Supporting Information

Enantioselective Cyclization of Bromoenynes: Mechanistic Understanding of Gold(I)-Catalyzed Alkoxycyclizations

Andrea Cataffo, Eduardo García-Padilla, Imma Escofet, Nicolás Fincias, Anna Arnanz, Giuseppe Zuccarello, Guilong Tian, Luyu Cai, Fereshteh Khorasanidarehdor, Feliu Maseras, and Antonio M. Echavarren*

Institute of Chemical Research of Catalonia (ICIQ), Barcelona Institute of Science and Technology (BIST),
Av. Països Catalans 16, 43007 Tarragona, Spain,

Departament de Química Analítica i Química Orgànica, Universitat Rovira i Virgili, C/Marcel·lí Domingo s/n, 43007

Tarragona, Spain

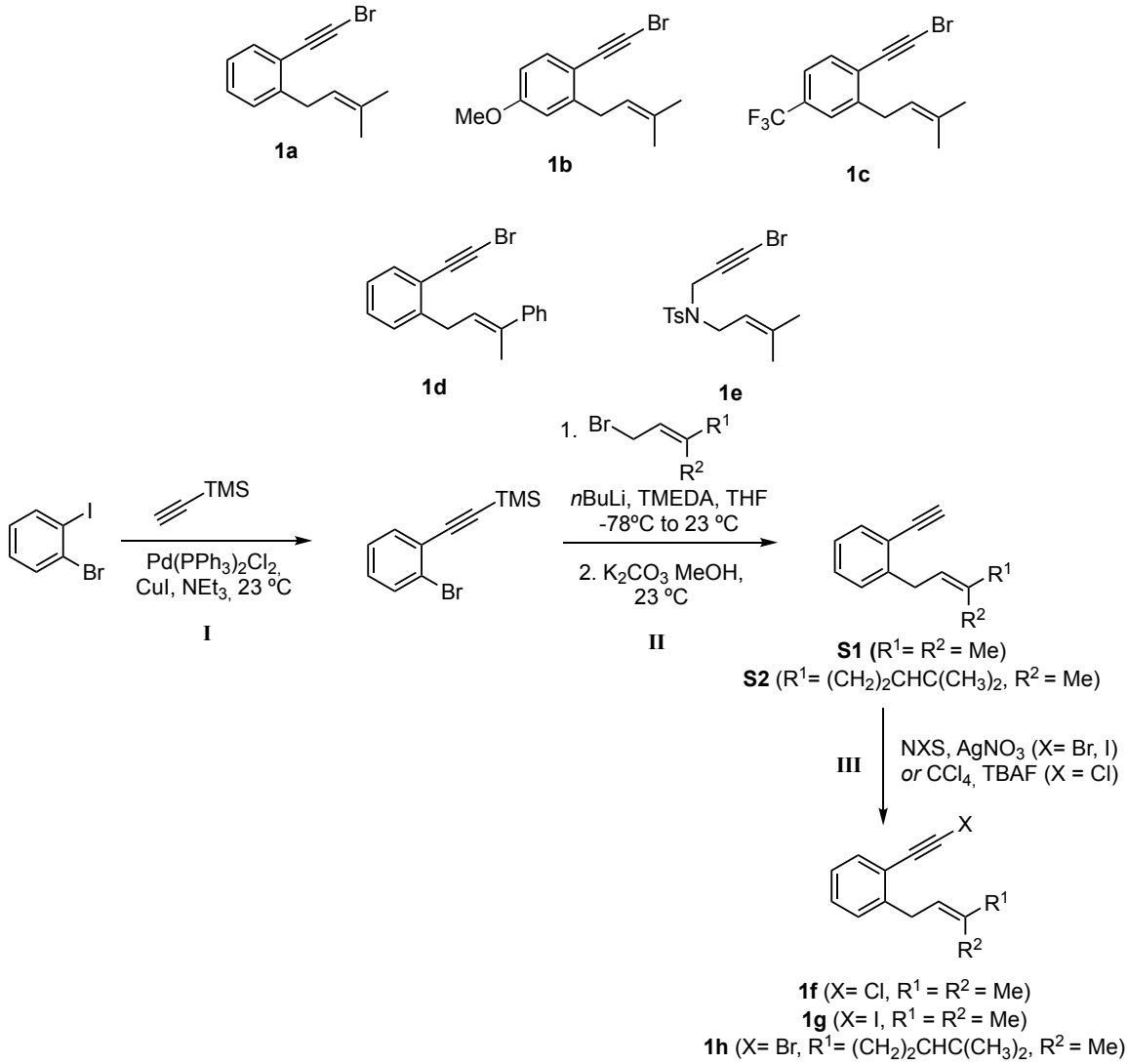
1. General information

Anhydrous reactions were performed under nitrogen or Ar in solvents dried by passing through an activated alumina column on a PureSolvTM solvent purification system (Innovative Technologies, Inc., MA). Analytical thin layer chromatography was carried out using TLC-aluminum sheets with 0.2 mm of silica gel (Merck GF234) using UV light as the visualizing agent, and an acidic solution of vanillin in ethanol or a basic aqueous solution of $KMnO_4$ as the developing agent. Flash column chromatography (FCC) was carried out manually using PanReac Silica Gel 60 (40–63 μm) or employing the automated flash column chromatographer CombiFlash Companion with disposable pre-packed normal phase silica gel columns (Teledyne Isco). Preparative TLC was performed on 20 cm × 20 cm silica gel plates (2.0 mm or 1.0 mm silica thickness, Analtech). Melting points were measured using a Mettler Toledo MP70 Melting Point apparatus. NMR spectra were recorded on Bruker Ultrashield 300, 400 or 500 MHz spectrometers using the residual solvent signal as internal standard [for ^{1}H NMR: $CDCl_3$ at 7.26 ppm, CD_2Cl_2 at 5.31 ppm, C_6D_6 at 7.16 ppm, for ^{13}C NMR: $CDCl_3$ at 77.16 ppm, CD_2Cl_2 at 54.00 ppm, C_6D_6 at 128.06 ppm]. All measurements were carried out at 24 °C unless otherwise stated. The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, br s = broad singlet. Coupling constants (*J*) are reported in Hertz (Hz). Infrared spectra were recorded on a Bruker ALPHA FTIR-ATR TR0 spectrometer with ATR module on a thin film (the sample was dissolved in a volatile solvent, then the solvent evaporated). The most intense absorption bands (ν) are listed in wavenumbers (cm^{-1}). Mass spectra were recorded on a Waters LCT Premier Spectrometer (ESI and APCI) or on an Autoflex Broker Daltonics (MALDI and LDI). Optical rotations were recorded using a Jasco P-1030 polarimeter equipped with a PMT detector using a 2 mL, 10 cm long cell. $[\alpha]_D^T$ values, reported in deg mL g^{-1} dm^{-1}, are calculated on the average value of at least ten consecutive readings. Concentrations (c) are quoted in mg/mL. HPLC analyses were performed on an Agilent Technologies 1200 series instrument. SFC analyses were performed on an Agilent Technologies 1260 Infinity II or on a Waters ACQUITY UPC2 instrument. X-Ray data were collected on a Kappa APEX II DUO diffractometer equipped with an APPEX 2 4K CCD area detector, a Microsource with $Mo_{K\alpha}$ radiation and an Oxford Cryostream 700 low temperature device. All reagents were used as purchased, with no further purification.

2. Synthesis of substrates for the alkoxycyclization of 1-bromo-1,6-enynes

Substrates **1a-e** were synthesized according to literature procedure.[1] The spectral data were in accordance with the reported data.

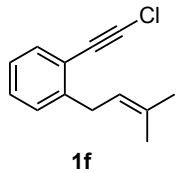
2.1. General procedure A for the synthesis of 1-bromo-1,6-enynes 1f-h



Step I-II: Precursors **S1,2** were prepared according to the literature procedure.[1]

Step III: 1f was prepared by adding TBAF·3H_2O (0.1 equiv) to a solution of **S1** in CCl_4 (1.7 M)[2] which was then stirred at 24 °C for 6 h and quenched by the addition of water. Compounds **1g,h** were instead prepared by dissolving **S1,2** (1 equiv) in acetone (0.05 M) and by adding NXS (1.1 equiv) and $AgNO_3$ (0.2 equiv) to the resulting solution which was then stirred at 24 °C for 2 h and quenched by the addition of water. For **1f-h** extraction of the aqueous phase in pentane (x3) was followed by the addition of a saturated NaCl solution to the organic phase, which was finally dried with anhydrous Na_2SO_4. The crudes were purified by flash column chromatography.

1-(Chloroethynyl)-2-(3-methylbut-2-en-1-yl)benzene (1f)



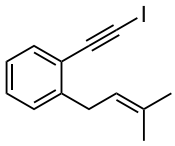
1f

1f was synthesized following the general procedure **A**. The pure product was isolated by flash column chromatography purification on silica gel (pentane) as a yellow oil (750 mg, 61%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.33 – 7.26 (m, 1H), 7.22 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.16 (td, J = 7.5, 1.4 Hz, 1H), 5.32 (ddq, *J* = 8.8, 5.8, 1.4 Hz, 1H), 3.53 (d, *J* = 7.4 Hz, 2H), 1.79 (d, *J* = 4.7 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 144.5, 133.1, 132.8, 128.9,

128.6, 125.9, 122.3, 121.6, 71.3, 68.5, 33.1, 25.9, 18.0. **HRMS** (APCI-): *m/z*: calculated for $C_{13}H_{12}Cl$: 203.0622 [M-H]$^-$; found: 203.0617.

1-(Iodoethynyl)-2-(3-methylbut-2-en-1-yl)benzene (1g)

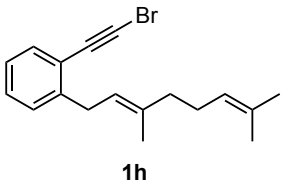


1g

1g was synthesized following the general procedure **A**. The pure product was isolated by flash column chromatography purification on silica gel (pentane) as a yellow oil (450 mg, 72%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.29 – 7.22 (m, 1H), 7.19 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.13 (td, *J* = 7.5, 1.5 Hz, 1H), 5.29 (ddq, *J* = 8.8, 5.9, 1.5 Hz, 1H), 3.51 (d, *J* = 7.4 Hz, 2H), 1.76 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 144.9, 133.2, 129.1, 128.5, 125.7, 122.9, 122.3, 93.3, 77.4, 33.1, 26.0, 18.2, 9.0. **HRMS** (APCI+): *m/z*: calculated for $C_{13}H_{14}I$: 297.0135 [M+H]$^+$; found: 297.0138.

(*E*)-1-(Bromoethynyl)-2-(3,7-dimethylocta-2,6-dien-1-yl)benzene (1h)

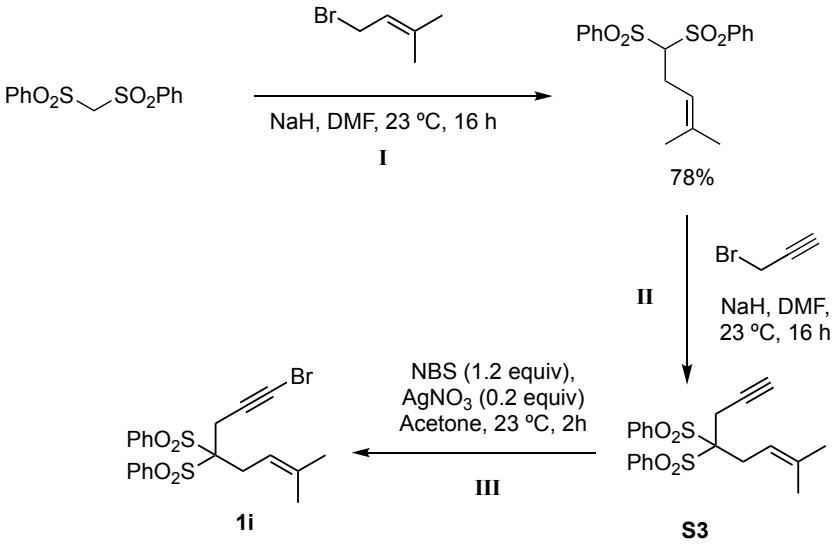


1h

1h was synthesized following the general procedure **A**. The pure product was isolated by flash column chromatography purification on silica gel (pentane) as a transparent oil (190 mg, 55%).

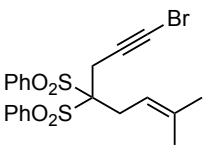
^{1}H NMR (400 MHz, C_6D_6) δ 7.35 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.12 – 7.01 (m, 1H), 6.99 (td, *J* = 7.6, 1.4 Hz, 1H), 6.82 (td, *J* = 7.5, 1.4 Hz, 1H), 5.36 (tq, *J* = 7.3, 1.3 Hz, 1H), 5.17 (ddq, *J* = 8.4, 5.5, 1.4 Hz, 1H), 3.54 (d, *J* = 7.3 Hz, 2H), 2.13 (q, *J* = 7.5 Hz, 2H), 2.09 – 2.02 (m, 2H), 1.66 (s, 3H), 1.62 (s, 3H), 1.52 (s, 3H). **^{13}C NMR** (101 MHz, C_6D_6) δ 144.8, 136.7, 133.1, 131.3, 129.1, 128.8, 127.9, 126.0, 124.8, 122.7, 79.8, 53.5, 40.1, 33.3, 27.0, 25.9, 17.8, 16.3. **HRMS** (APCI+): *m/z*: calculated for $C_{18}H_{22}Br$: 317.0899 [M+H]$^+$; found: 317.0894.

2.2. Procedure B for the synthesis of 1-bromo-1,6-enyne 1i



Step I-II: Precursor **S3** was synthesized according to the reported procedure.[3]

(1-Bromo-7-methyloct-6-en-1-yne-4,4-diyldisulfonyl)dibenzene (1i)



1i

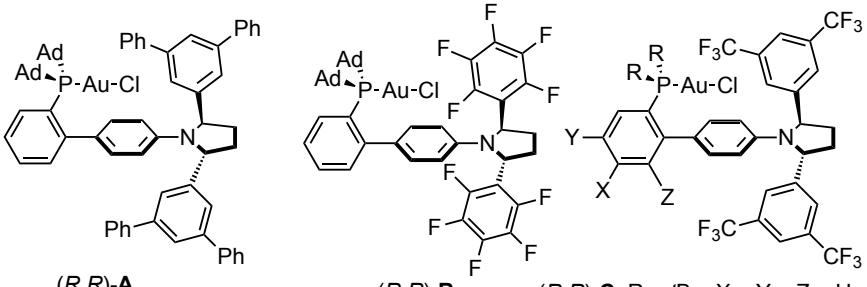
NBS (1.2 equiv) was added to a solution of **S3** in acetone (0.05 M) and the resulting solution was stirred at 24 °C for 2 h. The reaction was quenched by the addition of water and the aqueous phase was extracted in pentane (x3), the organic phase washed with saturated NaCl aqueous solution and finally dried with anhydrous Na_2SO_4. The pure product was isolated by flash column chromatography purification on silica gel (5:1 cyclohexane:EtOAc) to give **1i** as a white solid (229 mg, 73%).

M.p. 135-143 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.13 – 8.03 (m, 4H), 7.75 – 7.66 (m, 2H), 7.64 – 7.53 (m, 4H), 5.39 (ddt, J = 6.8, 5.4, 1.4 Hz, 1H), 3.22 (s, 2H), 2.99 (d, J = 1.3 Hz, 2H), 1.76 (d, J = 1.4 Hz, 3H), 1.57 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 137.7, 136.8, 134.8, 131.6, 128.7, 114.9, 89.1, 77.4, 72.5, 44.5, 28.5, 26.3, 21.9, 18.4. **HRMS** (ESI+): *m/z*: calculated for $C_{21}H_{21}BrNaO_4S_2$: 502.9957 [M+Na]$^+$; found: 502.9972.

3. Enantioselective gold(I)-catalyzed alkoxycyclization of 1-bromo-1,6-enynes.

3.1. Reaction Optimization

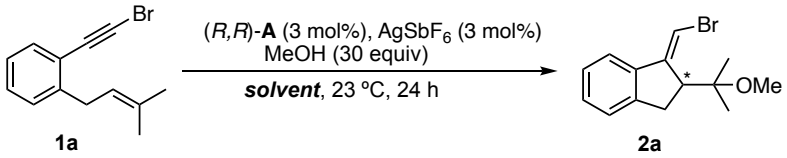
Catalysts (*R,R*)-**A-I** were synthesized according to literature procedures.[4] The spectral analysis were in accordance with the reported data.



(*R,R*)-**A** (*R,R*)-**B**

(*R,R*)-**C**: R = *t*Bu, X = Y = Z = H
(*R,R*)-**D**: R = Ad, X = Y = Z = H
(*R,R*)-**E**: R = Ad, X = CF_3, Y = Z = H
(*R,R*)-**F**: R = Ad, X = Z = H, Y = CF_3
(*R,R*)-**G**: R = Ad, X = CH_3, Y = Z = H
(*R,R*)-**H**: R = Ad, X = H, Y = Z = F
(*R,R*)-**I**: R = Ad, X= H, Y = Z = CF_3

After selecting the best performing catalyst in 1,2-dichloroethane (1,2-DCE), as described in the manuscript, different solvents were screened:

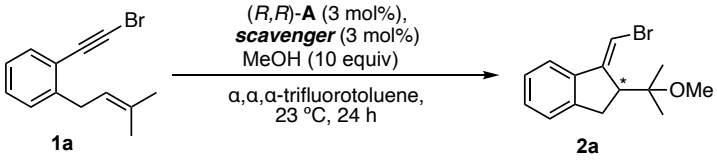


1a **2a**

Entry	Solvent	Yield 2a	*er 2a*
1	1,2-DCE	80%	81:19
2	CH_2Cl_2	73%	80:20
3	toluene	74%	78:22
4	C_6H_5Cl	64%	80:20
5	THF	54%	77:23
6	**α,α,α-trifluorotoluene**	**80%**	**81:19**

Table S1 – Solvent screening for the alkoxycyclization of **1a**.

Once selected α,α,α-trifluorotoluene as the best solvent at 24 °C, a screening of the chloride scavenger was performed:



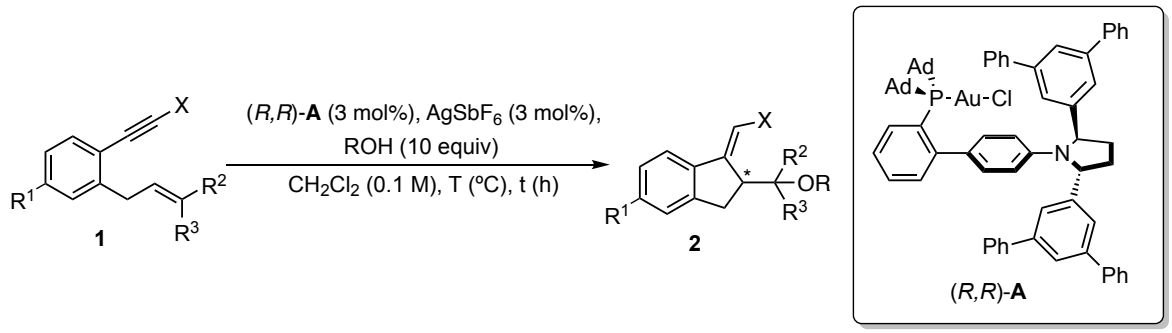
1a **2a**

Entry	Scavenger	Yield 2a	*er 2a*
1	**$AgSbF_6$**	**80%**	**83:17**

2	$NaBAr^F_4$	24%	82:18
3	$AgPF_6$	72%	81:19
4	$AgBF_4$	14%	81:19
5	AgTFA	16%	79:21

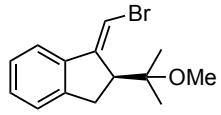
Table S2 – Chloride scavenger screening for the alkoxycyclization of **1a**.

3.2. General Procedure C for the enantioselective gold(I)-catalyzed alkoxycyclization of 1-bromo-1,6-enynes



1-Halo-6-enynes **1** (1 equiv) were weighted in a microwave vial together with gold catalyst (*R,R*)-**A** (3 mol%) and a stirring bar. The vial was capped and introduced in the glovebox where dry CH_2Cl_2 (0.1 M) and ROH (10 equiv) were added. $AgSbF_6$ (3 mol%) was weighted in the glovebox in a second vial and dissolved in the minimum quantity of dry CH_2Cl_2. Then, the two vials were taken out of the glovebox, they were both brought to the required temperature (specified below) and finally the solution of $AgSbF_6$ was added to the first vial. The reaction was stirred the time specified below. Once completed (monitored by TLC), three drops of NEt_3 were added. The crude products were purified by flash column chromatography on silica gel or preparative TLC.

(*S,E*)-1-(Bromomethylene)-2-(2-methoxypropan-2-yl)-2,3-dihydro-1*H*-indene (2a)



2a

2a was synthesized following the general procedure **C** performing the reaction at -60 °C for 4 days. The pure product was isolated by preparative TLC (2:1 CH_2Cl_2: cyclohexane) as a transparent oil, which slowly crystallizes when kept in a freezer (27.8 mg, 99%).

^{1}H NMR (400 MHz, C_6D_6) δ 7.05 – 6.96 (m, 1H), 6.99 – 6.91 (m, 3H), 6.38 (d, *J* = 1.4 Hz, 1H), 3.47 (d, *J* = 7.7 Hz, 1H), 3.08 (d, *J* = 16.4 Hz, 1H), 2.99 (s, 3H), 2.64 (dd, *J* = 16.2, 7.6 Hz, 1H), 1.33 (s, 3H), 0.76 (s, 3H). **^{13}C NMR** (101 MHz, C_6D_6) δ 149.6, 145.7, 141.7, 128.8, 126.8, 125.1, 120.0, 101.3, 78.5, 51.6, 49.0, 32.9, 25.1, 23.0. **HRMS** (ESI+): *m/z*: calculated for $C_{14}H_{17}BrNaO$: 303.0355 $[M+Na]^+$; found: 303.0348. **SFC** (OD-3 (100x3 mm, 3 µm), CO_2:MeOH 90:10, 1.2 mL/min, 25 °C, BPR 150 bar; 230 nm): 0.945 min (90), 1.064 min (10); **$[\alpha]_D^{26}$** = 75.9° (*c* = 0.24 in CH_2Cl_2). **X-Ray** data available at CCDC 2337764.[5]

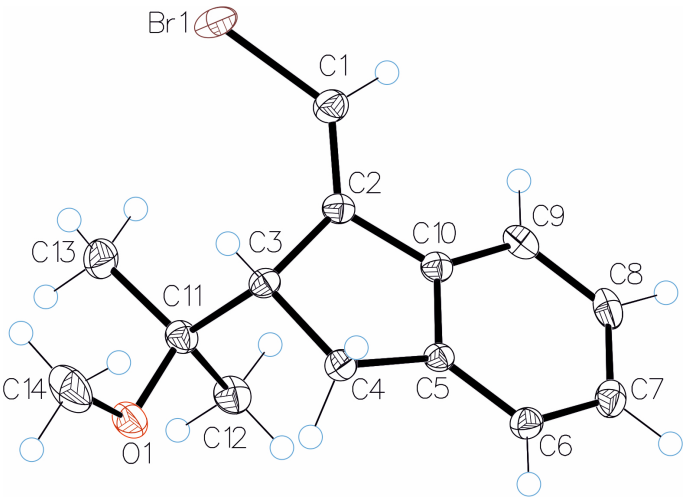
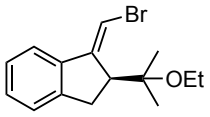


Table S3 - Crystal data and structure refinement for mo_AC013061B_0m (compound 2a).

Identification code	mo_AC013061B_0m
Empirical formula	$C_{14}H_{17}BrO$
Formula weight	281.18
Temperature/K	100.40
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	7.2267(12)
b/Å	11.976(2)
c/Å	14.973(3)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1295.9(4)
Z	4
ρ_{calc}g/cm^3	1.441
μ/mm^{-1}	3.150
F(000)	576.0
Crystal size/mm^3	0.3 × 0.2 × 0.1
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.356 to 61.224
Index ranges	-10 ≤ h ≤ 8, -14 ≤ k ≤ 17, -21 ≤ l ≤ 18
Reflections collected	14021
Independent reflections	3880 [R_{int} = 0.0303, R_{sigma} = 0.0283]
Data/restraints/parameters	3880/0/148
Goodness-of-fit on F^2	1.042
Final R indexes [I>=2σ (I)]	R_1 = 0.0249, wR_2 = 0.0634
Final R indexes [all data]	R_1 = 0.0298, wR_2 = 0.0653
Largest diff. peak/hole / e Å^{-3}	0.44/-0.40
Flack parameter	-0.007(4)

(*S,E*)-1-(Bromomethylene)-2-(2-ethoxypropan-2-yl)-2,3-dihydro-1*H*-indene (2b)

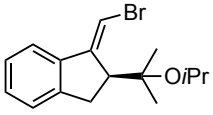


2b

2b was synthesized following the general procedure **C** performing the reaction at -60 °C for 4 days. The pure product was isolated by preparative TLC (pentane) as a transparent oil (26.6 mg, 90%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (dt, *J* = 7.3, 1.1 Hz, 1H), 7.24 – 7.19 (m, 2H), 7.19 – 7.13 (m, 1H), 6.64 (d, *J* = 1.4 Hz, 1H), 3.51 (dt, *J* = 7.6, 1.2 Hz, 1H), 3.45 (q, *J* = 7.0 Hz, 2H), 3.17 (d, *J* = 16.5 Hz, 1H), 2.94 (dd, *J* = 16.4, 7.5 Hz, 1H), 1.38 (s, 3H), 1.15 (t, *J* = 7.0 Hz, 3H), 0.75 (s, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.4, 145.5, 141.5, 128.7, 126.7, 125.1, 119.8, 100.8, 56.8, 51.3, 32.9, 25.9, 23.7, 16.2 ppm. **HRMS** (ESI+): *m/z*: calculated for $C_{15}H_{19}BrNaO$: 317.0511 $[M+Na]^+$; found: 317.0513. **SFC** (OD-3 (100x3 mm, 3 µm), CO_2:MeOH 95:5, 1.2 mL/min, 25 °C, BPR 150 bar; 254 nm): 1.409 min (90), 1.598 min (10); $[\alpha]_D^{26}$ = 97.4°(*c* = 0.44 in CH_2Cl_2).

(*S,E*)-1-(Bromomethylene)-2-(2-isopropoxypropan-2-yl)-2,3-dihydro-1*H*-indene (2c)

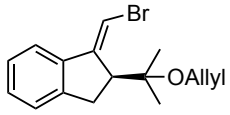


2c

2c was synthesized following the general procedure **C** performing the reaction at -60 °C for 4 days. The pure product was isolated by preparative TLC (pentane) as a transparent oil (19.5 mg, 63%).

^{1}H NMR (500 MHz, C_6D_6) δ 7.01 (m, 1H), 6.99 – 6.91 (m, 3H), 6.38 (d, J = 1.4 Hz, 1H), 3.67 (hept, J = 6.1 Hz, 1H), 3.47 (dt, J = 7.6, 1.2 Hz, 1H), 3.19 (d, J = 16.5 Hz, 1H), 2.68 (dd, J = 16.3, 7.6 Hz, 1H), 1.38 (s, 3H), 1.05 (dd, J = 13.9, 6.1 Hz, 6H), 0.75 (s, 3H). **^{13}C NMR** (126 MHz, C_6D_6) δ 149.6, 145.8, 141.8, 128.7, 126.7, 125.0, 120.0, 101.4, 79.1, 63.4, 52.8, 33.8, 26.4, 25.3, 25.0, 23.7. **HRMS** (ESI+): *m/z*: calculated for $C_{16}H_{21}BrNaO$: 331.0668 $[M+Na]^+$; found: 331.0666. **SFC** (IG (4.6 mm x 150 mmL, 3 µm), CO_2:IPA 97:3, 2 mL/min, 25 °C, 2000 psi; 290 nm): 2.140 min (10), 2.390 min (90); $[\alpha]_D^{26}$ = 61.3° (*c* = 0.45 in CH_2Cl_2).

(*S,E*)-2-(2-(Allyloxy)propan-2-yl)-1-(bromomethylene)-2,3-dihydro-1*H*-indene (2d)

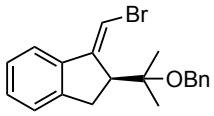


2d

2d was synthesized following the general procedure **C** performing the reaction at -60 °C for 4 days. The pure product was isolated by preparative TLC (pentane) as a transparent oil (10.9 mg, 35%).

^{1}H NMR (500 MHz, C_6D_6) δ 7.00 (ddd, *J* = 8.1, 5.5, 2.5 Hz, 1H), 6.98 – 6.92 (m, 3H), 6.37 (d, *J* = 1.4 Hz, 1H), 5.83 (ddt, *J* = 17.2, 10.5, 4.9 Hz, 1H), 5.21 (dq, *J* = 17.2, 1.9 Hz, 1H), 5.02 (dq, *J* = 10.5, 1.8 Hz, 1H), 3.71 (qdt, *J* = 12.7, 5.0, 1.7 Hz, 2H), 3.45 (d, *J* = 7.6 Hz, 1H), 3.13 (d, *J* = 16.5 Hz, 1H), 2.64 (ddd, *J* = 16.5, 7.7, 1.1 Hz, 1H), 1.34 (s, 3H), 0.82 (s, 3H). **^{13}C NMR** (126 MHz, C_6D_6) δ 149.6, 145.7, 141.7, 136.5, 128.7, 126.7, 125.1, 120.0, 114.6, 101.3, 78.8, 62.6, 52.1, 33.0, 25.8, 23.4. **HRMS** (APCI+): *m/z*: calculated for $C_{13}H_{14}Br$: 249.0273 $[M\text{-}OAllyl]^+$; found: 249.0271. **SFC** (OD-3 (100x3mm,3um), CO_2:MeOH 95:5, 1.2 mL/min, 25 °C, BPR 150 bar; 254 nm): 1.411 min (88), 1.627 min (12); $[\alpha]_D^{26}$ = 95.3° (*c* = 0.19 in CH_2Cl_2).

(*S,E*)-2-(2-(Benzyloxy)propan-2-yl)-1-(bromomethylene)-2,3-dihydro-1*H*-indene (2e)

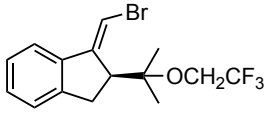


2e

2e was synthesized following the general procedure **C** performing the reaction at -60 °C for 4 days. The pure product was isolated by preparative TLC (pentane) as a transparent oil (24.7 mg, 69%). [1]

^{1}H NMR (400 MHz, C_6D_6) δ 7.24 – 7.18 (m, 4H), 7.14 – 7.09 (m, 1H), 7.01 (ddd, *J* = 7.2, 5.8, 2.6 Hz, 1H), 6.98 – 6.91 (m, 3H), 6.39 (d, *J* = 1.4 Hz, 1H), 4.33 – 4.20 (m, 2H), 3.52 (dt, *J* = 7.6, 1.2 Hz, 1H), 3.16 (d, *J* = 16.5 Hz, 1H), 2.65 (ddd, *J* = 16.4, 7.6, 1.2 Hz, 1H), 1.41 (s, 3H), 0.88 (s, 3H) ppm. **^{13}C** NMR (101 MHz, C_6D_6) δ 149.6, 145.7, 141.7, 140.2, 128.7, 128.4, 127.4, 127.2, 126.7, 125.1, 120.0, 101.3, 79.1, 63.8, 52.3, 33.1, 25.8, 23.5 ppm. **HRMS** (ESI+): *m/z*: calculated for $C_{20}H_{21}BrNaO$: 379.0668 $[M+Na]^+$; found: 379.0683. **SFC** (OD-3 (100x3mm,3um), CO_2:MeOH 80:20, 1.2 mL/min, 25 °C, BPR 150 bar; 254 nm): 1.274 min (88), 1.541 min (12); $[\alpha]_D^{26}$ = 92.8° (*c* = 0.38 in CH_2Cl_2).

(*S,E*)-1-(Bromomethylene)-2-(2-(2,2,2-trifluoroethoxy)propan-2-yl)-2,3-dihydro-1*H*-indene (2f)



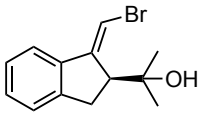
2f

2f was synthesized following the general procedure **C** performing the reaction at -60 °C for 4 days. The pure product was isolated by preparative TLC (pentane) as a yellow oil (10.9 mg, 35%).

^{1}H NMR (400 MHz, C_6D_6) δ 6.99 (m, 1H), 6.95 – 6.87 (m, 3H), 6.30 (d, *J* = 1.4 Hz, 1H), 3.34 – 3.21 (m, 3H), 2.98 (d, *J* = 16.6 Hz, 1H), 2.55 (dd, *J* = 16.6, 7.6 Hz, 1H), 1.13 (s,

3H), 0.61 (s, 3H) ppm. **^{13}C NMR** (101 MHz, C_6D_6) δ 148.7, 145.2, 141.2, 129.0, 126.9, 125.1, 120.0, 101.7, 80.4, 60.4 (q, *J* = 34.1 Hz), 51.7, 32.8, 25.3, 22.5 ppm. **^{19}F NMR** (376 MHz, C_6D_6) δ -74.1 ppm. **HRMS** (APCI+): *m/z*: calculated for $C_{15}H_{16}BrF_3O$: 348.0331 $[M]^+$; found: 348.0333. **SFC** (OD-3 (100x3mm,3um), CO_2:MeOH 98:2, 1.2 mL/min, 25 °C, BPR 150 bar; 254 nm): 1.204 min (61), 1.605 min (39); $[\alpha]_D^{26}$ = 13.0° (*c* = 0.17 in CH_2Cl_2).

(*S,E*)-2-(1-(Bromomethylene)-2,3-dihydro-1*H*-inden-2-yl)propan-2-ol (2g)

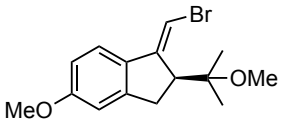


2g

2g was synthesized following the general procedure **C** performing the reaction at -60 °C for 4 days. The pure product was isolated by flash column chromatography purification on silica gel (10:1 cyclohexane:EtOAc) as a transparent oil (35.4 mg, 99%).

^{1}H NMR (400 MHz, C_6D_6) δ 7.06 – 6.95 (m, 1H), 6.98 – 6.89 (m, 3H), 6.36 (d, *J* = 1.4 Hz, 1H), 3.16 (dt, *J* = 7.5, 1.3 Hz, 1H), 2.80 – 2.71 (m, 1H), 2.63 (ddd, *J* = 16.5, 7.5, 1.1 Hz, 1H), 1.07 (s, 3H), 0.96 (s, 3H). **^{13}C NMR** (101 MHz, C_6D_6) δ 149.2, 145.5, 141.2, 128.8, 126.9, 125.1, 120.1, 101.6, 74.4, 55.1, 33.9, 28.7, 27.5. **HRMS** (ESI+): *m/z*: calculated for $C_{13}H_{15}BrNaO$: 289.0198 $[M+Na]^+$; found: 289.0195. **SFC** (IG-3 (100x3mm,3um), CO_2:MeOH 80:20, 1.2 mL/min, 25 °C, BPR 150 bar; 254 nm): 1.322 min (91), 2.790 min (9); $[\alpha]_D^{26}$ = 94.0° (*c* = 0.3 in CH_2Cl_2).

(*S,E*)-1-(Bromomethylene)-5-methoxy-2-(2-methoxypropan-2-yl)-2,3-dihydro-1*H*-indene (2h)

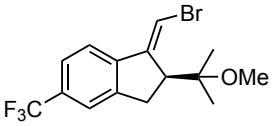


2h

2h was synthesized following the general procedure **C** performing the reaction at -60 °C for 5 days. The pure product was isolated by flash column chromatography purification on silica gel (100:1 pentane:Et_2O) as a transparent oil (24.4 mg, 78%).

^{1}H NMR (400 MHz, C_6D_6) δ 6.89 (d, *J* = 8.4 Hz, 1H), 6.63 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.56 (brs, 1H), 6.28 (d, *J* = 1.4 Hz, 1H), 3.52 (dt, *J* = 7.6, 1.2 Hz, 1H), 3.27 (s, 3H), 3.08 (d, *J* = 16.5 Hz, 1H), 3.02 (s, 3H), 2.65 (dd, *J* = 16.5, 7.6 Hz, 1H), 1.39 (s, 3H), 0.82 (s, 3H) ppm. **^{13}C NMR** (101 MHz, C_6D_6) δ 161.1, 149.0, 147.7, 134.6, 121.0, 113.7, 109.6, 98.7, 78.7, 54.9, 51.9, 49.0, 33.1, 25.2, 23.0 ppm. **HRMS** (APCI+): *m/z*: calculated for $C_{14}H_{16}BrO$: 279.0379 $[M\text{-}OMe]^+$; found: 279.0380. **SFC** (IG-3 (100x3mm,3um), CO_2:EtOH 90:10, 1.2 mL/min, 25 °C, BPR 150 bar; 254 nm): 1.161min (14), 1.418 min (86); $[\alpha]_D^{26}$ = 84.6° (*c* = 0.21 in CH_2Cl_2).

(*S,E*)-1-(Bromomethylene)-2-(2-methoxypropan-2-yl)-5-(trifluoromethyl)-2,3-dihydro-1*H*-indene (2i)

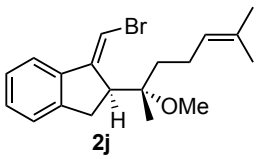


2i

2i was synthesized following the general procedure **C** performing the reaction at -60 °C for 5 days and using 5 mol% of **A** and of $AgSbF_6$. The pure product was isolated by preparative TLC (2:1 cyclohexane:CH_2Cl_2) followed by flash column chromatography in silica gel (20:1 cyclohexane:CH_2Cl_2) to give **2i** as a transparent oil (24.3 mg, 70%).

^{1}H NMR (400 MHz, C_6D_6) δ 7.18 (m, 2H), 6.70 (d, J = 7.9 Hz, 1H), 6.30 (d, J = 1.4 Hz, 1H), 3.34 (dt, J = 7.8, 1.2 Hz, 1H), 2.92 (s, 3H), 2.88 (m, 1H), 2.42 (dd, J = 16.8, 7.7 Hz, 1H), 1.21 (s, 3H), 0.65 (s, 3H). **^{13}C NMR** (101 MHz, C_6D_6) δ 148.29, 146.23, 144.94, 128.18, 127.94, 123.95 (q, *J* = 3.8 Hz), 122.11 (q, *J* = 3.8 Hz), 120.12, 104.09, 78.31, 52.00, 48.95, 32.69, 24.69, 22.66. **^{19}F NMR** (376 MHz, C_6D_6) δ -61.73. **HRMS** (APCI+): *m/z*: calculated for $C_{14}H_{13}BrF_3$: 317.0147 $[M\text{-}OMe]^+$; found: 317.0150. **SFC** (IG (4.6 mm x 150 mmL, 3 µm), CO_2:IPA 97:3, 2 mL/min, 25 °C, 2000 psi; 291 nm): 1.820 min (13), 2.080 min (87); $[\alpha]_D^{26}$ = 74.2° (*c* = 0.24 in CH_2Cl_2).

(*S,E*)-1-(Bromomethylene)-2-((*S*)-2-methoxy-6-methylhept-5-en-2-yl)-2,3-dihydro-1*H*-indene (2j)

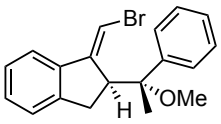


2j

2j was synthesized following the general procedure **C** performing the reaction at -40 °C for 5 days. The pure product was isolated by preparative TLC (100:1 pentane:Et_2O), as a transparent oil (18.5 mg, 53%) and as a single diastereomer.[6]

^{1}H NMR (500 MHz, C_6D_6) δ 7.05 – 6.97 (m, 1H), 6.98 – 6.92 (m, 3H), 6.36 (d, *J* = 1.4 Hz, 1H), 5.37 – 5.30 (m, 1H), 3.48 (d, *J* = 7.7 Hz, 1H), 3.13 (d, *J* = 16.4 Hz, 1H), 2.97 (s, 3H), 2.62 (ddd, J = 16.3, 7.6, 1.2 Hz, 1H), 2.36 – 2.21 (m, 1H), 2.15 – 2.02 (m, 2H), 1.84 – 1.71 (m, 1H), 1.70 (s, 3H), 1.60 (s, 3H), 0.81 (s, 3H). **^{13}C NMR** (126 MHz, C_6D_6) δ 149.7, 145.7, 142.0, 131.0, 128.8, 126.8, 125.6, 125.0, 120.0, 101.3, 80.2, 50.3, 48.8, 37.2, 32.5, 25.9, 22.7, 20.7, 17.8. **HRMS** (APCI+): *m/z*: calculated for $C_{18}H_{22}Br$: 317.0899 $[M\text{-}OMe]^+$; found: 317.0900. **SFC** (IG-3 (100x3mm,3um), CO_2:MeOH 97:3, 1.2 mL/min, 25 °C, BPR 150 bar; 254 nm): 1.461 min (6), 2.275 min (94); $[\alpha]_D^{26}$ = 61.1° (*c* = 0.21 in CH_2Cl_2).

(*S,E*)-1-(Bromomethylene)-2-((*R*)-1-methoxy-1-phenylethyl)-2,3-dihydro-1*H*-indene (2k)

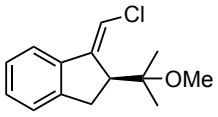


2k

2k was synthesized following the general procedure **C** performing the reaction at -40 °C for 4 days. The pure product was isolated by preparative TLC (7:1 cyclohexane:CH_2Cl_2), as a white solid (33.7 mg, 0.098 mmol, 98%) and as a single diastereomer.[6]

M.p. 64-72 °C. **^{1}H NMR** (400 MHz, C_6D_6) δ 7.40 – 7.33 (m, 2H), 7.24 – 7.16 (m, 2H), 7.16 – 7.07 (m, 1H), 7.04 – 6.89 (m, 5H), 6.40 (d, *J* = 1.4 Hz, 1H), 3.62 (dt, *J* = 7.8, 1.2 Hz, 1H), 3.23 (d, *J* = 16.6 Hz, 1H), 2.84 (s, 3H), 2.70 (dd, *J* = 16.6, 7.7 Hz, 1H), 1.26 (s, 3H). **^{13}C NMR** (101 MHz, C_6D_6) δ 148.0, 145.5, 144.2, 142.0, 128.5, 127.3, 126.6, 125.0, 119.9, 102.9, 81.9, 56.3, 50.3, 33.9, 30.2, 19.6, 1.4. **HRMS** (APCI+): *m/z*: calculated for $C_{18}H_{16}Br$: 311.0430 [M-OMe]$^+$; found: 311.0425. **SFC** (OJ-3 (100x3mm,3um), CO_2:MeOH 95:5, 1.2 mL/min, 25 °C, BPR 150 bar; 280 nm): 2.609 min (18), 3.641 min (82); **[α]$_D^{26}$** = 74.4° (*c* = 0.23 in CH_2Cl_2).

(*S*,*E*)-1-(Chloromethylene)-2-(2-methoxypropan-2-yl)-2,3-dihydro-1*H*-indene (2l)

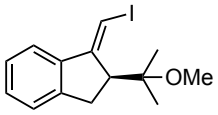


2l

2l was synthesized following the general procedure **C** performing the reaction at -40 °C for 24 h. The pure product was isolated by preparative TLC (pentane), as a yellow oil (23.1 mg, 98%).

^{1}H NMR (500 MHz, C_6D_6) δ 7.04 – 6.91 (m, 4H), 6.25 (d, *J* = 1.5 Hz, 1H), 3.51 (dt, *J* = 7.8, 1.3 Hz, 1H), 3.10 (d, *J* = 16.5 Hz, 1H), 2.99 (s, 3H), 2.66 (dd, *J* = 16.5, 7.7 Hz, 1H), 1.31 (s, 3H), 0.76 (s, 3H). **^{13}C NMR** (126 MHz, C_6D_6) δ 146.6, 145.6, 141.2, 128.7, 126.7, 125.0, 119.8, 112.3, 78.6, 49.9, 49.0, 33.1, 24.8, 22.8. **HRMS** (APCI+): *m/z*: calculated for $C_{13}H_{14}Cl$: 205.0779 [M-OMe]$^+$; found: 205.0777. **SFC** (IG-3 (100x3mm,3um), CO_2:MeOH 97:3, 1.2 mL/min, 25 °C, BPR 150 bar; 254 nm): 1.115 min (76), 1.256 min (24); **[α]$_D^{26}$** = 63.0° (*c* = 0.22 in CH_2Cl_2).

(*S*,*E*)-1-(Iodomethylene)-2-(2-methoxypropan-2-yl)-2,3-dihydro-1*H*-indene (2m)

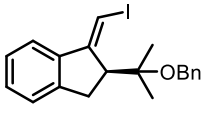


2m

2m was synthesized following the general procedure **C** performing the reaction at -60 °C for 6 days. The pure product was isolated by preparative TLC (pentane), as a yellow oil (26.3 mg, 80%).

^{1}H NMR (500 MHz, C_6D_6) δ 7.00 (ddd, *J* = 7.2, 6.0, 2.5 Hz, 1H), 6.97 – 6.90 (m, 3H), 6.45 (d, *J* = 1.3 Hz, 1H), 3.35 (dt, *J* = 7.5, 1.1 Hz, 1H), 3.04 (d, J = 16.4 Hz, 1H), 2.99 (s, 3H), 2.63 (ddd, *J* = 16.3, 7.5, 1.2 Hz, 1H), 1.34 (s, 3H), 0.76 (s, 3H). **^{13}C NMR** (126 MHz, C_6D_6) δ 155.6, 145.8, 142.3, 128.7, 126.7, 125.1, 120.3, 78.8, 73.0, 54.4, 48.9, 32.7, 25.2, 23.2. **HRMS** (APCI+): *m/z*: calculated for $C_{13}H_{14}I$: 297.0135 [M-OMe]$^+$; found: 297.0125. **SFC** (IBN-3 (100x3mm,3um), CO_2:MeOH 95:5, 1.2 mL/min, 25 °C, BPR 150 bar; 280 nm): 1.367 min (93), 1.530 min (7); **[α]$_D^{26}$** = -97.0° (*c* = 0.20 in CH_2Cl_2).

(S,*E*)-2-(2-(Benzyloxy)propan-2-yl)-1-(iodomethylene)-2,3-dihydro-1*H*-indene (2n)

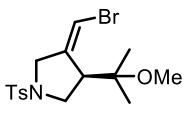


2n

2n was synthesized following the general procedure **C** performing the reaction at -60 °C for 4 days. The pure product was isolated by preparative TLC (30:1 cyclohexane:EtOAc), as a pale yellow solid (20.5 mg, 51%).

M.p. 64.5-65.5 °C. **^{1}H NMR** (400 MHz, C_6D_6) δ 7.24 – 7.17 (m, 4H), 7.15 – 7.09 (m, 1H), 7.04 – 6.94 (m, 3H), 6.91 (d, *J* = 7.2 Hz, 1H), 6.45 (d, *J* = 1.2 Hz, 1H), 4.27 (dd, *J* = 19.1, 12.0 Hz, 2H), 3.41 (d, *J* = 7.5 Hz, 1H), 3.13 (d, *J* = 16.4 Hz, 1H), 2.64 (dd, *J* = 16.3, 7.5 Hz, 1H), 1.43 (s, 3H), 0.88 (s, 3H). **^{13}C NMR** (101 MHz, C6D6) δ 155.6, 145.8, 142.3, 140.2, 128.7, 128.4, 127.5, 127.2, 126.7, 125.2, 120.3, 79.3, 73.1, 63.8, 55.1, 32.8, 26.2, 23.8. **HRMS** (ESI+): *m/z*: calculated for $C_{20}H_{21}INaO$[M+Na]$^+$: 427.0529; found: 427.0525. **SFC** (IBN-3 (100x3mm,3um), CO_2:EtOH 95:5, 1.2 mL/min, 25 °C, BPR 150 bar; 210 nm): 3.136 min (85), 3.471 min (15); **[α]$_D^{25}$** = 148.7° (*c* = 0.1 in CH_2Cl_2).

(*R*,*E*)-3-(Bromomethylene)-4-(2-methoxypropan-2-yl)-1-tosylpyrrolidine (2o)

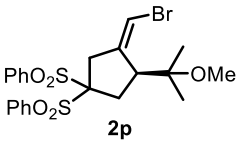


2o

2o was synthesized following the general procedure **C** performing the reaction at 24 °C for 24 h. The pure product was isolated by preparative TLC (10:1 cyclohexane:EtOAc), as a yellow oil (29.4 mg, 76%).

^{1}H NMR (500 MHz, C_6D_6) δ 7.73 (d, *J* = 8.2 Hz, 2H), 6.82 – 6.76 (m, 2H), 5.55 (s, 1H), 3.71 (dd, *J* = 10.1, 2.2 Hz, 1H), 3.66 (d, *J* = 1.6 Hz, 2H), 3.21 (dd, *J* = 10.1, 7.8 Hz, 1H), 2.79 – 2.71 (m, 1H), 2.55 (s, 3H), 1.89 (s, 3H), 0.87 (s, 3H), 0.84 (s, 3H). **^{13}C NMR** (126 MHz, C_6D_6) δ 142.80, 142.44, 135.44, 129.54, 103.68, 77.47, 53.66, 51.51, 48.85, 48.64, 34.44, 23.66, 22.73, 22.31, 21.10, 14.28. **HRMS** (ESI+): *m/z*: calculated for $C_{16}H_{22}BrNNaO_3S$: 410.0396 [M+Na]$^+$; found: 410.0396. **SFC** (IA-3 (100x3mm,3um), CO_2:MeOH 85:15, 1.2 mL/min, 25 °C, BPR 150 bar; 210 nm): 1.584 min (87), 2.022 min (13); **[α]$_D^{26}$** = -6.2° (*c* = 0.21 in CH_2Cl_2).

(*S*,*Z*)-(3-(Bromomethylene)-4-(2-methoxypropan-2-yl)cyclopentane-1,1-disulfonyl)dibenzene (2p)



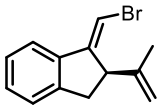
2p

2p was synthesized following the general procedure **C** performing the reaction at -40 °C for 48 h. The pure product was isolated by preparative TLC (3:1 CH_2Cl_2:cyclohexane), as a transparent oil (25.9 mg, 50%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 – 7.99 (m, 4H), 7.76 – 7.66 (m, 2H), 7.66 – 7.55 (m, 4H), 6.05 (dd, *J* = 2.4, 1.5 Hz, 1H), 3.51 (ddd, *J* = 15.7, 2.7, 1.4 Hz, 1H), 3.05 (s, 3H), 3.02 – 2.92 (m, 2H), 2.80 – 2.68 (m, 2H), 1.25 (s, 3H), 1.20 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.6, 137.4, 136.3, 134.9, 134.6, 131.3, 131.1, 129.0, 128.9, 103.2, 91.8, 78.5, 50.6, 49.4, 41.7, 32.4, 24.7, 23.5. **HRMS** (ESI+): *m/z*: calculated for $C_{22}H_{25}BrNaO_5S_2$: 535.0219 $[M+Na]^+$; found: 535.0238. **SFC** (OJ-3 (100x3mm,3um), CO_2:MeOH 80:20, 1.2 mL/min, 25 °C, BPR 150 bar; 230 nm): 1.057 min (11), 1.433 min (89); $[\alpha]_D^{26}$ = -22.6° (*c* = 0.21 in CH_2Cl_2).

4. Functionalization of alkoxycyclization products

(*R*,*E*)-1-(Bromomethylene)-2-(prop-1-en-2-yl)-2,3-dihydro-1*H*-indene (3)

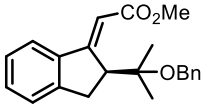


3

Under Ar atmosphere, **2g** (10.9 mg, 0.041 mmol) and Burgess reagent (14.6 mg, 0.061 mmol, 1.5 equiv) were dissolved in anhydrous THF (0.41 mL) and the mixture was stirred for 16 h at 24 °C. The reaction was quenched with the addition of 2 mL of H_2O and 2 mL of EtOAc. The aqueous phase was extracted with EtOAc (x3) and the combined organic layers were washed with saturated NaCl aqueous solution and dried with Na_2SO_4. The pure product was isolated by preparative TLC (pentane) as a yellow oil (10.0 mg, 98%).

^{1}H NMR (400 MHz, C_6D_6) δ 7.05 – 6.87 (m, 4H), 6.47 (d, *J* = 2.0 Hz, 1H), 4.92 (dp, *J* = 1.7, 0.8 Hz, 1H), 4.79 (p, *J* = 1.5 Hz, 1H), 3.67 (dtd, *J* = 8.8, 2.2, 0.8 Hz, 1H), 2.90 (dd, *J* = 16.7, 8.8 Hz, 1H), 2.52 (dd, *J* = 16.8, 2.3 Hz, 1H), 1.54 (dd, J = 1.5, 0.8 Hz, 3H). **^{13}C NMR** (101 MHz, C_6D_6) δ 149.4, 145.5, 144.9, 140.1, 129.0, 127.1, 125.7, 120.5, 111.8, 100.6, 51.4, 37.5, 19.8. **HRMS** (APCI+): *m/z*: calculated for $C_{13}H_{14}Br$: 249.0273 $[M+H]^+$; found: 249.0270. **SFC** (OJ-3 (100x3mm,3um), CO_2:MeOH 98:2, 1.2 mL/min, 25 °C, BPR 150 bar; 254 nm): 1.586 min (9), 1.768 min (91); $[\alpha]_D^{26}$ = 103.3° (*c* = 0.24 in CH_2Cl_2).

Methyl (S,E)-2-(2-(2-(Benzyloxy)propan-2-yl)-2,3-dihydro-1H-inden-1-ylidene)acetate (4)

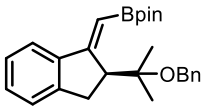


4

Following a modified procedure,[7] to a solution of **2n** (20 mg, 1.0 equiv) in MeOH (0.5 mL) was added *i*Pr_2NEt (26 µL, 0.15 mmol, 1.0 equiv) and $Pd(dppf)_2Cl_2$ (3.7 mg, 0.0050 mmol, 0.10 equiv). The reactor was sealed and flashed with CO 3 times. After stirring at 110 °C for 16 h under CO (10 bars), the reactor was cooled down to 24 °C, and the system was purged with Ar. The reaction mixture was filtered through a plug of Celite and concentrated under reduced pressure. The product was purified by flash column chromatography (20:1 cyclohexane:EtOAc) as a colorless oil (13.8 mg, 82%).

^{1}H NMR (400 MHz, C_6D_6) δ 7.21 – 7.17 (m, 5H), 7.13 – 7.08 (m, 1H), 7.05 (td, *J* = 7.4, 1.2 Hz, 1H), 6.99 – 6.90 (m, 2H), 6.44 (d, *J* = 1.5 Hz, 1H), 4.74 (d, *J* = 7.5 Hz, 1H), 4.38 (dd, *J* = 15.0, 11.5 Hz, 2H), 3.49 (s, 3H), 3.20 (d, *J* = 16.6 Hz, 1H), 2.72 (dd, *J* = 16.6, 7.3 Hz, 1H), 1.37 (s, 3H), 0.91 (s, 3H). **^{13}C NMR** (101 MHz, C_6D_6) δ 167.5, 162.6, 148.2, 142.1, 140.3, 130.6, 128.6, 128.3, 127.4, 127.1, 126.8, 125.1, 121.0, 112.3, 79.0, 63.9, 50.8, 49.5, 33.9, 23.7, 23.7. **HRMS** (ESI+): *m/z*: calculated for $C_{22}H_{24}NaO_3[M+Na]^+$: 359.1618; found: 359.1627. **SFC** (OJ-3 (100x3mm,3um), CO_2:MeOH 95:5, 1.2 mL/min, 25 °C, BPR 150 bar; 210 nm): 1.791 min (15), 2.600 min (85); $[\alpha]_D^{26}$ = 128.8° (*c* = 0.1 in CH_2Cl_2).

(*S*,*E*)-2-((2-(2-Methoxypropan-2-yl)-2,3-dihydro-1*H*-inden-1-ylidene)methyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5)

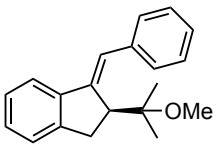


5

Following a modified procedure,[8] a mixture of **2a** (20.0 mg, 0.071 mmol), B_2Pin_2 (21.7 mg, 0.085 mmol, 1.2 equiv), and KOAc (20.9 mg, 0.213 mmol, 3 equiv) in dry 1,4-dioxane (0.35mL) was purged with N_2, and $Pd(dppf)Cl_2$ (2.60 mg, 0.0036 mmol, 0.05 equiv) was added. The mixture was stirred at 90 °C for 24 h. The solvent was removed under vacuo, and of Et_2O was added. The crude mixture was filtered through a pad of Celite and the pad washed with Et_2O. Then, water was added to the filtrate, and the mixture was extracted with Et_2O. The organic phase was washed with saturated NaCl aqueous solution, dried with Na_2SO_4, and concentrated in vacuo. The product was purified by preparative TLC (15:1 cyclohexane:EtOAc) as a yellow oil (15.2 mg, 65%).

^{1}H NMR (400 MHz, C_6D_6) δ 7.39 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.04 (dd, *J* = 3.9, 1.0 Hz, 2H), 6.98 (dq, *J* = 8.2, 4.3 Hz, 1H), 6.24 (d, *J* = 1.3 Hz, 1H), 4.07 (d, *J* = 7.5 Hz, 1H), 3.21 (d, *J* = 16.6 Hz, 1H), 3.16 (s, 3H), 2.83 (dd, *J* = 16.5, 7.6 Hz, 1H), 1.38 (s, 3H), 1.14 (s, 6H), 1.14 (s, 6H), 0.82 (s, 3H). **^{13}C NMR** (101 MHz, C_6D_6) δ 165.7, 147.0, 144.1, 129.4, 126.8, 125.0, 120.8, 82.9, 77.7, 50.8, 49.0, 33.3, 25.3, 24.9, 23.1, 22.5. **HRMS** (ESI+): *m/z*: calculated for $C_{20}H_{29}NaO_3B$: 350.2138 $[M+Na]^+$; found: 350.2133. **SFC** (IG-3 (100x3mm,3um), CO_2:MeOH 96:4, 1.2 mL/min, 25 °C, BPR 150 bar; 280 nm): 1.191 min (89), 1.512 min (11); $[\alpha]_D^{26}$ = 34.3° (*c* = 0.16 in CH_2Cl_2).

(*S*,*E*)-1-Benzylidene-2-(2-methoxypropan-2-yl)-2,3-dihydro-1*H*-indene (6)

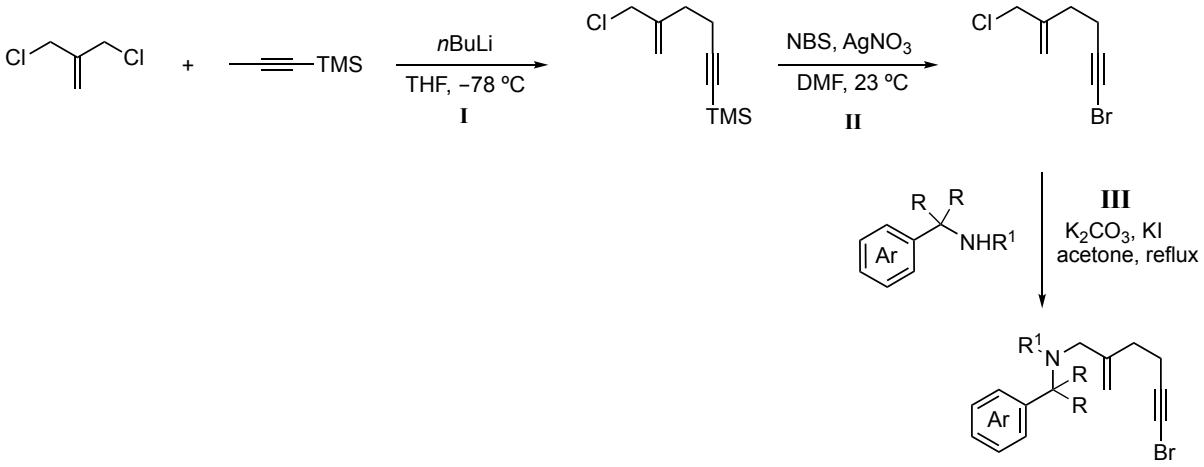


6

Phenylboronic acid (17.2 mg, 0.141 mmol, 1.8 equiv), $Pd(PPh_3)_2Cl_2$ (2.76 mg, 0.0039 mmol, 0.05 equiv) and K_2CO_3 (32.6 mg, 0.236 mmol, 3 equiv) were added to a solution of **2a** (22.1 mg, 0.076 mmol) in 1,4-dioxane (1.25 mL) and water (0.21 mL). The mixture was stirred for 3 h at 85 °C. Water was then added, the aqueous phase was extracted with Et_2O (x3) and the combined organic layers were joined, washed with saturated NaCl aqueous solution and dried with Na_2SO_4. The product was purified by preparative TLC (20:1 cyclohexane:EtOAc) as a white solid (16.2 mg, 74%).

M.p. 75-83 °C. **^{1}H NMR** (500 MHz, C_6D_6) δ 7.46 – 7.42 (m, 2H), 7.42 – 7.38 (m, 1H), 7.24 – 7.14 (m, 2H), 7.17 – 7.03 (m, 5H), 4.01 (d, *J* = 7.9 Hz, 1H), 3.23 (d, *J* = 16.6 Hz, 1H), 2.97 – 2.91 (m, 1H), 2.91 (s, 3H), 0.86 (s, 3H), 0.75 (s, 3H). **^{13}C NMR** (126 MHz, C_6D_6) δ 145.7, 145.7, 144.2, 139.5, 129.2, 128.6, 128.4, 128.4, 126.8, 124.9, 123.2, 120.0, 79.1, 48.8, 48.0, 33.6, 23.4, 22.1. **HRMS** (ESI+): *m/z*: calculated for $C_{20}H_{22}NaO$: 301.1563 $[M+Na]^+$; found: 301.1552. **SFC** (OJ-3 (100x3mm,3um), CO_2:MeOH 90:10, 1.2 mL/min, 25 °C, BPR 150 bar; 210 nm): 1.299 min (10), 1.542 min (90); $[\alpha]_D^{26}$ = -175.0° (*c* = 0.1 in CH_2Cl_2).

5. Synthesis of the substrates for the cyclization of 1-bromo-5-enynes

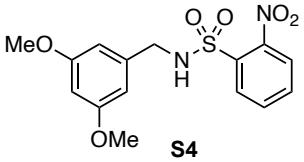


Step I-III: The 1-bromo-5-enynes substrates were synthesized by adapting a procedure reported in literature.[9]

5.1. General procedure D for the preparation of sulfonamide precursors S4-S8

To a solution of (3,5-dimethoxyphenyl)methanamine in CH_2Cl_2 was added NEt_3 (1.1 equiv) at 0 °C and the mixture was stirred for 10 min at this temperature. The corresponding sulfonyl chloride (1.2 equiv) was added, and the reaction mixture was allowed to warm up to 24 °C and stirred overnight. The reaction was quenched with water and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude was purified by flash column chromatography (cyclohexane/EtOAc 3:1 to 2:1).

***N*-(3,5-Dimethoxybenzyl)-2-nitrobenzenesulfonamide (S4)**

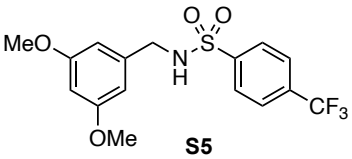


S4

The title compound (white solid, 88%) was synthesized according to general procedure **D** using 2-nitrobenzenesulfonyl chloride.

M.p. = 85 – 87 °C (cyclohexane/ EtOAc). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.04 – 7.99 (m, 1H), 7.85 – 7.80 (m, 1H), 7.72 – 7.62 (m, 2H), 6.34 (dd, *J* = 2.3, 0.6 Hz, 2H), 6.27 (t, *J* = 2.3 Hz, 1H), 5.72 (t, *J* = 6.3 Hz, 1H), 4.25 (d, *J* = 6.3 Hz, 2H), 3.70 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.0, 147.8, 137.9, 134.0, 133.4, 132.7, 131.0, 125.2, 105.6, 100.0, 55.3, 48.0. **HRMS** (ESI+) calculated for $[C_{15}H_{16}N_2NaO_6S]^+$ 375.0621 *m/z*; found $[M + Na]^+$ 375.0613 *m/z*.

***N*-(3,5-Dimethoxybenzyl)-4-(trifluoromethyl)benzenesulfonamide (S5)**

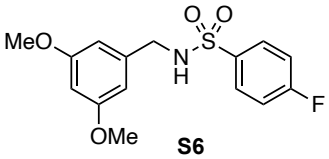


S5

The title compound (white solid, 89%) was synthesized according to general procedure **D** using 4-(trifluoromethyl)benzenesulfonyl chloride.

M.p. = 95 – 97 °C (cyclohexane/ EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.1 Hz, 2H), 7.75 (d, J = 7.9 Hz, 2H), 6.31 (t, J = 2.3 Hz, 1H), 6.27 (d, J = 2.3 Hz, 2H), 4.94 – 4.85 (m, 1H), 4.13 (d, J = 6.0 Hz, 2H), 3.71 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.1, 143.8, 137.9, 127.6, 126.2 (q, J = 7.6 Hz), 105.7, 99.8, 55.3, 47.5. **^{19}F NMR** (376 MHz, $CDCl_3$) δ –63.3. **HRMS** (ESI–) calculated for $[C_{16}H_{15}F_3NO_4S]^-$ 374.0679 *m/z*; found $[M - H]^-$ 374.0666 *m/z*.

***N*-(3,5-Dimethoxybenzyl)-4-fluorobenzenesulfonamide (S6)**

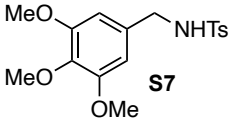


S6

The title compound (white solid, 93%) was synthesized according to general procedure **D** using 4-fluorobenzenesulfonyl chloride.

M.p. = 93 – 95 °C (cyclohexane/ EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.01 – 7.71 (m, 2H), 7.21 – 7.13 (m, 2H), 6.37 – 6.24 (m, 3H), 4.83 (brs, 1H), 4.08 (d, J = 6.2 Hz, 2H), 3.72 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.2 (d, J = 254.9 Hz), 161.2, 138.4, 136.2 (d, J = 3.3 Hz), 130.0, 129.9, 116.4 (d, J = 3.0 Hz), 105.8, 100.0, 55.5, 47.5. **^{19}F NMR** (376 MHz, $CDCl_3$) δ –105.3. **HRMS** (ESI–) calculated for $[C_{15}H_{15}FNO_4S]^-$ 324.0711 *m/z*; found $[M - H]^-$ 324.0709 *m/z*.

4-Methyl-*N*-(3,4,5-trimethoxybenzyl)benzenesulfonamide (S7)

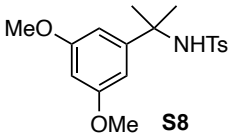


S7

The title compound (white solid, 93%) was synthesized according to general procedure **D** using tosyl chloride.

M.p. = 122-125 °C (cyclohexane/ EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.75 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 7.9 Hz, 2H), 6.36 (s, 2H), 4.89 (brs, 1H), 4.07 (d, J = 5.9 Hz, 2H), 3.79 (s, 3H), 3.75 (s, 6H), 2.42 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.4, 143.7, 137.6, 137.2, 132.1, 129.8, 129.8, 104.8, 60.9, 56.1, 47.7, 21.6. **HRMS** (ESI+) calculated for $[C_{17}H_{21}NNaO_5S]^+$ 374.1040 *m/z*; found [M + Na] 374.1033 *m/z*.

***N*-(2-(3,5-Dimethoxyphenyl)propan-2-yl)-4-methylbenzenesulfonamide (S8)**



S8

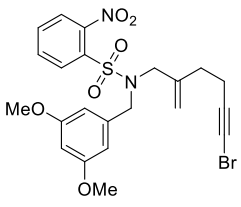
The title compound (brown gum, 60%) was synthesized according to general procedure **D** using tosyl chloride and 2-(3,5-dimethoxyphenyl)propan-2-amine.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, J = 8.3 Hz, 2H), 7.15 (d, J = 9.3 Hz, 2H), 6.41 (d, J = 2.2 Hz, 2H), 6.25 (t, J = 2.2 Hz, 1H), 5.20 (s, 1H), 3.69 (s, 6H), 2.38 (s, 3H), 1.60 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.7, 147.7, 142.8, 139.9, 129.3, 127.1, 104.4, 98.8, 58.8, 55.3, 29.9, 21.5. **HRMS** (ESI+) calculated for $[C_{18}H_{23}NNaO_4S]^+$ 372.1240 *m/z*; found $[M + Na]^+$ 372.1235 *m/z*.

5.2. General procedure E for the preparation of 1-bromo-5-enynes 9b-g

To a solution of the corresponding sulfonamides (1.2 equiv.) and 6-bromo-2-(chloromethyl)hex-1-en-5-yne (1.0 equiv) in acetone (0.14 M) was added K_2CO_3 (1.2 equiv) and KI (0.12 equiv) at 24 °C. The mixture was heated under refluxing conditions for 24 h before the solvent was evaporated. The residue was taken up in Et_2O and washed sequentially with water and saturated NaCl aqueous solution, dried over anhydrous Na_2SO_4. The solvent was evaporated, and the crude was purified by flash column chromatography (cyclohexane/EtOAc 3:1) to give target compounds. Enyne **9a** was described[9] and the spectral analysis is in accordance with the reported data.

***N*-(6-Bromo-2-methylenehex-5-yn-1-yl)-*N*-(3,5-dimethoxybenzyl)-2-nitrobenzenesulfonamide (9b)**

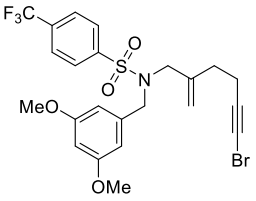


9b

The title compound (white solid, 86%) was synthesized according to general procedure **E** using *N*-(3,5-dimethoxybenzyl)-2-nitrobenzenesulfonamide (**S4**).

M.p. = 104 – 106 °C (cyclohexane/ EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02 (dd, J = 7.7, 1.3 Hz, 1H), 7.71 – 7.61 (m, 3H), 6.31 (t, J = 2.3 Hz, 1H), 6.28 (d, J = 2.2 Hz, 2H), 4.95 (d, J = 15.8 Hz, 2H), 4.45 (s, 2H), 3.91 (s, 2H), 3.68 (s, 6H), 2.25 (td, J = 7.2, 0.7 Hz, 2H), 2.09 (t, J = 7.2 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.0, 147.7, 140.9, 137.6, 134.2, 133.5, 131.8, 131.2, 124.2, 115.4, 105.9, 100.0, 79.2, 55.3, 51.7, 50.3, 38.7, 31.4, 18.1. **HRMS** (ESI+) calculated for $[C_{22}H_{24}BrN_2O_6S]^+$ 523.0533 *m/z*; found $[M + H]^+$ 523.0508 *m/z*.

***N*-(6-Bromo-2-methylenehex-5-yn-1-yl)-*N*-(3,5-dimethoxybenzyl)-4-(trifluoromethyl)benzenesulfonamide (9c)**

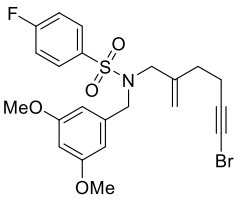


9c

The title compound (white solid, 80%) was synthesized according to general procedure **E** using *N*-(3,5-dimethoxybenzyl)-4-(trifluoromethyl)benzenesulfonamide (**S5**).

M.p. = 91 – 93 °C (cyclohexane/ EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.9 Hz, 2H), 7.76 (d, *J* = 8.8 Hz, 2H), 6.32 (t, *J* = 2.3 Hz, 1H), 6.20 (d, *J* = 2.3 Hz, 2H), 4.97 (s, 1H), 4.89 (s, 1H), 4.31 (s, 2H), 3.81 (s, 2H), 3.68 (s, 6H), 2.29 (td, *J* = 7.2, 0.8 Hz, 2H), 2.13 (t, *J* = 7.2 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.0, 144.3, 141.3, 137.5, 134.4 (d, *J* = 33.0 Hz), 127.7, 126.4 (q, *J* = 3.6 Hz), 115.8, 106.6, 99.9, 79.3, 55.4, 52.3, 50.9, 38.9, 31.6, 18.2. **^{19}F NMR** (376 MHz, $CDCl_3$) δ –63.2. **HRMS** (ESI+) calculated for $[C_{23}H_{23}BrF_3NNaO_4S]^+$ 568.0375 *m/z*; found $[M + Na]^+$ 568.0365 *m/z*.

***N*-(6-Bromo-2-methylenehex-5-yn-1-yl)-*N*-(3,5-dimethoxybenzyl)-4-fluorobenzenesulfonamide (9d)**

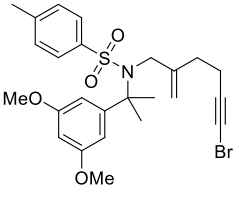


9d

The title compound (colorless oil, 89%) was synthesized according to general procedure **E** using *N*-(3,5-dimethoxybenzyl)-4-fluorobenzenesulfonamide (**S6**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 7.7 Hz, 2H), 6.33 (s, 2H), 4.92 (d, *J* = 1.4 Hz, 1H), 4.86 (d, *J* = 1.3 Hz, 1H), 4.27 (s, 2H), 3.81 (s, 3H), 3.73 (s, 6H), 3.72 (s, 2H), 2.43 (s, 3H), 2.22 (td, *J* = 7.5, 1.0 Hz, 2H), 2.10 (t, *J* = 7.3 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.1 (d, *J* = 257.3 Hz), 161.0, 141.6, 138.0, 136.7, 130.0 (d, *J* = 9.2 Hz), 116.4 (d, *J* = 22.6 Hz), 115.5, 106.6, 100.0, 79.4, 55.4, 52.2, 51.0, 38.8, 31.6, 18.2.**^{19}F NMR** (376 MHz, $CDCl_3$) δ –105.5. **HRMS** (ESI+) calculated for $[C_{22}H_{23}BrFNNaO_4S]^+$ 518.0407 *m/z*; found $[M + Na]^+$ 518.0426 *m/z*.

***N*-(6-bromo-2-methylenehex-5-yn-1-yl)-*N*-(2-(3,5-dimethoxyphenyl)propan-2-yl)-4-methylbenzenesulfonamide (9e)**

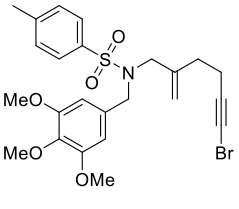


9e

The title compound (colorless oil, 36%) was synthesized according to general procedure **E** using *N*-(2-(3,5-dimethoxyphenyl)propan-2-yl)-4-methylbenzenesulfonamide (**S8**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.54 (m, 2H), 7.23 (d, *J* = 7.7 Hz, 2H), 6.38 (d, *J* = 2.2 Hz, 2H), 6.31 (t, *J* = 2.2 Hz, 1H), 3.93 (s, 2H), 3.70 (s, 6H), 2.41 (s, 3H), 2.34 – 2.26 (m, 2H), 2.25 – 2.19 (m, 2H), 1.67 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.6, 148.5, 145.2, 142.9, 140.6, 129.4, 127.4, 113.1, 105.0, 98.8, 79.9, 64.9, 55.3, 52.6, 38.5, 32.1, 29.5, 21.6, 18.5. **HRMS** (ESI+) calculated for $[C_{25}H_{30}BrNNaO_4S]^+$ 542.0971 *m/z*; found $[M + Na]^+$ 542.0967 *m/z*.

***N*-(6-bromo-2-methylenehex-5-yn-1-yl)-4-methyl-*N*-(3,4,5-trimethoxybenzyl)benzenesulfonamide (9f)**

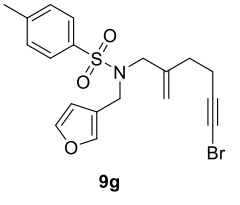


9f

The title compound (colorless oil, 88%) was synthesized according to general procedure **E** using 4-methyl-N-(3,4,5-trimethoxybenzyl)benzenesulfonamide (**S7**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 7.7 Hz, 2H), 6.33 (s, 2H), 4.92 (s, 1H), 4.86 (s, 1H), 4.27 (s, 2H), 3.81 (s, 3H), 3.73 (s, 6H), 3.72 (s, 2H), 2.43 (s, 3H), 2.22 (td, *J* = 7.1, 1.0 Hz, 2H), 2.10 (t, *J* = 7.3 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.3, 143.5, 142.0, 137.7, 131.6, 129.9, 127.4, 115.3, 105.8, 79.5, 61.0, 56.1, 52.1, 51.2, 38.7, 31.6, 21.7, 18.2. **HRMS** (ESI+) calculated for $[C_{24}H_{28}BrNNaO_5S]^+$ 544.0764 *m/z*; found $[M + Na]^+$ 544.0783 *m/z*.

***N*-(6-bromo-2-methylenehex-5-yn-1-yl)-*N*-(furan-3-ylmethyl)-4-methylbenzenesulfonamide (9g)**



9g

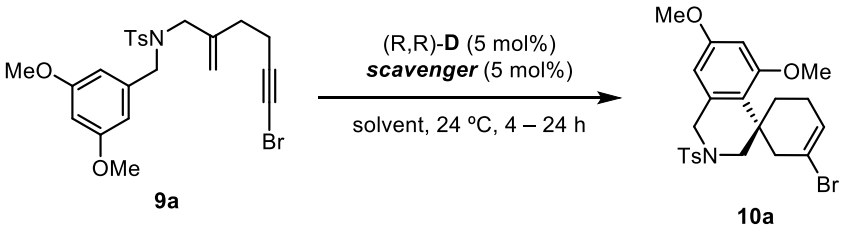
The title compound (colorless oil, 93%) was synthesized according to general procedure **E** using N-(furan-3-ylmethyl)-4-methylbenzenesulfonamide.[10]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.64 (m, 2H), 7.31 (s, 1H), 7.30 – 7.27 (m, 2H), 7.15 (s, 1H), 6.07 (s, 1H), 4.98 (s, 1H), 4.93 (s, 1H), 4.18 (s, 2H), 3.71 (s, 2H), 2.44 (s, 3H), 2.28 (t, *J* = 7.3 Hz, 2H), 2.13 (t, *J* = 7.3 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.6, 143.4, 142.0, 141.7, 137.5, 129.8, 127.4, 119.9, 115.4, 111.0, 79.5, 51.5, 41.1, 38.7, 31.5, 21.7, 18.2. **HRMS** (ESI+) calculated for $[C_{19}H_{20}BrNNaO_3S]^+$ 444.0239 *m/z*; found $[M + Na]^+$ 444.0234 *m/z*.

6. Enantioselective gold(I)-catalyzed 1-bromo-5-enyne cyclization

6.1. Reaction optimization

A chloride scavenger and solvent screening was performed with catalyst (*R,R*)-**D** and the $AgSbF_6/C_6H_5Br$ combination was chosen to continue with the optimization.



9a **10a**

Entry	Scavenger	Solvent	Conversion (%)	*er*
1	$AgSbF_6$	CH_2Cl_2	100	70:30
2	$AgBF_4$	PhMe	100	65:35
3	$AgSbF_6$	$PhCF_3$	100	76:24
4	$NaBAr^F{}_4$	$PhCF_3$	-[a]	70:30
5	$AgNTf_2$	$PhCF_3$	100	72:28
6	AgOTf	$PhCF_3$	100	63:37
7	$AgSbF_6$	C_6H_5Cl	100	82:18
8	$AgSbF_6$	xylenes	-	80:20
9	$AgSbF_6$	C_6H_6	100	81:19
10	$AgSbF_6$	*o*-xylene	-	80:20
11	$AgSbF_6$	*p*-xylene	100	78:22
12	$AgSbF_6$	1,2-dichlorobenzene	100	76:24
13	$AgSbF_6$	1,3-dichlorobenzene	100	78:22
14	**$AgSbF_6$**	**C_6H_5Br**	**100**	**82:18**
15	$AgSbF_6$	$Cl(CH_2)_2Cl$	100	64:36
16	$AgSbF_6$	$Cl_2(CH)_2Cl_2$	100	68:32
17	$AgSbF_6$	C_6H_5Cl:HFIP (10:1)	100	67:33
18	$AgSbF_6$	heptane	100	69:31

[a]Traces of product.

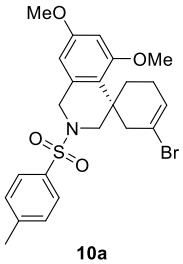
Table S4 – Solvent and chloride scavenger screening for the 1-bromo-5-enyne cascade cyclization.

6.2. General procedure F for the cyclization of 1-bromo-5-enynes

A 5 mL microwave vial was charged with $AgSbF_6$ (5 mol %) cooled to -40 °C and a solution of the corresponding enyne (1.0 equiv) and (*R,R*)-**F** (5 mol %) in chlorobenzene (0.05M) was added. The reaction was stirred for 7 days

at the same temperature and then quenched by addition of 3 drops of NEt_3. The volatiles were removed under reduced pressure, and the crude was purified by preparative TLC to give the target compound.

(*R*)-3-Bromo-5',7'-dimethoxy-2'-tosyl-2',3'-dihydro-1'*H*-spiro[cyclohexane-1,4'-isoquinolin]-3-ene (10a)

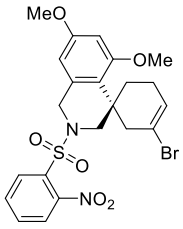


10a

The title compound (colorless gum, 21.9 mg, 61%, 71% brsm 92:8 *er*) was synthesized following the general procedure **F** using **9a**[9] (35.9 mg, 73 μmol). Purification was performed by preparative TLC (4:1 cyclohexane/EtOAc).

