Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Supporting Information

The rapid synthesis of oxazolines and their heterogeneous oxidation to oxazoles under flow conditions

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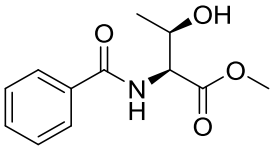
General experimental section

^{1}H-NMR spectra were recorded on a Bruker Avance DPX-400, DRX-500 Cryo or DRX-600 spectrometer with the residual solvent peak as the internal reference ($CDCl_3$ = 7.26 ppm). ^{1}H resonances are reported to the nearest 0.01 ppm. ^{13}C-NMR spectra were recorded on the same spectrometers with the central resonance of the solvent peak as the internal reference ($CDCl_3$ = 77.16 ppm). All ^{13}C resonances are reported to the nearest 0.1 ppm. The multiplicity of ^{1}H signals are indicated as: s = singlet, d = doublet, dd = doublet of doublet, ddd = doublet of doublet of doublet, t = triplet, q = quadruplet, m = multiplet, br. = broad, or combinations thereof. Coupling constants (*J*) are quoted in Hz and reported to the nearest 0.1 Hz. Where appropriate, averages of the signals from peaks displaying multiplicity were used to calculate the value of the coupling constant. Infrared spectra were recorded neat on a PerkinElmer Spectrum One FT-IR spectrometer using Universal ATR sampling accessories. Unless stated otherwise, reagents were obtained from commercial sources and used without purification. The removal of solvent under reduced pressure was carried out on a standard rotary evaporator. High resolution mass spectrometry (HRMS) was performed using a Waters Micromass LCT Premier™ spectrometer using time of flight with positive ESI, or conducted by Mr Paul Skelton on a Bruker BioApex 47e FTICR spectrometer using positive ESI or EI at 70 ev to within a tolerance of 5 ppm of the theoretically calculated value. Specific optical rotation was recorded on a Perkin-Elmer Model 343 digital polarimeter, using a Na/Hal lamp set at 589 nm and with a path length of 100 mm. All $[\alpha]_D$ values were measured using spectroscopy grade solvent at the specified concentration and temperature. The optimized flow reactions were performed using Vapourtec R2+/R4[1] and a Knauer K-120 HPLC[2] pump. Inductively Coupled Plasma-Mass Spectrometry (ICP-MS) analyses were conducted by Dr. Jason Day (Department of Earth Sciences, University of Cambridge) using a Perkin Elmer Elan DRCII quadrupole based inductively coupled plasma-mass spectrometer.

General procedure for the synthesis of peptides 1a-d and 1f-j

Methyl benzoyl-L-threoninate (1a): to a solution of benzoic acid (2.44 g, 20.0 mmol) and L-threonine methyl ester hydrochloride (3.39 g, 20.0 mmol) in CH_2Cl_2 (200 mL) was added *N*,*N*-diisopropylethylamine (6.79 mL, 40.0 mmol), 1-hydroxybenzotriazole hydrate (3.24 g, 24.0 mmol) and *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (4.60 g, 24.0 mmol). The reaction mixture was stirred under air at room temperature for five days and thereafter quenched with ammonium chloride solution (saturated, 200 mL). The aqueous layer was extracted with CH_2Cl_2 (4 × 100 mL), the combined organic layers were washed with hydrochloric acid (3 m, 2 × 100 mL), sodium bicarbonate solution (saturated, 2 × 100 mL) and brine (200 mL). The combined organic layers were dried over magnesium sulfate and concentrated *in vacuo*. The crude product was purified by flash column chromatography (*n*-hexane/ethyl acetate 2:1 → 1:3) and **1a** was obtained as a white solid (4.28 g, 18.0 mmol, 90 %).



^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm) = 7.87–7.82 (m, 2H), 7.56–7.49 (m, 1H), 7.47 – 7.40 (m, 2H), 6.98 (d, 1H, *J* = 8.5 Hz), 4.82 (dd, 1H, *J* = 8.8, 2.5 Hz), 4.55 – 4.34 (m, 1H), 3.79 (s, 3H), 2.54 (d, 1H, *J* = 5.0 Hz), 1.28 (d, 3H, *J* = 6.4 Hz).

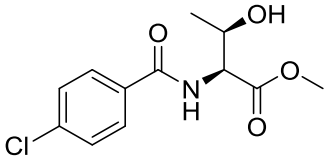
^{13}C-NMR (126 MHz, $CDCl_3$) δ (ppm) = 171.8, 168.1, 133.8, 132.1, 128.8, 127.3, 68.4, 57.7, 52.8, 20.2.

HR-MS: (ESI+) $C_{12}H_{16}NO_4^+$ $(M+H)^+$ calc.: 238.1079, det.: 238.1082.

FT-IR: neat, $\tilde{\nu}$ (cm^{-1}) = 3427 (m), 3354 (s), 2979 (w), 1741 (s), 1640 (s), 1576 (m), 1523 (s), 1485 (s), 1411 (w), 1312 (w), 1279 (m), 1256 (s), 1161 (m), 1106 (s), 1015 (s), 903 (w), 862 (w), 783 (w), 706 (s), 687 (s).

Specific rotation: $[\alpha]_D^{23.3}$ = +19.9 ° cm^3 g^{-1} dm^{-1} (*c* = 1 in $CHCl_3$).

Methyl (4-chlorobenzoyl)-L-threoninate (1b): prepared following the general procedure above, using 4-chlorobenzoic acid as starting material (isolated yield 95 %).



^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm) = 7.76 (d, 2H, *J* = 8.6 Hz), 7.38 (d, 2H, *J* = 8.6 Hz), 7.05 (d, 1H, *J* = 8.7 Hz), 4.77 (dd, 1H, *J* = 8.8, 2.5 Hz), 4.55 – 4.34 (m, 1H), 3.76 (s, 3H), 2.89 (s, 1H), 1.25 (d, 3H, *J* = 6.4 Hz).

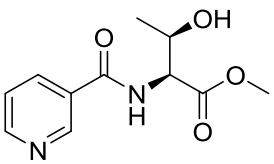
^{13}C-NMR (151 MHz, $CDCl_3$) δ (ppm) = 171.6, 167.1, 138.3, 132.1, 129, 128.8, 68.2, 57.9, 52.8, 20.2.

HR-MS: (ESI+) $C_{12}H_{15}ClNO_4^+$ $(M+H)^+$ calc.: 272.0690, det.: 272.0685.

FT-IR: neat, $\tilde{\nu}$ (cm^{-1}) = 3363 (m), 2971 (m), 1753 (s), 1635 (s), 1595 (m), 1544 (s), 1486 (m), 1438 (m), 1403 (m), 1376 (m), 1351 (s), 1312 (s), 1254 (m), 1205 (s), 1165 (s), 1123 (m), 1085 (s), 1014 (m), 934 (w), 846 (m), 826 (m), 769 (m), 757 (s), 699 (w), 680 (w).

Specific rotation: $[\alpha]_D^{24.0}$ = -32.8 ° cm^3 g^{-1} dm^{-1} (*c* = 1 in $CHCl_3$).

Methyl nicotinoyl-L-threoninate (1c): prepared following the general procedure above, using nicotinic acid as starting material (isolated yield 99 %).



^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm) = 9.03 (d, 1H, *J* = 1.9 Hz), 8.64 (dd, 1H, *J* = 4.9, 1.6 Hz), 8.15–8.13 (m, 1H), 7.40 (d, 1H, *J* = 8.9 Hz), 7.36–7.32 (m, 1H), 4.77 (dd, 1H, *J* = 8.9, 2.5 Hz), 4.45 (m, 1H), 4.21 (s, 1H), 3.70 (s, 3H), 1.24 (d, 1H, *J* = 6.5 Hz).

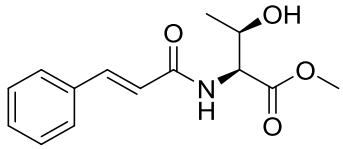
^{13}C-NMR (151 MHz, $CDCl_3$) δ (ppm) = 171.5, 166.2, 152.2, 148.3, 135.7, 129.8, 123.6, 67.8, 58.1, 52.7, 20.4.

HR-MS: (ESI+) $C_{11}H_{15}N_2O_4^+$ $(M+H)^+$ calc.: 239.1032, det.: 239.1033.

FT-IR: neat, $\tilde{\nu}$ (cm^{-1}) = 3324 (m), 1740 (s), 1650 (s), 1593 (m), 1528 (s), 1476 (w), 1437 (w), 1419 (w), 1318 (m), 1212 (m), 1169 (m), 1123 (m), 1083 (m), 1027 (w), 917 (w), 832 (w), 736 (m), 705 (s), 630 (m).

Specific rotation: $[\alpha]_D^{24.0}$ = +21.1 ° cm^3 g^{-1} dm^{-1} (*c* = 1 in $CHCl_3$).

Methyl cinnamoyl-L-threoninate (1d): prepared following the general procedure above, using *trans*-cinnamic acid as starting material (isolated yield 92 %).



^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm) = 7.66 (d, 1H, *J* = 15.6 Hz), 7.55–7.48 (m, 2H), 7.39–7.33 (m, 3H), 6.53 (d, 1H, *J* = 15.6 Hz), 6.53–6.52 (m, 1H), 4.78 (dd, 1H, *J* = 8.8, 2.4 Hz), 4.46–4.38 (m, 1H), 3.79 (s, 3H), 2.43 (d, 1H, *J* = 5.0 Hz), 1.27 (d, 3H, *J* = 6.4 Hz).

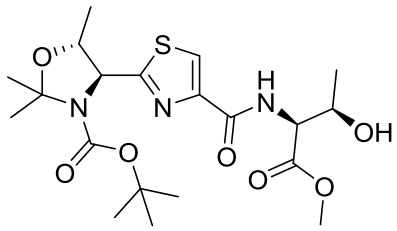
^{13}C-NMR (151 MHz, $CDCl_3$) δ (ppm) = 171.8, 166.5, 142.3, 134.7, 130.1, 129.0, 128.1, 120.0, 68.4, 57.5, 52.8, 20.2.

HR-MS: (ESI+) $C_{14}H_{18}NO_4^+$ $(M+H)^+$ calc.: 264.1236, det.: 264.1227.

FT-IR: neat, $\tilde{\nu}$ (cm^{-1}) = 3474 (w), 3301 (w), 1717 (s), 1654 (s), 1623 (s), 1544 (s), 1439 (m), 1376 (w), 1347 (m), 1284 (s), 1215 (s), 1147 (m), 1083 (s), 1018 (s), 976 (s), 869 (m), 764 (m), 732 (s), 693 (s), 626 (m).

Specific rotation: $[\alpha]_D^{24.0}$ = +27.9 ° cm^3 g^{-1} dm^{-1} (*c* = 1 in $CHCl_3$).

***tert*-Butyl (4S,5R)-4-(4-(((2S,3R)-3-hydroxy-1-methoxy-1-oxobutan-2-yl)carbamoyl)thiazol-2-yl)-2,2,5-trimethyloxazolidine-3-carboxylate (1e):** [3]



^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm) = 8.07 (s, 1H), 7.94 (d, 1H, *J* = 8.4 Hz), 4.69 (d, 1H, *J* = 8.4 Hz), 4.61 (s, 1H), 4.41 (m, 1H), 4.14 (m, 1H), 3.71 (s, 3H), 3.01 (m, 1H), 1.65 (m, 6H), 1-46-1.38 (m, 9H), 1.19–1.12 (m, 6H).

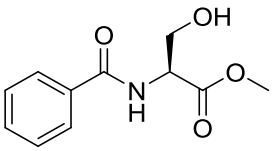
^{13}C-NMR (151 MHz, $CDCl_3$) δ (ppm) = 172.3, 171.1, 161.3, 151.3, 148.9, 148.8, 95.2, 94.8, 68.1, 67.7, 65.8, 57.3, 52.5, 28.2, 28.2, 28.0, 26.9, 26.5, 26.2, 25.5, 19.8, 18.0, 17.8.

HR-MS: (ESI+) $C_{20}H_{38}N_3O_8^+$ $(M+H)^+$ calc.: 459.1961, det.: 459.1974.

FT-IR: neat, $\tilde{\nu}$ (cm^{-1}) = 3406 (m), 2978 (m), 2939 (w), 1744 (m), 1702 (s), 1673 (s), 1540 (s), 1479 (m), 1364 (s), 1308 (m), 1259 (m), 1210 (m), 1169 (w), 1133 (w), 1086 (m), 855 (m), 781 (w), 755 (w).

Specific rotation: $[\alpha]_D^{23.8}$ = -28.0 ° cm^3 g^{-1} dm^{-1} (*c* = 1 in $CHCl_3$).

Methyl benzoyl-L-serinate (1f): prepared following the general procedure above, using benzoic acid and methyl serinate as starting materials (isolated yield 75 %).



^{1}H-NMR: (500 MHz, $CDCl_3$) δ (ppm) = 7.82–7.76 (m, 2H), 7.51–7.45 (m, 1H), 7.42–7.36 (m, 2H), 7.26 (d, 1H, *J* = 7.1 Hz), 4.82 (dt, 1H, *J* = 7.3, 3.6 Hz), 4.04 (ddd, 1H, *J* = 11.1, *J* = 6.1, 3.8 Hz), 3.98 (ddd, 1H, *J* = 11.1, *J* = 5.8, 3.4 Hz), 3.76 (s, 3H), 3.38 (t, 1H, *J* = 5.9 Hz).

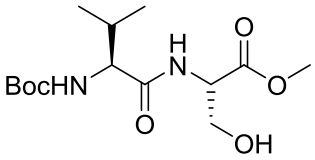
^{13}C-NMR: (126 MHz, $CDCl_3$) δ (ppm) = 171.20, 167.91, 133.52, 132.07, 128.70, 127.30, 63.30, 55.24, 52.90.

HR-MS: (ESI+) $C_{11}H_{14}NO_4^+$ $(M+H)^+$ calc.: 224.0917, det.: 224.0910.

IR: film; $\tilde{\nu}$ (cm^{-1}) = 3284 (m), 3063 (vw), 2953 (m), 1749 (s), 1625 (s), 1577 (m), 1539 (s), 1489 (m), 1454 (m), 1435 (m), 1370 (m), 1266 (m), 1210 (m), 1183 (m), 1111 (m), 1057 (s), 1029 (m), 1000 (w), 979 (m), 917 (m), 894 (w), 836 (m), 802 (m), 694 (s).

Specific rotation: $[\alpha]_D^{25.8}$ = +43.8 ° cm^3 g^{-1} dm^{-1} (*c* = 0.99 in $CHCl_3$).

Methyl (*tert*-butoxycarbonyl)-L-valyl-L-serinate (1i): prepared following the general procedure above, using *tert*-butoxycarbonyl-*L*-valine and methyl-*L*-serinate as starting materials (isolated yield 87 %).



^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.01 (d, 1H, ^{3}J = 7.7 Hz), 5.23 (d, 1H, *J* = 8.2 Hz), 4.67 (dt, 1H), 4.02 – 3.85 (m, 3H), 3.77 (s, 3H), 2.11 – 2.06 (m, 1H), 2.03 (d, 1H *J* = 4.8 Hz), 1.43 (s, 9H), 0.99 (d, 3H, *J* = 6.8 Hz), 0.95 (d, 3H *J* = 6.7 Hz).

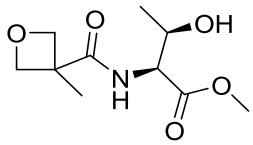
^{13}C-NMR (126 MHz, $CDCl_3$) δ (ppm) = 172.2, 170.9, 156.4, 80.4, 62.9, 60.5, 54.8, 53.6, 52.8, 31.0, 28.4, 19.3, 18.2, 14.3.

HR-MS: (ESI+) $C_{14}H_{27}N_2O_6^+$ $(M+H)^+$ calc.: 319.1869, det.: 319.1870.

FT-IR: film, $\tilde{\nu}$ (cm^{-1}) = 3308 (m), 2973 (m), 1659 (s), 1521 (m), 1367 (m), 1245 (m), 1162 (s), 1083 (m), 1046 (s), 879 (m).

Specific rotation: $[\alpha]_D^{23.2}$ = +11.5 ° cm^3 g^{-1} dm^{-1} (*c* = 1 in $CHCl_3$).

Methyl (3-methyloxetane-3-carbonyl)-L-threoninate (1j): prepared following the general procedure above, using 3-methyloxetane-3-carboxylic acid and methyl-*L*-threoninate as starting materials (isolated yield 60%).



^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 6.52 (d, *J* = 8.3 Hz, 1H), 4.94 (d, *J* = 6.0 Hz, 1H), 4.92 (d, *J* = 6.0 Hz, 1H), 4.64 (dd, *J* = 8.9, 2.3 Hz, 1H), 4.48 (d, *J* = 6.0 Hz, 2H), 4.47 (d, *J* = 6.0 Hz, 2H), 4.42–4.39 (m, 1H), 3.78 (s, 3H), 2.39 (s, 1H), 1.64 (s, 3H), 1.23 (d, *J* = 6.4 Hz, 3H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ = 175.1, 171.4, 79.9, 79.9, 67.8, 57.1, 52.7, 45.4, 22.0, 20.1.

FT-IR: neat, $\tilde{\nu}$ (cm^{-1}) = 3350, 2974, 2882, 1741, 1651, 1529, 1211, 1193, 972.

HR-MS: (ESI+) found: 232.1180 [$M+H^+$], calcd: 232.1185.

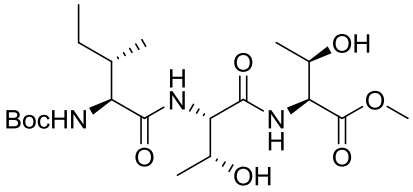
$[\alpha]_D^{23.7}$ = - 9.2 ° cm^3 g^{-1} dm^{-1} (*c* = 1 in $CHCl_3$)

Methyl (*tert*-butoxycarbonyl)-L-isoleucyl-L-threonyl-L-threoninate (1k):

To a solution of *tert*-butoxycarbonyl *L*-threonine (4.38 g, 20.0 mmol) and L-threonine methyl ester hydrochloride (3.39 g, 20.0 mmol) in CH_2Cl_2 (200 mL) was added *N*,*N*-diisopropylethylamine (6.97 mL, 40.0 mmol), 1-hydroxybenzotriazole hydrate (3.24 g, 24.0 mmol) and *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (4.60 g, 24.0 mmol). The reaction mixture was stirred for two days under air at room temperature and thereafter quenched with ammonium chloride solution (saturated, 300 mL). The aqueous layer was extracted with CH_2Cl_2 (4 × 200 mL), the combined organic layers were washed with hydrochloric acid (3 M, 200 mL), sodium bicarbonate solution (saturated, 200 mL) and brine (200 mL), dried over magnesium sulfate and concentrated *in vacuo*. The crude product was purified byflash column chromatography (*n*-hexane/ethyl acetate 1:1 → 1:5) and methyl (*tert*-butoxycarbonyl)-L-threonyl-L-threoninate was obtained as a white solid (3.56 g, 10.0 mmol, 53 %).

