Electronic Supplementary Information

Catalytic highly enantioselective transfer hydrogenation of β-trifluoromethyl nitroalkenes. An easy and general entry to optically active β-trifluoromethyl amines

Emilie Martinelli,[b§] Anna Chiara Vicini,[a§] Michele Mancinelli,[a] Andrea Mazzanti,[a] Paolo Zani[a] Luca Bernardi,[a]* and Mariafrancesca Fochi[a]*

a-Department of Industrial Chemistry "Toso Montanari"
School of Science
University of Bologna
V. Risorgimento, 4 I-40136 Bologna (Italy)

b-Chimie ParisTech – École Nationale Supérieure de Chimie de Paris; 11, rue Pierre et Marie Curie, 75231 PARIS Cedex 05, France

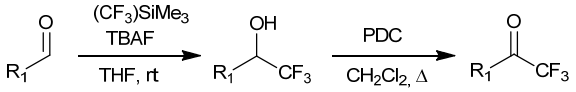
Table of contents:

General Methods. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Varian AS 400 or 600 spectrometer. Chemical shifts (δ) are reported in ppm relative to residual solvent signals for ^{1}H and ^{13}C NMR,[1] and using $CF_3C_6H_5$ as external reference calibrated at -63.72 ppm for ^{19}F NMR. ^{13}C NMR spectra were acquired with ^{1}H broad band decoupled mode. Data are reported either as: s = singlet, d = doublet, dd= double doublet, t = triplet, q = quartet, m = multiplet, br = broad, coupling constant(s) in Hz, integration. Mass spectra were recorded on a micromass LCT spectrometer using electrospray (ESI) ionisation techniques or by use of electronic impact ionization (EI^+). Optical rotations were measured on a Perkin-Elmer 241 polarimeter provided with a sodium lamp and are reported as follows: $[\alpha]^{T(^\circ C)}_{\lambda}$ (c = g/100 mL, solvent). The enantiomeric excess (ee) of the products was determined by chiral stationary phase HPLC (Daicel Chiralpak AD-H or Chiralcel OJ-H columns see below for further details), using a UV detector operating at 254 nm. Chromatographic purifications were performed using 70-230 mesh silica.

Materials. Analytical grade solvents and commercially available reagents were used as received, unless otherwise stated. THF was freshly distilled over Na and benzophenone, CH_2Cl_2 was freshly distilled over calcium hydride and Et_2O was freshly distilled over $LiAlH_4$. Pyridine was dried by standing on activated 4 Å molecular sieves. (Trifluoromethyl)trimethylsilane and nitromethane were obtained from commercial sources, and were used as received. Thionyl chloride was fleshly distilled prior to use. Trifluoromethyl ketones **6a**, **6e**, **6f**, **6j** and **6k** were obtained from commercial sources, and were used as received. Pyridinium dichromate PDC was prepared as reported in the literature.[2] Hantzsch esters **2** were prepared following literature procedure.[3] Chiral thioureas **3a** and **3b** were obtained from commercial sources whereas **3c-d** were prepared as reported in the literature.[4]

[1] H. E. Gottlieb, V. Kotlyar and A. Nudelman, *J. Org. Chem.*, 1997, **62**, 7512.
[2] E. J. Corey and G. Schmidt, *Tetrahedron Lett.,* 1979, **20**, 399–402.
[3] H. Leutbecher, G. Greiner, R. Amann, A. Stolz, U. Beifuss and J. Conrad*, Org. Biomol. Chem.,* 2011, **9**, 2667–2673.
[4] a) S. J. Zuend, M. P. Coughlin, M. P. Lalonde and E. N. Jacobsen, *Nature*, 2009, **451**, 968–971; b) S. E. Reisman, A. G. Doyle and E. N. Jacobsen, *J. Am. Chem. Soc.* 2008, **130**, 7198–7199.

General procedure for the synthesis of trifluoromethyl ketones 7b-d, 7g-k and 7l[5]



7	R_1
7b	4-MeC_6H_4
7c	3-MeC_6H_4
7d	2-MeC_6H_4
7g	4-$MeOC_6H_4$
7h	4-$CF_3C_6H_4$
7i	2-naphthyl
7k	$PhCH_2$
7l	$CH_3(CH_2)_8$

To a solution of aldehyde (10 mmol) in THF (12 mL) in a 100 mL round-bottom flask equipped with a stir bar, under nitrogen atmosphere, (trifluoromethyl)trimethylsilane (Ruppert's reagent) (13 mmol, 1.3 equiv) was added and the obtained solution was cooled to 0 °C in an ice−water bath. After approximately 10 min, TBAF (1 M in THF, 0.1 mmol, 0.1 mL, 0.01 equiv) was added dropwise via a syringe. After 10 min, the ice bath was removed and the solution was stirred for approximately 6 h at room temperature. To cleave the silyl ether intermediate, the reaction mixture was cooled to 0 °C in an ice bath and after 10 min, water (1.0 mL, 55 mmol, 5.5 equiv) and TBAF (1 M in THF, 1 mL, 1 mmol, 0.1 equiv) were added. The ice bath was removed and the reaction mixture was stirred at room temperature. When the cleavage was judged to be complete (determined by GC-MS or NMR), the contents of the flask were transferred to a separatory funnel. Brine (∼40 mL) and Et_2O (∼60 mL) were added, and the layers were partitioned. The aqueous layer was back-extracted (3 × ∼10 mL) with Et_2O. The combined ether layers were dried with $MgSO_4$, filtered and the solvent was removed *in vacuo* via rotary evaporation in a room-temperature water bath to afford crude alcohol, which was used in the next step after a short plug on silica gel.

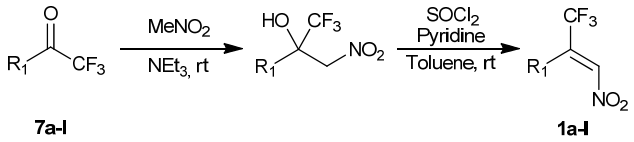
In a two-neck 50 mL round-bottom flask equipped with a stir bar and a condenser, to a solution of the α-CF_3 alcohol (8 mmol, 1 equiv) in DCM (30 mL), was added PDC (12 mmol, 1.5 equiv). The solution was refluxed for 18h. Dry Et_2O (30 mL) was added and the obtained suspension was stirred for an additional hour. The solvent was decanted and a second aliquot of dry Et_2O was added to the remaining solid.

The combined Et_2O organic phases were filtered through a plug of florisil and rinsed thoroughly (three to four times) with anhydrous diethyl ether. The solvent was removed *in vacuo* by rotary evaporation in a room-temperature water bath to give the crude α-CF_3 ketone **7** which was further

[5] C. B. Kelly, M. A. Mercadante, T. A. Hamlin, M. H. Fletcher and N. E. Leadbeater, *J. Org. Chem.*, 2012, **77**, 8131–8141.

purified by column chromatography on silica gel (eluent: diethyl ether/petroleum ether 1:50 (v/v)). The obtained spectroscopic data were in accord with those previously published.

General procedure for the synthesis of trifluoromethylated nitroalkenes 1a-j and 1l-m[6]



7a-l **1a-l**

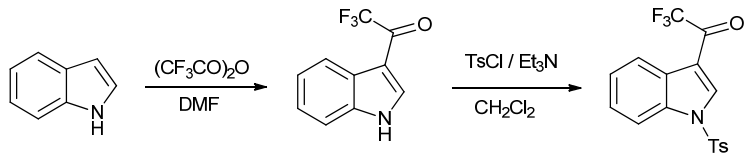
1	R_1
1a	C_6H_5
1b	4-MeC_6H_4
1c	3-MeC_6H_4
1d	2-MeC_6H_4
1e	4-FC_6H_4
1f	4-BrC_6H_4
1g	4-$MeOC_6H_4$
1h	4-$CF_3C_6H_4$
1i	2-naphthyl
1j	2-thienyl
1l	$PhCH_2$
1m	$CH_3(CH_2)_8$

To a solution of the trifluoromethyl ketone **6** (5 mmol, 1.0 equiv) in $MeNO_2$ (10 mL, 0.5 M), NEt_3 (1.0 mL, 7.5 mmol,1.5 equiv) was added. The mixture was stirred overnight at room temperature, then it was diluted with diethyl ether and washed successively with 1N HCl, water, and brine. The organic phase was dried over $MgSO_4$. After filtration, the solvent was removed *in vacuo* by rotary evaporation to afford the corresponding nitroalcohol that was used in the following step without further purification.

To a solution of the obtained nitroalcohol in toluene (0.25 M) were added $SOCl_2$ (0.55 mL, 7.5 mmol, 1.5 equiv) and pyridine (0.8 mL, 10 mmol, 2.0 equiv), successively at 0 °C. The mixture was stirred at room temperature for 3h and then diluted with diethyl ether. After washing with water and brine, the organic phase was separated and dried over $MgSO_4$. After filtration, the solvent was removed under vacuum and the residue was purified with chromatography on silica gel, (eluting with diethyl ether/petroleum ether 1:50 (v/v) or CH_2Cl_2/petroleum ether 1:10 (v/v)), to afford the trifluoromethylated nitroalkene **1**. The obtained spectroscopic data were in accord with that previously published.

[6] J.-R. Gao, H. Wu, B. Xiang, W.-B. Yu, L. Han and Y.-X. Jia, *J. Am. Chem. Soc.* 2013, **135**, 2983−2986.

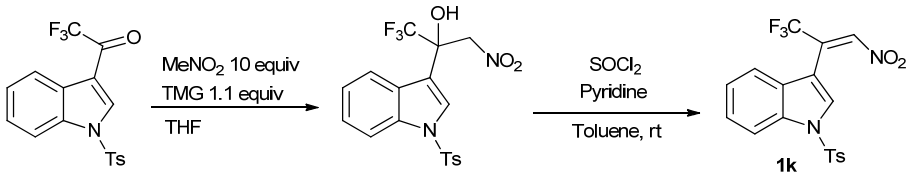
2,2,2-trifluoro-1-(1-tosyl-1H-indol-3-yl)ethanone



Trifluoroacetic anhydride (2.1 mL, 15.24 mmol) was added at 0 °C to a solution of lindole (0.85 g, 7.62 mmol) in *N*,*N*-dimethylformamide (DMF) (20 mL). The resulting mixture was stirred for 3 hr at room temperature. The solvent was removed and then the sticky oil was dissolved in Et_2O and washed with 1M HCl and water (3 times). The organic layer was dried over Na_2SO_4 filtered and evaporated *in vacuo* to give the trifluoro methylated ketone (1.73 g, 86 %) as a pink solid that was used in the next step without further purification.

To a stirred solution of the crude ketone (0.85g, 4.0 mmol) in CH_2Cl_2 (10 mL), were sequentially added Et_3N (0.67 mL, 4.8 mmol) and TsCl (0.92 g, 4.8 mmol). The reaction mixture was then stirred for 18 h at room temperature, then directly purified by chromatography on silica gel (n-hexane: CH_2Cl_2 9:1 then 4:1 as eluent) to afford the title compound in 95% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.44 (q, *J* = 1.6 Hz, 1H), 8.35 – 8.30 (d of m, *J* = 7.7 Hz, 1H), 7.98 – 7.95 (d of m, *J* = 8.3 Hz, 1H), 7.88 (d, *J* = 8.6 Hz, 1H), 7.47 – 7.38 (m, 2H), 7.33 (d, *J* = 8.6 Hz, 1H), 2.39 (s, 3H).

(*E*)-1-Tosyl-3-(3,3,3-trifluoro-1-nitroprop-1-en-2-yl)-1H-indole 1k[7]



To a solution of the 2,2,2-trifluoro-1-(1-tosyl-1H-indol-3-yl)ethanone (10 mmol) in THF (30 mL) was added $MeNO_2$ (10 equiv) and tetramethyl guanidine (TMG 1.1 equiv). The reaction mixture was stirred at room temperature for 30 min. After diluted with ethyl acetate and washed with 1N HCl until pH=7-8, and washed with water, brine and the organic phase was separated and dried over $MgSO_4$, followed by purification with flash chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:10 (v/v), to afford the nitro-aldol product (yield=75%).

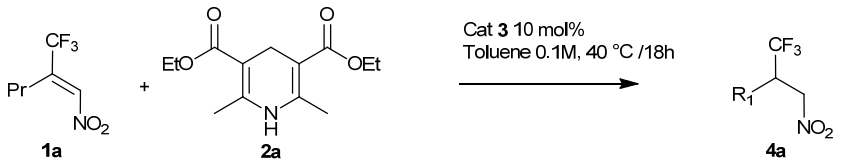
[7] C-H Ma, T-R Kang, L. He and Q.-Z. Liu *Eur. J. Org. Chem.* 2014, 3981–3985.

To a solution of the nitro-aldol product in toluene (0.25 M) were added $SOCl_2$ (1.5 eq.) and pyridine (2.0 equiv) successively at 0 °C. The mixture was stirred at room temperature for 6h and then diluted with ethyl acetate. After washing with water and brine, the organic phase was separated and dried over $MgSO_4$. The solvent was removed under vacuum and the residue was purified with chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:20 (v/v), to afford the title compound **1k** in 65% yield. The obtained spectroscopic data were in accord with that previously published.

Optimization of reaction parameters: selected results

Catalyst screening experiments

Table S1: catalyst screening



Entry	Catalyst	Conversion (%)[a]	ee (%)[b]
1	**3f**	97	+12
2	**3g**	80	-9
3	**3h**	>98	+20
4	**3i**	>98	+5
5	**3j**	60	-14
6	**3k**	>98	-17
7	**3l**	87	-24

[a] Determined on the crude mixture by ^{19}F NMR analysis. [b] Determined by chiral stationary phase HPLC.

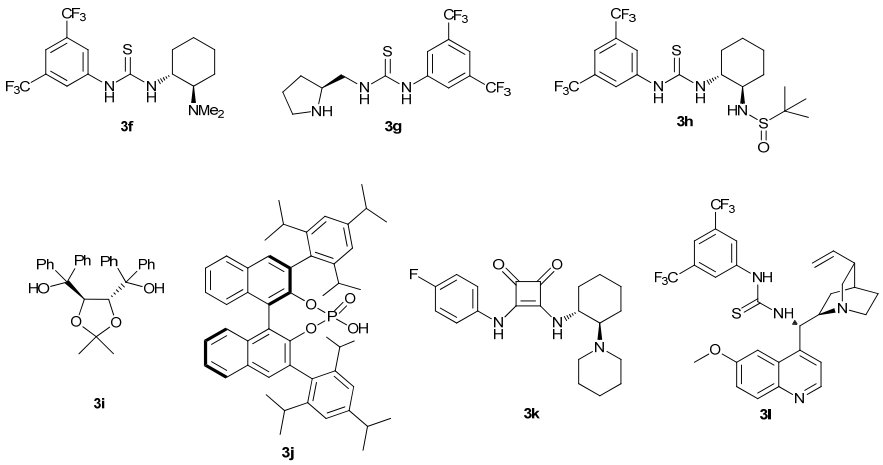
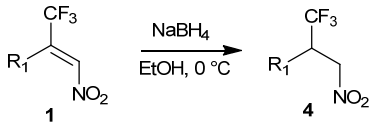


Figure S1.

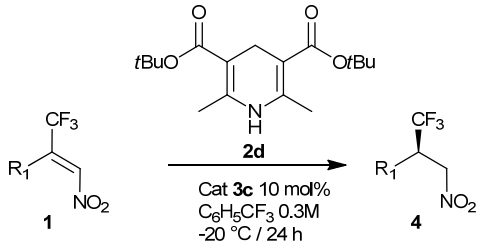
For catalyst screening: to a solution of **1a** (0.05 mmol) in toluene (0.5 mL, 0.1 M), catalyst **3** (0.005 mmol, 0.1 equiv) and Hantzsch ester **2a** (0.06 mmol, 1.2 equiv) were added. The reaction mixture was stirred for 24 h at 40 °C and then it was filtered through a plug of silica gel, and the plug was washed with Et_2O (2x). After removal of solvents, the reaction crude was analysed by ^{19}F NMR spectroscopy to determine the conversion of the starting trifluoromethylated nitroalkenes and by CSP HPLC to determine the enantiomeric excess.

General procedure for the synthesis of racemic trifluoromethylated nitroalkanes 4.



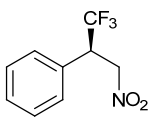
To a solution of trifluoromethylated nitroalkenes (0.1 mmol) in ethanol (0.3 mL) at 0°C, $NaBH_4$ (11 mg, 0.3 mmol, 3.0 equiv) was added in portions. The reaction mixture was stirred at 0°C for 30 min and then treated at 0 °C with a saturated aqueous NH_4Cl solution. The aqueous phase was extracted with Et_2O (3 x 2.5 mL). The combined organic phases were dried over $MgSO_4$. The volatile compounds were removed *in vacuo* via rotary evaporation in a room-temperature water bath and the crude product was purified by column chromatography (1-5 % Et_2O in *n*-hexane) to afford the pure trifluoromethylated nitroalkanes.

General Procedure for the Asymmetric Transfer Hydrogenation of trifluoromethylated nitroalkenes 1.



To a solution of trifluoromethylated nitroalkenes **1** (0.15 mmol) in trifluorotoluene (0.5 mL, 0.3 M), catalyst **3c** (7.6 mg, 0.015 mmol, 0.1 equiv) and Hantzsch ester **2d** (56 mg, 0.18 mmol, 1.2 equiv) were added. The reaction mixture was stirred for 24 h at -20 °C. The resulting mixture was purified by column chromatography eluting with diethyl ether/*n*-hexane 2:50 (v/v), to afford the trifluoromethylated nitroalkane.

(*R*)-1,1,1-Trifluoro-2-phenyl-3-nitropropane 4a. The title compound **4a** was prepared according to the general procedure. Yield: 70%; pale yellow oil; $[\alpha]^{25}_D$ +47 (c 1.1, CH_2Cl_2); ^1H NMR (600 MHz, $CDCl_3$) δ: 7.44 – 7.39 (m, 3H), 7.37 – 7.30 (m, 2H), 4.98 (dd, J_1 = 13.8, J_2 = 5.8 Hz, 1H), 4.83 (dd, J_1 = 13.8, J_2 = 8.9 Hz, 1H), 4.39–4.27 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 130.0 (br), 129.6, 129.3, 128.8, 125.0 (q, $^1J_{C\text{-}F}$ =282.1), 73.9, 48.1



(q, $^2J_{C\text{-}F}$ = 29.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -69.0 (d, *J* = 8.5 Hz, 3F); ESI MS(-) m/z: 218 (M^+-1). The enantiomeric excess of **4a** was determined by CSP HPLC analysis using a Daicel Chiralcel OJH column; *n*-hexane/2-propanol 9:1; 0.75 mL/min; λ = 254 nm. t_R (major) = 24.4 min; t_R (minor) = 31.0 min; ee 97%. The same procedure was repeated using 4.0 mmol (869 mg) of **1a** giving product **4a** in 94% yield and 95% ee.

(*R*)-1,1,1-Trifluoro-2-(4-methyl-phenyl)-3-nitropropane 4b. The title compound **4b** was prepared according to the general procedure. Yield: 80%; pale yellow oil; $[\alpha]^{25}_D$ +17.8 (c 1.1, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.21 (s, 4H), 4.95 (dd, J_1 = 13.6, J_2 = 5.8 Hz, 1H), 4.81 (dd, J_1 = 13.6, J_2 = 9.15 Hz, 1H), 4.33–4.24 (m, 1H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 139.6, 129.9, 128.6, 126.9, 125.0 (q, $^1J_{C\text{-}F}$ = 281.0 Hz), 74.0, 47.8 (q, $^2J_{C\text{-}F}$ = 28.8 Hz), 21.1; ^{19}F NMR (564 MHz, $CDCl_3$) δ: -69.1 (d, *J* = 8.6 Hz, 3F); EI MS m/z: 233 (M^+, 25), 186 (M^+-47, 100). The enantiomeric excess of **4b** was determined by CSP HPLC analysis using a Daicel Chiralcel OJH column; *n*-hexane/2-propanol 9:1; 0.75 mL/min; λ = 254 nm. t_R (major) = 17.5 min; t_R (minor) = 19.8 min; ee 94%.

(*R*)-1,1,1-Trifluoro-2-(3-methyl-phenyl)-3-nitropropane 4c. The title compound **4c** was prepared according to the general procedure. Yield: 80%; pale yellow oil; $[\alpha]^{25}_D$ +49.4 (c 1.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32–7.26 (m, 1H), 7.24–7.19 (m, 1H), 7.1 –7.10 (br s, 2H), 4.96 (dd, J_1 = 13.7, J_2 = 5.8 Hz, 1H), 4.82 (dd, J_1 = 13.7, J_2 = 8.9 Hz, 1H), 4.35–4.23 (m, 1H), 2.37 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 139.1, 130.35, 129.9, 129.5, 129.1, 125.7, 125.0 (q, $^1J_{C\text{-}F}$ = 280.4 Hz), 74.0, 48.0 (q, $^2J_{C\text{-}F}$ = 28.5 Hz), 21.3; ^{19}F NMR (564 MHz, $CDCl_3$) δ: -68.95 (d, *J* = 8.7 Hz, 3F); EI MS m/z: 233 (M^+, 25), 186 (M^+-47, 100). The enantiomeric excess of **4c** was determined by CSP HPLC analysis using a Daicel Chiralcel OJH column; *n*-hexane/2-propanol 9:1; 0.75 mL/min; λ = 254 nm. t_R (major) = 17.7 min; t_R (minor) = 22.1 min; ee 97%.

(*R*)-1,1,1-Trifluoro-2-(2-methyl-phenyl)-3-nitropropane 4d. The title compound **4d** was prepared according to the general procedure. Yield: 75%; pale yellow oil; $[\alpha]^{25}_D$ +19.0 (c 1.3, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32–7.22 (m, 5H), 5.00 (dd, J_1 = 13.9, J_2 = 5.7 Hz, 1H), 4.85 (dd, J_1 = 13.9, J_2 = 8.9 Hz, 1H), 4.78–4.66 (m, 1H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.1, 131.3, 129.3, 128.6, 126.8, 126.7, 125.2 (q, $^1J_{C\text{-}F}$ = 279.7 Hz), 73.9, 42.8 (q, $^2J_{C\text{-}F}$ = 28.4 Hz), 19.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -68.9 (d, *J* = 8.7

Hz, 3F); EI MS m/z: 233 (M^+, 22), 186 (M^+-47, 100). The enantiomeric excess of **4c** was determined by CSP HPLC analysis using a Daicel Chiralcel OJH column; *n*-hexane/2-propanol 9:1; 0.75 mL/min; λ = 254 nm. t_R (major) = 16.6 min; t_R (minor) = 57.6 min; ee 96%.

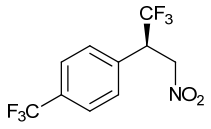
(*R*)-1,1,1-Trifluoro-2-(4-fluoro-phenyl)-3-nitropropane 4e. The title compound **4e** was prepared according to the general procedure. Yield: 73%; pale yellow oil; $[\alpha]^{25}_D$ +42.8 (c 1.4, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36–7.30 (m, 2H), 7.14–7.08 (m, 2H), 4.97 (dd, J_1 = 13.8, J_2 = 5.6 Hz, 1H), 4.81 (dd, J_1 = 13.8, J_2 = 9.4 Hz, 1H), 4.39–4.26 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.3 (d, $^1J_{C\text{-}F}$ = 249.2 Hz), 130.6 (d, $^3J_{C\text{-}F}$ = 8.1 Hz), 125.8 (m), 124.8 (q, $^1J_{C\text{-}F}$ = 279.5 Hz), 116.45 (d, $^2J_{C\text{-}F}$ = 21.8 Hz), 73.8, 47.4 (q, $^2J_{C\text{-}F}$ = 28.5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -69.2 (d, J = 8.9 Hz, 3F), -111.3 (s, 1F); ESI MS(-)m/z: 236 (M^+-1, 100). The enantiomeric excess of **4e** was determined by CSP HPLC analysis using a Daicel Chiralcel OJH column; *n*-hexane/2-propanol 9:1; 0.75 mL/min; λ = 254 nm. t_R (major) = 23.6 min; t_R (minor) = 33.7 min; ee 96%.

(*R*)-1,1,1-Trifluoro-2-(4-bromo-phenyl)-3-nitropropane 4f. The title compound **4f** was prepared according to the general procedure. Yield: 80%; pale yellow oil; $[\alpha]^{25}_D$ +33.6 (c 1.8, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.54 (d, J = 8.5 Hz, 2H), 7.20 (d, J = 8.5 Hz, 2H), 4.95 (dd, J_1 = 13.8, J_2 = 5.4 Hz, 1H), 4.79 (dd, J_1 = 13.8, J_2 = 9.3 Hz, 1H), 4.35–4.23 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 132.5, 130.35, 128.9, 124.6 (q, $^1J_{C\text{-}F}$ =279.5), 124.0, 73.5, 47.6 (q,$^2J_{C\text{-}F}$ = 28.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -70.0 (d, J = 8.7 Hz, 3F); ESI MS(-) m/z: 298 (M^{+91}Br-1, 98), 296 (M^{+89}Br-1, 100). The enantiomeric excess of **4f** was determined by CSP HPLC analysis using a Daicel Chiralcel OJH column; *n*-hexane/2-propanol 9:1; 0.75 mL/min; λ = 254 nm. t_R (major) = 25.9 min; t_R (minor) = 45.0 min; ee 96%.

(*R*)-1,1,1-Trifluoro-2-(4-methoxy-phenyl)-3-nitropropane 4g. The title compound **4g** was prepared according to the general procedure. Yield: 70%; pale yellow oil; $[\alpha]^{25}_D$ +45.0 (c 1.3, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.25 (d, J = 9.0 Hz, 2H), 6.92 d, J = 8.9 Hz, 2H), 4.94 (dd, J_1 = 13.8, J_2 = 5.8 Hz, 1H), 4.79 (dd, J_1 = 13.8, J_2 = 9.2 Hz, 1H), 4.33–4.21 (m, 1H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.4, 129.95, 125.05 (q, $^1J_{C\text{-}F}$ = 280.7 Hz), 121.8, 114.7, 74.0, 55.3, 47.4 (q, $^2J_{C\text{-}F}$ = 28.5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -69.3 (d, J = 9.2 Hz, 3F); EI MS m/z: 249 (M^+, 22), 202 (M^+-47, 100). The enantiomeric excess of **4g** was determined by CSP HPLC analysis using a Daicel Chiralcel ADH

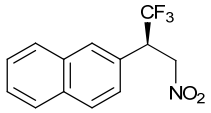
column; *n*-hexane/2-propanol 95:5; 0.75 mL/min; λ = 254 nm. t_R (major) = 15.2 min; t_R (minor) = 16.0 min; ee 98%.

(*R*)-1,1,1-Trifluoro-2-(4-(trifluoromethyl)phenyl)-3-nitropropane 4h. The title compound **4h**



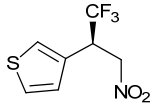
was prepared according to the general procedure. Yield: 85%; pale yellow oil; $[\alpha]^{25}_D$ +11.3 (c 1.7, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.69 (d, J = 8.2 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H), 5.01 (dd, J_1 = 13.9, J_2 = 5.3 Hz, 1H), 4.86 (dd, J_1 = 13.9, J_2 = 9.4 Hz, 1H), 4.45–4.37 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 133.9, 132 (q, $^2J_{C\text{-}F}$ =33.2 Hz), 129.3, 126.3 (q $^3J_{C\text{-}F}$ =3.8 Hz), 124.6 (q, $^1J_{C\text{-}F}$ = 279.5 Hz), 123.5 (q, $^1J_{C\text{-}F}$ = 272.8 Hz), 73.4, 47.9 (q, $^2J_{C\text{-}F}$ = 28.8 Hz); ^{19}F NMR (564 MHz, $CDCl_3$) δ: -63.1 (s, 3F), -68.7 (d, J = 8.7 Hz, 3F); EI MS m/z: 287 (M^+, 26), 240 (M^+-47, 100). The enantiomeric excess of **4h** was determined by CSP HPLC analysis using a Daicel Chiralcel OJH column; *n*-hexane/2-propanol 95:5; 0.75 mL/min; λ = 254 nm. t_R (major) = 23.6 min; t_R (minor) = 28.2 min; ee 94%.

(*R*)-2-(1,1,1-Trifluoro-3-nitropropan-2-yl)naphthalene 4i. The title compound **4i** was prepared



according to the general procedure. Yield: 82%; white solid mp; 99-100 °C; $[\alpha]^{25}_D$ +56.7 (c 1.5, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.94–7.80 (m, 4H), 7.59 – 7.51 (m, 2H), 7.42 (br d, 1H), 5.07 (dd, J_1 = 13.8, J_2 = 5.7 Hz, 1H), 4.95 (dd, J_1 = 13.8, J_2 = 9.0 Hz, 1H), 4.57–4.46 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 133.5, 133.1, 129.3, 128.9, 128.1, 127.7, 127.3, 127.2, 126.9, 125.3, 125.1 (q, $^1J_{C\text{-}F}$ = 279.9 Hz), 73.9, 48.3 (q, $^2J_{C\text{-}F}$ = 28.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -68.6 (d, J = 8.4 Hz, 3F); EI MS m/z: 269 (M^+, 39), 222 (M^+-47, 100). The enantiomeric excess of **4i** was determined by CSP HPLC analysis using a Daicel Chiralpak ADH column; *n*-hexane/2-propanol 9:1; 0.75 mL/min; λ = 254 nm. t_R (major) = 9.5 min; t_R (minor) = 10.6 min; ee 97%.

(*R*)-3-(1,1,1-Trifluoro-3-nitropropan-2-yl)thiophene 4j. The title compound **4j** was prepared



according to the general procedure. Yield: 83%; pale yellow oil; $[\alpha]^{25}_D$ +48.2 (c 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39 – 7.36 (m, 1H), 7.12 (br d, 1H), 7.04 (dd, J_1 = 5.2, J_2 = 3.6 Hz, 1H), 4.96 (dd, J_1 = 13.7, J_2 = 5.6 Hz, 1H), 4.78 (dd, J_1 = 13.7, J_2 = 9.2 Hz, 1H), 4.72–4.62 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 130.4, 128.8, 127,4, 127.2, 124.3 (q, $^1J_{C\text{-}F}$ = 279.0 Hz), 74.5, 43.7 (q, $^2J_{C\text{-}F}$ = 30.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -69.95 (d, J = 8.0 Hz, 3F); ESI MS(-) m/z: 224 (M^+-1). The enantiomeric excess of **4j** was determined by CSP HPLC

analysis using a Daicel Chiralcel OJH column; *n*-hexane/2-propanol 9:1; 0.75 mL/min; λ = 254 nm. t_R (major) = 27.7 min; t_R (minor) = 31.9 min; ee 95%.

(*R*)-(1-Tosyl-3-(1,1,1-trifluoro-3-nitropropan-2-yl)-1*H*-indole 4k. The title compound **4k** was prepared according to the general procedure. Yield: 78%; white solid; mp 114-115 °C; $[\alpha]^{25}_D$ +21.7 (c 2.3, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.98 (d, *J* = 8.3 Hz, 1H), 7.73 (d, *J* = 8.0 Hz, 2H), 7.69 (s, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.37 (t, *J* = 7.7 Hz, 1H), 7.30 (t, *J* = 7.7 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 5.01 (dd, J_1 = 13.7, J_2 = 6.2 Hz, 1H), 4.81 (dd, J_1 = 13.7, J_2 = 8.2 Hz, 1H), 4.69 – 4 .61(m, 1H) 2.33 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 145.6, 134.8, 134.5, 130.1, 128.9, 126.8, 125.7, 124.8 (q, $^1J_{C\text{-}F}$ = 278.0 Hz), 123.9, 119.0, 113.9, 115.5, 73.3, 40.0 (q, $^2J_{C\text{-}F}$ = 30.3 Hz), 21.5; ^{19}F NMR (564 MHz, $CDCl_3$) δ: -69.23 (d, *J* = 8.5 Hz, 3F); ES MS m/z: 412 (M^+, 6), 365 (M^+-47, 35), 155 ($CH_3C_6H_4SO_2$, 100). The enantiomeric excess of **4j** was determined by CSP HPLC analysis using a Daicel Chiralpak ADH column; *n*-hexane/2-propanol 9:1; 0.75 mL/min; λ = 254 nm. t_R (minor) = 16.9 min; t_R (major) = 18.1 min; ee 93%.

(*R*)-(3,3,3-Trifluoro-2-(nitromethyl)propyl)benzene 4l. The title compound **4l** was prepared according to the general procedure. Yield: 79%; pale yellow oil; $[\alpha]^{25}_D$ -12.2 (c 1.5, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.40–7.27 (m, 3H), 7.25–7.20 (m, 2H), 4.56 (dd, J_1 = 14.4, J_2 = 7.8 Hz, 1H), 4.32 (dd, J_1 = 14.4, J_2 = 5.0 Hz, 1H), 3.57–3.43 (m, 1H) 3.21 (dd, J_1 = 14.4, J_2 = 5.0 Hz, 1H), 2.70 (dd, J_1 = 14.4, J_2 = 10.25 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 135.0, 129.2, 129.0, 127.7, 126.0 (q, $^1J_{C\text{-}F}$ = 281.0 Hz), 71.9, 43.7 (q, $^2J_{C\text{-}F}$ = 27.1 Hz), 31.74 (q, $^3J_{C\text{-}F}$ = 2.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -70.95 (d, *J* = 8.0 Hz, 3F); ESI MS(-) m/z: 232 (M^+-1). The enantiomeric excess of **4k** was determined by CSP HPLC analysis using a Daicel Chiralcel OJH column; *n*-hexane/2-propanol 9:1; 0.75 mL/min; λ = 254 nm. t_R (major) = 17.3 min; t_R (minor) = 17.9 min; ee 90%.

(*R*)-1,1,1-Trifluoro-2-(nitromethyl)undecane 4m. The title compound **4m** was prepared according to the general procedure. Yield: 79%; pale yellow oil; $[\alpha]^{25}_D$ +1.8 (c 1.6, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 4.59 (dd, J_1 = 13.9, J_2 = 6.6 Hz, 1H), 4.38 (dd, J_1 = 13.9, J_2 = 6.2 Hz, 1H), 3.17–3.08 (m, 1H) 1.79–1.72 (m, 1H), 1.45–1.38 (m, 2H), 1.35–1.21 (m, 13H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 126.3 (q, $^1J_{C\text{-}F}$ = 281.0 Hz), 73.22 (q, $^3J_{C\text{-}F}$ = 2.8 Hz), 41.95 (q, $^2J_{C\text{-}F}$ = 27.4

Hz), 31.8, 29.4, 29.22, 29.18, 29.15, 26.23 (br s), 26.20, 22.6, 14.0; ^{19}F NMR (564 MHz, $CDCl_3$) δ: -70.63 (d, *J* = 8.7 Hz, 3F); EI MS m/z: 269 (M^+, 8), 153 (M^+-16, 20), 145 (M^+-124, 100) 127 (M^+-142, 27). The enantiomeric excess of **4l** was determined by CSP HPLC analysis using a Daicel Chiralcel OJH column; *n*-hexane/2-propanol 95:5; 0.3 mL/min; λ = 254 nm. t_R (major) = 16.7 min; t_R (minor) = 17.2 min; ee 91%.

