Electronic Supplementary Material (ESI) for Chemical Communications

Synthesis and Application of Recyclable Ionic Liquid-Supported Imidazolidinone Catalyst in Enantioselective 1,3-Dipolar Cycloaddition

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Supporting Information

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General methods

All nitrones were prepared according to previously reported methods.[1] All α,β-unsaturated aldehydes were purchased from chemical companies and used directly without further purification.

For HPLC analysis of the enantioselectivity of the products, the corresponding racemic isoxazolidine compounds were synthesized by using $InBr_3$ as catalyst in CH_2Cl_2.

Analytical thin layer chromatography (TLC) was performed using Merck 60 F254 precoated silica gel plate (0.2 mm thickness). Subsequent to elution, plates were visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. Further visualization was possible by staining with acidic solution of ceric molybdate or ethanol solution of ninhydride.

Flash chromatography was performed using Merck silica gel 60 with freshly distilled solvents. Columns were typically packed as slurry and equilibrated with the appropriate solvent system prior to use.

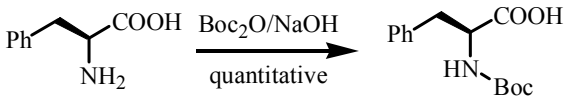
Infrared spectra were recorded on a Bio-Rad FTS 165 FTIR spectrometer. The oil samples were examined under neat conditions.

High Resolution Mass (HRMS) spectra were obtained using Finnigan MAT95XP GC/HRMS (Thermo Electron Corporation).

Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a Bruker Avance DPX 300 and Bruker AMX 400 spectrophotometer ($CDCl_3$ as solvent). Chemical shifts for ^{1}H NMR spectra are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-*d* (δ 7.2600, singlet). Multiplicities were given as: s (singlet); d (doublet); t (triplet); q (quartet); or m (multiplets). The number of protons (n) for a given resonance is indicated by nH. Coupling constants are reported as a *J* value in Hz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-*d* (δ 77.03, triplet). The proportion of diastereomers was determined from the integration of ^{1}H NMR and/or ^{13}C NMR spectra of crude reaction product.

Synthetic procedure to chiral imidazolidinone catalyst I-III

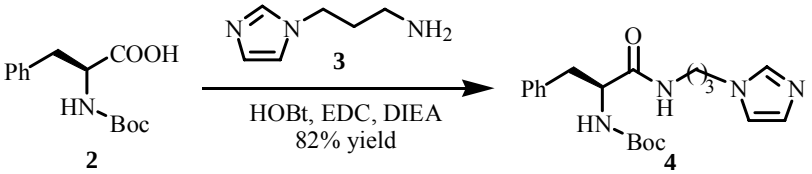
Step 1. Boc-protection of L-phenylalanine **1**[2]



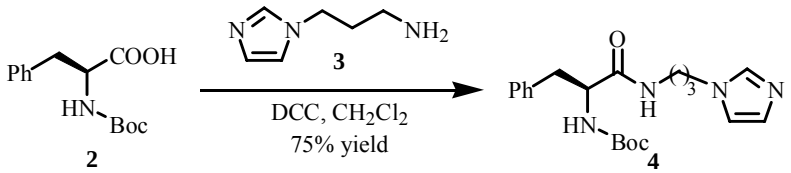
1 **2**

A 250 mL round-bottomed flask was charged with THF (60 mL), H_2O (30 mL), and L-phenylalanine **1** (30 mmol, 4.96 g) at room temperature. Di-*tert*-butyl dicarbonate (33 mmol, 7.2 g) was added to the reaction mixture followed by 10% aq. NaOH (37.5 mmol, 1.5 g in 13.5 mL water) and the reaction mixture was stirred at room temperature overnight. Then THF was removed in *vacuo* and CH_2Cl_2 (150 mL) was added to the reaction flask. 10% aq. HCl was added dropwise to the solution with stirring until the precipitate ceased forming at around pH = 4. The organic layer was separated from the aqueous media, washed with brine, dried with anhydrous $MgSO_4$ and concentrated in *vacuo* to give (*S*)-2-(*tert*-butoxycarbonylamino)-3-phenylpropanoic acid **2** in quantitative yield; it was used directly in next step without further purification.

Step 2. HOBt/EDC[3]- or DCC[4]-mediated coupling of **2** and **3**



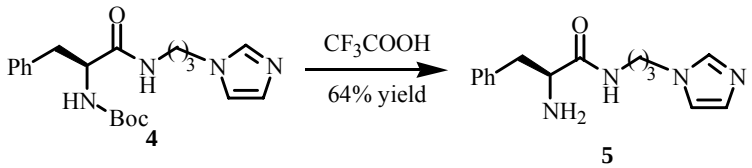
To a solution of (*S*)-2-(*tert*-butoxycarbonylamino)-3-phenylpropanoic acid **2** (15 mmol, 3.98 g), *N*-(3-aminopropyl)imidazole **3** (22.5 mmol, 2.82 g) and HOBt (24 mmol, 3.24 g) in THF (50 mL) was added EDC.HCl (18 mmol, 3.49 g). The reaction was stirred at room temperature for 2 hours then concentrated in *vacuo*. Water was added to the residue and the aqueous layer was extracted with ethyl acetate (30 mL x 3). The combined organic layer was washed with aq. HCl (1 M), saturated $NaHCO_3$, and brine sequentially. It was further dried over anhydrous Na_2SO_4, filtered and concentrated in *vacuo* to give a residue. It was purified by silica gel column chromatography using ethyl acetate and hexane as eluant to give (*S*)-*tert*-butyl 1-((1*H*-imidazol-1-yl)methylamino)-1-oxo-3-phenylpropan-2-ylcarbamate **4** in 82% yield.



A two-necked flask was charged with (*S*)-2-(*tert*-butoxycarbonylamino)-3-phenylpropanoic acid **2** (15 mmol, 3.98 g), *N*-(3-aminopropyl)imidazole **3** (22.5 mmol, 2.82 g) and anhydrous CH_2Cl_2 (50 mL) under nitrogen atmosphere. The reaction mixture was cooled to 0 °C in an ice-water bath, followed by dropwise addition of DCC (30 mmol, c = 1.0 M in CH_2Cl_2), then it was warmed to room temperature and stirred for overnight. After reaction, the precipitate was filtered and the filtrate was concentrated in *vacuo*. The residue was purified by silica gel column chromatography using ethyl acetate and hexane as eluant to give (*S*)-*tert*-butyl 1-((1*H*-imidazol-1-

yl)methylamino)-1-oxo-3-phenylpropan-2-ylcarbamate **4** in 75% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40 (s, 9H), 1.81-1.88 (m, 2H), 3.03 (d, *J* = 7.07 Hz, 2H), 3.08-3.21 (m, 2H), 3.74-3.85 (m, 2H), 4.29 (q, *J* = 7.37 Hz, 1H), 5.23 (s, 1H), 6.50 (t, *J* = 5.41 Hz, 1H), 6.87 (s, 1H), 7.02 (s, 1H), 7.20-7.31 (m, 5H), 7.41 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0 (C), 155.5 (C), 136.9 (CH), 136.6 (C), 129.1 (CH x 2), 128.5 (CH), 128.3 (CH x 2), 128.6 (CH), 118.8 (CH), 79.9 (C), 55.7 (CH), 43.9 (CH_2), 38.6 (CH_2), 35.9 (CH_2), 30.4 (CH_2), 28.0 (CH_3 x 3) ppm. HRMS (ESI, m/z): $[M+H]^+$, calcd. for $C_{20}H_{29}N_4O_3$: 373.2240, found: 373.2227.

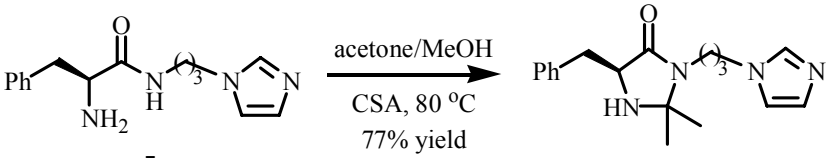
Step 3. CF_3COOH-mediated cleavage of Boc-protecting group in substrate **4**[5]



4 **5**

(*S*)-*Tert*-Butyl 1-((1*H*-imidazol-1-yl)methylamino)-1-oxo-3-phenylpropan-2-ylcarbamate **4** (20 mmol, 7.45 g) was dissolved in trifluoroacetic acid (160 mmol, 18.24 g) and stirred at room temperature for 2 days. After reaction, excess trifluoroacetic acid was neutralized by dropwise addition of saturated aq. Na_2CO_3 until pH = 10. Then it was extracted with CH_2Cl_2 (50 mL x 3). The combined organic layer was dried with anhydrous $MgSO_4$ and concentrated in *vacuo* to give crude product. It was further purified by silica gel column chromatography using dichloromethane and methanol as eluant to give (*S*)-*N*-((1*H*-imidazol-1-yl)methyl)-2-amino-3-phenylpropanamide **5** in 64% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.87-1.94 (m, 2H), 2.05 (brs, 2H), 2.75 (dd, *J* = 13.56, 8.62 Hz, 1H), 3.15 (dd, *J* = 13.56, 4.69 Hz, 1H), 3.22 (q, *J* = 6.41 Hz, 2H), 3.58 (dd, *J* = 8.48, 4.80 Hz, 1H), 3.86 (t, *J* = 6.92 Hz, 2H), 6.92 (s, 1H), 6.98 (s, 1H), 7.18-7.30 (m, 5H), 7.42 (s, 1H), 7.81 (t, *J* = 5.60 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.3 (C), 137.3 (CH), 136.6 (C), 128.9 (CH x 2), 128.7 (CH), 128.1 (CH x 2), 126.3 (CH), 118.6 (CH), 55.9 (CH), 44.0 (CH_2), 40.7 (CH_2), 35.7 (CH_2), 30.5 (CH_2) ppm. HRMS (ESI, m/z): $[M+H]^+$, calcd. for $C_{15}H_{21}N_4O$: 273.1715, found: 273.1713.

Step 4. Ring-closure of substrate **5** with acetone under acid catalysis[6]

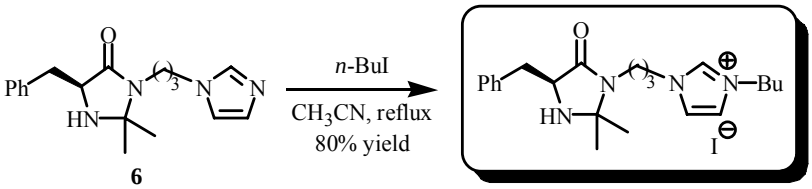


5 **6**

(*S*)-*N*-((1*H*-Imidazol-1-yl)methyl)-2-amino-3-phenylpropanamide **5** (10 mmol, 2.72 g) was dissolved in methanol (60 mL), followed by addition of acetone (30 mL) and CSA (2 mmol, 0.46 g). The reaction was stirred under refluxing for overnight. After reaction, the solvent was removed under vacuo and the residue was dissolved in CH_2Cl_2, washed with saturated $NaHCO_3$ and brine, and dried over $MgSO_4$. After removal of organic solvent under vacuo, the residue was purified by silica gel column chromatography using dichloromethane and methanol as eluant to give (*S*)-3-((1*H*-imidazol-1-yl)methyl)-5-benzyl-2,2-dimethylimidazolidin-4-one **6** in 77% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.10 (s, 3H), 1.22 (s, 3H), 1.90-1.98 (m, 2H), 2.86-2.93 (m, 1H), 3.02-3.11 (m, 2H), 3.30-3.37 (m, 1H), 3.78 (t, *J* = 5.24 Hz, 1H), 3.81-3.95 (m, 2H), 6.94 (s, 1H),

7.03 (s, 1H), 7.20-7.30 (m, 5H), 7.46 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.9 (C), 136.5 (CH), 136.2 (C), 129.2 (CH x 2), 128.8 (CH), 128.0 (CH x 2), 126.4 (CH), 118.2 (CH), 75.6 (C), 58.1 (CH), 44.1 (CH_2), 36.8 (CH_2), 36.2 (CH_2), 30.4 (CH_2), 27.4 (CH_3), 25.6 (CH_3) ppm. HRMS (ESI, m/z): $[M+H]^+$, calcd. for $C_{18}H_{25}N_4O$: 313.2028, found: 313.2031.

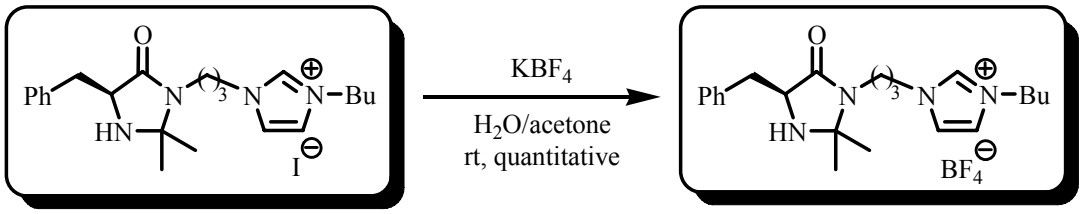
Step 5. Alkylation of substrate **6** for the formation of ionic liquid **I**[7]



6 catalyst **I**

(*S*)-3-((1*H*-Imidazol-1-yl)methyl)-5-benzyl-2,2-dimethylimidazolidin-4-one **6** (11 mmol, 3.44 g) was dissolved in CH_3CN (80 mL), followed by the addition of 1-iodobutane (12 mmol, 2.21 g). The reaction was stirred under refluxing for 23 hours. The progress of the reaction was monitored by ^{1}H NMR analysis. Excess 1-iodobutane (12 mmol, 2.21 g) was added and refluxed for another 23 hrs, and the process was repeated until all the starting material **6** was consumed as indicated by ^{1}H NMR analysis. After reaction, the solvent was evaporated in *vacuo* and the reaction mixture was purified by silica gel column chromatography using dichloromethane and methanol as eluant to give catalyst **I** in 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91 (t, *J* = 7.33 Hz, 3H), 1.23 (s, 6H), 1.31-1.36 (m, 2H), 1.83-1.90 (m, 2H), 1.98 -2.05 (m, 1H), 2.14-2.27 (m, 2H), 3.01-3.07 (m, 3H), 3.25-3.32 (m, 1H), 3.75 (t, *J* = 5.60 Hz, 1H), 4.17-4.26 (m, 3H), 4.37-4.44 (m, 1H), 7.16-7.25 (m, 5H), 7.42 (s, 1H), 7.84 (s, 1H), 9.90 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.3 (C), 136.9 (C), 136.2 (CH), 129.4 (CH x 2), 128.4 (CH x 2), 126.8 (CH), 123.1 (CH), 121.8 (CH), 76.7 (C), 58.9 (CH), 49.9 (CH_2), 47.2 (CH_2), 36.7 (CH_2), 36.3 (CH_2), 31.8 (CH_2), 30.6 (CH_2), 27.9 (CH_3), 26.0 (CH_3), 19.3 (CH_2), 13.3 (CH_3) ppm. HRMS (ESI, m/z): $[M-I]^+$, calcd. for $C_{22}H_{33}N_4O$: 369.2649, found: 369.2659.

