

Rh(III)-Catalyzed Cyclopropanation Initiated by C-H Activation: Ligand Development Enables a Diastereoselective [2+1] Annulation of N-Enoxyphthalimides and Alkenes

Supporting Information

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General methods

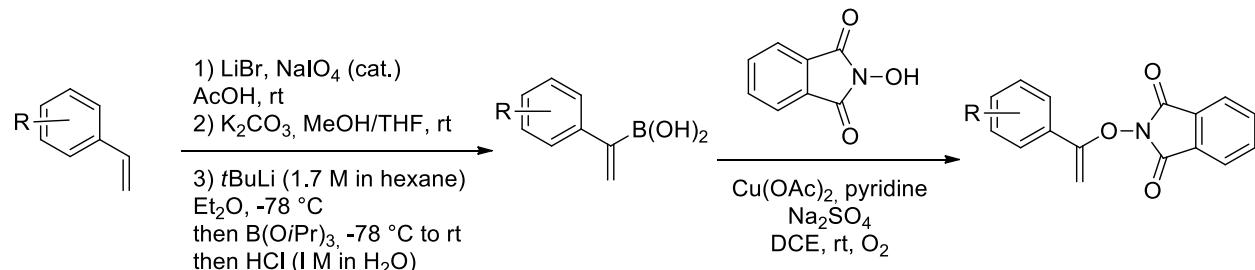
All reactions were carried out in oven-dried glassware with magnetic stirring. ACS grade and 2,2,2-trifluoroethanol and reagent grade cesium acetate were purchased from Sigma-Aldrich Co. and used without further purification. When necessary, organic solvents were routinely dried and/or distilled prior to use and stored over molecular sieves under argon. Alkenes **2a**, **2b**, **2c**, **2d**, **2h**, **2j**, **2k**, **2l** were purchased from Sigma-Aldrich Co and distilled under reduced pressure prior to use. Alkenes **2g**,¹ **2i**,² and (*E*)-**2a-d**,³ were prepared following literature procedure.

Column chromatography was performed on Silicycle® SilicaFlash® P60 (230-400 mesh). Thin layer chromatography was performed on Silicycle® 250μm silica gel 60A plates. Visualization was accomplished with UV light (254 nm) or potassium permanganate.

¹H NMR and ¹³C NMR spectra were collected at ambient temperature in CDCl₃ on a Varian 400 MHz. Chemical shifts are expressed as parts per million (δ , ppm) and are referenced to 7.26 (CHCl₃) for ¹H NMR and 77.36 (CDCl₃) for ¹³C NMR. Proton signal data uses the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and J = coupling constant. Mass spectra were obtained on a Fisons VG Autospec (HRMS) or an Agilent Technologies 6130 Quadropole Mass Spec (LRMS). Infrared spectra were collected on a Bruker Tensor 27 FT-IR spectrometer. Melting points (M.p.) were recorded using Büchi B-540 melting point apparatus and are uncorrected.

diastereomeric ratios were determined by integration of ¹H NMR spectra of product mixtures collected with first relaxation delay (d₁) = 15 seconds.

General procedure for the synthesis of N-enoxypythalimide.



(1,2-Dibromoethyl)benzene. Following a described procedure:⁴ To a solution of styrene (1 equiv) in AcOH (0.7 M) was successively added LiBr (1.2 equiv) then NaIO₄ (0.25 equiv). The reaction mixture was stirred overnight at rt. After completion of the reaction as shown by TLC, the volatiles were evaporated under reduced pressure. The resulting residue was partitioned between diethyl ether and water and the layers were separated. The aqueous layer was extracted with diethyl ether. The combined organic layers were washed with water, Na₂CO₃ sat. and brine, dried over Na₂SO₄ and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography to afford the corresponding product.

(1-Bromovinyl)benzene. Following a described procedure:⁵ To a solution of (1,2-dibromoethyl)benzene a mixture of MeOH/THF (1/1) was added potassium carbonate (2 equiv). The reaction mixture was stirred

¹ Galvani, G.; Lett, R.; Kouklovsky, C. *Chem. Eur. J.* **2013**, *19*, 15604.

² Riofsky, M. V.; John, J. P.; Zheng, M. M.; Kirshner, J.; Colby, D. A. *J. Org. Chem.* **2011**, *76*, 3676.

³ Lowpatch, K.; Young, D. W. *Org. Biomol. Chem.* **2005**, *3*, 3348.

⁴ Dewkar, G.K; Narina, S. V.; Sudalai, A. *Org. Lett.* **2003**, *23*, 4501.

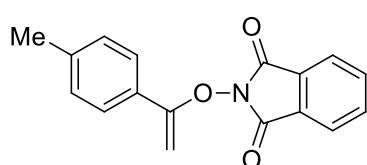
⁵ Zheng, X.; Blowers, P. *J. Mol. Cat. A* **2006**, *246*, 1.

at rt until complete disappearance of the starting material as shown by TLC (usually 3 h). The reaction was next quenched with water and the volatiles were evaporated under reduced pressure. The aqueous layer was extracted with diethyl ether then the combined organic layers were washed with brine, dried over Na₂SO₄ and evaporated under reduced pressure. The resulting (1-bromovinyl)benzene was obtained as a light sensitive colorless oil and used directly for the subsequent reactions without further purification.

(1-Phenylvinyl)boronic acid. Following a described procedure:⁶ To a solution of (1-bromovinyl)benzene in anhydrous diethyl ether cooled at -78 °C was added dropwise a solution of tert-butyllithium (1.7 M in hexane, 2.1 equiv). The resulting solution was stirred at -78 °C during 30 min. Triisopropyl borate was next added dropwise during 30 min to the reaction mixture maintained at -78 °C. After completion of the addition, the solution was stirred at -78 °C during 2 h then warmed up at rt and stirred overnight. The reaction was quenched with 1N aqueous HCl solution and stirred at rt during 2 h. The layers were separated and the aqueous layer was extracted with diethyl ether. The combining organic layers were washed with NaOH 1 M. The aqueous layers was acidified until pH = 1. The aqueous layer was then extracted with EtOAc and washed with brine, dried over Na₂SO₄ and evaporated under reduced pressure. The resulting (1-phenylvinyl)boronic acid was obtained as white solid and used directly for the subsequent reactions without further purification

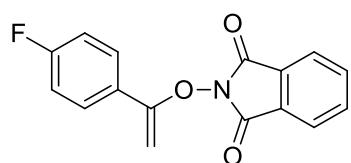
N-Enoxyphthalimide. Following a described procedure:⁷ N-hydroxyphthalimide (1 equiv), vinyl boronic acid (2 equiv), Cu(OAc)₂ (1 equiv), and anhydrous Na₂SO₄ (4 equiv). These solids were then diluted with 1,2-dichloroethane to form a 0.1 M solution of N-hydroxyphthalimide. Pyridine (3 equiv) was added to the resulting slurry via syringe. The reaction mixture was stirred at rt for 48 h under O₂ atmosphere. 1,2-Dichloroethane and pyridine were removed under reduced pressure and the crude reaction mixture was purified by pressure chromatography to give *N*-enoxyphthalimide **1** as a white solid.

2-((1-(p-tolyl)vinyl)oxy)isoindoline-1,3-dione (**1b**)



Yield = 69%. White solid. M. p. 149 °C. R_f (hexane/EtOAc 8:2) = 0.32. IR (neat, cm⁻¹) ν 3510, 3030, 1793, 1732, 1640, 1371, 1188. ¹H NMR (400 MHz, CDCl₃) δ 7.91 (dd, J = 5.5, 3.1 Hz, 2H), 7.80 (dd, J = 5.5, 3.1 Hz, 2H), 7.63 (d, J = 8.2 Hz, 2H), 7.21 (d, J = 8.2 Hz, 2H), 4.82 (d, J = 4.0 Hz, 1H), 4.52 (d, J = 4.0 Hz, 1H), 2.38 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 162.9, 160.7, 140.0, 135.1, 129.7, 129.4, 129.2, 126.6, 124.2, 86.2, 21.7. LRMS m/z (ESI + APCI) calcd for C₁₇H₁₄NO₃ [M+H] 280.1, found 280.1.

2-((1-(4-fluorophenyl)vinyl)oxy)isoindoline-1,3-dione (**1c**)



Yield = 56%. White solid. M. p. 124 °C. R_f (hexane/EtOAc 8:2) = 0.32. IR (neat, cm⁻¹) ν 1792, 1733, 1604, 1508, 1381, 1230. ¹H NMR (400 MHz, CDCl₃) δ 7.92 (dd, J = 5.4, 3.2 Hz, 2H), 7.81 (dd, J = 5.4, 3.2 Hz, 2H), 7.73 (dd, J = 8.8, 5.4 Hz, 2H), 7.09 (t, J = 8.8 Hz, 2H), 4.82 (d, J = 4.2 Hz, 1H), 4.57 (d, J = 4.2 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 163.9 (d, J = 249.4 Hz), 162.8, 162.7, 135.2, 129.2, 128.7 (d, J = 8.4 Hz), 128.7, 124.3, 115.8 (d, J = 21.8 Hz), 87.1. LRMS m/z (ESI + APCI) calcd for C₁₇H₁₁FNO₄ [M+MeOH+H] 316.1, found 316.1.

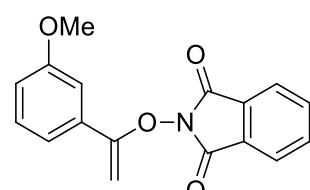
⁶ Arendsen, D. L. et al. WO0075145, 2000.

⁷ Patil, A. S.; Mo, D.-L.; Wang, H.-Y.; Mueller, D. S.; Anderson, L. L. *Angew. Chem., Int. Ed.* **2012**, 51, 7799.

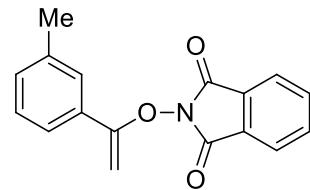
2-((1-(4-(tert-butyl)phenyl)vinyl)oxy)isoindoline-1,3-dione (1d)

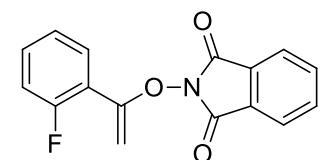
Yield = 78%. White solid. M. p. 158 °C. R_f (hexane/EtOAc 8:2) = 0.38. IR (neat, cm^{-1}) ν 2961, 1793, 1735, 1642, 1466, 1363, 1187, 1081. ^1H NMR (400 MHz, CDCl_3) δ 7.92 (dd, J = 5.2, 3.1 Hz, 2H), 7.80 (dd, J = 5.2, 3.1 Hz, 2H), 7.68 (d, J = 8.3 Hz, 2H), 7.43 (d, J = 8.3 Hz, 2H), 4.84 (d, J = 3.9 Hz, 1H), 4.52 (d, J = 3.9 Hz, 1H), 1.34 (s, 9H). ^{13}C NMR (101 MHz, CDCl_3) δ 162.8, 160.6, 153.2, 135.1, 129.7, 129.3, 126.4, 125.7, 124.2, 86.2, 35.1, 31.6. LRMS m/z (ESI + APCI) calcd for $\text{C}_{20}\text{H}_{20}\text{NO}_3$ [M+H] 322.1, found 322.1.

2-((1-(3-methoxyphenyl)vinyl)oxy)isoindoline-1,3-dione (1f)

 Yield = 67%. White solid. M. p. 102 °C. R_f (hexane/EtOAc 8:2) = 0.14. IR (neat, cm^{-1}) ν 2941, 1793, 1733, 1578, 1488, 1358, 1273, 1125. ^1H NMR (400 MHz, CDCl_3) δ 7.91 (dd, J = 5.5, 3.1 Hz, 2H), 7.81 (dd, J = 5.5, 3.1 Hz, 2H), 7.33 – 7.27 (m, 3H), 6.95 (dt, J = 6.9, 2.4 Hz, 1H), 4.88 (d, J = 4.0 Hz, 1H), 4.58 (d, J = 4.0 Hz, 1H), 3.85 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 162.8, 160.4, 159.9, 135.1, 133.8, 129.8, 129.2, 124.2, 119.2, 116.0, 111.9, 87.4, 55.7. LRMS m/z (ESI + APCI) calcd for $\text{C}_{17}\text{H}_{14}\text{NO}_4$ [M+H] 296.1, found 296.1.

2-((1-(m-tolyl)vinyl)oxy)isoindoline-1,3-dione (1g)

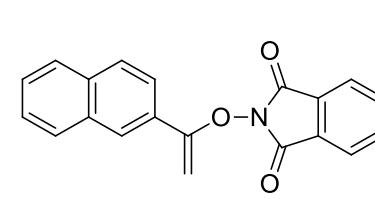
 Yield = 72%. White solid. M. p. 105 °C. R_f (hexane/EtOAc 8:2) = 0.31. . IR (neat, cm^{-1}) ν 3010, 1791, 1735, 1645, 1881, 1466, 1371, 1270, 979. ^1H NMR (400 MHz, CDCl_3) δ 7.91 (dd, J = 5.4, 3.1 Hz, 2H), 7.79 (dd, J = 5.4, 3.1 Hz, 2H), 7.59 – 7.48 (m, 2H), 7.28 (t, J = 7.6 Hz, 1H), 7.20 (d, J = 7.6 Hz, 1H), 4.84 (d, J = 4.0 Hz, 1H), 4.53 (d, J = 4.0 Hz, 1H), 2.38 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 162.8, 160.7, 138.4, 135.1, 132.4, 130.7, 129.2, 128.6, 127.3, 124.2, 123.8, 86.7, 21.78. LRMS m/z (ESI + APCI) calcd for $\text{C}_{18}\text{H}_{18}\text{NO}_4$ [M+MeOH+H] 312.1, found 312.1.



2-((1-(2-fluorophenyl)vinyl)oxy)isoindoline-1,3-dione (1h)

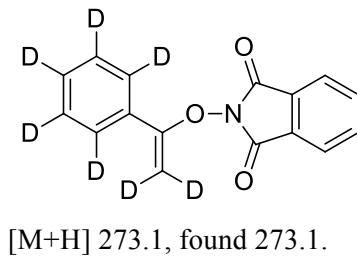
Yield = 34%. White solid. M. p. 146 °C. R_f (hexane/EtOAc 8:2) = 0.35. IR (neat, cm^{-1}) ν 3043, 1794, 1775, 1636, 1365, 1247, 1124. ^1H NMR (400 MHz, CDCl_3) δ 7.95 – 7.89 (m, 2H), 7.89 – 7.83 (m, 1H), 7.83 – 7.78 (m, 2H), 7.42 – 7.30 (m, 1H), 7.21 (t, J = 7.4 Hz, 1H), 7.13 (dd, J = 10.9, 8.5 Hz, 1H), 5.07 (d, J = 3.9 Hz, 1H), 4.86 (d, J = 3.9 Hz, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 162.8, 160.4 (d, J = 252.8 Hz), 154.3 (d, J = 3.4 Hz), 135.2, 131.3 (d, J = 8.7 Hz), 129.5 (d, J = 1.9 Hz), 129.2, 124.4 (d, J = 3.8 Hz), 124.3, 120.5 (d, J = 11.4 Hz), 116.5 (d, J = 22.5 Hz), 91.9 (d, J = 9.4 Hz). LRMS m/z (ESI + APCI) calcd for $\text{C}_{16}\text{H}_{11}\text{FNO}_3$ [M+H] 284.1, found 284.1.

2-((1-(naphthalen-2-yl)vinyl)oxy)isoindoline-1,3-dione (1j)

 Yield = 52%. White solid. M. p. 178 °C. R_f (hexane/EtOAc 8:2) = 0.36. IR (neat, cm^{-1}) ν 3057, 1791, 1732, 1466, 1374, 1223, 466, 1374, 1223. ^1H NMR (400 MHz, CDCl_3) δ 8.29 (s, 1H), 7.97 – 7.76 (m, 8H), 7.51 (dd, J = 6.2, 3.2 Hz, 2H), 5.03 (d, J = 4.1 Hz, 1H), 4.68 (d, J = 4.1 Hz, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 162.9, 160.5, 135.2, 134.1, 133.3, 129.7, 129.2, 129.0, 128.4, 128.0, 127.2, 126.8, 126.1, 124.3,

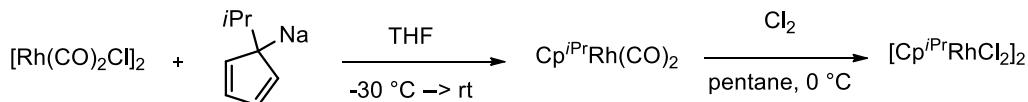
124.0, 87.5. LRMS m/z (ESI + APCI) calcd for $C_{20}H_{14}NO_3$ [M+H] 316.1, found 316.1.

D₅-2-((1-phenylvinyl)oxy)isoindoline-1,3-dione (1a-d₇)



Yield = 64%. White solid. M. p. 157 °C. R_f (hexane/EtOAc 8:2) = 0.27.
IR (neat, cm⁻¹) ν 2251, 1792, 1733, 1615, 1466, 1372, 1213, 1187, 1125, 1079, 963. ¹H NMR (300 MHz, CDCl₃) δ 7.93 (dd, J = 5.6, 3.0 Hz, 2H), 7.82 (dd, J = 5.6, 3.0 Hz, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 162.8, 160.5, 135.3, 132.3, 129.2, 124.2. LRMS m/z (ESI + APCI) calcd for $C_{16}H_{15}D_7NO_3$ [M+H] 273.1, found 273.1.

Preparation of [Cp^{iPr}RhCl₂]₂



Cp^{iPr}Rh(CO)₂: [Rh(CO)₂Cl]₂ (256 mg, 0.66 mmol, 1.0 equiv) was dissolved in 8.0 mL of THF in a round bottom flask under argon and a solution NaCp^{iPr} (171 mg, 1.32 mmol, 2.0 equiv) in 2.0 mL of THF was slowly added at -30 °C. The resulting solution was stirred at -30 °C during 3 h then at rt overnight. The reaction mixture was evaporated to dryness under reduced pressure. The black residue was taken off with pentane and the resulting yellow solution was directly loaded on a neutral alumina column. The column was rinsed with pentane. The yellow fraction was collected and evaporated under reduced pressure. The pure Cp^{iPr}Rh(CO)₂ complex (258 mg, yield=77%) was obtained as a yellow oil.

¹H NMR (300 MHz, C₆D₆) δ 4.94 (t, J = 2.2 Hz, 2H), 4.83 (t, J = 2.2 Hz, 2H), 2.30 – 2.06 (m, 1H), 0.93 (s, 3H), 0.91 (s, 3H). ¹³C NMR (101 MHz, C₆D₆) δ 193.2, 192.4, 121.0, 121.0, 86.2, 86.1, 85.2, 85.2, 26.3, 24.1. HRMS m/z (DART +APCI) calcd for $C_{10}H_{11}O_2Rh$ [M+H] 266.9891, found 266.9892.

[Cp^{iPr}RhCl₂]₂: Cp^{iPr}Rh(CO)₂ (230 mg, 0.86 mmol) was diluted in 6.0 mL of pentane. The resulting mixture was cooled at 0 °C and Cl₂ was slowly bubbled into the solution. An orange solid precipitated into the reaction flask. After 3 h, argon was bubbled into the reaction mixture to remove the excess of Cl₂. The precipitate was filtered and the solid was rinsed with pentane then dry under high vacuum overnight. The pure [Cp^{iPr}RhCl₂]₂ complex (54 mg, yield=22%) was obtained as an orange powder.

¹H NMR (400 MHz, DMSO) δ 6.00 (dd, J = 13.8, 1.8 Hz, 1H), 2.83 – 2.65 (m, 1H), 1.31 (s, 1H), 1.30 (s, 1H). ¹³C NMR (101 MHz, DMSO) δ 120.0, 88.5, 88.4, 85.4, 85.3, 41.4, 41.2, 41.0, 40.8, 40.6, 40.3, 40.1, 27.1, 22.3. HRMS m/z (DART +APCI) calcd for $C_{16}H_{22}Cl_4Rh_2$ [M+NH₄]⁺ 577.8935, found 577.8896.

General procedures for cyclopropanation reaction

- **Formation of 1,2-disubstituted cyclopropane (3)**

N-Enoxyphthalimide (20 mg, 0.075 mmol, 1.0 equiv), CsOAc (30 mg, 2.0 equiv), $[\text{Cp}^{\text{iPr}}\text{RhCl}_2]_2$ (2.2 mg, 0.05 equiv) were introduced in a screw cap vial equipped with a magnetic stir bar. Trifluoroethanol (0.4 mL) was added then alkene (9.6 μL , 0.090 mmol, 1.2 equiv). The reaction was stirred overnight at rt. After completion of the reaction as shown by TLC, the volatiles were evacuated under vacuum and the resulted residue was chromatographed on silica gel to afford the pure product.

Compounds 3aa,⁸ 3da,⁹ 3ac,¹⁰ 3ae,¹⁰ 3af,¹⁰ 3aj,¹⁰ 3ai,¹¹ 3al¹⁰ are described in the literature.

