Direct Asymmetric Amination of α-Branched Cyclic Ketones Catalyzed by a Chiral Phosphoric Acid

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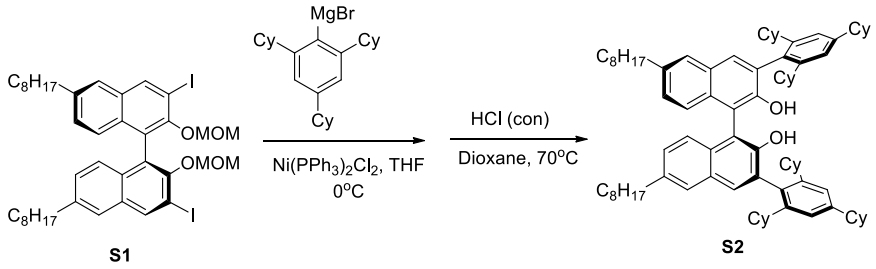
General Information:

Unless otherwise noted, all commercial reagents were used without further purification. 5Å MS were dried in oven at 200 ºC overnight and used when after cooling to rt. Dichloromethane, toluene, ether, THF and triethylamine were purified by passage through an activated alumina column under argon. Thin-layer chromatography (TLC) analysis of reaction mixtures was performed using Merck silica gel 60 F254 TLC plates, and visualized under UV or by staining with ceric ammonium molybdate or potassium permanganate. Flash column chromatography was carried out on Merck Silica Gel 60 Å, 230 X 400 mesh. Nuclear magnetic resonance (NMR) spectra were recorded using Bruker AV-600, DRX-500, AV-500, AVQ-400, AVB-400 and AV-300 spectrometers. ^{1}H and ^{13}C chemical shifts are reported in ppm downfield of tetramethylsilane and referenced to residual solvent peak ($CHCl_3$; $\delta H = 7.26$ and $\delta C = 77.16$, CH_3OH; $\delta H = 3.31$ and $\delta C = 49.00$). Multiplicities are reported using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad resonance. Mass spectral data were obtained from the Micro-Mass/Analytical Facility operated by the College of Chemistry, University of California, Berkeley. Enantiomeric excesses were determined on a Shimadzu VP Series Chiral HPLC using IA, IB, IC, OD, ASH columns. The synthesis of phosphoric acids **(*S*)-TRIP**[1], **(*R*)-TCYP**[2] has been previously described. Racemic products were synthesized by carrying out the amination reactions using **(±)-TRIP** as catalyst.

Synthesis of the chiral phosphoric acids:

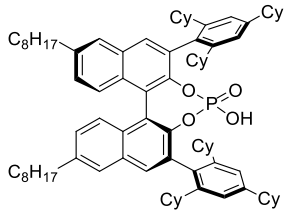
(*R*)-6,6'-dioctyl-3,3'-bis(2,4,6-tricyclohexylphenyl)-[1,1'-binaphthalene]-2,2'-diol (**S2**)



S1[3] and (2,4,6-tricyclohexylphenyl)magnesium bromide[2] were prepared according previous reports. Into a flame dried 250 mL flask, equipped with a stir bar was added **(*R*)-S1** (2.0g, 2.35 mmol) and $NiCl_2(PPh_3)_2$ (154 mg, 0.24 mmol) and THF 20 mL. The heterogeneous mixture was purged with N_2 and the above Grignard solution added slowly at 0 ºC. The resulting mixture was warmed to rt and stirred overnight, after which the mixture was quenched with satd. NH_4Cl solution. After extraction with Et_2O three times, the combined organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the residue, which was purified by flash chromatography (20:1 Hexane/DCM) to afford a syrup 2.3 g.

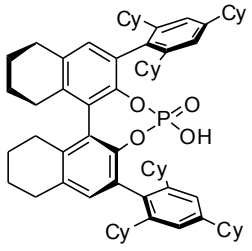
To the solution of the above syrup in dioxane (40 mL) was added HCl (conc., 4 mL) at rt. The mixture was heated to 70 ºC and stirred overnight. The mixture was then cooled to rt and concentrated *in vacuo* to afford a residue, which was diluted with DCM and washed with satd. $NaHCO_3$ solution and brine. The combined organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue, which was purified by flash chromatography (40:1 – 20:1, Hexane/DCM) to afford **S2** (2.0 g, 74% yield) as a white foam. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (s, 2H), 7.71 (s, 2H), 7.32 (d, J = 8.6 Hz, 2H), 7.26 (d, J = 8.5 Hz, 2H), 7.21 (s, 2H), 7.17 (s, 2H), 4.88 (s, 2H), 2.91 – 2.78 (m, 4H), 2.71 – 2.54 (m, 4H), 2.44 – 2.29 (m, 2H), 2.13 – 2.03 (m, 4H), 2.01 – 1.91 (m, 6H), 1.91 – 0.87 (m, 80H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.14, 147.92, 146.97, 146.71, 138.25, 131.72, 131.27, 130.06, 129.35, 129.20, 128.16, 126.88, 124.28, 122.39, 122.36, 112.96, 44.95, 41.96, 41.83, 36.15, 34.89, 34.68, 34.64, 34.61, 34.37, 34.05, 32.04, 31.62, 29.80, 29.67, 29.44, 27.27, 27.18, 27.10, 27.00, 26.91, 26.42, 26.21, 22.83, 14.27. m/z HRMS (ESI) found $[M+H]^+$ 1153.8767, $C_{84}H_{113}O_2^+$ requires 1153.746.

(*R*)-C_8-TCYP



To a solution of **S2** (2.0 g, 1.73 mmol) in anhydrous pyridine (7 mL) was added $POCl_3$ (473 uL, 5.20 mmol) at rt. The mixture was warmed to 90 ºC and stirred overnight, after which the mixture was cooled to rt and added to H_2O (7 mL) slowly. The mixture was then warmed to 105 ºC for 4 h, after which it was cooled to rt and acidified with 3N HCl solution. The mixture was extracted with DCM three times, and the combined organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue, which was purified by flash chromatography (20:1 – 2:1, Hexane/ Ethyl Acetate) to afford a white foam, which was diluted in Et_2O, washed with 3N HCl solution and concentrated *in vacuo* to give **(*R*)-C_8-TCYP** (1.5 g, 71% yield) as white a foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 15.9 Hz, 4H), 7.20 – 7.07 (m, 4H), 6.89 (d, *J* = 8.3 Hz, 4H), 2.75 (td, *J* = 7.1, 3.9 Hz, 4H), 2.50 – 2.36 (m, 2H), 2.23 – 2.03 (m, 4H), 1.96 – 1.82 (m, 10H), 1.80 – 0.49 (m, 80H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.88, 146.67, 146.28, 145.84, 145.77, 140.03, 132.05, 132.00, 131.20, 130.65, 127.71, 126.75, 126.45, 122.38, 121.74, 121.56, 44.85, 42.19, 41.86, 37.16, 36.05, 35.15, 34.79, 34.25, 33.28, 32.70, 32.06, 31.42, 29.72, 29.57, 29.46, 27.44, 27.29, 27.26, 27.06, 26.84, 26.50, 26.41, 26.03, 22.84, 14.27. ^{31}P NMR (162 MHz, $CDCl_3$) δ 1.35. m/z HRMS (ESI) found $[M-H]^-$ 1215.8308, $C_{84}H_{112}O_4P^-$ requires 1215.8304.

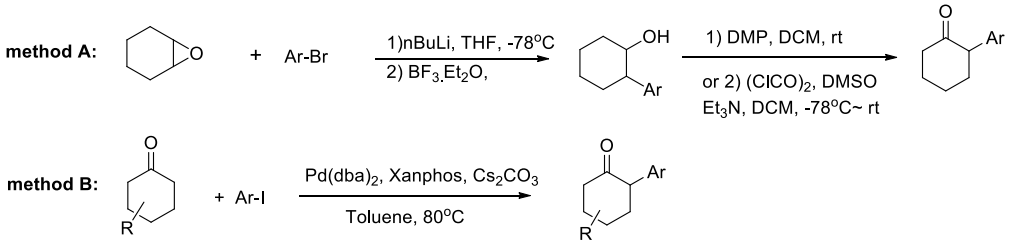
(*R*)-H_8-TCYP



(*R*)-H_8-TCYP was prepared from (*R*)-3,3'-diiodo-2,2'-bis(methoxymethoxy)-4a,5,5',6,6',7,7',8,8a,8'-decahydro-1,1'-binaphthalene[4] as the above procedures. ^{1}H NMR (500

MHz, $CDCl_3$) δ 6.89 – 6.81 (m, 6H), 2.89 – 2.78 (m, 2H), 2.72 (tt, *J* = 13.2, 6.1 Hz, 4H), 2.50 – 2.38 (m, 2H), 2.31 (dd, *J* = 16.8, 6.1 Hz, 2H), 2.16 (t, *J* = 12.1 Hz, 4H), 2.00 – 1.68 (m, 20H), 1.69 – 1.55 (m, 12H), 1.51 – 1.36 (m, 12H), 1.33 – 1.07 (m, 16H), 1.07 – 0.83 (m, 8H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.52, 146.46, 145.81, 144.91, 144.84, 136.10, 133.27, 132.31, 129.45, 129.42, 126.75, 122.37, 121.44, 44.80, 41.94, 41.80, 37.21, 34.96, 34.85, 34.18, 33.67, 32.77, 29.13, 27.98, 27.53, 27.30, 27.26, 27.01, 26.83, 26.58, 26.52, 23.10, 22.97. ^{31}P NMR (162 MHz, $CDCl_3$) δ -1.58. m/z HRMS (ESI) found $[M-H]^-$ 999.6391, $C_{68}H_{88}O_4P^-$ requires 999.6426.

Synthesis of the substrates:



Substrates **1a**, **1s** were commercial available. Synthesis of substrate **1b**[5], **1c**[5], **1e**[5], **1d**[6], **1f**[5], **1l**[5] and **1m**[5] was reported previous.

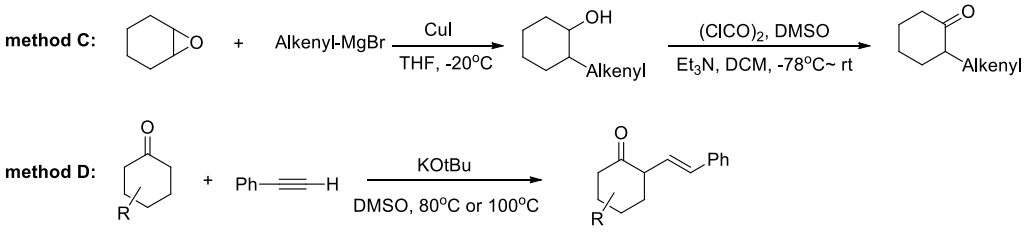
Substrate **1g**[7]**, 1i**[8]**, 1k**[8]**, 1x**[9] was synthesized in **method A**, whose ^1H NMR data matched the literature.

General procedure for **method A**: To a solution of ArBr or ArI (10 mmol) in THF was added *n*BuLi (4 mL, 2.5 N in heaxane, 10 mmol) at -78 ºC. After stirring for 1h at this temperature, cyclohexene oxide (5 mmol) was added followed by adding $BF_3.Et_2O$ (7.5 mmol). The reaction was quenched with satd. $NaHCO_3$ solution after stirring for another 3h at -78 ºC. The mixture was diluted with ethyl acetate and washed with 2N NaOH solution and brine. The combined organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue, which was purified by flash chromatography to afford the alcohol.

To the solution of alcohol (1.0 equiv.) in DCM was added DMP (1.2 equiv). After TLC monitoring the full conversion of the SM, the mixture was quenched with satd. $NaHCO_3$ solution and Na_2SO_3 solution. The mixture was extracted with DCM for three times, the combined organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue, which was purified by flash chromatography to afford the desired ketone.

1h, 1j[10] was synthesized in **method B**.

General procedure for **method B**: To a flame dried flask was added Cs_2CO_3 (6.5 g, 20 mmol), $Pd_2(dba)_3$ (184 mg, 0.2 mmol) and Xantphos (139 mmol, 0.24 mmol). After purging with N_2, toluene (10 mL), ketone (15 mmol) and phenyl iodide (1.11 mL, 10 mmol) were added. After stirring overnight at 80 ºC, the mixture was filtered and concentrated *in vacuo* to afford a residue, which was purified by flash chromatography to provide the desired ketone.



Substrate **1o**[11], **1p**[12] was synthesized in **method C**[11].

General procedure for **method C**: To a solution of CuI (190 mg, 1.0 mmol) in THF (10 mL) was added alkenyl magnesium bromide (13 mL, 1.0 N in THF, 13 mmol) at -78℃. After stirring for 30 min, cyclohexene oxide (1.0 mL, 10 mmol) was added and the mixture was warmed to -20℃. After stirring for another 2 h at this temperature, the mixture was quenched with satd. NH_4Cl solution and extracted with Et_2O for 3 times. The combined organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue, which was purified by flash chromatography to afford the alcohol.

To the solution of $(ClCO)_2$ (889 μL, 10.5 mmol) in DCM (20 mL) was added DMSO (1.5 mL, 21.0 mmol) at -78 ºC. After stirring for 0.5 h, a solution of the above alcohol (7.0 mmol) was added slowly into the mixture. After stirring for another 2h at -78 ºC, Et_3N (5.8 mL, 42.0 mmol) was added and the mixture was slowly warmed to rt. The mixture was quenched with satd. NH_4Cl solution after stirring for another 1h stirring. The mixture was extracted with DCM three times, and the combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue, which was purified by flash chromatography to afford desired ketone.

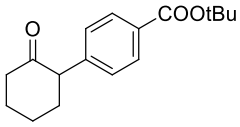
Substrates **1n**[13], **1t**, **1u**, **1v**[14], **1w**[14] was synthesized in **method D**[13-14].

General procedure for **method D**: To a solution of cyclic ketone (10 mmol) in DMSO (20 mL) was added phenylacetylene (1.1 mL, 10 mmol) and *t*BuOK (1.1 g, 10 mmol) at 80 ºC or 100 ºC.

After stirring of 45 mins after this temperature, the mixture was poured into a mixture of ice and satd. NH_4Cl solution. Upon extraction with Et_2O three times, the combined organic layer was washed with H_2O, brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue, which was purified by flash chromatography to afford desired ketone.

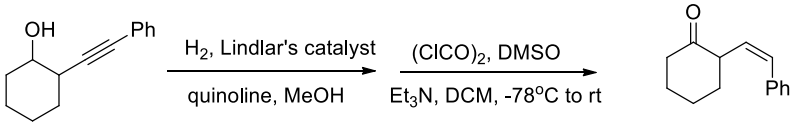
Data for the new compounds was given below:

tert-butyl 4-(2-oxocyclohexyl)benzoate (**1h**)



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.2 Hz, 2H), 7.18 (d, *J* = 8.3 Hz, 2H), 3.66 (dd, *J* = 12.2, 5.4 Hz, 1H), 2.63 – 2.40 (m, 2H), 2.27 (ddd, *J* = 12.2, 6.0, 3.6 Hz, 1H), 2.22 – 2.12 (m, 1H), 2.10 – 1.96 (m, 2H), 1.90 – 1.78 (m, 2H), 1.58 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.76, 165.78, 143.57, 130.77, 129.59, 128.59, 80.92, 57.51, 42.34, 35.14, 28.32, 27.88, 25.43. m/z HRMS (ESI) found $[M+Na]^+$ 297.1465, $C_{17}H_{22}O_3Na^+$ requires 297.1461.

(*Z*)-2-styrylcyclohexanone (**1q**)

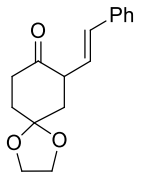


S3 **1q**

To a solution of **S3** (500 mg, 2.5 mmol) in MeOH (8 mL) was added Lindlar's catalyst (200 mg) and quinolone (1.2 uL). After purging with H_2, the mixture was stirred at rt for 2h. The mixture was filtered and concentrated in vacuo to afford a residue, which was purified by flash chromatography (4: 1, DCM/ Hexane) to afford the alkene-substituted alcohol (302 mg, 60% yield). The Swern Oxidation was carried out following the procedure in **Method C** to afford the desired ketone **1q**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 8.2, 6.7 Hz, 2H), 7.25 (d, *J* = 5.5 Hz, 1H), 7.19 (d, *J* = 7.1 Hz, 2H), 6.64 (d, *J* = 11.7 Hz, 1H), 5.78 (dd, *J* = 11.7, 9.7 Hz, 1H), 3.50 (td, *J* = 10.1, 5.4 Hz, 1H), 2.52 – 2.42 (m, 1H), 2.31 (td, *J* = 12.7, 6.1 Hz, 1H), 2.19 – 2.03 (m, 2H), 1.93 – 1.86 (m, 1H), 1.80 – 1.62 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.30, 136.95,

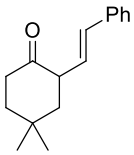
130.83, 129.37, 128.31, 128.26, 126.93, 50.16, 41.86, 34.98, 27.68, 24.33. m/z HRMS (EI) found $[M]^+$ 200.11991, $C_{14}H_{16}O^+$ requires 200.1201.

(*E*)-7-styryl-1,4-dioxaspiro[4.5]decan-8-one (**1s**)



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.33 (m, 2H), 7.30 (dd, *J* = 8.7, 6.6 Hz, 2H), 7.24 – 7.19 (m, 1H), 6.47 – 6.40 (m, 1H), 6.37 (d, *J* = 16.1 Hz, 1H), 4.14 – 4.01 (m, 4H), 3.53 (dt, *J* = 12.8, 6.3 Hz, 1H), 2.72 (dddd, *J* = 14.3, 13.0, 6.5, 1.2 Hz, 1H), 2.47 (ddd, *J* = 14.4, 4.9, 3.4 Hz, 1H), 2.21 (ddd, *J* = 13.3, 6.0, 3.2 Hz, 1H), 2.14 – 1.98 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.64, 136.96, 131.59, 128.50, 127.47, 126.46, 126.36, 107.15, 64.87, 64.71, 50.02, 40.84, 38.16, 34.52. m/z HRMS (EI) found $[M]^+$ 258.1254, $C_{16}H_{18}O_3^+$ requires 258.1256.

(*E*)-4,4-dimethyl-2-styrylcyclohexanone (**1t**)



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.35 (m, 2H), 7.29 (ddd, *J* = 7.7, 6.7, 1.4 Hz, 2H), 7.24 – 7.16 (m, 1H), 6.43 (dd, *J* = 16.1, 6.5 Hz, 1H), 6.34 (d, *J* = 16.2 Hz, 1H), 3.38 – 3.22 (m, 1H), 2.54 (dddd, *J* = 14.3, 13.2, 6.6, 1.0 Hz, 1H), 2.33 (ddd, *J* = 14.4, 4.6, 3.0 Hz, 1H), 1.87 (ddd, *J* = 13.2, 5.9, 3.1 Hz, 1H), 1.81 – 1.63 (m, 3H), 1.28 (s, 3H), 1.06 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.69, 137.21, 131.19, 128.50, 127.68, 127.33, 126.32, 49.70, 47.12, 39.76, 38.26, 31.43, 30.79, 24.58. m/z HRMS (EI) found $[M]^+$ 228.1514, $C_{16}H_{20}O^+$ requires 228.1514.

Synthesis of Products

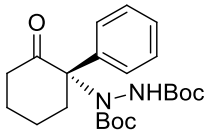
General procedure for asymmetric amination:

To the substrate **1** (0.30 mmol) in a 1 dram (15 x 45 mm) vial equipped with an 8 mm magnetic stirrer bar was added DCM (0.3 ml). Subsequently, *di*-tert-butyl azodicarboxylates (90 mg, 0.39

mmol), 5Å MS (50 mg), and **(*R*)-C$_8$-TCYP** (36 mg, 0.03 mmol or 18 mg, 0.015 mmol) were added. After all the reagents were dissolved, the mixture was warmed to 45 ºC with the cap open. After about 2h, the DCM was evaporated, leaving the mixture as syrup. After heated at 45 ºC for another 40h or 60h, the mixture was cooled to rt and directly purified by flash column chromatography to afford the desired product.

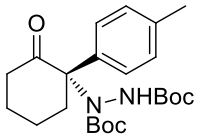
The relevant racemic products were synthesized in the same procedure expect **(±)-TRIP** (10 mol%) was used as catalyst.

(*S*)-di-*tert*-butyl 1-(2-oxo-1-phenylcyclohexyl)hydrazine-1,2-dicarboxylate (**2a**)



The reaction was carried out according the general procedure using **1a** (52 mg, 0.3 mmol) and **(*R*)-C$_8$-TCYP** (36 mg, 0.03 mmol). After stirring at 45 ºC for 60 h, the mixture was purified by flash column chromatography (7: 1, Hexane/ethyl acetate) to afford the title product **2a** (117 mg, 97% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.08 (m, 5H), 6.63 – 5.66 (m, 1H), 3.06 – 2.90 (m, 1H), 2.85 – 2.73 (m, 1H), 2.49 – 2.28 (m, 2H), 2.22 – 2.09 (m, 1H), 2.09 – 1.97 (m, 1H), 1.86 – 1.69 (m, 1H), 1.66 – 1.24 (m, 19H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.95, 155.55, 155.06, 151.03, 137.07, 128.44, 127.95, 127.78, 127.62, 83.63, 81.60, 80.98, 40.53, 28.13, 28.06, 27.93, 21.54. m/z HRMS (ESI) found $[M+Na]^+$ 427.2205, $C_{22}H_{32}N_2O_5Na^+$ requires 427.2203. $[\alpha]_D^{20}$ = +5.1 (c 1.0, $CHCl_3$). HPLC (Chiralpak OD column, 98:2 hexanes/isopropanol, 0.5 ml/min; tr= 17.0 min (minor), 18.2 min (major); 99% ee.

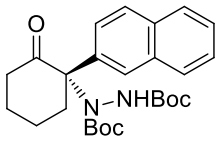
(*S*)-di-*tert*-butyl 1-(2-oxo-1-(p-tolyl)cyclohexyl)hydrazine-1,2-dicarboxylate (**2b**)



The reaction was carried out according the general procedure using **1b** (56 mg, 0.3 mmol) and **(*R*)-C$_8$-TCYP** (36 mg, 0.03 mmol). After stirring at 45℃ for 60 h, the mixture was purified by flash column chromatography (7: 1, Hexane/ EA) to afford the title product **2b** (122 mg, 97%

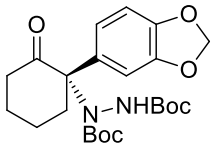
yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 – 7.04 (m, 4H), 6.59 – 5.63 (m, 1H), 3.08 – 2.66 (m, 2H), 2.46 – 2.32 (m, 2H), 2.31 (d, *J* = 4.8 Hz, 3H), 2.22 – 1.94 (m, 2H), 1.86 – 1.67 (m, 1H), 1.63 – 1.52 (m, 1H), 1.55 – 1.28 (m, 18H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.11, 155.62, 155.10, 137.75, 134.06, 129.34, 129.23, 128.58, 127.58, 81.55, 80.97, 40.58, 40.26, 28.18, 28.12, 27.98, 21.63, 21.03. m/z HRMS (ESI) found $[M+Na]^+$ 441.2368, $C_{23}H_{34}N_2O_5Na^+$ requires 441.2360. $[\alpha]_D^{20}$ = +6.5 (c 1.0, $CHCl_3$). HPLC (Chiralpak IC column, 92:8 hexanes/ isopropanol, 1 ml/min; tr= 11.9 min (minor), 13.1 min (major); 99% ee.

(*S*)-di-*tert*-butyl 1-(1-(naphthalen-2-yl)-2-oxocyclohexyl)hydrazine-1,2-dicarboxylate (**2c**)



The reaction was carried out according the general procedure using **1c** (67 mg, 0.3 mmol) and **(*R*)-C$_8$-TCYP** (36 mg, 0.03 mmol). After stirring at 45 ºC for 60h, the mixture was purified by flash column chromatography (8: 1, Hexane/ EA) to afford the title product **2c** (122 mg, 90% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.86 – 7.74 (m, 3H), 7.71 – 7.60 (m, 1H), 7.53 – 7.42 (m, 3H), 6.63 – 5.71 (m, 1H), 3.13 – 2.70 (m, 2H), 2.66 – 2.36 (m, 2H), 2.28 – 2.15 (m, 1H), 2.12 – 2.05 (m, 1H), 1.91 – 1.72 (m, 1H), 1.71 – 1.60 (m, 1H), 1.51 – 1.35 (m, 18H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.12, 155.61, 155.17, 134.88, 133.03, 132.84, 128.35, 128.11, 127.41, 126.54, 126.16, 125.98, 81.07, 40.73, 28.19, 28.11, 27.96, 21.69. m/z HRMS (ESI) found $[M+Na]^+$ 477.2362, $C_{26}H_{34}N_2O_5Na^+$ requires 477.2360. HPLC (Chiralpak OD column, 98:2 hexanes/ isopropanol, 0.5 ml/min; tr= 17.9 min (major), 20.3 min (minor); 97% ee.

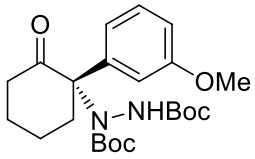
(*S*)-di-*tert*-butyl 1-(1-(benzo[d][1,3]dioxol-5-yl)-2-oxocyclohexyl)hydrazine-1,2-dicarboxylate (**2d**)



The reaction was carried out according the general procedure using **1d** (65 mg, 0.3 mmol) and **(*R*)-C$_8$-TCYP** (36 mg, 0.03 mmol). After stirring at 45 ºC for 40h, the mixture was purified by

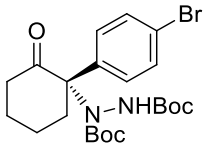
flash column chromatography (5: 1, Hexane/ EA) to afford the title product **2d** (108 mg, 80% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.85 – 6.76 (m, 1H), 6.76 – 6.65 (m, 2H), 6.00 – 5.63 (m, 3H), 3.05 – 2.69 (m, 2H), 2.43 – 2.22 (m, 2H), 2.17 – 1.92 (m, 2H), 1.79 – 1.66 (m, 1H), 1.66 – 1.52 (m, 1H), 1.54 – 1.32 (m, 18H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.95, 155.47, 155.13, 148.00, 147.34, 130.92, 130.26, 121.05, 108.69, 107.94, 101.30, 101.02, 81.07, 40.63, 28.20, 28.14, 27.85, 21.70. m/z HRMS (ESI) found $[M+Na]^+$ 471.2100, $C_{23}H_{32}N_2O_7Na^+$ requires 471.2102. $[\alpha]_D^{20}$ = +12.5 (c 1.0, $CHCl_3$). HPLC (Chiralpak IC column, 85:15 hexanes/ isopropanol, 1 ml/min; tr = 10.9 min (minor), 17.2 min (major); 98% ee.

(*S*)-di-*tert*-butyl 1-(1-(3-methoxyphenyl)-2-oxocyclohexyl)hydrazine-1,2-dicarboxylate (**2e**)



The reaction was carried out according the general procedure using **1e** (61 mg, 0.3 mmol) and **(*R*)-C$_8$-TCYP** (36 mg, 0.03 mmol). After stirring at 45 ºC for 60h, the mixture was purified by flash column chromatography (6: 1, Hexane/ EA) to afford the title product **2e** (114 mg, 88% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 – 7.19 (m, 1H), 6.88 – 6.75 (m, 3H), 6.42 – 5.63 (m, 1H), 3.75 (s, 3H), 3.09 – 2.70 (m, 2H), 2.49 – 2.27 (m, 2H), 2.25 – 1.95 (m, 2H), 1.82 – 1.69 (m, 1H), 1.62 – 1.53 (m, 1H), 1.48 – 1.35 (m, 18H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.91, 159.69, 159.14, 155.64, 155.10, 138.90, 129.50, 129.39, 120.72, 119.94, 114.07, 113.84, 113.34, 81.06, 75.25, 55.26, 40.70, 36.69, 28.18, 28.12, 21.61. m/z HRMS (ESI) found $[M+Na]^+$ 457.2310, $C_{23}H_{34}N_2O_6Na^+$ requires 457.2309. $[\alpha]_D^{20}$ = +5.3 (c 1.0, $CHCl_3$). HPLC (Chiralpak IA column, 90:10 hexanes/ isopropanol, 1 ml/min; tr= 10.1 min (minor), 13.1 min (major); 99% ee.

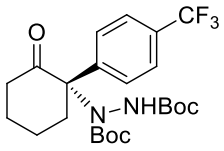
(*S*)-di-*tert*-butyl 1-(1-(4-bromophenyl)-2-oxocyclohexyl)hydrazine-1,2-dicarboxylate (**2f**)



The reaction was carried out according the general procedure using **1f** (76 mg, 0.3 mmol) and **(*R*)-C$_8$-TCYP** (36 mg, 0.03 mmol). After stirring at 45 ºC for 60h, the mixture was purified by

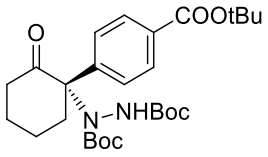
flash column chromatography (8: 1, Hexane/ethyl acetate) to afford the title product **2f** (136 mg, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.6 Hz, 2H), 7.18 – 7.09 (m, 2H), 6.66 – 5.75 (m, 1H), 3.10 – 2.93 (m, 1H), 2.89 – 2.58 (m, 1H), 2.48 – 2.33 (m, 1H), 2.32 – 1.94 (m, 3H), 1.86 – 1.68 (m, 1H), 1.57 – 1.26 (m, 19H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.70, 155.56, 155.16, 136.63, 131.54, 130.81, 129.51, 125.30, 122.27, 81.36, 40.48, 28.19, 28.09, 27.99, 21.38. m/z HRMS (ESI) found $[M+Na]^+$ 505.1313, $C_{22}H_{31}N_2O_5BrNa^+$ requires 505.1309. $[\alpha]_D^{20}$ = +0.4 (c 1.0, $CHCl_3$).HPLC (Chiralpak IC column, 93:7 hexanes/ isopropanol, 1 ml/min; tr = 9.0 min (minor), 16.0 min (major); 98% ee.

(*S*)-di-*tert*-butyl 1-(2-oxo-1-(4-(trifluoromethyl)phenyl)cyclohexyl)hydrazine-1,2-dicarboxylate (**2g**)



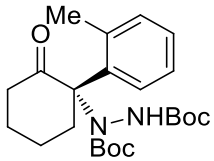
The reaction was carried out according the general procedure using **1g** (72 mg, 0.3 mmol) and **(*R*)-C$_8$-TCYP** (36 mg, 0.03 mmol). After stirring at 45 ºC for 60h, the mixture was purified by flash column chromatography (8: 1, Hexane/ EA) to afford the title product **2g** (101 mg, 71% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 – 7.51 (m, 2H), 7.44 – 7.30 (m, 2H), 6.64 – 5.69 (m, 1H), 3.17 – 2.95 (m, 1H), 2.92 – 2.67 (m, 1H), 2.61 – 2.36 (m, 1H), 2.32 – 2.15 (m, 1H), 2.15 – 2.05 (m, 1H), 1.87 – 1.71 (m, 1H), 1.64 – 1.55 (m, 1H), 1.52 – 1.34 (m, 18H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.71, 155.70, 155.21, 141.90, 130.07 (q, *J* = 32.6 Hz), 129.09, 128.11, 125.32 (q, *J* = 3.7 Hz), 125.14, 124.62 (q, *J* = 2.9 Hz), 122.98, 81.57, 40.48, 28.65, 28.20, 28.09, 28.00, 21.22. m/z HRMS (ESI) found $[M+Na]^+$ 495.2078, $C_{23}H_{31}F_3N_2O_5Na^+$ requires 495.2077. $[\alpha]_D^{20}$ = -3.4 (c 0.5, $CHCl_3$). HPLC (Chiralpak IC column, 93:7 hexanes/ isopropanol, 1 ml/min; tr = 6.7 min (minor), 10.6 min (major); 98% ee.

(*S*)-di-*tert*-butyl 1-(1-(4-(tert-butoxycarbonyl)phenyl)-2-oxocyclohexyl)hydrazine-1,2-dicarboxylate (**2h**)



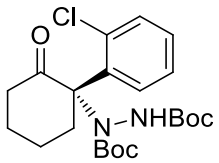
The reaction was carried out according the general procedure using **1h** (82 mg, 0.3 mmol) and **(*R*)-C$_8$-TCYP** (36 mg, 0.03 mmol). After stirring at 45 ºC for 60h, the mixture was purified by flash column chromatography (7: 1, Hexane/ EA) to afford the title product **2h** (115 mg, 76% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.01 – 7.84 (m, 2H), 7.57 – 7.20 (m, 2H), 6.80 – 5.00 (m, 1H), 3.13 – 2.51 (m, 2H), 2.45 – 1.95 (m, 4H), 1.86 – 1.67 (m, 1H), 1.65 – 1.09 (m, 28H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.58, 165.65, 165.39, 155.58, 155.20, 142.11, 131.52, 129.43, 128.84, 127.52, 81.94, 81.35, 81.16, 40.49, 36.68, 28.22, 28.17, 28.07, 27.97, 21.34. m/z HRMS (ESI) found $[M+Na]^+$ 527.2728, $C_{27}H_{40}N_2O_7Na^+$ requires 527.2728. $[\alpha]_D^{20}$ = +4.7 (c 1.0, $CHCl_3$). HPLC (Chiralpak IC column, 85:15 hexanes/ isopropanol, 1 ml/min; tr= 8.0 min (minor), 16.8 min (major); 97% ee.

(*S*)-di-*tert*-butyl 1-(2-oxo-1-(o-tolyl)cyclohexyl)hydrazine-1,2-dicarboxylate (**2i**)



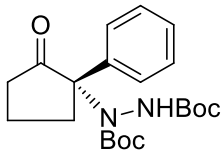
The reaction was carried out according the general procedure using **1i** (56 mg, 0.3 mmol) and **(*R*)-C$_8$-TCYP** (36 mg, 0.03 mmol). After stirring at 45 ºC for 60h, the mixture was purified by flash column chromatography (9: 1, Hexane/ethyl acetate) to afford the title product **2i** (117 mg, 73% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 – 7.11 (m, 3H), 7.01 (d, *J* = 7.5 Hz, 1H), 6.45 – 5.96 (m, 1H), 2.99 – 2.57 (m, 3H), 2.44 – 2.32 (m, 1H), 2.57 – 2.22 (m, 3H), 2.11 – 1.58 (m, 4H), 1.53 – 1.31 (m, 18H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.87, 155.40, 155.01, 138.46, 138.27, 137.65, 137.37, 135.36, 135.18, 133.41, 132.79, 129.45, 128.02, 127.85, 127.20, 125.95, 125.88, 125.19, 82.40, 81.49, 81.28, 80.88, 78.18, 41.52, 40.84, 40.53, 35.97, 35.90, 35.74, 28.29, 28.13, 27.76, 26.83, 23.05, 22.18, 21.68. m/z HRMS (ESI) found $[M+Na]^+$ 441.2358, $C_{23}H_{34}N_2O_5Na^+$ requires 441.2360. $[\alpha]_D^{20}$ = +57.3 (c 1.0, $CHCl_3$). HPLC (Chiralpak OD column, 98:2 hexanes/ isopropanol, 1 ml/min; tr = 7.6 min (major), 8.6 min (minor); 99% ee.

(*S*)-di-*tert*-butyl 1-(1-(2-chlorophenyl)-2-oxocyclohexyl)hydrazine-1,2-dicarboxylate (**2j**)



The reaction was carried out according the general procedure using **1j** (62 mg, 0.3 mmol) and **(*R*)-C$_8$-TCYP** (36 mg, 0.03 mmol). After stirring at 45 ºC for 60h, the mixture was purified by flash column chromatography (9: 1, Hexane/ethyl acetate) to afford the title product **2j** (98 mg, 78% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.34 (m, 1H), 7.33 – 7.11 (m, 3H), 6.67 – 6.24 (m, 1H), 3.40 – 2.74 (m, 2H), 2.71 – 2.58 (m, 1H), 2.58 – 2.44 (m, 1H), 2.11 – 1.83 (m, 3H), 1.66 – 1.53 (m, 1H), 1.62 – 1.38 (m, 18H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.20, 155.16, 154.92, 151.07, 135.75, 134.44, 132.34, 131.63, 129.11, 128.91, 128.73, 126.81, 100.04, 83.72, 81.60, 81.10, 77.67, 77.55, 40.84, 40.41, 40.15, 36.59, 36.40, 28.37, 28.25, 28.16, 28.06, 27.97, 27.93, 26.89, 21.55. m/z HRMS (ESI) found $[M+Na]^+$ 461.1813, $C_{22}H_{31}ClN_2O_5Na^+$ requires 461.1814. $[\alpha]_D^{20}$ = +33.2 (c 1.0, $CHCl_3$). HPLC (Chiralpak OD column, 98:2 hexanes/ isopropanol, 1 ml/min; tr= 9.8 min (minor), 10.8 min (major); 99% ee.

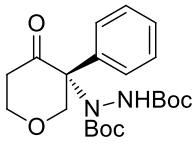
(*S*)-di-*tert*-butyl 1-(2-oxo-1-phenylcyclopentyl)hydrazine-1,2-dicarboxylate (**2k**)



The reaction was carried out according the general procedure using **1k** (48 mg, 0.3 mmol) and **(*R*)-C$_8$-TCYP** (36 mg, 0.03 mmol). After stirring at 45 ºC for 40h, the mixture was purified by flash column chromatography (8: 1, Hexane/ EA) to afford the title product **2k** (108 mg, 78% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 – 7.46 (m, 2H), 7.38 – 7.31 (m, 2H), 7.31 – 7.27 (m, 1H), 6.12 – 5.18 (m, 1H), 3.00 – 2.72 (m, 2H), 2.70 – 2.53 (m, 1H), 2.17 (dd, J = 19.0, 8.5 Hz, 1H), 2.11 – 2.02 (m, 1H), 1.72 – 1.57 (m, 1H), 1.48 – 1.28 (m, 18H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.82, 211.29, 155.00, 154.77, 154.57, 154.23, 154.06, 133.92, 133.14, 128.94, 128.71, 128.48, 128.40, 128.33, 128.29, 83.76, 82.13, 81.68, 80.91, 73.80, 73.55, 35.12, 34.87, 31.48, 31.18, 28.31, 28.22, 28.17, 28.13, 28.00, 18.19. m/z HRMS (ESI) found $[M+Na]^+$

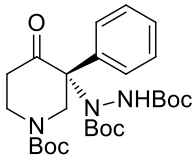
413.2050, $C_{21}H_{30}N_2O_5Na^+$ requires 417.2047. HPLC (Chiralpak OD column, 98.5:1.5 hexanes/ isopropanol, 0.5 ml/min; tr= 19.3 min (major), 20.7 min (minor); >95% ee.

(*R*)-di-*tert*-butyl 1-(4-oxo-3-phenyltetrahydro-2H-pyran-3-yl)hydrazine-1,2-dicarboxylate (**2l**)



The reaction was carried out according the general procedure using **1l** (53 mg, 0.3 mmol) and **(*R*)-C$_8$-TCYP** (36 mg, 0.03 mmol). After stirring at 45 ºC for 40h, the mixture was purified by flash column chromatography (20: 1, DCM/ Et_2O) to afford the title product **2l** (118 mg, 97% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 – 7.36 (m, 2H), 7.34 (t, *J* = 7.4 Hz, 2H), 7.30 (d, *J* = 7.2 Hz, 1H), 6.93 – 5.75 (m, 1H), 4.72 (d, *J* = 12.2 Hz, 1H), 4.60 – 4.36 (m, 1H), 4.29 – 3.84 (m, 2H), 2.91 – 2.57 (m, 1H), 2.52 – 2.35 (m, 1H), 1.48 – 1.26 (m, 18H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.96, 155.05, 134.58, 128.84, 128.69, 128.56, 128.42, 128.21, 128.04, 100.06, 82.25, 81.91, 81.14, 73.25, 71.45, 67.61, 67.06, 40.26, 28.20, 28.11, 28.00. m/z HRMS (ESI) found $[M+Na]^+$ 429.1997, $C_{21}H_{30}N_2O_6Na^+$ requires 429.1996. $[\alpha]_D^{20}$ = +83.0 (c 1.0, $CHCl_3$). HPLC (Chiralpak IC column, 85:15 hexanes/ isopropanol, 1 ml/min; tr = 5.6 min (major), 8.3 min (minor); 99% ee.

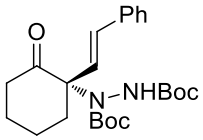
(*R*)-di-*tert*-butyl 1-(1-(tert-butoxycarbonyl)-4-oxo-3-phenylpiperidin-3-yl)hydrazine-1,2-dicarboxylate (**2m**)



The reaction was carried out according the general procedure using **1m** (82 mg, 0.3 mmol) and **(*R*)-C$_8$-TCYP** (36 mg, 0.03 mmol). After stirring at 45 ºC for 60h, the mixture was purified by flash column chromatography (10: 1, DCM/ Et_2O) to afford the title product **2m** (120 mg, 79% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 – 7.38 (m, 2H), 7.33 – 7.25 (m, 3H) , 6.51 – 5.50 (m, 1H) , 5.20 – 3.92 (m, 2H) , 3.81 – 3.25 (m, 1H) , 2.91 – 2.43 (m, 1H) , 2.48 – 1.98 (m, 1H) , 1.60 – 1.06 (m, 28H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.85, 155.84, 155.08, 154.00, 133.73, 129.03,

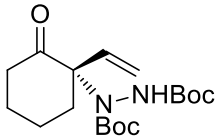
128.92, 128.80, 128.64, 128.56, 82.19, 81.70, 81.33, 80.88, 80.78, 80.41, 73.60, 48.07, 41.03, 39.20, 38.86, 28.63, 28.36, 28.21, 28.16, 28.04, 27.99, 27.77. m/z HRMS (ESI) found $[M+Na]^+$ 528.2681, $C_{26}H_{39}N_3O_7Na^+$ requires 528.2680. $[\alpha]_D^{20}$ = +38.0 (c 1.0, $CHCl_3$). HPLC (Chiralpak IC column, 85:15 hexanes/ isopropanol, 1 ml/min; tr = 6.6 min (major), 8.8 min (minor); 96% ee.

(*S*,*E*)-di-*tert*-butyl 1-(2-oxo-1-styrylcyclohexyl)hydrazine-1,2-dicarboxylate (**2n**)



The reaction was carried out according the general procedure using **1n** (60 mg, 0.3 mmol) and **(*R*)-C$_8$-TCYP** (18 mg, 0.015 mmol). After stirring at 45 ºC for 60h, the mixture was purified by flash column chromatography (10: 1, Hexane/ethyl acetate) to afford the title product **2n** (128 mg, 99% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.34 (m, 2H), 7.30 (t, *J* = 7.7 Hz, 2H), 7.26 – 7.19 (m, 1H), 6.51 – 6.25 (m, 2H), 6.24 – 6.05 (m, 1H), 3.14 – 2.80 (m, 1H), 2.64 (dt, *J* = 14.4, 4.6 Hz, 1H), 2.37 (dt, *J* = 12.5, 5.0 Hz, 1H), 2.20 – 2.00 (m, 2H), 1.99 – 1.84 (m, 1H), 1.82 – 1.67 (m, 1H), 1.65 – 1.34 (m, 19H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.94, 155.49, 136.26, 130.93, 128.64, 128.43, 128.10, 127.80, 126.73, 81.35, 72.60, 39.47, 28.24, 28.11, 21.80, 20.89. m/z HRMS (ESI) found $[M+Na]^+$ 453.2347, $C_{24}H_{34}N_2O_5Na^+$ requires 453.2360. $[\alpha]_D^{20}$ = -18.0 (c 1.0, $CHCl_3$). HPLC (Chiralpak IC column, 94:6 hexanes/ isopropanol, 1 ml/min; tr= 11.1 min (minor), 11.9 min (major); 98% ee.

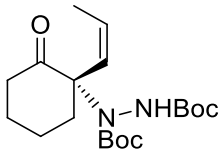
(*S*)-di-*tert*-butyl 1-(2-oxo-1-vinylcyclohexyl)hydrazine-1,2-dicarboxylate (**2o**)



The reaction was carried out according the general procedure using **1o** (37 mg, 0.3 mmol) and **(*R*)-C$_8$-TCYP** (18 mg, 0.015 mmol). After stirring at 45 ºC for 40h, the mixture was purified by flash column chromatography (7: 1, Hexane/ethyl acetate) to afford the title product **2o** (95 mg, 89% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.34 – 6.02 (m, 1H), 5.95 (dd, *J* = 17.7, 10.8 Hz, 1H),

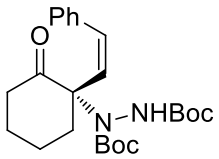
5.23 (d, *J* = 10.9 Hz, 1H), 4.96 (d, *J* = 17.7 Hz, 1H), 3.20 – 2.71 (m, 1H), 2.54 – 2.40 (m, 1H), 2.31 (dd, *J* = 10.9, 5.9 Hz, 1H), 2.16 – 1.92 (m, 2H), 1.82 – 1.57 (m, 2H), 1.58 – 1.25 (m, 19H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.08, 155.53, 136.37, 115.65, 81.37, 72.64, 39.33, 38.97, 29.04, 28.25, 28.13, 28.05, 27.99, 21.60, 20.58. m/z HRMS (ESI) found $[M+Na]^+$ 377.2049, $C_{18}H_{30}N_2O_5Na^+$ requires 377.2047. $[\alpha]_D^{20}$ = -54.5 (c 1.0, $CHCl_3$). HPLC (Chiralpak IC column, 93:7 hexanes/ isopropanol, 1 ml/min; tr= 10.1 min (minor), 25.0 min (major); 96% ee.

(*S*,*Z*)-di-*tert*-butyl 1-(2-oxo-1-(prop-1-en-1-yl)cyclohexyl)hydrazine-1,2-dicarboxylate (**2p**)



The reaction was carried out according the general procedure using **1p** (41 mg, 0.3 mmol) and **(*R*)-C$_8$-TCYP** (18 mg, 0.015 mmol). After stirring at 45 ºC for 60h, the mixture was purified by flash column chromatography (8: 1, Hexane/ EA) to afford the title product **2p** (108 mg, 98% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.61 – 5.86 (m, 1H), 5.80 – 5.30 (m, 2H), 2.86 – 2.27 (m, 3H), 2.22 – 1.97 (m, 1H), 2.00 – 1.70 (m, 4H), 1.59 (dd, *J* = 7.5, 1.9 Hz, 3H), 1.41 (d, *J* = 16.1 Hz, 18H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.26, 205.82, 155.59, 155.43, 155.25, 154.90, 130.95, 128.31, 128.08, 127.69, 81.61, 81.04, 80.78, 73.94, 73.11, 39.79, 39.15, 38.34, 37.11, 28.26, 28.16, 28.10, 27.97, 27.24, 21.93, 21.66, 14.56, 14.46. m/z HRMS (ESI) found $[M+Na]^+$ 391.2205, $C_{19}H_{32}N_2O_5Na^+$ requires 391.2203. $[\alpha]_D^{20}$ = +2.3 (c 1.0, $CHCl_3$). HPLC (Chiralpak IC column, 93:7 hexanes/ isopropanol, 1 ml/min; tr = 11.6 min (minor), 15.7 min (major); 99% ee.

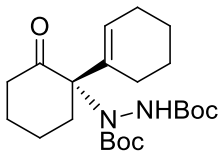
(*S*,*Z*)-di-*tert*-butyl 1-(2-oxo-1-styrylcyclohexyl)hydrazine-1,2-dicarboxylate (**2q**)



The reaction was carried out according the general procedure using **1q** (60 mg, 0.3 mmol) and **(*R*)-C$_8$-TCYP** (18 mg, 0.015 mmol). After stirring at 45 ºC for 60h, the mixture was purified by flash column chromatography (9: 1, Hexane/ethyl acetate) to afford the title product **2q** (128 mg, 99% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.32 (m, 2H), 7.30 – 7.25 (m, 1H), 7.19 – 6.99

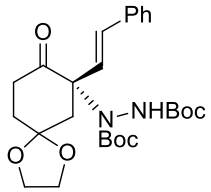
(m, 2H), 6.83 – 6.59 (m, 1H), 6.53 – 6.28 (m, 1H), 4.75 – 2.86 (m, 1H), 2.58 – 2.22 (m, 1H), 2.17 (d, *J* = 11.6 Hz, 1H), 2.07 – 1.88 (m, 1H), 1.84 – 1.54 (m, 3H), 1.53 – 1.45 (m, 1H), 1.45 – 1.31 (m, 19H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.98, 155.51, 155.11, 154.23, 138.16, 137.83, 132.06, 131.60, 129.65, 129.34, 128.86, 128.71, 128.45, 128.12, 127.76, 127.62, 127.10, 82.05, 80.70, 71.41, 39.74, 39.15, 37.51, 36.93, 36.18, 29.75, 28.24, 28.08, 28.05, 27.94, 21.66, 20.19. m/z HRMS (ESI) found $[M+Na]^+$ 453.2367, $C_{24}H_{34}N_2O_5Na^+$ requires 453.2360. HPLC (Chiralpak IC column, 92:8 hexanes/ isopropanol, 1 ml/min; tr= 10.7 min (minor), 14.5 min (major); 99% ee.

(*S*)-di-*tert*-butyl 1-(2-oxo-[1,1'-bi(cyclohexan)]-1'-en-1-yl)hydrazine-1,2-dicarboxylate (**2r**)



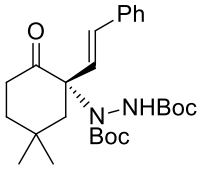
The reaction was carried out according the general procedure using **1r** (53 mg, 0.3 mmol) and **(*R*)-C$_8$-TCYP** (18 mg, 0.015 mmol). After stirring at 45 ºC for 60h, the mixture was purified by flash column chromatography (10: 1, Hexane/ethyl acetate) to afford the title product **2r** (118 mg, 96% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.24 – 5.47 (m, 1H), 5.41 (t, *J* = 3.8 Hz, 1H), 2.66 (dq, *J* = 12.0, 6.2 Hz, 1H), 2.52 (ddd, *J* = 13.5, 9.2, 3.5 Hz, 1H), 2.32 (ddd, *J* = 14.3, 8.9, 5.5 Hz, 1H), 2.21 (ddd, *J* = 14.1, 7.5, 3.4 Hz, 1H), 2.14 – 2.01 (m, 2H), 1.98 – 1.89 (m, 2H), 1.88 – 1.78 (m, 2H), 1.76 – 1.69 (m, 1H), 1.66 – 1.58 (m, 1H), 1.58 – 1.47 (m, 4H), 1.47 – 1.35 (m, 18H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.12, 206.43, 155.74, 155.25, 134.25, 133.78, 127.64, 127.45, 82.15, 81.21, 80.71, 40.87, 40.78, 40.73, 36.69, 33.98, 28.24, 28.20, 28.14, 27.96, 27.02, 26.06, 26.00, 25.87, 25.78, 22.85, 22.73, 22.06, 21.94. m/z HRMS (ESI) found $[M+Na]^+$ 431.2523, $C_{22}H_{36}N_2O_5Na^+$ requires 431.2516. HPLC (Chiralpak IC column, 96:4 hexanes/ isopropanol, 1 ml/min; tr= 16.4 min (minor), 37.6 min (major); 95% ee.

(*S,E*)-di-*tert*-butyl 1-(8-oxo-7-styryl-1,4-dioxaspiro[4.5]decan-7-yl)hydrazine-1,2-dicarboxylate (**2s**)



The reaction was carried out according the general procedure using **1s** (77 mg, 0.3 mmol) and **(*R*)-C$_8$-TCYP** (18 mg, 0.015 mmol). After stirring at 45 ºC for 60h, the mixture was purified by flash column chromatography (3: 1, Hexane/ethyl acetate) to afford the title product **2s** (120 mg, 82% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 15.3, 7.5 Hz, 2H), 7.33 – 7.13 (m, 3H), 6.93 – 5.87 (m, 3H), 4.22 – 3.85 (m, 4H), 3.00 – 2.71 (m, 1H), 2.74 – 2.47 (m, 1H), 2.45 – 2.30 (m, 1H), 2.23 (dd, *J* = 24.3, 14.5 Hz, 1H), 2.11 (m, 1H), 2.00 – 1.82 (m, 1H), 1.53 – 1.07 (m, 18H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.18, 204.93, 204.08, 155.34, 154.71, 154.17, 153.76, 137.21, 136.57, 136.51, 134.30, 130.73, 130.01, 128.61, 128.45, 128.28, 128.21, 127.80, 127.43, 127.34, 127.27, 126.88, 126.71, 107.69, 107.19, 107.07, 82.34, 81.60, 81.41, 80.92, 80.76, 68.98, 65.37, 65.14, 64.68, 64.17, 64.11, 64.02, 43.25, 42.07, 41.11, 36.78, 36.31, 36.20, 35.98, 35.09, 34.93, 32.13, 28.22, 28.16, 28.13, 27.66, 14.23. m/z HRMS (ESI) found $[M+Na]^+$ 511.2415, $C_{26}H_{36}N_2O_7Na^+$ requires 511.2415. $[\alpha]_D^{20}$ = -9.3 (c 1.0, $CHCl_3$). HPLC (Chiralpak ASH column, 80:20 hexanes/ isopropanol, 1 ml/min; tr= 24.1 min (minor), 28.3 min (major); 97% ee.

