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**Electronic Supplementary Information** 

# Synthesis of ketones via Organolithium Addition to Acid Chlorides Using Continuous Flow Chemistry

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### 1. Materials and Methods

All chemical reagents were purchased from Sigma-Aldrich, Alfa Aesar and TCI chemicals and were used without further purification. Reactions were monitored by thin layer chromatography (TLC) with 0.25-mm E. Merck pre-coated silica gel plates (Kieselgel 60F<sub>254</sub>, Merck). Products were detected by viewing under UV light and by staining with either an anisaldehyde solution composed of acetic acid, sulfuric acid and MeOH or by staining with a KMnO<sub>4</sub> solution composed of potassium carbonate, sodium hydroxide and water. Flash column chromatography was performed on Merck 60 silica gel (70-230 mesh). Micromixers with inner diameters of 250, 300 and 500 µm were purchased from VICI (ZT1C, ZT1M), YMC (YMC-P-V-025, YMC-P-0058) and ITEC (SIMM-V2). Stainless steel (SUS316) microtube reactors with inner diameters of 1000 µm were purchased from GL Science and were cut into appropriate lengths (50 and 100 cm). The micromixer and microtube reactors were connected with stainless steel fittings (GL Science, 1/16" OUW) to construct the microreaction system. The microfluidic system was dipped in a cooling bath to control the temperature. Solutions were continuously injected into the microfluidic system using syringe pumps (Harvard Model PhD 2000) equipped with gastight syringes purchased from SGE Analytical Science. After a steady state was reached, the product solution was collected for 90 sec unless otherwise noted. GC analysis was performed on a TRACE<sup>™</sup> 1300 Gas Chromatograph (Thermo Scientific) using TraceGold TG-5MS Amine (0.25mm  $\times$  0.25 $\mu$ m  $\times$  30m). <sup>1</sup>H and <sup>13</sup>C spectra were recorded on a Bruker AM-300 spectrometer. Chemical shifts are reported as  $\delta$  values relative to internal SiMe<sub>4</sub> or chloroform ( $\delta$  0.00 for <sup>1</sup>H and  $\delta$  77.0 for <sup>13</sup>C). IR spectra were measured as neat oil or solids on a Varian Scimitar 800 FT-IR spectrometer. High resolution spectra were obtained at the Korea Basic Science Institute Mass Spectrometry Service Center.



Figure 1. Micromixer types employed in this study.

2. Reaction between 1-bromo-4-methoxybenzene and benzoyl chlorides under standard

batch conditions.



#### Scheme 1.

(A) i. To a stirred solution of 1-bromo-4-methoxybenzene (0.187 g, 1.00 mmol) in dry THF (10 mL) at -78 °C was added *n*-BuLi (2.5 M in hexane, 0.44 mL, 1.10 mmol). The temperature was maintained at -78 °C, the reaction mixture was stirred for 1 h. A solution of benzoyl chloride (0.169 g, 1.20 mmol) in dry THF (1 mL) at -78 °C was then added, and the reaction mixture was stirred for a further 0.5 h. The reaction mixture was quenched with sat. NH<sub>4</sub>Cl aqueous solution, extracted with EtOAc (3 x 30 mL), dried with MgSO<sub>4</sub> and concentrated. The crude product was purified by flash column chromatography (eluent: *vide infra*) on silica gel. This afforded ketone **3a** in trace yield and tertiary alcohol **4a** (0.115 g, 0.36 mmol, 72 %) as a colorless solid.

(A) ii. To a stirred solution of 1-bromo-4-methoxybenzene (0.187 g, 1.00 mmol) in dry THF (10 mL) at -78 °C was added *n*-BuLi (2.5 M in hexane, 0.44 mL, 1.10 mmol). The temperature was maintained at -78 °C, the reaction mixture was stirred for 1 h. This solution was added by cannula at -78 °C to a solution of benzoyl chloride (0.169 g, 1.20 mmol) in dry THF (1 mL) at -78 °C and the reaction mixture was stirred for a further 0.5 h. The reaction mixture was quenched with sat. NH<sub>4</sub>Cl aqueous solution, extracted with EtOAc (3 x 30 mL), dried with MgSO<sub>4</sub> and concentrated. The crude product was purified by flash column chromatography (eluent: *vide infra*) on silica gel. This afforded ketone **3a** (0.017 g, 0.08 mmol, 8%) as a pale yellow solid and tertiary alcohol **4a** (0.120 g, 0.37 mmol, 75 %) as a colorless solid.

