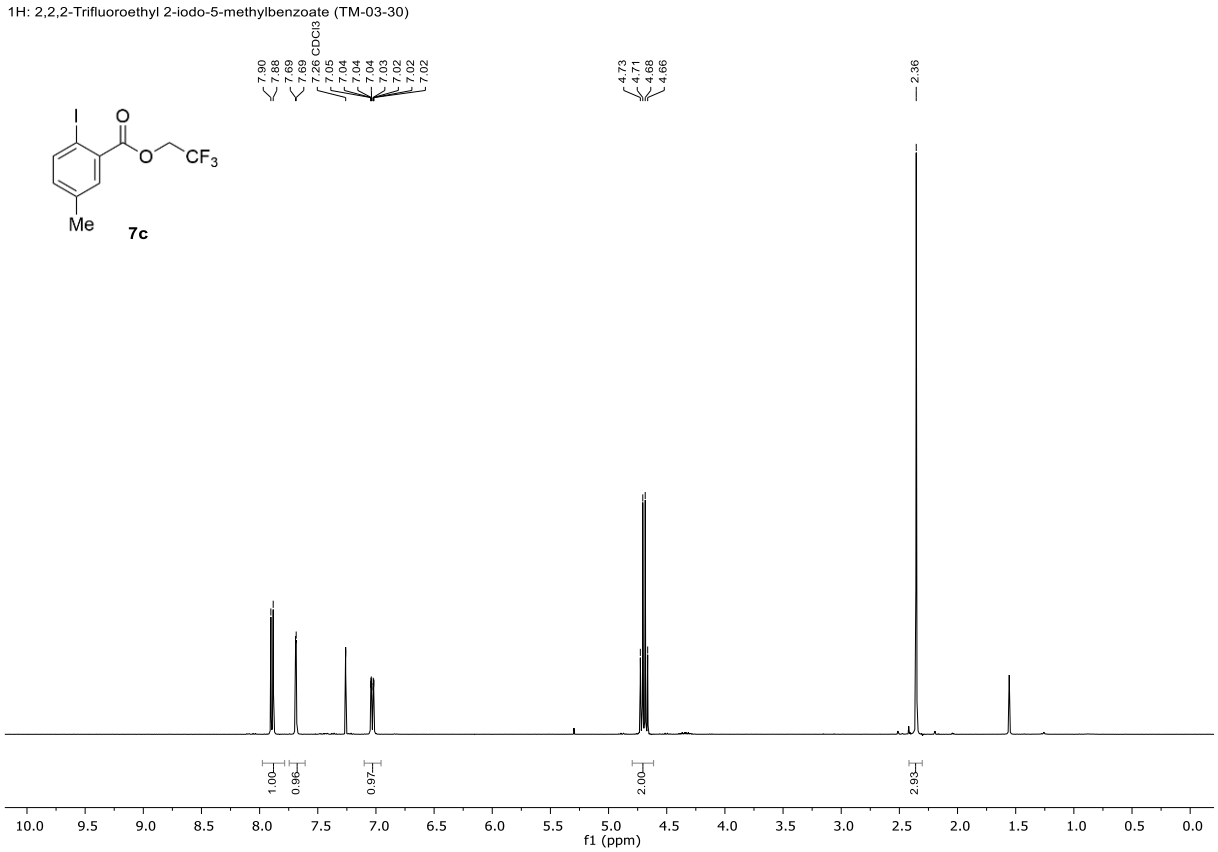
^{19}F-NMR (376 MHz, $CDCl_3$)

19F: 1,1,1,3,3,3-Hexafluoro-2-(2-iodo-5-methoxyphenyl)propan-2-ol (TM-03-48)

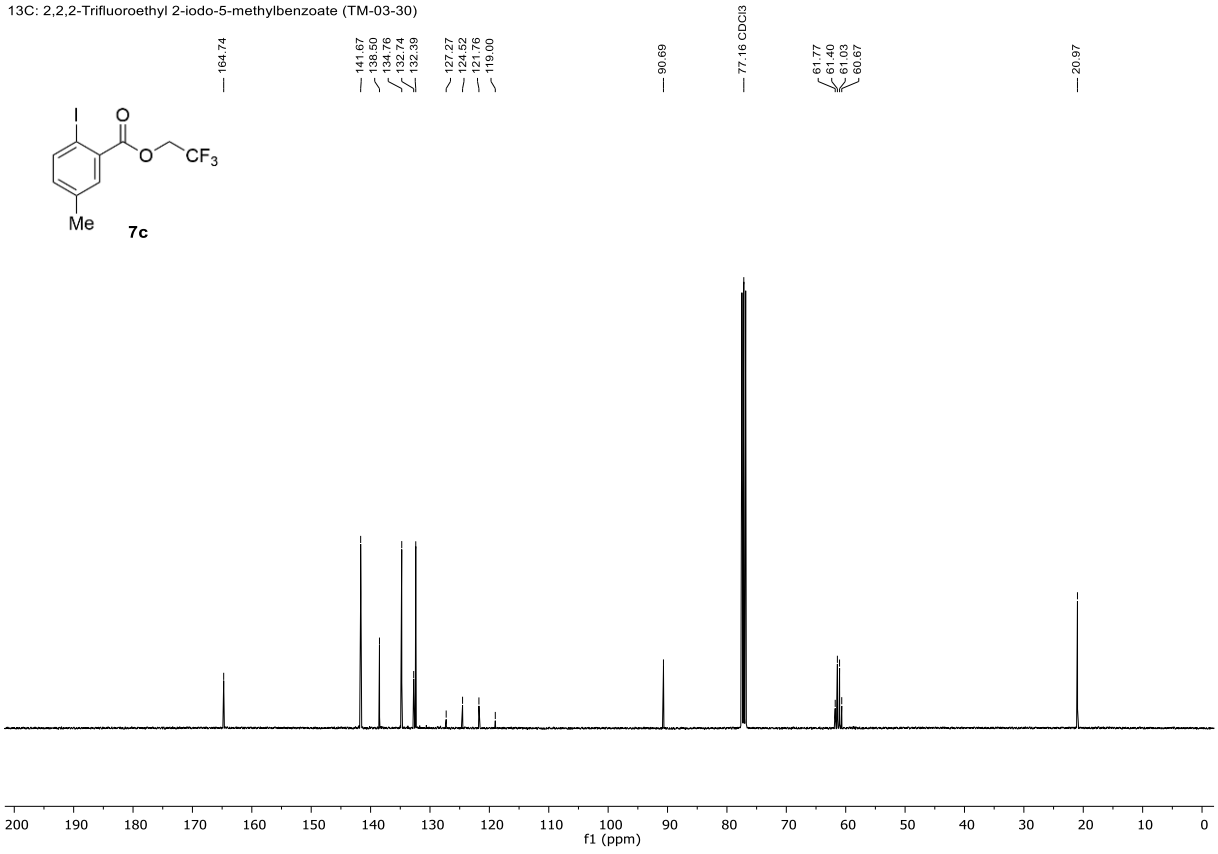


2,2,2-Trifluoroethyl 2-iodo-5-methylbenzoate (7c)

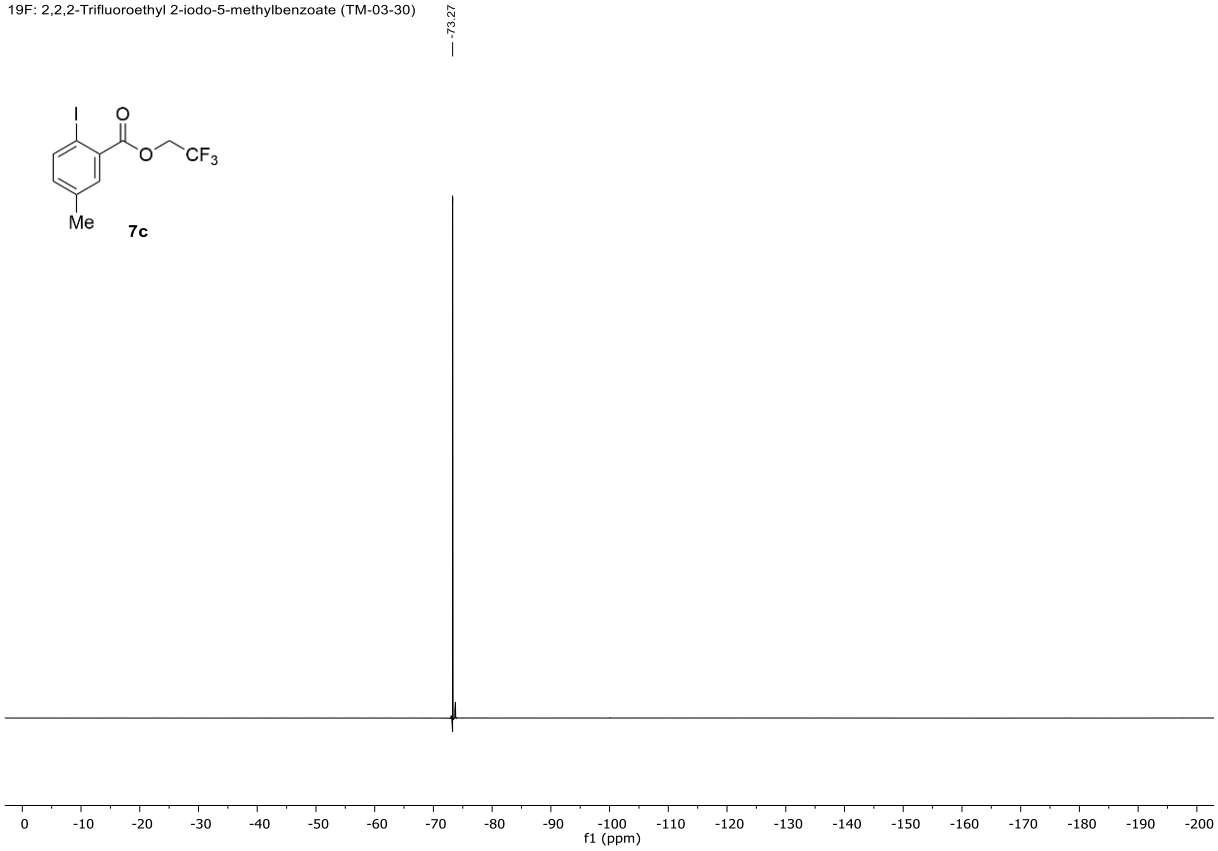
^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)

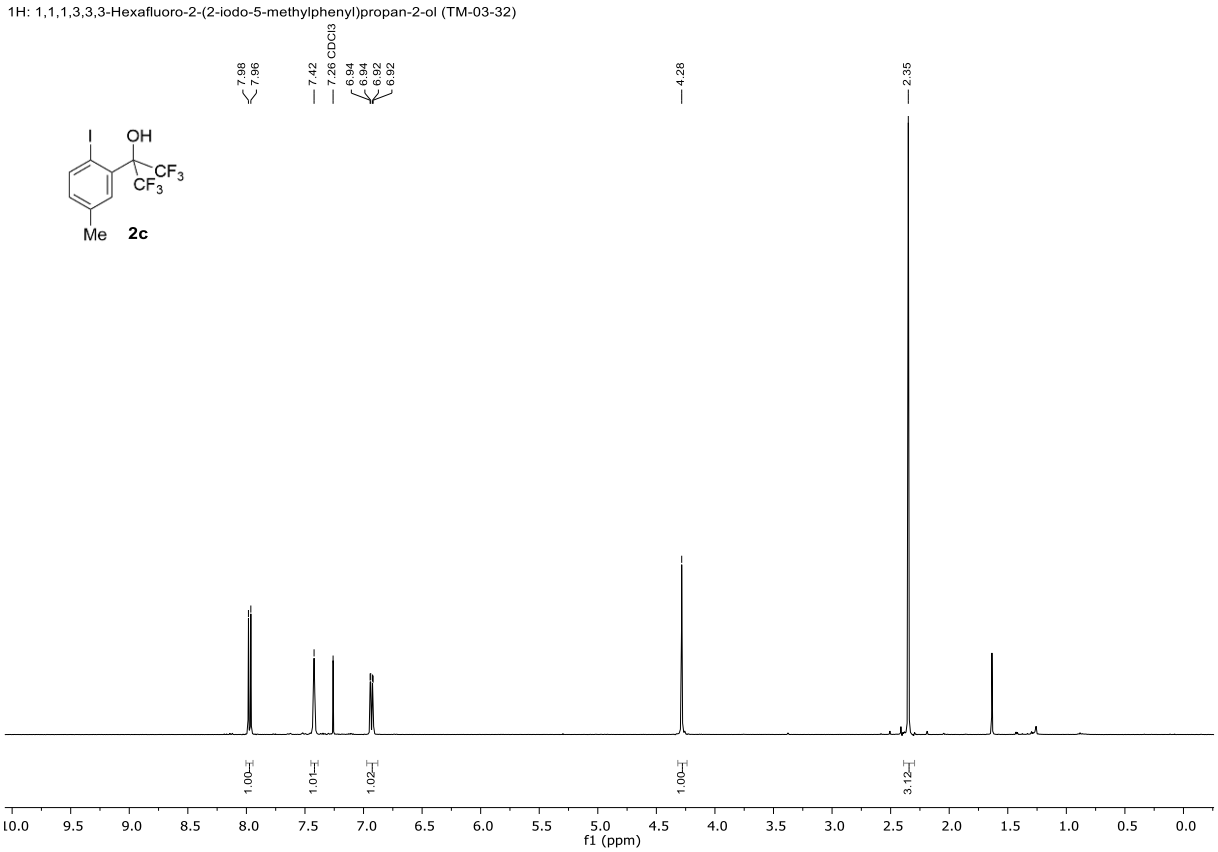


^{19}F-NMR (376 MHz, $CDCl_3$)

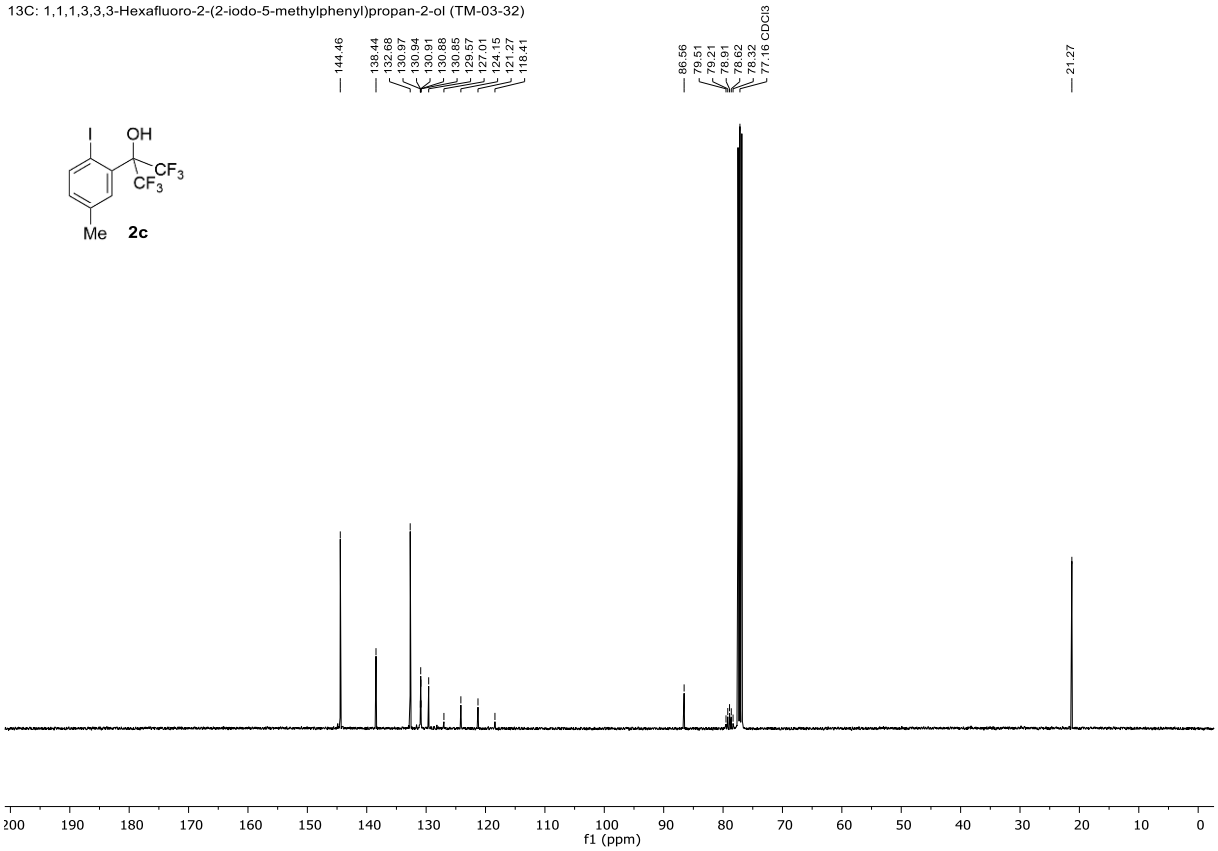


1,1,1,3,3,3-Hexafluoro-2-(2-iodo-5-methylphenyl)propan-2-ol (2c)

^{1}H-NMR (400 MHz, $CDCl_3$)

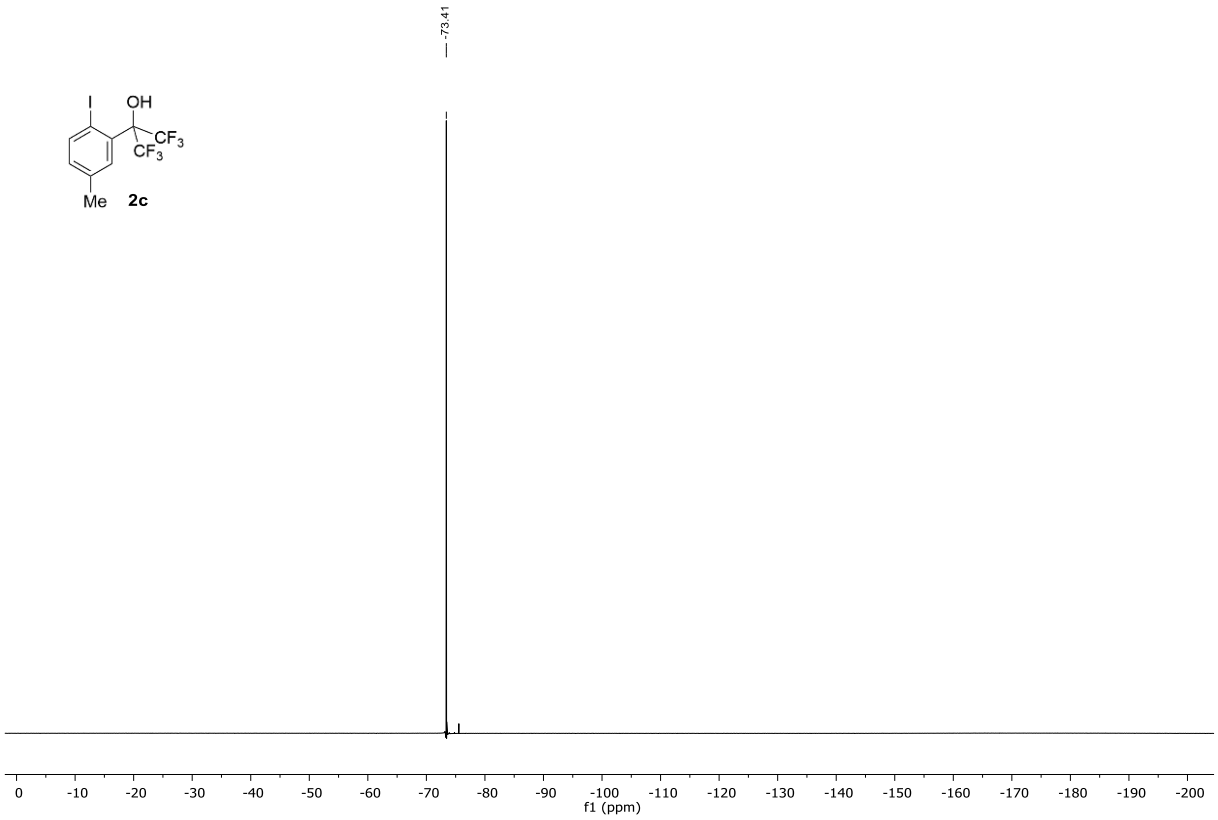


^{13}C-NMR (101 MHz, $CDCl_3$)



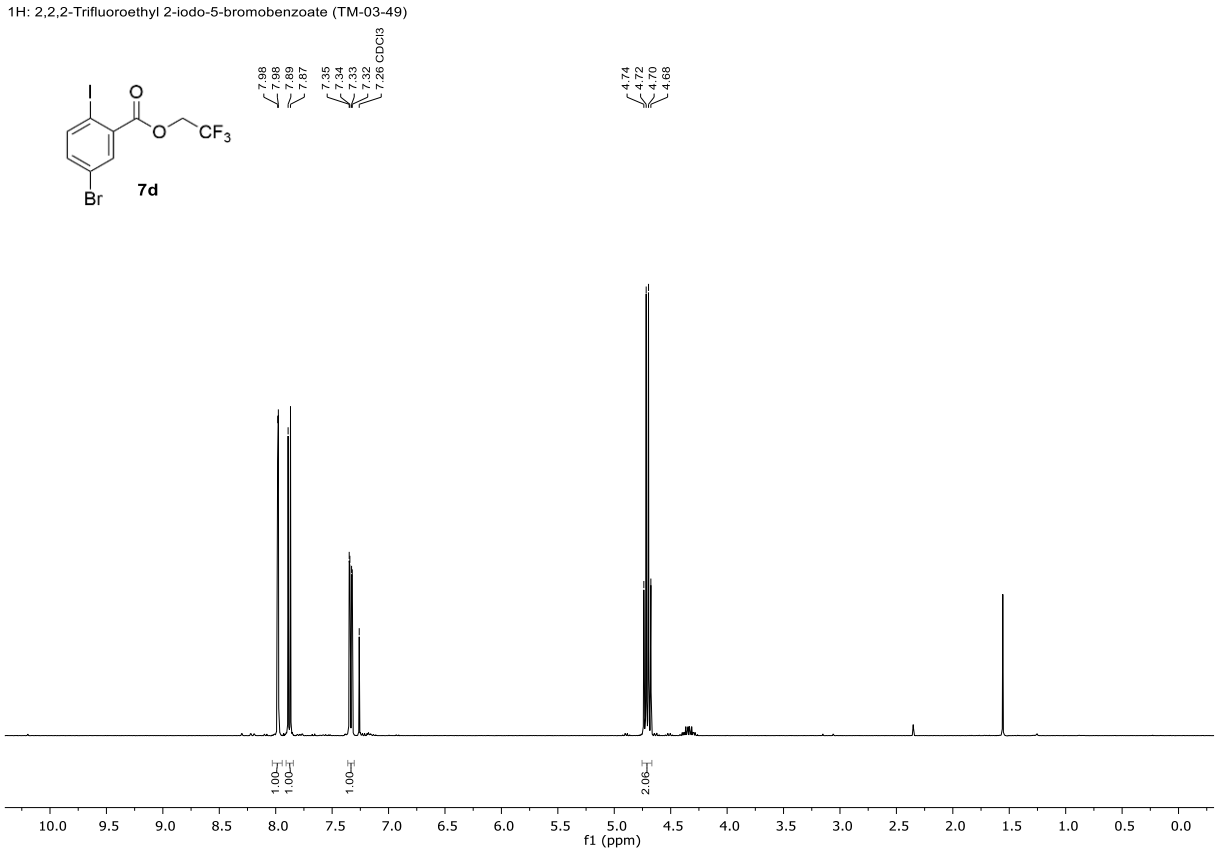
^{19}F-NMR (376 MHz, $CDCl_3$)

19F: 1,1,1,3,3,3-Hexafluoro-2-(2-iodo-5-methylphenyl)propan-2-ol (TM-03-32)

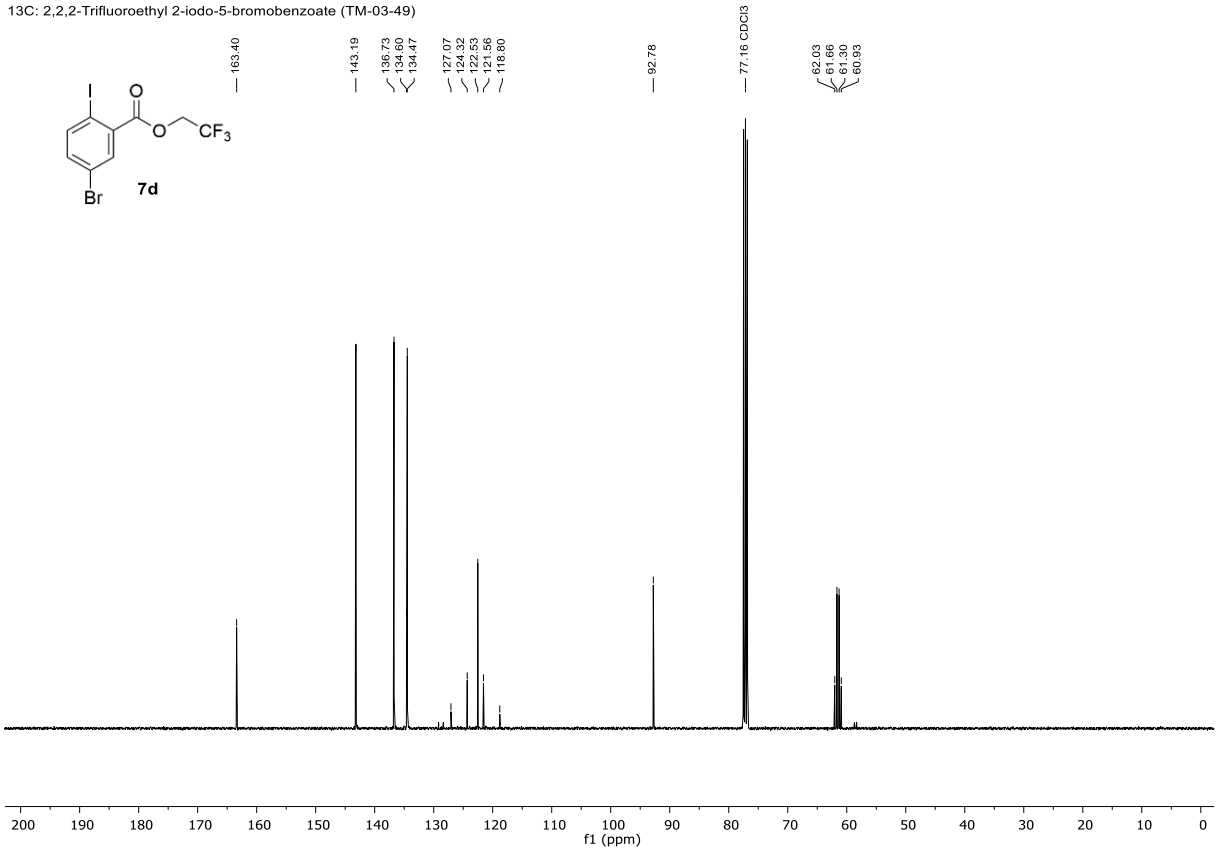


2,2,2-Trifluoroethyl 5-bromo-2-iodobenzoate (7d)

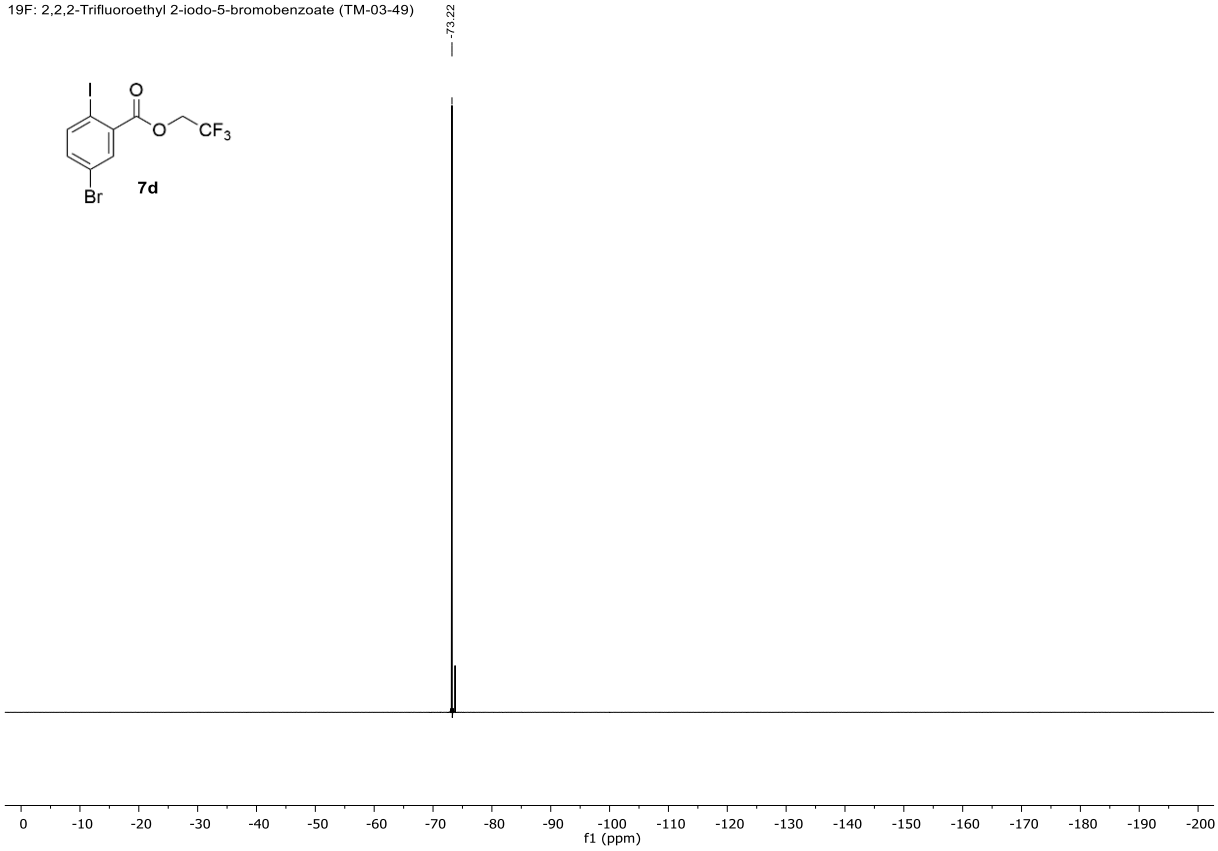
^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)

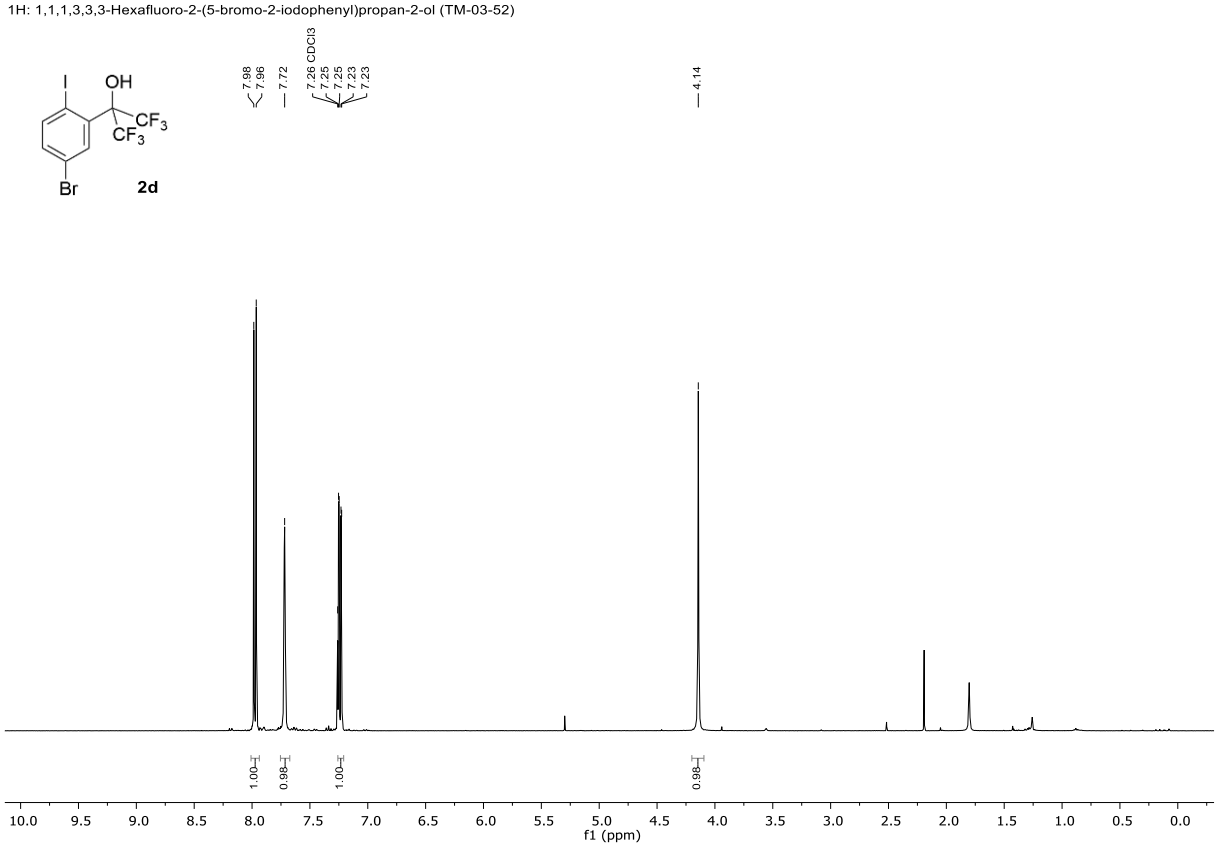


^{19}F-NMR (376 MHz, $CDCl_3$)

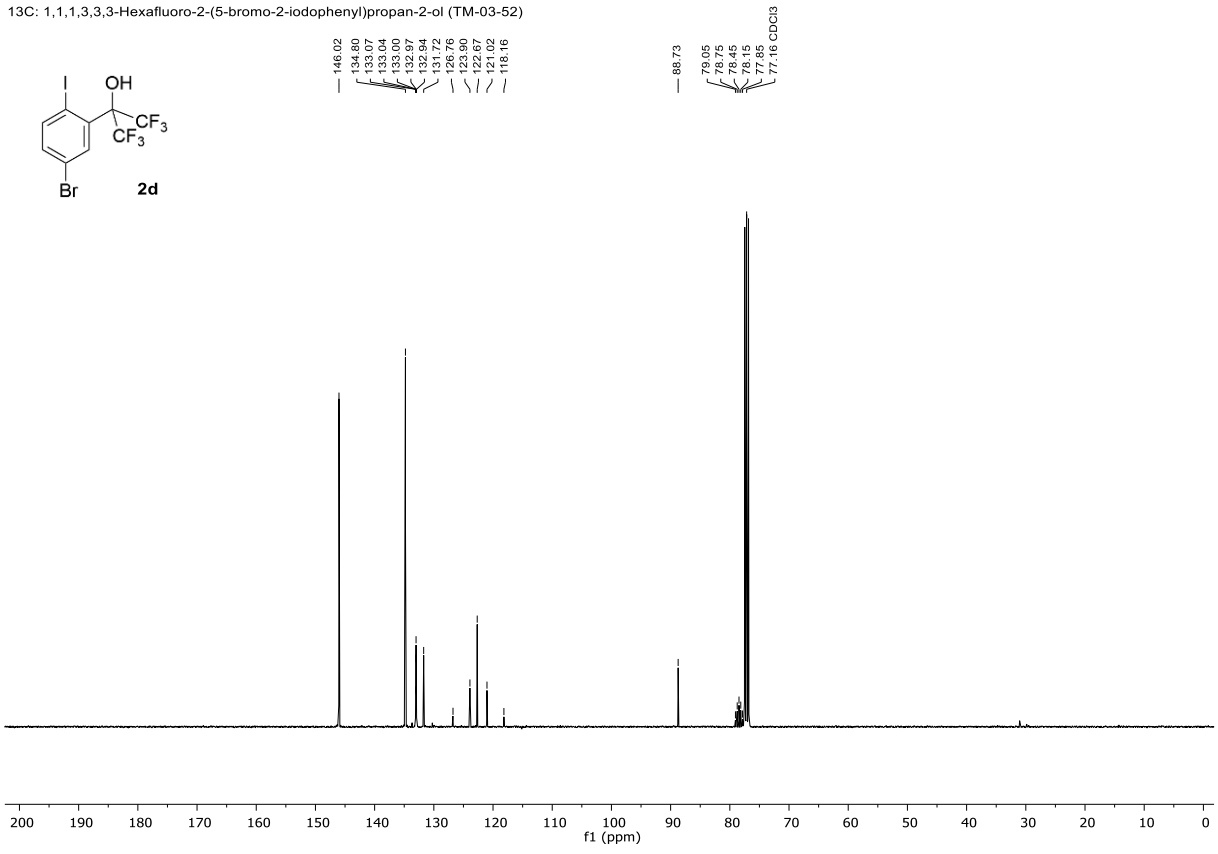


1,1,1,3,3,3-Hexafluoro-2-(5-bromo-2-iodophenyl)propan-2-ol (2d)

^{1}H-NMR (400 MHz, $CDCl_3$)

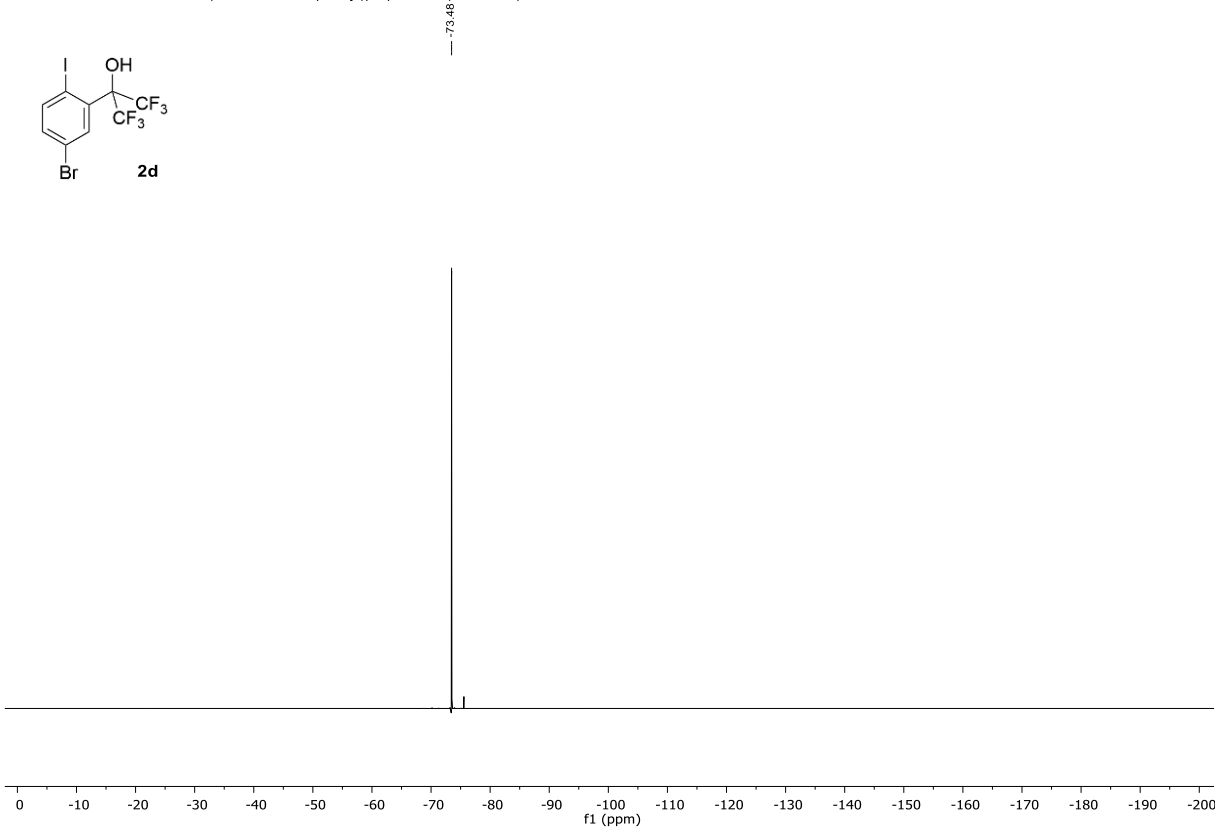


^{13}C-NMR (101 MHz, $CDCl_3$)



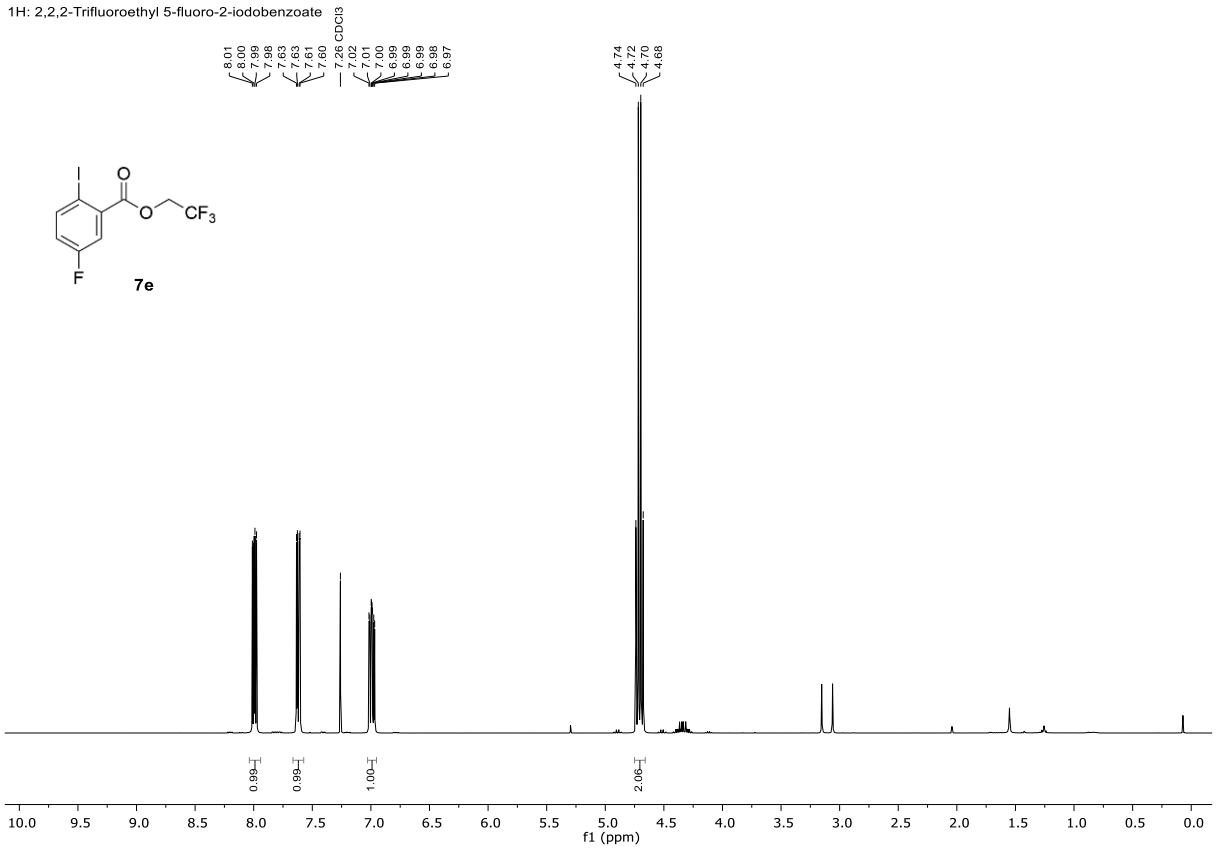
^{19}F-NMR (376 MHz, $CDCl_3$)

19F: 1,1,1,3,3,3-Hexafluoro-2-(5-bromo-2-iodophenyl)propan-2-ol (TM-03-52)

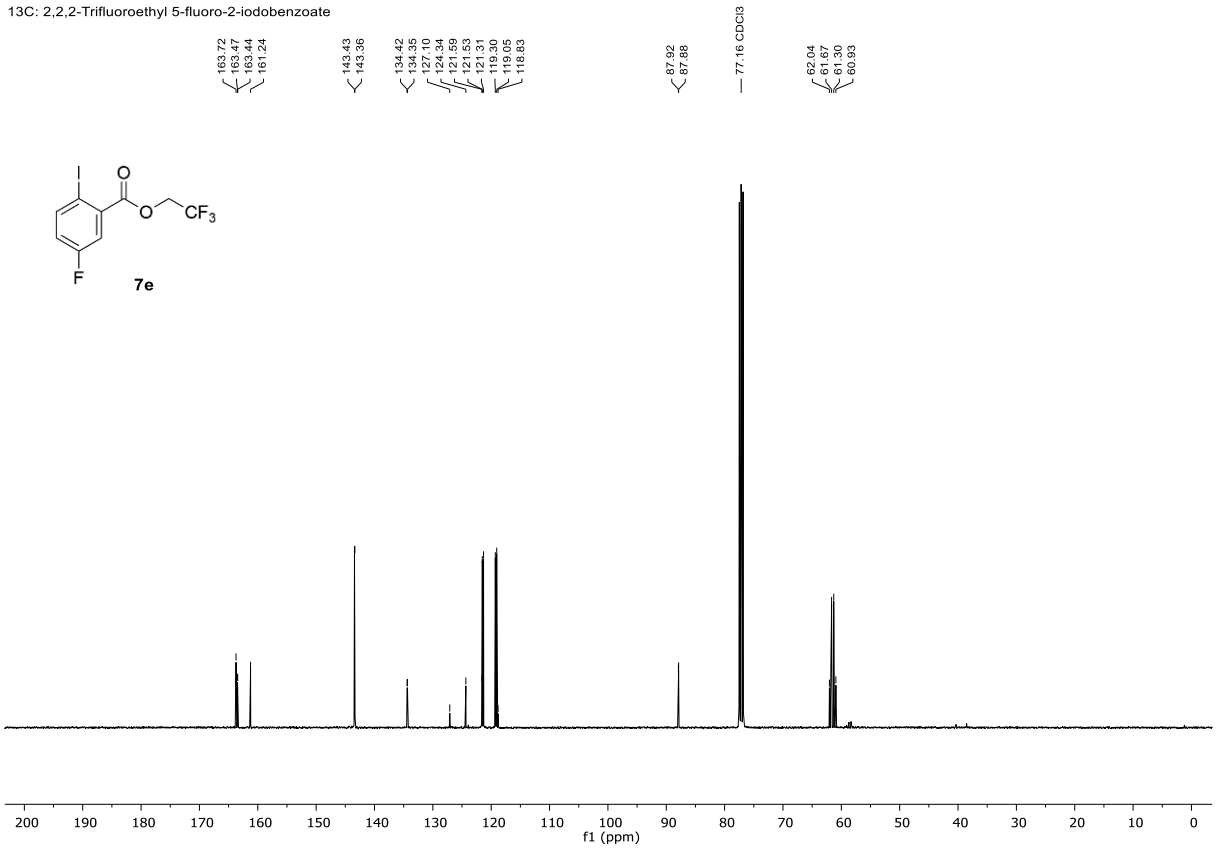


2,2,2-Trifluoroethyl 5-fluoro-2-iodobenzoate (7e)

^{1}H-NMR (400 MHz, $CDCl_3$)

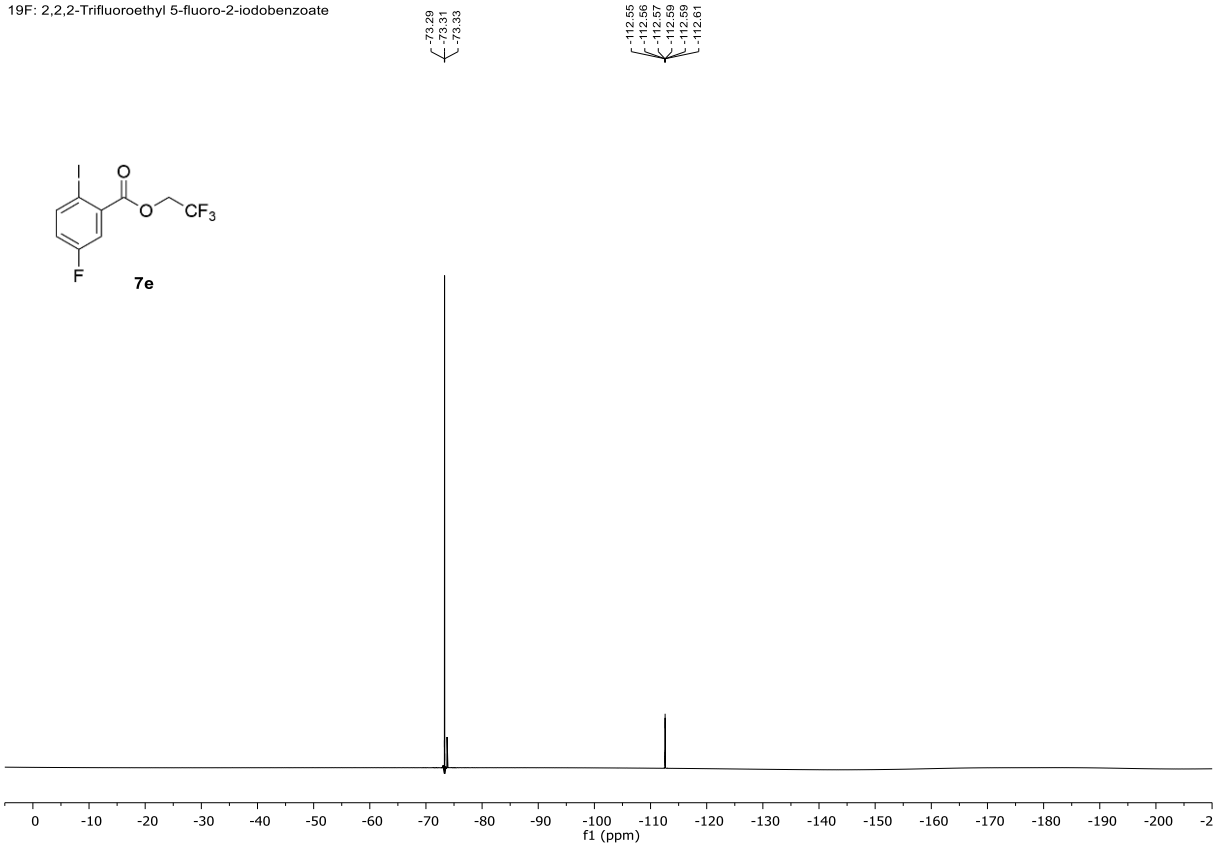


^{13}C-NMR (101 MHz, $CDCl_3$)