M.p. = 81 – 83°C (Et_2O). **HPLC** (Chiralpak IA (250 × 4.6mm, 5μm) at 25 °C, flow 1.0 mL/min, isocratic hexane/*i*PrOH 90:10, 280 nm), 13.2 min (92), 23.4 min (8). $[\alpha]_D^{26}$ = –257.5° ($CHCl_3$, c = 1.0). The spectral data were fully consistent with those previously reported.[9]

(*R*)-3-Bromo-5',7'-dimethoxy-2'-((2-nitrophenyl)sulfonyl)-2',3'-dihydro-1'*H*-spiro[cyclohexane-1,4'-isoquinolin]-3-ene (10b)

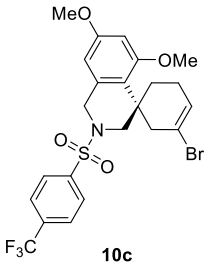


10b

The title compound (white solid, 6.80 mg, 18%, 69% brsm 90:10 *er*) was synthesized following the general procedure **F** using **9b.** Purification was performed by preparative TLC (2:1 cyclohexane/EtOAc).

M.p. = 62 – 64 °C (CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.06 – 8.01 (m, 1H), 7.76 – 7.71 (m, 2H), 7.65 – 7.61 (m, 1H), 6.35 (d, *J* = 2.5 Hz, 1H), 6.22 (d, *J* = 2.5 Hz, 1H), 6.11 – 6.07 (m, 1H), 4.47 (d, *J* = 15.2 Hz, 1H), 4.37 (d, *J* = 15.2 Hz, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.45 (d, *J* = 12.7 Hz, 1H), 3.37 (s, 2H), 3.34 (d, *J* = 7.3 Hz, 1H), 2.68 (ddd, *J* = 13.6, 11.7, 6.5 Hz, 1H), 2.34 – 2.06 (m, 4H), 1.51 (dd, *J* = 13.8, 5.9 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.7, 159.3, 134.4, 134.0, 131.9, 131.4, 131.2, 127.2, 124.3, 120.8, 120.7, 102.2, 98.9, 55.5, 55.4, 52.3, 49.4, 41.4, 39.6, 26.5, 24.2. **HRMS** (ESI+) calculated for $[C_{22}H_{24}BrN_2O_6S]^+$ 523.0533 m/z; found $[M + H]^+$ 523.0535 m/z. **HPLC** (Chiralpak IB (250 × 4.6mm, 5μm) at 25 °C, flow 1.0 mL/min, isocratic hexane/$_i$PrOH 80:20, 280 nm), 12.1 min (90), 14.1 min (10). $[\alpha]_D^{26}$ = +289.8° ($CHCl_3$, c = 0.35).

(*R*)-3-Bromo-5',7'-dimethoxy-2'-((4-(trifluoromethyl)phenyl)sulfonyl)-2',3'-dihydro-1'*H*-spiro[cyclohexane-1,4'-isoquinolin]-3-ene (10c)

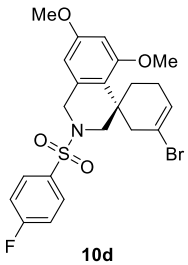


10c

The title compound (white solid, 18.6 mg, 47%, 68% brsm 92:8 *er*) was synthesized following the general procedure **F** using**9c.** Purification was performed by preparative TLC (5:1 cyclohexane/EtOAc).

M.p. = 92 – 94 °C (Et_2O). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.2 Hz, 2H), 7.84 (d, *J* = 8.9 Hz, 2H), 6.34 (d, *J* = 2.5 Hz, 1H), 6.16 (d, *J* = 2.5 Hz, 1H), 6.13 – 6.08 (m, 1H), 4.23 – 4.10 (m, 2H), 3.79 (s, 3H), 3.76 (s, 3H), 3.52 – 3.43 (m, 1H), 3.23 (d, *J* = 12.0 Hz, 1H), 3.06 (d, *J* = 12.0 Hz, 1H), 2.66 – 2.56 (m, 1H), 2.32 – 2.22 (m, 1H), 2.22 – 2.09 (m, 2H), 1.56 (dd, *J* = 13.7, 5.9 Hz, 1H). **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 159.6, 159.3, 140.2, 135.3 – 134.3 (m), 134.0, 128.4, 127.1, 126.6 (q, *J* = 3.7 Hz), 123.4 (q, *J* = 272.7 Hz), 121.0, 120.7, 102.3, 98.8, 55.44, 55.37, 52.2, 49.7, 41.4, 39.7, 26.5, 24.1. **^{19}F NMR** (376 MHz, $CDCl_3$) δ –62.5. **HRMS** (ESI+) calculated for $[C_{23}H_{23}BrF_3NNaO_4S]^+$ 568.0375 m/z; found $[M + Na]^+$ 568.0373 m/z. **HPLC** (Chiralpak IA (250 × 4.6mm, 5μm) at 25 °C, flow 1.0 mL/min, isocratic hexane/*i*PrOH 90:10, 280 nm), 10.1 min (92), 16.9 min (8). $[\alpha]_D^{26}$ = –182.1° ($CHCl_3$, c =1.0)

(*R*)-3-Bromo-2'-((4-fluorophenyl)sulfonyl)-5',7'-dimethoxy-2',3'-dihydro-1'*H*-spiro[cyclohexane-1,4'-isoquinolin]-3-ene (10d)



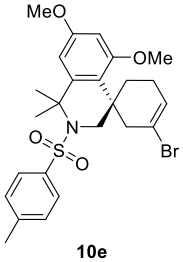
10d

The title compound (white solid, 18.7 mg, 38.0 μmol, 51%, 80% brsm 92:8 *er*) was synthesized following the general procedure **F** using **9d** (36.2 mg, 73 μmol). Purification was performed by preparative TLC (5:1 cyclohexane/Et_2O). **M.p.** = 75 – 77 °C (CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.82 (m, 2H), 7.30 – 7.20 (m, 2H), 6.34 (d, *J* = 2.5 Hz, 1H), 6.16 (d, *J* = 2.4 Hz, 1H), 6.12 – 6.05 (m, 1H), 4.21 – 4.04 (m, 2H), 3.79 (s, 3H), 3.75 (s, 3H), 3.53 – 3.41 (m, 1H), 3.21 (d, *J* = 11.9 Hz, 1H), 2.99 (d, *J* = 12.0 Hz, 1H), 2.64 – 2.52 (m, 1H), 2.32 – 2.04 (m, 3H), 1.56 (dd, *J* = 13.5, 5.8 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.47 (d, *J* = 255.3 Hz), 159.4 (d, *J* = 38.0 Hz), 134.3, 132.5 (d, *J* = 3.4 Hz), 130.6 (d, *J* = 9.2 Hz), 127.1, 121.1, 120.8, 116.8, 116.6, 102.4, 98.7, 55.4, 55.4, 52.3, 49.8, 41.5, 39.8, 26.5, 24.1. **^{19}F NMR** (376 MHz, $CDCl_3$) δ –104.8. **HRMS** (ESI+) calculated for $[C_{22}H_{24}BrFNO_4S]^+$ 496.0588 *m/z*; found $[M + H]^+$ 496.0589 *m/z.* **HPLC** (Chiralpak IA

(250 × 4.6mm, 5μm) at 25 °C, flow 1.0 mL/min, isocratic hexane/iPrOH 90:10, 220 nm), 11.3 min (92), 20.4 min (8). **[*α*]$_D^{26}$**= –227.5° ($CHCl_3$, c = 1.0).

(*R*)-3-Bromo-5',7'-dimethoxy-1',1'-dimethyl-2'-tosyl-2',3'-dihydro-1'*H*-spiro[cyclohexane-1,4'-isoquinolin]-3-ene (10e)

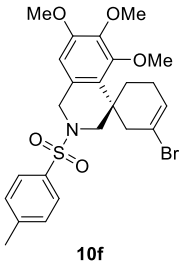


10e

The title compound (colorless gum, 20.4 mg, 54%, 93:7 *er*) was synthesized following the general procedure **F** using **9e** (38.0 mg, 73 μmol). Purification was performed by preparative TLC (1:1 toluene/CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.78 (d, *J* = 6.3 Hz, 2H), 7.29 (d, *J* = 8.3 Hz, 2H), 6.32 (dd, *J* = 12.2, 2.5 Hz, 2H), 5.97 – 5.91 (m, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.49 (brs, 1H), 3.28 (brs, 1H), 3.16 (d, *J* = 16.6 Hz, 1H), 2.67 (brs, 1H), 2.42 (s, 3H), 2.15 – 2.03 (m, 1H), 1.99 (brs, 2H), 1.86 (s, 3H), 1.81 (s, 3H), 1.37 – 1.27 (m, 1H). **^{13}C NMR** (101 MHz, CD_2Cl_2) *δ* 158.9, 158.8, 147.2, 143.6, 138.7, 129.8, 127.8, 126.8, 121.3, 121.2, 103.1, 97.3, 63.2, 55.4, 55.3, 49.1, 40.6, 39.5, 29.8, 26.5, 24.1, 21.7. **HRMS** (ESI+) calculated for $[C_{25}H_{30}BrNNaO_4S]^+$ 542.0971 *m/z*; found $[M + Na]^+$ 542.0978 *m/z*. **SFC (**Chiralpak ID (100 × 3.0 mm, 3 μm) at 35 °C, flow 1.2 mL/min, isocratic CO_2/IPA 75:25, ABRP pressure 150 bar, 210 nm), 2.00 min (93), 2.47 min (7). **[*α*]$_D^{26}$** = 14.37° ($CHCl_3$, c =1.0).

(*R*)-3-Bromo-5',6',7'-trimethoxy-2'-tosyl-2',3'-dihydro-1'*H*-spiro[cyclohexane-1,4'-isoquinolin]-3-ene (10f)

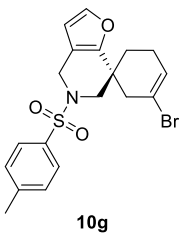


10f

The title compound (colorless gum, 24.0 mg, 63%, 86% brsm, 81:19 *er*) was synthesized following the general procedure **F** using **9f** (38.0 mg, 73 μmol). Purification was performed by preparative TLC (4:1 cyclohexane/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.73 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 6.30 (s, 1H), 6.14 – 6.05 (m, 1H), 4.14 (d, *J* = 14.3 Hz, 1H), 4.03 (d, *J* = 14.3 Hz, 1H), 3.92 (s, 3H), 3.80 (s, 3H), 3.79 (s, 3H), 3.38 (d, *J* = 18.6 Hz, 1H), 3.21 (d, *J* = 12.0 Hz, 1H), 2.91 (d, *J* = 12.0 Hz, 1H), 2.44 (s, 3H), 2.42 – 2.35 (m, 1H), 2.35 – 2.20 (m, 2H), 2.20 – 2.09 (m, 1H), 1.68 (dd, *J* = 13.0, 5.1 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ* 153.5, 152.5, 143.0, 141.6, 133.1, 130.0,128.00, 127.98, 127.2, 126.0, 120.7, 104.8, 61.0, 60.7, 56.0, 51.9, 49.6, 42.4, 40.1, 27.6, 24.2, 21.7. **HRMS** (ESI+) calculated for $[C_{24}H_{28}BrNNaO_5S]^+$ 544.0764 *m/z*; found $[M + Na]^+$ 544.0752 *m/z*. **SFC (**Chiralpak OJ (100 × 3.0 mm, 3 μm) at 35 °C, flow 1.2 mL/min, isocratic CO_2/MeOH 75:25, ABRP pressure 150 bar, 210 nm, 1.84 min (19), 2.57 min (81). **[*α*]$_D^{26}$** = –16.64° ($CHCl_3$, c = 1.0).

(*S*)-3-Bromo-5'-tosyl-5',6'-dihydro-4'*H*-spiro[cyclohexane-1,7'-furo[3,2-*c*]pyridin]-3-ene (10g)



10g

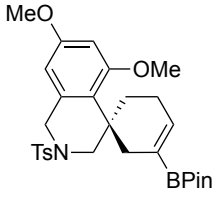
The title compound (colorless gum, 5.6 mg, 18 %, 26% brsm, 89:11 *er*) was synthesized following the general procedure **F** using **9g** (38.0 mg, 73 μmol). Purification was performed by preparative TLC (10:1 cyclohexane/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.76 – 7.69 (m, 2H), 7.37 – 7.30 (m, 2H), 7.26 (d, *J* = 1.9 Hz, 1H), 6.17 (d, *J* = 1.9 Hz, 1H), 6.13 (m, 1H), 4.15 (d, *J* = 13.9 Hz, 1H), 3.92 (d, *J* = 13.9 Hz, 1H), 3.35 (d, *J* = 11.8 Hz, 1H), 2.98 (d, *J* = 11.6 Hz, 1H), 2.86 (dq, *J* = 17.7, 2.7 Hz, 1H), 2.44 (s, 3H), 2.40 – 2.31 (m, 1H), 2.29 – 2.20 (m, 2H), 2.00 (ddd, *J* = 13.5, 9.7, 6.3 Hz, 1H), 1.75 (dt, *J* = 16.5, 4.0 Hz, 1H). **^{13}C NMR** (101 MHz, CD_2Cl_2) *δ* 153.2, 143.9, 142.2, 134.1, 130.0, 128.1, 127.7, 119.1, 113.1, 108.1, 51.9, 43.8, 41.5, 38.4, 29.9, 28.1, 24.3, 21.7. **HRMS** (ESI+) calculated for $[C_{19}H_{20}BrNNaO_3S]^+$ 444.0239 m/z; found $[M + Na]^+$ 444.0240 m/z. **SFC (**Chiralpak IG (100 × 3.0 mm, 3 μm) at 35 °C, flow 1.2 mL/min, isocratic CO_2/EtOH 75:25, ABRP pressure 150 bar, 210 nm), 2.171 min (89), 2.524 min (11). **[*α*]$_D^{26}$ =** –1.2° ($CHCl_3$, c = 0.4).

7. Product derivatization starting from 10a

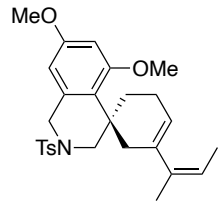
(*R*)-5',7'-Dimethoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2'-tosyl-2',3'-dihydro-1'*H*-spiro[cyclohexane-1,4'-isoquinolin]-3-ene (11)

To a solution of dry 1,4-dioxane (0.68 mL), in an oven-dried vial, were added **10a** (67 mg, 0.14 mmol), B_2Pin_2 (69 mg, 0.27 mmol, 2 equiv), and KOAc (40 mg, 0.41 mmol, 3 equiv). The solution was purged with Ar, and $Pd(dppf)Cl_2$ (10.0 mg, 0.01 mmol, 10 mol%) was added. The reaction mixture was stirred for 24 h at 90 °C. After the reaction was completed, the solvent was evaporated. Then, the reaction mixture was filtered through a pad of Celite and washed twice with Et_2O. The residue was purified by flash column chromatography using 15:1 cyclohexane:EtOAc to obtain **11** as a colourless foam (59.0 mg, 80%).



^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.69 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 8.1 Hz, 2H), 6.57 (d, *J* = 4.4 Hz, 1H), 6.32 (d, *J* = 2.5 Hz, 1H), 6.16 (d, *J* = 2.5 Hz, 1H), 4.04 (q, *J* = 14.5 Hz, 2H), 3.75 (s, 3H), 3.73 (s, 3H), 3.10 – 2.85 (m, 3H), 2.63 (ddd, *J* = 13.3, 11.2, 7.1 Hz, 1H), 2.43 (s, 3H), 2.32 – 2.10 (m, 2H), 2.00 (dd, *J* = 17.8, 2.1 Hz, 1H), 1.45 (dd, *J* = 13.4, 6.0 Hz, 1H), 1.25 (d, *J* = 2.8 Hz, 12H). **^{13}C NMR** (101 MHz, CD_2Cl_2) δ 160.2, 159.1, 144.2, 141.1, 134.7, 133.5, 130.1, 128.2, 123.3, 102.6, 98.6, 83.5, 55.6, 55.5, 52.6, 50.4, 37.2, 33.1, 27.4, 25.1, 24.9, 23.9, 21.7. **HRMS** (ESI+): *m/z*: calculated for $C_{29}H_{38}BNO_6S$: 539.2513 $[M+Na]^+$; found: 562.2404.

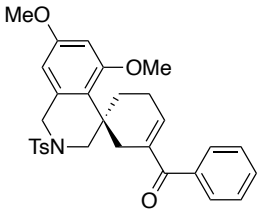
(*R*,*Z*)-3-(But-2-en-2-yl)-5',7'-dimethoxy-2'-tosyl-2',3'-dihydro-*1'H*-spiro[cyclohexane-1,4'-isoquinolin]-3-ene (12)



To a solution of **11** (53.9 mg, 0.10 mmol, 1 equiv) in 1,4-dioxane (1.0 mL), $Pd(PPh_3)_4$ (11.6 mg, 0.001 mmol, 10 mol%) was added. The vial was evacuated and backfilled with Ar three times. Then, (*Z*)-2-bromobut-2-ene (15.2 mL, 1.50 equiv) and NaOH (0.1 mL, 2M) were added in this order, and the resulting mixture was left stirring for 20 h at 100 °C. After the reaction was completed, it was filtered through pad of Celite (using as eluent EtOAc) and all volatiles were removed by rotatory evaporation. The residue was purified by flash column chromatography using 8:1 cyclohexane:Et_2O to obtain **12** as a white foam (36.0 mg, 77%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 7.8 Hz, 2H), 6.33 (d, *J* = 2.5 Hz, 1H), 6.15 (d, *J* = 2.5 Hz, 1H), 5.50 – 5.43 (m, 1H), 5.24 (qq, *J* = 6.7, 1.4 Hz, 1H), 4.19 – 4.11 (m, 1H), 4.00 (d, *J* = 14.4 Hz, 2H), 3.76 (s, 3H), 3.74 (s, 3H), 3.22 – 3.14 (m, 1H), 3.05 – 2.94 (m, 2H), 2.66 (ddd, *J* = 13.3, 11.6, 6.8 Hz, 1H), 2.43 (s, 3H), 2.30 – 2.10 (m, 2H), 1.88 (d, *J* = 18.3 Hz, 1H), 1.77 (t, *J* = 1.5 Hz, 3H), 1.66 (dd, *J* = 6.7, 1.5 Hz, 3H), 1.45 (dd, *J* = 13.6, 6.2 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.8, 158.8, 143.7, 139.5, 137.1, 134.4, 133.0, 129.8, 128.0, 122.9, 121.6, 119.6, 102.3, 98.7, 55.4, 55.2, 52.8, 50.2, 37.4, 34.0, 27.6, 23.4, 22.1, 21.7, 14.7. **HRMS** (ESI+): *m/z*: calculated for $C_{27}H_{33}NO_4S$: 467.2130 $[M+H]^+$; found: 468.2198.

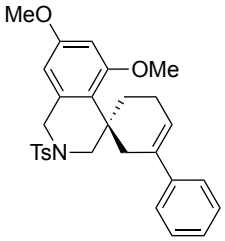
(*R*)-(5',7'-Dimethoxy-2'-tosyl-2',3'-dihydro-1'*H*-spiro[cyclohexane-1,4'-isoquinolin]-3-en-3-yl)(phenyl)methanonemalonate (14)



Under Ar, in an oven-dried microwave vial, **10a** (63 mg, 0.13 mmol) was dissolved in dry THF (0.80 mL). The solution was cooled down to -78 °C and, at the same temperature, *tert*-butyllithium (0.17 mL, 1.67 M, 2.1 equiv) was slowly added. The reaction mixture was left stirring for 2 h before adding a solution of *N*-methoxy-*N*-methylbenzamide (23 mg, 0.14 mmol, 1.1 equiv) in THF (0.50 mL). After its slowly addition, the reaction was left stirring over night at 24 °C, gradually worming it up. After the reaction was completed, it was quenched with a saturated solution of NH_4Cl. The organic layer was diluted with Et_2O, washed with saturated NaCl aqueous solution, dried over Na_2SO_4 and concentrated by rotatory evaporation. The residue was purified by flash column chromatography using 7:1 cyclohexane:EtOAc to obtain **14** as a white solid (40.5 mg, 61%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.66 (m, 4H), 7.54 – 7.47 (m, 3H), 7.35 (d, *J* = 8.0 Hz, 2H), 6.69 – 6.63 (m, 1H), 6.36 (d, *J* = 2.5 Hz, 1H), 6.19 (d, *J* = 2.5 Hz, 1H), 4.30 (d, *J* = 14.5 Hz, 1H), 4.02 (d, *J* = 14.5 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H) 3.49 – 3.33 (m, 2H), 2.82 (d, *J* = 12.0 Hz, 1H), 2.57 (t, *J* = 9.0 Hz, 2H), 2.35 (dd, *J* = 20.4, 15.9 Hz, 5H), 1.82 – 1.74 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 198.2, 159.7, 159.0, 144.0, 142.3, 138.8, 137.5, 134.5, 133.1, 131.5, 130.0, 129.4, 128.2, 128.0, 122.1, 102.4, 98.5, 55.4, 55.3, 52.1, 50.0, 37.2, 30.7, 26.7, 23.2, 21.6. **HRMS** (ESI+): *m/z*: calculated for $C_{30}H_{31}NO_5S$: 517.1923 $[M+Na]^+$; found: 541.1832.

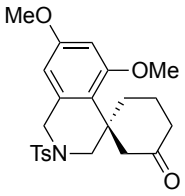
(*R*)-5',7'-Dimethoxy-3-phenyl-2'-tosyl-2',3'-dihydro-1'*H*-spiro[cyclohexane-1,4'-isoquinolin]-3-ene (15)



Under Ar, in an oven-dried microwave vial, phenylboronic acid (22 mg, 0.18 mmol, 1.8 equiv), $Pd(PPh_3)_2Cl_2$ (3.56 mg, 0.005 mmol, 5 mol%) and K_2CO_3 (42 mg, 0.31 mmol, 3 equiv) were added to a solution of **10a** (50.0 mg, 0.102 mmol) in 1,4-dioxane (1.67 mL) and water (0.28 mL). The solution was purged with Ar for 10 min before stirring it for 12 h at 85 °C. After the reaction was completed, it was quenched with the addition of water. Then, the aqueous phase was extracted with Et_2O (x3) and the combined organic layers were washed with saturated NaCl aqueous solution and dried with Na_2SO_4. The residue was purified by flash column chromatography using 20:1 cyclohexane/EtOAc to obtain **15** as a white foam (47 mg, 95%).

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.73 – 7.58 (m, 2H), 7.45 – 7.38 (m, 2H), 7.35 – 7.27 (m, 4H), 7.26 – 7.18 (m, 1H), 6.37 (d, *J* = 2.5 Hz, 1H), 6.21 (d, *J* = 2.5 Hz, 1H), 6.14 (dd, *J* = 4.7, 2.5 Hz, 1H), 4.22 (d, *J* = 14.5 Hz, 1H), 3.99 (d, *J* = 14.5 Hz, 1H), 3.77 (s, 3H), 3.75 (s, 3H) 3.35 – 3.23 (m, 2H), 2.90 (d, *J* = 11.8 Hz, 1H), 2.77 (ddd, *J* = 13.4, 10.6, 7.8 Hz, 1H), 2.42 – 2.26 (m, 4H), 1.70 – 1.40 (m, 3H) . **^{13}C NMR** (101 MHz, CD_2Cl_2) δ 160.2, 159.3, 144.3, 143.0, 136.1, 135.0, 133.5, 130.1, 128.6, 128.1, 127.1, 125.8, 123.3, 122.8, 102.7, 98.8, 55.6, 55.6, 52.9, 50.4, 38.0, 34.4, 27.7, 23.0, 21.7. **HRMS** (ESI+): *m/z*: calculated for $C_{29}H_{31}NO_4S$: 489.1974 $[M+Na]^+$; found: 512.1878.

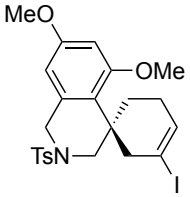
(*R*)-5',7'-Dimethoxy-2'-tosyl-2',3'-dihydro-1'*H*-spiro[cyclohexane-1,4'-isoquinolin]-3-one (13)



To a solution of **11** (30 mg, 0.06 mmol, 1 equiv) in THF (0.38 mL) were sequentially added $NaBO_3{\cdot}H_2O$ (18 mg, 0.17 mmol, 3 equiv) and water (0.38 mL). The reaction was left stirring for 2 h. After the reaction was completed, it was quenched by the addition of $N_2S_2O_3$. Then, the aqueous phase was extracted with Et_2O (x3) and the combined organic layers were washed with saturated NaCl aqueous solution and dried with Na_2SO_4. The residue was purified by flash column chromatography using 5:1 cyclohexane/EtOAc to obtain **13** as a white solid (22.0 mg, 92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.68 (m, 2H), 7.38 – 7.32 (m, 2H), 6.31 (d, *J* = 2.5 Hz, 1H), 6.14 (d, *J* = 2.4 Hz, 1H), 4.51 (dd, *J* = 14.8, 1.7 Hz, 1H), 3.74 (s, 3H), 3.71 (s, 3H), 3.74 – 3.63 (m, 2H), 3.21 (d, *J* = 15.5 Hz, 1H), 2.43 (s, 3H), 2.39 (dd, *J* = 7.5, 5.9 Hz, 2H), 2.31 (dd, *J* = 11.9, 1.2 Hz, 1H), 2.20 (ddd, *J* = 14.5, 8.9, 5.6 Hz, 1H), 2.09 – 1.99 (m, 1H), 1.98 – 1.87 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 210.9, 159.2, 158.8, 144.0, 133.7, 132.9, 130.0, 127.9, 121.6, 102.3, 98.3, 55.4, 54.5, 53.9, 49.2, 48.7, 40.8, 40.4, 31.9, 21.7, 20.9. The physical data of title compound matches to those previously reported.

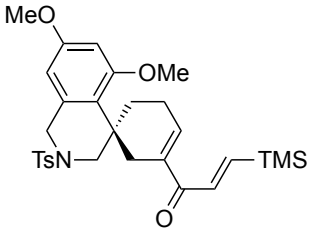
(*R*)-3-Iodo-5',7'-dimethoxy-2'-tosyl-2',3'-dihydro-1'*H* spiro[cyclohexane-1,4'-isoquinolin]-3-ene (10h)



A microwave vial was charged with **10a** (250.0 mg, 507.7 µmol) in butan-1-ol (2.50 mL), NaI (152.2 mg, 2.00 equiv, 1.02 mmol) and CuI (48.3 mg, 0.50 equiv, 253.4 µmol). The solution was degassed for 15 min. Then, DMEDA (9.0 mg, 4.36 µL, 0.20 equiv, 40.61 µmol) was added, the solution is stirred for 15 min at 24 °C then placed in a preheated hotplate at 120 °C and stirred for 24 h The reaction was cooled to 24 °C and filtered through a Pasteur pipette loaded with celite. The crude reaction was analysed by GC-MS showing complete bromide to Iodide exchange and was purified by column chromatography (cyclohexane to 1:4 EtOAc/cyclohexane), affording **10h** as an off-white solid (99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.70 (m, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 6.39 (d, *J* = 5.0 Hz, 1H), 6.32 (d, *J* = 2.5 Hz, 1H), 6.14 (d, *J* = 2.5 Hz, 1H), 4.14 (d, *J* = 14.5 Hz, 1H), 4.06 (d, *J* = 14.6 Hz, 1H), 3.79 (s, 3H), 3.74 (s, 3H), 3.56 – 3.45 (m, 1H), 3.22 (d, *J* = 11.9 Hz, 1H), 2.99 (d, *J* = 12.0 Hz, 1H), 2.60 (ddd, *J* = 13.4, 11.6, 6.3 Hz, 1H), 2.44 (s, 3H), 2.39 – 2.24 (m, 2H), 2.24 – 2.04 (m, 1H), 1.66 – 1.55 (m, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 159.6, 159.1, 143.9, 135.7, 134.5, 133.2, 130.0, 128.0, 121.3, 102.4, 98.6, 95.3, 55.4, 55.4, 52.3, 49.9, 45.7, 40.5, 26.2, 25.7, 21.7. **HRMS** (ESI+): *m/z*: calculated for $C_{23}H_{26}INNaO_4S$: 562.0519 $[M+Na]^+$; found: 562.0507.

(*E,R*)-)-1-(5',7'-Dimethoxy-2'-tosyl-2',3'-dihydro-1'*H*-spiro[cyclohexane-1,4'-isoquinolin]-3-en-3-yl)-3-(trimethylsilyl)prop-2-en-1-one 16

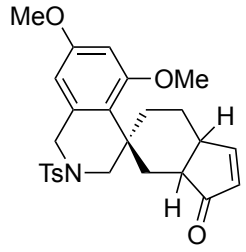


A tube was charged with (*E*)-trimethyl(2-(tributylstannyl)vinyl)silane (59.5 mg, 1.50 equiv, 153 µmol), $Pd(OAc)_2$ (2.29 mg, 0.10 equiv, 10.2 µmol), CuI (5.83 mg, 0.30 equiv, 30.6 µmol), triphenylphosphine (8.02 mg, 0.30 equiv, 30.6 µmol), and **11h** (55.0 mg, 102 µmol). The tube was flushed with Ar, and degassed THF (1.50 mL) was added. The reactor was sealed, and the system was flushed with CO 3 times, after which the reactor was pressurised to 5 bars. The reactor was placed in a preheated hot plate and stirred at 50 °C for 16 hours. The reactor was then removed from the hot plate, and the system was purged with Ar. The reaction was filtered through a plug of Celite and the reaction mixture was purified by flash column chromatography (cyclohexane to 1:4 EtOAc/cyclohexane), affording **16** (53.0 mg, 96 %).

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.74 – 7.63 (m, 2H), 7.38 – 7.32 (m, 2H), 7.20 – 7.12 (m, 1H), 7.12 – 7.05 (m, 1H), 7.08 – 7.03 (m, 1H), 6.34 (d, *J* = 2.6 Hz, 1H), 6.19 (d, *J* = 2.5 Hz, 1H), 4.17 (d, *J* = 14.5 Hz, 1H), 3.97 (d, *J* = 14.5 Hz, 1H), 3.74 (s, 3H), 3.73 (s, 2H), 3.22 – 3.15 (m, 2H), 2.67 (d, *J* = 12.0 Hz, 1H), 2.58 – 2.47 (m, 1H), 2.42 (s, 3H), 2.50 – 2.34 (m, 1H), 2.29 – 2.13 (m, 2H), 1.68 – 1.56 (m, 1H), 1.49 – 1.24 (m, 1H), 0.18 (s, 9H). **^{13}C NMR (126 MHz, CD_2Cl_2)** δ 190.6, 160.2, 159.5, 146.6, 144.5, 139.8, 138.7, 137.9, 135.0, 133.4, 130.3, 128.3, 122.5, 102.9, 98.8,

55.8, 55.7, 52.7, 50.4, 37.4, 30.5, 27.1, 23.6, 21.8, -1.5. **HRMS** (ESI+): *m/z*: calculated for $C_{29}H_{37}NNaO_5SSi$: 562.2054 $[M+Na]^+$; found: 562.2037.

(*R*)-5',7'-Dimethoxy-2'-tosyl-2',3a,3',6,7,7a-hexahydro-1'*H*-spiro[indene-5,4'-isoquinolin]-3(4*H*)-one (17).

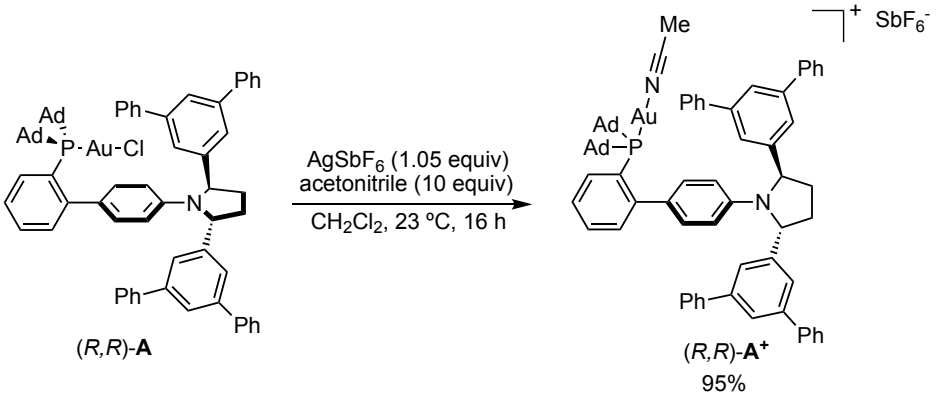


A 1 mL microwave vial was charged with (*E*)-1-(5',7'-dimethoxy-2'-tosyl-2',3'-dihydro-1'H-spiro[cyclohexane-1,4'-isoquinolin]-3-en-3-yl)-3-(trimethylsilyl)prop-2-en-1-one **16** (55.0 mg, 102 µmol) and CH_2Cl_2 (1.25 mL), which was previously passed through basic alumina). The solution was cooled to 0 °C and $FeCl_3$ (19.8 mg, 1.20 equiv, 122 µmol) was added in one portion. The solution was stirred at 0°C followed by TLC. After complete consumption of the starting material, the solution was filtered through Celite, the solvent was removed under vacuum, and the residue was purified by column chromatography (cyclohexane to 1:4 EtOAc/cyclohexane) affording **17** (37.8 mg, 79% yield) as a mixture of inseparable diastereoisomers in an 85:15 ratio.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.76 – 7.71 (m, 1.70H, Major), 7.68 (dd, *J* = 5.7, 2.6 Hz, 1H, Major + minor), 7.66 – 7.63 (m, 0.30H, minor), 7.43 – 7.35 (m, 2H, Major + minor), 6.35 (d, *J* = 2.5 Hz, 0.15H, minor), 6.31 (d, *J* = 2.5 Hz, 0.85H, Major), 6.16 (d, *J* = 1.8 Hz, 1H, Major + minor), 6.15 (d, *J* = 2.2 Hz, 1H, Major+ minor), 4.36 – 4.28 (m, 1H, Major + minor), 3.90 – 3.81 (m, 1H, Major + minor), 3.78 (s, 0.45H, minor), 3.74 (s, 0.45H, minor), 3.72 (s, 2.55H, Major), 3.71 (s, 2.55H, Major), 3.50 (dd, *J* = 11.9, 1.7 Hz, 0.85H, Major), 3.35 (dd, *J* = 11.9, 1.9 Hz, 0.15H, minor), 3.15 – 3.07 (m, 0.15H, minor), 2.91 (dddd, *J* = 14.8, 7.1, 4.8, 2.2 Hz, 0.85H, Major), 2.84 – 2.78 (m, 0.15H, minor), 2.59 – 2.51 (m, 1.85H, Major), 2.44 (s, 3H), 2.38 (dd, *J* = 14.8, 8.4 Hz, 0.15H, m), 2.27 – 2.21 (m, 0.15H, minor), 2.09 (ddd, *J* = 14.1, 4.5, 2.9 Hz, 1H, Major + minor), 1.98 – 1.81 (m, 3H, Major + minor), 1.63 (td, *J* = 13.1, 4.5 Hz, 1H, Major + minor), 1.31 – 1.20 (m, 1H, Major + minor). **^{13}C NMR (126 MHz, CD_2Cl_2)** δ 213.3 (minor), 212.9 (Major), 168.4 (minor), 167.9 (M), 159.6 (Major + minor), 159.4 (Major), 159.3 (minor), 144.6 (Major + minor), 134.4 (minor), 133.9 (Major), 133.6 (Major), 133.4 (Major), 133.1 (minor), 132.3 (minor), 130.4 (Major), 130.3 (minor), 128.3 (Major + minor), 124.6 (Major), 124.3 (minor), 102.7 (minor), 102.5 (Major), 98.6 (Major + minor), 55.8 (Major + minor), 55.6 (Major), 55.5 (minor), 55.3 (minor), 55.2 (Major), 50.1 (minor), 49.7 (Major), 44.2 (minor), 42.3 (minor), 42.1 (Major), 41.7 (Major), 37.2 (minor), 37.0 (Major), 34.3 (Major), 32.7 (minor), 31.4 (minor), 29.3 (Major), 26.6 (Major), 25.2 (minor), 23.3 (minor), 21.8 (Major). **HRMS** (ESI+): *m/z*: calculated for $C_{26}H_{29}NNaO_5S$: 490.1659 $[M+Na]^+$; found: 490.1653.

8. Experimental mechanistic studies

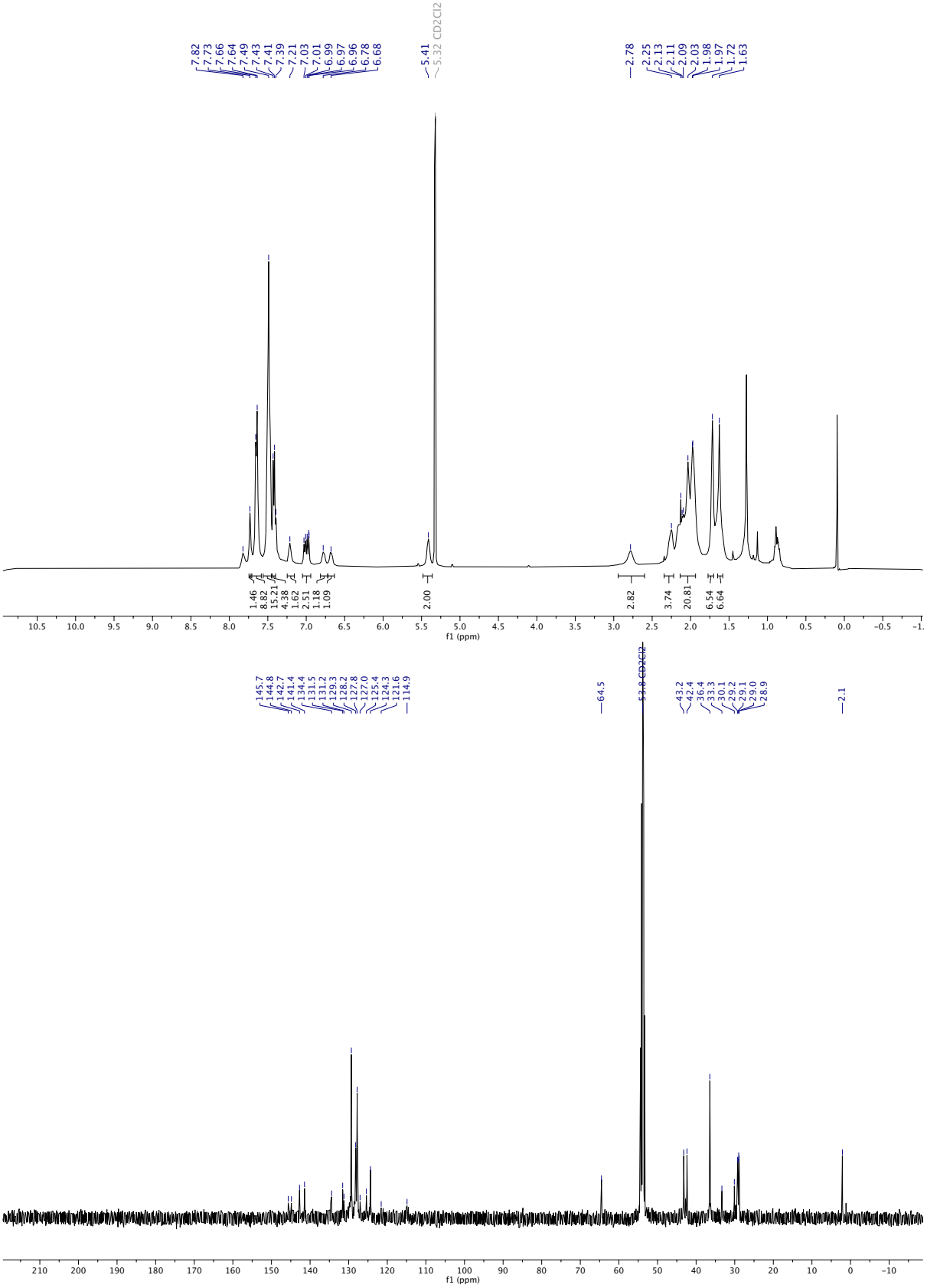
8.1. Synthesis of pre-activated catalyst (*R,R*)-A$^+$

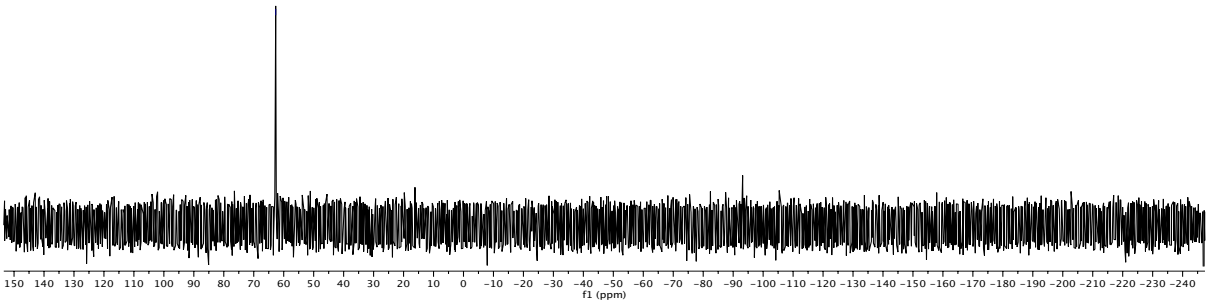


A solution of $AgSbF_6$ (5.95 mg, 0.0173 mmol, 1.05 equiv) in CH_2Cl_2 (0.25 mL) was added to a mixture of complex (*R,R*)-**A** (20.0 mg, 0.0165 mmol) in acetonitrile (8.6 µL, 0.165 mmol, 10 equiv) and CH_2Cl_2 (0.50 mL) under an atmosphere of Ar. The reaction was stirred at 24 °C for 16 h. The mixture was filtered through a path of Celite, washed with CH_2Cl_2 and concentrated to yield complex (*R,R*)-**A**$^+$ (22.7 mg, 0.0156 mmol, 95% yield) as a yellow solid. **M.p.** 243-280 °C.

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.73 (s, 1H), 7.68-7.60 (m, 8H), 7.54-7.45 (m, 15H), 7.44-7.38 (m, 4H), 7.21 (s, 1H), 7.05 – 6.94 (m, 2H), 6.78 (s, 1H), 6.68 (s, 1H), 5.41 (s, 2H), 2.78 (s, 2H), 2.25 (s, 3H), 2.18 – 1.90 (m, 20H), 1.72 (s, 6H), 1.63 (s, 6H). **^{13}C NMR** (101 MHz, CD_2Cl_2) δ 145.7, 144.8, 142.7, 141.4, 134.4, 131.5, 131.2, 129.3, 128.2, 127.8, 127.0, 125.4, 124.3, 121.6, 114.9, 64.5, 43.2, 42.4, 36.4, 33.3, 30.1, 29.2 (d, J = 9.9 Hz), 28.9 (d, J = 9.9 Hz), 2.1. **^{31}P NMR** (162 MHz, CD_2Cl_2) δ 62.7. **HRMS** (ESI+): *m/z*: calculated for $C_{72}H_{70}AuNP$: 1176.4906 $[M\text{-}MeCN\text{-}SbF_6]^+$; found: 1176.4869. **$[\alpha]_D^{26}$** = 74.5° (*c* = 0.2 in CH_2Cl_2).

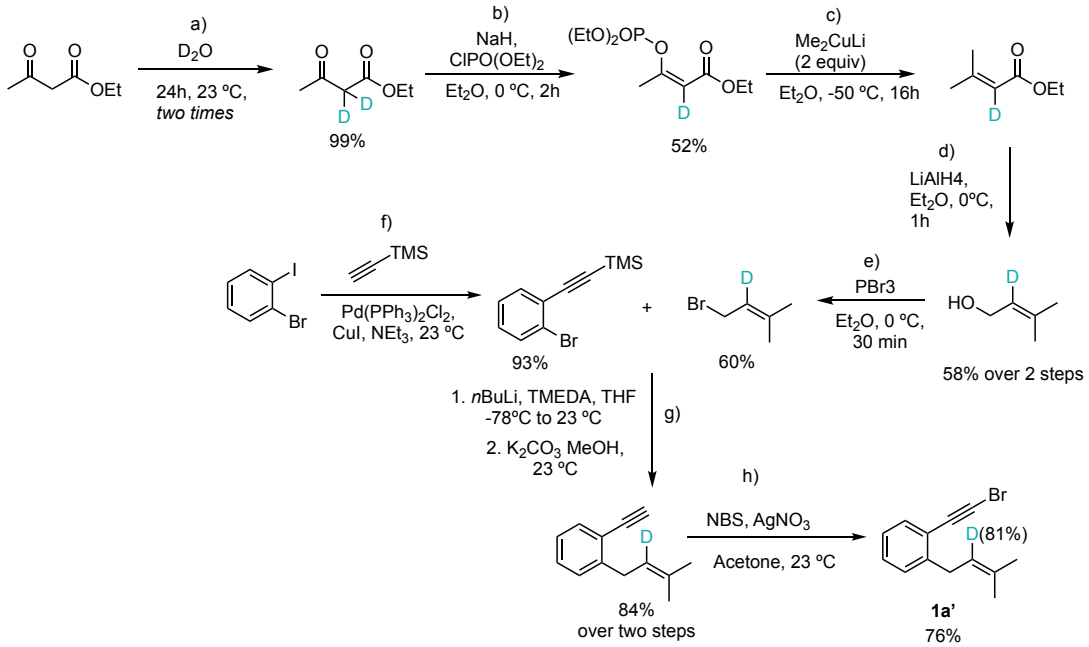
Both the **^{1}H NMR** and the **^{13}C NMR** of (*R,R*)-**A**$^{+}$ show broader signals than (*R,R*)-**A**.[4] Nevertheless, the presence of a single signal at 62.7 in the **^{31}P NMR**, downfield shifted with respect to neutral complex (*R,R*)-**A** (δ 65.3)[4] combined with the **HRMS**, correspond to a cationic species.

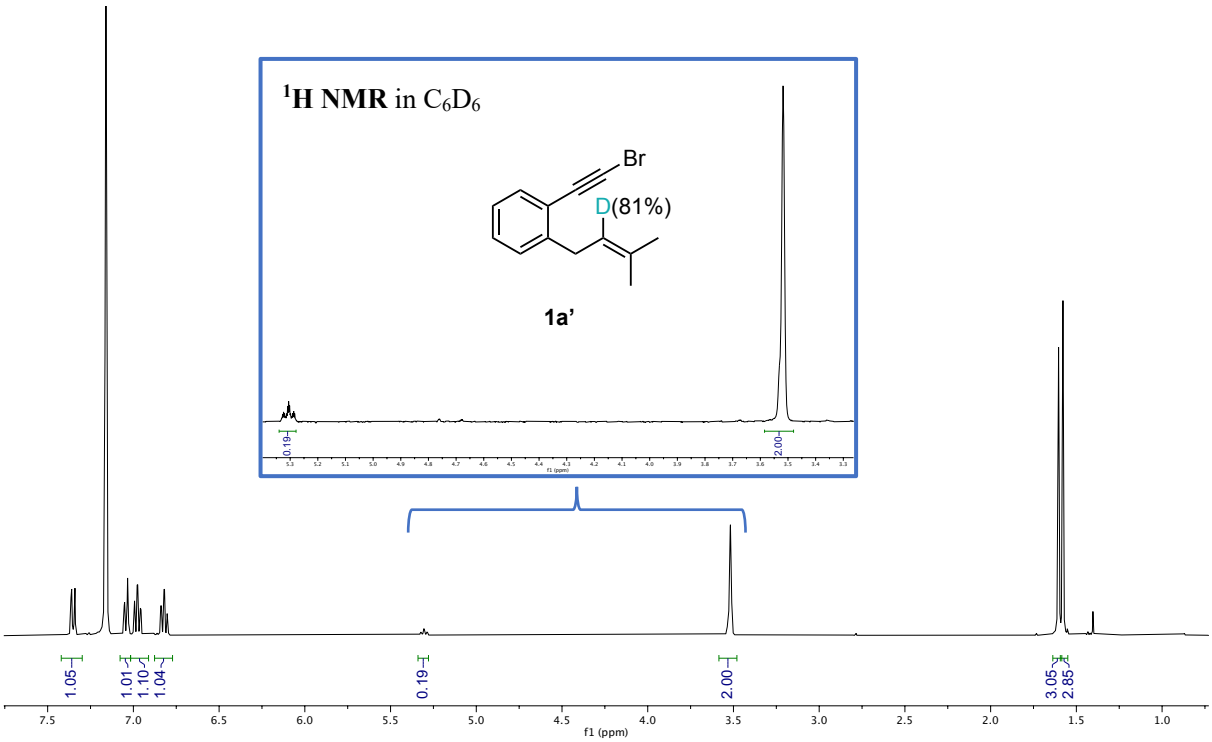


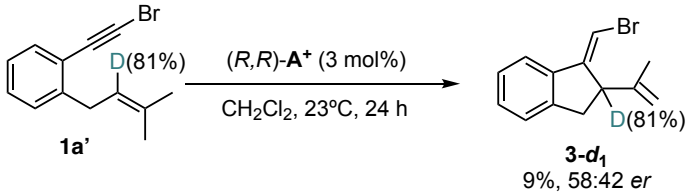


8.2. Deuterated substrate 1a' and product 5'

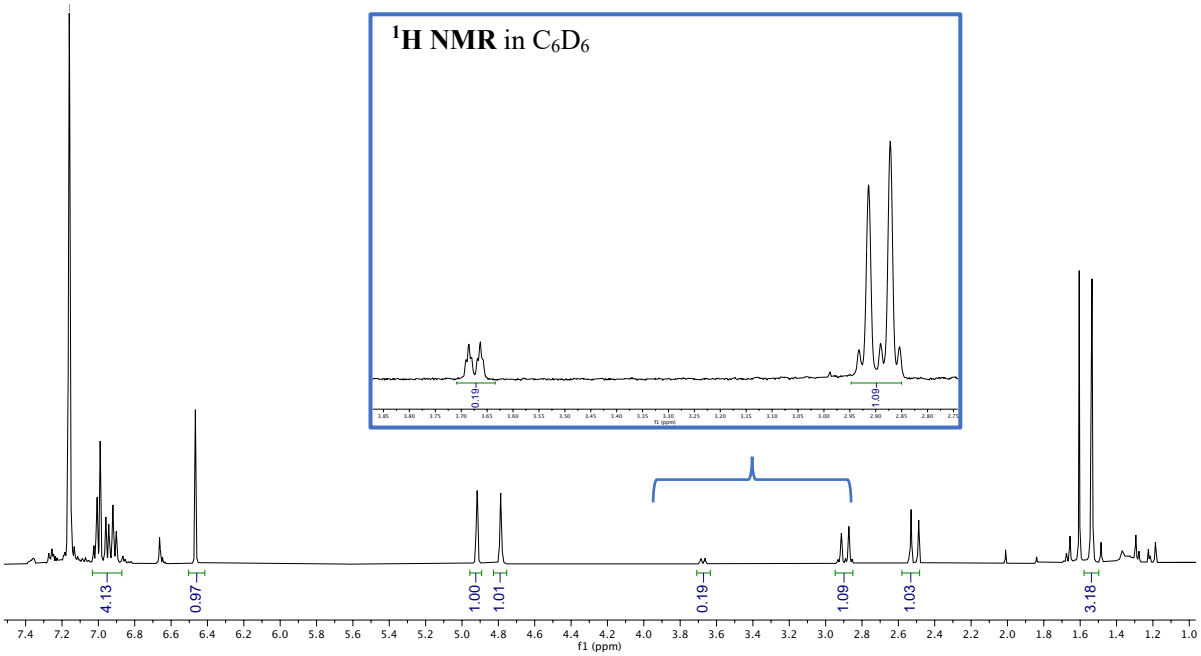
Substrate **1a'** was synthesized following the route depicted below which was adapted from different literature procedures.[11,12,13,14]



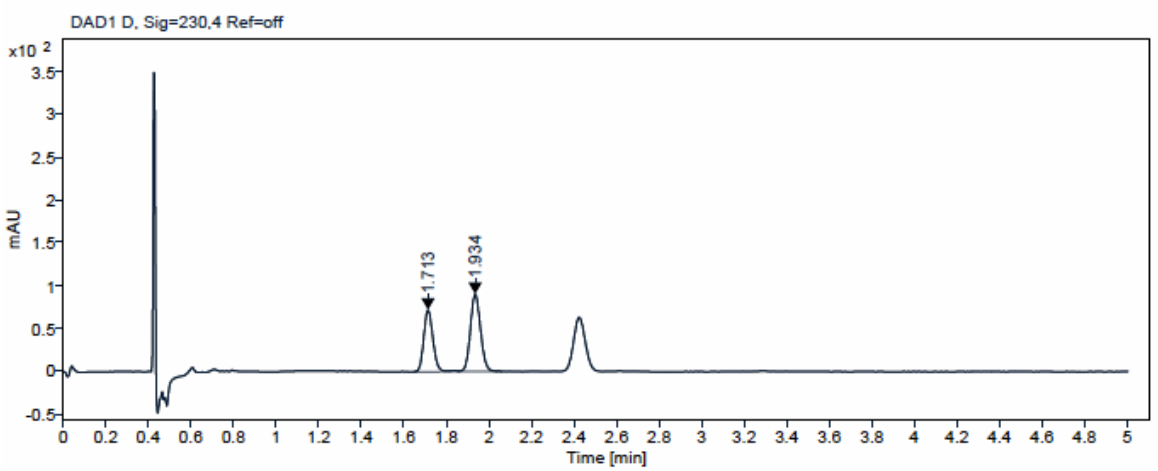




3-d_1
9%, 58:42 *er*



SFC **5'**

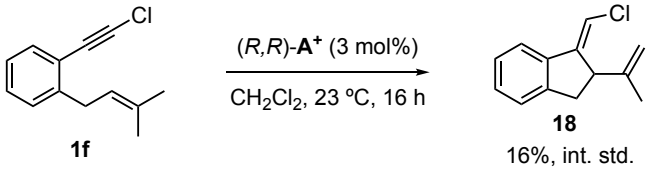


Signal: DAD1 D, Sig=230,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
1.713	BV R	0.0468	217.5327	71.9281	41.9586	
1.934	VV R	0.0520	300.9135	90.1225	58.0414	
		Sum	518.4462			

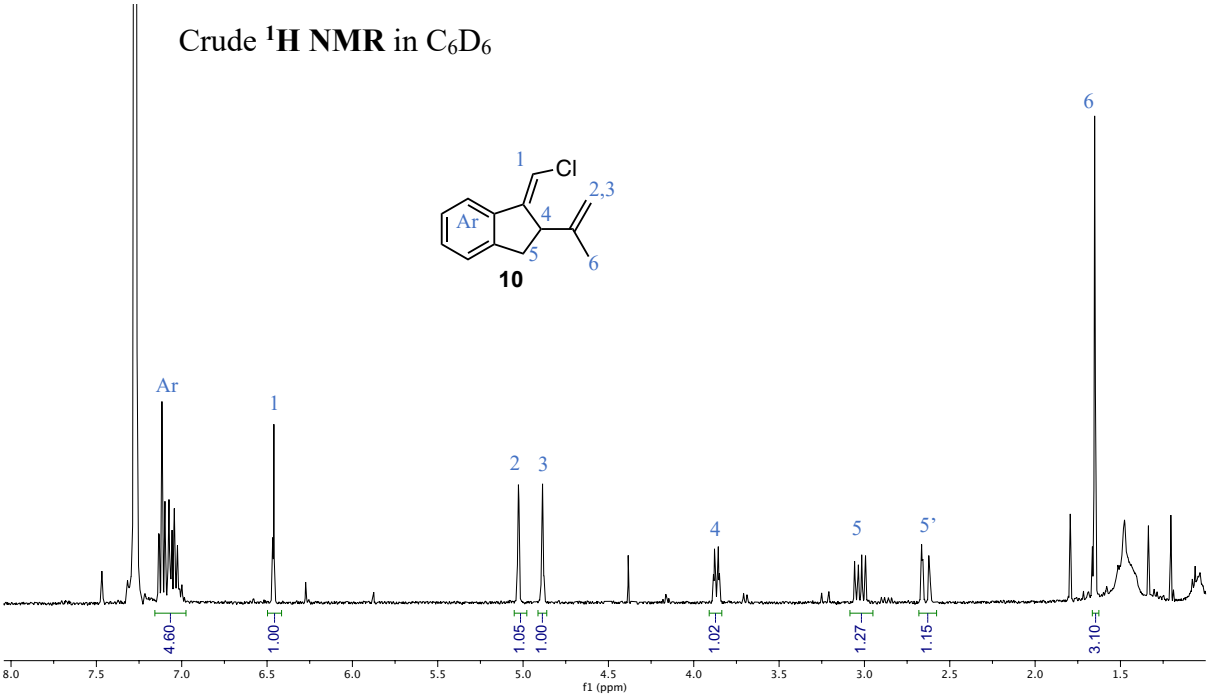
8.3. Other cyclization of enynes

Formal cycloisomerization product **18** was not purified since it underwent decomposition in silica gel.



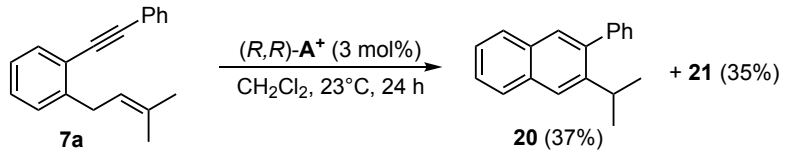
1f **18**

16%, int. std.

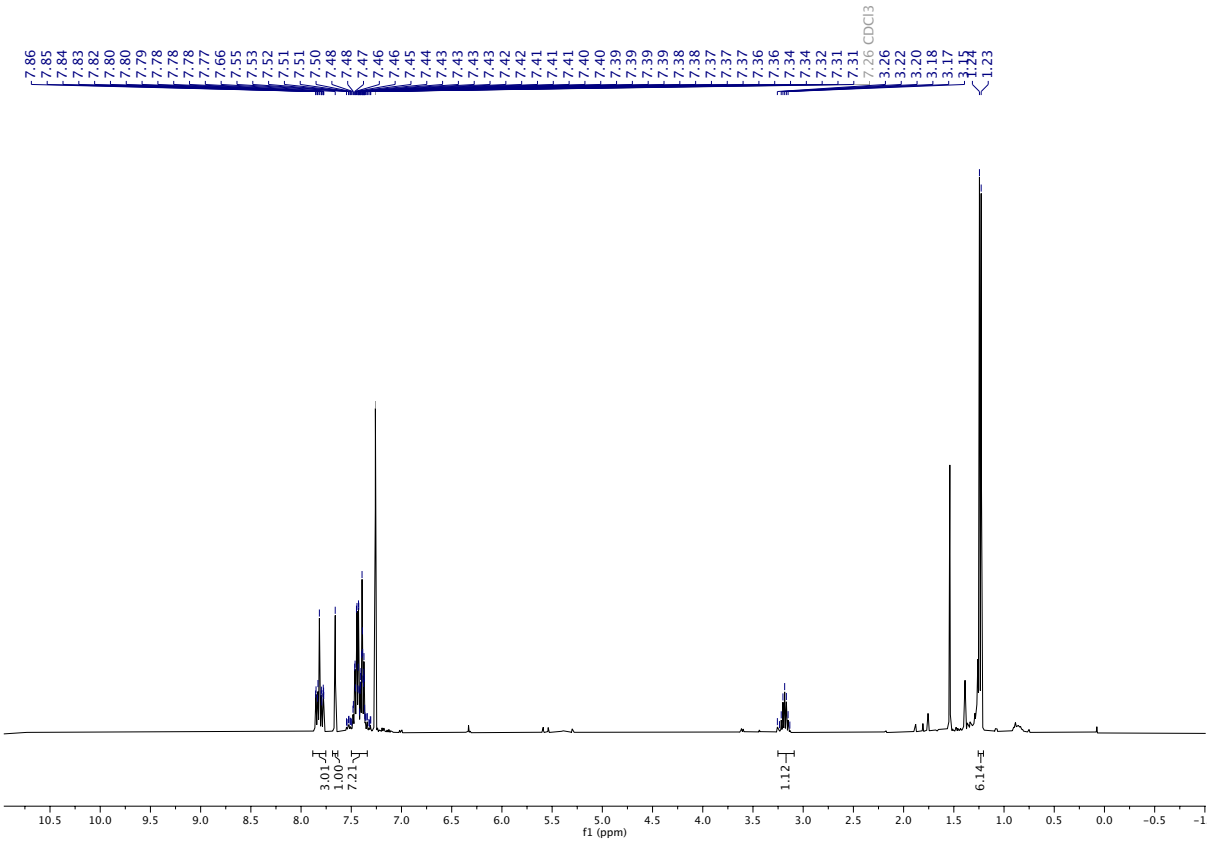


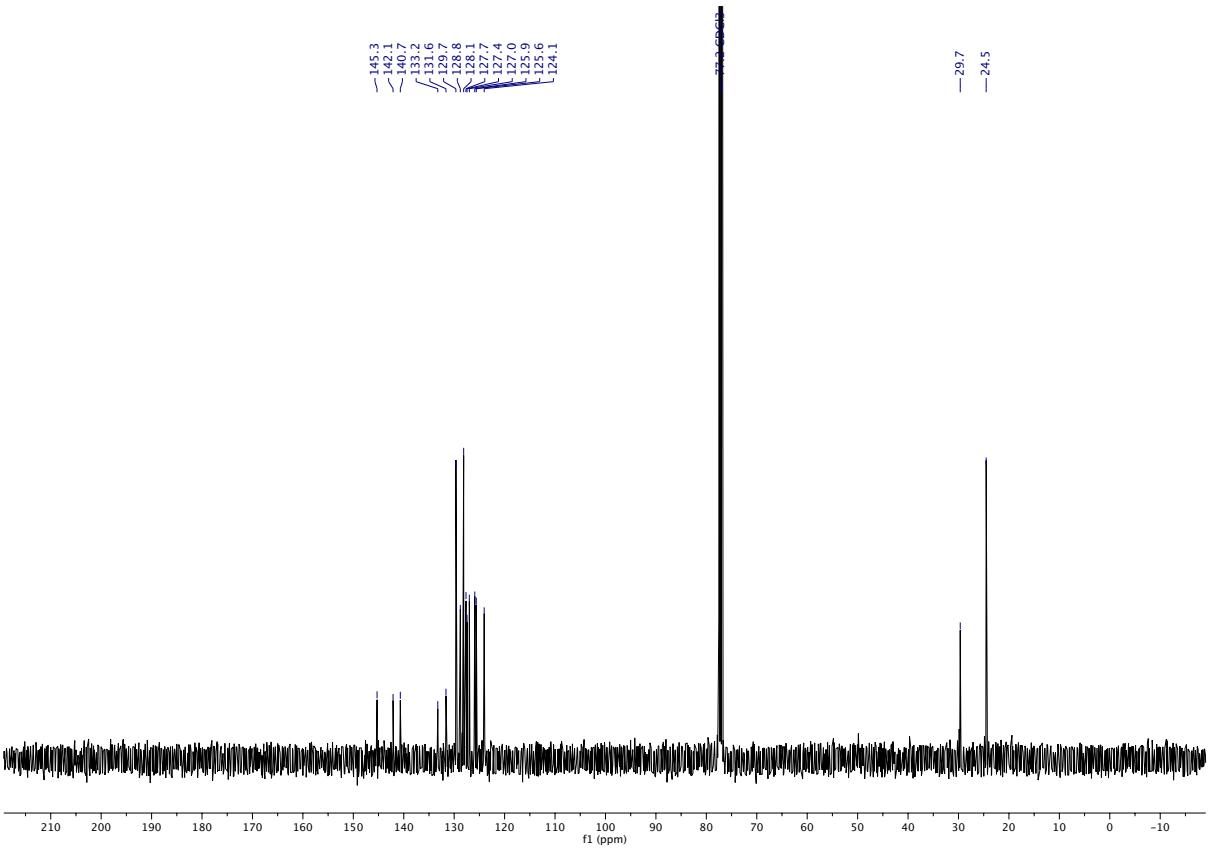
Products **8a, 19**[15] and 21,[16] have been reported.

When using (*R,R*)-**A**$^+$ under anhydrous conditions, naphthalene **20** was isolated (flash chromatography in pentane) (Table 5).

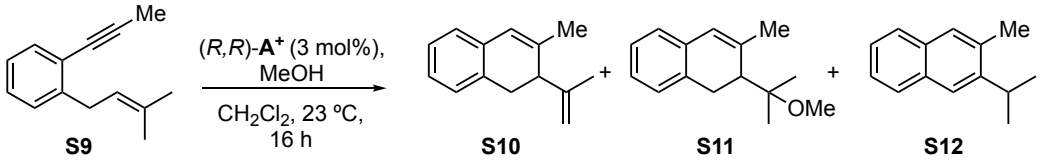


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.75 (m, 3H), .66 (s, 1H), 7.57 – 7.28 (m, 7H), 3.18 (dt, *J* = 13.7, 6.8 Hz, 1H), 1.24 (d, *J* = 6.9 Hz, 6H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.3, 142.1, 140.7, 133.2, 131.6, 129.7, 128.8, 128.1, 127.7, 127.4, 127.0, 125.9, 125.6, 124.1, 29.7, 24.5. **HRMS** (APCI+): *m/z*: calculated for $C_{19}H_{19}$: 247.1481 $[M+H]^+$; found: 247.1481.



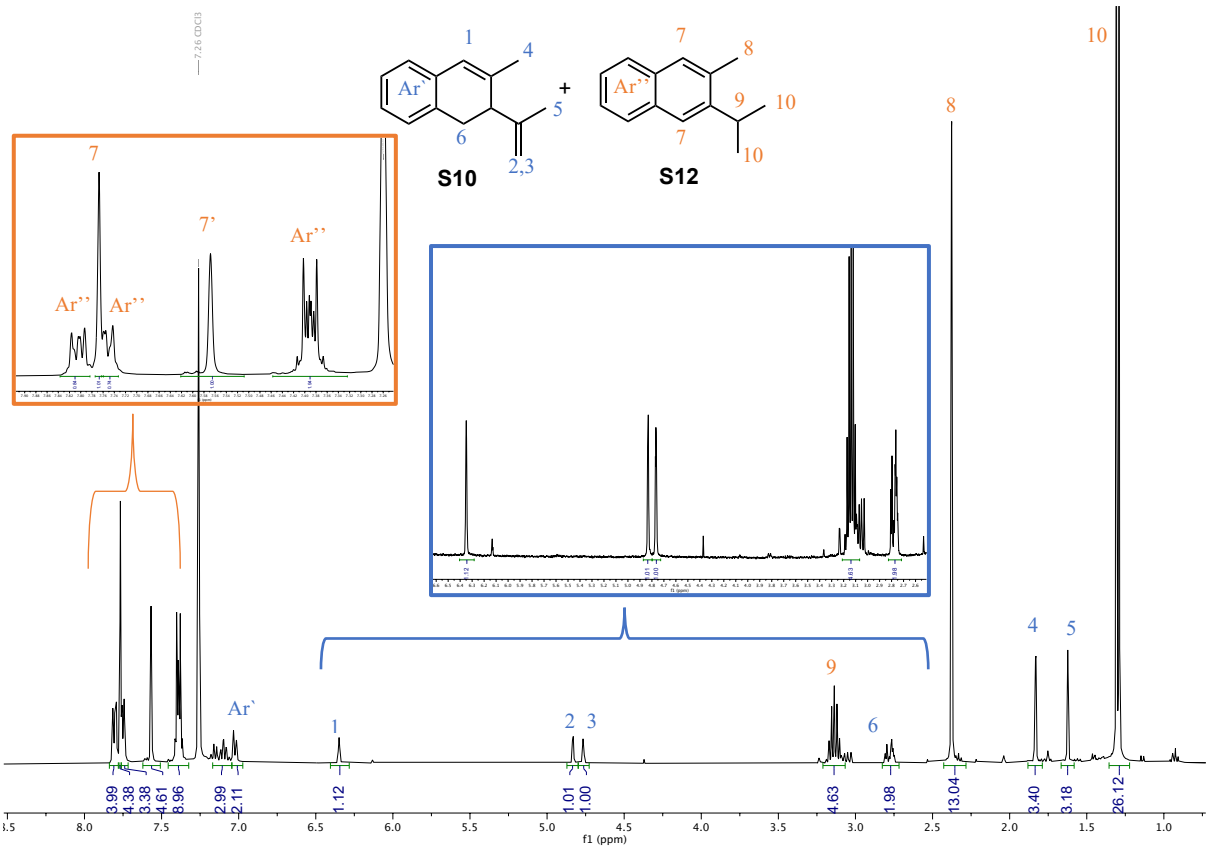


1,6-Enyne **S9** reacted in presence of (*R,R*)-**A**$^+$ in the absence of MeOH to form **S10** and naphthalene **S12**. Because of the low yield and decomposition of **S10** in silica gel it was not possible to measure with precision its *er*. When the reaction was carried put in the presence of MeOH, **S11** was isolated in 65% isolated yield (preparative TLC 50:1 hexane:EtOAc) and 91:9 *er*.

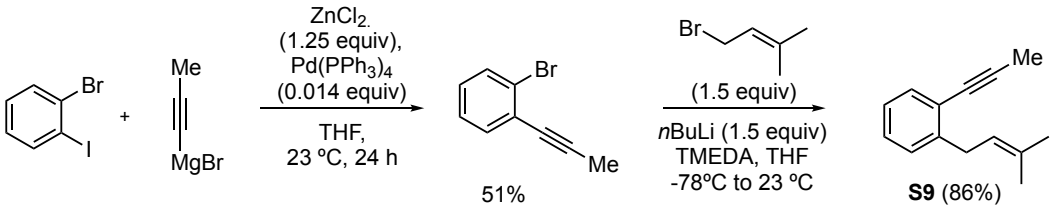


***n* MeOH**	**S10**	**S11**	**S12**
0	6%, ~ 78:22 *er*	/	12%
1	1%, er n.d.	77% (65%), 91:9 *er*	/

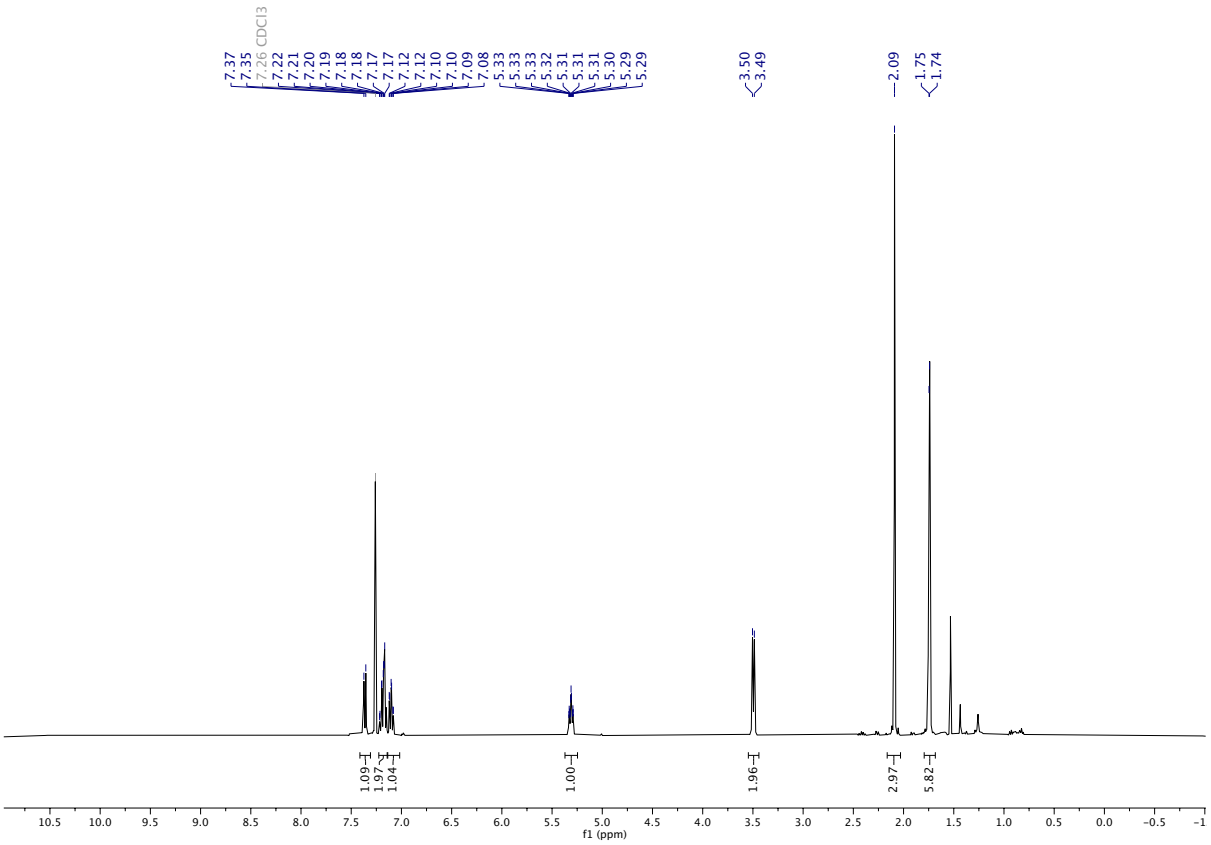
Table S5 - The reactions were performed under dry conditions using glovebox solvents. The reported yields were calculated by ^{1}H NMR integration using 1,1,2,2-tetrachloroethane as internal standard. Isolated yields in parenthesis. The *er* were measured on the pure isolated products.

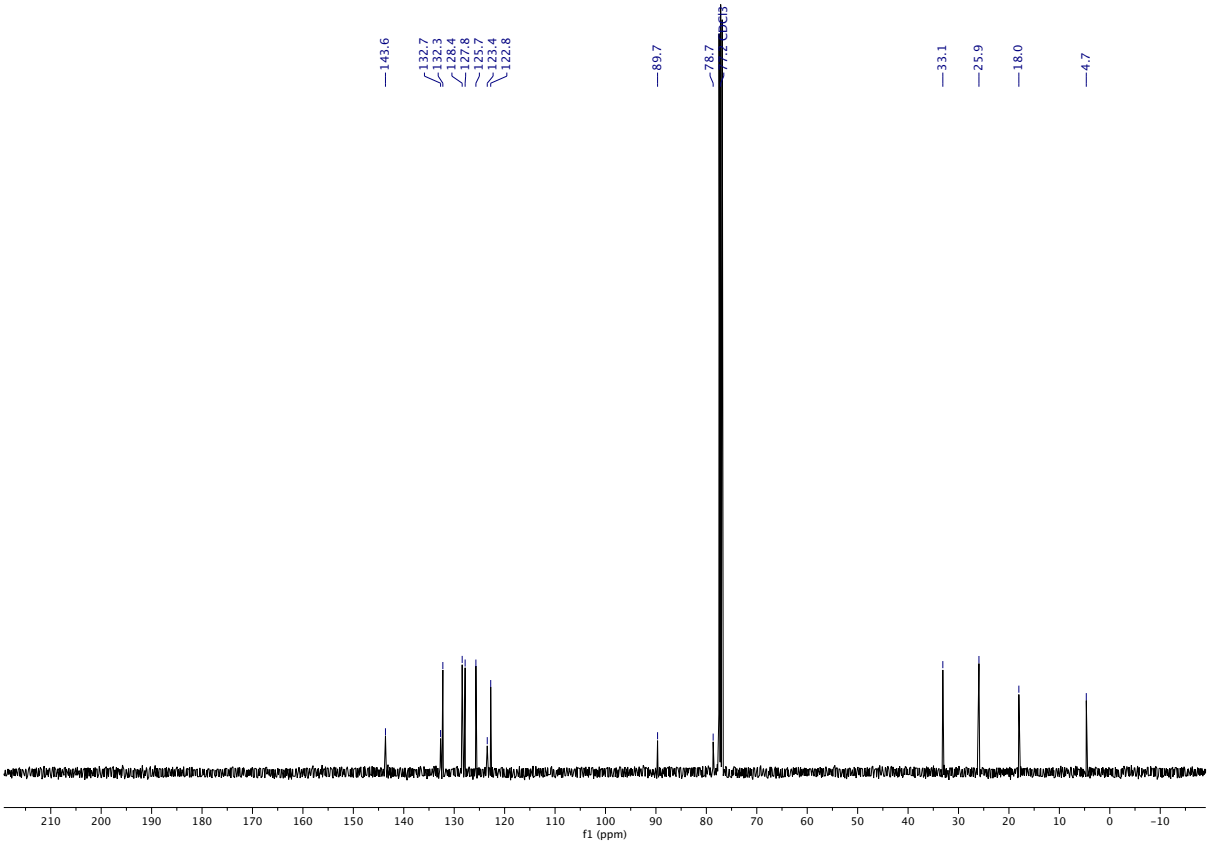


1-(3-Methylbut-2-en-1-yl)-2-(prop-1-yn-1-yl)benzene (S9)

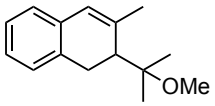


1,6-Enyne **S9** was synthesized starting from commercially available 2-bromoiodobenzene: following a literature procedure[17], 1-bromo-2-(prop-1-yn-1-yl)benzene was obtained in 51% isolated yield. Then, the latter was subjected to the same conditions used for synthesizing **S1-2** (page S5) and **S9** was obtained as a transparent oil in 86% yield after flash column chromatography (200:1 hexane/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 (d, J = 7.6 Hz, 1H), 7.24 – 7.14 (m, 2H), 7.10 (td, J = 7.3, 1.9 Hz, 1H), 5.31 (tt, J = 7.3, 1.5 Hz, 1H), 3.49 (d, J = 7.4 Hz, 2H), 2.09 (s, 3H), 1.74 (d, J = 2.1 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.6, 132.7, 132.3, 128.4, 127.8, 125.7, 123.4, 122.8, 89.7, 78.7, 33.1, 25.9, 18.0, 4.7. **HRMS** (APCI+): *m/z*: calculated for $C_{14}H_{17}$: 185.1325 $[M+H]^+$; found: 185.1323.



