

## Supporting Information

### Hexafluoro-2-Propanol-Promoted Intermolecular Friedel-Crafts Acylation Reaction

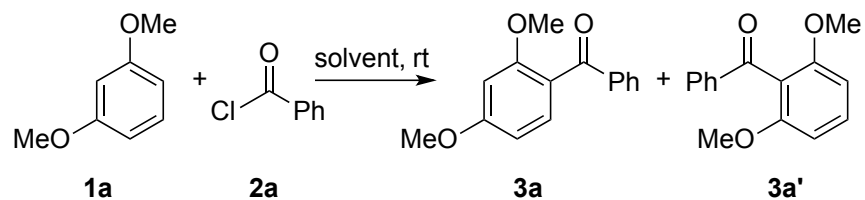
Rakesh H. Vekariya<sup>†</sup> and Jeffrey Aubé<sup>‡,\*</sup>

<sup>‡</sup>Division of Chemical Biology and Medicinal Chemistry, UNC Eshelman School of Pharmacy, 125 Mason Farm Road, CB 7363, University of North Carolina, Chapel Hill, NC, 27599-7363, USA, and <sup>†</sup>Department of Medicinal Chemistry, University of Kansas, Lawrence, KS, 66045, USA

### Table of Contents

Table S1. Examination of Concentration and Stoichiometry	S2
General information	S3
List of known compounds	S3
General Procedure for Solvent Screening (main text, Table 1)	S4
General Procedure for Concentration and Stoichiometry Screening (Table S1)	S4
General Procedure for the Friedel-Crafts reaction in HFIP	S4
Compound Preparation and Characterization	S5
Scale-Up Reactions and HFIP Recycling	S14
References	S15
<sup>1</sup> H and <sup>13</sup> C NMR spectra	S18

**Table S1. Examination of Concentration and Stoichiometry<sup>a</sup>**



entry	<b>1a</b> (equiv)	HFIP (mL)	yield, % <sup>b</sup> ( <b>3a/3a'</b> )
1	1	1	66 (91:9)
2	2	1	80 (92:8)
3	3	1	84 (91:9)
4	4	1	80 (92:8)
5	3	0.5	68 (92:8)
6	3	0.25	43 (92:8)
7 <sup>c</sup>	1	1	66 (92:8)

<sup>a</sup>To 1,3-dimethoxybenzene in HFIP, was added benzoyl chloride (0.75 mmol, 1 equiv).

The reaction mixture was stirred at rt for 5 h. <sup>b</sup>Isolated yields based on acyl chloride.

<sup>c</sup>Benzoyl chloride was added portionwise over a period of 2 h.

## General Information

Reactions were performed in oven-dried glassware or glass sample vial with a rubber-lined cap. Thin-layer chromatography (TLC) was performed using commercial glass-backed silica plates (250 microns) with an organic binder. Visualization was accomplished with UV light. Infrared (IR) spectra were acquired as thin films or solids. All nuclear magnetic resonance (NMR) spectra ( $^1\text{H}$ ,  $^{13}\text{C}$ ) were recorded on a 400/101 MHz instrument. NMRs were recorded in deuterated chloroform dimethyl sulfoxide. Chemical shifts are reported in parts per million (ppm) and are referenced to the center line of the solvent ( $\delta$  7.26 and 2.50 ppm with respect to  $\text{CDCl}_3$  and  $\text{DMSO}-d_6$  for  $^1\text{H}$  NMR and  $\delta$  77.16 and 39.52 ppm with respect to  $\text{CDCl}_3$  and  $\text{DMSO}-d_6$  for  $^{13}\text{C}$  NMR, respectively). Coupling constants are given in Hertz (Hz). HRMS data were collected with an electrospray ion source (ESI). Melting points were determined on an automated melting point apparatus and are uncorrected.

## List of known compounds

(2,4-Dimethoxyphenyl)(phenyl)methanone (**3a**),<sup>1</sup> (2,6-dimethoxyphenyl)(phenyl)methanone (**3a'**),<sup>2</sup> 1-(2,4-dimethoxyphenyl)ethan-1-one (**3b**),<sup>3</sup> 1-(2,6-dimethoxyphenyl)ethan-1-one (**3b'**),<sup>4</sup> phenyl(2,4,5-trimethoxyphenyl)methanone (**3c**),<sup>1</sup> 1-(2,4,5-trimethoxyphenyl)ethan-1-one (**3d**),<sup>4</sup> 1-(2,4-dimethoxyphenyl)-2-methylpropan-1-one (**3e**),<sup>5</sup> phenyl(2,4,6-trimethoxyphenyl)methanone (**3f**),<sup>6</sup> 1-(2,4,6-trimethoxyphenyl)ethan-1-one (**3g**),<sup>7</sup> (3,4-dimethoxyphenyl)(phenyl)methanone (**3i**),<sup>1</sup> (4-methoxyphenyl)(phenyl)methanone (**3j**),<sup>1</sup> phenyl(1H-pyrrol-2-yl)methanone (**3l**),<sup>8</sup> phenyl(1H-pyrrol-3-yl)methanone (**3l**),<sup>9</sup> (1H-indol-3-yl)(phenyl)methanone (**3m**),<sup>10</sup> (2-methyl-1H-indol-3-yl)(phenyl)methanone (**3n**),<sup>11</sup> (1-methyl-1H-indol-3-yl)(phenyl)methanone (**3o**),<sup>12</sup> (1H-indol-3-yl)(4-methoxyphenyl)methanone (**3p**),<sup>13</sup> 1-(1H-indol-3-yl)-2,2-dimethylpropan-1-one (**3q**),<sup>13</sup> (2-methylbenzo[b]thiophen-3-yl)(phenyl)methanone (**3r**),<sup>14</sup> benzoylferrocene (**3t**),<sup>15</sup> (4-methoxyphenyl)(2,4,6-trimethoxyphenyl)methanone (**3v**),<sup>16</sup> (4-chlorophenyl)(2,4,6-trimethoxyphenyl)methanone (**3x**),<sup>17</sup> 4-chlorobutyl benzoate.<sup>18</sup>

**General Procedure for Solvent Screening (main text, Table 1)**

To a solution of 1,3-dimethoxybenzene (104 mg, 0.75 mmol, 1.0 equiv) in HFIP and/or specified solvent (1.0 mL) in an oven-dried N<sub>2</sub>-flushed 2 dram vial, benzoyl chloride (87  $\mu$ L, 0.750 mmol, 1.0 equiv) was added. The resultant mixture was stirred at room temperature for 5 h. Reaction mixture was concentrated and crude was purified on a Combiflash purification system using a silica flash column (90:10 hexanes/EtOAc) to afforded **3a/3a'** as a mixture.

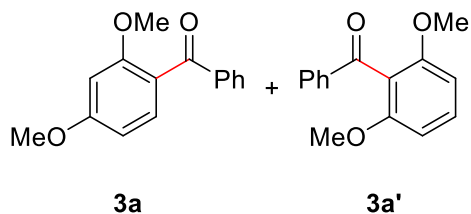
**General Procedure for Concentration and Stoichiometry Screening (Table S1)**

To a solution of 1,3-dimethoxybenzene (1.0–4.0 equiv as indicated in Table S1) in HFIP (1.0 mL, 0.5 mL or 0.25 mL as indicated in Table 2) in an oven-dried N<sub>2</sub>-flushed 2 dram vial, benzoyl chloride (87  $\mu$ L, 0.750 mmol, 1.0 equiv) was added (for entry 7, total amount of benzoyl chloride was divided into five portions, and each portion was added at 30 min interval over a period of 2 h). The resultant mixture was stirred at room temperature for 5 h. Reaction mixture was concentrated and crude was purified on a Combiflash purification system using a silica flash column (90:10 hexanes/EtOAc) to afforded **3a/3a'** as a mixture.

**General Procedure for the Friedel-Crafts reaction in HFIP**

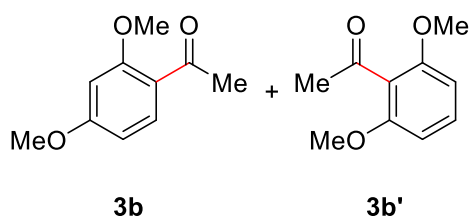
To a solution of arenes or heterocyclic arenes (2.25 mmol, 3.0 equiv) in HFIP (1.0 mL) in an oven-dried N<sub>2</sub>-flushed 2-dram vial, acid chloride (0.750 mmol, 1.0 equiv) was added. The resultant mixture was stirred at room temperature for 5 h, unless otherwise noted. Reaction mixture was concentrated and crude was purified on a Combiflash purification system using a normal phase silica flash column to afford ketone products.

## Compound Preparation and Characterization



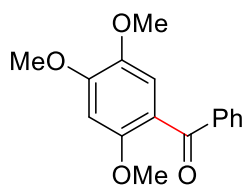
### **(2,4-Dimethoxyphenyl)(phenyl)methanone (3a)<sup>1</sup> and (2,6-dimethoxyphenyl)(phenyl)methanone (3a')<sup>2</sup>**

Following the general procedure, 1,3-dimethoxybenzene (311 mg, 2.25 mmol, 3.0 equiv) was reacted with benzoyl chloride (87  $\mu$ L, 0.750 mmol, 1.0 equiv) to give the known ketones **3a/3a'** (152 mg, 84%, **3a/3a'** = 91/9) as a mixture.



### **1-(2,4-Dimethoxyphenyl)ethan-1-one (3b)<sup>3</sup> and 1-(2,6-dimethoxyphenyl)ethan-1-one (3b')<sup>4</sup>**

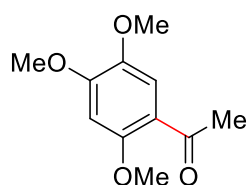
Following the general procedure, 1,3-dimethoxybenzene (311 mg, 2.25 mmol, 3.0 equiv) was reacted with acetyl chloride (53  $\mu$ L, 0.750 mmol, 1.0 equiv) to give the known ketones **3b/3b'** (109 mg, 81%, = 87/13) as a mixture.



**3c**

**Phenyl(2,4,5-trimethoxyphenyl)methanone (3c)<sup>1</sup>**

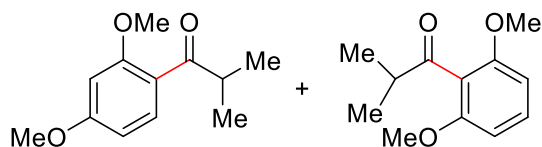
Following the general procedure, 1,2,4-trimethoxybenzene (378 mg, 2.25 mmol, 3.0 equiv) was reacted with benzoyl chloride (87  $\mu$ L, 0.750 mmol, 1.0 equiv) to give the known ketone **3c** (111 mg, 54%) as a yellow solid.



**3d**

**1-(2,4,5-Trimethoxyphenyl)ethan-1-one (3d)<sup>4</sup>**

Following the general procedure, 1,2,4-trimethoxybenzene (378 mg, 2.25 mmol, 3.0 equiv) was reacted with acetyl chloride (53  $\mu$ L, 0.750 mmol, 1.0 equiv) to give the known ketone **3d** (95 mg, 60%) as a white solid.