To a suspension of methyl (*tert*-butoxycarbonyl)-L-threonyl-L-threoninate (1.50 g, 4.50 mmol) in 1,4-dioxane (45 mL) was added a solution of hydrogen chloride in 1,4-dioxane (4 M, 12.0 mL, 48.0 mmol) and the mixture stirred overnight. When thin layer chromatography (*n*-hexane/ethyl acetate 1:3) showed that the reaction reached completion, the solvent was removed and the resulting white solid washed with Et_2O (3 × 30 mL) and methyl L-threonyl-L-threoninate hydrochloride was used for further coupling without analysis. To a suspension of *tert*-butoxycarbonyl L-isoleucine (1.06 g, 4.58 mmol) and methyl L-threonyl-L-threoninate hydrochloride (1.24 g, 4.58 mmol) in CH_2Cl_2 (30 mL) was added *N*,*N*-diisopropylethylamine (1.60 mL, 9.16 mmol), 1-hydroxybenzotriazole hydrate (0.74 g, 5.50 mmol) and *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (1.05 g, 5.50 mmol). The reaction mixture was stirred two days under air at room temperature and then quenched with

ammonium chloride solution (saturated, 50 mL). The aqueous layer was extracted with CH_2Cl_2 (4 × 50 mL), the combined organic layers were washed with aqueous hydrochloric acid (3 M, 2 × 50 mL), sodium bicarbonate solution (saturated, 2 × 50 mL) and brine (100 mL), dried over magnesium sulfate and concentrated *in vacuo*. The crude product was purified by flash column chromatography (*n*-hexane/ethyl acetate 1:1 → ethyl acetate/methanol 9:1) and **1k** was obtained as a white solid (1.64 g, 3.67 mmol, 80 %).



^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm) = 7.62 (d, 1H, *J* = 8.9 Hz), 7.24 (d, 1H, *J* = 7.6 Hz), 5.26 (d, 1H, *J* = 7.6 Hz), 4.57 (m, 1H), 4.56 (dd, 1H, *J* = 8.9, 3.0 Hz), 4.36 – 4.29 (m, 2H), 4.14 – 4.09 (m, 1H), 4.01 – 3.97 (m, 1H), 3.87 (d, 1H, *J* = 6.6 Hz), 3.75 (s, 3H), 1.90–1.83 (m, 1H), 1.55–1.48 (m, 1H), 1.41 (s, 9H), 1.20 (d, 3H, *J* = 6.5 Hz), 1.18 (d, 3H, *J* = 6.5 Hz), 1.17 – 1.09 (m, 1H), 0.93 (d, 3H, *J* = 6.8 Hz), 0.89 (t, 3H, *J* = 7.4 Hz).

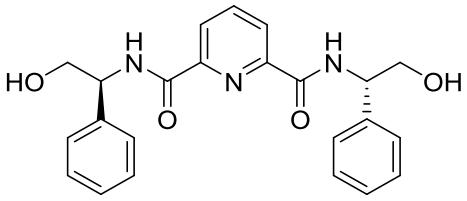
^{13}C-NMR (151 MHz, $CDCl_3$) δ (ppm) = 172.9, 171.3, 156.3, 80.6, 68.1, 67.3, 59.9, 58.2, 57.8, 52.7, 37.0, 31.1, 28.4, 25.0, 20.2, 18.4, 15.8, 11.5.

HR-MS: (ESI+) $C_{20}H_{38}N_3O_8^+$ $(M+H)^+$ calc.: 448.2659, det.: 448.2655.

FT-IR: neat, $\tilde{\nu}$ (cm^{-1}) = 3301 (m), 2972 (m), 1642 (s), 1517 (s), 1367 (m), 1244 (m), 1162 (s), 1018 (m), 863 (m).

Specific rotation: $[\alpha]_D^{24.0}$ = -37.7 ° cm^3 g^{-1} dm^{-1} (*c* = 1 in $CHCl_3$).

N^2,*N*^{6}-bis((S)-2-hydroxy-1-phenylethyl)pyridine-2,6-dicarboxamide (1l): [4]



^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.62 (d, *J* = 7.4 Hz, 2H), 8.23 (d, *J* = 7.8 Hz, 2H), 7.93 (t, *J* = 7.8 Hz, 1H), 7.41 – 7.19 (m, 10H), 5.21 (dt, *J* = 7.2, 4.9 Hz, 1H), 3.94 (t, *J* = 8.3 Hz, 2H), 3.14 (s, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 163.6, 148.5, 139.1, 138.8, 128.9, 127.9, 126.6, 125.1, 66.3, 55.8.

FT-IR: neat, $\tilde{\nu}$ (cm^{-1}) = 3303, 1653, 1524, 1445, 1241, 1071, 1030, 842, 751, 698.

HR-MS: (ESI^+) $C_{23}H_{24}N_3O_4^+$ $[M+H^+]$ calc.: 406.1767; found: 406.1765.

Specific rotation: $[\alpha]_D^{24.0}$ = - 94.7 ° cm^3 g^{-1} dm^{-1} (*c* = 1 in $CHCl_3$).

Flow scale-up experiment

A solution of Deoxo-Fluor® (60 mL, 50% in toluene) in CH_2Cl_2 (440 mL) and a solution of methyl benzoyl-L-threoninate (**1a**, 126.5 mmol, 30 g) in CH_2Cl_2 (500 mL) were combined at a tee mixer (each stream delivered at 3.0 mL min^{-1} flow rate) and reacted at rt in a 10 mL PFA reactor coil. The combined stream was then combined with a saturated $NaHCO_3$ aqueous solution (flow rate of 9 mL min^{-1}) and the solution passed through a magnetically-agitated mixing column prior to reaching an in-house liquid/liquid separator (**Figure S1**), from which the organic phase was collected and the aqueous waste discarded. Using this specific system, 10.2 g h^{-1} of (4S,5S)-5-methyl-2-phenyl-4,5-dihydro-oxazole-4-carboxylic acid methyl ester (**2a**) was generated in a single continuous run over 2 h 40 min, to produce 27.2 g of **2a** (98% yield).

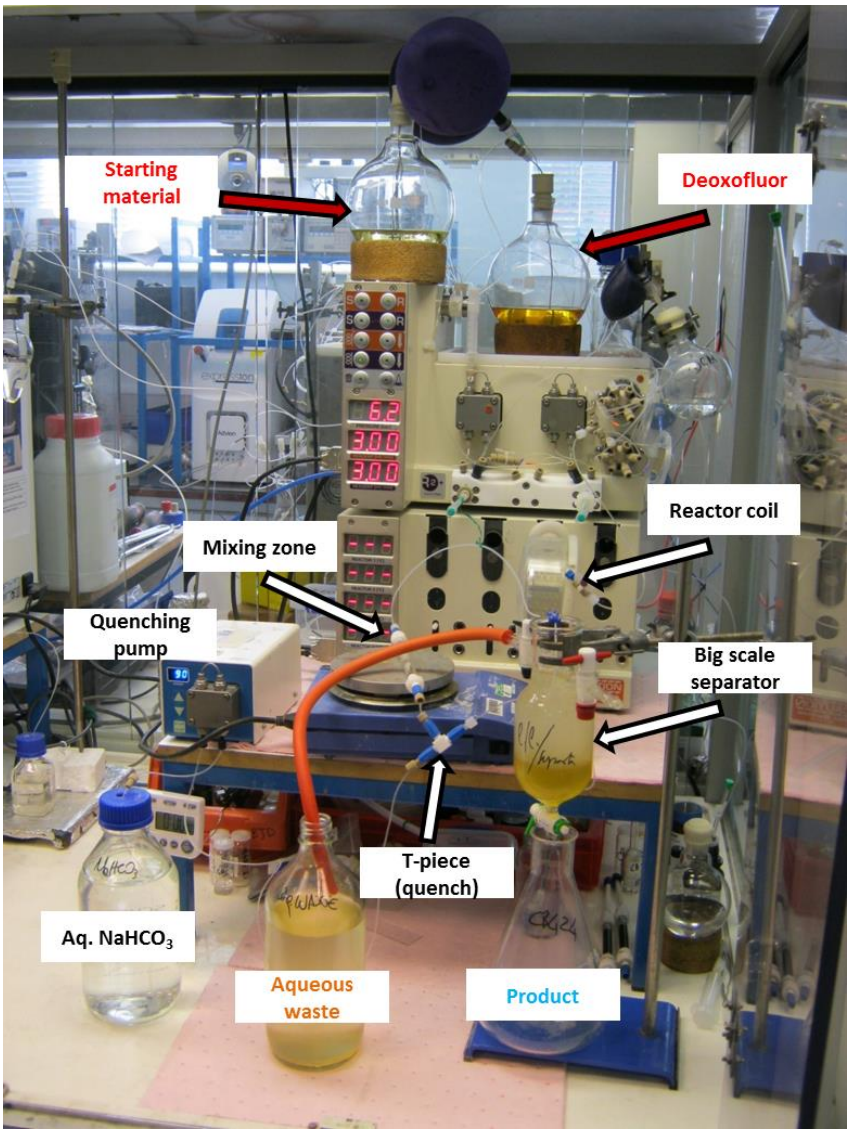
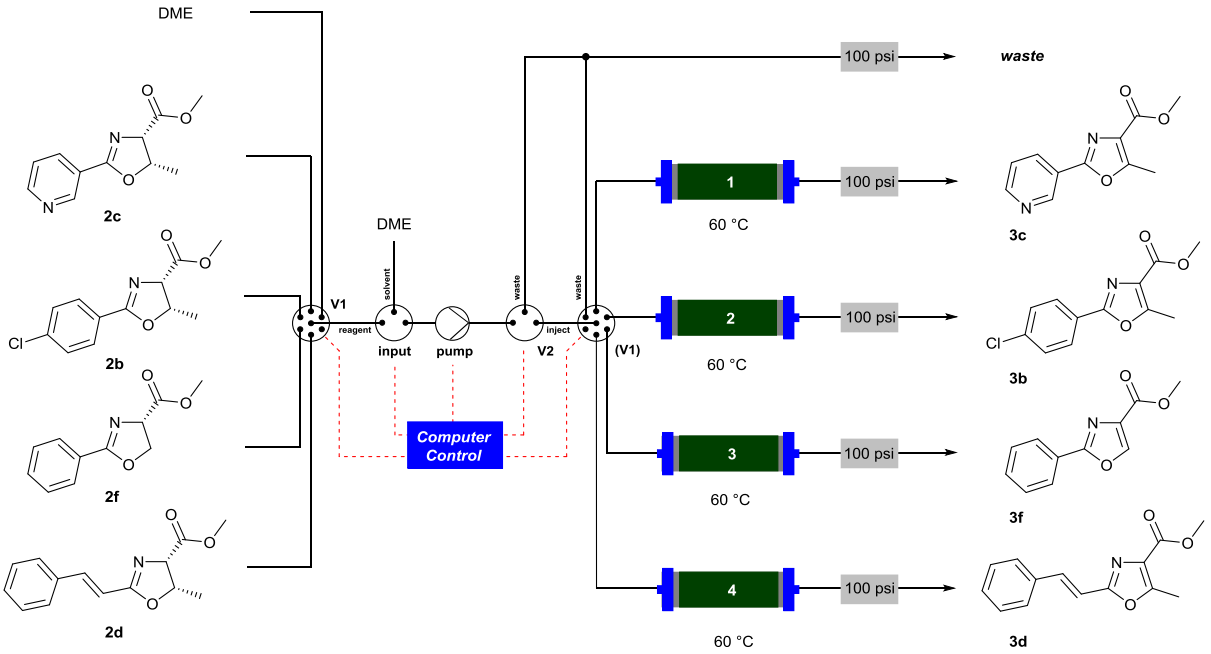
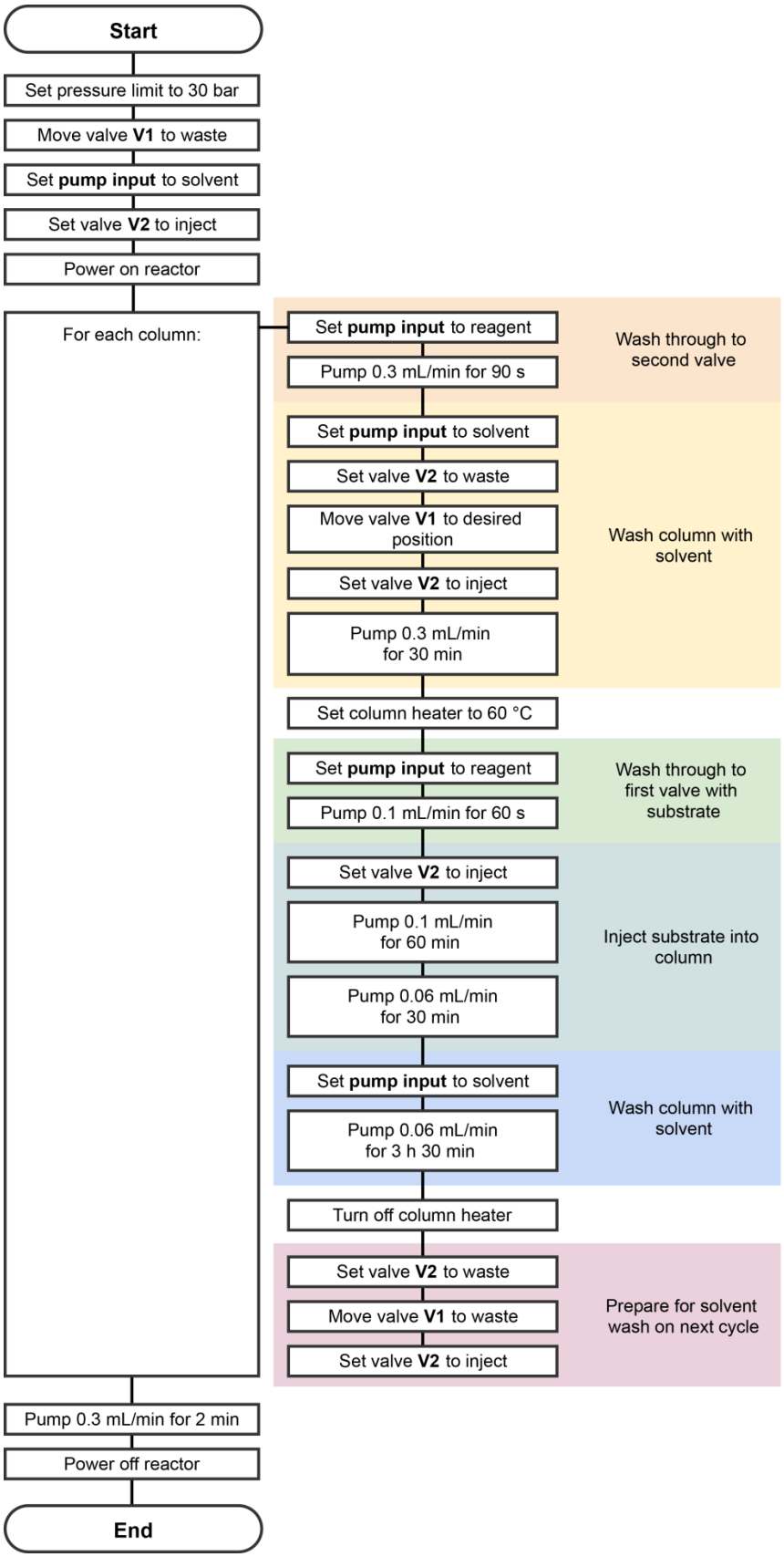


Figure S1. Picture for the scale up experiment set-up.

Automation



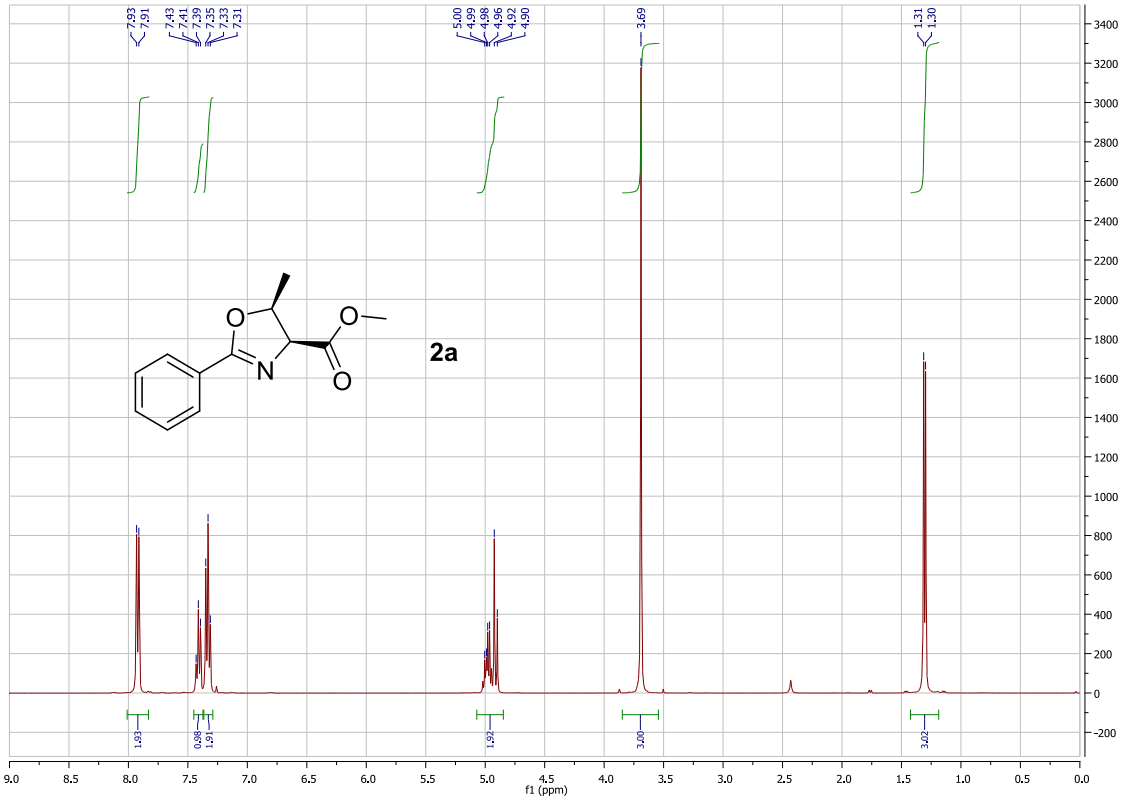
The Vapourtec R2+/R4 flow system (**pump**, **input** and **V2**) and multi-port switching valve (**V1**; Valco Vici Microelectrically actuated 10-position switching valve) were connected to the Raspberry Pi (Model B) computer via its ethernet port using a Brainboxes Ethernet-to-RS232 adapter (ES-257), which was configured according to the devices' baud-rate requirements (19200 bps for the R2+/R4 and 9600 bps for the valve), and a standard networking switch (Netgear ProSafe GS105). Installed on the computer was the control software platform (http://github.com/richardingham/octopus) running the control sequence (https://gist.github.com/richardingham/357eff35147ccd342dd7). The control sequence is depicted graphically below:

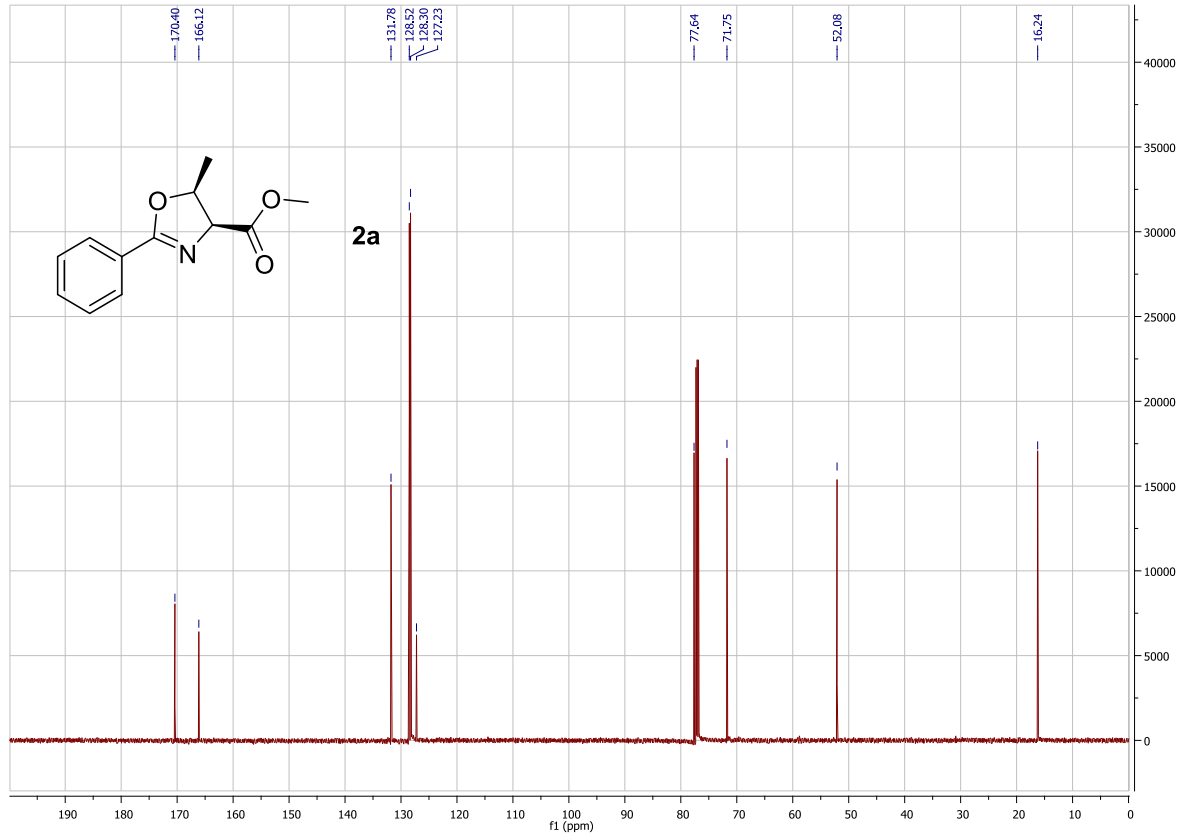

Start
Set pressure limit to 30 bar
Move valve V1 to waste
Set pump input to solvent
Set valve V2 to inject
Power on reactor
For each column:
Set pump input to reagent
Pump 0.3 mL/min for 90 s
Wash through to second valve
Set pump input to solvent
Set valve V2 to waste
Move valve V1 to desired position
Set valve V2 to inject
Pump 0.3 mL/min for 30 min
Wash column with solvent
Set column heater to 60 °C
Set pump input to reagent
Pump 0.1 mL/min for 60 s
Wash through to first valve with substrate
Set valve V2 to inject
Pump 0.1 mL/min for 60 min
Pump 0.06 mL/min for 30 min
Inject substrate into column
Set pump input to solvent
Pump 0.06 mL/min for 3 h 30 min
Wash column with solvent
Turn off column heater
Set valve V2 to waste
Move valve V1 to waste
Set valve V2 to inject
Prepare for solvent wash on next cycle
Pump 0.3 mL/min for 2 min
Power off reactor
End

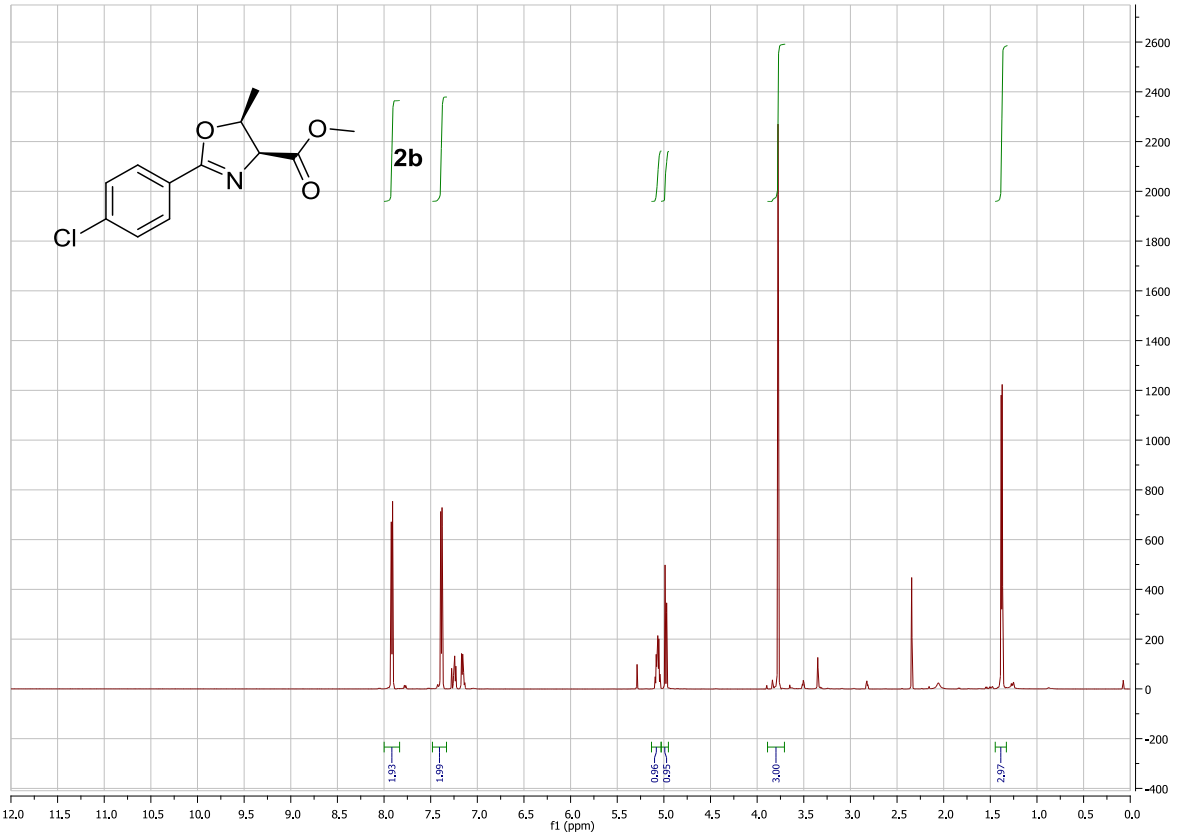
ICP-MS analysis

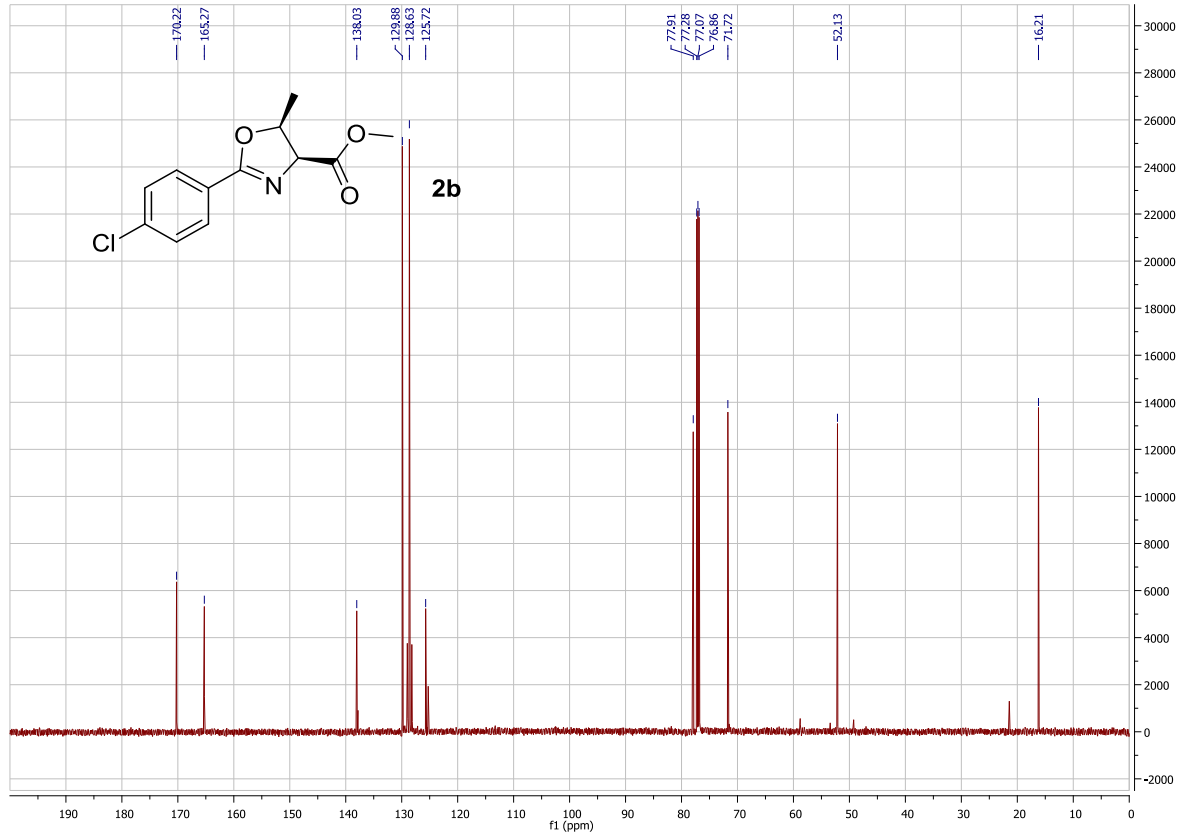
	Conc ppb Mn
Blank	
Standard 1	0.1
Standard 2	1.0
Standard 3	10.0
Standard 4	9.9
Standard 5	100.0
SPS-SW2 10x	9.9
Blk 1 HNO3	0.0
Blk 2 HNO3	0.0
3a	1.1
3f	3.6
SPS-SW2 10x	10.0

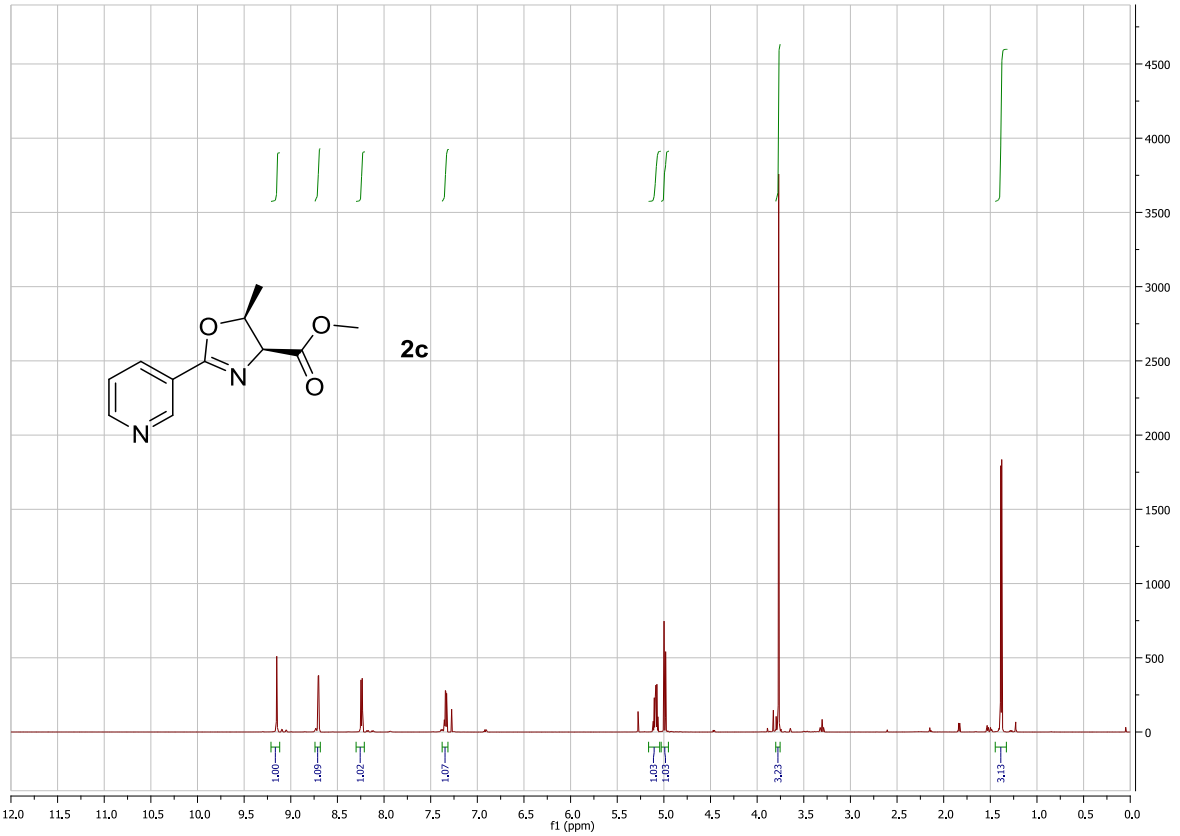
^{1}H-NMR and ^{13}C-NMR spectra






2b
Cl
O
N
O
O
1.93
1.99
0.96
0.95
3.00
2.97
f1 (ppm)


170.22
165.27
138.03
129.88
128.63
125.72
77.91
77.28
77.07
76.86
71.72
52.13
16.21
2b
Cl
O
N
O
O
f1 (ppm)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1.00
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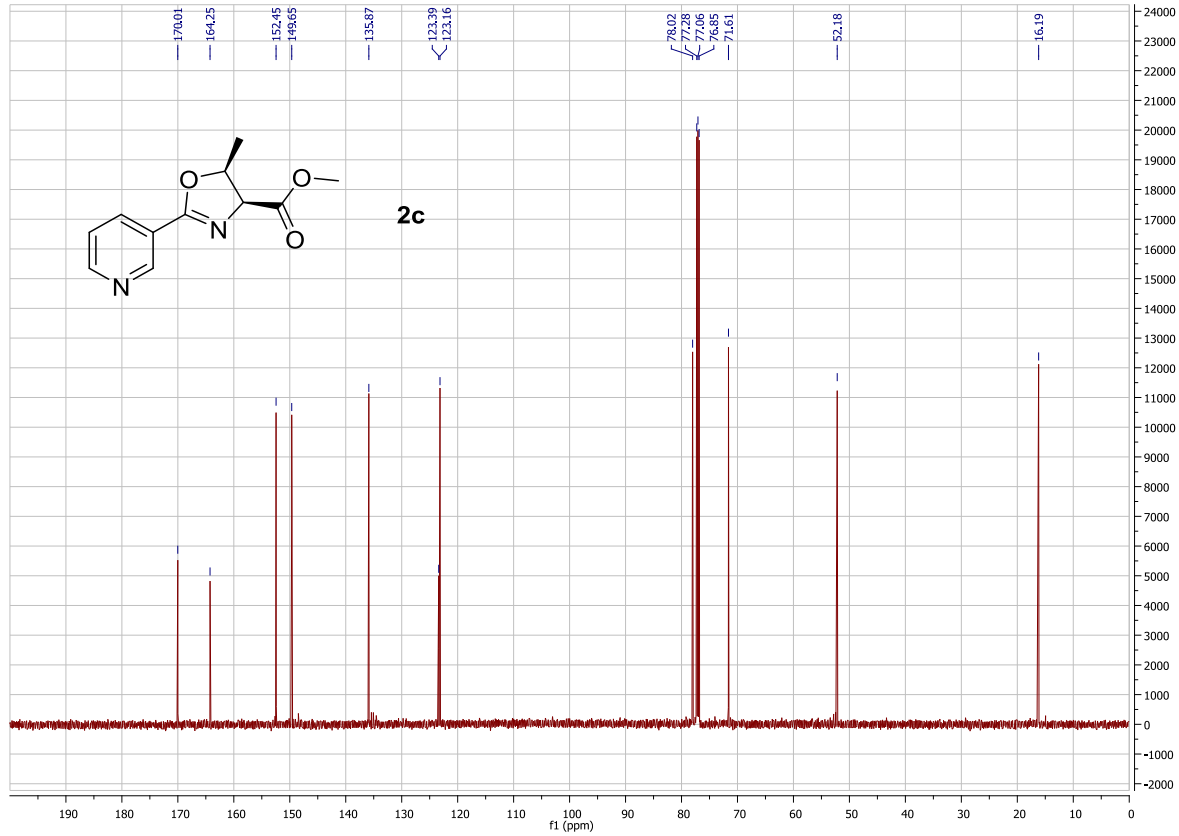
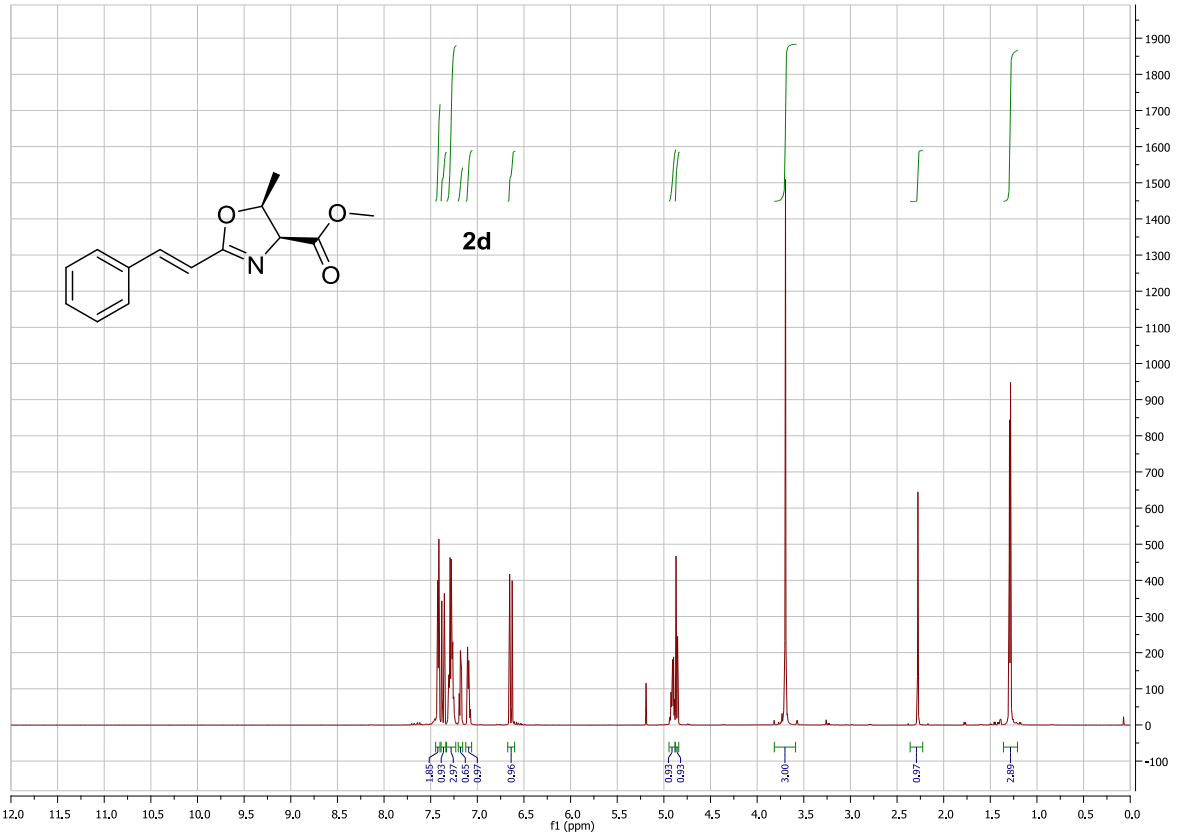
1.07
1.03
1.03
3.23
3.13
f1 (ppm)


