

# Enantiopurification by Co-crystallization within Cyclodextrin Metal-Organic Framework<sup>†</sup>

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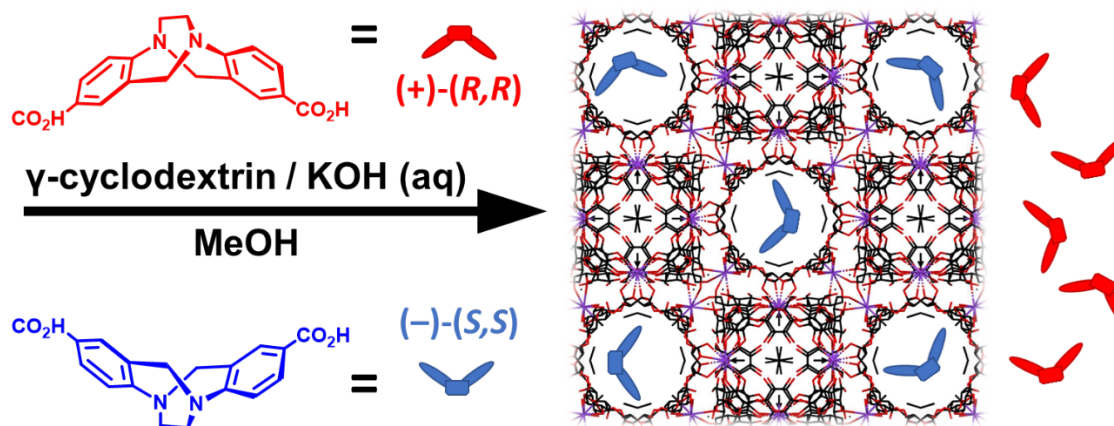
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<sup>†</sup> CCDC 2153996 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif), or by emailing [data\\_request@ccdc.cam.ac.uk](mailto:data_request@ccdc.cam.ac.uk), or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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## ■ Materials

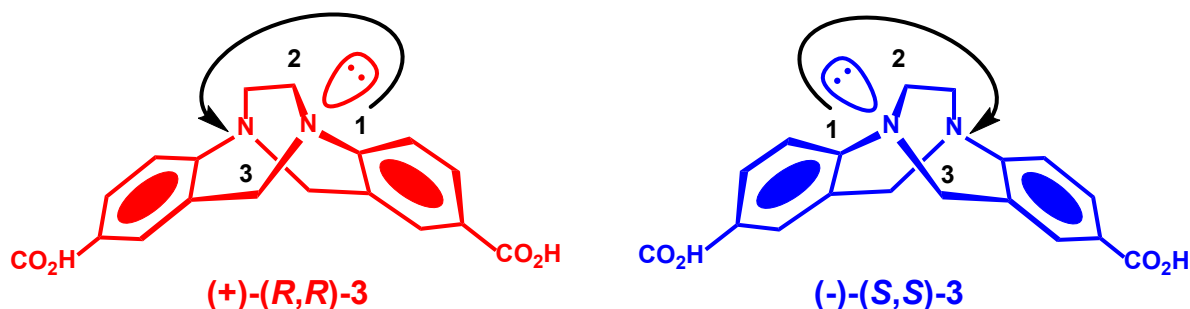
Sigma and Fisher Scientific supplied chromatography-grade solvents including acetone ( $\text{CH}_3\text{COCH}_3$ ), chloroform ( $\text{CHCl}_3$ ), dichloromethane ( $\text{CH}_2\text{Cl}_2$ ), dimethylformamide (DMF), ethyl acetate (EtOAc), and methanol (MeOH), ethanol (EtOH) and Hexanes. Reagent-grade starting materials supplied by Ambeed, Tokyo Chemical Industry (TCI) and Combi-Blocks which were used without extra purification.

### ■ X-Ray Diffractometry

A Rigaku Cu-Synergy X-ray diffractometer was used to collect crystallographic data. This data was processed and refined with Olex V2-1.3 software before depositing the structure in the Cambridge Crystallographic Data Centre (CCDC).

### ■ Nomenclature for R/S stereocenters

Following Cahn–Ingold–Prelog priority rule described in our earlier work [1], *R* and *S* enantiomers of TBA **3** were assigned in this work.



### ■ Optical Activity and Circular Dichroism

Optical activity was measured by Rudolph Autopol-IV optical polarimeter. Circular dichroism spectra were recorded by Jasco J-815, using 1 cm cuvette and HPLC-grade solvents at 25° C.