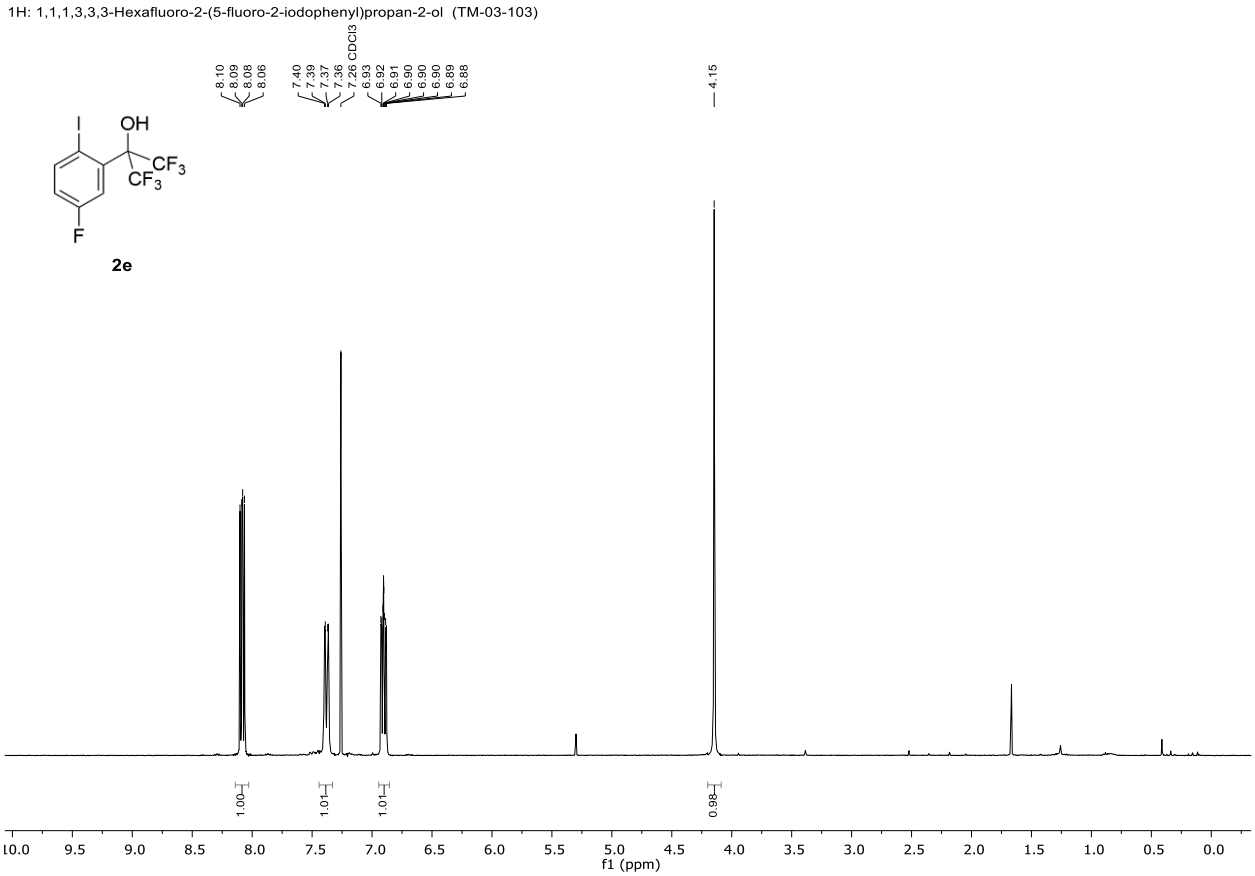
^{19}F-NMR (376 MHz, $CDCl_3$)

19F: 2,2,2-Trifluoroethyl 5-fluoro-2-iodobenzoate

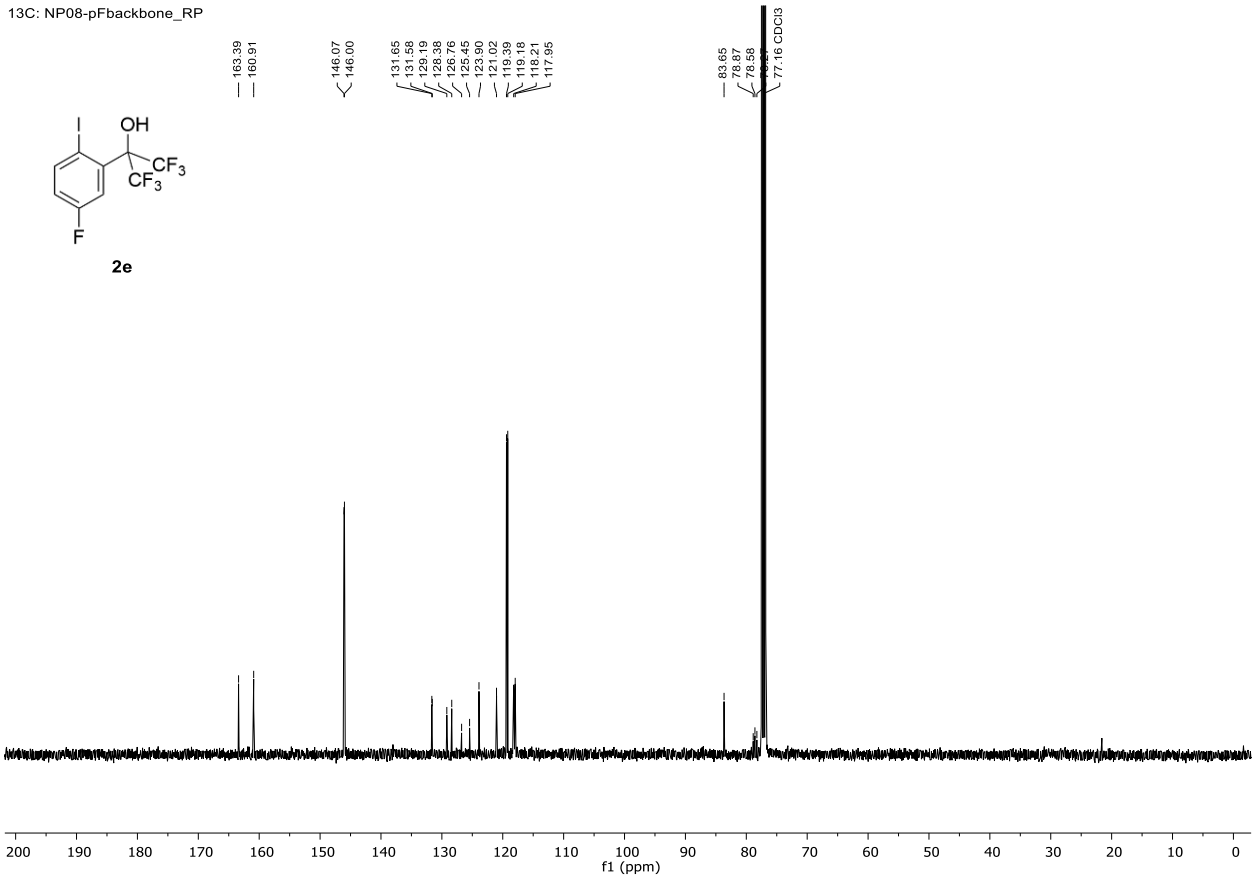


1,1,1,3,3,3-Hexafluoro-2-(5-fluoro-2-iodophenyl)propan-2-ol (2e)

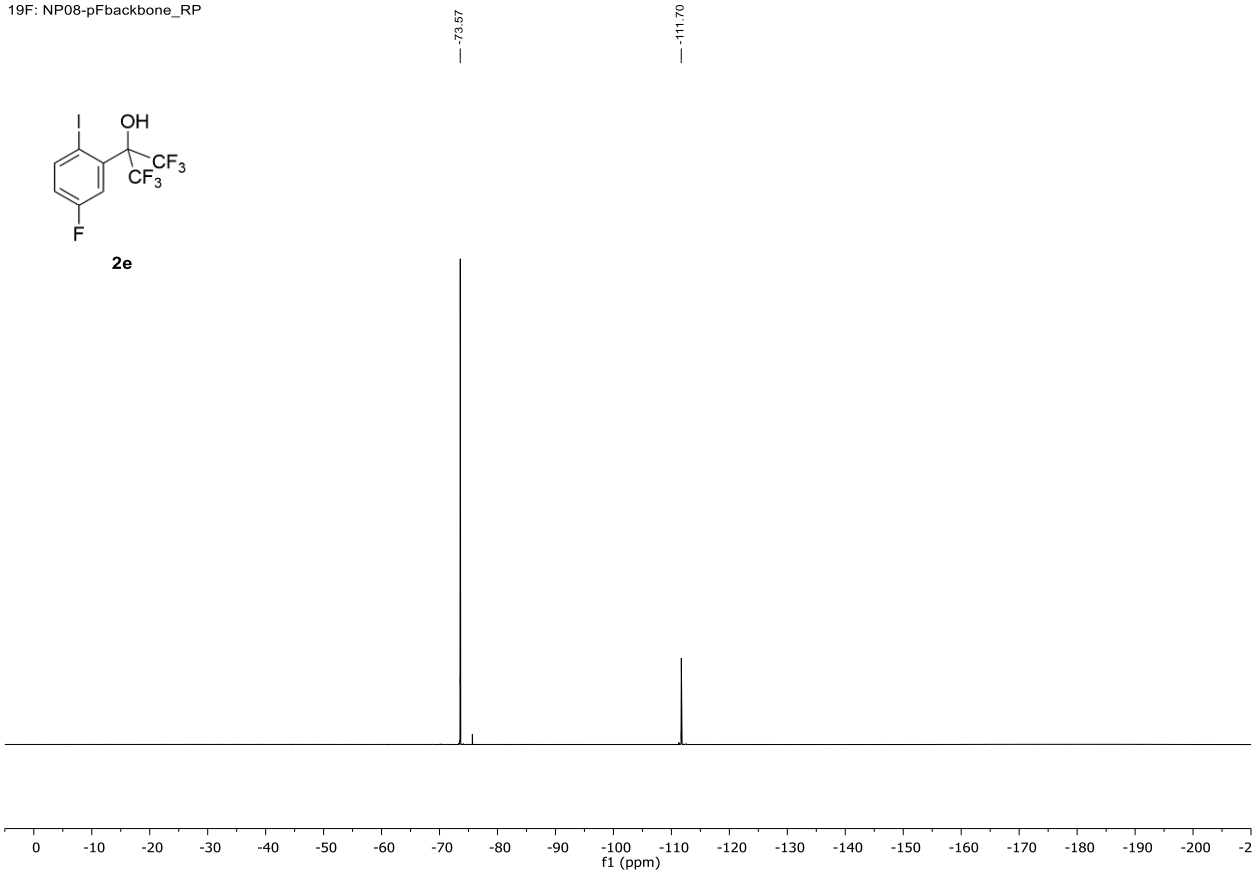
^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)

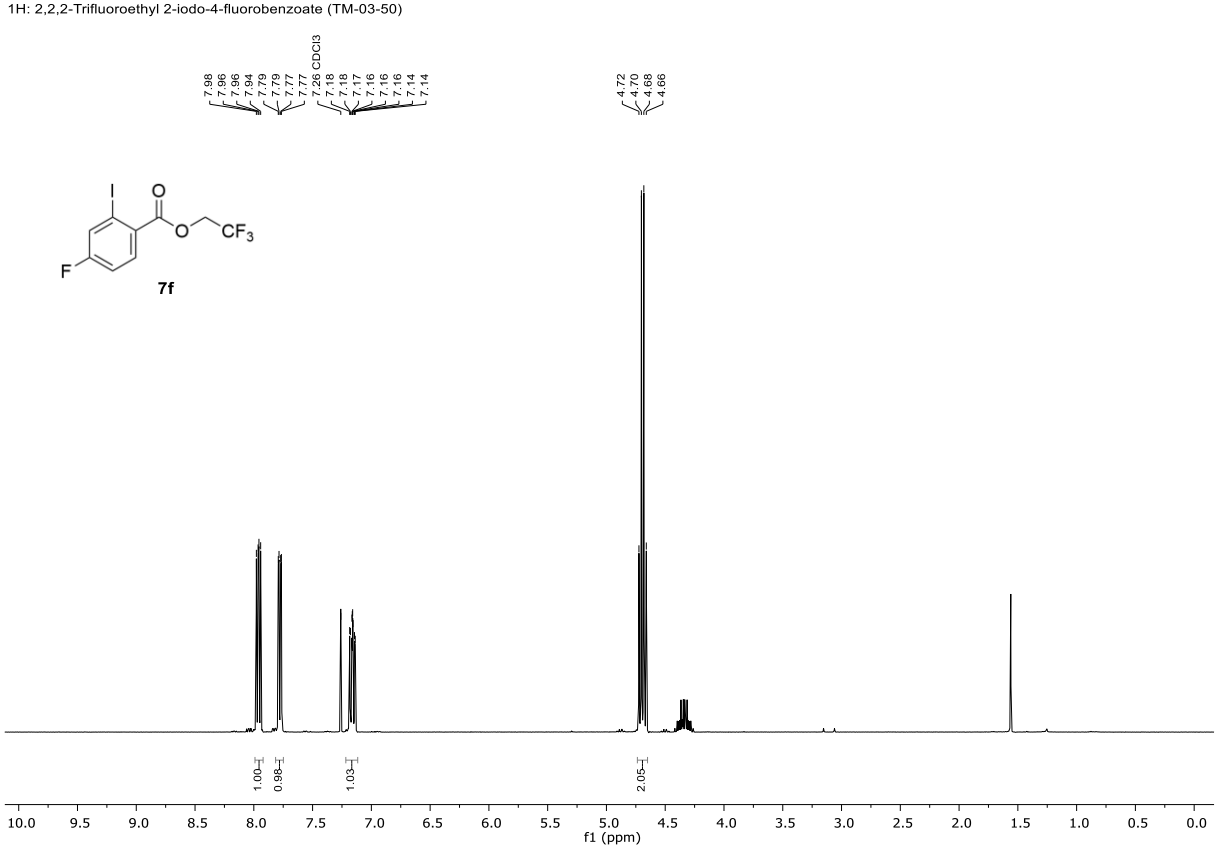


^{19}F-NMR (376 MHz, $CDCl_3$)

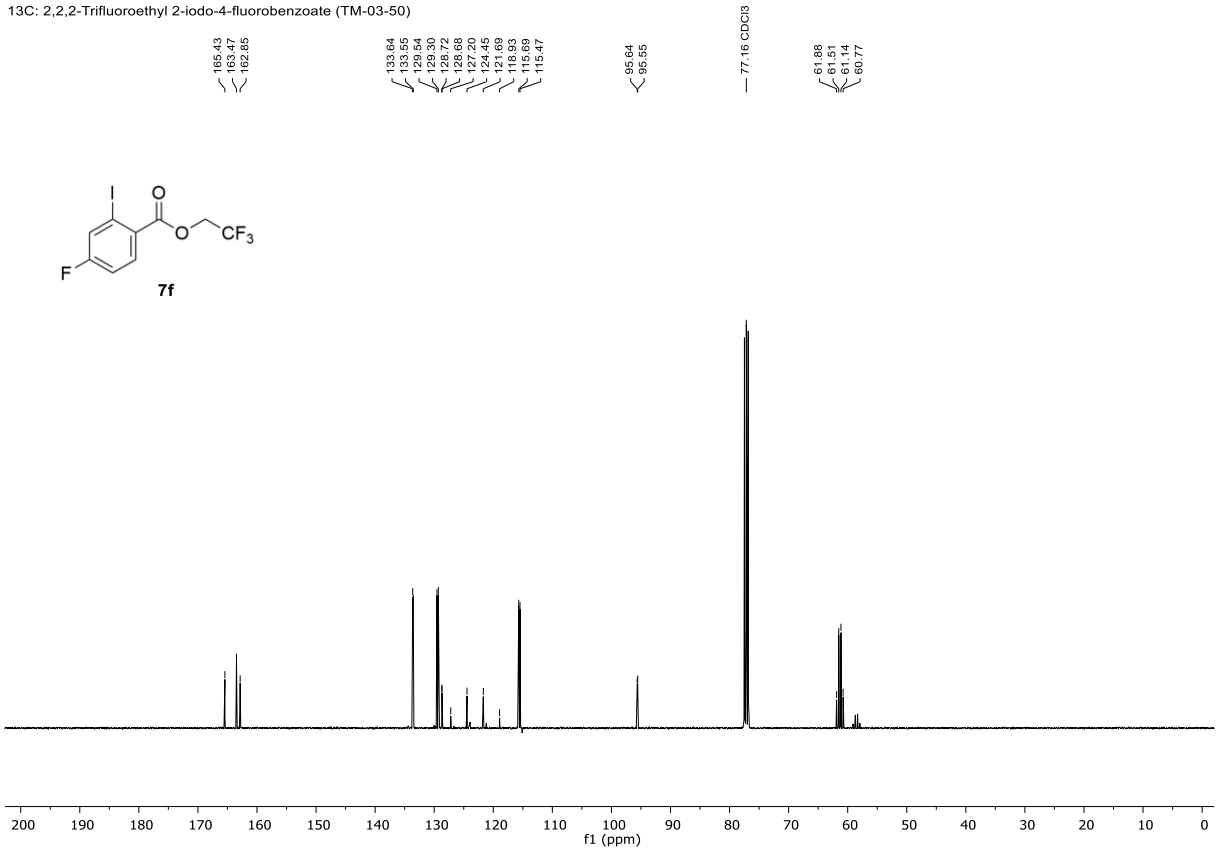


2,2,2-Trifluoroethyl 4-fluoro-2-iodobenzoate (7f)

^{1}H-NMR (400 MHz, $CDCl_3$)

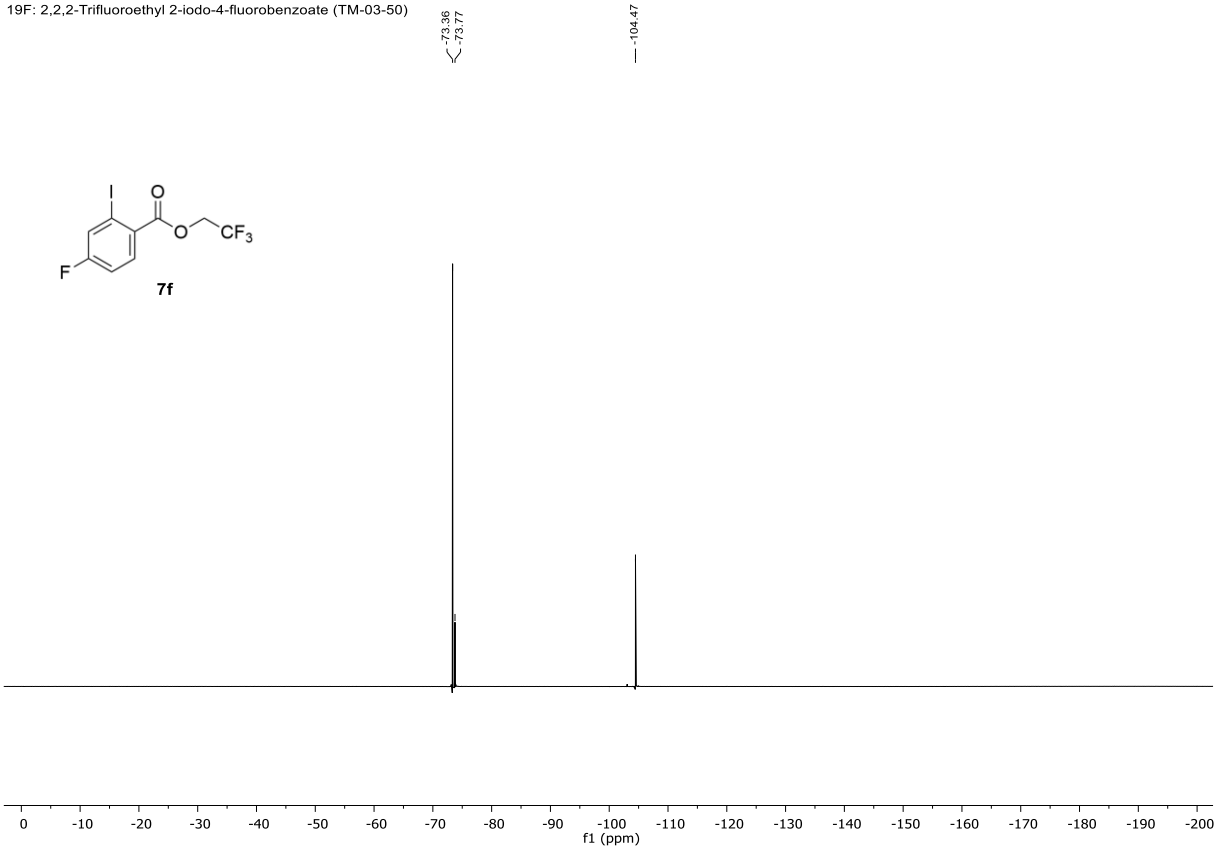


^{13}C-NMR (101 MHz, $CDCl_3$)



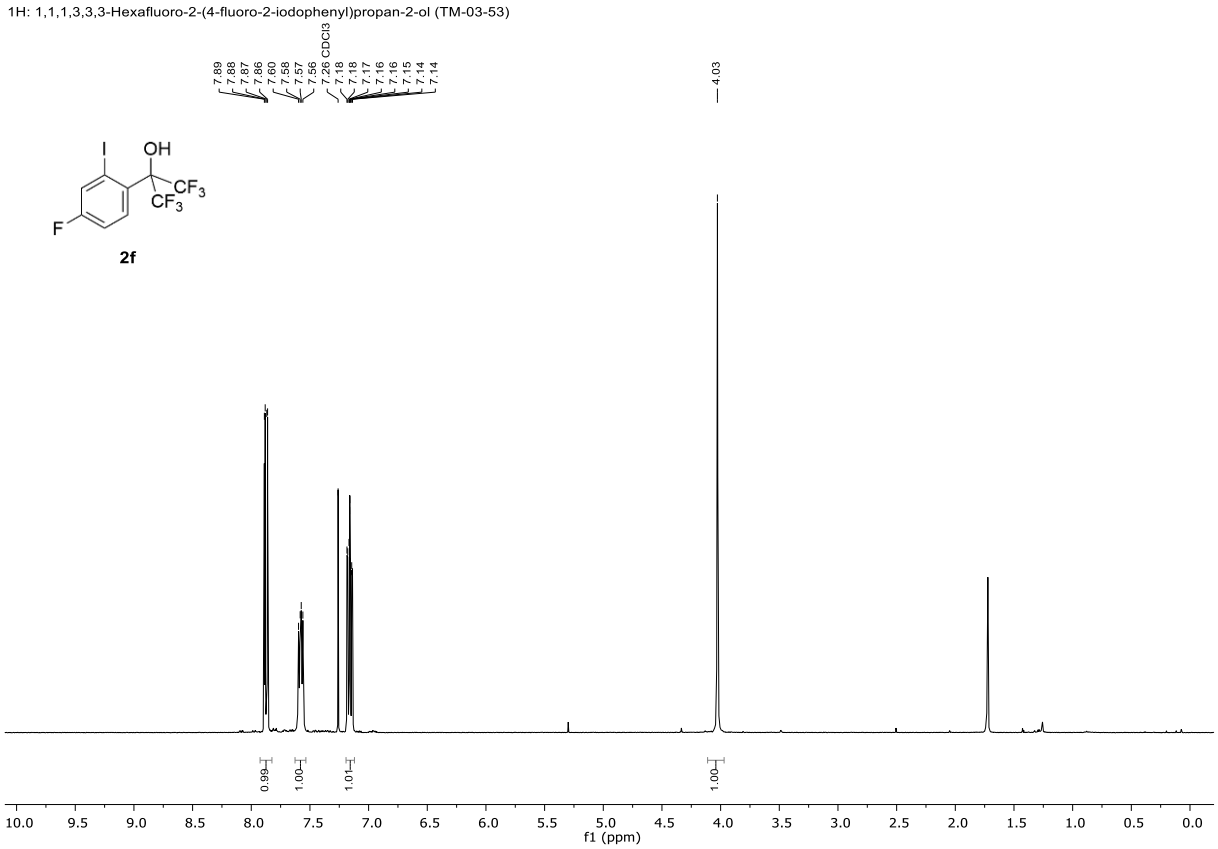
^{19}F-NMR (376 MHz, $CDCl_3$)

19F: 2,2,2-Trifluoroethyl 2-iodo-4-fluorobenzoate (TM-03-50)

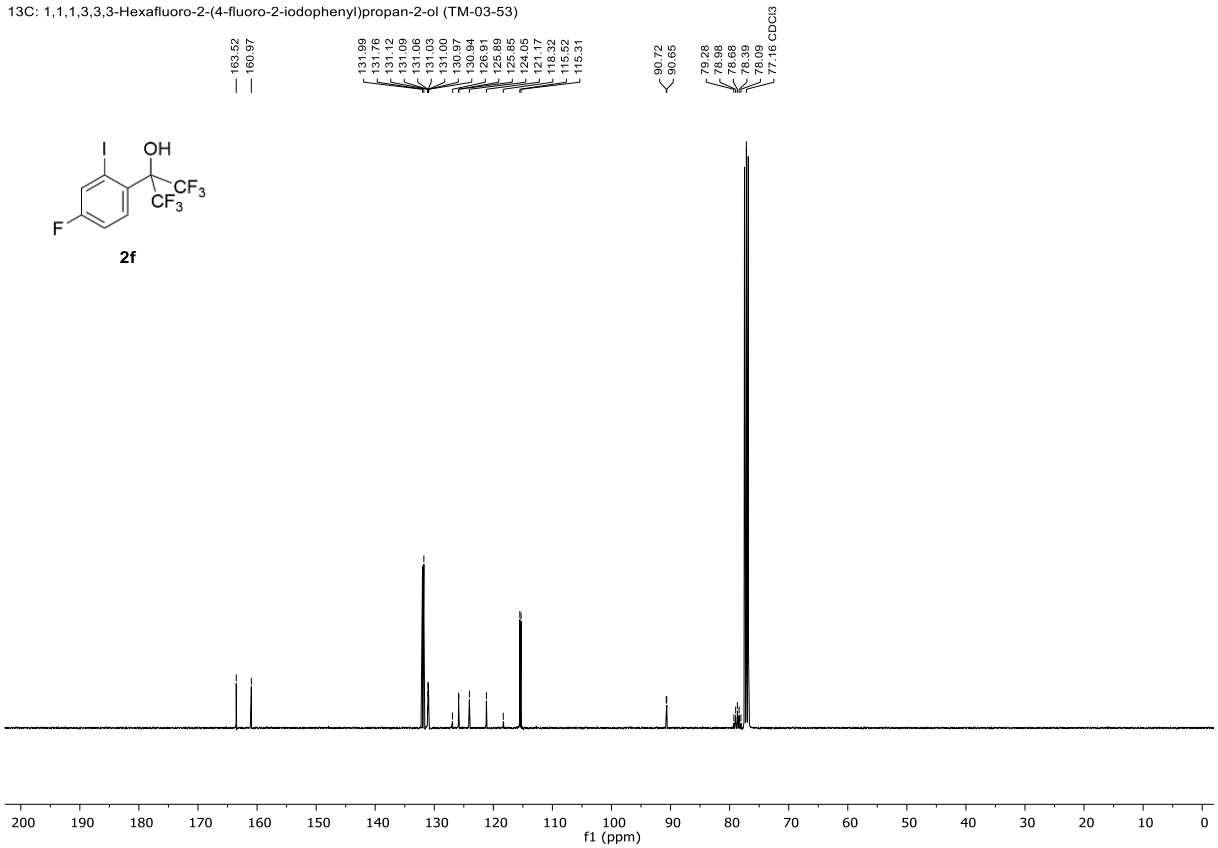


1,1,1,3,3,3-Hexafluoro-2-(4-fluoro-2-iodophenyl)propan-2-ol (2f)

^{1}H-NMR (400 MHz, $CDCl_3$)

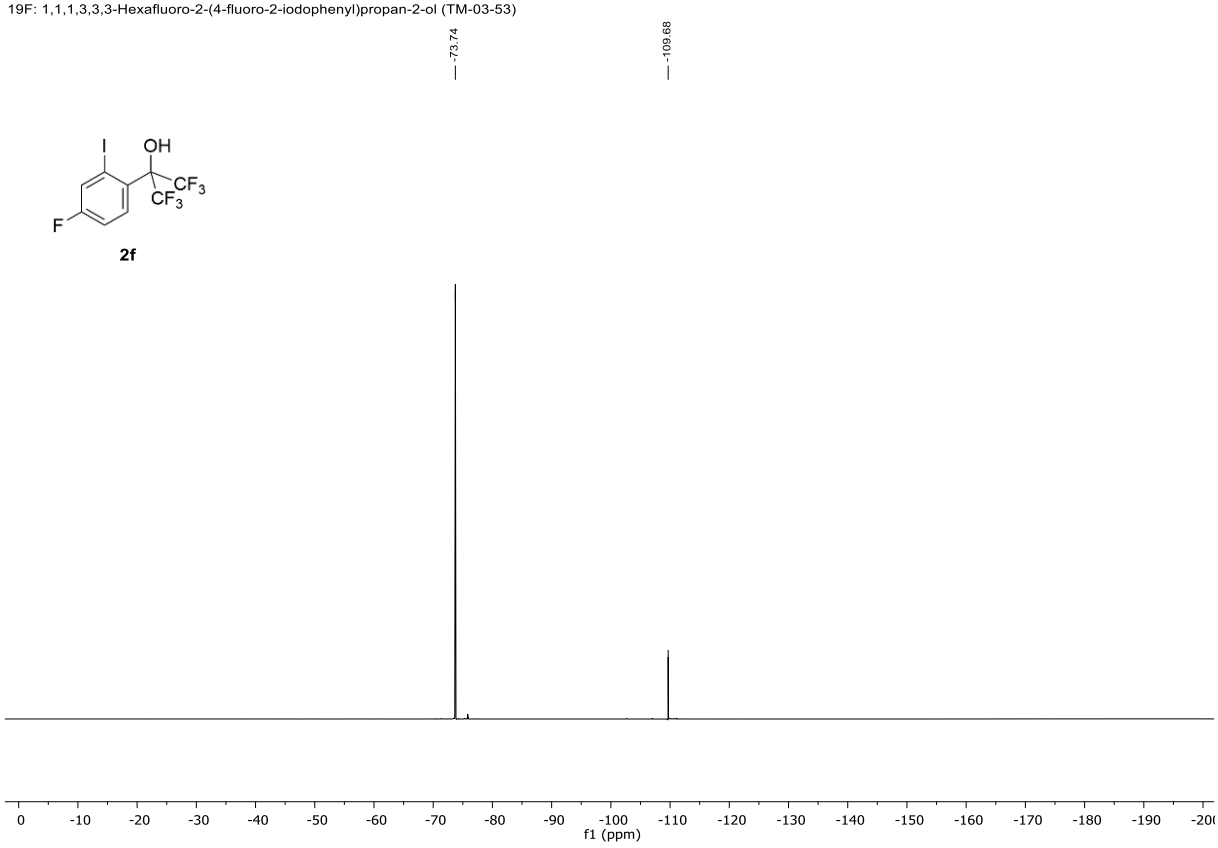


^{13}C-NMR (101 MHz, $CDCl_3$)



^{19}F-NMR (376 MHz, $CDCl_3$)

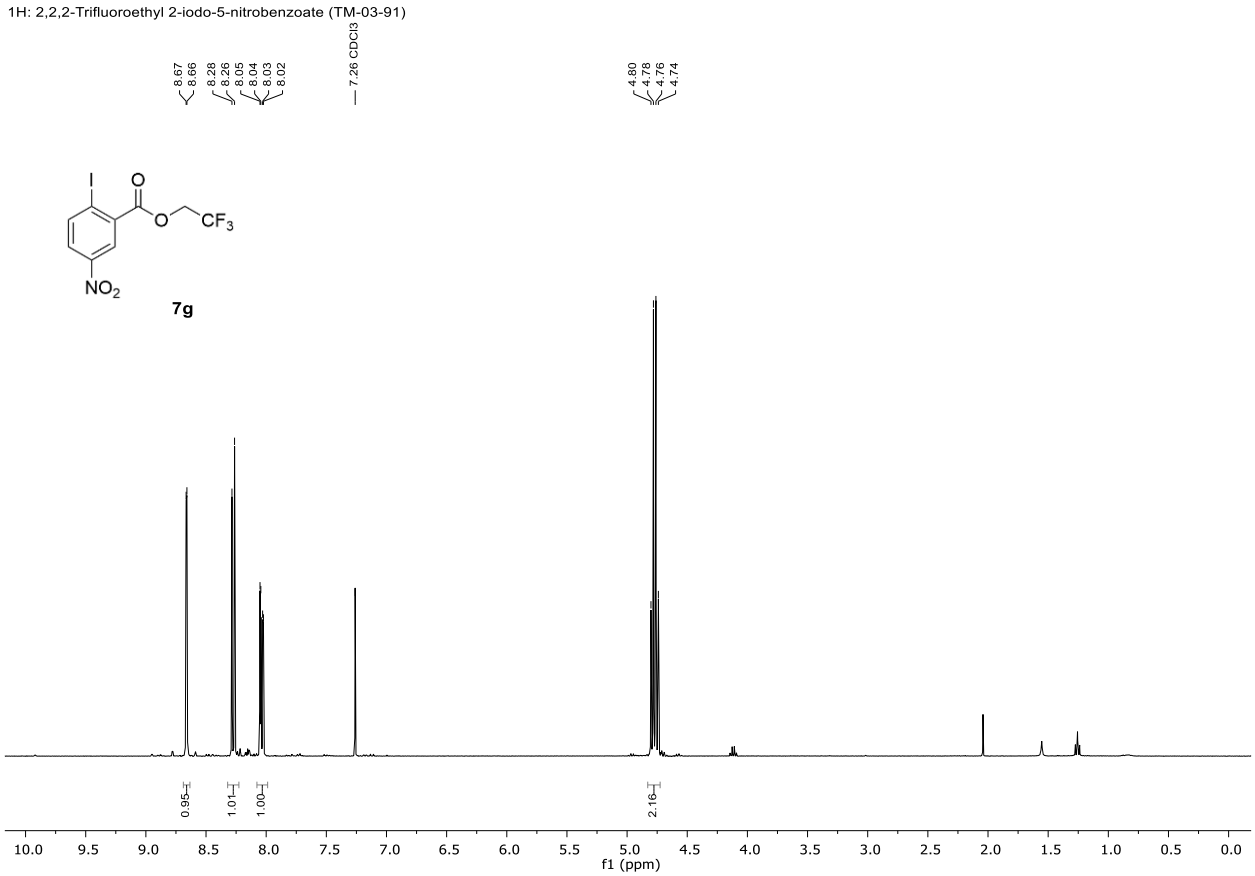
19F: 1,1,1,3,3,3-Hexafluoro-2-(4-fluoro-2-iodophenyl)propan-2-ol (TM-03-53)



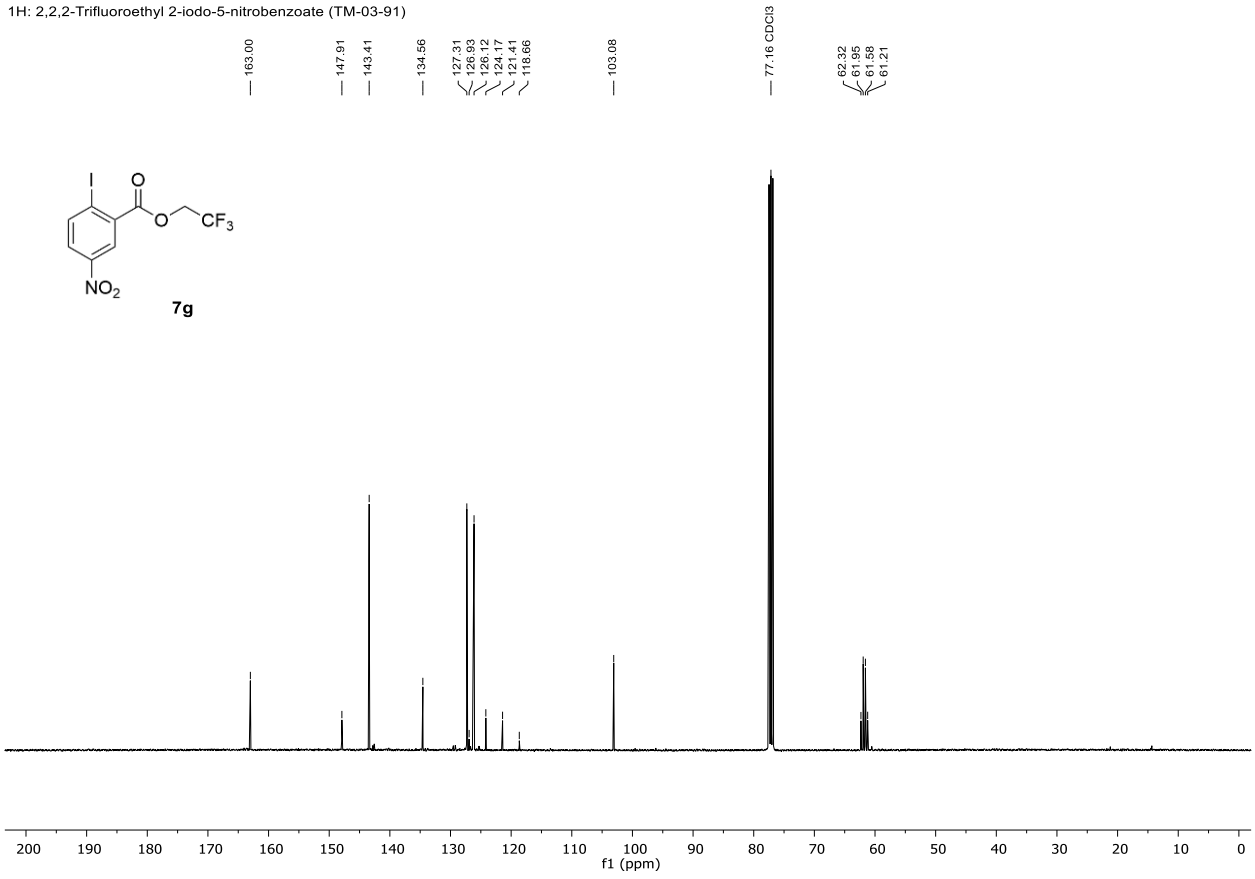
2f

2,2,2-Trifluoroethyl 2-iodo-5-nitrobenzoate (7g)

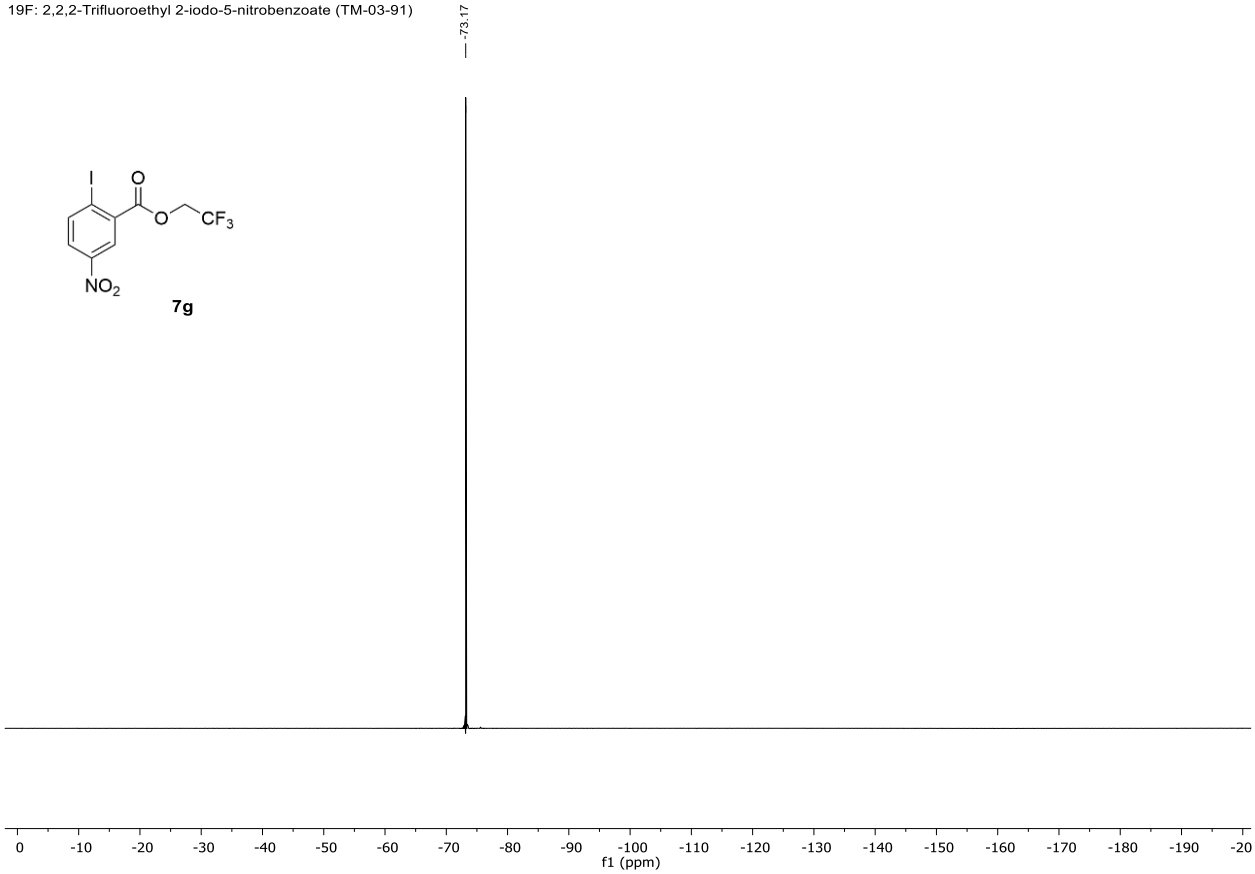
^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)

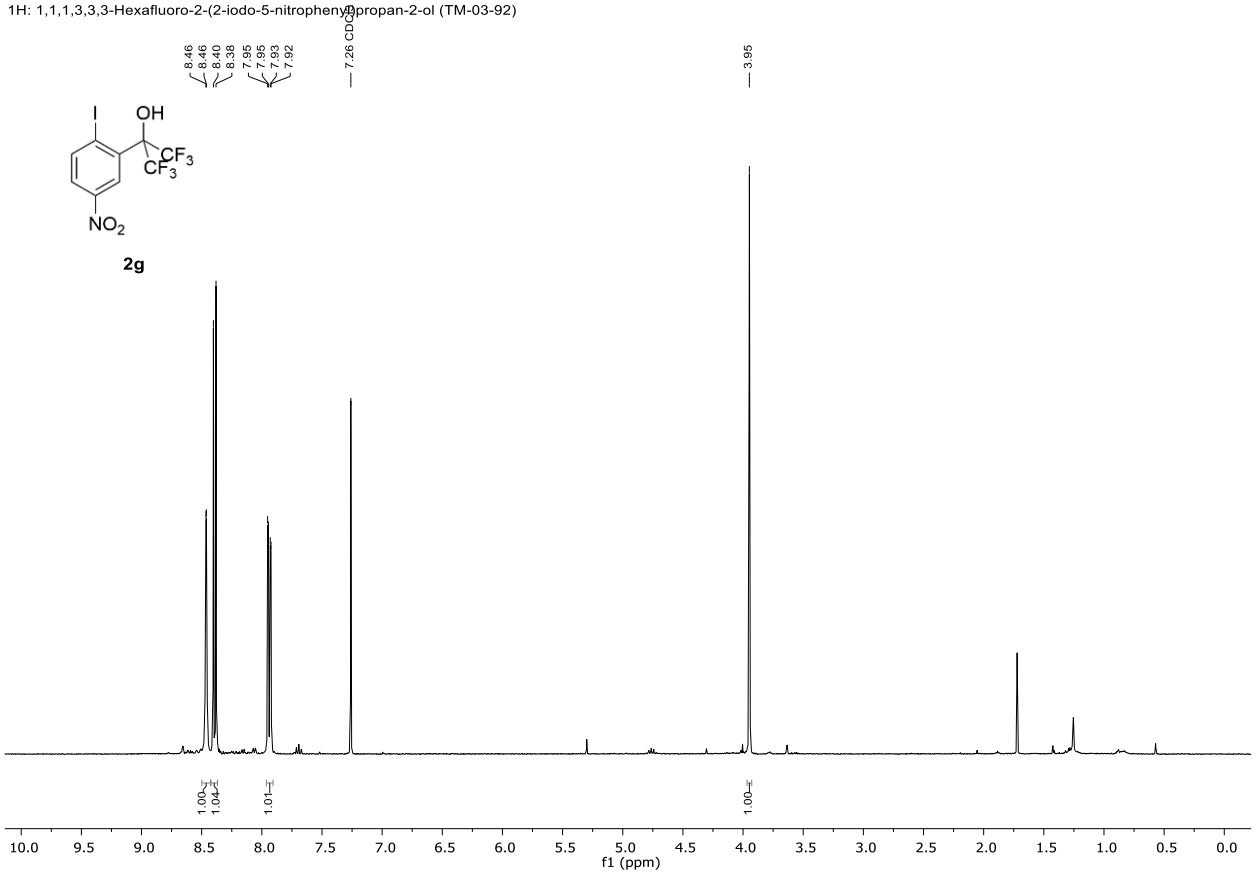


^{19}F-NMR (376 MHz, $CDCl_3$)

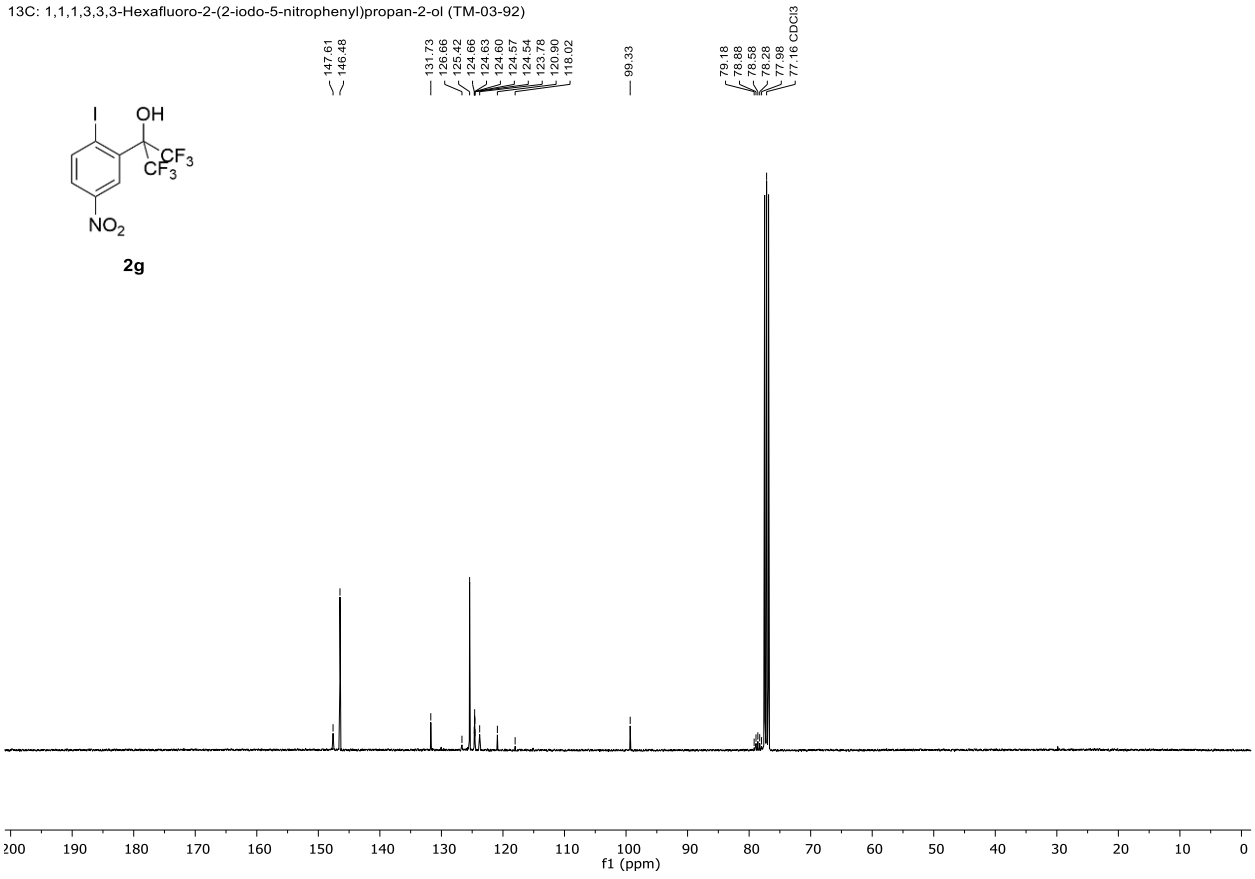


1,1,1,3,3,3-Hexafluoro-2-(2-iodo-5-nitrophenyl)propan-2-ol (2g)

^{1}H-NMR (400 MHz, $CDCl_3$)

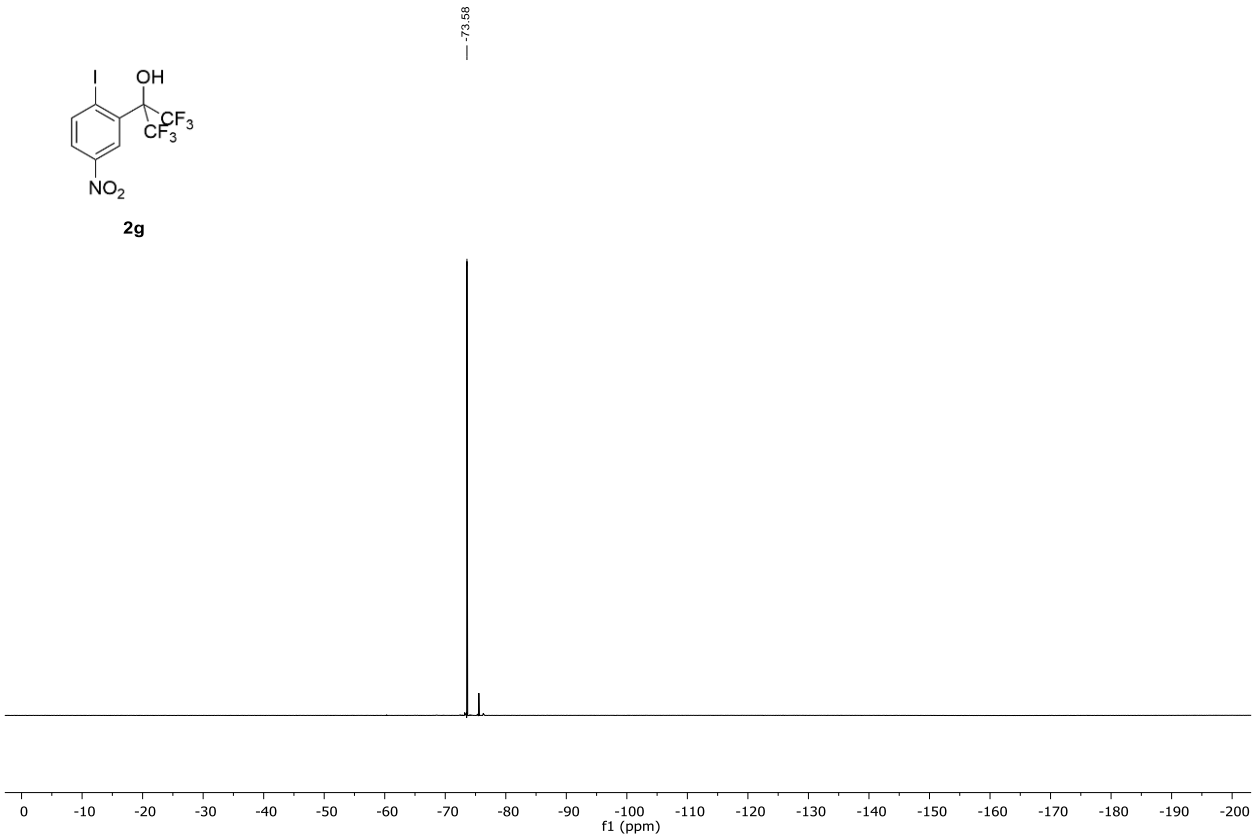


^{13}C-NMR (101 MHz, $CDCl_3$)