Ethyl 2-(4-methylbenzoyl)cyclopropanecarboxylate (3ba)

Colorless oil. R_f (hexane/EtOAc 9:1) = 0.34. IR (neat, cm^{-1}) ν 2980, 2925, 1726, 1668, 1606, 1329, 1204, 1176, 1005, 926, 821, 745. ^1H NMR (400 MHz, CDCl_3) δ 7.92 (d, J = 8.2 Hz, 2H), 7.28 (d, J = 8.2 Hz, 2H), 4.18 (q, J = 7.1 Hz, 2H), 3.16 (ddd, J = 4.0, 5.9, 9.1 Hz, 1H), 2.42 (s, 1H), 2.36 (ddd, J = 3.8, 5.9, 9.1 Hz, 1H), 1.63–1.54 (m, 2H), 1.28 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 196.9, 172.8, 144.6, 134.9, 129.7, 128.8, 61.4, 26.2, 24.9, 22.0, 18.1, 14.6. LRMS m/z (ESI + APCI) calcd for $\text{C}_{14}\text{H}_{17}\text{O}_3$ [$\text{M}+\text{H}$] 233.1, found 233.1.

Ethyl 2-(4-fluorobenzoyl)cyclopropanecarboxylate (3ca)

Colorless oil. R_f (hexane/EtOAc 9:1) = 0.31. IR (neat, cm^{-1}) ν 1792, 1733, 1636, 1604, 1508, 1361, 1230, 1188, 1083, 980, 875. ^1H NMR (400 MHz, CDCl_3) δ 8.17 – 7.95 (m, 2H), 7.16 (t, J = 8.6 Hz, 2H), 4.18 (q, J = 7.1 Hz, 2H), 3.13 (ddd, J = 3.7, 6.1, 8.9 Hz, 1H), 2.38 (ddd, J = 8.9, 6.1, 3.8 Hz, 1H), 1.64–1.56 (m, 2H), 1.29 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 195.8, 172.6, 167.6, 165.0, 133.8, 133.8, 131.3, 131.2, 116.3, 116.1, 61.5, 26.2, 25.0, 18.3, 14.5. LRMS m/z (ESI + APCI) calcd for $\text{C}_{13}\text{H}_{14}\text{FO}_3$ [$\text{M}+\text{H}$] 237.1, found 237.1.

Ethyl 2-([1,1'-biphenyl]-4-carbonyl)cyclopropanecarboxylate (3ea)

Colorless oil. R_f (hexane/EtOAc 9:1) = 0.28. IR (neat, cm^{-1}) ν 3058, 1776, 1669, 1603, 1365, 1331, 1179, 1003, 743. ^1H NMR (400 MHz, CDCl_3) δ 8.10 (d, J = 8.6 Hz, 2H), 7.72 (d, J = 8.6 Hz, 2H), 7.66 – 7.61 (m, 2H), 7.52 – 7.44 (m, 2H), 7.44 – 7.36 (m, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.23 (ddd, J = 8.7, 5.8, 3.8 Hz, 1H), 2.41 (ddd, J = 8.7, 5.9, 3.8 Hz, 1H), 1.68–1.59 (m, 2H), 1.30 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 196.9, 172.7, 146.4, 140.1, 136.1, 129.3, 129.2, 128.7, 127.7, 127.6, 61.5, 26.4, 25.1, 18.3, 14.6. LRMS m/z (ESI + APCI) calcd for $\text{C}_{19}\text{H}_{19}\text{O}_3$ [$\text{M}+\text{H}$] 295.1, found 295.1.

Ethyl 2-(3-methoxybenzoyl)cyclopropanecarboxylate (3fa)

⁸ Doyle, M. P.; Dorow, R. L.; Tamblyn, W. H. *J. Org. Chem.* **1982**, 47, 4059.

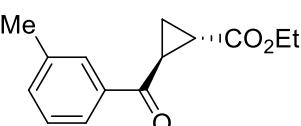
⁹ Phani Babu Tiruveedhula, V. V. N.; Witzigmann, C. M.; Verma, R.; Kabir, M. S.; Rott, M.; Schwan, W. R.; Medina-Bielski, S.; Lane, M.; Close, W.; Polanowski, R. L.; Sherman, D.; Monte, A.; Deschamps, J. R.; Cook, J. M. *Bio. Med. Chem.* **2013**, 21, 7830.

¹⁰ Papageorgiou, C. D.; Ley, S. V.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2003**, 42, 828.

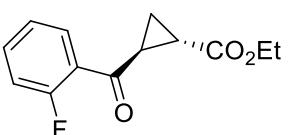
¹¹ Duhamel, P.; Poirier, J.-M.; Hennequin, L. *Tetrahedron Lett.* **1984**, 25, 1471.

Colorless oil. R_f (hexane/EtOAc 9:1) = 0.24. IR (neat, cm^{-1}) ν 3072, 2979, 2836, 1725, 1670, 1596, 1581, 1326, 1259, 1182, 1012, 745. ^1H NMR (400 MHz, CDCl_3) δ 7.63 (d, J = 7.7 Hz, 1H), 7.57 – 7.45 (m, 1H), 7.40 (t, J = 7.7 Hz, 1H), 7.14 (dd, J = 7.7, 2.6 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.86 (s, 3H), 3.16 (ddd, J = 8.7, 5.9, 3.9 Hz, 1H), 2.37 (ddd, J = 8.7, 5.9, 3.9 Hz, 1H), 1.64–1.56 (m, 2H), 1.29 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 197.2, 172.6, 160.2, 138.8, 130.0, 121.4, 120.3, 112.7, 61.5, 55.8, 26.4, 25.1, 18.3, 14.6. LRMS m/z (ESI + APCI) calcd for $\text{C}_{14}\text{H}_{17}\text{O}_4$ [M+H] 249.1, found 249.1.

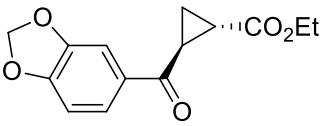
ethyl 2-(3-methylbenzoyl)cyclopropanecarboxylate (3ga)

 Colorless oil. R_f (hexane/EtOAc 9:1) = 0.34. IR (neat, cm^{-1}) ν 2980, 1744, 1670, 1602, 1585, 1328, 1205, 1184, 1162, 1051, 1014, 933, 739. ^1H NMR (400 MHz, CDCl_3) δ 7.82–7.81 (m, 2H), 7.45 – 7.30 (m, 2H), 4.18 (q, J = 7.1 Hz, 2H), 3.18 (ddd, J = 3.7, 5.9, 8.9 Hz, 1H), 2.42 (s, 3H), 2.37 (ddd, J = 3.9, 5.9, 8.7 Hz, 1H), 1.64–1.56 (m, 2H), 1.29 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 197.6, 172.8, 138.8, 137.4, 134.5, 129.1, 128.9, 125.9, 61.5, 26.4, 25.0, 21.7, 18.3, 14.6. LRMS m/z (ESI + APCI) calcd for $\text{C}_{14}\text{H}_{17}\text{O}_3$ [M+H] 233.1, found 233.1.

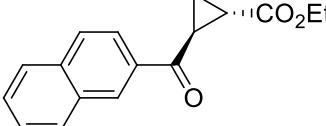
Ethyl 2-(2-fluorobenzoyl)cyclopropanecarboxylate (3ha)

 Colorless oil. R_f (hexane/EtOAc 9:1) = 0.31. IR (neat, cm^{-1}) ν 3073, 2982, 1704, 1675, 1587, 1447, 1327, 1252, 1206, 1185, 1167, 879. ^1H NMR (400 MHz, CDCl_3) δ 7.83–7.81 (m, 1H), 7.72 – 7.62 (m, 1H), 7.48 (td, J = 8.0, 5.5 Hz, 1H), 7.29 (tdd, J = 8.0, 2.6, 0.7 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.13 (ddd, J = 8.6, 6.0, 3.8 Hz, 1H), 2.39 (ddd, J = 8.6, 6.0, 3.8 Hz, 1H), 1.62 (m, 2H), 1.29 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 196.3 (d, J = 2.3 Hz), 172.4, 163.2 (d, J = 248.4 Hz), 139.4 (d, J = 6.2 Hz), 130.7 (d, J = 7.7 Hz), 124.4 (d, J = 3.0 Hz), 120.7 (d, J = 21.5 Hz), 115.4 (d, J = 22.5 Hz), 61.6, 26.4, 25.3, 18.4, 14.6. LRMS m/z (ESI + APCI) calcd for $\text{C}_{13}\text{H}_{14}\text{FO}_3$ [M+H] 267.1, found 267.1.

ethyl 2-(benzo[d][1,3]dioxole-5-carbonyl)cyclopropanecarboxylate (3ia)

 Colorless oil. R_f (hexane/EtOAc 9:1) = 0.34. IR (neat, cm^{-1}) ν 2982, 2906, 1725, 1665, 1603, 1489, 1447, 1325, 1276, 1182, 1037, 931. ^1H NMR (400 MHz, CDCl_3) δ 7.66 (dd, J = 8.2, 1.8 Hz, 1H), 7.46 (d, J = 1.8 Hz, 1H), 6.88 (d, J = 8.2 Hz, 1H), 6.06 (s, 2H), 4.18 (q, J = 7.2 Hz, 2H), 3.08 (ddd, J = 8.7, 5.8, 3.9 Hz, 1H), 2.34 (ddd, J = 8.6, 5.8, 3.8 Hz, 1H), 1.61–1.52 (m, 2H), 1.28 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 195.3, 1728, 152.4, 148.7, 132.3, 125.1, 108.3, 108.3, 102.3, 61.5, 26.1, 24.8, 18.0, 14.6. LRMS m/z (ESI + APCI) calcd for $\text{C}_{14}\text{H}_{15}\text{O}_5$ [M+H] 263.1, found 263.1.

ethyl 2-(2-naphthoyl)cyclopropanecarboxylate (3ja)

 Colorless oil. R_f (hexane/EtOAc 9:1) = 0.31. IR (neat, cm^{-1}) ν 3058, 2980, 1756, 1665, 1626, 1465, 1366, 1323, 1205, 1175, 1124, 1052, 862, 758. ^1H NMR (400 MHz, CDCl_3) δ 8.58 (s, 1H), 8.05 (dd, J = 8.6, 1.7 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H), 7.95 – 7.86 (m, 2H), 7.65 – 7.60 (m, 1H), 7.60 – 7.55 (m, 1H), 4.21 (q, J = 7.1 Hz, 2H), 3.36 (ddd, J = 3.7, 6.1, 8.9 Hz, 1H), 2.45 (ddd, J = 3.8, 6.1, 8.8 Hz, 1H), 1.71–1.63 (m, 2H), 1.31 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 197.2, 172.8, 136.1, 134.7, 132.9, 130.6, 130.0, 129.0, 128.9, 128.1, 127.3, 124.2, 61.5, 26.4, 25.1, 18.4, 14.6. LRMS m/z (ESI + APCI) calcd for $\text{C}_{17}\text{H}_{17}\text{O}_3$ [M+H] 269.1, found 269.1.

Butyl 2-benzoylcyclopropanecarboxylate (3ab)

Colorless oil. R_f (hexane/EtOAc 9:1) = 0.39. IR (neat, cm^{-1}) ν 2958, 2932, 1732, 1672, 1597, 1449, 1331, 1174, 1008. ^1H NMR (400 MHz, CDCl_3) δ 8.02 (d, J = 7.4 Hz, 2H), 7.60 (t, J = 7.4 Hz, 1H), 7.49 (t, J = 7.4 Hz, 2H), 4.13 (t, J = 6.7 Hz, 2H), 3.19 (ddd, J = 3.9, 5.5, 8.9 Hz, 1H), 2.38 (ddd, J = 3.9, 5.9, 9.2 Hz, 1H), 1.72 – 1.54 (m, 4H), 1.40 (sept, J = 7.4 Hz, 2H), 0.94 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 193.4, 168.7, 133.4, 129.7, 125.0, 124.6, 61.4, 27.0, 22.3, 21.0, 15.5, 14.2, 10.0. LRMS m/z (ESI + APCI) calcd for $\text{C}_{15}\text{H}_{19}\text{O}_3$ [M+H] 247.1, found 247.1.

Phenyl 2-benzoylcyclopropanecarboxylate (3ad)

Colorless oil. R_f (hexane/EtOAc 9:1) = 0.32. IR (neat, cm^{-1}) ν 3061, 1747, 1671, 1596, 1331, 1222, 1191, 1143, 1008, 923, 711. ^1H NMR (400 MHz, CDCl_3) δ 8.07 (d, J = 7.1 Hz, 2H), 7.62 (t, J = 7.1 Hz, 1H), 7.52 (t, J = 7.6 Hz, 2H), 7.23 (t, J = 7.6 Hz, 1H), 7.12 (d, J = 7.6 Hz, 2H), 7.13 (s, J = 8.3 Hz, 1H), 3.35 (ddd, J = 8.8, 5.9, 3.9 Hz, 1H), 2.64 (ddd, J = 8.6, 5.9, 3.9 Hz, 1H), 1.82 – 1.70 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 197.0, 171.3, 150.9, 137.3, 133.9, 129.8, 129.1, 128.7, 126.3, 121.8, 26.9, 24.8, 18.8. LRMS m/z (ESI + APCI) calcd for $\text{C}_{17}\text{H}_{15}\text{O}_3$ [M+H] 267.1, found 267.1.

2-benzoylcyclopropyl)-4-((tert-butyldimethylsilyl)oxy)butan-1-one (3ag)

Colorless oil. R_f (hexane/EtOAc 9:1) = 0.36. IR (neat, cm^{-1}) ν 2953, 2855, 1704, 1696, 1597, 1399, 1177, 1095, 834. ^1H NMR (400 MHz, CDCl_3) δ 8.01 (d, J = 7.4 Hz, 2H), 7.59 (t, J = 7.4 Hz, 1H), 7.48 (t, J = 7.4 Hz, 2H), 3.62 (t, J = 6.1 Hz, 2H), 3.22 (ddd, J = 3.9, 5.9, 8.9 Hz, 1H), 2.84 – 2.53 (m, 3H), 1.83 (quint, J = 6.1 Hz, 2H), 1.69 – 1.46 (m, 2H), 0.87 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 208.4, 197.7, 137.4, 133.7, 129.0, 128.6, 62.3, 40.7, 31.9, 28.1, 27.1, 26.3, 20.1, 18.7, -5.0. LRMS m/z (ESI + APCI) calcd for $\text{C}_{20}\text{H}_{31}\text{O}_3\text{Si}$ [M+H] 347.2, found 347.2.

2,2,2-trifluoroethyl 2-benzoylcyclopropanecarboxylate (3ah)

Colorless oil. R_f (hexane/EtOAc 9:1) = 0.32. IR (neat, cm^{-1}) ν 2359, 1749, 1673, 1597, 1449, 1278, 1179, 1002, 974, 711. ^1H NMR (400 MHz, CDCl_3) δ 8.02 (d, J = 7.4 Hz, 2H), 7.61 (t, J = 7.4 Hz, 1H), 7.51 (t, J = 7.4 Hz, 2H), 4.52 (q, J = 8.4 Hz, 2H), 3.26 (ddd, J = 9.2, 6.0, 3.9, 1H), 2.50 (ddd, J = 9.2, 5.7, 3.9 Hz, 1H), 1.75 – 1.66 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 195.6, 170.3, 136.1, 133.0, 128.1, 127.7, 122.1 (q, J = 277.3 Hz), 60.1 (q, J = 36.8 Hz), 25.8, 22.9, 17.6. LRMS m/z (ESI + APCI) calcd for $\text{C}_{13}\text{H}_{14}\text{F}_3\text{O}_3$ [M+H] 273.1, found 273.1.

2-benzoylcyclopropyl)(morpholino)methanone (3ak)

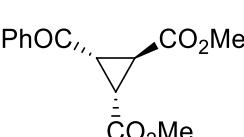
Colorless oil. R_f (DCM/EtOAc 9:1) = 0.26. IR (neat, cm^{-1}) ν 2963, 2919, 1717, 1670, 1637, 1447, 1386, 1324, 1221, 1115, 1006, 705. ^1H NMR (300 MHz, CDCl_3) δ 8.05 (dd, J = 8.4, 1.3 Hz, 2H), 7.72 – 7.57 (m, 1H), 7.55 – 7.38 (m, 2H), 3.72–3.62 (m, 8H), 3.28 (ddd, J = 8.6, 5.5, 3.9 Hz, 1H), 2.54 (ddd, J = 8.6, 5.9, 3.9 Hz, 1H), 1.64 (ddd, J = 8.6, 5.9, 3.1 Hz, 1H), 1.57 (ddd, J = 8.6, 5.9, 3.1 Hz, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 198.5, 169.7, 137.3, 133.8, 129.0, 128.7, 67.1, 46.4, 43.0, 26.1, 23.3, 18.6. LRMS m/z (ESI + APCI) calcd for

$C_{15}H_{17}NO_3$ [M+H] 260.1, found 260.1.

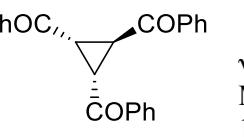
- *Formation of 1,2,3-trisubstituted cyclopropane (5)*

N-Enoxyphthalimide (20 mg, 0.075 mmol, 1.0 equiv), KOAc (15 mg, 2.0 equiv), $[Cp^*Rh(CH_3CN)_3](PF_6)_2^{12}$ (3.8 mg, 0.10 equiv) were introduced in a screw cap vial equipped with a magnetic stir bar. Trifluoroethanol (0.4 mL) was added then alkene (15.5 mg, 0.090 mmol, 1.2 equiv). The reaction was stirred overnight at rt. After completion of the reaction as shown by TLC, the volatiles were evacuated under vacuum and the resulted residue was chromatographed on silica gel to afford the pure product.

dimethyl 3-benzoylcyclopropane-1,2-dicarboxylate (5aa)

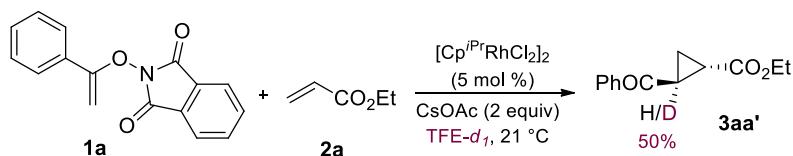
 Colorless oil. R_f (hexane/EtOAc 9:1) = 0.11. IR (neat, cm^{-1}) ν 2954, 1786, 1683, 1437, 1361, 1310, 1199, 1172, 1017. ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, J = 8.4, 1.3 Hz, 2H), 7.62 – 7.56 (m, 1H), 7.48 (t, J = 7.6 Hz, 2H), 3.77 (s, 3H), 3.58 (s, 3H), 3.29 (dd, J = 10.0, 5.8 Hz, 1H), 3.07 – 2.96 (m, 1H), 2.79 (dd, J = 10.0, 5.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.3, 171.4, 168.4, 136.6, 134.0, 129.1, 128.8, 52.9, 52.7, 33.1, 30.4, 26.0. LRMS m/z (ESI + APCI) calcd for $C_{14}H_{15}O_5$ [M+H] 263.1, found 263.1.

Cyclopropane-1,2,3-triyltris(phenylmethanone) (5ab)

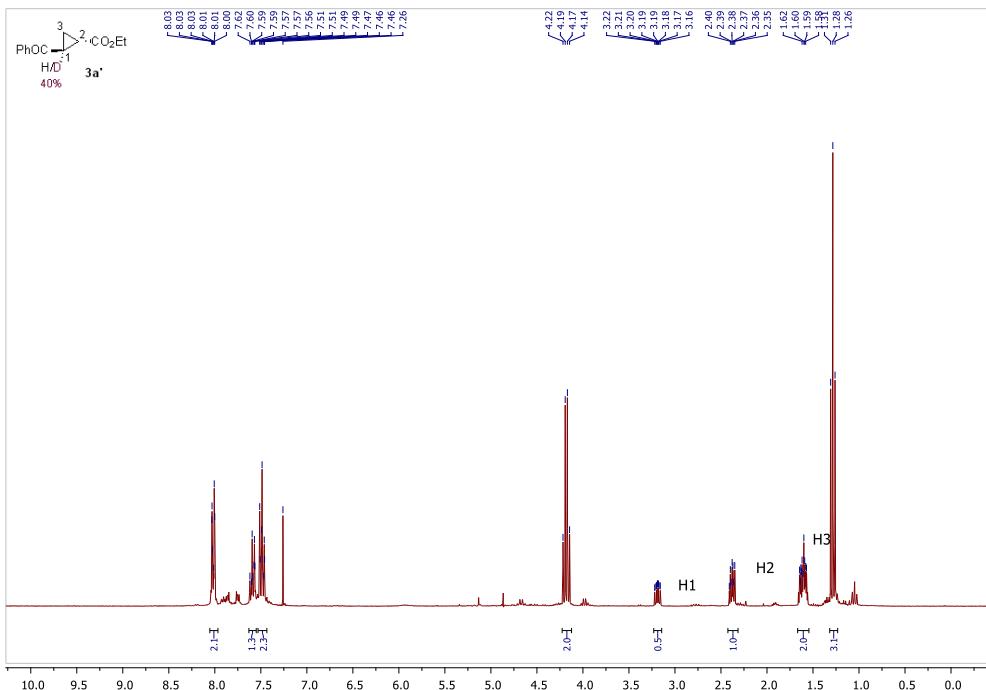
 Colorless oil. R_f (hexane/EtOAc 9:1) = 0.14. IR (neat, cm^{-1}) ν 3002, 1671, 1662, 1596, 1578, 1447, 1329, 1447, 1329, 1219. ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 – 8.10 (m, 2H), 8.01 (dd, J = 8.4, 1.3 Hz, 4H), 7.69 – 7.59 (m, 1H), 7.57 – 7.50 (m, 4H), 7.43 (dd, J = 8.4, 7.0 Hz, 4H), 4.24 (t, J = 5.6 Hz, 1H), 3.76 (d, J = 5.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.4, 193.3, 136.9, 134.3, 133.9, 129.2, 129.1, 129.0, 128.8, 128.5, 36.7, 30.8. LRMS m/z (ESI + APCI) calcd for $C_{24}H_{19}O_3$ [M+H] 354.1, found 354.1.

Mechanistic experiments

Chemoselectivity of the C-H functionalization



¹² Cusanelli, A.; Nicula-Dadci, L.; Frey, U.; Merbach, A. E. *Inorg. Chem.* **1997**, *36*, 2211.

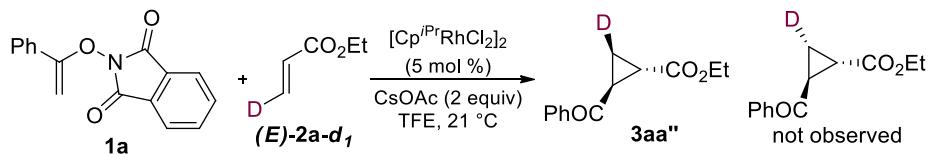


The reaction was run in *TFE-d*₁ following the standard procedure for cyclopropanation reaction. The degree of deuterium incorporation was determined by analysis of the crude ¹H NMR.

Integration of proton H1 and H2, indicating 50% of deuterium incorporation at position 1.

Deuterium labelling

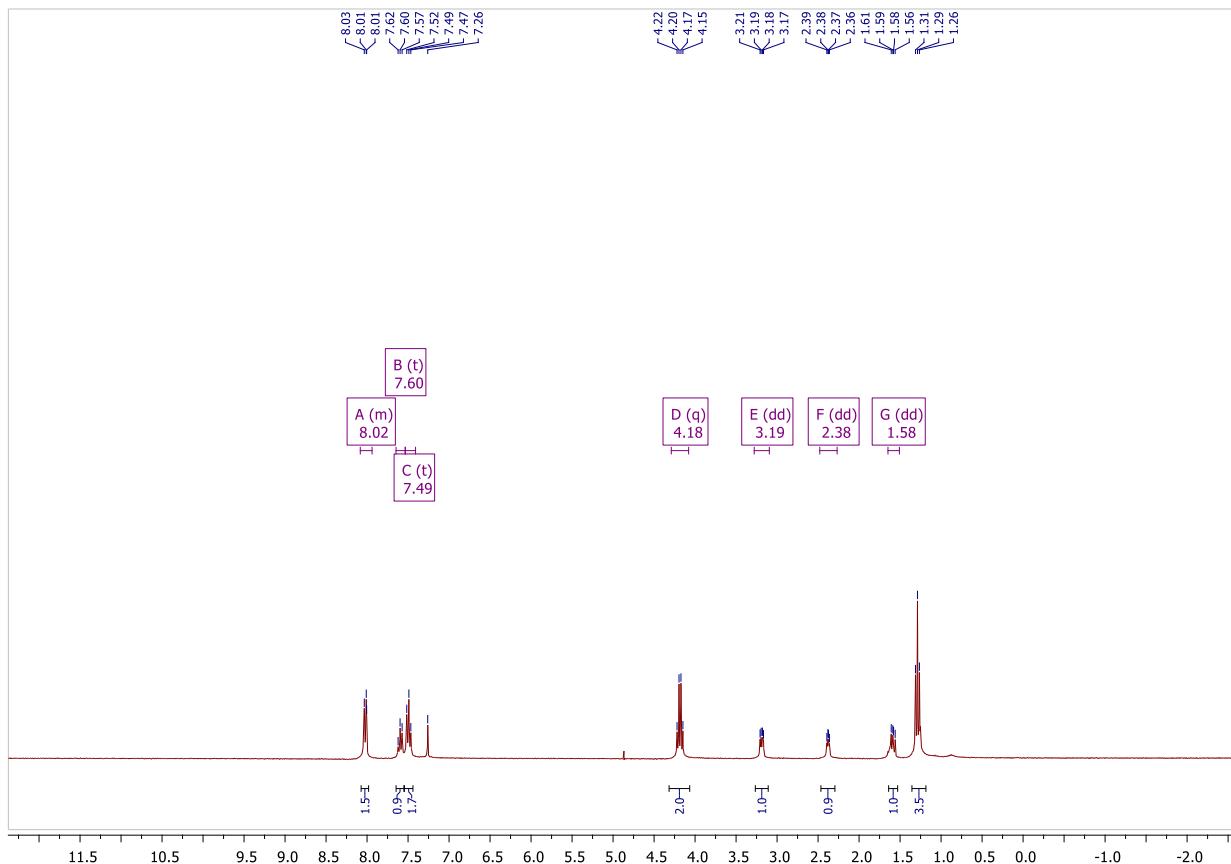
Experiment 1:



N-Enoxyphthalimide **1a** (20 mg, 0.075 mmol, 1.0 equiv), CsOAc (30 mg, 2.0 equiv), $[\text{Cp}^{\text{iPr}}\text{RhCl}_2]_2$ (2.2 mg, 0.05 equiv) were introduced in a screw cap vial equipped with a magnetic stir bar. Trifluoroethanol (0.4 mL) was added then alkne **(E)-2a-d₁** (9.6 μL , 0.090 mmol, 1.2 equiv). The reaction was stirred overnight at rt. After completion of the reaction as shown by TLC, the volatiles were evacuated under vacuum and the resulted residue was chromatographed on silica gel to afford the pure product **3aa''**.

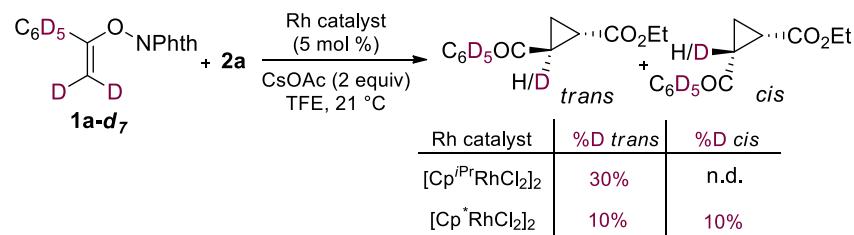
Analysis of the **3aa''** ¹H NMR showing an *anti* relationship between the deuterium atom and ester.

¹H NMR (300 MHz, CDCl₃) δ 8.08 – 7.94 (d, J = 7.3 Hz, 2H), 7.60 (t, J = 7.3 Hz, 1H), 7.49 (t, J = 7.5 Hz, 2H), 4.18 (q, J = 7.1 Hz, 2H), 3.19 (dd, J = 8.7, 3.8 Hz, 1H), 2.38 (dd, J = 5.3, 3.8 Hz, 1H), 1.58 (dd, J = 8.7, 5.3 Hz, 3H).



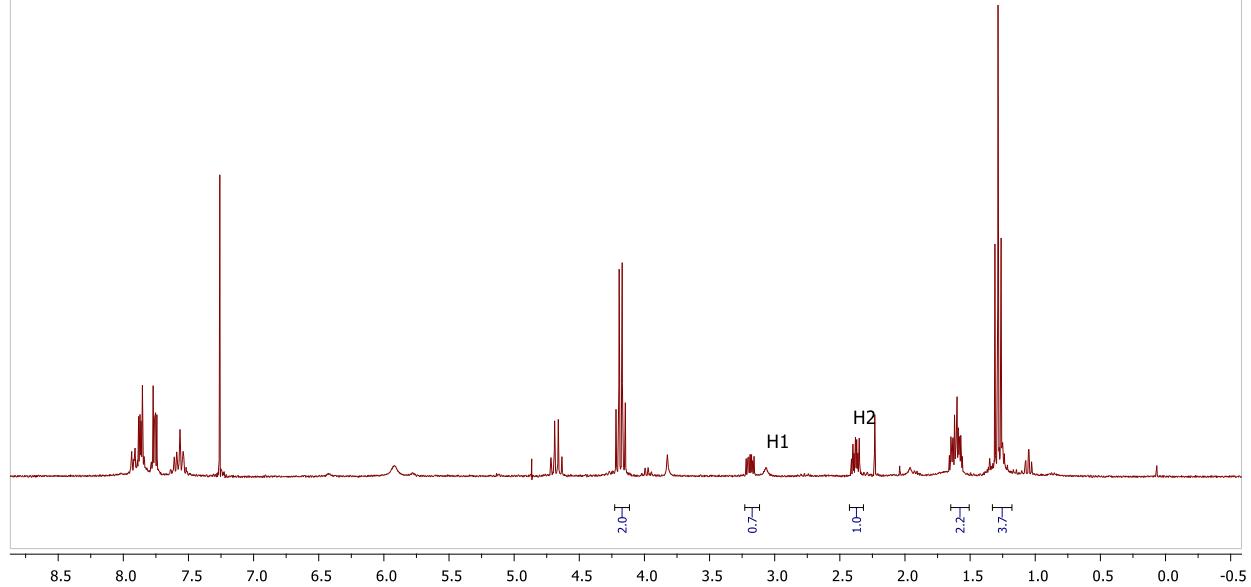
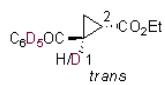
Experiment 2:

The reaction was run using **1a-d₇** as substrate following the standard procedure for cyclopropanation reaction.



With $[\text{Cp}^{\text{Pr}}\text{RhCl}_2]_2$:

Analysis of crude ^1H NMR: integration of proton H1 and H2, indicating 30% of deuterium at position 1.

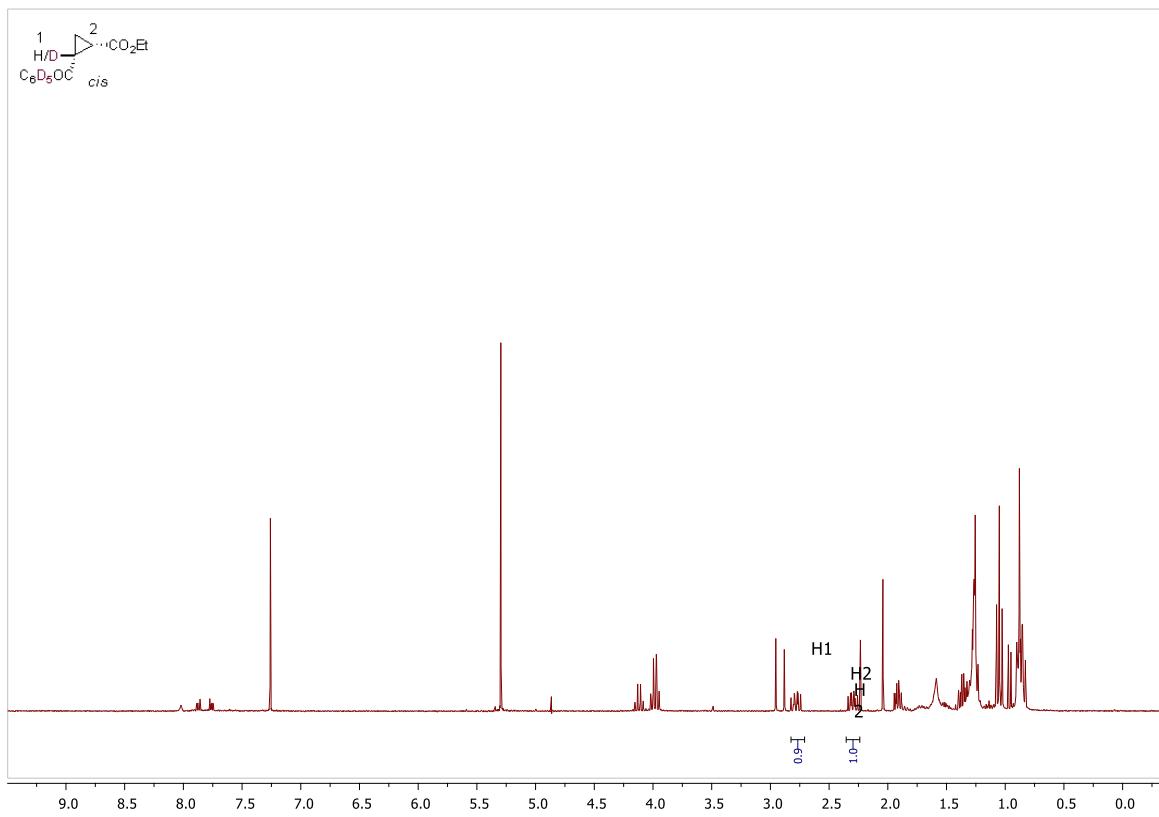
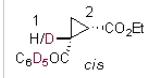
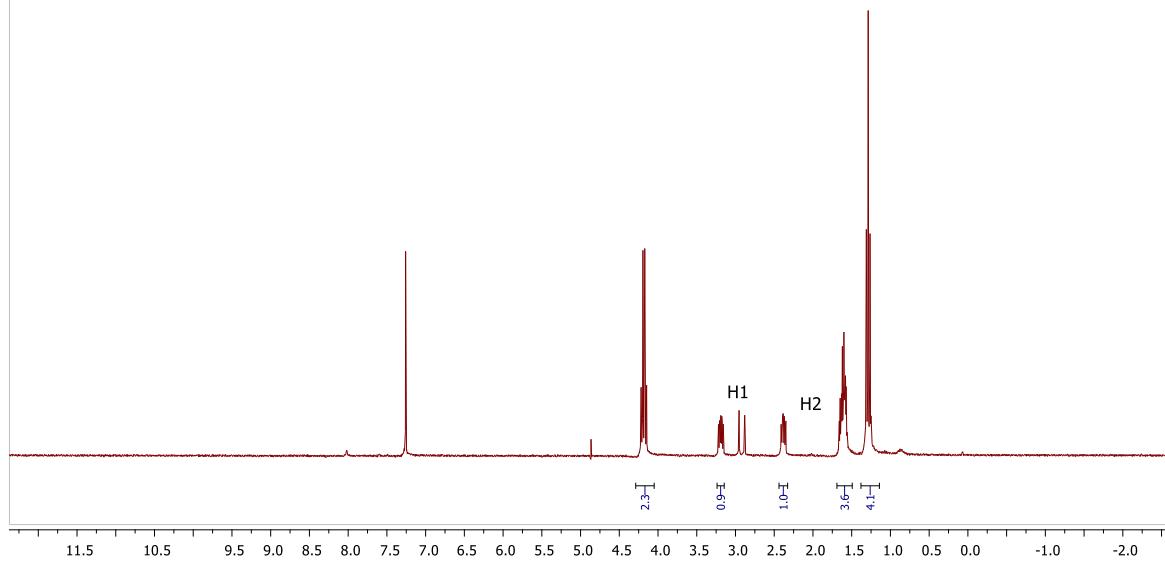
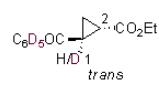


With $[\text{Cp}^*\text{RhCl}_2]_2$:

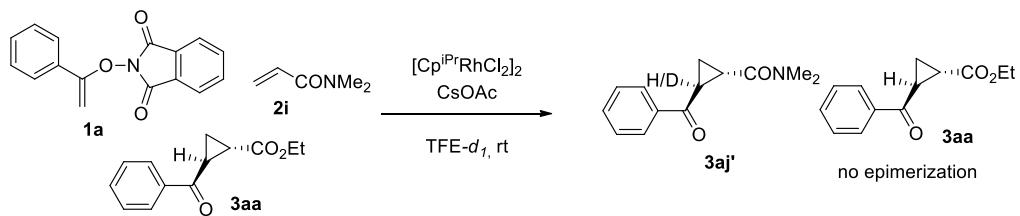
The trans and cis diastereoisomers were separated by column chromatography.

***trans* cyclopropane:** integration of proton H1 and H2, indicating 10% of deuterium at position 1.

***cis* cyclopropane:** integration of proton H1 and H2, indicating 10% of deuterium at position 1.

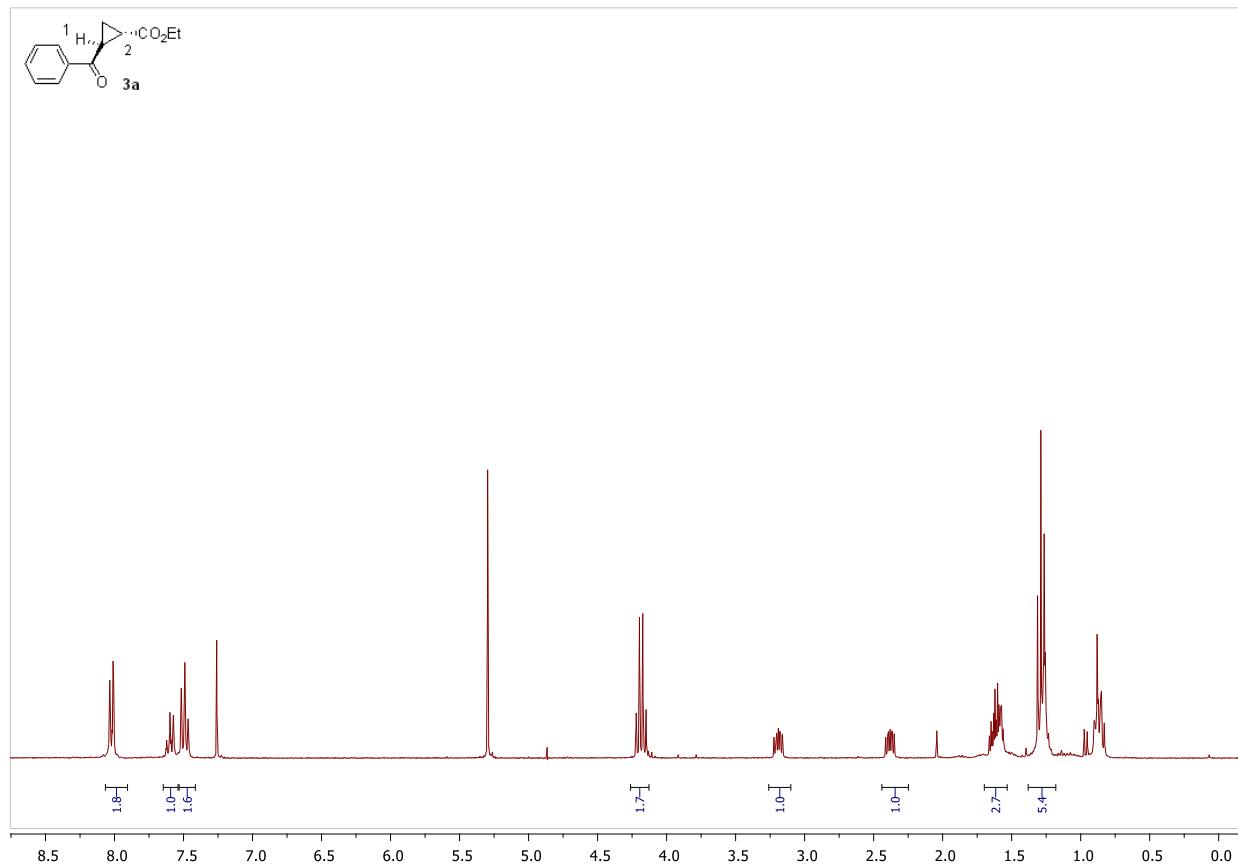


Control experiment

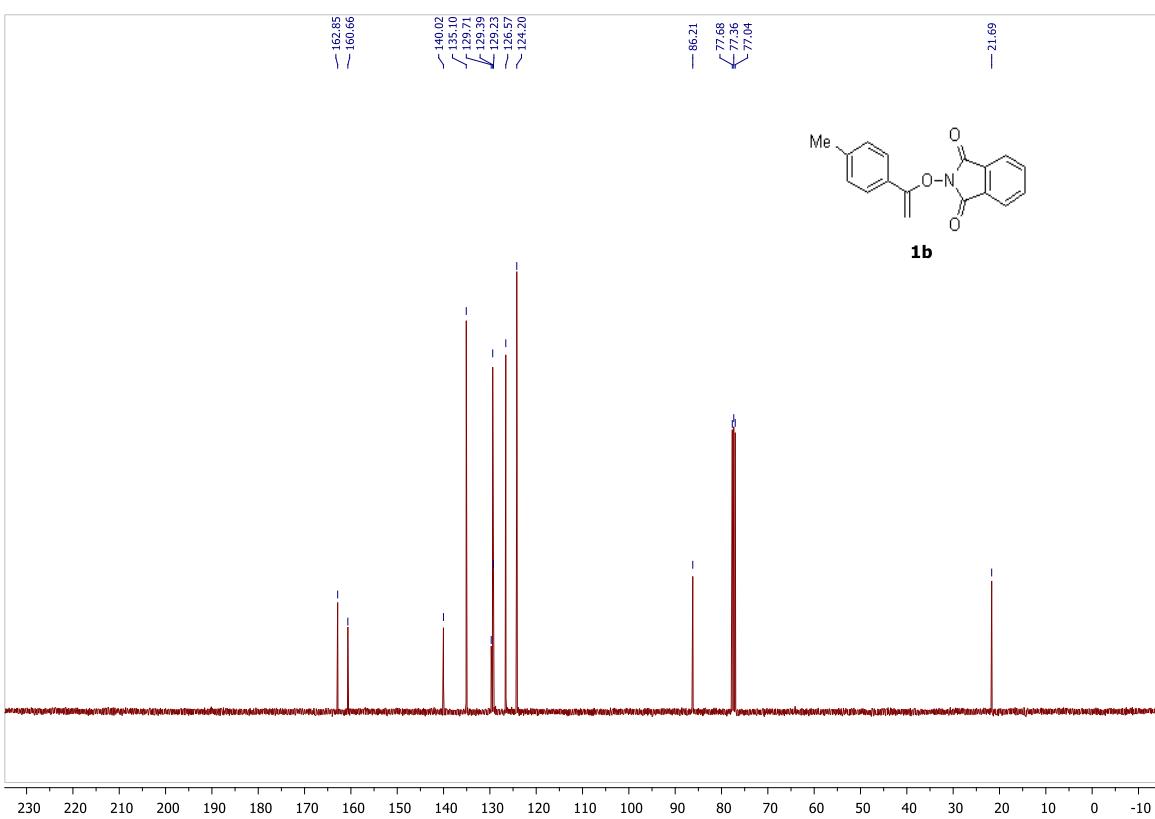
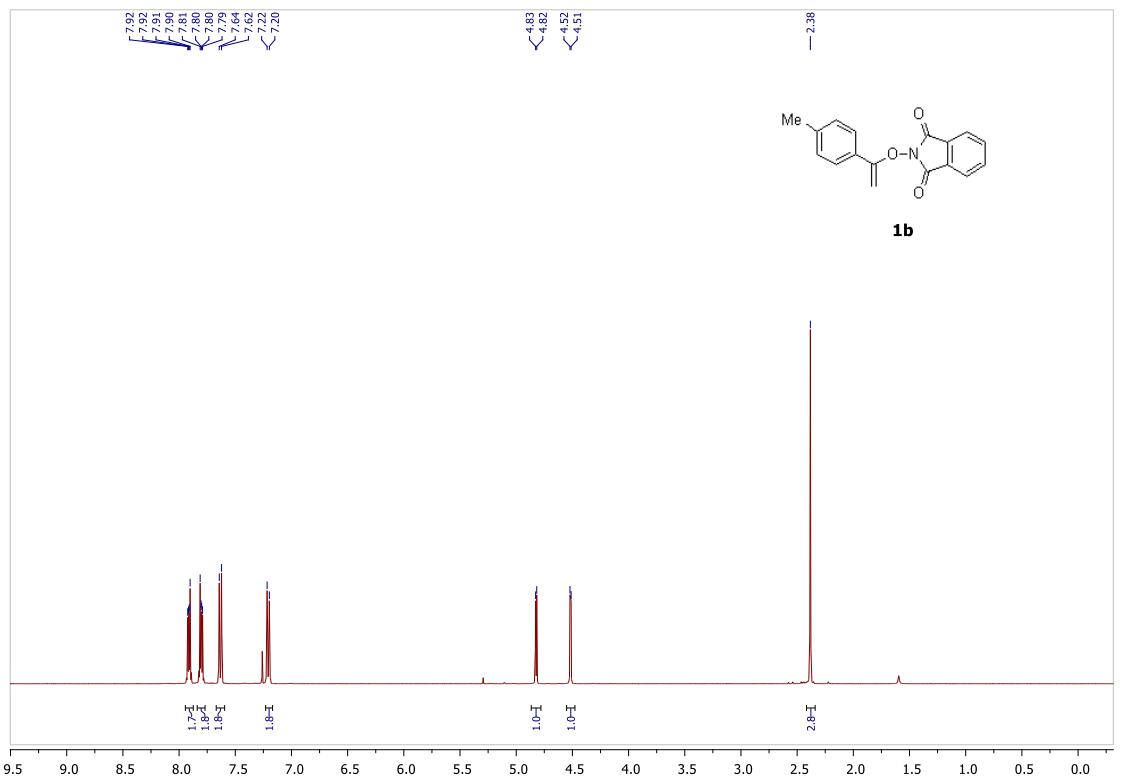


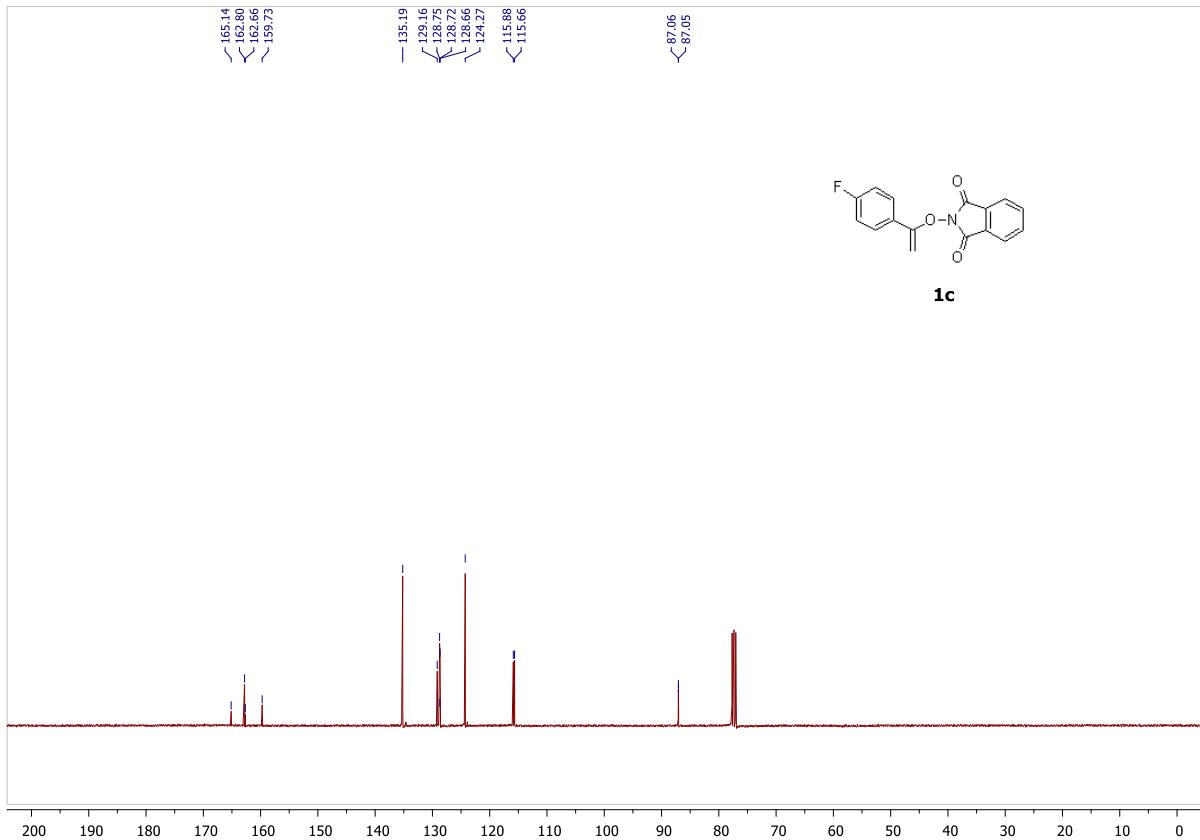
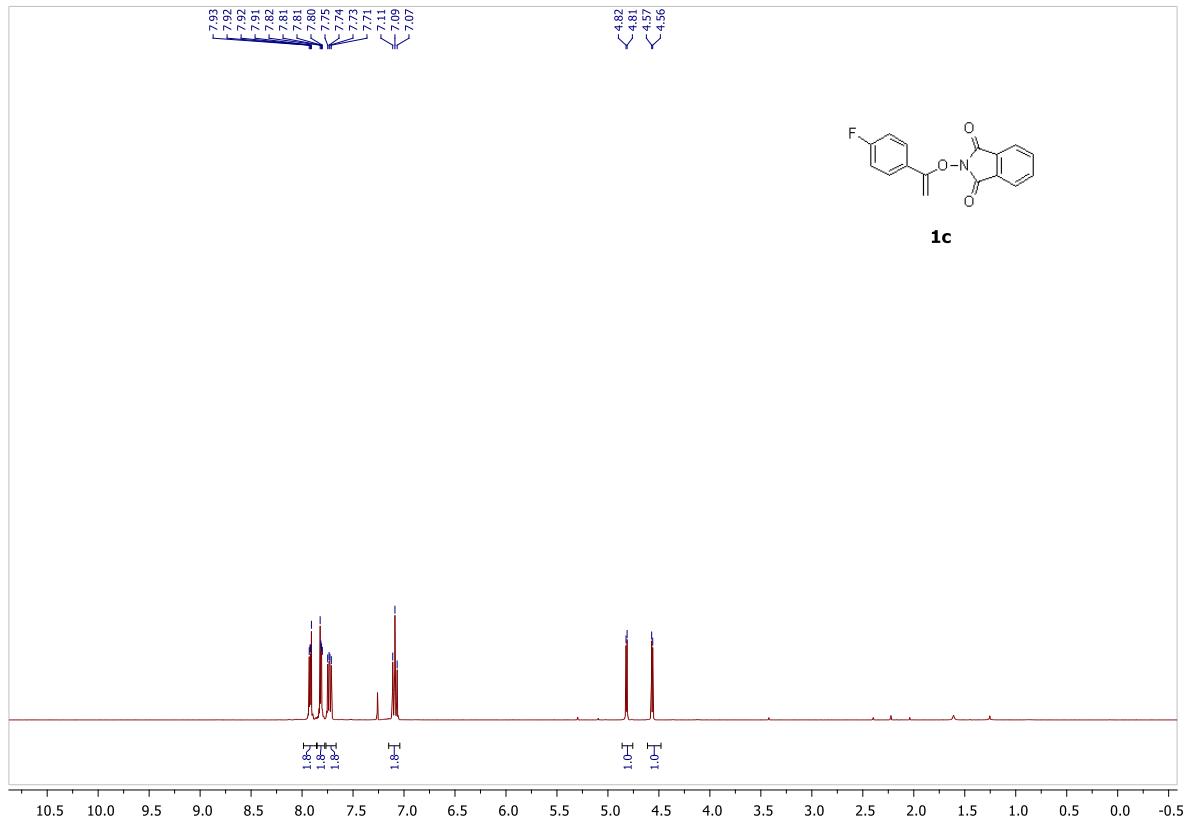
N-Enoylphthalimide **1a** (20 mg, 0.075 mmol, 1.0 equiv), **3aa** (10 mg), CsOAc (30 mg, 2.0 equiv), $[\text{Cp}^{\text{iPr}}\text{RhCl}_2]_2$ (2.2 mg, 0.05 equiv) were introduced in a screw cap vial equipped with a magnetic stir bar. Trifluoroethanol (0.4 mL) was added then acrylamide **2i** (9.6 μL , 0.090 mmol, 1.2 equiv). The reaction was stirred overnight at rt. After completion of the reaction as shown by TLC, the volatiles were evacuated under vacuum and the resulted residue was chromatographed on silica gel to afford the pure product **3aa**.

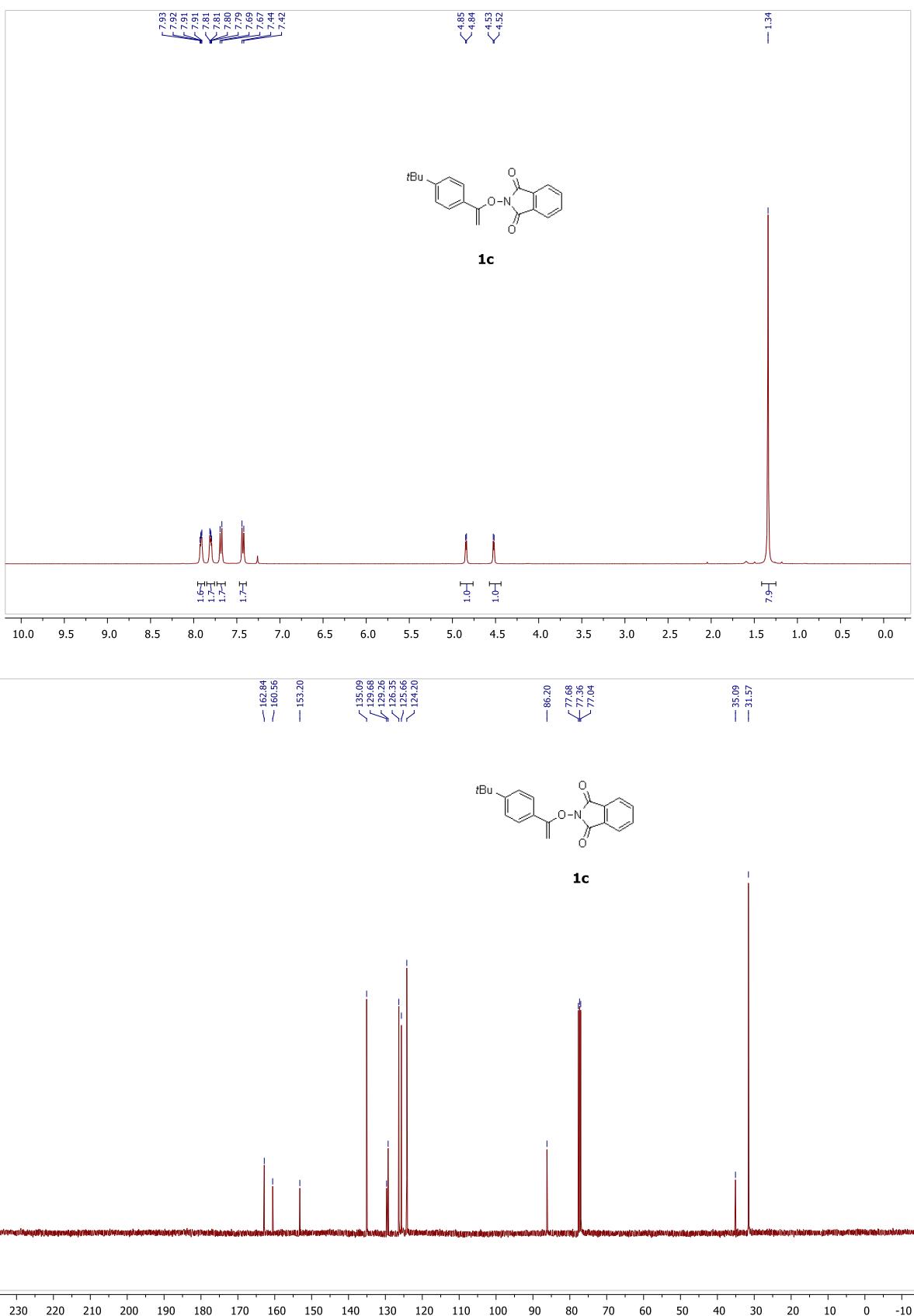
Analysis of ^1H NMR of compounds **3aa** shows no incorporation of deuterium, suggesting epimerization does not take place after formation of the cycloadduct.

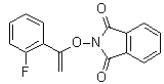
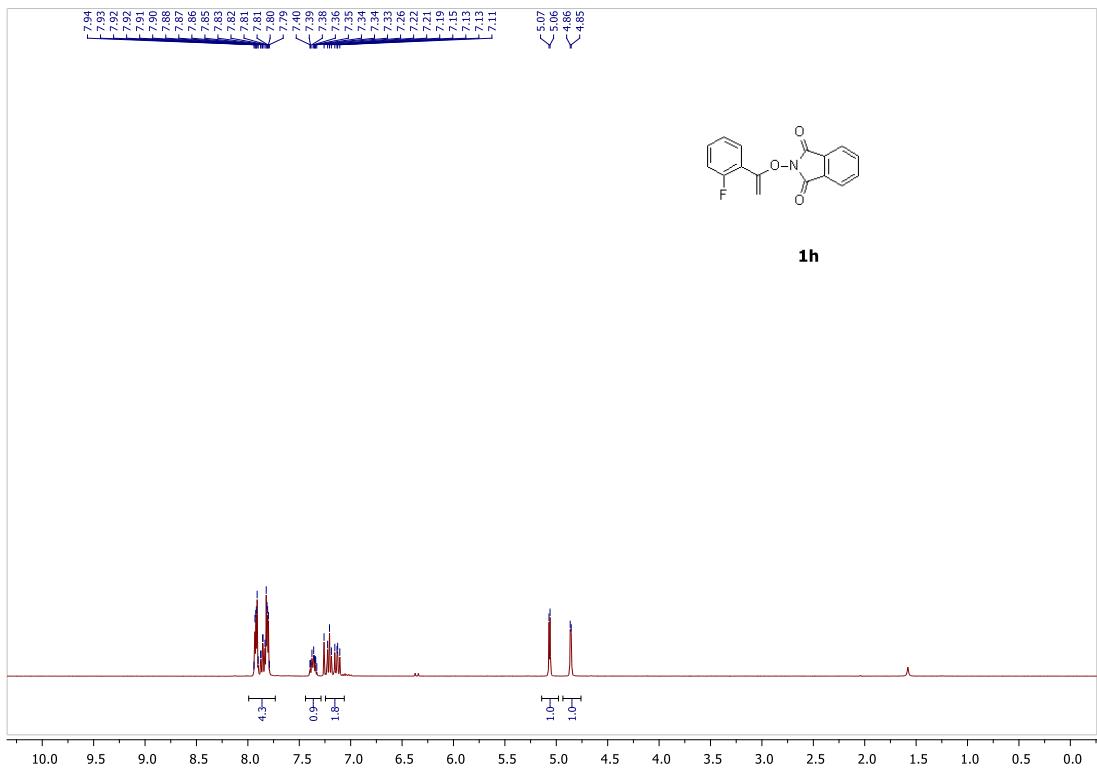


Spectra

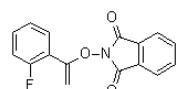
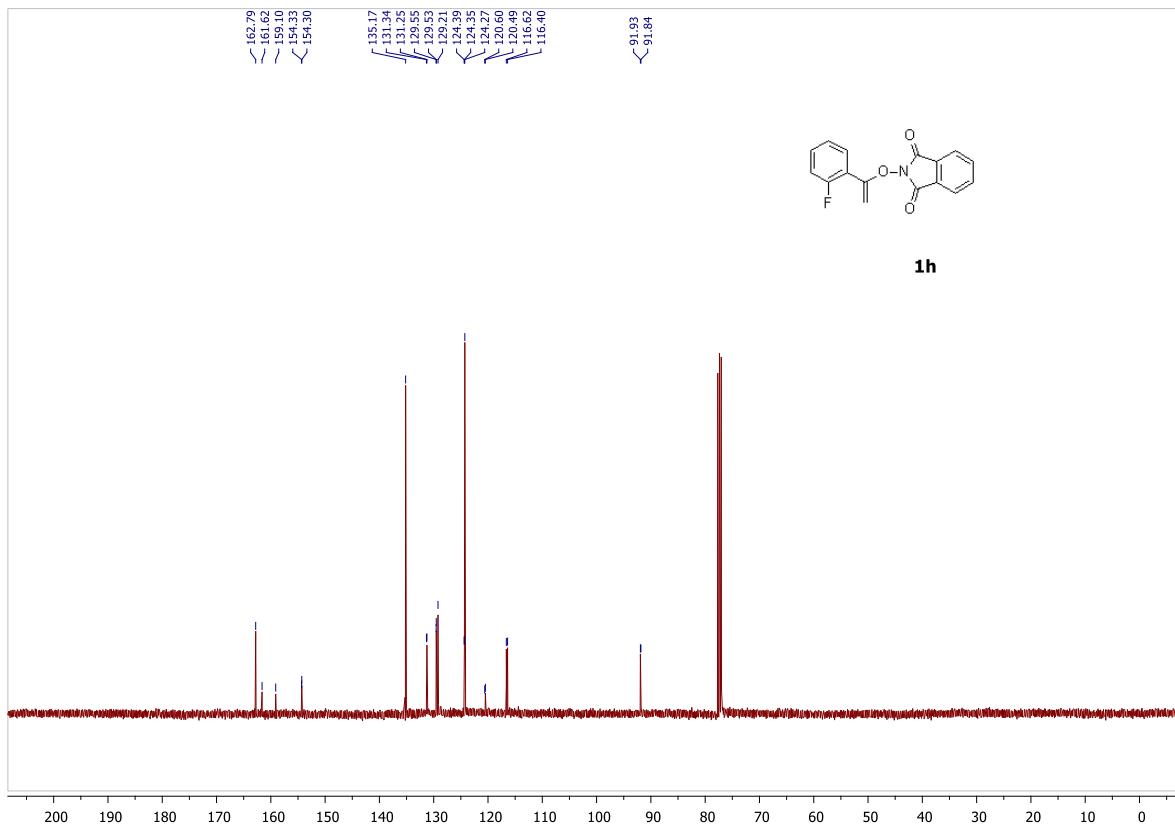




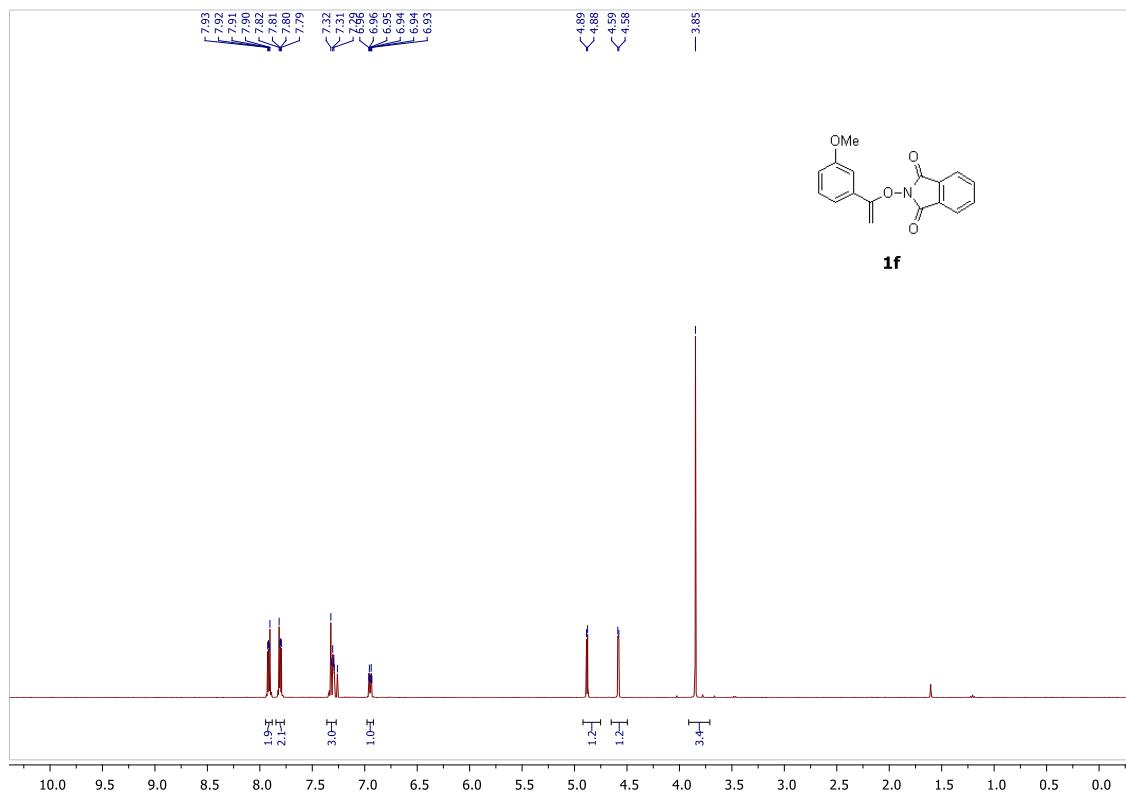


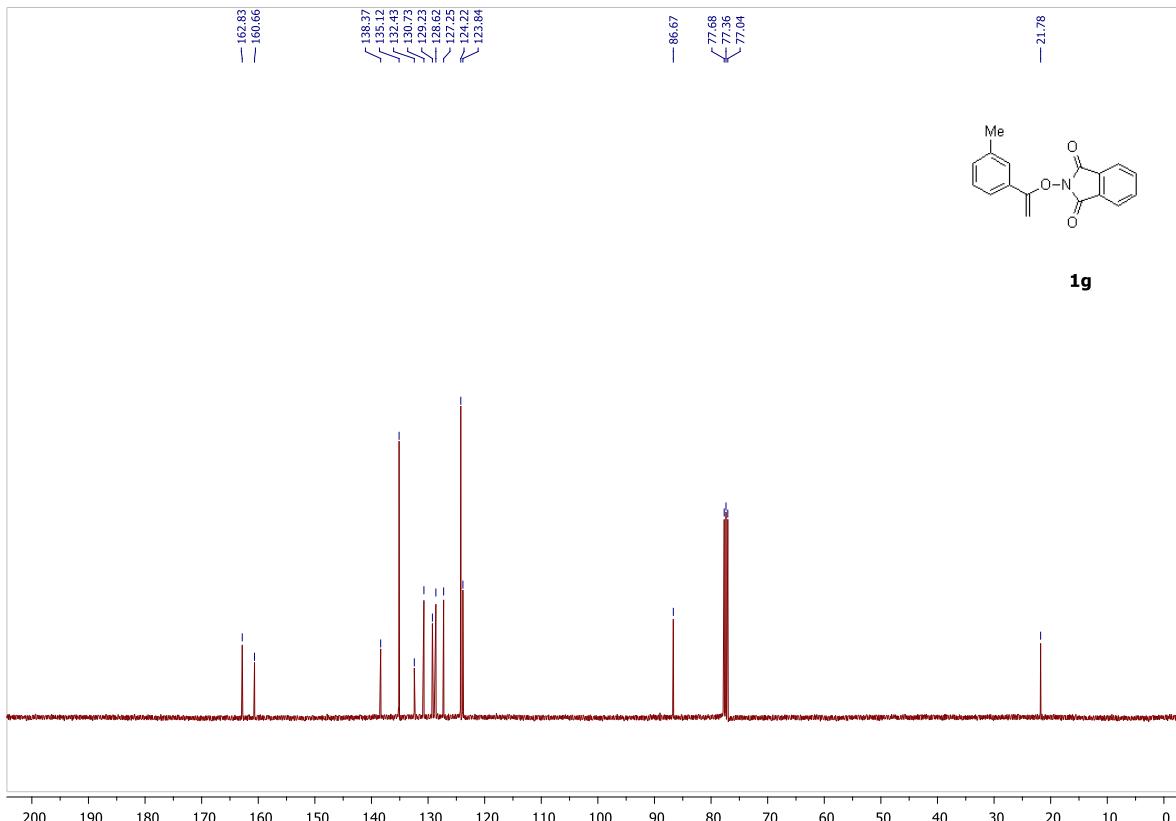
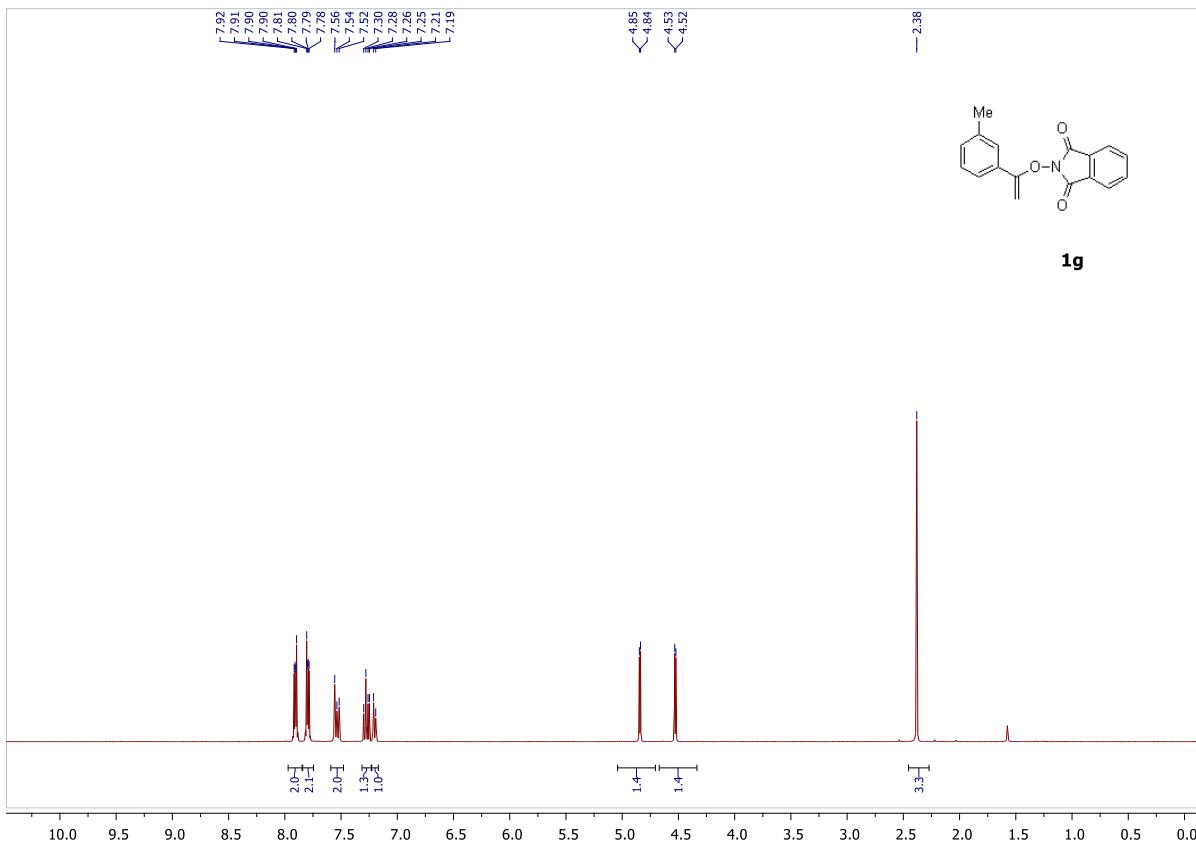


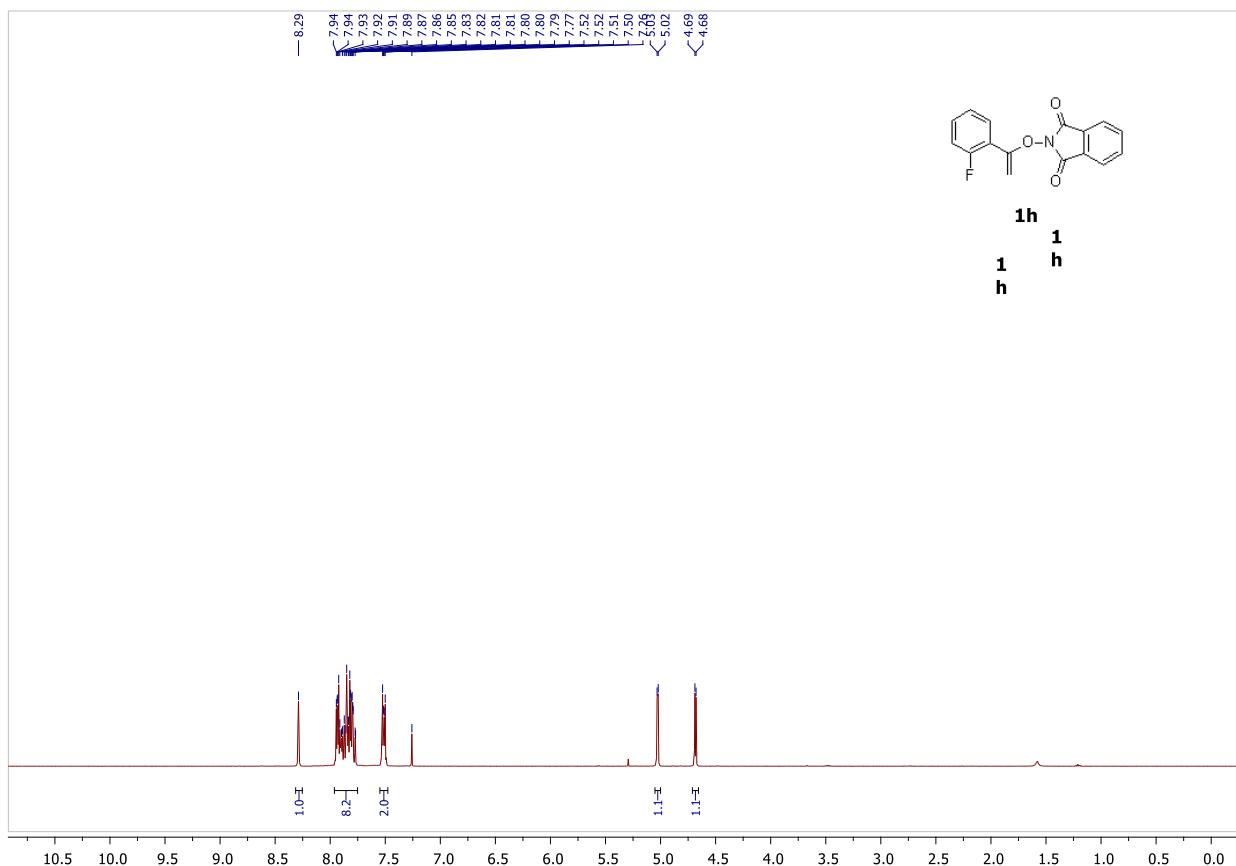
1h

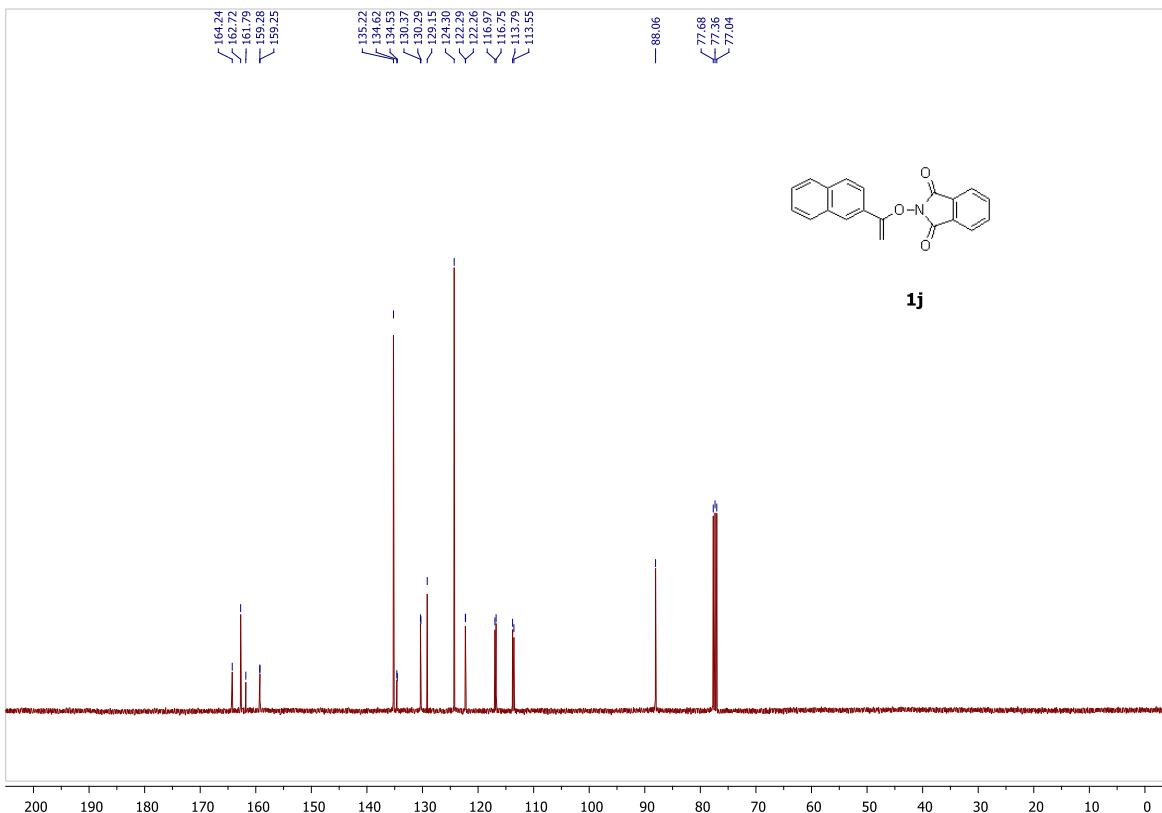
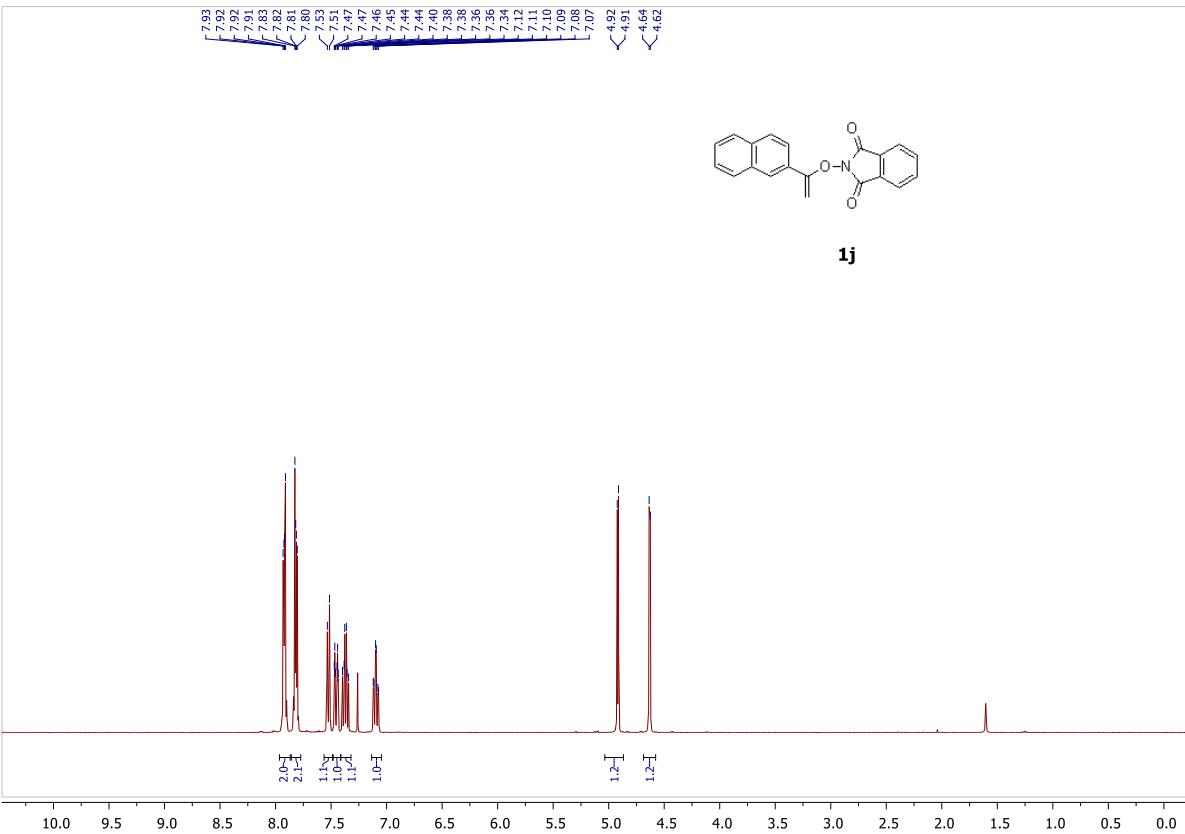


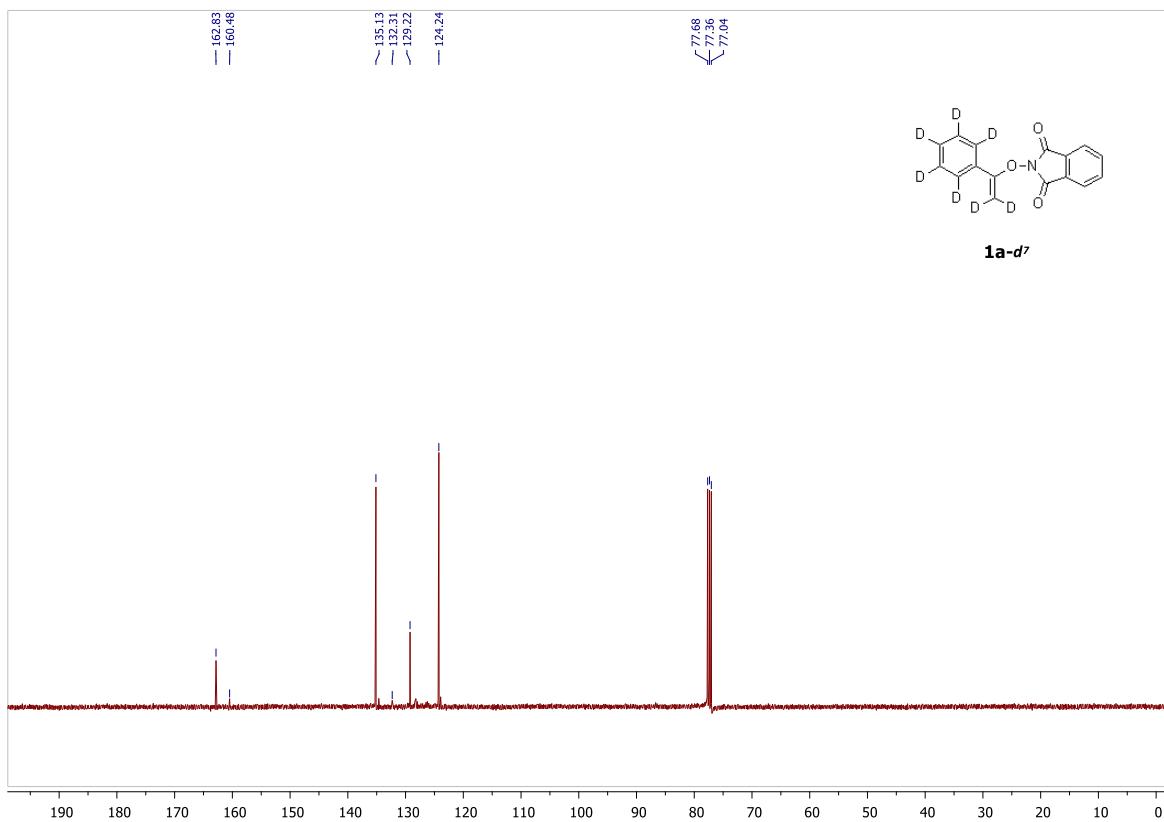
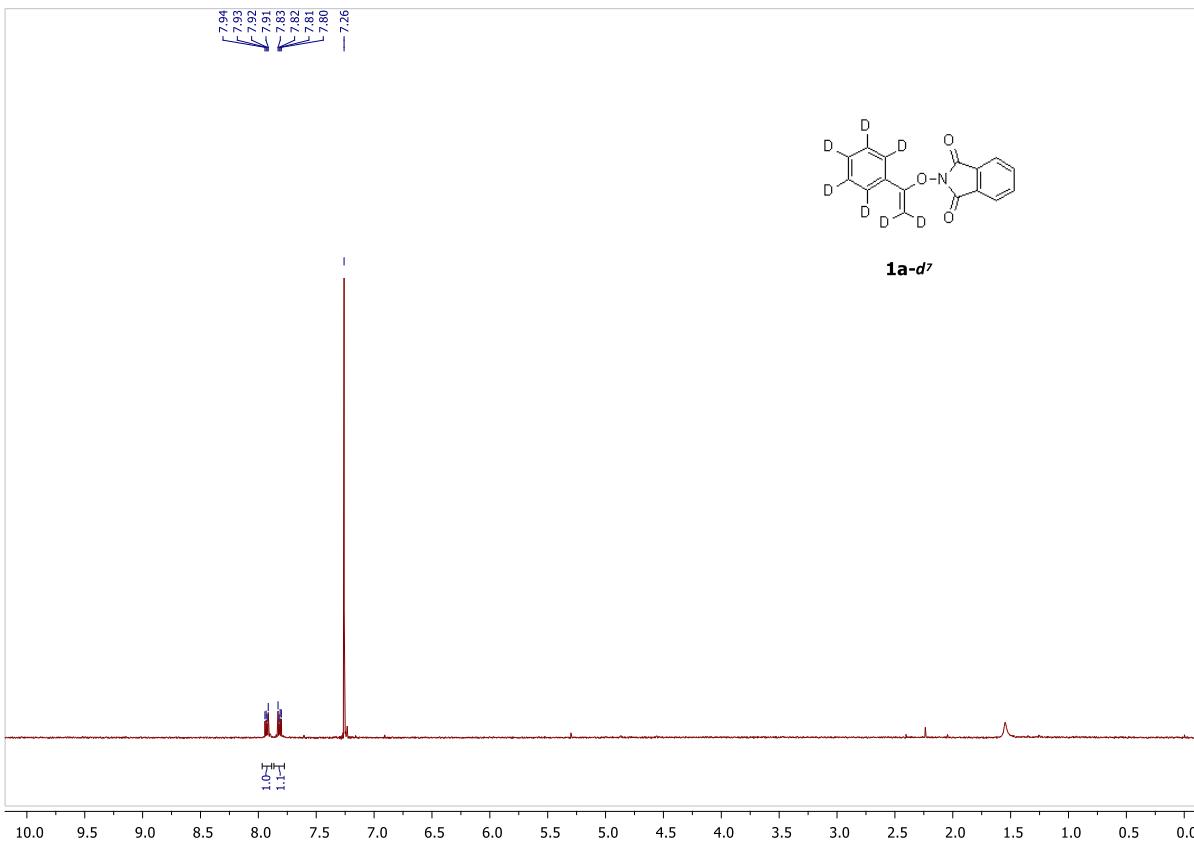
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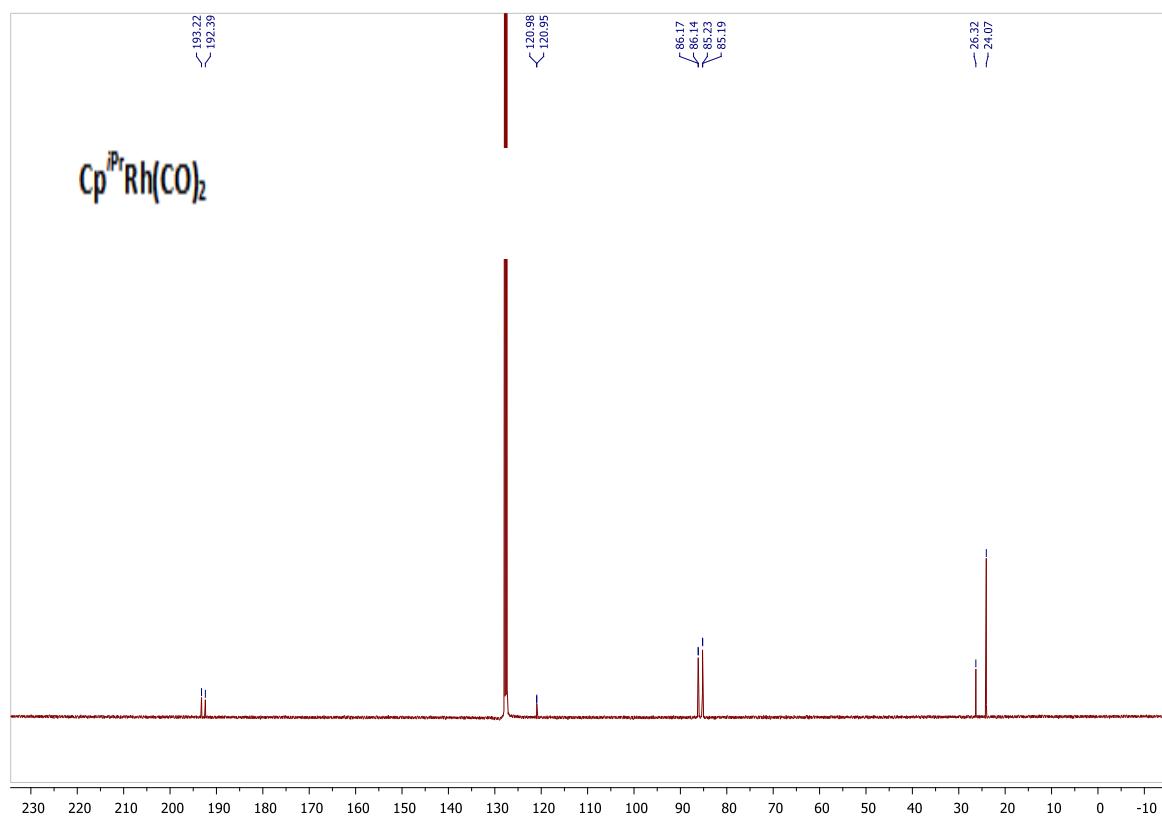
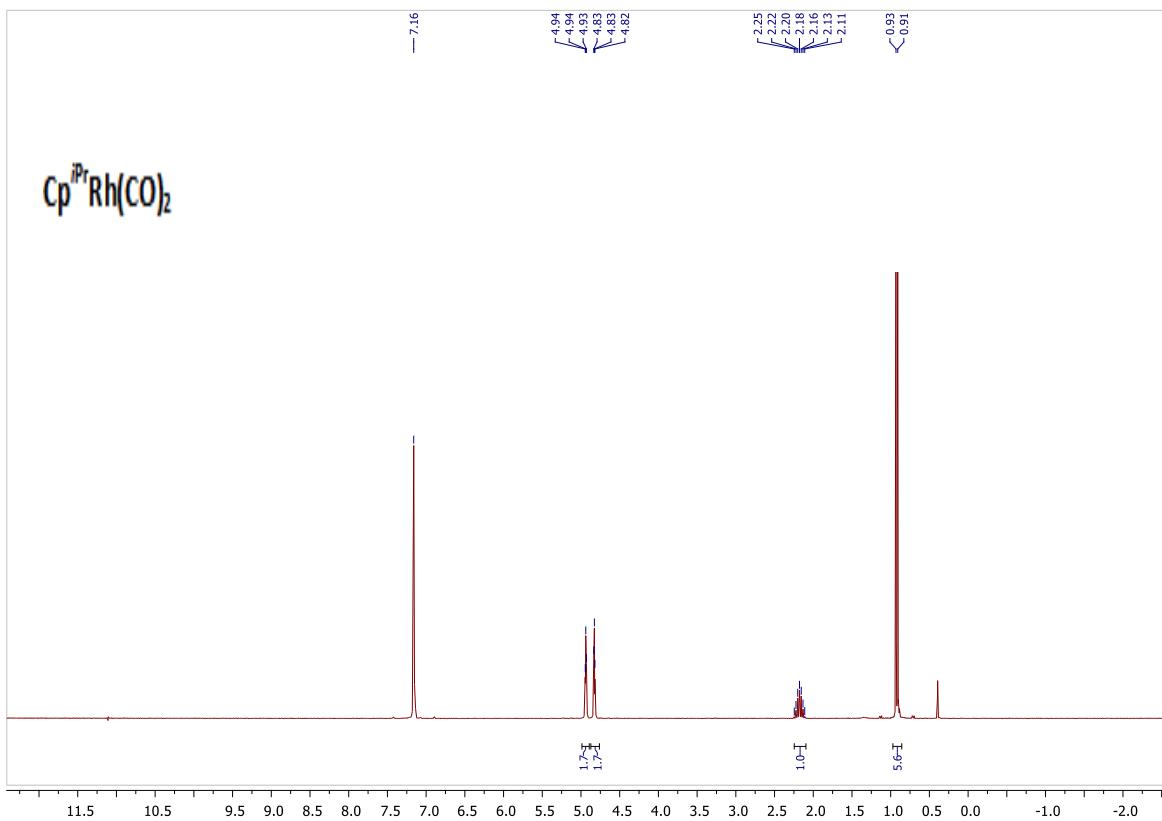


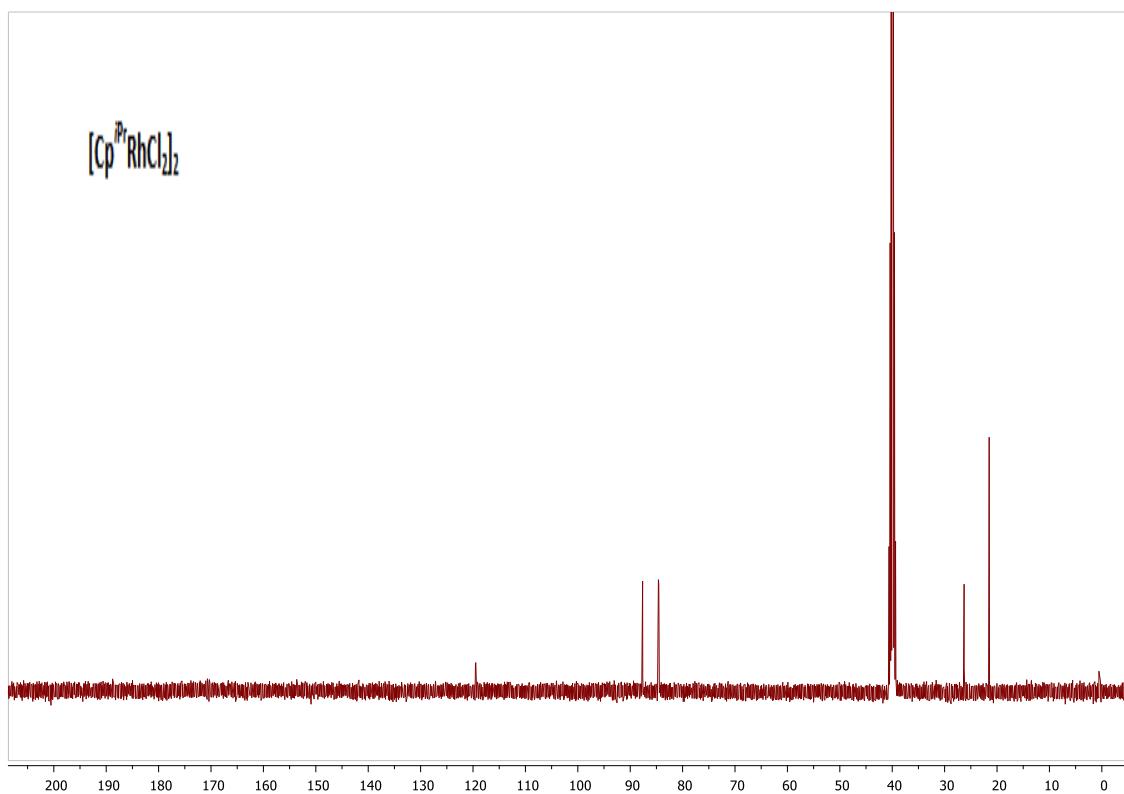
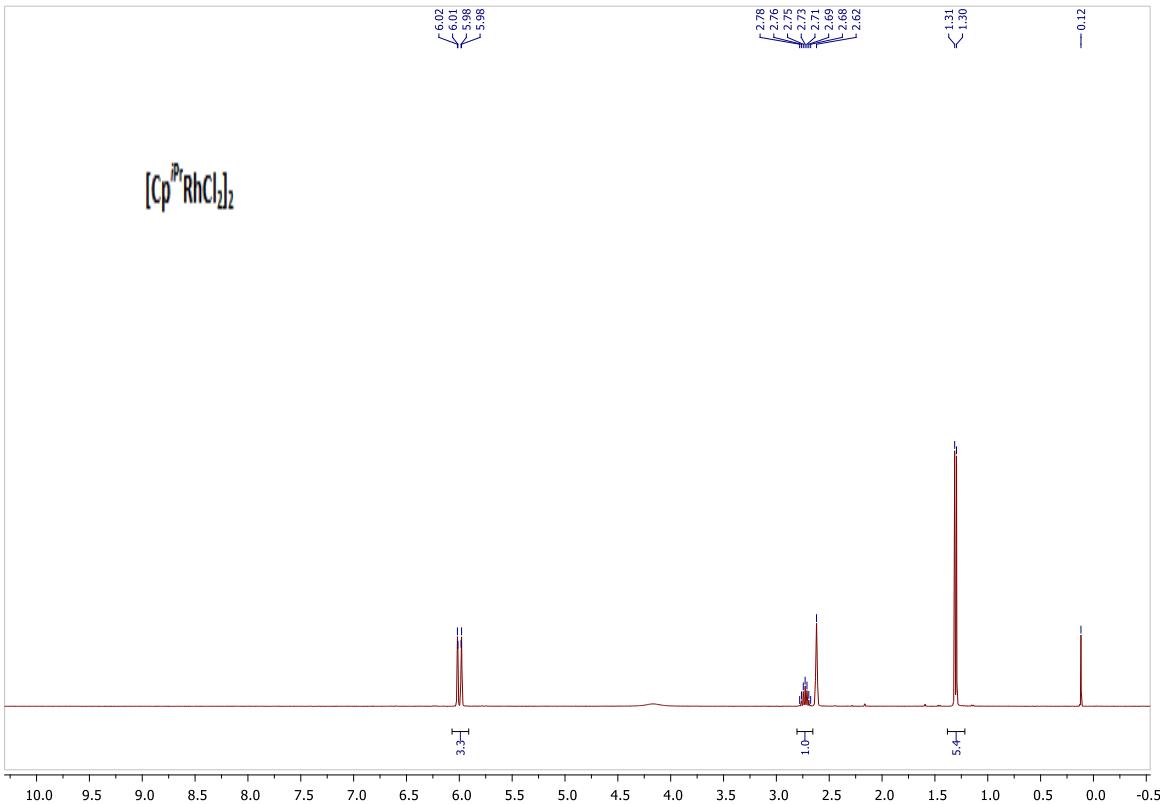


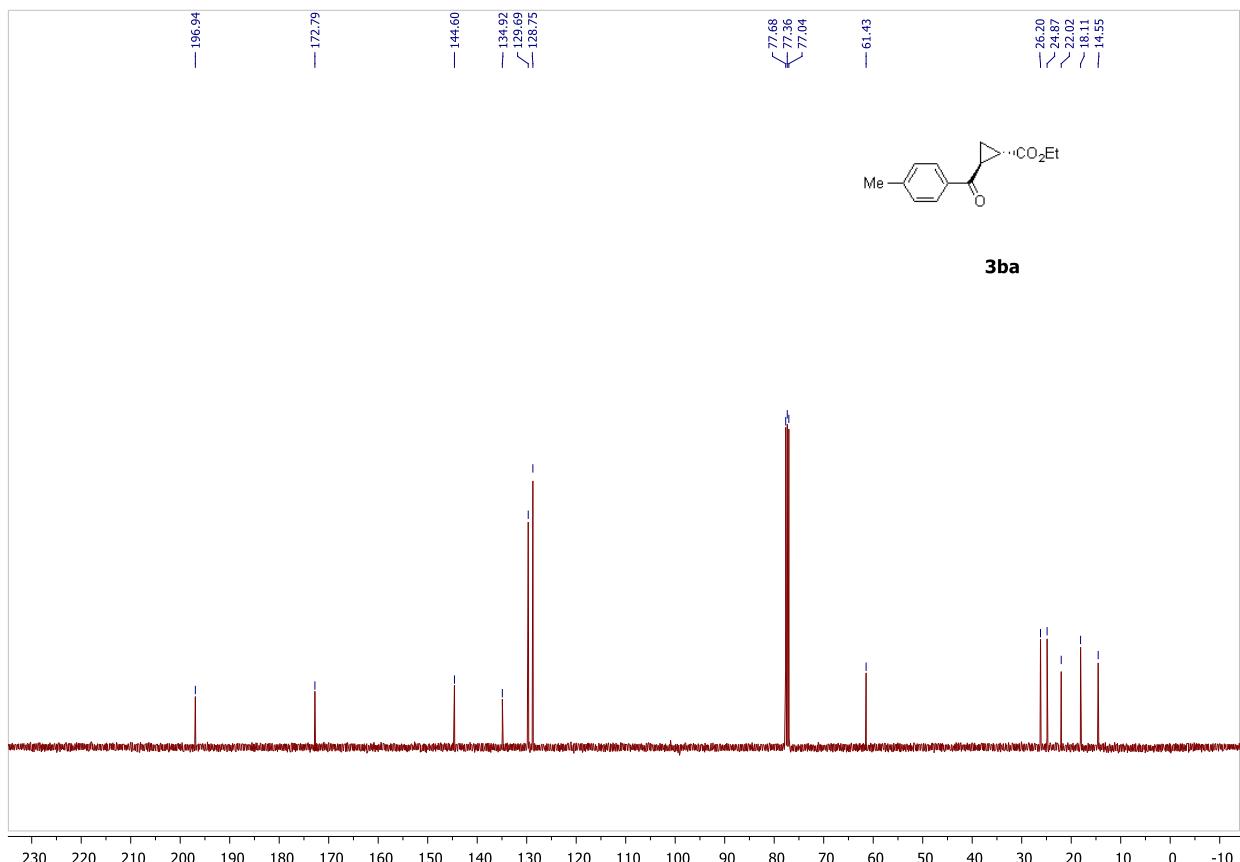
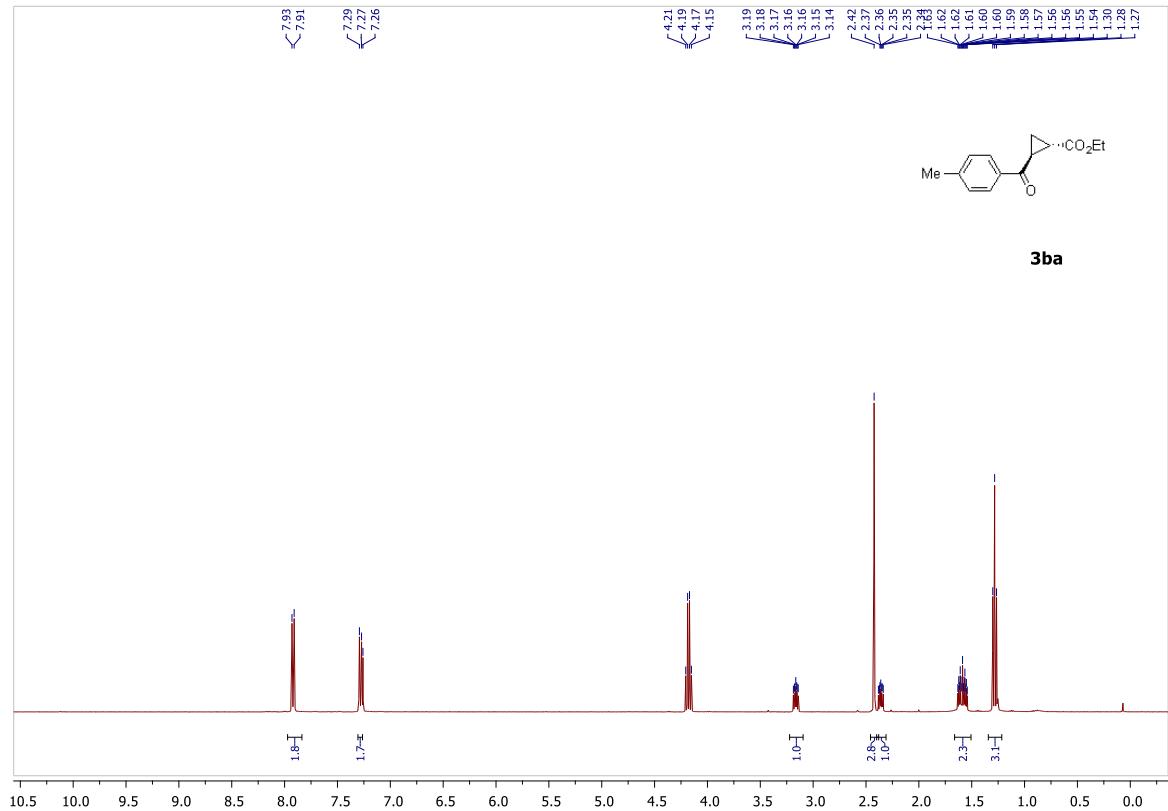


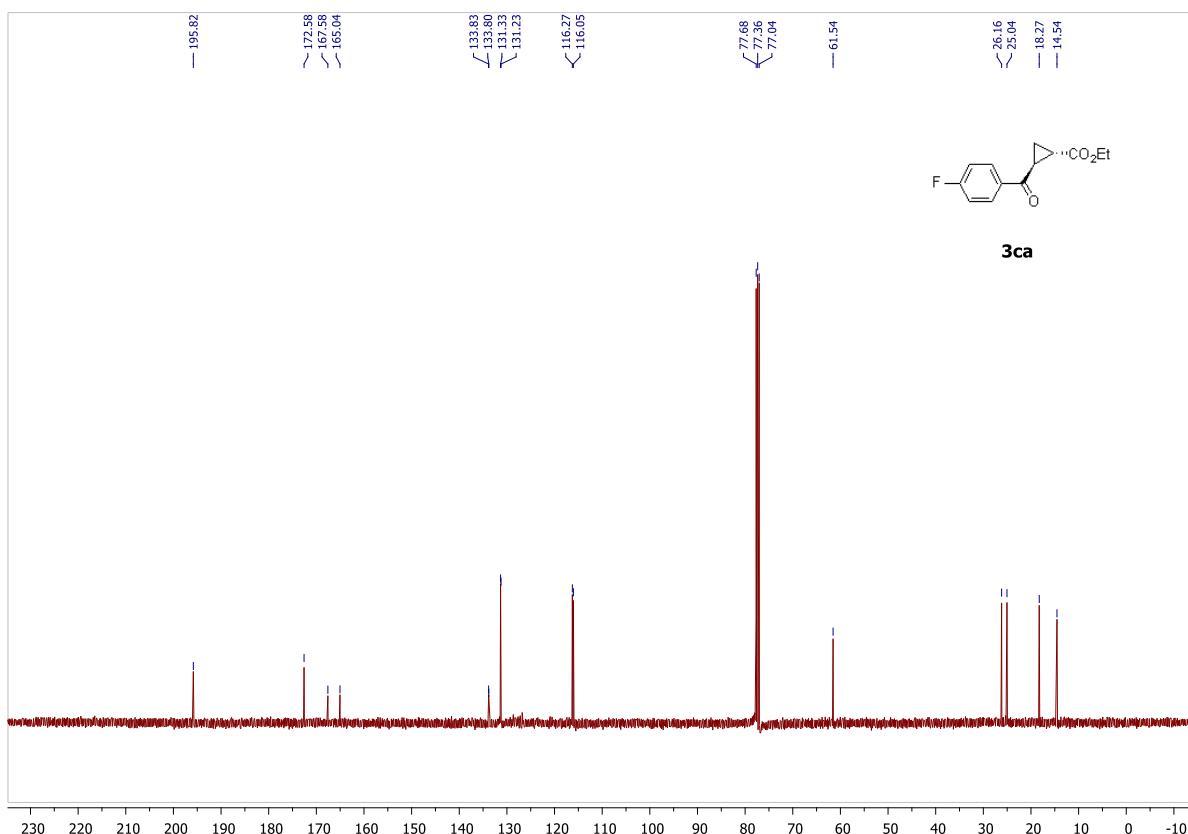
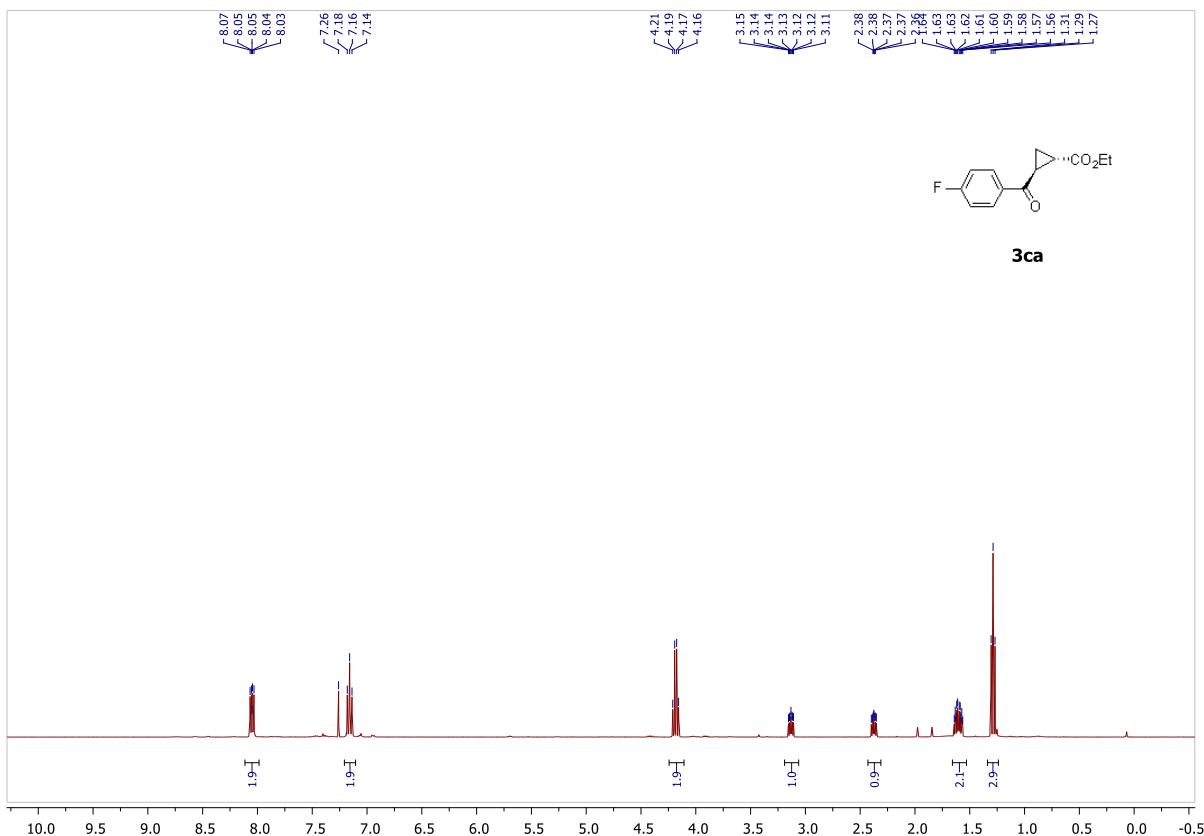


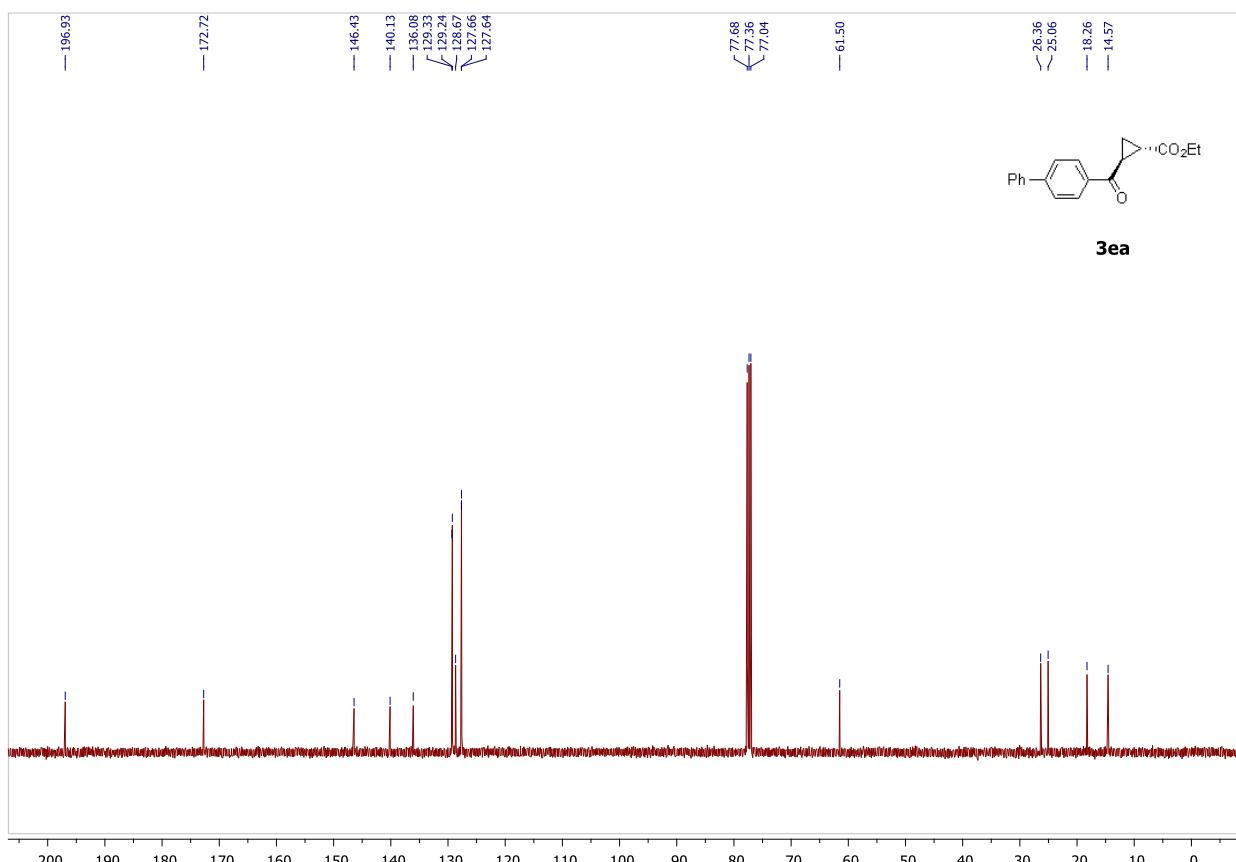
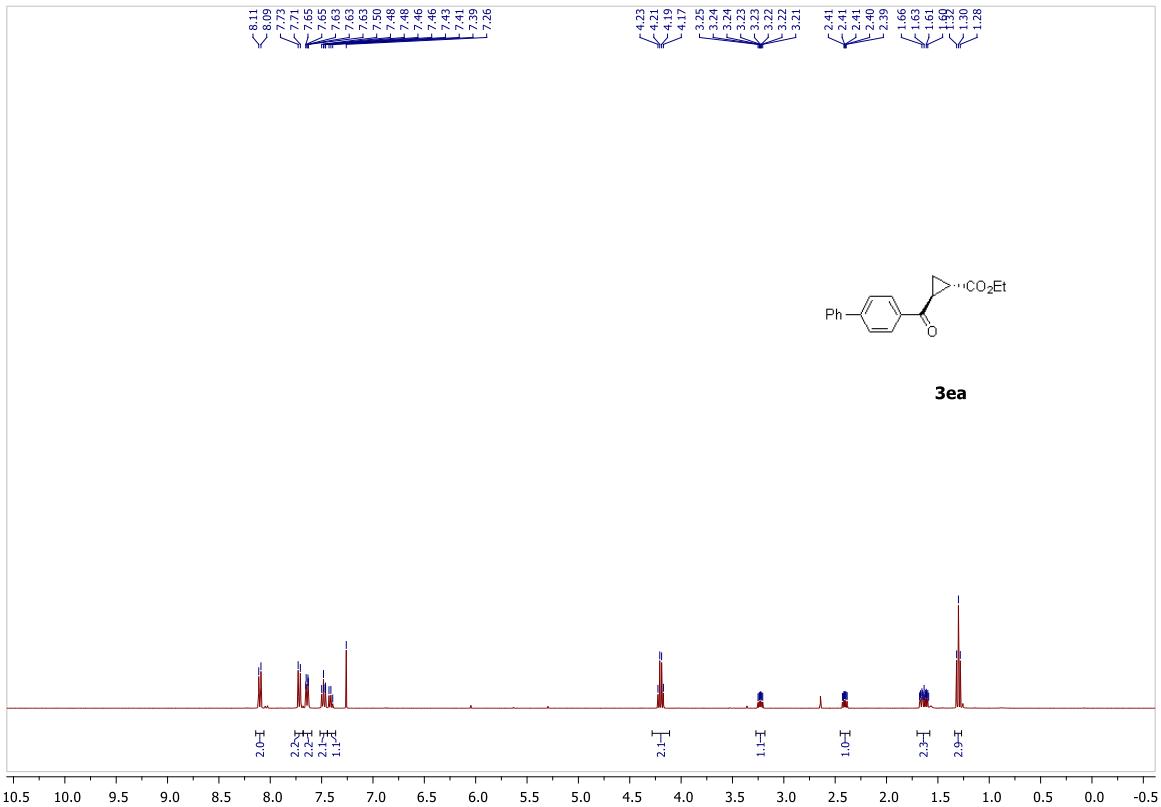


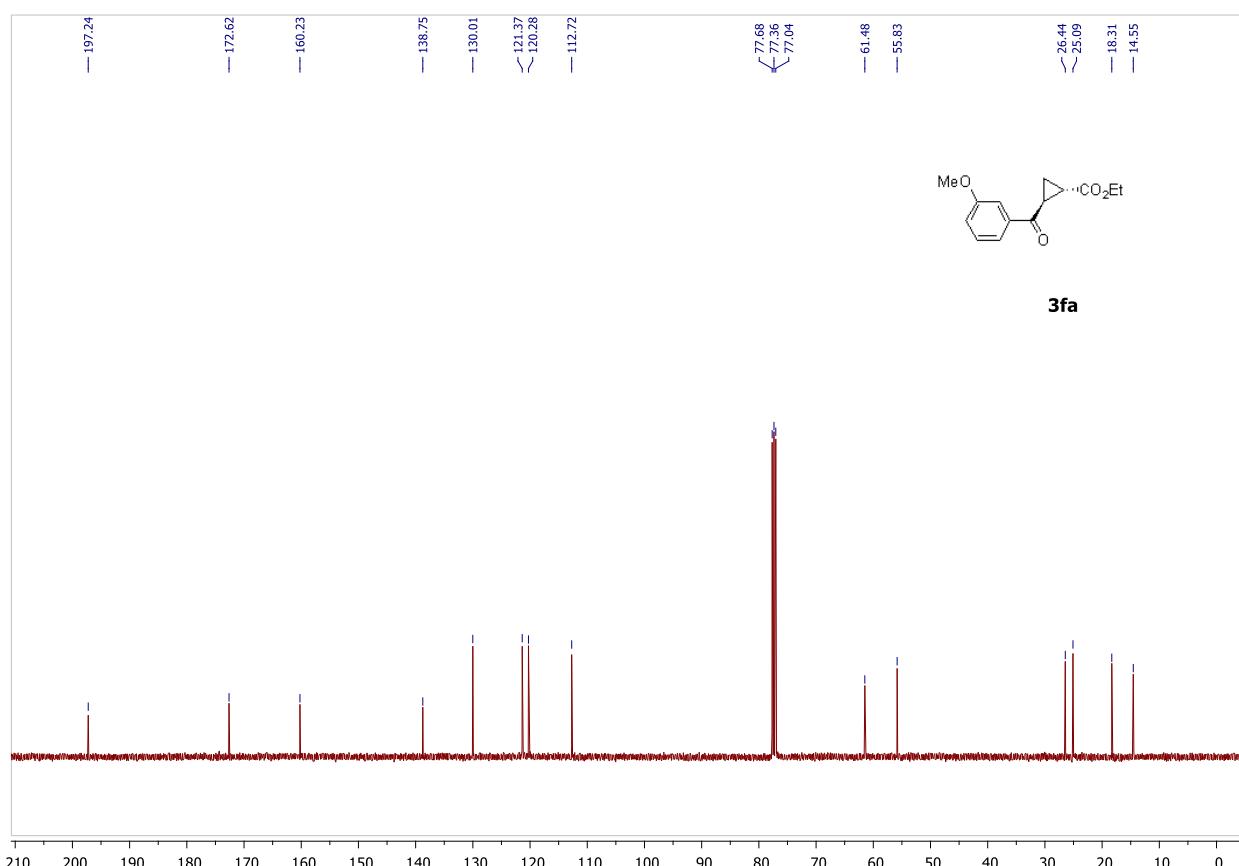
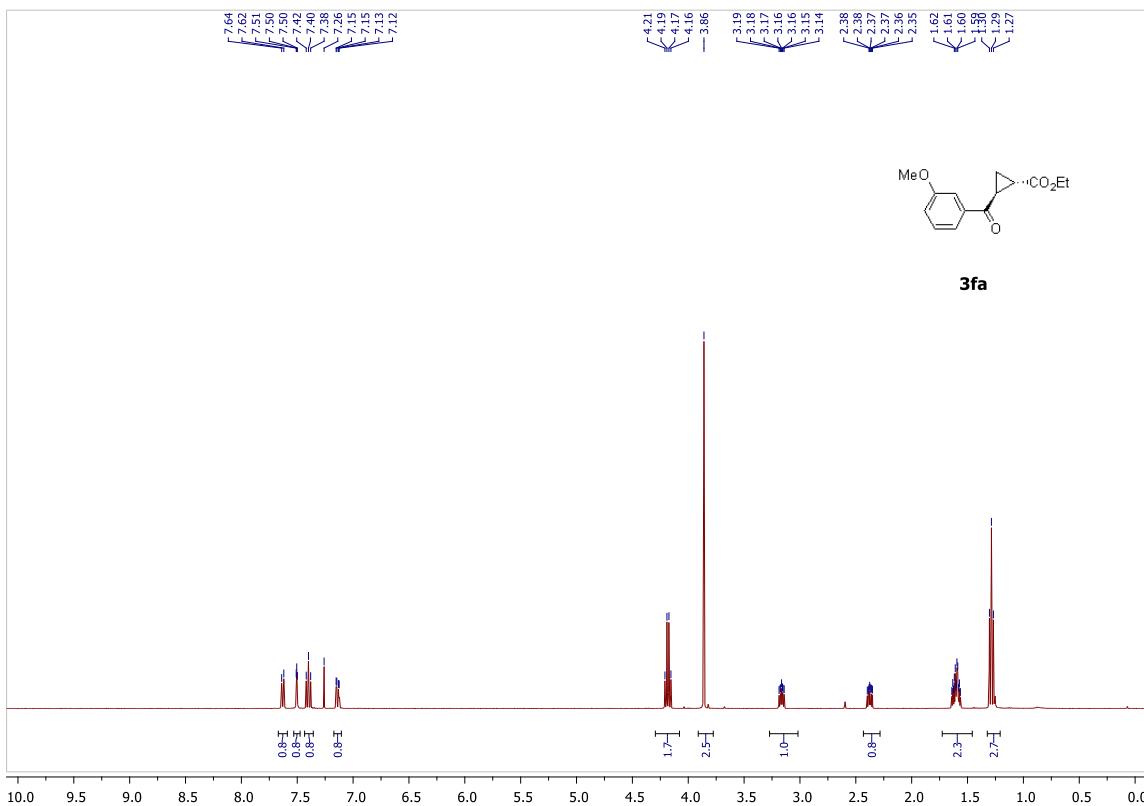


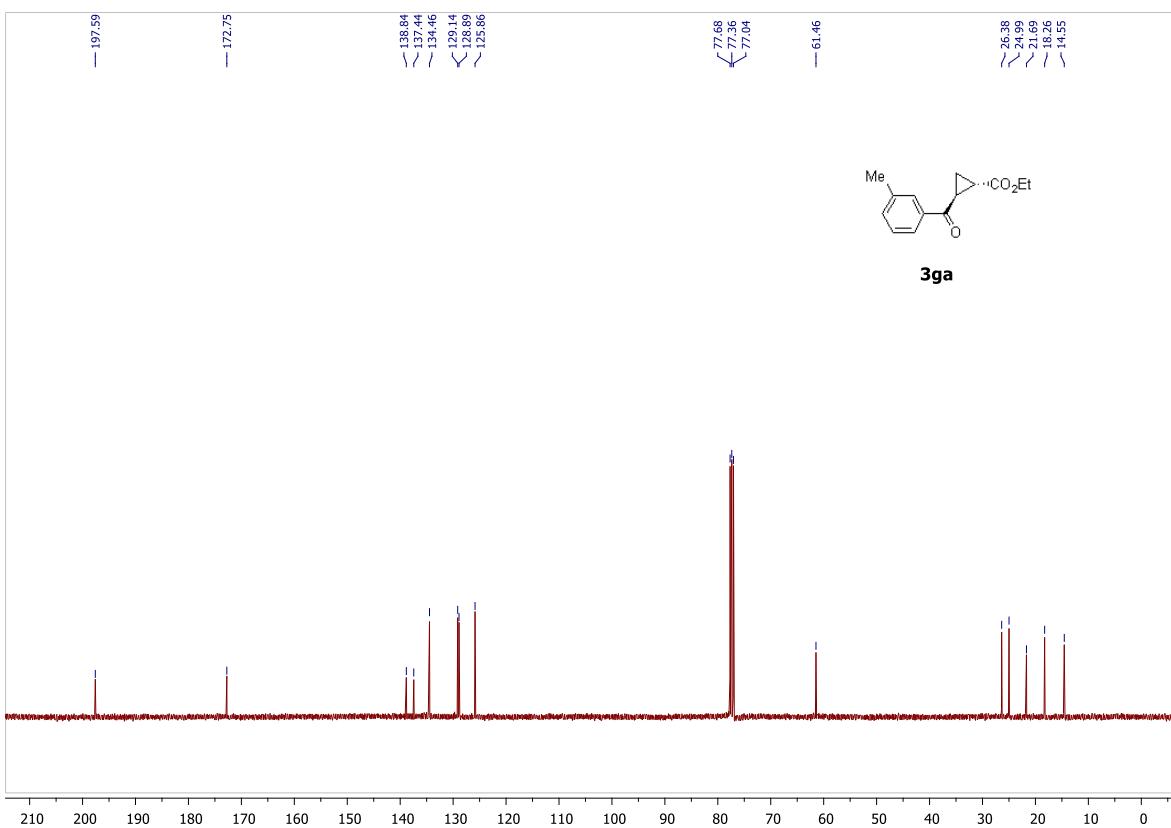
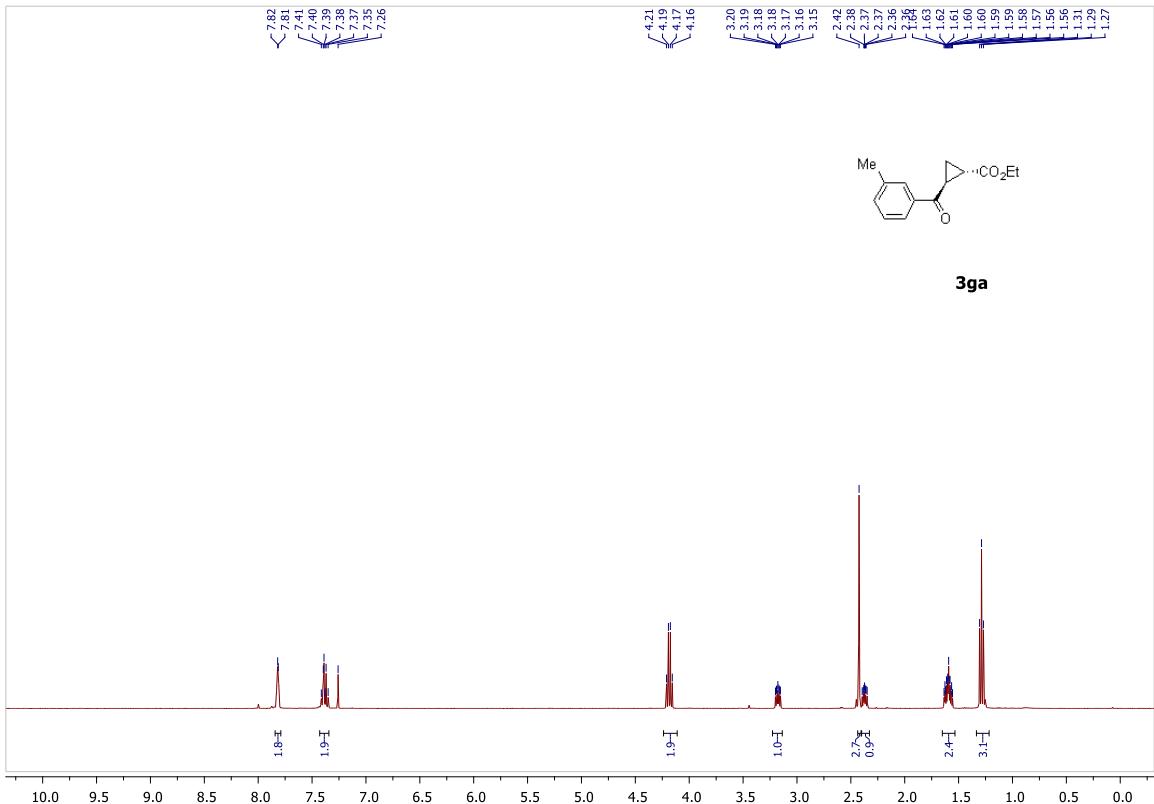


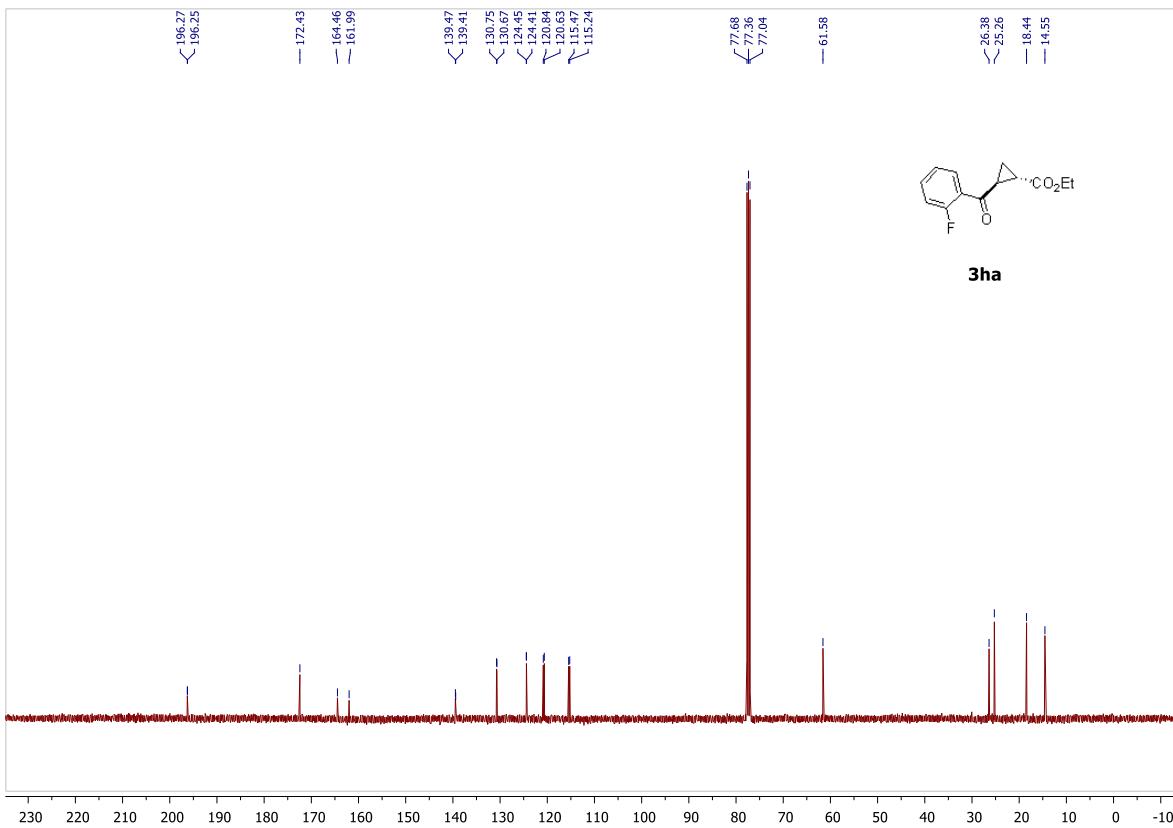
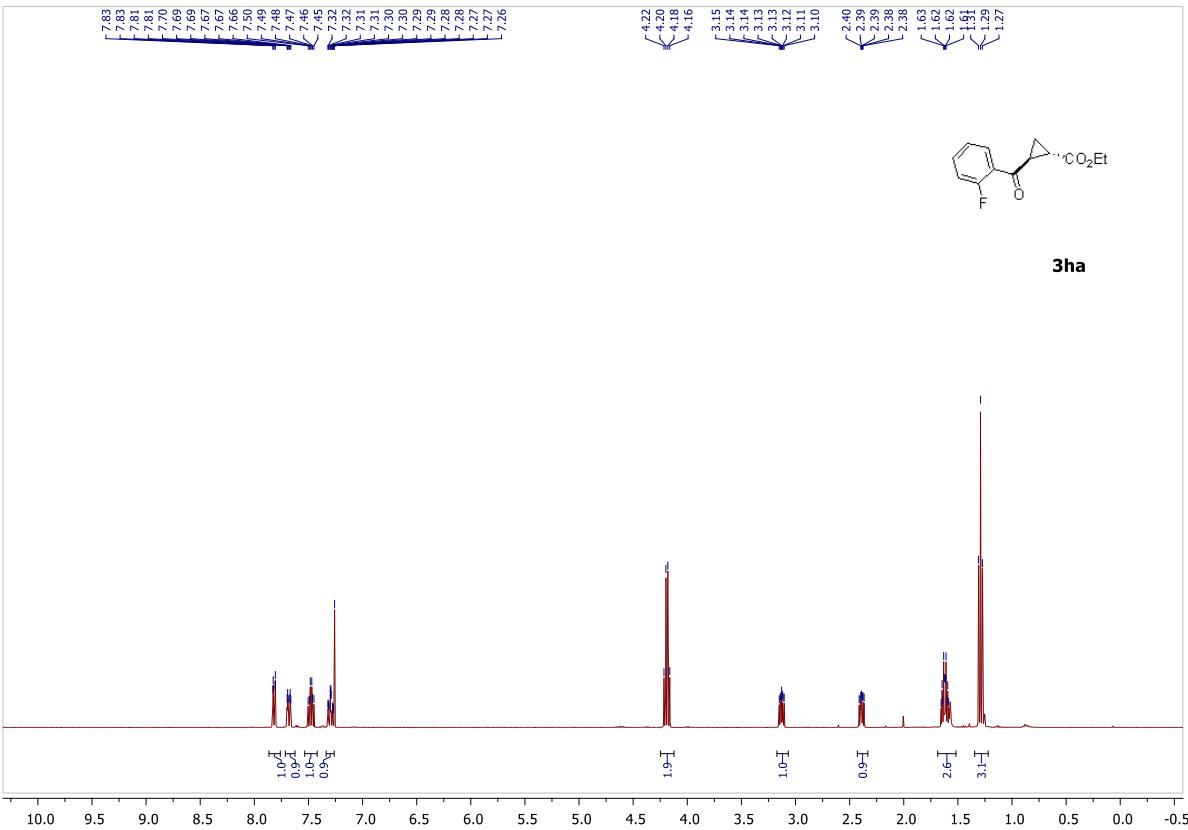


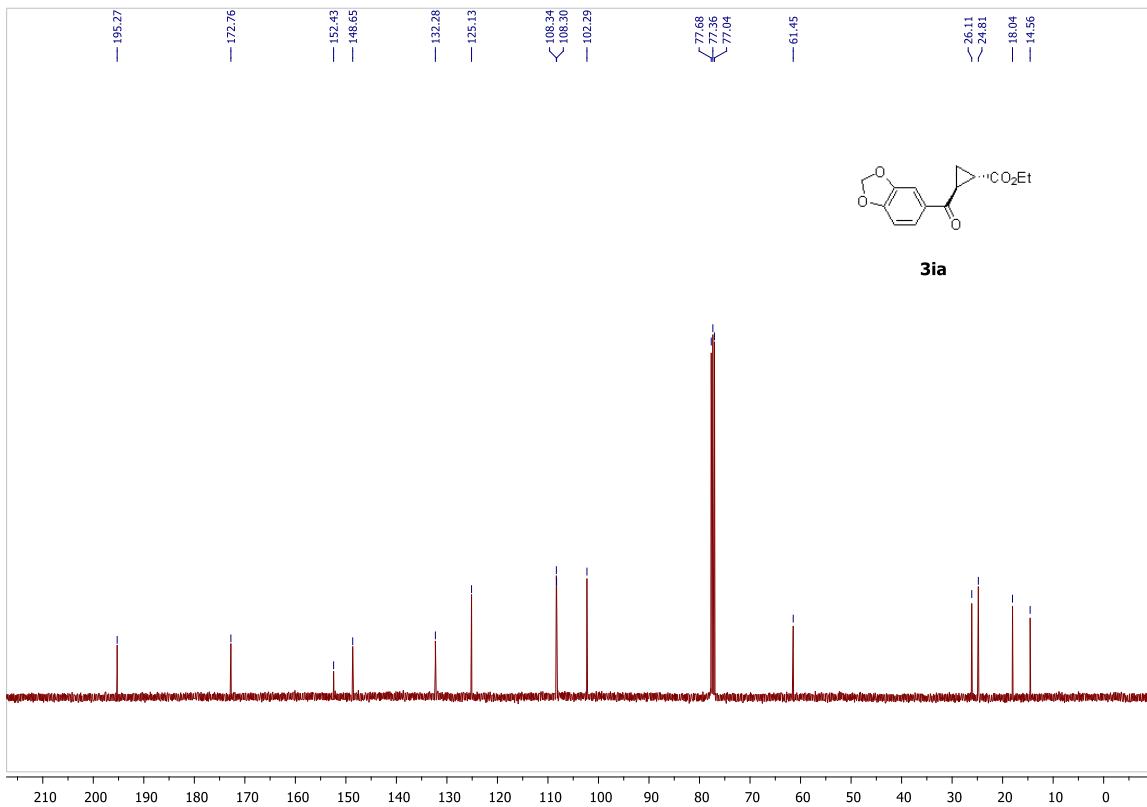
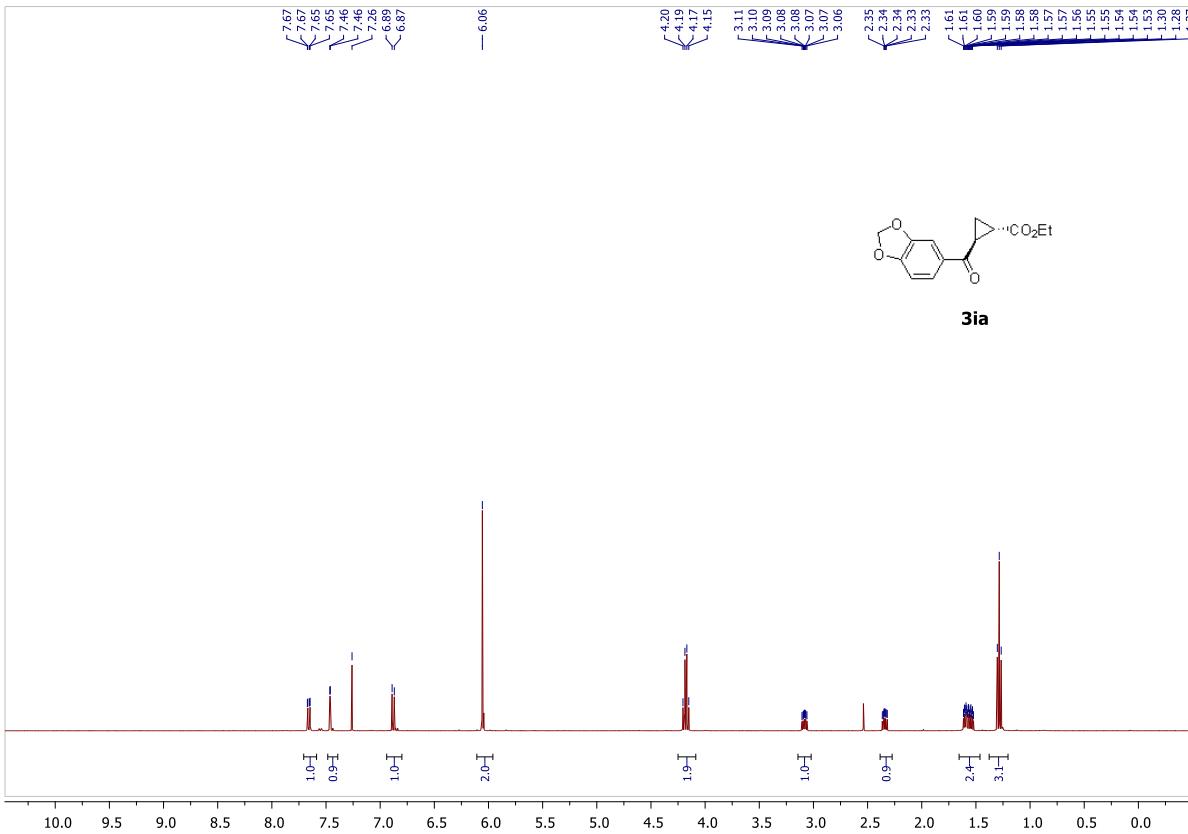


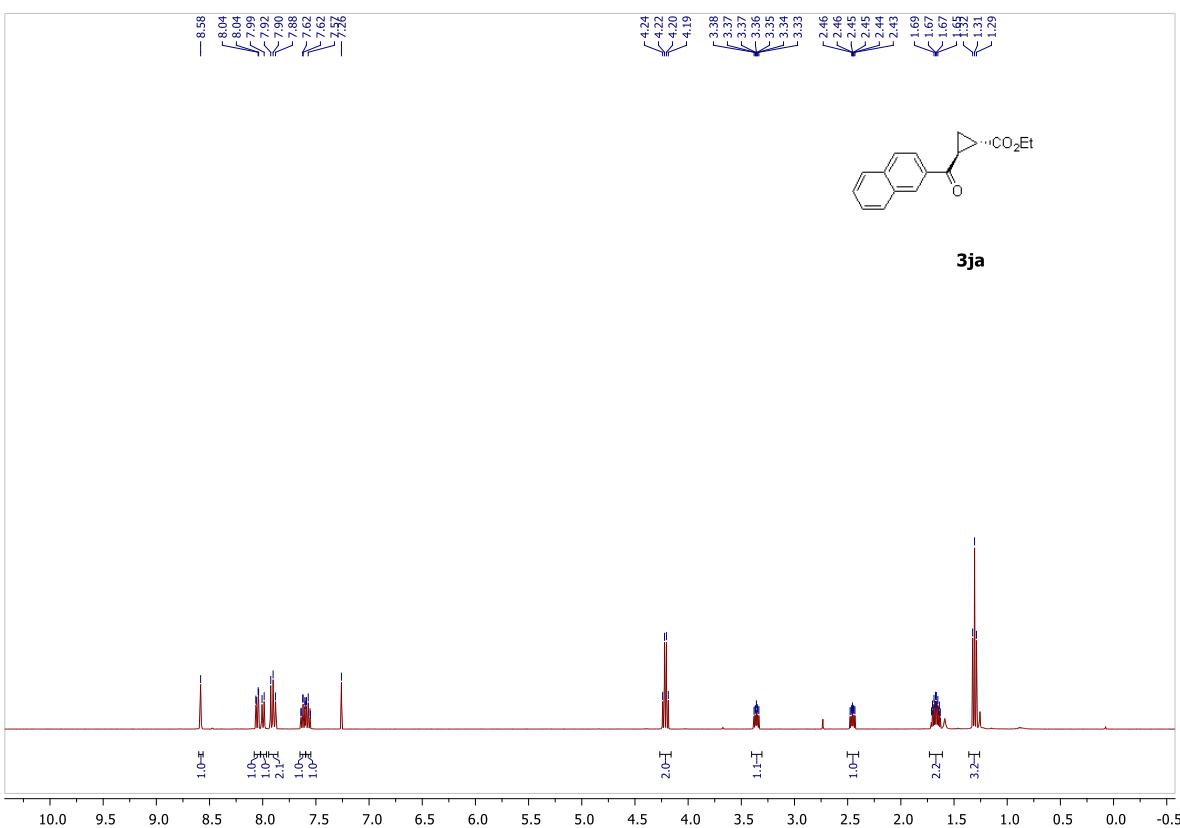




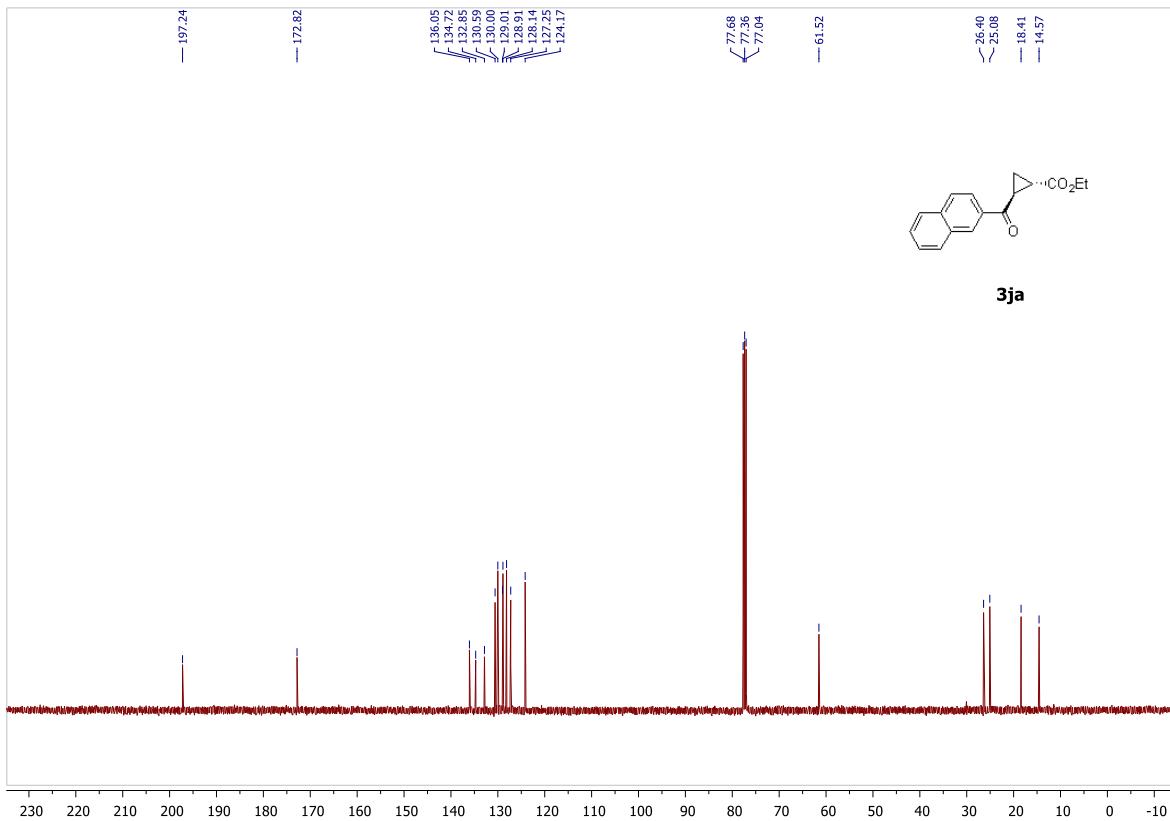








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