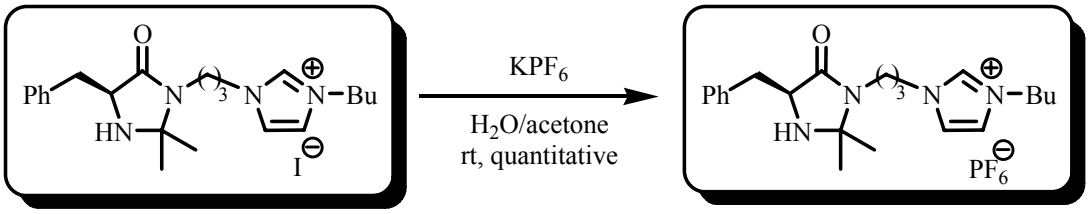
Step 6. Anion exchange for the preparation of catalysts **II** and **III**[7]



catalyst **I** catalyst **II**

A 150 mL round-bottomed flask was charged with catalyst **I** (5 mmol, 2.48 g), potassium tetrafluoroborate (6 mmol, 0.76 g), water (25 mL), and acetone (25 mL). The reaction mixture was stirred at room temperature for overnight. After reaction, acetone was removed and the aqueous layer was extracted with CH_2Cl_2 (50 mL x 3). The combined organic layer was washed with water (25 mL x 3), dried with anhydrous $MgSO_4$, filtered and concentrated in *vacuo* to give catalyst **II** in quantitative yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.86 (t, *J* = 7.31 Hz, 3H), 1.18 (s, 6H), 1.24-1.31 (m, 2H), 1.74-1.84 (m, 2H), 1.88-2.03 (m, 3H), 2.88-3.07 (m, 3H), 3.20-3.27 (m, 1H), 3.68 (dd, *J* = 7.26, 4.08 Hz, 1H), 4.06-4.19 (m, 4H), 7.14-7.20 (m, 5H), 7.38 (s, 1H), 7.58 (s,

1H), 9.00 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.9 (C=O), 137.1 (C), 135.4 (CH), 129.1 (CH x 2), 128.1 (CH x 2), 126.4 (CH), 122.5 (CH), 122.0 (CH), 76.3 (C), 58.7 (CH), 49.4 (CH_2), 47.0 (CH_2), 36.7 (CH_2), 36.0 (CH_2), 31.5 (CH_2), 30.0 (CH_2), 27.4 (CH_3), 25.5 (CH_3), 19.0 (CH_2), 13.0 (CH_3) ppm. HRMS (ESI, m/z): $[M\text{-}BF_4]^+$, calcd. for $C_{22}H_{33}N_4O$: 369.2649, found: 369.2650.



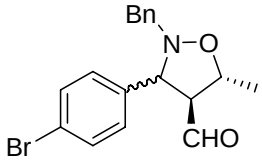
catalyst **I** catalyst **III**

A 150 mL round-bottomed flask was charged with catalyst **I** (5 mmol, 2.48 g), potassium hexafluorophosphate (6 mmol, 1.10 g), water (25 mL), and acetone (25 mL). The reaction mixture was stirred at room temperature for overnight. After reaction, acetone was removed and the aqueous layer was extracted with CH_2Cl_2 (50 mL x 3), the combined organic layer was washed with water (25 mL x 3), dried over anhydrous $MgSO_4$, filtered and concentrated in *vacuo* to give catalyst **III** in quantitative yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94 (t, J = 7.29 Hz, 3H), 1.25 (s, 6H), 1.29-1.41 (m, 2H), 1.80-1.90 (m, 2H), 1.98-2.09 (m, 3H), 2.93-3.16 (m, 3H), 3.27-3.38 (m, 1H), 3.76 (dd, J = 7.39, 4.24 Hz, 1H), 4.12-4.16 (m, 4H), 7.20-7.28 (m, 5H), 7.36 (s, 1H), 7.51 (s, 1H), 8.75 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.0 (C=O), 137.1 (C), 135.1 (CH), 129.0 (CH x 2), 128.1 (CH x 2), 126.4 (CH), 122.3 (CH), 122.0 (CH), 76.2 (C), 58.6 (CH), 49.4 (CH_2), 47.0 (CH_2), 36.8 (CH_2), 35.9 (CH_2), 31.3 (CH_2), 29.9 (CH_2), 27.3 (CH_3), 25.4 (CH_3), 18.9 (CH_2), 12.9 (CH_3) ppm. HRMS (ESI, m/z): $[M\text{-}PF_6]^+$, calcd. for $C_{22}H_{33}N_4O$: 369.2649, found: 369.2648.

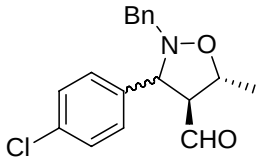
General procedure for the 1,3-dipolar cycloaddition

To a solution of the ionic liquid-supported imidazolidinone catalyst **I** (0.1 mmol, 0.05 g) in CH_3NO_2 (1.9 mL) and H_2O (0.1 mL) was added HBF_4 (0.1 mmol) and nitrone (0.5 mmol). After cooling the solution to -20 °C, *α,β*-unsaturated aldehyde (2 mmol) was added to the flask with stirring. Additional aldehyde (1 mmol x 3) was added to the reaction mixture at 24 h intervals until the specified reaction time was reached. The resulting solution was evaporated under *vacuo* and the residue was extracted with diethyl ether (5 mL x 5). The combined organic layer was washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated under *vacuo* and purified by silica gel column chromatography using hexane and ethyl acetate as eluant to afford the desired product. The remaining oil compound in the flask (catalyst **I**) was dried under *vacuo* and reused in further reactions by the addition of acid co-catalyst HBF_4 (0.1 mmol), CH_3NO_2 (1.9 mL), and H_2O (0.1 mL).

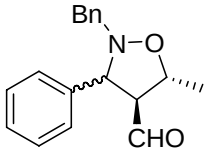
Spectroscopic data of the 1,3-dipolar cycloaddition products



(4*S*, 5*R*)-2-Benzyl-4-formyl-5methyl-3-(4-bromophenyl) isoxazolidine (Table 3, entry 1): ^{1}H NMR (400 MHz, $CDCl_3$): (endo isomer) δ 1.49 (d, *J* = 6.16 Hz, 3H), 3.03-3.07 (m, 1H), 3.85 (d, *J* = 14.13 Hz, 1H), 3.96 (d, *J* = 14.08 Hz, 1H), 4.16 (d, *J* = 7.48 Hz, 1H), 4.51-4.57 (m, 1H), 7.23-7.31 (m, 7H), 7.46 (d, *J* = 8.33 Hz, 2H), 9.78 (d, *J* = 1.16 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): (endo isomer) δ 198.2 (CH), 137.8(C), 136.9 (C), 132.1 (CH x 2), 129.2 (CH x 2), 128.5 (CH x 2), 128.3 (CH x 2), 127.3 (CH), 122.0 (C), 73.6 (CH), 71.6 (CH), 70.1 (CH), 59.7 (CH_2), 21.0 (CH_3) ppm. Enantiomeric ratio was determined by HPLC using Chiracel OD-H column (x 2) after reduction with $NaBH_4$/MeOH (2.5:97.5 *i*-PrOH/hexane, 2 mL/min flow rate), endo isomers t_r = 22.9 min (major enantiomer) and 31.9 min (minor enantiomer). HRMS (ESI, m/z): $[M+H]^+$, calcd. for $C_{18}H_{19}BrNO_2$: 360.0599, found: 360.0610.

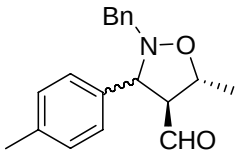


(4*S*, 5*R*)-2-Benzyl-4-formyl-5methyl-3-(4-chlorophenyl) isoxazolidine (Table 3, entry 2): ^{1}H NMR (400 MHz, $CDCl_3$): (endo isomer) δ 1.49 (d, *J* = 6.16 Hz, 3H), 3.05 (t, *J* = 5.64 Hz, 1H), 3.84 (d, *J* = 14.13 Hz, 1H), 3.96 (d, *J* = 14.00 Hz, 1H), 4.16 (d, *J* = 7.25 Hz, 1H), 4.51-4.57 (m, 1H), 7.23-7.37 (m, 9H), 9.78 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): (endo isomer) δ 198.3 (CH), 137.2 (C), 137.0 (C), 133.9 (C), 129.1 (CH x 2), 128.9 (CH x 2), 128.5 (CH x 2), 128.3 (CH x 2), 127.3 (CH), 73.6 (CH), 71.6 (CH), 70.1 (CH), 59.7 (CH_2), 21.0 (CH_3) ppm. Enantiomeric ratio was determined by HPLC using Chiracel OD-H column (x 2) after reduction with $NaBH_4$/MeOH (2:98 *i*PrOH/hexane, 1 mL/min flow rate); endo isomers t_r = 54.5 min (major enantiomer) and 72.2 min (minor enantiomer). HRMS (ESI, m/z): $[M+H]^+$, calcd. for $C_{18}H_{19}ClNO_2$: 316.1104, found: 316.1101. Spectroscopic data are identical to the published data.[6]

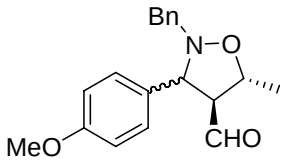


(4S, 5*R*)-2-Benzyl-5-methyl-3-phenylisoxazolidine-4-carbaldehyde (Table 3, entry 3): ^{1}H NMR (300 MHz, $CDCl_3$): (endo isomer) δ 1.49 (d, *J* = 6.21 Hz, 3H), 3.08-3.13 (m, 1H), 3.81 (d, *J* = 14.31 Hz, 1H), 4.00 (d, *J* = 14.31 Hz, 1H), 4.15 (d, *J* = 7.77 Hz, 1H), 4.50-4.58 (m, 1H), 7.20-7.45 (m, 10H), 9.78 (d, *J* = 2.34 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): (endo isomer) δ 198.6 (CH), 138.4 (C), 137.3 (C), 128.9 (CH x 2), 128.4 (CH x 2), 128.2 (CH x 2), 128.1 (CH), 127.6 (CH x 2), 127.1 (CH), 73.4 (CH), 71.5 (CH), 71.1 (CH), 59.5 (CH_2), 21.0 (CH_3) ppm. Enantiomeric ratio was determined by HPLC using Chiracel OD-H column (x 2) after reduction with $NaBH_4$/MeOH (1:99 *i*-PrOH/hexane, 1 mL/min flow rate), endo isomers t_r = 126.0 min (major enantiomer) and 141.6 min (minor enantiomer). HRMS (ESI, m/z): $[M+H]^+$, calcd. for

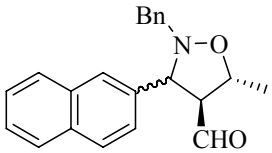
$C_{18}H_{20}NO_2$: 282.1494, found: 282.1495. Spectroscopic data are identical to the published data.[6,8]



(4*S*, 5*R*)-2-Benzyl-4-formyl-5methyl-3-(4-methylphenyl) isoxazolidine (Table 3, entry 4): ^{1}H NMR (400 MHz, $CDCl_3$): (endo isomer) δ 1.49 (d, *J* = 6.16 Hz, 3H), 2.34 (s, 3H), 3.07-3.11 (m, 1H), 3.78 (d, *J* = 14.40 Hz, 1H), 3.99 (d, *J* = 14.45 Hz, 1H), 4.09 (d, *J* = 7.76 Hz, 1H), 4.50-4.56 (m, 1H), 7.16-7.33 (m, 9H), 9.77 (d, *J* = 1.76 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): (endo isomer) δ 198.8 (CH), 138.0 (C), 137.5 (C), 135.1 (C), 129.6 (CH x 2), 128.4 (CH x 2), 128.2 (CH x 2), 127.6 (CH x 2), 127.1 (CH), 73.4 (CH), 71.6 (CH), 71.1 (CH), 59.4 (CH_2), 21.2 (CH_3), 21.1 (CH_3) ppm. Enantiomeric ratio was determined by HPLC using Chiracel OD-H column (x 2) after reduction with $NaBH_4$/MeOH (2:98 *i*PrOH/hexane, 2 mL/min flow rate); endo isomers t_r = 21.8 min (major enantiomer) and 35.0 min (minor enantiomer). HRMS (ESI, m/z): $[M+H]^+$, calcd. for $C_{19}H_{22}NO_2$: 296.1651, found: 296.1664. Spectroscopic data are identical to the published data.[8]

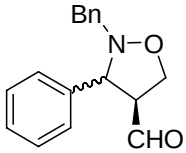


(4*S*, 5*R*)-2-Benzyl-4-formyl-5methyl-3-(4-methoxyphenyl) isoxazolidine (Table 3, entry 5): ^{1}H NMR (400 MHz, $CDCl_3$): (endo isomer) δ 1.49 (d, *J* = 6.20 Hz, 3H), 3.06-3.10 (m, 1H), 3.76 (d, *J* = 14.48 Hz, 1H), 3.80 (s, 3H), 3.99 (d, *J* = 14.44 Hz, 1H), 4.07 (d, *J* = 7.85 Hz, 1H), 4.49-4.55 (m, 1H), 6.89 (d, *J* = 8.60 Hz, 2H), 7.22-7.36 (m, 7H), 9.76 (d, *J* = 2.32 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): (endo isomer) δ 198.8 (CH), 159.5 (C), 137.4 (C), 129.9 (C), 128.9 (CH x 2), 128.4 (CH x 2), 128.2 (CH x 2), 127.1 (CH), 114.3 (CH x 2), 73.3 (CH), 71.5(CH), 70.9 (CH), 59.3 (CH_2), 55.3 (CH_3), 21.2 (CH_3) ppm. Enantiomeric ratio was determined by HPLC using Chiracel OD-H column (x 2) after reduction with $NaBH_4$/MeOH (2:98 *i*PrOH/hexane, 1 mL/min flow rate); endo isomers t_r = 79.9 min (major enantiomer) and 130.2 min (minor enantiomer). HRMS (ESI, m/z): $[M+H]^+$, calcd. for $C_{19}H_{22}NO_3$: 312.1600, found: 312.1609. Spectroscopic data are identical to the published data.[6,8]

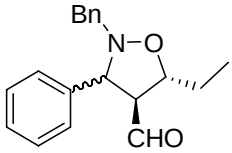


(4*S*, 5*R*)-2-Benzyl-4-formyl-5methyl-3-(2-napthyl) isoxazolidine (Table 3, entry 6): ^{1}H NMR (400 MHz, $CDCl_3$): (endo isomer) δ 1.53 (d, *J* = 6.12 Hz, 3H), 3.20 (t, *J* = 6.36 Hz, 1H), 3.87 (d, *J* = 14.32 Hz, 1H), 4.04 (d, *J* = 14.27 Hz, 1H), 4.33 (d, *J* = 7.56 Hz, 1H), 4.56-4.62 (m, 1H), 7.22-7.35 (m, 5H), 7.47-7.49 (m, 2H), 7.58 (d, *J* = 8.53 Hz, 1H), 7.81-7.86 (m, 4H), 9.82 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): (endo isomer) δ 198.6 (CH), 137.3 (C), 135.8 (C), 133.3(C), 133.2 (C), 128.9 (CH), 128.5 (CH x 2), 128.2 (CH x 2), 127.9 (CH), 127.7 (CH), 127.2 (CH), 126.9 (CH), 126.4 (CH), 126.3 (CH), 124.9 (CH), 73.6 (CH), 71.5(CH), 71.3 (CH), 59.6 (CH_2), 21.1

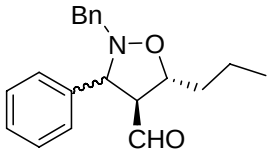
(CH_3) ppm. Enantiomeric ratios were determined by HPLC using Chiracel OD-H column (x 2) after reduction with $NaBH_4$/MeOH (2:98 *i*PrOH/hexane, 2 mL/min flow rate); endo isomers t_r = 46.8 min (major enantiomer) and 152.9 min (minor enantiomer). HRMS (ESI, m/z): $[M+H]^+$, calcd. for $C_{22}H_{22}NO_2$: 332.1651, found: 332.1656. Spectroscopic data are identical to the published data.[6,8]



