

# Combining 3D printing and liquid handling to produce user-friendly reactionware for chemical synthesis and purification

Philip J. Kitson,<sup>a</sup> Mark D. Symes<sup>a</sup>, Vincenza Dragone<sup>a</sup> and Leroy Cronin<sup>\*a</sup>

## Electronic Supplementary Information

*WestCHEM, School of Chemistry, The University of Glasgow, Glasgow, G12 8QQ, UK;*

*E-mail: [Lee.Cronin@glasgow.ac.uk](mailto:Lee.Cronin@glasgow.ac.uk). Web: [www.croninlab.com](http://www.croninlab.com)*

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## 1. General Experimental Remarks.

All chemical reagents and solvents were purchased from Sigma Aldrich and used without further purification except for 1,2,3,4,5-pentamethylcyclopentadiene (94%), (Alfa Aesar) and the acetoxy-silicone polymer (LOCTITE<sup>®</sup> 5366 bathroom sealant, Loctite Corp.). Pd/C (10% b/w) was supplied by Lancaster.

**3D printing:** 3D printing was achieved on a Bits from Bytes (BfB) 3DTouch<sup>™</sup> 3 extruder 3D printer supplied by Bits from Bytes, and a Fab@Home Version 0.24 RC6 freeform fabricator assembled from a kit by the authors. Labware was designed digitally using Autodesk123D free CAD software distributed by Autodesk inc. (<http://www.123dapp.com/>) and uploaded to the freeform fabricator for printing.

**<sup>1</sup>H NMR & <sup>13</sup>C NMR:** <sup>1</sup>H NMR and crude <sup>13</sup>C NMR spectra were recorded on a Bruker Avance 400 MHz machine at 298 K, and chemical shifts are reported in ppm relative to residual solvent (multiplicities are given as s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, with coupling constants reported in Hz). Final product <sup>13</sup>C and two dimensional NMR spectra were recorded on a Bruker Avance III 500 MHz machine at 298K.

**Mass Spectrometry:** Mass spectra were obtained using a Q-trap, time-of-flight MS (MicroTOF-Q MS) instrument equipped with an electrospray (ESI) source supplied by Bruker Daltonics Ltd. All analysis was carried out in MeOH, collected in positive ion mode. The spectrometer was calibrated with the standard tune-mix to give a precision of ca.1.5 ppm in the region of m/z 100-3000.

## 2. Digital Design and Fabrication of Reactionware

### Design Software

The 3D-printed reactionware used in this work was designed on the freely distributed 3D CAD software Autodesk123D (<http://www.123dapp.com/>) although any 3D modeling / CAD software with the ability to export models in a .STL file format would suffice for this, and there are a number of suitable alternative free / open source candidates available on the internet.

### Device Design

#### General reactor design

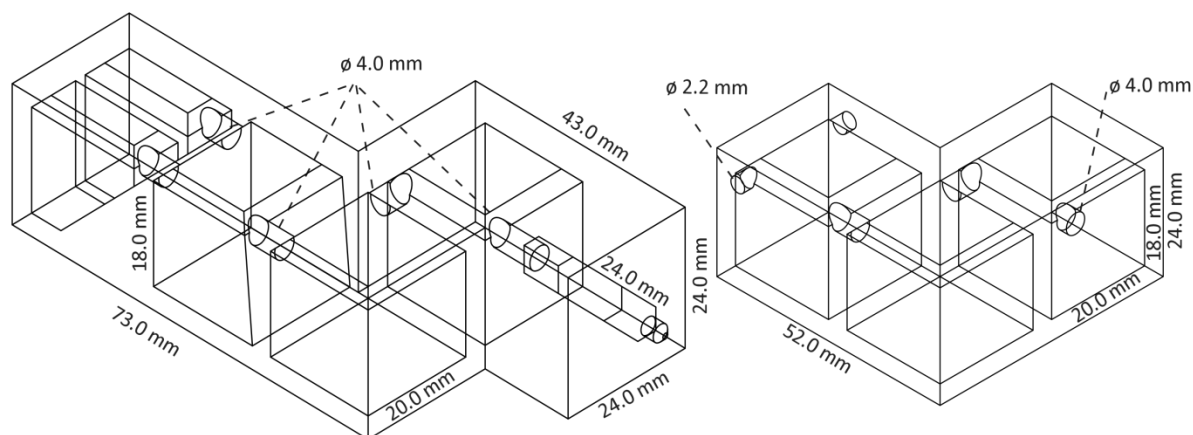
The devices used in this work were designed to provide three reaction chambers, one for each of the successive steps in the reaction sequence. The device design included the printing of active Lewis acid montmorillonite K10 and Pd/C catalysts in specially prepared 'ink' materials suitable for introduction into the reactor during the fabrication process by a 3D printing device. These catalytically active areas were present in the first (montmorillonite K10 Lewis acidic clay) and third (Pd/C 10%) reaction chambers of the designed device. The chambers were designed such that reactant transfer from chamber to chamber could be achieved by rotation of the reactor to allow gravity to pull the reaction mixture through. To allow this 4.0 mm internal channels between chambers were positioned so that through any of the envisioned 90° rotations of the device the reaction mixture would flow through only one of the available passages allowing the reaction to be controllably maneuvered through the reaction chambers of the device. The device design was achieved in two parts: one part representing the main architecture of the reactor, and a second part containing the regions into which the catalytically active inks were to be incorporated into the fabricated device.

#### Open and sealed reactor design

Two different reactors were envisioned and printed during the course of this work: an open reactor into which reactants and reagents can be introduced during the course of the synthetic procedure, and a sealed device in which all the necessary reactants and reagents are introduced during the fabrication of the reactor resulting in a self – contained reactor, including the incorporation of a short silica purification column. Whilst the key features of the two devices (*i.e.* the three reaction chambers for the three stages of the synthetic sequence) remained the same, the different intended purpose required two different architectures to be designed.

The open reactor required that there be openings in the initial chamber through which the initial starting materials could be injected, along with an opening in the final chamber for the subsequent retrieval of the crude product mixture once the synthesis was complete. To achieve this the initial chamber was designed with two 2.2 mm diameter openings on either side of the chamber through which starting materials and subsequent reagents could be introduced, and the final chamber was designed with a similar opening through which the final reaction mixture could be collected by a final 90° rotation of the device.

The sealed reactor required that provision be made in the design for chambers in which all the starting materials and subsequent reagents / solvents could be deposited during the printing process, but kept separate until the reaction was initiated by the user. To achieve this a section of the device was created to house two reactant chambers, oriented such that a rotation of 45° would induce the two reactant solutions contained within to flow together into the initial reaction chamber.



**Figure S1.** Diagram of the 3D-printed devices used for sequential organic synthesis, with dimensions.

## Device Fabrication

Both device design parts were exported from the design software as .STL files (available from the authors). The main architecture component .STL file was then interpreted by Bits from Bytes Axon 2 software which produces a 3D printer instruction file (.bfb file) which was subsequently transferred to the 3DTouch™ 3D printer. The catalyst areas' .STL file was interpreted by the Fab@Home software and transmitted to the Fab@Home Version 0.24 RC6 freeform fabricator. The main device architecture was printed using commercially available polypropylene in the form of 3 mm diameter welding rod which was automatically fed into the 3DTouch™ machine, and was suitably inert to the chemicals and conditions to be used in the subsequent experiments. After printing, the reactor was allowed to rest at room temperature for 12 hours to allow the complete curing of the silicone polymer mixture (see below) and the reactionware was repeatedly washed with distilled water until all traces of acetic acid (released during curing of the catalyst containing inks) had been removed and the reactor was subsequently dried under vacuum for 18h. Using this approach, we did not notice any serious adverse effects from acetic acid seepage into solution (which would lower the solution pH) during the subsequent reactions.

