Enantioselective Organocatalytic Substitution of α-Cyanoacetates on Imidoyl Chlorides – Synthesis of Optically Active Ketimines

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Supporting Information

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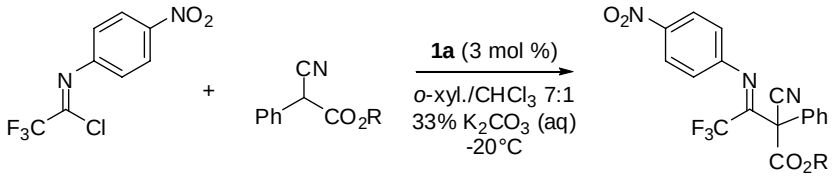
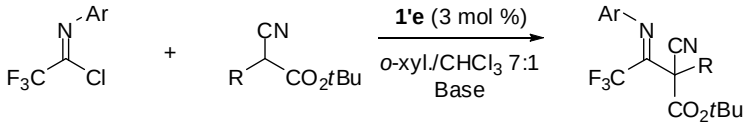
Table S1. Initial Screening Results – Ester Moiety



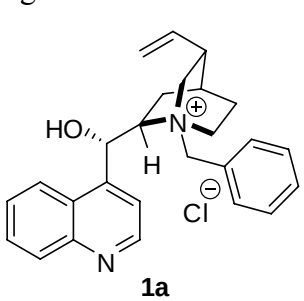
entry	R	ee (%)
1	Et	10
2	*i*-Bu	23
3	*t*-Bu	33

Table S2. Initial Screening Results – *N*-Substituents.

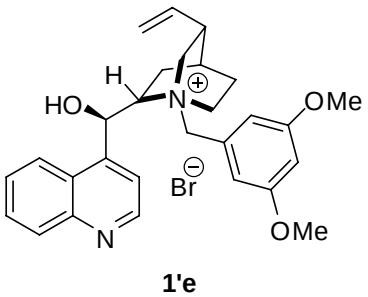


entry	R	Ar	Base	T (°C)	ee (%)
1	Ph	4-MeO-C_6H_4	33% K_2CO_3 (aq.)	R.T.	nr
2	Ph	4-NO_2-C_6H_4	33% K_2CO_3 (aq.)	-20	33
3	Ph	2-NO_2-C_6H_4	33% K_2CO_3 (aq.)	R.T.	55
4	Ph	2,4-$(NO_2)_2$-C_6H_3	33% K_2CO_3 (aq.)	-20	nd[a]
5[b]	*n*Pr	2-NO_2-C_6H_4	40% K_3PO_4 (aq.)	-20	76
6[b]	*n*Pr	2-NO_2-4-CF_3-C_6H_3	40% K_3PO_4 (aq.)	-20	50

[a] Rapid decomposition of the electrophile. nr = no reaction, nd = not determined.
[b] Catalyst loading = 6 mol%.



1a

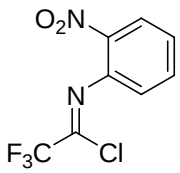


1'e

General Methods. NMR spectra were acquired on a Varian AS 400 spectrometer, running at 400 and 100 MHz for ^{1}H and ^{13}C, respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CHCl_3$, 7.26 ppm for ^{1}H NMR, $CDCl_3$, 77.0 ppm for ^{13}C NMR). ^{13}C NMR spectra were acquired on a broad band decoupled mode. Mass spectra were recorded on a Micromass LCT spectrometer using electrospray (ES^+) ionization techniques. Analytical thin layer chromatography (TLC) was performed using pre-coated aluminum-backed plates (Merck Kieselgel 60 F254) and visualized by ultraviolet irradiation or $KMnO_4$ dip. Melting points are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. The enantiomeric excess (ee) of the products was determined by chiral stationary phase HPLC (Daicel Chiralpak AS/AD or Daicel Chiralcel OD/OJ columns).

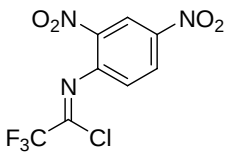
Materials. Analytical grade solvents and commercially available reagents were used as received. For flash chromatography (FC) silica gel purchased from Fluka (Silica gel 60, 230-400 mesh) and Mitsubishi Kagaku Iatron, Inc. (Iatrobeads, 6RS-8060) were used. Imidoyl chlorides were prepared following a literature procedure.[1] α-Substituted-α-cyanoacetates **3a**, **3e**, **3f** and **3i** were prepared as reported.[2,3] α-Substituted-α-cyanoacetates **3b**, **3d** and **3h** were prepared according to a known procedure.[4] Compound **3c** was obtained with a similar procedure (which afforded *tert*-butyl 2-cyano-3-(furan-2-yl)acrylate) followed by reduction of the latter with a literature reported procedure.[5] Racemic samples were prepared using TBAI as the catalyst.

(*Z*)-2,2,2-Trifluoro-*N*-(2-nitrophenyl)acetimidoyl chloride (2a):[1]



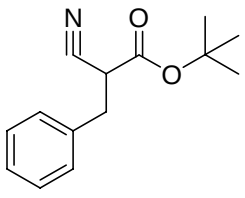
PPh_3 (17.25 g, 66 mmol) and Et_3N (3.65 mL, 26.5 mmol) were dissolved in CCl_4 (10 mL) at 0 °C and CF_3CO_2H (1.7 mL, 22 mmol) was added. After the solution was stirred at 0 °C for 15 min, 2-nitroaniline (3.66 g, 26.5 mmol) dissolved in CCl_4 (10 mL) was added. The mixture was then refluxed with stirring (3 h). Solvents were removed under reduced pressure, and the residue was diluted with hexane and filtered. Residual solids were washed with hexane several times. The filtrate was concentrated under reduced pressure, and the residue was distilled to afford **2** as a yellow oil (2.85 g, 60% yield). Bp: 170-173 °C (1 mbar). ^{1}H NMR ($CDCl_3$) 8.21 (d, *J* 8.3 Hz, 1H), 7.72 (t, *J* 7.4 Hz, 1H), 7.44 (t, *J* 7.5 Hz, 1H), 6.98 (d, *J* 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 139.1, 138.9, 136.9 (q, $^{2}J_{C\text{-}F}$ 44.0 Hz), 134.7, 126.9, 125.6, 120.6, 116.4 (q, $^{1}J_{C\text{-}F}$ 277.7 Hz).

(*Z*)-*N*-(2,4-Dinitrophenyl)-2,2,2-trifluoroacetimidoyl chloride:[1]



PPh_3 (8.65 g, 33 mmol) and Et_3N (1.83 mL, 13.2 mmol) were dissolved in CCl_4 (5 mL) at 0 °C and CF_3CO_2H (0.85 mL, 11 mmol) was added. After the solution was stirred at 0 °C for 15 min 2,4-dinitroaniline (2.42 g, 13.2 mmol) dissolved in CCl_4 (5 mL) was added. The mixture was then refluxed with stirring (3 h). Solvents were removed under reduced pressure, and the residue was diluted with hexane and filtered. Residual solids were washed with hexane several times. The filtrate was concentrated under reduced pressure, and the residue was distilled to afford the product as a yellow oil (1.21 g, 37% yield). Bp: 235-240 °C (1 mbar). ^{1}H NMR ($CDCl_3$) 9.10 (d, *J* 2.4 Hz, 1H), 8.58 (dd, *J* 8.7, 2.4 Hz, 1H), 7.19 (d, *J* 8.7 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 145.4, 143.6, 139.2 (q, $^{2}J_{C\text{-}F}$ 45.0 Hz), 130.4, 129.3, 122.0, 121.7, 116.2 (q, $^{1}J_{C\text{-}F}$ 278.5 Hz).

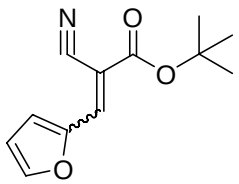
***tert*-Butyl 2-cyano-3-phenylpropanoate (3b):**



To a mixture of benzaldehyde (530.6 mg, 5 mmol) and *tert*-butyl cyanoacetate (705.8 mg, 5 mmol) 1.5 g of alumina (activity II-III) was added. The mixture was allowed to stir for 15 min. Then EtOH (20 mL) was added, the reaction mixture was cooled to 0 °C and $NaBH_4$ (191.2 mg, 5 mmol) was added. The reaction was stirred for 20 min and then poured into a separatory funnel with ice. HCl 1 M was added and the layers were separated. The

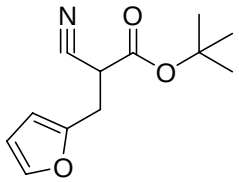
aqueous layer was washed twice with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$ and evaporated. FC on silica gel (pentane/Et_2O 9:1) afforded the product as a clear oil (392.9 mg, 34% yield, not optimized). ^{1}H NMR ($CDCl_3$) δ 7.40–7.22 (m, 5H), 3.63 (dd, *J* 8.3, 6.0 Hz, 1H), 3.30-3.12 (m, 2H), 1.44 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 164.3, 135.4, 128.9 (2C), 128.6 (2C), 127.5, 116.5, 84.0, 40.3, 35.6, 27.6 (3C). HRMS calc.: $C_{14}H_{17}NNaO_2$ 254.1157; found: 254.1165.

***tert*-Butyl 2-cyano-3-(furan-2-yl)acrylate:**



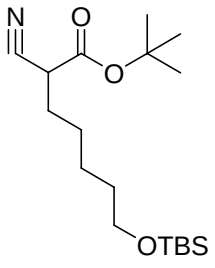
To a mixture of furfural (1.16 g, 12 mmol) and *tert*-butyl cyanoacetate (1.70 g, 12 mmol) 3.6 g of alumina (activity II-III) was added. The mixture was allowed to stir for 10 min. Then CH_2Cl_2 was added, the reaction mixture was filtrated and the solvent evaporated. FC on silica gel (pentane/Et_2O 9:1) afforded the product as a pale yellow solid (1.14 g, 43% yield, not optimized). ^{1}H NMR ($CDCl_3$) δ 7.93 (d, *J* 1.8 Hz, 1H), 7.73 (m, 1H), 7.38-7.34 (m, 1H), 6.64 (m, 1H), 1.56 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 161.3, 148.7, 147.8, 138.7, 121.0, 115.5, 113.7, 100.3, 83.5, 27.9 (3C). HRMS calc.: $C_{12}H_{13}NNaO_3$ 242.0793; found: 242.0781.

***tert*-Butyl 2-cyano-3-(furan-2-yl)propanoate (3c):**



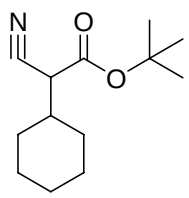
To a solution of *tert*-butyl 2-cyano-3-(furan-2-yl)acrylate (483.5 mg, 2.2 mmol) in anhyd. DMF (4.2 mL) was added $Pd(OAc)_2$ (9.9 mg, 2 mol%), HCOOK (371 mg, 4.4 mmol) and the reaction mixture was stirred under argon at 45 °C for 4 h. The mixture was cooled, diluted with water and extracted with Et_2O. The combined organic layer was washed with brine, dried over anhyd. $MgSO_4$ and concentrated. The residue was purified by FC over silica gel (pentane/EtOAc 9:1) affording the desired product as colorless oil (360 mg, 74% yield). ^{1}H NMR ($CDCl_3$) δ 7.35 (dd, *J* 1.8, 0.7 Hz, 1H), 6.32 (dd, *J* 3.2, 1.9 Hz, 1H), 6.23 (dd, *J* 3.2, 0.7 Hz, 1H), 3.73 (dd, *J* 7.7, 6.3 Hz, 1H), 3.25 (m, 2H), 1.47 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 163.9, 149.0, 142.2, 116.1, 110.4, 108.1, 84.2, 37.9, 28.4, 27.5 (3C). HRMS calc.: $C_{12}H_{15}NNaO_3$ 244.0950; found: 244.0952.

***tert*-Butyl 7-(tert-butyldimethylsilyloxy)-2-cyanoheptanoate (3g):**



A stirred solution of (5-bromopentyloxy)(*tert*-butyl)dimethylsilane[6] (422 mg, 1.5 mmol), *tert*-butyl cyanoacetate (318 mg, 2.25 mmol) and K_2CO_3 (622 mg, 4.5 mmol) in anhyd. DMF (3.3 mL) was heated to 70 °C for 4 h. The solution was cooled and concentrated under reduced pressure. The resulting mixture was suspended in EtOAc and washed with water (5 X) and brine followed by concentration under reduced pressure. FC on silica gel (pentane/EtOAc 9:1) afforded the product as a colorless oil (210 mg, 41% yield, not optimized). ^{1}H NMR ($CDCl_3$) δ 3.60 (t, *J* 6.3 Hz, 2H), 3.38 (t, *J* 6.5 Hz, 1H), 1.91 (q, *J* 7.7 Hz, 2H), 1.58-1.34 (m, 15H), 0.89 (s, 9H), 0.04 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 165.0, 116.8, 83.6, 62.6, 38.4, 32.2, 29.7, 27.6 (3C), 26.4, 25.8 (3C), 25.0, 18.2, -5.4 (2C). HRMS calc.: $C_{18}H_{35}NNaO_3Si$ 364.2284; found: 364.2278.

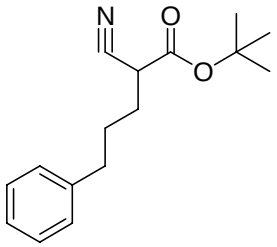
***tert*-Butyl 2-cyano-2-cyclohexylacetate (3d):**



Tert-butyl cyanoacetate (1.41 g, 10 mmol), cyclohexanone (1.96 g, 20 mmol) and 3g of alumina (activity II-III) were stirred at 100 °C for 2 d. Then EtOH (10 mL) was added, the reaction mixture was cooled to 0° C and $NaBH_4$ (378 mg, 10 mmol) was added. The reaction was stirred for 1h and then poured into a separatory funnel with ice. HCl 1 M was added and the layers were separated. The aq. layer was washed twice with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$ and evaporated. FC on silica gel (pentane/Et_2O 9:1) afforded the product as a clear oil (580 mg, 26% yield, not optimized). ^{1}H NMR ($CDCl_3$) δ 3.27 (d, *J* 5.8 Hz,

1H), 2.01 (m, 1H), 1.85-1.60 (m, 5H), 1.49 (s, 9H), 1.37-1.10 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 164.6, 115.9, 83.5, 45.3, 38.6, 30.8, 29.1, 27.6 (3C), 25.6, 25.4, 25.3. HRMS calc.: $C_{13}H_{21}NNaO_2$ 246.1470; found: 246.1470.

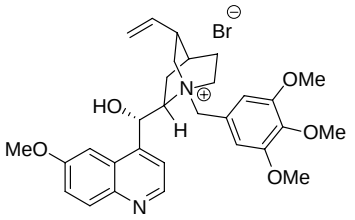
***tert*-Butyl 2-cyano-5-phenylpentanoate (3h):**



To a mixture of 3-phenylpropionaldehyde (671 mg, 5 mmol) and *tert*-butyl cyanoacetate (705.8 mg, 5 mmol) 1.5 g of alumina (activity II-III) was added. The mixture was allowed to stir for 10 min. Then EtOH (20 mL) was added, the reaction mixture was cooled to 0 °C and $NaBH_4$ (191.2 mg, 5 mmol) was added. The reaction was stirred for 30 min and then poured into a separatory funnel with ice. 1M HCl was added and the layers were separated. The aq. layer was washed twice with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$ and evaporated. FC on silica gel (pentane/Et_2O 9:1) afforded the product as a clear oil (869 mg, 67% yield, not optimized). ^{1}H NMR ($CDCl_3$) δ 7.37-7.10 (m, 5H), 3.42 (t, *J* 6.6 Hz, 1H), 2.70 (t, *J* 7.3 Hz, 2H), 2.00-1.90 (m, 2H), 1.90-1.78 (m, 2H), 1.50 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 164.9, 140.8, 128.4 (2C), 128.2 (2C), 126.0, 116.7, 83.8, 38.3, 34.9, 29.1, 28.2, 27.6 (3C). HRMS calc.: $C_{16}H_{21}NNaO_2$ 282.1470; found: 282.1461.

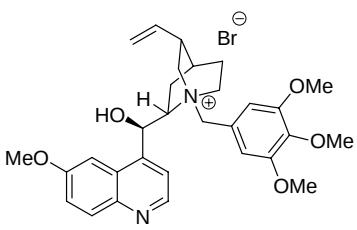
Synthesis of catalysts

***N*-(3,4,5-Trimethoxybenzyl)quinidinium bromide (1h):**



To a stirred solution of 3,4,5-trimethoxybenzyl bromide[7] (240 mg, 0.92 mmol) in toluene (6 mL) was added quinidine (238.5 mg, 0.73 mmol). The reaction mixture was heated at 80 °C for 16 h, and then cooled followed by addition of Et_2O. The resulting precipitate was collected by suction filtration, washed several times with Et_2O, giving **1h** as a white solid (365 mg, 85% yield). Mp: 167-172°C. ^{1}H NMR ($CDCl_3$) δ 8.55 (d, *J* 4.5, 1H), 7.89 (d, *J* 9.2 Hz, 1H), 7.75 (d, *J* 4.6 Hz, 1H), 7.47 (m, 1H), 7.24 (m 1H), 7.20- 7.06 (m, 2H), 6.70 (m, 1H), 6.47 (br, 1H), 5.89 (m, 1H), 5.67 (d, *J* 12.3 Hz, 1H), 5.48 (d, *J* 12.0 Hz, 1H), 5.21 (m, 2H), 4.53 (m, 1H), 4.07 (m, 1H), 3.90-3.70 (m, 13H), 3.53 (t, *J* 12.1 Hz, 1H), 3.08 (q, *J* 12.2 Hz, 1H), 2.43 (m, 1H), 2.03 (m, 1H), 1.90-1.72 (m, 2H), 1.24 (br, 1H), 0.93 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 158.0, 153.2, 147.0, 143.7, 142.8, 135.4, 131.5, 129.0, 128.2, 126.1, 125.2, 122.0, 120.5, 120.2, 118.1, 111.1, 102.9, 67.6, 66.6, 62.7, 60.6, 56.6 (3C), 56.1, 54.2, 38.2, 27.1, 24.0, 21.8. HRMS calc.: $C_{30}H_{37}N_2O_5^+$ 505.2697; found: 505.2705. $[\alpha]_D^{rt}$ +111 (c 0.26, $CHCl_3$).