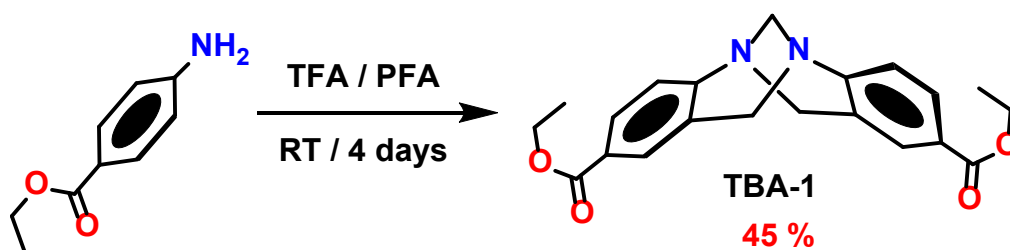
### ■ Nuclear Magnetic Resonance (NMR) Spectroscopic Analysis

NMR spectra were recorded at 300 K using Bruker Avance III 600 MHz, Bruker Neo 600 MHz, and Bruker Avance III 500 MHz instruments running Topspin (version 4.0.8) for the analysis and plotting of the acquired spectra. Deuterated chloroform ( $\text{CDCl}_3$ ), dimethyl sulfoxide ( $\text{CD}_3\text{SOCD}_3$ ), methanol ( $\text{CD}_3\text{OD}$ ), and deuterium oxide ( $\text{D}_2\text{O}$ ) were purchased from Cambridge Isotope Laboratories (CIL) and used for NMR spectroscopic analysis.

### ■ Chiral High-Performance Liquid Chromatography (HPLC)

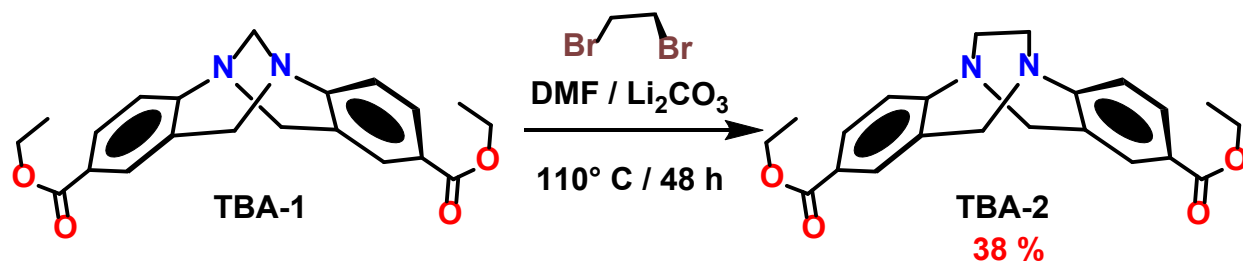
Chiral HPLC chromatograms were recorded by multi-channel optical detection at 235, and 245 nm using Agilent's 1260 Infinity HPLC instrument equipped with a Phenomenex chiral analytical column (Chirex 3126 (*D*)-penicillamine, 150 × 4.6 mm, 5 μm). The applied mobile phases included HPLC-Plus-grade H<sub>2</sub>O and MeCN purchased from Sigma Aldrich. Copper (II) sulfate (2 mM) was added to the aqueous mobile phase (10% *v/v*) used for the analytical chiral separations only.

### ■ Synthesis of Tröger's base analog (±)-1



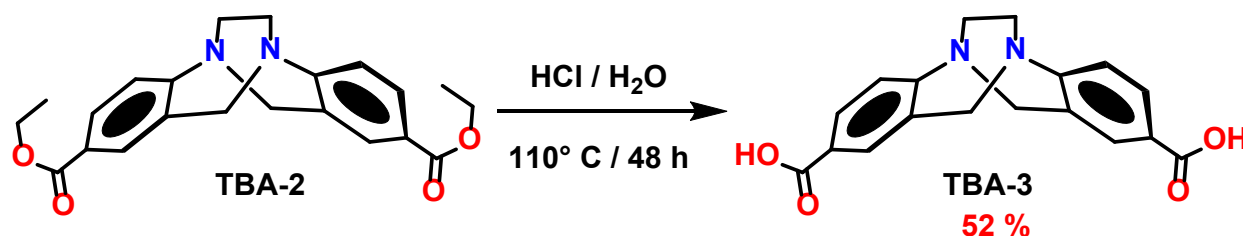
Ethyl 4-aminobenzoate (12.5 g) was crushed with mortar and pestle and gradually added to trifluoroacetic acid (TFA, 200 mL) while mixing them with a magnetic stir bar until fully homogenous. Paraformaldehyde (PFA, 4.0 g, excess) was added before sealing the flask and allowing the mixture to stir at rt for 10 days. The reaction mixture was concentrated to about one-fourth of its initial volume using a vacuum pump equipped with two traps filled with dry ice/acetone and sodium hydroxide pellets. This concentrate was then poured on 200 g of crushed ice and basified to a pH of 8 with the addition of saturated sodium carbonate solution before extraction with EtOAc (2 × 50 mL). These organic layers were then combined, rinsed with saturated sodium hydrogen carbonate solution (3 × 30 mL), dried over magnesium sulfate, and paper-filtered. The filtrate was then dried by a rotavap, and the remaining crude was subjected to normal-phase flash chromatography giving 9.5 g (77% yield) of TBA (±)-1 as a white solid. *R<sub>f</sub>* 0.35 (silica gel; EtOAc–hexanes–DCM, 2:3:5 *v/v*). <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ 7.85 (dd, *J* = 8.8, 2.8 Hz, 2H), 7.64 (d, *J* = 2.8 Hz, 2H), 7.19 (d, *J* = 8.8 Hz, 2H), 4.76 (d, *J* = 16.5 Hz, 2H), 4.35 (s, 2H), 4.27 (d, *J* = 16.5 Hz, 2H), 4.30 (q, *J* = 6.1 Hz, 4H), 1.33 (t, *J* = 6.5 Hz, 6H). For alternative see [2].