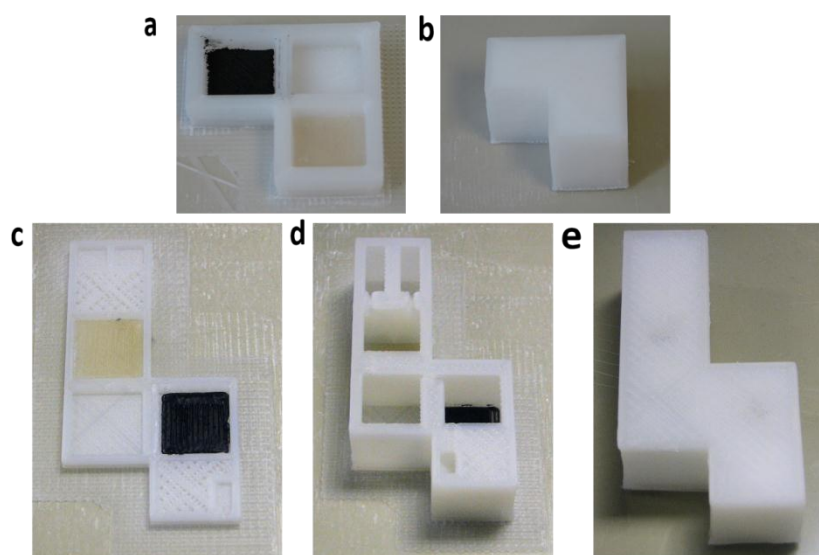
The printing was conducted in a layer-by-layer fashion by the 3DTouch™ printer with pre-programmed pauses in the printing process to allow the printing of the catalytically active regions by the Fab@Home device. During the pauses the partially printed device was transferred from the 3DTouch™ machine to the Fab@Home device, where the catalyst regions were deposited from 10 mL syringes *via* a tapered dispensing tip with an internal diameter of 0.838 mm.

Catalytic materials for printing were prepared by first thinning the silicone polymer with toluene (30% by mass) followed by the addition of the appropriate active material. The Pd/C reduction catalyst ink was obtained by mixing 0.5 g Pd/C (10% Pd w/w) with 6 g of a silicone / toluene mixture and the montmorillonite K10 Lewis acid catalyst was prepared by mixing 0.5 g montmorillonite K10 powder with 6 g of a similarly prepared silicone / toluene mixture. These mixtures gave pastes of sufficient viscosity to print in a similar manner to the original silicone polymer. The Fab@Home 3D printer utilized in this work was configured with two syringe tools which were filled with the appropriate printing materials, allowing the printer to deposit two materials without changing the device configuration. The printed (pre – curing) mass of catalyst – containing material is given in table ST1.

**Table ST1.** Mass of catalyst printed into reaction chambers of 3D printed reactionware:

Catalyst	Printed Mass (g)	Catalyst Mass (g)
Montmorillonite K10	0.419	0.035
10% Pd/C	0.230	0.019

Once printing of the catalytic regions was complete, a small magnetic stirrer bar was placed in each of the three reaction chambers and the partially printed device was returned to the 3DTouch™ printer and carefully aligned such that the printing of the reactor architecture was resumed in the same position in which the printing was paused so that the final device conformed to the initial CAD designs. During the printing of the sealed device, the printing was resumed after 24 hours to give the catalyst regions sufficient time to cure before the addition of reagents, and paused once again towards the end of the print program and returned to the Fab@Home 3D printer to allow the introduction of starting materials and other reagents into their appropriate chambers.



**Figure S2.** Photographs of the 3D printed reactors during the printing process. (a) Open reactor after printing of the catalytic regions. (b) Completed open reactor. (c) Sealed reactor after printing of the catalytic regions. (d) Sealed reactor after addition of reactants, reagents and packing of silica column. (e) Completed sealed reactor.

The printed devices conformed to the CAD design dimensions with less than 5% difference in any dimension, indicating a high degree of accuracy in the printing process.

### 3. General Procedure for Sequential Synthesis in the 3D printed Reactor

#### Open reactor

Solutions of acrolein (1 mmol, 56 mg, 47  $\mu$ L) and either 1,2,3,4-tetramethyl-1,3-cyclopentadiene (1 mmol, 122 mg, 99  $\mu$ L) or 1,2,3,4,5-pentamethylcyclopentadiene (1 mmol, 136 mg, 118  $\mu$ L) in chloroform (1 mL each) were simultaneously injected into the 3D printed multi-step reactor *via* the inlet ports designed into the initial reactor chamber. The reaction mixture was stirred in this initial chamber (in contact with the montmorillonite K10 Lewis acid catalyst region) for 5 hours.

The reactor was then rotated through 90° (see manuscript Figure 2) to allow the reaction mixture to flow into the second reaction chamber. In order to ensure maximum transference of reaction mixture into the second reaction chamber, the reactor was returned to its original orientation and a small aliquot of chloroform (0.5 mL) was added to the initial chamber *via* the inlet ports, where it was briefly stirred before being transferred into the second chamber. Once the Reactor was in its second orientation a solution of aniline (1 mmol, 93 mg, 95.1  $\mu$ L) in chloroform (1 mL) was injected into the reactor *via* one of the inlet ports and was allowed to flow directly into the second reaction chamber. The reaction was then allowed to stir for a further 2 hours to allow complete imine formation.

A mixture of triethyl silane (TES, 10 mmol, 1.16 g, 844  $\mu$ L) and methanol (0.875 mL) was then introduced *via* one of the initial inlet ports and allowed to flow directly into the second reaction chamber, where it mixed with the reaction mixture. This solution was then transferred to the third reaction chamber by a further 90° rotation of the reactor. Upon contact of the reaction mixture with the Pd/C in silicone catalyst, hydrogen gas was evolved. The reaction mixture was stirred in the final reaction chamber for 20 minutes before the reaction mixture was decanted by another 90° rotation of the reactor which allowed the reaction mixture to flow out of the outlet port designed into the final chamber. The final reaction chamber was washed with chloroform (3 x 2 mL) and the collected washings were combined with the final reaction mixture.

The solvent was then removed under vacuum and the crude product was purified by silica gel chromatography, eluting with 10% EtOAc-Hexane to give the product as a mixture of structural isomers.