(*S*)-2-Benzyl-3-phenylisoxazolidine-4-carbaldehyde (Table 3, entry 7): ^{1}H NMR (300 MHz, $CDCl_3$): (endo isomer) δ 3.37-3.44 (m, 1H), 3.75 (d, *J* = 14.11 Hz, 1H), 3.97 (d, *J* = 14.17 Hz, 1H), 4.04 (d, *J* = 7.35 Hz, 1H), 4.20-4.29 (m, 2H), 7.21-7.48 (m, 10H), 9.76 (d, *J* = 2.10 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): (endo isomer) δ 197.8 (CH), 137.1 (C), 136.2 (C), 128.0 (CH x 2), 127.7 (CH x 2), 127.3 (CH), 127.2 (CH x 2), 126.8 (CH x 2), 126.3 (CH), 69.7 (CH), 64.9 (CH_2), 63.3 (CH), 58.7 (CH_2) ppm. Enantiomeric ratios were determined by HPLC using Chiracel OD-H column (x 2) after reduction with $NaBH_4$/MeOH (2:98 *i*PrOH/hexane, 2 mL/min flow rate); endo isomers t_r = 49.5 min (major enantiomer) and 60.4 min (minor enantiomer). HRMS (ESI, m/z): $[M+H]^+$, calcd. for $C_{17}H_{18}NO_2$: 268.1338, found: 268.1333. Spectroscopic data are identical to the published data.[6]



(4*S*, 5*R*)-2-Benzyl-5-ethyl-3-phenylisoxazolidine-4-carbaldehyde (Table 3, entry 8): ^{1}H NMR (300 MHz, $CDCl_3$): (endo isomer) δ 0.96 (t, *J* = 7.38 Hz, 3H), 1.64-1.78 (m, 1H), 1.92-2.07 (m, 1H), 3.12-3.17 (m, 1H), 3.79 (d, *J* = 14.39 Hz, 1H), 3.99 (d, *J* = 14.40 Hz, 1H), 4.13 (d, *J* = 7.80 Hz, 1H), 4.26 (dd, *J* = 5.61, 12.90 Hz, 1H), 7.20-7.44 (m, 10H), 9.79 (d, *J* = 2.34 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): (endo isomer) δ 198.7 (CH), 138.3 (C), 137.5 (C), 129.0 (CH x 2), 128.4 (CH x 2), 128.2 (CH), 128.2 (CH x 2), 127.6 (CH x 2), 127.1 (CH), 78.8 (CH), 71.1 (CH), 70.1 (CH), 59.4 (CH_2), 28.5 (CH_2), 10.2 (CH_3) ppm.. Enantiomeric ratios were determined by HPLC using Chiracel AD-H column after reduction with $NaBH_4$/MeOH (2.6:97.4 *i*PrOH/hexane, 2 mL/min flow rate); endo isomers t_r = 13.3 min (major enantiomer) and 9.9 min (minor enantiomer). HRMS (ESI, m/z): $[M+H]^+$, calcd. for $C_{19}H_{22}NO_2$: 296.1651, found: 296.1652.



(4*S*, 5*R*)-2-Benzyl-3-phenyl-5-propylisoxazolidine-4-carbaldehyde (Table 3, entry 9): ^{1}H NMR (300 MHz, $CDCl_3$): (endo isomer) δ 0.93 (t, *J* = 7.36 Hz, 3H), 1.30-1.50 (m, 2H), 1.59-1.70 (m, 1H), 1.91-2.04 (m, 1H), 3.11-3.16 (m, 1H), 3.79 (d, *J* = 14.34 Hz, 1H), 3.99 (d, *J* = 14.39 Hz, 1H), 4.12 (d, *J* = 7.77 Hz, 1H), 4.32-4.38 (m, 1H), 7.20-7.44 (m, 10H), 9.78 (d, *J* = 2.43 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): (endo isomer) δ 198.8 (CH), 138.3 (C), 137.4 (C), 129.0 (CH x 2), 128.4 (CH x 2), 128.2 (CH), 128.2 (CH x 2), 127.6 (CH x 2), 127.1 (CH), 77.3 (CH), 71.0 (CH),

70.4 (CH), 59.4 (CH_2), 37.6 (CH_2), 19.2 (CH_2), 13.9 (CH_3) ppm. Enantiomeric ratios were determined by HPLC using Chiracel AD-H column after reduction with $NaBH_4$/MeOH (2:98 *i*PrOH/hexane, 2 mL/min flow rate); endo isomers t_r = 16.2 min (major enantiomer) and 11.3 min (minor enantiomer). HRMS (ESI, m/z): $[M+H]^+$, calcd. for $C_{20}H_{24}NO_2$: 310.1807, found: 310.1813. Spectroscopic data are identical to the published data.[8]

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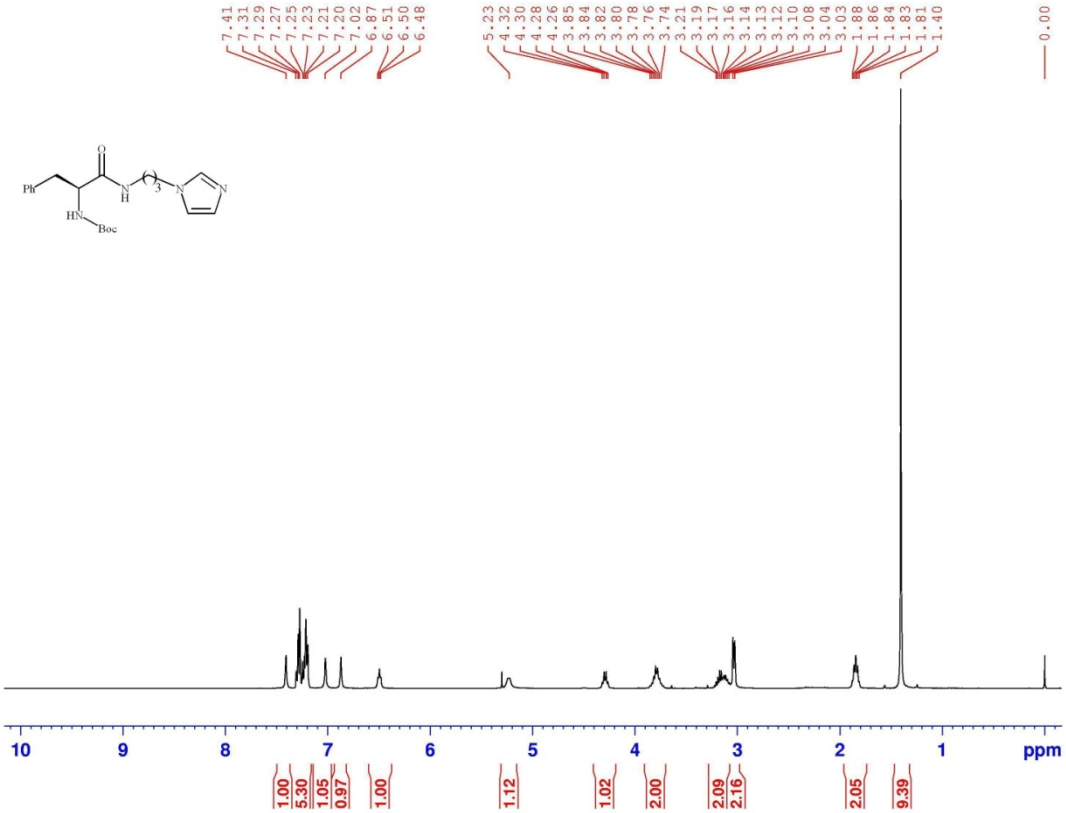
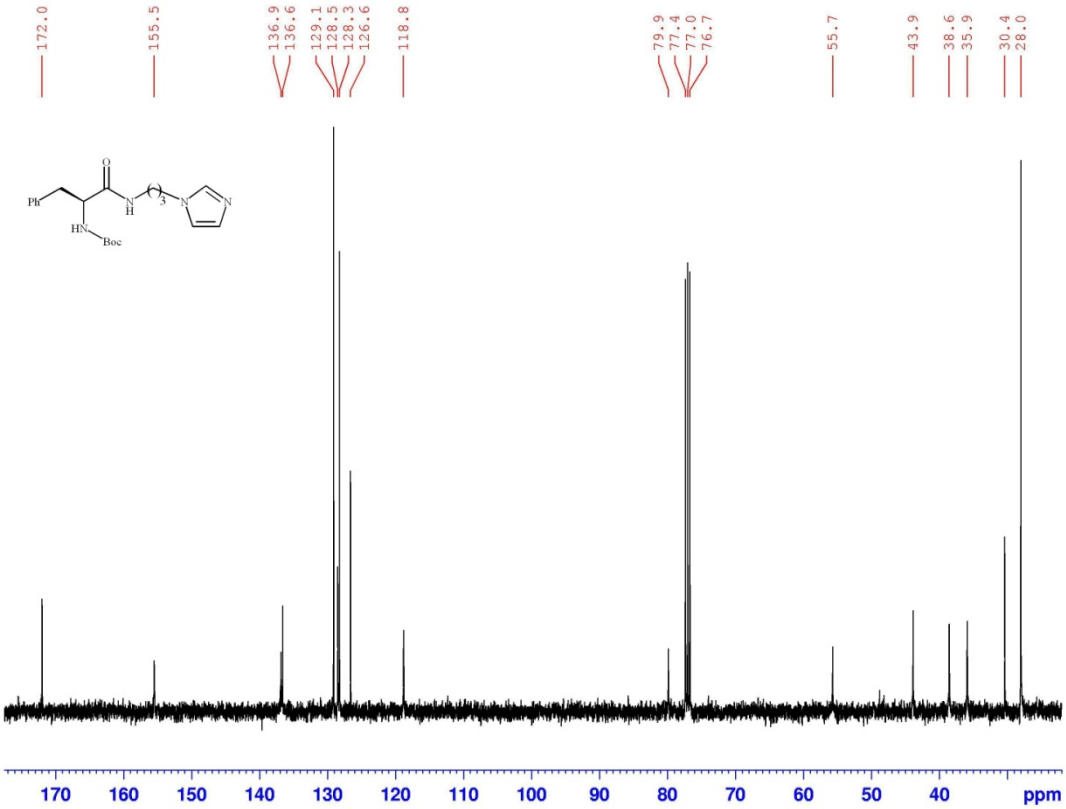
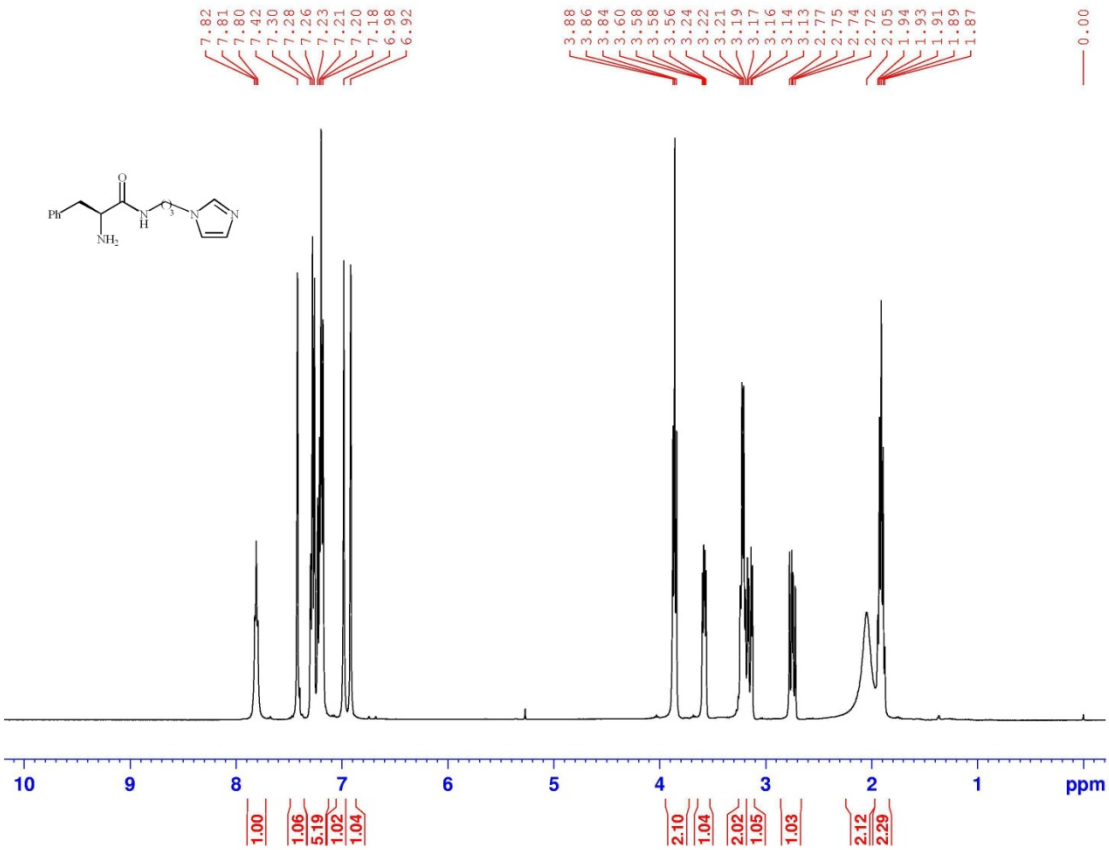
Copies of ^{1}H and ^{13}C NMR spectra of products