^{19}F-NMR (376 MHz, $CDCl_3$)

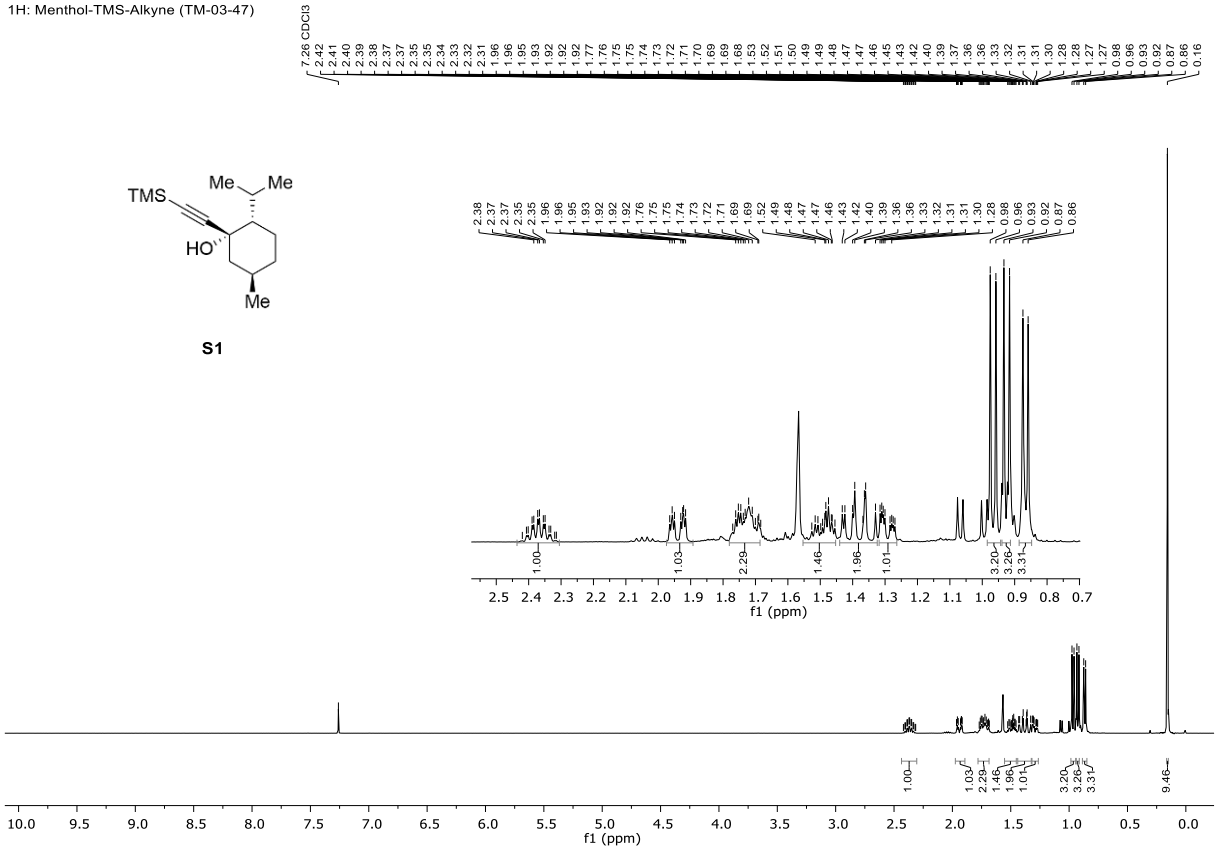
19F: 1,1,1,3,3,3-Hexafluoro-2-(2-iodo-5-nitrophenyl)propan-2-ol (TM-03-92)



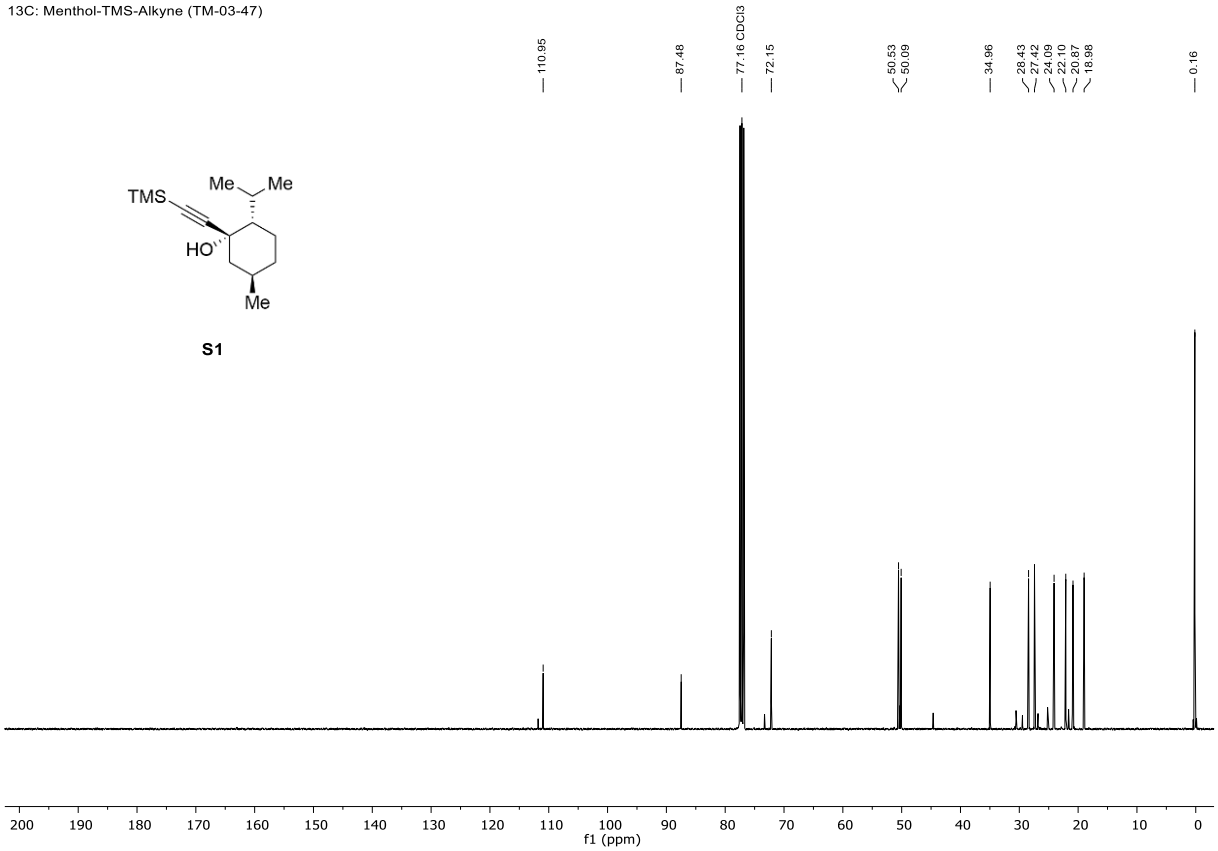
2g

(1*S*,2*S*,5*R*)-2-Isopropyl-5-methyl-1-((trimethylsilyl)ethynyl)cyclohexan-1-ol (S1)

^{1}H-NMR (400 MHz, $CDCl_3$)

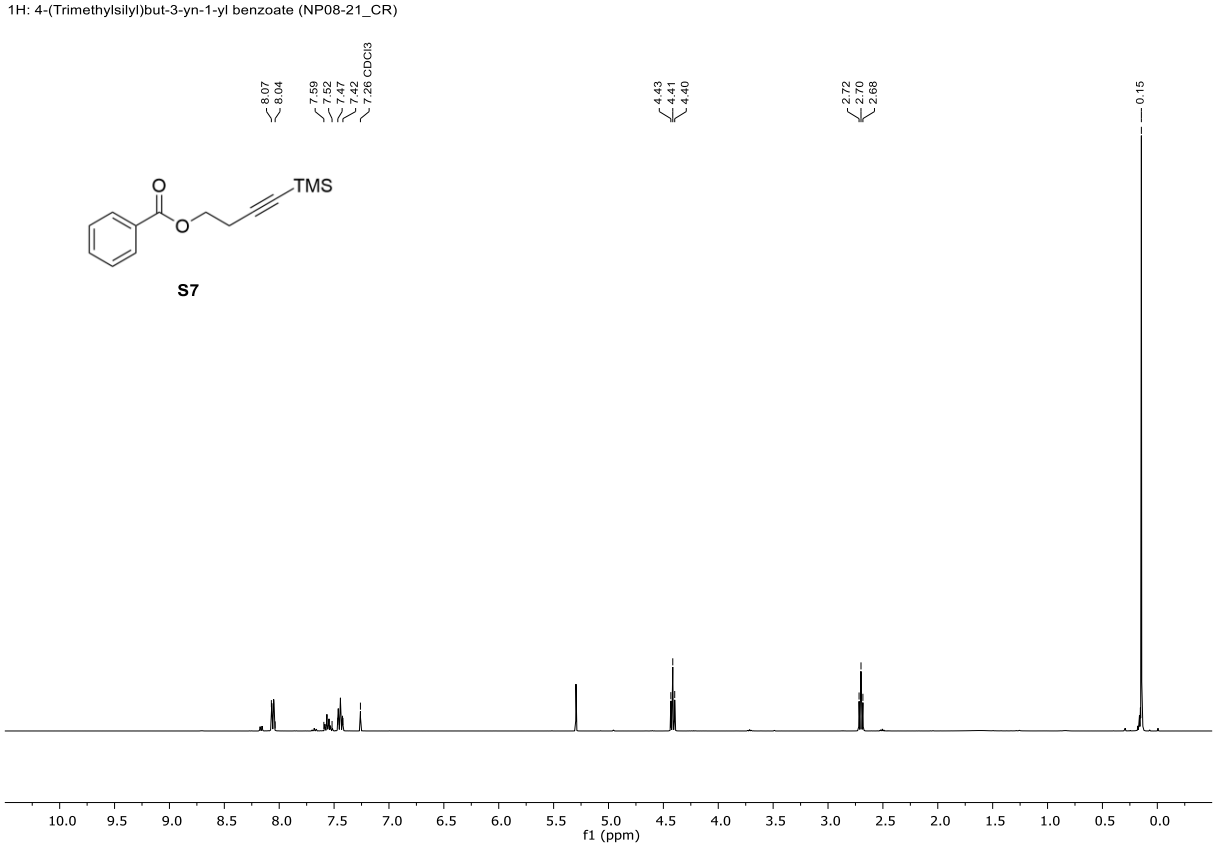


^{13}C-NMR (101 MHz, $CDCl_3$)

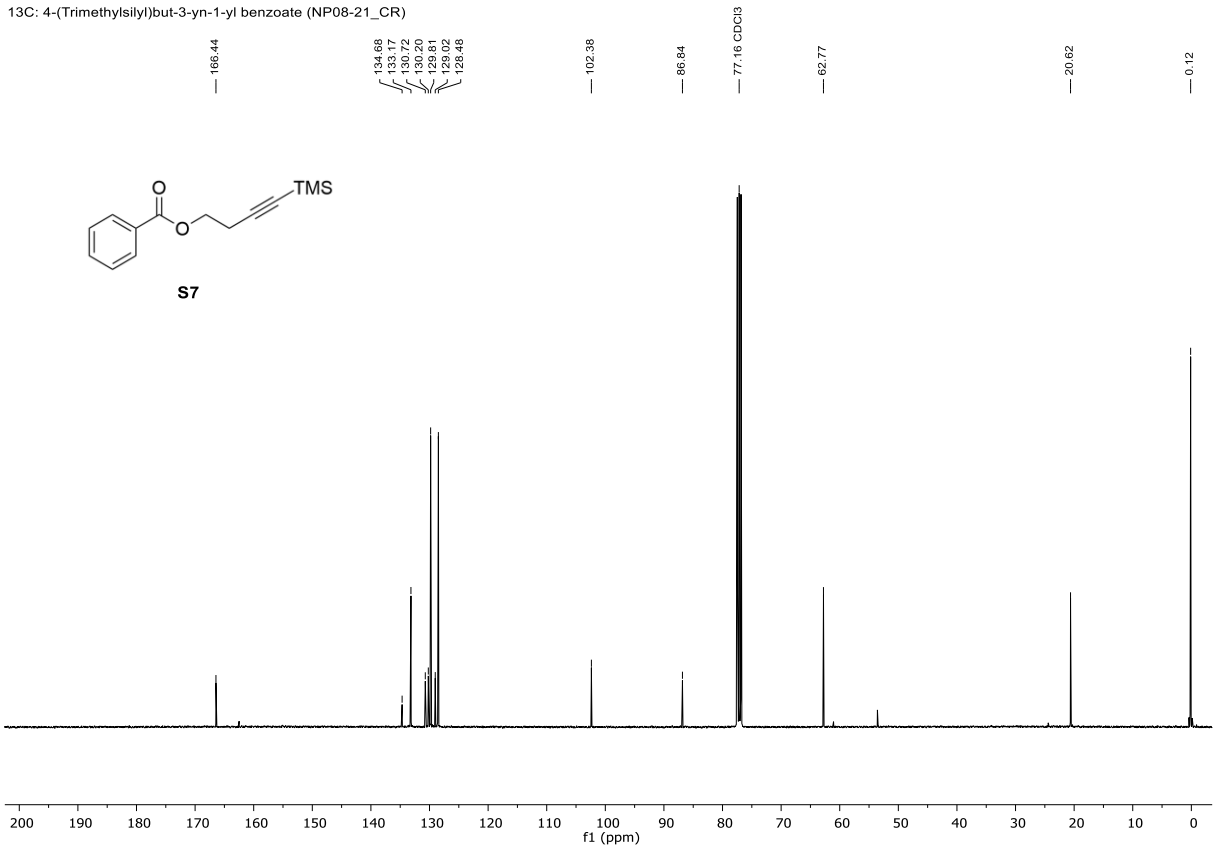


4-(Trimethylsilyl)but-3-yn-1-yl benzoate (S7)

^{1}H-NMR (400 MHz, $CDCl_3$)

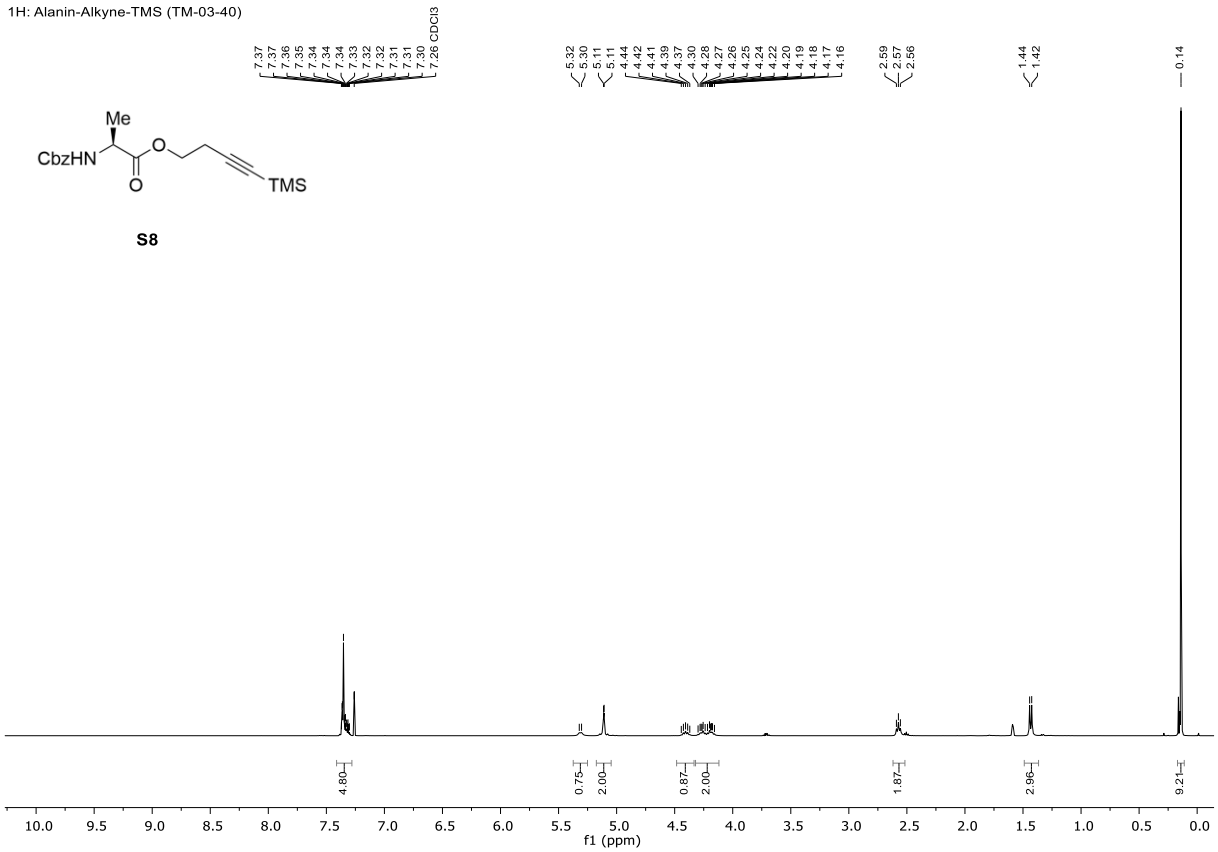


^{13}C-NMR (101 MHz, $CDCl_3$)

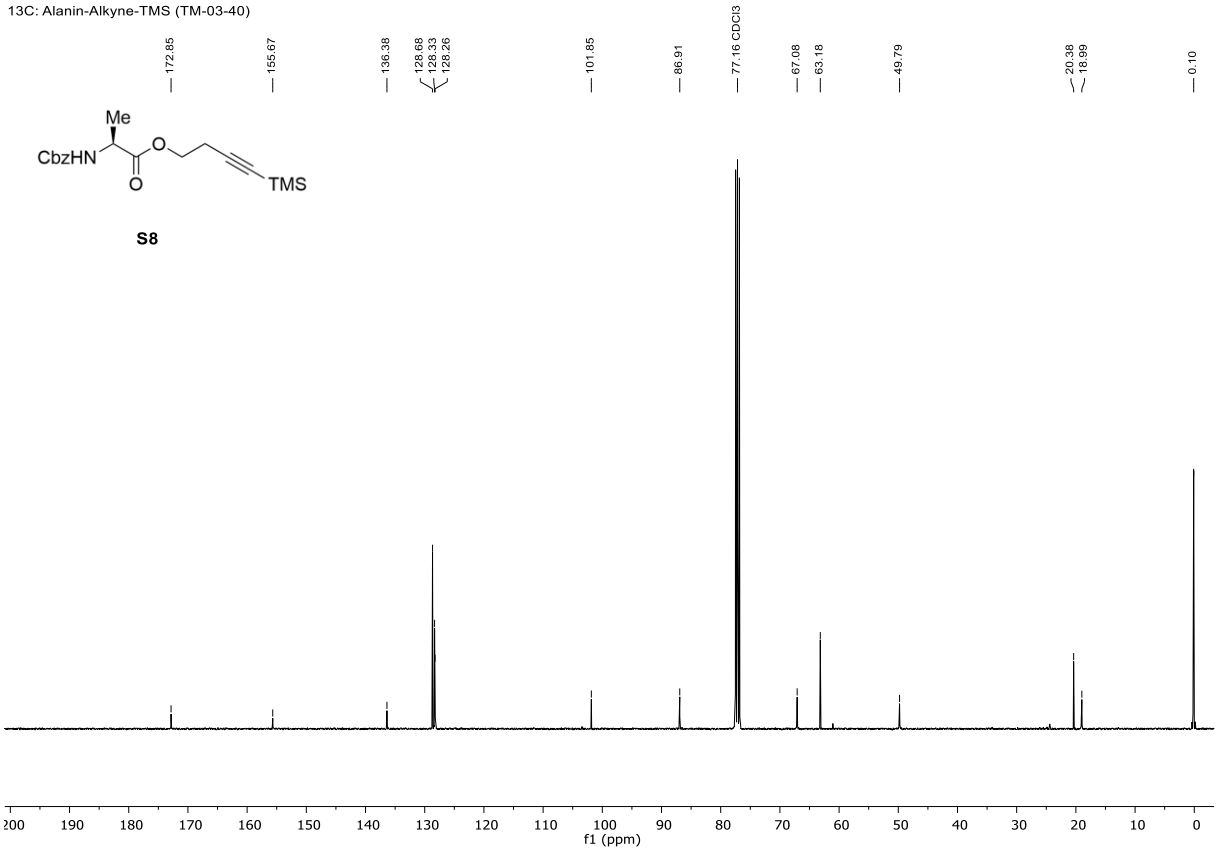


4-(Trimethylsilyl)but-3-yn-1-yl ((benzyloxy)carbonyl)-L-alaninate (S8)

^{1}H-NMR (400 MHz, $CDCl_3$)

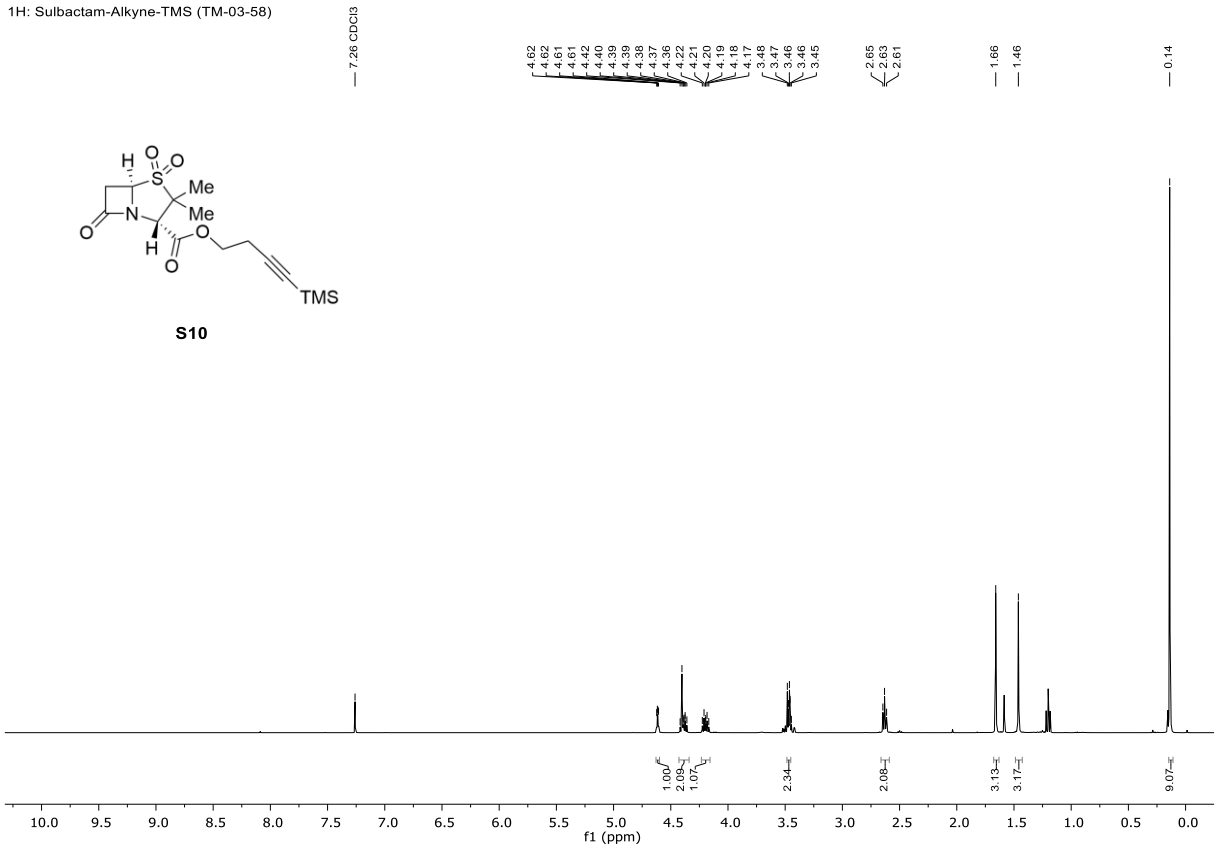


^{13}C-NMR (101 MHz, $CDCl_3$)

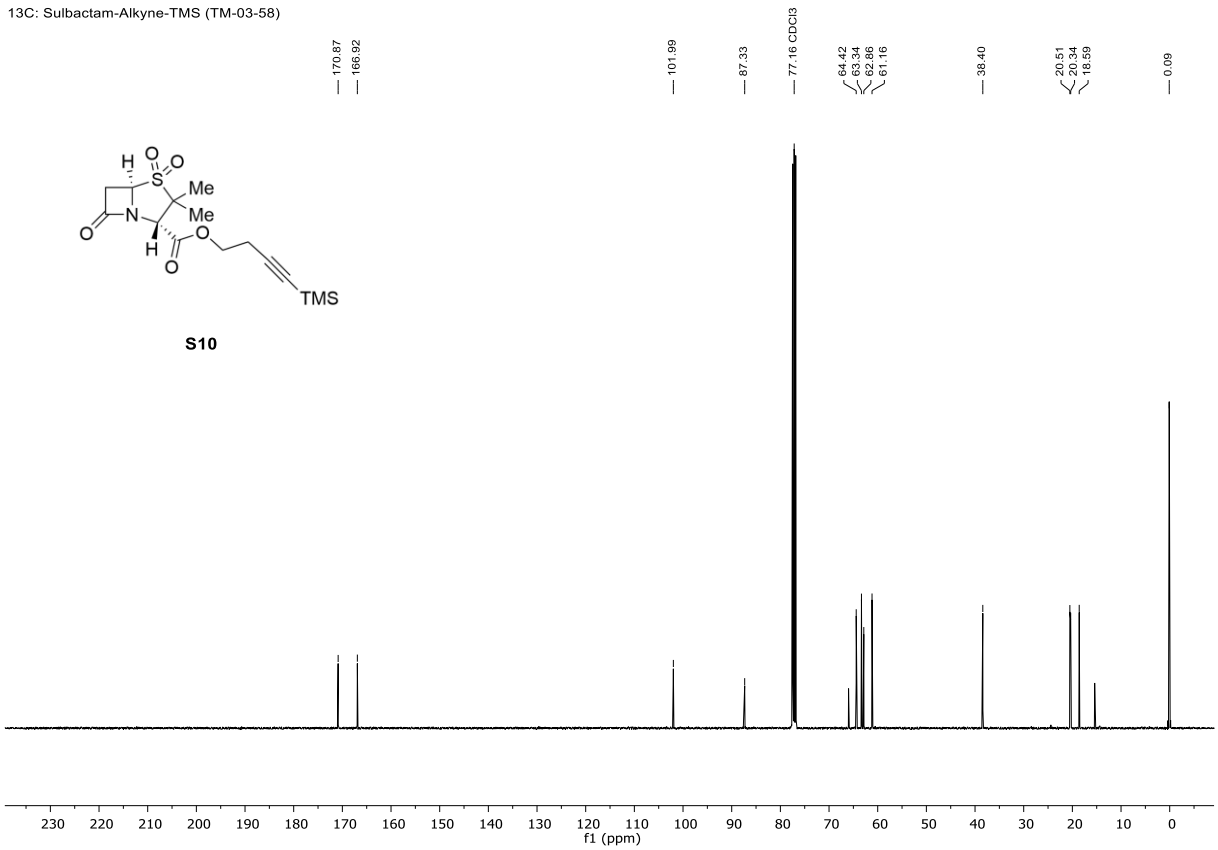


4-(Trimethylsilyl)but-3-yn-1-yl (2*S*,5*R*)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate 4,4-dioxide (S10)

^{1}H-NMR (400 MHz, $CDCl_3$)

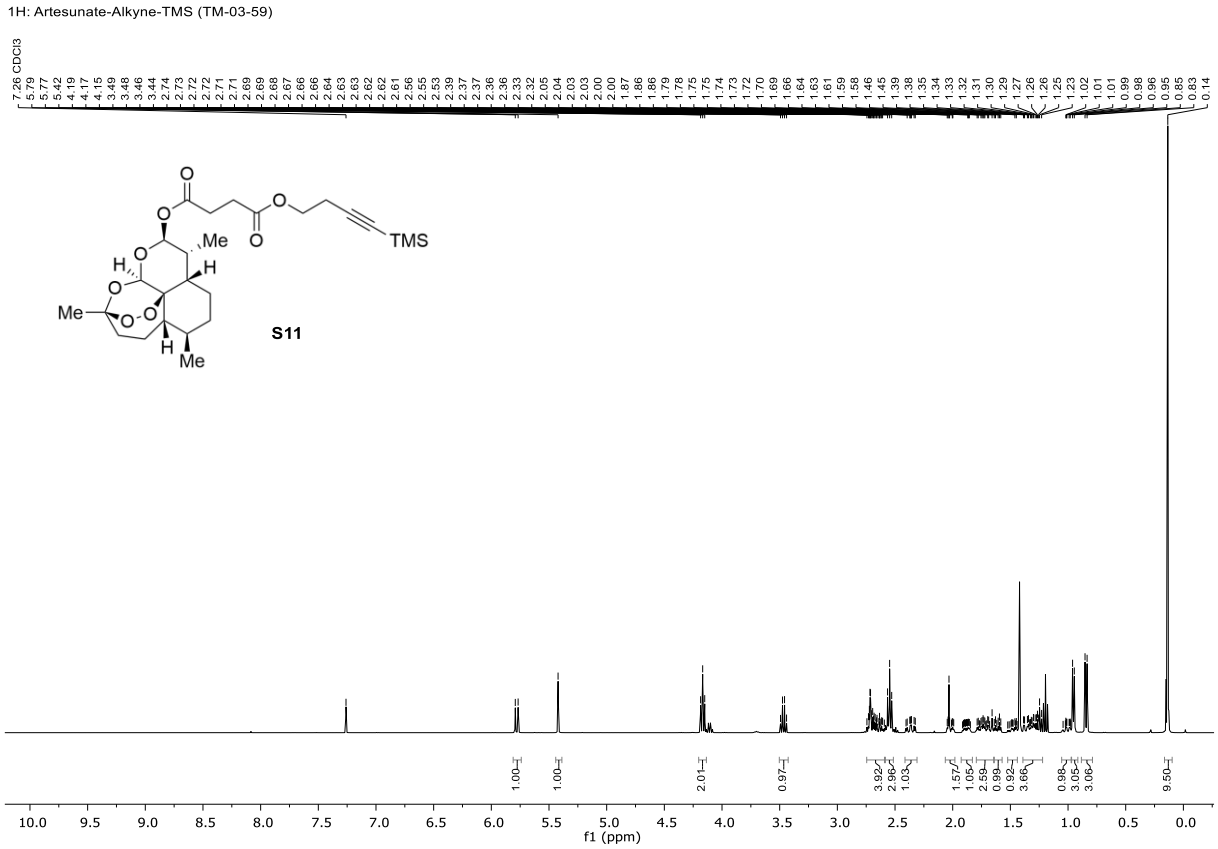


^{13}C-NMR (101 MHz, $CDCl_3$)

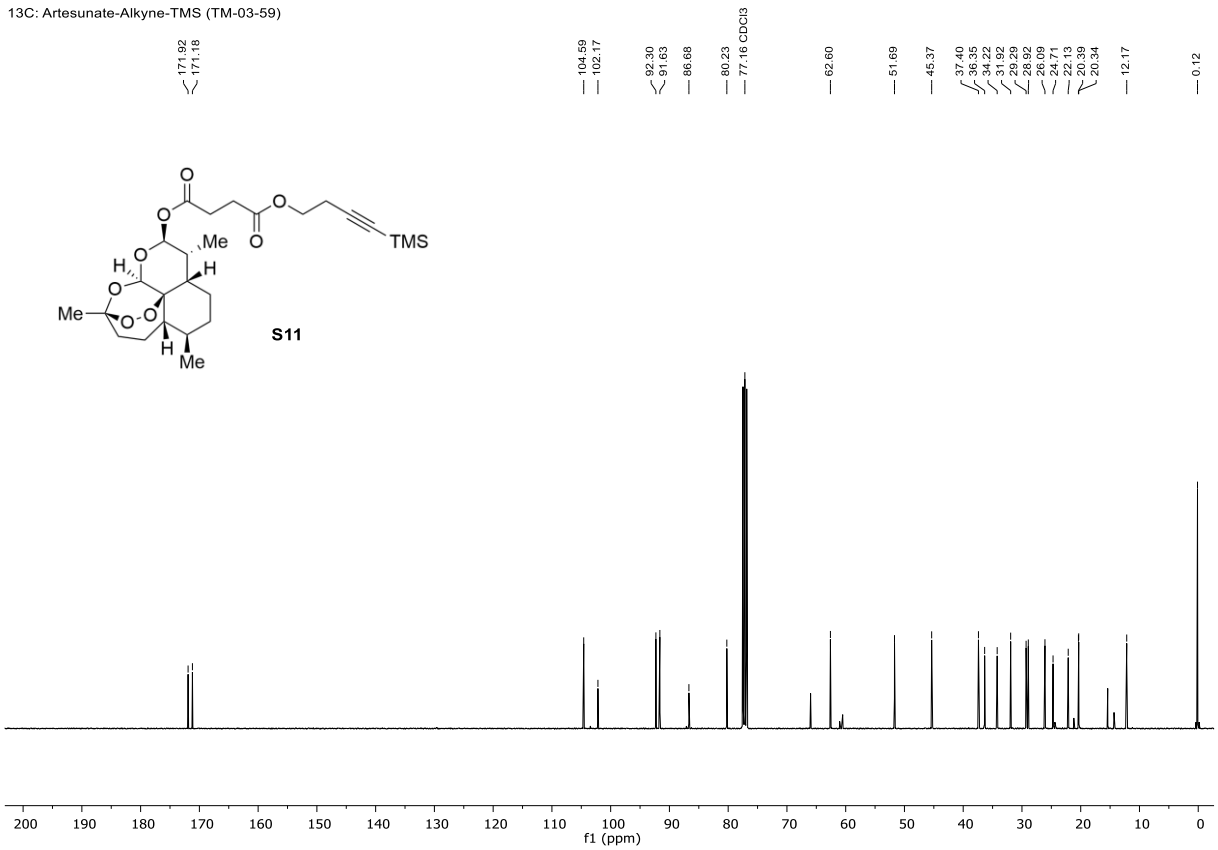


(3*R*,5*aS*,6*R*,8*aS*,9*R*,10*S*,12*R*,12*aR*)-3,6,9-Trimethyldecahydro-12*H*-3,12-epoxy[1,2]dioxepino[4,3-*i*]isochromen-10-yl (4-(trimethylsilyl)but-3-yn-1-yl) succinate (S11)

^{1}H-NMR (400 MHz, $CDCl_3$)

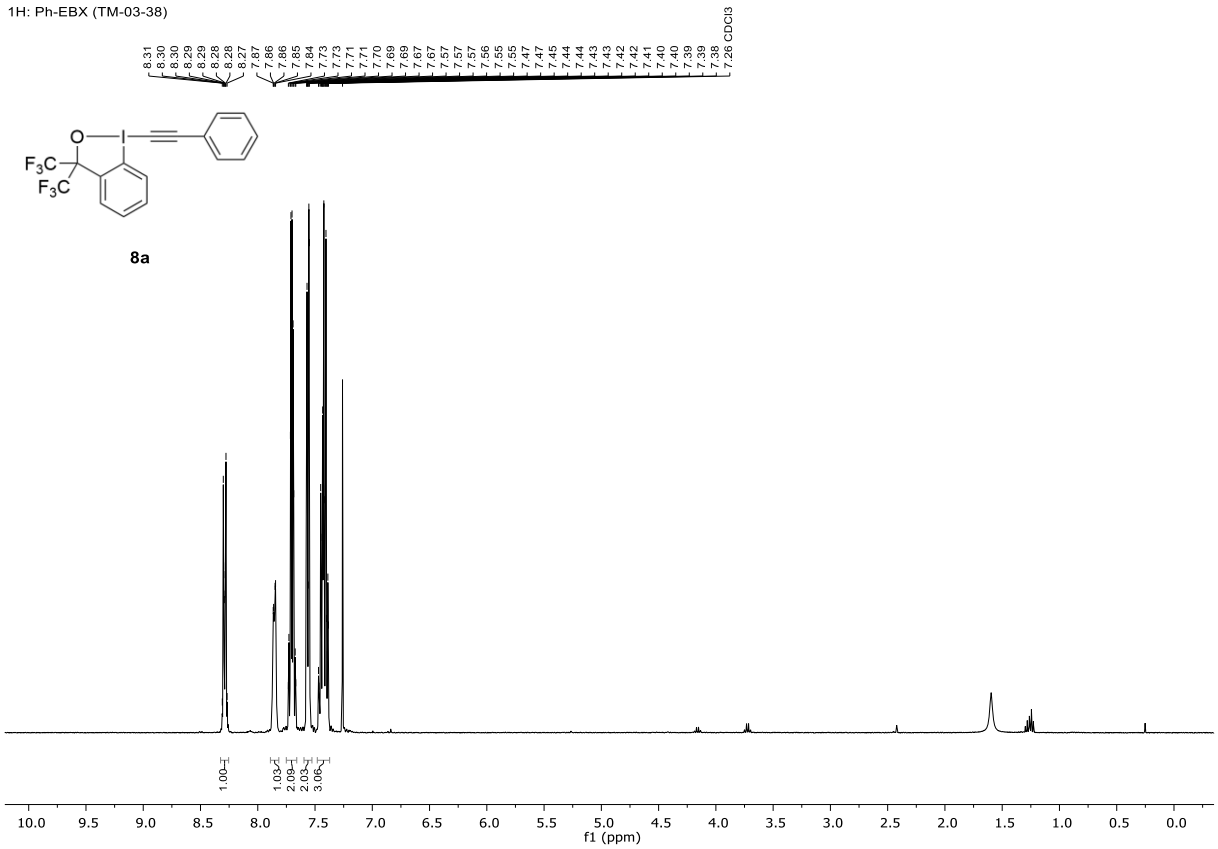


^{13}C-NMR (101 MHz, $CDCl_3$)

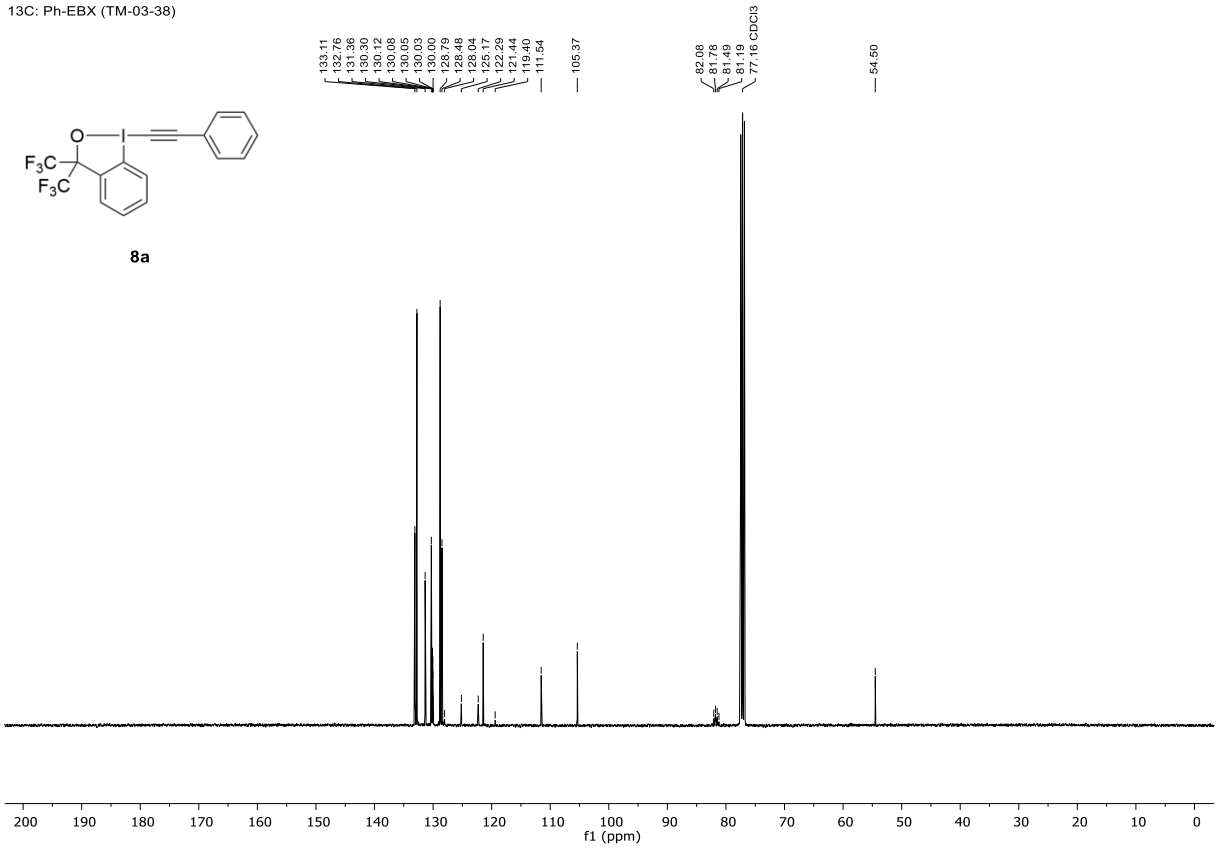


1-(Phenylethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (8a)

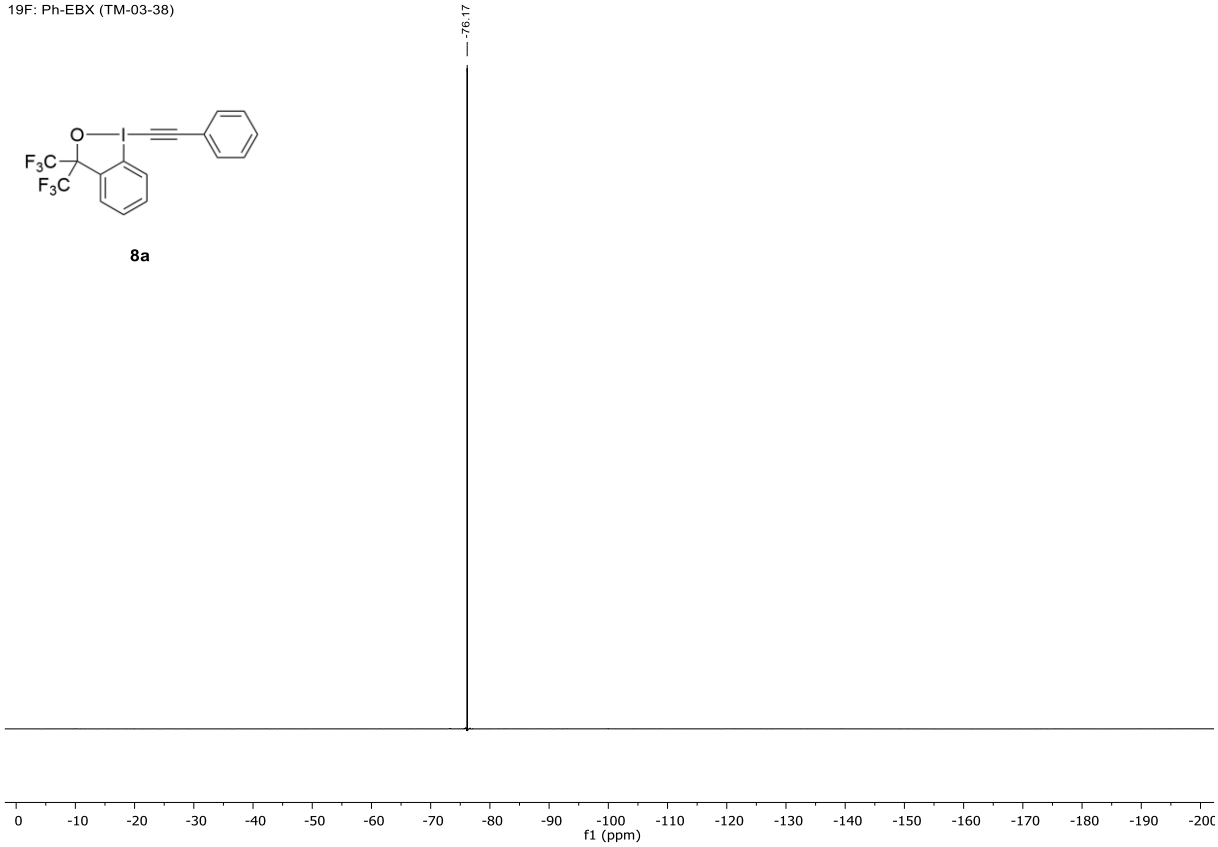
^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)



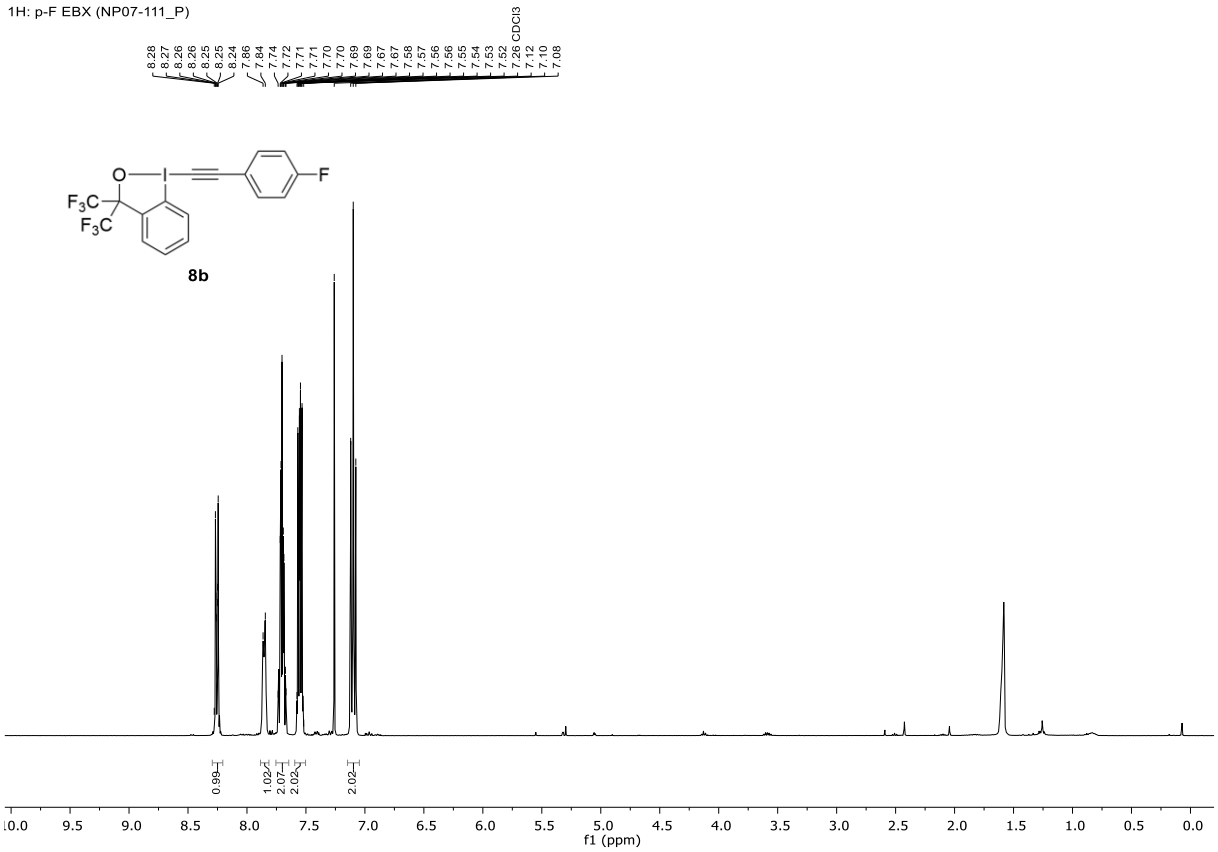
^{19}F-NMR (376 MHz, $CDCl_3$)



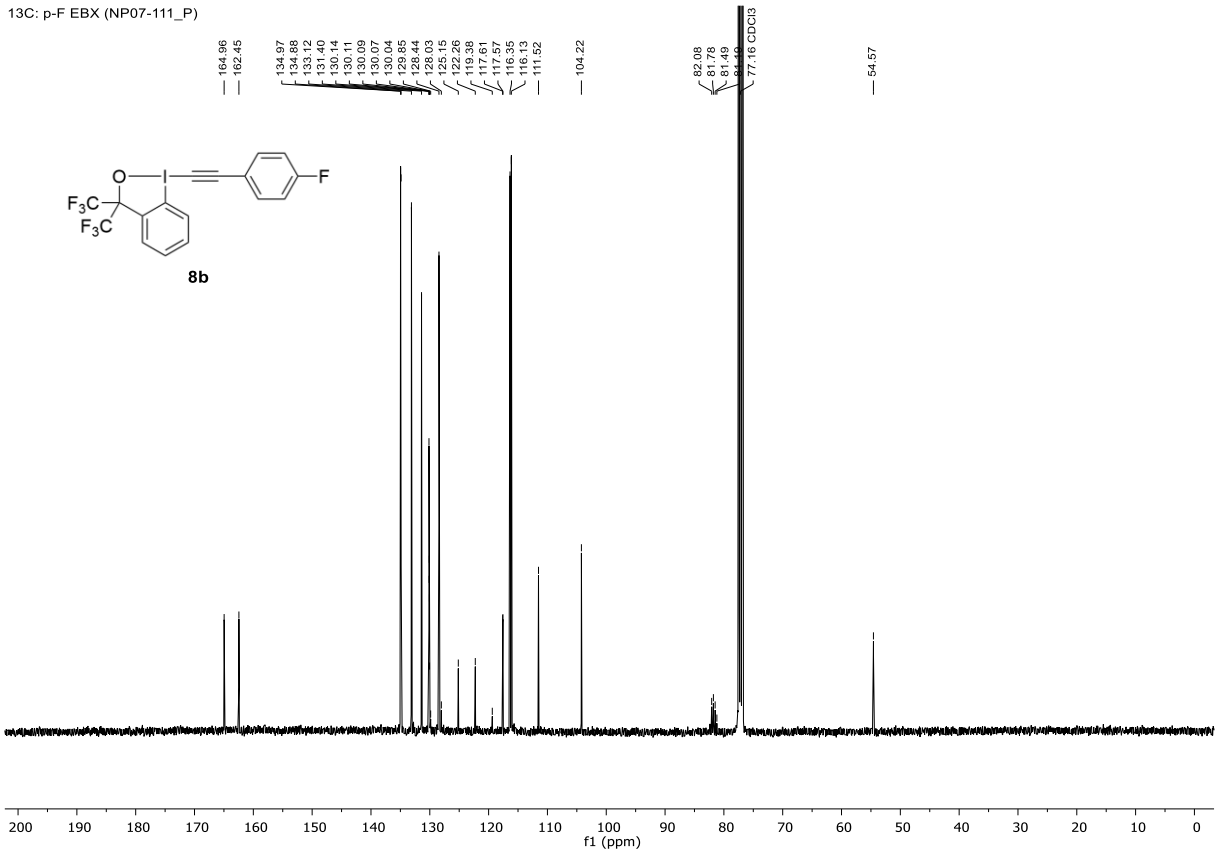
8a

1-((4-Fluorophenyl)ethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (8b)