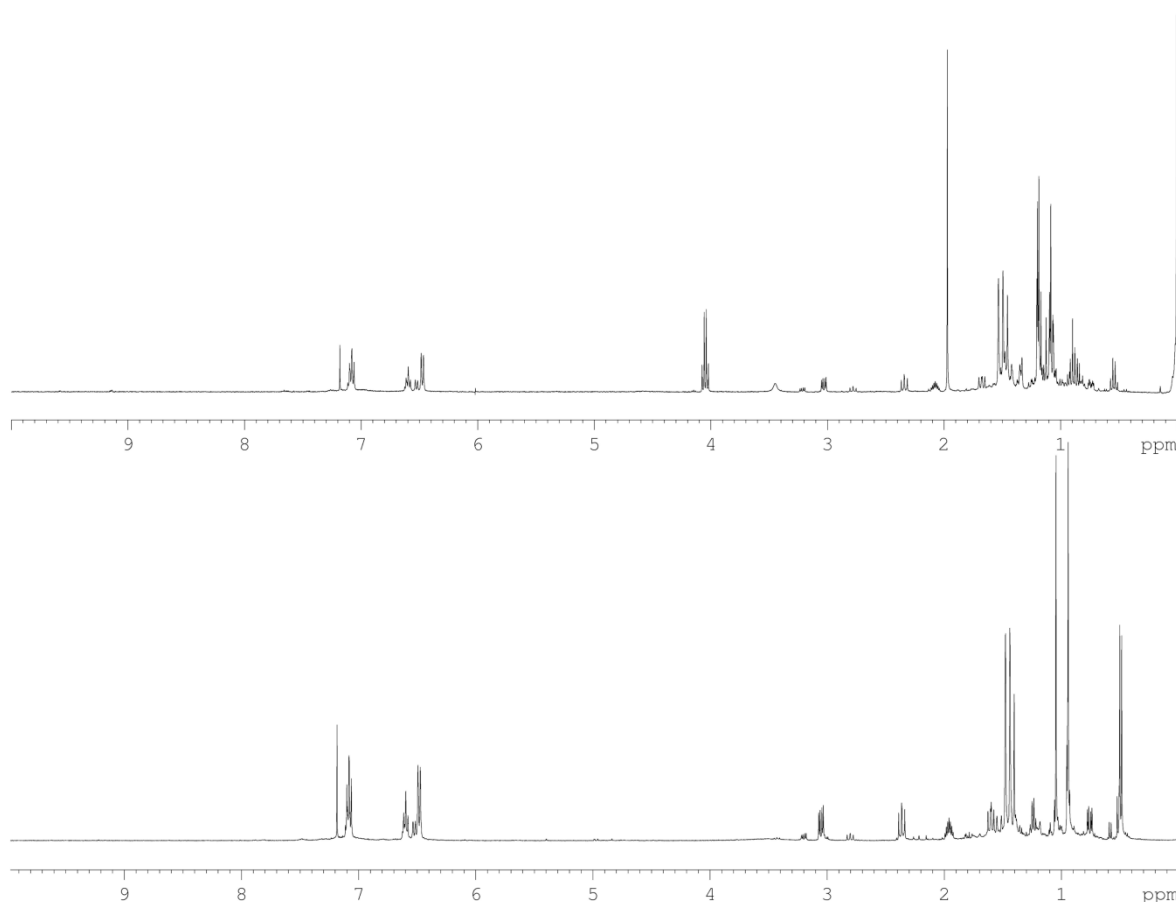
#### Sealed Reactor

During the reactor fabrication process solutions of acrolein (1 mmol, 56 mg, 47  $\mu$ L) and either 1,2,3,4-tetramethyl-1,3-cyclopentadiene (1 mmol, 122 mg, 99  $\mu$ L) or 1,2,3,4,5-pentamethylcyclopentadiene (1 mmol, 136 mg, 118  $\mu$ L) in 5% diethyl ether / hexane (0.750 mL each) were introduced into the starting material chambers of the sealed device and a mixture of the reagents necessary for the second and third reactions in the sequence, i.e. a solution of aniline (1mmol) in a mixture of TES (10 mmol) and MeOH (0.200 mL), were added into the second reaction chamber by the Fab@home 3D printer acting as a liquid handling robot.

The reaction sequence is initiated by the rotation of the reactor by 45° to induce the starting material solutions to flow into the initial reaction chamber. Thereafter a similar set of rotations to those described above are performed on the sealed reactor device to affect the desired reaction

sequence. Upon completion of the process the reaction mixture is retrieved by pushing a needle through the sealed opening at the bottom of the purification column and slowly drawing the reaction mixture through the built in purification column using a syringe. Once the initial reaction mixture had been collected a further aliquot of hexane (2 mL) was introduced to the third reaction chamber, which was subsequently drawn through the purification column and combined with the initial sample in order to maximise the yield of target compound.

The solvent was then removed under vacuum to give a purified sample of the product as a mixture of structural isomers. The purity of the obtained samples was calculated by  $^1\text{H}$  NMR by calculating the percentage contribution of the product signals to the total integral of the entire NMR spectrum (excluding identified solvent signals) giving sample purities obtained directly from the 3D printed reactionware of 78 and 82 % for compounds **3a** and **3b** respectively. This compares with sample purities of 92 and 97% for samples obtained from full column chromatography.



**Figure S3:**  $^1\text{H}$  NMR spectra of (top) purified sample of reaction product **3a** obtained from sealed reaction vessel, signals at 4.05 ppm and 1.96 ppm arise from impurities of TES incompletely removed under vacuum and (bottom) purified sample of reaction product **3b** obtained from sealed reaction vessel

#### 4. Traditional (Glassware) Procedure for Sequential Synthesis

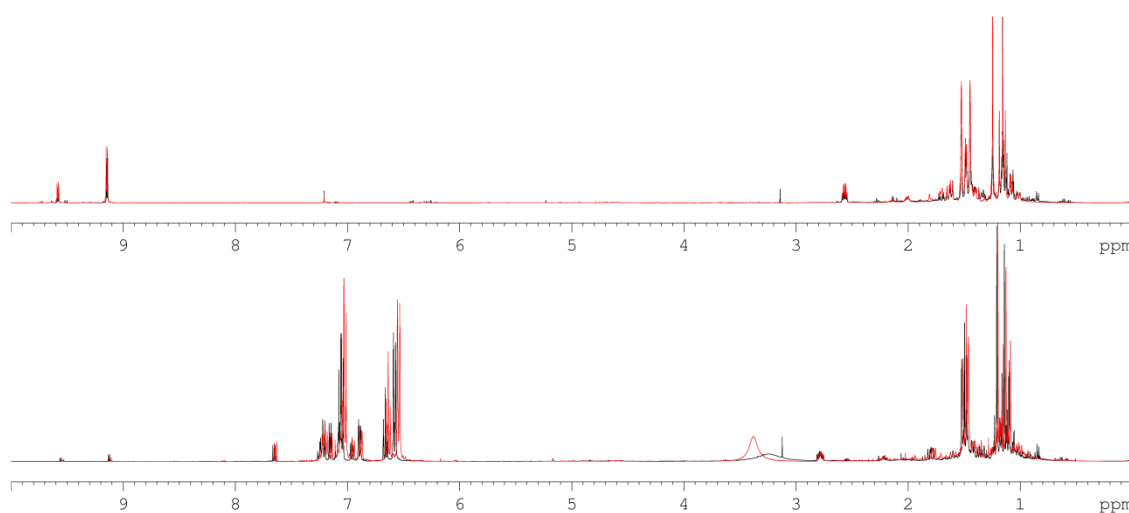
To a stirred solution of and either 1,2,3,4-tetramethyl-1,3-cyclopentadiene (1 mmol, 122 mg, 99  $\mu\text{L}$ ) or 1,2,3,4,5-pentamethylcyclopentadiene (1 mmol, 136 mg, 118  $\mu\text{L}$ ) in chloroform (1 mL) was added montmorillonite K10 (30 mg) followed by a solution of acrolein (1 mmol, 56 mg, 47  $\mu\text{L}$ ) in chloroform (1 mL). The reaction mixture was allowed to stir at room temperature for 5



hours. The reaction mixture was then filtered to remove the montmorillonite catalyst and the reaction mixture transferred to a new round bottomed flask, into which was added solution of aniline (1 mmol, 93 mg, 95.1  $\mu$ L) in chloroform (1 mL). The reaction mixture was then stirred for a further 2 hours to allow complete imine formation. To the stirred reaction mixture was then added 10% Pd/C (20 mg) followed by the addition of a mixture of triethyl silane (TES, 10 mmol, 1.16 g, 844  $\mu$ L) and methanol (0.875 mL). The reaction mixture was then stirred for 20 minutes, and the resulting reaction mixture filtered to remove the Pd/C catalyst. The solvent was then removed under vacuum and the crude product was purified by silica gel chromatography, eluting with 10% EtOAc-Hexane to give the product as a mixture of structural isomers (**3a**, yield: 102.8 mg 40.0% based on original starting materials; **3b**, yield 105.5 mg 38.9% based on original starting materials).

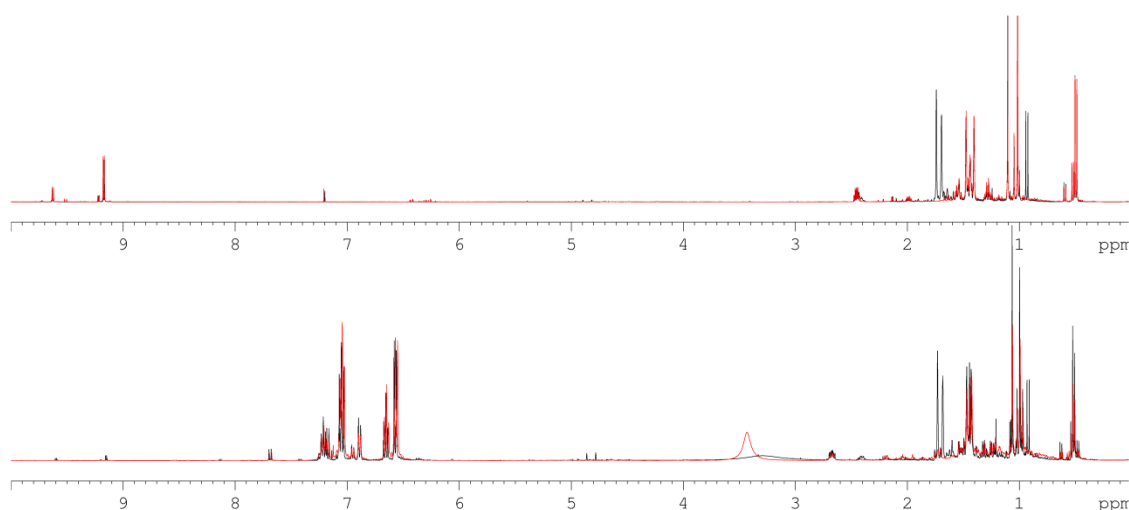
## 5. $^1\text{H}$ NMR Comparison of Glassware Vs. Printed reactor

In order to ascertain the suitability of 3D printed reactors for carrying out synthetically useful transformations it was necessary to compare the results of each stage in the reaction sequence with the corresponding stage in the traditionally carried out reaction procedure (i.e carried out in traditional glassware) The sequential reaction was followed by  $^1\text{H}$  NMR in a series of experiments carried out in accordance with the above general procedures in deuterated solvents where the reaction mixture at each stage of the synthesis was extracted from the reactor by pushing a needle through the side of the device and removing the contents.