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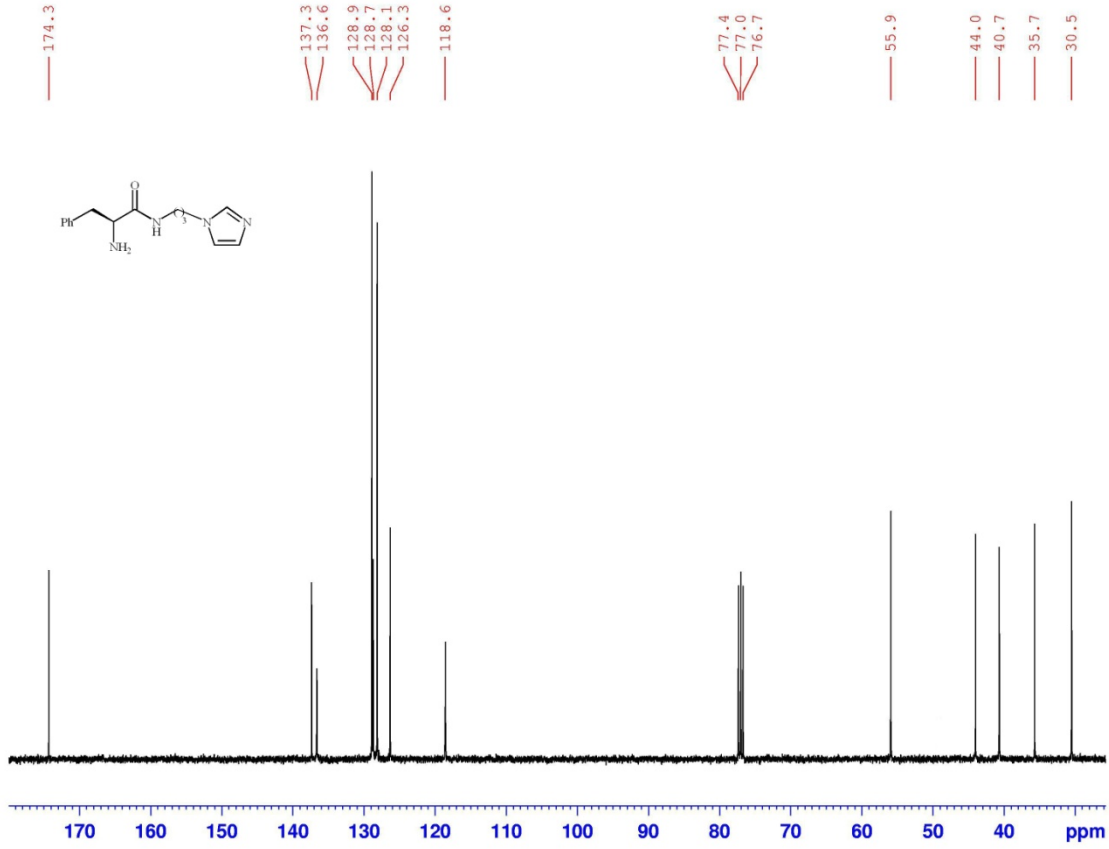
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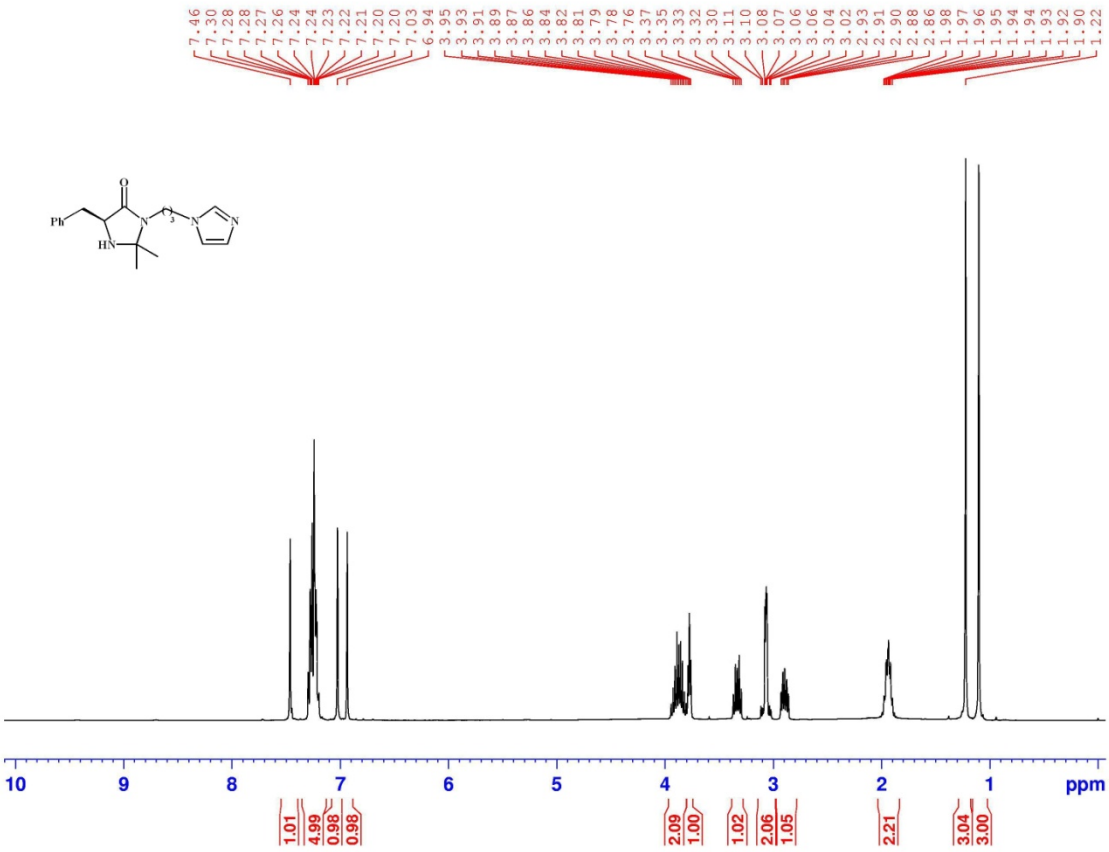
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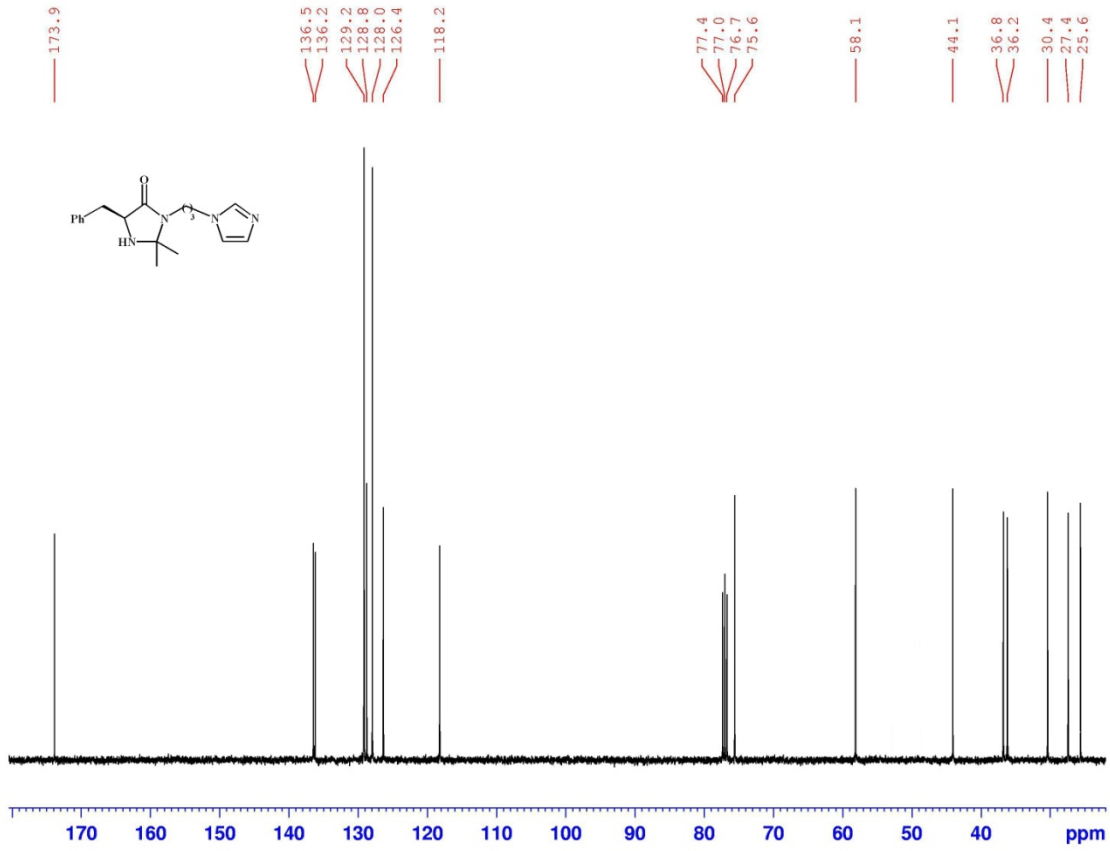
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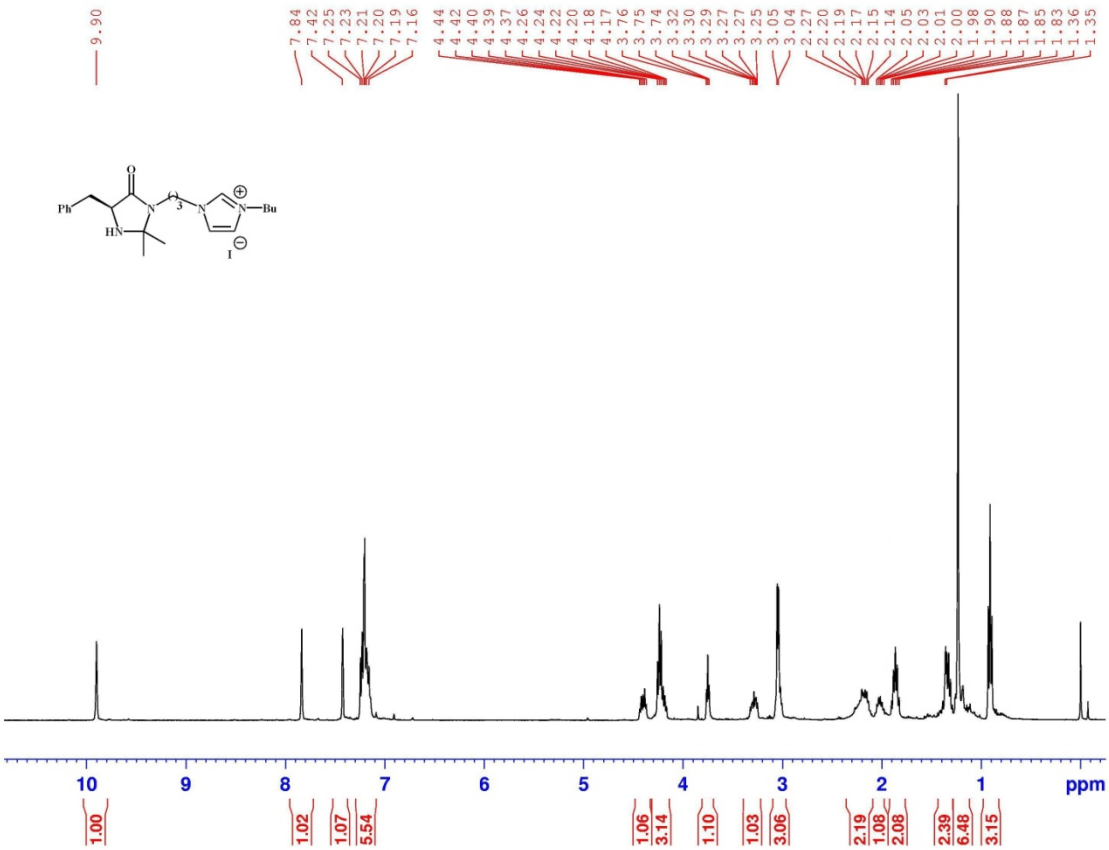
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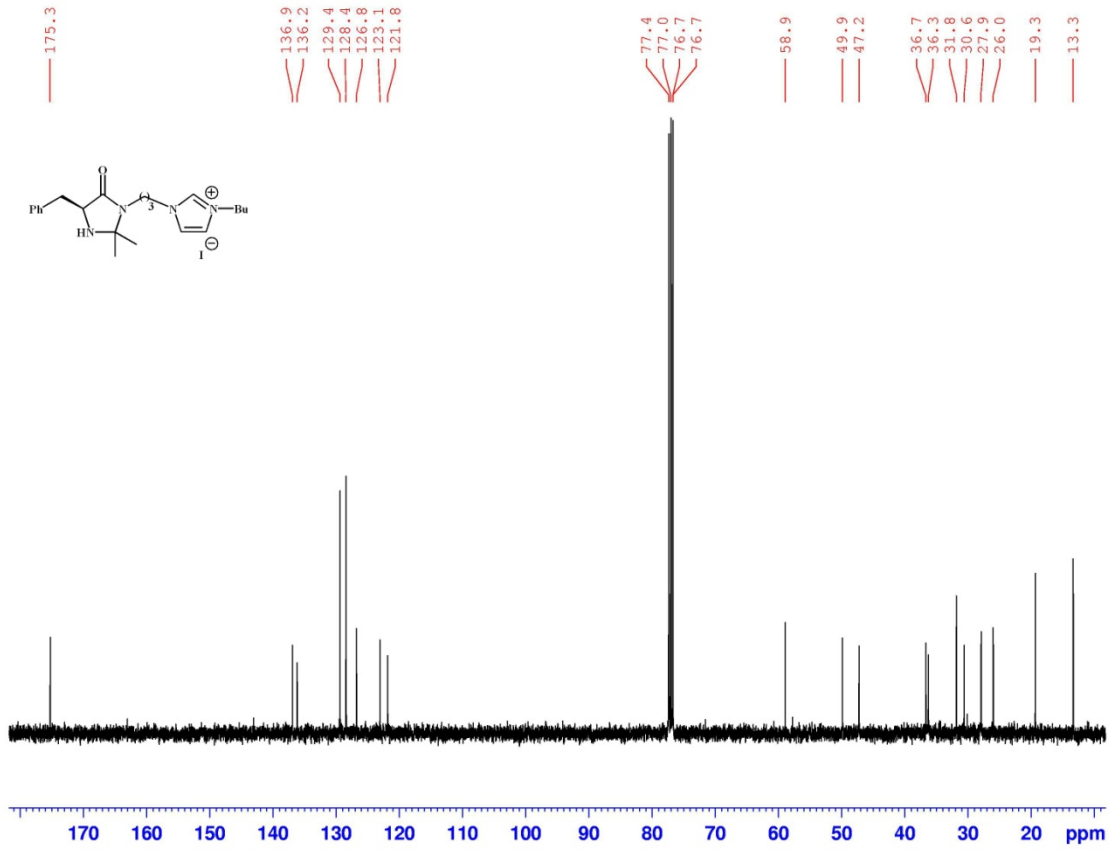
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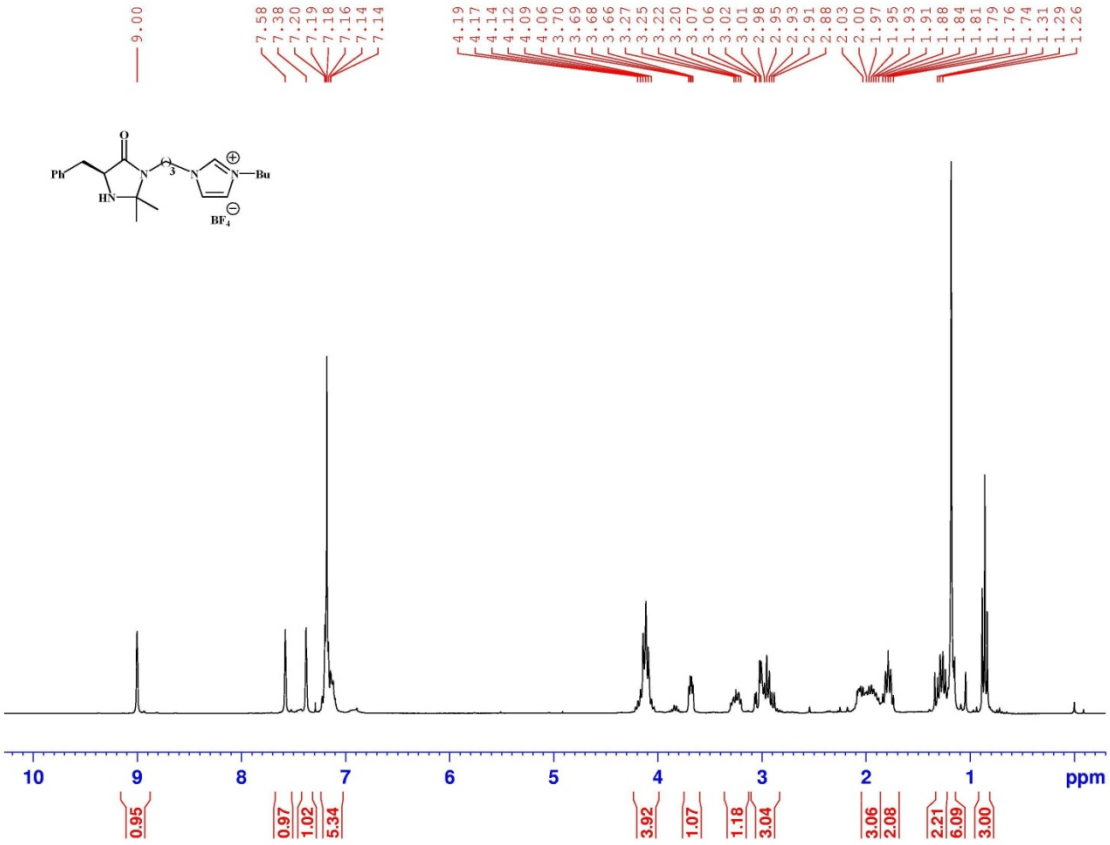
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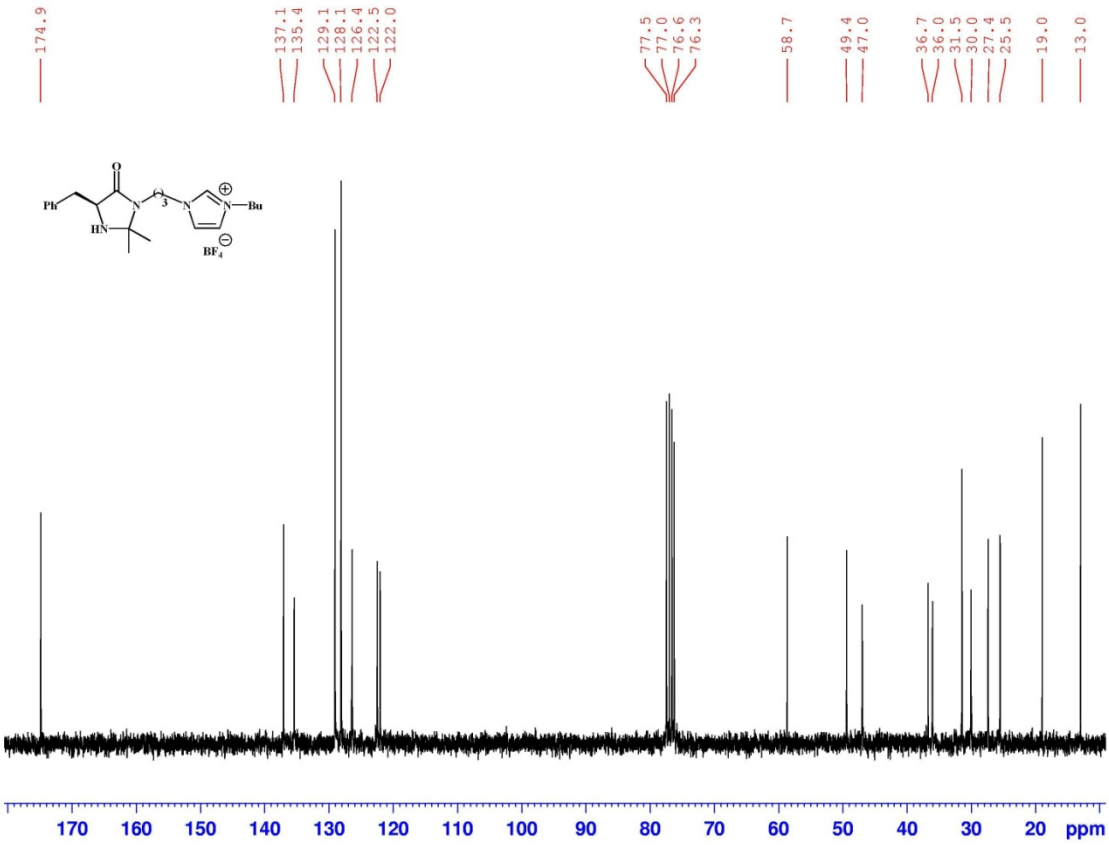
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25.5
19.0
13.0
Ph
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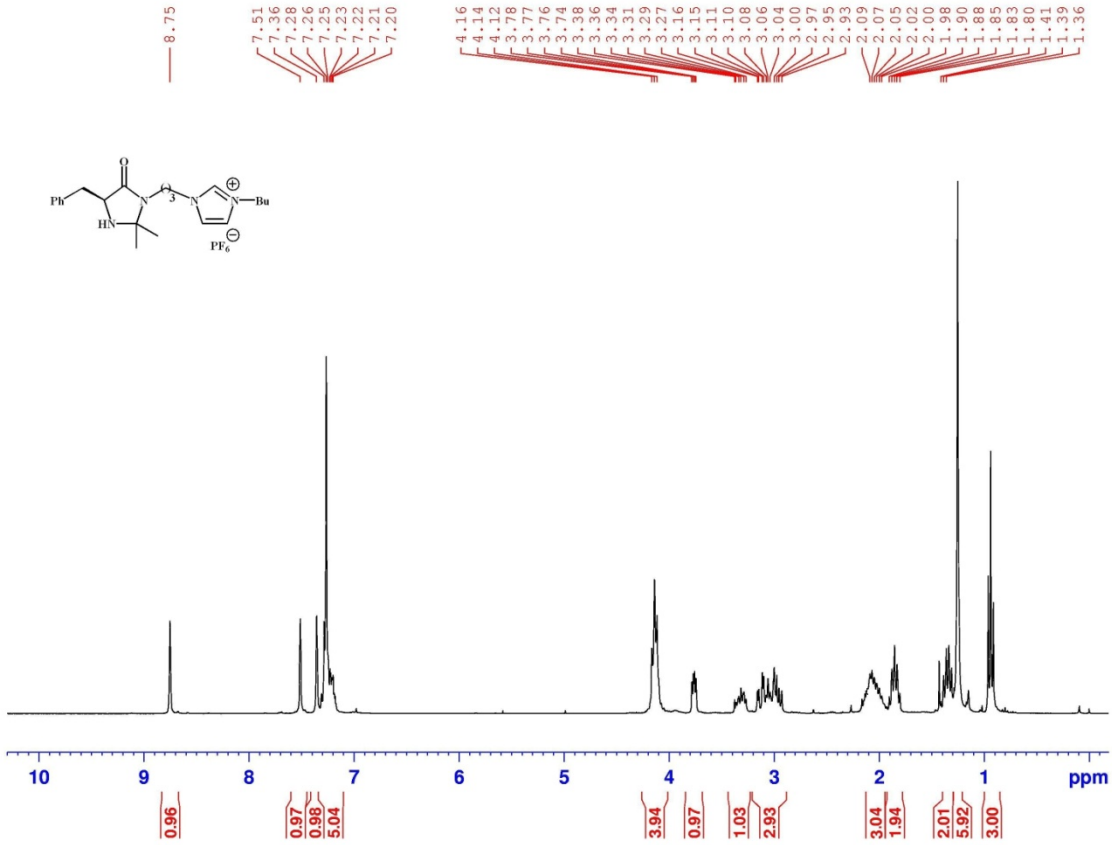
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3.10
3.08
3.06
3.04
3.00
2.97
2.95
2.93
2.09
2.07
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1.90
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HN
Bu
PF6
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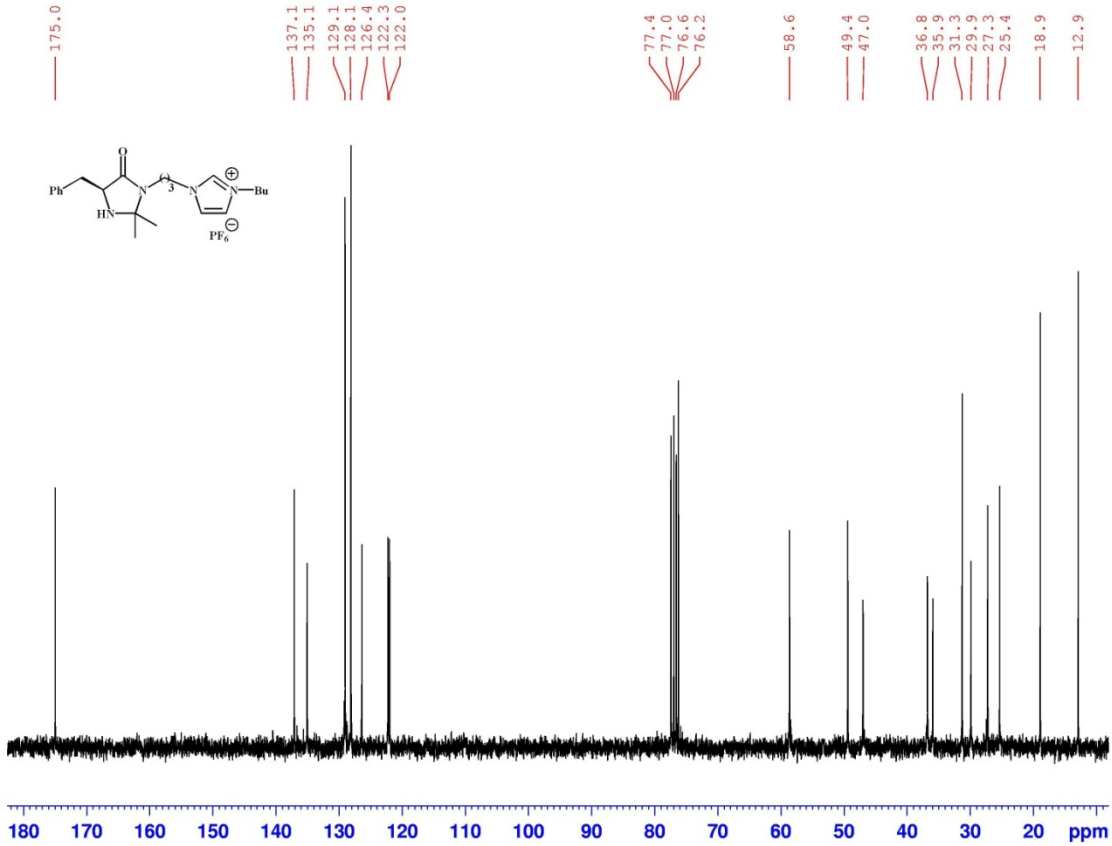
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49.4
47.0
36.8
35.9
31.3
29.9
27.3
25.4
18.9
12.9
Ph
HN