^{1}H-NMR (400 MHz, $CDCl_3$)

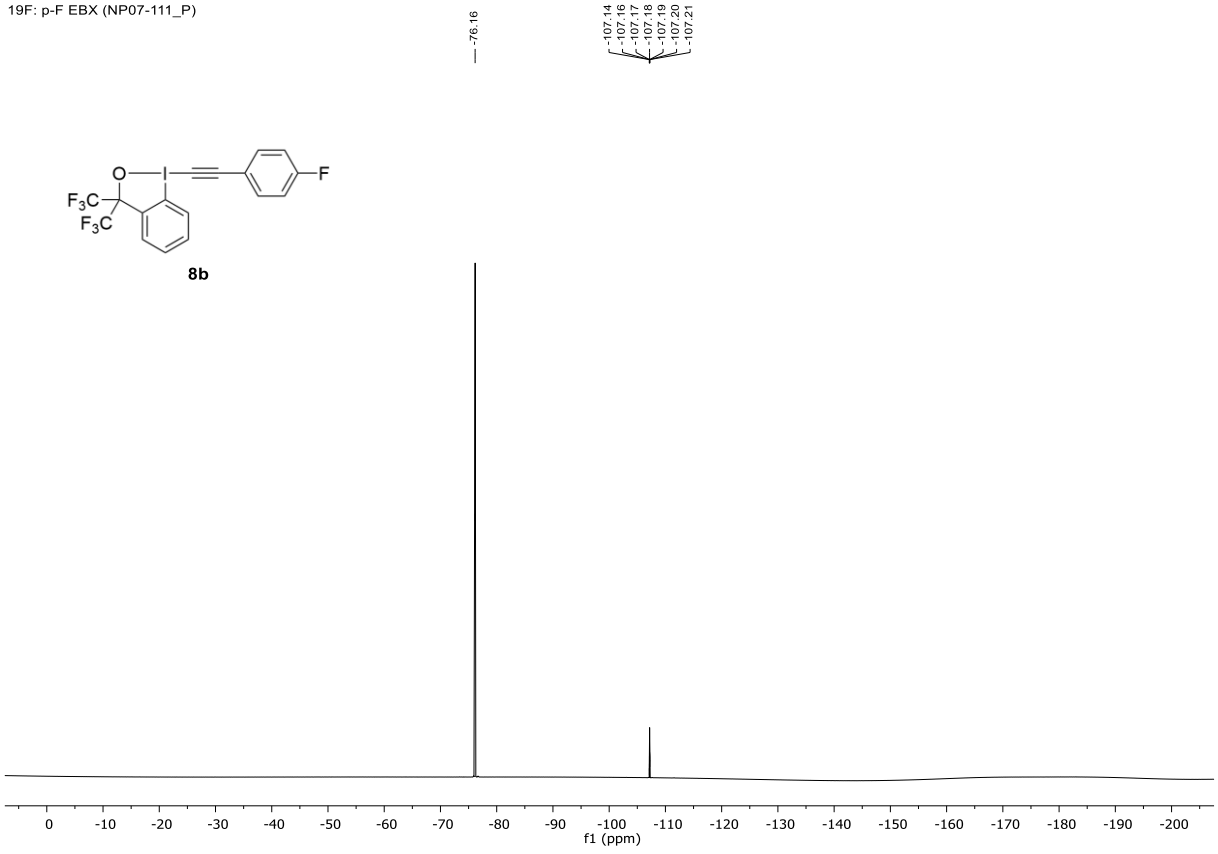


^{13}C-NMR (101 MHz, $CDCl_3$)



^{19}F-NMR (376 MHz, $CDCl_3$)

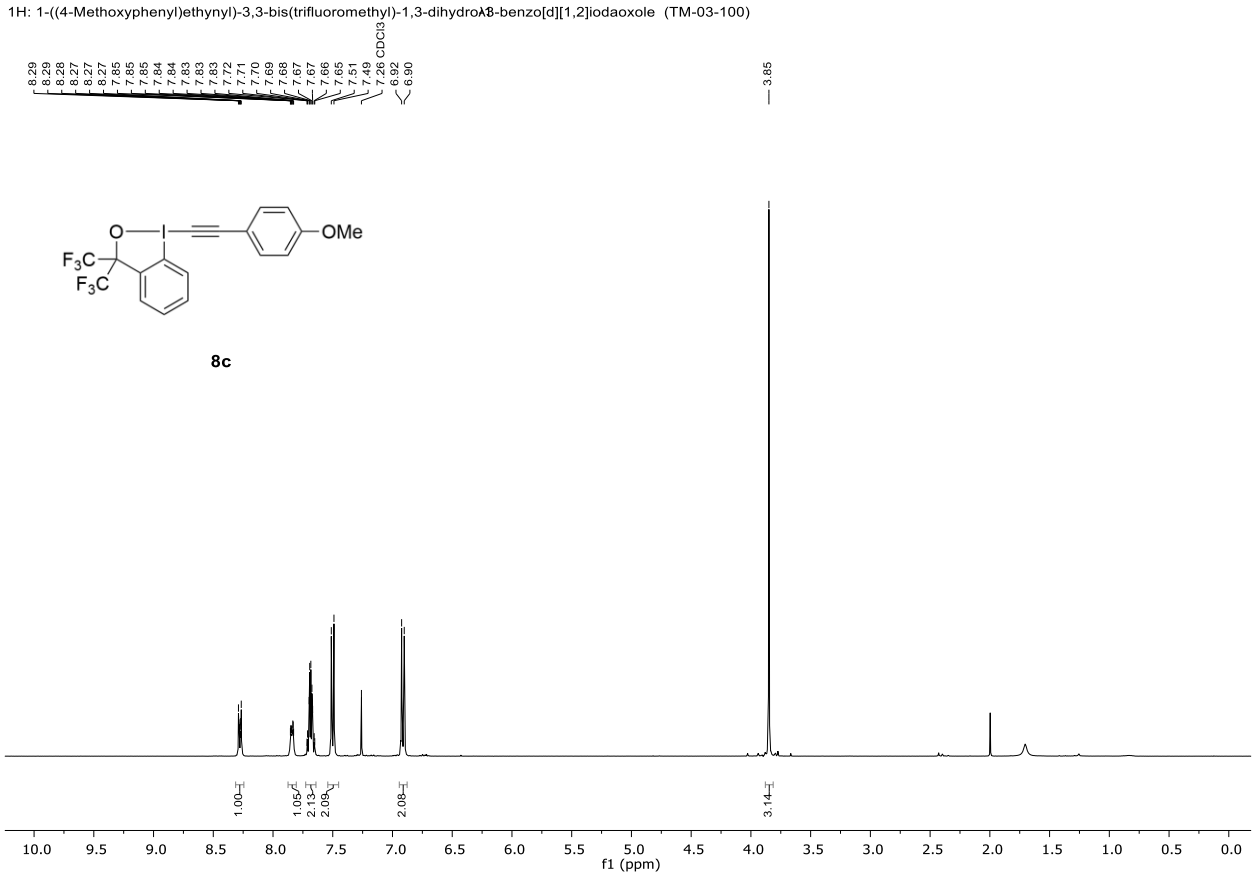
19F: p-F EBX (NP07-111_P)



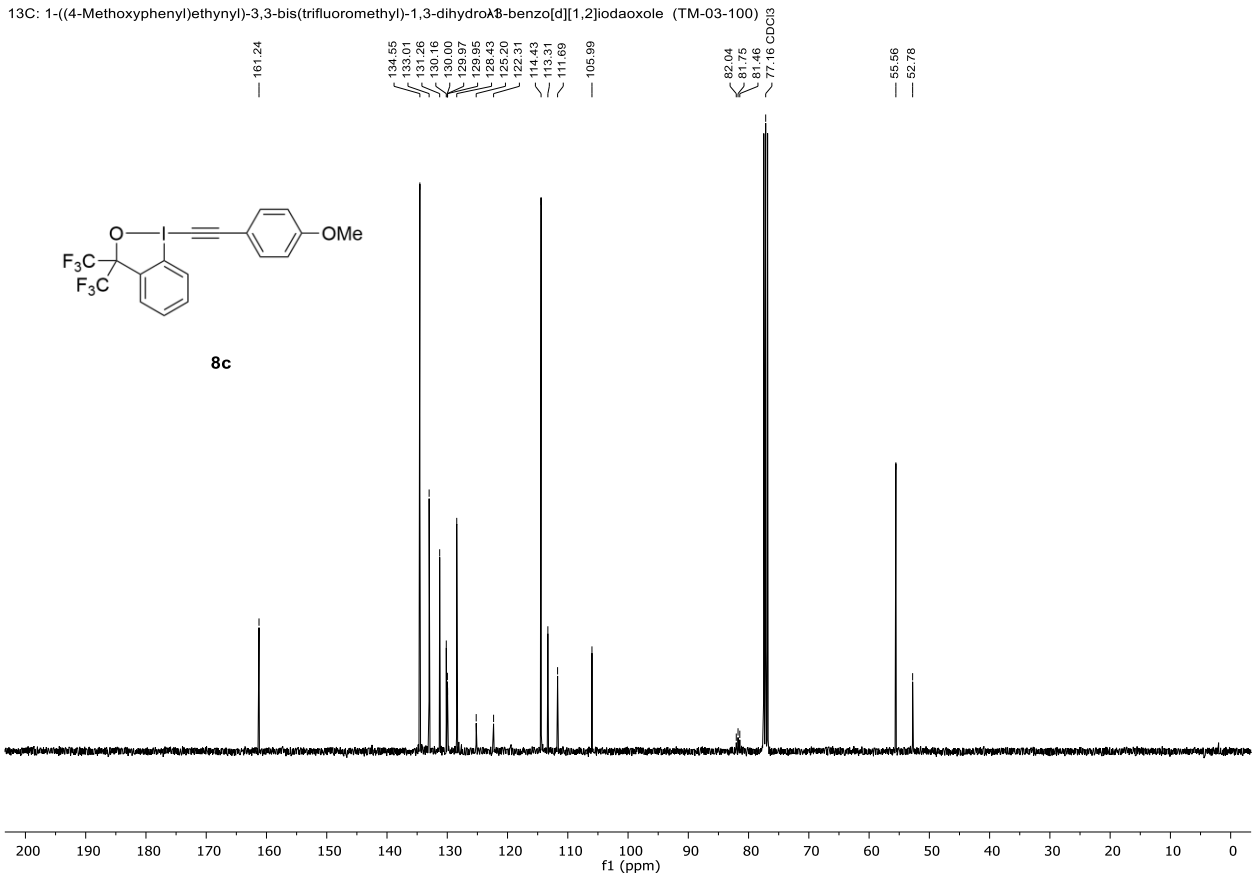
8b

1-((4-Methoxyphenyl)ethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (8c)

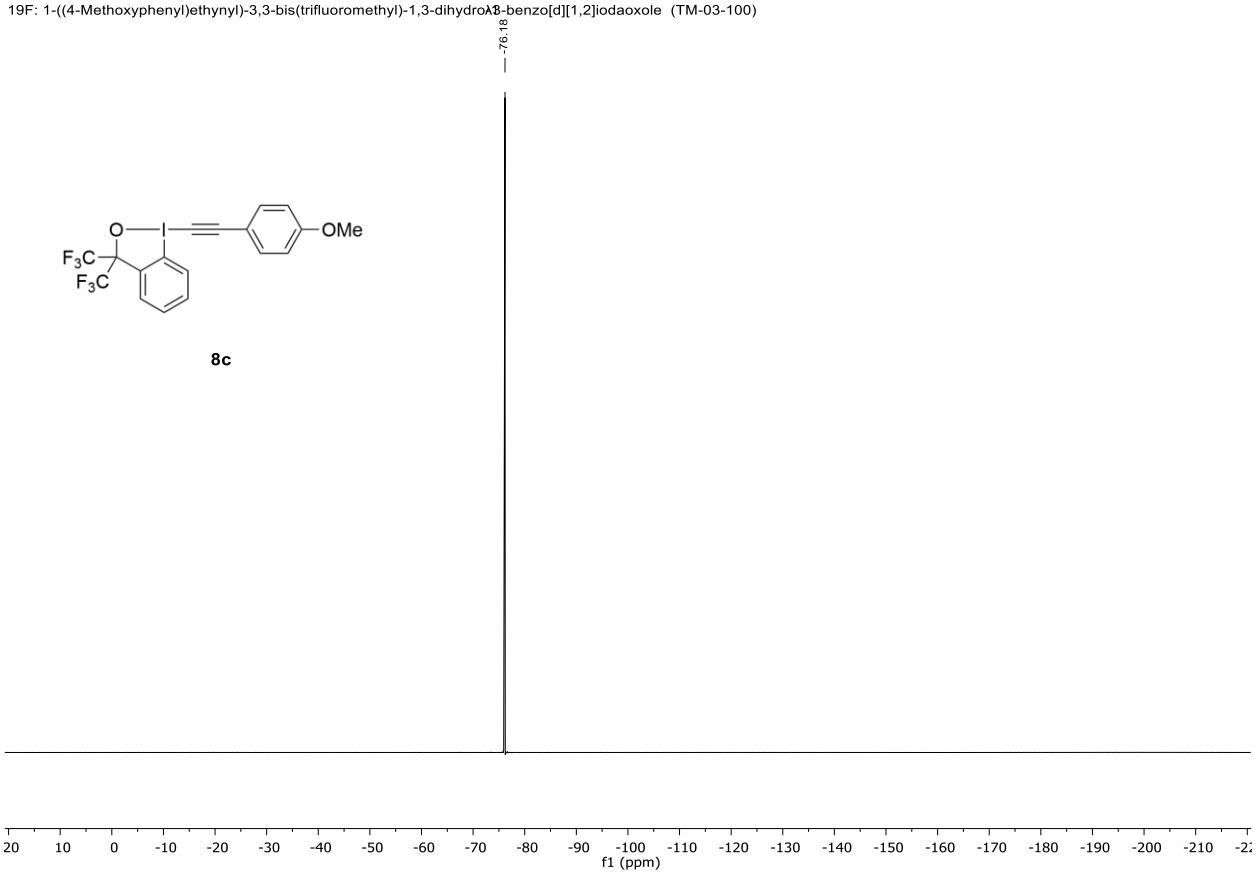
^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)



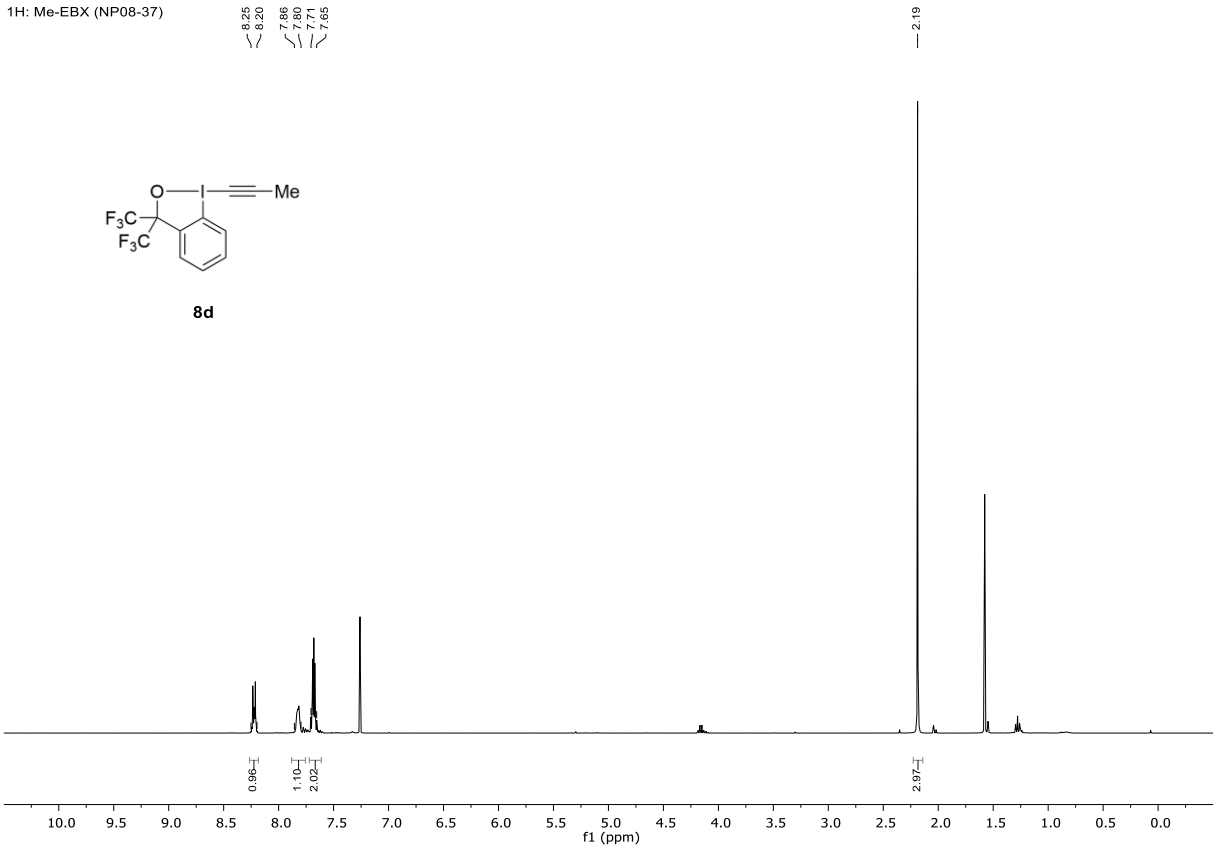
^{19}F-NMR (376 MHz, $CDCl_3$)



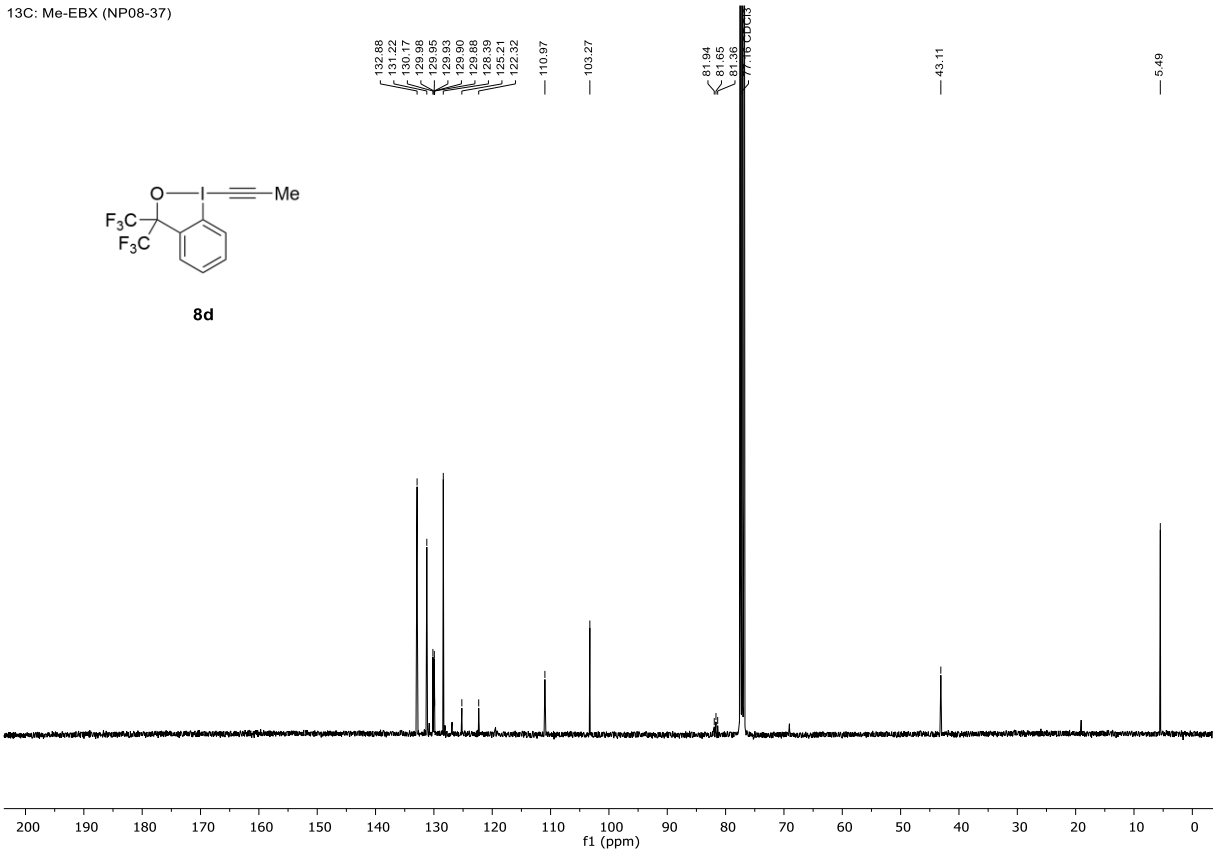
8c

1-(Prop-1-yn-1-yl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (8d)

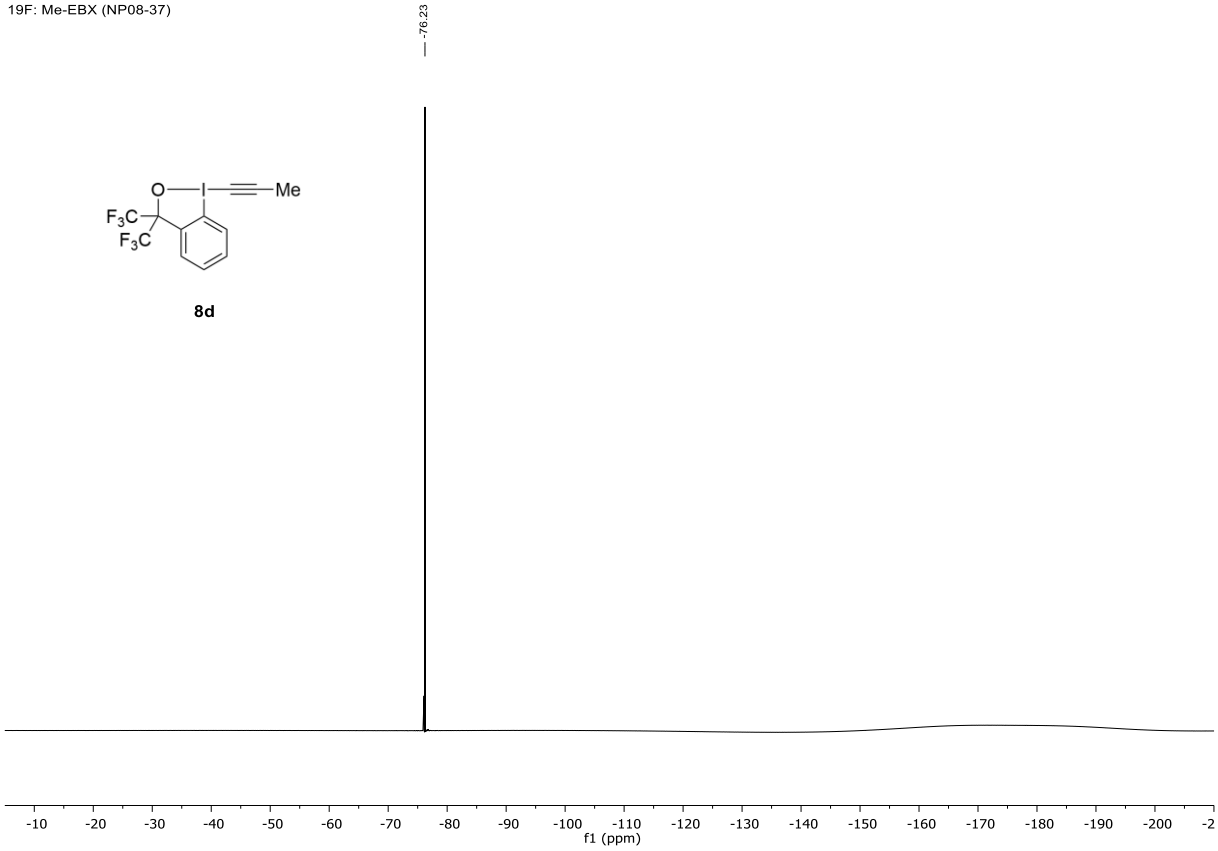
^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)

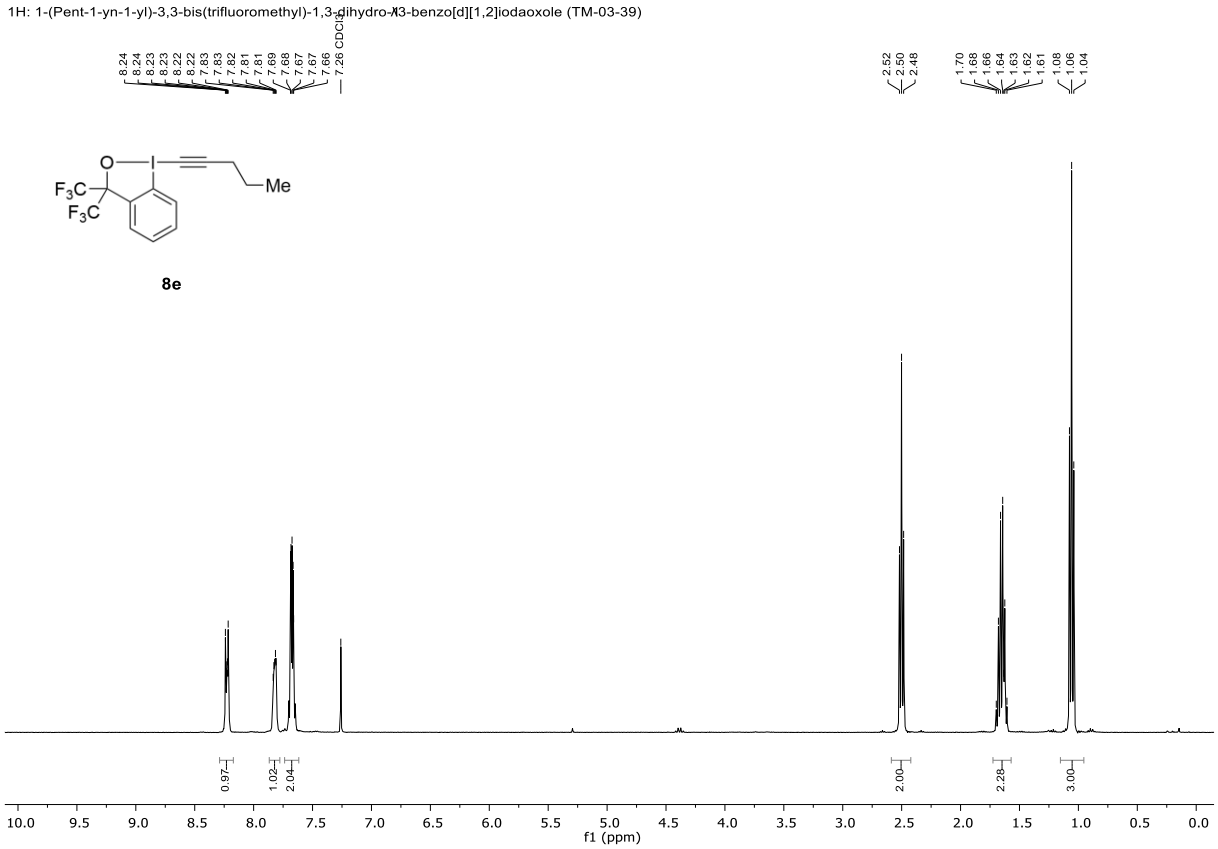


^{19}F-NMR (376 MHz, $CDCl_3$)

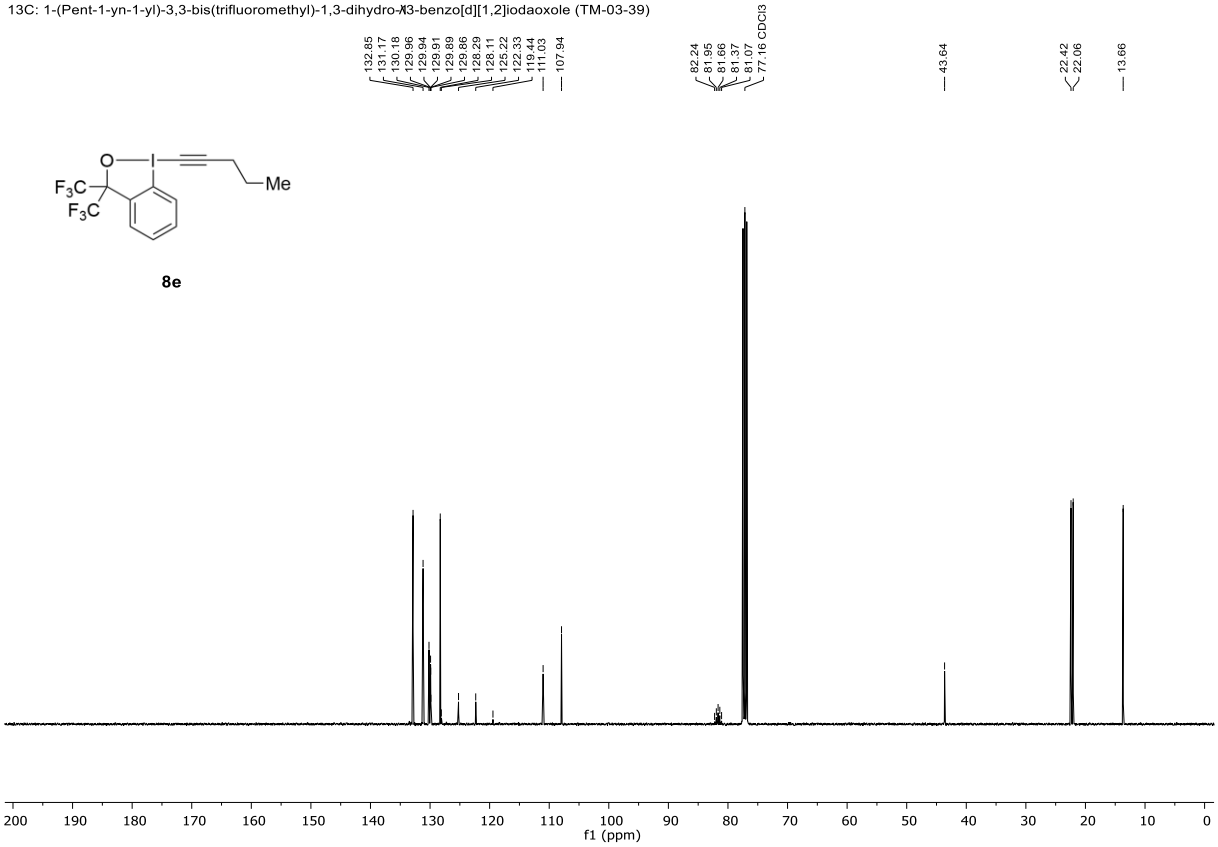


1-(Pent-1-yn-1-yl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (8e)

^{1}H-NMR (400 MHz, $CDCl_3$)

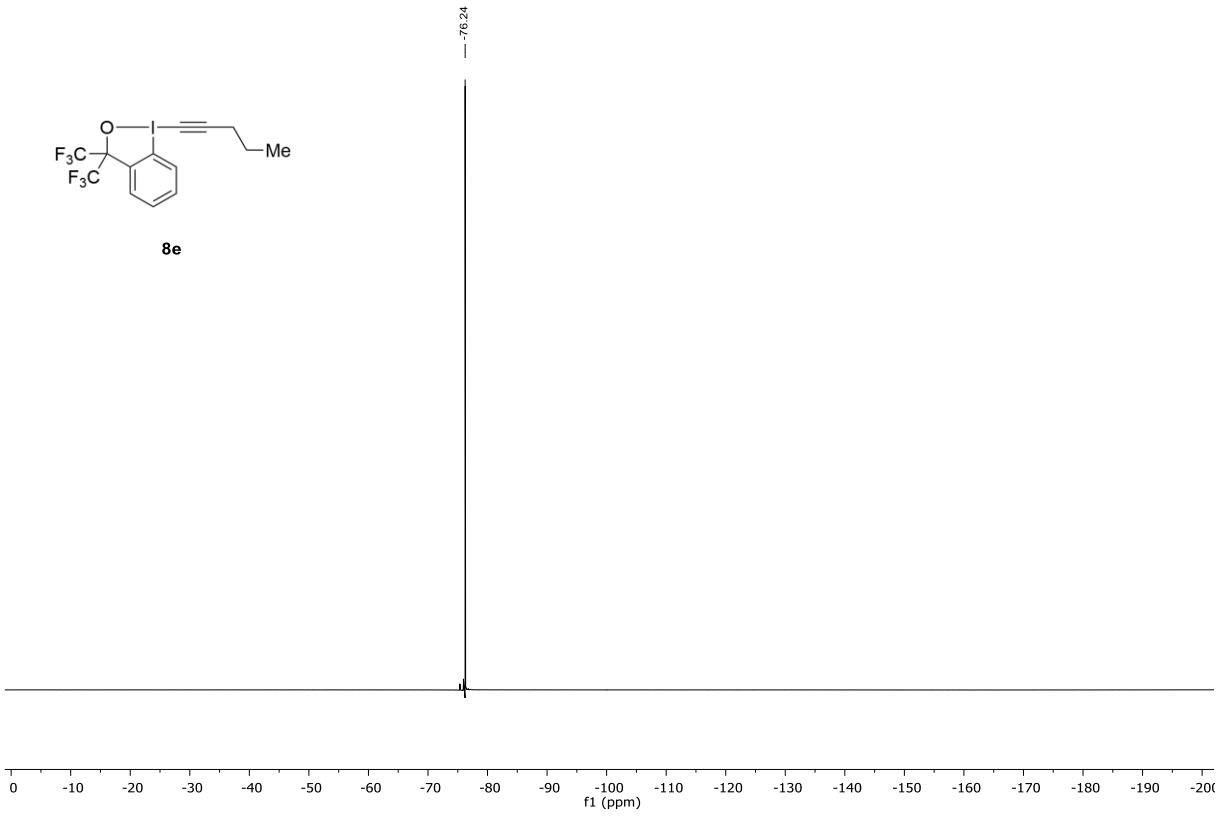


^{13}C-NMR (101 MHz, $CDCl_3$)



^{19}F-NMR (376 MHz, $CDCl_3$)

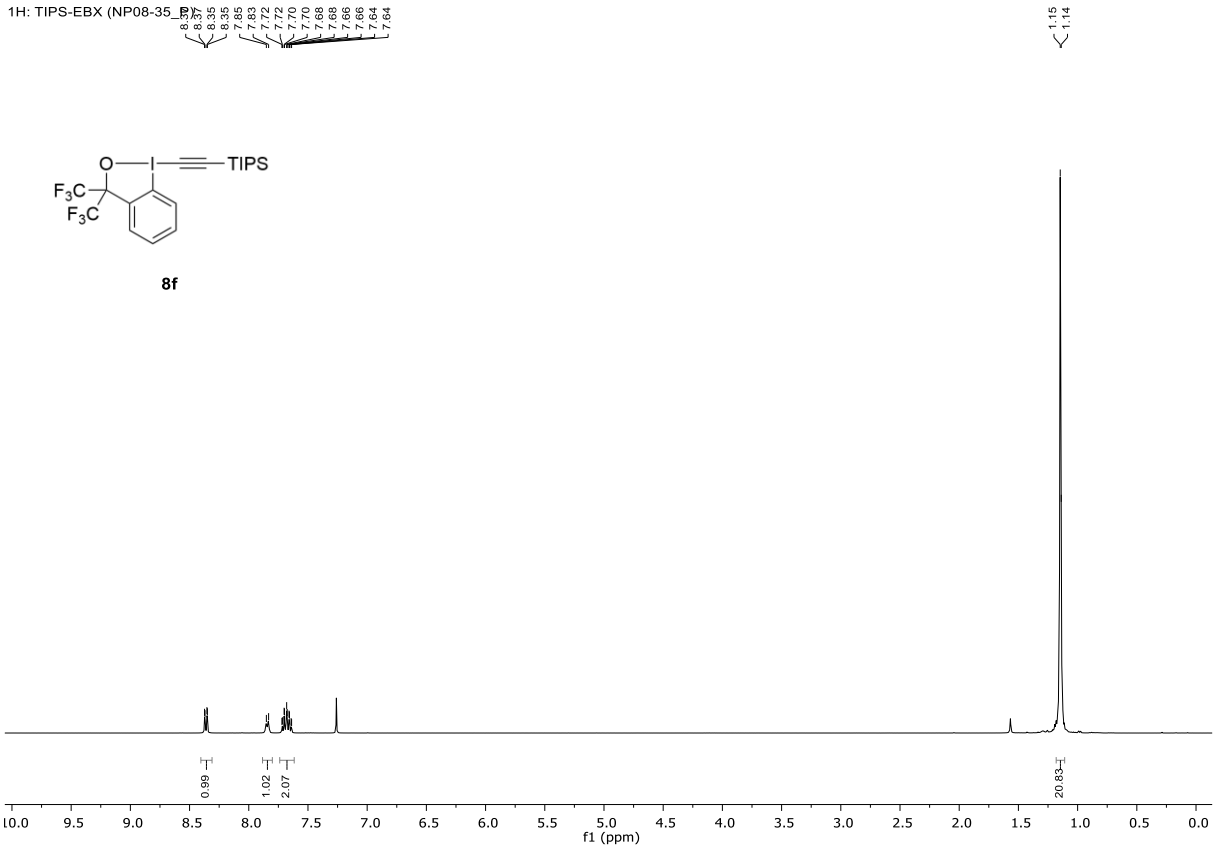
19F: 1-(Pent-1-yn-1-yl)-3,3-bis(trifluoromethyl)-1,3-dihydro-λ3-benzo[d][1,2]iodaoxole (TM-03-39)



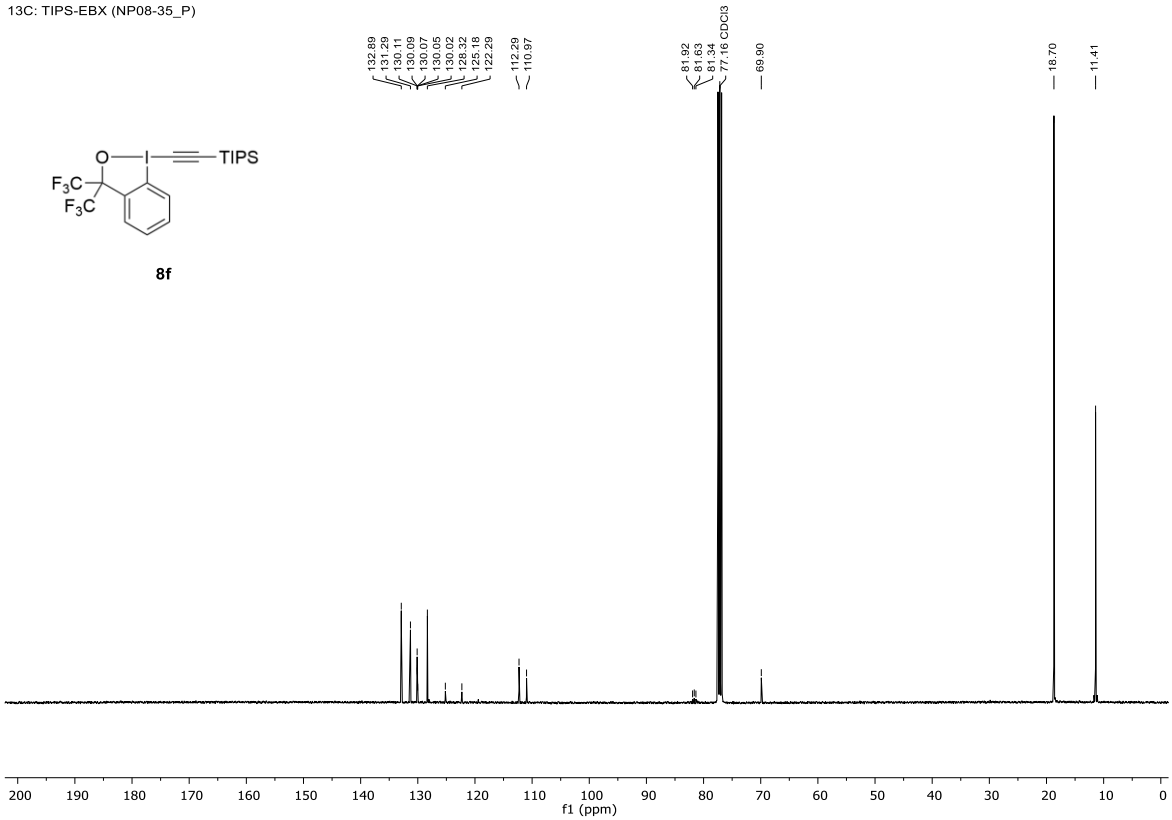
8e

((3,3-Bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (8f)

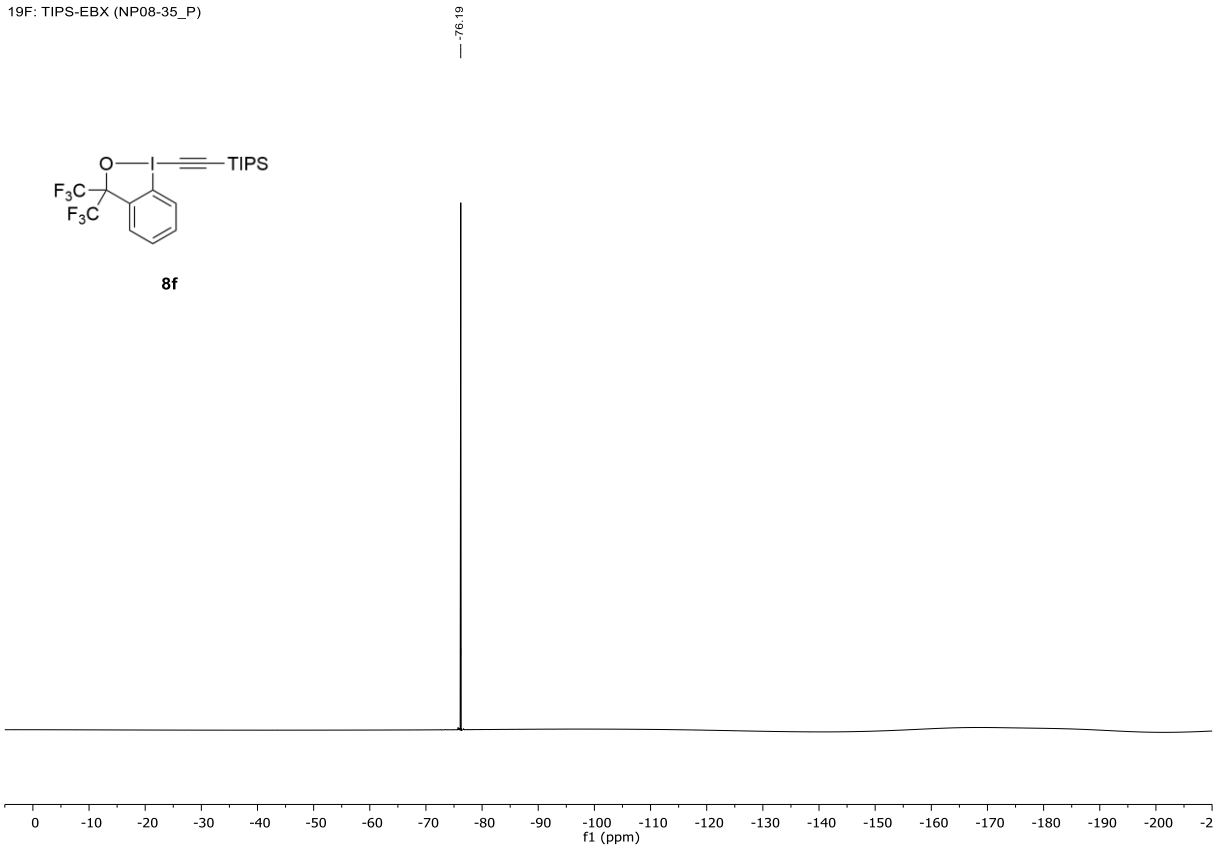
^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)



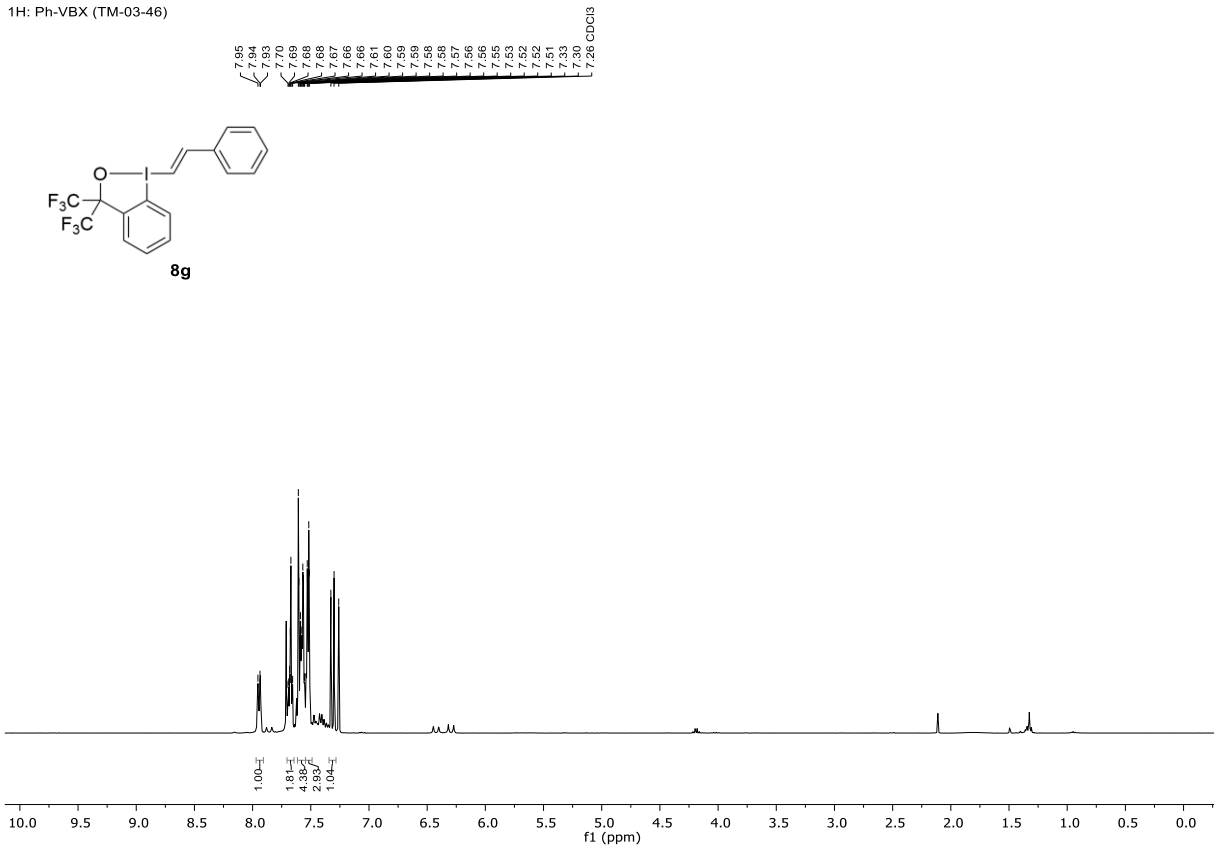
^{19}F-NMR (376 MHz, $CDCl_3$)



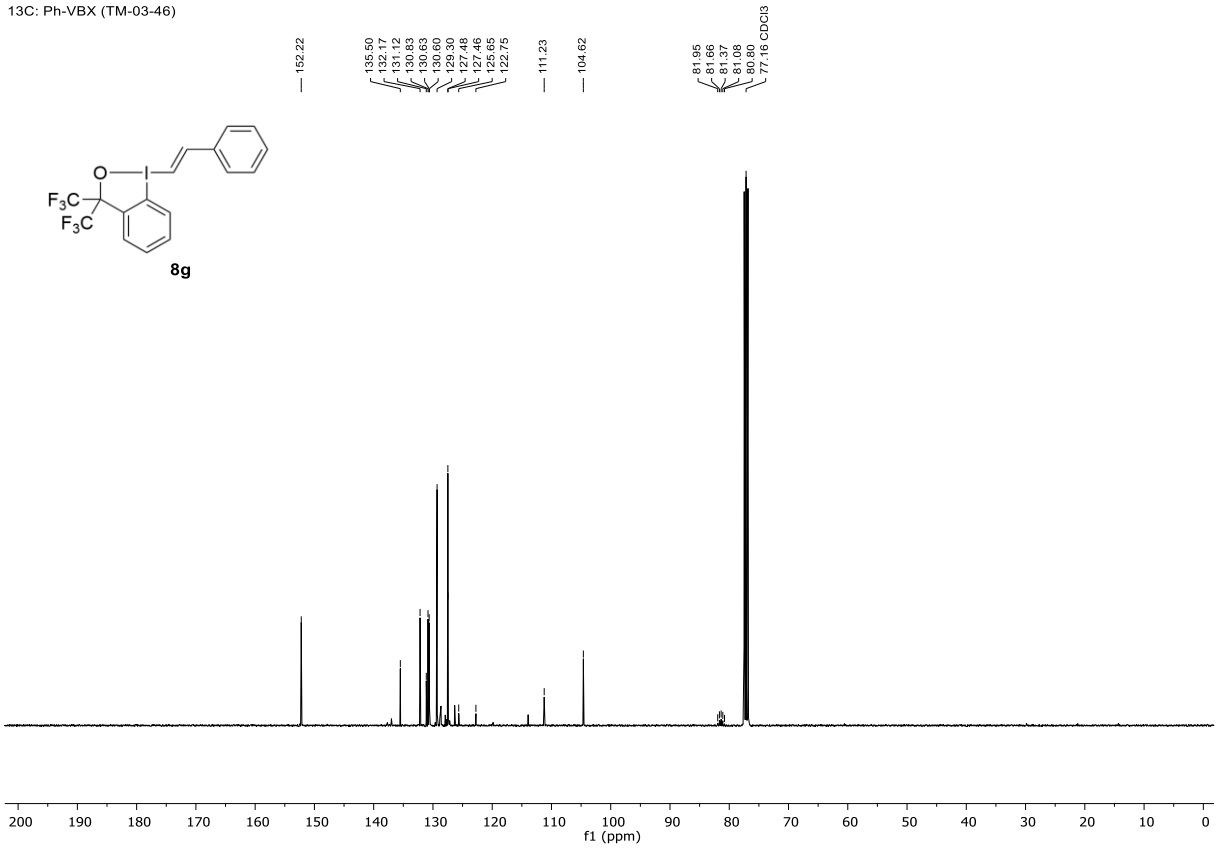
8f

(*E*)-1-Styryl-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (8g)

