Electronic Supplementary Material (ESI) for ChemComm.

Visible light-assisted organocatalytic α-acyloxylation of ketones using carboxylic acids and *N*-halosuccinimides

Nagaraju Sakkani, Dhiraj K. Jha, Emily Whatley, and John C.-G. Zhao*

Department of Chemistry, University of Texas at San Antonio

Supporting Information

Table of Contents

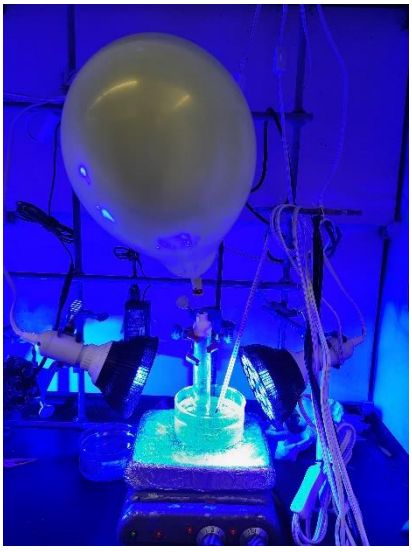
General Information

Unless otherwise specified, all reactions were monitored by TLC on silica gel aluminum plates (200 μm) and visualized by UV. Column chromatography was performed on silica gel (40-63μm). ^{1}H NMR spectra were recorded on a 500 MHz or a 300 MHz spectrometer (126 MHz or 75 MHz for ^{13}C NMR). All deuterated solvents were parched form Cambridge Isotope Laboratories. Infrared spectra were measured on a Bruker Vector 22 instrument. Wolezek blue light LED (460 nm, 36 W) was purchased from Amazon.com. Melting points were recorded on MEL-TEMP melting point apparatus in open capillaries and uncorrected. HRMS were conducted by the RCMI Core Facilities, Department of Chemistry, UTSA. Unless specified below, all chemicals are commercial products and were used as received.

Experimental Procedures

Representative experimental procedure for the α-acyloxylation reaction

An oven-dried culture tube (22 mm ×150 mm) was backfilled three-times with argon. To this tube, chlorobenzene (5 mL), cyclohexanone (**1a**, 294 mg, 3.0 mmol), pyrrolidine (**4a**, 14 mg, 0.20 mmol, 20 mol %), and benzoic acid (**2a**, 122 mg, 1.0 mmol) were added. The resulted solution was stirred for 15 min. at room temperature under argon. Then Na_2CO_3 (106 mg, 1.0 mmol) and 4Å molecular sieves (100 mg) were added. The culture tube was then place in a silicon oil bath that was preheated at 70 °C and NIS (**3c**, 248 mg, 1.1 mmol) was added. The reaction mixture was further stirred under the irradiation of blue LED lights (2 × 36 W, 460 nm) at this temperature for 18 h. After the completion of the reaction, the organic volatiles were evaporated under reduced pressure. The crude reaction mixture obtained was purified by flash column chromatography using 2 to 5% EtOAc in hexane to give product **5a** as a white solid (190 mg, 87%). For a typical setup of the experiment, please see the photo to the right.



Gram-scale synthesis of compound 5a

An oven-dried round-bottom flask (100 mL) was backfilled three-times with argon. To this flask, chlorobenzene (35 mL), cyclohexanone (**1a**, 2,059 mg, 21.0 mmol), pyrrolidine (**4a**, 100 mg, 1.4

mmol, 20 mol %), and benzoic acid (**2a**, 855 mg, 7.0 mmol) were added. The resulted solution was stirred for 15 min. at room temperature under argon. Then Na_2CO_3 (742 mg, 7.0 mmol) and 4Å molecular sieves (700 mg) were added. The flask was then place in a silicon oil bath that was preheated at 70 °C and stirred for 10 min. before NIS (**3c**, 1,733 mg, 7.7 mmol) was added. The reaction mixture was further stirred under the irradiation of blue LED lights (4 × 36 W, 460 nm) at this temperature for 18 h. After the completion of the reaction, the organic volatiles were evaporated under reduced pressure. The crude reaction mixture obtained was purified by flash column chromatography using 2 to 5% EtOAc in hexane to give product **5a** as a white solid (1,125 mg, 74%).

Control experiment with preformed enamine 7

An oven-dried culture tube (22 mm ×150 mm) was backfilled three-times with argon. To this tube, chlorobenzene (5 mL), enamine (**7**, 294 mg, 3.0 mmol) and benzoic acid (**2a**, 122 mg, 1.0 mmol) were added at room temperature under argon. Then Na_2CO_3 (106 mg, 1.0 mmol) followed by NIS (**3c**, 248 mg, 1.1 mmol) were added. The culture tube was then place in a silicon oil bath that was preheated at 70 °C and the reaction mixture was further stirred under the irradiation of blue LED lights (2 × 36 W, 460 nm) at this temperature for 18 h. After the completion of the reaction, the organic volatiles were evaporated under reduced pressure. The crude reaction mixture obtained was purified by flash column chromatography using 2 to 5% EtOAc in hexane to give product **5a** as a white solid (42 mg, 19%).

Control experiment with sodium benzoate (2a′)

An oven-dried culture tube (22 mm ×150 mm) was backfilled three-times with argon. To this tube, DMF (5 mL), cyclohexanone (**1a**, 294 mg, 3.0 mmol), pyrrolidine (**4a**, 14 mg, 0.20 mmol, 20 mol %), and sodium benzoate (**2a′**, 144 mg, 1.0 mmol) were added at room temperature under argon. The resulted solution was stirred for 15 min. at room temperature under argon. Then Na_2CO_3 (106 mg, 1.0 mmol) and 4Å molecular sieves (100 mg) were added, followed by NIS (**3c**, 248 mg, 1.1 mmol). The culture tube was then place in a silicon oil bath that was preheated at 70 °C and the reaction mixture was further stirred under the irradiation of blue LED lights (2 × 36 W, 460 nm) at this temperature for 18 h. This reaction failed to give the desired product according the ^{1}H NMR spectrum and TLC of the crude reaction product.

Radical inhibition experiment with TEMPO

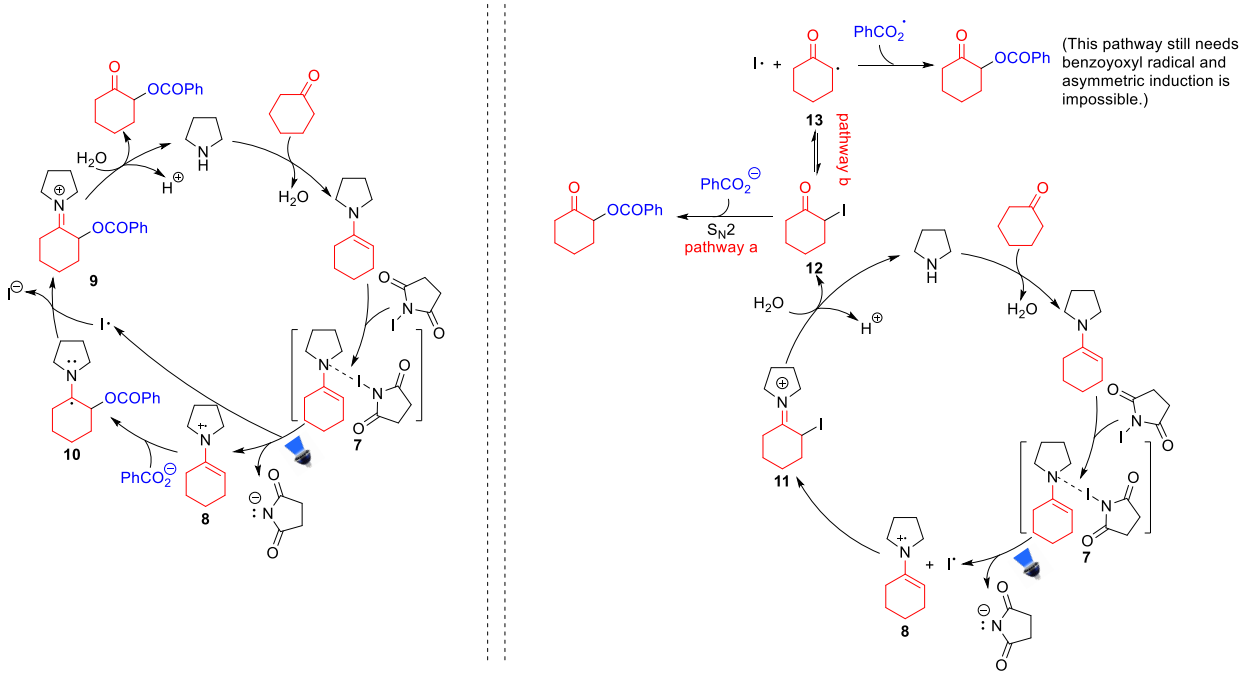
An oven-dried culture tube was backfilled three-times with argon. To this tube, chlorobenzene (5 mL), cyclohexanone (**1a**, 294 mg, 3.0 mmol), pyrrolidine (**4a**, 14 mg, 0.20 mmol, 20 mol %), and benzoic acid (**2a**, 122 mg, 1.0 mmol) were added. The resulted solution was stirred for 15 min. at room temperature under argon. Then TEMPO (781 mg, 5.0 mmol), Na_2CO_3 (106 mg, 1.0 mmol), and 4Å molecular sieves (100 mg) were sequentially added, followed by NIS (**3c**, 248 mg, 1.1 mmol). The culture tube was then place in a silicon oil bath that was preheated at 70 °C and the reaction mixture was further stirred under the irradiation of blue LED lights (2 × 36 W, 460 nm) at this temperature for 18 h. This reaction failed to give the desired product according the ^{1}H NMR spectrum and TLC of the crude reaction product.

Light on-and-off experiment

The light on-and-off experiment was carried out by following exactly the Representative Experimental Procedure using cyclohexanone and benzoic acid as the starting materials, except that the blue LED light was turned on for 30 min and then off for 30 min during the 18 h reaction time. Afterwards, the organic volatiles were evaporated under reduced pressure. The crude reaction mixture obtained was purified by flash column chromatography using 2 to 5% EtOAc in hexane to give product **5a** as a white solid (89 mg, 41%). For a total 9 h of light irradiation (50% irradiation time of the normal reaction), roughly a 50% of the normal yield (87%) was obtained. This result indicates that the reaction yield directly correlates to the blue light irradiation time and the reaction is not a radical chain reaction initiated by the light irradiation.

Alternative Mechanistic Proposals of the α-Acyloxylation Reaction

(We thank the reviewers for their contributions to the mechanistic proposals discussed below!)

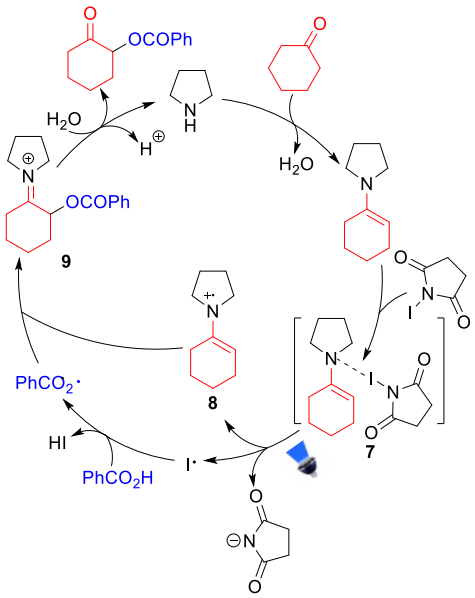


Scheme S-1. Disfavored alternative mechanistic proposals for the α-acyloxylation reaction

As shown in Scheme S-1, alternatively, the electron transfer between the enamine and NIS in the halogen bond complex **7** can lead to the formation of the enamine cation radical **8**, an iodine radical, and a succinimide anion. The reaction of **8** and benzoate anion leads to the formation of the α-amino radical intermediate **10** (Left catalytic cycle, Scheme S-1), which then reacts with the iodine radical to generate the iminium intermediate **9** (via recombination and elimination or electron transfer). Hydrolysis of **9** then produces product **5a**. Alternatively, **8** can react with iodine radical to give intermediate **11** (Pathway **a**, right catalytic cycle, Scheme S-1), which gives the α-iodoketone intermediate **12**. An S_N2 reaction between **12** and benzoate will yield the desired product **5a**. While these mechanisms do not involve a benzoyloxyl radical, we do not favor them mainly because the control reaction with sodium benzoate (**2a′**) in DMF failed to yield the desired product **5a**, which is against the prediction of the proposed mechanisms.

Another possibility is that the α-iodoketone intermediate **12** can undergo homolysis of the C-I bond to yield intermediate **13** (Pathway **b**, right catalytic cycle, Scheme S-1), which then reacts with a benzoyloxyl radical to give **5a**. This pathway is ruled out because asymmetric induction will then not be possible in this reaction, which is not true. In addition, this pathway still requires a benzoyloxyl radical like the mechanism we proposed in the manuscript (Scheme 2).

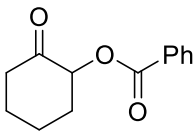
On the other hand, if the homolytic cleavage of C-I bond happens on the iminium intermediate **11**, an intermediate with a similar electronic nature as **12**, then the asymmetric induction is still possible; however, this homolysis will regenerate the intermediate **8** and the iodine radical. Moreover, the reaction, like in pathway **b** and our proposed mechanism (see main text), will still need a benzoyloxyl radical (except it is now generated from the iodine radical instead of the succinimidyl radical) to yield the final product **5a**. According to Ocaam's razor, the proposed involvement of intermediate **11** is not necessary: Instead, we can propose a mechanism simply based on the iodine radical (Scheme S-2). We cannot completely rule out this possibility at this stage. Nevertheless, we still prefer the mechanism proposed in the main text because we did not observe any formation of the halogenated products when cyclohexanone was reacted with NIS, NBS, or NCS.



Scheme S-2. Alternative plausible mechanism for the α-acyloxylation reaction

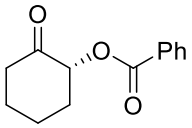
Compound Characterization Data

2-Oxocyclohexyl benzoate (5a)[4c]



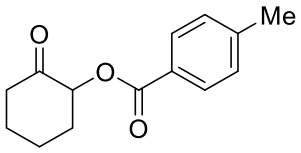
Purified flash column chromatography using 2 to 5% EtOAc in hexane (Rf = 0.40 in 10% ethyl acetate in hexane). White solid; 190 mg, 87% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, *J*=7.9 Hz, 2H), 7.57 (t, *J* = 7.2 Hz, 1H), 7.45 (t, *J*=7.5 Hz, 2H), 5.41 (dd, *J*=12.1, 6.3 Hz, 1H), 2.57 (d, *J*=12.4 Hz, 1H), 2.52–2.38 (m, 2H), 2.13 (dd, *J*=8.2, 4.8 Hz, 1H), 1.93 (ddt, *J*=38.8, 26.0, 13.2 Hz, 3H), 1.76–1.61 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.3, 165.5, 133.1, 129.8, 128.3, 77.0, 40.7, 33.2, 27.2, 23.8.

(*R*)-2-Oxocyclohexyl benzoate [(*R*)-5a][16]



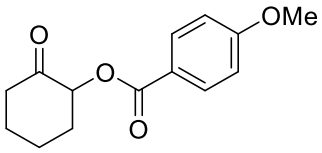
This compound was synthesized by following the Representative Experimental Procedure using compound **4d** (20 mol % loading) as the catalyst. Purified by flash column chromatography using 2 to 5% EtOAc in hexane. White solid; 81 mg, 37% yield, 44% ee. $[\alpha]^{25}_{D}$ = +8.2 (*c* = 0.36, $CHCl_3$) [lit.[17] $[\alpha]^{25}_{D}$ = +19.9 (*c* = 0.87, 99% ee, $CHCl_3$)]. The ee value of this product was determined by HPLC analysis using a ChiralPak AD-H column (90:10 hexane/isopropanol at 1.0 mL/min, λ = 220 nm). Major enantiomer: t_R = 7.3 min, minor enantiomer: t_R = 9.7 min.

2-Oxocyclohexyl 4-methylbenzoate (5b)[4c]



Purified flash column chromatography using 5 to 10% EtOAc in hexane (Rf = 0.30 in 15% ethyl acetate in hexane). White solid; 189 mg, 81% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, *J*=8.0 Hz, 2H), 7.24 (d, *J*=7.9 Hz, 2H), 5.40 (dd, *J*=12.0, 6.2 Hz, 1H), 2.58–2.37 (m, 3H), 2.41 (s, 3H), 2.13–1.65 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.4, 165.5, 143.8, 129.8, 129.0, 126.9, 76.8, 40.7, 33.2, 27.2, 23.7, 21.6.

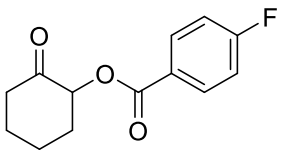
2-Oxocyclohexyl 4-methoxybenzoate (5c)[4c]



Purified flash column chromatography using 10 to 15% EtOAc in hexane (Rf = 0.30 in 15% ethyl acetate in hexane). White solid; 172 mg, 73% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, *J*=8.5 Hz, 2H), 6.91 (d, *J*=8.5 Hz, 2H), 5.38 (dd, *J*=11.8, 6.1 Hz, 1H), 3.84 (s, 3H), 2.68–2.28 (m, 3H), 2.13–1.64

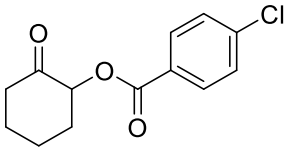
(m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.6, 165.2, 163.5, 131.9, 122.0, 113.6, 76.7, 55.4, 40.7, 33.2, 27.2, 23.7.

2-Oxocyclohexyl 4-fluorobenzoate (5d)[18]



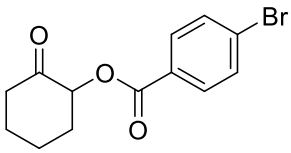
Purified flash column chromatography using 5 to 15% EtOAc in hexane (Rf = 0.40 in 15% ethyl acetate in hexane). White solid; 194 mg, 82% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (dd, *J*=8.0, 5.8 Hz, 2H), 7.12 (t, *J*=8.5 Hz, 2H), 5.40 (dd, *J*=12.0, 6.3 Hz, 1H), 2.60–2.36 (m, 3H), 2.16–1.79 (m, 4H), 1.69 (tt, *J*=22.5, 8.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.2, 165.8 (d, *J* = 254.5 Hz), 164.5, 132.4 (d, *J* = 10.0 Hz), 126.0, 115.7 (d, *J* = 22.6 Hz), 77.0, 40.7, 33.1, 27.1, 23.7.

2-Oxocyclohexyl 4-chlorobenzoate (5e)[4c]



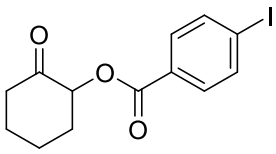
Purified flash column chromatography using 8 to 20% EtOAc in hexane (Rf = 0.40 in 20% ethyl acetate in hexane). White solid; 197 mg, 78% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J*=8.0 Hz, 2H), 7.42 (d, *J*=8.0 Hz, 2H), 5.40 (dd, *J*=11.7, 6.0 Hz, 1H), 2.49 (ddd, *J*=26.1, 19.2, 9.2 Hz, 3H), 2.19–1.57 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.1, 164.6, 139.5, 131.2, 128.7, 128.1, 77.20, 40.7, 33.1, 27.1, 23.7.