■ Synthesis of Tröger's base analog (±)-2



Tröger's base analog (±)-1 (2.2 g), 1,2-dibromoethane (12.0 mL), and lithium carbonate (10.0 g) were mixed at 130° C in DMF (40.0 mL) for 48 h. The mixture was then reduced to about one-fifth of its initial volume using a rotavap with a hot bath at 70° C. The remaining residue was divided between water and EtOAc (100 mL, 1:1). The organic layer was separated, rinsed with saturated sodium carbonate solution (3 × 30 mL), dried over magnesium sulfate, and paper-filtered. The filtrate was then dried by a rotavap, and the remaining residue was subjected to normal-phase flash chromatography giving 780 mg of the purified product TBA (±)-2 (35% yield).  $R_f$  0.25 (silica gel; EtOAc–hexane, 30% *v/v*).  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.70 (dd,  $J$  = 8.8, 2.8 Hz, 2H), 7.60 (d,  $J$  = 2.8 Hz, 2H), 7.11 (d,  $J$  = 8.8 Hz, 2H), 4.63 (d,  $J$  = 17.5 Hz, 2H), 4.53 (d,  $J$  = 17.5 Hz, 2H), 4.26 (q,  $J$  = 6.9 Hz, 4H), 3.55–3.67 (m, 4H), 1.31 (t,  $J$  = 7.1 Hz, 6H).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ): 166.2, 154.9, 136.1, 130.6, 128.7, 127.9, 126.8, 60.8, 58.8, 54.3, 14.4.

■ Synthesis of Tröger's base analog (±)-3



Tröger's base analog ( $\pm$ )-2 (500 mg), sodium hydroxide (200 mg), and DI water (20 mL) were mixed and refluxed under nitrogen gas for 48 h. The mixture was allowed to cool to rt, filtered (glass microfiber), acidified with HCl solution, and concentrated with a rotavap before being injected into a C18 reversed-phase chromatography column. Purified hydrolyzed TBA ( $\pm$ )-3 eluted at 50% H<sub>2</sub>O–MeOH. The collected and combined column fractions were reduced to one-tenth of their initial volume, chilled in a fridge and then filtered. The obtained solid was rinsed with ice-cold water and further dried under high vacuum overnight to obtain TBA 3, 390 mg, 91% yield. <sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>OD):  $\delta$  7.68 (dd,  $J$  = 8.2, 2.3 Hz, 2H), 7.61 (d,  $J$  = 2.3 Hz, 2H), 7.16 (d,  $J$  = 8.2 Hz, 2H), 4.73 (d,  $J$  = 17.3 Hz, 2H), 4.53 (d,  $J$  = 17.3 Hz, 2H), 3.72 (m, 2H), 3.56 (m, 2H). <sup>13</sup>C NMR (150 MHz, CD<sub>3</sub>OD): 169.4, 156.3, 137.7, 131.8, 129.7, 128.8, 128.1, 59.5, 55.1. MS (ESI +):  $m/z$  [M + H]<sup>+</sup> calcd for [C<sub>18</sub>H<sub>17</sub>N<sub>2</sub>O<sub>4</sub>]<sup>+</sup>: 325.34; found: 325.3.

#### ■ Preparation of potassium salt of Tröger's base analog ( $\pm$ )-3

TBA ( $\pm$ )-3 (973 mg, 3 mmol) and KOH (366 mg, 6 mmol) were sonicated in HPLC-grade MeOH until fully dissolved. This solution was reduced by rotavap and then dried under high vacuum at room temperature resulting in 1242 mg of potassium salt of ( $\pm$ )-3.