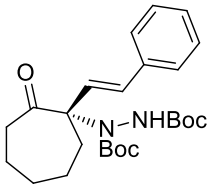
(*S,E*)-di-*tert*-butyl 1-(5,5-dimethyl-2-oxo-1-styrylcyclohexyl)hydrazine-1,2-dicarboxylate (**2t**)



The reaction was carried out according the general procedure using **1t** (68 mg, 0.3 mmol) and **(*R*)-C$_8$-TCYP** (18 mg, 0.015 mmol). After stirring at 45 ºC for 60h, the mixture was purified by flash column chromatography (9: 1, Hexane/ethyl acetate) to afford the title product **2t** (113 mg, 82% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.23 (m, 5H), 6.55 – 6.21 (m, 2H), 6.04 (d, *J* = 16.5 Hz, 1H), 2.73 (d, *J* = 14.1 Hz, 1H), 2.63 – 2.39 (m, 2H), 2.28 – 2.01 (m, 1H), 2.01 – 1.73 (m, 1H), 1.60 – 1.52 (m, 1H), 1.49 – 1.33 (m, 18H), 1.07 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.01, 205.97, 155.55, 154.28, 136.30, 133.79, 129.05, 128.73, 128.37, 126.77, 81.98, 80.87, 71.55, 48.84, 40.46, 36.79, 36.56, 32.68, 31.10, 28.32, 28.17, 27.97, 26.58, 22.72, 22.70, 14.20,

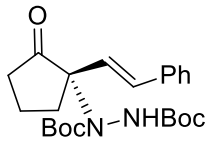
14.17. m/z HRMS (ESI) found $[M+Na]^+$ 481.2670, $C_{26}H_{38}N_2O_5Na^+$ requires 481.2673. $[\alpha]_D^{20}$ = +66.0 (c 1.0, $CHCl_3$). HPLC (Chiralpak IC column, 92:8 hexanes/ isopropanol, 1 ml/min; tr= 6.1 min (minor), 8.2 min (major); 98% ee.

(*S*,*E*)-di-*tert*-butyl 1-(2-oxo-1-styrylcycloheptyl)hydrazine-1,2-dicarboxylate (**2u**)



The reaction was carried out according the general procedure using **1u** (64 mg, 0.3 mmol) and **(*R*)-C$_8$-TCYP** (18 mg, 0.015 mmol). After stirring at 45 ºC for 60h, the mixture was purified by flash column chromatography (9: 1, Hexane/ EA) to afford the title product **2u** (80 mg, 60% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.35 (m, 2H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.23 (t, *J* = 7.4 Hz, 1H), 6.94 – 5.86 (m, 3H), 3.55 – 2.57 (m, 1H), 2.52 – 2.34 (m, 1H), 2.33 – 2.18 (m, 1H), 2.12 – 1.89 (m, 1H), 1.91 – 1.53 (m, 6H), 1.53 – 1.38 (m, 18H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.25, 155.90, 155.14, 137.38, 136.50, 135.73, 128.63, 128.51, 128.36, 127.89, 126.72, 126.46, 82.06, 81.44, 29.40, 28.28, 28.20, 28.12, 28.01, 24.18, 22.74. m/z HRMS (ESI) found $[M+Na]^+$ 467.2519, $C_{25}H_{36}N_2O_5Na^+$ requires 467.2516. $[\alpha]_D^{20}$ = -9.3 (c 1.0, $CHCl_3$). HPLC (Chiralpak IC column, 93:7 hexanes/ isopropanol, 1 ml/min; tr= 7.0 min (major), 7.9 min (minor); 72% ee.

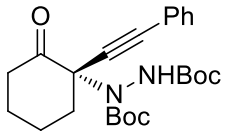
(*S,E*)-di-*tert*-butyl 1-(2-oxo-1-styrylcyclopentyl)hydrazine-1,2-dicarboxylate (**2v**)



The reaction was carried out according the general procedure using **1v** (56 mg, 0.3 mmol) and **(*R*)-C$_8$-TCYP** (18 mg, 0.015 mmol). After stirring at 45 ºC for 40h, the mixture was purified by flash column chromatography (9: 1, Hexane/ethyl acetate) to afford the title product **2v** (123 mg, 99% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.33 (m, 2H), 7.31 (t, *J* = 7.4 Hz, 2H), 7.28 – 7.24 (m, 1H), 6.59 (d, *J* = 16.3 Hz, 1H), 6.48 – 6.14 (m, 1H), 5.90 (dd, *J* = 16.3, 4.3 Hz, 1H), 2.87 – 2.36 (m, 3H), 2.27 (dd, *J* = 18.8, 8.3 Hz, 1H), 2.13 – 1.98 (m, 1H), 1.86 – 1.66 (m, 1H),

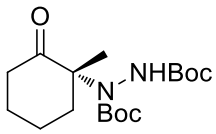
1.53 – 1.32 (m, 18H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.56, 212.01, 155.42, 154.12, 153.62, 136.25, 135.97, 133.47, 133.42, 128.71, 128.48, 128.35, 126.82, 124.93, 124.58, 82.17, 81.77, 81.19, 72.67, 35.04, 34.81, 31.93, 28.28, 28.21, 28.17, 27.97, 18.30. m/z HRMS (ESI) found $[M+Na]^+$ 439.2208, $C_{23}H_{32}N_2O_5Na^+$ requires 439.2203. $[\alpha]_D^{20}$ = +115.5 (c 1.0, $CHCl_3$). HPLC (Chiralpak IC column, 93:7 hexanes/ isopropanol, 1 ml/min; tr= 6.6 min (minor), 7.4 min (major); 99% ee.

(*S*)-di-tert-butyl 1-(2-oxo-1-(phenylethynyl)cyclohexyl)hydrazine-1,2-dicarboxylate (**2w**)



The reaction was carried out according the general procedure using **1w** (59 mg, 0.3 mmol) and **(*R*)-C$_8$-TCYP** (18 mg, 0.015 mmol). After stirring at 45℃ for 40 h, the mixture was purified by flash column chromatography (10: 1, hexanes/ ethyl acetate) to afford the title product **2w** (42 mg, 33% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.36 (m, 2H), 7.34 – 7.26 (m, 3H), 6.63 – 6.02 (m, 1H), 3.07 – 2.13 (m, 4H), 2.13 – 1.90 (m, 2H), 1.90 – 1.65 (m, 2H), 1.46 (d, *J* = 6.7 Hz, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.27, 153.50, 152.30, 149.75, 131.97, 131.75, 129.05, 128.79, 128.72, 128.33, 122.27, 115.47, 85.08, 83.63, 81.67, 81.32, 79.67, 38.44, 36.73, 28.29, 28.23, 28.16, 28.02, 27.61, 27.55, 22.51, 21.97, 21.20. m/z HRMS (EI) found $[M]^+$ 428.2307, $C_{24}H_{32}N_2O_5^+$ requires 428.2311. $[\alpha]_D^{20}$ = +44.5 (c 1.0, $CHCl_3$). HPLC (Chiralpak OD column, 98:2 hexanes/isopropanol, 0.5 ml/min; tr= 17.3 min (minor), 24.2 min (major); 93% ee.

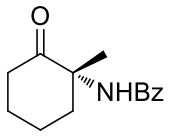
(*R*)-di-tert-butyl 1-(1-methyl-2-oxocyclohexyl)hydrazine-1,2-dicarboxylate (**2x**)



The reaction was carried out according the general procedure using **1x** (33 mg, 0.3 mmol) and **(*R*)-C$_8$-TCYP** (18 mg, 0.015 mmol). After stirring at 45℃ for 40 h, the mixture was purified by flash column chromatography (5: 1, hexanes/ ethyl acetate) to afford the title product **2x** (96 mg, 94% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 – 6.19 (m, 1H), 3.03 – 2.48 (m, 1H), 2.49 – 2.12

(m, 2H), 2.05 – 1.80 (m, 1H), 1.73 – 0.99 (m, 25H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.46, 208.91, 155.65, 155.04, 154.81, 82.14, 81.26, 81.08, 69.96, 68.86, 39.89, 38.76, 38.31, 29.42, 28.15, 28.02, 21.77, 20.99, 20.23. m/z HRMS (EI) found $[M]^+$ 342.2158, $C_{17}H_{30}N_2O_5^+$ requires 342.2155. $[\alpha]_D^{20}$ = -18.9 (c 1.0, $CHCl_3$).

(*R*)-N-(1-methyl-2-oxocyclohexyl)benzamide (**S4**)

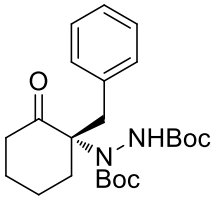


To a solution of **2x** (78 mg, 0.23 mmol) in DCM (3 mL) was added TFA (1.5 ml) at rt. After stirring for 3h, acetone (1.5 mL) was added and the mixture was stirred for another 10 min before concentration *in vacuo*.

To the solution of the above residue in HOAc (3 ml) was added active zinc powder (300 mg). After purging with N_2, the mixture was stirred overnight. After filtration, the filtrate was concentrated *in vacuo* to afford a residue, which was diluted with DCM and basified with satd. Na_2CO_3 solution. Extraction with DCM five times to afford the organic layer, which was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue.

To the solution of the above residue in DCM (3 mL) was added Et_3N (95 uL, 0.68 mmol) and BzCl (53 uL, 0.46 mmol) at rt. After stirring for 3 h, satd. $NaHCO_3$ solution was added into the mixture, which was then extracted with DCM for 3 times. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue, which was purified by flash chromatography (3: 1, Hexane/ ethyl acetate) to afford **S4** (11 mg, 21% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.6 Hz, 1H), 7.66 (s, 1H), 7.53 – 7.46 (m, 1H), 7.43 (dd, *J* = 8.2, 6.7 Hz, 1H), 3.07 (ddd, *J* = 11.0, 4.2, 2.2 Hz, 1H), 2.66 (ddd, *J* = 13.8, 12.1, 6.3 Hz, 1H), 2.56 – 2.45 (m, 1H), 2.09 (ddd, *J* = 9.4, 5.9, 3.2 Hz, 1H), 1.88 – 1.75 (m, 3H), 1.72 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.94, 166.21, 135.17, 131.54, 128.66, 127.05, 62.80, 38.92, 37.55, 27.98, 22.04, 21.36. $[\alpha]_D^{20}$ = +9.2 (c 0.5, $CHCl_3$). HPLC (Chiralpak IC column, 80:20 hexanes/isopropanol, 1.0 ml/min; tr= 12.6 min (minor), 15.7 min (major); 86% ee.

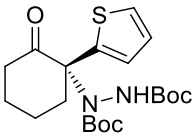
(*S*)-di-tert-butyl 1-(1-benzyl-2-oxocyclohexyl)hydrazine-1,2-dicarboxylate (**2y**)



The reaction was carried out according the general procedure using **1y** (57 mg, 0.3 mmol) and **(*R*)-C$_8$-TCYP** (36 mg, 0.03 mmol). After stirring at 45℃ for 40 h, the mixture was purified by flash column chromatography (10: 1, Hexane/ EA) to afford the title product **2y** (111 mg, 89% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.26 (m, 3H), 7.11 – 6.99 (m, 2H), 5.18 – 4.43 (m, 1H), 3.58 – 2.87 (m, 2H), 2.83 – 2.63 (m, 1H), 2.57 – 2.38 (m, 1H), 2.35 – 2.19 (m, 1H), 2.15 – 2.00 (m, 1H), 1.88 – 1.57 (m, 2H), 1.53 – 1.33 (m, 20H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.42, 210.05, 155.71, 155.41, 155.12, 154.59, 137.65, 137.23, 130.34, 130.24, 128.99, 128.79, 127.32, 126.96, 82.62, 82.47, 82.02, 81.23, 72.16, 71.48, 71.40, 40.48, 39.20, 38.96, 38.52, 38.16, 37.98, 36.74, 30.44, 30.11, 29.95, 28.18, 20.07. $[\alpha]_D^{20}$ = -92.5 (c 1.0, $CHCl_3$). HPLC (Chiralpak IA column, 97:3 hexanes/isopropanol, 1 ml/min; tr= 11.6 min (minor), 12.8 min (major); 99% ee.

Kinetic resolution procedure:

(*R*)-di-*tert*-butyl 1-(2-oxo-1-(thiophen-2-yl)cyclohexyl)hydrazine-1,2-dicarboxylate (**2z**)



To a solution of **1z** (54 mg, 0.3 mmol) in DCM (0.6 mL) was added *di*-tertbutyl azodicarboxylates (90 mg, 0.39 mmol), 5Å MS (50 mg), and **(*R*)-C$_8$-TCYP** (36 mg, 0.03 mmol). After stirring for 60 at rt, the mixture was purified by flash column chromatography (10: 1 to 6: 1, Hexane/ethyl acetate) to afford the recovered starting material **1z** (24 mg, 45% yield, 96% ee) and the title product **2z** (68 mg, 55% yield, 93% ee). HPLC data for recovered **1z**: HPLC (Chiralpak IC column, 95:5 hexanes/ isopropanol, 1 ml/min; tr = 17.8 min (major), 20.2 min (minor); 96% ee. Data for **2z**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, J = 5.1 Hz, 1H), 6.95 (t, J = 4.4 Hz, 1H), 6.93 – 6.87 (m, 1H, 6.06 – 5.55 (m, 1H), 3.17 – 2.80 (m, 2H), 2.50 – 2.36 (m, 1H), 2.29 – 1.98 (m, 3H), 1.80 – 1.66 (m, 1H), 1.63 – 1.55 (m, 1H), 1.52 – 1.38 (m, 18H). ^{13}C

NMR (125 MHz, $CDCl_3$) δ 155.24, 141.54, 129.32, 126.47, 126.42, 120.92, 114.48, 112.17, 83.71, 81.73, 81.28, 72.40, 39.65, 28.20, 28.08, 27.97, 21.24. m/z HRMS (ESI) found $[M+Na]^+$ 433.1767, $C_{20}H_{30}N_2O_5SNa^+$ requires 433.1768. $[\alpha]_D^{20}$ = -53.8 (c 1.0, $CHCl_3$). HPLC (Chiralpak IC column, 92:8 hexanes/ isopropanol, 1 ml/min; tr= 12.4 min (minor), 17.8 min (major); 93% ee.

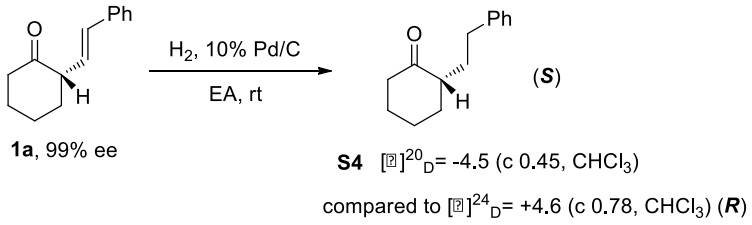
Kinetic resolution conditions for **1n** and **1t**:

To a solution of **1n or 1t** (0.3 mmol) in DCM (3 mL) was added *di*-tert-butyl azodicarboxylates (90 mg, 0.36 mmol), 5 Å MS (50 mg), and **(*R*)-C_8-TCYP** (18 mg, 0.015 mmol). After stirring for 40h at rt, the mixture was purified by flash column chromatography (15: 1 to 10: 1, hexane/ ethyl acetate) to afford the recovered starting material and the amination product.

For **1n**: Starting ketone **1n** (25 mg, 41% yield, 99% ee) was recovered with product **2a** (76 mg, 59% yield, 99% ee) obtained. HPLC data for recovered **1n**: HPLC (Chiralpak IC column, 95:5 hexanes/ isopropanol, 1 ml/min; tr = 15.8 min (major), 20.5 min (minor); 99% ee.

For **1t**: Starting ketone **1t** (20 mg, 30% yield, 97% ee) was recovered with product **2t** (96 mg, 70% yield, 97% ee) obtained. HPLC data for recovered **1a**: HPLC (Chiralpak IC column, 95:5 hexanes/ isopropanol, 1 ml/min; tr = 14.6 min (major), 21.1 min (minor); 97% ee.

Determine of the absolute configuration of recovered 1a:



1a, 99% ee

S4 $[\alpha]^{20}_D$= -4.5 (c 0.45, $CHCl_3$)

compared to $[\alpha]^{24}_D$= +4.6 (c 0.78, $CHCl_3$) (***R***)

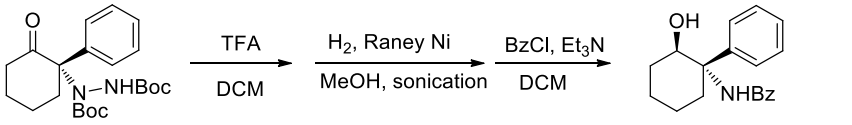
To a solution of **1a** (14 mg, 0.07 mmol) in ethyl acetate (2 mL) was added 10% Pd/C (40 mg) at rt. After purging with H_2, the mixture was stirred at rt for 3h. Filtration and concentration in vacuo gave a residue, which was purified by flash column chromatography (20 :1, hexane/ ethyl acetate) to give the title product **S4** (6.7 mg, 47% yield). The absolute configuration of the stereocenter was determined to be (*S*) by comparison of the optical rotation of **S4** with literature[15].

Large-scale synthesis example:

To the substrate **1a** (348 mg, 2.0 mmol) in a 1 dram (15 x 45 mm) vial equipped with an 8 mm magnetic stirrer bar was added DCM (1.0 ml). Subsequently, *di*-tert-butyl azodicarboxylates (598 mg, 2.6 mmol), 5Å MS (300 mg), and **(*R*)-C$_8$-TCYP** (240 mg, 0.2 mmol) were added. After all the reagents were dissolved, the mixture was warmed to 45 ºC with the cap open. After about 2h, the DCM was evaporated, leaving the mixture as syrup. After heated at 45 ºC for another 48 h, the mixture was cooled to rt and directly purified by flash column chromatography (10: 1 to 3: 1 hexane: ethyl acetate) to afford the desired product **2a** (775 mg, 96% yield, 99% ee) with recovery of **(*R*)-C$_8$-TCYP** (83 mg).

Transformation of the products:

N-((*1S,2R*)-2-hydroxy-1-phenylcyclohexyl)benzamide (**3a**)



2a, 99% ee

3a, 70% yield, 99% ee

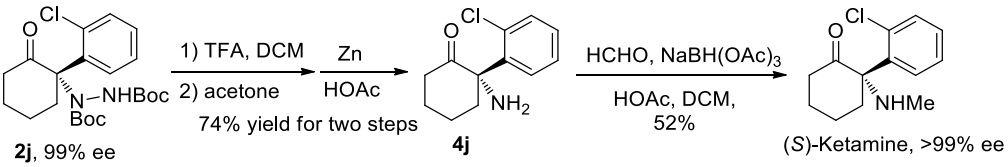
To a solution of **2a** (130 mg, 0.322 mmol) in DCM (3 mL) was added TFA (1.5 mL) at rt. After stirring for 3 h, the mixture was concentrated to afford a residue.

To the solution of the above residue in MeOH (4 mL) was added Raney Ni (200 mg). After purging with H_2, the mixture was stirred overnight under sonication. Then the mixture was filtered and concentrated to give a residue.

To the solution of the above residue in DCM (3 mL) was added Et_3N (134 uL, 0.97 mmol) and BzCl (75 uL, 0.64 mmol) at rt. After stirring for 3 h, satd. $NaHCO_3$ solution was added into the mixture, which was then extracted with DCM for 3 times. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue, which was purified by flash chromatography (3: 1, Hexane/ ethyl acetate) to afford **3a** (66 mg, 70% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.4 Hz, 2H), 7.65 (d, *J* = 7.8 Hz, 2H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.30 – 7.23 (m, 1H), 6.46 (s, 1H), 4.13 (t, *J* = 4.9 Hz, 1H), 3.45 – 2.56 (brs, 1H), 2.53 – 2.31 (m, 2H), 2.09 – 1.89 (m, 2H), 1.83 – 1.68 (m, 1H), 1.65 – 1.43 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.99, 142.50, 135.08, 131.73, 128.75, 128.61, 127.43, 127.19, 127.01, 74.64, 62.14, 31.29, 29.88, 21.61, 21.13.

m/z HRMS (ESI) found $[M+H]^+$ 296.1645, $C_{19}H_{22}NO_2^+$ requires 296.1645. $[\alpha]_D^{20}$ = -32.6 (c 1.0, $CHCl_3$). HPLC (Chiralpak IA column, 90:10 hexanes/ isopropanol, 1 ml/min; tr= 17.1 min (minor), 18.5 min (major); 99% ee.

(*S*)-Ketamine:

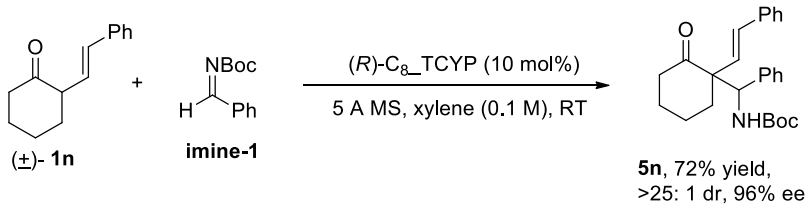


To a solution of **2j** (255 mg, 0.58 mmol) in DCM (5 mL) was added TFA (2.5 ml) at rt. After stirring for 3h, acetone (3 mL) was added and the mixture was stirred for another 10 min before concentration *in vacuo*.

To the solution of the above residue in HOAc (5 ml) was added active zinc powder (500 mg). After purging with N_2, the mixture was stirred overnight. After filtration, the filtrate was concentrated *in vacuo* to afford a residue, which was diluted with DCM and basified with satd. Na_2CO_3 solution. Extraction with DCM five times to afford the organic layer, which was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue, which was purified by flash chromatography (1: 1, Hexane/ EA) to afford **4j** (96 mg, 74% yield). The ^1H NMR was matched with the literature[16].

To the solution of **4j** (12.0 mg, 0.54 mmol) in MeOH (1 mL) was added HCHO (5.2 uL, 37% aqueous solution, 0.065 mmol), HOAc (3.1 uL, 0.054 mmol) and $NaBH(OAc)_3$ (17 mg, 0.081) successively. After stirring overnight, satd. Na_2CO_3 solution was added. The mixture was extracted with Et_2O three times and the combined organic layer was then dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue, which was purified by flash chromatography (3: 2, Hexane/ethyl acetate) to afford (*S*)-Ketamine (6.6 mg, 52% yield). The ^1H NMR was matched with the literature[17]. $[\alpha]_D^{20}$ = -55.5 (c 0.47, EtOH), compared to $[\alpha]_D^{20}$ = -56.3 (c 1.20, EtOH)[17]. HPLC (Chiralpak ASH column, 95:5 hexanes/ isopropanol, 1 ml/min; tr= 6.5 min (major), 7.3 min (minor); >99% ee.

Asymmetric Mannich reaction example:



To a solution of **1n** (60 mg, 0.3 mmol) in xylene (3.0 mL) was added **imine-1** (92 mg, 0.45 mmol), 5 Å MS (50 mg), and **(*R*)-C$_8$-TCYP** (36 mg, 0.03 mmol). After stirring for 40h at rt, the mixture was purified by fast column chromatography (10: 1, Hexane/ EA) to afford the desired product **5n** (87 mg, 72% yield, 96% ee). Data for **5n**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.21 (m, 10H), .43 – 6.13 (m, 3H), 4.76 (d, *J* = 10.4 Hz, 1H), 2.60 (ddd, *J* = 15.3, 11.6, 6.2 Hz, 1H), 2.42 (dt, *J* = 15.5, 4.7 Hz, 1H), 2.07 – 1.95 (m, 1H), 1.92 – 1.69 (m, 5H), 1.25 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 213.35, 155.48, 139.71, 136.74, 133.22, 131.75, 129.28, 128.66, 128.19, 127.97, 127.42, 126.56, 79.25, 60.51, 59.85, 40.55, 35.97, 32.00, 28.34, 25.93, 21.33. m/z HRMS (ESI) found $[M+H]^+$ 406.2382, $C_{26}H_{32}NO_3^+$ requires 406.2377. HPLC (Chiralpak IC column, 97:3 hexanes/ isopropanol, 1 ml/min; tr= 11.4 min (major), 19.0 min (minor); 96% ee.

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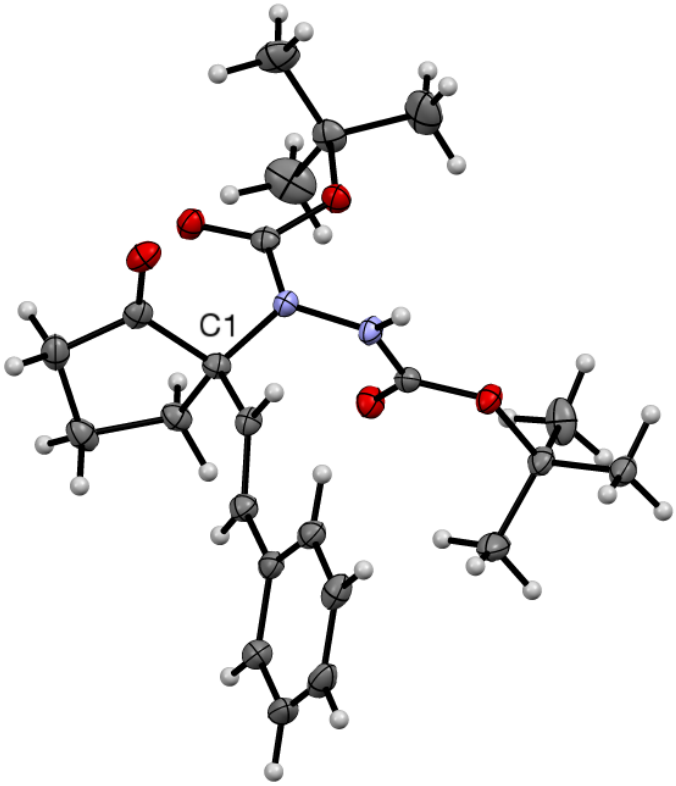
X-Ray Crystal Structure Data for 2v



A colorless block 0.13 x 0.06 x 0.03 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using phi and omega scans. Crystal-to-detector distance was 60 mm and exposure time was 5 seconds per frame using a scan width of 1.0°. Data collection was 99.7% complete to 67.00° in θ. A total of 21859 reflections were collected covering the indices, -12<=h<=10, -12<=k<=12, -13<=l<=13. 4110 reflections were

found to be symmetry independent, with an R_{int} of 0.0338. Indexing and unit cell refinement indicated a primitive, orthorhombic lattice. The space group was found to be P2(1) (No. 4). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by direct methods (SHELXL-2013) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2013). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-97. Absolute stereochemistry was unambiguously determined to be *S* at C1.

Table 1. Crystal data and structure refinement for xy001.

Identification code	XY001	
Empirical formula	C1.77 H2.46 F0 N0.15 O0.38	
Formula weight	32.04	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P 2(1)	
Unit cell dimensions	a = 10.2527(6) Å	α= 90°.
	b = 10.1344(6) Å	β= 95.063(2)°.
	c = 11.1386(6) Å	γ = 90°.
Volume	1152.84(11) $Å^3$	
Z	26	
Density (calculated)	1.200 Mg/m^3	
Absorption coefficient	0.686 mm^{-1}	
F(000)	448	

Crystal size	0.130 x 0.060 x 0.030 mm^3
Theta range for data collection	3.984 to 68.228°.
Index ranges	-12<=h<=10, -12<=k<=12, -13<=l<=13
Reflections collected	21859
Independent reflections	4110 [R(int) = 0.0338]
Completeness to theta = 67.000∞	99.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7531 and 0.7121
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4110 / 1 / 277
Goodness-of-fit on F^2	1.027
Final R indices [I>2sigma(I)]	R1 = 0.0253, wR2 = 0.0649
R indices (all data)	R1 = 0.0255, wR2 = 0.0651
Absolute structure parameter	0.04(3)
Extinction coefficient	n/a
Largest diff. peak and hole	0.180 and -0.196 $e.Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)

for xy001. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(14)	5333(2)	7760(2)	5606(1)	18(1)
C(15)	7142(2)	7625(2)	7186(2)	21(1)
C(16)	8144(2)	7042(2)	6415(2)	34(1)
C(17)	6463(2)	6577(2)	7874(2)	32(1)
C(18)	7743(2)	8678(2)	8036(2)	25(1)
C(19)	3752(2)	7923(2)	3126(1)	18(1)
N(2)	4432(1)	8656(1)	5130(1)	18(1)
O(3)	5331(1)	6604(1)	5339(1)	22(1)
O(4)	4936(1)	8358(1)	2923(1)	22(1)
O(5)	6161(1)	8382(1)	6411(1)	20(1)
C(1)	2291(2)	7599(2)	4723(1)	18(1)
C(2)	2293(2)	6084(2)	4724(2)	22(1)
C(3)	835(2)	5700(2)	4530(2)	26(1)
C(4)	234(2)	6731(2)	3647(2)	27(1)
C(5)	1060(2)	7955(2)	3855(1)	21(1)
C(6)	2039(2)	8219(2)	5914(1)	19(1)

C(7)	1827(2)	7548(2)	6908(1)	21(1)
C(8)	1535(2)	8094(2)	8077(1)	21(1)
C(9)	1287(2)	7219(2)	9004(2)	26(1)
C(10)	1027(2)	7685(2)	10127(2)	31(1)
C(11)	990(2)	9023(2)	10352(2)	31(1)
C(12)	1235(2)	9904(2)	9442(2)	27(1)
C(13)	1510(2)	9444(2)	8318(2)	22(1)
C(20)	5512(2)	7966(2)	1802(2)	26(1)
C(21)	4749(2)	8584(2)	713(2)	36(1)
C(22)	5560(3)	6473(2)	1724(2)	45(1)
C(23)	6871(2)	8552(3)	1995(2)	45(1)
N(1)	3456(1)	8230(1)	4280(1)	18(1)
O(1)	813(1)	9040(1)	3466(1)	25(1)
O(2)	2973(1)	7359(1)	2424(1)	22(1)

Table 3. Bond lengths [Å] and angles [°] for xy001.

C(14)-O(3)	1.209(2)	N(2)-H(2)	0.8800
C(14)-O(5)	1.337(2)	O(4)-C(20)	1.482(2)
C(14)-N(2)	1.369(2)	C(1)-N(1)	1.477(2)
C(15)-O(5)	1.4802(19)	C(1)-C(6)	1.510(2)
C(15)-C(17)	1.515(3)	C(1)-C(2)	1.536(2)
C(15)-C(16)	1.515(3)	C(1)-C(5)	1.563(2)
C(15)-C(18)	1.521(2)	C(2)-C(3)	1.541(2)
C(16)-H(16A)	0.9800	C(2)-H(2A)	0.9900
C(16)-H(16B)	0.9800	C(2)-H(2B)	0.9900
C(16)-H(16C)	0.9800	C(3)-C(4)	1.528(3)
C(17)-H(17A)	0.9800	C(3)-H(3A)	0.9900
C(17)-H(17B)	0.9800	C(3)-H(3B)	0.9900
C(17)-H(17C)	0.9800	C(4)-C(5)	1.508(3)
C(18)-H(18A)	0.9800	C(4)-H(4A)	0.9900
C(18)-H(18B)	0.9800	C(4)-H(4B)	0.9900
C(18)-H(18C)	0.9800	C(5)-O(1)	1.201(2)
C(19)-O(2)	1.211(2)	C(6)-C(7)	1.333(2)
C(19)-O(4)	1.330(2)	C(6)-H(6)	0.9500
C(19)-N(1)	1.382(2)	C(7)-C(8)	1.470(2)
N(2)-N(1)	1.3839(18)	C(7)-H(7)	0.9500

C(8)-C(13)	1.395(3)		
C(8)-C(9)	1.400(2)	O(3)-C(14)-O(5)	127.54(15)
C(9)-C(10)	1.385(3)	O(3)-C(14)-N(2)	124.10(15)
C(9)-H(9)	0.9500	O(5)-C(14)-N(2)	108.34(13)
C(10)-C(11)	1.380(3)	O(5)-C(15)-C(17)	109.82(14)
C(10)-H(10)	0.9500	O(5)-C(15)-C(16)	109.35(14)
C(11)-C(12)	1.390(3)	C(17)-C(15)-C(16)	112.22(16)
C(11)-H(11)	0.9500	O(5)-C(15)-C(18)	102.48(13)
C(12)-C(13)	1.388(2)	C(17)-C(15)-C(18)	110.85(15)
C(12)-H(12)	0.9500	C(16)-C(15)-C(18)	111.66(15)
C(13)-H(13)	0.9500	C(15)-C(16)-H(16A)	109.5
C(20)-C(23)	1.512(3)	C(15)-C(16)-H(16B)	109.5
C(20)-C(22)	1.516(3)	H(16A)-C(16)-H(16B)	109.5
C(20)-C(21)	1.519(3)	C(15)-C(16)-H(16C)	109.5
C(21)-H(21A)	0.9800	H(16A)-C(16)-H(16C)	109.5
C(21)-H(21B)	0.9800	H(16B)-C(16)-H(16C)	109.5
C(21)-H(21C)	0.9800	C(15)-C(17)-H(17A)	109.5
C(22)-H(22A)	0.9800	C(15)-C(17)-H(17B)	109.5
C(22)-H(22B)	0.9800	H(17A)-C(17)-H(17B)	109.5
C(22)-H(22C)	0.9800	C(15)-C(17)-H(17C)	109.5
C(23)-H(23A)	0.9800	H(17A)-C(17)-H(17C)	109.5
C(23)-H(23B)	0.9800	H(17B)-C(17)-H(17C)	109.5
C(23)-H(23C)	0.9800	C(15)-C(18)-H(18A)	109.5

C(15)-C(18)-H(18B)	109.5	C(3)-C(2)-H(2B)	110.8
H(18A)-C(18)-H(18B)	109.5	H(2A)-C(2)-H(2B)	108.9
C(15)-C(18)-H(18C)	109.5	C(4)-C(3)-C(2)	104.37(14)
H(18A)-C(18)-H(18C)	109.5	C(4)-C(3)-H(3A)	110.9
H(18B)-C(18)-H(18C)	109.5	C(2)-C(3)-H(3A)	110.9
O(2)-C(19)-O(4)	127.31(14)	C(4)-C(3)-H(3B)	110.9
O(2)-C(19)-N(1)	121.40(15)	C(2)-C(3)-H(3B)	110.9
O(4)-C(19)-N(1)	111.27(13)	H(3A)-C(3)-H(3B)	108.9
C(14)-N(2)-N(1)	118.72(13)	C(5)-C(4)-C(3)	105.94(14)
C(14)-N(2)-H(2)	120.6	C(5)-C(4)-H(4A)	110.5
N(1)-N(2)-H(2)	120.6	C(3)-C(4)-H(4A)	110.5
C(19)-O(4)-C(20)	119.50(13)	C(5)-C(4)-H(4B)	110.5
C(14)-O(5)-C(15)	120.35(12)	C(3)-C(4)-H(4B)	110.5
N(1)-C(1)-C(6)	108.63(13)	H(4A)-C(4)-H(4B)	108.7
N(1)-C(1)-C(2)	115.59(14)	O(1)-C(5)-C(4)	126.85(16)
C(6)-C(1)-C(2)	114.58(14)	O(1)-C(5)-C(1)	124.62(15)
N(1)-C(1)-C(5)	109.02(12)	C(4)-C(5)-C(1)	108.48(14)
C(6)-C(1)-C(5)	104.80(13)	C(7)-C(6)-C(1)	124.78(15)
C(2)-C(1)-C(5)	103.41(13)	C(7)-C(6)-H(6)	117.6
C(1)-C(2)-C(3)	104.56(14)	C(1)-C(6)-H(6)	117.6
C(1)-C(2)-H(2A)	110.8	C(6)-C(7)-C(8)	127.24(16)
C(3)-C(2)-H(2A)	110.8	C(6)-C(7)-H(7)	116.4
C(1)-C(2)-H(2B)	110.8	C(8)-C(7)-H(7)	116.4

C(13)-C(8)-C(9)	118.15(16)	C(22)-C(20)-C(21)	112.56(18)
C(13)-C(8)-C(7)	123.21(15)	C(20)-C(21)-H(21A)	109.5
C(9)-C(8)-C(7)	118.64(16)	C(20)-C(21)-H(21B)	109.5
C(10)-C(9)-C(8)	120.77(18)	H(21A)-C(21)-H(21B)	109.5
C(10)-C(9)-H(9)	119.6	C(20)-C(21)-H(21C)	109.5
C(8)-C(9)-H(9)	119.6	H(21A)-C(21)-H(21C)	109.5
C(11)-C(10)-C(9)	120.62(17)	H(21B)-C(21)-H(21C)	109.5
C(11)-C(10)-H(10)	119.7	C(20)-C(22)-H(22A)	109.5
C(9)-C(10)-H(10)	119.7	C(20)-C(22)-H(22B)	109.5
C(10)-C(11)-C(12)	119.34(17)	H(22A)-C(22)-H(22B)	109.5
C(10)-C(11)-H(11)	120.3	C(20)-C(22)-H(22C)	109.5
C(12)-C(11)-H(11)	120.3	H(22A)-C(22)-H(22C)	109.5
C(13)-C(12)-C(11)	120.34(18)	H(22B)-C(22)-H(22C)	109.5
C(13)-C(12)-H(12)	119.8	C(20)-C(23)-H(23A)	109.5
C(11)-C(12)-H(12)	119.8	C(20)-C(23)-H(23B)	109.5
C(12)-C(13)-C(8)	120.79(17)	H(23A)-C(23)-H(23B)	109.5
C(12)-C(13)-H(13)	119.6	C(20)-C(23)-H(23C)	109.5
C(8)-C(13)-H(13)	119.6	H(23A)-C(23)-H(23C)	109.5
O(4)-C(20)-C(23)	101.83(14)	H(23B)-C(23)-H(23C)	109.5
O(4)-C(20)-C(22)	109.42(16)	C(19)-N(1)-N(2)	120.11(13)
C(23)-C(20)-C(22)	111.46(19)	C(19)-N(1)-C(1)	117.61(13)
O(4)-C(20)-C(21)	110.26(14)	N(2)-N(1)-C(1)	117.61(12)
C(23)-C(20)-C(21)	110.78(17)		

Symmetry transformations used to generate equivalent atoms: -x, y+1/2, -z

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for xy001. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(14)	20(1)	19(1)	16(1)	1(1)	2(1)	-2(1)
C(15)	20(1)	21(1)	22(1)	2(1)	-4(1)	1(1)
C(16)	22(1)	31(1)	49(1)	-12(1)	2(1)	3(1)
C(17)	42(1)	28(1)	26(1)	8(1)	-7(1)	-8(1)
C(18)	25(1)	26(1)	23(1)	1(1)	-5(1)	-2(1)
C(19)	19(1)	16(1)	19(1)	2(1)	2(1)	3(1)
N(2)	20(1)	15(1)	18(1)	-2(1)	-3(1)	-1(1)
O(3)	25(1)	16(1)	26(1)	-2(1)	-2(1)	0(1)
O(4)	19(1)	26(1)	20(1)	-1(1)	4(1)	-2(1)
O(5)	23(1)	16(1)	21(1)	0(1)	-5(1)	1(1)
C(1)	20(1)	17(1)	18(1)	1(1)	2(1)	0(1)
C(2)	24(1)	18(1)	23(1)	-1(1)	5(1)	-2(1)
C(3)	29(1)	23(1)	28(1)	-5(1)	9(1)	-7(1)
C(4)	22(1)	35(1)	25(1)	-6(1)	3(1)	-5(1)
C(5)	19(1)	28(1)	16(1)	-3(1)	4(1)	2(1)
C(6)	18(1)	18(1)	19(1)	-1(1)	0(1)	1(1)
C(7)	21(1)	21(1)	20(1)	1(1)	0(1)	0(1)
C(8)	16(1)	28(1)	18(1)	3(1)	-1(1)	0(1)

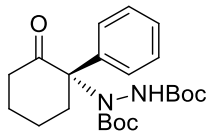
C(9)	26(1)	32(1)	21(1)	4(1)	-1(1)	-5(1)
C(10)	26(1)	49(1)	17(1)	7(1)	-1(1)	-10(1)
C(11)	22(1)	54(1)	16(1)	-5(1)	1(1)	-2(1)
C(12)	21(1)	36(1)	24(1)	-5(1)	-2(1)	3(1)
C(13)	19(1)	30(1)	18(1)	1(1)	0(1)	2(1)
C(20)	22(1)	30(1)	26(1)	-3(1)	10(1)	2(1)
C(21)	36(1)	49(1)	23(1)	2(1)	12(1)	7(1)
C(22)	49(1)	32(1)	58(1)	-4(1)	24(1)	12(1)
C(23)	26(1)	69(2)	42(1)	-8(1)	14(1)	-8(1)
N(1)	18(1)	20(1)	15(1)	-1(1)	0(1)	-2(1)
O(1)	26(1)	28(1)	21(1)	0(1)	0(1)	7(1)
O(2)	21(1)	27(1)	19(1)	-3(1)	1(1)	0(1)

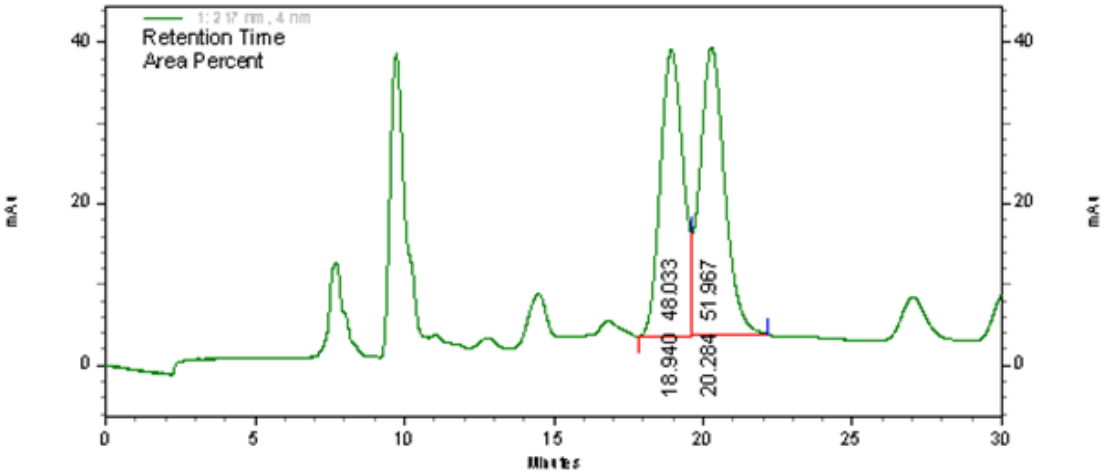
Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for xy001.

	x	y	z	U(eq)
H(16A)	8476	7736	5910	52
H(16B)	7732	6347	5900	52
H(16C)	8870	6667	6936	52
H(17A)	7094	6177	8479	49
H(17B)	6107	5896	7313	49
H(17C)	5750	6981	8275	49
H(18A)	7062	9059	8495	37
H(18B)	8129	9373	7568	37
H(18C)	8426	8281	8593	37
H(2)	4471	9487	5360	22
H(2A)	2695	5737	5501	26
H(2B)	2783	5737	4064	26
H(3A)	731	4801	4186	32
H(3B)	421	5730	5300	32
H(4A)	252	6419	2806	33
H(4B)	-685	6912	3802	33

H(6)	2030	9155	5958	22
H(7)	1869	6614	6854	25
H(9)	1297	6295	8860	32
H(10)	872	7078	10748	37
H(11)	800	9338	11120	37
H(12)	1214	10827	9590	33
H(13)	1682	10055	7705	27
H(21A)	4710	9542	823	54
H(21B)	3859	8224	628	54
H(21C)	5186	8386	-13	54
H(22A)	5986	6116	2478	68
H(22B)	6058	6213	1051	68
H(22C)	4667	6124	1594	68
H(23A)	6805	9511	2084	68
H(23B)	7359	8348	1300	68
H(23C)	7329	8175	2725	68

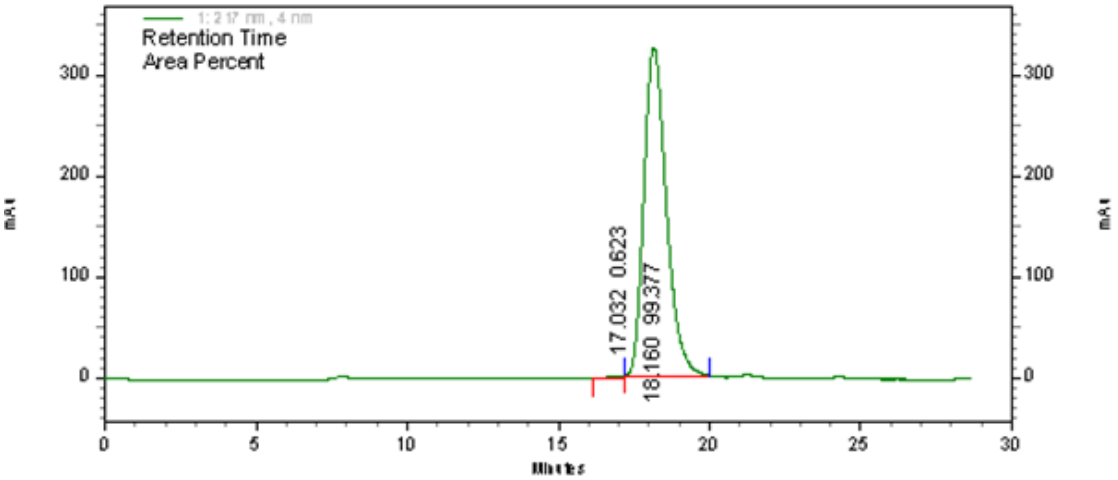
(*S*)-di-*tert*-butyl 1-(2-oxo-1-phenylcyclohexyl)hydrazine-1,2-dicarboxylate (**2a**)





1: 217 nm, 4 nm
Results

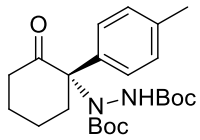
Pk #	Retention Time	Area Percent	Lambda Max
1	18.940	48.033	202
2	20.284	51.967	202

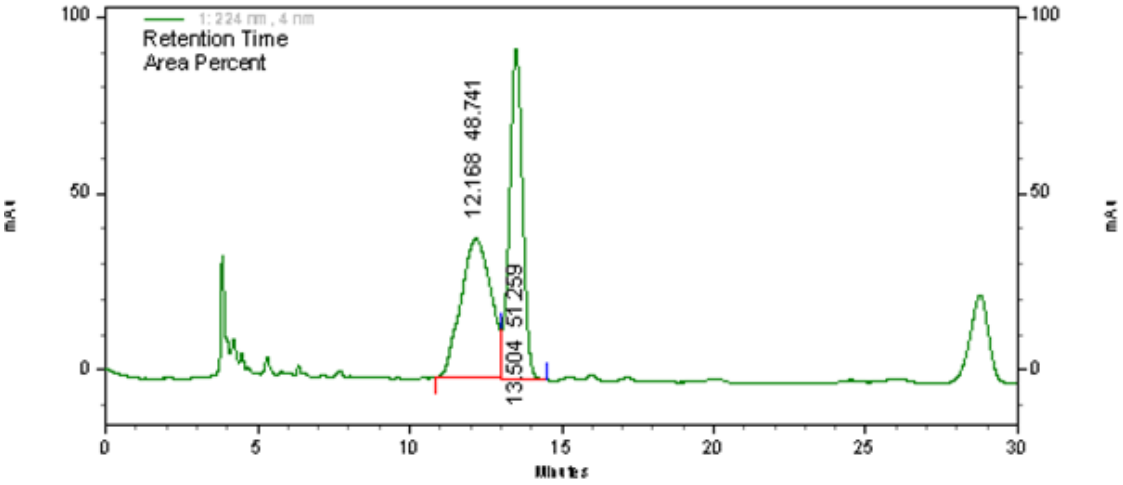


1: 217 nm, 4 nm
Results

Pk #	Retention Time	Area Percent	Lambda Max
1	17.032	0.623	667
2	18.160	99.377	190

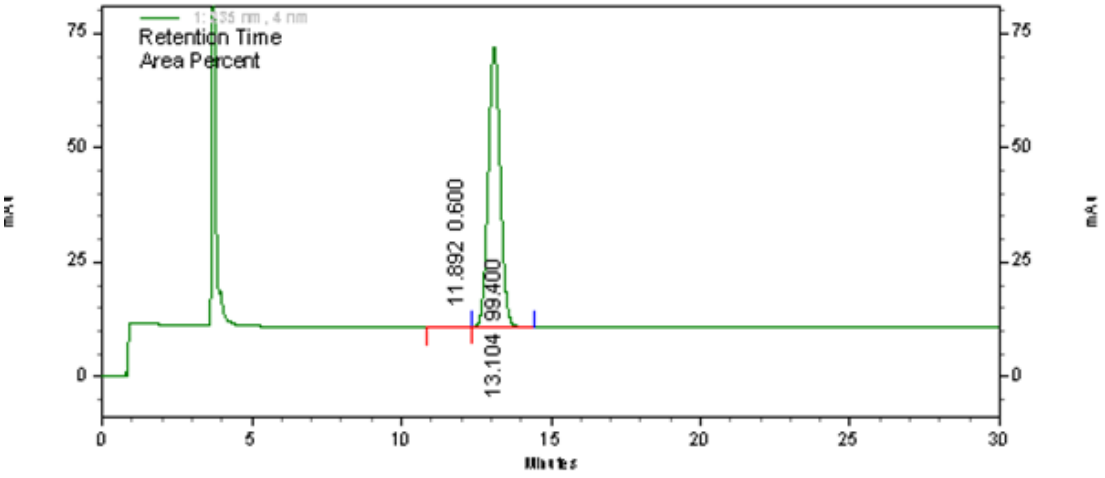
(*S*)-di-*tert*-butyl 1-(2-oxo-1-(p-tolyl)cyclohexyl)hydrazine-1,2-dicarboxylate (**2b**)





1: 224 nm, 4 nm
Results

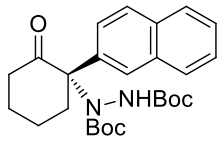
Pk #	Retention Time	Area Percent	Lambda Max
1	12.168	48.741	205
2	13.504	51.259	205

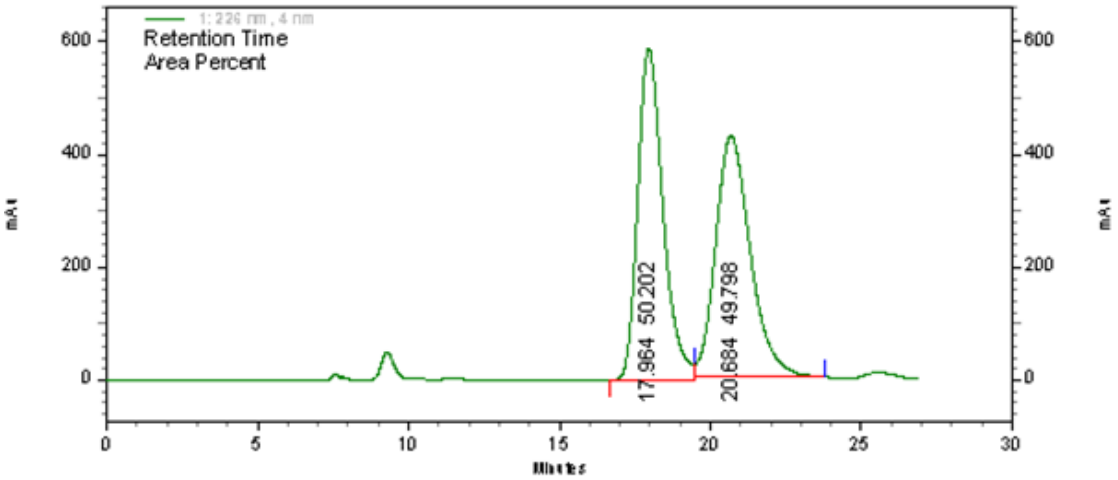


1: 235 nm, 4 nm
Results

Pk #	Retention Time	Area Percent	Lambda Max
1	11.892	0.600	205
2	13.104	99.400	205