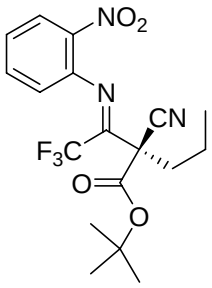
***N*-(3,4,5-Trimethoxybenzyl)quininium bromide (1'h):**



To a stirred solution of 3,4,5-trimethoxybenzyl bromide[7] (493 mg, 1.89 mmol) in toluene (12 mL) was added quinidine (490 mg, 1.51 mmol). The reaction mixture was heated at 80 °C for 15 h, then was cooled and Et_2O was added. The resulting precipitate was collected by suction filtration, washed several times with Et_2O, giving **1'h** as a red solid (724 mg, 82% yield). Mp: 208-213°C. ^{1}H NMR ($CDCl_3$) δ 8.75 (d, *J* 4.3 Hz, 1H), 8.06 (d, *J* 9.5 Hz, 1H), 7.72 (d, *J* 4.7 Hz, 1H), 7.37 (dd, *J* 9.0, 2.1 Hz, 1H), 7.30 (m, 1H), 7.20-7.09 (m, 2H), 6.72 (d, *J* 6.3 Hz, 1H), 6.53 (d, *J* 5.1 Hz, 1H), 6.14 (d, *J* 11.6 Hz, 1H), 5.63 (m, 1H), 5.20-5.08 (m, 3H), 4.53 (d, *J* 12.3 Hz, 1H), 3.97-3.66 (m, 14H), 3.25-3.05 (m, 2H), 2.65 (m, 1H), 2.57-2.25 (m, 2H), 2.07 (m, 1H), 1.79 (m, 1H), 1.59 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 158.2, 153.5, 147.4, 144.0, 143.2, 139.7, 136.2, 132.0, 129.0, 128.2, 126.0, 121.5, 120.9, 120.4, 118.3, 111.1, 102.1, 69.7, 63.9, 63.5, 61.4, 60.8, 56.8 (2C), 56.5, 51.2, 38.1, 26.7, 24.8, 21.5. HRMS calc.: $C_{30}H_{37}N_2O_5^+$ 505.2697; found: 505.2697. $[\alpha]_D^{rt}$ -113 (c 0.31, $CHCl_3$).

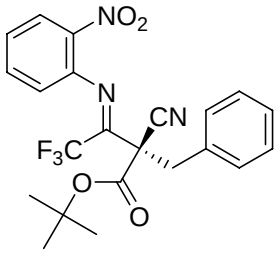
General procedure for catalytic substitution:
To a sample vial equipped with a magnetic stirring bar was added **3** (0.20 mmol), *o*-xylene/$CHCl_3$ (7:1) 1.3 mL, **2** (0.26 mmol), and the catalyst **1** (6 mol%, 0.012 mmol). The mixture was stirred for a short time at ambient temperature and was then placed at -20 °C. When the mixture had cooled, a cold (-20 °C) solution of 20% aq. KOH (0.6 mL) was added and the biphasic mixture was vigorously stirred for the time stated below. After the reaction was judged to be complete by TLC analysis, the organic phase was collected, and the aq. layer was extracted two times with toluene. The combined organic fractions were loaded onto Iatrobeads and the product was obtained by FC eluting with CH_2Cl_2 in hexane (1:3 to 1:1).

(*S*, *Z*)-*tert*-Butyl 2-cyano-2-(2,2,2-trifluoro-1-(2-nitrophenylimino)ethyl)pentanoate (4a):



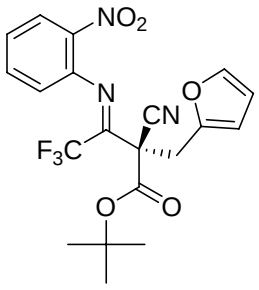
The title compound was obtained according to the general procedure (18 h) as a viscous yellow oil (60.5 mg, 76% yield). ^{1}H NMR ($CDCl_3$) δ 8.21 (dd, *J* 8.3, 1.3 Hz, 1H), 7.63 (m, 1H), 7.33 (m, 1H), 6.80 (d, *J* 8.0 Hz, 1H), 2.21 (dd, *J* 9.3, 7.7 Hz, 2H), 1.70-1.50 (m, 2H), 1.48 (s, 9H), 0.97 (t, *J* 7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 163.0, 150.5 (q, $^2J_{C\text{-}F}$ 30.6 Hz), 141.4, 137.2, 134.6, 125.8, 125.7, 119.1, 117.0 (q, $^1J_{C\text{-}F}$ 290.1 Hz), 114.7, 86.9, 55.6, 36.3, 27.8 (3C), 18.5, 14.0. HRMS calc.: $C_{18}H_{20}F_3N_3NaO_4$ 422.1304; found: 422.1309. The ee was determined by HPLC using two serial Chiralpak AD columns [hexane/*i*PrOH (98:2)]; flow rate 1.0 mL/min; τ_{major} = 14.0 min, τ_{minor} = 14.9 min (86% ee). $[\alpha]_D^{rt}$ -82 (c 0.44, $CHCl_3$).

(*S*, *Z*)-*tert*-Butyl 2-benzyl-2-cyano-4,4,4-trifluoro-3-(2-nitrophenylimino)butanoate (4b):



The title compound was obtained according to the general procedure (17 h) as a viscous yellow oil (88.5 mg, 99 % yield). ^{1}H NMR ($CDCl_3$) δ 8.13 (d, *J* 8.3 Hz, 1H), 7.51 (t, *J* 7.5 Hz, 1H), 7.39-7.20 (m, 6H), 6.50 (br, 1H), 3.60 (d, *J* 14.2 Hz, 1H), 3.50 (d, *J* 14.2 Hz, 1H), 1.37 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 162.0, 149.9 (q, $^2J_{C\text{-}F}$ 30.8 Hz), 140.7, 136.8, 134.3, 132.5, 130.5 (2C), 128.6 (2C), 128.2, 125.6, 125.3, 118.8, 116.7 (q, $^1J_{C\text{-}F}$ 290.0 Hz), 114.3, 86.9, 56.3, 39.9, 27.3 (3C). HRMS calc.: $C_{22}H_{20}F_3N_3NaO_4$ 470.1304; found: 470.1297. The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (99:1)]; flow rate 1.0 mL/min; τ_{major} = 13.5 min, τ_{minor} = 16.8 min (62% ee). $[\alpha]_D^{rt}$ -18 (c 1.00, $CHCl_3$).

(*S*, *Z*)-*tert*-Butyl 2-cyano-4,4,4-trifluoro-2-(furan-2-ylmethyl)-3-(2-nitrophenylimino)butanoate (4c):



The title compound was obtained according to the general procedure (17 h) as a pale yellow solid (61.2 mg, 70 % yield). ^{1}H NMR ($CDCl_3$) δ 8.22 (d, *J* 8.3 Hz, 1H), 7.62 (t, *J* 7.9 Hz, 1H), 7.43 (m, 1H), 7.33 (m, 1H), 6.70 (d, *J* 7.5 Hz, 1H), 6.40 (m, 2H), 3.75 (d, *J* 15.3 Hz, 1H), 3.67 (d, *J* 15.3 Hz, 1H), 1.52 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 161.7, 149.7 (q, $^2J_{C\text{-}F}$ 31.0 Hz), 146.8, 142.9, 140.8, 137.0, 134.3, 125.7, 125.4, 118.8, 116.7 (q, $^1J_{C\text{-}F}$ 289.9 Hz), 113.9, 110.9, 110.6, 87.1, 55.3, 33.2, 27.4 (3C). HRMS calc.: $C_{20}H_{18}F_3N_3NaO_5$ 460.1096; found: 460.1107. The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 8.4 min, τ_{minor} = 9.8 min (65% ee). $[\alpha]_D^{rt}$ +1 (c 0.97, MeOH).

The purified compound was crystallized by diffusing hexane into a solution of the compound in EtOAc, which afforded crystals suitable for X-ray analysis. Compound **4h** crystallizes in the acentric space group $P2_12_12_1$. The absence of significant anomalous scatterers at 17.4 keV (MoKα-radiation) necessitates the use of CuKα-radiation which enables a distinction to be made based on

the anomalous signal in the oxygen atoms. The method is based on the Bayesian analysis by Rob Hooft (‘*Determination of Absolute Structure using Bayesian Statistics on Bijvoet Differences*’ R.W.W. Hooft, L.H. Straver & A.L.Spek). The result of this analysis is shown graphically below. The scatter plot shows that the presented enantiomorph is the correct one with the associated 'Hooft y' parameter: -0.06(8), while the Flack parameter is 0.08(14).

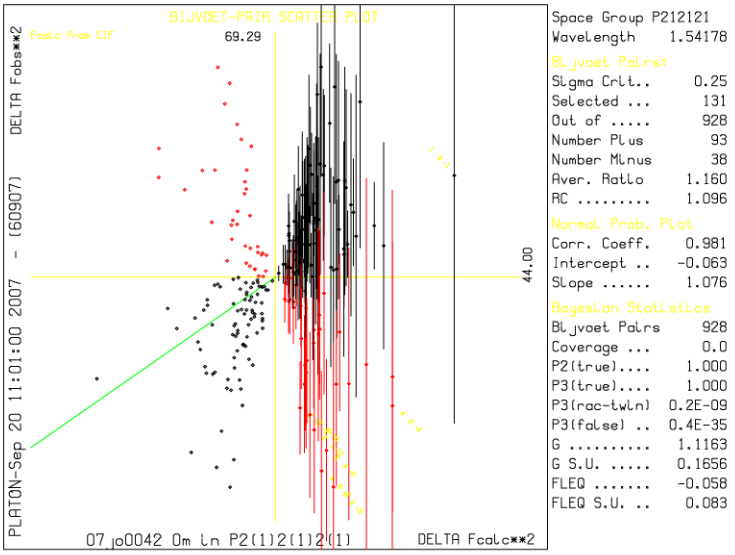


Figure S1 Scatter plot of the calculated vs the observed Bijvoet difference. The points are expected to follow a line from lower left to upper right for the correct handedness.

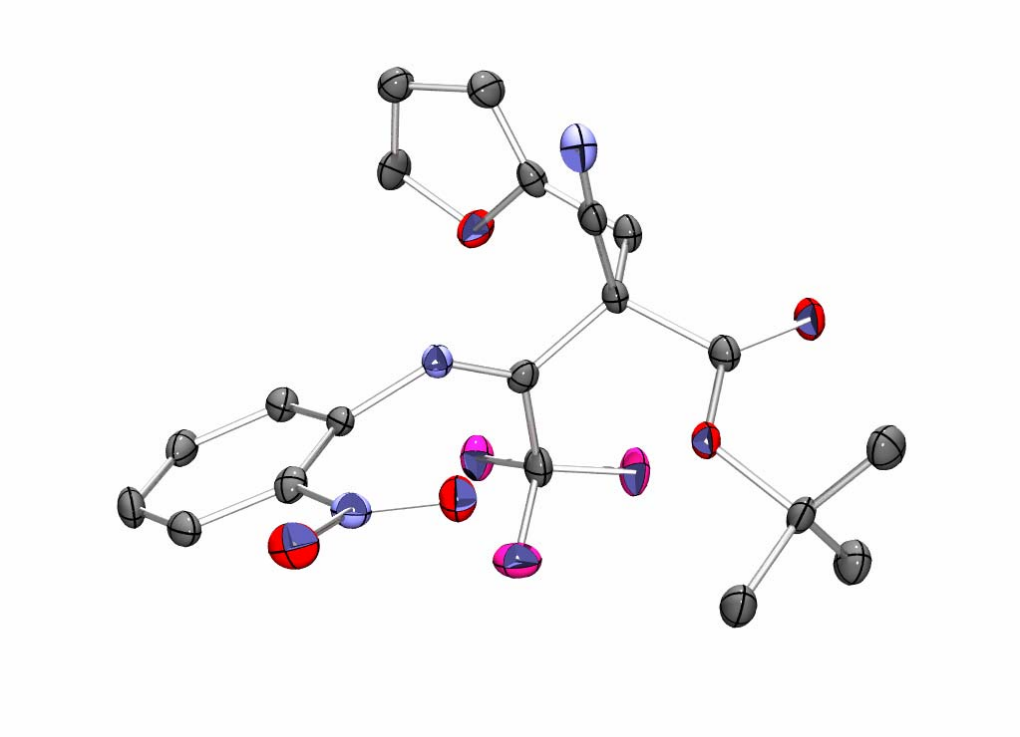
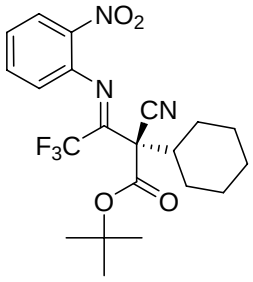


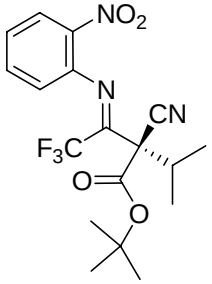
Figure S2 X-ray crystal structure of **4c** – hydrogens are omitted for clarity

(*S, Z*)-*tert*-Butyl 2-cyano-2-cyclohexyl-4,4,4-trifluoro-3-(2-nitrophenylimino)butanoate (4d):



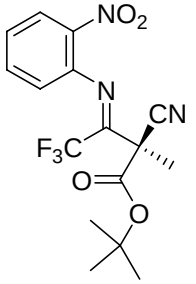
The title compound was obtained according to the general procedure (using 0.6 mmol of **3d**) (7 d) as a viscous yellow oil (26 mg, 30 % yield). ^{1}H NMR ($CDCl_3$) δ 8.15 (d, *J* 7.4 Hz, 1H), 7.56 (t, *J* 8.0 Hz, 1H), 7.25 (t, *J* 7.3 Hz, 1H), 6.71 (d, *J* 7.9 Hz, 1H), 2.53 (t, *J* 11.7 Hz, 1H), 2.00 (t, *J* 12.1 Hz, 1H), 1.86-1.08 (m, 9H), 1.49 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 162.2, 149.4 (q, $^{2}J_{C\text{-}F}$ 30.3 Hz), 141.5, 136.6, 134.4, 125.5, 125.4, 118.7, 116.9 (q, $^{1}J_{C\text{-}F}$ 290.7 Hz), 113.8, 86.6, 60.1, 41.8, 28.9, 28.4, 27.6 (3C), 26.0, 25.9, 25.6. HRMS calc.: $C_{21}H_{24}F_3N_3NaO_4$ 462.1617; found: 462.1622. The ee was determined by HPLC using two serial Chiralpak AD columns [hexane/*i*PrOH (99:1)]; flow rate 1.0 mL/min; τ_{major} = 19.1 min, τ_{minor} = 20.5 min (86% ee). $[\alpha]_D^{rt}$ -58 (c 1.01, $CHCl_3$).

(*S, Z*)-*tert*-Butyl 2-cyano-4,4,4-trifluoro-2-isopropyl-3-(2-nitrophenylimino)butanoate (4e):



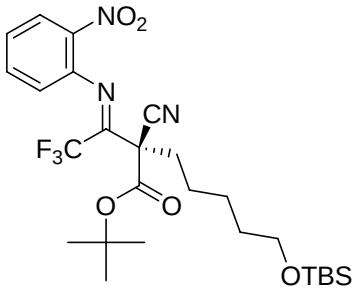
The title compound was obtained according to the general procedure (using 0.6 mmol of **3e**) (7 d) as a viscous yellow oil (21.5 mg, 27% yield). ^{1}H NMR ($CDCl_3$) δ 8.22 (d, *J* 8.3 Hz, 1H), 7.63 (t, *J* 8.6 Hz, 1H), 7.32 (t, *J* 8.5 Hz, 1H), 7.78 (d, *J* 8.2 Hz, 1H), 2.94 (m, 1H), 1.57 (s, 9H), 1.29 (d, *J* 6.7 Hz, 3H), 1.21 (d, *J* 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 162.3, 149.5 (q, $^{2}J_{C\text{-}F}$ 30.6 Hz), 141.4, 136.7, 134.4, 125.5, 125.4, 118.6, 116.9 (q, $^{1}J_{C\text{-}F}$ 290.8 Hz), 113.5, 86.7, 60.4, 32.9, 27.6 (3C), 19.0, 18.4. HRMS calc.: $C_{18}H_{20}F_3N_3NaO_4$ 422.1304; found: 422.1309. The ee was determined by HPLC using two serial Chiralpak AD columns [hexane/*i*PrOH (99:1)]; flow rate 1.0 mL/min; τ_{major} = 16.8 min, τ_{minor} = 17.8 min (90% ee). $[\alpha]_D^{rt}$ -75 (c 0.52, $CHCl_3$).

(*S, Z*)-*tert*-Butyl 2-cyano-4,4,4-trifluoro-2-methyl-3-(2-nitrophenylimino)butanoate (4f):



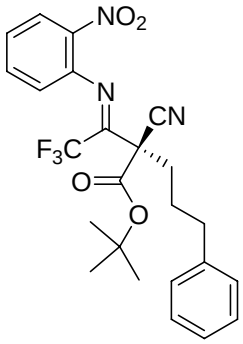
The title compound was obtained according to the general procedure (12 h) as a green solid (67 mg, 90 % yield). ^{1}H NMR ($CDCl_3$) δ 8.21 (d, *J* 8.3 Hz, 1H), 7.64 (t, *J* 8.0 Hz, 1H), 7.33 (t, *J* 7.3 Hz, 1H), 6.83 (d, *J* 8.0 Hz, 1H), 1.98 (s, 3H), 1.55 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 163.2, 150.8 (q, $^{2}J_{C\text{-}F}$ 30.7 Hz), 140.9, 137.0, 134.4, 125.7, 125.4, 118.9, 116.7 (q, $^{1}J_{C\text{-}F}$ 289.6 Hz), 115.1, 86.7, 50.5, 27.4 (3C), 21.0. HRMS calc.: $C_{16}H_{16}F_3N_3NaO_4$ 394.0991; found: 394.0988. The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (99:1)]; flow rate 1.0 mL/min; τ_{major} = 8.8 min, τ_{minor} = 9.2 min (84% ee). $[\alpha]_D^{rt}$ -34 (c 0.82, $CHCl_3$).