#### ■ Enantiopurification of Tröger's base analog (–)-(S,S)-3

Stock solution of  $\gamma$ -CD (2075 mg, 1.6 mmol) and KOH (718 mg, 12.8 mmol) in HPLC-grade H<sub>2</sub>O (32 mL) was prepared and gradually added to the potassium salt of TBA ( $\pm$ )-3 and sonicated to obtain a saturated solution of ( $\pm$ )-3. The resulting solution was passed through a 0.2  $\mu$ m microfilter and poured in a nitrogen-flushed beaker. EtOH (40 mL) was allowed to diffuse slowly into the solution at rt over 10 days. Pale yellow cubic crystals of enantioenriched 3 $\subset$ CD-MOF were isolated, placed on a sintered filter and rinsed with a 1:3 blend of H<sub>2</sub>O–EtOH (3  $\times$  5 mL), and then pure EtOH (3  $\times$  5 mL). The first crop of enantioenriched 3 $\subset$ CD-MOF crystals were digested in H<sub>2</sub>O, with sonification at room temperature. The pH of this solution was adjusted at 5 with the

addition of HCl before isolating enantioenriched TBA 3 from the solution with a C18 reversed-phase chromatography column using H<sub>2</sub>O–MeOH gradient. The isolated fractions containing enantioenriched 3 were combined, rotavaped and dried under high-vacuum to afford the first crop of enantioenriched TBA 3. Enantioenriched 3 was dissolved in a minimal volume of fresh  $\gamma$ -CD stock solution and was subjected to the diffusion of EtOH in order to obtain the second crop of enantioenriched 3 $\subset$ CD-MOF crystals and repeating the steps over and over again until obtaining the third crop of crystals, *i.e.* (–)-(S,S)-3 $\subset$ CD-MOF, which was then collected, rinsed, digested in H<sub>2</sub>O and chromatographed to obtain enantiopure (–)-(S,S)-3 as mentioned.

#### ■ Enantiopurification of Tröger's base analog (+)-(R,R)-3

The mother liquor was rotavaped to eliminate its EtOH and extra water content by reaching ~30% of its initial volume. The concentrate was then subjected to the diffusion of EtOH in order to eliminate (–)-(S,S)-3 enriched CD-MOF crystals from it. This step was repeated one more time to eliminate any remaining (–)-(S,S)-3 enriched CD-MOF crystals. The final mother liquor was then acidified with the addition of HCl before isolating (+)-(R,R)-3 from it with a C18 reversed-phase chromatography column and H<sub>2</sub>O–MeOH gradient. The isolated fractions containing (+)-(R,R)-3 were combined, rotavaped and dried under high-vacuum to obtain an off-white solid.

The remaining solutions of TBA 3 from the crystallization steps were then combined, acidified with addition of HCl and chromatographed with a C18 column, rotavaped and dried under high-vacuum to recover all remaining amounts of TBA 3 for storage.

## ■ Nuclear Magnetic Resonance (NMR) Spectroscopic Analysis Results

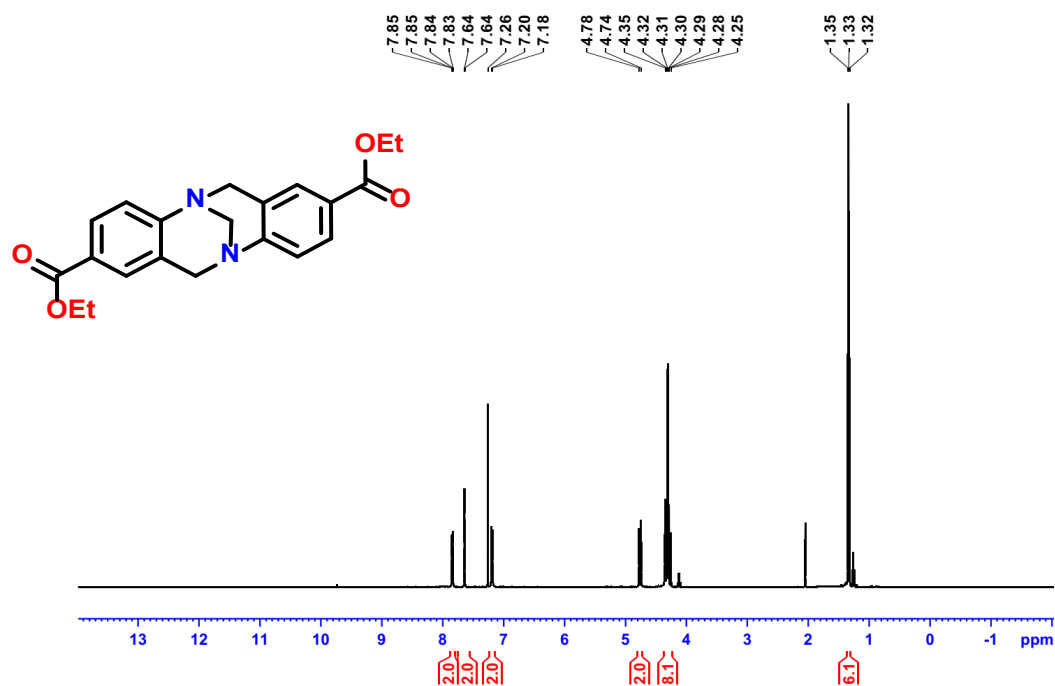


Figure S1. <sup>1</sup>H NMR Spectrum of TBA 1 in CDCl<sub>3</sub>, 600 MHz, 300K