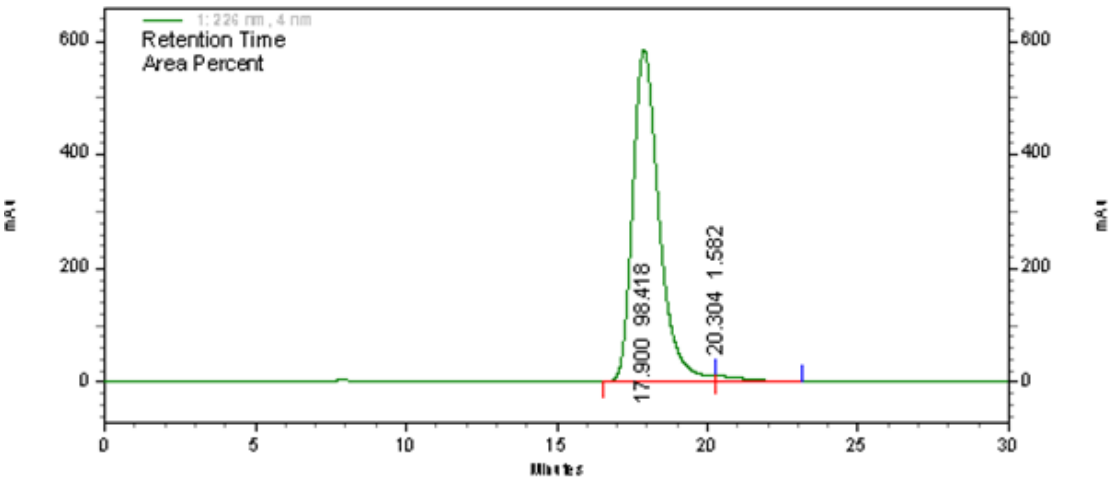
(*S*)-di-*tert*-butyl 1-(1-(naphthalen-2-yl)-2-oxocyclohexyl)hydrazine-1,2-dicarboxylate (**2c**)





1: 226 nm, 4 nm
Results

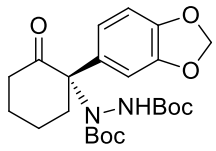
Pk #	Retention Time	Area Percent	Lambda Max
1	17.964	50.202	224
2	20.684	49.798	224

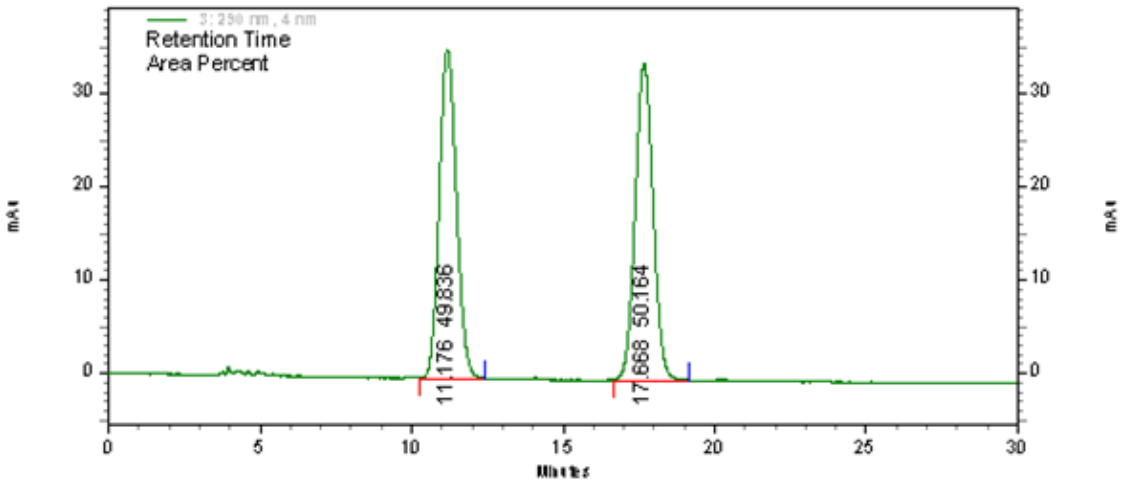


1: 226 nm, 4 nm
Results

Pk #	Retention Time	Area Percent	Lambda Max
1	17.900	98.418	224
2	20.304	1.582	667

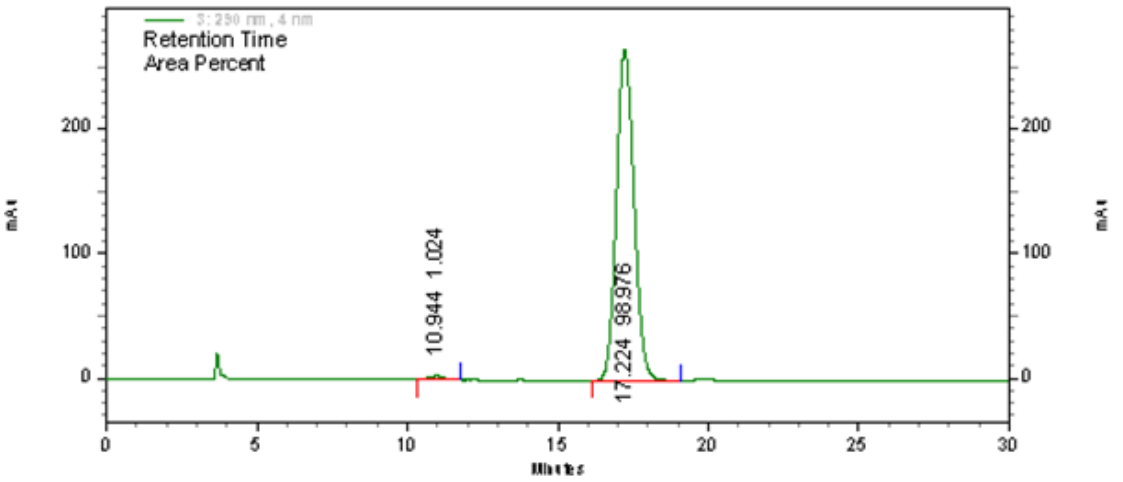
(*S*)-di-*tert*-butyl 1-(1-(benzo[d][1,3]dioxol-5-yl)-2-oxocyclohexyl)hydrazine-1,2-dicarboxylate (**2d**)





3: 290 nm, 4 nm
Results

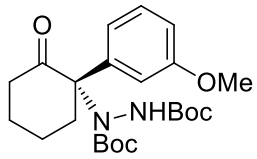
Pk #	Retention Time	Area Percent	Lambda Max
1	11.176	49.836	206
2	17.668	50.164	206

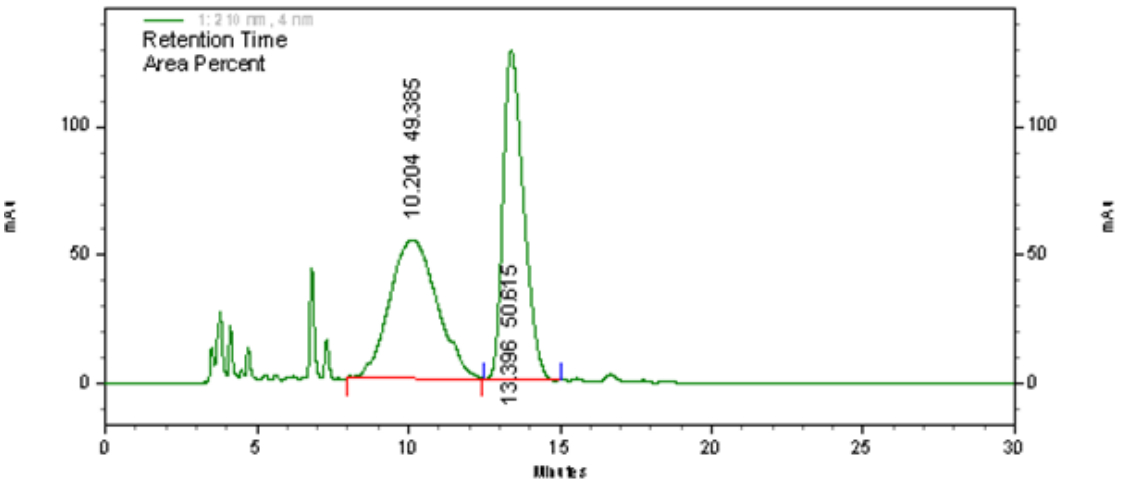


3: 290 nm, 4 nm
Results

Pk #	Retention Time	Area Percent	Lambda Max
1	10.944	1.024	206
2	17.224	98.976	193

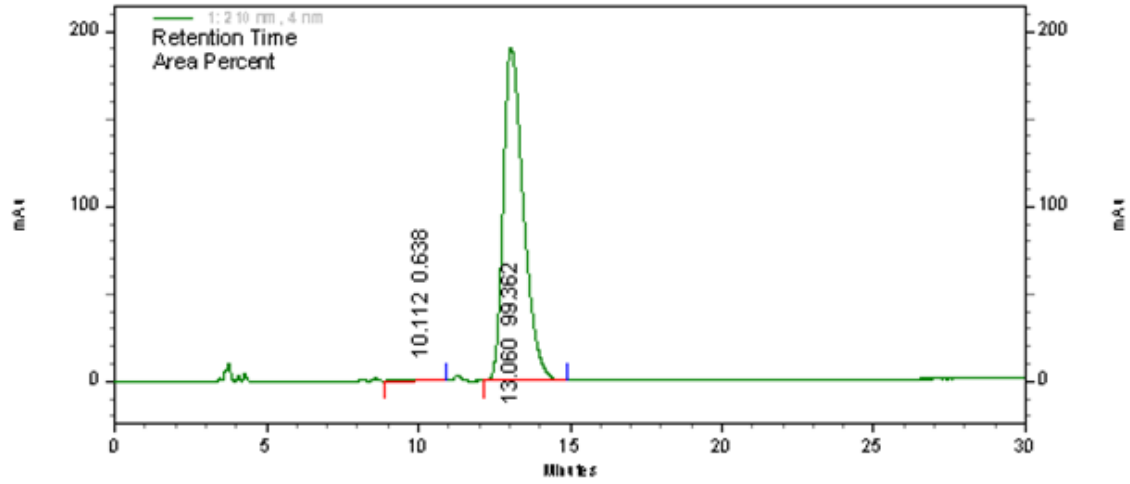
(*S*)-di-*tert*-butyl 1-(1-(3-methoxyphenyl)-2-oxocyclohexyl)hydrazine-1,2-dicarboxylate (**2e**)





1: 210 nm, 4 nm
Results

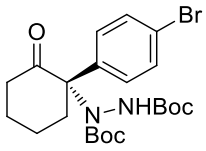
Pk #	Retention Time	Area Percent	Lambda Max
1	10.204	49.385	206
2	13.396	50.615	206

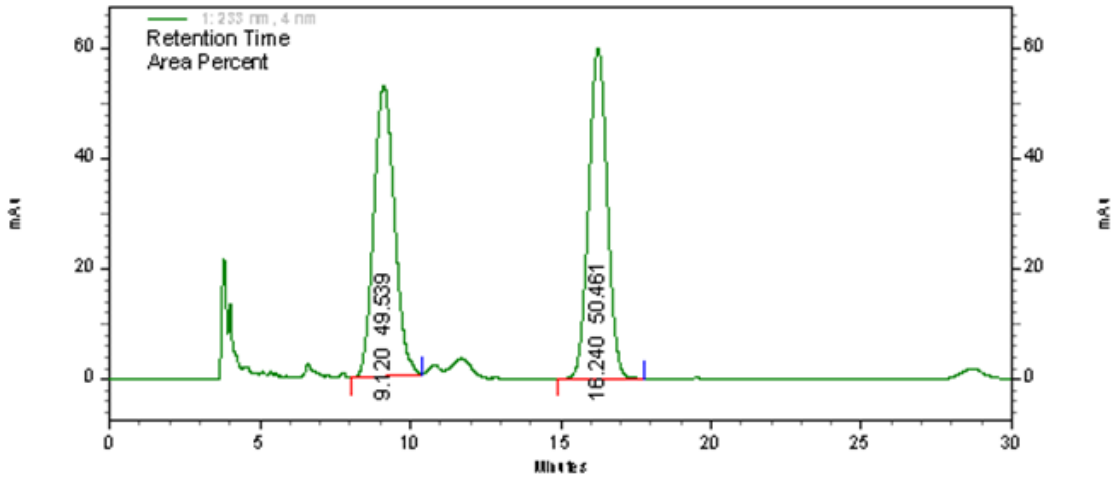


1: 210 nm, 4 nm
Results

Pk #	Retention Time	Area Percent	Lambda Max
1	10.112	0.638	206
2	13.060	99.362	206

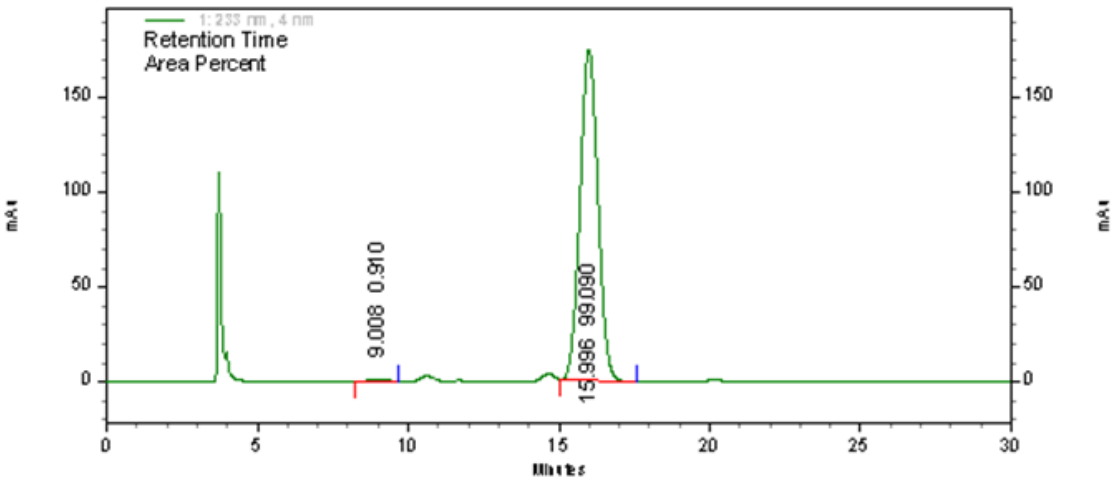
(*S*)-di-*tert*-butyl 1-(1-(4-bromophenyl)-2-oxocyclohexyl)hydrazine-1,2-dicarboxylate (**2f**)





1: 233 nm, 4 nm
Results

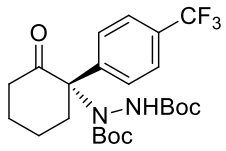
Pk #	Retention Time	Area Percent	Lambda Max
1	9.120	49.539	204
2	16.240	50.461	204

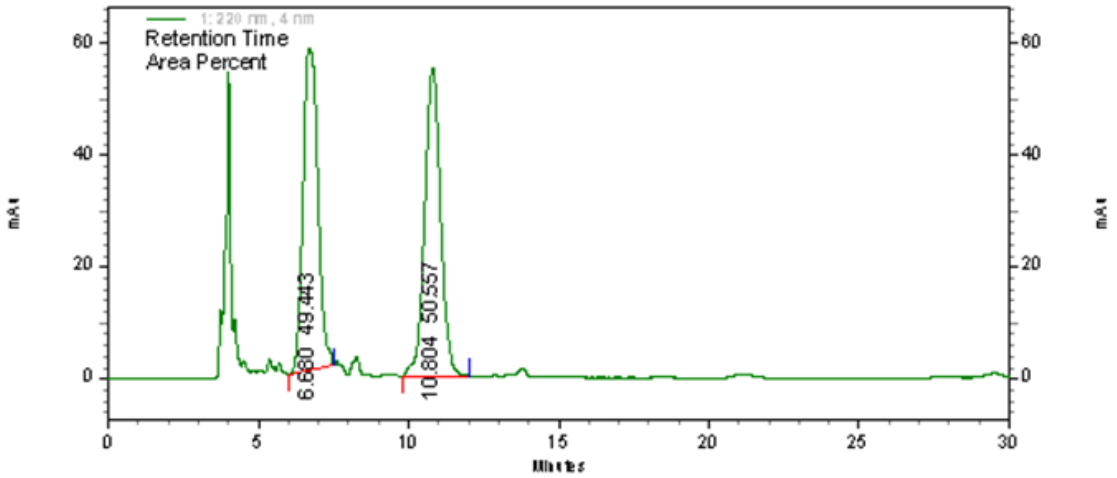


1: 233 nm, 4 nm
Results

Pk #	Retention Time	Area Percent	Lambda Max
1	9.008	0.910	662
2	15.996	99.090	202

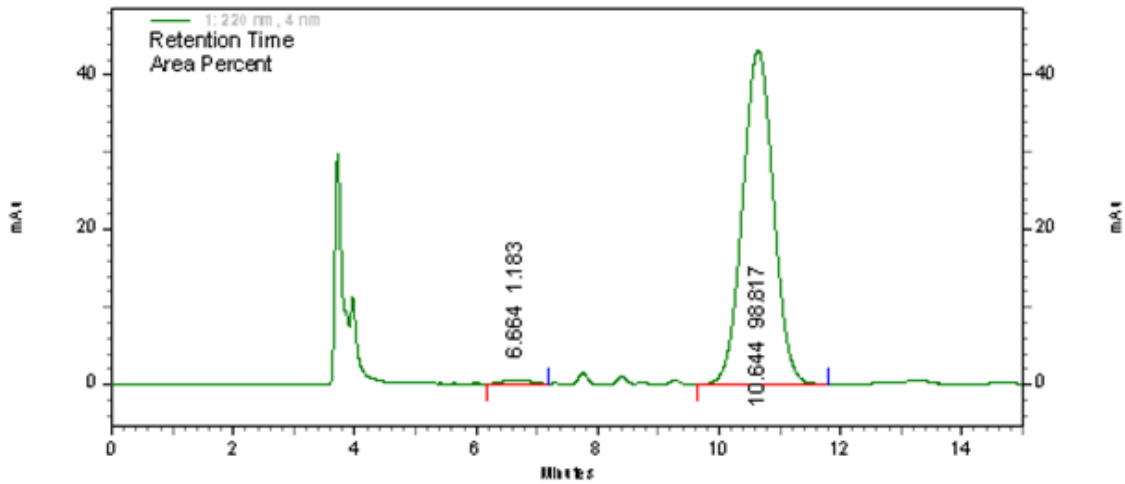
(*S*)-di-*tert*-butyl 1-(2-oxo-1-(4-(trifluoromethyl)phenyl)cyclohexyl)hydrazine-1,2-dicarboxylate (**2g**)





1: 220 nm, 4 nm
Results

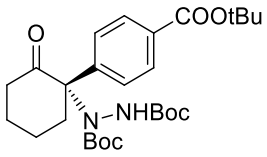
Pk #	Retention Time	Area Percent	Lambda Max
1	6.680	49.443	263
2	10.804	50.557	662

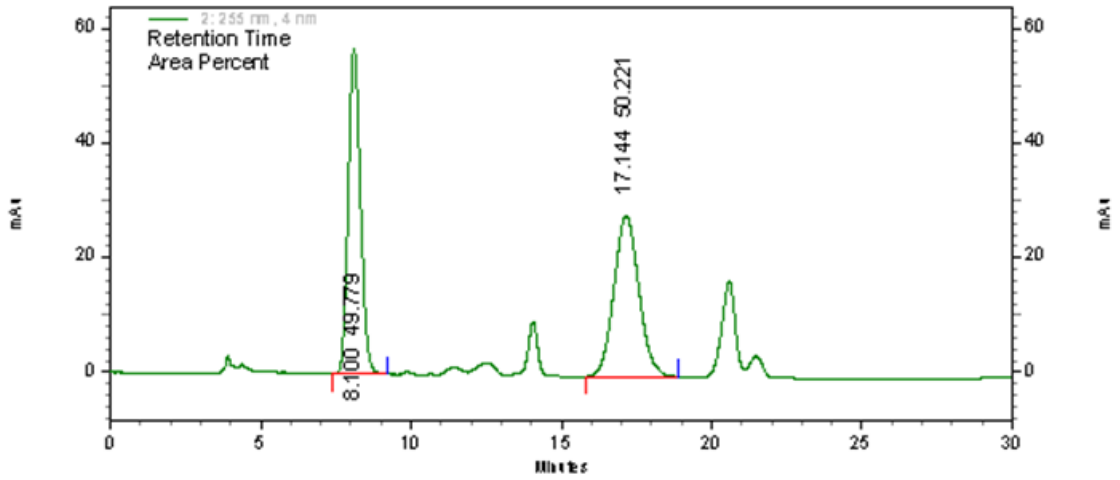


1: 220 nm, 4 nm
Results

Pk #	Retention Time	Area Percent	Lambda Max
1	6.664	1.183	647
2	10.644	98.817	263

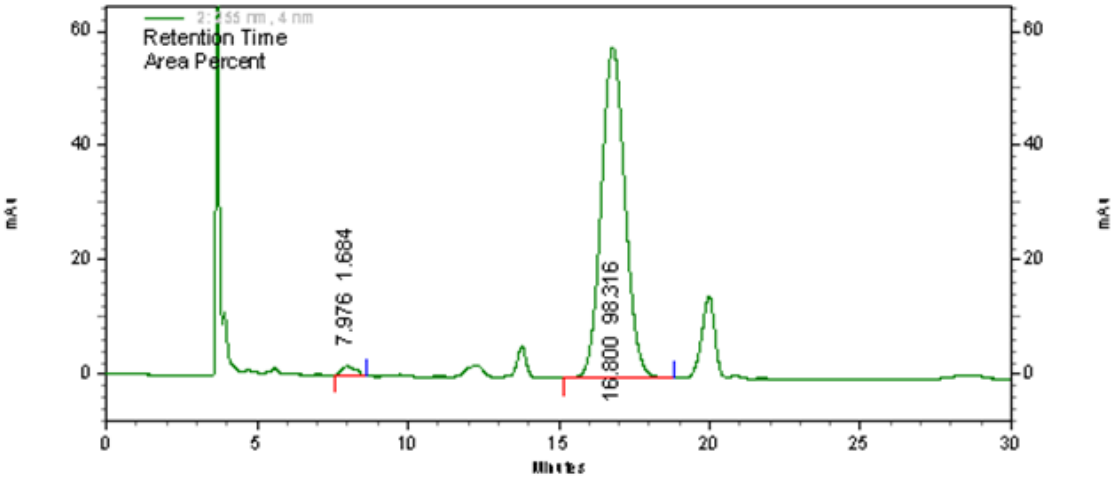
(*S*)-di-*tert*-butyl 1-(1-(4-(tert-butoxycarbonyl)phenyl)-2-oxocyclohexyl)hydrazine-1,2-dicarboxylate (**2h**)





2: 255 nm, 4 nm
Results

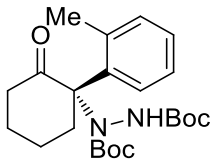
Pk #	Retention Time	Area Percent	Lambda Max
1	8.100	49.779	205
2	17.144	50.221	237

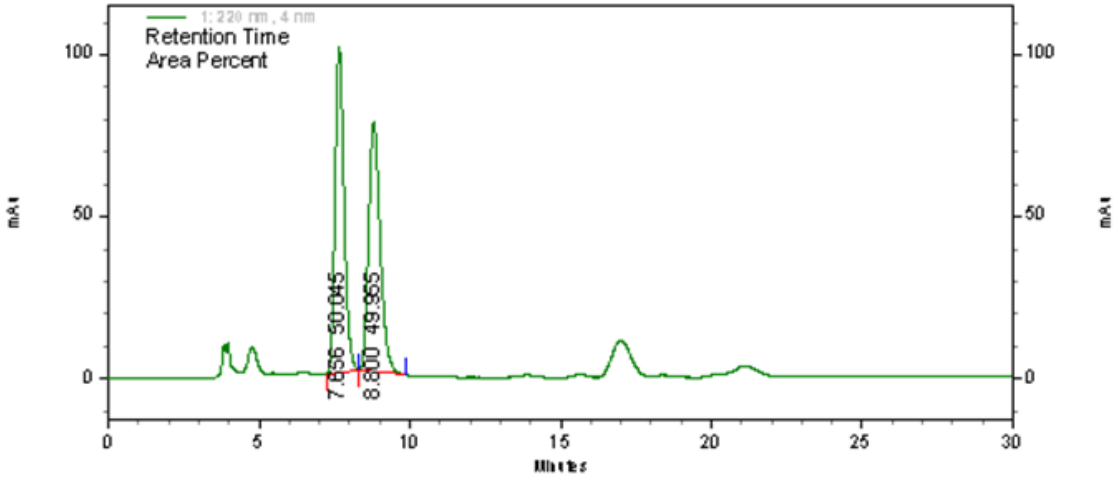


2: 255 nm, 4 nm
Results

Pk #	Retention Time	Area Percent	Lambda Max
1	7.976	1.684	239
2	16.800	98.316	205

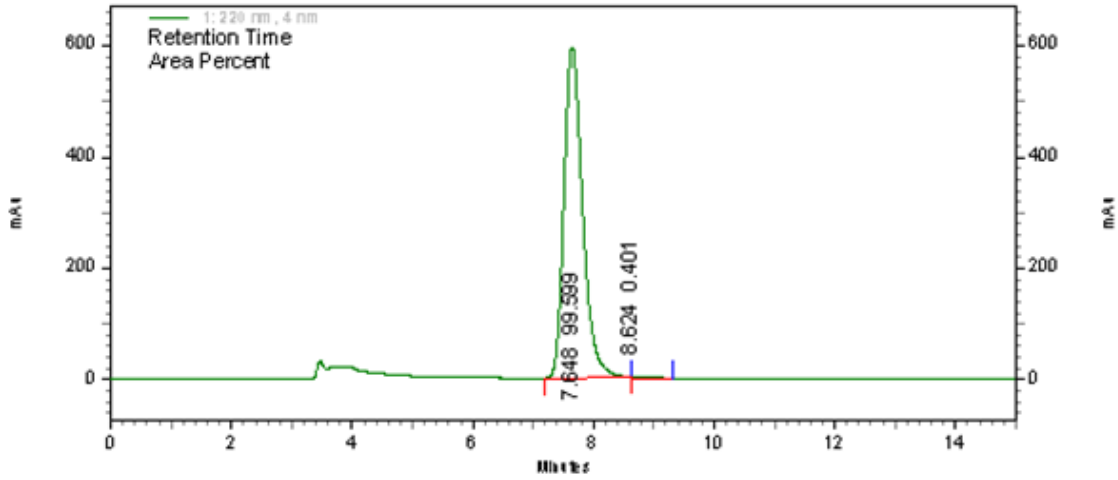
(*S*)-di-*tert*-butyl 1-(2-oxo-1-(o-tolyl)cyclohexyl)hydrazine-1,2-dicarboxylate (**2i**)





1: 220 nm, 4 nm
Results

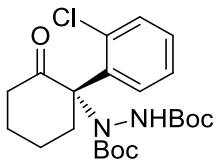
Pk #	Retention Time	Area Percent	Lambda Max
1	7.656	50.045	667
2	8.800	49.955	668

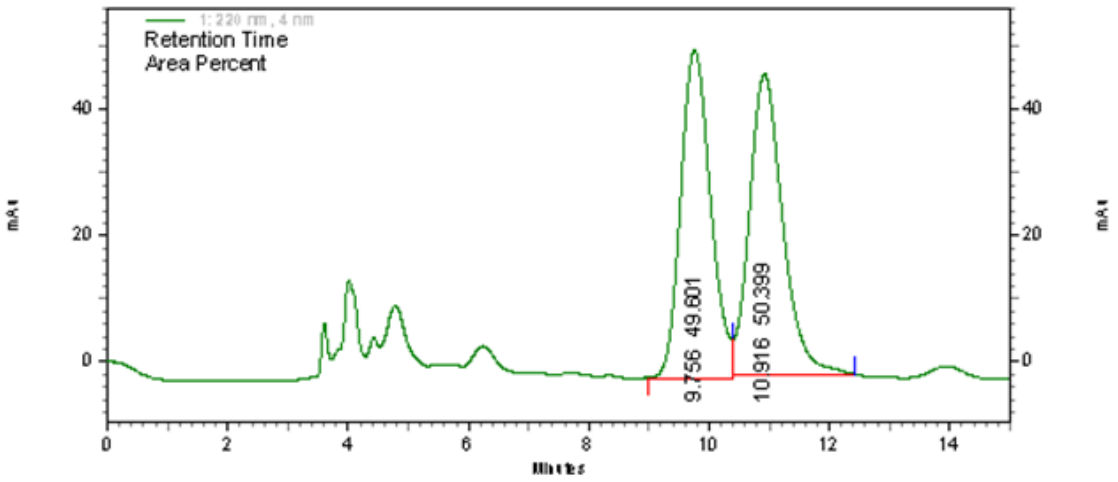


1: 220 nm, 4 nm
Results

Pk #	Retention Time	Area Percent	Lambda Max
1	7.648	99.599	198
2	8.624	0.401	664

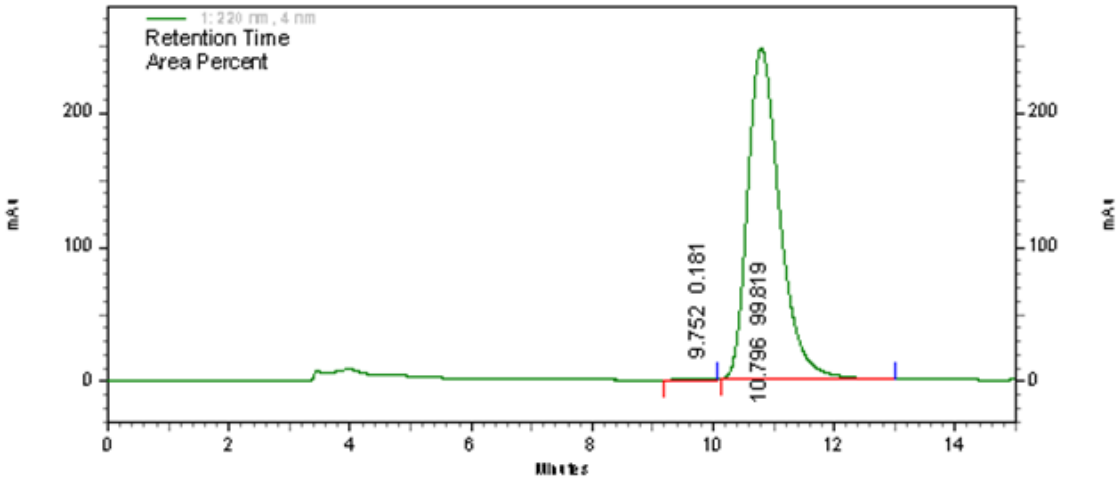
(*S*)-di-*tert*-butyl 1-(1-(2-chlorophenyl)-2-oxocyclohexyl)hydrazine-1,2-dicarboxylate (**2j**)





1: 220 nm, 4 nm
Results

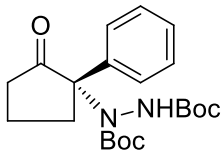
Pk #	Retention Time	Area Percent	Lambda Max
1	9.756	49.601	202
2	10.916	50.399	203

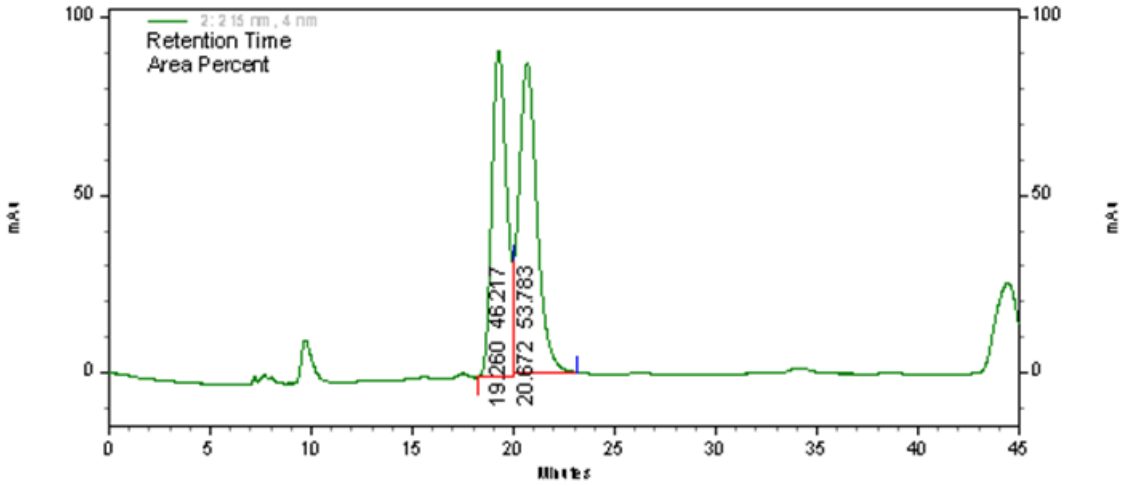


1: 220 nm, 4 nm
Results

Pk #	Retention Time	Area Percent	Lambda Max
1	9.752	0.181	664
2	10.796	99.819	664

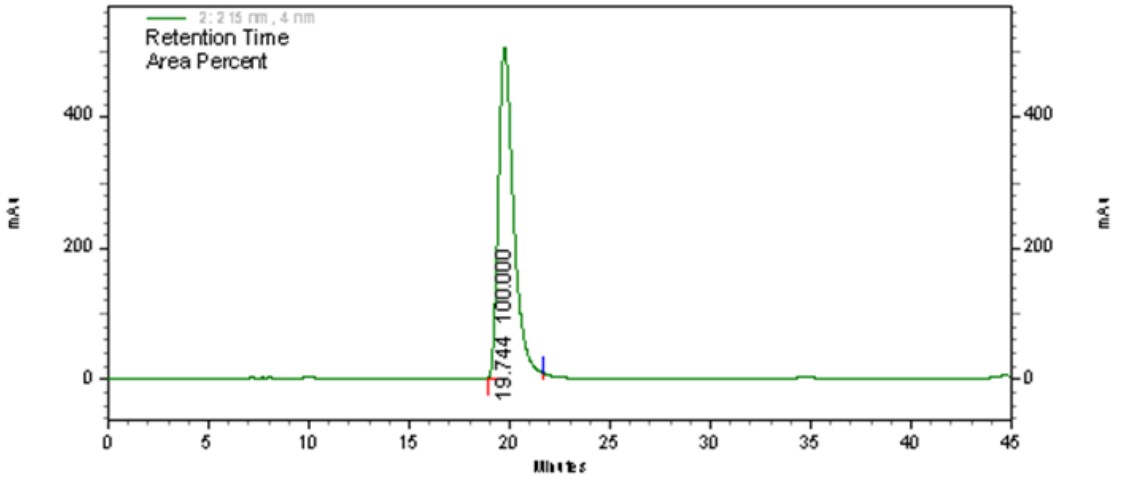
(*S*)-di-*tert*-butyl 1-(2-oxo-1-phenylcyclopentyl)hydrazine-1,2-dicarboxylate (**2k**)





2: 215 nm, 4 nm
Results

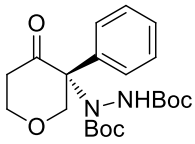
Pk #	Retention Time	Area Percent	Lambda Max
1	19.260	46.217	210
2	20.672	53.783	661

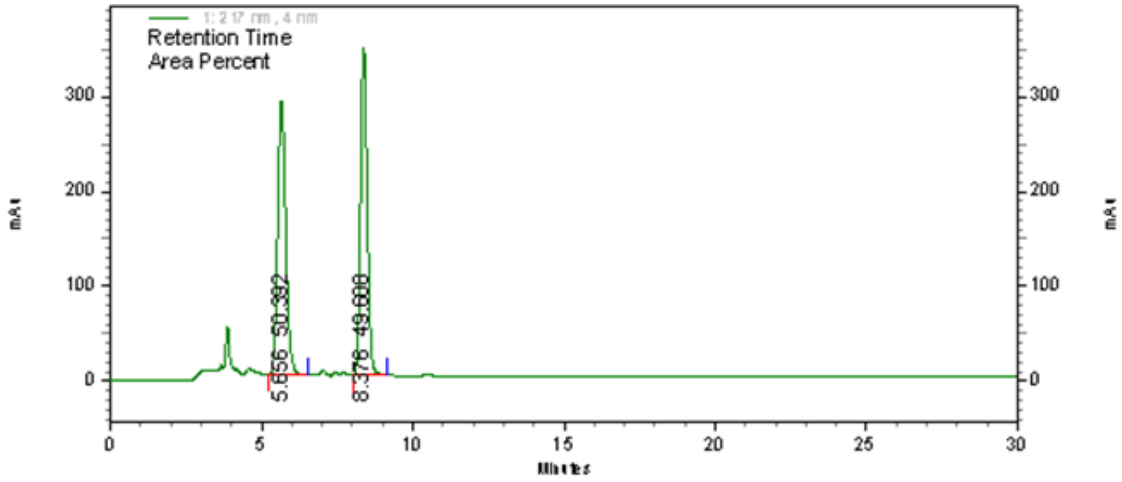


2: 215 nm, 4 nm
Results

Pk #	Retention Time	Area Percent	Lambda Max
1	19.744	100.000	193

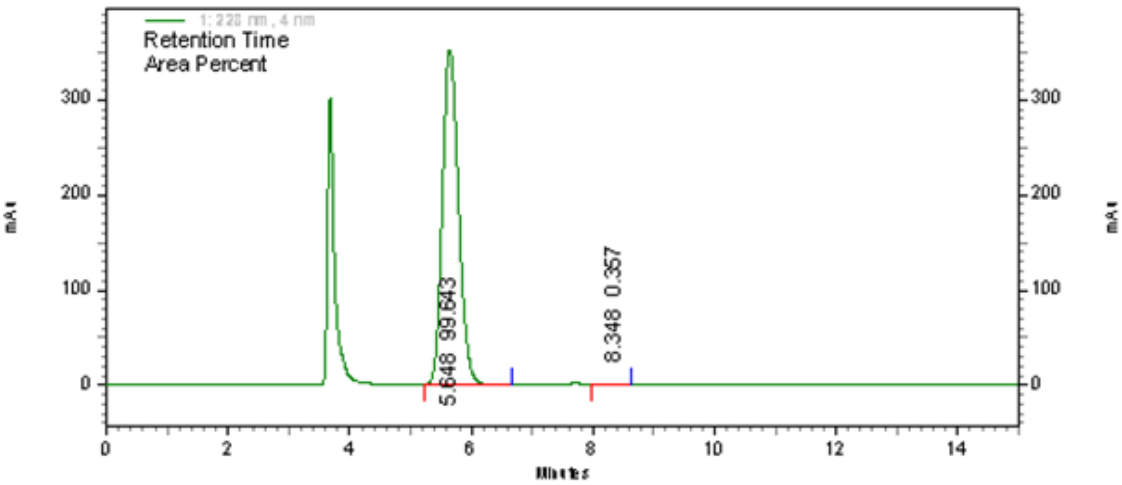
(*R*)-di-*tert*-butyl 1-(4-oxo-3-phenyltetrahydro-2H-pyran-3-yl)hydrazine-1,2-dicarboxylate (**2l**)





1: 217 nm, 4 nm
Results

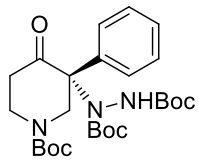
Pk #	Retention Time	Area Percent	Lambda Max
1	5.656	50.392	206
2	8.376	49.608	206

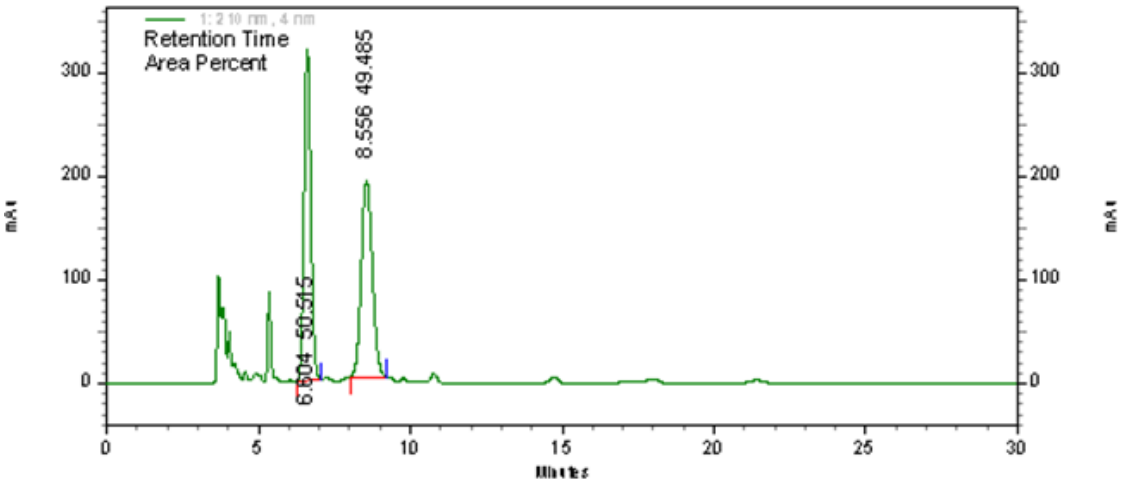


1: 228 nm, 4 nm
Results

Pk #	Retention Time	Area Percent	Lambda Max
1	5.648	99.643	198
2	8.348	0.357	664

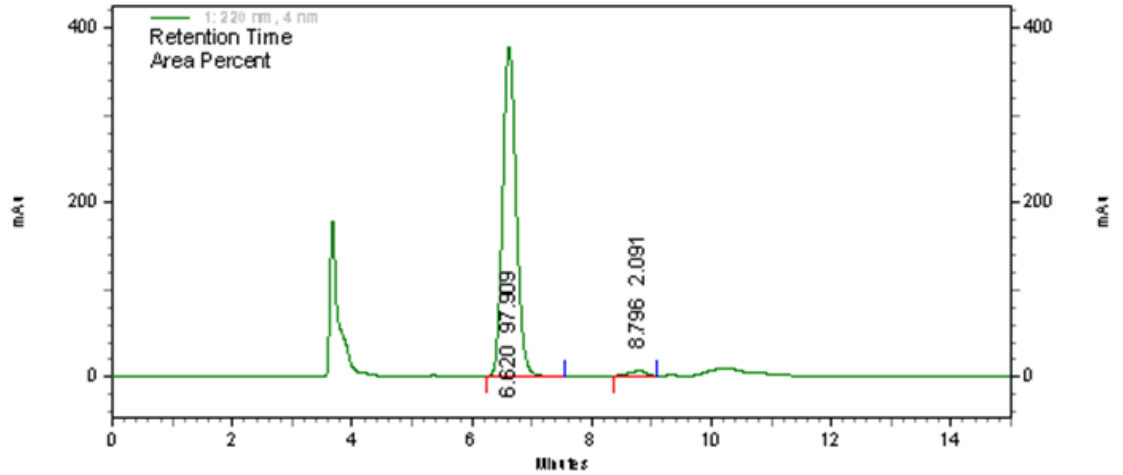
(*R*)-di-*tert*-butyl 1-(1-(tert-butoxycarbonyl)-4-oxo-3-phenylpiperidin-3-yl)hydrazine-1,2-dicarboxylate (**2m**)





1: 210 nm, 4 nm
Results

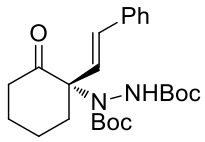
Pk #	Retention Time	Area Percent	Lambda Max
1	6.604	50.515	206
2	8.556	49.485	206

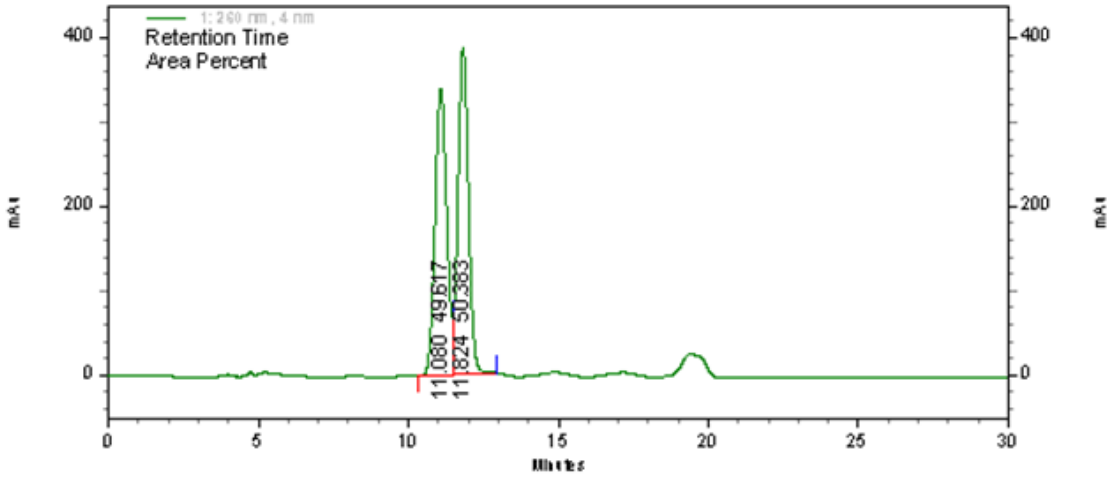


1: 220 nm, 4 nm
Results

Pk #	Retention Time	Area Percent	Lambda Max
1	6.620	97.909	195
2	8.796	2.091	662

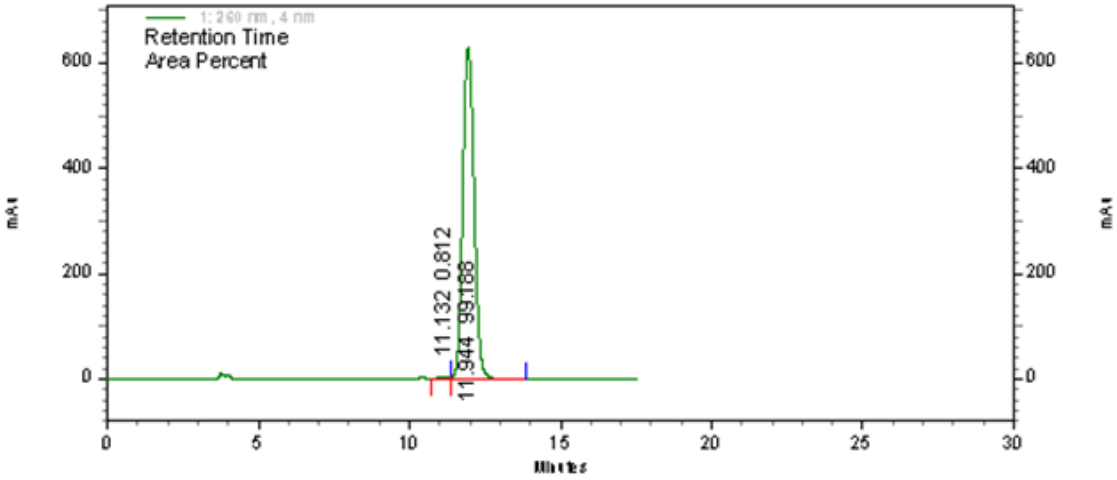
(*S*,*E*)-di-*tert*-butyl 1-(2-oxo-1-styrylcyclohexyl)hydrazine-1,2-dicarboxylate (**2n**)





1: 260 nm, 4 nm
Results

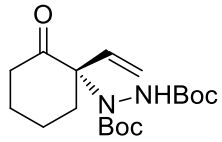
Pk #	Retention Time	Area Percent	Lambda Max
1	11.080	49.617	207
2	11.824	50.383	207

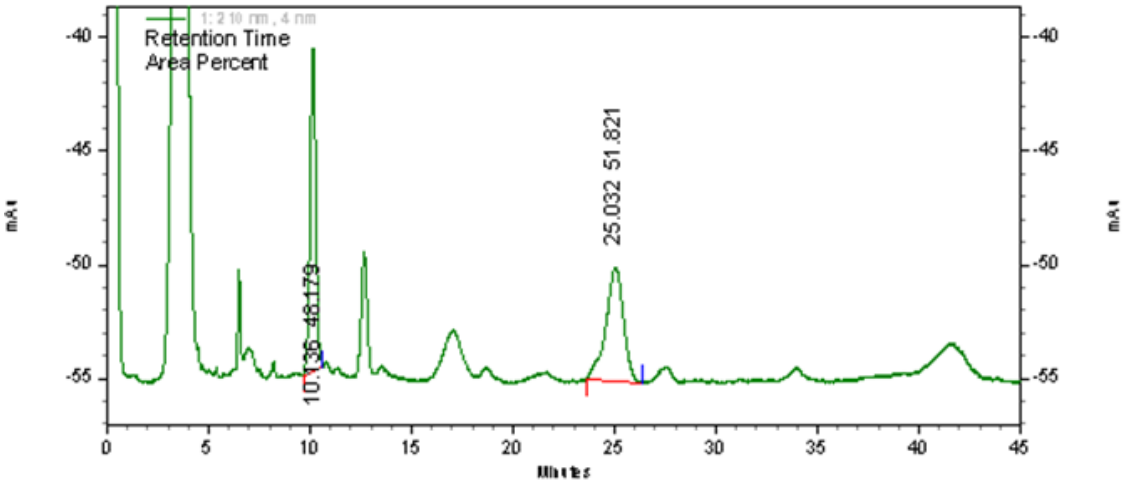


1: 260 nm, 4 nm
Results

Pk #	Retention Time	Area Percent	Lambda Max
1	11.132	0.812	208
2	11.944	99.188	193

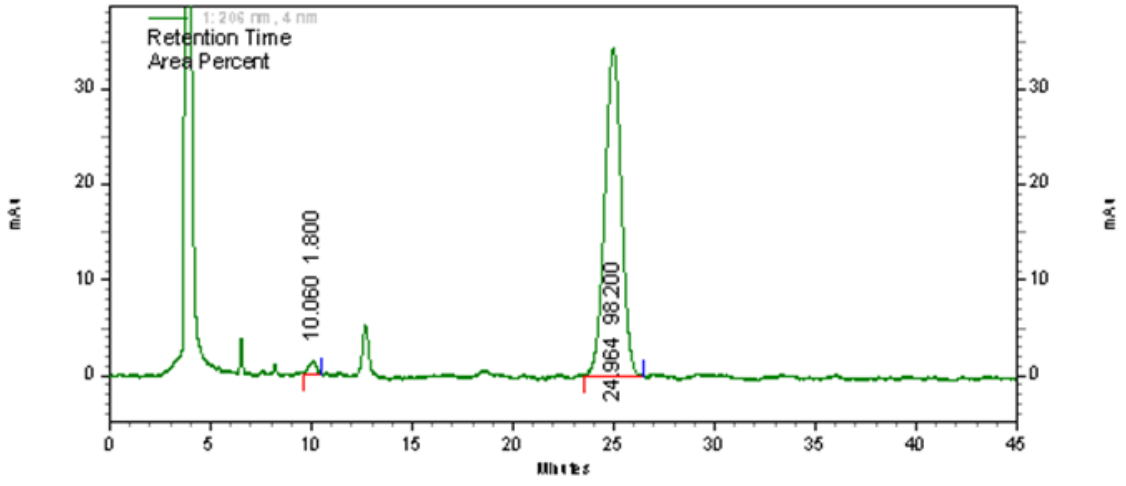
(*S*)-di-*tert*-butyl 1-(2-oxo-1-vinylcyclohexyl)hydrazine-1,2-dicarboxylate (**2o**)





1: 210 nm, 4 nm
Results

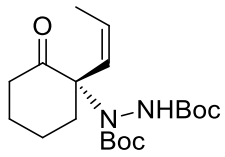
Pk #	Retention Time	Area Percent	Lambda Max
1	10.136	48.179	662
2	25.032	51.821	675

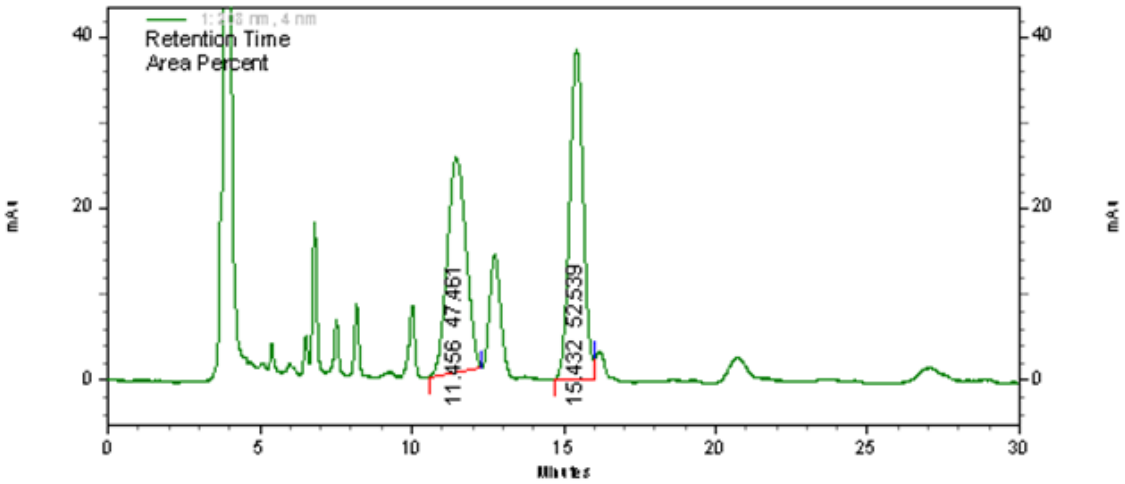


1: 206 nm, 4 nm
Results

Pk #	Retention Time	Area Percent	Lambda Max
1	10.060	1.800	660
2	24.964	98.200	205