2-Oxocyclohexyl 4-bromobenzoate (5f)



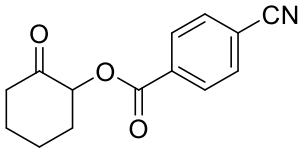
Purified flash column chromatography using 8 to 20% EtOAc in hexane (Rf = 0.40 in 20% ethyl acetate in hexane). White solid; 219 mg, 74% yield. m.p. 109-110 ℃. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, *J*=8.1 Hz, 2H), 7.60 (d, *J*=8.2 Hz, 2H), 5.41 (dd, *J*=12.1, 6.3 Hz, 1H), 2.49 (ddt, *J*=10.7, 6.2, 3.9 Hz, 3H), 2.10 (dddd, *J*=22.4, 10.0, 6.1, 3.1 Hz, 2H), 1.99–1.61 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.1, 164.8, 131.7, 131.4, 128.6, 128.3, 77.2, 40.7, 33.1, 27.1, 23.8. ν_{max} (neat, cm^{-1}): 1741, 1664, 1360, 1260, 1140. HRMS (ESI, m/z) calcd for $C_{13}H_{13}BrNaO_3$ ($[M+Na]^+$): 318.9940; found: 318.9930.

2-Oxocyclohexyl 4-iodobenzoate (5g)



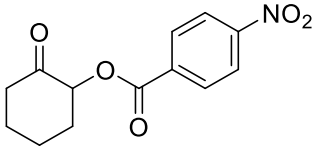
Purified flash column chromatography using 5 to 15% EtOAc in hexane (Rf = 0.40 in 15% ethyl acetate in hexane). White solid; 240 mg, 70% yield. m.p. 113-114 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J*=2.3 Hz, 4H), 5.39 (dd, *J*=12.1, 6.3 Hz, 1H), 2.63–2.36 (m, 3H), 2.20–1.98 (m, 2H), 1.98–1.61 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.0, 165.0, 137.7, 131.3, 129.1, 101.0, 77.2, 40.7, 33.1, 27.1, 23.7. ν_{max} (neat, cm^{-1}): 1730, 1693, 1391, 1233, 1113. HRMS (ESI, m/z) calcd for $C_{13}H_{14}IO_3$ ($[M+H]^+$): 344.9982; found: 344.9972.

2-Oxocyclohexyl 4-cyanobenzoate (5h)



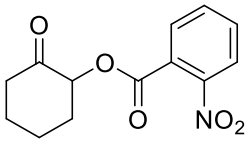
Purified flash column chromatography using 10 to 20% EtOAc in hexane (Rf = 0.40 in 20% ethyl acetate in hexane). White solid; 175 mg, 72% yield. m.p. 160-162 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, *J*=7.1 Hz, 2H), 7.72 (d, *J*=7.1 Hz, 2H), 5.52–5.21 (m, 1H), 2.64–2.30 (m, 3H), 2.14–1.62 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.7, 163.8, 133.5, 132.1, 130.3, 117.9, 116.4, 77.6, 40.6, 33.0, 27.0, 23.6. ν_{max} (neat, cm^{-1}): 2242, 1672, 1640, 1381, 1224, 1140. HRMS (ESI, m/z) calcd for $C_{14}H_{13}NNaO_3$ ($[M+Na]^+$): 266.0788; found: 266.0780.

2-Oxocyclohexyl 4-nitrobenzoate (5i)[4c]



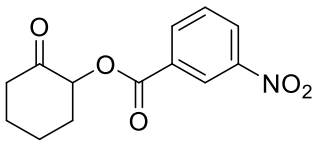
Purified flash column chromatography using 10 to 30% EtOAc in hexane (Rf = 0.50 in 25% ethyl acetate in hexane). White solid; 201 mg, 76% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (dd, *J*=19.2, 8.1 Hz, 4H), 5.43 (dd, *J*=11.7, 6.1 Hz, 1H), 2.62–2.41 (m, 3H), 2.19–1.66 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.6, 163.6, 150.6, 135.1, 130.9, 123.4, 77.8, 40.6, 33.0, 27.0, 23.7.

2-Oxocyclohexyl 2-nitrobenzoate (5j)



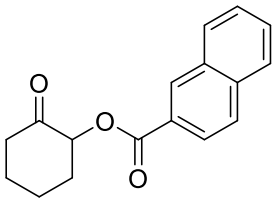
Purified flash column chromatography using 10 to 30% EtOAc in hexane (Rf = 0.50 in 30% ethyl acetate in hexane). White solid; 192 mg, 73% yield. m.p. 111-112 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (dd, *J*=14.6, 7.8 Hz, 2H), 7.66 (dt, *J*=29.7, 7.5 Hz, 2H), 5.49–5.31 (m, 1H), 2.47 (ddd, *J*=24.7, 19.2, 9.6 Hz, 3H), 2.15–1.91 (m, 2H), 1.88–1.55 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.7, 164.4, 147.8, 133.1, 131.9, 130.3, 127.2, 123.8, 78.0, 40.6, 32.6, 27.0, 23.5. ν_{max} (neat, cm^{-1}): 1740, 1680, 1380, 1260, 1130. HRMS (ESI, m/z) calcd for $C_{13}H_{13}NNaO_5$ ($[M+Na]^+$): 286.0686; found: 286.0672.

2-Oxocyclohexyl 3-nitrobenzoate (5k)



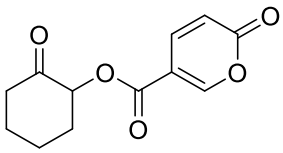
Purified flash column chromatography using 10 to 30% EtOAc in hexane (Rf = 0.50 in 30% ethyl acetate in hexane). White solid; 207 mg, 79% yield. m.p. 115-116 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.90 (s, 1H), 8.42 (t, *J*=7.9 Hz, 2H), 7.68 (d, *J*=7.4 Hz, 1H), 5.45 (dd, *J*=11.3, 5.7 Hz, 1H), 2.54 (dd, *J*=49.4, 8.4 Hz, 3H), 2.19–1.67 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.6, 163.4, 148.2, 135.5, 131.4, 129.6, 127.6, 124.8, 77.8, 40.6, 33.0, 27.0, 23.7. ν_{max} (neat, cm^{-1}): 1743, 1687, 1388, 1264, 1134. HRMS (ESI, m/z) calcd for $C_{13}H_{13}NNaO_5$ ($[M+Na]^+$): 286.0686; found: 286.0673.

2-Oxocyclohexyl 2-naphthoate (5l)



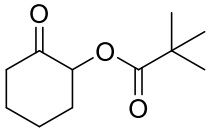
Purified flash column chromatography using 5 to 15% EtOAc in hexane (Rf = 0.30 in 15% ethyl acetate in hexane). White solid; 223 mg, 83% yield. m.p. 120-122 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.13 (d, *J*=8.4 Hz, 1H), 8.06–7.82 (m, 3H), 7.58 (dt, *J*=14.4, 6.9 Hz, 2H), 5.50 (dd, *J*=11.9, 6.0 Hz, 1H), 2.69–2.40 (m, 3H), 2.23–1.95 (m, 3H), 1.80 (dq, *J*=25.9, 12.6 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.4, 165.7, 135.6, 132.4, 131.4, 129.4, 128.3, 128.1, 127.7, 126.9, 126.6, 125.4, 77.1, 40.8, 33.3, 27.2, 23.8. ν_{max} (neat, cm^{-1}): 1748, 1671, 1320, 1242, 1170. HRMS (ESI, m/z) calcd for $C_{17}H_{16}NaO_3$ ($[M+Na]^+$): 291.0992; found: 291.0987.

2-Oxocyclohexyl 2-oxo-2*H*-pyran-5-carboxylate (5n)



Purified flash column chromatography using 10 to 40% EtOAc in hexane (Rf = 0.40 in 30% ethyl acetate in hexane). Colorless liquid; 160 mg, 68% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.81 (d, *J*=9.7 Hz, 1H), 6.36 (d, *J*=9.8 Hz, 1H), 5.35 (dd, *J*=11.3, 6.4 Hz, 1H), 2.67–2.32 (m, 3H), 2.25–1.98 (m, 2H), 1.88–1.63 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.6, 162.0, 159.8, 158.5, 141.7, 115.2, 111.5, 77.4, 40.6, 32.9, 27.0, 23.7. ν_{max} (neat, cm^{-1}): 1713, 1653, 1431, 1316, 1086. HRMS (ESI, m/z) calcd for $C_{12}H_{13}O_5$ ($[M+H]^+$): 237.0757; found: 237.0750.

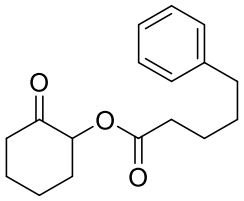
2-Oxocyclohexyl pivalate (5o)[18]



Purified flash column chromatography using 5 to 15% EtOAc in hexane (Rf = 0.30 in 15% ethyl acetate in hexane). Colorless liquid; 151 mg, 76% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.10 (dd, *J*=11.6, 6.3 Hz, 1H), 2.51–2.31 (m, 2H),

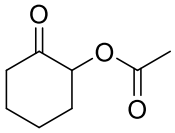
2.25 (tt, *J*=9.8, 2.7 Hz, 1H), 2.11–2.01 (m, 1H), 2.02–1.89 (m, 1H), 1.83–1.68 (m, 2H), 1.67–1.53 (m, 1H), 1.23 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.4, 177.5, 76.1, 40.6, 38.6, 32.8, 27.1, 23.6.

2-Oxocyclohexyl 5-phenylpentanoate (5p)



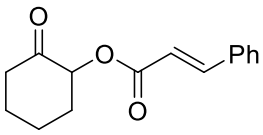
Purified flash column chromatography using 5 to 10% EtOAc in hexane (Rf = 0.40 in 10% ethyl acetate in hexane). Colorless liquid; 187 mg, 68% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (t, *J*=7.4 Hz, 2H), 7.24–7.16 (m, 3H), 5.19 (dd, *J*=11.5, 6.6 Hz, 1H), 2.67 (t, *J*=6.9 Hz, 2H), 2.56–2.40 (m, 4H), 2.30 (qd, *J*=6.9, 2.9 Hz, 1H), 2.10 (dtd, *J*=9.4, 6.2, 3.1 Hz, 1H), 2.05–1.92 (m, 1H), 1.80–1.61 (m, 7H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.5, 172.6, 142.2, 128.4, 128.3, 125.7, 76.4, 40.7, 35.5, 33.8, 33.0, 30.8, 27.1, 24.5, 23.7. ν_{max} (neat, cm^{-1}): 2938, 1743, 1723, 1451, 1216. HRMS (ESI, m/z) calcd for $C_{17}H_{23}O_3$ ($[M+H]^+$): 275.1642; found: 275.1632.

2-Oxocyclohexyl acetate (5q)[4c]



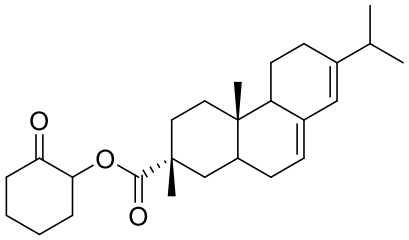
Purified flash column chromatography using 5 to 20% EtOAc in hexane (Rf = 0.40 in 20% ethyl acetate in hexane). Colorless liquid; 102 mg, 65% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.14 (dd, *J*=11.7, 6.4 Hz, 1H), 2.48 (dd, *J*=13.6, 1.5 Hz, 1H), 2.37 (td, *J*=13.7, 6.1 Hz, 1H), 2.27 (ddd, *J*=5.9, 4.7, 2.6 Hz, 1H), 2.12 (s, 3H), 2.10–2.03 (m, 1H), 2.00–1.91 (m, 1H), 1.80–1.68 (m, 2H), 1.65–1.54 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.5, 170.0, 76.5, 40.6, 33.0, 27.1, 23.7, 20.7.

2-Oxocyclohexyl *trans*-cinnamate (5r)[3]



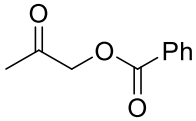
Purified flash column chromatography using 5 to 15% EtOAc in hexane (Rf = 0.30). White solid; 201 mg, 82% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J*=16.0 Hz, 1H), 7.47 (dd, *J*=74.2, 2.8 Hz, 5H), 6.55 (d, *J*=16.0 Hz, 1H), 5.33 (dd, *J*=11.5, 6.2 Hz, 1H), 2.61–2.36 (m, 3H), 2.08 (dddd, *J*=19.6, 13.5, 6.5, 3.3 Hz, 2H), 1.91–1.77 (m, 2H), 1.68 (dddd, *J*=17.3, 13.1, 8.7, 4.2 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.6, 165.8, 145.6, 134.3, 130.4, 128.8, 128.1, 117.4, 76.6, 40.7, 33.2, 27.2, 23.8.

2-Oxocyclohexyl (2*R*,4a*S*)-7-isopropyl-2,4a-dimethyl-1,2,3,4,4a,4b,5,6,10,10a-decahydrophenanthrene-2-carboxylate (5s)



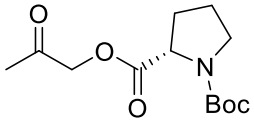
Purified flash column chromatography using 5 to 15% EtOAc in hexane (Rf = 0.40 in 15% ethyl acetate in hexane). Colorless liquid: 244 mg, 61% yield; a mixture of two diastereomers (dr: 50:50). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.78 (d, *J*=5.1 Hz, 3H), 5.40 (d, *J*=19.9 Hz, 3H), 5.12 (dd, *J*=16.9, 10.4 Hz, 3H), 2.52–2.31 (m, 9H), 2.29–1.51 (m, 70H), 1.31–1.10 (m, 20H), 0.99 (dd, *J*=15.7, 9.0 Hz, 19H), 0.84 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.5, 204.4, 177.6, 177.4, 145.0, 144.6, 135.2, 135.1, 122.6, 122.4, 121.1, 120.9, 77.3, 76.4, 76.2, 50.9, 50.8, 46.5, 46.4, 44.9, 44.8, 40.7, 40.6, 38.3, 38.2, 37.4 37.3, 34.8, 34.5,32.3 32.9, 27.4, 27.2, 27.1, 25.5, 25.3, 23.8, 23.7, 22.4, 21.4, 20.8, 18.1, 17.1, 17.0, 14.1, 14.0. ν_{max} (neat, cm^{-1}): 2936, 1717, 1659, 1449, 1240, 1146. HRMS (ESI, m/z) calcd for$C_{26}H_{39}O_3$ ($[M+H]^+$): 399.2894; found: 399.2879.

2-Oxopropyl benzoate (5t)[4c]



Purified flash column chromatography using 5 to 15% EtOAc in hexane (Rf = 0.40 in 15% ethyl acetate in hexane). Colorless liquid; 132 mg, 74% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16–8.01 (m, 2H), 7.66–7.55 (m, 1H), 7.46 (t, *J*=7.7 Hz, 2H), 4.88 (d, *J*=1.4 Hz, 2H), 2.22 (d, *J*=1.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.8, 165.8, 133.4, 129.8, 129.1, 128.5, 68.7, 26.1.

1-(*tert*-Butyl) 2-(2-oxopropyl) (*S*)-pyrrolidine-1,2-dicarboxylate (5u)[4c]



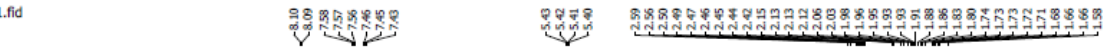
Purified flash column chromatography using 5 to 20% EtOAc in hexane (Rf = 0.40 in 20% ethyl acetate in hexane). Colorless liquid: 190 mg, 70% yield; a mixture of two rotamers (55:45 ratio). ^{1}H NMR (500 MHz, $CDCl_3$) δ major rotamer:4.62 (d, *J*=16.8 Hz, 1H), 4.46 (d, *J*=16.8 Hz, 1H), 4.24 (dd, *J*=8.3, 3.7 Hz, 1H), 3.48–3.37 (m, 1H), 3.31–3.24 (m, 1H), 2.12–2.07 (m, 2H), 2.05 (s, 3H), 1.80 (dt, *J*=12.0, 7.1 Hz, 2H), 1.31 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.6, 172.2, 153.6, 79.7, 68.1, 58.5, 46.2, 29.8, 28.1, 25.9, 23.4. Minor rotamer 4.70 (d, *J*=16.8 Hz, 1H), 4.57 (d, *J*=16.8 Hz, 1H), 4.30 (dd, *J*=8.1, 3.5 Hz, 1H), 3.51–3.48 (m, 1H), 3.34 (dd, *J*=12.6, 4.7 Hz, 1H), 2.23–2.12 (m, 2H), 2.05 (s, 3H), 1.97–1.84 (m, 2H), 1.33 (d, *J*=14.8 Hz, 9H), ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.7, 172.3, 154.3, 79.8, 68.4, 58.7, 46.5, 30.8, 28.3, 26.0, 24.2.

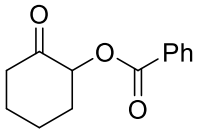
Additional References

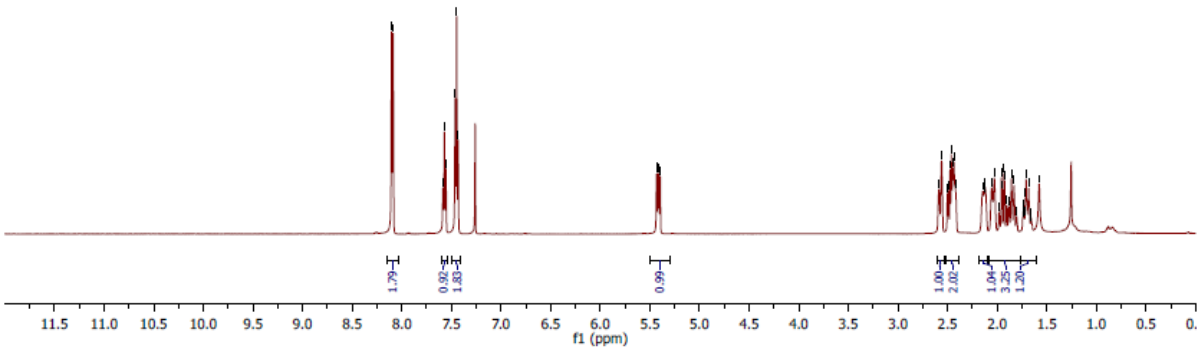
16. B. Hao, M. J. Gunaratna, M. Zhang, S. Weerasekara, S. N. Seiwald, V. T. Nguyen, A. Meier, D. H. Hua, *J. Am. Chem. Soc.* 2016, **138**, 16839-16848.
17. Y. Zhu, L. Shu, Y. Tu; Shi, Y. *J. Org. Chem*. 2001, **66**, 1818-1826.
18. D. A. Smithen, C. J. Mathews, N. C. O. Tomkinson, *Org. Biomol. Chem.* 2012, **10**, 3756-3762.