(B) i. To a stirred solution of 1-bromo-4-methoxybenzene (0.187 g, 1.00 mmol) in dry THF (10 mL) at -78 °C was added *n*-BuLi (2.5 M in hexane, 0.44 mL, 1.10 mmol). The temperature was maintained at -78 °C, the reaction mixture was stirred for 1 h. A solution of 2-methoxybenzoyl chloride (0.205 g, 1.20 mmol) in dry THF (1 mL) at -78 °C was added, and the reaction mixture was stirred for a further 0.5 h. The reaction mixture was quenched with sat. NH4Cl aqueous solution, extracted with EtOAc (3 x 30 mL), dried with MgSO<sub>4</sub> and concentrated. The crude product was purified by flash column chromatography on silica gel (eluent: *vide infra*). This afforded ketone product **3d** (0.034 g, 0.14 mmol, 14 %) as a white solid and tertiary alcohol **4d** (0.091 g, 0.26 mmol, 52 %) as a pale yellow oil.

(B) ii. To a stirred solution of 1-bromo-4-methoxybenzene (0.187 g, 1.00 mmol) in dry THF (10 mL) at -78 °C was added *n*-BuLi (2.5 M in hexane, 0.44 mL, 1.10 mmol). The temperature was maintained at -78 °C, the reaction mixture was stirred for 1 h. This solution was added by cannula at -78 °C to a solution of 2-methoxybenzoyl chloride (0.205 g, 1.20 mmol) in dry THF (1 mL) at -78 °C and the reaction mixture was stirred for a further 0.5 h. The reaction mixture was quenched with sat. NH<sub>4</sub>Cl aqueous solution, extracted with EtOAc (3 x 30 mL), dried with MgSO<sub>4</sub> and concentrated. The crude product was purified by flash column chromatography on silica gel (eluent: *vide infra*). This afforded ketone product **3d** (0.097 g, 0.40 mmol, 40 %) as a white solid and tertiary alcohol **4d** (0.040 g, 0.115 mmol, 23 %) as a pale yellow oil.



## **3. General Procedure**

Figure 2. Flow chemistry reaction set-up employed in this study.



Figure 3. Pre-cooling coil employed in this study.



Figure 4. Schematic representation of continuous flow set up

A microfluidic system consisting of two T-shaped micromixers (**M1** and **M2**), two microtube reactors (**R1** and **R2**) and three tube pre-temperature-retaining units (**P1**, **P2** and **P3** (inner diameter  $\emptyset$  =1000 µm, L=50 cm) were assembled as shown in the schematic representation above. A solution of 1-bromo-4-methoxybenzene (0.10 M in THF) (flow rate: 4.0 mL min<sup>-1</sup>) and a solution of *n*-BuLi (0.44 M in hexane) (flow rate: 1.0 mL min<sup>-1</sup>) were introduced to **M1** ( $\emptyset$  =250 µm) by syringe pumps. The resulting solution was passed through **R1** ( $\emptyset$  =1000 µm, L=100 cm) and was mixed with a solution of benzoyl chloride (0.075 M in

CH<sub>2</sub>Cl<sub>2</sub>) (flow rate: 8.0 mL min<sup>-1</sup>) in **M2** ( $\emptyset$  =250 µm). The resulting solution was passed through **R2** ( $\emptyset$  =1000 µm, L=50 cm). After a steady state was reached, the product solution was collected for 90 sec and immediately quenched with a sat. NH<sub>4</sub>Cl aqueous solution, extracted with EtOAc (3 x 20 mL) and purified by flash column chromatography on silica gel.



*Compound (3a)*. The general procedure was used employing 1-bromo-4-methoxybenzene and benzoyl chloride. Flash chromatography on silica gel using hexane/ethyl acetate (10:1) provided pure **3a** (0.084 g, 0.40 mmol, 66 %) as a pale yellow solid. R<sub>f</sub> 0.47 (hexane/ethyl acetate = 3:1); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.82 (d, *J* = 8.8 Hz, 2H), 7.77-7.72 (m, 2H), 7.59-7.51 (m, 1H), 7.50-7.42 (m, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 3.87 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  195.4, 163.1, 138.2, 132.5, 131.8, 130.0, 129.6, 128.1, 113.5, 55.4. Data is consistent with that reported in the literature.<sup>1</sup> **4a** (0.012 g, 0.04 mmol, 13 %) as a colorless solid. R<sub>f</sub> 0.35 (hexane/ethyl acetate = 3:1); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.30-7.22 (m, 5H), 7.15 (d, *J* = 9.0 Hz, 4H), 6.80 (d, *J* = 8.9 Hz, 4H), 3.75 (s, 6H), 2.88 (br, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  158.6, 147.4, 139.5, 129.2, 127.9, 127.8, 127.1, 113.2, 81.5, 55.3. Data is consistent with that reported in the literature.<sup>2</sup>