(*S, Z*)-*tert*-Butyl 7-(tert-butyldimethylsilyloxy)-2-cyano-2-(2,2,2-trifluoro-1-(2-nitrophenylimino)ethyl)heptanoate (4g):



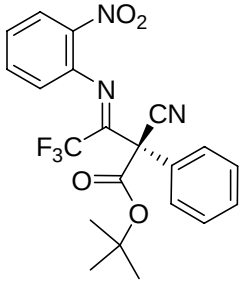
The title compound was obtained according to the general procedure (16 h) as a viscous yellow oil (106 mg, 95 % yield). ^{1}H NMR ($CDCl_3$) δ 8.22 (d, *J* 8.3 Hz, 1H), 7.63 (t, *J* 7.7 Hz, 1H), 7.33 (m, 1H), 6.80 (d, *J* 7.9 Hz, 1H), 3.60 (t, *J* 6.3 Hz, 2H), 2.31 (t, *J* 8.4 Hz, 2H), 1.76-1.40 (m, 6H), 1.55 (s, 9H), 0.87 (s, 9H), 0.03 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 162.7, 150.3 (q, $^{2}J_{C\text{-}F}$ 30.6 Hz), 141.1, 136.9, 134.3, 125.6, 125.4, 118.8, 116.8 (q, $^{1}J_{C\text{-}F}$ 290.1 Hz), 114.4, 86.6, 62.7, 55.3, 34.1, 32.3, 27.5 (3C), 25.9 (3C), 25.5, 24.5, 18.3, -5.4 (2C). HRMS calc.: $C_{26}H_{38}F_3N_3NaO_5Si$ 580.2431; found: 580.2432. The ee was determined by HPLC using two serial Chiralpak AD columns [hexane/*i*PrOH (99:1)]; flow rate 1.0 mL/min; τ_{major} = 10.5 min, τ_{minor} = 11.0 min (88% ee). $[\alpha]_D^{rt}$ -28 (c 1.02, $CHCl_3$).

(*S, Z*)-*tert*-Butyl 2-cyano-5-phenyl-2-(2,2,2-trifluoro-1-(2-nitrophenylimino)ethyl)pentanoate (4h):



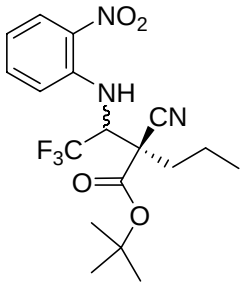
The title compound was obtained according to the general procedure (16 h) as a viscous yellow oil (93 mg, 98 % yield). ^{1}H NMR ($CDCl_3$) δ 8.14 (d, *J* 8.3 Hz, 1H), 7.54 (m, 1H), 7.25 (t, *J* 8.0 Hz, 1H), 7.22-7.07 (m, 5H), 6.69 (d, *J* 8.0 Hz, 1H), 2.66 (t, *J* 7.4, 2H), 2.32-2.21 (m, 2H), 2.01-1.81 (m, 2H), 1.45 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 162.6, 150.1 (q, $^{2}J_{C\text{-}F}$ 30.6 Hz), 141.0, 140.6, 136.9, 134.3, 128.4 (2C), 128.2 (2C), 126.0, 125.6, 125.4, 118.8, 116.7 (q, $^{1}J_{C\text{-}F}$ 290.2 Hz), 114.2, 86.7, 55.0, 35.1, 33.4, 27.4 (3C), 26.2. HRMS calc.: $C_{24}H_{24}F_3N_3NaO_4$ 498.1617; found: 498.1631. The ee was determined by HPLC using a Chiralcel OD column [hexane/*i*PrOH (99:1)]; flow rate 1.0 mL/min; τ_{minor} = 16.8 min, τ_{major} = 17.8 min (90% ee). $[\alpha]_D^{rt}$ -33 (c 0.35, $CHCl_3$).

(*S, Z*)-*tert*-Butyl 2-cyano-4,4,4-trifluoro-3-(2-nitrophenylimino)-2-phenylbutanoate (4i):



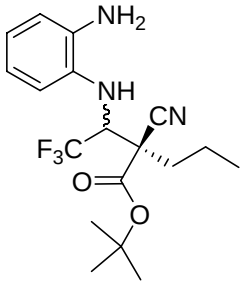
The title compound was obtained according to the general procedure (using 0.6 mL of 40% K_3PO_4 as a base) (5 d) as a viscous yellow oil (67.5 mg, 78 % yield). ^{1}H NMR ($CDCl_3$) δ 8.17 (d, *J* 8.4 Hz, 1H), 7.69 (d, *J* 7.9 Hz, 2H), 7.58 (t, *J* 7.9 Hz, 1H), 7.50-7.38 (m, 3H), 7.31-7.25 (m, 1H), 6.76 (d, *J* 8.1 Hz, 1H), 1.56 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 161.9, 151.0 (q, $^{2}J_{C\text{-}F}$ 31.3 Hz), 140.9, 136.7, 134.3, 129.7, 129.2, 129.0 (2C), 128.2 (2C), 125.5, 125.4, 118.9, 116.7 (q, $^{1}J_{C\text{-}F}$ 289.9 Hz), 113.9, 87.3, 27.5 (3C). HRMS calc.: $C_{21}H_{18}F_3N_3NaO_4$ 456.1147; found: 456.1143. The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (99:1)]; flow rate 1.0 mL/min; τ_{major} = 19.0 min, τ_{minor} = 20.2 min (34% ee). $[\alpha]_D^{rt}$ -5 (c 1.00, $CHCl_3$).

(*S*)-*tert*-Butyl 2-cyano-2-(2,2,2-trifluoro-1-(2-nitrophenylamino)ethyl)pentanoate (5):



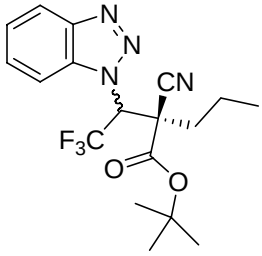
To a solution of **4c** (81.3 mg, 0.20 mmol) in EtOH (2 mL) was added $LiClO_4$ (21.2 mg, 0.20 mmol, 1 equiv.). The mixture was cooled to -78 °C and at this temperature $NaBH_4$ (15.2 mg, 0.40 mmol, 2 equiv.) was added. This mixture was stirred for 1 h at -78 °C and then an additional equivalent of $NaBH_4$ was added. After 20 min the yellow mixture was allowed to warm to rt and was quenched by the addition of 2 mL sat. aq. NH_4Cl. The mixture was diluted with water and extracted 3 x with Et_2O. The combined organic extracts were washed with water and brine and dried over Na_2SO_4. The product was obtained after FC on SiO_2 eluting with hexane/Et_2O 4:1 as a bright yellow oil (68.6 mg, 84%, dr 7:1). Major diastereomer: ^{1}H NMR ($CDCl_3$) δ 8.74 (br d, *J* 10.4 Hz, 1H), 8.22 (d, *J* 8.5 Hz, 1H), 7.54 (t, *J* 8.6 Hz, 1H), 6.95 (d, *J* 8.6 Hz, 1H), 6.87 (t, *J* 8.4 Hz, 1H), 4.62 (m, 1H), 2.07 (td, *J* 12.8, 4.7 Hz, 1H), 1.91 (td, *J* 12.8, 4.2 Hz, 1H), 1.70-1.50 (m, 2H), 1.44 (s, 9H), 0.96 (t, *J* 7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 165.1, 142.6, 136.4, 133.8, 127.1, 124.0 (q, $^{1}J_{C\text{-}F}$ 290.1 Hz), 118.4, 116.1, 113.8, 86.5, 58.7, (q, $^{2}J_{C\text{-}F}$ 30.2 Hz), 51.3, 36.7, 27.5 (3C), 18.5, 13.7. HRMS calc.: $C_{18}H_{22}F_3N_3NaO_4$ 424.1460; found: 424.1454.

(*S*)-*tert*-Butyl 2-(1-(2-aminophenylamino)-2,2,2-trifluoroethyl)-2-cyanopentanoate (6):



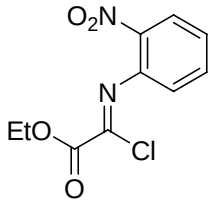
To a stirred solution of **5** (107.3 mg, 0.27 mmol) in EtOH, $Pd(OH)_2$ on carbon 20% (10% w/w, 10.7 mg) was added. Hydrogen atmosphere was created with balloon technique. After 20 h the reaction mixture was filtered on celite and evaporated. FC on silica gel (hexane/Et_2O 7:3) afforded the product as a clear oil (88.2 mg, 99% yield). Major diastereomer: ^{1}H NMR ($CDCl_3$) δ 6.90-6.70 (m, 4H), 4.50 (m, 1H), 4.38 (d, *J* 11.0 Hz, 1H), 3.28 (br, 2H), 2.16-1.82 (m, 2H), 1.70-1.55 (m, 2H), 1.41 (s, 9H), 0.96 (t, *J* 7.3 Hz, 3H). ^{13}C NMR δ ($CDCl_3$) δ 165.7, 134.8, 134.1, 124.6 (q, $^1J_{C\text{-}F}$ 285.9 Hz), 121.0, 120.7, 118.1, 116.7, 114.2, 85.7, 59.4 (q, $^2J_{C\text{-}F}$ 29.4 Hz), 52.8, 36.4, 27.4 (3C), 18.6, 13.6. HRMS calc.: $C_{18}H_{24}F_3N_3NaO_2$ 394.1718; found: 394.1717.

(*S*)-*tert*-Butyl 2-(1-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-2,2,2-trifluoroethyl)-2-cyanopentanoate (7):



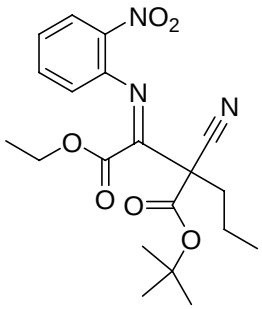
To a stirred solution of **7** (37.1 mg, 0.1 mmol) in EtOH (4.2 mL) and AcOH (0.6 mL) a 0.8 M aqueous solution of $NaNO_2$ (1.2 mL, 1 mmol) was added. The mixture was stirred for 3 h at room temperature, then a saturated aq. solution of $NaHCO_3$ was added. The phases were separated and the aq. phase was extracted twice with CH_2Cl_2. The collected organic phase was dried over $MgSO_4$ and evaporated. FC on silica gel (hexane/Et_2O 9:1) afforded the product as a white solid (26.7 mg, 70% yield). Major diastereomer: ^{1}H NMR ($CDCl_3$) δ 8.10 (d, *J* 8.4 Hz, 1H), 7.75 (d, *J* 8.4 Hz, 1H), 7.60 (t, *J* 8.1 Hz, 1H), 7.44 (t, *J* 8.1 Hz, 1H), 5.70 (q, *J* 7.1 Hz, 1H), 2.37 (m, 1H), 2.20 (td, *J* 13.0, 4.6 Hz, 1H), 1.90-1.60 (m, 2H), 1.44-1.20 (m, 3H) 1.06 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 163.5, 145.6, 133.1, 128.9, 124.9, 122.7 (q, $^1J_{C\text{-}F}$ 284.6 Hz), 120.3, 115.8, 110.1, 88.5, 63.8 (q, $^2J_{C\text{-}F}$ 32.3 Hz), 52.0, 38.3, 27.0 (3C), 18.7, 13.6. HRMS calc.: $C_{18}H_{21}F_3N_4NaO_2$ 405.1514; found: 405.1521.

Ethyl 2-chloro-2-(2-nitrophenylimino)acetate (2b):



To a solution of ethyl 2-(2-nitrophenylamino)-2-oxoacetate[8] (463.5 mg, 1.95 mmol) in CCl_4 (20 mL) Ph_3P (1.02 g, 3.9 mmol) was added. The mixture was refluxed for 16 h, then solvent was removed and the crude mixture was loaded Iatrobeads and the product was obtained by FC eluting with CH_2Cl_2/hexane 3:1 as a clear oil (135.5 mg, 27% yield). ^{1}H NMR ($CDCl_3$) δ 8.18 (d, *J* 8.4 Hz, 1H), 7.68 (t, *J* 8.0 Hz, 1H), 7.38 (t, *J* 8.0 Hz, 1H), 6.95 (d, *J* 8.0 Hz, 1H), 4.48 (q, *J* 7.1 Hz, 2H), 1.45 (t, *J* 7.1 Hz, 3H).

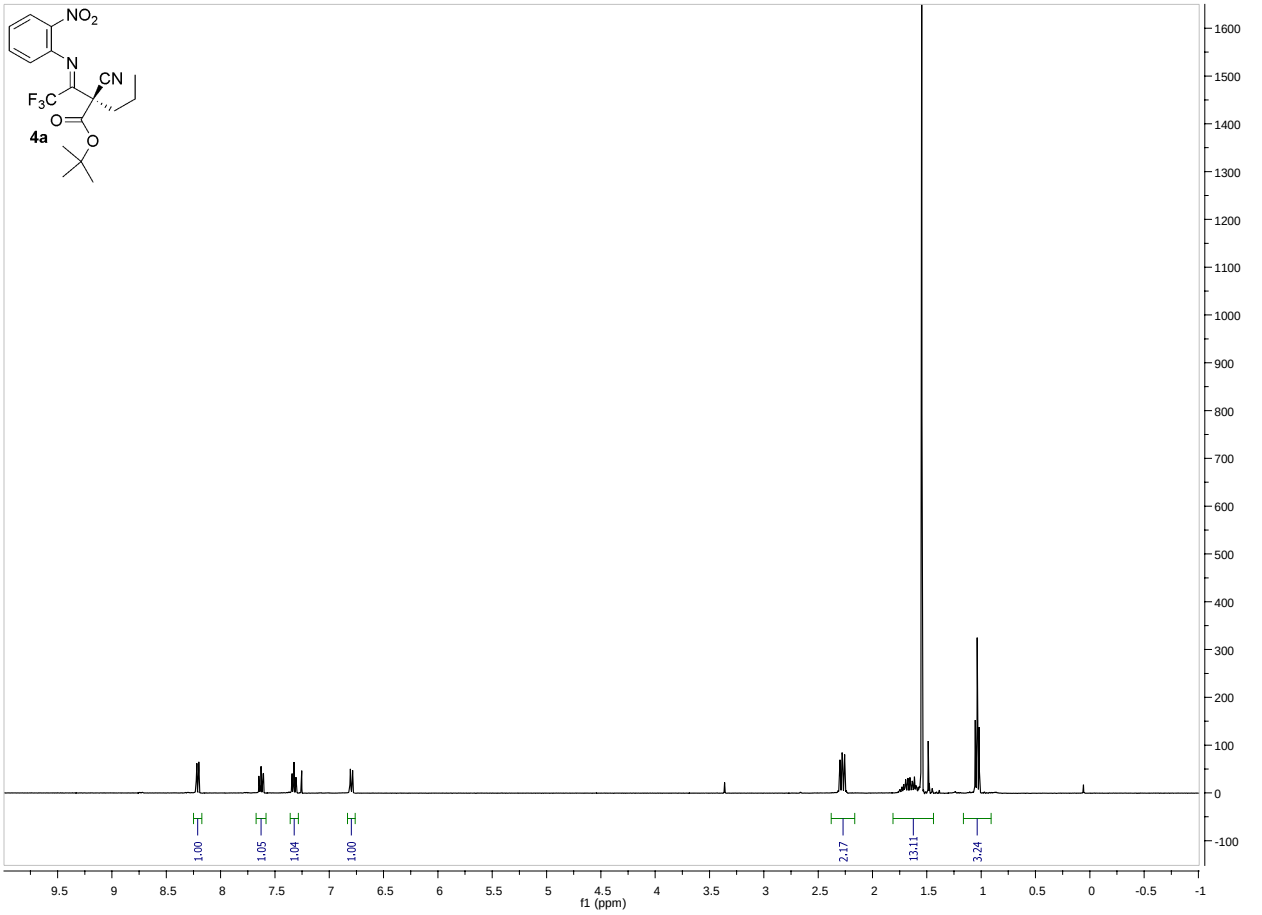
(*Z*)-1-*tert*-Butyl 4-ethyl 2-cyano-3-(2-nitrophenylimino)-2-propylsuccinate (8):



To a sample vial equipped with a magnetic stirring bar was added **3a** (9.1 mg, 0.05 mmol), *o*-xylene/$CHCl_3$ (7:1) 0.33 mL, **2b** (16.7 mg, 0.065 mmol), and the catalyst **1i** (0.5 mg, 0.0005 mmol). The mixture was stirred for a short time at ambient temperature and was then placed at -20 °C. When the mixture had cooled, a cold (-20 °C) solution of 40% aq. K_3PO_4 (0.17 mL) was added and the biphasic mixture was vigorously stirred for 20 h. Then the organic phase was collected, and the aqueous layer was extracted two times with toluene. The combined organic fractions were loaded onto Iatrobeads and the product was obtained by FC eluting with hexane/DCM/Et_2O 94:4:2 as a clear oil (14.2 mg, 71% yield). ^{1}H NMR ($CDCl_3$) δ 8.17 (d, *J* 8.4 Hz, 1H), 7.56 (t, *J* 7.5 Hz, 1H), 7.27 (t, *J* 8.4 Hz, 1H), 6.70 (d, *J* 8.0 Hz, 1H), 4.08 (m, 2H), 2.38-2.21 (m, 2H), 1.80-1.55 (m, 2H), 1.54 (s, 9H), 1.07-0.98 (m, 6H). ^{13}C NMR ($CDCl_3$) δ 164.1, 158.8, 154.1, 144.7, 138.0, 134.5, 125.5, 125.0, 119.0, 116.2, 85.7, 63.0, 56.2, 36.5, 27.9 (3C), 18.6, 14.1, 13.7. HRMS calc.: $C_{20}H_{25}N_3NaO_6$ 426.1641; found: 426.1640. The ee was determined by HPLC

using a Chiralpak AD column [hexane/*i*PrOH (97:3)]; flow rate 1.0 mL/min; τ_{major} = 10.2 min, τ_{minor} = 10.7 min (59% ee). $[\alpha]_D^{rt}$ -8.2 (c 0.62, $CHCl_3$).