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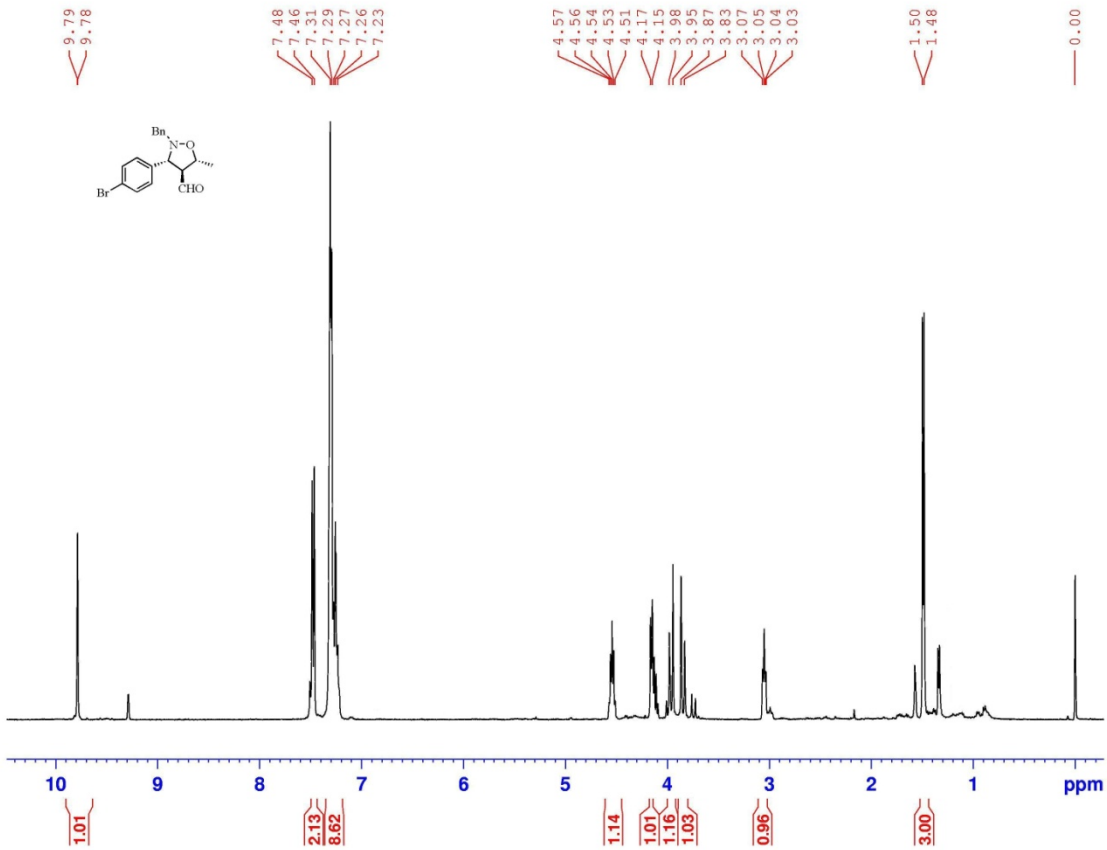
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4.17
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3.95
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3.83
3.07
3.05
3.04
3.03
1.50
1.48
0.00
Bn
N-O
Br
CHO
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8
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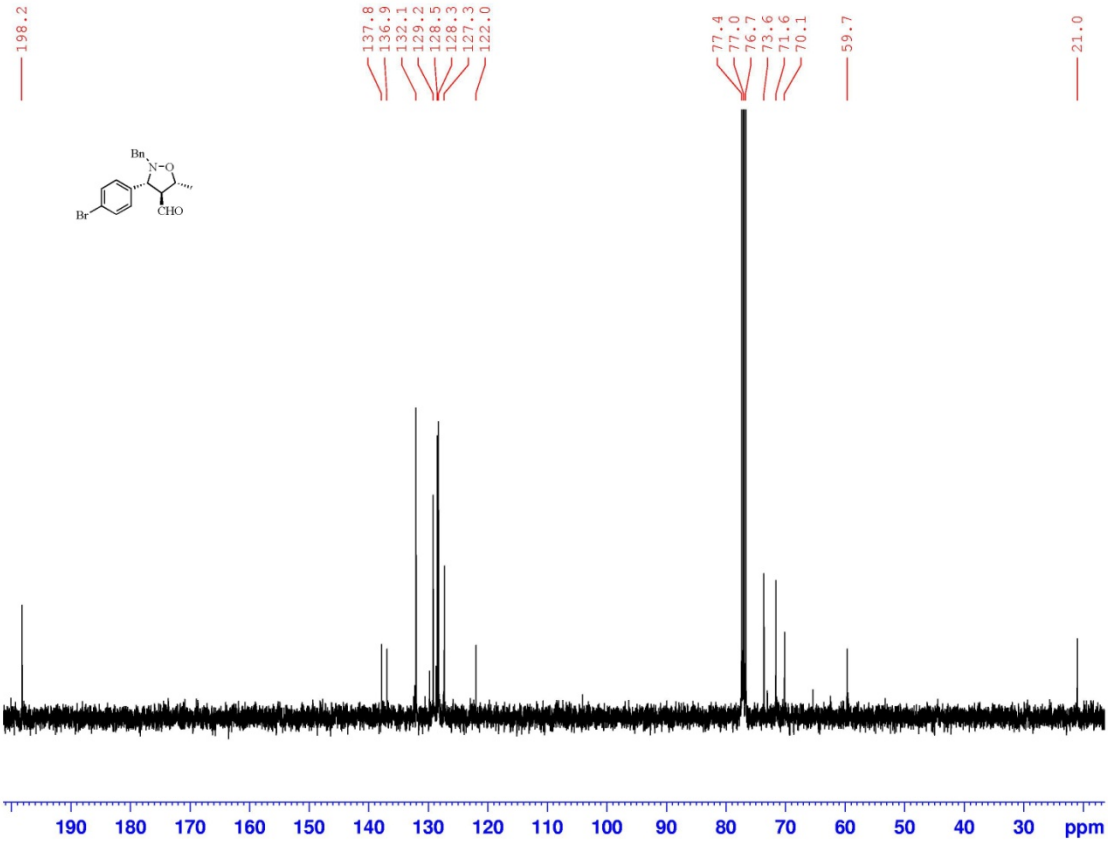
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73.6
71.6
70.1
59.7
21.0
Bn
N-O
Br
CHO
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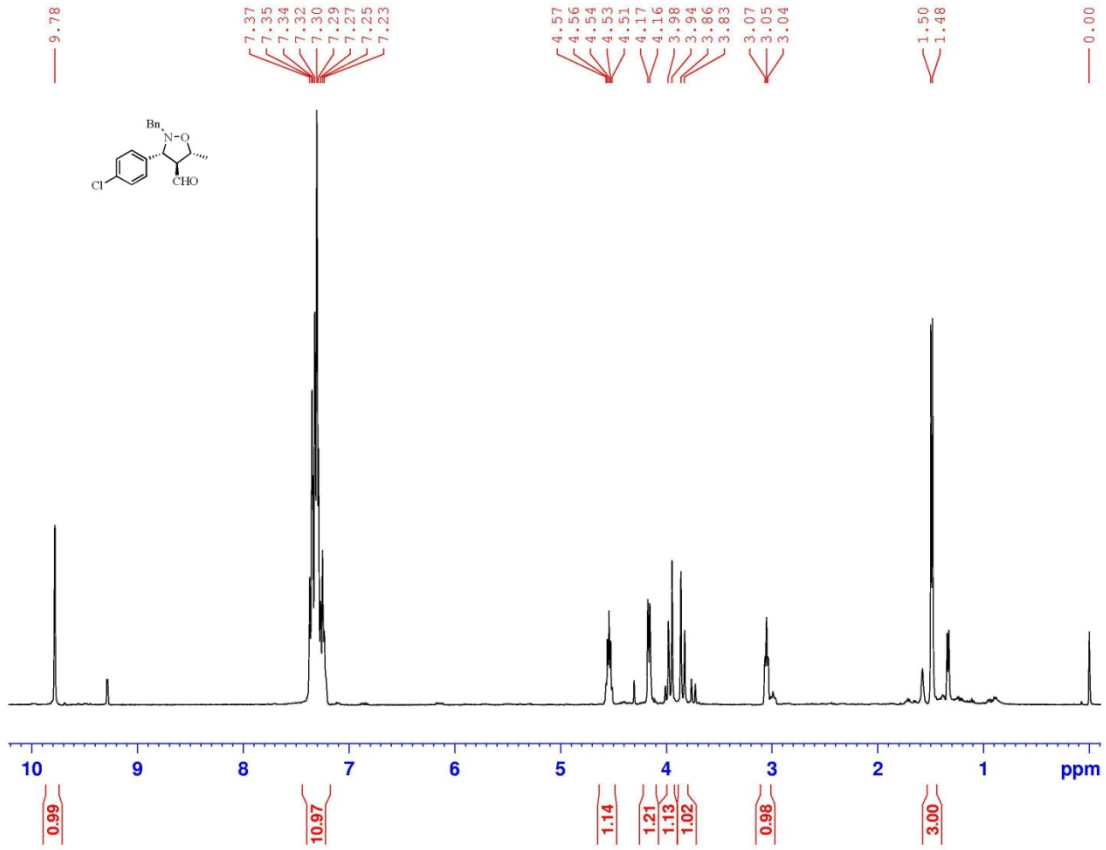
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4.53
4.51
4.17
4.16
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3.94
3.86
3.83
3.07
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3.04
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1.48
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N
O
Cl
CHO
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7
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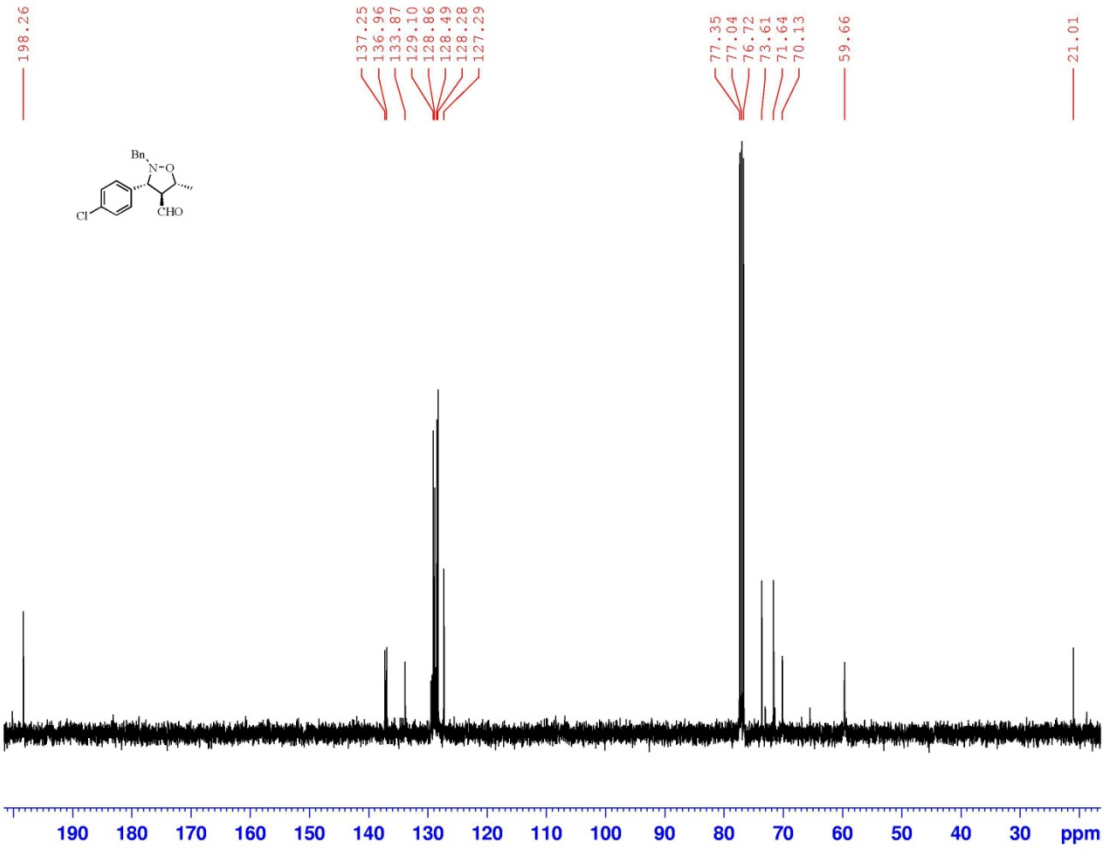
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N
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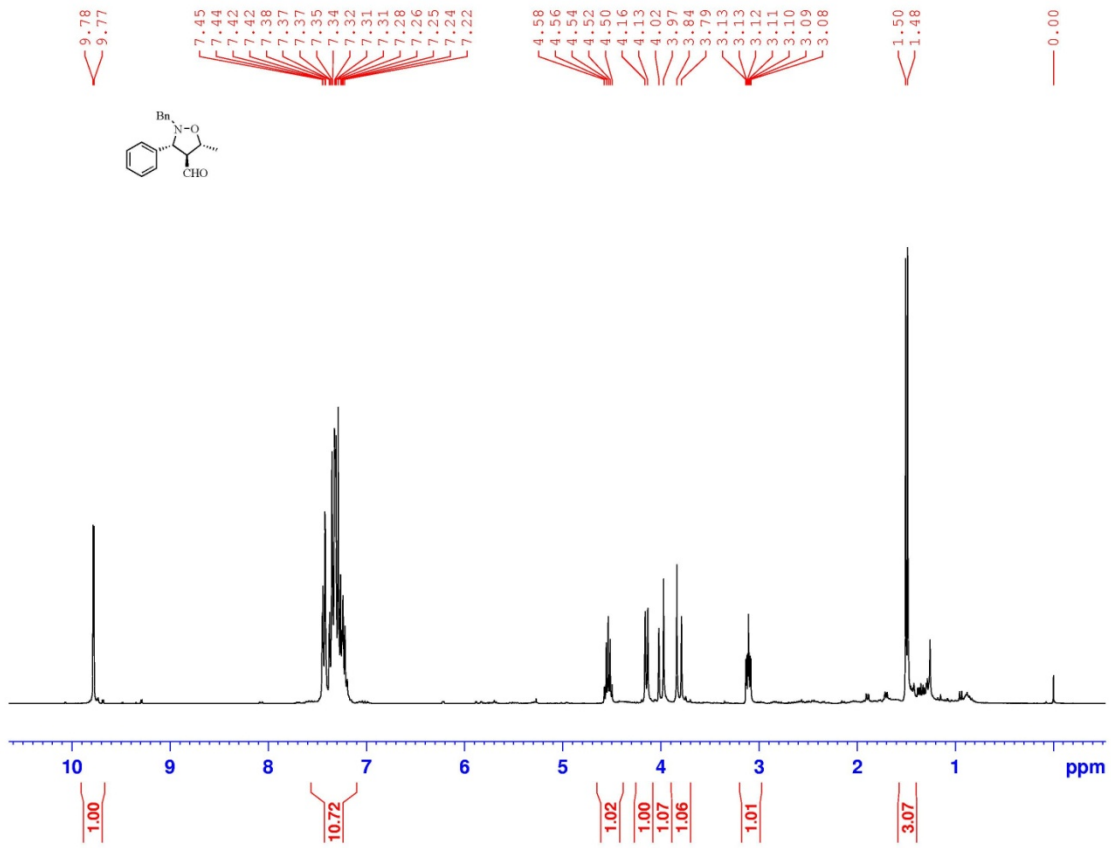
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7.28