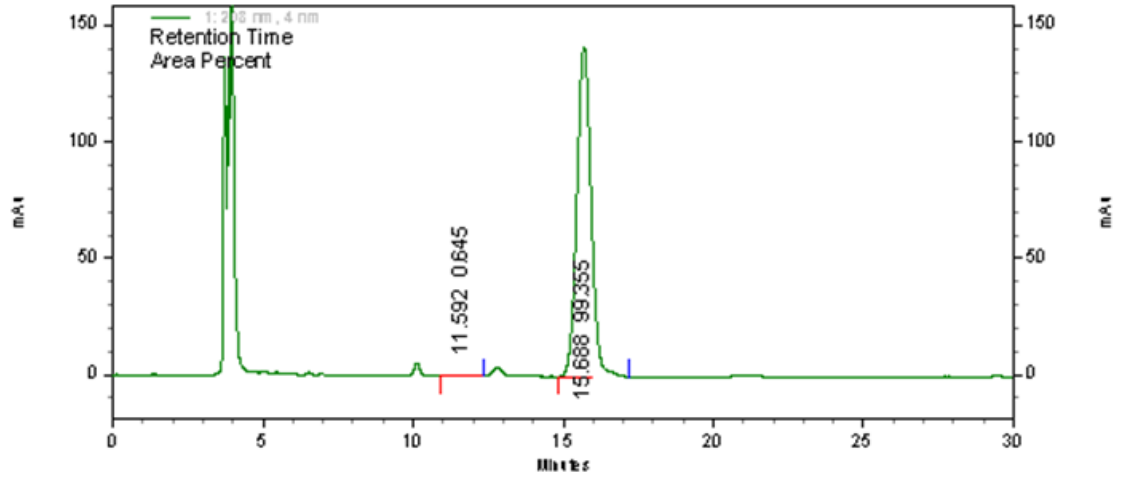
(*S*,*Z*)-di-*tert*-butyl 1-(2-oxo-1-(prop-1-en-1-yl)cyclohexyl)hydrazine-1,2-dicarboxylate (**2p**)





1: 208 nm, 4 nm
Results

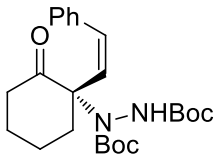
Pk #	Retention Time	Area Percent	Lambda Max
1	11.456	47.461	205
2	15.432	52.539	664

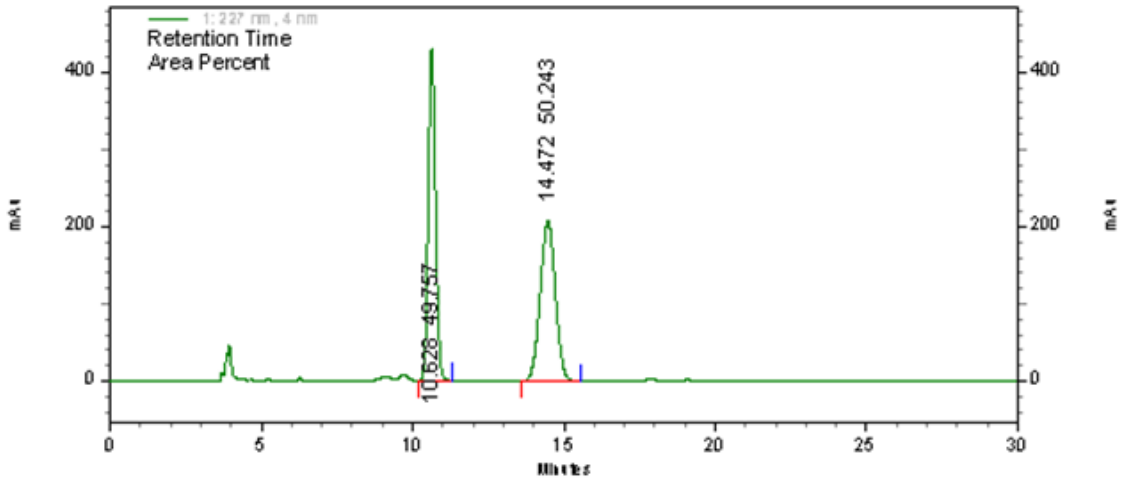


1: 208 nm, 4 nm
Results

Pk #	Retention Time	Area Percent	Lambda Max
1	11.592	0.645	663
2	15.688	99.355	205

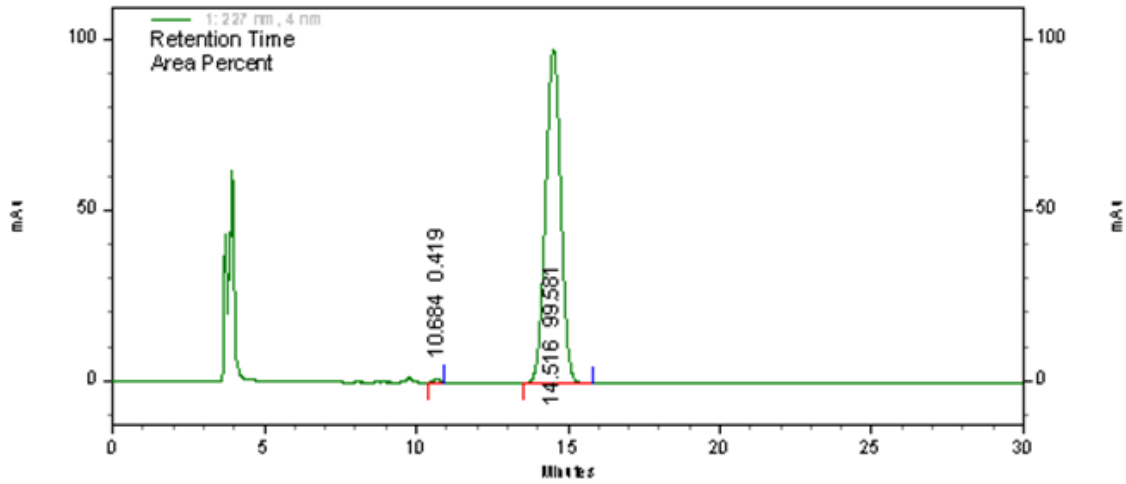
(*S*,*Z*)-di-*tert*-butyl 1-(2-oxo-1-styrylcyclohexyl)hydrazine-1,2-dicarboxylate (**2q**)





1: 227 nm, 4 nm
Results

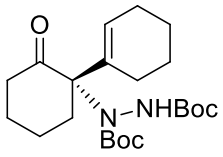
Pk #	Retention Time	Area Percent	Lambda Max
1	10.628	49.757	192
2	14.472	50.243	206

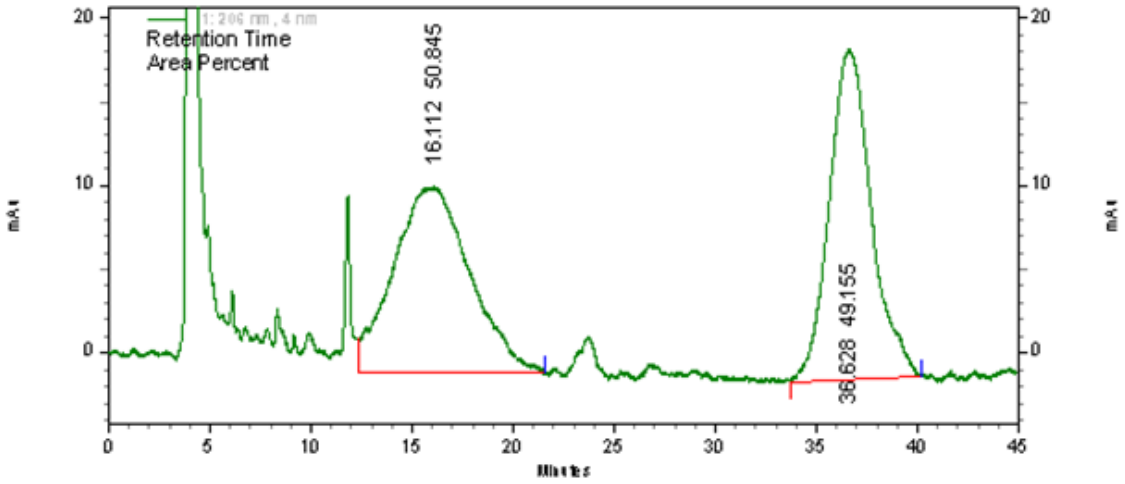


1: 227 nm, 4 nm
Results

Pk #	Retention Time	Area Percent	Lambda Max
1	10.684	0.419	206
2	14.516	99.581	206

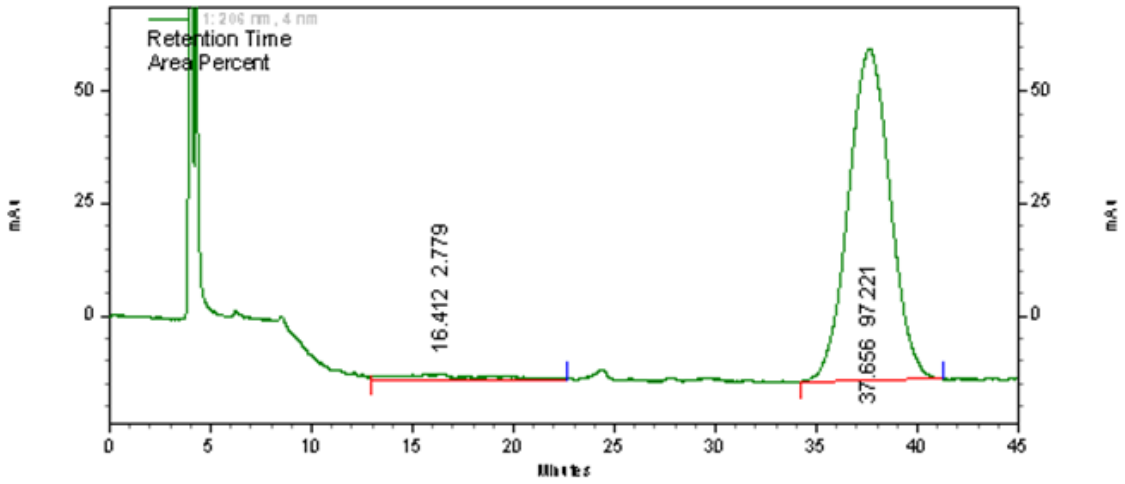
(*S*)-di-*tert*-butyl 1-(2-oxo-[1,1'-bi(cyclohexan)]-1'-en-1-yl)hydrazine-1,2-dicarboxylate (**2r**)





1: 206 nm, 4 nm
Results

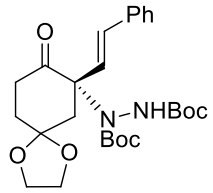
Pk #	Retention Time	Area Percent	Lambda Max
1	16.112	50.845	674
2	36.628	49.155	675

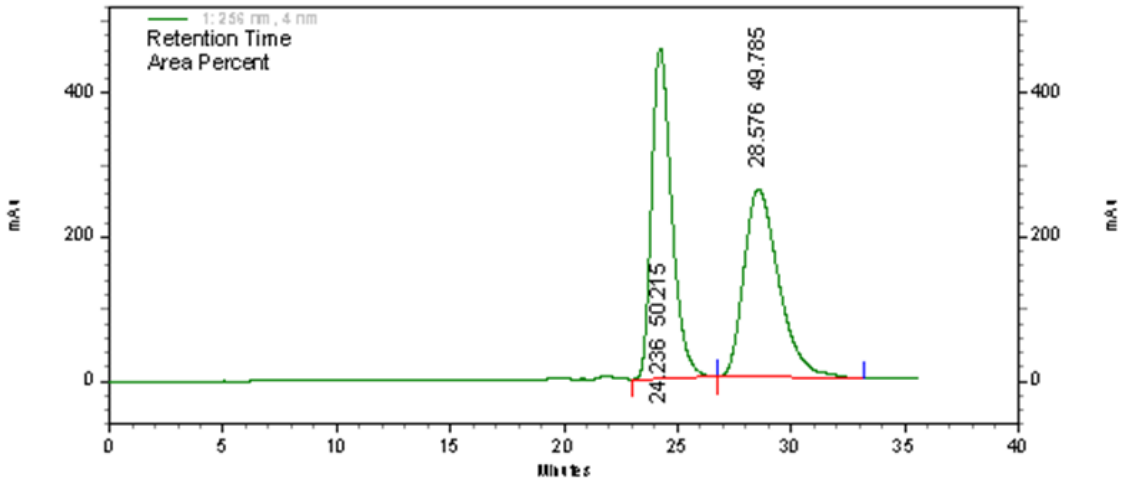


1: 206 nm, 4 nm
Results

Pk #	Retention Time	Area Percent	Lambda Max
1	16.412	2.779	667
2	37.656	97.221	668

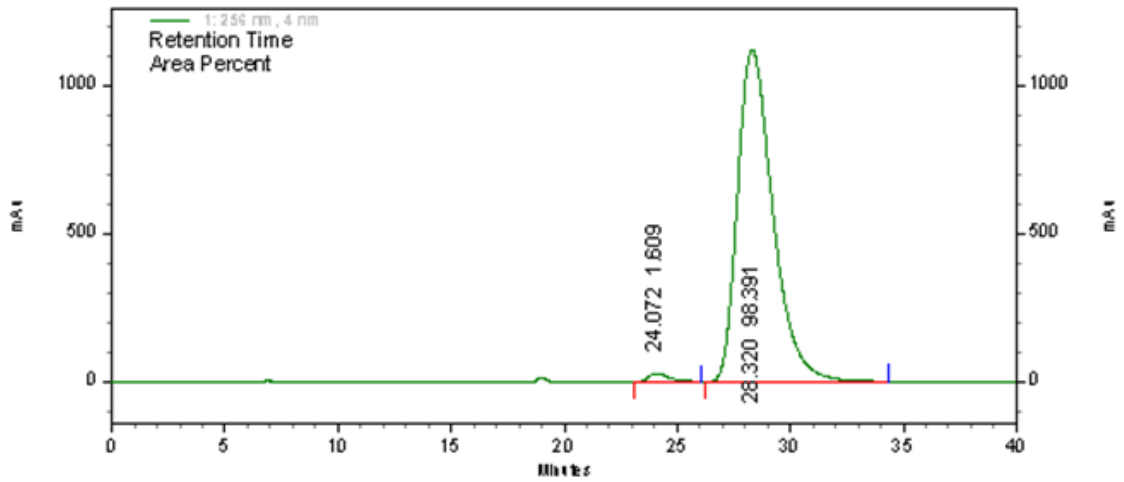
(*S,E*)-di-*tert*-butyl 1-(8-oxo-7-styryl-1,4-dioxaspiro[4.5]decan-7-yl)hydrazine-1,2-dicarboxylate (**2s**)





1: 256 nm, 4 nm
Results

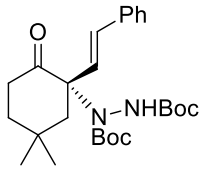
Pk #	Retention Time	Area Percent	Lambda Max
1	24.236	50.215	193
2	28.576	49.785	190

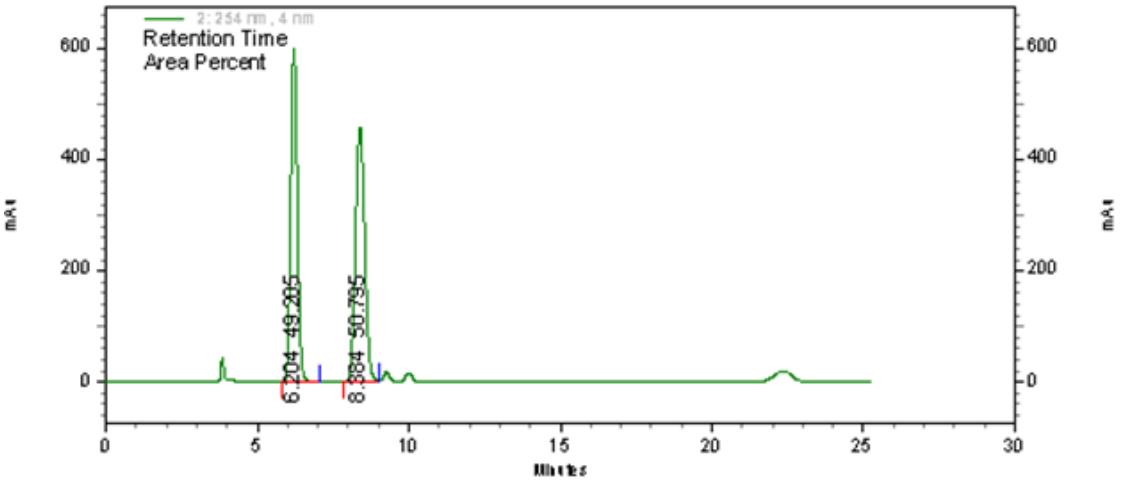


1: 256 nm, 4 nm
Results

Pk #	Retention Time	Area Percent	Lambda Max
1	24.072	1.609	666
2	28.320	98.391	199

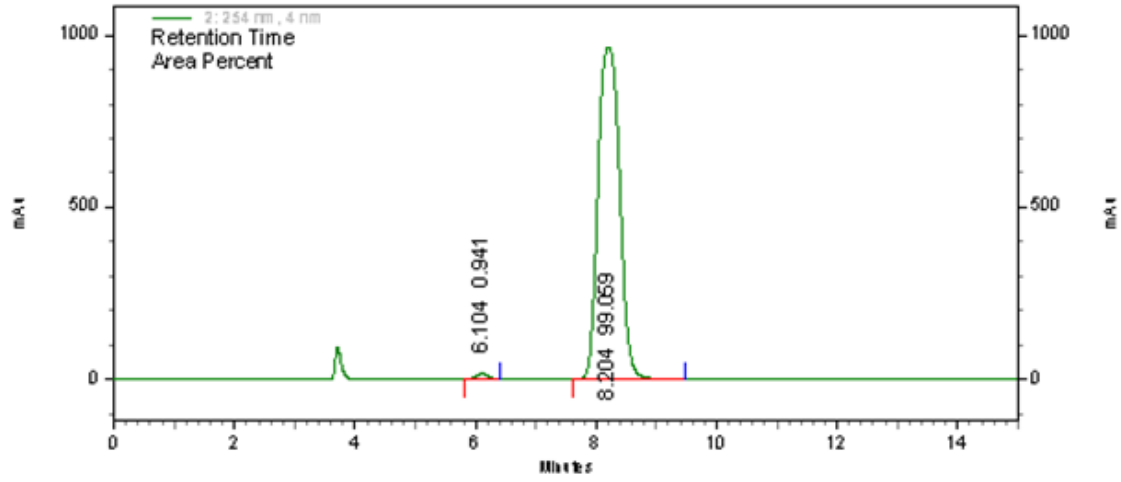
(*S,E*)-di-*tert*-butyl 1-(5,5-dimethyl-2-oxo-1-styrylcyclohexyl)hydrazine-1,2-dicarboxylate (**2t**)





2: 254 nm, 4 nm
Results

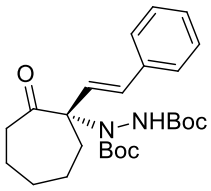
Pk #	Retention Time	Area Percent	Lambda Max
1	6.204	49.205	190
2	8.384	50.795	207

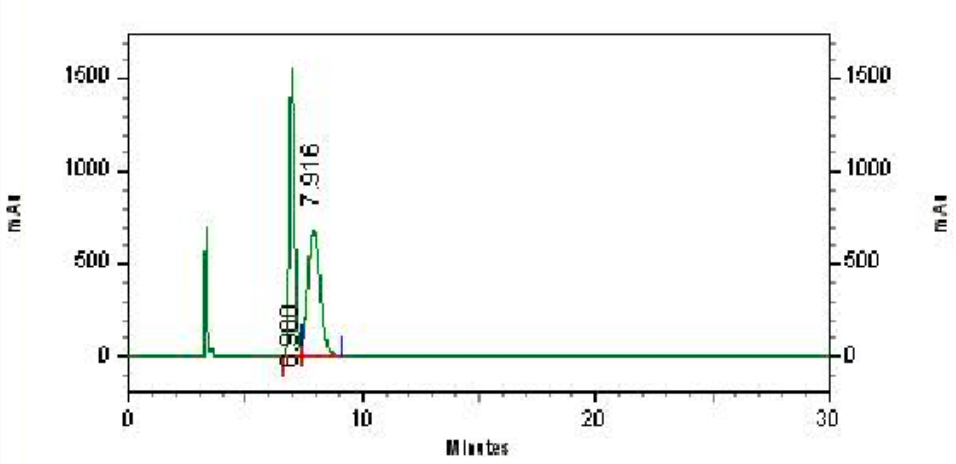


2: 254 nm, 4 nm
Results

Pk #	Retention Time	Area Percent	Lambda Max
1	6.104	0.941	207
2	8.204	99.059	199

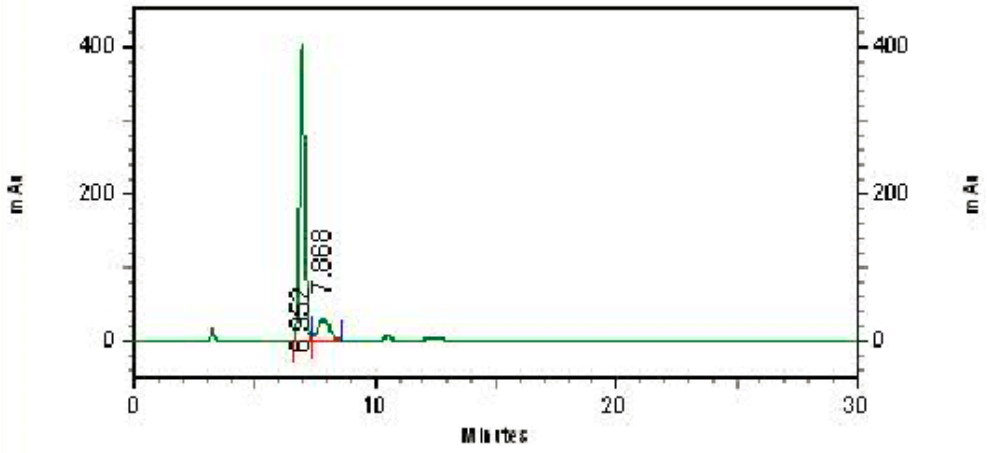
(*S*,*E*)-di-*tert*-butyl 1-(2-oxo-1-styrylcycloheptyl)hydrazine-1,2-dicarboxylate (**2u**)





2: 251 nm, 4 nm Results

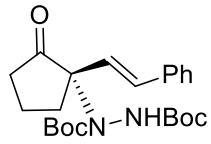
Retention Time	Area	Area Percent	Lambda Max
6.980	24708884	49.414	246
7.916	25294847	50.586	204

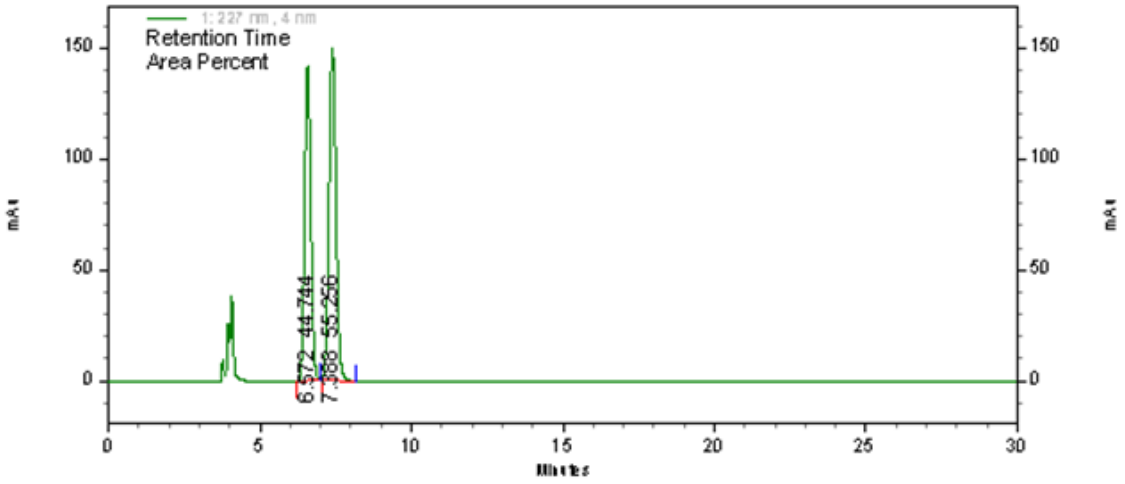


2: 251 nm, 4 nm Results

Retention Time	Area	Area Percent	Lambda Max
6.952	6018615	85.829	204
7.868	993721	14.171	203

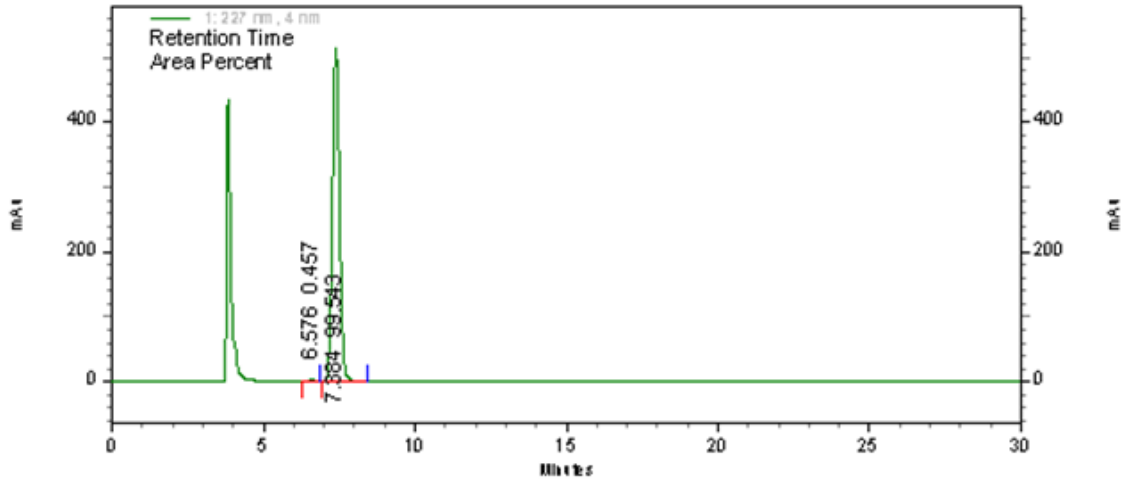
(*S,E*)-di-*tert*-butyl 1-(2-oxo-1-styrylcyclopentyl)hydrazine-1,2-dicarboxylate (**2v**)





1: 227 nm, 4 nm
Results

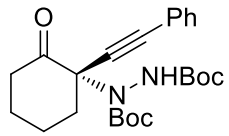
Pk #	Retention Time	Area Percent	Lambda Max
1	6.572	44.744	192
2	7.388	55.256	192

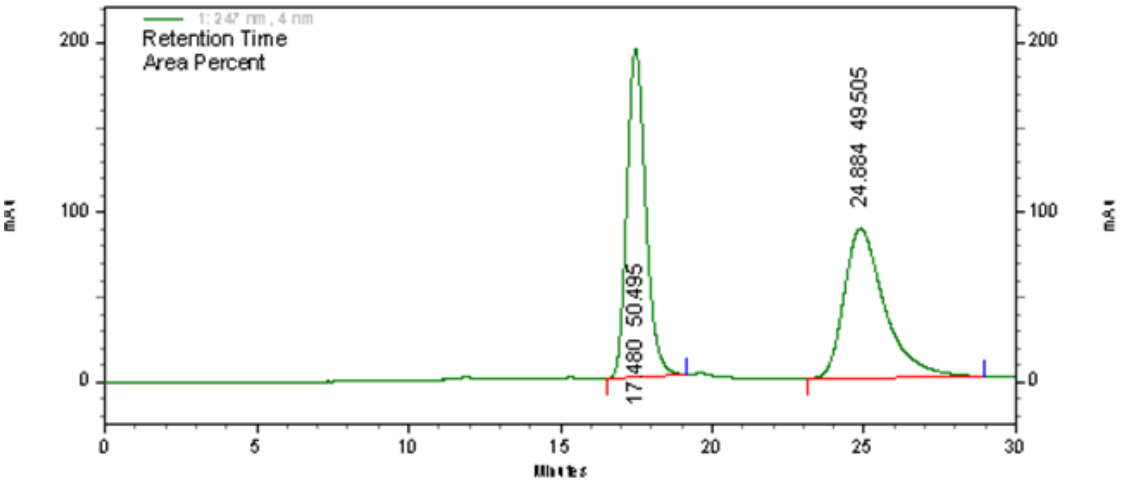


1: 227 nm, 4 nm
Results

Pk #	Retention Time	Area Percent	Lambda Max
1	6.576	0.457	254
2	7.384	99.543	203

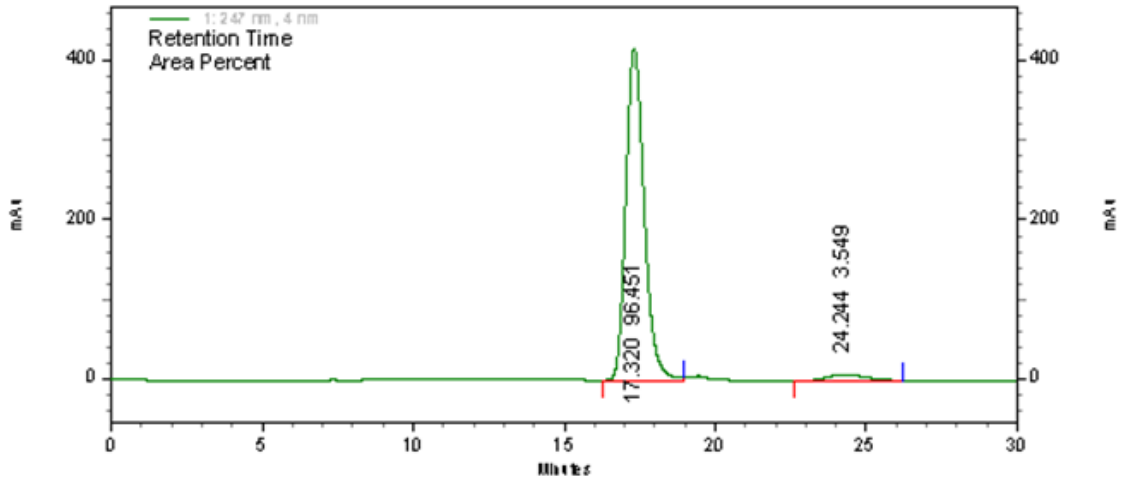
(*S*)-di-tert-butyl 1-(2-oxo-1-(phenylethynyl)cyclohexyl)hydrazine-1,2-dicarboxylate (**2w**)





1: 247 nm, 4 nm
Results

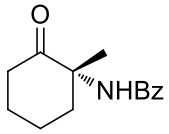
Pk #	Retention Time	Area Percent	Lambda Max
1	17.480	50.495	244
2	24.884	49.505	245

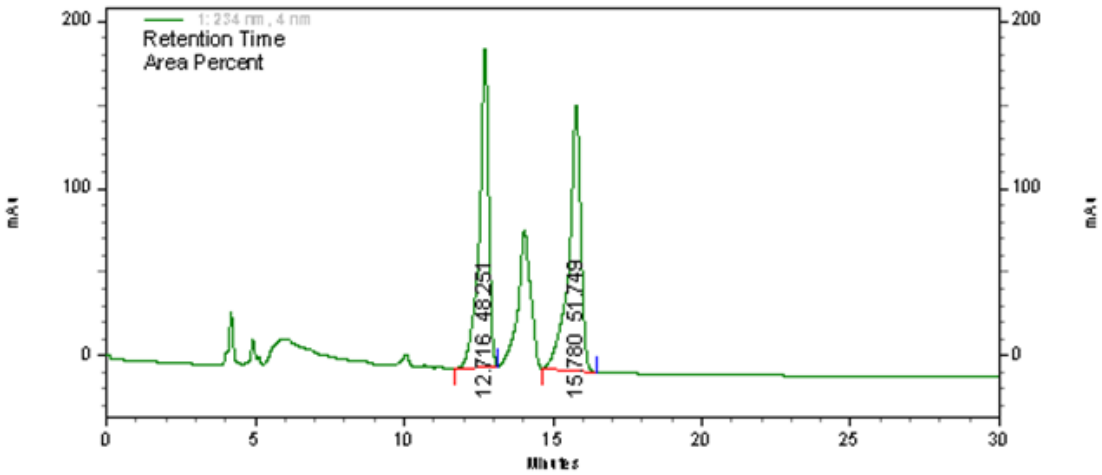


1: 247 nm, 4 nm
Results

Pk #	Retention Time	Area Percent	Lambda Max
1	17.320	96.451	206
2	24.244	3.549	233

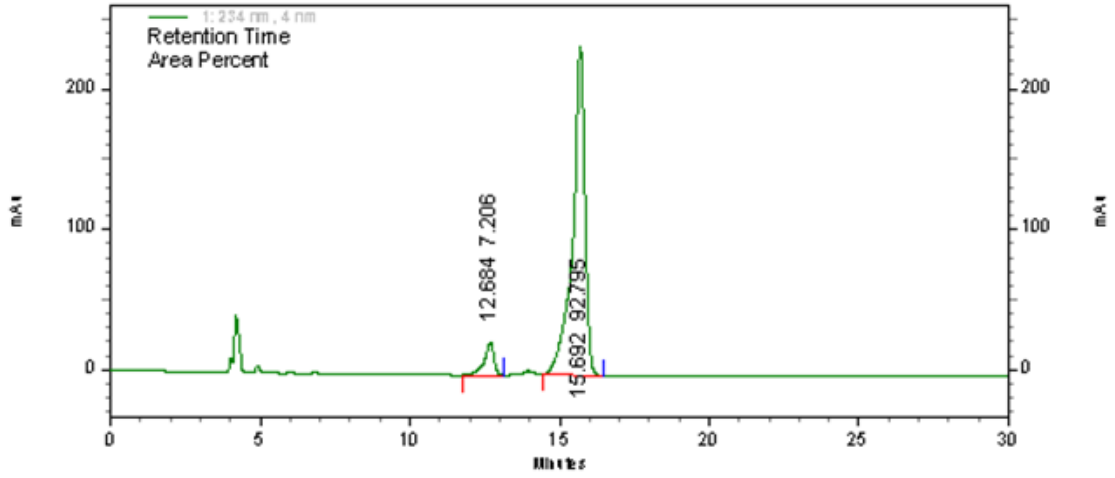
(*R*)-N-(1-methyl-2-oxocyclohexyl)benzamide (**S4**)





1: 234 nm, 4 nm
Results

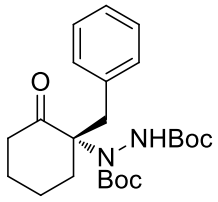
Pk #	Retention Time	Area Percent	Lambda Max
1	12.716	48.251	202
2	15.780	51.749	202

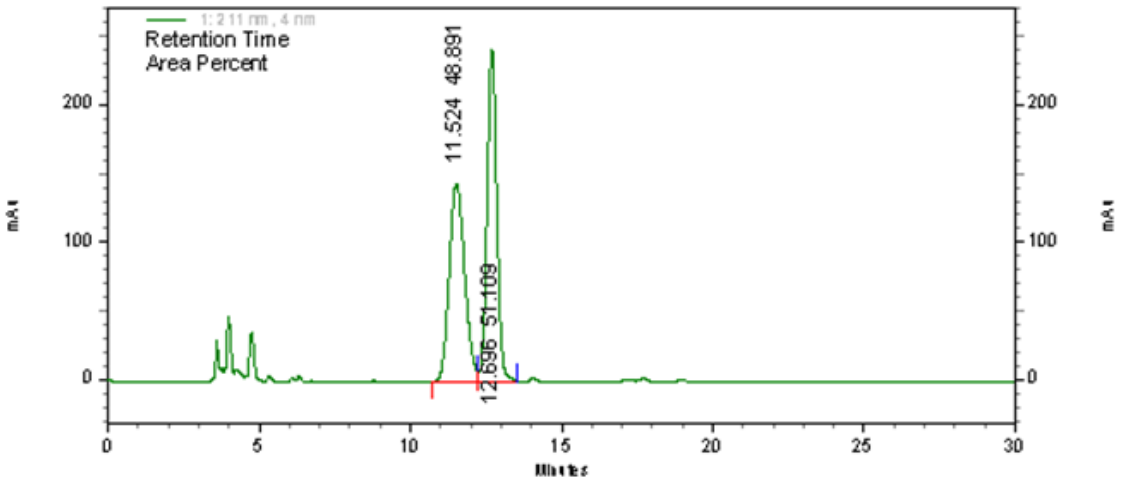


1: 234 nm, 4 nm
Results

Pk #	Retention Time	Area Percent	Lambda Max
1	12.684	7.206	203
2	15.692	92.795	202

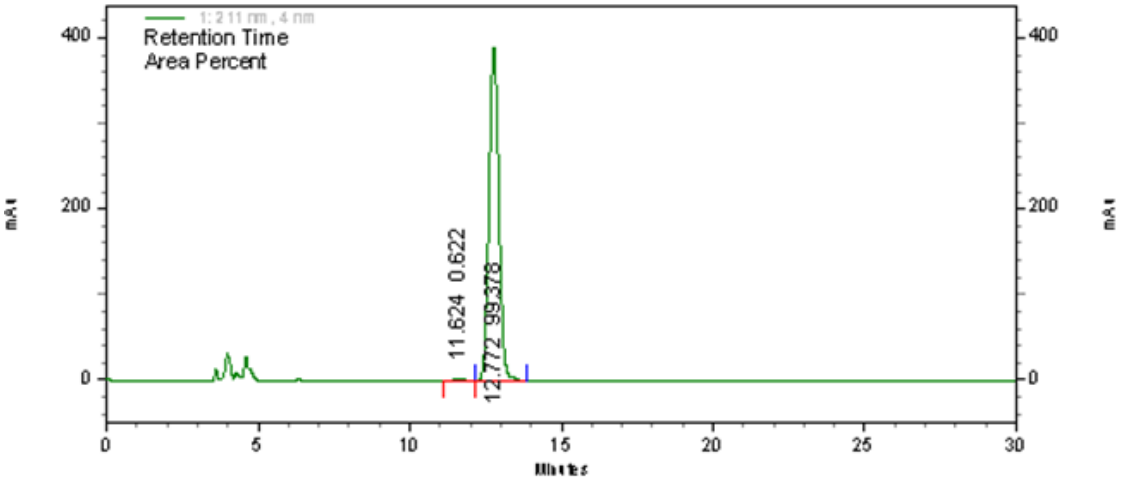
(*S*)-di-tert-butyl 1-(1-benzyl-2-oxocyclohexyl)hydrazine-1,2-dicarboxylate (**2y**)





1: 211 nm, 4 nm
Results

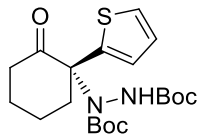
Pk #	Retention Time	Area Percent	Lambda Max
1	11.524	48.891	203
2	12.696	51.109	203

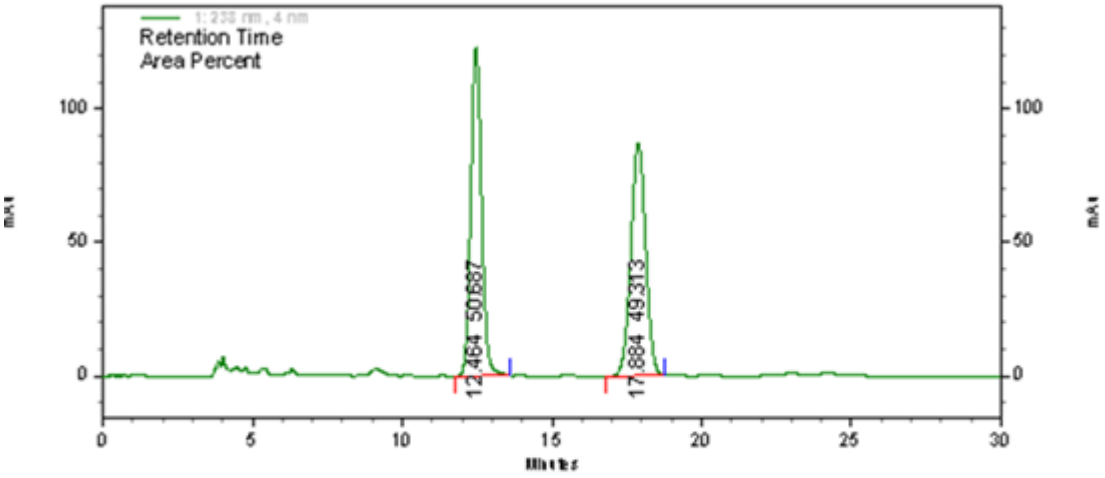


1: 211 nm, 4 nm
Results

Pk #	Retention Time	Area Percent	Lambda Max
1	11.624	0.622	681
2	12.772	99.378	681

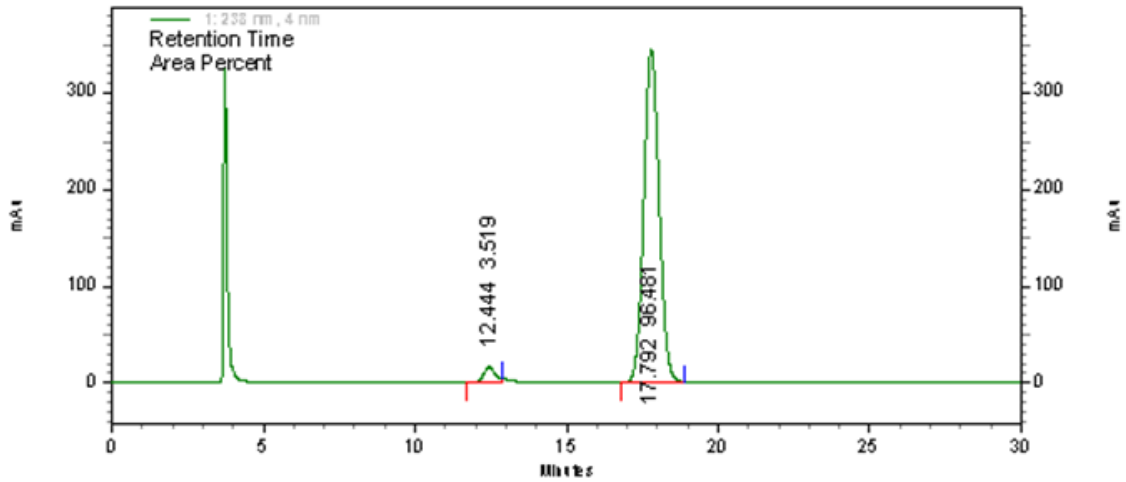
(*R*)-di-*tert*-butyl 1-(2-oxo-1-(thiophen-2-yl)cyclohexyl)hydrazine-1,2-dicarboxylate (**2z**)





1: 238 nm, 4 nm
Results

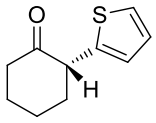
Pk #	Retention Time	Area Percent	Lambda Max
1	12.464	50.687	237
2	17.884	49.313	237

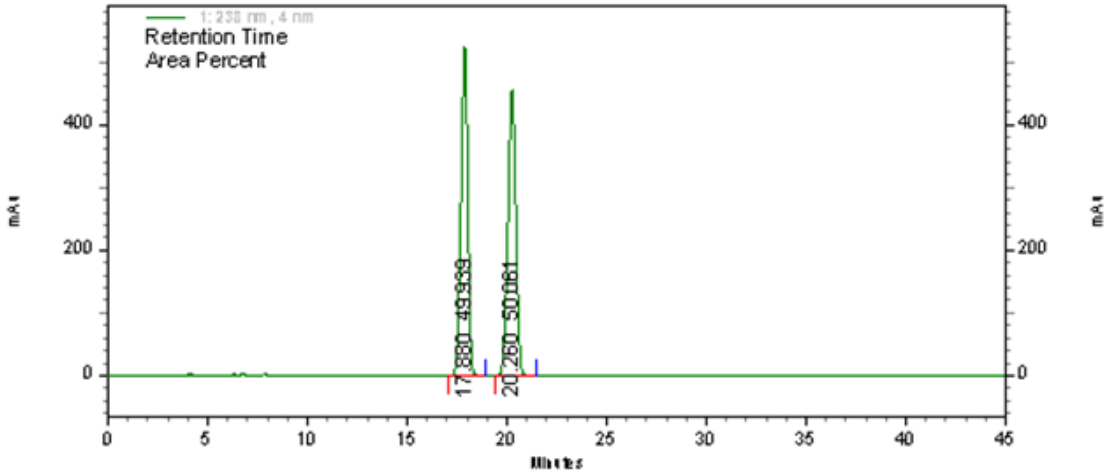


1: 238 nm, 4 nm
Results

Pk #	Retention Time	Area Percent	Lambda Max
1	12.444	3.519	237
2	17.792	96.481	237

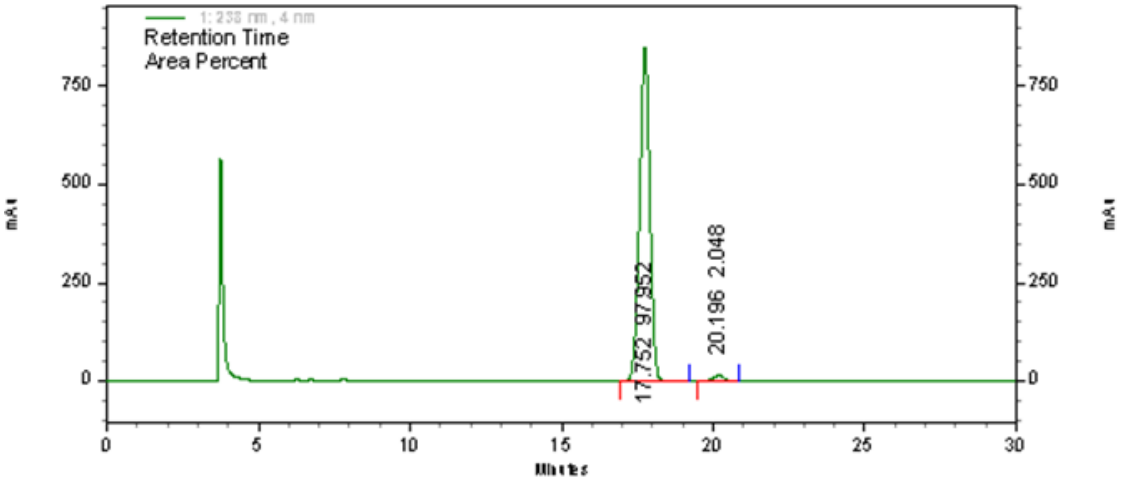
(*R*)-2-(thiophen-2-yl)cyclohexanone (**1z**)





1: 238 nm, 4 nm
Results

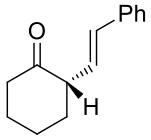
Pk #	Retention Time	Area Percent	Lambda Max
1	17.880	49.939	231
2	20.260	50.061	232

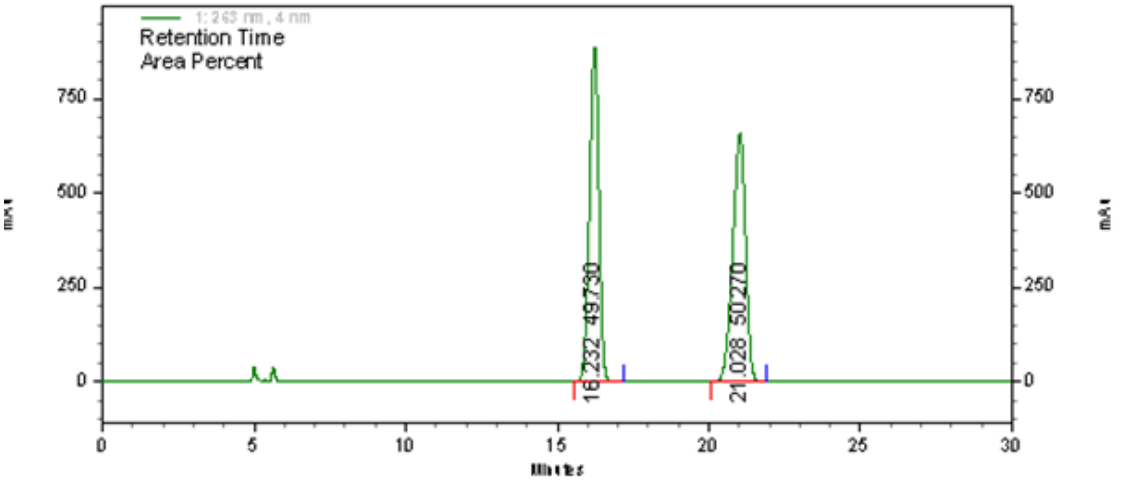


1: 238 nm, 4 nm
Results

Pk #	Retention Time	Area Percent	Lambda Max
1	17.752	97.952	190
2	20.196	2.048	669

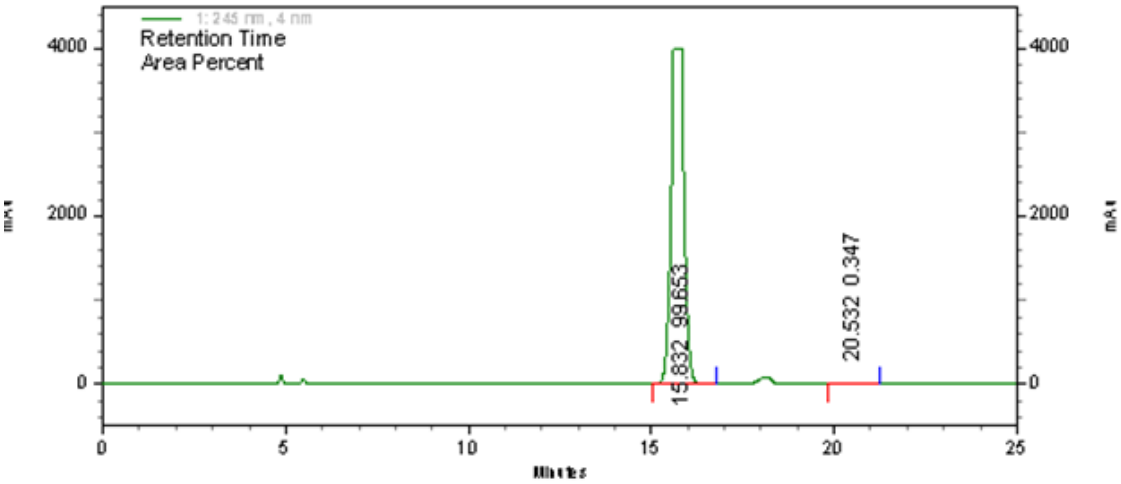
(*S,E*)-2-styrylcyclohexanone (**1n**)





1: 263 nm, 4 nm
Results

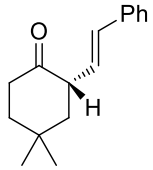
Pk #	Retention Time	Area Percent	Lambda Max
1	16.232	49.730	201
2	21.028	50.270	198

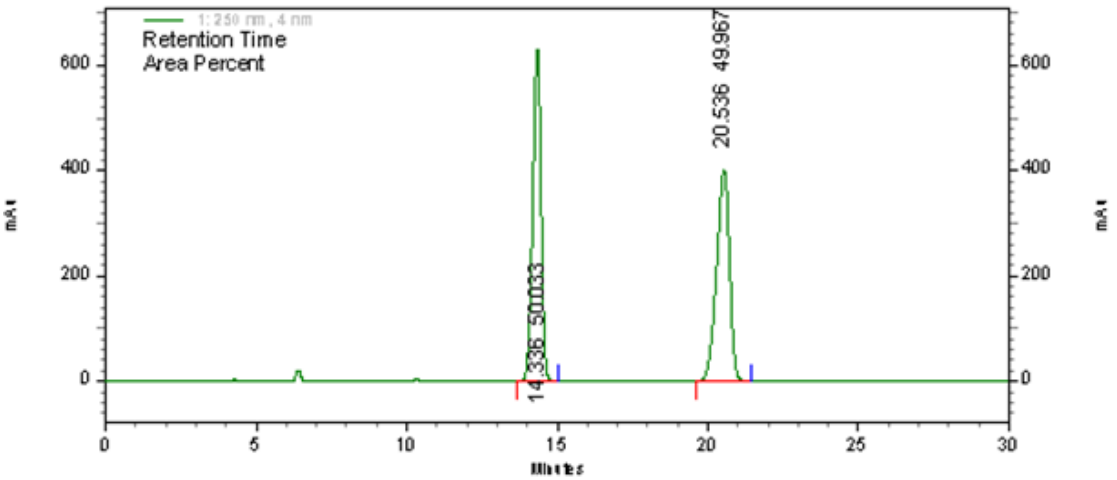


1: 245 nm, 4 nm
Results

Pk #	Retention Time	Area Percent	Lambda Max
1	15.832	99.653	246
2	20.532	0.347	664