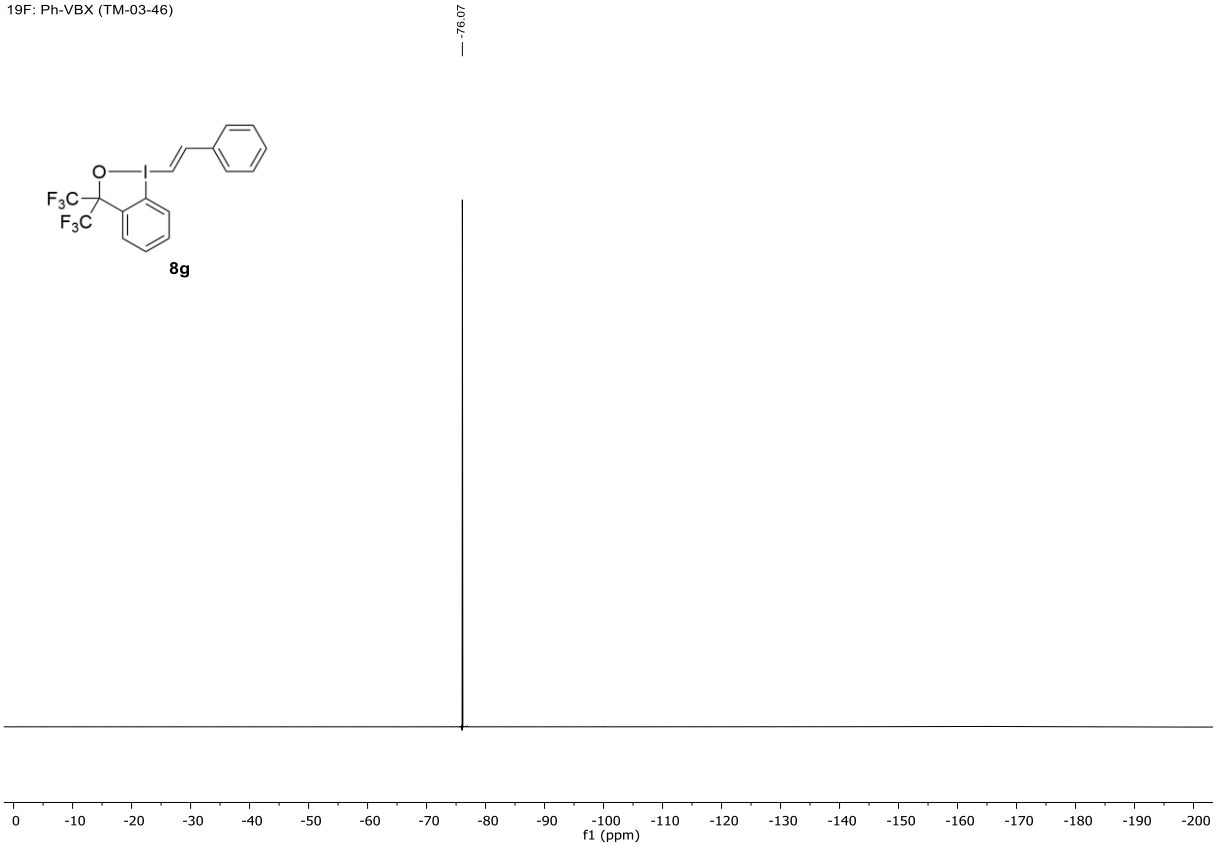
^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)

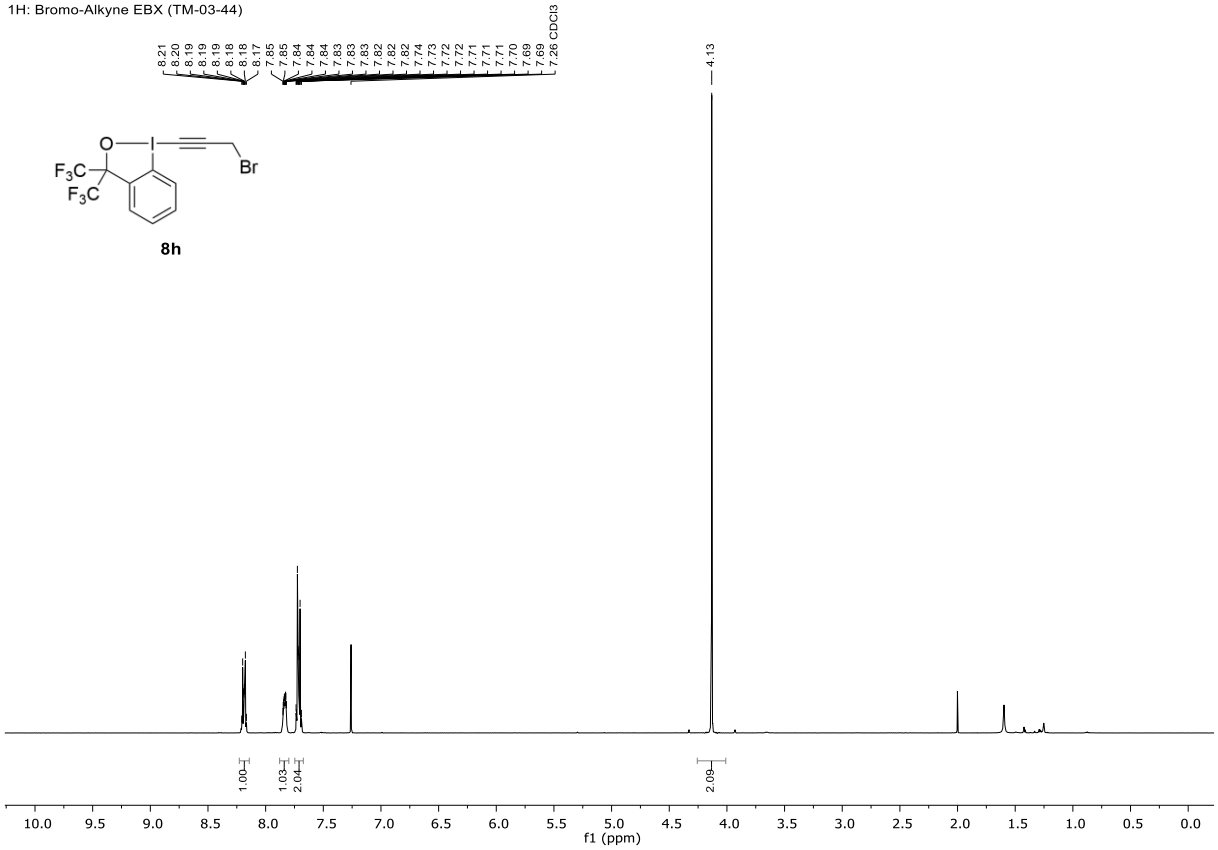


^{19}F-NMR (376 MHz, $CDCl_3$)

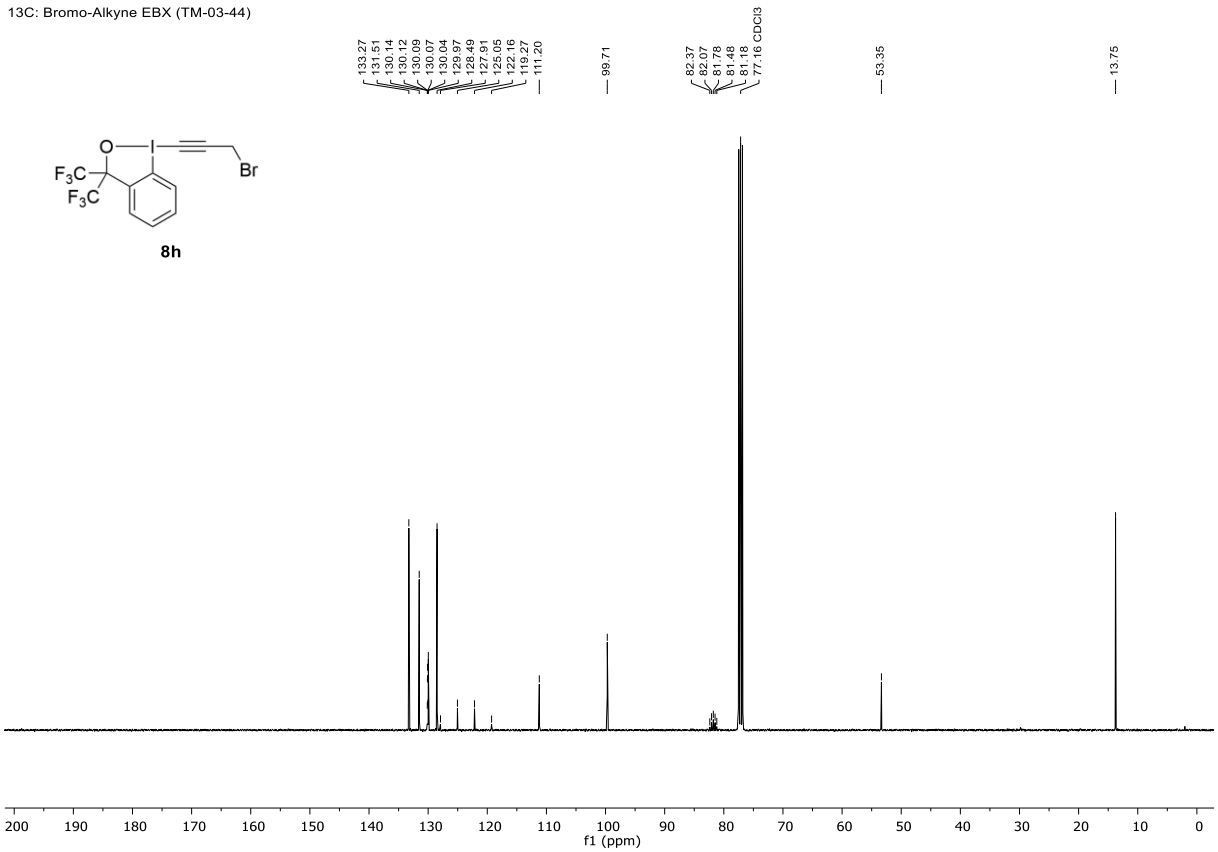


1-(3-Bromoprop-1-yn-1-yl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (8h)

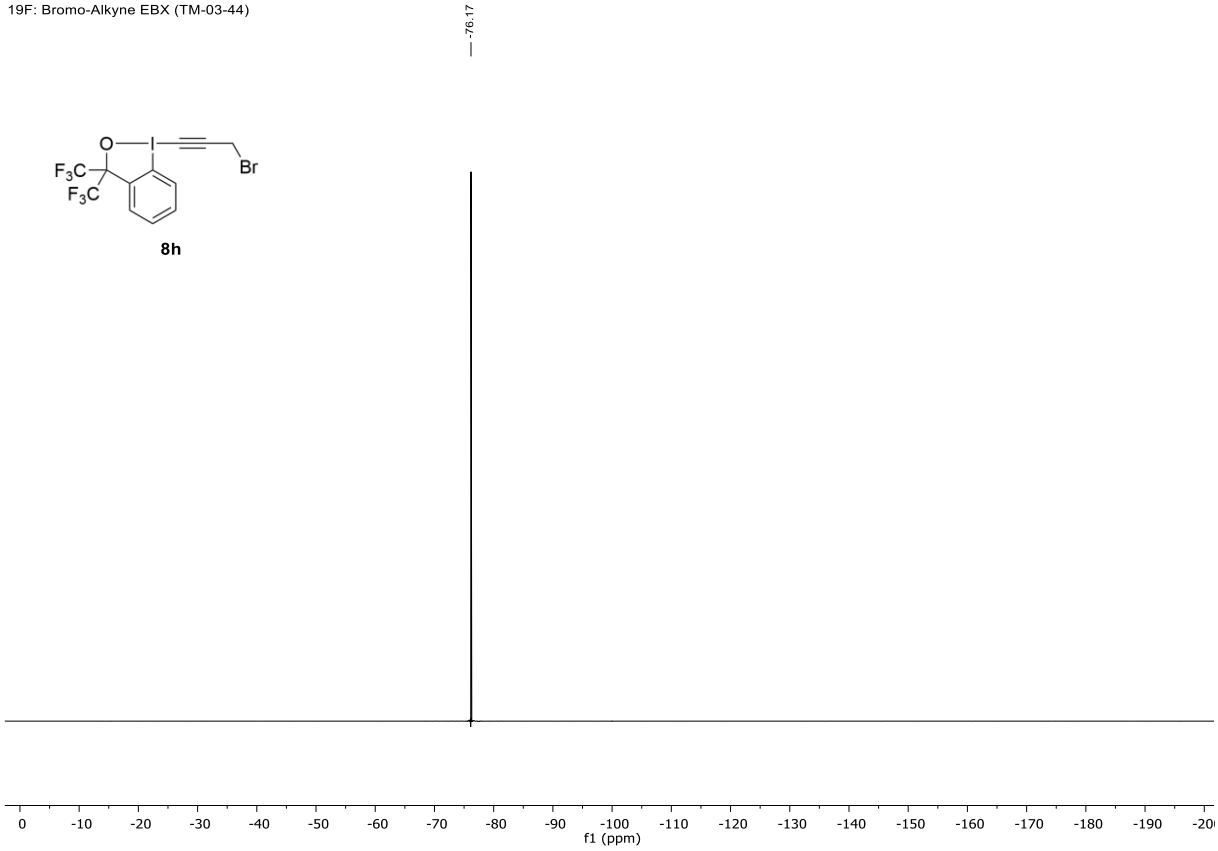
^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)

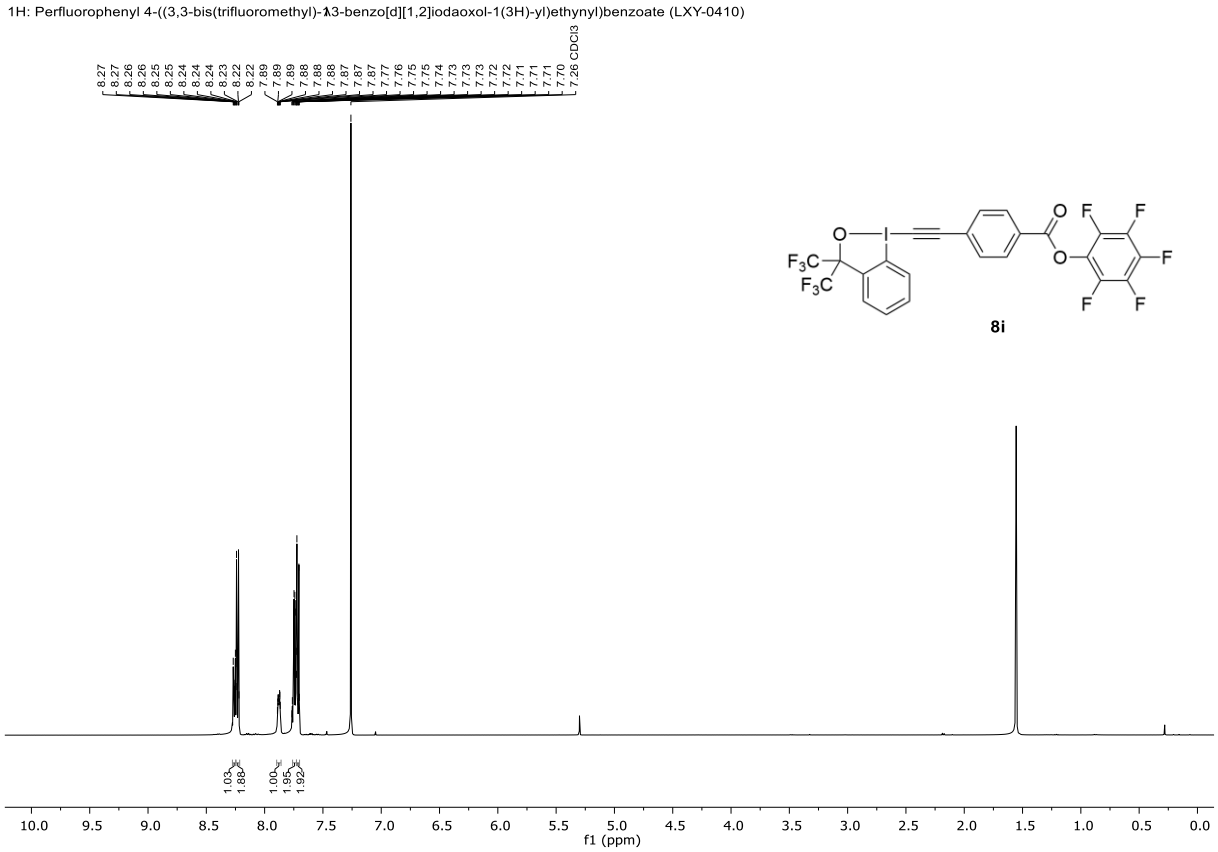


^{19}F-NMR (376 MHz, $CDCl_3$)

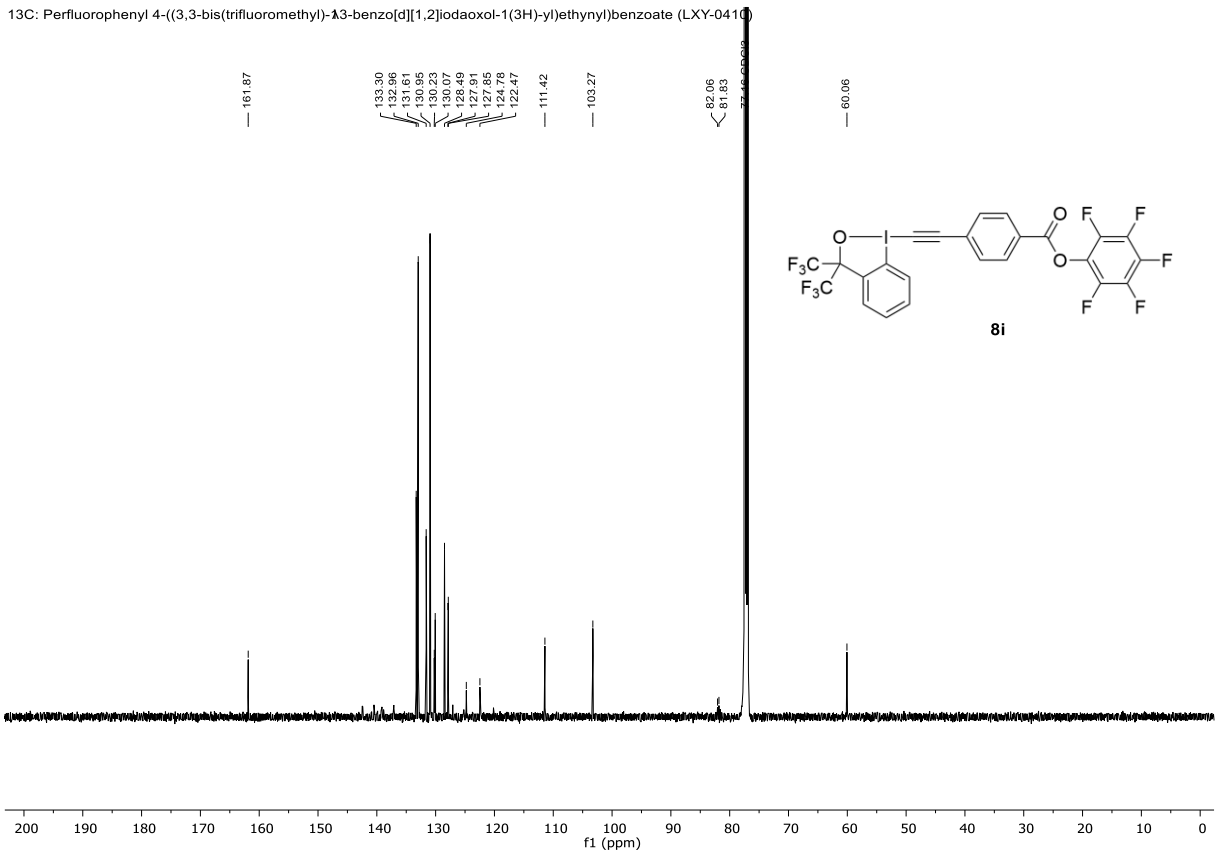


Perfluorophenyl 4-((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)benzoate (8i)

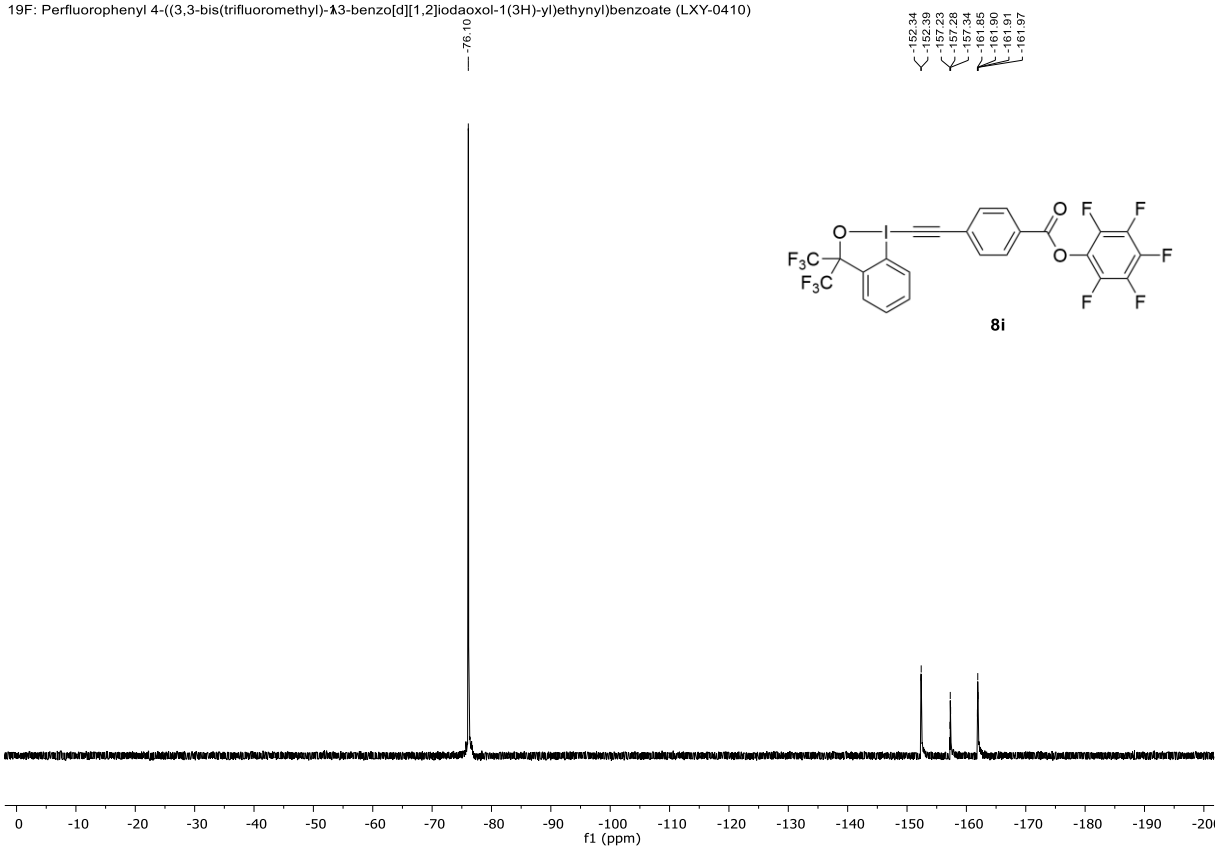
^{1}H-NMR (500 MHz, $CDCl_3$)



^{13}C-NMR (126 MHz, $CDCl_3$)

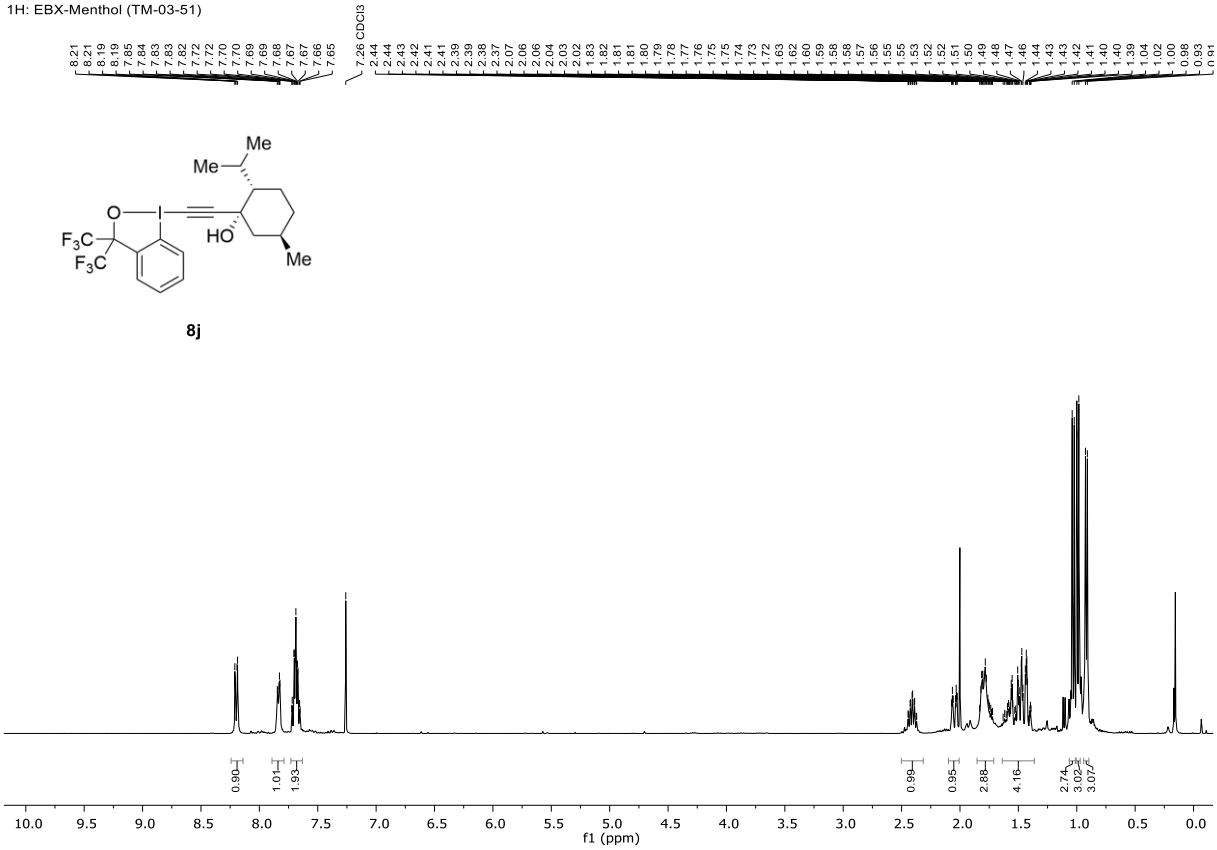


^{19}F-NMR (376 MHz, $CDCl_3$)

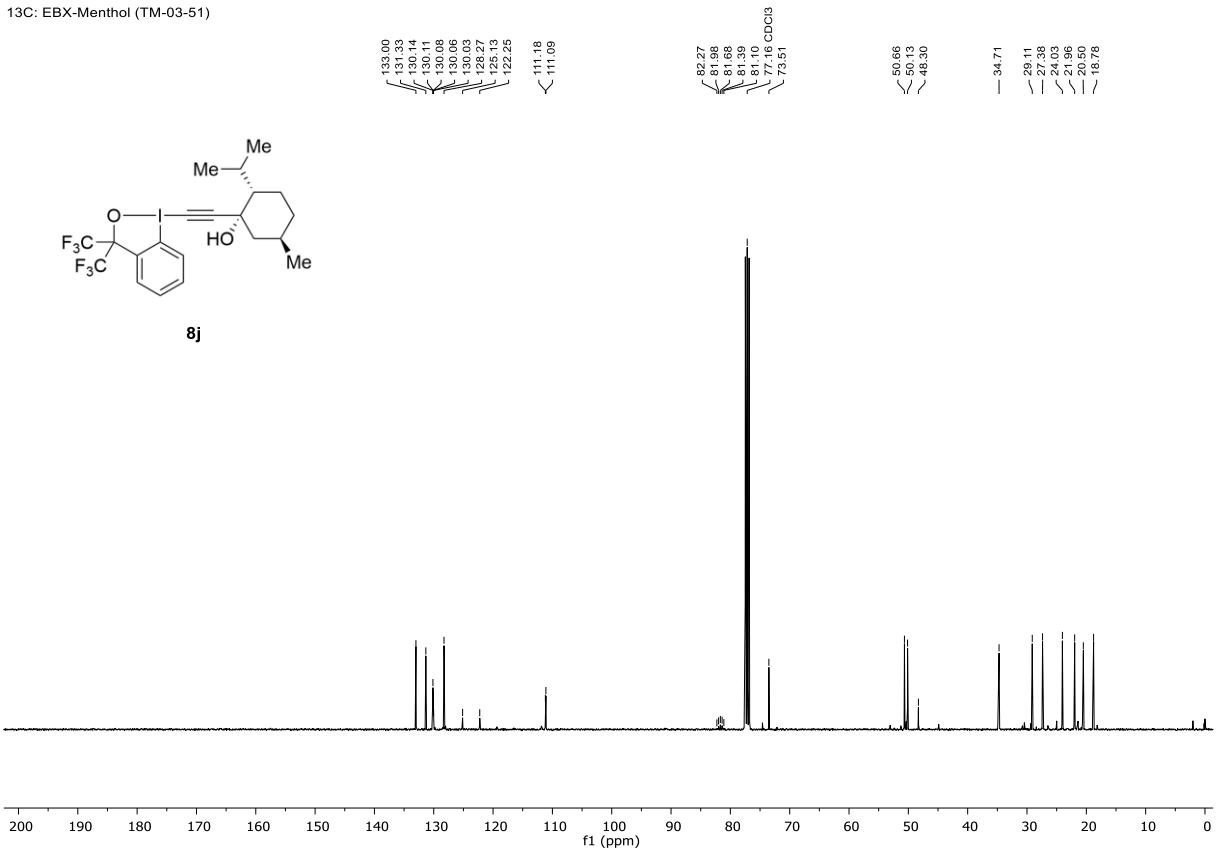


(1*S*,2*S*,5*R*)-1-((3,3-Bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3H)-yl)ethynyl)-2-isopropyl-5-methylcyclohexan-1-ol (8j)

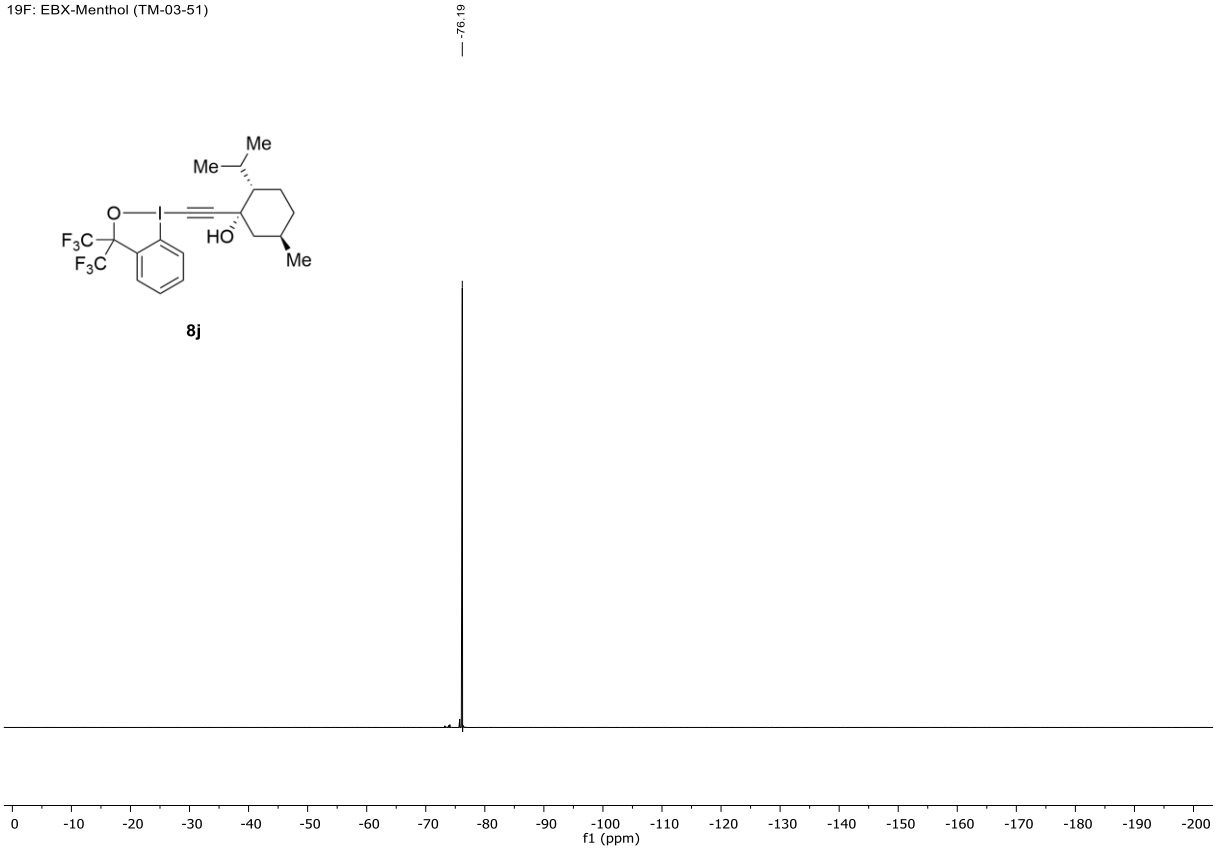
^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)



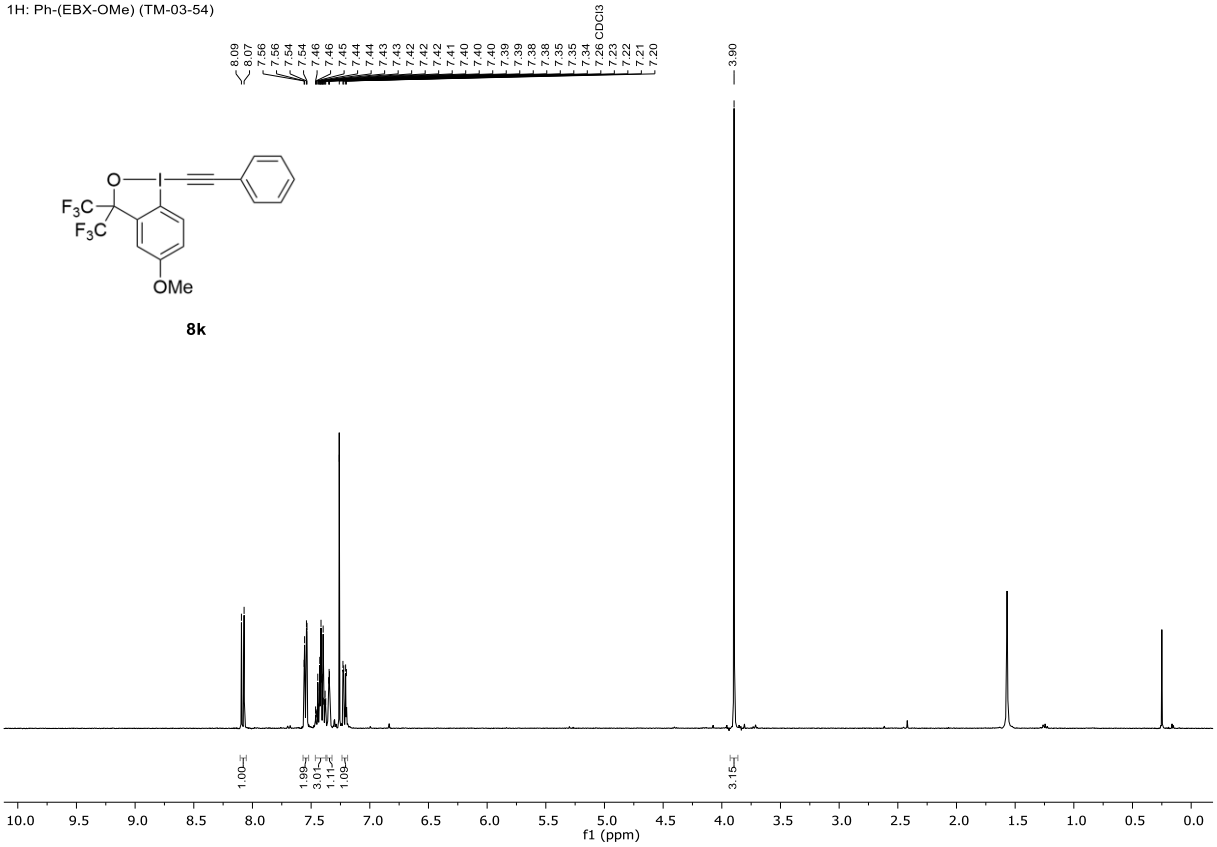
^{19}F-NMR (376 MHz, $CDCl_3$)



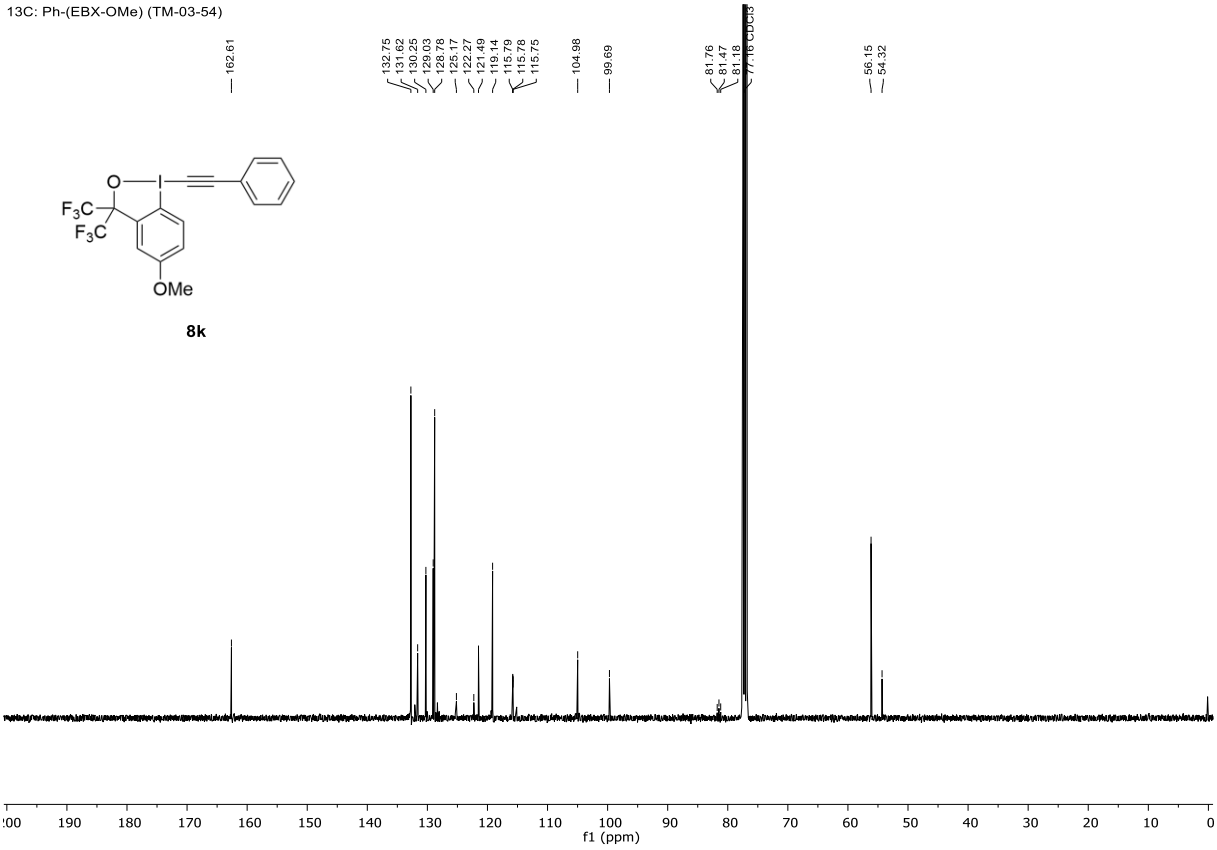
8j

5-Methoxy-(1-phenylethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (8k)

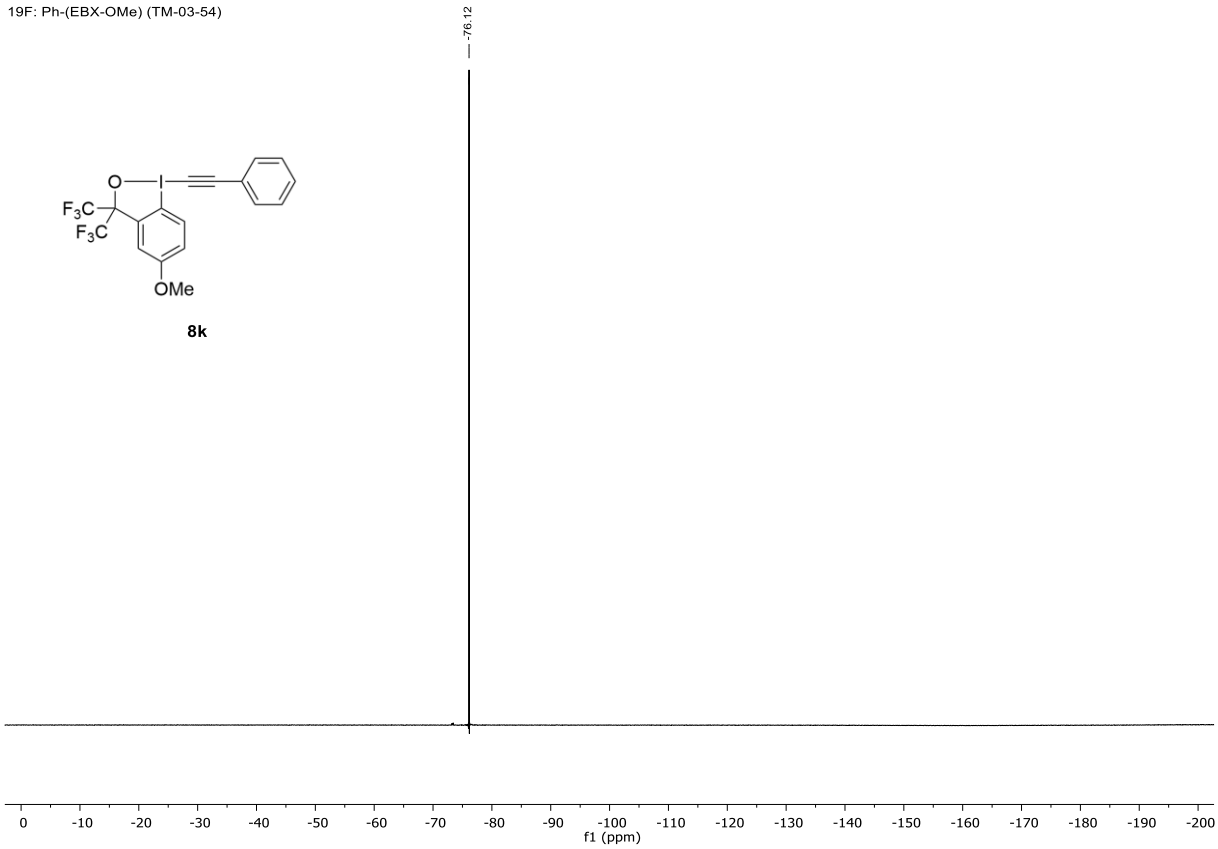
^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)



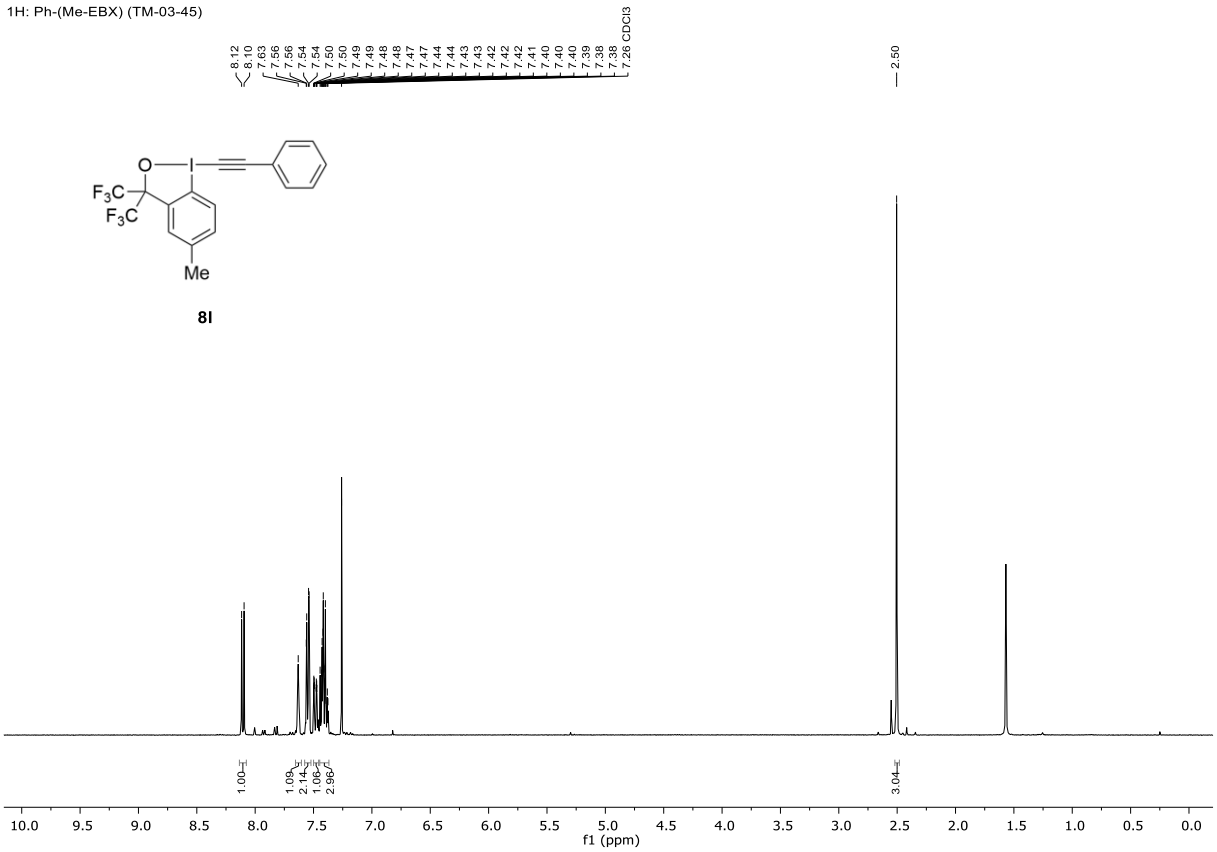
^{19}F-NMR (376 MHz, $CDCl_3$)



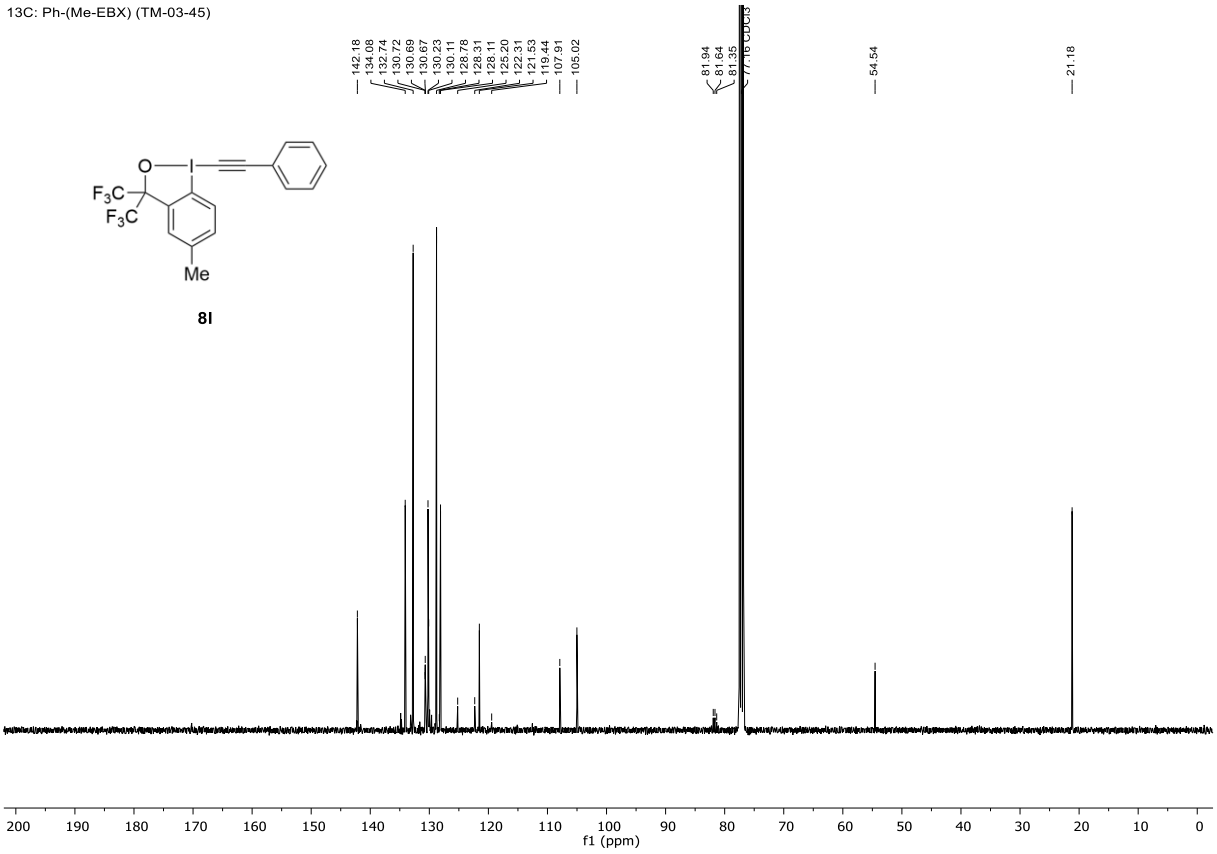
8k

5-Methyl-(1-phenylethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (8l)