170.01
164.25
152.45
149.65
135.87
123.39
123.16
78.02
77.28
77.06
76.85
71.61
52.18
16.19
2c
f1 (ppm)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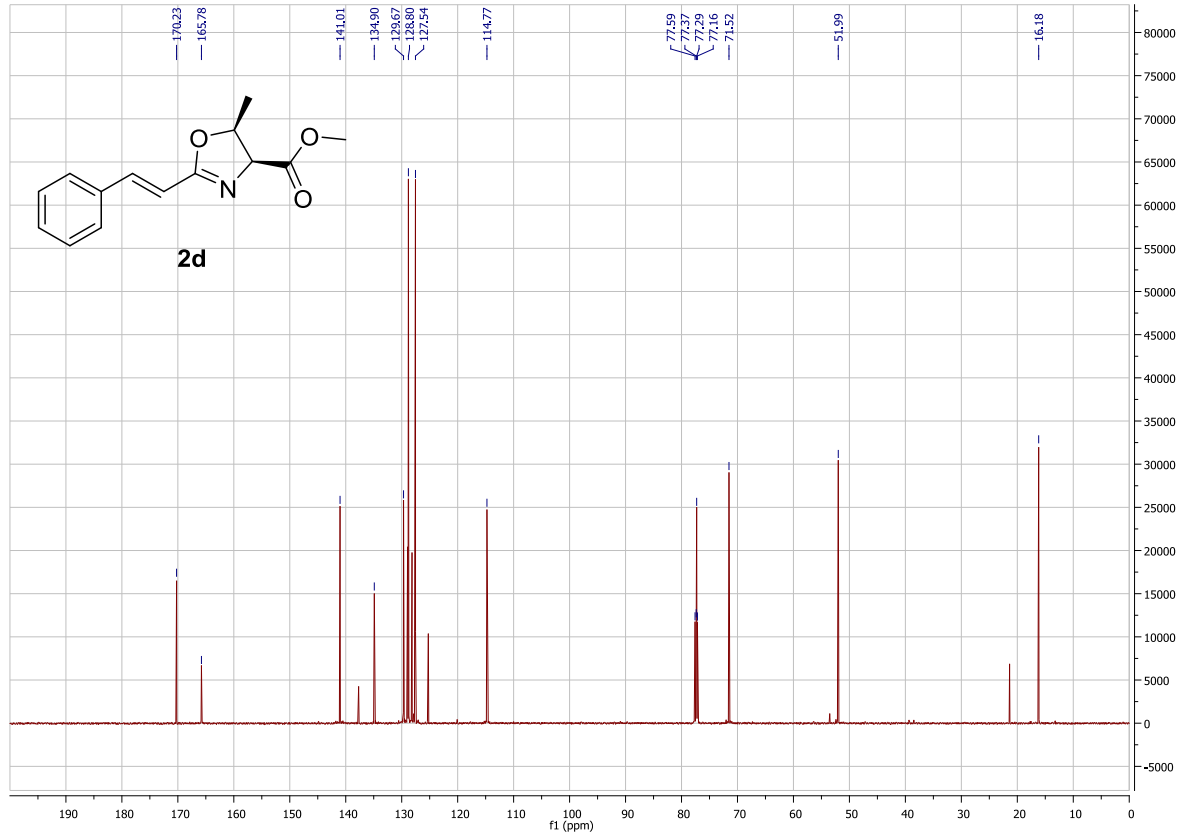
0.97
0.96
0.93
0.93
3.00
0.97
2.89
f1 (ppm)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165.78
141.01
134.90
129.67
128.80
127.54
114.77
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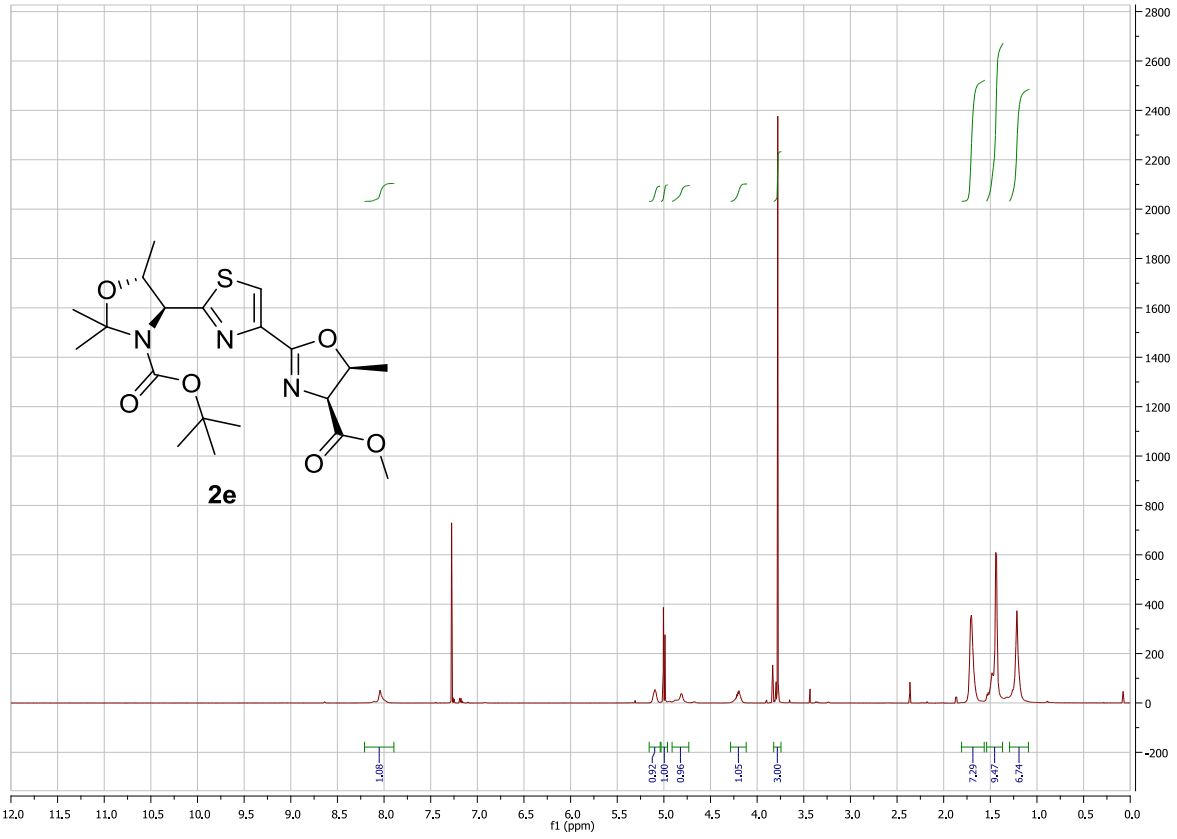
77.37
77.29
77.16
71.52
51.99
16.18
2d
f1 (ppm)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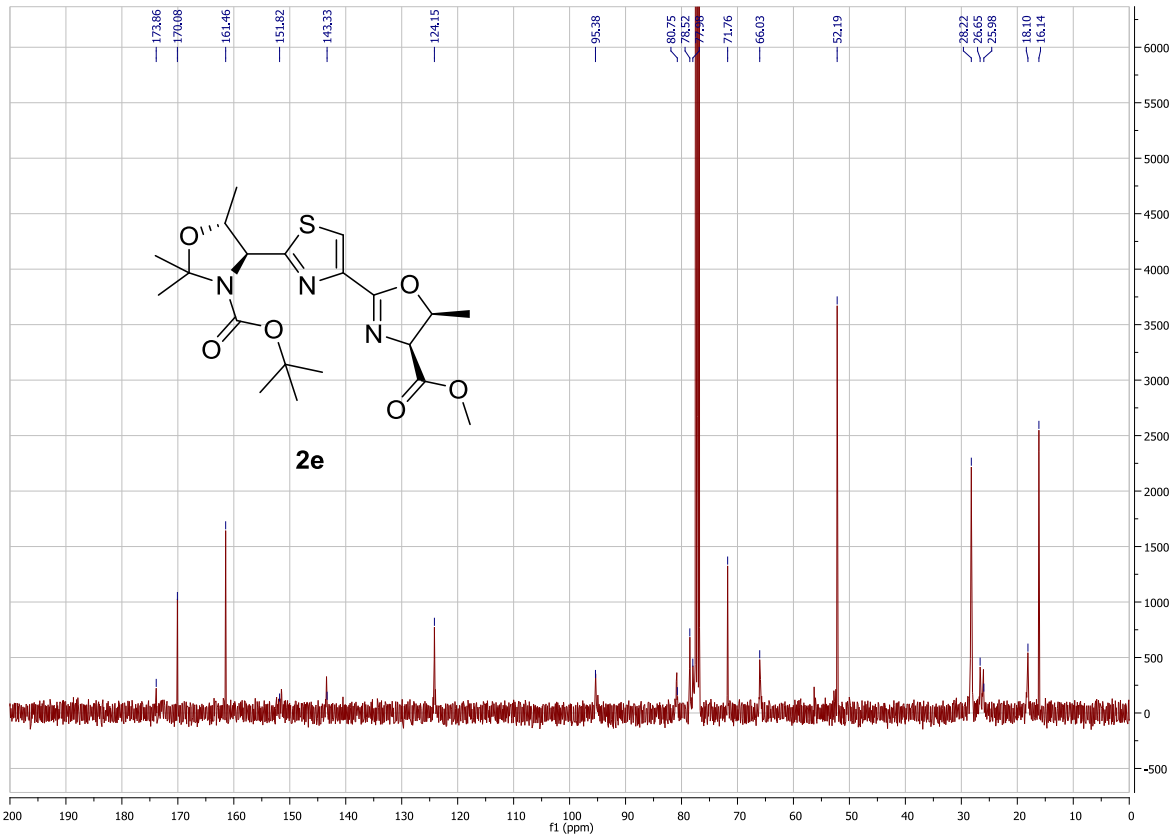
1.08
0.92
1.00
0.96
1.05
3.00
7.29
9.47
6.74
f1 (ppm)


173.86
170.08
161.46
151.82
143.33
124.15
95.38
80.75
78.52
71.76
66.03
52.19
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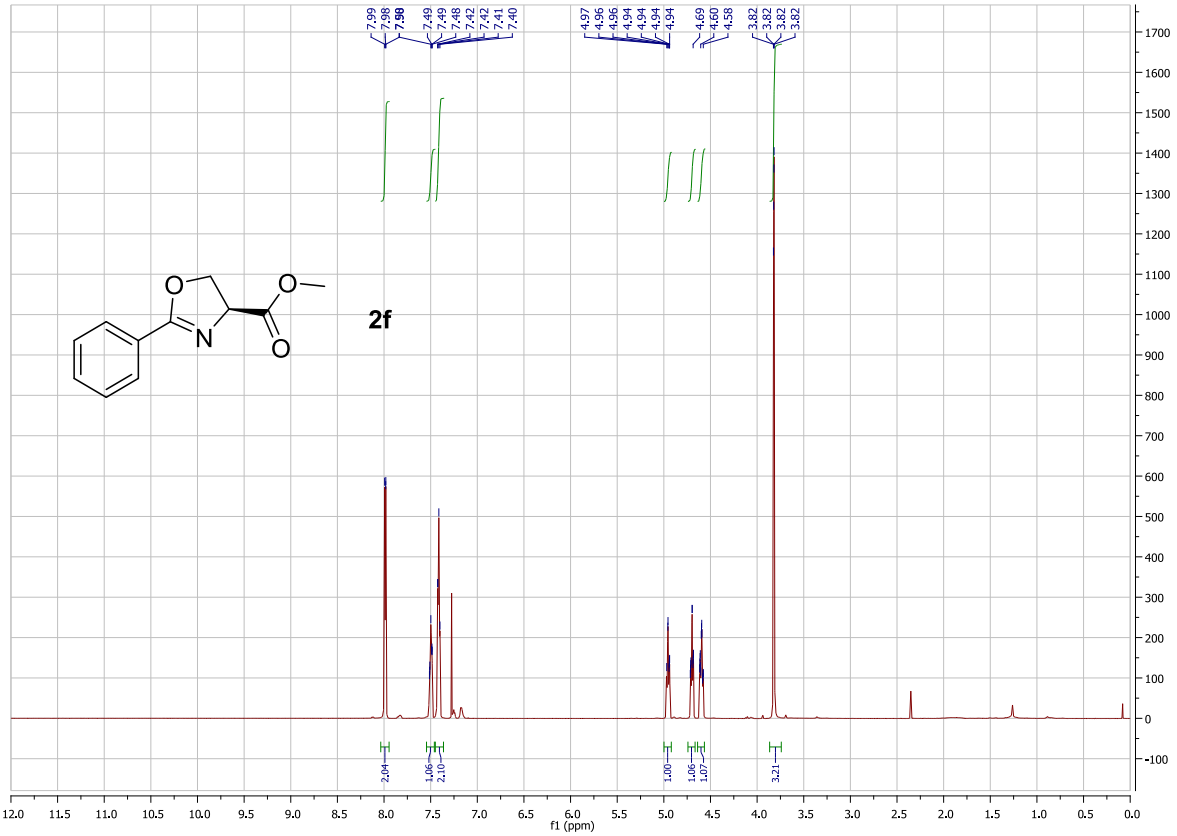
25.98
18.10
16.14
2e
f1 (ppm)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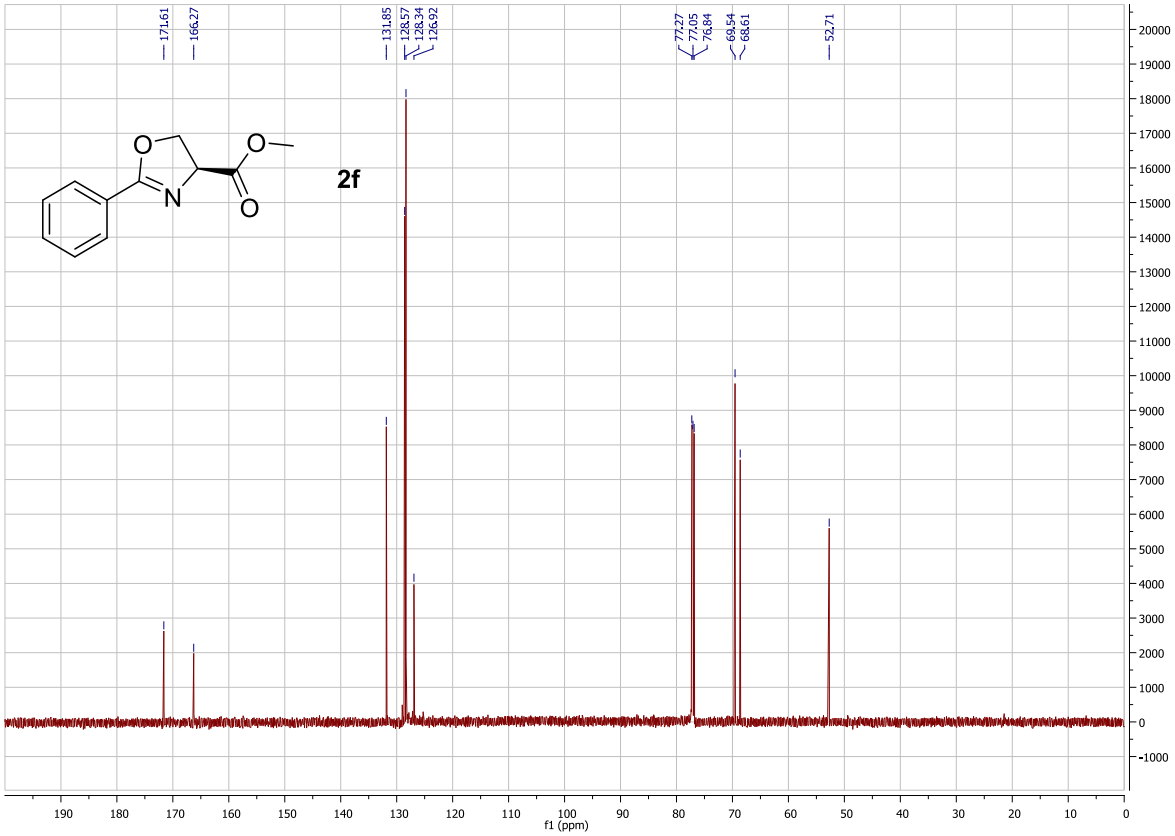
7.98
7.49
7.49
7.48
7.42
7.42
7.41
7.40
4.97
4.96
4.96
4.94
4.94
4.94
4.94
4.69
4.60
4.58
3.82
3.82
3.82
3.82
2f
2.04
1.06
2.10
1.00
1.06
1.07
3.21
f1 (ppm)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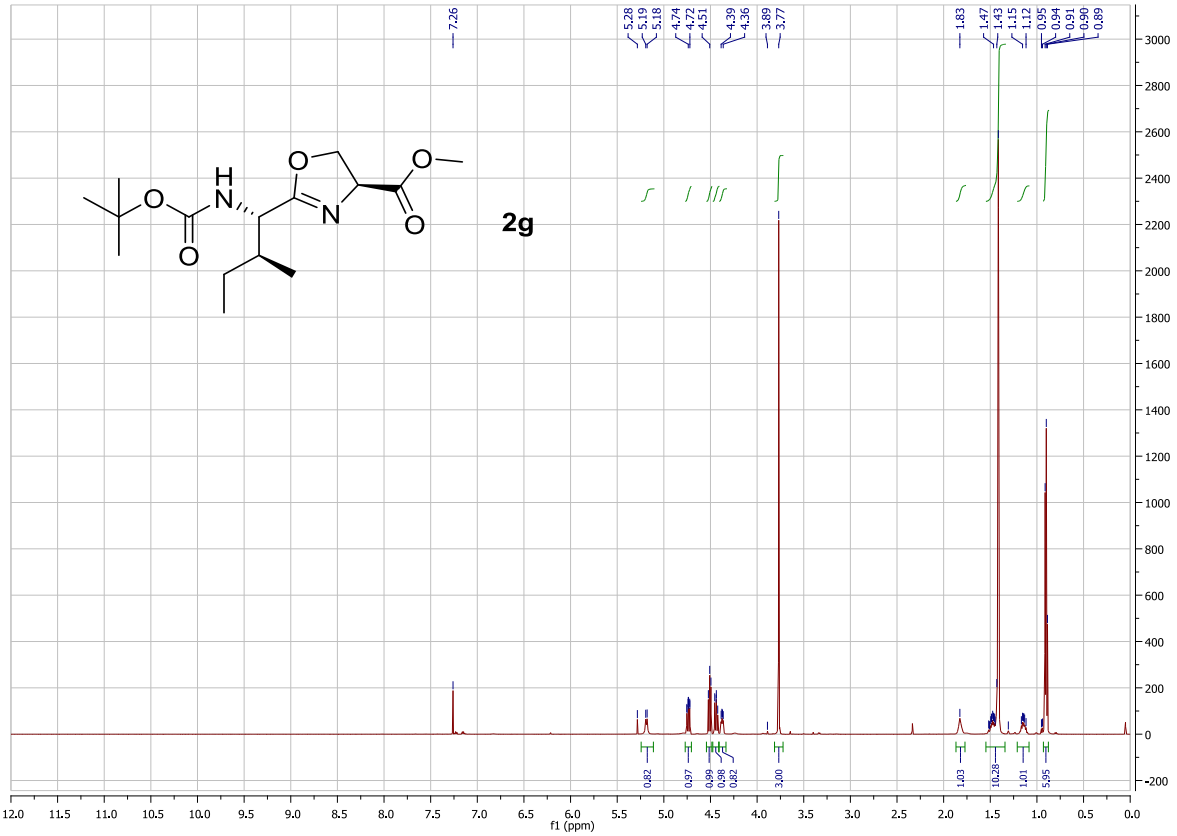
128.57
128.34
126.92
77.27
77.05
76.84
69.54
68.61
52.71
2f
f1 (ppm)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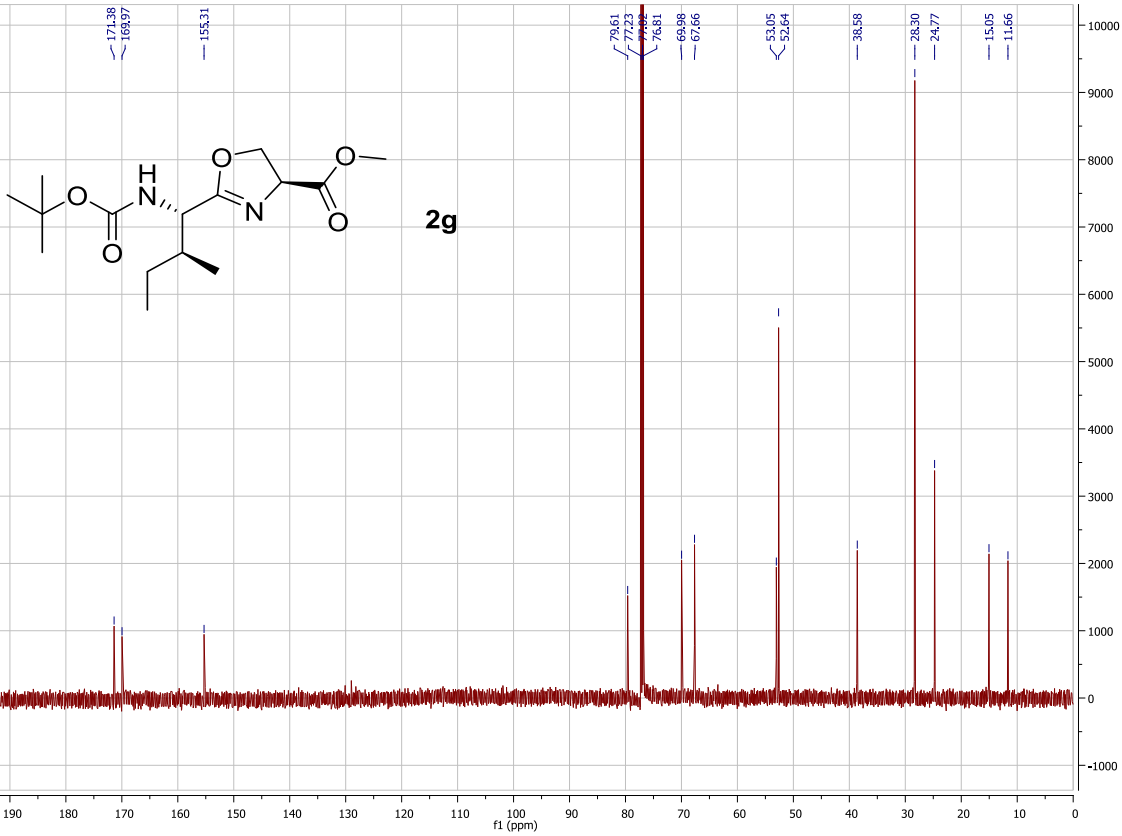
5.28
5.19
5.18
4.74
4.72
4.51
4.39
4.36
3.89
3.77
1.83
1.47
1.43
1.15
1.12
0.95
0.94
0.91
0.90
0.89
0.82
0.97
0.99
0.98
0.82
3.00
1.03
16.28
1.01
5.95
f1 (ppm)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169.97
155.31
79.61
77.23
77.02
76.81
69.98
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53.05
52.64
38.58
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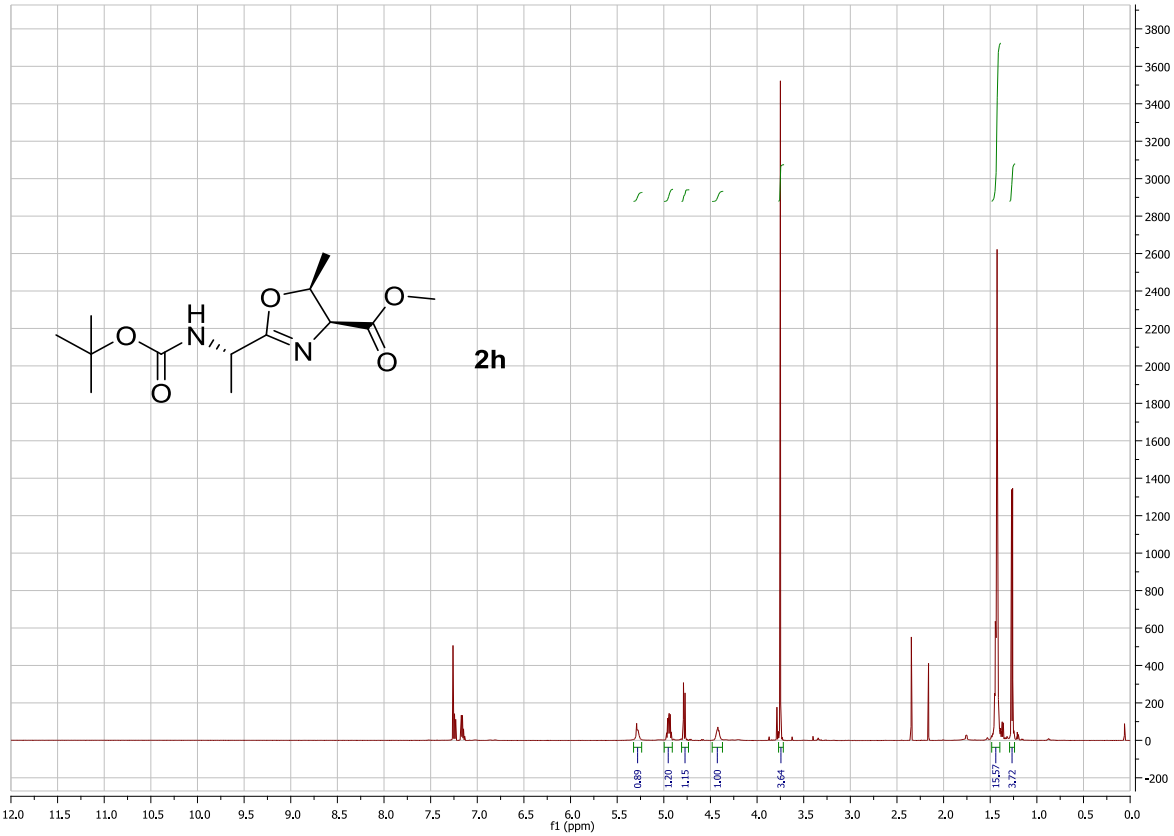
24.77
15.05
11.66
f1 (ppm)