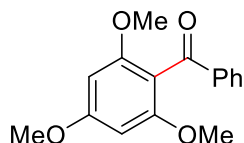


**3e**

**3e'**

**1-(2,4-Dimethoxyphenyl)-2-methylpropan-1-one (3e)<sup>5</sup> and 1-(2,6-dimethoxyphenyl)-2-methylpropan-1-one (3e')**

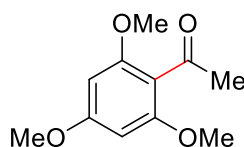
Following the general procedure, 1,3-dimethoxybenzene (311 mg, 2.25 mmol, 3.0 equiv) was reacted with isobutyryl chloride (79  $\mu$ L, 0.750 mmol, 1.0 equiv) to give the known ketones **3e/3e'** (95 mg, 61%, **3e/3e'** = 99/1, ratio was determined by GCMS) as a colorless oil.



**3f**

### Phenyl(2,4,6-trimethoxyphenyl)methanone (**3f**)<sup>6</sup>

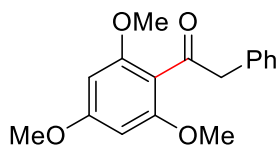
Following the general procedure, 1,3,5-trimethoxybenzene (378 mg, 2.25 mmol, 3.0 equiv) was reacted with benzoyl chloride (87  $\mu$ L, 0.750 mmol, 1.0 equiv) to give the known ketone **3f** (176 mg, 86%) as a white solid.



**3g**

### 1-(2,4,6-Trimethoxyphenyl)ethan-1-one (**3g**)<sup>7</sup>

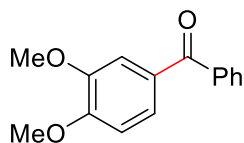
Following the general procedure, 1,3,5-trimethoxybenzene (378 mg, 2.25 mmol, 3.0 equiv) was reacted with acetyl chloride (53  $\mu$ L, 0.750 mmol, 1.0 equiv) to give the known ketone **3g** (145 mg, 92%) as a white solid.



**3h**

### 2-Phenyl-1-(2,4,6-trimethoxyphenyl)ethan-1-one (**3h**)

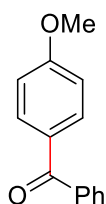
Following the general procedure, 1,3,5-trimethoxybenzene (378 mg, 2.25 mmol, 3.0 equiv) was reacted with phenylacetyl chloride (99  $\mu$ L, 0.750 mmol, 1.0 equiv) to give the title ketone (171 mg, 84%) as a yellow solid. Mp: 66–68 °C; TLC (20% EtOAc/hexanes):  $R_f$  = 0.50;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.37.24 (m, 2H), 7.20 (dt,  $J$  = 5.8, 1.5 Hz, 3H), 6.06 (s, 2H), 4.03 (s, 2H), 3.80 (s, 3H), 3.73 (s, 6H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  201.6, 162.5, 158.3, 135.0, 130.0, 128.3, 126.6, 113.3, 90.7, 55.9, 55.5, 51.7. IR (neat) 1698  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{17}\text{H}_{19}\text{O}_4$   $[\text{M} + \text{H}]^+$ : 287.1283, found: 287.1280.



**3i**

**(3,4-Dimethoxyphenyl)(phenyl)methanone (3i)<sup>1</sup>**

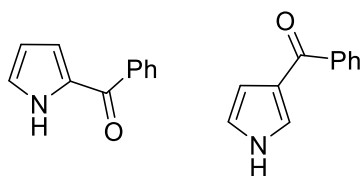
Following the general procedure, 1,2-dimethoxybenzene (311 mg, 2.25 mmol, 3.0 equiv) was reacted with benzoyl chloride (87  $\mu$ L, 0.750 mmol, 1.0 equiv) to give the known ketone **3i** (73 mg, 36%) as a white solid.



**3j**

**(4-Methoxyphenyl)(phenyl)methanone (3j)<sup>1</sup>**

Following the general procedure, anisole (243 mg, 2.25 mmol, 3.0 equiv) was reacted with benzoyl chloride (87  $\mu$ L, 0.750 mmol, 1.0 equiv) to give the known ketone **3j** (69 mg, 34%) as a colorless oil.



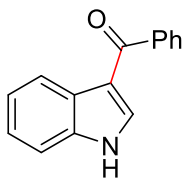
**3l<sub>2</sub> + 3l<sub>3</sub>**

58% (72:28)

**Phenyl(1H-pyrrol-2-yl)methanone (3l<sub>2</sub>)<sup>8</sup> and phenyl(1H-pyrrol-3-yl)methanone (3l<sub>3</sub>)<sup>9</sup>**

Following the general procedure, pyrrole (151 mg, 2.25 mmol, 3.0 equiv) was reacted with benzoyl chloride (87  $\mu$ L, 0.750 mmol, 1.0 equiv) to give the known ketones **3l<sub>2</sub>** (86 mg, 42%) and **3l<sub>3</sub>** (21 mg, 16%) as a brown solid.

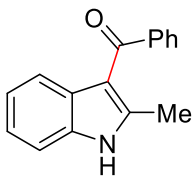




**3m**

**(1H-Indol-3-yl)(phenyl)methanone (3m)<sup>10</sup>**

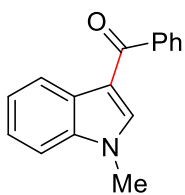
Following the general procedure, indole (264 mg, 2.25 mmol, 3.0 equiv) was reacted with benzoyl chloride (87  $\mu$ L, 0.750 mmol, 1.0 equiv) to give the known ketone **3m** (119 mg, 72%) as a pale yellow solid.



**3n**

**(2-Methyl-1H-indol-3-yl)(phenyl)methanone (3n)<sup>11</sup>**

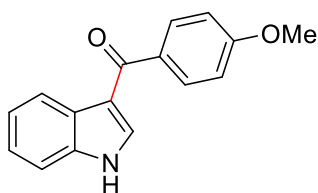
Following the general procedure, 2-methyl-1H-indole (295 mg, 2.25 mmol, 3.0 equiv) was reacted with benzoyl chloride (87  $\mu$ L, 0.750 mmol, 1.0 equiv) to give the known ketone **3n** (144 mg, 82%) as a yellow solid.



**3o**

**(1-Methyl-1H-indol-3-yl)(phenyl)methanone (3o)<sup>12</sup>**

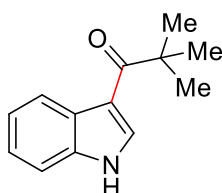
Following the general procedure, 1-methyl-1H-indole (295 mg, 2.25 mmol, 3.0 equiv) was reacted with benzoyl chloride (87  $\mu$ L, 0.750 mmol, 1.0 equiv) to give the known ketone **3o** (152 mg, 86%) as a white solid.



**3p**

**(1H-Indol-3-yl)(4-methoxyphenyl)methanone (3p)<sup>13</sup>**

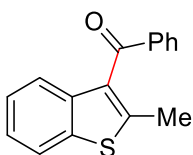
Following the general procedure, indole (264 mg, 2.25 mmol, 3.0 equiv) was reacted with 4-methoxybenzoyl chloride (103  $\mu$ L, 0.750 mmol, 1.0 equiv) to give the known ketone **3p** (99 mg, 53%) as a brown solid.



**3q**

**1-(1H-Indol-3-yl)-2,2-dimethylpropan-1-one (3q)<sup>13</sup>**

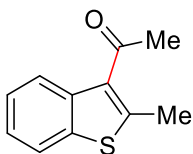
Following the general procedure, indole (264 mg, 2.25 mmol, 3.0 equiv) was reacted with pivaloyl chloride (92  $\mu$ L, 0.750 mmol, 1.0 equiv) to give the known ketone **3q** (137 mg, 91%) as a brown solid.



**3r**

**(2-Methylbenzo[b]thiophen-3-yl)(phenyl)methanone (3r)<sup>14</sup>**

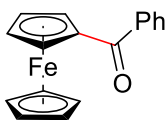
Following the general procedure, 2-methylbenzo[b]thiophene (334 mg, 2.25 mmol, 3.0 equiv) was reacted with benzoyl chloride (87  $\mu$ L, 0.750 mmol, 1.0 equiv) to give the known ketone **3r** (121 mg, 64%) as a white solid.



**3s**

**1-(2-Methylbenzo[b]thiophen-3-yl)ethan-1-one (3s)**

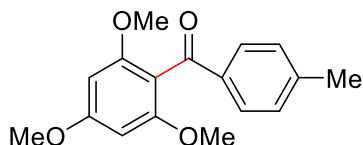
Following the general procedure, 2-methylbenzo[b]thiophene (334 mg, 2.25 mmol, 3.0 equiv) was reacted with acetyl chloride (53  $\mu$ L, 0.750 mmol, 1.0 equiv) to give title ketone (67 mg, 47%) as a white solid. Mp: 66–68 °C; TLC (20% EtOAc/hexanes):  $R_f$  = 0.40;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.18 (dt,  $J$  = 8.3, 0.9 Hz, 1H), 7.75 (ddd,  $J$  = 8.0, 1.3, 0.7 Hz, 1H), 7.41 (ddd,  $J$  = 8.3, 7.1, 1.3 Hz, 1H), 7.33 (ddd,  $J$  = 8.2, 7.1, 1.2 Hz, 1H), 2.79 (s, 3H), 2.66 (s, 3H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ) 196.0, 149.1, 138.5, 137.4, 133.1, 125.3, 124.5, 123.9, 121.8, 32.0, 17.2; IR (neat) 1637  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{11}\text{H}_{11}\text{OS}$   $[\text{M} + \text{H}]^+$ : 191.0531, found: 191.0529.



**3t**

**Benzoylferrocene (3t)<sup>15</sup>**

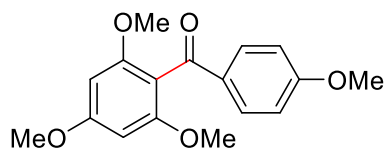
Following the general procedure, ferrocene (419 mg, 2.25 mmol, 3.0 equiv) was reacted with benzoyl chloride (87  $\mu$ L, 0.750 mmol, 1.0 equiv) to give the known ketone **3t** (135 mg, 62%) as a red solid.



**3u**

***p*-Tolyl(2,4,6-trimethoxyphenyl)methanone (3u)**

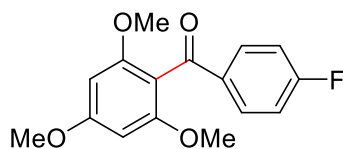
Following the general procedure, 1,3,5-trimethoxybenzene (378 mg, 2.25 mmol, 3.0 equiv) was reacted with 4-methylbenzoyl chloride (99  $\mu$ L, 0.750 mmol, 1.0 equiv) to give title ketone (190 mg, 93%) as a white solid. Mp: 142–144 °C; TLC (20% EtOAc/hexanes):  $R_f$  = 0.50;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) 7.74 (d,  $J$  = 8.2 Hz, 2H), 7.21 (d,  $J$  = 8.0 Hz, 2H), 6.17 (s, 2H), 3.86 (s, 3H), 3.68 (s, 6H), 2.39 (s, 3H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  194.8, 162.4, 158.7, 143.9, 135.9, 129.7, 129.2, 111.3, 90.8, 55.9, 55.6, 21.8; IR (neat) 1655  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{17}\text{H}_{19}\text{O}_4$   $[\text{M} + \text{H}]^+$ : 287.1283, found: 287.1279.



