

## ELECTRONIC SUPPLEMENTARY INFORMATION

### Meso-scale Microwave-Assisted Continuous Flow Reactions Utilizing a Selective Heating Matrix

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## General Experimental Information

Commercially available reagents were used without further purification. Microwave batch reactions were performed in a commercially available CEM Discover® SP microwave synthesizer using external IR temperature measurement unless otherwise noted. Continuous flow reactions were performed using one or two Series 1 pumps available from Scientific Systems, Inc.<sup>S11</sup> and a modified CEM Discover SP with custom flow cell, fiber optic temperature monitoring/management, and a pressurized collection vessel. Purification of reaction products was carried out by recrystallization as described below, rotary evaporation, or by flash column chromatography. Visualization of thin layer chromatography plates was accomplished with UV light or an iodine chamber. <sup>1</sup>H-NMR spectra were recorded in ppm using solvent as an internal standard (CDCl<sub>3</sub> at 7.26 ppm). Proton decoupled <sup>13</sup>C-NMR were recorded in ppm using solvent as an internal standard (CDCl<sub>3</sub> at 77.16 ppm).

### 10 Construction of Continuous Flow Microwave Reactor

The instrument used for continuous flow microwave reactions (Figure S11) was based on a modified CEM Discover SP (Part# 925484) platform. Reaction solution pumping was performed by the aforementioned Series 1 pumps (Part# 110SFN01) with individual flow controls after which a T-fitting combined the separate flow paths (if necessary). The Discover SP was modified by removing the IR temperature sensor, allowing entrance of the flow tubing thorough the underside of the microwave (Figure S12). The tubing was joined to a modified 10-mL microwave vessel with a tapered, male threaded inlet, and the vessel was sealed with a microwave attenuator and locking cover. The locking cover incorporated a sapphire fiber optic thermowell for internal temperature feedback and monitoring and an outlet for the flow path. The tubing from this outlet was connected to the pressurized collection vessel (Figure S13) constructed of PTFE and PFA Teflon®, borosilicate glass, aluminium, 316 stainless steel, and PEEK. The pressurized collection vessel was connected 20 to a nitrogen or argon tank, a waste/evacuation vessel, and a system pressure gauge. Valves were installed to manually control system pressurization and evacuation of the collection vessel. A one way valve (BPR) was installed in a connection to the system pressure gauge which allowed excess pressure to safely vent through the waste/evacuation line.

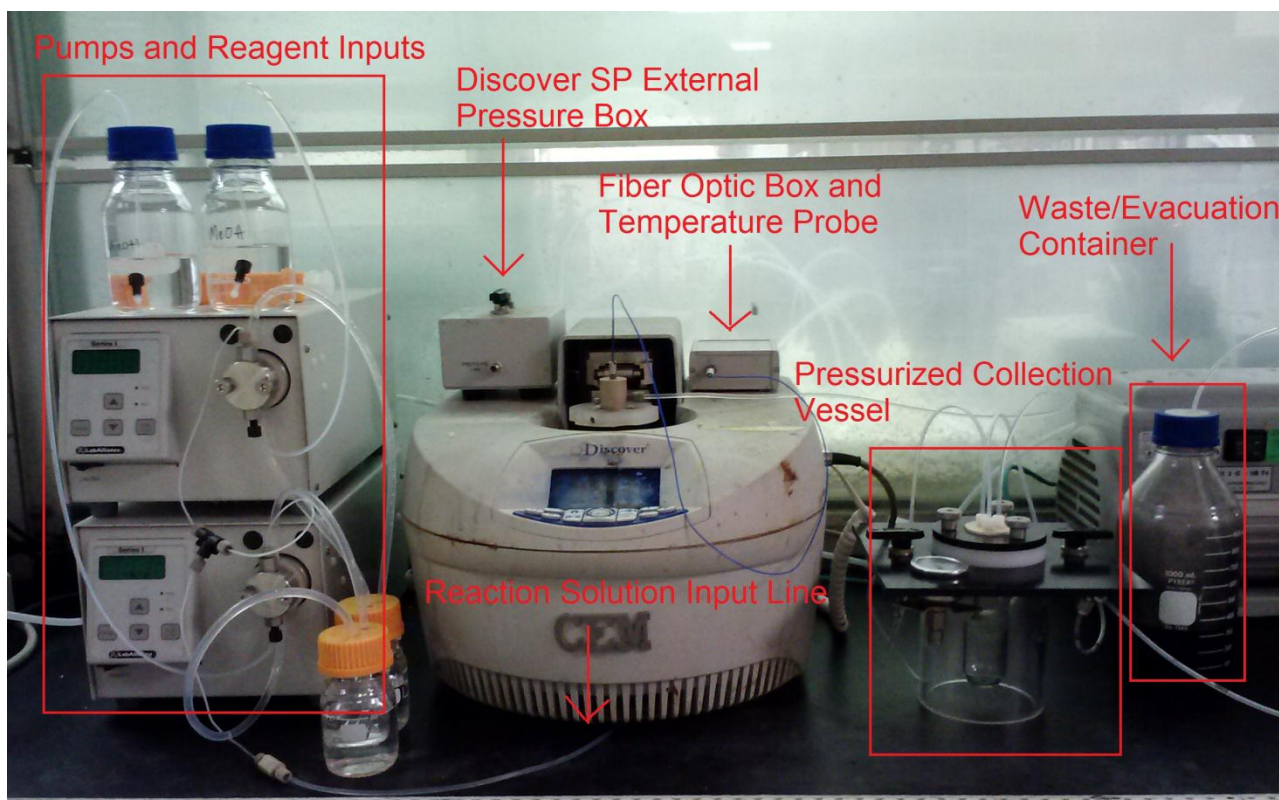


Fig. S11 Complete continuous flow microwave system setup



**Fig. S12** Flow system microwave inlet, vessel assembly, and outlet

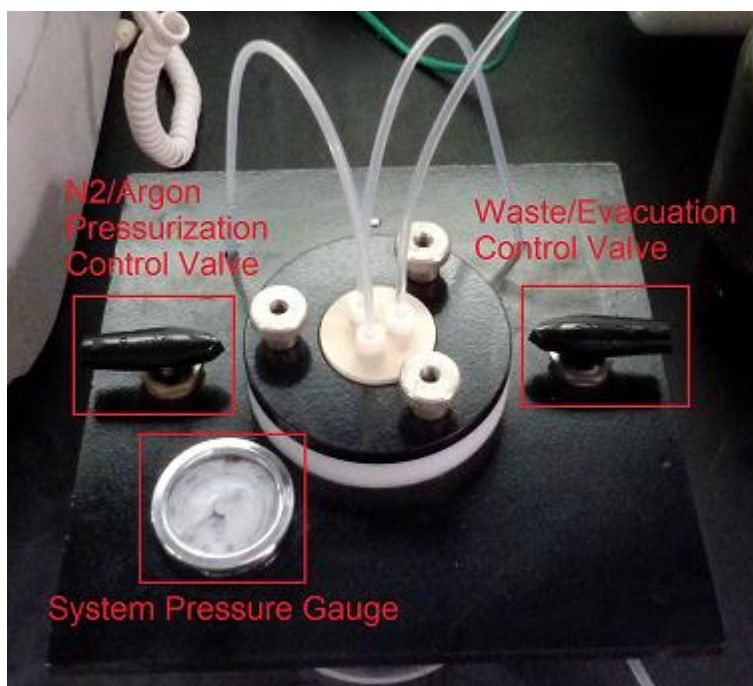


Fig. S13 Pressurized collection vessel of continuous flow system

## Experimental Procedures

### Procedure for the microwave-assisted *N*-Boc deprotection of *tert*-butyl 1-indolecarboxylate in a sealed tube

5 A stock solution of 1.15 M *tert*-butyl 1-indolecarboxylate (**1**) in acetonitrile was prepared and added (as indicated in Table 1) to a 10- or 35-mL microwave reaction vial containing a magnetic stirring bar. The samples were capped and heated in a CEM Discover SP microwave synthesizer to 180 °C for 10 minutes (Standard method; 180 °C; 10 minute hold time). The solution was cooled to room temperature and the contents analyzed by TLC (10% ethyl acetate/hexanes) and GC/MS. The solvent was removed under reduced pressure to furnish indole (**2**) as a white solid which did not require any purification. Spectroscopic data were in accordance with  
10 reported data.<sup>S12</sup>

### Procedure for the microwave-assisted *N*-Boc deprotection of *tert*-butyl 1-indolecarboxylate in a continuous flow reactor