2g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1.00
3.64
15.57
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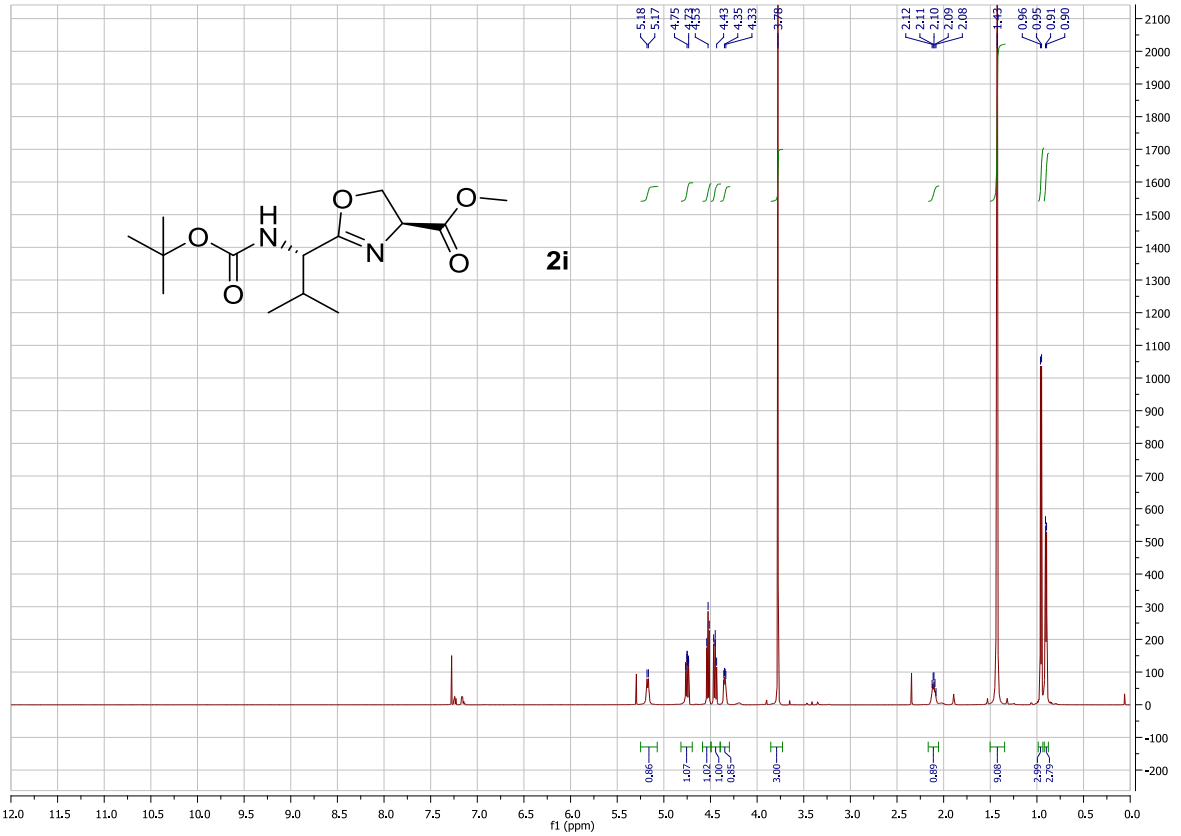
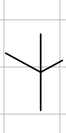
f1 (ppm)

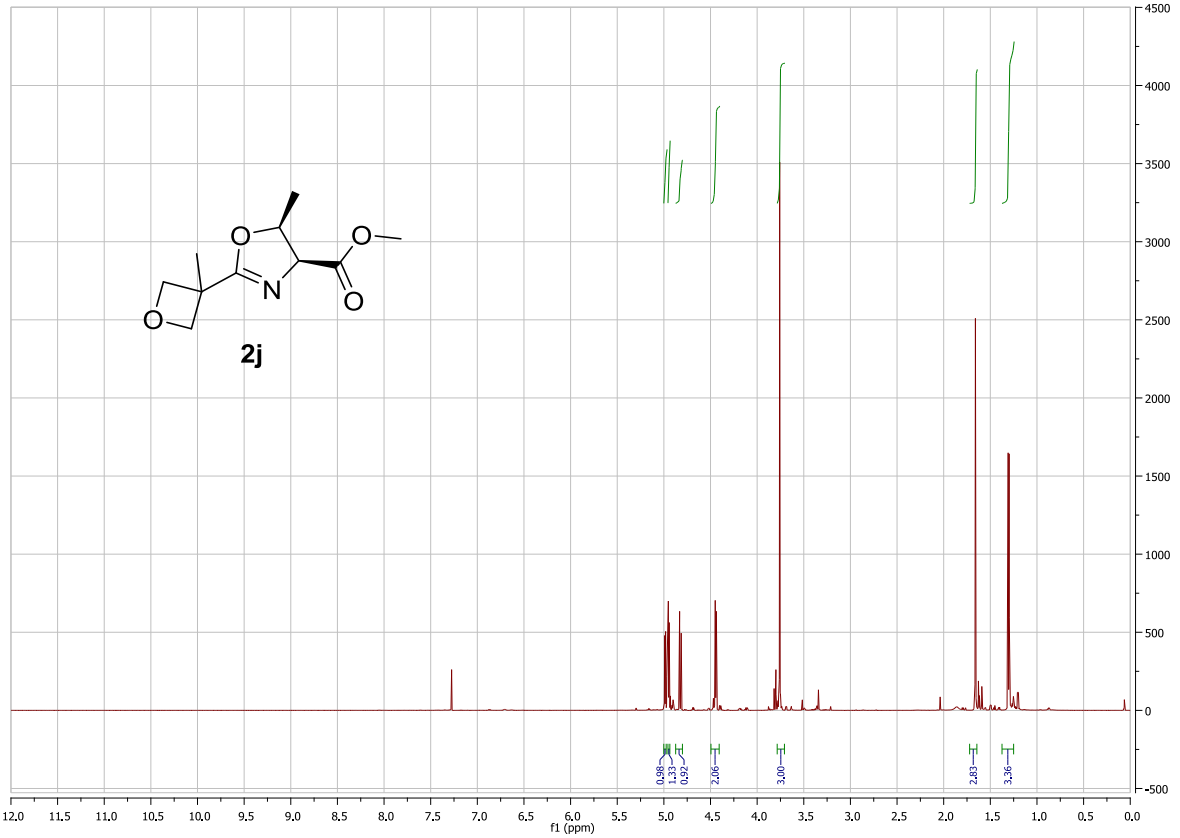

5.18
5.17
4.75
4.73
4.53
4.43
4.35
4.33
3.78
2.12
2.11
2.10
2.09
2.08
1.43
0.96
0.95
0.91
0.90
0.86
1.07
1.02
1.00
0.85
3.00
0.89
9.08
2.99
2.79
f1 (ppm)



2i

171.41
170.07
155.47
79.61
77.24
77.03
76.82
70.06
67.68
53.66
52.63
31.75
28.28
18.72
17.23
f1 (ppm)