**Figure S4:** Comparison of  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz) spectra of the crude Reaction Mixtures of compounds **1a** (top) and **2a** (bottom). Red spectra are of reaction mixtures obtained from 3D printed reactor, black spectra are of reaction mixtures at the equivalent stage in the sequence using traditional glassware.





**Figure S5:** Comparison of  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz) spectra of the crude Reaction Mixtures of compounds **1b** (top) and **2b** (bottom). Red spectra are of reaction mixtures obtained from 3D printed reactor, black spectra are of reaction mixtures at the equivalent stage in the sequence using traditional glassware. Extra peaks observed in the black spectra at approx. 0.9 ppm and 1.7 ppm result from an excess of starting material 1,2,3,4,5-pentamethylcyclopentadiene present in the initial reaction mixture.

## 6. Crude Reaction Mixture Analysis

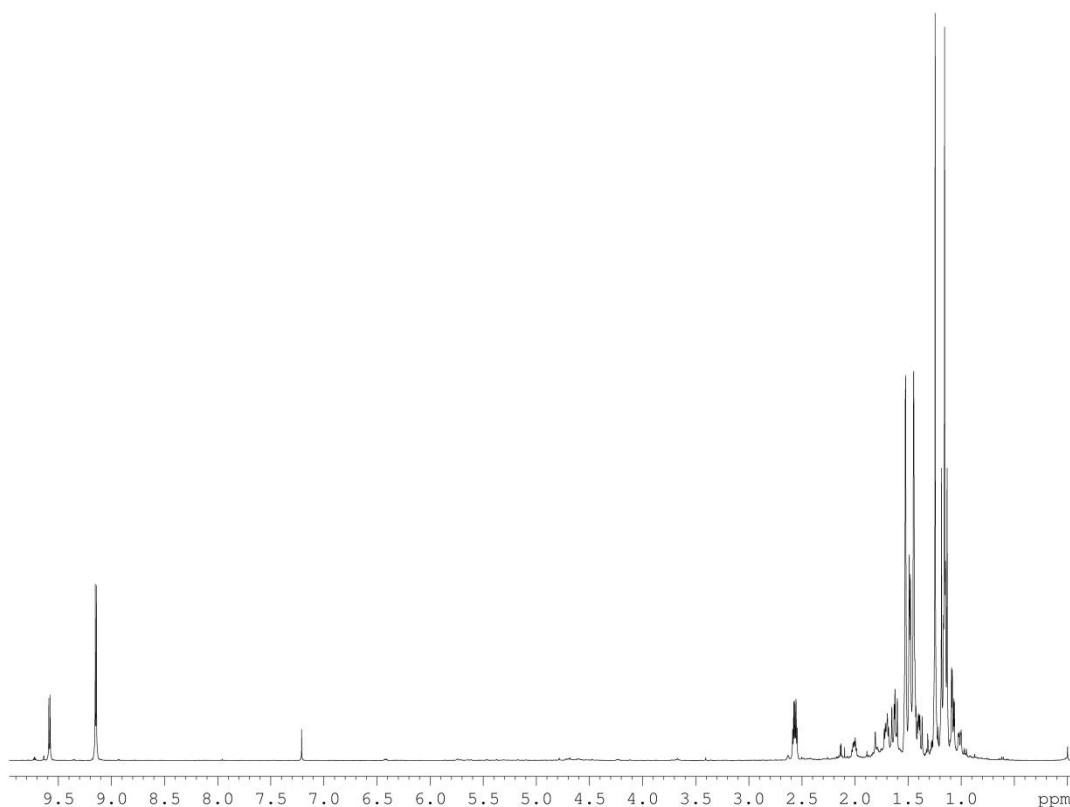
The products of reaction steps 1 and 2 (i.e. **1a,b** and **2a,b**) were not isolated and the crude reaction mixtures were analysed to ensure the reaction was proceeding as planned. Analysis of the crude reaction mixtures did not allow the unambiguous assignment of  $^{13}\text{C}$  NMR signals, and all signals assigned to the reaction products are given here.

### 1,4,5,6-Tetramethyl-bicyclo[2.2.1]hept-5-ene-2-carbaldehyde, $\text{C}_{12}\text{H}_{18}\text{O}$ (**1a**)



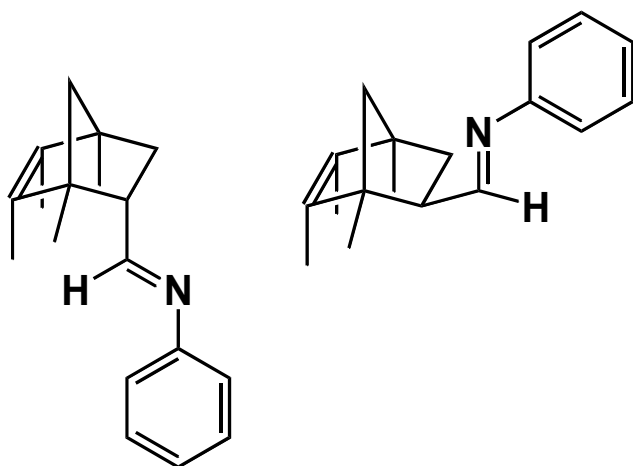
Major: Minor 1:0.37

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): (Major product):** δ 9.15 (d, 1H, *J*=4.2 Hz), 2.57 (dt, 1H, *J*<sub>1</sub>=8.8 Hz, *J*<sub>2</sub>=4.2 Hz), 1.60-1.65 (m, 2H), 1.53 (s, 3H), 1.45 (s, 3H), 1.37-1.41 (m, 2H), 1.25 (s, 3H), 1.16 (s, 3H). **(Minor product):** δ 9.58 (d, H, *J*=5.0 Hz), 1.99-2.03 (m, 1H), 1.69-1.73 (m, 2H), 1.49 (s, 3H), 1.48 (s, 3H), 1.33-1.39 (m, 2H), 1.19 (s, 3H), 1.13 (s, 3H). **<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): (Major + Minor products):** δ 8.9 (CH<sub>3</sub>), 9.3 (CH<sub>3</sub>), 9.6 (CH<sub>3</sub>), 11.2 (CH<sub>3</sub>), 15.4 (CH<sub>3</sub>), 16.7 (CH<sub>3</sub>), 17.0 (CH<sub>3</sub>), 17.2 (CH<sub>3</sub>), 25.9 (CH<sub>2</sub>), 30.7 (CH<sub>2</sub>), 36.2 (C<sub>q</sub>), 37.5 (C<sub>q</sub>), 50.9 (CH), 55.4 (CH<sub>2</sub>), 55.8 (CH), 60.8 (C<sub>q</sub>), 61.1 (CH<sub>2</sub>), 61.2 (C<sub>q</sub>), 134.4 (C=C), 137.5 (C=C), 138.4 (C=C), 140.3 (C=C), 205.5 (C-aldehyde), 205.7 (C-aldehyde).



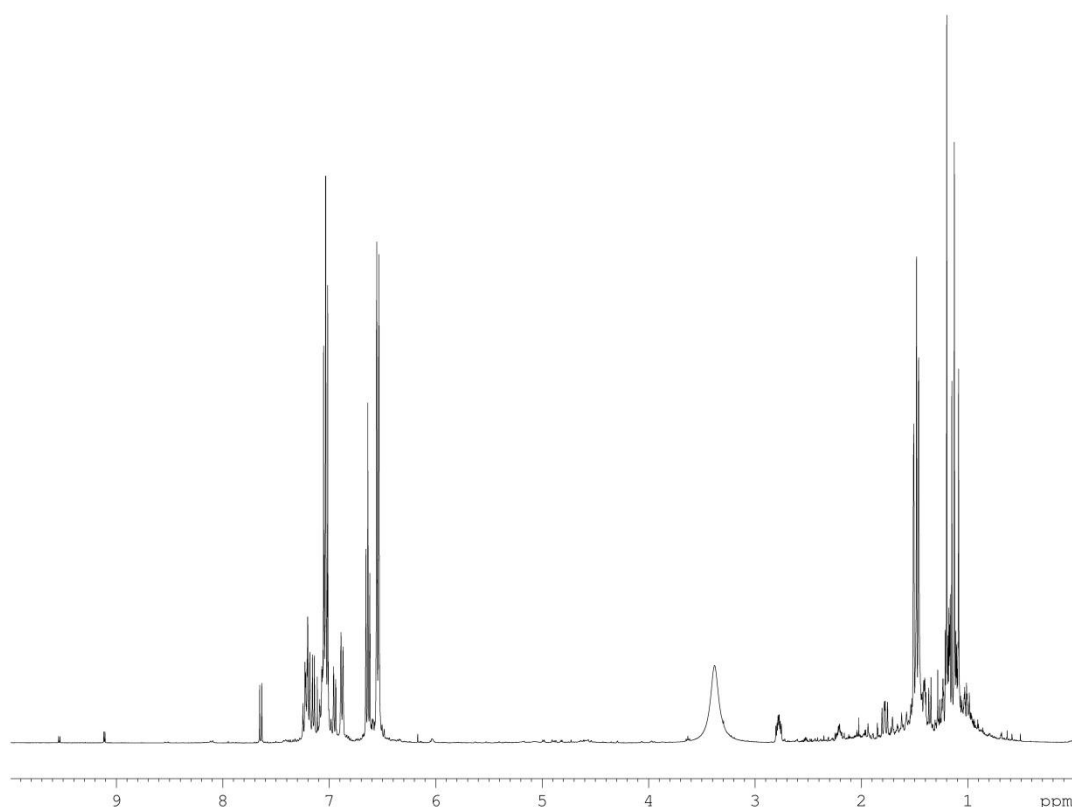
**Figure S6:** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) spectrum of the crude Reaction Mixture after reaction in the first reaction chamber, containing intermediate **1a**.

**Phenyl-(1,4,5,6-tetramethyl-bicyclo[2.2.1]hept-5-en-2-ylmethylene)-amine C<sub>18</sub>H<sub>23</sub>N (2a)**



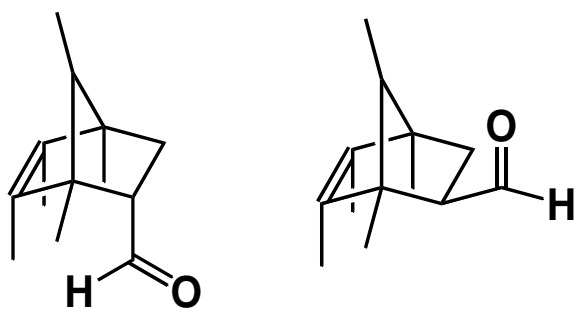
**Major: Minor 1:0.37**

**$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz): (Major product):**  $\delta$  7.39-7.26 (m, 5H), 6.99 (d, 1H,  $J = 7.9$  Hz), 2.69-2.64 (m, 1H), 2.91-2.86 (m, 4H), 1.61 (s, 3H), 1.59 (s, 3H), 1.32 (s, 3H), 1.28 (s, 3H).  
**(Minor product):**  $\delta$  7.77 (d, 1H,  $J = 7.8$  Hz), 7.39-7.26 (m, 5H), 2.55 – 2.50 (m, 1H), 2.91-2.86 (m, 4H), 1.64 (s, 3H), 1.56 (s, 3H), 1.26 (s, 3H), 1.21 (s, 3H).  **$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz): (Major + Minor product)**  $\delta$  9.2 ( $\text{CH}_3$ ), 9.9 ( $\text{CH}_3$ ), 11.5 ( $\text{CH}_3$ ), 12.5 ( $\text{CH}_3$ ), 16.2 ( $\text{CH}_3$ ), 17.0 ( $\text{CH}_3$ ), 17.1 ( $\text{CH}_3$ ), 17.9 ( $\text{CH}_3$ ), 39.7 ( $\text{CH}_2$ ), 40.8 ( $\text{CH}_2$ ), 50.7 (CH), 50.9 ( $\text{C}_q$ ), 51.9 ( $\text{C}_q$ ), 52.6 ( $\text{C}_q$ ), 55.5 ( $\text{C}_q$ ), 55.6 (CH), 56.3 ( $\text{CH}_2$ ), 60.7 ( $\text{CH}_2$ ), 114.7 (C=C), 115.8 (C=C), 118.4 (C=C), 119.0 (C=C), 120.6 (CH-Ar), 120.8 (CH-Ar), 125.3 (CH-Ar), 125.4 (CH-Ar), 129.5 (CH-Ar), 129.7 (CH-Ar), 139.5 (CH-Ar), 134.9 (CH-Ar), 140.4 (CH-Ar), 140.6 (CH-Ar), 152.3 ( $\text{C}_q$ -Ar), 152.4 ( $\text{C}_q$ -Ar), 170.6 (C-Imine), 170.8 (C-Imine).



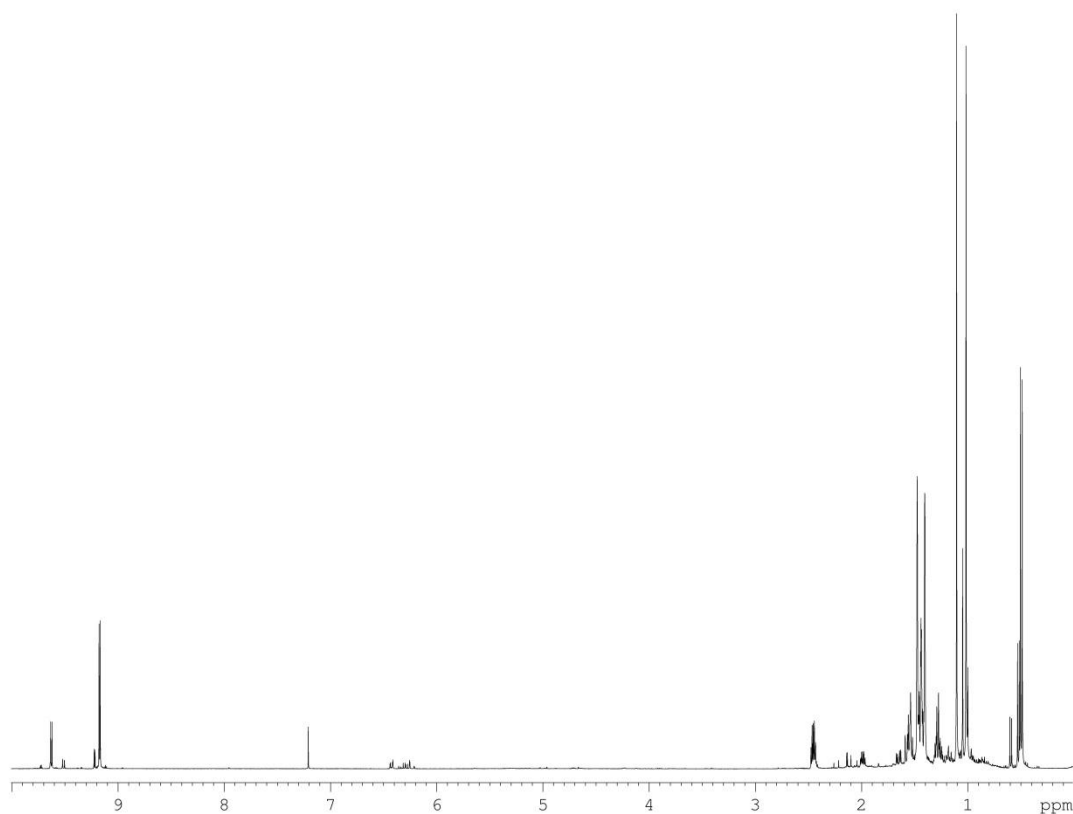
**Figure S7:**  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz) spectrum of the crude Reaction Mixture after reaction in the second reaction chamber, containing intermediate **2a**, along with unreacted aniline.