General Procedure for the nitro group reduction with Pd/C

To a stirred solution of compound 4 (0.14 mmol) in CH_3OH (1 mL) were sequentially added Pd/C 10% (10 mg) and $HCOONH_4$ (45 mg, 0.7 mmol). The reaction mixture was stirred at room temperature overnight, then filtered on a celite pad, the pad washed several times with CH_3OH and the solvent evaporated under reduced pressure. The white residue was dissolved in EtOAc, washed with sat. Na_2CO_3, and the aqueous phase extracted twice with EtOAc. The combined organic phases were dried over Na_2SO_4, filtered and evaporated affording compound 5. The crude product was used in the next steps without further purification.

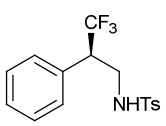
To a stirred solution of crude **5** (0.14 mmol) in CH_2Cl_2 (1.0 mL), were sequentially added Et_3N (23 μL, 0.17 mmol) and TsCl (32 mg, 0.17 mmol). The reaction mixture was then stirred for 18 h at room temperature, then directly purified by chromatography on silica gel (CH_2Cl_2 as eluent).

General Procedure for the nitro group reduction with $NiCl_2$•$6H_2O$

To a suspension of **4** (0.14 mmol) and $NiCl_2$•$6H_2O$ (33 mg, 0.14 mmol) in methanol (0.7 mL) was added $NaBH_4$ (26 mg, 0.7 mmol) at 0 °C and the mixture was stirred at room temperature for 1h. The mixture was then cooled to 0 °C, quenched with sat. NH_4Cl and extracted with CH_2Cl_2 (a filtration of the solution through a pad of silica gel to remove the metal may be useful for the nextstep). The organic layers were washed with brine and dried over $MgSO_4$. After filtration and concentration under vacuum, the crude product **5** was used in the next step without further purification.

To a stirred solution of crude **5** (0.14 mmol) in CH_2Cl_2 (1.0 mL), were sequentially added Et_3N (23 μL, 0.17 mmol) and TsCl (32 mg, 0.17 mmol). The reaction mixture was then stirred for 18 h at room temperature, then directly purified by chromatography on silica gel (CH_2Cl_2 as eluent).

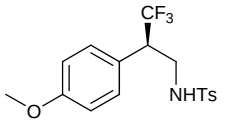
(*R*)-4-Methyl-*N*-(3,3,3-trifluoro-2-phenylpropyl)benzenesulfonamide 6a. The title compound **6a**



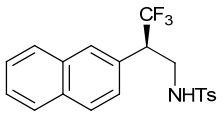
was prepared according to the general procedure in 87% yield as a white solid; mp 130-133 °C; $[\alpha]^{25}_D$ +12 (c 0.7, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.67 (br d, *J* = 8.3 Hz, 2H), 7.38–7.32 (m, 3H), 7.31 (br d, *J* = 8.2 Hz, 2H), 7.17–7.13 (m, 2H),

4.47–4.39 (br d, 1H), 3.67–3.61 (m, 1H), 3.52–3.43 (m, 1H), 3.37–3.31 (m, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 142.9, 135.5, 130.5, 128.9, 128.2, 128.02, 127.98, 126.1, 124.6 (q, $^1J_{C\text{-}F}$ = 280.9 Hz), 49.1 (q, $^2J_{C\text{-}F}$ = 26.5 Hz), 41.1 (q, $^1J_{C\text{-}F}$ = 3.0 Hz), 21.5; ^{19}F NMR (564 MHz, $CDCl_3$) δ: -68.6 (d, *J* = 9.0 Hz, 3F); EI MS m/z: 343 (M^+, 20), 184 (M^+-159, 60). The enantiomeric excess of the product was determined by CSP HPLC using a Daicel Chiralpak AS column (*n*-hexane/i-PrOH = 9:1, 1.0mL/min, t_R (major) = 44.3 min; t_R (minor) = 66.3 min); ee 97%.

(*R*)-4-Methyl-N-(3,3,3-trifluoro-2-(4-methoxyphenyl)propyl)benzenesulfonamide 6b. The title compound **6b** was prepared according to the general procedure in 75% yield as a white solid; mp 151-152 °C; $[\alpha]^{25}_D$ +11 (c 1.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.67 (br d, *J* = 8.3 Hz, 2H), 7.31 (br d, *J* = 8.0 Hz, 2H), 7.06 (br d, *J* = 8.7 Hz, 2H), 6.86 (br d, *J* = 8.7 Hz, 2H), 4.48 – 4.39 (dd, J_1 = 8.2, J_2 = 4.7 Hz, 1H), 3.8 (s, 3H), 3.66 – 3.57 (m, 1H), 3.47–3.36 (m, 1H),3.33–3.24 (m, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.0, 143.9, 136.5, 130.1, 129.9, 127.1, 125.7 (q, $^1J_{C\text{-}F}$ = 281.7 Hz), 123.1, 114.6, 55.3, 49.2 (q, $^2J_{C\text{-}F}$ = 26.7 Hz), 42.1 (q, $^1J_{C\text{-}F}$ = 3.0 Hz), 21.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -69.1 (d, *J* = 9.2 Hz, 3F); EI MS m/z: 373 (M^+, 15), 189 (M^+-184, 40), 184 (M^+-189, 80).



(*R*)-4-Methyl-N-(3,3,3-trifluoro-2-(naphthalen-2-yl)propyl)benzenesulfonamide 6c. The title compound **6c** was prepared according to the general procedure in 83% yield as a white solid; mp 187-188 °C; $[\alpha]^{25}_D$ +7.2 (c 2.4, CH_2Cl_2); ^{1}H NMR (600 MHz, $(CD_3)_2CO$) δ: 7.94 – 7.86 (m, 3H), 7.83 (s, 1H), 7.68 (br d, *J* = 8.1 Hz, 2H), 7.57 – 7.53 (m, 2H), 7.44 (br d, *J* = 8.8 Hz, 1H), 7.32 (br d, *J* = 8.1 Hz, 2H), 6.79 – 6.73 (br t, *J* = 6.4 Hz, 1H), 4.00 – 3.91 (m, 1H), 3.75 – 3.68 (m, 1H), 3.65 – 3.58 (m, 1H), 2.39 (s, 3H);^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.2, 137.9,133.3, 130.0, 129.6, 129.2, 128.4, 128.0, 127.6, 126.85, 126.84, 126.5, 126.4, 126.3 (q, $^1J_{C\text{-}F}$ = 279.1 Hz), 50.25 (q, $^2J_{C\text{-}F}$ = 25.8 Hz), 42.1 (q, $^1J_{C\text{-}F}$ = 3.0 Hz), 20.5; ^{19}F NMR (564 MHz, $CDCl_3$) δ: -68.8 (d, *J* = 9.4 Hz, 3F); EI MS m/z: 393 (M^+, 10), 209 (M^+-184, 20), 184 (M^+-209, 60), 155 ($CH_3C_6H_4SO_2$, 100).



Determination of the absolute configuration of the nitroalkane 4g.

The reference method to assign the absolute configuration (AC) relies on the X-ray anomalous scattering (the "Bijovet method").[8] This approach requires the preparation of enantiopure single crystals, and the presence of a suitable heavy atom in the molecule (Z ≥ Si when using the standard Mo-Kα radiation[9]). With the exception of **4i** and **4k**, all the prepared compounds are viscous oils, and the second requirement is fulfilled only for **4k**. Despite many attempts, suitable crystals of **4k** could not be obtained. The direct assignment by X-ray crystallography is therefore unfeasible without chemical derivatization. Nevertheless, the determination of the AC of chiral molecules by chiro-optical techniques such as optical rotation (OR), electronic circular dichroism (ECD), and vibrational circular dichroism (VCD) has recently gained feasibility and reliability thanks to the development of the density functional theory approach (DFT and TD-DFT).[10]

A sample of racemic **4g** was separated by CSP HPLC using a Daicel Chiralpak® ADH column (250x21.2 mm) with hexane/*i*PrOH (95:5, 20 mL/min) as eluent (Figure S2), in order to have analytically pure samples of both the enantiomers at the maximum available ee.

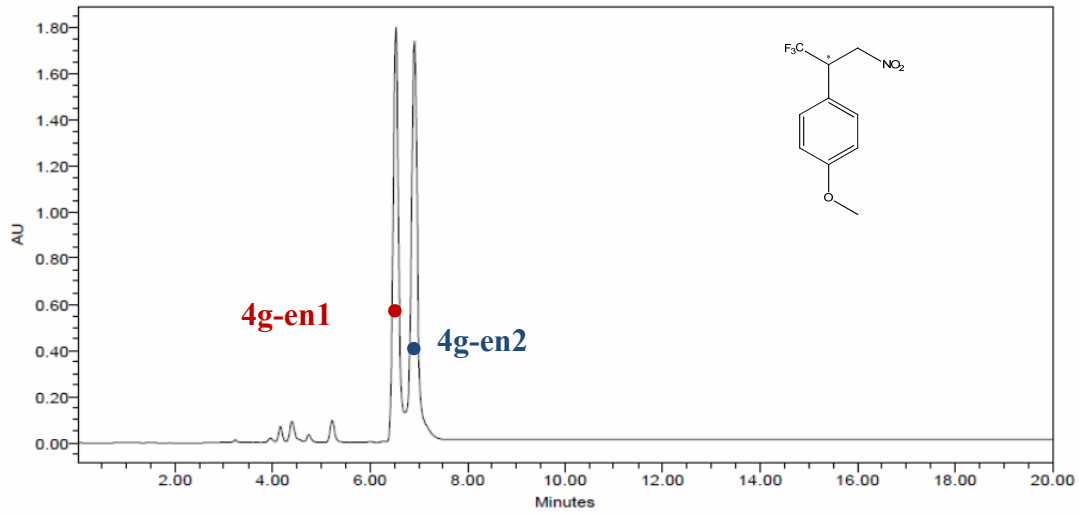


Figure S2: HPLC trace of the semi-preparative resolution of the enantiomeric pair of **4g**.

Due to the lack of strong UV absorption bands and to the weak Electronic Circular Dichroism spectrum, the AC assignment was tackled using two different techniques: ECD and VCD spectroscopy.

[8] A. F. Peerdeman; A. J. Van Bommel and J. M. Bijvoet, *Nature* 1951, **168**, 271–271.
[9] R. W. W Hooft; L. H. Stravera, and A. L. Spek, *J. Appl. Cryst,* 2008, **41**, 96–103
[10] For reviews see: a) G. Bringmann, T. Bruhn, K. Maksimenka and Y. Hemberger, *Eur. J. Org. Chem*. 2009, 2717–2727. b) T.D. Crawford, M.C. Tam, and M.L. Abrams, *J. Chem. Phys. A* 2007, **111**, 12057–12068. c) G. Pescitelli, L. Di Bari, and N. Berova, N. *Chem. Soc. Rev.* 2011, **40**, 4603–4625. d) A. Mazzanti and D. Casarini, *WIREs Comput. Mol. Sci.* 2012, **2**, 613–641

Conformational analysis

As the first stage for AC assignment, we performed a conformational search on compound **4g**, assuming *S* absolute configuration. The whole conformational space was explored by means of Monte Carlo searching together with the MMFF94 molecular mechanics force field as implemented in Titan 1.0.5 (Wavefunction inc.). The energy minima enclosed in a 5 kcal/mol window where then optimized with DFT using DFT at the B3LYP/6-31+G(d,p) level. After DFT optimization four conformation (Figure S3) were found to be enclosed in a very narrow energy window (1 kcal/mol). DFT calculations were also run including the solvent (acetonitrile and $CHCl_3$) using the PCM approach[11] without relevant modifications to the energy differences among the four conformations. The four conformation are grouped into two pairs that differ because of the position of the methoxy group. As a consequence, the two energies within each pair are almost identical. The two pairs display a different dihedral angle of the nitro group that is gauche to the phenyl group in the best conformations GS1 and GS2 (C_{ipso}-CH-CH_2-N dihedral ≈ -60°), and anti in the less favoured (GS3 and GS4). The third available conformation (C_{ipso}-CH-CH_2-N dihedral ≈ +60°) is higher in energy due to the steric interference of the CF_3 group. All the computational data are reported in Table S2.

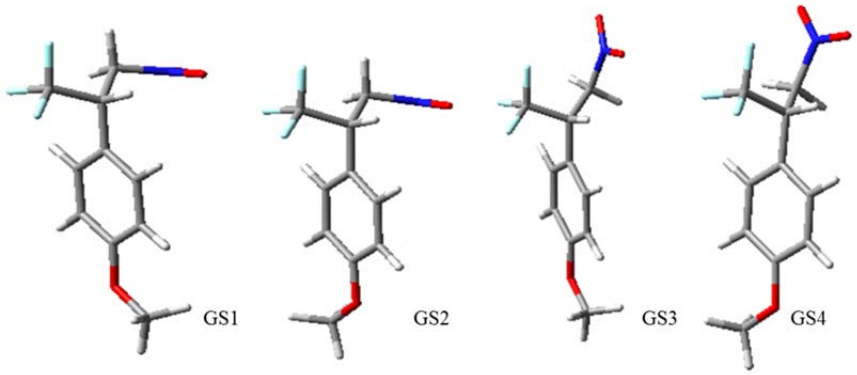


Figure S3.

Table S2. Computational data for compound **4g**. Energies calculated at the B3LYP/6-31+G(d,p) level

Conf.	Total Energies			H°		
	Gas Phase	ACN	$CHCl_3$	Gas Phase	ACN	$CHCl_3$
GS1	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**
GS2	0.08	0.04	0.04	0.08	0.04	0.04
GS3	0.76	0.20	0.36	0.76	0.20	0.36
GS4	0.83	0.24	0.40	0.83	0.24	0.40

[11] J. Tomasi, B. Mennucci, and R. Cammi, *Chem. Rev.* 2005, **105**, 2999–3093.

It has been pointed out[12] that the calculations of entropy data needed to extract the Gibbs free energy are thwarted by the existence of low-frequency vibrational modes that should be treated in the anharmonic field. For this reason only the ZPE-corrected enthalpies are reported in Table S2.

ECD simulation

The electronic excitation energies and rotational strengths have been calculated for the isolated molecule in the gas phase for the four conformations of **4g** using TD-DFT with four different methods (functionals), to ascertain if different computational approaches provide different shapes of the simulated spectra (Figure S4).[13] Simulations were performed with the hybrid functionals BH&HLYP[14] and M06-2X,[15] with ωB97XD that includes empirical dispersion,[16] and CAM-B3LYP that includes long range correction using the Coulomb Attenuating Method.[17] The calculations employed the 6-311++G(2d,p) basis set that has proven many times to provide good accuracy at a moderate computational cost.[18] Rotational strengths were calculated in both length and velocity representation, the resulting values being very similar (RMS differences < 5%). For this reason the errors due to basis set incompleteness should be very small.[19]

[12] a) Y. Lan, and K. N. Houk, *J. Am. Chem. Soc.* 2010, **132**, 17921–17927. b) C. P. A. Anconi, C. S. Nascimento Jr, H. F. Dos Santos, and W. B. De Almeida, *Chem. Phys. Lett.* 2006, **418**, 459–466. c) S. E. Wheeler, A. J. McNeil, P. Muller; T. M Swager, and K. N. Houk, *J. Am. Chem. Soc*. 2010, **132**, 3304–3311.
[13] C. E. Check and T. M. Gilbert. *J. Org. Chem.* 2005, **70**, 9828–9834.
[14] In Gaussian 09 the BH&HLYP functional has the form: $0.5*E_X^{HF} + 0.5*E_X^{LSDA} + 0.5*\Delta E_X^{Becke88} + E_C^{LYP}$
[15] Y. Zhao and D .G. Truhlar, *Theor. Chem. Acc*. 2008, **120**, 215–241.
[16] J-D. Chai and M. Head-Gordon, *Phys. Chem. Chem. Phys.*, 2008, **10**, 6615–6620.
[17] T. Yanai, D. Tewand, N. Handy, *Chem. Phys. Lett.* 2004, **393**, 51–57.
[18] a) M. Ambrogi; A. Ciogli, M. Mancinelli; S. Ranieri and A. Mazzanti, *J. Org. Chem.* 2013, **78**, 3709–3719. b) G. Cera, M. Chiarucci, A. Mazzanti, M. Mancinelli and M. Bandini, *Org. Lett.* 2012, **14**, 1350–1353; c) F. Pesciaioli, P. Righi, A. Mazzanti, G. Bartoli and G. Bencivenni *Chem. Eur. J.* 2011, **17**, 2482–2485; d) S. Duce, F. Pesciaioli, L. Gramigna, L. Bernardi, A. Mazzanti, A. Ricci, G. Bartoli and G. Bencivenni, *Adv. Synt. Catal.* 2011, **353**, 860–864; e) L. Bernardi, M. Comes-Franchini, M. Fochi, V. Leo, A. Mazzanti and A. Ricci, *Adv. Synt. Catal.* 2010, **352**, 3399–3406.
[19] P. J. Stephens, D. M. McCann, F. J. Devlin, J. R. Cheeseman, and M. J. Frisch, *J. Am. Chem. Soc.* 2004, **126**, 7514–7521.

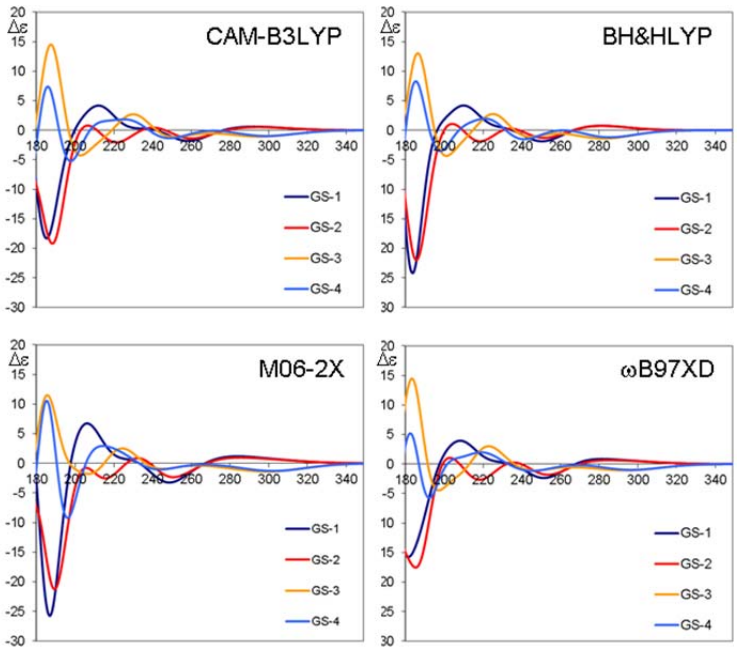


Figure S4. TD-DFT simulated spectra calculated for the four conformations of (*S*)-**4g** using four different functionals (CAM-B3LYP, BH&HLYP, M06-2X, ωB97-XD) and the same 6-311++G(2d,p) basis set. For each conformation the first 40 excited states were calculated, and the spectrum was obtained using a 0.25 eV line width at half height.

Although the spectra calculated within the same functional for the four conformations are quite different, the good agreement of the simulated spectra for the same conformation on varying the functional represent a good proof of the simulations consistency. While the Cotton effect at about 185 nm is simulated as opposite in the two pair of conformations, all the simulations suggest a weak negative band in the 260 nm region. The UV transition responsible for this band is localized in the HOMO-LUMO transition (calculated component ≈ 92%). The HOMO MO is localized mainly on the phenyl group, while the LUMO is localized mainly on the nitro group (Figure S5). The relative disposition of the phenyl and nitro group is determined only by the configuration of the stereogenic centre, thus this transition is calculated to have CD sign independent from the conformation considered.

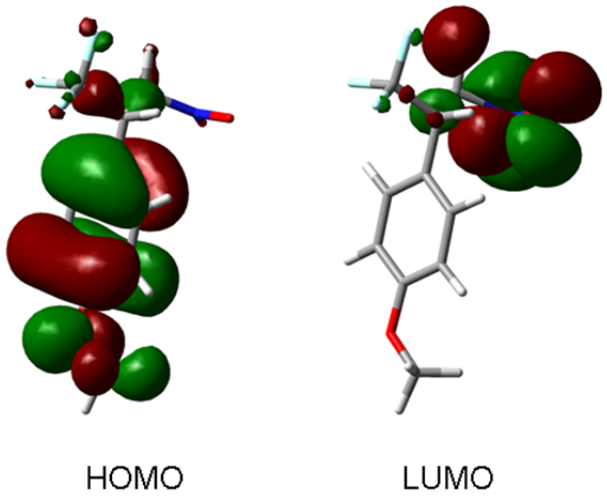


Figure S5. MO involved of **4g** (GS1 conformation) in the UV transition calculated at 259 nm.

The simulated spectra to be compared with the experimental were obtained using Boltzmann weighting using total energies (Figure S6). All the four simulation are in a good agreement with the experimental ECD spectrum of the second eluted enantiomer, to which the *S* absolute configuration should be assigned.

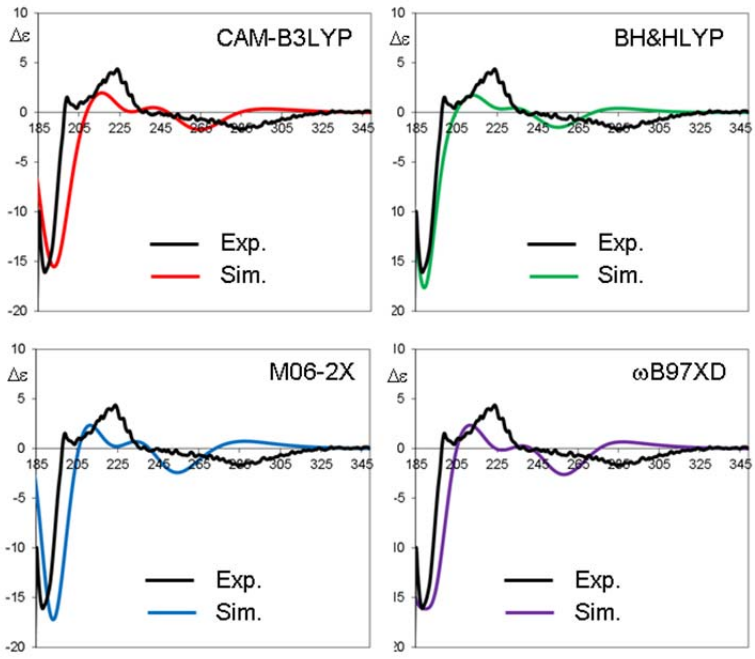


Figure S6. Simulations of the experimental ECD spectrum of **4g**. For each quarter, the black line correspond to the experimental spectrum (acetonitrile solution, $1.0 \cdot 10^{-4}$ M, 0.2 cm path length, Δε in Mol L^{-1} cm^{-1}) and the colored line to the TD-DFT simulations (6-311++G(2d,p) basis set). The simulated spectra were vertically scaled and red-shifted by 4-8 nm to get the best match with the experimental spectrum. All the simulations are for the *S* absolute configuration.

VCD simulation

A 70 mM sample in $CDCl_3$ (14.75 mg/0.85 mL) of each enantiomer has been prepared and placed in a 0.1 mm path length cell with BaF_2 windows. IR and VCD spectra were recorded in the 2000-1000 cm^{-1} region on a ChiralIR-2X FT-VCD spectrometer (Biotools, Inc.) equipped with single PEM at 36kHz and 4 cm^{-1} resolution, with the parameters optimized for 1400 cm^{-1}. 12 blocks of 3120 scans were acquired for each enantiomer with a total acquisition time of 12 hours. The spectrum of each enantiomer was obtained by subtracting the spectrum of the opposite enantiomer and halving the resulting spectrum. This approach allows the removal of all the possible artifacts arising from the solvent, from the cell position and geometry, and for baseline artifacts. The IR and VCD spectra are reported in Figure S7.

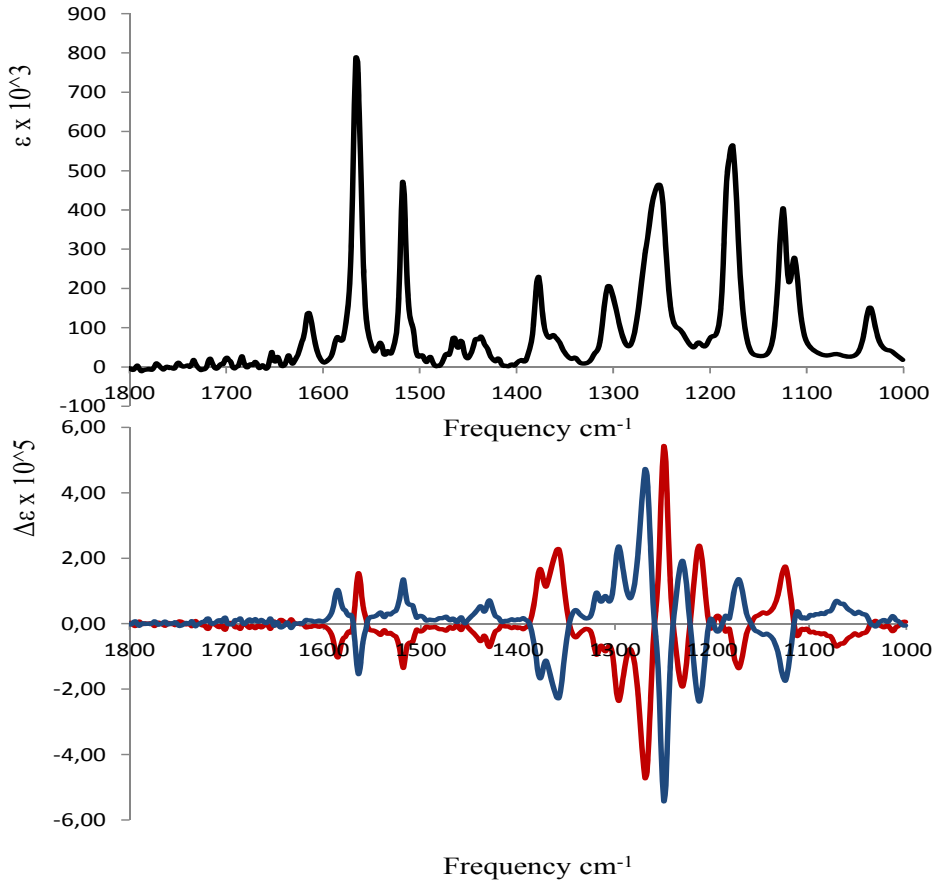


Figure S7. IR spectrum (top) and VCD spectra of the two enantiomers of **4g**.

The VCD spectra of the four conformations were theoretically calculated assuming the *S* absolute configuration at the B3LYP/6-31+G(d,p) level, providing the spectra of Figure S8.

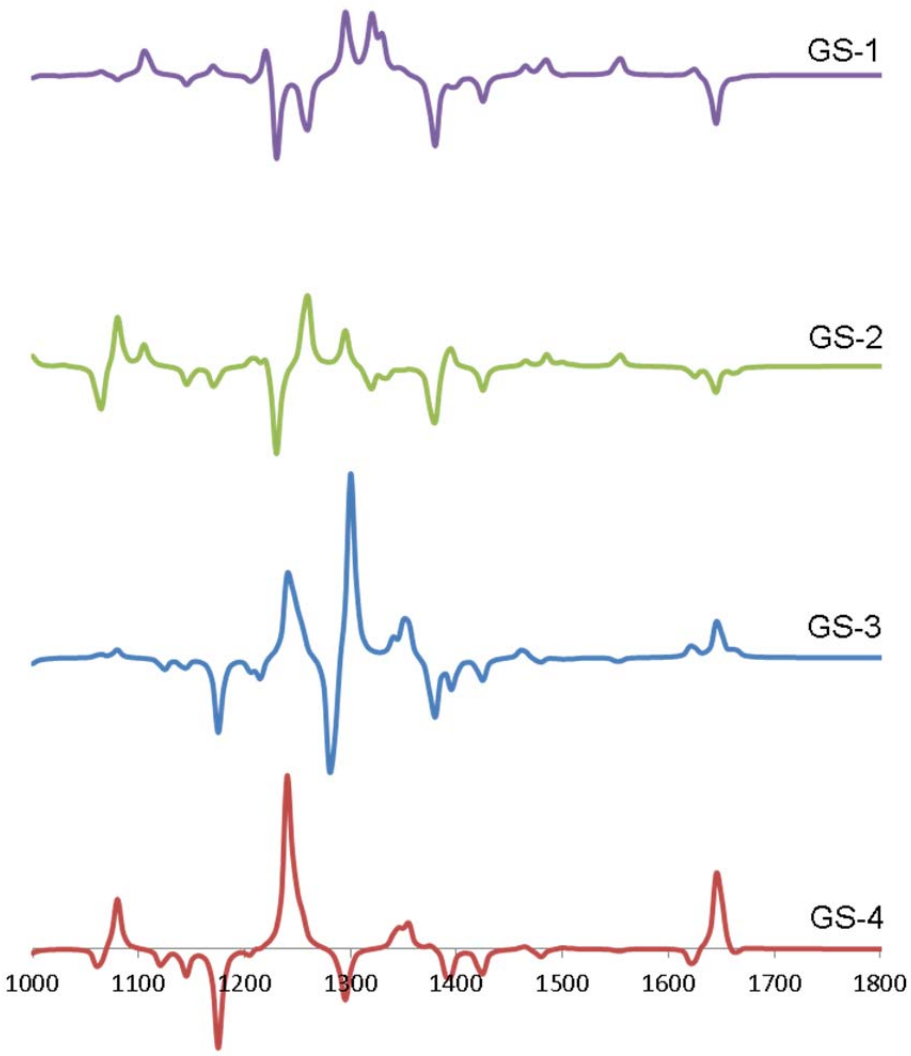


Figure S8. Simulated VCD spectra for the four conformations of (*S*)-**4g.**

The calculated IR and VCD spectra to be compared with the experimental ones were calculated as the weighted sum of the four spectra using Boltzmann distribution (Figure S9). The spectrum of the second eluted enantiomer is well reproduced by the simulation obtained supposing *S* absolute configuration. It must be noted that the frequency calculation loses performance on lowering the frequency, because at low energy the frequencies should be calculated in the anharmonic field. For this reason the best signals to be compared are those at higher frequency (the 1350-1600 cm^{-1} region that in this case entails 7 CD bands), that is nicely fitted by the simulations in terms of sign and intensity. Besides, the two negative bands at 1360 and 1370 cm^{-1} are also well reproduced. The VCD assignment is also in agreement with that suggested by ECD, thus the *S* absolute

configuration can be satisfactorily assigned to the second eluted enantiomer of **4g** (i.e. to the minor enantiomer obtained in the enantioselective reduction).

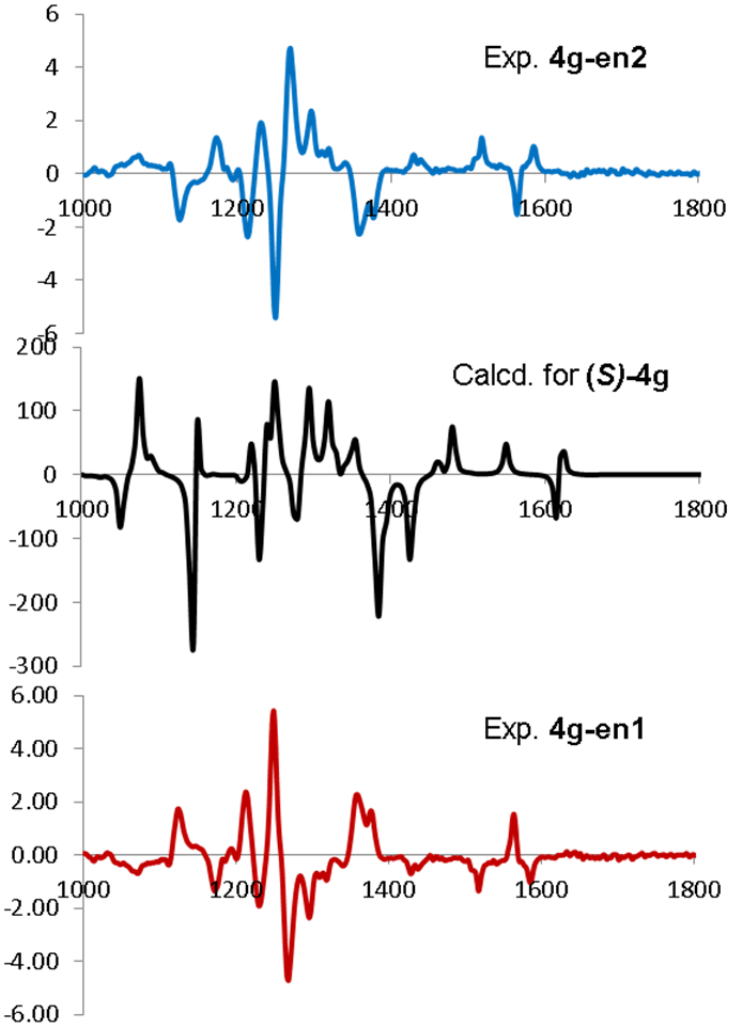
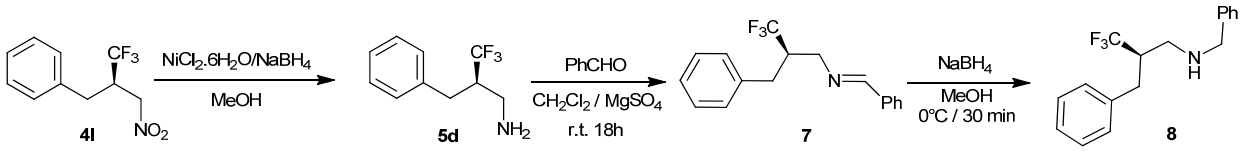


Figure S9. Top and bottom spectra are the VCD spectra of the two enantiomers of **4g**. The middle trace is the simulated spectrum obtained after Boltzmann averaging of the VCD spectra of the four conformations.

Thus, to conclude, the catalytic enantioselective reaction promoted by the thiourea catalyst **3c** gave mainly the (*R*) enantiomer of **4g**. Assuming a similar reaction pathway and transition state for the remaining compounds **4**, the same absolute configuration was assigned to the remaining compounds **4**.

Confirmation of the absolute configuration of nitroalkane 4l by chemical correlation



(3,3,3-Trifluoro-2-(nitromethyl)propyl)benzene **4l** (47 mg, 0.2 mmol) was reacted according with the general procedure for the nitro group reduction with $NiCl_2$•$6H_2O$ (see page S14). The corresponding 2-benzyl-3,3,3-trifluoropropan-1-amine **5d** was converted into imine **7** by reaction with benzaldehyde (1 equiv) in CH_2Cl_2 (0.4M) in the presence of $MgSO_4$ at room temperature. The crude product **7** was recovered by filtration and after evaporation of the solvent it was directly reduced with $NaBH_4$ (2 equiv) in MeOH (0.2 M) at 0 °C for 30 min. The solvent was then removed in *vacuo*, and the crude product **8** was dissolved in water and extracted with CH_2Cl_2 (3 x 2.5 mL) Purification was achieved using chromatography on silica gel (*n*-hexane/CH_2Cl_2/EtOAc = 8:1.5:0.5 as eluent) to provide amine **8** (45% yield over 3 steps).

The obtained spectroscopic data of **8** were in accordance with that previously published.[20] The absolute configuration of **8** was determined to be *R* by comparison of the optical rotation value with the one previously published (obtained: $[\alpha]^{25}_D$ –49.8 (c 1.1, $CHCl_3$); reported for the *S* enantiomer (ee = 87%): $[\alpha]^{25}_D$ +41.8 (c 1.23, $CHCl_3$);[20]

[20] D. A. Nagib. M. E. Scott and D. W. C. MacMillan, *J. Am. Chem. Soc.*, *2009*, **131**, 10875–10877.