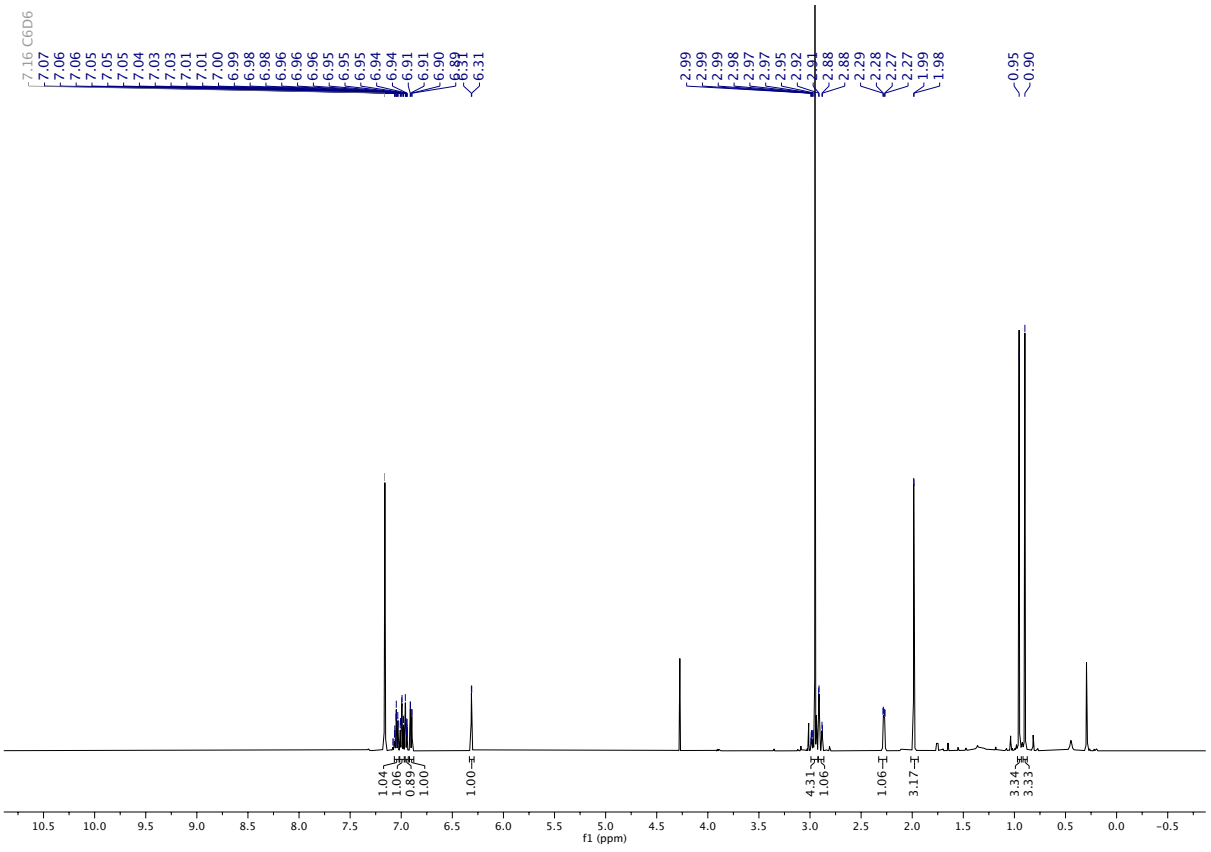


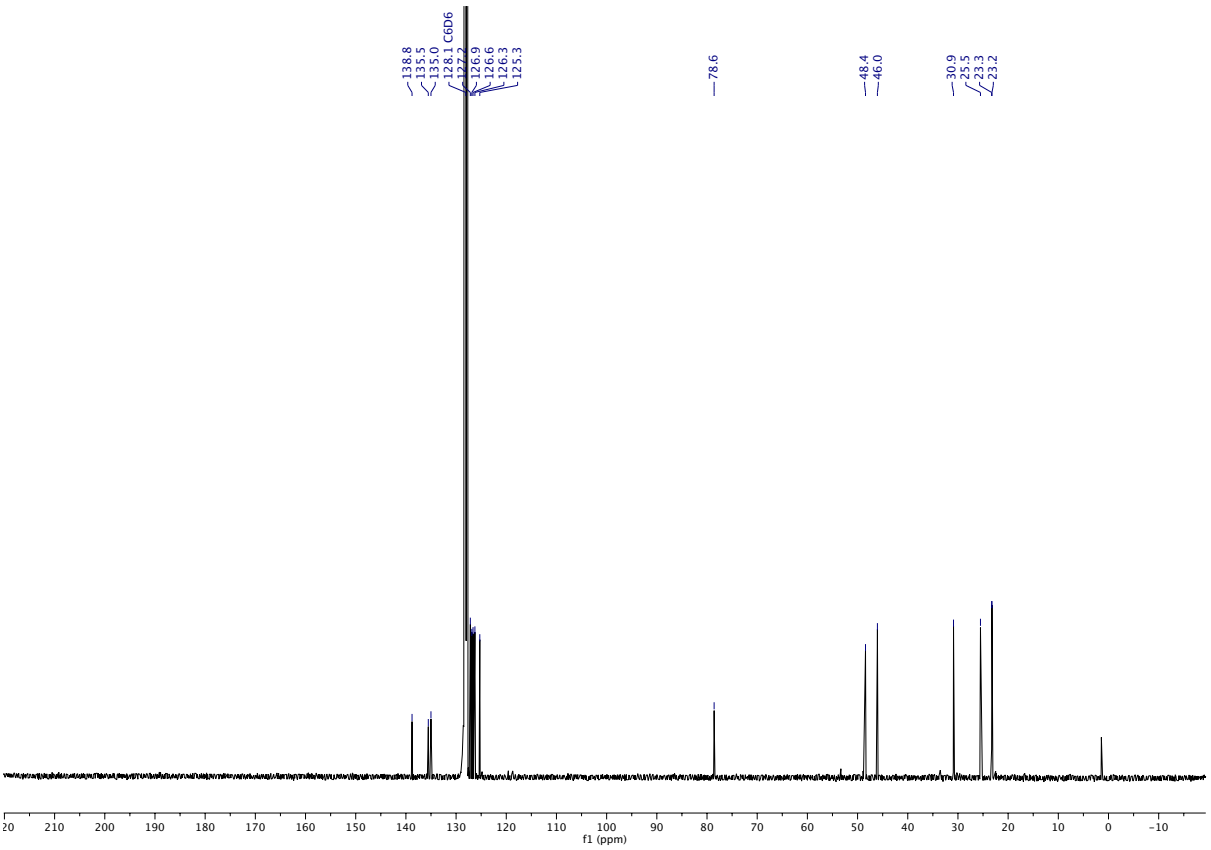
2-(2-Methoxypropan-2-yl)-3-methyl-1,2-dihydronaphthalene (S11)



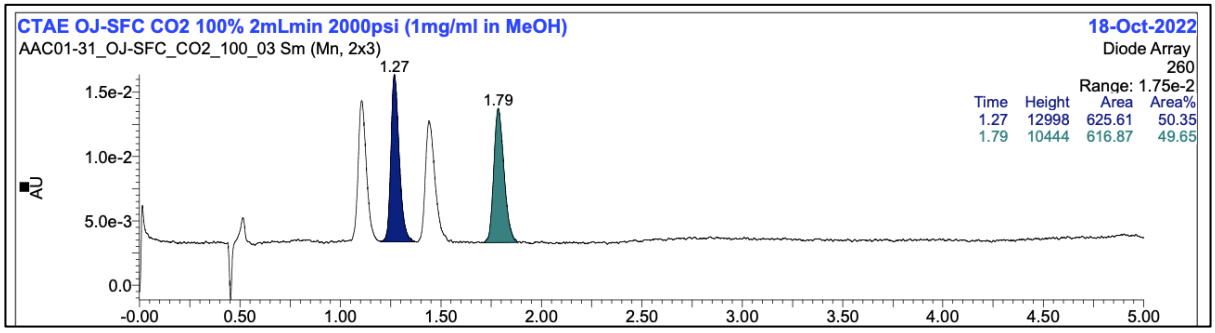
S11

^{1}H NMR (500 MHz, C_6D_6) δ 7.05 (tt, J = 7.3, 1.3 Hz, 1H), 6.99 (td, J = 7.3, 1.4 Hz, 1H), 6.96 (s, 1H), 6.98 – 6.88 (m, 1H), 6.31 (d, J = 1.6 Hz, 1H), 3.01 – 2.95 (m, 1H), 2.95 (s, 3H), 2.90 (dd, J = 16.3, 1.9 Hz, 1H), 2.28 (dd, J = 7.9, 1.9 Hz, 1H), 1.98 (d, J = 1.5 Hz, 3H), 0.95 (s, 3H), 0.90 (s, 3H). **^{13}C NMR** (126 MHz, C_6D_6) δ 138.8, 135.5, 135.0, 127.2, 126.9, 126.6, 126.3, 125.3, 78.6, 48.4, 46.0, 30.9, 25.5, 23.3, 23.2. **HRMS** (APCI+): *m/z*: calculated for $C_{14}H_{17}$: 185.1325 [M-MeOH]$^+$; found: 185.1326. **SFC** (OJ (3um, 4, 0.3x15 cm), CO_2 100, 2 mL/min, 25 °C, 2000 psi; 260 nm): 1.240 min (9), 1.750 min (91); **$[\alpha]_D^{26}$** = -157.4° (*c* = 0.19 in CH_2Cl_2).



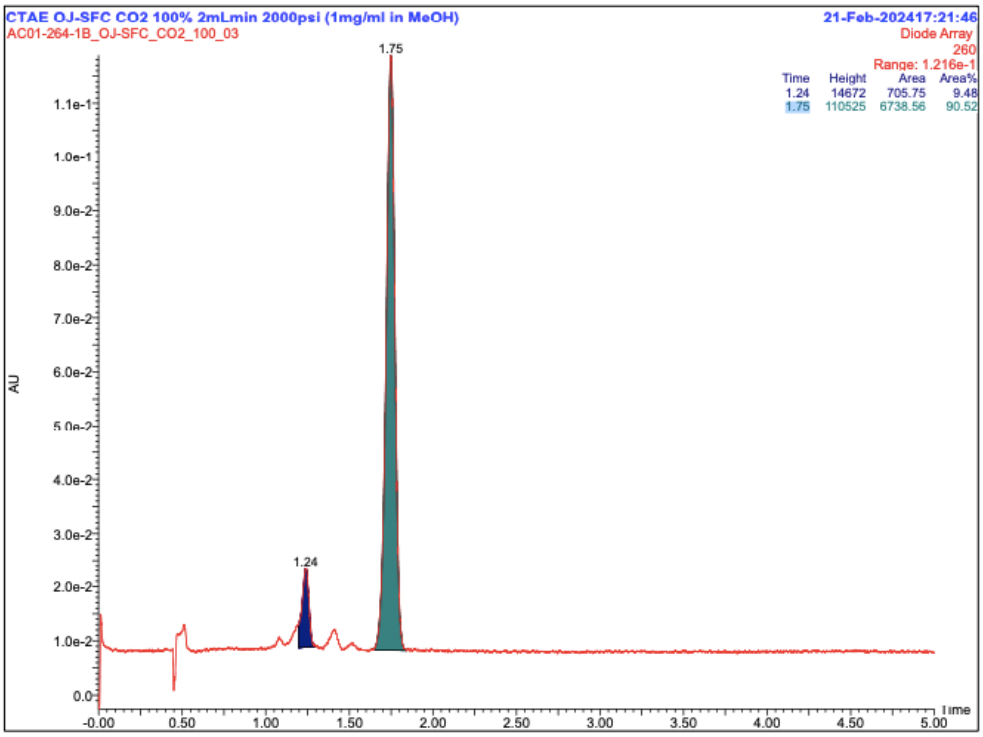


SFC racemic **S11***

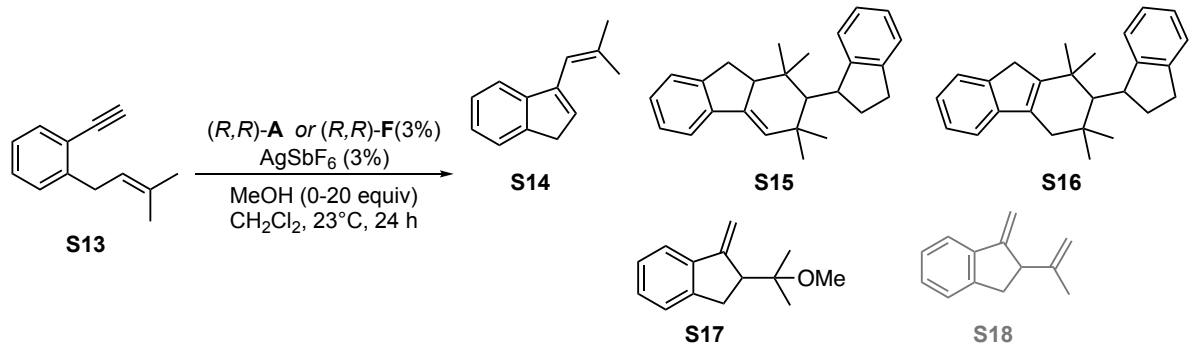


* In the non-stereoselective reaction the *5-exo-dig* product was also observed (the other two peaks in the spectrum) but it could not be separated by column chromatography from the product of *6-endo-dig* cyclization.

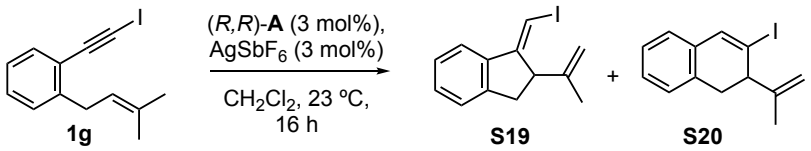
SFC enantioenriched **S11**



Terminal enyne **S13** was also tested, but as expected,[18] it afforded diene **S14**, together with dimerization products **S15-16** and product **S17** when MeOH was added to the reaction mixture, but no trace of cycloisomerization product **S18** was observed.

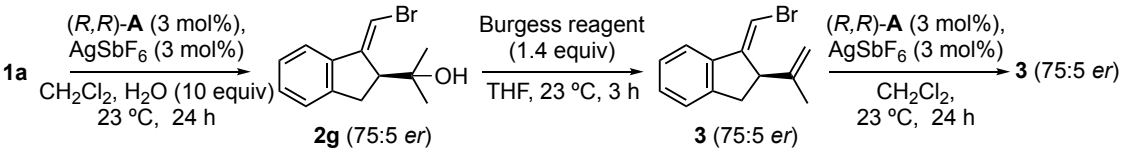


Iodoenyne **1g** was not included in this study since, in absence of MeOH, a mixture of *5-exo-dig* and *6-endo-dig* cycloisomerization products **S19** and **S20** which could not be separated by column chromatography.



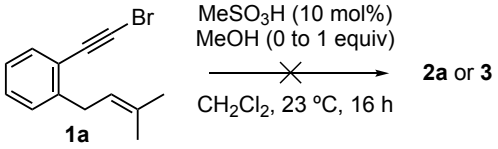
8.4. Further mechanistic studies

To exclude the possibility that the racemization occur on product **3** after the protodeauration step via a reversible gold(I) or Brønsted-acid mediated double bond isomerization,[19] we performed the enantioselective hydroxycyclization of **1a** using complex (*R,R*)-**A** to form **2g** (75:25 *er*, reaction performed at 23 °C (note that higher er was obtained at -60 °C, see Table 1, entry 12), followed by alcohol elimination with the Burgess reagent (see Scheme 3) to afford enantioenriched **3** with the same *er* (75:25 *er*). The *er* of compound **3** remained unchanged when subjected again to the same alkoxycyclization conditions.



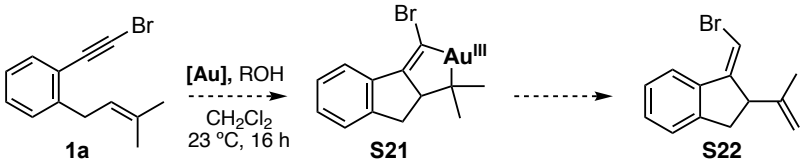
The *er* of **2a** (80:20 *er*) also remained unchanged when subjected again to the same alkoxycyclization conditions.

Neither **2a** nor **3** were formed when **1a** was treated with $MeSO_3H$ in the presence or absence of MeOH.

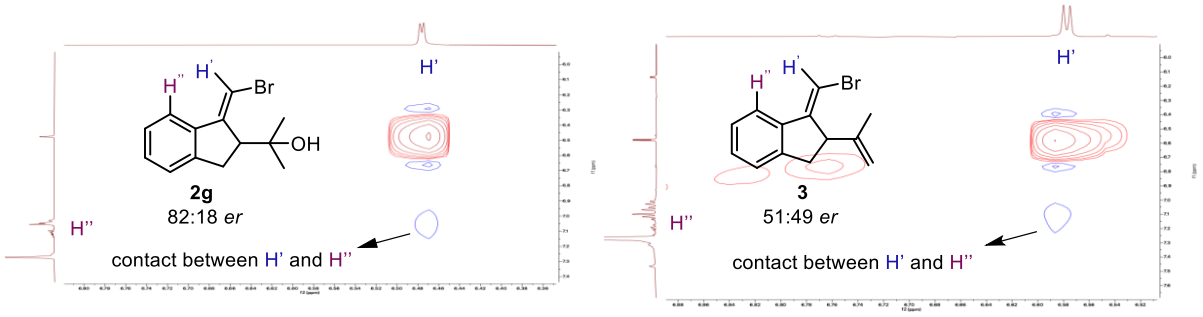


8.5. Determination of the *E*-configuration of 2g and 3

Product **S22**, the *Z*-isomer of **3**, could in principle be formed by an oxidative-cyclometallation to form **S21**, followed by elimination.



To exclude this scenario, NOESY spectroscopy was run on both enantioenriched **2g** (82:18 *er*) and racemic **3** (51:49 *er*) formed **1a** (Table 3, entry 3). As shown below, NOE correlations confirmed the *E*-configuration of **2g** and **3**.



9. DFT Calculations

9.1. Computational methods

The calculations were performed in Gaussian09.[20] The stationary points were characterized by vibrational analysis. Transition states were identified by the presence of one imaginary frequency while minima by a full set of real frequencies. The connectivity of the transition states was confirmed by the relaxation of each transition state towards both previous and next intermediates. All the energies are potential energies (E) and free energies (G) in solution at 298.15 K and 1 atm in kcal/mol. A data set collection of computational results is available in the ioChem-BD[21] repository and can be accessed via https://doi.org/10.19061/iochem-bd-1-307.

1-Bromo-1,6-enynes:

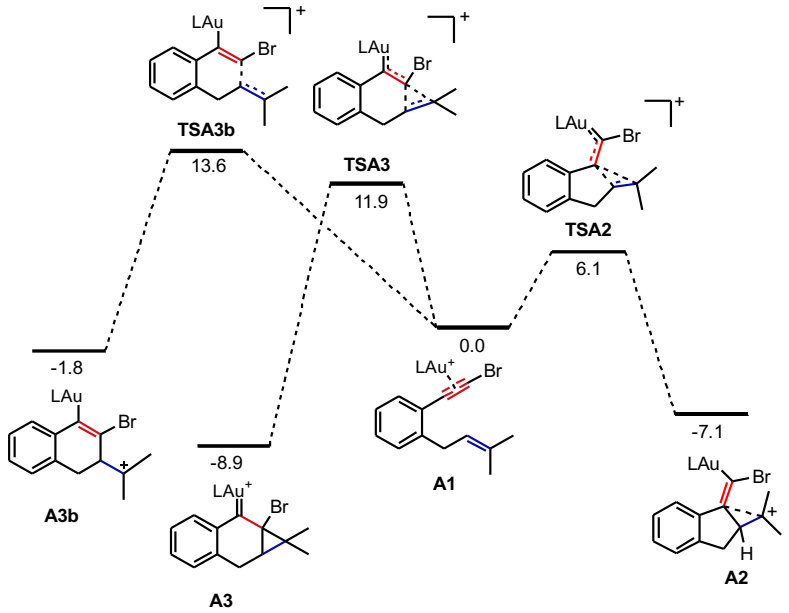
DFT was applied using B3LYP[22] using Grimme's D3 empirical dispersion correction,[23] modelling the solvent (CH_2Cl_2) with implicit solvation using the polarisable continuum model.[24] Gold was modelled with the Stuttgart-Dresden basis set and effective core potential,[25] bromine with LANL2TZ(f)[26] and all other non-metal atoms with Pople basis set[27] 6-311+G(d,p). Single-point energy calculations were performed with the 6-311+G(d,p) basis set for non-metal atoms and SDD basis set and ECP for gold.

1-Bromo-1,5-enynes:

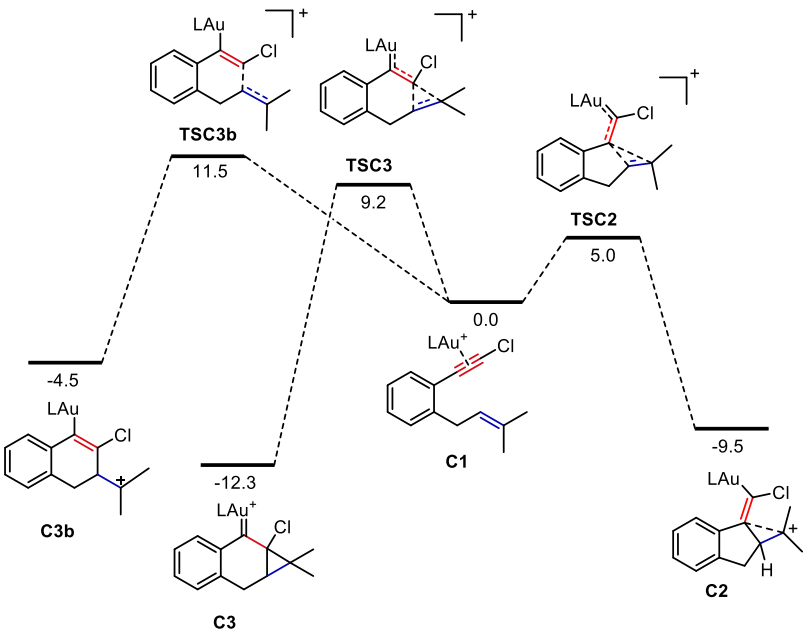
DFT was applied using BP86-D3[28] that has proved its efficiency in other DFT studies of gold-catalyzed transformations.[29] The SDD basis set and ECP was used to describe Au.[25] Br atom was described by ECP with the LANL2DZ basis set.[26] Polarization functions were added Br (ζf= 0.428).[30] The 6-31G(d) basis set[27] was employed for all remaining atoms (C, H, P, F, and N). Full geometry optimizations were carried out in chlorobenzene, through an implicit polarizable continuum model (PCM).[24]

9.2. Initial cyclizations

The different possible cyclizations of the haloenynes were studied (Schemes S1 and S2), reproducing the experimentally observed selectivity and confirming trimethylphosphine to be an adequate ligand for the computational study.

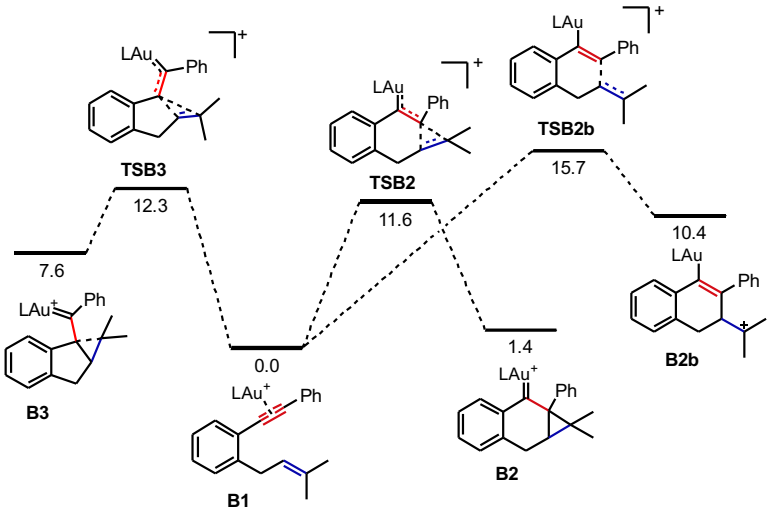


Scheme S1- Competition between 5-*exo*-dig and 6-*endo*-dig barriers with gold(I) bromoenyne complex **A1**, consistent with the experimental observations. Free energy in kcal mol^{-1}, B3LYP-D3/6-311G+(d,p) + SDD, PCM.

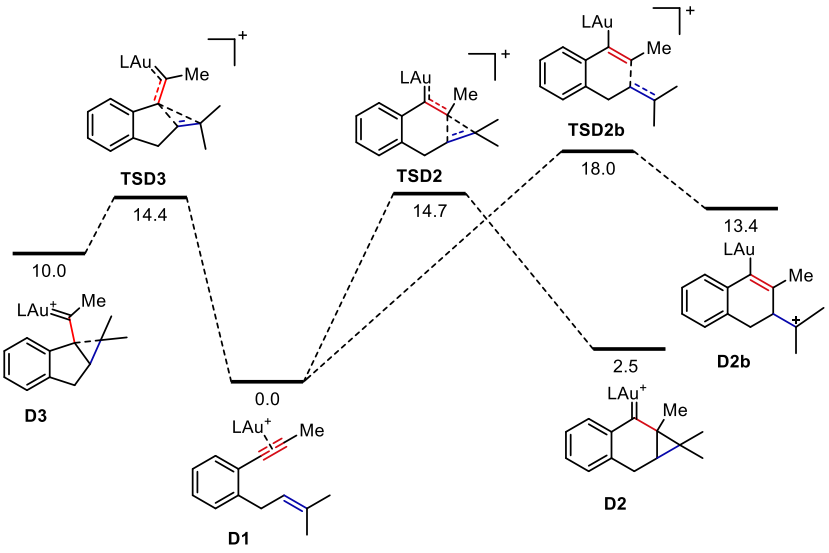


Scheme S2 - Competition between 5-*exo*-dig and 6-*endo*-dig barriers with gold(I) chloroenyne complex **C1**, consistent with the experimental observations. Free energy in kcal mol^{-1}, B3LYP-D3/6-311G+(d,p) + SDD, PCM.

The same pathways were found for the cyclization of substrates bearing Ph (Scheme S3) and Me (Scheme S4) groups at C1 of the alkyne, showing an increased preference for the 6-*endo*-dig products, although somewhat less selective than that seen experimentally.



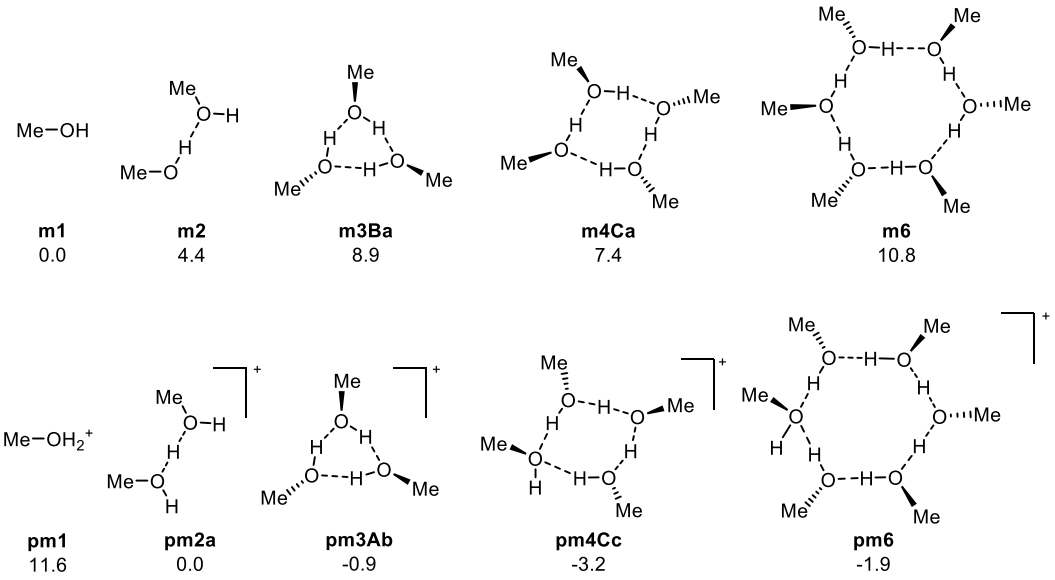
Scheme S3 - Competition between 5-*exo*-dig and 6-*endo*-dig barriers with gold(I) phenylenyne complex **B1**. Free energy in kcal mol^{-1}.



Scheme S4 - Competition between 5-*exo*-dig and 6-*endo*-dig barriers with gold(I) methylenyne complex **D1**. Free energy in kcal mol^{-1}.

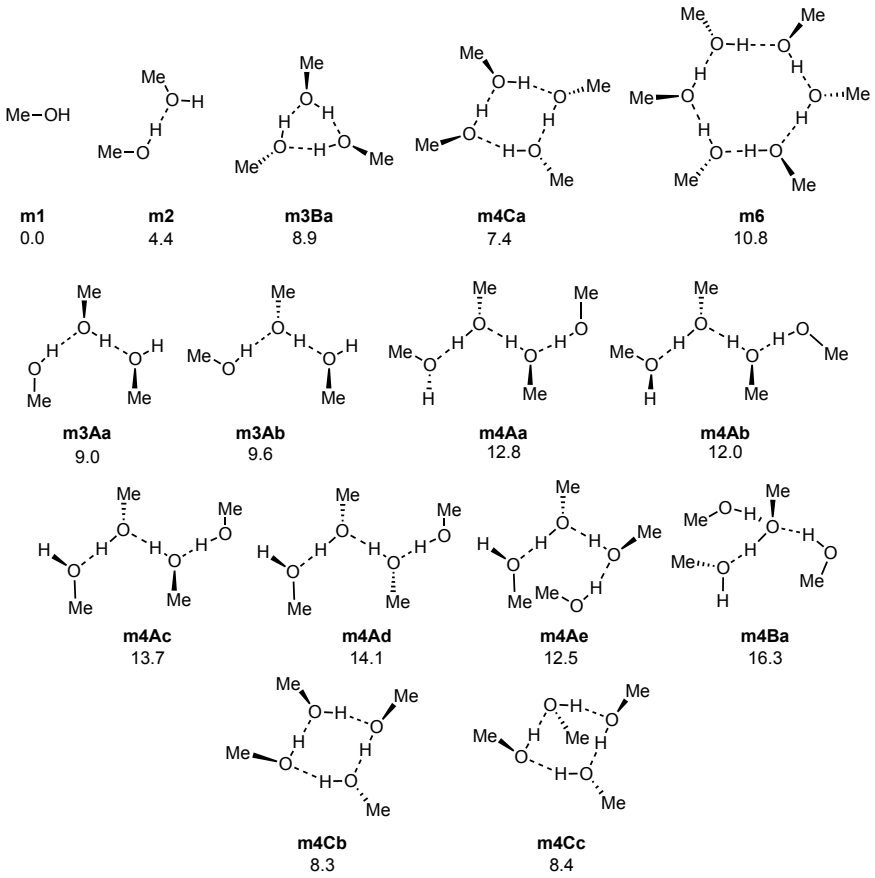
9.3. MeOH clusters

We studied whether MeOH exists as a monomer or as a higher oligomer in CH_2Cl_2, which could bring non-trivial changes in pKa due to the solvation of protons. Previous work on the MeOH cluster speciation within MeOH had found tetramers, hexamers, octamers and tridecamers to be most favored.[31] We calculated several neutral and protonated clusters of MeOH, optimizing with B3LYP/6-31G(d) and running single point calculations with 6-311+G(d,p), using PCM implicit solvation for CH_2Cl_2 (Schemes S5-S7). The results showed that the main neutral species was monomeric MeOH (**m1**), while protonation resulted in higher order clusters being favored.

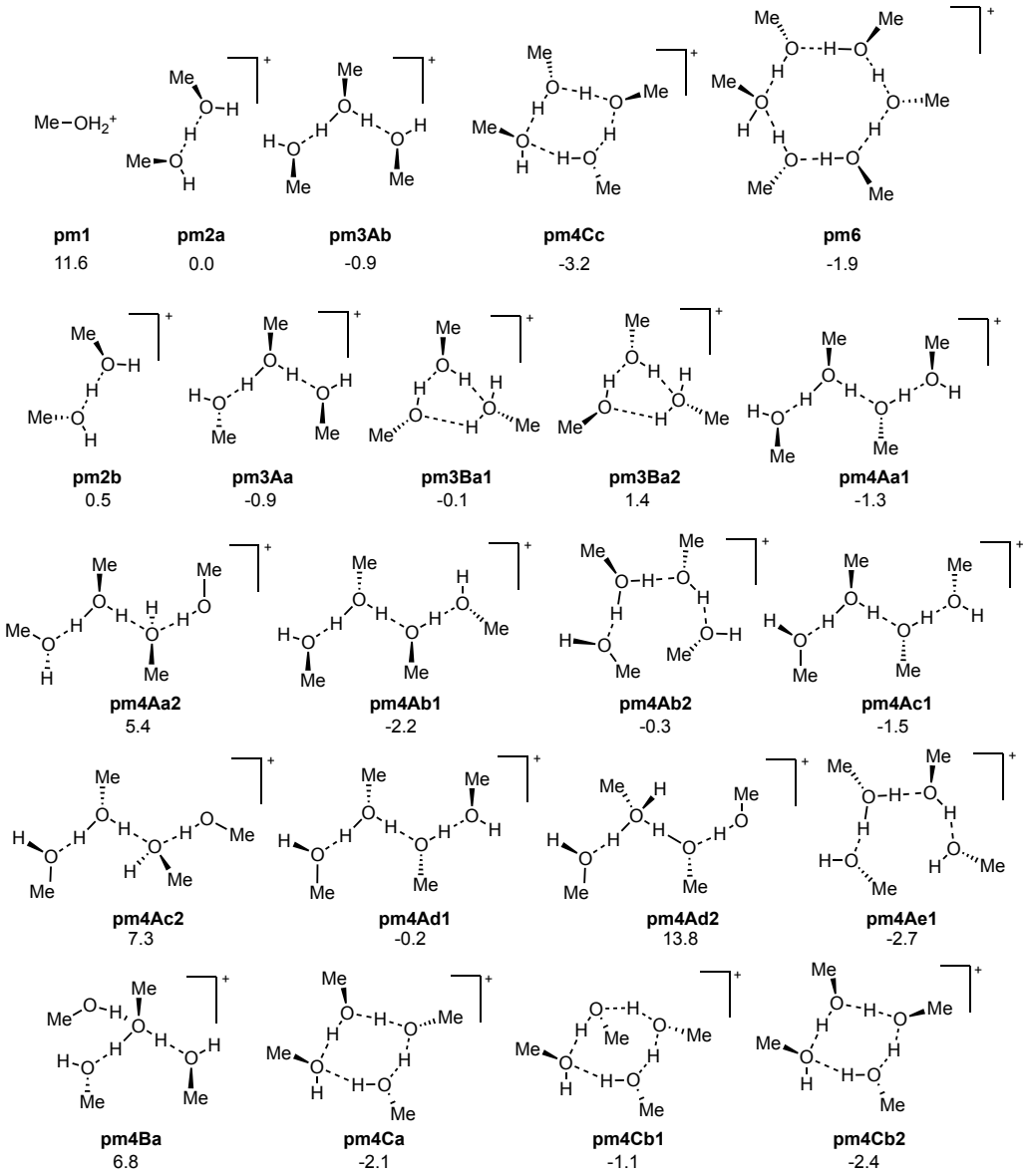


Scheme S5 - Most stable calculated neutral and protonated MeOH clusters for each molecularity (in CH_2Cl_2 modelled with PCM). Free energy in kcal mol^{-1}.

We used monomeric MeOH **m1** as the reference for the neutral alcohol, while $[H(MeOH)_2]^+$, **pm2a**, was used as the simplest stable model as an approximation. Given a high enough concentration of alcohol, all deprotonated intermediates can be stabilized by a further 3.2 kcal mol^{-1} forming **pm4Cc**. The energies of other disfavored clusters were also calculated analogously. All energies can be found in **Table S12** below and their structures are available in the data repository.[21]

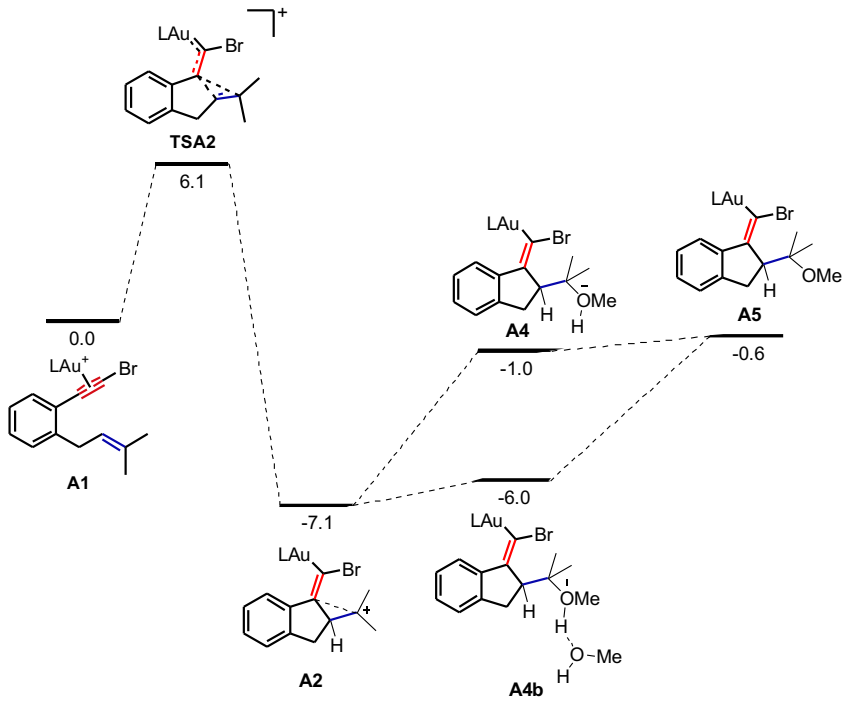


Scheme S6 - Structures and free energies (kcal mol^{-1}) of all studied neutral MeOH clusters.



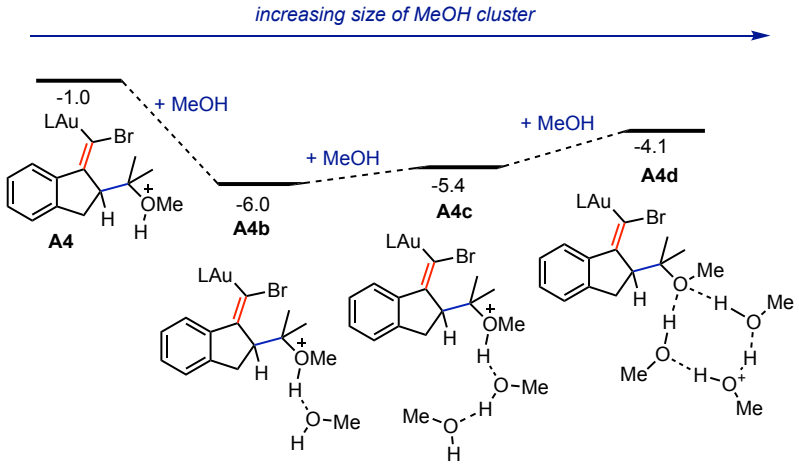
Scheme S7 - Structures and free energies (kcal mol^{-1}) of all studied protonated MeOH clusters.

When modeling the nucleophilic attack, we found that proton shuttling away from **A4** requires a MeOH dimer, which can occur through immediate dissociation of a protonated MeOH dimer from the cation once a third MeOH attaches or via intermediates of higher molecularity (Scheme S8), the exact nature of which presumed to depend strongly on the exact concentration of MeOH.



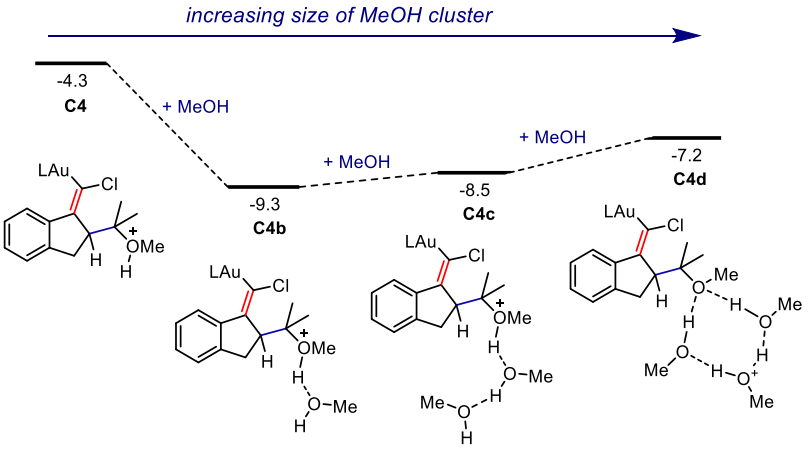
Scheme S8 - Formation of the alkoxycyclization product shown with MeOH and its dimer, with the deprotonation sink modelled as $[H(MeOH)_2]^+$. Only subsequent protodemetallation is irreversible. Free energies (kcal mol^{-1})

This suggests that the alkoxycyclization needs a larger cluster than the monomer to be attacked productively to prevent charge build-up on the oxygen (Scheme S5). Modelling **A4** with several MeOH clusters showed the dimer (**A4b**) to be preferred.



Scheme S9 - MeOH addition to the bromoenyne carbocation shows the preferred cluster to be the dimer in **A4b**. The differences in stability are primarily dependent on entropic contributions. Free energy in kcal mol^{-1}.

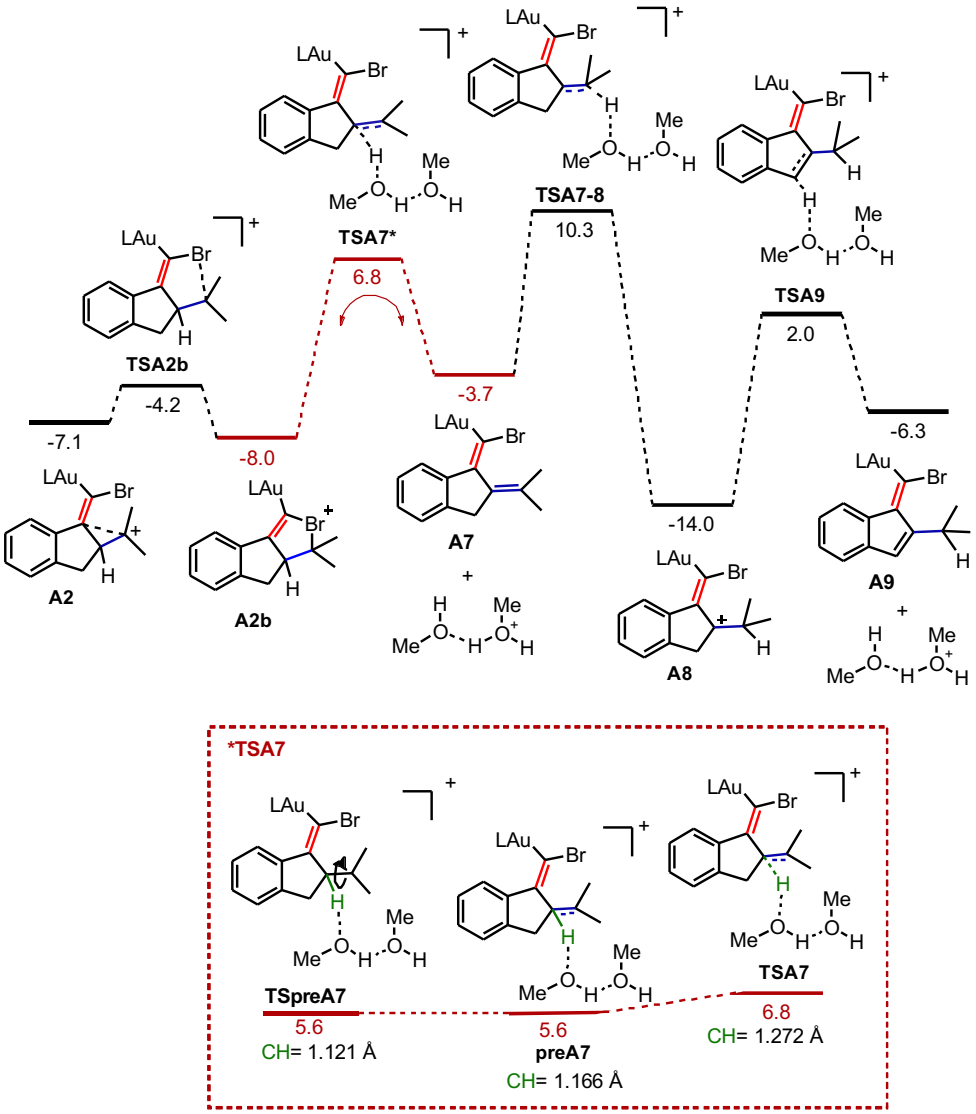
Analogously to the bromoenynes, the intermediates of chloroenyne alkoxycyclization are also most stable with a MeOH dimer (Scheme 10).



Scheme S10 - In the MeOH addition to the chloroenyne carbocation, the preferred cluster was also found to be the dimer in **C4b**. Free energy in kcal mol^{-1}.

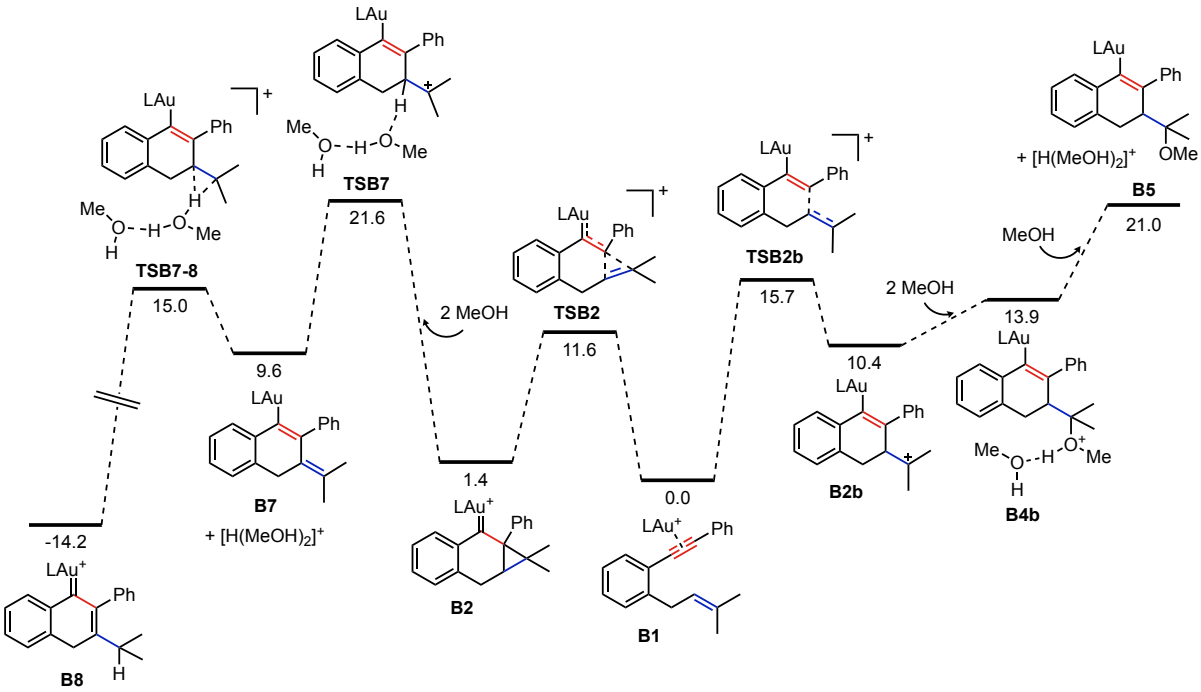
9.4. Discarded racemization pathway (reversible deprotonation)

A reversible deprotonation mechanism was considered for addressing the observed racemization (**Scheme S9**). The deprotonation pathway would form strained conjugated diene **A7** that could lead to enantiomeric scrambling by reprotonation **TSA7** on the other face of the alkene. **TSA7** is a multistep process consisting of **TSpreA7**, which leads to high-energy intermediate **preA7**, and **TSA7** which leads to **A7**. However, several factors make this mechanism unlikely. Experimentally, the cyclization of deuterated **3-*d*$_1$** did not show any scrambling or change in isotopic ratio (Scheme 8 in the manuscript), which would not be expected in a reversible proton exchange mechanism. The barrier **TSA7** is 3.1 kcal mol^{-1} higher than the direct elimination (**TSA6**), requiring in both cases two molecules of MeOH and thus having identical molecularity. In addition, vinylgold(I) **A7** constitutes an example of a neutral gold(I) complex and so is subject to protodemetallation: if formed, **A7** should undergo rapid protodeauration, which we had calculated to be barrierless for a neutral intermediate, however, this product was never observed experimentally. Therefore, **A7** would have to be unable to undergo protodeauration, for which there would be no explanation as the reverse reaction also requires protonated MeOH. In addition, **A8** could be formed under these conditions. Deprotonation **TSA9** at the benzylic position would be significantly more favorable than the reverse reaction (by 8.3 kcal mol^{-1}), as both processes require a MeOH dimer. These results suggest that reversible deprotonations are very unlikely to be the origin of racemization. In contrast, the 1,2-H shift through **TSA8** was found to be favored since it has lower energy barrier than the deprotonation **TSA7** (see Scheme 9 in the manuscript).



Scheme S11 - Discarded racemization pathway through reversible deprotonation in the bromoenyne cyclization. Free energy in kcal mol^{-1}.

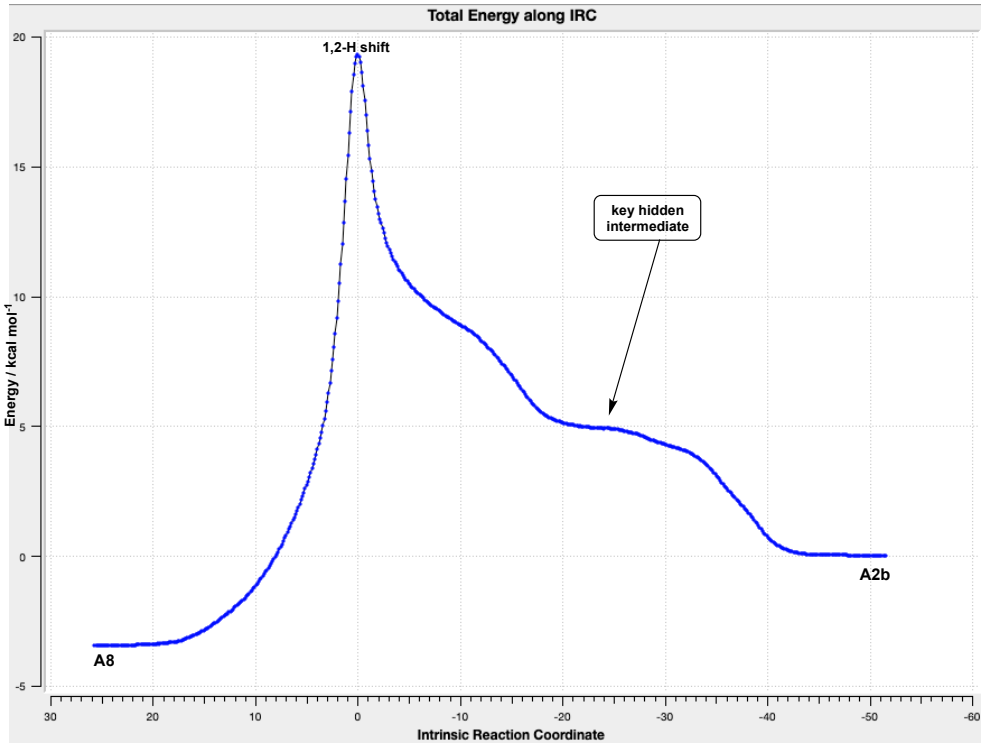
Analogous calculations with the phenylenyne show a similar pattern, with **TSB7** being outcompeted by all alternative productive deprotonations explored in the manuscript. In addition, this pathway is also outcompeted by alkoxycyclization even in the regime with a low concentration of methanol. As discussed previously, formation of **B8** is irreversible and so does not lead to racemization, instead forming the experimentally observed isopropylnaphthalene product. These calculations suggest that the main pathway for formation of this product is not a series of proton transfers but, rather, the 1,2-hydride shift, as is the case for the bromoenynes.



Scheme S12 - Discarded deprotonation pathway in the phenylenyne cyclization. Free energy in kcal mol^{-1}.

9.5. Hidden intermediate

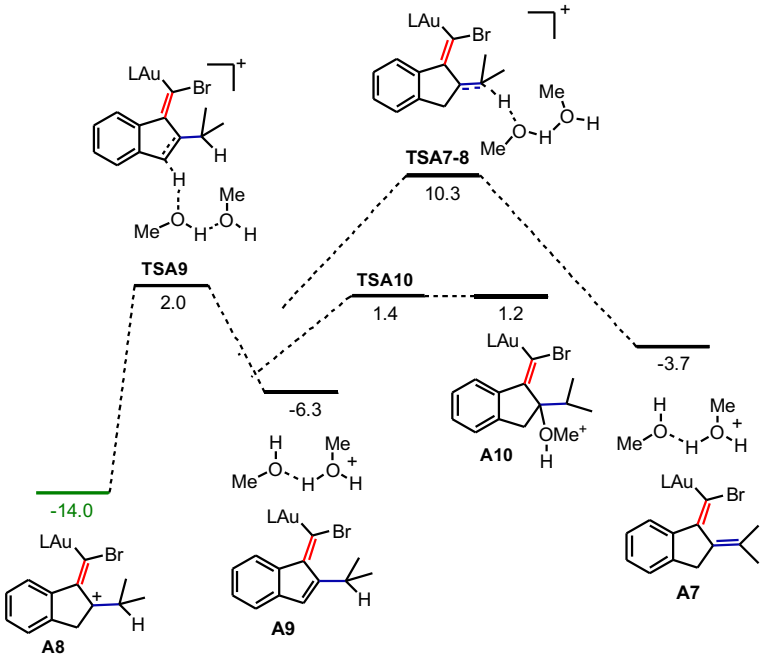
A hidden intermediate was located by IRC analysis of the 1,2-hydride shift **TSA2b-8**, and the same geometry appears in the relaxation of **TSA2b** as a non-stationary geometry. This hidden intermediate is not a downhill bifurcation point, but an intermediate geometry that relaxes in a barrierless manner, corresponding to the open-form carbocationic vinylgold(I) complex often found as a full intermediate in enyne cyclizations.



Scheme S13 - Key hidden intermediate as located in the IRC of the 1,2-hydride shift.

9.6. Alternative fates of Int7

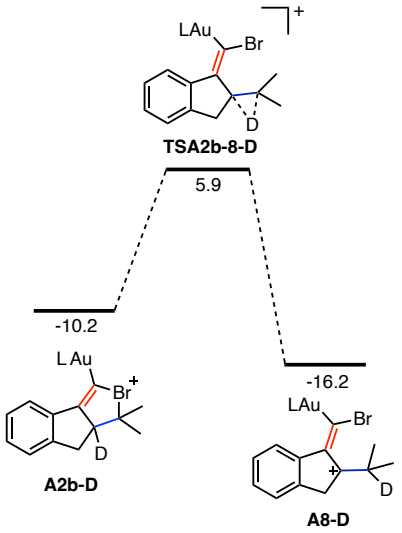
Once formed, intermediate **A8** could in principle evolve to several elimination or alkoxycyclized products (Scheme 7). Deprotonation at the stereogenic center to form diene **A7** presents a 24.3 kcal/mol barrier, which is higher than the reverse shift to give **A2b** back (21.3 kcal/mol). Nucleophilic attack on the tertiary carbocation to afford **A10** through **TSA10** presents a nearly inexistent barrier for MeOH dissociation to form **A8** again. Finally, while the benzylic deprotonation can seem very competitive on first impression, at low enough concentrations of MeOH in which **TSA2b-8** is accessed and entropically favoured, the reversibility of the intramolecular hydride shift is reasonable.



Scheme S14 – Alternative pathways in which 1,2-hydride shift intermediate **A8** could be trapped. Free energy in kcal mol^{-1}.

9.7. Deuterium labeling

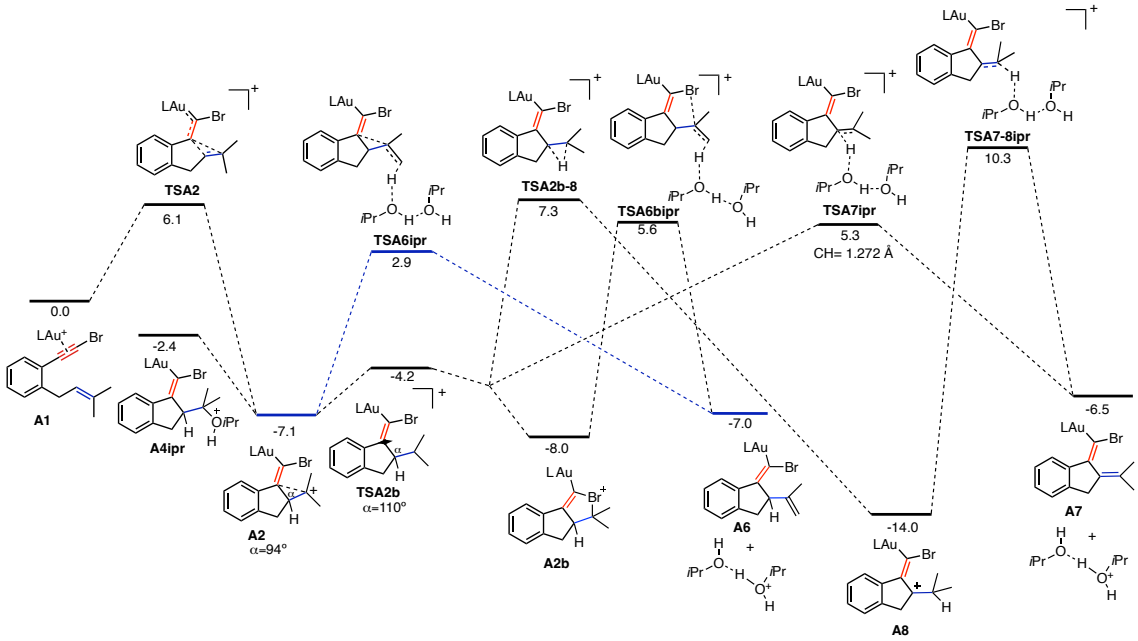
We calculated the 1,2-hydride shift racemization barriers for the deuterium-labelled bromoenyne (**Scheme S15**). The $\Delta G^{\ddagger}$, at 16.1 kcal mol^{-1}, was 0.8 kcal mol^{-1} higher than with ^{1}H, consistent with the slower racemization observed experimentally.



Scheme S15 -. Deuterium-labelled 1,2-hydride shift barriers.

9.8. Isopropanol attack

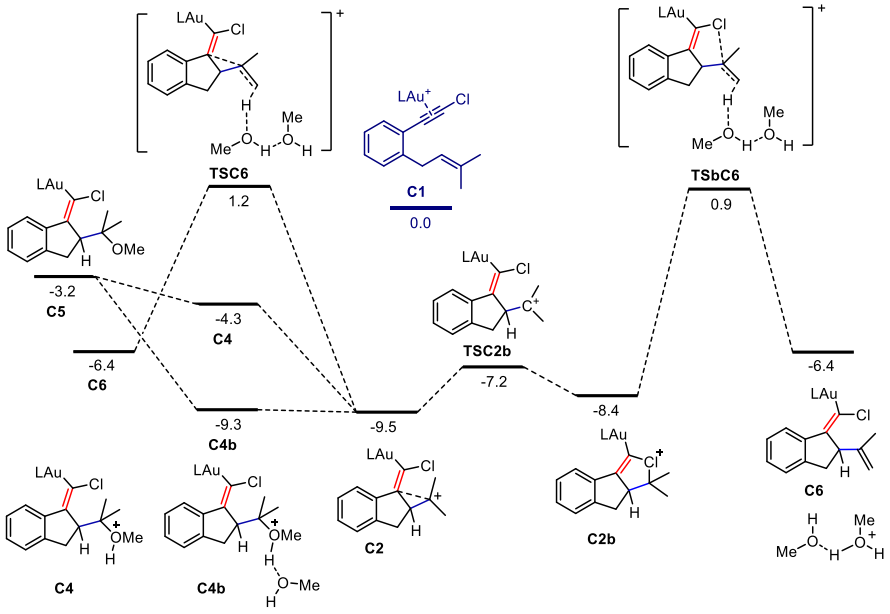
The alcohol attack and alcohol-mediated elimination mechanisms were calculated using isopropanol, as a bulkier and somewhat more basic example (**Scheme S16**). As also found experimentally (Table 3, in manuscript), less racemization is expected, as the elimination steps in particular are lower in energy than with MeOH.



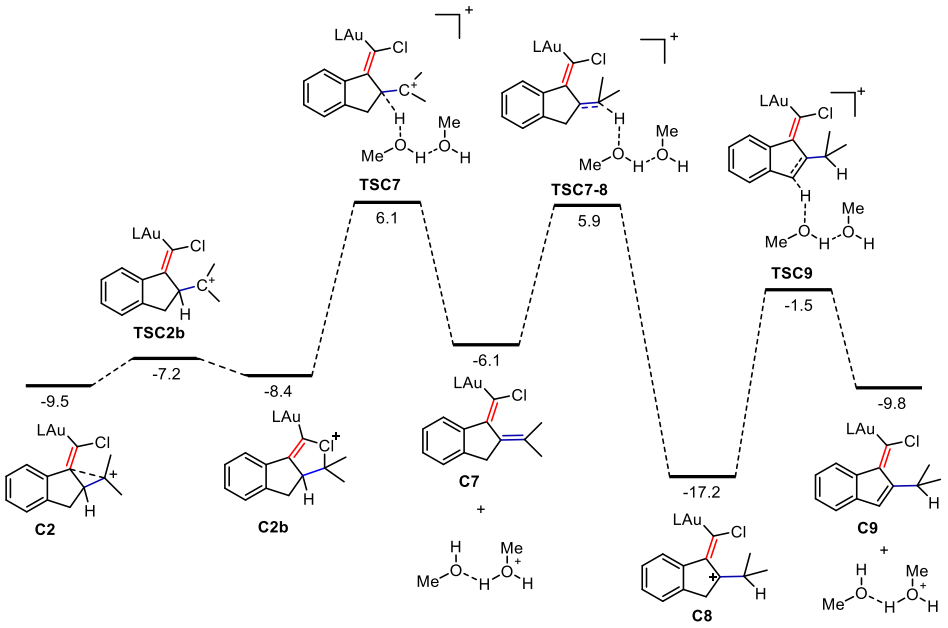
Scheme S16 - Gold(I)-catalysed alkoxycyclization and cycloisomerization pathways of bromoenyne complex **A1** with isopropanol-mediated nucleophilic attack or elimination. Free energy in kcal mol^{-1}.

9.9. Additional chloroenyne and methylenyne calculations

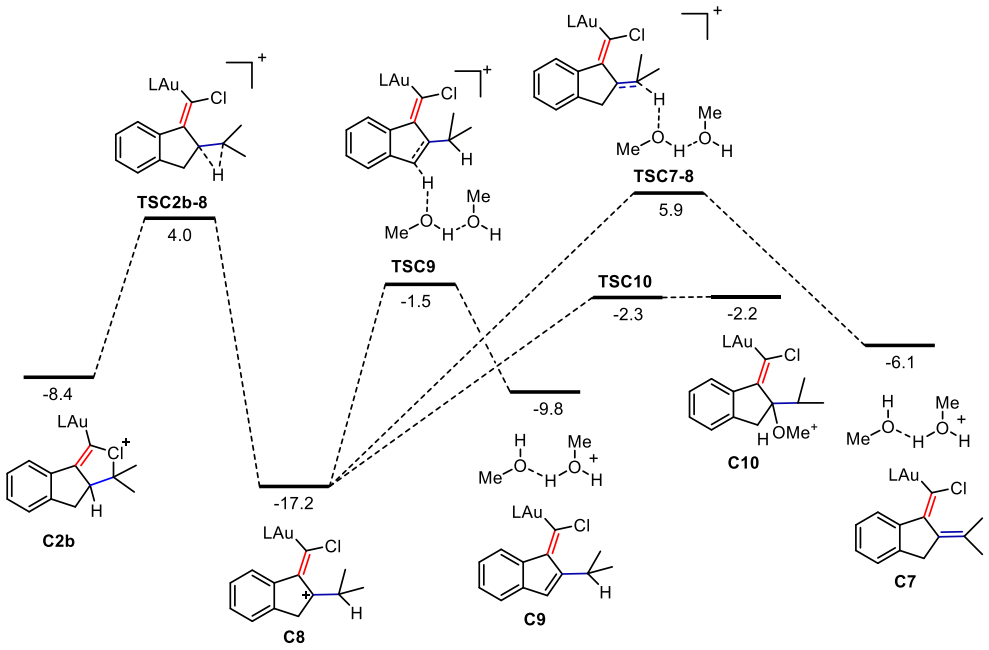
The pathways with chloroenyne complex **C1** are very similar to those of the bromoenyne, with analogous conclusions derived from the computational results (**Schemes 17-19**).



Scheme S17 - Gold(I)-catalysed 5-*exo*-dig cyclization of chloroenyne **C1** followed by MeOH-mediated nucleophilic attack/elimination to afford **C5** and **C6**. Free energy in kcal mol^{-1}.

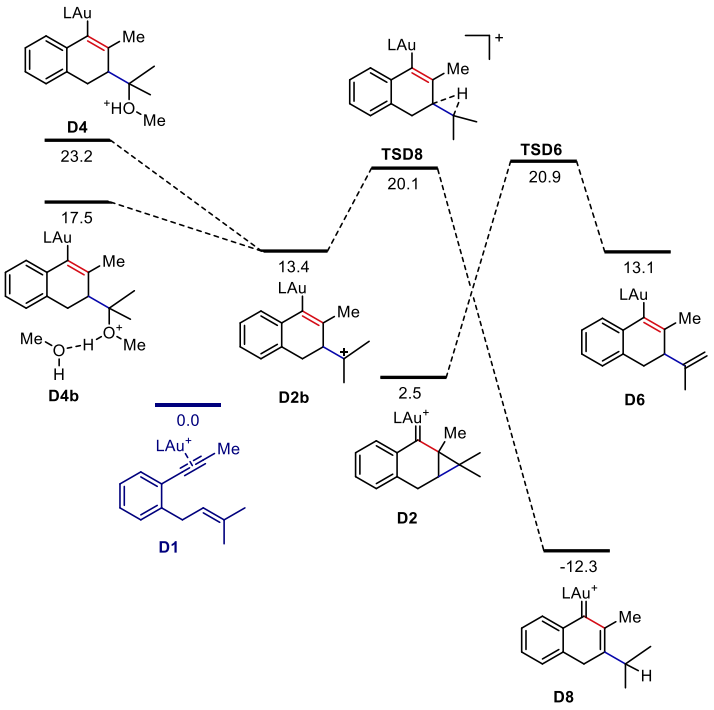


Scheme S18 - Discarded racemization pathway through reversible deprotonation in the chloroenyne cyclization. Free energy in kcal mol^{-1}.

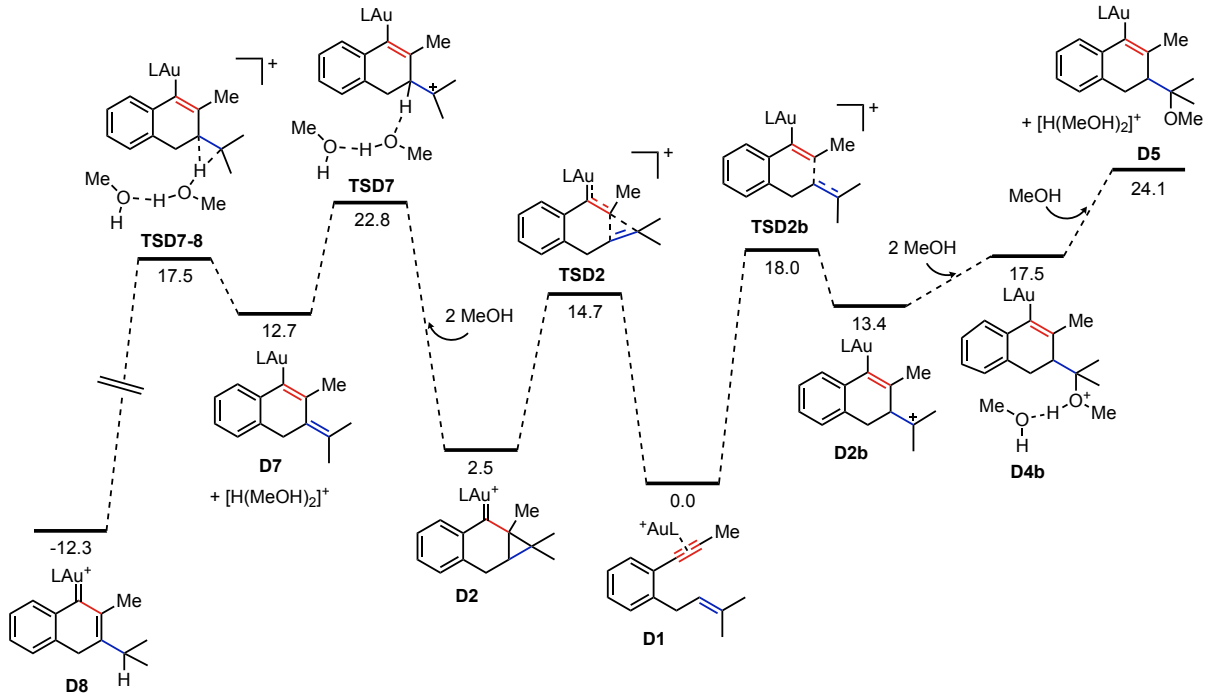


Scheme S19 - Pathway of racemization of **C2** through a reversible 1,2-H shift alongside outcompeted quenching pathways that require MeOH. Free energy in kcal mol^{-1}.

The evolution of methylenyne complex **D1** is analogous to phenylenyne complex **B1**, with its 1,2-hydride shift also being irreversible and forming the precursor to an experimentally observed naphthalene product (**Scheme S20**). A deprotonation pathway was also found not to be competitive (**Scheme S21**).



Scheme S20 - Gold(I)-catalyzed 6-*endo*-dig cyclization of methylenyne complex **B1** followed by MeOH-mediated nucleophilic attack or elimination. Free energy in kcal mol^{-1}.



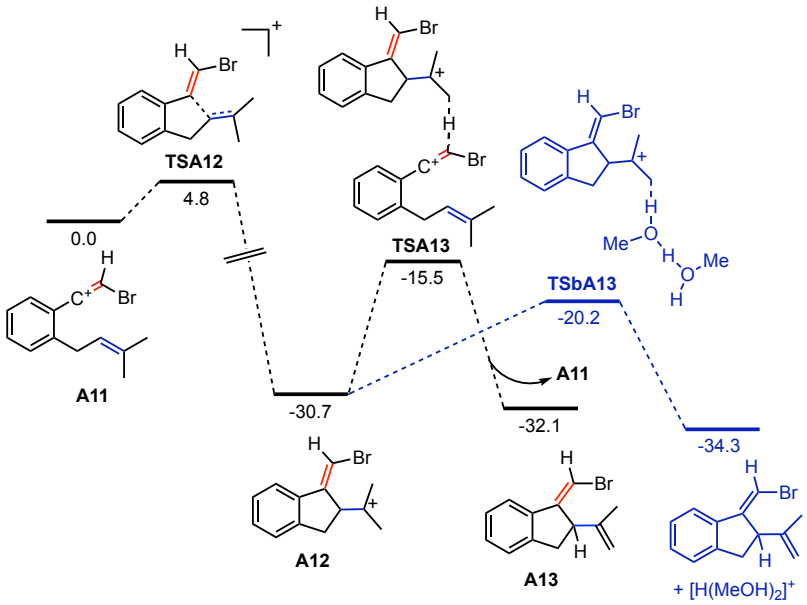
Scheme S21 - Discarded deprotonation pathway in the methylenyne cyclization. Free energy in kcal mol^{-1}.

9.10. Brønsted acid catalysis

Silver catalysis or Brønsted acid catalysis, with varying kinetics, could in principle form racemic products along the enantioenriched ones from the gold(I)-catalysed pathway. The former was disproven by experiments using a cationic version of the chiral catalyst, which showed high racemization of the elimination product regardless. Brønsted acid involvement has been found in isomerization of gold(I)-catalysed products, and such acidic protons are well-understood to originate from cationic intermediates such as **A2** or **A2b**.[32] It remained unclear

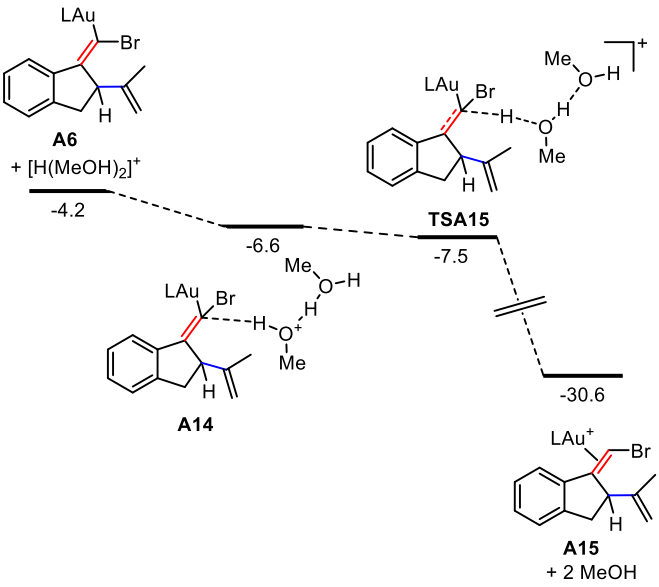
whether these protons could catalyse these same cycloisomerizations as gold(I), potentially explaining the formation of partially racemic product.

The Brønsted acid-catalysed cyclization was calculated, displaying low barriers for cyclization (**TSA12**) and moderately high barriers for proton transfer to the next enyne (**TSA13**). Nevertheless, the feasibility of this catalytic cycle does not depend exclusively on having accessible transition states: the reaction medium can intercept most of these intermediates. This is because even if all barriers are acceptable for 24 °C processes, all intermediates in this system are extremely acidic. As a consequence, the presence of traces of water or any suitable proton shuttles that would be protonated preferentially stop the chain reaction (Scheme **S17**, pathway shown in blue) – from the relative energies, even 10 mol% of MeOH (or water) would completely deprotonate these structures. In addition, proton catalysis would presumably also form the *Z* isomer of **A13**, as no major steric or electronic factors would impede the *Z*-type reactivity as opposed to gold(I) catalysis; this product was never found experimentally.



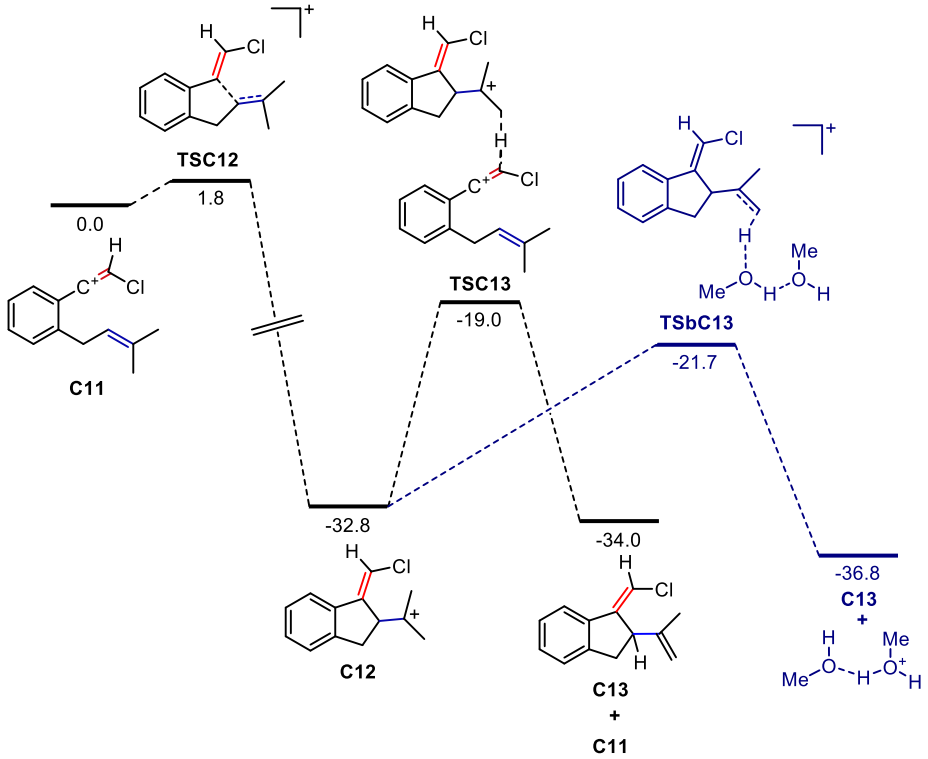
Scheme S22 - Mechanism of the proton-catalysed cyclization of bromoenynes. In blue, MeOH model for side-deprotonations. Free energy in kcal mol^{-1}.

Similarly, either intermediate **A12**, other protonated organic fragments, or the protonated traces of MeOH or water can protodemetallate the catalyst: the process is completely barrierless (**Scheme S23**). Hence, we conclude that the Brønsted acid-catalysed pathway is not competitive under the reaction conditions and cannot be responsible for the racemization.

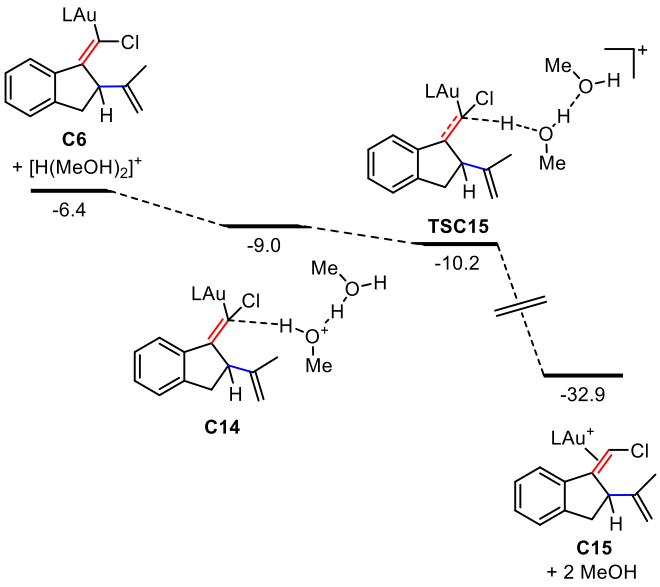


Scheme S23 - Mechanism of protodemetallation of a model vinylgold(I) intermediate. The potential energy of intermediate **A14** is lower than that of **TSA15**. Free energy in kcal mol^{-1}.

The same pathways were calculated with chloroenynes leading to the same overall mechanistic picture (**Schemes S24-25**).



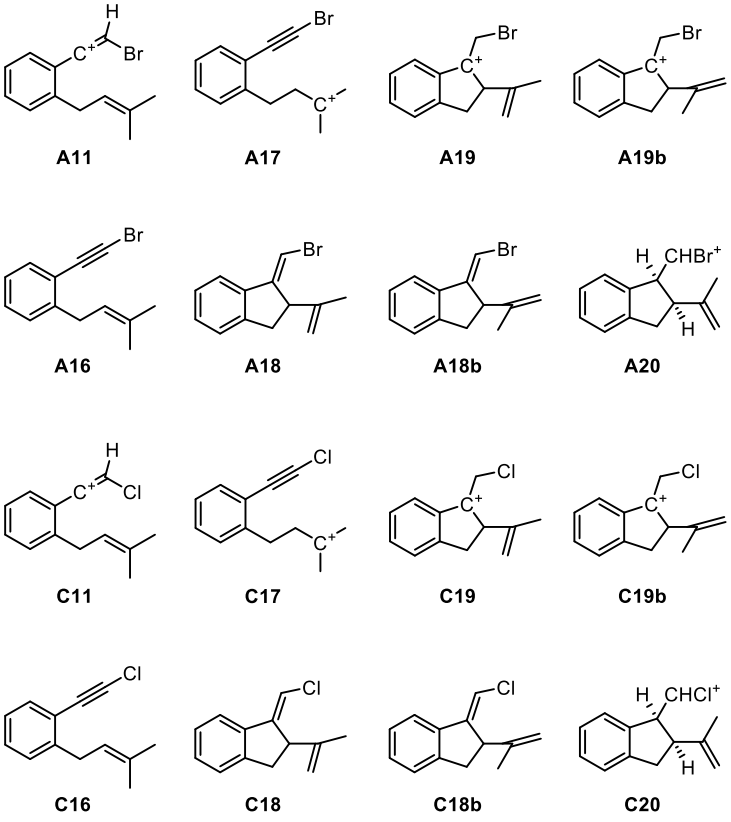
Scheme S24 - Mechanism of the proton-catalysed cyclization of chloroenynes. In blue, MeOH model for side-deprotonations. Free energy in kcal mol^{-1}.



Scheme S25- Mechanism of the protodemetallation of **C6** with the protonated MeOH dimer. **C14** has a lower electronic energy than **TSC15**. Free energy in kcal mol^{-1}.

Even if we ignore entropic contributions and consider the protonated MeOH tetramer to be the real speciation of the free proton, as the difference in energy between the two MeOH clusters is of only 3.2 kcal mol^{-1}, the greatest overall barrier for the protodemetallation would be of about 0.8 kcal mol^{-1} after adding the predissociation cost for the tetramer. This is an upper bound, however, as it is very likely that the dissociation of two neutral MeOH molecules can be aided by precoordination to **A6**. The model presented in **Scheme S25** is therefore our best proposal for protodemetallation in spite of simplifying the MeOH speciation in such a pK_a-sensitive process.

Several protonated intermediates were calculated (**Scheme S26**) and their energies collected in the "computed structures and energies" section below.



Scheme S26 -Structures of neutral and protonated haloenynes and of their cyclised products.