*Compound (3b)*. The general procedure was used employing 1-bromo-4-methoxybenzene and 4-methoxybenzoyl chloride. Flash chromatography on silica gel using hexane/ethyl acetate (10:1) provided pure **3b** (0.092 g, 0.38 mmol, 63 %) as a pale yellow solid. R<sub>f</sub> 0.38 (hexane/ethyl acetate = 3:1); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.78 (d, *J* = 8.9 Hz, 4H), 6.95 (d,

<sup>&</sup>lt;sup>1</sup> Y. -X. Liao and Q. -S. Hu, J. Org. Chem., 2010, 75, 6986.

<sup>&</sup>lt;sup>2</sup> M. Horn and H. Mayr, Chem. Eur. J., 2010, 16, 7469.

J = 8.8 Hz, 4H), 3.87 (s, 6H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  194.3, 162.7, 132.1, 130.6, 113.4, 55.4. Data is consistent with that reported in the literature.<sup>1</sup> **4b** (0.010 g, 0.03 mmol, 9 %) as a colorless solid. R<sub>f</sub> 0.36 (hexane/ethyl acetate = 3:1); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.15 (d, J = 9.0 Hz, 6H), 6.81 (d, J = 9.0 Hz, 6H), 3.77 (s, 9H), 2.78 (br, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  158.5, 139.7, 129.0, 113.1, 81.1, 55.2. Data is consistent with that reported in the literature.<sup>2</sup>



*Compound (3c)*. The general procedure was used employing 1-bromo-4-methoxybenzene and 3-methoxybenzoyl chloride. Flash chromatography on silica gel using hexane/ethyl acetate (15:1) provided pure **3c** (0.090 g, 0.37 mmol, 62 %) as a pale yellow solid. R<sub>f</sub> 0.21 (hexane/ether = 5:1); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.84 (d, *J* = 8.8 Hz, 2H), 7.41-7.26 (m, 3H), 7.14-7.07 (m, 1H), 6.96 (d, *J* = 8.8 Hz, 2H), 3.89 (s, 3H), 3.86 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  195.3, 163.2, 159.4, 139.6, 132.5, 130.1, 129.1, 122.4, 118.2, 114.1, 113.5, 55.4, 55.39. Data is consistent with that reported in the literature.<sup>1</sup>



*Compound (3d)*. The general procedure was used employing 1-bromo-4-methoxybenzene and 2-methoxy benzoylchloride. Flash chromatography on silica gel using hexane/ethyl acetate/toluene (20:1:1) provided pure **3d** (0.112 g, 0.46 mmol, 77 %) as a white solid. R<sub>f</sub> 0.12 (hexane/ethyl acetate/toluene = 10:1:1); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.81 (d, *J* = 8.7 Hz, 2H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.32 (dd, *J* = 7.5 and 1.8 Hz, 1H), 7.08-6.97 (m, 2H), 6.96 (d, *J* = 6.9 Hz, 2H), 3.87 (s, 3H), 3.75 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  195.1, 163.5, 157.0, 132.3, 131.4, 130.6, 129.2, 129.17, 120.4, 113.4, 111.3, 55.6, 55.4. Data is consistent with that reported in the literature.<sup>1</sup> **4d** (trace) as a pale yellow oil. R<sub>f</sub> 0.19 (hexane/ethyl acetate/toluene = 10:1:1); IR (neat) 3522, 2954, 2836, 1608, 1583, 1507, 1463, 1246, 1172, 1026, 829, 756, 590 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.31-7.24 (m, 1H), 7.13 (d, *J* = 8.9 Hz, 4H), 6.97-6.93 (m, 1H), 6.86-6.78 (m, 5H), 6.53 (dd, *J* = 7.7 and 1.7 Hz, 1H), 5.26 (br, 1H), 3.80 (s, 6H), 3.68 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  158.4, 157.3, 139.2, 135.6, 130.2, 128.9, 128.8, 120.4, 112.9, 112.0, 81.5, 55.7, 55.2; HRMS-FAB: *m/z* 350.1512 [M<sup>+</sup>; calcd. for C<sub>22</sub>H<sub>22</sub>O<sub>4</sub> <sup>+</sup>:

350.1513].