Measurement of the evolution of the reaction with time

The measurement of the reaction rate was achieved by performing a reaction in the standard conditions described above and by comparing the obtained results with a blank experiment performed without the organocatalyst. The conversion was determined by ^{19}F-NMR at 1, 2.5, 5, 8 and 24 hours and the obtained results are reported in Table S3 and in Figure S10.

Table S3 Conversion values (determined by ^{19}F NMR) of the catalysed (**3c**, 10 mol%) and non-catalysed reaction between nitroalkene **1a** and Hantzsch ester **2d** under the optimized reaction conditions (trifluorotoluene solvent, 0.3 M -20 °C) at different times.

time (h)	conversion with cat (%)	conversion without cat (%)
0	0	0
1	33	0
2.5	45	0
5	65	2
8	75	3
24	94	8

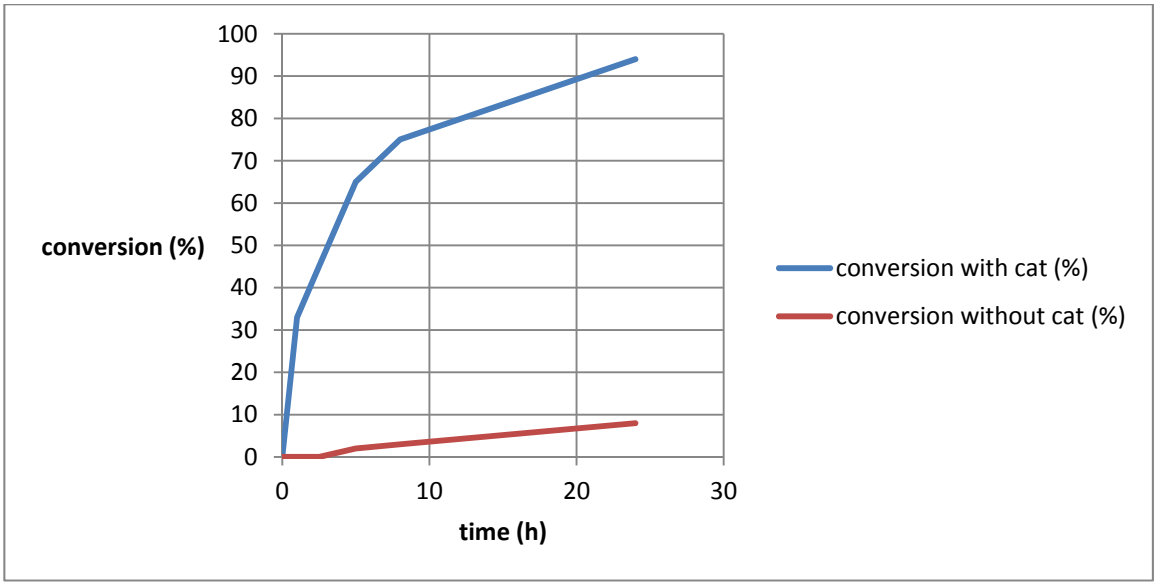
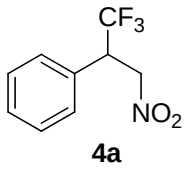
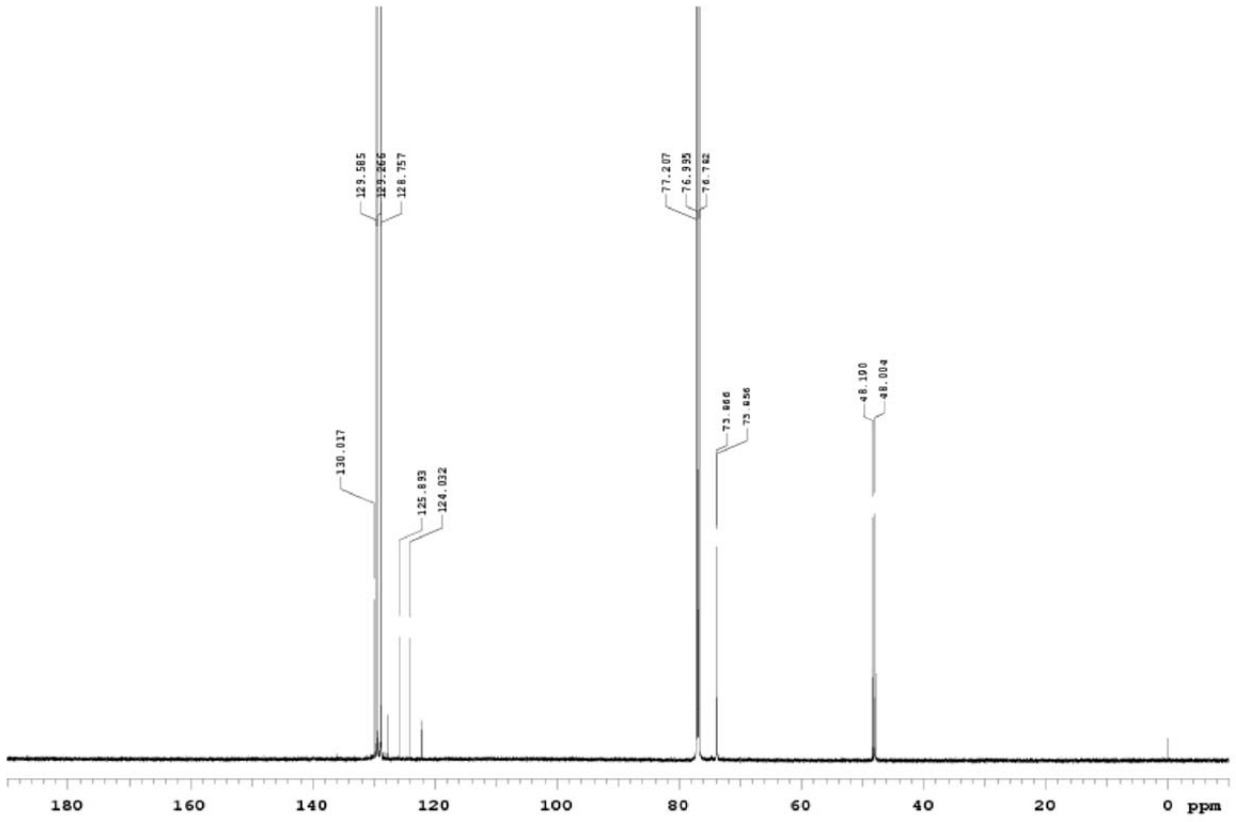


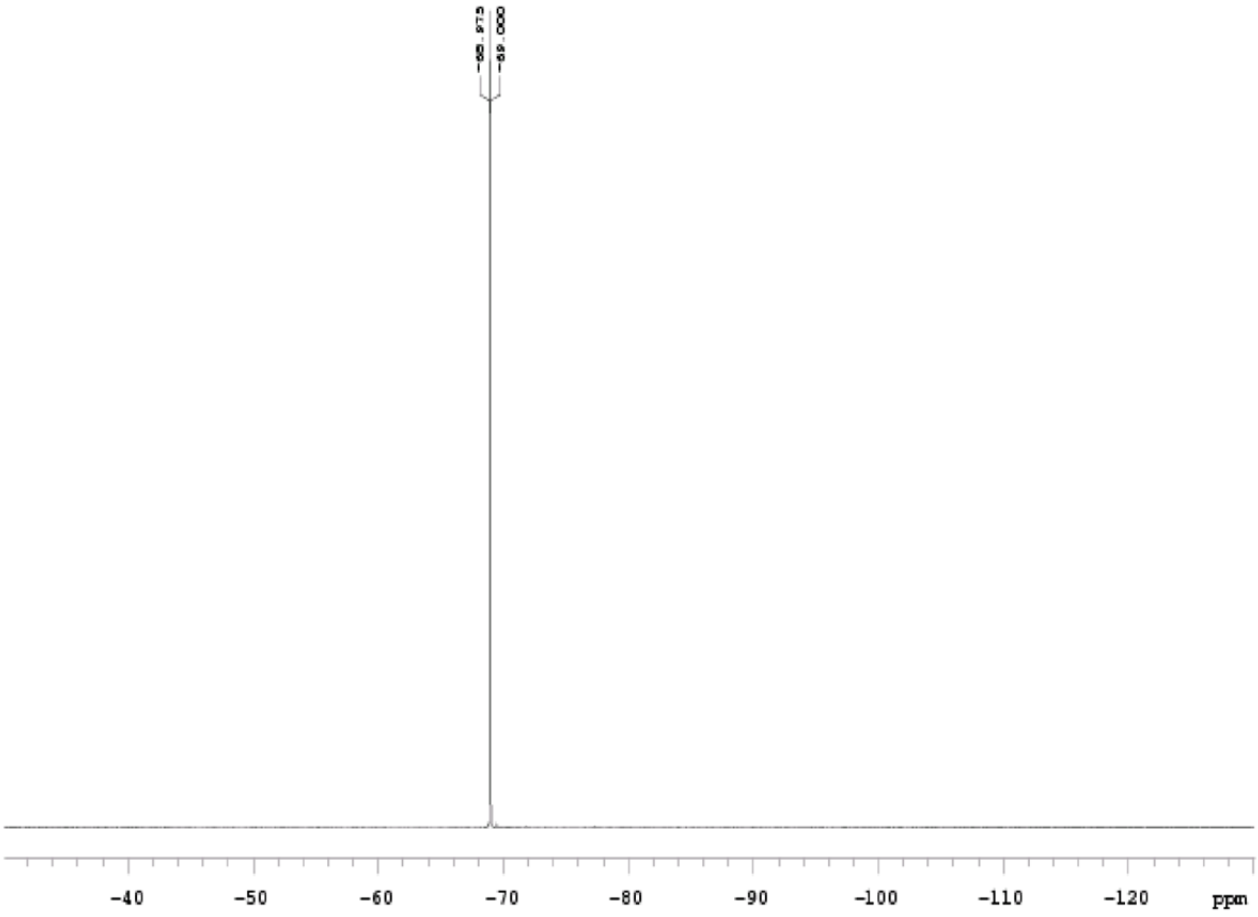
Figure S10 Evolution of the catalyzed and non-catalyzed reaction with time.

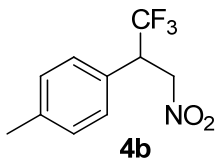
Copies of the ^{1}H, ^{13}C and ^{19}F NMR spectra of products 4 and 6



4a

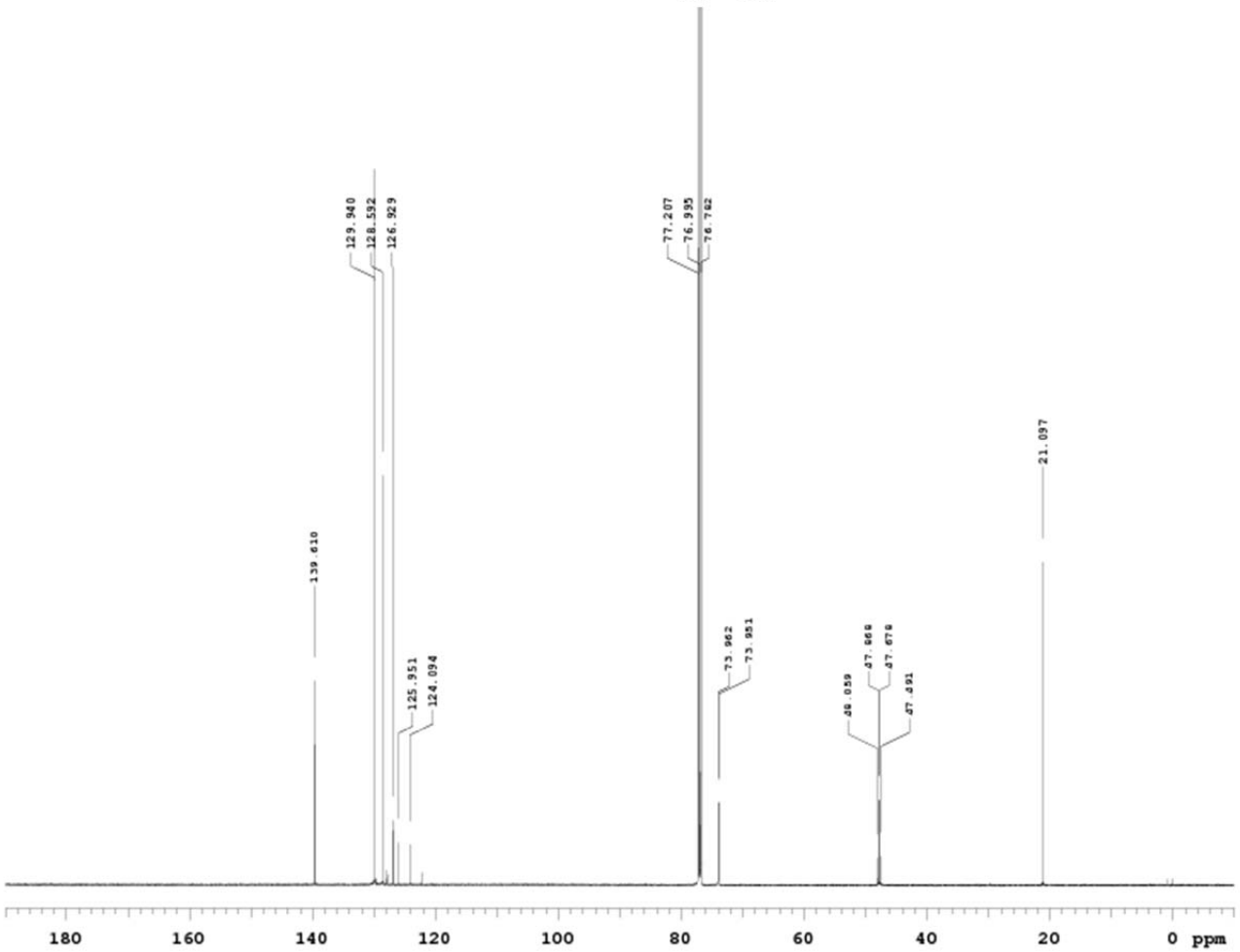


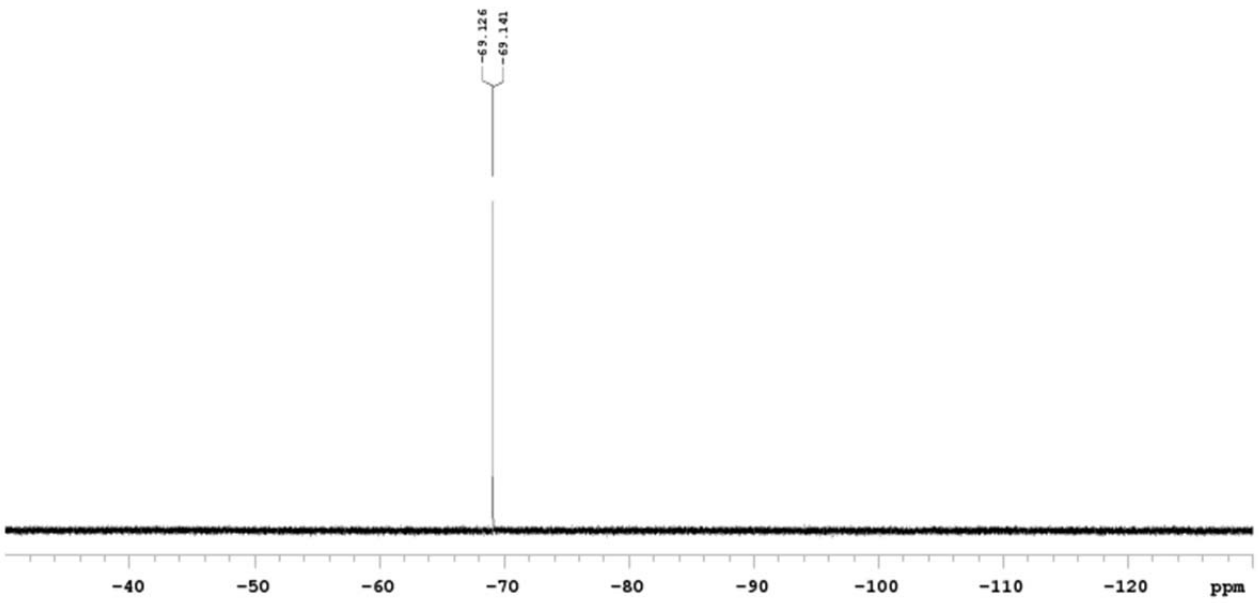

-40
-50
-60
-70
-80
-90
-100
-110
-120
ppm

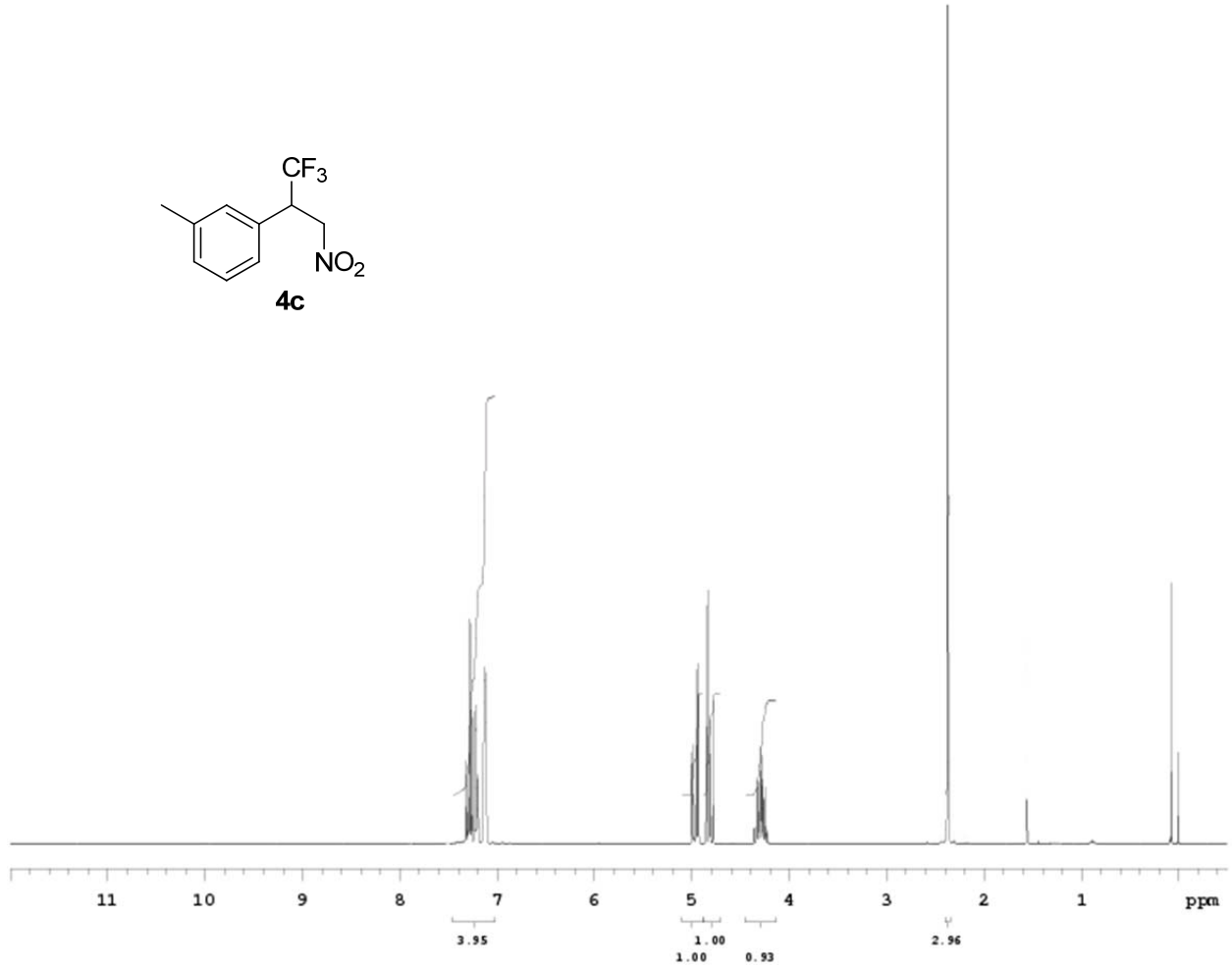

CF3
NO2

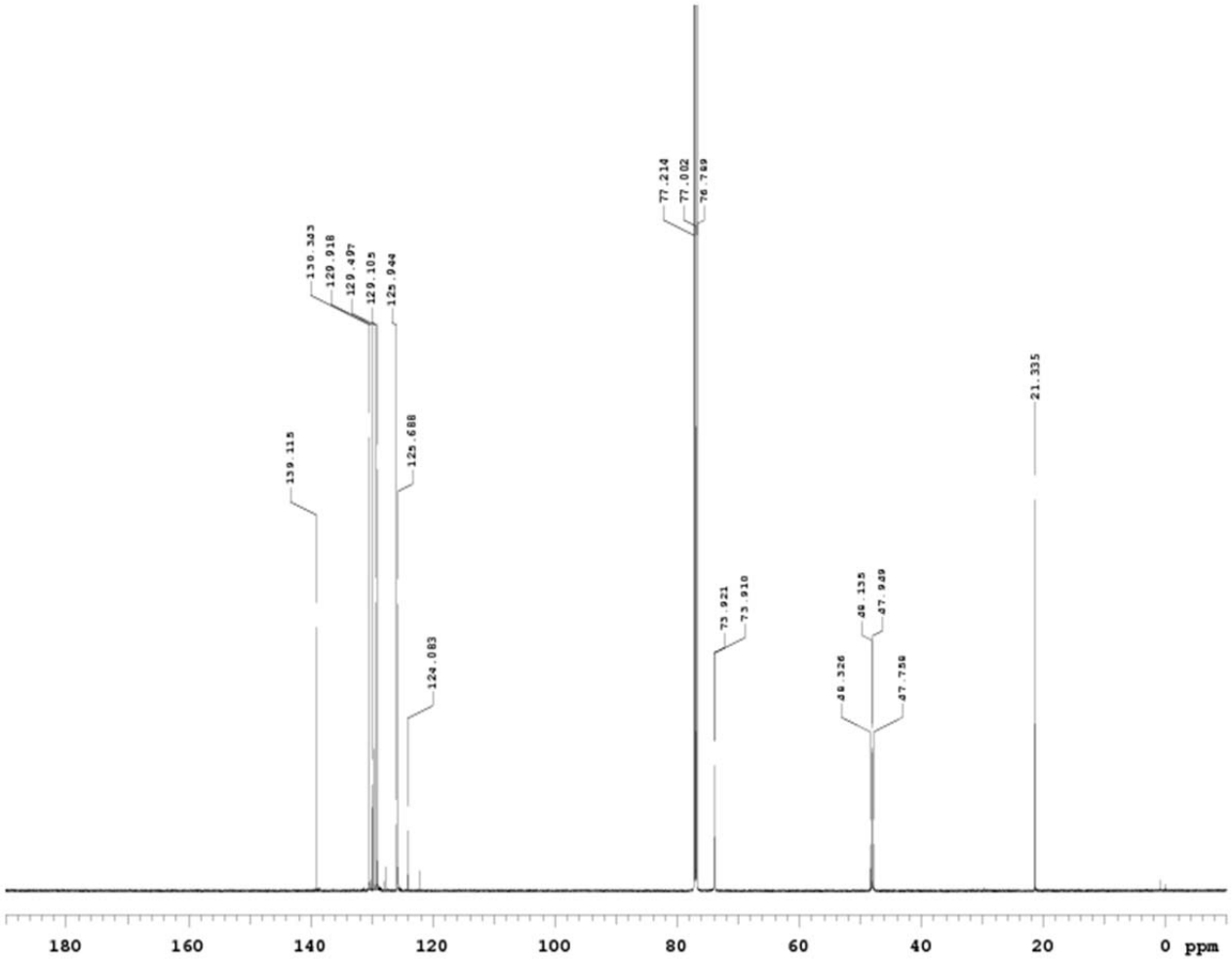
4b

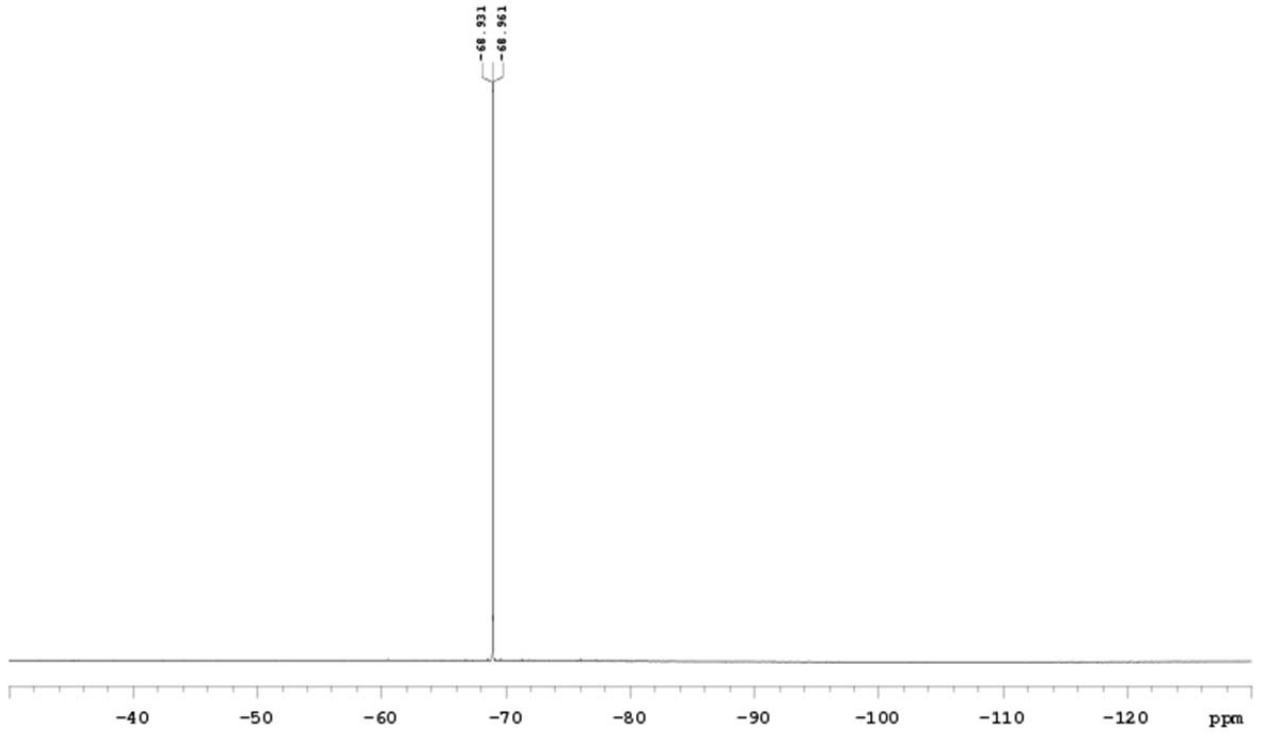
11
10
9
8
7
6
5
4
3
2
1
ppm
3.98
1.06
1.06
1.00
3.13

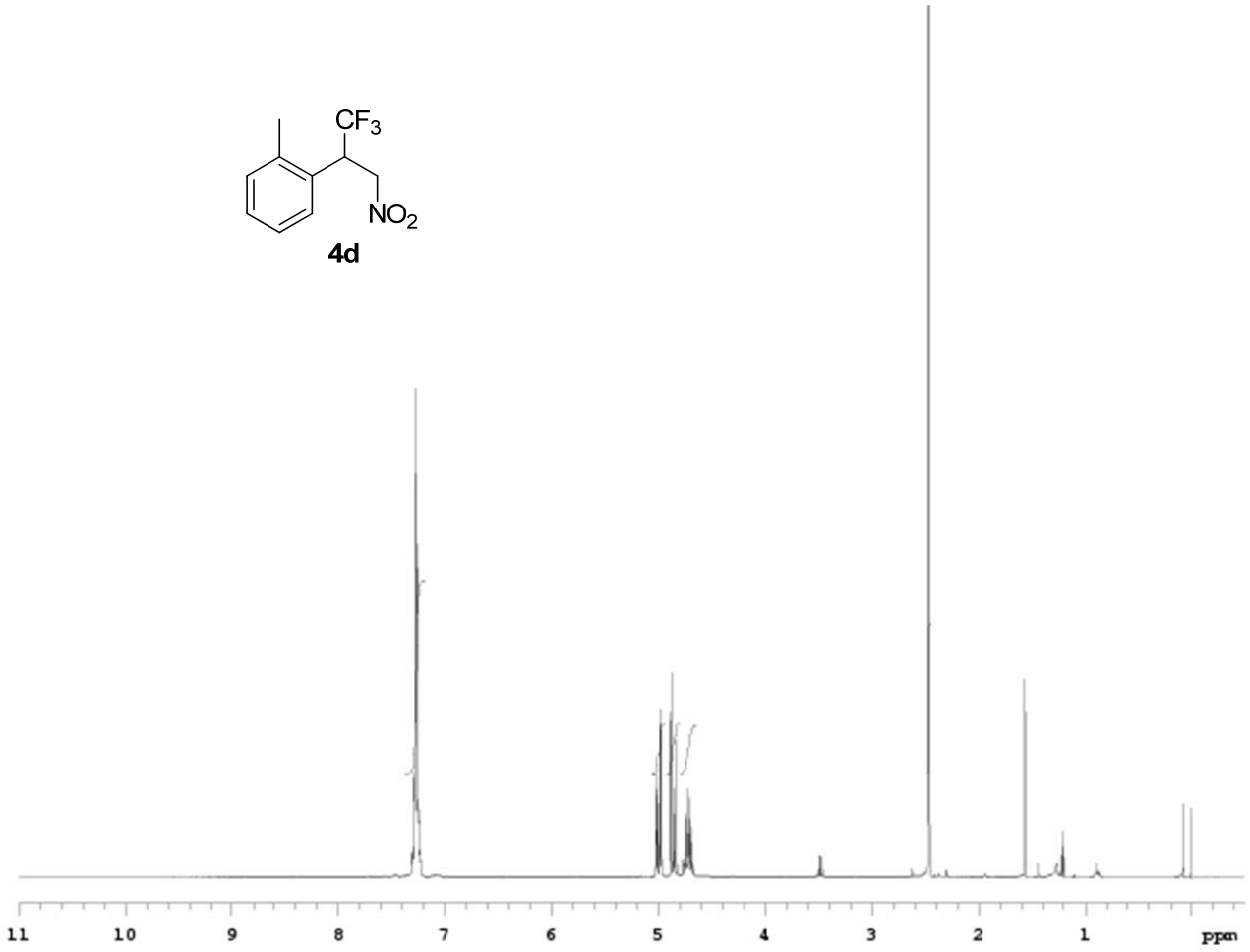

129.940
128.592
126.929
77.207
76.995
76.782
139.610
125.951
124.094
73.962
73.951
46.059
47.868
47.674
47.491
21.097
180
160
140
120
100
80
60
40
20
0 ppm

