Supporting Information for:

Photochemical bromination of 2,5-dimethylbenzoic acid as key step of an improved alkyne-functionalized blue box synthesis

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1. Materials, methods, and instruments

All reagents and solvents were purchased from commercial sources and used as received, unless otherwise stated. Template 2-[2-[5-[2-(2-hydroxyethoxy)ethoxy]naphthalen-1-yl]oxyethoxy] ethanol[1] and **6**$^{4+}$[2] were prepared according to reported procedures. Non-deuterated solvents employed were dry, except for *o*-dichlorobenzene and benzene.

All reactions were performed under an inert atmosphere and the glassware was dried with the help of a heating gun using standard Schlenk techniques. UV lamp used for photochemical bromination is from Herolab GmbH laboratory equipment (6 W). For the LED strip, Eventek DC power supply was used. Organic solutions were concentrated under reduced pressure on a Buchi rotatory evaporator. $CDCl_3$ was treated by passing it through an alumina plug to remove acid traces. Thin-layer chromatography (TLC) was performed on silica gel TLC Al foils with fluorescent indicator 254 nm (0.25 mm thick, 60 F254, Merck, Germany) and visualized using UV light (254 and 365 nm) and standard laboratory stains (*e.g.* potassium permanganate solution). Column chromatography was carried out either on silica gel (Merck silica gel 60 0.040-0.063 mm) or on a Buchi Pure C-810 automated chromatography system with Flash cartridges (FlashPure EcoFlex C18 4 g), with the indicated solvent system.

NMR experiments were performed on Bruker UltraShield Plus Avance III spectrometer 400 MHz at 298 K. Chemical shifts (δ) are expressed in ppm and are referred to the residual non-deuterated solvent peak.

Attenuated Transmitted Reflectance-Fourier-transform infrared spectroscopy (ATR-FTIR) was performed on ThermoScientific Nicolet iS50 FT-IR equipped with a diamond crystal. Spectra were recorded with 4 cm^{-1} resolution and 60 scans accumulation.

Mass analysis was performed by LC/MS Thermo Scientific Trace 1300 using UPLC-ESI-Orbitrap-HRMS (≤5 ppm) or by ESI-infusion, using a ThermoFisher Orbitrap: Exactive Plus coupled with Extend Mass Range:Source ESI.

Both cyclic voltammetry (CV) and differential pulse voltammetry (DPV) were measured using Autolab PGSTAT100 or PGSTAT204. The typical three-electrode setup was used, with a glassy carbon electrode (diameter = 3 mm), a platinum wire electrode, and a silver wire as working electrode, counter electrode, and reference electrode, respectively. All analyses were performed in dry acetonitrile in the presence of tetraethylammonium hexafluorophosphate ($TEAPF_6$) as a supporting electrolyte. Ferrocene was used as an internal standard (E vs SCE = 0.395 V).[3] The total volume was 3 mL, with 50 µL as the maximum amount of ferrocene solution added. Thorough degassing was carried out using a solvent-saturated Ar flow. Typically, in both CV and DPV, the potential range was swept from +0.8 V to -1.1 V. The working electrode was washed and polished after every potential sweep using a polishing alumina slurry (0.05 µm particles). The whole system was kept inside the Faraday cage to minimize electrical noise. All the measurements were carried out at room temperature (20-23°C).

2. Attempted synthesis of 2 via thermal bromination

General procedure

Under an inert atmosphere, in two necks round bottom flask, 690 mg (4.6 mmol, 1 eq.) of 2,5-dimethyl benzoic acid **1** is dissolved in 15 mL of benzene, *o*-dichlorobenzene or dry ACN. Then, 1.8 g (10 mmol, 2.2 eq) of NBS and 38 mg of AIBN (0.23 mmol, 0.05 eq.) is added to the reaction mixture. The solution is heated or refluxed for 4 h. At the end of the reaction, an aliquot was taken, dried under a vacuum, dissolved in $CDCl_3$ and ^{1}H-NMR spectrum was recorded.

Insights from attempts to purify 2

Compound **2** was attempted to be isolated by liquid/liquid extraction. $CHCl_3$ was added to the mixture obtained using thermal bromination method and *o*-DCB at 105°C. The crude was washed with $NaHCO_3$ aqueous solution (pH=8.5), to convert the carboxylic acid of **2** into its respective ionic carboxylate and recover it from the aqueous phase. Both organic and aqueous solutions were dried and then analysed by ^{1}H-NMR. NMR analysis of the organic phase showed only intense peaks assigned to side product **II**, and traces of it were observed in the aqueous phase. This observation suggests that compound **2** is highly sensitive to basic solution and converted to **II** during the extraction.

Isolation of II

Synthesis of **II** was carried out using refluxing ACN as solvent, following the general procedure above. After the reaction time, the crude was evaporated as much as possible and purified by column chromatography. After the separation, a white solid was obtained. The solid was dissolved in the minimal amount of an acetone/ CH_2Cl_2 (3:1) solution and precipitated with cyclohexane to isolate pure compound **II** (365 mg, 35%). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 5.33 (s, CH_2O), 4.57 (s, CH_2Br) 7.48 (d, *J*=7.7 Hz, 1H), 7.74 (dd, *J*=7.79 Hz, *J*=2.6 Hz, 1H), 7.95 (d, *J* =2.6 Hz, 1H). HRMS: m/z calcd. for $[M+H]^+$: 226.9702, found: 226,9700. Characterization consistent with literature data.[4]

3. Attempted synthesis of 2 from II

Opening of **II** to give **2** was attempted according to a modified procedure reported in the literature.[5] 100 mg (0.44 mmol) of **II** are dissolved in 0.7 mL of glacial acetic acid, followed by 1.4 mL of HBr 33 wt.% solution (dropwise addition). After addition of the acid, the solution turned from colorless to red. The reaction mixture was stirred at room temperature for 2 h, then heated for 1.5 h at 70°C, then cooled to rt and left stirring overnight. After this time, the mixture is quenched by pouring it onto the ice, and a solid is formed. The solid is collected, dried, and analyzed by ^{1}H-NMR. NMR spectrum showed that the mixture contains both starting material **II** and desired molecule **2**. The best conversion was achieved by heating 6 h instead of 1.5 h, resulting in a ratio of 22:78 (**II**:**2**), as assessed by ^{1}H-NMR.