**3v**

**(4-Methoxyphenyl)(2,4,6-trimethoxyphenyl)methanone (3v)<sup>16</sup>**

Following the general procedure, 1,3,5-trimethoxybenzene (378 mg, 2.25 mmol, 3.0 equiv) was reacted with 4-methoxybenzoyl chloride (103  $\mu$ L, 0.750 mmol, 1.0 equiv) to give the known ketone **3v** (189 mg, 83%) as a white solid.

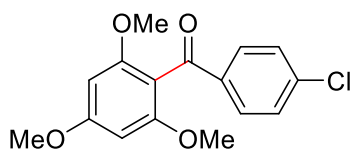


**3w**

**(4-Fluorophenyl)(2,4,6-trimethoxyphenyl)methanone (3w)**

Following the general procedure, 1,3,5-trimethoxybenzene (378 mg, 2.25 mmol, 3.0 equiv) was reacted with 4-fluorobenzoyl chloride (90  $\mu$ L, 0.750 mmol, 1.0 equiv) to give

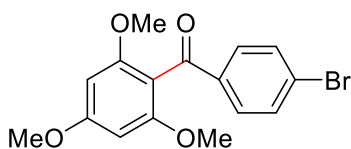
title ketone (161 mg, 79%) as a white solid. Mp: 152–154 °C; TLC (20% EtOAc/hexanes):  $R_f$  = 0.40;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.90–7.81 (m, 2H), 7.11–7.02 (m, 2H), 6.17 (s, 2H), 3.86 (s, 3H), 3.69 (s, 6H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  193.5, 165.9 (d,  $J_{\text{C-F}}$  = 255 Hz, 1C), 162.7, 158.8, 134.9 (d,  $J_{\text{C-C-C-F}}$  = 3 Hz, 1C), 132.2 (d,  $J_{\text{C-C-F}}$  = 9 Hz, 2C), 115.5 (d,  $J_{\text{C-C-F}}$  = 22 Hz, 2C), 110.7, 90.8, 55.9, 55.6; IR (neat) 1657  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{16}\text{H}_{16}\text{FO}_4$   $[\text{M} + \text{H}]^+$ : 291.1033, found: 291.1032.



**3x**

**(4-Chlorophenyl)(2,4,6-trimethoxyphenyl)methanone (3x)<sup>17</sup>**

Following the general procedure, 1,3,5-trimethoxybenzene (378 mg, 2.25 mmol, 3.0 equiv) was reacted with 4-chlorobenzoyl chloride (96  $\mu\text{L}$ , 0.750 mmol, 1.0 equiv) to give the known ketone **3x** (140 mg, 69%) as a white solid.

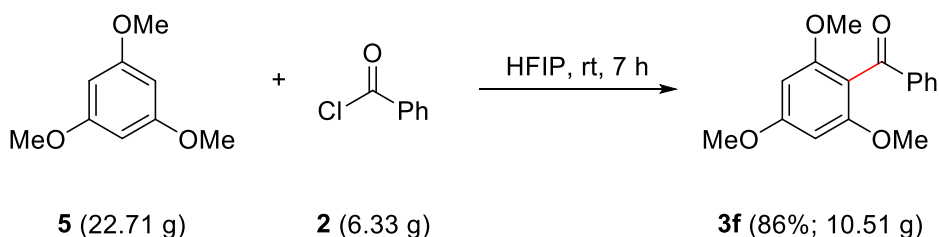


**3y**

**(4-Bromophenyl)(2,4,6-trimethoxyphenyl)methanone (3y)**

Following the general procedure, 1,3,5-trimethoxybenzene (378 mg, 2.25 mmol, 3.0 equiv) was reacted with 4-bromobenzoyl chloride (165 mg, 0.750 mmol, 1.0 equiv) to give the title ketone (151 mg, 74%) as a white solid. Mp: 188–190 °C; TLC (20% EtOAc/hexanes):  $R_f$  = 0.60;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.69 (d,  $J$  = 8.6 Hz, 2H), 7.54 (d,  $J$  = 8.5 Hz, 2H), 6.16 (s, 2H), 3.86 (s, 3H), 3.68 (s, 6H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  194.0, 162.8, 158.9, 137.2, 131.7, 131.1, 128.1, 110.4, 90.8, 55.9, 55.6; IR (neat) 1657  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{16}\text{H}_{16}\text{BrO}_4$   $[\text{M} + \text{H}]^+$ : 351.0232, found: 351.0229.

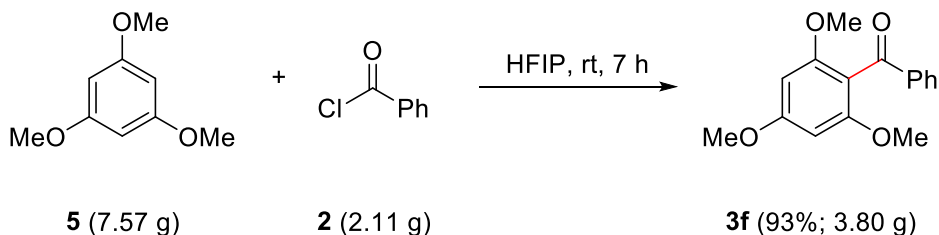
### Scale-Up Reactions and HFIP Recycling



#### *Initial reaction:*

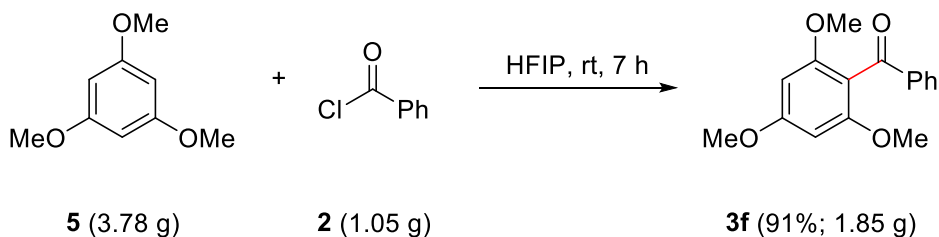
To a solution of 1,3,5-trimethoxybenzene (22.7 g, 135 mmol, 3.0 equiv) in HFIP (57 mL, 12 equiv) in an oven-dried flask benzoyl chloride (6.33 g, 5.22 mL, 45 mmol, 1.0 equiv) was added. The resultant mixture was stirred at room temperature for 7 h. HFIP solvent was recovered by distillation directly from the reaction pot (40–50 °C, under vacuum (5 millibar)) (46 mL, 81%). The remaining product was purified on a Combiflash purification system using solid loading on a silica flash column (80:20 hexanes/EtOAc) to afford **3f** (10.51 g, 86%) as a white solid.

#### *Second reaction, using recovered HFIP*



To a solution of 1,3,5-trimethoxybenzene (7.57 g, 45 mmol, 3.0 equiv) in HFIP (19 mL, 12 equiv), obtained by distillation from previous reaction, in an oven-dried flask, benzoyl chloride (2.11 g, 1.74 mL, 15 mmol, 1.0 equiv) was added. The resultant mixture was stirred at room temperature for 7 h. HFIP solvent was recovered by distillation as described above (18 mL, 95%). The crude was purified on a Combiflash purification system using a silica flash column (80:20 hexanes/EtOAc) to afford **3f** (3.80 g, 93%) as a white solid.

Third reaction, using doubly recovered HFIP



To a solution of 1,3,5-trimethoxybenzene (3.78 g, 22.5 mmol, 3.0 equiv) in HFIP (9.5 mL, 12 equiv), obtained by distillation from previous reaction, in an oven-dried flask, benzoyl chloride (1.05 g, 0.87 mL, 7.5 mmol, 1.0 equiv) was added. The resultant mixture was stirred at room temperature for 7 h. HFIP solvent was recovered by distillation (9 mL, 95%). The crude was purified on a Combiflash purification system using a silica flash column (80:20 hexanes/EtOAc) to afford **3f** (1.85 g, 91%) as a white solid.

## References

- Tran, P. H.; Hansen, P. E.; Hoang, H. M.; Chau, D.-K. N.; Le, T. N., Indium triflate in 1-isobutyl-3-methylimidazolium dihydrogen phosphate: an efficient and green catalytic system for Friedel–Crafts acylation. *Tetrahedron Letters* **2015**, 56 (17), 2187-2192.
- Lindh, J.; Sjöberg, P. J. R.; Larhed, M., Synthesis of Aryl Ketones by Palladium(II)-Catalyzed Decarboxylative Addition of Benzoic Acids to Nitriles. *Angewandte Chemie* **2010**, 122 (42), 7899-7903.
- Morizur, V.; Szafrank, J.; Bonhomme, D.; Olivero, S.; Desmurs, J. R.; Duñach, E., Catalysis of the acylation of aromatic derivatives by metallic tosylates. *Tetrahedron* **2015**, 71 (38), 6813-6817.
- Lindh, J.; Sjöberg, P. J. R.; Larhed, M., Synthesis of Aryl Ketones by Palladium(II)-Catalyzed Decarboxylative Addition of Benzoic Acids to Nitriles. *Angewandte Chemie International Edition* **2010**, 49 (42), 7733-7737.
- Prostota, Y.; Coelho, P. J.; Pina, J.; Seixas de Melo, J., Fast photochromic sterically hindered benzo[1,3]oxazines. *Journal of Photochemistry and Photobiology A: Chemistry* **2010**, 216 (1), 59-65.