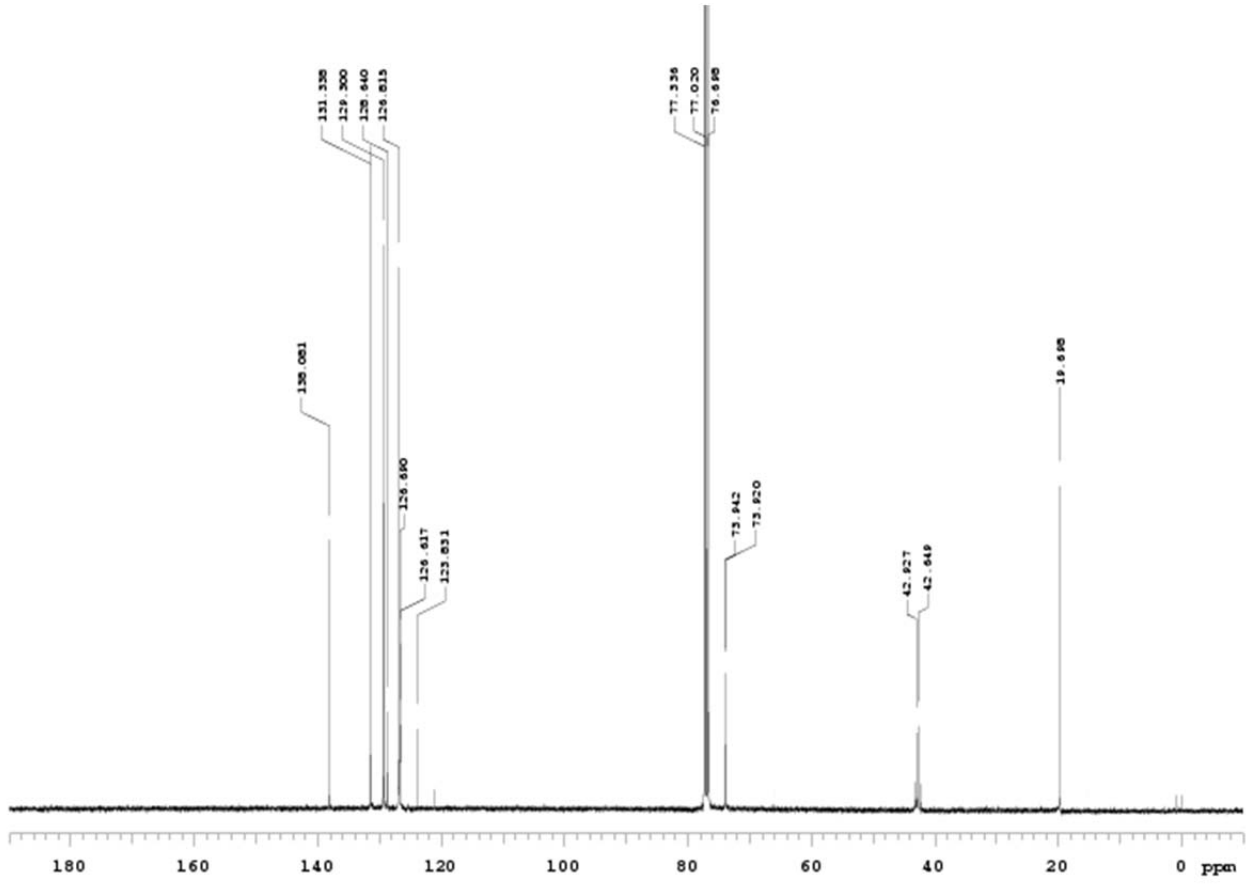

-69.126
-69.141
-40
-50
-60
-70
-80
-90
-100
-110
-120
ppm

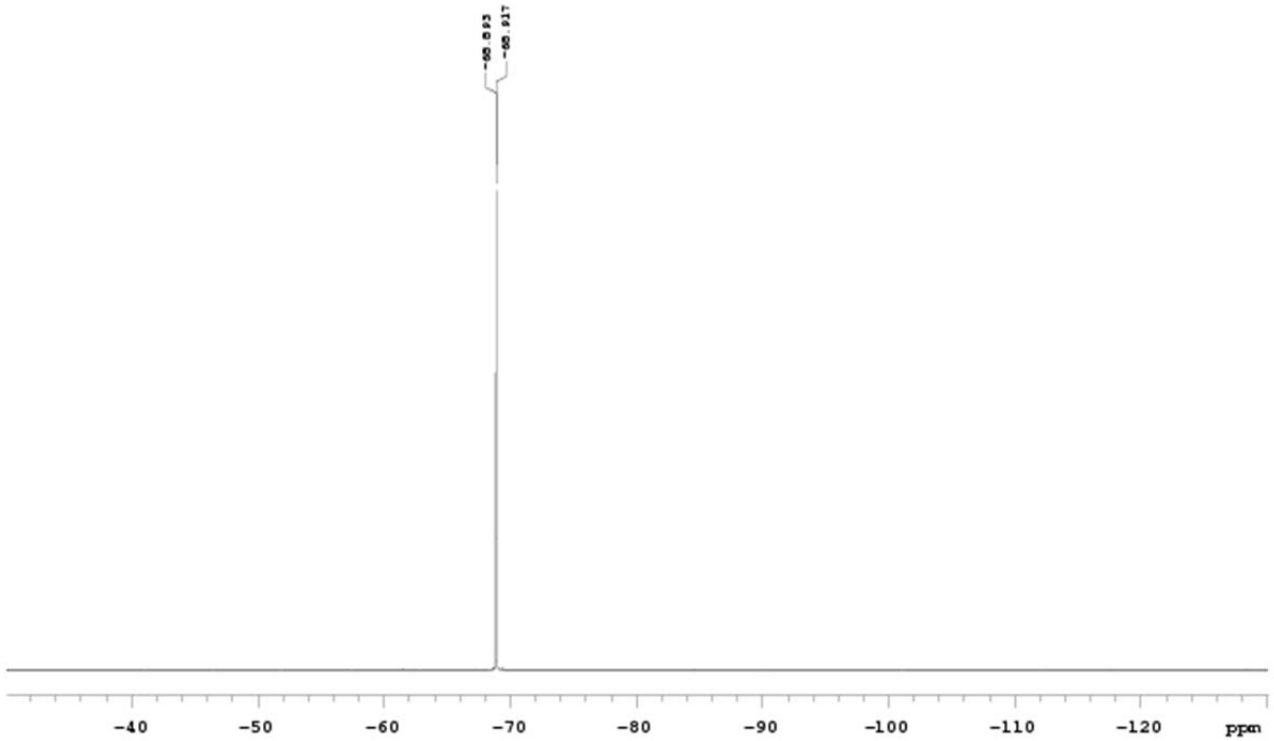

CF3
NO2
4c
11
10
9
8
7
6
5
4
3
2
1
ppm
3.95
1.00
1.00
0.93
2.96

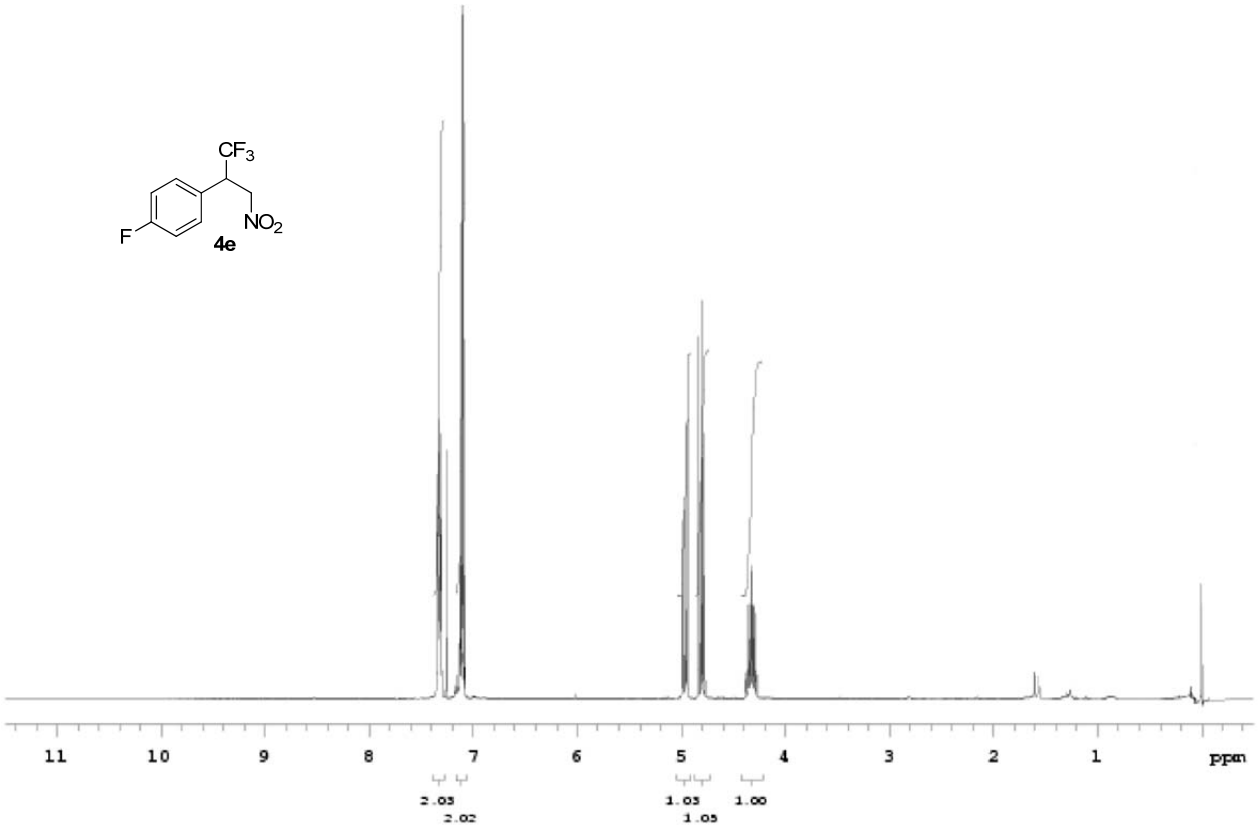

130.323
129.918
129.497
129.105
125.944
125.688
124.083
139.115
77.214
77.002
76.789
73.921
73.910
48.135
47.949
47.756
48.326
21.335
180
160
140
120
100
80
60
40
20
0 ppm

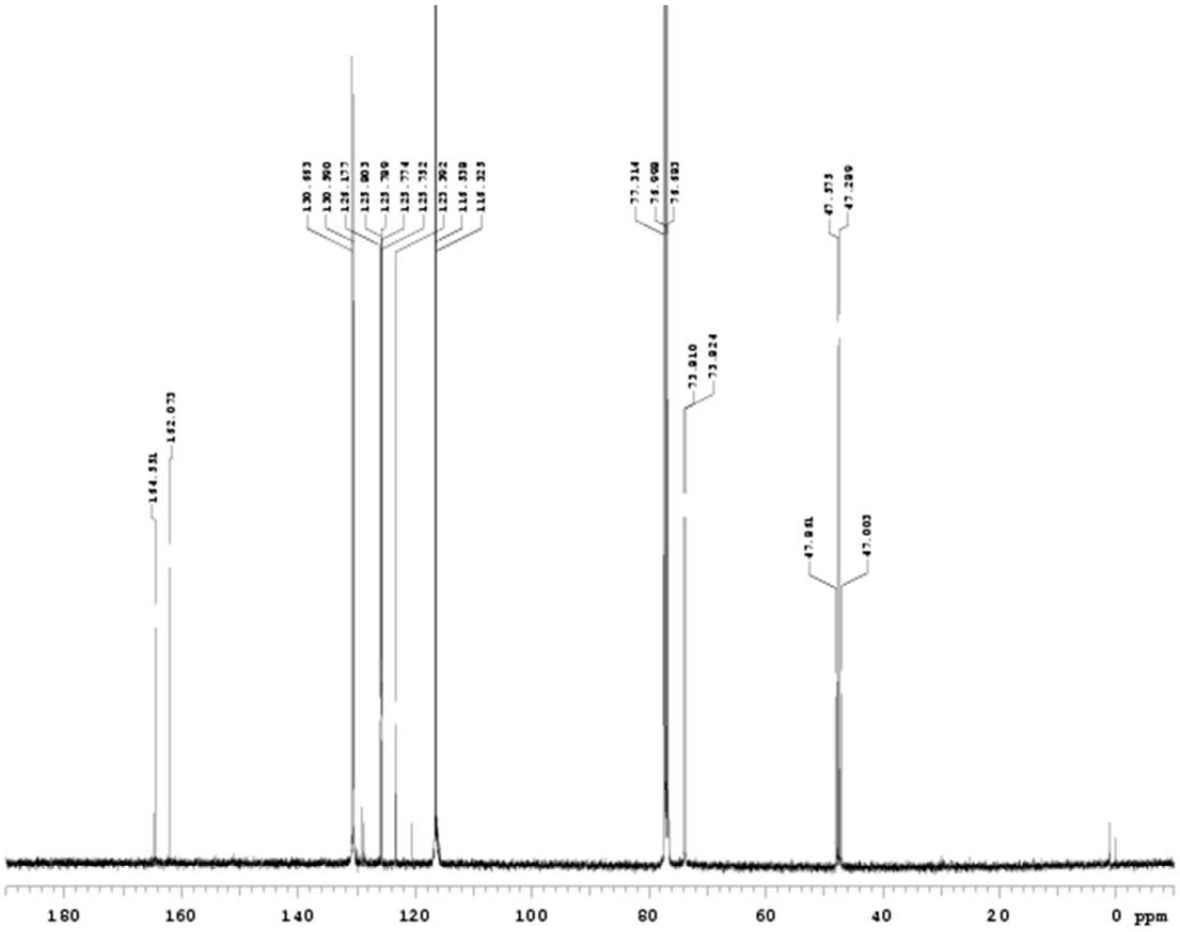

-68.931
-68.961
-40
-50
-60
-70
-80
-90
-100
-110
-120
ppm

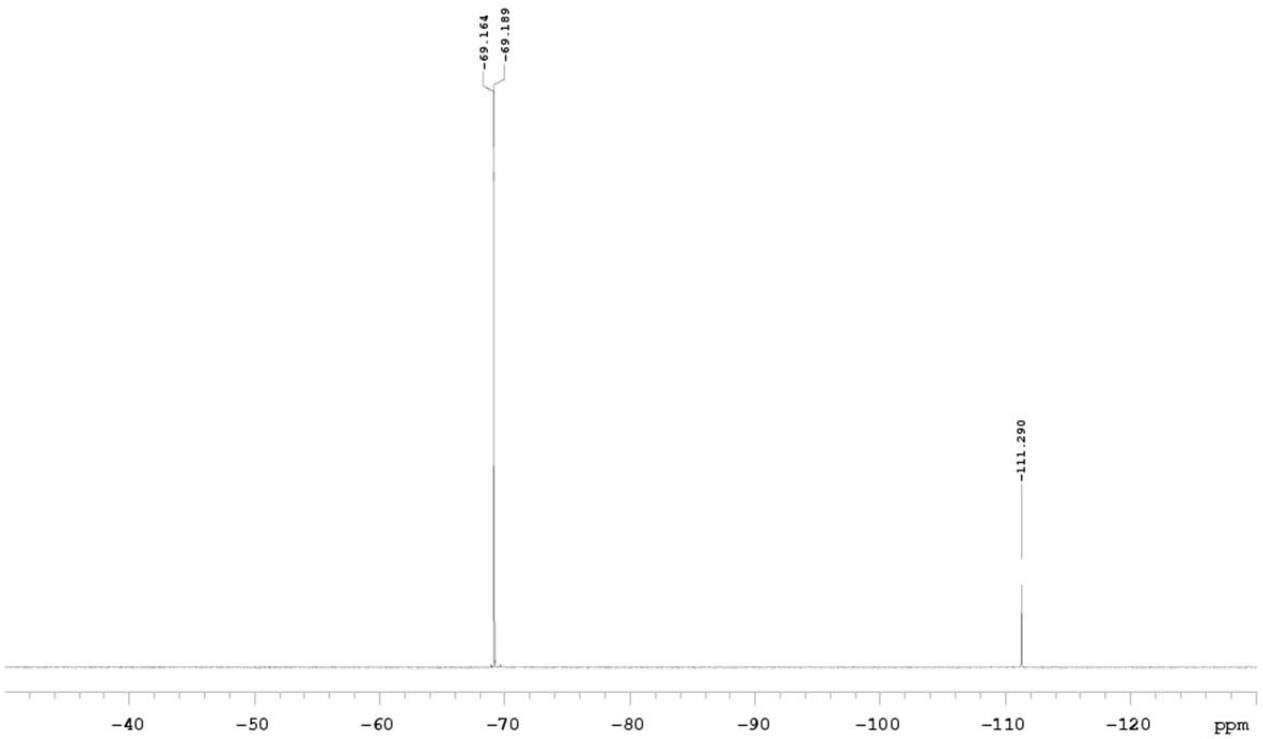

CF3
NO2
4d
11
10
9
8
7
6
5
4
3
2
1
ppm

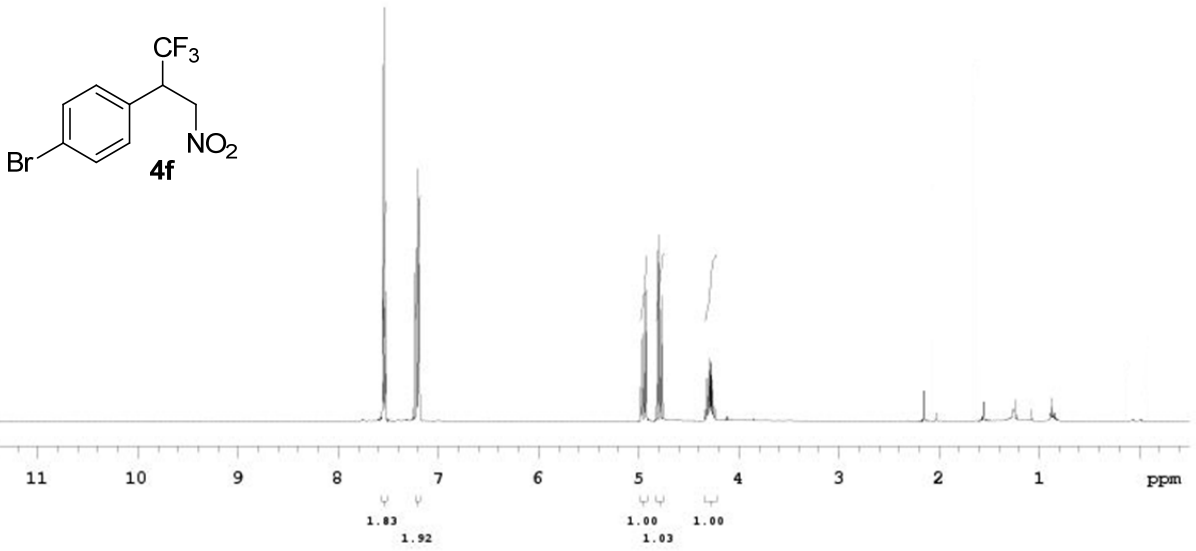

131.338
129.300
128.640
126.615
139.051
126.680
126.617
123.831
77.336
77.020
76.698
73.842
73.820
42.827
42.649
19.698
180
160
140
120
100
80
60
40
20
0 ppm

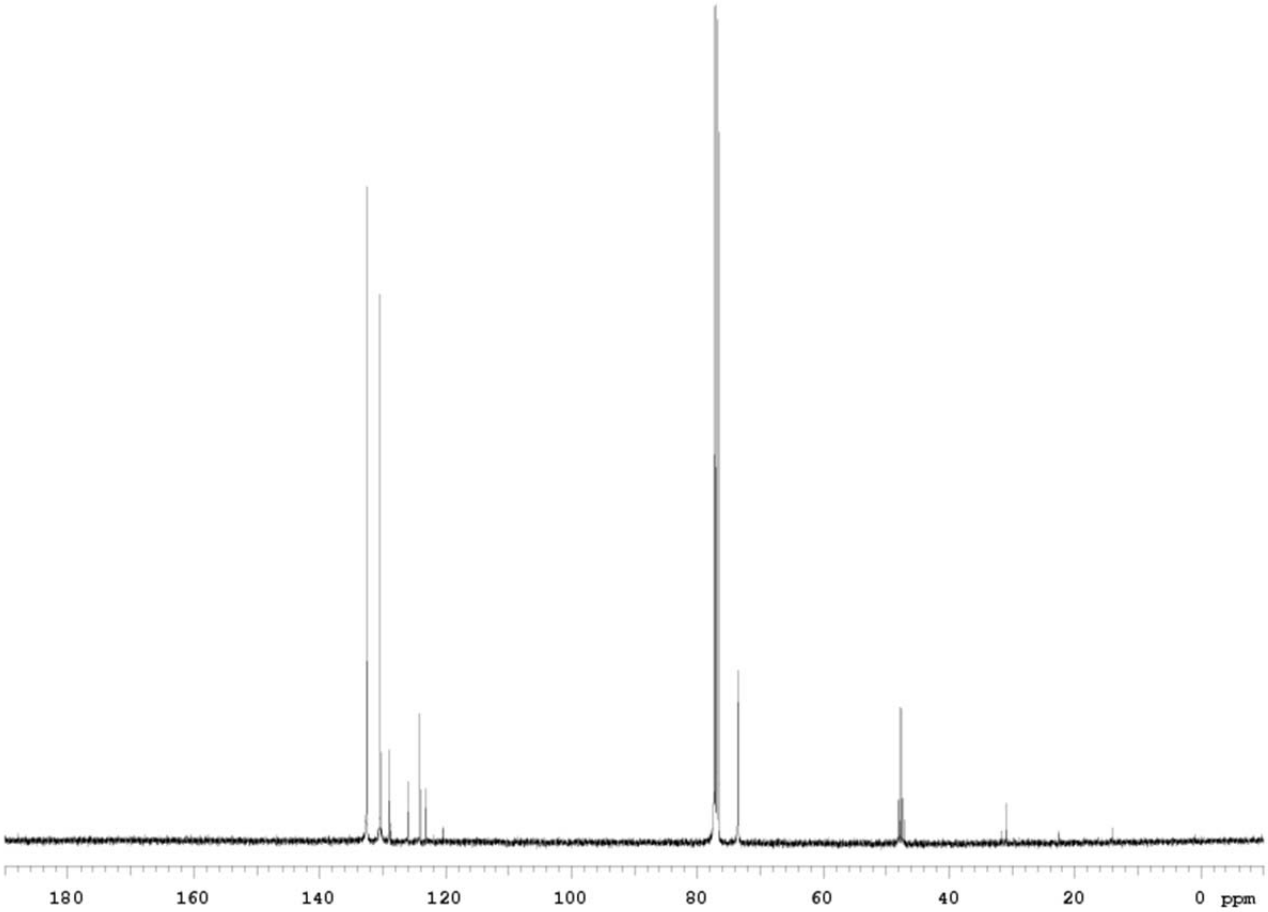

-68.593
-68.617
-40
-50
-60
-70
-80
-90
-100
-110
-120
ppm

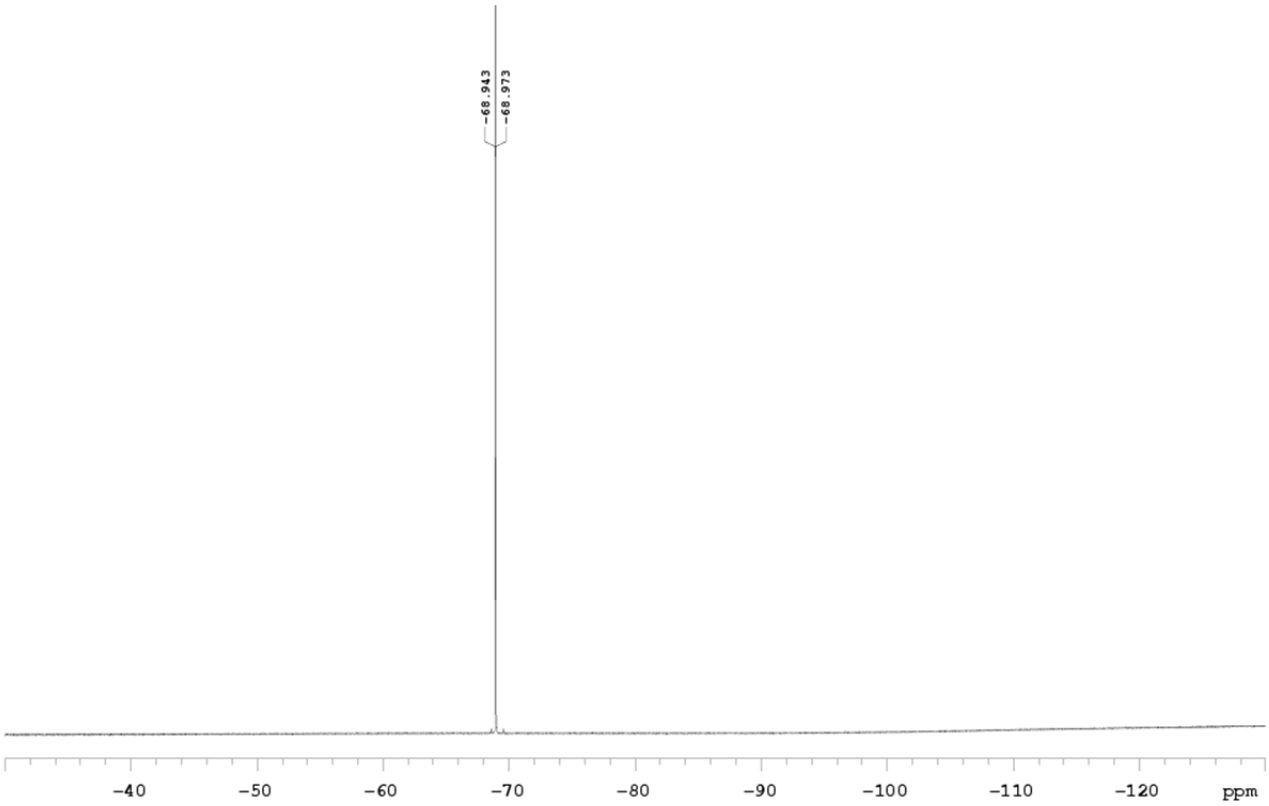

CF3
NO2
F
4e
11
10
9
8
7
6
5
4
3
2
1
ppm
2.03
2.02
1.03
1.05
1.00

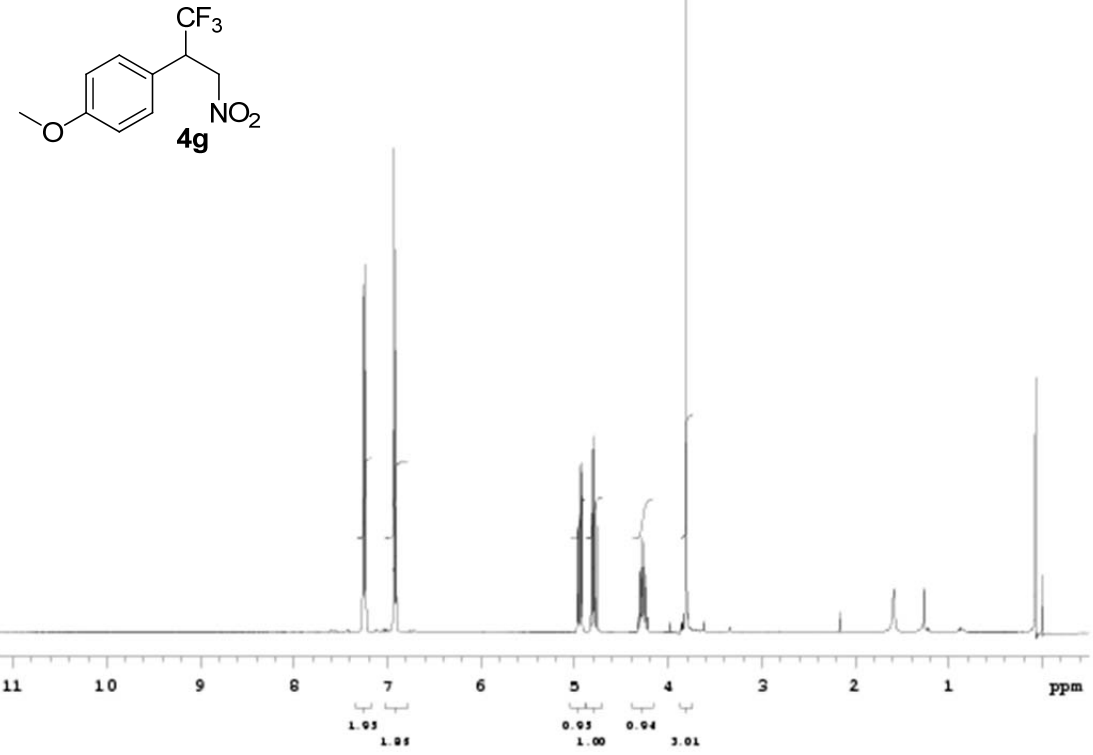

180
160
140
120
100
80
60
40
20
0 ppm

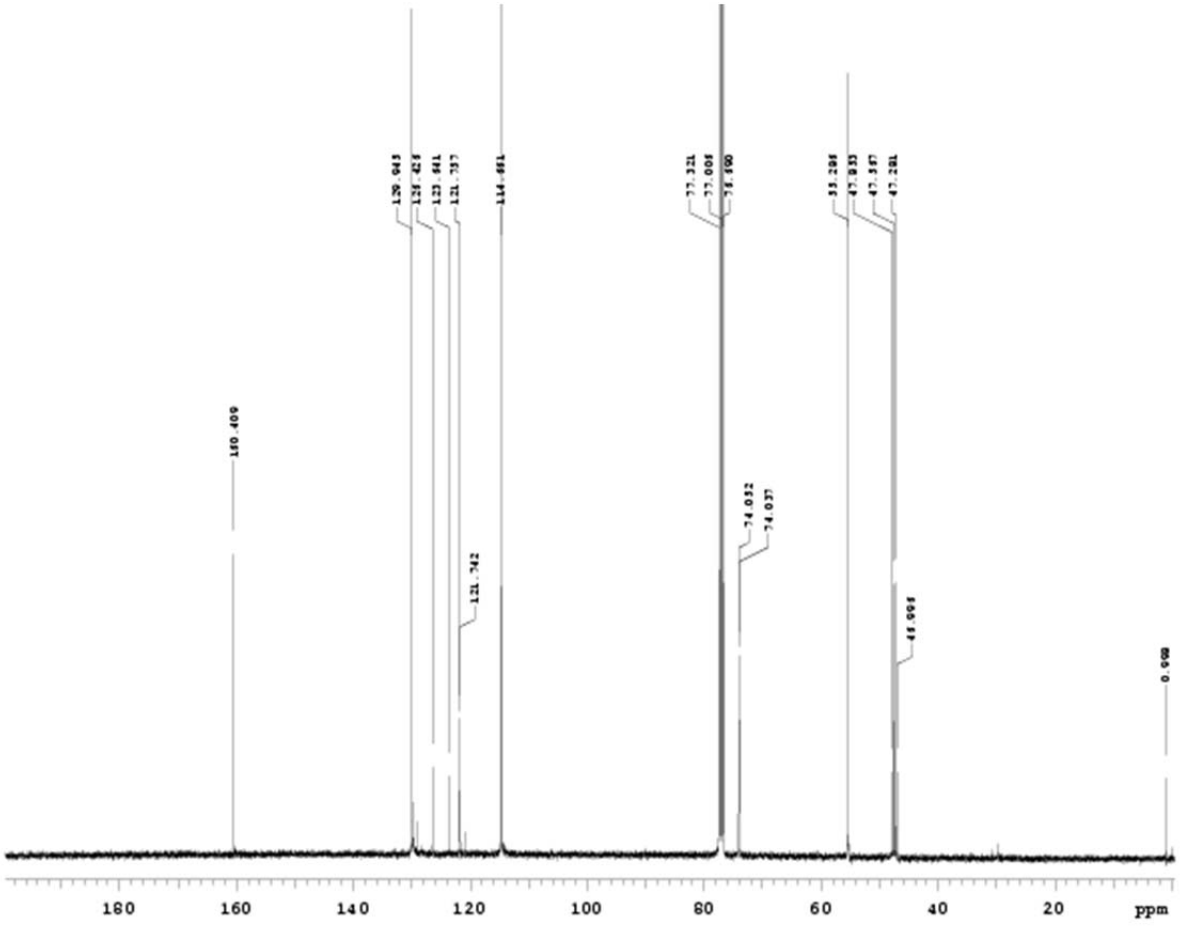

-69.164
-69.189
-111.290
-40
-50
-60
-70
-80
-90
-100
-110
-120
ppm

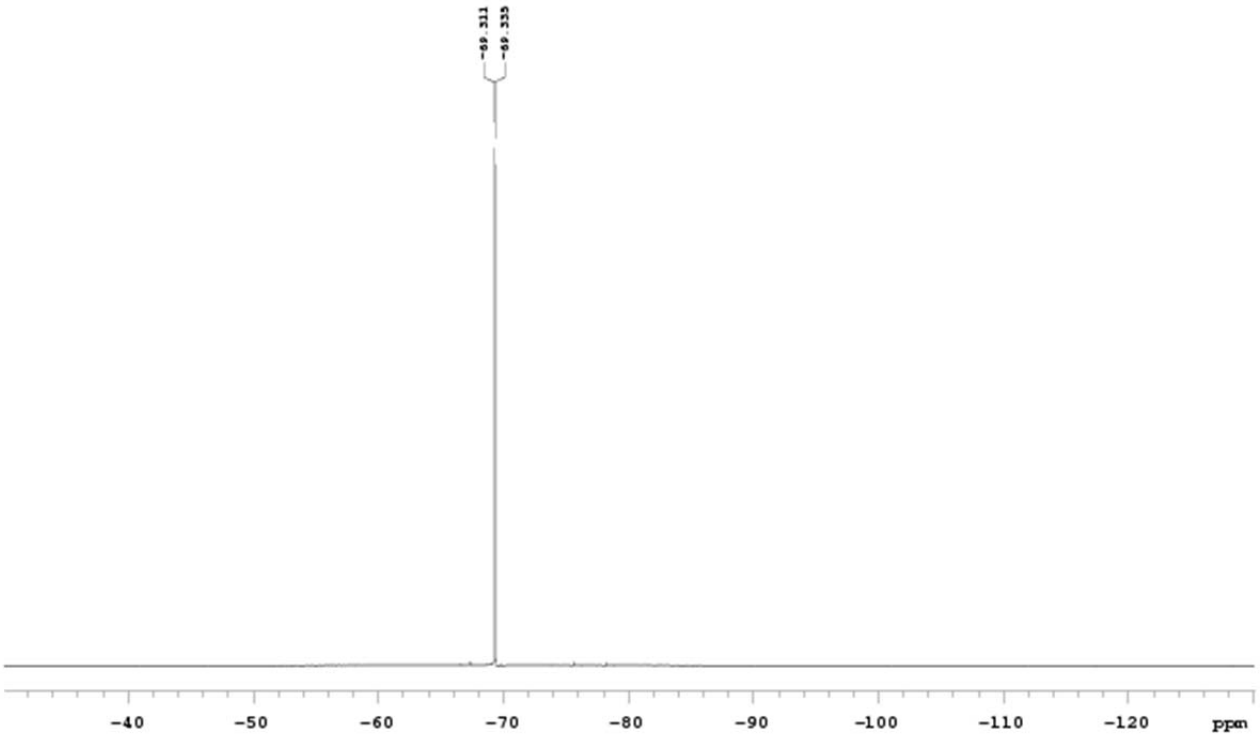

CF3
NO2
Br
4f
11
10
9
8
7
6
5
4
3
2
1
ppm
1.03
1.92
1.00
1.03
1.00

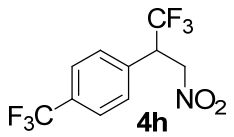

180
160
140
120
100
80
60
40
20
0 ppm


-68.943
-68.973
-40
-50
-60
-70
-80
-90
-100
-110
-120
ppm

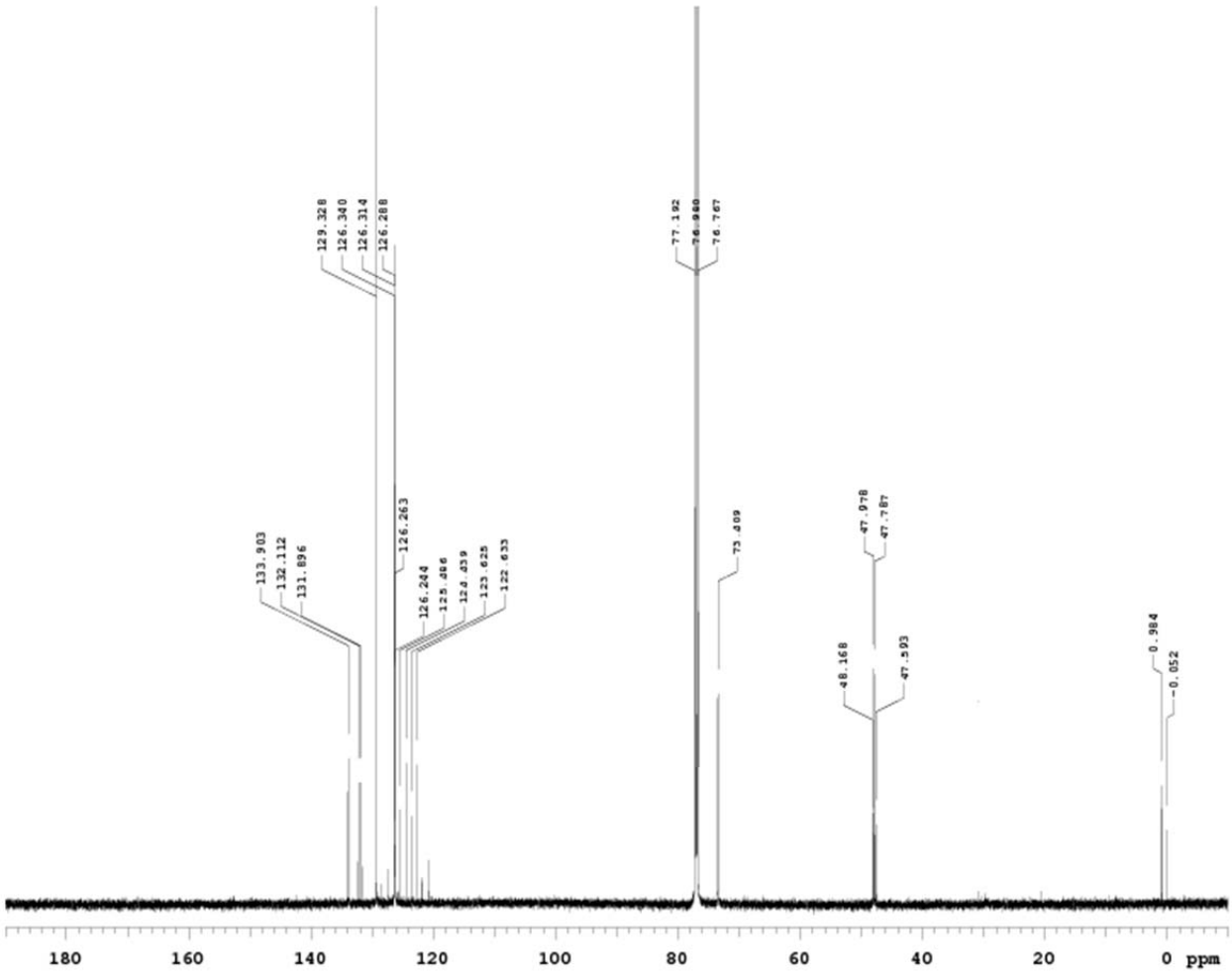

CF3
NO2
O
4g
11
10
9
8
7
6
5
4
3
2
1
ppm
1.93
1.95
0.93
1.00
0.94
3.01

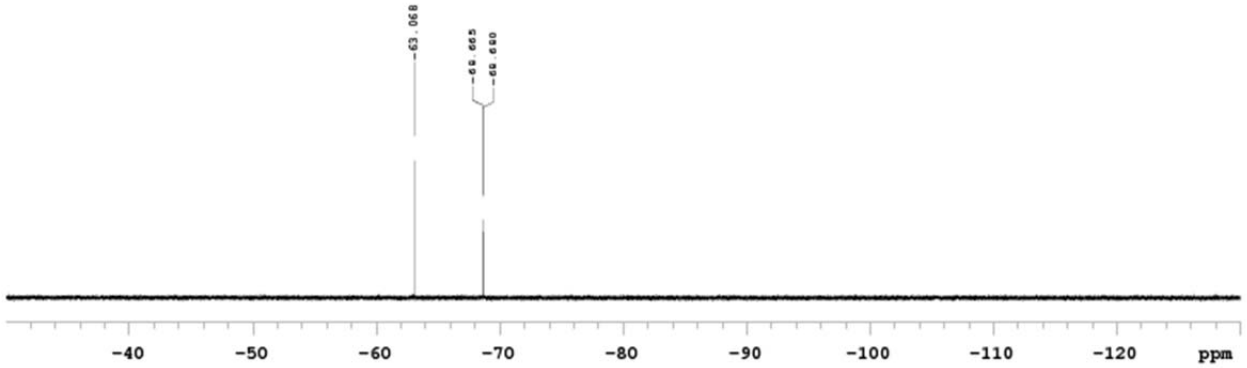

160.409
130.945
129.424
123.841
121.737
121.742
114.681
77.321
77.006
76.690
74.032
74.037
55.298
47.853
47.547
47.281
45.904
0.000
180
160
140
120
100
80
60
40
20
ppm