9.11. Computed structures and energies

Table S6 - Bromoenyne alkoxycyclizations and eliminations. B3LYP-D3/6-31G(d)+SDD(Au), PCM (CH_2Cl_2); HLT: B3LYP-D3/6-311+G(d,p)+SDD(Au), PCM (CH_2Cl_2)

Code	E / Hartree	G / Hartree	E_{HLT} / Hartree
A1	-1113.13464	-1112.85505	-1113.33394
A3	-1113.16085	-1112.87697	-1113.35242
A3b	-1113.14297	-1112.86204	-1113.33814
A2	-1113.15203	-1112.87100	-1113.34666
A2b	-1113.15711	-1112.87231	-1113.35191
A4	-1228.89794	-1228.56056	-1229.13569
A4b	-1344.65133	-1344.26485	-1344.93511
A4c	-1460.39336	-1459.95976	-1460.72359
A4d	-1576.14378	-1575.65734	-1576.51668
A6	-1112.73494	-1112.46477	-1112.93629
A8	-1113.16513	-1112.88273	-1113.35902
A10	-1228.89361	-1228.55740	-1229.13103
preA7	-1344.61378	-1344.23986	-1344.90405
A7	-1112.73530	-1112.46582	-1112.93477
A9	-1112.74134	-1112.47004	-1112.94073
A5	-1228.48931	-1228.16490	-1228.72711
A14	-1344.63822	-1344.25738	-1344.93044
A15	-1113.19126	-1112.90672	-1113.38766
TSA2	-1113.12555	-1112.84759	-1113.32251
TSA2b	-1113.14676	-1112.86582	-1113.34196
TSA6	-1344.61714	-1344.24224	-1344.90804
TSbA6	-1344.61393	-1344.24070	-1344.90529
TSA2b-8	-1113.12629	-1112.84641	-1113.32258
TSA10	-1228.89154	-1228.55600	-1229.13003

TSA7-8	-1344.60842	-1344.23315	-1344.89776
TSA9	-1344.62047	-1344.24575	-1344.91058
TSA3	-1113.11694	-1112.83725	-1113.31510
TSA3b	-1113.11387	-1112.83520	-1113.31128
TSA15	-1344.63477	-1344.26039	-1344.92535
TSpreA7	-1344.61275	-1344.23918	-1344.90365
TSA7	-1344.61311	-1344.23834	-1344.90298
A2b-D	-1113.15711	-1112.87585	-1113.35191
A8-D	-1113.16513	-1112.88630	-1113.35902
TSA2b-8-D	-1113.12629	-1112.84871	-1113.32258
preA7ipr	-1501.90603	-1501.42256	-1502.23841
A4ipr	-1307.54328	-1307.15276	-1307.80304
TSA7ipr	-1501.90518	-1501.42174	-1502.23782
TSpreA7ipr	-1501.90382	-1501.42212	-1502.23722
TSA6bipr	-1501.90414	-1501.42030	-1502.23777
TSA6ipr	-1501.90939	-1501.42551	-1502.24222
TSA7-8ipr	-1501.89894	-1501.41483	-1502.23054
A8jp	-2236.44404	-2235.65179	-2236.91715
TSA2b-8jp	-2236.40323	-2235.61477	-2236.87892
TSA6jp	-2467.89165	-2467.00786	-2468.46303
TSA9jp	-2467.89839	-2467.01455	-2468.46810

Table S7 - Protonated bromoenyne intermediates and Brønsted acid-mediated transition states. B3LYP-D3/6-31G(d) + SDD(Au), PCM (CH_2Cl_2); HLT: B3LYP-D3/6-311+G(d,p) + SDD(Au), PCM (CH_2Cl_2)

Code	E / Hartree	G / Hartree	E_{HLT} / Hartree
A16	-516.31696	-516.14242	-516.45851
A17	-516.72082	-516.53590	-516.85712
A11	-516.72827	-516.54188	-516.86144

A18	-516.37653	-516.19633	-516.51479
A19	-516.79350	-516.60236	-516.92398
A20	-516.73515	-516.54532	-516.86982
A18b	-516.37763	-516.19733	-516.51546
A19b	-516.79434	-516.60182	-516.92502
A12	-516.78248	-516.59236	-516.91401
TSA12	-516.72587	-516.53840	-516.85840
TSA13	-1033.10169	-1032.71809	-1033.37085
TSbA13	-748.25503	-747.96901	-748.48143

Table S8- Phenylenyne alkoxycyclizations and eliminations. B3LYP-D3/6-31G(d) + SDD(Au), PCM (CH_2Cl_2); HLT: B3LYP-D3/6-311+G(d,p) + SDD(Au), PCM (CH_2Cl_2)

Code	E / Hartree	G / Hartree	E_{HLT} / Hartree
B1	-1331.64504	-1331.27826	-1331.90458
B3	-1331.64125	-1331.27105	-1331.89583
B2	-1331.65775	-1331.28456	-1331.90880
B2b	-1331.63523	-1331.26629	-1331.89011
B8	-1331.67977	-1331.30850	-1331.93166
B4	-1447.37601	-1446.95076	-1447.67393
B4b	-1563.13038	-1562.65696	-1563.47366
B6_cisoid	-1331.21994	-1330.86035	-1331.48095
B6_transoid	-1331.22127	-1330.86192	-1331.48298
B7	-1331.22638	-1330.86796	-1331.48606
B5	-1446.96615	-1446.55378	-1447.26415
TSB3	-1331.62799	-1331.26163	-1331.88449
TSB2	-1331.63013	-1331.26334	-1331.88611
TSB2b	-1331.62457	-1331.25726	-1331.88005
TSB2b-8	-1331.62122	-1331.25306	-1331.87751

TSB6 cisoid	-1563.10236	-1562.63992	-1563.45354
TSB6 transoid	-1563.10346	-1562.64033	-1563.45480
TSbB6	-1563.09951	-1562.63848	-1563.44953
TSB7-8	-1562.11162	-1562.64878	-1563.46140
TSB7	-1563.10227	-1562.63887	-1563.45150

Table S9 - Chloroenyne alkoxycyclizations and eliminations. B3LYP-D3/6-31G(d)+SDD(Au), PCM (CH_2Cl_2); HLT: B3LYP-D3/6-311+G(d,p)+SDD(Au), PCM (CH_2Cl_2)

Code	E / Hartree	G / Hartree	E_{HLT} / Hartree
C1	-1560.14643	-1559.86888	-1560.37830
C3	-1560.18199	-1559.89613	-1560.40628
C3b	-1560.16403	-1559.88029	-1560.39169
C2	-1560.17308	-1559.88862	-1560.40030
C2b	-1560.17286	-1559.88678	-1560.40026
C4	-1675.91807	-1675.57925	-1676.18875
C4b	-1791.67123	-1791.28355	-1791.98796
C4c	-1907.41313	-1906.97808	-1907.77634
C4d	-2023.16365	-2022.67571	-2023.56949
C6_cisoid	-1559.75412	-1559.48183	-1559.98850
C6_transoid	-1559.75482	-1559.48245	-1559.98881
C8	-1560.18681	-1559.90162	-1560.41331
C10	-1675.91375	-1675.57617	-1676.18426
C7	-1559.75527	-1559.48331	-1559.98782
C9	-1559.76242	-1559.48939	-1559.99477
C5	-1675.50909	-1675.18282	-1675.77993
C14	-1791.65686	-1791.27443	-1791.98223
C15	-1560.21018	-1559.92433	-1560.43908
TSC2	-1560.14277	-1559.86317	-1560.37236

TSC2b	-1560.16750	-1559.88431	-1560.39539
TSC6	-1791.63640	-1791.25956	-1791.96037
TSbC6	-1791.63343	-1791.25962	-1791.95780
TSC2b-8	-1560.14674	-1559.86547	-1560.37569
TSC10	-1675.91278	-1675.57558	-1676.18394
TSC7-8	-1791.63036	-1791.25372	-1791.95271
TSC9	-1791.64228	-1791.26483	-1791.96524
TSC3	-1560.13509	-1559.85529	-1560.36582
TSC3b	-1560.13246	-1559.85246	-1560.36249
TSC15	-1791.65321	-1791.27806	-1791.97682
TSC7	-1791.63207	-1791.25345	-1791.95430

Table S10 - Protonated chloroenyne intermediates and Brønsted acid-mediated transition states. B3LYP-D3/6-31G(d) + SDD(Au), PCM (CH_2Cl_2); HLT: B3LYP-D3/6-311+G(d,p) + SDD(Au), PCM (CH_2Cl_2)

Code	E / Hartree	G / Hartree	E_{HLT} / Hartree
C16	-963.33602	-963.15979	-963.50938
C17	-963.73963	-963.55263	-963.90782
C11	-963.74652	-963.55842	-963.91134
C18	-963.39829	-963.21625	-963.56847
C19	-963.81138	-963.61815	-963.97405
C20	-963.75392	-963.56475	-963.92030
C18b	-963.39948	-963.21746	-963.56929
C19b	-963.81198	-963.61738	-963.97495
C12	-963.80394	-963.61202	-963.96737
TSC12	-963.74527	-963.55611	-963.90954
TSC13	-1927.14080	-1926.75340	-1927.47410
TSbC13	-1195.27656	-1194.98874	-1195.53486

Table S11- Methylenyne alkoxycyclizations and eliminations. B3LYP-D3/6-31G(d)+SDD(Au), PCM (CH_2Cl_2); HLT: B3LYP-D3/6-311+G(d,p)+SDD(Au), PCM (CH_2Cl_2)

Code	E / Hartree	G / Hartree	E_{HLT} / Hartree
D1	-1139.89809	-1139.58126	-1140.11037
D3	-1139.89339	-1139.57114	-1140.09979
D2	-1139.91008	-1139.58564	-1140.11405
D2b	-1139.88461	-1139.56456	-1140.09218
D8	-1139.93143	-1139.60784	-1140.13669
D4	-1255.62729	-1255.24846	-1255.87768
D4b	-1371.38163	-1370.95431	-1371.67760
D6_cisoid	-1139.47123	-1139.16037	-1139.68441
D6_transoid	-1139.47432	-1139.16448	-1139.68781
D7	-1139.47544	-1139.16614	-1139.68769
D5	-1255.21765	-1254.85216	-1255.46802
TSD3	-1139.88036	-1139.56214	-1140.08883
TSD2	-1139.88003	-1139.56107	-1140.08910
TSD2b	-1139.87572	-1139.55626	-1140.08435
TSD2b-8	-1139.87139	-1139.55275	-1140.08015
TSD6 cisoid	-1371.35259	-1370.93902	-1371.65597
TSD6 transoid	-1371.35520	-1370.94143	-1371.65866
TSbD6	-1371.35143	-1370.93871	-1371.65372
TSD7-8	-1371.36185	-1370.94787	-1371.66429
TSD7	-1371.35291	-1370.93952	-1371.65521

Table S12- MeOH and isopropanol clusters, neutral and protonated. B3LYP-D3/6-31G(d) + SDD(Au), PCM (CH_2Cl_2); HLT: B3LYP-D3/6-311+G(d,p) + SDD(Au), PCM (CH_2Cl_2). MeOH clusters named as (p)mNX, where p = protonated, N = number of MeOH units, X is a specific conformation or bonding arrangement.

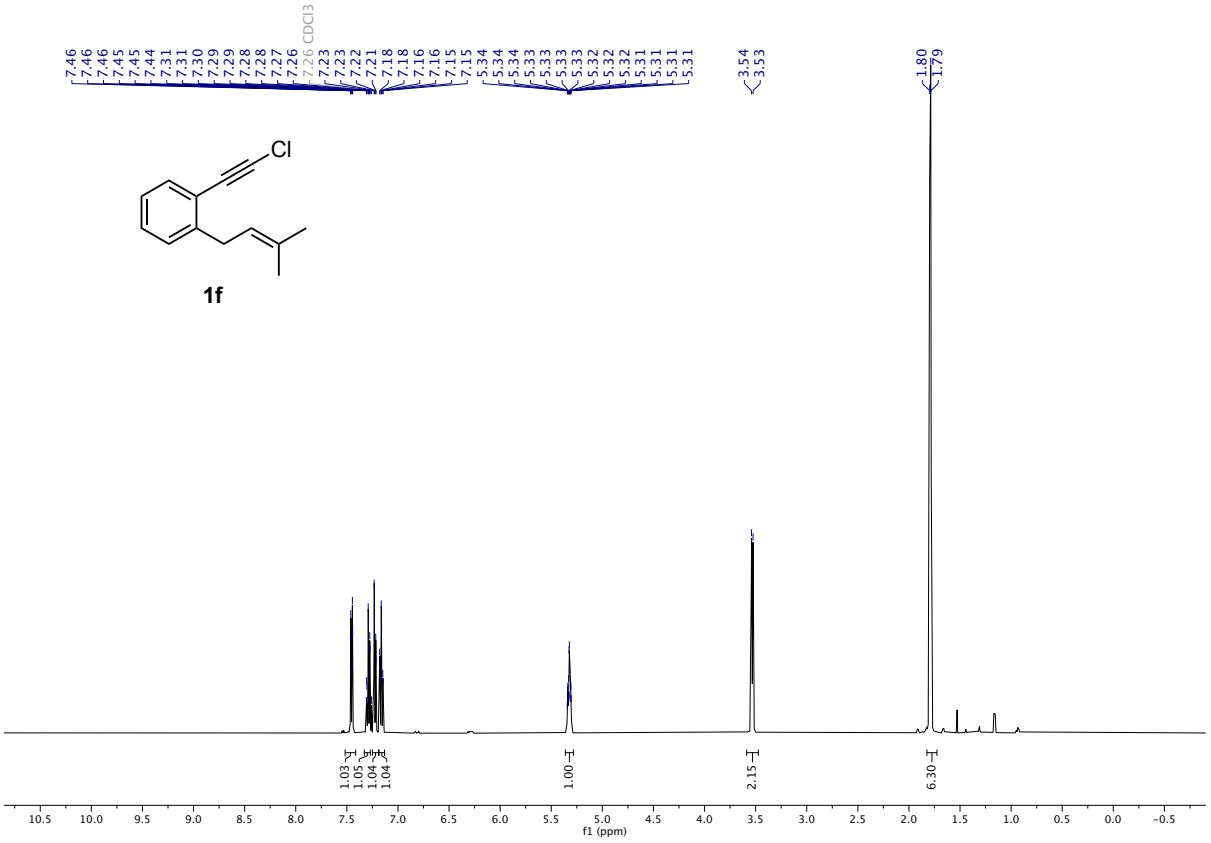
Code	E / Hartree	G / Hartree	E_{HLT} / Hartree
iPrOH	-194.36003	-194.27882	-194.43549
H(iPrOH)2	-389.15998	-388.96869	-389.29922

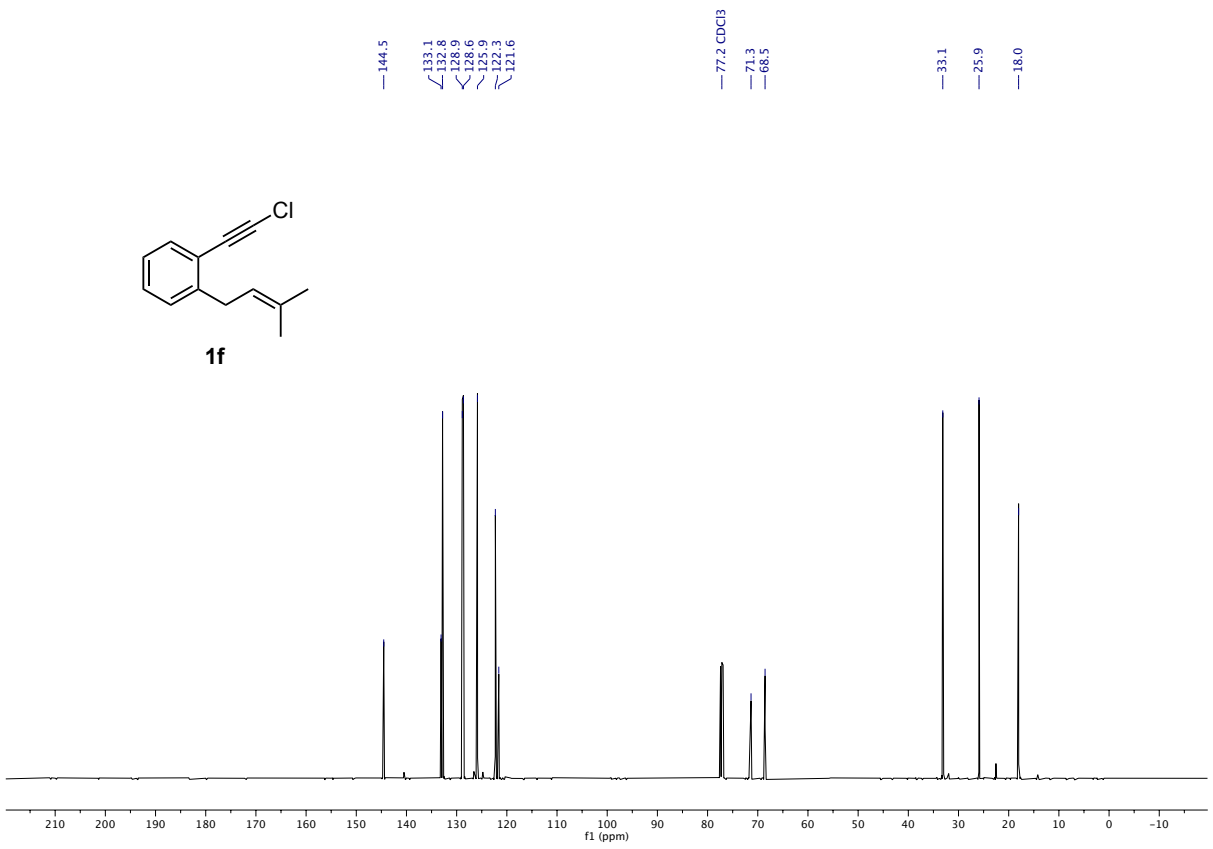
m1	-115.71753	-115.68892	-115.77095
m2a	-231.44894	-231.37568	-231.55089
m3Aa	-347.18581	-347.06447	-347.33398
m3Ab	-347.18621	-347.06409	-347.33379
m3Ba	-347.19120	-347.06844	-347.33560
m4Aa	-462.91964	-462.75266	-463.11603
m4Ab	-462.91704	-462.75296	-463.11435
m4Ac	-462.92175	-462.75309	-463.11616
m4Ad	-462.92134	-462.75161	-463.11660
m4Ae	-462.91962	-462.75287	-463.11618
m4Ba	-462.92093	-462.74893	-463.11537
m4Ca	-462.93417	-462.76548	-463.12630
m4Cb	-462.93455	-462.76452	-463.12622
m4Cc	-462.93485	-462.76428	-463.12651
m6	-694.40525	-694.14719	-694.69483
pm1	-116.11177	-116.07015	-116.16045
pm2a	-231.86924	-231.78377	-231.96507
pm2b	-231.86908	-231.78287	-231.96504
pm3Aa	-347.61601	-347.48003	-347.75928
pm3Ab	-347.61657	-347.48011	-347.75989
pm3Ba1	-347.61374	-347.48034	-347.75549
pm3Ba2	-347.61320	-347.47791	-347.75495
pm4Aa1	-463.35503	-463.17494	-463.54641
pm4Aa2	-463.34621	-463.16431	-463.53760
pm4Ab1	-463.35576	-463.17747	-463.54614
pm4Ab2	-463.35748	-463.17519	-463.54711
pm4Ac1	-463.35554	-463.17566	-463.54653
pm4Ac2	-463.34644	-463.16171	-463.53742

pm4Ad1	-463.35676	-463.17462	-463.54672
pm4Ad2	-463.32905	-463.14892	-463.52242
pm4Ae1	-463.35834	-463.17867	-463.54821
pm4Ba	-463.34349	-463.16137	-463.53559
pm4Ca	-463.36402	-463.17992	-463.55165
pm4Cb1	-463.36299	-463.17870	-463.55030
pm4Cb2	-463.36399	-463.18046	-463.55162
pm4Cc	-463.36431	-463.18178	-463.55191
pm6	-694.84076	-694.56696	-695.12572

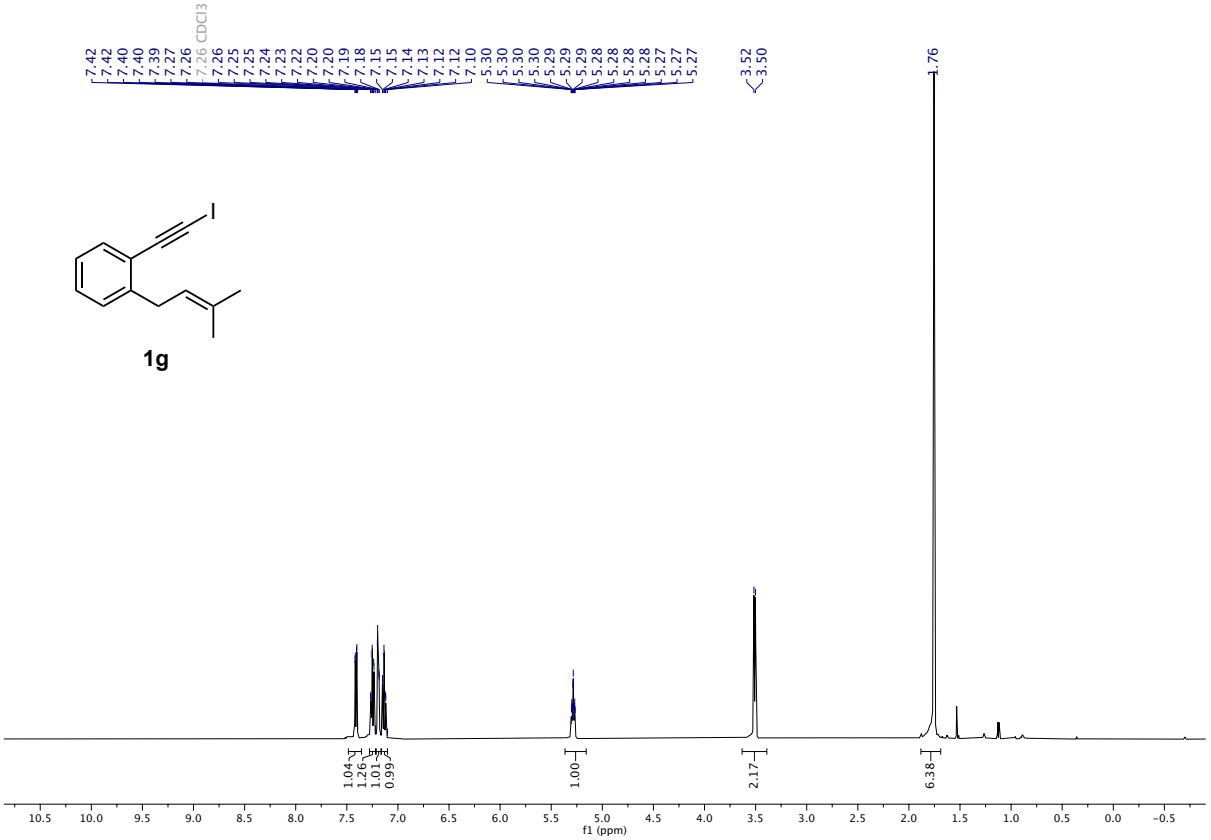
10. NMR spectra, SFC and HPLC traces

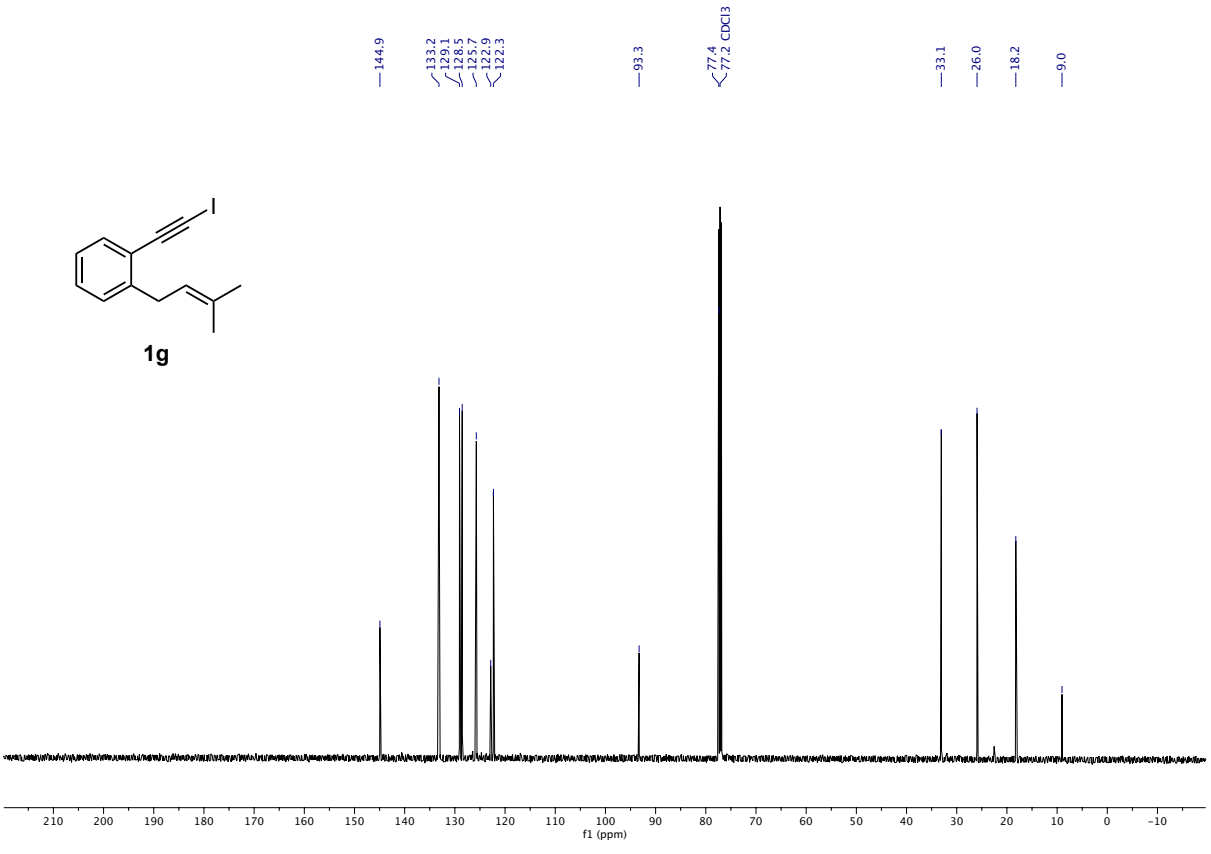
1-(Chloroethynyl)-2-(3-methylbut-2-en-1-yl)benzene (1f)



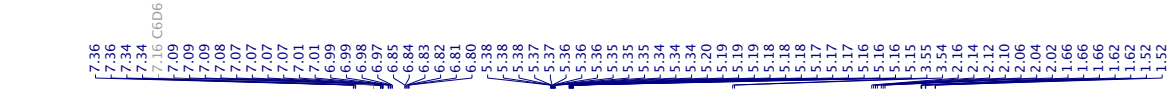

144.5
133.1
132.8
128.9
128.6
125.9
122.3
121.6
77.2 CDCl3
71.3
68.5
33.1
25.9
18.0
Cl
1f
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

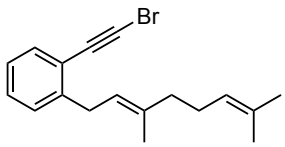
1-(Iodoethynyl)-2-(3-methylbut-2-en-1-yl)benzene (1g)



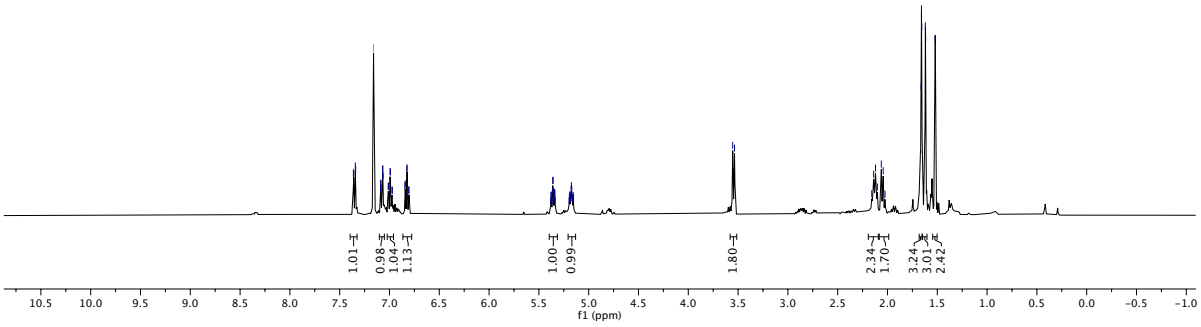


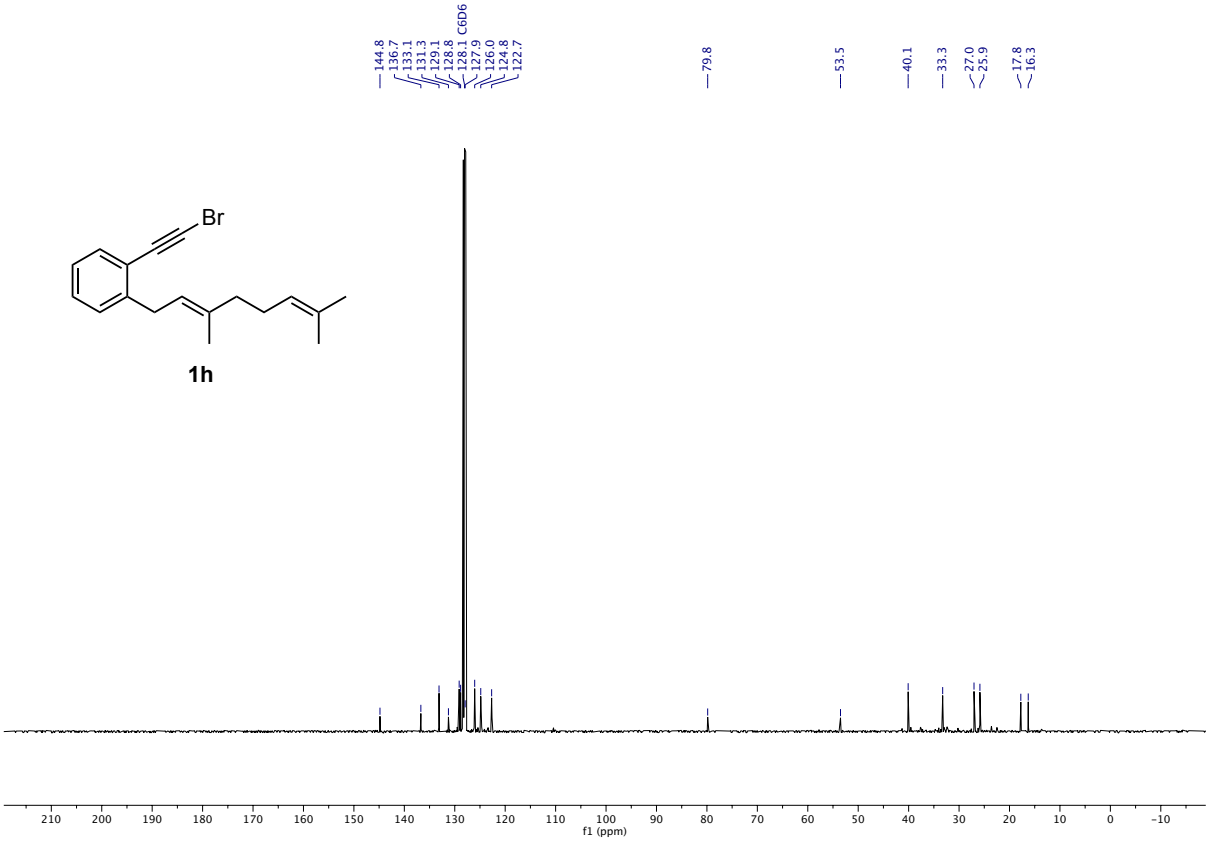
(*E*)-1-(Bromoethynyl)-2-(3,7-dimethylocta-2,6-dien-1-yl)benzene (1h)





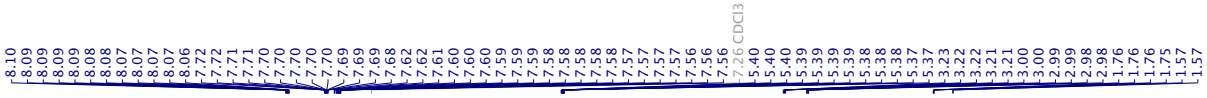
1h

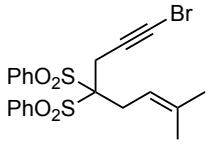




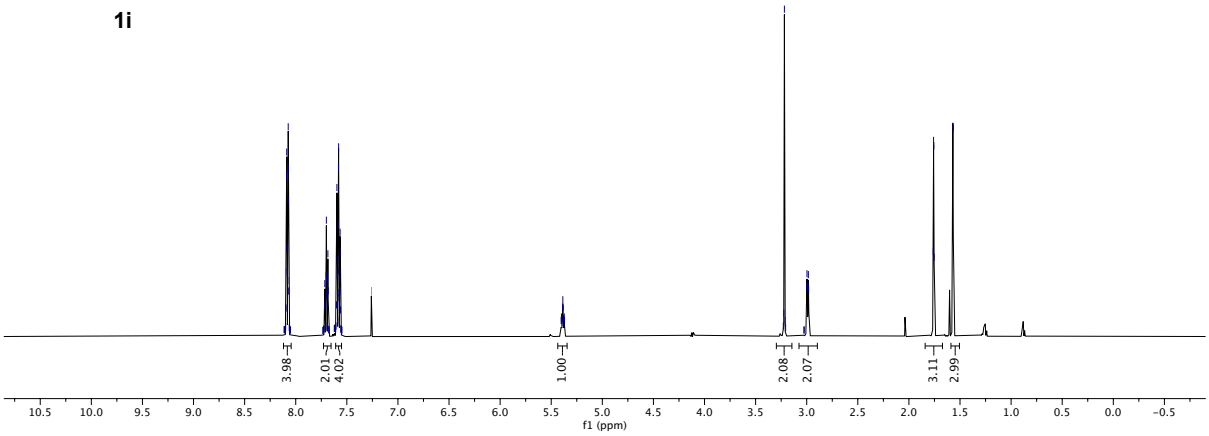
1h

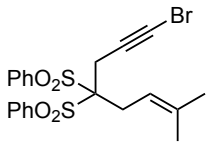
(1-Bromo-7-methyloct-6-en-1-yne-4,4-diyldisulfonyl)dibenzene (1i)





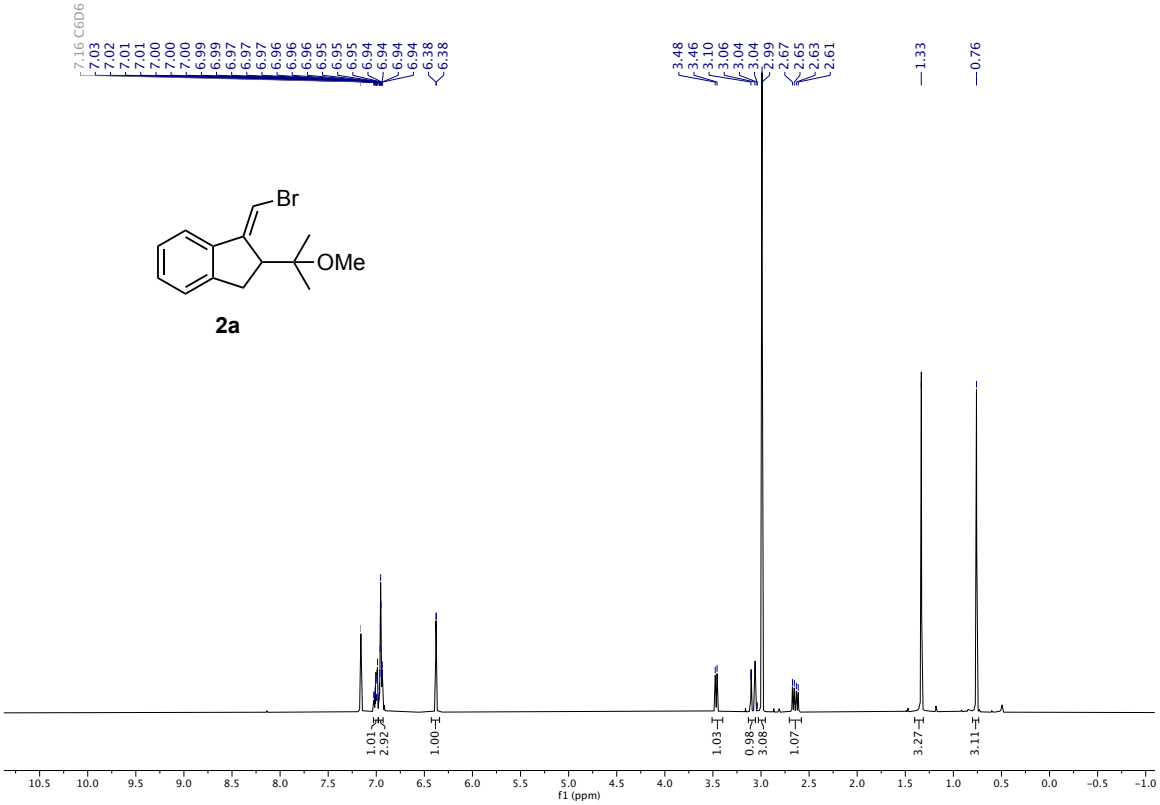
1i

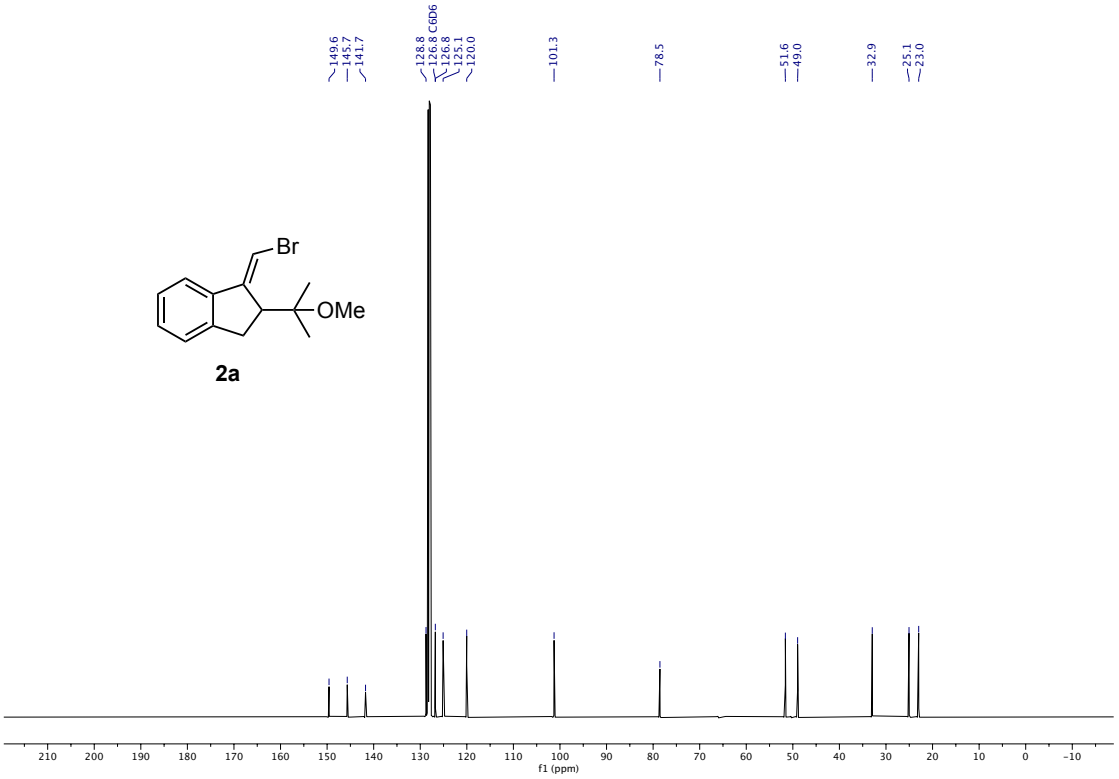




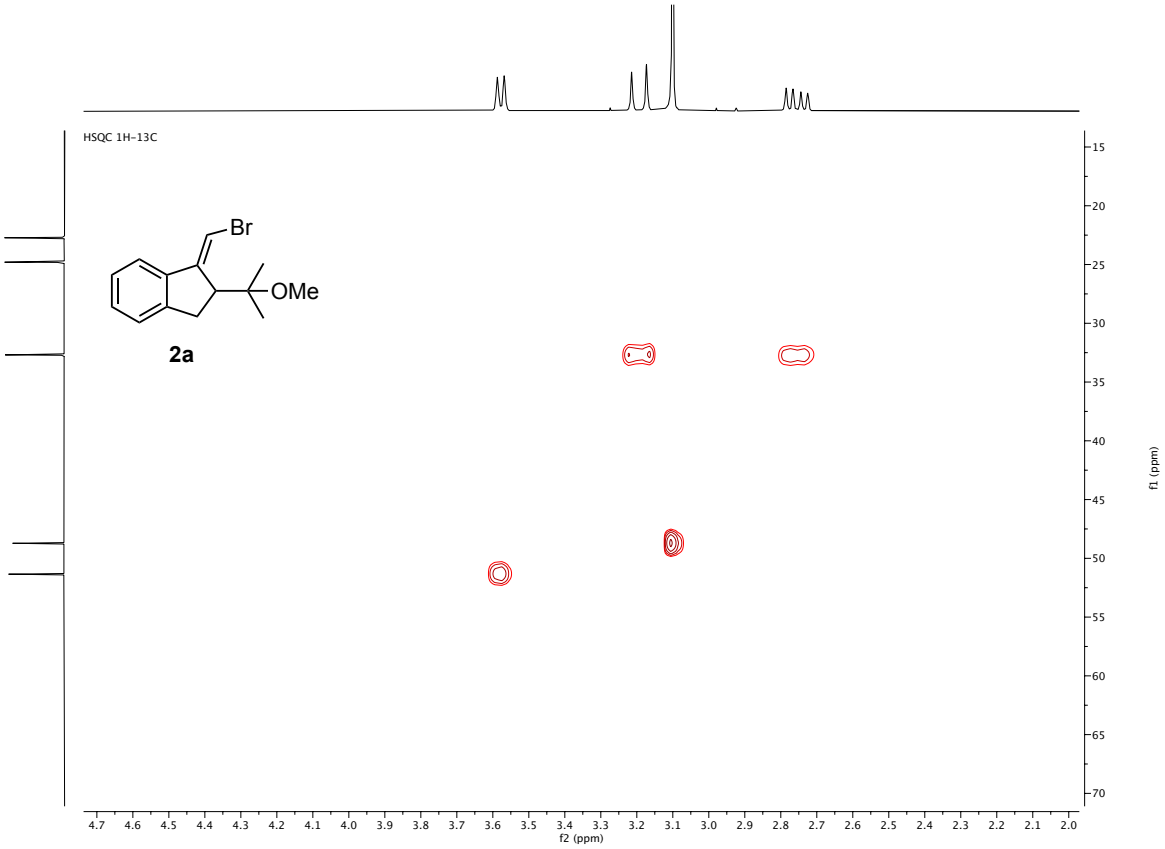
1i

(*S,E*)-1-(Bromomethylene)-2-(2-methoxypropan-2-yl)-2,3-dihydro-1*H*-indene (2a)

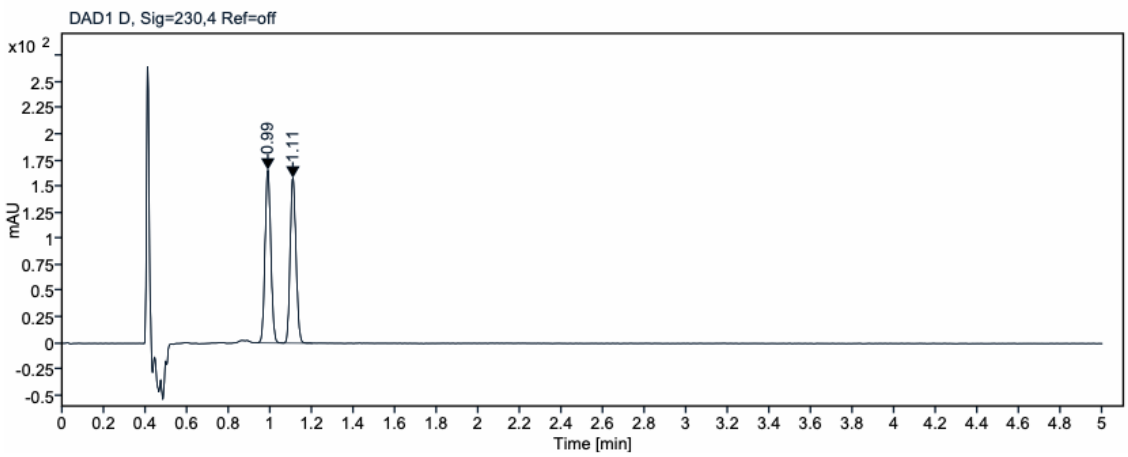




HSQC



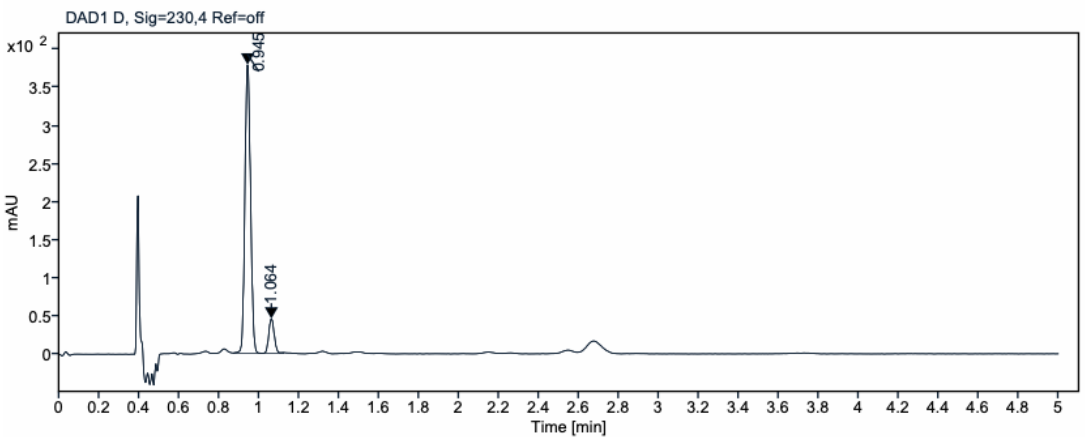
SFC racemic **2a**



Signal: DAD1 D, Sig=230,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
0.990	BB	0.0302	322.6286	165.6839	51.0808	
1.110	BV R	0.0303	308.9757	158.1593	48.9192	
		Sum	631.6043			

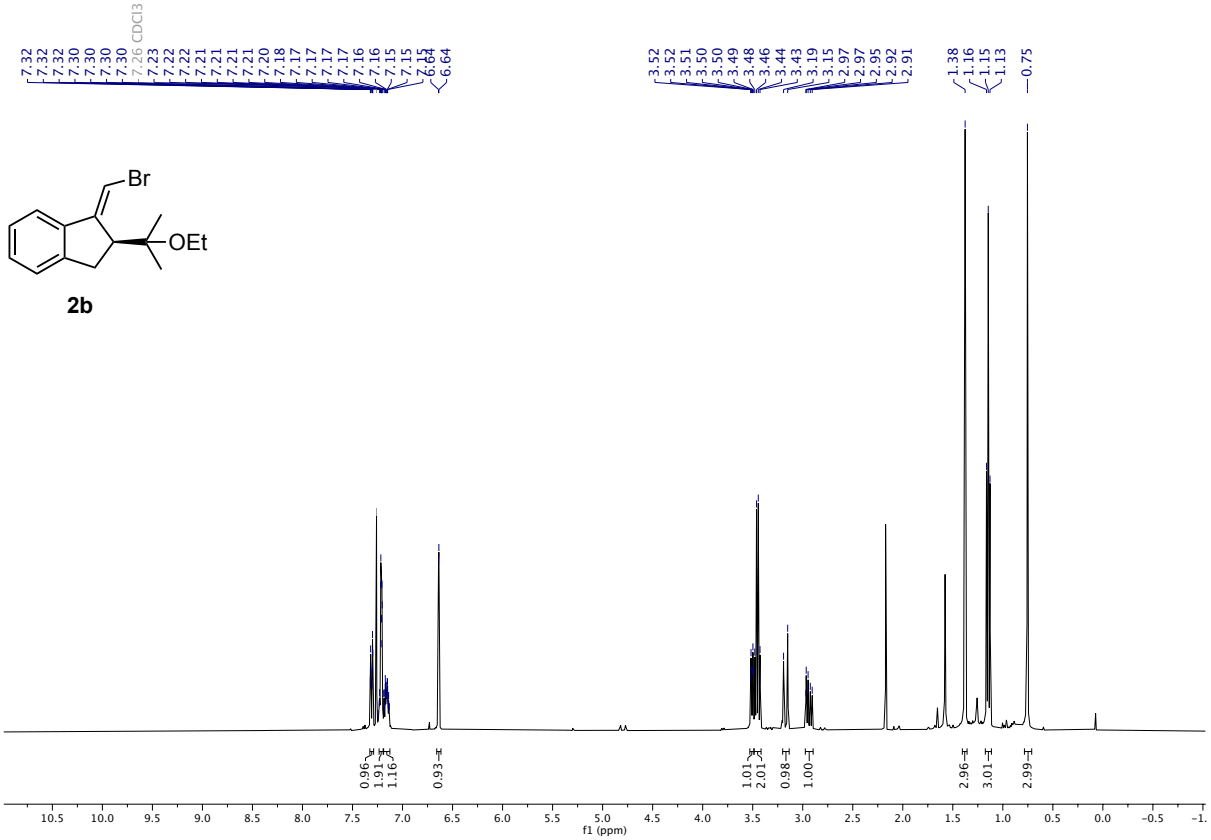
SFC enantioenriched **2a**



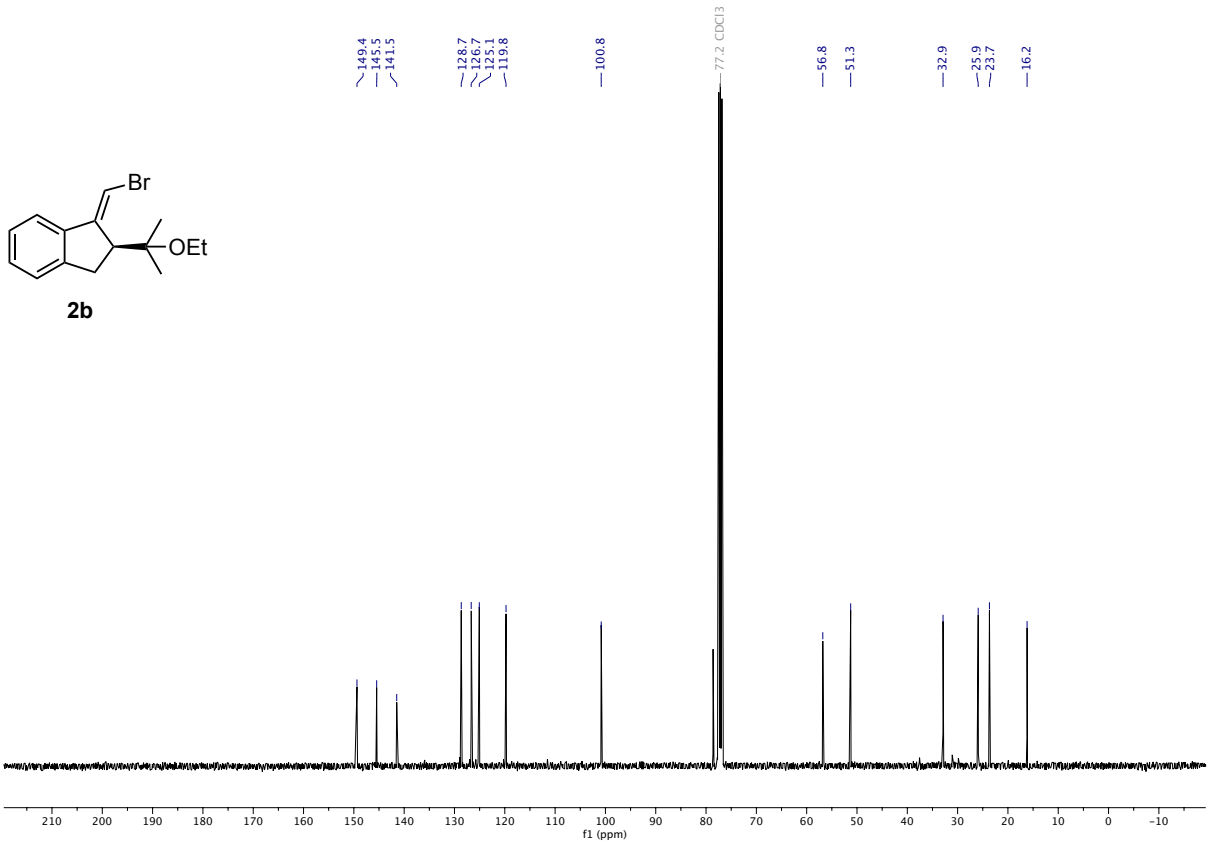
Signal: DAD1 D, Sig=230,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
0.945	MM	0.0328	747.0959	379.5270	89.5409	
1.064	MM	0.0319	87.2665	45.5315	10.4591	
		Sum	834.3625			

(*S,E*)-1-(Bromomethylene)-2-(2-ethoxypropan-2-yl)-2,3-dihydro-1*H*-indene (2b)

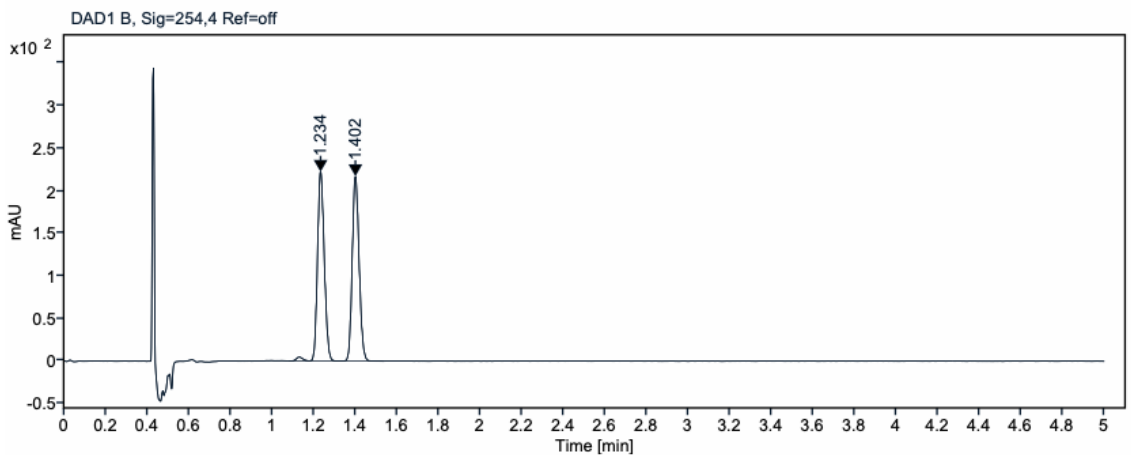


2b



2b

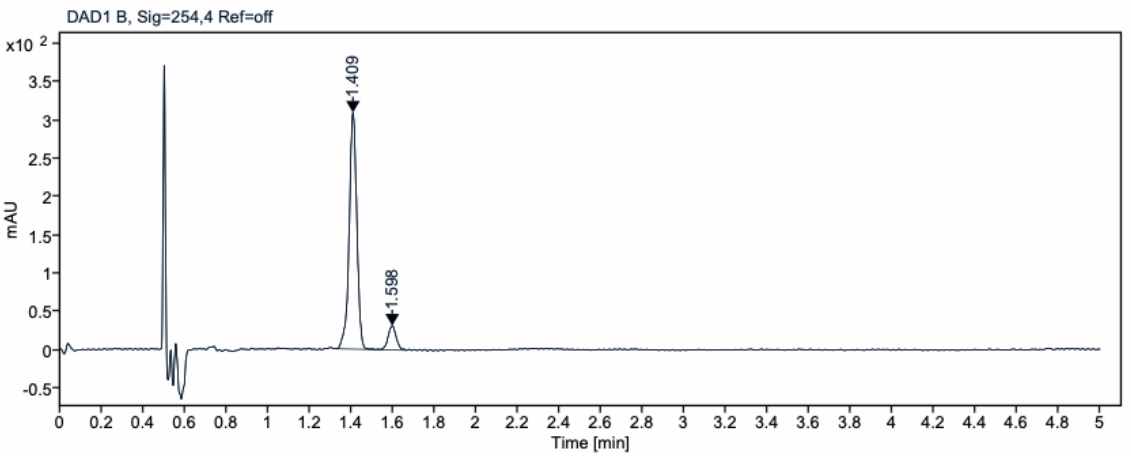
SFC racemic **2b**



Signal: DAD1 B, Sig=254,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
1.234	VB R	0.0348	511.7739	222.1886	50.5976	
1.402	BV R	0.0359	499.6845	217.0972	49.4024	
		Sum	1011.4585			

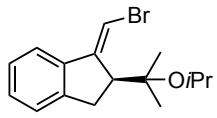
SFC enantioenriched **2b**



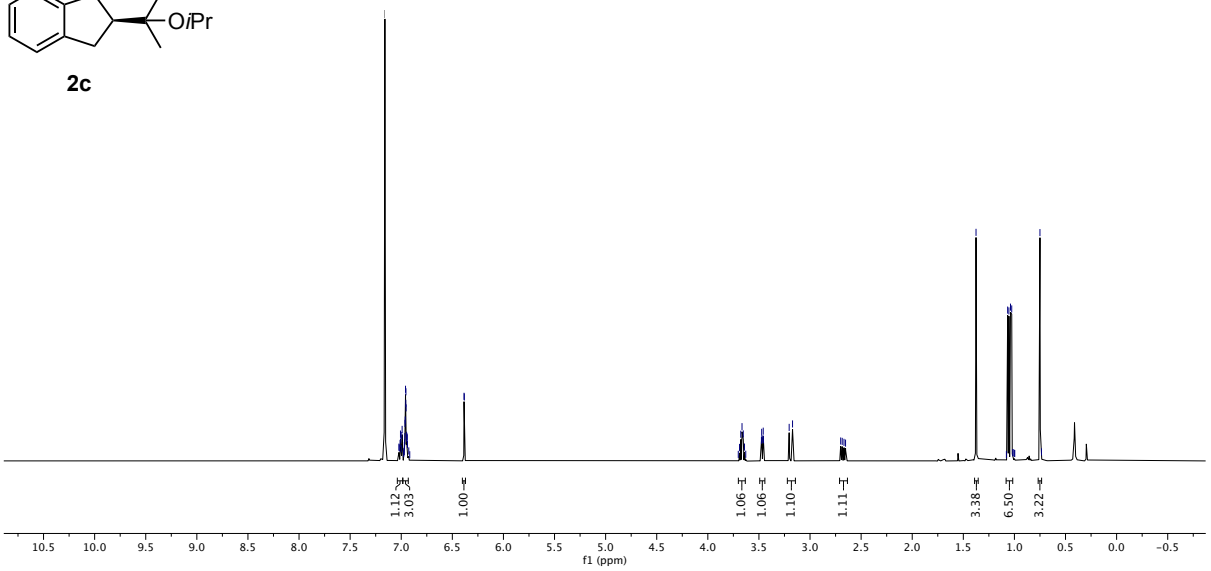
Signal: DAD1 B, Sig=254,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
1.409	BV R	0.0394	791.3926	308.7930	90.1459	
1.598	VV R	0.0425	86.5090	31.4973	9.8541	
		Sum	877.9016			

(*S*,*E*)-1-(Bromomethylene)-2-(2-isopropoxypropan-2-yl)-2,3-dihydro-1*H*-indene (2c)

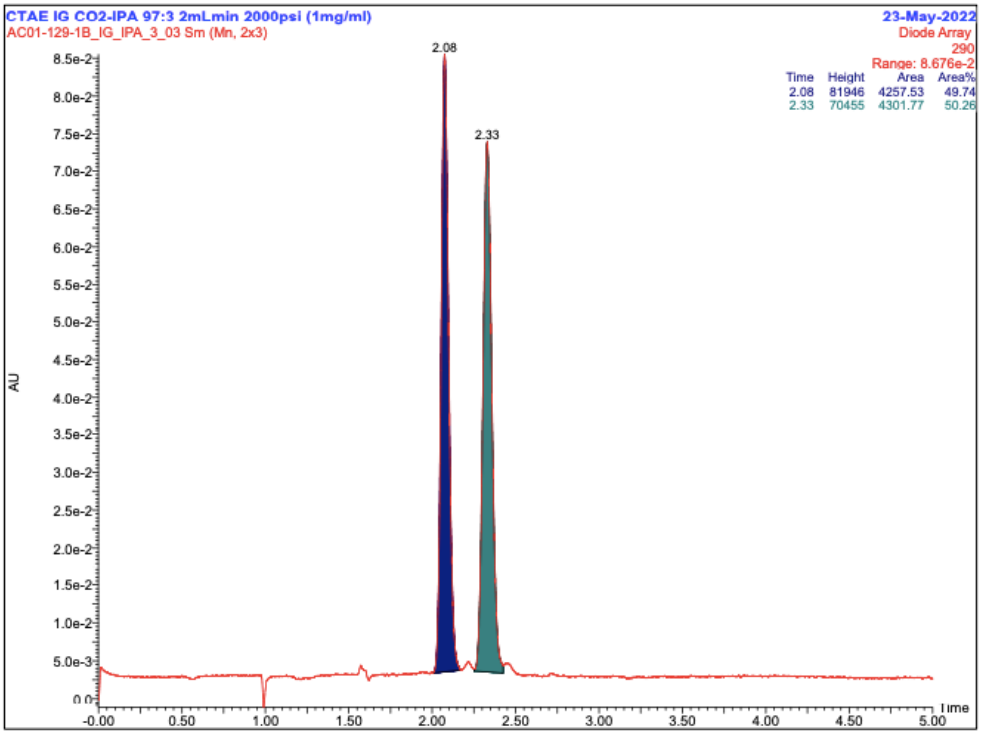


2c

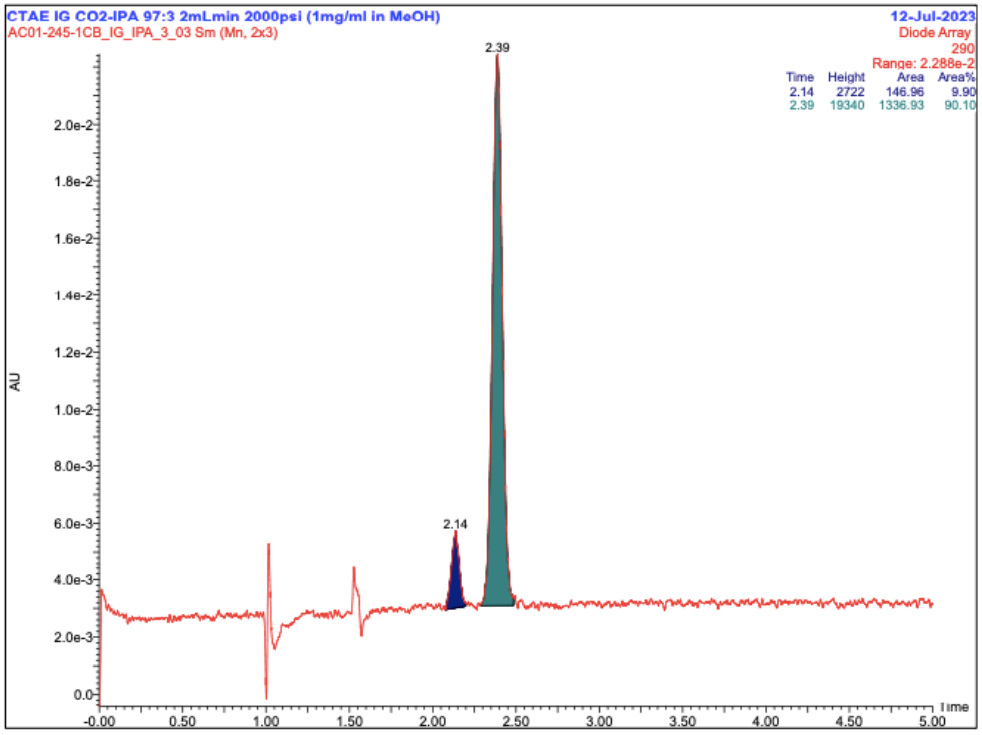


2c

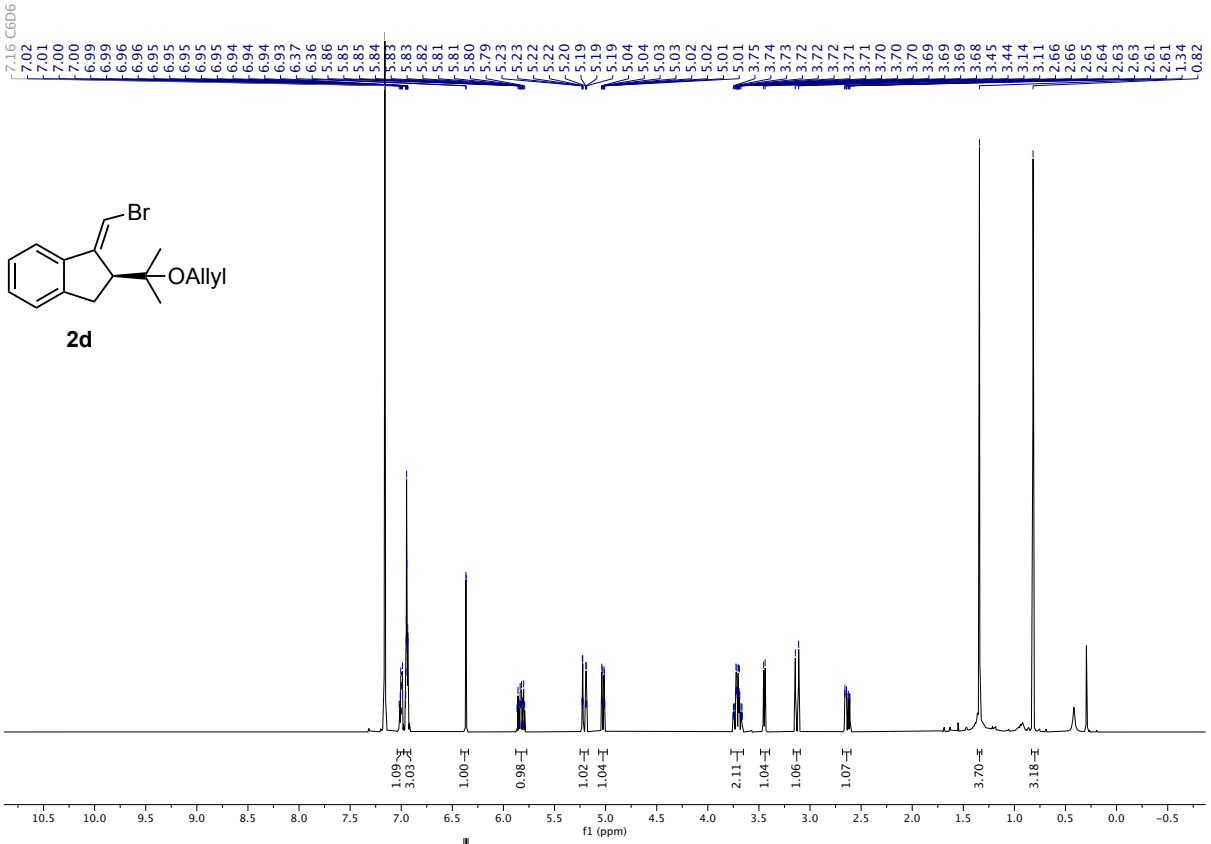
SFC racemic **2c**

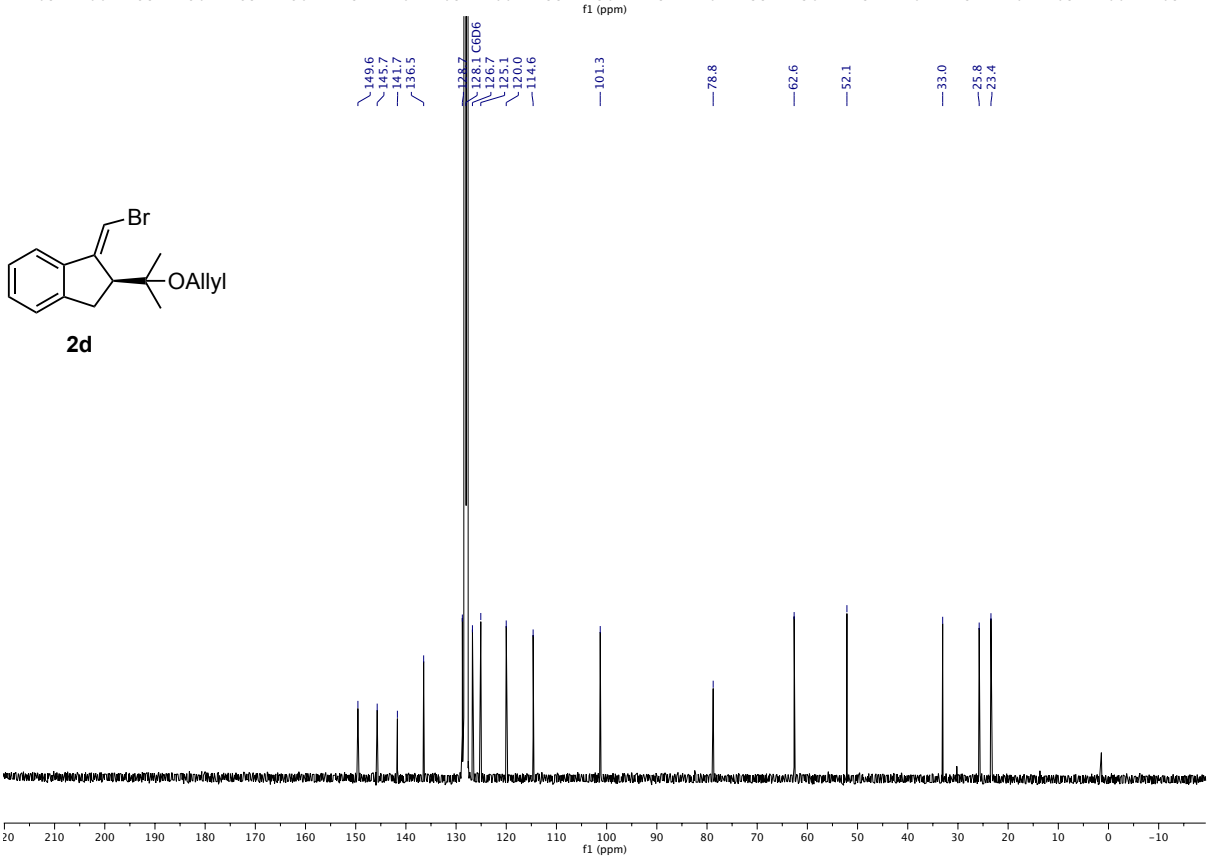


SFC enantioenriched **2c**

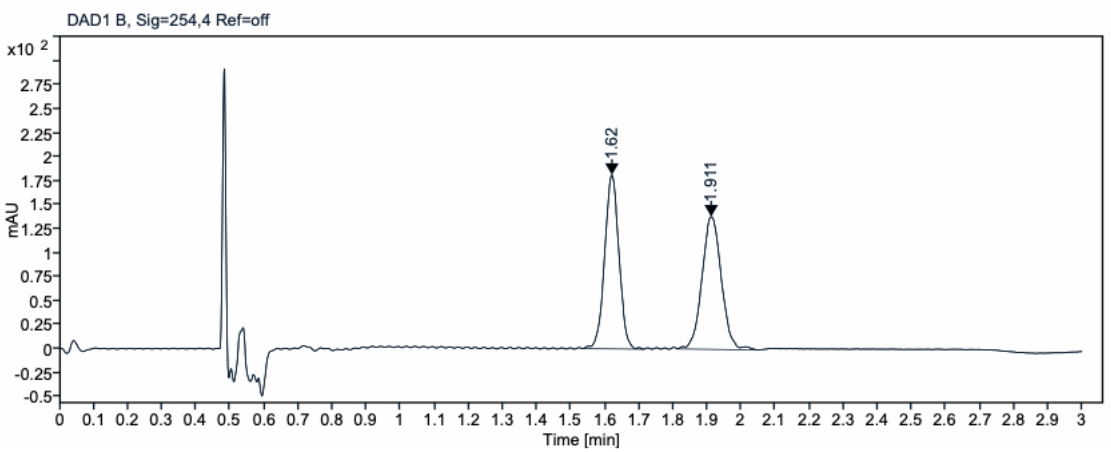


(*S,E*)-2-(2-(Allyloxy)propan-2-yl)-1-(bromomethylene)-2,3-dihydro-1*H*-indene (2d)





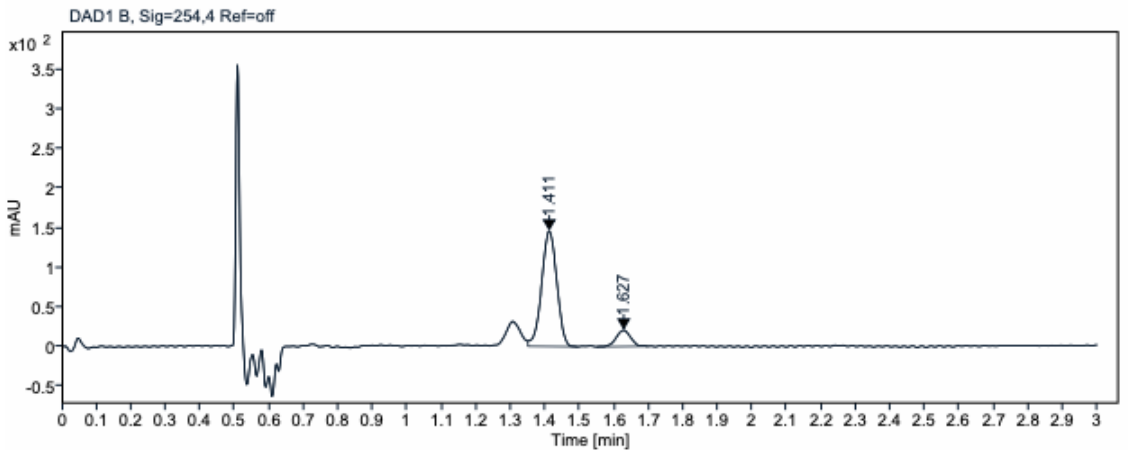
SFC racemic **2d**



Signal: DAD1 B, Sig=254,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
1.620	VV R	0.0456	530.4476	181.3040	49.2463	
1.911	VV R	0.0592	546.6832	138.2796	50.7537	
		Sum	1077.1307			

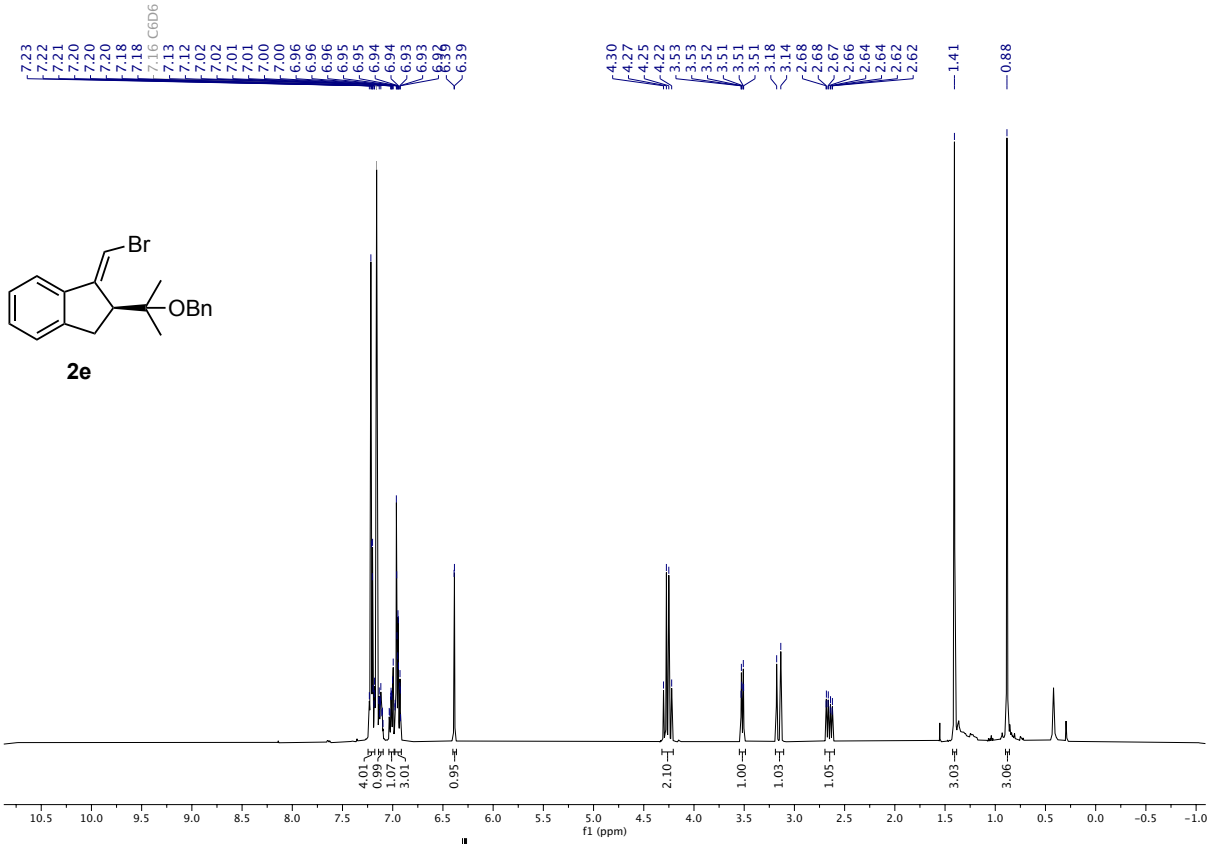
SFC enantioenriched **2d**

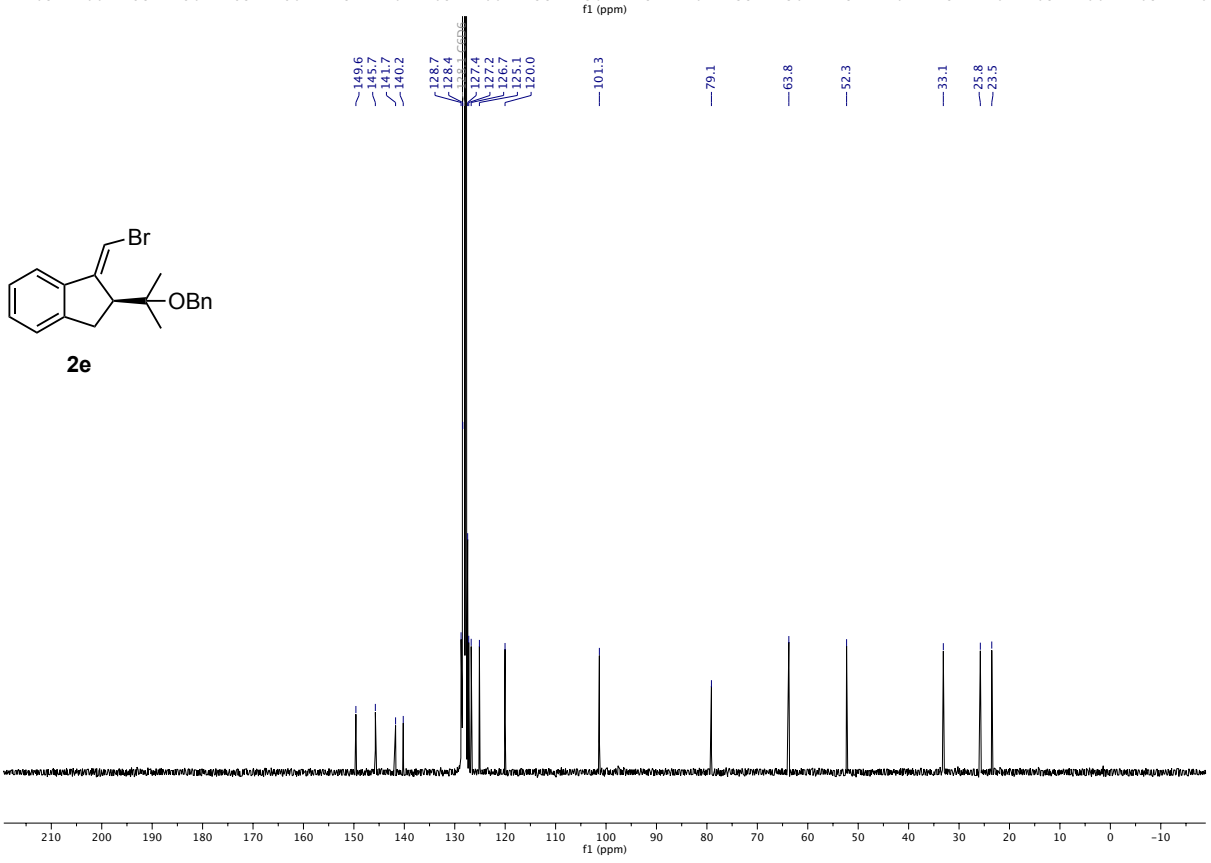


Signal: DAD1 B, Sig=254,4 Ref=off

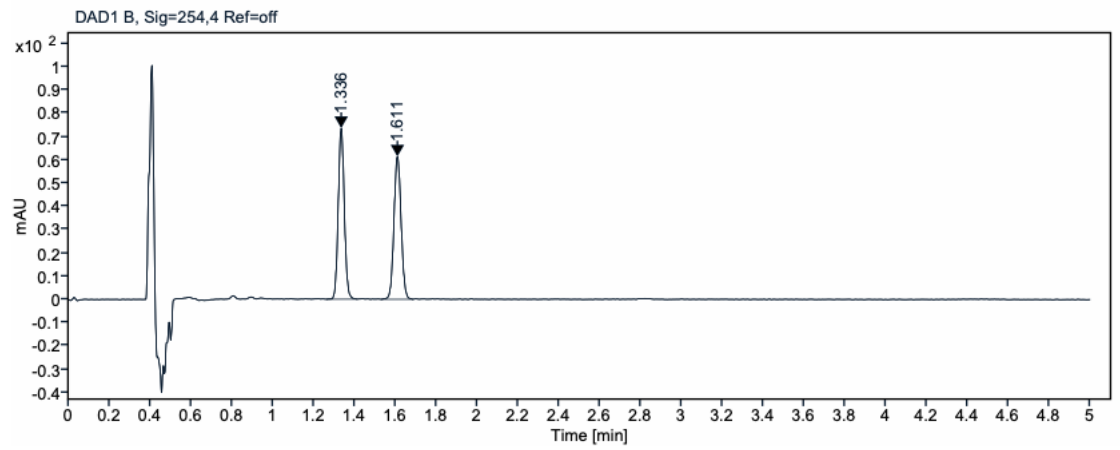
RT [min]	Type	Width [min]	Area	Height	Area%	Name
1.411	VB	0.0482	446.4383	145.8975	88.1009	
1.627	VV R	0.0457	60.2970	20.5658	11.8991	
		Sum	506.7353			

(*S*,*E*)-2-(2-(Benzyloxy)propan-2-yl)-1-(bromomethylene)-2,3-dihydro-1*H*-indene (2e)





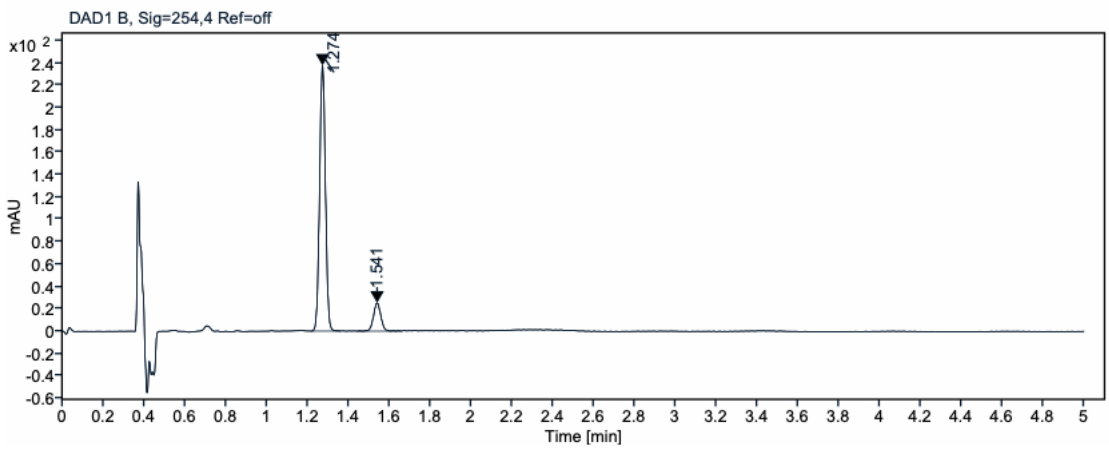
SFC racemic **2e**



Signal: DAD1 B, Sig=254,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
1.336	BB	0.0321	152.2652	73.5601	50.3723	
1.611	BB	0.0380	150.0143	61.3826	49.6277	
		Sum	302.2795			