2i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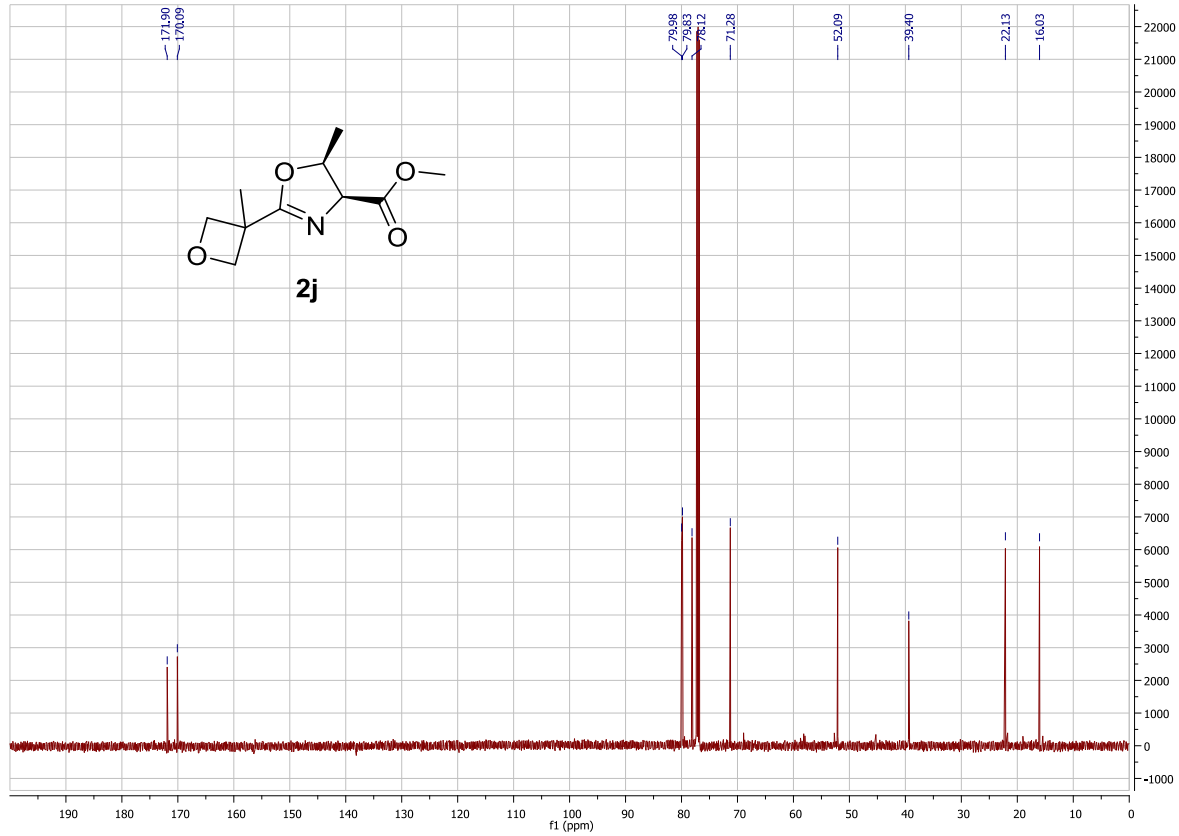
1.33
0.92
2.06
3.00
2.83
3.36
f1 (ppm)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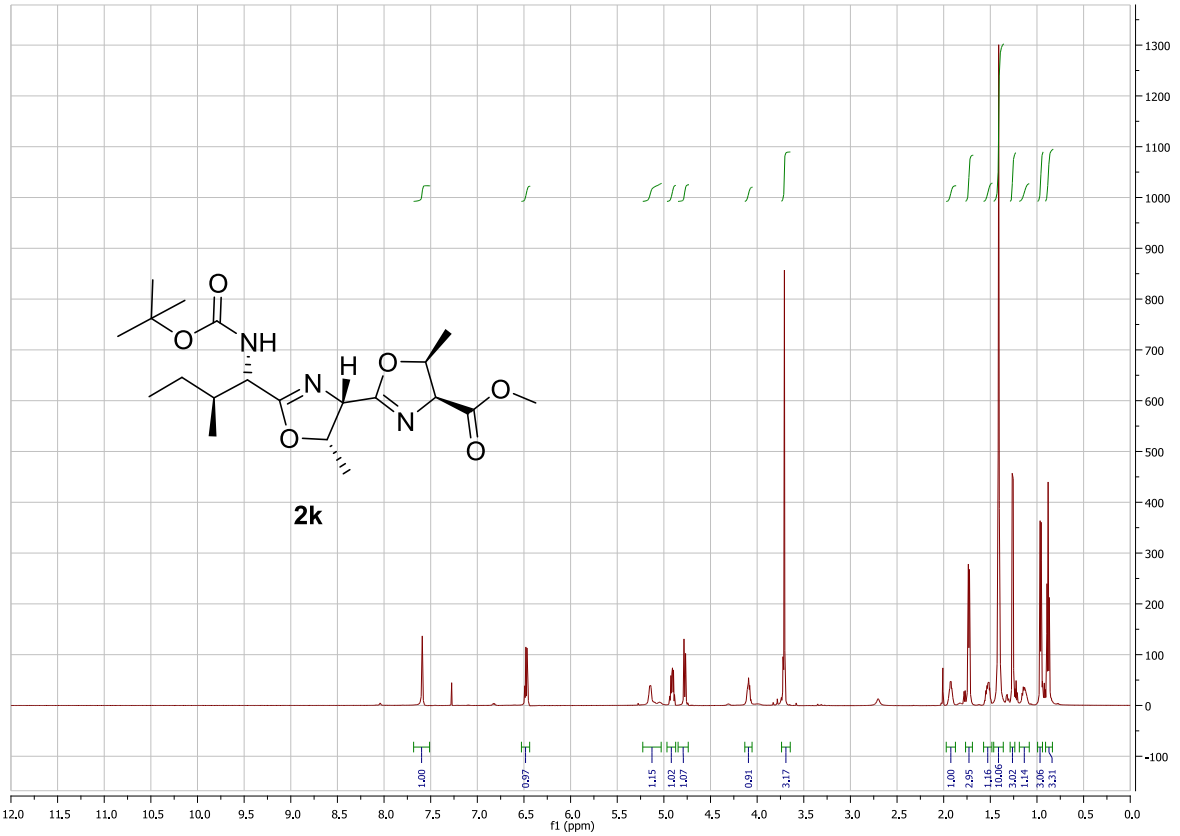
170.09
79.98
79.83
78.12
71.28
52.09
39.40
22.13
16.03
2j
f1 (ppm)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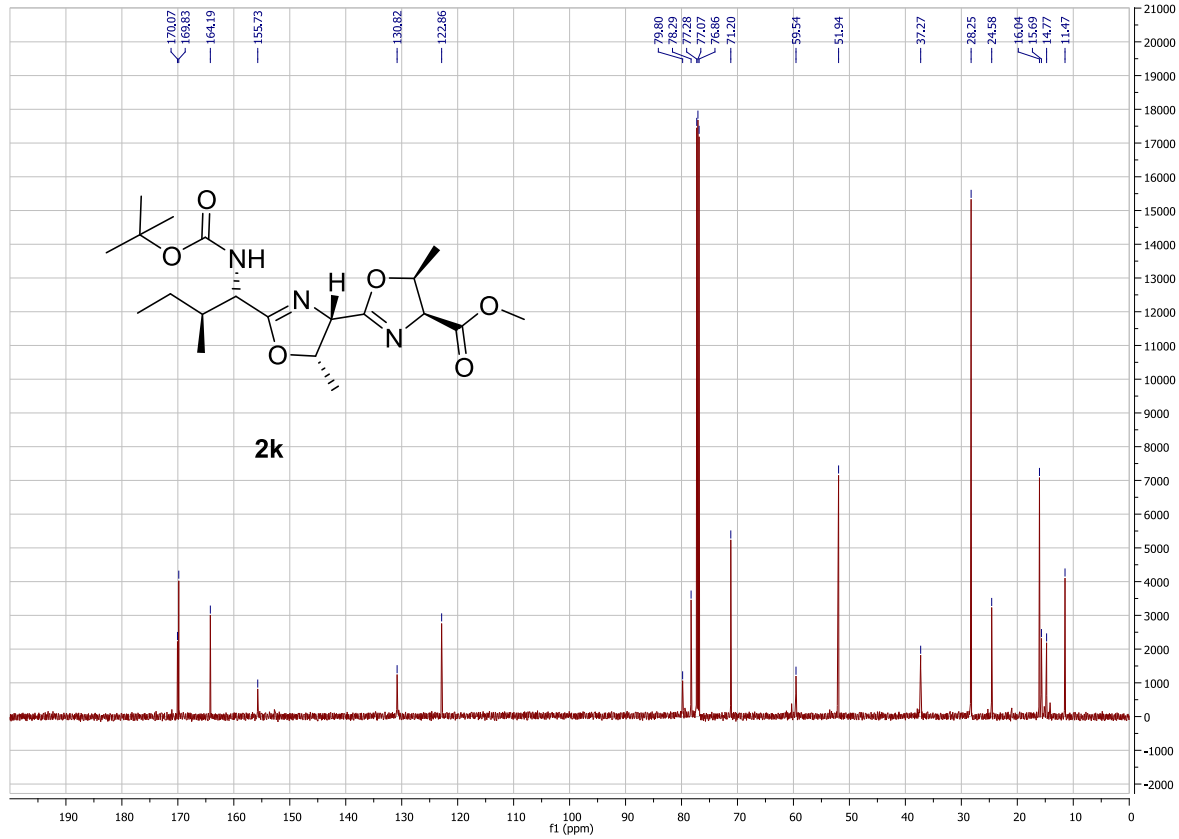
f1 (ppm)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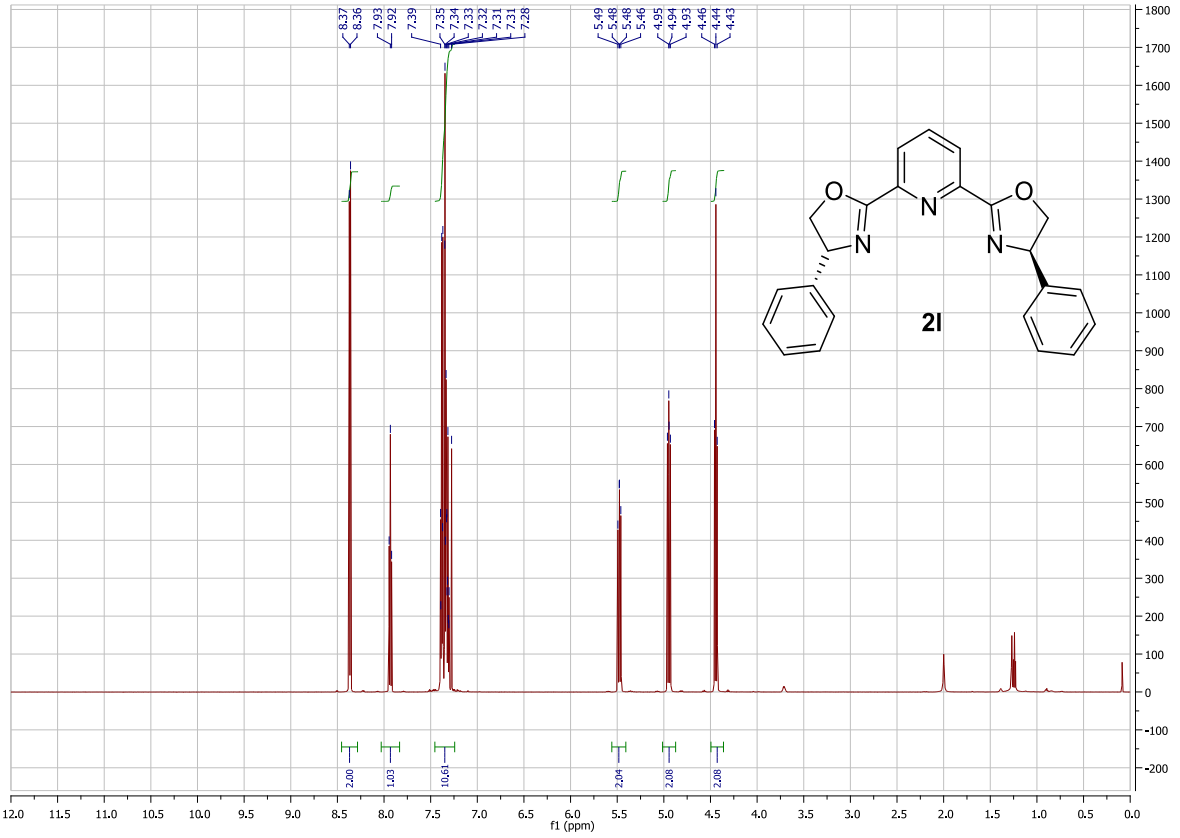
155.73
130.82
122.86
79.80
78.29
77.28
77.07
76.86
71.20
59.54
51.94
37.27
28.25
24.58
16.04
15.69
14.77
11.47
2k
f1 (ppm)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7.92
7.39
7.35
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7.33
7.32
7.31
7.31
7.28
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5.48
5.48
5.46
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4.94
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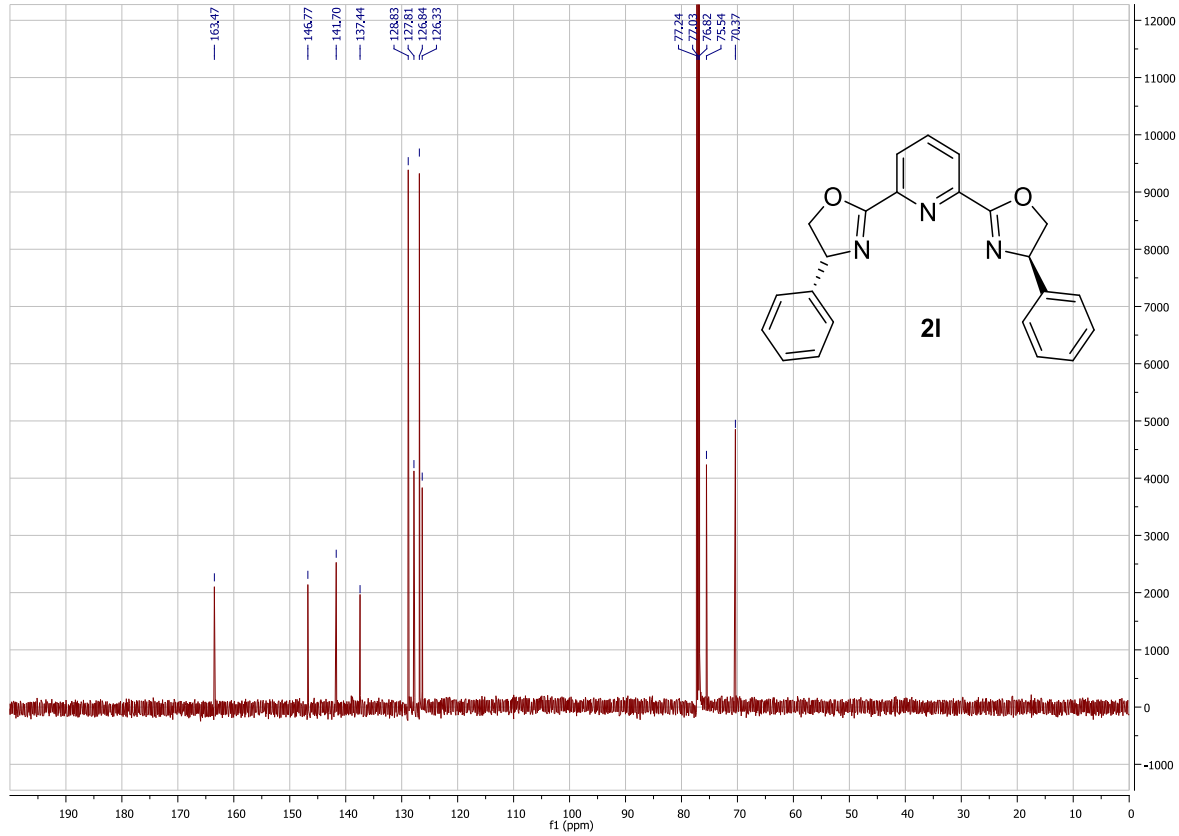
2.04
2.08
2.08
f1 (ppm)
2l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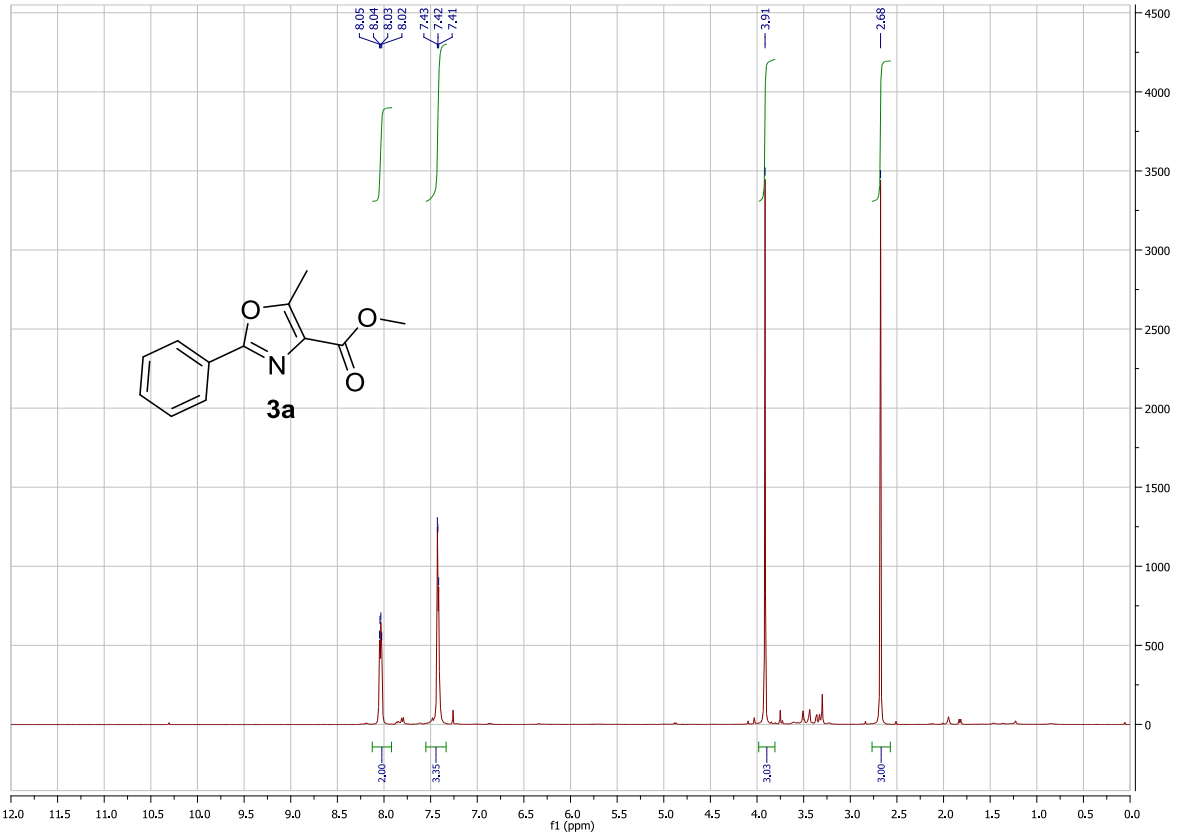
126.84
126.33
77.24
77.03
76.82
75.54
70.37
f1 (ppm)
2l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8.04
8.03
8.02
7.43
7.42
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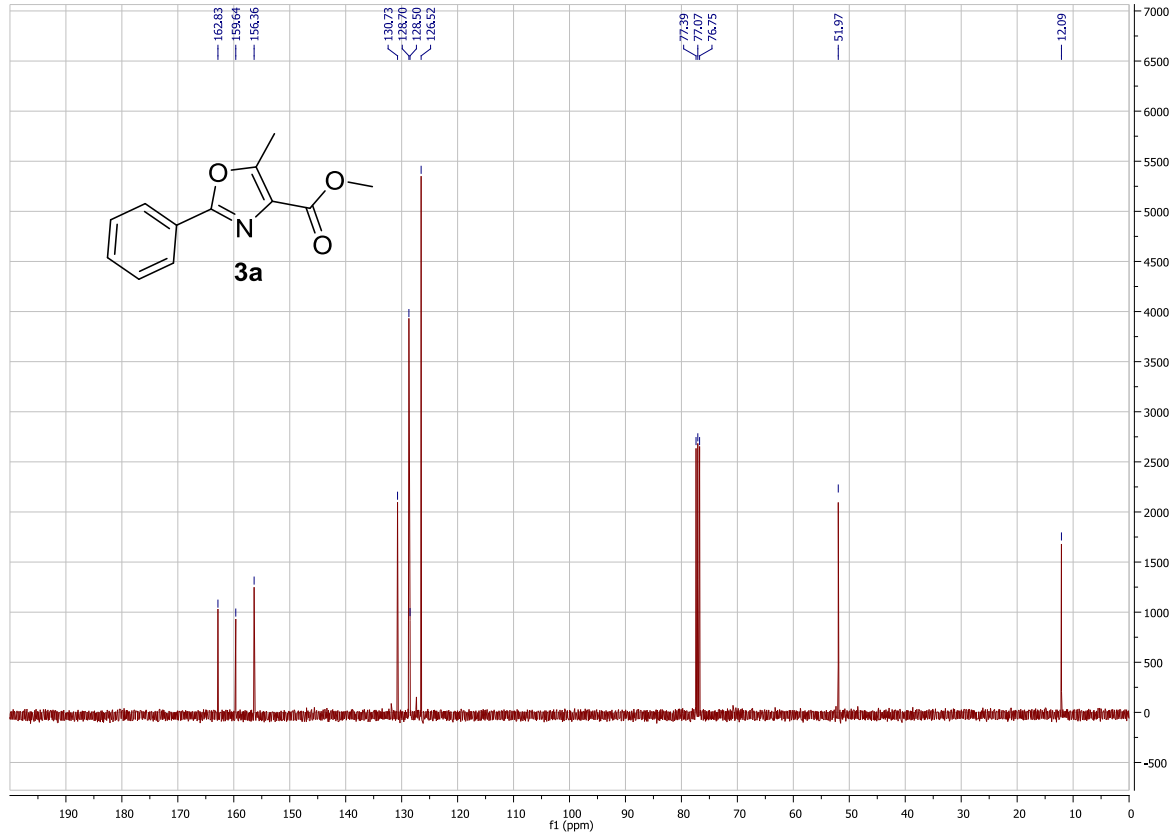
3.91
2.68
O
O
N
O
3a
2.00
3.35
3.03
3.00
f1 (ppm)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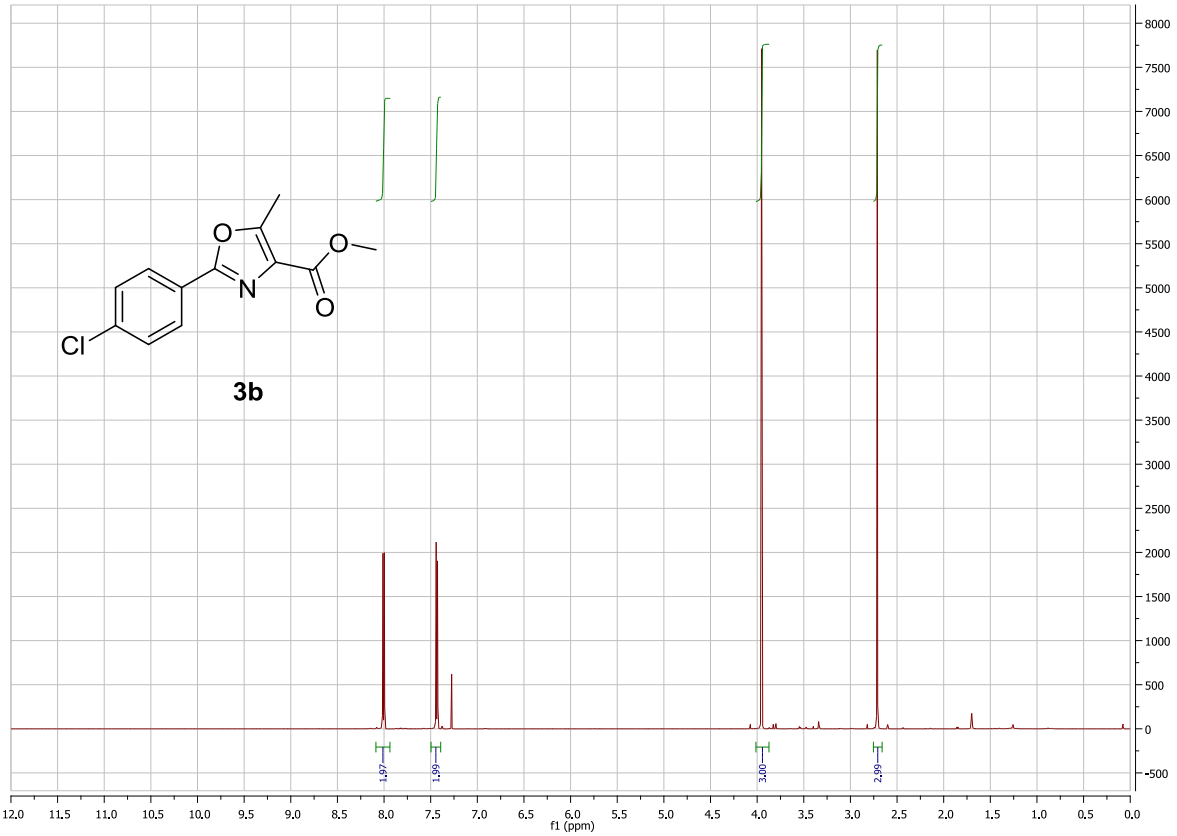
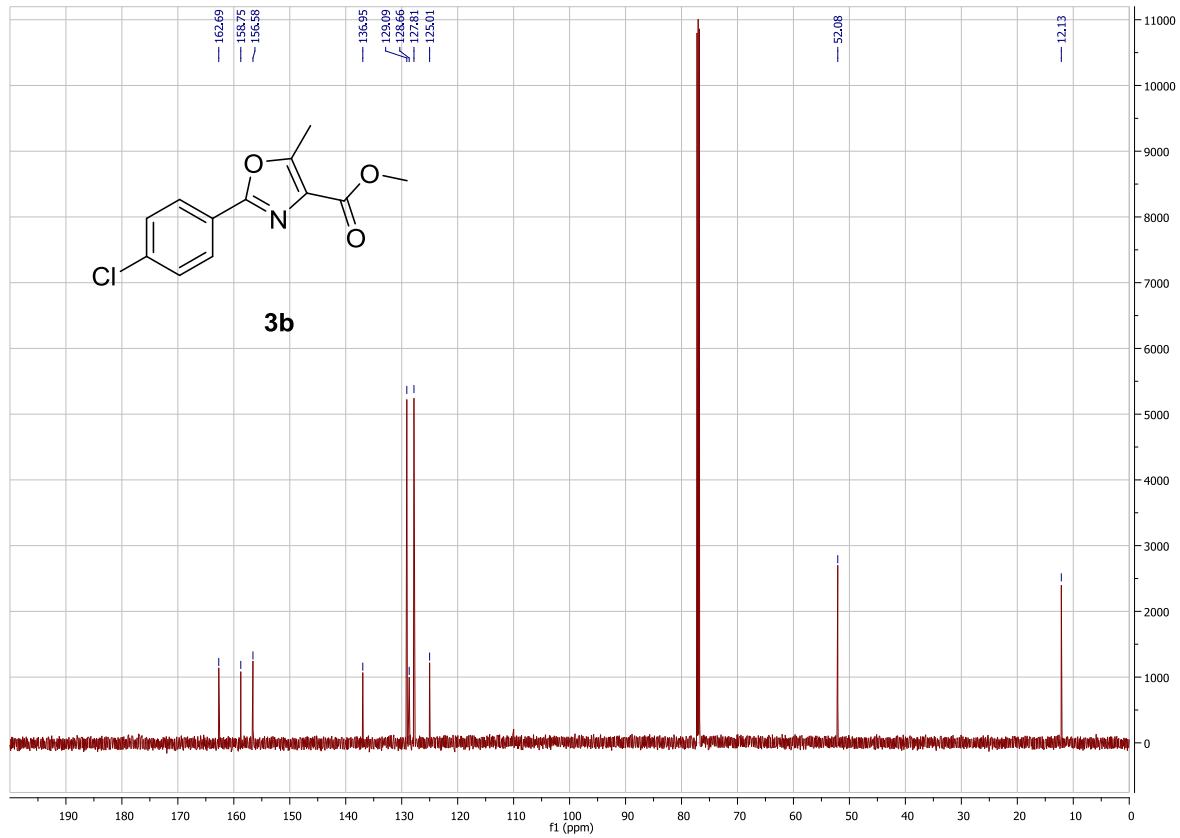
77.07
76.75
51.97
12.09
O
O
N
O
3a
f1 (ppm)