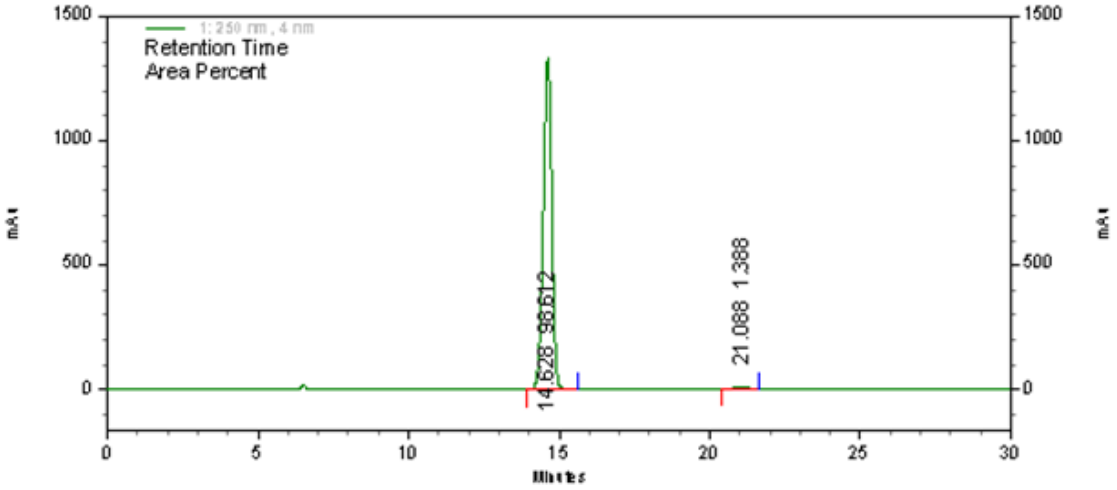
(*S,E*)-4,4-dimethyl-2-styrylcyclohexanone (**1t**)





1: 250 nm, 4 nm
Results

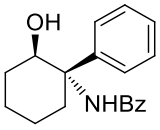
Pk #	Retention Time	Area Percent	Lambda Max
1	14.336	50.033	193
2	20.536	49.967	190

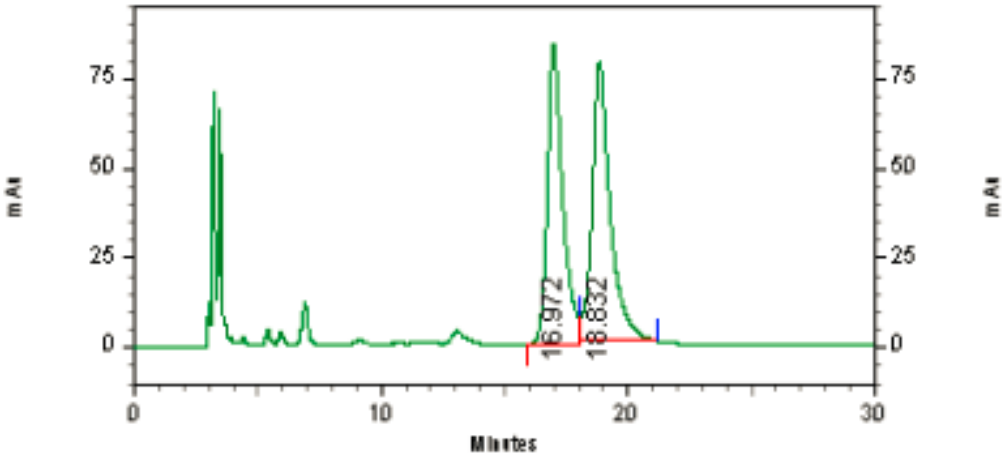


1: 250 nm, 4 nm
Results

Pk #	Retention Time	Area Percent	Lambda Max
1	14.628	98.612	199
2	21.088	1.388	665

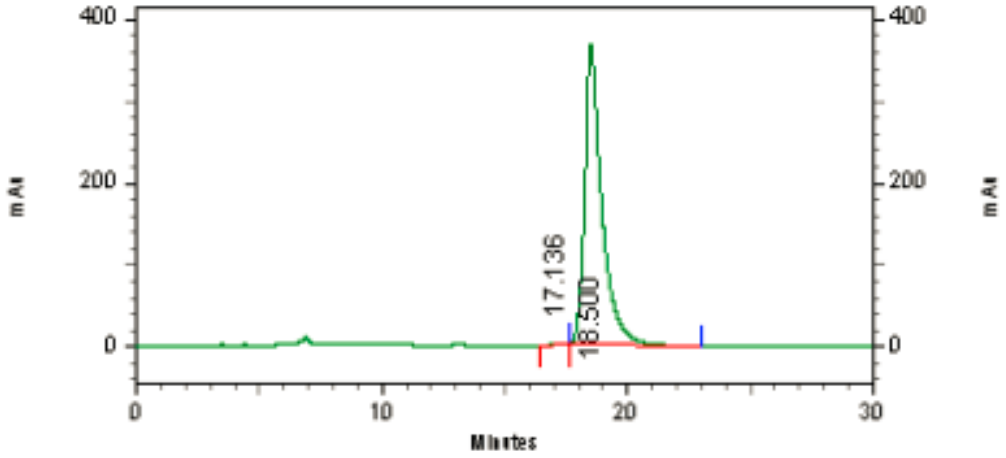
N-((*1S,2R*)-2-hydroxy-1-phenylcyclohexyl)benzamide (**3a**)





1: 220 nm, 4 nm Results

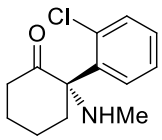
Retention Time	Area	Area Percent	Lambda Max
16.972	3648823	48.166	202
18.832	3926701	51.834	202

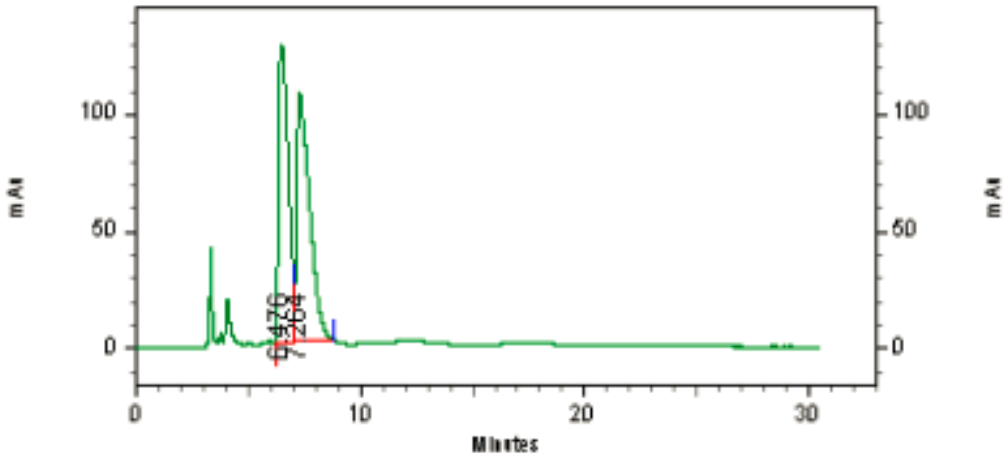


1: 239 nm, 4 nm Results

Retention Time	Area	Area Percent	Lambda Max
17.136	100177	0.564	201
18.500	17662885	99.436	202

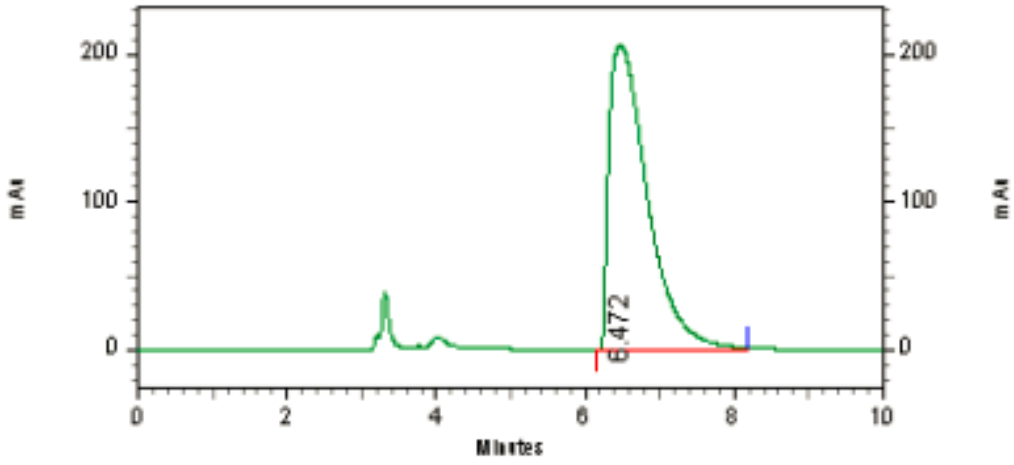
(*S*)-Ketamine:





1: 220 nm, 4 nm Results

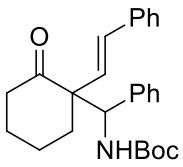
Retention Time	Area	Area Percent	Lambda Max
6.476	3938863	48.210	202
7.264	4231347	51.790	202

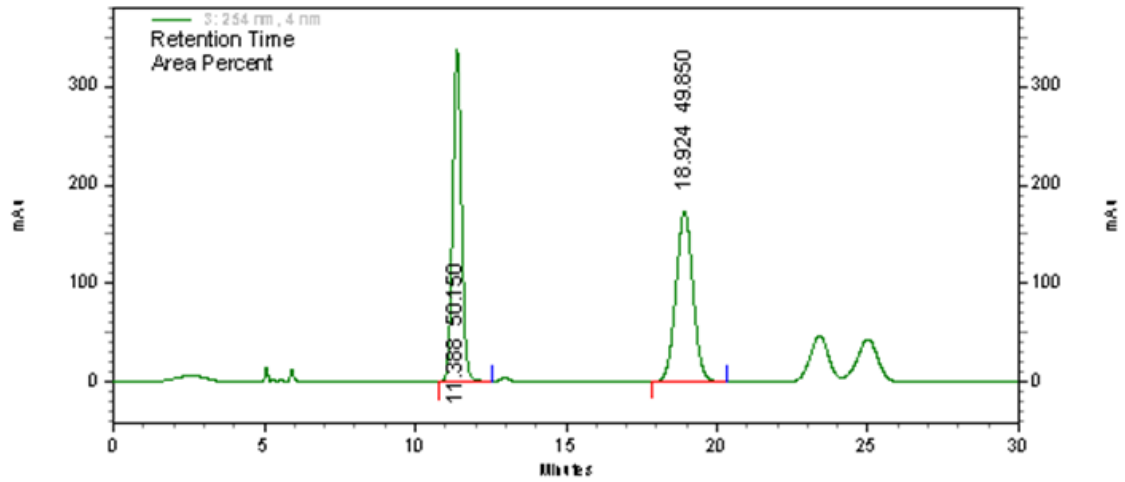


1: 220 nm, 4 nm Results

Retention Time	Area	Area Percent	Lambda Max
6.472	7474102	100.000	202

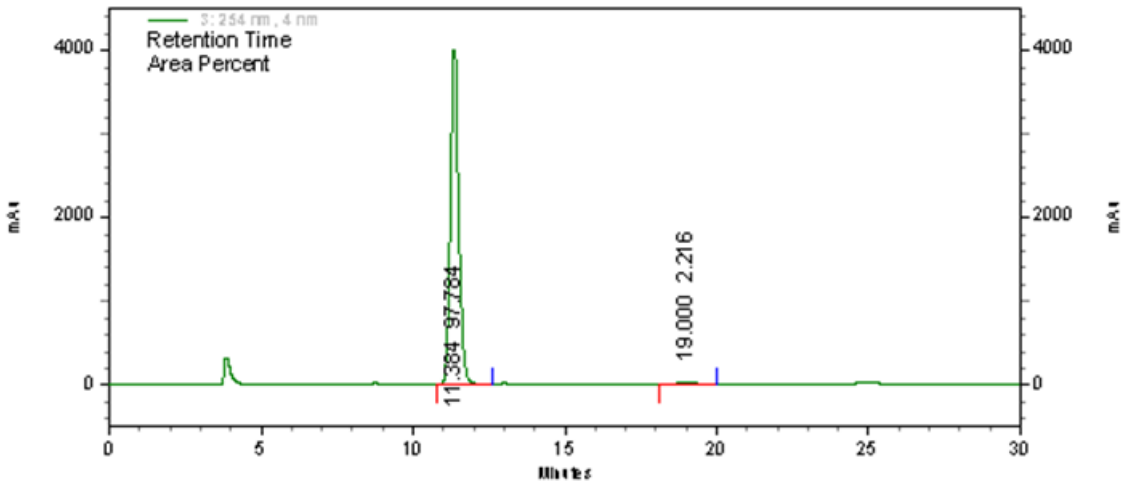
(*E*)-tert-butyl ((2-oxo-1-styrylcyclohexyl)(phenyl)methyl)carbamate (**5n**)





3: 254 nm, 4 nm
Results

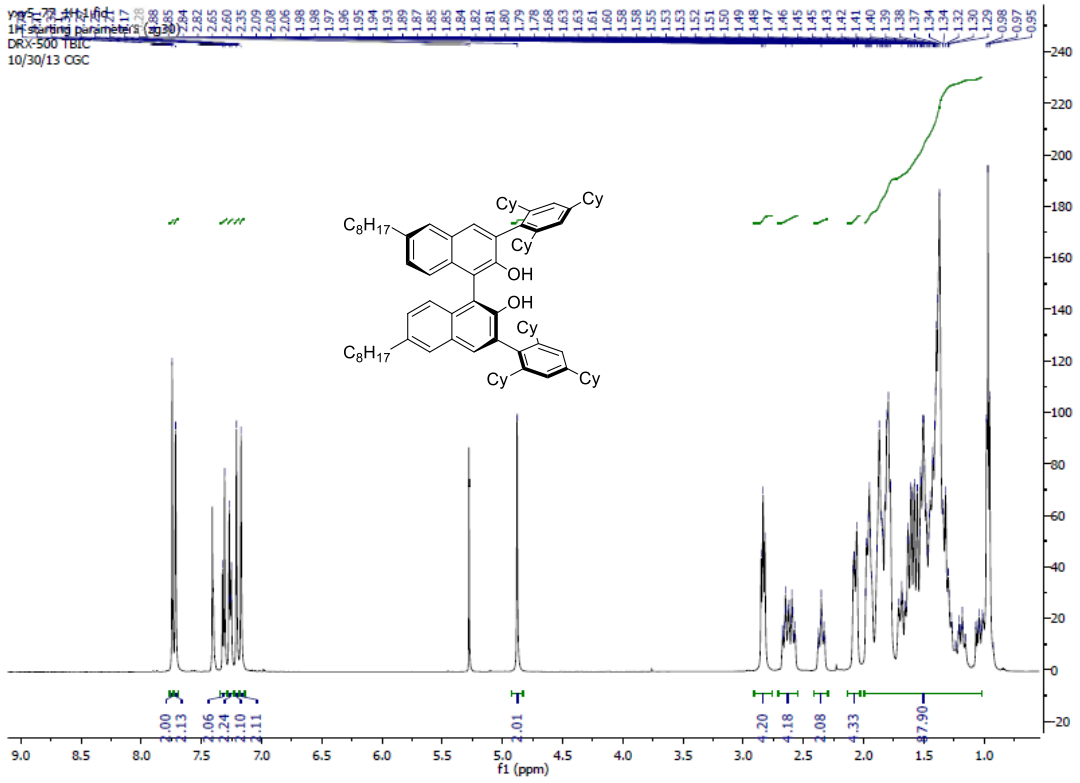
Pk #	Retention Time	Area Percent	Lambda Max
1	11.388	50.150	191
2	18.924	49.850	205

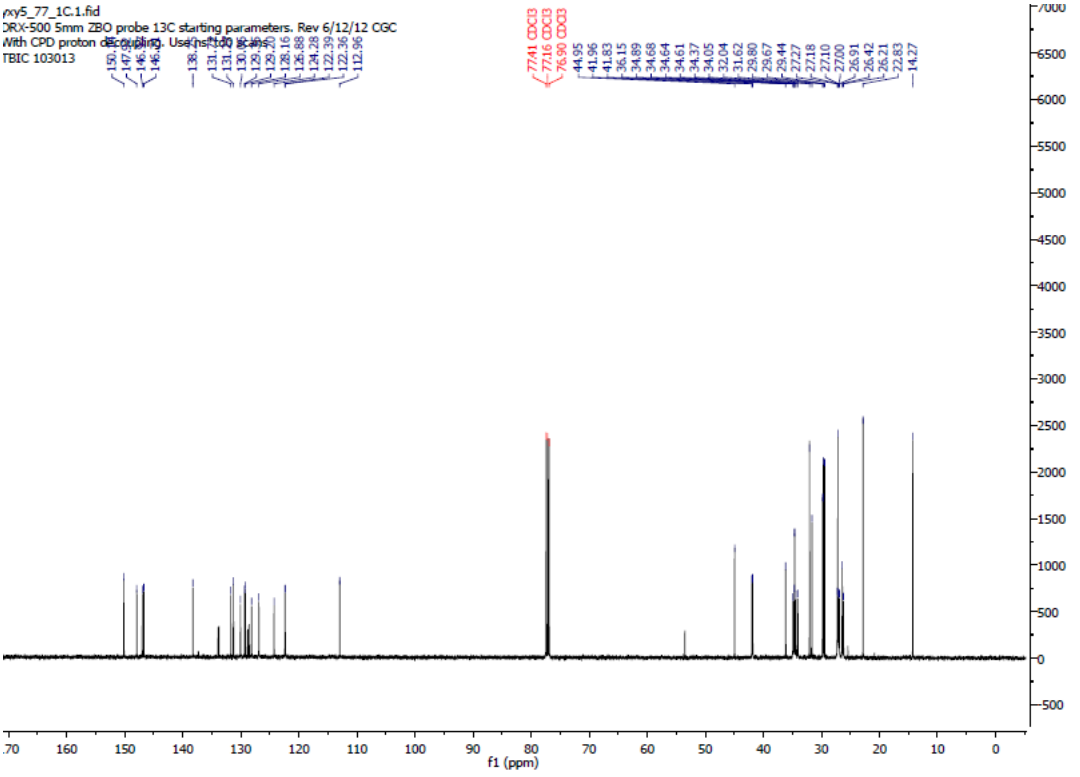


3: 254 nm, 4 nm
Results

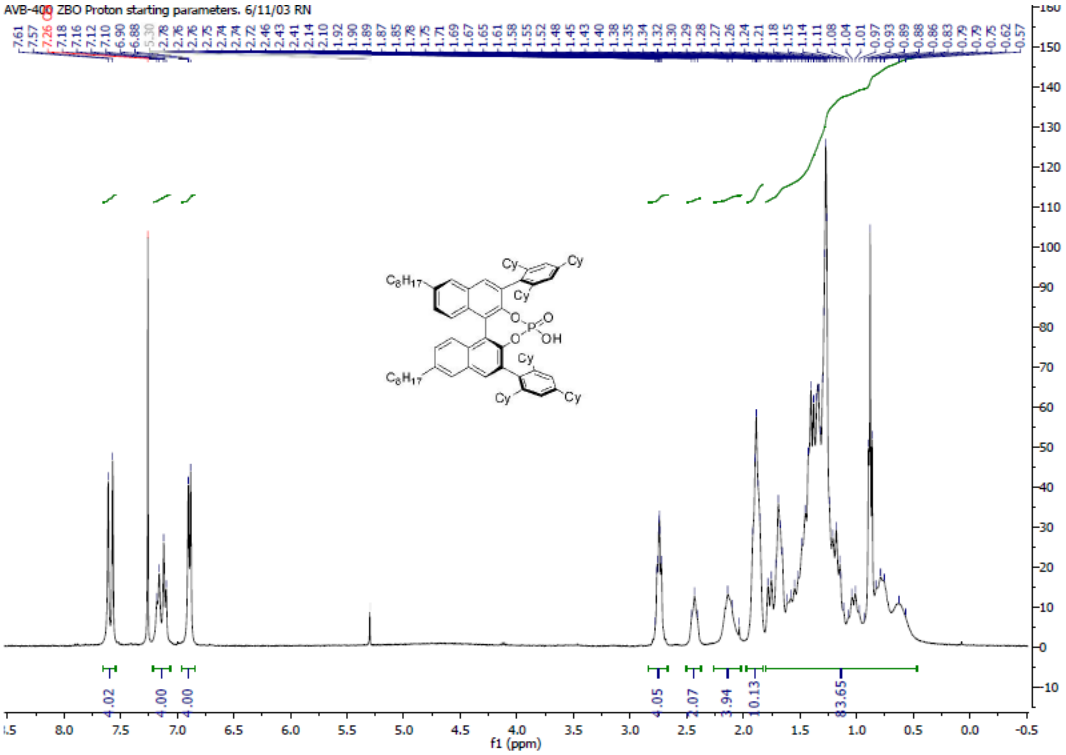
Pk #	Retention Time	Area Percent	Lambda Max
1	11.384	97.784	252
2	19.000	2.216	676

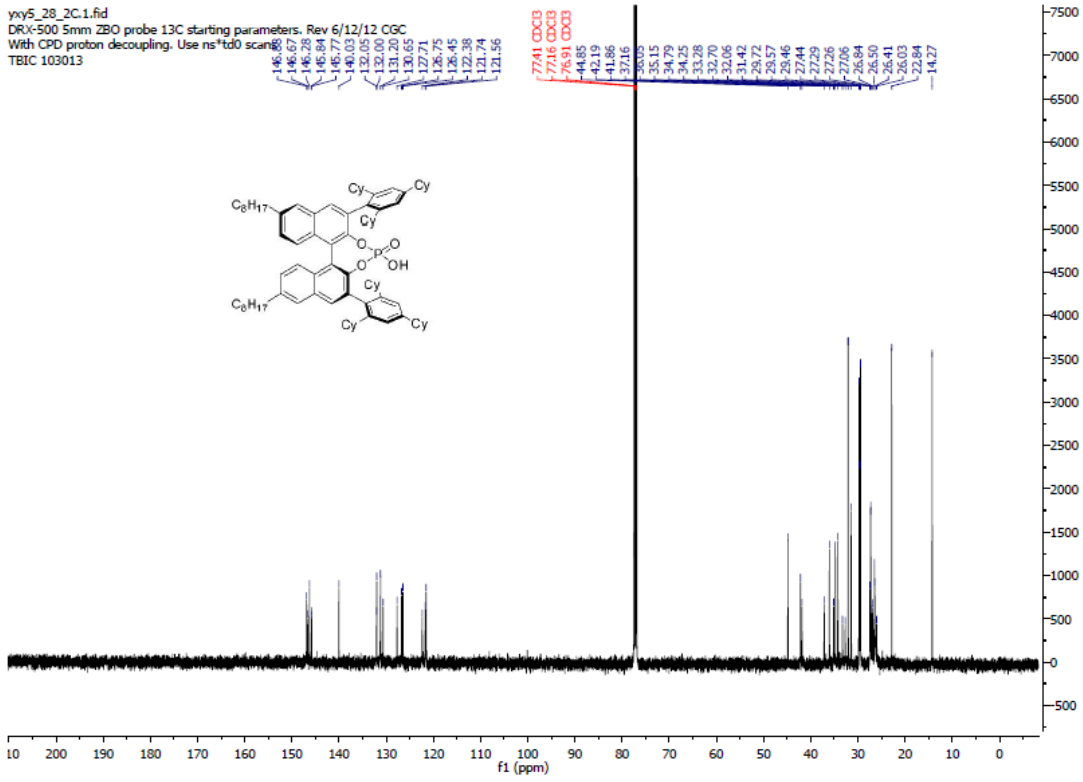
(*R*)-6,6'-dioctyl-3,3'-bis(2,4,6-tricyclohexylphenyl)-[1,1'-binaphthalene]-2,2'-diol (**S2**)

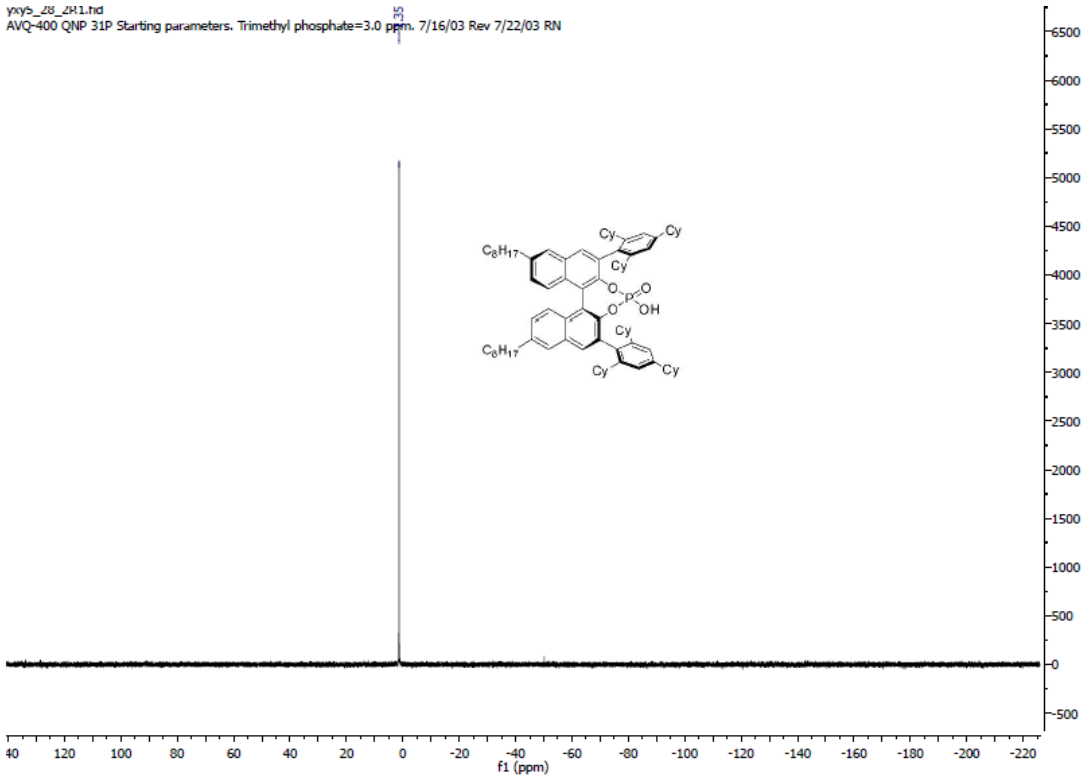




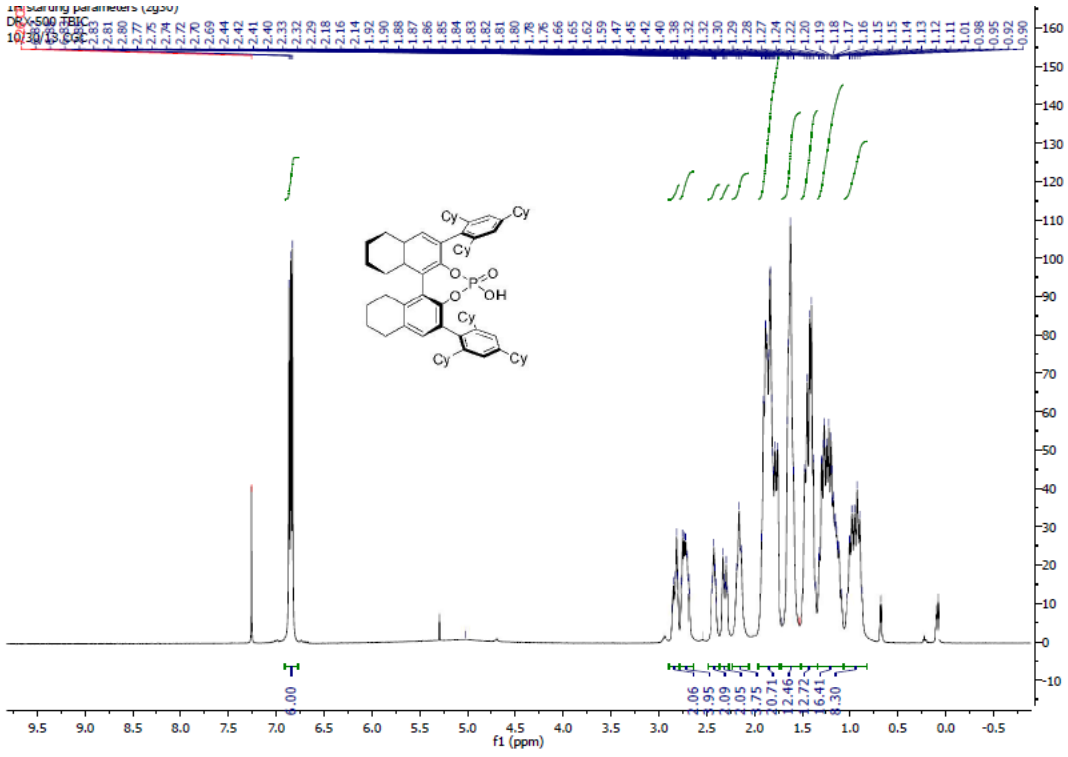
(*R*)-C_8_TCYP

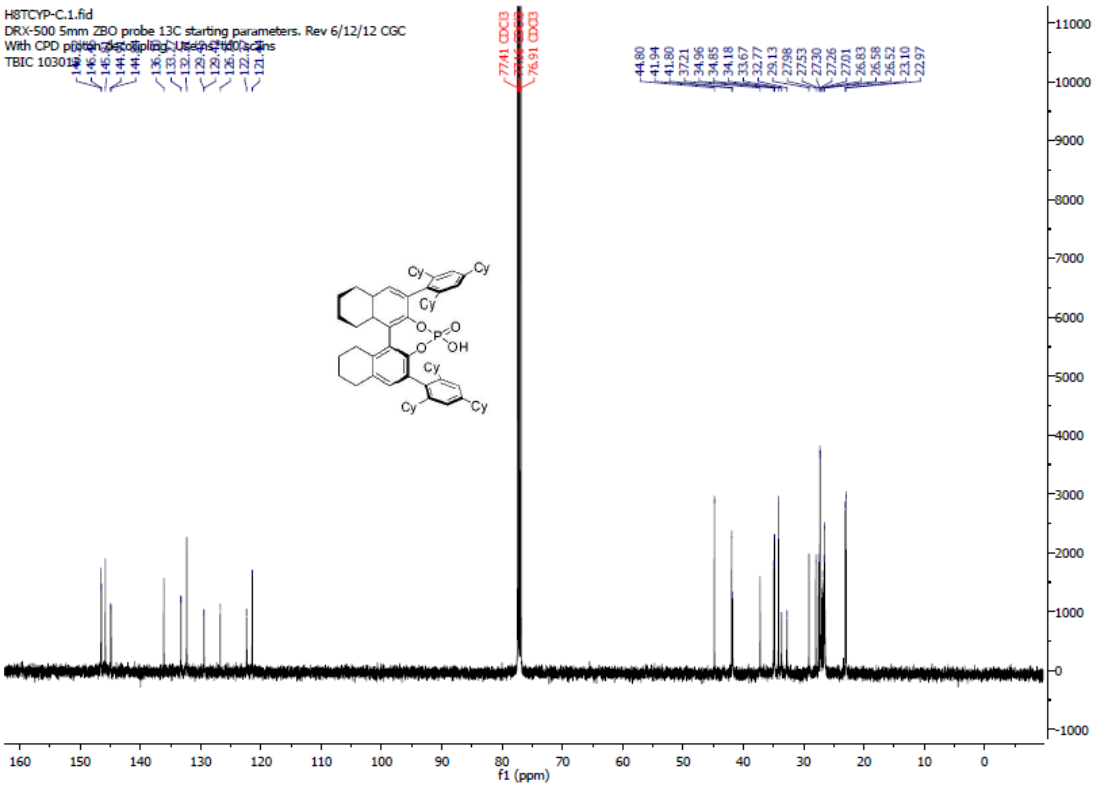

AVB-400 ZBO Proton starting parameters. 6/11/03 RN
f1 (ppm)

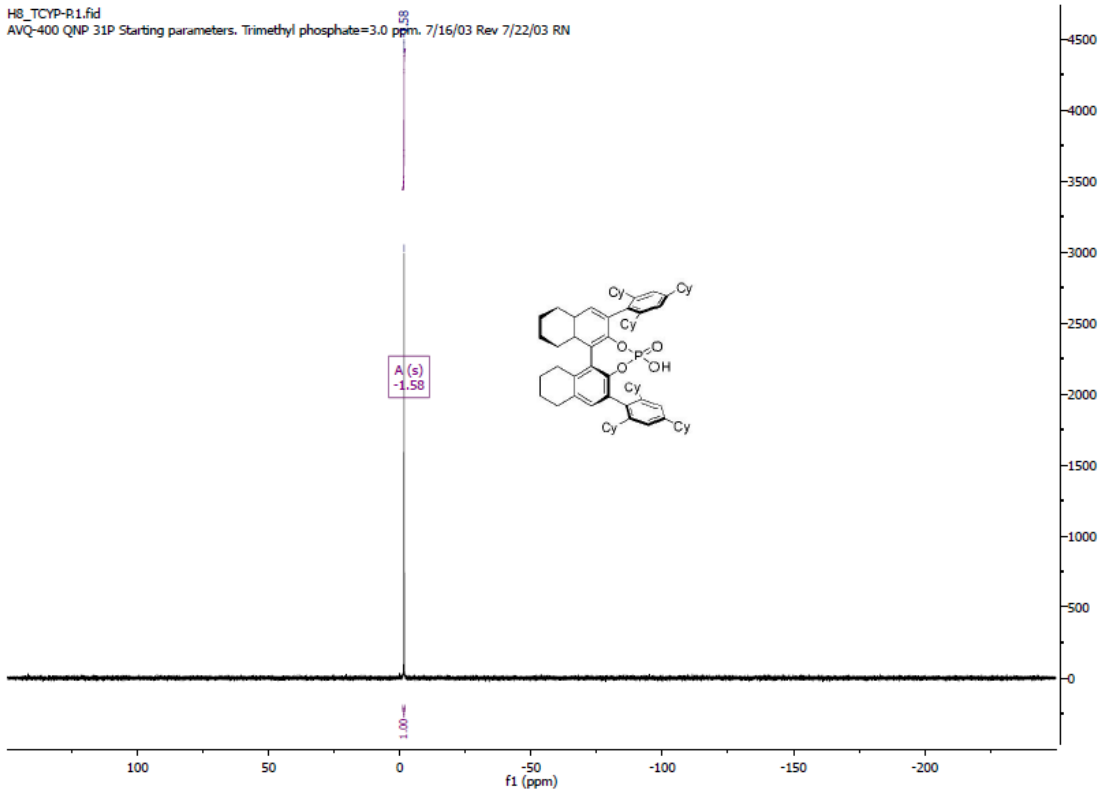

yxy5_28_2C.1.fid
DRX-500 5mm ZBO probe 13C starting parameters. Rev 6/12/12 CGC
With CPD proton decoupling. Use ns*td0 scans
TBIC 103013
f1 (ppm)


AVQ-400 QNP 31P Starting parameters. Trimethyl phosphate=3.0 ppm. 7/16/03 Rev 7/22/03 RN
f1 (ppm)

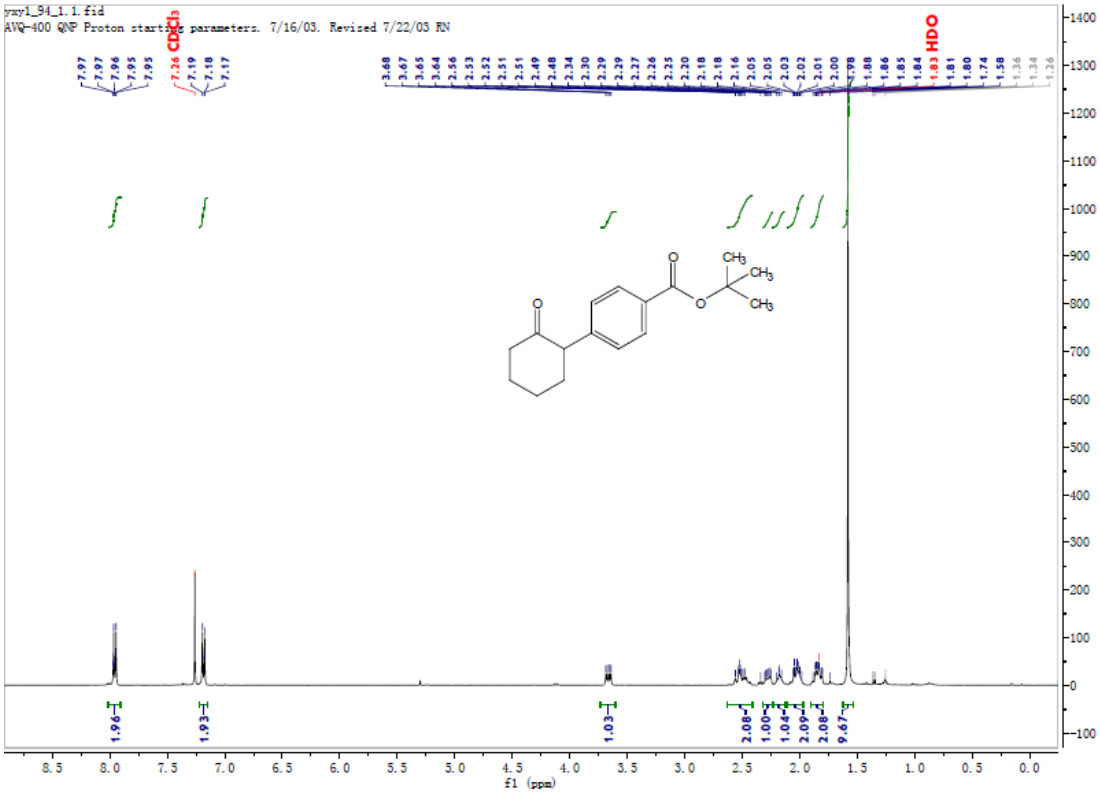
(*R*)-H_8_TCYP

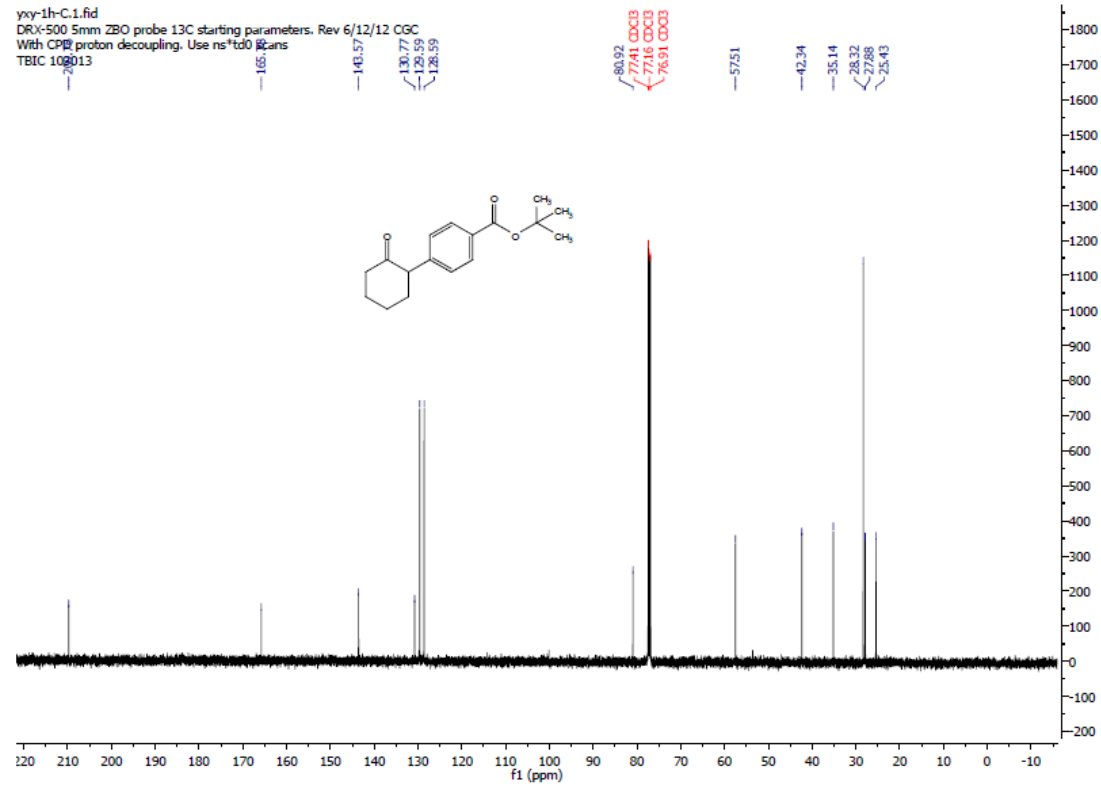

f1 (ppm)


H8TCYP-C.1.fid
DRX-500 5mm ZBO probe 13C starting parameters. Rev 6/12/12 CGC
With CPD
TBIC 103012
77.41 CDCl3
76.91 CDCl3
44.80
41.94
41.80
37.21
34.96
34.65
34.18
33.67
32.77
29.13
27.98
27.53
27.30
27.26
27.01
26.83
26.58
26.52
23.10
22.97
Cy
OH
f1 (ppm)

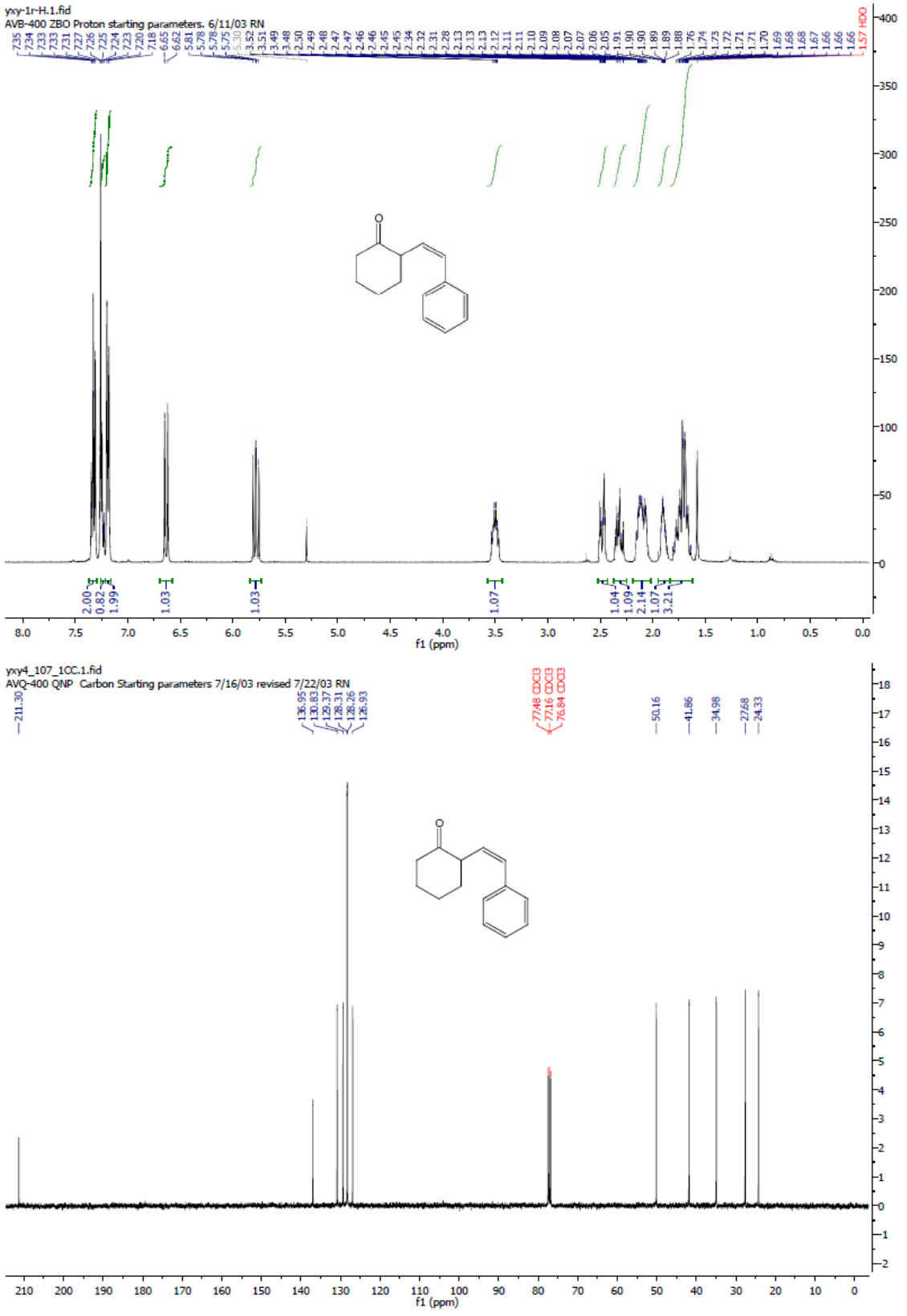

H8_TCYP-P.1.fid
AVQ-400 QNP 31P Starting parameters. Trimethyl phosphate=3.0 ppm. 7/16/03 Rev 7/22/03 RN
A (s)
-1.58
1.00
Cy
OH
f1 (ppm)

tert-butyl 4-(2-oxocyclohexyl)benzoate (**1h**)

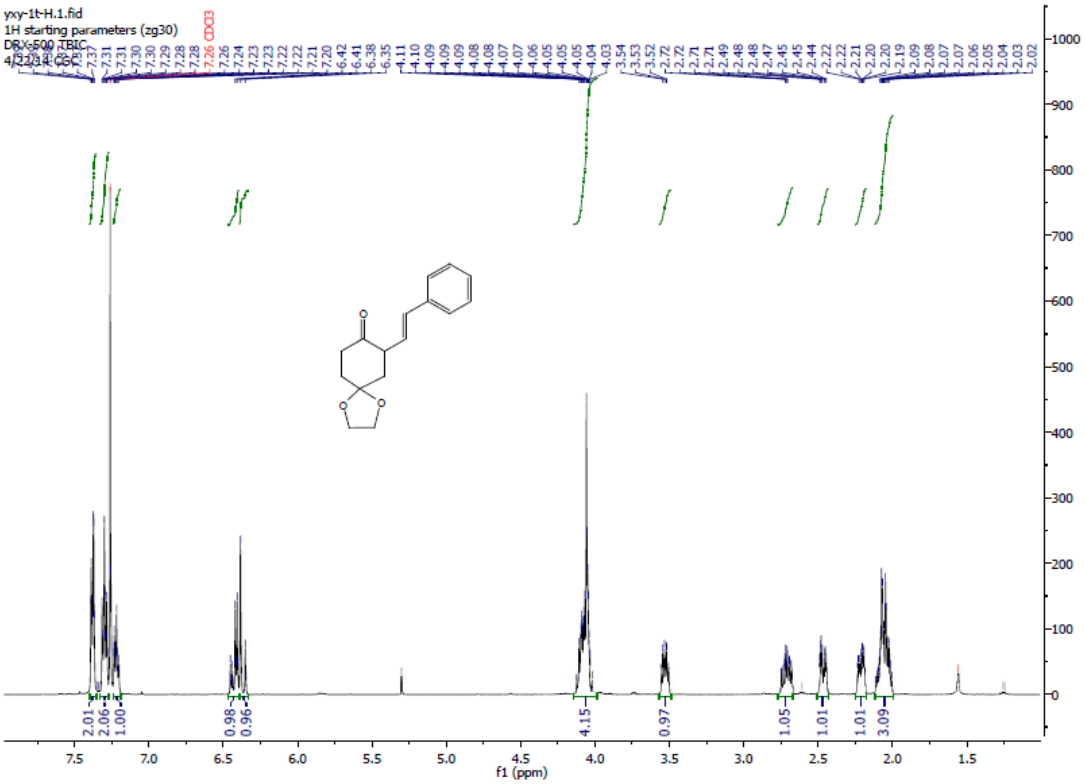


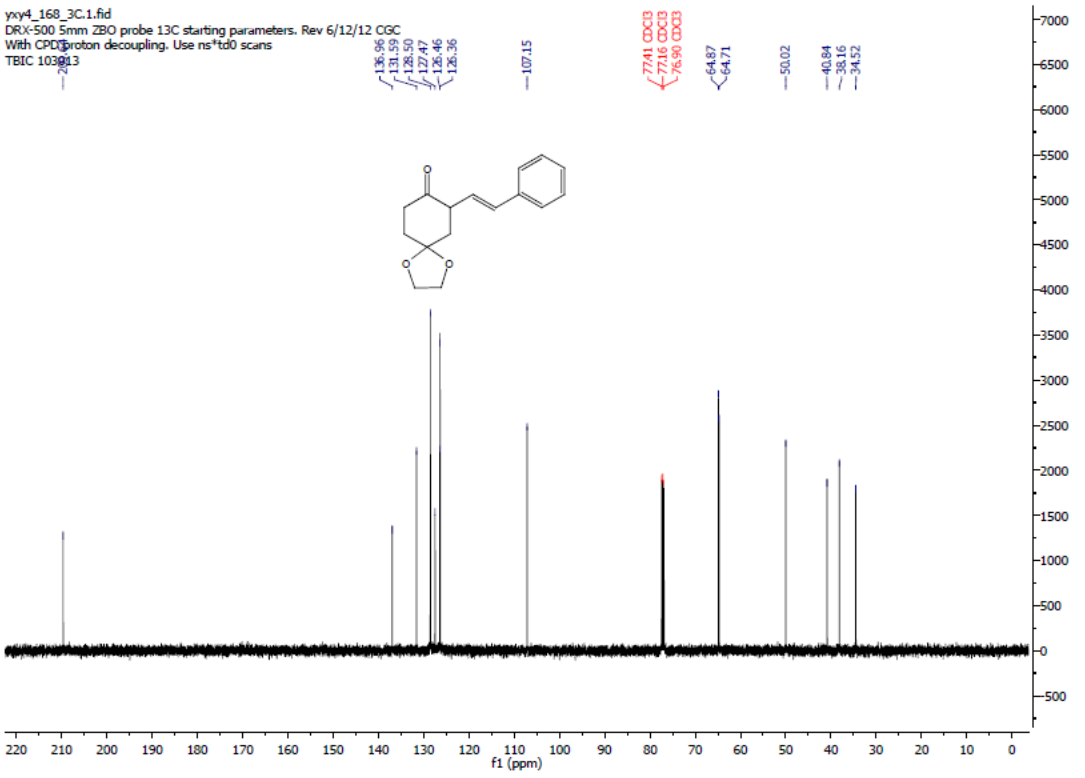


(*Z*)-2-styrylcyclohexanone (**1q**)