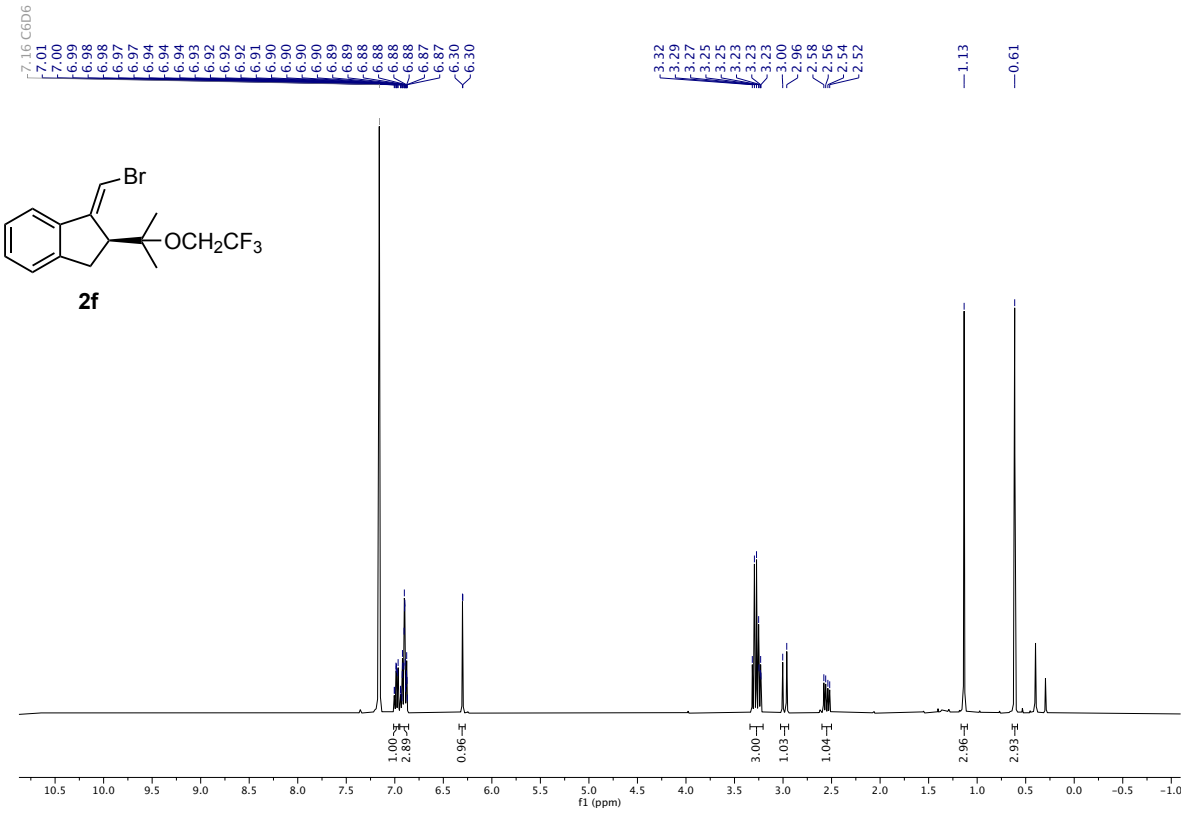
SFC enantioenriched **2e**

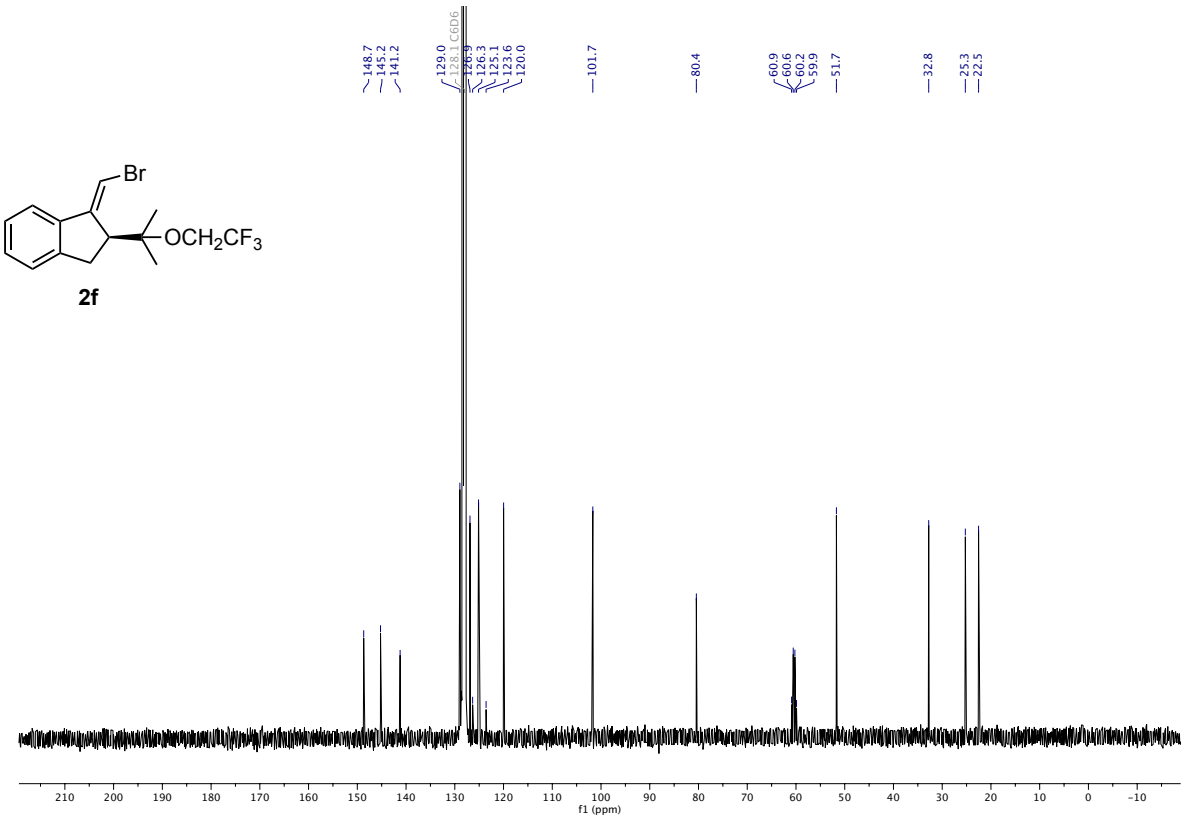


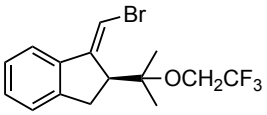
Signal: DAD1 B, Sig=254,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
1.274	BV R	0.0306	470.5033	237.3411	88.0987	
1.541	VV R	0.0390	63.5606	25.1775	11.9013	
		Sum	534.0639			

(*S*,*E*)-1-(Bromomethylene)-2-(2-(2,2,2-trifluoroethoxy)propan-2-yl)-2,3-dihydro-1*H*-indene (2f)

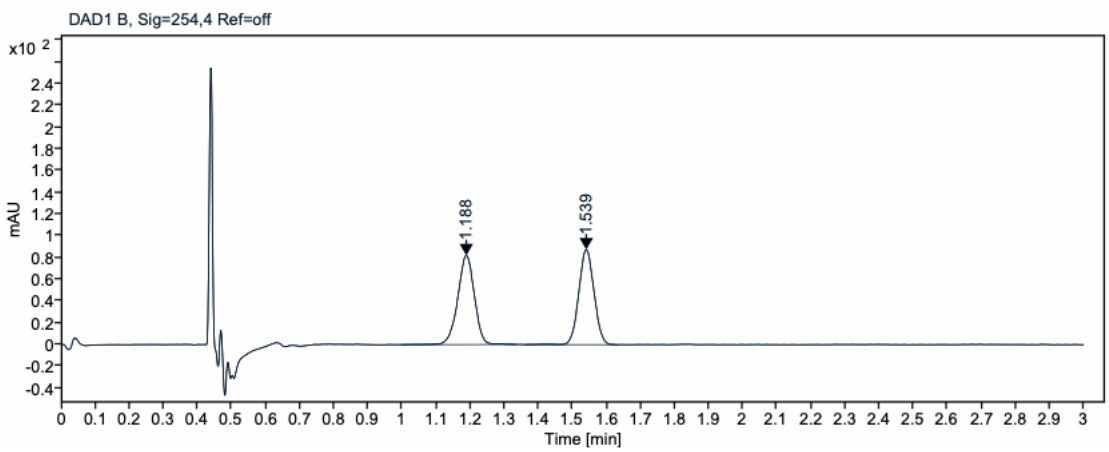






2f

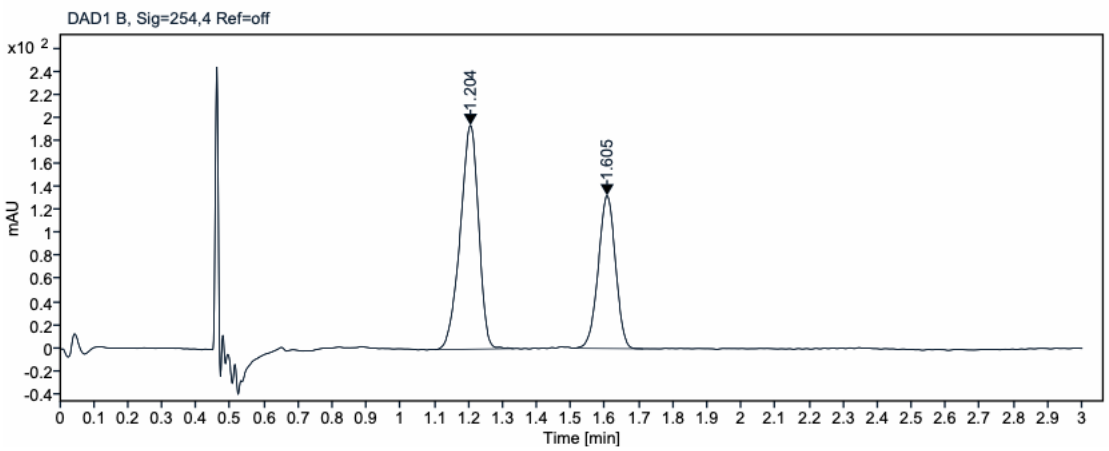
SFC racemic **2f**



Signal: DAD1 B, Sig=254,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
1.188	VV R	0.0518	279.5270	81.9931	50.6221	
1.539	VB R	0.0484	272.6572	87.4622	49.3779	
		Sum	552.1842			

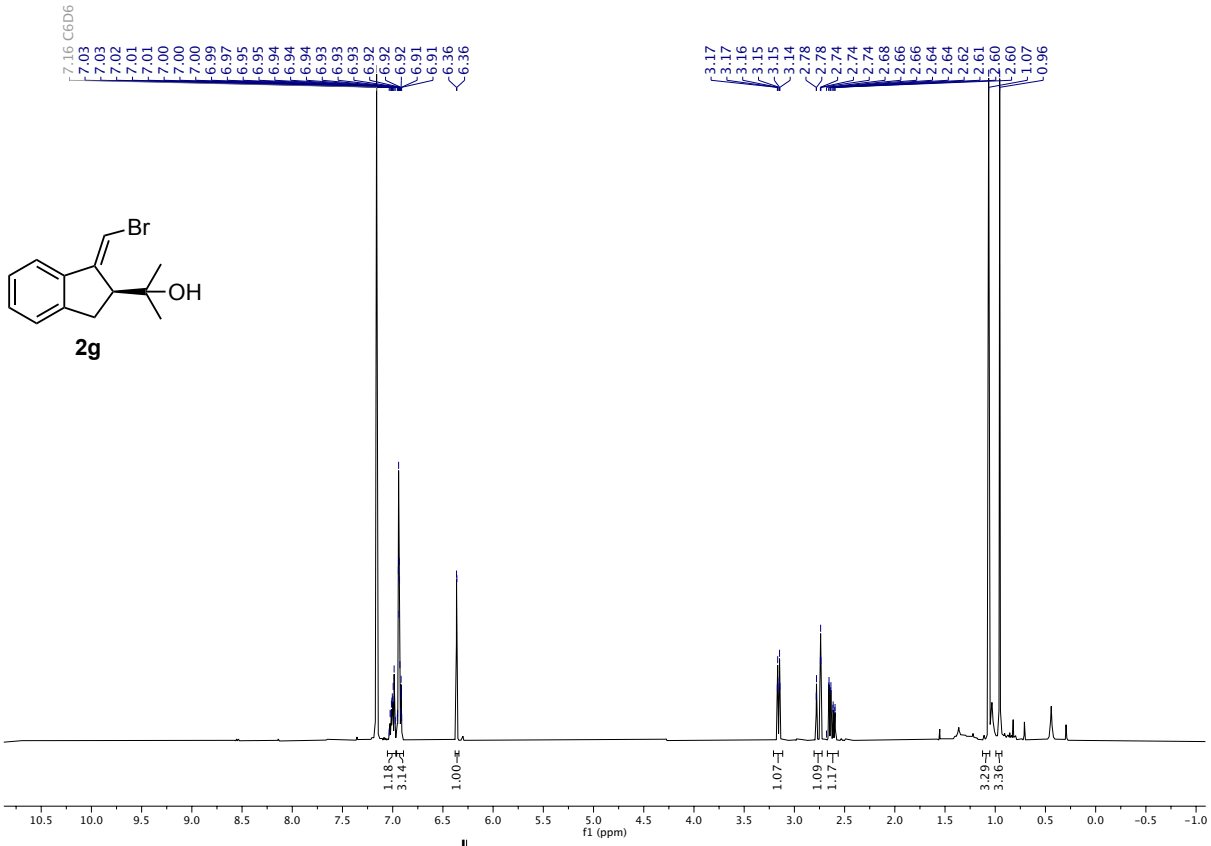
SFC enantioenriched **2f**

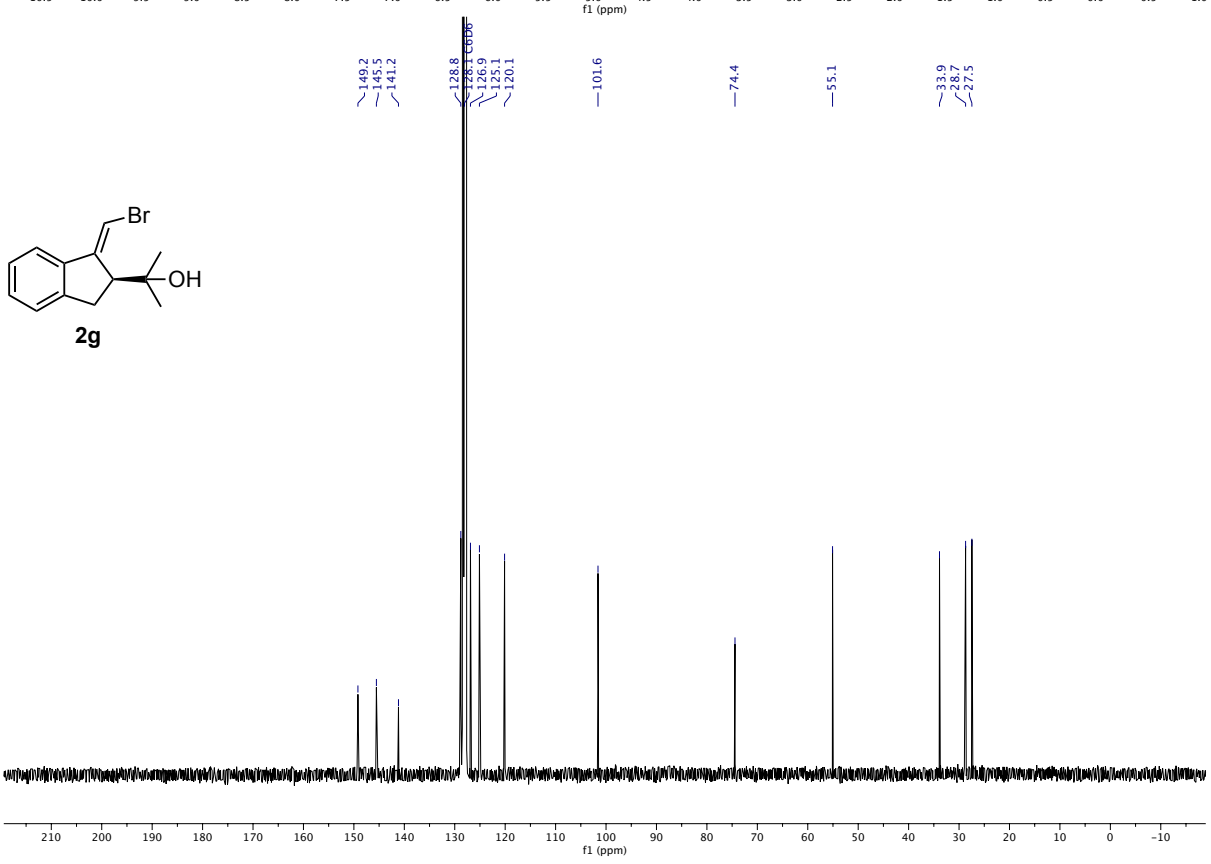


Signal: DAD1 B, Sig=254,4 Ref=off

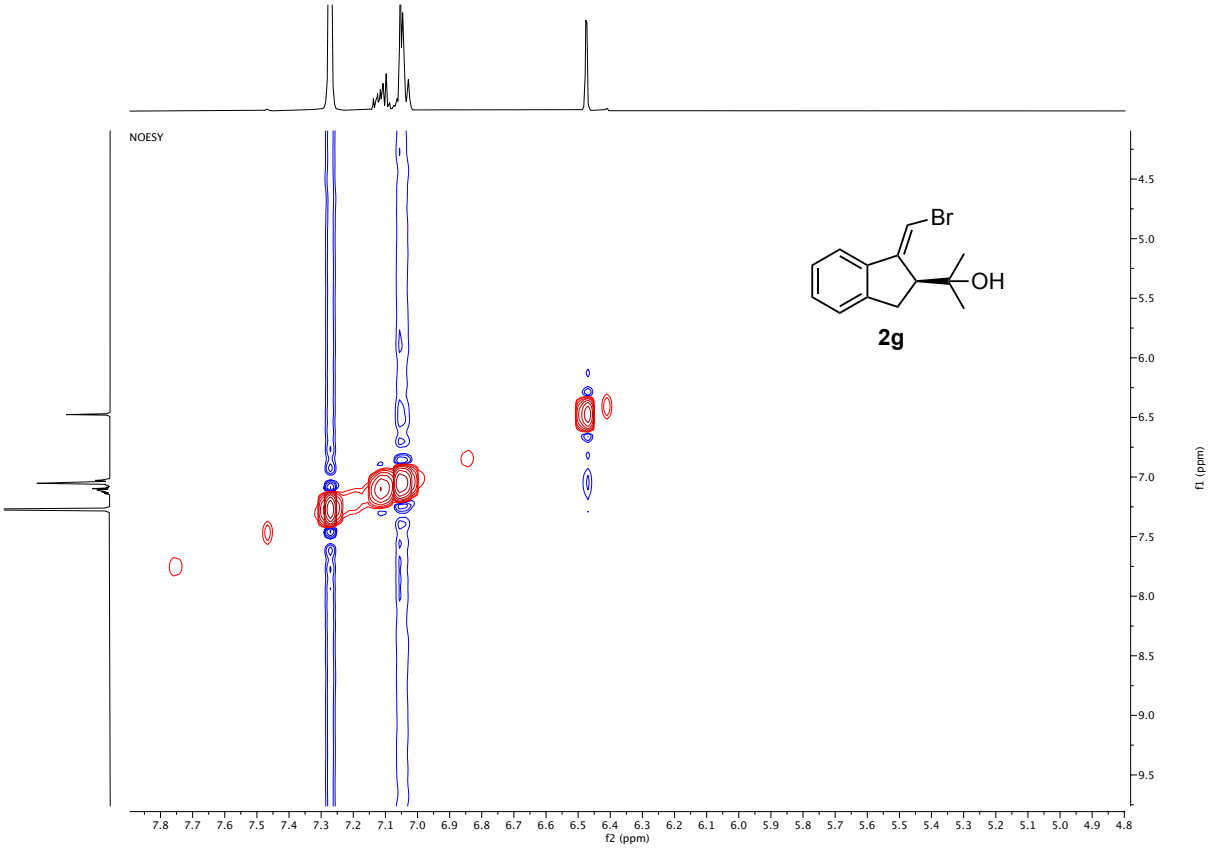
RT [min]	Type	Width [min]	Area	Height	Area%	Name
1.204	BV R	0.0569	729.3004	193.9670	60.9740	
1.605	BB	0.0546	466.7832	132.4602	39.0260	
		Sum	1196.0836			

(*S,E*)-2-(1-(Bromomethylene)-2,3-dihydro-1*H*-inden-2-yl)propan-2-ol (2g)

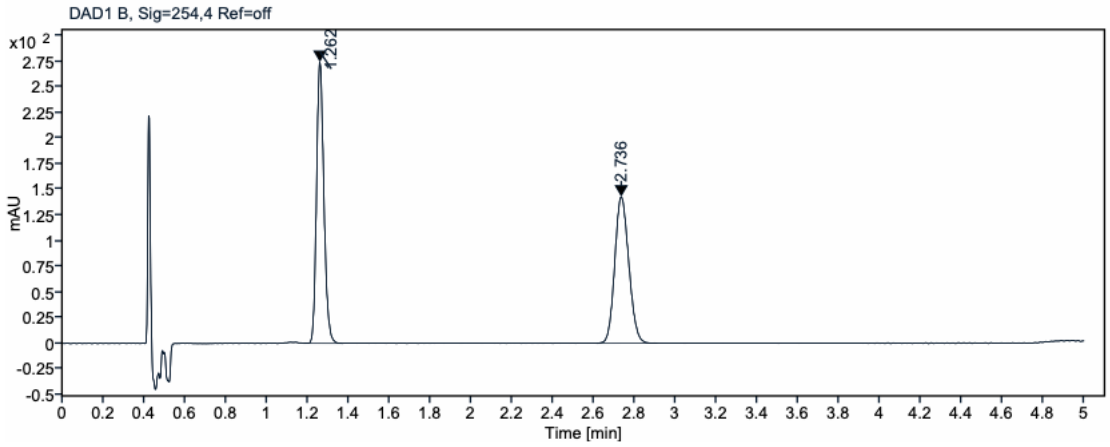




NOESY



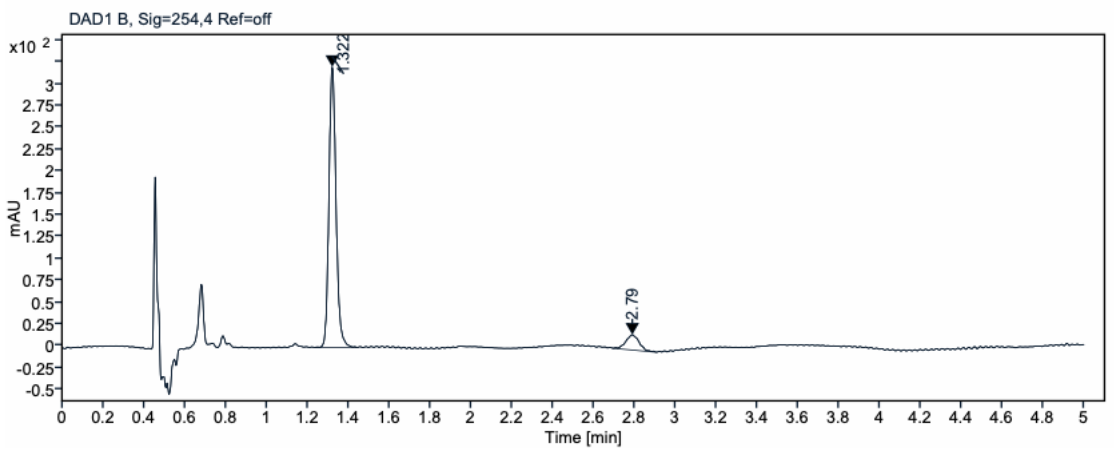
SFC racemic **2g**



Signal: DAD1 B, Sig=254,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
1.262	VB R	0.0388	687.6851	274.1008	50.1711	
2.736	BV R	0.0748	682.9933	142.7814	49.8289	
		Sum	1370.6783			

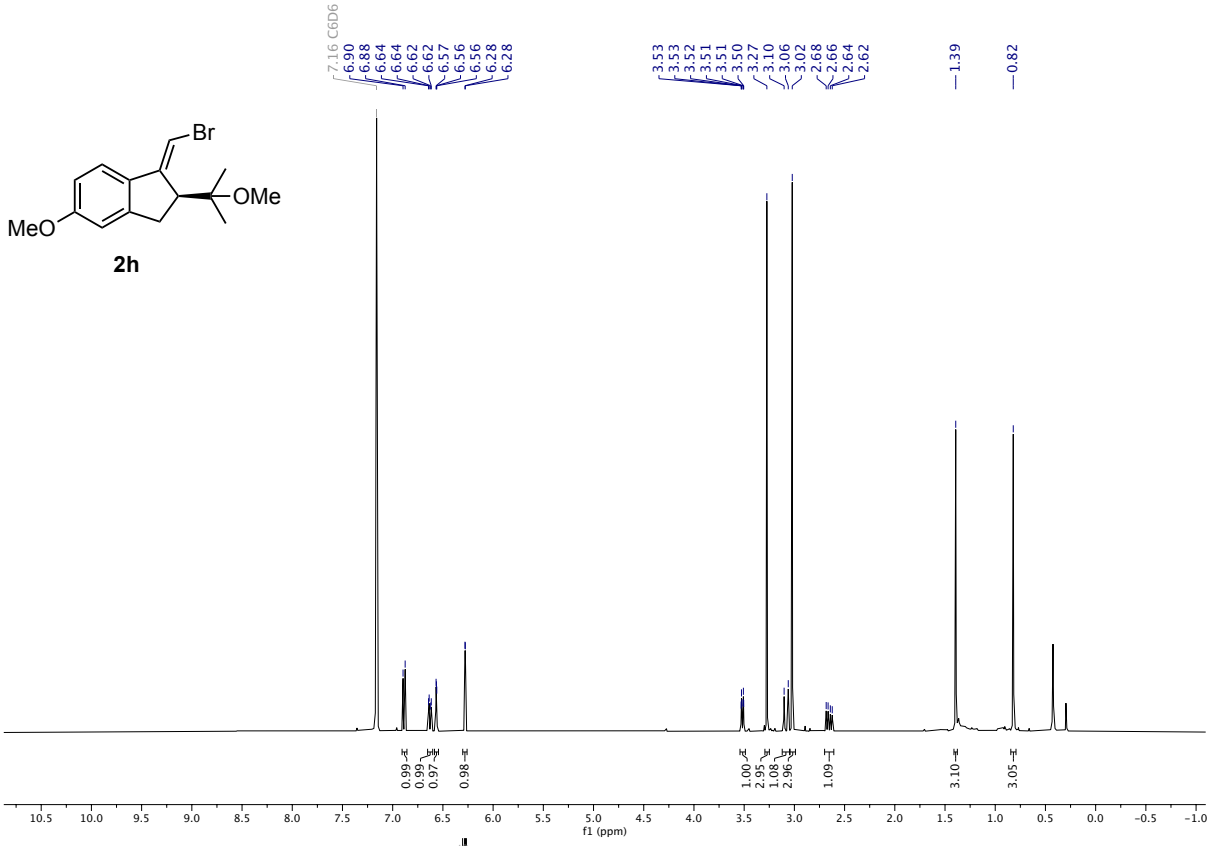
SFC enantioenriched **2g**

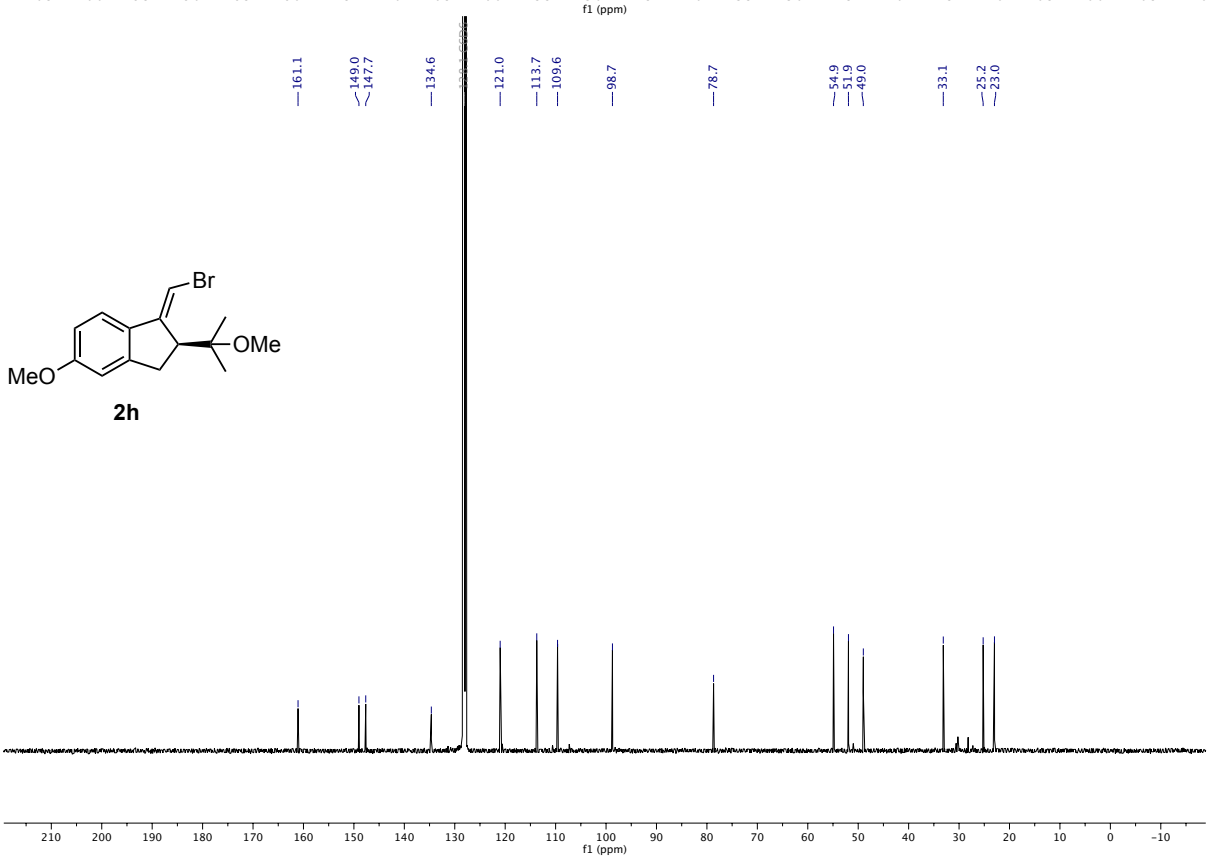


Signal: DAD1 B, Sig=254,4 Ref=off

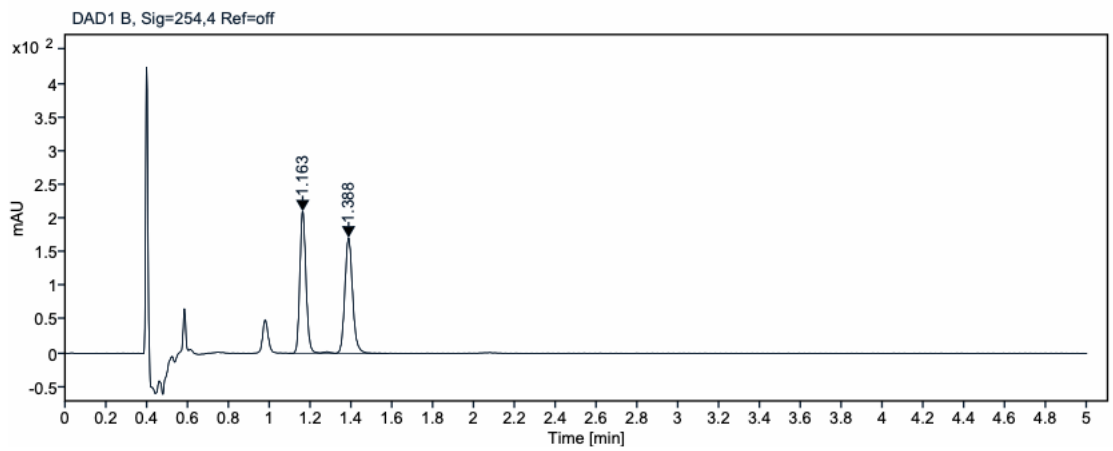
RT [min]	Type	Width [min]	Area	Height	Area%	Name
1.322	VV R	0.0372	775.9993	320.8516	90.7901	
2.790	VV R	0.0590	78.7184	17.4909	9.2099	
		Sum	854.7176			

(*S*,*E*)-1-(Bromomethylene)-5-methoxy-2-(2-methoxypropan-2-yl)-2,3-dihydro-1*H*-indene (2h)





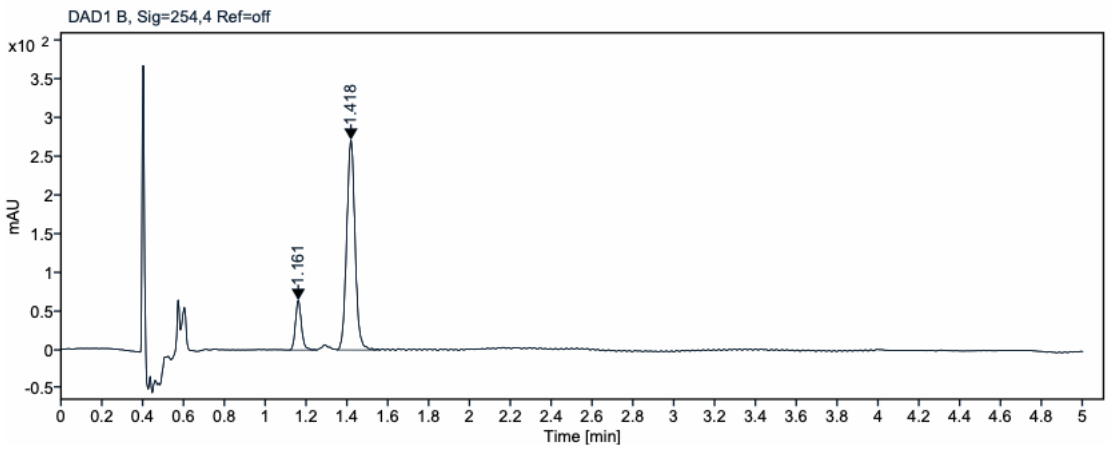
SFC racemic **2h**



Signal: DAD1 B, Sig=254,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
1.163	VV R	0.0327	444.7247	210.4368	49.4931	
1.388	BV R	0.0404	453.8337	171.4258	50.5069	
		Sum	898.5584			

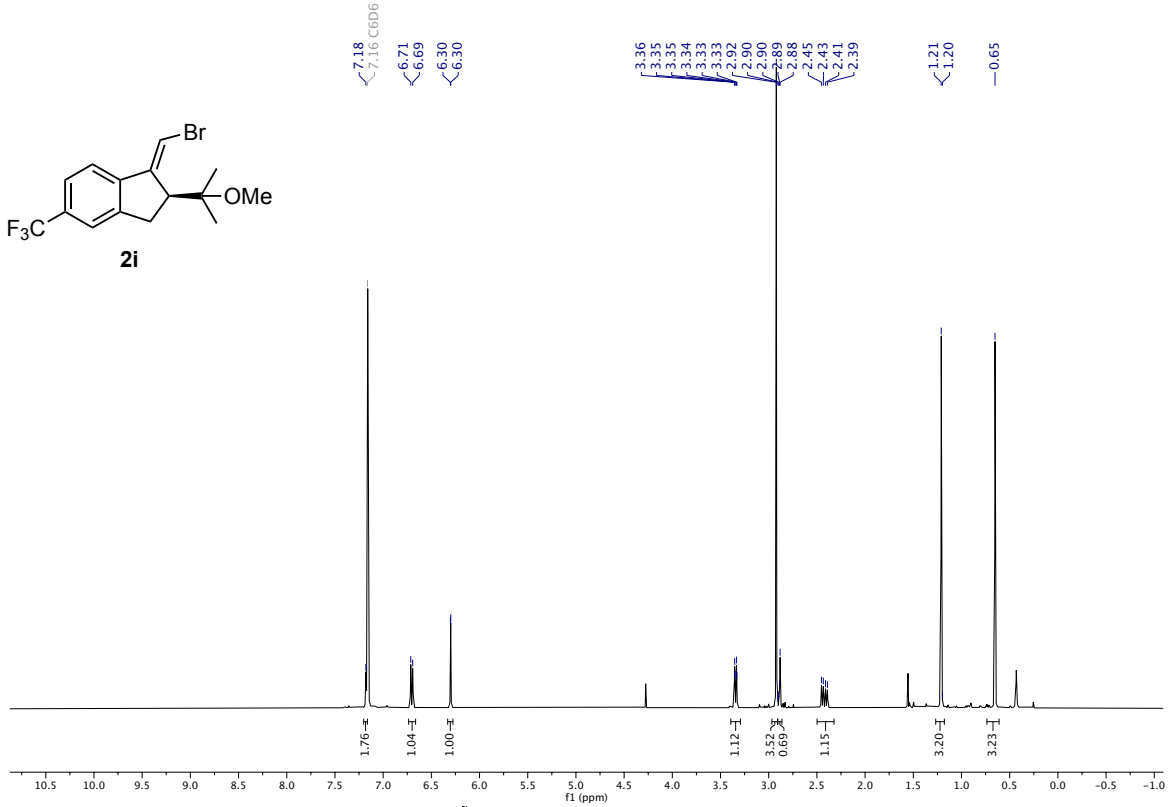
SFC enantioenriched **2h**

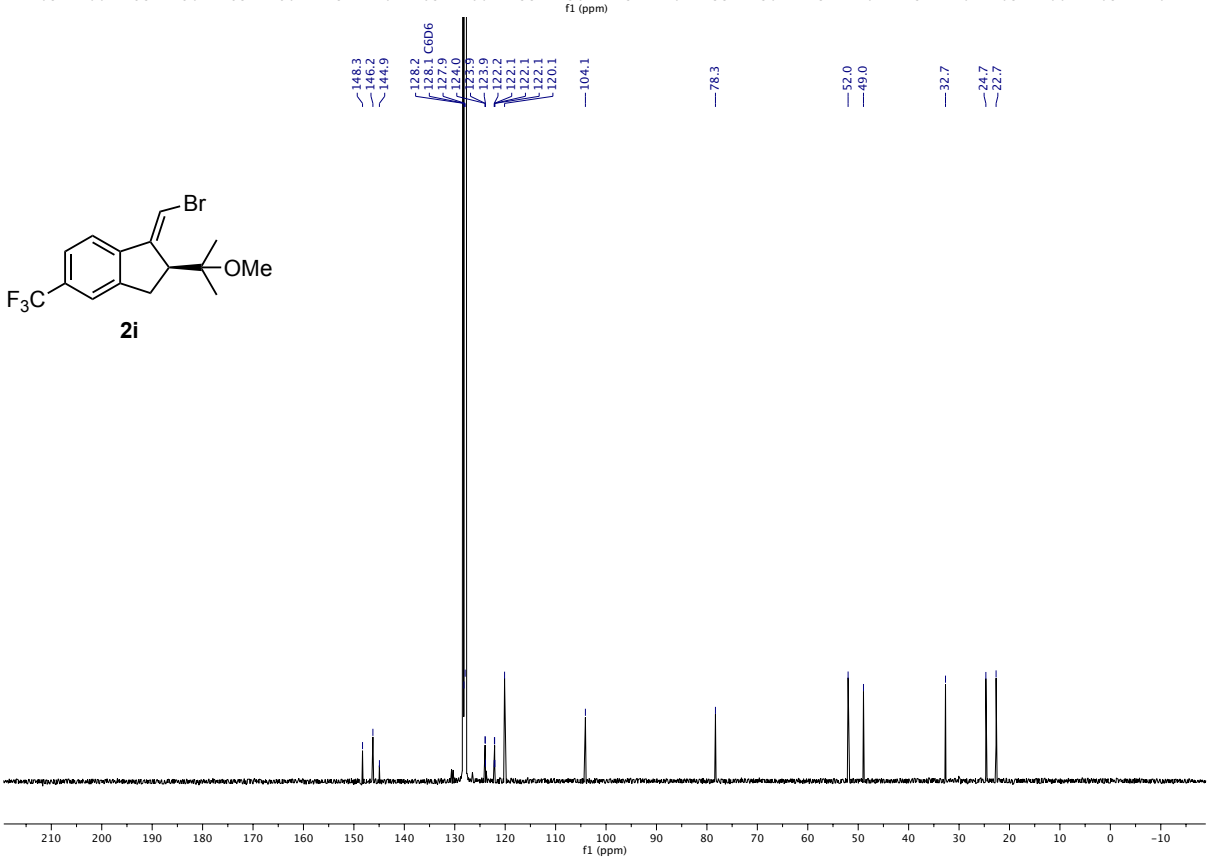


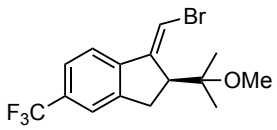
Signal: DAD1 B, Sig=254,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
1.161	BV R	0.0313	131.1040	64.2472	14.4480	
1.418	BV R	0.0443	776.3168	271.9676	85.5520	
		Sum	907.4209			

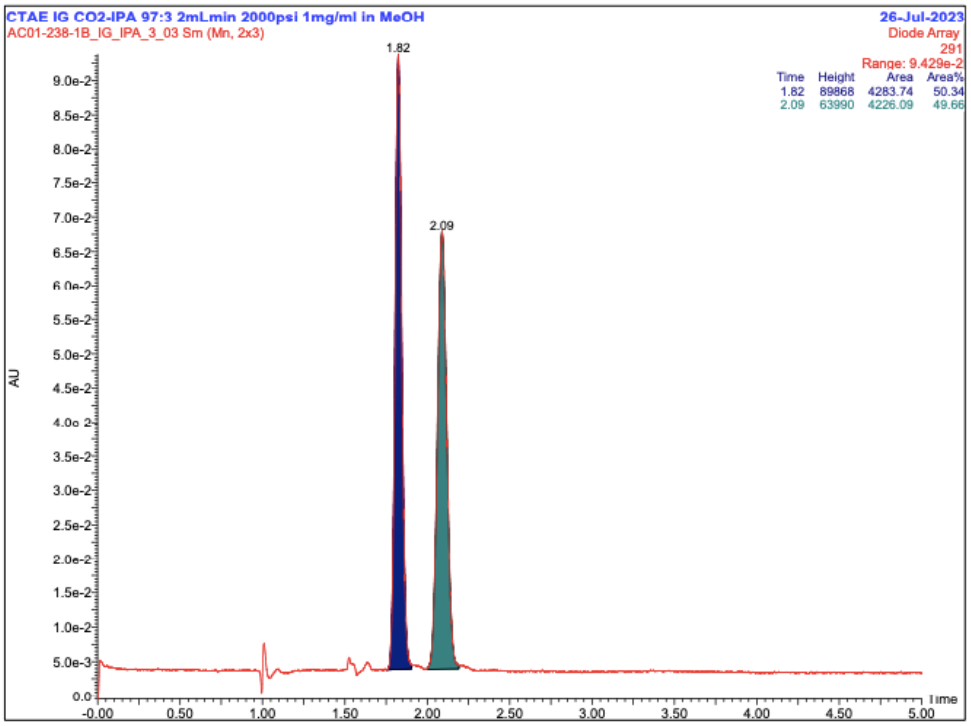
(*S*,*E*)-1-(Bromomethylene)-2-(2-methoxypropan-2-yl)-5-(trifluoromethyl)-2,3-dihydro-1*H*-indene (2i)





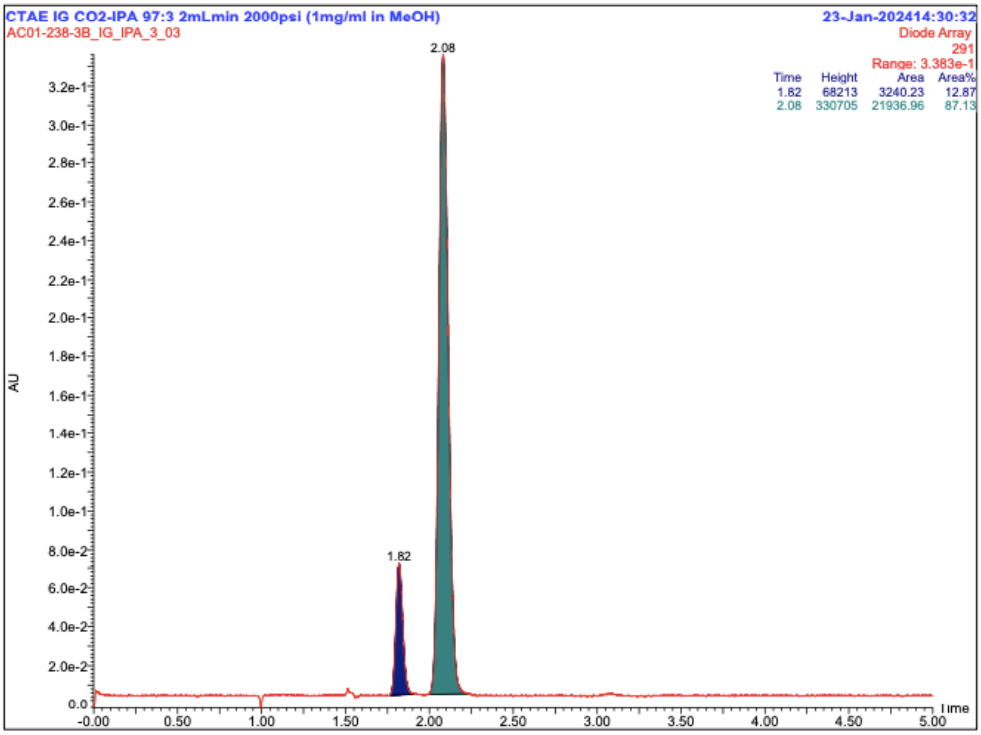


2i

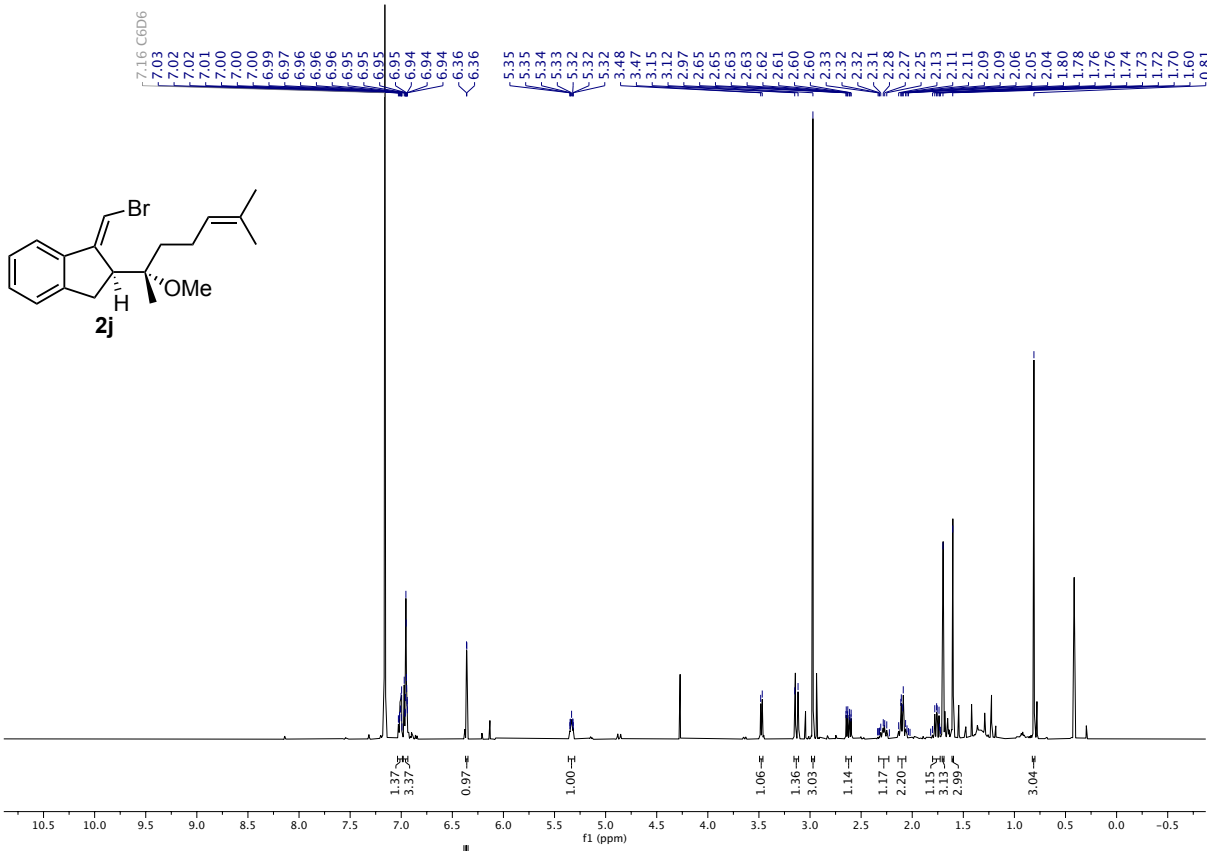


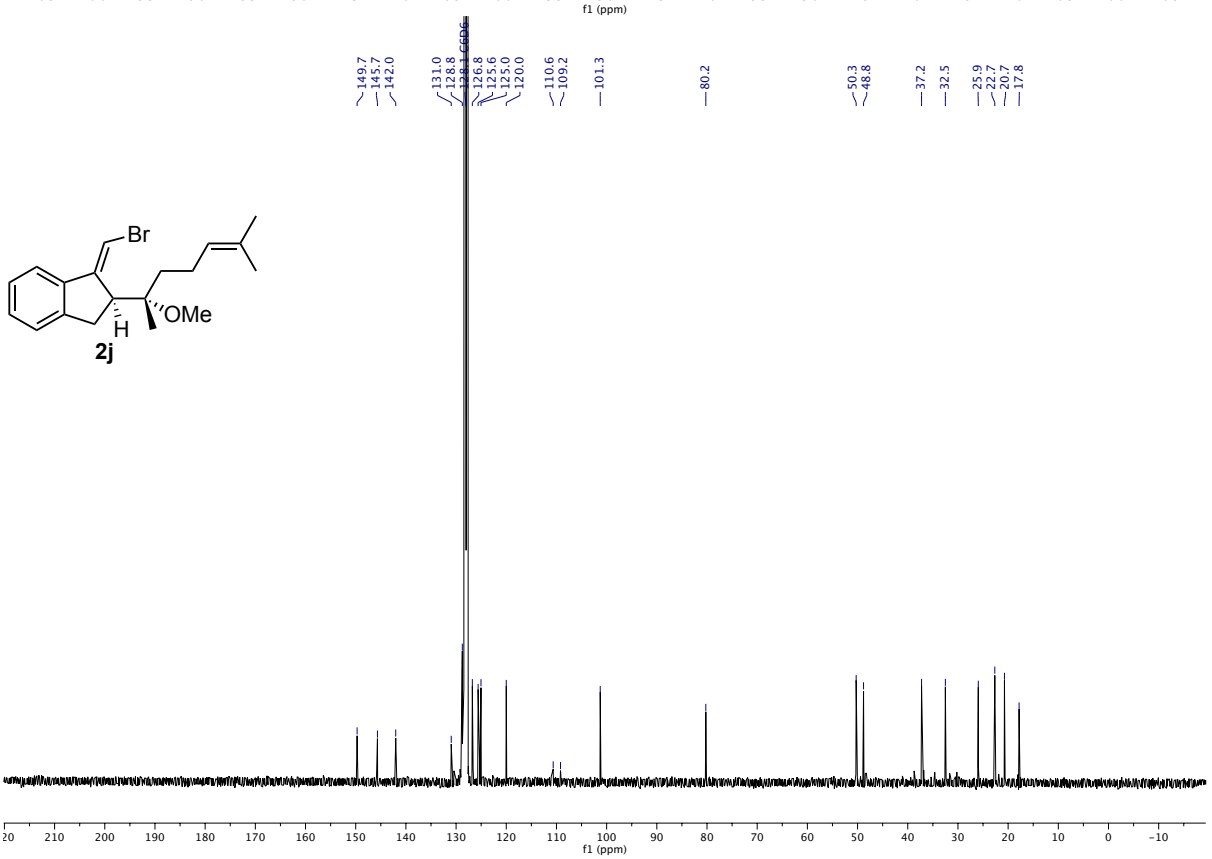
SFC racemic **2i**

SFC enantioenriched **2i**

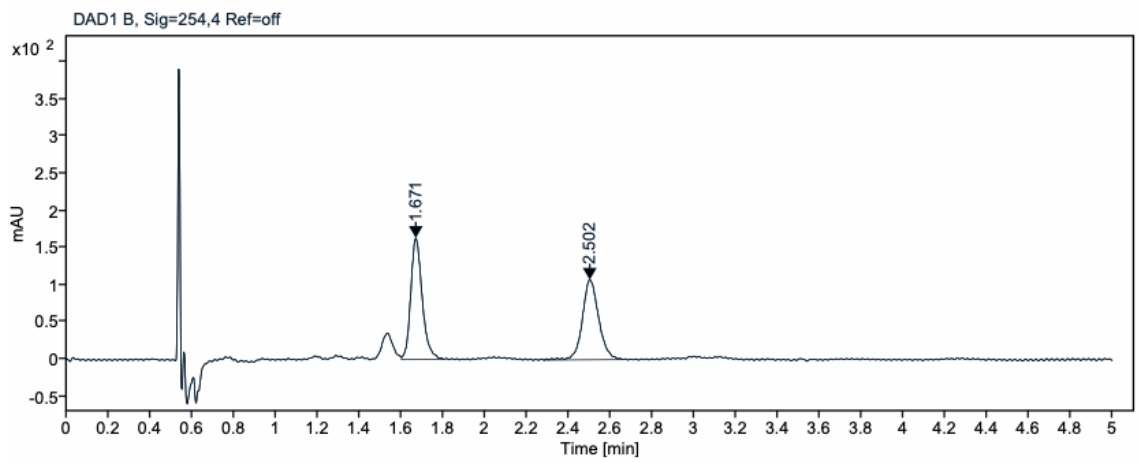


(*S*,*E*)-1-(Bromomethylene)-2-((*S*)-2-methoxy-6-methylhept-5-en-2-yl)-2,3-dihydro-1*H*-indene (2j)





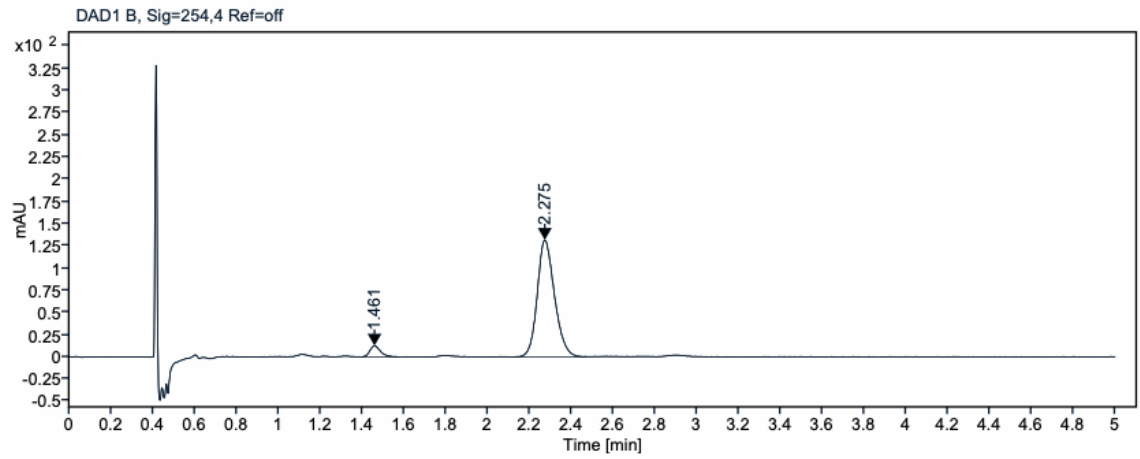
SFC racemic **2j**



Signal: DAD1 B, Sig=254,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
1.671	VV R	0.0590	622.3201	163.2508	51.5372	
2.502	VV R	0.0821	585.1961	107.3694	48.4628	
		Sum	1207.5162			

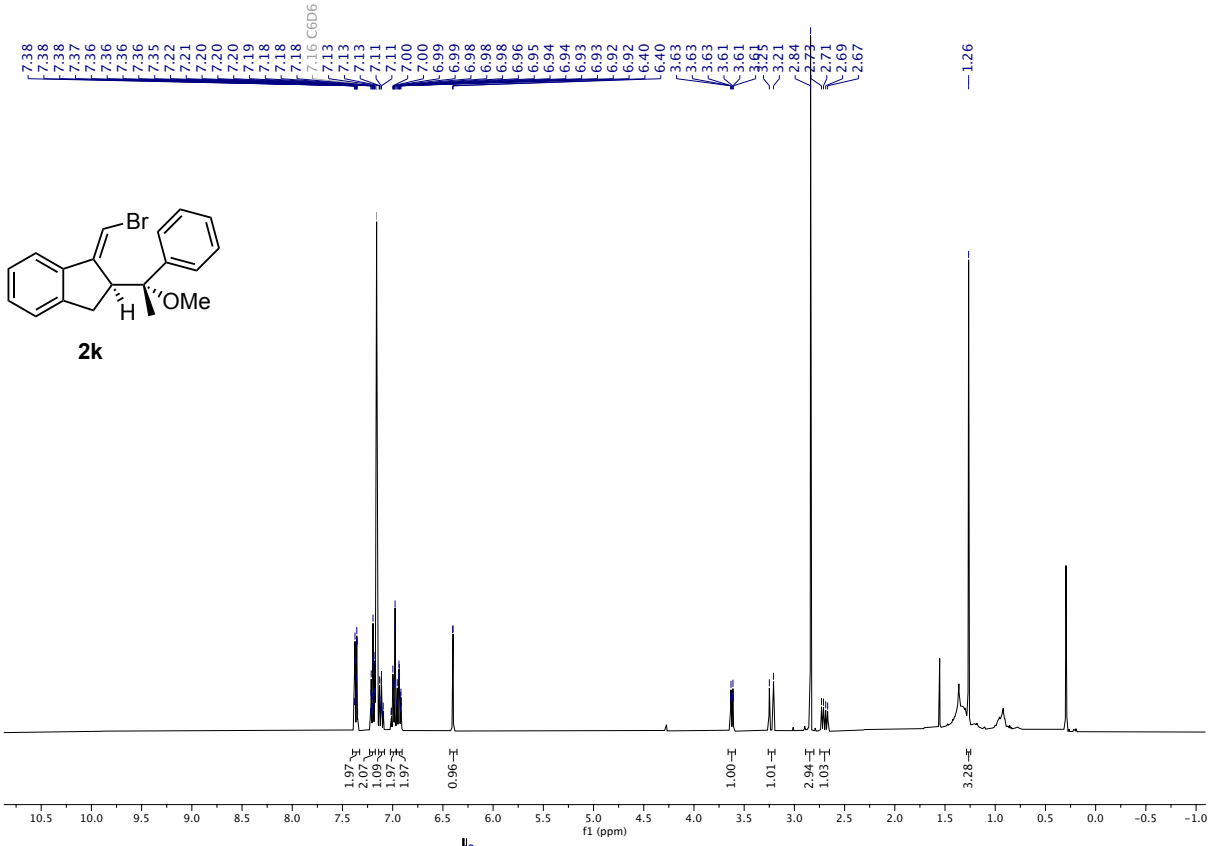
SFC enantioenriched **2j**



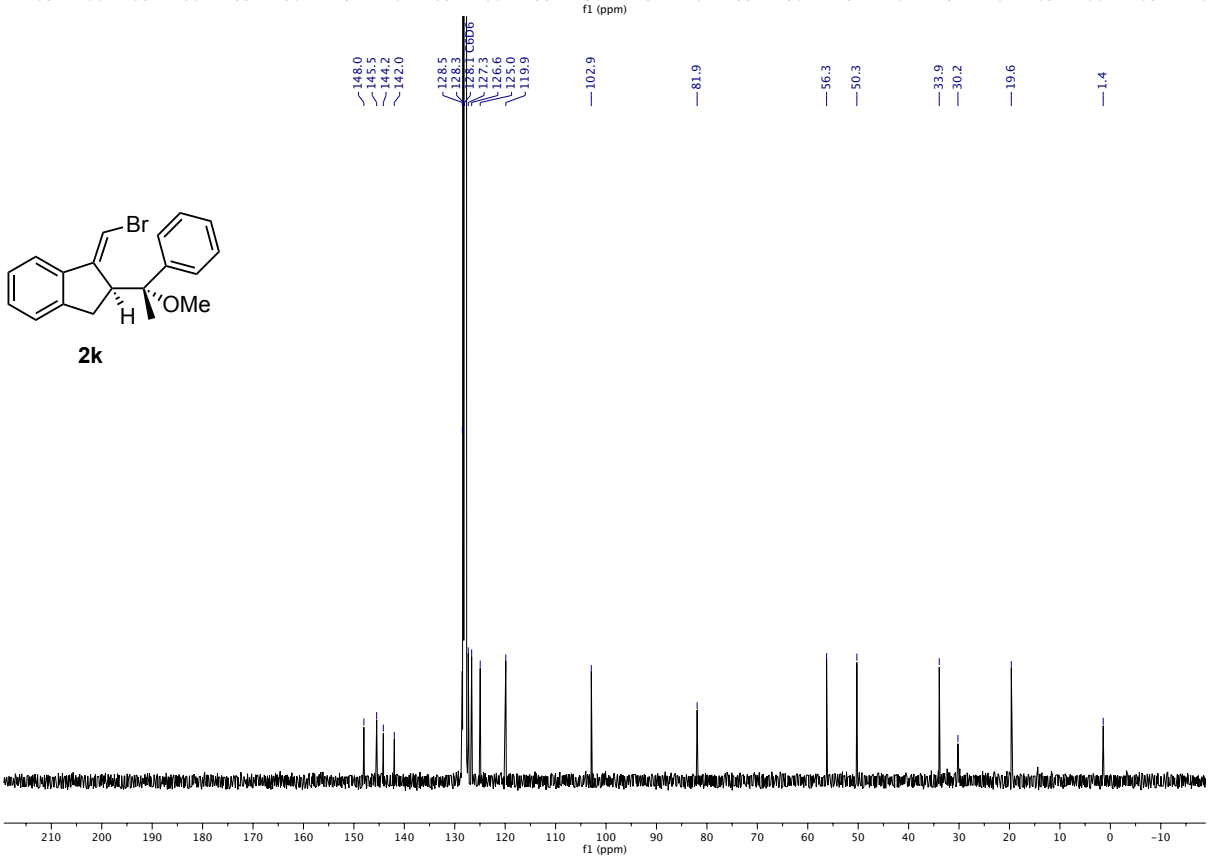
Signal: DAD1 B, Sig=254,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
1.461	BV R	0.0536	44.1781	12.5472	5.5459	
2.275	VV R	0.0888	752.4136	131.5023	94.4541	
		Sum	796.5916			

(*S*,*E*)-1-(Bromomethylene)-2-((*R*)-1-methoxy-1-phenylethyl)-2,3-dihydro-1*H*-indene (2k)

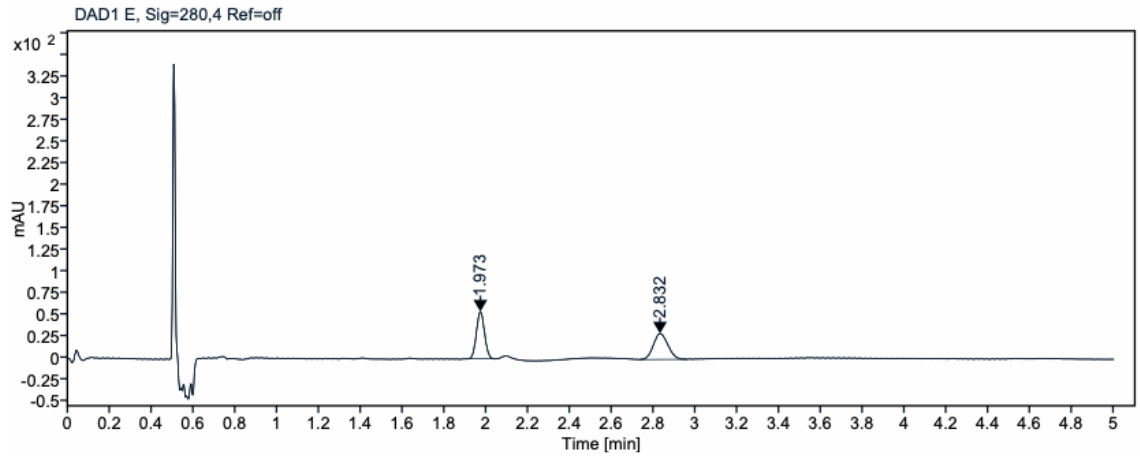


2k



2k

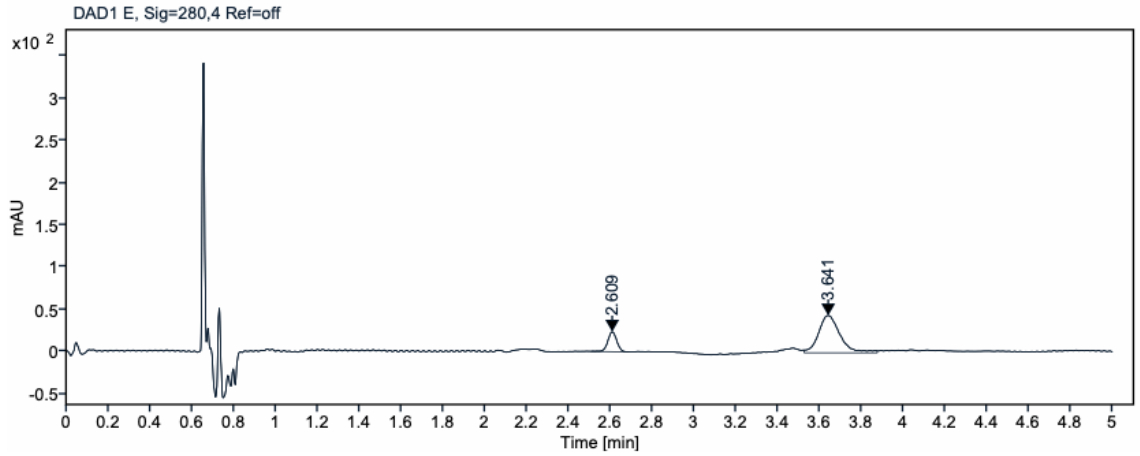
SFC racemic **2k**



Signal: DAD1 E, Sig=280,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
1.973	MM	0.0448	145.1981	54.0087	50.0545	
2.832	BV R	0.0754	144.8820	29.7123	49.9455	
		Sum	290.0801			

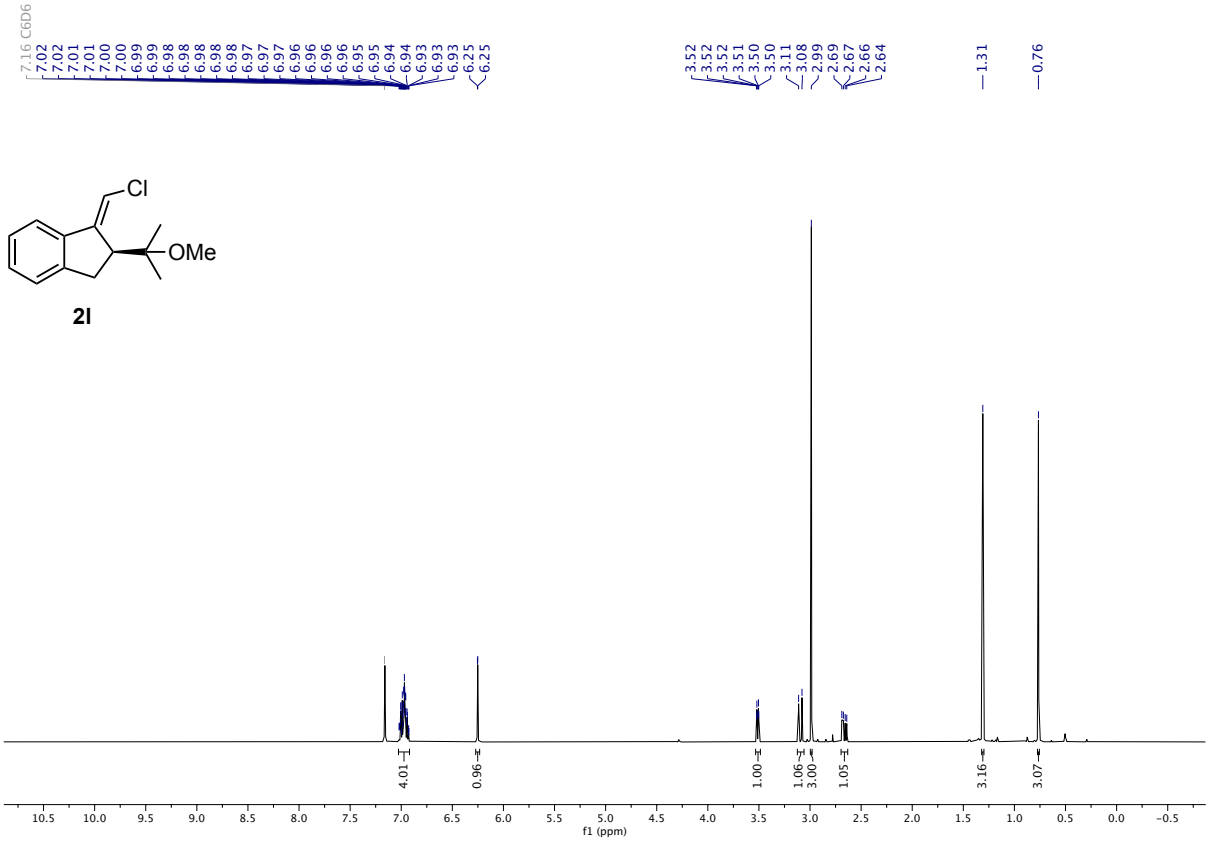
SFC enantioenriched **2k**

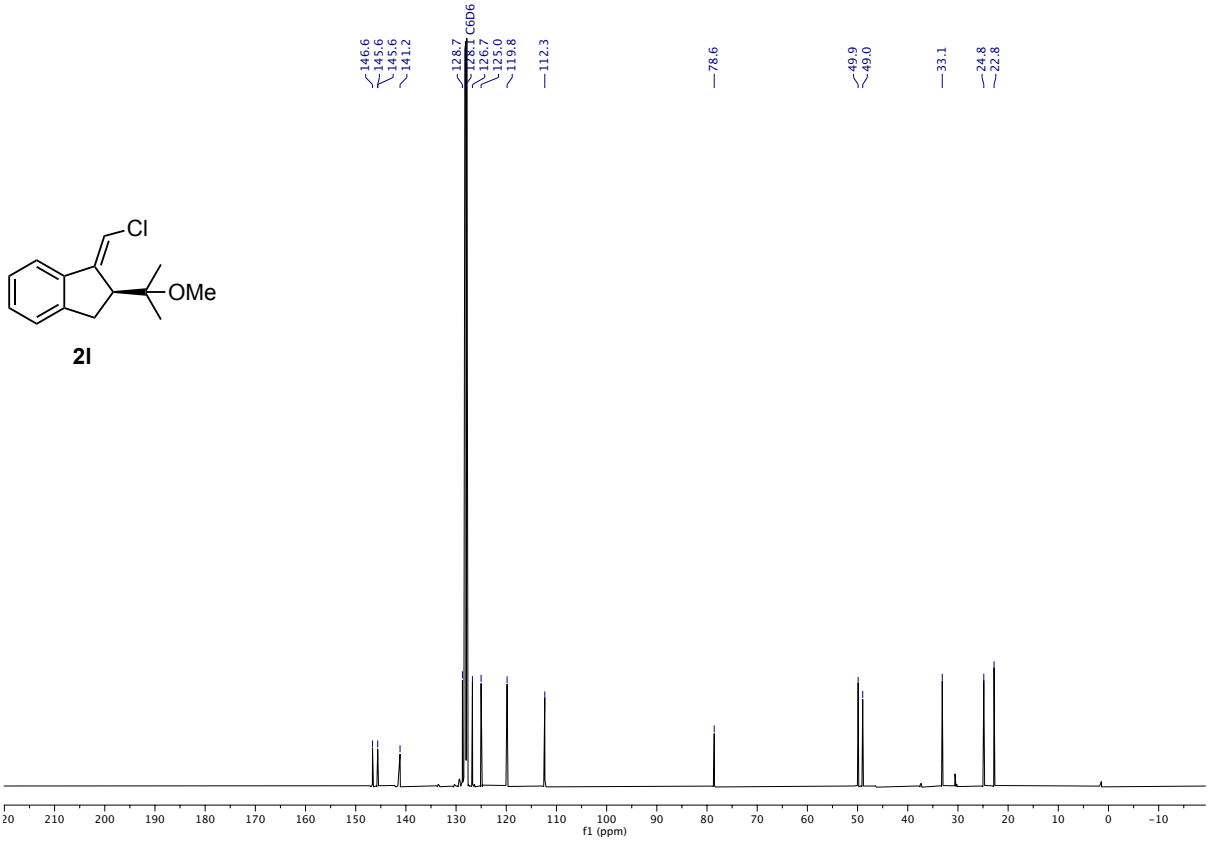


Signal: DAD1 E, Sig=280,4 Ref=off

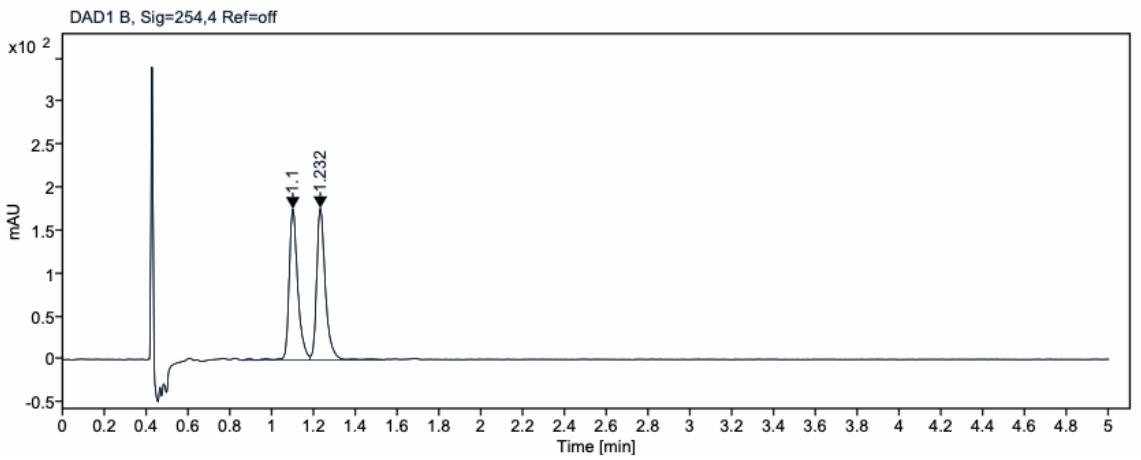
RT [min]	Type	Width [min]	Area	Height	Area%	Name
2.609	VB R	0.0471	69.5686	23.4877	18.1249	
3.641	MM	0.1190	314.2608	44.0196	81.8751	
		Sum	383.8294			

(*S*,*E*)-1-(Chloromethylene)-2-(2-methoxypropan-2-yl)-2,3-dihydro-1*H*-indene (2l)





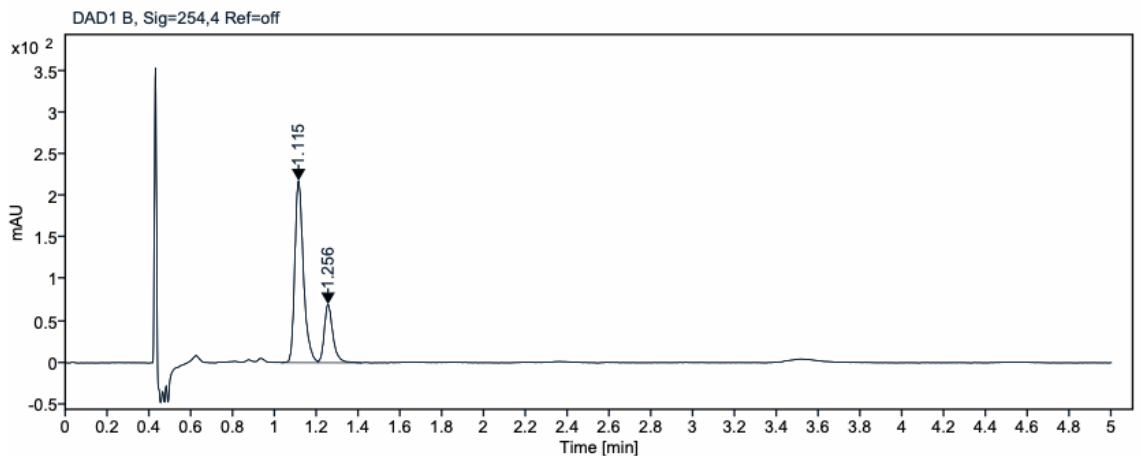
SFC racemic **2l**



Signal: DAD1 B, Sig=254,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
1.100	VV R	0.0432	508.6760	176.0486	49.8670	
1.232	VV R	0.0433	511.3888	176.6477	50.1330	
		Sum	1020.0648			

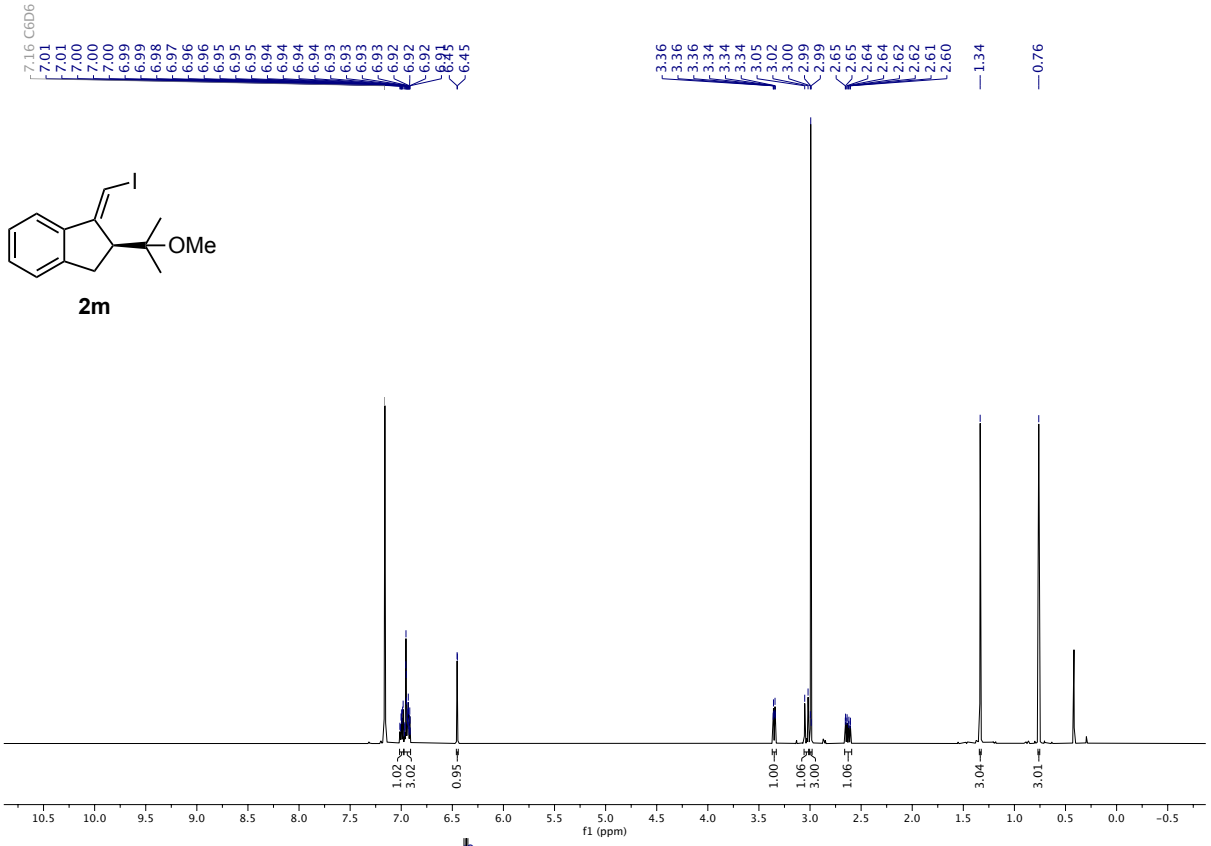
SFC enantioenriched **2l**

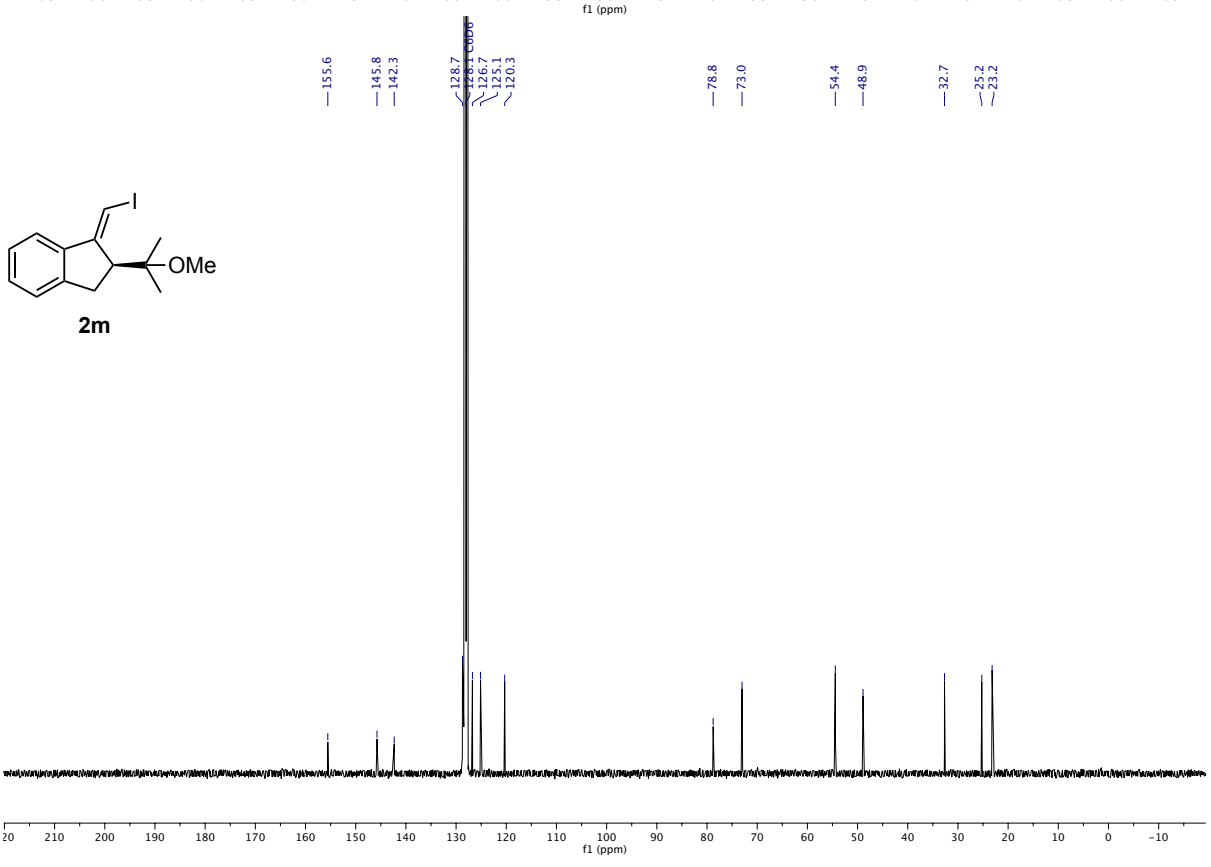


Signal: DAD1 B, Sig=254,4 Ref=off

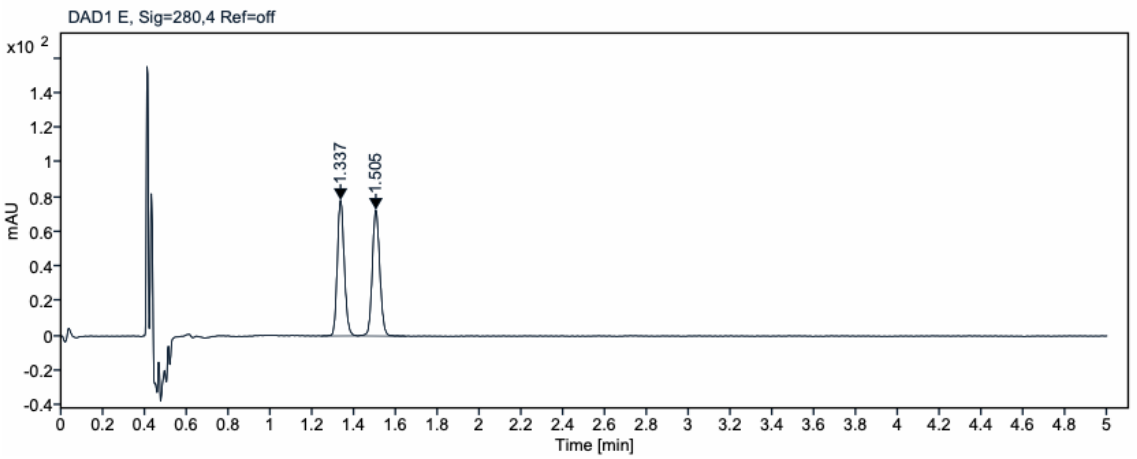
RT [min]	Type	Width [min]	Area	Height	Area%	Name
1.115	BV	0.0440	627.5121	218.5681	75.6597	
1.256	VB	0.0436	201.8750	70.0255	24.3403	
		Sum	829.3872			