7.26
7.25
7.24
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4.54
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4.50
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3.13
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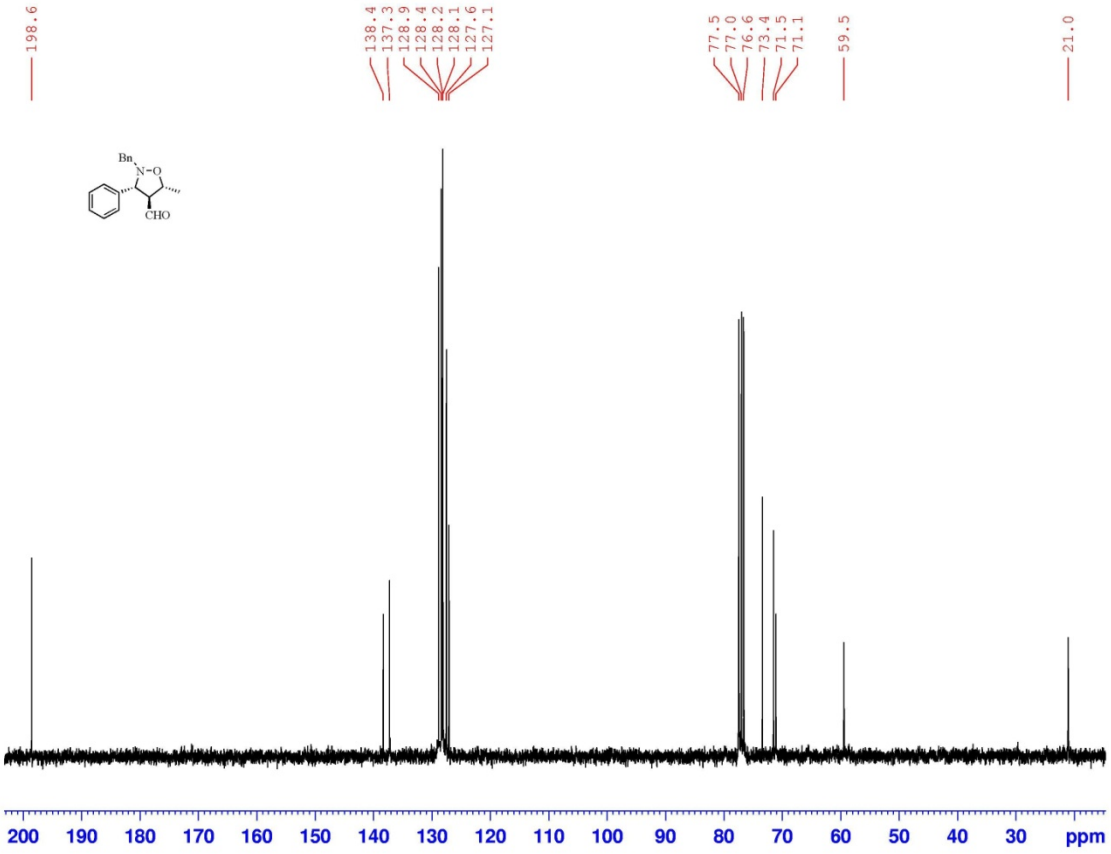
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127.6
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77.0
76.6
73.4
71.5
71.1
59.5
21.0
Bn
N
O
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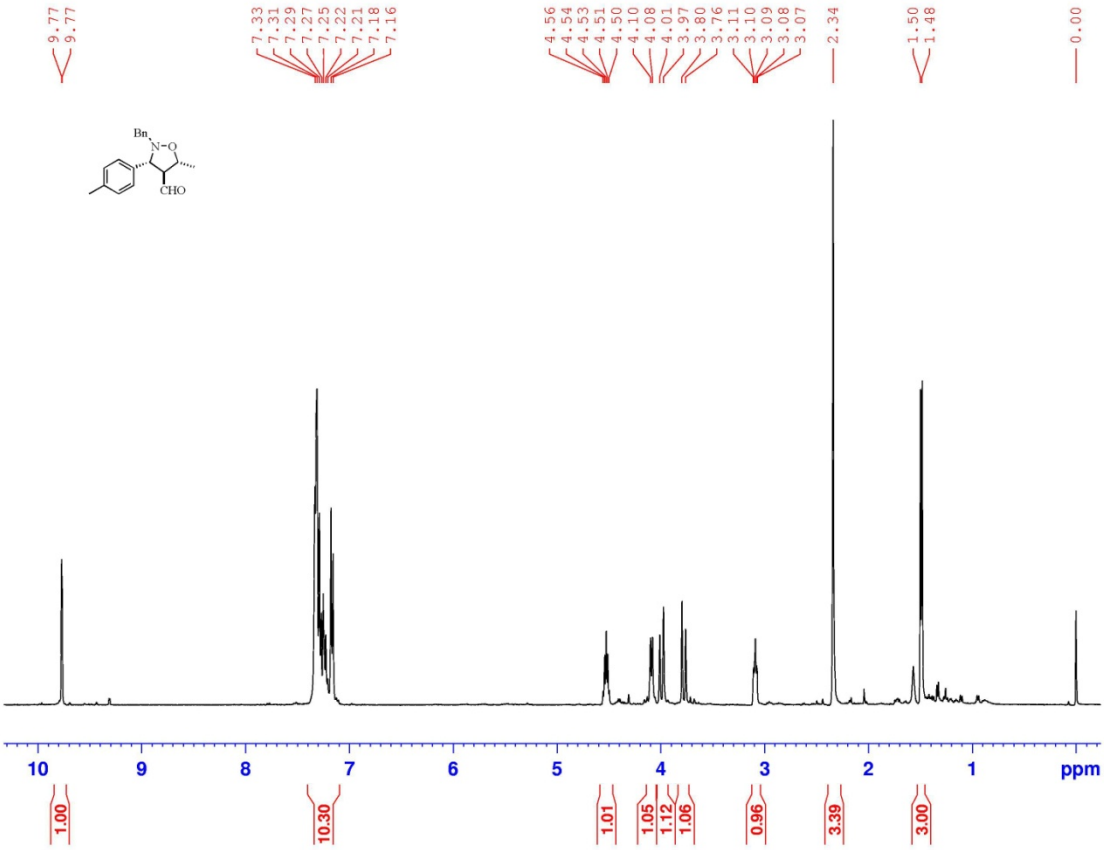
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4.53
4.51
4.50
4.10
4.08
4.01
3.97
3.80
3.76
3.11
3.10
3.09
3.08
3.07
2.34
1.50
1.48
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Bn
N-O
CHO
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9
8
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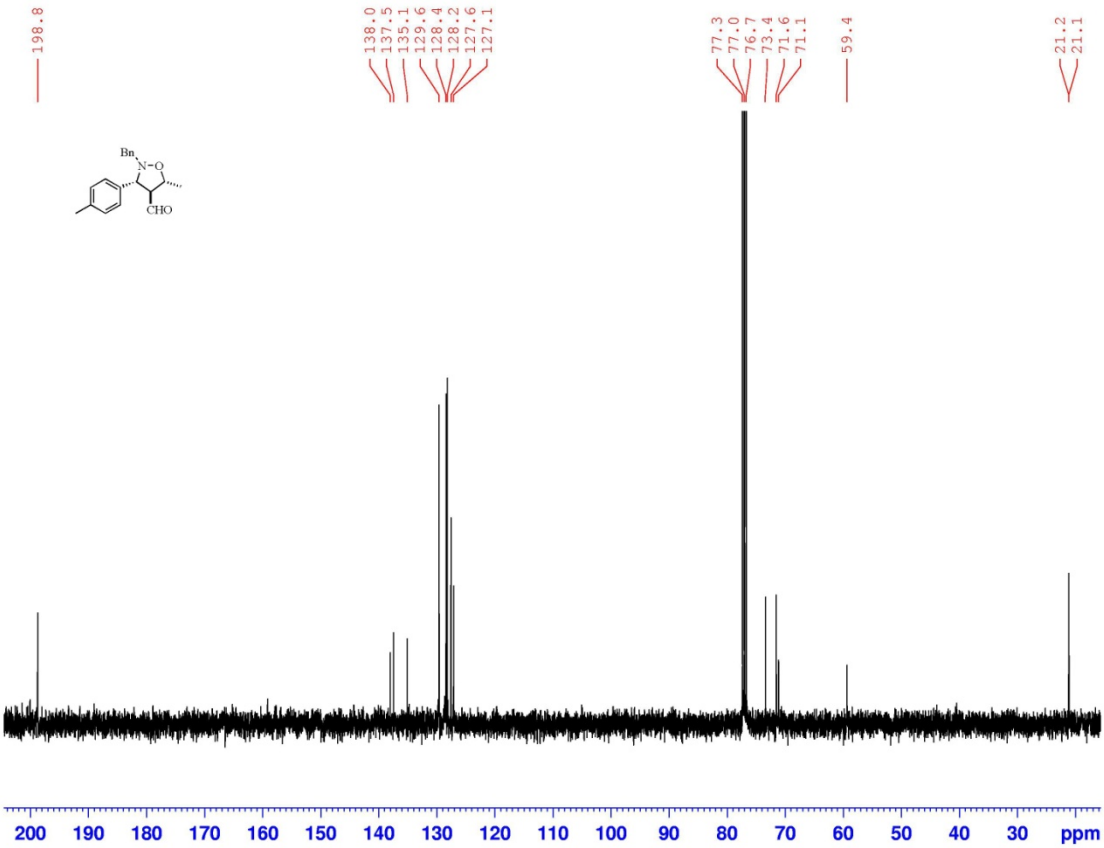
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71.1
59.4
21.2
21.1
Bn
N-O
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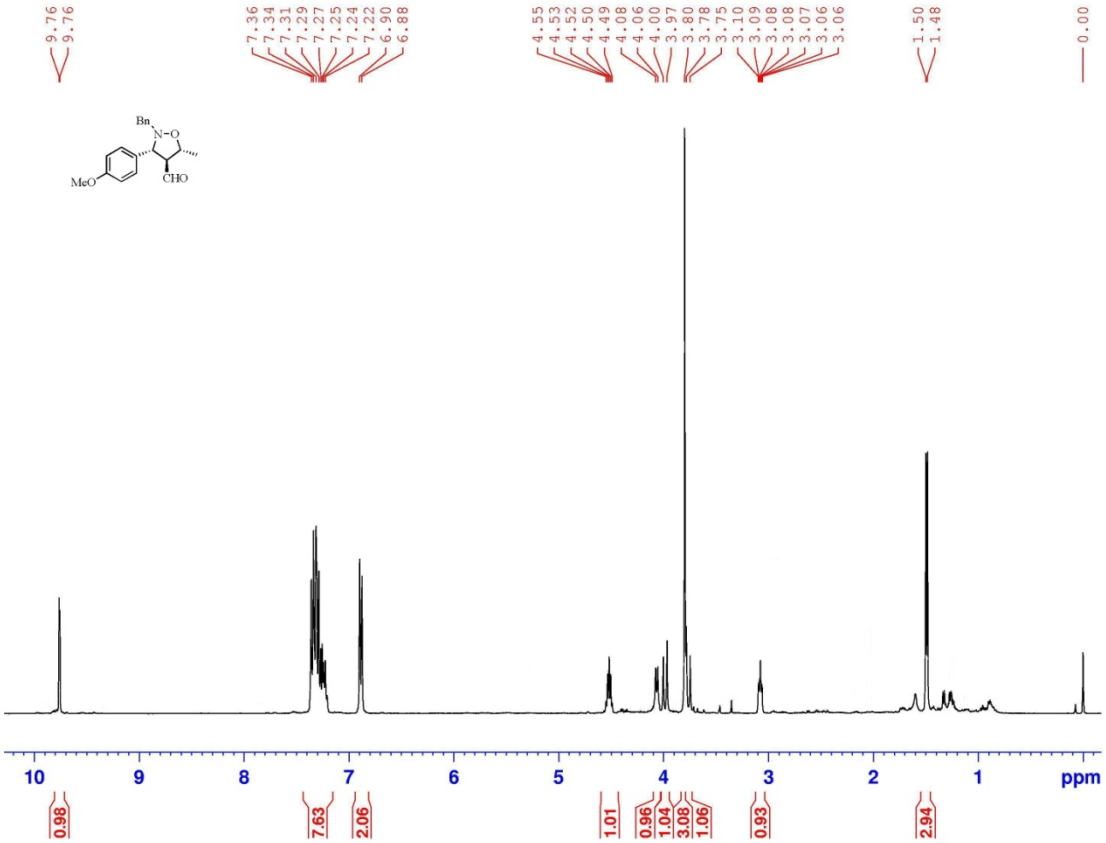
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4.53
4.52
4.50
4.49
4.08
4.06
4.00
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3.78
3.75
3.10
3.09
3.08
3.08
3.07
3.06
3.06
1.50