**1,4,5,6,7-Pentamethyl-bicyclo[2.2.1]hept-5-ene-2-carbaldehyde,  $\text{C}_{13}\text{H}_{20}\text{O}$ , (**1b**)**



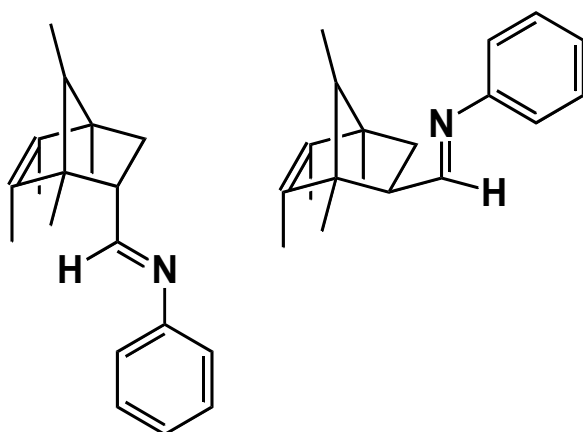
**Major: Minor 1:0.2**

**$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz): (Major product):**  $\delta$  9.17 (d, 1H,  $J = 4.2$  Hz), 2.45 (dt, 1H,  $J_1 = 4.2$  Hz,  $J_2 = 8.6$  Hz), 1.56 (d, 2H,  $J = 8.6$  Hz), 1.48 (s, 3H), 1.41 (s, 3H), 1.28 (q, 1H,  $J = 6.4$  Hz), 1.11 (s, 3H), 1.02 (s, 3H), 0.50 (d, 3H,  $J = 6.4$  Hz); **(Minor product):**  $\delta$  9.63 (d, 1H,  $J = 4.6$  Hz), 2.45 (dt, 1H,  $J_1 = 4.6$  Hz,  $J_2 = 8.9$  Hz), 1.58 (d, 2H,  $J = 8.9$  Hz), 1.44 (s, 3H), 1.43 (s, 3H), 1.29 (q, 1H,  $J = 6.5$  Hz), 1.11 (s, 3H), 1.05 (s, 3H), 0.53 (d, 3H,  $J = 6.5$  Hz).  **$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz): (Major + Minor product)**  $\delta$  7.2 ( $\text{CH}_3$ ), 7.9 ( $\text{CH}_3$ ), 9.4 ( $\text{CH}_3$ ), 9.9 ( $\text{CH}_3$ ), 10.1 ( $\text{CH}_3$ ), 11.7 ( $\text{CH}_3$ ), 13.5 ( $\text{CH}_3$ ), 14.1 ( $\text{CH}_3$ ), 14.7 ( $\text{CH}_3$ ), 15.1 ( $\text{CH}_3$ ), 36.3 ( $\text{CH}_2$ ), 37.4 ( $\text{CH}_2$ ), 52.7 (CH), 56.3 ( $\text{C}_q$ ), 56.9 ( $\text{C}_q$ ), 58.6 (CH), 61.0 (CH), 61.7 ( $\text{C}_q$ ), 61.9 ( $\text{C}_q$ ), 62.2 (CH), 130.7 (C=C), 134.8 (C=C), 136.6 (C=C), 137.3 (C=C), 206.3 (C-aldehyde), 206.5 (C-aldehyde).



**Figure S8:**  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz) spectrum of the crude Reaction Mixture after reaction in the first reaction chamber, containing intermediate **1b**.

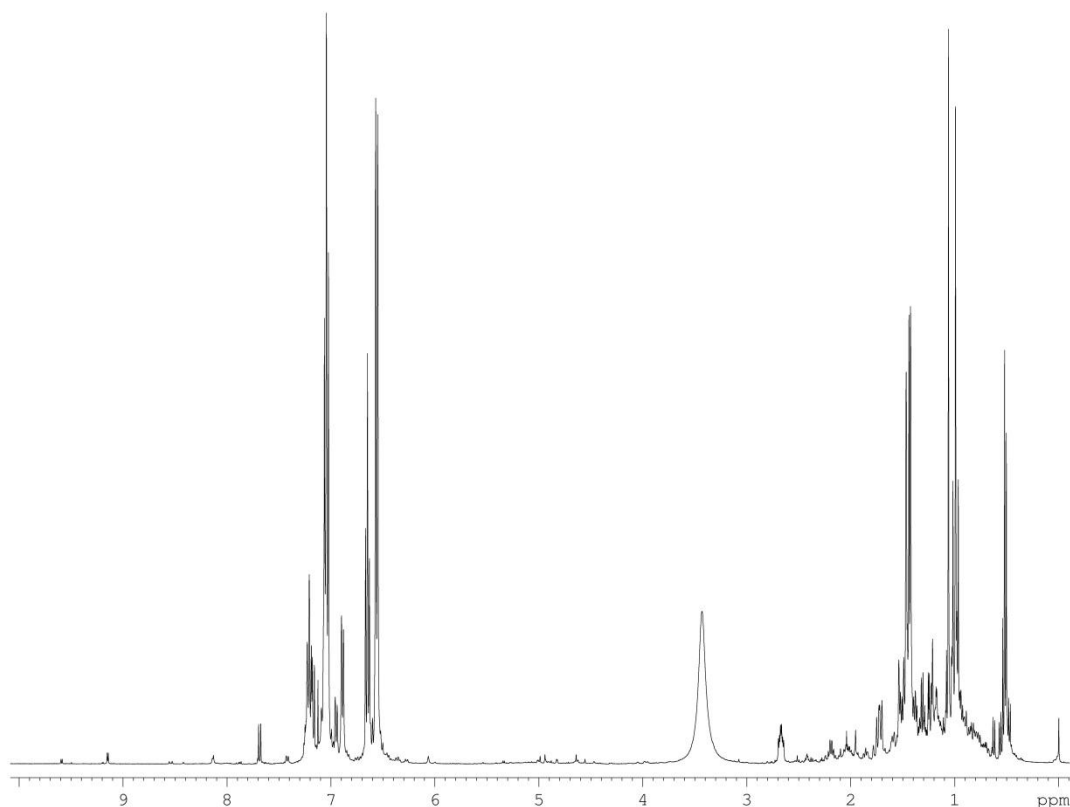
(1,4,5,6,7-Pentamethyl-bicyclo[2.2.1]hept-5-en-2-ylmethylene)-phenyl-amine,  $\text{C}_{19}\text{H}_{25}\text{N}$ ,  
(**2b**)



**Major: Minor 1:0.2**

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz): (**Major product**):  $\delta$  7.83 – 7.28 (m, 5H), 7.00 (d, 1H,  $J = 8.0$  Hz), 2.65 (dt, 1H,  $J_1 = 8.0$  Hz,  $J_2 = 8.7$  Hz), 1.76 (d, 2H,  $J = 8.7$  Hz), 1.56 (s, 3H), 1.28 (s, 3H), 1.44 (q, 1H,  $J = 6.5$  Hz), 1.18 (s, 3H), 1.12 (s, 3H), 0.63 (d, 3H,  $J = 6.5$  Hz). (**Minor product**):  $\delta$  7.81 (d,

1H,  $J = 8.0$  Hz), 7.83 – 7.28 (m, 5H, Ar), 2.29 (q, 1H,  $J = 6.26$  Hz), 2.22 – 2.15 (m, 1H), 1.79 (d, 2H,  $J = 8.3$  Hz), 1.59 (s, 3H), 1.55 (s, 3H), 1.14 (s, 3H), 1.09 (s, 3H), 0.65 (d, 3H,  $J = 6.3$  Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz): (Major product)  $\delta$  7.8 ( $\text{CH}_3$ ), 7.9 ( $\text{CH}_3$ ), 8.0 ( $\text{CH}_3$ ), 8.1 ( $\text{CH}_3$ ), 9.5 ( $\text{CH}_3$ ), 9.7 ( $\text{CH}_3$ ), 14.9 ( $\text{CH}_2$ ), 15.4 ( $\text{CH}_2$ ), 40.55 ( $\text{CH}_3$ ), 44.2 ( $\text{CH}_3$ ), 53.4 (CH), 53.6 ( $\text{CH}_3$ ), 55.1 ( $\text{CH}_3$ ), 58.4 (CH), 57.1 (CH), 58.9 (CH), 61.1 ( $\text{C}_q$ ), 61.4 ( $\text{C}_q$ ), 61.8 ( $\text{C}_q$ ), 62.1 ( $\text{C}_q$ ), 114.5 (C=C), 114.7 (C=C), 115.7 (C=C), 115.8 (C=C), 120.4 (CH-Ar), 120.5 (CH-Ar), 120.7 (CH-Ar), 120.9 (CH-Ar), 125.3 (CH-Ar),  $\delta$  125.4 (CH-Ar), 129.5 (CH-Ar), 129.7 (CH-Ar), 135.2 (CH-Ar), 136.5 (CH-Ar), 152.3 ( $\text{C}_q$ -Ar), 152.4 ( $\text{C}_q$ -Ar), 170.7 (C-Imine), 170.8 (C-Imine).