(*S*,*E*)-1-(Iodomethylene)-2-(2-methoxypropan-2-yl)-2,3-dihydro-1*H*-indene (2m)





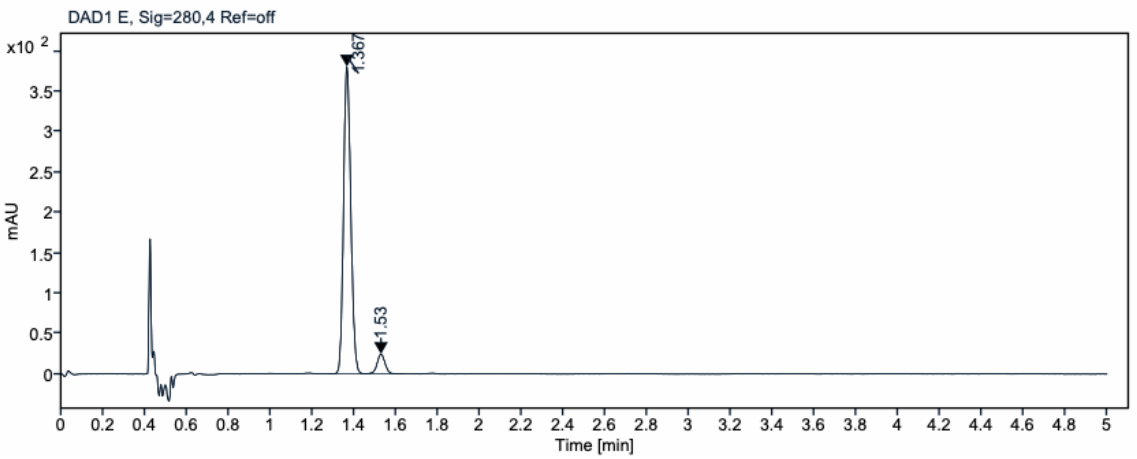
SFC racemic **2m**



Signal: DAD1 E, Sig=280,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
1.337	VB R	0.0360	181.1034	78.2533	49.9259	
1.505	BV R	0.0386	181.6407	72.7075	50.0741	
		Sum	362.7440			

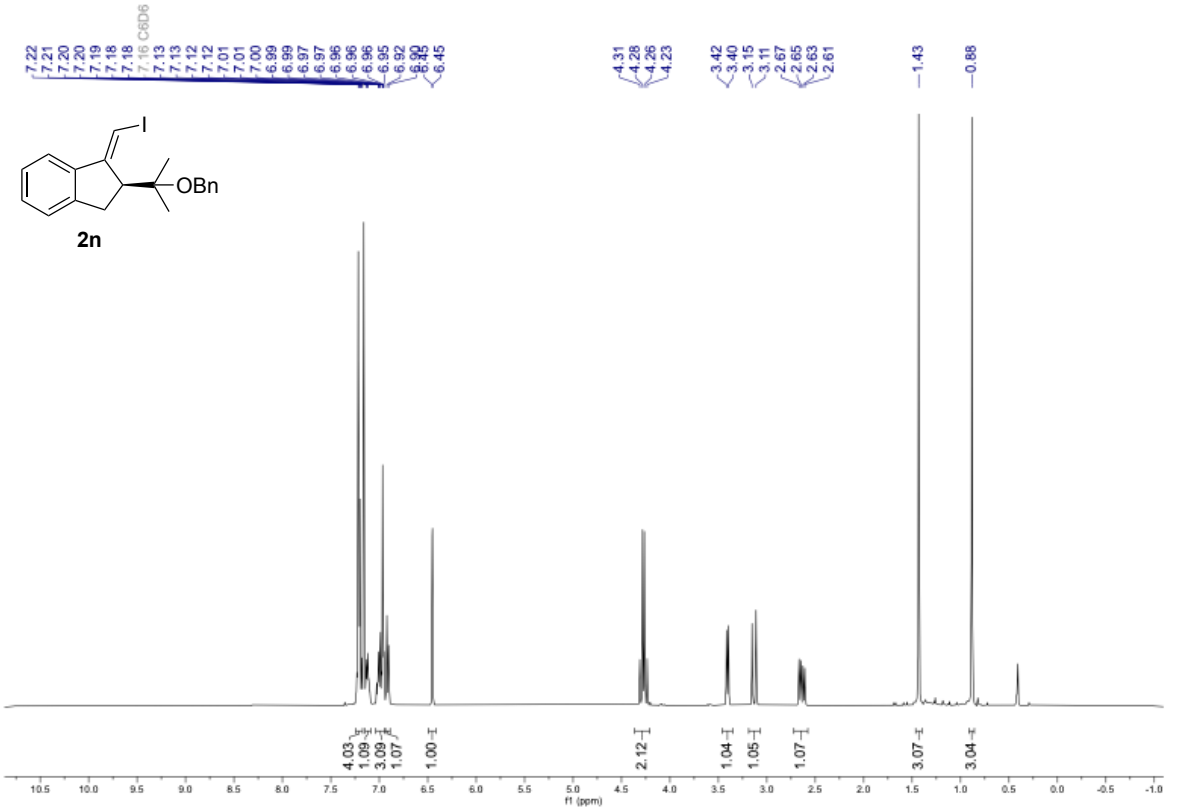
SFC enantioenriched **2m**

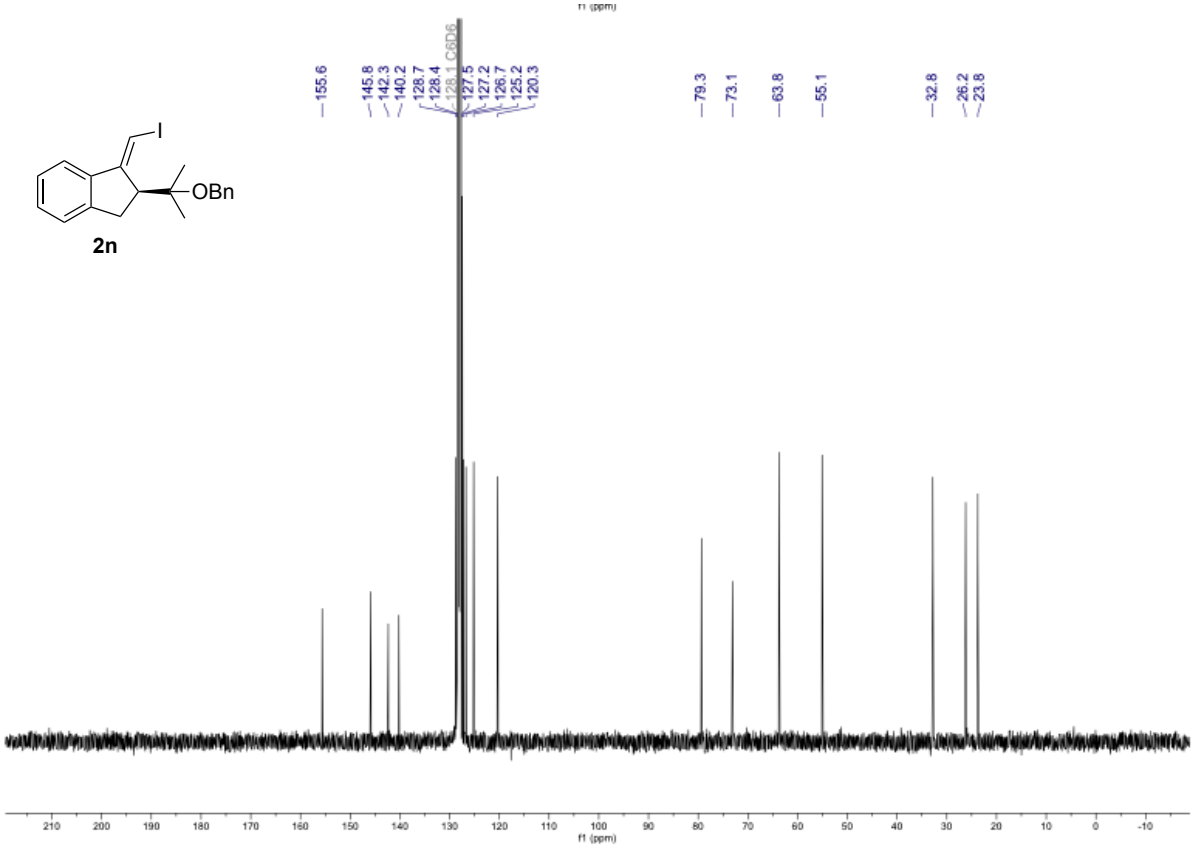


Signal: DAD1 E, Sig=280,4 Ref=off

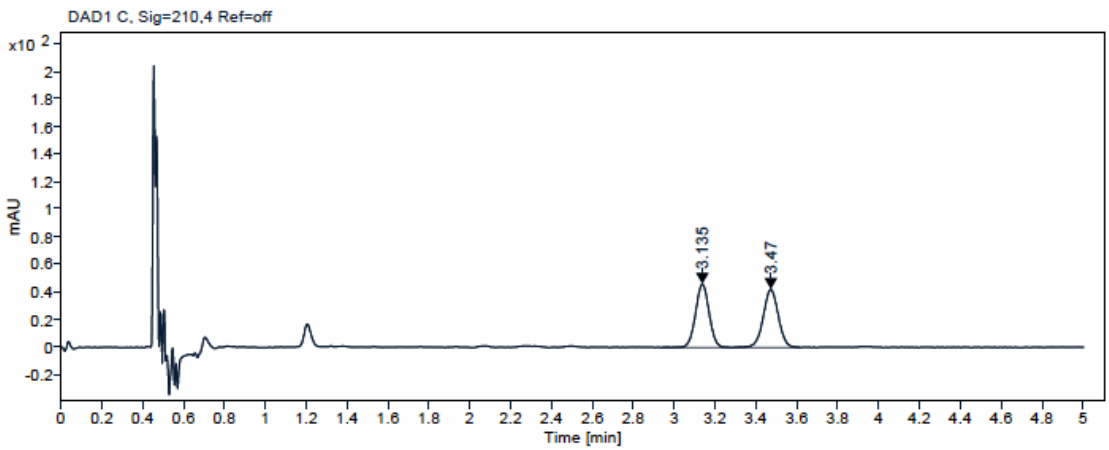
RT [min]	Type	Width [min]	Area	Height	Area%	Name
1.367	VV R	0.0376	919.1964	381.2606	93.4163	
1.530	VV R	0.0403	64.7817	24.5299	6.5837	
		Sum	983.9781			

(*S*,*E*)-2-(2-(Benzyloxy)propan-2-yl)-1-(iodomethylene)-2,3-dihydro-1*H*-indene (2n)





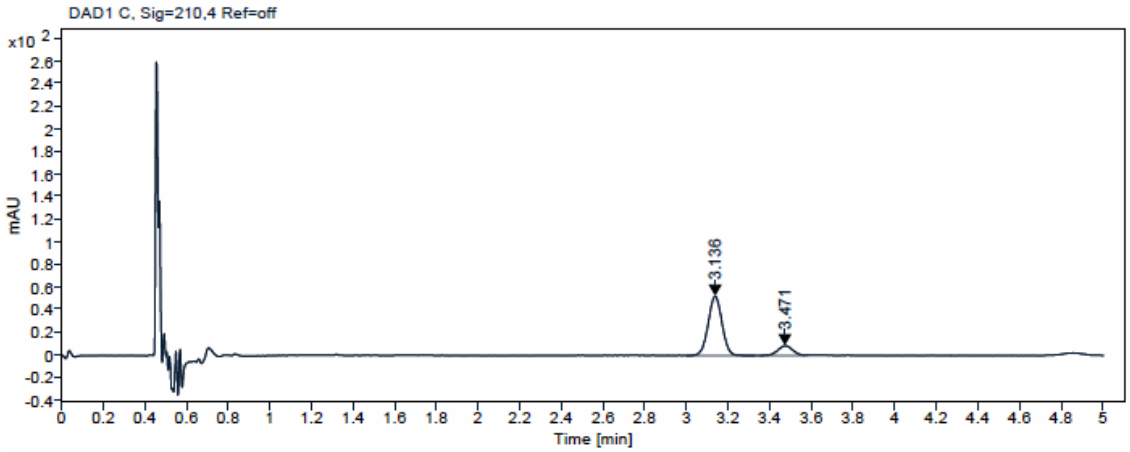
SFC racemic **2n**



Signal: DAD1 C, Sig=210,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
3.135	VV R	0.0715	212.7444	45.9451	49.5155	
3.470	VV R	0.0805	216.9075	42.1637	50.4845	
		Sum	429.6520			

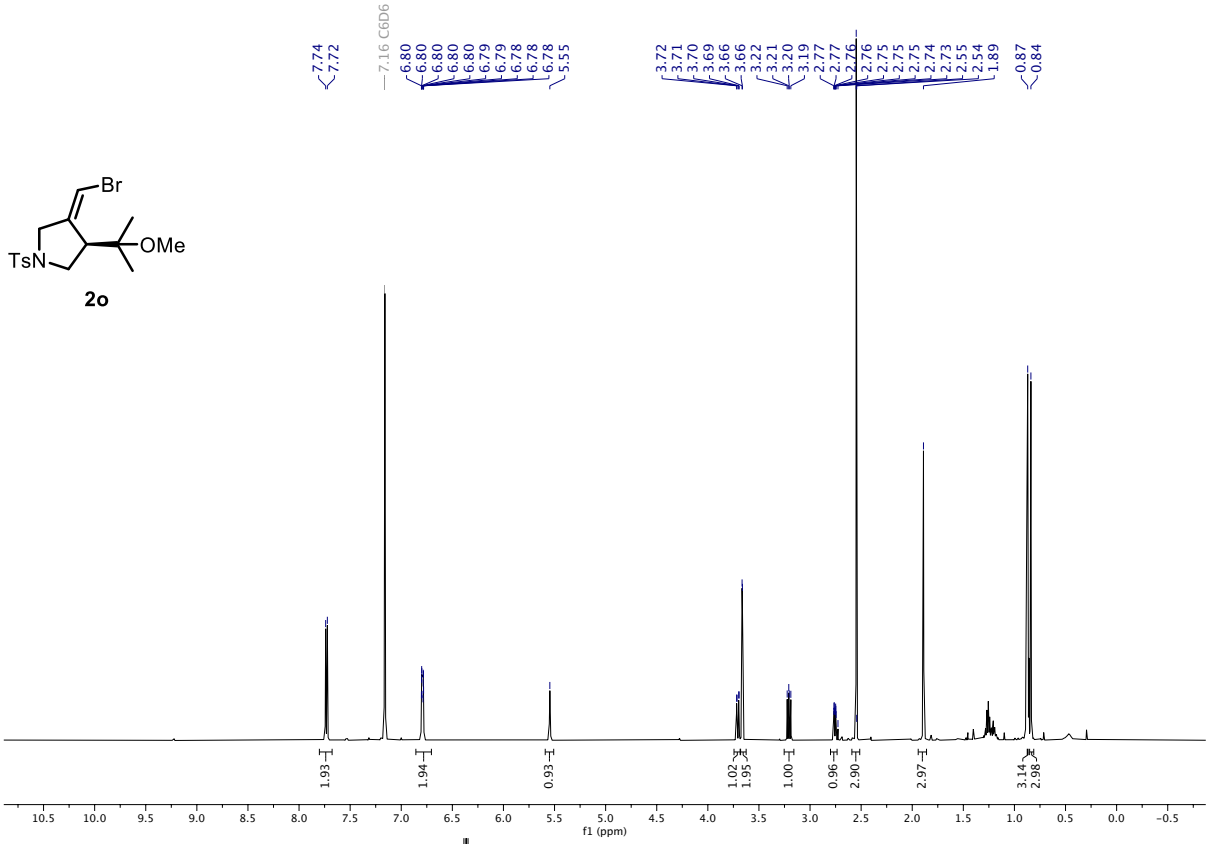
SFC enantioenriched **2n**

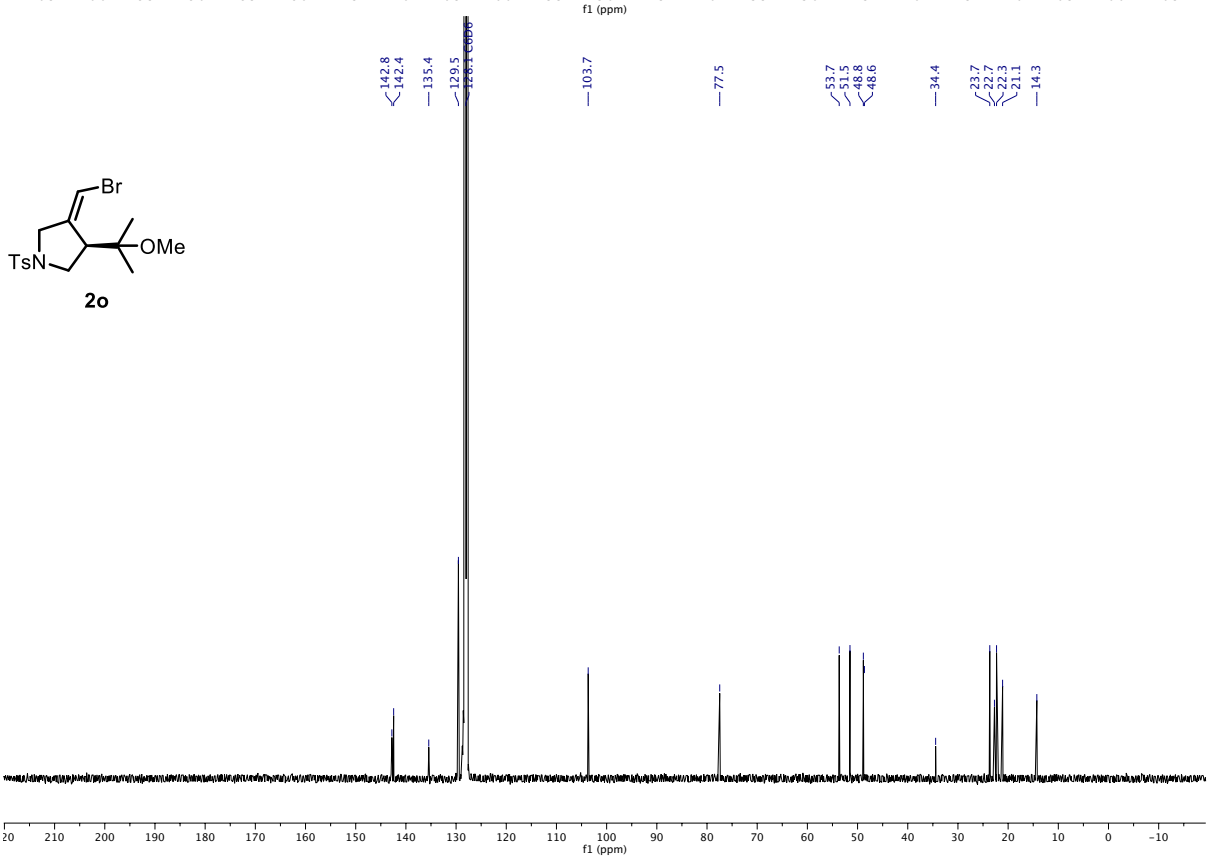


Signal: DAD1 C, Sig=210,4 Ref=off

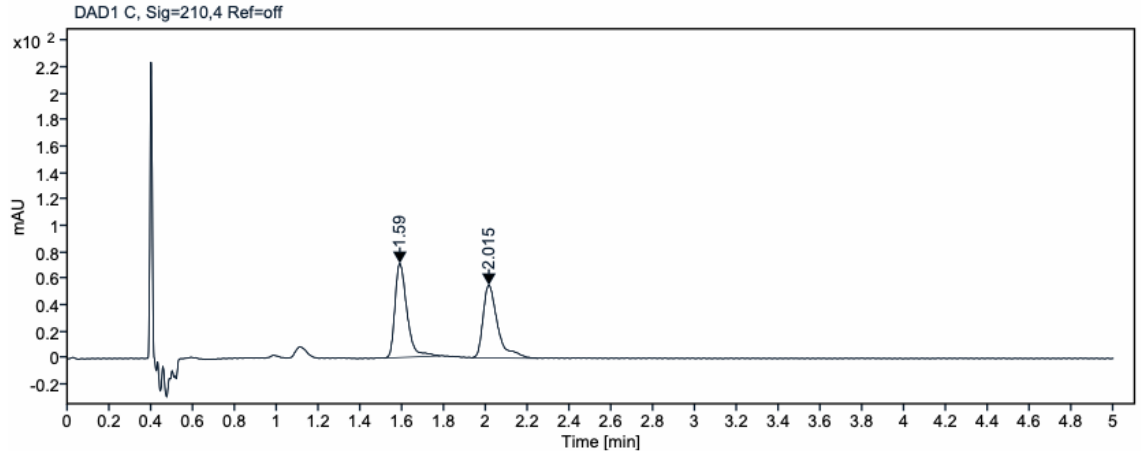
RT [min]	Type	Width [min]	Area	Height	Area%	Name
3.136	VV R	0.0717	241.2574	52.4436	84.9553	
3.471	BB	0.0706	42.7241	8.5720	15.0447	
		Sum	283.9815			

(*R*,*E*)-3-(Bromomethylene)-4-(2-methoxypropan-2-yl)-1-tosylpyrrolidine (2o)





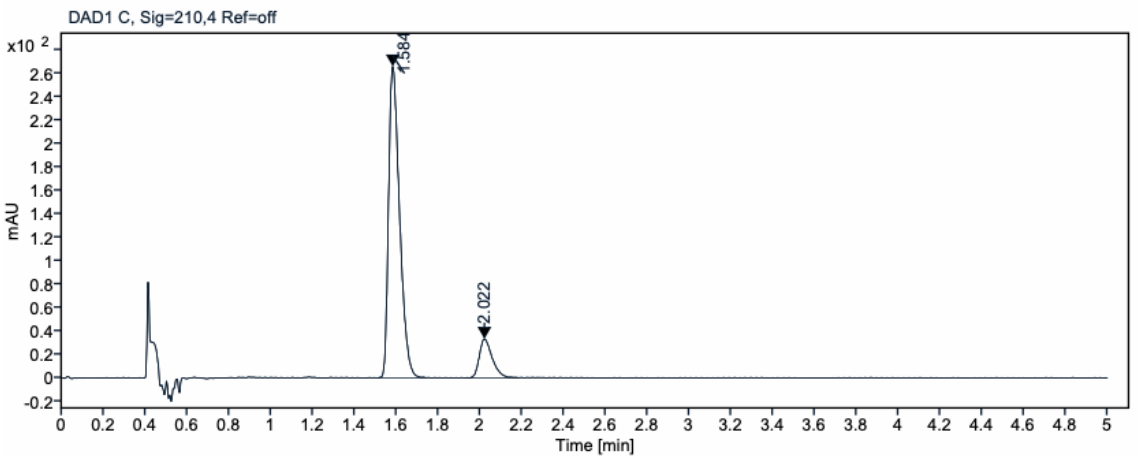
SFC racemic **2o**



Signal: DAD1 C, Sig=210,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
1.590	BV R	0.0604	282.8968	71.0692	51.4705	
2.015	BV R	0.0717	266.7324	54.8527	48.5295	
		Sum	549.6292			

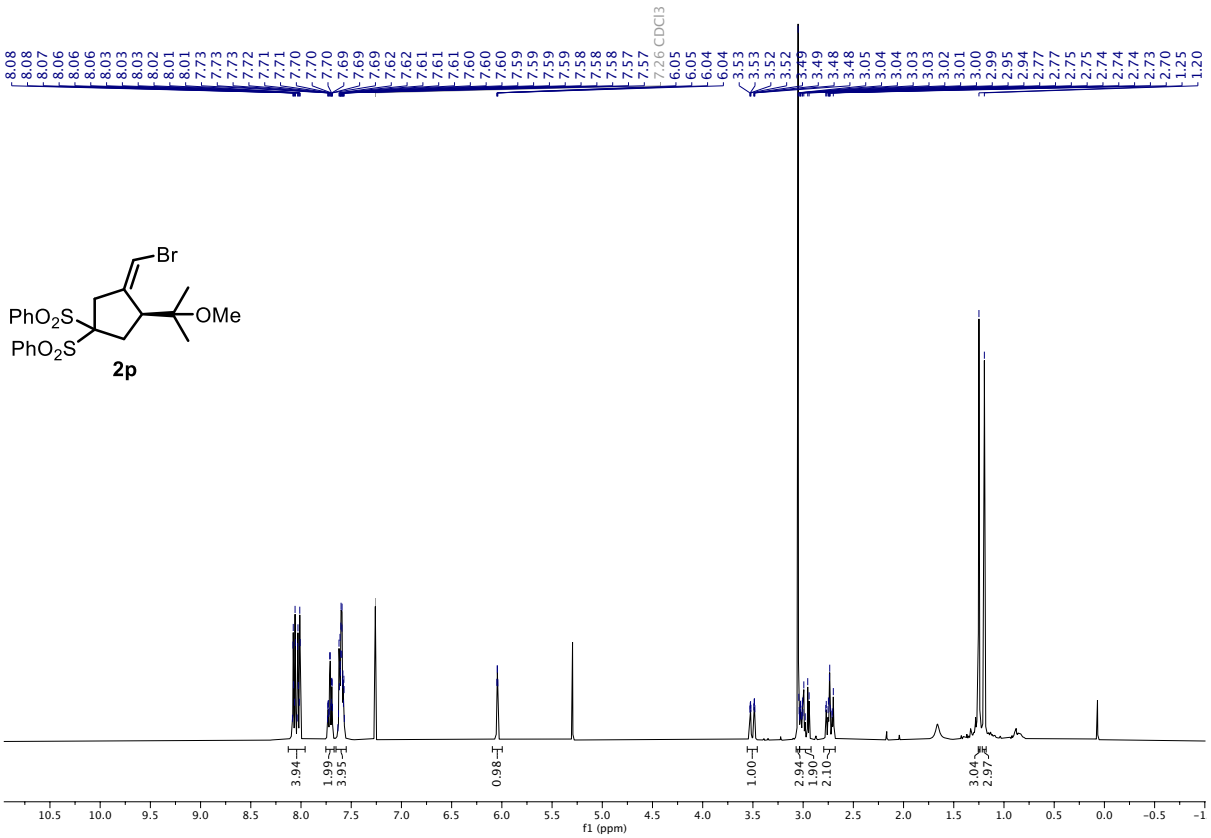
SFC enantioenriched **2o**

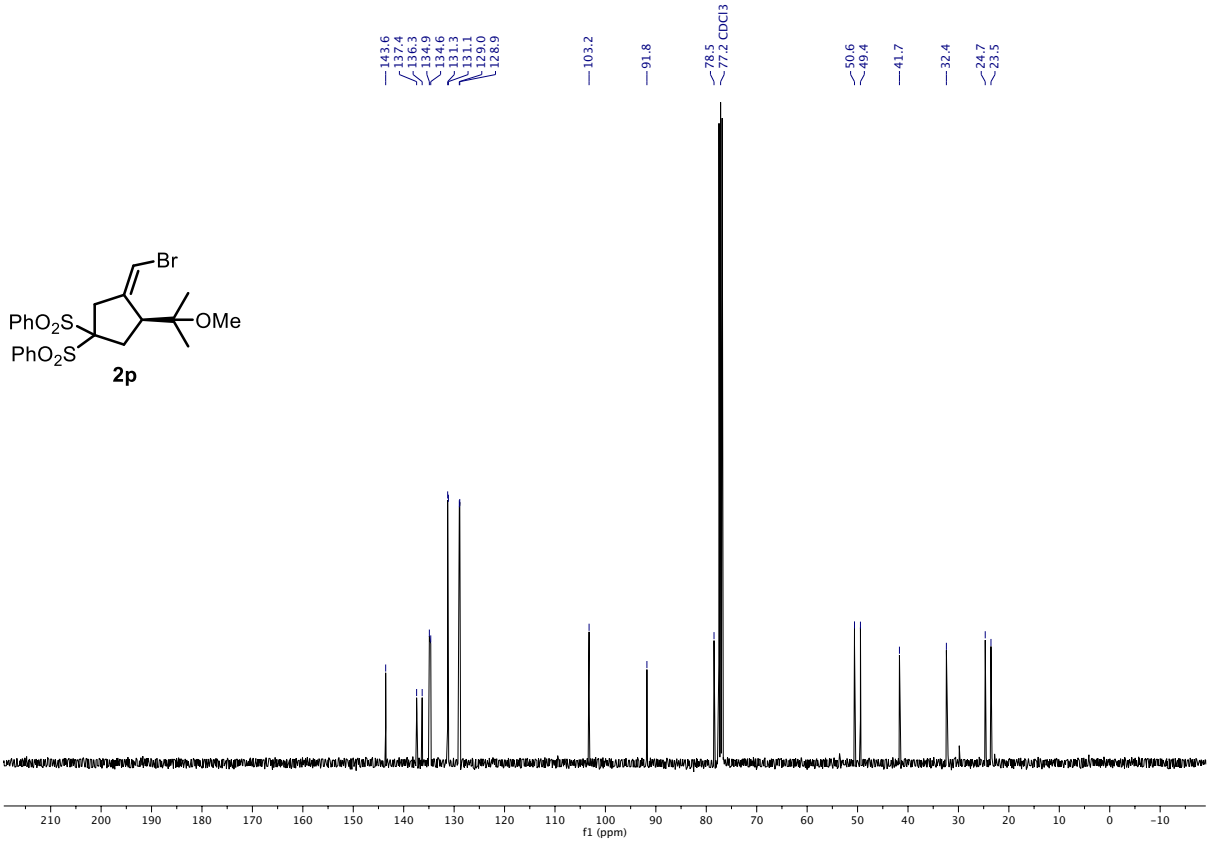


Signal: DAD1 C, Sig=210,4 Ref=off

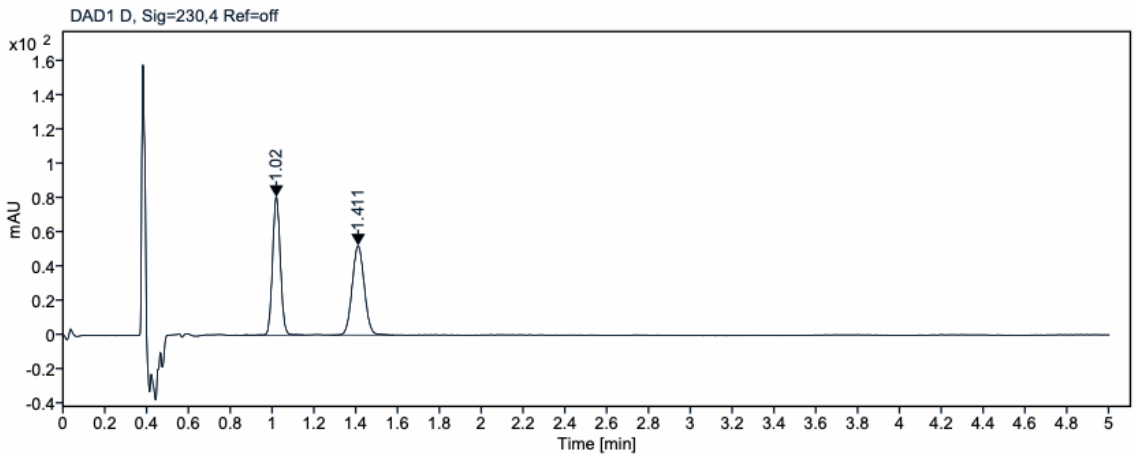
RT [min]	Type	Width [min]	Area	Height	Area%	Name
1.584	BV R	0.0561	974.7511	266.7286	87.1384	
2.022	VV R	0.0658	143.8736	33.3962	12.8616	
		Sum	1118.6247			

(*S*,*Z*)-(3-(Bromomethylene)-4-(2-methoxypropan-2-yl)cyclopentane-1,1-disulfonyl)dibenzene (2p)





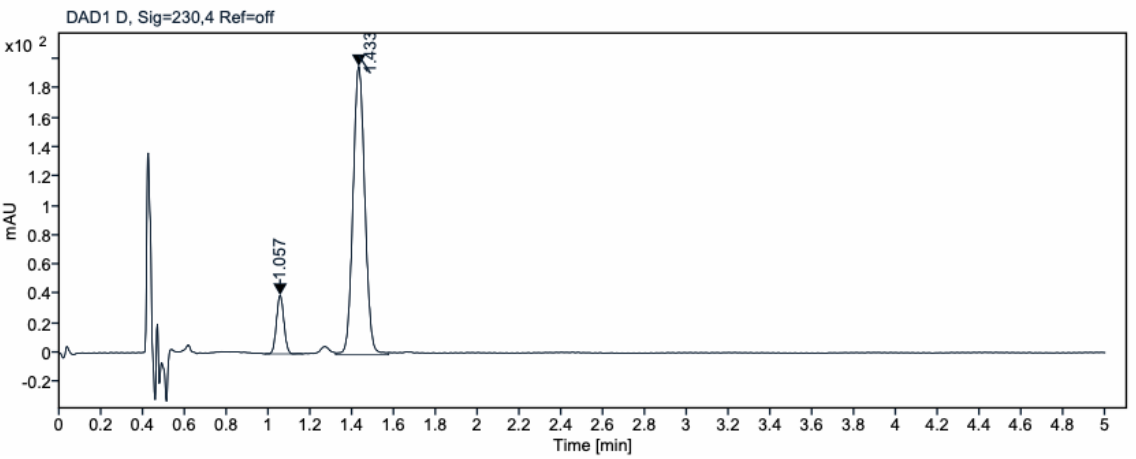
SFC racemic **2p**



Signal: DAD1 D, Sig=230,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
1.020	VB R	0.0404	210.1210	80.5557	49.9835	
1.411	BV R	0.0631	210.2595	52.1287	50.0165	
		Sum	420.3805			

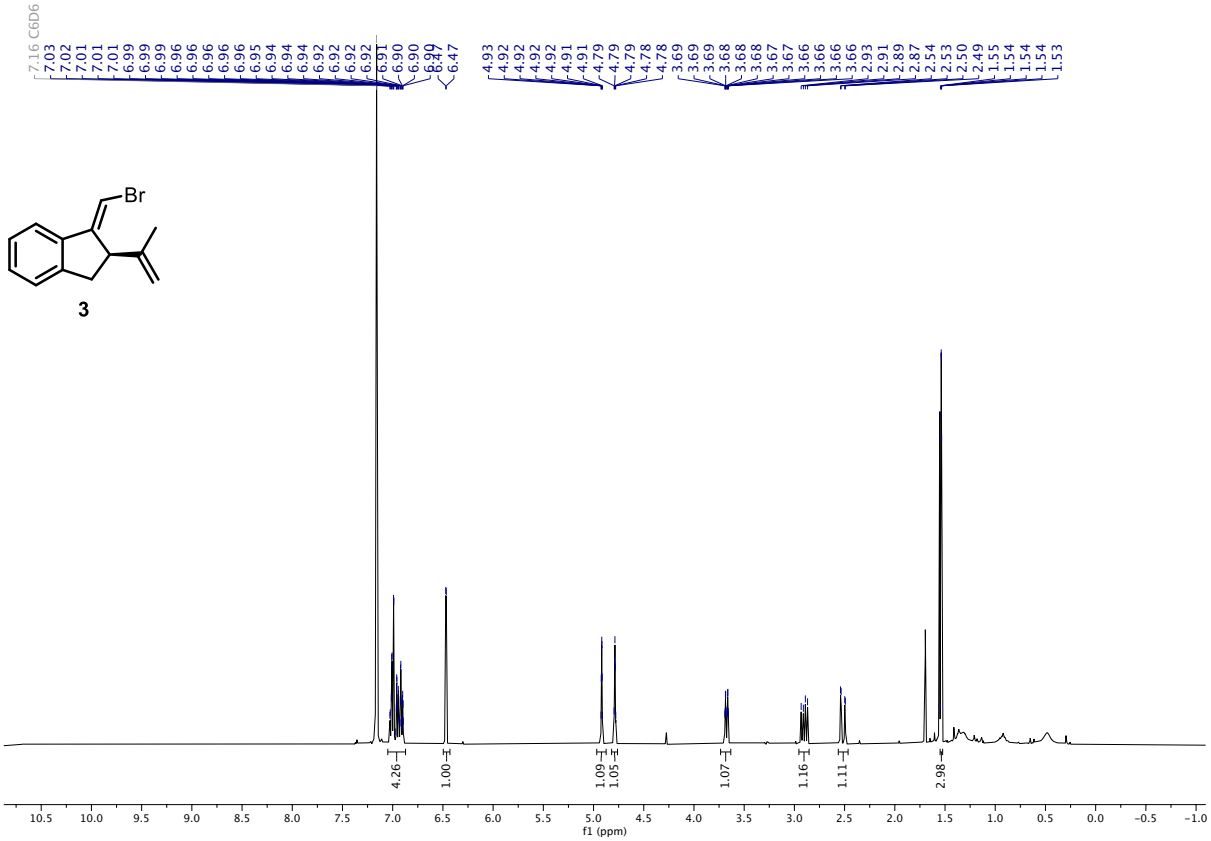
SFC enantioenriched **2p**

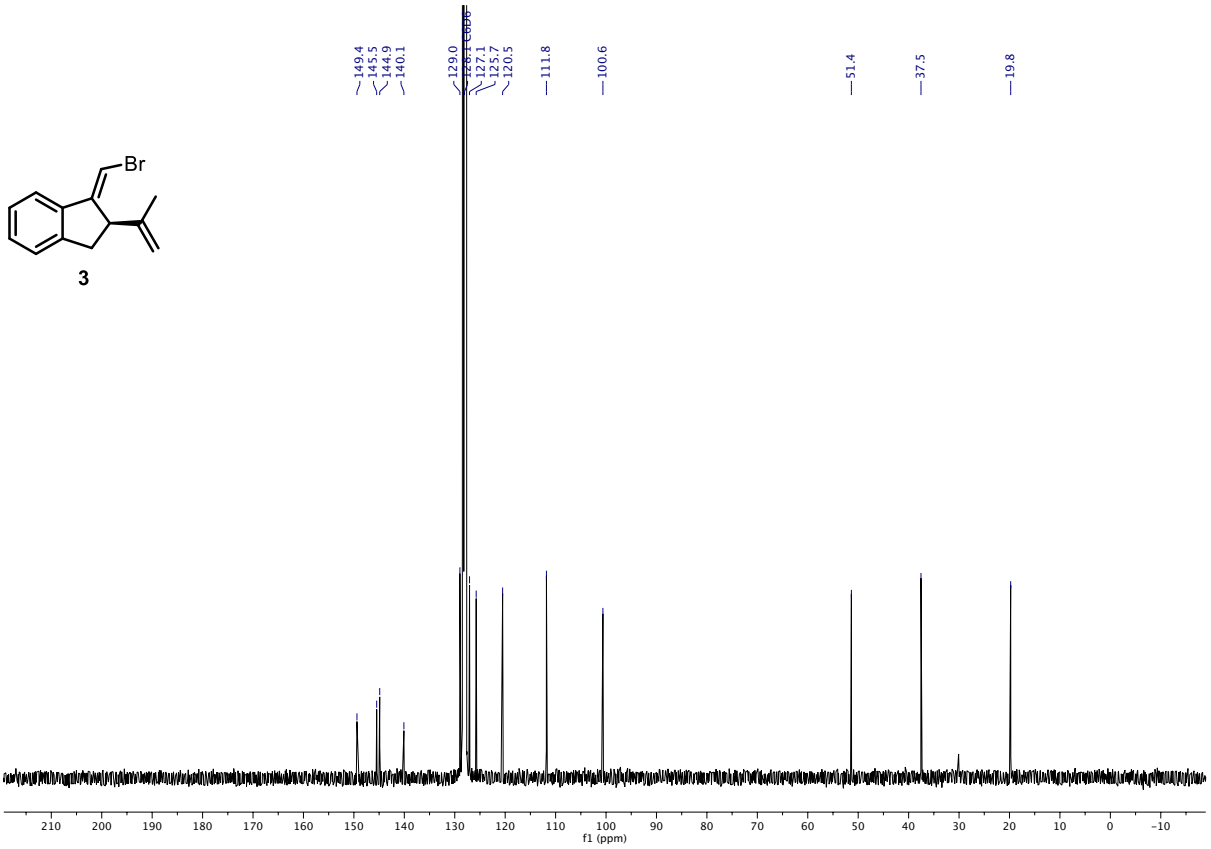


Signal: DAD1 D, Sig=230,4 Ref=off

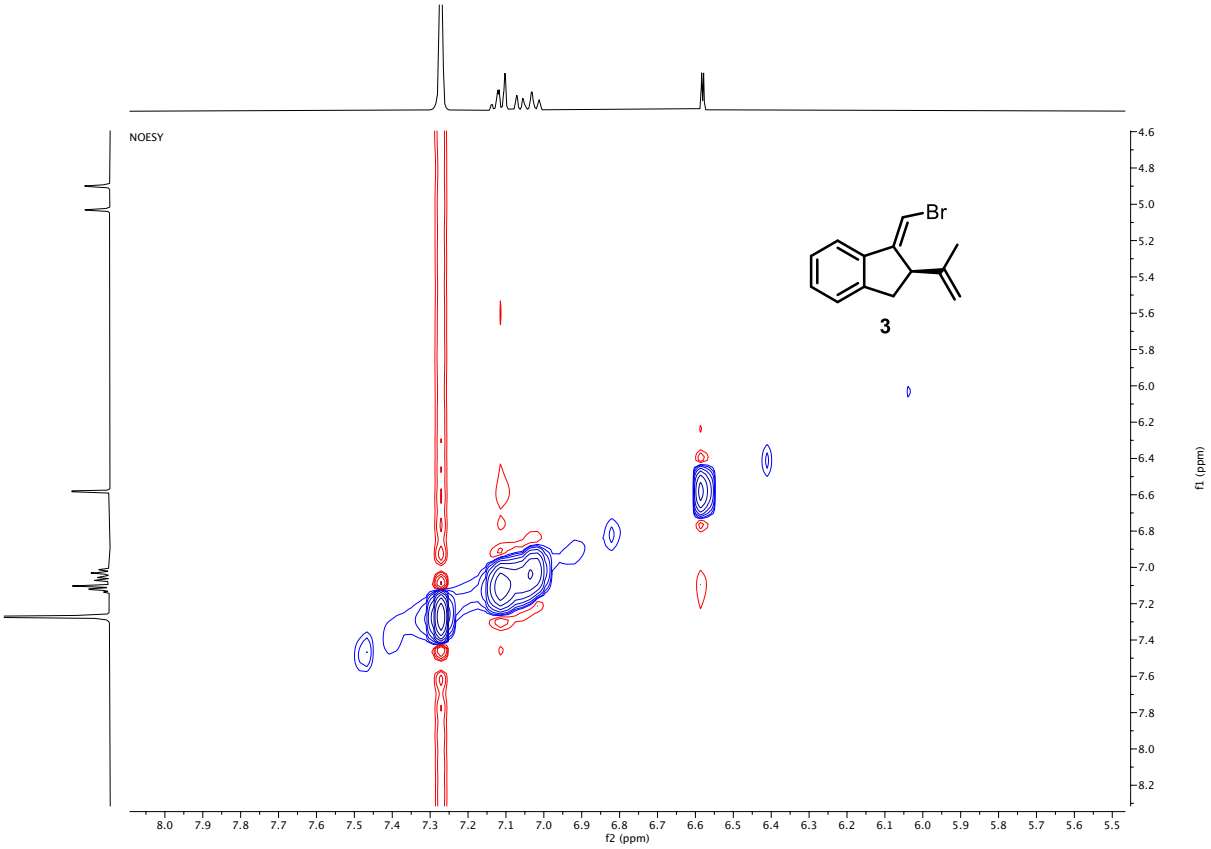
RT [min]	Type	Width [min]	Area	Height	Area%	Name
1.057	VV R	0.0389	98.8730	39.8901	11.3444	
1.433	MM	0.0656	772.6818	196.4503	88.6556	
		Sum	871.5547			

(*R*,*E*)-1-(Bromomethylene)-2-(prop-1-en-2-yl)-2,3-dihydro-1*H*-indene (3)

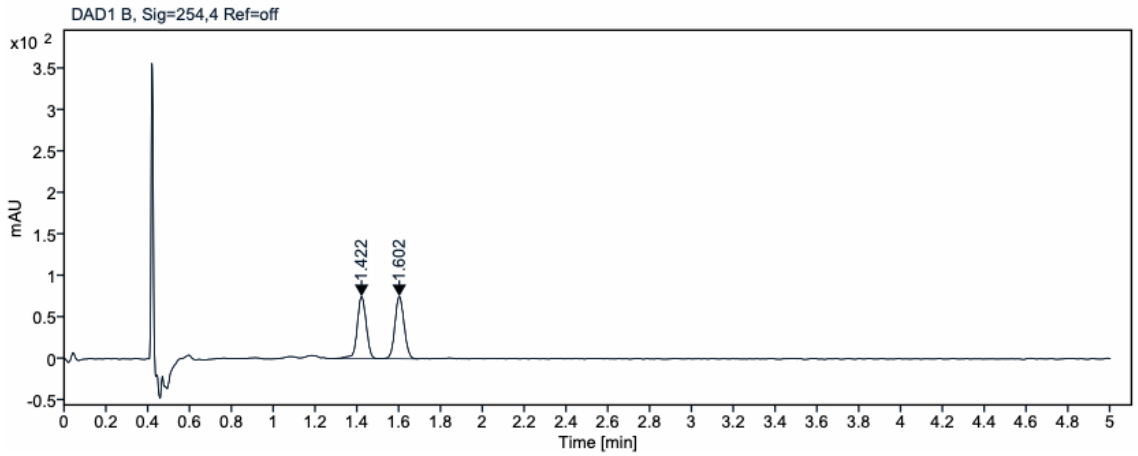




NOESY



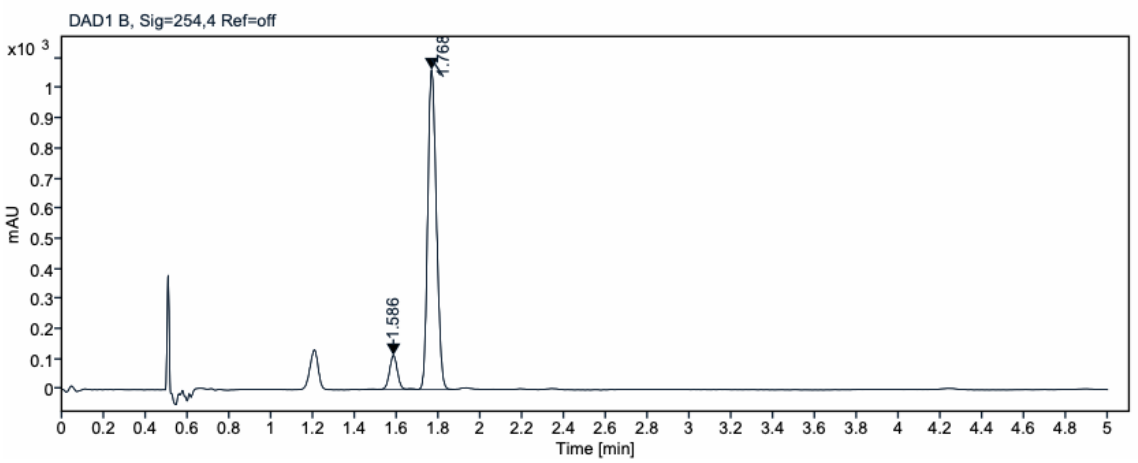
SFC racemic **3**



Signal: DAD1 B, Sig=254,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
1.422	BV R	0.0471	225.9430	75.0482	49.6106	
1.602	BB	0.0476	229.4896	75.2020	50.3894	
		Sum	455.4326			

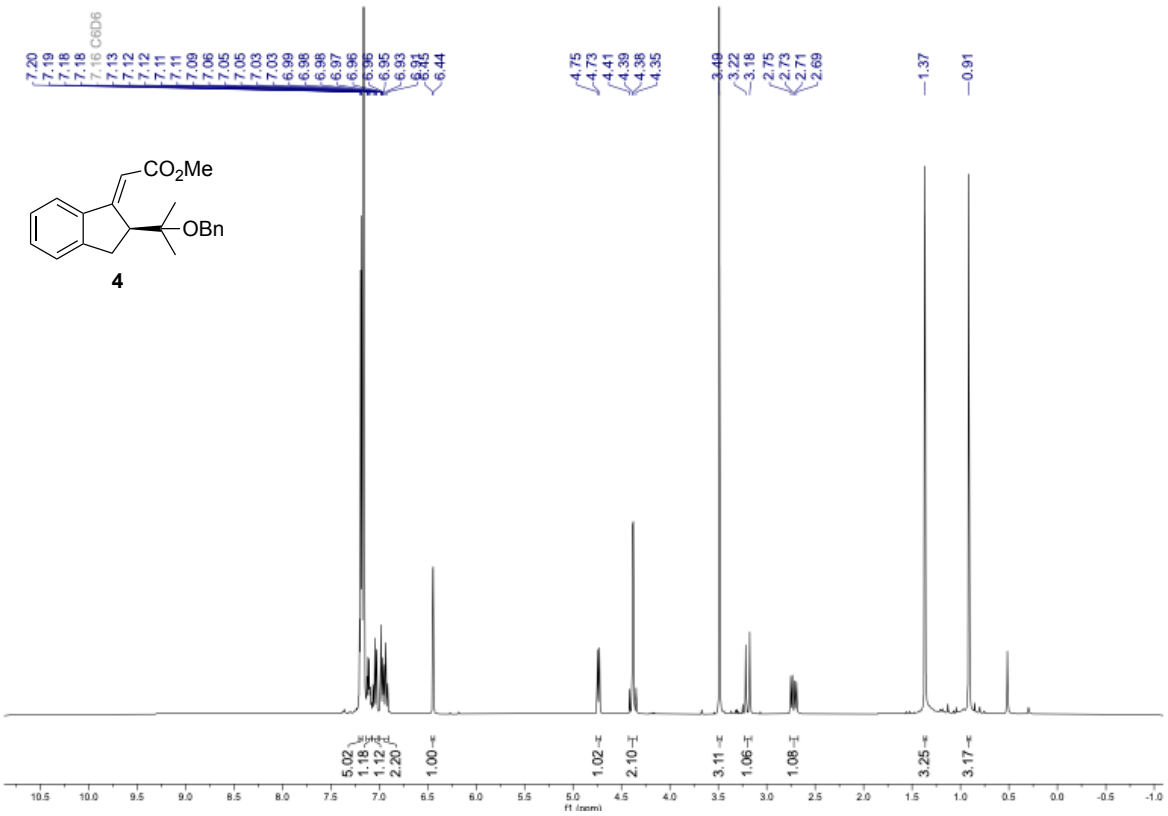
SFC enantioenriched **3**

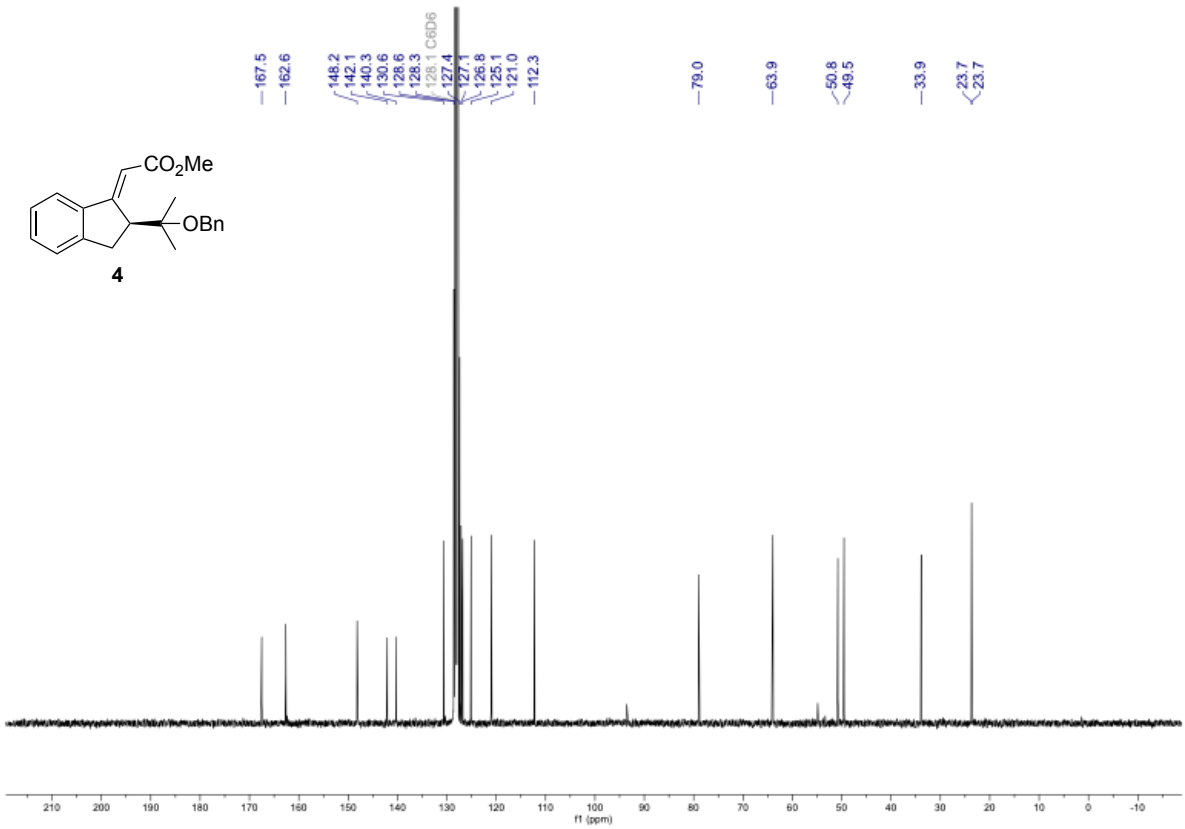


Signal: DAD1 B, Sig=254,4 Ref=off

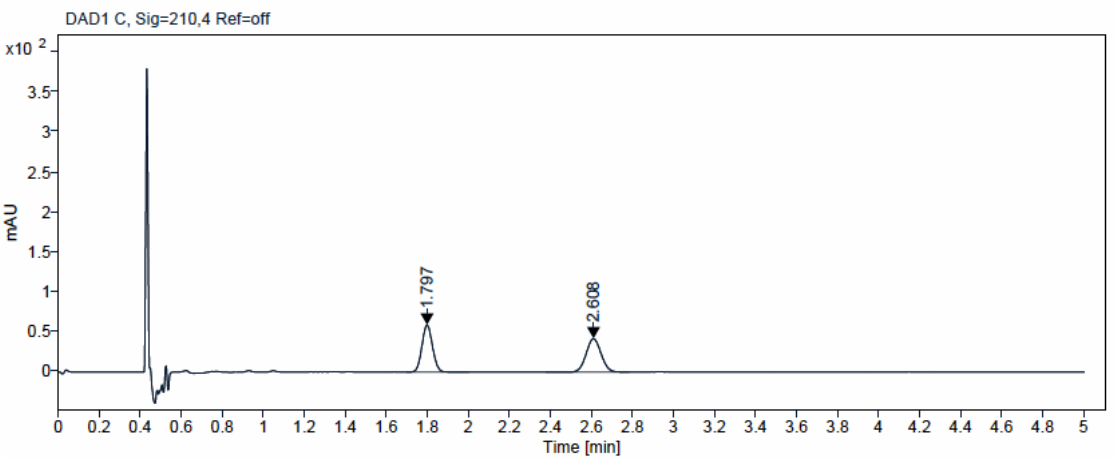
RT [min]	Type	Width [min]	Area	Height	Area%	Name
1.586	VV R	0.0419	303.9811	113.0646	9.0624	
1.768	BB	0.0450	3050.3433	1061.5714	90.9376	
		Sum	3354.3244			

Methyl (*S*,*E*)-2-(2-(2-(Benzyloxy)propan-2-yl)-2,3-dihydro-1*H*-inden-1-ylidene)acetate (4)





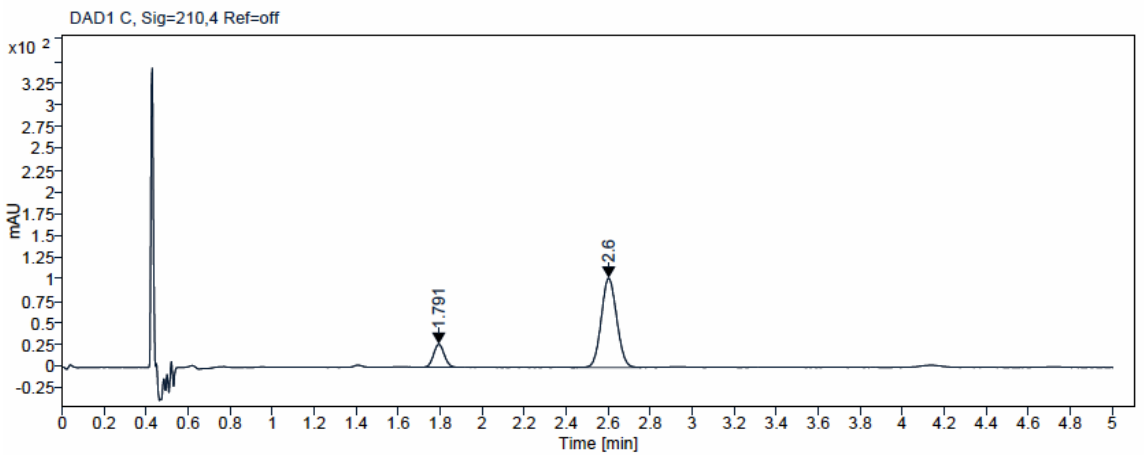
SFC racemic **4**



Signal: DAD1 C, Sig=210,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
1.797	VV R	0.0556	212.1956	58.8028	49.9619	
2.608	VV R	0.0800	212.5193	41.7036	50.0381	
		Sum	424.7149			

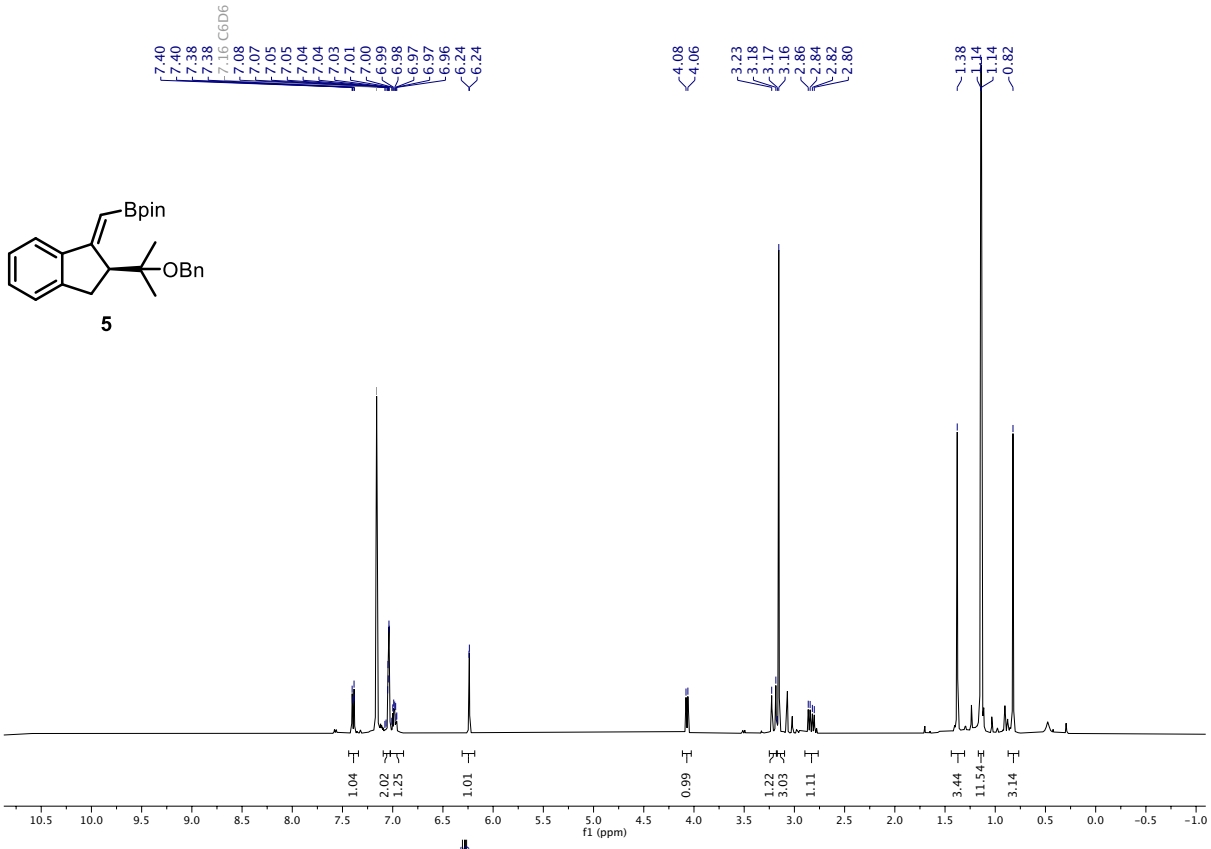
SFC enantioenriched **4**

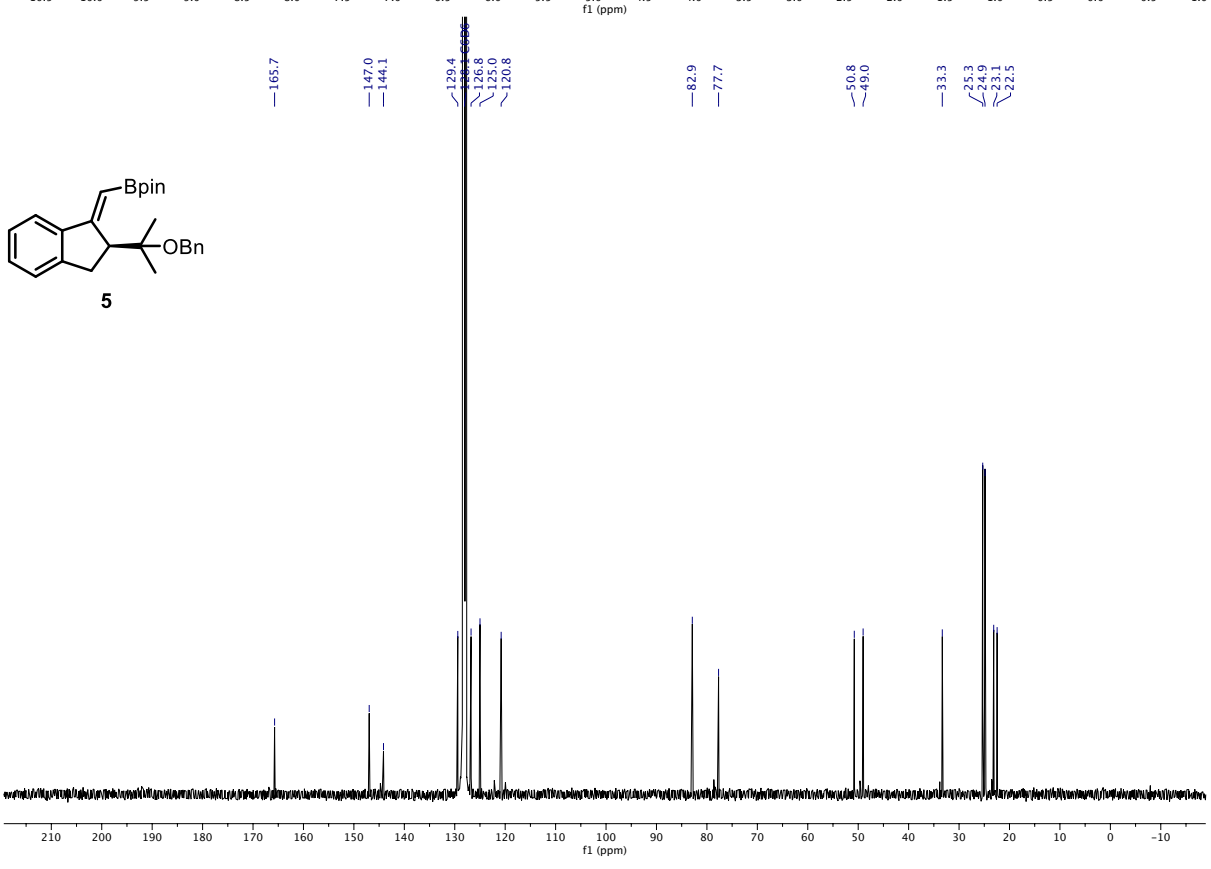


Signal: DAD1 C, Sig=210,4 Ref=off

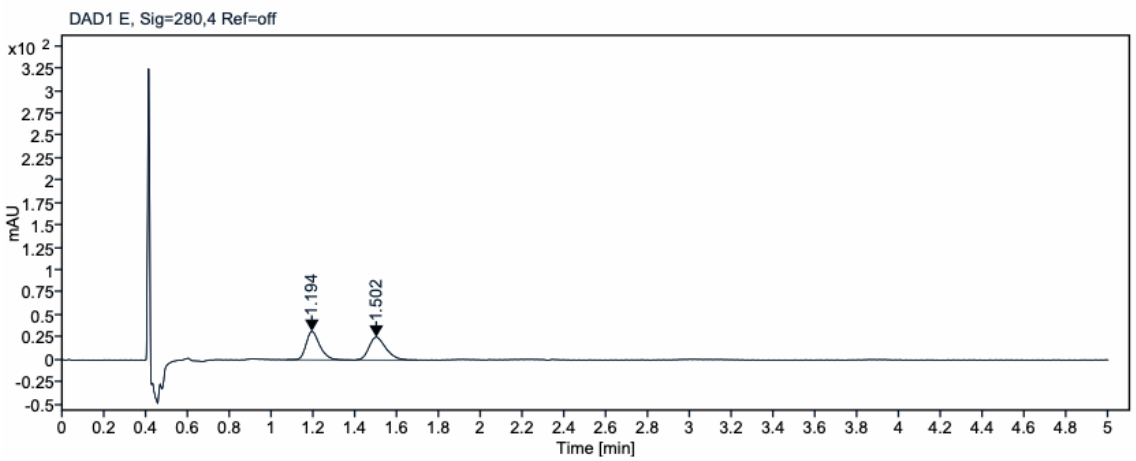
RT [min]	Type	Width [min]	Area	Height	Area%	Name
1.791	BB	0.0556	93.5834	26.2364	15.2032	
2.600	VB R	0.0801	521.9662	102.0897	84.7968	
		Sum	615.5496			

(*S*,*E*)-2-((2-(2-Methoxypropan-2-yl)-2,3-dihydro-1*H*-inden-1-ylidene)methyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5)





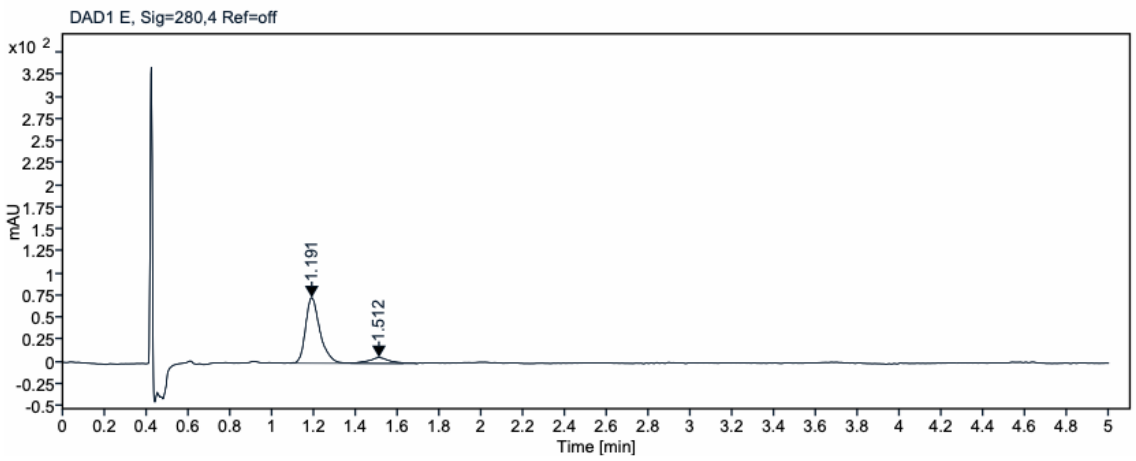
SFC racemic **5**



Signal: DAD1 E, Sig=280,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
1.194	VV R	0.0688	144.6492	31.6625	50.1572	
1.502	BV R	0.0831	143.7427	25.3527	49.8428	
		Sum	288.3919			

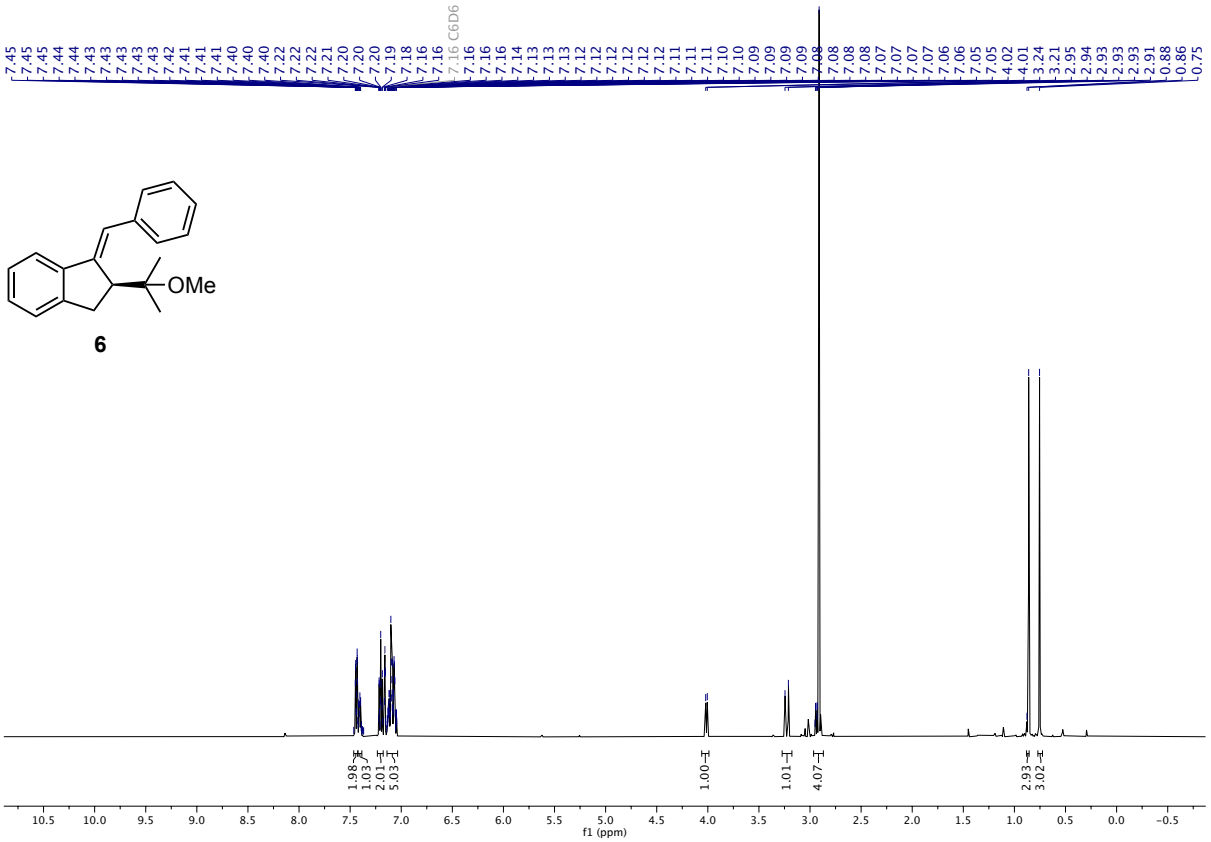
SFC enantioenriched **5**

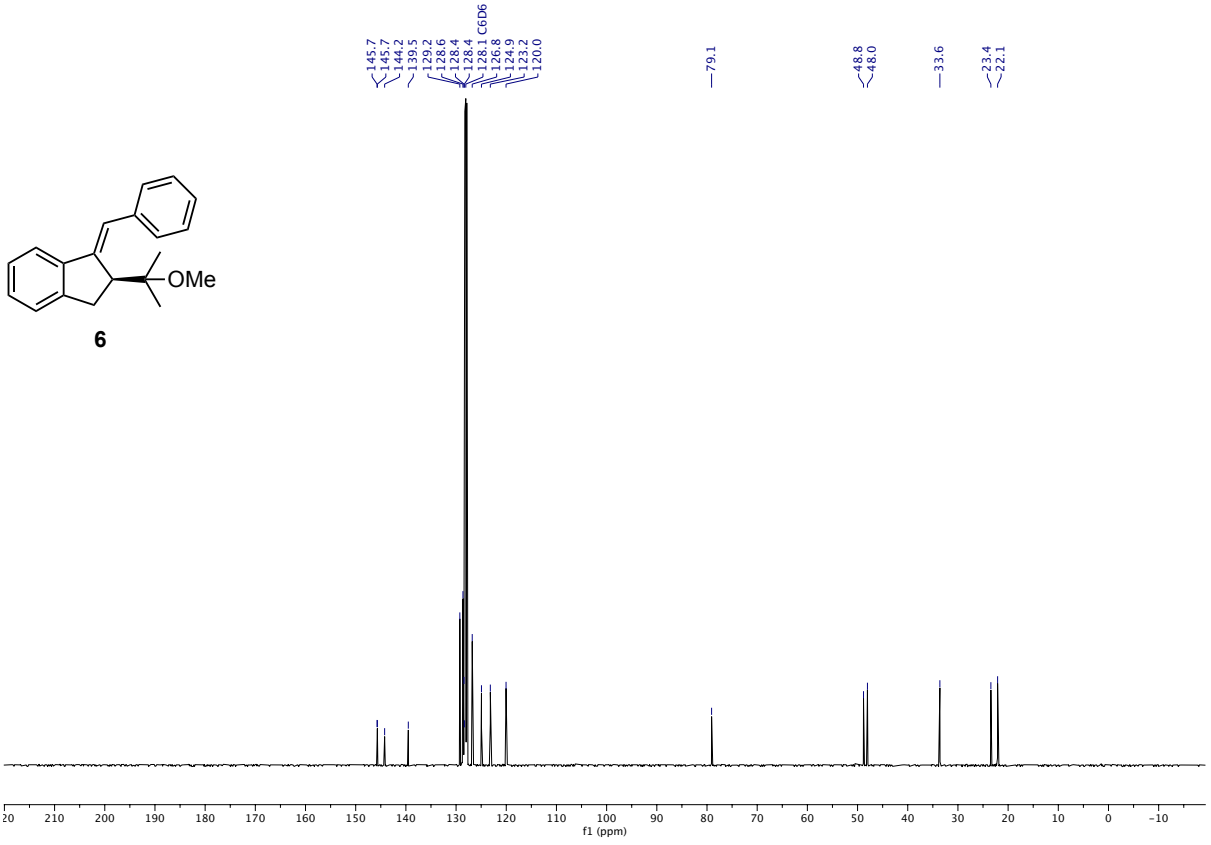


Signal: DAD1 E, Sig=280,4 Ref=off

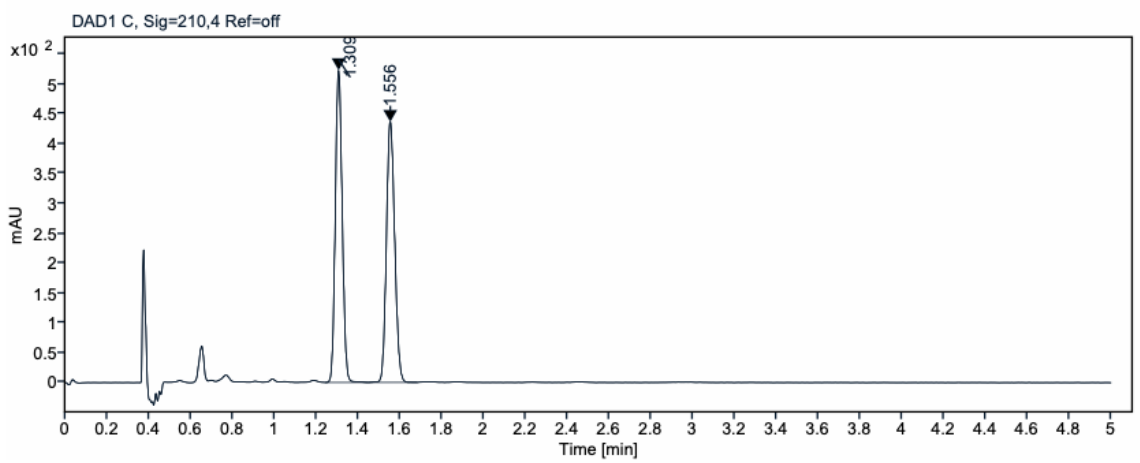
RT [min]	Type	Width [min]	Area	Height	Area%	Name
1.191	VV R	0.0702	356.9990	74.0853	88.8881	
1.512	VV E	0.0906	44.6285	6.6658	11.1119	
		Sum	401.6274			

(*S*,*E*)-1-Benzylidene-2-(2-methoxypropan-2-yl)-2,3-dihydro-1*H*-indene (6)