1.48
0.00
Bn
N-O
MeO
CHO
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6
5
4
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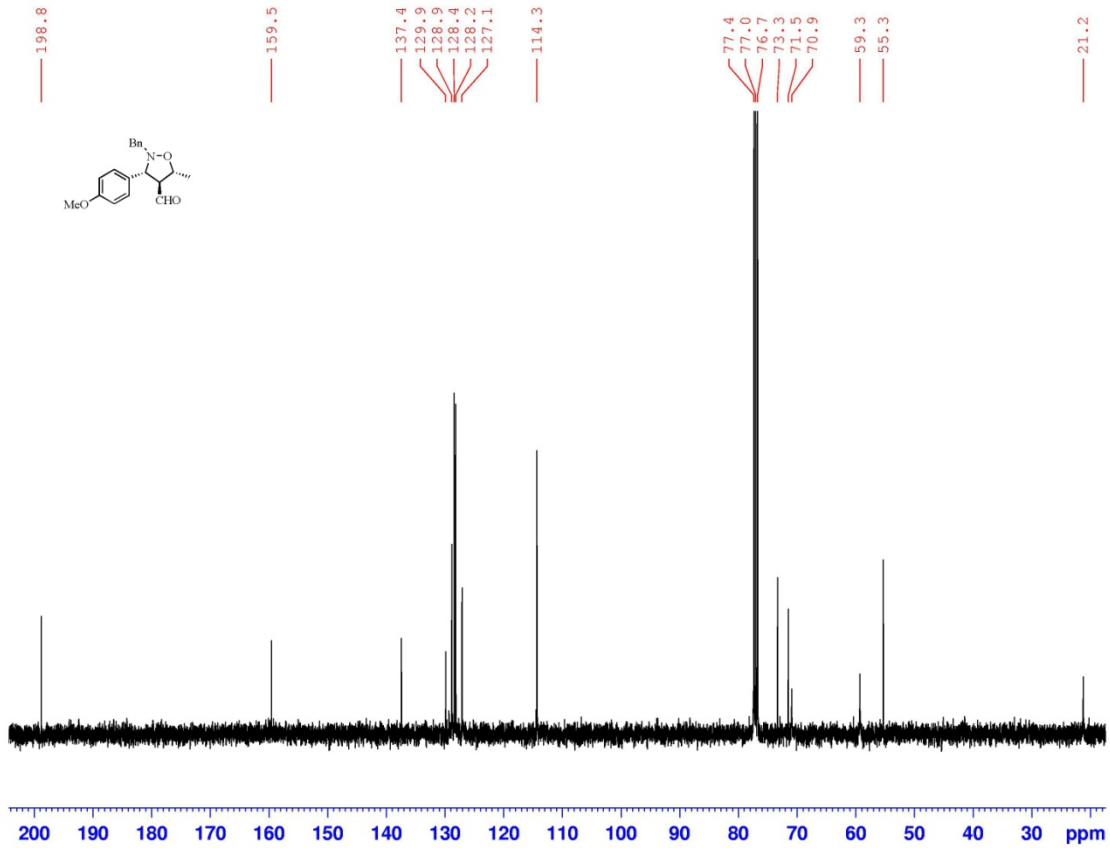
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73.3
71.5
70.9
59.3
55.3
21.2
Bn
N-O
MeO
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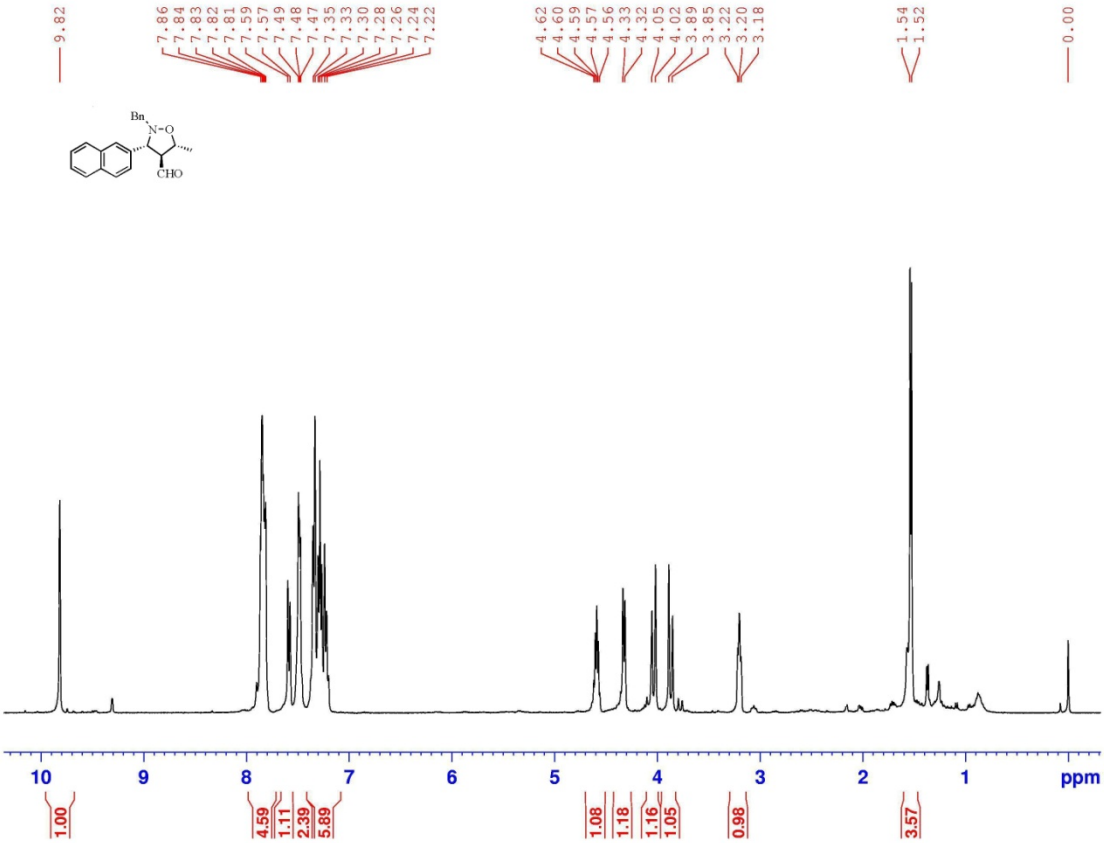
ppm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7.22
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N-O
CHO
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4
3
2
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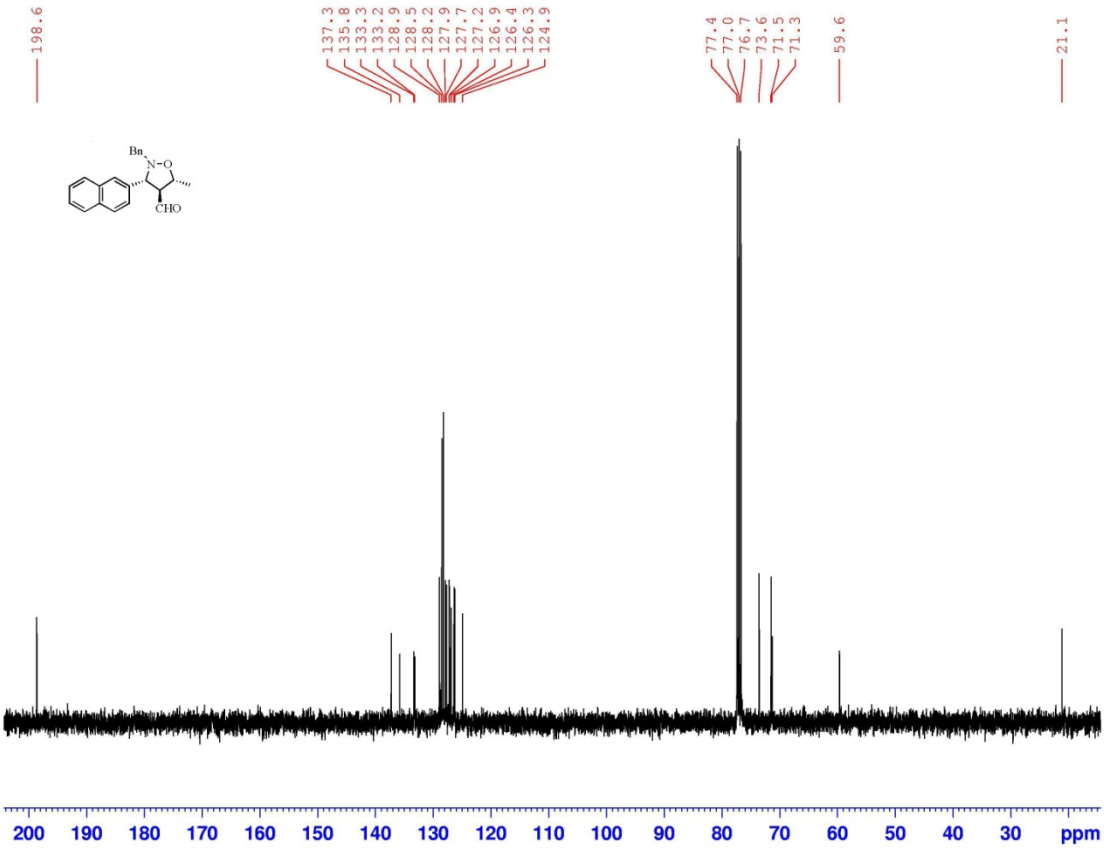
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124.9
77.4
77.0
76.7
73.6
71.5
71.3
59.6
21.1
Bn
N-O
CHO
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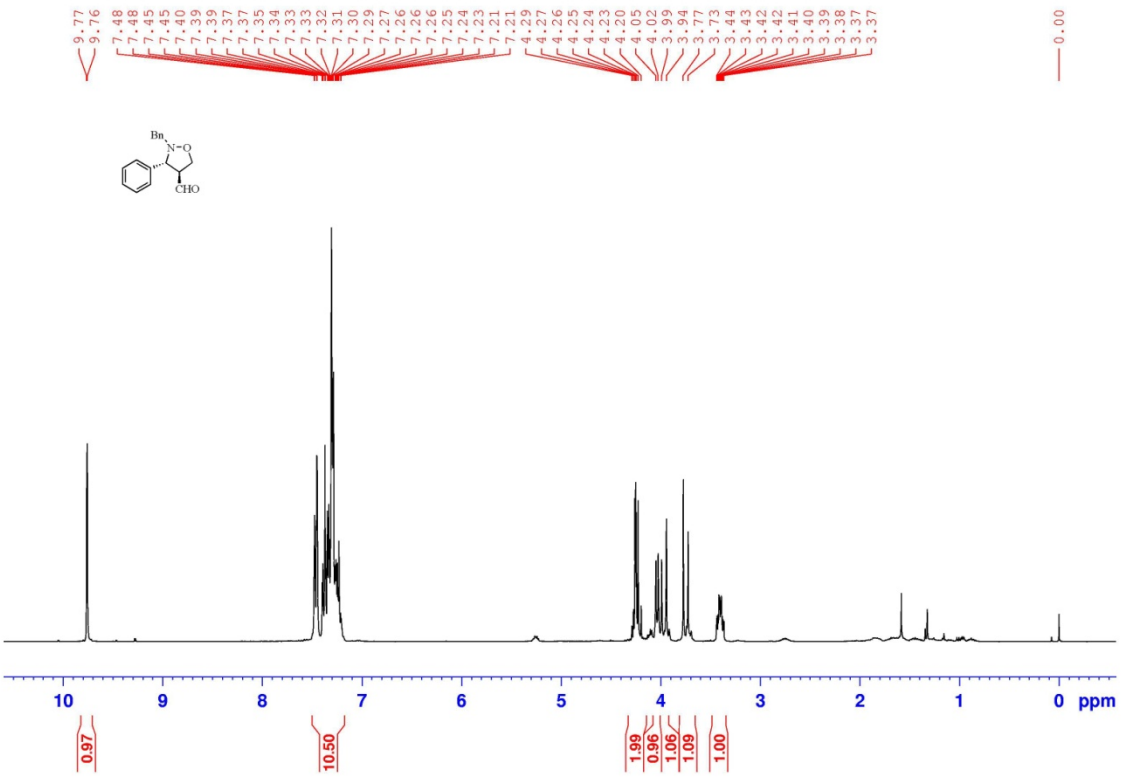
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4.24
4.23
4.20
4.05
4.02
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3.39
3.38
3.37
3.37
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Bn
N-O
CHO
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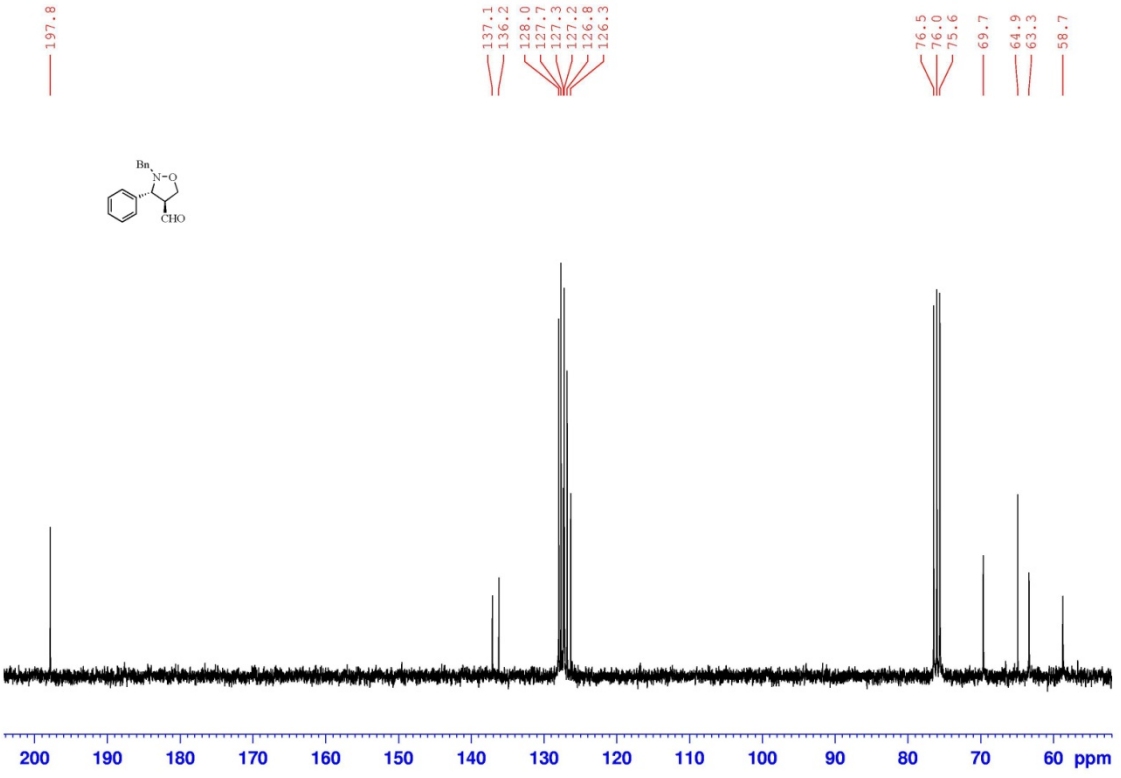
1.00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76.0
75.6
69.7
64.9
63.3
58.7
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N-O
