Supporting Information

Dynamic flow synthesis of porous organic cages

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Materials. 1,3,5-Triformylbenzene was purchased from Manchester Organics, (1R,2R)-(−)-1,2-cyclohexanediamine was purchased from TCI-UK, and ethylene diamine and TFA were purchased from Sigma Aldrich. All solvents were purchased from Fisher. All chemicals were used as received.

Nuclear Magnetic Resonance (NMR) Spectroscopy. Solution 1H and 13C NMR spectra were recorded at 400 MHz and 101 MHz respectively using a Bruker Avance 400 NMR spectrometer at ambient probe temperature. Chemical shifts are reported in ppm (δ) with reference to internal residual protonated species of the deuterated solvent used for 1H and 13C analysis.

Analytical HPLC. HPLC data was obtained using a Dionex UltiMate 3000 system. The column used for the analysis of CC1, CC3, and the scrambled cage reactions was a Thermo Scientific Syncronis C8, 150 x 4.6 mm, 3 μm (97203-154630, 12475). The mobile phase was isocratic methanol at a flow rate of 1 mL/min. The column oven temperature was set to 30 °C. Detection for HPLC analysis was conducted at 254 nm.

Preparative HPLC. The column used to purify the desymmetrised cage CC135 was a Thermo Scientific Syncronis C8, 150 x 50 mm, 5 μm (97205-159370, 12105). The mobile phase was methanol at a flow rate of 40 mL/min. The column oven temperature was set to 30 °C. The injection volume was 700 μL and the sample concentration was 100 mg/mL in chloroform. Detection for HPLC UV analysis was conducted at 254 nm.

Liquid Chromatography Mass Spectrometry (LCMS). LCMS was conducted on an Agilent Technologies 6530B system using a Thermo Scientific Syncronis C8 column, 150 x 4.6 mm, 3 μm (97203-154630, 12459), with mass detection using an accurate-mass QTOF Dual ESI mass spectrometer (capillary voltage 4000 V, fragmentor 225 V) in positive-ion detection mode. The mobile phase was isocratic methanol containing 0.1% formic acid at a flow rate of 0.75 mL/min for a 15 minute run time.
**Thermogravimetric Analysis (TGA).** Thermogravimetric analysis was carried out using a Q5000IR analyser (TA instruments) with an automated vertical overhead thermobalance. The sample was heated under nitrogen at a rate of 5 °C/min.

**Fourier Transform Infrared Spectroscopy (FTIR).** IR spectra were recorded using a Bruker Tensor 27 FT-IR spectrometer with Quest ATR (diamond crystal puck) attachment running Opus 6.5 software. Samples were analysed as dry powders for 16 scans with a resolution of 4 cm⁻¹. Spectra were recorded in transmission mode.

**Flow equipment:** Flow reactions were performed on a Vapourtec R-Series Integrated Flow Chemistry System (commercially available, http://www.vapourtec.co.uk). The reactor coils and tubing were PTFE and supplied by Vapourtec. Back-pressure regulators (BPRs) were obtained from Vapourtec.
Figure S1  Schematic of cage-cage packing in the crystal structures in CC1α and CC3α. a, CC1α packs in a window-to-arene fashion. These window-to-arene ‘stacks’ are arranged in a pseudo-hexagonal manner resulting in isolated void volume, as illustrated here in orange. b, CC3α is directed by the cyclohexyl groups (red) to pack window-to-window, thus generating an interconnected diamondoid pore network, as illustrated here in yellow.1
**CC3 Batch Synthesis**

For **CC3-R**, dichloromethane (100 mL) was added slowly onto solid 1,3,5-triformylbenzene (5.0 g, 30.86 mmol) without stirring at room temperature. Trifluoroacetic acid (100 μL) was added directly to this suspension as a catalyst for imine bond formation. Finally, a solution of (R,R)-1,2-diaminocyclohexane (5.0 g, 44.64 mmol) in dichloromethane (100 mL) was added. The unmixed reaction was covered and left to stand. Over 5 days, all of the solid 1,3,5-triformylbenzene was consumed, and octahedral crystals grew on the sides of the vessel. The crystalline product was removed by filtration and washed with 95:5 ethanol/dichloromethane. Yield: 6.5 g, 83 %.