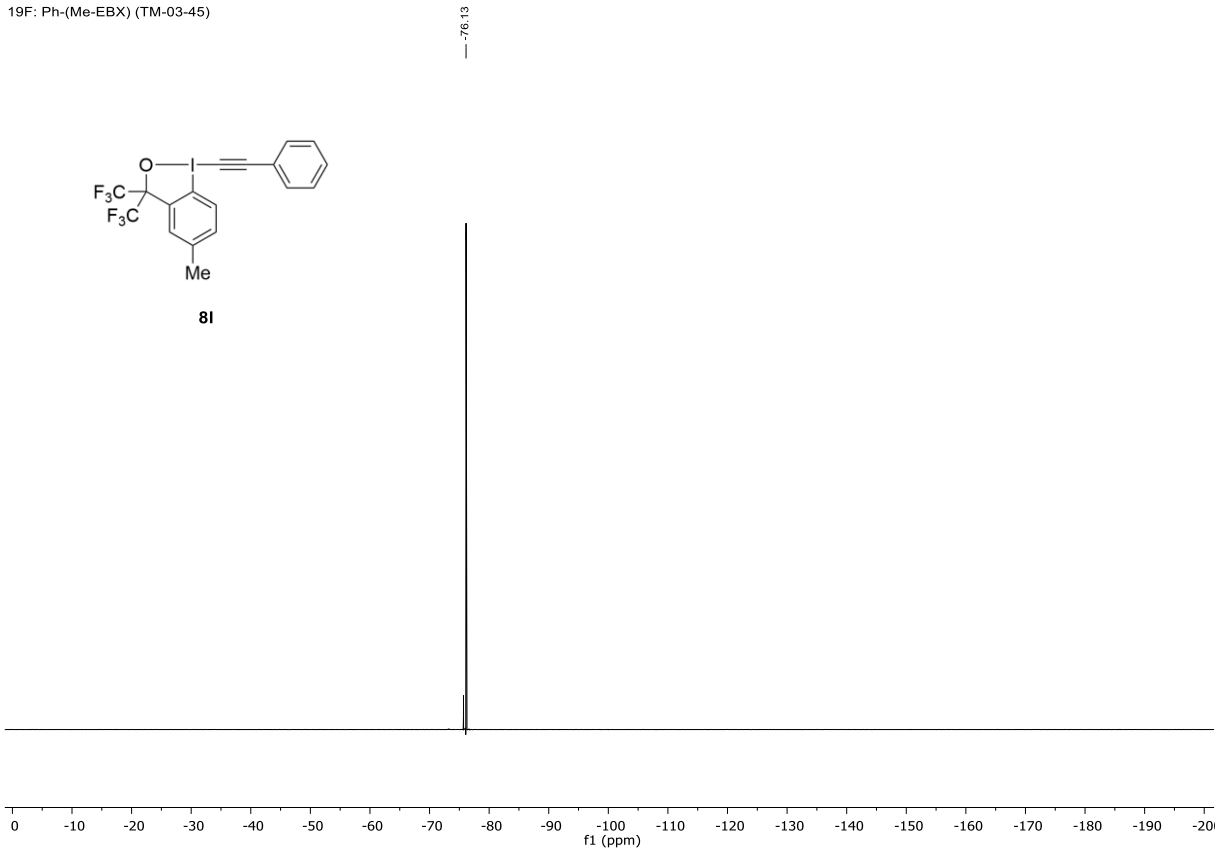
^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)

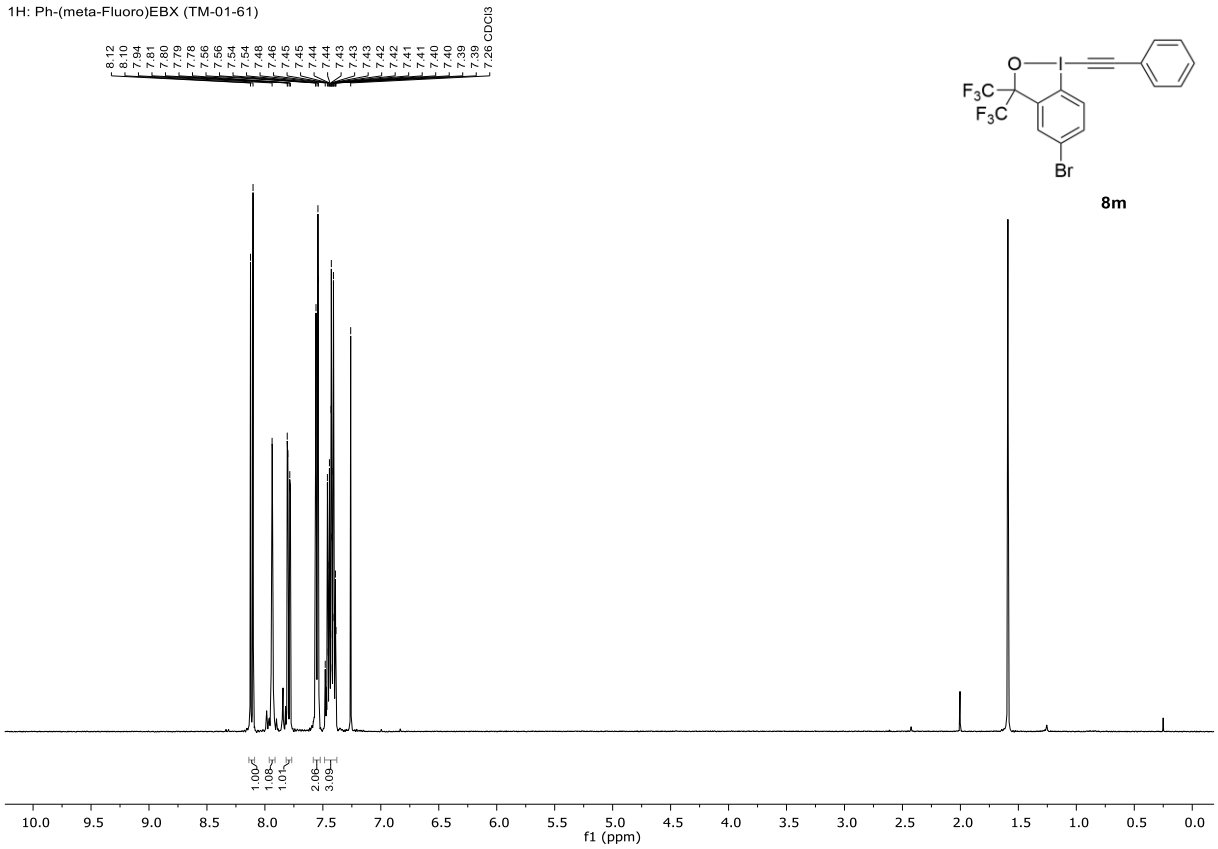


^{19}F-NMR (376 MHz, $CDCl_3$)

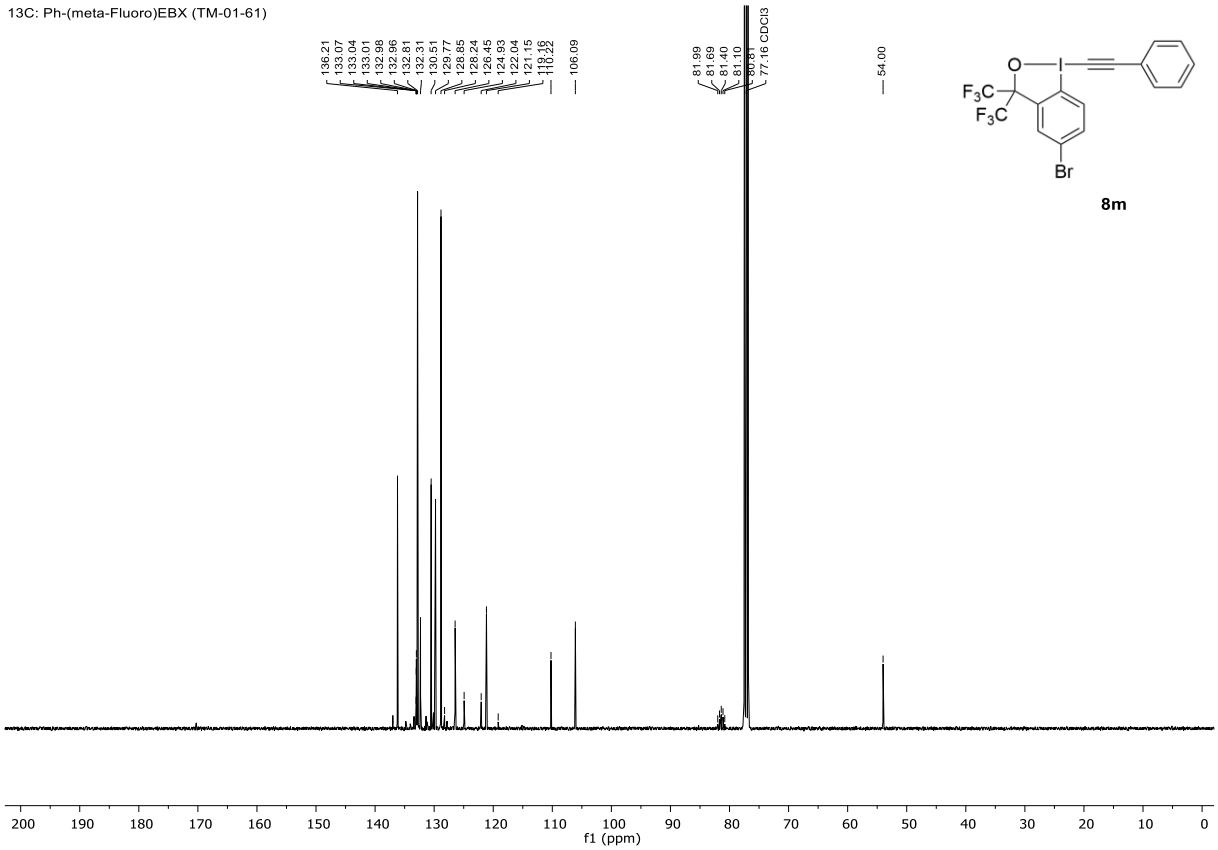


5-Bromo-(1-phenylethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (8m)

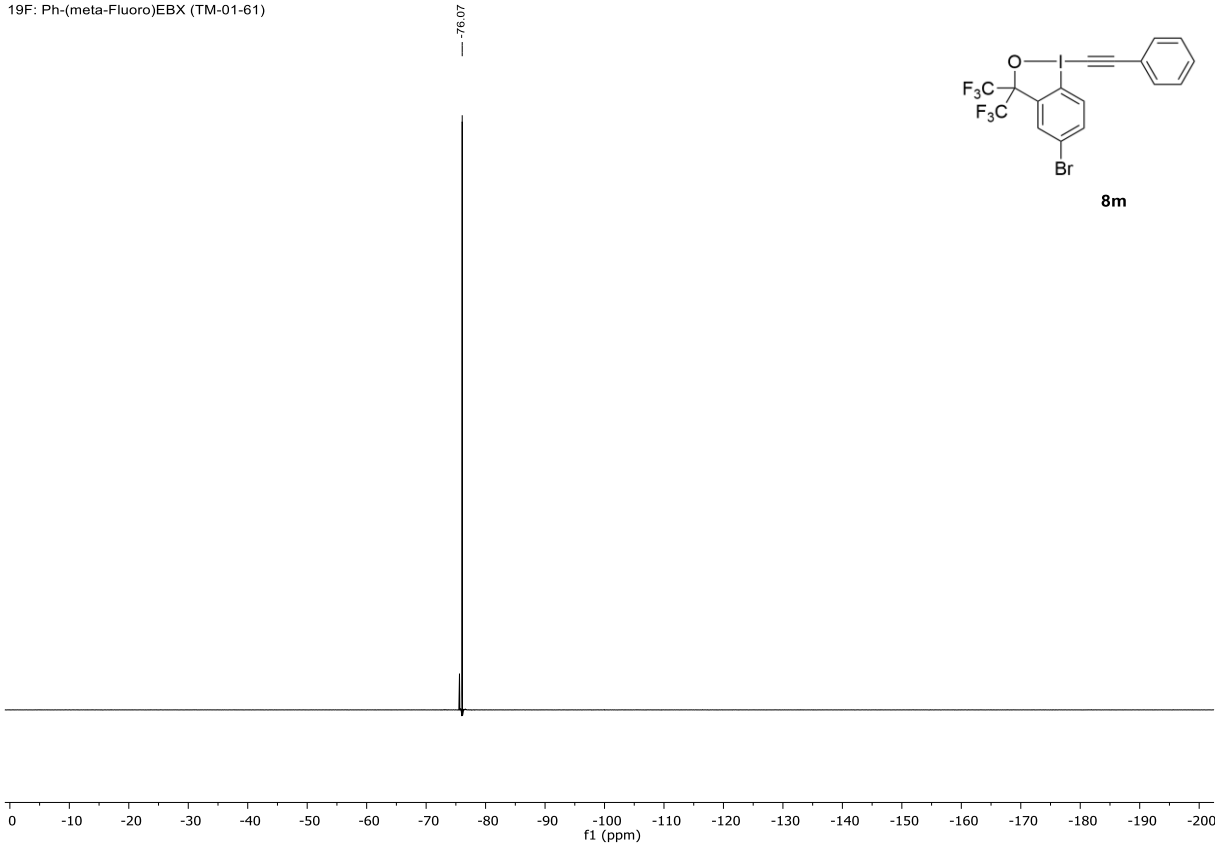
^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)

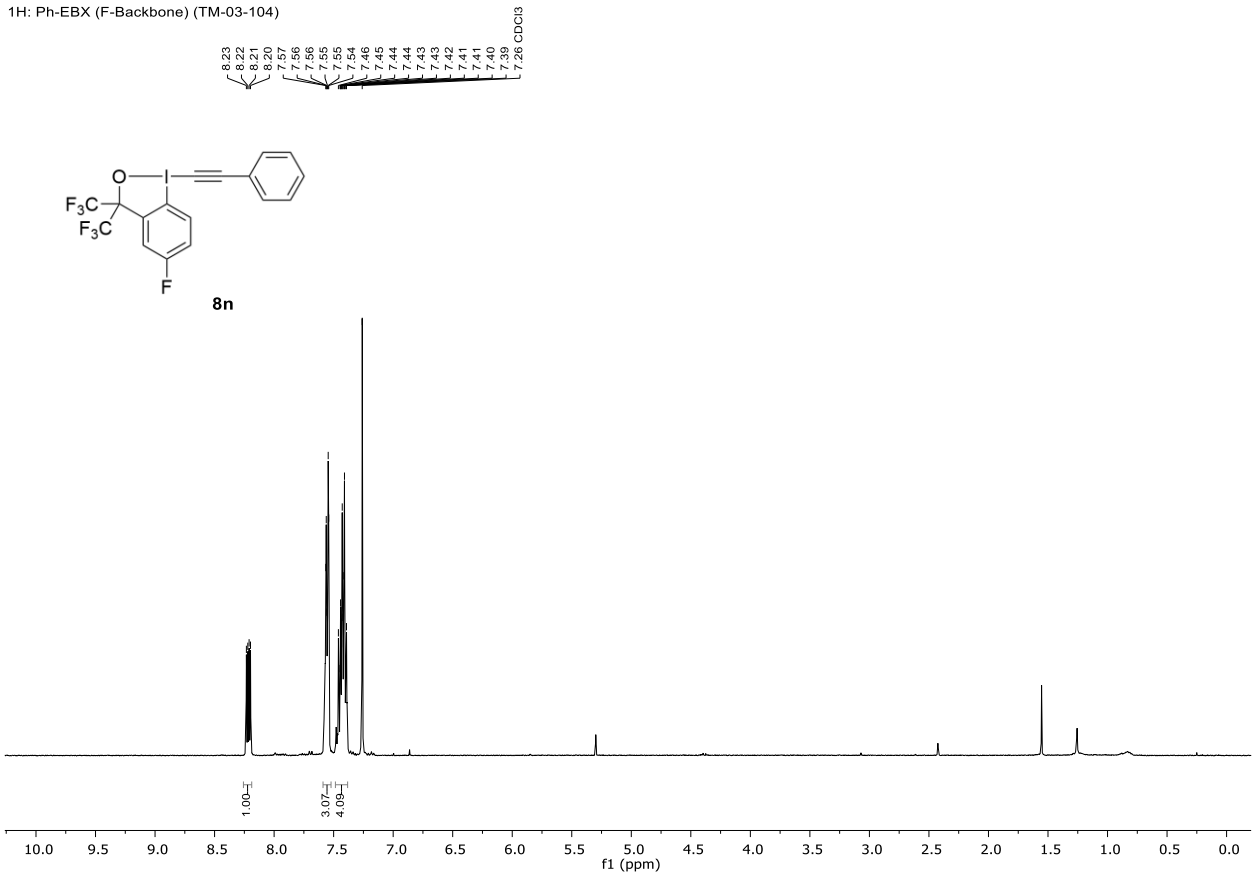


^{19}F-NMR (376 MHz, $CDCl_3$)

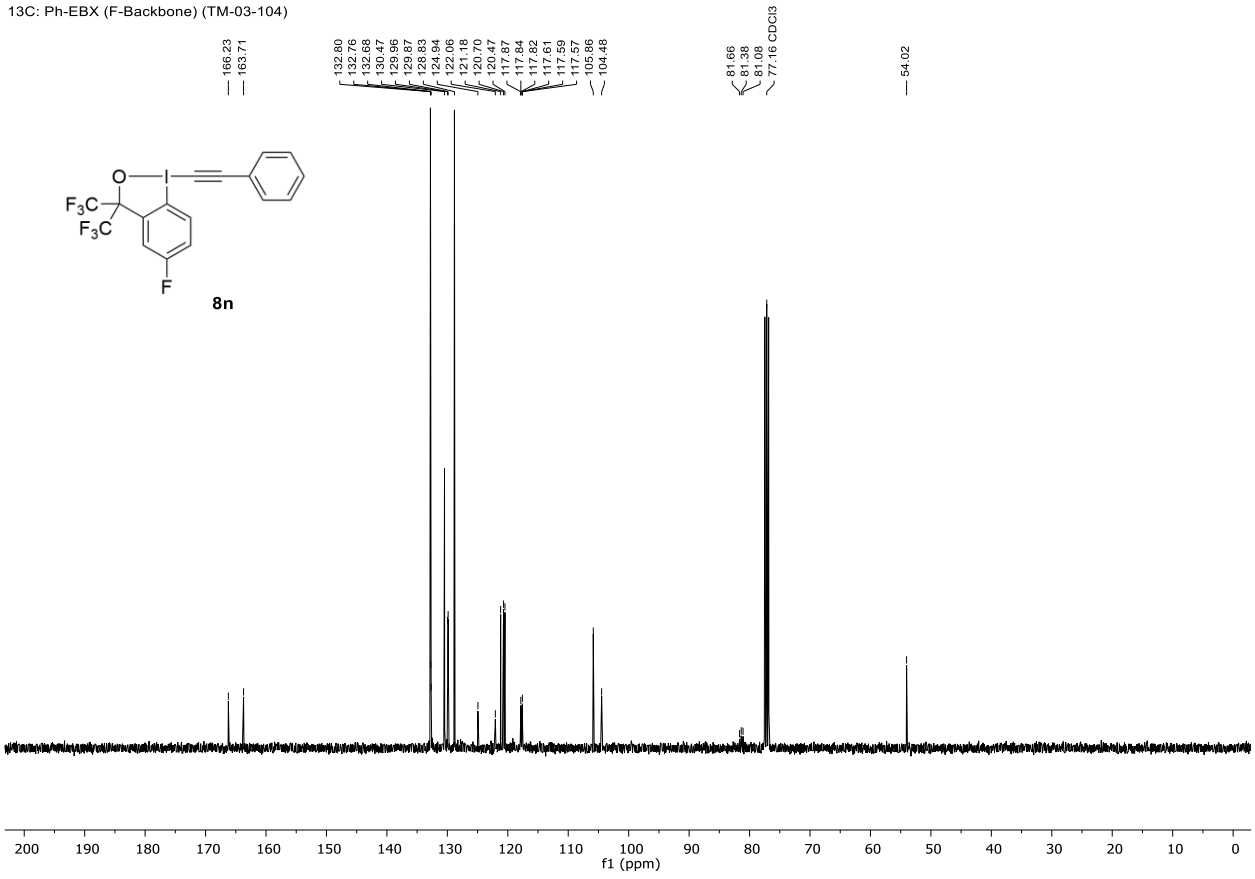


5-Fluoro-(1-phenylethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (8n)

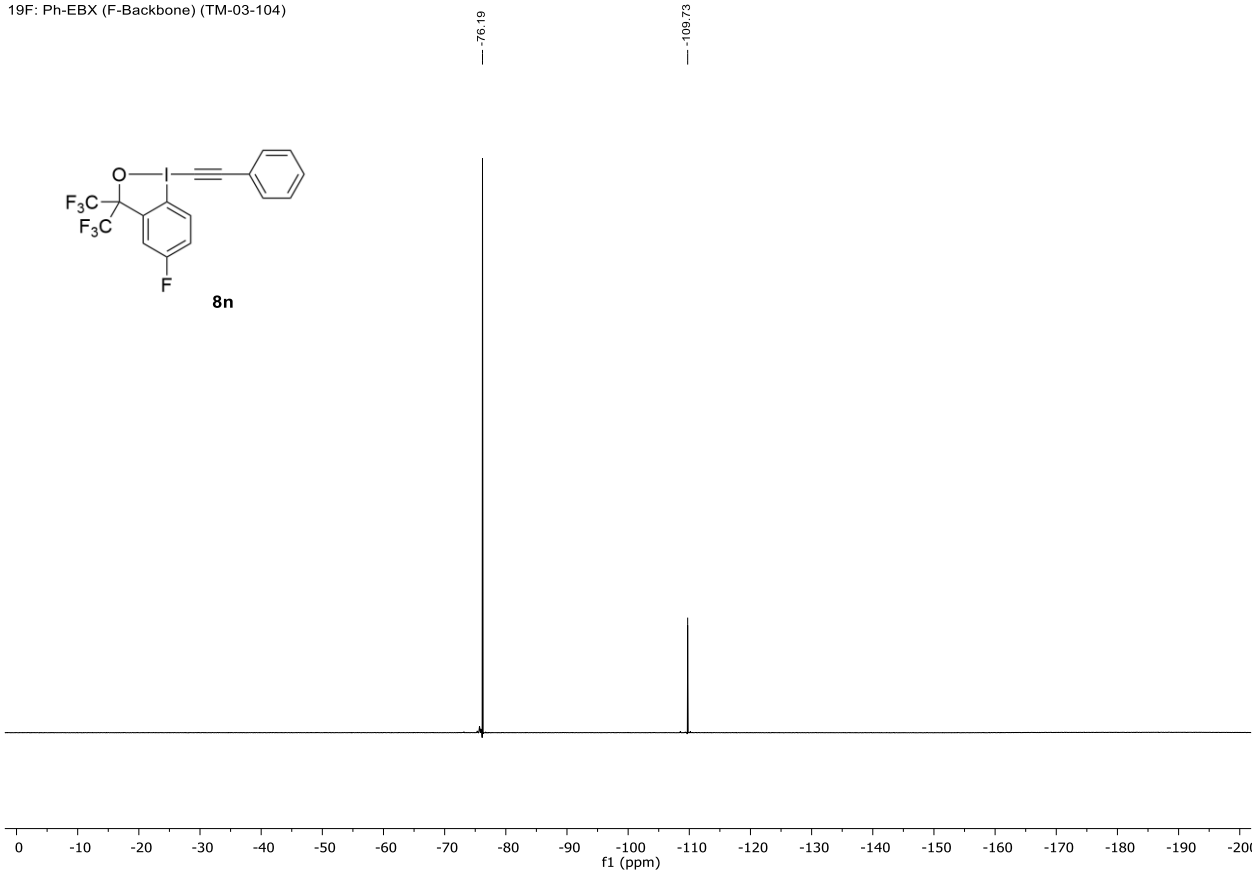
^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)

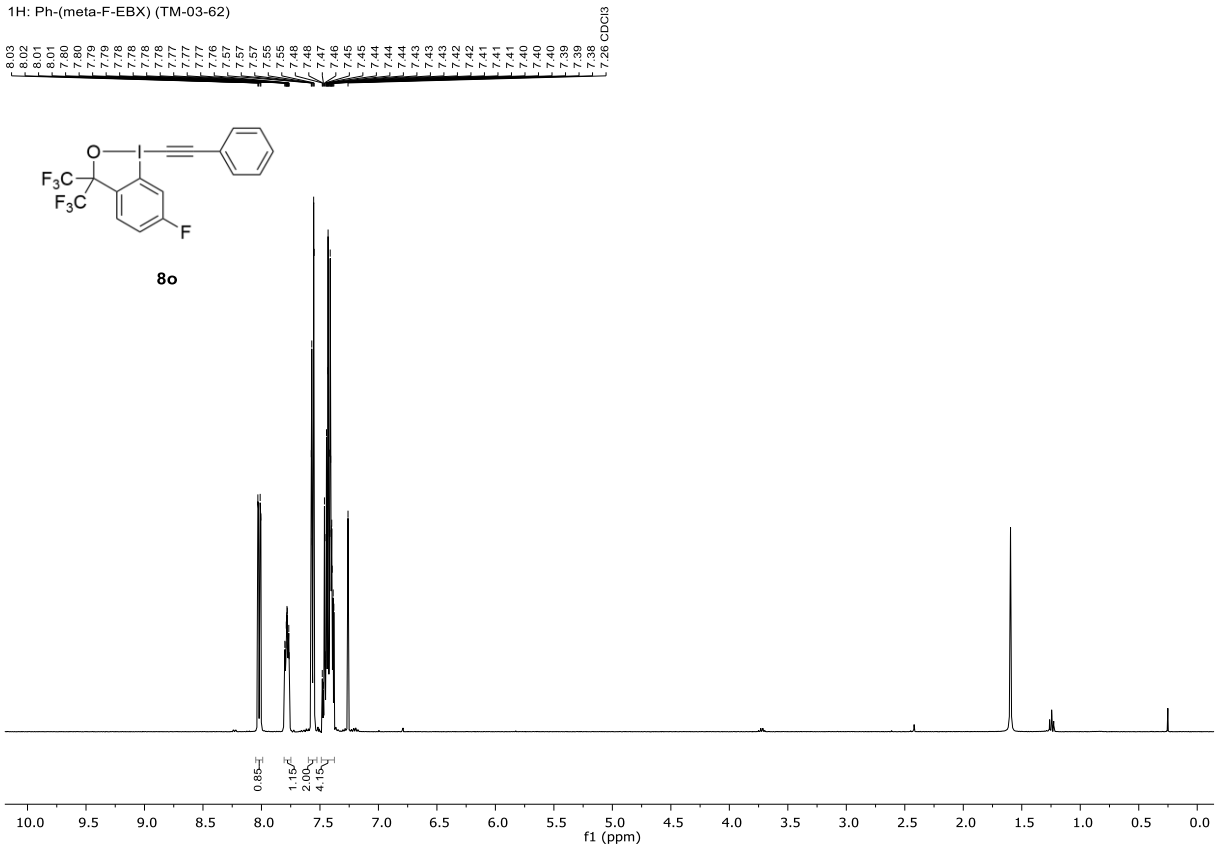


^{19}F-NMR (376 MHz, $CDCl_3$)

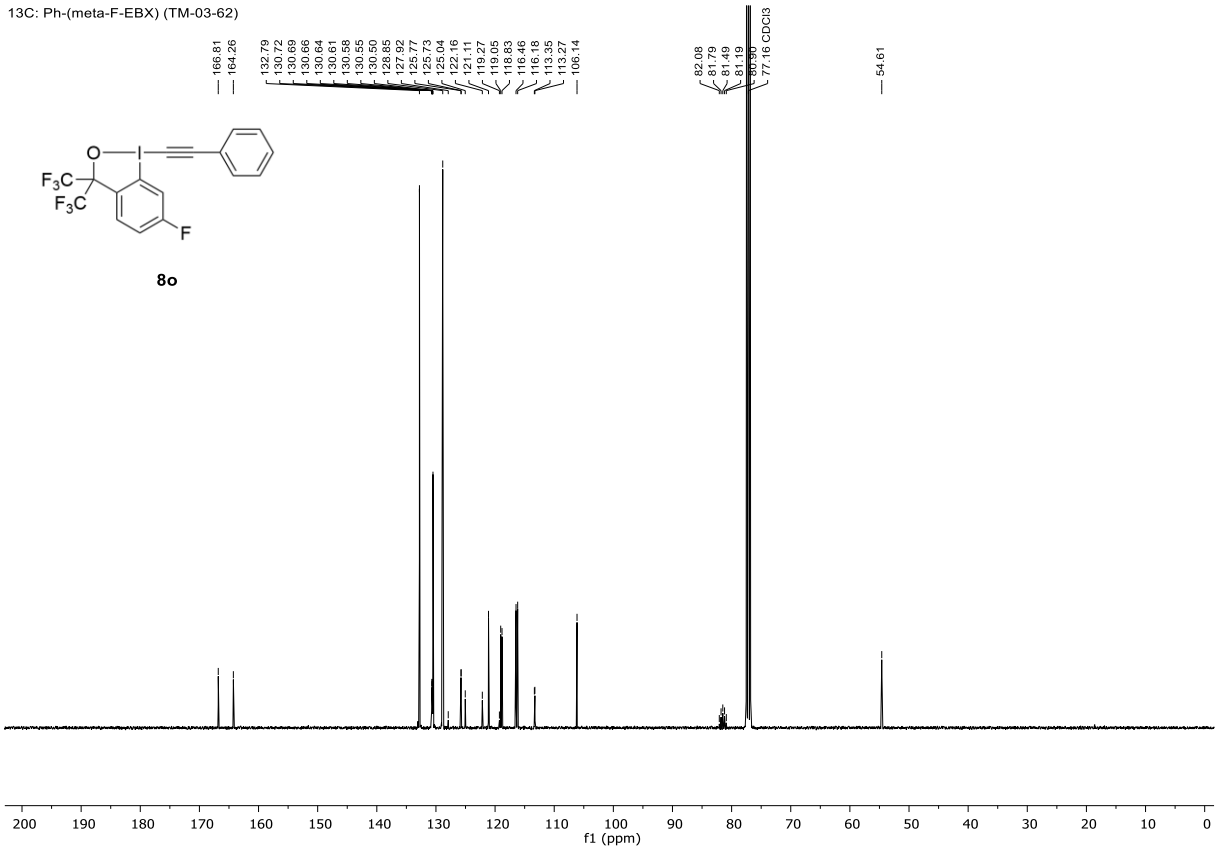


6-Fluoro-(1-phenylethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (8o)

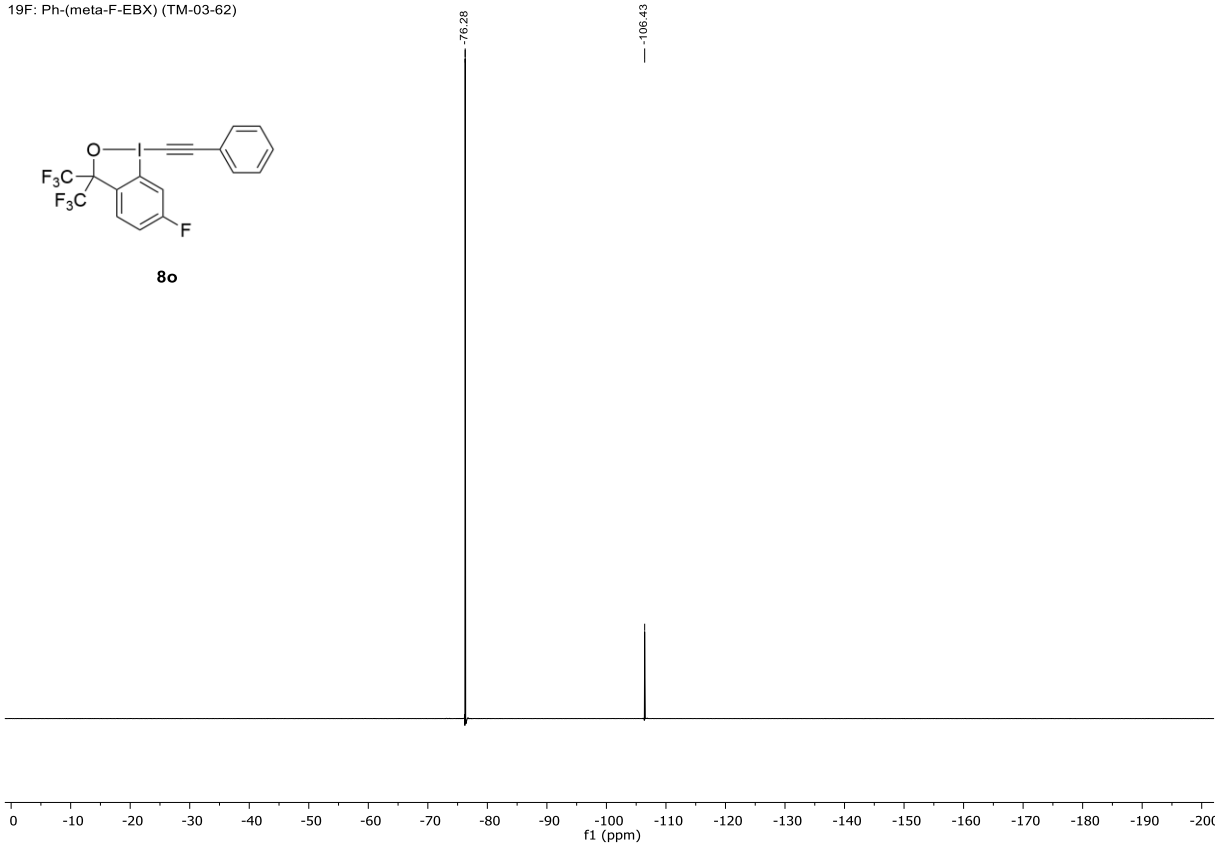
^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)



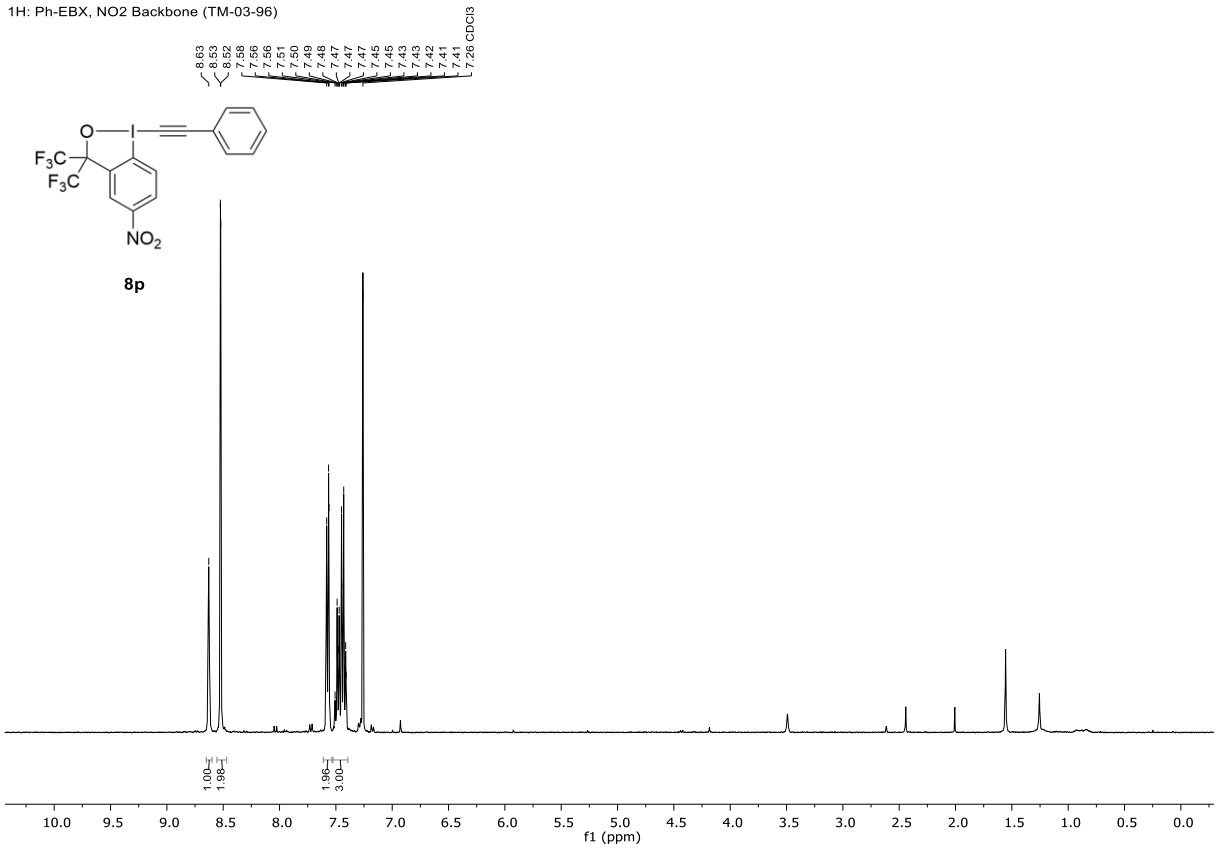
^{19}F-NMR (376 MHz, $CDCl_3$)



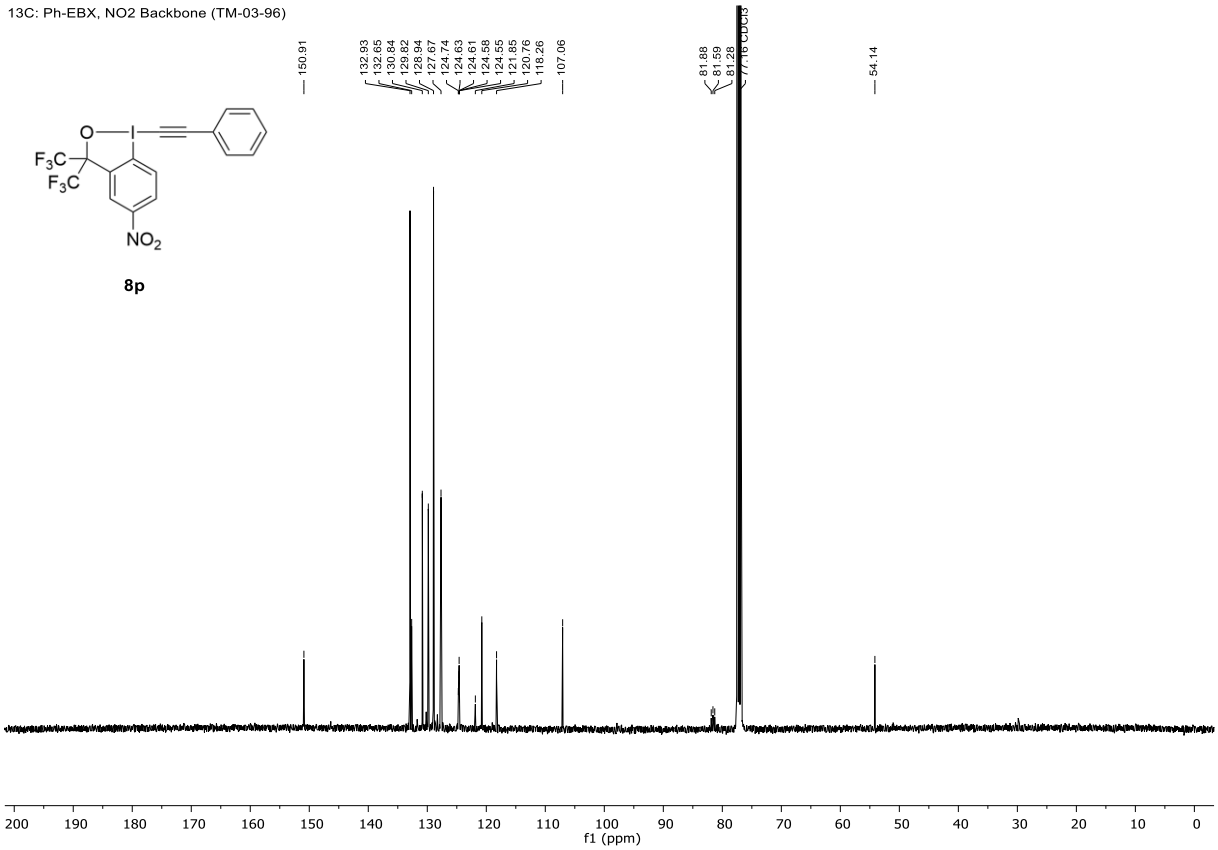
8o

5-Nitro-(1-phenylethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (8p)

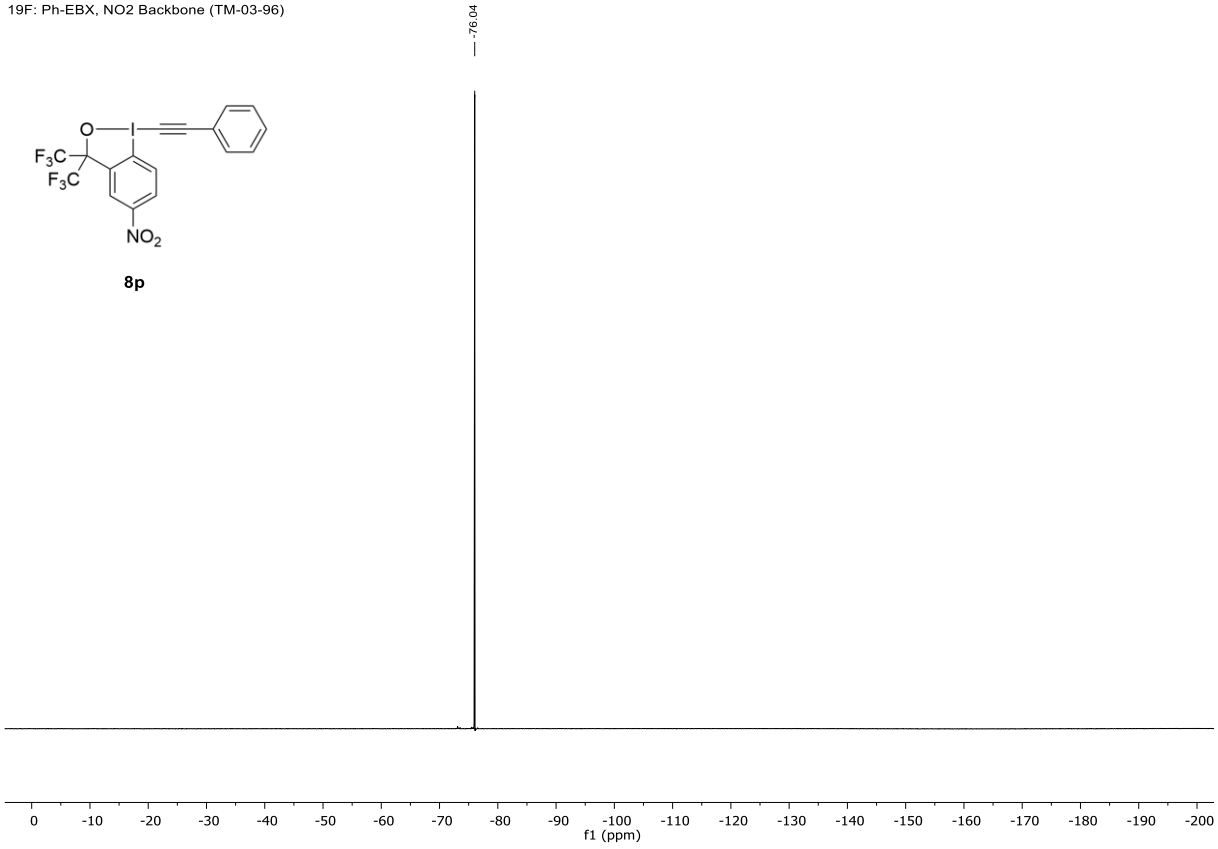
^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)

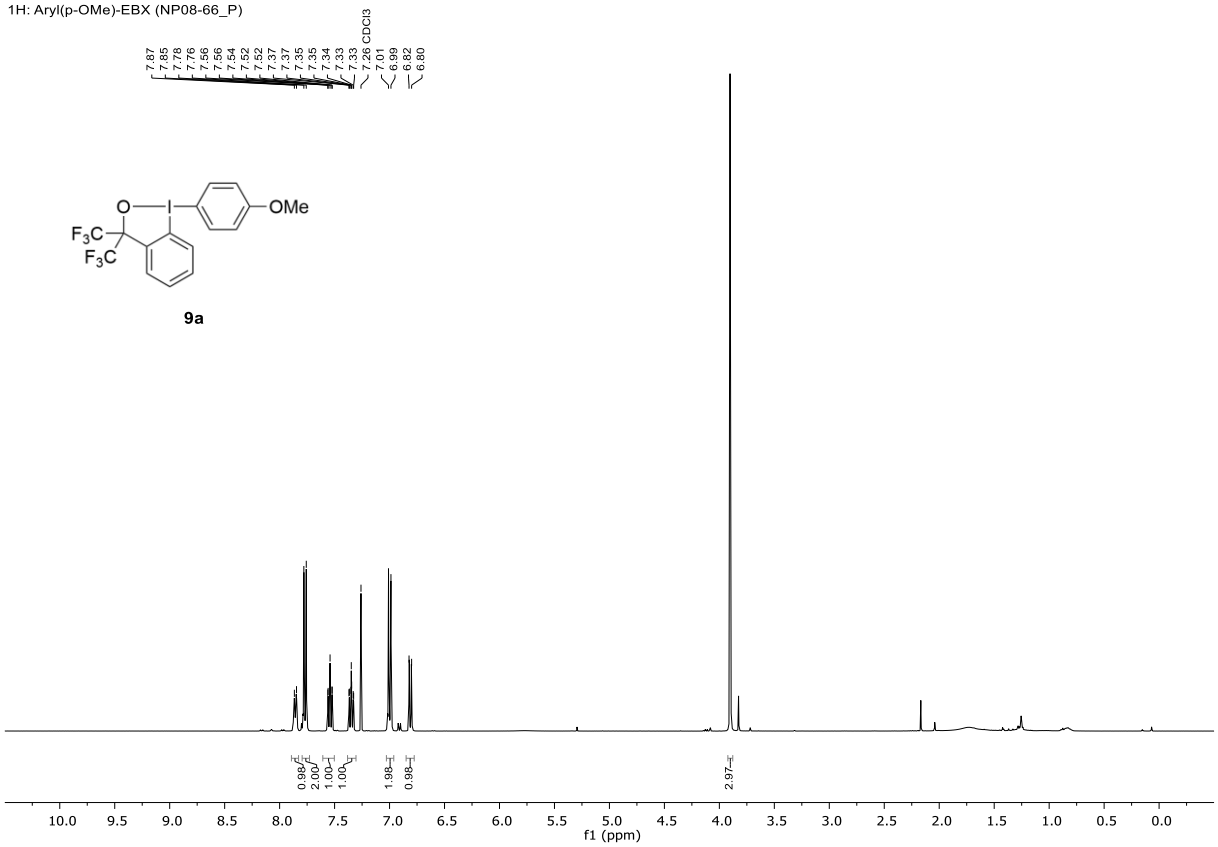


^{19}F-NMR (376 MHz, $CDCl_3$)

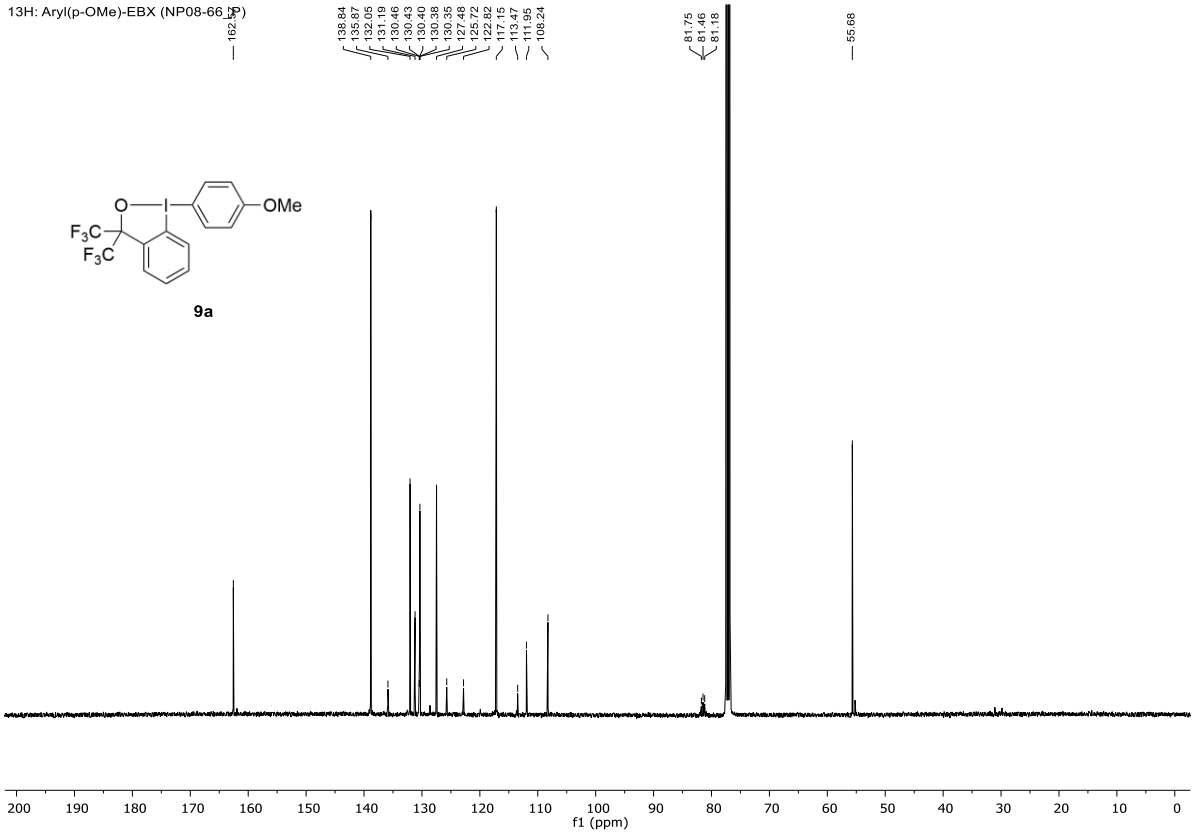


1-(4-Methoxyphenyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (9a)