O
O
N
O
Cl
3b
1.97
1.99
3.00
2.99
f1 (ppm)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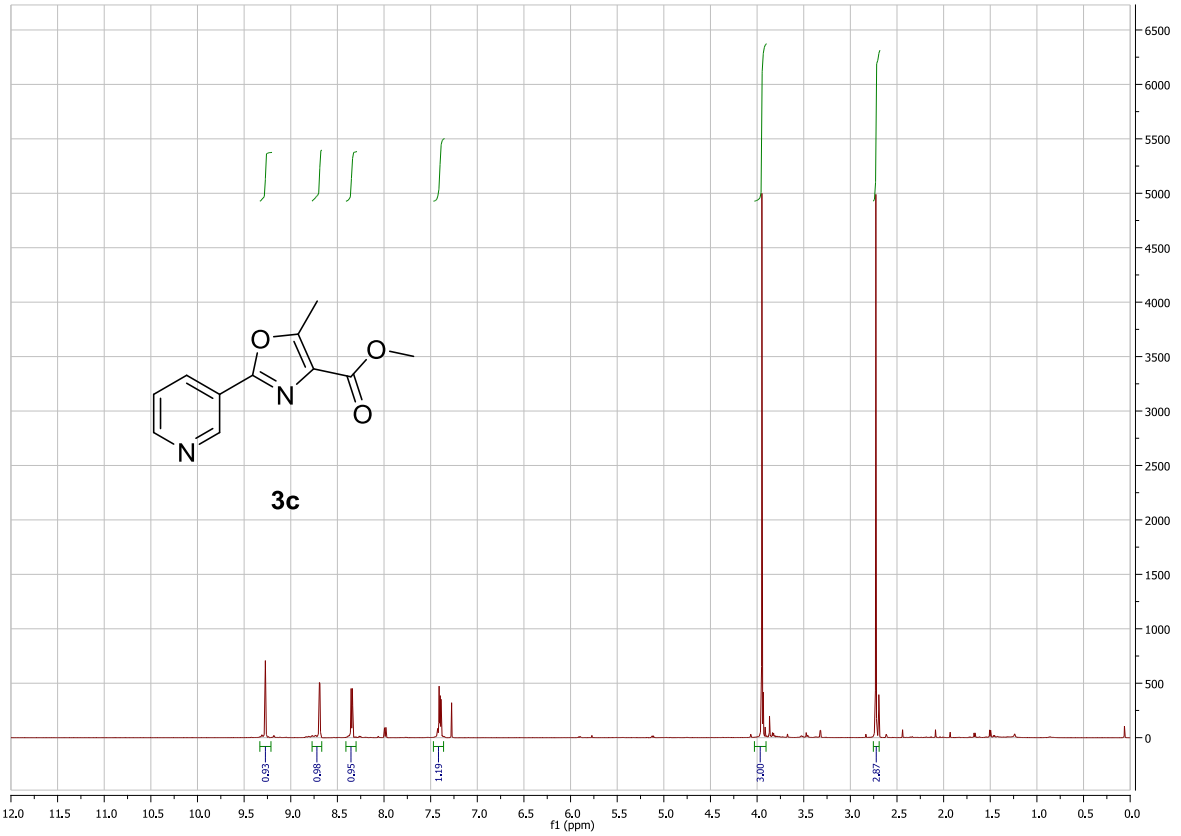
12.13
O
O
N
O
Cl
3b
f1 (ppm)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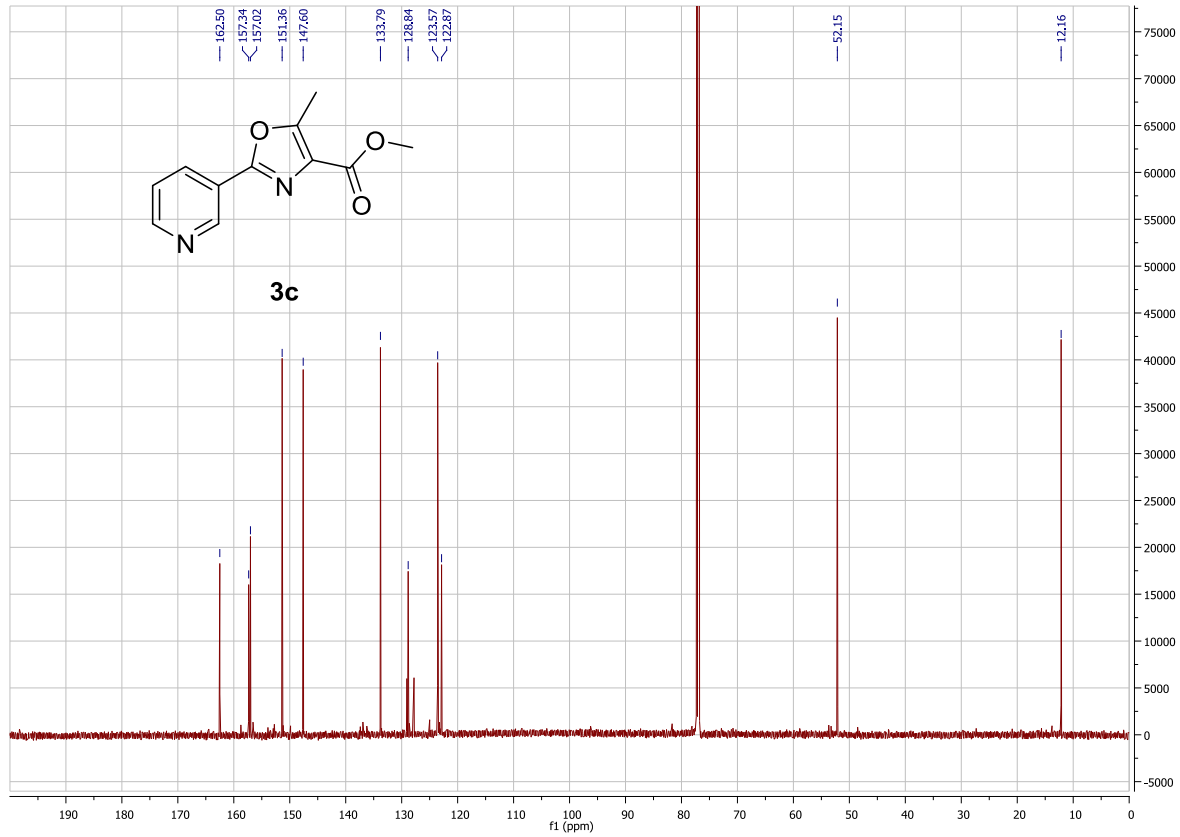
f1 (ppm)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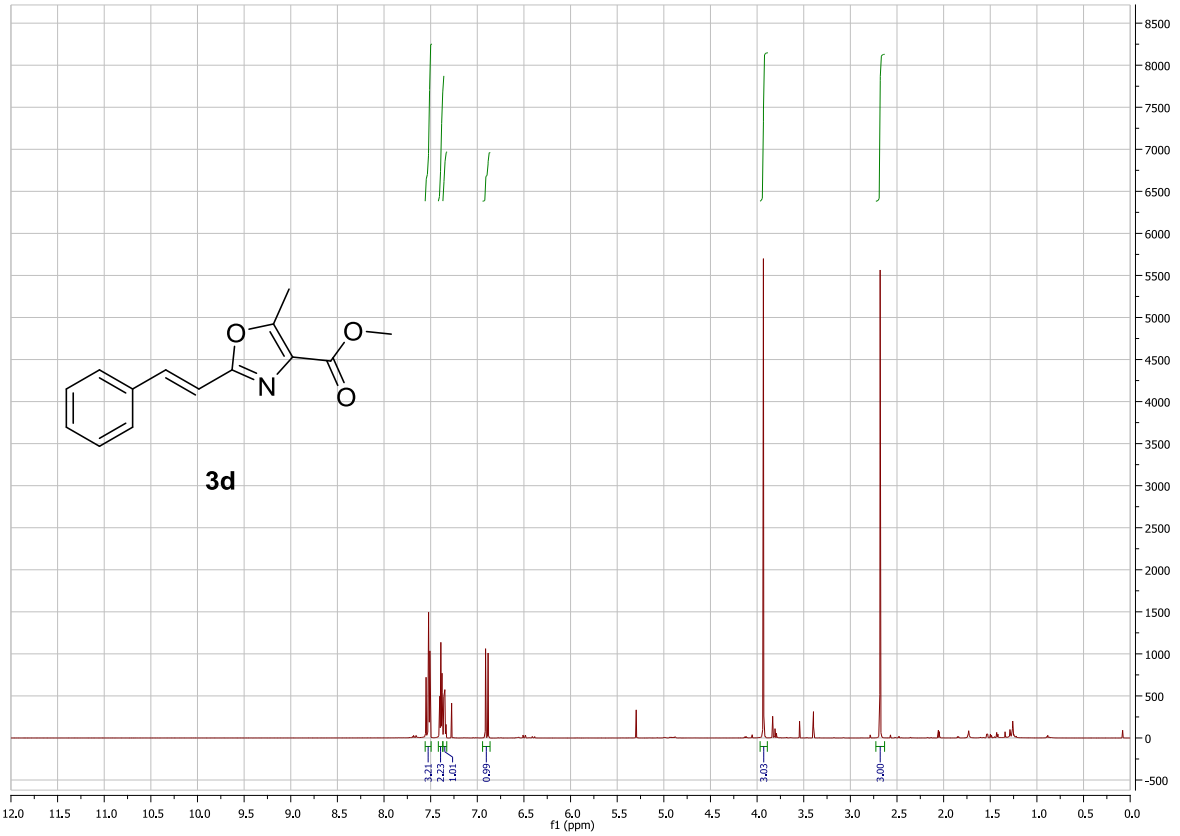
123.57
122.87
52.15
12.16
3c
f1 (ppm)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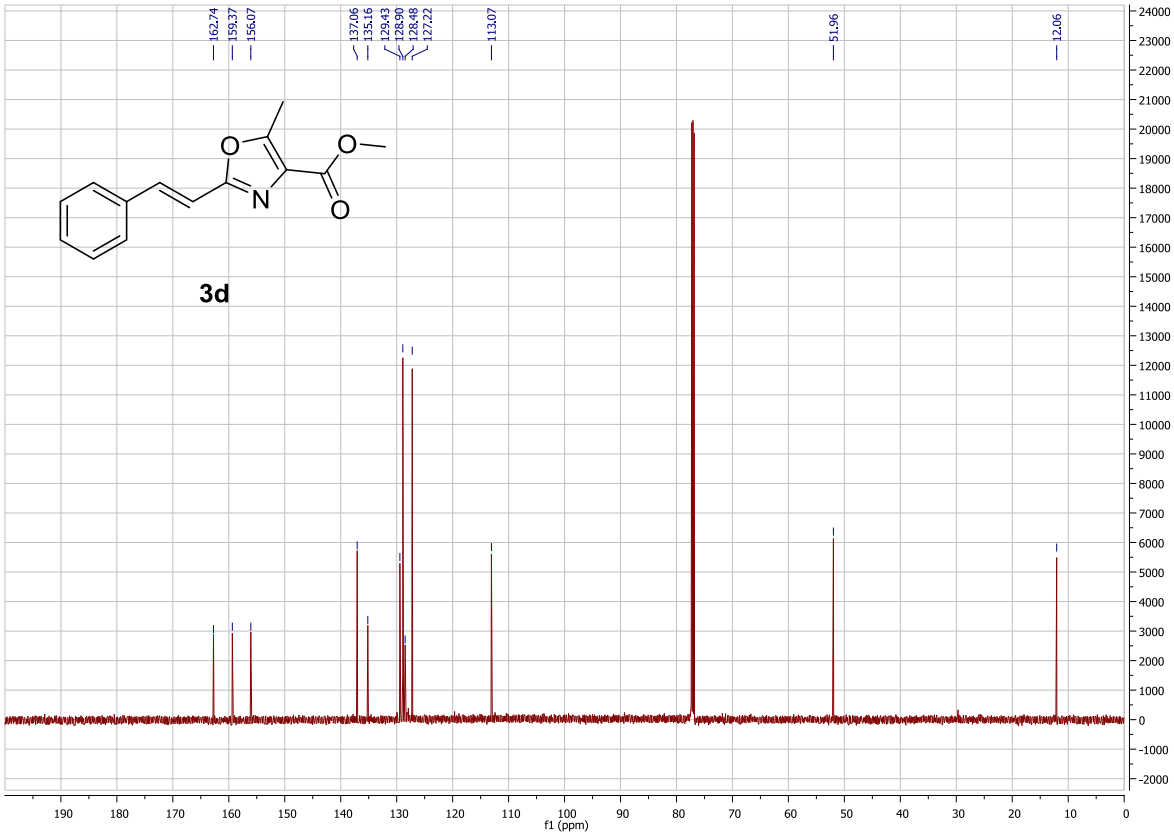
3.03
3.00
f1 (ppm)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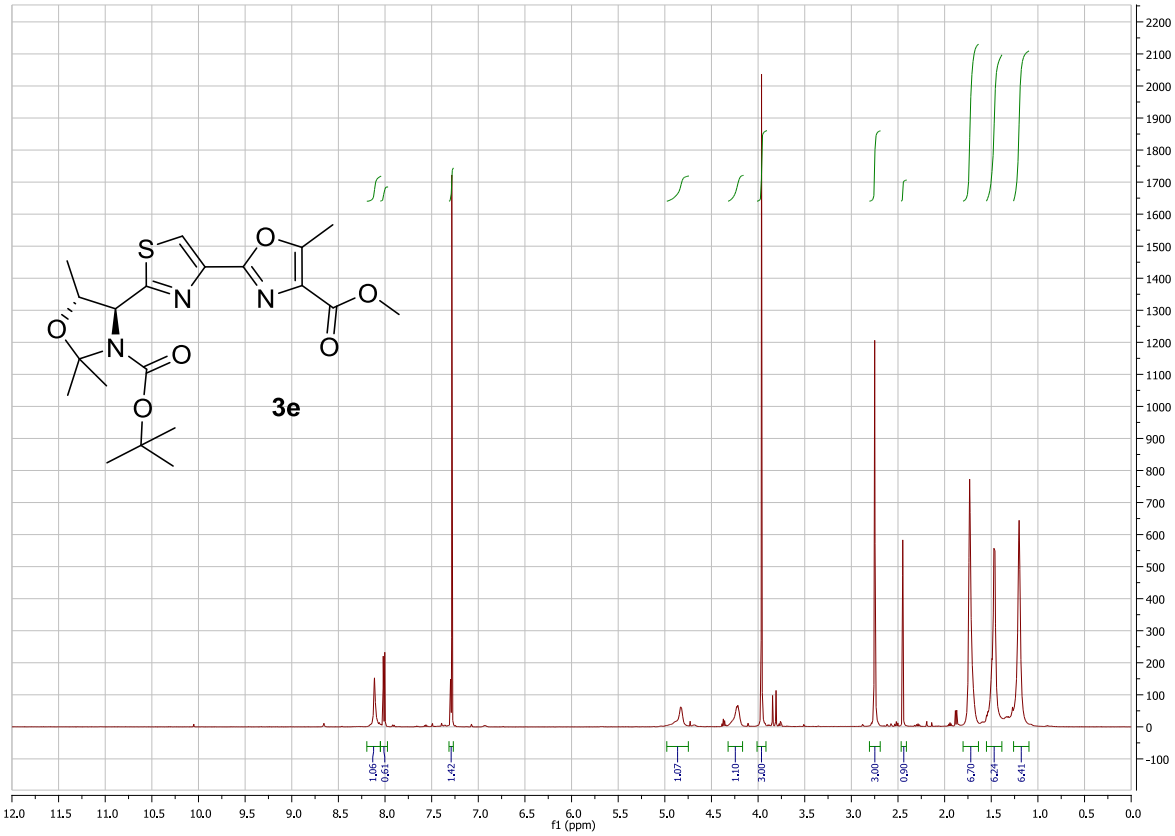
113.07
51.96
12.06
3d
f1 (ppm)