Spectra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N
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F3C
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4a
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1.05
1.04
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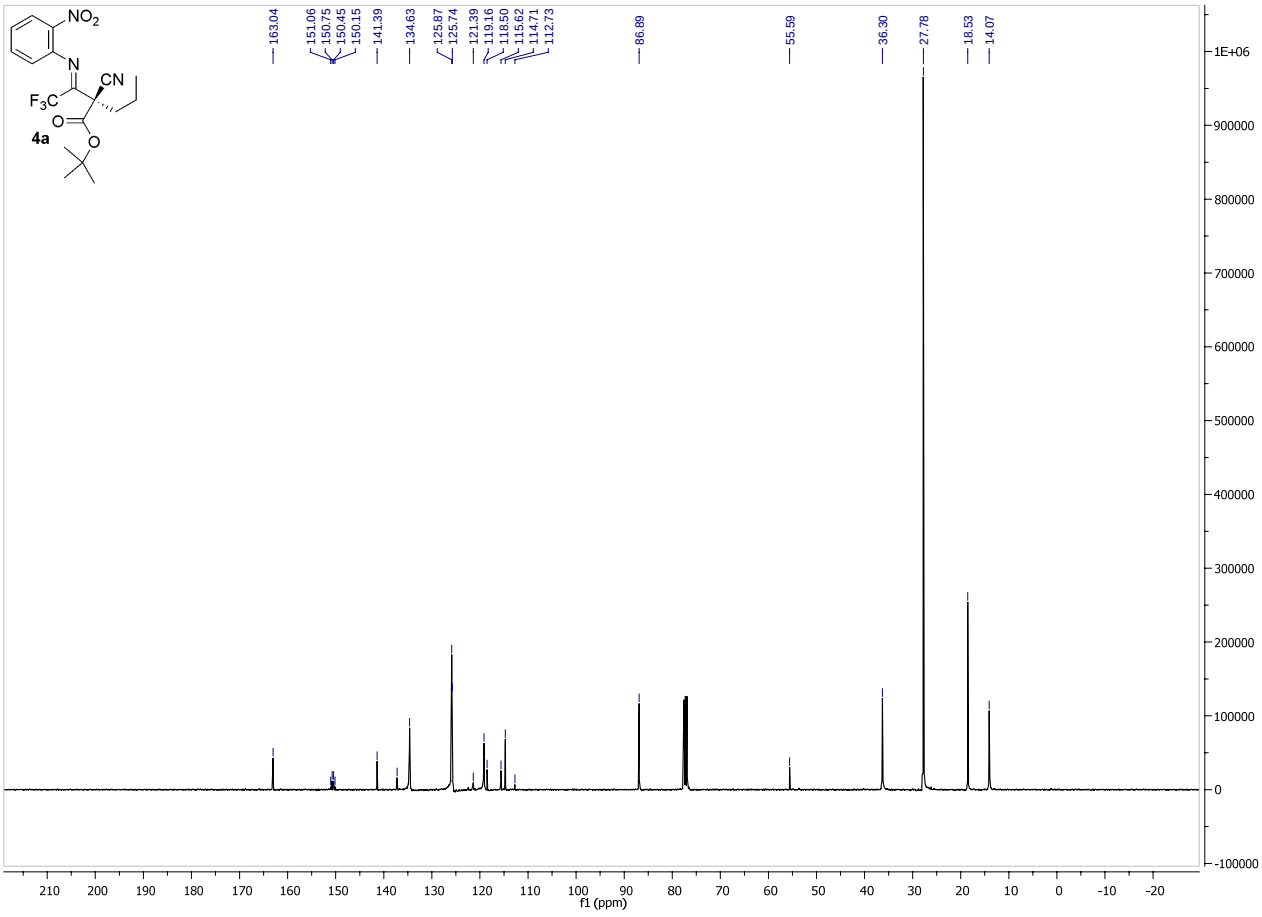
2.17
13.11
3.24
f1 (ppm)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4a
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150.75
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150.15
141.39
134.63
125.87
125.74
121.39
119.16
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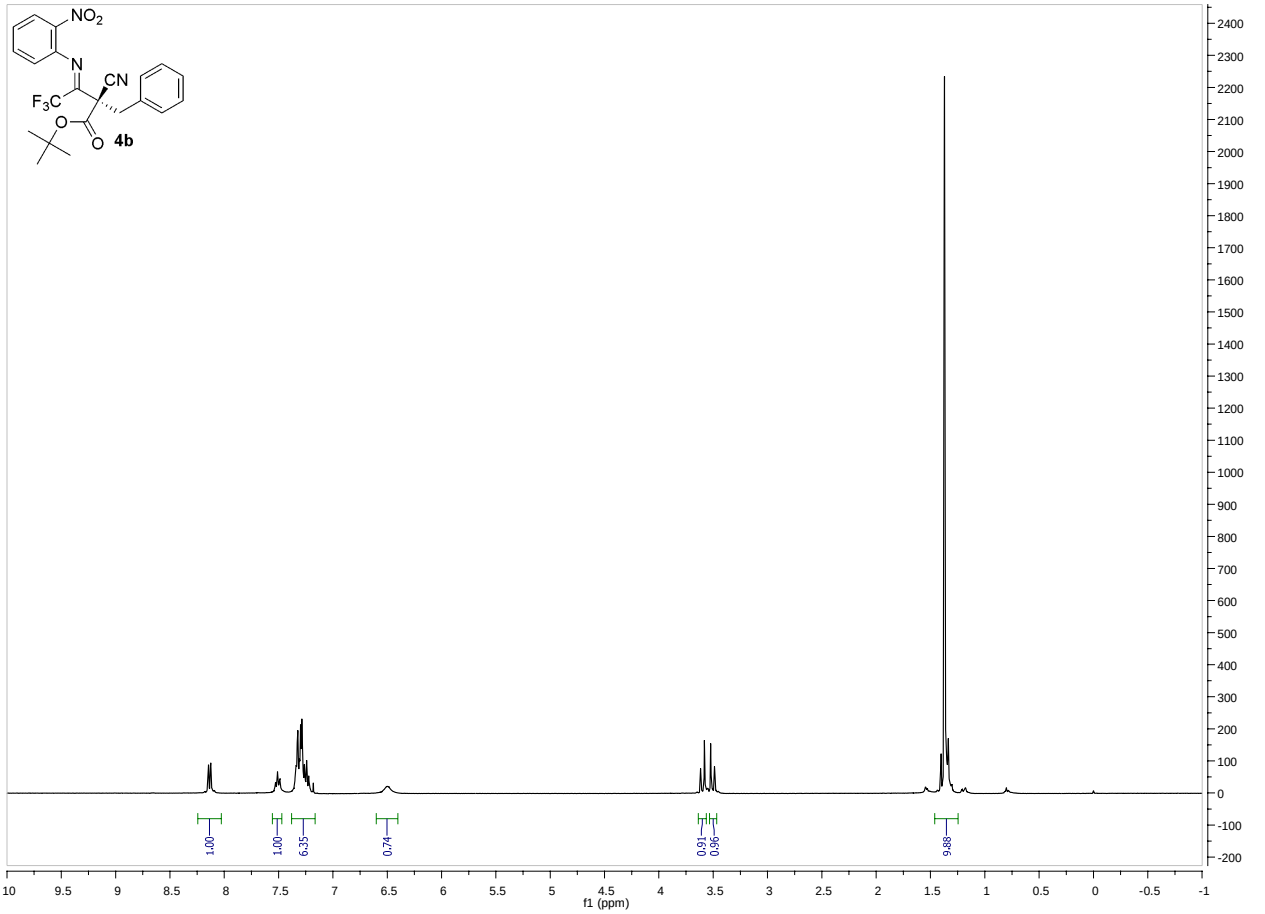
36.30
27.78
18.53
14.07
f1 (ppm)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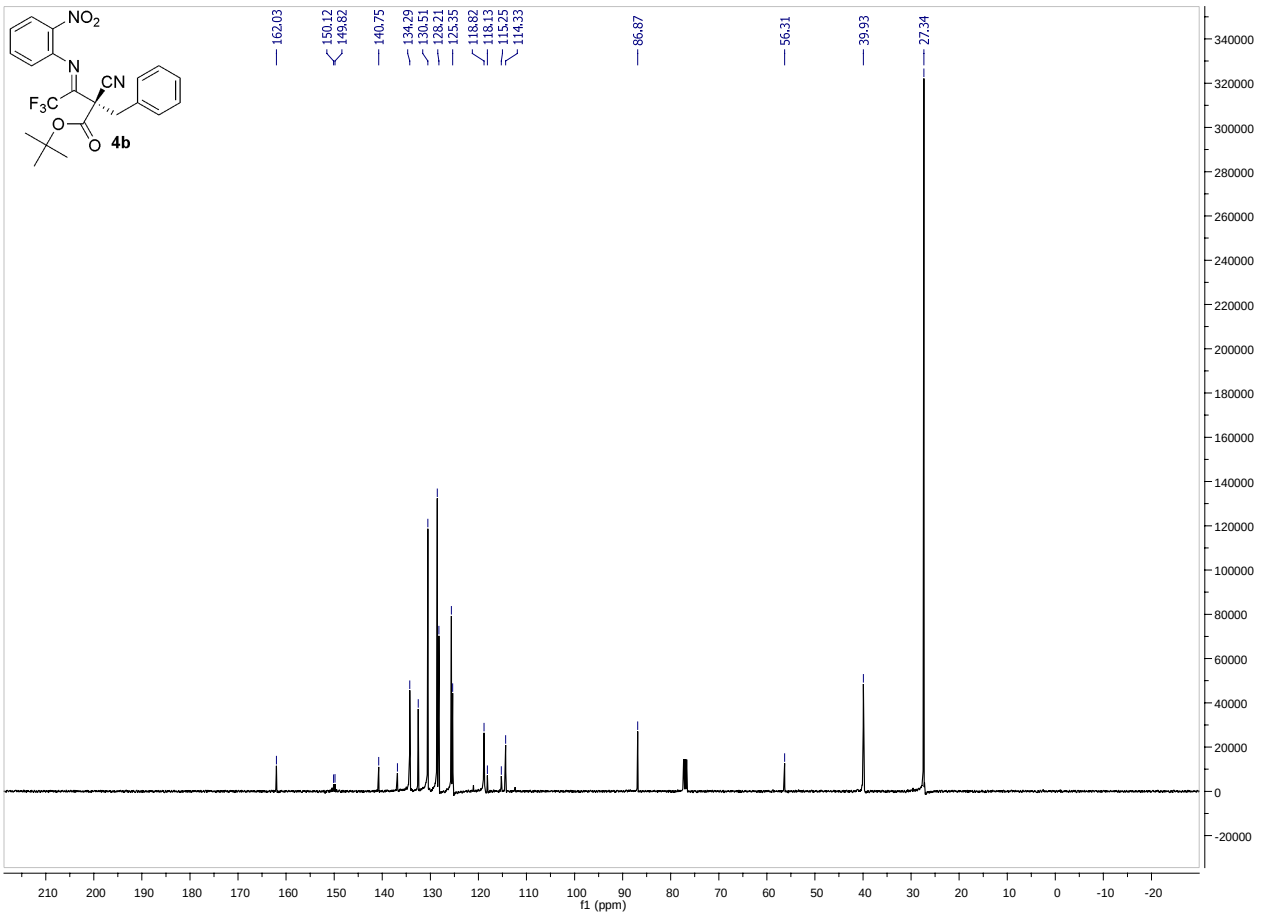
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O
4b
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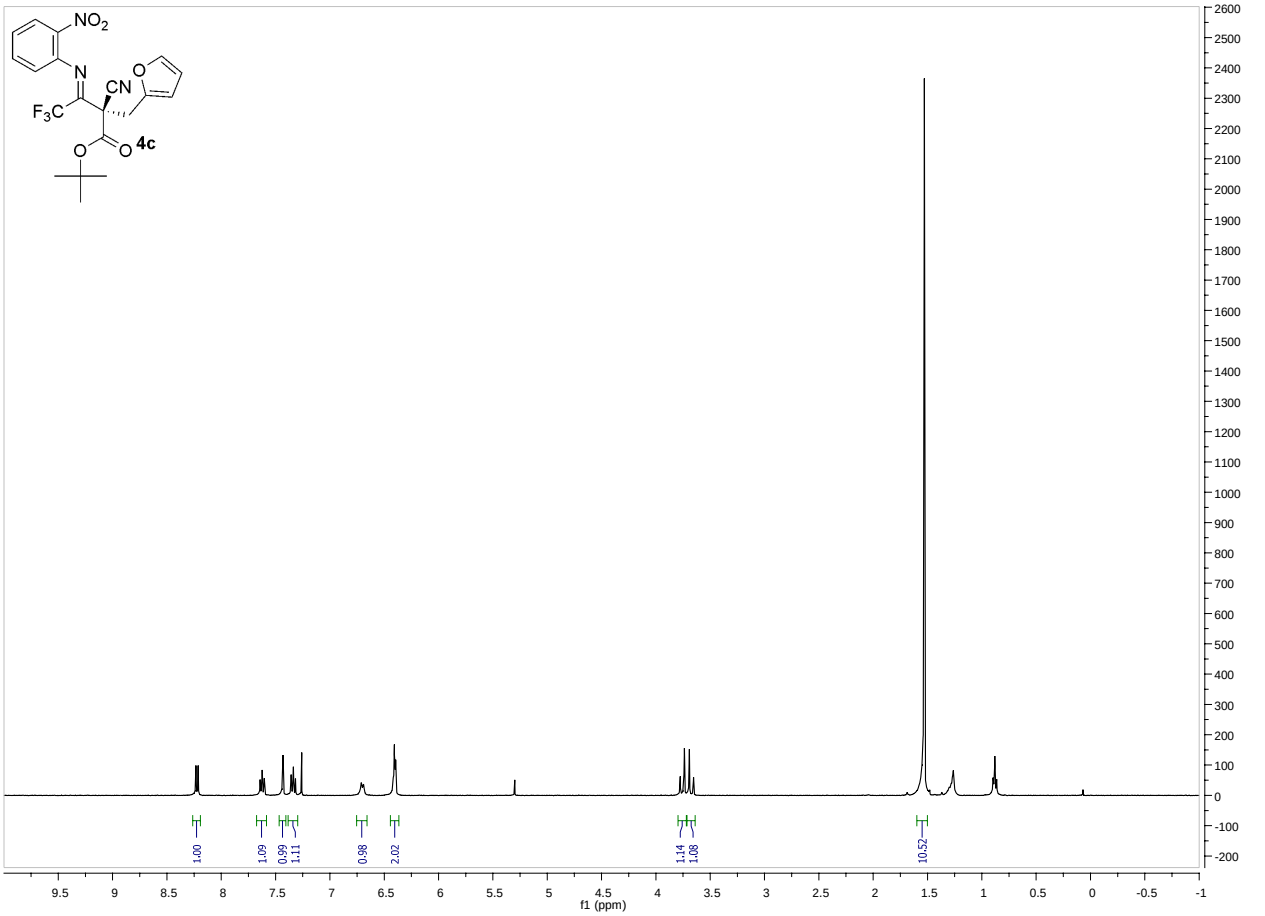
f1 (ppm)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F3C
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0.98
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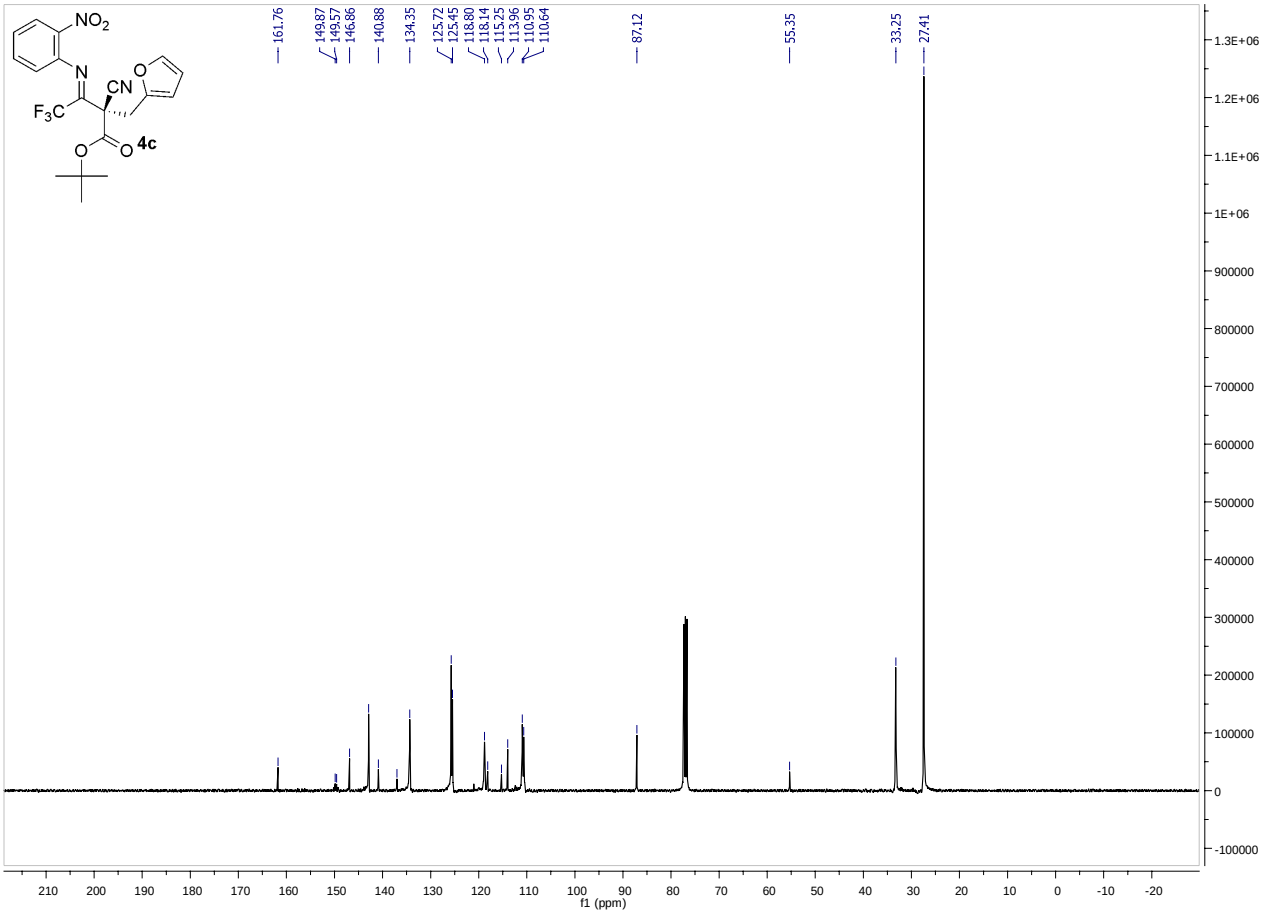
1.14
1.08
10.52
f1 (ppm)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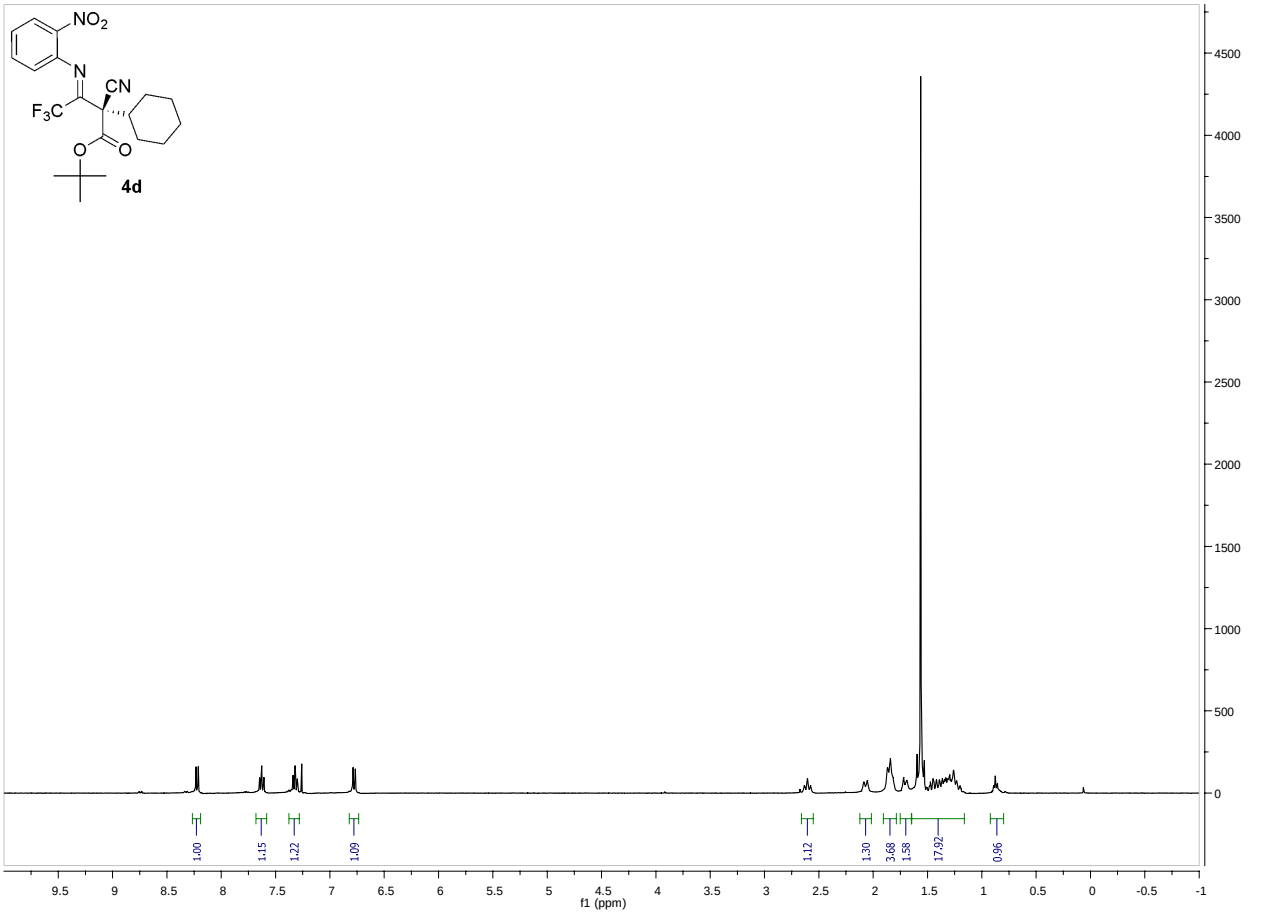
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17.92
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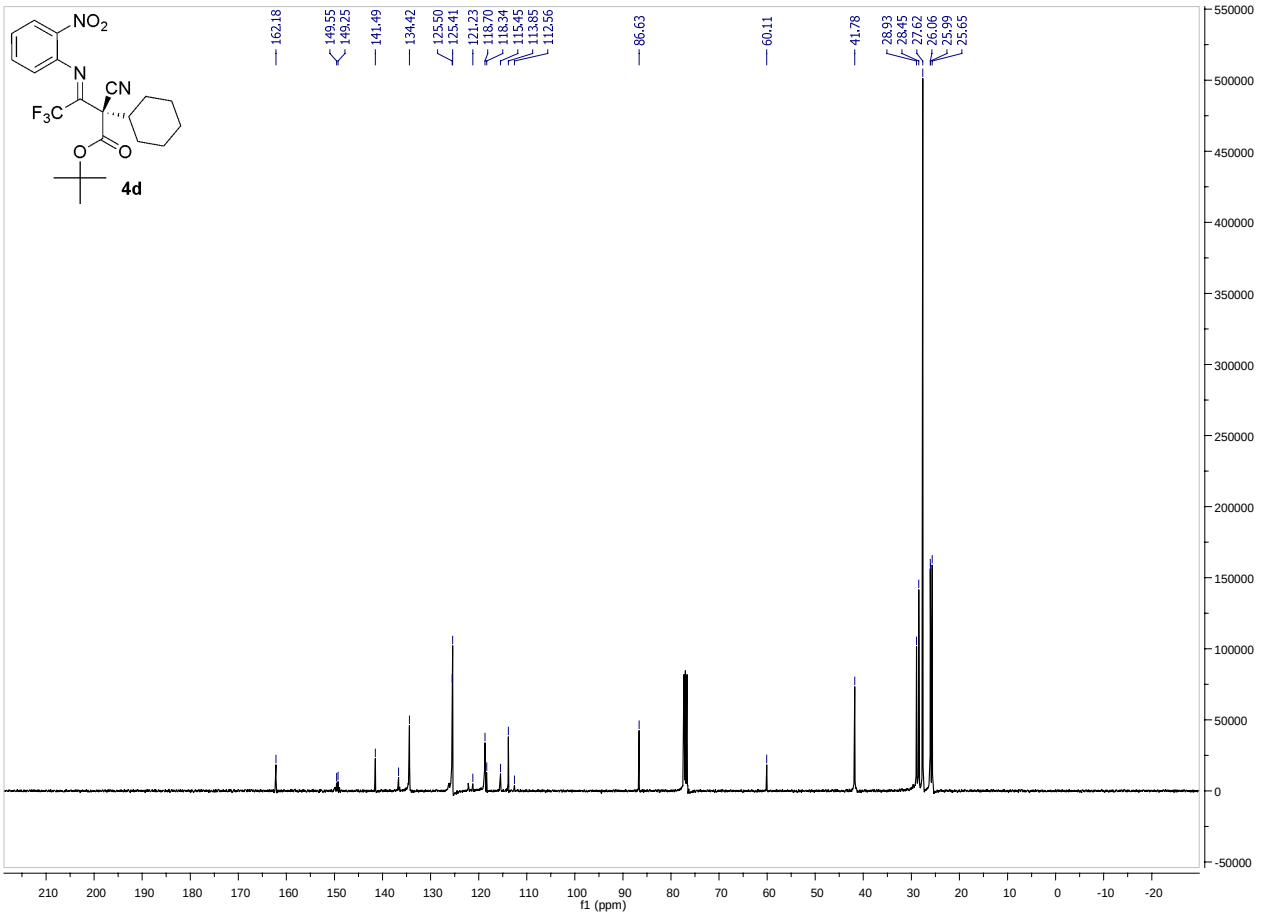
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F3C
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121.23
118.70
118.34
115.45
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112.56
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60.11