4. Photochemical setup

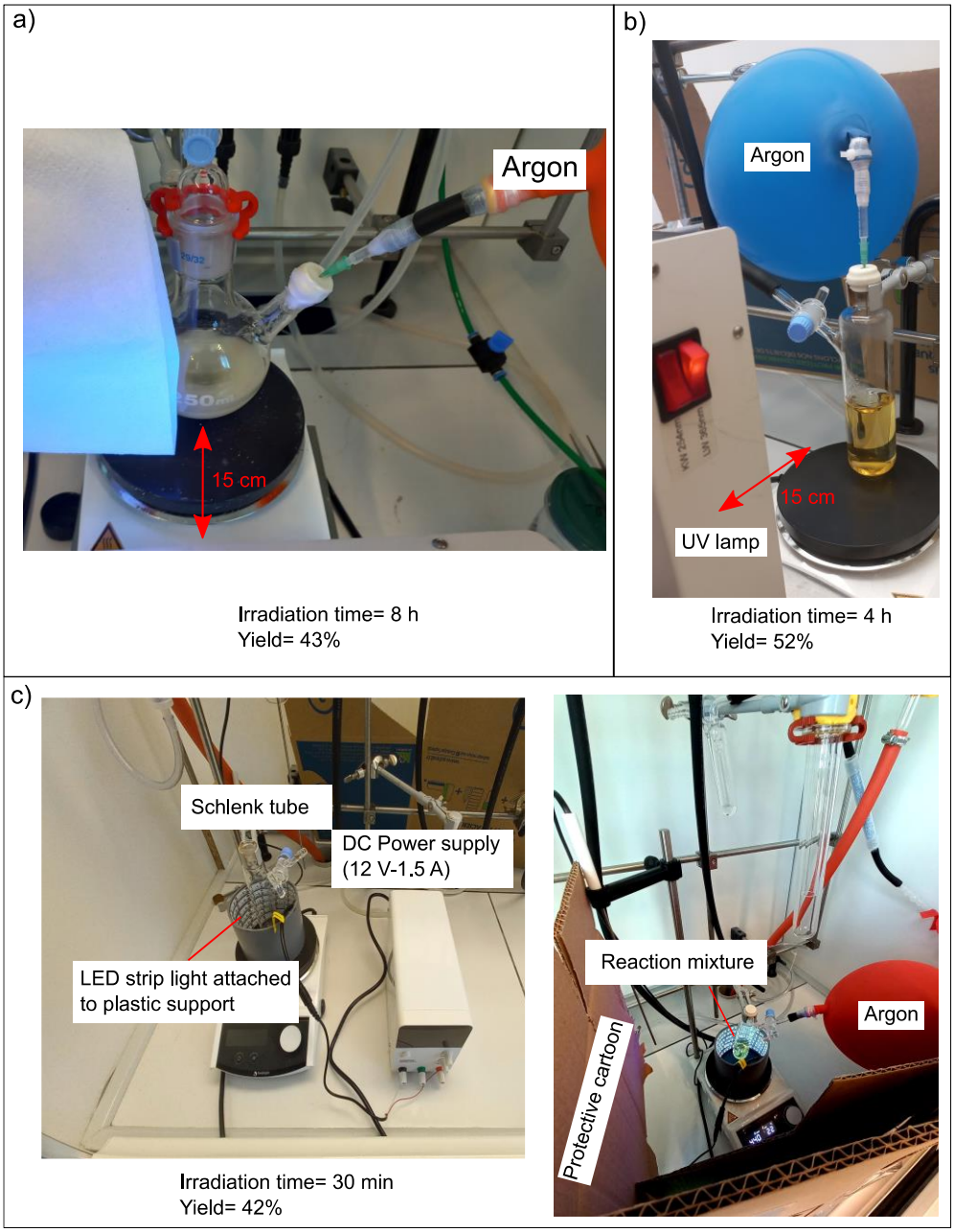

Figure S1. Photochemical reaction setup for the bromination of **1** in various conditions: a) in round bottom flask using a 6 W UV lamp, b) in Schlenk tube using a 6 W UV lamp, and c) in Schlenk tube using LED strip. The employed wavelength is 365 nm in all cases. Irradiation time refers to the time required to consume entirely the starting material (as confirmed by NMR).

5. Attempts to prepare 3 with other coupling agents

Esterification of 2 using EDC

The coupling reaction of **2** to give **3** using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) was attempted according to a modified procedure.[6] In a Schlenk tube, 150 mg of **2** (0.49 mmol, 1 eq), 101 mg of propargyl alcohol (0.49 mmol, 3.7 eq) and 6 mg of 4-dimethylaminopyridine (DMAP) (0.049, 0.1 eq) were dissolved in 1 mL of CH_2Cl_2. After stirring for 10 min, 112 mg of EDC (0.72 mmol, 1.47 eq) dissolved in 1 mL of CH_2Cl_2 were added dropwise to the first mixture at rt. After 24 h, 5 mL of CH_2Cl_2 was added and the mixture was extracted with 20 mL saturated

solution of $NaHCO_3$, then with 20 mL of water, and finally 20 mL of brine solution. The organic phase was collected and dried under vacuum to give **3** as a white solid (12% yield, 20 mg).

Esterification of 2 using HBTU

The coupling reaction of **2** to give **3** using (2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) was attempted according to a modified procedure.[7] In an oven-dried round-bottomed flask equipped with a magnetic stir bar,150 mg of **2** (0.49 mmol, 1 eq.), 185 mg of HBTU (0.49 mmol, 1 eq.), and 305 mg of DMAP (0.98 mmol 2.5 eq.) were dissolved in anhydrous DMF (3 mL). The resulting mixture was stirred at rt for 30 min under a nitrogen atmosphere. After this time, a solution of propargyl alcohol (0.49 mmol, 1 eq.) in DMF (1 mL) was injected into the reaction mixture. The solution was left stirring at rt for 48 h. The reaction mixture was diluted with CH_2Cl_2 (15 mL) and the resulting mixture was washed with 5% HCl (2 × 3 mL), 1M $NaHCO_3$ (2 × 3 mL) and water (2 × 3 mL). The organic layer was collected, dried over $MgSO_4$, filtered and concentrated to give a white solid containing traces of ester.