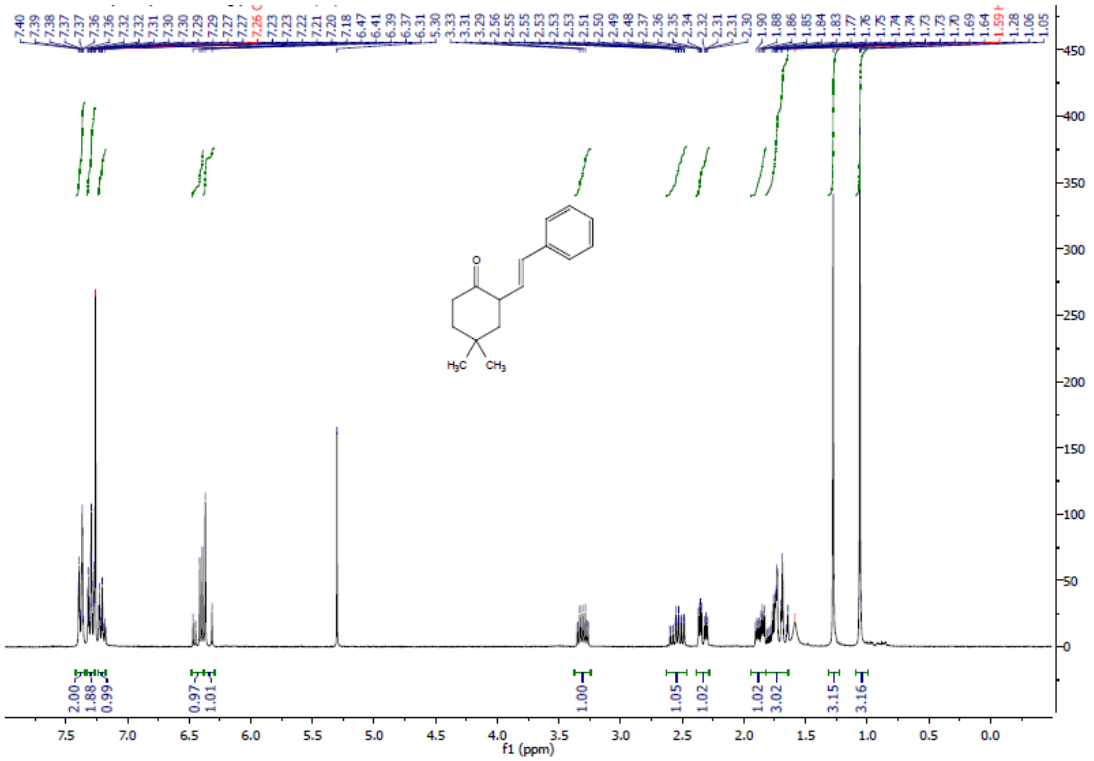


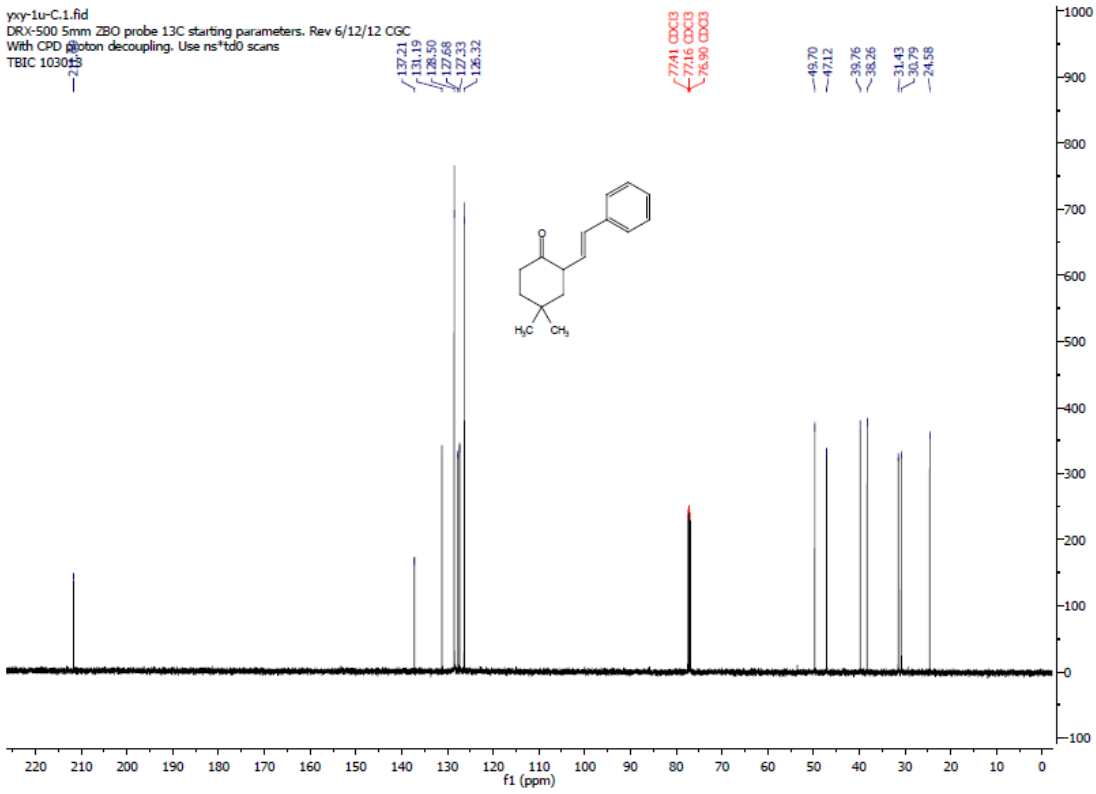
(*E*)-7-styryl-1,4-dioxaspiro[4.5]decan-8-one (**1t**)



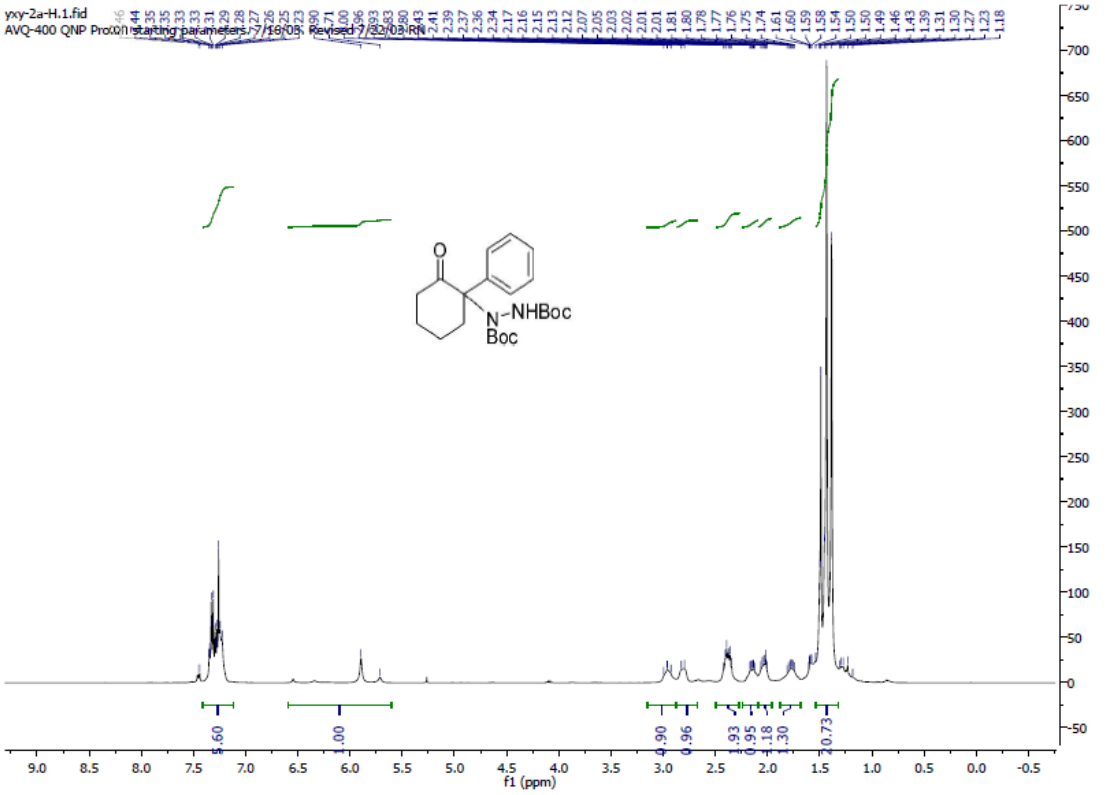


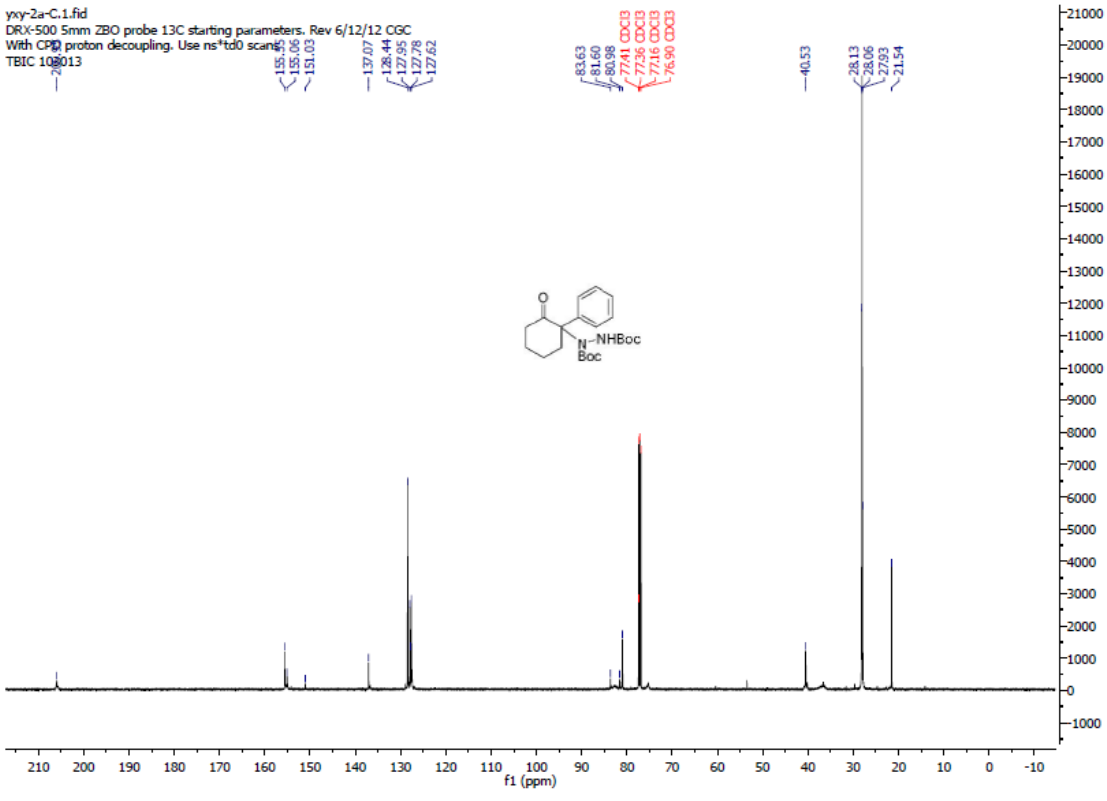
(*E*)-4,4-dimethyl-2-styrylcyclohexanone (**1u**)



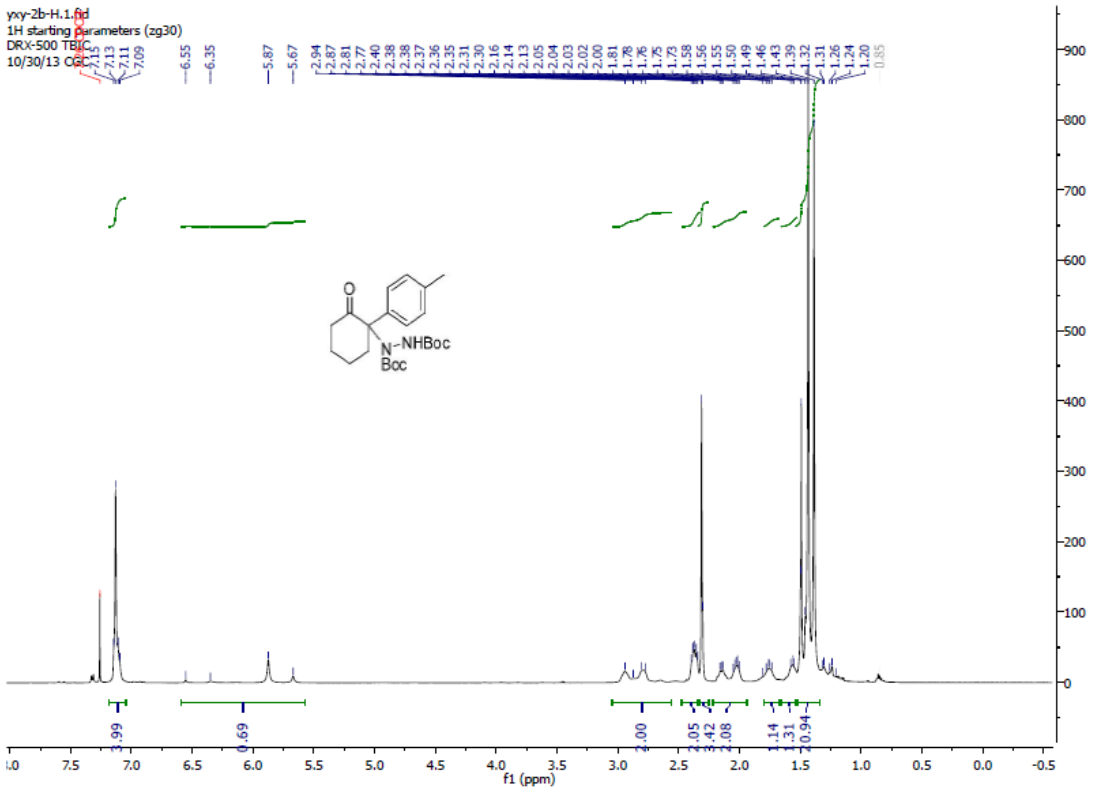


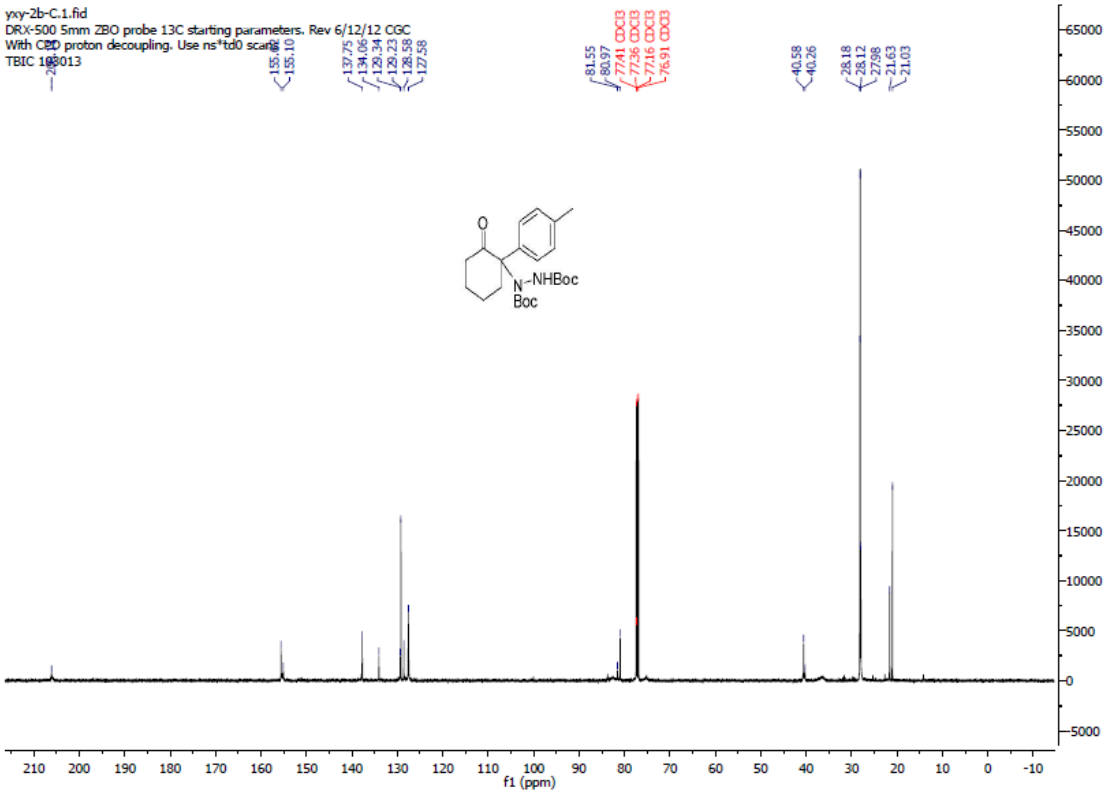
(*S*)-di-*tert*-butyl 1-(2-oxo-1-phenylcyclohexyl)hydrazine-1,2-dicarboxylate (**2a**)



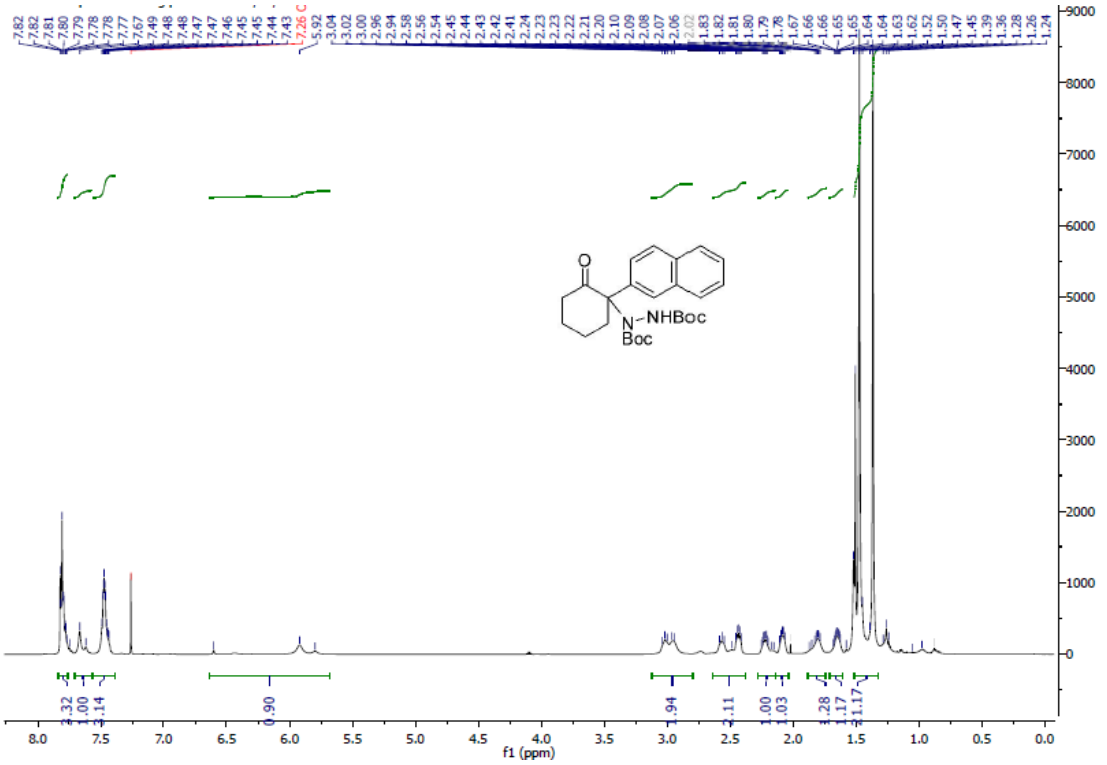


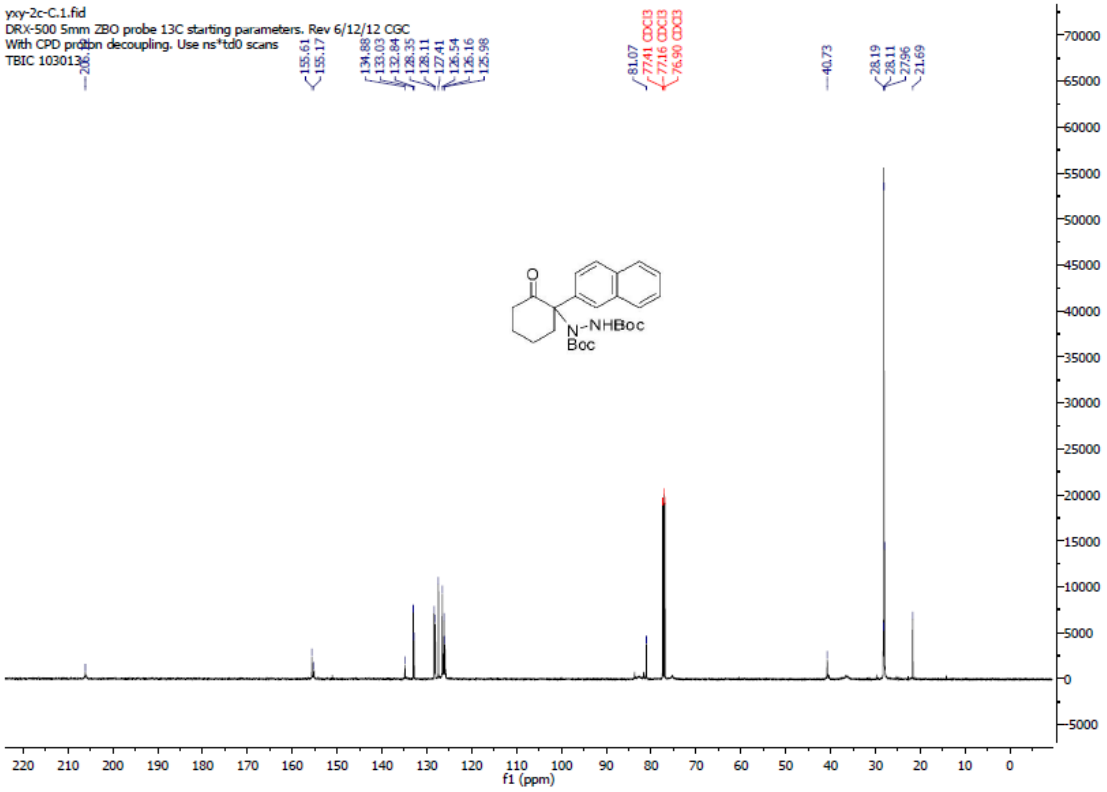
(*S*)-di-*tert*-butyl 1-(2-oxo-1-(p-tolyl)cyclohexyl)hydrazine-1,2-dicarboxylate (**2b**)



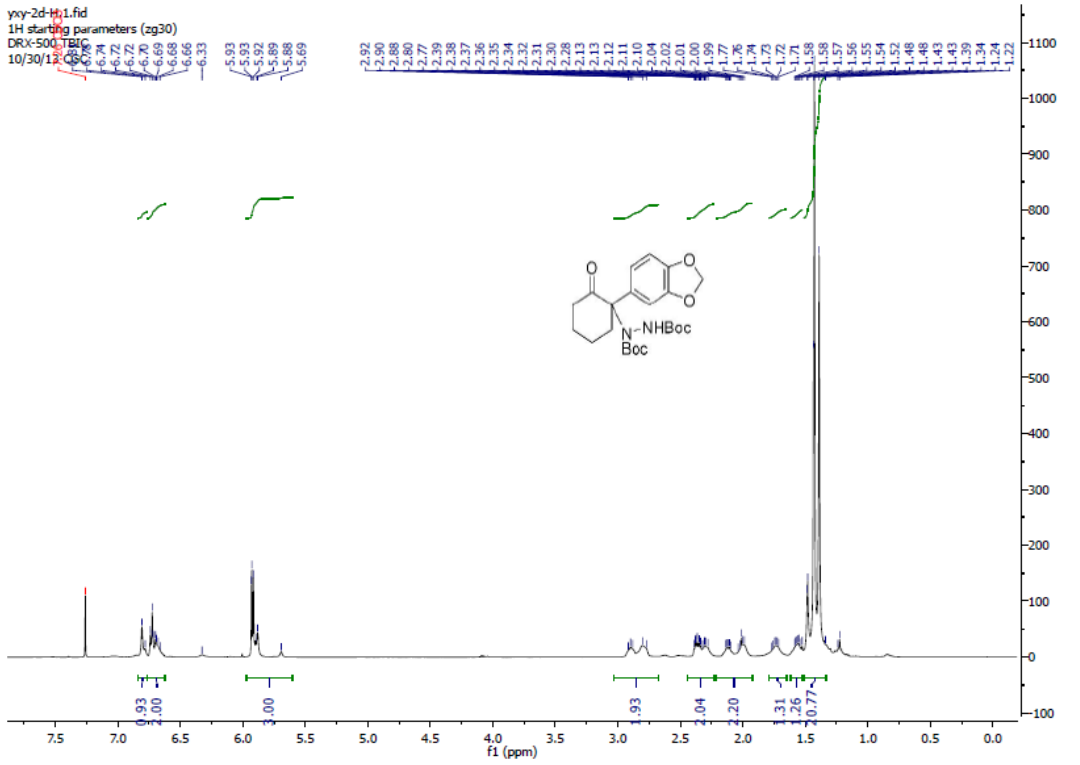


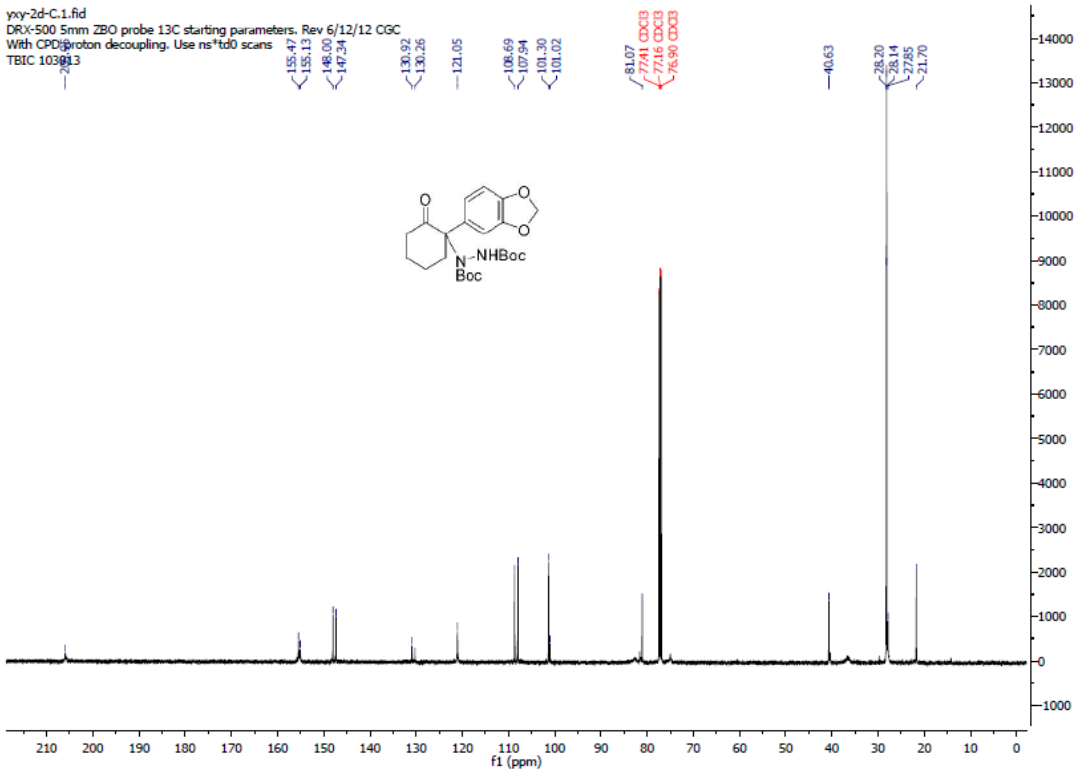
(*S*)-di-*tert*-butyl 1-(1-(naphthalen-2-yl)-2-oxocyclohexyl)hydrazine-1,2-dicarboxylate (**2c**)



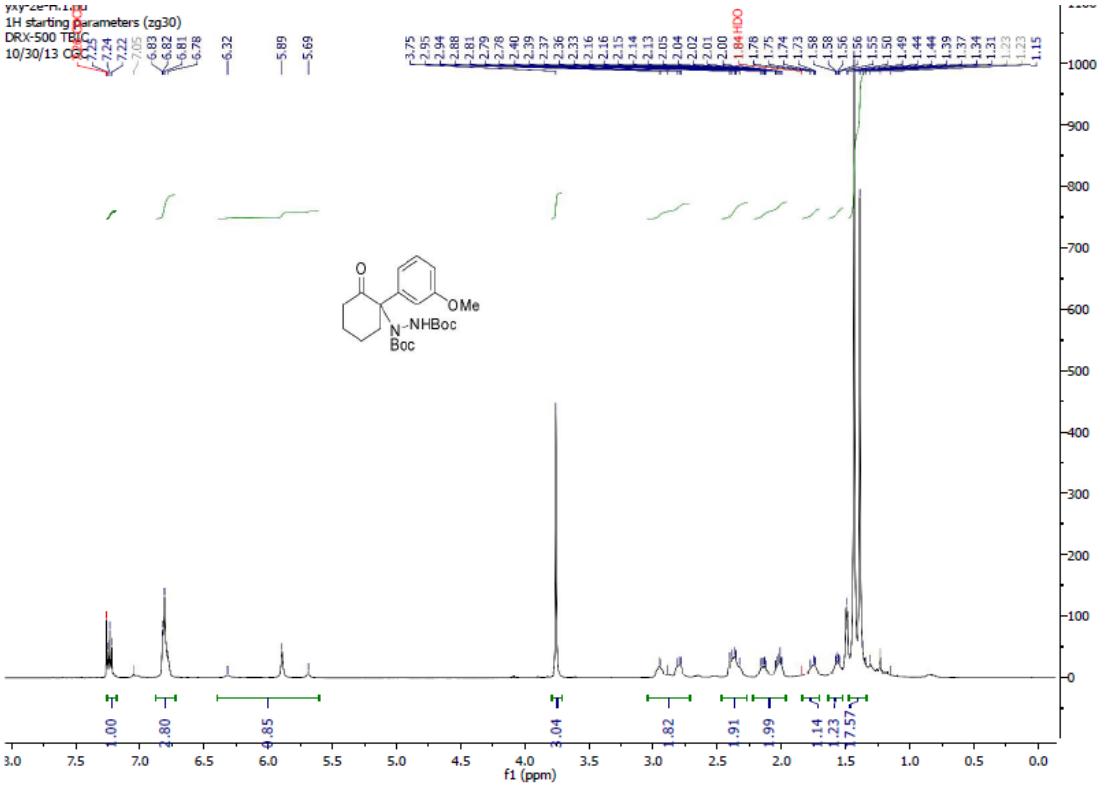


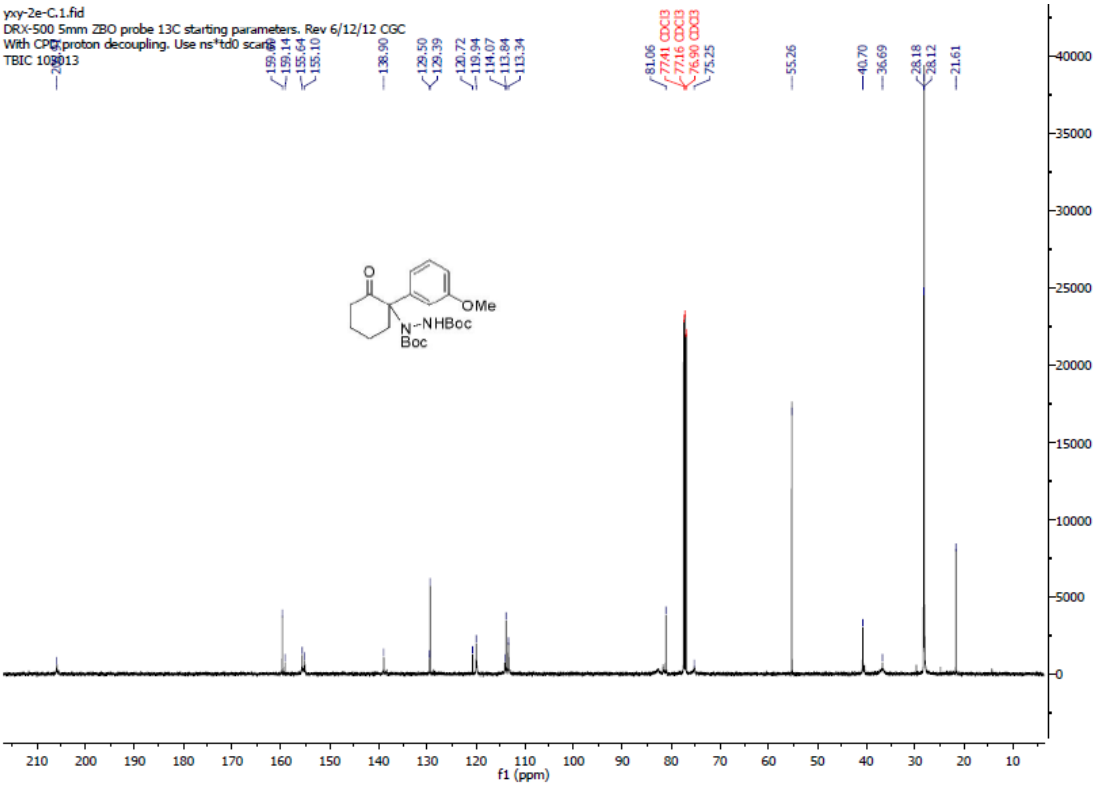
(*S*)-di-*tert*-butyl 1-(1-(benzo[d][1,3]dioxol-5-yl)-2-oxocyclohexyl)hydrazine-1,2-dicarboxylate (**2d**)



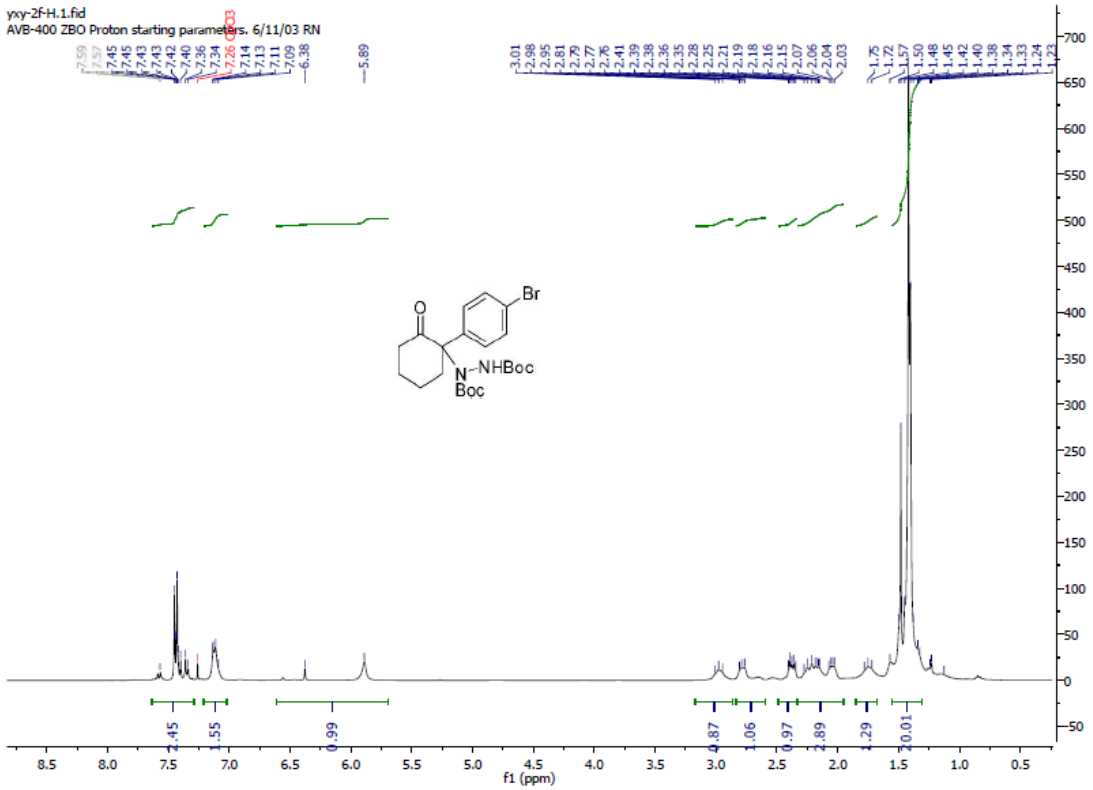


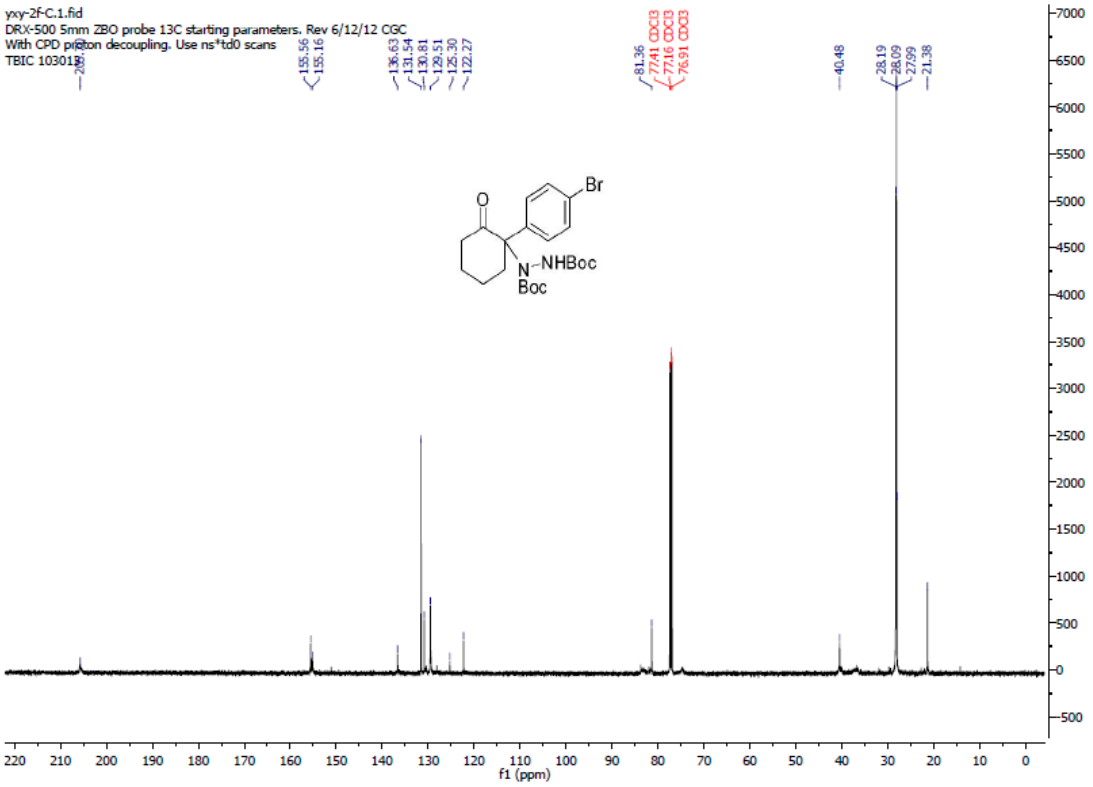
(*S*)-di-*tert*-butyl 1-(1-(3-methoxyphenyl)-2-oxocyclohexyl)hydrazine-1,2-dicarboxylate (**2e**)



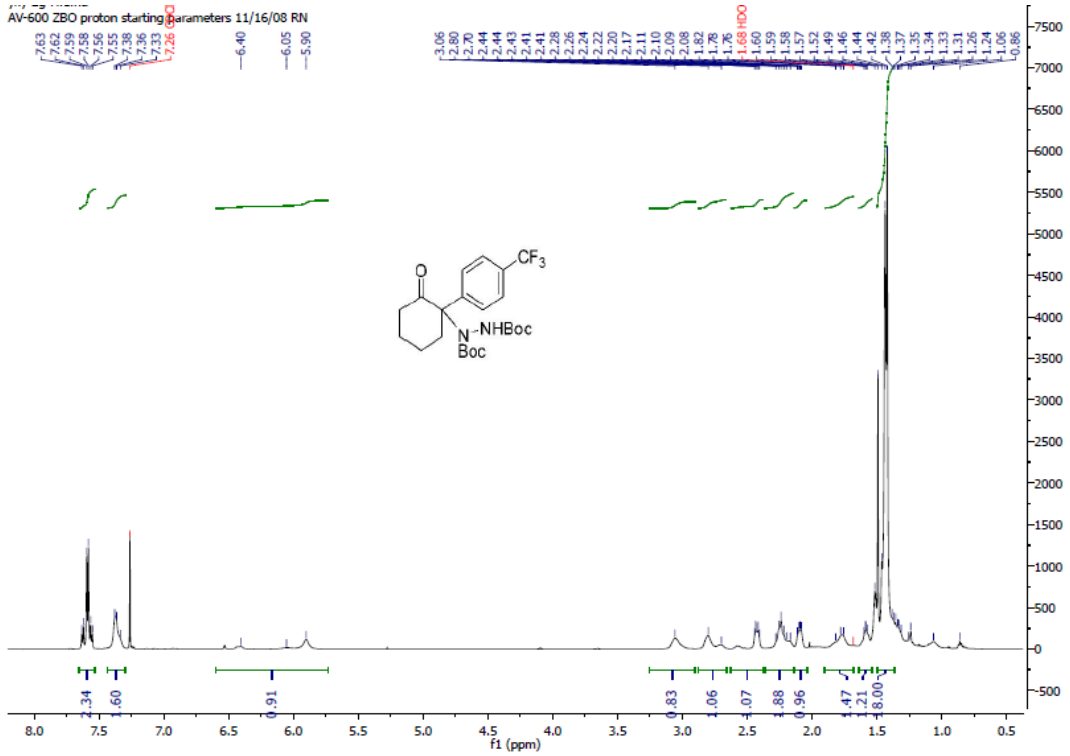


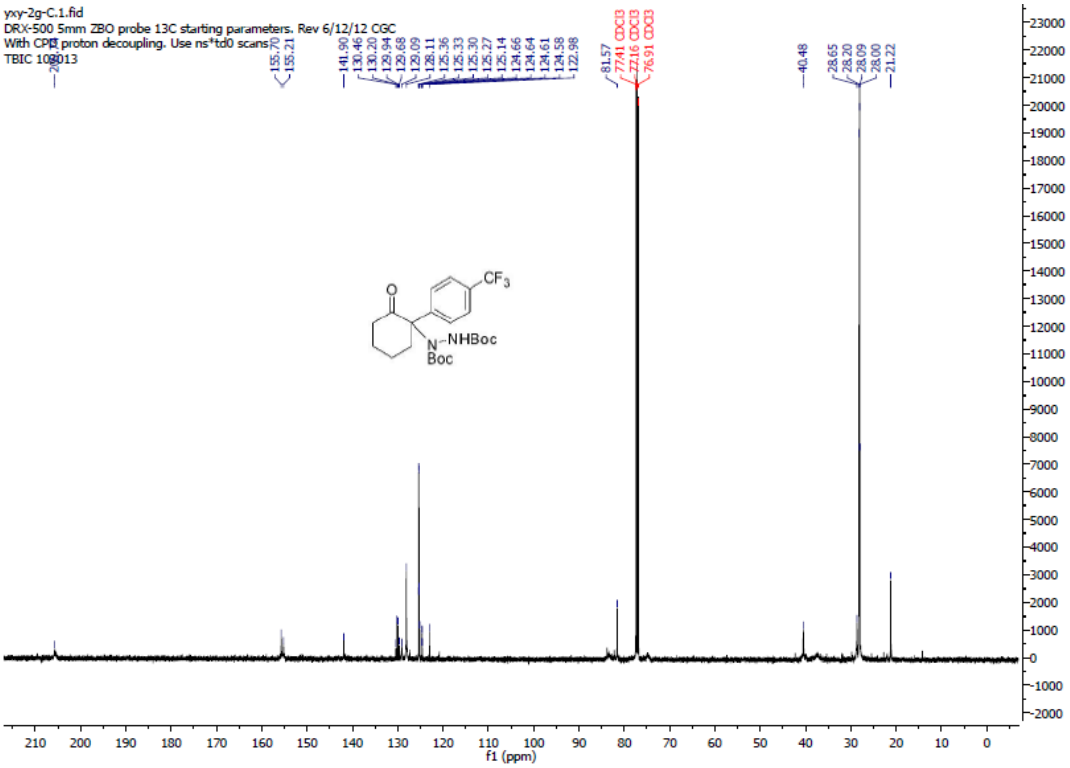
(*S*)-di-*tert*-butyl 1-(1-(4-bromophenyl)-2-oxocyclohexyl)hydrazine-1,2-dicarboxylate (**2f**)



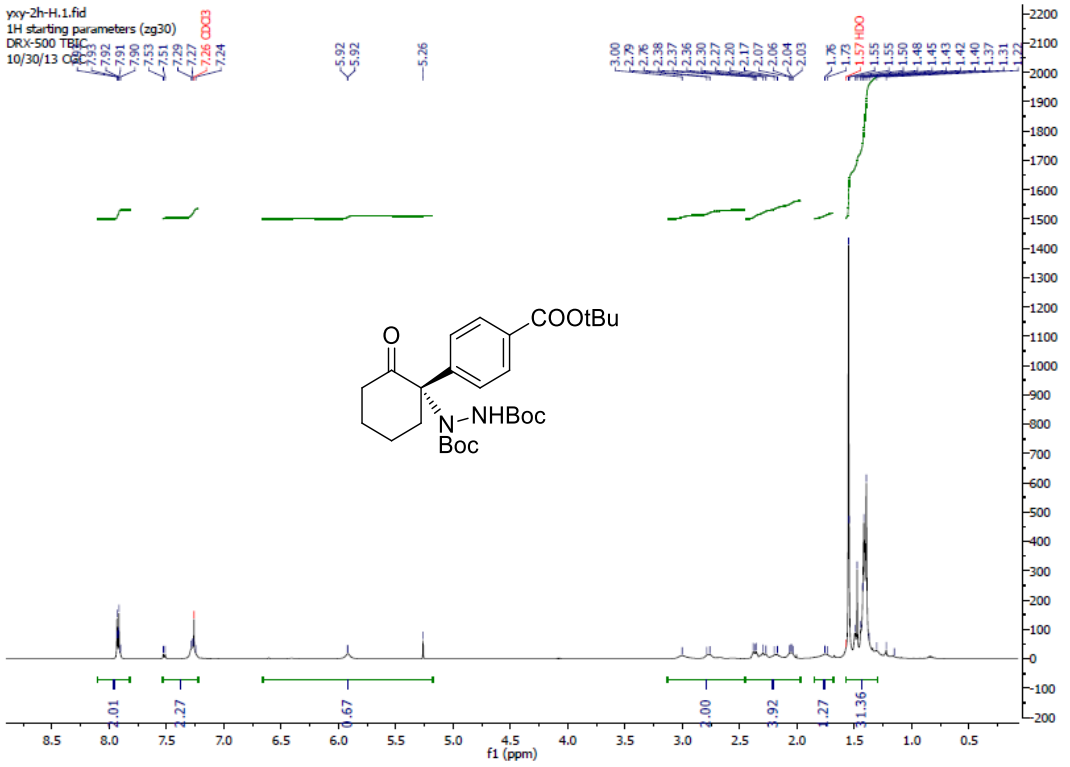


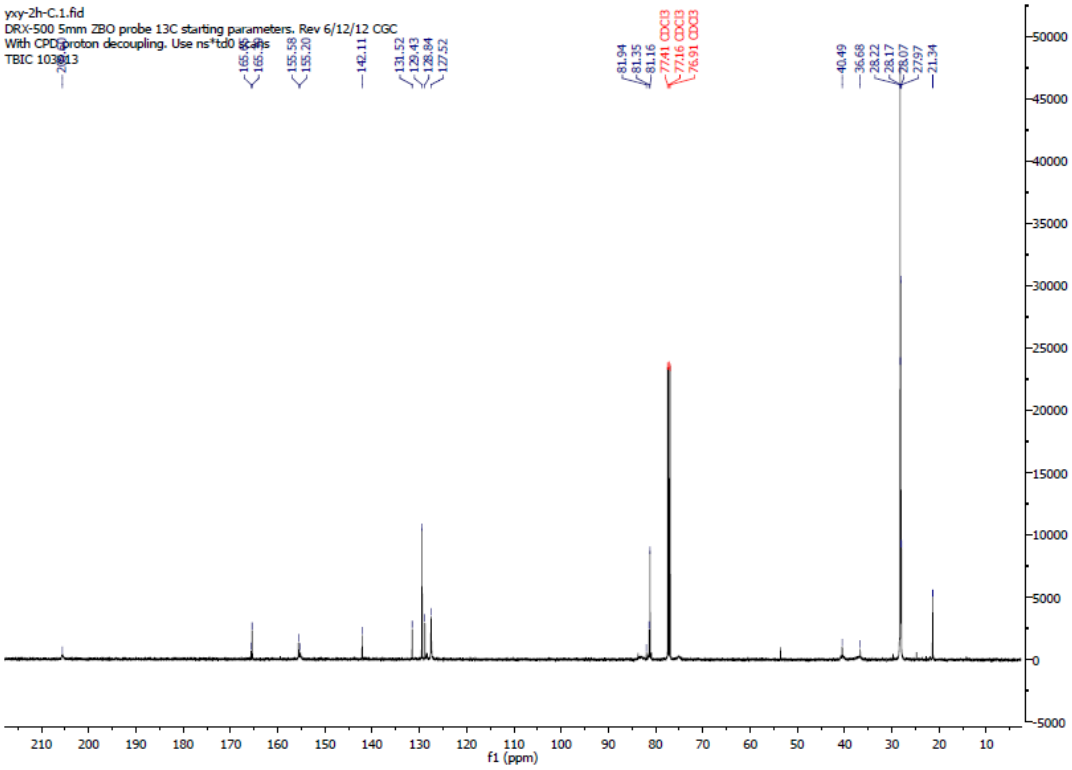
(*S*)-di-*tert*-butyl 1-(2-oxo-1-(4-(trifluoromethyl)phenyl)cyclohexyl)hydrazine-1,2-dicarboxylate (**2g**)



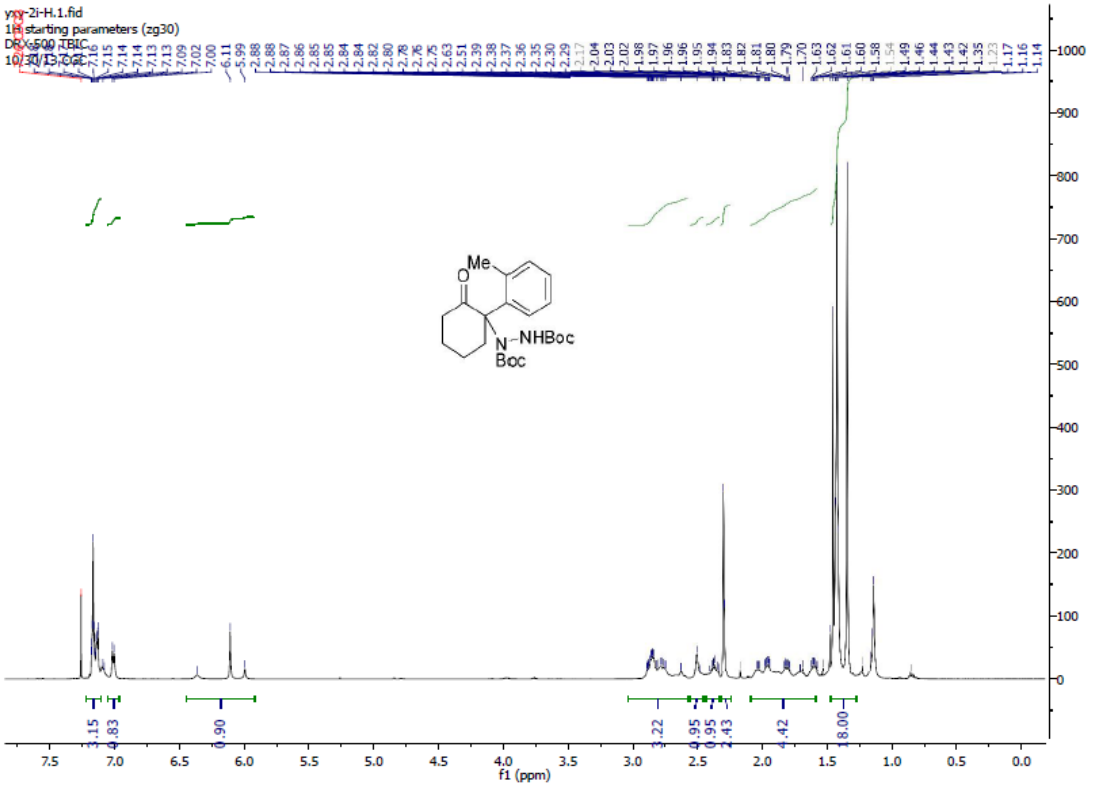


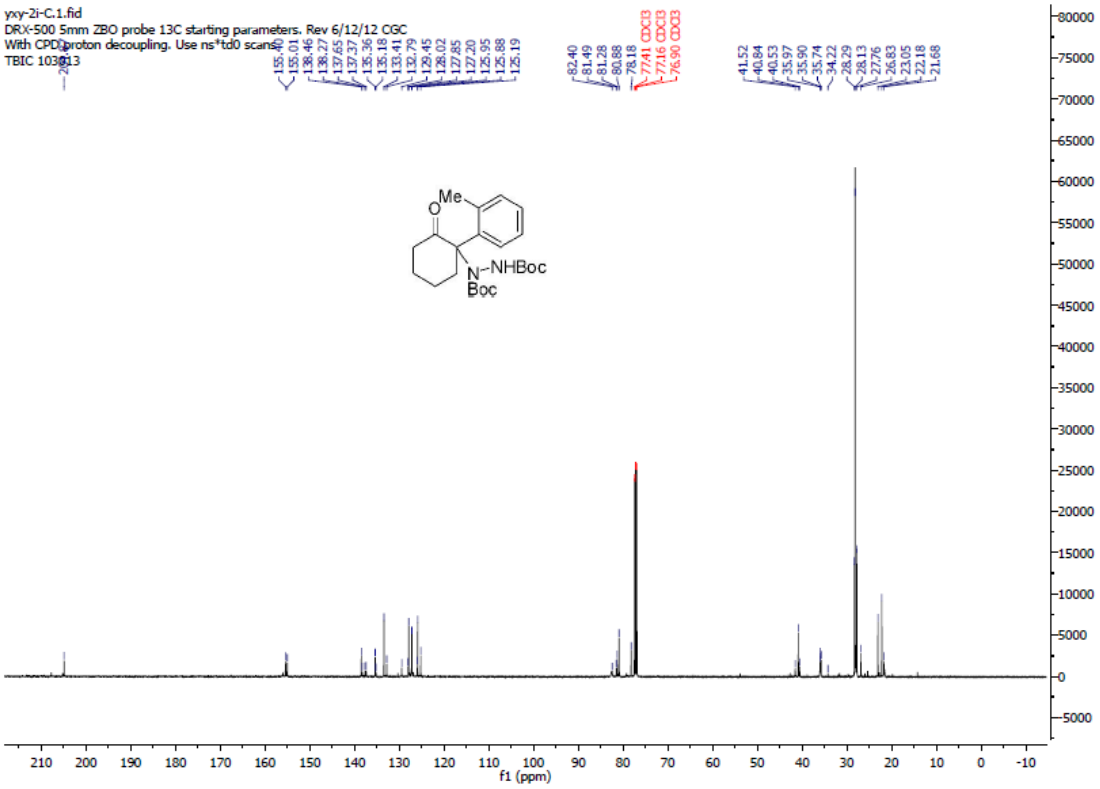
(*S*)-di-*tert*-butyl 1-(1-(4-(tert-butoxycarbonyl)phenyl)-2-oxocyclohexyl)hydrazine-1,2-dicarboxylate (**2h**)