*Compound (3e)*. The general procedure was used employing 1-bromo-4-methoxybenzene and 2-methylbenzoyl chloride. Flash chromatography on silica gel using hexane/dichloromethane (2:1) provided pure **3e** (0.100 g, 0.44 mmol, 74 %) as a colorless oil. R<sub>f</sub> 0.28 (hexane/dichloromethane = 1:1); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.79 (d, *J* = 8.9 Hz, 2H), 7.40-7.33 (m, 1H), 7.31-7.21 (m, 3H), 6.92 (d, *J* = 8.9 Hz, 2H), 3.86 (s, 3H), 2.30 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  197.3, 163.6, 139.1, 136.1, 132.4, 130.7, 130.4, 129.7, 127.8, 125.1, 113.6, 55.4, 19.7. Data is consistent with that reported in the literature.<sup>3</sup> **4e** (0.010 g, 0.03 mmol, 10 %) as a pale yellow solid. R<sub>f</sub> 0.11 (hexane/dichloromethane = 1:1); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.22-7.07 (m, 6H), 7.05-6.98 (m, 1H), 6.82 (d, *J* = 8.9 Hz, 4H), 6.76 (d, *J* = 7.7 Hz, 1H), 3.78 (s, 6H), 2.93 (br, 1H), 2.14 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  158.4, 144.9, 139.2, 137.9, 132.4, 129.3, 128.8, 127.6, 124.8, 113.1, 82.5, 55.2, 22.1. Data is consistent with that reported in the literature.<sup>4</sup>



*Compound (3f)*. The general procedure was used employing 1-bromo-4-methoxybenzene and 3-nitrobenzoyl chloride. Flash chromatography on silica gel using hexane/ethyl acetate (10:1) provided pure **3f** (0.065 g, 0.25 mmol, 42 %) as a pale yellow solid. m.p. 58-60 °C; R<sub>f</sub> 0.59 (hexane/ethyl acetate = 3:1); IR (neat) 2924, 2849, 1597, 1472, 1346, 1260, 1181, 1025, 956, 918, 850, 728, 668 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  8.58 (t, *J* = 1.8 Hz, 1H), 8.41 (ddd, *J* 

<sup>&</sup>lt;sup>3</sup> H. Xu, K. Ekoue-Kovi and C. Wolf, J. Org. Chem., 2008, 73, 7638.

<sup>&</sup>lt;sup>4</sup> G. Dyker, M. Hagel, O. Muth and C. Schirrmacher, Eur. J. Org. Chem., 2006, 2134.

= 8.2, 2.4 and 1.0 Hz, 1H), 8.10 (dt, J = 7.6 and 1.2 Hz, 1H), 7.82 (d, J = 9.0 Hz, 2H), 7.70 (t, J = 8.0 Hz, 1H), 7.01 (d, J = 9.0 Hz, 2H), 3.92 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 192.8, 163.9, 148.0, 139.8, 135.2, 132.6, 129.5, 128.8, 126.2, 124.4, 114.0, 55.6; HRMS-FAB: m/z 257.0683 [M<sup>+</sup>; calcd. for C<sub>14</sub>H<sub>11</sub>O<sub>4</sub>N<sup>+</sup>: 257.0683]. **4f** (0.043 g, 0.12 mmol, 39 %) as a pale yellow solid. m.p. 75-76 °C; R<sub>f</sub> 0.48 (hexane/ethyl acetate = 3:1); IR (neat) 3451, 2956, 2837, 1608, 1511, 1464, 1350, 1252, 1178, 1034, 828, 734 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.30-8.24 (m, 1H), 8.11 (d, J = 8.0 Hz, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.46 (t, J = 8.0 Hz, 1H), 7.15 (d, J = 8.8 Hz, 4H), 6.85 (d, J = 8.7 Hz, 4H), 3.80 (s, 6H), 2.85 (br, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 159.1, 149.5, 148.0, 138.2, 133.8, 129.0, 128.7, 122.5, 122.1, 113.6, 81.0, 55.3; HRMS-FAB: m/z 365.1258 [M<sup>+</sup>; calcd. for C<sub>21</sub>H<sub>19</sub>O<sub>5</sub>N<sup>+</sup>: 365.1258].