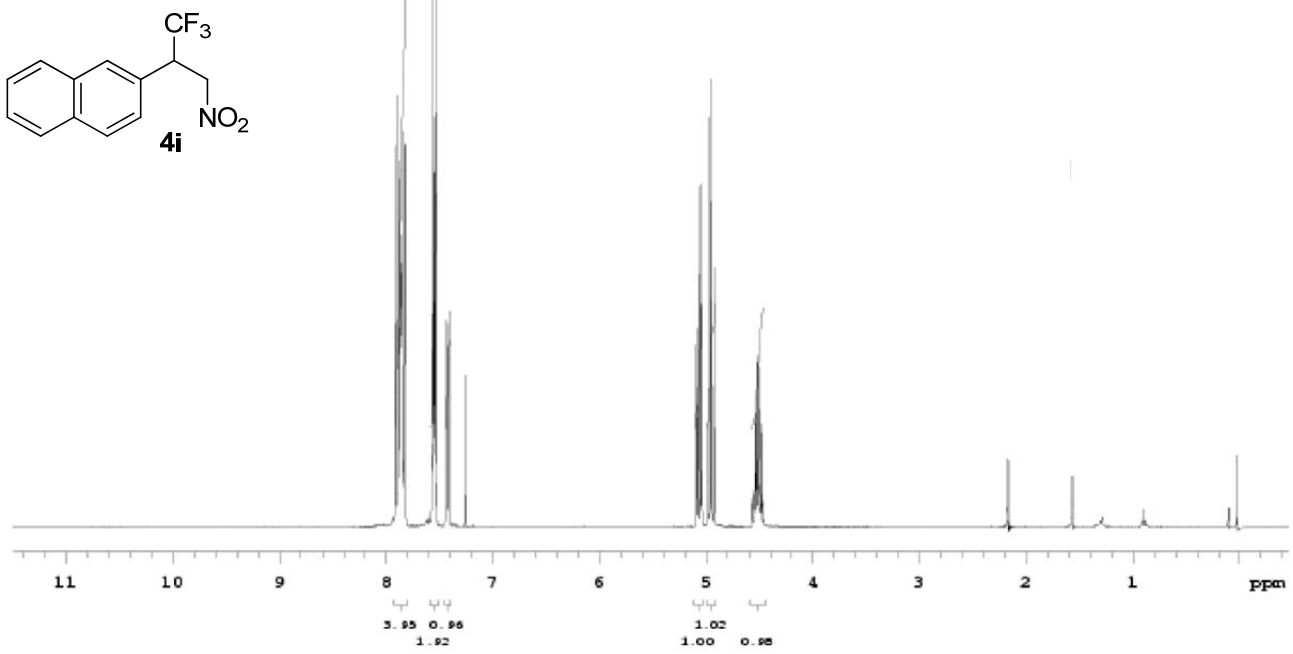

-69.311
-69.339
-40
-50
-60
-70
-80
-90
-100
-110
-120
ppm

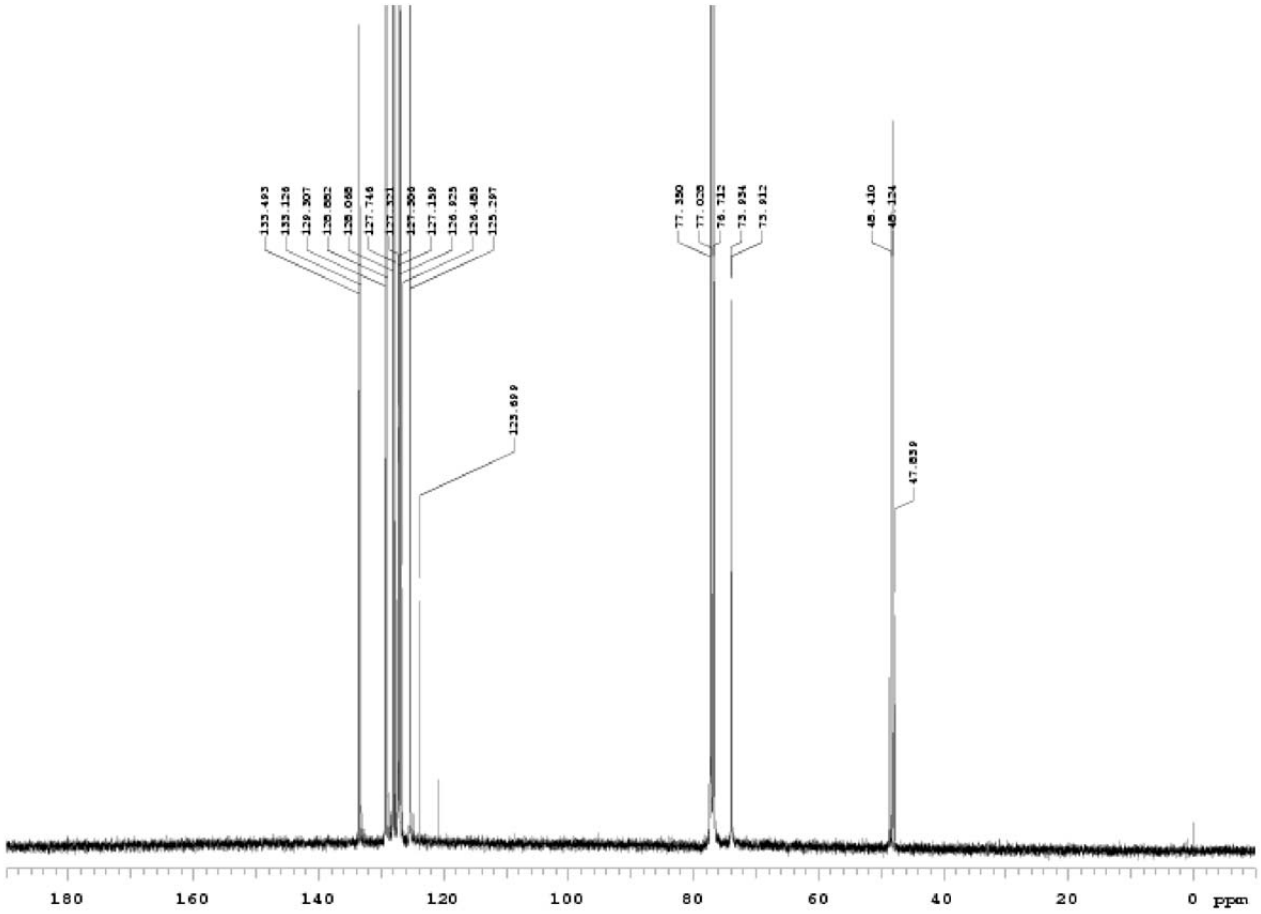

CF3
F3C
NO2
4h

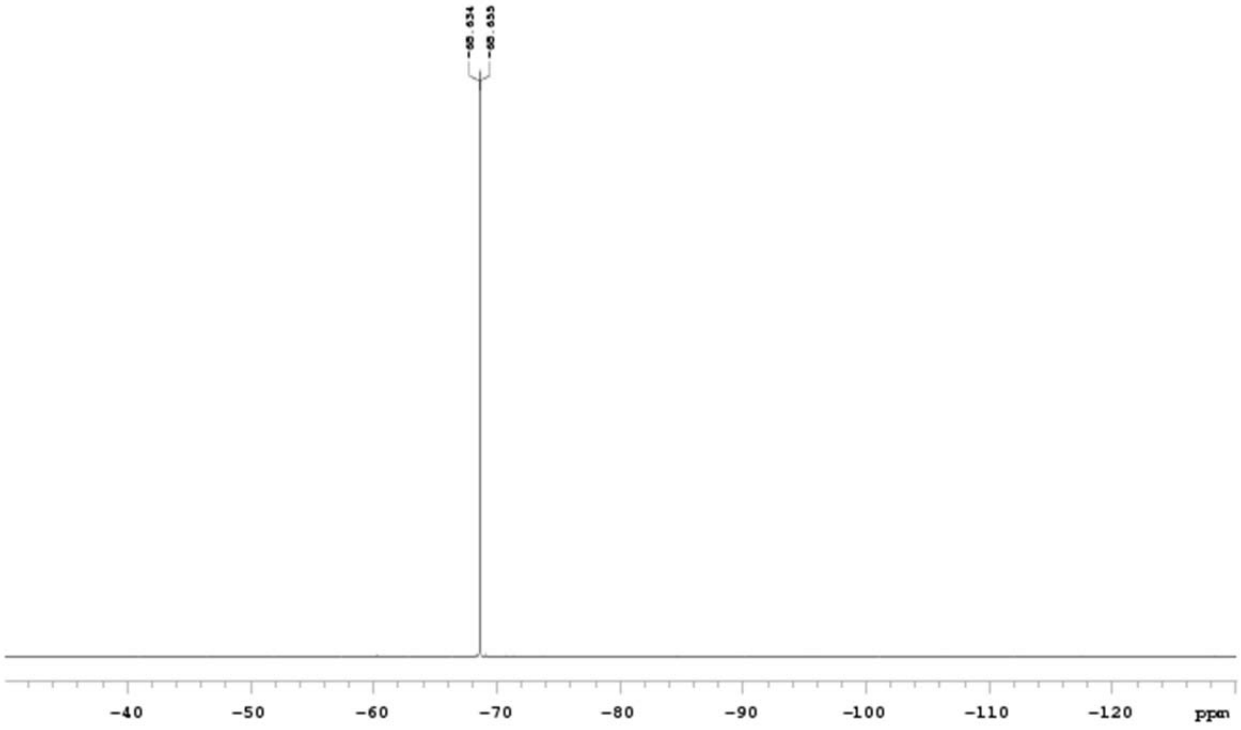
11
10
9
8
7
6
5
4
3
2
1
ppm
1.92
1.93
1.00
1.01
0.95

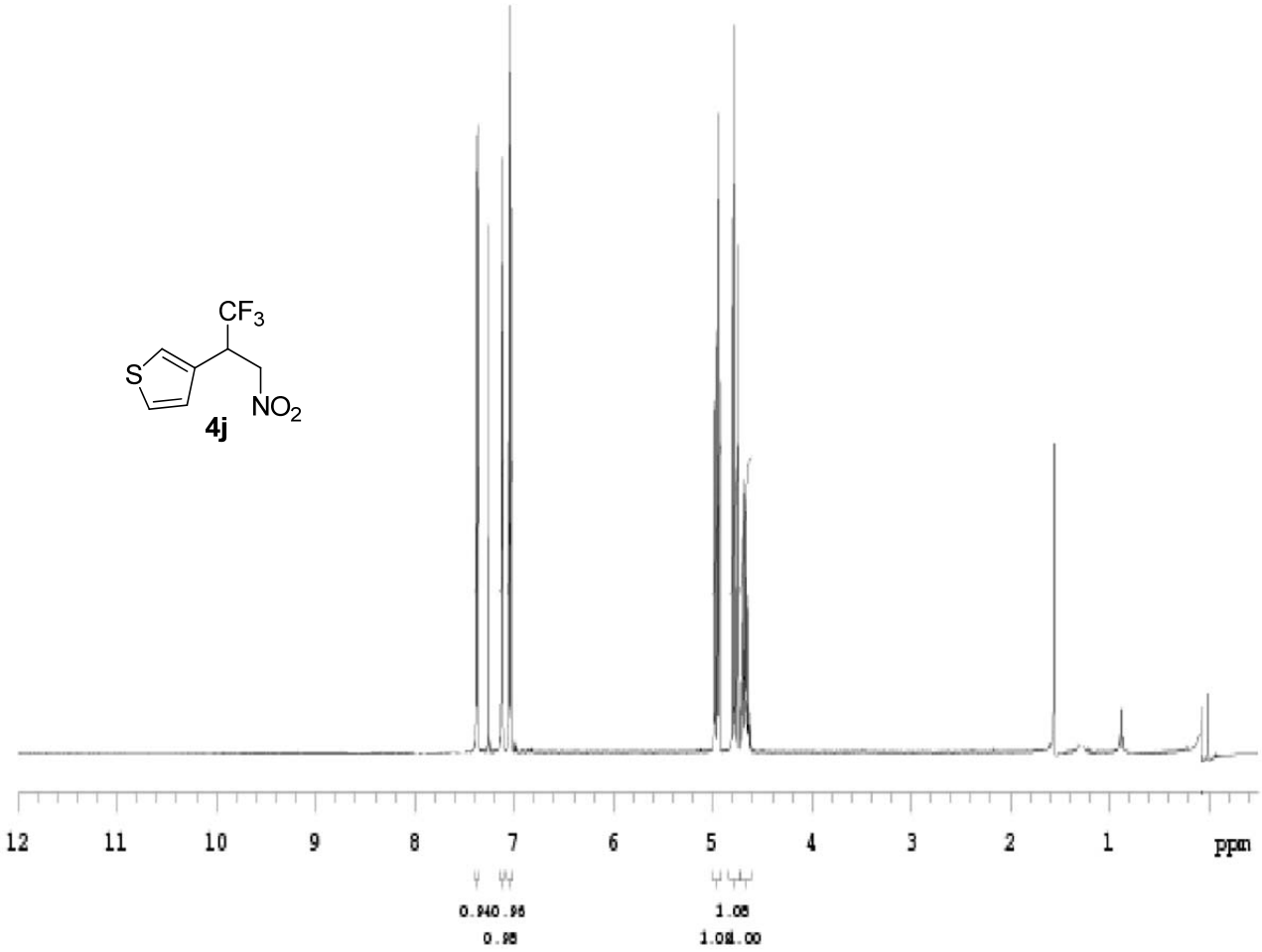

129.328
126.340
126.314
126.288
126.263
126.244
125.486
124.439
123.625
122.633
133.903
132.112
131.896
77.192
76.980
76.767
73.409
48.168
47.978
47.787
47.593
0.984
-0.052
180
160
140
120
100
80
60
40
20
0
ppm

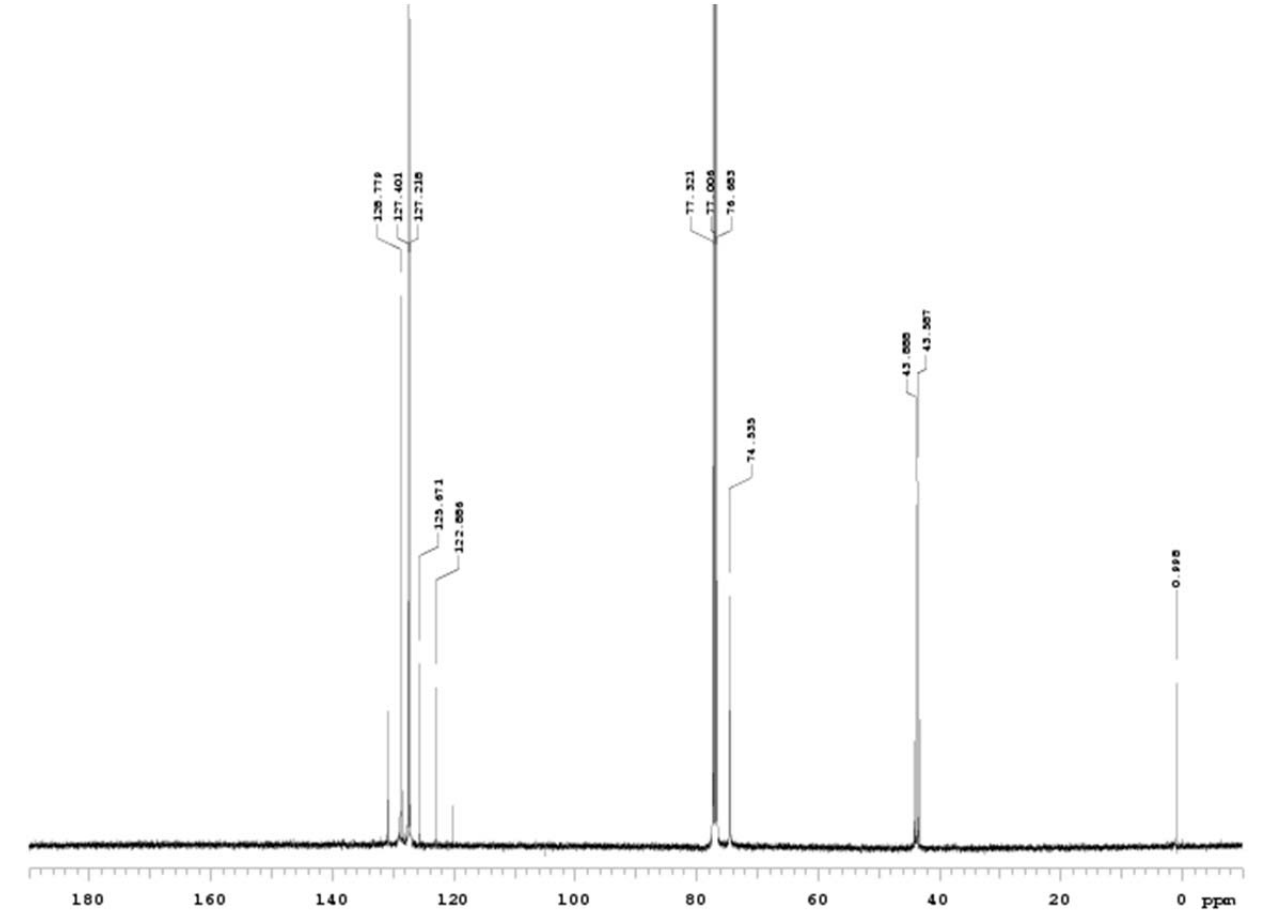

-63.068
-69.665
-69.680
-40
-50
-60
-70
-80
-90
-100
-110
-120
ppm

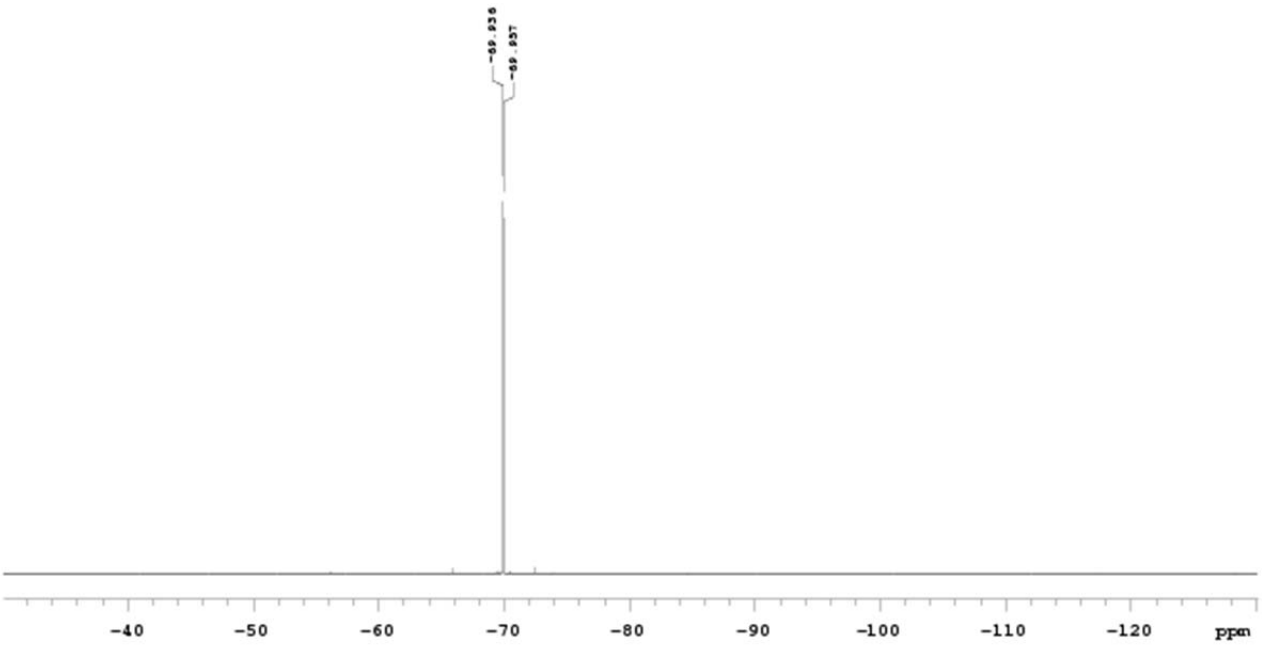

CF3
NO2
4i
11
10
9
8
7
6
5
4
3
2
1
ppm
3.95
0.96
1.92
1.02
1.00
0.98

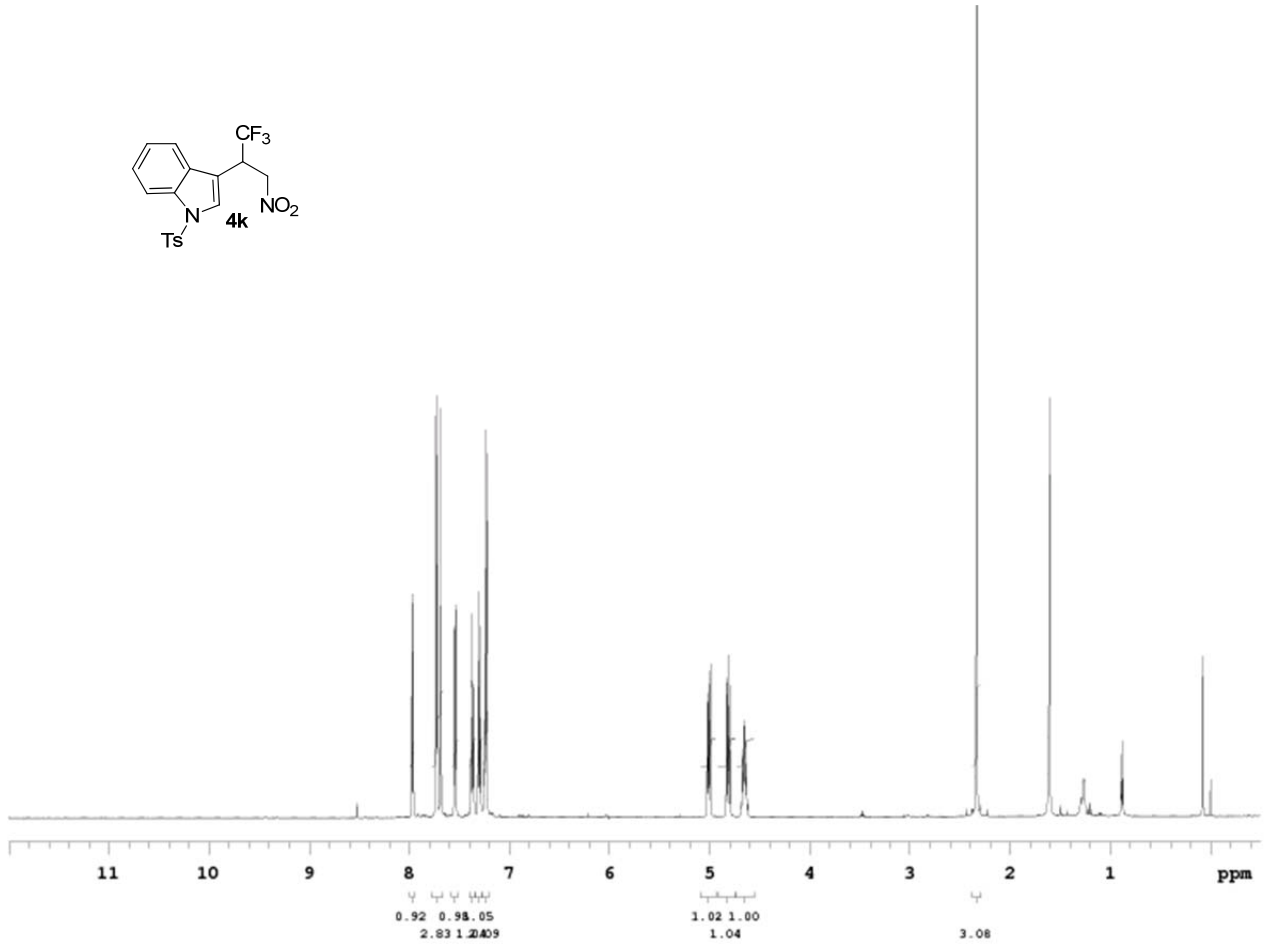

133.493
133.126
129.307
128.882
128.068
127.746
127.321
127.306
127.159
126.925
126.485
125.297
123.699
77.380
77.028
76.732
73.824
73.612
48.430
48.124
47.859
180
160
140
120
100
80
60
40
20
0 ppm

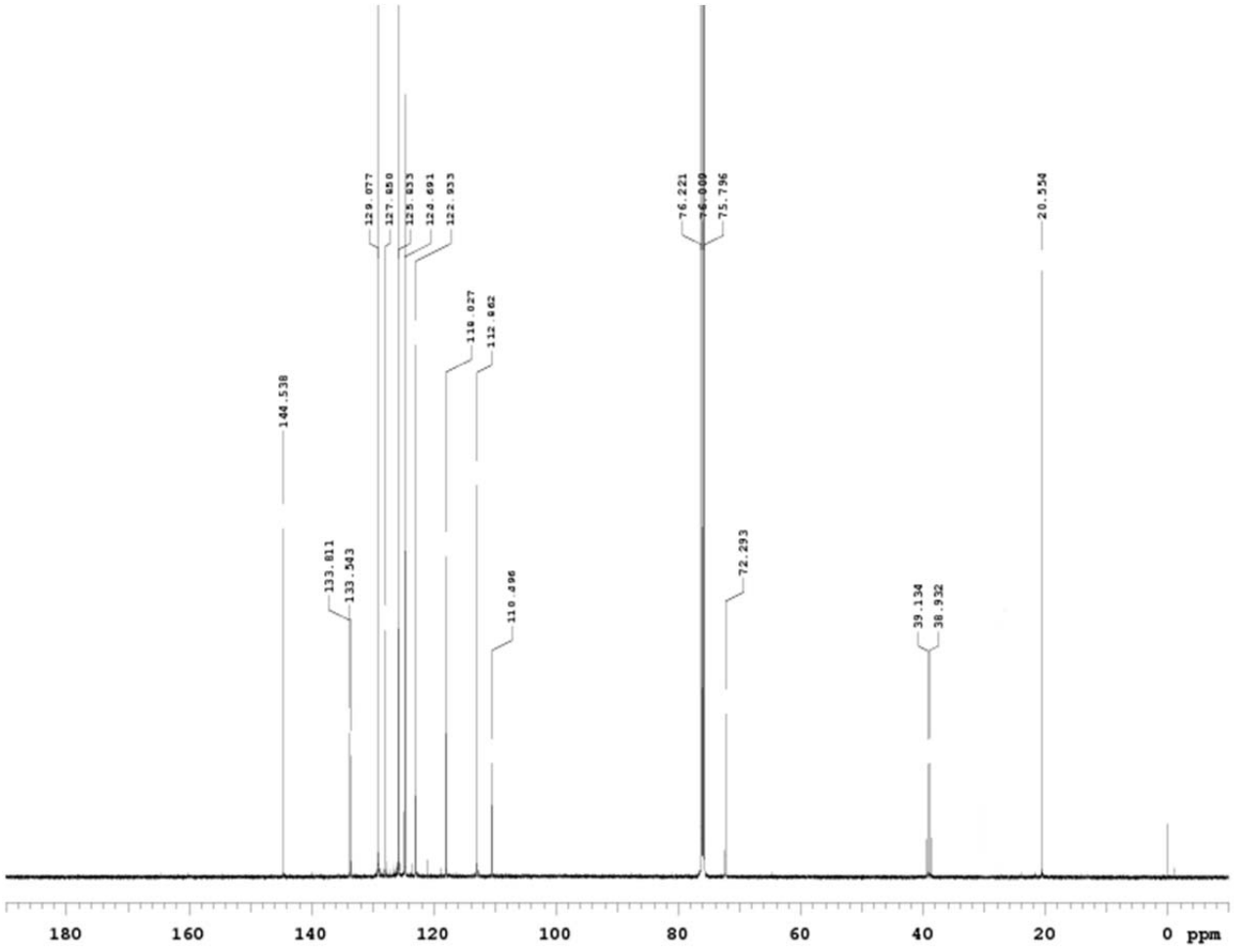

-68.634
-68.655
-40
-50
-60
-70
-80
-90
-100
-110
-120
ppm

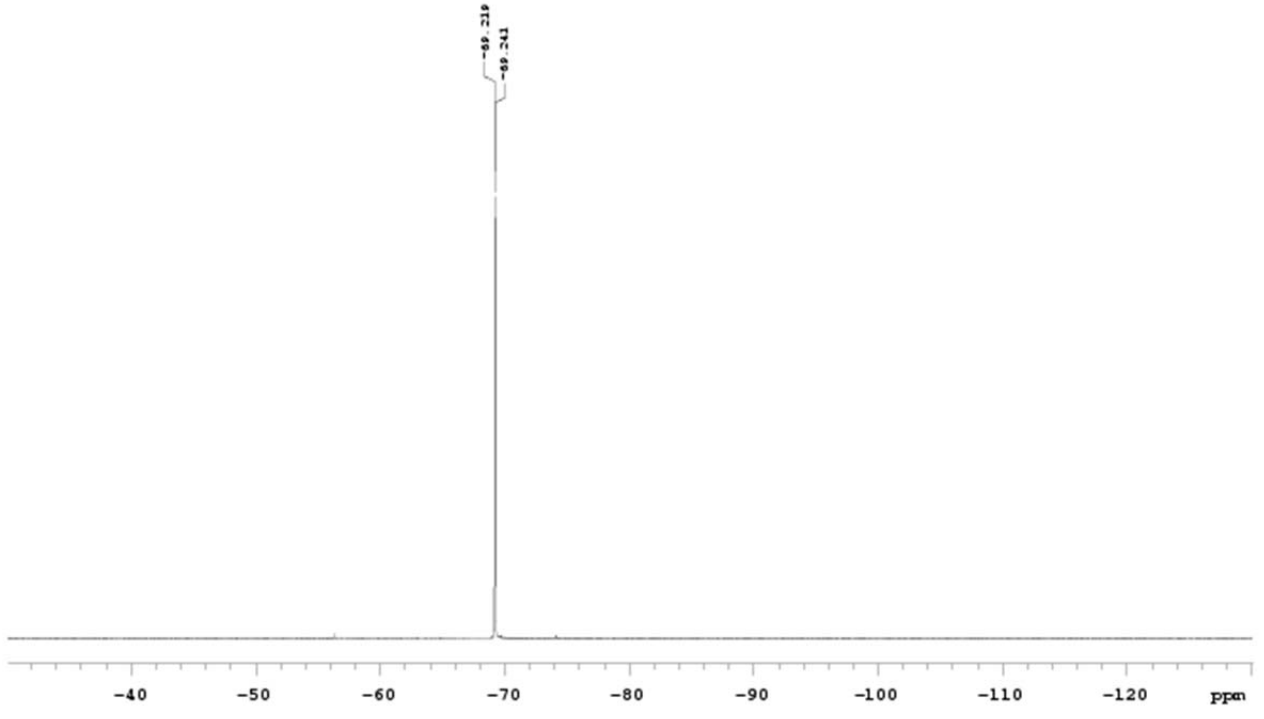

CF3
S
NO2
4j
12
11
10
9
8
7
6
5
4
3
2
1
ppm
0.94
0.96
0.98
1.05
1.01
1.00

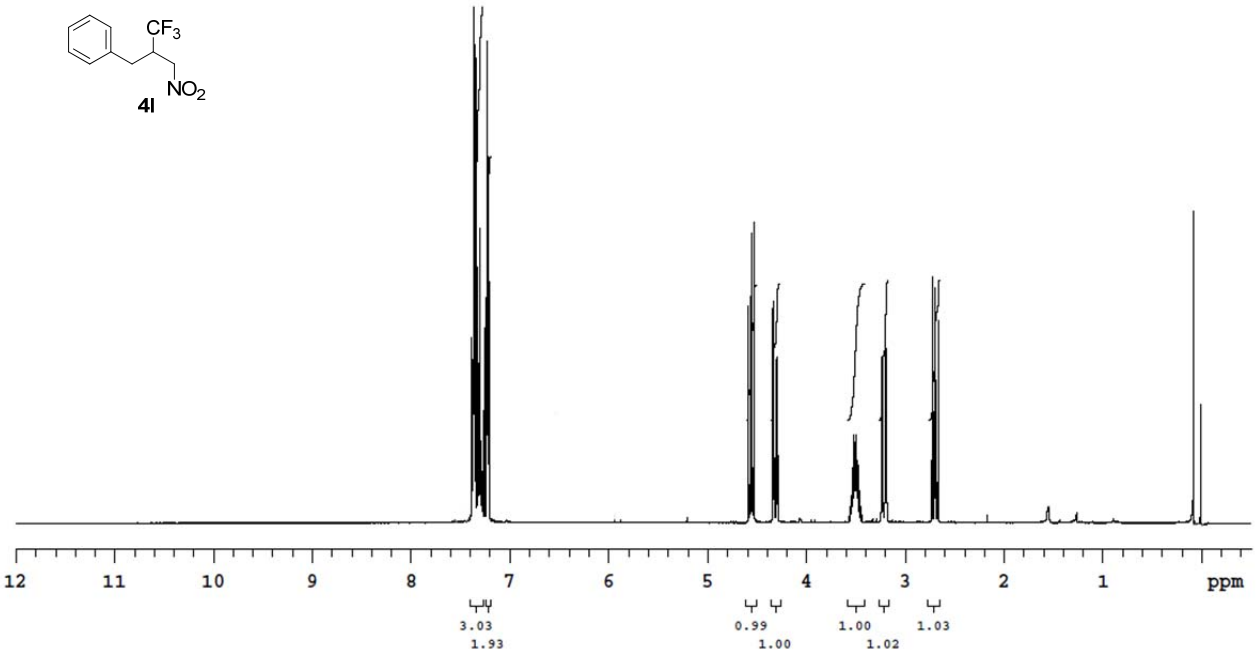

129.779
127.401
127.218
77.321
77.000
76.683
74.539
43.888
43.557
125.671
122.886
0.998
180
160
140
120
100
80
60
40
20
0
ppm