**Scheme S1** Batch synthesis of CC3-R.
CC1 Batch Synthesis

A solution of 1,3,5-triformylbenzene (3.75 g, 23.13 mmol) in dichloromethane (1150 mL) was added drop-wise over 48 hours (ca.0.4 mL/min) via pressure equalizing dropping funnel to a solution of ethylenediamine (2.08 g, 34.69 mmol) in dichloromethane (850 mL) in a 2-litre 3-necked round bottom flask cooled in an ice bath. The stirring rate used was 400 rpm. After complete addition, the reaction was allowed to stir for another 24 hours at room temperature. The solution was then filtered through filter paper (loss of solid to filter paper was 0.030 g). The solvent was removed from the filtrate via rotary evaporation (temperature of the water bath maintained below 20 °C) and the crude product was re-dissolved in chloroform (100 mL) and the solution re-filtered. The residue in the filter paper was washed with chloroform (50 mL). The two fractions of the organic filtrate were combined and the solvent removed under vacuum on a rotary evaporator (temperature of the water bath maintained below 20 °C) to give the product as a beige powder.

Yield: 4.25 g, 94%.

Scheme S2  Batch synthesis of CC1.
Development of CC3-R Synthesis in Flow

**Figure S2** Schematic of flow reactor set-up showing the range of parameters tested during development.

**Flow system set-up:**

System solvent: DCM
Reagent A: 0.083 M 1,2-\(R,R\)-cyclohexanediamine in DCM (0.948 g/100 mL of DCM)
Reagent B: 0.083 M 1,3,5-triformylbenzene in DCM (1.34 g/100 mL of DCM)
Flow rate A: 0.12–1.50 mL/min
Flow rate B: 0.08–1.00 mL/min
Reactor volume: 2–10 mL
Reactor temperature: 40–120 °C
Back pressure regulator: 8 bar

The Vapourtec reactor was assembled using a combination of the R-2+ Pump Module and R-4 Reactor Module. Samples were collected manually after 1.5x reactor volume had eluted and were immediately diluted with DCM and analysed by HPLC. A summary of all the conditions screened during the optimisation of the CC3-R synthesis is given in table S1.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Flow rate A (mL/min)</th>
<th>Flow rate B (mL/min)</th>
<th>Total flow rate (mL/min)</th>
<th>Reactor volume (mL)</th>
<th>Residence time (min)</th>
<th>Reactor temperature (°C)</th>
<th>Peak area, CC3-R (% a/a)</th>
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Table S1  Evaluation of temperature, flow rate, residence time and reactant stoichiometry on CC3-R synthesis.
Figure S3  Off-line HPLC analysis of flow reactor at steady state showing the effect of temperature on the synthesis of CC3-R over the range 40–120 °C (Table S1 entries 1–9).
Figure S4  Off-line HPLC analysis of flow reactor at steady state showing the effect of residence time on the synthesis of CC3-R over the range 4–20 min (Table S1 entries 10–12, 18).
**Figure S5** Off-line HPLC analysis of flow reactor at steady state showing the effect of total flow rate on the synthesis of CC3-R over the range 0.2–2.0 mL/min (Table S1 entries 10–12, 18).
Figure S6  Off-line HPLC analysis of flow reactor at steady state showing the effect of reactant stoichiometry on the synthesis of CC3-R (Table S1 entries 17–20).
Scale-up of CC3-R Synthesis Using the Flow Reactor