6. Mondal, M.; Puranik, V. G.; Argade, N. P., A Facile Phenol-Driven Intramolecular Diastereoselective Thermal/Base-Catalyzed Dipolar [2 + 2] Annulation Reactions: An Easy Access to Complex Bioactive Natural and Unnatural Benzopyran Congeners. *The Journal of Organic Chemistry* **2007**, 72 (6), 2068-2076.
7. Zhang, B.; Duan, D.; Ge, C.; Yao, J.; Liu, Y.; Li, X.; Fang, J., Synthesis of Xanthohumol Analogues and Discovery of Potent Thioredoxin Reductase Inhibitor as Potential Anticancer Agent. *Journal of Medicinal Chemistry* **2015**, 58 (4), 1795-1805.
8. Boominathan, S. S. K.; Hu, W.-P.; Senadi, G. C.; Wang, J.-J., Silver(I)-Catalyzed Conia-Ene Reaction: Synthesis of 3-Pyrrolines via a 5-endo-dig Cyclization. *Advanced Synthesis & Catalysis* **2013**, 355 (18), 3570-3574.
9. Chen, Q.; Wang, T.; Zhang, Y.; Wang, Q.; Ma, J., A facile, highly efficient synthesis of fully *N*-confused Calix[5]pyrrole *Synthetic Communications* **2002**, 32 (7), 1041-1049.
10. Wynne, J. H.; Lloyd, C. T.; Jensen, S. D.; Boson, S.; Stalick, W. M., 3-Acylindoles via a One-Pot, Regioselective Friedel-Crafts Reaction. *Synthesis* **2004**, 2004 (14), 2277-2282.
11. Coffman, K. C.; Palazzo, T. A.; Hartley, T. P.; Fettingner, J. C.; Tantillo, D. J.; Kurth, M. J., Heterocycle-Heterocycle Strategies: (2-Nitrophenyl)isoxazole Precursors to 4-Aminoquinolines, 1H-Indoles, and Quinolin-4(1H)-ones. *Organic Letters* **2013**, 15 (8), 2062-2065.
12. Zhang, P.; Xiao, T.; Xiong, S.; Dong, X.; Zhou, L., Synthesis of 3-Acylindoles by Visible-Light Induced Intramolecular Oxidative Cyclization of *o*-Alkynylated *N,N*-Dialkylamines. *Organic Letters* **2014**, 16 (12), 3264-3267.
13. Guchhait, S. K.; Kashyap, M.; Kamble, H., ZrCl<sub>4</sub>-Mediated Regio- and Chemoselective Friedel-Crafts Acylation of Indole. *The Journal of Organic Chemistry* **2011**, 76 (11), 4753-4758.
14. Sidduri, A.; Rozema, M. J.; Knochel, P., Selective mono- and polymethylene homologations of copper reagents using (iodomethyl)zinc iodide. *The Journal of Organic Chemistry* **1993**, 58 (10), 2694-2713.

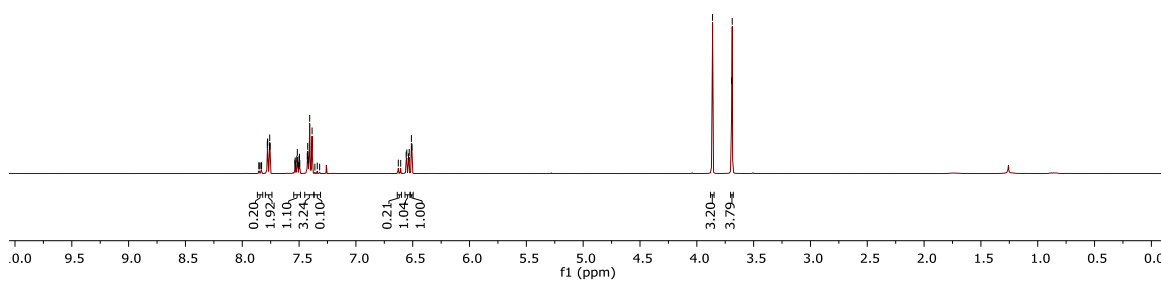
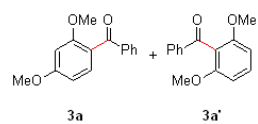


15. Lu, B.; Wang, Q.; Zhao, M.; Xie, X.; Zhang, Z., Ruthenium-Catalyzed Enantioselective Hydrogenation of Ferrocenyl Ketones: A Synthetic Method for Chiral Ferrocenyl Alcohols. *The Journal of Organic Chemistry* **2015**, *80* (19), 9563-9569.
16. O'Keefe, B. M.; Simmons, N.; Martin, S. F., Carbonylative Cross-Coupling of ortho-Disubstituted Aryl Iodides. Convenient Synthesis of Sterically Hindered Aryl Ketones. *Organic Letters* **2008**, *10* (22), 5301-5304.
17. Ushijima, S.; Dohi, S.; Moriyama, K.; Togo, H., Facile preparation of aromatic ketones from aromatic bromides and arenes with aldehydes. *Tetrahedron* **2012**, *68* (5), 1436-1442.
18. Enthaler, S.; Weidauer, M., Synthesis of  $\delta$ - and  $\epsilon$ -Cyanoesters by Zinc-Catalyzed Ring-Opening of Cyclic Ethers with Acid Chlorides and Subsequent Cyanation. *Catalysis Letters* **2012**, *142* (2), 168-175.

## **$^1\text{H}$ and $^{13}\text{C}$ NMR Spectra**

7.8332  
7.7796  
7.7763  
7.7762  
7.7607  
7.7584  
7.7551  
7.5374  
7.5340  
7.5306  
7.5198  
7.5156  
7.5106  
7.5005  
7.4970  
7.4936  
7.4278  
7.4240  
7.4199  
7.4067  
7.3857  
6.6059  
6.5577  
6.5520  
6.5366  
6.5310  
6.5117  
6.5062

3.8615  
3.6932  
3.6883

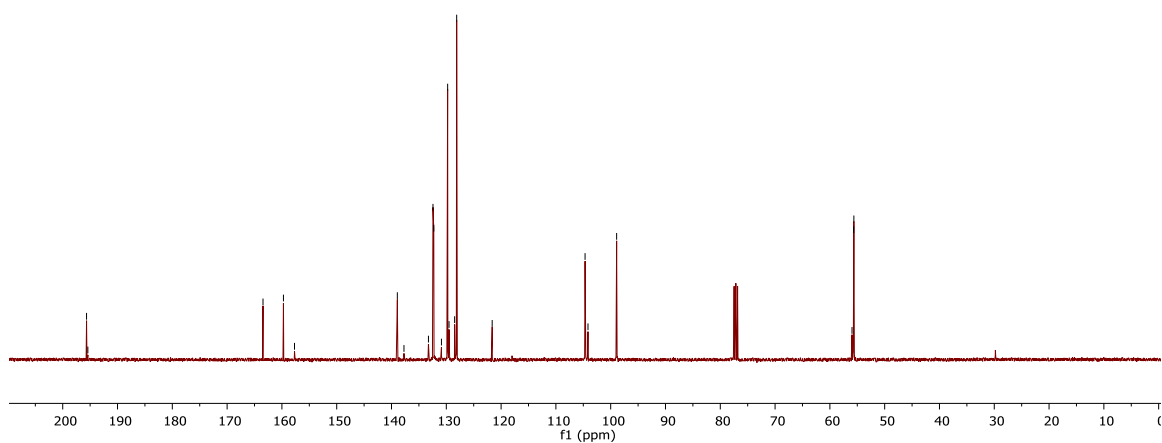
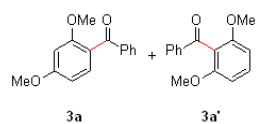


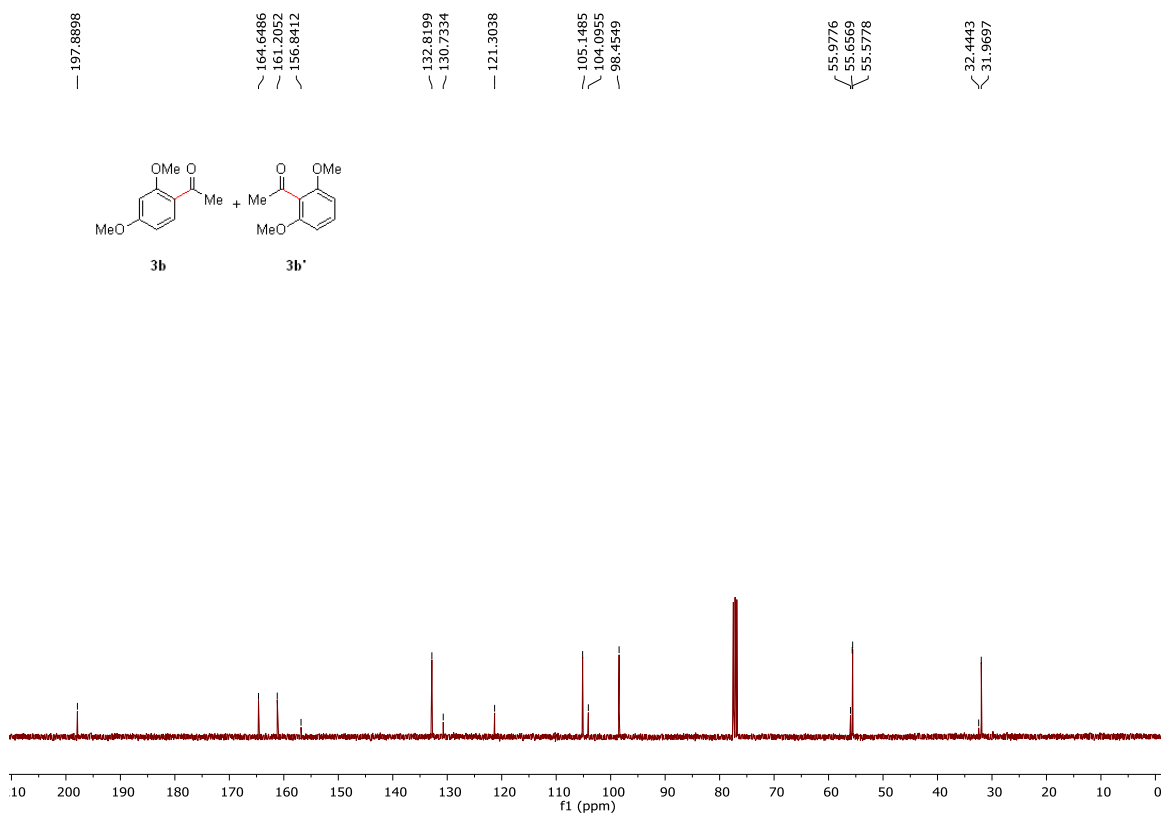
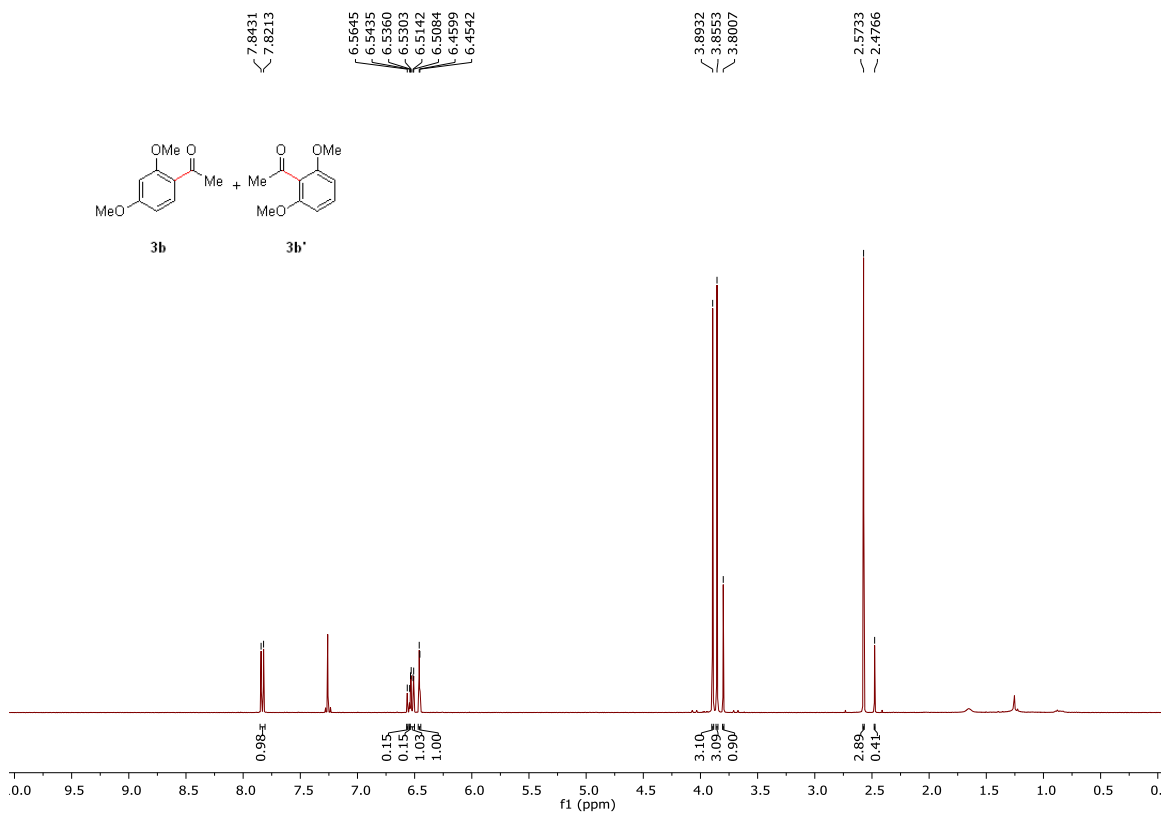
195.6537  
195.4147