Copy of NMKR Spectra

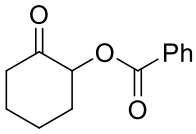
IV-NS-744-1.1.fid

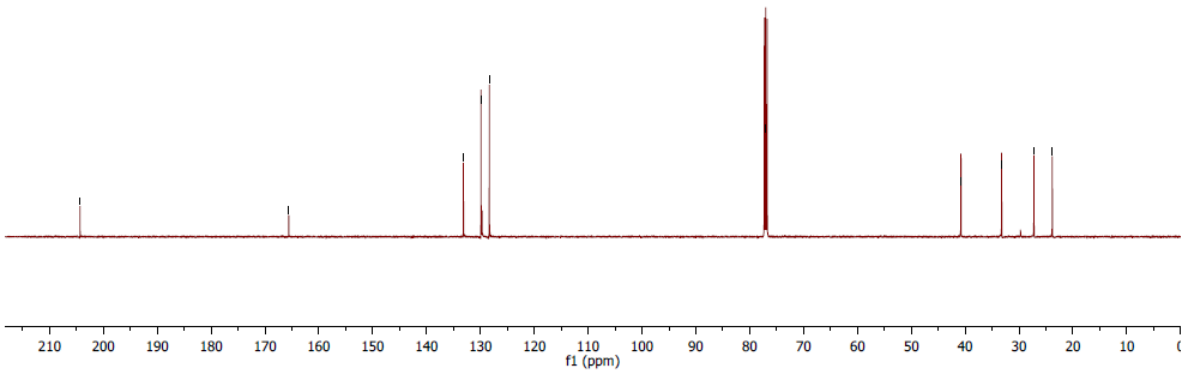


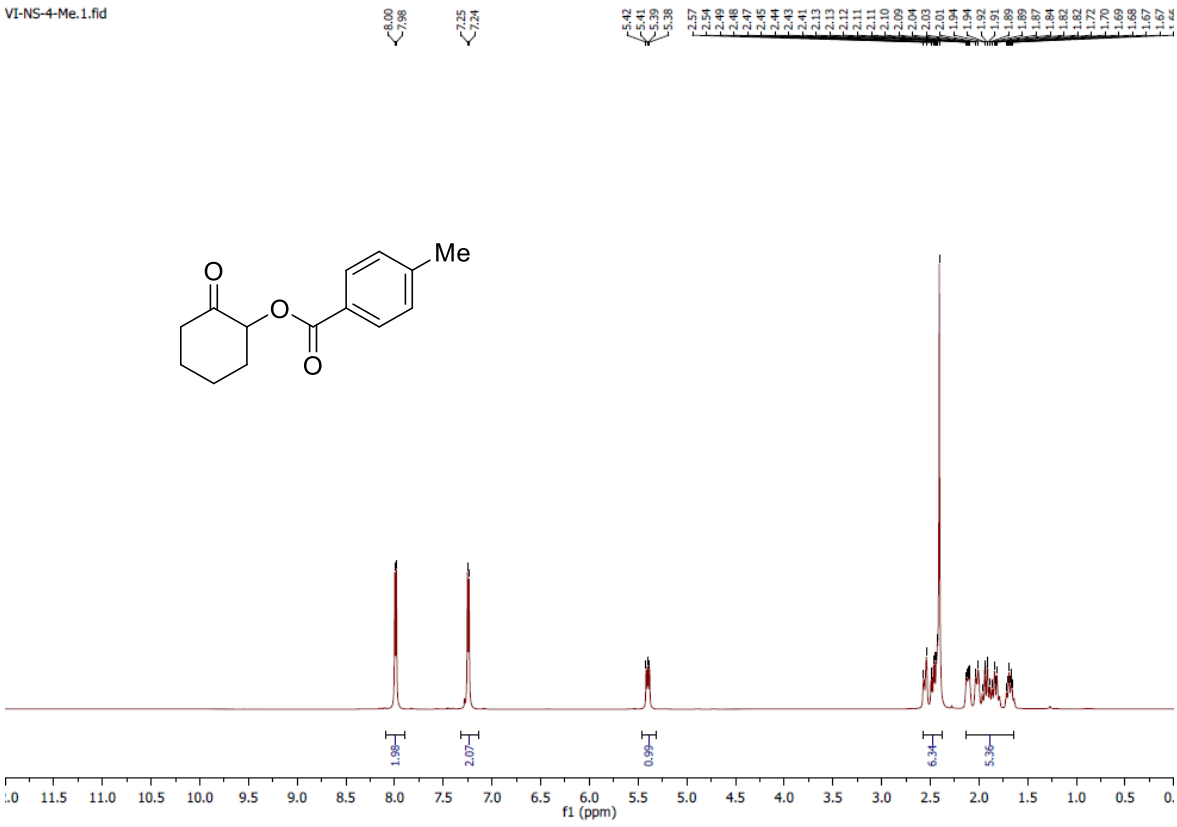


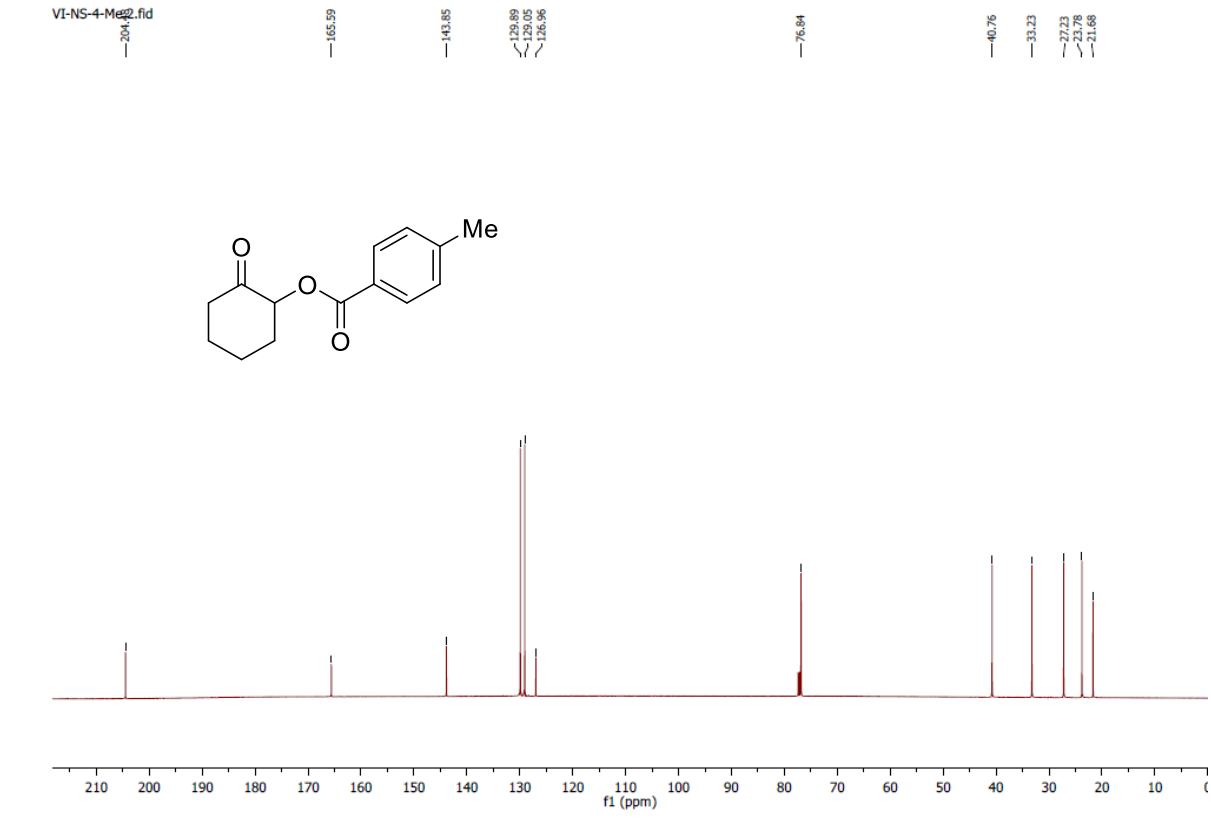


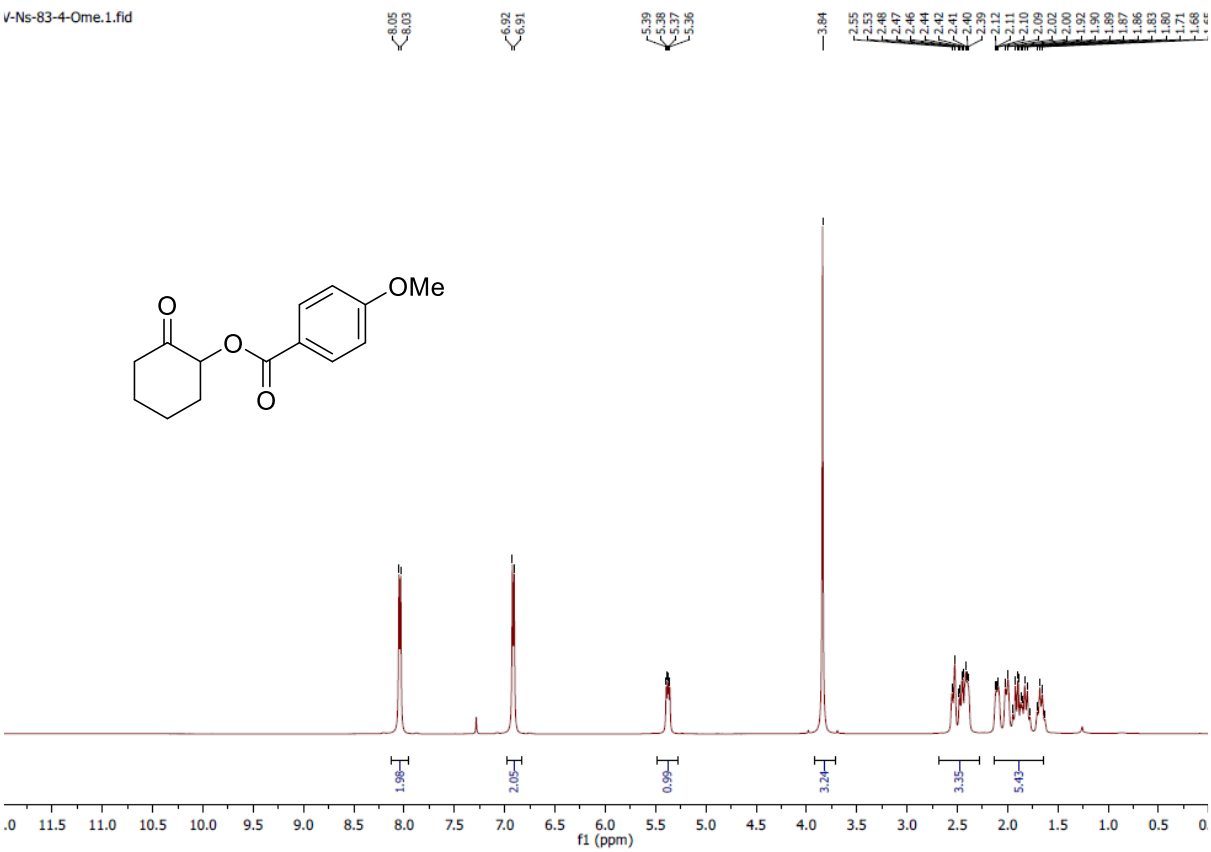
IV-NS-744-13.fid

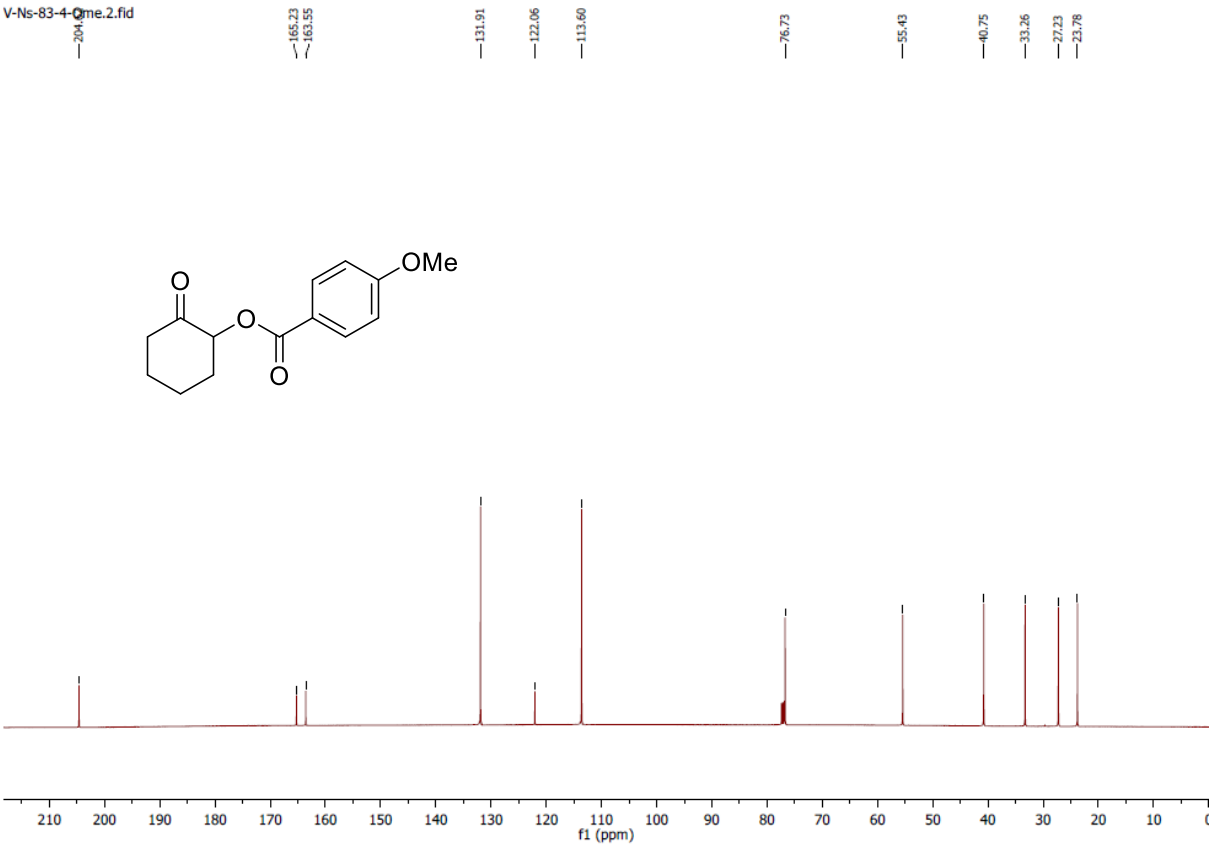


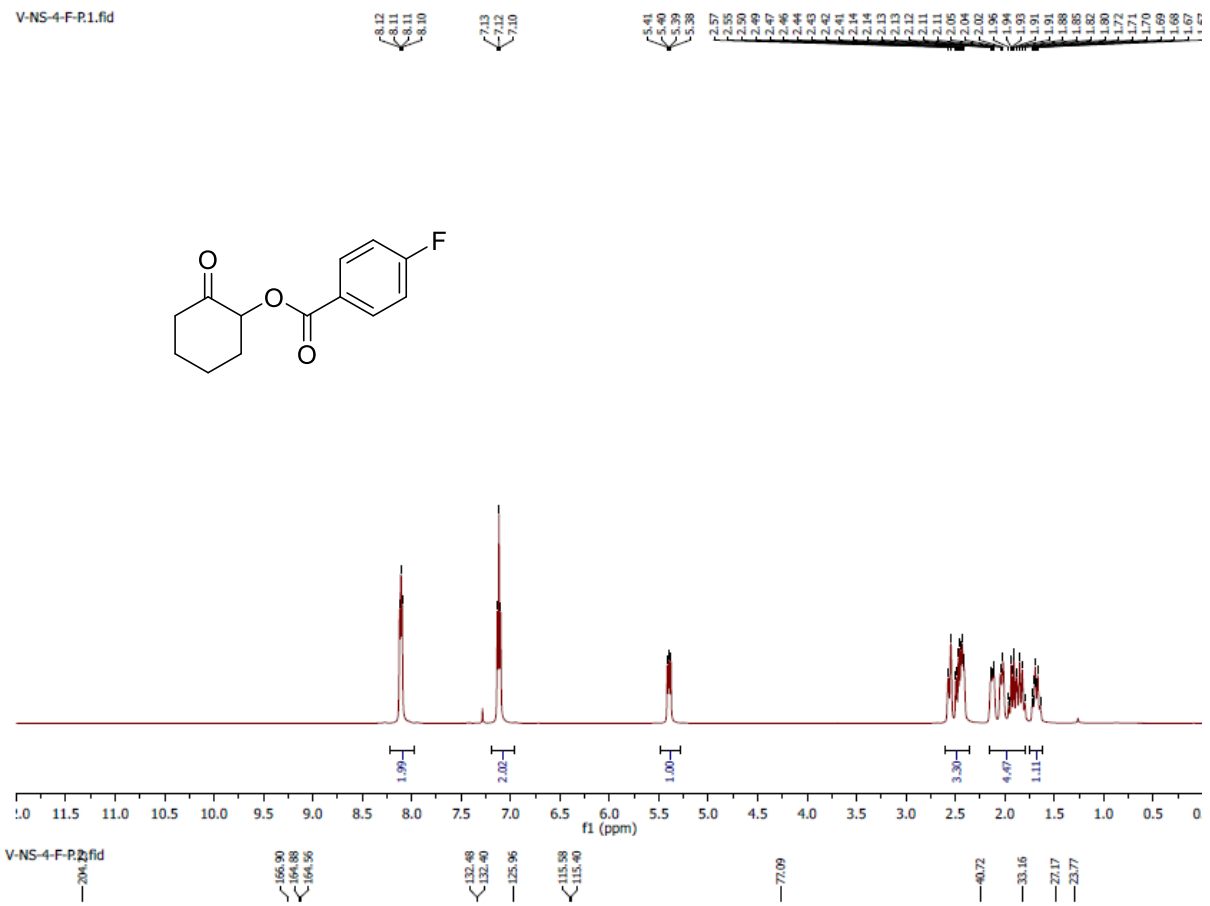


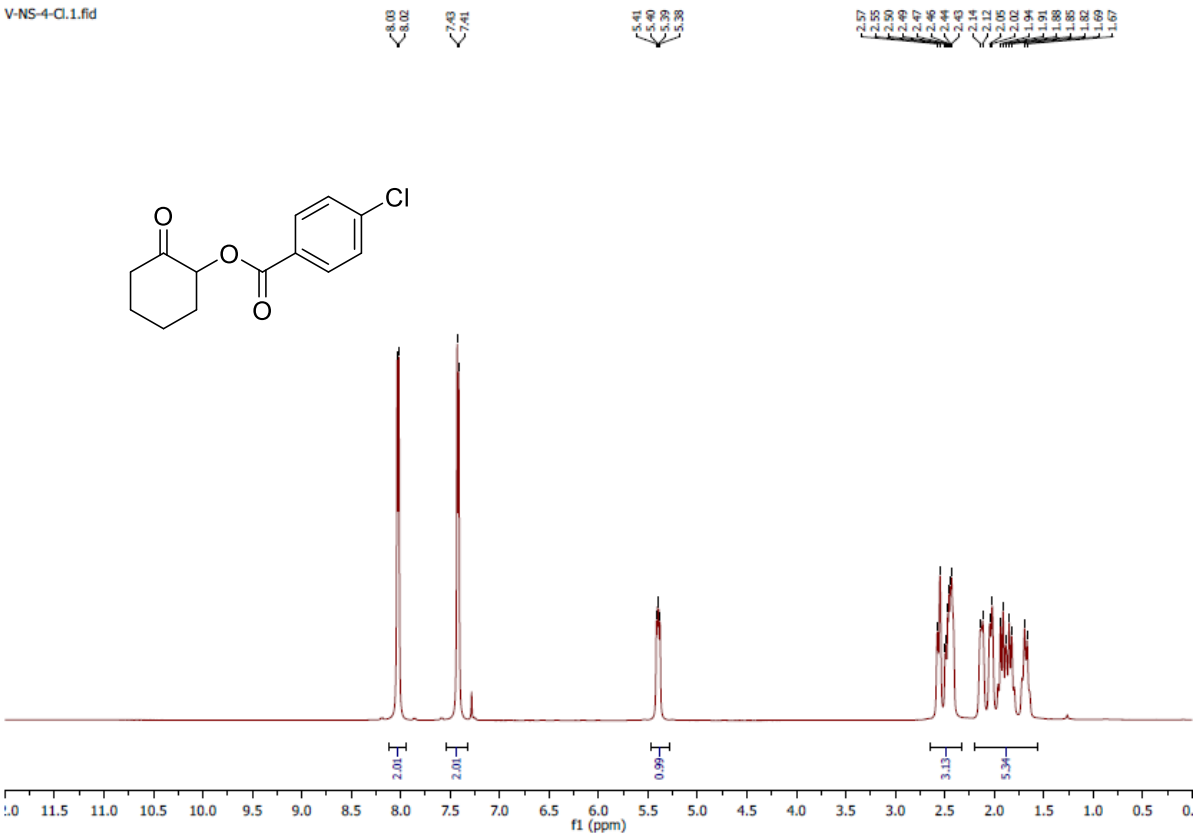

VI-NS-4-Me.1.fid
Me
f1 (ppm)