**Figure S7** Schematic of flow reactor set-up showing the optimised parameters for the synthesis of CC3-R.

**Flow system set-up:**

- **System solvent:** DCM
- **Reagent A:** 0.083 M 1,2-\(R,R\)-cyclohexanediamine in DCM (0.948 g/100 mL of DCM)
- **Reagent B:** 0.083 M 1,3,5-triformylbenzene in DCM (1.34 g/100 mL of DCM)
- **Reagent C:** Hexane
- **Flow rate A:** 0.62 mL/min
- **Flow rate B:** 0.38 mL/min
- **Flow rate C:** 4 mL/min
- **Reactor volume:** 10 mL
- **Reactor temperature:** 100 °C
- **Back pressure regulator:** 8 bar

The Vapourtec reactor was assembled using the R-2+/R-2 Pump Modules with the R-4 Reactor Module. The reaction was run using the conditions outlined above. Once the system had reached steady state the suspension was collected for 110 min. The suspension was isolated by filtration and dried to constant weight in a vacuum oven at 60 °C to afford CC3-R (0.918 g, 95%).

\(^1\)H NMR (CDCl\(_3\)): \(\delta_H 8.16 (s, \text{CH=N}, 12\text{H}), 7.89 (s, \text{ArH}, 12\text{H}), 3.33 (m, \text{CHN}, 12\text{H}), 1.9–1.4 (m, \text{CH\(_2\)}, 48\text{H}) \text{ppm.} \n\)

\(^13\)C NMR (CDCl\(_3\)): \(\delta_C 159.3, 136.9, 129.7, 74.9, 33.2, 24.6 \text{ppm. MS (ES+): 1117.7 ([M+H]^+). HPLC: 99.2\% a/a.} \)
Fig. S8 $^1$H NMR in CDCl$_3$ of CC3-R.

Fig. S9 $^{13}$C NMR in CDCl$_3$ of CC3-R.
Fig. S10 Mass spectrum (ES+) of CC3-R
Fig. 11 HPLC trace of CC3-R
Scale-up of CC1 Synthesis Using the Flow Reactor

**Figure S12** Schematic of flow reactor set-up showing the parameters for the synthesis of CC1.

**Flow system set-up:**

- **System solvent:** DCM
- **Reagent A:** 0.083 M ethylenediamine in 1:3 MeOH/DCM (0.499 g/(25 mL MeOH + 75 mL of DCM))
- **Reagent B:** 0.083 M 1,3,5-triformylbenzene in DCM (1.34 g/100 mL of DCM)
- **Flow rate A:** 0.62 mL/min
- **Flow rate B:** 0.38 mL/min
- **Reactor volume:** 10 mL
- **Reactor temperature:** 100 °C
- **Back pressure regulator:** 8 bar

The Vapourtec reactor was assembled using the R-2+ Pump Module with the R-4 Reactor Module. The reaction was run using the conditions outlined above. Once the system had reached steady state the reaction mixture was collected for 53 min. The solution was evaporated to dryness at 20 °C, the residue redissolved in the minimum amount of DCM, filtered and poured into an approximately equal volume of hexane to afford a white suspension. The solid was collected by filtration, then dried to constant weight in a vacuum oven at 50 °C to afford **CC1** (0.310 g, 93 %).

\(^1^\)H NMR (CDCl\(_3\)): \(\delta_H 8.19 \text{ (s, CH=N, 12H)}, 7.93 \text{ (s, ArH, 12H)}, 4.03 \text{ (s, CH\(_2\), 12H) ppm.}\)

\(^{13}\)C NMR (CDCl\(_3\)): \(\delta_C 161.5, 136.7, 129.8, 61.8 \text{ ppm. MS (ES+): 793.4 ([M+H]\(^+\]), 815.4 ([M+Na]\(^+\)). HPLC: 100 % a/a.}
Fig. S13 $^1$H NMR in CDCl$_3$ of CC1.

Fig. S14 $^{13}$C NMR in CDCl$_3$ of CC1.
Fig. S15  Mass spectrum (ES+) of CC1.