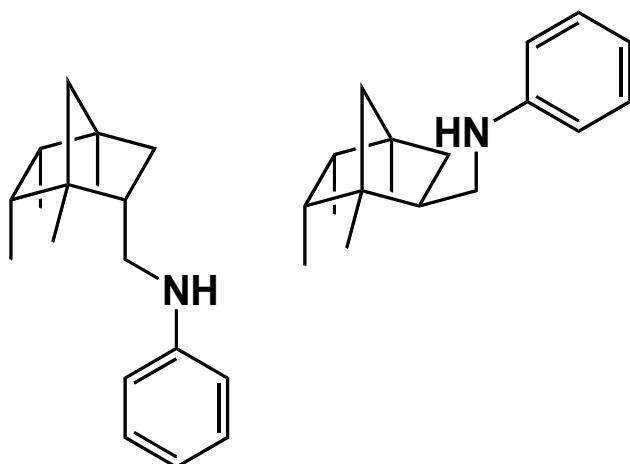


**Figure S9:**  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz) spectrum of the crude Reaction Mixture after reaction in the second reaction chamber, containing intermediate **2b**, along with unreacted aniline.

## 7. Final Product Analysis

In both cases the  $^1\text{H}$  NMR signals arising from the N-H of the minor product could not be identified due to the low intensity of the signal and masking from the major product N-H signal.  $^{13}\text{C}$  NMR signals were assigned to the major and minor products by relative signal intensity and 2D HSQC and HMBC experiments.

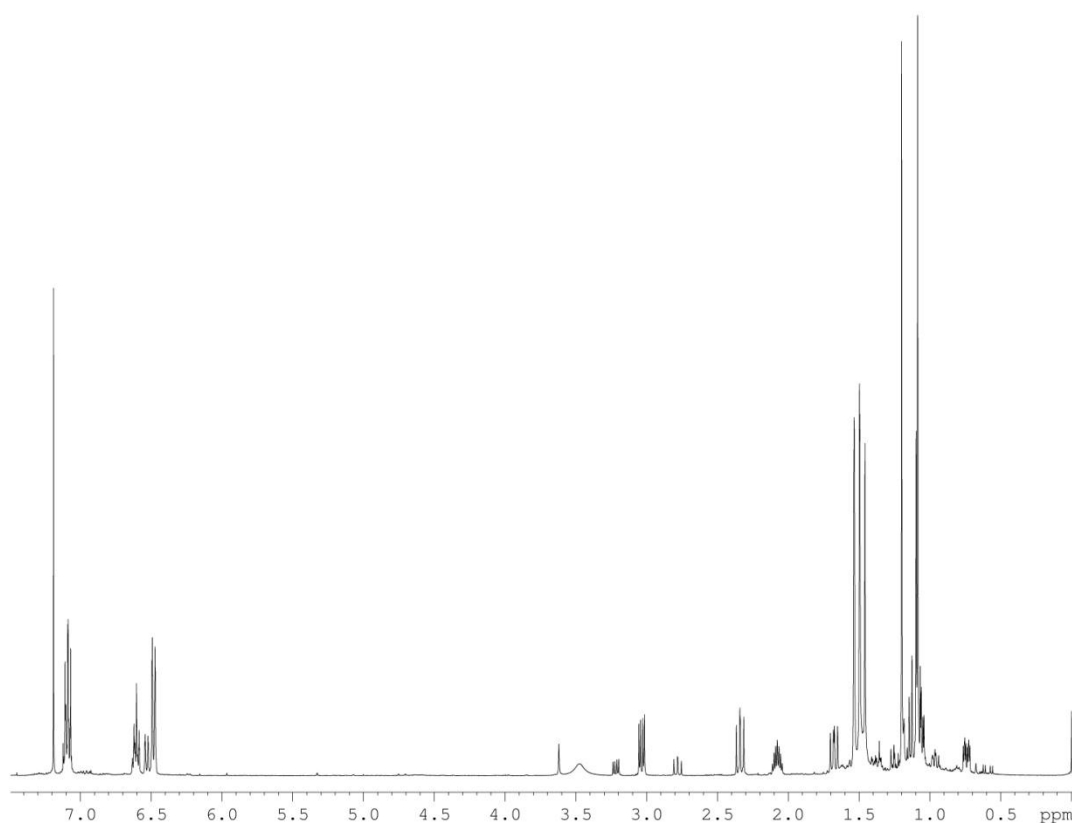
**Phenyl-(1,4,5,6-tetramethyl-bicyclo[2.2.1]hept-2-ylmethyl)-amine,  $\text{C}_{18}\text{H}_{27}\text{N}$  (**3a**)**



**Major: Minor; 1:0.30**

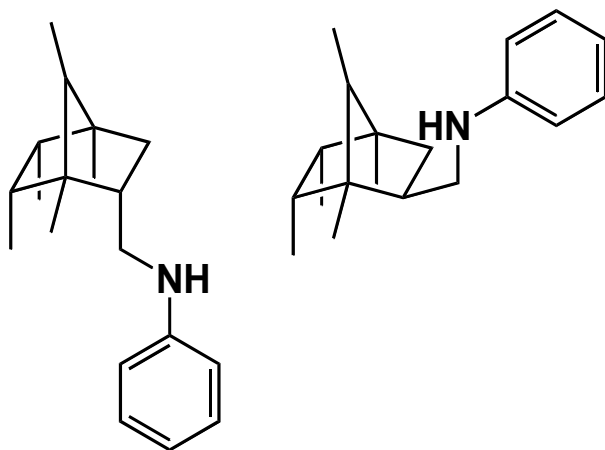
**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): (Major product):**  $\delta$  7.19 - 7.16 (m, 2H) 6.71 (tt, 1H,  $J_1=7.2$  Hz  $J_2=1.0$  Hz), 6.56 (dt, 2H,  $J_1=8.5$  Hz  $J_2=1.0$  Hz), 3.4 (broad s, 1H), 3.14 (dd, 1H,  $J_1=11.0$  Hz  $J_2=4.6$  Hz), 2.44 (dd, 1H,  $J_1=11.0$  Hz  $J_2=9.9$  Hz), 2.22-2.15 (m, 1H), 1.79 (m, 1H),  $\delta$  1.64 (d, 3H,  $J=1.0$  Hz), 1.60 (d, 3H,  $J=1.0$ ), 1.31 (s, 3H), 1.23-1.21 (m, 2H), 1.19 (s, 3H), 1.18-1.16 (m, 1H), 1.09-1.04 (m, 1H), 0.87-0.83 (m, 1H). **(Minor product):**  $\delta$  7.21 - 7.19 (m, 2H) 6.72 (tt, 1H,  $J_1=7.3$  Hz  $J_2=1.1$  Hz), 6.64 (dt, 2H,  $J_1=8.6$  Hz  $J_2=1.0$  Hz), 3.32 (dd, 1H,  $J_1=11.0$  Hz  $J_2=5.0$  Hz), 2.90 (dd, 1H,  $J_1=11.1$  Hz  $J_2=10.1$  Hz), 1.75 - 1.70 (m, 1H), 1.61 - 1.60 (m, 3H), 1.63 - 1.58 (m, 3H), 1.56 (s, 3H), 1.52 - 1.47 (m, 1H), 1.46 - 1.45 (m, 1H), 1.38 - 1.35 (m, 1H), 1.26 - 1.24 (m, 1H), 1.20 (s, 3H), 1.15 - 1.13 (m, 1H), 0.95 - 0.90 (m, 1H); **<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): (Major product)**  $\delta$  9.2 (CH<sub>3</sub>), 11.9 (CH<sub>3</sub>), 16.6 (CH<sub>3</sub>), 17.7 (CH<sub>3</sub>), 40.5 (CH<sub>2</sub>), 42.3 (CH), 47.4 (CH<sub>2</sub>), 48.9 (CH), 49.7 (C<sub>q</sub>), 53.1 (C<sub>q</sub>), 61.3 (CH<sub>2</sub>), 61.6 (CH), 112.6 (CH-Ar), 117.0 (CH-Ar), 129.1 (CH-Ar), 135.2 (C<sub>q</sub>-Ar). **(Minor product)**  $\delta$  9.0 (CH<sub>3</sub>), 9.4 (CH<sub>3</sub>), 15.0 (CH<sub>3</sub>), 17.7 (CH<sub>3</sub>), 42.2 (CH<sub>2</sub>), 44.8 (CH), 48.1 (CH<sub>2</sub>), 49.9 (C<sub>q</sub>), 52.5 (C<sub>q</sub>), 55.3 (CH<sub>2</sub>), 55.7 (CH), 64.6 (CH), 112.7 (CH-Ar), 117.1 (CH-Ar), 129.2 (CH-Ar), 135.7 (C<sub>q</sub>-Ar). **HMRS (MH<sup>+</sup>) calcd. for C<sub>18</sub>H<sub>28</sub>N:** 258.2216, **found:** 258.2240. **Isolated yield:** Open reactor: 96.2 mg (37.4%, based on original starting materials), Sealed Reactor: 82.0 mg (31.9%, based on original starting materials).