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28.45
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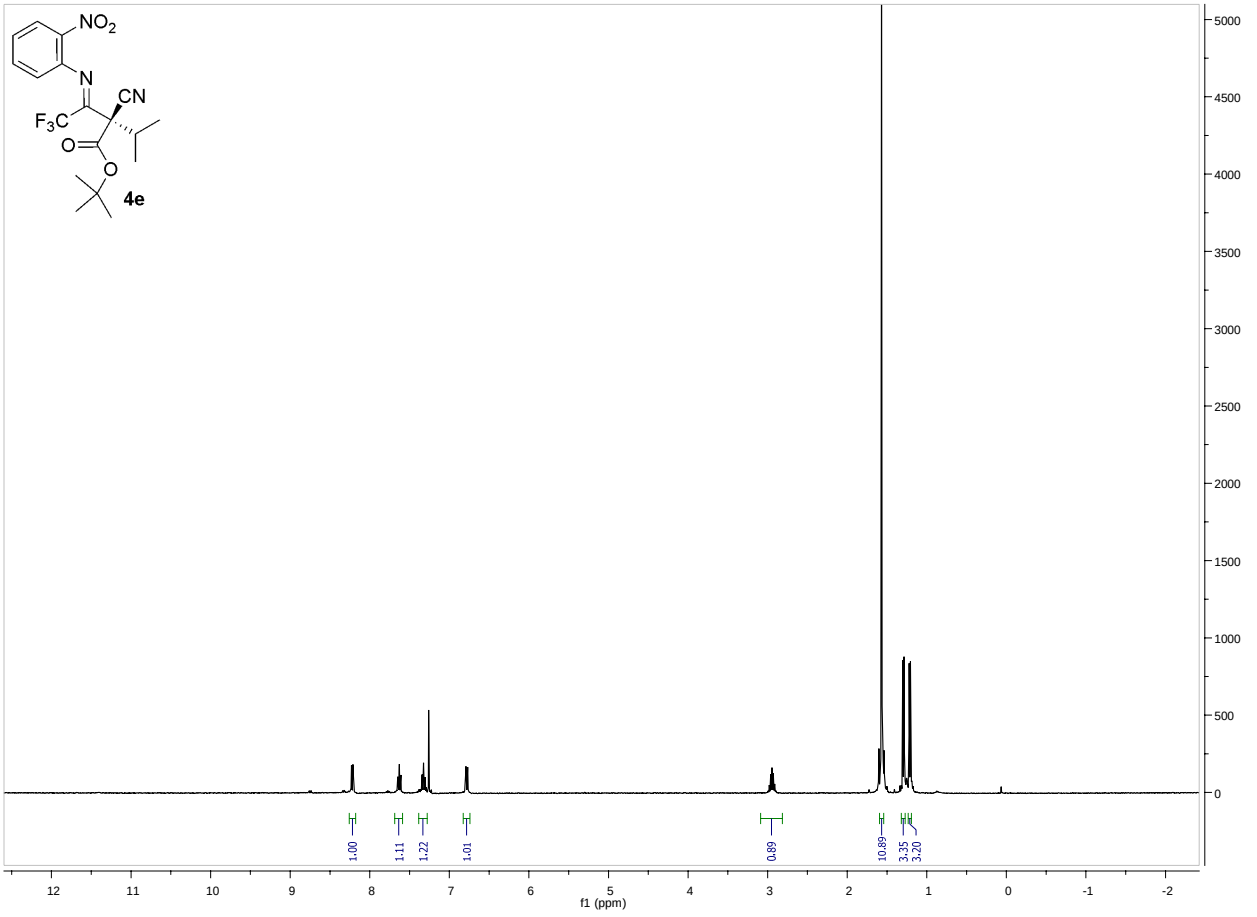
26.06
25.99
25.65
f1 (ppm)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N
CN
F3C
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O
4e
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0.89
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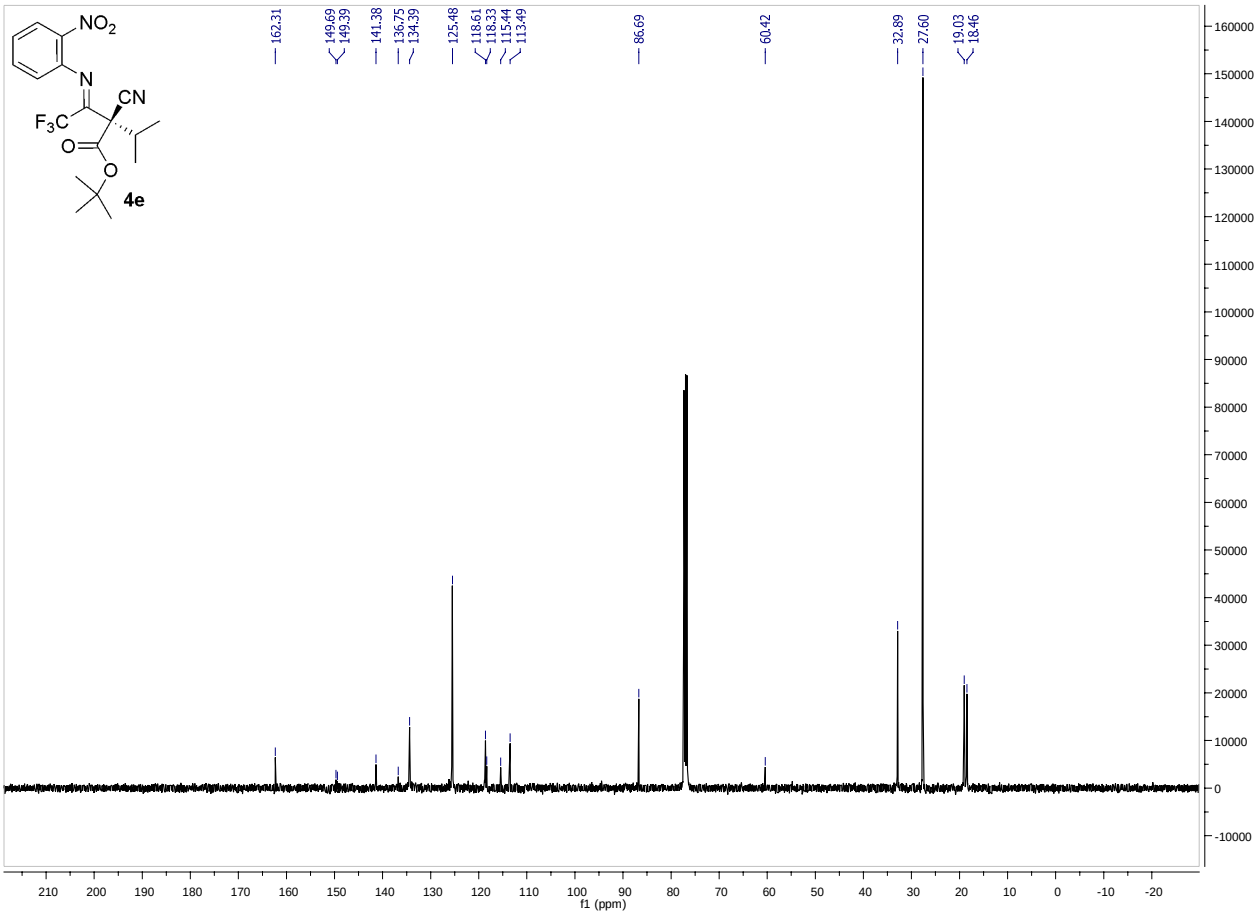
3.20
f1 (ppm)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CN
F3C
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60.42
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27.60
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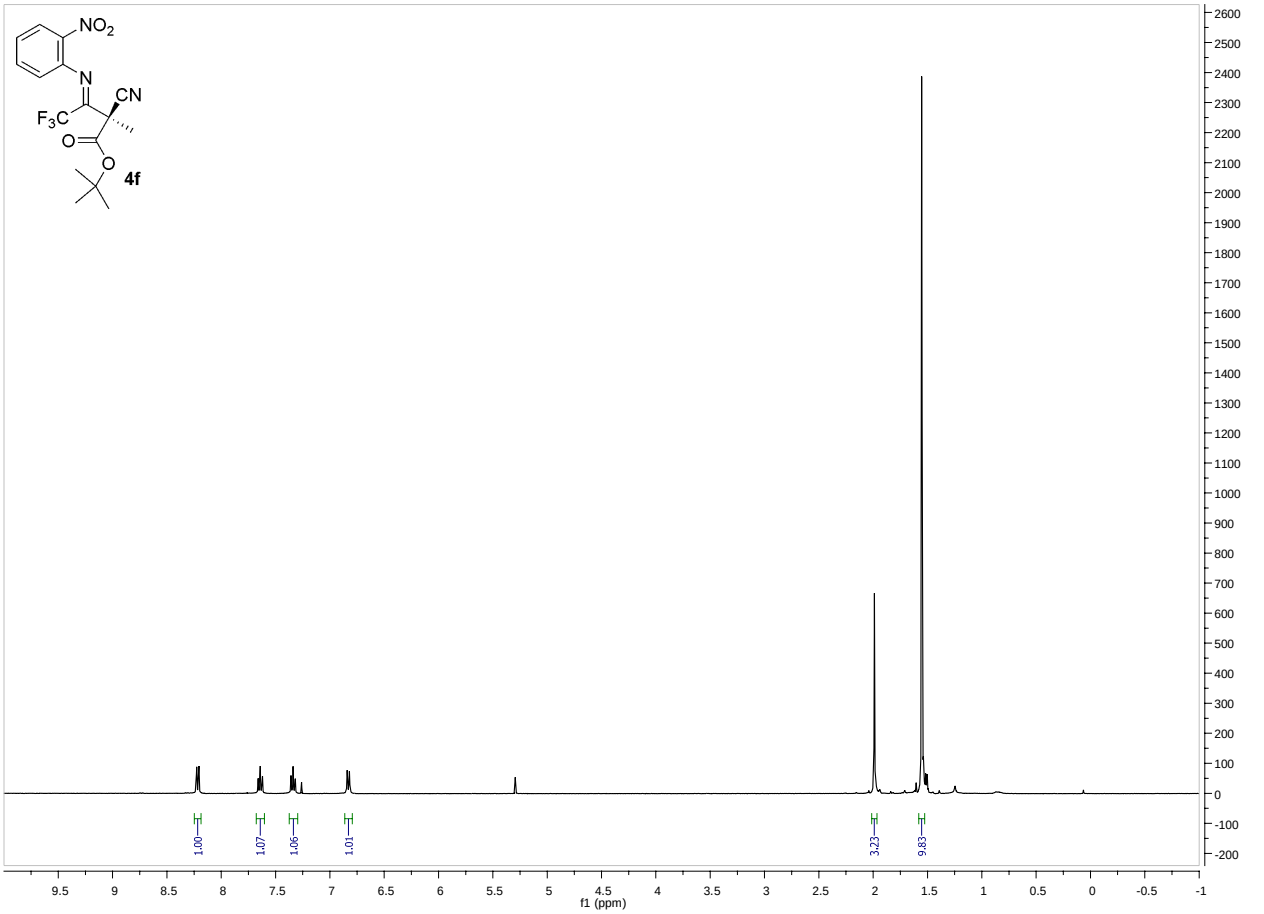
18.46
f1 (ppm)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CN
F3C
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O
4f
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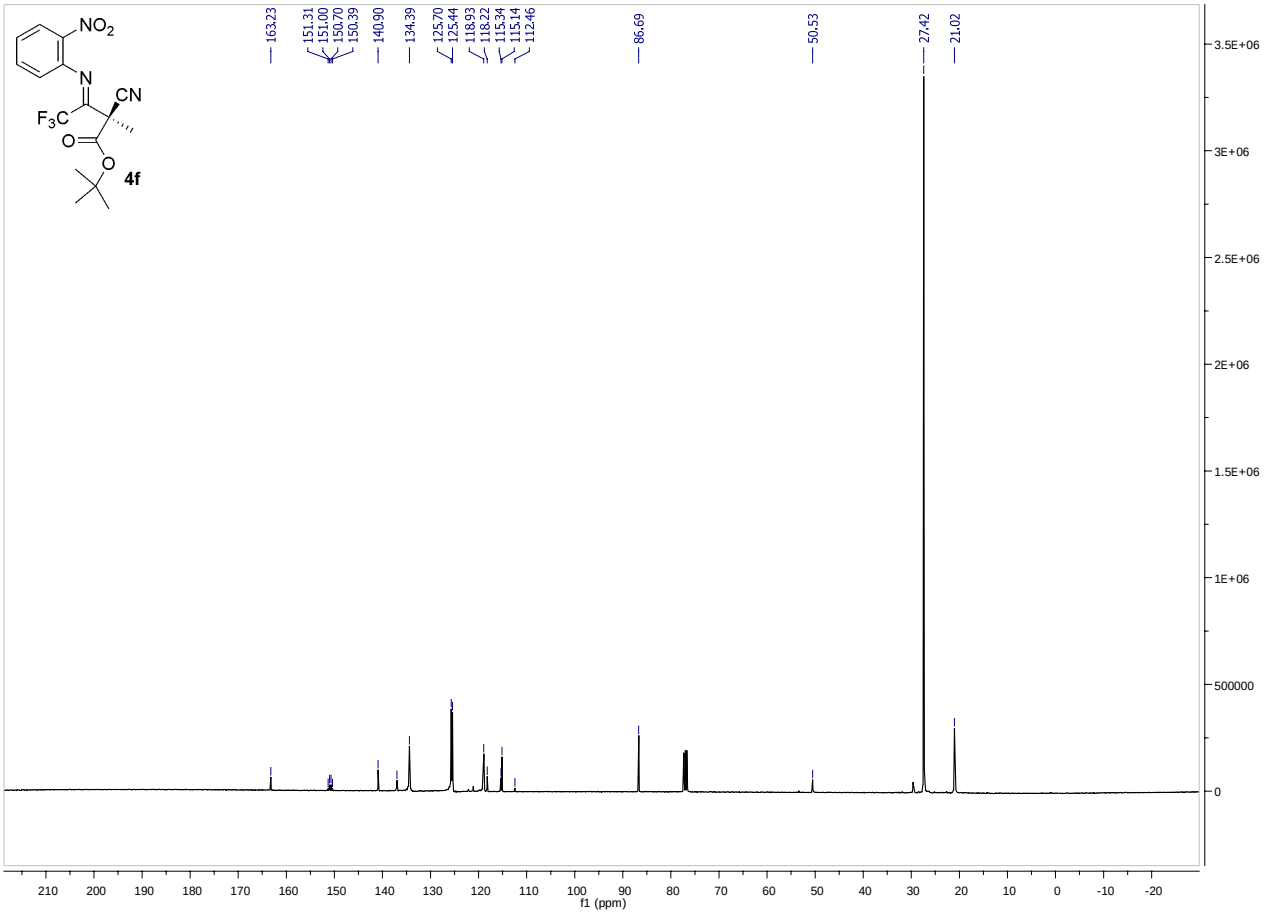
f1 (ppm)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CN
F3C
O
O
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118.22
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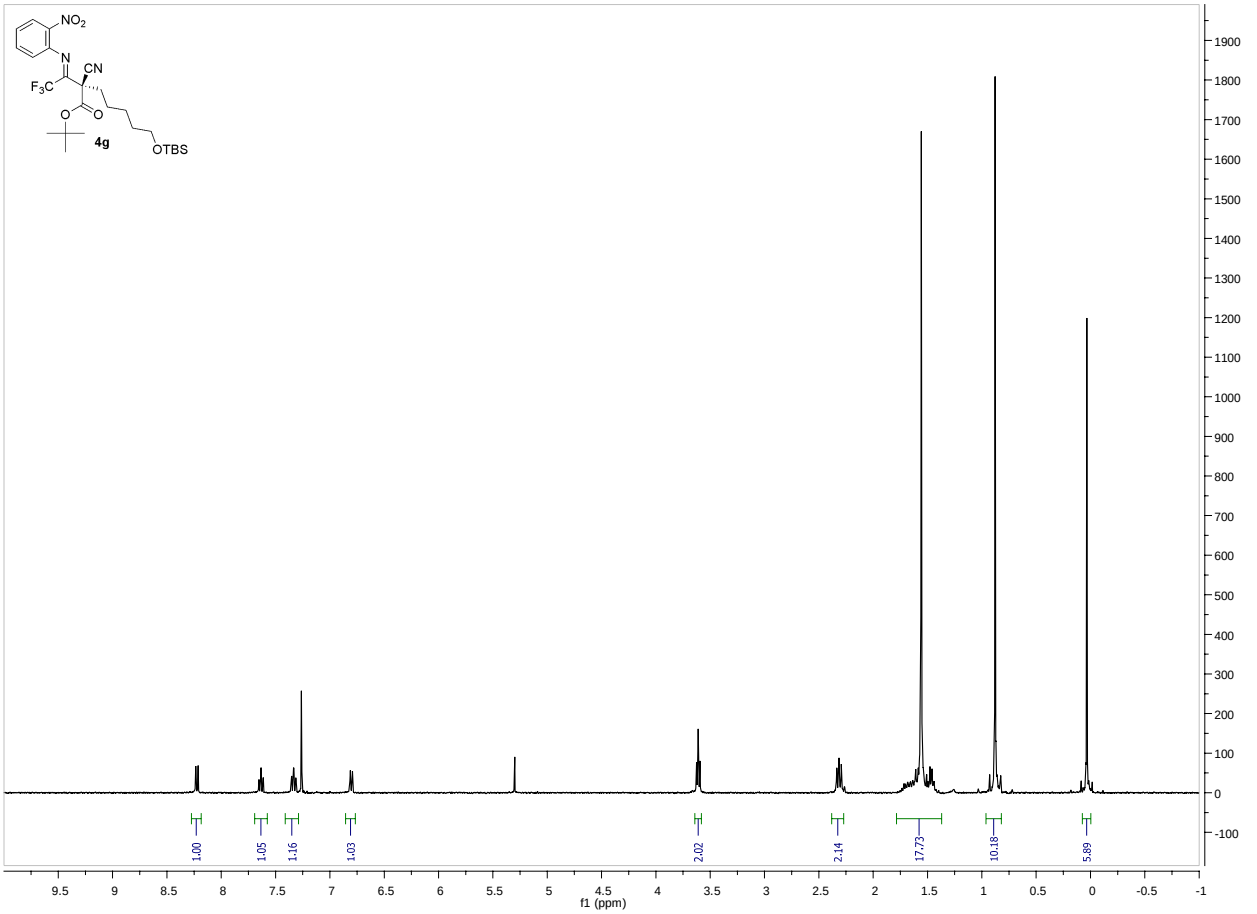
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CN
F3C
O
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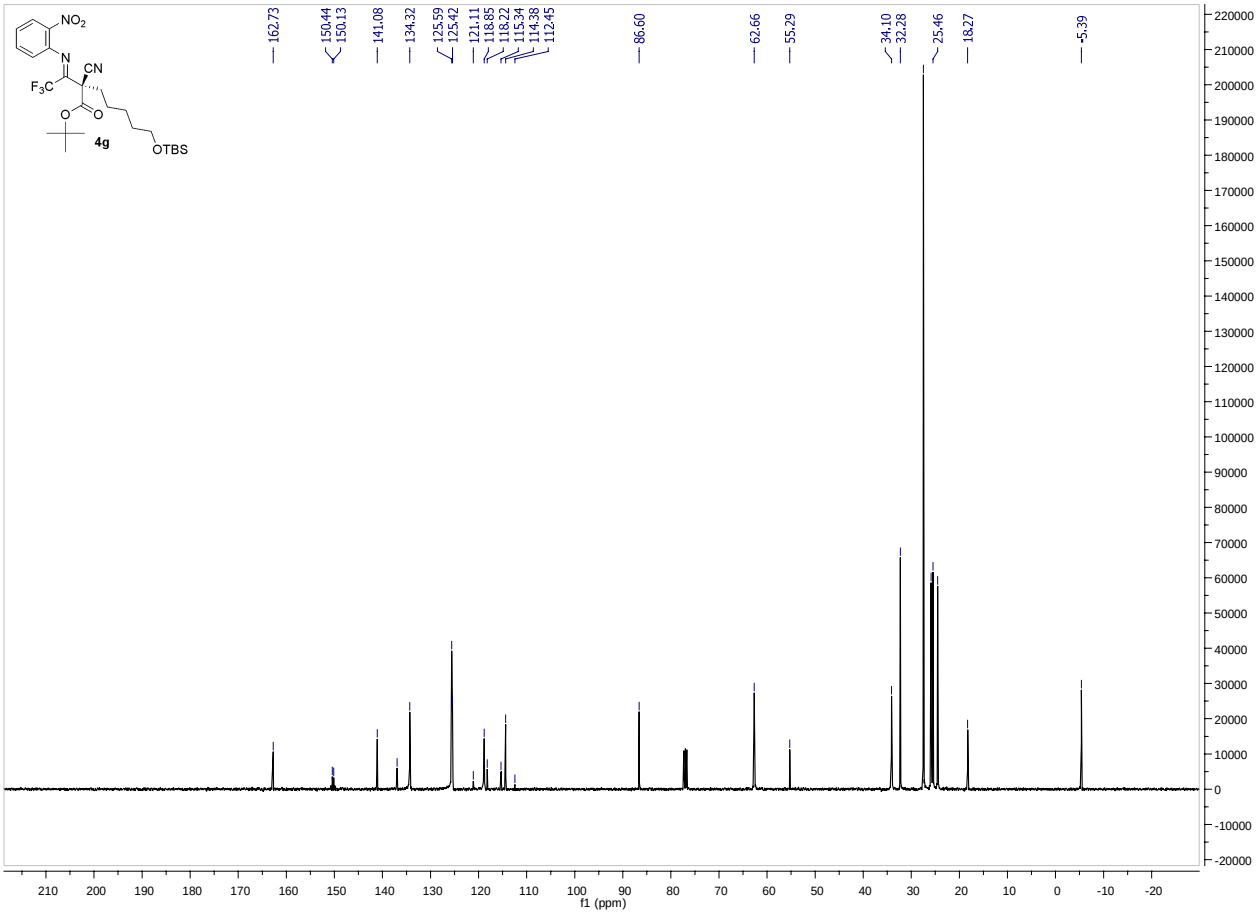
10.18
5.89
f1 (ppm)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CN
F3C
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O
4g
OTBS
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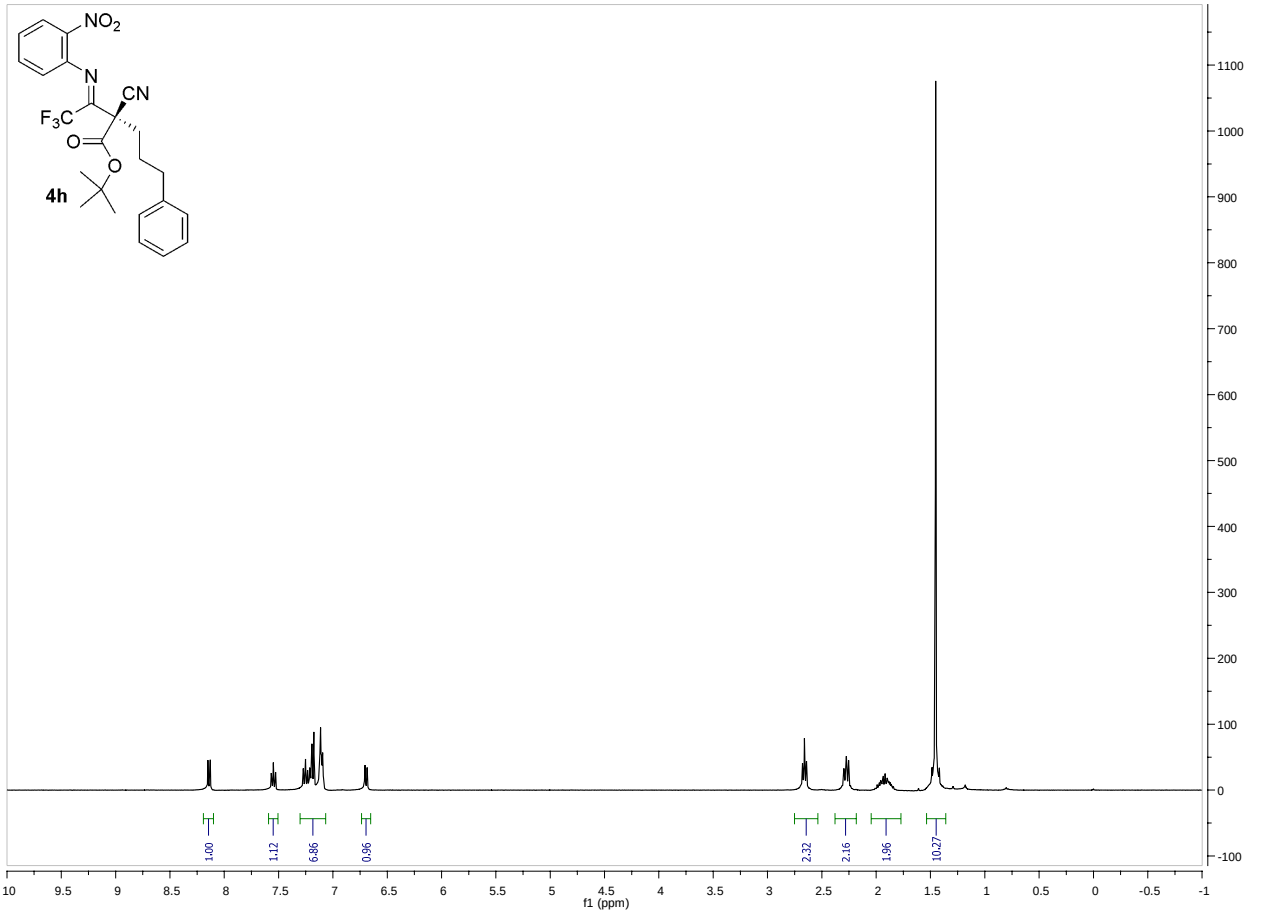
134.32
125.59
125.42
121.11
118.85
118.22
115.34
114.38