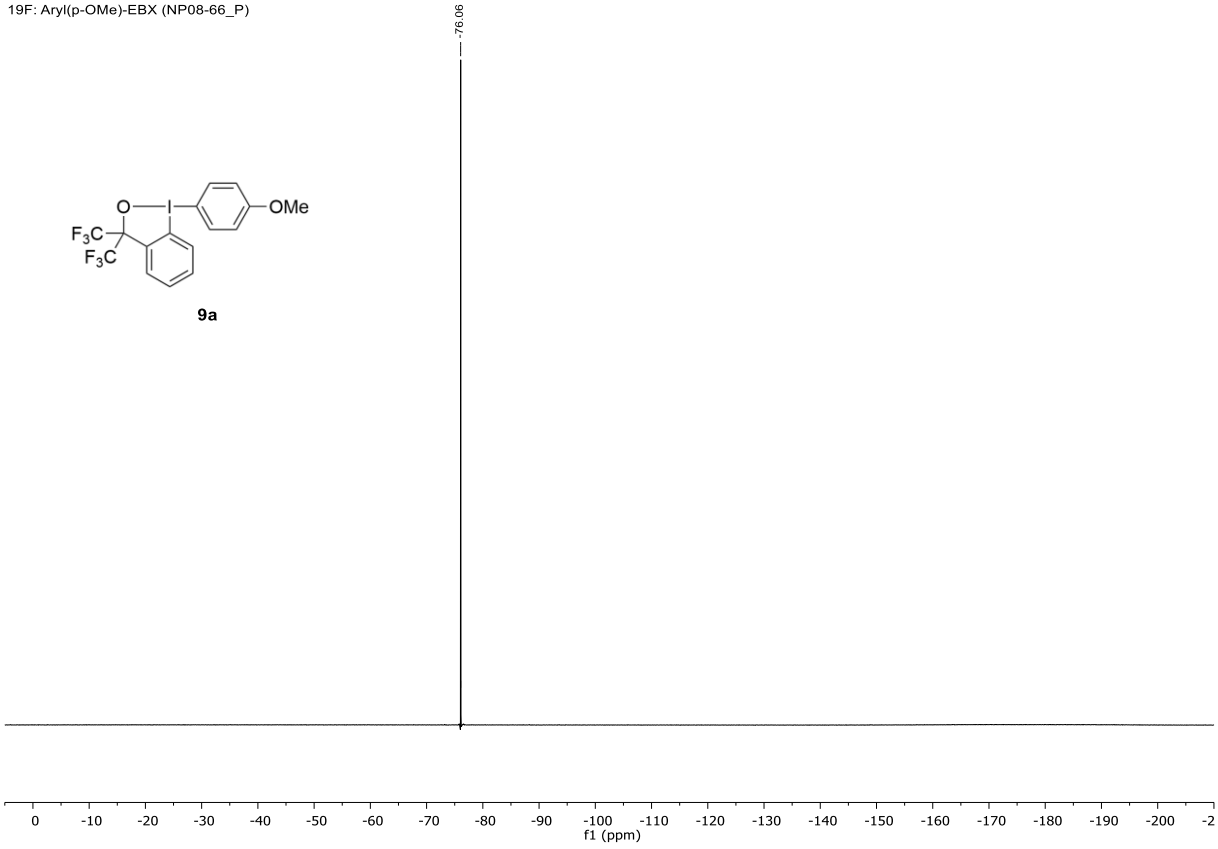
^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)



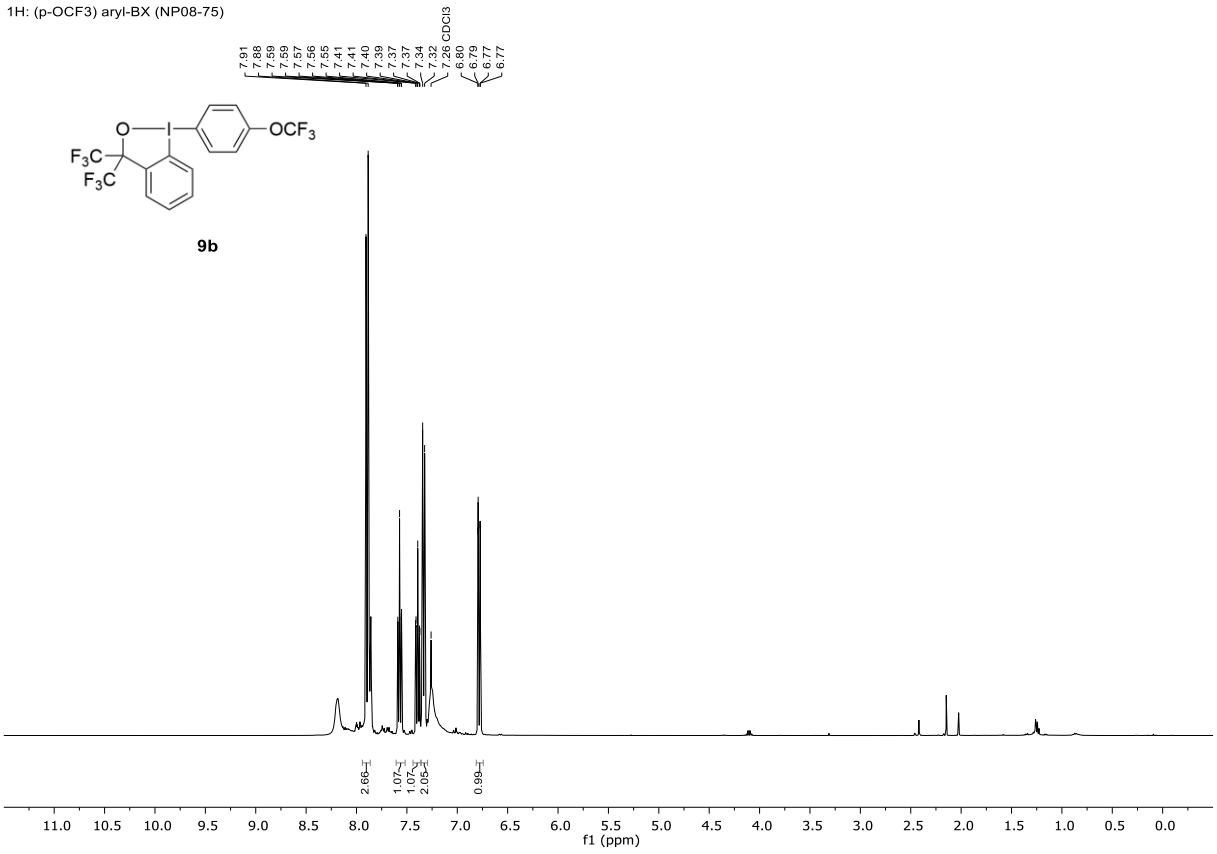
^{19}F-NMR (376 MHz, $CDCl_3$)



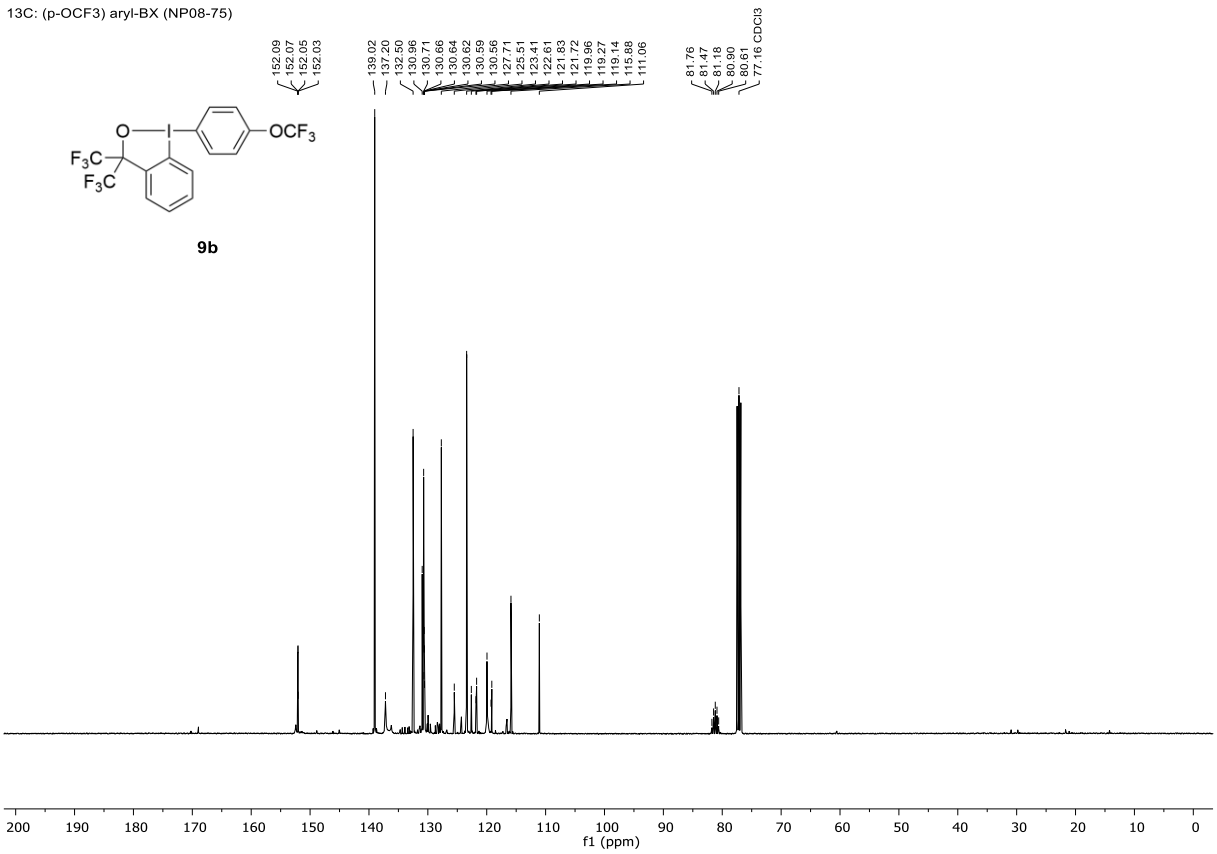
9a

1-(4-(Trifluoromethoxy)phenyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (9b)

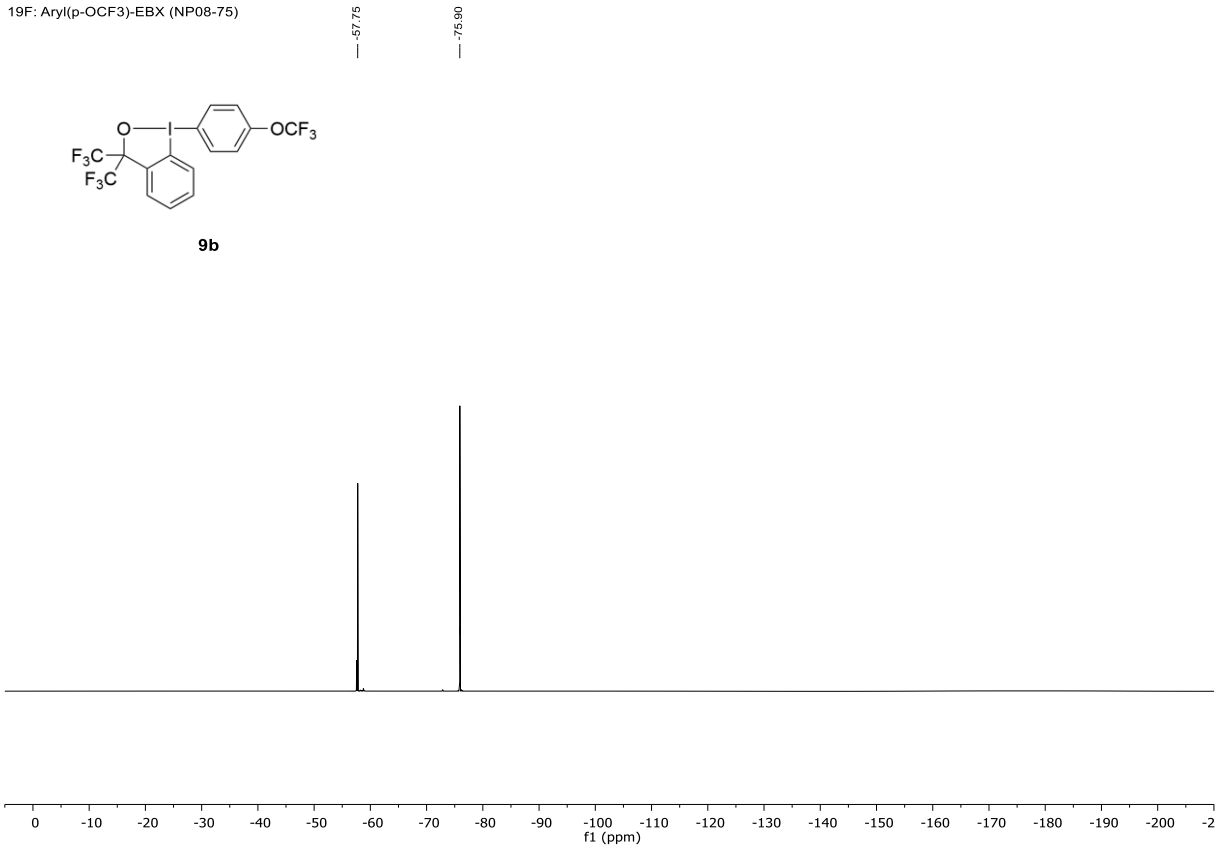
^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)



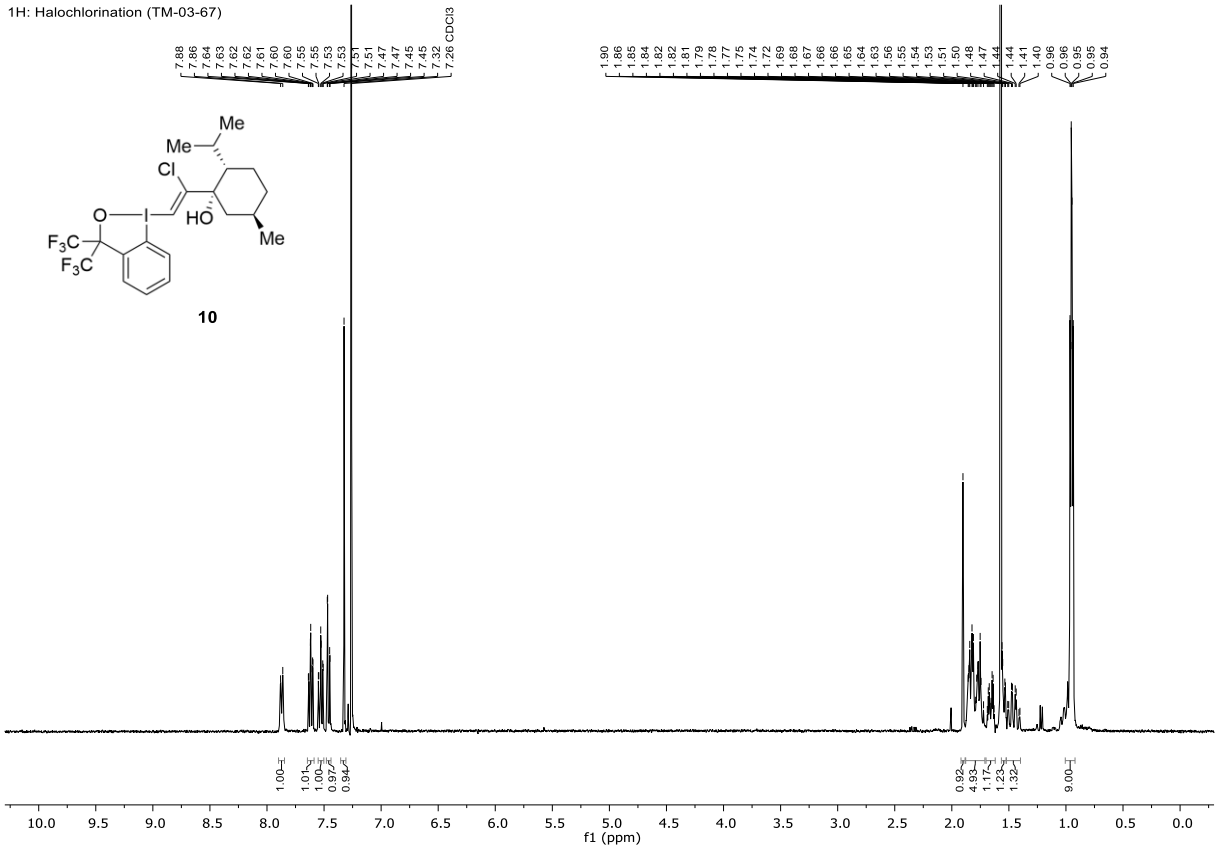
^{19}F-NMR (376 MHz, $CDCl_3$)



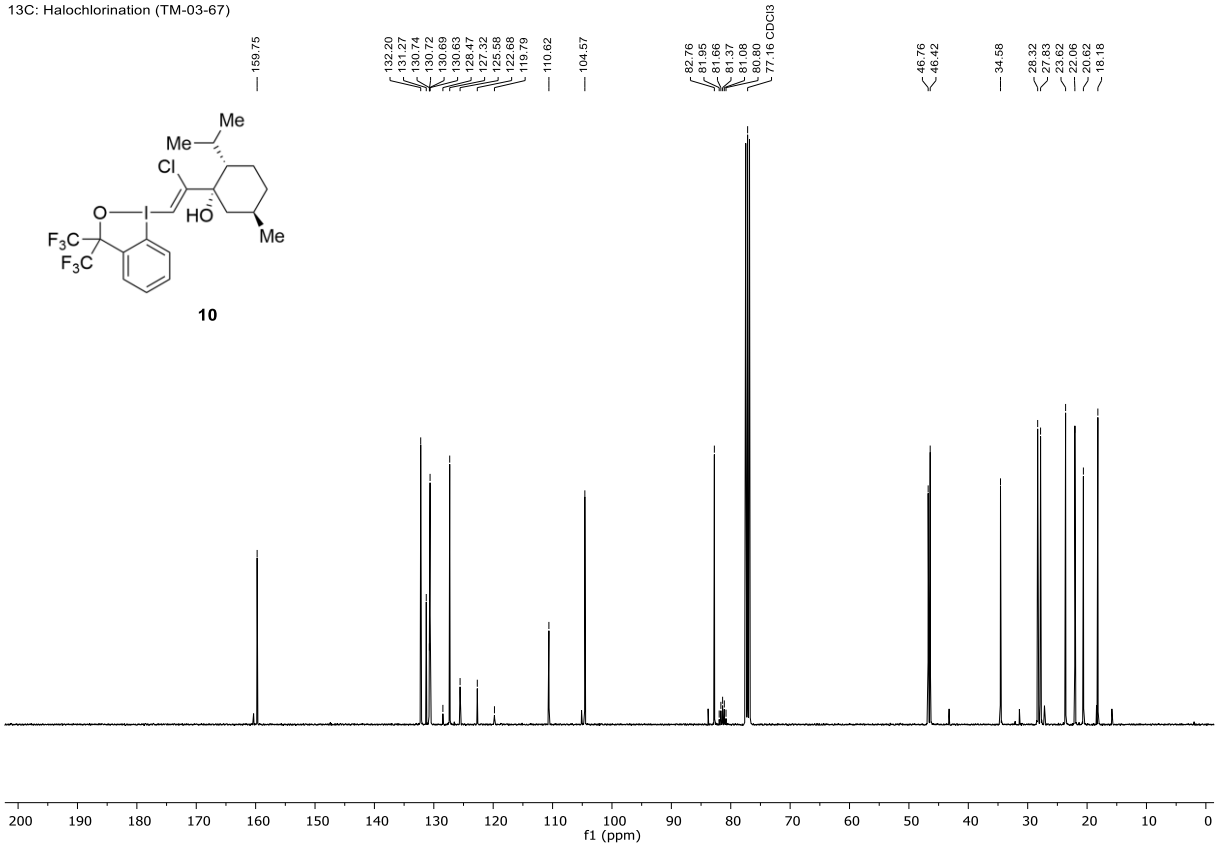
9b

(1*S*,2*S*,5*R*)-1-((*Z*)-2-(3,3-Bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)-1-chloro-vinyl)-2-isopropyl-5-methylcyclohexan-1-ol (10)

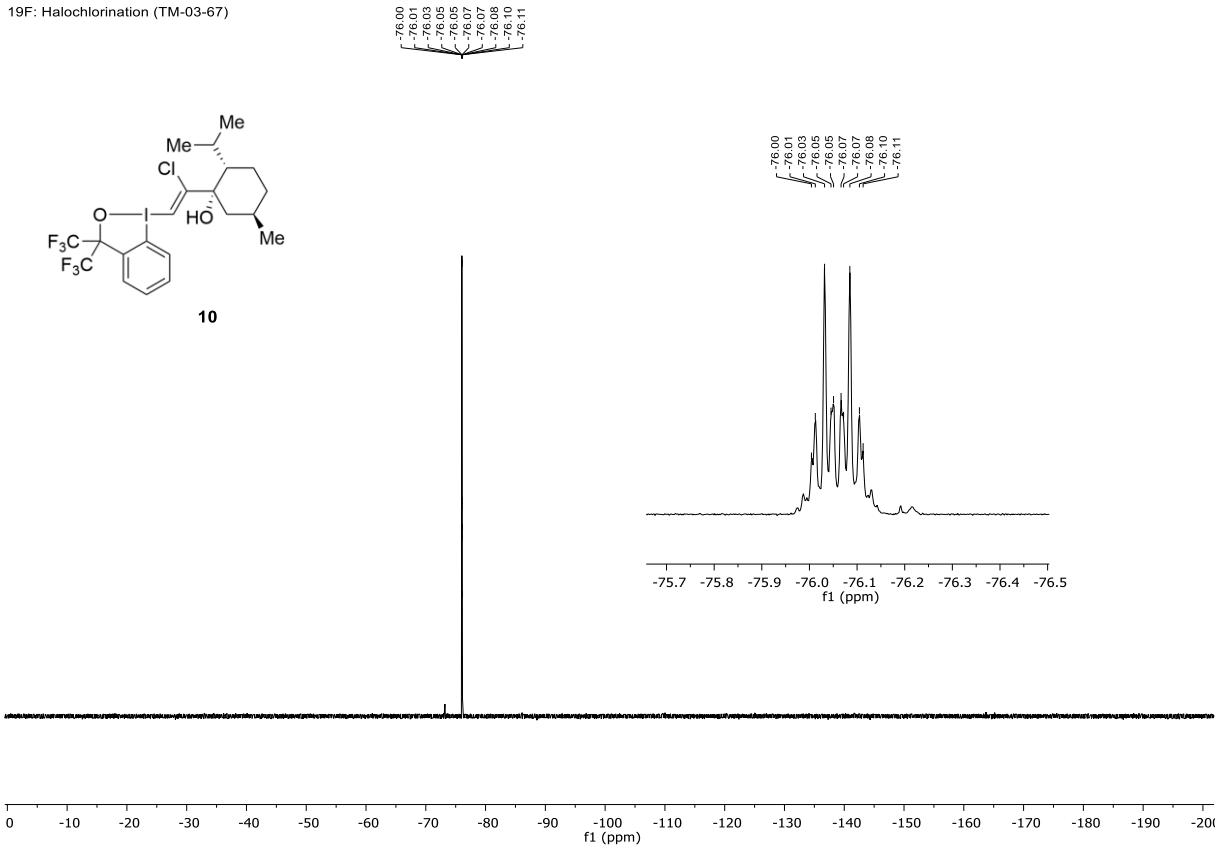
^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)

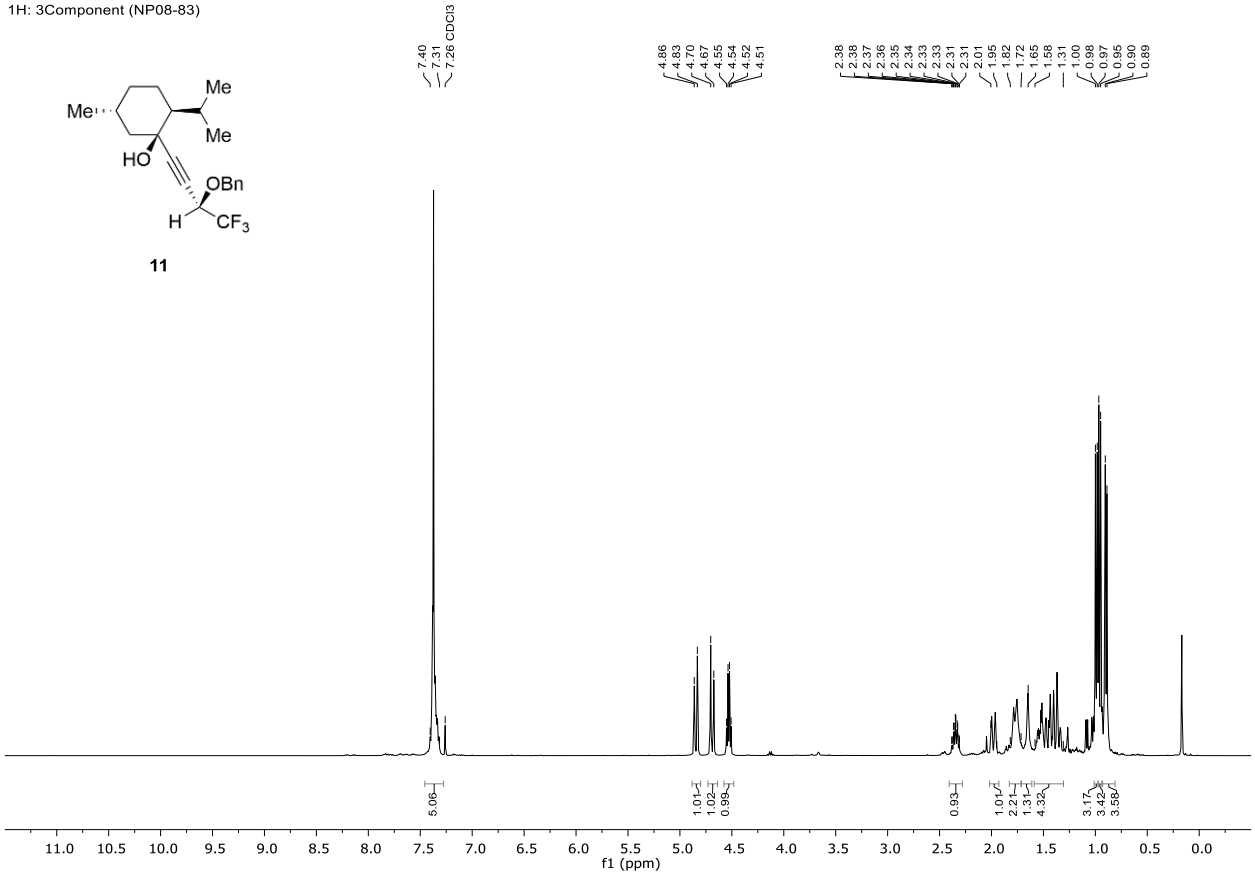


^{19}F-NMR (376 MHz, $CDCl_3$)

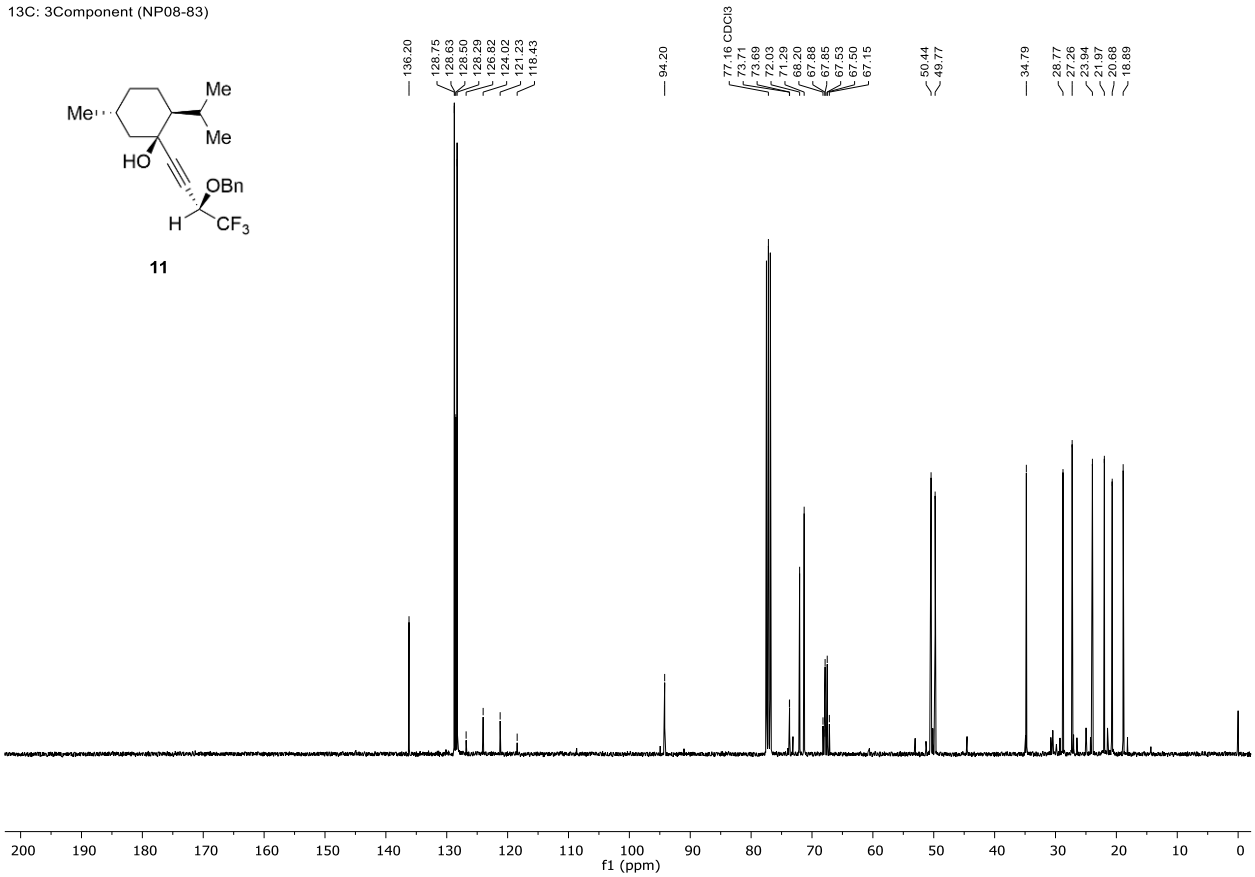


(1*S*,2*S*,5*R*)-1-((*S*)-3-(Benzyloxy)-4,4,4-trifluorobut-1-yn-1-yl)-2-isopropyl-5-methylcyclohexan-1-ol (11)

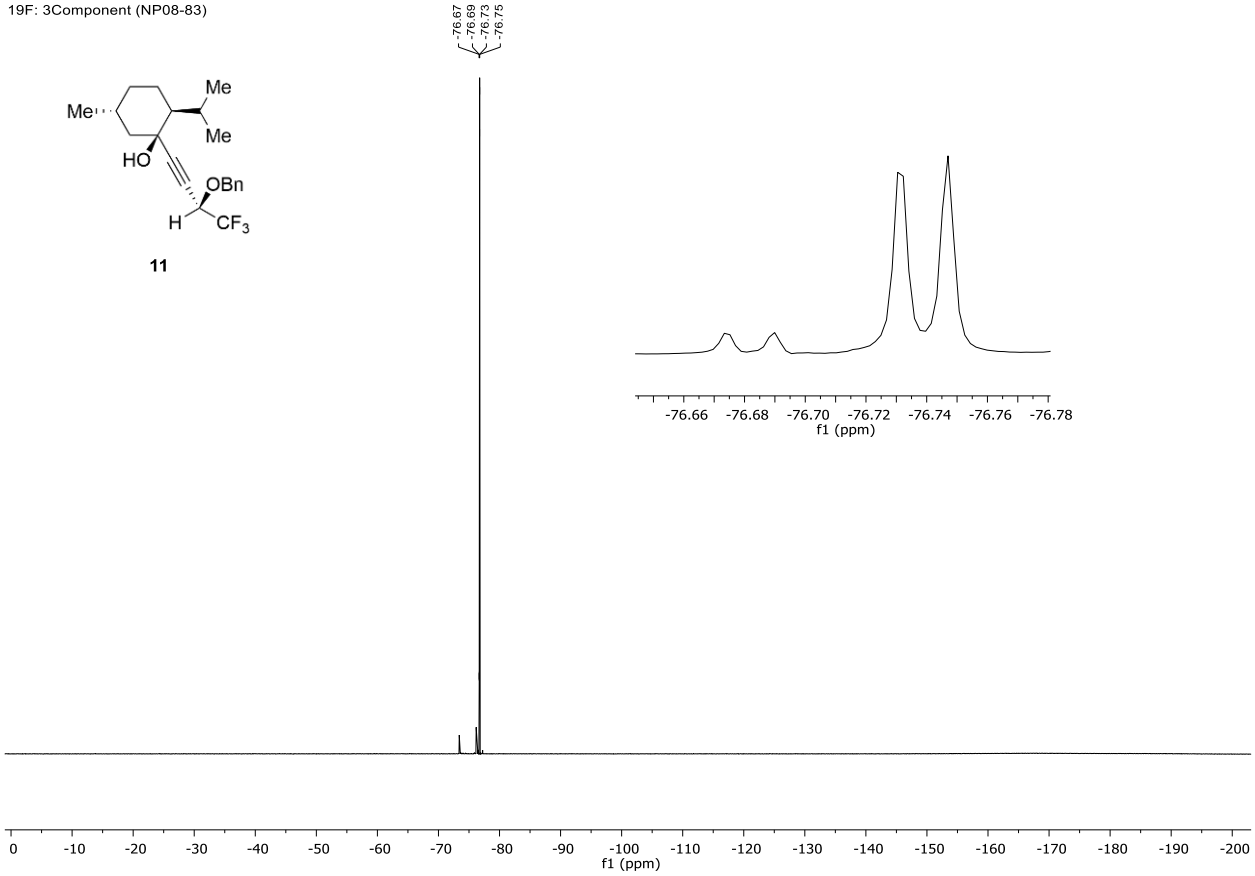
^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)

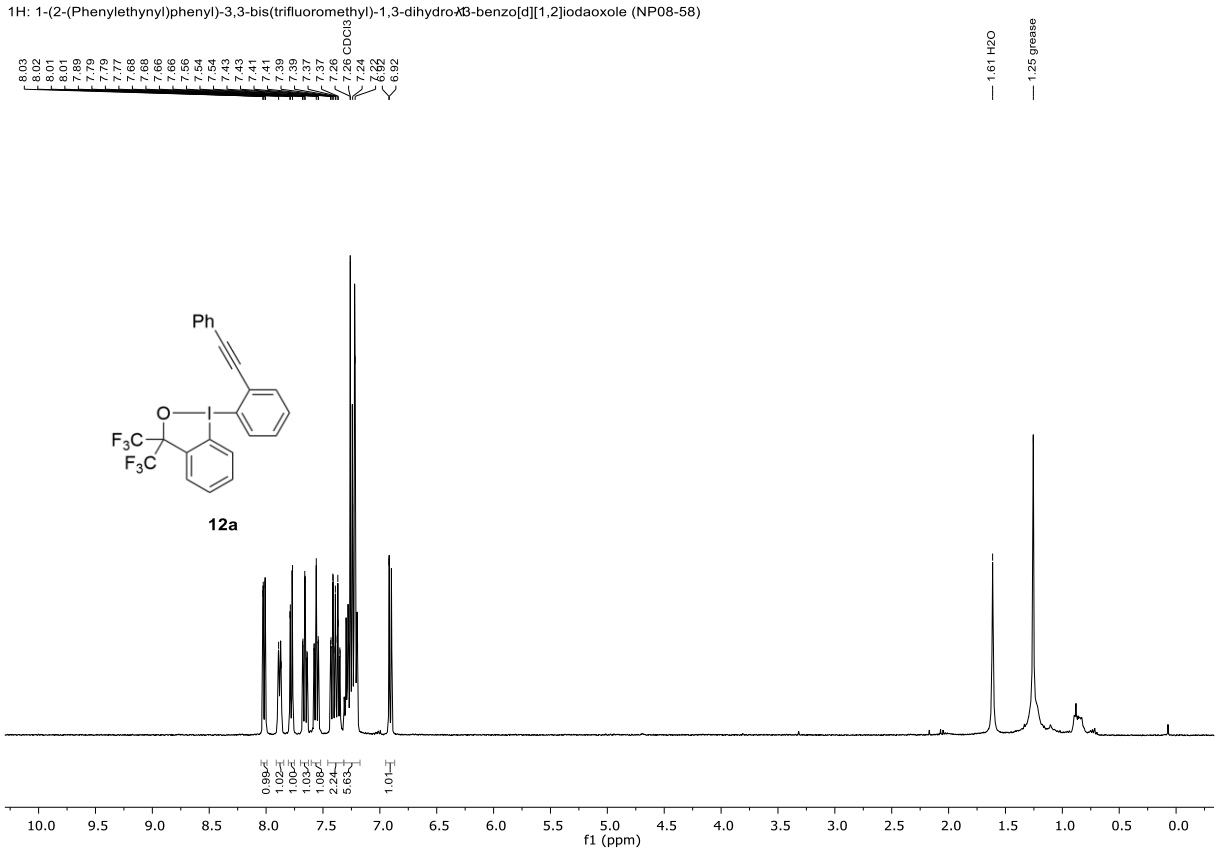


^{19}F-NMR (376 MHz, $CDCl_3$)

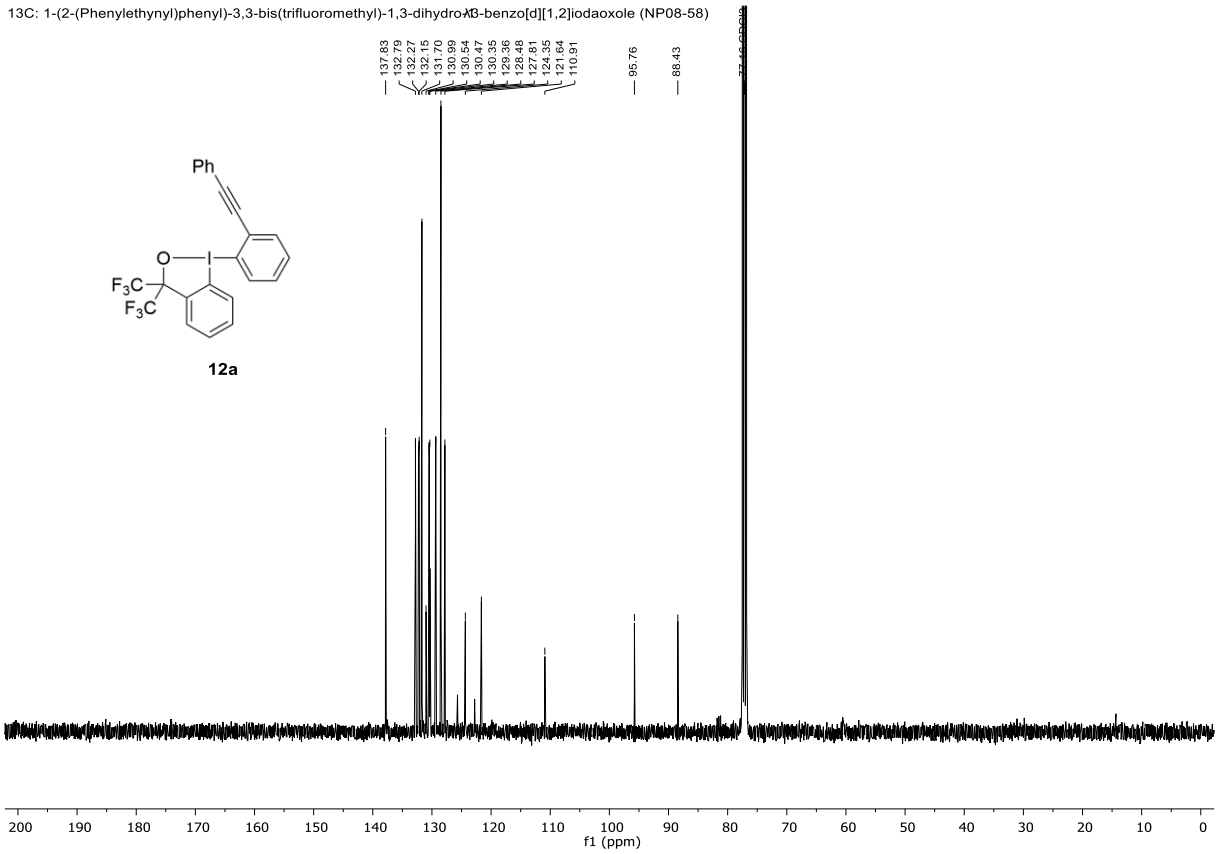


1-(2-(Phenylethynyl)phenyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (12a)

^{1}H-NMR (400 MHz, $CDCl_3$)

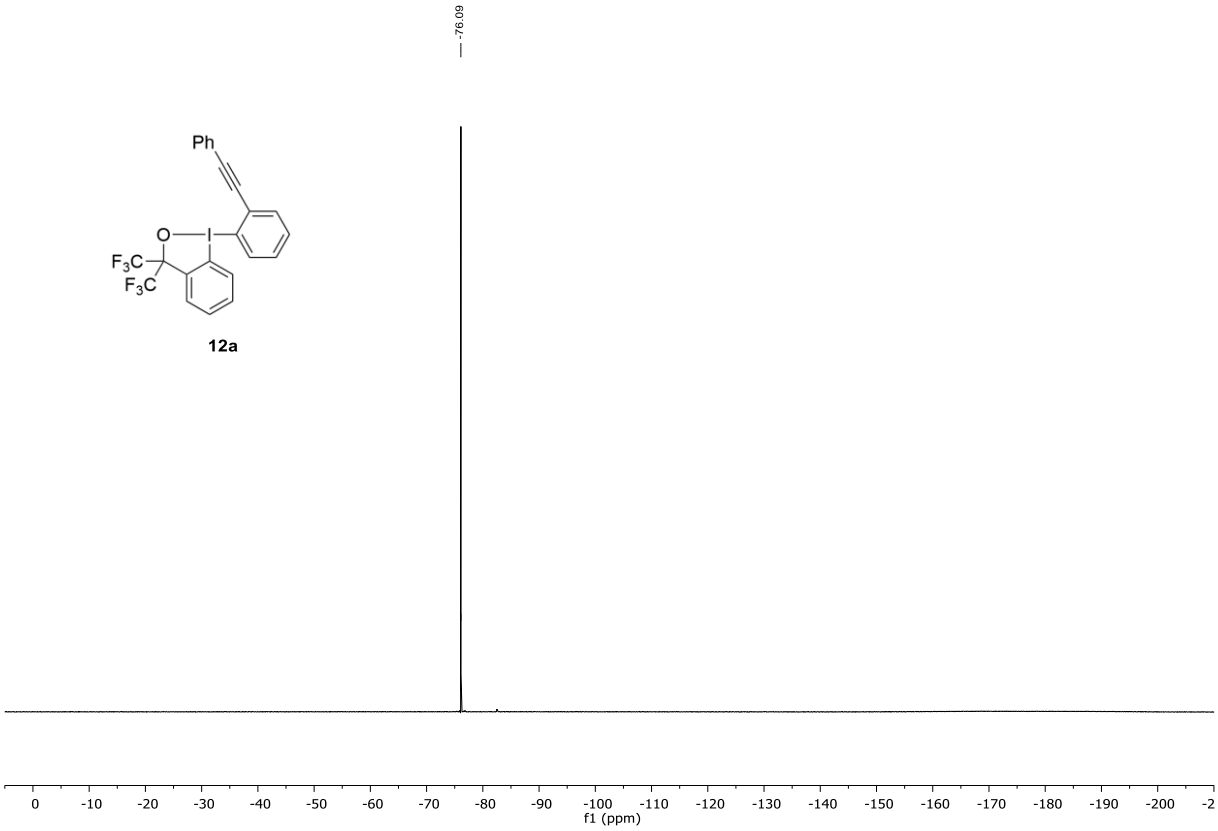


^{13}C-NMR (101 MHz, $CDCl_3$)



^{19}F-NMR (376 MHz, $CDCl_3$)

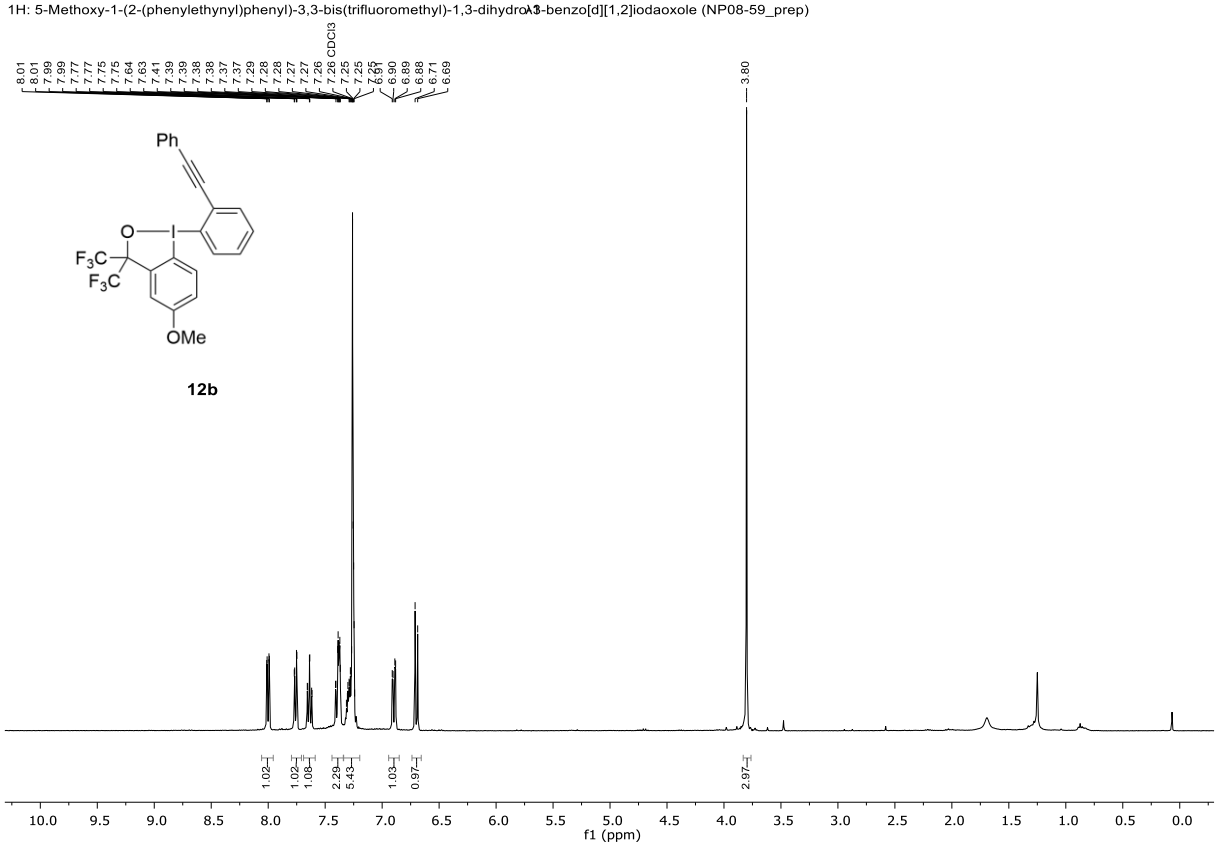
19F: 1-(2-(Phenylethynyl)phenyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ3-benzo[d][1,2]iodaoxole (NP08.58)



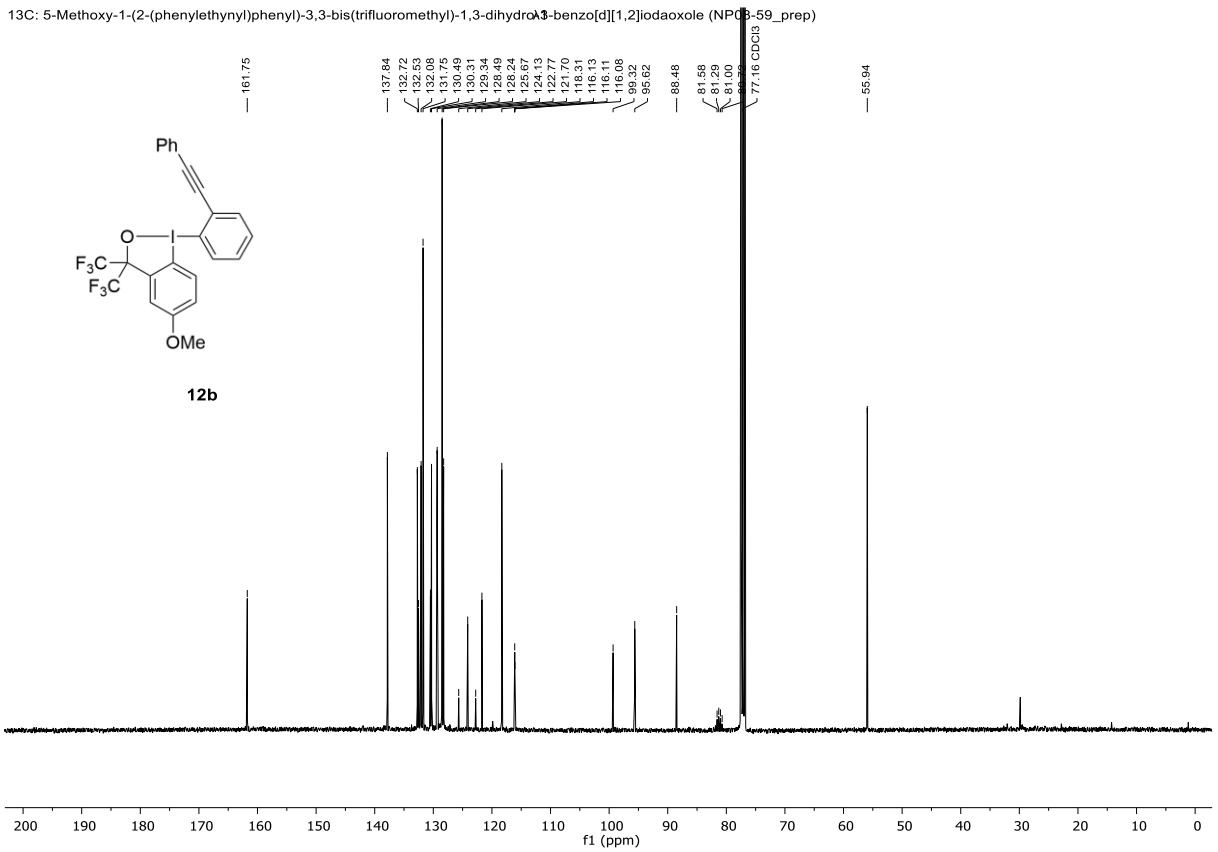
12a

5-Methoxy-1-(2-(phenylethynyl)phenyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (12b)

^{1}H-NMR (400 MHz, $CDCl_3$)