3e
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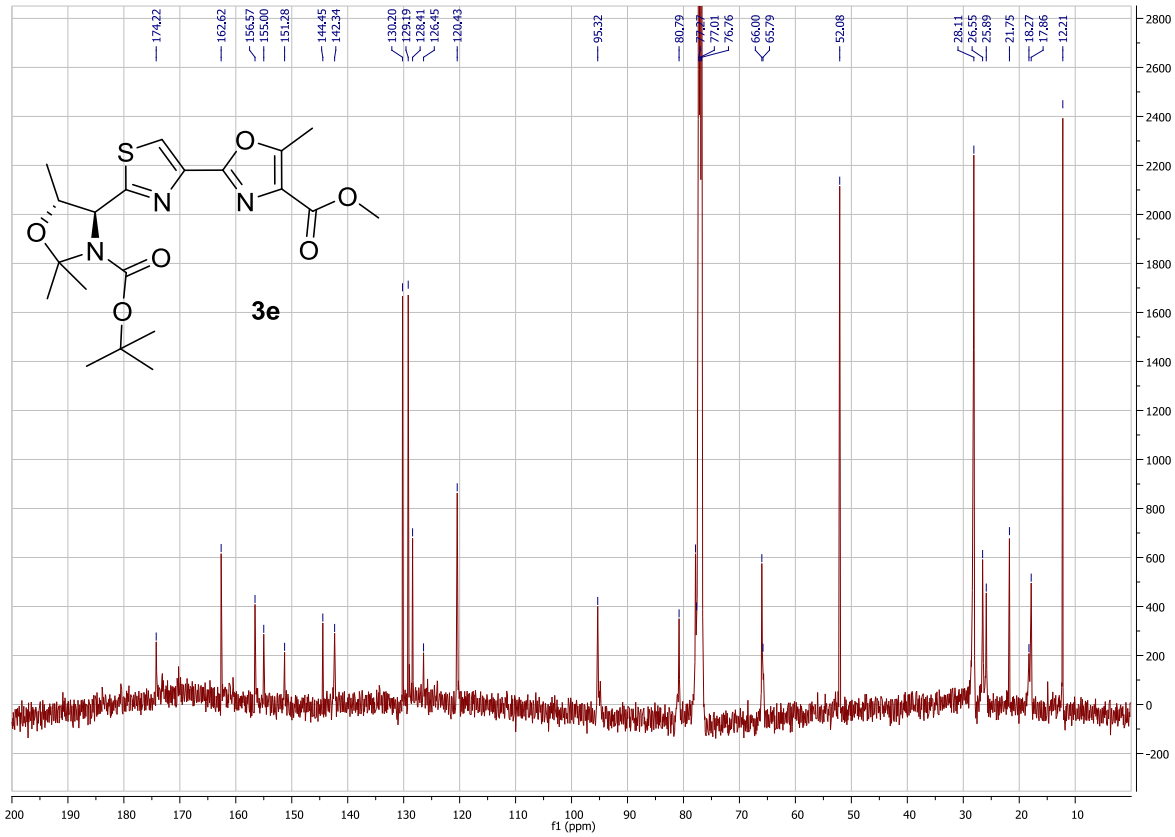
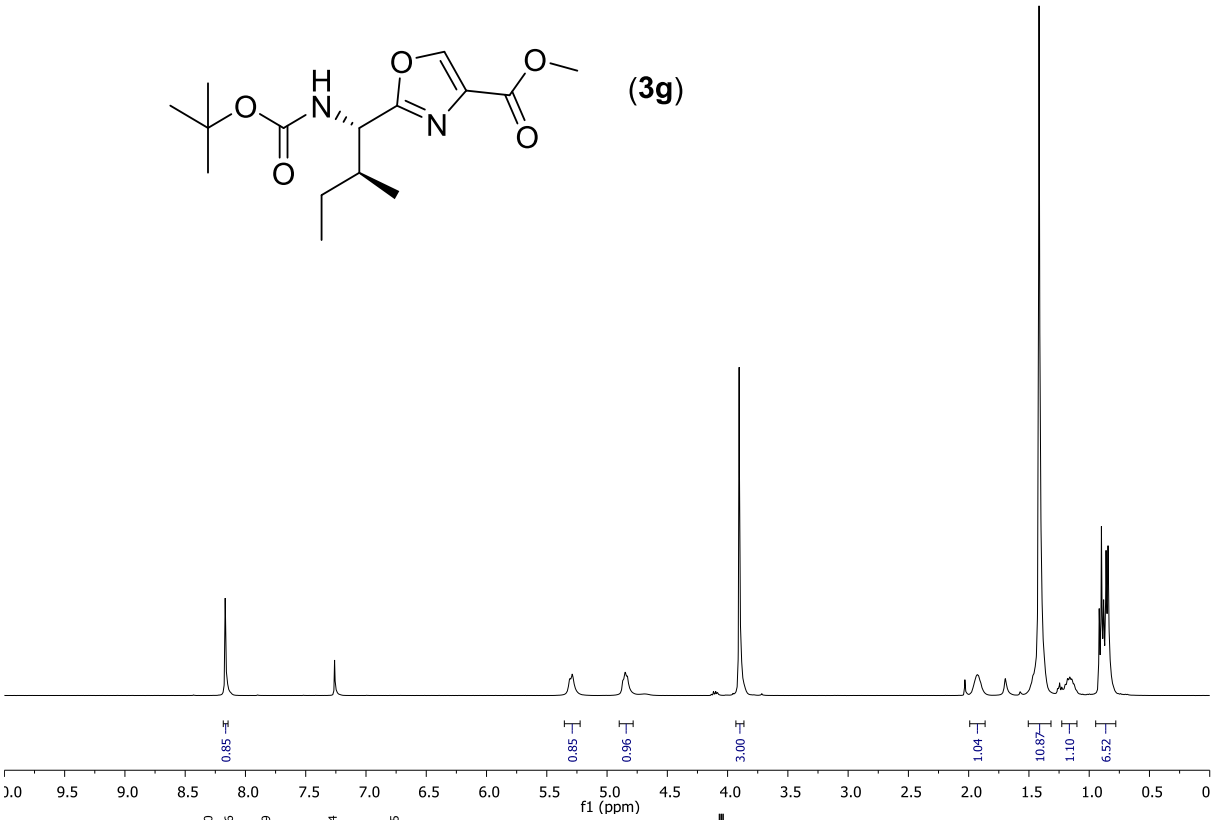
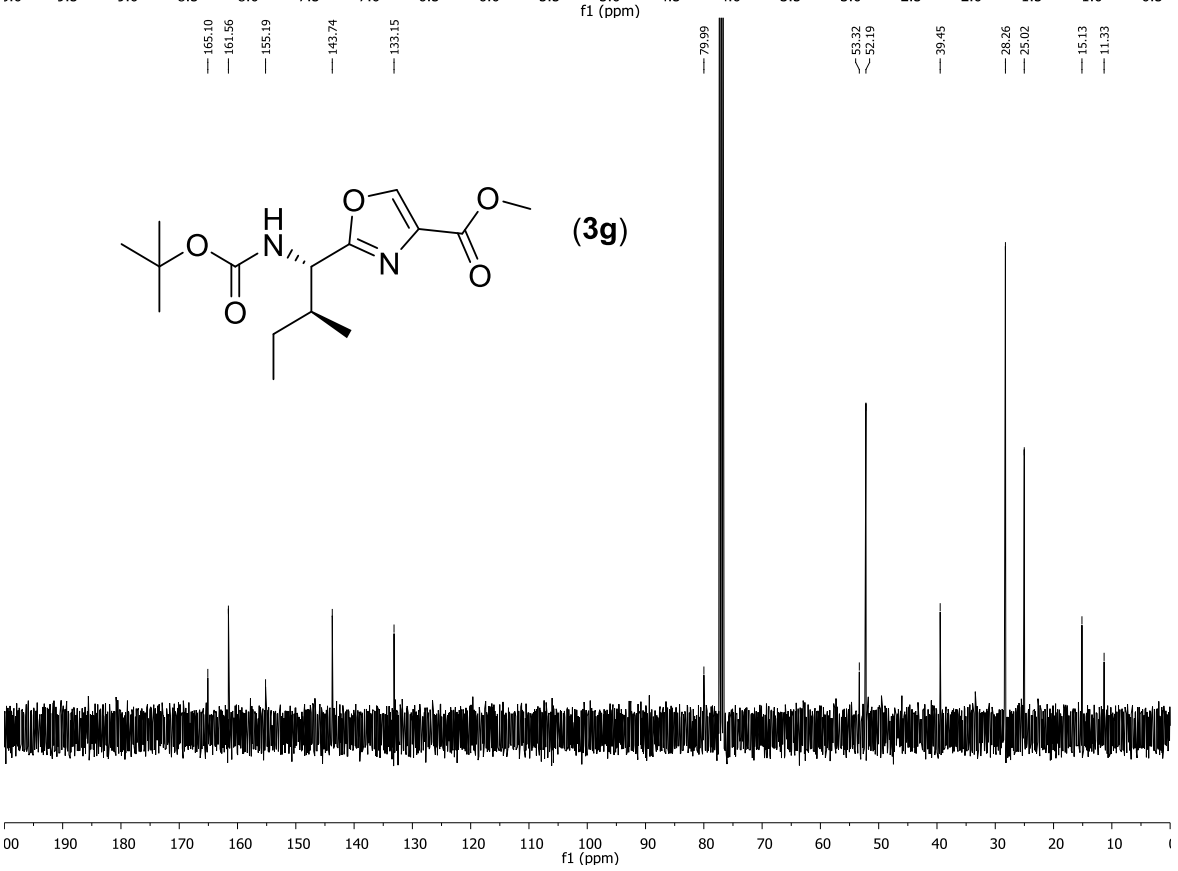
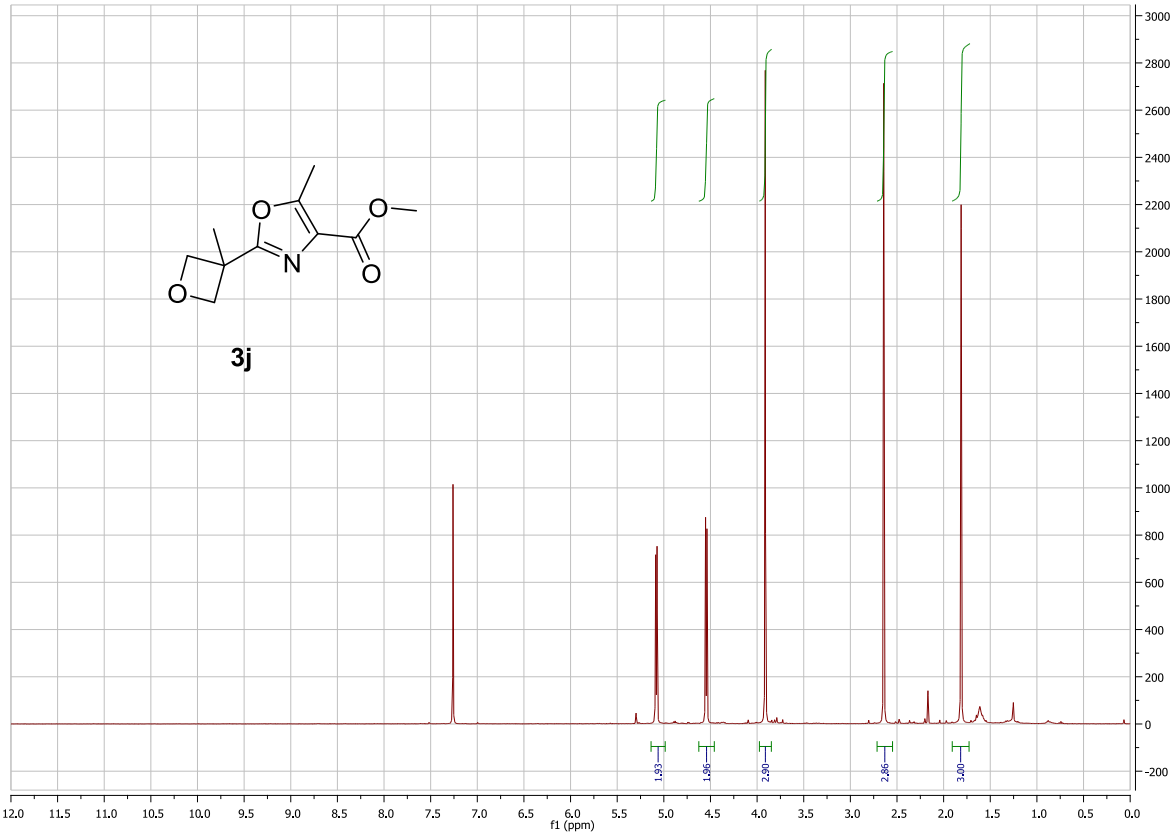
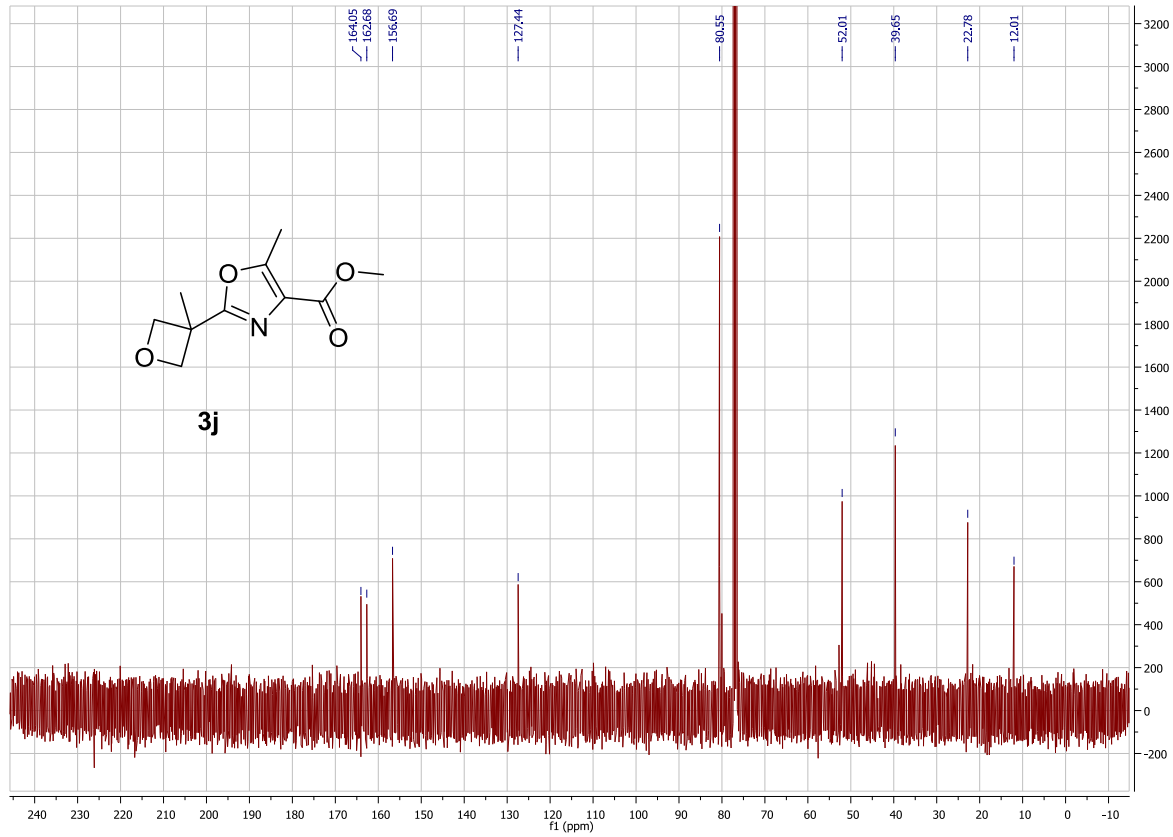
1.07
1.10
3.00
3.00
0.90
6.70
6.24
6.41
f1 (ppm)

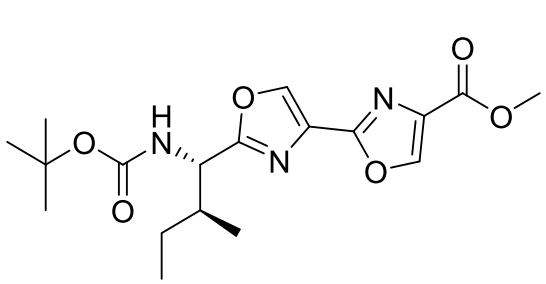

174.22
162.62
156.57
155.00
151.28
144.45
142.34
130.20
129.19
128.41
126.45
120.43
95.32
80.79
77.37
77.01
76.76
66.00
65.79
52.08
28.11
26.55
25.89
21.75
18.27
17.86
12.21
3e
f1 (ppm)


(3g)
0.85
0.85
0.96
3.00
1.04
10.87
1.10
6.52
f1 (ppm)


165.10
161.56
155.19
143.74
133.15
79.99
53.32
52.19
39.45
28.26
25.02
15.13
11.33
(3g)
f1 (ppm)

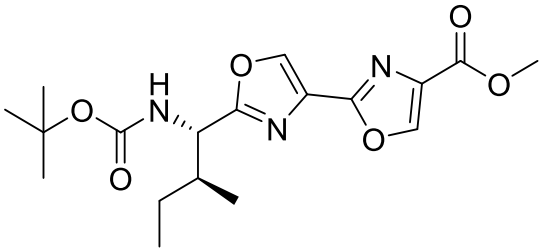

3j
1.93
1.96
2.90
2.86
3.00
f1 (ppm)


164.05
162.68
156.69
127.44
80.55
52.01
39.65
22.78
12.01
3j
f1 (ppm)



(5)

1.13
0.85
0.84
0.96
3.00
1.06
8.94
1.10
6.03
f1 (ppm)



(5)

165.51
161.31
143.68
139.29
134.33
129.64
80.08
53.37
52.31
39.47
28.29
25.09
15.16
11.39
f1 (ppm)

References

1. http://www.vapourtec.co.uk/
2. http://www.knauer.net/en/downloads/pumps.html.
3. Z. E. Wilson, *unpublished results*.
4. Prepared following the procedure reported in: *Synthesis* **2012**, 4, 635-647.