6. Synthesis of benzyl azide

This molecule has been prepared according to a modified literature procedure.[1] Under an argon atmosphere, sodium azide (780 mg, 12 mmol, 2.4 eq.) was added to a solution of benzyl bromide (860 mg, 5.0 mmol, 1 eq.) in DMF (7.5 mL). The mixture was stirred at 60°C for 72 h. Then water (50 mL) was added to the reaction medium, and the resulting solution was extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with 5% LiCl aqueous solution (3 × 50 mL) and dried over $MgSO_4$. The solvent was then evaporated under reduced pressure, affording the target molecule as a yellowish oil (584 mg,88%). The obtained product was used without further purification. ^{1}H NMR (500 MHz, 25°C, $CDCl_3$) δ: 7.36 (m, 5H, Ph-H), 4.34 (s, 1H, CH_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 135.51, 129.00, 128.38, 54.94. IR (cm^{-1}): 2085; 1245; 802. ESI-infusion: m/z calcd. for $[M-N_3]^+$: 91.0542, found: 91.0548. Characterization consistent with literature data.[1]

7. Characterization

Compound 2.

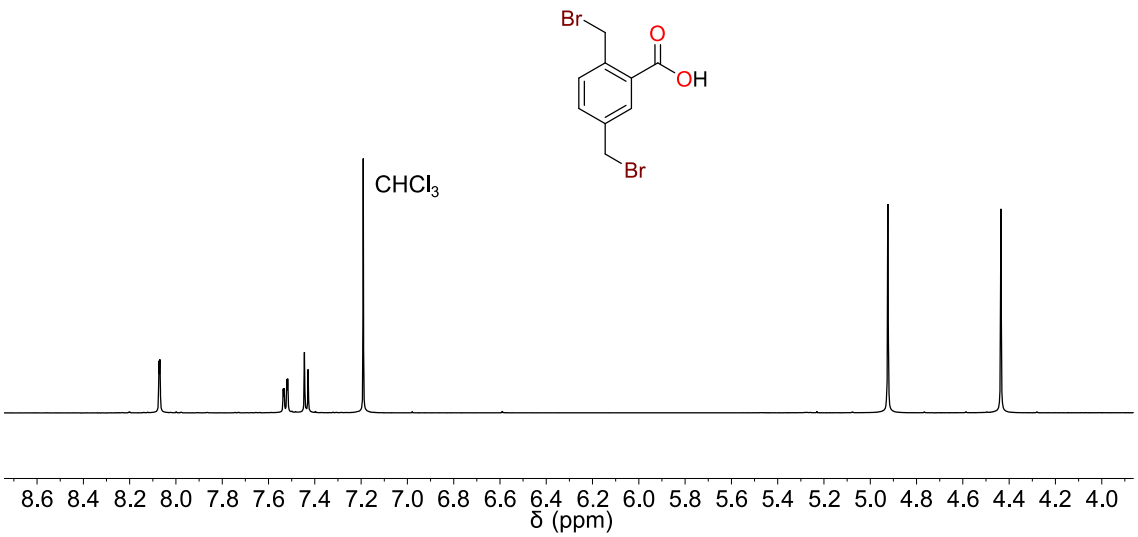

Figure S2. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) of **2**.

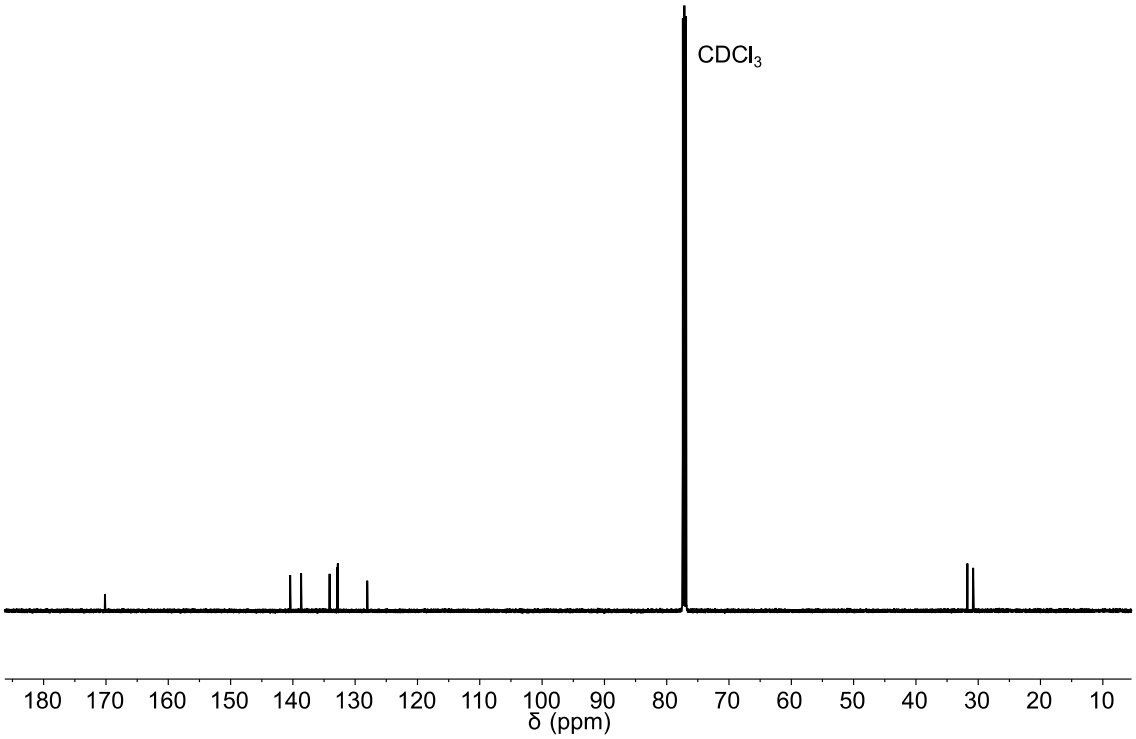

Figure S3. ^{13}C-NMR (500 MHz, $CDCl_3$, 298 K) of **2**.