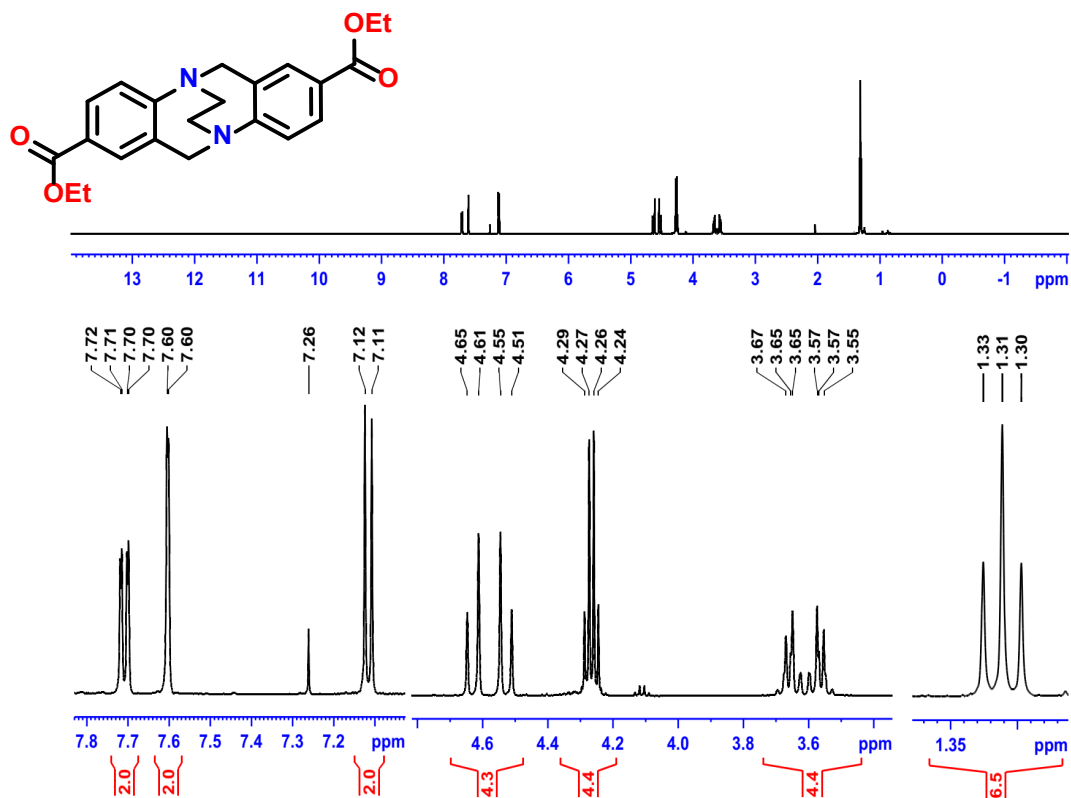
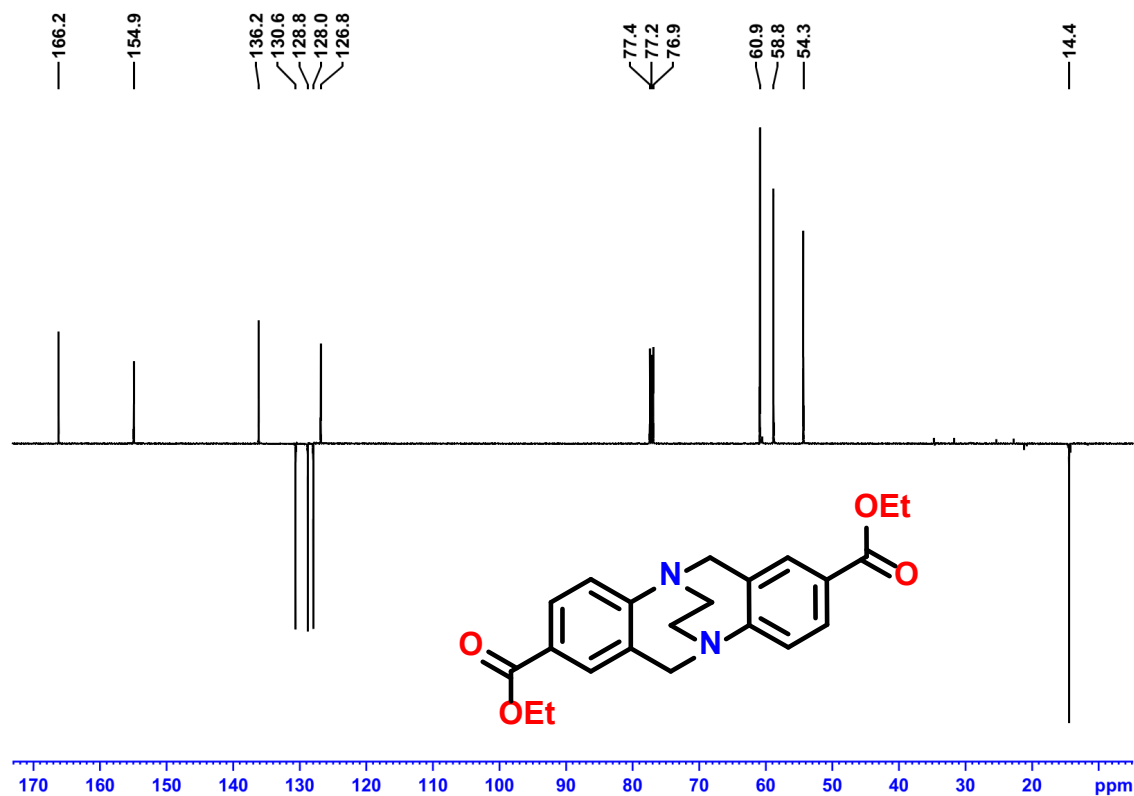