112.45
86.60
62.66
55.29
34.10
32.28
25.46
18.27
-5.39
f1 (ppm)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CN
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O
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2.16
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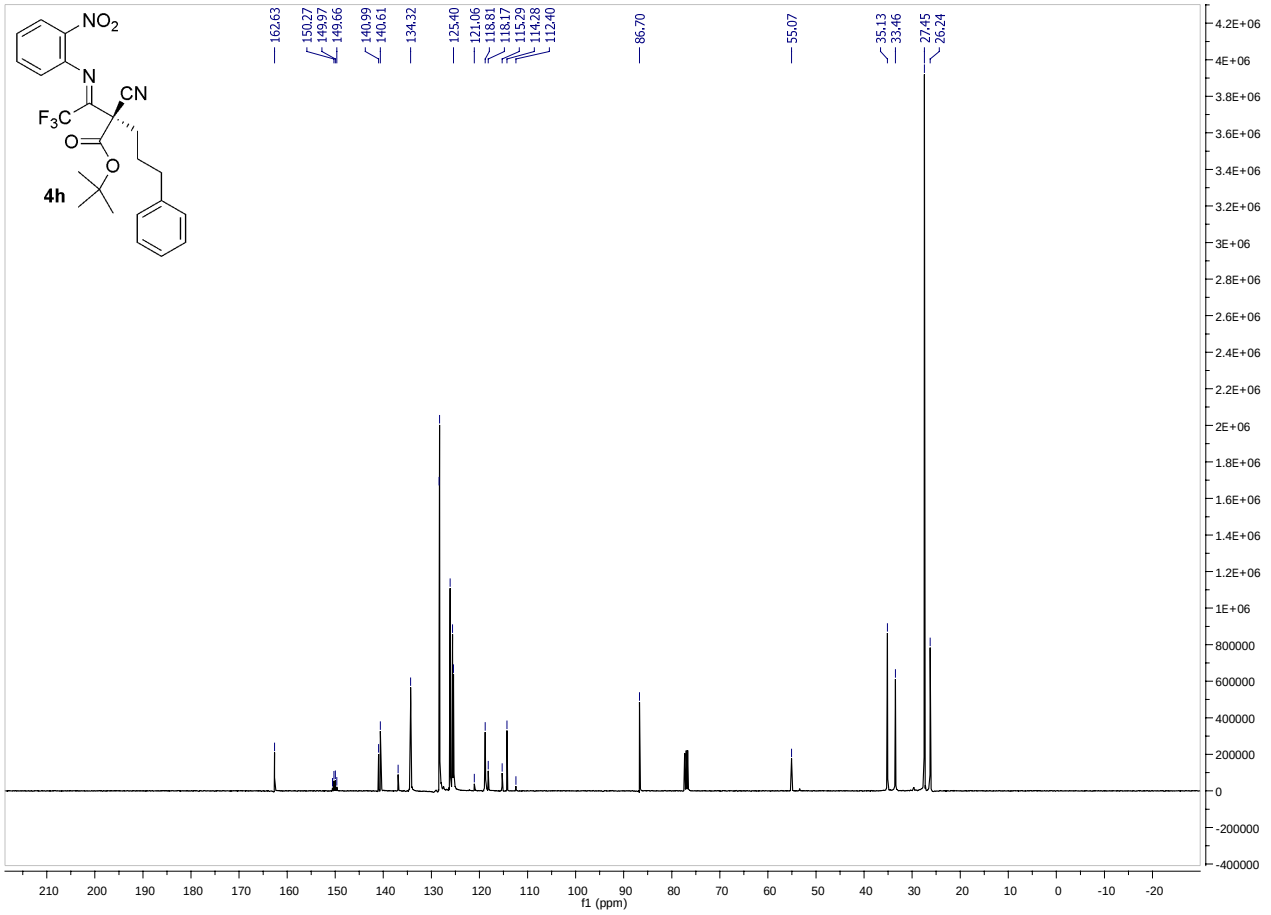
10.27
f1 (ppm)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CN
F3C
O
O
4h
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150.27
149.97
149.66
140.99
140.61
134.32
125.40
121.06
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114.28
112.40
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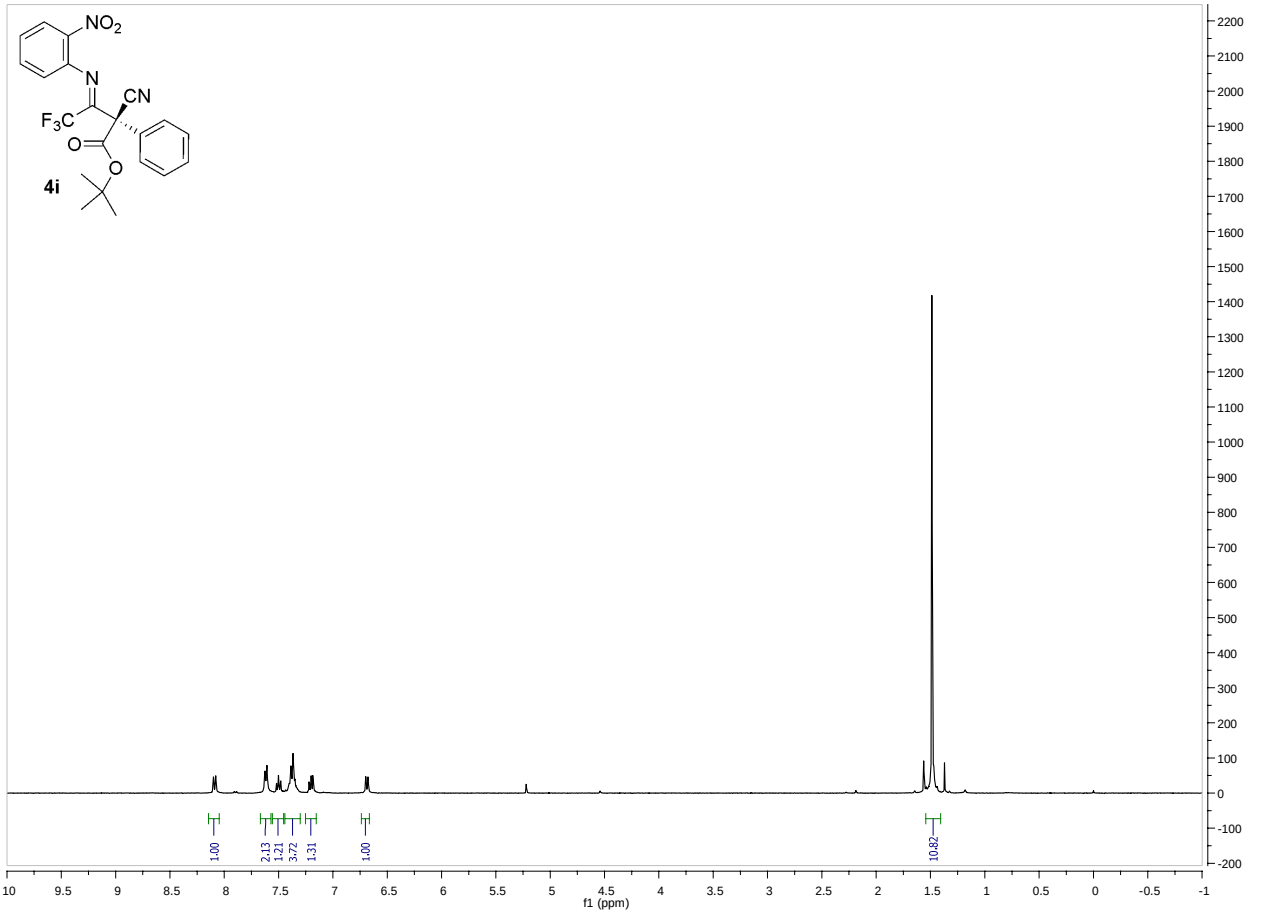
55.07
35.13
33.46
27.45
26.24
f1 (ppm)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1.21
3.72
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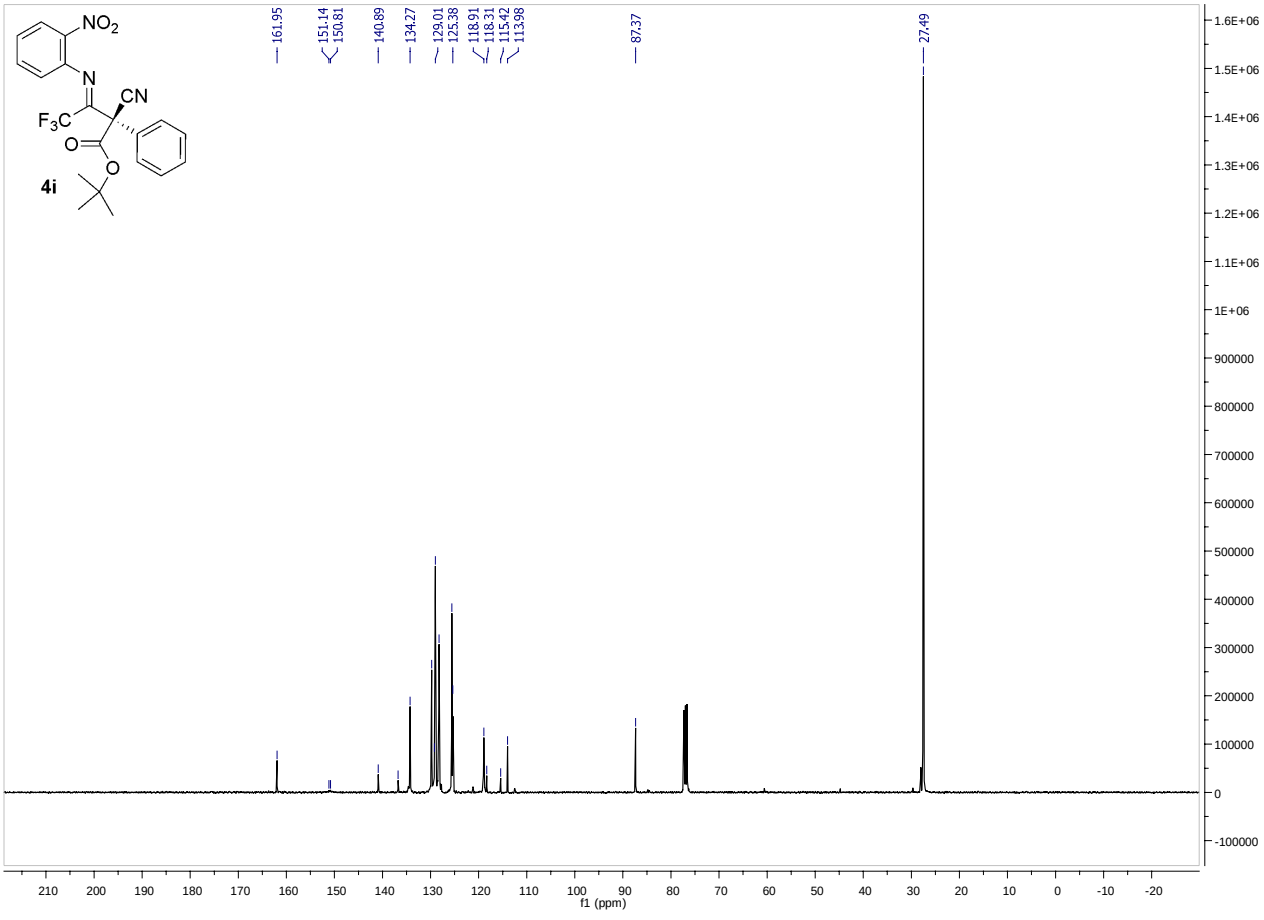
1.00
10.82
f1 (ppm)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CN
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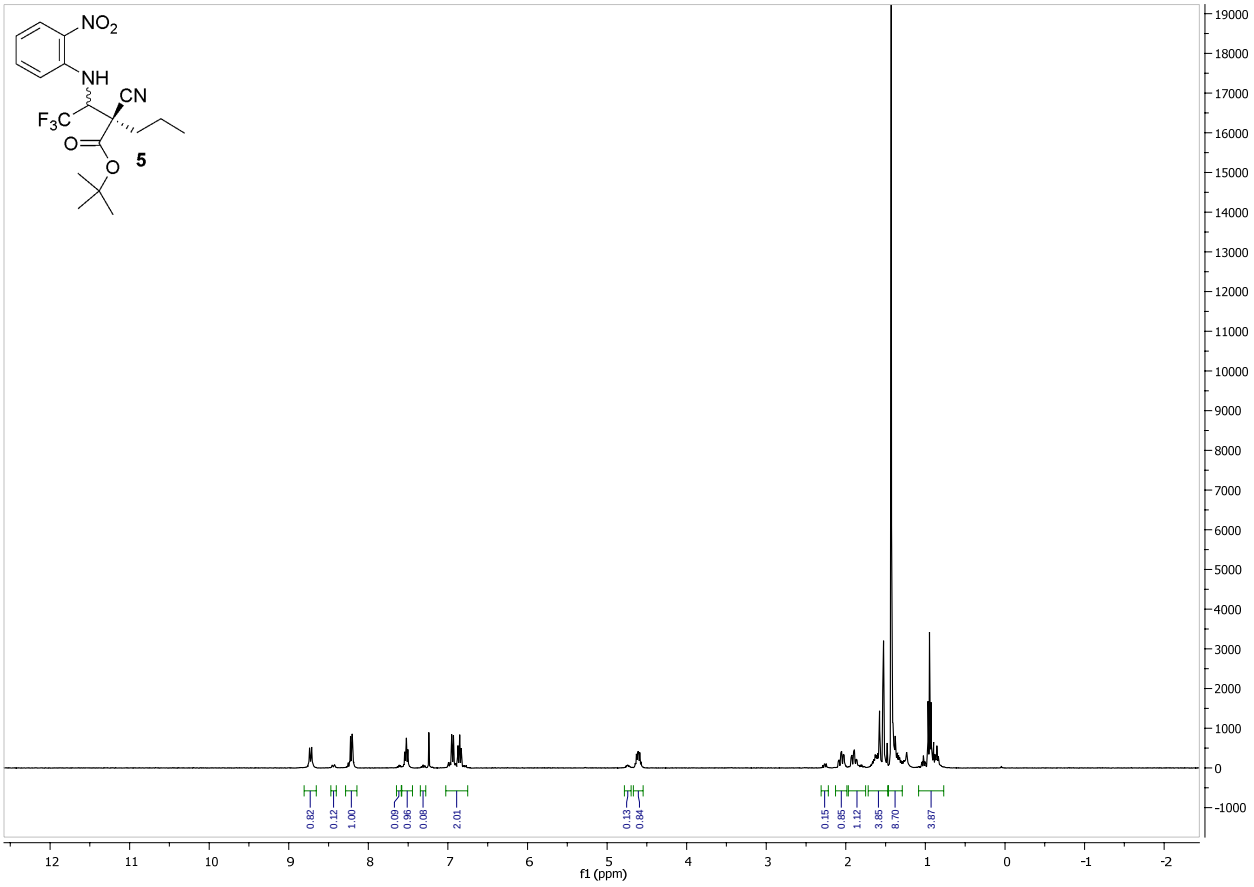
f1 (ppm)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CN
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O
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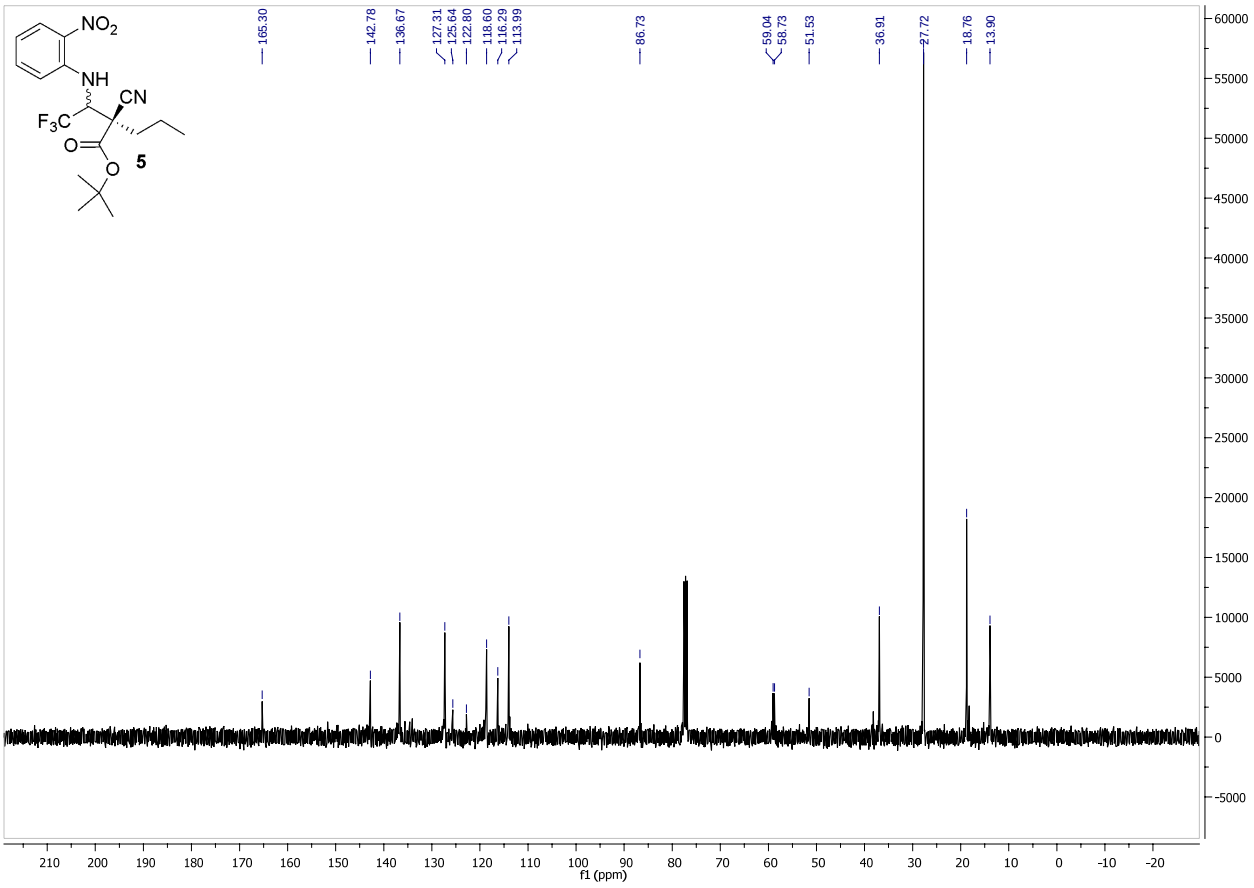
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F3C
O
O
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122.80
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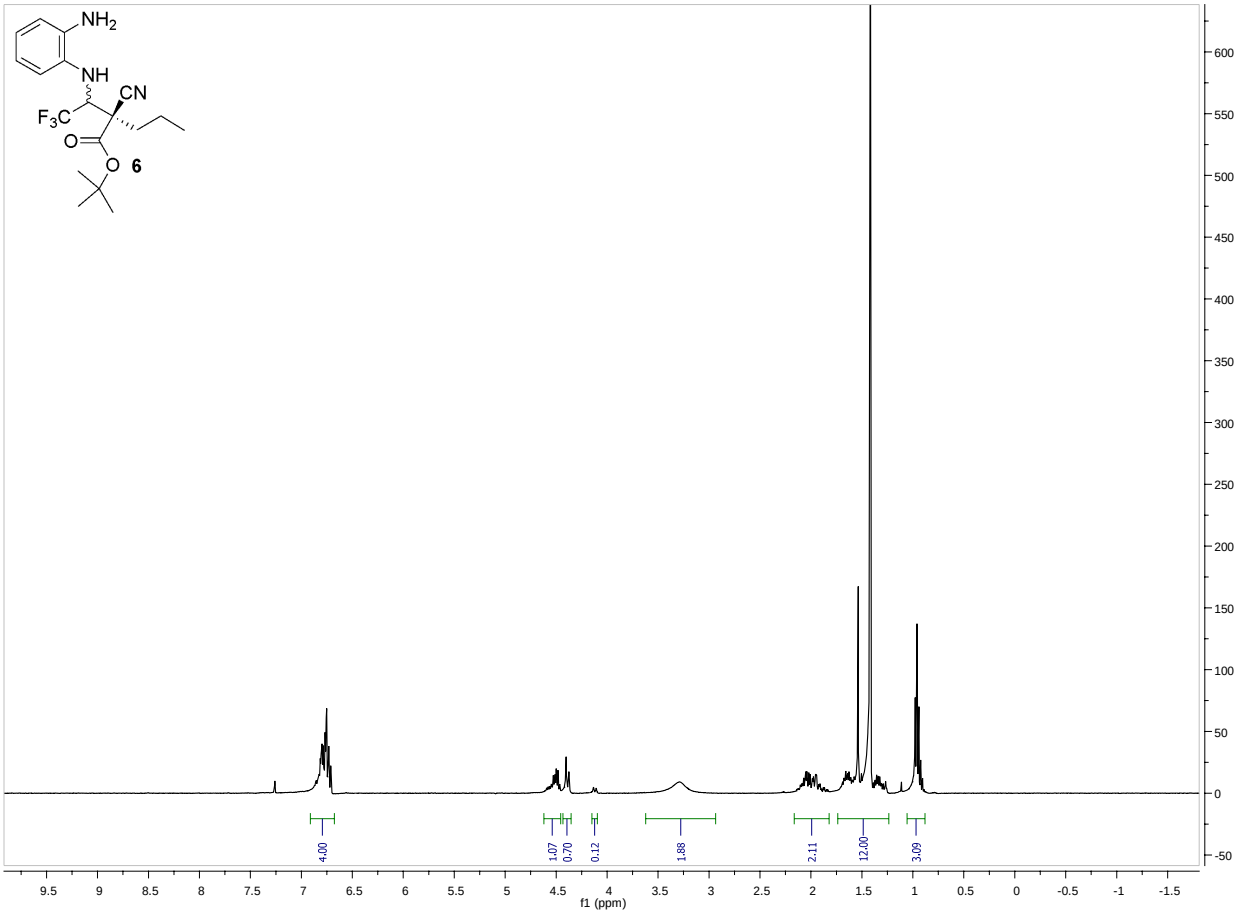
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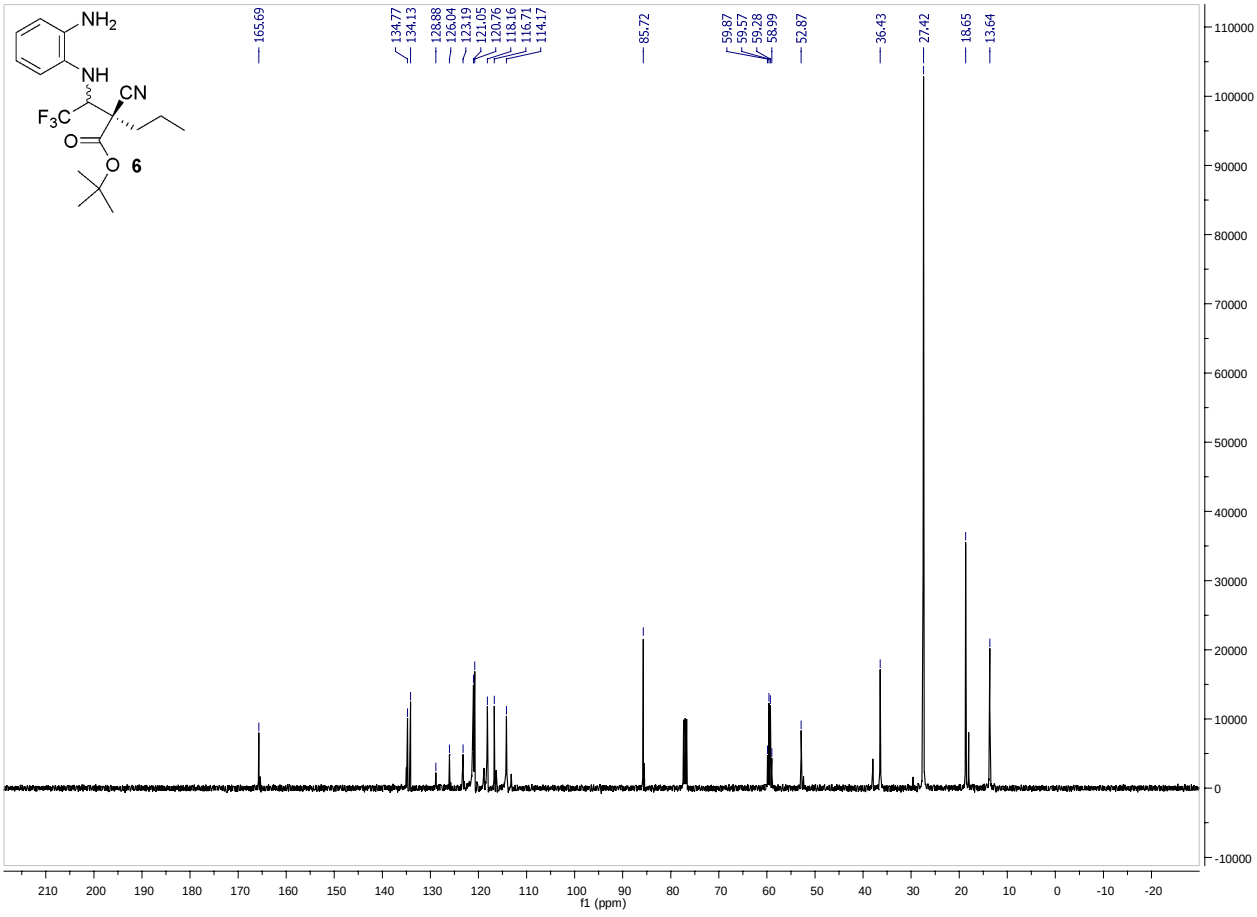
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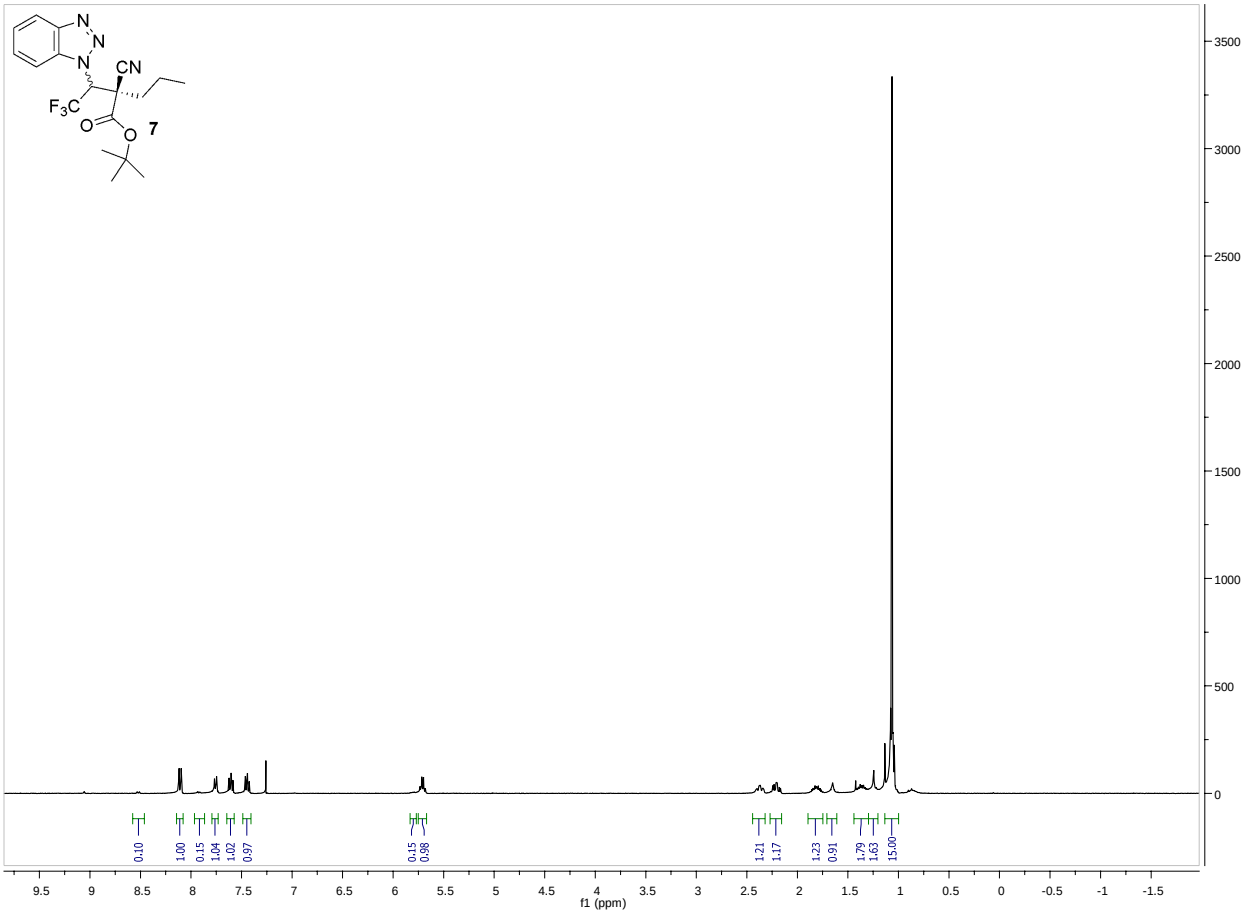
f1 (ppm)