*Compound (3g)*. The general procedure was used employing 1-bromo-4-methoxybenzene and hexanoyl chloride. Flash chromatography on silica gel using hexane/ethyl acetate (30:1) provided pure **3g** (0.068 g, 0.33 mmol, 55 %) as a pale yellow oil. R<sub>f</sub> 0.38 (hexane/ethyl acetate = 30:1); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.94 (d, *J* = 9.0 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 3.86 (s, 3H), 2.90 (t, *J* = 7.3 Hz, 2H), 1.79-1.65 (m, 2H), 1.41-1.29 (m, 4H), 0.95-0.86 (m, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  199.1, 163.2, 130.2, 130.1, 113.6, 55.4, 38.2, 31.5, 24.2, 22.5, 13.9. Data is consistent with that reported in the literature.<sup>1</sup> **4g'** (0.014 g, 0.05 mmol, 16 %) as a pale yellow oil. R<sub>f</sub> 0.20 (hexane/ethyl acetate = 30:1); IR (neat) 2956, 2929, 1606, 1513, 1285, 1245, 1173, 1107, 1037, 830, 588 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.14 (d, *J* = 8.8 Hz, 2H), 7.09 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 6.79 (d, *J* = 8.8 Hz, 2H), 5.93 (t, *J* = 7.4 Hz, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 2.15-2.05 (m, 2H), 1.44-1.24 (m, 4H), 0.86 (t, *J* = 7.2 Hz, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  158.5, 158.3, 140.3, 136.1, 132.9, 131.0, 128.4, 128.3, 113.4, 113.37, 55.3, 55.2, 32.3, 29.5, 22.4, 14.0; HRMS-FAB: *m*/z 296.1771 [M<sup>+</sup>; calcd. for C<sub>20</sub>H<sub>24</sub>O<sub>2</sub><sup>+</sup>: 296.1771].



*Compound (3h)*. The general procedure was used employing 1-bromo-4-methoxybenzene and pivaloyl chloride. Flash chromatography on silica gel using hexane/ethyl acetate (40:1) provided pure **3h** (0.082 g, 0.43 mmol, 71 %) as a pale yellow oil.  $R_f 0.37$  (hexane/ethyl acetate

= 20:1); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.85 (d, *J* = 9.0 Hz, 2H), 6.90 (d, *J* = 9.0 Hz, 2H), 3.85 (s, 3H), 1.37 (s, 9H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  206.3, 162.0, 130.9, 130.1, 113.2, 55.3, 43.8, 28.4. Data is consistent with that reported in the literature.<sup>5</sup>



*Compound (3i)*. The general procedure was used employing 1-bromo-4-methoxybenzene and 6-chloronicotinoyl chloride. Flash chromatography on silica gel using hexane/ether (10:1) provided pure **3i** (0.067 g, 0.27 mmol, 45 %) as a pale yellow solid. R<sub>f</sub> 0.28 (hexane/ether = 3:1); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  8.75-8.72 (m, 1H), 8.04 (dd, *J* = 8.2 and 2.5 Hz, 1H), 7.81 (d, *J* = 8.8 Hz, 2H), 7.47 (dd, *J* = 8.3 and 0.5 Hz, 1H), 7.00 (d, *J* = 8.9 Hz, 2H), 3.91 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  192.1, 163.9, 154.4, 150.7, 139.6, 132.6, 132.4, 129.1, 124.2, 114.0, 55.6. Data is consistent with that reported in the literature.<sup>6</sup> **4i** (0.043 g, 0.12 mmol, 40 %) as a pale yellow oil. R<sub>f</sub> 0.10 (hexane/ether = 3:1); IR (neat) 3272, 2957, 2837, 1608, 1581, 1511, 1461, 1252, 1176, 1105, 1034, 829, 740, 590 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  8.28 (dd, *J* = 2.6 and 0.6 Hz, 1H), 7.62 (dd, *J* = 8.4 and 2.7 Hz, 1H), 7.26-7.22 (m, 1H), 7.13 (d, *J* = 8.9 Hz, 4H), 6.84 (d, *J* = 9.0, 4H), 3.80 (s, 6H), 2.93 (br, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  159.0, 150.0, 149.1, 141.8, 138.3, 138.0, 128.9, 123.3, 113.5, 79.8, 55.3; HRMS-FAB: *m/z* 355.0968 [M<sup>+</sup>; calcd for C<sub>20</sub>H<sub>18</sub>O<sub>3</sub>N<sup>35</sup>Cl<sup>+</sup>: 355.0970].