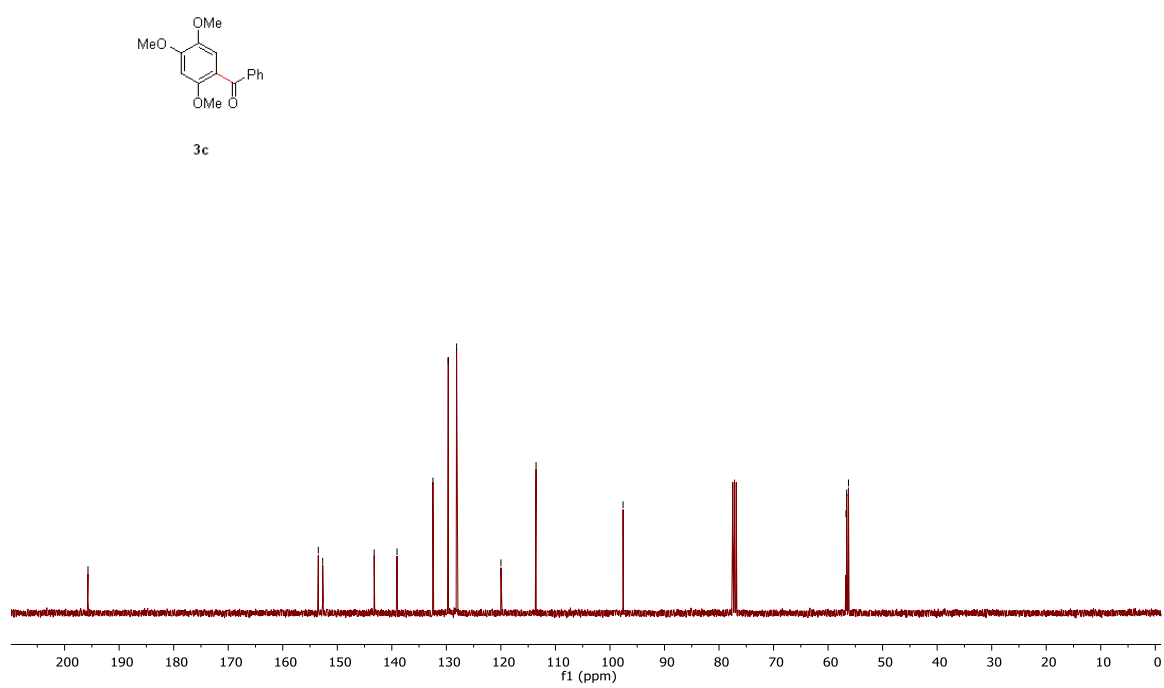
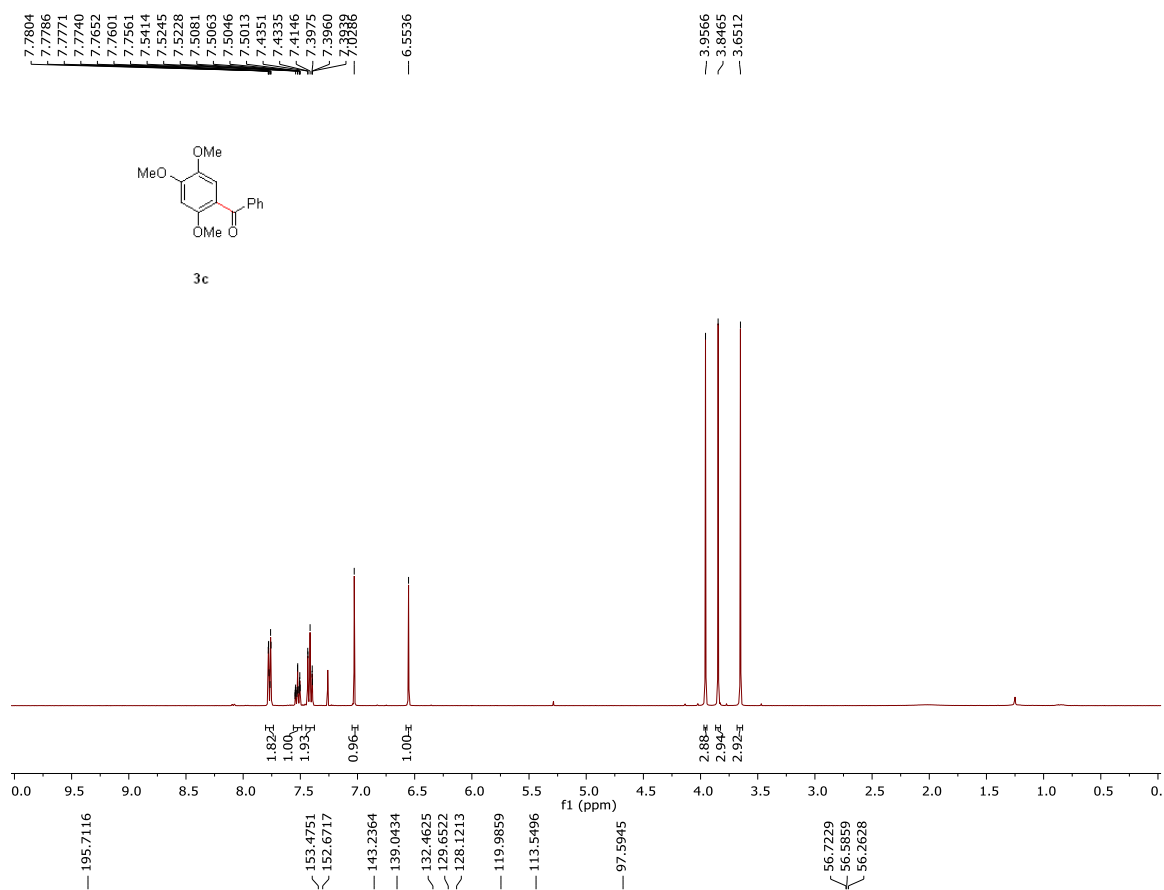
163.4501  
159.7194  
157.7038  
138.9352  
137.7248  
133.2581  
132.4313  
132.2872  
130.8856  
129.7550  
129.5010  
128.4803  
128.1044  
121.6280

