# Electronic Supplementary Information

## α-Arylation of (Hetero)aryl Ketones in Aqueous Surfactant Media

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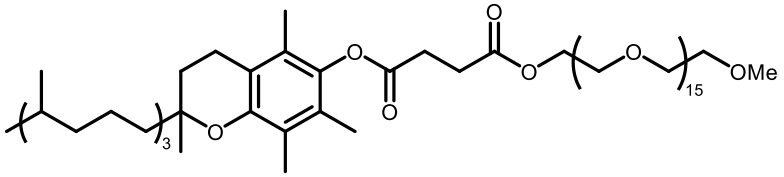
# 1. General Information

All commercial reagents were used without further purification unless otherwise noted. Organic solvents specified as dry and/or degassed such as THF, toluene, and DCM were either taken from a solvent purification system (Pure-Solv 400, Innovative Technology, Inc. (now Inert, Inc.)), or degassed using a stream of bubbling argon for a minimum of 1 h and involved less than 25 mL of volume. All other solvents were used as received, such as MeOH, EtOAc, hexanes, and $Et_2O$, unless otherwise noted, and purchased from Fisher Scientific. Potassium *t*-butoxide was purchased from Millipore-Sigma (catalog #156671) and stored in an argon purged glove box. All palladium catalysts and ligands were stored in an argon purged glove box. Specifically, di-μ-bromobis(tri-*t*-butylphosphine)dipalladium(I) ($[Pd(\mu\text{-}Br)(t\text{-}Bu)_3P]_2$) was purchased from Strem (catalog #46-0355) and kept rigorously oxygen-free in its solid state within a glove box. Starting ketones and halides were purchased either from Millipore-Sigma or Combi-Blocks. The surfactant, TPGS-750-M, was prepared via a standard literature procedure,[1] or can be purchased from Millipore-Sigma (catalog #733857 for a 2 wt % solution of the wax dissolved in water). A standard 2 wt % aqueous solution of TPGS-750-M was typically prepared on a 100 g scale by dissolving 2 g of the wax into 98 g of thoroughly degassed (steady stream of argon, minimum of 1 h bubbling time with stirring) HPLC grade water in a 250 mL round bottomed flask equipped with a stir bar and allowed to dissolve overnight with vigorous stirring under argon pressure (**NOTE**: Do not attempt to degas the aqueous phase with surfactant wax submerged; vigorous foaming to the point of overflowing will occur). The 2 wt % TPGS-750-M/$H_2O$ solution, once prepared, was kept under argon pressure at all times. Thin-layer chromatography (TLC) was performed using Silica Gel 60 $F_{254}$ plates (Merck, 0.25 mm thick). Flash chromatography is either performed in glass columns or an automated Biotage system using Silica Gel 60 (Silicycle, 40-63 nm). $^1H$ and $^{13}C$ NMR were recorded at 25 °C on a Varian Unity Inova 400 MHz, a Varian Unity Inova 500 MHz, or on a Varian Unity Inova 600 MHz spectrometer in $CDCl_3$ with residual $CHCl_3$ ($^1H$ =

7.26 ppm, $^{13}C$ = 77.16 ppm) or in DMSO-$d_6$ with residual $(CH_3)_2SO$ ($^1H$ = 2.50 ppm, $^{13}C$ = 39.52 ppm) as internal standards. Chemical shifts are reported in parts per million (ppm). NMR Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, t = triplet, td = triplet of doublets, q = quartet, quin = quintet, m = multiplet), coupling constant (if applicable), and integration. High-resolution mass analyses (HRMS) were recorded on a Waters Micromass LCT TOF ES+ Premier mass spectrometer using ESI ionization.

[1] B. H. Lipshutz, S. Ghorai, A. R. Abela, R. Moser, T. Nishikata, C. Duplais, A. Krasovskiy, *J. Org. Chem.*, **2011**, *76*, 4379–4391.




**TPGS-750-M**

# 2. General Procedures

**General Procedure A: 0.5 mmol scale α-arylation of ketones using 0.125 mol % [Pd(μ-Br)(*t*-Bu)$_3$P]$_2$**

To a flame dried 1-dram vial inside of an argon purged glove box was added [Pd(μ-Br)(*t*-Bu)$_3$P]$_2$ (5 mg) and the vial was sealed using a rubber septum and maintained under a steady pressure of argon. Rigorously degassed DCM (500 μL) was then added through the septum and the vial was stirred at ambient temperature until the solids had dissolved to prepare a very dark green catalyst stock solution. To another flame dried 1-dram vial equipped with an oven dried stir bar inside of a glove box was added K-O-*t*-Bu (135 mg, 1.2 mmol, 2.4 equiv), followed by any solid ketone (0.6 mmol, 1.2 equiv) and solid aryl halide (0.5 mmol, 1.0 equiv) (or oils thereof) used for the reaction, and the vial was sealed using a rubber septum. This vial was then placed under argon pressure on a manifold and a 48 μL aliquot of the catalyst solution was added through the septum (0.48 mg, 6.25 x $10^{-4}$ mmol, 0.125 mol %). A vacuum was then pulled on the reaction vial for 2 min to remove all DCM and the vial was backfilled with argon. 2 wt % TPGS-750-

M/$H_2O$ was then added (0.5 mL, 1.0 M) via syringe through the rubber septum followed by any neat liquid reagents via syringe. The contents of the vial were then allowed to stir vigorously (~1500 RPM) under constant argon pressure in a 1-dram vial aluminum block reactor at 45 °C internal temperature (aluminum block set to heat to 50 °C). The reaction was then monitored by thin-layer chromatography and gas chromatography until deemed complete. The contents of the vial were then extracted using EtOAc (3 x 1 mL) and dried directly onto $SiO_2$ to be purified via column chromatography.

**General Procedure B: 0.5 mmol scale α-arylation of ketones using 0.25 mol % [Pd(μ-Br)(*t*-Bu)$_3$P]$_2$**

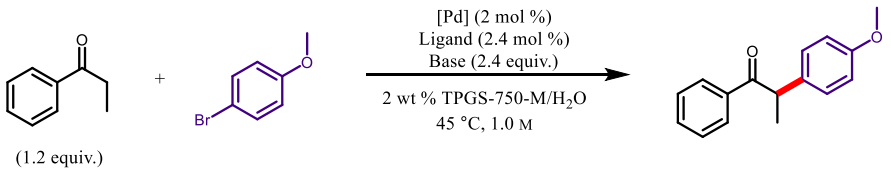
To a flame dried 1-dram vial equipped with an oven dried stir bar inside of a glove box was added [Pd(μ-Br)(*t*-Bu)$_3$P]$_2$ (1 mg, 1.25 x $10^{-3}$ mmol, 0.25 mol %), K-O-*t*-Bu (135 mg, 1.2 mmol, 2.4 equiv), followed by any solid ketone (0.6 mmol, 1.2 equiv), and solid aryl halide (0.5 mmol, 1.0 equiv) (or any oils thereof) used for the reaction. The vial was then sealed using a rubber septum inside of the glovebox and then transferred to a manifold under argon pressure. 2 wt % TPGS-750-M/$H_2O$ was then added (0.5 mL, 1.0 M) via syringe through the rubber septum followed by any neat liquid reagents via syringe. The contents of the vial were then allowed to stir vigorously (~1500 RPM) under constant argon pressure in a 1-dram vial aluminum block reactor at 45 °C internal temperature (aluminum block set to heat to 50 °C). The reaction was then monitored by thin-layer chromatography and gas chromatography until deemed complete. The contents of the vial were then extracted using EtOAc (3 x 1 mL) and dried directly onto $SiO_2$ to be purified via column chromatography.

**General Procedure C: 0.5 mmol scale α-arylation of ketones using 1.0 mol % [Pd(μ-Br)(*t*-Bu)$_3$P]$_2$**

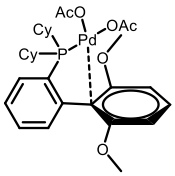
To a flame dried 1-dram vial equipped with an oven dried stir bar inside of a glove box was added [Pd(μ-Br)(*t*-Bu)$_3$P]$_2$ (4 mg, 0.005 mmol, 1.0 mol %). The remainder of the experimental then follows General Procedure B.

# 3. Reaction Optimization

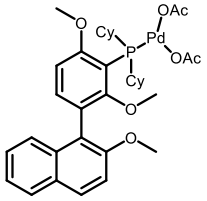
## 3.1 Primary Ligand Screen – 2 mol % Pd



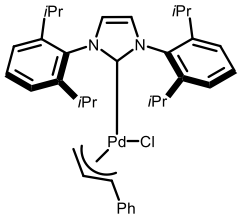

(1.2 equiv.)



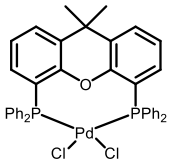
**SPhos**
Li*t*-OBu: Trace



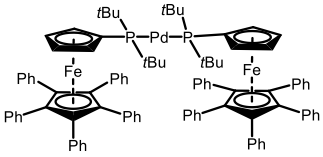
**EvanPhos**
Li*t*-OBu: Trace



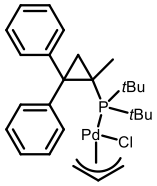
**CX 31**
Li*t*-OBu: Trace



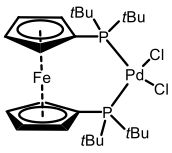
**Pd(Xantphos)$Cl_2$**
Li*t*-OBu: Trace



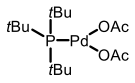
**Pd(Qphos)$_2$**
Li*t*-OBu: 30%



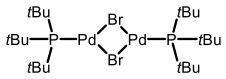
**c-BRIDP-Pd-(π–allyl)Cl**
Li*t*-OBu: 37%
K*t*-OBu: 74%



**Pd[dtbpf]$Cl_2$**
Li*t*-OBu: 60%
K*t*-OBu: 90%



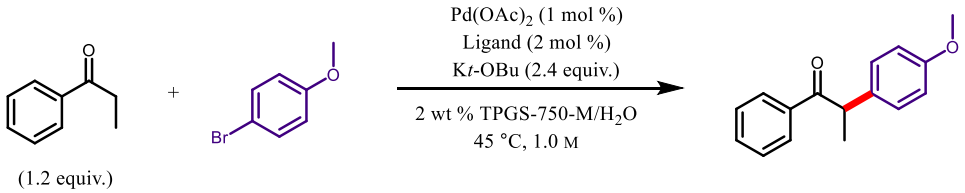
**tri-*tert*-butylphosphine**
K*t*-OBu: 99%

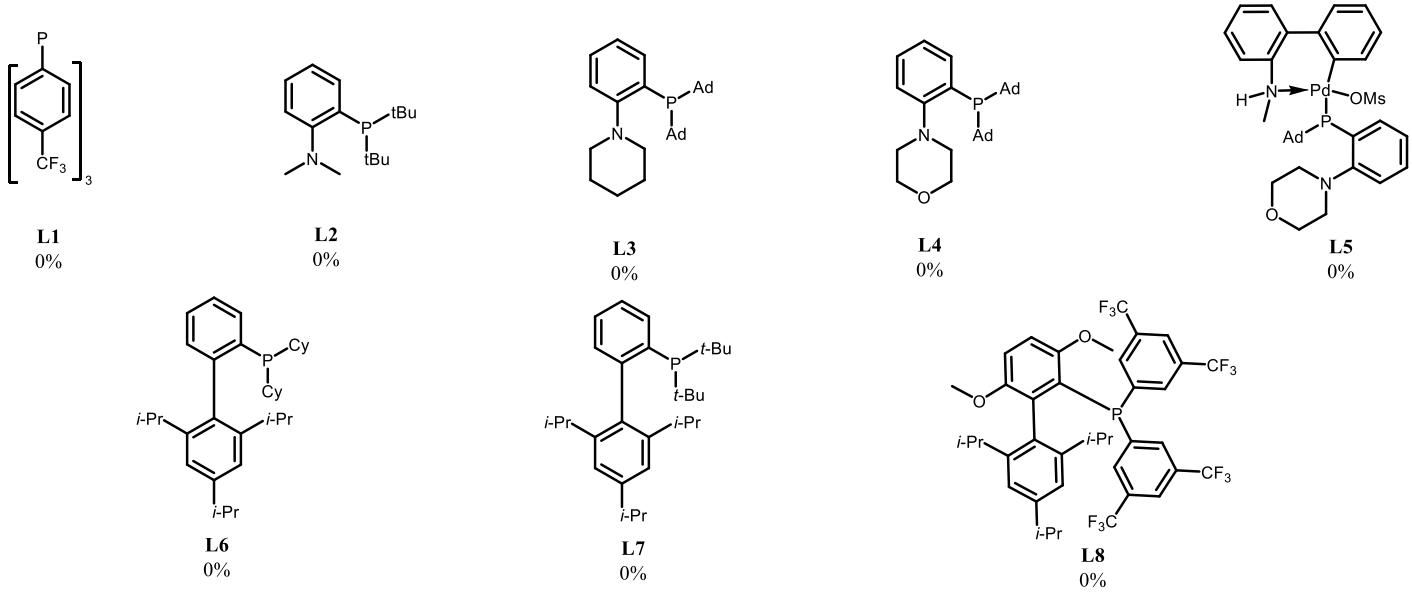


[Pd(μ-Br)(*t*-Bu)$_3$P]$_2$
K*t*-OBu: 97%

**Conditions:** 0.5 mmol 4-bromoanisole, 0.6 mmol (1.2 equiv) propiophenone, 2 mol % $Pd(OAc)_2$ (or Pd complex), 2.4% ligand (if applicable), 1.2 mmol (2.4 equiv) K-O-*t*-Bu, 2 wt % TPGS-750-M/$H_2O$ (0.5 mL, 1.0 M), 45 °C, 16 h. Yields are for isolated product. In the case of $Pd(OAc)_2$/L combinations, pre-complexation in organic solvent vs. aqueous medium yields no difference in activity.

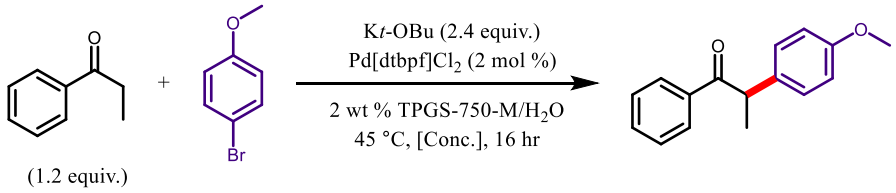
### 3.2 Secondary Ligand Screen – 1 mol % Pd




**Conditions:** 0.5 mmol 4-bromoanisole, 0.6 mmol (1.2 equiv) propiophenone, 1 mol % $Pd(OAc)_2$ (or Pd complex), 2% ligand, 1.2 mmol (2.4 equiv) K-O-*t*-Bu, 2 wt % TPGS-750-M/$H_2O$ (0.5 mL, 1.0 M), 45 °C, 16 h. Pre-complexation in organic solvent vs. aqueous medium yields no difference in activity.

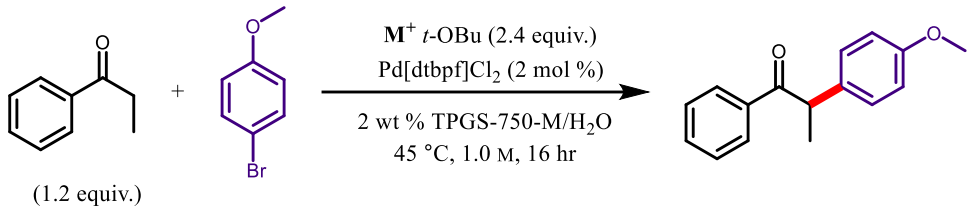
### 3.3 Global Concentration Screening




| entry | concentration (M) | yield (%) |
|---|---|---|
| 1 | 0.5 | 85 |
| **2** | **1.0** | **90** |

**Conditions:** 0.5 mmol 4-bromoanisole, 0.6 mmol (1.2 equiv) propiophenone, 2 mol % $Pd[dtbpf]Cl_2$, 1.2 mmol (2.4 equiv) , 2 wt % TPGS-750-M/$H_2O$, 45 °C, 16 h.

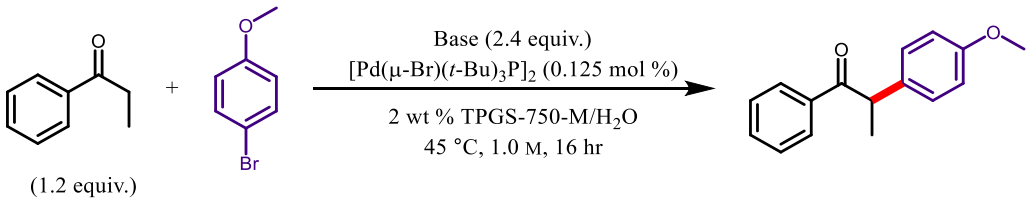
### 3.4 Base Cation Screening




| entry | cation | yield (%) |
|---|---|---|
| 1 | $Li^+$ | 66 |
| 2 | $Na^+$ | 80 |
| **3** | **$K^+$** | **90** |

**Conditions:** 0.5 mmol 4-bromoanisole, 0.6 mmol (1.2 equiv) propiophenone, 2 mol % Pd[dtbpf]$Cl_2$, 1.2 mmol (2.4 equiv) K-O-*t*-Bu, 2 wt % TPGS-750-M/$H_2O$, 45 °C, 16 h.

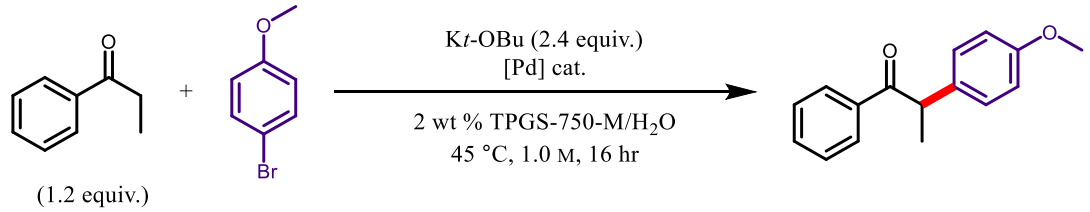
### 3.5 Base Screening




| entry | base | $pK_a$ conjugate acid | yield (%) |
|---|---|---|---|
| 1 | KOH | 15.7 | 63 |
| 2 | KOH (on water) | 15.7 | 40 |
| 3 | KOH / T*i*PS-OH | 14.9 | 35 |
| **4** | **K-O-t-Bu** | **17** | **97** |
| 5 | $K_3PO_4 \cdot H_2O$ | 12.3 | 57 |
| 6 | $Et_3N$ | 10.8 | trace |

**Conditions:** 0.5 mmol 4-bromoanisole, 0.6 mmol (1.2 equiv) propiophenone, 0.125 mol % $[Pd(\mu\text{-}Br)(t\text{-}Bu)_3P]_2$, 1.2 mmol (2.4 equiv) base, 2 wt % TPGS-750-M/$H_2O$ (0.5 mL, 1.0 M), 45 °C, 16 h.

### 3.6 Catalyst Loading Screening

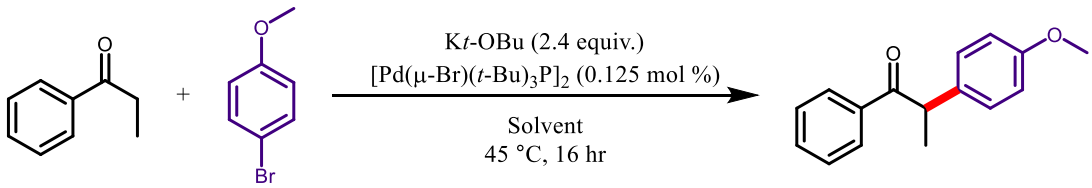



(1.2 equiv.)

| entry | Pd (mol %) | yield (%) Pd[dtbpf]$Cl_2$ | yield (%) [Pd(μ-Br)(*t*-Bu)$_3$P]$_2$ |
|---|---|---|---|
| 1 | 2 | 90 | 97 |
| 2 | 0.5 | 38 | 91 |
| **3** | **0.25** | trace | **97** |
| 4 | 0.125 | N/A | Incomplete |

**Conditions:** 0.5 mmol 4-bromoanisole, 0.6 mmol (1.2 equiv) propiophenone, [Pd] cat., 1.2 mmol (2.4 equiv) K-*t*-O-Bu, 2 wt % TPGS-750-M/$H_2O$ (0.5 mL, 1.0 M), 45 °C, 16 h.

### 3.7 Reaction Medium Screening

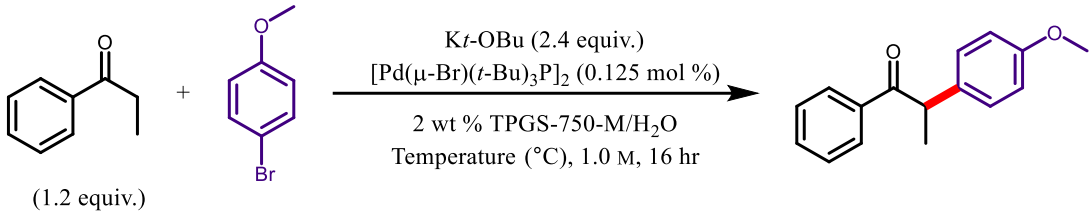



(1.2 equiv.)

| entry | medium | yield (%) |
|---|---|---|
| 1 | water | 76 |
| **2** | **2 wt % TPGS-750-M/$H_2O$** | **97** |
| 3 | 2 wt % Nok/$H_2O$ | 80 |
| 4 | 2 wt % Coolade/$H_2O$ | 89 |
| 5 | 2 wt % Triton X-100/$H_2O$ | 82 |
| 6 | 2 wt % Brij-35/$H_2O$ | 39 |
| 7 | 5 wt % PTS-1000/$H_2O$ | 74 |
| 8 | 2 wt % SDS/$H_2O$ | 45 |
| 9 | toluene (1.0 M) | 48 |
| 10 | toluene (0.2 M) | 60 |

**Conditions**: 0.5 mmol 4-bromoanisole, 0.6 mmol (1.2 equiv) propiophenone, 0.125 mol % [Pd(μ-Br)(*t*-Bu)$_3$P]$_2$, 1.2 mmol (2.4 equiv) K-*t*-OBu, solvent (0.5 mL, 1.0 M. unless otherwise noted), 45 °C, 16 h.

### 3.8 Reaction Temperature Screening

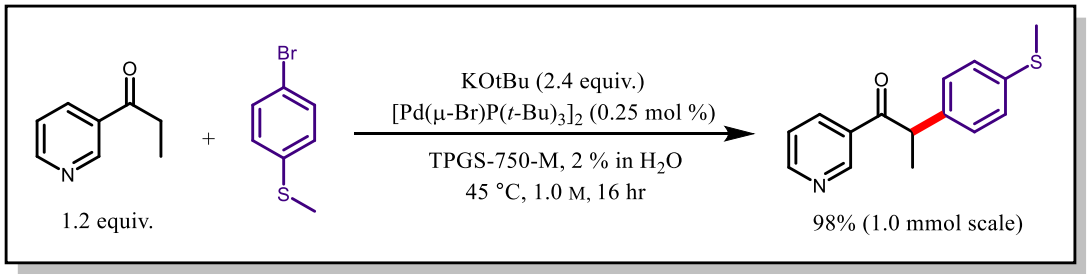



| entry | temperature (°C) | yield (%) |
|---|---|---|
| 1 | 30 | 38 |
| **2** | **45** | **97** |

**Conditions**: 0.5 mmol 4-bromoanisole, 0.6 mmol (1.2 equiv) propiophenone, 0.125 mol % [Pd(μ-Br)(*t*-Bu)$_3$P]$_2$, 1.2 mmol (2.4 equiv) K-O-*t*-Bu, solvent (0.5 mL, 1.0 M ), 16 h.

# 4. Results and Discussion

### 4.1 α-Arylation of ketones at 1.0 mmol Scale

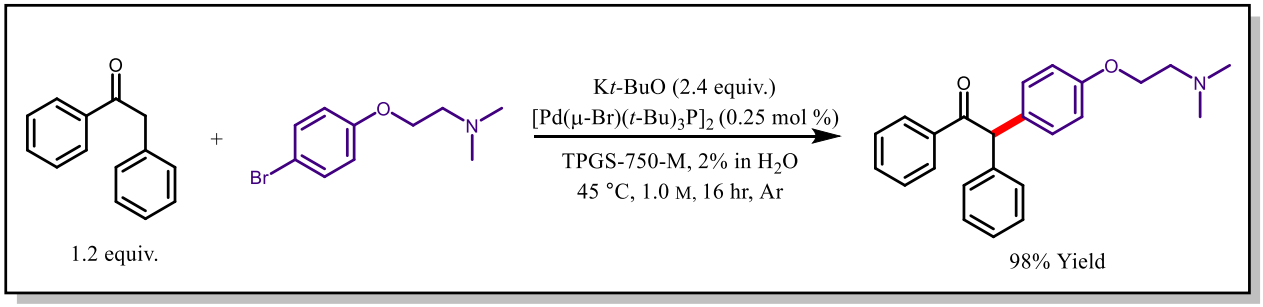



To a flame dried 1-dram vial equipped with an oven dried stir bar was added [Pd(μ-Br)(*t*-Bu)$_3$P]$_2$ (2 mg, 2.50 x $10^{-3}$ mmol, 0.25 mol %) and K-O-*t*-Bu (270 mg, 2.4 mmol, 2.4 equiv) inside of a glove box. The vial was then sealed using a rubber septum and removed from the glove box. 1-(Pyridin-3-yl)propan-1-one (162 mg, 1.2 mmol, 1.2 equiv) and 4-bromothioanisole (203 mg, 1.0 mmol, 1.0 equiv) were then added very quickly to the uncapped vial and the vial was resealed. The vial was then adapted to an argon/vacuum manifold and the headspace was evacuated and backfilled with argon three times. 2 wt % TPGS-750-M/H$_2$O (1.0 mL, 1.0 M) was then added through the septum and the contents of the vial were then allowed to stir vigorously (~1500 RPM) under constant argon pressure in a 1-dram vial aluminum block reactor at

45 °C internal temperature (aluminum block set to heat to 50 °C) for 16 h. After completion, the contents of the vial were then extracted with EtOAc (3 x 1.0 mL) and dried directly onto $SiO_2$ to be purified via flash chromatography (50% EtOAc/hexanes). The resulting product was then dried under high vacuum to afford a yellow-orange oil which solidifies slowly over time (252.7 mg, 98% yield).

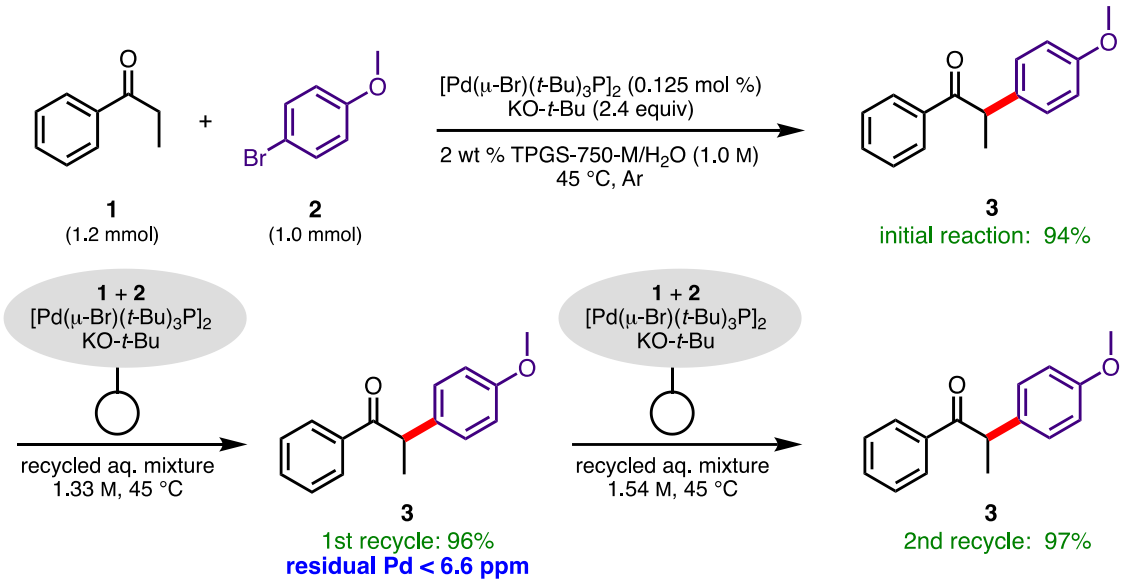
Note: additional 1 mmol scale reactions can be seen in **Sections 4.3 and 4.4.**

**4.2 Synthesis of a Tamoxifen intermediate**

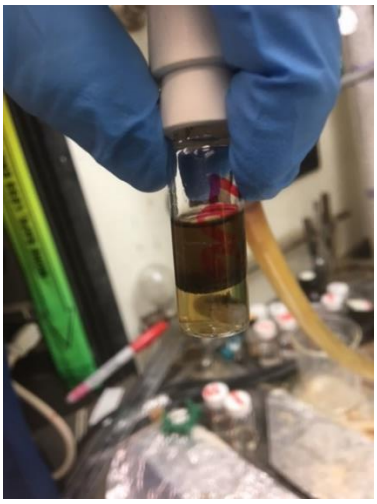



To a flame dried 1-dram vial equipped with an oven dried stir bar was added $[Pd(\mu\text{-}Br)(t\text{-}Bu)_3P]_2$ (1 mg, 1.25 X $10^{-3}$ mmol, 0.25 mol %), K-O-*t*-Bu (135 mg, 1.2 mmol, 2.4 equiv), and deoxybenzoin (118 mg, 0.6 mmol, 1.2 equiv). The vial was then sealed using a rubber septum inside of the glovebox and then transferred to a manifold under argon pressure. 2 wt % TPGS-750-M/$H_2O$ was then added (0.5 mL, 1.0 M) via syringe through the rubber septum followed by 2-(4-bromophenoxy)-*N,N*-dimethylethan-1-amine (122 mg, 0.5 mmol, 1.0 equiv) as a liquid through the septum. The contents of the vial were then allowed to stir vigorously (~1500 RPM) under constant argon pressure in a 1-dram vial aluminum block reactor at 45 °C internal temperature (aluminum block set to heat to 50 °C). The reaction was then monitored by thin-layer chromatography until deemed complete. The contents of the vial were then extracted using EtOAc (3 x 1 mL). The combined organics were then dried onto $SiO_2$ and purified via flash chromatography (MeOH/DCM/$Et_3N$ 10:90:1). The product was then dried under high vacuum to result in an amber oil (177.1 mg, 98% yield).

### 4.3 Aqueous recycling study




**Initial Reaction:** To a flame dried 1-dram vial equipped with an oven dried magnetic stir bar was added $[Pd(\mu\text{-}Br)(t\text{-}Bu)_3P]_2$ (1 mg, 1.25 x $10^{-3}$ mmol, 0.125 mol %) and K-O-*t*-Bu (270 mg, 2.4 mmol, 2.4 equiv) inside of an argon purged glove box. The vial was then sealed using a rubber septum, removed from the glove box, and connected via syringe needle to a manifold under argon pressure. 2 wt % TPGS-750-M/$H_2O$ (1.0 mL, 1.0 M) followed by 160 µL of **1** (160 mg, 1.2 mmol, 1.2 equiv) and 125 µL of **2** (187 mg, 1.0 mmol, 1.0 equiv) were then added to the vial via syringe through the septum, and the contents of the vial were then allowed to stir vigorously (~1500 RPM) under constant argon pressure in a 1-dram vial aluminum block reactor at 45 °C internal temperature (aluminum block set to heat to 50 °C). After 2 h, the contents of the vial were then extracted using methyl *t*-butyl ether (MTBE; 1.0 mL x 3) which had been thoroughly degassed with argon. **Note:** The extraction is performed while the vial is still maintained under strict air-free conditions. The extraction solvent is added through the septum to the reaction mixture under argon pressure, allowed to extract via stirring, and then removed under argon pressure using a syringe using a long needle.



*Initial reaction post extraction and settling with MTBE*

The combined organics were then dried directly onto $SiO_2$ and purified via flash chromatography (8% EtOAc/hexanes) and dried under vacuum to afford product as a white solid (226 mg, 94% yield). The remaining volume of aqueous phase was then determined to be 750 µL.

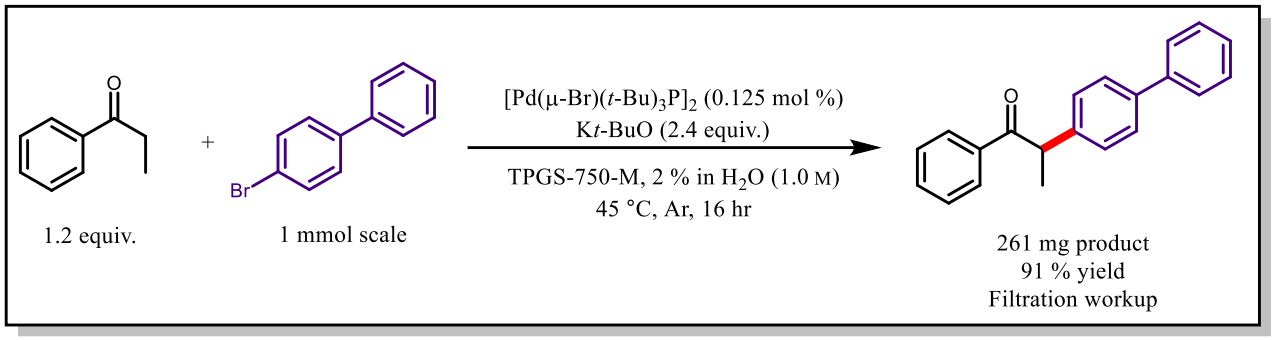
**First Recycle:** To a separate flamed dried 1-dram vial equipped with an oven dried stir bar was added $[Pd(\mu\text{-}Br)(t\text{-}Bu)_3P]_2$ (1 mg, 1.25 x $10^{-3}$ mmol, 0.125 mol %) and K-O-*t*-Bu (270 mg, 2.4 mmol, 2.4 equiv) inside of an argon purged glove box. The vial was then sealed using a rubber septum, removed from the glove box, and connected via syringe needle to a manifold under argon pressure. The remaining TPGS-750-M aqueous phase from the initial reaction was then added (0.75 mL, 1.33 M), followed by 160 µL of **1** (160 mg, 1.2 mmol, 1.2 equiv) and 125 µL of **2** (187 mg, 1.0 mmol, 1.0 equiv) via syringe through the septum, and the contents of the vial were then allowed to stir vigorously (~1500 RPM) under constant argon pressure in a 1-dram vial aluminum block reactor at 45 °C internal temperature (aluminum block set to heat to 50 °C). After 2 h, the contents of the vial were then extracted under argon using MTBE (1.0 mL x 3) which had been thoroughly degassed with argon as previously mentioned. The combined organics were then dried directly onto $SiO_2$ and purified via flash chromatography (8% EtOAc/hexanes) and dried

under vacuum to afford product as a white solid (230 mg, 96% yield). The remaining volume of aqueous phase was determined to be 650 µL.

**Second Recycle:** To a separate flamed dried 1-dram vial equipped with an oven dried stir bar was added $[Pd(\mu\text{-}Br)(t\text{-}Bu)_3P]_2$ (1 mg, 1.25 x $10^{-3}$ mmol, 0.125 mol %) and K-O-*t*-Bu (270 mg, 2.4 mmol, 2.4 equiv) inside of an argon purged glove box. The vial was then sealed using a rubber septum, removed from the glove box, and connected via syringe needle to a manifold under argon pressure. The remaining TPGS-750-M aqueous phase from the first recycle was then added (0.65 mL, 1.54 M), followed by 160 µL of **1** (160 mg, 1.2 mmol, 1.2 equiv) and 125 µL of **2** (187 mg, 1.0 mmol, 1.0 equiv) via syringe through the septum, and the contents of the vial were then allowed to stir vigorously (~1500 RPM) under constant argon pressure in a 1-dram vial aluminum block reactor at 45 °C internal temperature (aluminum block set to heat to 50 °C). After 16 h, the contents of the vial were then extracted using MTBE (1.0 mL x 3) which had been thoroughly degassed with argon as previously mentioned. The combined organics were then dried directly onto $SiO_2$ and purified via flash chromatography (8% EtOAc/hexanes) and dried under vacuum to afford product as a white solid (232.1 mg, 97% yield). After the second recycle, the aqueous phase had accumulated too much salt for a third viable recycle study to be performed without adding fresh water or surfactant.

*Aqueous phase post recycling two times*

**4.4 E Factor evaluation**




**E Factor for Filtered Product:** To a flame dried 1-dram vial equipped with an oven dried stir bar was added $[Pd(\mu\text{-}Br)(t\text{-}Bu)_3P]_2$ (1 mg, 1.25 x $10^{-3}$ mmol, 0.125 mol %), K-O-*t*-Bu (270 mg, 2.4 mmol, 2.4 equiv), and 4-bromo-1,1'-biphenyl (233 mg, 1.0 mmol, 1.0 equiv) inside of an argon purged glove box. The vial was then sealed using a rubber septum, removed from the glove box, and connected via syringe needle to a manifold under argon pressure. 2 wt % TPGS-750-M/$H_2O$ (1.0 mL, 1.0 M) and propiophenone (160 mg, 1.2 mmol, 1.2 equiv) were then added to the vial via syringe through the septum, and the contents of the vial were then allowed to stir vigorously (~1500 RPM) under constant argon pressure in a 1-dram vial aluminum block reactor at 45 °C internal temperature (aluminum block set to heat to 50 °C). After 16 h, a

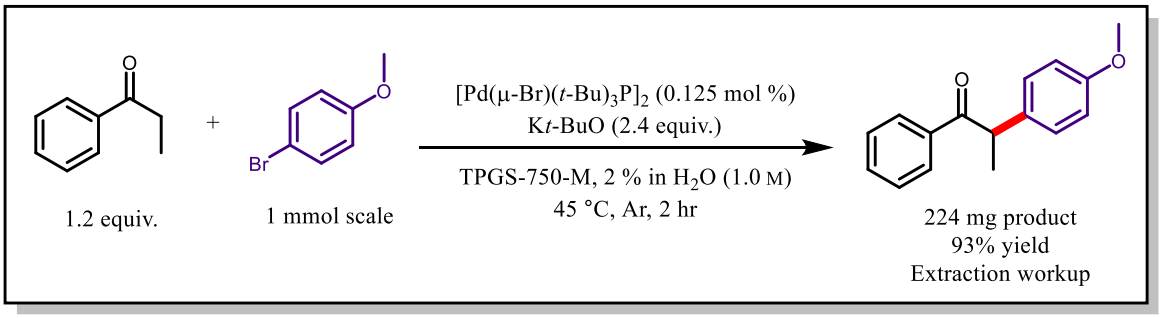
grey solid mass had formed and was suspended in 1.0 mL of deionized water. The solids were then filtered and washed with water (2 x 1.0 mL) and dried over vacuum suction to afford product as an off-white solid (261 mg, 91% yield).

The E Factor was determined by the mass of excess organics, in this case *t*-BuOH and propiophenone, over the mass of the desired product:

*E Factor = (mass waste organics) / (mass product)*

*= (mass$_{t\text{-}BuOH}$ + mass$_{propiophenone}$) / (mass$_{product}$)*

*= (179 mg + 27 mg) / 261 mg =* ***0.79***




**E Factor for extracted product:** To a flame dried 1-dram vial equipped with an oven dried stir bar was added [Pd(μ-Br)(*t*-Bu)$_3$P]$_2$ (1 mg, 1.25 x $10^{-3}$ mmol, 0.125 mol %) and K-O-*t*-Bu (270 mg, 2.4 mmol, 2.4 equiv) inside of an argon purged glove box. The vial was then sealed using a rubber septum, removed from the glove box, and connected via syringe needle to a manifold under argon pressure. 2 wt % TPGS-750-M/$H_2O$ (1.0 mL, 1.0 M) followed by 160 μL of propiophenone (160 mg, 1.2 mmol, 1.2 equiv) and 125 μL of 4-bromoanisole (187 mg, 1.0 mmol, 1.0 equiv) were then added to the vial via syringe through the septum, and the contents of the vial were then allowed to stir vigorously (~1500 RPM) under constant argon pressure in a 1-dram vial aluminum block reactor at 45 °C internal temperature (aluminum block set to heat to 50 °C) for 2 h. The contents of the vial were then carefully extracted with MTBE (3 x 270 μL),

and the combined organics were dried directly onto $SiO_2$ and purified via flash chromatography (8% EtOAc/hexanes) to afford the product as a white solid after drying on high vac (224 mg, 93% yield).

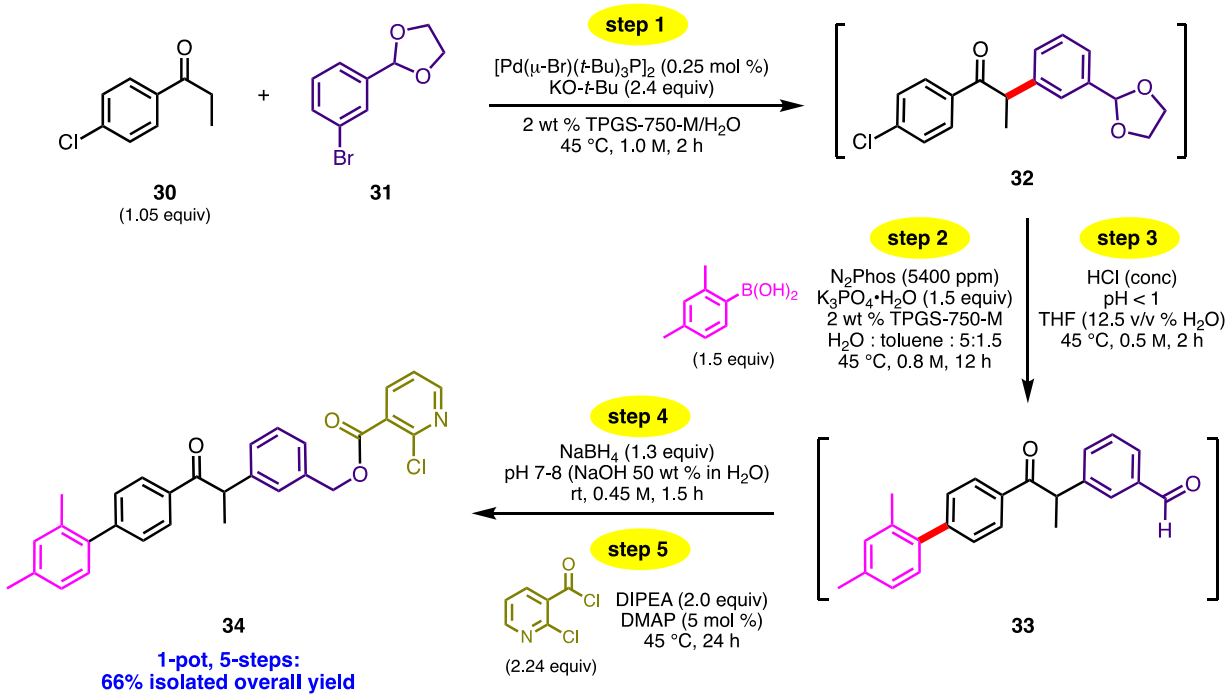
The E Factor was determined by the mass of excess organics, in this case *t*-BuOH, propiophenone, and MTBE used for the extraction (density of MTBE = 0.74 g/mL; therefore 270 µL = 200 mg).

*E Factor = (mass waste organics) / (mass product)*

$= (mass_{t\text{-}BuOH} + mass_{propiophenone} + mass_{MTBE}) / (mass_{product})$

*= (179 mg + 27 mg + 3*(200 mg)) / 224 mg =* ***3.6***

**4.5 Procedures for tandem sequences**




**Step 1:** To a flame dried 1-dram vial equipped with an oven dried stir bar was added $[Pd(\mu\text{-}Br)(t\text{-}Bu)_3P]_2$ (1 mg, 1.25 x $10^{-3}$ mmol, 0.25 mol %) and K-O*t*-Bu (135 mg, 1.2 mmol, 2.4 equiv) inside of an argon purged glove box and sealed with a rubber septum. Very quickly outside of the glove box, 4'-chloropropiophenone (90 mg, 0.525 mmol, 1.05 equiv) and 2-(3-bromophenyl)-1,3-dioxolane (114 mg, 0.5 mmol, 1 equiv) were

then added and the vial was resealed. The vial was then connected to a manifold and the headspace was evacuated and backfilled with argon three times. 2 wt % TPGS-750-M/$H_2O$ (0.5 mL, 1.0 M) was then added via syringe through the septum and the contents of the vial were then allowed to stir vigorously (~1500 RPM) under constant argon pressure in a 1-dram vial aluminum block reactor at 45 °C internal temperature (aluminum block set to heat to 50 °C) for 2 h where the reaction was deemed complete by TLC. In one iteration of this multistep study, this reaction was worked up via extraction using EtOAc (3 x 1.0 mL). The combined organics were then dried onto $SiO_2$ and purified by flash chromatography (20% EtOAc/hexanes) to afford product as a clear oil (128.1 mg, 81% yield).

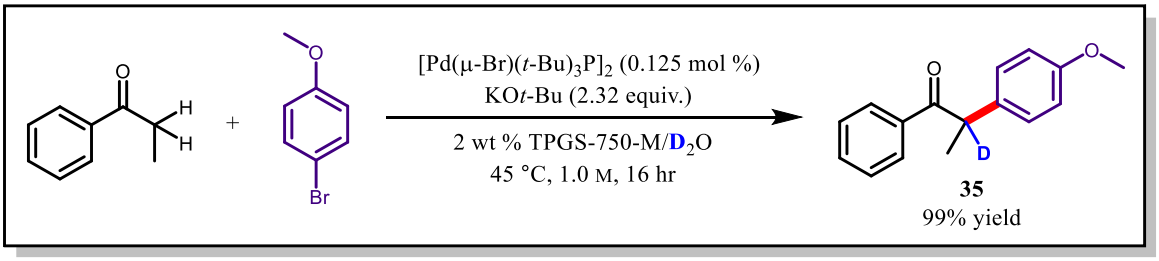
**Steps 2-3:** In the situation where the reaction from Step 1 continues through the 1-pot series, to the unsealed reaction vial was added (2,4-dimethylphenyl)boronic acid (113 mg, 0.75 mmol, 1.5 equiv) and $K_3PO_4 \cdot H_2O$ (173 mg, 0.75 mmol, 1.5 equiv). The vial was then sealed with a new rubber septum and the headspace was purged using argon and a vent needle for 5 min. Following this, a sample of $N_2$Phos/toluene stock solution* (150 µL) was added to the vial through the septum and the reaction was allowed to stir vigorously (~1500 RPM) under constant argon pressure in a 1-dram vial aluminum block reactor at 45 °C internal temperature (aluminum block set to heat to 50 °C) for 12 h until deemed complete by TLC. The pH of this mixture was then adjusted to pH <1 using conc. HCl (300 µL) and THF (100 µL) was added to help disperse the solids. The hydrolysis reaction was allowed to stir at 45 °C internal temperature for 3 h until deemed complete by TLC. In one iteration of this multistep study, this reaction series (Steps 1-3) was worked up via extraction using EtOAc (3 x 1.0 mL). The combined organics were dried onto $SiO_2$ and purified by flash chromatography (15% EtOAc/hexanes) to afford product as an opaque white oil (137.7 mg, 80% yield).

*$N_2$Phos stock solution was prepared by dissolving 7.5 mg of $N_2$Phos into rigorously degassed toluene (0.5 mL).

**Steps 4-5**: In the situation where the reaction from Step 3 continues through the 1-pot series, the pH of the reaction was adjusted to pH 7-8 using 50 wt % NaOH aqueous solution (100 µL followed by dropwise

addition to desired pH). To the resulting stirring mixture at rt was added $NaBH_4$ (10 mg, 0.26 mmol) and the vial was sealed and allowed to react with noticeable bubbling for 30 min. A second portion of $NaBH_4$ (15 mg, 0.40 mmol) was then added and the reaction was allowed to continue to stir to rt for 1 h until deemed complete by TLC. 2-Chloronicotinoyl chloride (100 mg, 0.56 mmol, 1.12 equiv), DIPEA (175 µL, 2.0 equiv), and DMAP (3 mg, 0.025 mmol, 5 mol %) were added and allowed to stir vigorously for 12 h at 45 °C internal temperature. A second portion of the acid chloride was then added (50 mg, 0.28 mmol, 0.56 equiv) and allowed to react further for 6 h, followed by a third portion (50 mg, 0.28 mmol, 0.56 equiv) for another 6 h until the benzyl alcohol was consumed by TLC. The 5-step, 1-pot reaction was then extracted using EtOAc (3 x 1.0 mL). The combined organics were then dried onto $SiO_2$ and purified by flash chromatography (25% EtOAc/hexanes). The organics were then isolated via solvent evaporation and dried under high vac to result in product as a clear oil (161.6 mg, 66% yield).

**4.6 Synthesis of deuterated analogue 35**



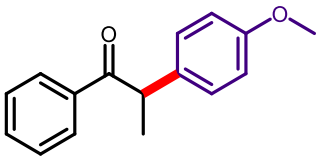

A solution of 2 wt % TPGS-750-M in $D_2O$ was prepared first by degassing 14.7 mL of $D_2O$ (Cambridge Isotope) with argon in a flamed dried 25 mL flask for 1 h followed by addition of 300 mg of fresh TPGS-750-M wax. This mixture was allowed to stir vigorously overnight under argon pressure resulting in a homogeneous mixture. The solution was kept under an argon atmosphere at all times.

To a flame dried 1-dram vial equipped with an oven dried stir bar was added $[Pd(\mu\text{-}Br)(t\text{-}Bu)_3P]_2$ (1 mg, $1.25 \times 10^{-3}$ mmol, 0.125 mol %) and K-O-*t*-Bu (270 mg, 2.4 mmol, 2.32 equiv) inside of a glove box. The vial was then sealed using a rubber septum and transferred to an argon-purged manifold and kept under

constant argon pressure. 2 wt % TPGS-750-M/$D_2O$ (1.0 mL, 1.0 M) was then added followed by propiophenone (160 µL, 160 mg, 1.2 mmol, 1.16 equiv) and 4-bromoanisole (130 µL, 194 mg, 1.035 mmol, 1.0 equiv) via syringe through the septum. The resulting mixture was then allowed to stir vigorously (~1500 RPM) under constant argon pressure in a 1-dram vial aluminum block reactor at 45 °C internal temperature (aluminum block set to heat to 50 °C) for 16 h until deemed complete by TLC. The product mixture was then extracted with EtOAc (3 x 1.0 mL), dried onto $SiO_2$, and purified via flash chromatography (8% EtOAc/hexanes). The combined organics were then dried to constant mass on high vacuum resulting in deuterated product **35** as an off-white solid (248.1 mg, 99% yield).

# 5. Analytical Data

**Synthesis of 2-(4-methoxyphenyl)-1-phenylpropan-1-one (3)**



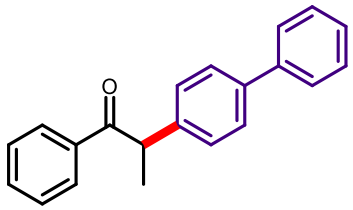

Compound **3** was obtained using the General Procedure A on a 0.5 mmol scale. The crude product was purified by silica gel column chromatography (eluent: 7% EtOAc/93% hexanes) to provide the desired compound as a clear oil that slowly solidifies to a white solid over time (115.9 mg, 97% yield). $R_f$ = 0.38 (1:9 EtOAc/hexanes).

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.95 (d, *J* = 7.3 Hz, 2H), 7.47 (t, *J* = 7.3 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.20 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 4.64 (q, *J* = 6.8 Hz, 1H), 3.75 (s, 3H), 1.51 (d, *J* = 6.8 Hz, 3H).

**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 200.5, 158.4, 136.5, 133.4, 132.7, 128.8, 128.7, 128.4, 114.3, 55.2, 46.9, 19.5.

Spectral data matched those previously reported.[2]

## Synthesis of 2-([1,1'-biphenyl]-4-yl)-1-phenylpropan-1-one (4)



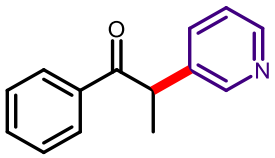
Compound **4** was obtained using the General Procedure A on a 0.5 mmol scale. The crude product was purified by silica gel chromatography (eluent: 5% EtOAc/95% hexanes) to provide the desired compound as a white solid (143.1 mg, 99% yield). $R_f$ = 0.35 (0.5:9.5 EtOAc/hexanes).

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 8.04 – 7.95 (m, 2H), 7.60 – 7.45 (m, 5H), 7.45 – 7.28 (m, 7H), 4.75 (q, *J* = 6.9 Hz, 1H), 1.58 (d, *J* = 6.9 Hz, 3H).

**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 200.3, 140.6, 140.4, 139.8, 136.4, 132.8, 128.8, 128.7, 128.5, 128.2, 127.7, 127.2, 127.0, 47.4, 19.5.

Spectral data matched those previously reported.[3]

## Synthesis of 1-phenyl-2-(pyridin-3-yl)propan-1-one (5)



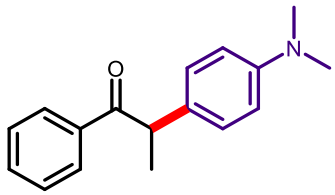
Compound **5** was obtained using the General Procedure C on a 0.5 mmol scale. The crude product was purified by silica gel chromatography (eluent: 0% to 50% EtOAc gradient/hexanes) to provide the desired compound as a white solid (102.1 mg, 97% yield). $R_f$ = 0.32 (1:1 EtOAc/hexanes).

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 8.59 (s, 1H), 8.44 (d, *J* = 4.0 Hz, 1H), 7.93 (d, *J* = 7.8 Hz, 2H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.49 (t, *J* = 7.2 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.22 – 7.15 (m, 1H), 4.73 (q, *J* = 6.8 Hz, 1H), 1.54 (d, *J* = 6.9 Hz, 3H).

**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 199.5, 149.5, 148.4, 136.9, 135.9, 135.0, 133.2, 128.7, 128.6, 123.8, 44.9, 19.4.

Spectral data matched those previously reported.[4]

## Synthesis of 2-(4-(dimethylamino)phenyl)-1-phenylpropan-1-one (6)



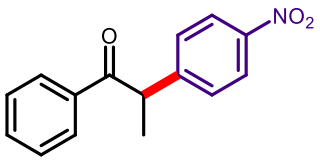

Compound **6** was obtained using the General Procedure A on a 0.5 mmol scale. The crude product was purified by silica gel chromatography (eluent: 0% to 8% EtOAc gradient/hexanes) to provide the desired compound as a yellow solid (119.2 mg, 94% yield). $R_f$ = 0.52 (1:4 EtOAc/hexanes).

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.99 (d, *J* = 7.9 Hz, 2H), 7.47 (t, *J* = 7.3 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.18 (d, *J* = 8.7 Hz, 2H), 6.68 (d, *J* = 8.7 Hz, 2H), 4.63 (q, *J* = 6.8 Hz, 1H), 2.91 (s, 6H), 1.53 (d, *J* = 6.8 Hz, 3H).

**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 200.7, 149.4, 136.7, 132.5, 129.0, 128.8, 128.4, 128.4, 113.0, 46.9, 40.5, 19.5.

Spectral data matched those previously reported.[5]

## Synthesis of 2-(4-nitrophenyl)-1-phenylpropan-1-one (7)



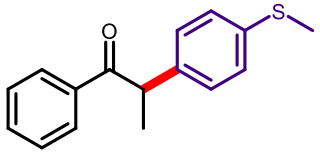

Compound **7** was obtained using the General Procedure B (aryl bromide) or General Procedure C (aryl chloride) on a 0.5 mmol scale. The crude product was purified by silica gel chromatography (eluent: 0% to 10% EtOAc gradient/hexanes) to provide the product as an orange oil (bromide: 68.9 mg, 54% yield; chloride: 76.7 mg, 60% yield). $R_f$ = 0.47 (1:4 EtOAc/hexanes).

**$^1$H NMR (600 MHz, $CDCl_3$):** δ 8.15 (d, *J* = 8.7 Hz, 2H), 7.93 (d, *J* = 7.4 Hz, 2H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.47 (d, *J* = 8.7 Hz, 2H), 7.42 (t, *J* = 7.8 Hz, 2H), 4.83 (q, *J* = 6.9 Hz, 1H), 1.58 (d, *J* = 6.9 Hz, 3H).

**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 199.2, 148.8, 147.0, 136.0, 133.5, 128.9, 128.8, 124.3, 47.5, 19.5.

**HRMS (ESI):** *m/z* calcd for $C_{15}H_{12}NO_3$-$H^+$: 254.0817 [*M*-H]$^-$; found: 254.0808.

## Synthesis of 2-(4-(methylthio)phenyl)-1-phenylpropan-1-one (8)



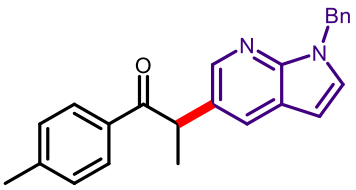

Compound **8** was obtained using the General Procedure B on a 0.5 mmol scale. The crude product was purified by silica gel chromatography (eluent: 5% EtOAc/95% hexanes) to provide the product as a yellow crystalline solid (116.6 mg, 91% yield). $R_f$ = 0.39 (1:9 EtOAc/hexanes).

**$^1$H NMR (500 MHz, $CDCl_3$):** δ 7.97 – 7.92 (m, 2H), 7.51 – 7.45 (m, 1H), 7.41 – 7.35 (m, 2H), 7.23 – 7.16 (m, 4H), 4.65 (q, *J* = 6.9 Hz, 1H), 2.43 (s, 3H), 1.52 (d, *J* = 6.9 Hz, 3H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)**: δ 200.2, 138.3, 137.0, 136.4, 132.8, 128.8, 128.5, 128.3, 127.2, 47.3, 19.4, 15.8.

Spectral data matched those previously reported.[6]

### Synthesis of 2-(1-benzyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1-(p-tolyl)propan-1-one (9)



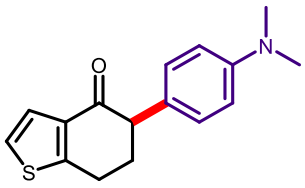

Compound **9** was obtained using the General Procedure B on a 0.5 mmol scale. The crude product was purified by silica gel chromatography (eluent: 10% EtOAc/90% hexanes) to provide the product as an off-white solid (152.4 mg, 86%). $R_f$ = 0.23 (1:9 EtOAc/hexanes).

**$^1$H NMR (500 MHz, $CDCl_3$):** δ 8.37 (d, *J* = 2.2 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 2H), 7.84 (d, *J* = 2.2 Hz, 1H), 7.31 – 7.22 (m, 3H), 7.21 – 7.16 (m, 4H), 7.13 (d, *J* = 3.6 Hz, 1H), 6.40 (d, *J* = 3.5 Hz, 1H), 5.50 – 5.39 (m, 2H), 4.84 (q, *J* = 6.8 Hz, 1H), 2.33 (s, 3H), 1.61 (d, *J* = 6.9 Hz, 3H).

**$^{13}$C NMR (126 MHz, $CDCl_3$):** δ 199.8, 146.9, 143.5, 143.1, 137.5, 133.7, 129.1, 128.8, 128.6, 128.4, 127.5, 127.4, 127.4, 120.5, 99.9, 47.7, 44.8, 21.4, 19.9.

**HRMS (ESI):** *m/z* calcd for $C_{24}H_{22}N_2O+H^+$: 355.1810 $[M+H]^+$; found 355.1806.

### Synthesis of 5-(4-(dimethylamino)phenyl)-6,7-dihydrobenzo[b]thiophen-4(5H)-one (10)



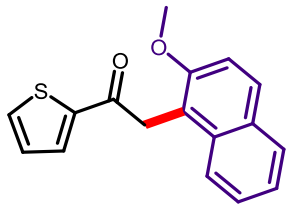
Compound **10** was obtained using the General Procedure B on a 0.5 mmol scale. The crude product was purified by silica gel chromatography (eluent: 8% EtOAc/92% hexanes) to provide the product as a grey solid (99.1 mg, 73% yield). $R_f$ = 0.80 (1:9 EtOAc/hexanes).

**$^1$H NMR (500 MHz, $CDCl_3$):** δ 7.46 (d, *J* = 5.3 Hz, 1H), 7.10 – 7.04 (m, 3H), 6.75 – 6.70 (m, 2H), 3.69 (t, *J* = 7.2 Hz, 1H), 3.11 (q, *J* = 6.1 Hz, 2H), 2.94 (s, 6H), 2.46 (td, *J* = 6.8, 5.3 Hz, 2H).

**$^{13}$C NMR (126 MHz, $CDCl_3$):** δ 193.7, 155.2, 149.7, 137.6, 129.0, 126.9, 125.4, 123.3, 112.9, 52.2, 40.7, 32.7, 24.5.

**HRMS (ESI):** *m/z* calcd for $C_{16}H_{17}NOS+H^+$: 272.1109 $[M+H]^+$; found 272.1111.

## Synthesis of 2-(2-methoxynaphthalen-1-yl)-1-(thiophen-2-yl)ethan-1-one (11)



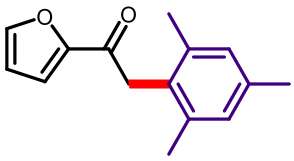

Compound **11** was obtained using the General Procedure B on a 0.5 mmol scale, in this case increasing the aryl ketone to 0.85 mmol (1.7 equiv). The crude product was purified by silica gel chromatography (eluent: 0% to 10% EtOAc gradient/hexanes) to provide the product as a white solid (125.2 mg, 89%). $R_f$ = 0.44 (1:4 EtOAc/hexanes).

**$^1$H NMR (500 MHz, $CDCl_3$):** δ 7.94 (d, *J* = 3.7 Hz, 1H), 7.90 (d, *J* = 8.6 Hz, 1H), 7.87 – 7.79 (m, 2H), 7.61 (d, *J* = 4.9 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.31 (d, *J* = 9.0 Hz, 1H), 7.13 (t, *J* = 4.4 Hz, 1H), 4.73 (s, 2H), 3.94 (s, 3H).

**$^{13}$C NMR (126 MHz, $CDCl_3$):** δ 190.9, 154.8, 144.1, 133.6, 133.5, 132.1, 129.3, 129.2, 128.5, 128.0, 126.9, 123.5, 123.3, 116.4, 113.2, 56.6, 36.7.

**HRMS (ESI):** *m/z* calcd for $C_{17}H_{14}O_2S+Na^+$: 305.0612 [*M*+Na]$^+$; found 305.0618.

### Synthesis of 1-(furan-2-yl)-2-mesitylethan-1-one (12)



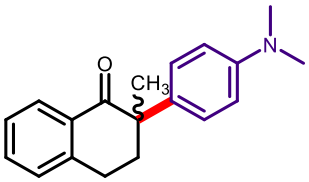
Compound **12** was obtained using the General Procedure B on a 0.5 mmol scale, in this case increasing the aryl ketone to 0.85 mmol (1.7 equiv.). The crude product was purified by silica gel chromatography (eluent: 0% to 10% EtOAc gradient/hexanes) to provide the product as a white solid (83.1 mg, 73% yield). $R_f$ = 0.41 (1:4 EtOAc/hexanes).

**$^1$H NMR (500 MHz, $CDCl_3$):** δ 7.62 (s, 1H), 7.20 (d, *J* = 2.9 Hz, 1H), 6.90 (s, 2H), 6.59 – 6.53 (m, 1H), 4.22 (s, 2H), 2.29 (s, 3H), 2.24 (s, 6H).

**$^{13}$C NMR (126 MHz, $CDCl_3$):** δ 186.5, 152.7, 146.1, 137.0, 136.4, 128.8, 128.5, 116.8, 112.2, 39.2, 20.9, 20.3

**HRMS (ESI):** *m/z* calcd for $C_{15}H_{16}O_2+Na^+$: 251.1048 [*M*+Na]$^+$; found: 251.1057.

### Synthesis of 2-(4-(dimethylamino)phenyl)-2-methyl-3,4-dihydronaphthalen-1(2H)-one (13)



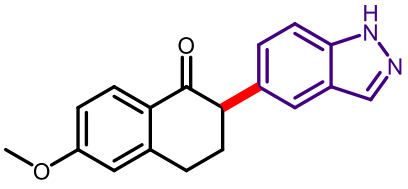
Compound **13** was obtained using the General Procedure B on a 0.5 mmol scale. The crude product was purified by silica gel chromatography (eluent: 0% to 10% EtOAc gradient/hexanes) to provide the product as a white powder (125.0 mg, 90%). $R_f$ = 0.63 (1:4 EtOAc/hexanes).

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 8.16 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.40 (td, *J* = 7.4, 1.6 Hz, 1H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.16 – 7.05 (m, 3H), 6.70 – 6.61 (m, 2H), 2.89 (s, 7H), 2.79 (dt, *J* = 17.0, 4.1 Hz, 1H), 2.59 (dt, *J* = 13.9, 4.0 Hz, 1H), 2.24 (ddd, *J* = 14.1, 11.9, 4.6 Hz, 1H), 1.50 (s, 3H).

**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 201.6, 149.2, 143.7, 132.8, 132.8, 129.2, 128.6, 127.9, 127.0, 126.4, 112.6, 49.5, 40.5, 36.0, 27.4, 26.2.

**HRMS (ESI):** *m/z* calcd for $C_{19}H_{21}NO+Na^+$: 302.1521 $[M+Na]^+$; found: 302.1525.

### Synthesis of 2-(1H-indazol-5-yl)-6-methoxy-3,4-dihydronaphthalen-1(2H)-one (14)



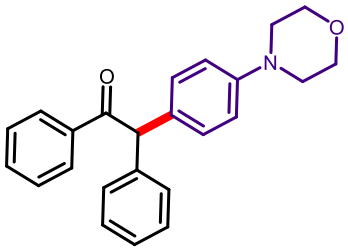

Compound **14** was obtained using the General Procedure B on a 0.5 mmol scale using the THP protected bromide. After completing the coupling reaction by TLC, the aqueous phase was acidified using conc. HCl to pH< 1 and allowed to stir at 45 °C until complete deprotection to form product **14**. The aqueous phase was neutralized using satd. $NaHCO_3$ and extracted with EtOAc (3 x 1 mL). The crude product was purified by silica gel chromatography (eluent: 60% EtOAc/30% hexanes) to provide the product as a white solid (95.0 mg, 65% yield over two steps). $R_f$ = 0.33 (3:2 EtOAc/hexanes).

**$^1$H NMR (500 MHz, DMSO):** δ 12.98 (s, 1H), 8.00 (s, 1H), 7.89 (d, *J* = 8.3 Hz, 1H), 7.52 (s, 1H), 7.48 (d, *J* = 8.7 Hz, 1H), 7.17 (d, *J* = 8.7 Hz, 1H), 6.99 – 6.87 (m, 2H), 3.96 (dd, *J* = 11.5, 4.6 Hz, 1H), 3.85 (s, 3H), 3.11 (td, *J* = 11.4, 5.5 Hz, 1H), 2.96 (dt, *J* = 17.1, 4.8 Hz, 1H), 2.39 (tt, *J* = 10.9, 5.7 Hz, 1H), 2.29 (dq, *J* = 9.0, 4.5 Hz, 1H).

**$^{13}$C NMR (126 MHz, DMSO):** δ 196.7, 163.2, 146.9, 138.9, 133.2, 132.5, 129.2, 127.3, 126.0, 122.9, 119.5, 113.5, 112.6, 109.7, 55.5, 53.2, 31.2, 28.6.

**HRMS (ESI):** *m/z* calcd for $C_{18}H_{16}N_2O_2$+$Na^+$: 315.1110 [*M*+Na]$^+$; found 315.1111.

### Synthesis of 2-(4-morpholinophenyl)-1,2-diphenylethan-1-one (15)



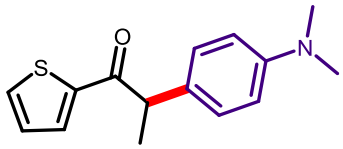

Compound **15** was obtained using the General Procedure B on a 0.5 mmol scale. The crude product was purified by silica gel chromatography (eluent: 30% EtOAc/70% hexanes) to provide the product as a white powder (178.0 mg, 99% yield). $R_f$ = 0.33 (3:7 EtOAc/hexanes).

**$^1$H NMR (500 MHz, $CDCl_3$):** δ 8.03 (d, *J* = 7.7 Hz, 2H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.41 (t, *J* = 7.7 Hz, 2H), 7.36 – 7.30 (m, 2H), 7.30 – 7.25 (m, 3H), 7.21 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.99 (s, 1H), 3.91 – 3.78 (m, 4H), 3.19 – 3.09 (m, 4H).

**$^{13}$C NMR (126 MHz, $CDCl_3$):** δ 198.4, 150.1, 139.5, 136.9, 132.8, 130.1, 129.8, 129.0, 128.9, 128.5, 128.5, 126.9, 115.7, 66.8, 58.5, 49.0.

**HRMS (ESI):** *m/z* calcd for $C_{24}H_{23}NO_2$+$Na^+$: 380.1627 [*M*+Na]$^+$; found: 380.1630.

### Synthesis of 2-(4-(dimethylamino)phenyl)-1-(thiophen-2-yl)propan-1-one (16)



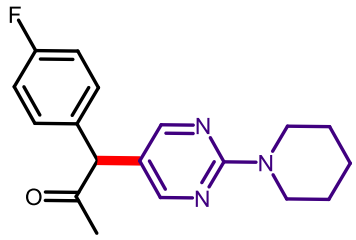

Compound **16** was obtained using the General Procedure B on a 0.5 mmol scale. The crude product was purified by silica gel chromatography (eluent: 0% to 10% EtOAc gradient/hexanes) to provide the product as a yellow solid (129.9 mg, 99% yield). $R_f$ = 0.45 (1:4 EtOAc/hexanes).

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.70 (d, *J* = 4.1 Hz, 1H), 7.52 (d, *J* = 4.9 Hz, 1H), 7.21 (d, *J* = 8.8 Hz, 2H), 7.03 (t, *J* = 4.3 Hz, 1H), 6.69 (d, *J* = 8.8 Hz, 2H), 4.43 (q, *J* = 6.8 Hz, 1H), 2.91 (s, 6H), 1.52 (d, *J* = 6.8 Hz, 3H).

**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 193.8, 149.6, 143.9, 133.2, 132.3, 128.9, 128.4, 128.0, 112.9, 48.4, 40.5, 19.1

**HRMS (ESI):** *m/z* calcd for $C_{15}H_{17}NOS+Na^+$: 282.0929 $[M+Na]^+$; found: 282.0933.

## Synthesis of 1-(4-fluorophenyl)-1-(2-(piperidin-1-yl)pyrimidin-5-yl)propan-2-one (17)



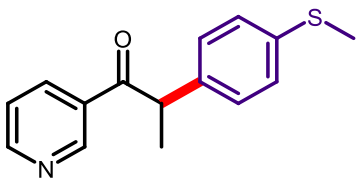

Compound **17** was obtained using the General Procedure B, modified to run at an internal temperature of 70 °C, and, as a separate trial, General Procedure C, both on a 0.5 mmol scale. The crude product was purified by silica gel chromatography (eluent: 25% EtOAc/75% hexanes) to provide the product as a yellow oil (Procedure B: 83.0 mg, 53% yield; Procedure C: 105.1 mg, 67% yield). $R_f$ = 0.28 (1:3 EtOAc/hexanes).

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 8.12 (s, 2H), 7.23 – 7.13 (m, 2H), 7.09 – 6.97 (m, 2H), 4.82 (s, 1H), 3.78 – 3.66 (m, 4H), 2.22 (s, 3H), 1.68 – 1.52 (m, 6H).

**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 205.4, 162.1 (d, *J* = 246.9 Hz), 160.8, 157.7, 133.3 (d, *J* = 3.4 Hz), 130.1 (d, *J* = 8.1 Hz), 118.5, 115.9 (d, *J* = 21.6 Hz), 58.8, 44.7, 29.5, 25.6, 24.7.

**HRMS (ESI):** *m/z* calcd for $C_{18}H_{20}FN_3O+H^+$: 314.1669 $[M+H]^+$; found: 314.1674.

**Synthesis of 2-(4-(methylthio)phenyl)-1-(pyridin-3-yl)propan-1-one (18)**



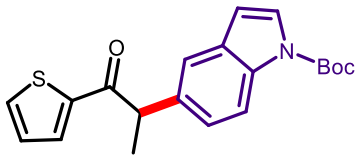

Compound **18** was obtained using the General Procedure B on a 0.5 mmol scale. The crude product was purified by silica gel chromatography (eluent: 35% EtOAc/65% hexanes) to provide the product as a yellow solid (125.6, 98% yield). $R_f$ = 0.36 (2:3 EtOAc/hexanes).

**$^1$H NMR (500 MHz, $CDCl_3$):** δ 9.12 (d, *J* = 2.6 Hz, 1H), 8.65 (dd, *J* = 4.9, 1.8 Hz, 1H), 8.16 (dt, *J* = 7.9, 1.9 Hz, 1H), 7.31 (ddd, *J* = 8.0, 4.8, 0.8 Hz, 1H), 7.16 (s, 4H), 4.57 (q, *J* = 6.9 Hz, 1H), 2.41 (s, 3H), 1.51 (d, *J* = 6.7 Hz, 3H).

**$^{13}$C NMR (126 MHz, $CDCl_3$):** δ 198.9, 153.1, 150.1, 137.6, 137.2, 136.1, 131.6, 128.2, 127.3, 123.6, 48.0, 19.0, 15.7.

**HRMS (ESI):** *m/z* calcd for $C_{15}H_{15}NOS+H^+$: 258.0953 $[M+H]^+$; found: 258.0955.

**Synthesis of *t*-butyl 5-(1-oxo-1-(thiophen-2-yl)propan-2-yl)-1H-indole-1-carboxylate (19)**



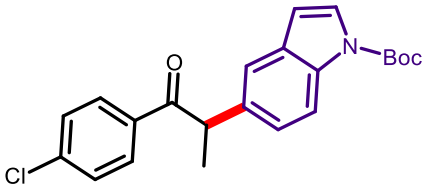

Compound **19** was obtained using the General Procedure C on a 0.5 mmol scale. The crude product was purified by silica gel chromatography (eluent: 10% EtOAc/90% hexanes) to provide the product as a yellow oil (152.1 mg, 87% yield). $R_f$ = 0.33 (1:9 EtOAc/hexanes).

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 8.07 (d, *J* = 8.7 Hz, 1H), 7.68 (dd, *J* = 3.8, 1.2 Hz, 1H), 7.57 (d, *J* = 3.8 Hz, 1H), 7.54 – 7.47 (m, 2H), 7.28 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.00 (dd, *J* = 5.0, 3.8 Hz, 1H), 6.52 (d, *J* = 3.7 Hz, 1H), 4.60 (q, *J* = 6.9 Hz, 1H), 1.65 (s, 9H), 1.58 (d, *J* = 6.8 Hz, 3H).

**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 193.5, 149.7, 143.7, 135.8, 133.4, 132.5, 131.1, 128.0, 126.4, 124.1, 119.9, 115.6, 107.2, 83.7, 49.3, 28.1, 19.5

**HRMS (ESI):** *m/z* calcd for $C_{20}H_{21}NO_3S+Na^+$: 378.1140 [*M*+Na]$^+$; found: 378.1131.

### Synthesis of *t*-butyl 5-(1-(4-chlorophenyl)-1-oxopropan-2-yl)-1H-indole-1-carboxylate (20)



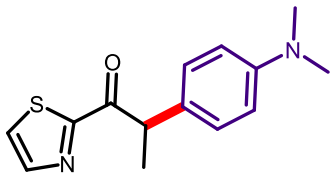

Compound **20** was obtained using the General Procedure C on a 0.5 mmol scale. The crude product was purified by silica gel chromatography (eluent: 5% EtOAc/95% hexanes) to provide the product as a white oil (116.3 mg, 61% yield). $R_f$ = 0.30 (0.5:9.5 EtOAc/hexanes).

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 8.07 (d, *J* = 8.6 Hz, 1H), 7.89 (d, *J* = 8.6 Hz, 2H), 7.57 (d, *J* = 3.9 Hz, 1H), 7.42 (d, *J* = 2.0 Hz, 1H), 7.31 (d, *J* = 8.6 Hz, 2H), 7.21 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.50 (d, *J* = 3.7 Hz, 1H), 4.69 (q, *J* = 6.8 Hz, 1H), 1.64 (s, 9H), 1.56 (d, *J* = 6.8 Hz, 3H).

**$^{13}$C NMR (101 MHz, $CDCl_3$)**: δ 199.2, 149.6, 139.0, 135.6, 134.8, 131.2, 130.2, 128.7, 126.5, 123.9, 120.0, 115.8, 107.1, 83.8, 48.0, 28.1, 19.7.

**HRMS (ESI):** *m/z* calcd for $C_{22}H_{22}ClNO_3+Na^+$+$CH_3OH$: 438.1448 [*M*+Na+$CH_3OH$]$^+$; found 438.1451.

**Synthesis of 2-(4-(dimethylamino)phenyl)-1-(thiazol-2-yl)propan-1-one (21)**



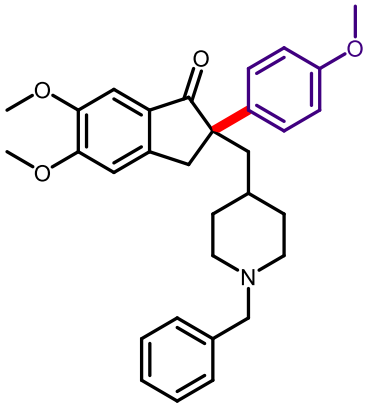
Compound **21** was obtained using the General Procedure C on a 0.5 mmol scale. The crude product was purified by silica gel chromatography (eluent: 7% EtoAC/93% hexanes) to provide the product as a yellow solid (37.9 mg, 29% yield. $R_f$ = 0.20 (1:9 EtOAc/hexanes).

**$^1$H NMR (500 MHz, $CDCl_3$)**: δ 7.97 (d, *J* = 3.0 Hz, 1H), 7.58 (d, *J* = 3.0 Hz, 1H), 7.28 (d, *J* = 8.8 Hz, 2H), 6.67 (d, *J* = 8.8 Hz, 2H), 5.05 (q, *J* = 7.1 Hz, 1H), 2.90 (s, 6H), 1.55 (d, *J* = 7.1 Hz, 3H).

**$^{13}$C NMR (126 MHz, $CDC_3$):** δ 194.0, 167.1, 149.7, 144.6, 129.1, 127.4, 126.1, 112.8, 46.0, 40.5, 18.0.

**HRMS (ESI):** *m/z* calcd for $C_{14}H_{16}N_2OS+Na^+$: 283.0881 [*M*+Na]$^+$; found 283.0887.

**Synthesis of 2-((1-benzylpiperidin-4-yl)methyl)-5,6-dimethoxy-2-(4-methoxyphenyl)-2,3-dihydro-1H-inden-1-one (22)**



Compound **22** was obtained using General Procedure C on a 0.5 mmol scale, in this case using 0.5 mmol of the aryl ketone and 0.6 mmol of the aryl bromide. The crude product was purified by silica gel

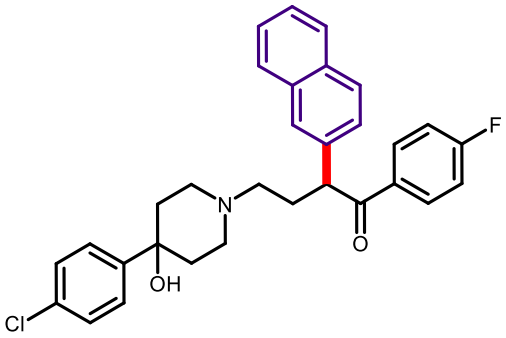
chromatography (eluent: 5% MeOH/95% DCM) to provide the product as a white solid (151.2 mg, 62% yield). $R_f$ = 0.28 (0.5:9.5 MeOH/DCM).

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.36 – 7.20 (m, 7H), 7.15 (s, 1H), 6.89 (s, 1H), 6.84 – 6.76 (m, 2H), 3.98 (s, 3H), 3.89 (s, 3H), 3.75 (s, 3H), 3.59 – 3.45 (m, 3H), 3.28 (d, *J* = 17.1 Hz, 1H), 2.89 – 2.74 (m, 2H), 2.20 (d, *J* = 12.1 Hz, 1H), 2.00 – 1.81 (m, 3H), 1.54 – 1.34 (m, 5H).

**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 206.3, 158.1, 155.6, 149.6, 147.5, 134.2, 129.6, 128.3, 128.2, 127.6, 127.4, 113.8, 107.0, 105.1, 62.9, 56.5, 56.2, 56.0, 55.2, 53.4, 51.1, 44.5, 41.0, 33.3, 32.5.

**HRMS (ESI):** *m/z* calcd for $C_{31}H_{35}NO_4$+$H^+$: 486.2644 [*M*+H]$^+$; found 486.2647.

## Synthesis of 4-(4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl)-1-(4-fluorophenyl)-2-(naphthalen-2-yl)butan-1-one (23)



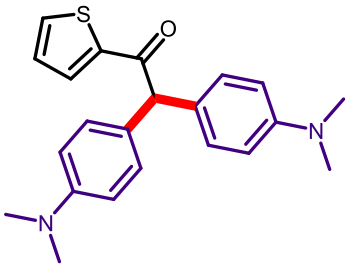

Compound **23** was obtained using General Procedure C on a 0.5 mmol scale, in this case using 0.5 mmol of the aryl ketone and 0.6 mmol of the aryl bromide. The crude product was purified by silica gel chromatography (eluent: 5% MeOH/95% DCM) to provide the product as a white solid (190.2 mg, 76% yield). $R_f$ = 0.27 (0.5:9.5 MeOH/DCM).

**$^1$H NMR (400 MHz, $CDCl_3$)**: δ 8.14 – 7.99 (m, 2H), 7.84 – 7.69 (m, 4H), 7.52 – 7.39 (m, 3H), 7.36 – 7.23 (m, 4H), 7.06 (t, *J* = 8.6 Hz, 2H), 5.29 (s, 1H), 4.84 (t, *J* = 6.9 Hz, 1H), 2.89 – 2.71 (m, 2H), 2.65 (dq, *J* = 15.2, 7.6 Hz, 1H), 2.58 – 2.33 (m, 4H), 2.16 – 1.79 (m, 4H), 1.64 (d, *J* = 13.9 Hz, 2H).

**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 197.7, 165.6 (d, *J* = 254.8 Hz), 146.8, 136.9, 133.7, 133.5 (d, *J* = 3.0 Hz), 132.9, 132.6, 131.5 (d, *J* = 9.3 Hz), 129.0, 128.5, 127.8, 127.8, 127.1, 126.4, 126.2, 126.2, 126.1, 115.7 (d, *J* = 21.8 Hz), 71.0, 56.6, 51.8, 49.9, 48.8, 38.2, 38.1, 31.4.

**HRMS (ESI):** *m/z* calcd for $C_{31}H_{29}ClFNO_2$+$H^+$: 502.1949 [*M*+H]$^+$; found: 502.1949.

### Synthesis of 2,2-*bis*(4-(dimethylamino)phenyl)-1-(thiophen-2-yl)ethan-1-one (24)



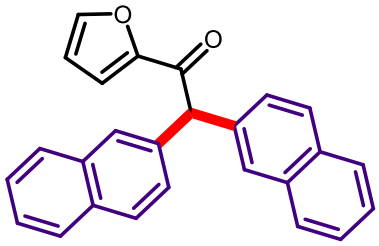

Compound **24** was obtained using the General Procedure B on a 0.5 mmol scale. The crude product was purified by silica gel chromatography (eluent: 0% to 20% EtOAc gradient/hexanes) to provide the product as a yellow solid (90.2 mg, 99% yield). $R_f$ = 0.27 (1:4 EtOAc/hexanes).

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.76 (d, *J* = 3.3 Hz, 1H), 7.55 (d, *J* = 4.7 Hz, 1H), 7.19 (d, *J* = 8.5 Hz, 4H), 7.10 – 7.01 (m, 1H), 6.70 (d, *J* = 8.5 Hz, 4H), 5.71 (s, 1H), 2.92 (s, 12H).

**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 192.3, 149.6, 144.6, 133.4, 132.5, 129.6, 128.0, 127.4, 112.7, 58.9, 40.6.

**HRMS (ESI):** *m/z* calcd for $C_{22}H_{24}N_2OS$+$Na^+$: 387.1507 [*M*+Na]$^+$; found: 387.1507.

### Synthesis of 1-(furan-2-yl)-2,2-di(naphthalen-2-yl)ethan-1-one (25)



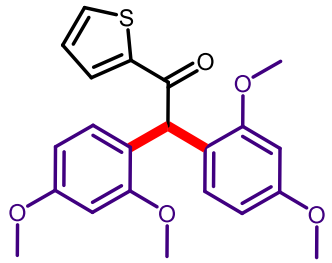
Compound **25** was obtained using the General Procedure B on a 0.5 mmol scale. The crude product was purified by silica gel chromatography (eluent: 0% to 15% EtOAc gradient/hexanes) to provide the product as a tan solid (83.3 mg, 92%% yield). $R_f$ = 0.27 (1:4 EtOAc/hexanes).

**$^1$H NMR (500 MHz, $CDCl_3$):** δ 7.89 – 7.76 (m, 8H), 7.58 – 7.55 (m, 1H), 7.55 – 7.51 (m, 2H), 7.47 (dd, *J* = 6.2, 3.3 Hz, 4H), 7.33 (d, *J* = 3.5 Hz, 1H), 6.50 (dd, *J* = 3.5, 1.5 Hz, 1H), 6.24 (s, 1H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)**: δ 187.3, 152.7, 146.8, 136.0, 133.5, 132.6, 128.4, 128.0, 127.9, 127.6, 127.4, 126.2, 126.1, 118.5, 112.6, 59.0.

**HRMS (ESI):** *m/z* calcd for $C_{26}H_{18}O_2$+$Na^+$: 385.1205 [*M*+Na]$^+$; found: 385.1204.

**Synthesis of 2,2-*bis*(2,4-dimethoxyphenyl)-1-(thiophen-2-yl)ethan-1-one (26)**



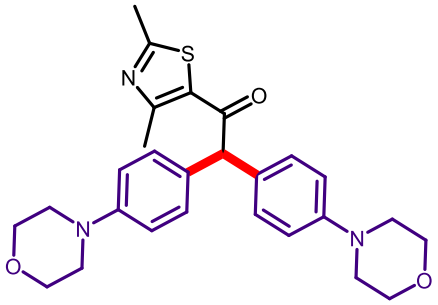

Compound **26** was obtained using the General Procedure B on a 0.5 mmol scale. The crude product was purified by silica gel chromatography (eluent: 0% to 20% EtOAc gradient/hexanes) to provide the product as a white solid (80.2 mg, 81% yield). $R_f$ = 0.18 (1:4 EtOAc/hexanes).

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.81 – 7.70 (m, 1H), 7.58 – 7.49 (m, 1H), 7.07 – 7.00 (m, 1H), 6.95 (d, *J* = 8.4 Hz, 2H), 6.49 (d, *J* = 2.3 Hz, 2H), 6.42 (dd, *J* = 8.5, 2.4 Hz, 2H), 6.36 (s, 1H), 3.78 (s, 6H), 3.77 (s, 6H).

**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 192.5, 160.0, 157.8, 144.3, 132.6, 131.7, 130.3, 127.8, 119.4, 104.0, 98.8, 55.6, 55.3, 46.2.

**HRMS (ESI):** *m/z* calcd for $C_{22}H_{22}O_5S$+$Na^+$: 421.1086 [*M*+Na]$^+$; found: 421.1079.

**Synthesis of 1-(2,4-dimethylthiazol-5-yl)-2,2-*bis*(4-morpholinophenyl)ethan-1-one (27)**



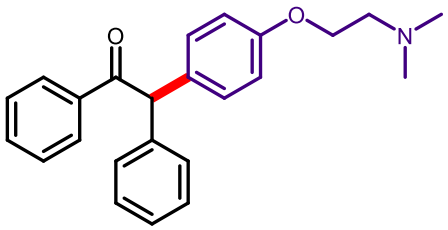
Compound **27** was obtained using the General Procedure C on a 0.5 mmol scale. The crude product was purified by silica gel chromatography (eluent: 0% to 75% EtOAc gradient/hexanes) to afford the product as a light-yellow solid (105.7 mg, 88% yield). $R_f$ = 0.18 (1:1 EtOAc/hexanes).

**$^1$H NMR (500 MHz, $CDCl_3$):** δ 7.14 (d, *J* = 8.6 Hz, 4H), 6.85 (d, *J* = 8.6 Hz, 4H), 5.38 (s, 1H), 3.87 – 3.79 (m, 8H), 3.17 – 3.07 (m, 8H), 2.70 (s, 3H), 2.62 (s, 3H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)**: δ 191.9, 168.3, 160.5, 150.3, 129.9, 129.8, 129.6, 115.6, 66.9, 62.9, 49.1, 19.4, 18.3.

**HRMS (ESI):** *m/z* calcd for $C_{27}H_{31}N_3O_3S+Na^+$: 500.1984 [*M*+Na]$^+$; found: 500.1984.

**Synthesis of 2-(4-(2-(dimethylamino)ethoxy)phenyl)-1,2-diphenylethan-1-one (29)**



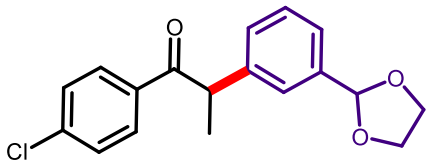
Compound **29** was obtained using the procedure outlined in Section 4.2. The crude product was purified by silica gel chromatography (eluent: 1:9:0.1 MeOH/DCM/$Et_3N$) to provide the product as a viscous yellow oil (177.1 mg, 98% yield). $R_f$ = 0.30 (1:9:0.1 MeOH/DCM/$Et_3N$).

**$^1$H NMR (400 MHz, $CDCl_3$)**: δ 8.02 – 7.97 (m, 2H), 7.54 – 7.47 (m, 1H), 7.44 – 7.37 (m, 2H), 7.35 – 7.28 (m, 2H), 7.26 – 7.23 (m, 3H), 7.22 – 7.15 (m, 2H), 6.90 – 6.85 (m, 2H), 5.98 (s, 1H), 4.06 (t, *J* = 5.7 Hz, 2H), 2.77 (t, *J* = 5.7 Hz, 2H), 2.36 (s, 6H).

**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 198.4, 157.8, 139.4, 136.8, 133.0, 131.3, 130.1, 129.0, 128.9, 128.7, 128.6, 127.0, 114.8, 65.6, 58.6, 58.0, 45.6.

**HRMS (ESI):** *m/z* calcd for $C_{24}H_{25}NO_2$+$H^+$: 360.1964 [*M*+H]$^+$; found: 360.1962.

## Synthesis of 2-(3-(1,3-dioxolan-2-yl)phenyl)-1-(4-chlorophenyl)propan-1-one (32)



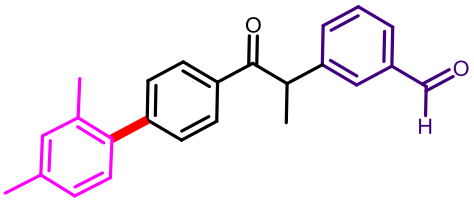

Compound **32** was obtained using the procedure outlined in Section 4.5, Step 1. The crude product was purified by silica gel chromatography (eluent: 20% EtOAc/80% hexanes) to provide the product as a clear oil (128.1 mg, 81% yield). $R_f$ = 0.39 (3:7 EtOAc/hexanes).

**$^1$H NMR (500 MHz, $CDCl_3$)**: δ 7.89 – 7.83 (m, 2H), 7.38 (t, *J* = 1.9 Hz, 1H), 7.35 – 7.28 (m, 4H), 7.24 (dt, *J* = 7.3, 1.8 Hz, 1H), 5.75 (s, 1H), 4.63 (q, *J* = 6.9 Hz, 1H), 4.16 – 3.94 (m, 4H), 1.52 (d, *J* = 6.7 Hz, 3H).

**$^{13}$C NMR (126 MHz, $CDCl_3$):** δ 199.0, 141.4, 139.3, 138.9, 134.8, 130.3, 129.3, 128.9, 128.6, 126.0, 125.4, 103.6, 65.4, 65.4, 48.1, 19.6.

**HRMS (ESI):** *m/z* calcd for $C_{18}H_{17}ClO_3$+$Na^+$: 339.0764 [*M*+Na]$^+$; found: 339.0774.

**Synthesis of 3-(1-(2',4'-dimethyl-[1,1'-biphenyl]-4-yl)-1-oxopropan-2-yl)benzaldehyde (33)**



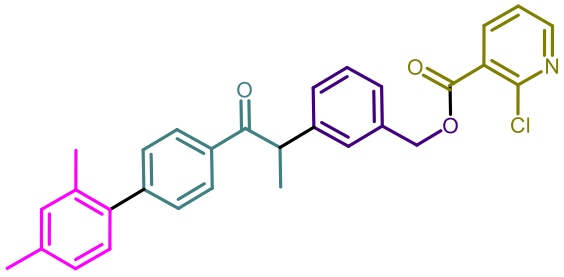

Compound **33** was obtained using the procedure outlined in Section 4.5, Step 1 and Steps 2-3 in tandem. The crude product was purified by silica gel chromatography (eluent: 15% EtOAc/85% hexanes) to provide the product as an opaque clear oil (115.2 mg, 67% yield over three steps). $R_f$ = 0.61 (3:7 EtOAc/hexanes).

**$^1$H NMR (500 MHz, $CDCl_3$)**: δ 10.01 (s, 1H), 8.01 (d, *J* = 8.6 Hz, 2H), 7.89 (s, 1H), 7.79 – 7.74 (m, 1H), 7.65 – 7.61 (m, 1H), 7.50 (t, *J* = 7.7 Hz, 1H), 7.37 (d, *J* = 8.6 Hz, 2H), 7.12 – 7.03 (m, 3H), 4.86 (q, *J* = 6.9 Hz, 1H), 2.36 (s, 3H), 2.22 (s, 3H), 1.61 (d, *J* = 7.0 Hz, 3H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)**: δ 199.5, 192.1, 147.1, 142.6, 137.7, 137.7, 137.1, 134.9, 134.4, 133.9, 131.3, 129.7, 129.7, 129.5, 129.0, 128.6, 128.6, 126.7, 47.3, 21.1, 20.3, 19.6.

**HRMS (ESI):** *m/z* calcd for $C_{24}H_{22}O_2$+$Na^+$: 365.1518 [*M*+Na]$^+$; found 363.1995.

**Synthesis of 3-(1-(2',4'-dimethyl-[1,1'-biphenyl]-4-yl)-1-oxopropan-2-yl)benzyl 2-chloronicotinate (34)**



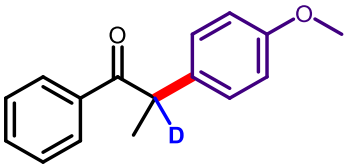
Compound **34** was obtained using the procedure outlined in Section 4.5, Step 1, Steps 2-3, and Steps 4-5 in tandem. The crude product was purified by silica gel chromatography (eluent: 25% EtOAc/75% hexanes) to provide the product as a clear oil (161.6 mg, 66% yield over five steps). $R_f$ = 0.35 (3:7 EtOAc/hexanes).

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 8.49 (dd, *J* = 4.9, 1.8 Hz, 1H), 8.20 – 8.11 (m, 1H), 8.01 (d, *J* = 8.2 Hz, 2H), 7.45 (s, 1H), 7.41 – 7.24 (m, 6H), 7.07 (d, *J* = 11.9 Hz, 3H), 5.37 (s, 2H), 4.79 (q, *J* = 6.9 Hz, 1H), 2.36 (s, 3H), 2.21 (s, 3H), 1.58 (d, *J* = 6.8 Hz, 3H).

**$^{13}$C NMR (101 MHz, $CDCl_3$)**: δ 199.8, 164.3, 152.0, 150.1, 146.8, 142.0, 140.4, 137.7, 137.7, 135.8, 134.9, 134.5, 131.3, 129.5, 129.5, 129.4, 128.6, 128.1, 127.8, 127.0, 126.8, 126.6, 122.1, 67.6, 47.5, 21.1, 20.3, 19.6.

**HRMS (ESI):** *m/z* calcd for $C_{30}H_{26}ClNO_3$+$Na^+$: 506.1499 [*M*+Na]$^+$; found: 506.1492.

**Synthesis of 2-(4-methoxyphenyl)-1-phenylpropan-1-one-2-d (35)**




Compound **35** was obtained using the procedure outlined in Section 4.6. The crude product was purified by silica gel chromatography (eluent: 8% EtOAc/92% hexanes) to provide the product as an off-white solid (248.1 mg, 99% yield). $R_f$ = 0.31 (8% EtOAc/92% hexanes).

**$^1$H NMR (500 MHz, $CDCl_3$):** δ 7.97 (d, *J* = 7.1 Hz, 2H), 7.50 – 7.43 (m, 1H), 7.41 – 7.35 (m, 2H), 7.23 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 3.73 (s, 3H), 1.52 (s, 3H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)**: δ 200.6, 158.5, 128.8, 128.8, 128.5, 114.4, 55.2, 46.5 (t, J = 19.5 Hz), 19.4.

**HRMS (EI):** *m/z* calcd for $C_{16}H_{15}O_2D^+$: 241.1213 [*M*]$^+$; found: 241.1217.

# 6. References

[2] Pichette Drapeau, M.; Fabre, I.; Grimaud, L.; Ciofini, I.; Ollevier, T.; Taillefer, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 10587–10591.

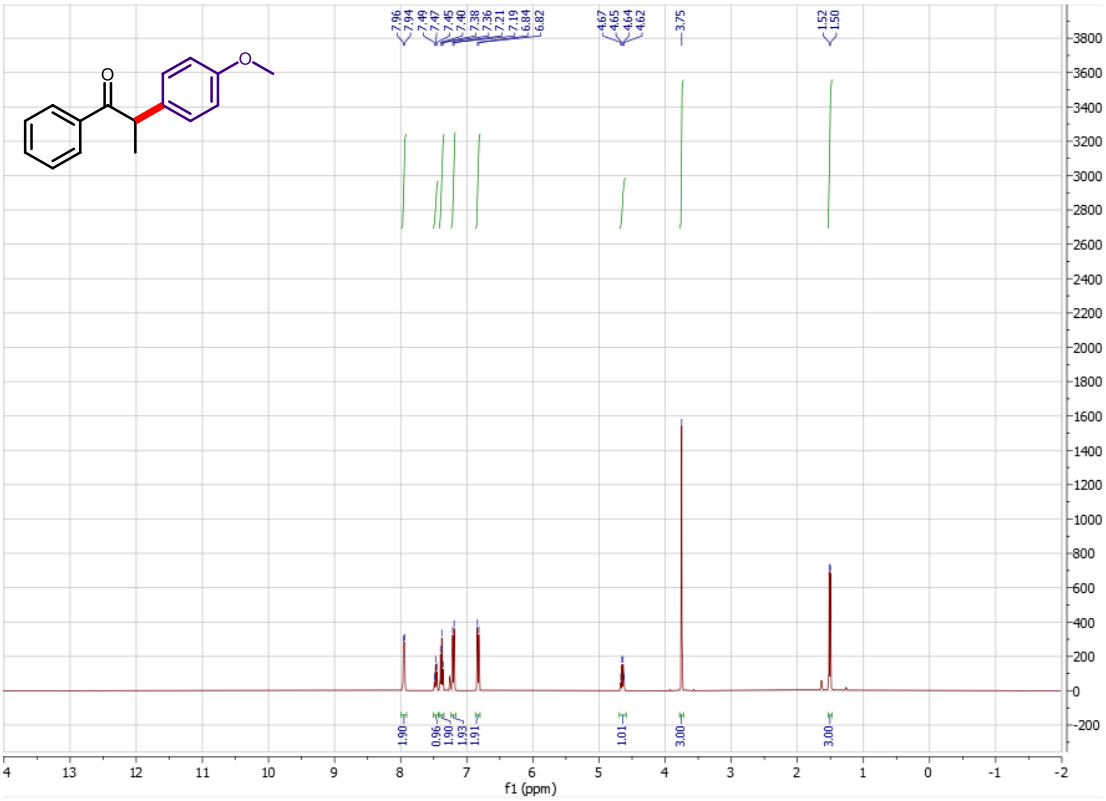
[3] Matsubara, K.; Ueno, K.; Koga, Y.; Hara, K. *J. Org. Chem.* **2007**, *72*, 5069–5076.

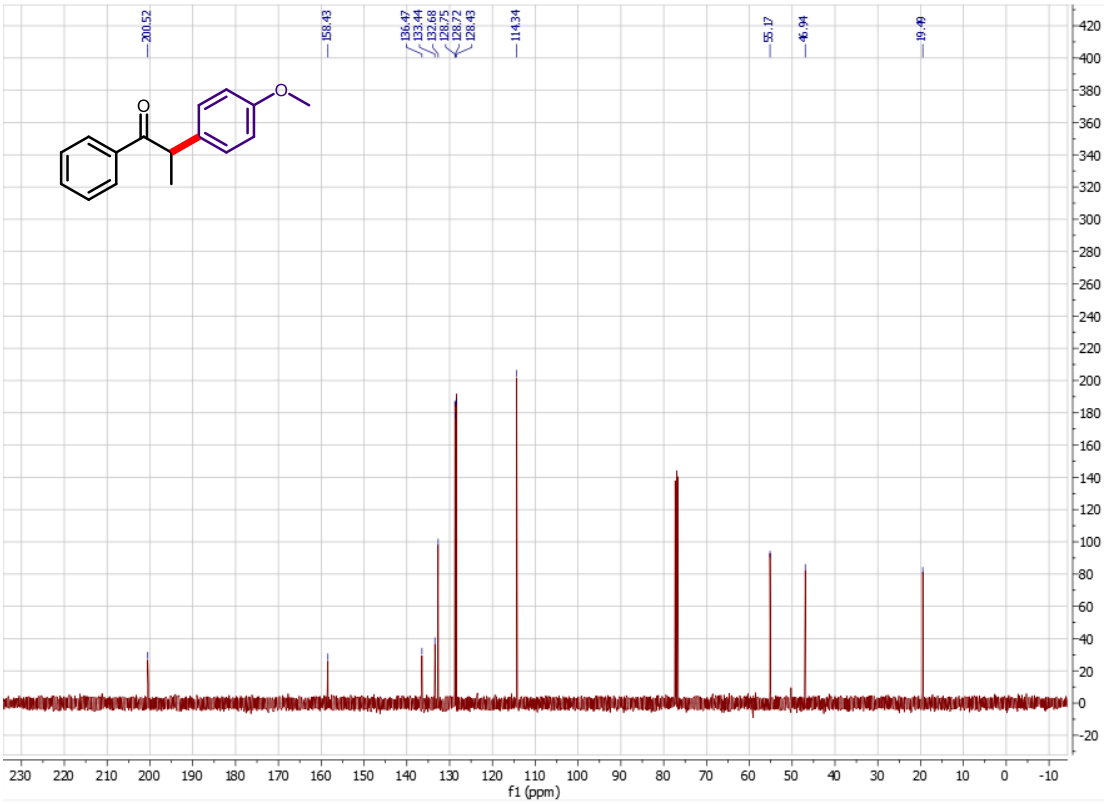
[4] Marelli, E.; Corpet, M.; Davies, S. R.; Nolan, S. P. *Chem. Eur. J.* **2014**, *20*, 17272–17276.

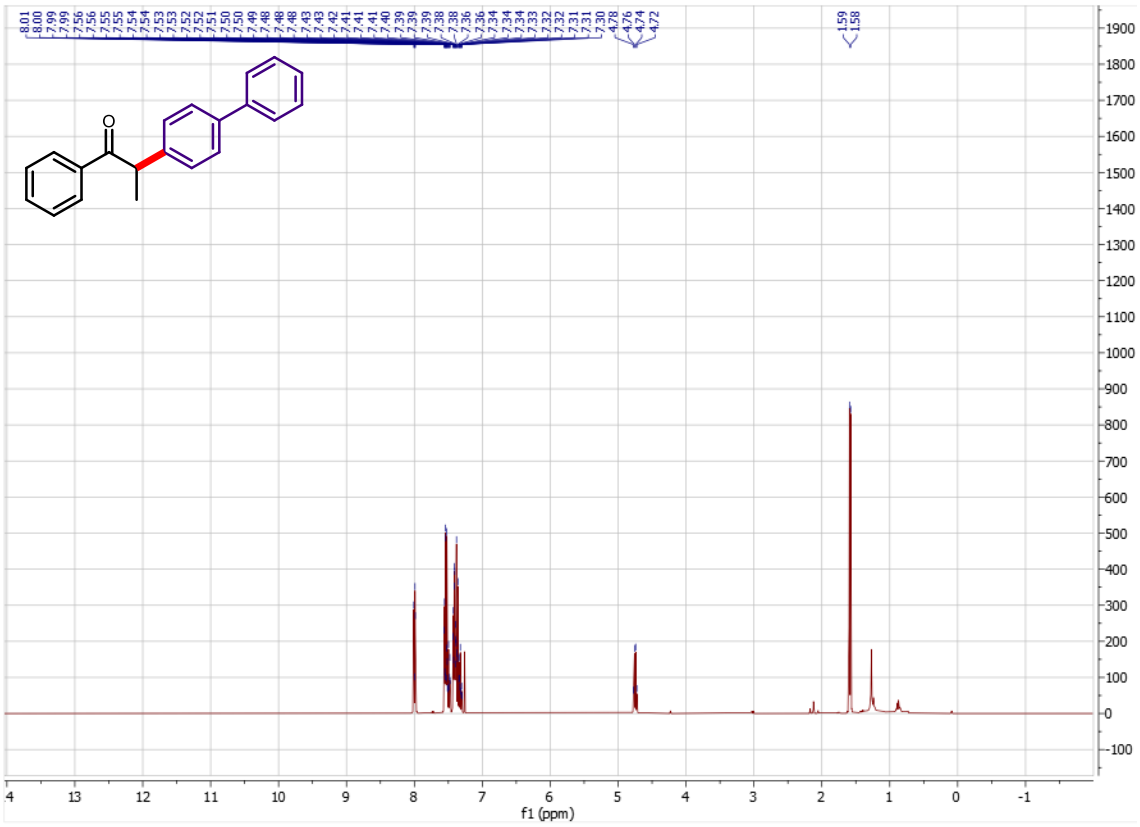
[5] Marelli, E.; Renault, Y.; Sharma, S. V.; Nolan, S. P.; Goss, R. J. M. *Chem. Eur. J.* **2017**, *23*, 3832–3836.

[6] Lundin, P. M.; Esquivias, J.; Fu, G. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 154–156.

## 7. NMR Spectral Data

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8.00
7.99
7.99
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7.56
7.55
7.55
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7.54
7.53
7.53
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7.41
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7.40
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7.33
7.32
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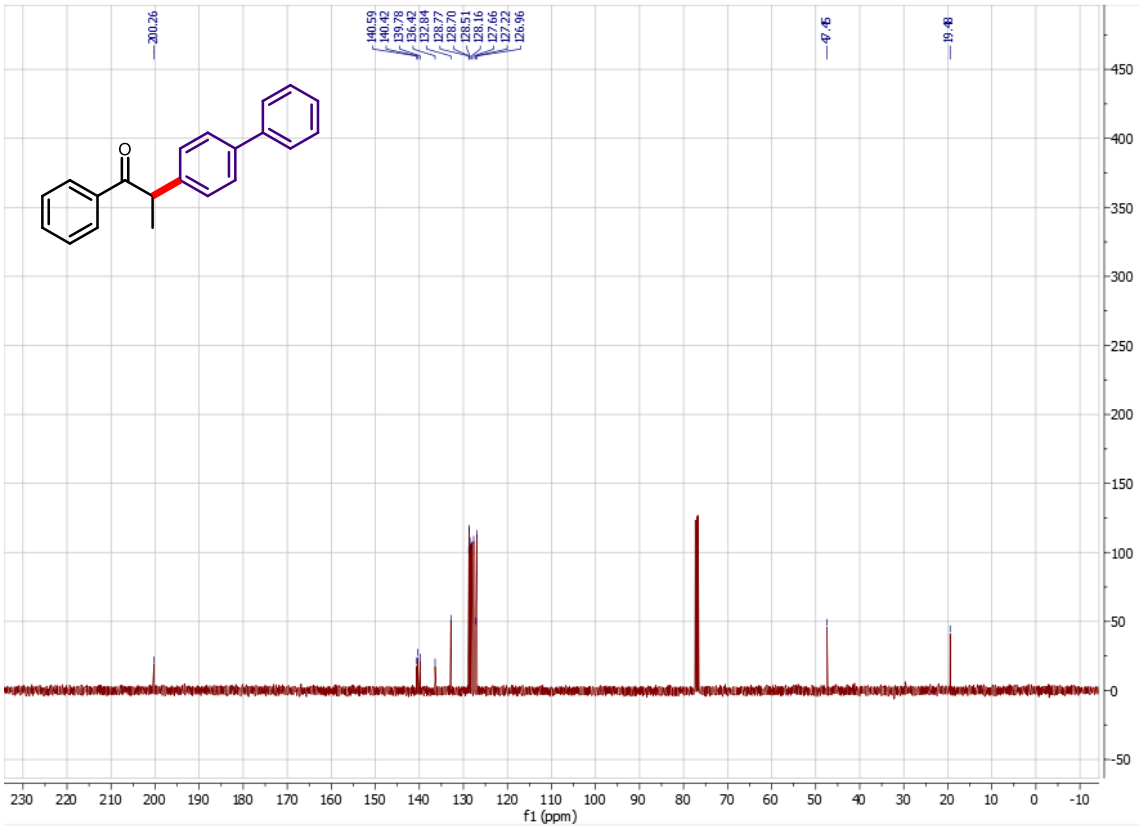
4.74
4.72
1.59
1.58
O
f1 (ppm)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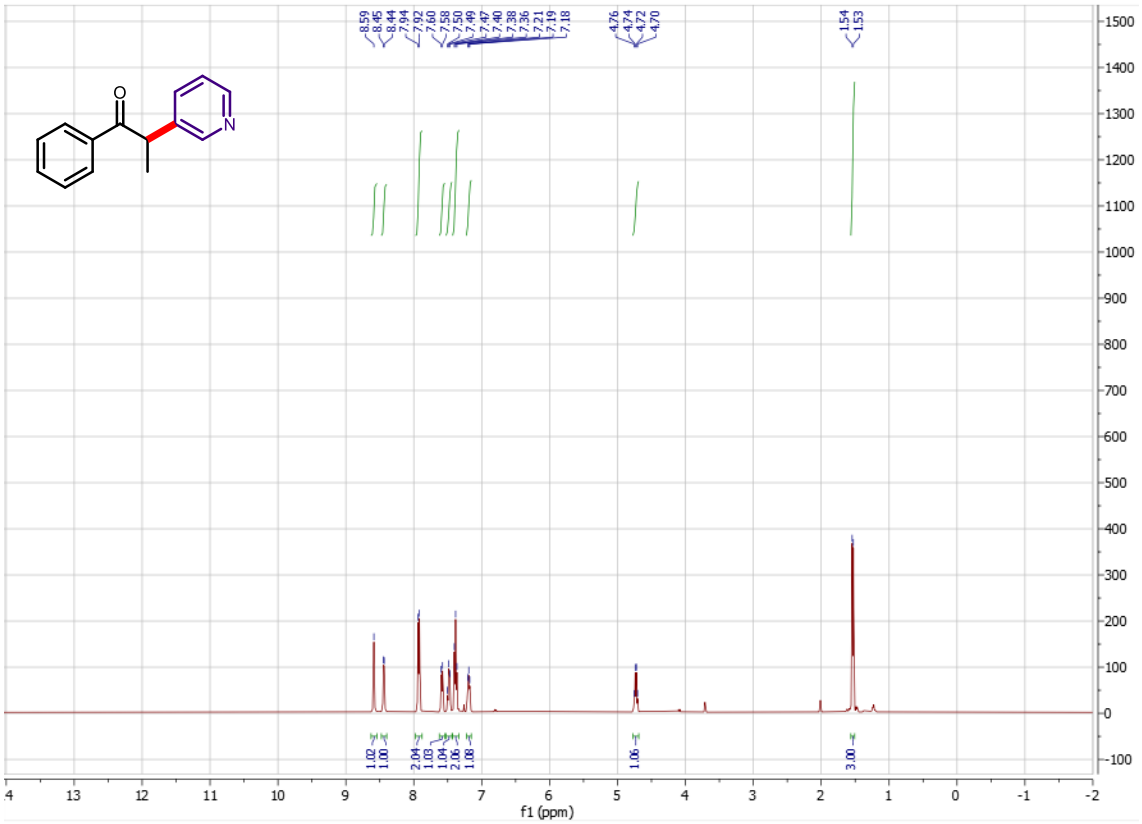
126.96
47.45
19.48
O
f1 (ppm)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8.45
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7.60
7.58
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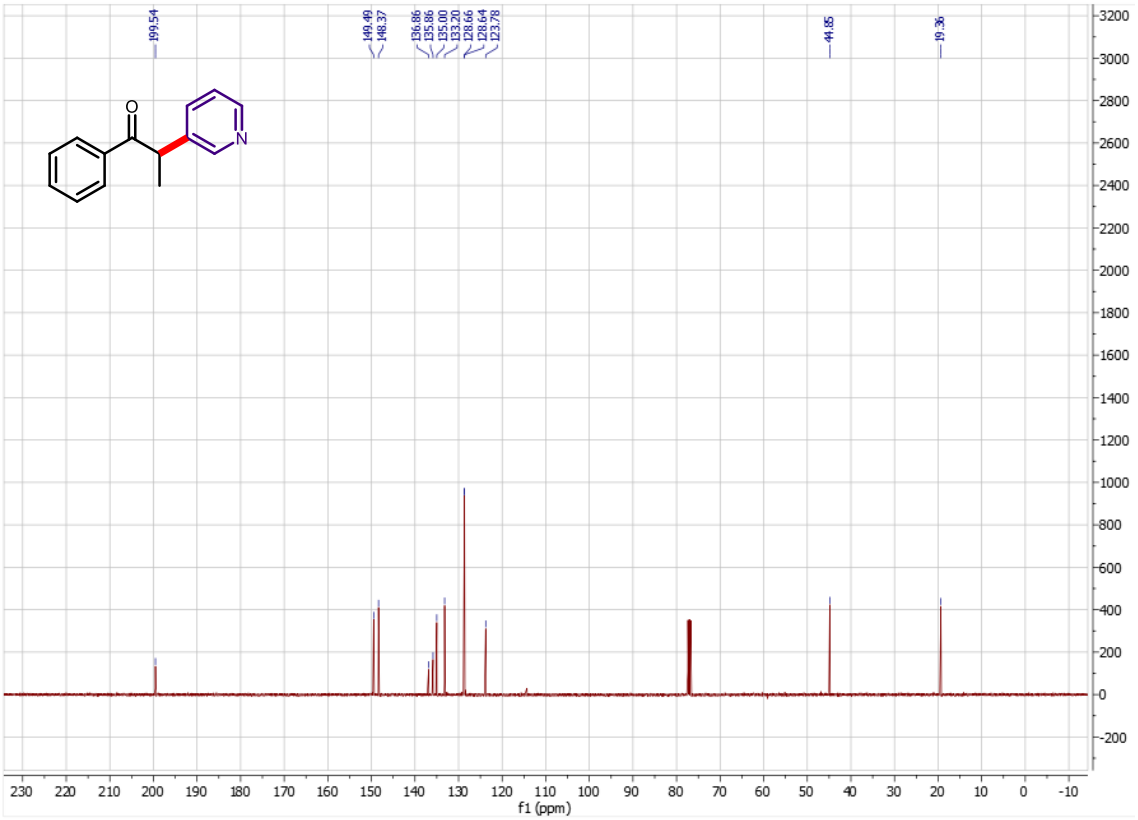
7.47
7.40
7.38
7.36
7.21
7.19
7.18
4.76
4.74
4.72
4.70
1.54
1.53
1.02
1.00
2.04
1.03
1.04
2.06
1.08
1.06
3.00
f1 (ppm)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135.00
133.20
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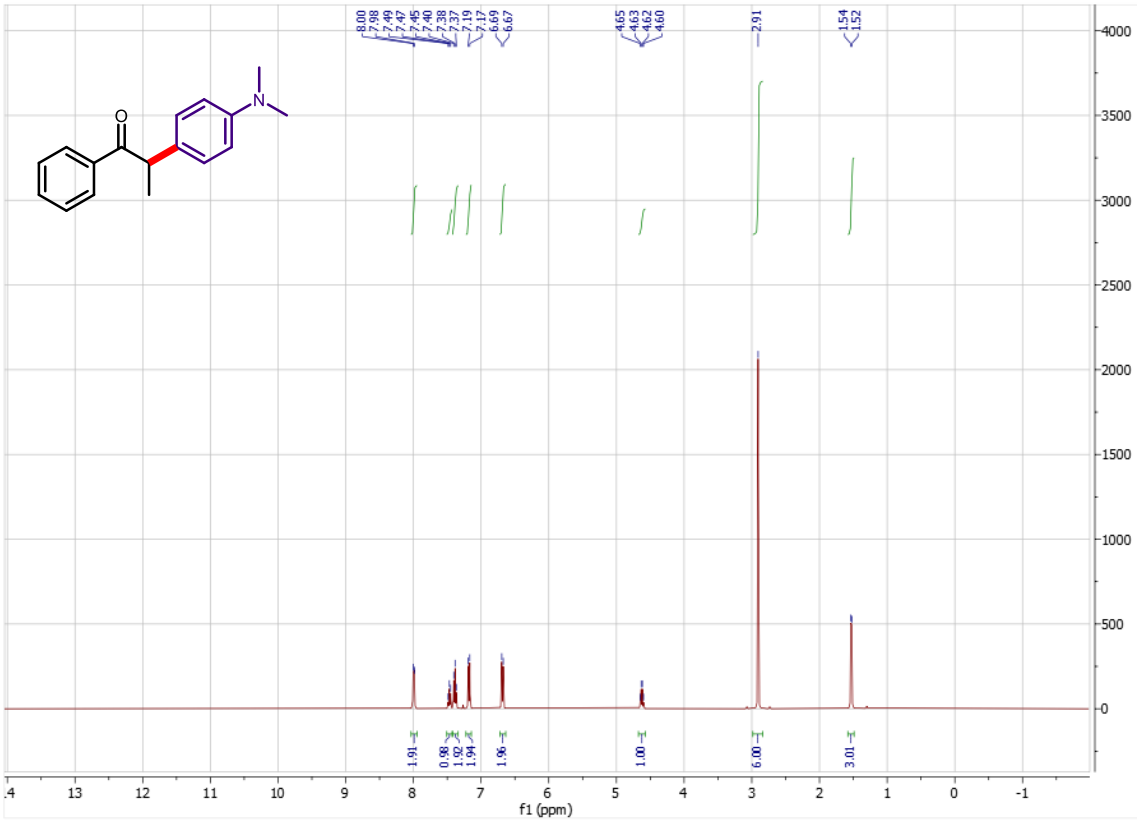
19.36
f1 (ppm)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4.63
4.62
4.60
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1.91
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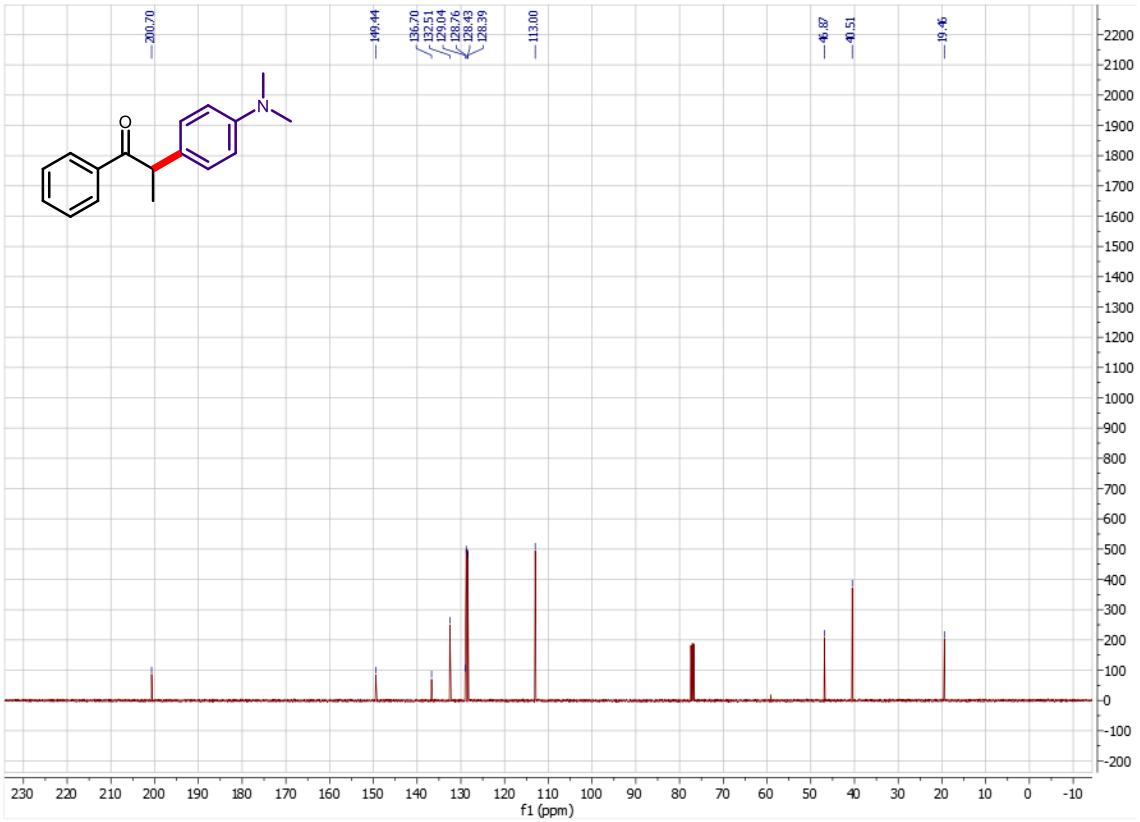
1.92
1.94
1.96
1.00
6.00
3.01
f1 (ppm)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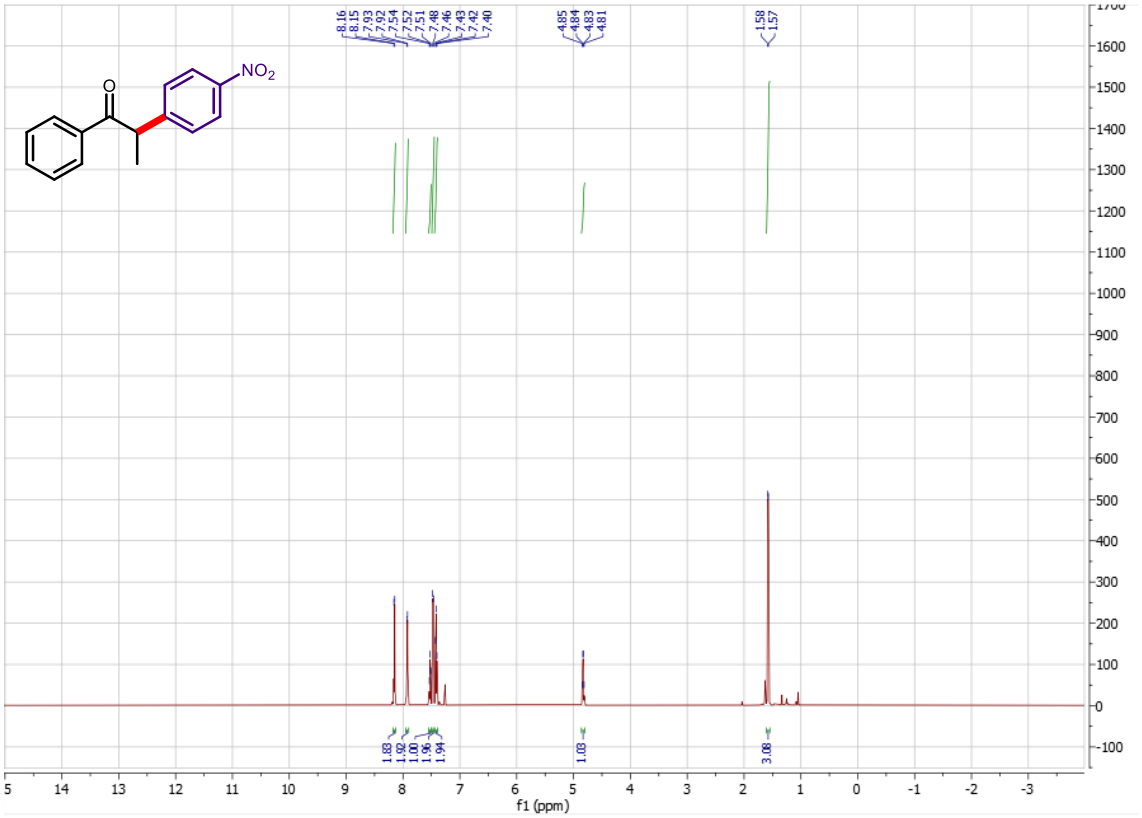
40.51
19.46
f1 (ppm)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8.15
7.93
7.92
7.54
7.52
7.51
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7.42
7.40
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4.84
4.83
4.81
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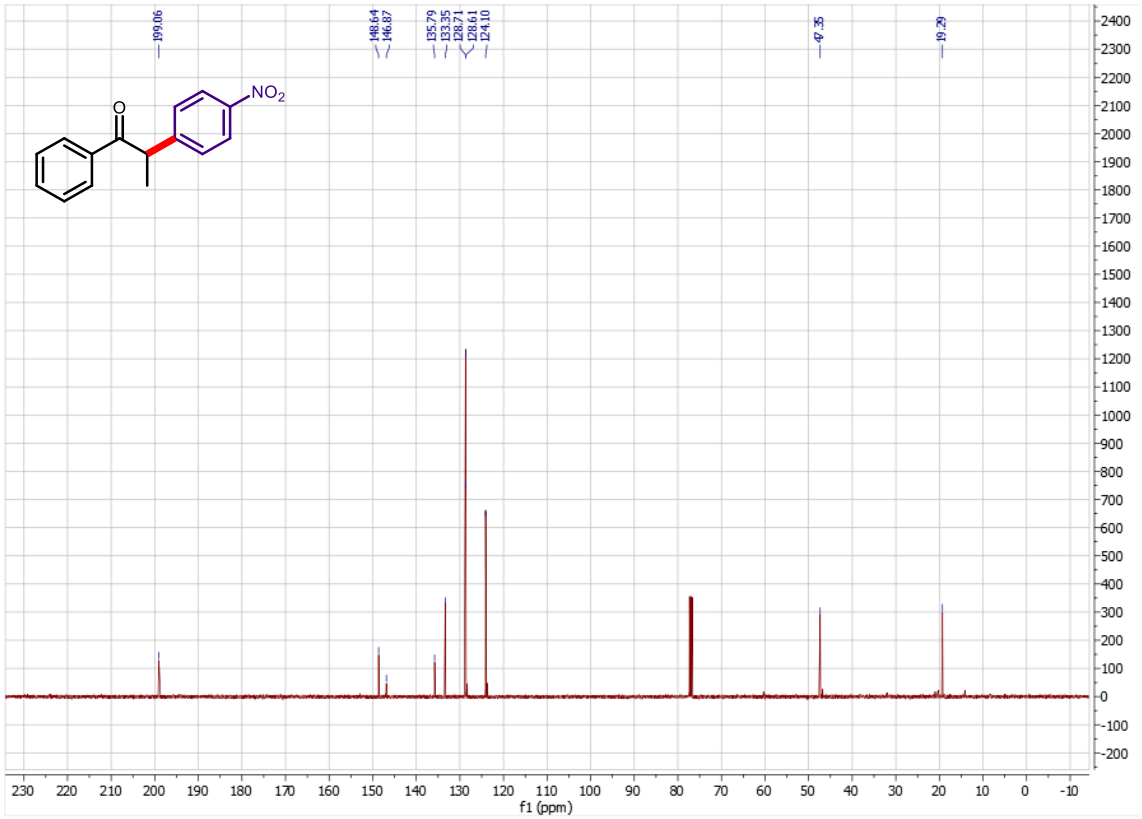
1.03
3.08
NO2
O
f1 (ppm)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NO2
O
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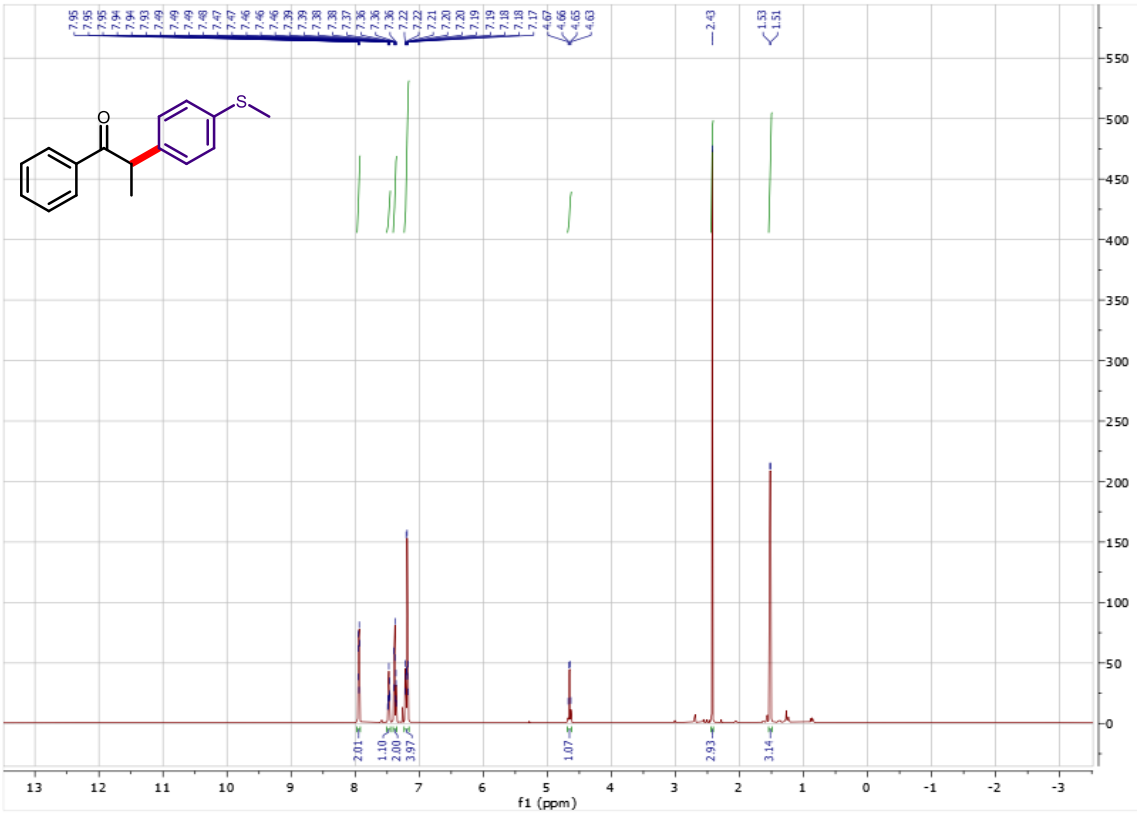
O
S
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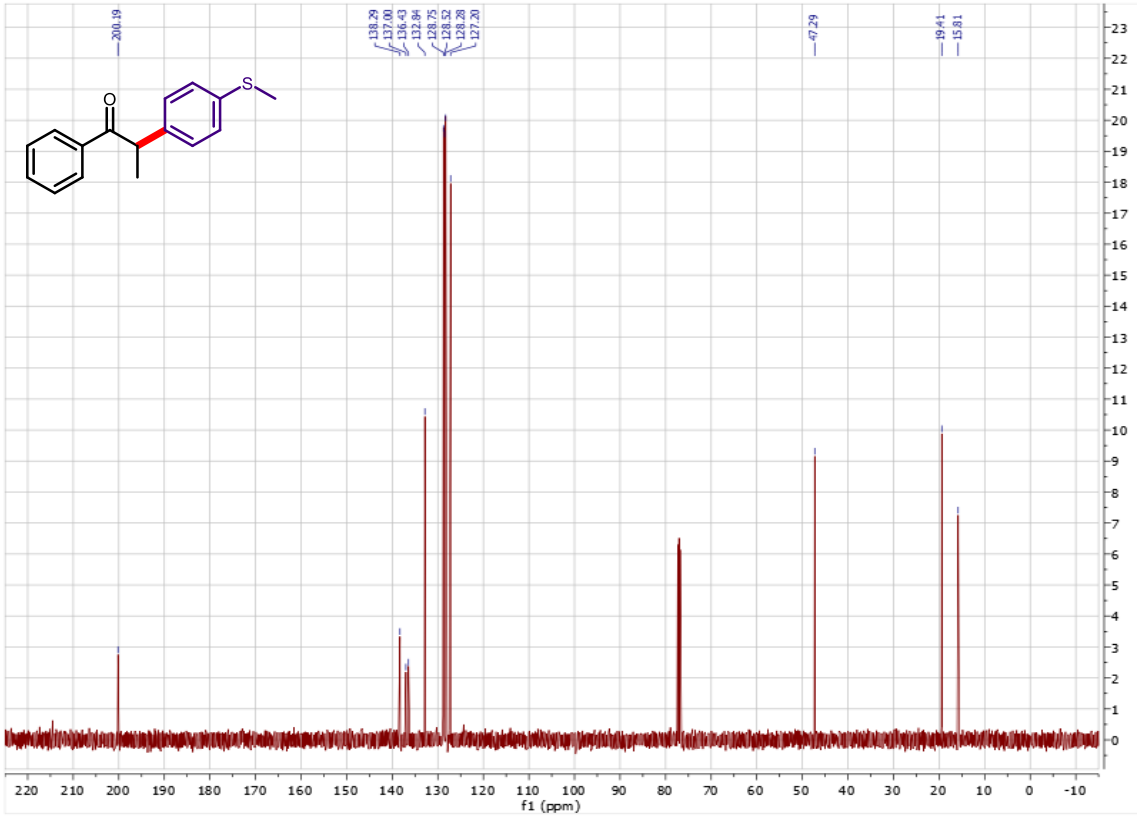
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S
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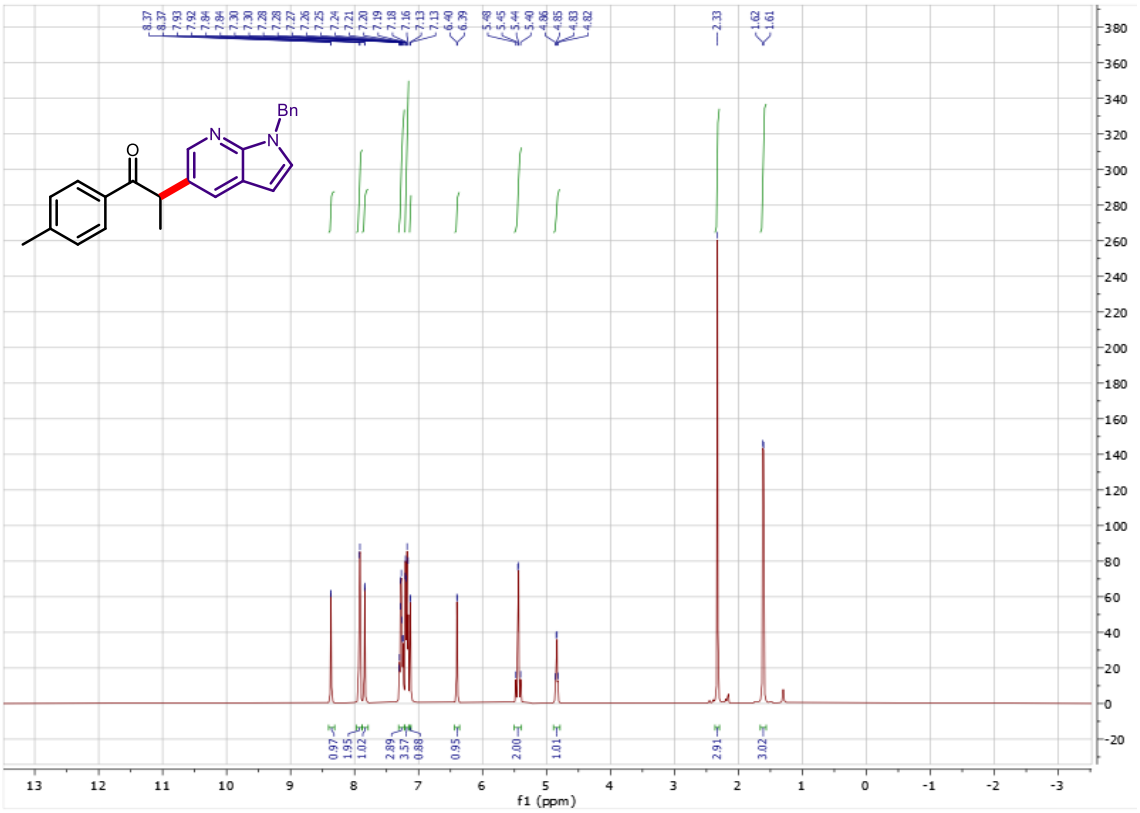
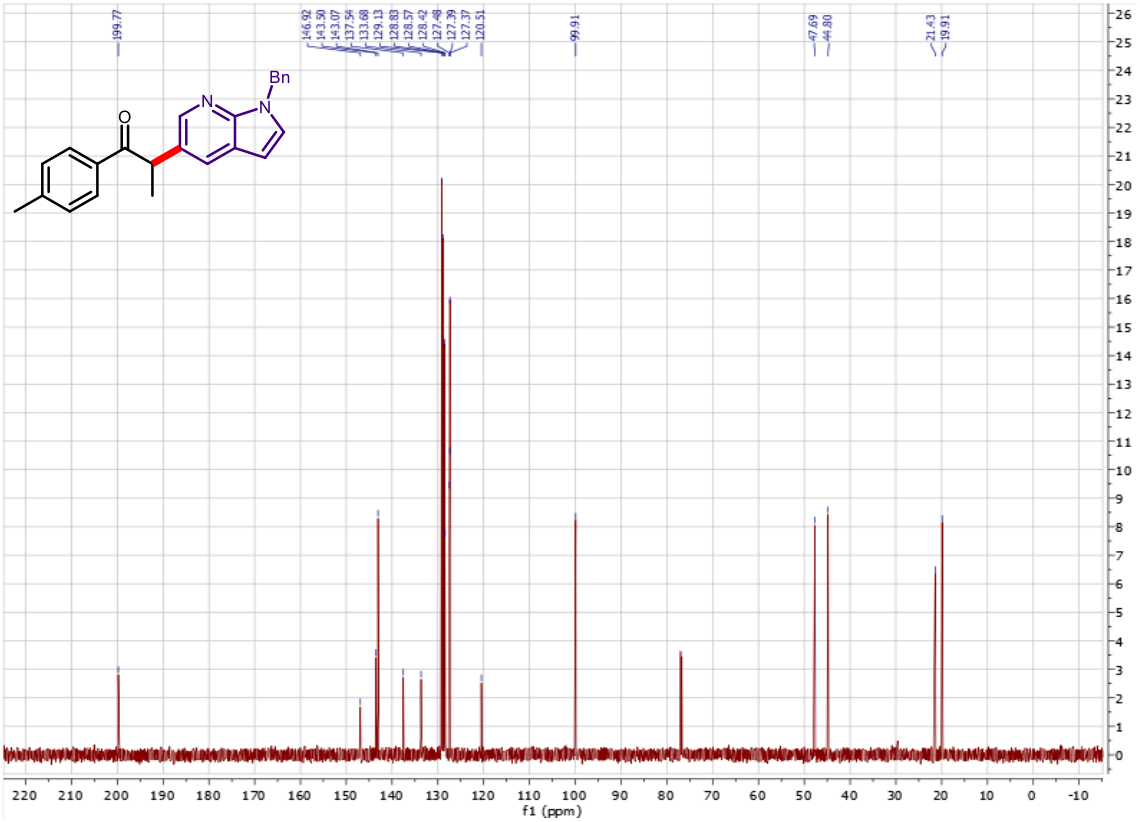

Bn
N
N
O
f1 (ppm)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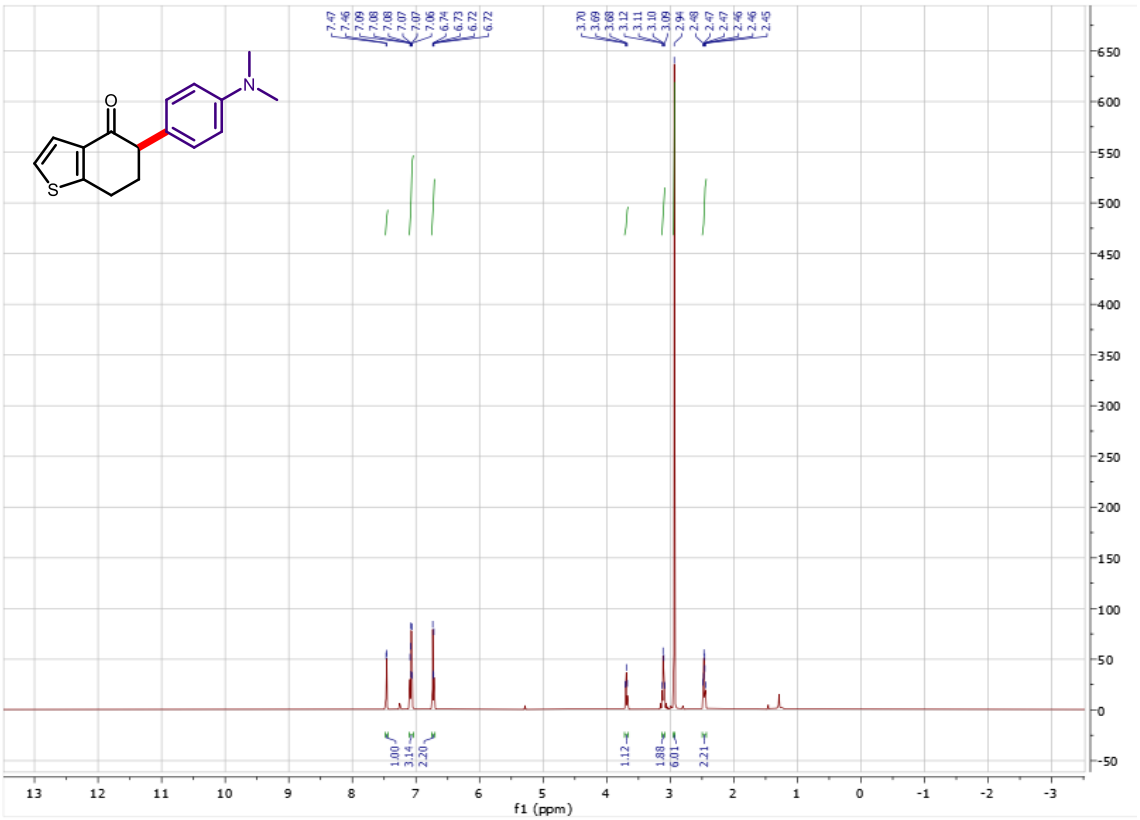
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7.08
7.08
7.07
7.07
7.06
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6.72
6.72
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3.69
3.68
3.12
3.11
3.10
3.09
2.94
2.48
2.47
2.47
2.46
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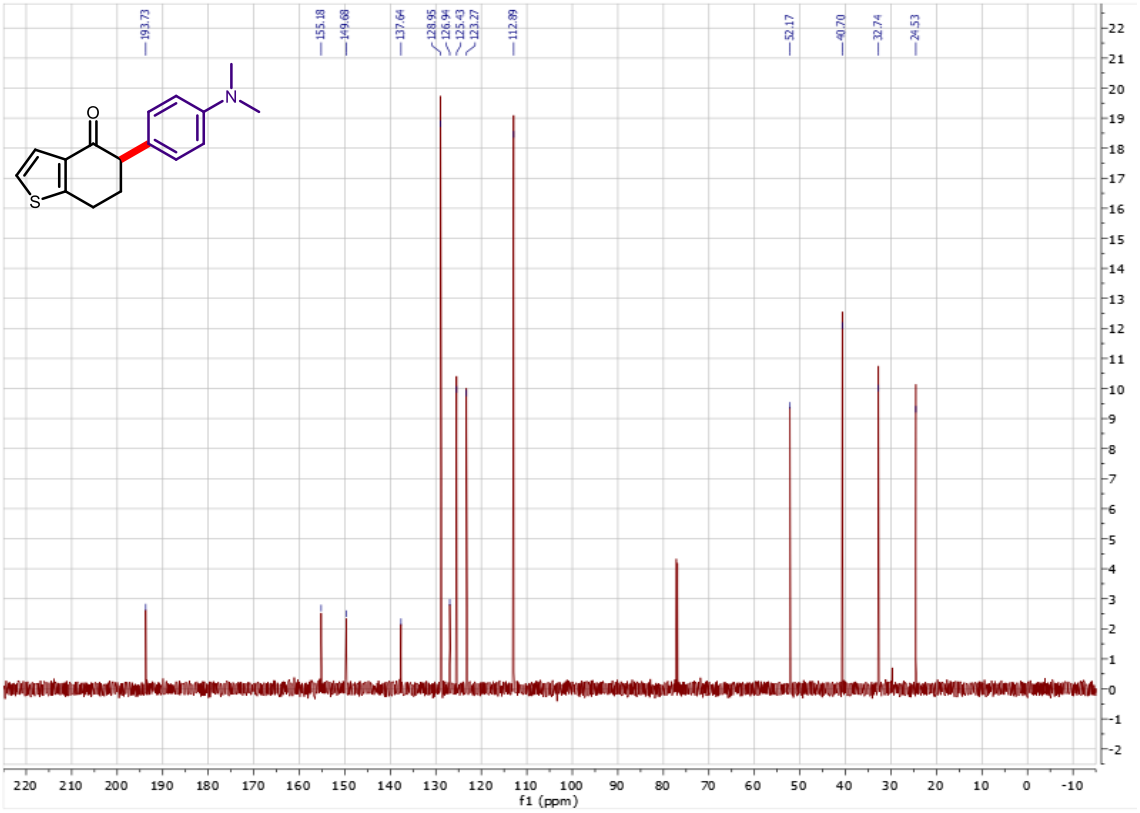
6.01
2.21
O
N
S
f1 (ppm)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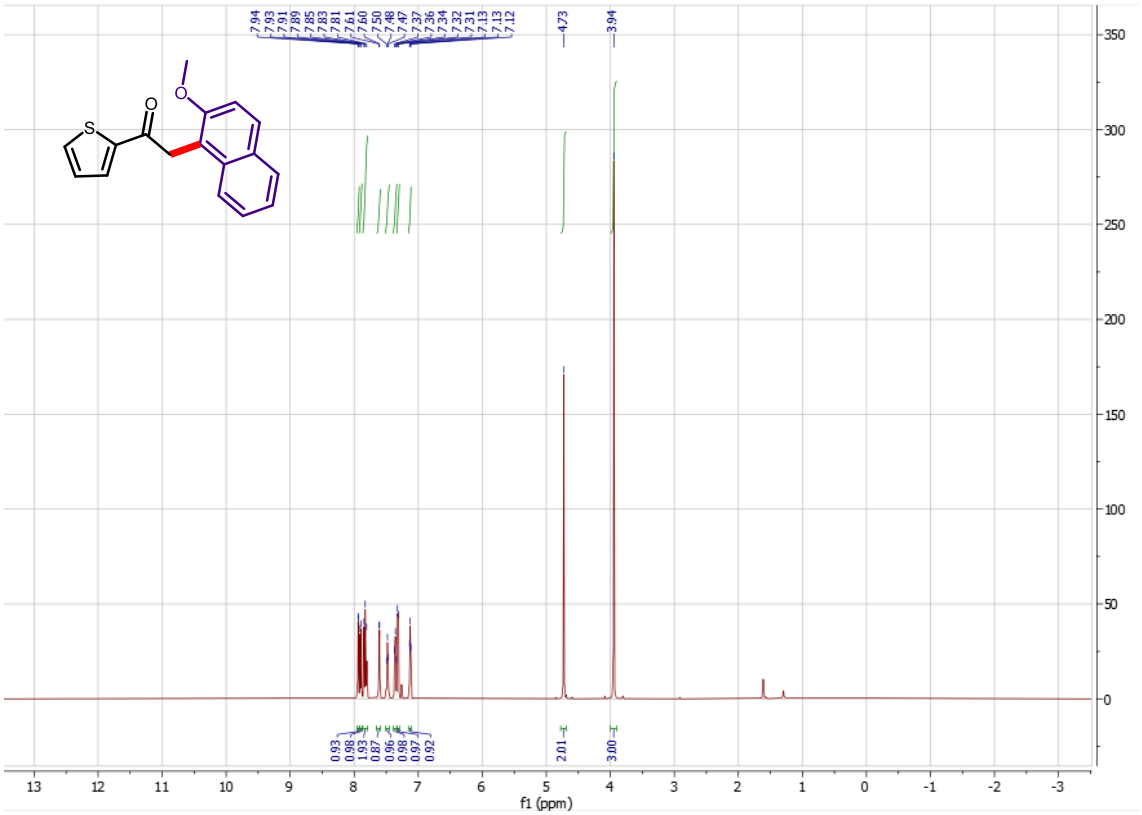
O
N
S
f1 (ppm)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7.93
7.91
7.89
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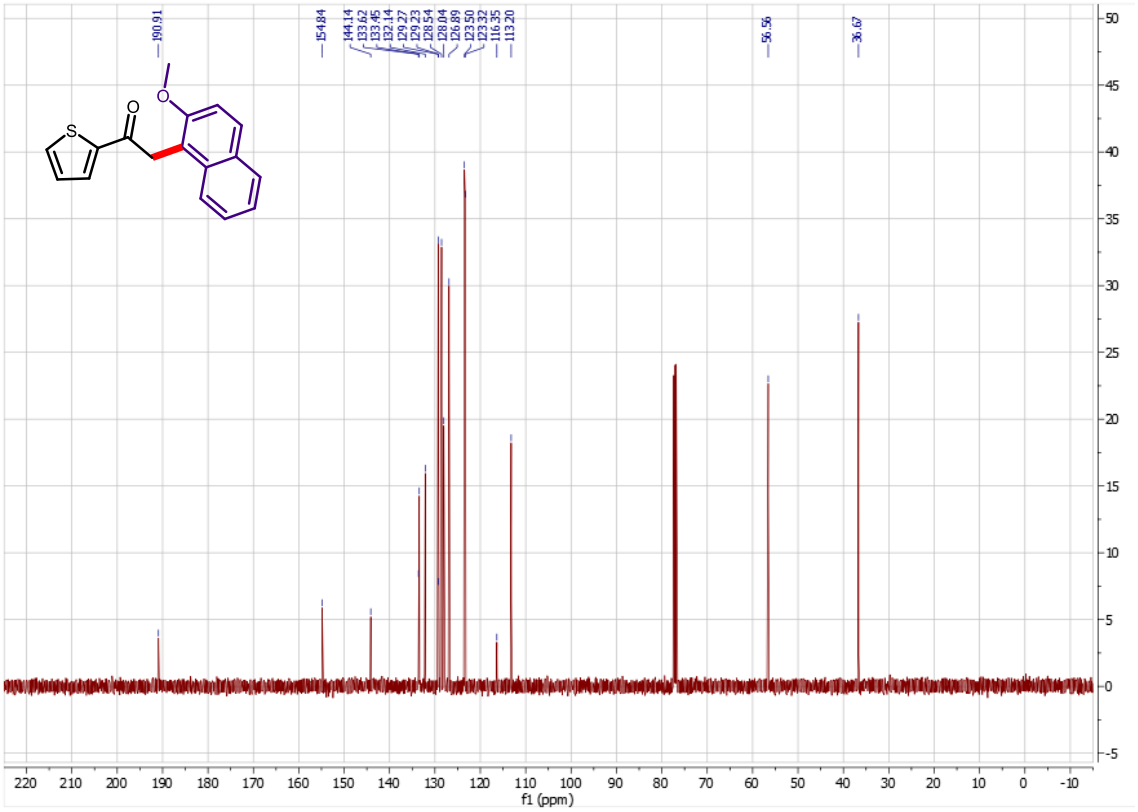
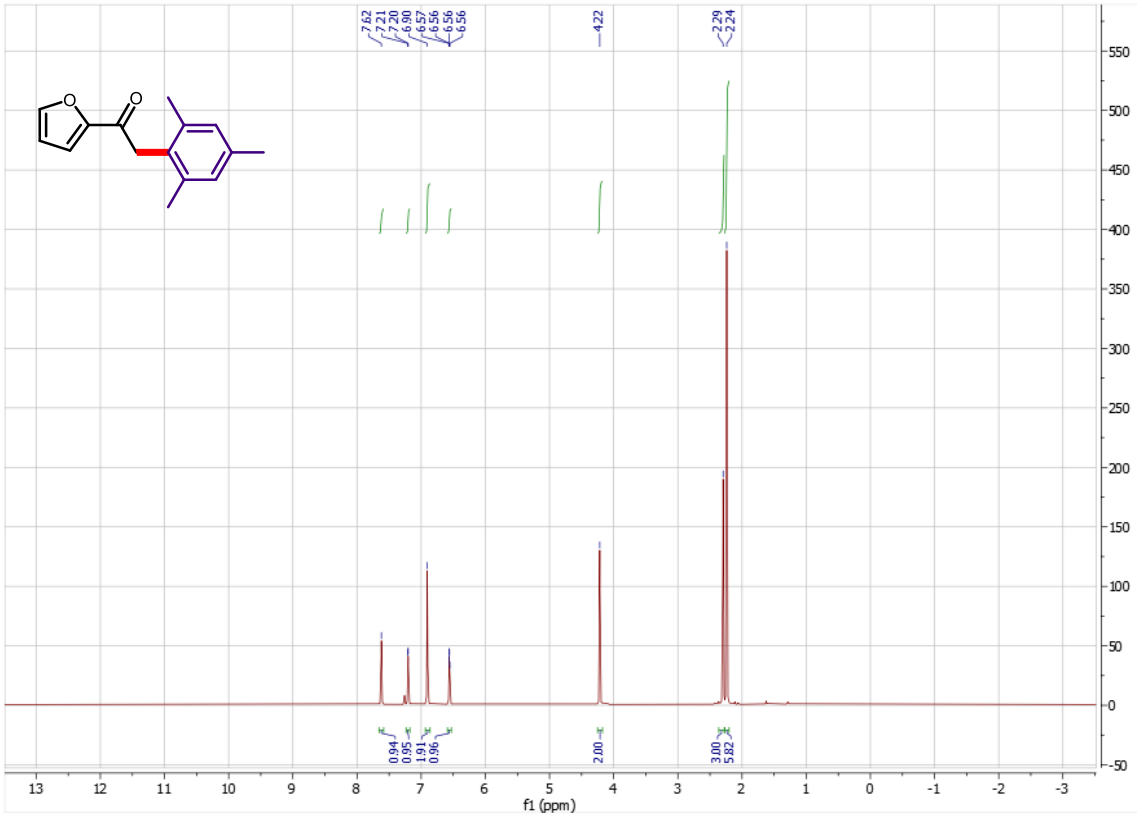
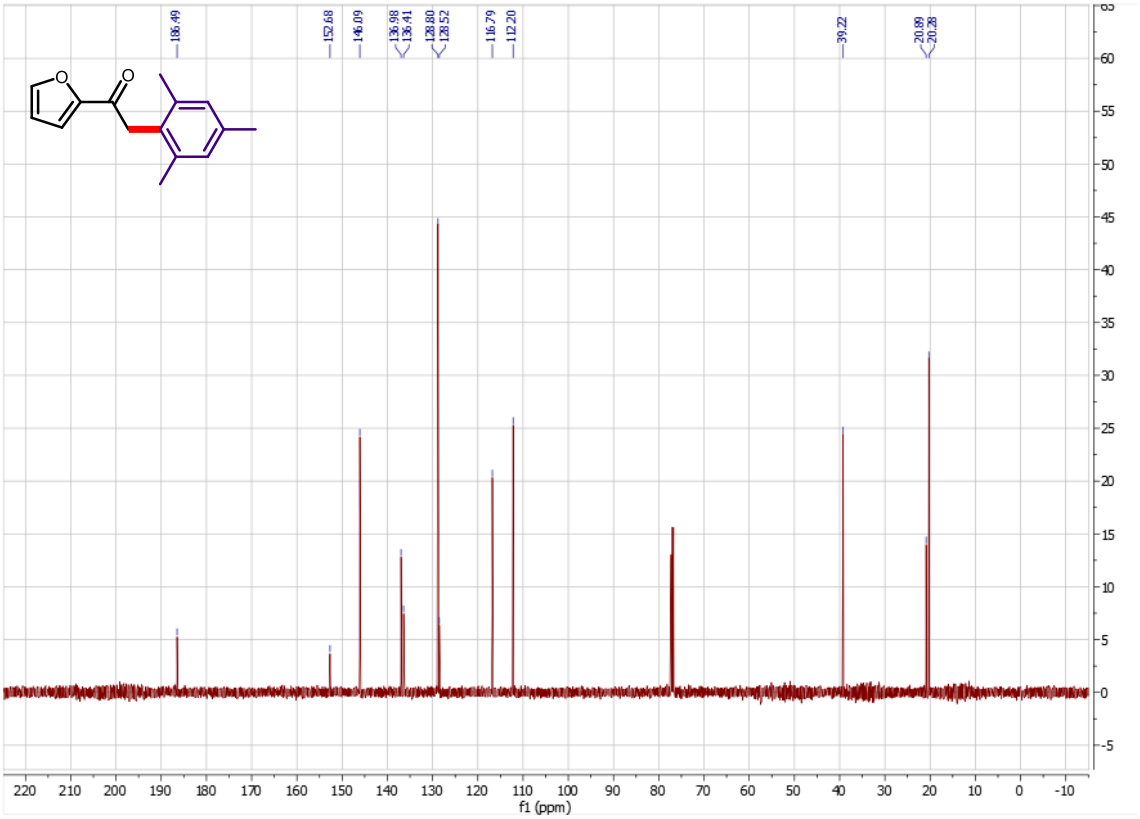
7.83
7.81
7.61
7.60
7.50
7.48
7.47
7.37
7.36
7.34
7.32
7.31
7.13
7.12
4.73
3.94
0.93
0.98
1.93
0.87
0.96
0.98
0.97
0.92
2.01
3.00
f1 (ppm)


190.91
154.84
144.14
133.62
133.45
132.14
129.27
129.23
128.54
128.04
126.89
123.50
123.32
116.35
113.20
56.56
36.67
f1 (ppm)


7.62
7.21
7.20
6.90
6.57
6.56
6.56
6.56
4.22
2.29
2.24
0.94
0.95
1.91
0.96
2.00
3.00
5.82
f1 (ppm)


186.49
152.68
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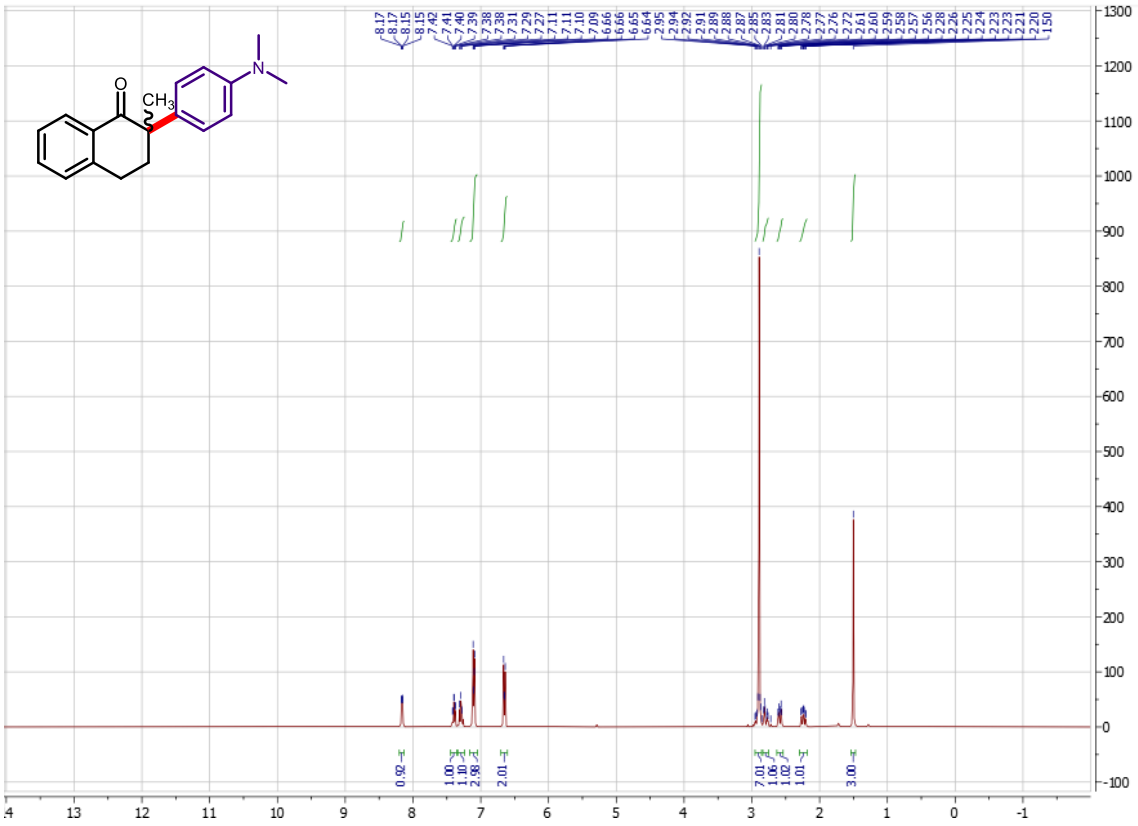
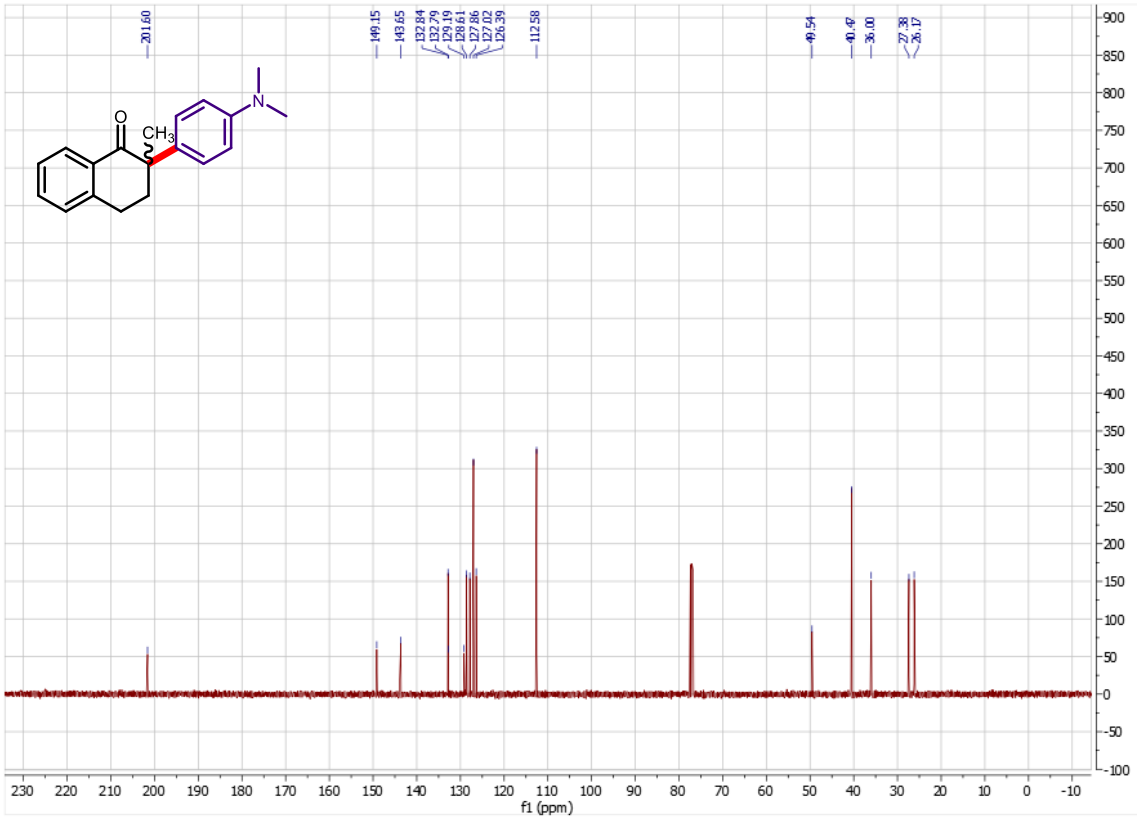
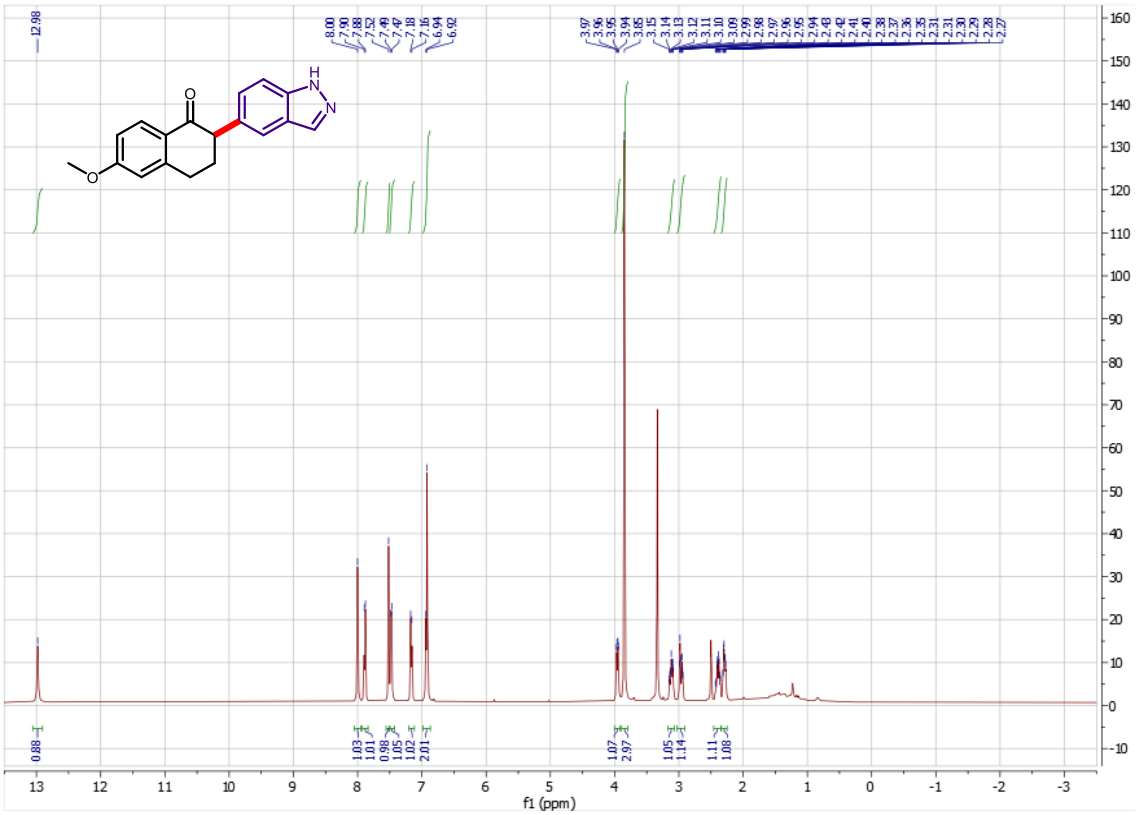
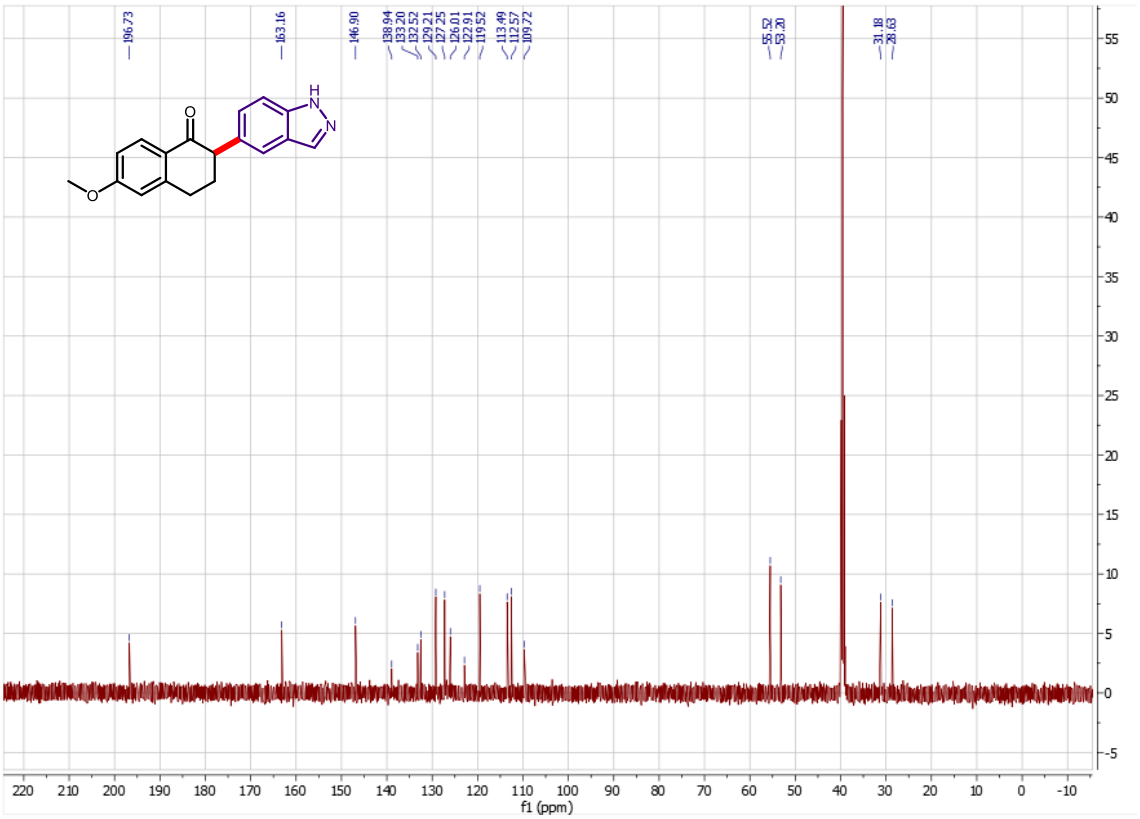
128.80
128.52
116.79
112.20
39.22
20.89
20.28
f1 (ppm)


O
CH3
N


O
CH3
N
f1 (ppm)


f1 (ppm)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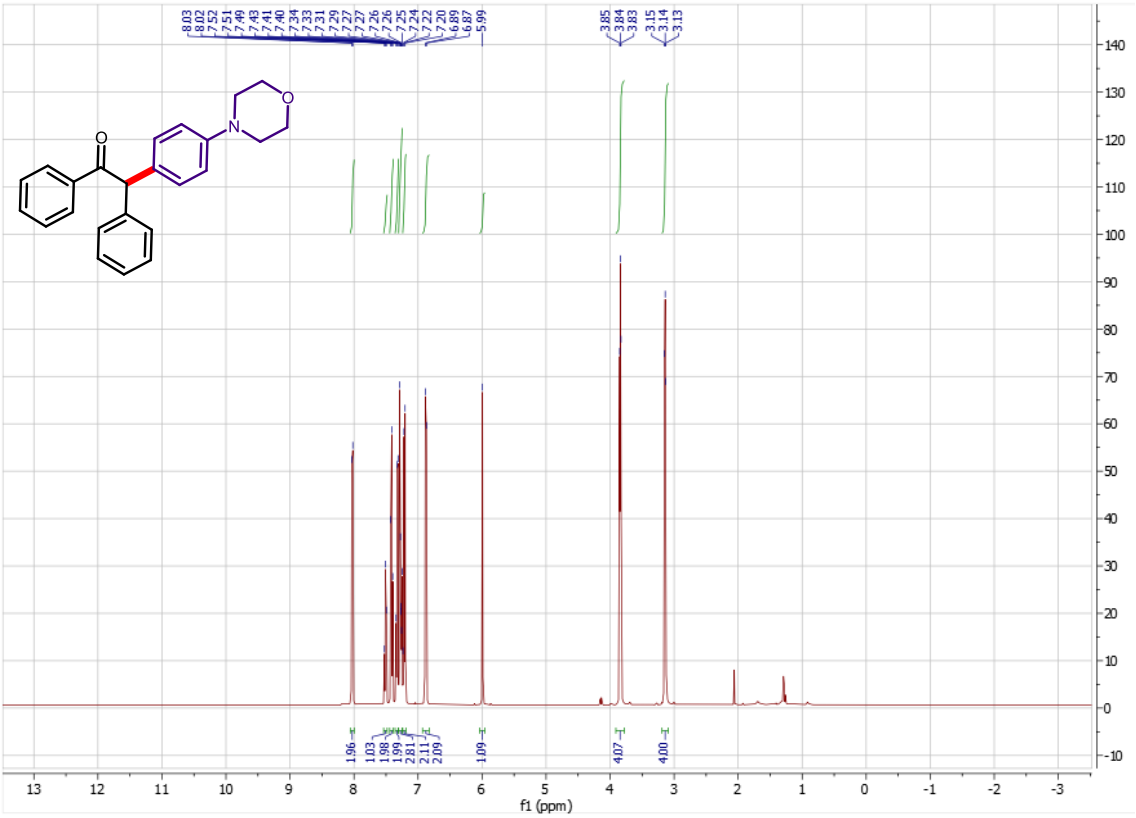
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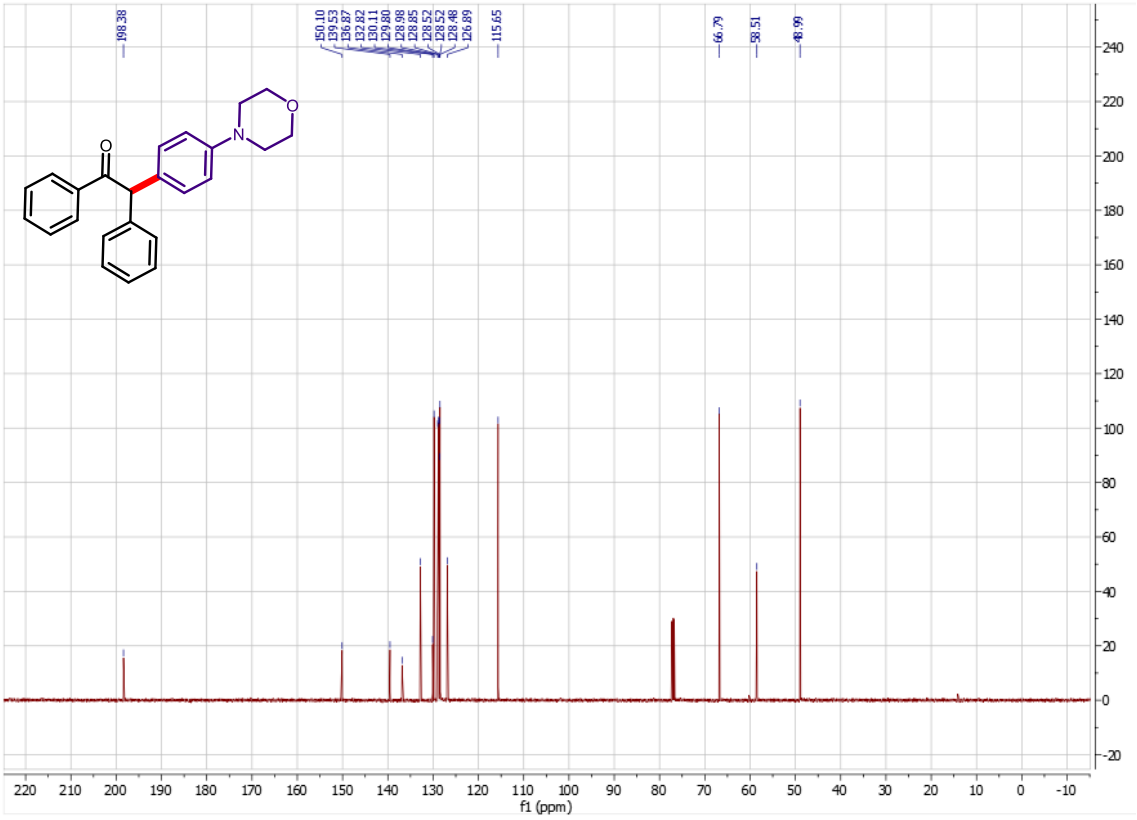
8.02
7.52
7.51
7.49
7.43
7.41
7.40
7.34
7.33
7.31
7.29
7.27
7.27
7.26
7.26
7.25
7.24
7.22
7.20
6.89
6.87
5.99
3.85
3.84
3.83
3.15
3.14
3.13
1.96
1.03
1.98
1.99
2.81
2.11
2.09
1.09
4.07
4.00
f1 (ppm)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150.10
139.53
136.87
132.82
130.11
129.80
128.98
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128.52
128.52
128.48
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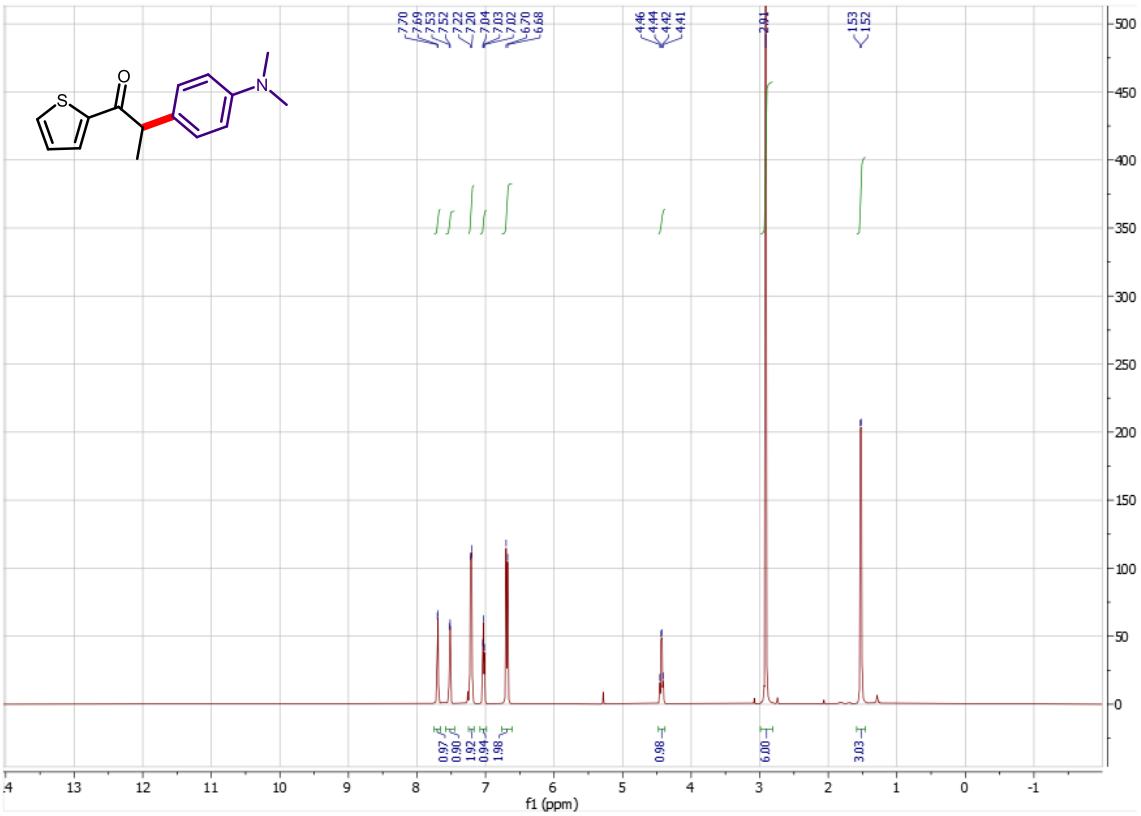
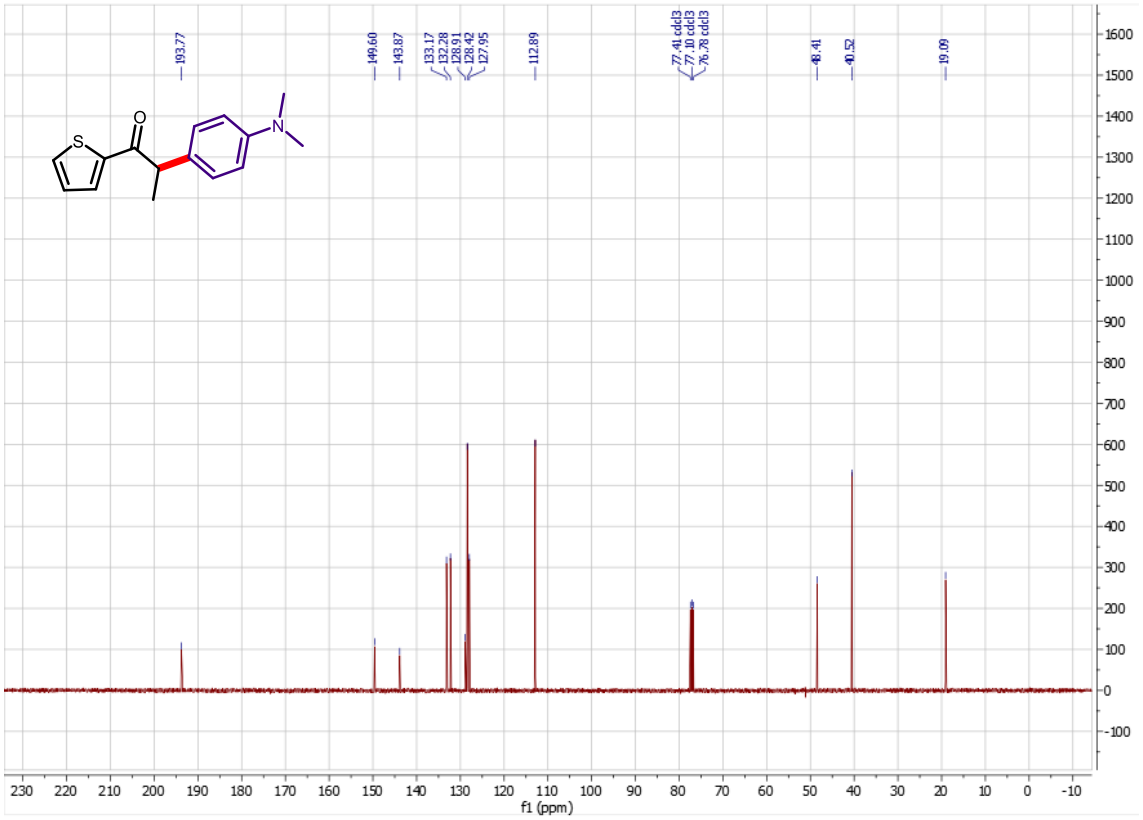
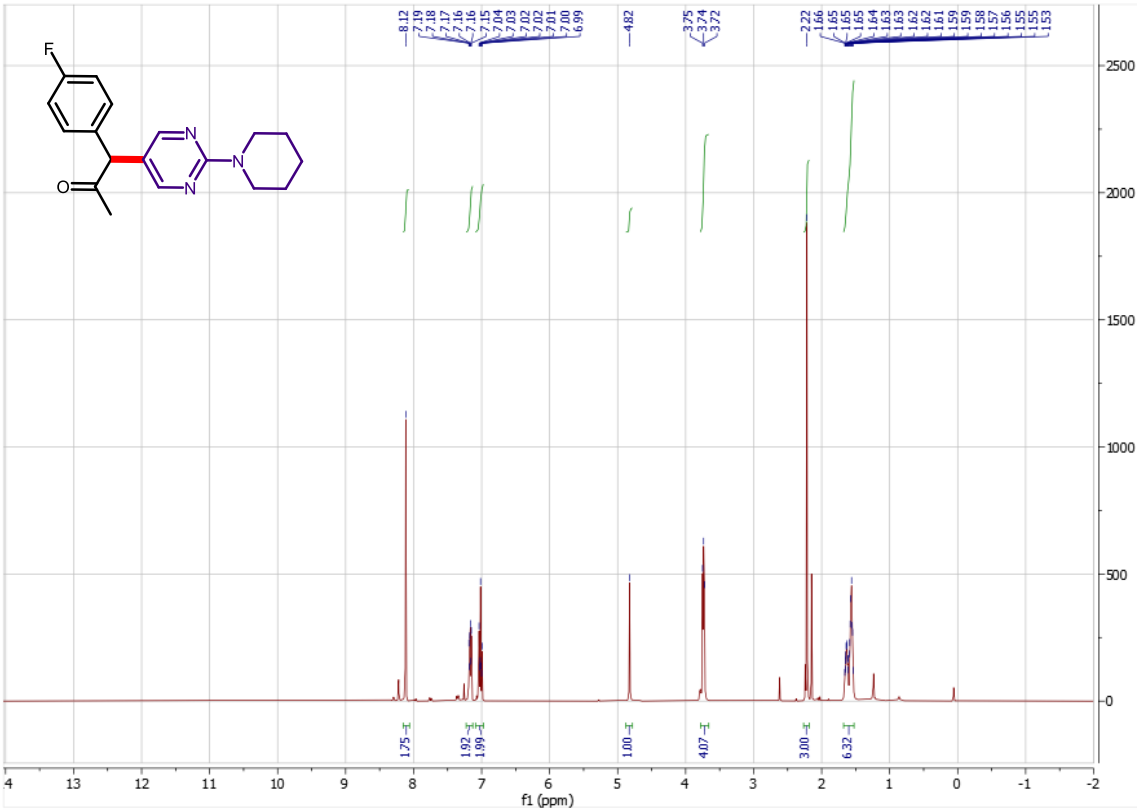
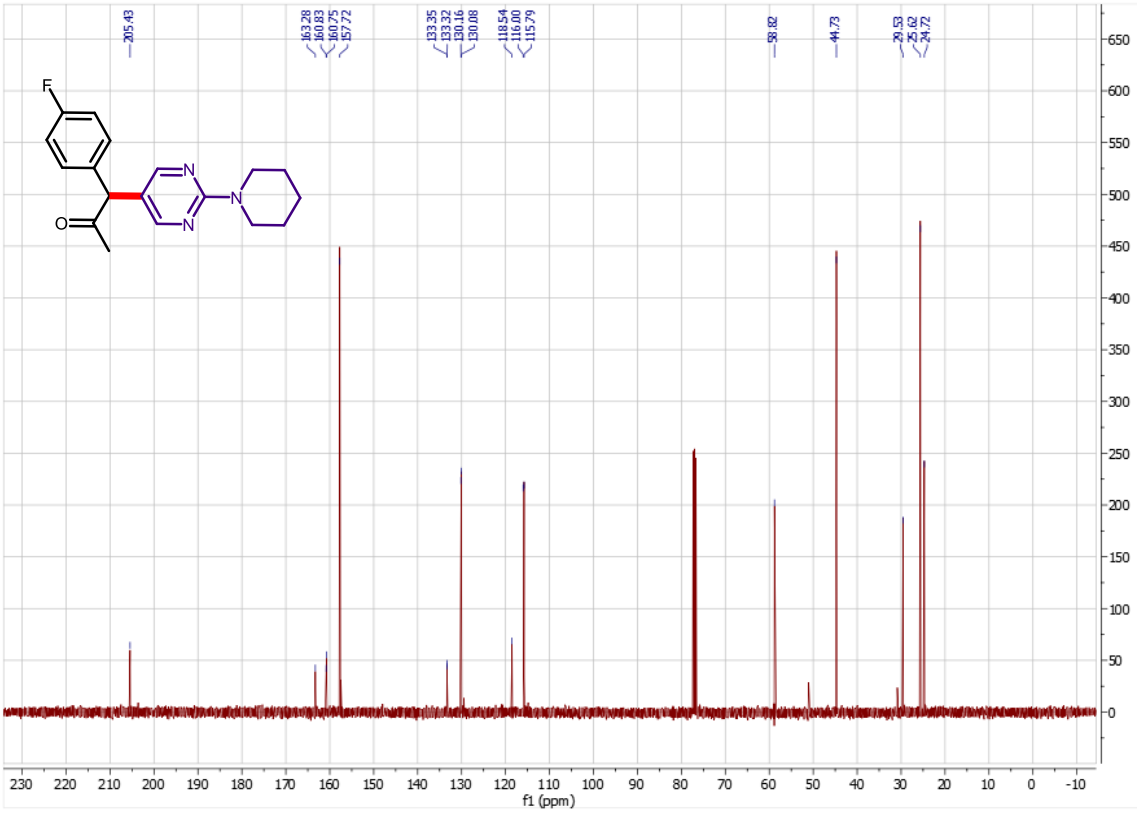
115.65
66.79
58.51
48.99
f1 (ppm)


7.70
7.69
7.53
7.52
7.22
7.20
7.04
7.03
7.02
6.70
6.68
4.46
4.44
4.42
4.41
2.01
1.53
1.52
0.97
0.90
1.92
0.94
1.98
0.98
6.00
3.03
f1 (ppm)


193.77
149.60
143.87
133.17
132.28
128.91
128.42
127.95
112.89
77.41 cdcl3
77.10 cdcl3
76.78 cdcl3
48.41
40.52
19.09
f1 (ppm)


F
O
N
N
N
8.12
7.19
7.18
7.17
7.16
7.16
7.15
7.04
7.03
7.02
7.02
7.01
7.00
6.99
4.82
3.75
3.74
3.72
2.22
1.66
1.65
1.65
1.65
1.64
1.63
1.63
1.62
1.62
1.61
1.59
1.59
1.58
1.57
1.56
1.55
1.55
1.53
1.75
1.92
1.99
1.00
4.07
3.00
6.32
f1 (ppm)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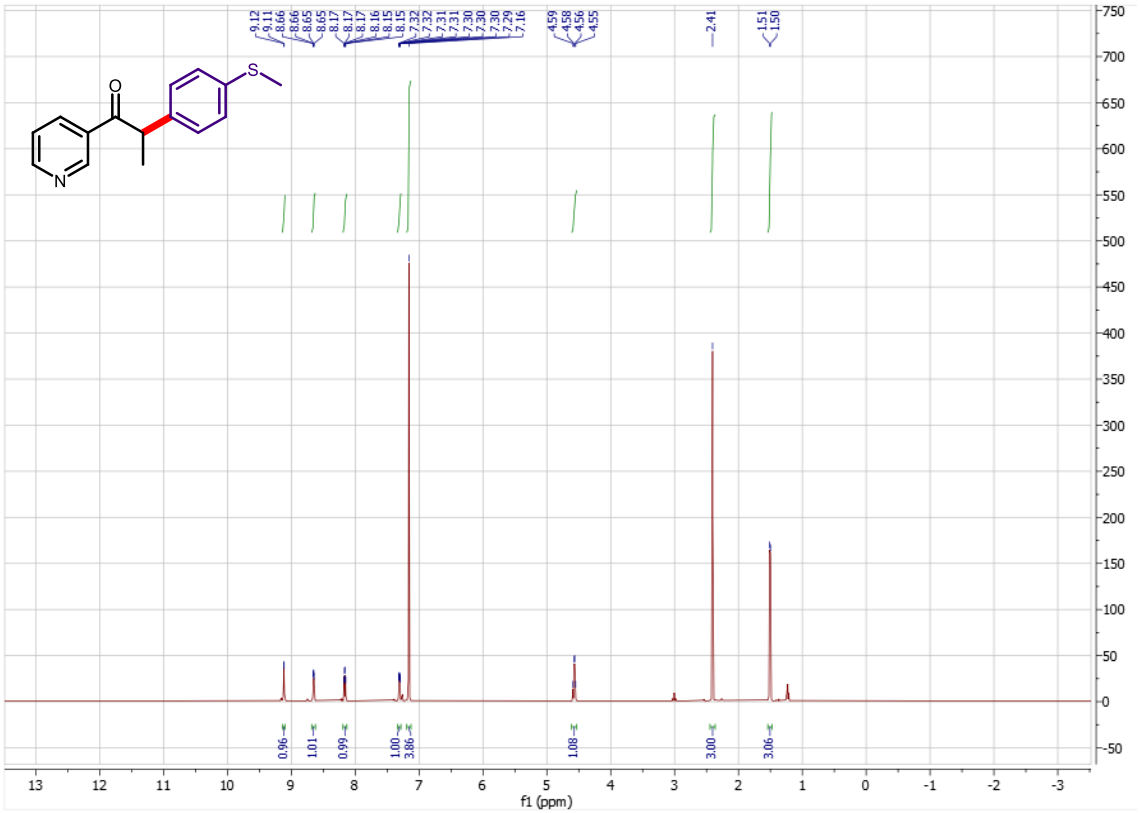
O
N
N
N
205.43
163.28
160.83
160.75
157.72
133.35
133.32
130.16
130.08
118.54
116.00
115.79
58.82
44.73
29.53
25.62
24.72
f1 (ppm)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9.11
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8.66
8.65
8.65
8.17
8.17
8.17
8.16
8.15
8.15
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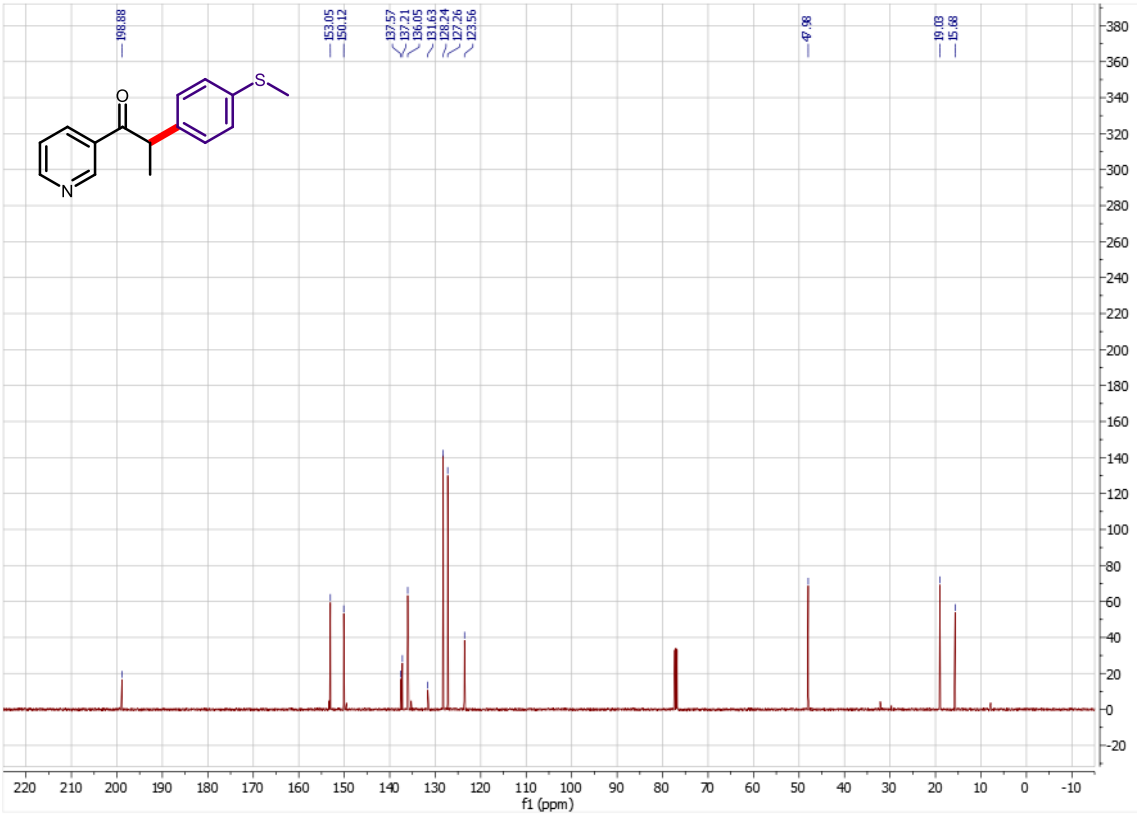
7.32
7.31
7.31
7.30
7.30
7.30
7.29
7.16
4.59
4.58
4.56
4.55
2.41
1.51
1.50
0.96
1.01
0.99
1.00
3.86
1.08
3.00
3.06
f1 (ppm)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153.05
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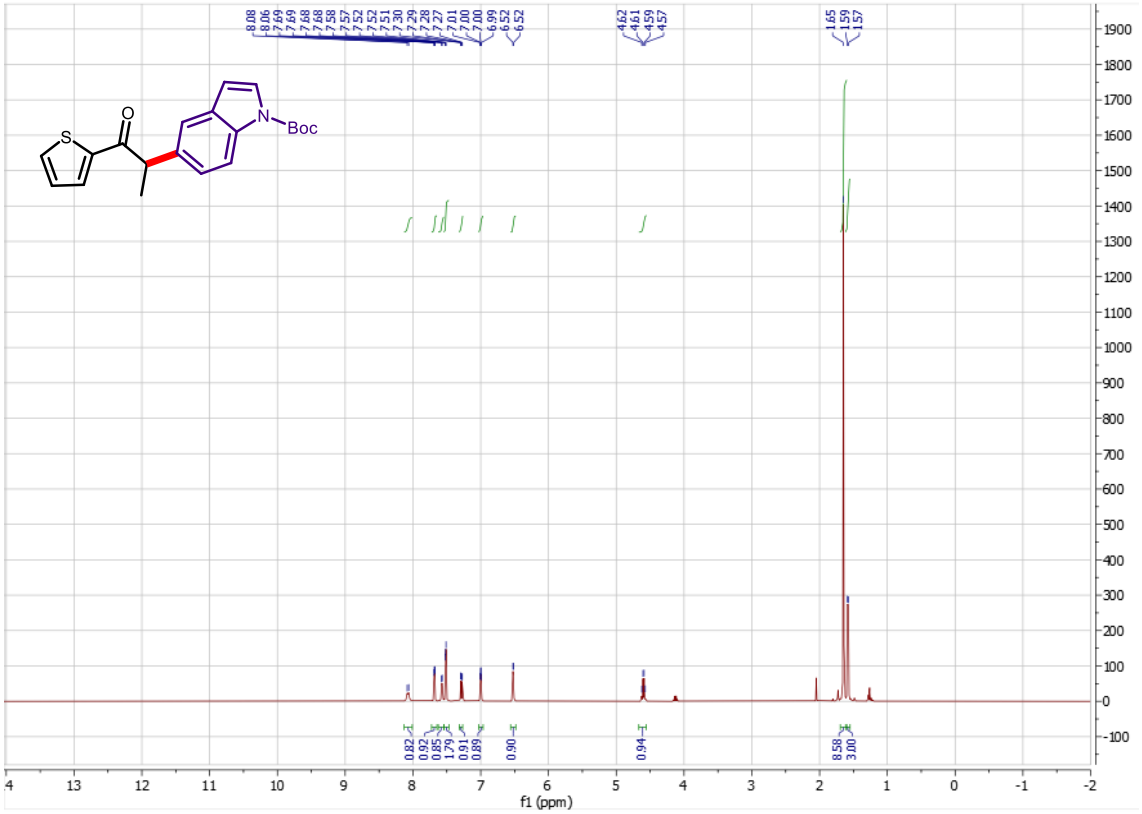
136.05
131.63
128.24
127.26
123.56
47.98
19.03
15.68
f1 (ppm)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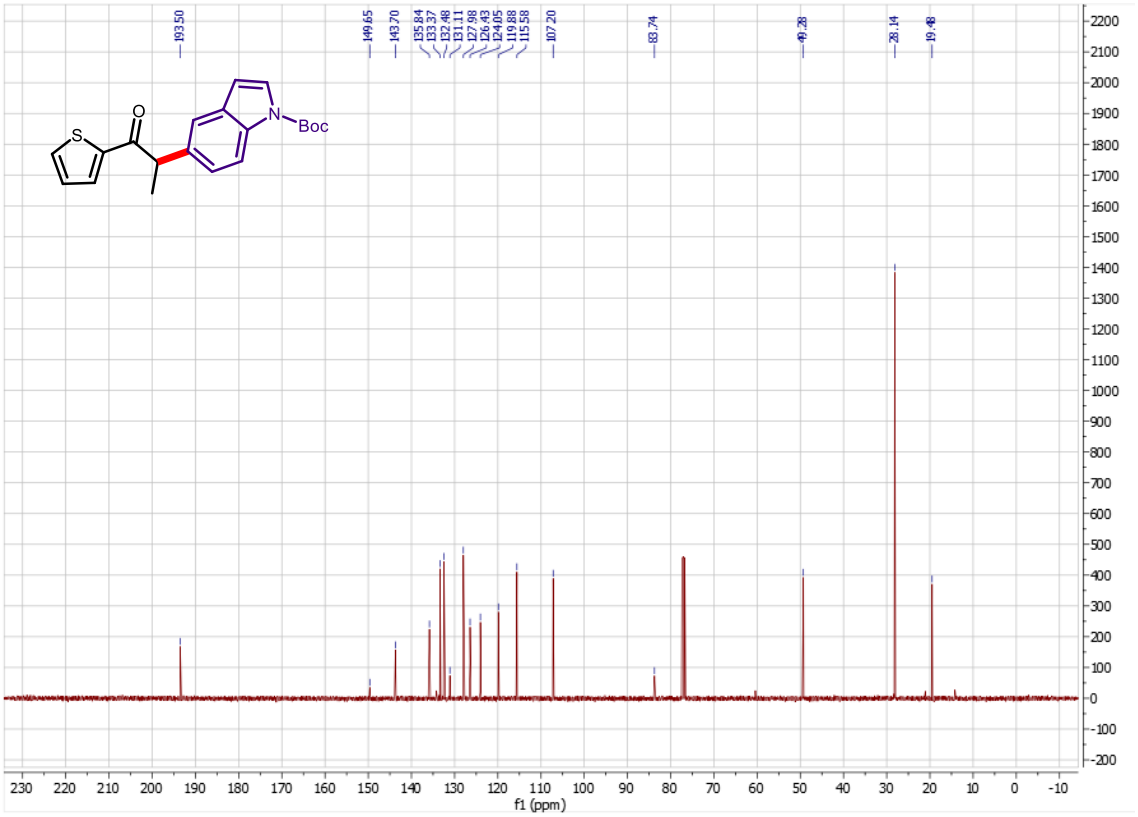
8.06
7.69
7.69
7.68
7.68
7.58
7.57
7.52
7.51
7.30
7.29
7.28
7.27
7.01
7.00
7.00
6.99
6.52
6.52
4.62
4.61
4.59
4.57
1.65
1.59
1.57
O
S
N
Boc
0.82
0.92
0.85
1.79
0.91
0.89
0.90
0.94
8.58
3.00
f1 (ppm)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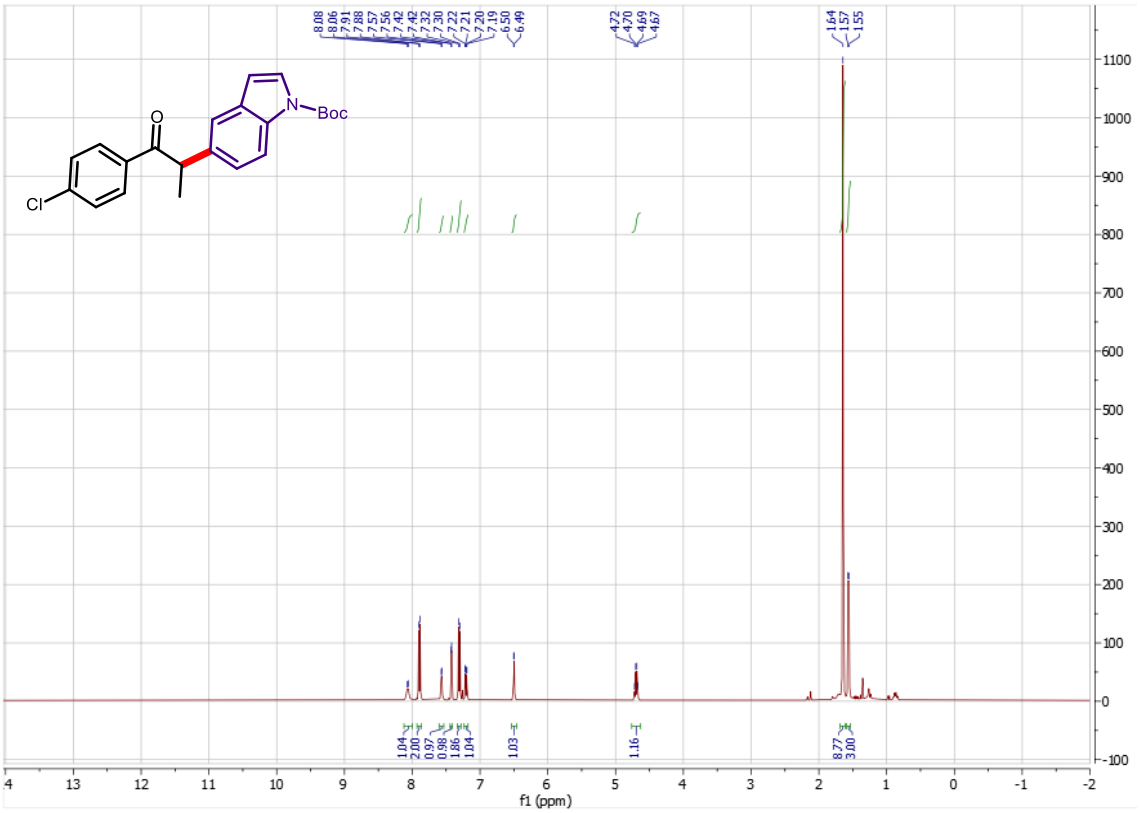
132.48
131.11
127.98
126.43
124.05
119.88
115.58
107.20
83.74
49.28
28.14
19.48
O
S
N
Boc
f1 (ppm)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7.91
7.88
7.57
7.56
7.42
7.42
7.32
7.30
7.22
7.21
7.20
7.19
6.50
6.49
4.72
4.70
4.69
4.67
1.64
1.57
1.55
Boc
N
O
Cl
1.04
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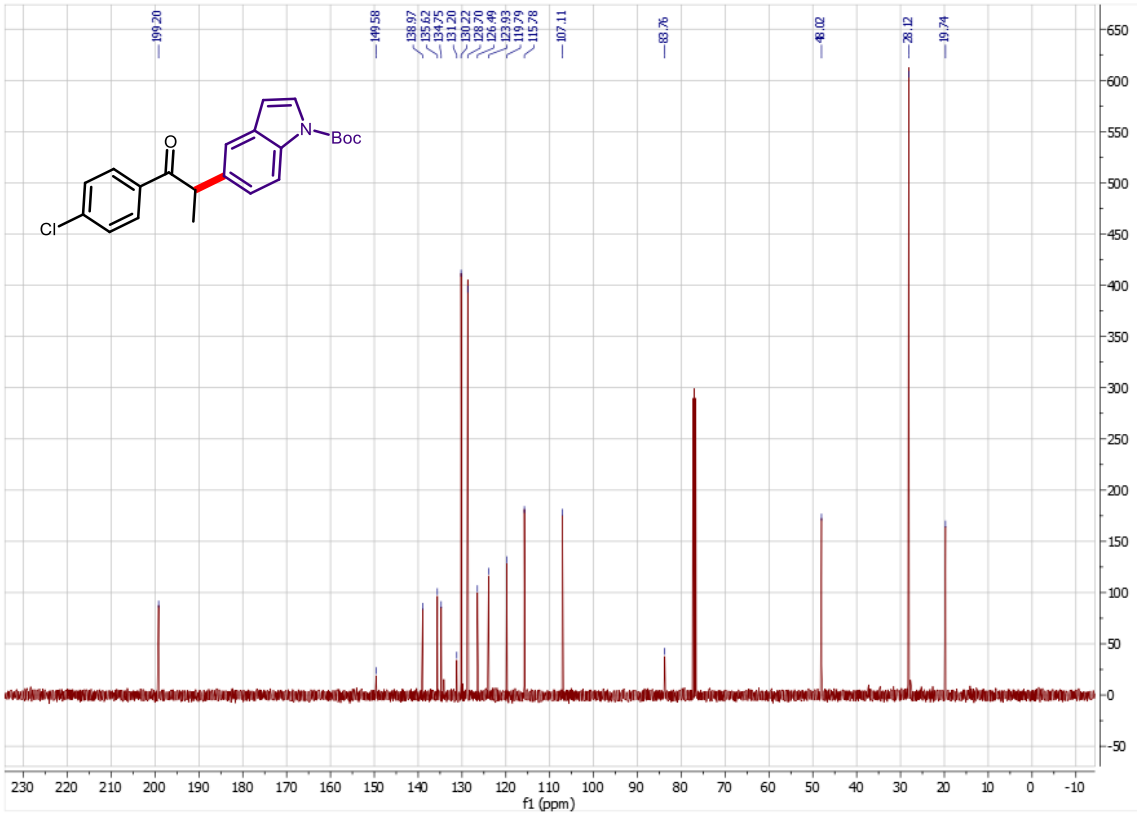
0.97
0.98
1.86
1.04
1.03
1.16
8.77
3.00
f1 (ppm)


199.20
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131.20
130.22
128.70
126.49
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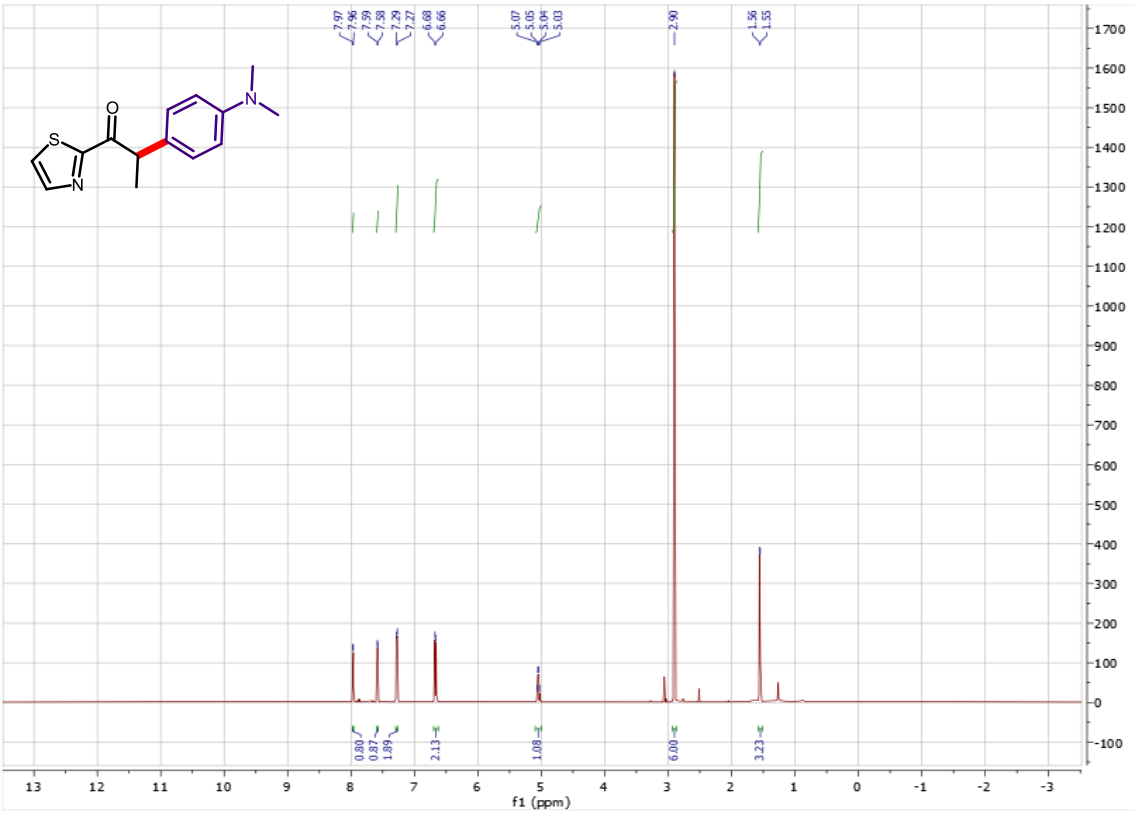
119.79
115.78
107.11
83.76
48.02
28.12
19.74
Boc
N
O
Cl
f1 (ppm)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7.96
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7.58
7.29
7.27
6.68
6.66
5.07
5.05
5.04
5.03
2.90
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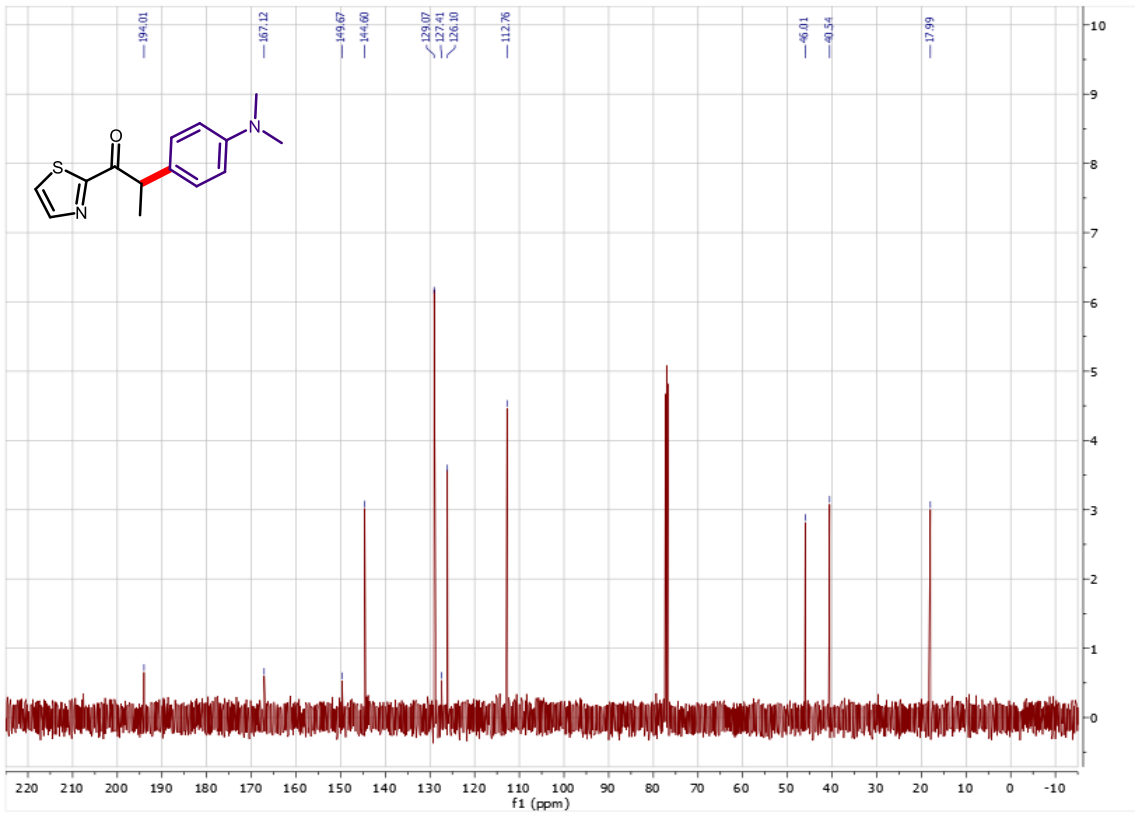
1.55
0.80
0.87
1.89
2.13
1.08
6.00
3.23
f1 (ppm)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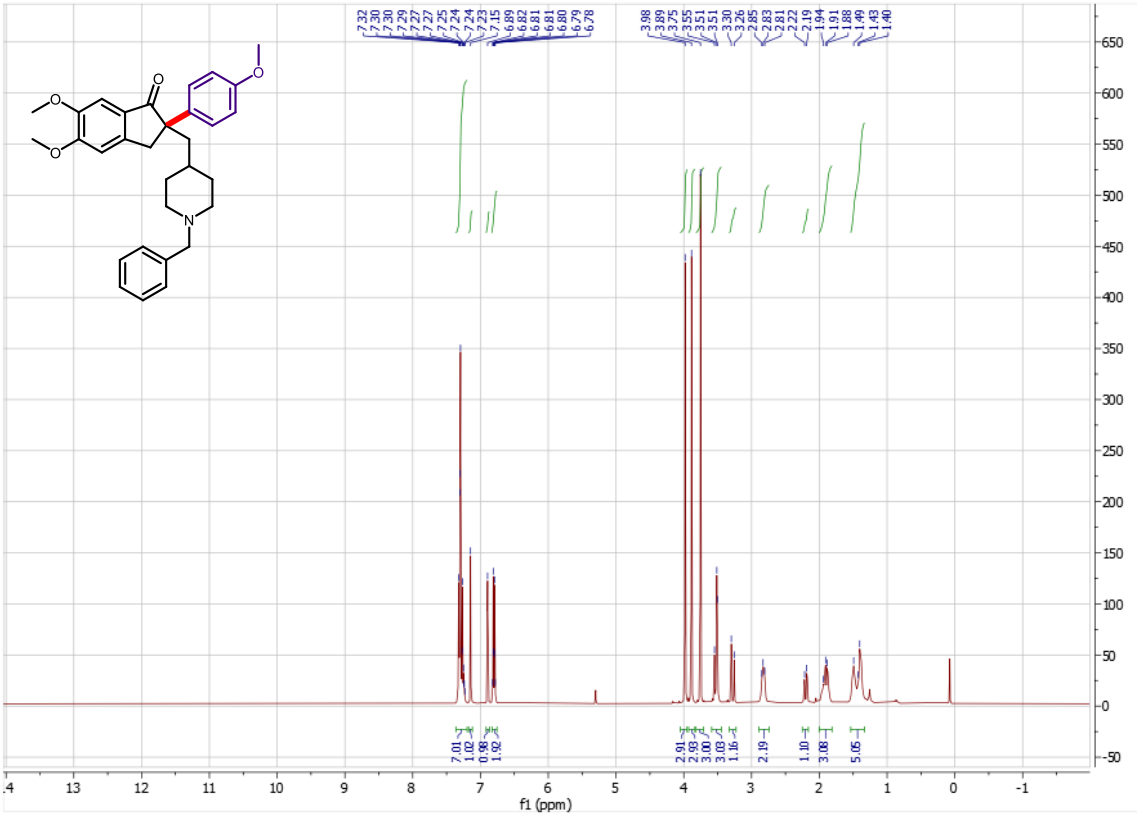
112.76
46.01
40.54
17.99
f1 (ppm)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7.23
7.15
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6.81
6.81
6.80
6.79
6.78
3.98
3.89
3.75
3.55
3.51
3.51
3.30
3.26
2.85
2.83
2.81
2.22
2.19
1.94
1.91
1.88
1.49
1.48
1.46
7.01
1.02
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1.92
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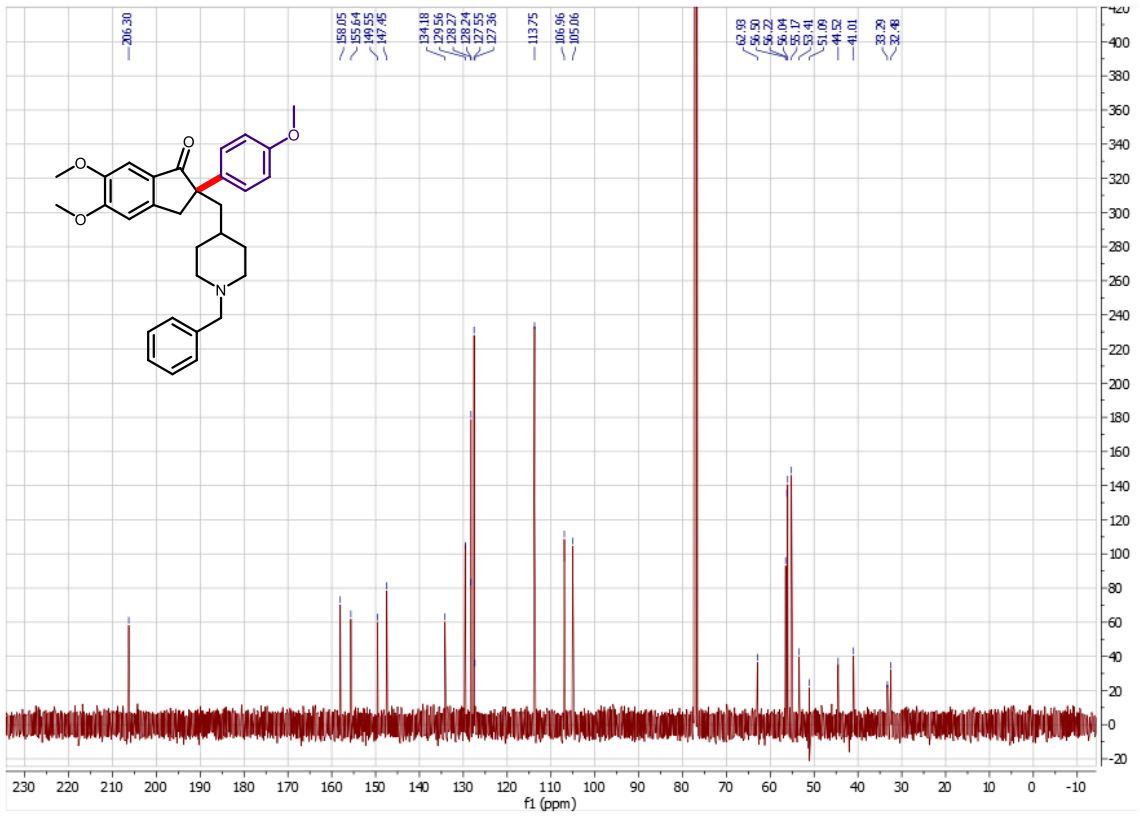
2.93
2.00
3.03
1.16
2.19
1.10
3.08
5.05
f1 (ppm)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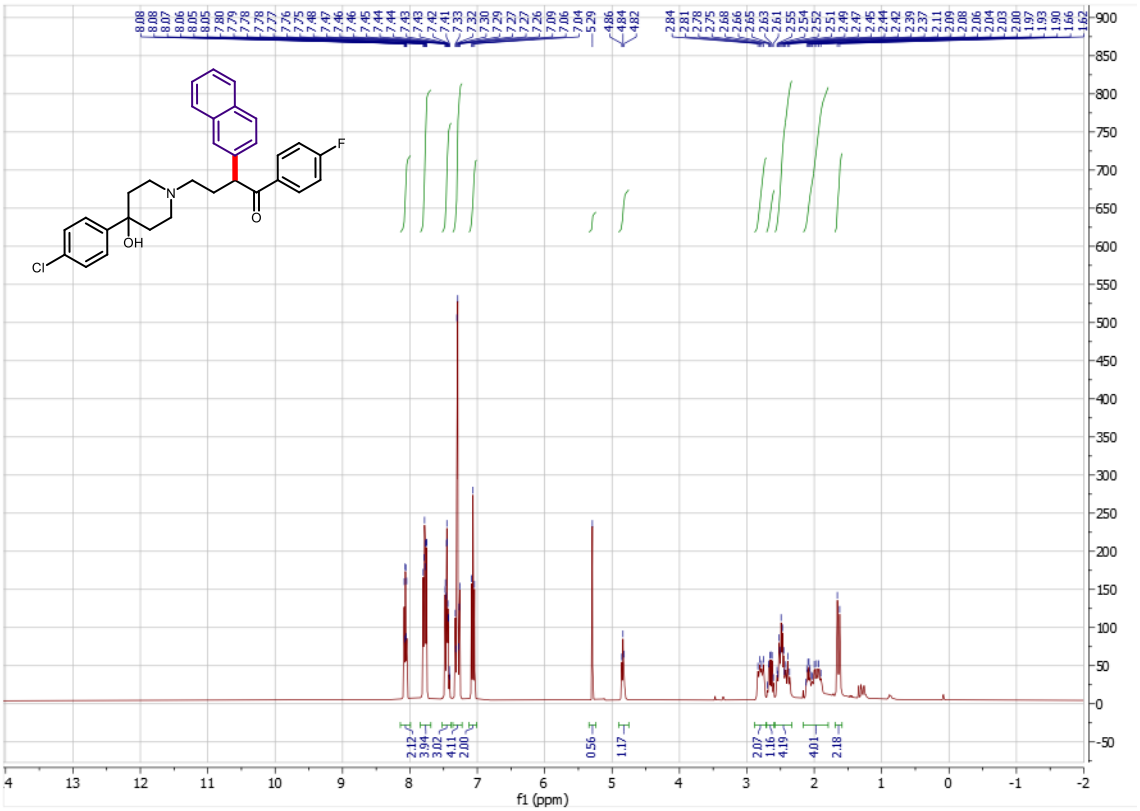
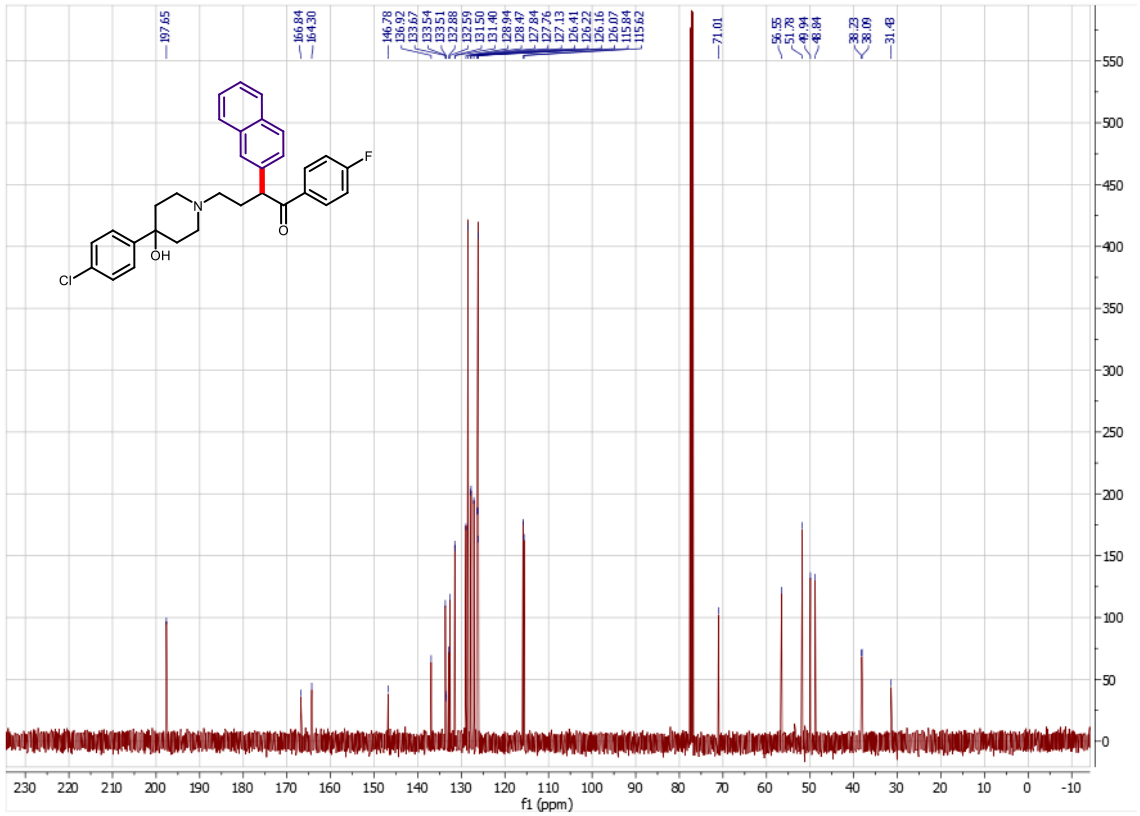
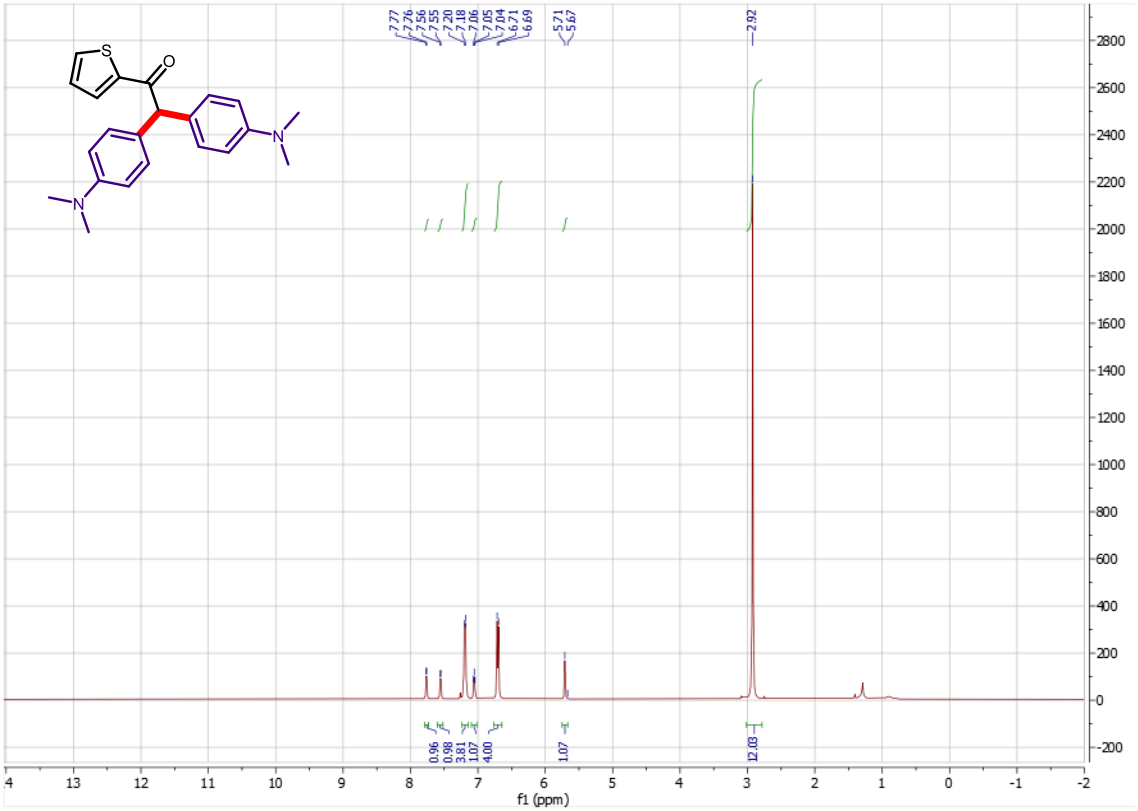
128.27
128.24
127.55
127.36
113.75
106.96
105.06
62.93
56.50
56.22
56.04
55.17
53.41
51.09
44.52
41.01
33.29
32.48
f1 (ppm)


F
N
O
OH
Cl
f1 (ppm)


F
N
O
OH
Cl
f1 (ppm)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7.18
7.06
7.05
7.04
6.71
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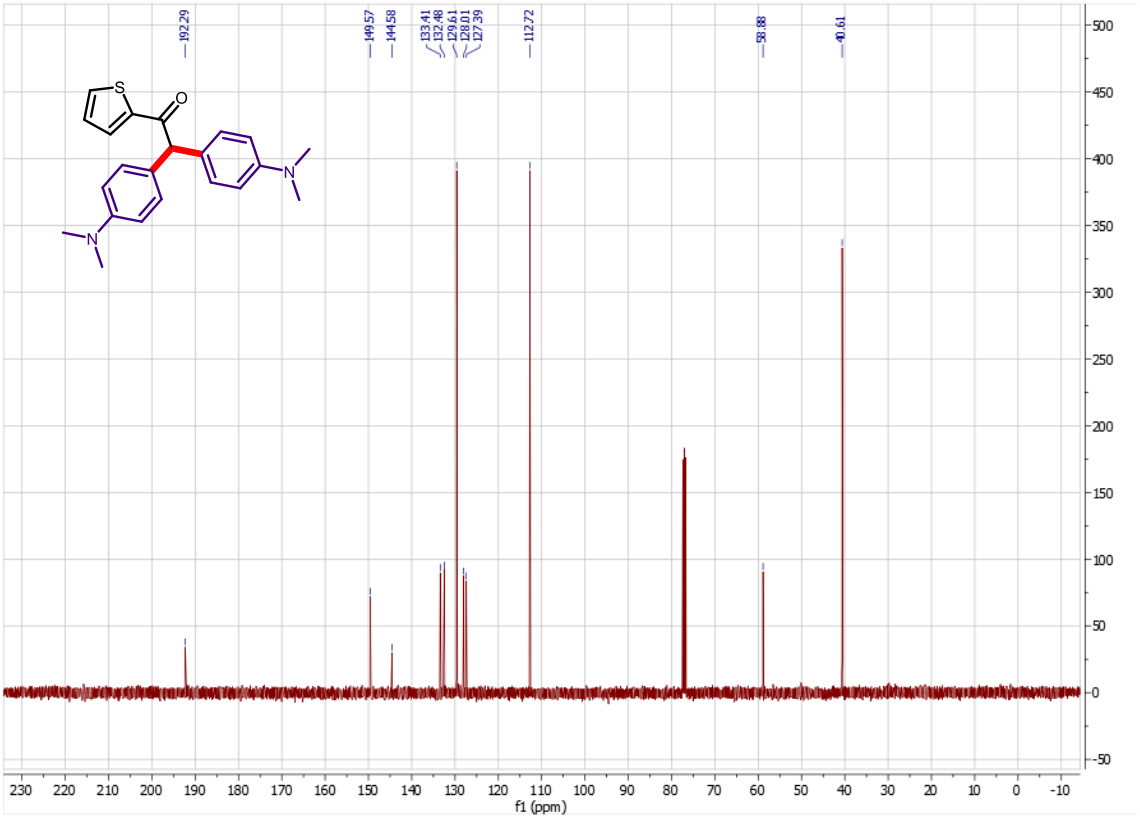
5.71
5.67
2.92
0.96
0.98
3.81
1.07
4.00
1.07
12.03
f1 (ppm)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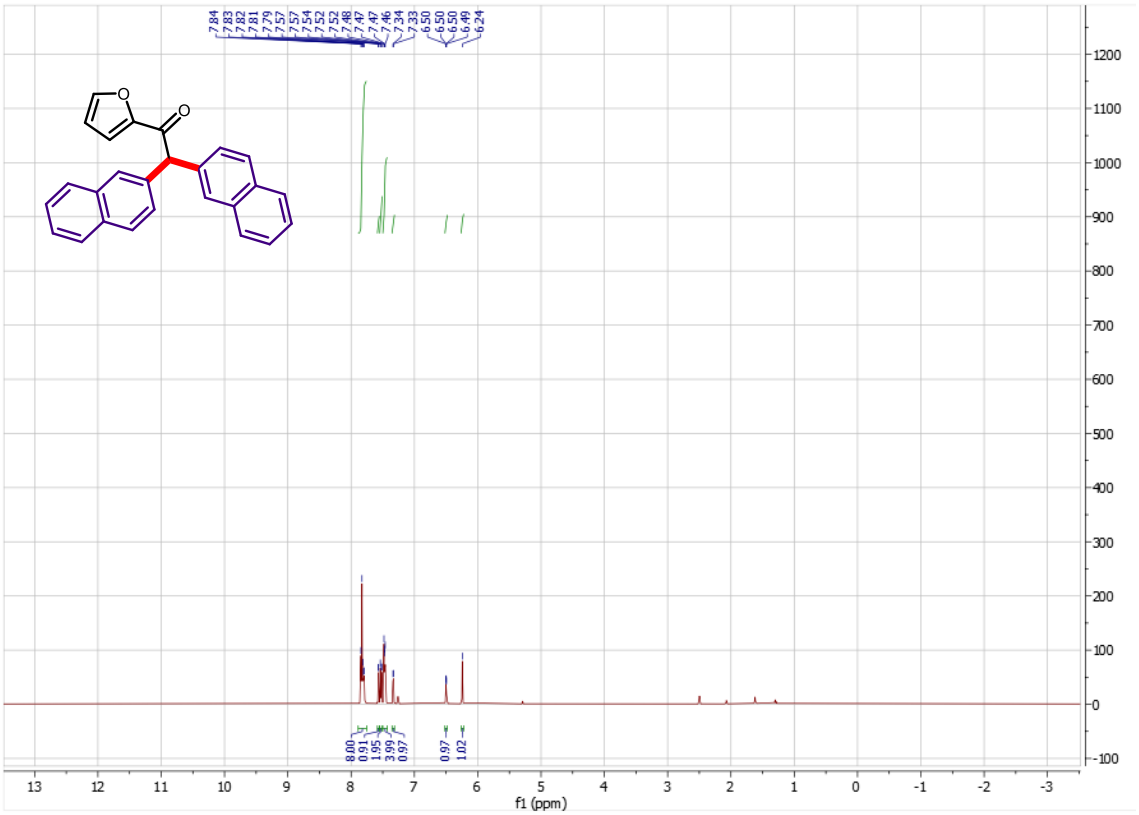
129.61
128.01
127.39
112.72
59.88
40.61
f1 (ppm)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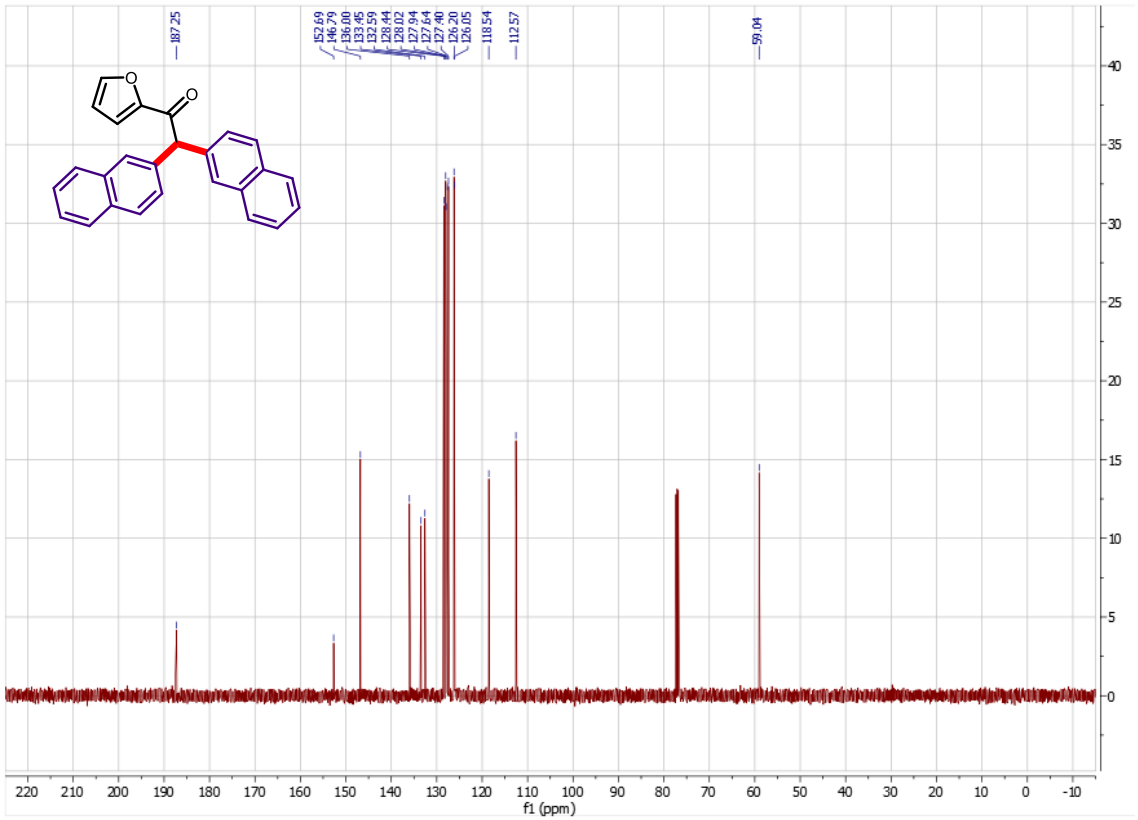
7.52
7.48
7.47
7.47
7.46
7.34
7.33
6.50
6.50
6.50
6.49
6.24
8.00
0.91
1.95
3.99
0.97
0.97
1.02
f1 (ppm)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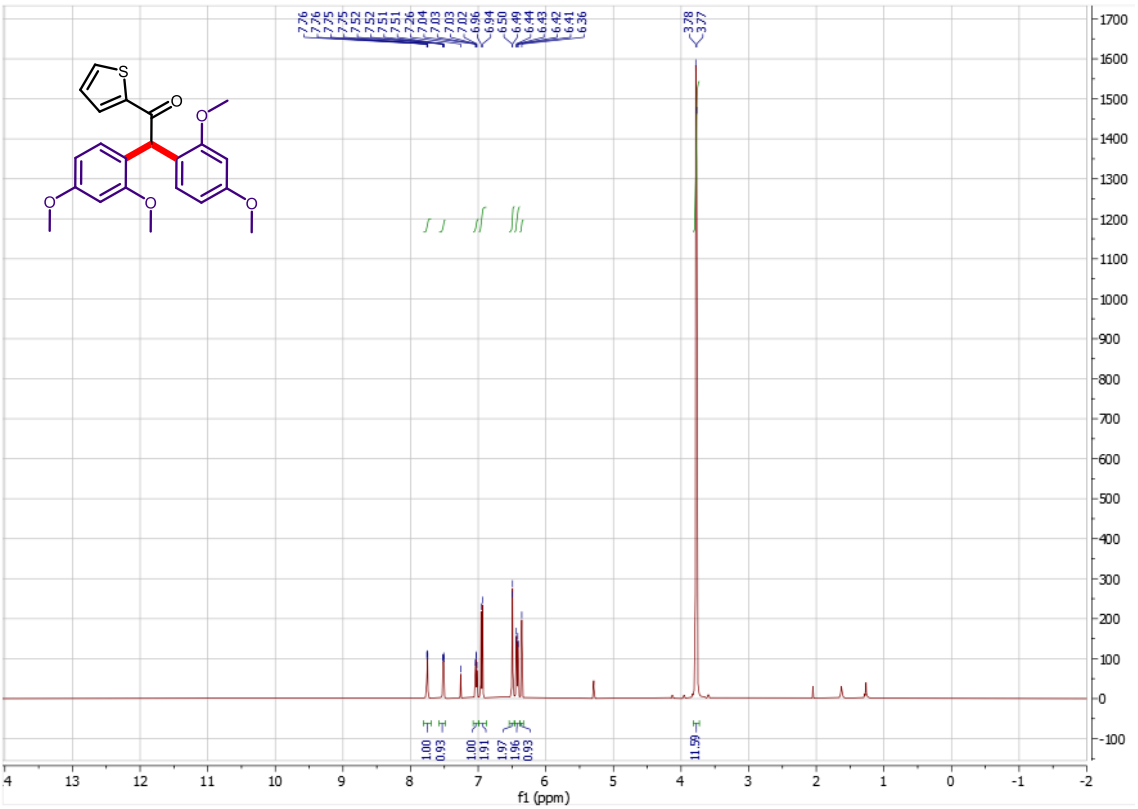
127.64
127.40
126.20
126.05
118.54
112.57
59.04
f1 (ppm)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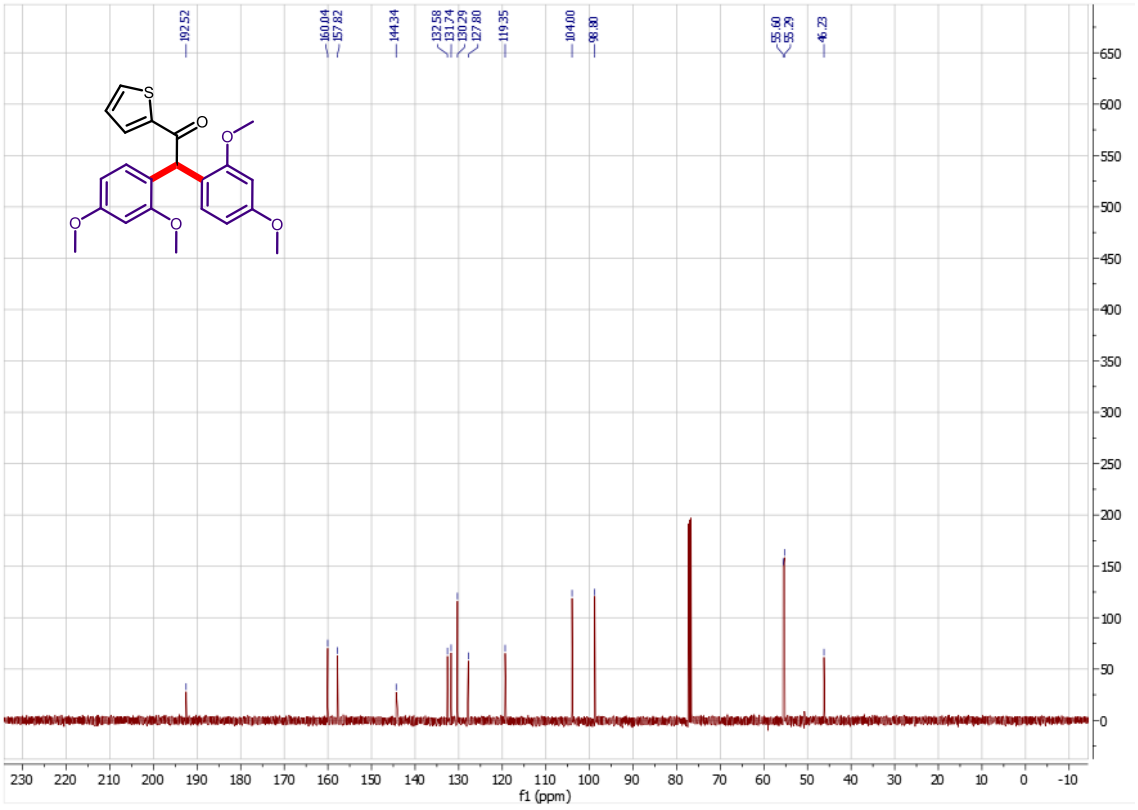
7.25
7.25
7.52
7.52
7.51
7.51
7.04
7.03
7.03
7.02
6.96
6.94
6.50
6.49
6.44
6.43
6.42
6.41
6.36
3.78
3.77
1.00
0.93
1.00
1.91
1.97
1.96
0.93
11.59
f1 (ppm)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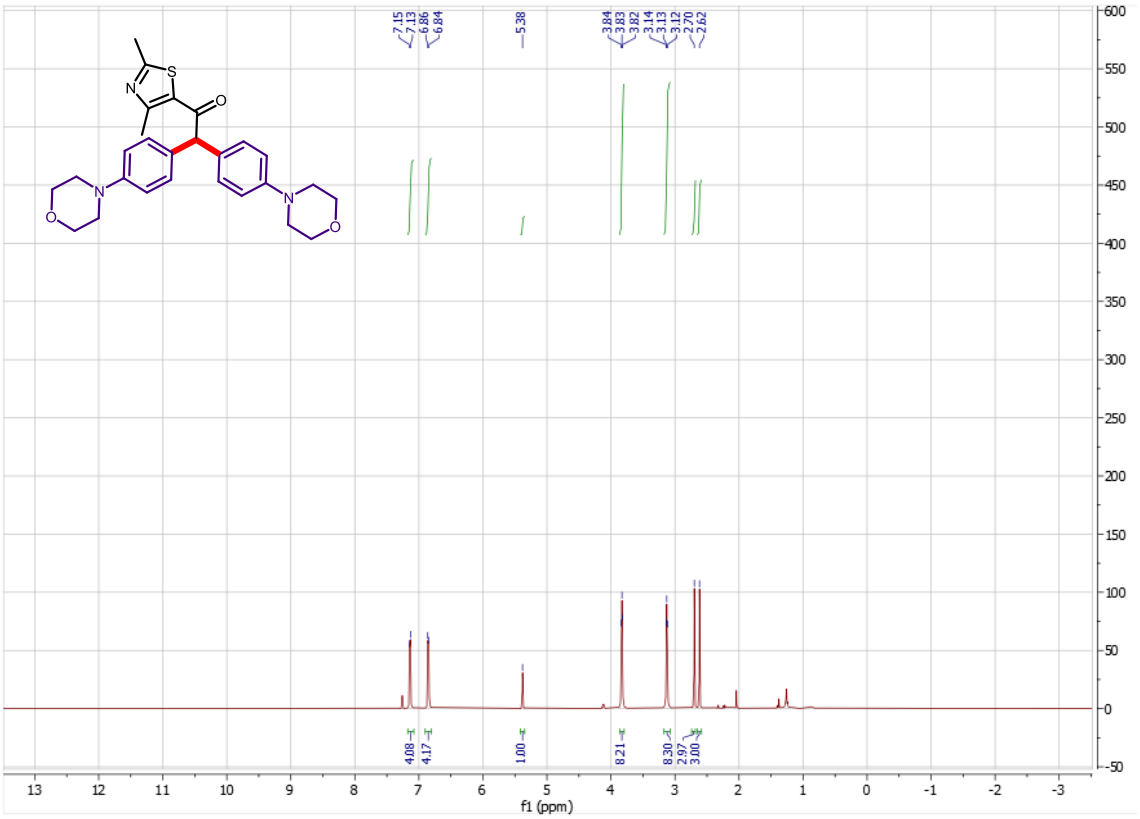
160.04
157.82
144.34
132.58
131.74
130.29
127.80
119.35
104.00
98.80
55.60
55.29
46.23
f1 (ppm)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7.13
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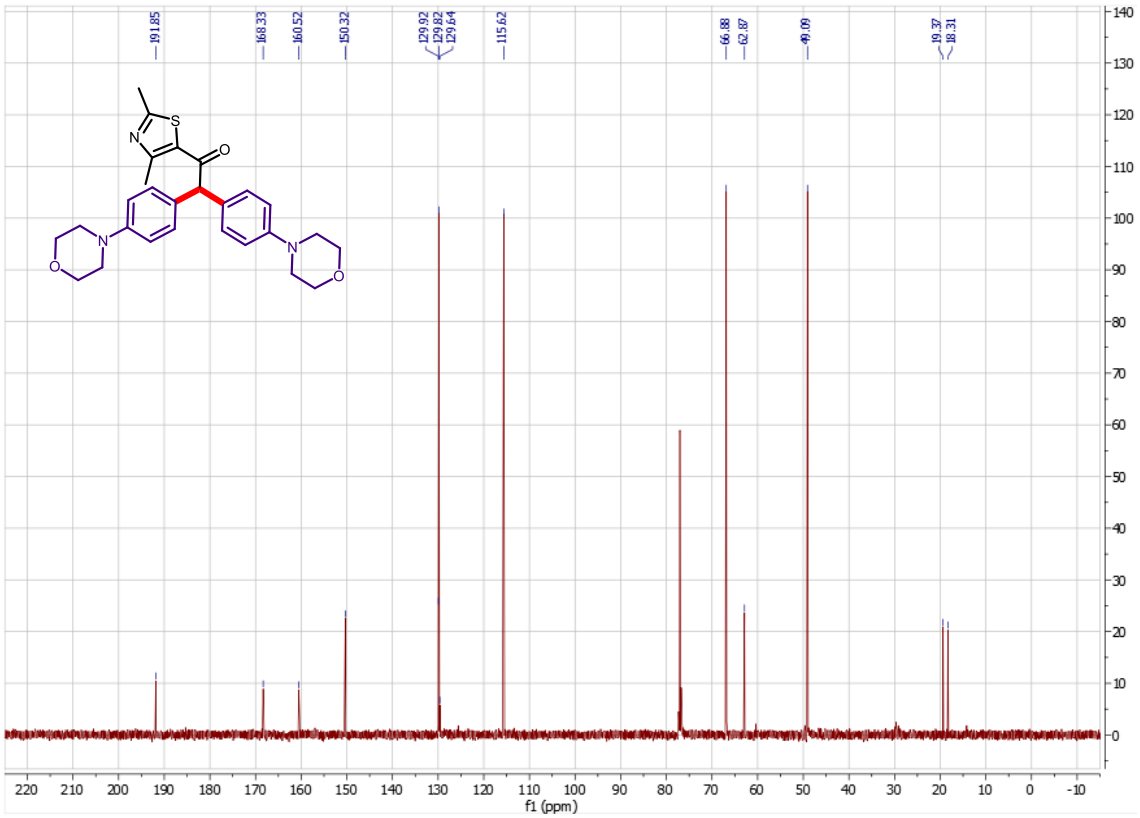
6.84
5.38
3.84
3.83
3.82
3.14
3.13
3.12
2.70
2.62
4.08
4.17
1.00
8.21
8.30
2.97
3.00
f1 (ppm)


191.85
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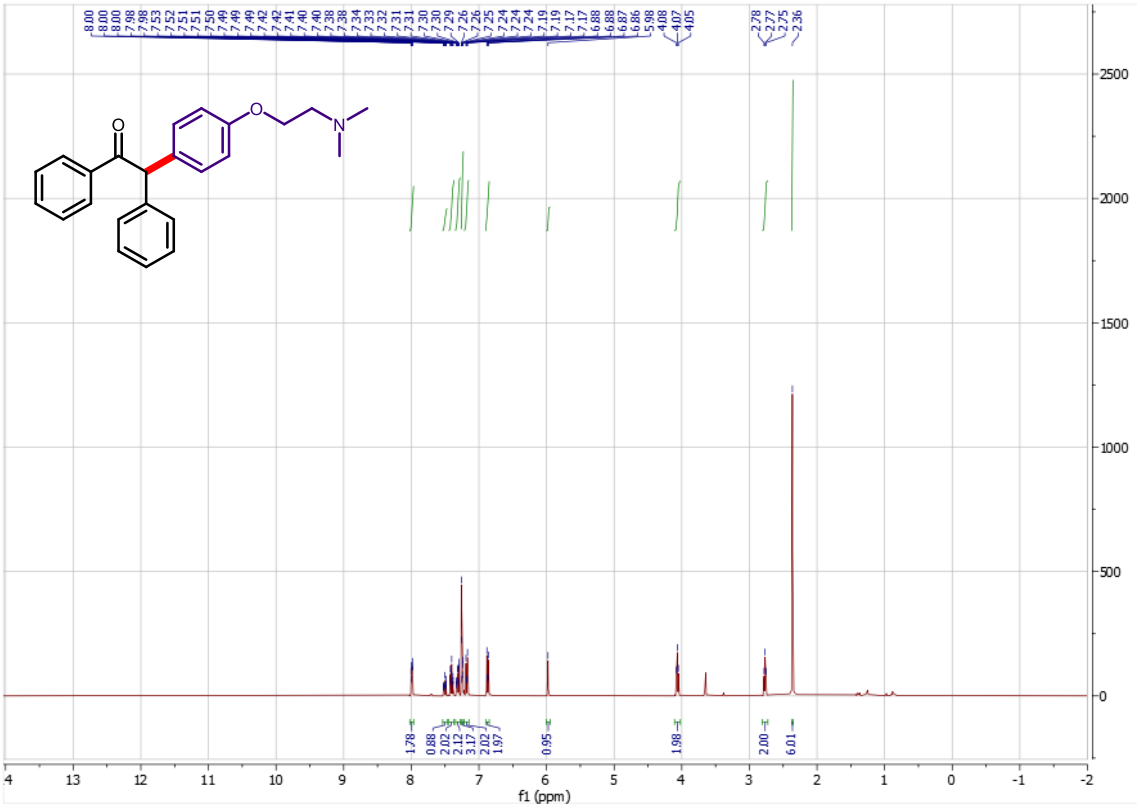
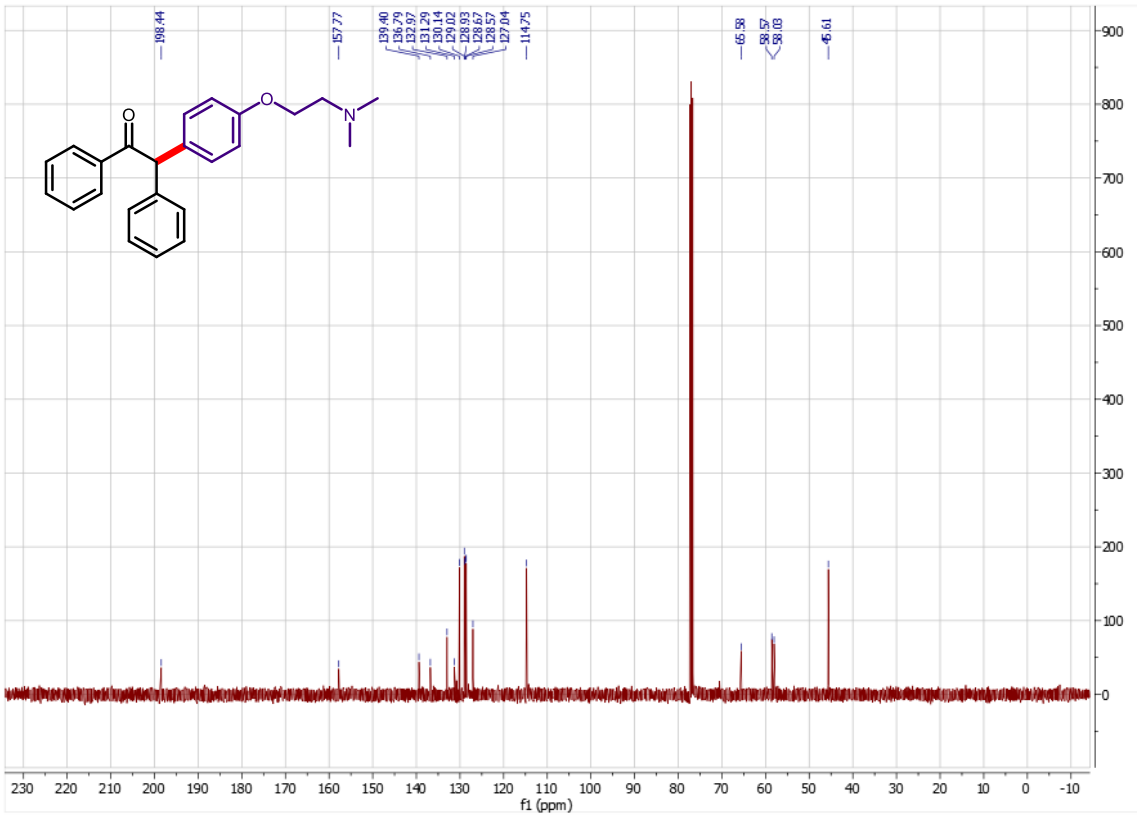
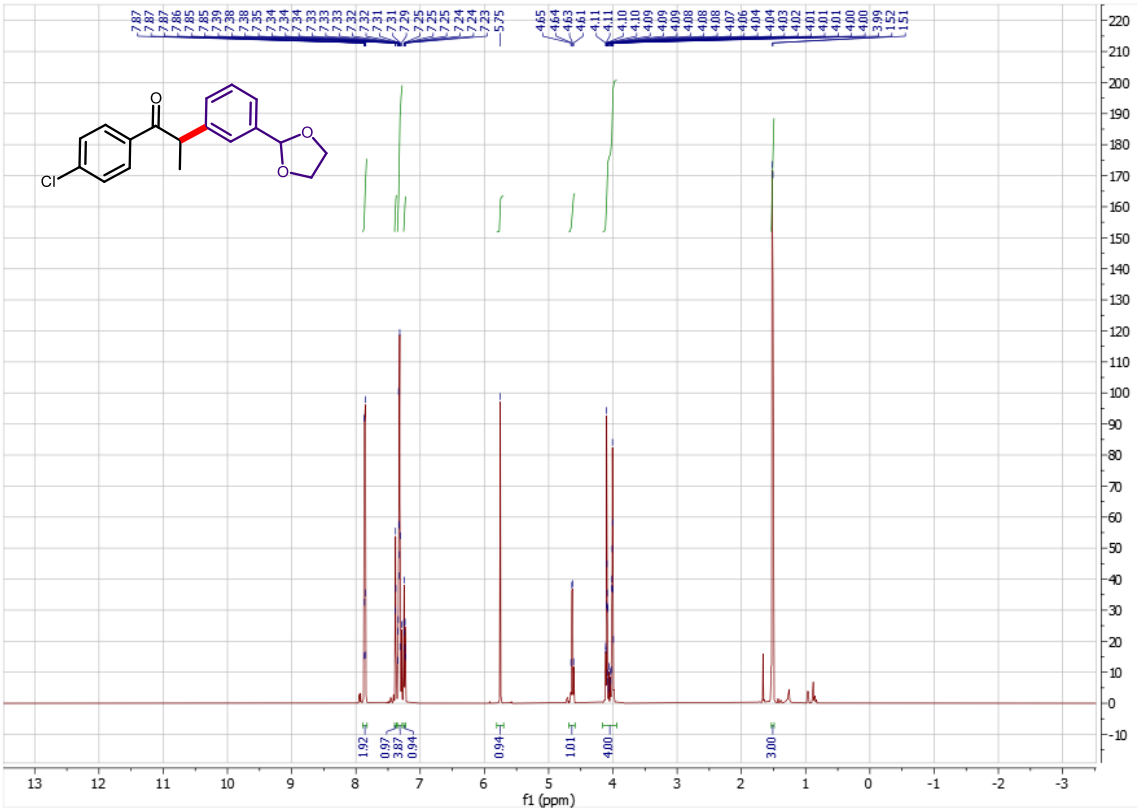
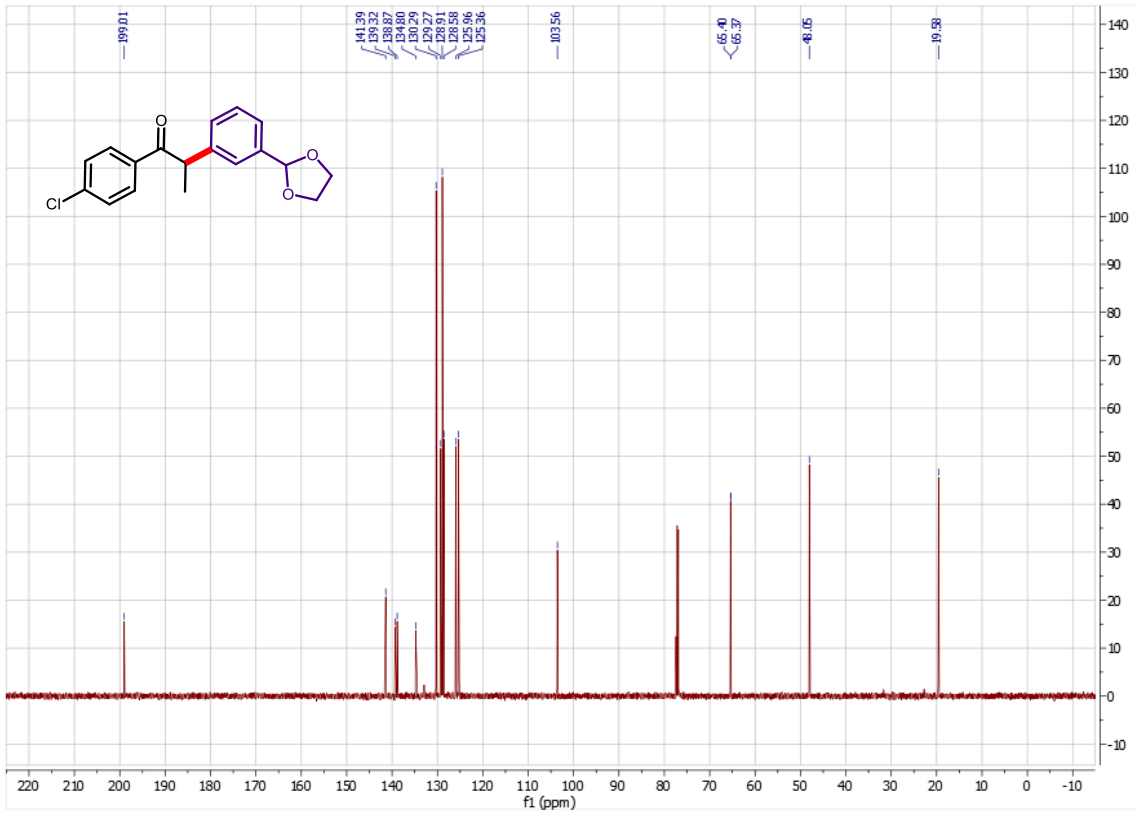
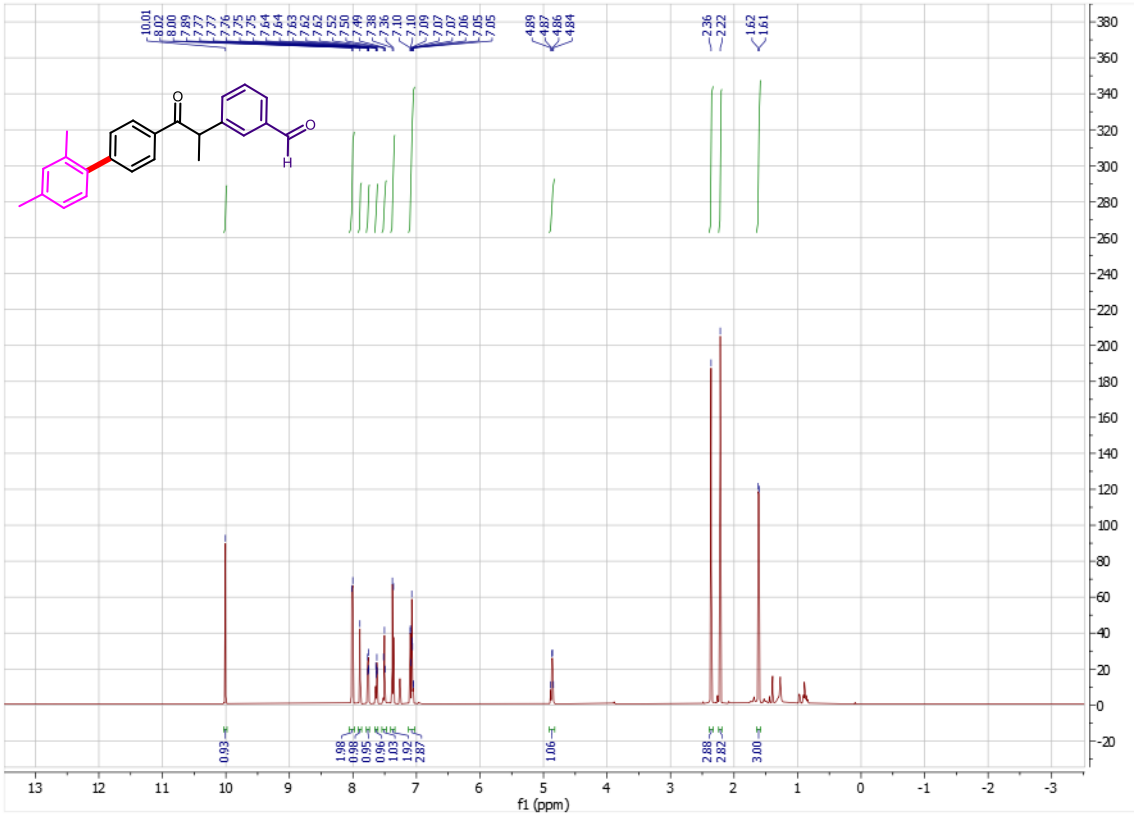
129.92
129.82
129.64
115.62
66.88
62.87
49.09
19.37
18.31
f1 (ppm)


f1 (ppm)


f1 (ppm)


Cl
O
O
O
f1 (ppm)


Cl
O
O
O
f1 (ppm)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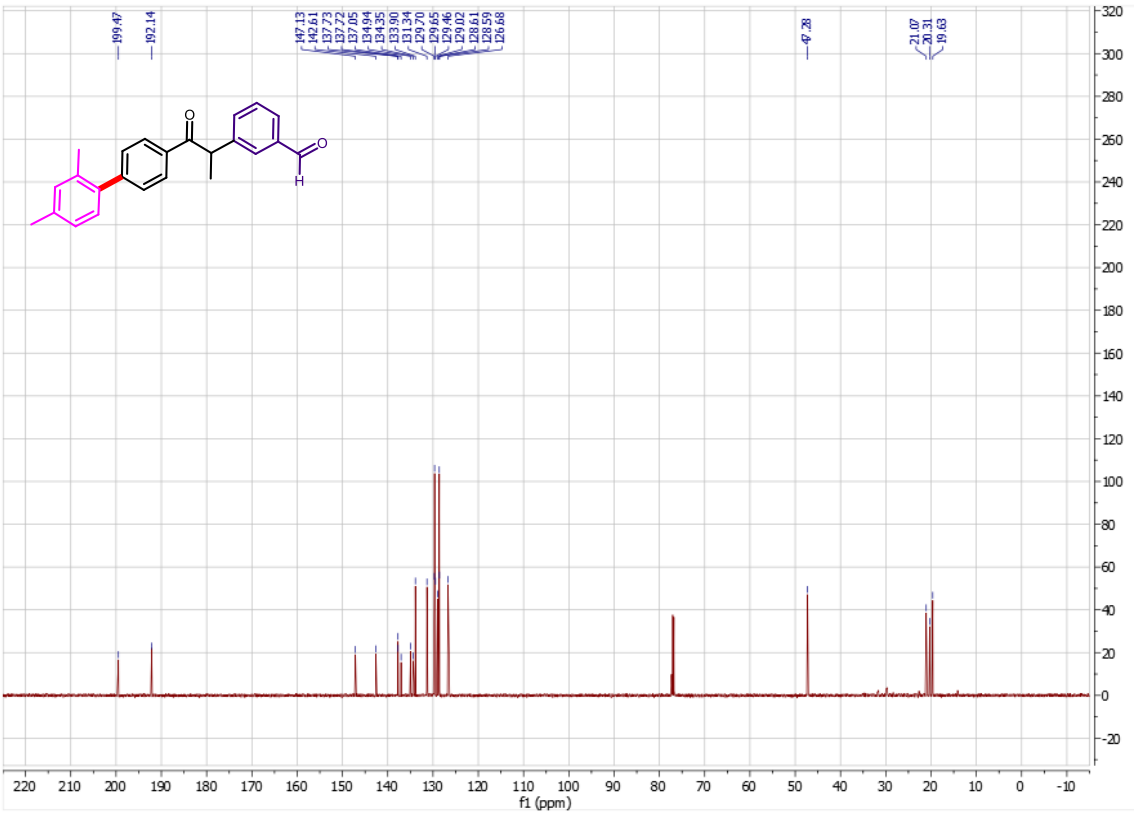
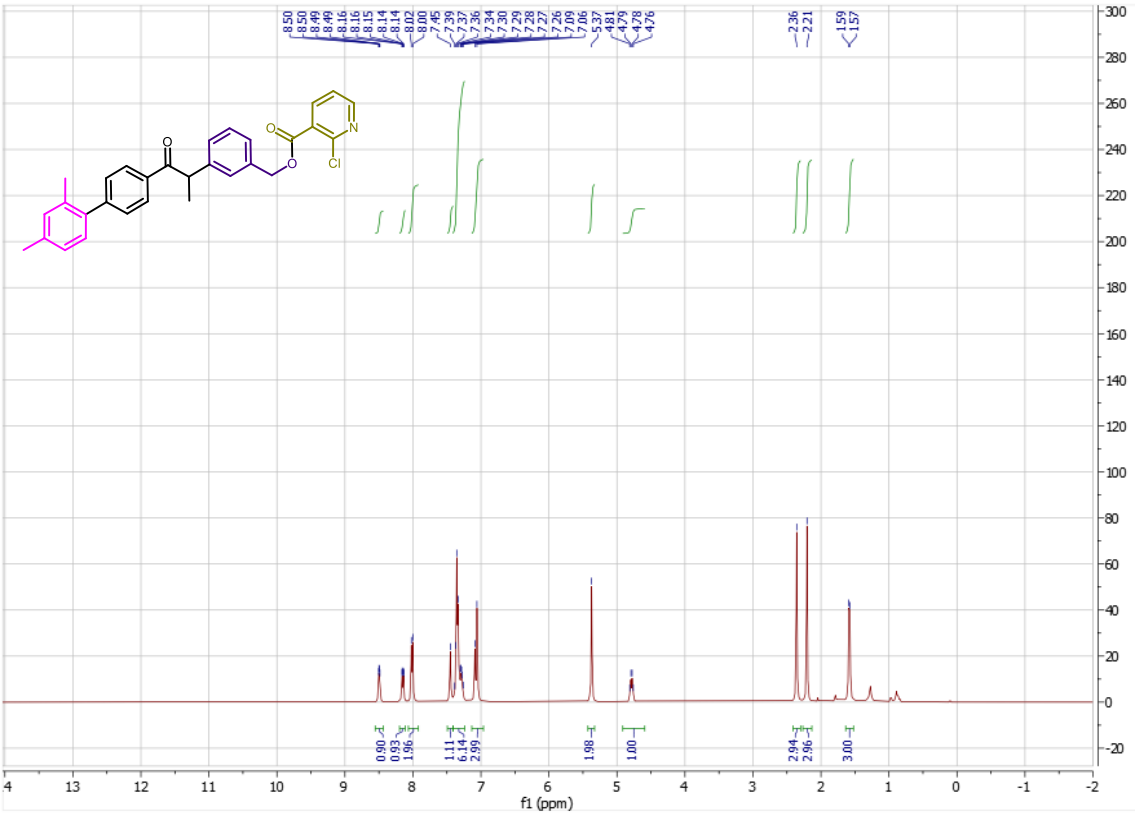
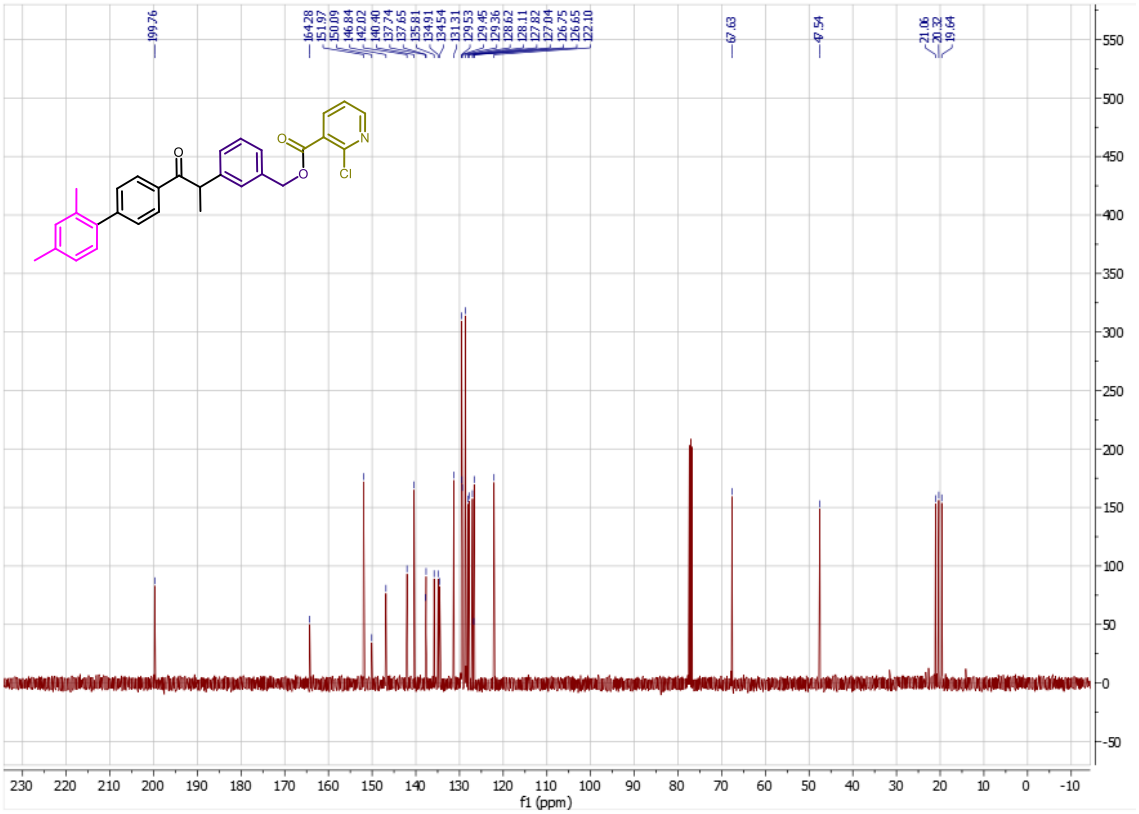
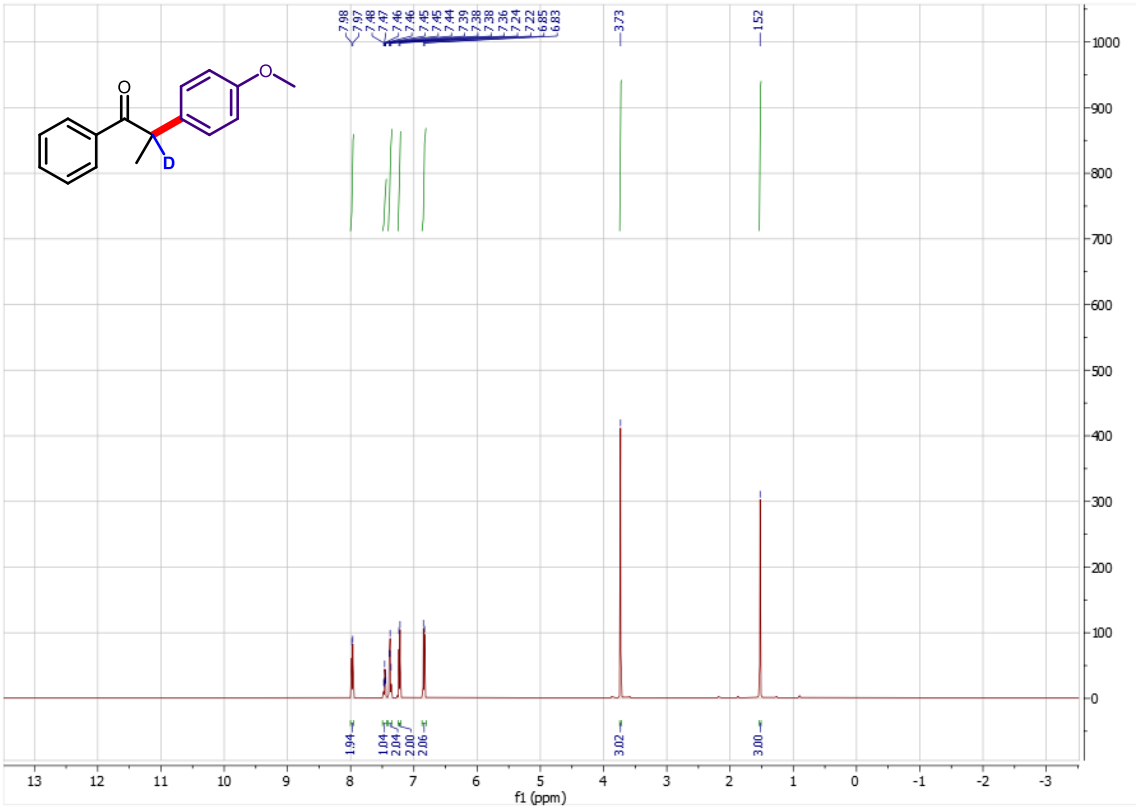
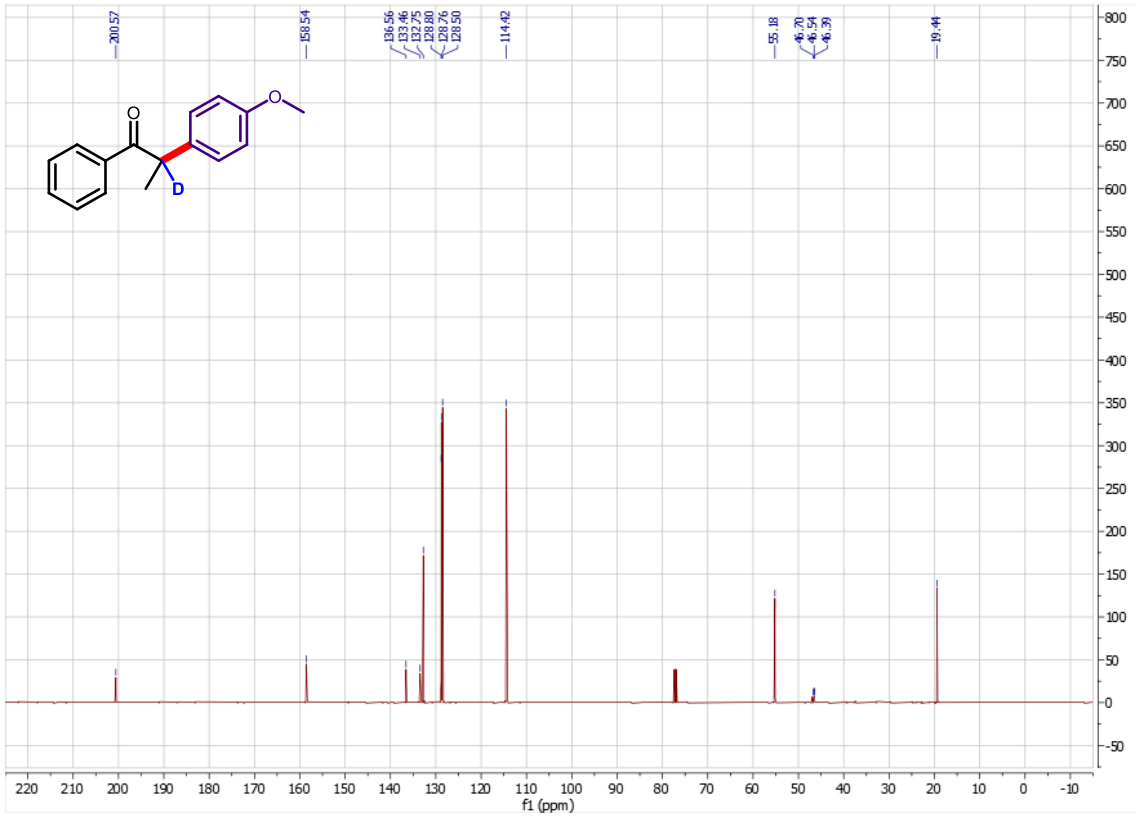
8.02
8.00
7.89
7.77
7.77
7.76
7.75
7.75
7.64
7.64
7.63
7.62
7.62
7.52
7.50
7.49
7.38
7.36
7.10
7.10
7.09
7.07
7.07
7.06
7.05
7.05
4.89
4.87
4.86
4.84
2.36
2.22
1.62
1.61
O
O
H
0.93
1.98
0.98
0.95
0.96
1.03
1.92
2.87
1.06
2.88
2.82
3.00
f1 (ppm)


199.47
192.14
147.13
142.61
137.73
137.22
137.05
134.64
134.35
133.90
131.34
129.70
129.65
129.46
129.02
128.61
128.59
126.68
49.28
21.07
20.31
19.63
O
O
H
f1 (ppm)


8.50
8.49
8.16
8.15
8.14
8.13
8.02
8.00
7.45
7.39
7.37
7.36
7.34
7.30
7.29
7.28
7.27
7.26
7.09
7.06
5.37
4.81
4.79
4.78
4.76
2.36
2.21
1.59
1.57
O
O
O
N
Cl
0.90
0.93
1.96
1.11
6.14
2.99
1.98
1.00
2.94
2.96
3.00
f1 (ppm)


199.76
164.28
151.97
150.09
146.84
142.02
140.40
137.74
137.65
135.81
134.91
134.54
131.31
129.53
129.45
129.36
129.22
128.11
127.82
127.04
126.75
126.65
122.10
67.63
47.54
21.06
20.32
19.64
O
O
O
N
Cl
f1 (ppm)


7.98
7.97
7.48
7.47
7.46
7.46
7.45
7.45
7.44
7.39
7.38
7.36
7.24
7.22
6.85
6.83
3.73
1.52
O
O
D
1.94
1.04
2.04
2.00
2.06
3.02
3.00
f1 (ppm)


200.57
158.54
136.56
133.46
132.75
128.80
128.76
128.50
114.42
55.18
46.70
46.54
46.39
19.44
O
O
D
f1 (ppm)