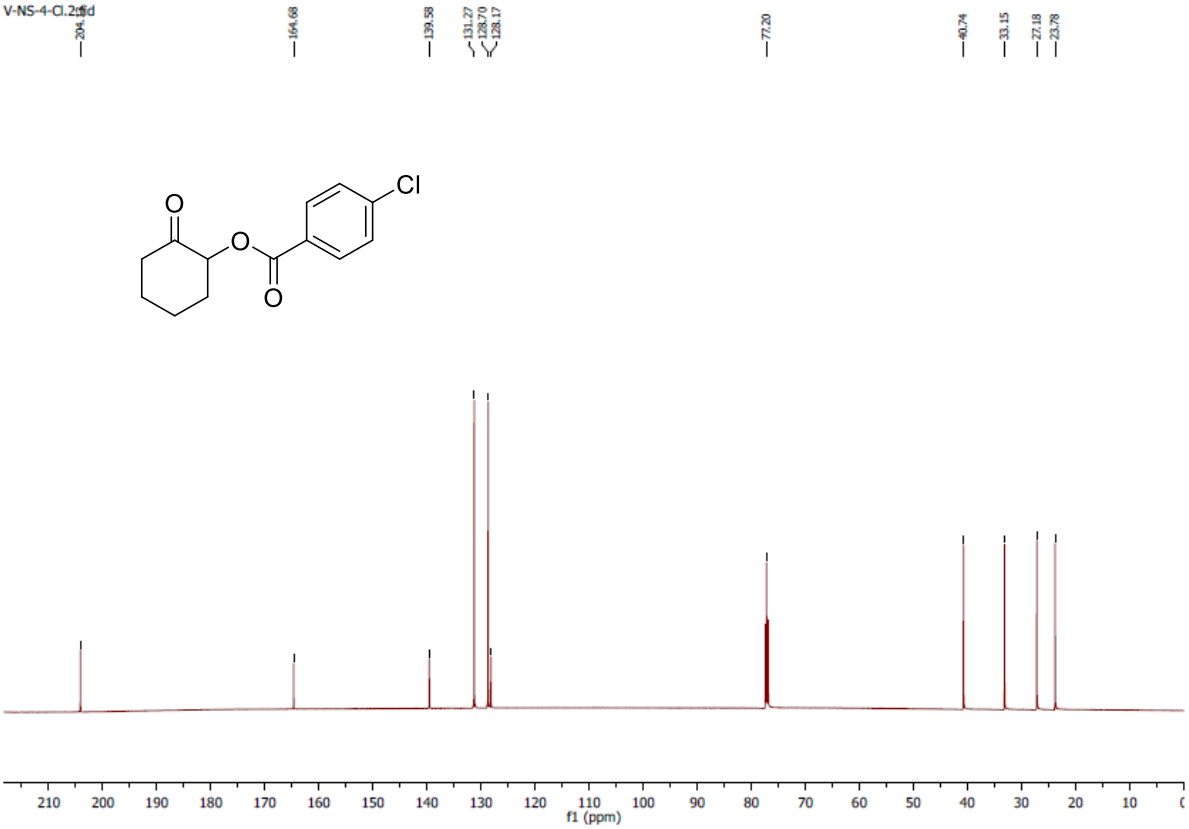

VI-NS-4-Me2.fid
Me
f1 (ppm)

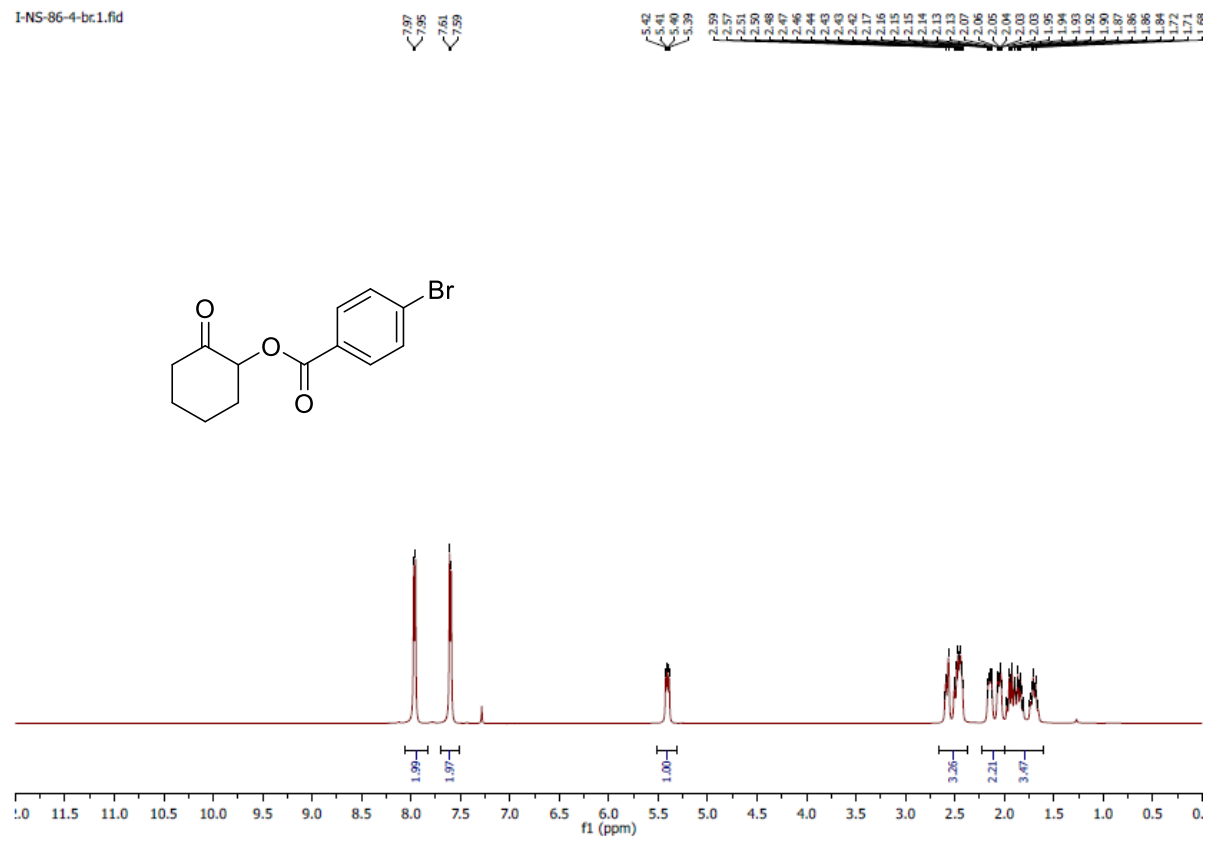

V-Ns-83-4-Ome.1.fid
OMe
f1 (ppm)

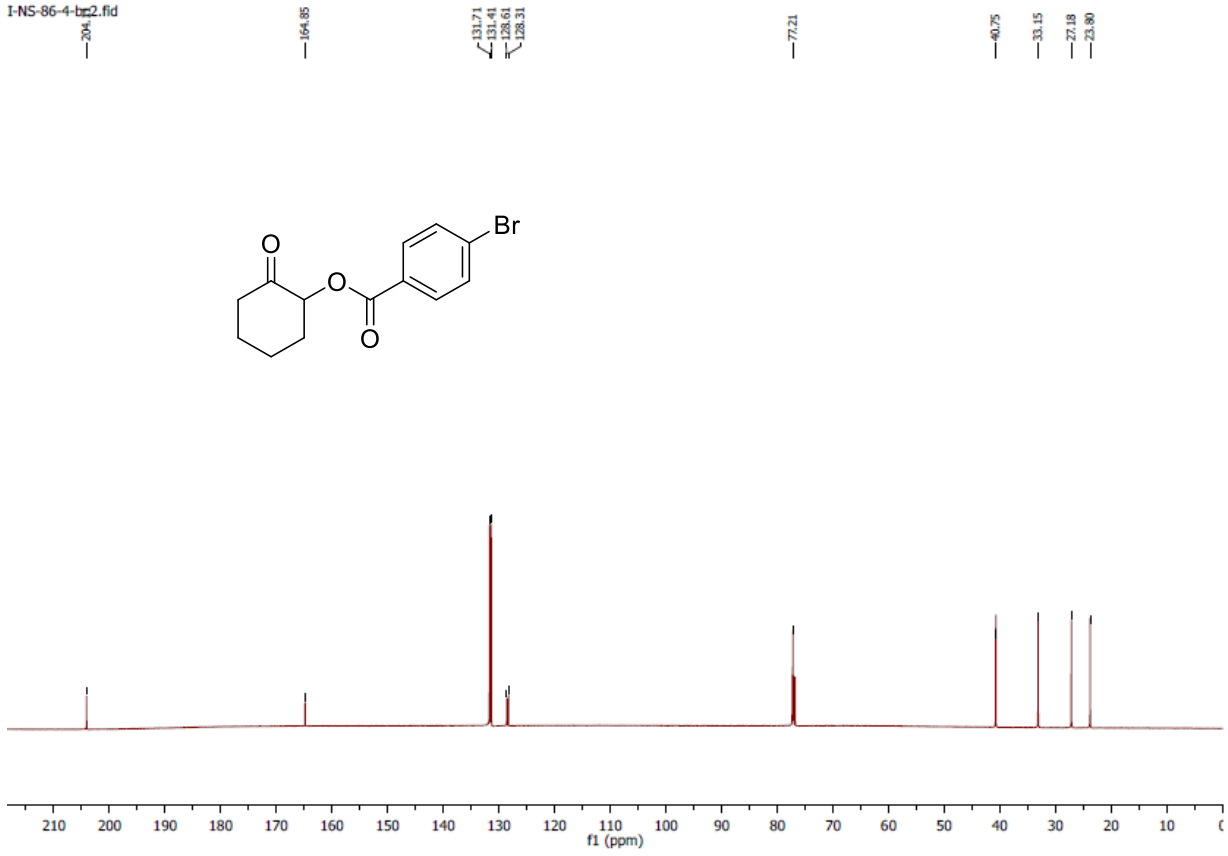

V-Ns-83-4-Ome.2.fid
OMe
f1 (ppm)


V-NS-4-F-P.1.fid
8.12
8.11
8.11
8.10
7.13
7.12
7.10
5.41
5.40
5.39
5.38
2.57
2.55
2.39
2.49
2.47
2.46
2.44
2.43
2.42
2.41
2.14
2.14
2.13
2.13
2.12
2.11
2.11
2.05
2.04
2.02
1.96
1.94
1.93
1.91
1.91
1.88
1.85
1.82
1.80
1.72
1.71
1.70
1.69
1.68
1.67
O
O
O
F
1.99
2.03
1.00
3.30
4.47
1.11
f1 (ppm)
V-NS-4-F-P.2.fid
166.90
164.88
164.56
132.48
132.40
125.96
115.58
115.40
77.09
40.72
33.16
27.17
23.77
O
O
O
F
f1 (ppm)

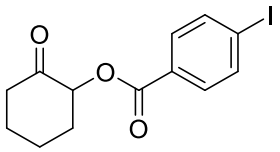

V-NS-4-Cl.1.fid
8.03
8.02
7.43
7.41
5.41
5.40
5.39
5.38
2.57
2.55
2.50
2.49
2.47
2.46
2.44
2.43
2.14
2.12
2.05
2.02
1.94
1.91
1.88
1.85
1.82
1.69
1.67
Cl
O
O
O
2.01
2.01
0.99
3.13
5.34
f1 (ppm)

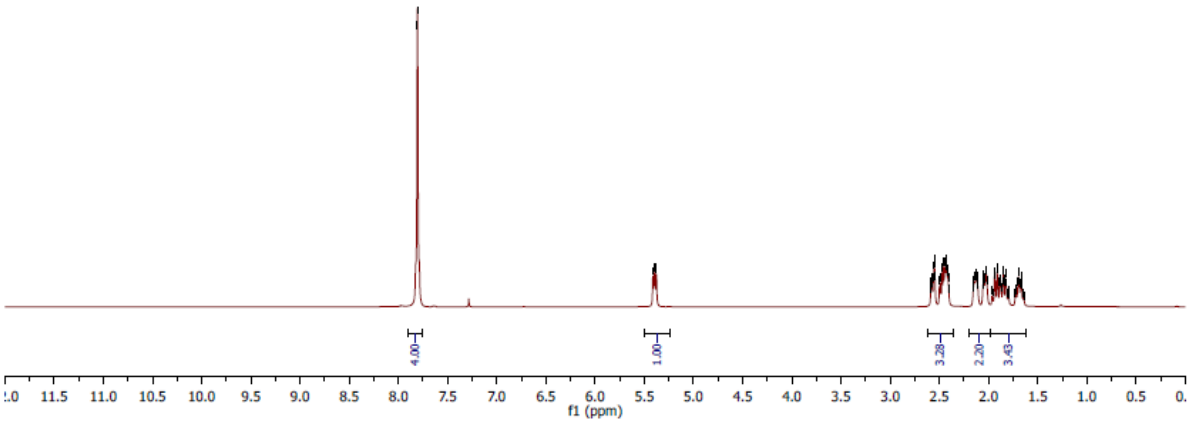

V-NS-4-Cl.2.fid
204.
164.68
139.58
131.27
128.70
128.17
77.20
40.74
33.15
27.18
23.78
Cl
O
O
O
f1 (ppm)


I-NS-86-4-br.1.fid
Br
O
O
O
1.99
1.97
1.00
3.26
2.21
3.47
f1 (ppm)

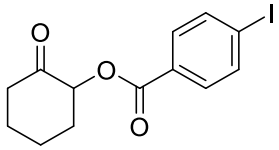

I-NS-86-4-br.2.fid
164.85
131.71
131.41
128.61
128.31
77.21
40.75
33.15
27.18
23.80
Br
O
O
O
f1 (ppm)