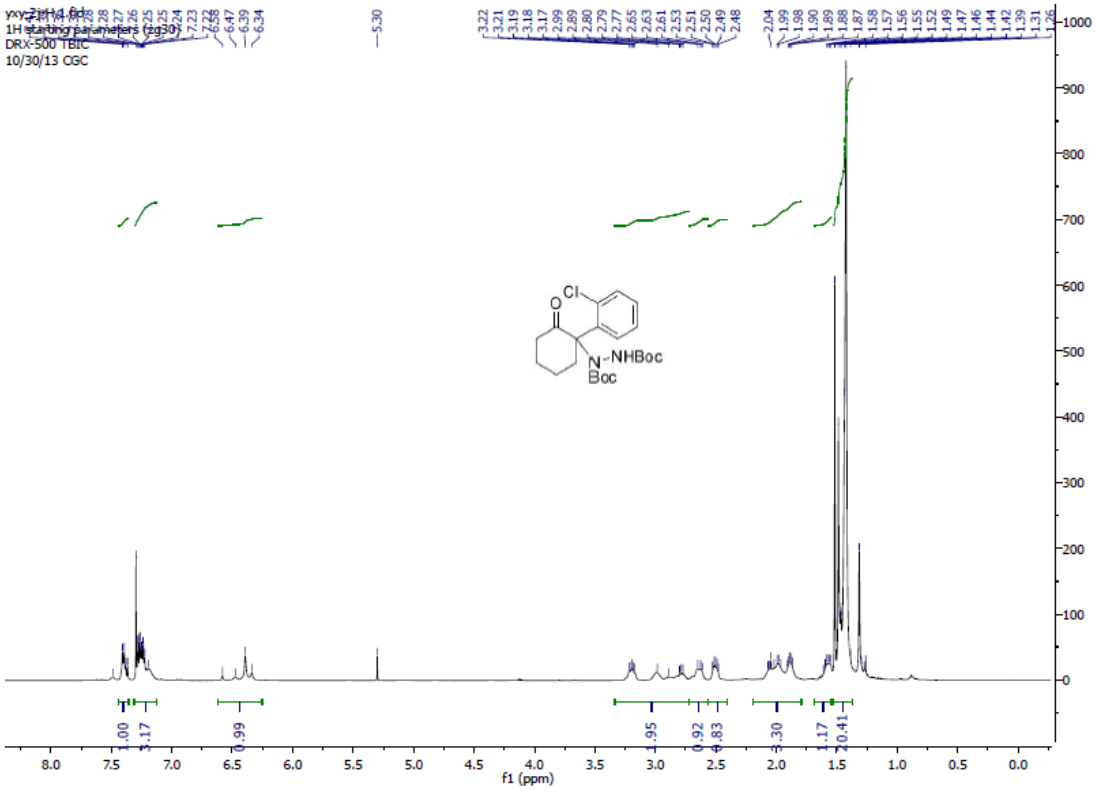


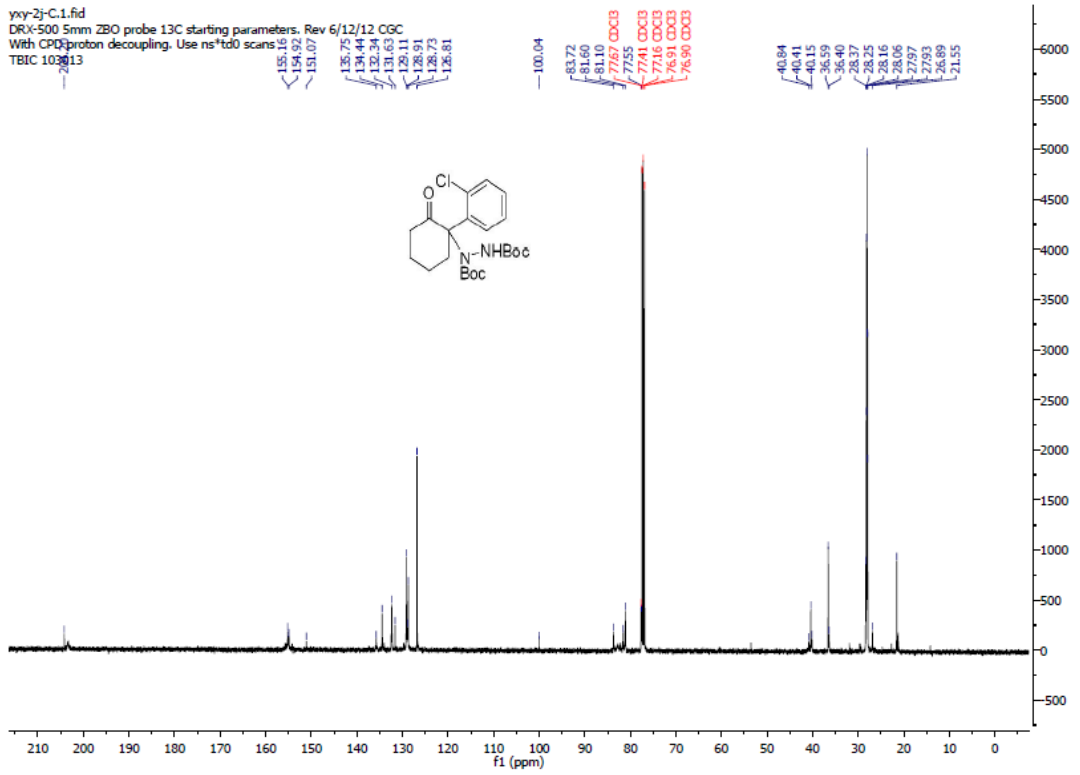
(*S*)-di-*tert*-butyl 1-(2-oxo-1-(o-tolyl)cyclohexyl)hydrazine-1,2-dicarboxylate (**2i**)



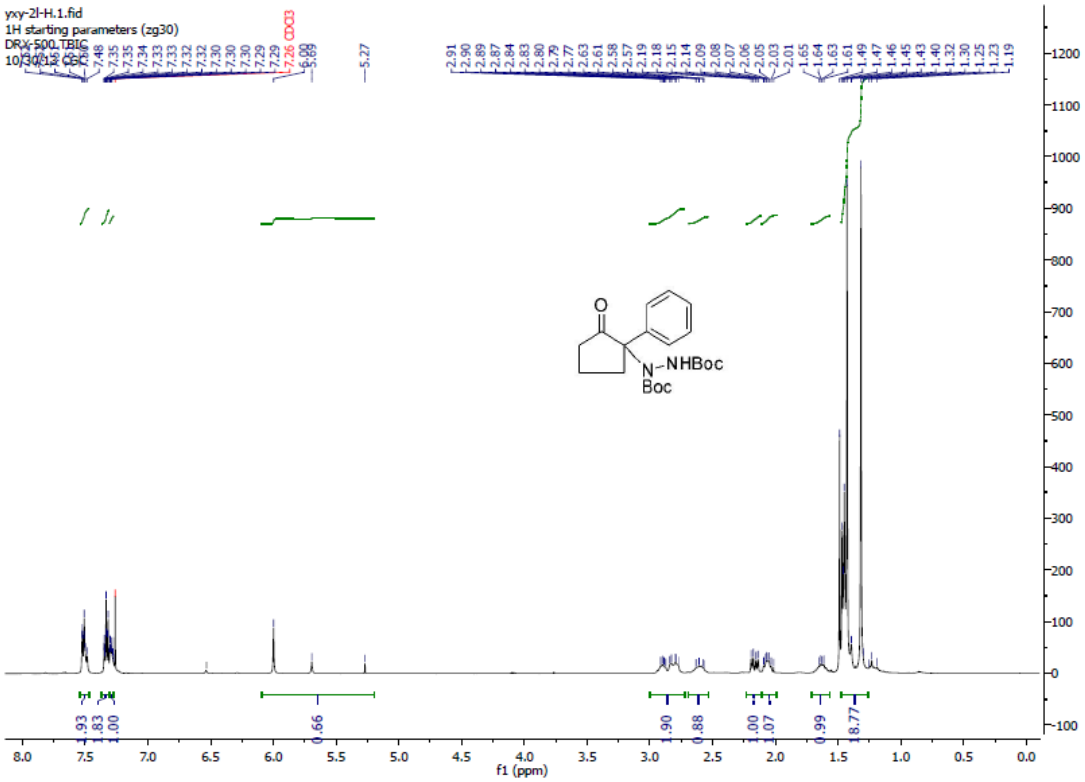


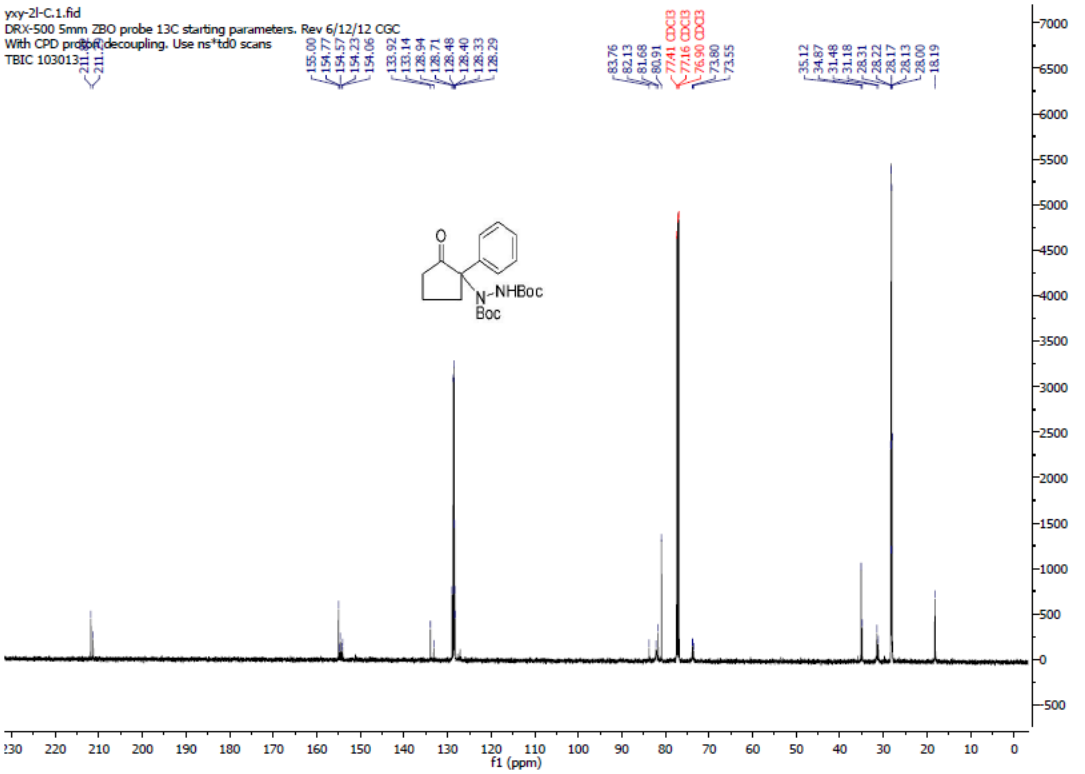
(*S*)-di-*tert*-butyl 1-(1-(2-chlorophenyl)-2-oxocyclohexyl)hydrazine-1,2-dicarboxylate (**2j**)



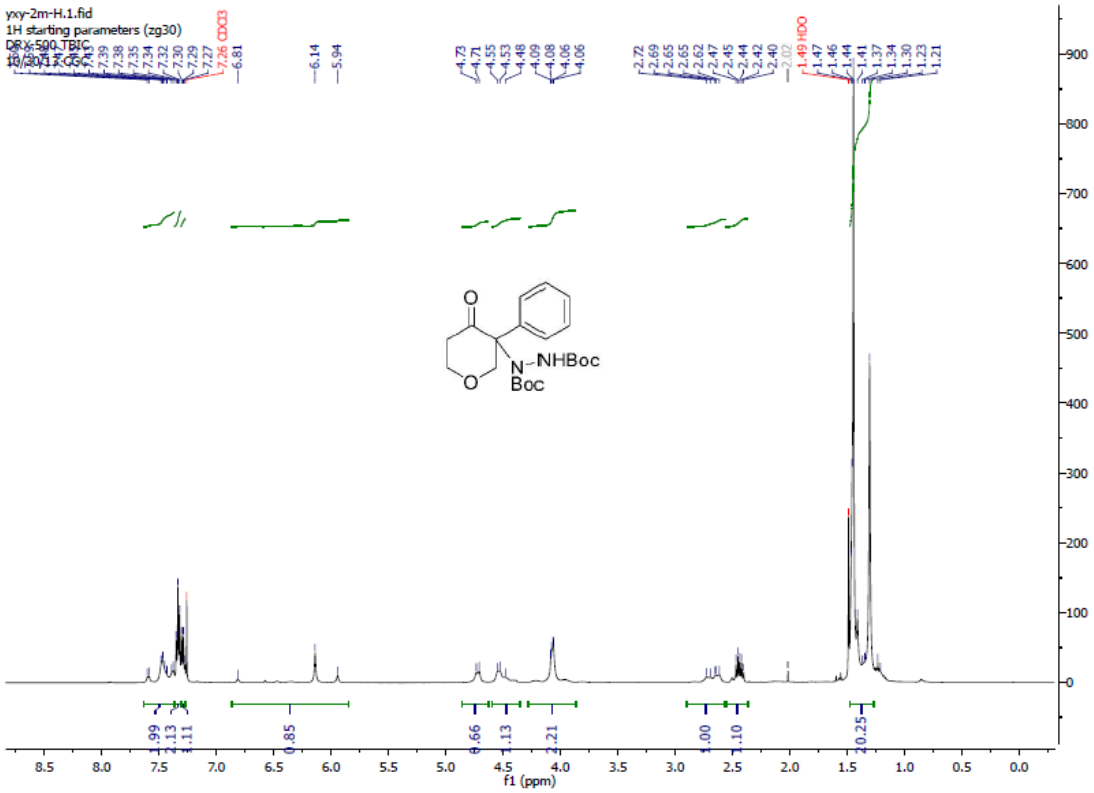


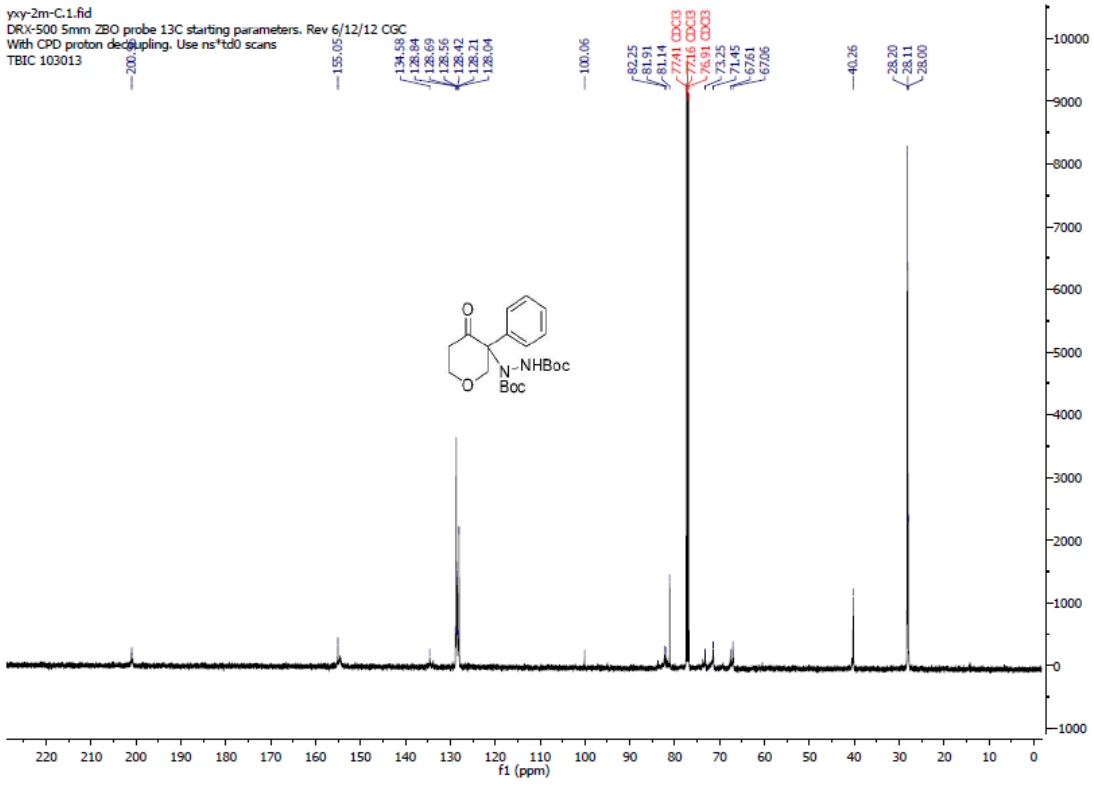
(*S*)-di-*tert*-butyl 1-(2-oxo-1-phenylcyclopentyl)hydrazine-1,2-dicarboxylate (**2k**)



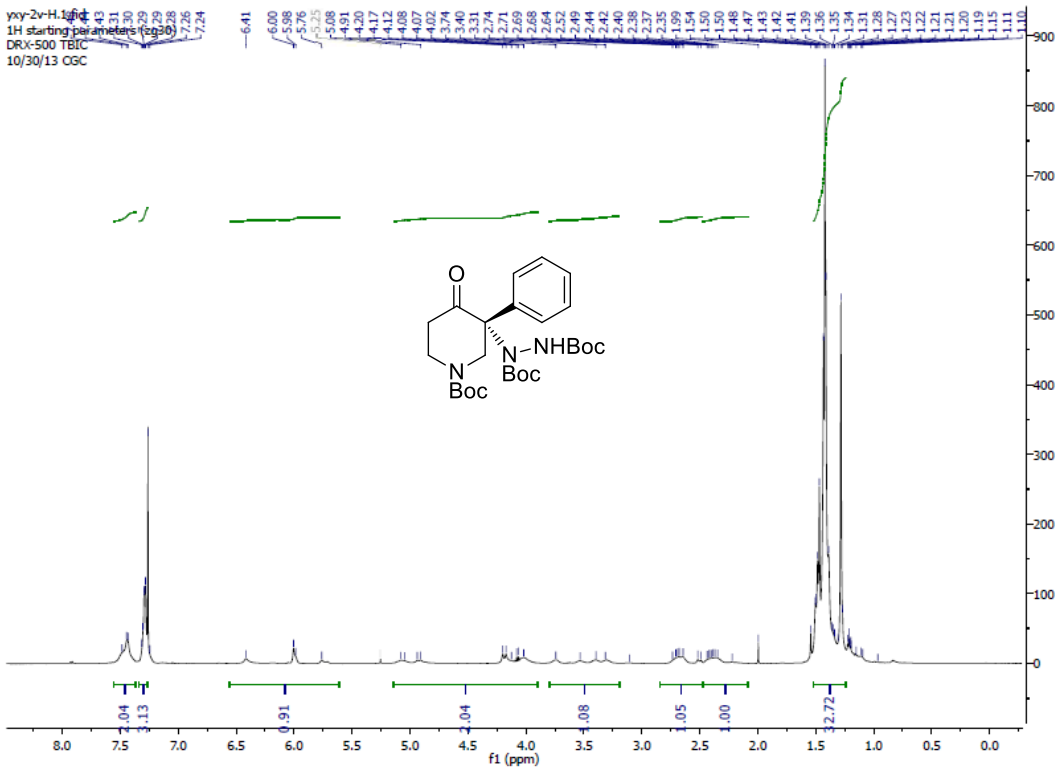


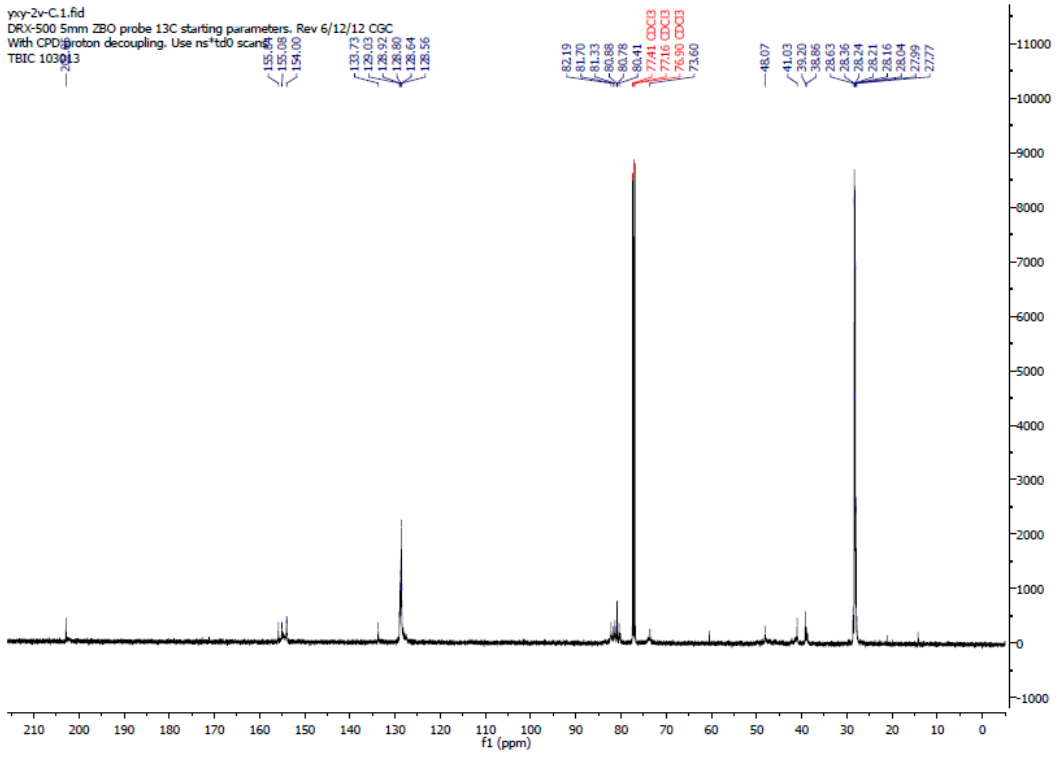
(*R*)-di-*tert*-butyl 1-(4-oxo-3-phenyltetrahydro-2H-pyran-3-yl)hydrazine-1,2-dicarboxylate (**2l**)



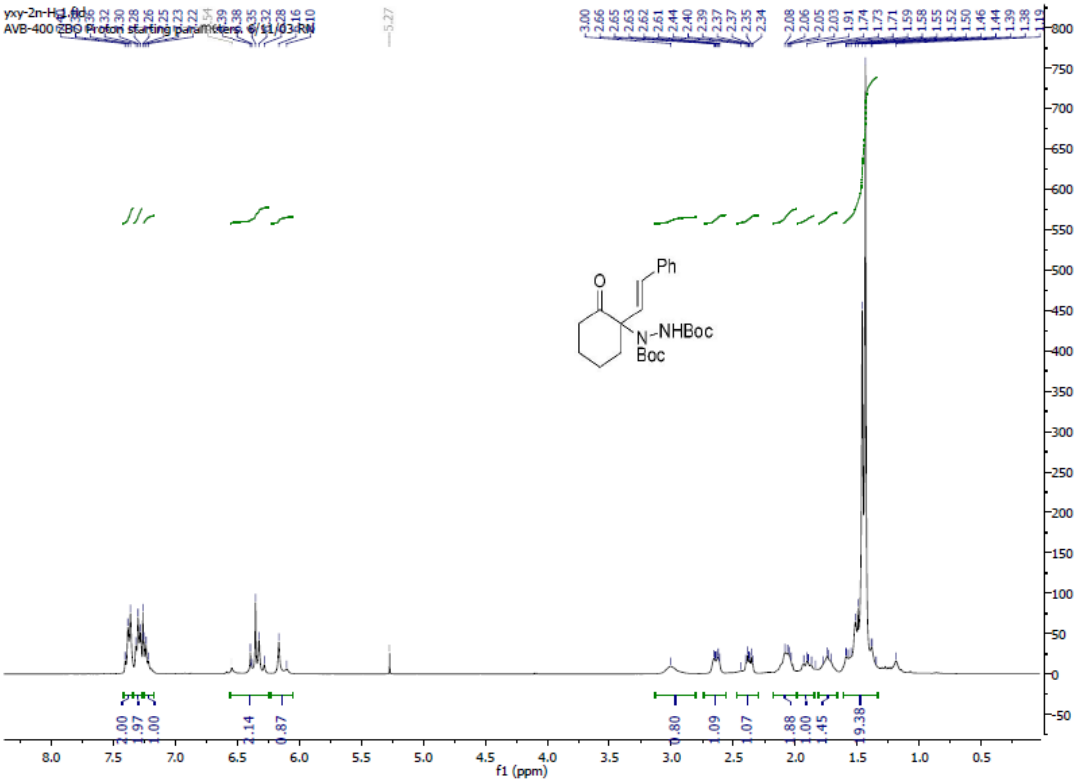


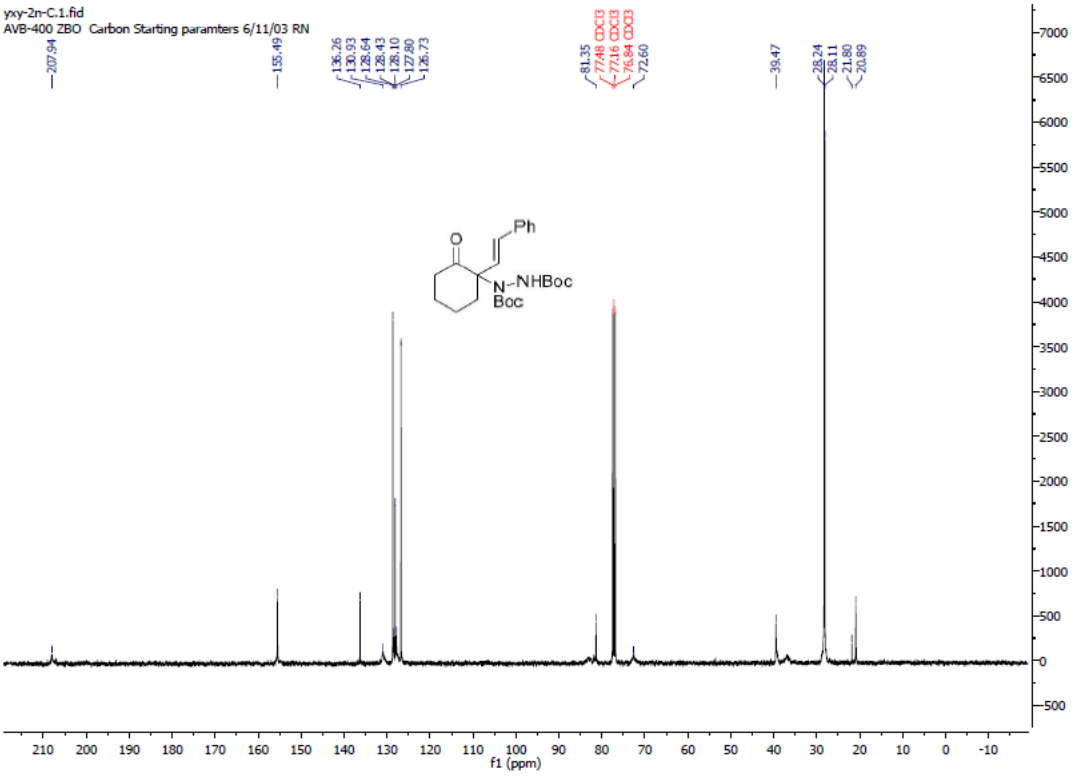
(*R*)-di-*tert*-butyl 1-(1-(tert-butoxycarbonyl)-4-oxo-3-phenylpiperidin-3-yl)hydrazine-1,2-dicarboxylate (**2m**)



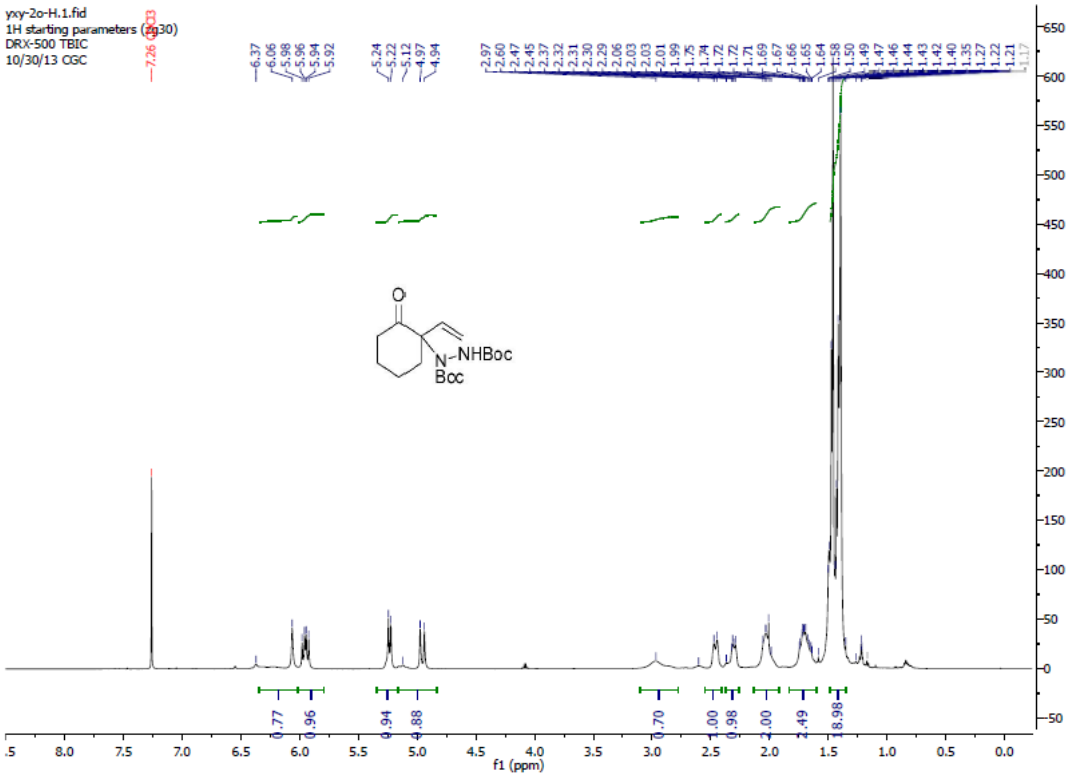


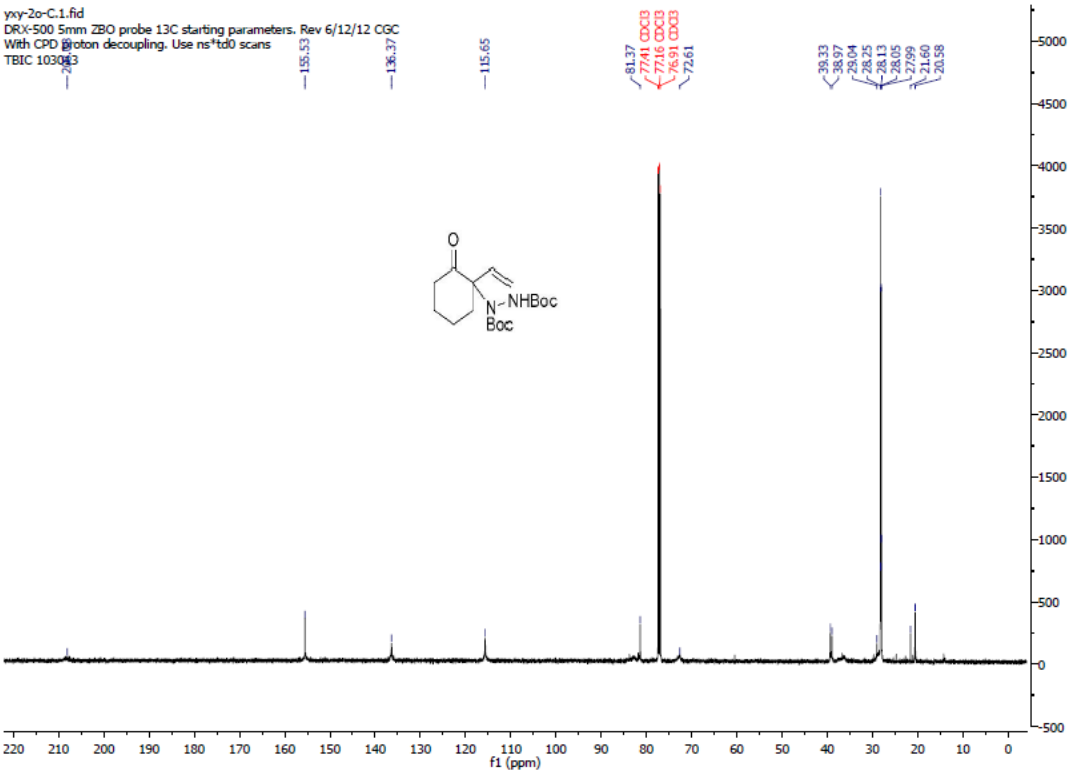
(*S*,*E*)-di-*tert*-butyl 1-(2-oxo-1-styrylcyclohexyl)hydrazine-1,2-dicarboxylate (**2n**)



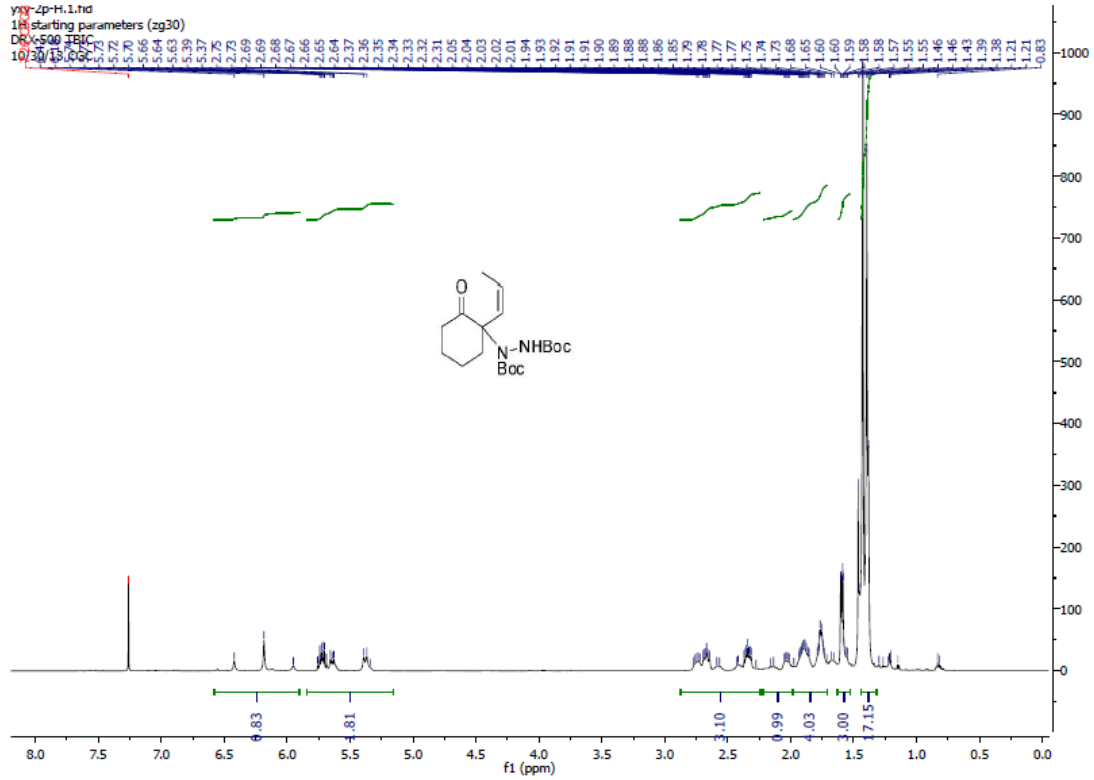


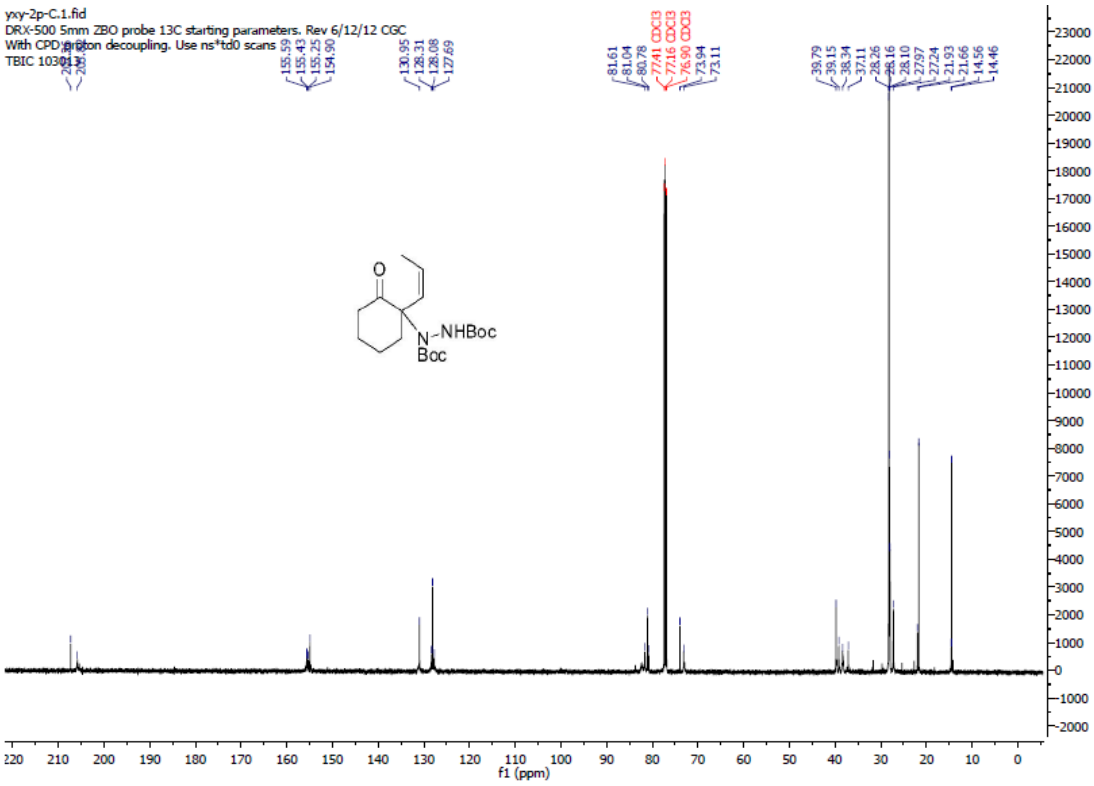
(*S*)-di-*tert*-butyl 1-(2-oxo-1-vinylcyclohexyl)hydrazine-1,2-dicarboxylate (**2o**)



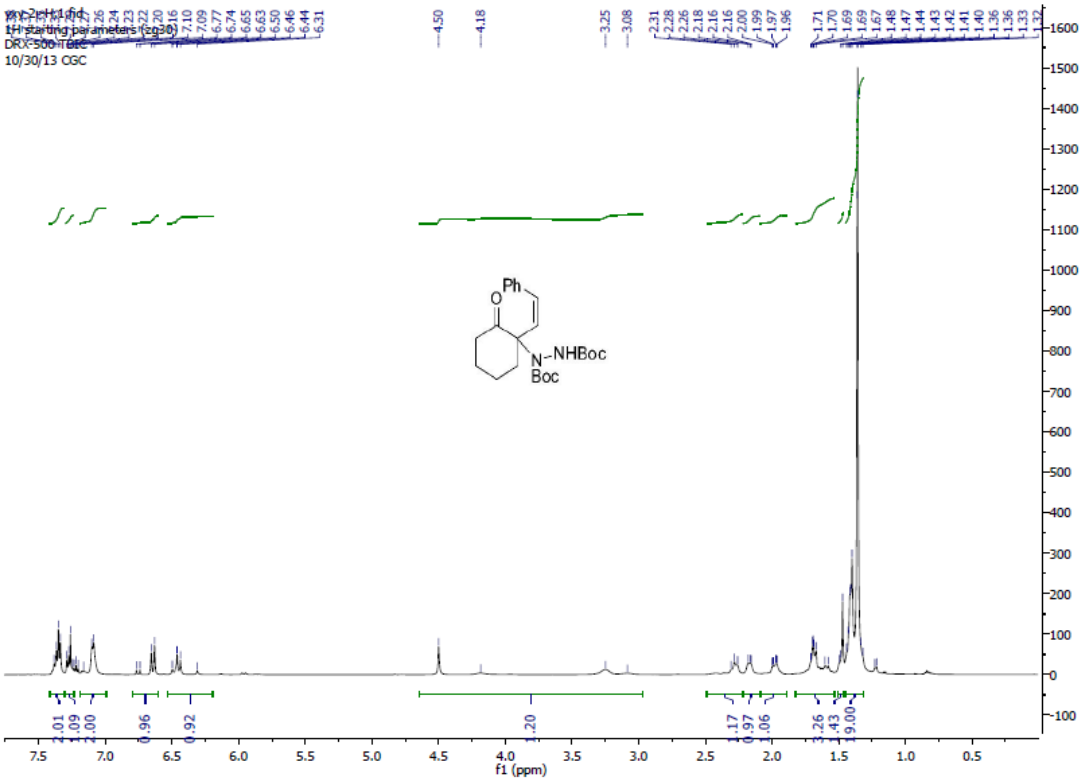


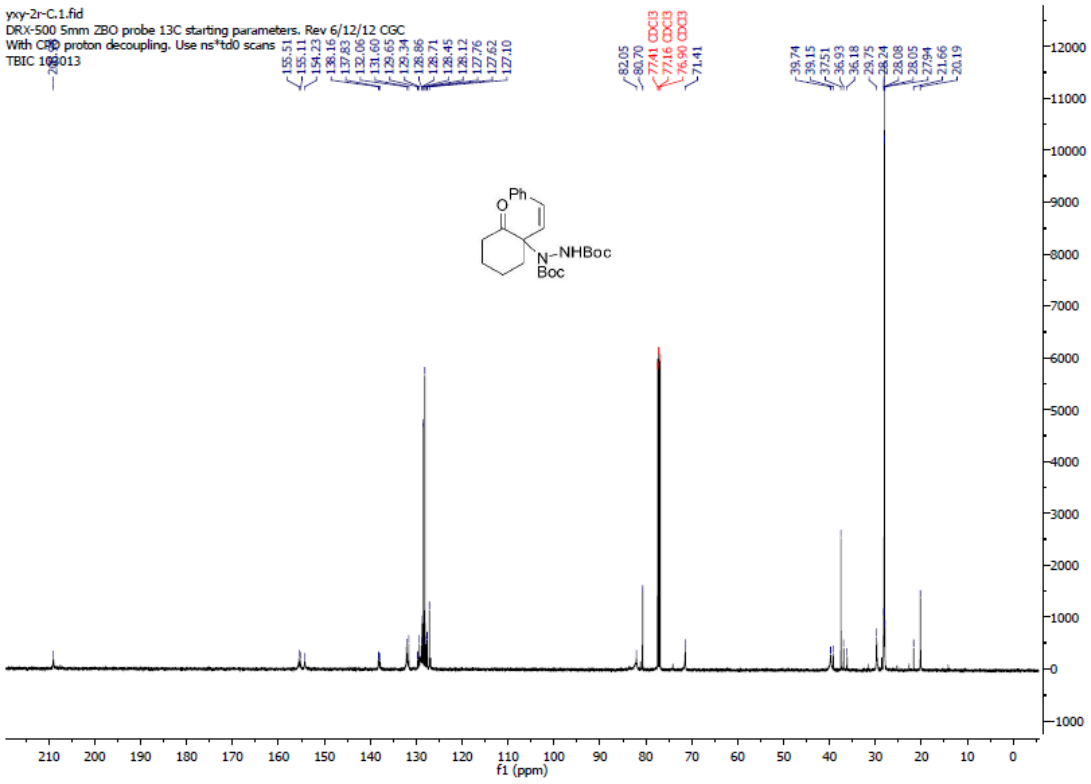
(*S*,*Z*)-di-*tert*-butyl 1-(2-oxo-1-(prop-1-en-1-yl)cyclohexyl)hydrazine-1,2-dicarboxylate (**2p**)



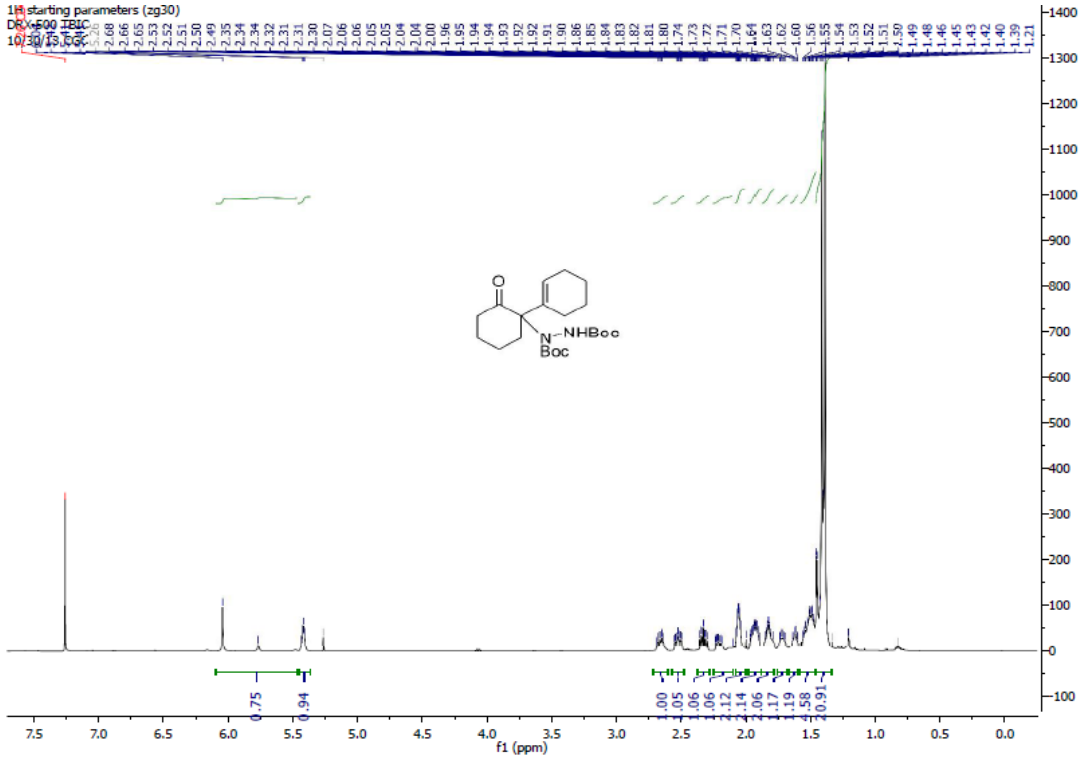


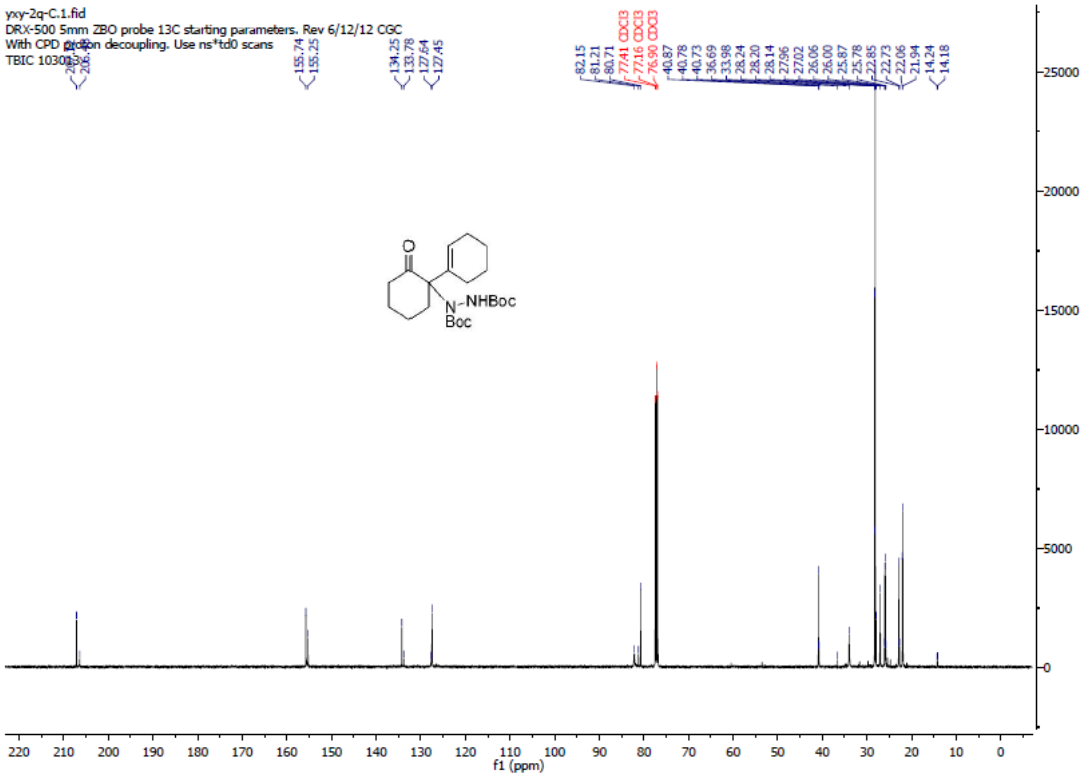
(*S*,*Z*)-di-*tert*-butyl 1-(2-oxo-1-styrylcyclohexyl)hydrazine-1,2-dicarboxylate (**2q**)