Fig. S16  HPLC trace of CC1
Dynamic covalent scrambling of CC1 and CC3-R

**Fig. S17** Schematic representation of all possible cage isomers formed via the dynamic covalent scrambling of ethylenediamine (EDA) and R,R-1,2-cyclohexanediamine (CHDA) with 1,3,5-triformylbenzene (TFB).
Flow Procedure

Fig. S18 Schematic of flow reactor set-up showing the parameters for the synthesis of scrambled CC1/CC3-R.

Flow system set-up:
System solvent: DCM
Reagent A: 0.083 M ethylenediamine in1:3 MeOH/DCM (0.499 g/(25 mL MeOH + 75 mL of DCM))
Reagent B: 0.083 M 1,2-\(R,R\)-cyclohexanediamine in DCM (0.948 g/100 mL of DCM)
Reagent C: 0.083 M 1,3,5-triformylbenzene in DCM (1.34 g/100 mL of DCM)
Flow rate A: x mL/min (x = 0–0.62)
Flow rate B: 0.62-x mL/min
Flow rate C: 0.38 mL/min
Reactor volume: 10 mL
Reactor temperature: 100 °C
Back pressure regulator: 8 bar

The Vapourtec reactor was assembled using the R-2+/R-2 Pump Modules Pump Module with the R-4 Reactor Module. The dynamic covalent scrambling was run with all whole number ratios of EDA to CHDA, e.g. 6:0 (CC1), 5:1, 4:2… 0:6 (CC3-R). A sample of each reaction was taken after steady state had been reached and analysed off-line using HPLC (Fig. S19).
Percentage composition of scrambled cage mixtures

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<tr>
<th>EDA:CHDA</th>
<th>CC1</th>
<th>CC1(^2)3(^1)</th>
<th>CC1(^3)3(^2)</th>
<th>CC1(^3)3(^3)</th>
<th>CC1(^2)3(^4)</th>
<th>CC1(^3)3(^5)</th>
<th>CC3</th>
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<tbody>
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<td>-</td>
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<td>16.6</td>
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<td>5.7</td>
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</table>

**Fig. S19** Off-line HPLC analysis and peak table of cages CC1 and CC3, and mixtures containing all whole number ratios of EDA to CHDA.
Fig. S20  Off-line LCMS analysis of scrambled cage mixture formed using a ratio of 3:3 EDA to CHDA. a) Overlaid TIC (total ion count, black trace) with EICs (extracted ion counts) for each cage - 1^6 (EIC: dark blue, 792.6988-796.6226), 1^53^1 (EIC: purple, 847.0709-850.8294), 1^43^2 (EIC: red, 900.9525-905.9598), 1^33^3 (EIC: green, 955.0125-960.2186), 1^23^4 (EIC: blue, 1009.0914-1014.3463), 1^13^5 (EIC: orange, 1063.3910-1067.8532) and 3^6 (EIC: pink, 1116.9488-1122.8294); b) Accurate mass spectra for each LC peak as seen in the TIC, all showing [M+H]^+ and [M+2H]^{2+} ions. From top to bottom - 1^6 found [M+H]^+ 793.4268, 1^53^1 found [M+H]^+ 847.4737 and [M+2H]^{2+} 424.2416, 1^43^2 found [M+H]^+ 901.5210 and [M+2H]^{2+} 451.2654, 1^33^3 found [M+H]^+ 955.5678 and [M+2H]^{2+} 478.2889, 1^23^4 found [M+H]^+ 1009.6147 and [M+2H]^{2+} 505.3125, 1^13^5 found [M+H]^+ 1063.6618 and [M+2H]^{2+} 532.3363, and 3^6 found [M+H]^+ 1117.7091 and [M+2H]^{2+} 559.3600.
Preparation and Isolation of Desymmetrised Cage, CC$_1^1$3$_5$