Compound 3.

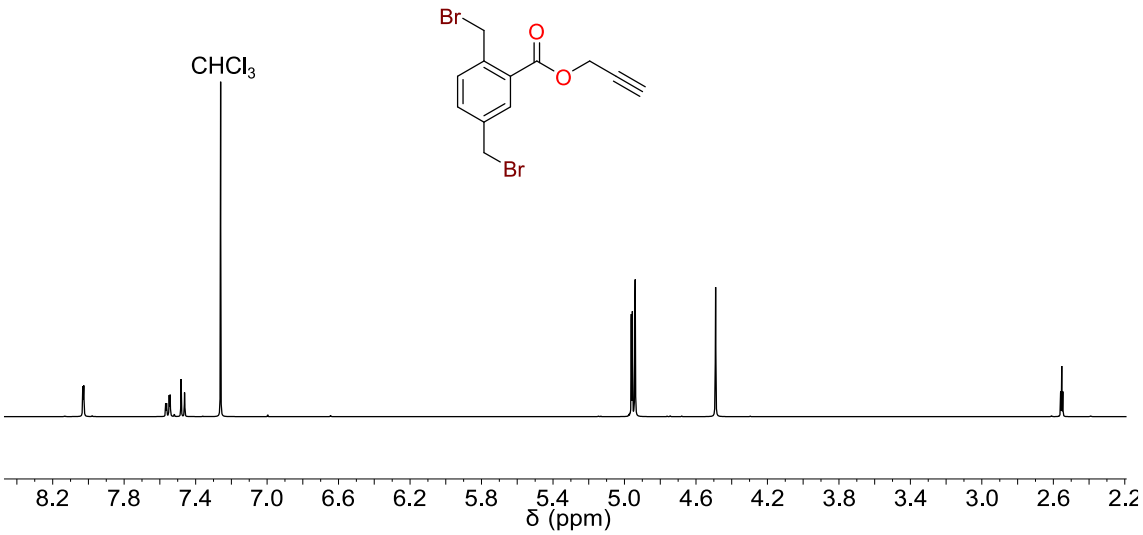

Figure S4. ^{1}H-NMR (400 MHz, $CDCl_3$, 298 K) of **3.**

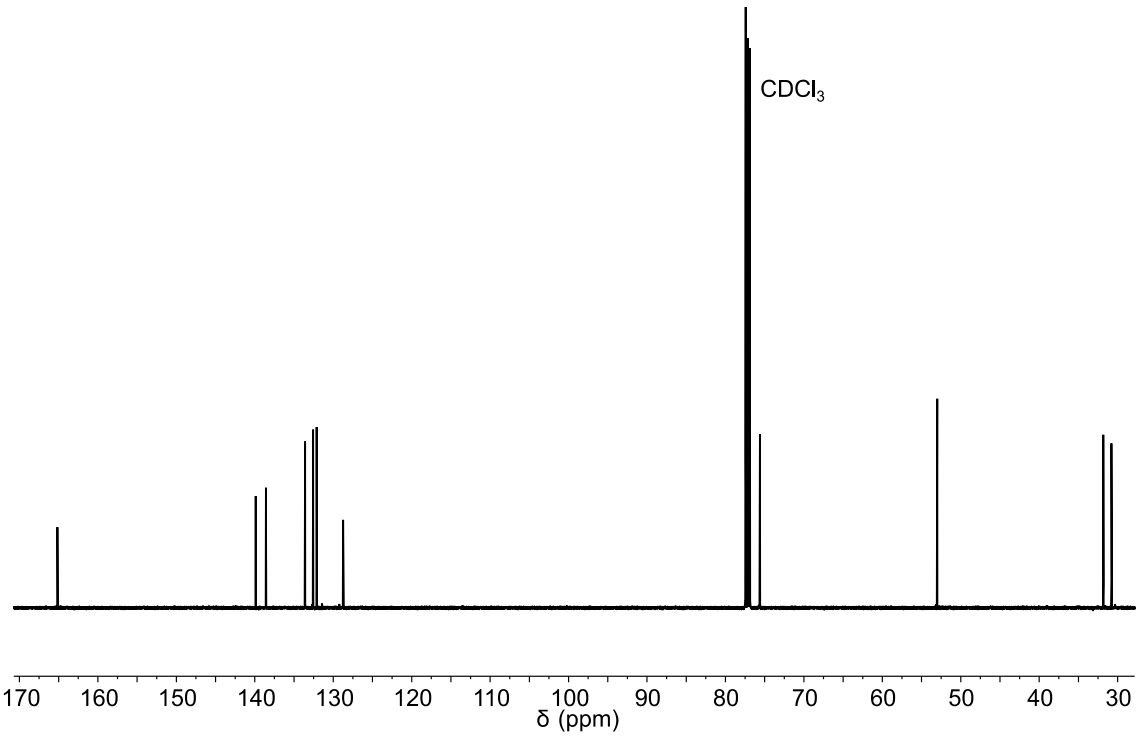

Figure S5. ^{13}C-NMR (126 MHz, $CDCl_3$, 298 K) of **3.**

Compound 4$(PF_6)_4$.