CHO
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170
160
150
140
130
120
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100
90
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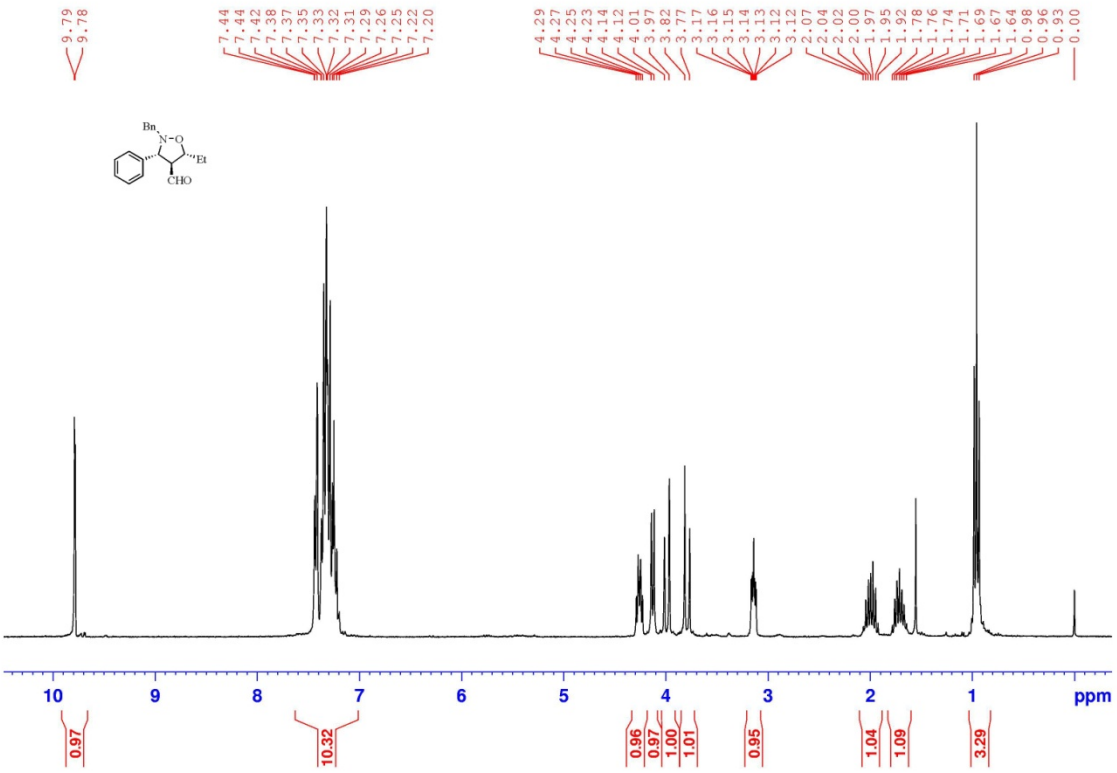
70
60 ppm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4.23
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3.14
3.13
3.12
3.12
2.07
2.04
2.02
2.00
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0.96
0.93
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Bn
N
O
Et
CHO
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7
6
5
4
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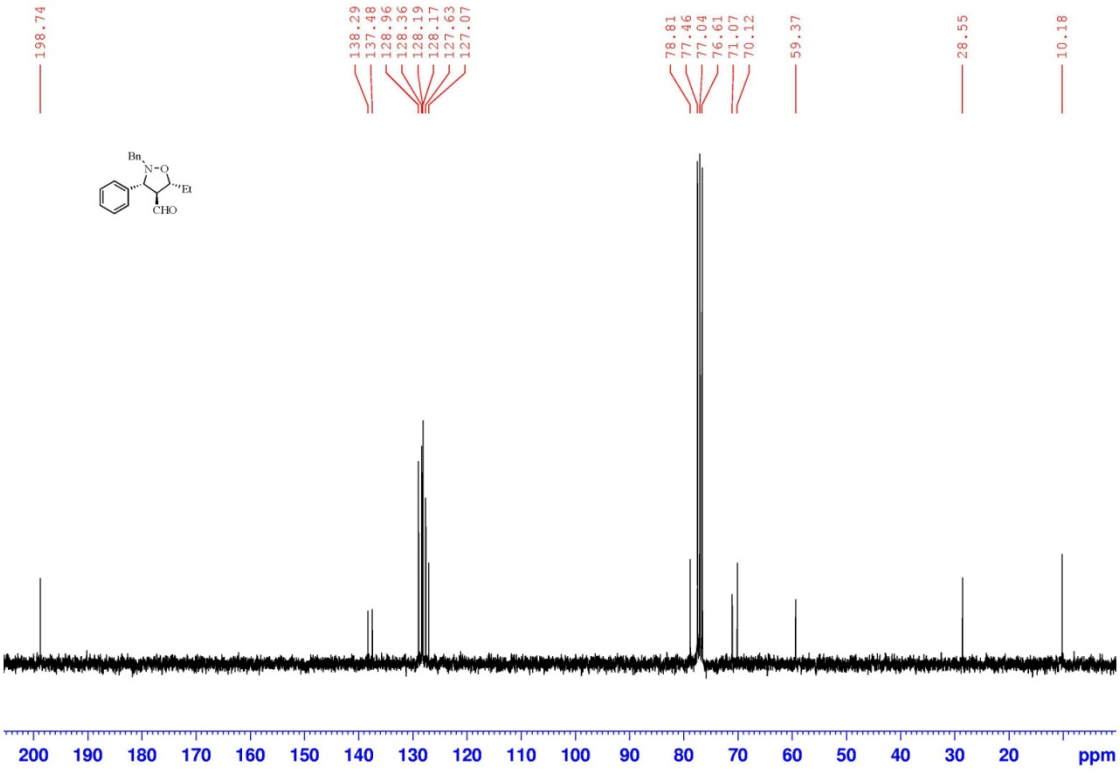
3.29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71.07
70.12
59.37
28.55
10.18
Bn
N
O
Et
CHO
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80
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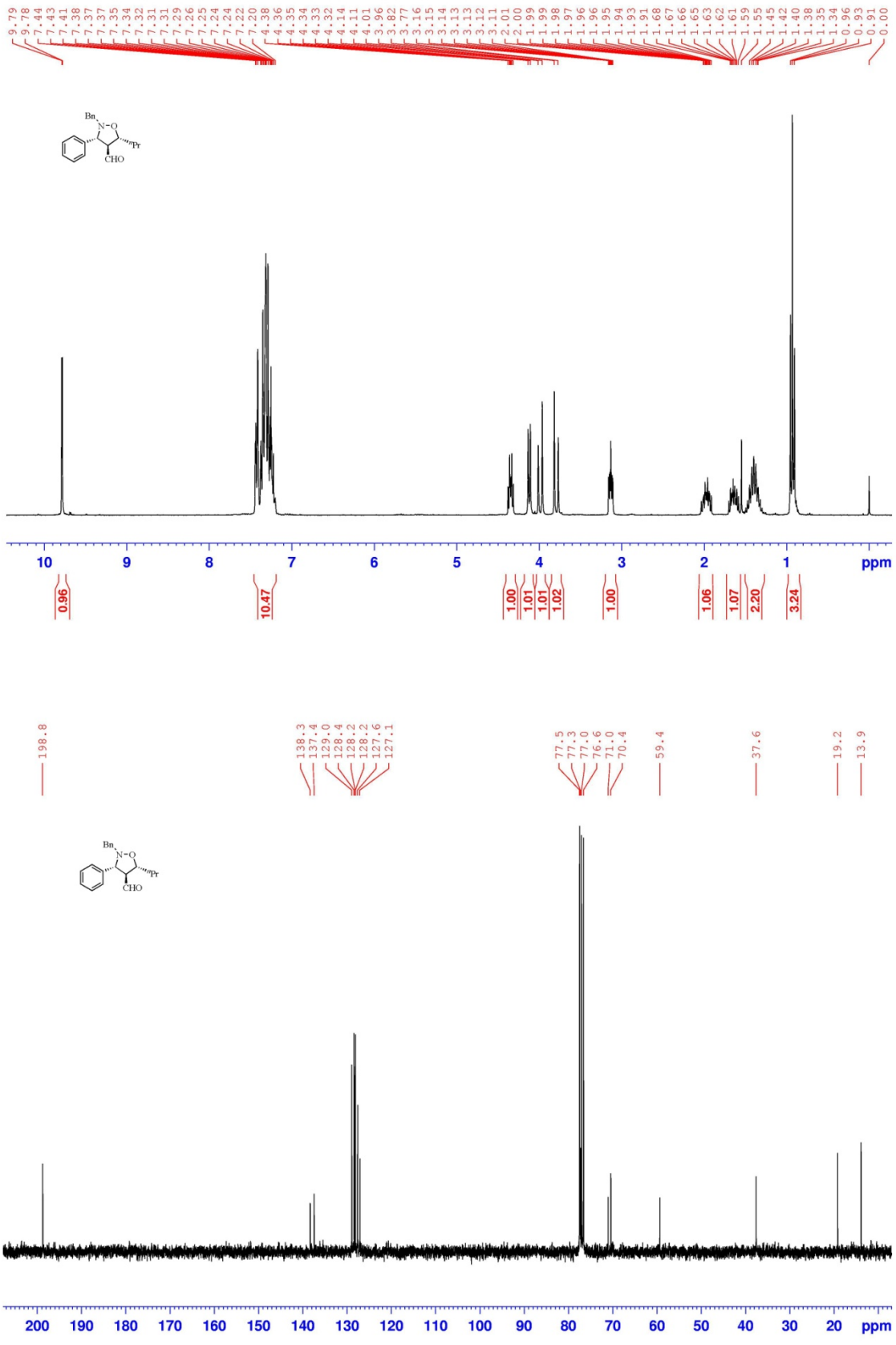
20
ppm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Bn
N
O
nPr
CHO
10 9 8 7 6 5 4 3 2 1 ppm
0.96 10.47 1.00 1.01 1.01 1.02 1.00 1.06 1.07 2.20 3.24
198.8 138.3 137.4 129.0 128.4 128.2 128.2 127.6 127.1 77.5 77.3 77.0 76.6 71.0 70.4 59.4 37.6 19.2 13.9
Bn
N
O
nPr
CHO
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm