



## Supporting Information

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# Palladium-catalyzed oxidative cyclization of *N*-aryl enamines - from anilines to indoles

Sebastian Würtz, Souvik Rakshit, Julia J. Neumann, Thomas Dröge, Frank  
Glorius\*

*Westfälische Wilhelms-Universität Münster, Organisch-Chemisches Institut, Corrensstraße 40, 48149 Münster*

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## 1. General information

All reactions were carried out in flame dried reaction vessels with Teflon screw caps under argon. All new compounds were fully characterized, starting materials **1u** and **1w** are commercially available.

NMR-spectra were recorded on a Bruker ARX-300, AV-300, AV-400 MHz or on a Varian Associated, Varian 600 unity plus. Chemical shifts ( $\delta$ ) are quoted in ppm downfield of tetramethylsilane. Coupling constants ( $J$ ) are quoted in Hz.

Infrared spectra were recorded on a Varian Associated FT-IR 3100 Excalibur. The wave numbers ( $\nu$ ) of recorded IR-signals are quoted in  $\text{cm}^{-1}$ . ESI mass spectra were recorded on a Bruker Daltonics MicroTof.

GC/MS Spectra were recorded on a Agilent Technologies 7890A GC-system with Agilent 5975C VL MSD or 5975 inert Mass Selective Detector (EI) and a HP-5MS column (0.25 mm x 30 m, Film: 0.25  $\mu\text{m}$ ). For control of the conversion and characterization of the products, 4 different methods were used (table 1.1). The methods used start with the injection temperature  $T_0$ , after holding this temperature for 3 min, the column is heated to the temperature  $T_1$  (ramp) and hold for additional 3 min.

**Table 1.1:** GC/MS methods.

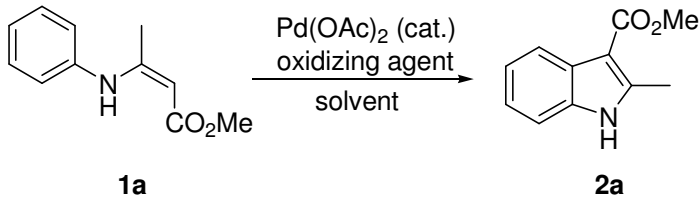
| method   | $T_0$ [ $^{\circ}\text{C}$ ] | ramp/ $\text{K}\cdot\text{min}^{-1}$ | $T_1$ [ $^{\circ}\text{C}$ ] |
|----------|------------------------------|--------------------------------------|------------------------------|
| <b>A</b> | <b>50</b>                    | <b>20</b>                            | <b>280</b>                   |
| <b>B</b> | <b>50</b>                    | <b>40</b>                            | <b>290</b>                   |
| <b>C</b> | <b>70</b>                    | <b>20</b>                            | <b>280</b>                   |
| <b>D</b> | <b>70</b>                    | <b>40</b>                            | <b>290</b>                   |

## 2. Optimization study

Our investigation started with the search for the right oxidizing agent, in order to reoxidize the palladium(0) species formed at the end of one catalytic cycle. Early on, silver carbonate is found to be an efficient oxidizing agent, being mild enough not to decompose the substrate (table 2.1, entry 1). Other silver salts lead to greatly reduced yields. The commonly used oxidizing agents benzoquinone and potassium peroxodisulfate<sup>[1]</sup> failed to provide substantial amounts of product (table 2.1, entries 5, 6). Among the copper salts tested, anhydrous copper(II) acetate is found to be optimal. The role of the base is essential, since  $\text{K}_2\text{CO}_3$  is needed for full conversion (when toluene is used as a solvent). The use of  $\text{Cs}_2\text{CO}_3$  instead of

K<sub>2</sub>CO<sub>3</sub> leads to a greatly reduced yield (table 2.1, entries 12-14). The effect of the base is remarkable, especially since C-H-activations of electron-rich aromatics often run in acidic media in order to increase the electrophilicity of the palladium catalyst.<sup>[2]</sup> The addition of AcOH, however, results in the rapid decomposition of the starting material (table 1 of manuscript, entry 16).

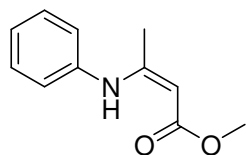
**Table 2.1:** Optimization of reaction conditions.

|  |                                              |                                              |                        |
|------------------------------------------------------------------------------------|----------------------------------------------|----------------------------------------------|------------------------|
| entry                                                                              | oxidizing agent                              | base                                         | yield [%] <sup>a</sup> |
| 1                                                                                  | Ag <sub>2</sub> CO <sub>3</sub>              | -                                            | 38 <sup>b</sup>        |
| 2                                                                                  | AgNO <sub>3</sub>                            | K <sub>2</sub> CO <sub>3</sub>               | 11                     |
| 3                                                                                  | AgOTf                                        | K <sub>2</sub> CO <sub>3</sub>               | 7                      |
| 4                                                                                  | AgOTf                                        | -                                            | 0                      |
| 5                                                                                  | Benzoquinone                                 | K <sub>2</sub> CO <sub>3</sub>               | 0                      |
| 6                                                                                  | K <sub>2</sub> S <sub>2</sub> O <sub>8</sub> | K <sub>2</sub> CO <sub>3</sub>               | 0                      |
| 7                                                                                  | NMO                                          | K <sub>2</sub> CO <sub>3</sub>               | 17                     |
| 8                                                                                  | CuCl <sub>2</sub> ·2H <sub>2</sub> O         | -                                            | 0                      |
| 9                                                                                  | CuBr <sub>2</sub>                            | -                                            | 0                      |
| 10                                                                                 | Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O       | -                                            | 18                     |
| 11                                                                                 | CuCO <sub>3</sub> ·Cu(OH) <sub>2</sub>       | -                                            | 18                     |
| 12                                                                                 | Cu(OAc) <sub>2</sub>                         | -                                            | 25                     |
| 13                                                                                 | Cu(OAc) <sub>2</sub>                         | Cs <sub>2</sub> CO <sub>3</sub> <sup>b</sup> | 7                      |
| 14                                                                                 | Cu(OAc) <sub>2</sub>                         | K <sub>2</sub> CO <sub>3</sub> <sup>b</sup>  | 32                     |
| 15 <sup>c</sup>                                                                    | Cu(OAc) <sub>2</sub>                         | K <sub>2</sub> CO <sub>3</sub> <sup>b</sup>  | 80 (72) <sup>d</sup>   |

Reaction conditions: **1a** (0.25 mmol), Pd(OAc)<sub>2</sub> (10 mol%), oxidizing agent (0.5 mmol), base (0.5 mmol), toluene (3mL), 110°C 12-16 h; a) GC yield determined using internal standard; b) 0.75 mmol base; c) **1a** (0.25 mmol), Pd(OAc)<sub>2</sub> (10 mol%), Cu(OAc)<sub>2</sub> (0.75 mmol), K<sub>2</sub>CO<sub>3</sub> (0.75 mmol) in DMF, 80 °C, 12 h; d) isolated yield in brackets.

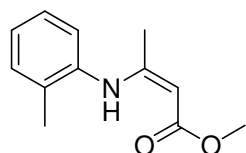
### 3. N-aryl enaminecarboxylate substrates

#### (Z)-Methyl-3-(phenylamino)but-2-enoate (1a)<sup>[3]</sup>



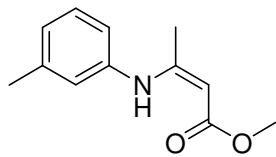
Following a modified procedure of C. A. Brandt,<sup>[3]</sup> a mixture of methyl acetoacetate (0.22 mL, 2 mmol, 1 eq), aniline (0.18 mL, 2 mmol, 1 eq) and acetic acid (0.01 mL, 0.2 mmol, 0.1 eq) is stirred at room temperature for 18 h. At the end of the reaction, EtOH (5 mL) is added, the solution is dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure. The residue is purified by flash chromatography (silica, pentane/EtOAc/NEt<sub>3</sub> 97:2:1). The pure product is obtained as a yellow solid (313 mg, 1.64 mmol, 82%). **R<sub>F</sub>** (pentane/EtOAc/NEt<sub>3</sub> 95:4:1): 0.24; **<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):** 1.99 (d, *J* = 0.5 Hz, 3H), 3.68 (s, 3H, CH<sub>3</sub>), 4.69 (d, *J* = 0.5 Hz, 1H, CH), 7.07-7.18 (m, 3H, CH<sub>ar</sub>), 7.30-7.35 (m, 2H, CH<sub>ar</sub>), 10.36 (br s, 1H, NH); **<sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz):** 20.3 (CH<sub>3</sub>), 50.2 (CH<sub>3</sub>), 85.5 (CH), 124.5 (CH<sub>ar</sub>), 124.9 (CH<sub>ar</sub>), 129.0 (CH<sub>ar</sub>), 139.2 (CH<sub>ar</sub>), 159.1 (C<sub>q</sub>), 170.7 (CO); **GC-MS R<sub>t</sub> (method B):** 11.0 min, **(EI) m/z (%):** 192.1 (13), 191.1 (86), 176 (10), 160.1 (62), 159 (37), 144 (46), 132.1 (60), 131.1 (45), 130.1 (72), 119.0 (13), 118.0 (100), 117.0 (20), 93.0 (10), 77.0 (63), 65.0 (14), 51.0 (18).

#### (Z)-Methyl-3-(*o*-tolylamino)but-2-enoate (1b)<sup>[4]</sup>



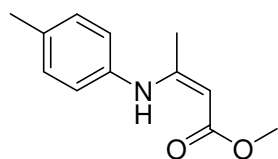
Following a modified procedure by G. Bartoli,<sup>[5]</sup> a mixture of methyl acetoacetate (7.43 mL, 69 mmol, 1.5 eq), *o*-toluidine (4.82 g, 45 mmol, 1.0 eq), Zn(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O (1.08 g, 2.9 mmol, 6.4 mol%) and MgSO<sub>4</sub>·xH<sub>2</sub>O (5.40 g, 45 mmol, 1.0 eq) in CH<sub>2</sub>Cl<sub>2</sub> (40 mL) is stirred at room temperature for 10 h. The crude mixture is filtered, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue is purified by flash chromatography (silica, pentane/EtOAc/NEt<sub>3</sub> 97:2:1). The pure product is obtained as a pale yellow solid (7.83 g, 38.3 mmol, 85%). **R<sub>F</sub>** (pentane/EtOAc/NEt<sub>3</sub> 89:10:1): 0.58; **<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):** 1.85 (s, 3H, CH<sub>3</sub>), 2.28 (s, 3H, CH<sub>3</sub>), 3.68 (s, 3H, CH<sub>3</sub>), 4.71 (s, 1H, CH), 7.05-7.24 (m, 4H), 10.13 (s, 1H, NH); **<sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz):** 18.0 (CH<sub>3</sub>), 20.0 (CH<sub>3</sub>), 50.2 (CH<sub>3</sub>), 84.7 (CH), 126.0 (CH<sub>ar</sub>), 126.3 (CH<sub>ar</sub>), 126.4 (CH<sub>ar</sub>), 130.7 (CH<sub>ar</sub>), 133.9 (CH<sub>ar</sub>), 137.9 (CH<sub>ar</sub>), 159.9 (C<sub>q</sub>), 170.9 (CO); **GC-MS R<sub>t</sub> (method B):** 10.29 min, **(EI) m/z (%):** 205.1 (56), 190.0 (14), 174.0 (29), 173.0 (16), 158.0 (14), 146.1 (18), 145.0 (15), 144.0 (32), 132.0 (100), 131.0 (19), 130.0 (36), 91.0 (23).

### (Z)-Methyl-3-(*m*-tolylamino)but-2-enoate (1c)



Following a modified procedure by G. Bartoli,<sup>[5]</sup> a mixture of methyl acetoacetate (7.43 mL, 69 mmol, 1.5 eq), *m*-toluidine (4.82 g, 45 mmol, 1.0 eq), Zn(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O (1.08 g, 2.9 mmol, 6.4 mol%) and MgSO<sub>4</sub>·xH<sub>2</sub>O (5.40 g, 45 mmol, 1.0 eq) in CH<sub>2</sub>Cl<sub>2</sub> (40 mL) is stirred at room temperature for 10 h. The crude mixture is filtered, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue is purified by flash chromatography (silica, pentane/EtOAc/NEt<sub>3</sub> 97:2:1). The pure product is obtained as a red oil (6.56 g, 32.0 mmol, 71%). **R<sub>F</sub>** (pentane/EtOAc/NEt<sub>3</sub> 89:10:1): 0.57; **<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)**: 1.99 (d, *J* = 0.30 Hz, 3H, CH<sub>3</sub>), 2.34 (s, 3H, CH<sub>3</sub>), 3.68 (s, 3H, CH<sub>3</sub>), 4.68 (d, *J* = 0.30 Hz, 1H, CH), 6.89-6.91 (m, 2H, CH<sub>ar</sub>), 6.97 (d, *J* = 7.80 Hz, 1H, CH<sub>ar</sub>), 7.21 (m, 1H, CH<sub>ar</sub>), 10.32 (s, 1H, NH); **<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)**: 20.2 (CH<sub>3</sub>), 21.2 (CH<sub>3</sub>), 50.1 (CH<sub>3</sub>), 85.2 (CH), 121.3 (CH<sub>ar</sub>), 124.9 (CH<sub>ar</sub>), 125.6 (CH<sub>ar</sub>), 128.7 (CH<sub>ar</sub>), 138.7 (C<sub>ar</sub>), 139.0 (C<sub>ar</sub>), 159.0 (C<sub>q</sub>), 170.0 (CO); **GC-MS R<sub>t</sub> (method B)**: 11.6 min, **(EI) m/z (%)**: 206.1 (14), 205.1 (100), 174.1 (54), 173.0 (30), 172.1 (11), 158.1 (33), 146.1 (65), 145.1 (53), 144.1 (70), 133.0 (11), 132.1 (78), 131.1 (19), 130.1 (26), 91.0 (42), 77.1 (11), 65.0 (18); **ESI-MS**: calculated [C<sub>12</sub>H<sub>15</sub>NNaO<sub>2</sub>]<sup>+</sup>: 228.0995 and [C<sub>12</sub>H<sub>16</sub>NO<sub>2</sub>]<sup>+</sup>: 206.1176, found: [C<sub>12</sub>H<sub>15</sub>NNaO<sub>2</sub>]<sup>+</sup>: 228.0994 and [C<sub>12</sub>H<sub>16</sub>NO<sub>2</sub>]<sup>+</sup>: 206.1176. **ATR-FTIR (cm<sup>-1</sup>)**: 2948, 1654, 1584, 1491, 1437, 1383, 1358, 1270, 1246, 1153, 1090, 786, 697, 651.

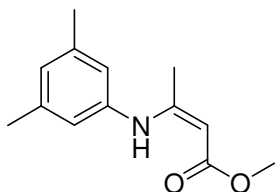
### (Z)-Methyl-3-(*p*-tolylamino)but-2-enoate (1d)<sup>[4]</sup>



Following a modified procedure by G. Bartoli,<sup>[5]</sup> a mixture of methyl acetoacetate (7.43 mL, 69 mmol, 1.5 eq), *p*-toluidine (4.82 g, 45 mmol, 1.0 eq), Zn(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O (0.54 g, 1.45 mmol, 3 mol%), molecular sieves (4 Å, 5 g) and MgSO<sub>4</sub>·xH<sub>2</sub>O (5.40 g, 45 mmol, 1.0 eq) in CH<sub>2</sub>Cl<sub>2</sub> is stirred at 40 °C for 10 h. The crude mixture is filtered, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue is purified by flash chromatography (silica, pentane/EtOAc/NEt<sub>3</sub> 97:2:1). The pure product is obtained as a yellow solid (7.01 g, 34.2 mmol, 76%). **R<sub>F</sub>** (pentane/EtOAc/NEt<sub>3</sub> 89:10:1): 0.53; **<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)**: 1.95 (d, *J* = 0.4 Hz, 3H, CH<sub>3</sub>), 2.33 (s, 3H, CH<sub>3</sub>), 3.68 (s, 3H, CH<sub>3</sub>), 4.67 (d, *J* = 0.5 Hz, 1H, CH), 6.98 (d, *J* = 8.3 Hz, 2H, CH<sub>ar</sub>), 7.12 (d, *J* = 8.1 Hz, 2H, CH<sub>ar</sub>), 10.26 (s, 1H, NH); **<sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)**: 20.1 (CH<sub>3</sub>), 20.8 (CH<sub>3</sub>), 50.2 (CH<sub>3</sub>), 84.8 (CH), 124.7 (CH<sub>ar</sub>), 129.6 (CH<sub>ar</sub>), 134.9 (CH<sub>ar</sub>), 136.5 (CH<sub>ar</sub>), 159.4 (C<sub>q</sub>), 170.7 (CO); **GC-MS R<sub>t</sub>**

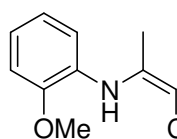
**(method B):** 11.7 min, **(EI) m/z (%)**: 206.1 (12), 205.1 (100), 174.1 (53), 173.1 (67), 172.0 (13), 158.1 (46), 146.1 (28), 145.0 (28), 144.1 (60), 132.1 (76), 130.1 (27), 91.0 (34), 77.0 (13), 65.0 (14).

**(Z)-Methyl-3-(3,5-dimethylphenylamino)but-2-enoate (1e)**



Following a modified procedure of C. A. Brandt,<sup>[3]</sup> a mixture of methyl acetoacetate (4.42 mL, 41 mmol, 1.0 eq), 3,5-dimethylaniline (5.12 mL, 41 mmol, 1.0 eq) and acetic acid (0.5 mL, 8.2 mmol, 0.2 eq) is stirred at room temperature for 18 h. At the end of the reaction, EtOH (40 mL) is added, the solution is dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue is purified by flash chromatography (silica, pentane/EtOAc/NEt<sub>3</sub> 96:3:1). The pure product is obtained as yellow oil (4.4 g, 20.1 mmol, 49%). **R<sub>F</sub>** (pentane/EtOAc/NEt<sub>3</sub> 89:10:1): 0.61; **<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)**: 1.99 (s, 3H, CH<sub>3</sub>), 2.29 (s, 6H, 2xCH<sub>3</sub>), 3.68 (s, 3H, CH<sub>3</sub>), 4.66 (s, 1H, CH), 6.71 (s, 2H, CH<sub>ar</sub>), 6.80 (s, 1H, CH<sub>ar</sub>), 10.28 (s, 1H, NH); **<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)**: 20.3 (CH<sub>3</sub>), 21.2 (CH<sub>3</sub>), 50.1 (CH<sub>3</sub>), 85.0 (CH), 122.2 (CH<sub>ar</sub>), 126.7 (CH<sub>ar</sub>), 138.7 (CH<sub>ar</sub>), 139.0 (C<sub>ar</sub>), 159.3 (C<sub>q</sub>), 170.6 (CO); **GC-MS R<sub>t</sub> (method A)**: 12.2 min, **(EI) m/z (%)**: 219.1 (90), 206.8 (16), 188.1 (53), 187.0 (43), 186.1 (30), 172.2 (36), 160.1 (100), 159.0 (78), 158.1 (53), 146.0 (90), 145.0 (38), 144 (75), 105.0 (36), 91.0 (16), 77.0 (30); **ESI-MS**: calculated [C<sub>12</sub>H<sub>15</sub>NNaO<sub>2</sub>]<sup>+</sup>: 242.1151, found: [C<sub>12</sub>H<sub>15</sub>NNaO<sub>2</sub>]<sup>+</sup>: 242.1144. **ATR-FTIR (cm<sup>-1</sup>)**: 2949, 2919, 1652, 1589, 1495, 1433, 1383, 1358, 1270, 1247, 1184, 1154, 1056, 1001, 929, 849, 787, 671, 609.

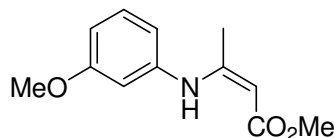
**(Z)-Methyl 3-(2-methoxyphenylamino)but-2-enoate (1f)**



Following a modified procedure by G. Bartoli,<sup>[5]</sup> *o*-anisidine (4.23 mL, 37.5 mmol, 1.5 eq), methyl acetoacetate (2.70 mL, 25 mmol, 1 eq), Zn(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O (465 mg, 1.25 mmol, 5 mol %), MgSO<sub>4</sub>·xH<sub>2</sub>O (903 mg, 7.5 mmol, 30 mol%) are stirred in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) at rt for 16 h. After addition of molecular sieves (4 Å, 5 g) the mixture is stirred for additional 1.5 h at 60 °C. The mixture is cooled to rt, filtered and the solvents are evaporated. After rapid flash chromatography (silica, pentane/EtOAc/NEt<sub>3</sub> 10:1:0.1), the product is obtained as a nearly colorless oil (1.88 g, 34%). **R<sub>F</sub>** (Pentane/EtOAc 5:1): 0.38; **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)**: 2.01 (s, 3 H, CH<sub>3</sub>), 3.69 (s, 3H, CH<sub>3</sub>), 3.87 (s, 3H, CH<sub>3</sub>), 4.72 (s, 1H, CH), 6.88-6.92 (m, 2H, CH<sub>ar</sub>), 7.09-7.14 (m, 2 H, CH<sub>ar</sub>), 10.26 (s, 1 H, NH); **<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)**: 20.4 (CH<sub>3</sub>), 50.2 (CH<sub>3</sub>), 55.7 (CH<sub>3</sub>), 85.9 (CH); 111.1 (CH<sub>ar</sub>), 120.3 (CH<sub>ar</sub>), 124.5 (CH<sub>ar</sub>), 125.5 (CH<sub>ar</sub>), 128.8 (C<sub>ar</sub>), 152.7 (C<sub>ar</sub>), 159.1

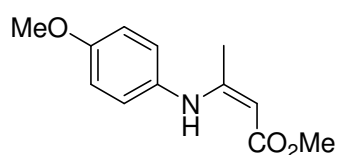
(C<sub>q</sub>), 170.6 (CO); **GC/MS: R<sub>t</sub> (method B):** 12.3 min, **(EI) m/z (%):** 221 (100), 189 (56), 175 (47), 160 (43), 148 (95), 77 (34); **ESI-MS:** calculated [C<sub>12</sub>H<sub>15</sub>NNaO<sub>3</sub>]<sup>+</sup>: 244.0944, found: 244.0951; **ATR-FTIR [cm<sup>-1</sup>]:** 2948, 1657, 1615, 1507, 1478, 1271, 1160, 1027, 788, 749.

**(Z)-Methyl 3-(phenylamino)but-2-enoate (1g)**



Following a modified procedure by G. Bartoli,<sup>[5]</sup> *m*-anisidine (4.5 mL, 37.5 mmol, 1.5 eq), methyl acetoacetate (2.7 mL, 25 mmol, 1.0 eq), Zn(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O (465 mg, 1.25 mmol, 5 mol %), MgSO<sub>4</sub>·xH<sub>2</sub>O (903 mg, 7.5 mmol, 30 mol%) are stirred in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) at rt for 13.5 h. After addition of molecular sieves (4 Å, 5 g) the mixture is stirred for additional 5 h at 60 °C. The mixture is cooled to rt, filtered and the solvents are evaporated. After rapid flash chromatography (silica, pentane/EtOAc/NEt<sub>3</sub> 10:1:0.1), the product is obtained as a nearly colorless oil (4.78 g, 86%). **R<sub>F</sub>** (Pentane/EtOAc 10:1): 0.29; **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** 2.02 (s, 3 H, CH<sub>3</sub>), 3.68 (s, 3H, CH<sub>3</sub>), 3.79 (s, 3H, CH<sub>3</sub>), 4.69 (s, 1H, CH), 6.62 (t, *J* = 2.18 Hz, 1H, CH<sub>ar</sub>), 6.67-6.72 (m, 2H, CH<sub>ar</sub>), 7.22 (t, *J* = 8.1 Hz, 2H, CH<sub>ar</sub>), 10.35 (s, 1 H, NH); **<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** 20.4 (CH<sub>3</sub>), 50.25 (CH<sub>3</sub>), 55.3 (CH<sub>3</sub>), 85.8 (CH), 110.1 (CH<sub>ar</sub>), 110.5 (CH<sub>ar</sub>), 116.6 (CH<sub>ar</sub>), 129.7 (CH<sub>ar</sub>), 140.5 (C<sub>ar</sub>), 159.0 (C<sub>ar</sub>), 160.2 (C<sub>q</sub>), 170.7 (CO); **GC/MS: R<sub>t</sub> (method A):** 12.5 min, **(EI) m/z (%):** 221 (27), 162 (28), 148 (46) 44 (100); **ESI-MS:** calculated [C<sub>12</sub>H<sub>15</sub>NNaO<sub>3</sub>]<sup>+</sup>: 244.0944, found: 244.0954; **ATR-FTIR [cm<sup>-1</sup>]:** 3001, 2949, 1655, 1587, 1277, 1252, 1154.

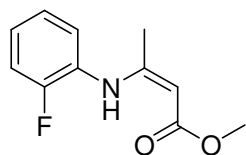
**(Z)-Methyl 3-(4-methoxyphenylamino)but-2-enoate (1h)<sup>[4]</sup>**



Following a modified procedure by G. Bartoli,<sup>[5]</sup> *p*-anisidine (3.33 g, 27.0 mmol, 1.5 eq), methyl acetoacetate (1.94 mL, 18 mmol, 1.0 eq), Zn(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O (465 mg, 1.25 mmol, 7 mol%), MgSO<sub>4</sub>·xH<sub>2</sub>O (903 mg, 7.5 mmol, 42 mol%) and molecular sieves (4 Å, 5 g) are stirred in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) at rt for 23 h. The mixture is filtered and the solvents are evaporated. After rapid flash chromatography (silica, pentane/EtOAc/NEt<sub>3</sub> 10:1:0.1), the product is obtained as a yellow solid (3.64 g, 92%). **R<sub>F</sub>** (pentane/EtOAc 10:1): 0.38; **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** 1.88 (s, 3H, CH<sub>3</sub>), 3.67 (s, 3H, CH<sub>3</sub>), 3.79 (s, 3H, CH<sub>3</sub>), 4.65 (s, 1H, CH), 6.84 (d, *J* = 8.9 Hz, 2 H, CH<sub>ar</sub>), 7.01 (d, *J* = 8.8 Hz, 2H, CH<sub>ar</sub>), 10.13 (s, 1H, NH); **<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** 20.0 (CH<sub>3</sub>), 50.1 (CH<sub>3</sub>), 55.4 (CH<sub>3</sub>), 84.3 (CH), 114.1 (CH<sub>ar</sub>), 126.8 (CH<sub>ar</sub>), 132.0 (C<sub>ar</sub>), 157.5 (C<sub>ar</sub>), 160.1 (C<sub>q</sub>), 170.7 (CO); **ESI-MS:** calculated [C<sub>12</sub>H<sub>15</sub>NNaO<sub>3</sub>]<sup>+</sup>: 244.0944, found: 244.0924; **EI-MS: m/z (%) =** 221 (M<sup>+</sup>, 95), 189 (100),

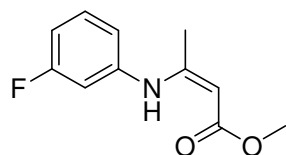
174 (74), 148 (82); **ATR-FTIR** [ $\text{cm}^{-1}$ ]: 3263, 3001, 1647, 1595, 1510, 1240, 1155, 1031, 786.

**(Z)-Methyl-3-(2-fluorophenylamino)but-2-enoate (1i)**



Following a modified procedure of G. Bartoli,<sup>[5]</sup> methyl acetoacetate (2.6 mL, 24 mmol, 1.2 eq), 2-fluoroaniline (2.22 g, 20 mmol, 1.0 eq),  $\text{Zn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$  (2.40 g, 6.4 mmol, 32 mol%) and  $\text{MgSO}_4 \cdot x\text{H}_2\text{O}$  (2.41 g, 20 mmol, 1.0 eq) in  $\text{CH}_2\text{Cl}_2$  (20 ml) is stirred at room temperature for 10 h. The crude mixture is filtered, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuum. The residue is purified by flash chromatography (silica, pentane/EtOAc/ $\text{NEt}_3$  95:4:1) and the pure product is obtained as a white solid (1.714 g, 8.2 mmol, 41 %). **R<sub>F</sub>** (pentane/EtOAc/ $\text{NEt}_3$  79:20:1): 0.72; **<sup>1</sup>H NMR (300 MHz,  $\text{CDCl}_3$ )**: 1.95 (s, 3H,  $\text{CH}_3$ ), 3.68 (s, 3H,  $\text{CH}_3$ ), 4.77 (s, 1H, CH), 7.07-7.18 (m, 4H,  $\text{CH}_{\text{ar}}$ ), 10.18 (s, 1H, NH); **<sup>13</sup>C NMR (75 MHz,  $\text{CDCl}_3$ )**: 19.87 ( $\text{CH}_3$ ), 50.3 ( $\text{CH}_3$ ), 86.6 (CH), 116.0 (d,  $J_{(\text{C},\text{F})} = 20.3$  Hz,  $\text{C}_{\text{ar}}$ ), 124.1 (d,  $J_{(\text{C},\text{F})} = 4.0$  Hz,  $\text{C}_{\text{ar}}$ ), 126.4 (d,  $J_{(\text{C},\text{F})} = 7.6$  Hz,  $\text{C}_{\text{ar}}$ ), 126.5 ( $\text{C}_{\text{ar}}$ ), 127.3 (d,  $J_{(\text{C},\text{F})} = 12.1$  Hz,  $\text{C}_{\text{ar}}$ ), 156.5 (d,  $J_{(\text{C},\text{F})} = 246.9$  Hz,  $\text{C}_{\text{ar}}$ ), 158.9 ( $\text{C}_{\text{q}}$ ), 170.6 (CO); **ESI-MS**: calculated  $[\text{C}_{11}\text{H}_{12}\text{FNNaO}_2]^+$ : 232.0744, found: 232.0743. **ATR-FTIR** [ $\text{cm}^{-1}$ ]: 3272, 3000, 2950, 1650, 1596, 1476, 1430, 1349, 1241, 1191, 1185, 1101, 1057, 1004, 960, 913, 832, 768, 658, 615.

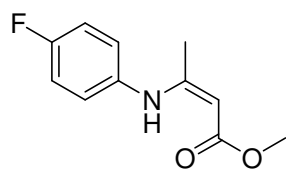
**(Z)-Methyl-3-(3-fluorophenylamino)but-2-enoate (1j)**



Following a modified procedure of Y. Wang,<sup>[4]</sup> methyl acetoacetate (2.6 mL, 24 mmol, 1.2 eq), 3-fluoroaniline (2.22 g, 20 mmol, 1 eq),  $\text{InBr}_3$  (354 mg, 1.0 mmol, 5 mol%) and  $\text{MgSO}_4 \cdot x\text{H}_2\text{O}$  (2.41 g, 20 mmol, 1 eq) in  $\text{CH}_2\text{Cl}_2$  (20 ml) is stirred at room temperature for 10 h. The crude mixture is filtered, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuum. The residue is purified by flash chromatography (silica, pentane/EtOAc/ $\text{NEt}_3$  95:3:1) and the pure product is obtained as a colorless oil (3.81 g, 18.4 mmol, 92 %). **R<sub>F</sub>** (pentane/EtOAc/ $\text{NEt}_3$  89:10:1): 0.60; **<sup>1</sup>H-NMR (300 MHz,  $\text{CDCl}_3$ )**: 2.07 (d,  $J = 0.6$  Hz, 3H,  $\text{CH}_3$ ), 3.72 (s, 3H,  $\text{CH}_3$ ), 4.77 (d,  $J = 0.6$  Hz, 1H, CH), 6.81-6.90 (m, 3H,  $\text{CH}_{\text{ar}}$ ), 7.28-7.34 (m, 1H,  $\text{CH}_{\text{ar}}$ ), 10.46 (s, 1H, NH); **<sup>13</sup>C-NMR (75 MHz,  $\text{CDCl}_3$ )**: 20.4 ( $\text{CH}_3$ ), 50.4 ( $\text{CH}_3$ ), 86.9 (CH), 110.9 (d,  $J_{(\text{C},\text{F})} = 23.5$  Hz,  $\text{CH}_{\text{ar}}$ ), 111.4 (d,  $J_{(\text{C},\text{F})} = 21.4$  Hz,  $\text{CH}_{\text{ar}}$ ), 119.4 (d,  $J_{(\text{C},\text{F})} = 2.9$  Hz,  $\text{CH}_{\text{ar}}$ ), 130.2 (d,  $J_{(\text{C},\text{F})} = 9.5$  Hz,  $\text{CH}_{\text{ar}}$ ), 140.9 (s,  $\text{C}_{\text{ar}}$ ), 158.2 ( $\text{C}_{\text{q}}$ ), 162.9 (d,  $J_{(\text{C},\text{F})} = 246.4$  Hz,  $\text{C}_{\text{ar}}$ ), 170.7 (CO); **ESI-MS**: calculated  $[\text{C}_{11}\text{H}_{12}\text{FNNaO}_2]^+$ : 232.0744, found: 232.0749. **ATR-FTIR** [ $\text{cm}^{-1}$ ]:

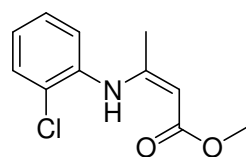
2949, 1656, 1584, 1491, 1440, 1384, 1360, 1240, 1178, 1140, 1057, 1013, 931, 861, 788, 690, 653.

### (Z)-Methyl-3-(4-fluorophenylamino)but-2-enoate (1k)



Following a modified procedure of Y. Wang,<sup>[4]</sup> methyl acetoacetate (2.6 mL, 24 mmol, 1.2 eq), 4-fluoroaniline (2.22 g, 20 mmol, 1.0 eq), InBr<sub>3</sub> (354 mg, 1.0 mmol, 5 mol%) and MgSO<sub>4</sub>·xH<sub>2</sub>O (2.41 g, 20 mmol, 1 eq) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) is stirred at room temperature for 10 h. The crude mixture is filtered, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum. The residue is purified by flash chromatography (silica, pentane/EtOAc/NEt<sub>3</sub> 95:3:1) and the pure product is obtained as a white solid (3.23 g, 15.6 mmol, 78 %). **R<sub>F</sub>** (pentane/EtOAc/NEt<sub>3</sub> 89:10:1): 0.68; **<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>)**: 1.91 (s, 3H, CH<sub>3</sub>), 3.68 (s, 3H, CH<sub>3</sub>), 4.69 (s, 1H, CH), 7.02-7.05 (m, 4H, CH<sub>ar</sub>), 10.21 (s, 1H, NH); **<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>)**: 20.1 (s, CH<sub>3</sub>), 50.3 (s, CH<sub>3</sub>), 85.4 (s, CH), 115.8 (d, *J*<sub>(C,F)</sub> = 22.6 Hz, CH<sub>ar</sub>), 126.8 (d, *J*<sub>(C,F)</sub> = 8.3 Hz, CH<sub>ar</sub>), 135.2 (s, C<sub>ar</sub>), 160.4 (d, *J*<sub>(C,F)</sub> = 244.9 Hz, C<sub>ar</sub>), 159.3 (s, C<sub>q</sub>), 170.8 (s, CO); **GC-MS R<sub>t</sub> (method B)**: 12.5 min, **(EI) m/z (%)**: 207.1 (77), 206.9 (100); **ESI-MS**: calculated [C<sub>11</sub>H<sub>12</sub>FNNaO<sub>2</sub>]<sup>+</sup>: 232.0744, found: 232.0740. **ATR-FTIR [cm<sup>-1</sup>]**: 3281, 3077, 3010, 2958, 1646, 1606, 1591, 1510, 1483, 1433, 1385, 1351, 1261, 1231, 1209, 1164, 1095, 1060, 1008, 946, 855, 824, 782, 666.

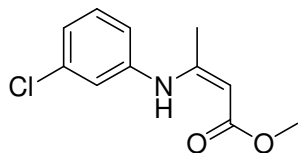
### (Z)-Methyl-3-(2-chlorophenylamino)but-2-enoate (1l)



Following a modified procedure of Y. Wang,<sup>[4]</sup> a mixture of methyl acetoacetate (2.6 mL, 24 mmol, 1.2 eq), 2-chloroaniline (2.55 g, 20 mmol, 1.0 eq), InBr<sub>3</sub> (351 mg, 1.0 mmol, 5 mol%) and MgSO<sub>4</sub>·xH<sub>2</sub>O (2.41 g, 20 mmol, 1 eq) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) is stirred at room temperature for 10 h. The crude mixture is filtered, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue is purified by flash chromatography (silica, pentane/EtOAc/NEt<sub>3</sub> 95:4:1). The pure product is obtained as a white solid (3.74 g, 16.6 mmol, 83%). **R<sub>F</sub>** (pentane/EtOAc/NEt<sub>3</sub> 89:10:1): 0.68; **<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)**: 1.97 (d, *J* = 0.6 Hz, 3H, CH<sub>3</sub>), 3.71 (s, 3H, CH<sub>3</sub>), 4.79 (s, 1H, CH), 7.08-7.14 (m, 1H, CH<sub>ar</sub>), 7.18-7.24 (m, 2H, CH<sub>ar</sub>), 7.43 (dd, *J* = 7.9 Hz, *J* = 1.3 Hz, 1H, CH<sub>ar</sub>), 10.36 (s, 1H, NH); **<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)**: 20.2 (CH<sub>3</sub>), 50.4 (CH<sub>3</sub>), 87.3 (CH), 125.9 (CH<sub>ar</sub>), 126.0 (CH<sub>ar</sub>), 127.1 (CH<sub>ar</sub>), 129.2 (C<sub>ar</sub>), 130.0 (CH<sub>ar</sub>), 136.6 (C<sub>ar</sub>), 158.2 (C<sub>q</sub>), 170.5 (CO); **ESI-MS**: calculated [C<sub>11</sub>H<sub>12</sub>ClNNaO<sub>2</sub>]<sup>+</sup>: 248.0449, found:

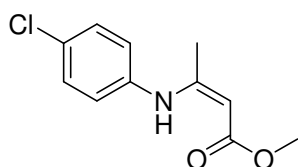
248.0440. **ATR-FTIR** [ $\text{cm}^{-1}$ ]: 3474, 3373, 2948, 1656, 1611, 1487, 1464, 1443, 1385, 1360, 1269, 1224, 1164, 1056, 1005, 918, 790, 741, 678, 639.

**(Z)-Methyl-3-(2-chlorophenylamino)but-2-enoate (1m)**



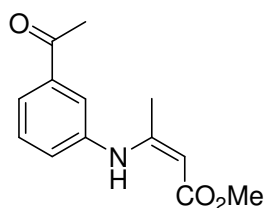
Following a modified procedure of Y. Wang,<sup>[4]</sup> a mixture of methyl acetoacetate (2.6 mL, 24 mmol, 1.2 eq), 3-chloroaniline (2.55 g, 20 mmol, 1 eq),  $\text{InBr}_3$  (351 mg, 1.0 mmol, 5 mol%) and  $\text{MgSO}_4 \cdot x\text{H}_2\text{O}$  (2.41 g, 20 mmol, 1 eq) in  $\text{CH}_2\text{Cl}_2$  (10 mL) is stirred at room temperature for 10 h. The crude mixture is filtered, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The residue is purified by flash chromatography (silica, pentane/EtOAc/ $\text{NEt}_3$  95:4:1). The pure product is obtained as a white solid (3.60 g, 16.0 mmol, 80%). **R<sub>F</sub>** (pentane/EtOAc/ $\text{NEt}_3$  89:10:1): 0.63; **<sup>1</sup>H NMR (300 MHz,  $\text{CDCl}_3$ )**: 2.07 (s, 3H,  $\text{CH}_3$ ), 3.73 (s, 3H,  $\text{CH}_3$ ), 4.79 (s, 1H, CH), 7.01 (d,  $J = 8.7$  Hz, 1H,  $\text{CH}_{\text{ar}}$ ), 7.14-7.17 (m, 2H,  $\text{CH}_{\text{ar}}$ ), 7.28-7.32 (d,  $J = 8.10$  Hz, 1H,  $\text{CH}_{\text{ar}}$ ), 10.47 (s, 1H, NH); **<sup>13</sup>C NMR (75 MHz,  $\text{CDCl}_3$ )**: 20.2 ( $\text{CH}_3$ ), 50.2 ( $\text{CH}_3$ ), 86.9 (CH), 121.9, 123.8 ( $\text{CH}_{\text{ar}}$ ), 124.6 ( $\text{CH}_{\text{ar}}$ ), 129.9 ( $\text{CH}_{\text{ar}}$ ), 134.4 ( $\text{C}_{\text{ar}}$ ), 140.5 ( $\text{C}_{\text{ar}}$ ), 157.9 ( $\text{C}_{\text{q}}$ ), 170.4 (CO); **ESI-MS**: calculated [ $\text{C}_{11}\text{H}_{12}\text{ClNNaO}_2$ ]<sup>+</sup>: 248.0449, found: 248.0457. **ATR-FTIR** [ $\text{cm}^{-1}$ ]: 3274, 1645, 1608, 1575, 1474, 1433, 1347, 1255, 1219, 1161, 1060, 1008, 959, 971, 882, 786, 737, 713, 681, 644.

**(Z)-Methyl-3-(2-chlorophenylamino)but-2-enoate (1n)<sup>[4]</sup>**



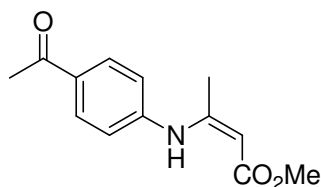
Following a modified procedure of Y. Wang,<sup>[4]</sup> a mixture of methyl acetoacetate (2.6 mL, 24 mmol, 1.2 eq), 4-chloroaniline (2.55 g, 20 mmol, 1.0 eq),  $\text{InBr}_3$  (351 mg, 1.0 mmol, 5 mol%) and  $\text{MgSO}_4 \cdot x\text{H}_2\text{O}$  (2.41 g, 20 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL) is stirred at room temperature for 10 h. The crude mixture is filtered, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The residue is purified by flash chromatography (silica, pentane/EtOAc/ $\text{NEt}_3$  95:3:1). The pure product is obtained as a yellow solid (3.42, 15.2 mmol, 76%). **<sup>1</sup>H NMR (300 MHz,  $\text{CDCl}_3$ )**: 1.97 (d,  $J = 0.5$  Hz, 3 H,  $\text{CH}_3$ ), 3.67 (s, 3H,  $\text{CH}_3$ ), 4.71 (d,  $J = 0.5$  Hz, 1H, CH), 6.98-7.03 (m, 2H,  $\text{CH}_{\text{ar}}$ ), 7.25-7.30 (m, 2H,  $\text{CH}_{\text{ar}}$ ), 10.32 (s, 1H, NH); **<sup>13</sup>C NMR (75 MHz,  $\text{CDCl}_3$ )**: 20.2 ( $\text{CH}_3$ ), 50.3 ( $\text{CH}_3$ ), 86.3 (CH), 125.6 ( $\text{CH}_{\text{ar}}$ ), 129.1 ( $\text{CH}_{\text{ar}}$ ), 130.4 ( $\text{C}_{\text{ar}}$ ), 137.9 ( $\text{C}_{\text{ar}}$ ), 158.5 ( $\text{C}_{\text{q}}$ ), 170.7 (CO).

### (Z)-Methyl 3-(3-acetylphenylamino)but-2-enoate (1o)



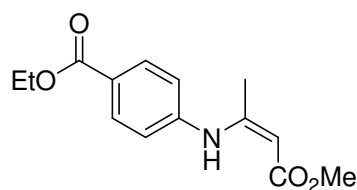
Following a modified procedure by G. Bartoli,<sup>[5]</sup> 3-aminoacetophenone (5.41 g, 40 mmol, 1.0 eq), methyl acetoacetate (4.31 mL, 40 mmol, 1 eq), Zn(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O (745 mg, 2 mmol, 5 mol %), MgSO<sub>4</sub>·xH<sub>2</sub>O (2.4 g, 20 mmol, 0.5 eq) are stirred in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) at 60 °C for 17 h. The mixture is cooled to rt, filtered and the solvents are evaporated. After rapid flash chromatography (silica, pentane/EtOAc/NEt<sub>3</sub> 5:1:0.5), the product is obtained as a yellow solid (6.86 g, 74%). **R<sub>F</sub>** (pentane/EtOAc/NEt<sub>3</sub> 5:1:0.1): 0.62; **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)**: 1.87 (s, 3H, CH<sub>3</sub>), 2.43 (s, 3H, CH<sub>3</sub>), 3.53 (s, 3H, CH<sub>3</sub>), 4.59 (s, 1H, CH), 7.10-7.12 (m, 1H, CH<sub>ar</sub>), 7.26 (t, *J* = 7.8 Hz, 1H, CH<sub>ar</sub>), 7.51 (t, *J* = 1.8 Hz, CH<sub>ar</sub>), 7.56 (dt, *J* = 7.8 Hz, *J* = 1.2 Hz, 1H, CH<sub>ar</sub>), 10.31 (s, 1H, NH); **<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)**: 20.2 (CH<sub>3</sub>), 26.6 (CH<sub>3</sub>), 50.3 (CH<sub>3</sub>), 86.8 (CH), 123.4 (CH<sub>ar</sub>), 124.6 (CH<sub>ar</sub>), 128.4 (CH<sub>ar</sub>), 129.3 (CH<sub>ar</sub>), 138.0 (C<sub>ar</sub>), 139.8 (C<sub>ar</sub>), 158.2 (C<sub>q</sub>), 170.6 (CO), 197.3 (CO); **ESI-MS**: calculated [C<sub>13</sub>H<sub>15</sub>NNaO<sub>3</sub>]<sup>+</sup>: 256.0944, found: 256.0984; **ATR-FTIR [cm<sup>-1</sup>]**: 3126, 2956, 1682, 1629, 1585, 1512, 1465, 1272, 1212, 1157, 780, 729, 679.

### (Z)-Methyl 3-(4-acetylphenylamino)but-2-enoate (1p)



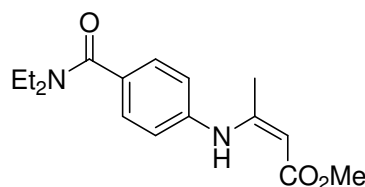
Following a modified procedure by G. Bartoli,<sup>[5]</sup> 4-aminoacetophenone (5.41 g, 40 mmol, 1.0 eq), methyl acetoacetate (4.31 mL, 40 mmol, 1 eq), Zn(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O (745 mg, 2 mmol, 5 mol %), MgSO<sub>4</sub>·xH<sub>2</sub>O (2.4 g, 20 mmol, 0.5 eq) are stirred in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) at 60 °C for 17 h. The mixture is cooled to rt, filtered and the solvents are evaporated. After rapid flash chromatography (silica, pentane/EtOAc/NEt<sub>3</sub> 5:1:0.5), the product is obtained as a yellow solid (3.04 g, 30%). **R<sub>F</sub>** (pentane/EtOAc/NEt<sub>3</sub> 5:1:0.1): 0.54; **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)**: 2.14 (d, *J* = 0.5 Hz, 3H, CH<sub>3</sub>), 2.55 (s, 3H, CH<sub>3</sub>), 3.68 (s, 3H, CH<sub>3</sub>), 4.79 (d, *J* = 0.6 Hz, 1H, CH), 7.09 (d, *J* = 8.4 Hz, 2H, CH<sub>ar</sub>), 7.90 (d, *J* = 8.4 Hz, 2H, CH<sub>ar</sub>), 10.67 (s, 1H, NH); **<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)**: 20.8 (CH<sub>3</sub>), 26.3 (CH<sub>3</sub>), 50.5 (CH<sub>3</sub>), 88.9 (CH), 121.5 (CH<sub>ar</sub>), 129.7 (CH<sub>ar</sub>), 132.4 (C<sub>ar</sub>), 144.0 (C<sub>ar</sub>), 157.0 (C<sub>q</sub>), 170.5 (CO), 196.6 (CO); **ESI-MS**: calculated [C<sub>13</sub>H<sub>15</sub>NNaO<sub>3</sub>]<sup>+</sup>: 256.0944, found: 256.0954; **ATR-FTIR [cm<sup>-1</sup>]**: 3180, 3118, 2950, 1640, 1594, 1351, 1264, 1163, 785.

**(Z)-Ethyl 4-(4-methoxy-4-oxobut-2-en-2-ylamino) benzoate (1q)**



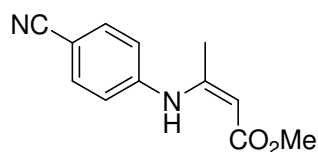
Following a modified procedure by G. Bartoli,<sup>[5]</sup> ethyl-4-aminobenzoate (6.61 g, 40 mmol, 1.0 eq), methyl acetoacetate (4.31 mL, 40 mmol, 1.0 eq),  $\text{Zn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$  (745 mg, 2 mmol, 5 mol%),  $\text{MgSO}_4 \cdot x\text{H}_2\text{O}$  (2.4 g, 20 mmol, 0.5 eq) are stirred in  $\text{CH}_2\text{Cl}_2$  (10 mL) at 60 °C for 14 h. The mixture is cooled to rt, filtered and the solvents are evaporated. After rapid flash chromatography (silica, pentane/EtOAc/ $\text{NEt}_3$  5:1:0.5), the product is obtained as a yellow solid (5.20 g, 49%). **R<sub>F</sub>** (pentane/EtOAc/ $\text{NEt}_3$  10:3:0.1): 0.53; **<sup>1</sup>H NMR (400 MHz,  $\text{CDCl}_3$ )**: 1.38 (t,  $J$  = 7.1 Hz, 3H,  $\text{CH}_3$ ), 2.12 (s, 3H,  $\text{CH}_3$ ), 3.69 (s, 3H,  $\text{CH}_3$ ), 4.35 (q,  $J$  = 7.1 Hz, 2H,  $\text{CH}_2$ ), 4.78 (s, 1H, CH), 7.08 (d,  $J$  = 8.7 Hz, 1H,  $\text{CH}_{\text{ar}}$ ), 7.98 (d,  $J$  = 8.7 Hz,  $\text{CH}_{\text{ar}}$ ), 10.63 (s, 1H, NH); **<sup>13</sup>C NMR (100 MHz,  $\text{CDCl}_3$ )**: 14.3 ( $\text{CH}_3$ ), 20.7 ( $\text{CH}_2$ ), 50.4 ( $\text{CH}_3$ ), 60.8 ( $\text{CH}_3$ ), 88.4 (CH), 121.8 ( $\text{CH}_{\text{ar}}$ ), 125.6 ( $\text{C}_{\text{ar}}$ ), 130.8 ( $\text{CH}_{\text{ar}}$ ), 143.7 ( $\text{C}_{\text{ar}}$ ), 157.3 ( $\text{C}_q$ ), 166.0 (CO), 170.5 (CO); **ESI-MS**: calculated  $[\text{C}_{14}\text{H}_{17}\text{NNaO}_4]^+$ : 286.1050, found: 286.1042; **ATR-FTIR [ $\text{cm}^{-1}$ ]**: 3001, 1707, 1637, 1601, 1362, 1263, 1162, 1104, 918, 763.

**(Z)-Methyl 3-(4-(diethylcarbamoyl)phenylamino)but-2-enoate (1r)**



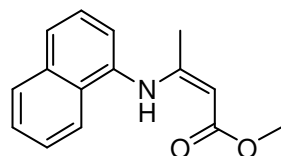
Following a modified procedure of Y. Wang,<sup>[4]</sup> a mixture of methyl acetoacetate (0.54 mL, 5 mmol, 1.0 eq), 4-amino-*N,N*-diethylbenzamide (961 mg, 5 mmol, 1.0 eq) and  $\text{InBr}_3$  (18 mg, 0.05 mmol, 1 mol%) in  $\text{CH}_2\text{Cl}_2$  (5 mL) is stirred at 80 °C for 24 h. After completion of the reaction, the solvent is removed under reduced pressure. Purification by flash chromatography (silica, pentane/EtOAc/ $\text{NEt}_3$  4/1/0.05) afforded the product as an off-white solid (1.16 g, 3.99 mmol, 80%). **R<sub>F</sub>** (pentane/EtOAc/ $\text{NEt}_3$  1:1:0.02): 0.30; **<sup>1</sup>H NMR (400 MHz,  $\text{CDCl}_3$ )**: 1.15 (br s, 6H,  $2 \times \text{CH}_3$ ), 2.01 (s, 3H,  $\text{CH}_3$ ), 3.27 (br s, 2H,  $\text{CH}_2$ ), 3.49 (br s, 2H,  $\text{CH}_2$ ), 3.65 (s, 3H,  $\text{CH}_3$ ), 4.70 (s, 1H, CH), 7.04-7.07 (m, 2H,  $\text{CH}_{\text{ar}}$ ), 7.321-7.33 (m, 2H,  $\text{CH}_{\text{ar}}$ ), 10.43 (s, 1H, NH); **<sup>13</sup>C NMR (100 MHz,  $\text{CDCl}_3$ )**: 13.0 ( $\text{CH}_3$ ), 14.3 ( $\text{CH}_3$ ), 20.5 ( $\text{CH}_3$ ), 39.4 ( $\text{CH}_2$ ), 43.5 ( $\text{CH}_2$ ), 50.4 ( $\text{CH}_3$ ), 86.9 (CH), 123.5 ( $\text{CH}_{\text{ar}}$ ), 127.6 ( $\text{CH}_{\text{ar}}$ ), 133.4 ( $\text{C}_{\text{ar}}$ ), 140.3 ( $\text{C}_{\text{ar}}$ ), 158.4 (C), 170.6 (CO), 170.8 (CO); **GC-MS, R<sub>t</sub> (method A)**: 14.8 min, **(EI) m/z (%)**: 289.1 (41), 218.0 (100), 186 (15), 130 (12); **ESI-MS**: calculated  $[\text{C}_{16}\text{H}_{22}\text{N}_2\text{NaO}_3]^+$ : 313.1523, found: 313.1508; **ATR-FTIR [ $\text{cm}^{-1}$ ]**: 3193, 2974, 2946, 1655, 1598, 1568, 1522, 1472, 1433, 1388, 1365, 1271, 1230, 1161, 1099, 1061, 1012, 942, 917, 866, 848, 796, 760, 718, 648, 612.

**(Z)-Methyl 3-(4-cyanophenylamino)but-2-enoate (1s)<sup>[6]</sup>**



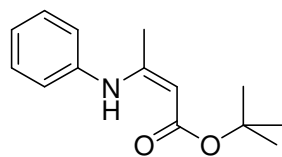
Following a modified procedure of Y. Wang,<sup>[4]</sup> a mixture of methyl acetoacetate (0.54 mL, 5 mmol, 1.0 eq), 4-aminobenzonitrile (591 mg, 5 mmol, 1.0 eq) and  $\text{InCl}_3$  (11 mg, 0.05 mmol, 1 mol%) is stirred at 50 °C for 3 h. After purification by flash chromatography (silica, pentane/EtOAc/ $\text{NEt}_3$  7:3:0.1) the product is obtained as white needles (615 mg, 2.84 mmol, 28%).  $R_F$  (pentane/EtOAc/ $\text{NEt}_3$  5:1:0.06): 0.15;  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ): 2.16 (s, 3H,  $\text{CH}_3$ ), 3.70 (s, 3H,  $\text{CH}_3$ ), 4.84 (d,  $J = 0.7$  Hz, 1H,  $\text{CH}$ ), 7.09-7.12 (m, 2H,  $\text{CH}_{\text{ar}}$ ), 7.57-7.60 (m, 2H,  $\text{CH}_{\text{ar}}$ ), 10.72 (s, 1H, NH);  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ ): 21.0 ( $\text{CH}_3$ ), 50.8 ( $\text{CH}_3$ ), 90.13 (CH), 106.6 ( $\text{C}_{\text{ar}}$ ), 119.0 (CN), 122.0 ( $\text{CH}_{\text{ar}}$ ), 133.5 ( $\text{CH}_{\text{ar}}$ ), 143.5 ( $\text{C}_{\text{ar}}$ ), 156.5 (C), 170.6 (CO); GC-MS,  $R_t$  (method B): 8.8 min, (EI)  $m/z$  (%): 216.1 (41), 185.1 (25), 168.9 (19), 143.0 (100), 101.9 (35); ESI-MS: calculated  $[\text{C}_{12}\text{H}_{12}\text{N}_2\text{NaO}_2]^+$ : 239.0791, found: 239.0788; ATR-FTIR [ $\text{cm}^{-1}$ ]: 3280, 3130, 3009, 2954, 2219, 1641, 1602, 1569, 1520, 1434, 1386, 1280, 1234, 1169, 1057, 958, 919, 825, 784, 720, 649, 597, 542, 477, 439.

**(Z)-Methyl-3-(1-naphthylamino)but-2-enoate (1t)**



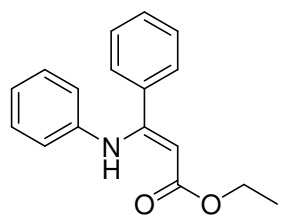
Following a modified procedure of Y. Wang,<sup>[4]</sup> a mixture of methyl acetoacetate (2.6 mL, 24 mmol, 1.2 eq), 1-naphthylamine (2.86 g, 20 mmol, 1 eq),  $\text{InBr}_3$  (354 mg, 1.0 mmol, 5 mol%) and  $\text{MgSO}_4$  (2.41 g, 20 mmol, 1 eq) in  $\text{CH}_2\text{Cl}_2$  (20 mL) is stirred at room temperature for 3 h. The crude mixture is filtered, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The residue is purified by flash chromatography (silica, pentane/EtOAc/ $\text{NEt}_3$  96:2:1). The pure product is obtained as a white solid (4.97, 17.0 mmol, 85%).  $R_F$  (pentane/EtOAc/ $\text{NEt}_3$  89:10:1): 0.55;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ): 1.59 (s, 3H,  $\text{CH}_3$ ), 3.48 (s, 3H,  $\text{CH}_3$ ), 4.56 (s, 1H, CH), 7.00 (d,  $J = 7.2$  Hz, 1H,  $\text{CH}_{\text{ar}}$ ), 7.17 (t,  $J = 8.1$  Hz, 1H,  $\text{CH}_{\text{ar}}$ ), 7.22-7.31 (m, 2H,  $\text{CH}_{\text{ar}}$ ), 7.48 (d,  $J = 8.3$  Hz, 1H,  $\text{CH}_{\text{ar}}$ ), 7.59-7.62 (m, 1H,  $\text{CH}_{\text{ar}}$ ), 7.78-7.81 (m, 1H,  $\text{CH}_{\text{ar}}$ ), 10.30 (s, 1H, NH);  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ ): 19.9 ( $\text{CH}_3$ ), 50.3 ( $\text{CH}_3$ ), 85.2 (CH), 122.6 ( $\text{CH}_{\text{ar}}$ ), 123.6 ( $\text{CH}_{\text{ar}}$ ), 125.2 ( $\text{CH}_{\text{ar}}$ ), 126.4 ( $\text{CH}_{\text{ar}}$ ), 126.6 ( $\text{CH}_{\text{ar}}$ ), 126.7 ( $\text{CH}_{\text{ar}}$ ), 128.1 ( $\text{CH}_{\text{ar}}$ ), 130.4 ( $\text{C}_{\text{ar}}$ ), 134.2 ( $\text{C}_{\text{ar}}$ ), 135.2 ( $\text{C}_{\text{ar}}$ ), 160.6 ( $\text{C}_{\text{q}}$ ), 171.0 (CO); ESI-MS: calculated  $[\text{C}_{15}\text{H}_{15}\text{NNaO}_2]^+$ : 264.0995, found: 264.0960. ATR-FTIR [ $\text{cm}^{-1}$ ]: 3224, 3047, 2998, 2952, 1642, 1590, 1507, 1488, 1459, 1432, 1376, 1328, 1253, 1189, 1156, 1083, 1051, 999, 940, 864, 779, 738, 738, 696, 663.

**(Z)-tert-butyl-3-(phenylamino)-but-2-enoate (1v)**<sup>[5]</sup>



Following a modified procedure by G. Bartoli<sup>[5]</sup>, aniline (6.99 g, 6.84 mL, 75.0 mmol, 1.5 eq), *tert*-butyl acetoacetate (7.91 g, 8.29 mL, 50.0 mmol, 1.0 eq), Zn(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O (931 mg, 2.50 mmol, 5 mol%) and MgSO<sub>4</sub> (1.81 g, 15.0 mmol, 0.3 eq) were stirred in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) at rt for 24 h. The mixture is diluted with CH<sub>2</sub>Cl<sub>2</sub> (100 mL), filtered through Celite and the solvents were evaporated. After rapid flash column chromatography (silica, pentane/EtOAc gradient 99/1-90/10, 1% NEt<sub>3</sub>), the product is obtained as a slightly yellow solid (11.35 g, 48.7 mmol, 97%). **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** 1.51 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 1.88 (s, 3 H, CH<sub>3</sub>), 4.64 (s, 1 H, CH), 7.07-7.14 (m, 3H, CH<sub>ar</sub>), 7.28-7.32 (m, 3H, CH<sub>ar</sub>), 10.37 (s, 1H, NH); **<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** 20.3 (CH<sub>3</sub>), 28.7 (C(CH<sub>3</sub>)<sub>3</sub>), 78.6 (C(CH<sub>3</sub>)<sub>3</sub>), 88.0 (CH), 124.4 (CH<sub>ar</sub>), 124.7 (CH<sub>ar</sub>), 129.1 (CH<sub>ar</sub>), 139.7 (C<sub>ar</sub>), 158.1 (C<sub>q</sub>), 170.5 (CO); **ESI-MS:** calculated [C<sub>14</sub>H<sub>19</sub>NNaO<sub>2</sub>]<sup>+</sup>: 256.1308, found: 256.1305.

**(Z)-Ethyl-3-(phenylamino)-3-phenylpropenoate (1x)**<sup>[7]</sup>



Following a modified procedure by Wentrup,<sup>[7a]</sup> aniline (11.64 g, 11.4 mL, 125 mmol, 5.0 eq), ethyl benzoylacetate (4.81 g, 4.3 mL, 25 mmol, 1.0 eq) and AcOH (7.2 mL, 125 mmol, 5.0 eq.) were stirred at 80 °C for 5 h. The mixture is diluted with water (50 mL), extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 100 mL), the combined organic phase is washed with brine, dried and concentrated. After flash column chromatography (silica, pentane/EtOAc gradient 85/15-0/100), the product is obtained as a slightly yellow solid (5.82 g, 21.8 mmol, 87%). **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** 1.31 (t, *J* = 7.1 Hz, 3H, CH<sub>3</sub>), 4.21 (q, *J* = 7.1 Hz, 2 H, CH<sub>2</sub>), 5.00 (s, 1 H, CH), 6.66 (d, *J* = 8.0 Hz, 2H, CH<sub>ar</sub>), 6.89 (t, *J* = 7.2 Hz, 1H, CH<sub>ar</sub>), 7.04-7.08 (m, 2H, CH<sub>ar</sub>), 7.24-7.36 (m, 5H, CH<sub>ar</sub>), 10.31 (s, 1H, NH); **<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** 14.6 (CH<sub>3</sub>), 59.4 (CH<sub>2</sub>), 91.3 (CH), 122.3 (CH<sub>ar</sub>), 123.0 (CH<sub>ar</sub>), 128.3 (CH<sub>ar</sub>), 128.5 (CH<sub>ar</sub>), 128.7 (CH<sub>ar</sub>), 129.5 (CH<sub>ar</sub>), 136.1 (C<sub>ar</sub>), 140.5 (C<sub>ar</sub>), 159.2 (C<sub>q</sub>), 170.2 (CO); **ESI-MS:** calculated [C<sub>17</sub>H<sub>17</sub>NNaO<sub>2</sub>]<sup>+</sup>: 290.1151, found: 290.1149.

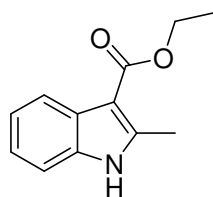
## 4. Typical procedure for the palladium-catalyzed cyclization

### a. General procedure

The enaminecarboxylate **1** (1 mmol) is stirred with Pd(OAc)<sub>2</sub> (0.1 mmol), Cu(OAc)<sub>2</sub> (3 mmol) and K<sub>2</sub>CO<sub>3</sub> (3 mmol) in DMF (12 mL) at the indicated temperature. When all starting material is consumed (TLC, GC, GC/MS-analysis) the mixture is cooled to rt and filtered through celite. The filter residue is washed with ethylacetate (100 mL) and the organic phase is washed with aqueous ammonia (5-10%, 100 mL). After extraction of the aqueous layer with ethylacetate (3x 100 mL), the organic layers were combined, washed with brine (100 mL) and dried with MgSO<sub>4</sub>. The solvents were removed under reduced pressure and the crude product **2** is purified by flash chromatography.

### b. Modified procedure with Cu(OAc)<sub>2</sub>·H<sub>2</sub>O

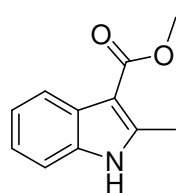
#### Ethyl 2-methyl-indole-3-carboxylate (**2u**)



Pd(OAc)<sub>2</sub> (11.2 mg, 0.05 mmol, 5 mol%), Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (599 mg, 3.0 mmol, 3.0 eq), K<sub>2</sub>CO<sub>3</sub> (415 mg, 3.0 mmol, 3.0 eq) are weighed on the bench under air into a not specially dried reaction vessel. Ethyl 3-anilinocrotonate (205 mg, 1.00 mmol) in DMF (12 mL) is added, the reaction vessel is evacuated and backfilled with Argon, closed and placed into a preheated oil bath at 140 °C for 15 min. After standard workup and purification by flash column chromatography (silica, pentane/EtOAc 4:1) the product is obtained as a light brown solid. (143 mg, 0.70 mmol, 70%). The product is of the same analytical purity as the one obtained under water-free conditions.

### c. One-pot procedure

#### Methyl 2-methyl-indole-3-carboxylate (**2a**)<sup>[8]</sup>

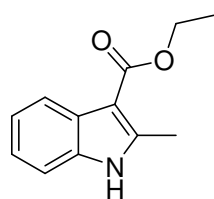


In a glovebox, InBr<sub>3</sub> (17.7 mg, 0.05 mmol, 0.01 eq) is weighed into a flame-dried 3 mL reaction tube. Aniline (466 mg, 456 µL, 5.00 mmol, 1.00 eq) and methyl acetoacetate were added subsequently under argon, the Teflon screw cap is closed and the mixture is stirred vigorously for 20 min at rt. Reaction

control via GC and GC/MS showed clean conversion to the enamine and only traces of aniline left. In the case of methyl 3-(phenylamino)but-2-enoate, the reaction mixture became solid and 3 mL DMF were added to allow efficient stirring. The mixture was transferred with a syringe into a 150 mL reaction flask containing Pd(OAc)<sub>2</sub> (56.1 mg, 0.25 mmol, 5 mol%), Cu(OAc)<sub>2</sub> (2.72 g, 15.0 mmol, 3.0 eq), K<sub>2</sub>CO<sub>3</sub> (2.07 g, 15.0 mmol, 3.0 eq) and DMF (50 mL), product residues were rinsed into the bigger flask with DMF (2 x 3mL). The reaction vessel was evacuated and backfilled with Argon three times, closed and placed into a preheated oil bath at 140 °C. The reaction mixture was stirred for 20 min (no more enamine substrate detectable by GC, GC/MS and TLC), cooled to rt, diluted with EtOAc (100 mL) and filtered through a short pad of silica and sea sand. The red-brown solid was washed with EtOAc (2 x 50 mL) and the combined filtrates were concentrated on a rotary evaporator and in high vacuum to yield 1.11 g of a black tar. The crude product was adsorbed on silica from a CH<sub>2</sub>Cl<sub>2</sub>-solution and purified by flash column chromatography (silica, pentane/EtOAc gradient, 95/5 – 60/40) to yield 680 mg (3.59 mmol, 72%) methyl 2-methyl-indole-3-carboxylate (**2a**) as a light brown solid. The product is of the same analytical purity as the one obtained from the isolated methyl 3-(phenylamino)-but-2-enoate (**1a**).

#### d. Large-Scale Indole Synthesis with reduced catalyst amount

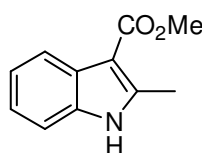
##### Ethyl 2-methyl-indole-3-carboxylate (**2u**)



Following the general procedure, ethyl 3-anilinocrotonate (2.05 g, 10.0 mmol) is stirred with Pd(OAc)<sub>2</sub> (44.8 mg, 0.20 mmol, 2 mol%), Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (5.99 g, 30.0 mmol, 3.0 eq), K<sub>2</sub>CO<sub>3</sub> (4.15 g, 30.0 mmol, 3.0 eq) and DMF (120 mL) under Argon in a preheated oil bath at 140 °C for 17 h. The reaction mixture is diluted with EtOAc (300 mL) and filtered through a short pad of silica. The solid is washed with EtOAc (2 x 100 mL), the combined filtrates are evaporated to dryness. After purification by flash column chromatography (silica, pentane/EtOAc 4:1) the product is obtained as a light brown solid (1.26 g, 6.20 mmol, 62%). The product is of the same analytical purity as the one obtained on a 1.0 mmol scale.

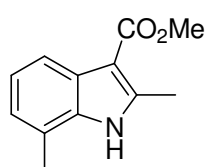
## 5. Characterization of indole products

### Methyl 2-methyl-indole-3-carboxylate (2a)<sup>[8]</sup>



Following the general procedure, the mixture is stirred in a preheated oil bath at 80 °C for 12 h. After purification by flash chromatography (silica, pentane/EtOAc 5:1) the product is obtained as an orange solid (136 mg, 0.72 mmol, 72%). **R<sub>F</sub>** (pentane/EtOAc 10:3): 0.20; **<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** 2.79 (s, 3H, CH<sub>3</sub>), 3.99 (s, 3H, CH<sub>3</sub>), 7.24-7.36 (m, 3H, CH<sub>ar</sub>), 8.16 (d, *J* = 7.4 Hz, 1H, CH<sub>ar</sub>), 8.53 (bs, 1H, NH); **<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** 14.1 (CH<sub>3</sub>), 50.8 (CH<sub>3</sub>), 104.4 (C<sub>ar</sub>), 110.5, 121.2, 121.7, 122.3 (CH<sub>ar</sub>), 127.1 134.5, 144.1 (C<sub>ar</sub>), 166.6 (CO).

### Methyl-2,7-dimethyl-3-indolecarboxylate (2b)

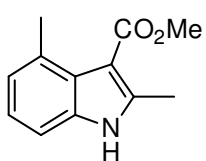
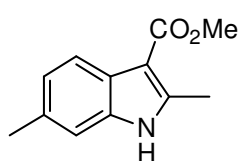


Following the general procedure, the mixture is stirred in a preheated oil bath at 110 °C for 14 h. After purification by flash chromatography (silica, pentane/EtOAc 4:1) the product is obtained as a brown solid (166 mg, 0.82 mmol, 82%). **R<sub>F</sub>** (pentane/EtOAc 7:3): 0.51; **<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**

2.48 (s, 3H, CH<sub>3</sub>), 2.75 (s, 3H, CH<sub>3</sub>), 3.94 (s, 3H, CH<sub>3</sub>), 7.00 (d, *J* = 7.2 Hz, 1H, CH<sub>ar</sub>), 7.15 (t, *J* = 7.5 Hz, 1H, CH<sub>ar</sub>), 7.95 (d, *J* = 8.0 Hz, 1H, CH<sub>ar</sub>), 8.57 (s, 1H, NH); **<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** 13.2 (CH<sub>3</sub>), 15.4 (CH<sub>3</sub>), 49.8 (CH<sub>3</sub>), 103.8 (C<sub>ar</sub>), 117.9 (C<sub>ar</sub>), 118.7 (CH<sub>ar</sub>), 120.8 (CH<sub>ar</sub>), 122.0 (CH<sub>ar</sub>), 125.7 (C<sub>ar</sub>), 132.9 (C<sub>ar</sub>), 142.7 (C<sub>ar</sub>), 165.7 (CO); **GC-MS R<sub>t</sub> (method B):** 9.1 min, **(EI) m/z (%):** 204.0 (14), 203.0 (84), 188.0 (14), 173.0(13), 172.0 (100), 171.1 (13), 144.1 (23), 143.0 (26), 142.0 (14), 115.0 (24); **ESI-MS:** calculated [C<sub>12</sub>H<sub>13</sub>NNaO<sub>2</sub>]<sup>+</sup>: 226.0838, found: 226.0822; **ATR-FTIR [cm<sup>-1</sup>]:** 3299, 3026, 2952, 1658, 1547, 1442, 1201, 1091, 809, 677, 596.

### Methyl-2,6-dimethyl-3-indolecarboxylate (2c)

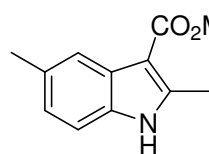
Following the general procedure, the mixture is stirred in a preheated oil bath at 80 °C for 16 h. After purification by flash chromatography (silica, pentane/EtOAc 4:1) the product is obtained as a brown solid (138 mg, 0.68 mmol, 68%) as a mixture of 4- and 6-substituted isomers (6-Me/4-Me 88:12). **R<sub>F</sub>** (pentane/EtOAc 7:3): 0.56; **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):**



2.44 (s, 3H, CH<sub>3</sub> of 6-Me), 2.64 (s, 3H, CH<sub>3</sub> of 4-Me), 2.70 (s, 3H, CH<sub>3</sub> of 4-Me), 2.71 (s, 3H, CH<sub>3</sub> of 6-Me), 3.90 (s, 3H, CH<sub>3</sub> of 4-Me), 3.92 (s, 3H, CH<sub>3</sub> of 6-Me), 7.05 (d, *J* = 8.00 Hz, 1H, CH<sub>ar</sub> of 6-Me), 7.08 (s, 1H, CH<sub>ar</sub> of 6-Me), 7.95 (d, *J* = 8.00 Hz, 1H, CH<sub>ar</sub> of 6-Me), 8.28 (s, 1H, NH); **<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** 14.1 (CH<sub>3</sub>), 21.6 (CH<sub>3</sub>), 50.7

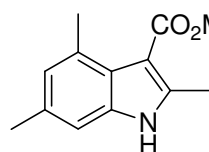
(CH<sub>3</sub>), 50.9 (CH<sub>3</sub>), 104.3 (C<sub>ar</sub>), 110.5 (CH<sub>ar</sub>), 120.9 (CH<sub>ar</sub>), 123.3 (CH<sub>ar</sub>), 124.8 (C<sub>ar</sub>), 132.1 (C<sub>ar</sub>), 134.8 (C<sub>ar</sub>), 143.4 (C<sub>ar</sub>), 166.6 (CO); Signals of the minor isomer are too weak to be detected! **GC-MS R<sub>t</sub> (method C):** 12.1 (for 4-Me) and 12.2 (for 6-Me), **(EI) m/z (%):** 203.9 (14), 203.1 (65), 202.9 (15), 172.2 (61), 171.0 (100), 144.0 (34), 143.0 (79), 142.7 (11), 142.0 (11), 114.9 (24) [for b] and 204.0 (13), 203.1 (100), 188.0 (19), 173.0 (11), 172.0 (81), 171.0 (15), 144.0 (20), 144.1 (24), 142.0 (13), 115.0 (15) [for 6-Me]; **ESI-MS:** calculated [C<sub>12</sub>H<sub>13</sub>NNaO<sub>2</sub>]<sup>+</sup>: 226.0838, found: 226.0841. **ATR-FTIR [cm<sup>-1</sup>]:** 3299, 3026, 2952, 1658, 1547, 1442, 1201, 1091, 809, 677, 596.

### Methyl-2,5-dimethyl-3-indolecarboxylate (2d)<sup>[9]</sup>



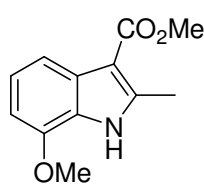
Following the general procedure, the mixture is stirred in a preheated oil bath at 80 °C for 12 h. After purification by flash chromatography (silica, pentane/EtOAc 4:1) the product is obtained as a pale brown solid (145 mg, 0.72 mmol, 72%). **GC-MS R<sub>t</sub> (method C):** 12.2 min, **(EI) m/z (%):** 204 (20), 188 (12), 173 (19), 172 (89), 171 (19), 144 (19), 143 (20), 115 (15), 85 (11), 203 (100), 204 (20). **<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** 2.48 (s, 3H, CH<sub>3</sub>), 2.70 (s, 3H, CH<sub>3</sub>), 3.95 (s, 3H, CH<sub>3</sub>), 7.02 (dd, *J* = 8.1 Hz, *J* = 1.2 Hz, CH<sub>ar</sub>), 7.14 (d, *J* = 8.1 Hz, 1H, CH<sub>ar</sub>), 7.91 (s, 1H, CH<sub>ar</sub>), 8.62 (s, 1H, NH); **<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** 14.2 (CH<sub>3</sub>), 21.6 (CH<sub>3</sub>), 50.8 (CH<sub>3</sub>), 103.7 (C<sub>ar</sub>), 110.2 (CH<sub>ar</sub>), 120.9 (CH<sub>ar</sub>), 123.7 (C<sub>ar</sub>), 127.3 (C<sub>ar</sub>), 131.1 (C<sub>ar</sub>), 132.8 (C<sub>ar</sub>), 144.2 (C<sub>ar</sub>), 166.8 (CO).

### Methyl-2,4,6-trimethyl-3-indolecarboxylate (2e)



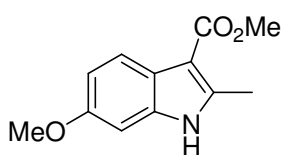
Following the general procedure, the mixture is stirred in a preheated oil bath at 110 °C for 12 h. After purification by flash chromatography (silica, pentane/EtOAc 4:1) the product is obtained as a pale orange solid (135 mg, 0.62 mmol, 62%). **R<sub>F</sub>** (pentane/EtOAc 7:3): 0.55; **<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** 2.37 (s, 3H, CH<sub>3</sub>), 2.57 (s, 3H, CH<sub>3</sub>), 2.68 (s, 3H, CH<sub>3</sub>), 3.89 (s, 3H, CH<sub>3</sub>), 6.82 (s, 1H, CH<sub>ar</sub>), 6.84 (s, 1H, CH<sub>ar</sub>), 8.45 (s, 1H, NH); **<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** 14.4 (CH<sub>3</sub>), 21.2 (CH<sub>3</sub>), 22.1 (CH<sub>3</sub>), 50.8 (CH<sub>3</sub>), 105.5 (C<sub>ar</sub>), 108.4 (CH<sub>ar</sub>), 123.2 (C<sub>ar</sub>), 125.6 (CH<sub>ar</sub>), 130.7 (C<sub>ar</sub>), 132.1 (C<sub>ar</sub>), 135.5 (C<sub>ar</sub>), 141.9 (C<sub>ar</sub>), 166.8 (CO); **GC-MS R<sub>t</sub> (method B):** 9.4 min, **(EI) m/z (%):** 218.0 (17), 217.1 (100), 206.0 (10), 186.1 (72), 185.0 (65), 158.1 (28), 157.1 (94), 156.1 (25), 143.9 (13), 130.0 (13), 127.9 (12), 115.0 (26); **ESI-MS:** calculated [C<sub>13</sub>H<sub>15</sub>NNaO<sub>2</sub>]<sup>+</sup>: 240.0995, found: 240.0997; **ATR-FTIR [cm<sup>-1</sup>]:** 3306, 3230, 2951, 2920, 1664, 1442, 1418, 1334, 1199, 1151, 1099, 1024.

### Methyl 7-methoxy-2-methyl-indole-3-carboxylate (2f)



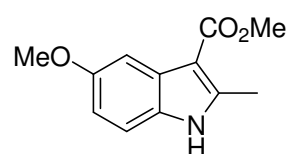
Following the general procedure, the mixture is stirred in a preheated oil bath at 140 °C for 30 min. After purification by flash chromatography (silica, pentane/EtOAc 5:1) the product is obtained as an orange solid. (140 mg, 0.64 mmol, 64%). **R<sub>F</sub>** (pentane/EtOAc 10:3): 0.50; **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)**: 2.74 (s, 3H, CH<sub>3</sub>), 3.93 (s, 3H, CH<sub>3</sub>), 3.94 (s, 3H, CH<sub>3</sub>), 6.66 (d, *J* = 7.5 Hz, 1H, CH<sub>ar</sub>), 7.13 (t, *J* = 8.0 Hz, 1H, CH<sub>ar</sub>), 7.67 (d, *J* = 8.1 Hz, 1H, CH<sub>ar</sub>), 8.62 (s, 1H, NH); **<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)**: 14.1 (CH<sub>3</sub>), 50.7 (CH<sub>3</sub>), 55.3 (CH<sub>3</sub>), 102.5 (CH<sub>ar</sub>), 104.9 (C<sub>ar</sub>), 113.9 (CH<sub>ar</sub>), 122.1 (CH<sub>ar</sub>), 124.7 (C<sub>ar</sub>), 128.4 (C<sub>ar</sub>), 143.3 (C<sub>ar</sub>), 145.3 (C<sub>ar</sub>), 166.6 (CO); **GC/MS R<sub>t</sub> (method B)**: 9.3 min, **(EI) m/z (%)**: 219.1 (100), 204.1 (18), 188 (85), 173 (32); **ESI-MS**: calculated [C<sub>12</sub>H<sub>13</sub>NNaO<sub>3</sub>]<sup>+</sup>: 242.0788, found: 242.0789. **ATR-FTIR [cm<sup>-1</sup>]**: 3342, 3317, 1670, 1452, 1277, 1083, 1026, 792, 737, 682, 646.

### Methyl 6-methoxy-2-methyl-indole-3-carboxylate (2g)



Following the general procedure, the mixture is stirred in a preheated oil bath at 140 °C for 30 min. After purification by flash chromatography (silica, pentane/EtOAc 5:1) the product is obtained as an orange solid. (141 mg, 0.64 mmol, 64%). **R<sub>F</sub>** (pentane/EtOAc 10:3): 0.56; **<sup>1</sup>H NMR (300 MHz, d<sup>6</sup>-DMSO)**: 2.61 (s, 3H, CH<sub>3</sub>), 3.76 (s, 3H, CH<sub>3</sub>), 3.78 (s, 3H, CH<sub>3</sub>), 6.76 (dd, *J* = 8.7 Hz, *J* = 2.3, 1H, CH<sub>ar</sub>), 6.85 (d, *J* = 2.2 Hz, 1H, CH<sub>ar</sub>), 7.76 (d, *J* = 8.7 Hz, CH<sub>ar</sub>), 11.63 (s, 1H, NH); **<sup>13</sup>C NMR (75 MHz, d<sup>6</sup>-DMSO)**: 13.5 (CH<sub>3</sub>), 50.3 (CH<sub>3</sub>), 55.1 (CH<sub>3</sub>), 94.6, 102.4, 110.3, 120.6, 120.9, 135.4, 143.4, 155.5 (C<sub>ar</sub>), 165.4 (CO); **GC/MS R<sub>t</sub> (method A)**: 14.1 min, **(EI) m/z (%)**: 219 (100), 204 (42), 188 (27), 172 (24), 159 (13), 144 (11); **ESI-MS**: calculated [C<sub>12</sub>H<sub>13</sub>NNaO<sub>3</sub>]<sup>+</sup>: 242.0788, found: 242.0791; **ATR-FTIR [cm<sup>-1</sup>]**: 3278, 1660, 1627, 1552, 1454, 1337, 1198, 1158, 1092, 812.

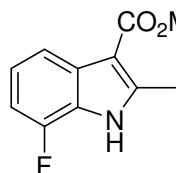
### Methyl 5-methoxy-2-methyl-indole-3-carboxylate (2h)



Following the general procedure, the mixture is stirred in a preheated oil bath at 140 °C for 30 min. After purification by flash chromatography (silica, pentane/EtOAc 5:1) the product is obtained as an orange solid. (149 mg, 0.68 mmol, 68%). **R<sub>F</sub>** (pentane/EtOAc 10:3): 0.52; **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)**: 2.71 (s, 3H, CH<sub>3</sub>), 3.88 (s, 3H, CH<sub>3</sub>), 3.93 (s, 3H, CH<sub>3</sub>), 6.83 (dd, *J* = 8.7 Hz, *J* = 2.5 Hz, 1H, CH<sub>ar</sub>), 7.18 (d, *J* = 8.7 Hz, 1H, CH<sub>ar</sub>), 7.61 (d, *J* = 2.5 Hz, CH<sub>ar</sub>), 8.38 (s, 1H,

NH); **<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)**: 14.4 (CH<sub>3</sub>), 50.8 (CH<sub>3</sub>), 55.8 (CH<sub>3</sub>), 103.4 (CH<sub>ar</sub>), 104.3 (C<sub>ar</sub>), 111.2 (CH<sub>ar</sub>), 112.1 (CH<sub>ar</sub>), 128.0 (C<sub>ar</sub>), 129.3 (C<sub>ar</sub>), 144.2 (C<sub>ar</sub>), 155.6 (C<sub>ar</sub>), 166.5 (CO); **GC/MS R<sub>t</sub> (method B)**: 9.5 min; **(EI) m/z (%)**: 219 (100), 204 (28), 188 (48), 176 (10); **ESI-MS**: calculated [C<sub>12</sub>H<sub>13</sub>NNaO<sub>3</sub>]<sup>+</sup>: 242.0788, found: 242.0798; **ATR-FTIR [cm<sup>-1</sup>]**: 3271, 1656, 1587, 1452, 1194, 1162, 1087, 1027, 850, 702.

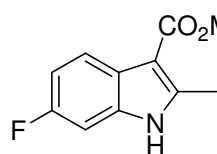
### Methyl-7-fluoro-2-methyl-indole-3-carboxylate (2i)<sup>[10]</sup>



Following the general procedure, the mixture is stirred in a preheated oil bath at 110 °C for 5 h. After purification by flash chromatography (silica, pentane/EtOAc 4:1) the product is obtained as a yellow solid (161 mg, 0.78 mmol, 78 %). **R<sub>F</sub>** (pentane/EtOAc 7:3): 0.70; **<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)**: 2.77 (s, 3H, CH<sub>3</sub>), 3.93 (s, 3H, CH<sub>3</sub>), 6.91 (ddd, *J* = 10.8 Hz, *J* = 8.1 Hz, *J* = 0.6 Hz, 1H, CH<sub>ar</sub>), 7.11 (dt, *J* = 8.1 Hz, *J* = 5.1 Hz, 1H, CH<sub>ar</sub>), 7.84 (d, *J* = 8.1 Hz, 1H, CH<sub>ar</sub>), 8.56 (s, 1H, NH); **<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)**: 14.2 (CH<sub>3</sub>), 50.9 (CH<sub>3</sub>), 105.3 (C<sub>ar</sub>), 107.3 (d, *J*<sub>(C,F)</sub> = 15.7 Hz, C<sub>ar</sub>), 116.9 (d, *J*<sub>(C,F)</sub> = 3.5 Hz, CH<sub>ar</sub>), 121.9 (d, *J*<sub>(C,F)</sub> = 6.2 Hz, CH<sub>ar</sub>), 122.7 (d, *J*<sub>(C,F)</sub> = 13.3 Hz, C<sub>ar</sub>), 130.4 (d, *J*<sub>(C,F)</sub> = 4.5 Hz, C<sub>ar</sub>), 144.6 (C<sub>ar</sub>), 148.7 (d, *J*<sub>(C,F)</sub> = 243.6 Hz, C<sub>ar</sub>), 166.2 (CO). **GC-MS R<sub>t</sub> (method B)**: 8.6 min, **(EI) m/z (%)**: 207.0 (69), 177.0 (11), 176.0 (100), 175.0 (12), 148.0 (16), 147.0 (15), 146.0 (12), 101.0 (13); **ESI-MS**: calculated [C<sub>11</sub>H<sub>10</sub>FNNaO<sub>2</sub>]<sup>+</sup>: 230.0588, found: 230.0592; **ATR-FTIR [cm<sup>-1</sup>]**: 3271, 3008, 2949, 1660, 1581, 1474, 1452, 1372, 1309, 1275, 1217, 1157, 1106, 1064, 1040, 998, 874, 827, 792, 767, 710, 629, 600.

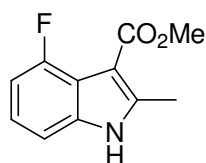
### Methyl-6-fluoro-2-methyl-3-indolecarboxylate & Methyl-4-fluoro-2-methyl-3-indolecarboxylate (2j)

Following the general procedure, the mixture was stirred in a preheated oil bath at 110 °C for 14 h. After purification by flash chromatography (silica, pentane/EtOAc 4:1), the 4- and 6-substituted isomers are obtained as pale brown solids (153 mg, 0.74 mmol, 74 %) (6-F/4-F = 53:47).



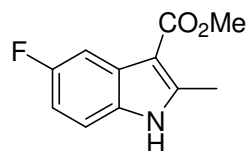
**R<sub>F</sub>** (pentane/EtOAc 7:3): 0.63; **<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)**: 2.74 (s, 3H, CH<sub>3</sub>), 3.93 (s, 3H, CH<sub>3</sub>), 7.18 (dd, *J* = 8.4 Hz, *J* = 1.8 Hz, 1H, CH<sub>ar</sub>), 7.29 (d, *J* = 1.2 Hz, 1H, CH<sub>ar</sub>), 7.99 (d, *J* = 8.7 Hz, 1H), 8.27 (s, 1H, NH); **<sup>13</sup>C NMR (75 MHz, d<sup>6</sup>-DMSO)**: 13.8 (CH<sub>3</sub>), 50.7 (CH<sub>3</sub>), 101.7 (C<sub>ar</sub>), 106.9 (d, *J*<sub>(C,F)</sub> = 21.5 Hz, CH<sub>ar</sub>), 107.7 (d, *J*<sub>(C,F)</sub> = 3.6 Hz, CH<sub>ar</sub>), 114.2 (d, *J*<sub>(C,F)</sub> = 18.7 Hz, C<sub>ar</sub>), 122.5 (d, *J*<sub>(C,F)</sub> = 8.0 Hz, CH<sub>ar</sub>), 137.7 (d, *J*<sub>(C,F)</sub> = 10.8 Hz, C<sub>ar</sub>), 144.8 (C<sub>ar</sub>), 154.7 (d,

$J_{(C,F)} = 248.9$  Hz,  $C_{ar}$ ), 164.6 (CO). **GC-MS  $R_t$  (method B):** 9.0 min, **(EI)  $m/z$  (%):** 207.0 (65), 177.0 (10), 176.0 (100), 175.0 (10), 147.9 (16), 145.9 (14), 101.0 (15); **ESI-MS:** calculated  $[C_{11}H_{10}FNNaO_2]^+$ : 230.0588, found: 230.0597; **ATR-FTIR  $[cm^{-1}]$ :** 3309, 3010, 2954, 1678, 1630, 1582, 1538, 1444, 1364, 1371, 1261, 1205, 1096, 1024, 984, 807, 762, 723, 692, 636, 591.



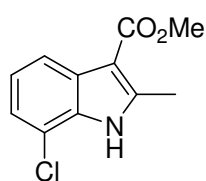
**$R_F$**  (pentane/EtOAc 7:3): 0.54;  **$^1H$  NMR (300 MHz,  $CDCl_3$ ):** 2.71 (s, 3H,  $CH_3$ ), 3.93 (s, 3H,  $CH_3$ ), 6.93-7.00 (m, 2H,  $CH_{ar}$ ), 8.01 (dd,  $J = 5.4$  Hz,  $J = 9.5$  Hz, 1H,  $CH_{ar}$ ), 8.75 (s, 1H, NH);  **$^{13}C$  NMR (75 MHz,  $CDCl_3$ ):** 14.1 ( $CH_3$ ), 50.9 ( $CH_3$ ), 97.2 (d,  $J_{(C,F)} = 26.3$  Hz,  $CH_{ar}$ ), 104.3 ( $C_{ar}$ ), 110. (d,  $J_{(C,F)} = 23.6$  Hz,  $CH_{ar}$ ), 122.0 (d,  $J_{(C,F)} = 9.6$  Hz,  $CH_{ar}$ ), 123.5 ( $C_{ar}$ ), 134.4 (d,  $J_{(C,F)} = 12.3$  Hz,  $C_{ar}$ ), 144.5 ( $C_{ar}$ ), 159.7 (d,  $J_{(C,F)} = 238.6$  Hz,  $C_{ar}$ ), 166.4 (CO). **GC-MS  $R_t$  (method B):** 8.9 min, **(EI)  $m/z$  (%):** 208.0 (11), 207.0 (88), 192 (19), 177 (11), 176 (100), 174.9 (18), 174 (12), 147.9 (28), 147.0 (23), 146.0 (18), 120.0 (13), 101.0 (17); **ESI-MS:** calculated  $[C_{11}H_{10}FNNaO_2]^+$ : 230.0588, found: 230.0590; **ATR-FTIR  $[cm^{-1}]$ :** 3256, 3011, 2946, 1652, 1599, 1549, 1467, 1448, 1382, 1344, 1280, 1204, 1138, 1107, 1090, 1025, 984, 956, 838, 810, 786, 727, 686, 611.

### Methyl-5-fluoro-2-methyl-indole-3-carboxylate (2k)



Following the general procedure, the mixture is stirred in a preheated oil bath at 110 °C for 5 h. After purification by flash chromatography (silica, pentane/EtOAc 4:1) the product is obtained as a brown solid (153 mg, 0.74 mmol, 74 %).  **$R_F$**  (pentane/EtOAc 7:3): 0.42;  **$^1H$  NMR (300 MHz,  $CDCl_3$ ):** 2.74 (s, 3H,  $CH_3$ ), 3.93 (s, 3H,  $CH_3$ ), 6.92 (dt,  $J = 9.0$  Hz,  $J = 2.6$  Hz, 1H,  $CH_{ar}$ ), 7.21 (dd,  $J = 8.8$  Hz,  $J = 4.4$  Hz, 1H,  $CH_{ar}$ ), 7.75 (dd,  $J = 10.4$  Hz,  $J = 2.6$  Hz, 1H,  $CH_{ar}$ ), 8.47 (s, 1H, NH);  **$^{13}C$  NMR (75 MHz,  $CDCl_3$ ):** 14.3 ( $CH_3$ ), 50.9 ( $CH_3$ ), 104.8 ( $C_{ar}$ ), 106.8 (d,  $J_{(C,F)} = 25.3$  Hz,  $CH_{ar}$ ), 110.5 (d,  $J_{(C,F)} = 26.3$  Hz,  $CH_{ar}$ ), 111.1 (d,  $J_{(C,F)} = 9.8$  Hz,  $CH_{ar}$ ), 127.9 (d,  $J_{(C,F)} = 11.7$  Hz,  $C_{ar}$ ), 130.8 ( $C_{ar}$ ), 145.5 ( $C_{ar}$ ), 159.1 (d,  $J_{(C,F)} = 235.9$  Hz,  $C_{ar}$ ), 166.2 (CO). **GC-MS  $R_t$  (method B):** 8.9 min, **(EI)  $m/z$  (%):** 207.0 (76), 177.0 (11), 176.0 (100), 175.0 (17), 174.0 (10), 148.0 (16), 147.0 (12), 146.0 (10), 101.1 (11); **ESI-MS:** calculated  $[C_{11}H_{10}FNNaO_2]^+$ : 230.0588, found: 230.0581; **ATR-FTIR  $[cm^{-1}]$ :** 3272, 2951, 1983, 1846, 1548, 1441, 1337, 1296, 1189, 1156, 1109, 1087, 1008, 974, 877, 826, 804, 776, 709, 631, 600.

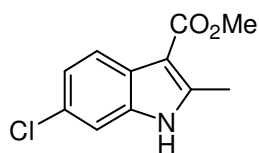
### Methyl-7-chloro-2-methyl-indole-3-carboxylate (2l)



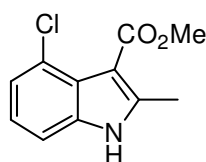
Following the general procedure, the mixture is stirred in a preheated oil bath at 80 °C for 12 h. After purification by flash chromatography (silica, pentane/EtOAc 4:1) the product is obtained as an orange solid (119 mg, 0.53 mmol, 53%).  $R_F$  (pentane/EtOAc 7:3): 0.59;  $^1H$  NMR (400 MHz,  $CDCl_3$ ): 2.78 (s, 3H,  $CH_3$ ), 3.93 (s, 3H,  $CH_3$ ), 7.13-7.21 (m, 2H,  $CH_{ar}$ ), 7.98 (d,  $J = 7.7$  Hz, 1H,  $CH_{ar}$ ), 8.51 (s, 1H, NH);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ ): 14.2 ( $CH_3$ ), 50.9 ( $CH_3$ ), 105.7 ( $C_{ar}$ ), 115.9 ( $C_{ar}$ ), 119.9 ( $CH_{ar}$ ), 121.8 ( $CH_{ar}$ ), 122.5 ( $CH_{ar}$ ), 128.5 ( $C_{ar}$ ), 131.7 ( $C_{ar}$ ), 144.4 ( $C_{ar}$ ), 166.0 (CO). GC-MS  $R_t$  (method B): 9.0 min, (EI)  $m/z$  (%): 225.0 (25), 223.0 (68), 208.0 (11), 194.0 (37), 193 (19), 192.0 (100), 191.0 (14), 164.0 (16), 162.9 (10), 128.0 (18), 102.0 (14), 101.1 (23), 75.0 (13); ESI-MS: calculated  $[C_{11}H_{10}ClNNaO_2]^+$ : 246.0292, found: 246.0287; ATR-FTIR [ $cm^{-1}$ ]: 3280, 2960, 1656, 1436, 1364, 1301, 1266, 1228, 1185, 1139, 1094, 1031, 981, 945, 867, 792, 734, 701, 589, 476.

### Methyl-6-chloro-2-methyl-indole-3-carboxylate & Methyl-4-chloro-2-methyl-indole-3-carboxylate (2m)<sup>[10]</sup>

Following the general procedure, the mixture is stirred in a preheated oil bath at 80 °C for 14 h. After purification by flash chromatography (silica, pentane/EtOAc 4:1), two products are obtained as brown solids (168 mg, 0.75 mmol, 75%) (6-Cl/4-Cl = 88:12).



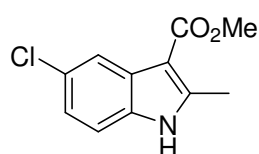
$R_F$  (pentane/EtOAc 7:3): 0.50;  $^1H$  NMR (300 MHz,  $d^6$ -DMSO): 2.67 (s, 3H,  $CH_3$ ), 3.84 (s, 3H,  $CH_3$ ), 7.17 (d,  $J = 8.5$  Hz, 1H,  $CH_{ar}$ ), 7.44 (s, 1H,  $CH_{ar}$ ), 7.91 (d,  $J = 8.5$  Hz, 1H,  $CH_{ar}$ ), 12.01 (s, 1H, NH);  $^{13}C$  NMR (75 MHz,  $d^6$ -DMSO): 14.6 ( $CH_3$ ), 51.5 ( $CH_3$ ), 103.7 ( $C_{ar}$ ), 111.9 ( $CH_{ar}$ ), 122.1 ( $CH_{ar}$ ), 122.5 ( $CH_{ar}$ ), 126.4 ( $C_{ar}$ ), 127.2 ( $C_{ar}$ ), 136.2 ( $C_{ar}$ ), 146.7 ( $C_{ar}$ ), 166.1 (CO). GC-MS  $R_t$  (method B): 9.5 min, (EI)  $m/z$  (%): 225.0 (35), 224.0 (11), 223.1 (87), 208.0 (14), 194.0 (36), 193.0 (16), 192.0 (100), 191.0 (22), 165.0 (10), 164.0 (22), 163.0 (17), 128.0 (14), 102.0 (113), 101.0 (15); ESI-MS: calculated  $[C_{11}H_{10}ClNNaO_2]^+$ : 246.0292, found: 246.0302; ATR-FTIR [ $cm^{-1}$ ]: 3319, 3003, 2954, 2909, 1659, 1546, 1495, 1458, 1435, 1411, 1346, 1272, 1199, 1132, 1097, 1065, 1009, 908, 807, 779, 736, 709, 670.



$R_F$  (pentane/EtOAc 7:3): 0.38;  $^1H$  NMR (300 MHz,  $d^6$ -DMSO): 2.57 (s, 3H,  $CH_3$ ), 3.82 (s, 3H,  $CH_3$ ), 7.11-7.18 (m, 2H,  $CH_{ar}$ ), 7.34-7.39 (m, 1H,  $CH_{ar}$ ), 12.07 (s, 1H, NH);  $^{13}C$  NMR (75 MHz,  $d^6$ -DMSO): 14.2 ( $CH_3$ ), 51.7 ( $CH_3$ ), 105.0 ( $C_{ar}$ ), 111.3 ( $CH_{ar}$ ), 123.1 ( $CH_{ar}$ ), 123.4 ( $CH_{ar}$ ), 124.2

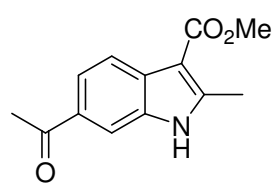
(C<sub>ar</sub>), 124.9 (C<sub>ar</sub>), 137.5, 144.2 (C<sub>ar</sub>), 165.9 (CO). **GC-MS R<sub>t</sub> (method B):** 9.6 min, **(EI) m/z (%)**: 281.0 (26), 225 (18), 223.0 (40), 207.9 (29), 207.0 (91), 194.0 (19), 191.9 (20), 78.0 (20), 73.0 (18), 44 (100), 39.9 (27); **ESI-MS:** calculated [C<sub>11</sub>H<sub>10</sub>ClNNaO<sub>2</sub>]<sup>+</sup>: 246.0292, found: 246.0302; **ATR-FTIR [cm<sup>-1</sup>]**: 3268, 3010, 2854, 1657, 1542, 1487, 1459, 1450, 1411, 1346, 1251, 1199, 1120, 1112, 1065, 1019, 909, 821, 732, 673, 625, 591.

### Methyl-5-chloro-2-methyl-indole-3-carboxylate (2n)



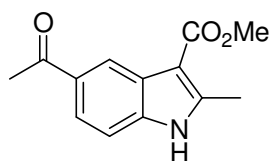
Following the general procedure, the mixture is stirred in a preheated oil bath at 80 °C for 12 h. After purification by flash chromatography (silica, pentane/EtOAc 4:1) the product is obtained as a pale brown solid (143 mg, 0.64 mmol, 64%). **R<sub>F</sub>** (pentane/EtOAc 7:3): 0.51; **<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)**: 2.74 (s, 3H, CH<sub>3</sub>), 3.94 (s, 3H, CH<sub>3</sub>), 7.13-7.22 (m, 2H, CH<sub>ar</sub>), 8.06 (d, *J* = 2.0 Hz, 1H, CH<sub>ar</sub>), 8.46 (s, 1H, NH); **<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)**: 14.2 (CH<sub>3</sub>), 50.9 (CH<sub>3</sub>), 104.4 (C<sub>ar</sub>), 111.4 (CH<sub>ar</sub>), 120.9 (CH<sub>ar</sub>), 122.7 (CH<sub>ar</sub>), 127.6 (C<sub>ar</sub>), 128.2 (C<sub>ar</sub>), 132.8 (C<sub>ar</sub>), 145.2 (C<sub>ar</sub>), 166.0 (CO). **GC-MS R<sub>t</sub> (method B):** 9.4 min, **(EI) m/z (%)**: 225.0 (37), 223.1 (81), 208.1 (14), 194.0 (31), 193.1 (11), 192.1 (100), 191.0 (29), 165.1 (9), 164.0 (20), 163.0 (15), 128.0 (11), 102.0 (11), 73.1 (12); **ESI-MS:** calculated [C<sub>11</sub>H<sub>10</sub>ClNNaO<sub>2</sub>]<sup>+</sup>: 246.0292, found: 246.0252; **ATR-FTIR [cm<sup>-1</sup>]**: 3310, 3000, 2944, 2902, 1649, 1547, 1491, 1432, 1411, 1382, 1273, 1199, 1132, 1091, 1063, 1009, 921, 802, 771, 726, 709, 671, 624.

### Methyl 6-acetyl-2-methyl-indole-3-carboxylate (2o)



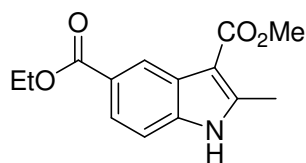
Following the general procedure, the mixture is stirred in a preheated oil bath at 140 °C for 30 min. After purification by flash chromatography (silica, CH<sub>2</sub>Cl<sub>2</sub>/EtOAc 10:1) the product is obtained as an orange/red solid (125 mg, 0.54 mmol, 54%). **R<sub>F</sub>** (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc 10:1): 0.20; **<sup>1</sup>H NMR (300 MHz, d<sup>6</sup>-DMSO)**: 2.60 (s, 3H, CH<sub>3</sub>), 2.69 (s, 3H, CH<sub>3</sub>), 3.83 (s, 3H, CH<sub>3</sub>), 7.75 (dd, *J* = 8.4 Hz, *J* = 1.6 Hz, 1H, CH<sub>ar</sub>), 7.94-7.98 (m, 2H, CH<sub>ar</sub>), 12.20 (s, 1H, NH); **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)**: 2.67 (s, 3H, CH<sub>3</sub>), 2.80 (s, 3H, CH<sub>3</sub>), 3.95 (s, 3H, CH<sub>3</sub>), 7.82 (dd, *J* = 8.4 Hz, *J* = 1.5 Hz, 1H, CH<sub>ar</sub>), 8.06 (d, *J* = 1.0 Hz, 1H, CH<sub>ar</sub>), 8.12 (d, *J* = 8.4 Hz, 1H, CH<sub>ar</sub>); **<sup>13</sup>C NMR (75 MHz, d<sup>6</sup>-DMSO)**: 13.9 (CH<sub>3</sub>), 26.6 (CH<sub>3</sub>), 50.6 (CH<sub>3</sub>), 103.1, 111.9, 119.8, 121.0, 130.4, 130.8, 134.2, 148.2 (C<sub>ar</sub>), 165.0 (CO), 197.3 (CO); **GC/MS R<sub>t</sub> (method A):** 15.2 min, **(EI) m/z (%)**: 231 (67), 261 (100), 200 (19), 156 (41); **ESI-MS:** calculated [C<sub>13</sub>H<sub>13</sub>NNaO<sub>3</sub>]<sup>+</sup>: 254.0788, found: 254.0779; **ATR-FTIR [cm<sup>-1</sup>]**: 3266, 2951, 1698, 1663, 1613, 1544, 1357, 1291, 1199, 1097, 821, 785, 724.

### Methyl 5-acetyl-2-methyl-indole-3-carboxylate (2p)



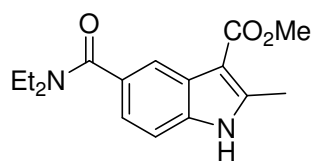
Following the general procedure, the mixture is stirred in a preheated oil bath at 140 °C for 30 min. After purification by flash chromatography (silica, pentane/EtOAc 2:1 – 1:1.5) the product is obtained as an orange solid. (120 mg, 0.52 mmol, 52%). **R<sub>F</sub>** (pentane/EtOAc 2:1): 0.21; **<sup>1</sup>H NMR (300 MHz, d<sup>6</sup>-DMSO)**: 2.61 (s, 3H, CH<sub>3</sub>), 2.67 (s, 3H, CH<sub>3</sub>), 3.85 (s, 3H, CH<sub>3</sub>), 7.44 (d, *J* = 8.5 Hz, 1H, CH<sub>ar</sub>), 7.77 (dd, *J* = 8.5 Hz, *J* = 1.6 Hz, 1H, CH<sub>ar</sub>), 8.56 (s, 1H, CH<sub>ar</sub>), 12.16 (s, 1H, NH); **<sup>13</sup>C NMR (75 MHz, d<sup>6</sup>-DMSO)**: 13.7 (CH<sub>3</sub>), 26.6 (CH<sub>3</sub>), 50.6 (CH<sub>3</sub>), 103.7, 111.7, 121.7, 122.2, 126.2, 130.4, 137.5, 148.2 (C<sub>ar</sub>), 165.1 (CO), 197.4 (CO); **GC/MS R<sub>t</sub> (method B)**: 10.2 min, **(EI) m/z (%)**: 231 (50), 216 (100), 200 (18), 156 (46); **ESI-MS**: calculated [C<sub>13</sub>H<sub>13</sub>NNaO<sub>3</sub>]<sup>+</sup>: 254.0788, found: 254.0777; **ATR-FTIR [cm<sup>-1</sup>]**: 3223, 1689, 1663, 1609, 1445, 1356, 1278, 1234, 1184, 951, 915, 812, 747.

### 5-Ethyl 3-methyl 2-methyl-indole-3,5-dicarboxylate (2q)



Following the general procedure, the mixture is stirred in a preheated oil bath at 140 °C for 30 min. After purification by flash chromatography (silica, CH<sub>2</sub>Cl<sub>2</sub>/EtOAc 20:1) the product is obtained as a yellow solid (166 mg, 0.64 mmol, 64%). **R<sub>F</sub>** (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc 10:1): 0.39; **<sup>1</sup>H NMR (300 MHz, d<sup>6</sup>-DMSO)**: 1.34 (t, *J* = 7.1 Hz, 3H, CH<sub>3</sub>), 2.67 (s, 3H, CH<sub>3</sub>), 3.84 (s, 3H, CH<sub>3</sub>), 4.32 (q, *J* = 7.1 Hz, 2H, CH<sub>2</sub>), 7.44 (dd, *J* = 8.5 Hz, *J* = 0.5 Hz, 1H, CH<sub>ar</sub>), 7.77 (dd, *J* = 8.5 Hz, *J* = 1.7 Hz, 1H, CH<sub>ar</sub>), 8.60 (d, *J* = 1.3 Hz, 1H, CH<sub>ar</sub>), 12.17 (s, 1H, NH); **<sup>13</sup>C NMR (75 MHz, d<sup>6</sup>-DMSO)**: 13.7 (CH<sub>3</sub>), 14.23 (CH<sub>3</sub>), 50.6 (CH<sub>3</sub>), 60.2 (CH<sub>2</sub>), 103.5, 111.1, 122.4, 122.6, 122.7, 126.3, 137.4, 146.4 (C<sub>ar</sub>), 165.0 (CO), 166.5 (CO); **GC/MS R<sub>t</sub> (method B)**: 10.5 min, **(EI) m/z (%)**: 261 (100), 246 (9), 230 (34), 216 (72), 202 (23), 156 (39); **ESI-MS**: calculated [C<sub>14</sub>H<sub>15</sub>NNaO<sub>4</sub>]<sup>+</sup>: 284.0893, found: 284.0879; **ATR-FTIR [cm<sup>-1</sup>]**: 3261, 2983, 1684, 1615, 1450, 1279, 1189, 1075, 765, 720.

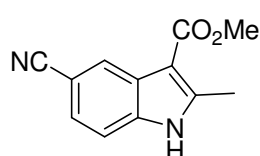
### Methyl 5-(diethylcarbamoyl)-2-methyl-indole-carboxylate (2r)



Following the general procedure, the mixture is stirred in a preheated oil bath at 140 °C for 30 min. After purification by flash chromatography (silica, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 24:1) the product is obtained as an orange solid (203 mg, 0.70 mmol, 70 %). **R<sub>F</sub>** (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 10:1): 0.47; **<sup>1</sup>H-NMR (400 MHz, d<sub>6</sub>-DMSO)**: 1.12 (s, 6H, 2xCH<sub>3</sub>), 2.66 (s, 3H, CH<sub>3</sub>), 3.31 (br s, 4H, 2xCH<sub>2</sub>), 3.81 (s, 3H, CH<sub>3</sub>), 7.12 (dd, *J* = 8.3 Hz, *J* = 1.5 Hz, 1H,

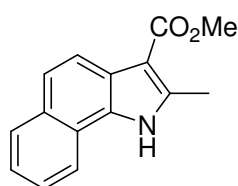
CH<sub>ar</sub>), 7.39 (d,  $J = 8.3$  Hz, 1H, CH<sub>ar</sub>), 7.91 (s,  $J = 1.5$  Hz, 1H, CH<sub>ar</sub>), 12.01 (s, 1H, NH); **<sup>13</sup>C-NMR (100 MHz, d<sub>6</sub>-DMSO)**: 13.7 (CH<sub>3</sub>), 43.0 (CH<sub>2</sub>), 50.6 (CH<sub>3</sub>), 103.0 (C<sub>ar</sub>), 111.1 (CH<sub>ar</sub>), 118.5 (C<sub>ar</sub>), 120.4 (CH<sub>ar</sub>), 126.1 (CH<sub>ar</sub>), 130.0 (C<sub>ar</sub>), 135.0 (C<sub>ar</sub>), 145.9 (C<sub>ar</sub>), 165.3 (CO), 171.1 (CO); **GC-MS, R<sub>t</sub> (method B)**: 10.2 min, **(EI) m/z (%)**: 287.1 (36), 257.1 (8), 216.0 (100), 156 (36); **ESI-MS**: calculated [C<sub>16</sub>H<sub>20</sub>N<sub>2</sub>NaO<sub>3</sub>]<sup>+</sup>: 311.1366, found: 311.1361; **ATR-FTIR (cm<sup>-1</sup>)**: 2982, 2928, 2749, 1685, 1579, 1446, 1388, 1361, 1325, 1288, 1248, 1167, 1125, 1098, 1079, 1025, 951, 913, 862, 819, 766, 715, 676, 645, 586.

### Methyl 5-cyano-2-methyl-indole-carboxylate (2s)



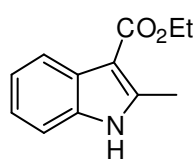
Following the general procedure, the mixture is stirred in a preheated oil bath at 140 °C for 30 min. After purification by flash chromatography (silica, pentane/EtOAc 7:3) the product is obtained as a white solid (139 mg, 0.65 mmol, 65%). **R<sub>F</sub>** (pentane/EtOAc 7:3): 0.14; **<sup>1</sup>H NMR (300 MHz, d<sub>6</sub>-DMSO)**: 2.65 (s, 3H, CH<sub>3</sub>), 3.83 (s, 3H, CH<sub>3</sub>), 7.46-7.52 (m, 2H, CH<sub>ar</sub>), 8.22 (s, 1H, CH<sub>ar</sub>), 12.33 (s, 1H, NH); **<sup>13</sup>C NMR (75 MHz, d<sub>6</sub>-DMSO)**: 13.6 (CH<sub>3</sub>), 50.8 (CH<sub>3</sub>), 103.2 (C<sub>ar</sub>), 103.2 (C<sub>ar</sub>), 112.6 (CH<sub>ar</sub>), 120.4 (CN), 124.7 (C<sub>ar</sub>), 125.1 (CH<sub>ar</sub>), 126.5 (CH<sub>ar</sub>), 136.7 (C<sub>ar</sub>), 147.4 (C<sub>ar</sub>), 164.8 (CO); **GC-MS, R<sub>t</sub> (method B)**: 10.2 min, **(EI) m/z (%)**: 214.0 (60), 183.0 (100), 155.0 (12); **ESI-MS**: calculated [C<sub>12</sub>H<sub>10</sub>N<sub>2</sub>NaO<sub>2</sub>]<sup>+</sup>: 237.0634, found: 237.0625; **ATR-FTIR (cm<sup>-1</sup>)**: 3272, 3009, 2955, 2217, 1665, 1619, 1469, 1435, 1302, 1280, 1206, 1188, 1153, 1126, 1092, 1009, 959, 889, 809, 781, 716.

### Methyl 2-methyl-benz[*g*]indole-3-carboxylate (2t)<sup>[11]</sup>



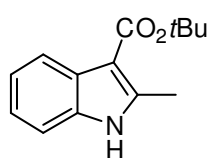
Following the general procedure, the mixture is stirred in a preheated oil bath at 80 °C for 14 h. After purification by flash chromatography (silica, pentane/EtOAc 4:1) the product is obtained as a yellow solid (203 mg, 0.85 mmol, 85%). **<sup>1</sup>H NMR (300 MHz, d<sub>6</sub>-DMSO)**: 2.76 (s, 3H, CH<sub>3</sub>), 3.85 (s, 3H, CH<sub>3</sub>), 7.40-7.46 (m, 1H, CH<sub>ar</sub>), 7.55-7.61 (m, 2H, CH<sub>ar</sub>), 7.93 (d,  $J = 8.0$  Hz, 1H, CH<sub>ar</sub>), 8.09 (d,  $J = 8.7$  Hz, 1H, CH<sub>ar</sub>), 8.37 (d,  $J = 8.3$  Hz, 1H, CH<sub>ar</sub>), 12.57 (s, 1H, NH); **<sup>13</sup>C NMR (75 MHz, d<sub>6</sub>-DMSO)**: 13.7 (CH<sub>3</sub>), 50.5 (CH<sub>3</sub>), 104.4 120.5, 120.6, 121.3, 121.5, 122.9, 123.9, 125.8, 128.4, 129.3, 129.7, 142.3 (C<sub>ar</sub>), 165.6 (CO). **GC-MS R<sub>t</sub> (method B)**: 10.6 min, **(EI) m/z (%)**: 240.0 (16), 239.0 (100), 224.0 (33), 208.0 (43), 207.0 (12), 206.0 (10), 180.0 (22), 179.0 (27), 178.0 (20), 153.0 (16), 152.0 (27), 151.0 (16).

### Ethyl 2-methyl-indole-3-carboxylate (**2u**)<sup>[12]</sup>



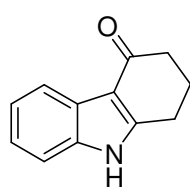
Following the general procedure, ethyl 3-anilinocrotonate (205 mg, 1.0 mmol) is stirred with Pd(OAc)<sub>2</sub> (11.2 mg, 0.05 mmol, 5 mol%), Cu(OAc)<sub>2</sub> (545 mg, 3.0 mmol, 3.0 eq), K<sub>2</sub>CO<sub>3</sub> (415 mg, 3.0 mmol, 3.0 eq) and DMF (12 mL) under Argon in a preheated oil bath at 140 °C for 15 min. After standard workup and purification by flash column chromatography (silica, pentane/EtOAc 4:1) the product is obtained as a light brown solid. (144 mg, 0.71 mmol, 71 %). **R<sub>F</sub>** (pentane/EtOAc 4:1): 0.34. **<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** 1.46 (t, *J* = 7.1 Hz, 3H, CH<sub>3</sub>), 2.71 (s, 3H, CH<sub>3</sub>), 4.43 (q, *J* = 7.1 Hz, 2H, CH<sub>2</sub>), 7.17-7.31 (m, 3H, CH<sub>ar</sub>), 8.12-8.15 (m, 1H, CH<sub>ar</sub>), 8.69 (s, 1H, NH); **<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** 14.3 (CH<sub>3</sub>), 14.7 (CH<sub>3</sub>), 59.7 (CH<sub>2</sub>), 104.6 (C<sub>ar</sub>), 110.7 (CH<sub>ar</sub>), 121.4 (CH<sub>ar</sub>), 121.8 (CH<sub>ar</sub>), 122.4 (CH<sub>ar</sub>), 127.3 (C<sub>ar</sub>), 134.7 (C<sub>ar</sub>), 144.3 (C<sub>ar</sub>), 166.4 (CO). **GC-MS, R<sub>t</sub> (method B):** 9.1 min, **(EI) m/z (%):** 203 (100), 188 (5), 174 (37), 158 (80), 130 (24), 103 (9); **ESI-MS:** calculated [C<sub>12</sub>H<sub>13</sub>NNaO<sub>2</sub>]<sup>+</sup>: 226.0838, found: 226.0849. **ATR-FTIR [cm<sup>-1</sup>]:** 3298, 2983, 1635, 1620, 1581, 1548, 1494, 1455, 1438, 1370, 1333, 1269, 1195, 1113, 1091, 1010, 783, 732, 689, 673, 580.

### *tert*-butyl 2-methyl-indole-3-carboxylate (**2v**)



Following the general procedure, (*Z*)-*tert*-butyl-3-(phenylamino)but-2-enoate (233 mg, 1.00 mmol) is stirred with Pd(OAc)<sub>2</sub> (11.2 mg, 0.05 mmol, 5 mol%), Cu(OAc)<sub>2</sub> (545 mg, 3.0 mmol, 3.0 eq.), K<sub>2</sub>CO<sub>3</sub> (415 mg, 3.0 mmol, 3.0 eq.) and DMF (12 mL) under Argon in a preheated oil bath at 140 °C for 15 min. After purification by flash column chromatography (silica, pentane/EtOAc 4:1) the product is obtained as an orange-brown solid. (183 mg, 0.79 mmol, 79%). **R<sub>F</sub>** (pentane/EtOAc 4:1): 0.48. **<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** 1.67 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 2.71 (s, 3H, CH<sub>3</sub>), 7.15-7.24 (m, 2H, CH<sub>ar</sub>), 7.25-7.30 (m, 1H, CH<sub>ar</sub>), 8.08-8.11 (m, 1H, CH<sub>ar</sub>), 8.38 (s, 1H, NH); **<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** 14.4 (CH<sub>3</sub>), 28.8 (C(CH<sub>3</sub>)<sub>3</sub>), 80.0 (C(CH<sub>3</sub>)<sub>3</sub>), 106.0 (C<sub>ar</sub>), 110.6 (CH<sub>ar</sub>), 121.4 (CH<sub>ar</sub>), 121.6 (CH<sub>ar</sub>), 122.3 (CH<sub>ar</sub>), 127.3 (C<sub>ar</sub>), 134.5 (C<sub>ar</sub>), 143.6 (C<sub>ar</sub>), 165.7 (CO). **GC-MS, R<sub>t</sub> (method B):** 9.2 min, **(EI) m/z (%):** 231 (24), 175 (100), 158 (41), 130 (35); **ESI-MS:** calculated [C<sub>14</sub>H<sub>17</sub>NNaO<sub>2</sub>]<sup>+</sup>: 254.1151, found: 254.1139. **ATR-FTIR [cm<sup>-1</sup>]:** 3292, 2978, 2934, 1652, 1582, 1548, 1458, 1439, 1388, 1366 1314, 1274, 1215, 1166, 1114, 1095, 1007, 847, 789, 741, 695, 583.

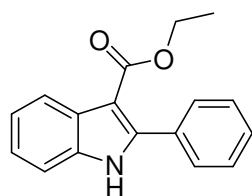
### 1,2-Dihydrocarbazol-4(3-H)-one (2w)<sup>[13]</sup>



Following the general procedure, the mixture is stirred in a preheated oil bath at 140 °C for 24 h. After purification by flash chromatography (silica, pentane/EtOAc 7:3) the product is obtained as a white solid (157 mg, 0.85 mmol, 85%). **R<sub>F</sub>** (pentane/EtOAc 7:3): 0.23; **<sup>1</sup>H-NMR (300 MHz, d<sup>6</sup>-**

**DMSO)**: 2.08-2.14 (m, 2H, CH<sub>2</sub>), 2.42 (t, *J* = 6.6 Hz, 2H, CH<sub>2</sub>), 2.95 (t, *J* = 6.2 Hz, 2H, CH<sub>2</sub>), 7.12-7.19 (m, 2H, CH<sub>ar</sub>), 7.39-7.42 (m, 1H, CH<sub>ar</sub>), 7.97-7.99 (m, 1H, CH<sub>ar</sub>), 11.85 (s, 1H, NH); **<sup>13</sup>C-NMR (75 MHz, d<sup>6</sup>-DMSO)**: 22.7 (CH<sub>2</sub>), 23.4 (CH<sub>2</sub>), 37.8 (CH<sub>2</sub>), 111.5 (CH<sub>ar</sub>), 111.8 (C<sub>ar</sub>), 120.2 (CH<sub>ar</sub>), 121.5 (C<sub>ar</sub>), 122.4 (CH<sub>ar</sub>), 124.6 (C<sub>ar</sub>), 135.9 (C<sub>ar</sub>), 152.3 (C<sub>ar</sub>), 192.9 (CO); **GC-MS R<sub>t</sub> (method B)**: 9.9 min, **(EI) m/z (%)**: 186.1 (13), 185.0 (100), 158.0 (10), 157.0 (100), 129.0 (67), 128.0 (16), 102.0 (15).

### Ethyl 2-phenyl-1H-indole-3-carboxylate (2x)<sup>[14]</sup>



(*Z*)-ethyl 3-phenyl-3-(phenylamino)acrylate (267 mg, 1.00 mmol), Pd(OAc)<sub>2</sub> (22.4 mg, 0.10 mmol, 0.10 eq.), Cu(OAc)<sub>2</sub> (545 mg, 3.0 mmol, 3.0 eq.) and K<sub>2</sub>CO<sub>3</sub> (415 mg, 3.0 mmol, 3.0 eq.) were weighed into a flame-dried microwave reaction vessel and suspended in DMF

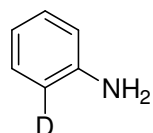
(12 mL). The reaction tube is closed, a temperature sensor is installed and the reaction mixture is exposed to microwave irradiation to maintain the temperature at 180 °C (short pulses of 300-850 W). Following standard work-up of the general procedure, an orange oil is obtained. After purification by flash column chromatography (silica, pentane/EtOAc 98/2-0/100) the product is obtained as a yellow solid. (182 mg, 0.68 mmol, 68%). **R<sub>F</sub>** (pentane/EtOAc 4:1): 0.58; **<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)**: 1.32 (t, *J* = 7.1 Hz, 3H, CH<sub>3</sub>), 4.29 (q, *J* = 7.1 Hz, 2H, CH<sub>2</sub>), 7.24-7.42 (m, 6H, CH<sub>ar</sub>), 7.62-7.65 (m, 2H, CH<sub>ar</sub>), 8.23-8.26 (m, 1H, CH<sub>ar</sub>), 8.74 (s, 1H, NH); **<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)**: 14.4 (CH<sub>3</sub>), 59.8 (CH<sub>2</sub>), 104.7 (C<sub>ar</sub>), 111.2 (CH<sub>ar</sub>), 122.1 (CH<sub>ar</sub>), 122.2 (CH<sub>ar</sub>), 123.3 (CH<sub>ar</sub>), 127.7 (C<sub>ar</sub>), 128.2 (CH<sub>ar</sub>), 129.3 (CH<sub>ar</sub>), 129.7 (CH<sub>ar</sub>), 132.1 (C<sub>ar</sub>), 135.3 (C<sub>ar</sub>), 144.7 (C<sub>ar</sub>), 165.6 (CO); **GC/MS, R<sub>t</sub> (method A)**: 15.7 min, **(EI) m/z (%)**: 265 (95), 237 (13), 220 (100), 193 (45), 165 (31), 95 (7); **ESI-MS**: calculated [C<sub>17</sub>H<sub>15</sub>NNaO<sub>2</sub>]<sup>+</sup>: 288.0995, found: 288.0985; **ATR-FTIR [cm<sup>-1</sup>]**: 3248, 2981, 1659, 1544, 1488, 1451, 1428, 1375, 1333, 1269, 1210, 1170, 1126, 1045, 1027, 934, 871, 834, 788, 765, 742, 722, 687, 609.

## 6. Mechanistic Experiments

### a. Determination of Intramolecular Kinetic Isotope Effect

#### Synthesis of deuterated substrates

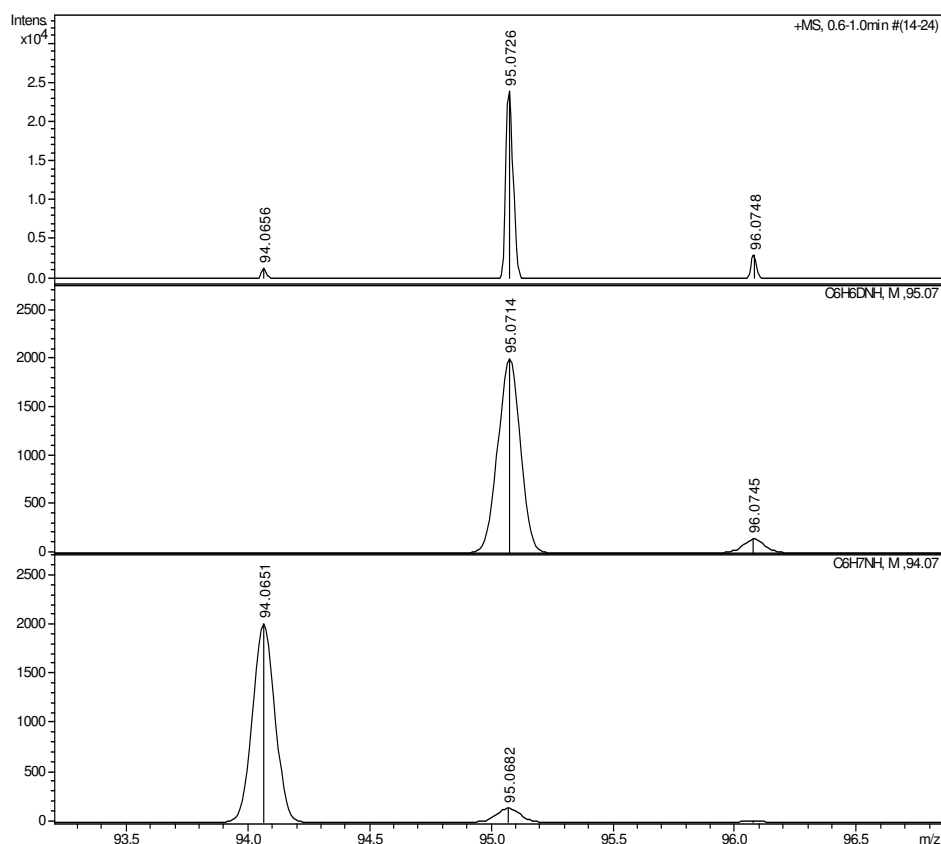
##### 2-Deuterio-aniline<sup>[15]</sup>



Following a modified procedure by Witkop et al.,<sup>[16]</sup> 2-deuterio-aniline is synthesised by catalytic hydrogenolysis of 2-bromoaniline. 2-Bromoaniline (4.30 g, 25.0 mmol) is dissolved in diethylether (25 mL) and washed with deuterium oxide (3 x 15 mL) to replace most of the amine protons by deuterium. The ethereal solution is dried (MgSO<sub>4</sub>) and concentrated. The yellowish liquid is dissolved in dry THF (25 mL) in a 100 mL-two-necked round-bottom flask equipped with a tee-branch connected to a vacuo/Argon line and to a Schlenk flask. Dry triethylamine (2.78 g, 3.82 mL, 27.5 mmol, 1.10 eq.), 10% Pd/C (215 mg, 5 w% relative to bromoaniline) and deuterium oxide (1.38 g, 1.25 mL, 68.7 mmol, 2.75 eq.) were added to the solution with stirring. Deuterium gas is generated in the separate Schlenk flask connected to the reaction flask by slow addition of deuterium oxide (approx. 8 mL) with a syringe through a septum to a suspension of sodium (approx. 5 g) in dry THF (120 mL). The reaction flask is evacuated and backfilled with the generated deuterium gas five times and stirred at rt under D<sub>2</sub> atmosphere for 10 h. Since reaction control by GCMS analysis still showed remaining 2-bromoaniline, the generation and purging with D<sub>2</sub> is repeated and the mixture is stirred at rt for further 5 h. The reaction mixture is diluted with diethylether (50 mL), filtered through Celite and concentrated to give a brown liquid. The crude product is solved in diethylether (20 mL), washed with water (5 mL) to replace most of the nitrogen-bound deuterium by protons, dried (MgSO<sub>4</sub>) and concentrated. Bulb-to-bulb distillation (30 mbar, 85-95 °C) yielded the desired product as a clear and colorless liquid (1.85 g, 19.7 mmol, 79%). <sup>1</sup>H NMR and ESI-MS showed deuterium incorporation > 95%. **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** 3.65 (s, 2H, NH<sub>2</sub>), 6.72 (dd, 1H, *J* = 8.4 Hz, *J* = 1.1 Hz, 6-CH), 6.82 (dt, 1H, *J* = 7.4 Hz, *J* = 1.1 Hz, 4-CH), 7.20-7.24 (m, 2H, 3-CH, 5-CH); **<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** 114.8 (t, *J*<sub>CD</sub> = 23.8 Hz, 2-CD), 115.1 (6-CH), 118.5 (4-CH), 129.2 (CH<sub>ar</sub>), 129.3 (CH<sub>ar</sub>), 146.4 (1-CN<sub>2</sub>H); **<sup>2</sup>H NMR (77 MHz, CHCl<sub>3</sub>):** 6.76 (s), 3.65 (s). **GC/MS, R<sub>t</sub> (method B):** 5.5 min; **(EI) m/z (%):** 94 (100), 67 (37) 52 (12), 39 (18); **ESI-MS:** calculated [C<sub>6</sub>H<sub>7</sub>DN]<sup>+</sup>: 95.0714, found: 95.0726; **ATR-FTIR [cm<sup>-1</sup>]:** 3356, 1620, 1596, 1482, 1455, 1307, 1264, 762.

## ESI-MS spectra of 2-deuterio-aniline

Experiment:



Measured:

| # | m/z     | Res. | S/N   | I     | FWHM   |
|---|---------|------|-------|-------|--------|
| 2 | 94.0656 | 3875 | 45.5  | 1314  | 0.0243 |
| 3 | 95.0726 | 2892 | 825.7 | 23864 | 0.0329 |
| 4 | 96.0748 | 3869 | 106.1 | 3066  | 0.0248 |

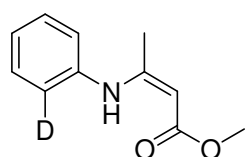
simulated for C<sub>6</sub>H<sub>6</sub>DNH:

| # | m/z     | Res. | S/N | I    | FWHM   |
|---|---------|------|-----|------|--------|
| 1 | 95.0714 | 951  |     | 2000 | 0.1000 |
| 2 | 96.0745 | 961  |     | 139  | 0.1000 |
| 3 | 97.0774 | 971  |     | 4    | 0.1000 |

simulated for C<sub>6</sub>H<sub>7</sub>NH:

| # | m/z     | Res. | S/N | I    | FWHM   |
|---|---------|------|-----|------|--------|
| 1 | 94.0651 | 941  |     | 2000 | 0.1000 |
| 2 | 95.0682 | 951  |     | 139  | 0.1000 |
| 3 | 96.0712 | 961  |     | 4    | 0.1000 |

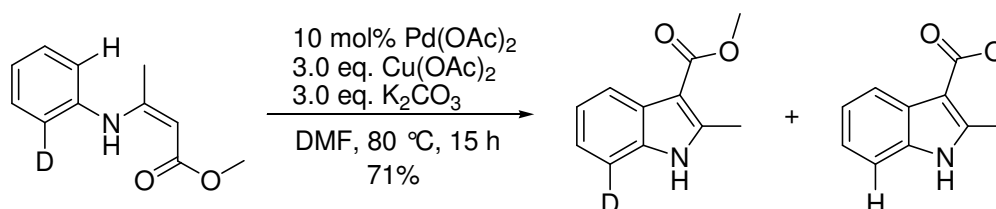
## (Z)-Methyl 3-(2'-deuterio-phenylamino)but-2-enoate



Following a modified procedure by Wang et al.,<sup>[4]</sup> 2-deuterio-aniline (492 mg, 5.23 mmol, 1.00 eq.) and methyl acetoacetate (646 mg, 600  $\mu$ L, 5.56 mmol, 1.06 eq.) are stirred with InBr<sub>3</sub> (17.7 mg, 0.05 mmol, 1 mol%) at rt for 3 h. The reaction mixture is loaded directly onto a column with silica pretreated with pentane/EtOAc/NEt<sub>3</sub> 19/1/0.2 and purified by rapid column chromatography to yield the desired product as a white solid (879 mg, 4.57 mmol, 87%). <sup>1</sup>H

**NMR (500 MHz, CDCl<sub>3</sub>):** 1.99 (s, 3H, CH<sub>3</sub>), 3.68 (s, 3H, CH<sub>3</sub>), 4.70 (s, 1H, CH), 7.08 (d, 1H, *J* = 7.9 Hz, CH<sub>ar</sub>), 7.15 (dt, 1H, *J* = 7.4 Hz, *J* = 1.0 Hz, CH<sub>ar</sub>), 7.30-7.34 (m, 2H, CH<sub>ar</sub>); **<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** 20.4 (CH<sub>3</sub>), 50.4 (CH<sub>3</sub>), 85.7 (CH), 124.3 (t, *J*<sub>CD</sub> = 24.4 Hz, CD), 124.5 (CH<sub>ar</sub>), 125.1 (CH<sub>ar</sub>), 129.1 (CH<sub>ar</sub>), 129.2 (CH<sub>ar</sub>), 139.3 (C<sub>ar</sub>), 159.2 (C<sub>q</sub>) 170.8 (CO); **<sup>2</sup>H NMR (77 MHz, CHCl<sub>3</sub>):** 7.14 (s); **GC/MS, R<sub>t</sub> (method A):** 11.2 min; **(EI) m/z (%):** 192 (75), 177 (8), 161 (63), 145 (48), 131 (77), 119 (100), 104 (4), 94 (13), 78 (69), 66 (19), 52 (15), 39 (11); **ESI-MS:** calculated [C<sub>11</sub>H<sub>12</sub>DNNaO<sub>2</sub>]<sup>+</sup>: 215.0901, found: 215.0894; **ATR-FTIR [cm<sup>-1</sup>]:** 3251, 2995, 1645, 1602, 1585, 1494, 1470, 1434, 1383, 1357, 1252, 1190, 1160, 1117, 1056, 1007, 989, 914, 855, 824, 779, 666.

### Determination of Intramolecular Kinetic Isotope Effect (KIE)



Following the general procedure, (Z)-Methyl 3-(2'-deuterio-phenylamino)but-2-enoate (96 mg, 0.50 mmol) is stirred with Pd(OAc)<sub>2</sub> (11.2 mg, 0.05 mmol, 10 mol%), Cu(OAc)<sub>2</sub> (272 mg, 1.5 mmol, 3.0 eq.), K<sub>2</sub>CO<sub>3</sub> (207 mg, 1.5 mmol, 3.0 eq.) and DMF (6 mL) under Argon in a preheated oil bath at 80 °C for 15 h. The mixture was diluted with EtOAc (20 mL), filtered through a short pad of silica, the red-brown solid is washed with EtOAc (3 x 20 mL) and the combined filtrates were concentrated. After purification by flash column chromatography (silica, pentane/EtOAc 4:1) the product is obtained as a light brown solid. (67 mg, 0.35 mmol, 71 %). **R<sub>F</sub>** (pentane/EtOAc 4:1): 0.32. **<sup>1</sup>H NMR (600 MHz, C<sub>6</sub>D<sub>6</sub>):** 2.36 (s, 3H, CH<sub>3</sub>), 3.64 (s, 3H, CH<sub>3</sub>), 6.78 (s, 1H, NH), 6.96 (d, *J* = 8.1 Hz, 0.17H, 7-CH), 7.19-7.21 (m, 1H, CH<sub>ar</sub>), 7.30 (t, *J* = 8.1 Hz, 1H, CH<sub>ar</sub>), 8.49 (d, *J* = 8.0 Hz, CH<sub>ar</sub>); **GC-MS, R<sub>t</sub> (method A):** 12.8 min, **(EI) m/z (%):** 191 (14), 190 (78), 189 (16), 175 (12), 159 (100), 131 (23), 103 (13), 78 (12); **ESI-MS:** calculated [C<sub>11</sub>H<sub>11</sub>NNaO<sub>2</sub>]<sup>+</sup>: 212.0682, found: 212.0681; calculated [C<sub>11</sub>H<sub>10</sub>DNNaO<sub>2</sub>]<sup>+</sup>: 213.0745, found: 213.0744.

Intramolecular KIE determined by ESI-MS: *k<sub>H</sub>*/*k<sub>D</sub>* = 4.54.

Intramolecular KIE determined by <sup>1</sup>H NMR: *k<sub>H</sub>*/*k<sub>D</sub>* = 4.56.

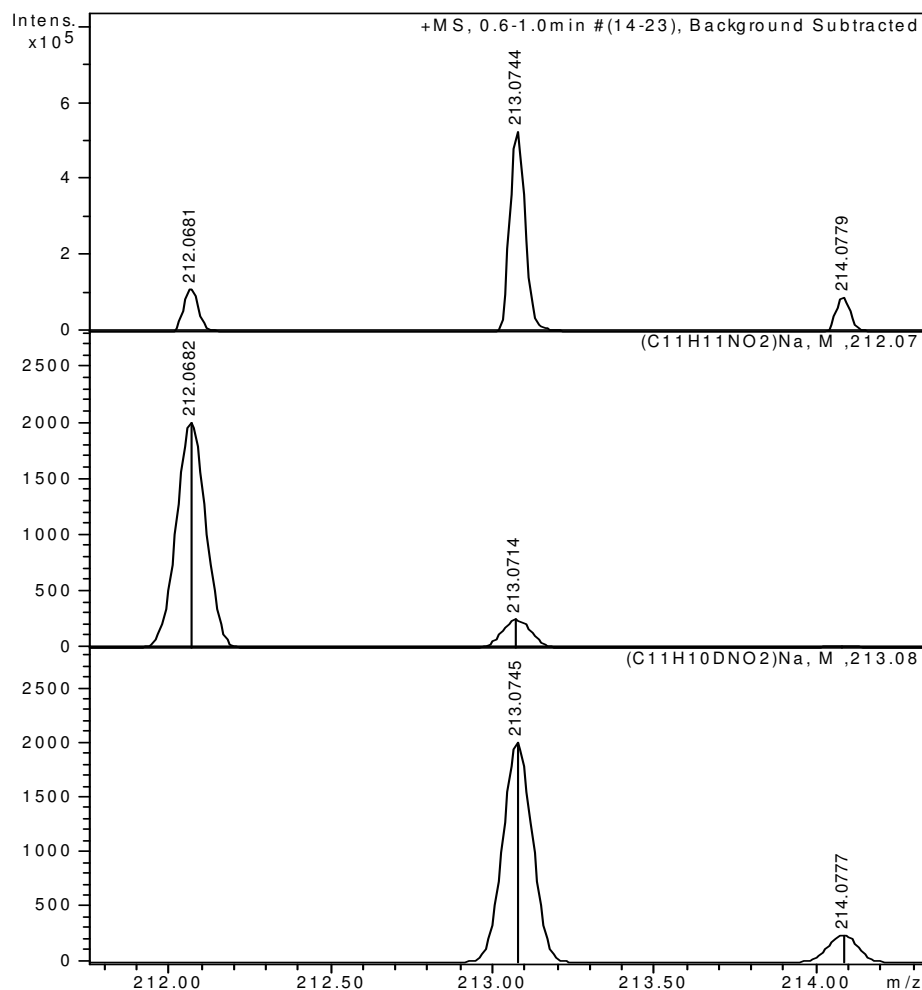
→ Averaged Intramolecular KIE: *k<sub>H</sub>*/*k<sub>D</sub>* = 4.6.

## ESI-MS spectra of Intramolecular Kinetic Isotope Effect:

Experiment:

Simulation of  
 $C_{11}H_{11}NNaO_2$ :

Simulation of  
 $C_{11}H_{10}DNNaO_2$



measured:

| # | m/z      | Res. | S/N    | I      | FWHM   | Area  |
|---|----------|------|--------|--------|--------|-------|
| 3 | 212.0681 | 4326 | 1762.7 | 112520 | 0.0490 | 6021  |
| 4 | 213.0744 | 4164 | 8267.4 | 525224 | 0.0512 | 28950 |
| 5 | 214.0779 | 4423 | 1428.0 | 90291  | 0.0484 | 4759  |

simulated for  $C_{11}H_{11}NNaO_2$ :

| # | m/z      | Res. | S/N | I    | FWHM   | Area |
|---|----------|------|-----|------|--------|------|
| 1 | 212.0682 | 2121 |     | 2000 | 0.1000 | 0    |
| 2 | 213.0714 | 2131 |     | 249  | 0.1000 | 0    |
| 3 | 214.0738 | 2141 |     | 22   | 0.1000 | 0    |

simulated for  $C_{11}H_{10}DNNaO_2$ :

| # | m/z      | Res. | S/N | I    | FWHM   | Area |
|---|----------|------|-----|------|--------|------|
| 1 | 213.0745 | 2131 |     | 2000 | 0.1000 | 0    |
| 2 | 214.0777 | 2141 |     | 249  | 0.1000 | 0    |
| 3 | 215.0801 | 2151 |     | 22   | 0.1000 | 0    |

## Determination of Intramolecular Kinetic Isotope Effect by ESI-MS:

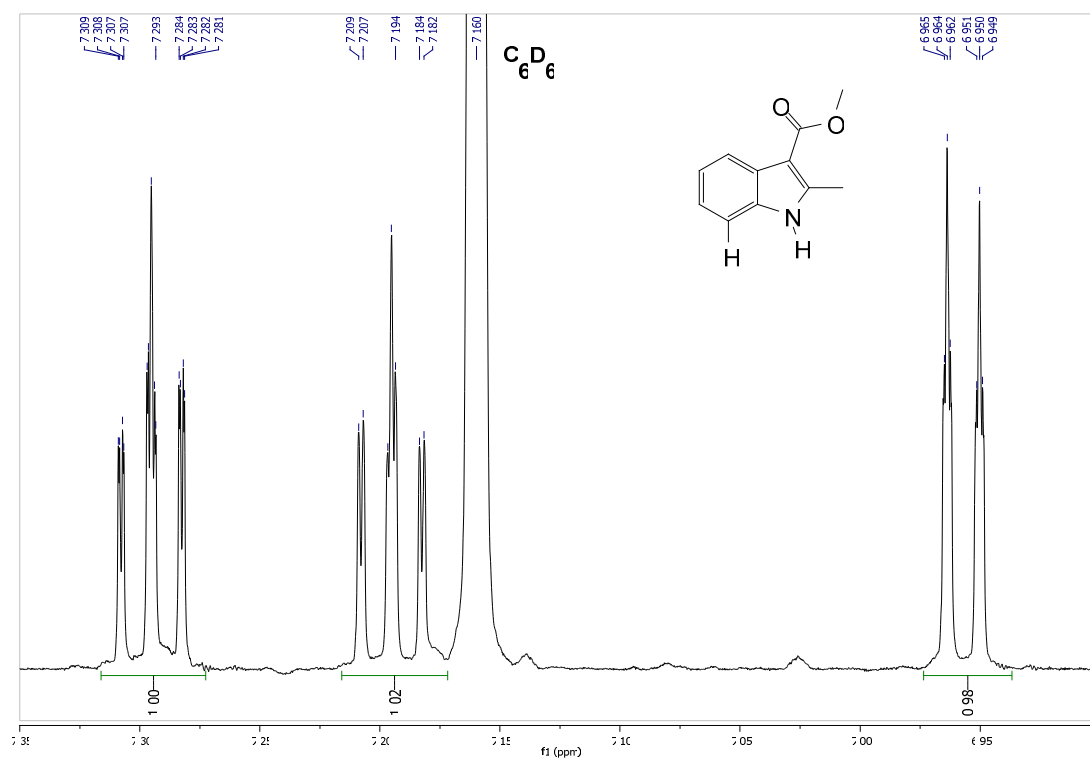
calculated for non-deuterated product:  $[C_{11}H_{11}NNaO_2]^+$ : 212.0682, found: 212.0681 (intensity: 112520).

calculated for deuterated product:  $[C_{11}H_{10}DNNaO_2]^+$ : 213.0745, found: 213.0744 (intensity: 525224, corrected intensity (reduced by carbon-isotope signal of  $C_{11}H_{11}NNaO_2$ ): 511215).

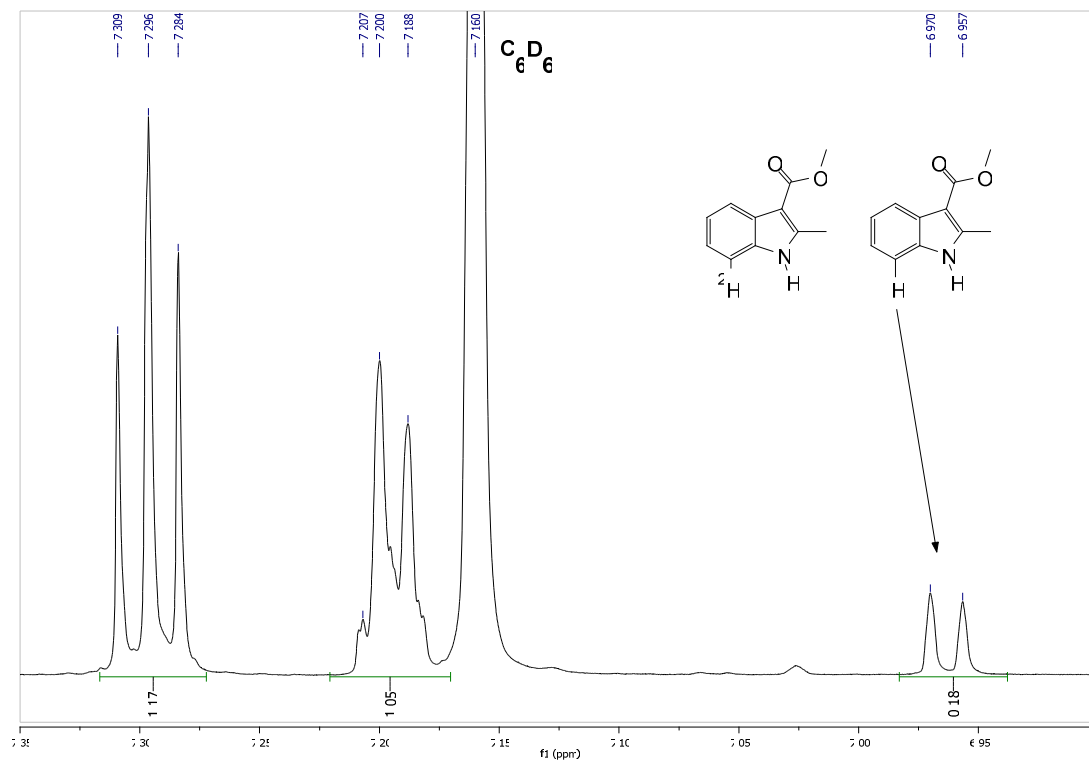
→ ESI-MS-ratio:  $[C_{11}H_{11}NNaO_2]^+ / [C_{11}H_{10}DNNaO_2]^+ = k_H/k_D = 4.54$ .

### Determination of Intramolecular Kinetic Isotope Effect by $^1H$ NMR:

$^1H$  NMR of the product obtained from (Z)-Methyl 3-(phenylamino)-but-2-enoate

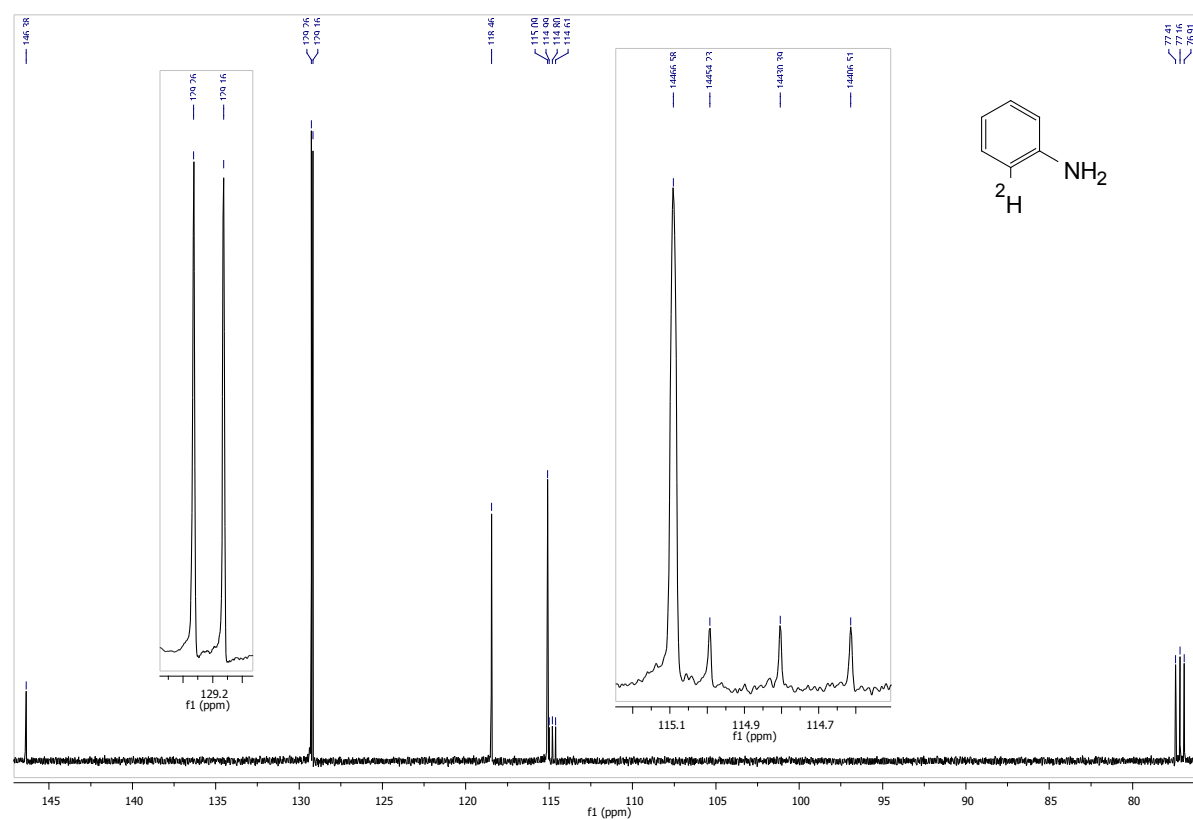
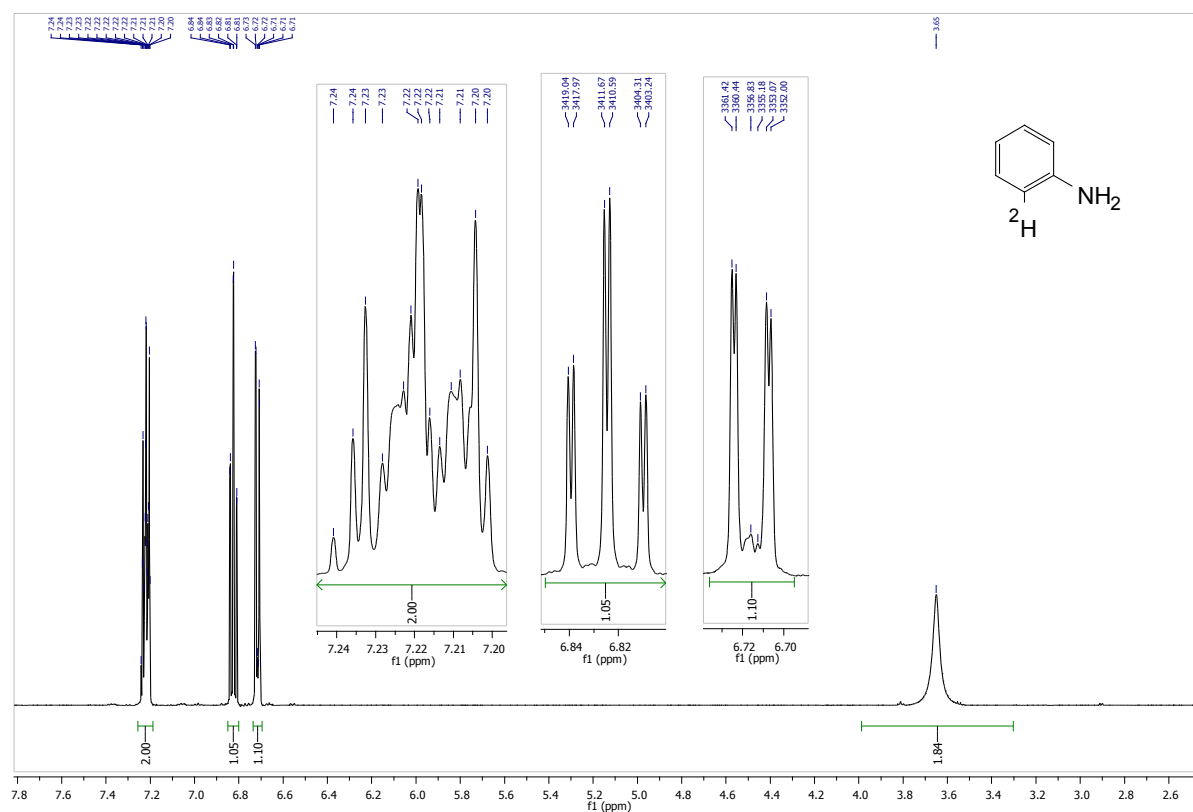


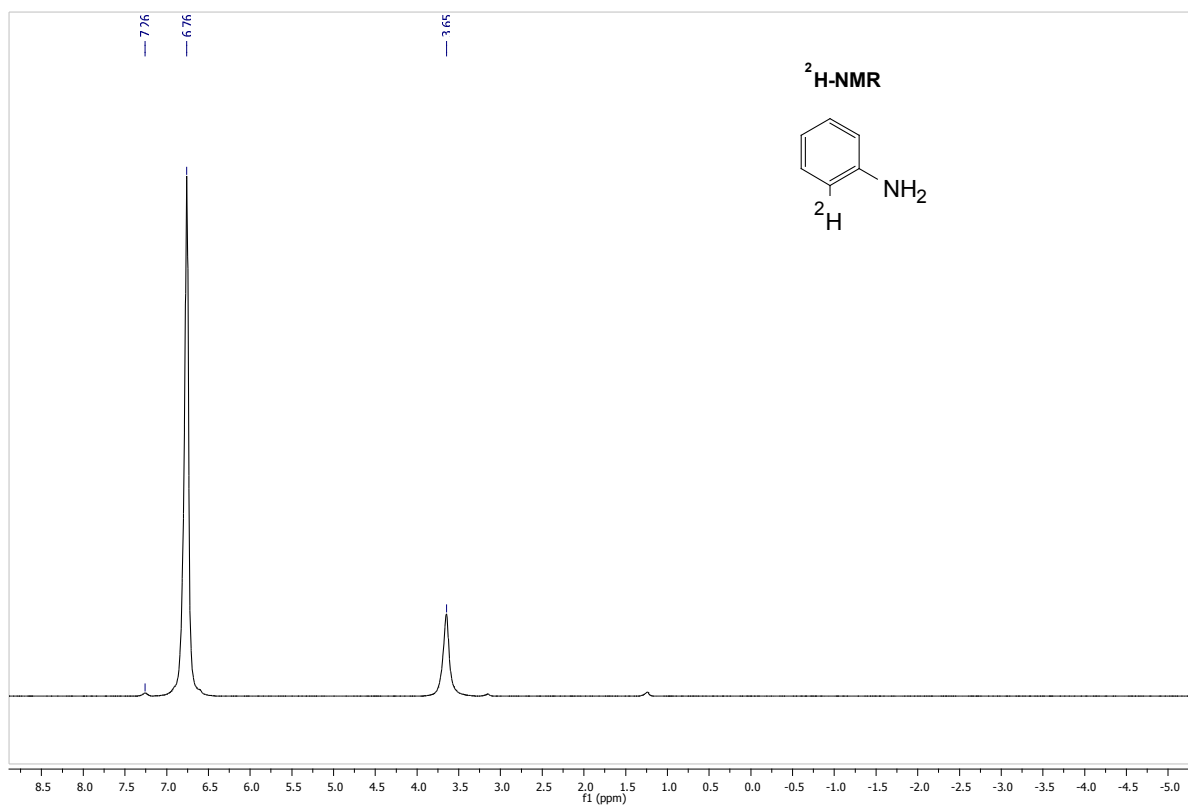
$^1H$  NMR of the product obtained from (Z)-Methyl 3-(2'-deuterio-phenylamino)-but-2-enoate



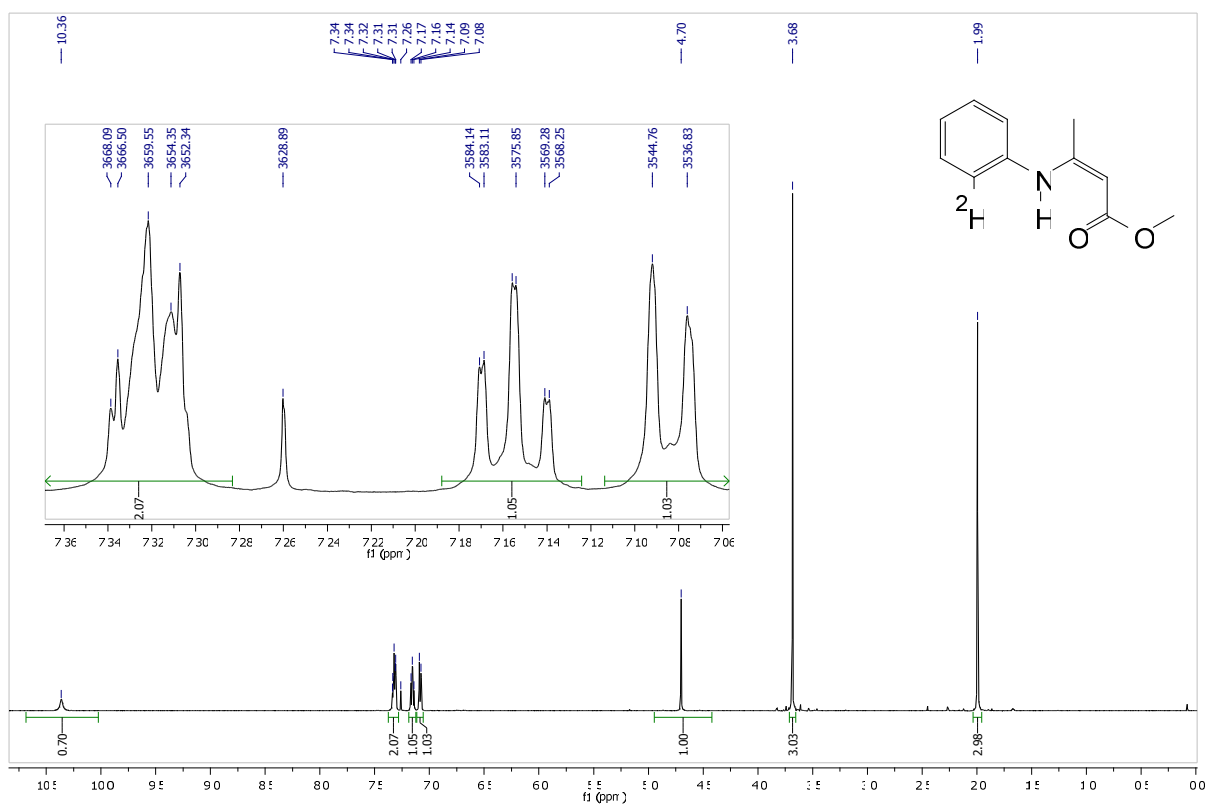
$$\rightarrow k_H/k_D = (1.00 - 0.18)/0.18 = 4.56$$

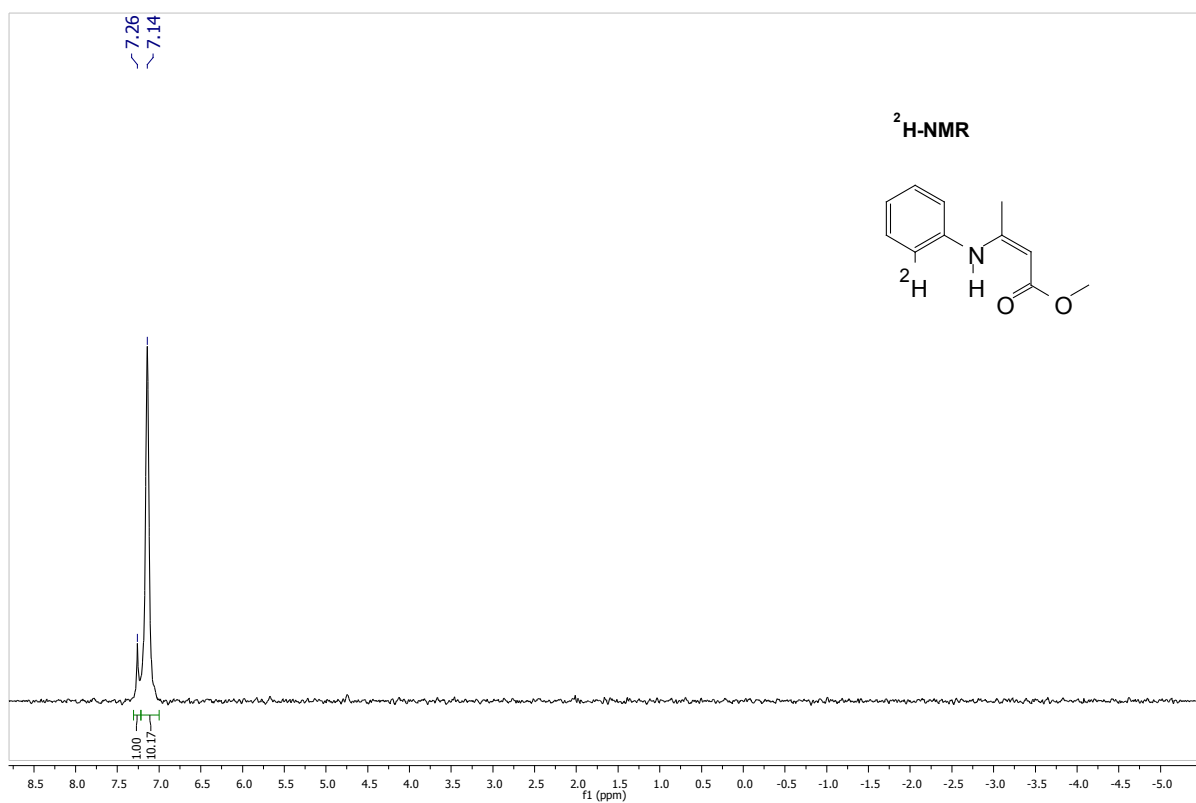
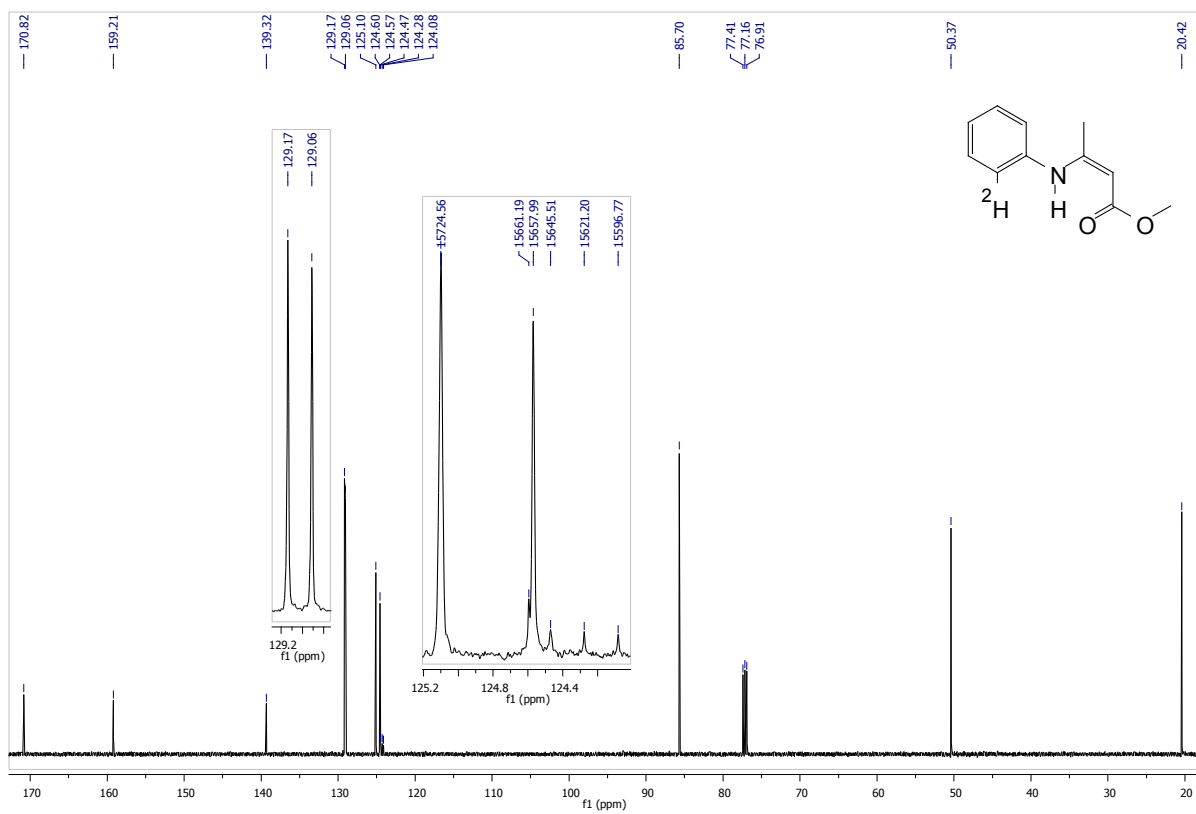
## 2-Deuterio-aniline





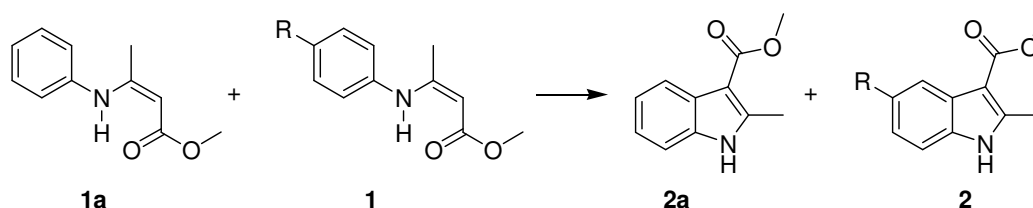
### Methyl 3-(2'-deuterio-phenylamino)but-2-enoate





## b. Competition Experiments

### General Procedure for the Competition Experiments



47.8 mg (0.25 mmol) (*Z*)-Methyl 3-(phenylamino)-but-2-enoate as the standard substrate **1a** and 0.25 mmol of a para-substituted competing substrate (**1**, R = Me, Cl, OMe) were weighed into a flame-dried reaction flask containing Pd(OAc)<sub>2</sub> (5.6 mg, 0.025 mmol, 5 mol%), Cu(OAc)<sub>2</sub> (273 mg, 1.5 mmol, 3.00 eq.) and K<sub>2</sub>CO<sub>3</sub> (207 mg, 1.5 mmol, 3.0 eq.). The flask is evacuated and backfilled with Argon three times, DMF (6 mL) and *n*-decane as an internal standard (25  $\mu$ L) were added under Argon. The mixture is placed into a preheated oil bath and stirred at 80 °C under Argon. Every 10 minutes, an aliquot of 60  $\mu$ L from the reaction solution is taken under standard Schlenk technique with sufficient Argon flow without cooling of the solution. The aliquot is diluted with CH<sub>2</sub>Cl<sub>2</sub> and filtered over a short pad of silica with additional CH<sub>2</sub>Cl<sub>2</sub> (2 mL). The sample is analysed by GC and GCMS as ratios of substrates and products to the internal standard *n*-decane. After the indicated time period, the reaction flask is cooled to rt by running tap water, diluted with diethylether (20 mL), filtered through a short pad of silica and sea sand, pretreated with diethylether. The solid residue is washed thoroughly with diethylether (2 x 20 mL), the combined filtrates were evaporated to dryness and analyzed by <sup>1</sup>H NMR to confirm the GC analysis.

Competition Experiment R = H vs R = Me

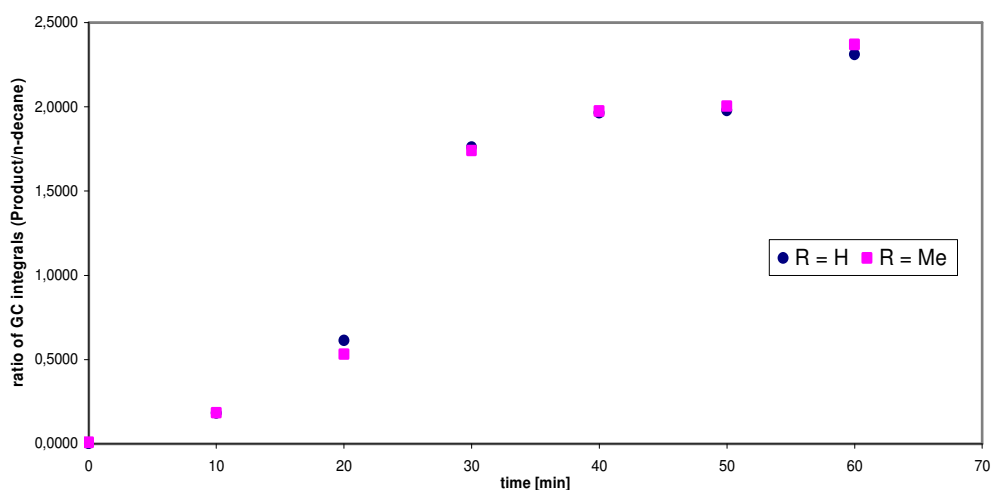


Figure 6.1: Product formation versus time for **2a** (R = H) and **2d** (R = Me)

### R=H vs. R=Me

| Time<br>(min) | Standard | Substrate1<br>(R <sub>para</sub> =H) | Substrate2<br>(R <sub>para</sub> =Me) | Product1<br>(R <sub>para</sub> =H) | Product2<br>(R <sub>para</sub> =Me) | Substrate1/<br>Standard | Substrate2/<br>Standard | Product1/<br>Standard | Product2/<br>Standard |
|---------------|----------|--------------------------------------|---------------------------------------|------------------------------------|-------------------------------------|-------------------------|-------------------------|-----------------------|-----------------------|
| 0             | 23,631   | 37,270                               | 35,202                                | 0,071                              | 0,184                               | 1,5772                  | 1,4897                  | 0,0030                | 0,0078                |
| 10            | 21,222   | 34,487                               | 27,476                                | 3,849                              | 3,915                               | 1,6251                  | 1,2947                  | 0,1814                | 0,1845                |
| 20            | 22,138   | 24,773                               | 23,863                                | 13,591                             | 11,783                              | 1,1190                  | 1,0779                  | 0,6139                | 0,5323                |
| 30            | 17,704   | 8,842                                | 9,955                                 | 31,169                             | 30,819                              | 0,4994                  | 0,5623                  | 1,7606                | 1,7408                |
| 40            | 17,837   | 5,876                                | 5,876                                 | 35,036                             | 35,218                              | 0,3294                  | 0,3294                  | 1,9642                | 1,9744                |
| 50            | 17,743   | 5,217                                | 5,377                                 | 35,123                             | 35,553                              | 0,2940                  | 0,3030                  | 1,9795                | 2,0038                |
| 60            | 15,589   | 4,315                                | 4,546                                 | 36,034                             | 36,946                              | 0,2768                  | 0,2916                  | 2,3115                | 2,3700                |

Table 6.1: GC-integrals for **2a** (R = H) and **2d** (R = Me)

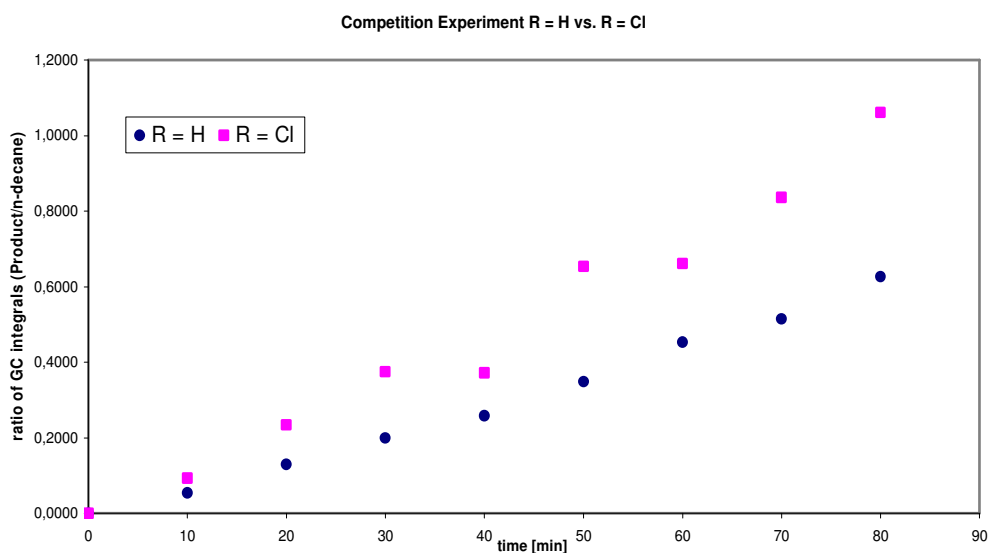


Figure 6.2: Product formation versus time for **2a** (R = H) and **2n** (R = Cl)

### R=H vs. R=Cl

| Time<br>(min) | Standard | Substrate1<br>(R <sub>para</sub> =H) | Substrate2<br>(R <sub>para</sub> =Cl) | Product1<br>(R <sub>para</sub> =H) | Product2<br>(R <sub>para</sub> =Cl) | Substrate1/<br>Standard | Substrate2/<br>Standard | Product1/<br>Standard | Product2/<br>Standard |
|---------------|----------|--------------------------------------|---------------------------------------|------------------------------------|-------------------------------------|-------------------------|-------------------------|-----------------------|-----------------------|
| 0             | 22,035   | 40,483                               | 37,323                                | 0,000                              | 0,000                               | 1,8372                  | 1,6938                  | 0,0000                | 0,0000                |
| 10            | 21,607   | 36,235                               | 33,579                                | 1,166                              | 2,011                               | 1,6770                  | 1,5541                  | 0,0540                | 0,0931                |
| 20            | 23,166   | 35,428                               | 29,022                                | 2,993                              | 5,432                               | 1,5293                  | 1,2528                  | 0,1292                | 0,2345                |
| 30            | 22,485   | 30,442                               | 25,791                                | 4,491                              | 8,433                               | 1,3539                  | 1,1470                  | 0,1997                | 0,3751                |
| 40            | 25,484   | 28,749                               | 25,345                                | 6,591                              | 9,488                               | 1,1281                  | 0,9945                  | 0,2586                | 0,3723                |
| 50            | 18,889   | 25,028                               | 19,286                                | 6,595                              | 12,350                              | 1,3250                  | 1,0210                  | 0,3491                | 0,6538                |
| 60            | 22,722   | 27,465                               | 20,590                                | 10,287                             | 15,012                              | 1,2087                  | 0,9062                  | 0,4527                | 0,6607                |
| 70            | 22,619   | 25,473                               | 19,607                                | 11,634                             | 18,910                              | 1,1262                  | 0,8668                  | 0,5143                | 0,8360                |
| 80            | 21,370   | 21,187                               | 16,437                                | 13,397                             | 22,669                              | 0,9914                  | 0,7692                  | 0,6269                | 1,0608                |

Table 6.2: GC-integrals for **2a** (R = H) and **2n** (R = Cl)

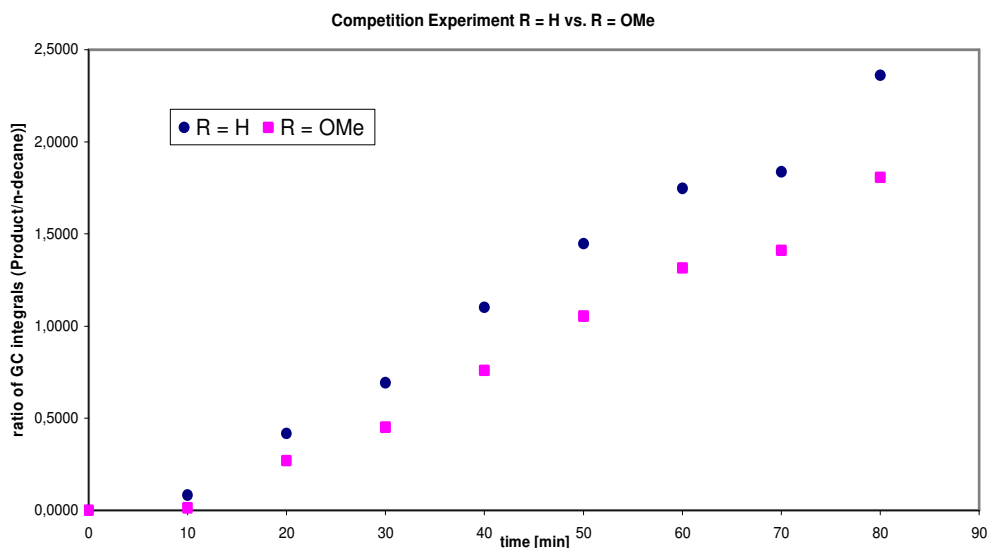


Figure 6.3: Product formation versus time for **2a** (R = H) and **2h** (R = OMe)

#### R=H vs. R=OMe

| Time<br>(min) | Standard | Substrate1<br>(R <sub>para</sub> =H) | Substrate2<br>(R <sub>para</sub> =OMe) | Product1<br>(R <sub>para</sub> =H) | Product2<br>(R <sub>para</sub> =OMe) | Substrate1/<br>Standard | Substrate2/<br>Standard | Product1/<br>Standard | Product2/<br>Standard |
|---------------|----------|--------------------------------------|----------------------------------------|------------------------------------|--------------------------------------|-------------------------|-------------------------|-----------------------|-----------------------|
| 0             | 25,588   | 41,430                               | 30,414                                 | 0,000                              | 0,000                                | 1,6191                  | 1,1886                  | 0,0000                | 0,0000                |
| 10            | 26,851   | 40,251                               | 25,780                                 | 2,190                              | 0,376                                | 1,4991                  | 0,9601                  | 0,0816                | 0,0140                |
| 20            | 24,839   | 31,935                               | 18,189                                 | 10,340                             | 6,677                                | 1,2857                  | 0,7323                  | 0,4163                | 0,2688                |
| 30            | 19,789   | 20,212                               | 14,783                                 | 13,686                             | 8,928                                | 1,0214                  | 0,7470                  | 0,6916                | 0,4512                |
| 40            | 22,470   | 20,842                               | 12,545                                 | 24,717                             | 17,065                               | 0,9275                  | 0,5583                  | 1,1000                | 0,7595                |
| 50            | 19,762   | 14,006                               | 10,459                                 | 28,603                             | 20,800                               | 0,7087                  | 0,5292                  | 1,4474                | 1,0525                |
| 60            | 19,442   | 10,594                               | 7,193                                  | 33,961                             | 25,567                               | 0,5449                  | 0,3700                  | 1,7468                | 1,3150                |
| 70            | 18,230   | 8,260                                | 5,239                                  | 33,494                             | 25,728                               | 0,4531                  | 0,2874                  | 1,8373                | 1,4113                |
| 80            | 16,919   | 6,045                                | 4,529                                  | 39,934                             | 30,550                               | 0,3573                  | 0,2677                  | 2,3603                | 1,8057                |

Table 6.3: GC-integrals for **2a** (R = H) and **2h** (R = OMe)

As shown in Figures 6.1-3, there is no big difference in the rate of product formation of the standard substrate **1a** (R = H) and the *para*-methyl-substituted enaminecarboxylate **1d**, whereas the electron-withdrawing substituted substrate **1n** (R = Cl) seems to react faster and the electron-donating substituted substrate **1h** (R = OMe) seems to react slower compared to the standard substrate. Deviations from expected curve progression (linearity for very low conversions, exponential in principle) are presumably caused by inhomogeneties of the oil bath temperature and/or inadequate stirring.

These results were confirmed by proton NMR of the crude products (see below).

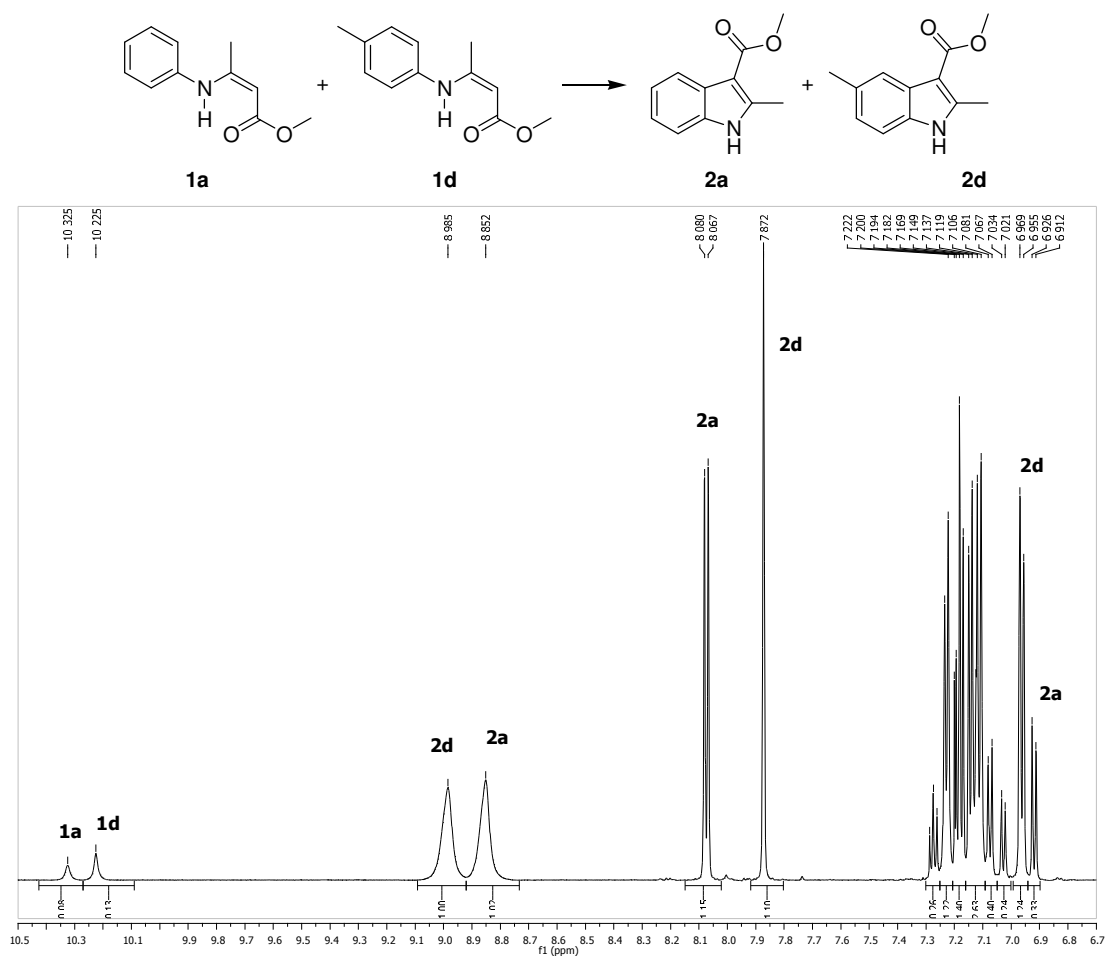


Fig. 6.4: Downfield-region of the <sup>1</sup>H NMR from the mixture of **1a**, **1d**, **2a** and **2d**

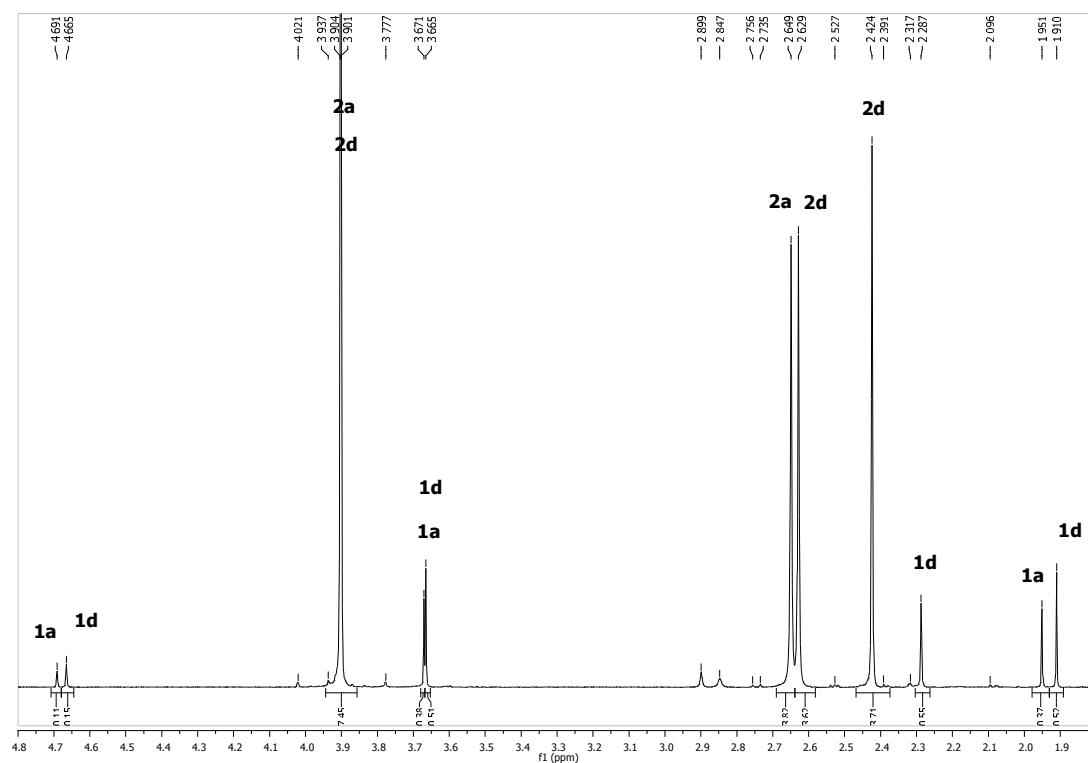


Fig. 6.5: Upfield-region of the <sup>1</sup>H NMR from the mixture of **1a**, **1d**, **2a** and **2d**

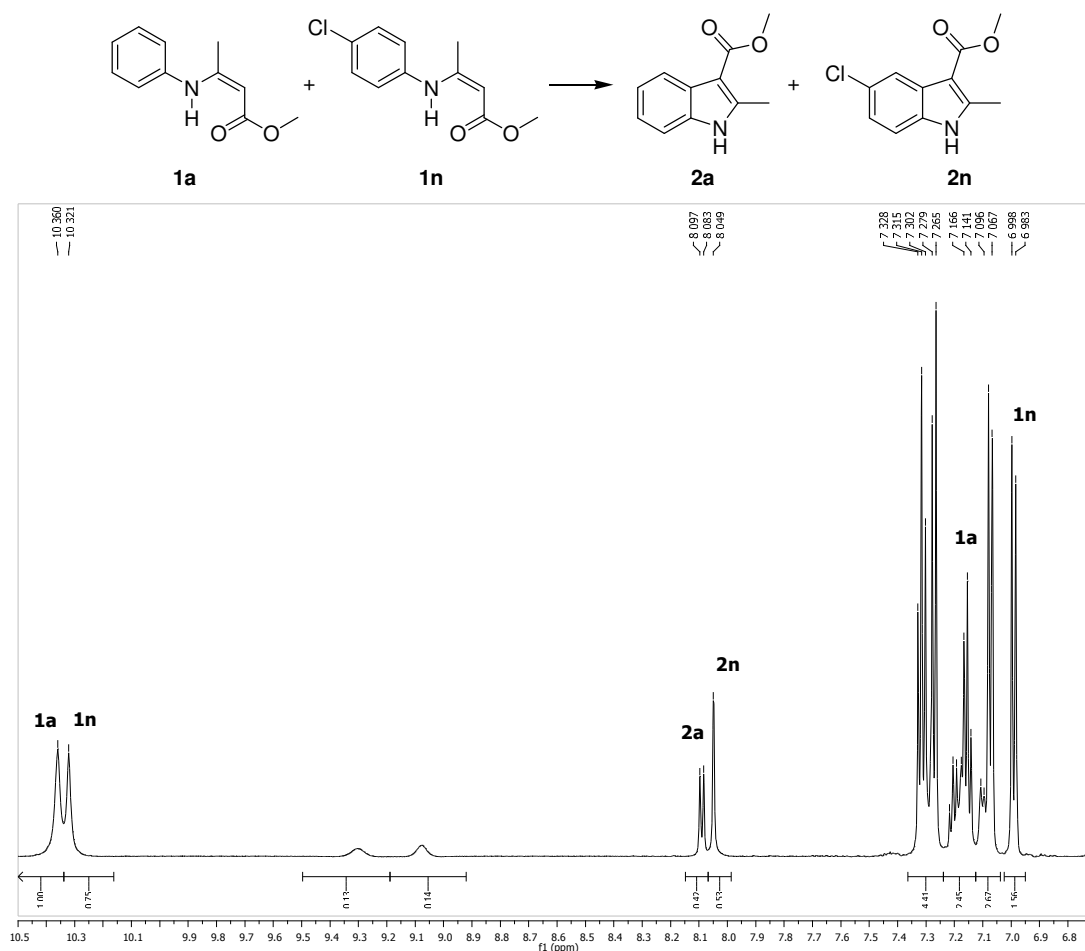


Fig. 6.6: Downfield-region of the  $^1\text{H}$  NMR from the mixture of **1a**, **1n**, **2a** and **2n**

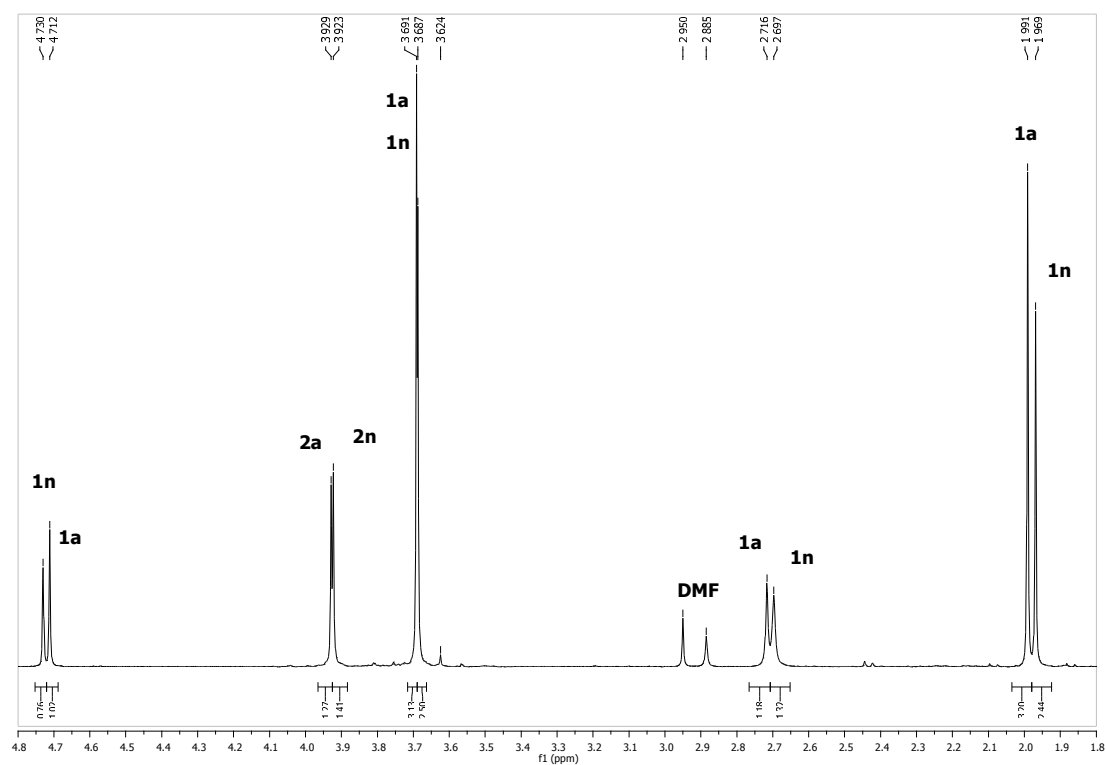


Fig. 6.7: Upfield-region of the  $^1\text{H}$  NMR from the mixture of **1a**, **1n**, **2a** and **2n**

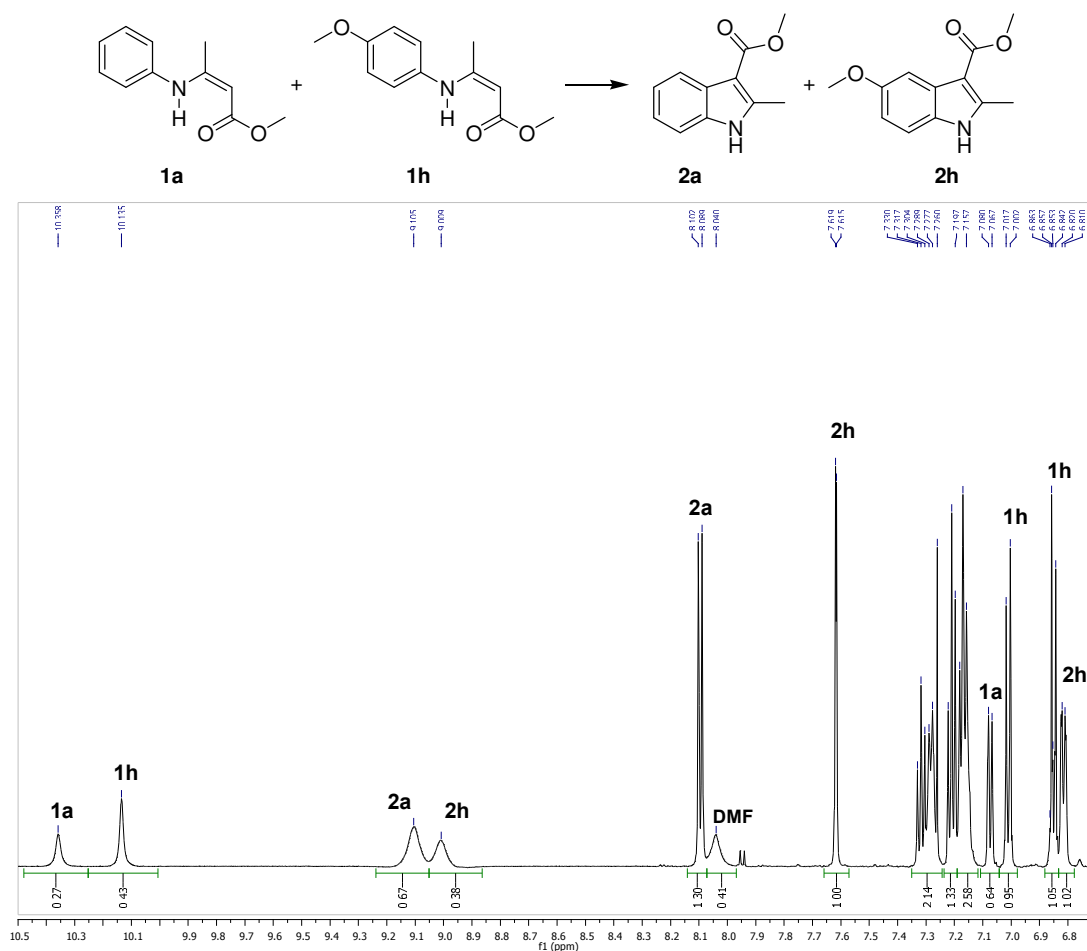


Fig. 6.8: Downfield-region of the <sup>1</sup>H NMR from the mixture of **1a**, **1h**, **2a** and **2h**

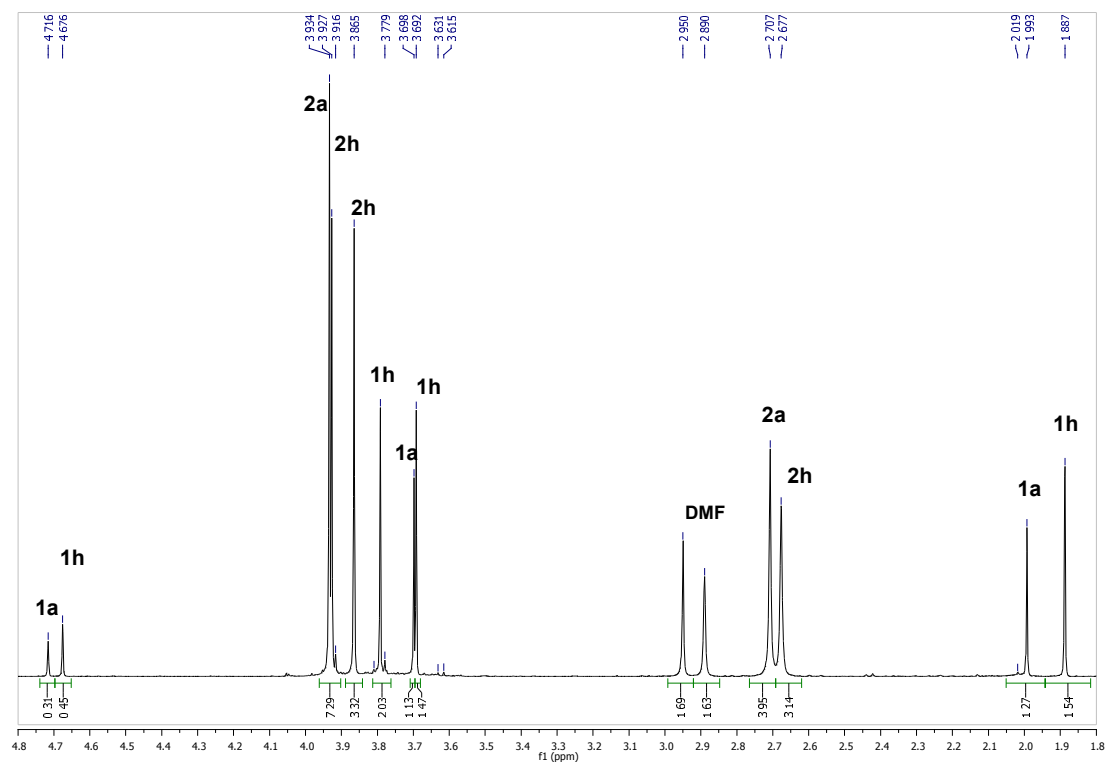


Fig. 6.9: Upfield-region of the <sup>1</sup>H NMR from the mixture of **1a**, **1h**, **2a** and **2h**

Careful examination and comparison of the  $^1\text{H}$  NMR spectra of the crude mixture from the competition experiment **1a** vs. **1d** (Figures 6.4 and 6.5) showed that there is almost no difference in the amount of product formed in the competition experiment of **1a** ( $\text{R} = \text{H}$ ) and **1d** ( $\text{R} = \text{Me}$ ). Comparing the separate product signals at 8.07 and 7.87 ppm, respectively, shows a product ratio  $2\text{a}/2\text{d} = 1.15/1.10 = 1.04$ . This is in accordance with the approximate equal amount of remaining substrate (e. g. signals at 4.69 and 4.67 ppm, respectively indicate a ratio  $1\text{a}/1\text{d} = 0.11/0.15 = 0.73$ ).

Figure 6.6 shows that more indole product from the electron-withdrawing substrate **1n** ( $\text{R} = \text{Cl}$ ) is formed than from the standard substrate **1a** ( $\text{R} = \text{H}$ ). The product signals at 8.09 and 8.05 ppm suggest a ratio  $2\text{n}/2\text{a} = 0.53/0.42 = 1.26$ . The faster substrate consumption of the chloro-compounds as can be seen from the signals around 4.7 ppm ( $1\text{n}/1\text{a} = 0.76/1.02 = 0.75$ ) or around 1.98 ppm ( $1\text{n}/1\text{a} = 2.44/3.20 = 0.76$ ) is consistent with this result.

In agreement with this electronic influence on the reaction course, the product formation of the methoxy-substituted substrate **1h** is slowed down compared to the unsubstituted (*Z*)-Methyl 3-(phenylamino)-but-2-enoate **1a**. Both the signal pair at 8.10, 7.62 ppm as well as the one around 2.7 ppm prove a product ratio  $2\text{a}/2\text{h} = 1.30/1.00 = 1.30$  or  $2\text{a}/2\text{h} = 3.95/3.14 = 1.26$ . The remaining substrate proportion of  $1\text{a}/1\text{h} = 1.27/1.54 = 0.82$  is in accordance with this finding.

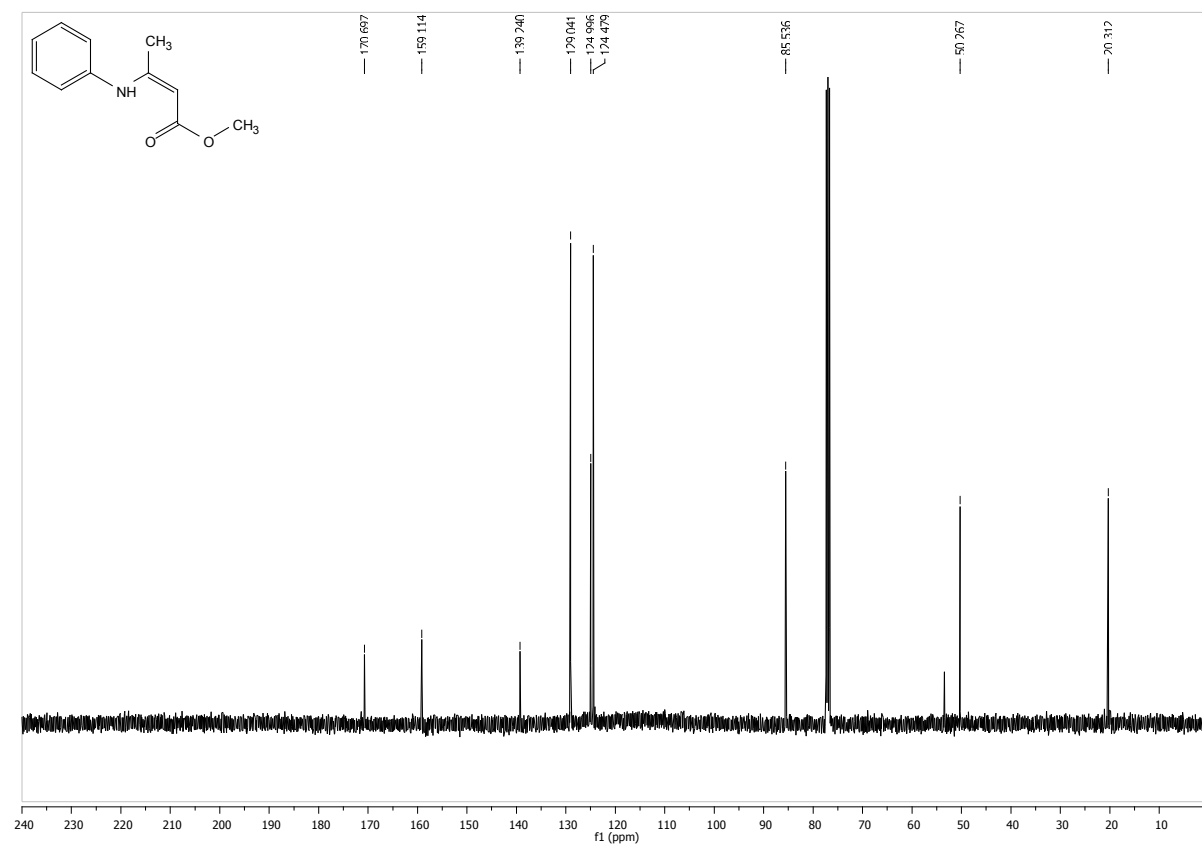
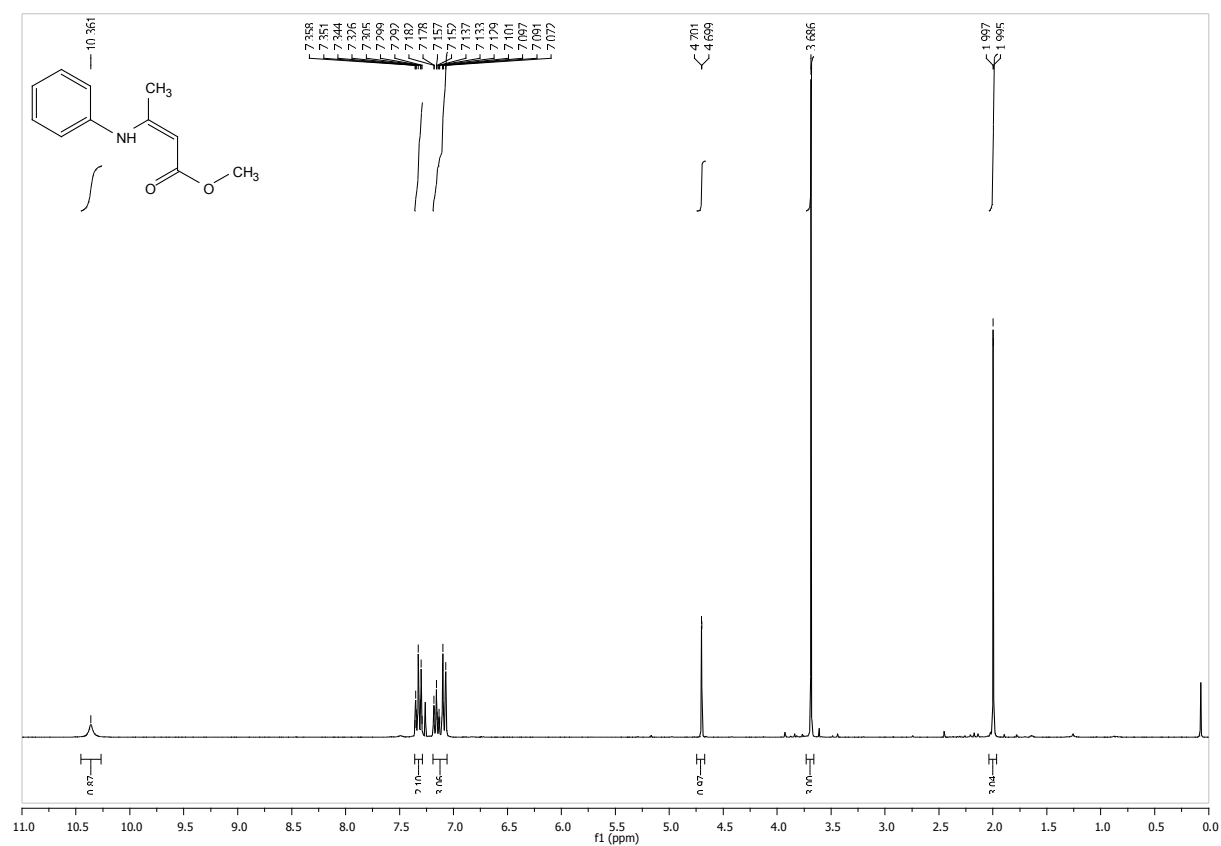
## 7. References

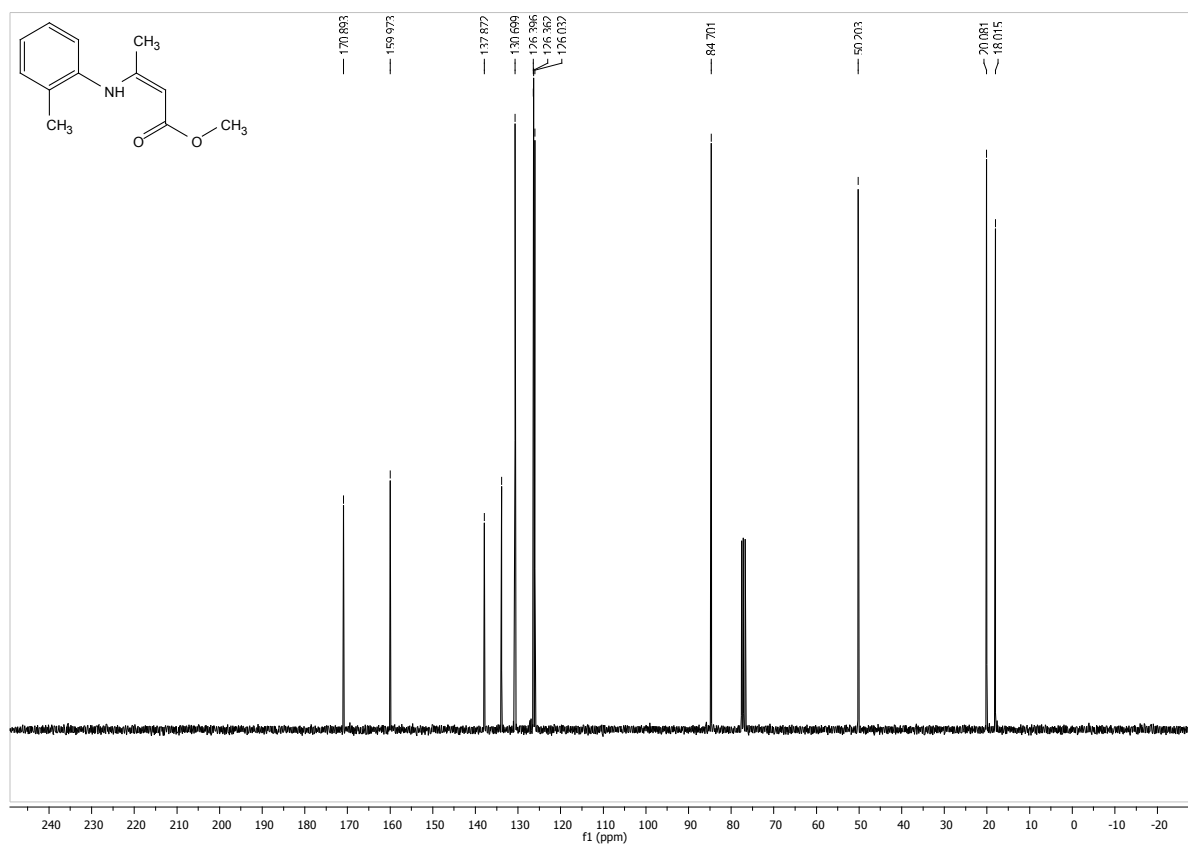
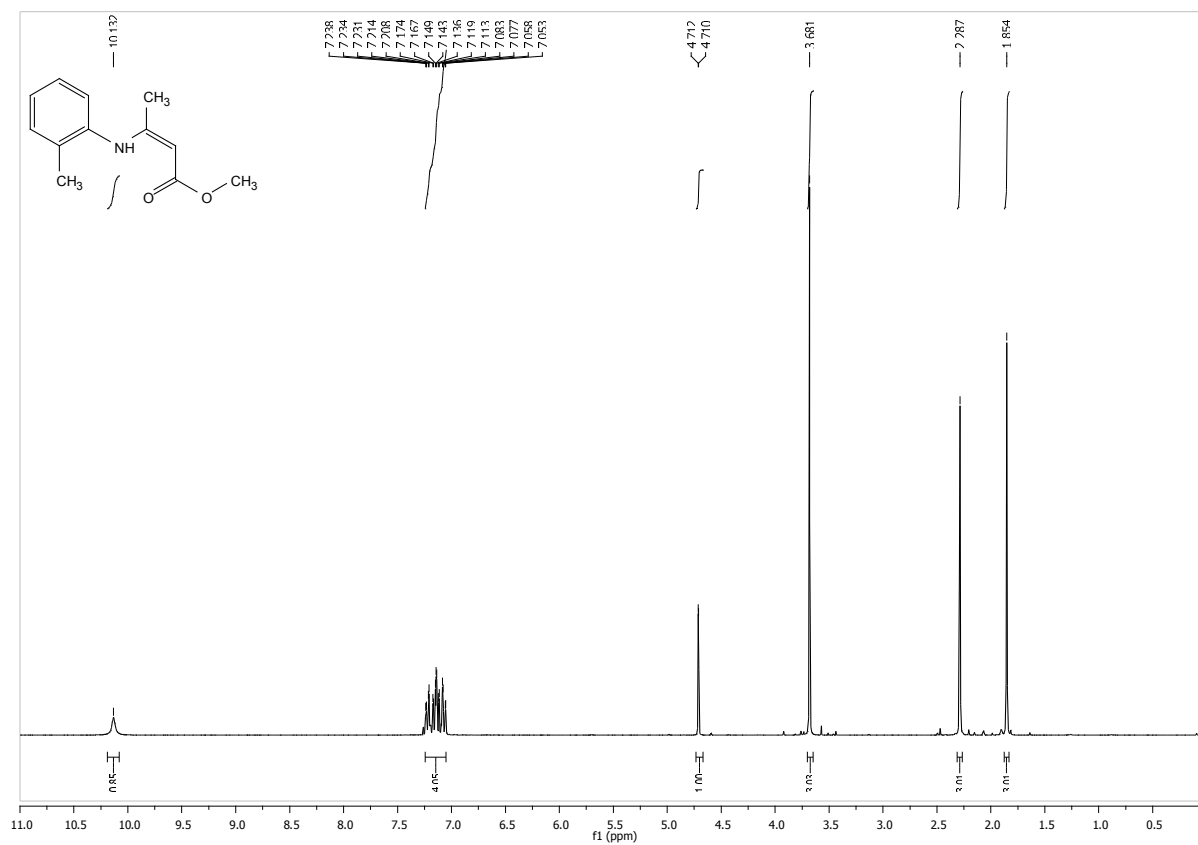
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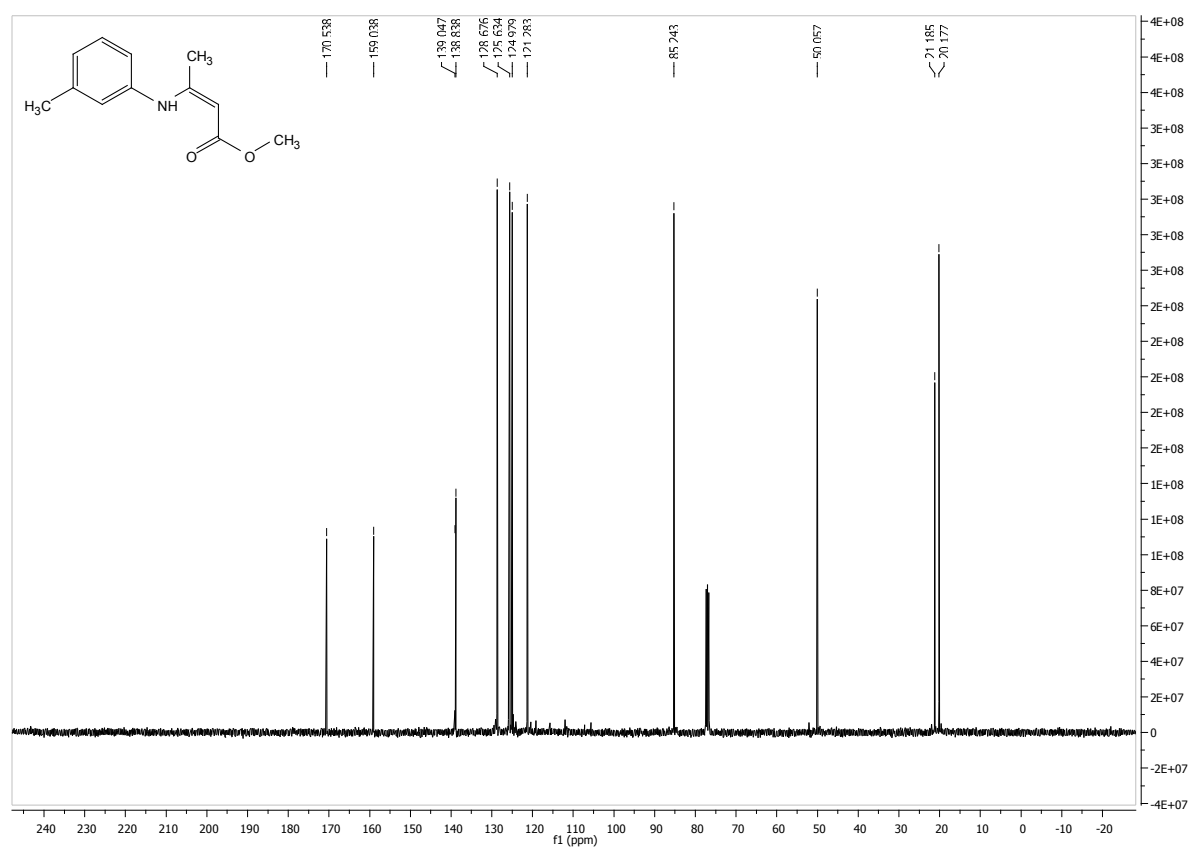
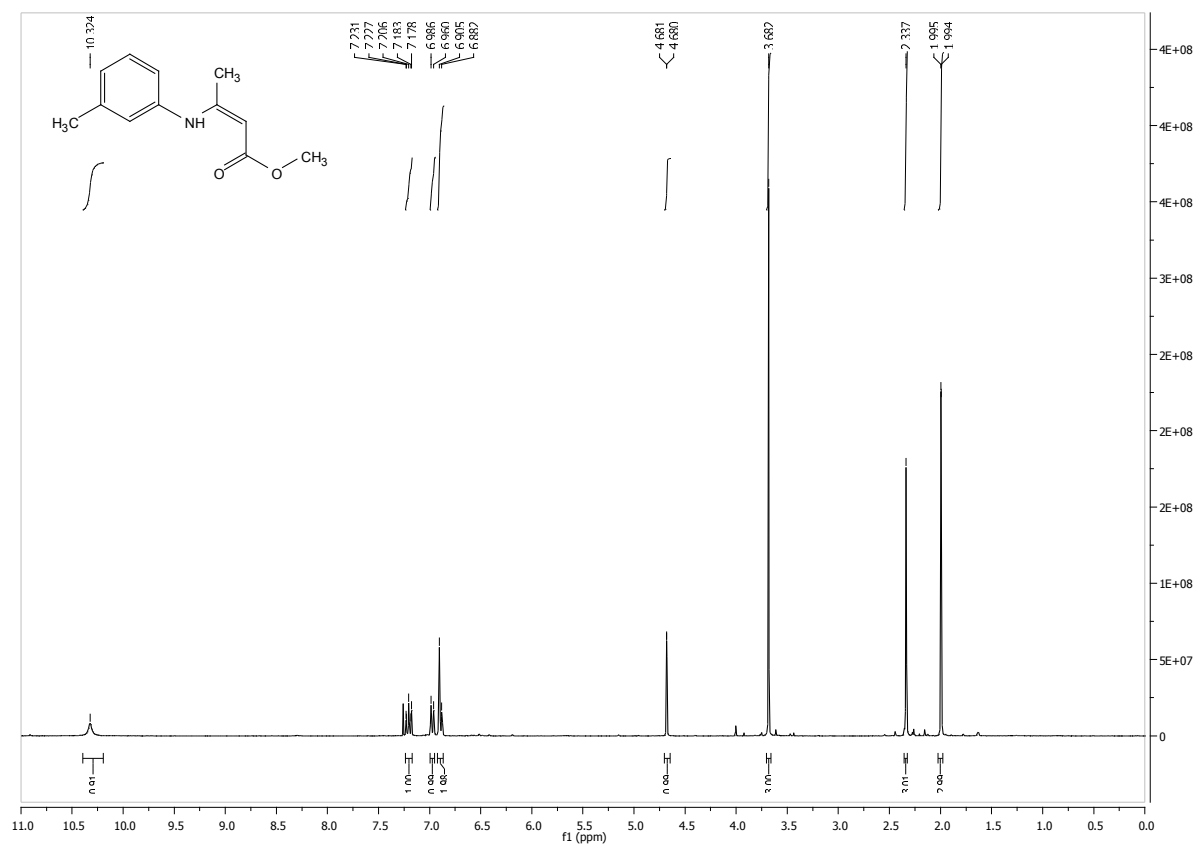
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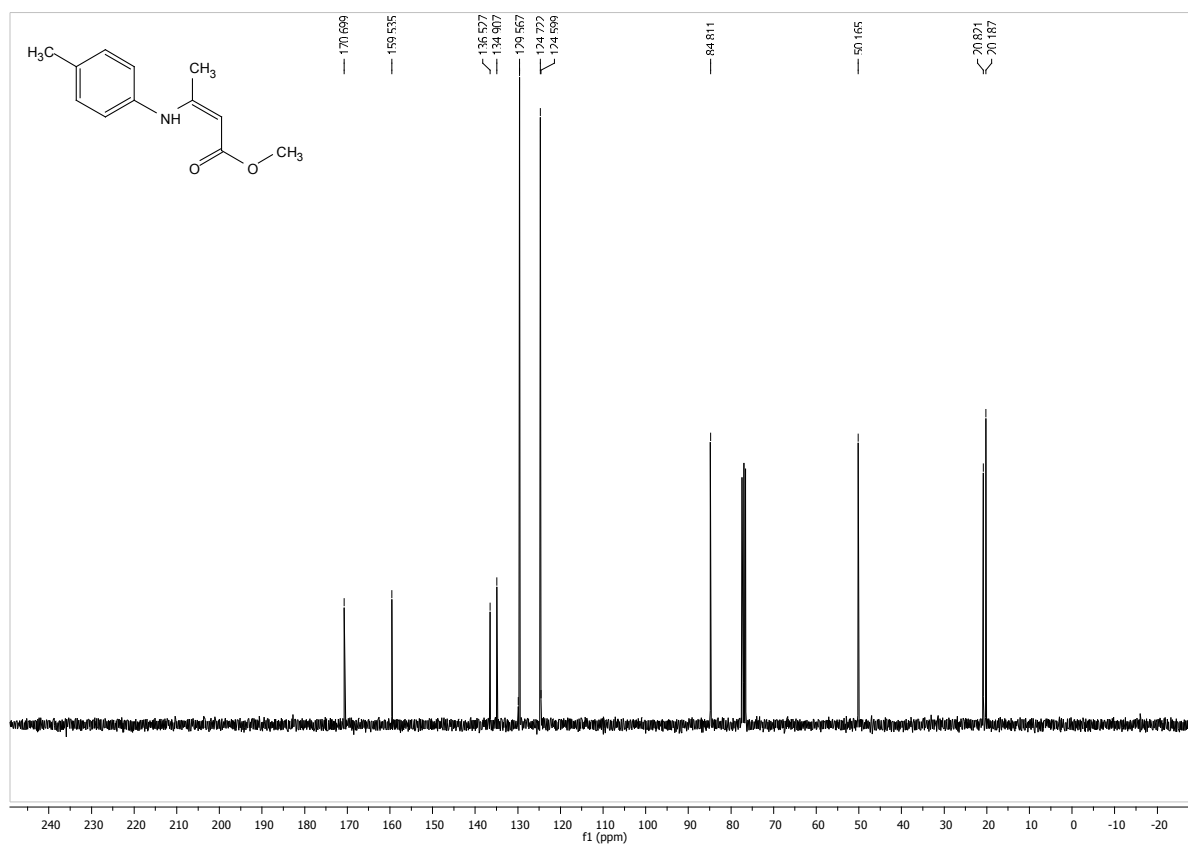
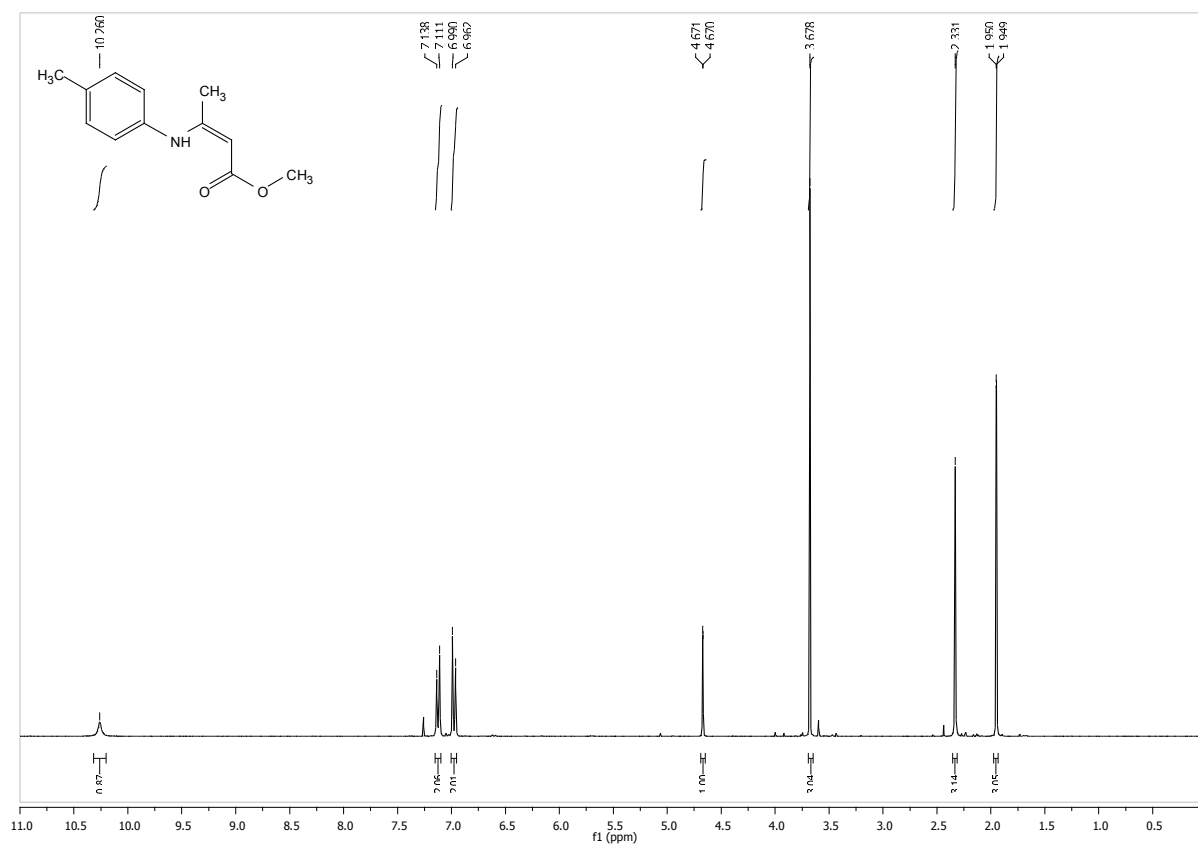
## 8. Scans of $^1\text{H}$ and $^{13}\text{C}$ spectra

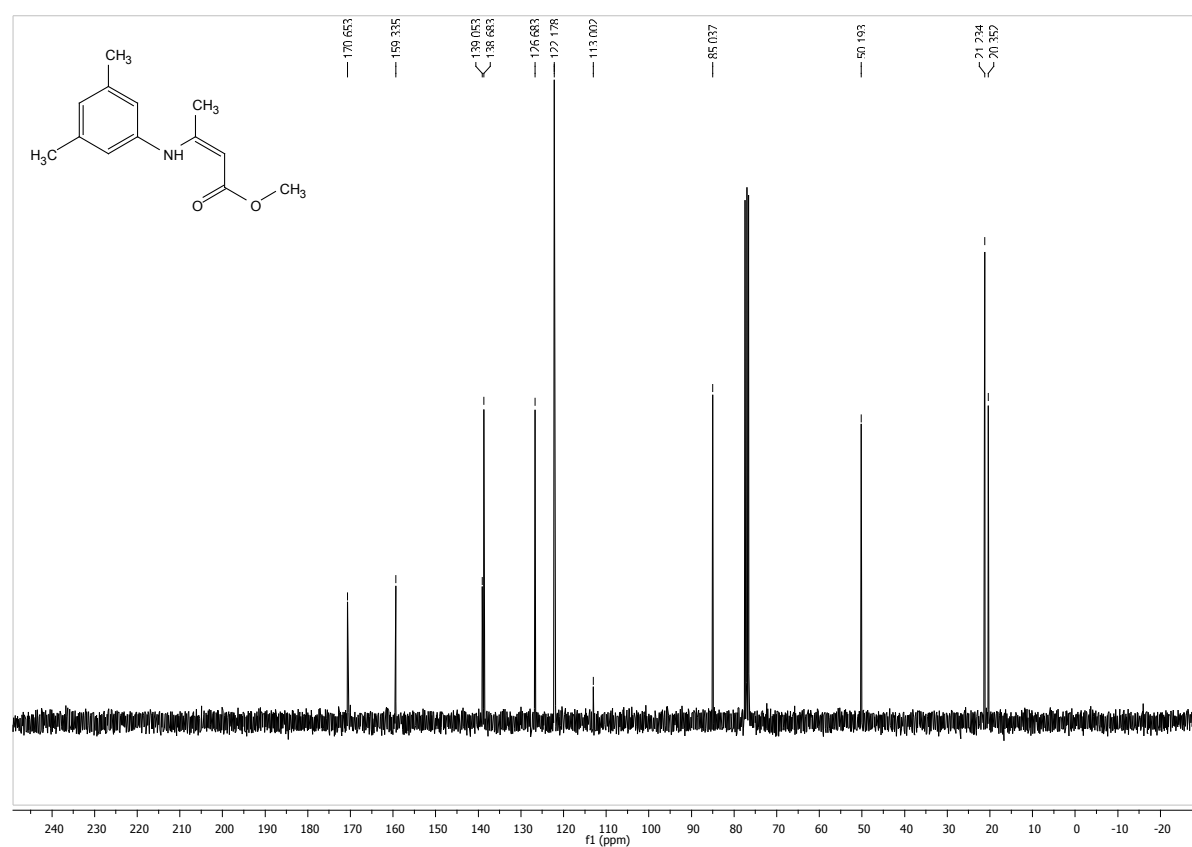
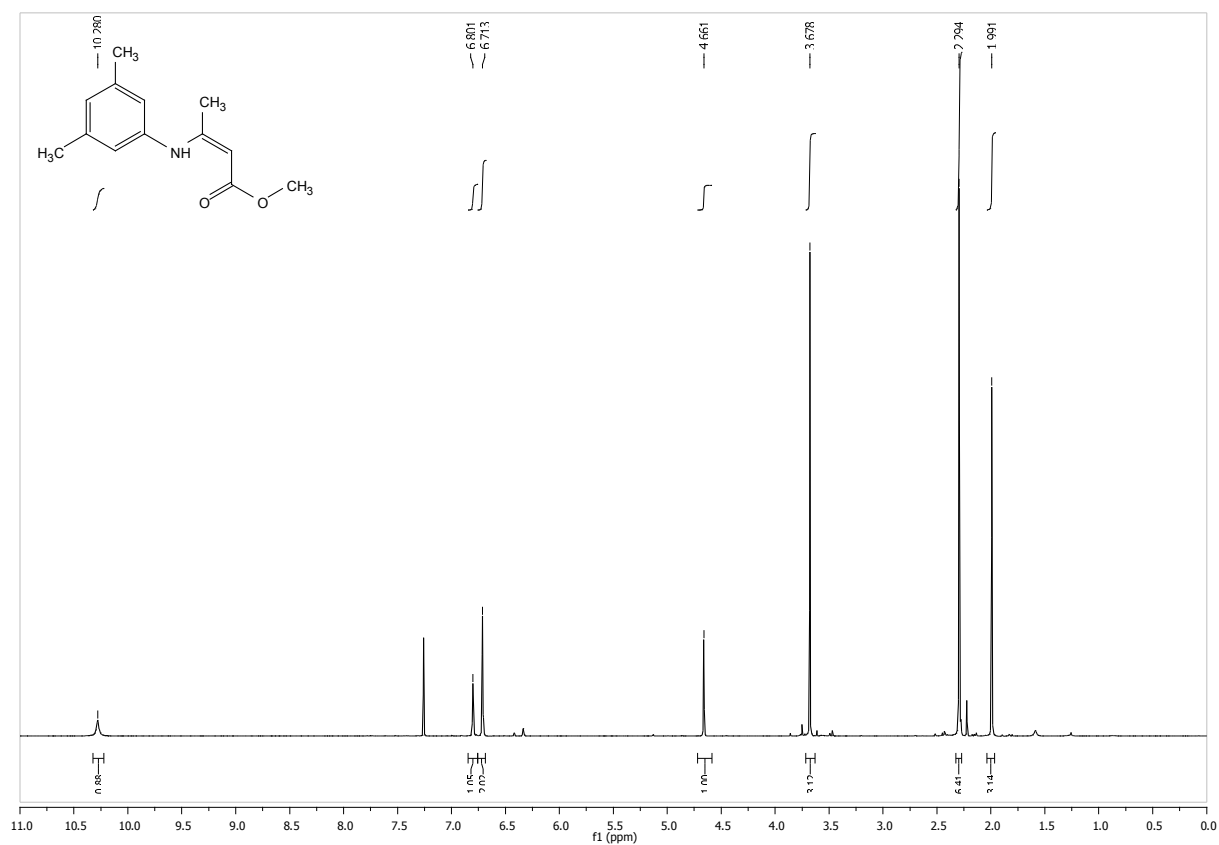
### a. Substrates

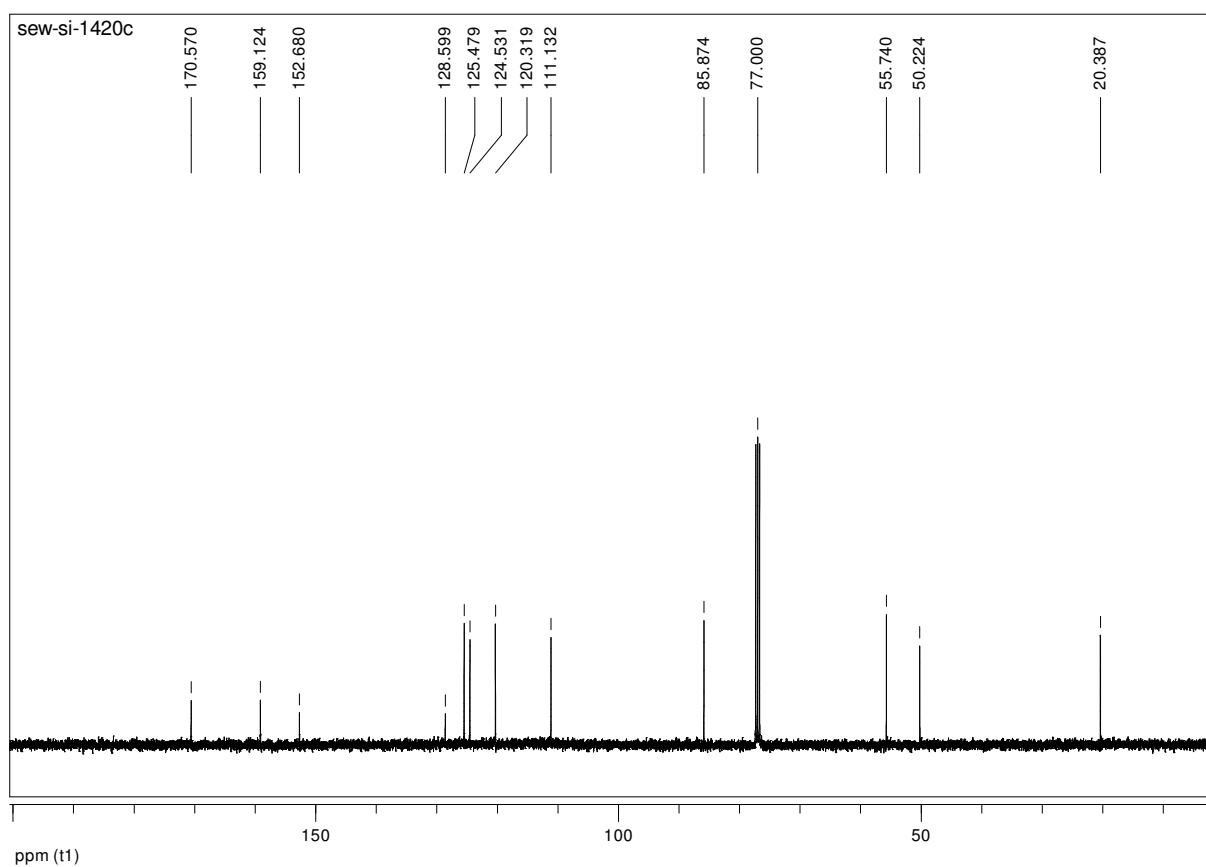
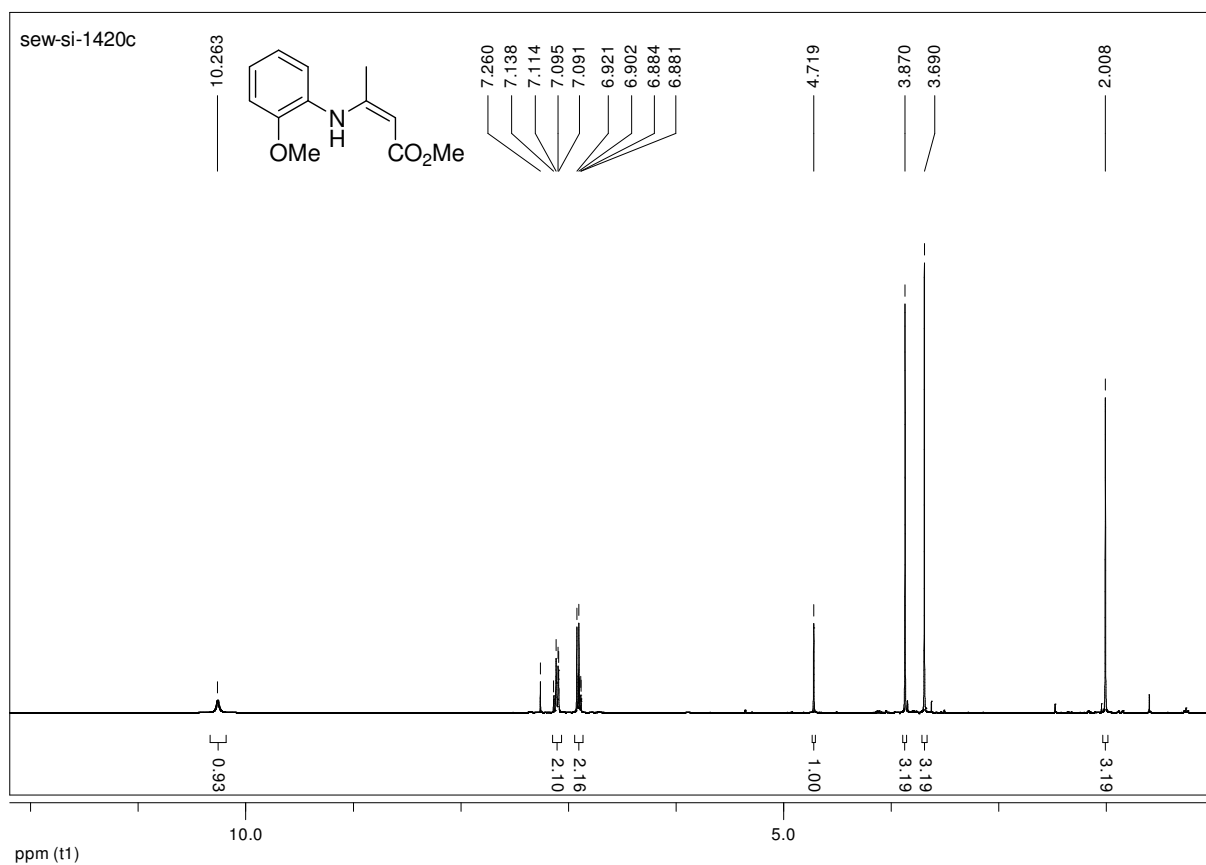


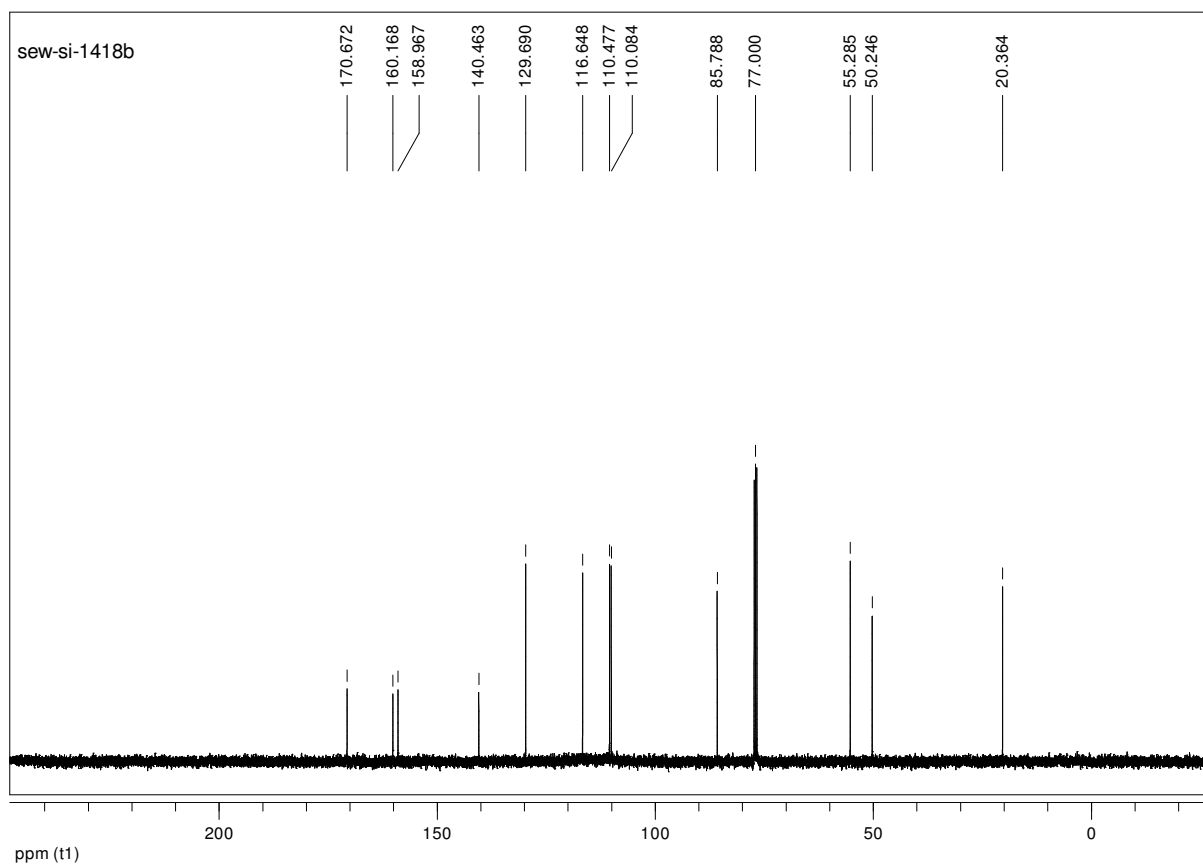
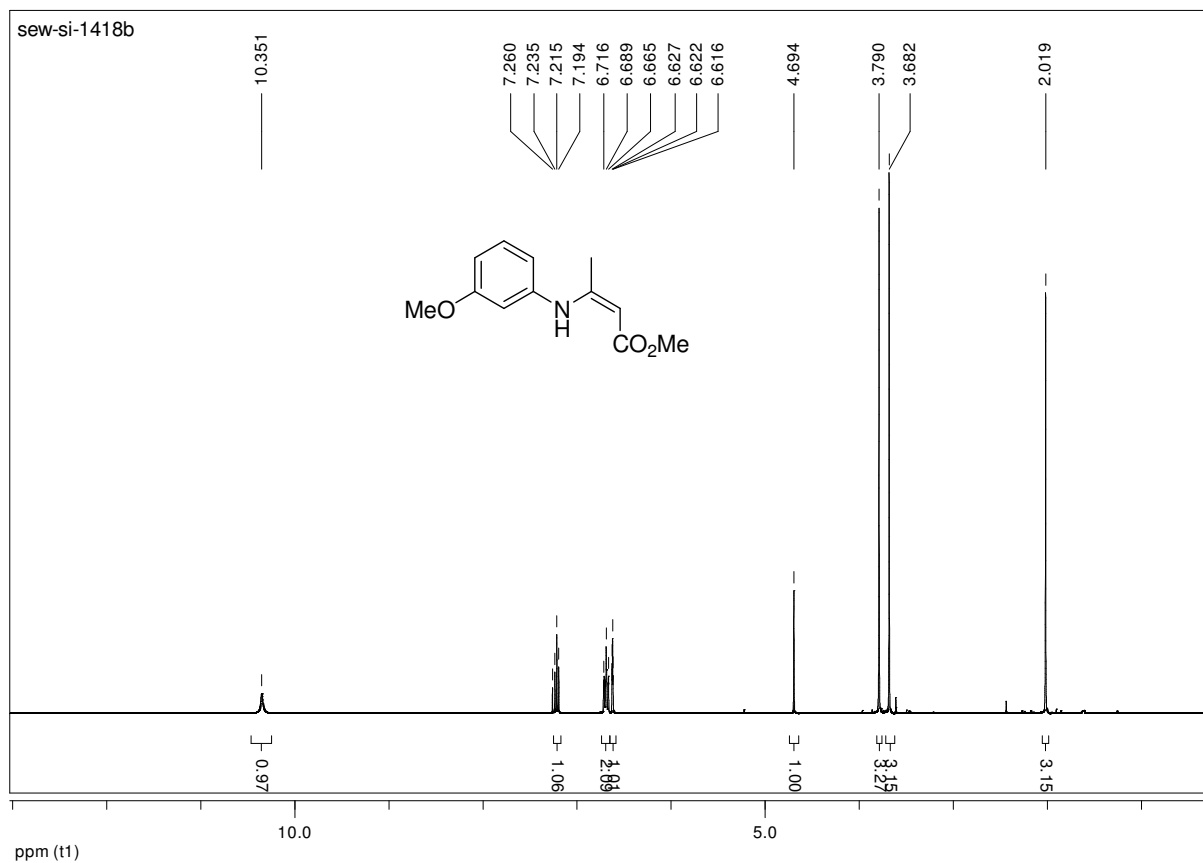


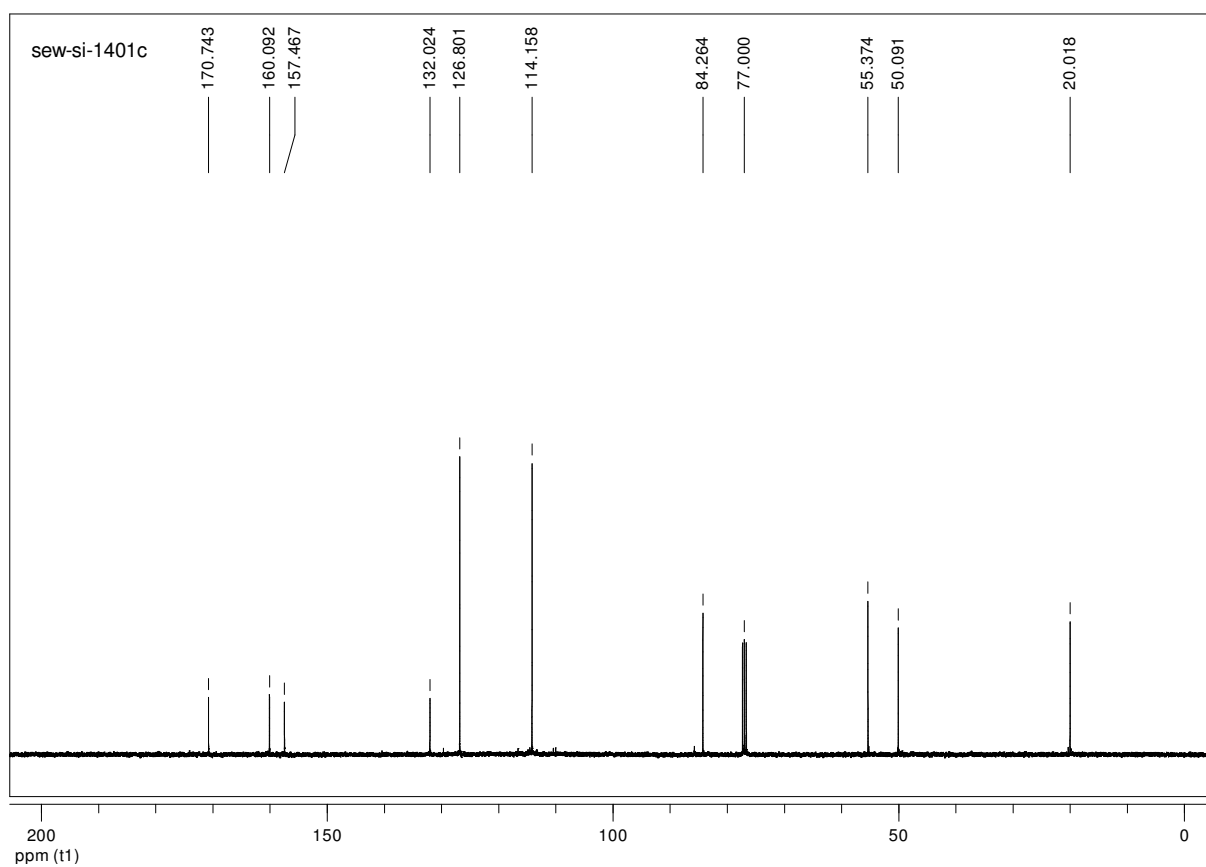
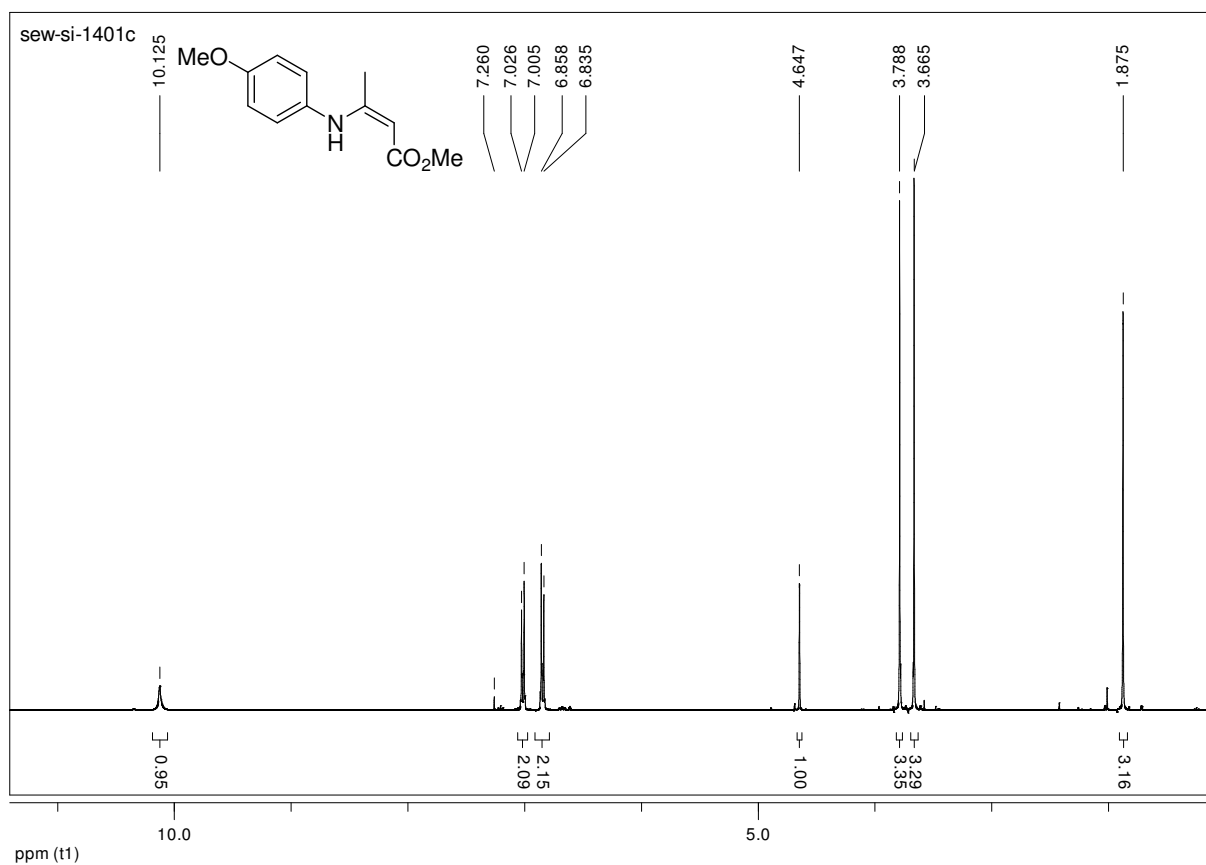


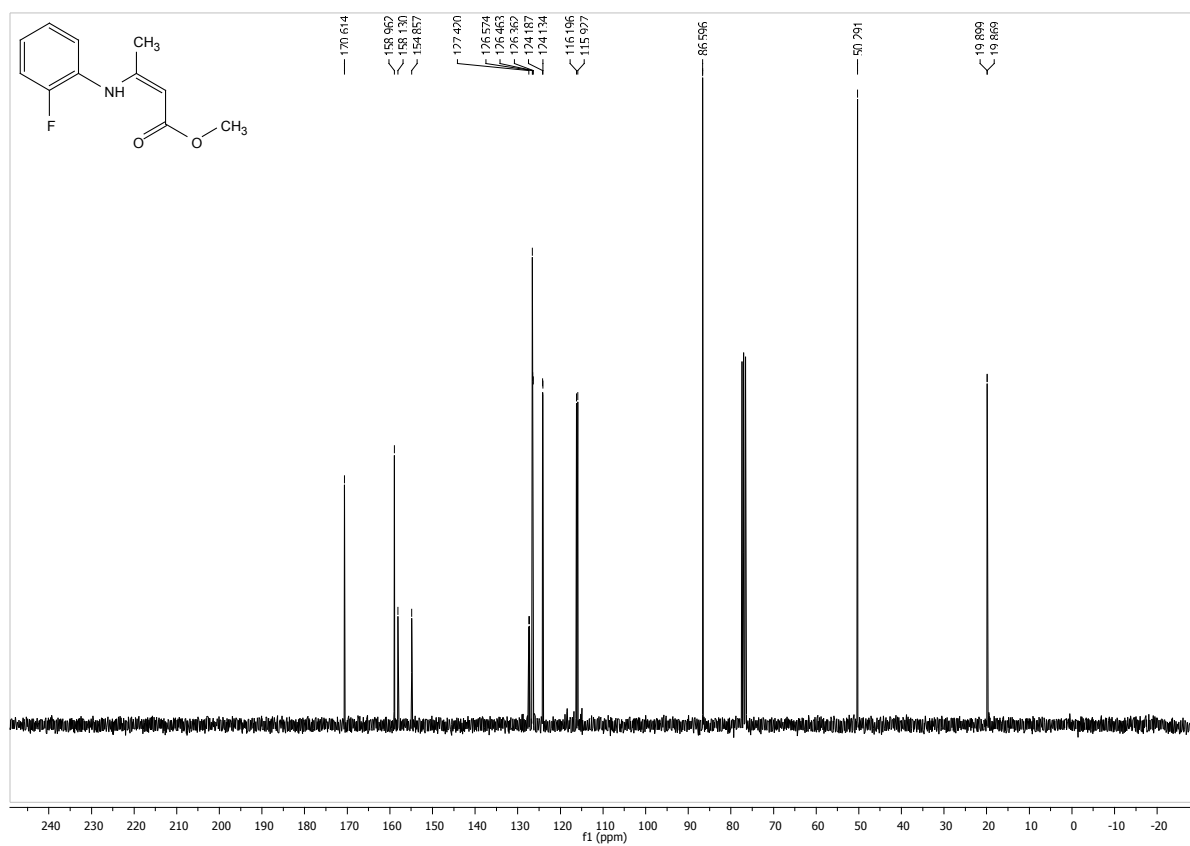
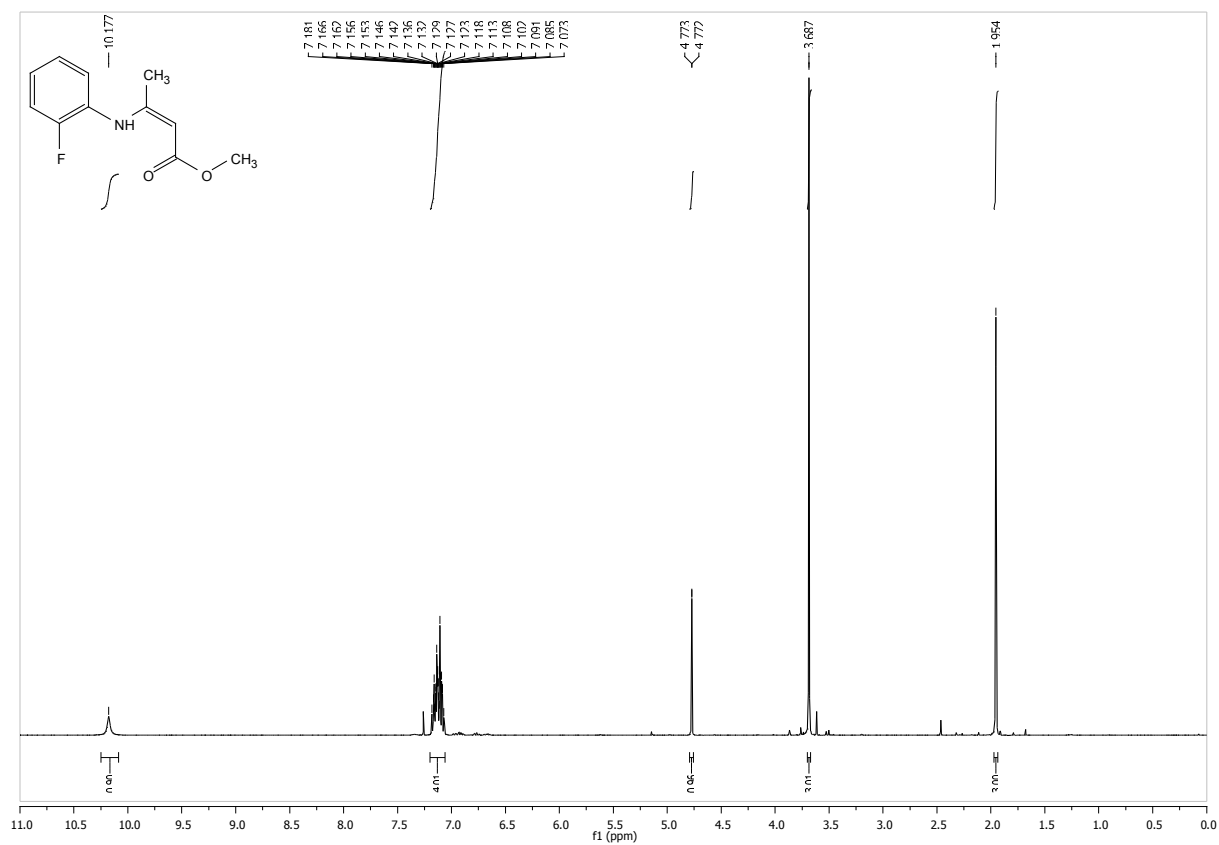


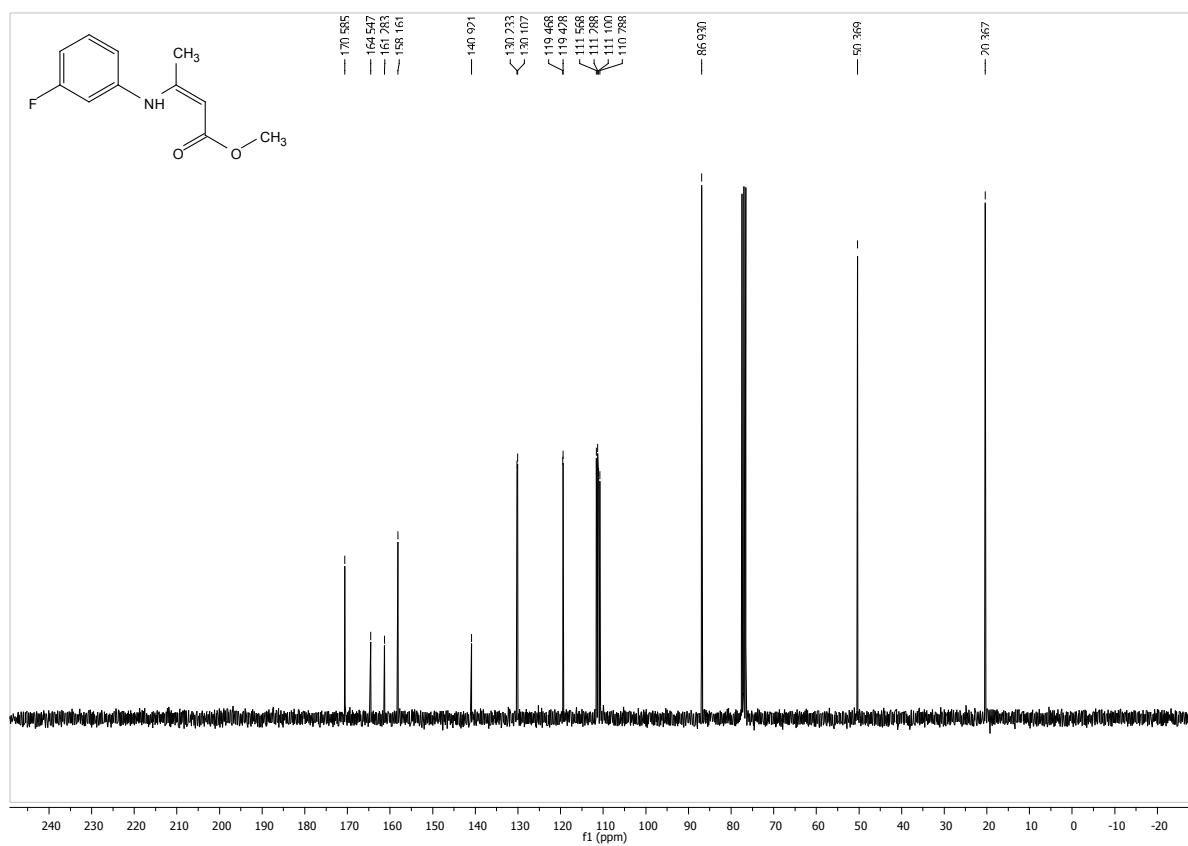
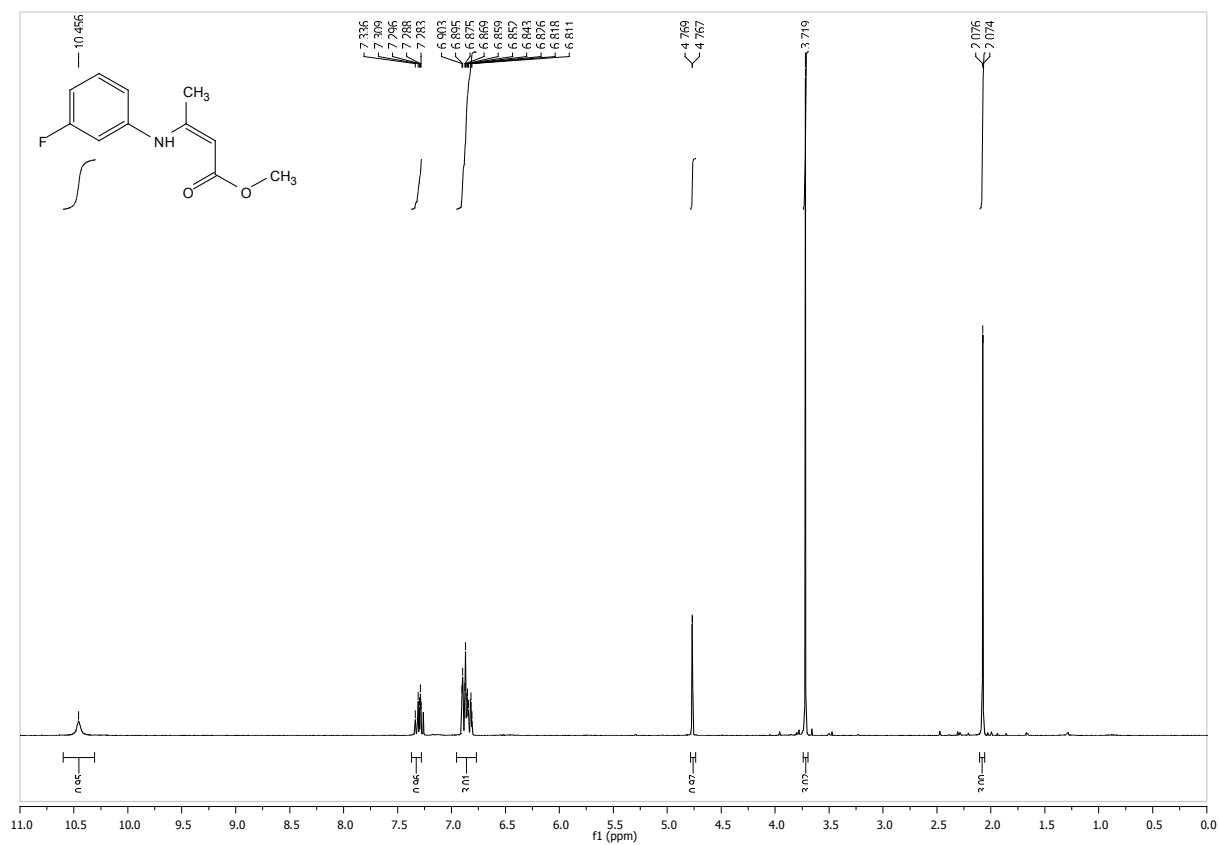


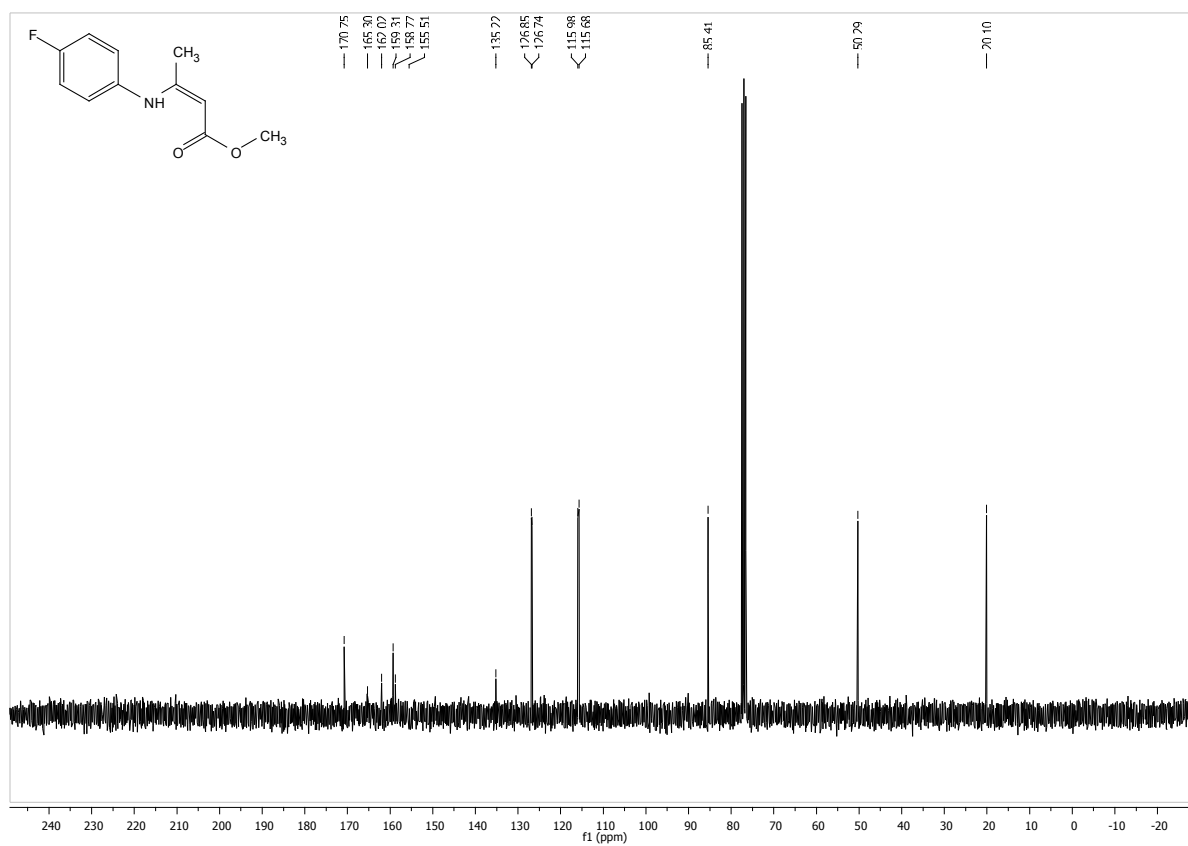
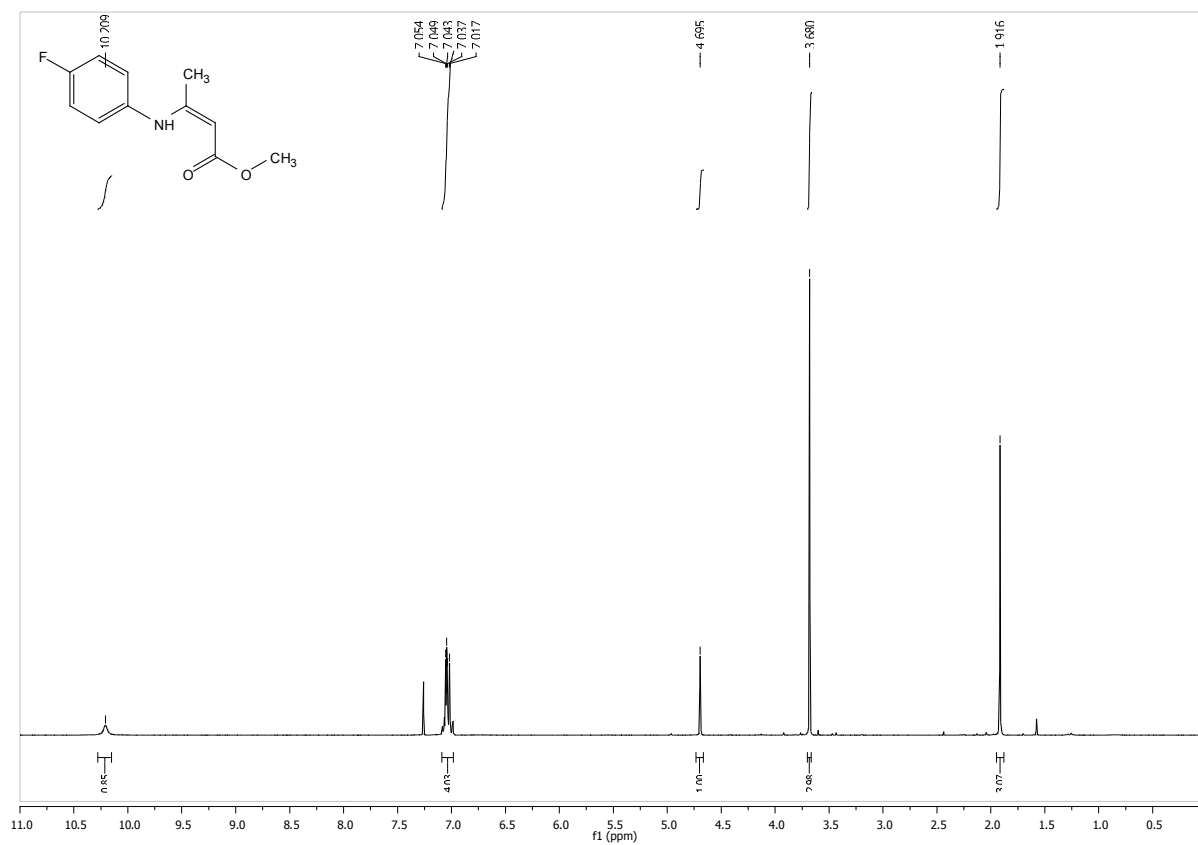


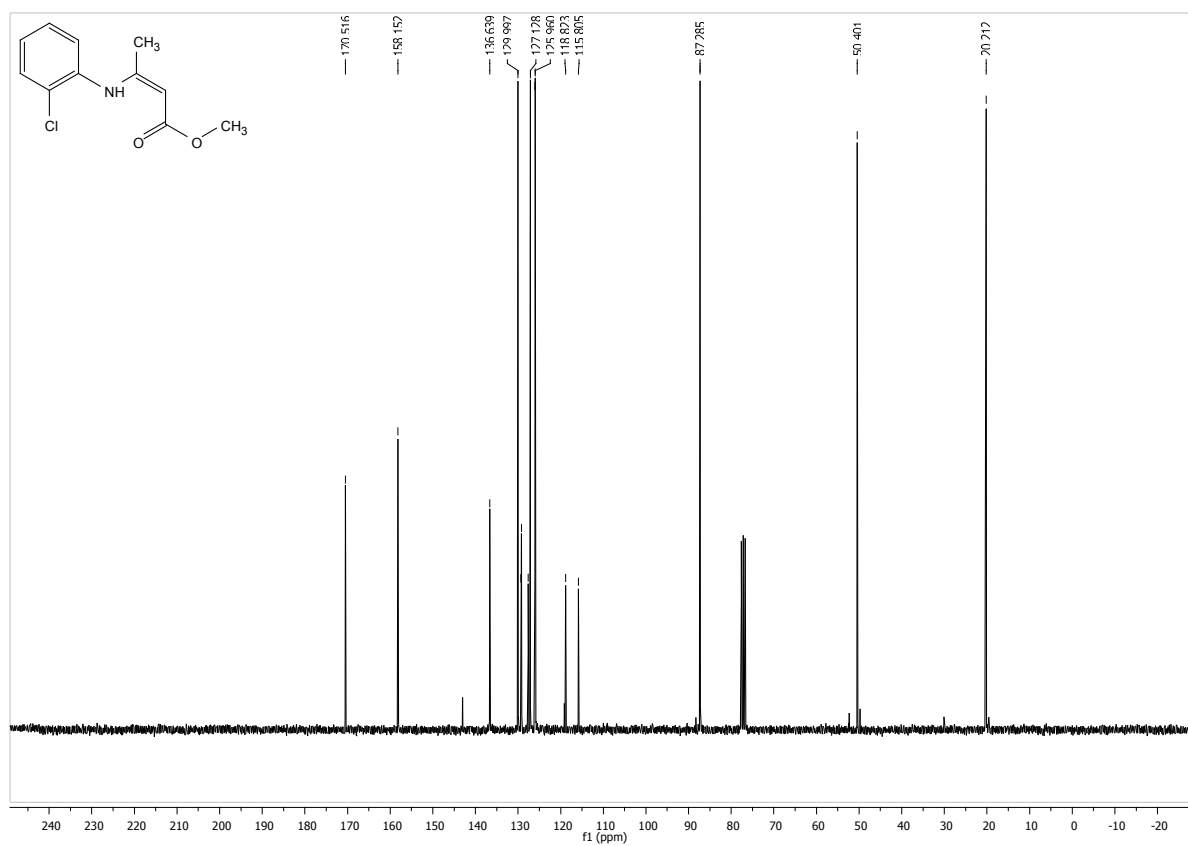
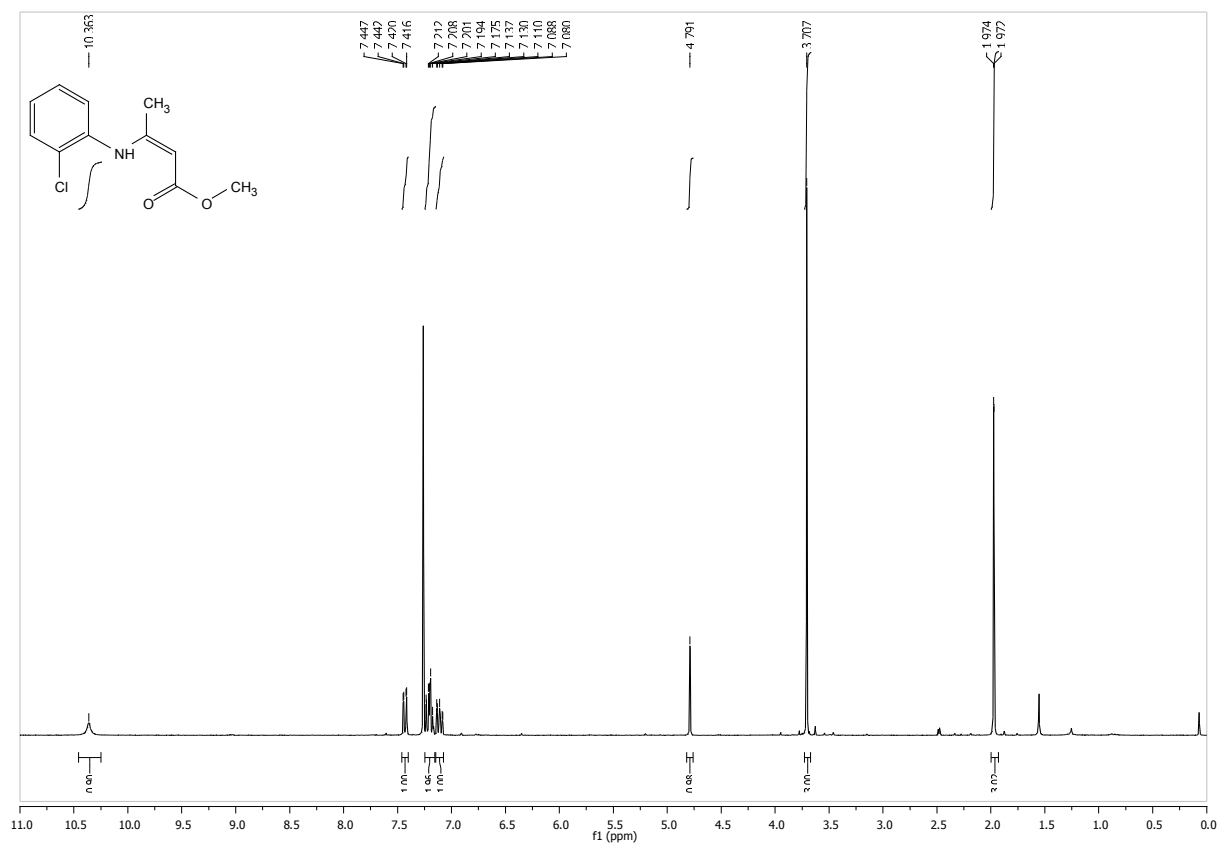


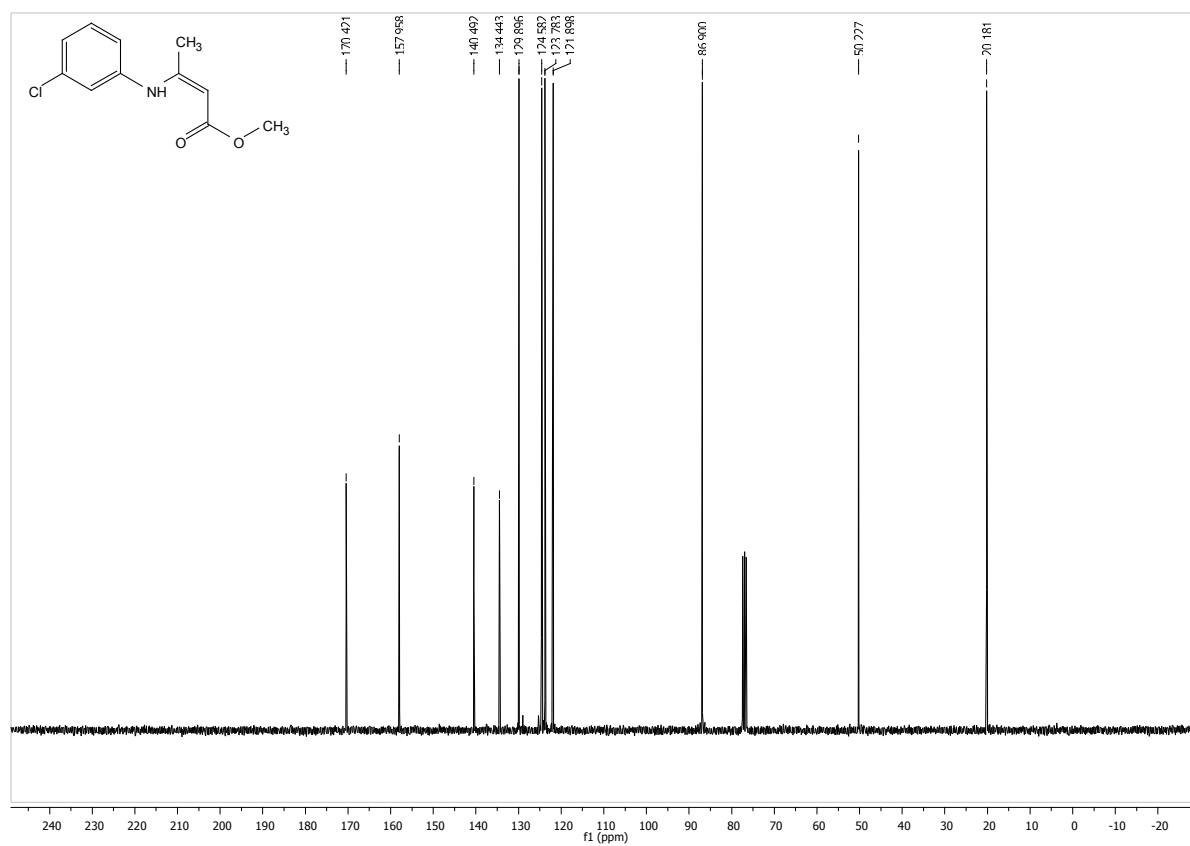
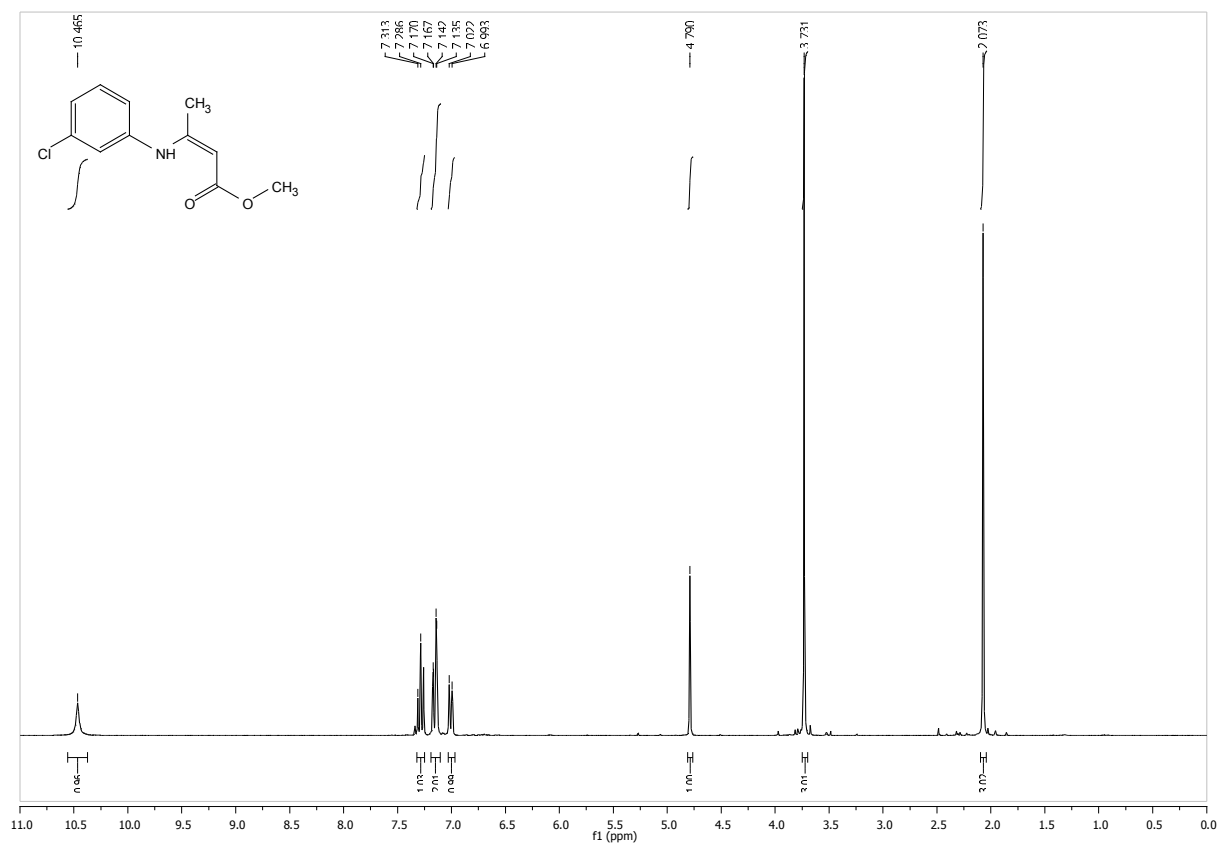


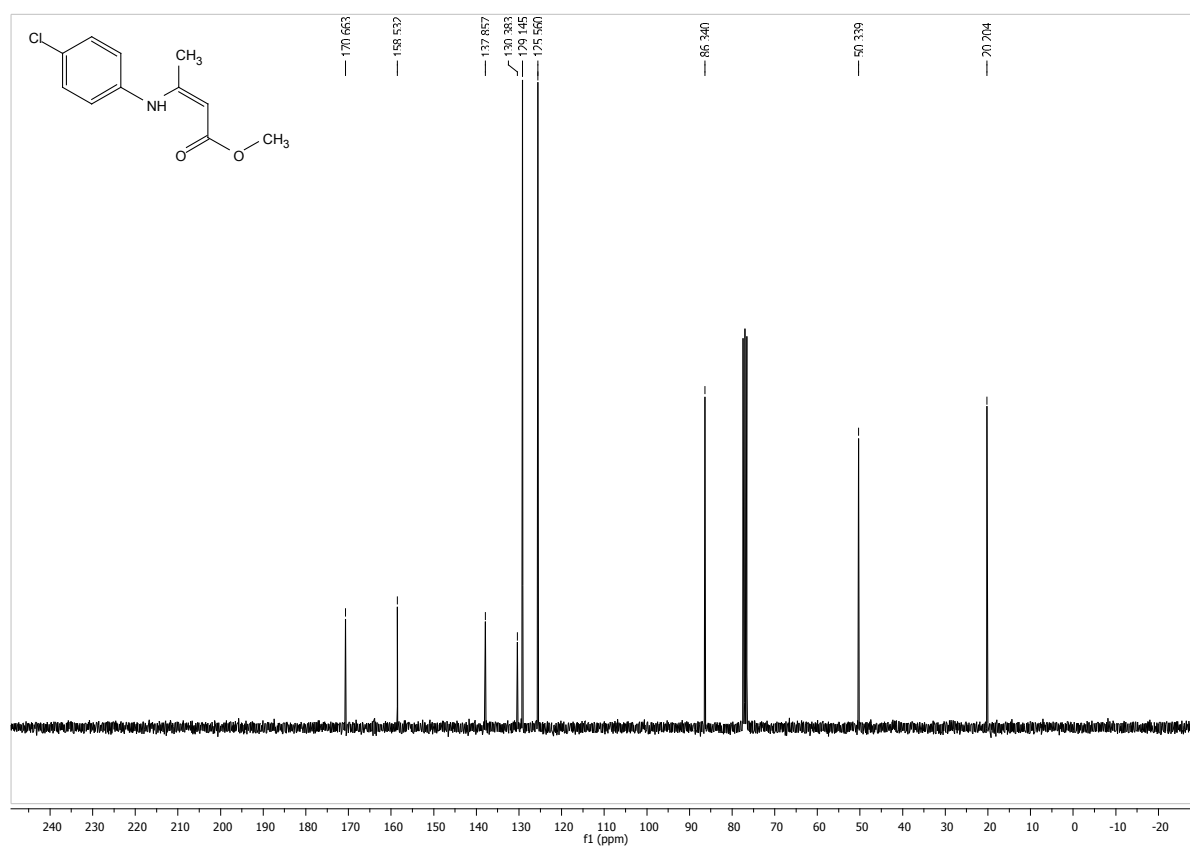
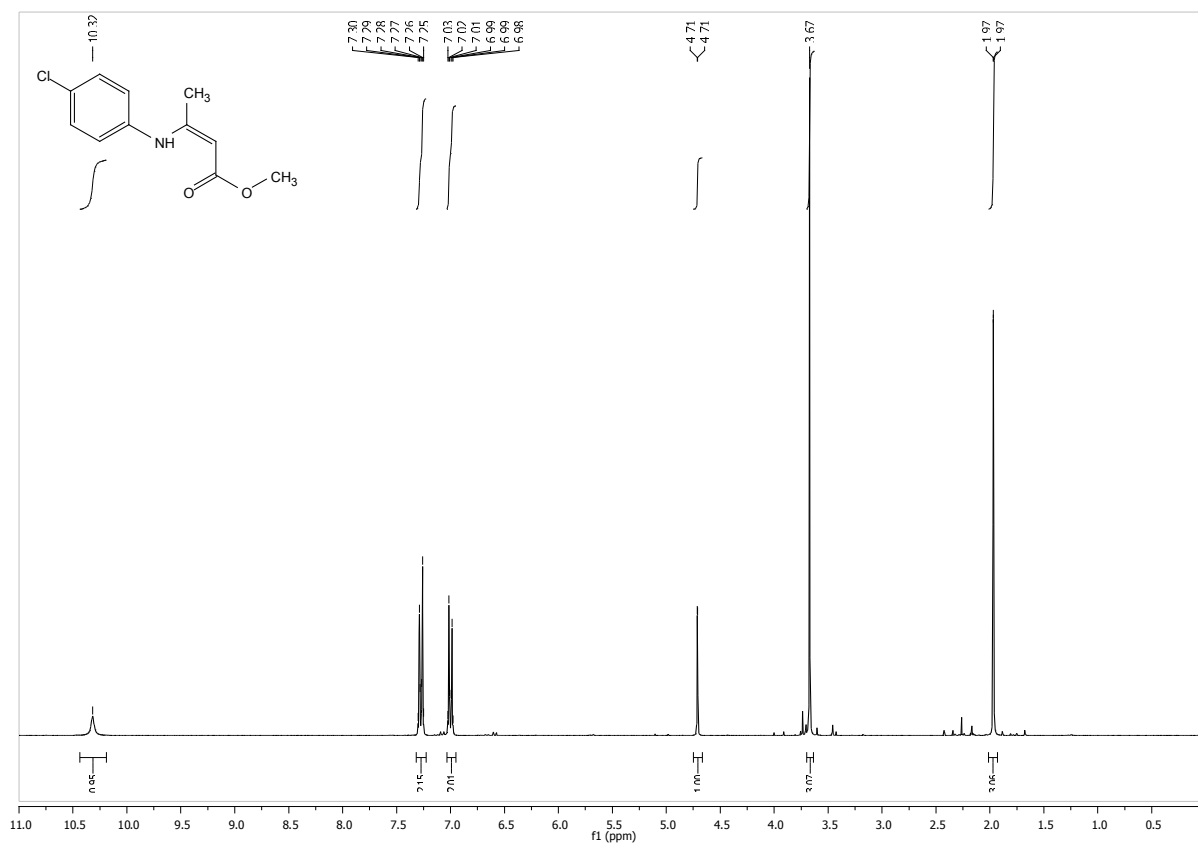


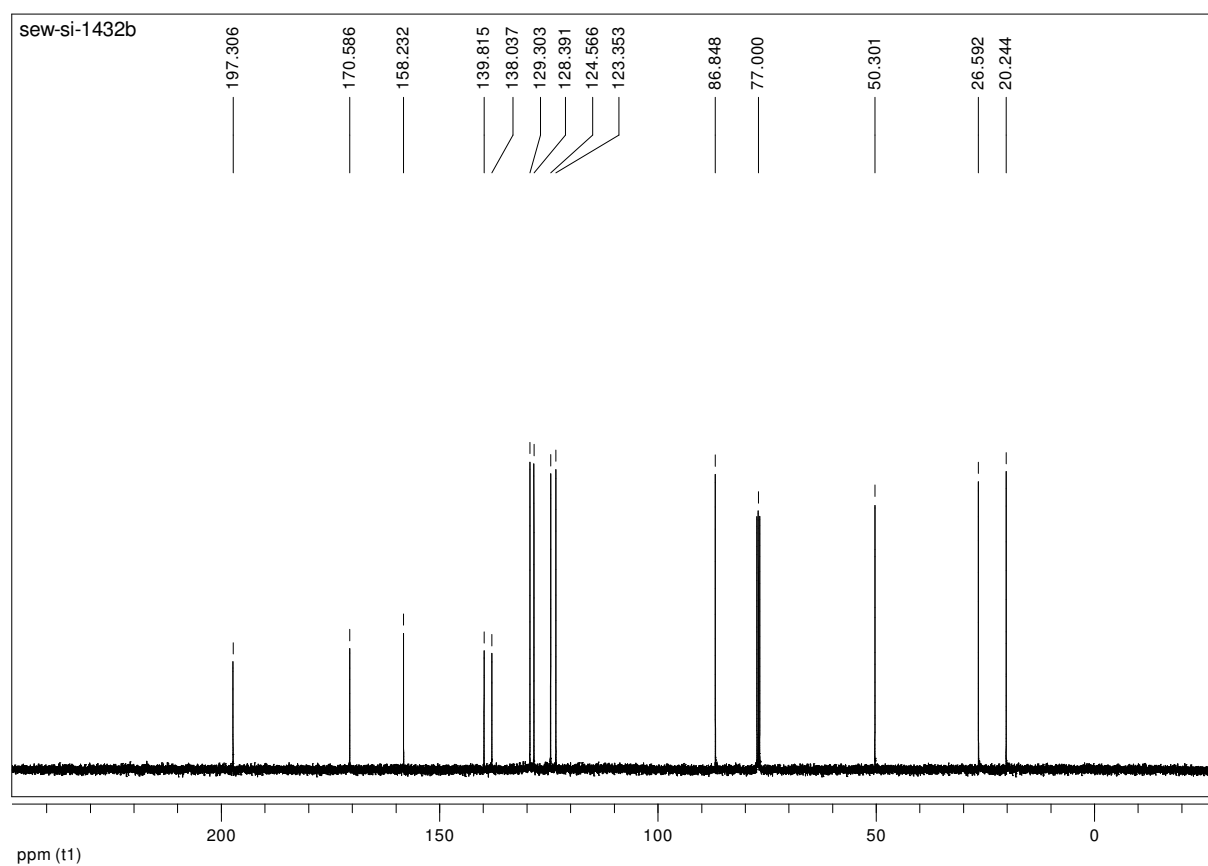
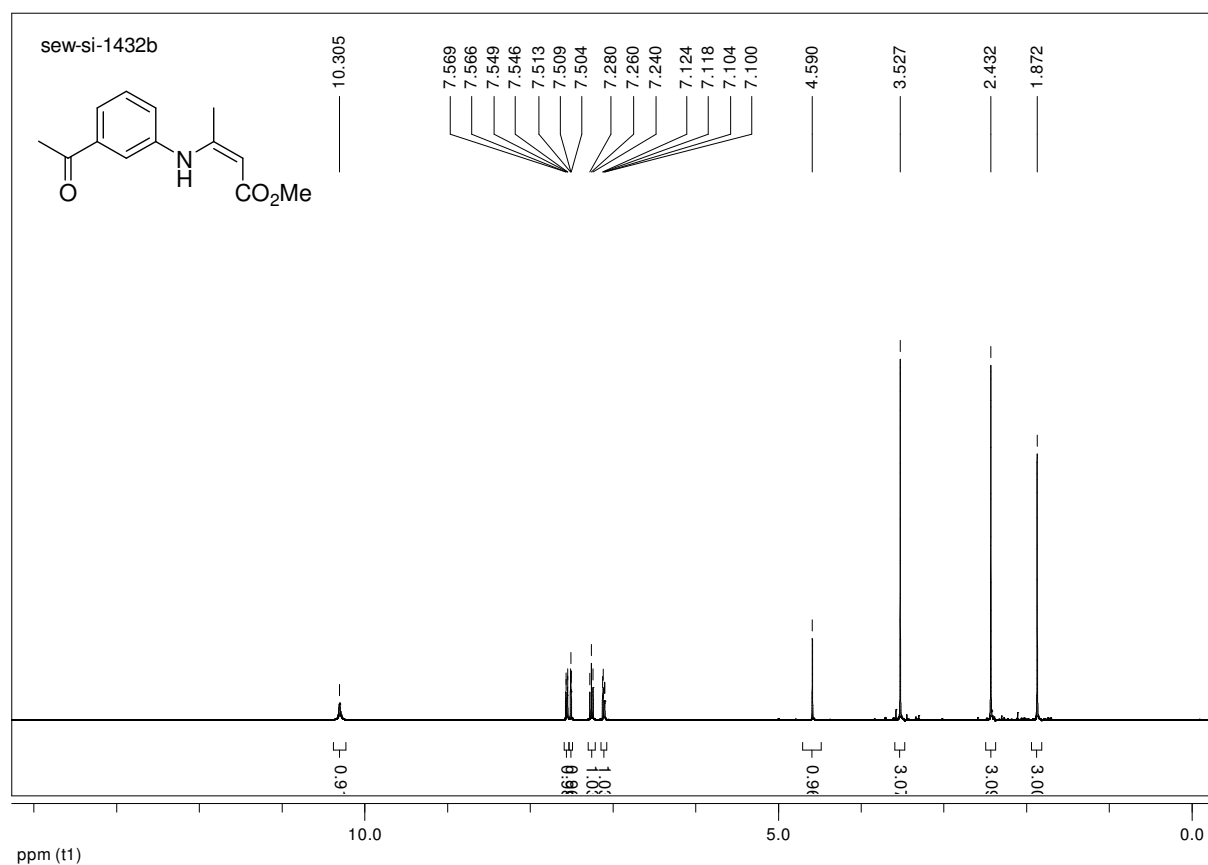


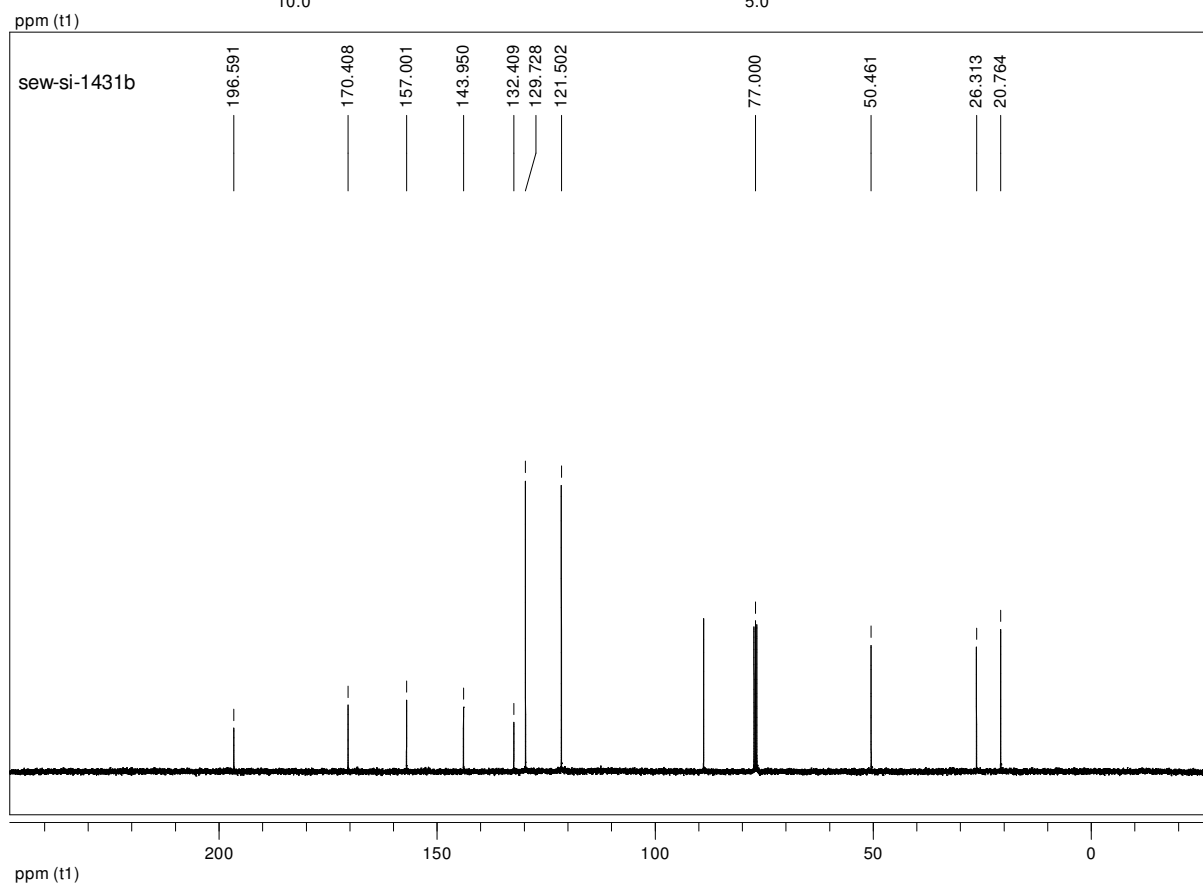
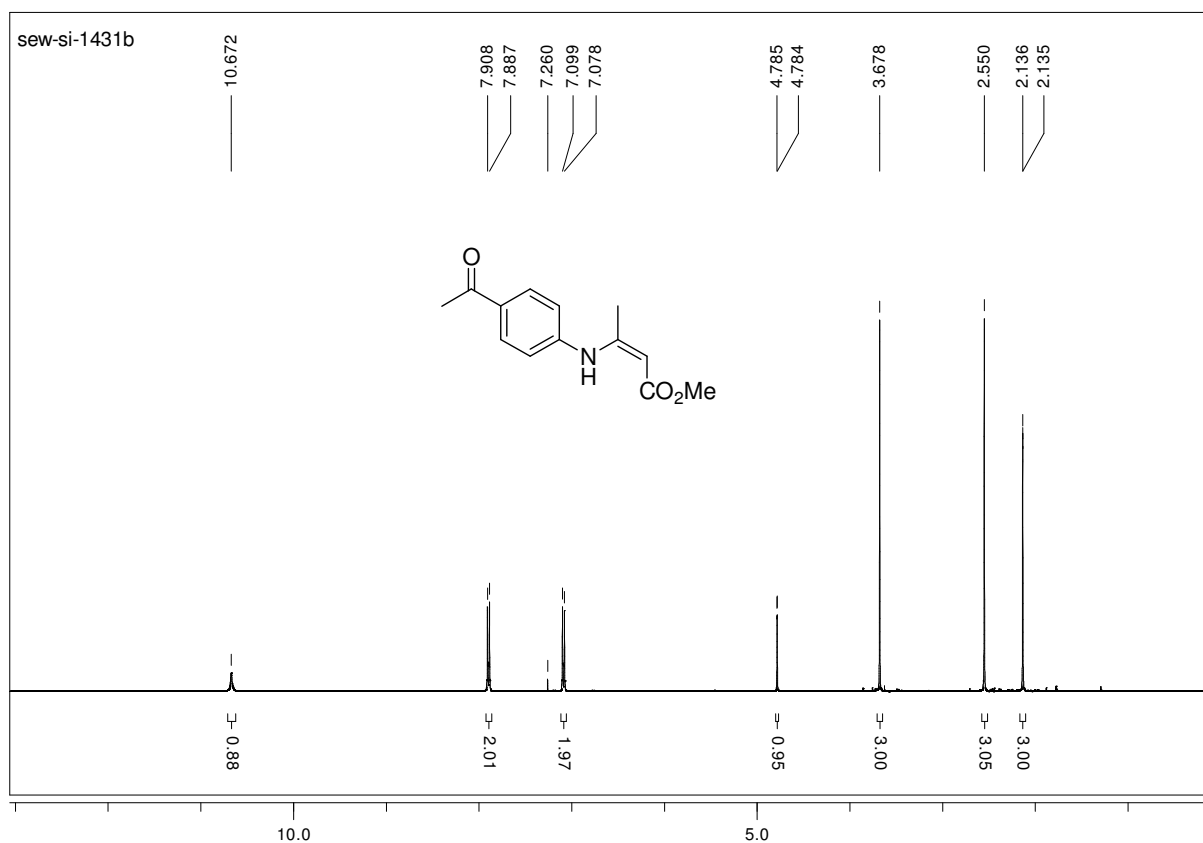


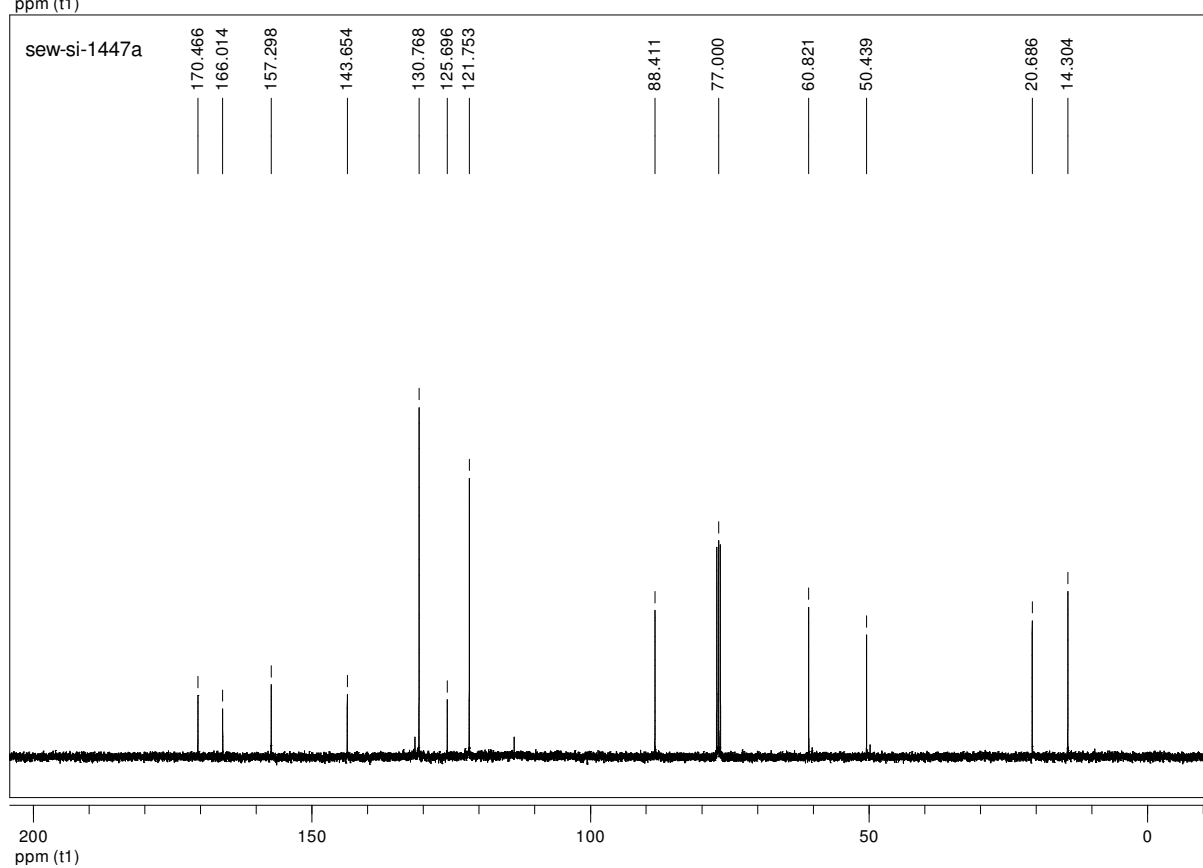
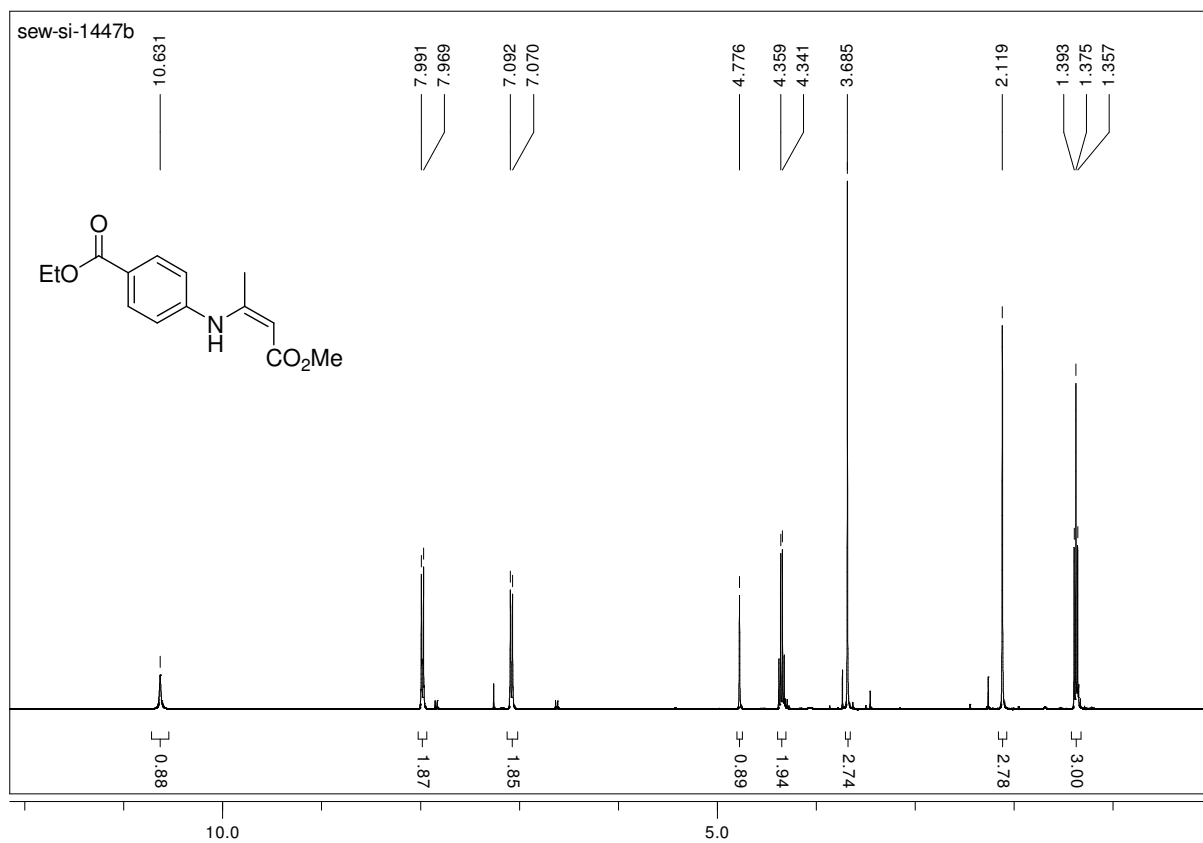


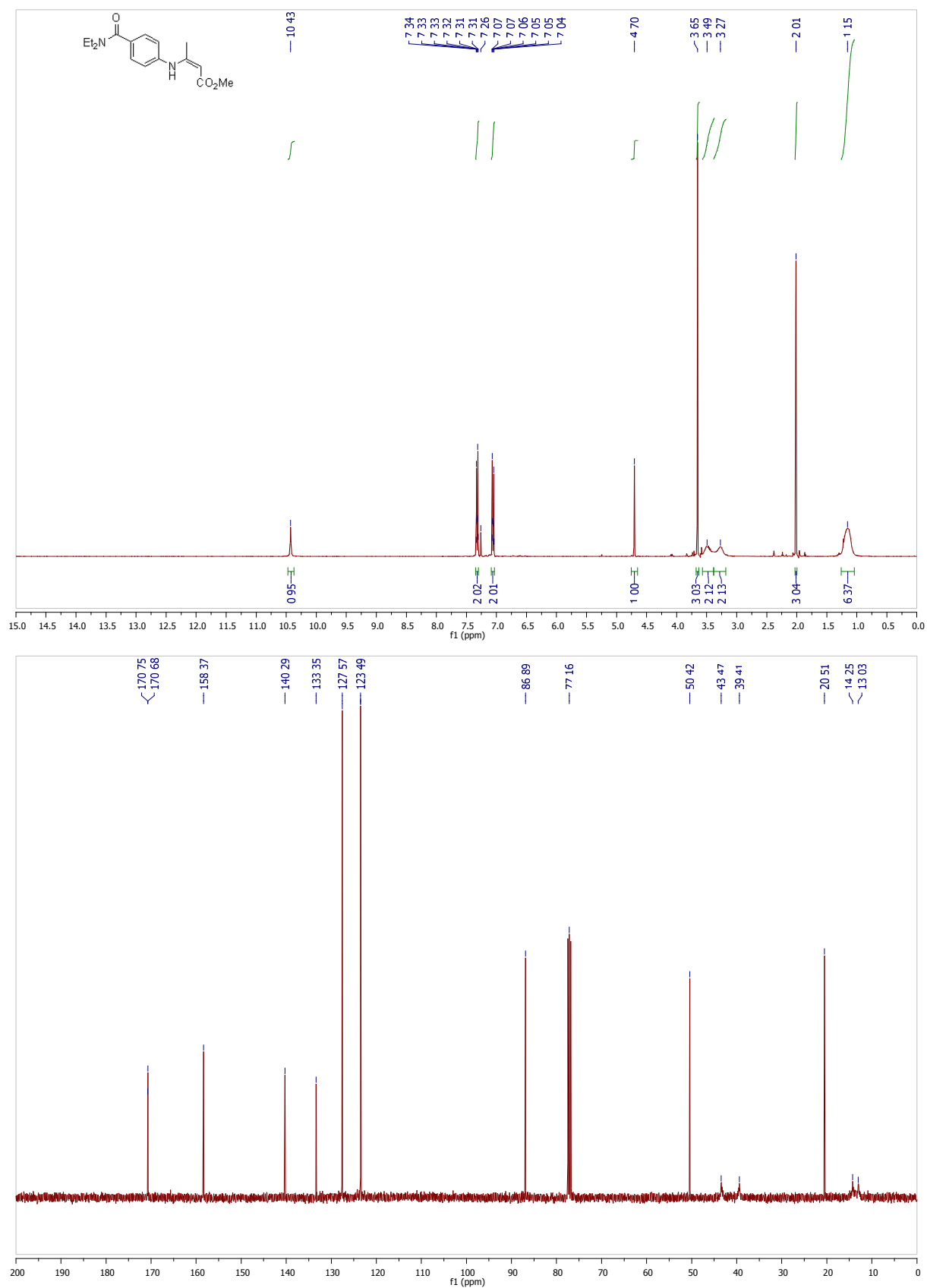


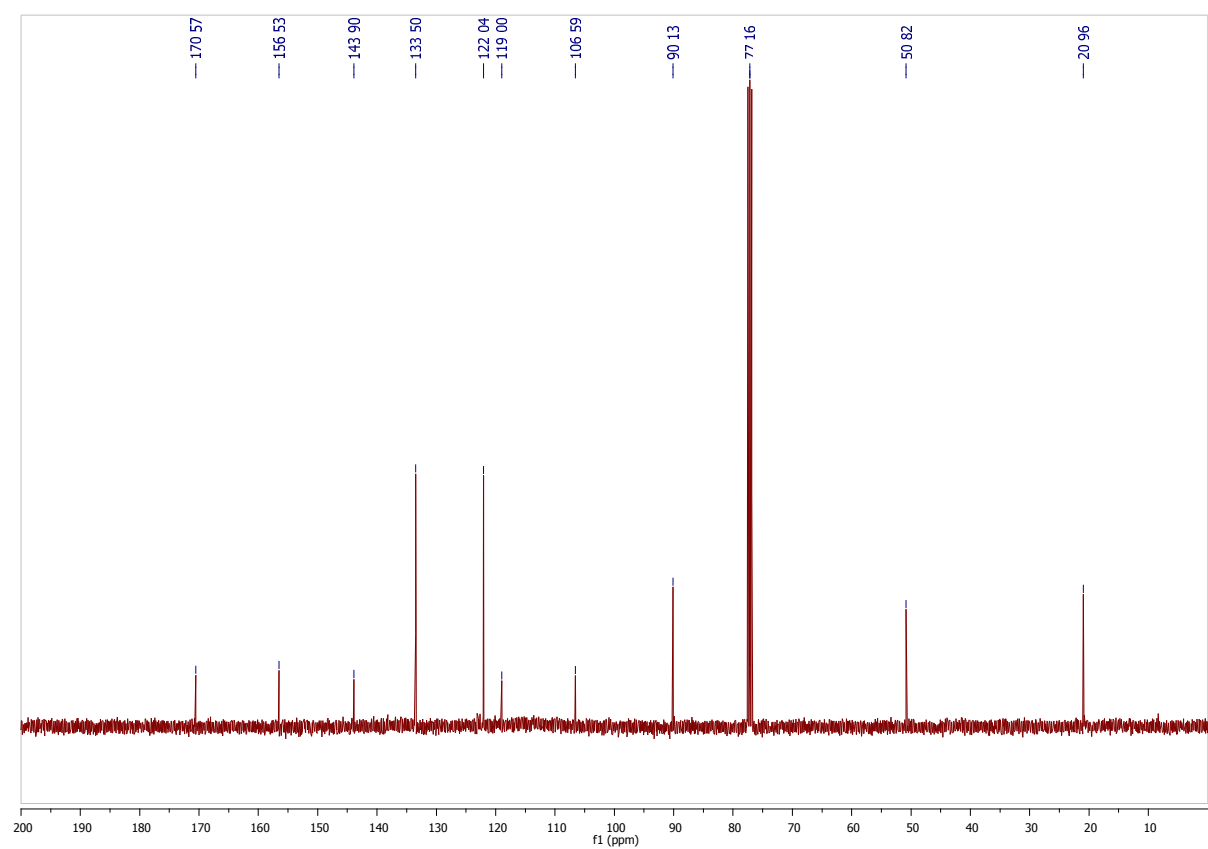
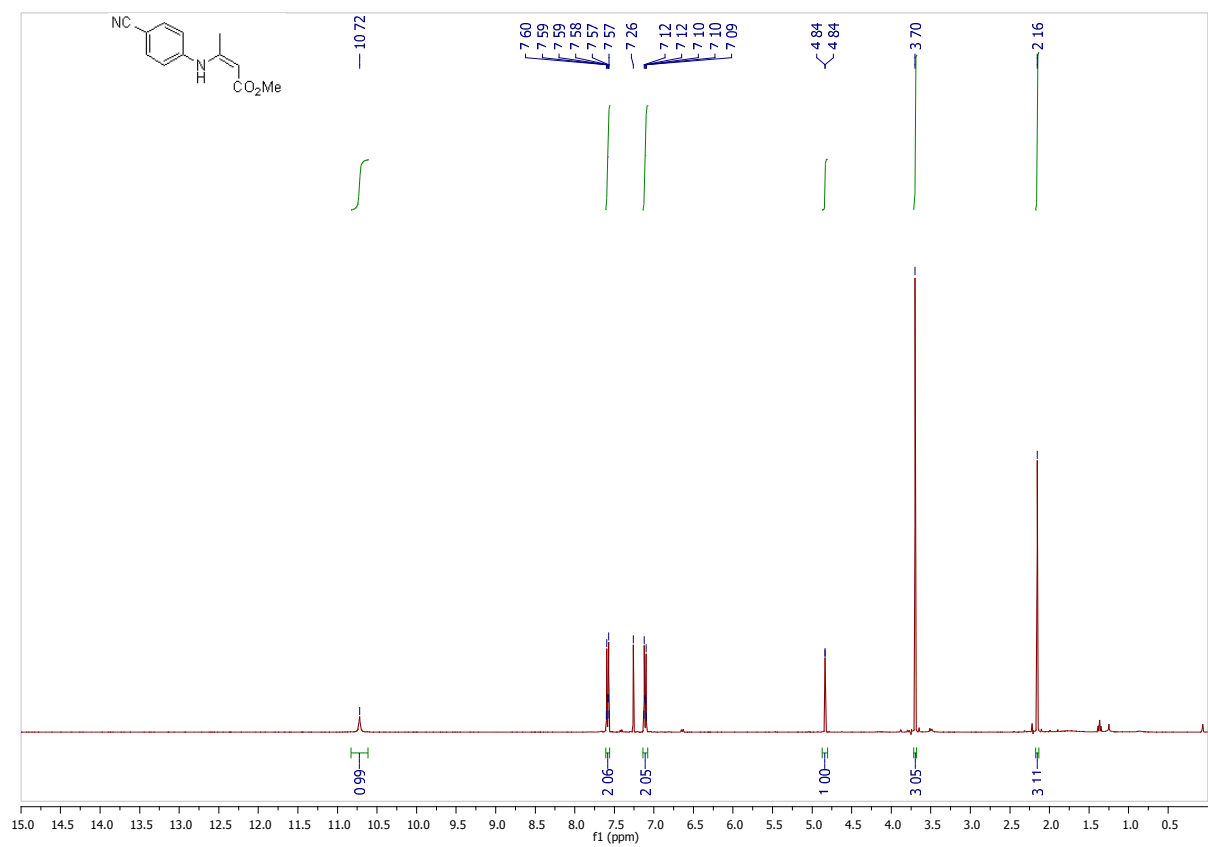


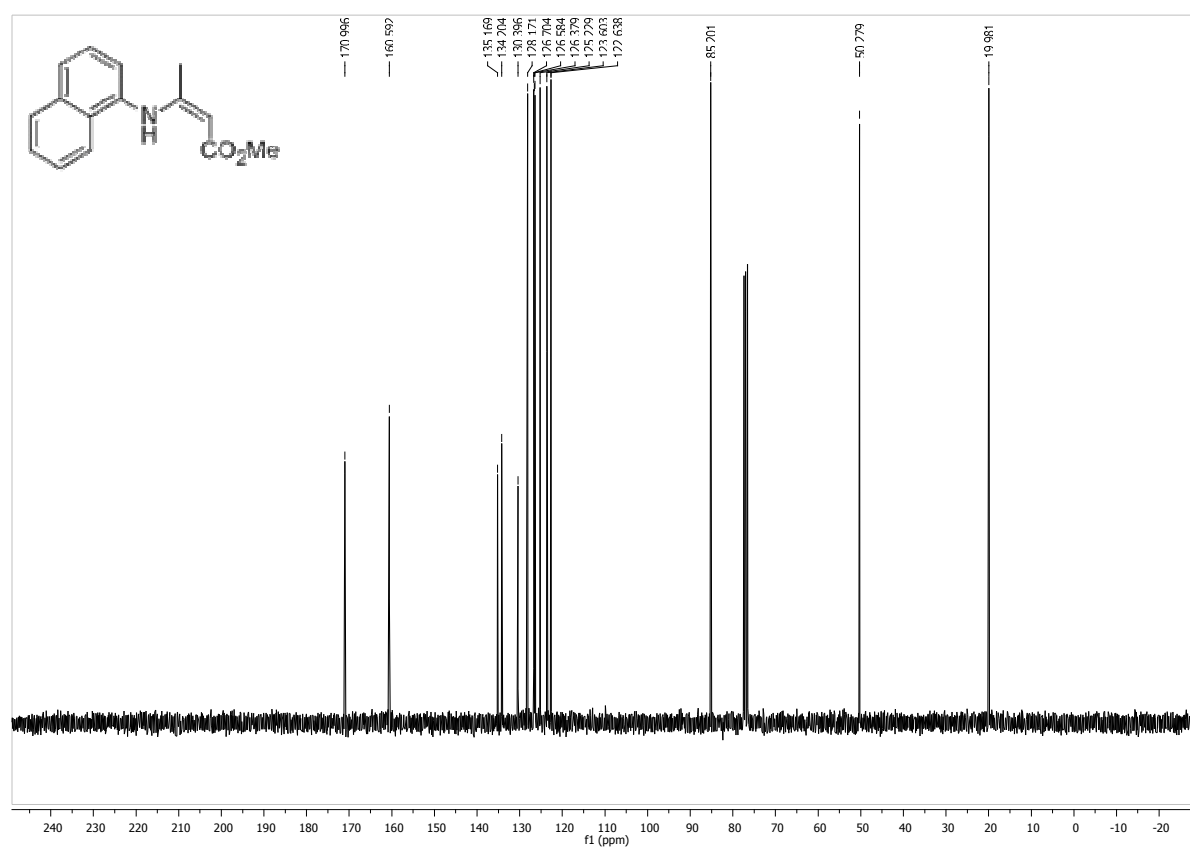
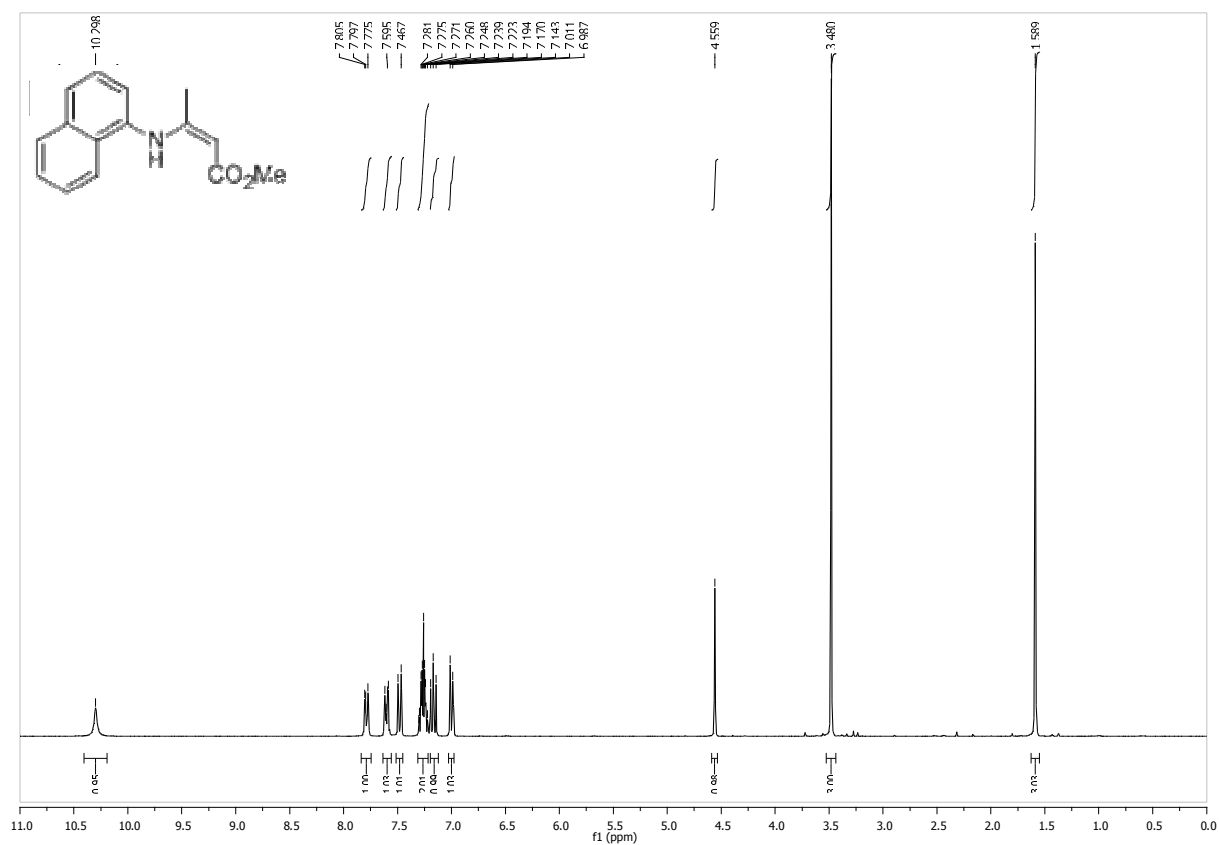


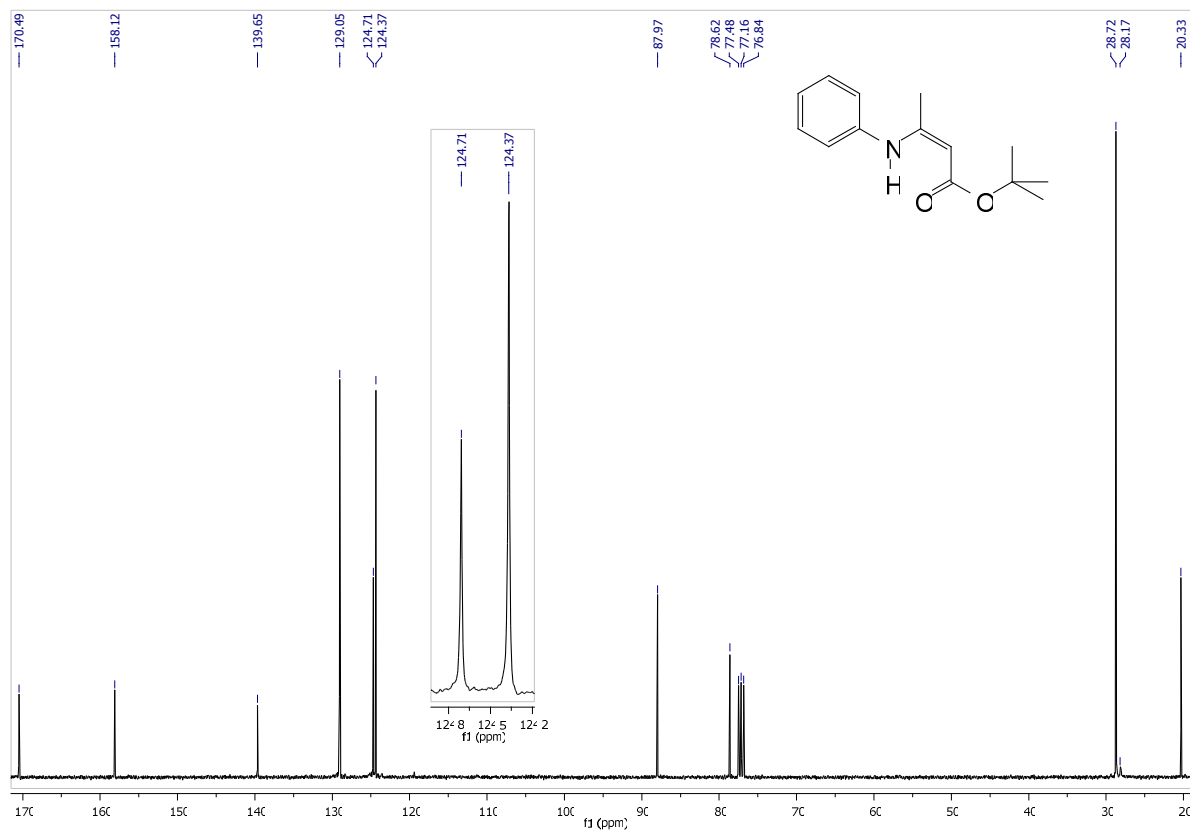
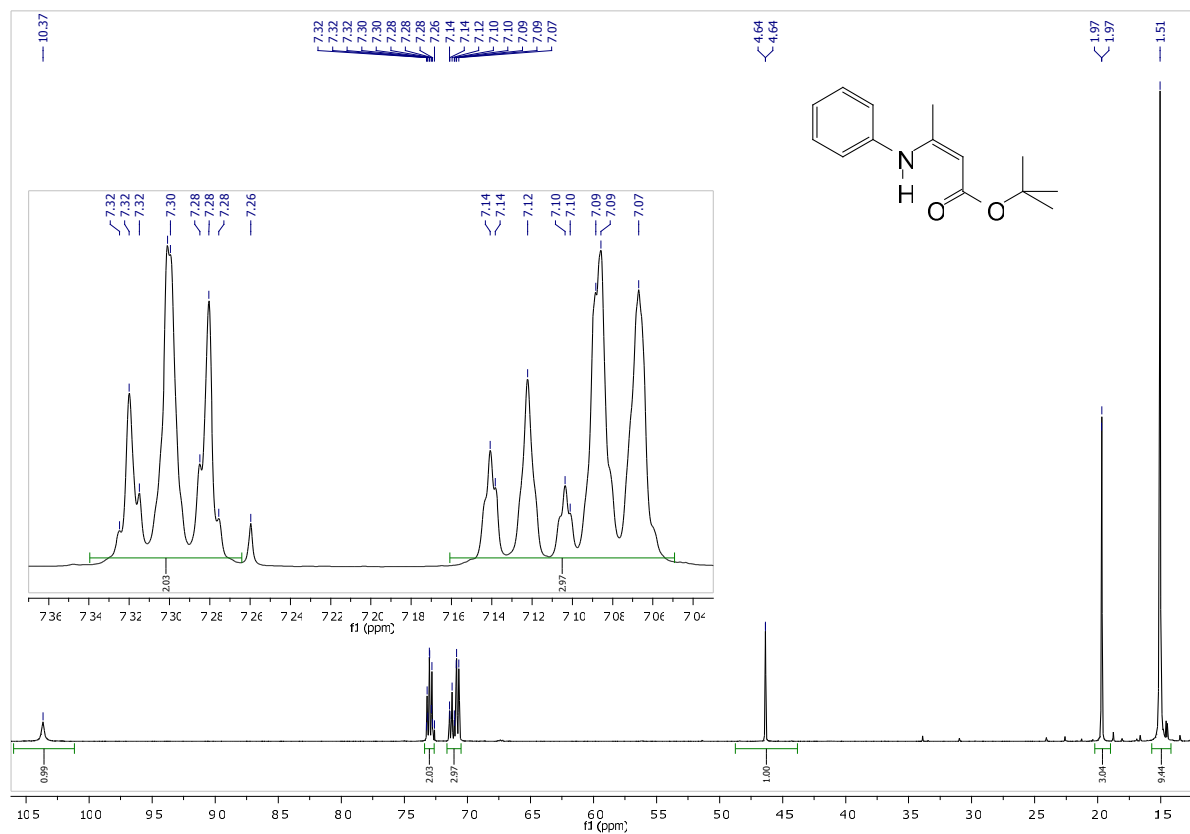


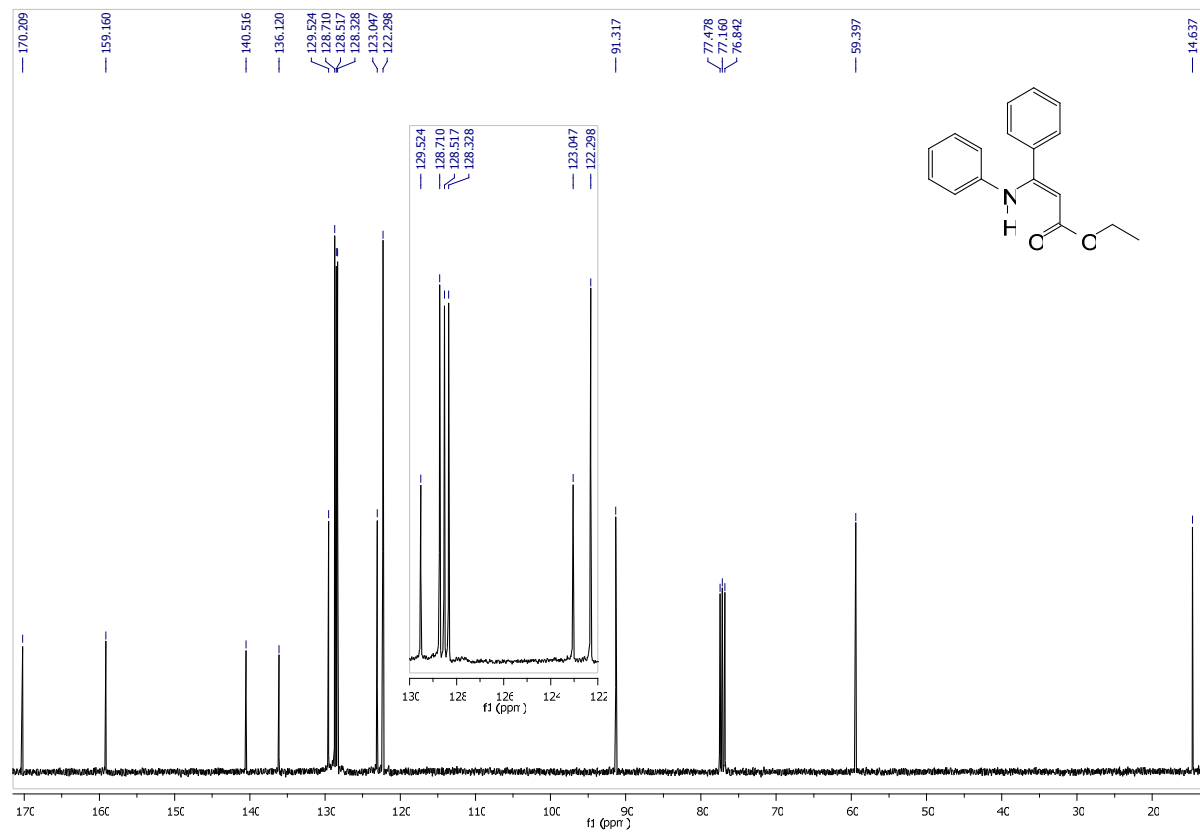
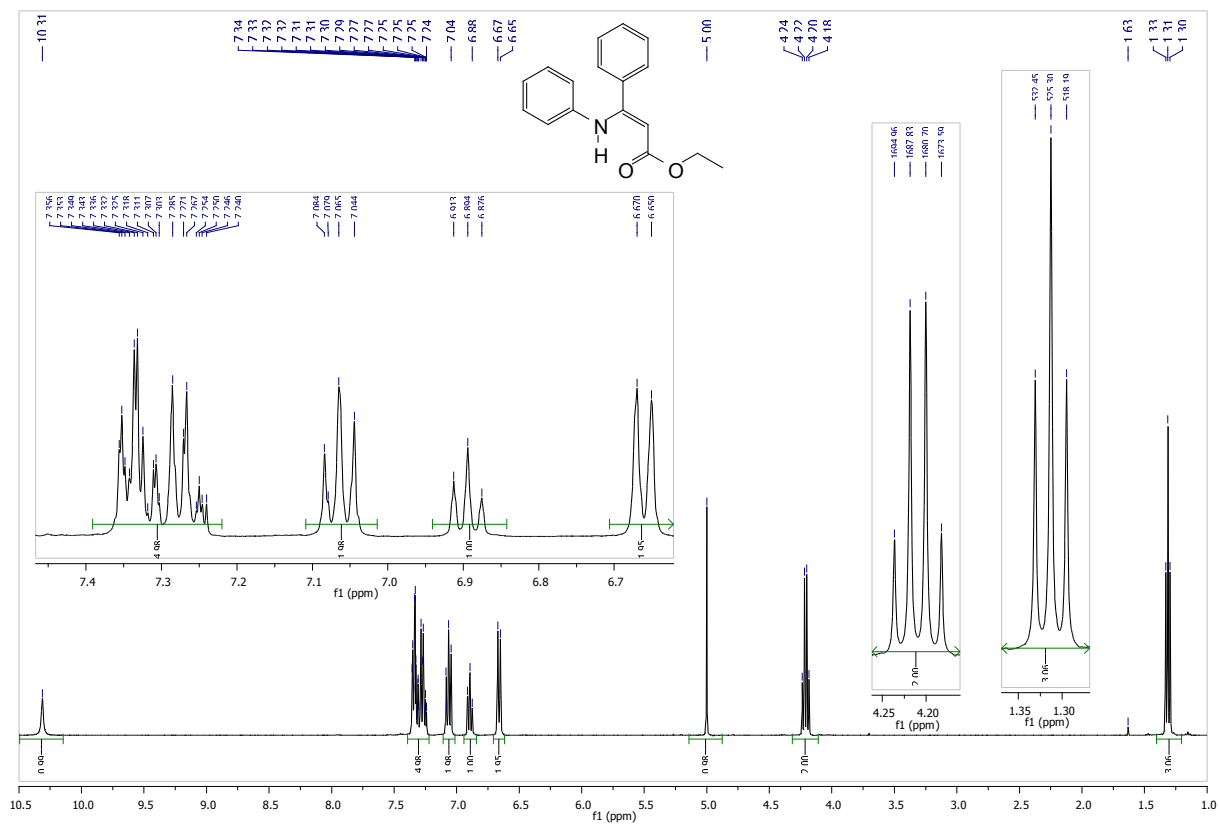












## a. Products