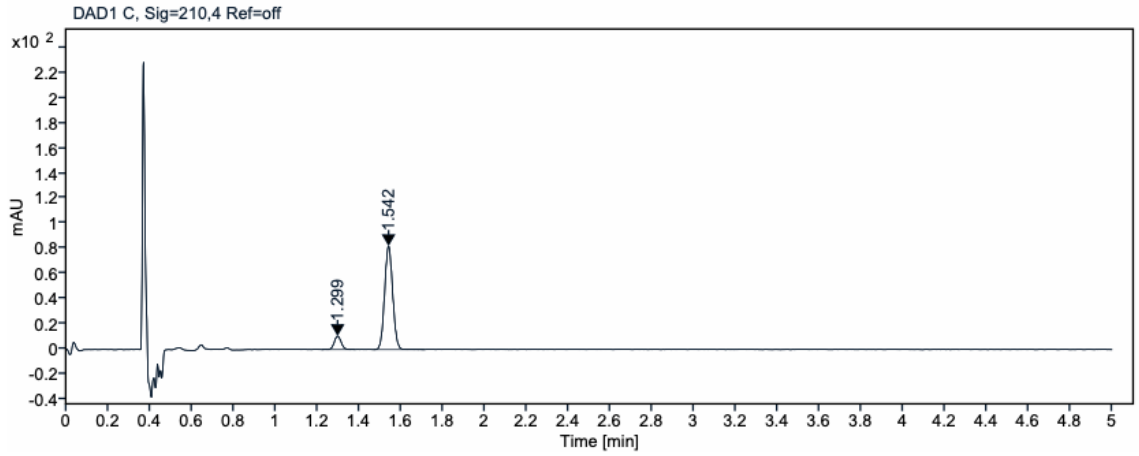
SFC racemic **6**



Signal: DAD1 C, Sig=210,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
1.309	BB	0.0358	1201.8523	523.4111	49.9934	
1.556	BV R	0.0431	1202.1703	436.7412	50.0066	
		Sum	2404.0226			

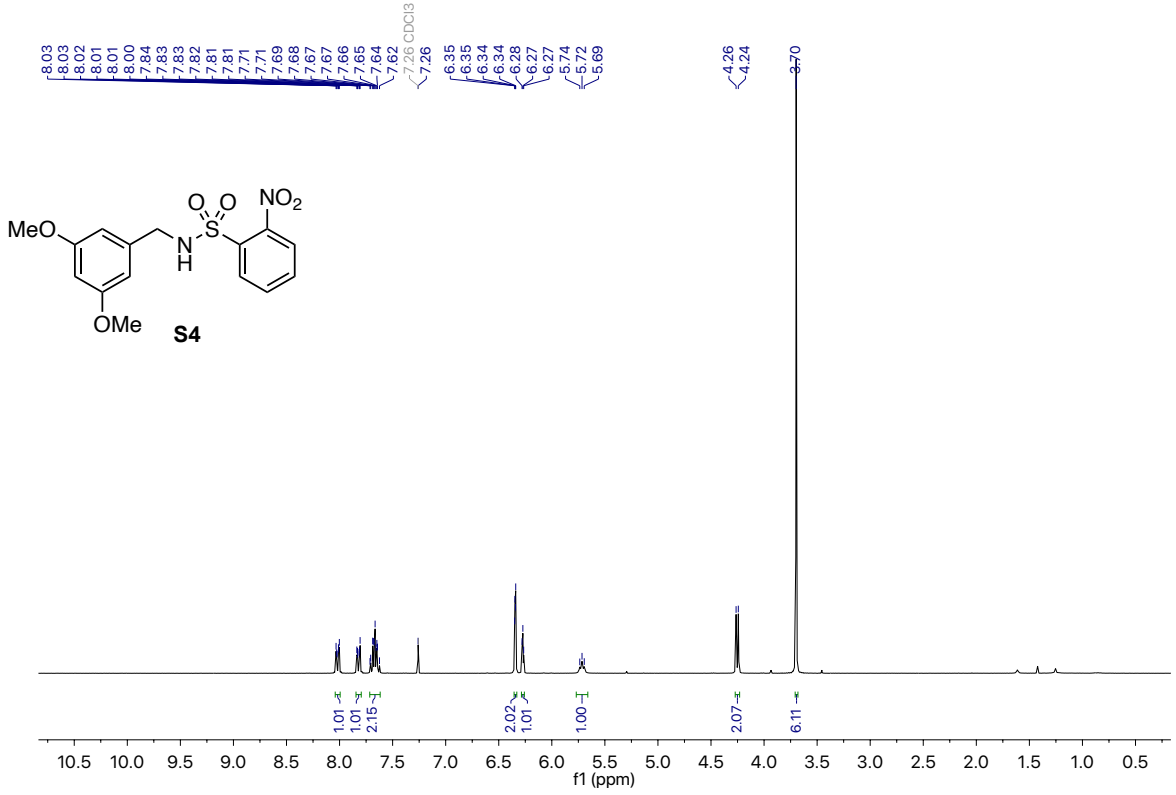
SFC enantioenriched **6**

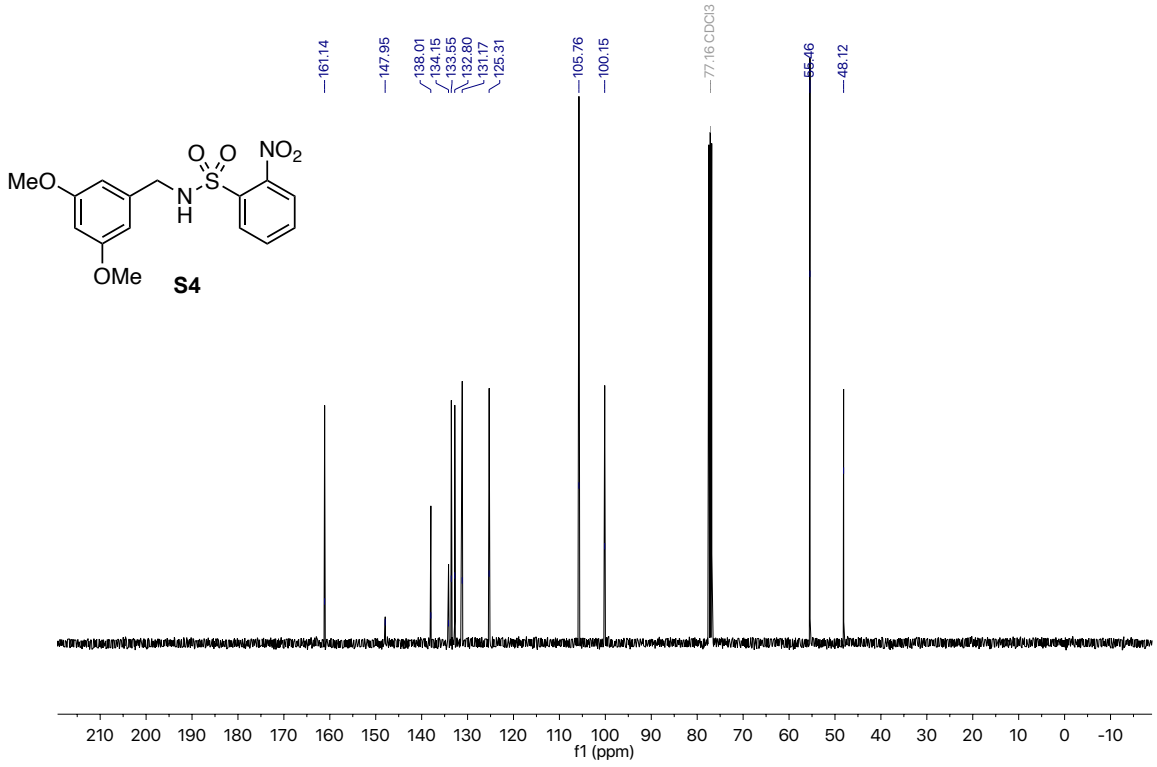


Signal: DAD1 C, Sig=210,4 Ref=off

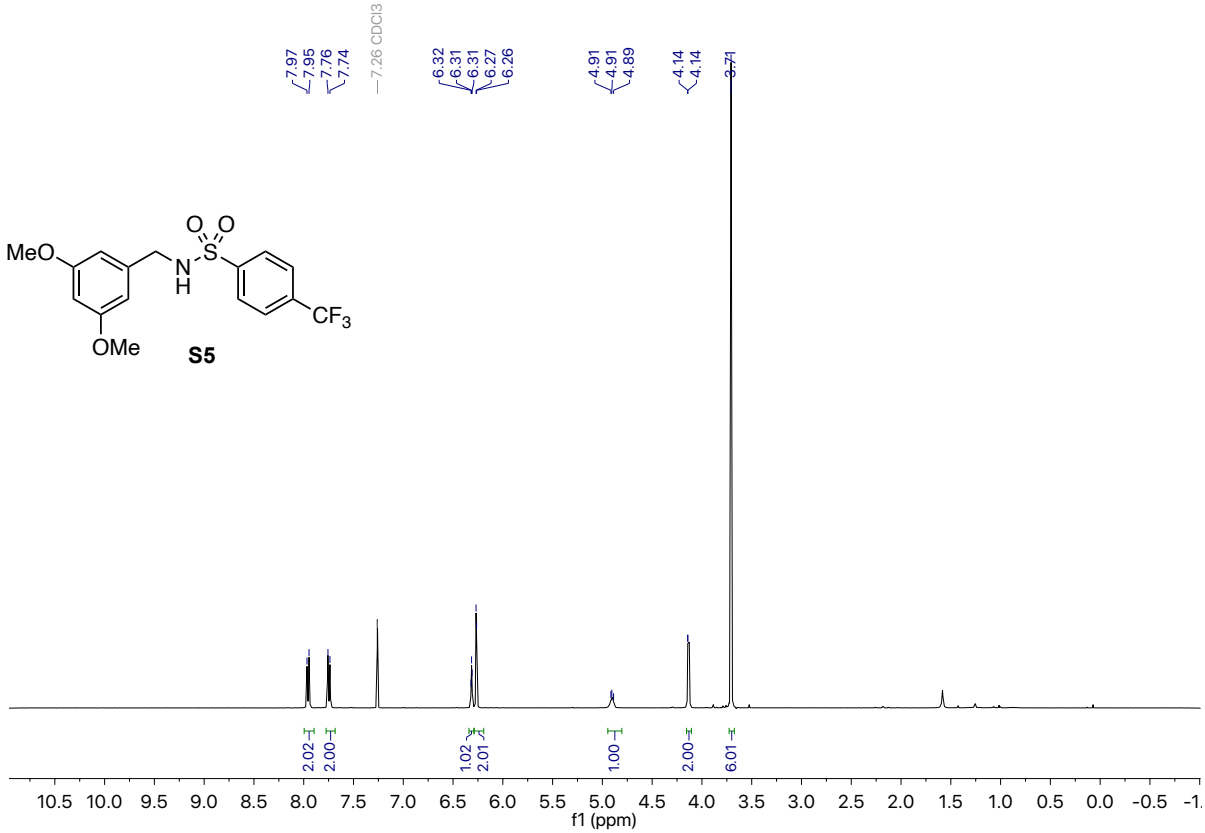
RT [min]	Type	Width [min]	Area	Height	Area%	Name
1.299	VV R	0.0362	24.7660	10.6177	10.0563	
1.542	BV R	0.0420	221.5067	82.1018	89.9437	
		Sum	246.2727			

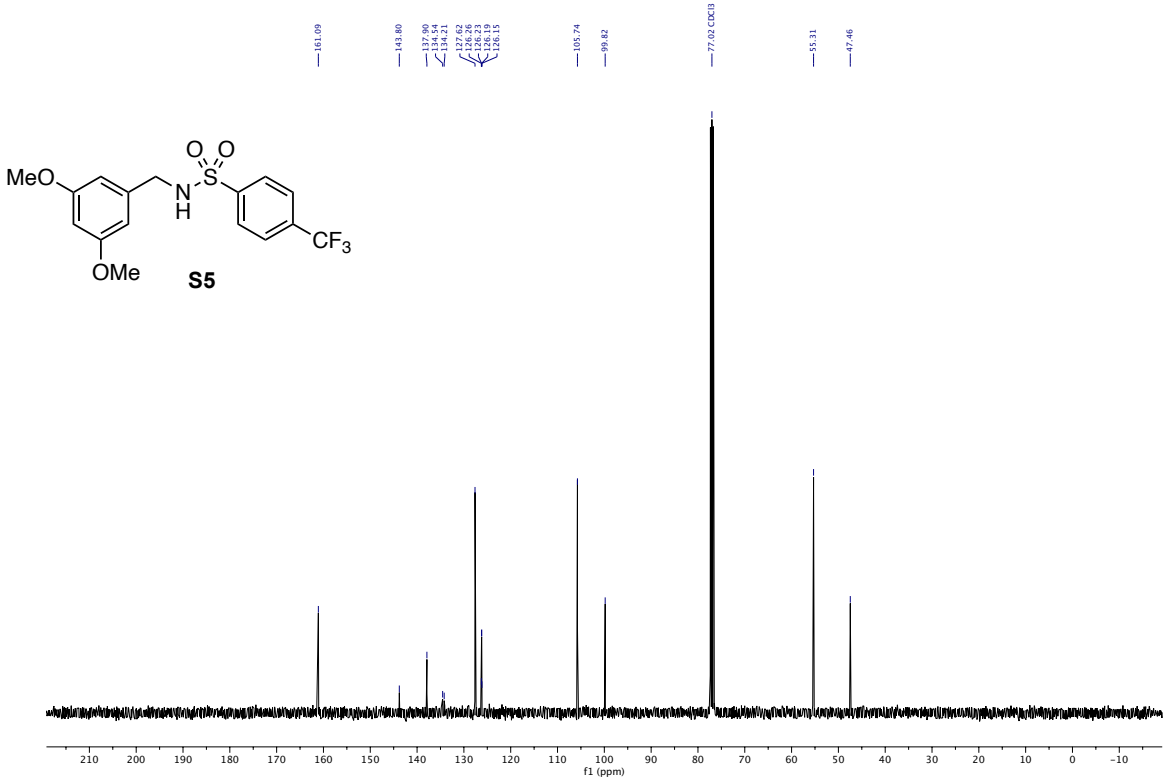
***N*-(3,5-Dimethoxybenzyl)-2-nitrobenzenesulfonamide (S4)**





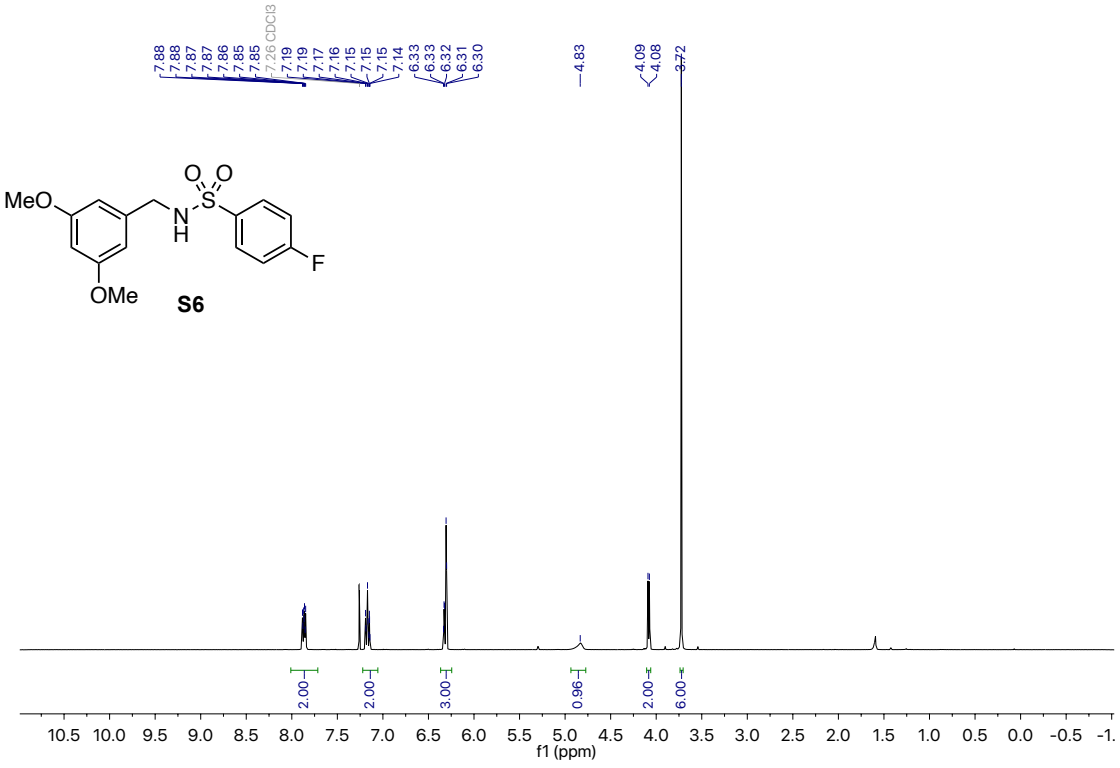
***N*-(3,5-Dimethoxybenzyl)-4-(trifluoromethyl)benzenesulfonamide (S5)**

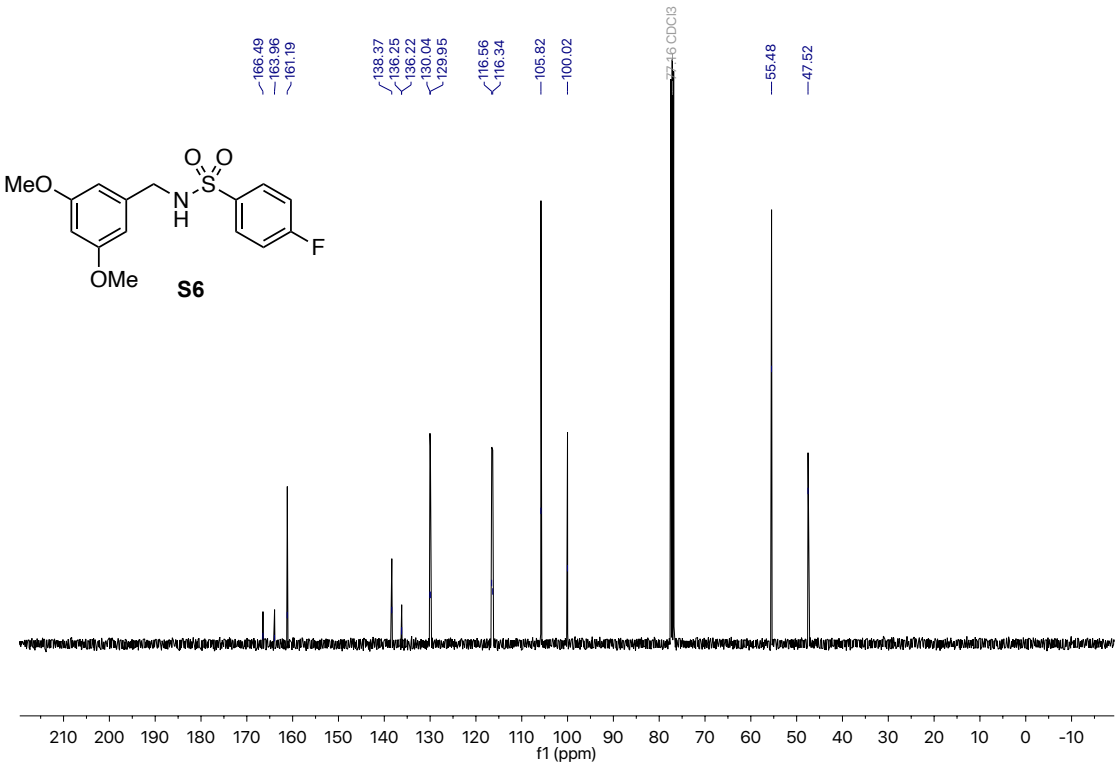


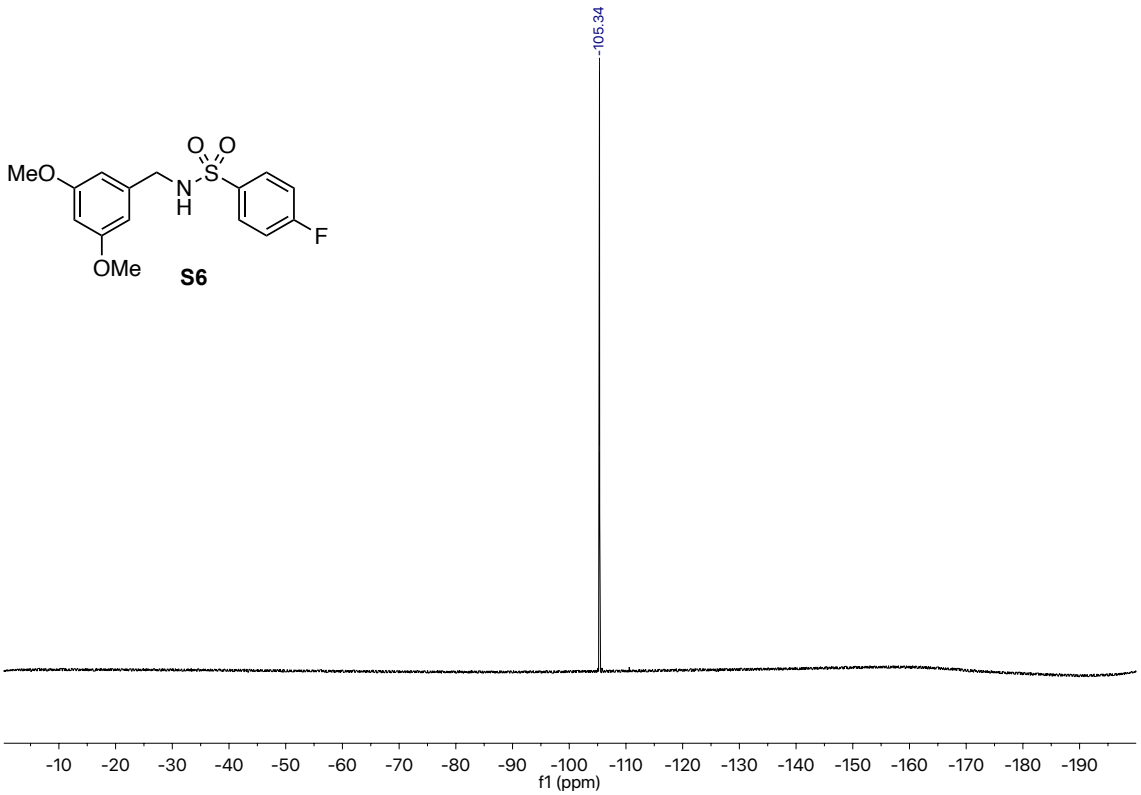



MeO
OMe
O
O
S
N
H
CF3
S5
-63.27
-10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

***N*-(3,5-Dimethoxybenzyl)-4-fluorobenzenesulfonamide (S6)**

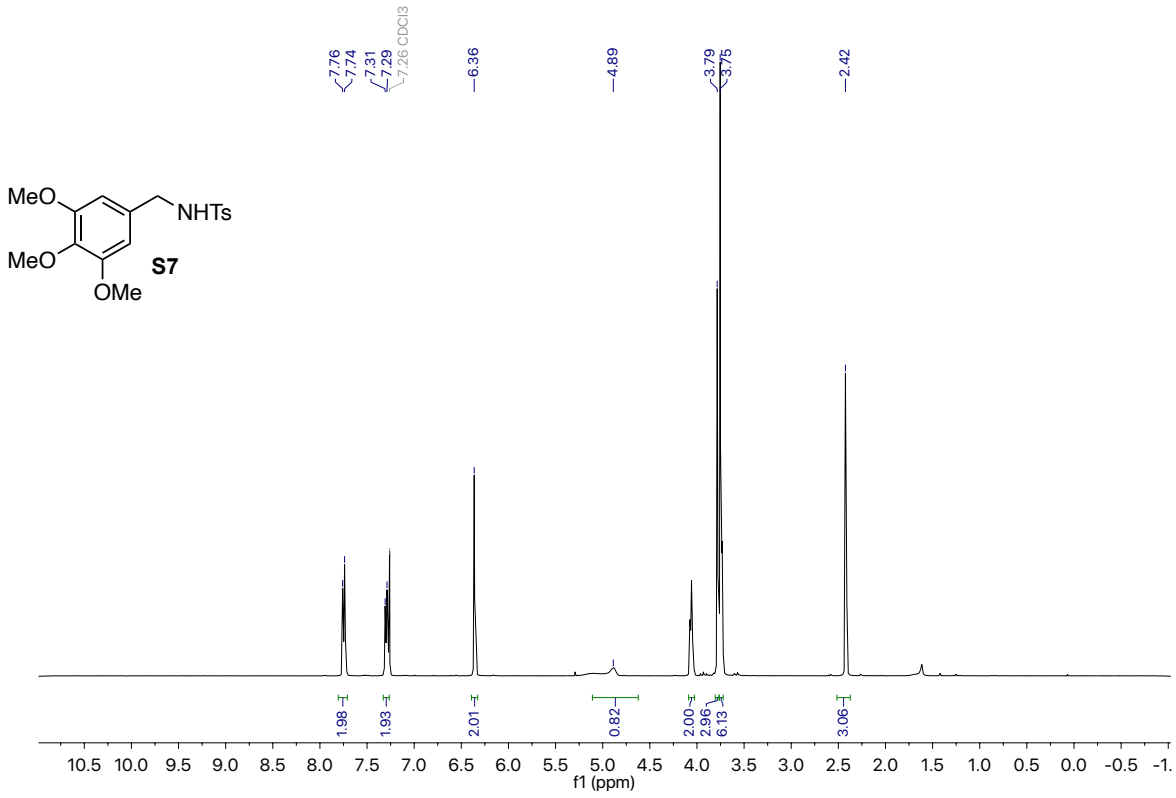


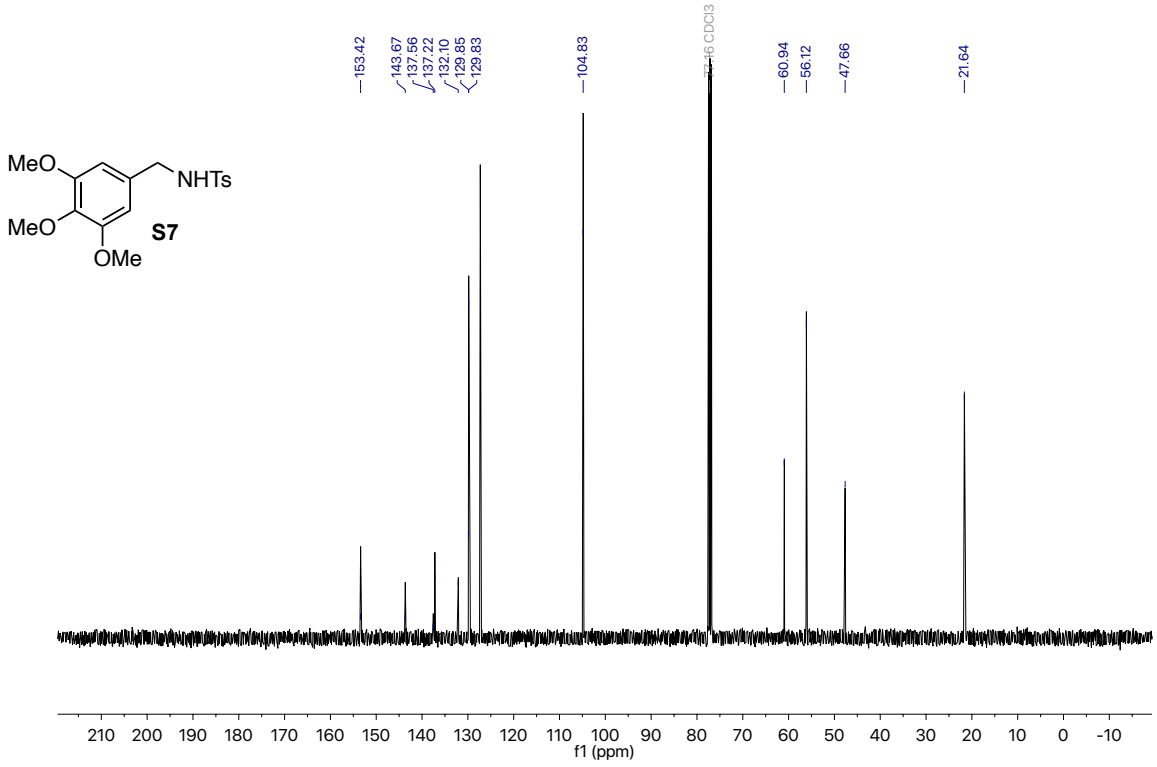



-105.34
MeO
OMe
O
O
S
N
H
F
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

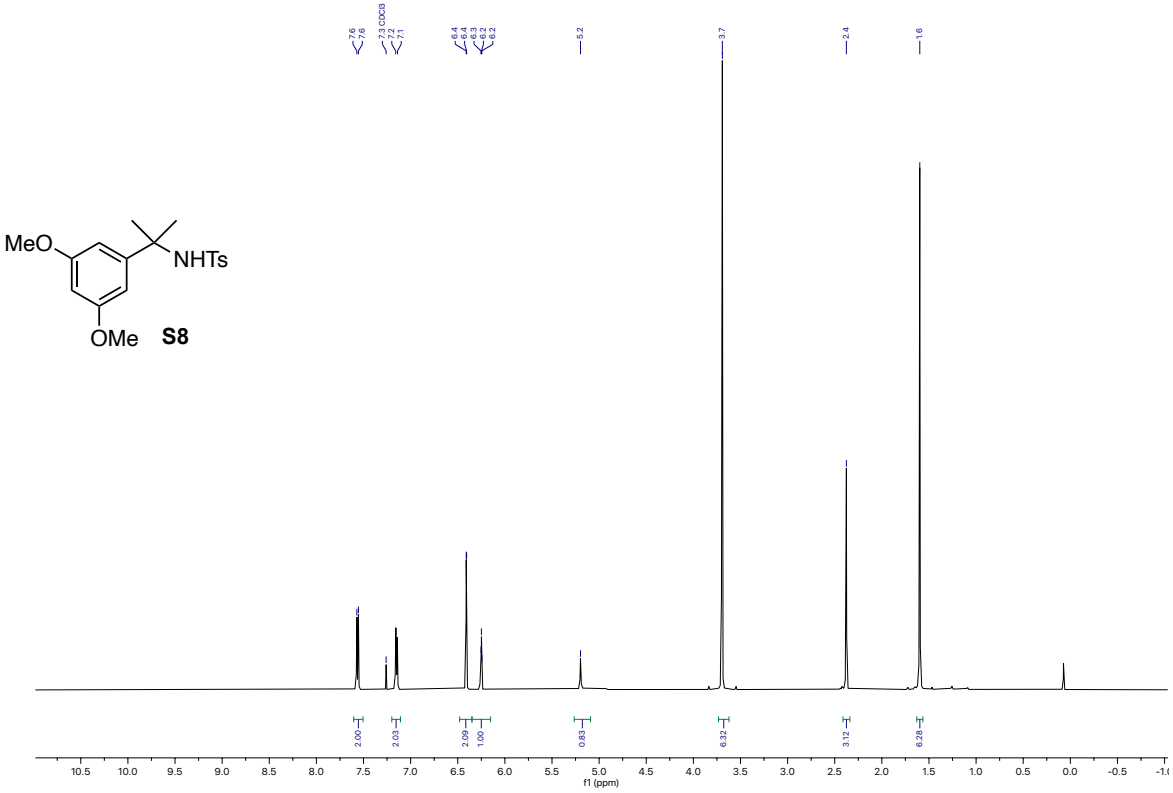
S6

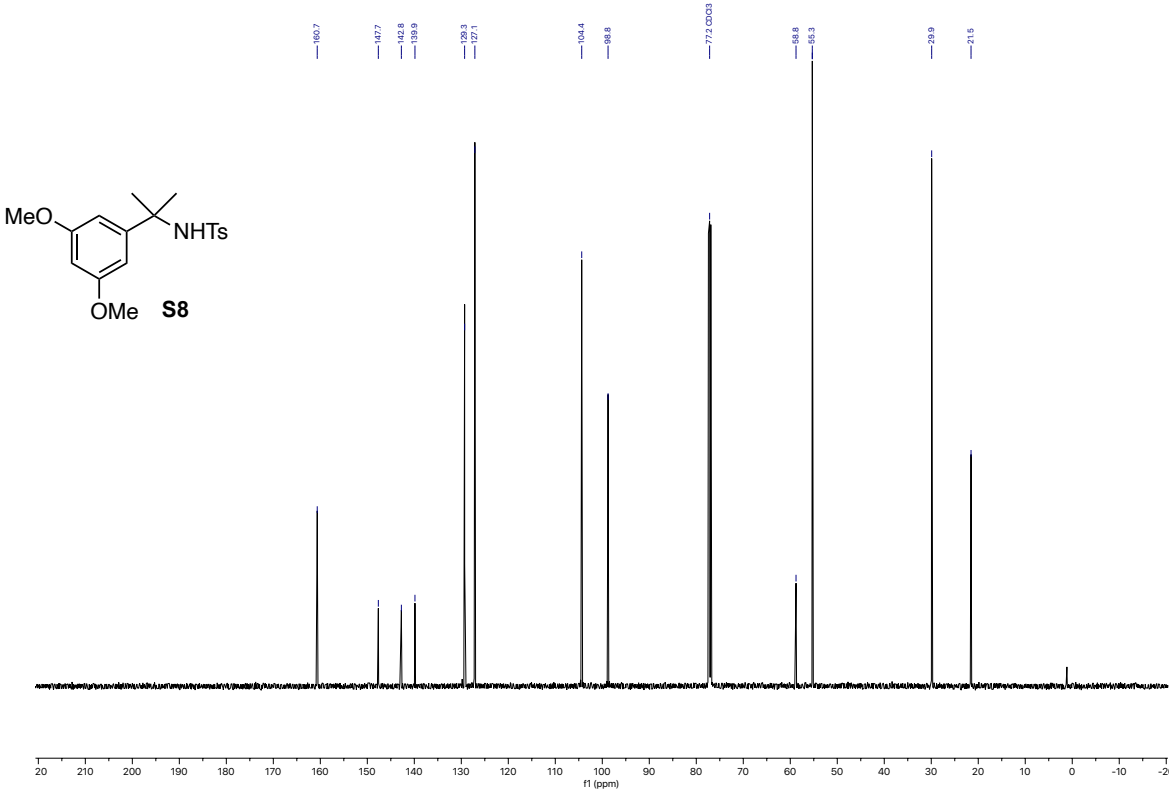
4-Methyl-*N*-(3,4,5-trimethoxybenzyl)benzenesulfonamide (S7)



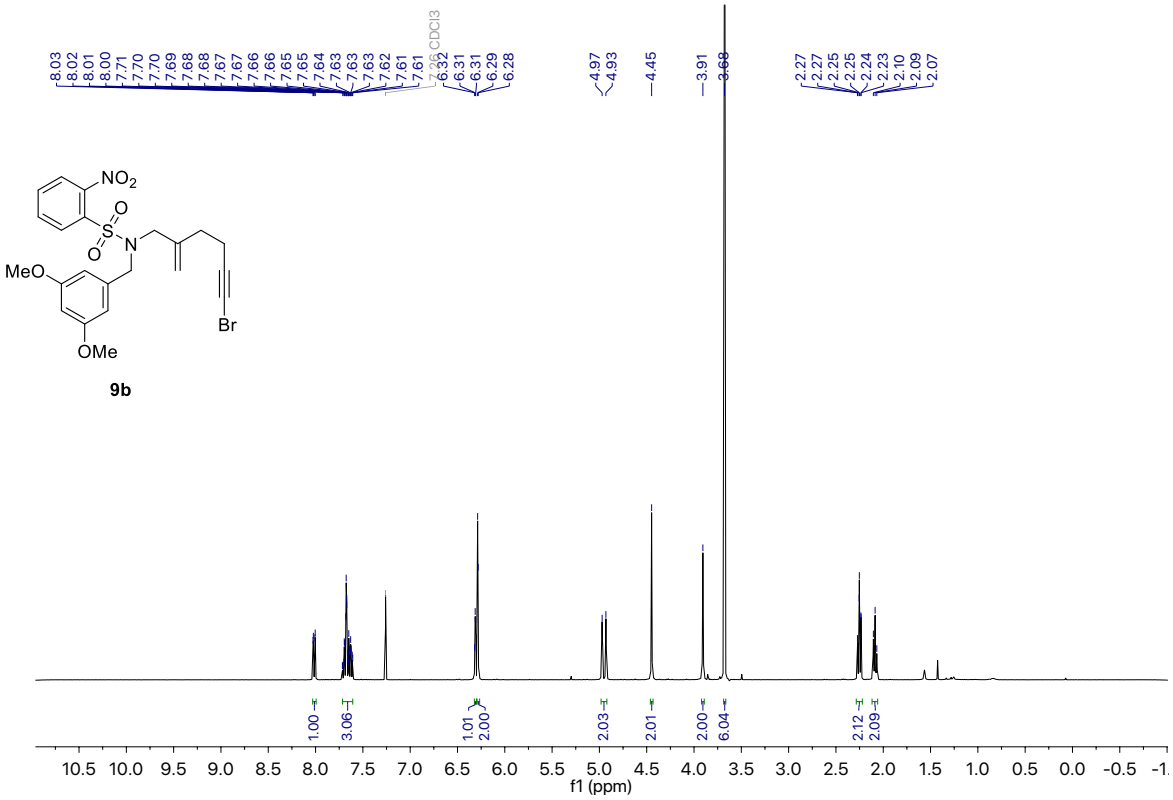


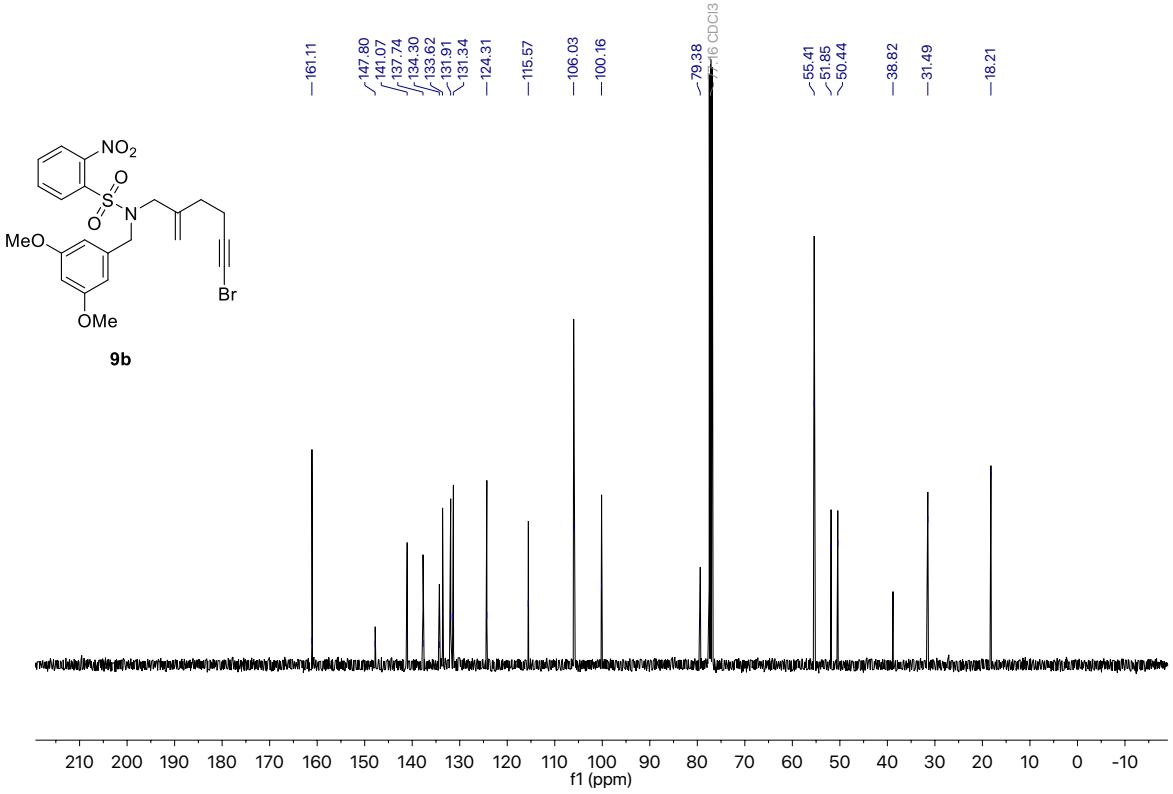
***N*-(2-(3,5-Dimethoxyphenyl)propan-2-yl)-4-methylbenzenesulfonamide (S8)**



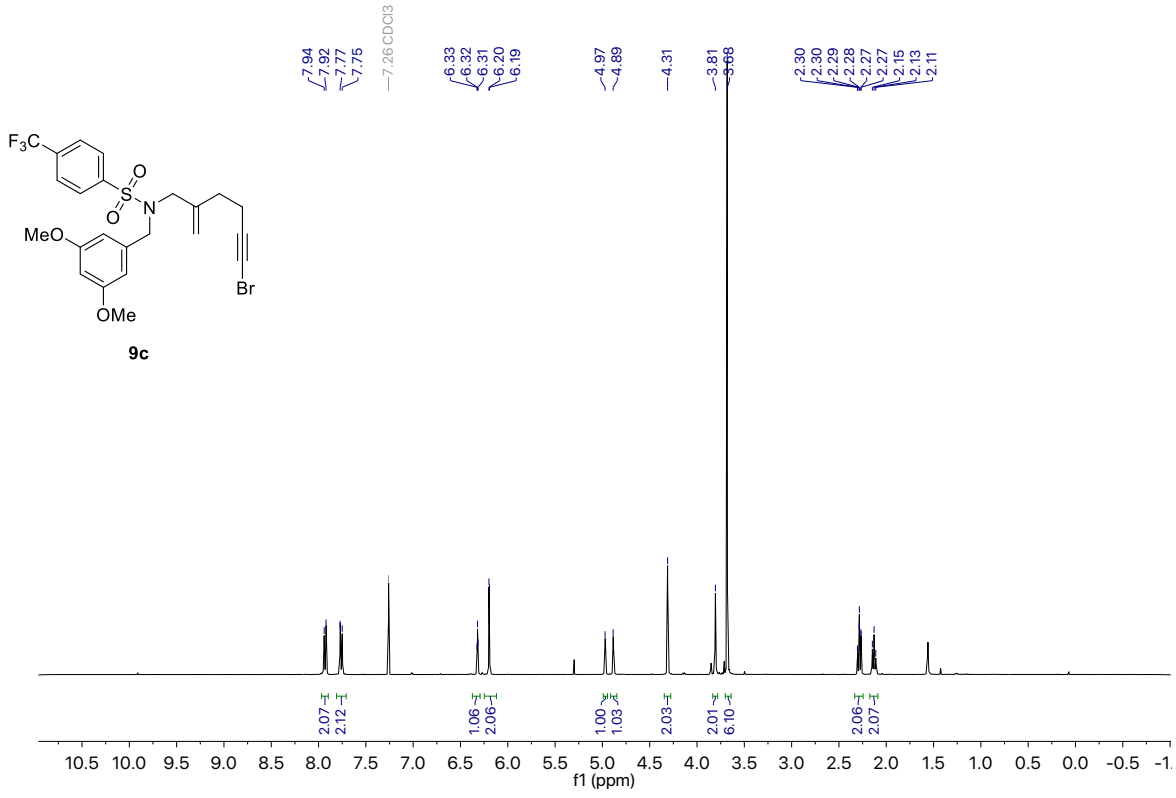


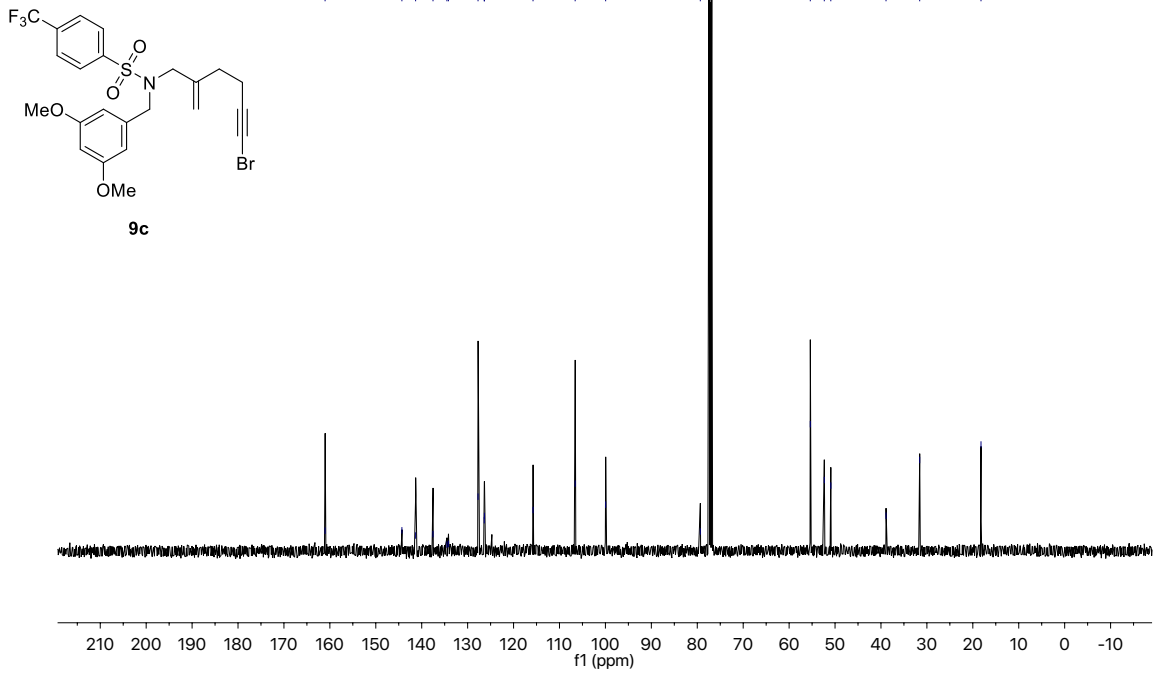
***N*-(6-Bromo-2-methylenehex-5-yn-1-yl)-*N*-(3,5-dimethoxybenzyl)-2-nitrobenzenesulfonamide (9b)**

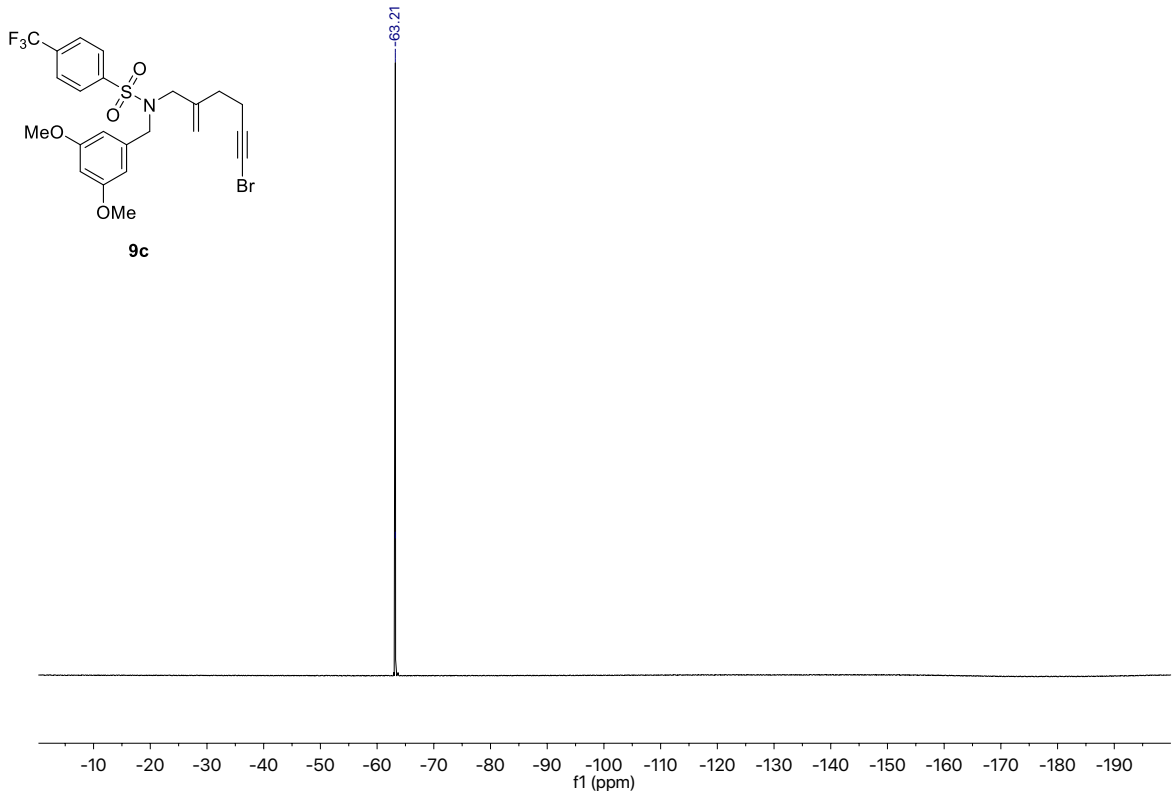




***N*-(6-Bromo-2-methylenehex-5-yn-1-yl)-*N*-(3,5-dimethoxybenzyl)-4-(trifluoromethyl)benzenesulfonamide (9c)**

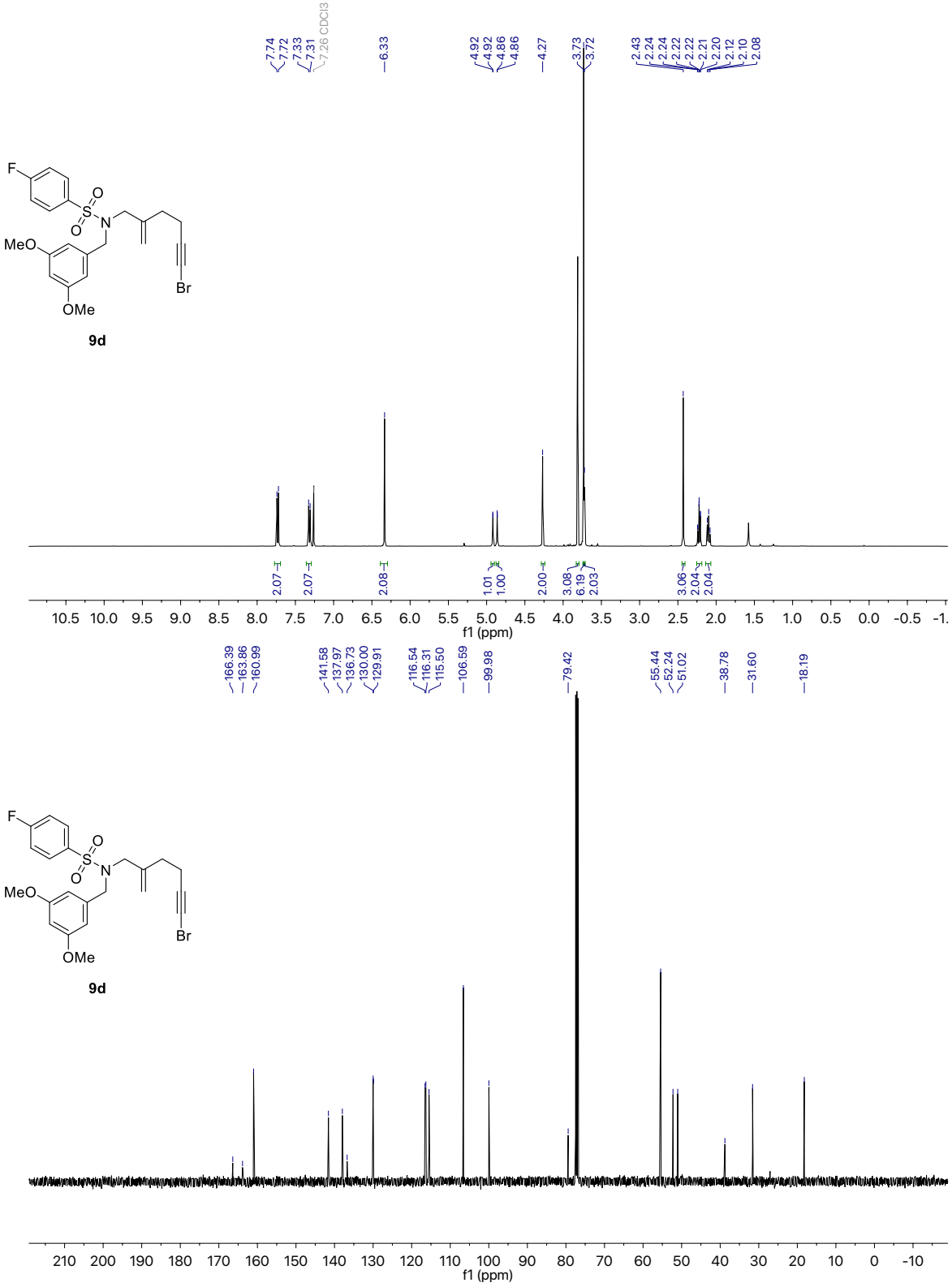


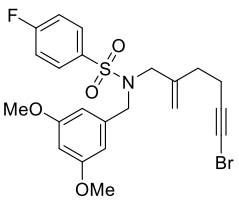



F3C
O
O
S
N
MeO
OMe
Br
-63.21
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

9c

***N*-(6-Bromo-2-methylenehex-5-yn-1-yl)-*N*-(3,5-dimethoxybenzyl)-4-fluorobenzenesulfonamide (9d)**

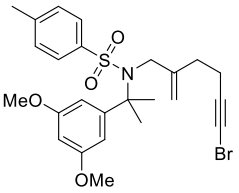



F
O
S
O
N
MeO
OMe
Br

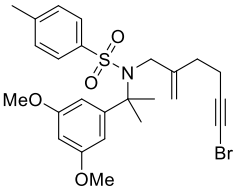
9d

-105.49
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

_N_-(6-Bromo-2-methylenehex-5-yn-1-yl)-_N_-(2-(3,5-dimethoxyphenyl)propan-2-yl)-4-methylbenzenesulfonamide (9e)

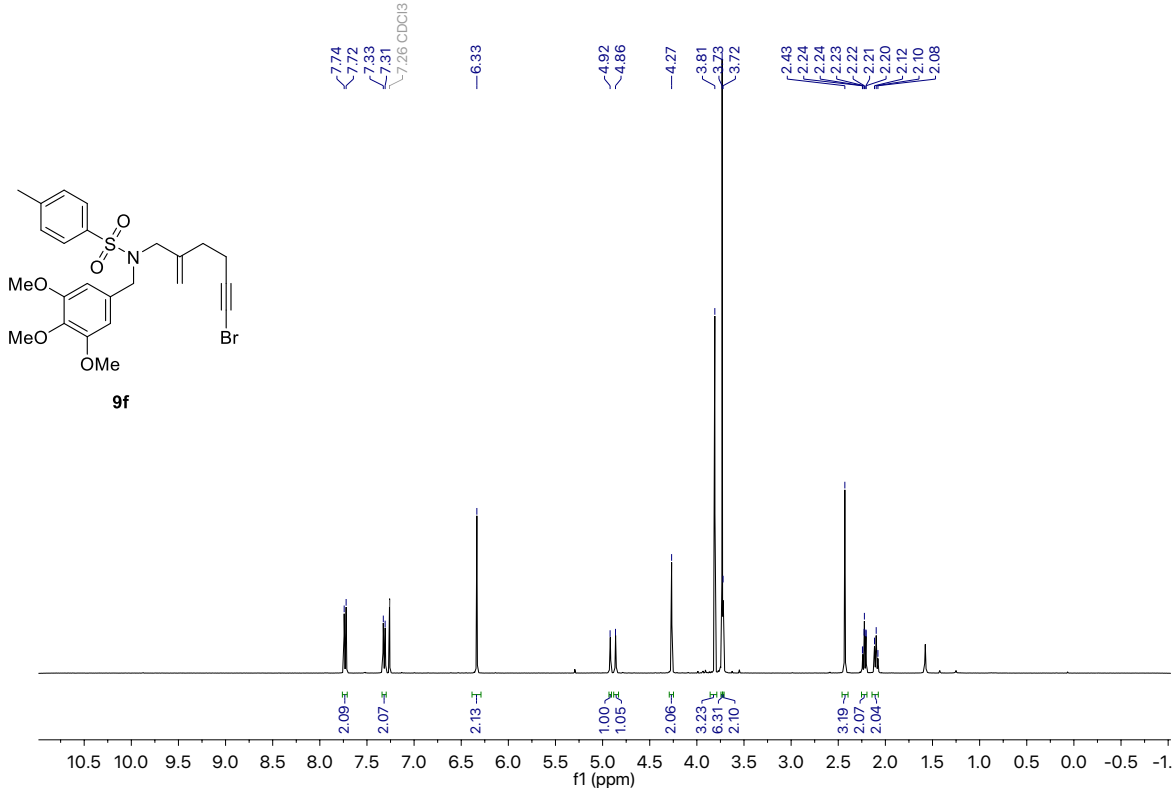


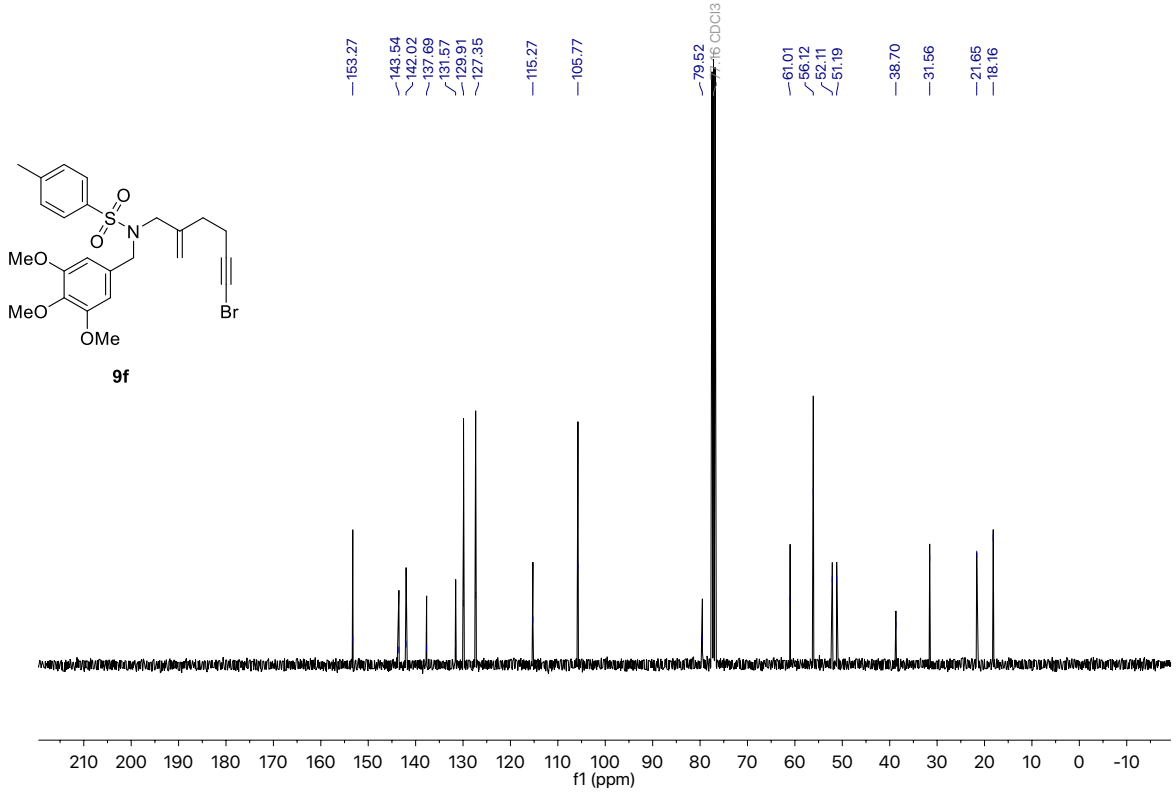
9e



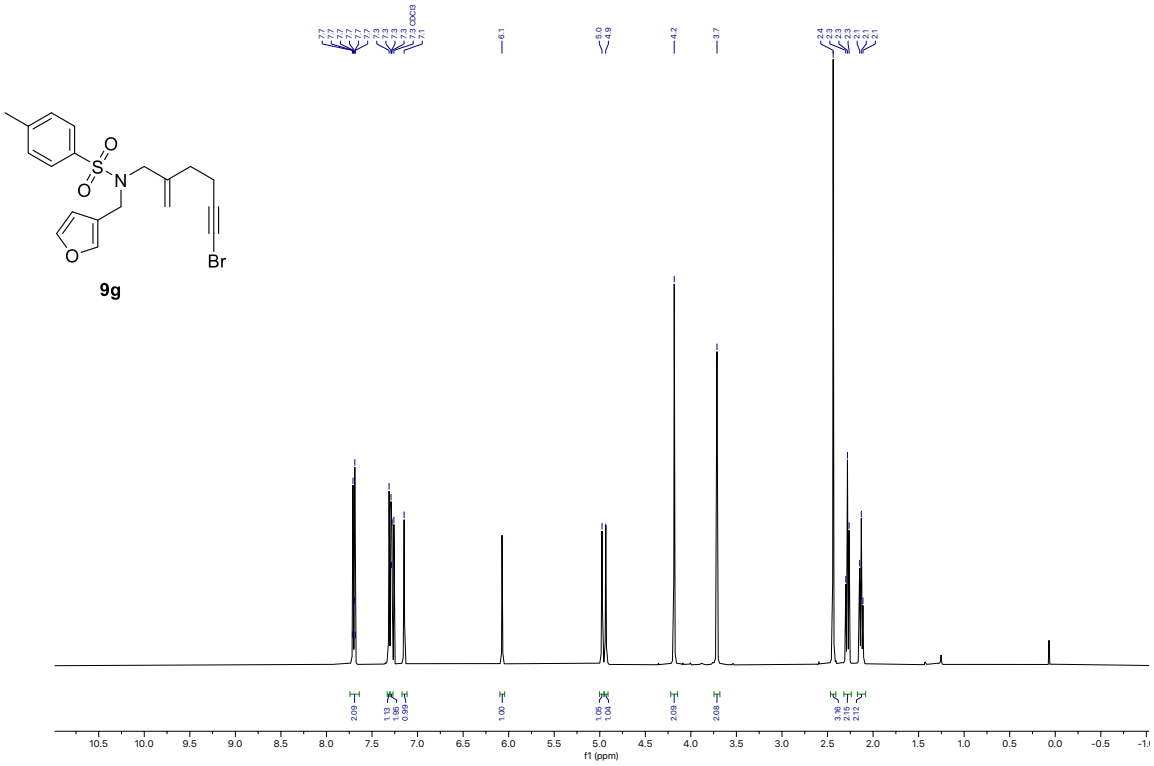
9e

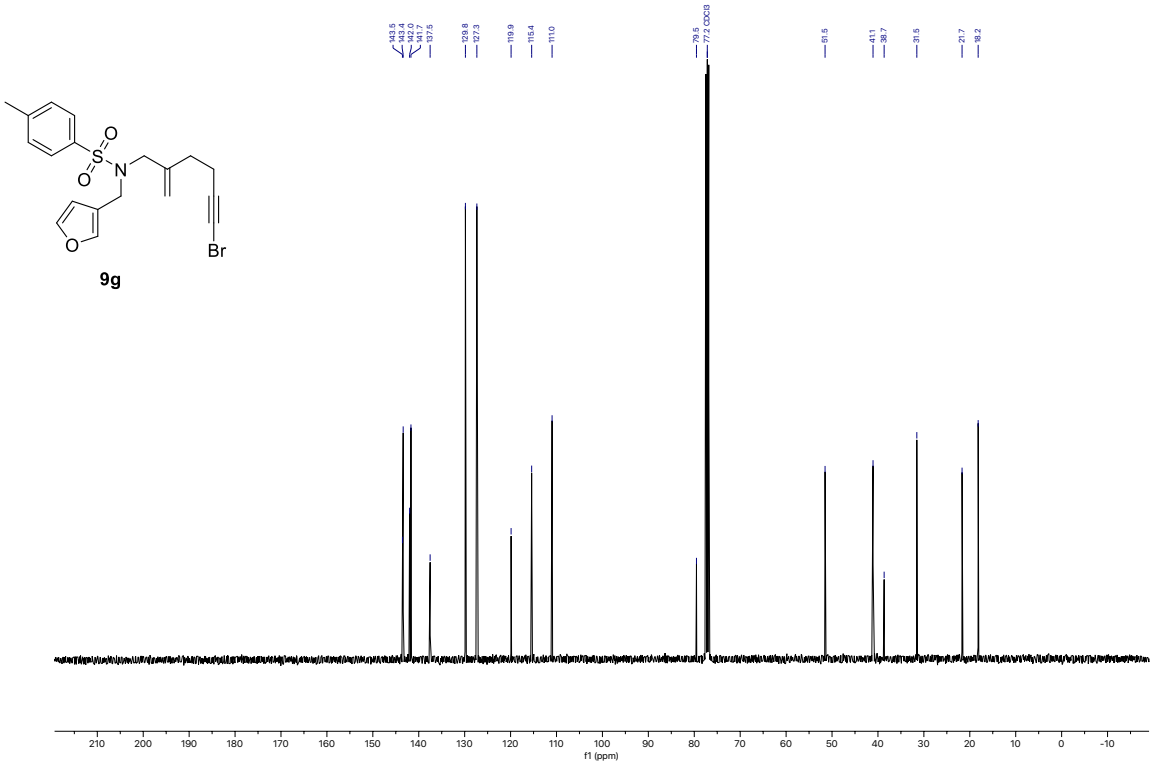
***N*-(6-Bromo-2-methylenehex-5-yn-1-yl)-4-methyl-*N*-(3,4,5-trimethoxybenzyl)benzenesulfonamide (9f)**



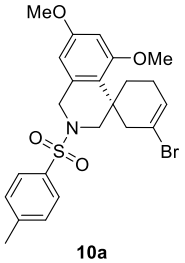


***N*-(6-Bromo-2-methylenehex-5-yn-1-yl)-*N*-(furan-3-ylmethyl)-4-methylbenzenesulfonamide (9g)**





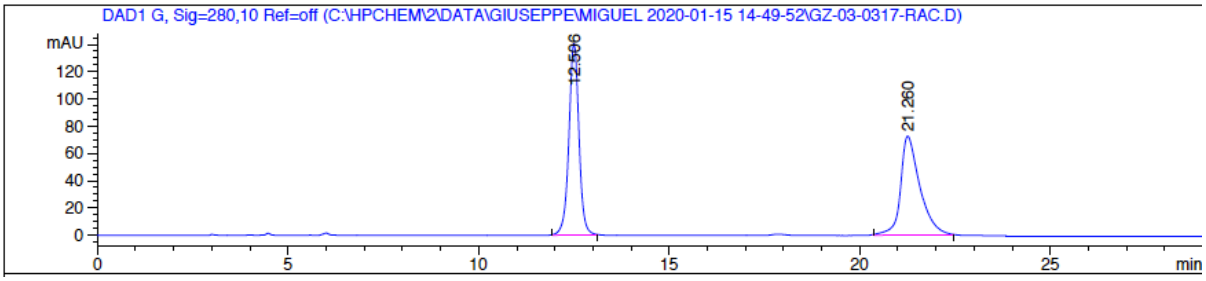
(*R*)-3-Bromo-5',7'-dimethoxy-2'-tosyl-2',3'-dihydro-1'*H*-spiro[cyclohexane-1,4'-isoquinolin]-3-ene (10a)



10a

SFC racemic **10a**

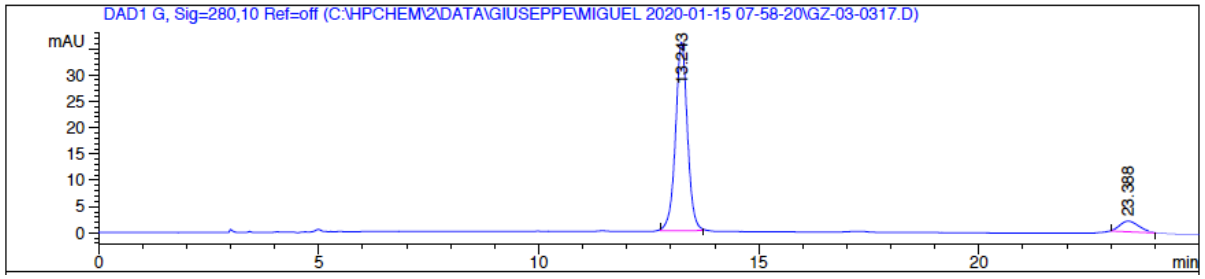
```
Sample Info      : IA, 1 ml/min
                   Hex:IPA= 90:10
                   GZ-03-0317-rac

=====================================================================
```



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.506	BB	0.2751	2546.47070	140.76143	49.9015
2	21.260	BB	0.5148	2556.52368	72.60278	50.0985
Totals :				5102.99438	213.36421	

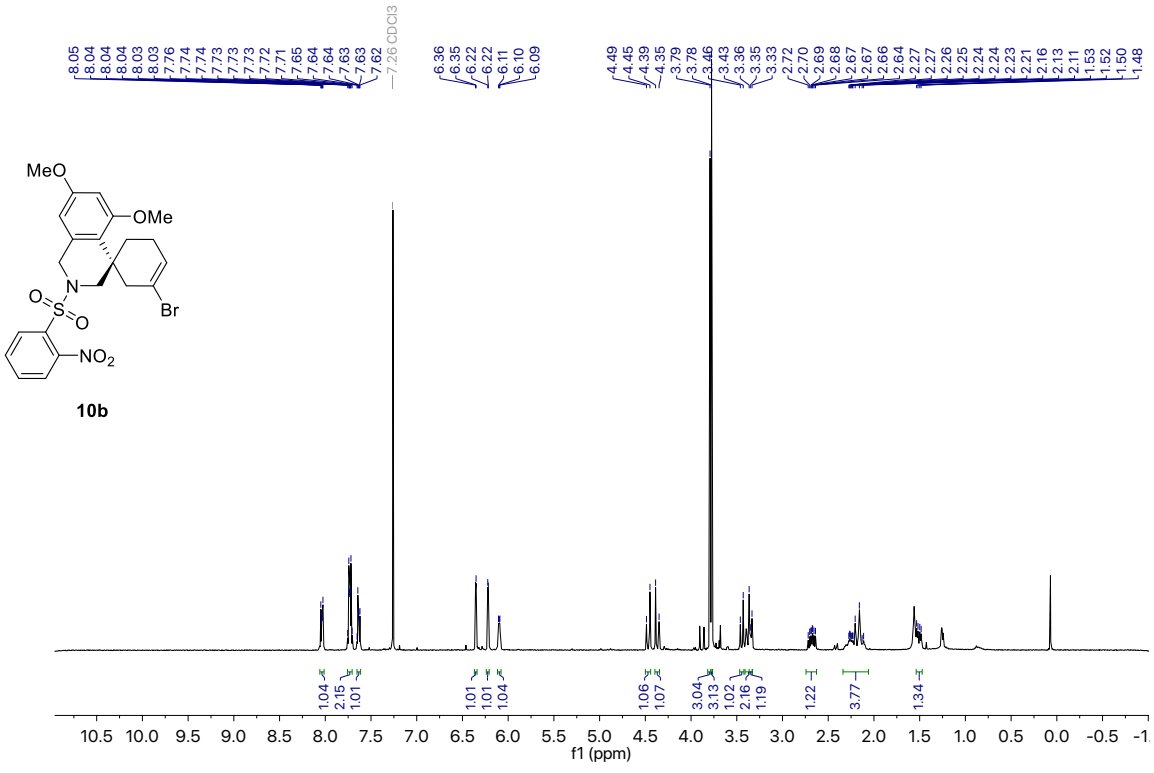
SFC enantioenriched **10a**

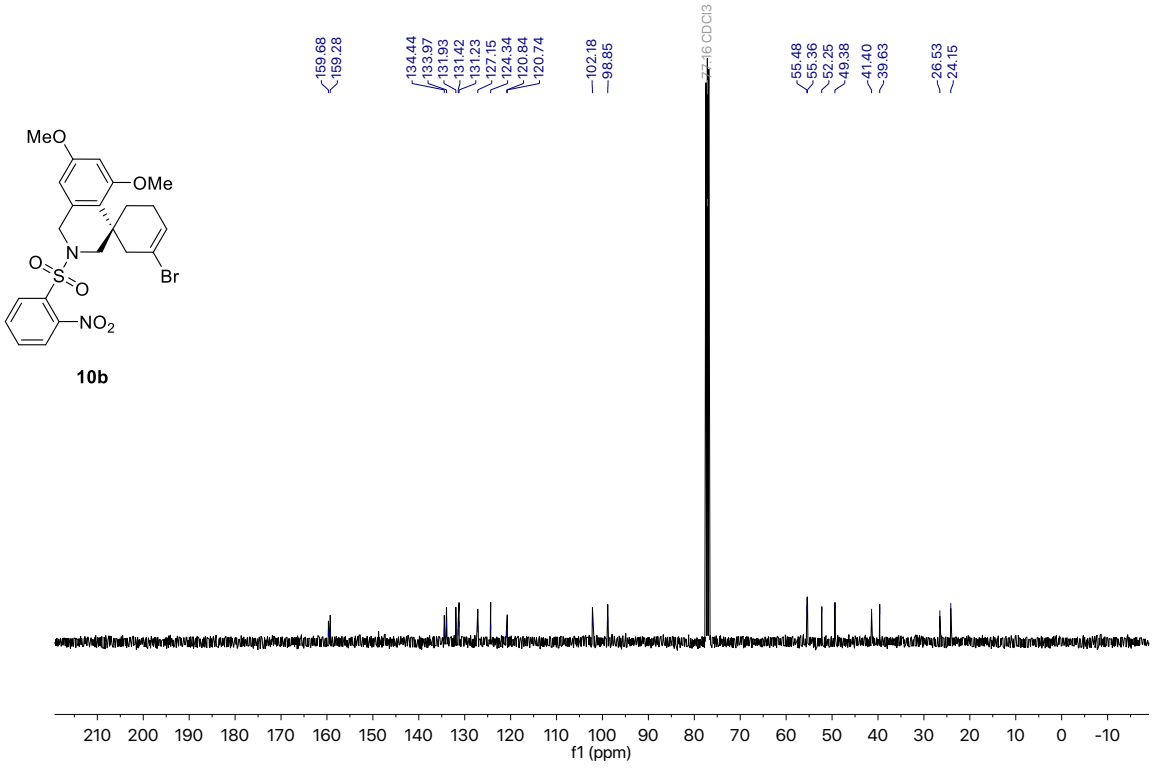
```
Sample Info      : IA, 1 ml/min
                   Hex:IPA= 90:10
                   GZ-03-0318

=====================================================================
```



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.243	BB	0.2859	674.56195	35.78954	91.6345
2	23.388	BB	0.4426	61.58186	2.02616	8.3655
Totals :				736.14381	37.81570	

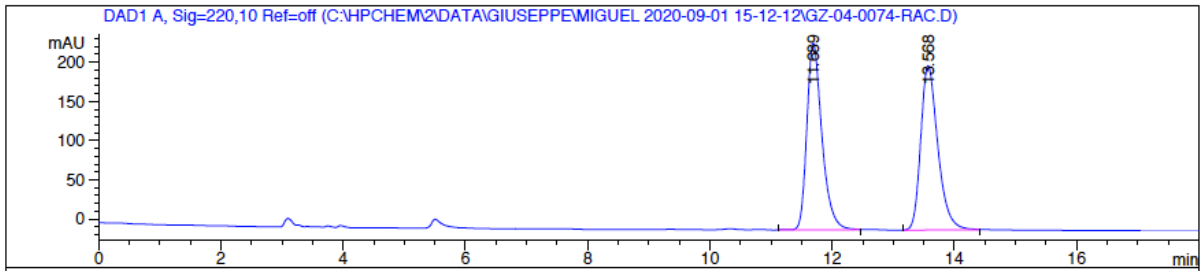
(*R*)-3-Bromo-5',7'-dimethoxy-2'-((2-nitrophenyl)sulfonyl)-2',3'-dihydro-1'*H*-spiro[cyclohexane-1,4'-isoquinolin]-3-ene (10b)





SFC racemic **10b**

```
Sample Info     : IB, 1 ml/min
                  Hex:IPA= 80:20
                  GZ-04-0074-rac

================================================================================
```

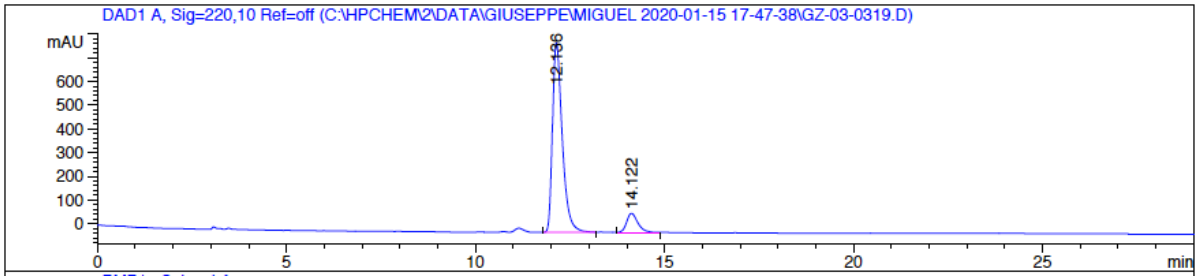


Signal 1: DAD1 A, Sig=220,10 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.689	BB	0.2605	4087.83984	237.83284	50.0503
2	13.568	BB	0.2990	4079.63086	209.62668	49.9497

SFC enantioenriched **10b**

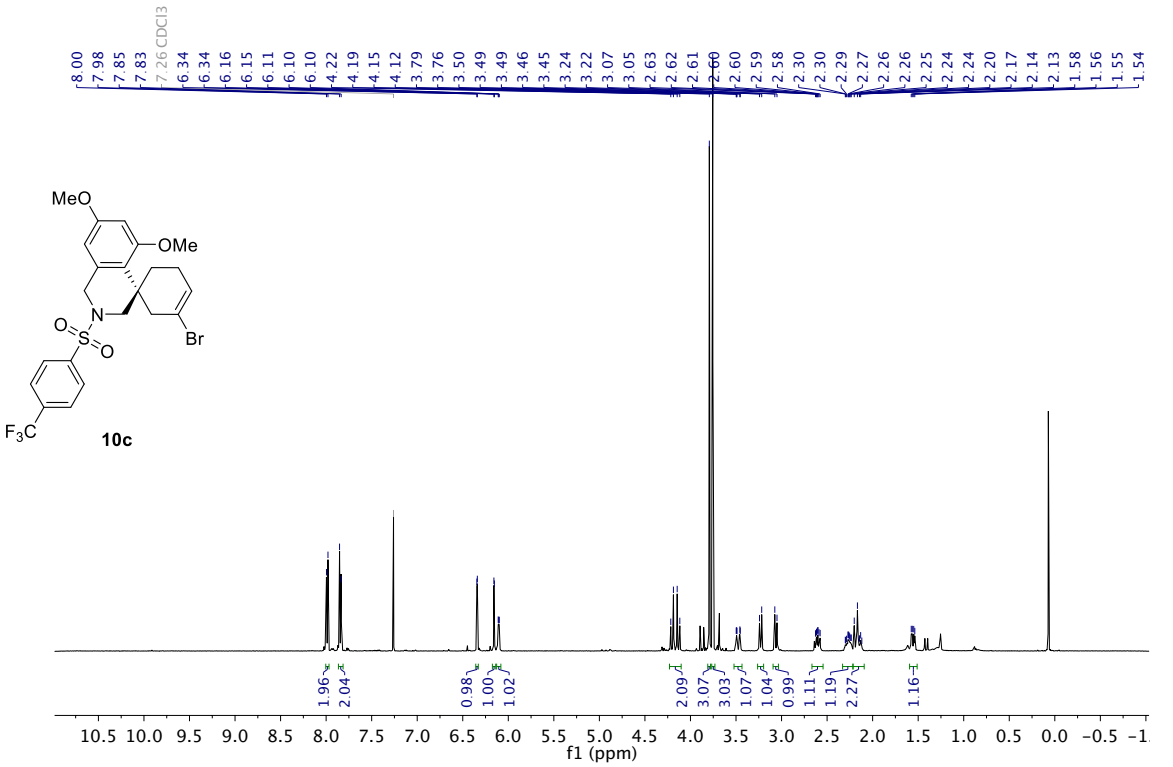
```
Sample Info     : IB, 1 ml/min
                  Hex:IPA= 80:20
                  GZ-03-0319

================================================================================
```