7
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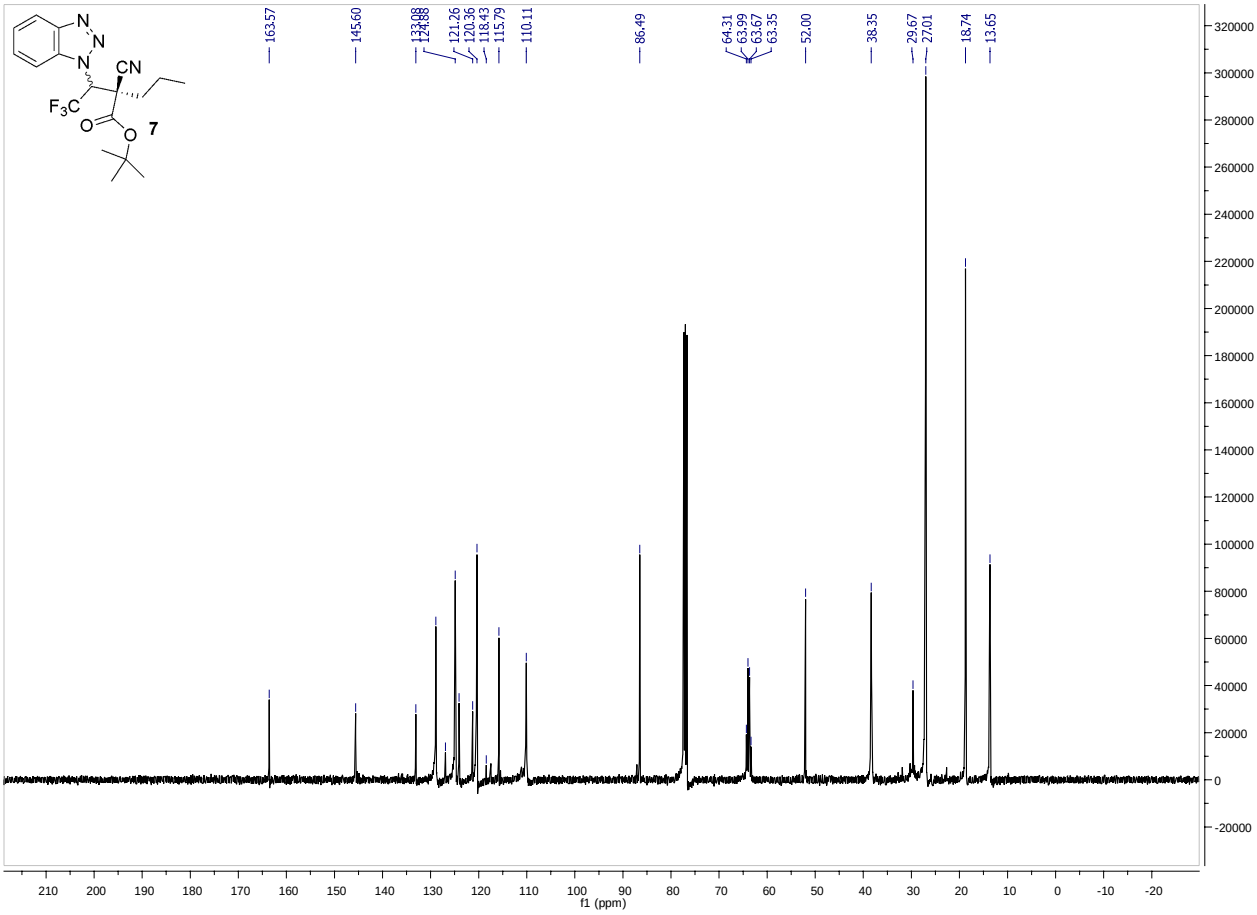
15.00
f1 (ppm)