The input line of the pump was placed in a 1-L stock solution of 1.15 M *tert*-butyl 1-indolecarboxylate (**1**) (234 mL; 1.15 mol) in acetonitrile (766 mL). The flow cell was packed with sand or a 10% w/w Fe<sub>3</sub>O<sub>4</sub> and sand mixture leaving approximately 1 cm of empty  
15 space at the top, which was filled with sand. The cell was sealed with a locking cover incorporating a sapphire thermowell for fiber optic temperature measurement, and the pump flow rate set as indicated in Table 1. The temperature was monitored internally using a fiber optic temperature probe. Once the starting material emerged from the collection line, the cell was pressurized with argon or nitrogen (240 psi). The microwave power was set at 100 W and gradually increased until a temperature of 220 °C was reached. After the target temperature was reached, the first 20 mL of product collected was discarded to allow for the previously unreacted starting material to exit  
20 the flow cell. After collection of the subsequent 20 mL, the reaction mixture was evacuated from the collection vessel to furnish unpurified deprotected product. TLC (10% ethyl acetate/hexanes) showed complete consumption of starting material, however, a small amount of impurity was present (R<sub>f</sub> = 0) that was easily removed by a silica plug (10% ethyl acetate/hexanes). The solvent was removed under reduced pressure to furnish indole (**2**) as a white solid. Spectroscopic data were in accordance with reported data.<sup>S12</sup>

### 25 Procedure for the microwave-assisted synthesis of $\beta$ -alanine **5** by Michael addition in a sealed tube

To a 10- or 35-mL microwave reaction vial containing a magnetic stirring bar and methyl acrylate (**4**) (2.30 mL; 25.5 mmol) was added diethyl amine (**3**) (1.76 mL; 17 mmol) and 200 mg Fe<sub>3</sub>O<sub>4</sub> (if required as stated in Table 2). The vial was capped and heated in a CEM Discover SP microwave synthesizer to 220 °C as indicated in Table 2 (Fixed Power method; 300 W; 220 °C control temperature; 15 minute or 5 minute total time). The solution was cooled to room temperature and the contents analyzed by GC/MS. The remaining  
30 starting material(s) were removed under reduced pressure to give methyl 3-(diethylamino)propanoate (**5**) as a colorless oil which did not require any further purification. Spectroscopic data were in accordance with reported data.<sup>S13</sup>

### General procedure for the microwave-assisted synthesis of Michael addition products **5**, **9**, and **10** in a continuous flow reactor

The input line of each pump was placed in a screw cap Schott bottle filled with methyl acrylate or Michael donor. The flow cell was packed with sand or a 10% w/w Fe<sub>3</sub>O<sub>4</sub> and sand mixture leaving approximately 1 cm of empty space at the top, which was filled with sand. The cell was sealed with a locking cover incorporating a sapphire thermowell for fiber optic temperature measurement, and the pump flow rate set as indicated in Tables 2 or 3. The temperature was monitored internally using a fiber optic temperature probe. Once the mixture of starting materials emerged from the collection line, the cell was pressurized with argon or nitrogen (240 psi). The microwave power was set at 100 W and gradually increased until a temperature of 220 °C was reached. After the target temperature was reached, the first 20 mL of product collected was discarded to allow for the previously unreacted starting material to exit the flow cell. After collection of the subsequent 20 mL, the reaction mixture was evacuated from the collection vessel to furnish unpurified Michael addition product.

**Methyl 3-(diethylamino)propanoate (5)**. Prepared according to general procedure using methyl acrylate (**4**) (2.24 mL, 25.0 mmol) and diethyl amine (**3**) (1.72 mL, 16.6 mmol).<sup>S14</sup> Removed remaining starting material(s) under reduced pressure to afford **5** as a colorless oil. Spectroscopic data were in accordance with reported data.<sup>S13</sup>

**Methyl 3-(benzylamino)propanoate (9)**. Prepared according to general procedure using methyl acrylate (**4**) (0.92 mL, 10.2 mmol) and benzyl amine (1.06 mL, 9.7 mmol).<sup>S15</sup> Purified by flash column chromatography (SiO<sub>2</sub>; 50% ethyl acetate/hexanes with 2% triethylamine) to afford **9** as a colorless oil. Spectroscopic data were in accordance with reported data.<sup>S13</sup>

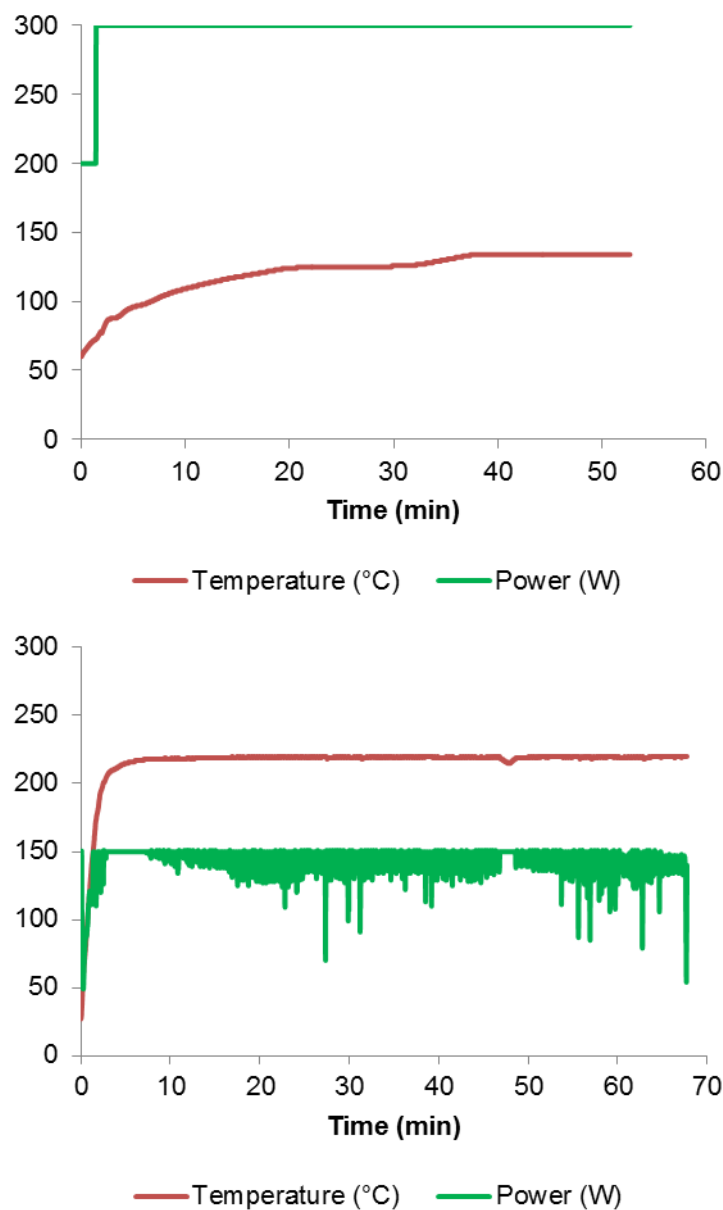
**Methyl 2-cyclohexanonepropionate (10)**. Prepared according to general procedure using methyl acrylate (**4**) (1.81 mL, 20.1 mmol) and 1-(1-cyclohexen-1-yl)pyrrolidine (2.16 mL, 13.4 mmol).<sup>S14</sup> The crude reaction mixture was diluted with ethyl acetate and washed with a solution of saturated ammonium chloride. The organic layer was separated and aqueous layer washed two more times with ethyl acetate. The combined organic washes were dried over magnesium sulfate, then filtered and concentrated in vacuo. The concentrate was purified by flash column chromatography (SiO<sub>2</sub>; 30% ethyl acetate/hexanes) to afford **10** as a colorless oil. Spectroscopic data were in accordance with reported data.<sup>S16</sup>

### Procedure for the microwave-assisted Diels Alder cycloaddition of diethyl acetylenedicarboxylate and furan in a sealed tube

To a 10-mL microwave reaction vial containing a magnetic stirring bar and diethyl acetylenedicarboxylate (**6**) (1.60 mL; 10 mmol) was added furan (**7**) (2.18 mL; 30 mmol) and 200 mg Fe<sub>3</sub>O<sub>4</sub> (if required as stated in Table 4). Microwave reactions were sealed with a locking cover incorporating a sapphire thermowell for fiber optic temperature measurement and heated in a CEM Discover SP microwave synthesizer to 150 °C for 10 minutes (Standard method; 150 °C; 10 minute hold time). Conventional reactions were sealed with a locking cover incorporating a sapphire thermowell for fiber optic temperature measurement and heated in a pre-heated oil bath to 150 °C for 10 minutes. The temperatures of both microwave and conventional reactions were monitored internally using a fiber optic temperature probe. The solution was cooled to room temperature and the contents analyzed by TLC (30% ethyl acetate/hexanes) and GC/MS. The crude reaction mixture was purified by flash column chromatography (SiO<sub>2</sub>; 30% ethyl acetate/hexanes) to obtain diethyl 7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate (**8**) as an orange oil. Spectroscopic data were in accordance with reported data.<sup>S17</sup>

### Procedure for the microwave-assisted Diels Alder cycloaddition of diethyl acetylenedicarboxylate and furan in a continuous flow reactor

The input line of the pump was placed in a 1-L stock solution of diethyl acetylenedicarboxylate (**6**) (424 mL; 2.65 mol) and furan (**7**) (578 mL; 7.95 mol). The flow cell was packed with sand or a 10% w/w Fe<sub>3</sub>O<sub>4</sub> and sand mixture leaving approximately 1 cm of empty space at the top, which was filled with sand. The cell was sealed with a locking cover incorporating a sapphire thermowell for fiber optic temperature measurement, and the pump flow rate set to 0.5 mL/min. The temperature was monitored internally using a fiber optic temperature probe. Once the mixture of starting materials emerged from the collection line, the cell was pressurized with argon or nitrogen (240 psi). The microwave power was set at 100 W and gradually increased until a temperature of 150 °C was reached. After the target temperature was reached, the first 20 mL of product collected was discarded to allow for the previously unreacted starting material to exit the flow cell. After collection of the subsequent 20 mL, the reaction mixture was evacuated from the collection vessel and analyzed by TLC (30% ethyl acetate/hexanes) and GC/MS. The crude reaction mixture was purified by flash column chromatography (SiO<sub>2</sub>; 30% ethyl acetate/hexanes) to obtain diethyl 7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate (**8**) as an orange oil. Spectroscopic data were in accordance with reported data.<sup>S17</sup>



**Fig. S14** Temperature and power profiles for the microwave-assisted *N*-Boc deprotection of *tert*-butyl 1-indolecarboxylate in a continuous flow reactor with a sand packed flow cell (top; Table 1, entry 3) and with a 10% w/w Fe<sub>3</sub>O<sub>4</sub> and sand mixture packed flow cell (bottom, Table 1, entry 4).

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**Table S11** Reagent flow rates for continuous flow microwave assisted Michael additions at a total flow rate of 1 mL/min

Reagents	MW	Density (g/mL)	Equivalents	Flow Rate (mL/min)	Flow Rate (mmol/min)
benzyl amine	107.15	0.981	1.00	0.53	4.85
methyl acrylate	86.09	0.956	1.06	0.46	5.12
diethylamine	73.14	0.707	1.00	0.43	4.16
methyl acrylate	86.09	0.956	1.50	0.56	6.26
1-pyrrolidino-1-cyclohexene	151.25	0.94	1.00	0.54	3.36
methyl acrylate	86.09	0.956	1.50	0.45	5.04

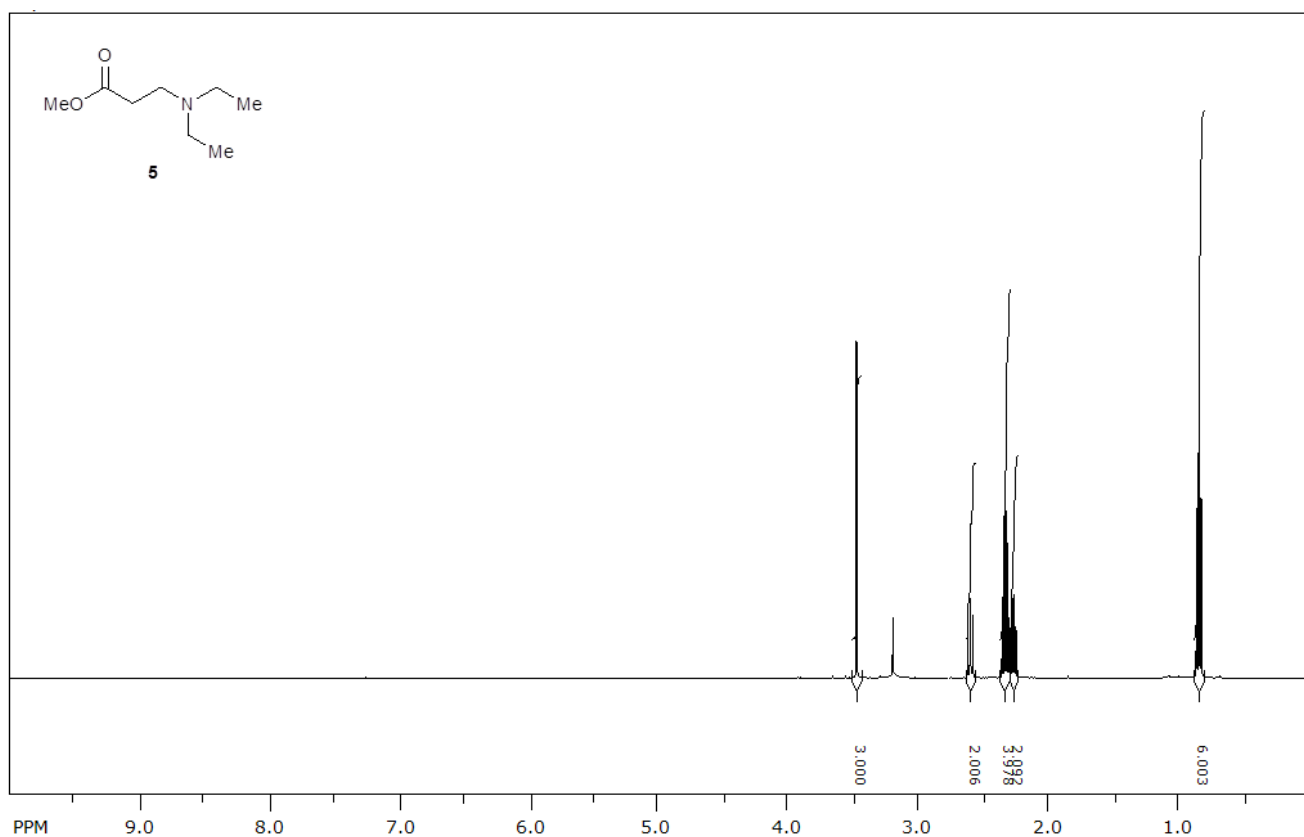
**Table SI2** Reagent flow rates for continuous flow microwave assisted Michael additions at a total flow rate of 2 mL/min

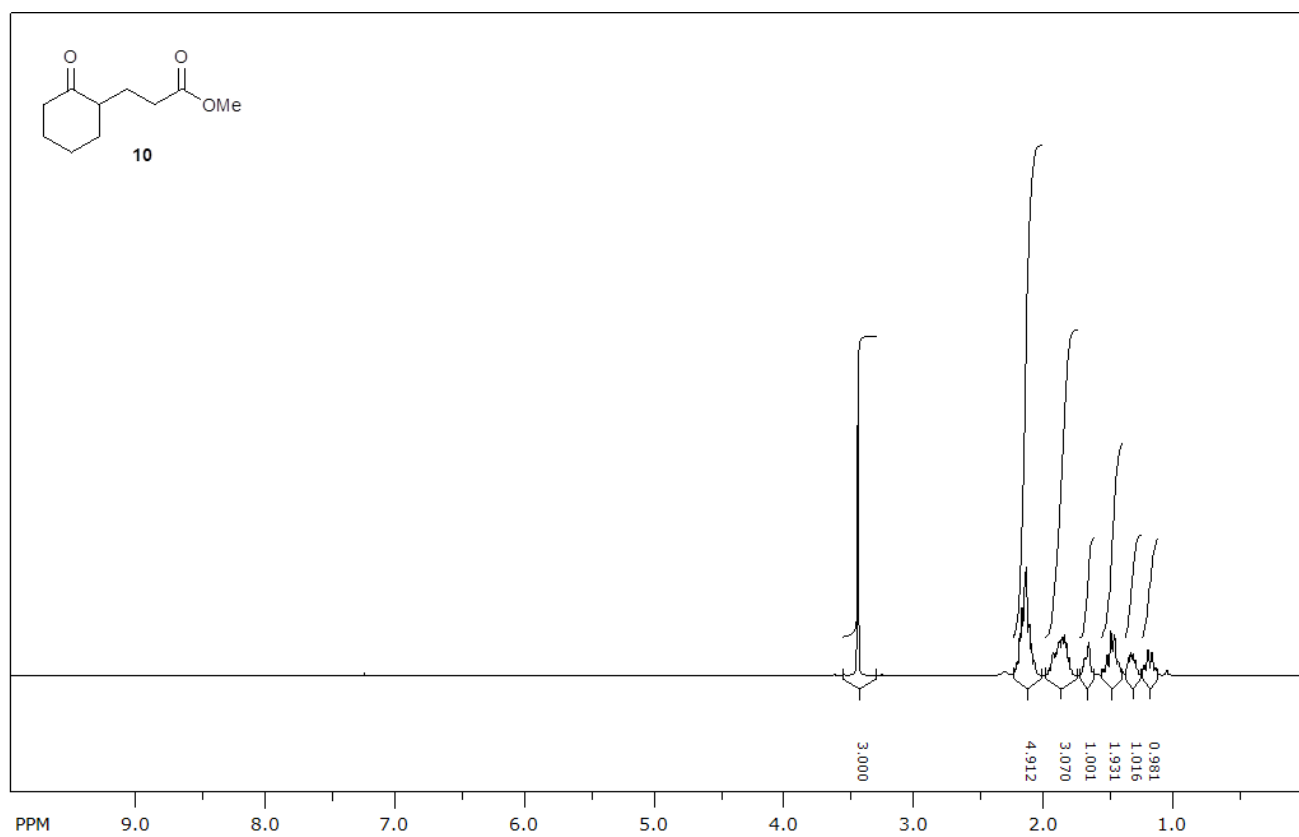
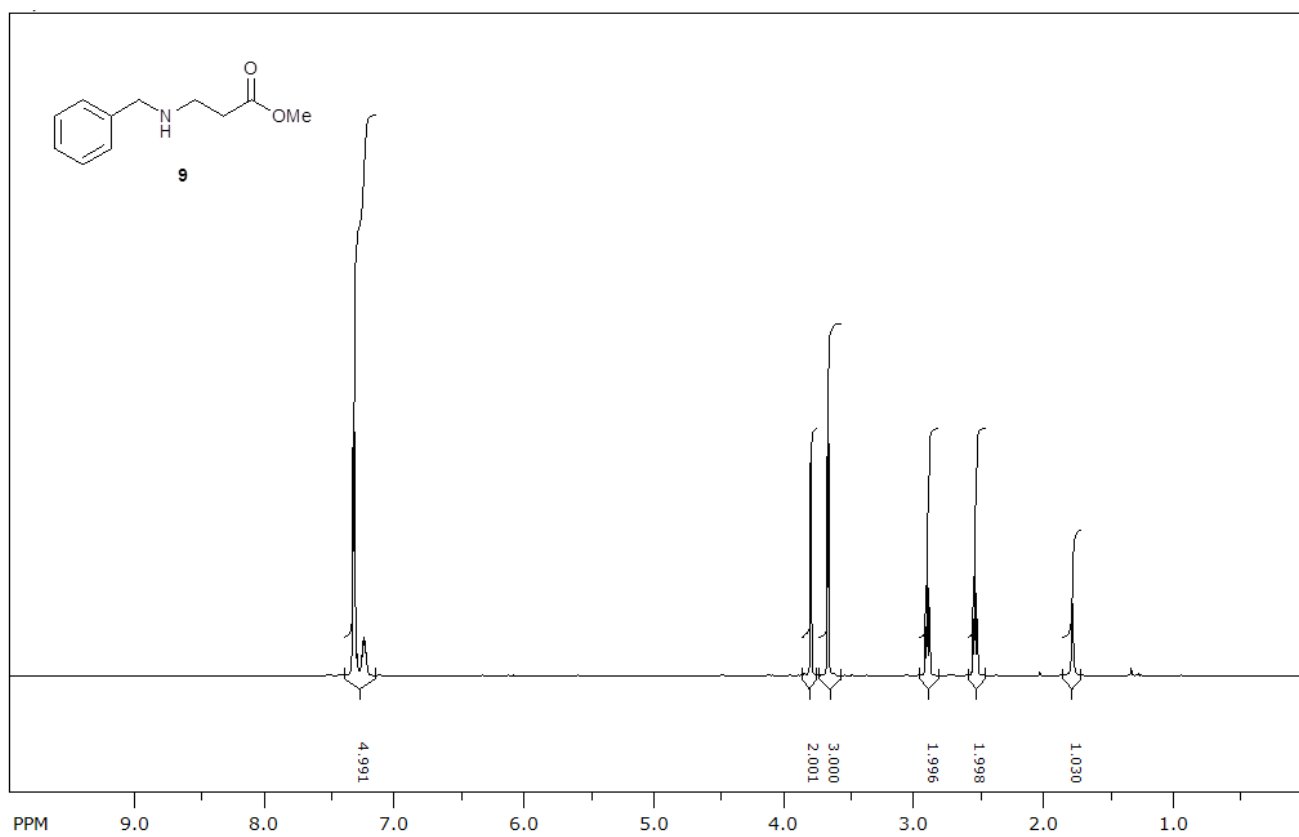
Reagents	MW	Density (g/mL)	Equivalents	Flow Rate (mL/min)	Flow Rate (mmol/min)
benzyl amine	107.15	0.981	1.00	1.07	9.80
methyl acrylate	86.09	0.956	1.06	0.93	10.3
diethylamine	73.14	0.707	1.00	0.86	8.31
methyl acrylate	86.09	0.956	1.50	1.13	12.5
1-pyrrolidino-1-cyclohexene	151.25	0.94	1.00	1.08	6.71
methyl acrylate	86.09	0.956	1.50	0.91	10.1