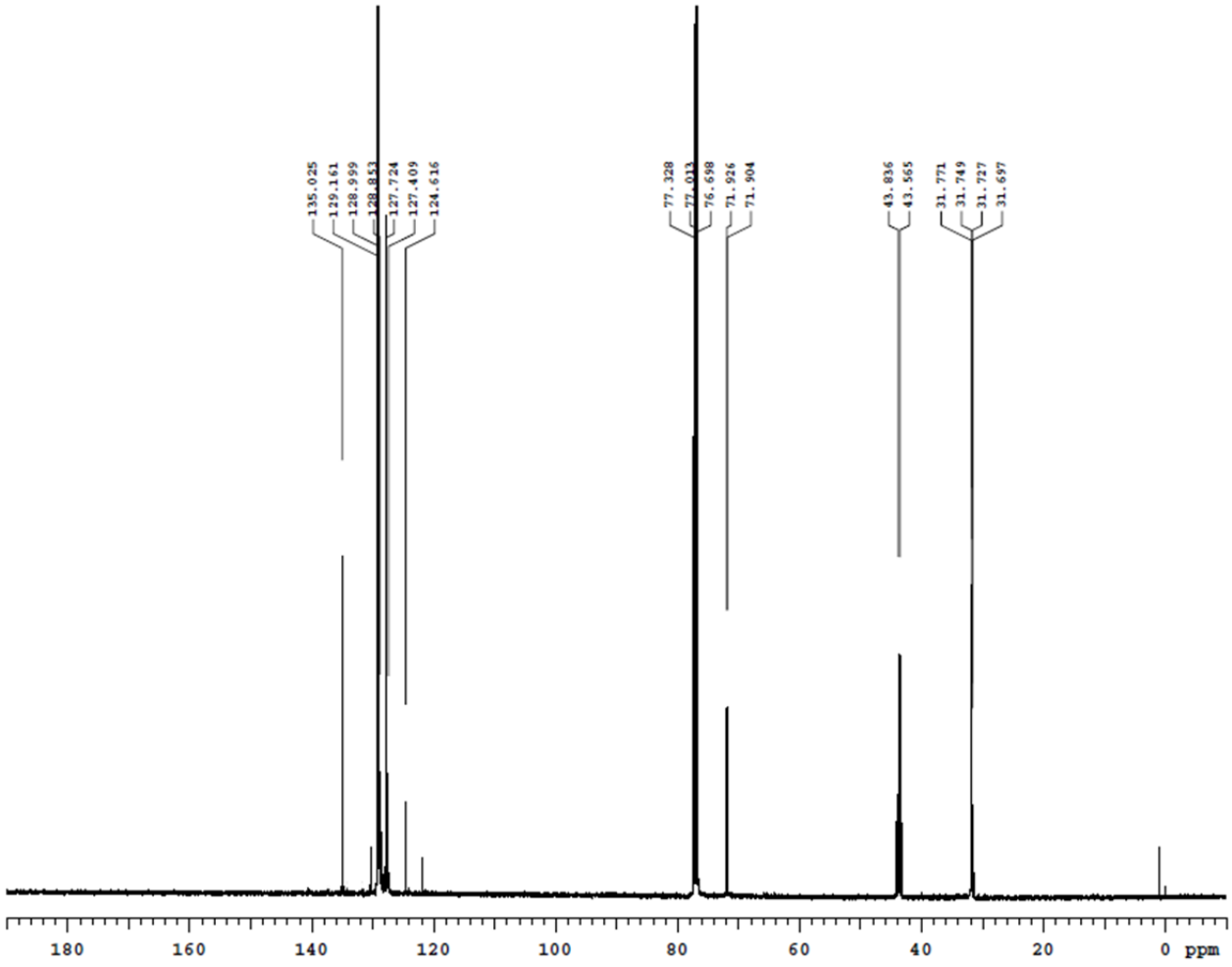

-69.936
-69.857
-40
-50
-60
-70
-80
-90
-100
-110
-120
ppm

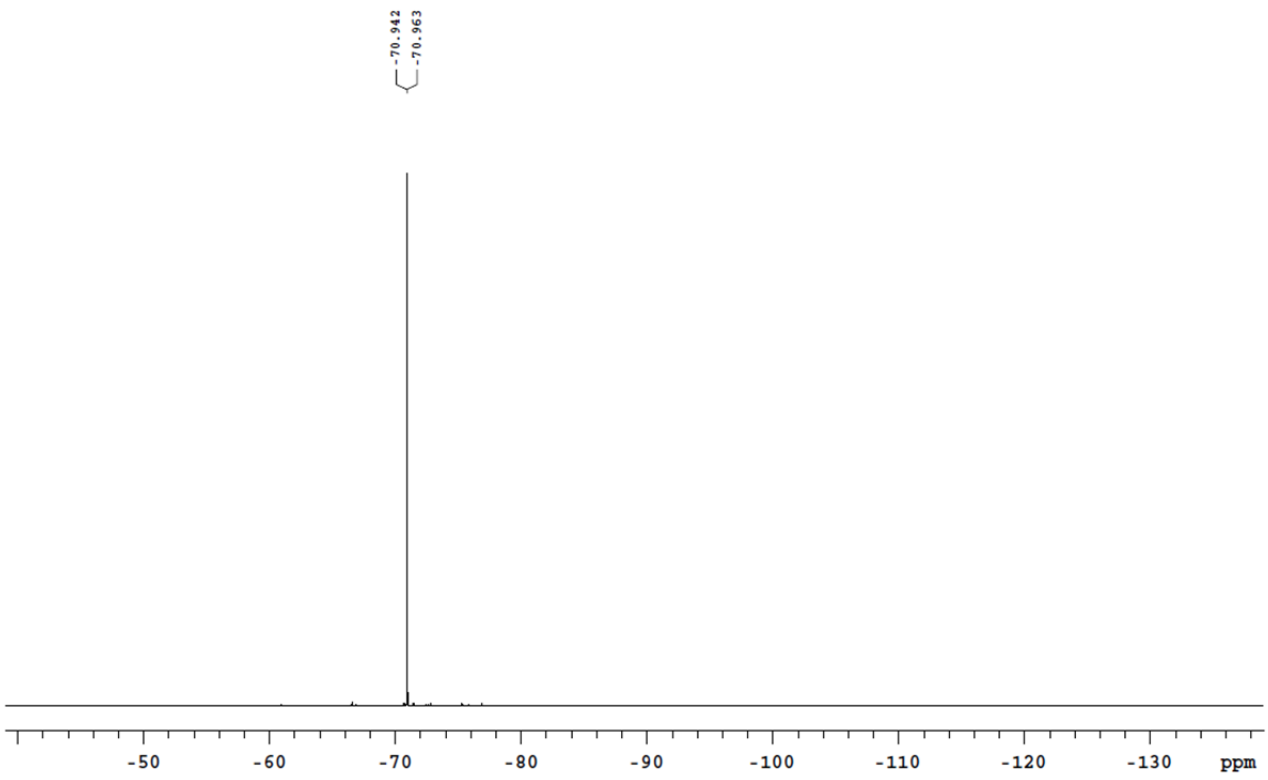

CF3
NO2
N
Ts
4k
11
10
9
8
7
6
5
4
3
2
1
ppm
0.92
0.98
1.05
1.02
1.00
3.08
1.04

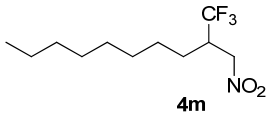

144.538
133.811
133.543
129.077
127.650
125.933
124.691
122.933
119.027
112.662
110.896
76.221
76.000
75.796
72.293
39.134
38.932
20.554
180
160
140
120
100
80
60
40
20
0 ppm


-69.219
-69.241
-40
-50
-60
-70
-80
-90
-100
-110
-120
ppm


CF3
NO2
4l
12
11
10
9
8
7
6
5
4
3
2
1
ppm
3.03
1.93
0.99
1.00
1.00
1.02
1.03

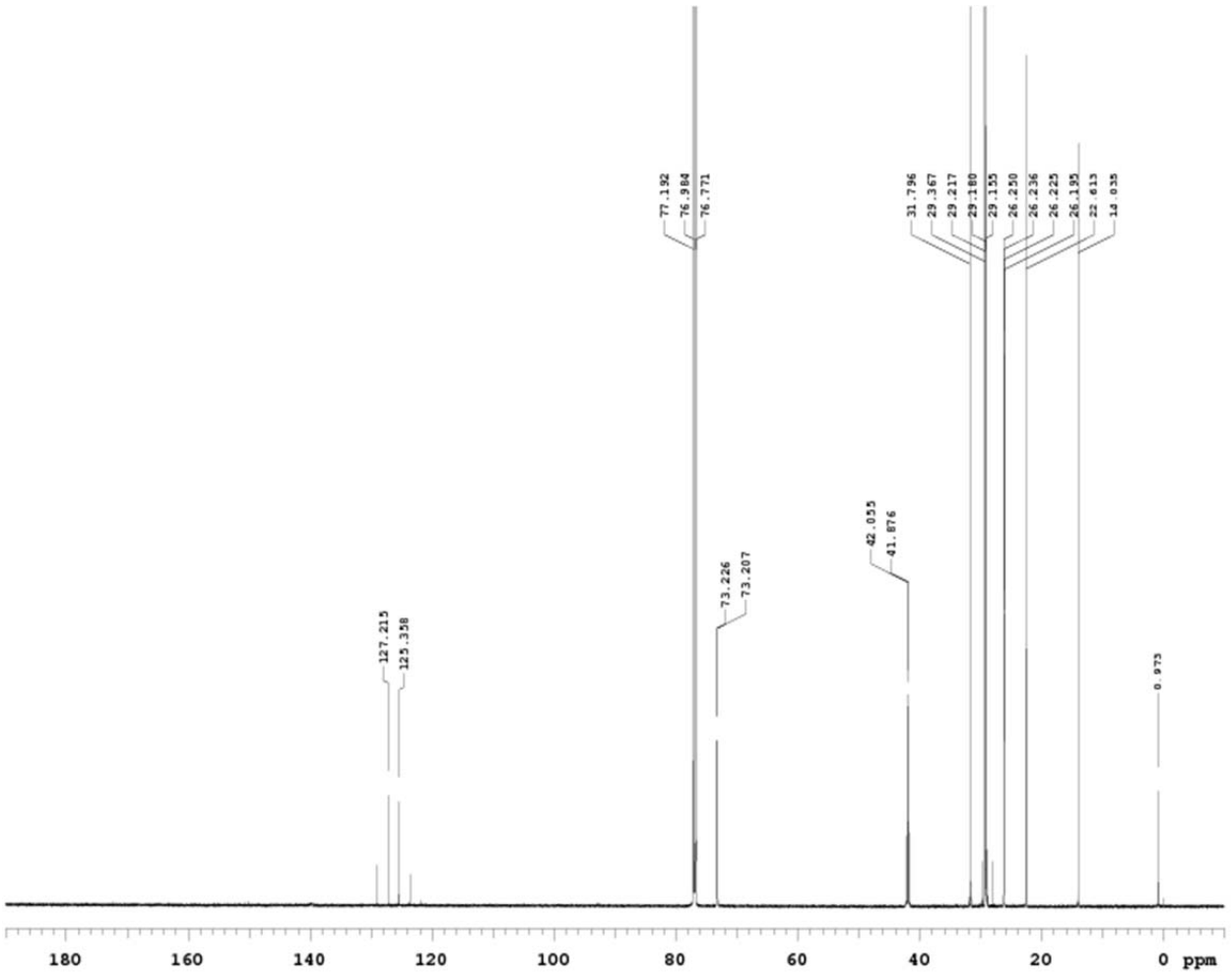

135.025
129.161
128.999
128.853
127.724
127.409
124.616
77.328
77.013
76.698
71.926
71.904
43.836
43.565
31.771
31.749
31.727
31.697
180
160
140
120
100
80
60
40
20
0 ppm

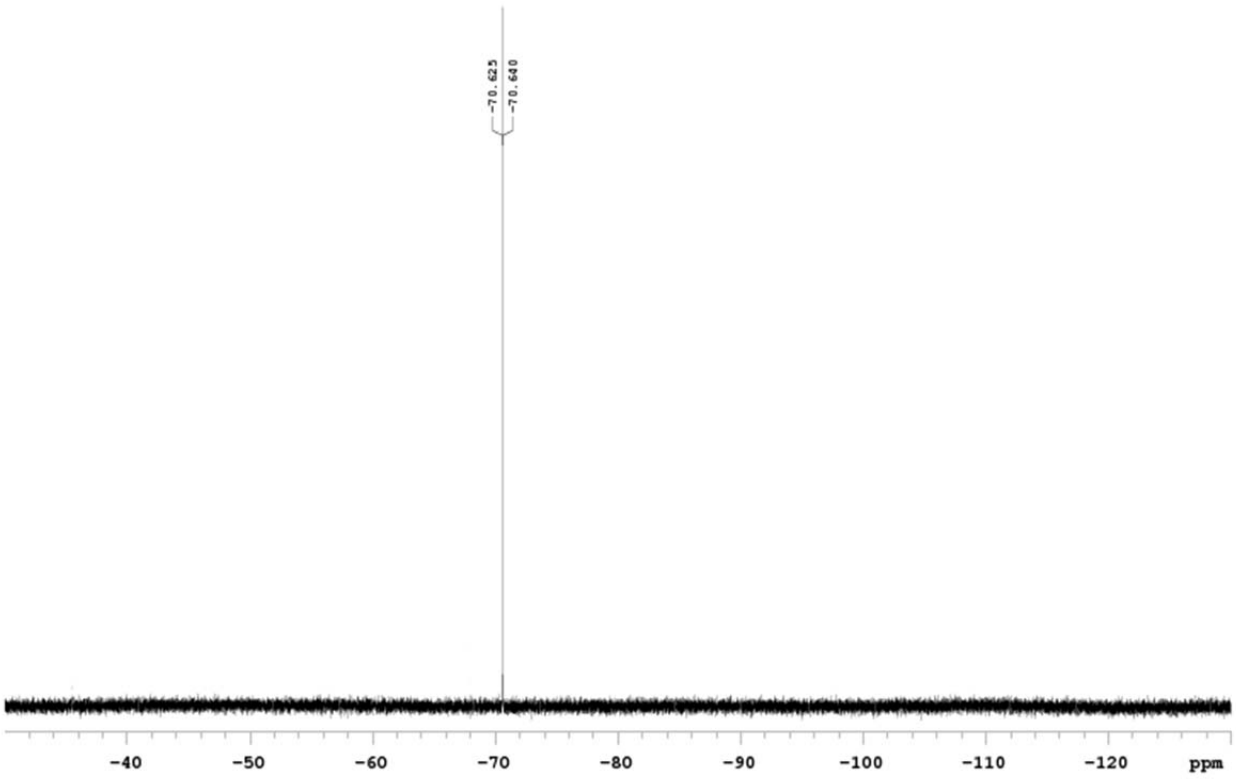

-70.942
-70.963
-50
-60
-70
-80
-90
-100
-110
-120
-130
ppm

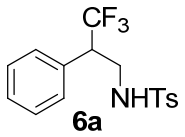

CF3
NO2

4m

11
10
9
8
7
6
5
4
3
2
1
ppm
0.99
1.00
0.96
1.00
16.99
3.37

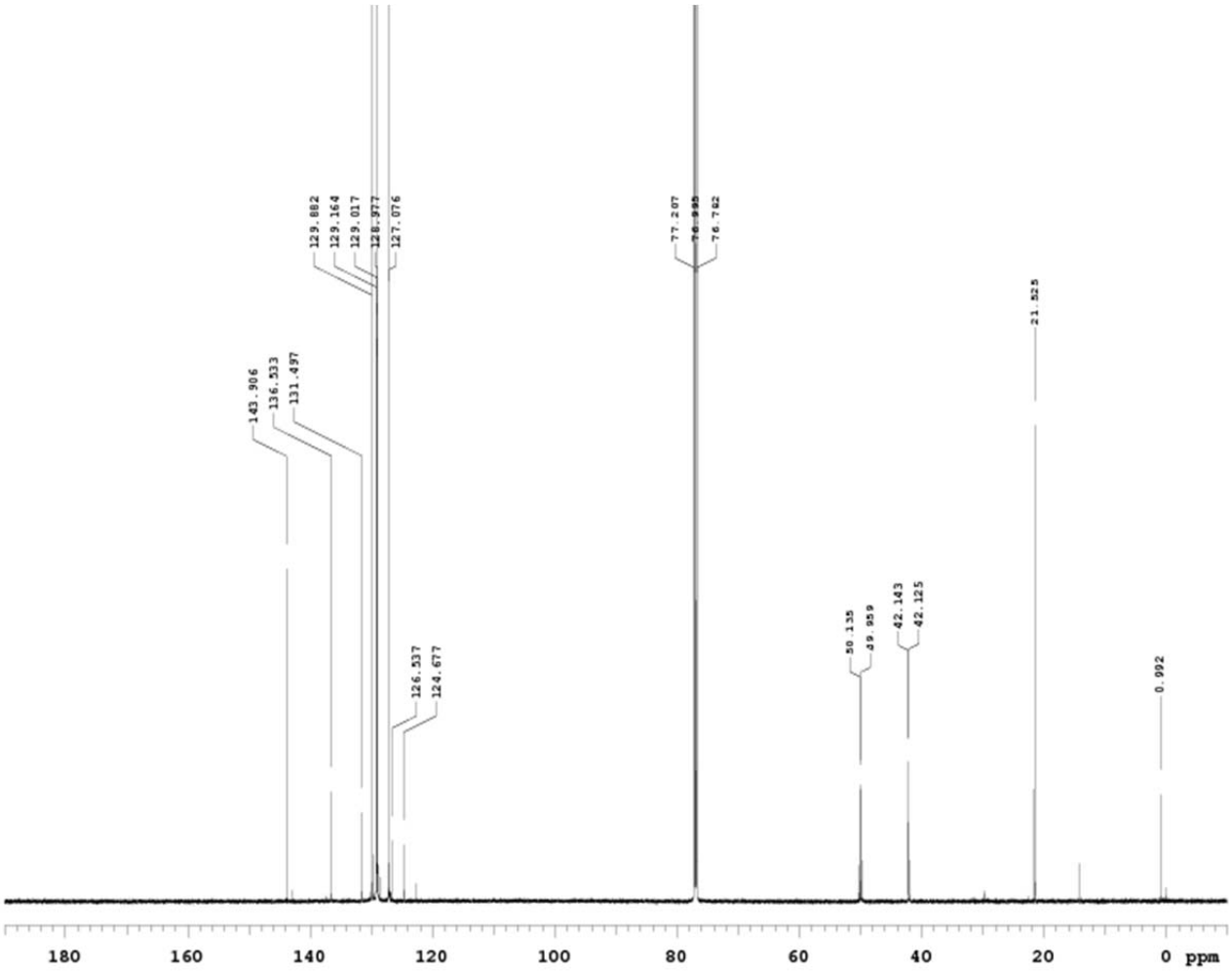

77.192
76.984
76.771
73.226
73.207
42.055
41.876
31.796
29.367
29.217
29.180
29.155
26.250
26.236
26.225
26.195
22.613
14.035
127.215
125.358
0.973
180
160
140
120
100
80
60
40
20
0 ppm

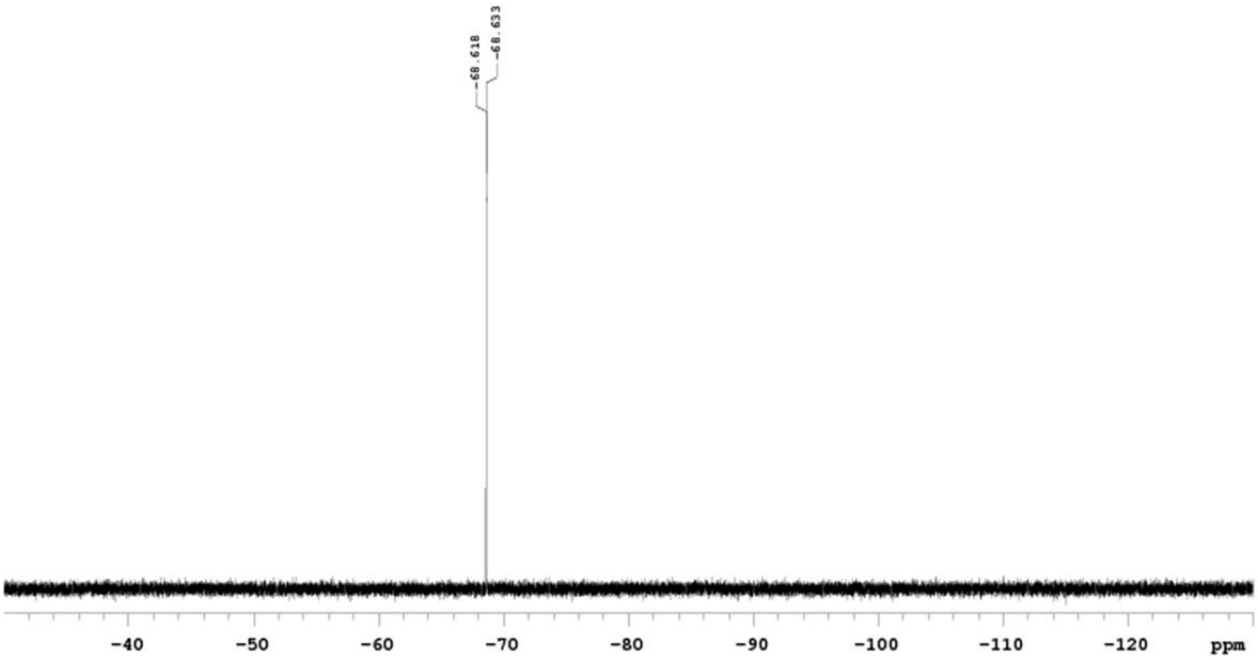

-70.625
-70.640
-40
-50
-60
-70
-80
-90
-100
-110
-120
ppm

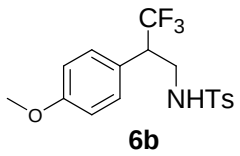

CF3
NHTs

6a

11
10
9
8
7
6
5
4
3
2
1
ppm
1.99
2.03
4.93
1.00
1.061.07
1.04
2.99

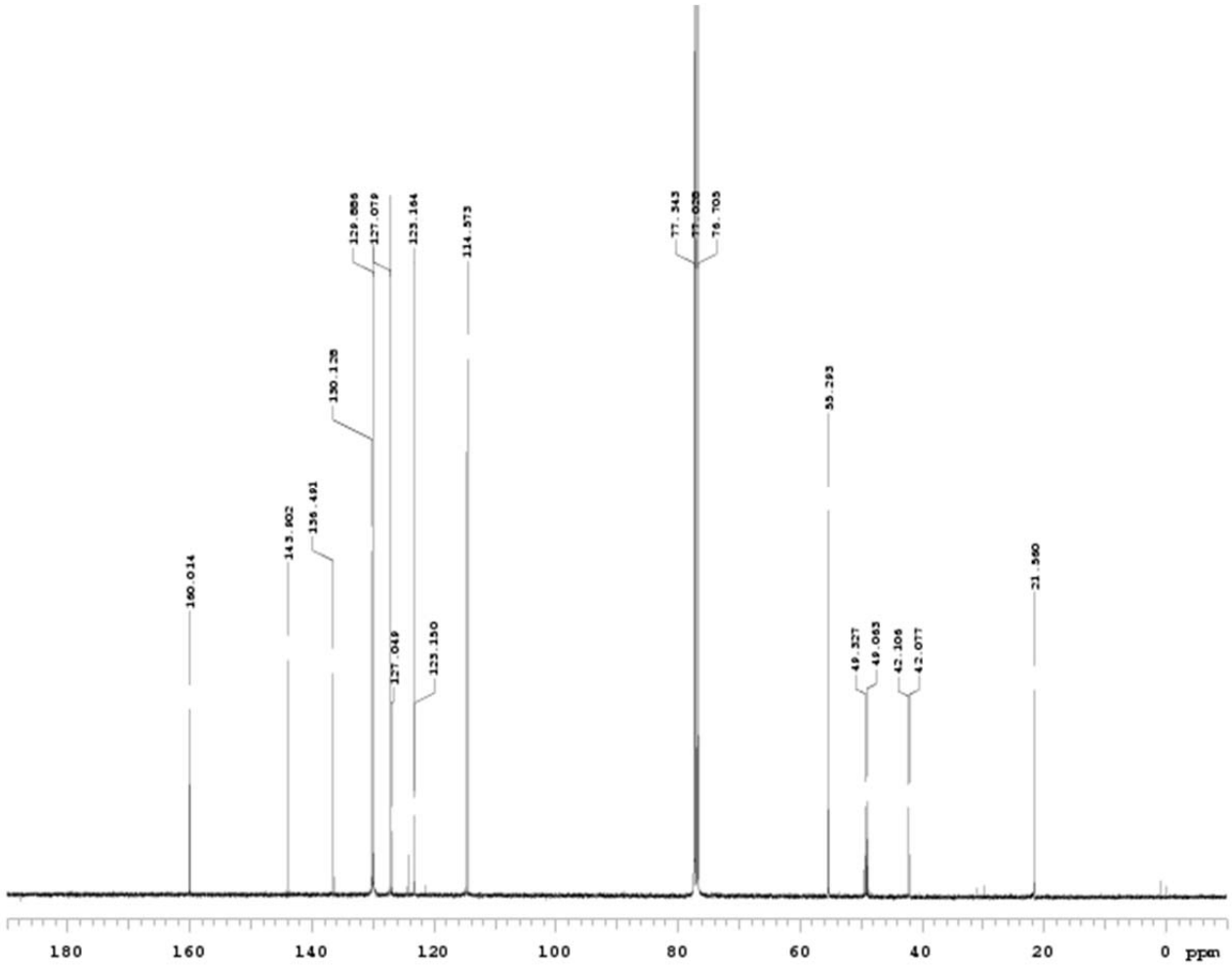

129.882
129.164
129.017
128.977
127.076
143.906
136.533
131.497
77.207
76.762
21.525
50.135
49.959
42.143
42.125
126.537
124.677
0.992
180
160
140
120
100
80
60
40
20
0
ppm

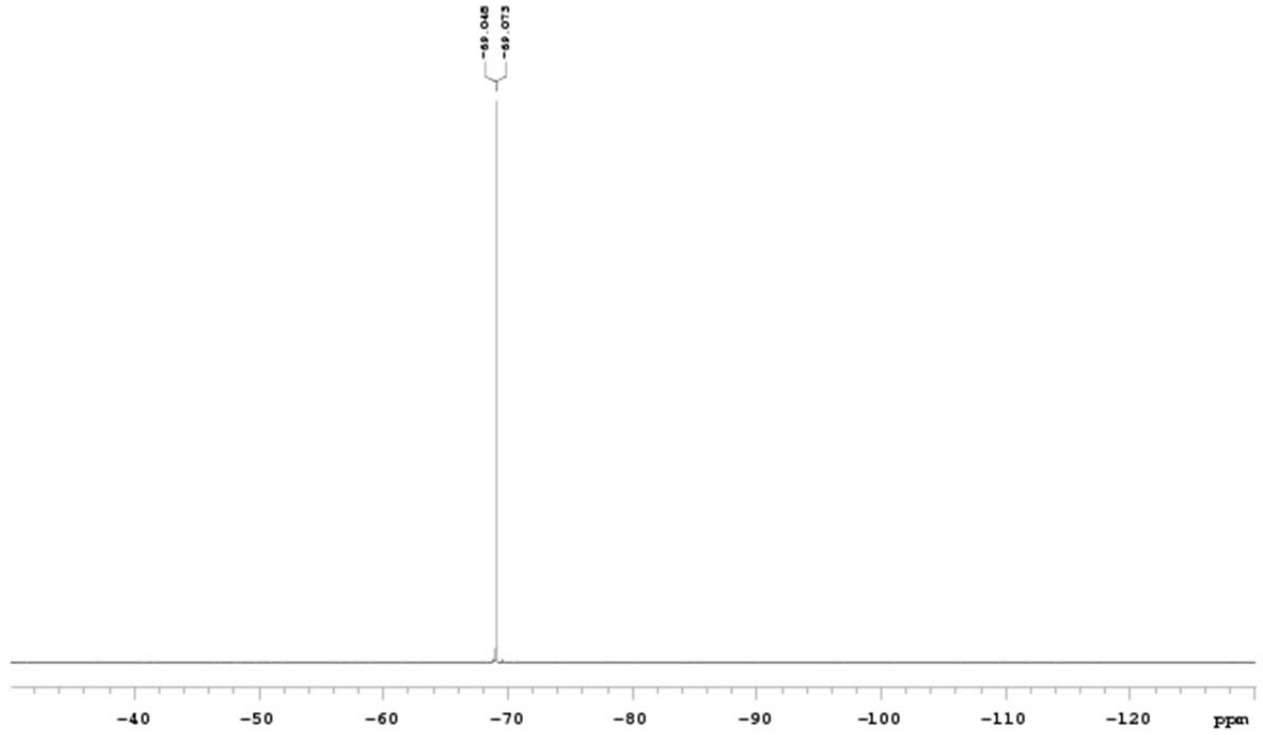

-68.618
-68.633
-40
-50
-60
-70
-80
-90
-100
-110
-120
ppm

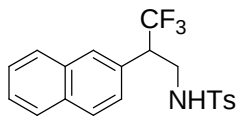

CF3
NHTs
O

6b

11
10
9
8
7
6
5
4
3
2
1
ppm
1.96
2.01
2.11
2.04
1.00
1.14
3.23
2.22
3.21

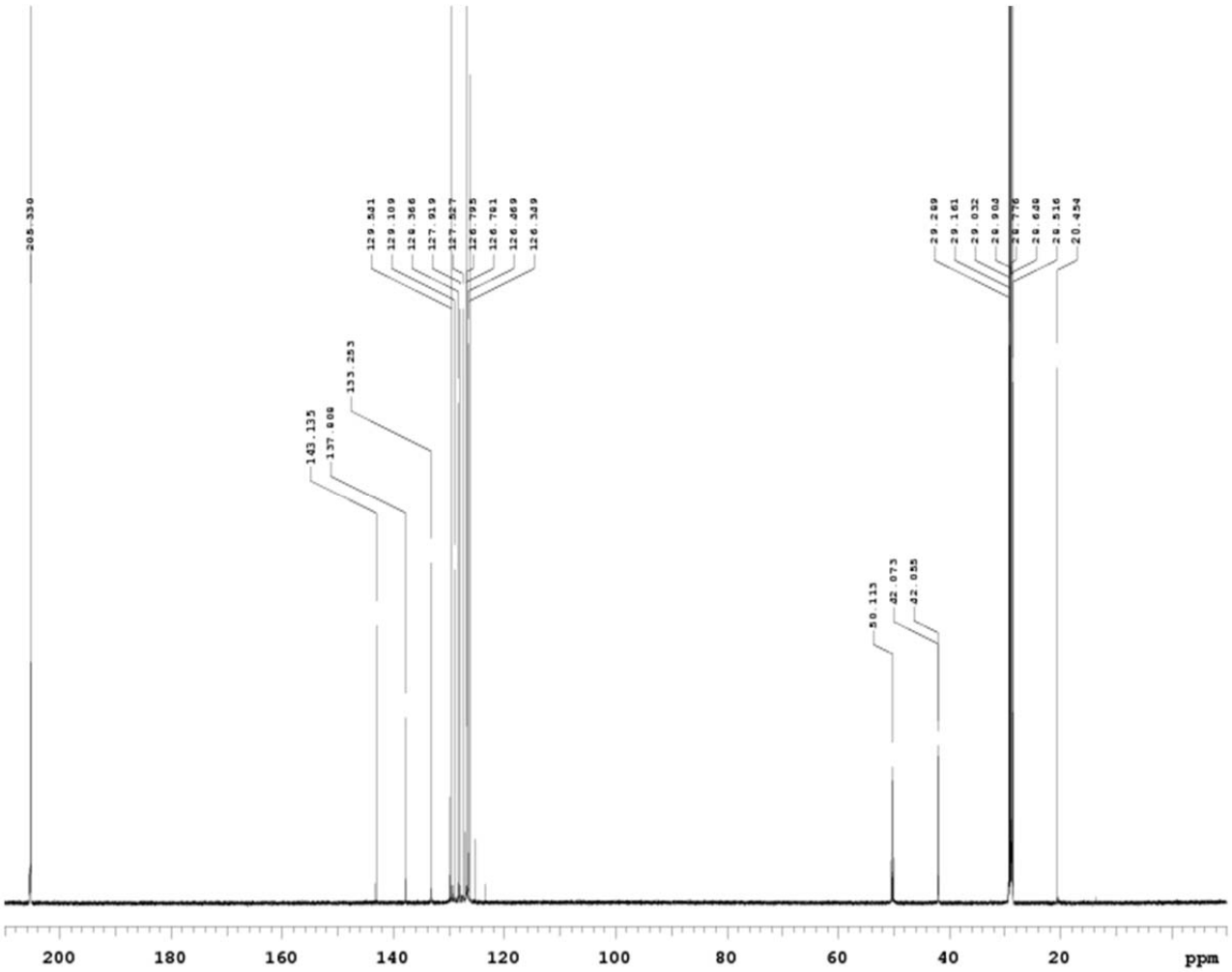

160.014
143.802
136.491
130.135
129.886
127.079
127.049
123.164
123.150
114.573
77.343
77.028
76.705
55.293
49.327
49.063
42.106
42.077
21.360
180
160
140
120
100
80
60
40
20
0 ppm

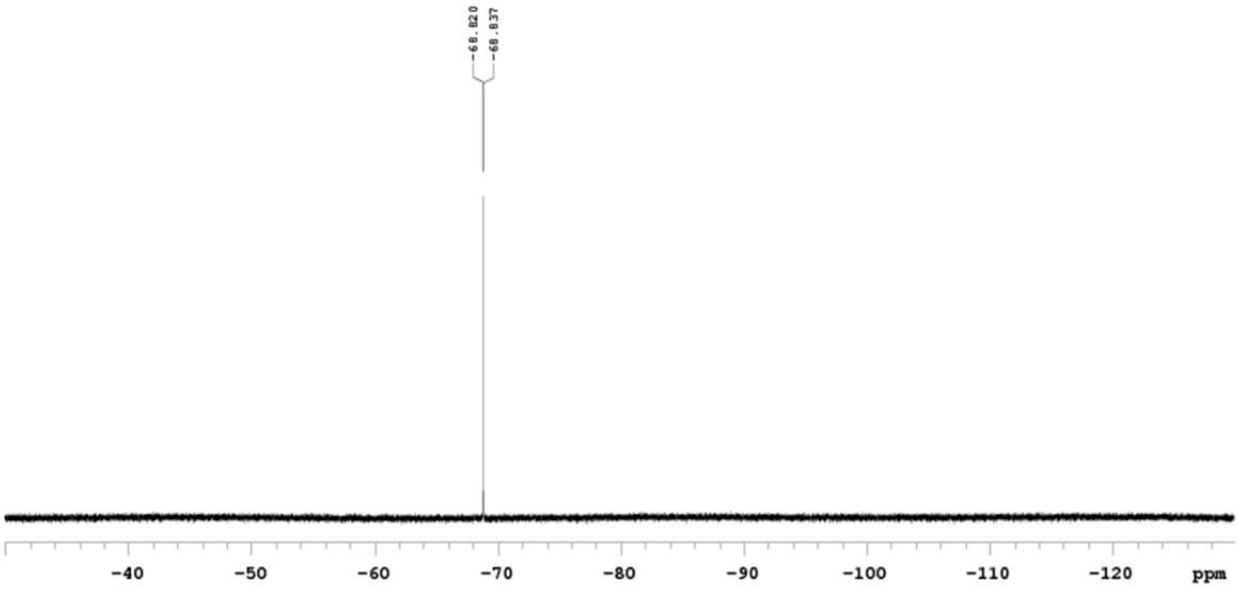

-69.048
-69.073
-40
-50
-60
-70
-80
-90
-100
-110
-120
ppm


CF3
NHTs

6c

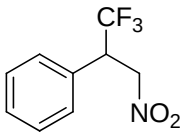
10
9
8
7
6
5
4
3
2
1
ppm


205.330
129.541
129.109
128.366
127.919
127.527
126.795
126.761
126.469
126.349
143.135
137.608
133.253
29.269
29.161
29.032
29.903
28.776
28.626
28.516
20.454
50.113
42.073
42.055
200
180
160
140
120
100
80
60
40
20
ppm