*Compound (3j)*. The general procedure was used employing 1-bromo-4-methoxybenzene and thiophene-2-carbonyl chloride. Flash chromatography on silica gel using hexane/ethyl acetate

<sup>&</sup>lt;sup>5</sup> T. Fujihara, K. Semba, J. Terao and Y. Tsuji, Angew. Chem. Int. Ed., 2010, 49, 1472.

<sup>&</sup>lt;sup>6</sup> C. Duplais, F. Bures, I. Sapountzis, T. J. Korn, G. Cahiez and P. Knochel, *Angew. Chem. Int. Ed.*, 2004, **43**, 2968.

(20:1) provided pure **3j** (0.072 g, 0.33 mmol, 55 %) as a white solid.  $R_f$  0.46 (hexane/ethyl acetate = 10:1); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.90 (d, *J* = 8.8 Hz, 2H), 7.69 (dd, *J* = 4.9 and 0.7 Hz, 1H), 7.64 (dd, *J* = 3.7 and 0.8 Hz, 1H), 7.15 (dd, *J* = 4.8 and 3.6 Hz, 1H), 6.98 (d, *J* = 8.8 Hz, 2H), 3.88 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  187.0, 163.1, 143.6, 134.1, 133.5, 131.6, 130.5, 127.8, 113.6, 55.4. Data is consistent with that reported in the literature.<sup>7</sup> **4j** (0.013 g, 0.04 mmol, 13 %) as a red oil.  $R_f$  0.23 (hexane/ethyl acetate = 10:1); IR (neat) 3471, 3001, 2955, 2836, 1608, 1584, 1509, 1463, 1302, 1250, 1176, 1033, 830, 705, 606, 577 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.30-7.23 (m, 5H), 6.96-6.91 (m, 1H), 6.83 (d, J = 8.9 Hz, 4H), 6.70 (dd, J = 3.6 and 1.2 Hz, 1H), 3.80 (s, 6H), 2.88 (br, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  158.9, 152.9, 139.1, 128.5, 126.5, 126.4, 125.4, 113.1, 79.5, 55.2; HRMS-FAB: *m*/*z* 326.0971 [M<sup>+</sup>; calcd. for C<sub>19</sub>H<sub>18</sub>O<sub>3</sub><sup>32</sup>S<sup>+</sup>: 326.0971].



*Compound (3k)*. The general procedure was used employing 1-bromo-4-methoxybenzene and methyl 4-(chlorocarbonyl)benzoate. Flash chromatography on silica gel using hexane/ethyl acetate (10:1) provided pure **3k** (0.071 g, 0.26 mmol, 44 %) as a pale yellow solid. R<sub>f</sub> 0.50 (hexane/ethyl acetate = 3:1); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  8.14 (d, *J* = 8.3 Hz, 2H), 7.87-7.75 (m, 4H), 6.97 (d, *J* = 8.7 Hz, 2H), 3.96 (s, 3H), 3.90 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  194.8, 166.4, 163.6, 142.1, 132.7, 132.6, 129.5, 129.4 (2), 113.7, 55.5, 52.4. Data is consistent with that reported in the literature.<sup>8</sup>



*Compound (5a)*. The general procedure was used employing 1-bromo-4-methylbenzene and pivaloyl chloride. Flash chromatography on silica gel using hexane/ethyl acetate (40:1) provided pure **5a** (0.069 g, 0.39 mmol, 65 %) as a pale yellow oil.  $R_f 0.25$  (hexane/ethyl acetate = 30:1); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.66 (d, *J* = 6.6 Hz, 2H), 7.20 (d, *J* = 8.1, 2H), 2.38 (s,

<sup>&</sup>lt;sup>7</sup> Z. Zhang, M. G. Lindale and L. S. Liebeskind, J. Am. Chem. Soc., 2011, **133**, 6403.

<sup>&</sup>lt;sup>8</sup> W. S. Bechara, G. Pelletier and A. B. Charette, Nat. Chem., 2012, 4, 228.