7
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115.79
110.11
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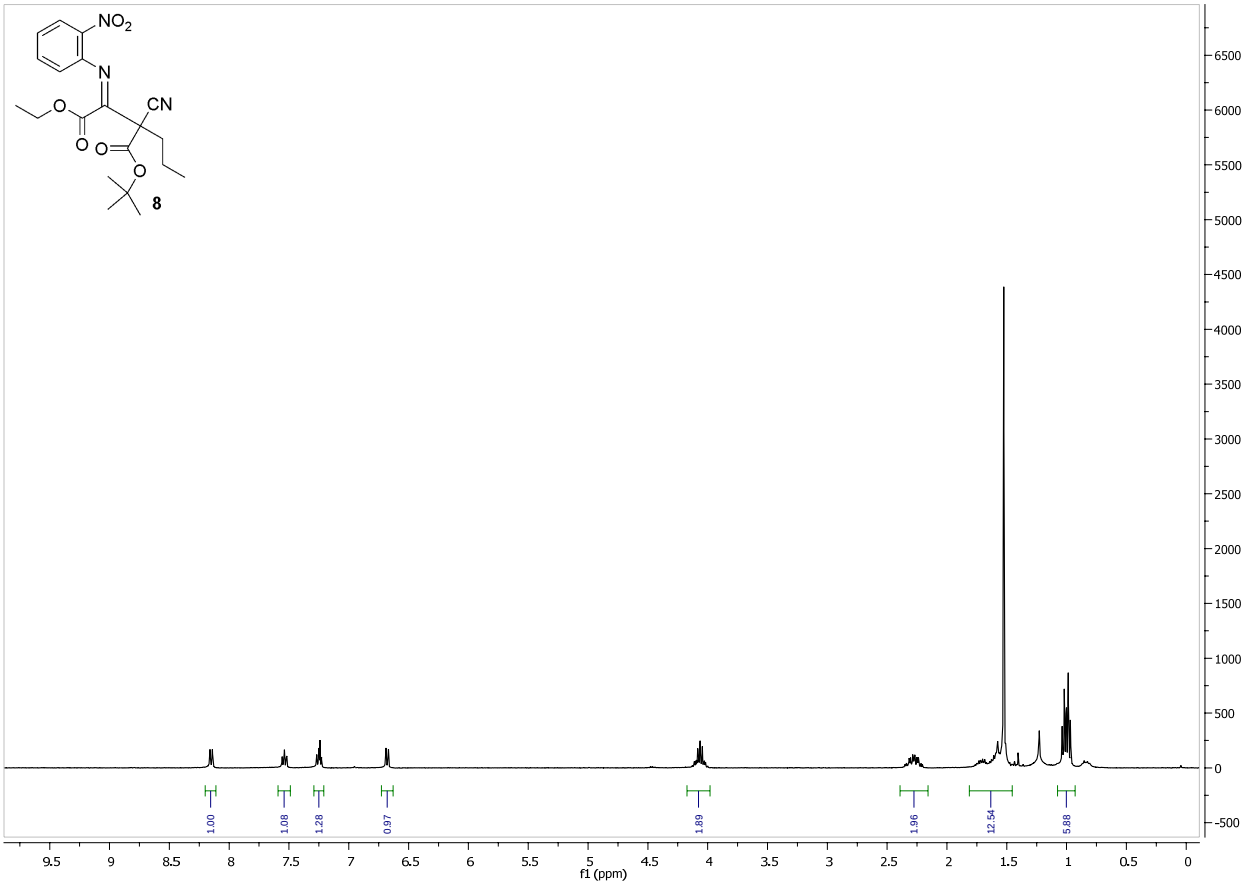
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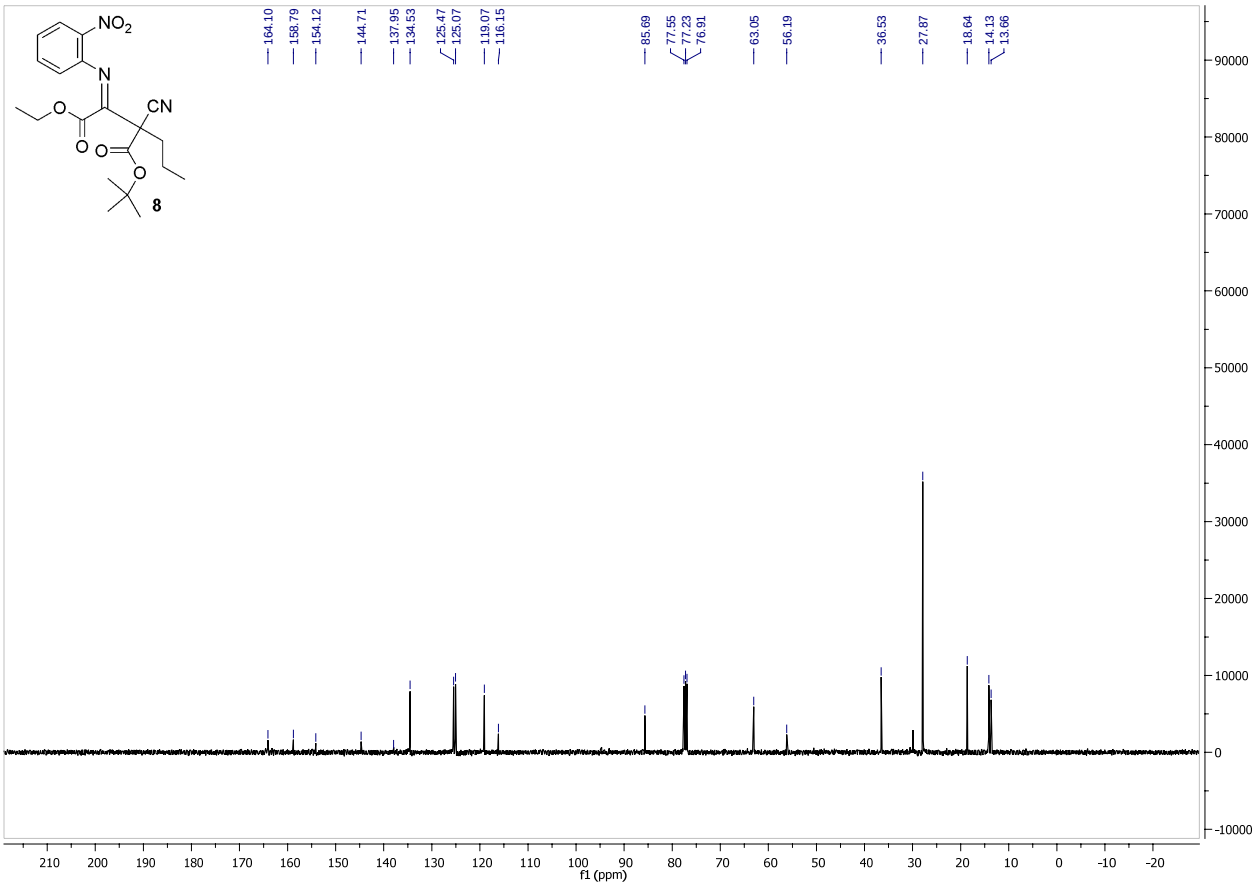
f1 (ppm)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O
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O
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125.07
119.07
116.15
85.69
77.55
77.23
76.91
63.05
56.19
36.53
27.87
18.64
14.13
13.66
f1 (ppm)

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