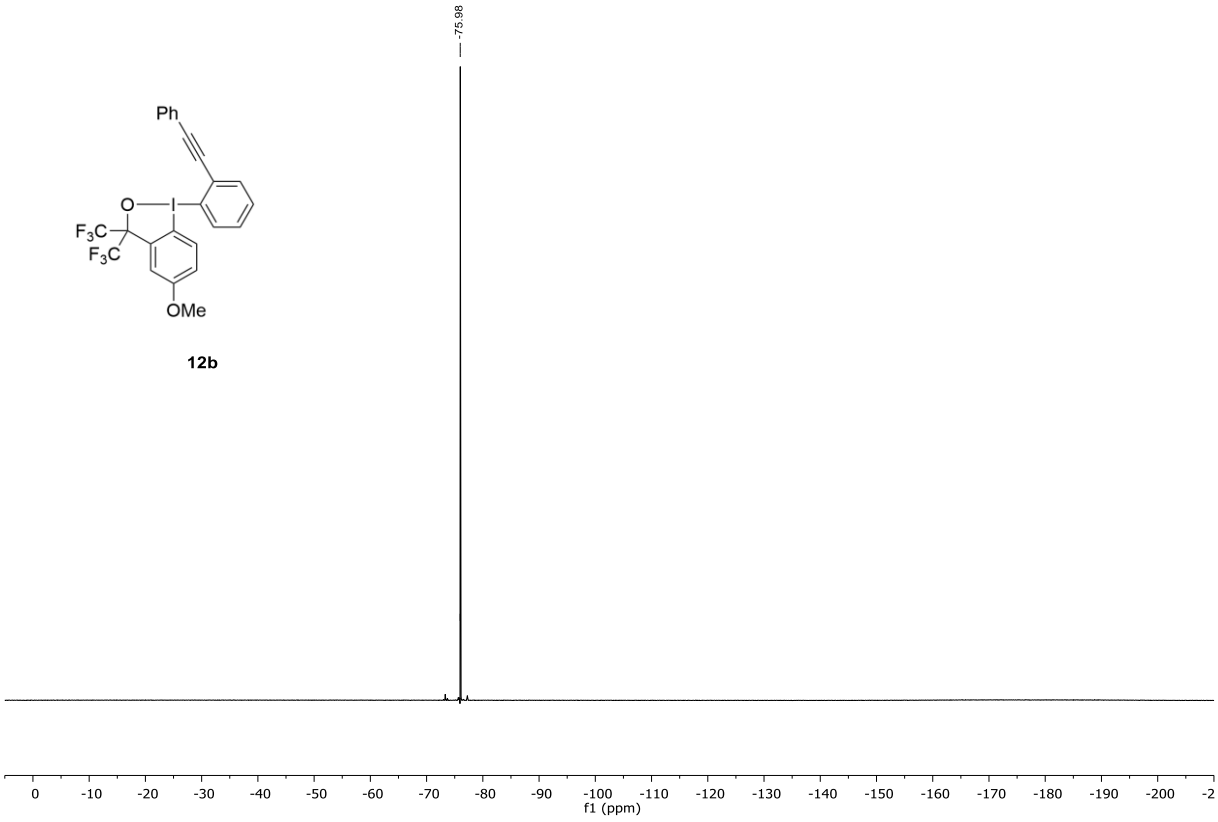


^{13}C-NMR (101 MHz, $CDCl_3$)



^{19}F-NMR (376 MHz, $CDCl_3$)

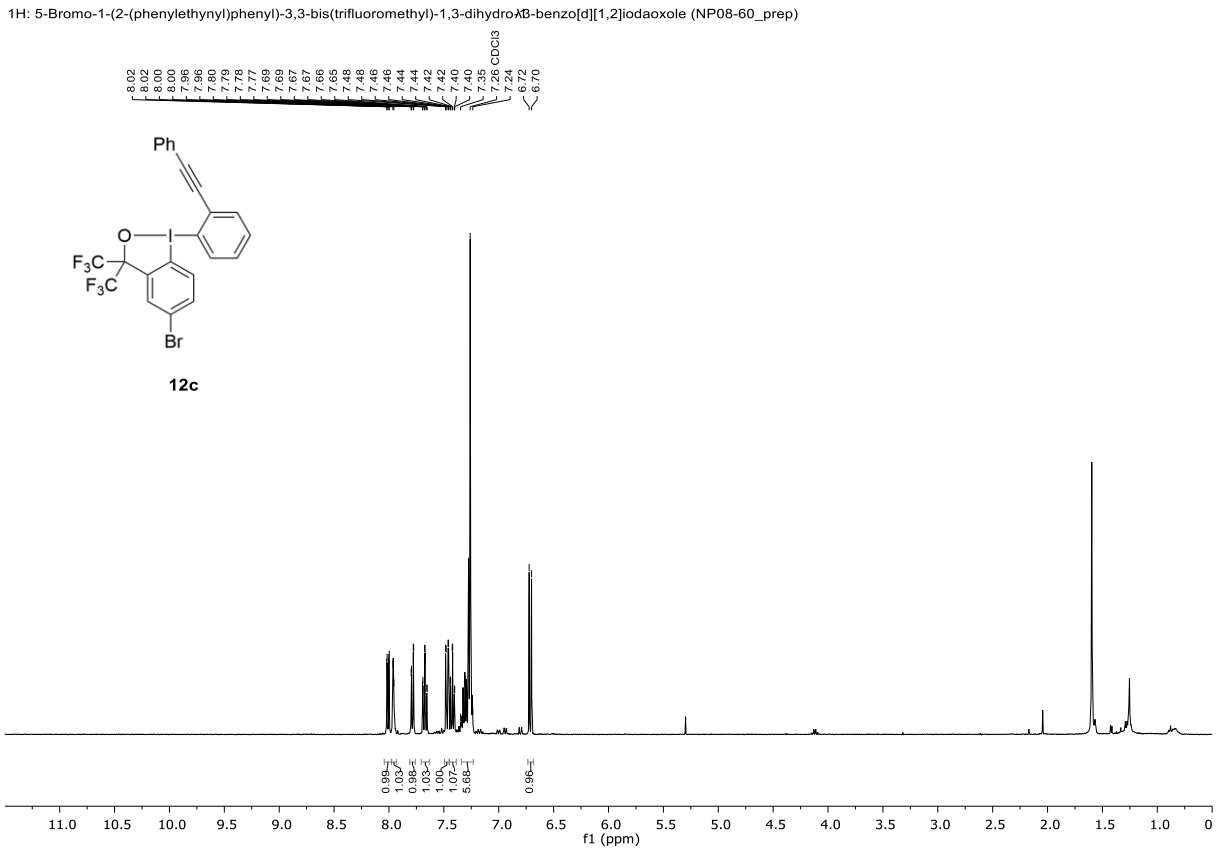
19F. 5-Methoxy-1-(2-(phenylethynyl)phenyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ3-benzo[d][1,2]iodaoxole (NP08-59_prep)



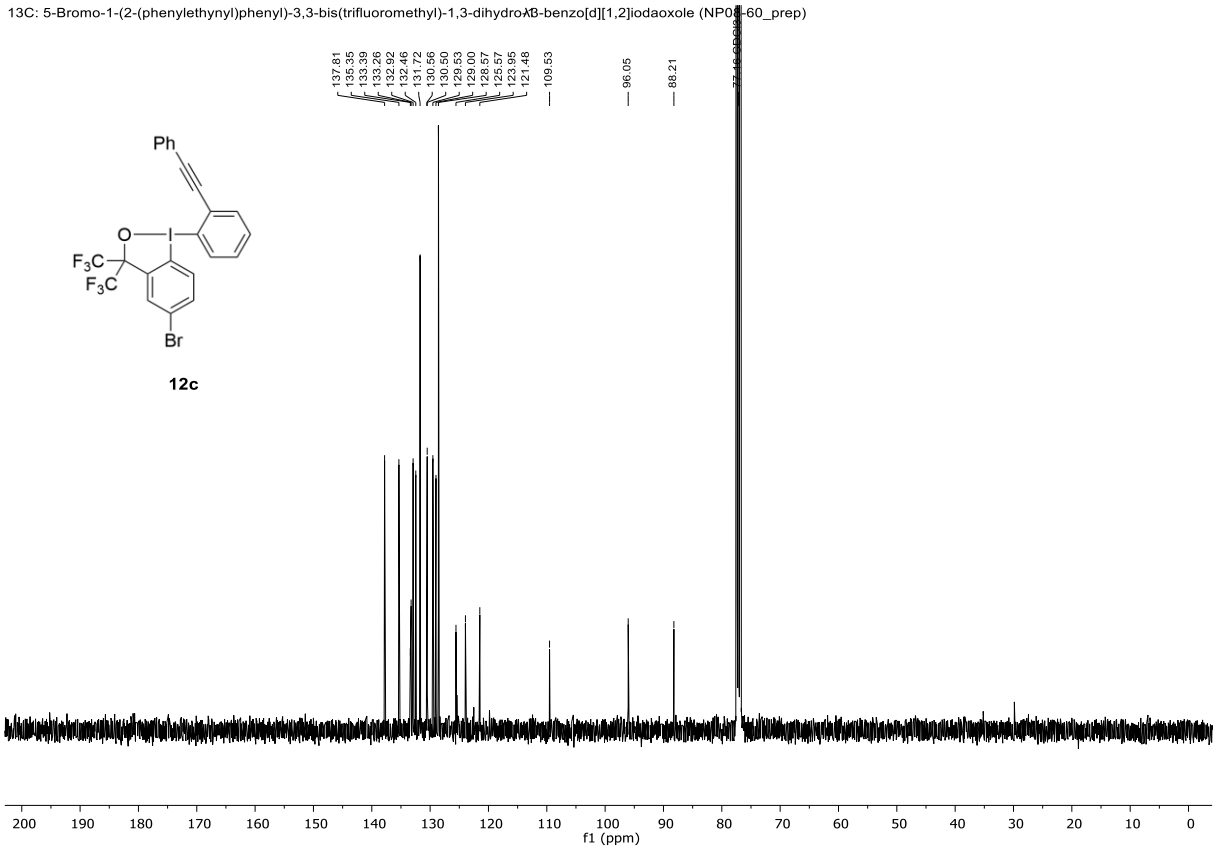
12b

5-Bromo-1-(2-(phenylethynyl)phenyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[d][1,2]iodaoxole (12c)

^{1}H-NMR (400 MHz, $CDCl_3$)

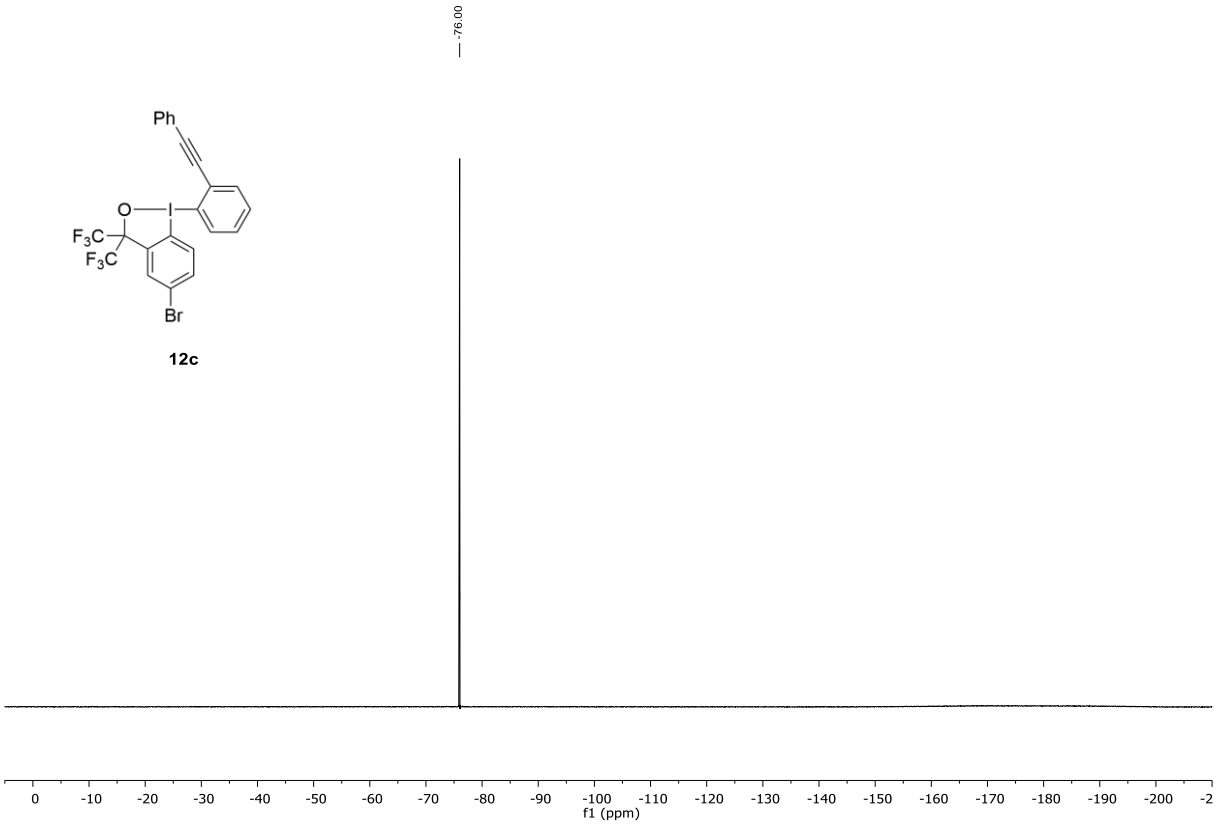


^{13}C-NMR (101 MHz, $CDCl_3$)



^{19}F-NMR (376 MHz, $CDCl_3$)

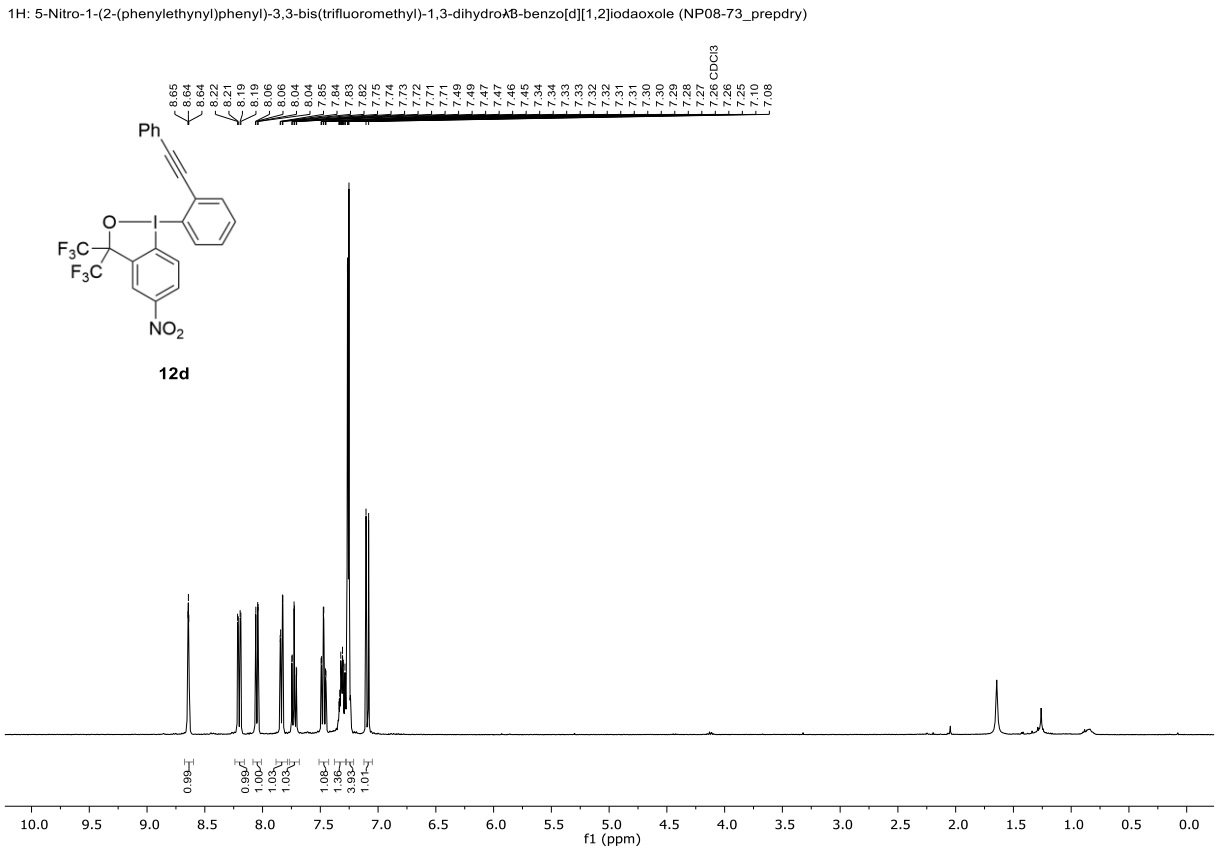
19F: 5-Bromo-1-(2-(phenylethynyl)phenyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-λ3-benzo[d][1,2]iodaoxole (NP08-60_prep)



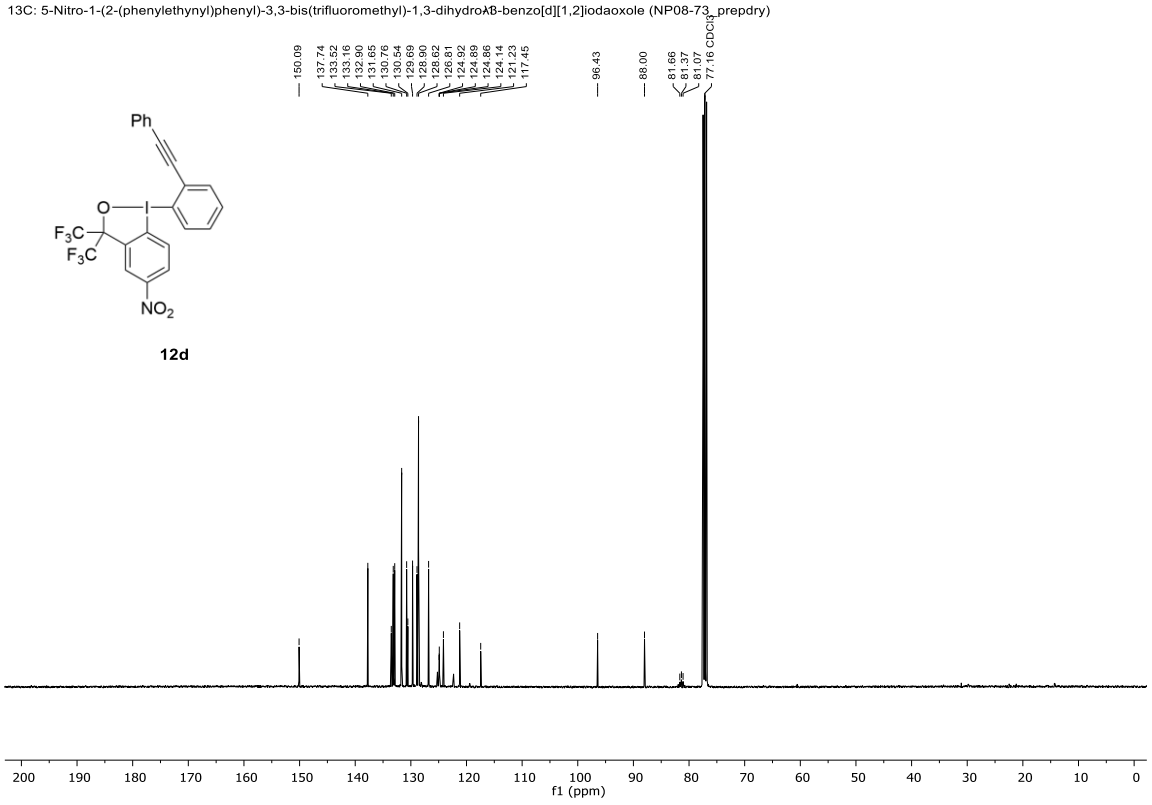
12c

5-Nitro-1-(2-(phenylethynyl)phenyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[d][1,2]iodaoxole (12d)

^{1}H-NMR (400 MHz, $CDCl_3$)

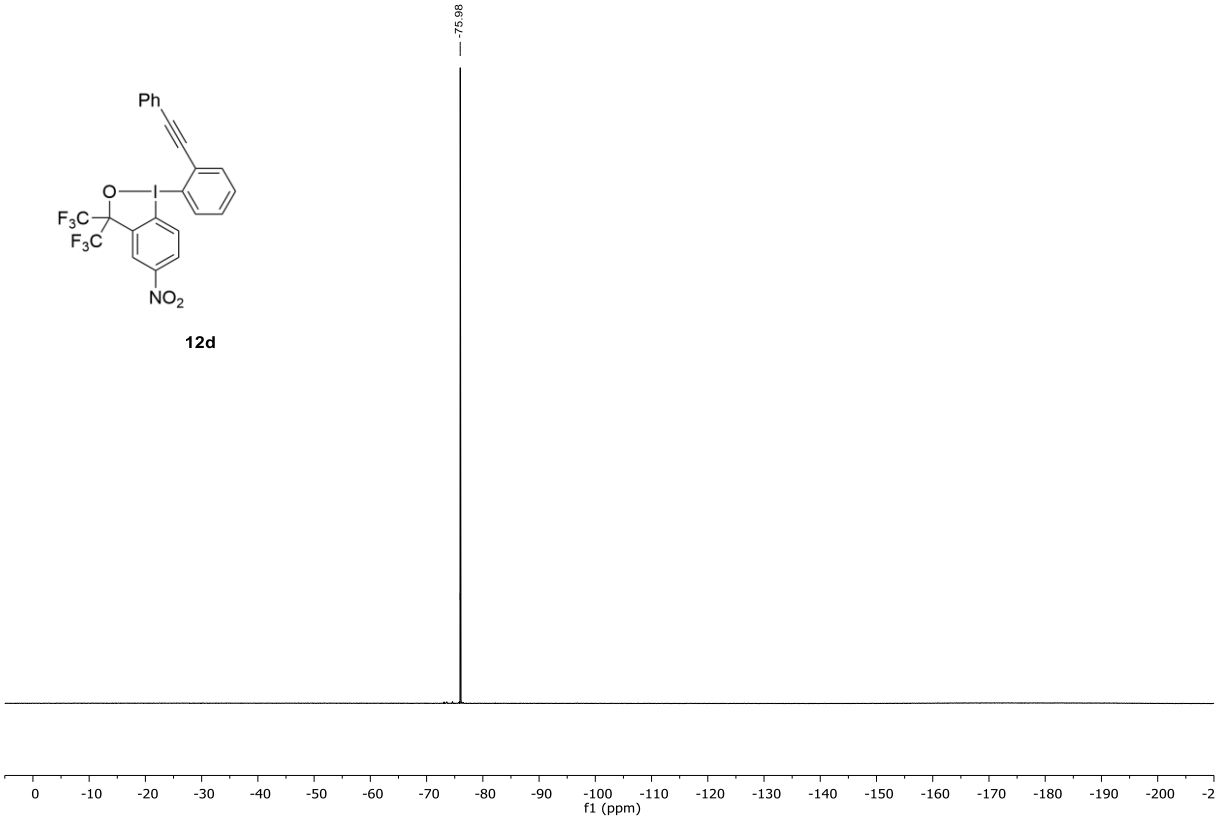


^{13}C-NMR (101 MHz, $CDCl_3$)



^{19}F-NMR (376 MHz, $CDCl_3$)

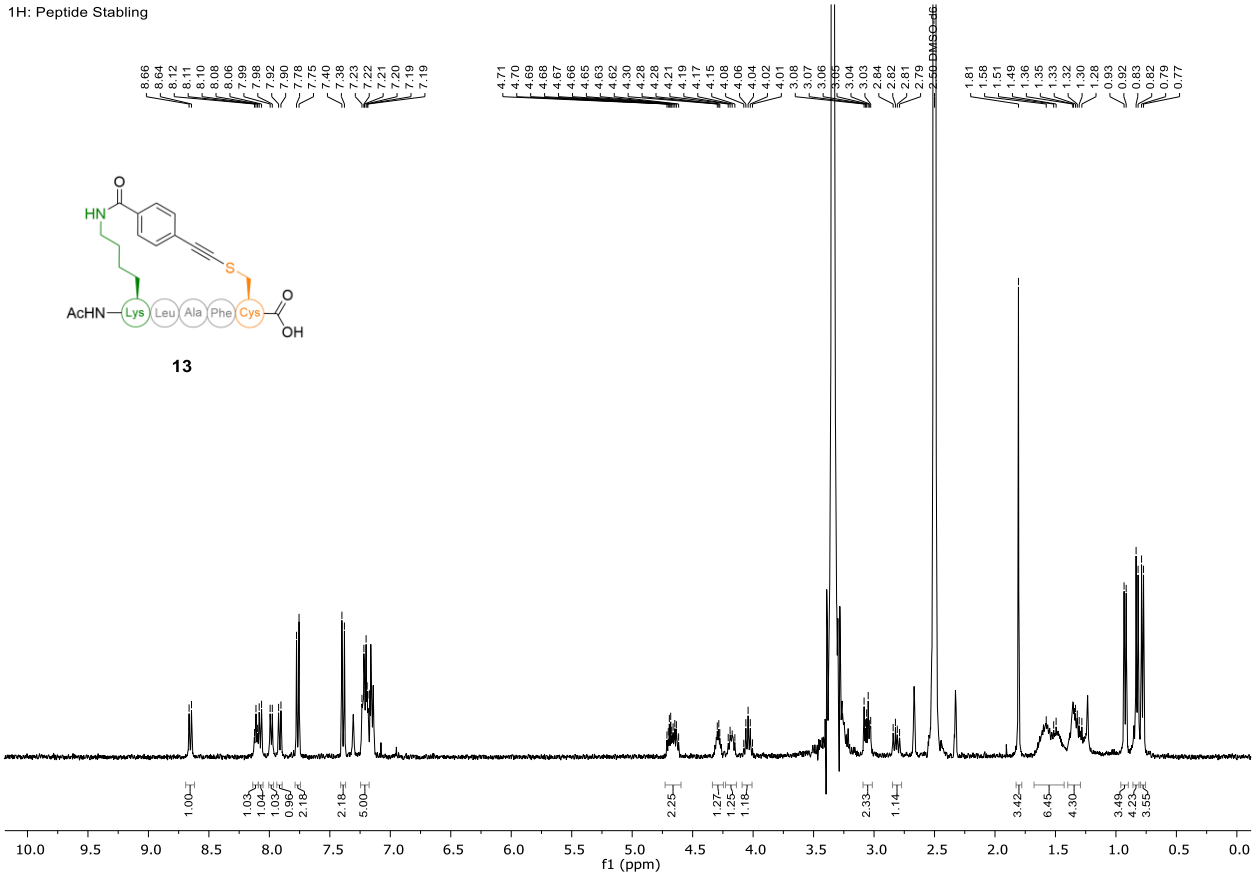
19F: 5-Nitro-1-(2-(phenylethynyl)phenyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ3-benzo[d][1,2]iodaoxole (NP08-73_prepdry)



12d

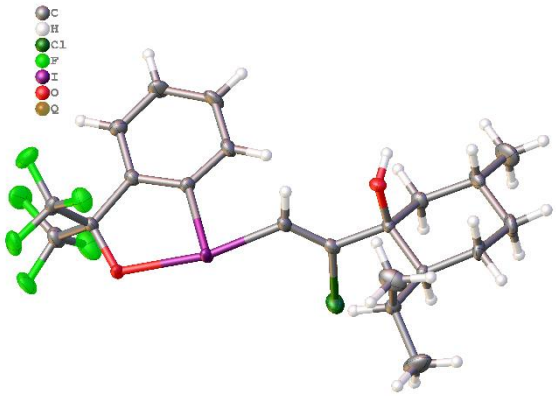
Peptide Stabling (13)

^{1}H-NMR (400 MHz, DMSO-d_6)



13

4. Crystallographic Data: CCDC Number 2294510



Experimental.[21] Single clear pale colourless prism-shaped crystals of tm-03-67 were used as supplied. A suitable crystal with dimensions 0.22 × 0.17 × 0.15 mm^3 was selected and mounted on a SuperNova, Dual, Cu at home/near, AtlasS2 diffractometer. The crystal was kept at a steady T = 140.00(10) K during data collection. The structure was solved with the ShelXT (Sheldrick, 2015) solution program using dual methods and by using Olex2 1.5 (Dolomanov et al., 2009) as the graphical interface. The model was refined with ShelXL 2019/3 (Sheldrick, 2015) using full matrix least squares minimisation on $\boldsymbol{F^2}$.

Crystal Data. $C_{21}H_{24}ClF_6IO_2$, M_r = 584.75, monoclinic, $P2_1$ (No. 4), a = 8.94012(13) Å, b = 12.9377(2) Å, c = 9.96505(14) Å, □ = 93.8561(13)°, □ = □ = 90°, V = 1149.99(3) Å^3, T = 140.00(10) K, Z = 2, Z' = 1, □(Cu K□) = 12.598, 12606 reflections measured, 4506 unique (R_{int} = 0.0294) which were used in all calculations. The final wR_2 was 0.0793 (all data) and R_1 was 0.0306 (I≥2 □(I)).

Compound	tm-03-67 (**10**)
Formula	$C_{21}H_{24}ClF_6IO_2$
$D_{calc.}$/ g cm^{-3}	1.689
μ/mm^{-1}	12.598
Formula Weight	584.75
Colour	clear pale colourless
Shape	prism-shaped
Size/mm^3	0.22×0.17×0.15
T/K	140.00(10)
Crystal System	monoclinic
Flack Parameter	-0.008(6)
Hooft Parameter	-0.015(6)
Space Group	$P2_1$
a/Å	8.94012(13)
b/Å	12.9377(2)
c/Å	9.96505(14)
α/°	90
β/°	93.8561(13)
γ/°	90
V/Å^3	1149.99(3)
Z	2
Z'	1
Wavelength/Å	1.54184
Radiation type	Cu K_α
Θ_{min}/°	4.447
Θ_{max}/°	76.067
Measured Refl's.	12606
Indep't Refl's	4506
Refl's I≥2 σ(I)	4498
R_{int}	0.0294
Parameters	284
Restraints	1
Largest Peak	0.810
Deepest Hole	-0.745
GooF	1.036
wR_2 (all data)	0.0793
wR_2	0.0793
R_1 (all data)	0.0306
R_1	0.0306

Structure Quality Indicators

Reflections:	d min (CuKα) 2Θ=152.1°	0.79	I/σ(I)	36.7	Rint m=2.80	2.94%	Full 135.4° 99% to 152.1°	100
Refinement:	Shift	0.000	Max Peak	0.8	Min Peak	-0.7	GooF	1.036	Hooft	-.015(6)

A clear pale colourless prism-shaped crystal with dimensions 0.22 × 0.17 × 0.15 mm^3 was mounted. Data were collected using a SuperNova, Dual, Cu at home/near, AtlasS2 diffractometer operating at T = 140.00(10) K.

Data were measured using ω scans with Cu K_α radiation. The diffraction pattern was indexed and the total number of runs and images was based on the strategy calculation from the program CrysAlisPro 1.171.42.95a (Rigaku OD, 2023). The maximum resolution that was achieved was Θ = 76.067˚ (0.79 Å).

The unit cell was refined using CrysAlisPro 1.171.42.95a (Rigaku OD, 2023) on 10897 reflections, 86% of the observed reflections.

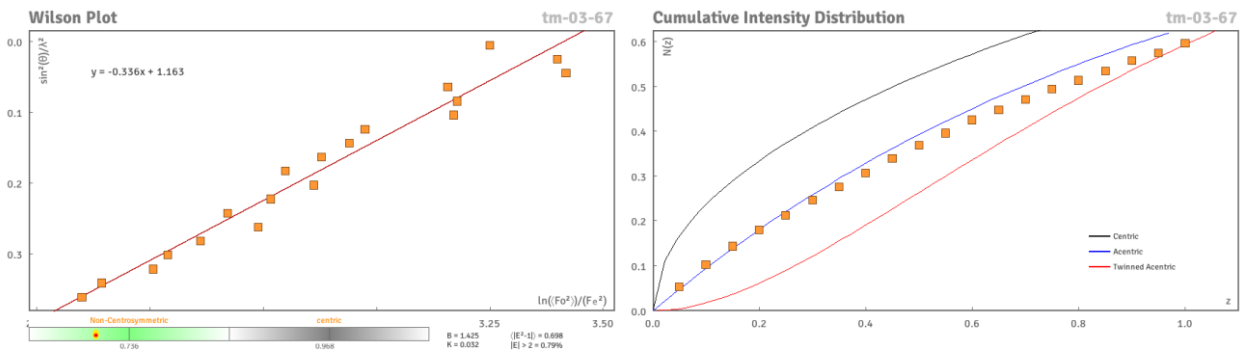
Data reduction, scaling and absorption corrections were performed using CrysAlisPro 1.171.42.95a (Rigaku OD, 2023). The final completeness is 100.00 % out to 76.067˚ in Θ. A gaussian absorption correction was performed using CrysAlisPro 1.171.42.95a (Rigaku Oxford Diffraction, 2023). The numerical absorption correction was based on gaussian integration over a multifaceted crystal model. The empirical absorption correction was done using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm. The absorption coefficient □ of this crystal is 12.598 mm^{-1} at this wavelength (λ = 1.54184Å) and the minimum and maximum transmissions are 0.147 and 0.485.

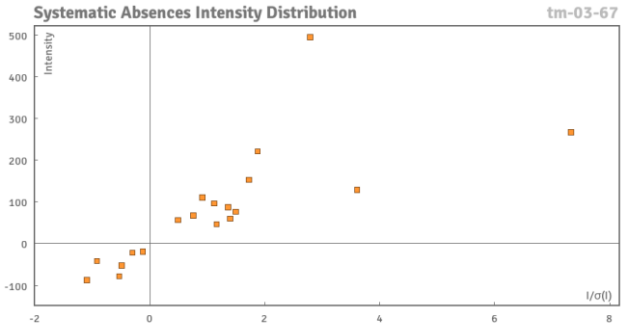
The structure was solved and the space group $P2_1$ (# 4) determined by the ShelXT (Sheldrick, 2015) structure solution program using dual methods and refined by full matrix least squares minimisation on F^2 using version 2019/3 of ShelXL (Sheldrick, 2015). All non-hydrogen atoms were refined anisotropically. Hydrogen atom positions were calculated geometrically and refined using the riding model.

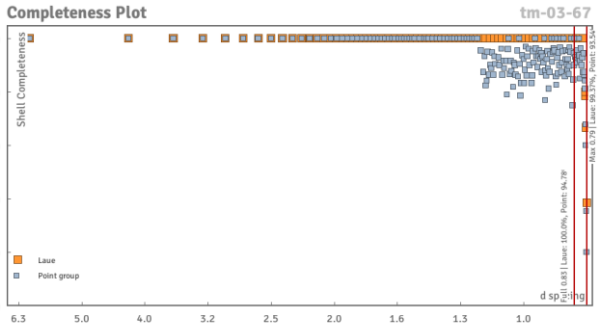
There is a single formula unit in the asymmetric unit, which is represented by the reported sum formula. In other words: Z is 2 and Z' is 1. The moiety formula is C21 H24 Cl F6 I O2.

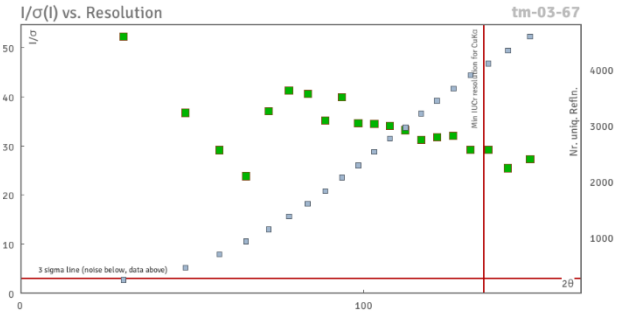
The Flack parameter was refined to -0.008(6). Determination of absolute structure using Bayesian statistics on Bijvoet differences using the Olex2 results in -0.015(6). The chiral atoms in this structure are: C12(S), C13(S), C16(R). Note: The Flack parameter is used to determine chirality of the crystal studied, the value should be near 0, a value of 1 means that the stereochemistry is wrong and the model should be inverted. A value of 0.5 means that the crystal consists of a racemic mixture of the two enantiomers.

Data Plots: Diffraction Data

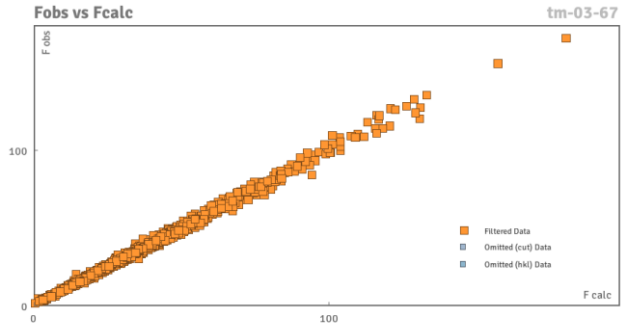


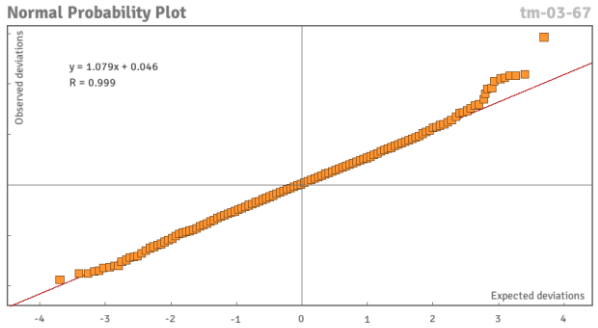






Data Plots: Refinement and Data





Reflection Statistics

Total reflections (after filtering)	12626	Unique reflections	4506
Completeness	0.935	Mean I/σ	34.02
hkl_{max} collected	(10, 14, 12)	hkl_{min} collected	(-11, -16, -12)
hkl_{max} used	(11, 14, 12)	hkl_{min} used	(-11, -16, 0)
Lim d_{max} collected	100.0	Lim d_{min} collected	0.77
d_{max} used	12.94	d_{min} used	0.79
Friedel pairs	1703	Friedel pairs merged	0
Inconsistent equivalents	4	R_{int}	0.0294
R_{sigma}	0.0272	Intensity transformed	0
Omitted reflections	0	Omitted by user (OMIT hkl)	0
Multiplicity	(2847, 1703, 962, 485, 197, 57, 29, 1, 1)	Maximum multiplicity	11
Removed systematic absences	20	Filtered off (Shel/OMIT)	0

Table 1: Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for tm-03-67. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{ij}.

Atom	x	y	z	U_{eq}
I1	1610.2(2)	4848.2(3)	6775.9(2)	20.07(11)
Cl1	3651.7(12)	5977.6(11)	9402.0(11)	26.5(2)
F1	-1684(4)	2449(5)	8023(4)	42.6(11)
F2	-2396(4)	1654(3)	6189(5)	42.5(9)
F3	-3352(3)	3124(4)	6645(4)	35.4(9)
F4	-179(4)	3756(3)	3898(3)	32.4(7)
F5	-1121(5)	2238(3)	3901(4)	36.5(8)
F6	-2527(4)	3566(3)	4142(4)	33.0(7)
O1	-816(4)	4167(3)	6475(4)	21.9(7)
O2	6859(4)	5674(3)	6839(3)	19.0(7)
C1	1912(6)	3228(4)	6828(4)	17.5(8)
C2	3293(5)	2825(4)	7237(4)	21.1(9)
C3	3498(6)	1760(4)	7145(5)	25.2(10)
C4	2339(6)	1147(4)	6603(6)	27.6(10)
C5	944(6)	1572(4)	6235(5)	23.1(9)
C6	695(5)	2632(4)	6352(5)	18.0(9)
C7	-827(5)	3174(4)	6031(5)	18.9(9)
C8	-2074(6)	2589(5)	6722(6)	27.7(10)
C9	-1180(6)	3172(4)	4482(5)	23.7(10)
C10	3947(5)	5145(4)	6975(5)	20.3(9)
C11	4624(5)	5613(4)	8014(4)	18.1(8)
C12	6307(5)	5887(4)	8122(4)	16.4(8)
C13	6557(5)	7044(4)	8478(4)	16.5(8)
C14	8241(5)	7263(4)	8600(5)	23.5(10)
C15	9044(6)	6597(5)	9697(5)	28.3(11)
C16	8775(5)	5453(5)	9414(5)	24.7(10)
C17	7097(5)	5208(4)	9225(4)	21.4(9)
C18	5646(5)	7807(4)	7546(5)	20.1(9)
C19	6320(7)	8025(5)	6211(6)	37.3(14)
C20	5405(9)	8812(5)	8292(7)	45.7(16)
C21	9537(7)	4764(7)	10502(6)	40.7(13)

Table 2: Anisotropic Displacement Parameters (×10^4) for tm-03-67. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2} \times U_{11} + ... + 2hka^* \times b^* \times U_{12}]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
I1	11.63(14)	11.72(16)	36.31(16)	-5.91(11)	-2.35(9)	-0.57(10)
Cl1	17.0(5)	36.3(7)	26.7(5)	-3.0(4)	5.3(4)	-2.7(5)
F1	29(2)	62(3)	37.9(18)	15.3(19)	5.9(14)	-0.2(15)
F2	28.8(17)	22.9(18)	77(2)	-5.4(17)	11.0(16)	-11.9(14)
F3	11.8(16)	37(3)	58(2)	-1.7(14)	4.0(15)	0.2(11)
F4	26.5(15)	35(2)	35.5(15)	8.0(13)	-0.3(12)	-2.2(14)
F5	50(2)	20.8(19)	36.5(16)	-8.9(12)	-11.4(15)	3.2(15)
F6	22.4(15)	29.0(18)	45.2(17)	4.9(14)	-15.2(13)	-0.3(13)
O1	12.1(15)	12.8(18)	40.0(17)	-8.9(13)	-3.2(12)	0.3(12)
O2	15.5(14)	20(2)	21.6(15)	-3.5(11)	2.8(11)	3.1(13)
C1	15.8(18)	12(2)	24(2)	-1.5(14)	0.8(15)	-1.7(19)
C2	12(2)	24(3)	28(2)	0.3(18)	0.6(16)	0.0(18)
C3	16(2)	21(3)	39(2)	7.5(19)	-0.4(17)	7.9(18)
C4	27(3)	12(2)	44(3)	2.6(19)	1(2)	3.5(19)
C5	21(2)	17(3)	31(2)	-3.1(18)	0.9(18)	0.5(19)
C6	14(2)	17(3)	22.4(19)	0.3(16)	-0.5(16)	1.3(18)
C7	12.7(19)	16(2)	28(2)	-2.7(16)	-2.0(16)	1.6(17)
C8	17(2)	25(3)	42(3)	2(2)	1.3(19)	-2.9(19)
C9	24(2)	14(2)	32(2)	-3.0(18)	-8.2(19)	-1.0(19)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C10	12.0(19)	16(2)	32(2)	-2.6(15)	-0.9(16)	0.6(15)
C11	12.7(18)	16(2)	26(2)	2.0(16)	3.2(15)	1.1(16)
C12	11.3(18)	18(2)	19.7(18)	-4.1(16)	-0.1(14)	0.6(16)
C13	14(2)	15(2)	20.2(17)	-1.8(15)	-1.5(14)	-1.4(16)
C14	16(2)	24(3)	30(2)	-4(2)	-3.3(19)	-7.5(19)
C15	17(2)	35(3)	32(2)	-1(2)	-9.3(18)	-3(2)
C16	16(2)	33(3)	25(2)	-1.9(18)	-3.8(16)	6(2)
C17	20(2)	19(2)	24.7(19)	1.6(15)	-2.7(17)	3.0(17)
C18	18(2)	15(2)	27(2)	-1.1(17)	-2.4(16)	1.0(17)
C19	37(3)	39(4)	36(3)	15(2)	8(2)	11(3)
C20	64(4)	24(3)	47(3)	-8(2)	-11(3)	16(3)
C21	35(3)	42(4)	43(2)	5(3)	-12(2)	17(3)

Table 3: Bond Lengths in Å for tm-03-67.

Atom	Atom	Length/Å
I1	O1	2.341(3)
I1	C1	2.114(5)
I1	C10	2.120(5)
Cl1	C11	1.748(4)
F1	C8	1.332(7)
F2	C8	1.345(7)
F3	C8	1.333(6)
F4	C9	1.334(6)
F5	C9	1.342(6)
F6	C9	1.330(6)
O1	C7	1.359(6)
O2	C12	1.428(5)
C1	C2	1.376(7)
C1	C6	1.390(7)
C2	C3	1.393(8)
C3	C4	1.385(8)
C4	C5	1.390(7)

Atom	Atom	Length/Å
C5	C6	1.396(7)
C6	C7	1.545(6)
C7	C8	1.547(7)
C7	C9	1.555(6)
C10	C11	1.312(7)
C11	C12	1.542(6)
C12	C13	1.550(7)
C12	C17	1.541(6)
C13	C14	1.529(6)
C13	C18	1.549(6)
C14	C15	1.532(7)
C15	C16	1.523(8)
C16	C17	1.533(7)
C16	C21	1.528(8)
C18	C19	1.524(7)
C18	C20	1.521(8)

Table 4: Bond Angles in ° for tm-03-67.

Atom	Atom	Atom	Angle/°
C1	I1	O1	75.26(17)
C1	I1	C10	93.11(19)
C10	I1	O1	168.10(15)
C7	O1	I1	112.6(3)
C2	C1	I1	119.6(4)
C2	C1	C6	123.8(5)
C6	C1	I1	116.5(4)
C1	C2	C3	118.3(5)
C4	C3	C2	119.6(5)
C3	C4	C5	120.7(5)
C4	C5	C6	120.8(5)
C1	C6	C5	116.6(5)
C1	C6	C7	118.5(5)
C5	C6	C7	124.9(4)
O1	C7	C6	112.0(4)
O1	C7	C8	107.9(4)
O1	C7	C9	108.8(4)
C6	C7	C8	109.7(4)
C6	C7	C9	108.8(4)

Atom	Atom	Atom	Angle/°
C8	C7	C9	109.7(4)
F1	C8	F2	107.3(5)
F1	C8	F3	107.1(5)
F1	C8	C7	110.5(4)
F2	C8	C7	114.0(4)
F3	C8	F2	106.5(4)
F3	C8	C7	111.1(5)
F4	C9	F5	106.0(5)
F4	C9	C7	109.6(4)
F5	C9	C7	114.7(4)
F6	C9	F4	107.1(4)
F6	C9	F5	107.2(4)
F6	C9	C7	111.8(4)
C11	C10	I1	123.9(3)
C10	C11	Cl1	121.4(4)
C10	C11	C12	123.9(4)
C12	C11	Cl1	114.7(3)
O2	C12	C11	106.7(3)
O2	C12	C13	109.8(4)

Atom	Atom	Atom	Angle/°
O2	C12	C17	111.0(4)
C11	C12	C13	111.3(4)
C17	C12	C11	108.5(4)
C17	C12	C13	109.6(3)
C14	C13	C12	108.8(4)
C14	C13	C18	113.9(4)
C18	C13	C12	114.6(4)
C13	C14	C15	111.4(4)
C16	C15	C14	110.7(4)
C15	C16	C17	111.4(4)
C15	C16	C21	112.2(5)
C21	C16	C17	110.7(5)
C16	C17	C12	111.6(4)
C19	C18	C13	114.8(4)
C20	C18	C13	109.8(4)
C20	C18	C19	110.2(5)

Table 5: Torsion Angles in ° for tm-03-67.

Atom	Atom	Atom	Atom	Angle/°
I1	O1	C7	C6	21.8(4)
I1	O1	C7	C8	142.6(3)
I1	O1	C7	C9	-98.4(4)
I1	C1	C2	C3	-174.2(3)
I1	C1	C6	C5	172.6(3)
I1	C1	C6	C7	-9.0(5)
I1	C10	C11	Cl1	3.7(6)
I1	C10	C11	C12	-176.2(3)
Cl1	C11	C12	O2	-171.7(3)
Cl1	C11	C12	C13	-52.0(4)
Cl1	C11	C12	C17	68.6(4)
O1	C7	C8	F1	-70.9(6)
O1	C7	C8	F2	168.2(4)
O1	C7	C8	F3	47.9(6)
O1	C7	C9	F4	56.5(5)
O1	C7	C9	F5	175.6(4)
O1	C7	C9	F6	-62.1(5)
O2	C12	C13	C14	-63.3(4)
O2	C12	C13	C18	65.5(5)
O2	C12	C17	C16	64.3(5)
C1	C2	C3	C4	2.4(7)
C1	C6	C7	O1	-10.0(6)
C1	C6	C7	C8	-129.8(5)
C1	C6	C7	C9	110.2(5)
C2	C1	C6	C5	-3.1(7)
C2	C1	C6	C7	175.3(4)
C2	C3	C4	C5	-4.4(8)
C3	C4	C5	C6	2.7(8)
C4	C5	C6	C1	1.0(7)
C4	C5	C6	C7	-177.2(5)
C5	C6	C7	O1	168.2(4)
C5	C6	C7	C8	48.4(6)
C5	C6	C7	C9	-71.5(6)
C6	C1	C2	C3	1.4(7)
C6	C7	C8	F1	51.4(6)
C6	C7	C8	F2	-69.5(5)
C6	C7	C8	F3	170.1(4)
C6	C7	C9	F4	-65.7(5)
C6	C7	C9	F5	53.3(6)
C6	C7	C9	F6	175.7(4)
C8	C7	C9	F4	174.4(4)
C8	C7	C9	F5	-66.6(6)
C8	C7	C9	F6	55.8(6)
C9	C7	C8	F1	170.8(5)
C9	C7	C8	F2	49.9(6)
C9	C7	C8	F3	-70.5(6)

Atom	Atom	Atom	Atom	Angle/°
C10	C11	C12	O2	8.2(6)
C10	C11	C12	C13	128.0(5)
C10	C11	C12	C17	-111.4(5)
C11	C12	C13	C14	178.8(4)
C11	C12	C13	C18	-52.4(5)
C11	C12	C17	C16	-178.8(4)
C12	C13	C14	C15	-59.8(5)
C12	C13	C18	C19	-80.5(6)
C12	C13	C18	C20	154.7(5)
C13	C12	C17	C16	-57.2(5)
C13	C14	C15	C16	57.7(6)
C14	C13	C18	C19	45.7(6)
C14	C13	C18	C20	-79.1(6)
C14	C15	C16	C17	-54.3(5)
C14	C15	C16	C21	-179.0(4)
C15	C16	C17	C12	55.0(5)
C17	C12	C13	C14	58.9(4)
C17	C12	C13	C18	-172.3(4)
C18	C13	C14	C15	171.0(4)
C21	C16	C17	C12	-179.5(5)

Table 6: Hydrogen Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for tm-03-67. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{ij}.

Atom	x	y	z	U_{eq}
H2	7435.46	5160.61	6902.47	28
H2A	4085.9	3261.38	7573.5	25
H3	4426.62	1456.89	7451.3	30
H4	2500.69	428.63	6480.43	33
H5	149.32	1135.31	5900.64	28
H10	4537.75	4926.09	6270.26	24
H13	6195.43	7140.71	9397.71	20
H14A	8409.7	8002.19	8815.94	28
H14B	8668.1	7119.75	7728.13	28
H15A	10133.26	6741.51	9736.27	34
H15B	8670.95	6775.19	10581.38	34
H16	9228.45	5287.41	8548.59	30
H17A	6628.36	5323.79	10084.68	26
H17B	6962.96	4471	8979.22	26
H18	4636.62	7490.93	7334.71	24
H19A	7289.25	8372.33	6378.08	56
H19B	5640.76	8471.44	5658.01	56
H19C	6464.47	7372.79	5736.74	56
H20A	4884.89	8668.05	9106.76	69
H20B	4796.67	9282.65	7709.99	69
H20C	6376.98	9133.02	8540.41	69
H21A	10613.52	4915.7	10587.81	61
H21B	9384.91	4036.71	10254.29	61
H21C	9102.34	4897.91	11361.94	61

Table 7: Hydrogen Bond information for tm-03-67.

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/deg
O2	H2	O1[1]	0.84	2.09	2.890(5)	159.1
C2	H2A	F3[1]	0.95	2.53	3.120(5)	120.1

[1]1+x,+y,+z

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