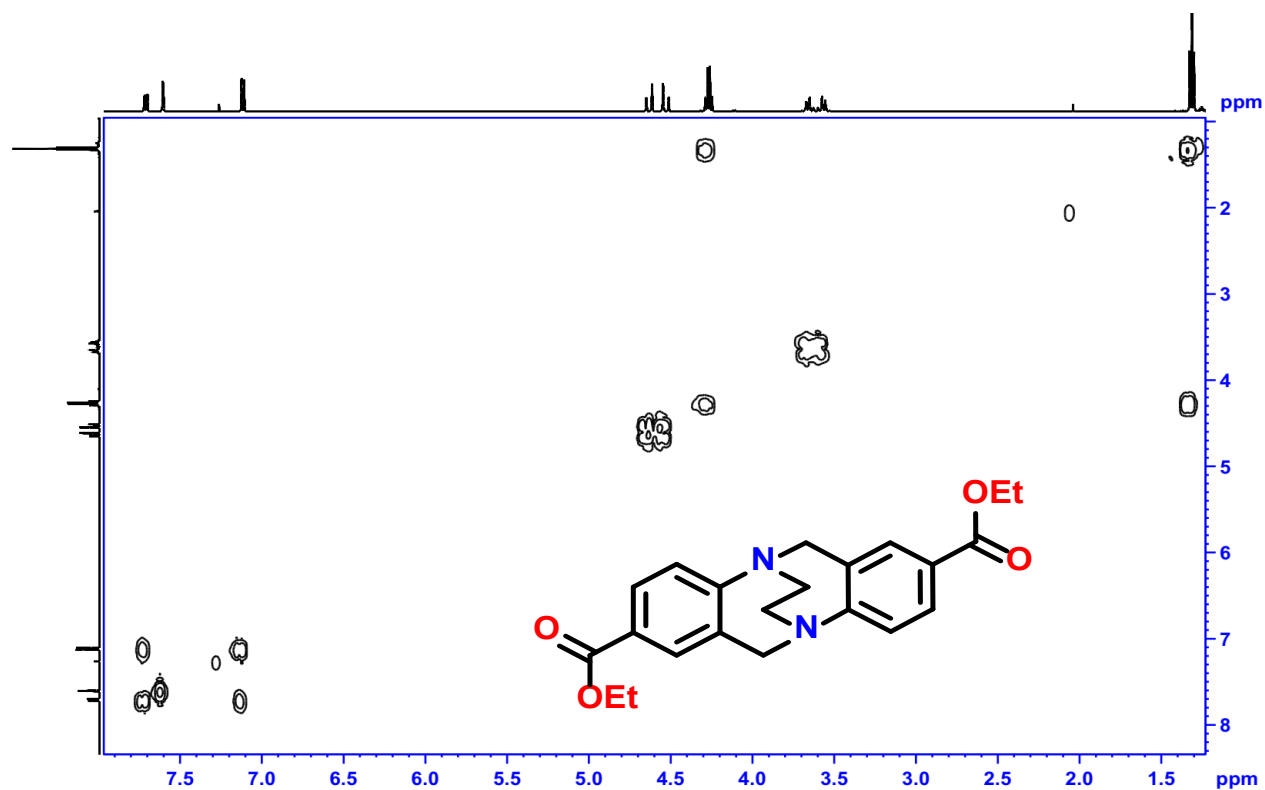