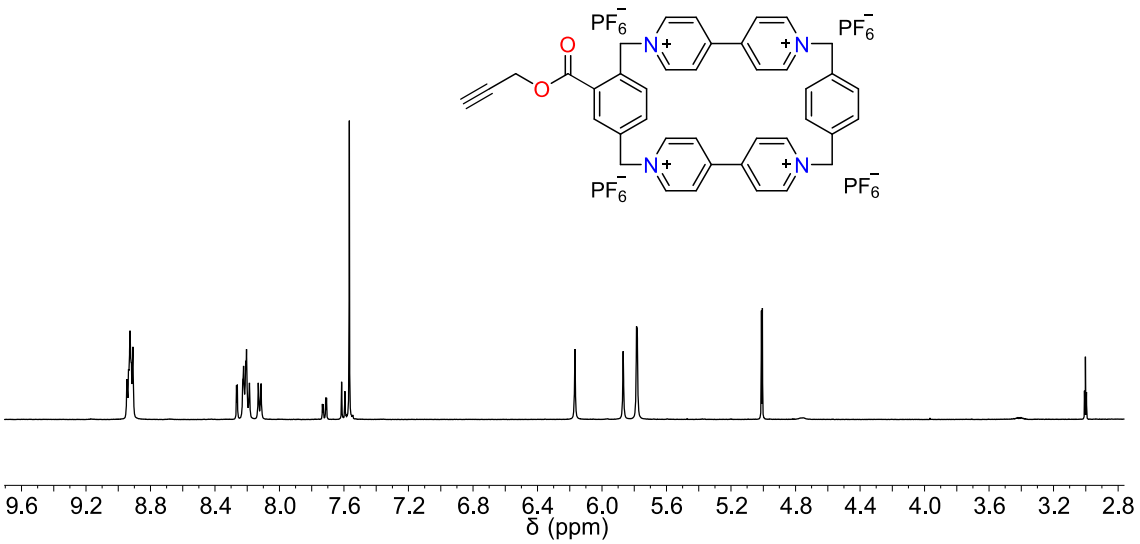

Figure S6. ^{1}H-NMR (400 MHz, CD_3CN, 298 K) of **4**$(PF_6)_4$.

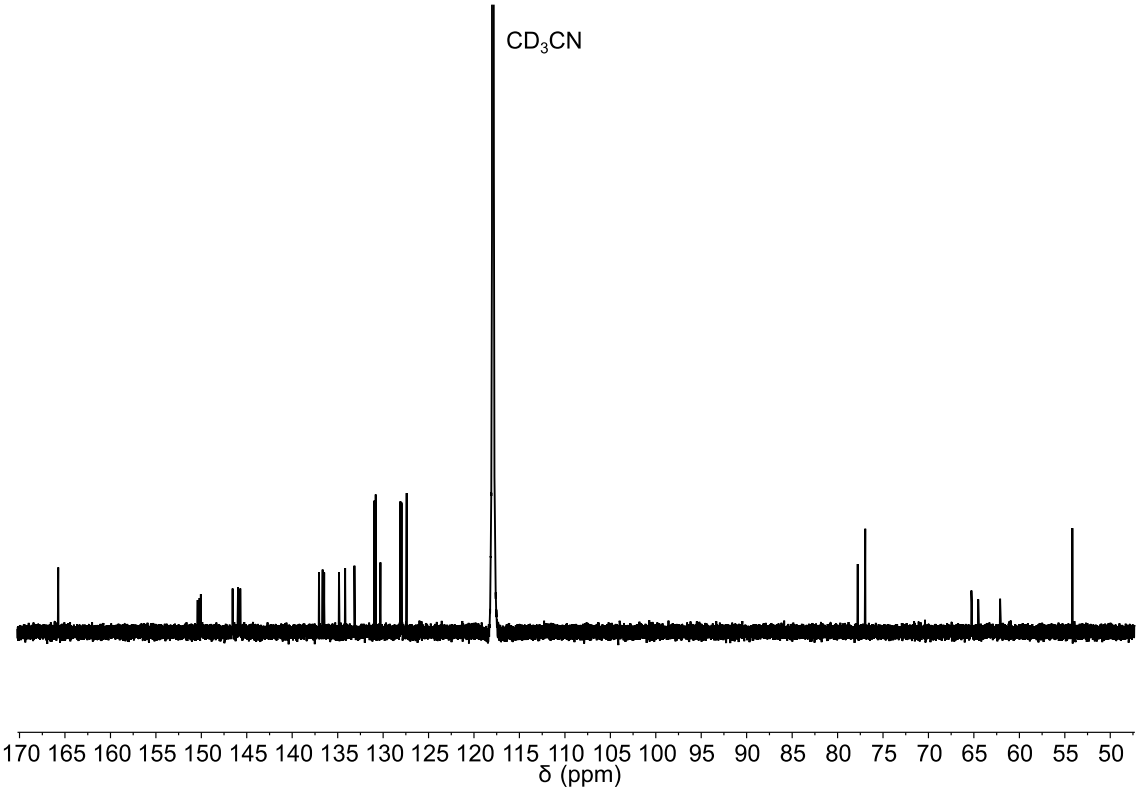

Figure S7. ^{13}C-NMR (126 MHz, CD_3CN, 298 K) of **4**$(PF_6)_4$.

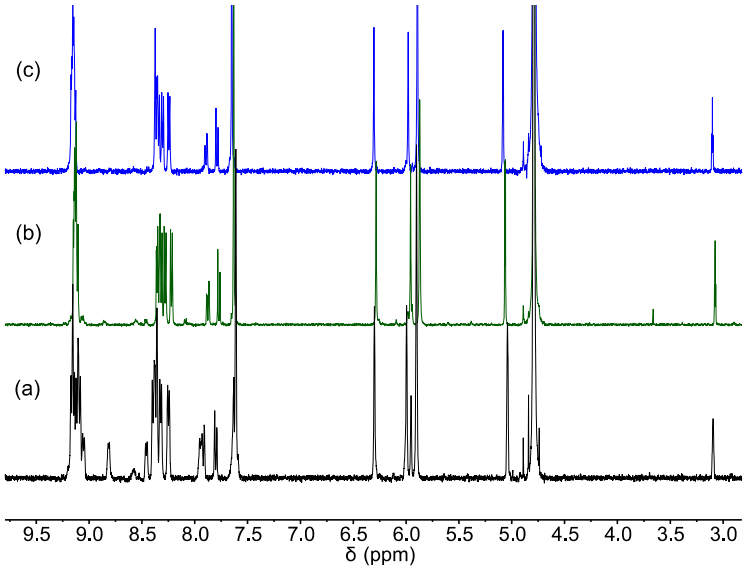

Figure S8. ^{1}H NMR of the template-directed synthesis of $\mathbf{4}^{4+}$ in different conditions. NMR recorded after the liquid/liquid extraction workup. a) After 5 days with NaI as catalyst, b) after 10 days without NaI as a catalyst, and c) after 10 days with NaI as a catalyst.