3H), 1.35 (s, 9H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  208.3, 141.4, 135.4, 128.7, 128.3, 44.0, 28.1, 21.4. Data is consistent with that reported in the literature.<sup>9</sup>



*Compound (5b)*. The general procedure was used employing 3-bromothiophene and pivaloyl chloride. Flash chromatography on silica gel using hexane/ethyl acetate (40:1) provided pure **5b** (0.087 g, 0.53 mmol, 86 %) as a pale yellow oil. R<sub>f</sub> 0.21 (hexane/ethyl acetate = 30:1); IR (neat) 2971, 1663, 1476, 1399, 1159, 981, 864, 748 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  8.02 (q, *J* = 1.5 Hz, 1H), 7.56 (dd, *J* = 5.1 and 1.2, 1H), 7.28 (dd, *J* = 5.1 and 3.0, 1H), 1.36 (s, 9H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  201.0, 139.7, 131.3, 128.7, 125.0, 43.9, 27.8; HRMS-FAB: *m/z* 168.0603 [M<sup>+</sup>; calcd. for C<sub>9</sub>H<sub>12</sub>O<sup>32</sup>S<sup>+</sup>: 168.0603].



*Compound (5c)*. The general procedure was used employing 4-bromobenzonitrile and pivaloyl chloride. Flash chromatography on silica gel using hexane/ethyl acetate (10:1) provided pure **5c** (0.056 g, 0.30 mmol, 50 %) as a pale yellow oil. R<sub>f</sub> 0.40 (hexane/ethyl acetate = 3:1); IR (neat) 2973, 2232, 1681, 1478, 1401, 1276, 1193, 955, 847, 766 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.71 (s, 4H), 1.33 (s, 9H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  208.4, 142.7, 132.0, 128.0, 118.1, 114.2, 44.4, 27.6; HRMS-FAB: *m/z* 187.0992 [M<sup>+</sup>; calcd. for C<sub>12</sub>H<sub>13</sub>NO<sup>+</sup>: 187.0992].



*Compound (5d)*. The general procedure was used employing 1-bromo-3-methoxybenzene and 2-methoxybenzoyl chloride. Flash chromatography on silica gel using hexane/ethyl acetate (40:1) provided pure **5d** (0.105 g, 0.43 mmol, 72 %) as a pale yellow oil.  $R_f$  0.30 (hexane/ethyl acetate = 20:1); IR (neat) 2941, 1734, 1653, 1489, 1245, 1109, 1023, 967, 830, 760, 637, 540 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.50-7.41 (m, 2H), 7.37-7.27 (m, 3H), 7.14-7.07 (m, 1H),

<sup>&</sup>lt;sup>9</sup> L. J. Gooßen, F. Rudolphi, C. Oppel and N. Rodríguez, *Angew. Chem. Int. Ed.*, 2008, **47**, 3043.

7.07-6.96 (m, 2H), 3.86 (s, 3H), 3.75 (s, 3H);  ${}^{13}$ C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  196.2, 159.6, 157.3, 139.1, 131.8, 129.4. 129.1, 128.8, 123.1, 120.4, 119.6, 113.4, 111.4, 55.6, 55.4; HRMS-FAB: *m/z* 242.0938 [M<sup>+</sup>; calcd. for C<sub>15</sub>H<sub>14</sub>O<sub>3</sub><sup>+</sup>: 242.0937].



*Compound* (*5e*). The general procedure was used employing 3-bromofuran and 2methoxybenzoyl chloride. Flash chromatography on silica gel using hexane/ethyl acetate (40:1) provided pure **5e** (0.079 g, 0.39 mmol, 65 %) as a pale yellow oil. R<sub>f</sub> 0.30 (hexane/ethyl acetate = 20:1); IR (neat) 3131, 2926, 2839, 1598, 1512, 1436, 1391, 1246, 1150, 1014, 828, 752, 599 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.75 (dd, *J* = 1.4 and 0.8 Hz, 1H), 7.48-7.41 (m, 2H), 7.41-7.37 (m, 1H), 7.03-6.97 (m, 2H), 6.85 (dd, *J* = 1.9 and 0.8 Hz, 1H), 3.80 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  189.4, 156.9, 149.7, 143.8, 131.9, 129.4, 129.0, 128.2, 120.2, 111.5, 109.3, 55.6; HRMS-FAB: *m/z* 202.0625 [M<sup>+</sup>; calcd. for C<sub>12</sub>H<sub>10</sub>O<sub>3</sub><sup>+</sup>: 202.0624].



*Compound (5f)*. The general procedure was used employing 3-bromothiophene and 3methoxybenzoyl chloride. Flash chromatography on silica gel using hexane/ethyl acetate (40:1) provided pure **5f** (0.089 g, 0.41 mmol, 68 %) as a pale yellow solid. m.p. 68-70 °C; R<sub>f</sub> 0.16 (hexane/ethyl acetate = 30:1); IR (neat) 3106, 2938, 2836, 1727, 1658, 1596, 1485, 1389, 1411, 1275, 1180, 994, 875, 744 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.95 (dd, *J* = 2.9 and 1.2 Hz, 1H), 7.61 (dd, *J* = 2.9 and 1.2 Hz, 1H), 7.43-7.36 (m, 4H), 7.16-7.11 (m, 1H), 3.87 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  189.7, 159.6, 141.2, 139.9, 133.9, 129.3, 128.6, 126.1, 122.0, 118.6, 113.8, 55.4; HRMS-FAB: *m/z* 218.0396 [M<sup>+</sup>; calcd. for C<sub>12</sub>H<sub>10</sub>O<sub>2</sub><sup>32</sup>S<sup>+</sup>: 218.0396].



*Compound* (5g). The general procedure was used employing 4-bromobenzonitrile and 2-methylbenzoyl chloride. Flash chromatography on silica gel using hexane/ethyl acetate (30:1)

provided pure **5g** (0.074 g, 0.34 mmol, 56 %) as a white solid. m.p. 249-250 °C; R<sub>f</sub> 0.16 (hexane/ethyl acetate = 30:1); IR (neat) 2964, 2231, 1667, 1295, 1265, 927, 857, 748, 665 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.88 (d, *J* = 8.5 Hz, 2H), 7.76 (d, *J* = 8.5 Hz, 2H), 7.48-7.41 (m, 1H), 7.36-7.27 (m, 3H), 2.36 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  196.8, 141.2, 137.5, 137.0, 132.3, 131.4, 131.2, 130.3, 129.0, 125.4, 118.0, 116.2, 20.2; HRMS-FAB: *m/z* 221.0833 [M<sup>+</sup>; calcd. for C<sub>15</sub>H<sub>11</sub>ON<sup>+</sup>: 221.0835].



*Compound (5h).* The general procedure was used employing 3-bromofuran and 2methylbenzoyl chloride. Flash chromatography on silica gel using hexane/ethyl acetate (40:1) provided pure **5h** (0.084 g, 0.45 mmol, 75 %) as a pale yellow oil. R<sub>f</sub> 0.29 (hexane/ethyl acetate = 30:1); IR (neat) 3132, 2928, 1650, 1557, 1511, 1455, 1386, 1316, 1188, 1151, 1014, 885, 742, 601 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.70 (dd, *J* = 1.4 and 0.8 Hz, 1H), 7.48 (t, *J* = 1.8 Hz, 1H), 7.45-7.35 (m, 2H), 7.30-7.22 (m, 2H), 6.88 (dd, *J* = 1.9 and 0.7 Hz, 1H), 3.40 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  191.7, 149.7, 144.2, 139.1, 136.6, 131.2, 130.4, 128.2, 127.9, 125.2, 109.4, 19.7; HRMS-FAB: *m*/*z* 186.0676 [M<sup>+</sup>; calcd. for C<sub>12</sub>H<sub>10</sub>O<sub>2</sub><sup>+</sup>: 186.0675].

# Large scale synthesis of 2,2-dimethyl-1-(thiophen-3-yl)propan-1-one (5b) (5 mmol scale) using optimized continuous flow conditions

The general procedure was used employing 3-bromothiophene, pivaloyl chloride and *n*-BuLi. The product stream was collected for 12.5 min and immediately quenched with sat. NH<sub>4</sub>Cl aqueous solution, extracted with EtOAc (3 x 100 mL), dried with MgSO<sub>4</sub> and concentrated. The crude product was purified by flash column chromatography on silica gel using hexane/ethyl acetate (40:1), yielding **5b** (0.715 g, 4.25 mmol, 85 %) as a pale yellow oil. R<sub>f</sub> 0.21 (hexane/ethyl acetate = 30:1)







0=



0





0=









0=

























S36

0=







OMe



OMe





OMe





OMe











OMe





OMe





OMe

































0=