**Figure S10:**  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz) spectrum of product **3a**

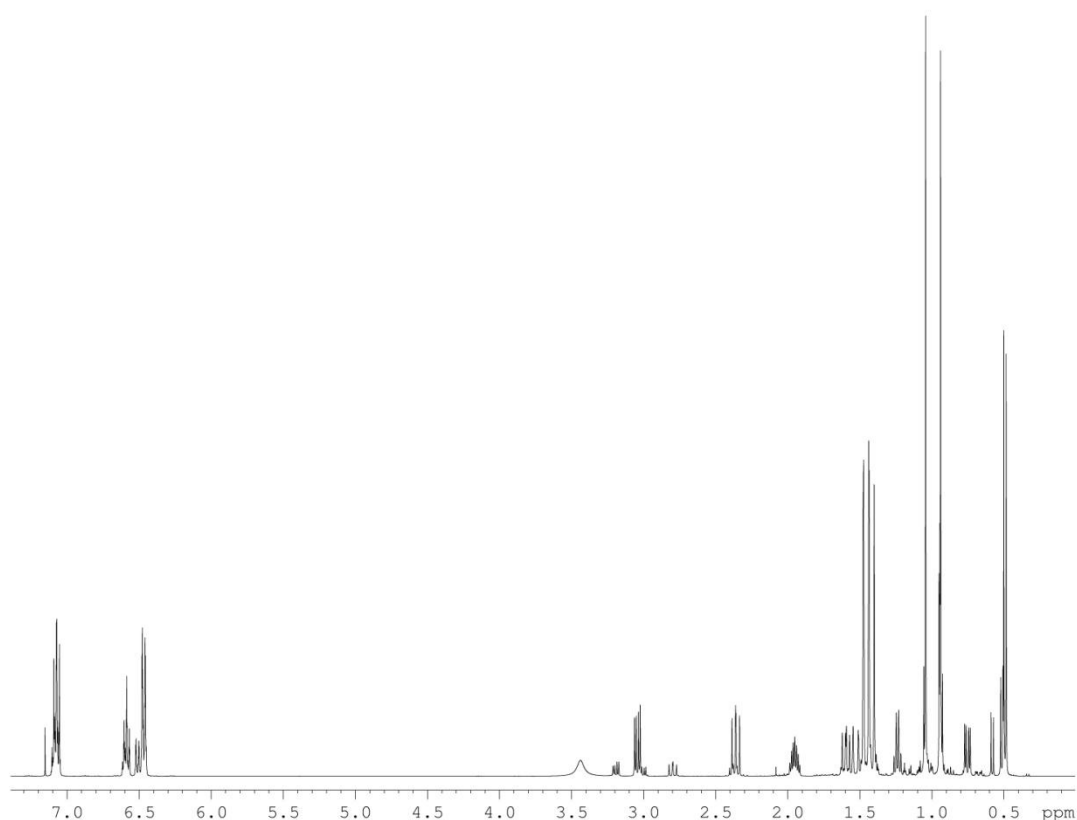
(1,4,5,6,7-Pentamethyl-bicyclo[2.2.1]hept-2-ylmethyl)-phenyl-amine,  $\text{C}_{19}\text{H}_{29}\text{N}$ , (**3b**)



**Major: Minor; 1:0.2**

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz): (**Major product**)  $\delta$  7.10 – 7.06 (m, 2H), 6.59 (tt, 1H,  $J_1=7.3$ ,  $J_2=1.0$  Hz), 6.48 (dt, 2H,  $J_1=8.6$ ,  $J_2=1.0$  Hz), 3.4 (broad s, 1H), 3.05 (dd, 1H,  $J_1=11.0$ ,  $J_2=4.6$  Hz), 2.38 – 2.34 (m, 1H), 1.99 – 1.94 (m, 1H), 1.63 – 1.58 (m, 1H), 1.56 – 1.51 (m, 1H), 1.48 (d, 3H,  $J=1.0$  Hz), 1.44 (d, 3H,  $J=1.2$  Hz), 1.43 – 1.40 (m, 1H), 1.24 (q, 1H,  $J=6.4$  Hz), 1.05 (s, 3H), 0.98 – 0.93 (m, 1H), 0.94 (s, 3H), 0.50 (d, 3H,  $J=6.4$  Hz). (**Minor product**)  $\delta$  7.11 – 7.08 (m, 2H), 6.60 (dt, 1H,  $J_1=7.3$ ,

$J_2=1.1$  Hz), 6.52 (dt, 2H,  $J_1=8.6$ ,  $J_2=1.1$  Hz), 3.20 (dd, 1H,  $J_1=11.3$ ,  $J_2=5.0$  Hz), 3.01 (dd, 1H,  $J_1=11.1$ ,  $J_2=4.1$ ), 2.83 – 2.78 (m, 1H), 2.41 – 2.36 (m, 1H), 1.77 – 1.73 (m, 1H), 1.48 – 1.47 (m, 3H), 1.43 – 1.44 (m, 3H), 1.39 – 1.37 (m, 1H), 1.21 – 1.18 (m, 1H), 1.06 (s, 3H), 0.96 (s, 3H), 0.68 – 0.64 (m, 1H), 0.52 (d, 3H,  $J=4.5$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz): (Major product)  $\delta$  7.8 ( $\text{CH}_3$ ), 9.6, ( $\text{CH}_3$ ), 9.7 (CH), 12.2 ( $\text{CH}_3$ ), 14.8 (CH), 14.3 ( $\text{CH}_3$ ), 15.4 ( $\text{CH}_3$ ), 40.6 ( $\text{CH}_2$ ), 47.1 ( $\text{CH}_2$ ), 48.6 (CH), 52.5 ( $\text{C}_q$ ), 55.9 ( $\text{C}_q$ ), 61.8 (CH), 112.7 (CH-Ar), 117.0 (CH-Ar) 129.1 (CH-Ar), 134.9 ( $\text{C}_q$ -Ar). (Minor product)  $\delta$  8.0 ( $\text{CH}_3$ ), 9.3( $\text{CH}_3$ ), 9.4 (CH), 12.04 (CH), 12.8 ( $\text{CH}_3$ ), 13.8 ( $\text{CH}_3$ ), 15.3 ( $\text{CH}_3$ ), 42.1 ( $\text{CH}_2$ ), 45.6 (CH), 47.6 ( $\text{CH}_2$ ), 52.6 ( $\text{C}_q$ ), 55.2 ( $\text{C}_q$ ), 61.7 (CH), 112.8 (CH-Ar), 117.1 (CH-Ar), 129.1 (CH-Ar), 135.3 ( $\text{C}_q$ -Ar). HMRS ( $\text{MH}^+$ ) calcd. for  $\text{C}_{19}\text{H}_{29}\text{N}$ : 272.2373, found: 272.2399. Isolated yield: Open Reactor: 85.0 mg (31.3%, based on original starting materials), Sealed Reactor: 78.5 mg (28.9%, based on original starting materials)



**Figure S11:**  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz) spectrum of product **3b**