**Flow system set-up:**
- System solvent: DCM
- Reagent A: 0.083 M ethylenediamine in 1:3 MeOH/DCM (0.499 g/(25 mL MeOH + 75 mL of DCM))
- Reagent B: 0.083 M 1,2-$R$-$R$-cyclohexanediamine in DCM (0.948 g/100 mL of DCM)
- Reagent C: 0.083 M 1,3,5-triformylbenzene in DCM (1.34 g/100 mL of DCM)
- Flow rate A: 0.103 mL/min
- Flow rate B: 0.517 mL/min
- Flow rate C: 0.38 mL/min
- Reactor volume: 10 mL
- Reactor temperature: 100 °C
- Back pressure regulator: 8 bar

The Vapourtec reactor was assembled using the R-2+/R-2 Pump Modules Pump Module with the R-4 Reactor Module. The reaction was run using the conditions outlined above. Once the system had reached steady state the reaction mixture was collected for 71 min. The solvent was removed under vacuum at 30 °C to afford the scrambled cage product as a white solid. The scrambled cage was dissolved in chloroform (10 mL) and purified by preparative HPLC. The product-containing fractions were concentrated to dryness under vacuum at 20 °C to afford CC$_1^1$3$_5$ (0.13 g, 21 %) as a white solid. Residual solvent was removed overnight in a vacuum oven at 90 °C.

**Fig. S21** Schematic of flow reactor set-up showing the parameters for the synthesis of scrambled CC$_1^1$3$_5$. 

![Flow reactor set-up](image-url)
The methanol solvate phase was prepared by dissolving CC1$_3$5 (~ 5 mg) in dichloromethane (1 mL). Methanol (0.5 mL) was added and the resulting clear solution was then evaporated under N$_2$ flow in a desiccator. Needle crystals were formed after approximately 24 h.

IR (ν$_{max}$/cm$^{-1}$): 2929, 2845, 1646, 1595, 1443, 1154, 695. $^1$H NMR (CDCl$_3$): δ$_H$ 8.16 (m, CH=N, 6H), 8.15 (s, CH=N, 6H), 7.91 (d, J=1.5 Hz, ArH, 4H), 7.89 (s, ArH, 6H), 7.85 (dd, J=1.5 Hz, ArH, 2H), 4.23 (d, J=8.9 Hz, CH$_2$, 2H), 3.77 (d, J=8.9 Hz, CH$_2$, 2H), 3.34 (m, CH-N, 10 H), 1.84–1.46 (m, 20 × CH$_2$, 40 H) ppm. $^{13}$C NMR (CDCl$_3$): δ$_C$ 161.85 (CH=N), 159.41 (CH=N), 159.37 (CH=N), 159.29 (CH=N), 159.20 (CH=N), 159.13 (CH=N), 159.07 (CH=N), 136.89 (Ar C-H), 136.80 (Ar C-H), 136.78 (Ar C-H), 136.41 (Ar C-H), 129.85 (Ar C), 129.80 (Ar C), 129.70 (Ar C), 129.58 (Ar C), 129.48 (Ar C), 74.98 (cHex CH), 74.79 (cHex CH), 61.65 (cHex CH$_2$), 33.16 (cHex CH$_2$), 24.53 (cHex CH$_2$) ppm. HRMS (ES)$^+$ calc for C$_{68}$H$_{78}$N$_{12}$ [M+H]$^+$: 1063.6551; found 1063.6591. HPLC: 97 % a/a.

Figure S22  TGA data for non-oven dried CC1$_3$5. The sample has a 12 % weight loss at around 200 °C, which is attributed to the evaporation of water and residual methanol.
Figure 23 $^1$H NMR (CDCl$_3$) of oven dried CC$_1^1$3$_5$.