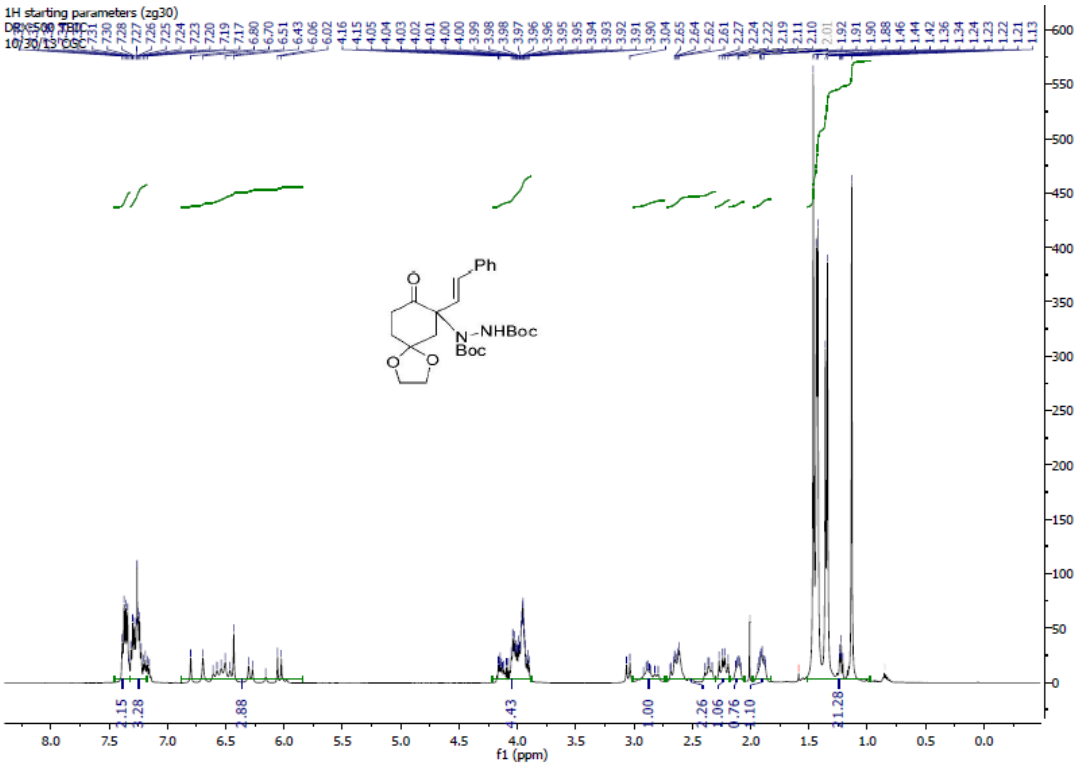


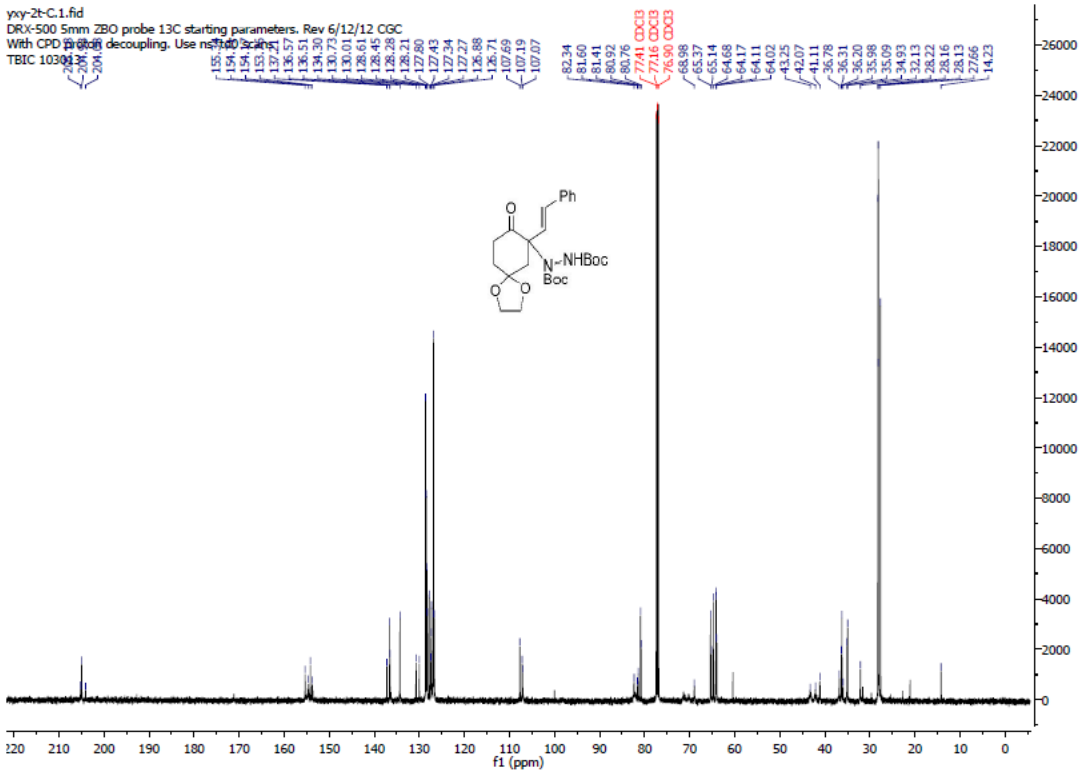
(*S*)-di-*tert*-butyl 1-(2-oxo-[1,1'-bi(cyclohexan)]-1'-en-1-yl)hydrazine-1,2-dicarboxylate (**2r**)



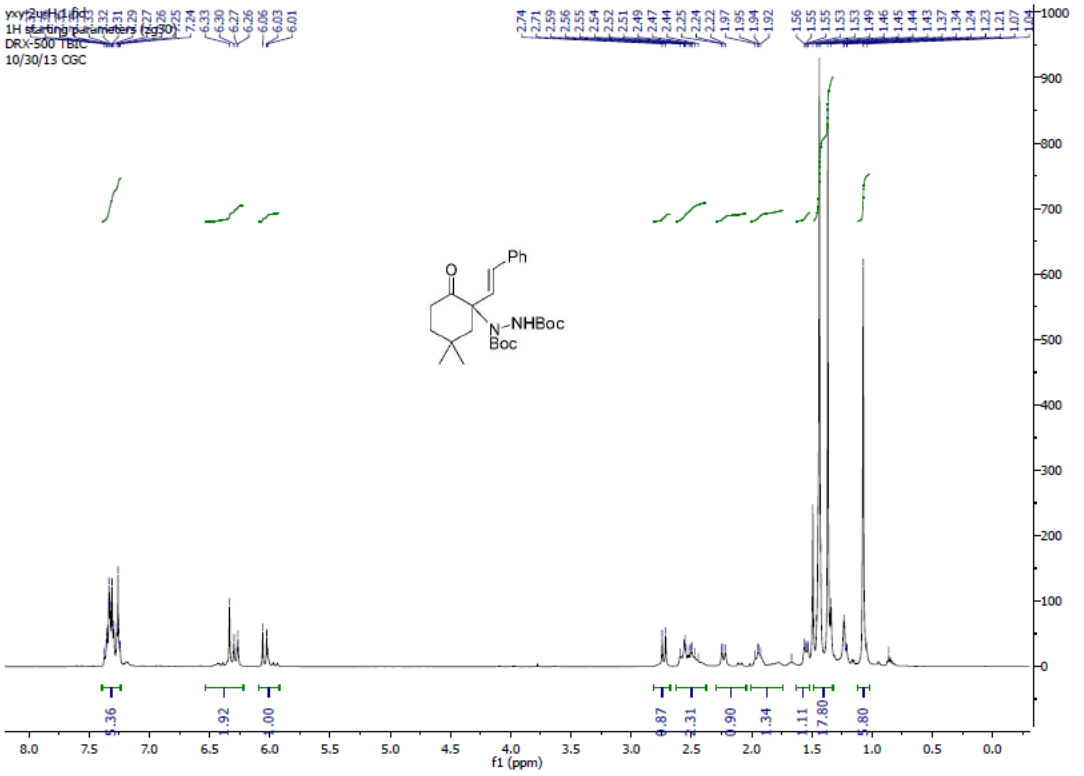


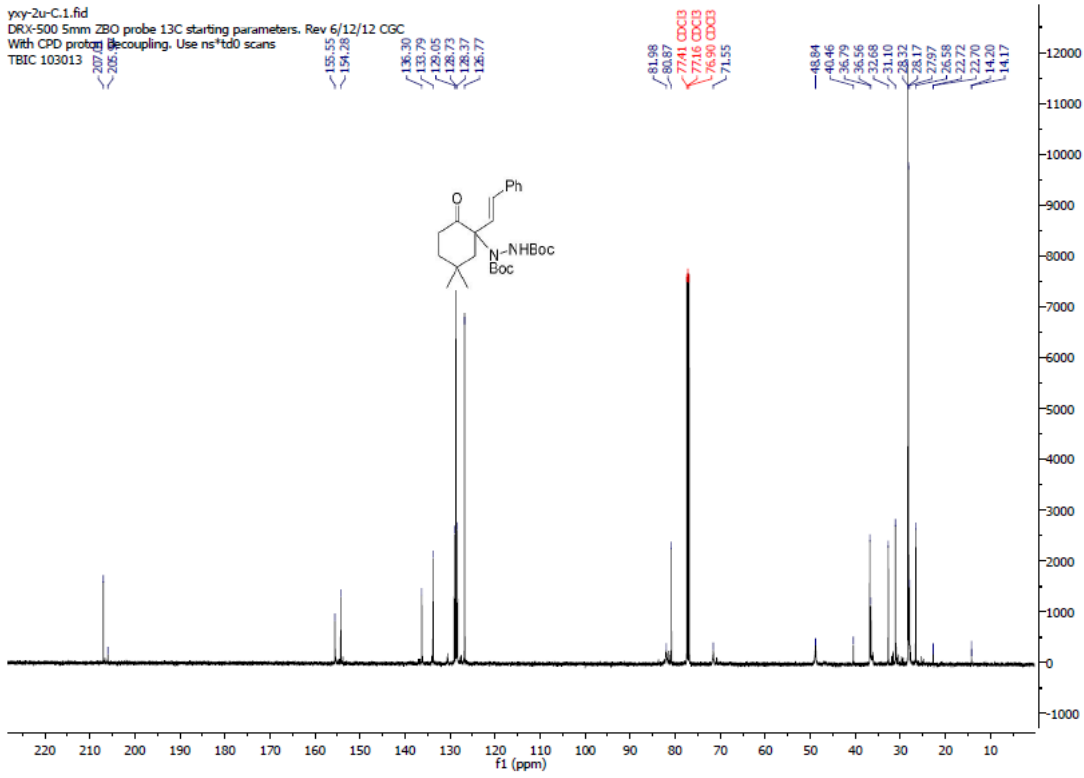
(*S,E*)-di-*tert*-butyl 1-(8-oxo-7-styryl-1,4-dioxaspiro[4.5]decan-7-yl)hydrazine-1,2-dicarboxylate (**2s**)



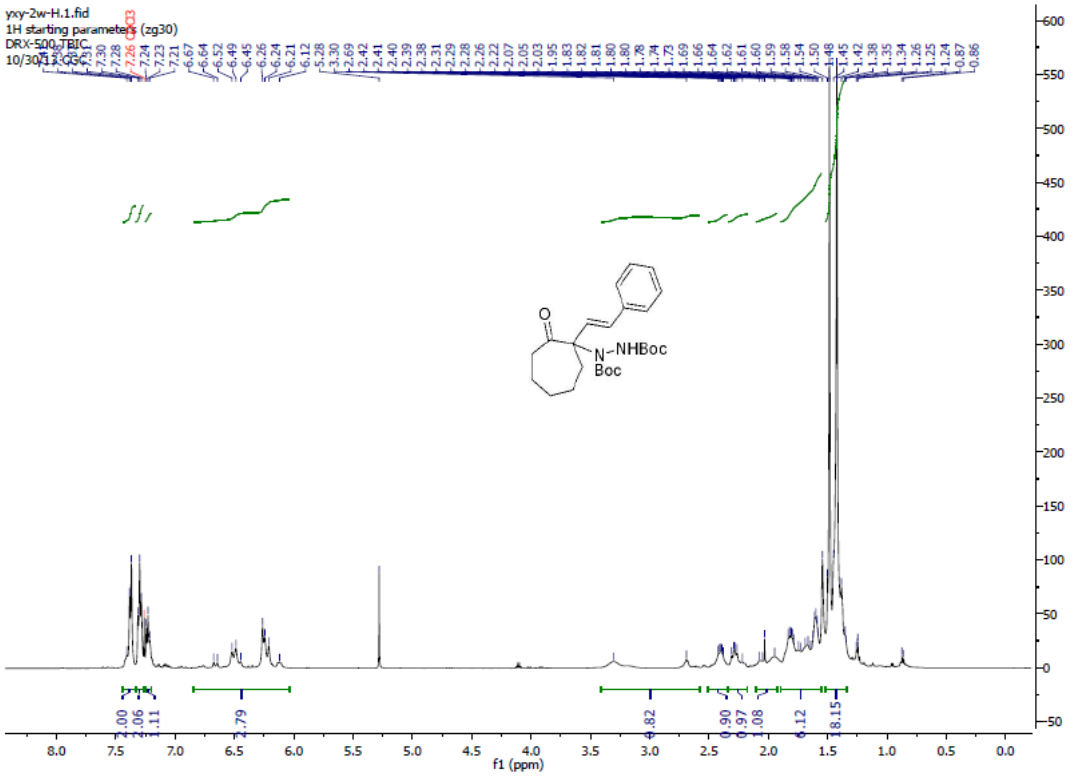


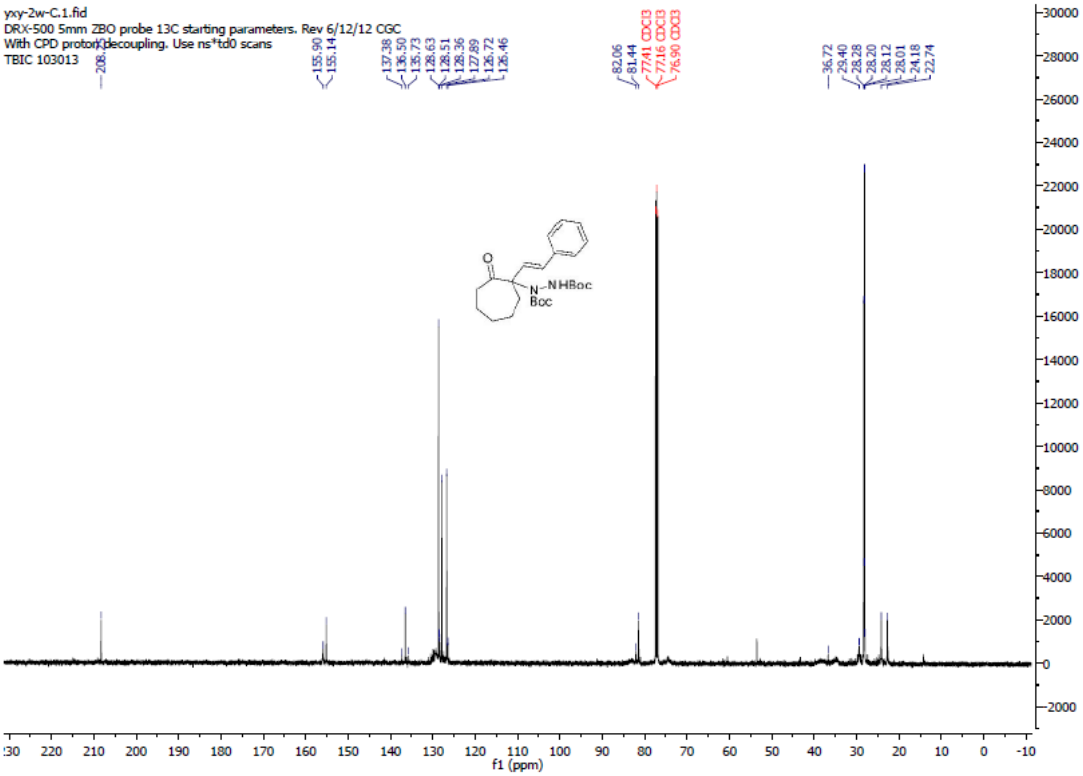
(*S,E*)-di-*tert*-butyl 1-(5,5-dimethyl-2-oxo-1-styrylcyclohexyl)hydrazine-1,2-dicarboxylate (**2t**)



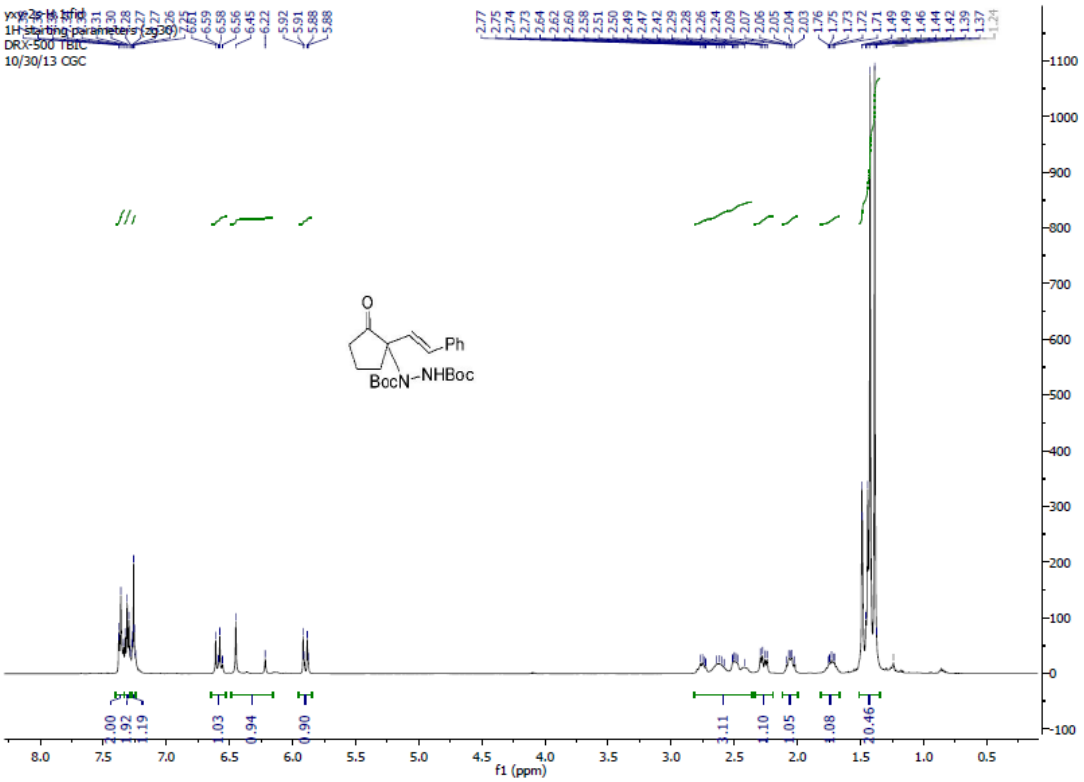


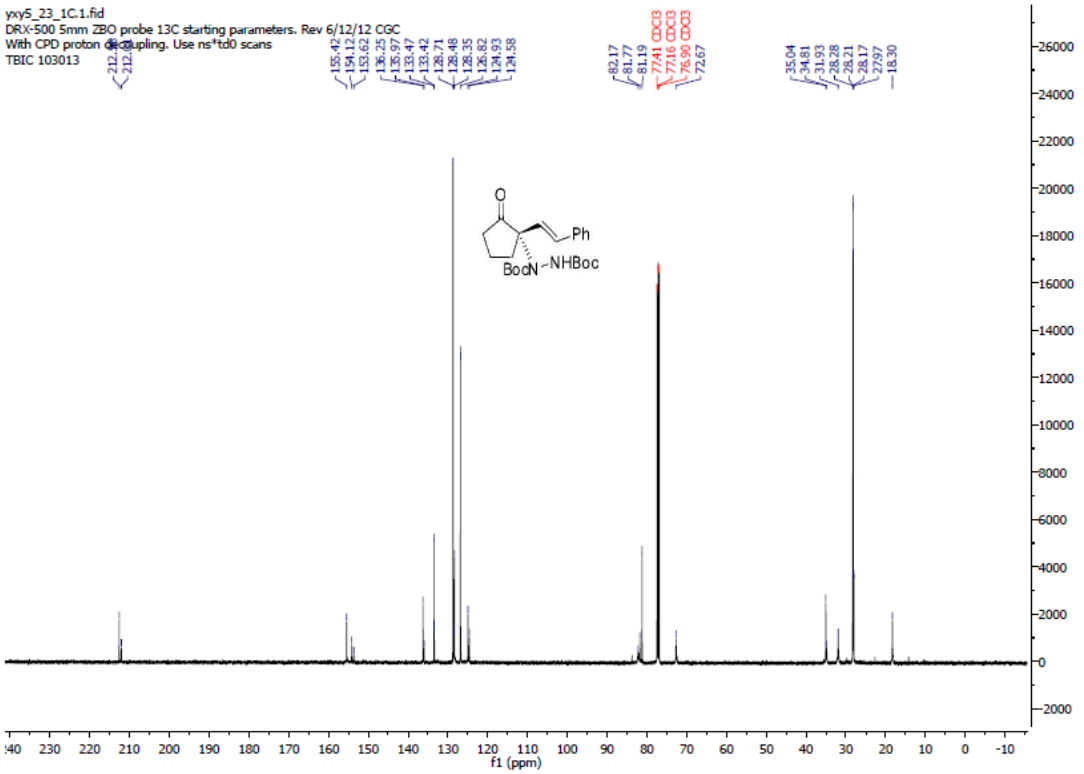
(*S*,*E*)-di-*tert*-butyl 1-(2-oxo-1-styrylcycloheptyl)hydrazine-1,2-dicarboxylate (**2u**)



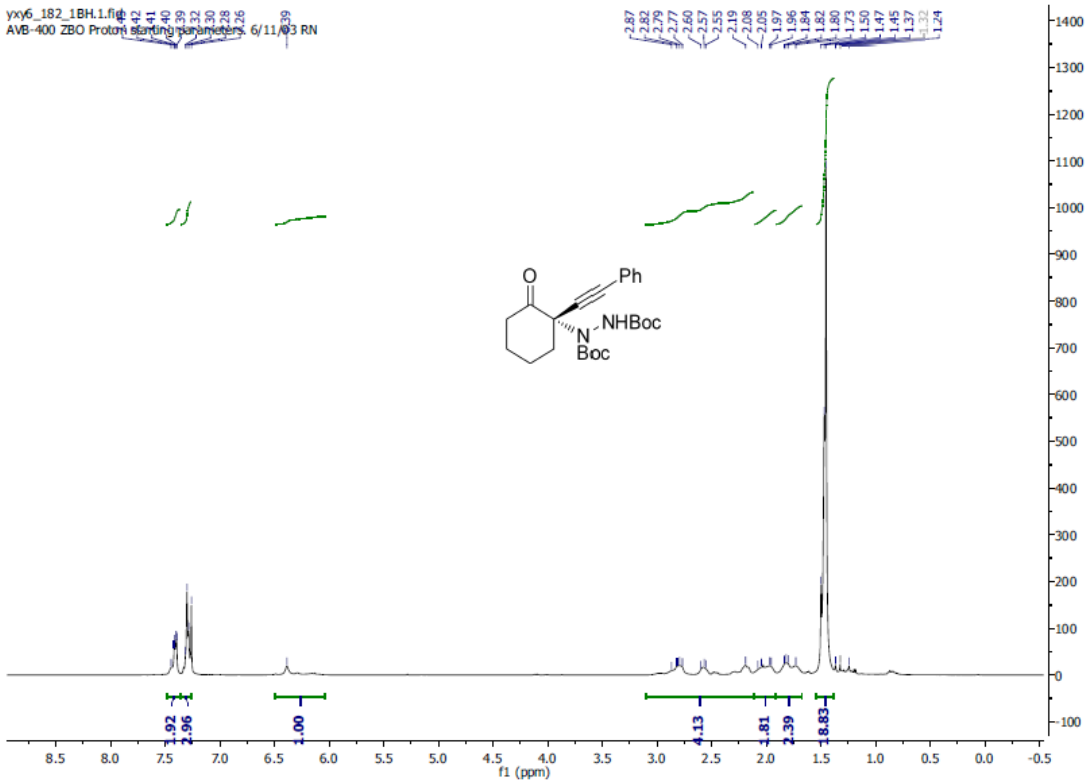


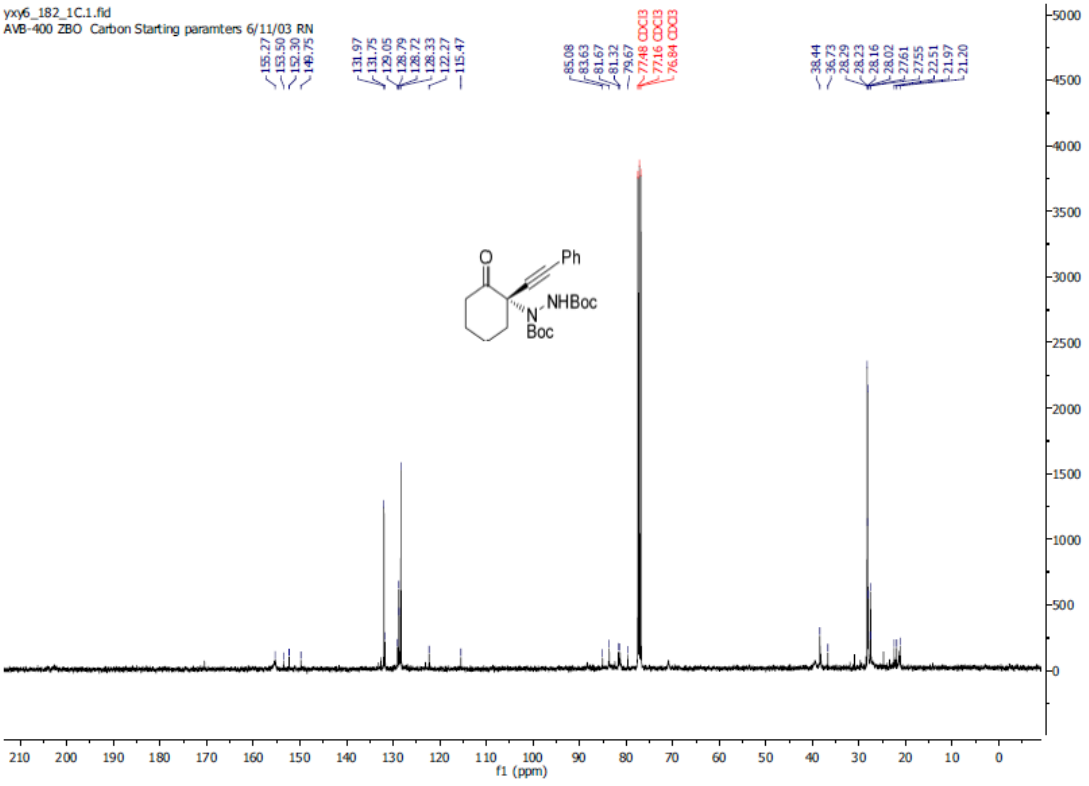
(*S,E*)-di-*tert*-butyl 1-(2-oxo-1-styrylcyclopentyl)hydrazine-1,2-dicarboxylate (**2v**)



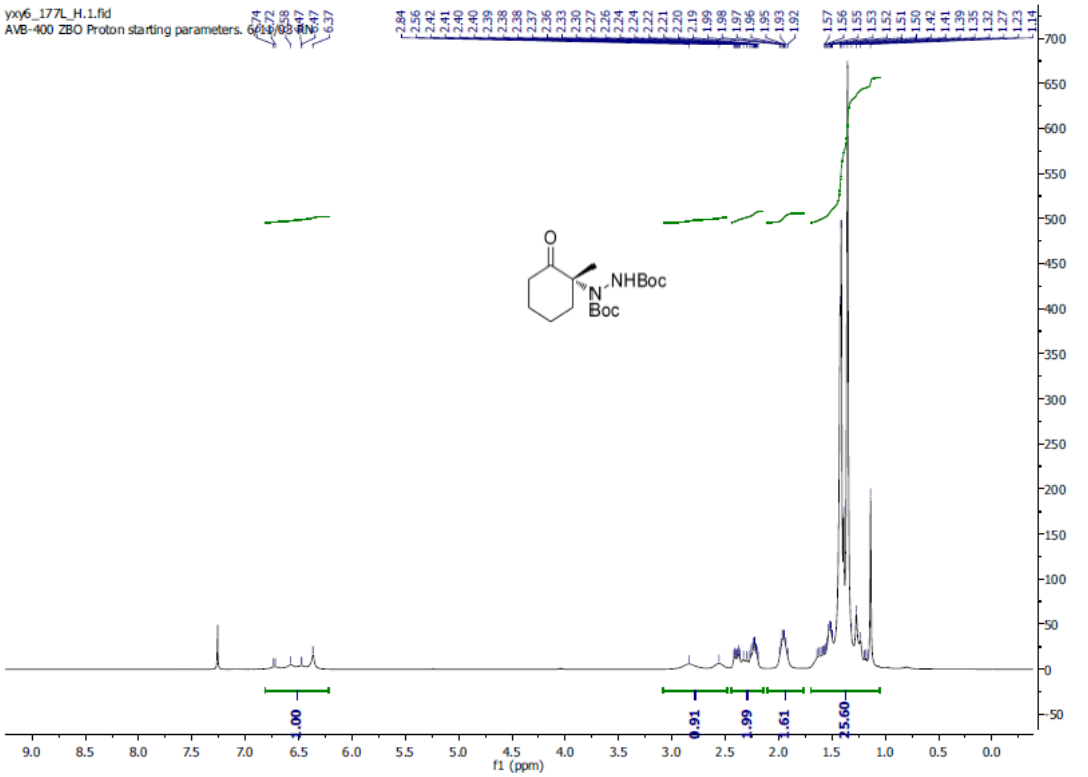


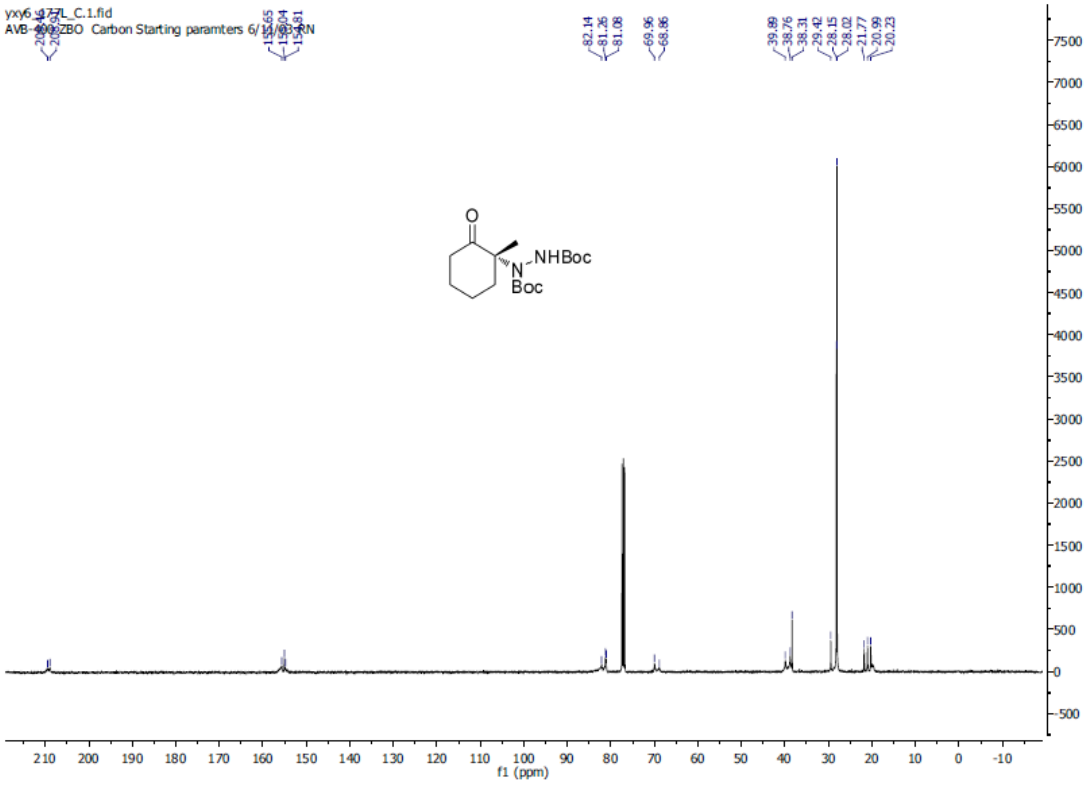
(S)-di-tert-butyl 1-(2-oxo-1-(phenylethynyl)cyclohexyl)hydrazine-1,2-dicarboxylate (**2w**)



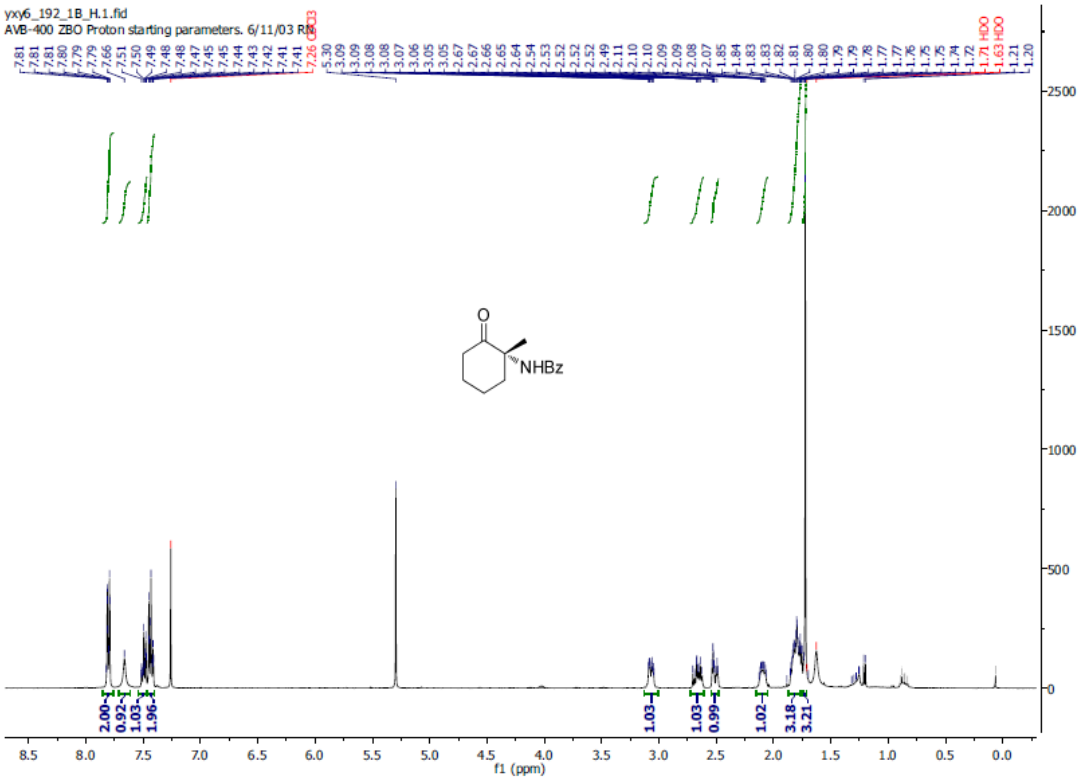


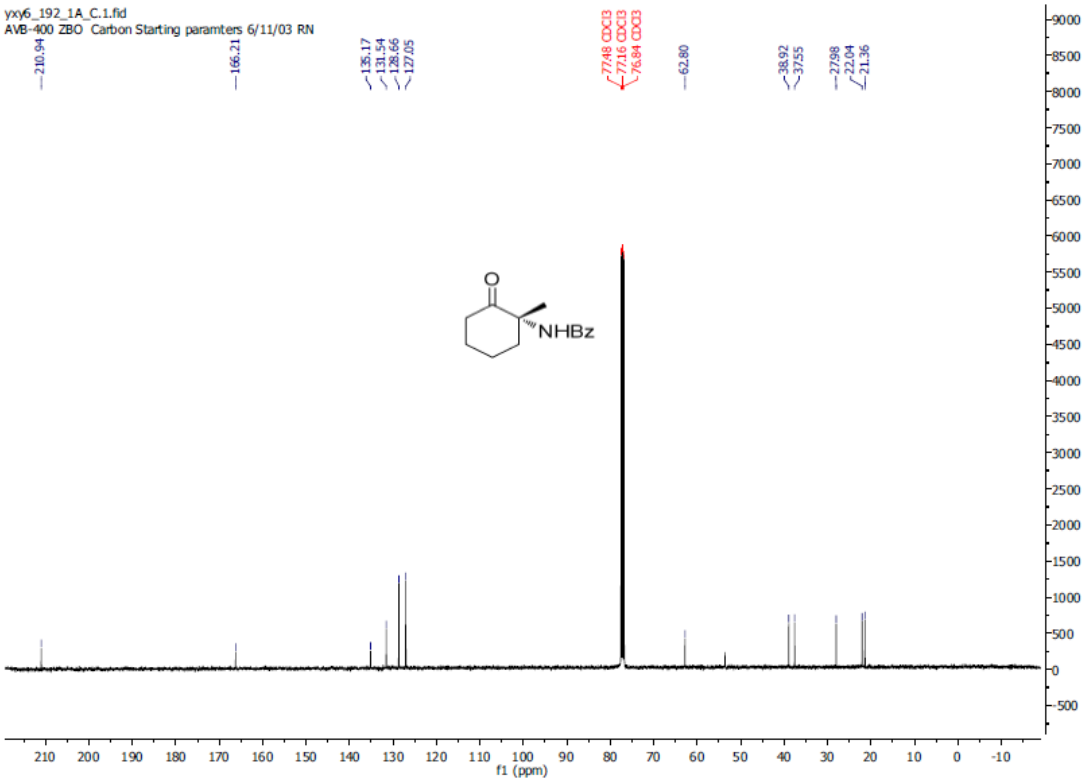
(*R*)-di-tert-butyl 1-(1-methyl-2-oxocyclohexyl)hydrazine-1,2-dicarboxylate (**2x**)



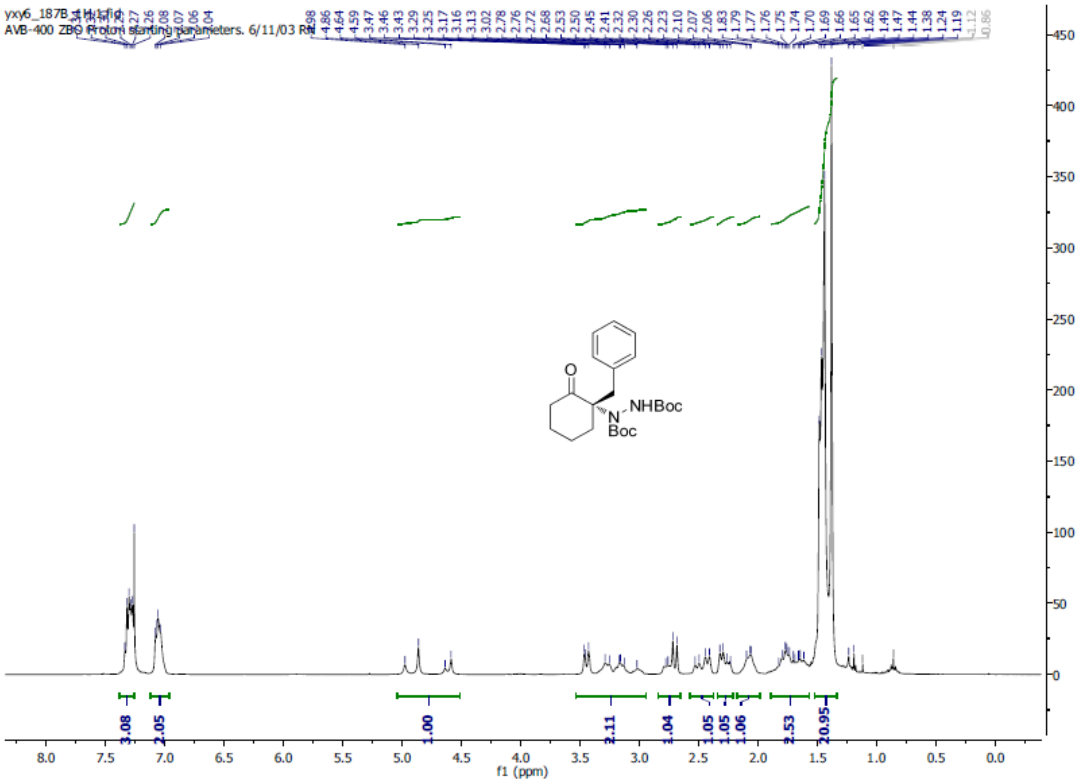


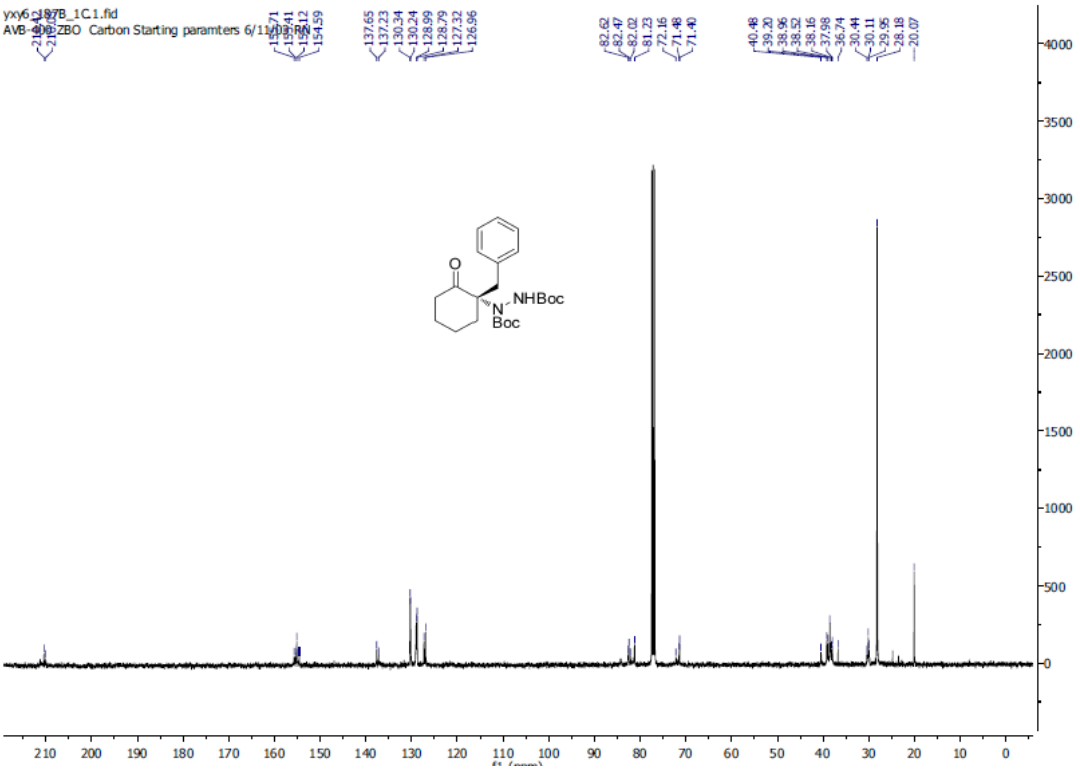
(*R*)-*N*-(1-methyl-2-oxocyclohexyl)benzamide (**S4**)



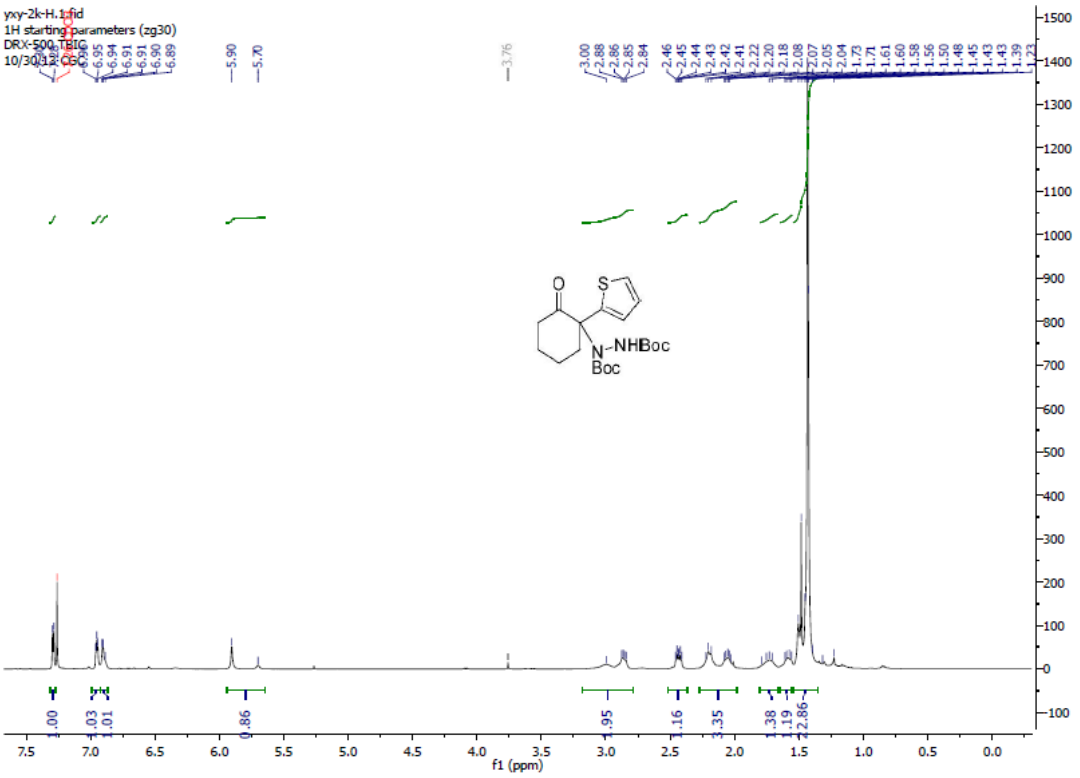


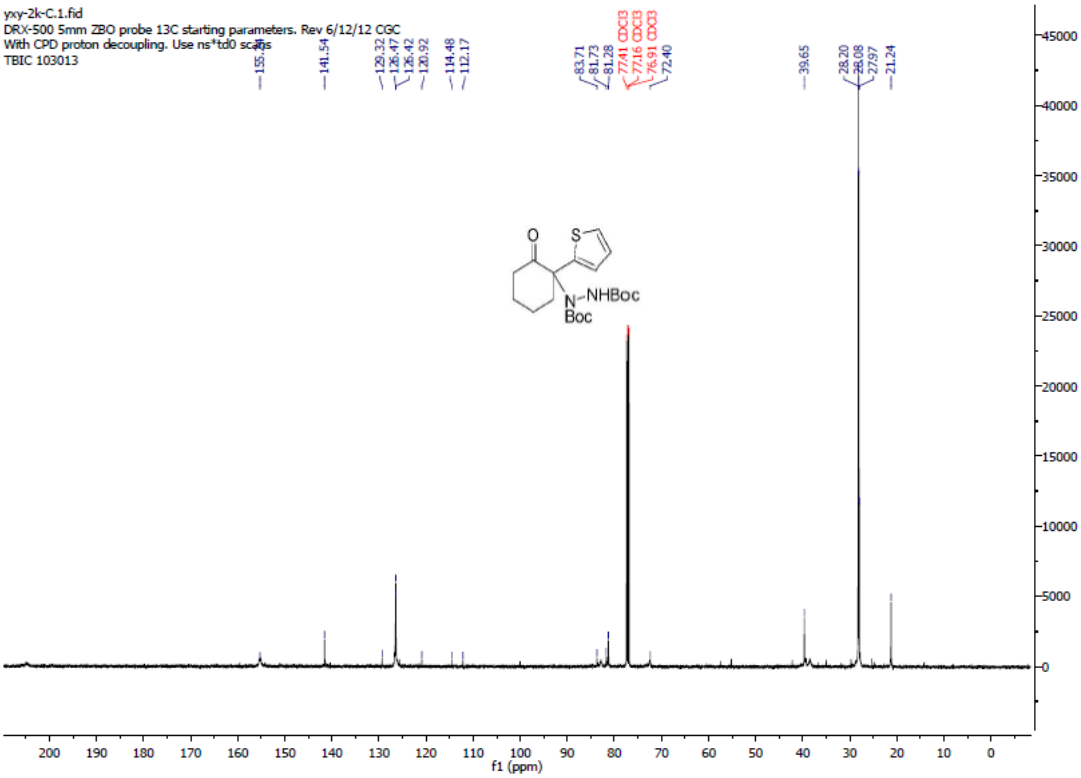
(*S*)-di-tert-butyl 1-(1-benzyl-2-oxocyclohexyl)hydrazine-1,2-dicarboxylate (**2y**)



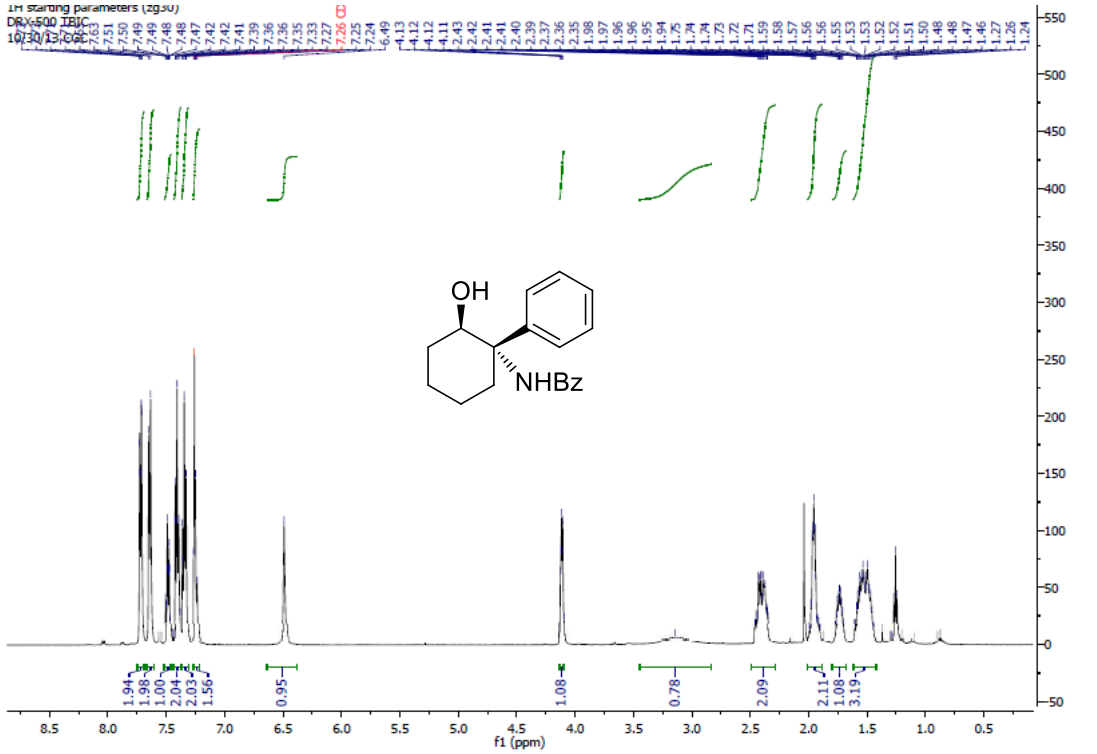


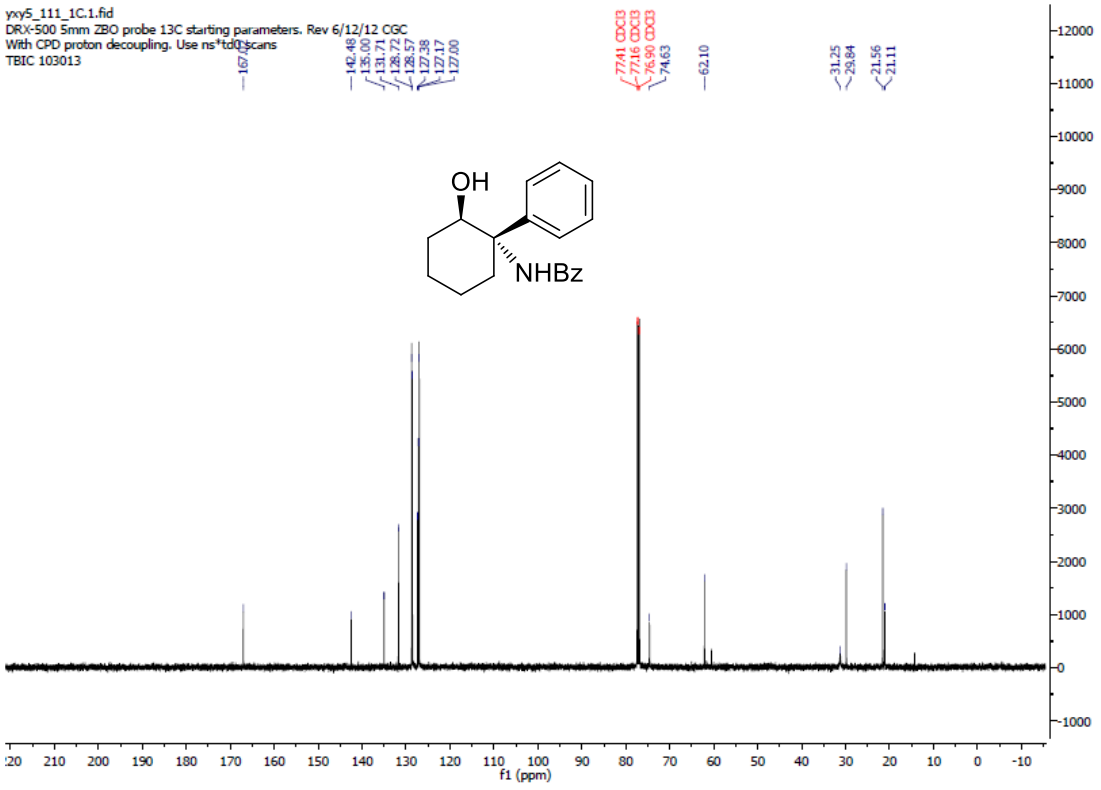
(*R*)-di-*tert*-butyl 1-(2-oxo-1-(thiophen-2-yl)cyclohexyl)hydrazine-1,2-dicarboxylate (**2z**)





N-((*1S,2R*)-2-hydroxy-1-phenylcyclohexyl)benzamide (**3a**)





(*E*)-tert-butyl ((2-oxo-1-styrylcyclohexyl)(phenyl)methyl)carbamate (**5n**)