Compound 5$(PF_6)_4$**.**

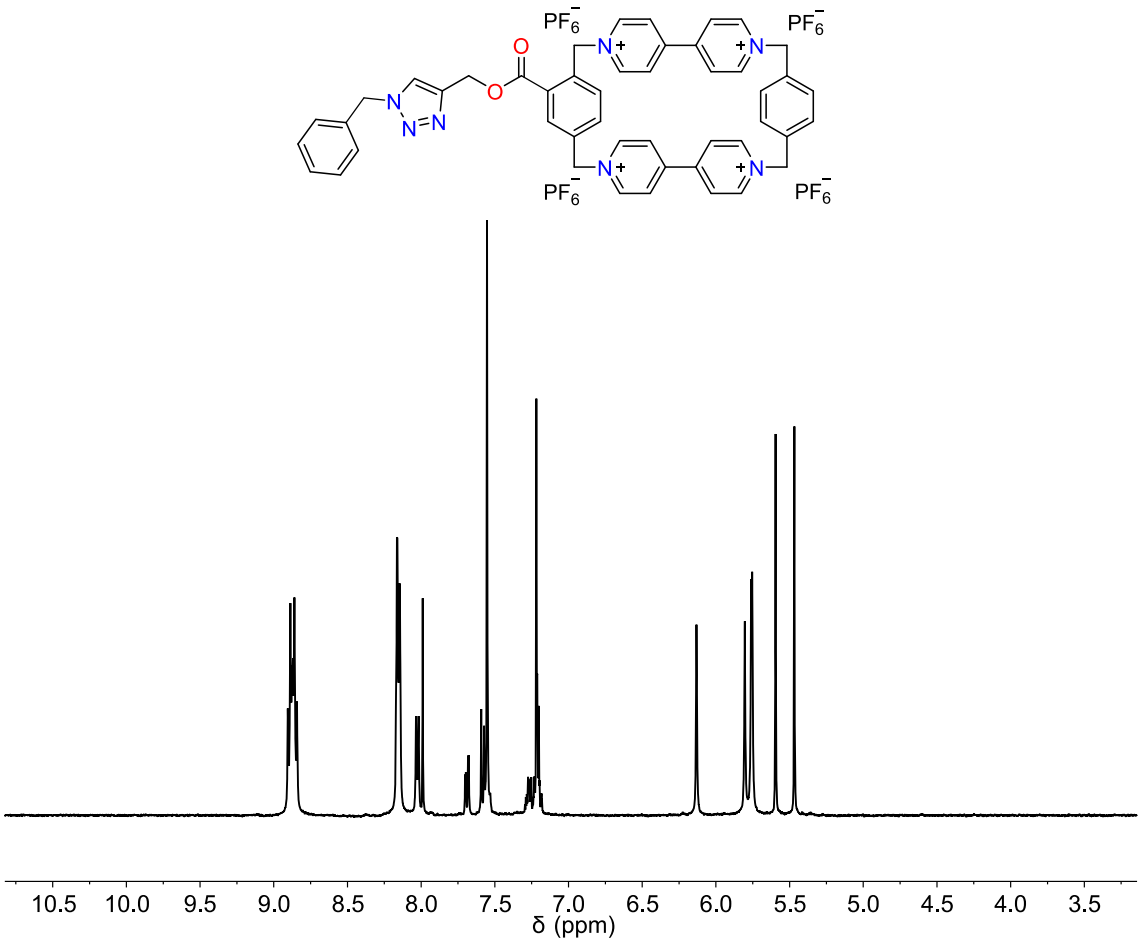

Figure S9. ^{1}H-NMR (400 MHz, CD_3CN, 298 K) of **5**$(PF_6)_4$.