Figure S24 COSY NMR (CDCl$_3$) of oven dried CC$_1^1$3$_5$. 
Figure S25 $^{13}$C NMR (CDCl$_3$) of CCl$_1^3$.3
Figure S26  MALDI-TOF mass spectra of oven dried CC1\textsuperscript{1}3\textsuperscript{5}.
**Figure S27** Off-line HPLC analysis of oven dried CC1\textsuperscript{13}F\textsuperscript{5}.

**Fig S28** FTIR spectrum of oven dried CC1\textsuperscript{13}F\textsuperscript{5}.
Fig S29  HPLC analysis of CC1\textsuperscript{13} before and after recrystallization from methanol. Purity before and after recrystallisation is 97 % by peak area.
Single Crystal X-ray Crystallography

Single crystal X-ray data for \([\text{CC}1^3\text{S}^5]\)-4.5(MeOH)-2.9(H_2O) was recorded on a Rigaku MicroMax-007 HF rotating anode diffractometer (Mo-Kα radiation, \(\lambda = 0.71073\) Å, Kappa 4-circle goniometer, Rigaku Saturn724+ detector). Empirical absorption corrections, using equivalent reflections, were applied by the program SADABS. The structure was solved by direct methods using SHELXS, and refined by full-matrix least squares on \(|F^2|\) by SHELXL interfaced through the programme OLEX2. Unless stated all non-hydrogen atoms were refined anisotropically, and all hydrogen atoms were fixed in geometrically estimated positions and refined using the riding model. Supplementary single crystal XRD data, including structure factors, is available free of charge from the Cambridge Crystallographic Data Centre (CCDC) via www.ccdc.cam.ac.uk/data_request/cif.

Crystal data for \([\text{CC}1^3\text{S}^5]\)-4.5(MeOH)-2.9(H_2O); CCDC number 1411292. Formula C_{72.50}H_{101.8}N_{12}O_{7.4}; \(M = 1259.41\) g·mol\(^{-1}\); monoclinic space group \(I2\), colourless crystal; \(a = 21.656(2), b = 19.8282(19), c = 22.267(3)\) Å; \(\beta = 106.0482(19)°\); \(V = 9188.8(19)\) Å\(^3\); \(\rho = 0.910\) g·cm\(^{-3}\); \(\mu = 0.060\) mm\(^{-1}\); \(F(000) = 2719\); crystal size = 0.31 x 0.09 x 0.09 mm\(^3\); \(T = 100(2)\) K; 21476 reflections measured (1.161 < \(\Theta < 21.966°\)), 9999 unique \((R_{int} = 0.0701)\), 6175 \((I > 2\sigma(I))\); \(R_1 = 0.1310\) for observed and \(R_1 = 0.1878\) for all reflections; \(wR_2 = 0.3209\) for all reflections; max/min difference electron density = 0.671 and -0.440 e·Å\(^{-3}\); data/restraints/parameters = 9999/229/878; GOF = 1.683. The asymmetric unit for \([\text{CC}1^3\text{S}^5]\)-4.5(MeOH)-2.9(H_2O) comprises one complete \(\text{CC}1^3\text{S}^5\) molecule and a number of partially occupied solvent molecules. During refinement a 0.95 Å resolution limit was applied. The one ethyl vertex was disordered over four cage vertices. For each partially occupied cyclohexyl ring site occupancies were determined using free variables in addition to a SUMP card that was used to ensure the chemical formula of the cage molecule refined to $C_{68}H_{78}N_{12}$ in accordance with experimental data. Ten MeOH solvent C-O bond distances were restrained during refinement (DFIX in SHELX) and the four partially occupied cyclohexyl rings were refined with rigid-body restraints (RIGU is SHELX). For a displacement ellipsoid plot see Fig. S30.
Fig. S30  Displacement ellipsoid plot from the single crystal structure \( [\text{CCl}_3] \cdot 4.5(\text{MeOH}) \cdot 2.9(\text{H}_2\text{O}) \). Solvent and cyclohexyl disorder omitted for clarity. Ellipsoids displayed at 50% probability level.
References