-68.820
-68.837
-40
-50
-60
-70
-80
-90
-100
-110
-120
ppm

Copies of the HPLC traces

(*R*)-1,1,1-Trifluoro-2-phenyl-3-nitropropane 4a

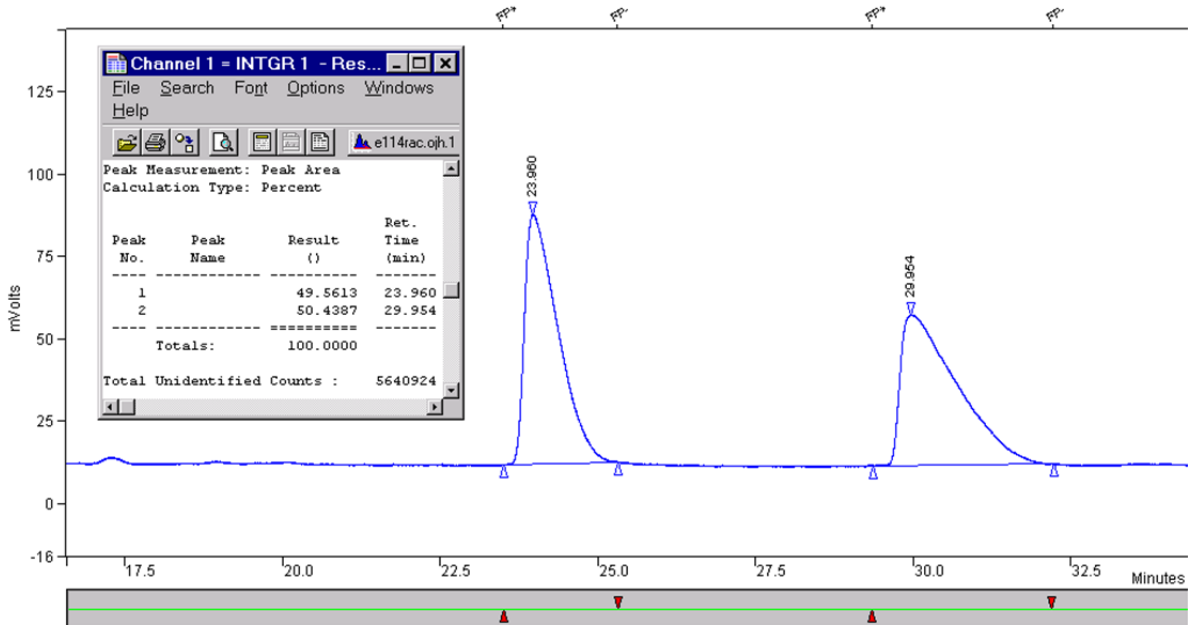


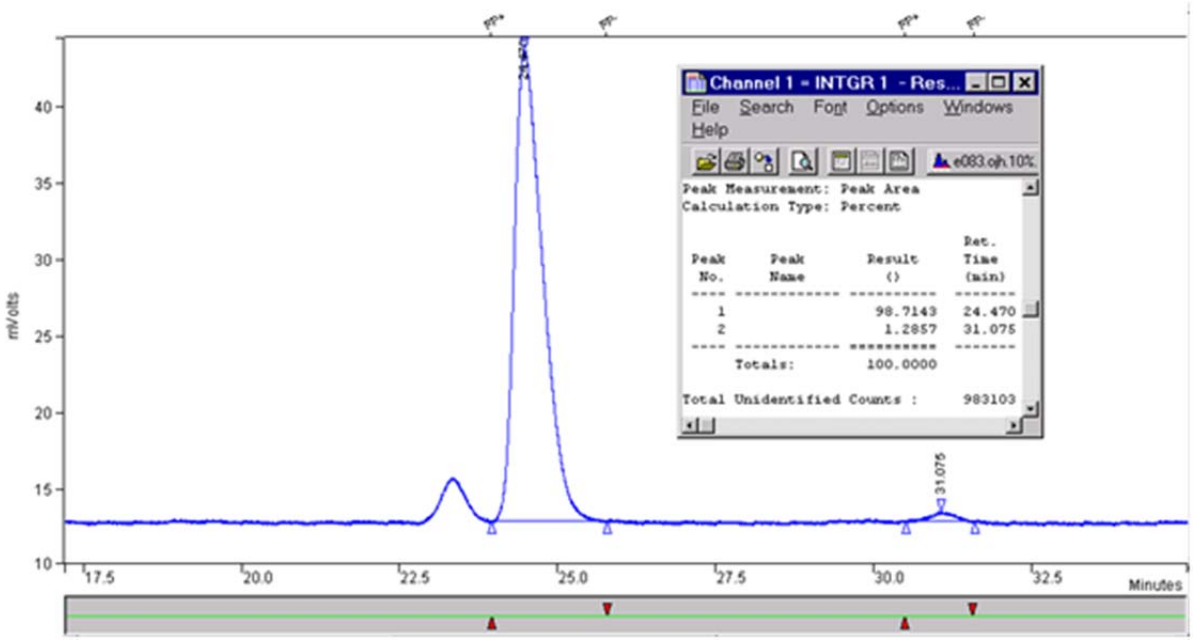
4a

Daicel Chiralcel OJH column

n-hexane/2-propanol 9:1; 0.75 mL/min; λ = 254 nm

t_R (major) = 24.5 min; t_R (minor) = 31.1 min; ee 97%.



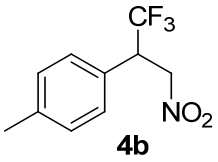


(*R*)-1,1,1-Trifluoro-2-(4-methyl-phenyl)-3-nitropropane 4b

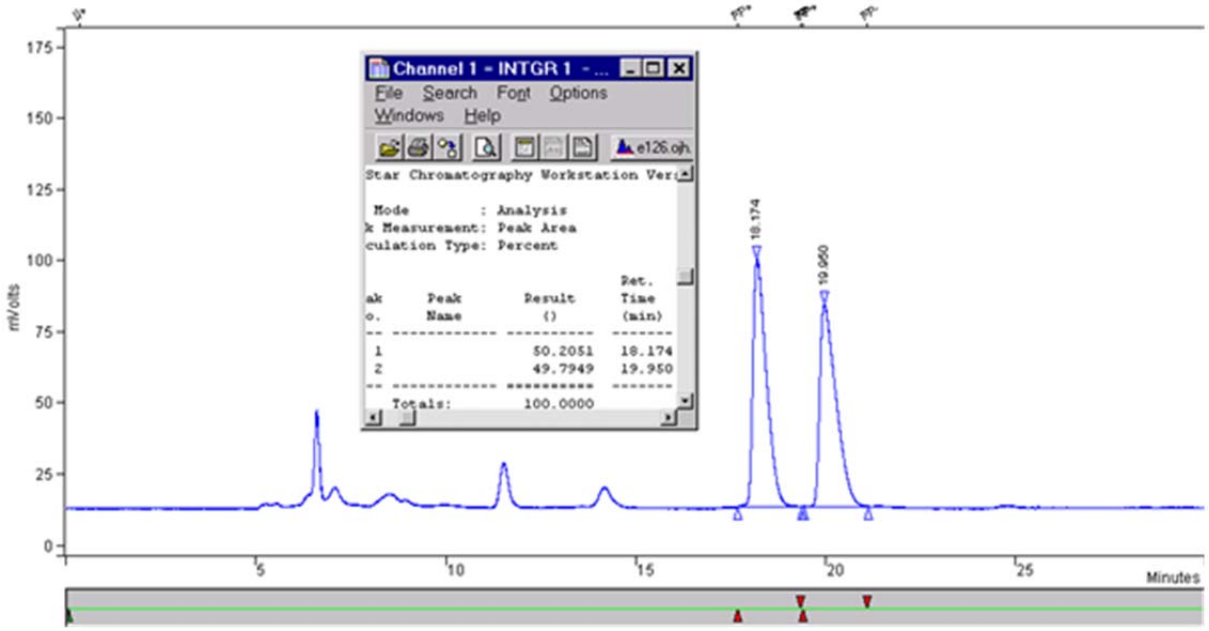
Daicel Chiralcel OJH column

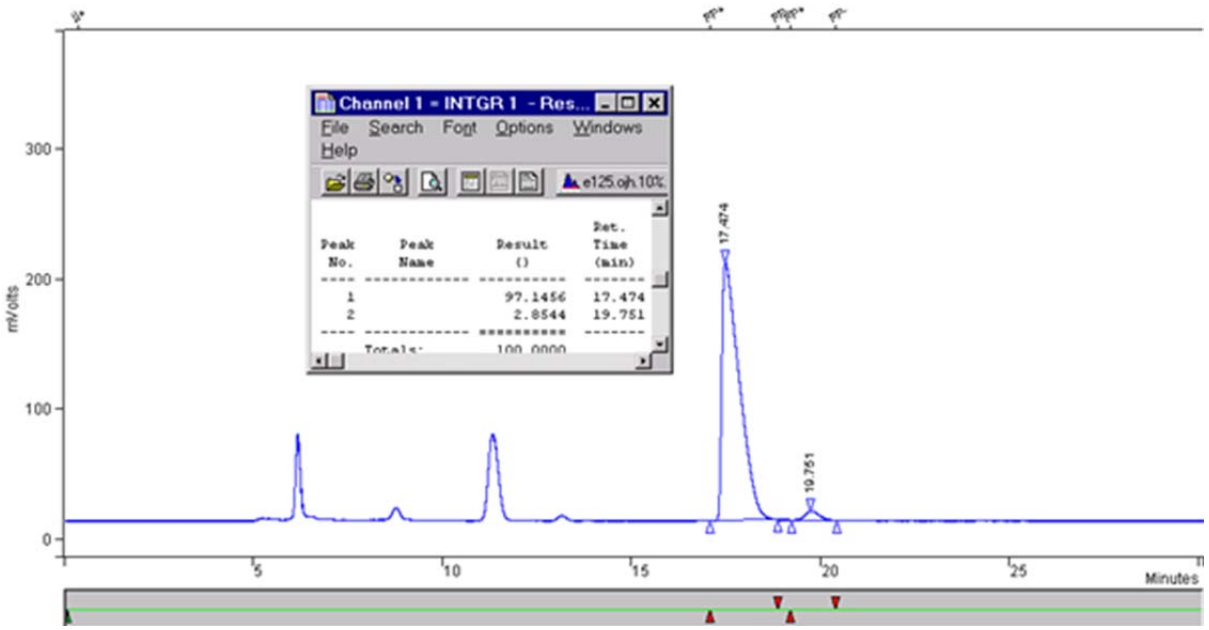
n-hexane/2-propanol 9:1; 0.75 mL/min; λ = 254 nm.

t_R (major) = 17.5 min; t_R (minor) = 19.8 min; ee 94%.

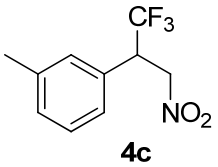


4b





(*R*)-1,1,1-Trifluoro-2-(3-methyl-phenyl)-3-nitropropane 4c

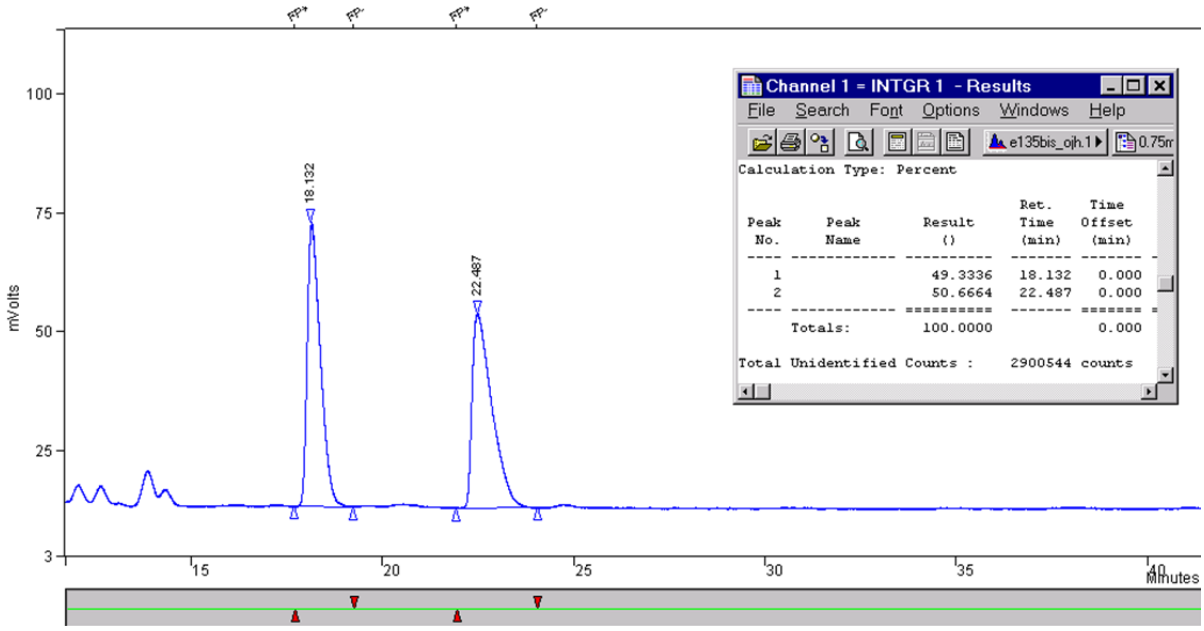


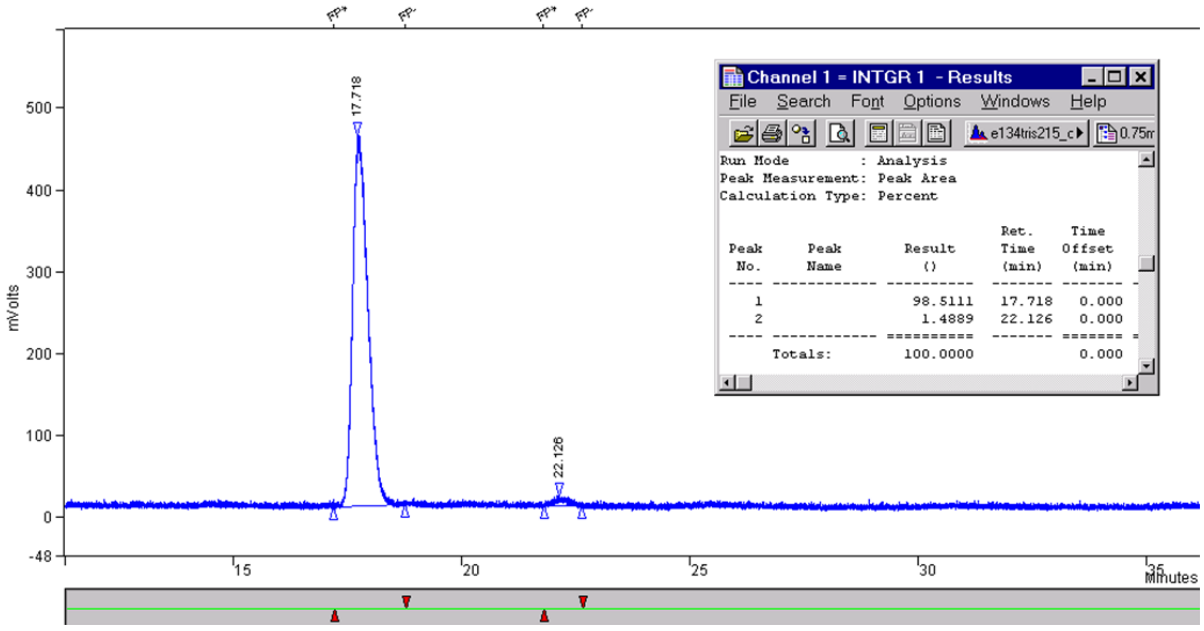
4c

Daicel Chiralcel OJH column

n-hexane/2-propanol 9:1; 0.75 mL/min; λ = 254 nm

t_R (major) = 17.7 min; t_R (minor) = 22.1 min; ee 97%.



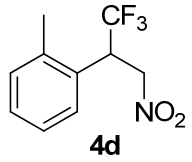


(*R*)-1,1,1-Trifluoro-2-(2-methyl-phenyl)-3-nitropropane 4d

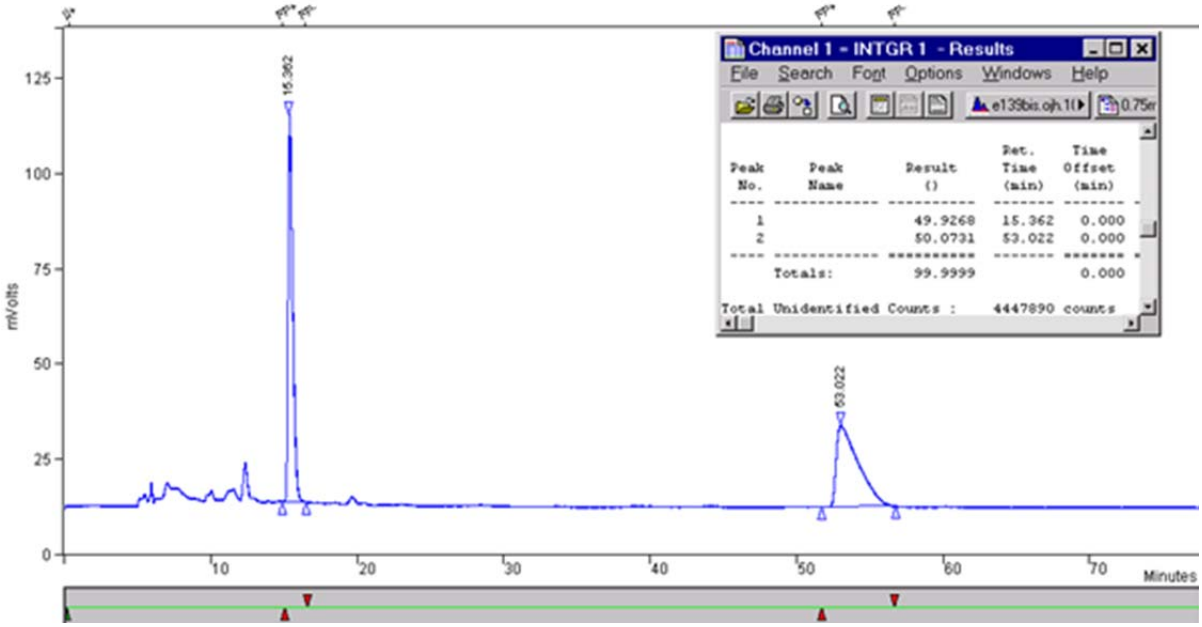
Daicel Chiralcel OJH column

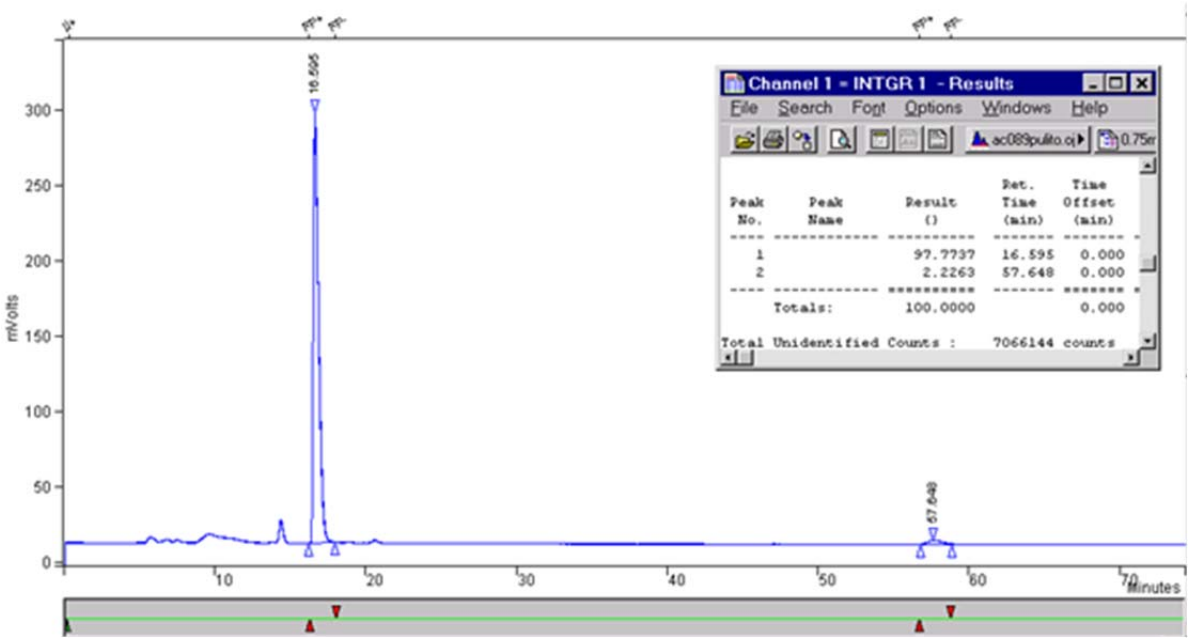
n-hexane/2-propanol 9:1; 0.75 mL/min; λ = 254 nm

t_R (major) = 16.6 min; t_R (minor) = 57.6 min; ee 96%.



4d



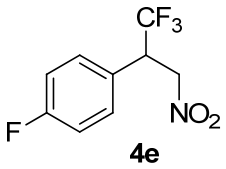


(*R*)-1,1,1-Trifluoro-2-(4-fluoro-phenyl)-3-nitropropane 4e

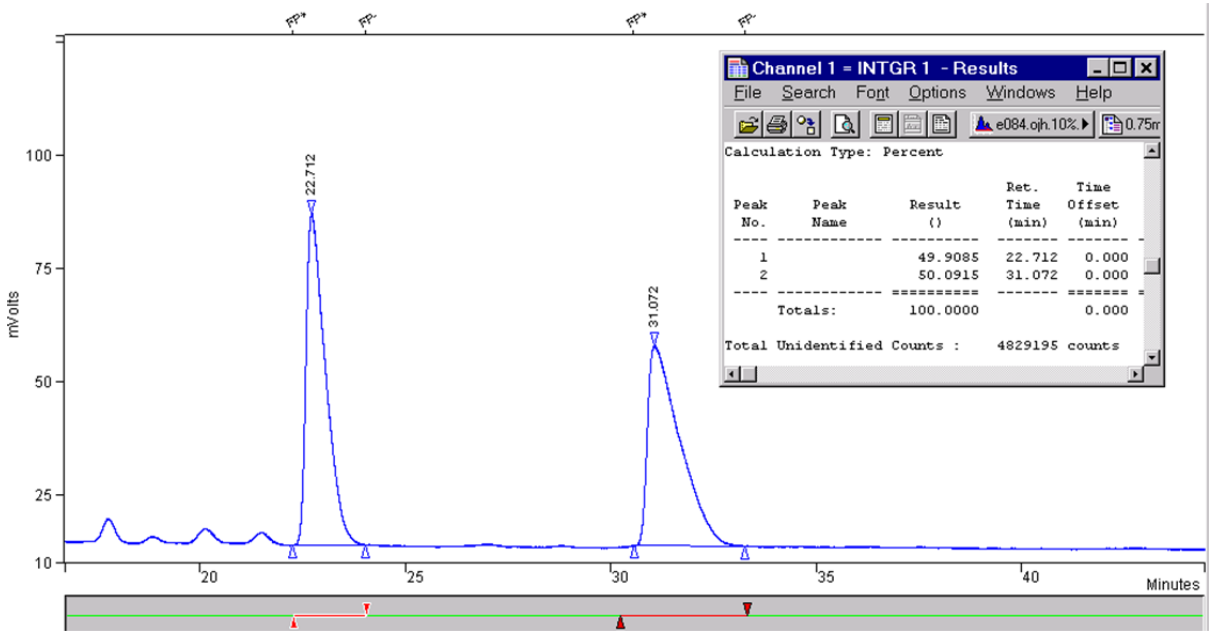
Daicel Chiralcel OJH column

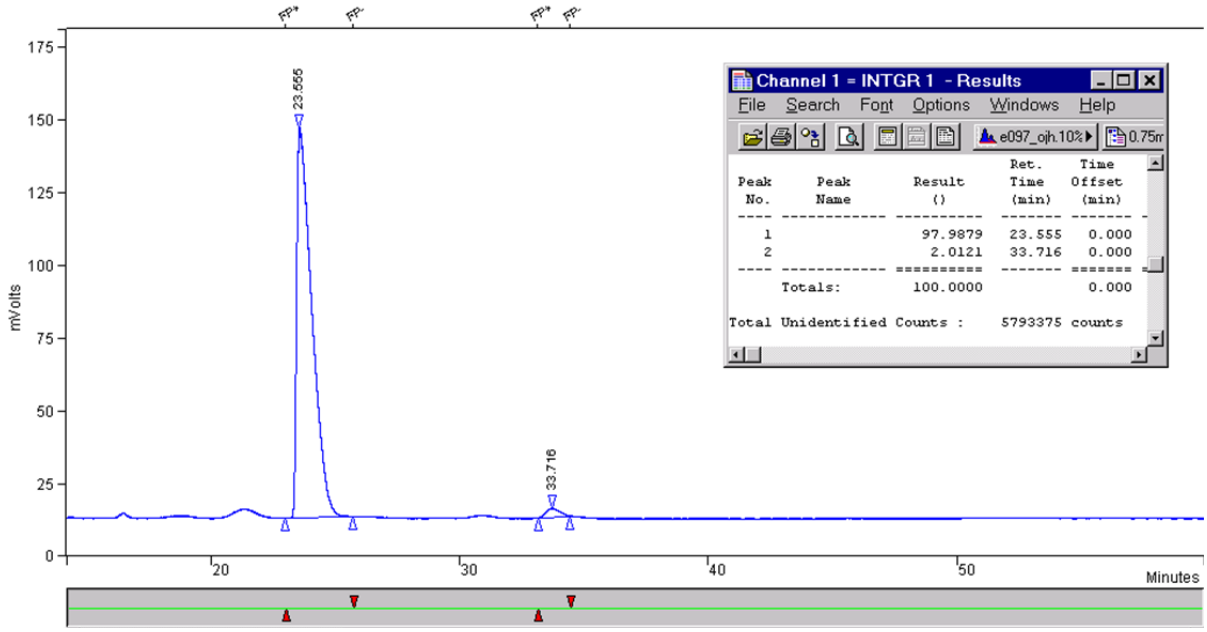
n-hexane/2-propanol 9:1; 0.75 mL/min; λ = 254 nm

t_R (major) = 23.6 min; t_R (minor) = 33.7 min; ee 96%.



4e



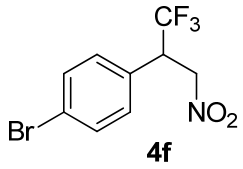


(*R*)-1,1,1-Trifluoro-2-(4-bromo-phenyl)-3-nitropropane 4f

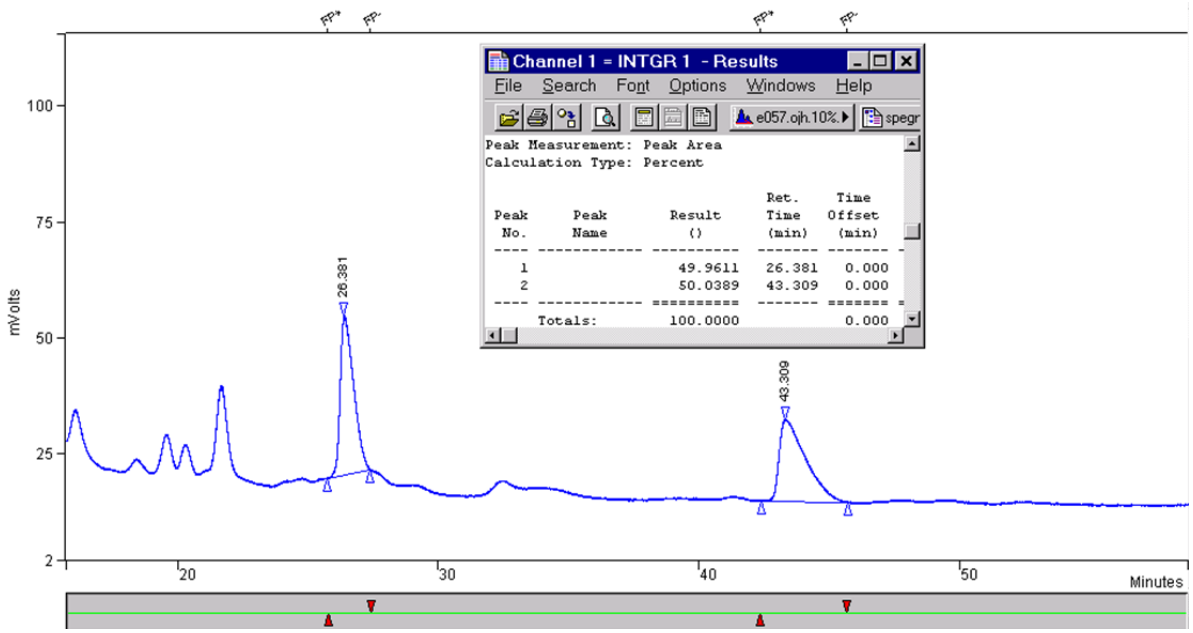
Daicel Chiralcel OJH column

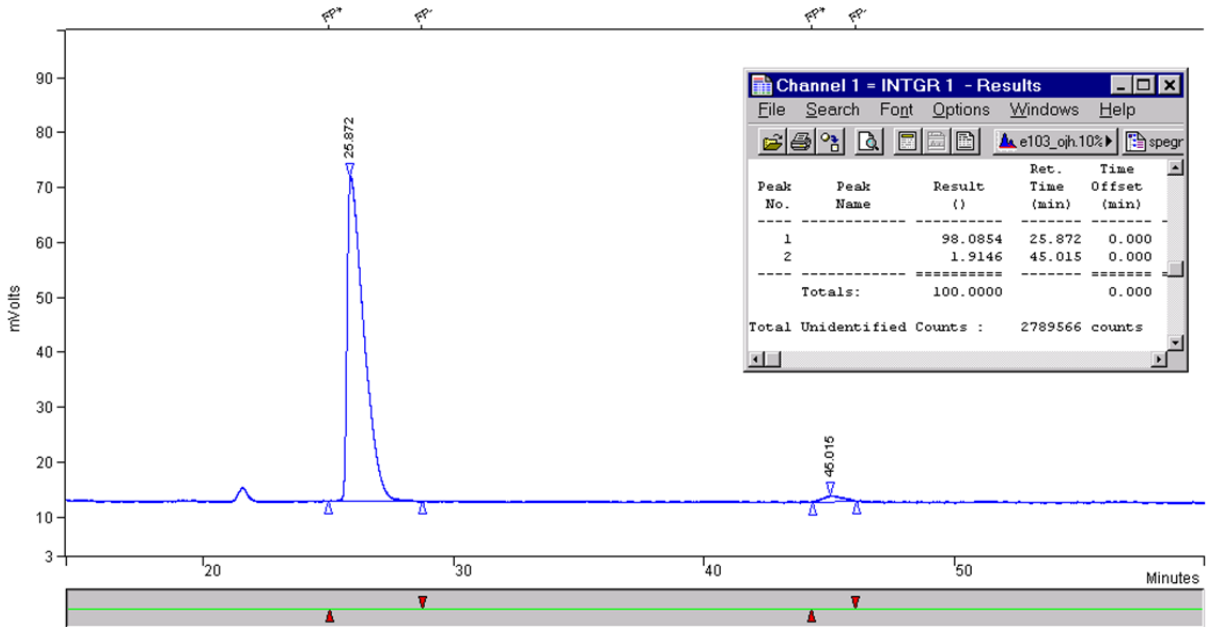
n-hexane/2-propanol 9:1; 0.75 mL/min; λ = 254 nm

t_R (major) = 25.9 min; t_R (minor) = 45.0 min; ee 96%.