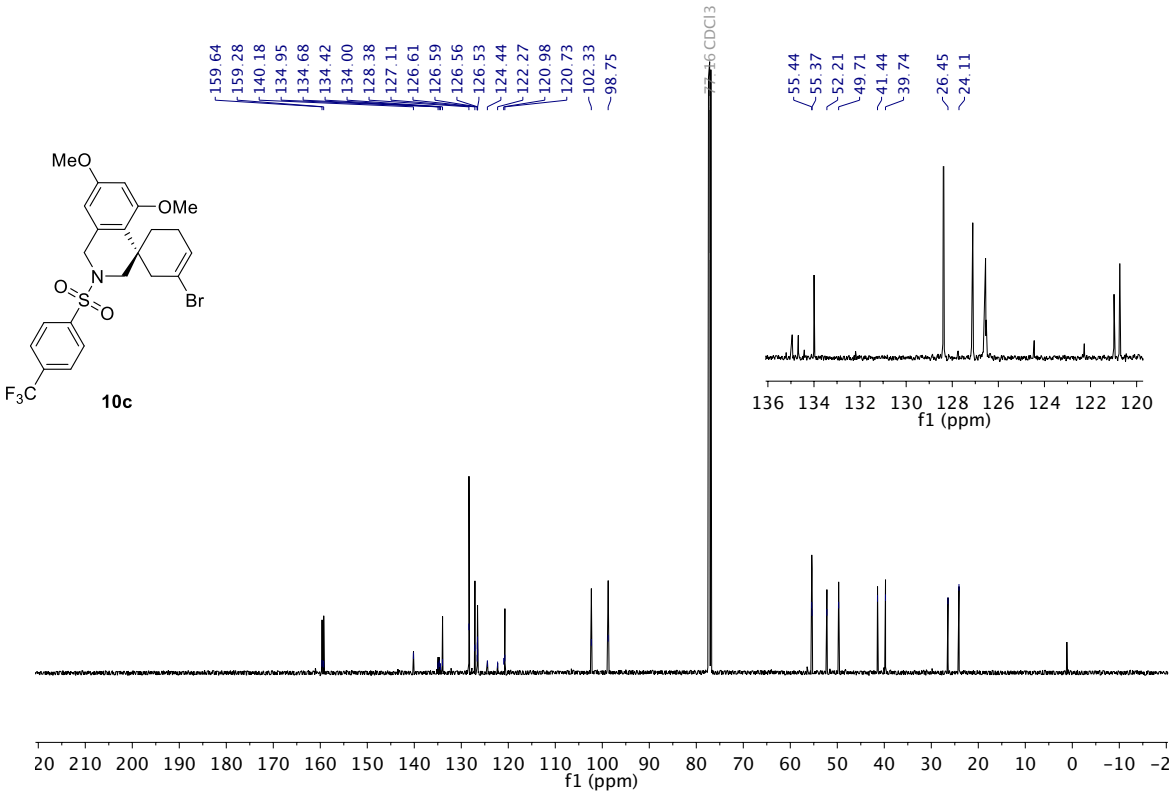


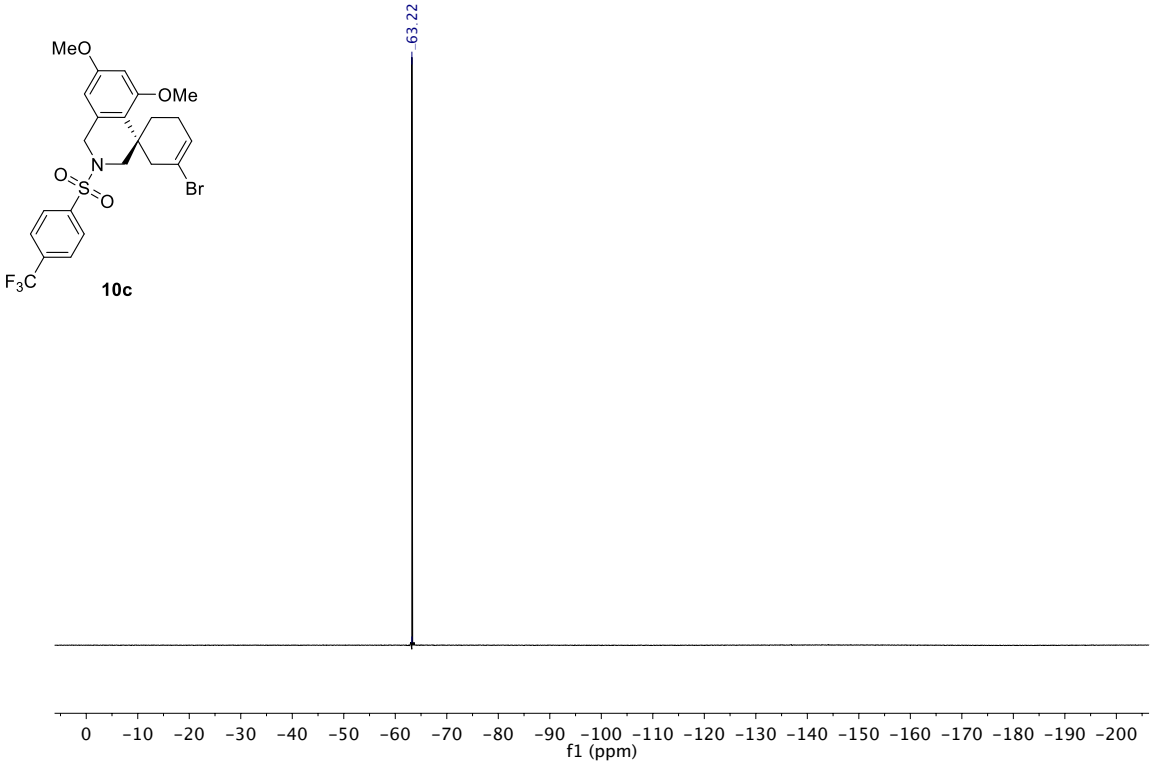
Signal 1: DAD1 A, Sig=220,10 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.136	BB	0.2704	1.42830e4	799.43097	89.5874
2	14.122	BB	0.3160	1660.09351	80.68880	10.4126

(*R*)-3-Bromo-5',7'-dimethoxy-2'-((4-(trifluoromethyl)phenyl)sulfonyl)-2',3'-dihydro-1'*H*-spiro[cyclohexane-1,4'-isoquinolin]-3-ene (10c)

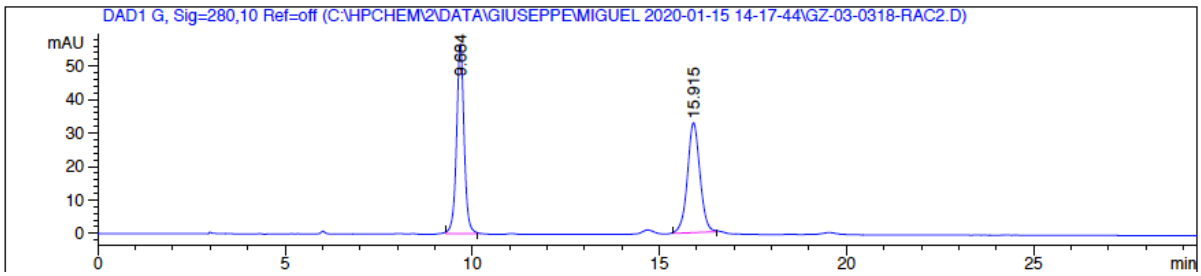






SFC racemic **10c**

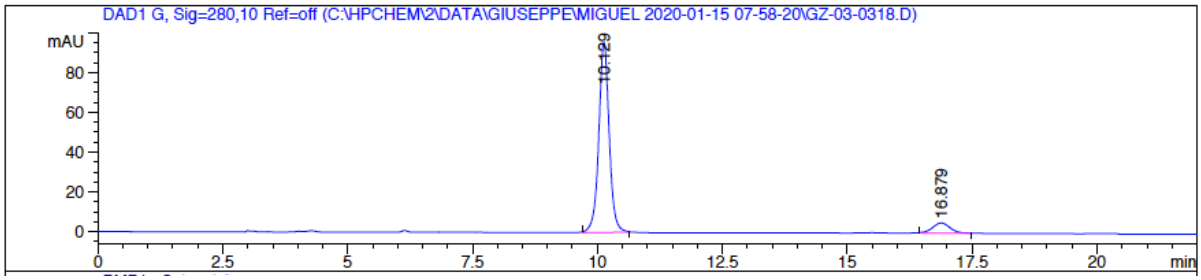
```
Sample Info     : IA, 1 ml/min
                  Hex:IPA= 90:10
                  GZ-03-0318-rac2

======================================================================
```




```
Signal 1: DAD1 G, Sig=280,10 Ref=off

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   9.684 BB    0.2104  789.54810   56.70955  50.8977
   2  15.915 BB    0.3527  761.69635   32.83299  49.1023

Totals :                  1551.24445   89.54253
```

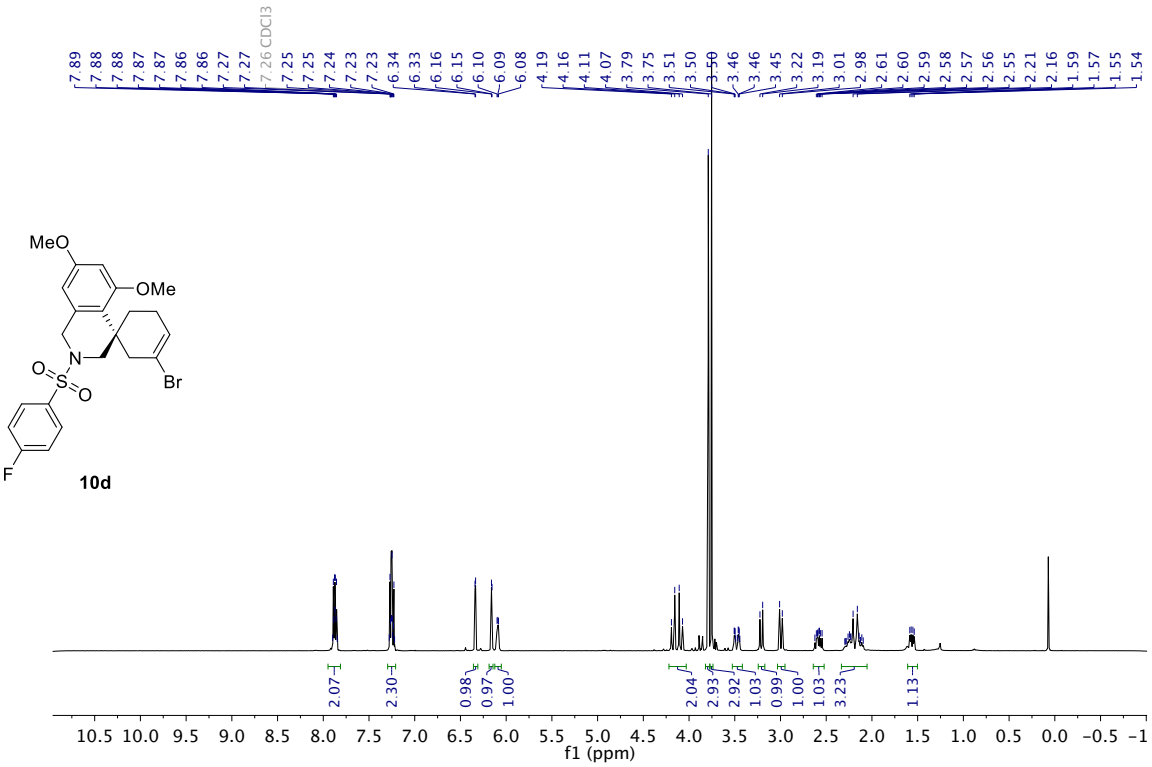
SFC enantioenriched **10c**

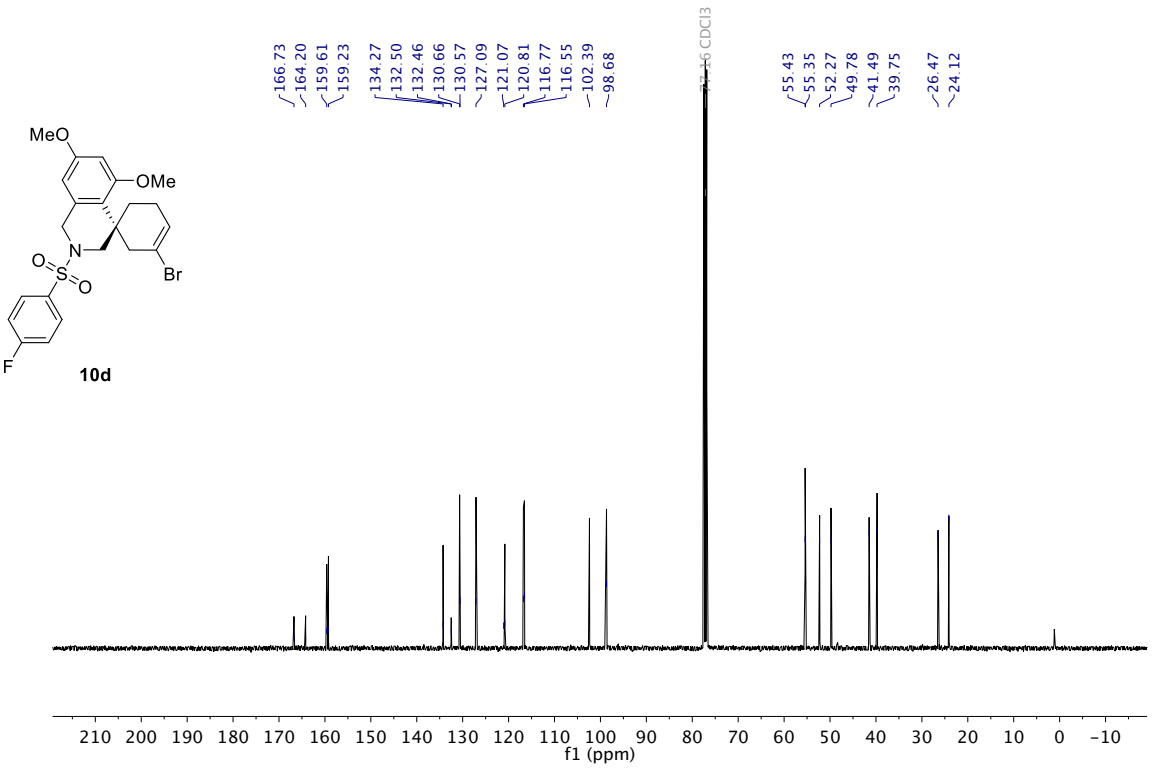
```
Sample Info     : IA, 1 ml/min
                  Hex:IPA= 90:10
                  GZ-03-0318

=====================================================================
```

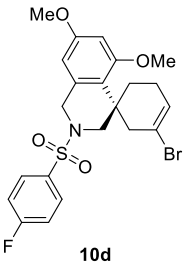


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.129	BB	0.2194	1390.19971	95.74094	91.9482
2	16.879	BB	0.3613	121.73895	5.08557	8.0518
Totals :				1511.93865	100.82651	

(*R*)-3-Bromo-2'-((4-fluorophenyl)sulfonyl)-5',7'-dimethoxy-2',3'-dihydro-1'*H*-spiro[cyclohexane-1,4'-isoquinolin]-3-ene (10d)



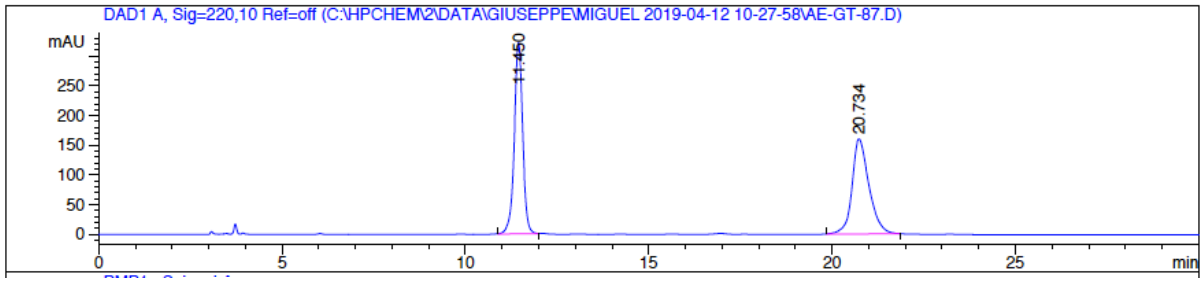




10d

SFC racemic **10d**

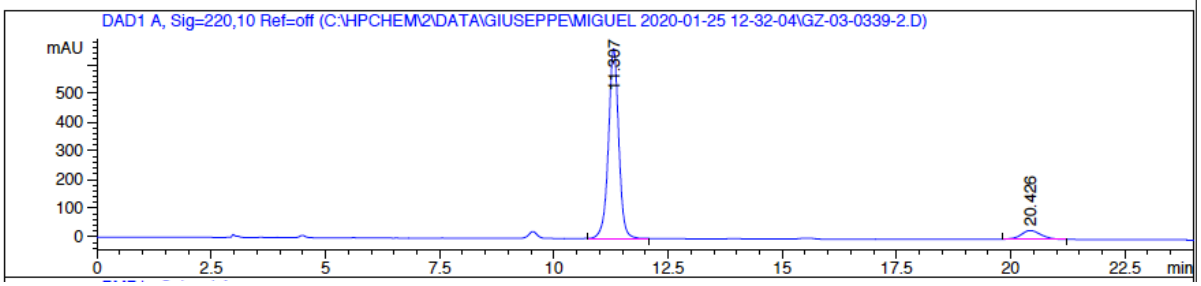
```
Sample Info     : IA, 1 ml/min
                  90:10 HEX:IPA
                  AE-GT-87

==========================================================================
```




```
Signal 1: DAD1 A, Sig=220,10 Ref=off

Peak RetTime Type  Width     Area      Height     Area
  #   [min]       [min]   [mAU*s]     [mAU]       %
----|-------|----|--------|----------|----------|--------|
   1  11.450 BB    0.2411 5111.86572  322.18506  49.7989
   2  20.734 BB    0.4770 5153.15234  160.33481  50.2011
```

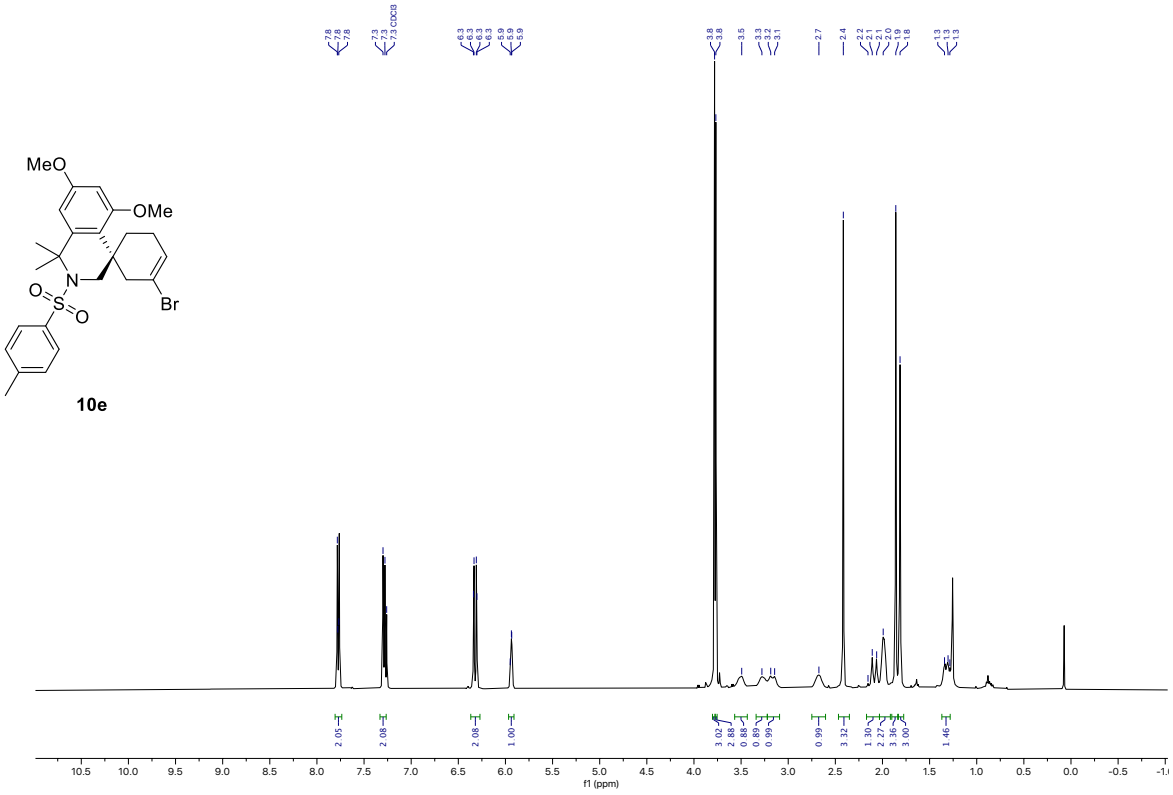
SFC enantioenriched **10d**

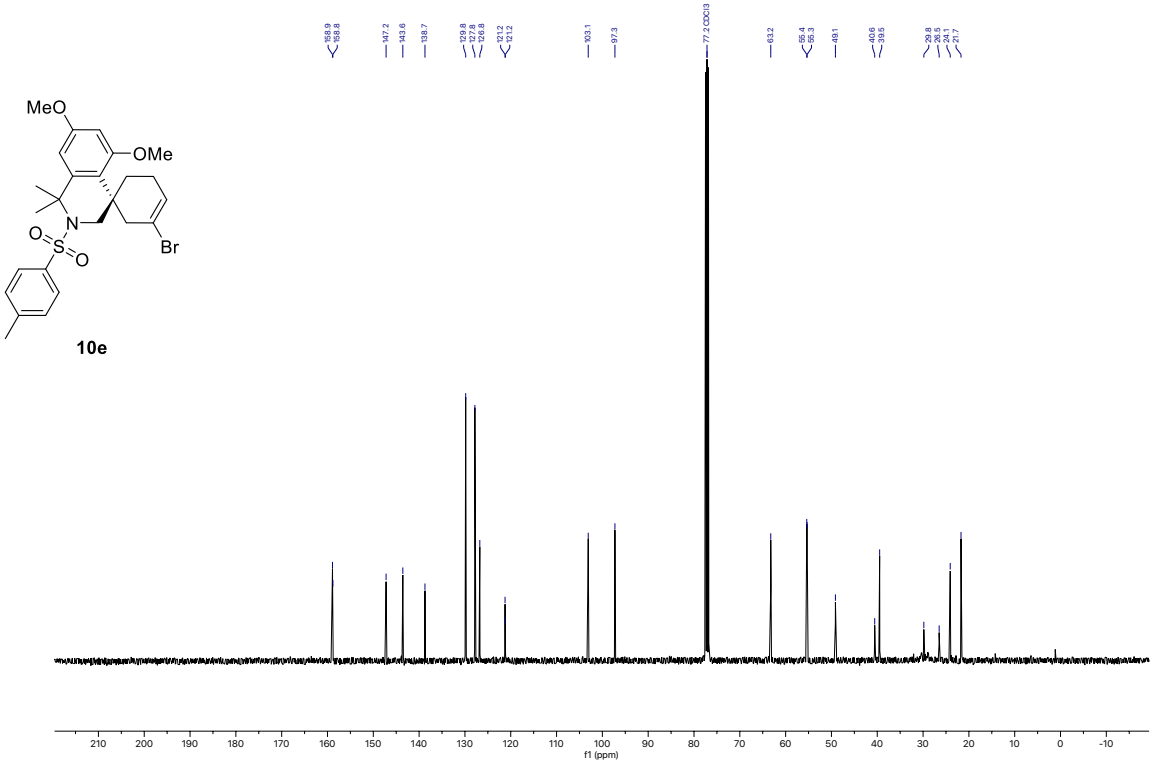
```
Sample Info      : IA, 1 ml/min
                   Hex:IPA= 90:10
                   GZ-03-0339-2

==================================================================
```



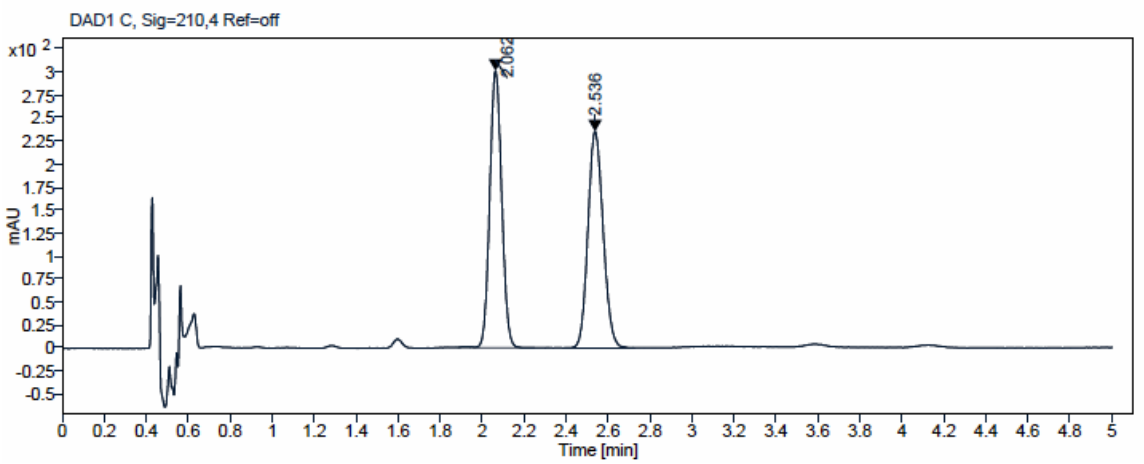
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.307	BB	0.2396	1.04242e4	662.27344	91.6504
2	20.426	BB	0.4692	949.67029	30.84594	8.3496

(*R*)-3-Bromo-5',7'-dimethoxy-1',1'-dimethyl-2'-tosyl-2',3'-dihydro-1'*H*-spiro[cyclohexane-1,4'-isoquinolin]-3-ene (10e)





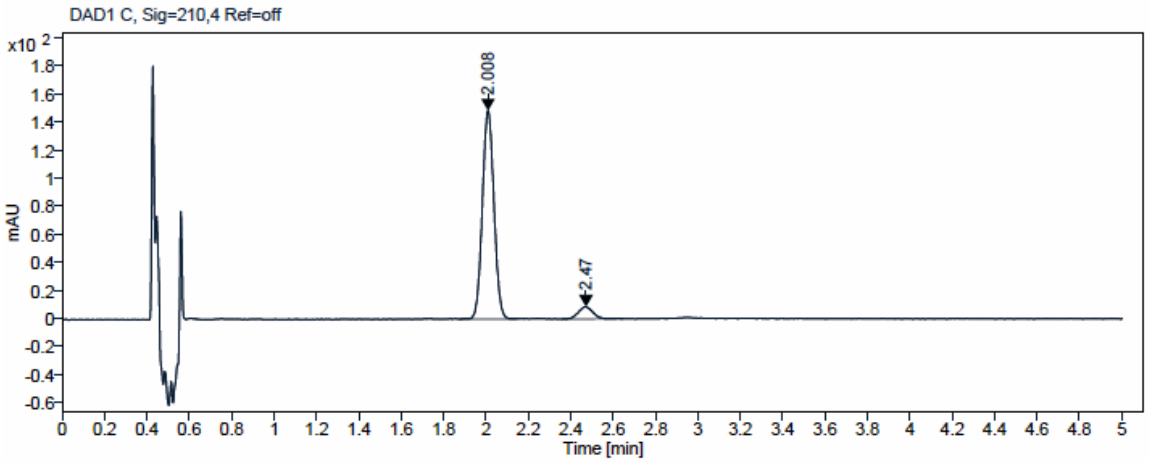
SFC racemic **10e**



Signal: DAD1 C, Sig=210,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
2.062	VV R	0.0622	1191.7931	301.1457	50.0533	
2.536	VV R	0.0789	1189.2562	235.5728	49.9467	
		Sum	2381.0493			

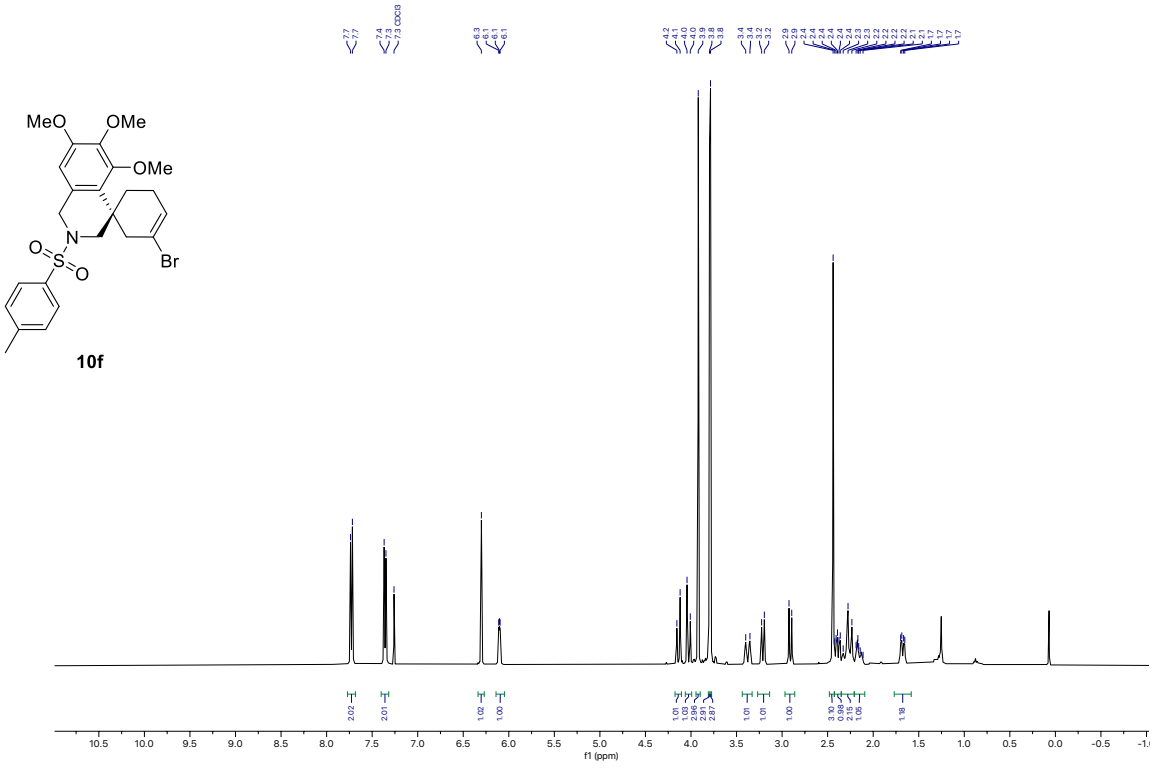
SFC enantioenriched **10e**

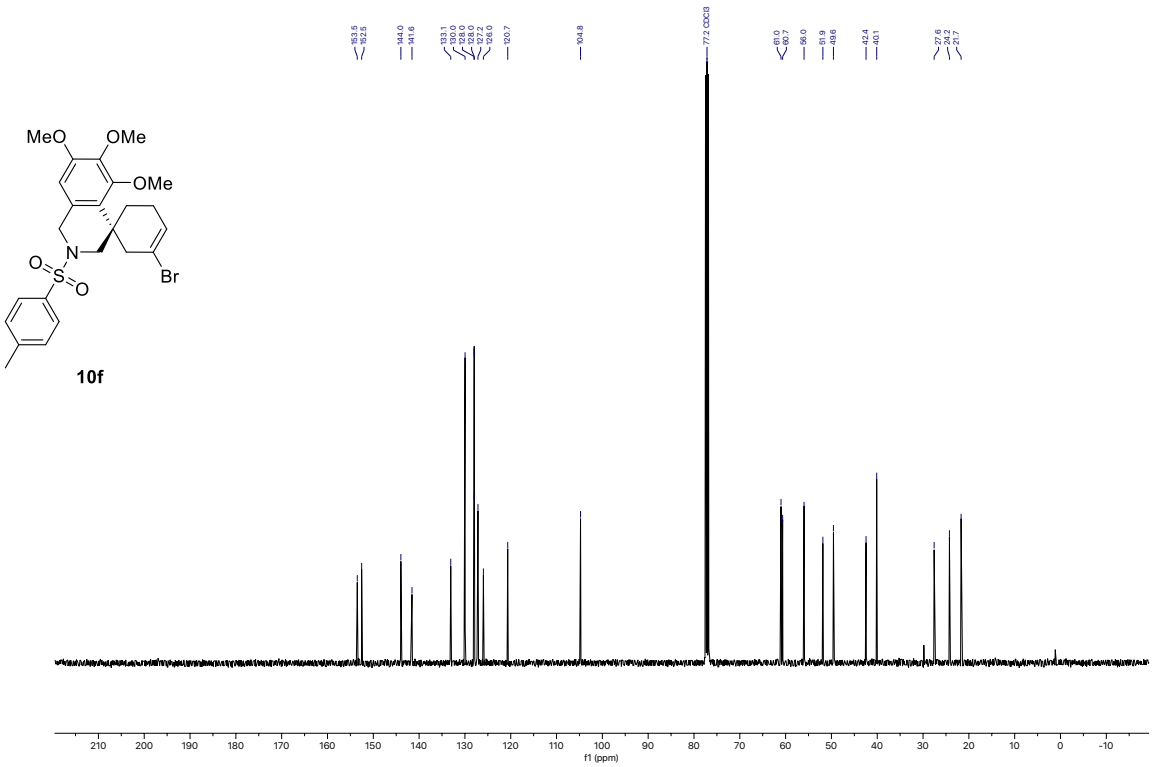


Signal: DAD1 C, Sig=210,4 Ref=off

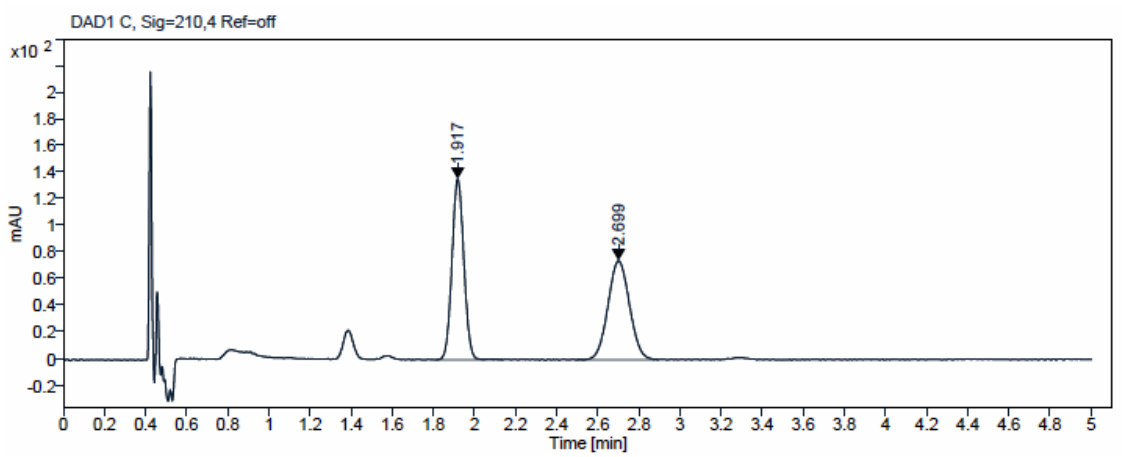
RT [min]	Type	Width [min]	Area	Height	Area%	Name
2.008	VV R	0.0594	562.6505	147.9788	93.0995	
2.470	VV R	0.0603	41.7036	8.4983	6.9005	
		Sum	604.3541			

(*R*)-3-Bromo-5',6',7'-trimethoxy-2'-tosyl-2',3'-dihydro-1'*H*-spiro[cyclohexane-1,4'-isoquinolin]-3-ene (10f)





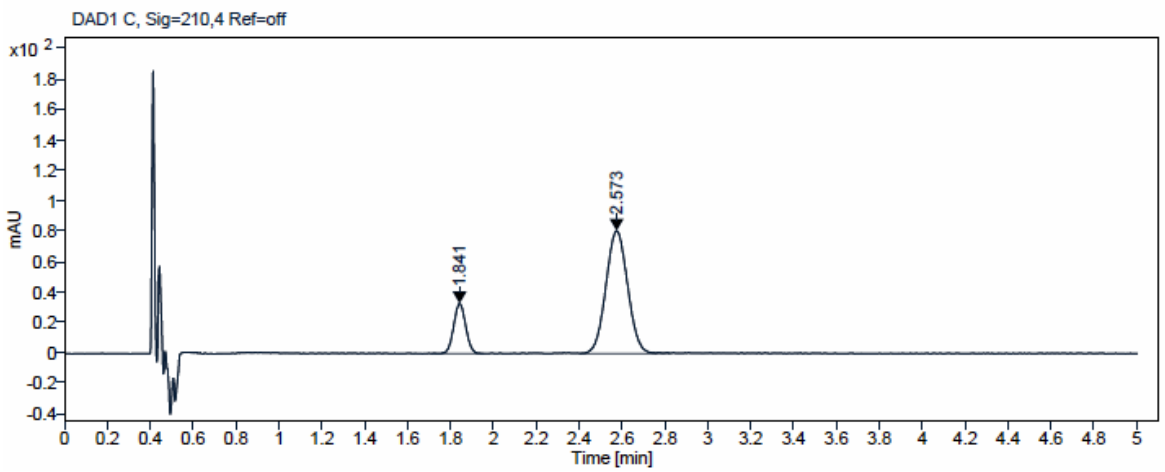
SFC racemic **10f**



Signal: DAD1 C, Sig=210,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
1.917	BV R	0.0635	545.4316	135.3487	50.2620	
2.699	VV R	0.1128	539.7448	74.2599	49.7380	
		Sum	1085.1765			

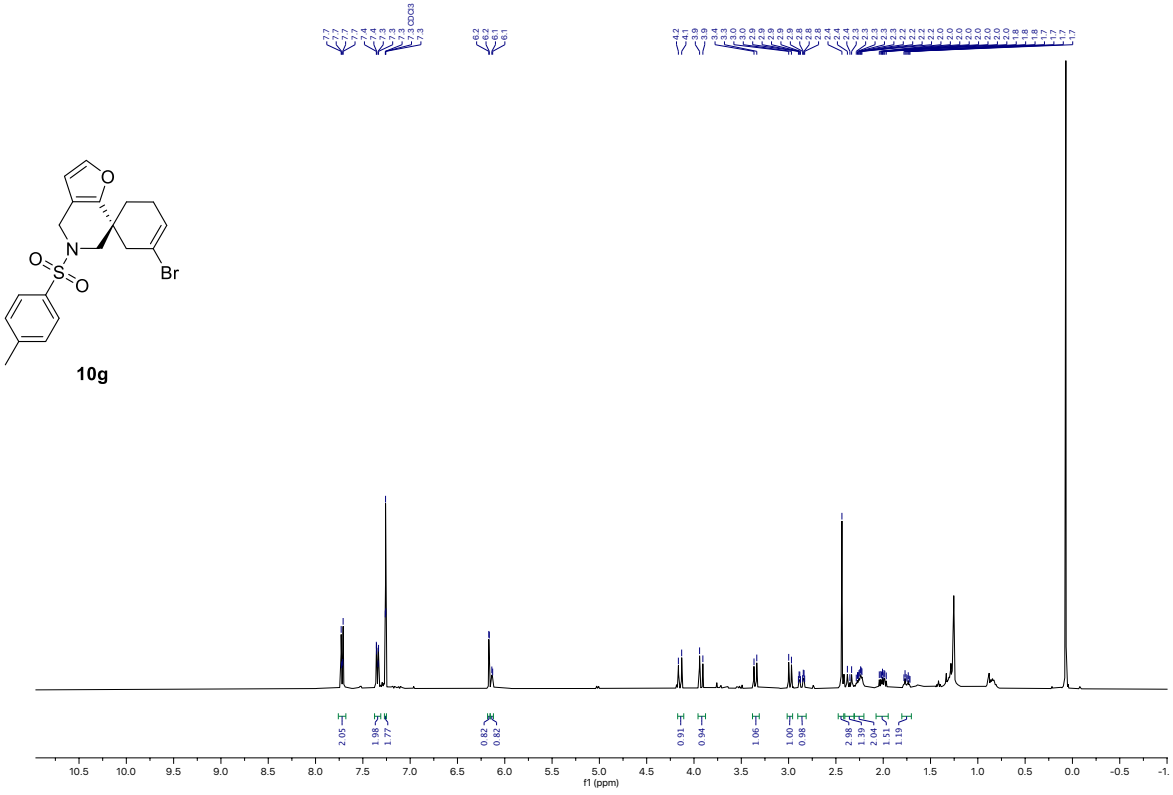
SFC enantioenriched **10f**

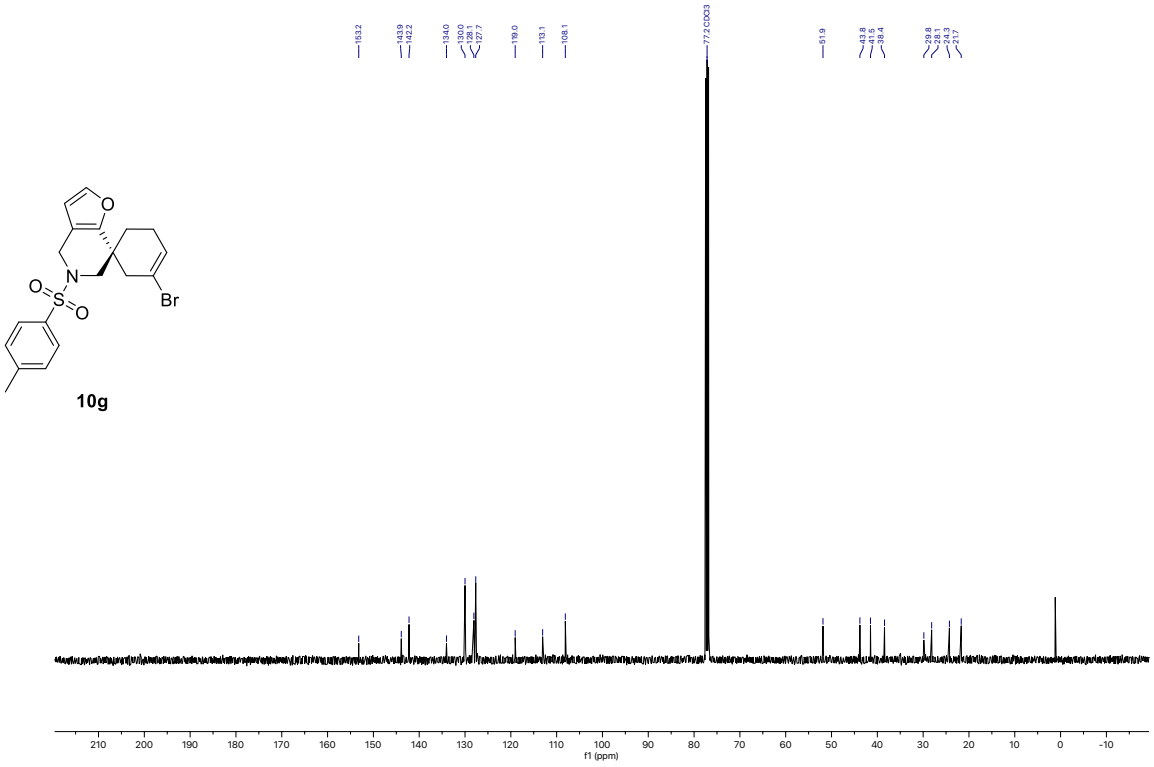


Signal: DAD1 C, Sig=210,4 Ref=off

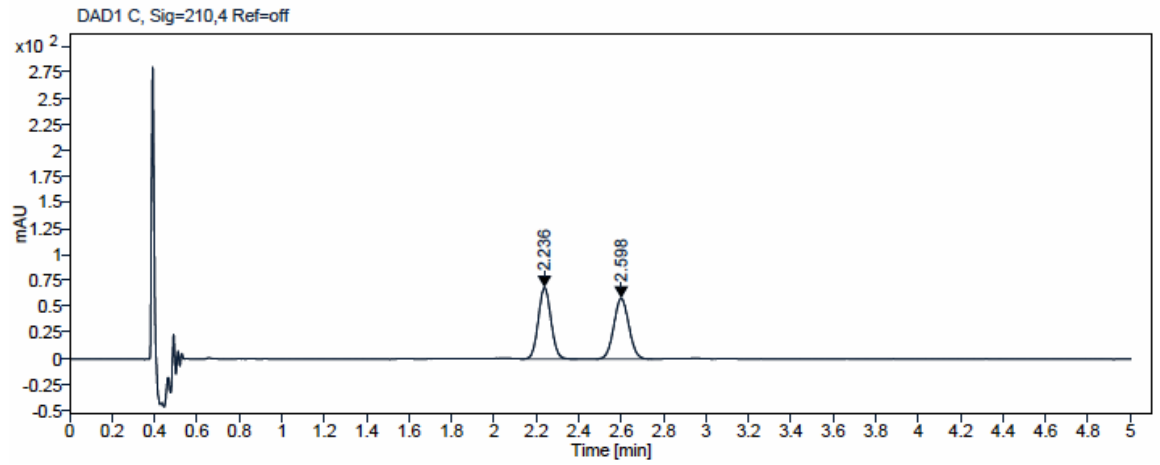
RT [min]	Type	Width [min]	Area	Height	Area%	Name
1.841	VV R	0.0614	129.6038	32.9600	18.6063	
2.573	VV R	0.1091	566.9546	80.5722	81.3937	
		Sum	696.5584			

(*S*)-3-Bromo-5'-tosyl-5',6'-dihydro-4'*H*-spiro[cyclohexane-1,7'-furo[3,2-*c*]pyridin]-3-ene (10g)





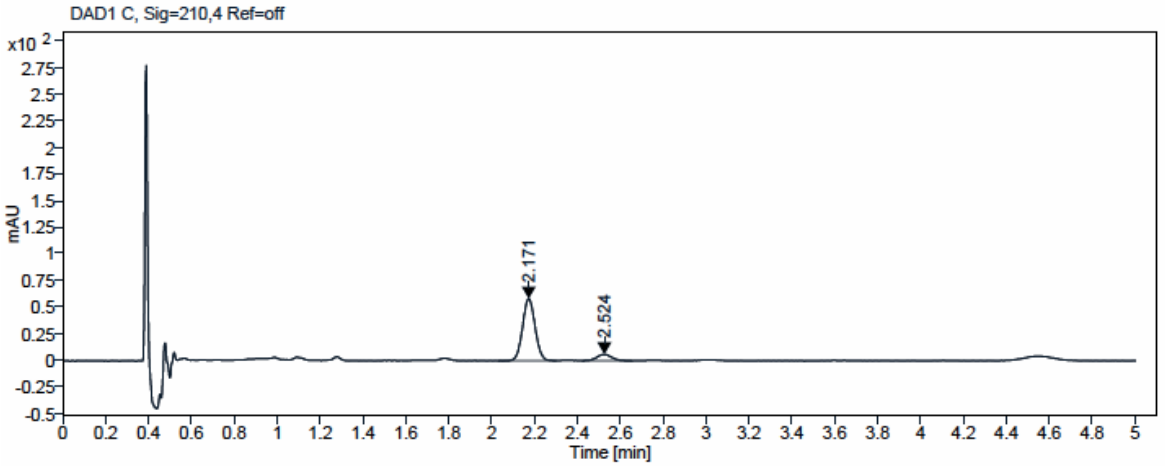
SFC racemic **10g**



Signal: DAD1 C, Sig=210,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
2.236	VB R	0.0647	286.8841	68.6864	49.8462	
2.598	VV R	0.0782	288.6543	58.3890	50.1538	
		Sum	575.5384			

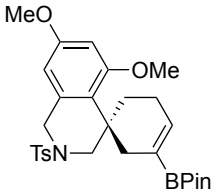
SFC enantioenriched **10g**

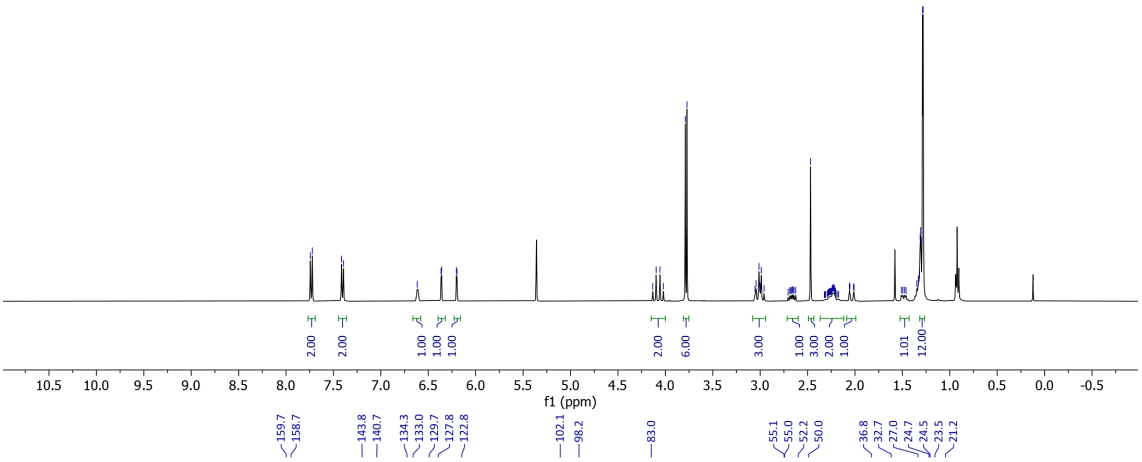


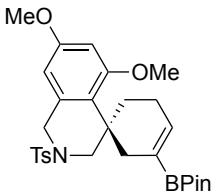
Signal: DAD1 C, Sig=210,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
2.171	VB R	0.0627	236.1474	58.3093	88.6941	
2.524	BV R	0.0734	30.1018	6.0182	11.3059	
		Sum	266.2492			

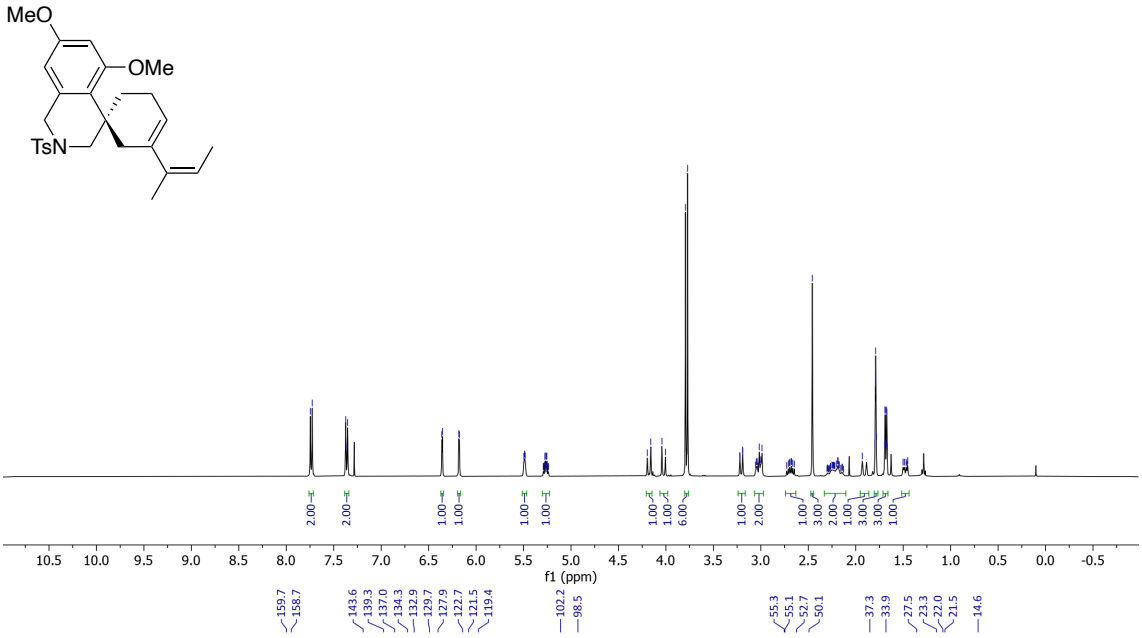
(*R*)-5',7'-Dimethoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2'-tosyl-2',3'-dihydro-1'*H*-spiro[cyclohexane-1,4'-isoquinolin]-3-ene (11)

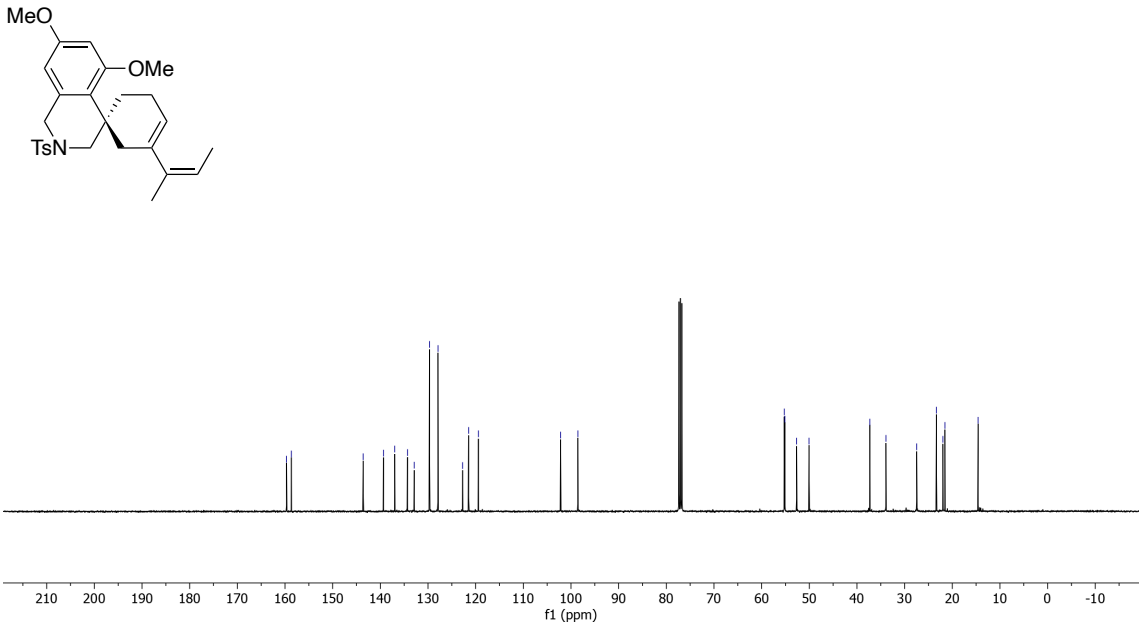




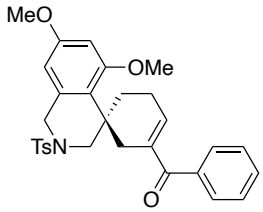


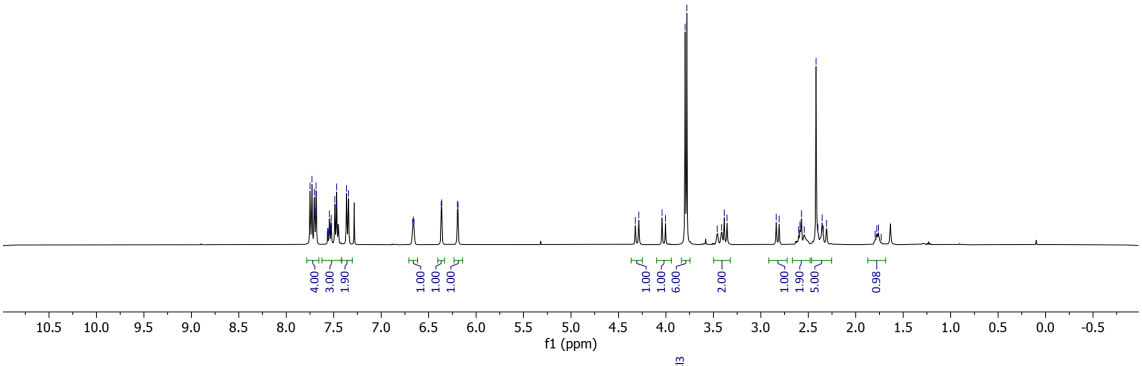
(*R,Z*)-3-(But-2-en-2-yl)-5',7'-dimethoxy-2'-tosyl-2',3'-dihydro-1'*H*-spiro[cyclohexane-1,4'-isoquinolin]-3-ene (12)

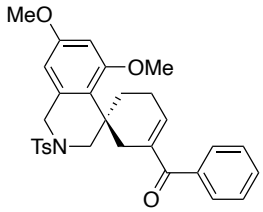


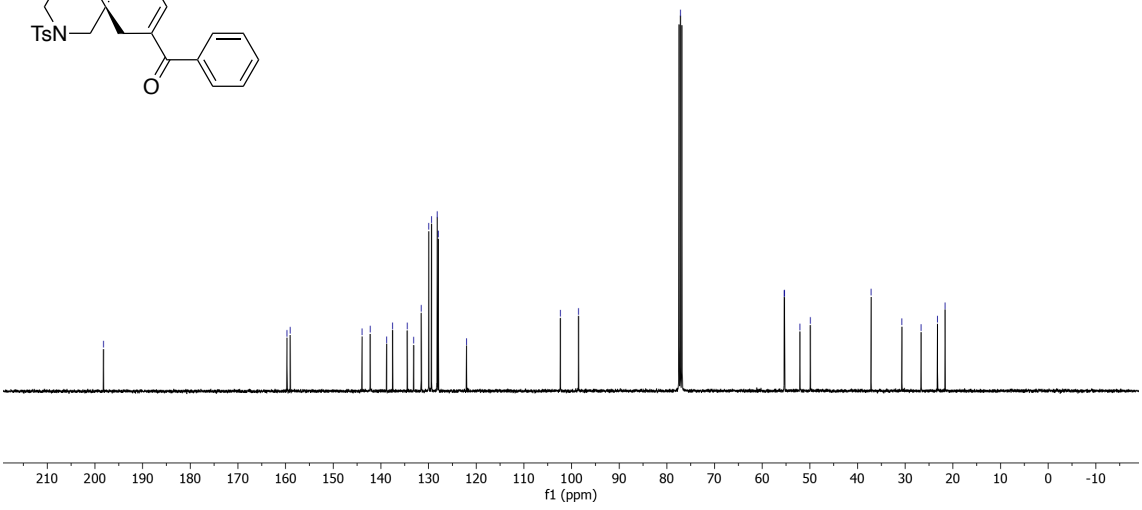


(*R*)-(5',7'-Dimethoxy-2'-tosyl-2',3'-dihydro-1'*H*-spiro[cyclohexane-1,4'-isoquinolin]-3-en-3-yl)(phenyl)methanonemalonate (14)

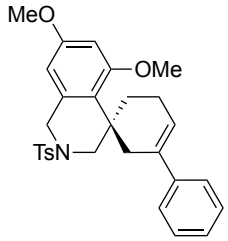


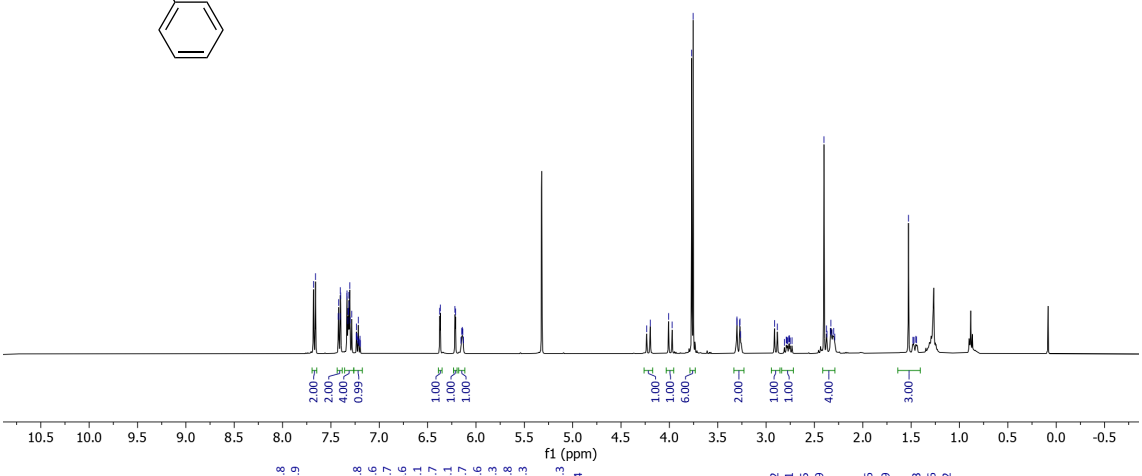


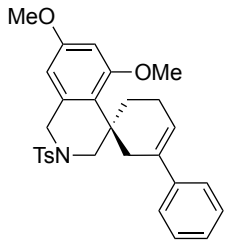




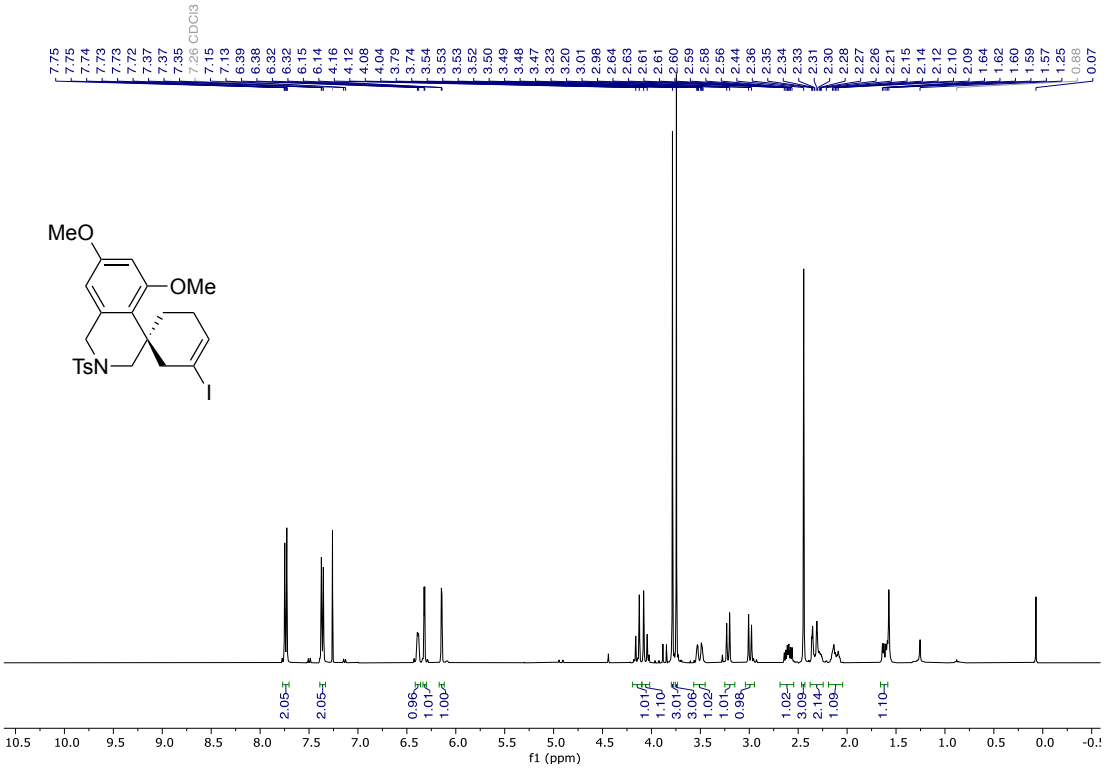
(*R*)-(5',7'-Dimethoxy-3-phenyl-2'-tosyl-2',3'-dihydro-1'*H*-spiro[cyclohexane-1,4'-isoquinolin]-3-ene (15)

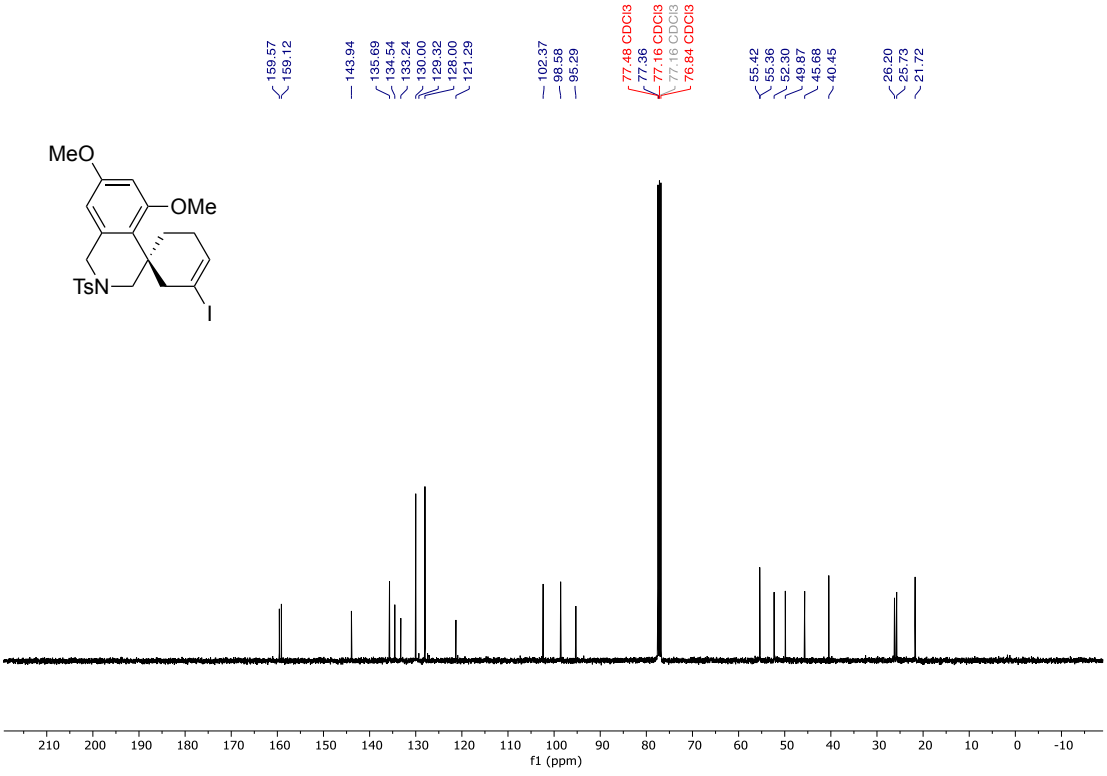




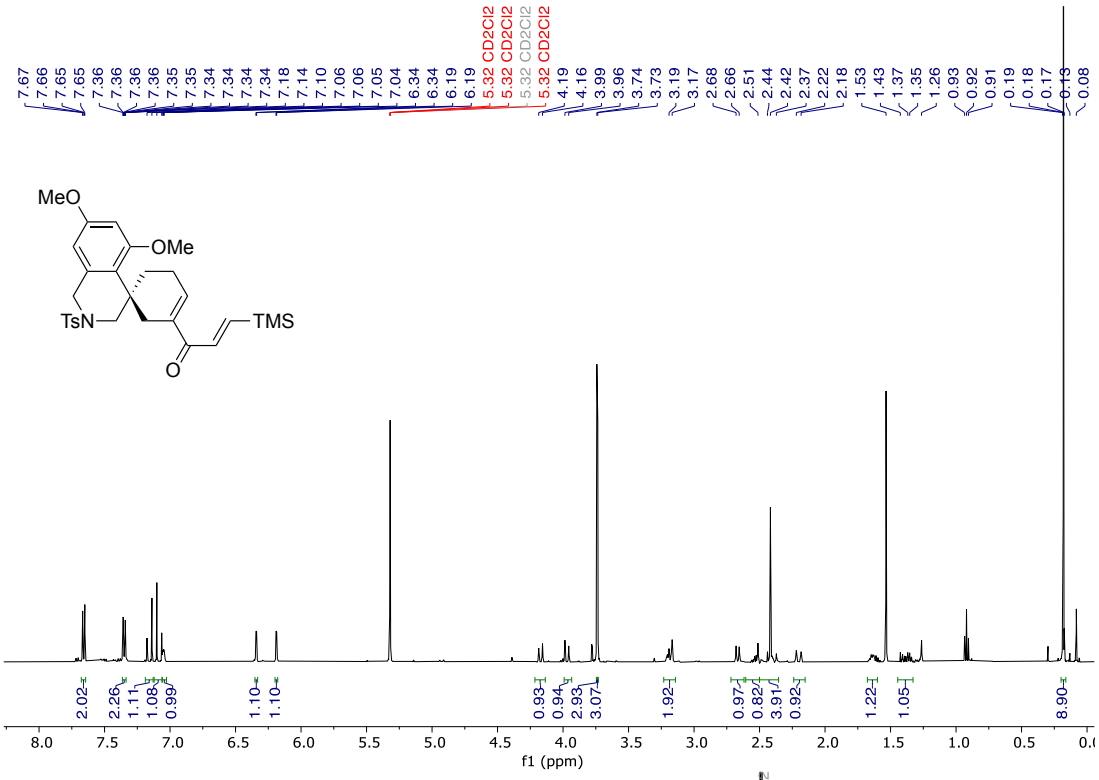


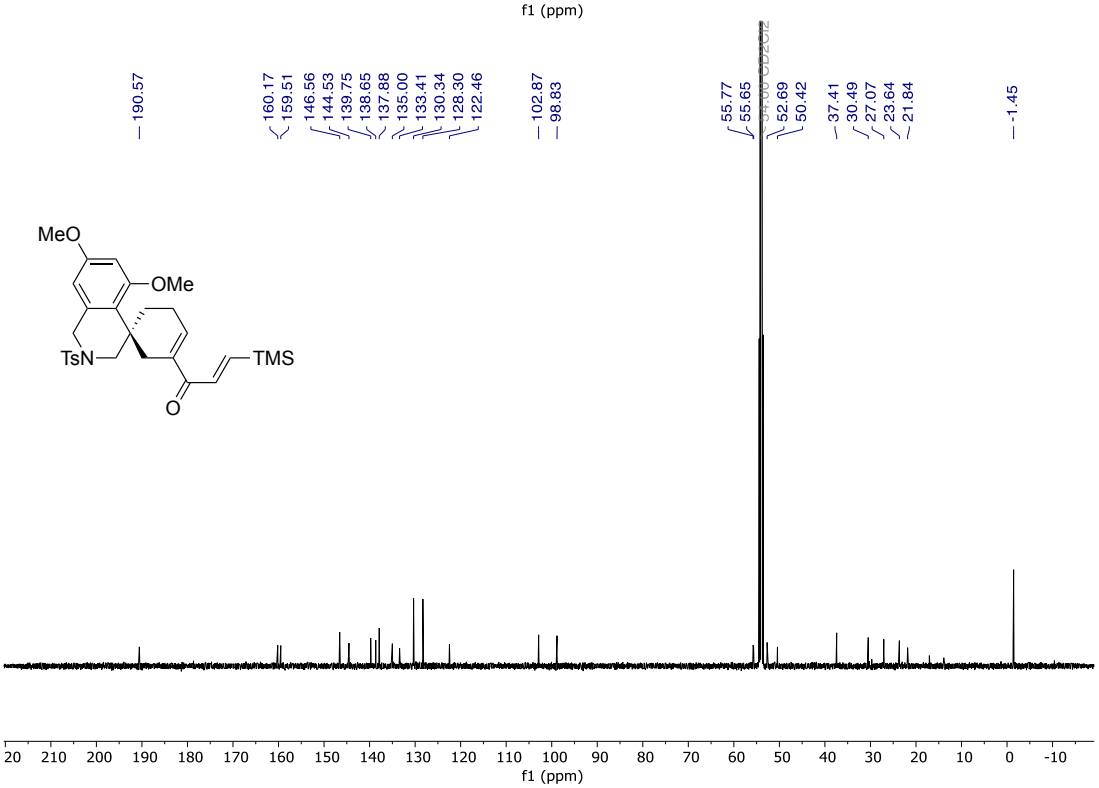
(*R*)-(3-Iodo-5',7'-dimethoxy-2'-tosyl-2',3'-dihydro-1'*H* spiro[cyclohexane-1,4'-isoquinolin]-3-ene (10h)



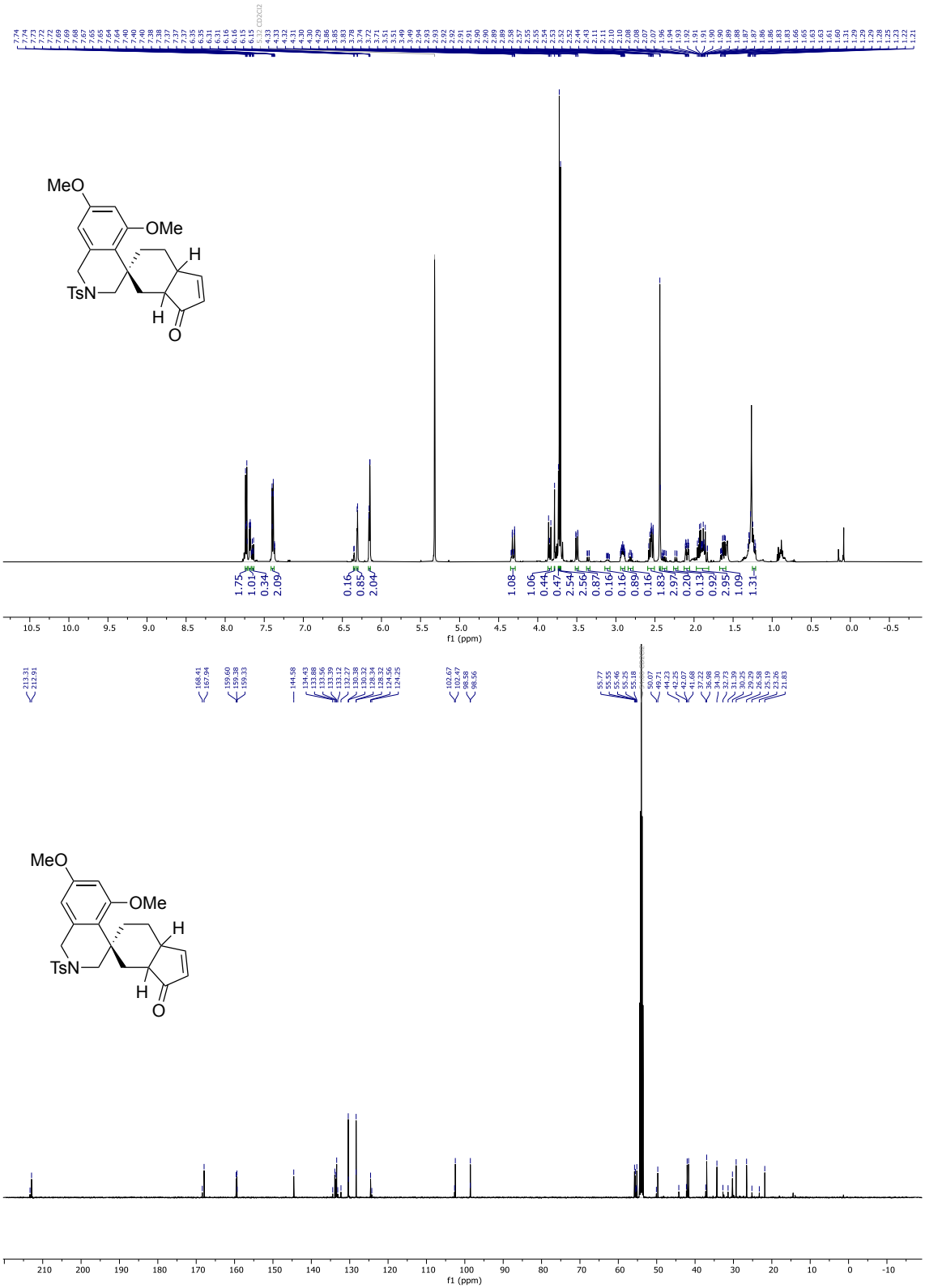


(*R*,*E*)-1-(5',7'-Dimethoxy-2'-tosyl-2',3'-dihydro-1'*H*-spiro[cyclohexane-1,4'-isoquinolin]-3-en-3-yl)-3-(trimethylsilyl)prop-2-en-1-one (16)





(*R*)-5',7'-Dimethoxy-2'-tosyl-2',3a,3',6,7,7a-hexahydro-1'*H*-spiro[indene-5,4'-isoquinolin]-3(4H)-one (17)



References

1 A. Cataffo, M. Peña-López, R. Pedrazzani, A. M. Echavarren, *Angew. Chem. Int. Ed.* 2023, **62**, e202312874.

2 X. Zeng, Y. Tu, Z. Zhang, C. You, J. Wu, Z. Ye and J. Zhao *J. Org. Chem.* 2019, **84**, 4458–4466.

3 M.P. Muñoz, M. Méndez, C. Nevado, D.J. Cárdenas, A. M. Echavarren, *Synthesis,* 2003, **18***,* 2898–2902.

4 a) G. Zuccarello, J. G. Mayans, I. Escofet, D. Scharnagel, M. S. Kirilova, A. H. Pérez-Jimeno, P. Calleja, J. R. Boothe, A. M. Echavarren, *J. Am. Chem. Soc.* 2019, **141**, 11858–11863. b) G. Zuccarello, L. J. Nannini, A. Arroyo-Bondía, N. Fincias, I. Arranz, A. H. Pérez-Jimeno, M. Peeters, I. Martín-Torres, A. Sadurní, V. García-Vázquez, Y. Wang, S. M. Kirillova, M. Montesinos-Magraner, U. Caniparoli, G. D. Núñez, F. Maseras, M. Besora, I. Escofet and A. M. Echavarren, *JACS Au* 2023, **3**, 1742–1754.

5 These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures. Single crystal was measured on a Bruker APEX-II CCD diffractometer. The crystal was kept at 100.40 K during data collection. Programs used: Olex2 (O.V, Dolomanov, L.J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann, *J. Appl. Cryst*. **2009**, 42, 339-341), data collection (Apex2 V2011.4-0), data reduction (SAINT V8.34A), structure solution (SIR2014, M. C. Burla, R. Caliandro, B. Carrozzini, G. L. Cascarano, C. Cuocci, C. Giacovazzo, M. Mallamo, A. Mazzone, G. Polidori, *J. Appl. Cryst.* 2015, **48**, 306), structure refinement (SHELXTL Version 2018/3, G. M. Sheldrick, *Acta Crystallogr. C Struct. Chem.* 2015, **71**, 3), absorption correction (SADABS 2014/4, G. M. Sheldrick, 2008).

6 The structure of **2j** was assigned by analogy with related products resulting in the *anti*-stereospecific reaction of 1,6-enynes with *E* alkenes: a) C. Nieto-Oberhuber, M. P. Muñoz, S. López, E. Jiménez-Núñez, C. Nevado, E. Herrero-Gómez, M. Raducan, A. M. Echavarren, *Chem. Eur. J.* 2006, **12**, 1677–1693. b) E. Jiménez-Núñez, C. K. Claverie, C. Bour, D. J. Cárdenas, A. M. Echavarren, *Angew. Chem. Int. Ed.* 2008, **47**, 7892–7895.

7 O. Christin and E. Roulland, *Synthesis.* 2024, **56**, 2239–2246.

8 C. Cruché, W. Neiderer and Shawn K. Collins, *ACS Catal.* 2021, **11**, 8829–8836.

9 Z. Rong, A. M. Echavarren, *Org. Biomol. Chem.* 2017, **15**, 2163–2167.

10 Y. W. Sun, X. Y. Tang, M. Shi, *Chem. Commun.* 2015, **51**, 13937–13940.

11 Steps a, b, and e: H.V. Thulasiram, R. M. Phan, S. B. Rivera, and C. Dale Poulter, *J. Org. Chem.* **2006**, *71*, 4, 1739–1741.

12 Step c: F. W. Sum and L. Weiler, *Tetrahedron*, **1981**, 37,1, 303-317.

13 Step d: C. A. Citron, P. Rabe, L. Barra, C. Nakano, T. Hoshino and Jeroen S. Dickschat, *Eur. J. Org. Chem.* 2014, 7684–7691.

14 Steps f-h: A. Cataffo, M. Peña-López, R. Pedrazzani and A. M. Echavarren, *Angew. Chem. Int. Ed.* 2023, **62**, e202312874.

15 A. Franchino, À. Martí, A. M. Echavarren, *J. Am. Chem. Soc.* **2022**, *144*, 3497–3509.

16 A. M. Sanjuán, A. Martínez, P. García-García, M. A. Fernández-Rodríguez, R. Sanz, *Beilstein J. Org. Chem*. 2013, **9**, 2242–2249.

17 S. Kassamba, A. Perez-Luna, F. Ferreira and M. Durandetti, *Chem. Commun.,* 2022, **58**, 3901–3904

18 M. Álvarez-Pérez, M. Frutos, A. Viso, R. Fernández de la Pradilla, M. C. de la Torre, M. A. Sierra, H. Gornitzka, C. Hemmert, *J. Org. Chem.* 2017, **82**, 7546–7554.

19 a) R. E. M. Brooner, B. D. Robertson, R. A. Widenhoefer, *Organometallics,* 2014, **33**, 6466–6473. b) D. Pflästerer, S. Schumacher, M. Rudolph, A. S. K. Hashmi, *Chem. Eur. J.* 2015, **21**, 11585–11589. c) V. W. Bhoyare, A. G. Tathe, V. Gandon, N. T. Patil, *Angew. Chem. Int. Ed.,* 2023, **62**, e202312786*.*

20 Gaussian 09, Revision B1, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2009.

21 Álvarez-Moreno, M.; de Graaf, C.; Lopez, N.; Maseras, F.; Poblet, J. M.; Bo, C., *J. Chem. Inf. Model.* **2015**, 55, 95−103.

22 a) A. D. Becke, *J. Chem. Phys.* 1993, **98**, 5648; b) A. D. Becke, *J. Chem. Phys.* 1993, **98**, 1372; c) C. Lee, W. Yang and R. G. Parr, *Phys. Rev. B* 1988, **37**, 785.

23 S. Grimme, *WIREs Comput. Mol. Sci.* 2011, **1**, 211–228.

24 E. Cancès, B. Mennucci and J. Tomasi, *J. Chem. Phys.* 1997, **107**, 3032−3041.

25 D. Andrae, U. Häußermann, M. Dolg, H. Stoll and H. Preuß, *Theor. Chim. Acta* 1990, **77**, 123–141.

26 W. R. Wadt and P. J. Hay, *J. Chem. Phys.* 1985, **82**, 284–298.

27 W. J. Hehre, R. Ditchfield and J. A. Pople, *J. Chem. Phys.* 1972, **56**, 2257–2261.

28 (a) Becke, A. D. *Phys. Rev. A*. **1988**, *38*, 3098–3100. (b) Perdew, J. P. *Phys. Rev. B*. **1986**, *33,* 8822–8824.

29 (a) Kang, R., Chen, H., Shaik, S., Yao, J. *J. Chem. Theory Comput.* **2011**, 7, 4002−4011. (b) Ciancaleoni, G.; Rampino, S.; Zuccaccia, D.; Tarantelli, F.; Belanzoni, P.; Belpassi, L. *J. Chem. Theory Comput.* **2014**, *10*, 1021−1034.

30 (a) Höllwarth, A.; Böhme, M.; Dapprich, S.; Ehlers, A. W.; Gobbi, A.; Jonas, V.; Köhler, K. F.; Stegmann, R.; Veldkamp, A.; Frenking, G. *Chem. Phys. Lett*. **1993**, *208*, 237–240. (b) Ehlers, A.; Böhme, M.; Dapprich, S.; Gobbi, A.; Höllwarth, A.; Jonas, V.; Köhler,K.; Stegmann, R.; Veldkamp, A.; Frenking, G. *Chem. Phys. Lett*. **1993**, *208*, 111−114.

31 a) S. L. Boyd and R. J. Boyd, *J. Chem. Theory Comput.*, 2007, **3**, 54–61; b) S. Teh, P.-J. Hsu and J.-L. Kuo, *Phys. Chem. Chem. Phys.*, 2021, **23**, 9166–9175.

32 N. Kim, R. E. M. Brooner and R. A. Widenhoefer, *Organometallics*, 2017, **36**, 673–678.