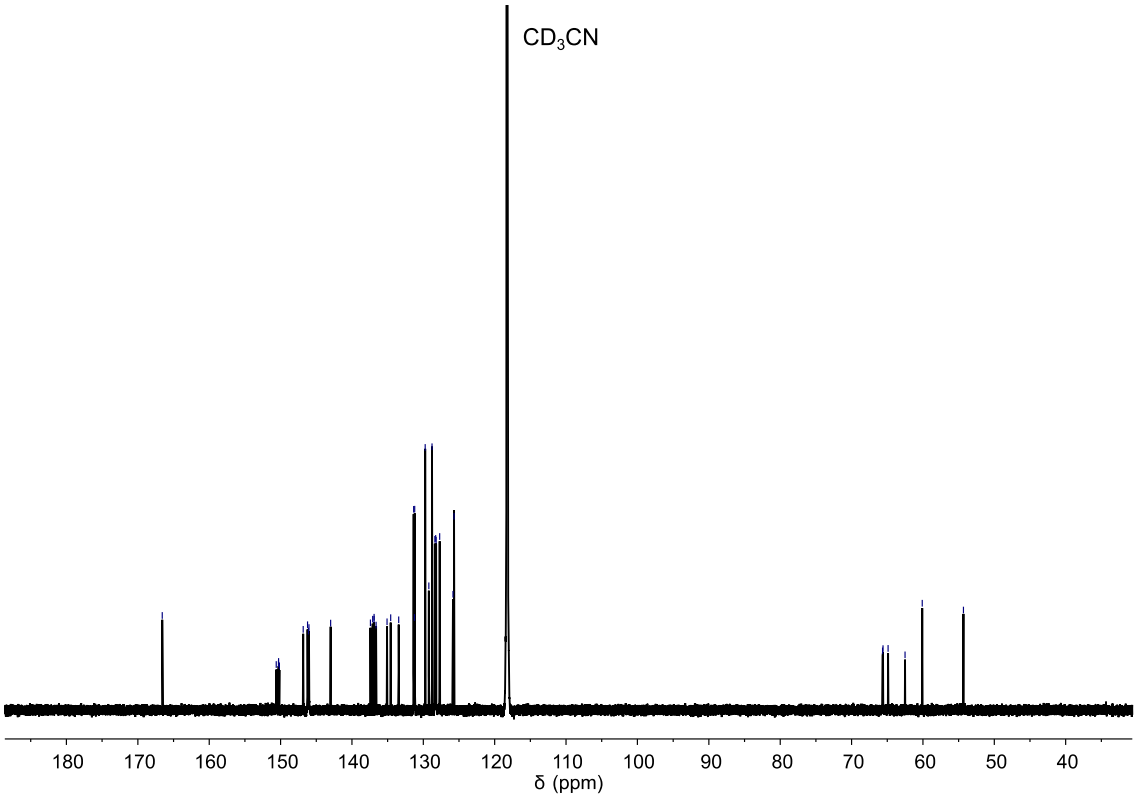

Figure S10. ^{13}C-NMR (126 MHz, CD_3CN, 298 K) of **5**$(PF_6)_4$.

Benzyl azide.

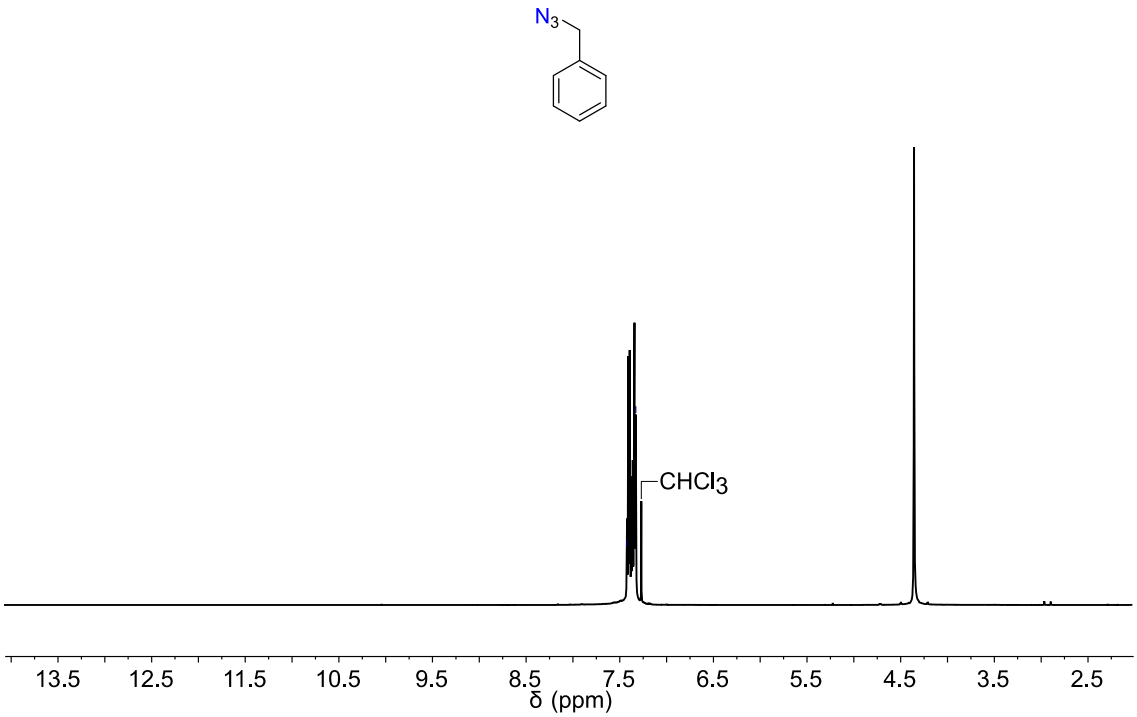

Figure S11. ^{1}H-NMR (400 MHz, $CDCl_3$, 298 K) of benzyl azide.

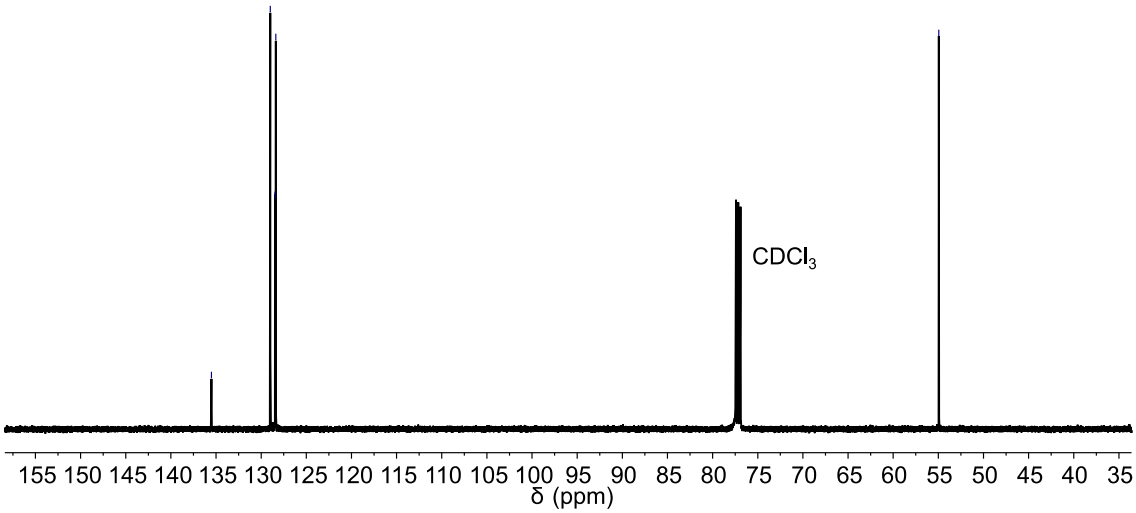

Figure S12. ^{13}C-NMR (126 MHz, $CDCl_3$, 298 K) of benzyl azide.