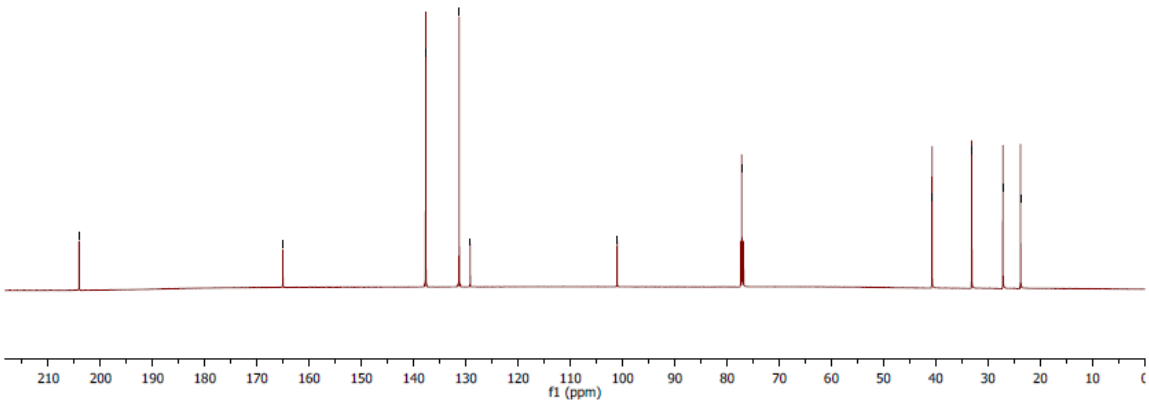
I-NS-102-4-I.1.fid

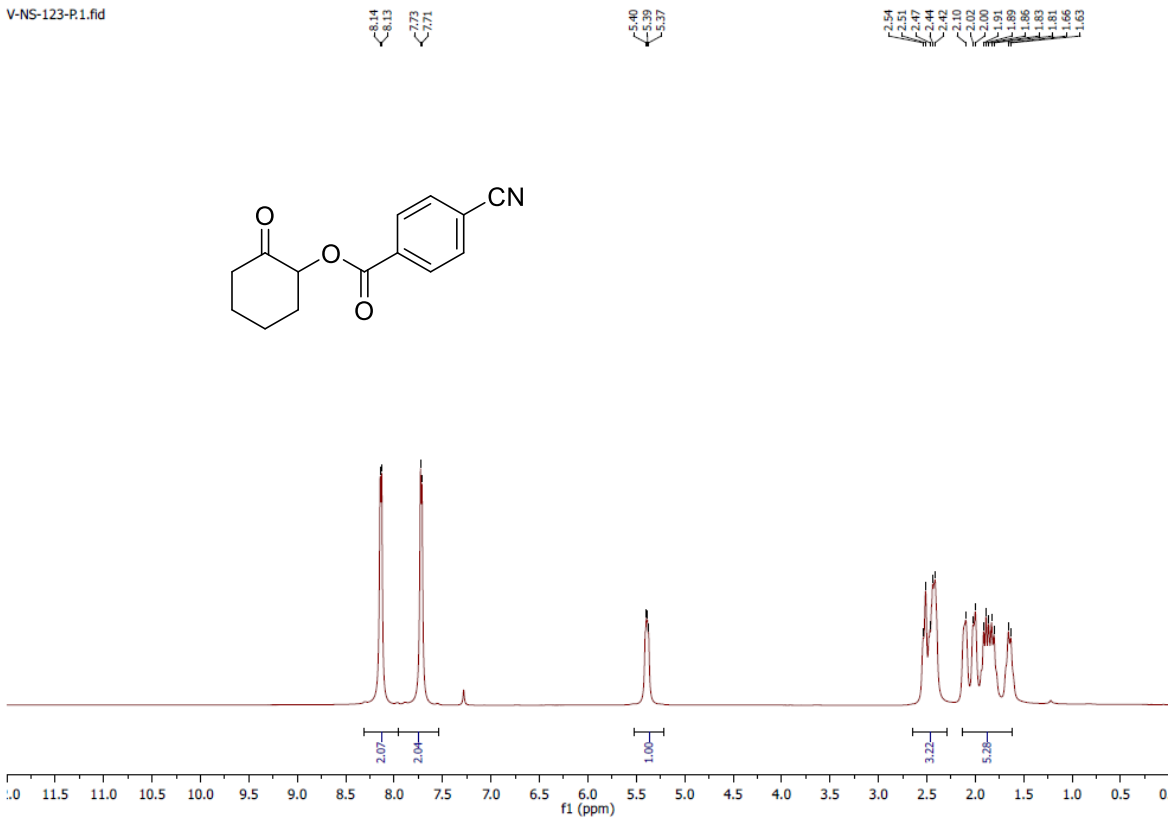


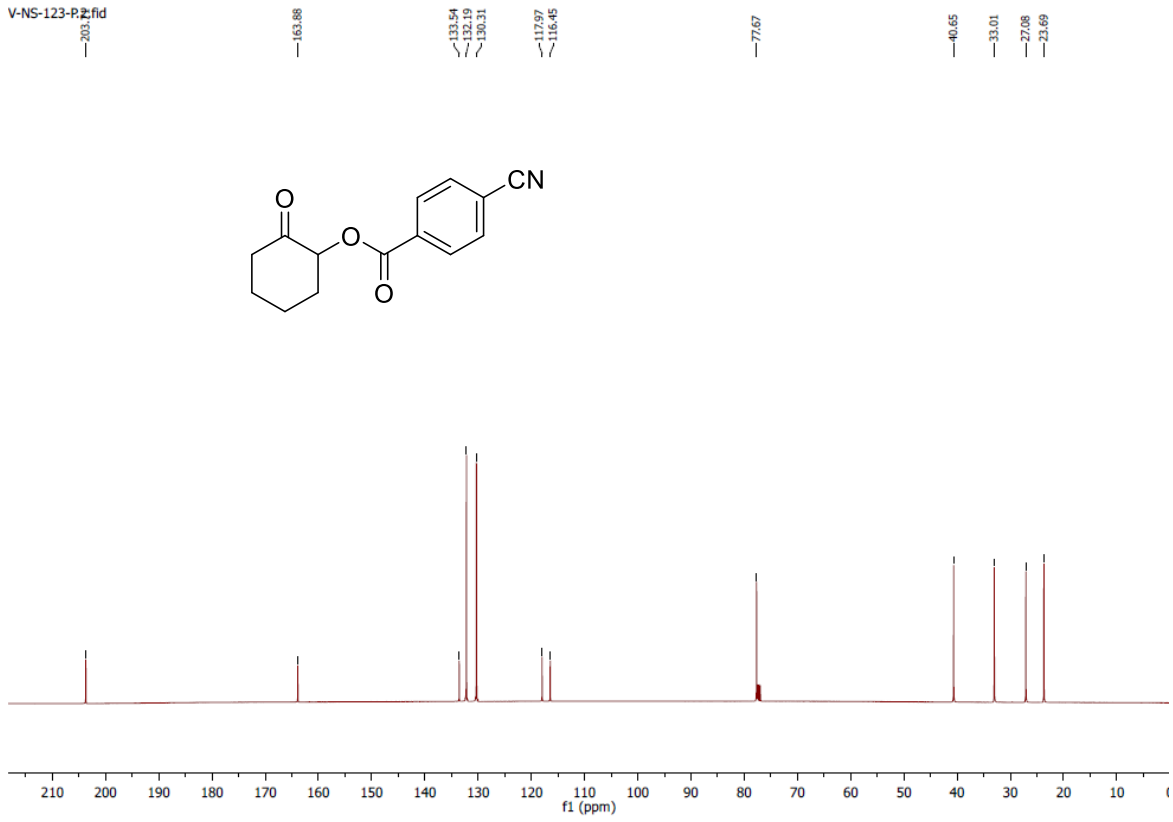


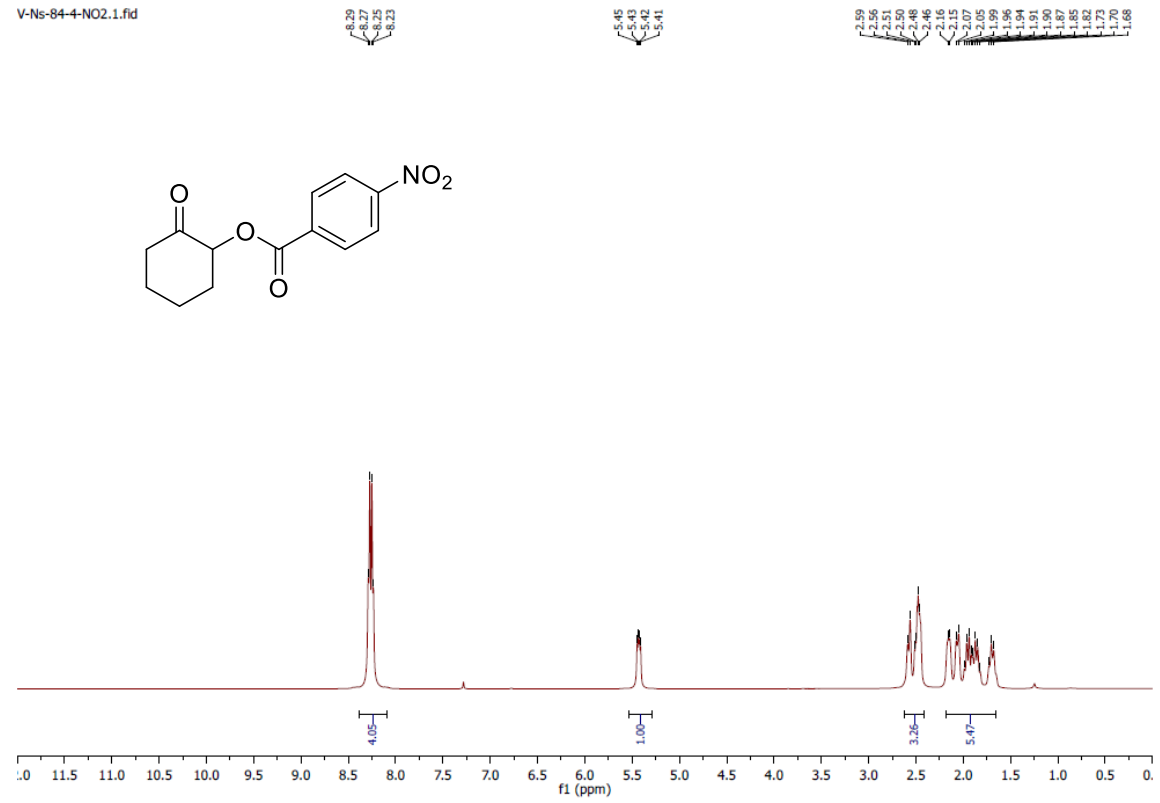
I-NS-102-4-C2.fid

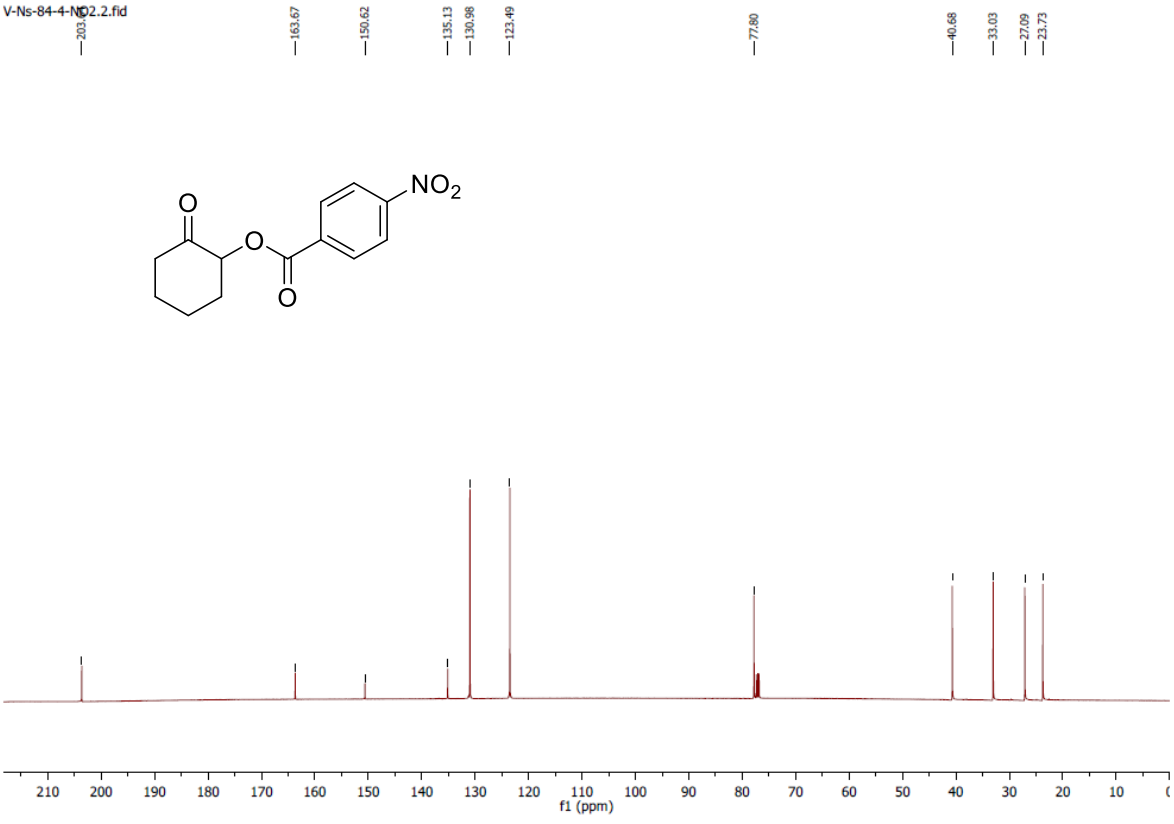


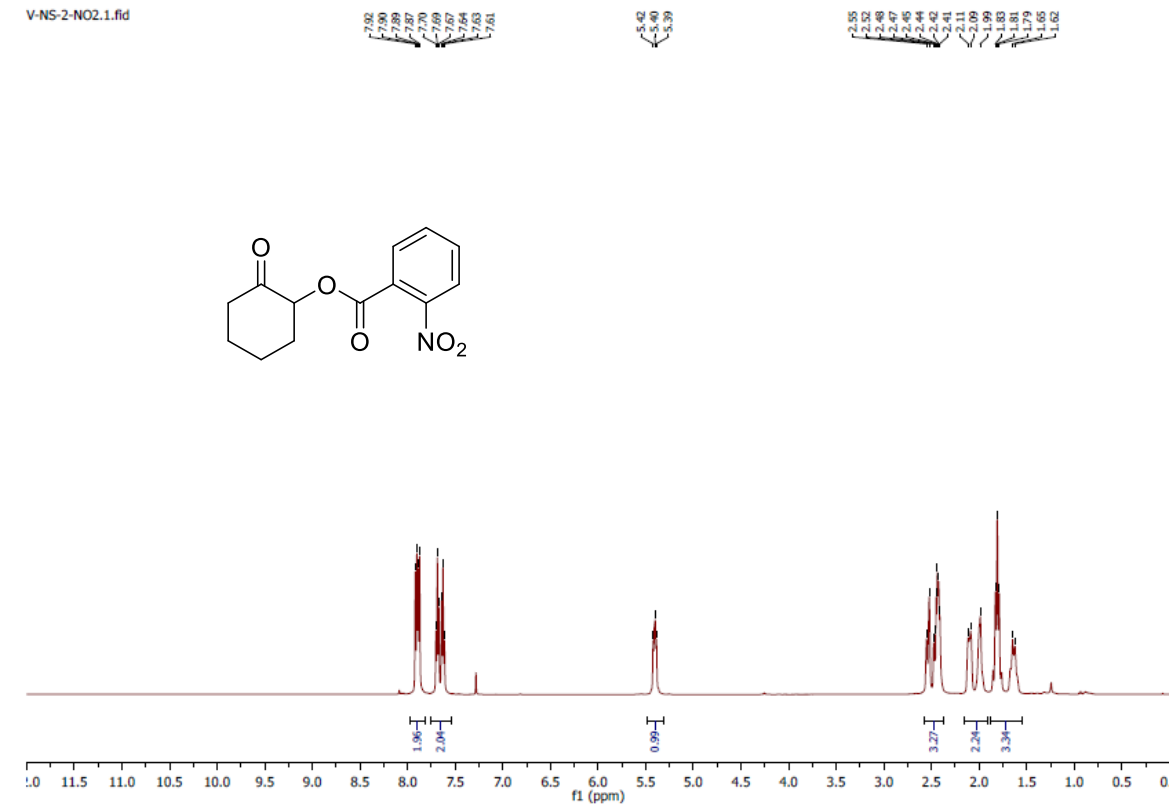


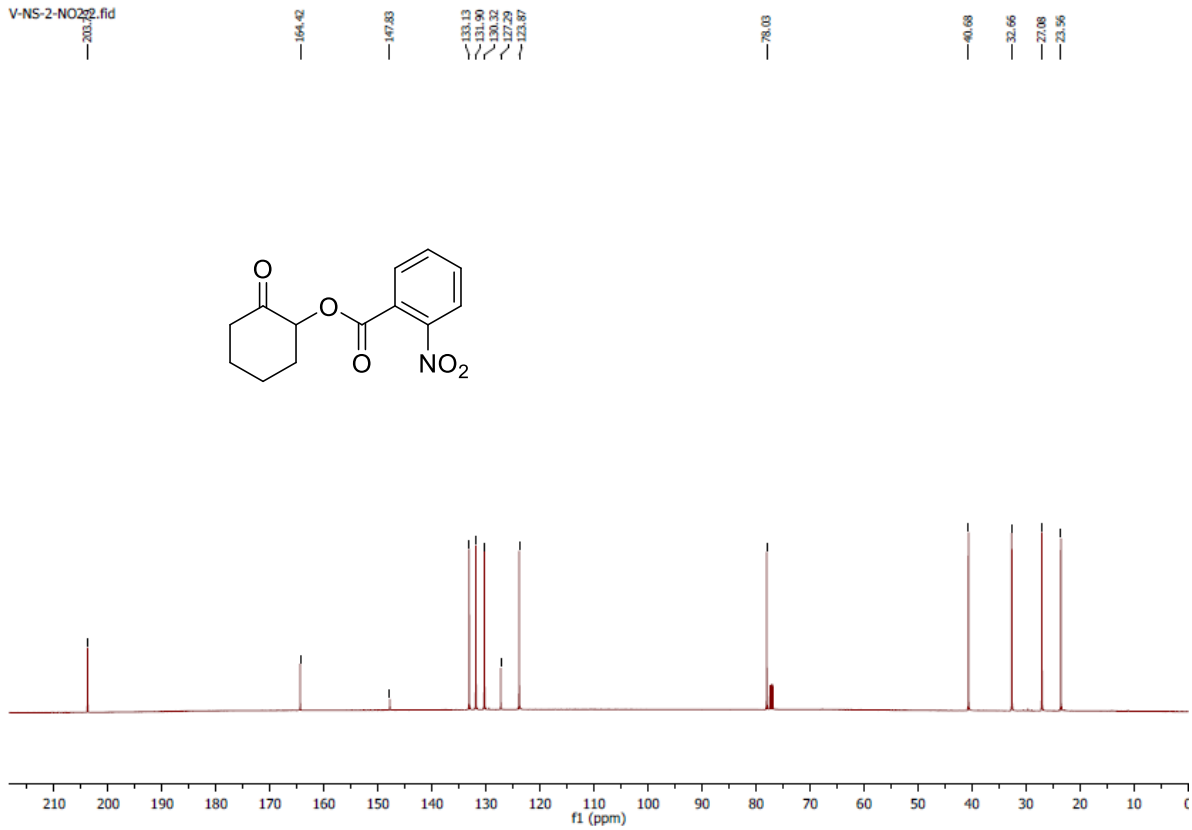

V-NS-123-P.1.fid
8.14
8.13
7.73
7.71
5.40
5.39
5.37
2.54
2.51
2.47
2.44
2.42
2.10
2.02
2.00
1.91
1.89
1.86
1.83
1.81
1.66
1.63
CN
O
O
O
2.07
2.04
1.00
3.22
5.28
f1 (ppm)

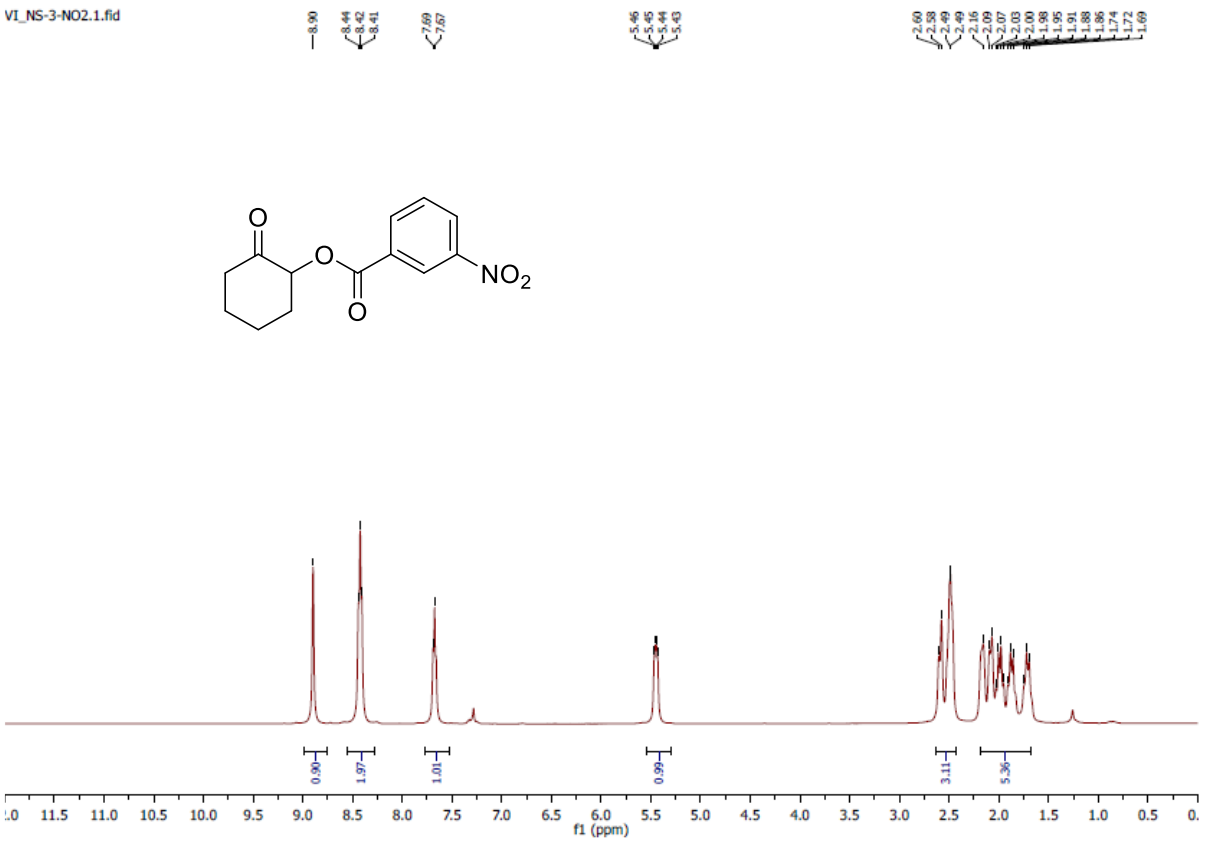

V-NS-123-P.2.fid
203.72
163.88
133.54
132.19
130.31
117.97
116.45
77.67
40.65
33.01
27.08
23.69
CN
O
O
O
f1 (ppm)

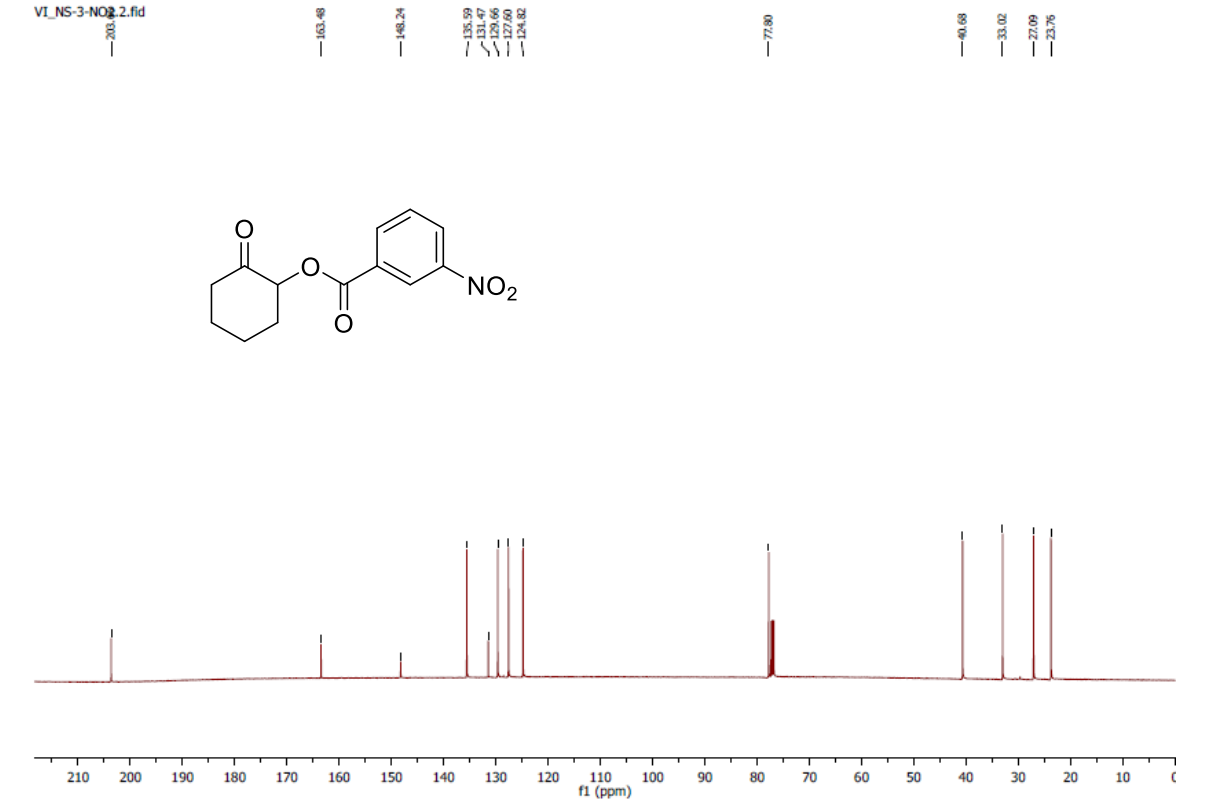

V-Ns-84-4-NO2.1.fid
8.29
8.27
8.25
8.23
5.45
5.43
5.42
5.41
2.59
2.56
2.51
2.50
2.48
2.46
2.16
2.15
2.07
2.05
1.99
1.96
1.94
1.91
1.90
1.87
1.85
1.82
1.73
1.70
1.68
O
O
O
NO2
4.05
1.00
3.26
5.47
f1 (ppm)

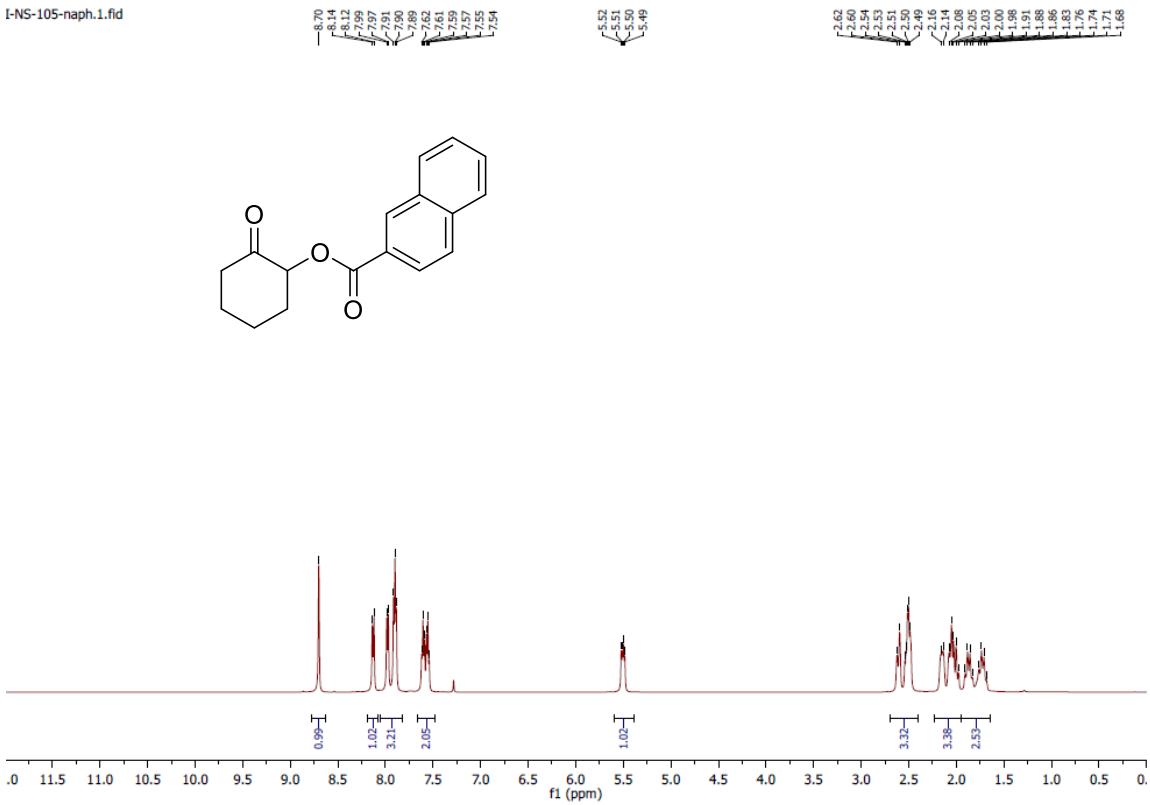

V-Ns-84-4-NO2.2.fid
203.62
163.67
150.62
135.13
130.98
123.49
77.80
40.68
33.03
27.09
23.73
O
O
O
NO2
f1 (ppm)

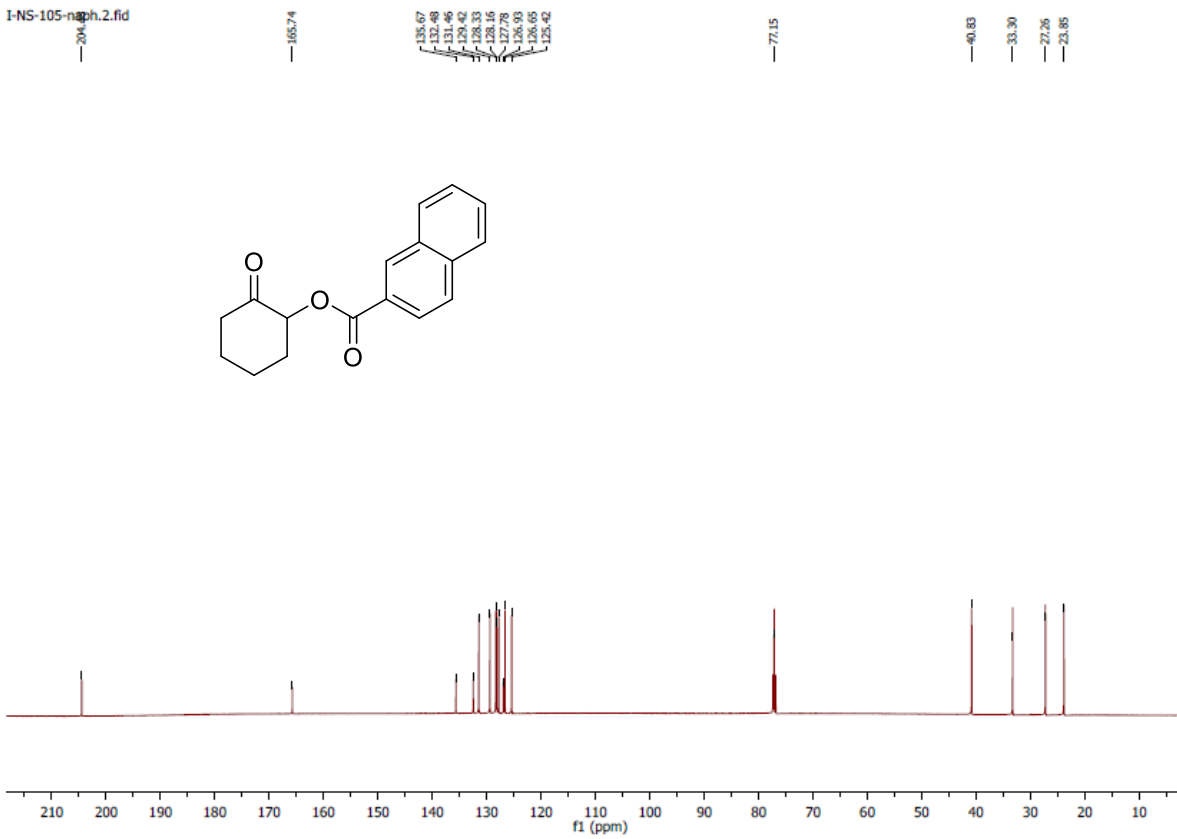

V-NS-2-NO2.1.fid
7.92
7.90
7.89
7.87
7.70
7.69
7.67
7.64
7.63
7.61
5.42
5.40
5.39
2.55
2.52
2.48
2.47
2.45
2.44
2.42
2.41
2.11
2.09
1.99
1.83
1.81
1.79
1.65
1.62
O
O
O
NO2
1.96
2.04
0.99
3.27
2.24
3.34
f1 (ppm)


V-NS-2-NO2.2.fid
164.42
147.83
133.13
131.90
130.32
127.29
125.87
78.03
40.68
32.66
27.08
23.56
O
O
O
NO2
f1 (ppm)

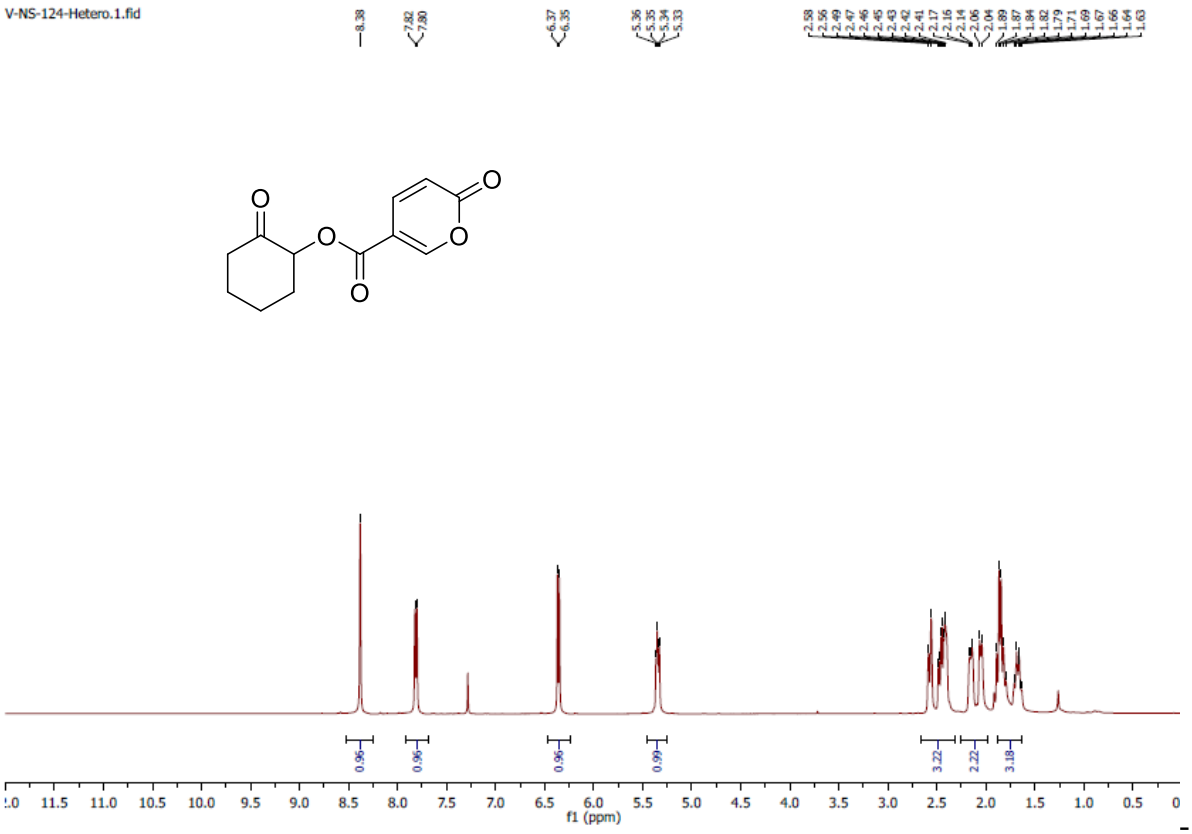

VI_NS-3-NO2.1.fid
8.90
8.44
8.42
8.41
7.69
7.67
5.46
5.45
5.44
5.43
2.60
2.58
2.49
2.49
2.49
2.16
2.09
2.07
2.03
2.00
1.98
1.95
1.91
1.88
1.86
1.74
1.72
1.69
O
O
O
NO2
0.90
1.97
1.01
0.99
3.11
5.36
f1 (ppm)


VI_NS-3-NO2.2.fid
203.48
163.48
148.24
135.59
131.47
129.66
127.60
124.82
77.80
40.68
33.02
27.09
23.76
O
O
O
NO2
f1 (ppm)

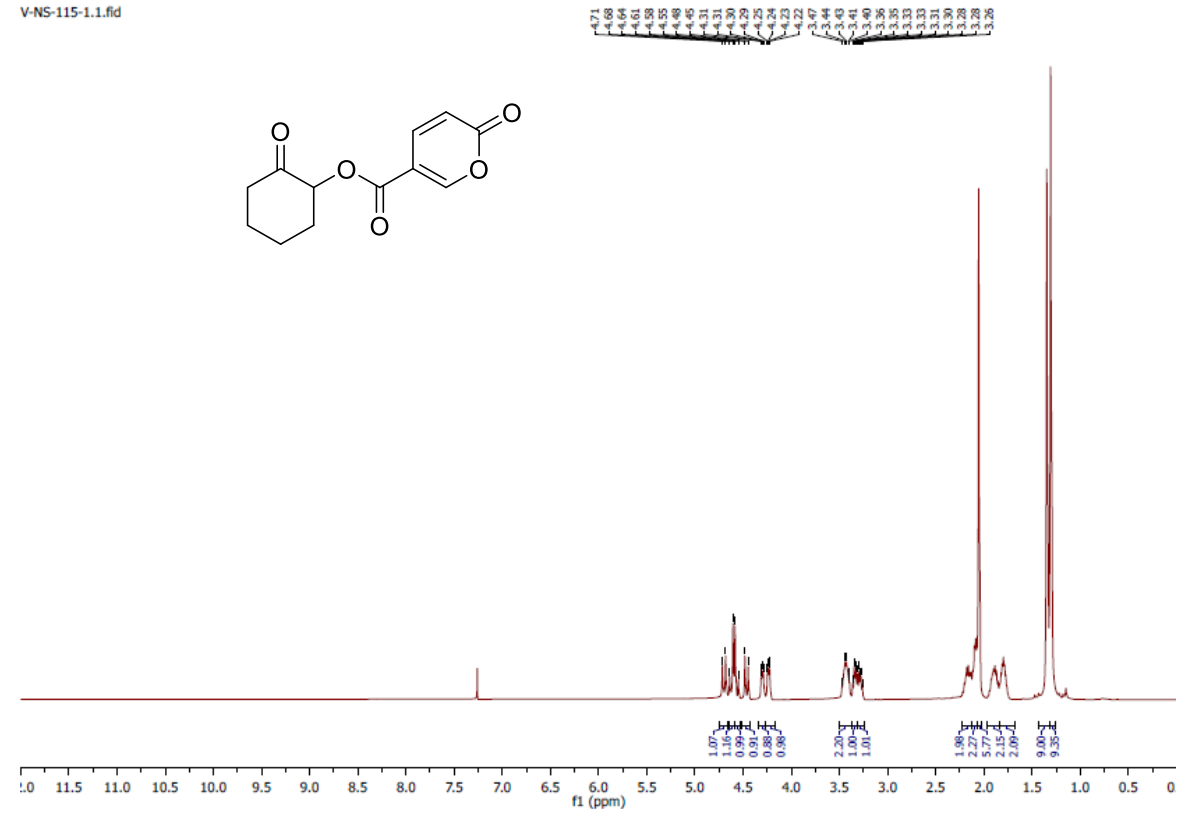

I-NS-105-naph.1.fid
f1 (ppm)

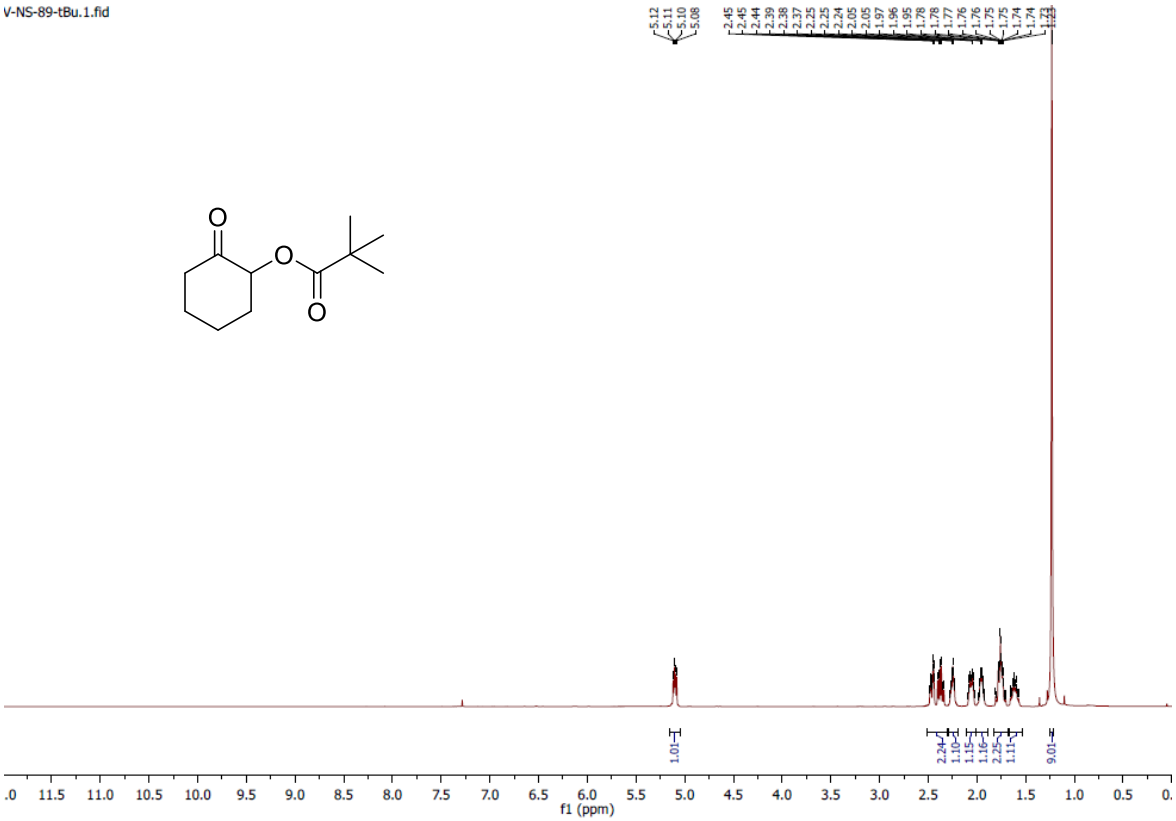

I-NS-105-naph.2.fid
f1 (ppm)

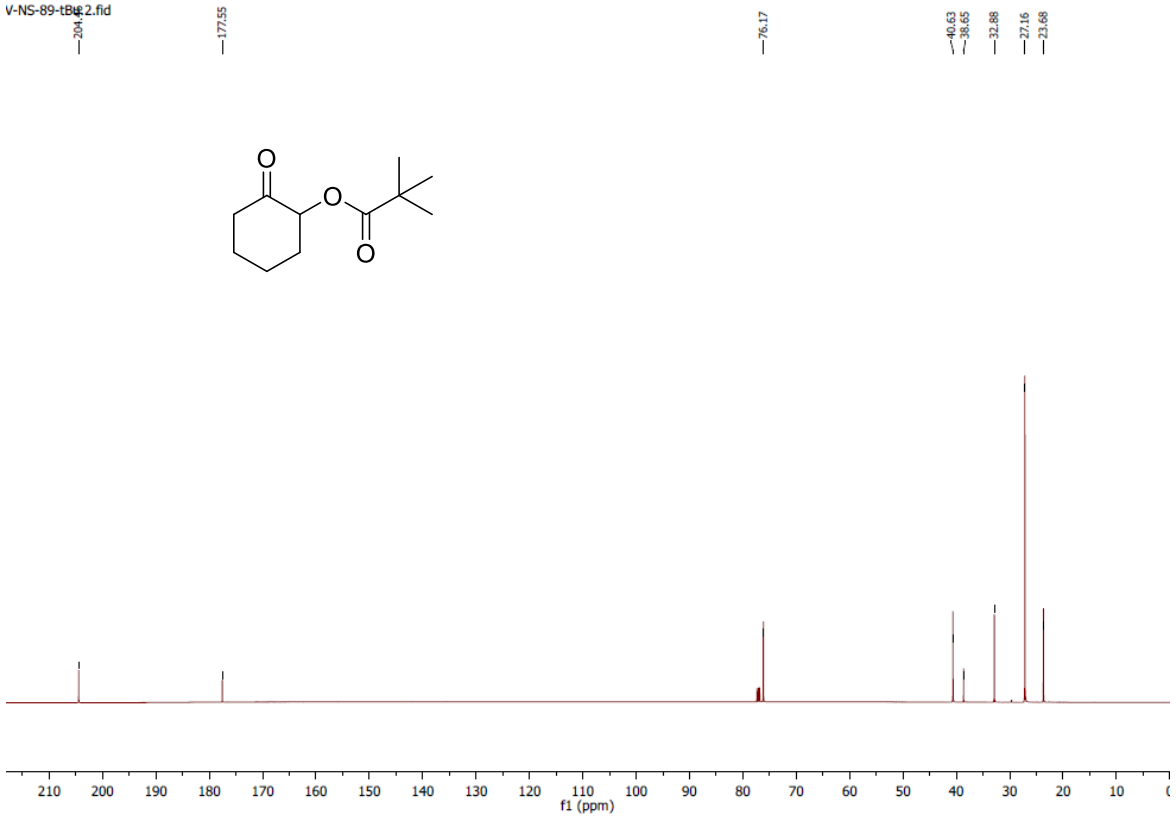
V-NS-124-Hetero.1.fid

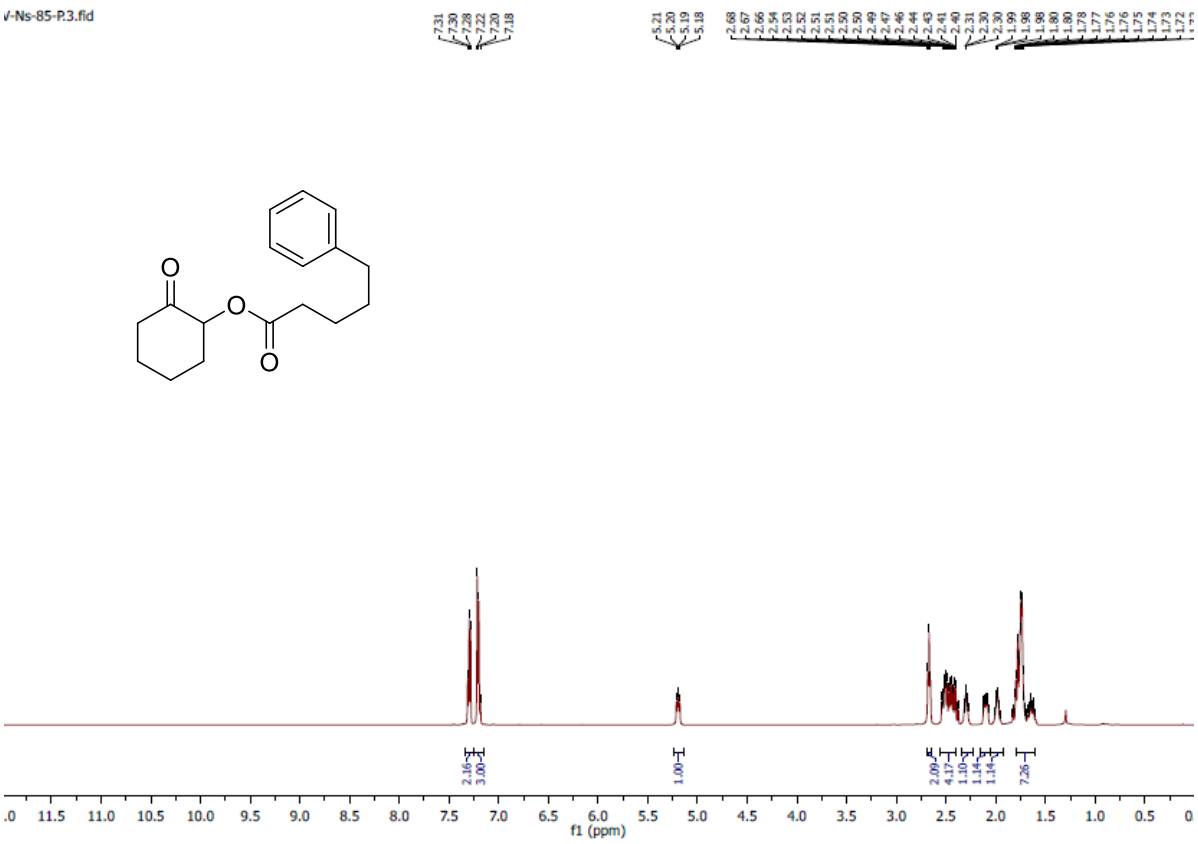


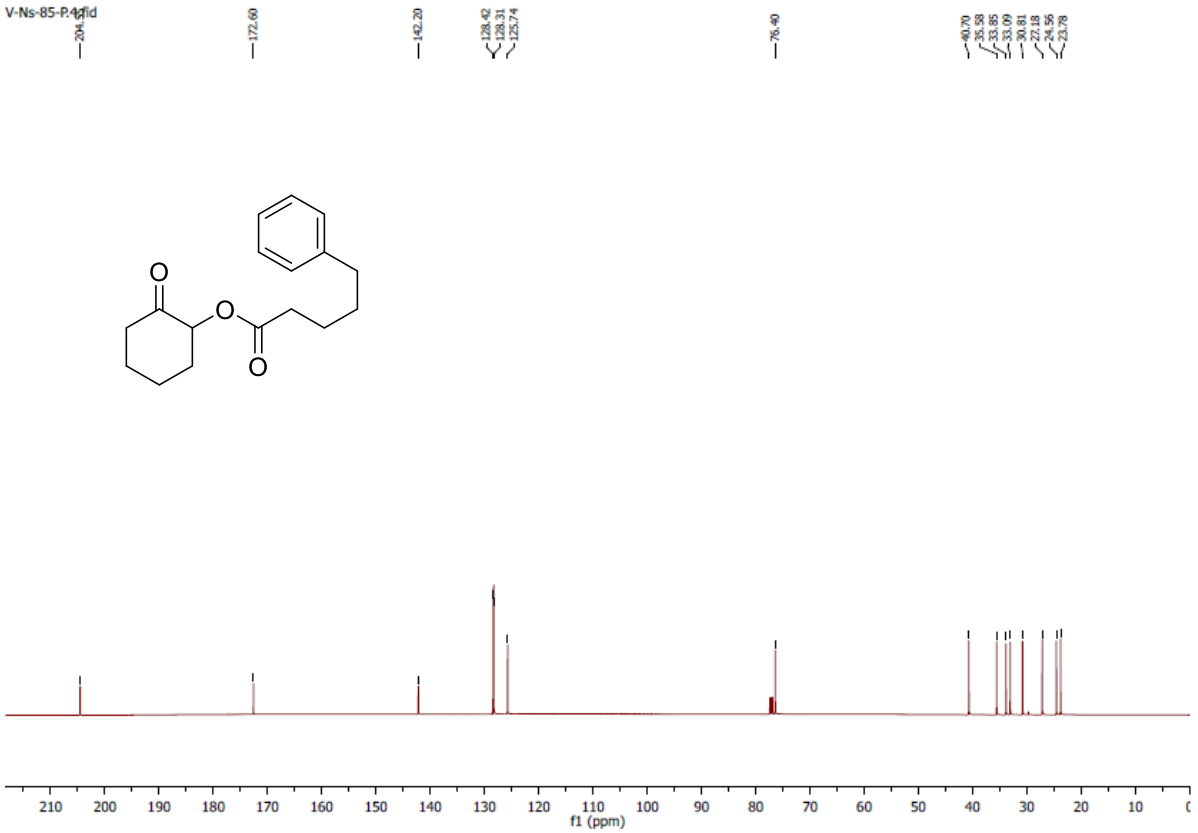
V-NS-115-1.1.fid



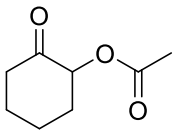

V-NS-89-tBu.1.fid
f1 (ppm)

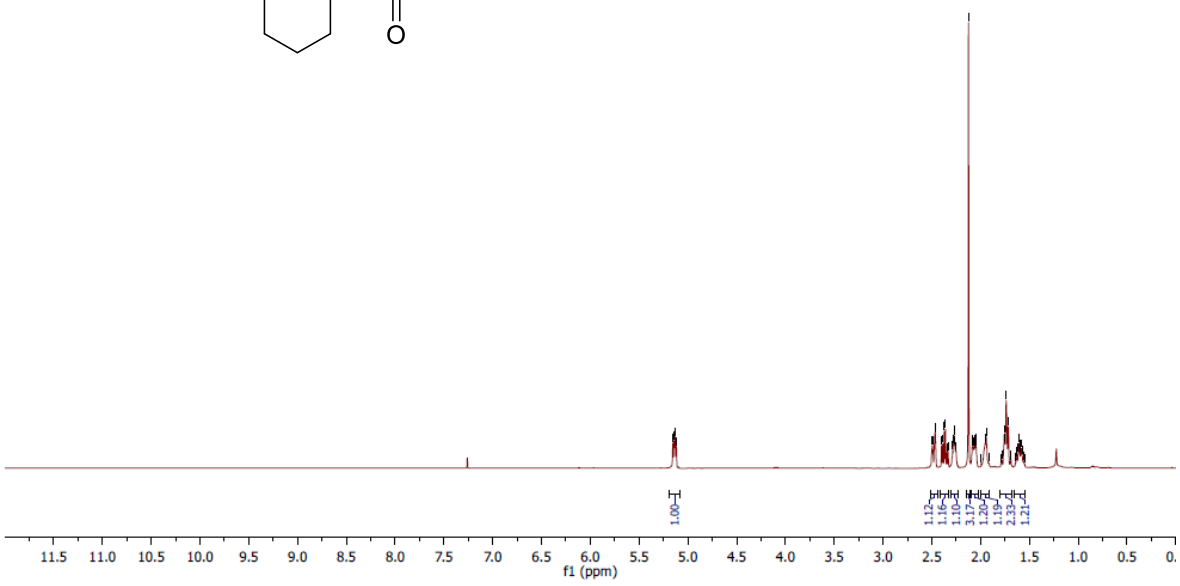

V-NS-89-tBu2.fid
f1 (ppm)


V-Ns-85-P3.fid
f1 (ppm)

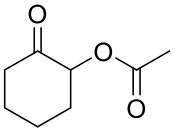

V-Ns-85-P4.fid
f1 (ppm)

V-NS-103-F1.1.fid

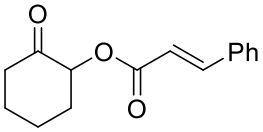


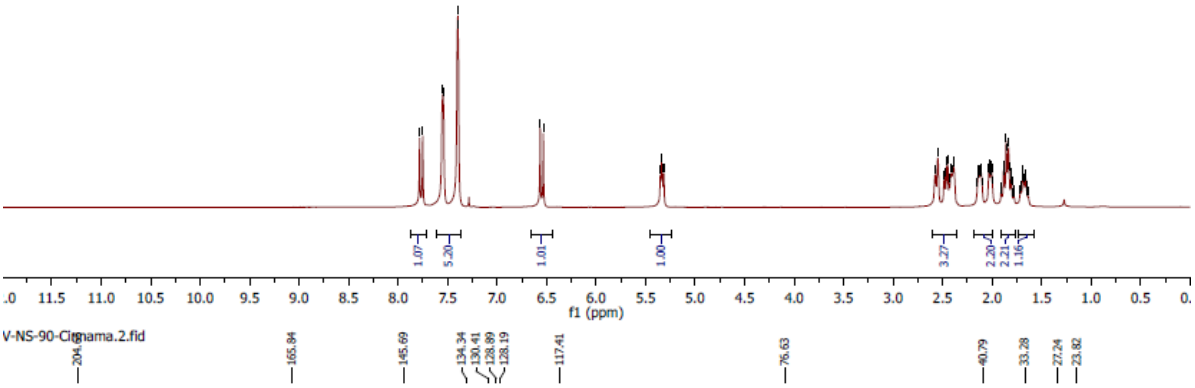


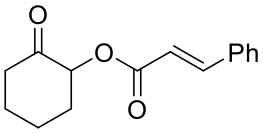
V-NS-103-F1.2.fid

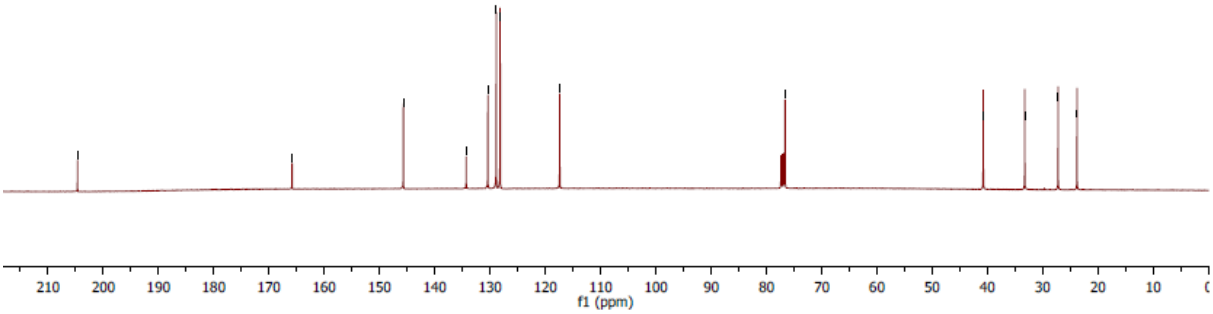


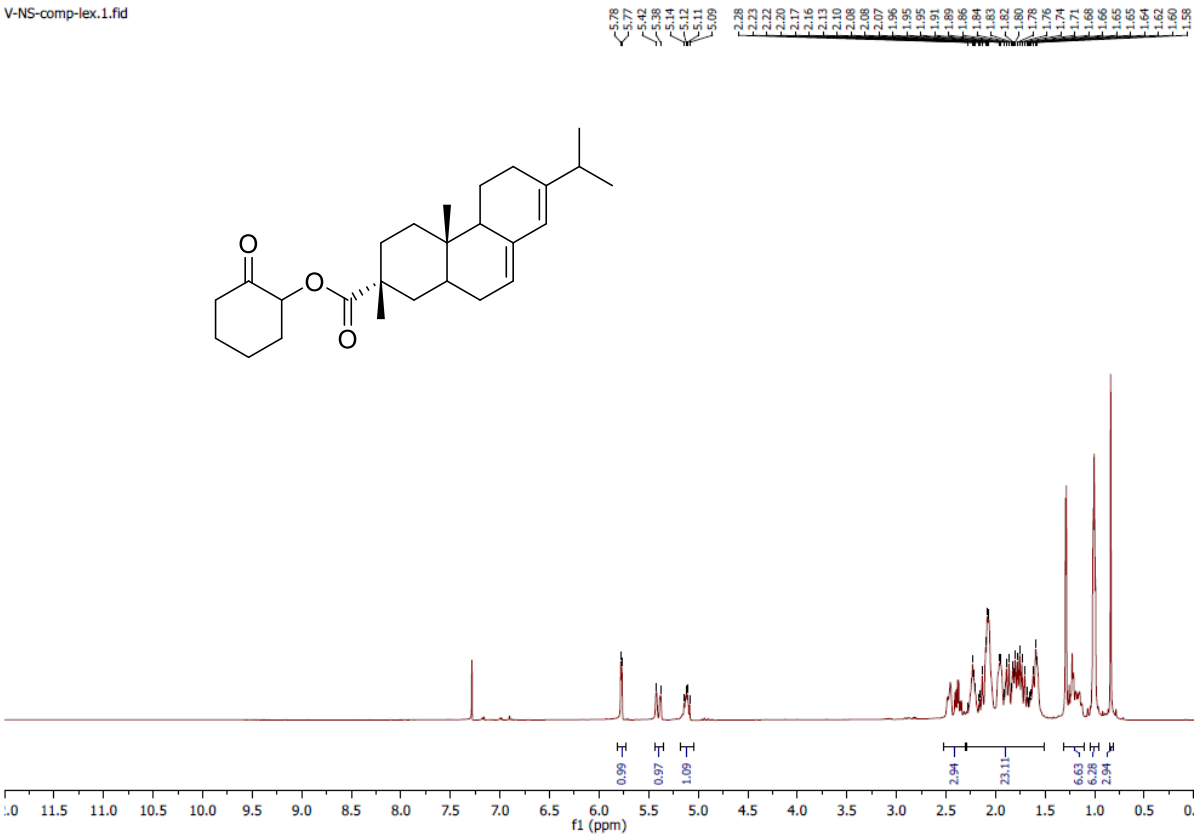

V-NS-90-Cinnama.1.fid

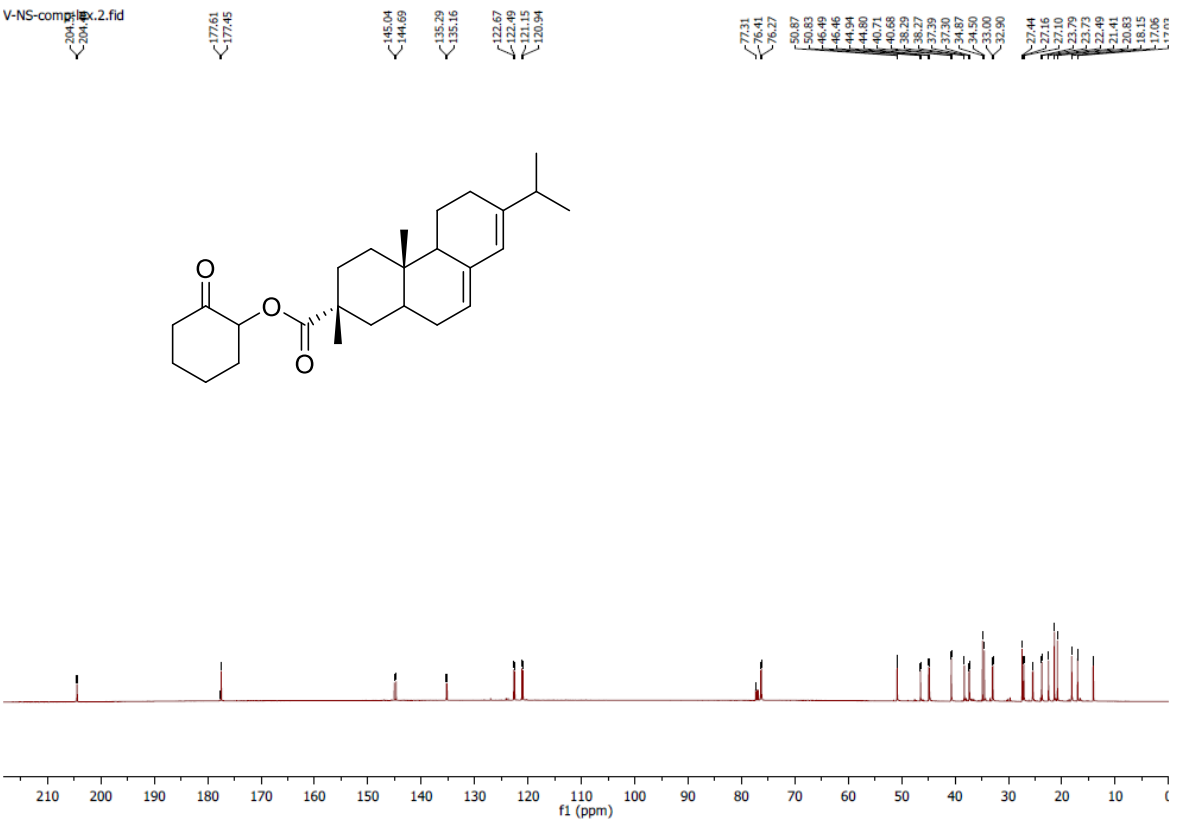

O
O
O
Ph

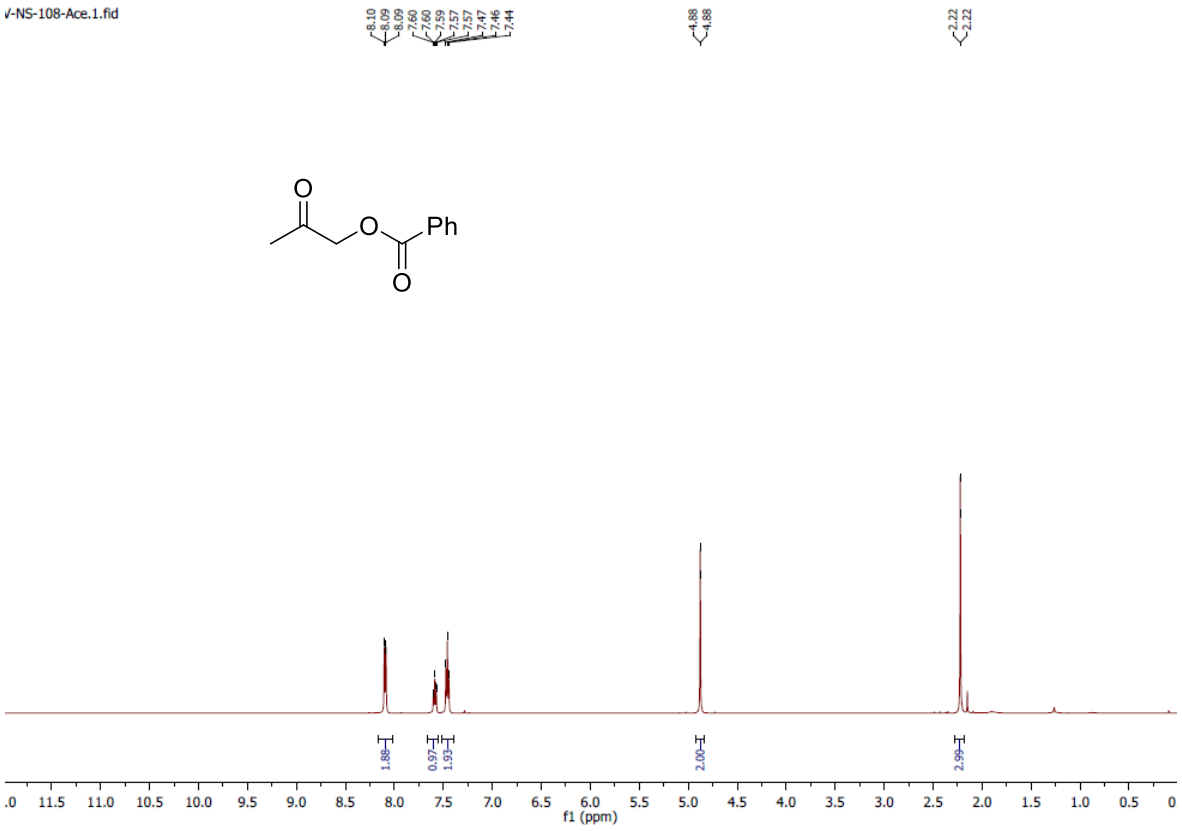

1.07
5.20
1.01
1.00
3.27
2.20
2.21
1.16
f1 (ppm)
V-NS-90-Cinnama.2.fid
165.84
145.69
134.34
130.41
128.89
128.19
117.41
76.63
40.79
33.28
27.24
23.82

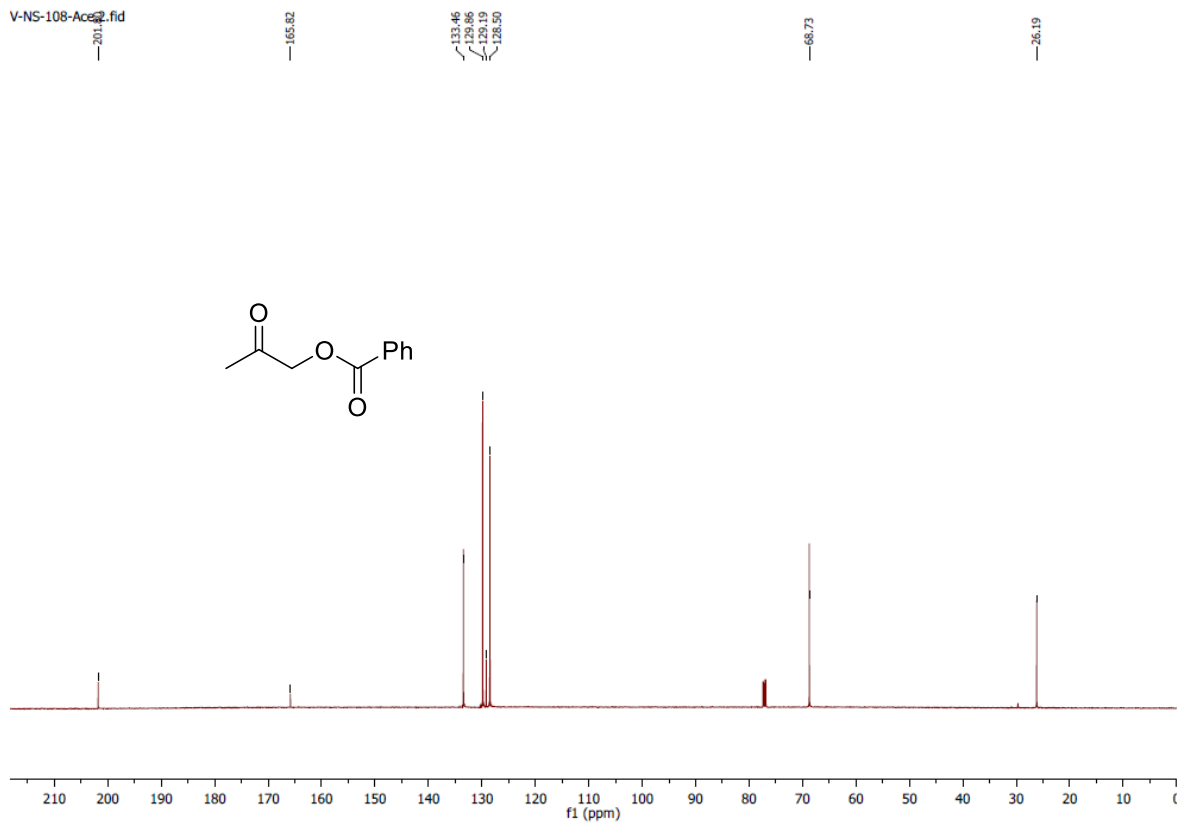

O
O
O
Ph

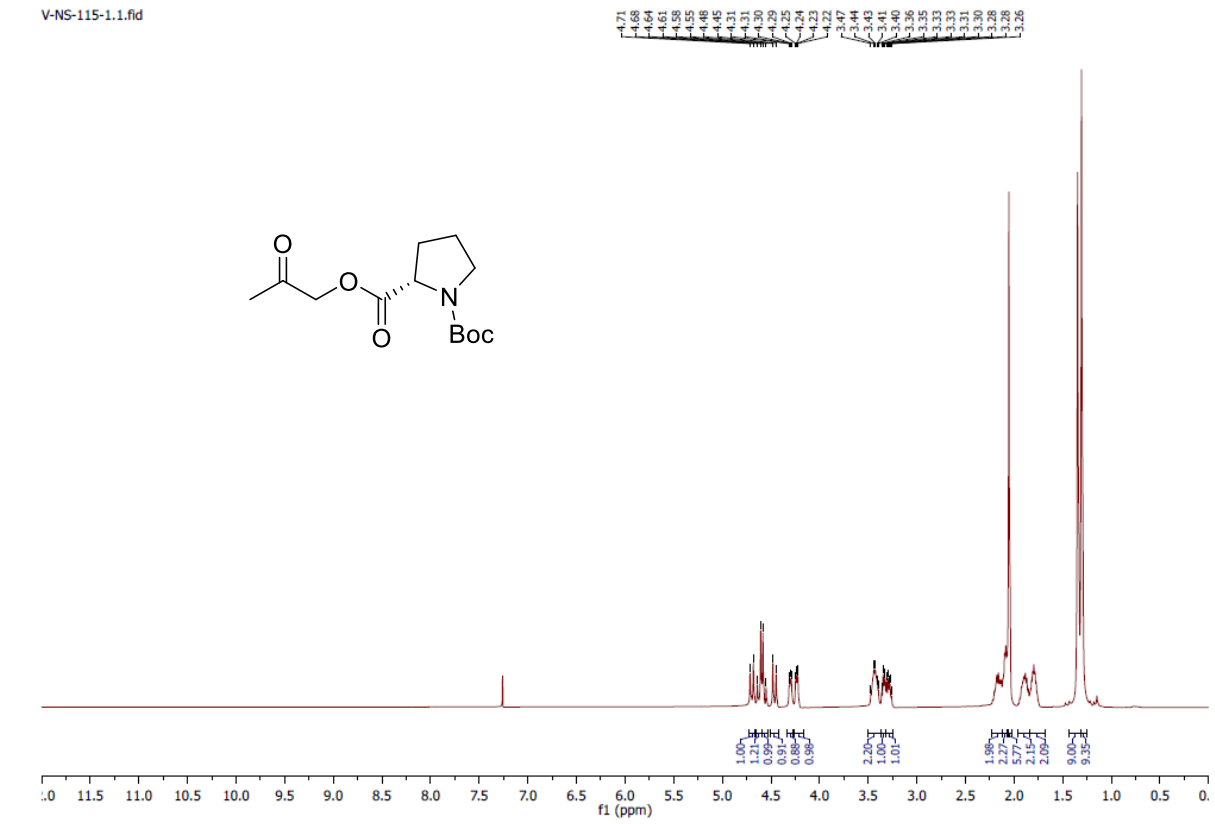

f1 (ppm)

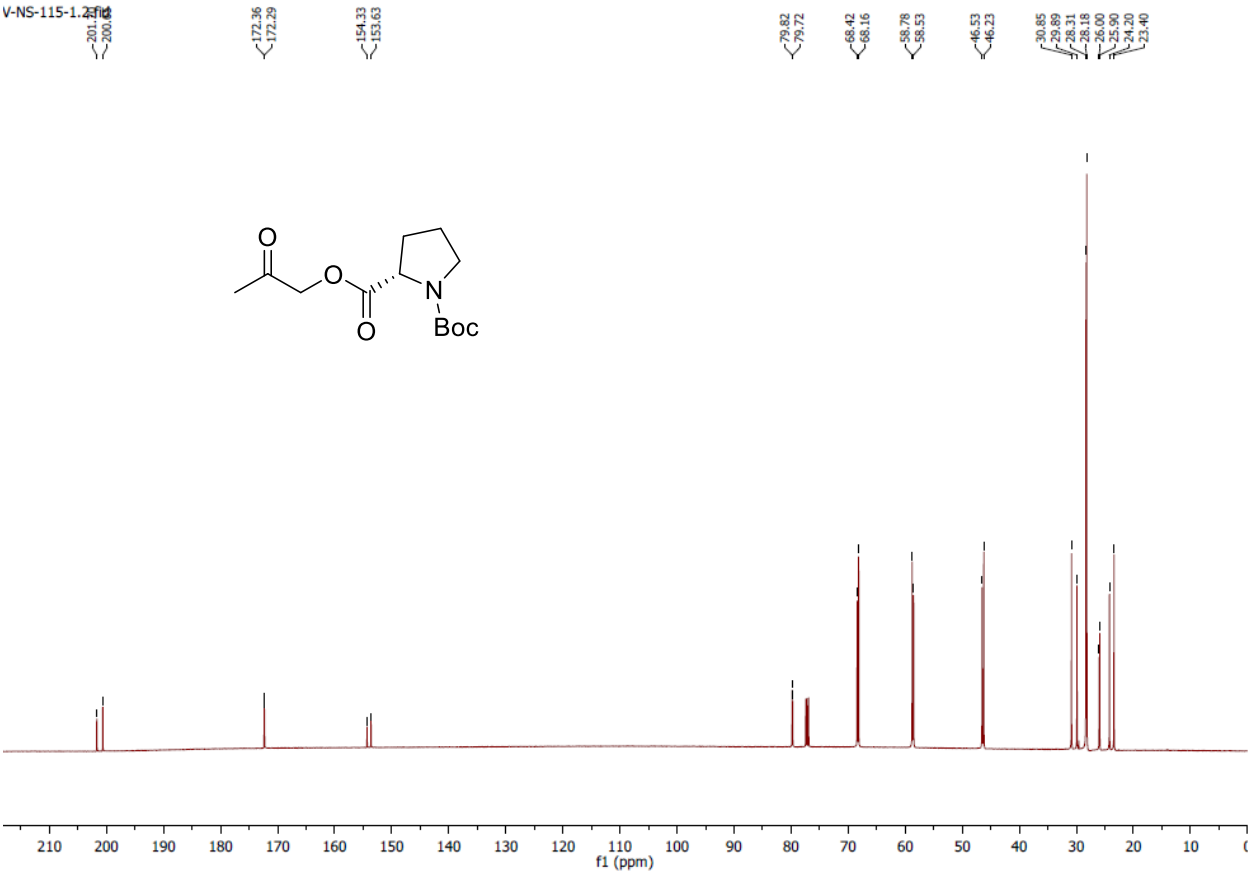

V-NS-comp-lex.1.fid
f1 (ppm)


V-NS-comp-lex.2.fid
f1 (ppm)


V-NS-108-Ace.1.fid
8.10
8.09
8.09
7.60
7.60
7.59
7.57
7.57
7.47
7.46
7.44
4.88
4.88
2.22
2.22
O
O
Ph
O
1.88
0.97
1.93
2.00
2.99
f1 (ppm)


V-NS-108-Ace2.fid
201.52
165.82
133.46
129.86
129.19
128.50
68.73
26.19
O
O
Ph
O
f1 (ppm)


V-NS-115-1.1.fid
O
O
O
N
Boc
f1 (ppm)


V-NS-115-1.2.fid
O
O
O
N
Boc
f1 (ppm)

Copy of HPLC Chromatograms

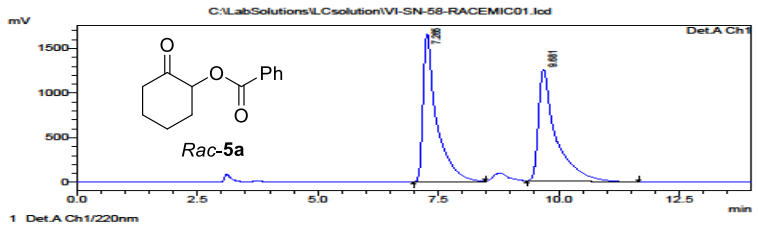
5/27/2022 10:26:58 1 / 1

==== Shimadzu LCsolution Analysis Report ====

C:\LabSolutions\LCsolution\VI-SN-58-RACEMIC01.lcd

Acquired by	: Admin
Sample Name	:
Sample ID	: VI-NS-58
Vail #	:
Injection Volume	: 1 uL
Data File Name	: VI-SN-58-RACEMIC01.lcd
Method File Name	: ChiralPak AD-H-10%-1.0 mL-220nm.lcm
Batch File Name	:
Report File Name	: Default.lcr
Data Acquired	: 5/23/2022 6:21:39 PM
Data Processed	: 5/24/2022 9:42:38 AM

<Chromatogram>



PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.365	32053322	1658214	50.749	57.013
2	9.681	31107035	1250294	49.251	42.987
Total		63160357	2908508	100.000	100.000

C:\LabSolutions\LCsolution\VI-SN-58-RACEMIC01.lcd

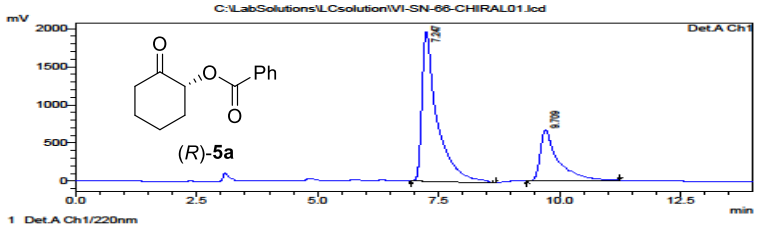
5/27/2022 12:56:44 1 / 1

==== Shimadzu LCsolution Analysis Report ====

C:\LabSolutions\LCsolution\VI-SN-66-CHIRAL01.lcd

Acquired by	: Admin
Sample Name	:
Sample ID	: VI-SN-66
Vail #	:
Injection Volume	: 1 uL
Data File Name	: VI-SN-66-CHIRAL01.lcd
Method File Name	: ChiralPak AD-H-10%-1.0 mL-220nm.lcm
Batch File Name	:
Report File Name	: Default.lcr
Data Acquired	: 5/27/2022 12:39:55 PM
Data Processed	: 5/27/2022 12:54:00 PM

<Chromatogram>



PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.347	42601638	1961064	71.962	74.750
2	9.709	16598891	662439	28.038	25.250
Total		59200529	2623502	100.000	100.000

C:\LabSolutions\LCsolution\VI-SN-66-CHIRAL01.lcd