**Table SI3** Reagent flow rates for continuous flow microwave assisted Michael additions at a total flow rate of 5 mL/min

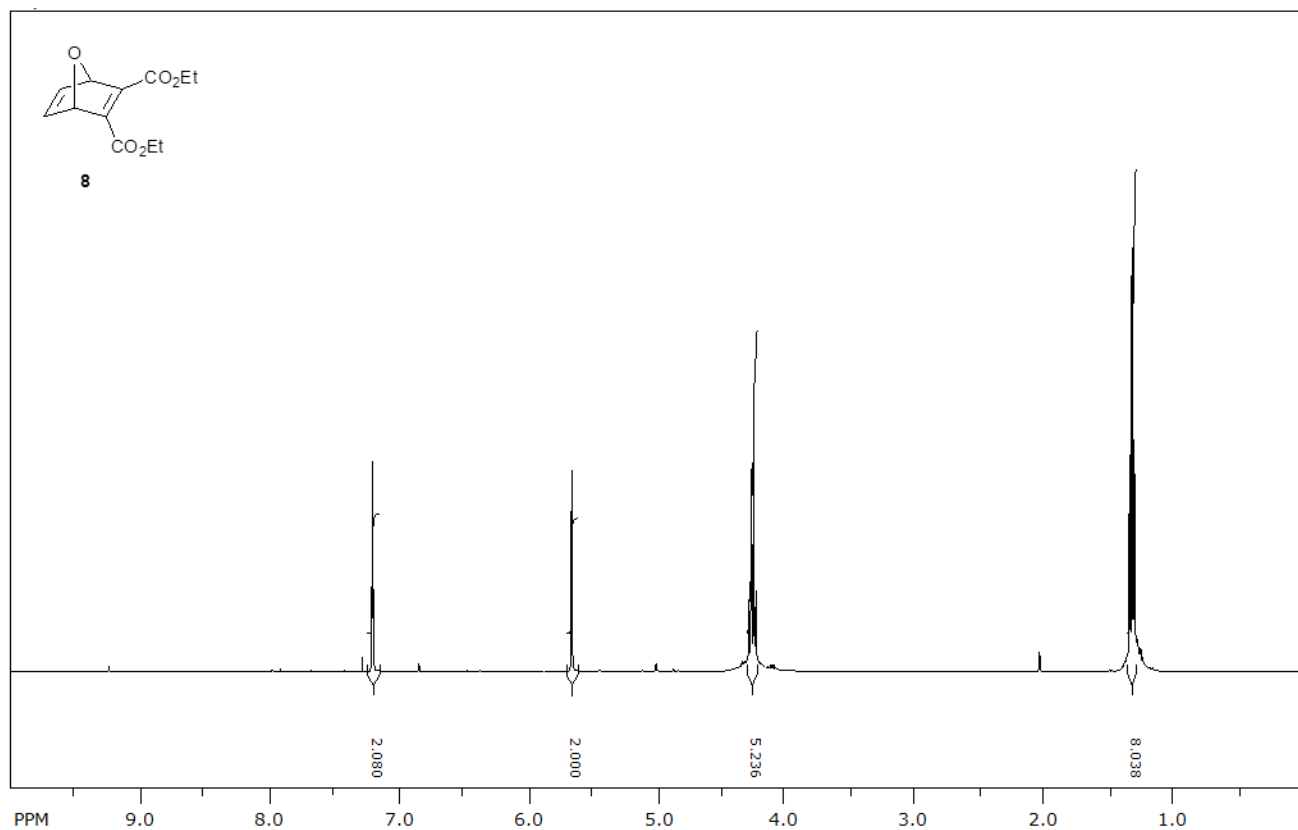
Reagents	MW	Density (g/mL)	Equivalents	Flow Rate (mL/min)	Flow Rate (mmol/min)
benzyl amine	107.15	0.981	1.00	2.67	24.4
methyl acrylate	86.09	0.956	1.06	2.32	25.8
diethylamine	73.14	0.707	1.00	2.16	20.9
methyl acrylate	86.09	0.956	1.50	2.83	31.4
1-pyrrolidino-1-cyclohexene	151.25	0.94	1.00	2.72	16.9
methyl acrylate	86.09	0.956	1.50	2.28	25.4

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## 5 SI References

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