Figure S2. <sup>1</sup>H NMR Spectrum of TBA 2 in CDCl<sub>3</sub>, 600 MHz, 300K





**Figure S3.** DEPT135 NMR Spectrum of TBA 2 in CDCl<sub>3</sub>, 150 MHz, 300K



**Figure S4.** COSY NMR Spectrum of TBA 2 in CDCl<sub>3</sub>, 600 MHz, 300K

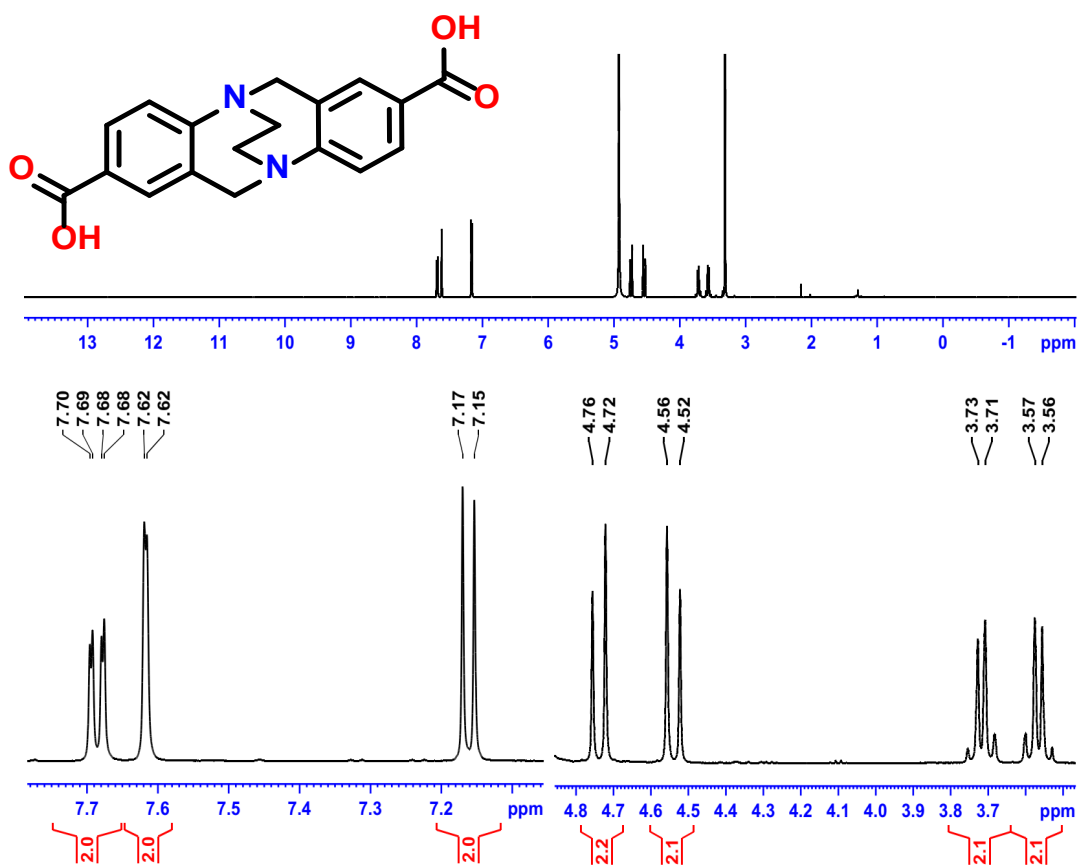


Figure S5. <sup>1</sup>H NMR Spectrum of TBA 3 in CD<sub>3</sub>OD, 600 MHz, 300K