4f



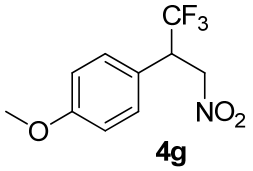


(*R*)-1,1,1-Trifluoro-2-(4-methoy-phenyl)-3-nitropropane 4g

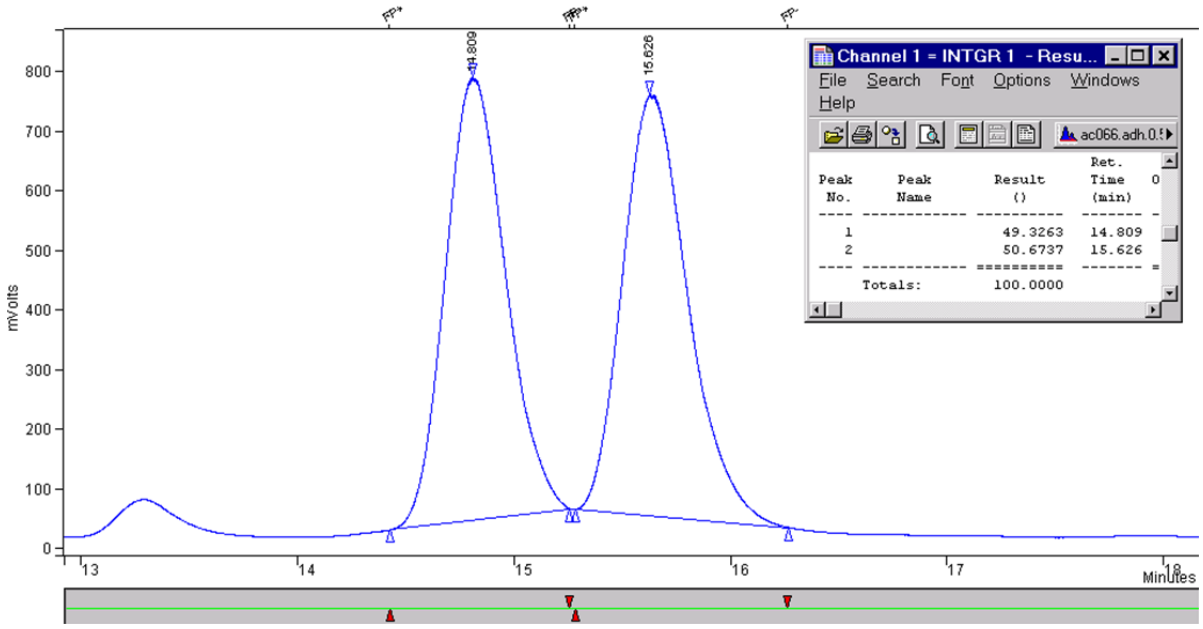
Daicel Chiralcel ADH column

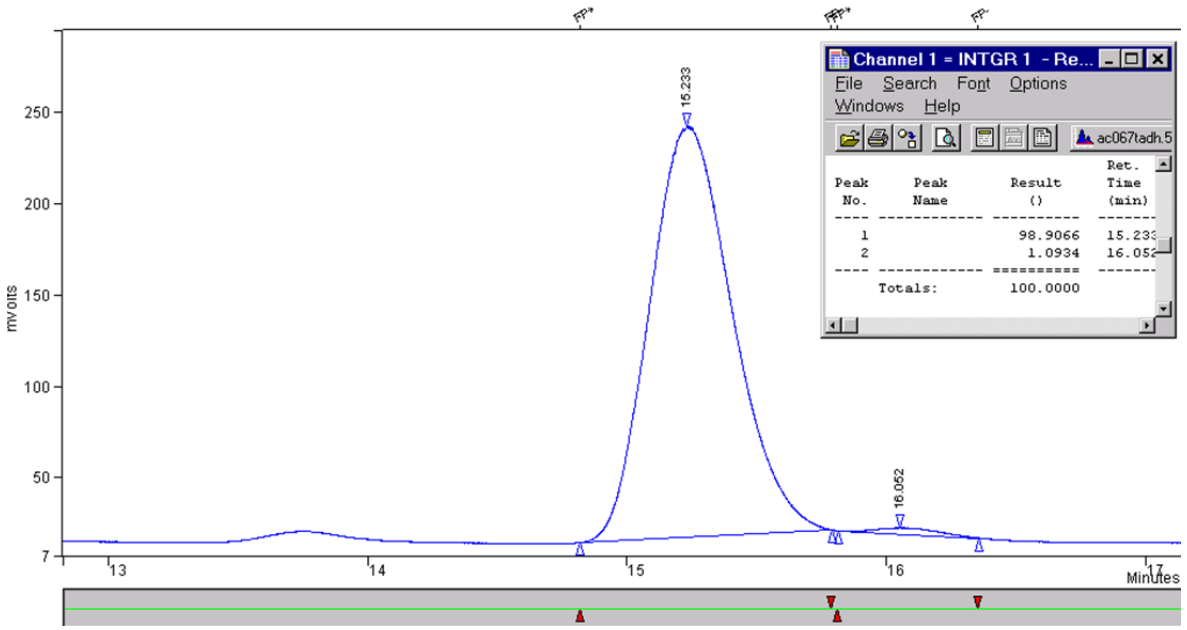
n-hexane/2-propanol 95:5; 0.75 mL/min; λ = 254 nm

t_R (major) = 15.2 min; t_R (minor) = 16.05 min; ee 98%.



4g



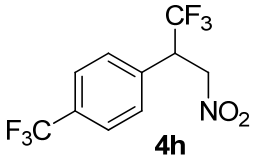


(*R*)-1,1,1-Trifluoro-2-(4-trifluoromethyl-phenyl)-3-nitropropane 4h

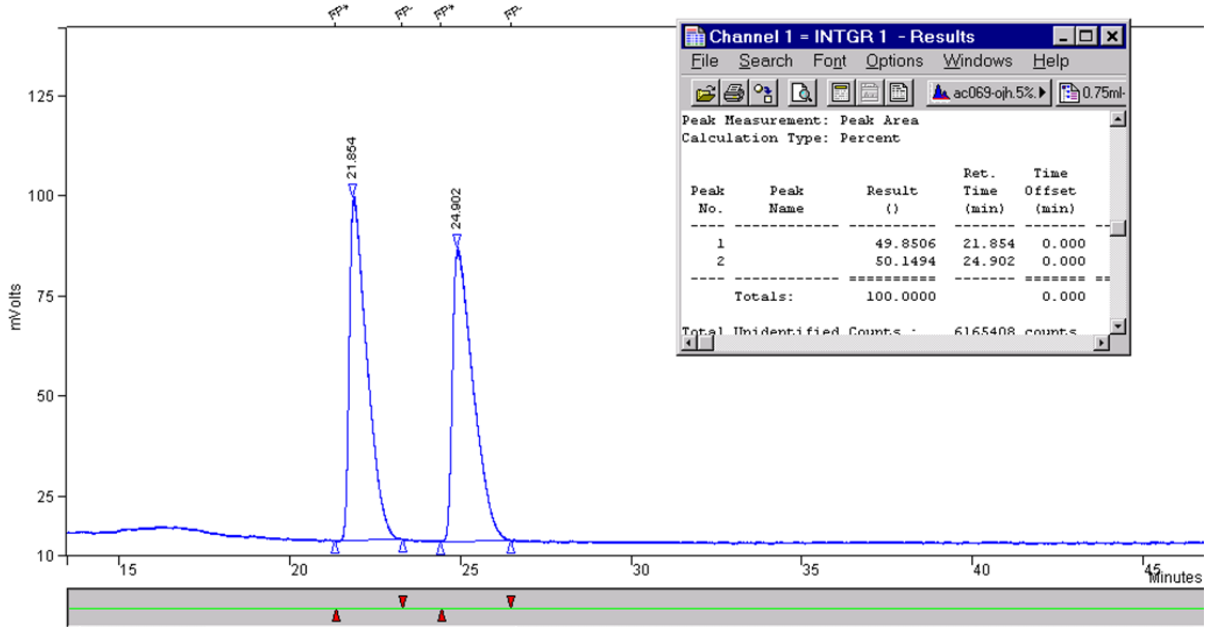
Daicel Chiralcel OJH column

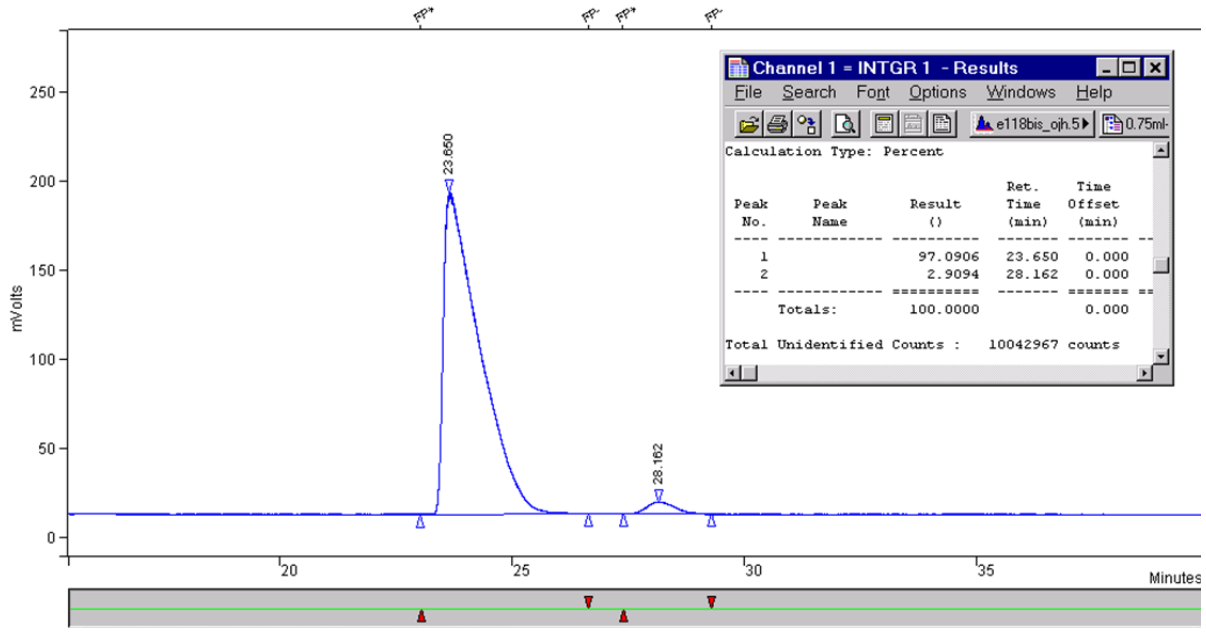
n-hexane/2-propanol 95:5; 0.75 mL/min; λ = 254 nm

t_R (major) = 23.6 min; t_R (minor) = 28.2 min; ee 94%.

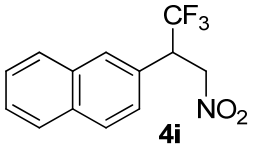


4h





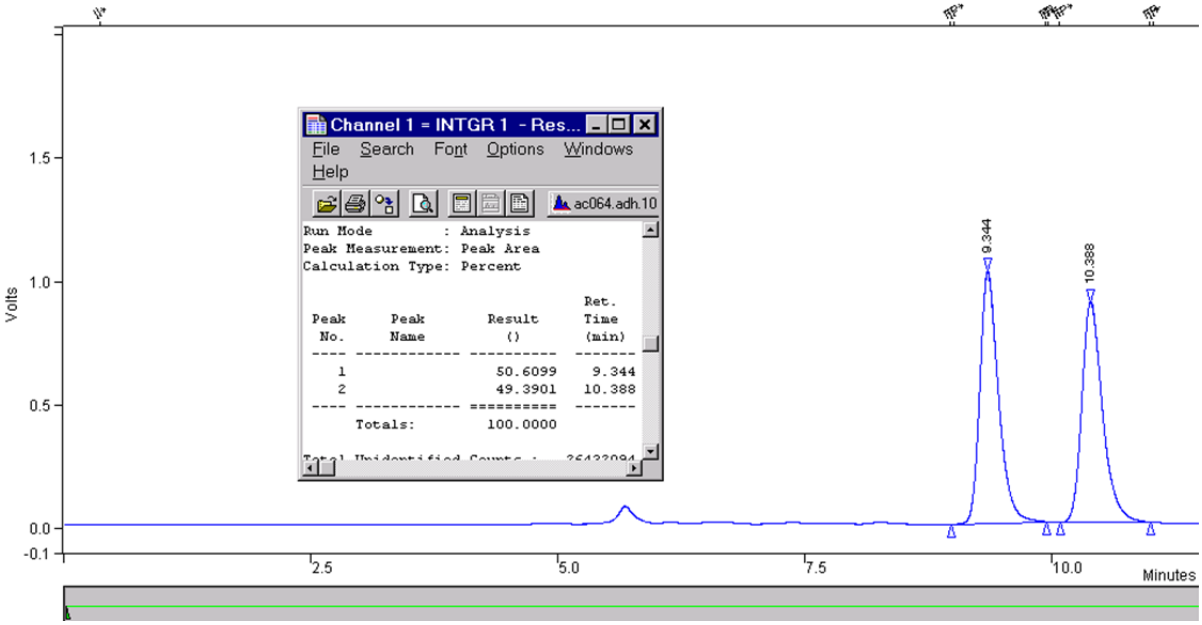
(*R*)-2-(1,1,1-Trifluoro-3-nitropropan-2-yl)naphthalene 4i

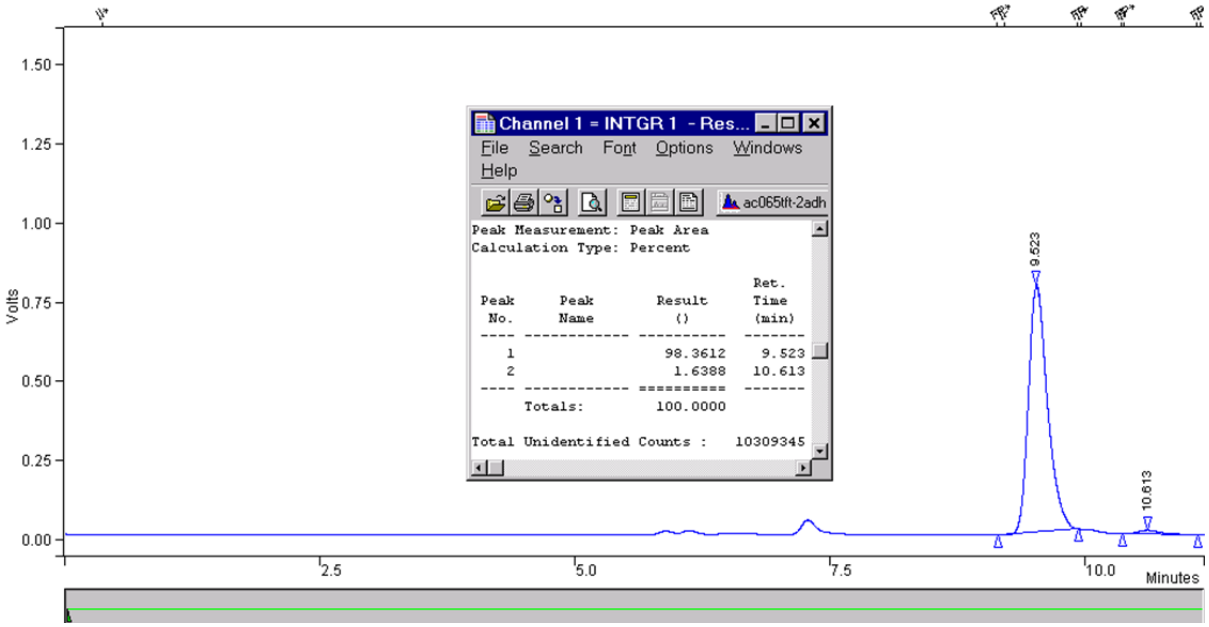


Daicel Chiralpak ADH column

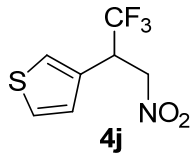
n-hexane/2-propanol 9:1; 0.75 mL/min; λ = 254 nm

t_R (major) = 9.5 min; t_R (minor) = 10.6 min; ee 97%.





(*R*)-3-(1,1,1-Trifluoro-3-nitropropan-2-yl)thiophene 4j

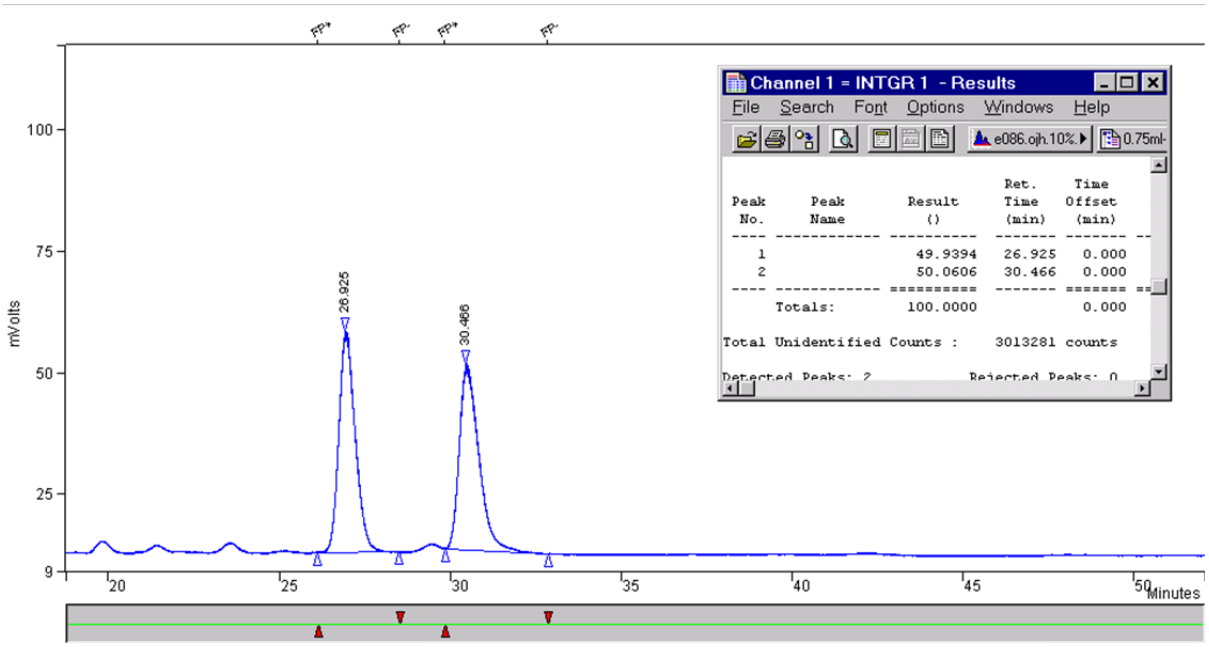


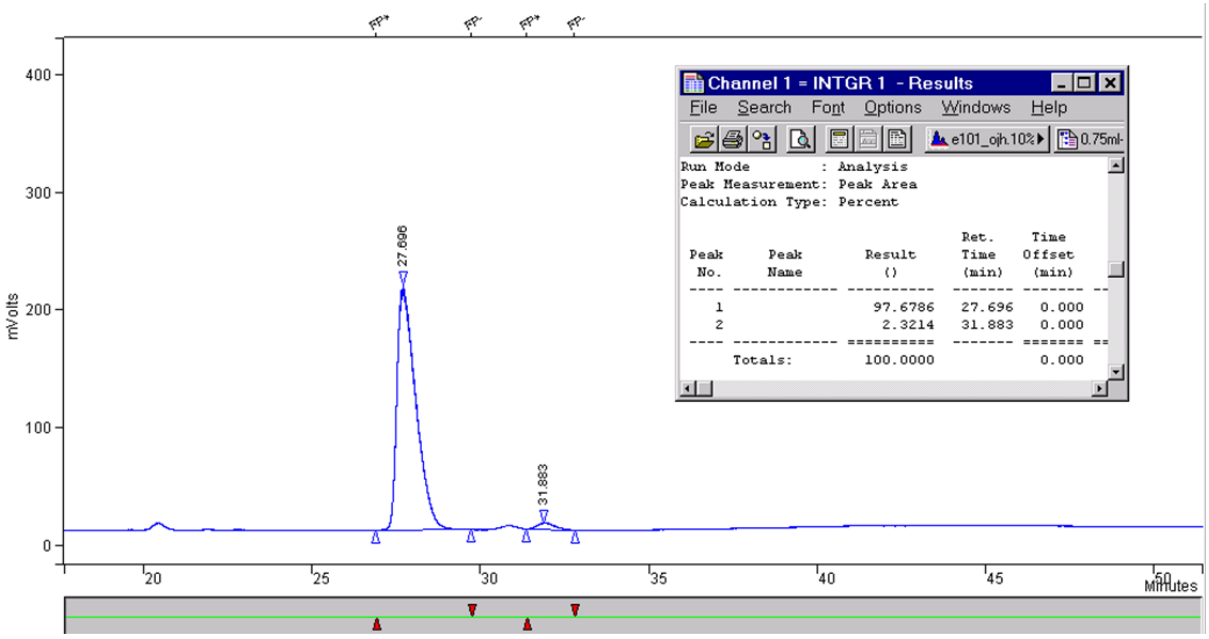
4j

Daicel Chiralcel OJH column

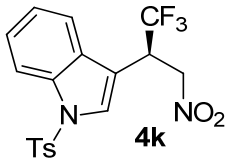
n-hexane/2-propanol 9:1; 0.75 mL/min; λ = 254 nm

t_R (major) = 27.7 min; t_R (minor) = 31.9 min; ee 95%.





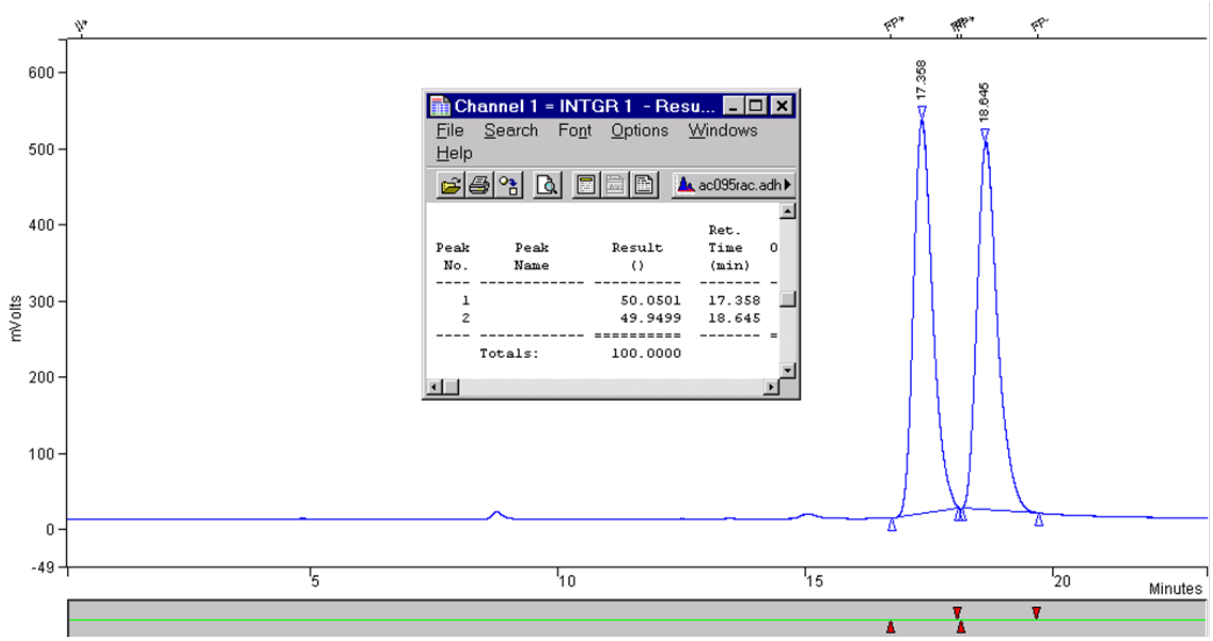
(*R*)-(1-tosyl-3-(1,1,1-trifluoro-3-nitropropan-2-yl)-1H-indole 4k.

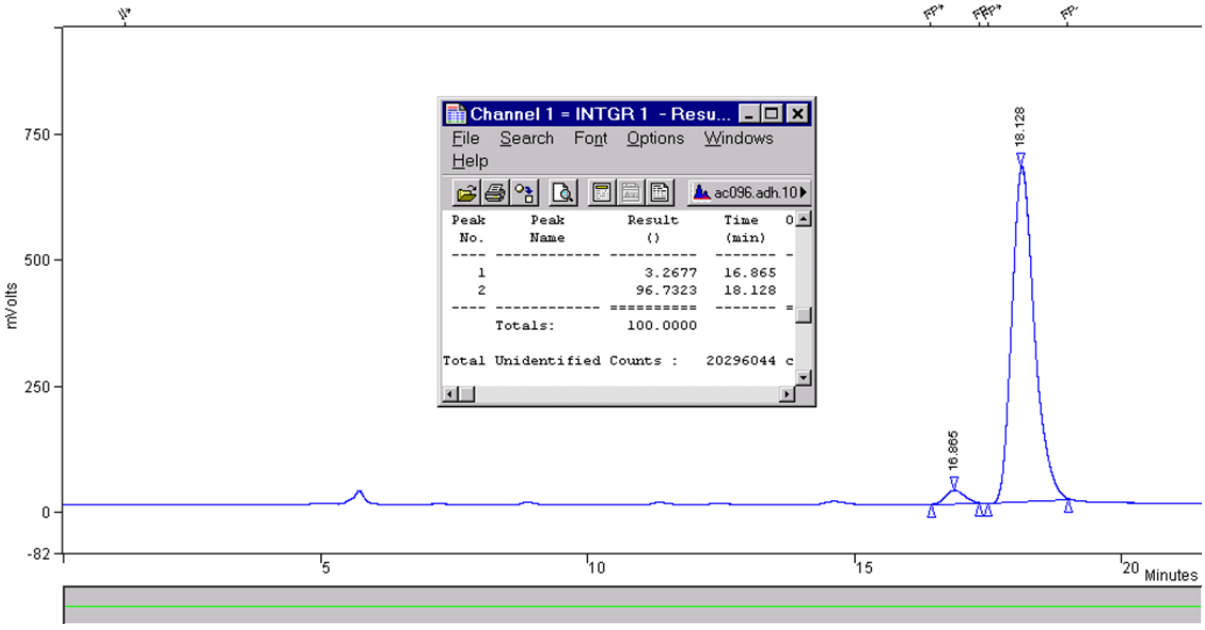


Daicel Chiralcel ADH column;

n-hexane/2-propanol 9:1; 0.75 mL/min; λ = 254 nm.

t_R (minor) = 16.9 min; t_R (major) = 18.1 min; ee 93%.



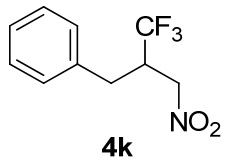


(*R*)-(3,3,3-Trifluoro-2-(nitromethyl)propyl)benzene 4k

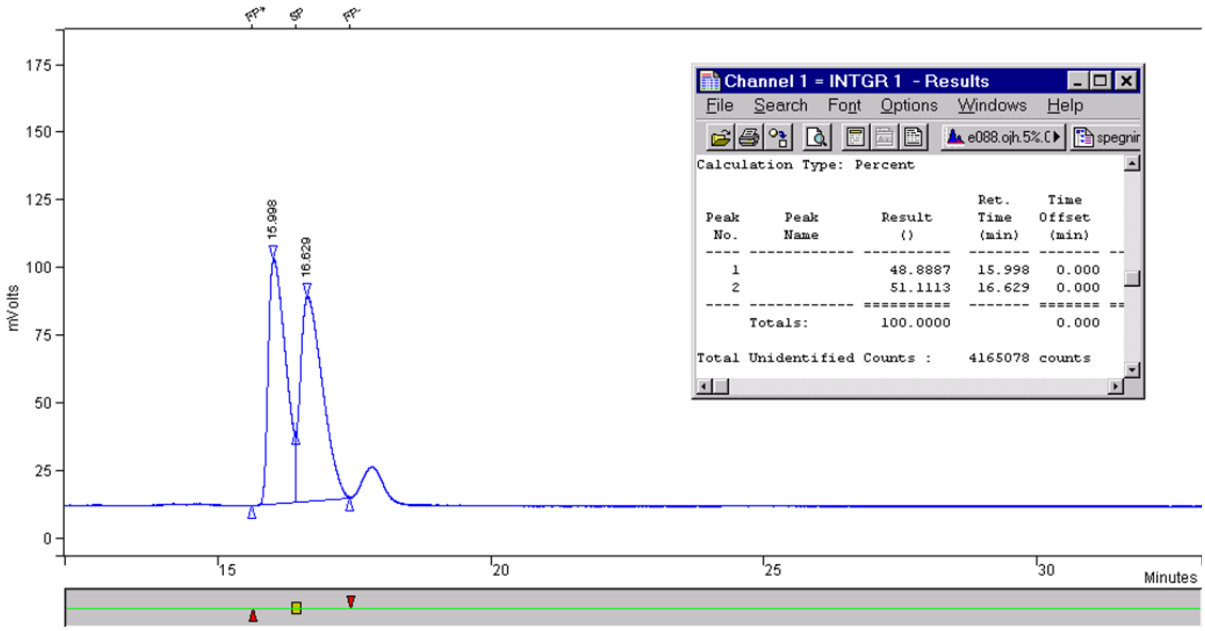
Daicel Chiralcel OJH column

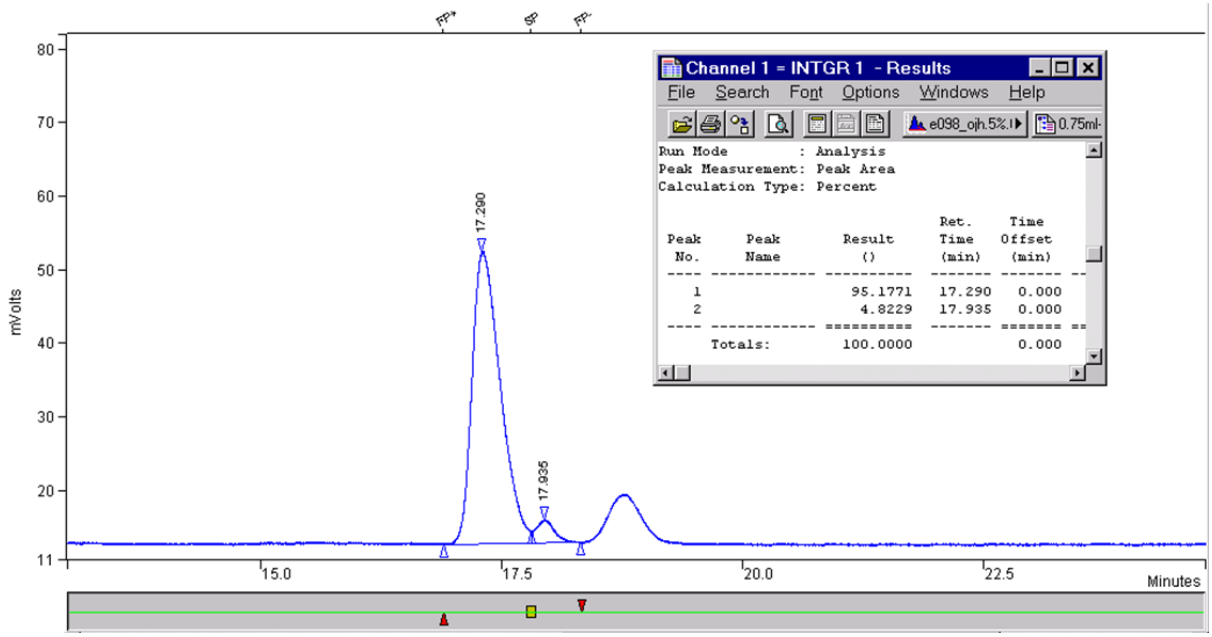
n-hexane/2-propanol 95:5; 075 mL/min; λ = 254 nm

t_R (major) = 17.3 min; t_R (minor) = 17.9 min; ee 90%.

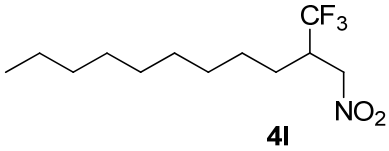


4k





(R)-1,1,1-Trifluoro-2-(nitromethyl)undecane 4l

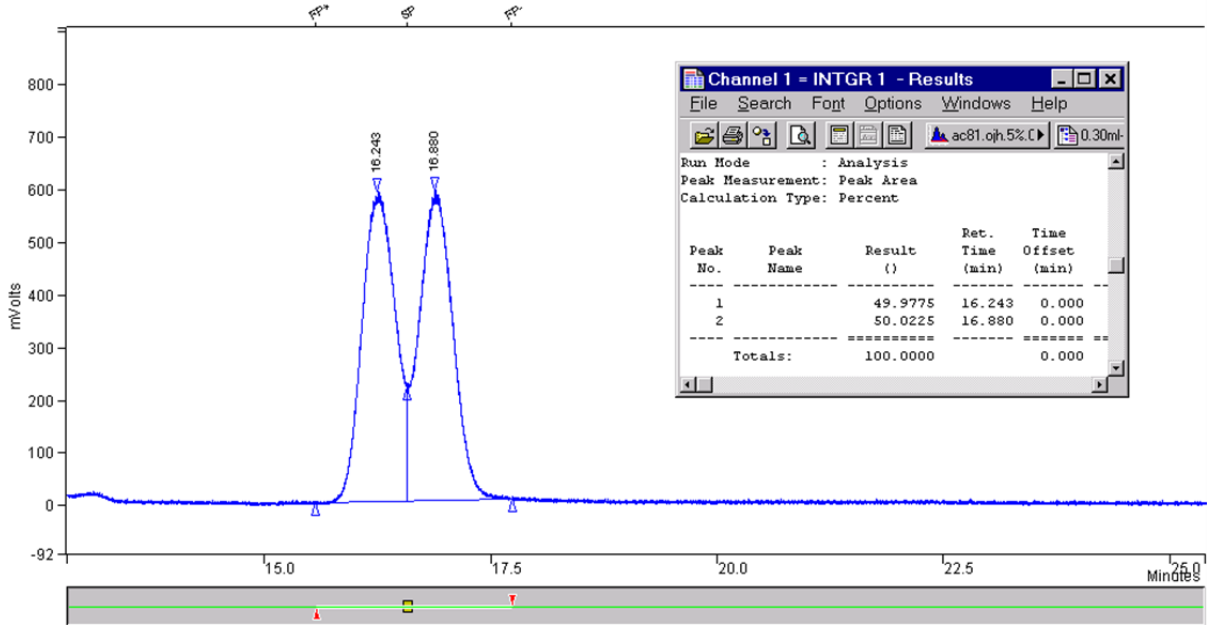


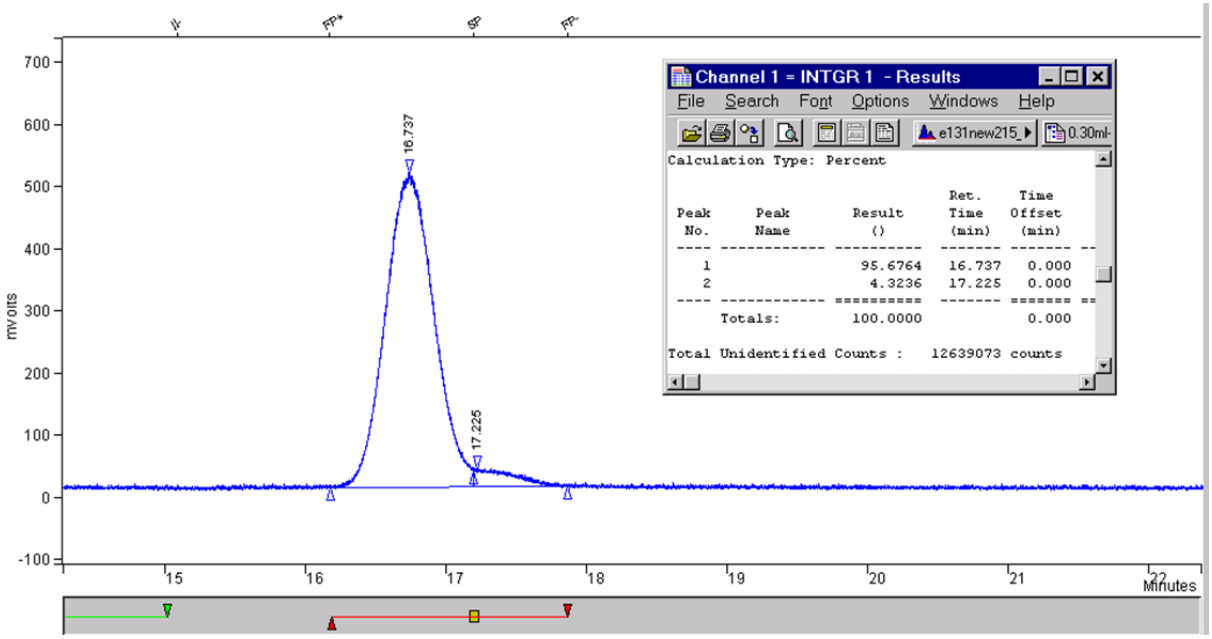
4l

Daicel Chiralcel OJH column

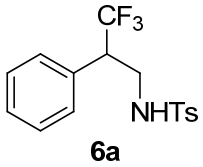
n-hexane/2-propanol 95:5; 0.3 mL/min; λ = 254 nm

t_R (major) = 16.7 min; t_R (minor) = 17.2 min; ee 91%.





(*R*)-4-Methyl-N-(3,3,3-trifluoro-2-phenylpropyl)benzenesulfonamide 6a



6a

Daicel Chiralpak AS column

n-hexane/i-PrOH = 9:1, 1.0 mL/min; λ = 254 nm

t (major) = 44.3 min; t (minor) = 66.3 min) ee 97%.