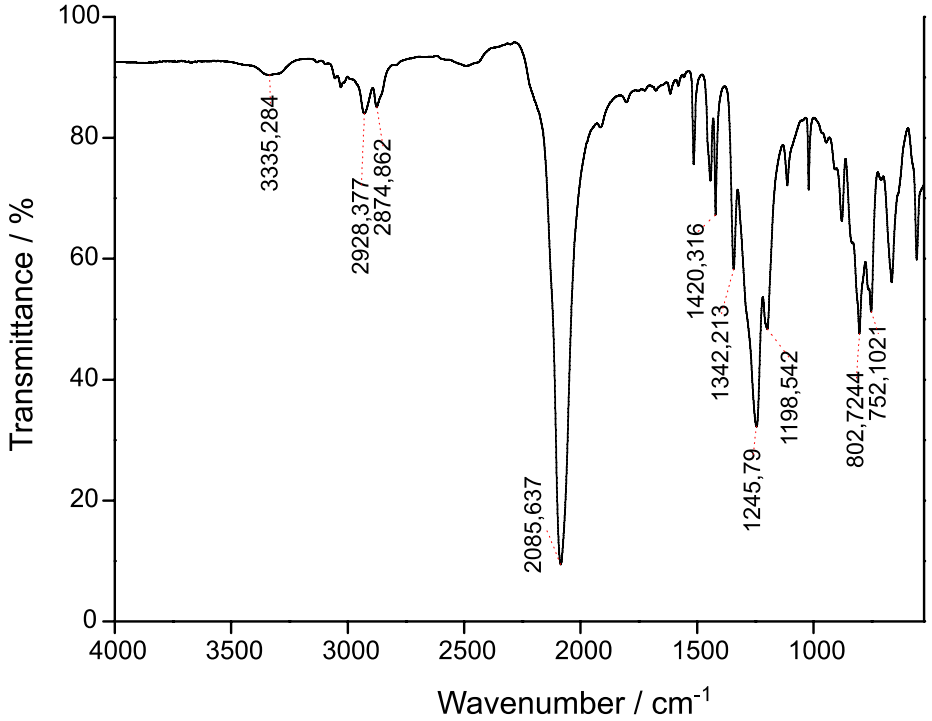

Figure S13. ATR-FTIR spectrum of benzyl azide.

8. Electrochemical characterization of pseudorotaxane [$6^{2+(+\bullet)}\subset 5^{2(+\bullet)}$]

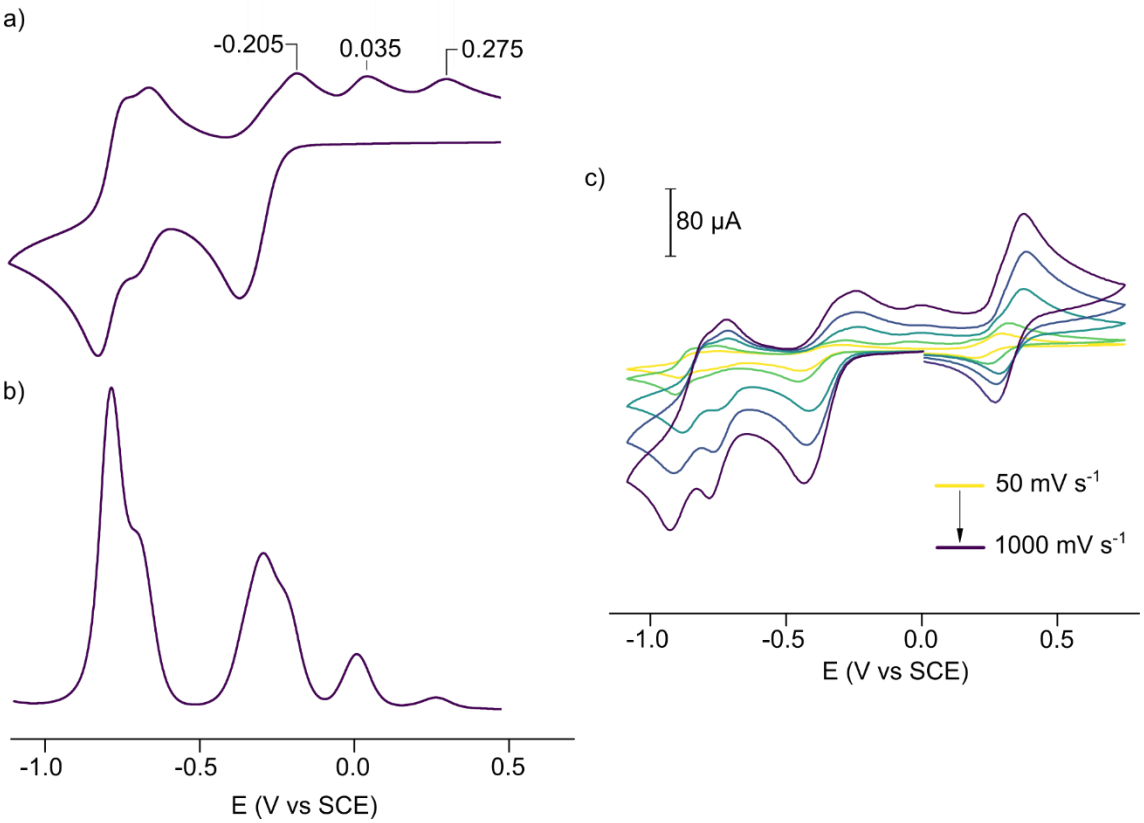

Figure S14. a) CV (200 mV s^{-1}) and b) DPV of an equimolar mixture of $\mathbf{5}^{4+}$ and $\mathbf{6}^{4+}$ internally referenced to ferrocene (E vs SCE = 0.395 V), added in subsequent experiments. c) Scan rate dependence study of an equimolar mixture of $\mathbf{5}^{4+}$ and $\mathbf{6}^{4+}$. The scan rates vary from 50 mV·s^{-1} (yellow) through 75, 200, 500, leading up to 1000 mV·s^{-1} (purple).

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