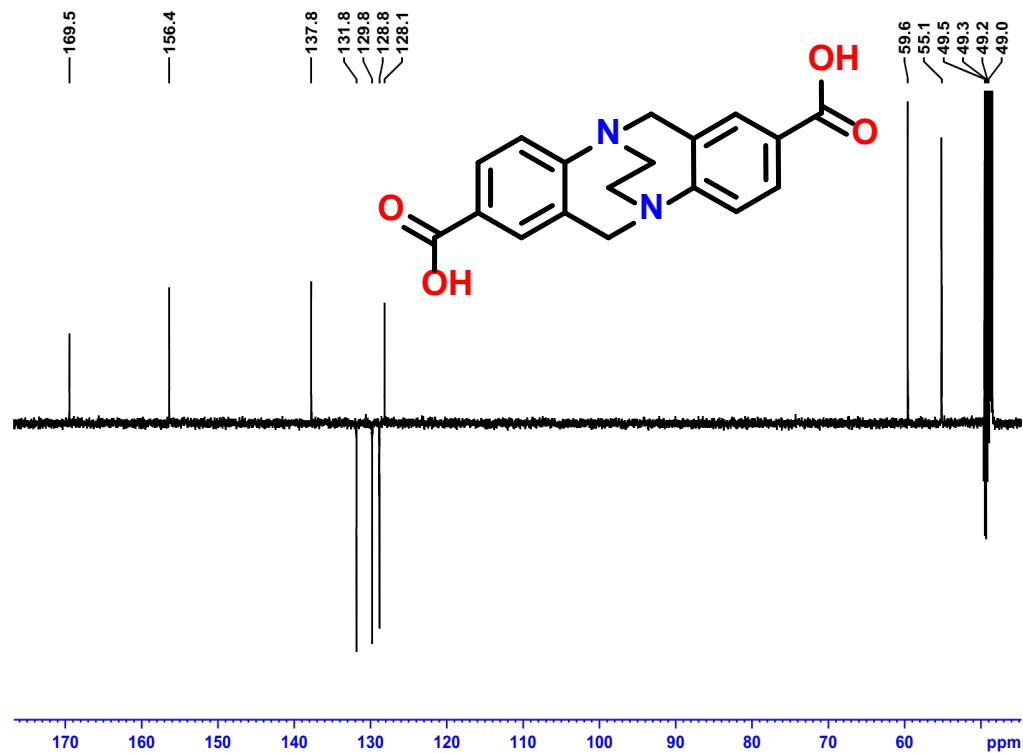
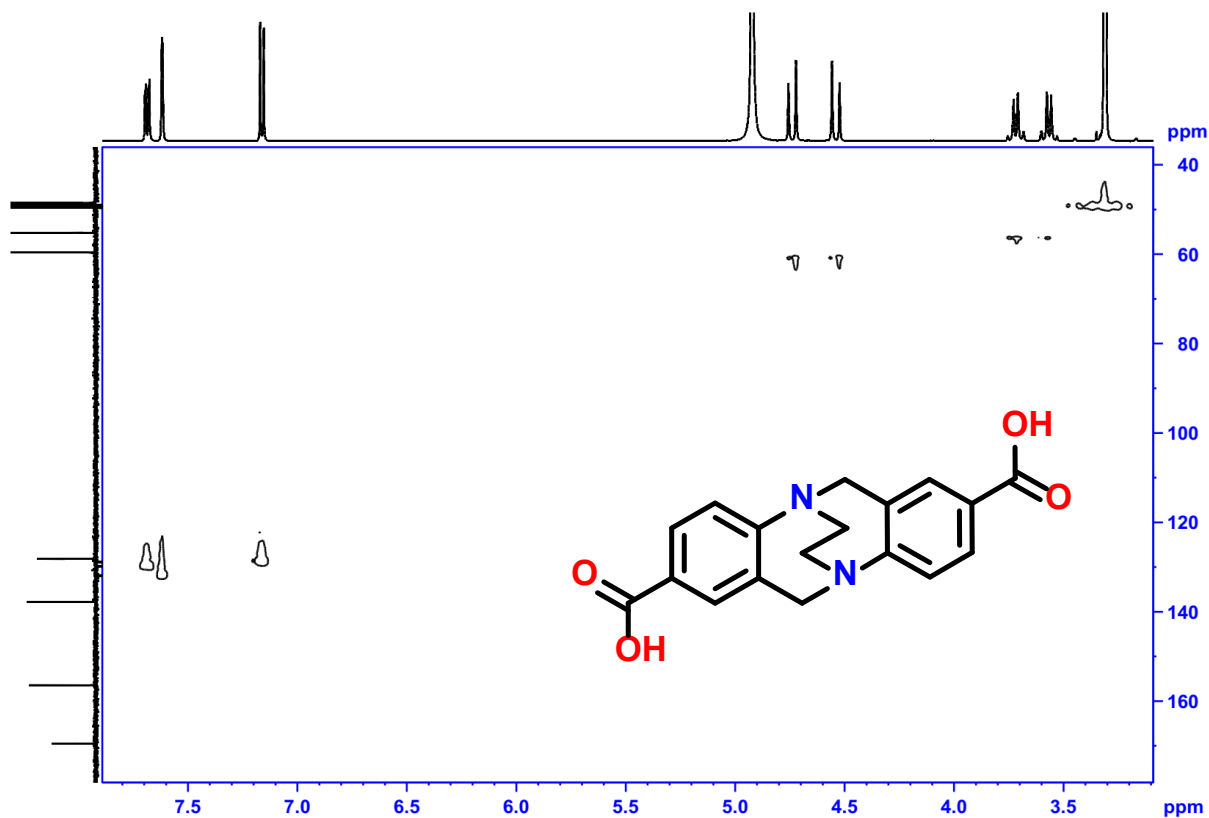


Figure S6. DEPT135 NMR Spectrum of TBA 3 in CD<sub>3</sub>OD, 150 MHz, 300K



**Figure S7.** HSQC NMR Spectrum of TBA 3 in  $\text{CD}_3\text{OD}$ , 600 MHz, 300K

## ■ References

1. Kazem-Rostami, M., A nitrogen-based chiral catenane for enantioenriching photocatalytic aerobic oxidation. *New J. Chem.* **2022**, 46, 21898.
2. Goswami, S.; Ghosh, K.; Dasgupta, S., Troger's base molecular scaffolds in dicarboxylic acid recognition. *J. Org. Chem.* **2000**, 65, 1907.