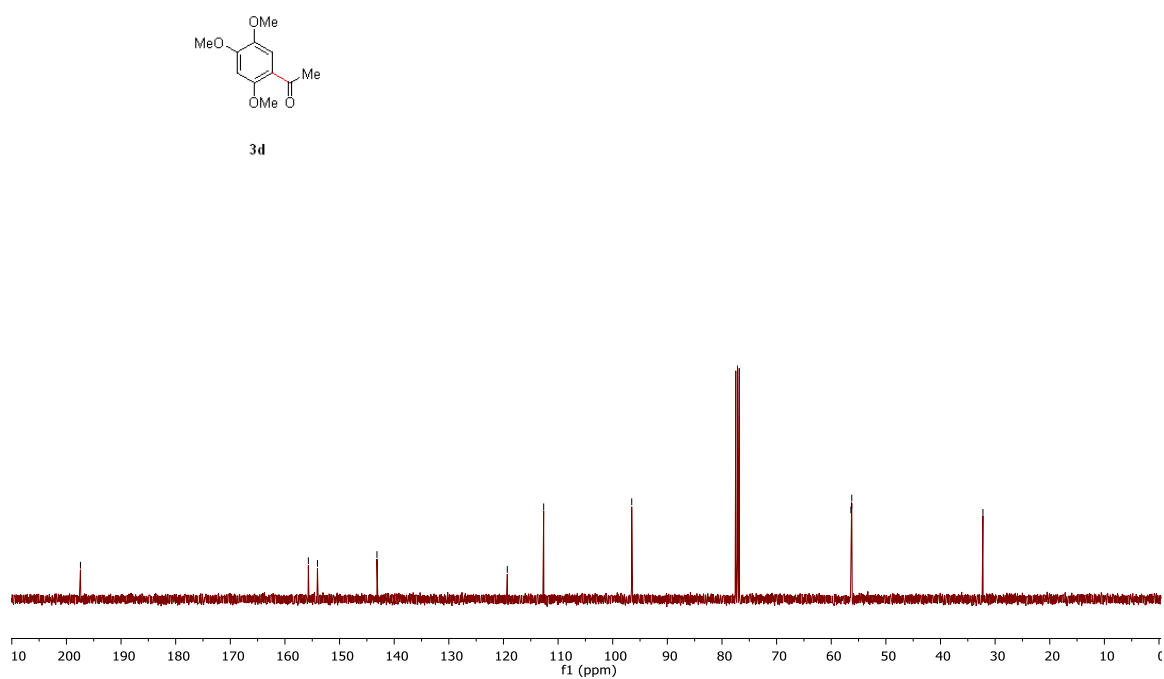
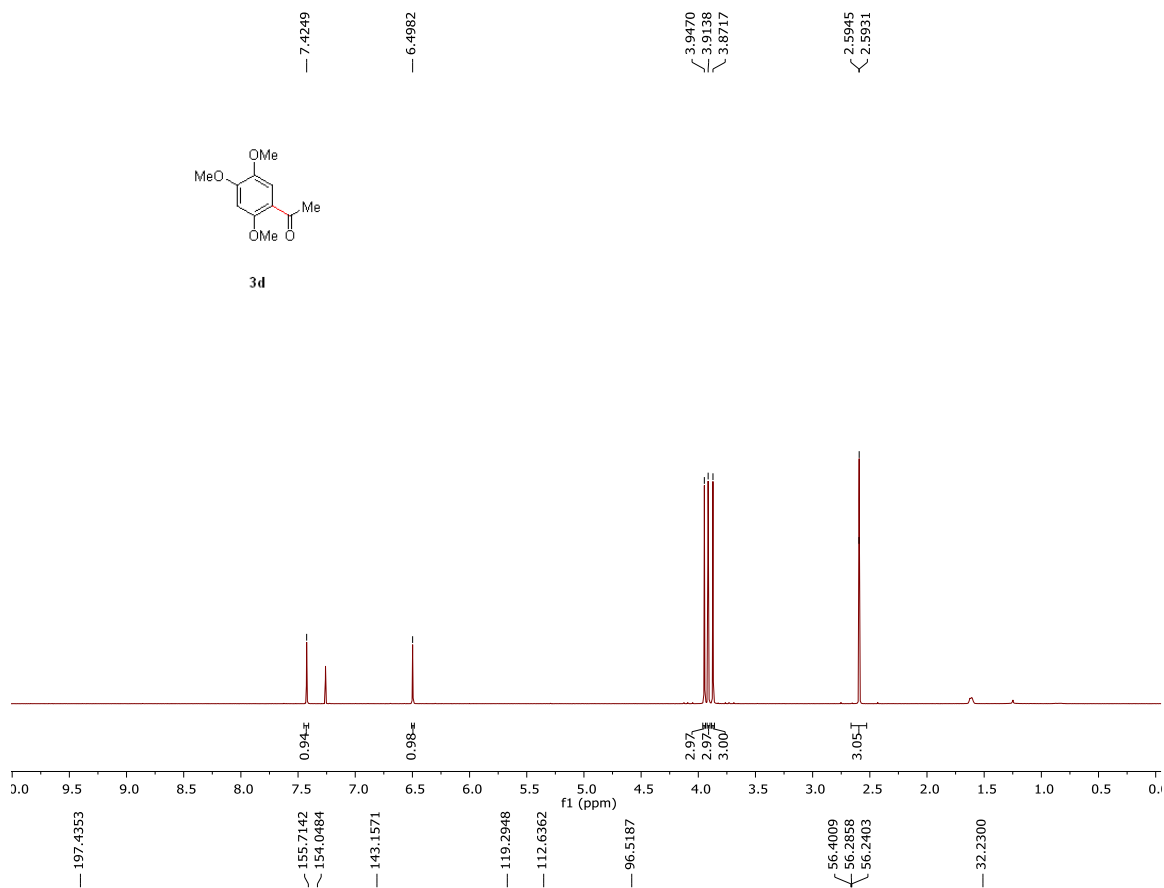
104.6754  
104.1432  
98.9143

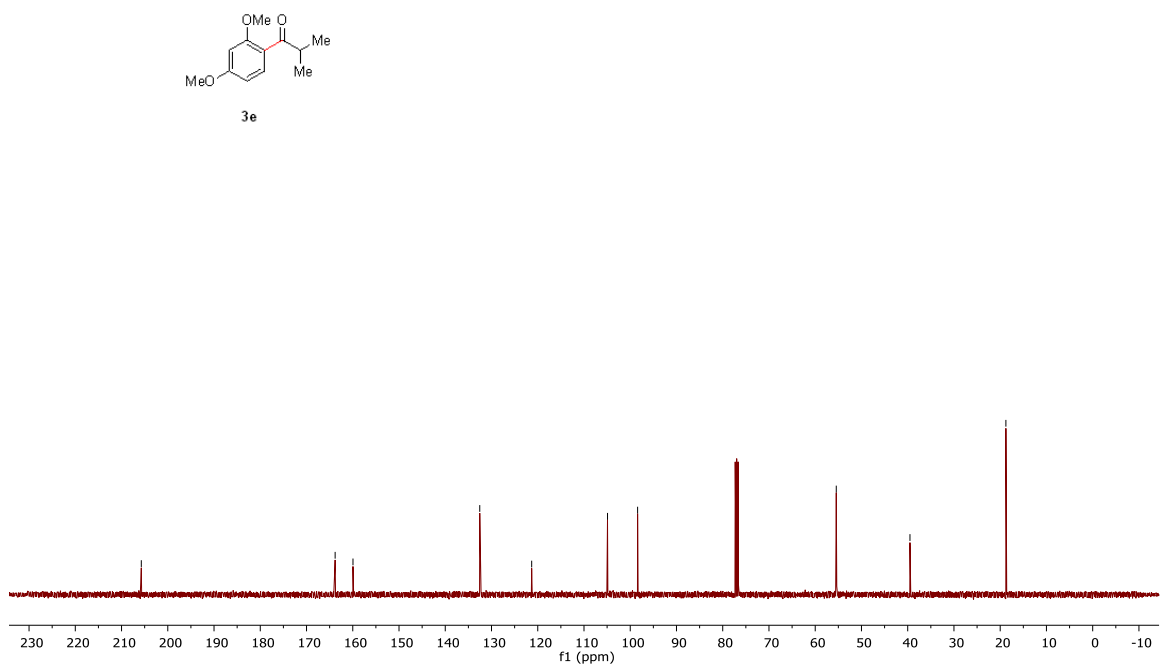
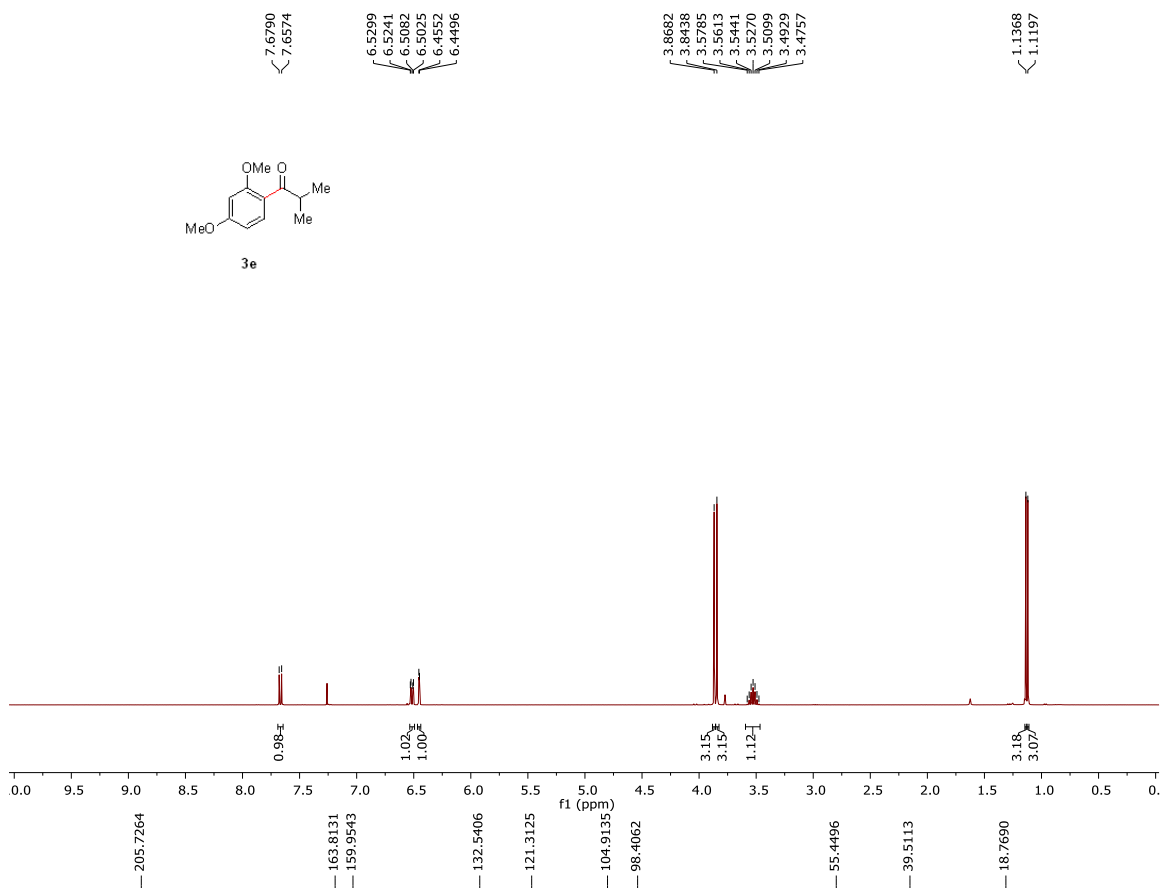
55.9615  
55.6605  
55.6228

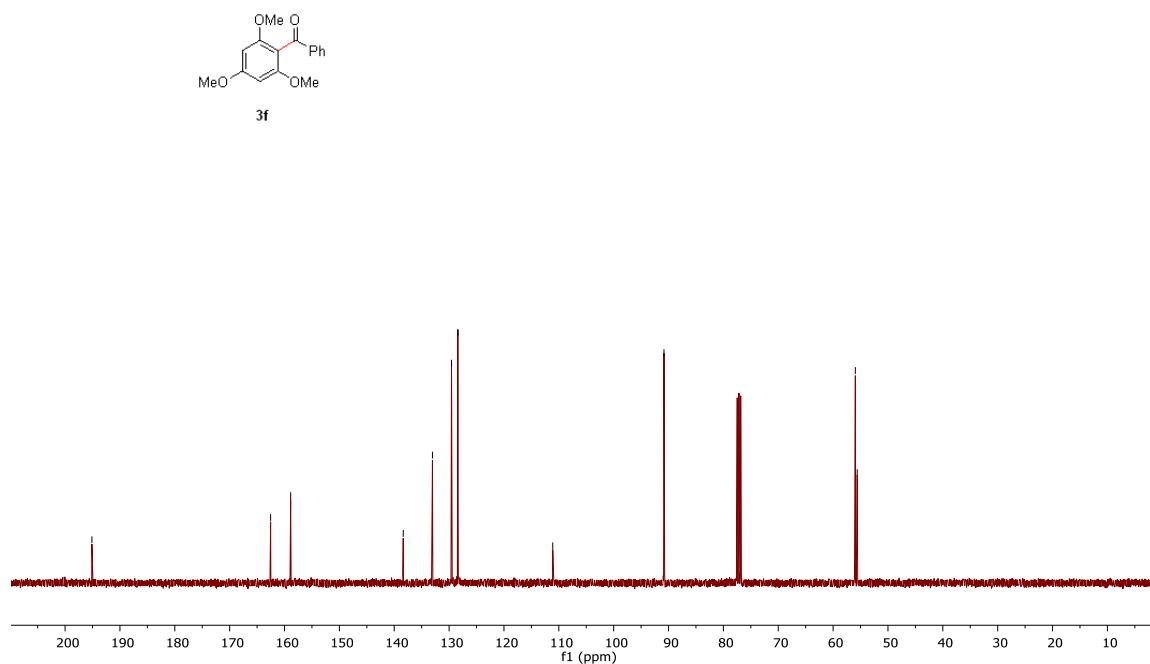
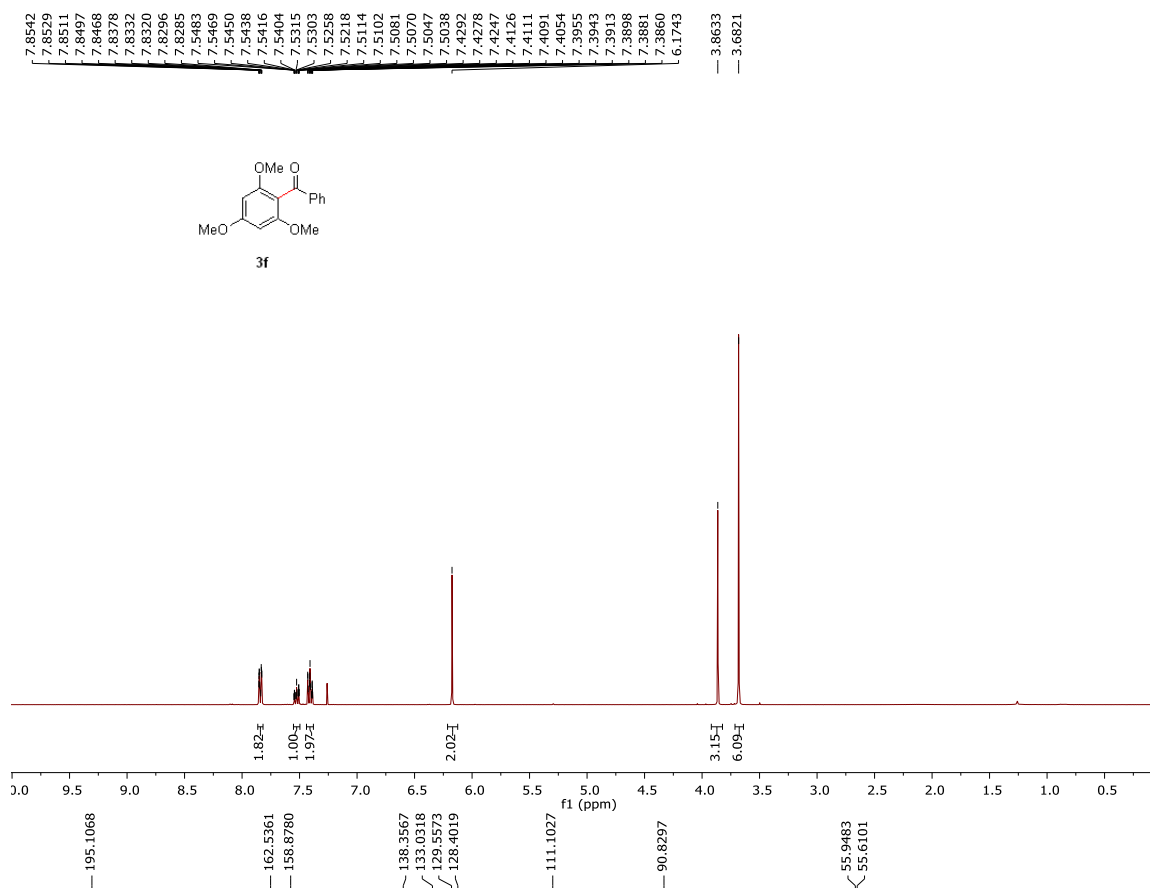




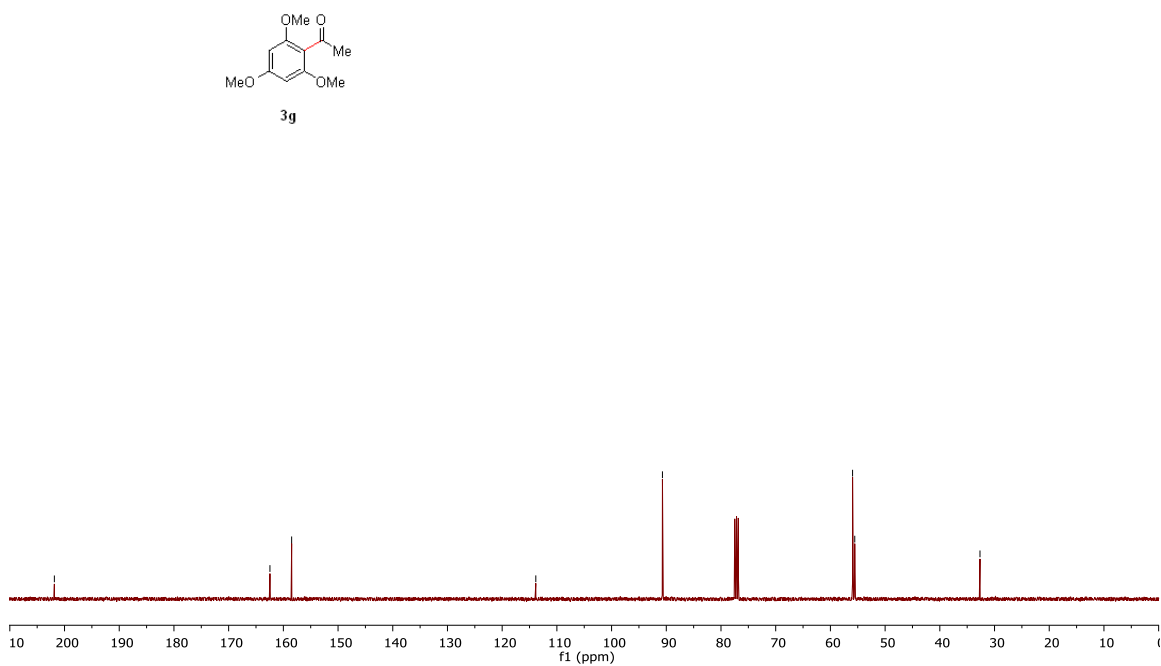
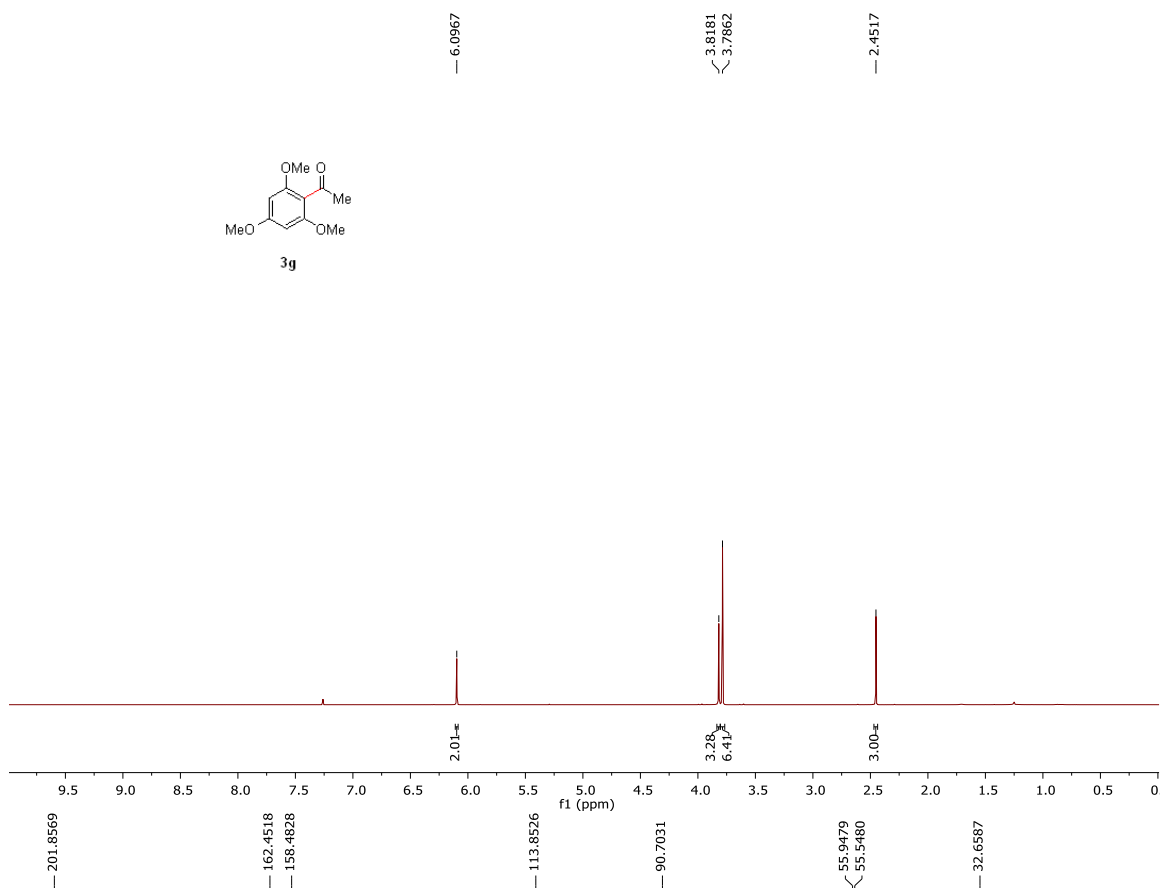


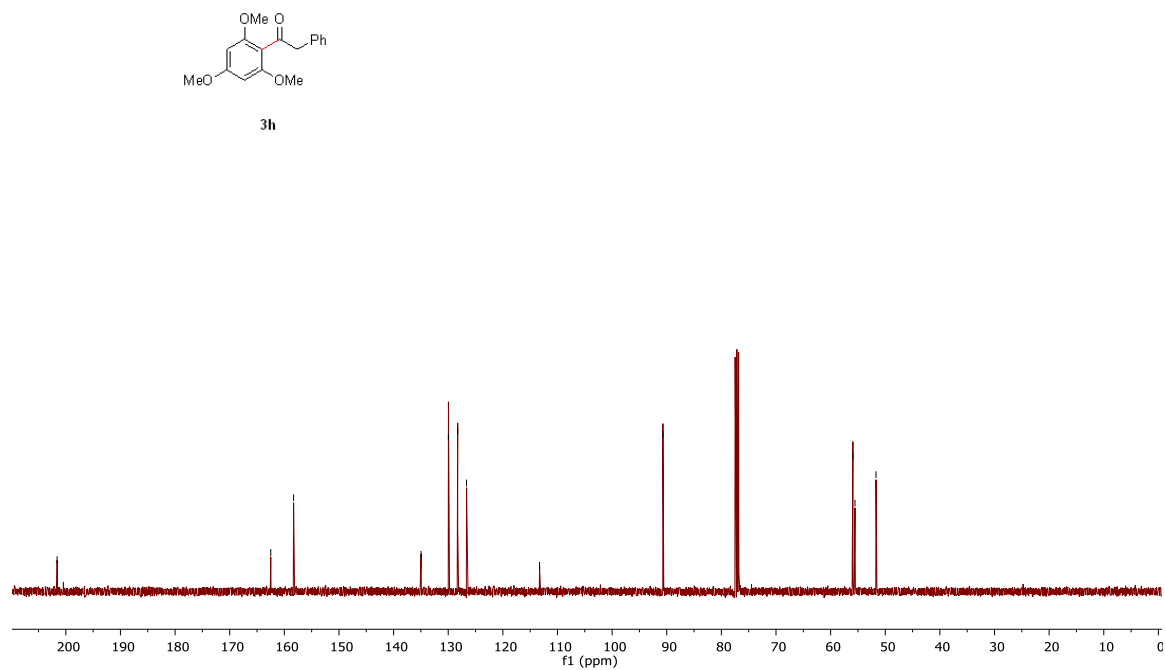
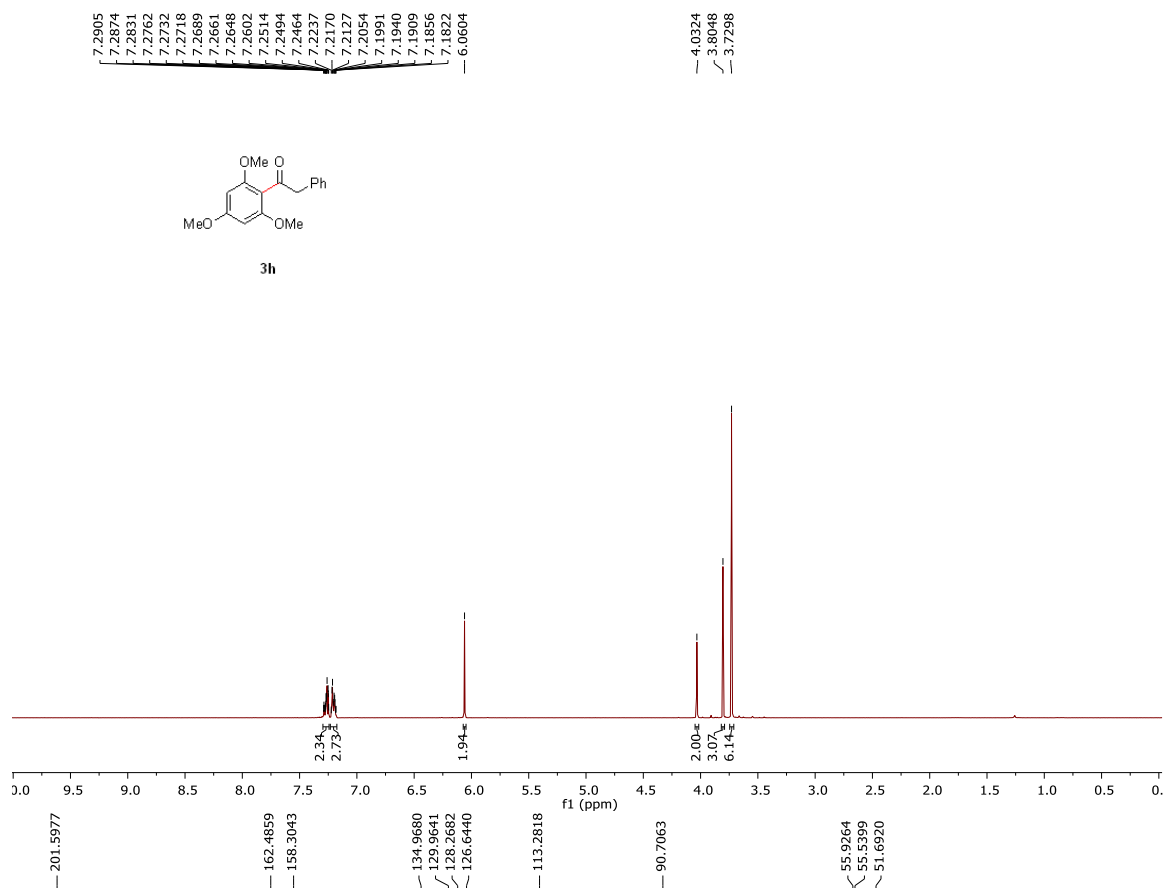


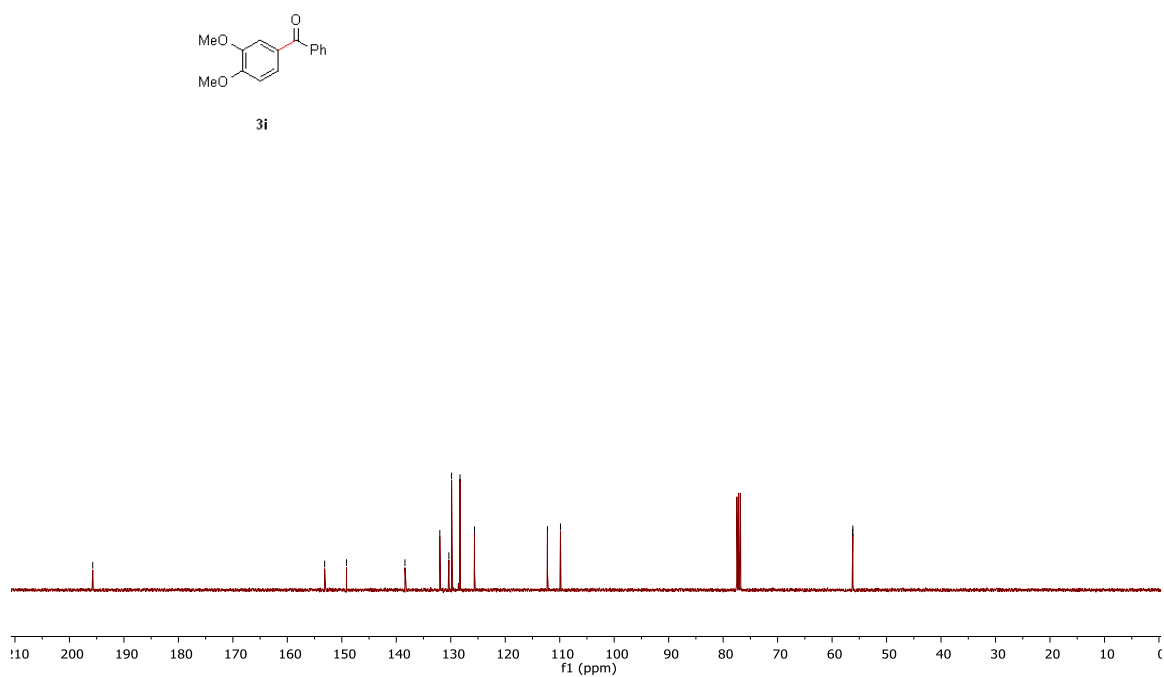
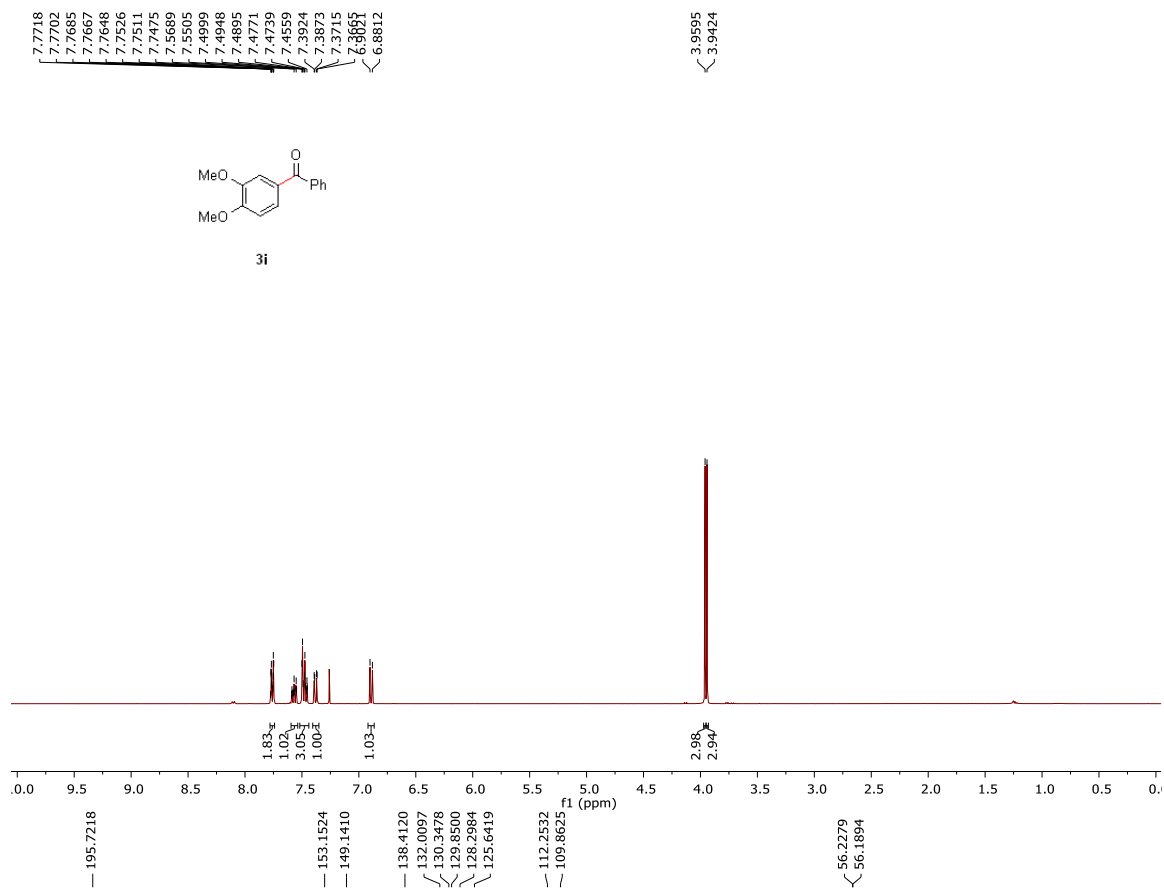












7.8496  
7.8480  
7.8427  
7.8410  
7.8374  
7.8358  
7.8256  
7.8242  
7.8200  
7.8184  
7.8131  
7.8115  
7.7676  
7.7660  
7.7643  
7.7625  
7.7606  
7.7589  
7.7466  
7.7451  
7.7432  
7.7416  
7.7370  
7.5854  
7.5835  
7.5819  
7.5801  
7.5785  
7.5706  
7.5693  
7.5642  
7.5599  
7.5583  
7.5499  
7.5484  
7.5465  
7.5448  
7.5428  
7.5414  
7.4900  
7.4884  
7.4864  
7.4735  
7.4707  
7.4691  
7.4525  
7.4506  
6.9820  
6.9751  
6.9711  
6.9577  
6.9536  
6.9467

