Supporting Information

Supramolecular Protecting Groups Can Impart Prosthetic Stereoselectivity to Catalytic Systems Employing Unmodified Achiral Heterogenous Catalysts.

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1. General Materials and Methods

Commercially available reagents and solvents were used as received. Column chromatography was performed on Kiesel gel silica gel 60 (230-400 mesh).

Temperature-controlled catalysis reactions (-20 °C to rt, which is 298 K unless otherwise stated) were performed using a Polar Bear Plus Crystal device fitted with a reactor block specific to 20 ml scintillation vials. Reactions were performed in 20 ml scintillation vials, using 5 mm PTFE stirrer bars. Other synthesis reactions performed as specific in individual preparative descriptions.

The NMR spectra were obtained using Bruker-400 (400 MHz) spectrometer, except spectra recoded at -20 °C (253 K) obtained using a Bruker-600 spectrometer. Chemical shifts (δ) are given in ppm and coupling constants *J* are given in hertz (Hz). All spectra were acquired at 298 K unless otherwise stated.

HPLC was performed using an Agilent 1100 instrument, equipped with a Diode Array Detector, applying conditions as specified below.

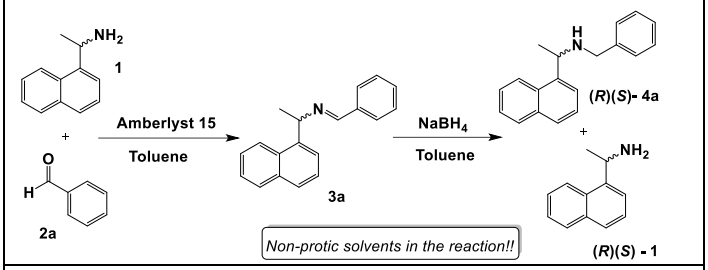
2. Catalysis Of Model Reductive Amination By Unselective Solid Catalyst.

Standard catalytic reaction procedure:

(where parameters vary, they are specified along with result data; other parameters and actions remain constant)

In a 20 ml vial with a stir bar amine (**1**, 0.1 mmol), aldehyde (e.g. **2a**, 1eq, 0.05 mmol), **TIPS-β-CD** (0.4 mmol) and toluene (2 ml) were added; The mixture was left stirring for 15 min at -20 °C, then Amberlyst 15 (50 mol%) was added, this mixture was left stirring for 1 hour at -20°C. Sodium borohydride (0.2 mmol) was added to this mixture and it was left stirring at -20°C for 1 hour to obtain the secondary amine (e.g. **4a)**. The reaction mixture was extracted with ethyl acetate (5 ml) - water (5 ml), the resulting ethyl acetate solution was extracted twice with a10% citric acid solution in water (5 ml) and washed with brine (5 ml) and then dried over anhydrous $NaSO_4$. After removal of the solvent *in vacuo*, the crude mixture was purified by silica gel column chromatography, eluting with a gradient of ethyl acetate in hexane, starting from 100% hexane and increasing the ethyl acetate content in 5% increments up to 50% (v/v). The product was dissolved in IPA-H_2O (50/50) and injected into HPLC (CHIRALPAK® IF reverse phase column, isocratic 10 mM NH_4HCO_3, pH = 8.6/IPA) to calculate enantiomeric excesses. *[Stereochemistry of products was confirmed using products from authentic samples of both amine enantiomers, acquired commercially]*

Table S1. Catalyst screening and reaction conditions optimisation.[a]



Entry	Amberlyst 15 (mmol %)	$NaBH_4$ (equiv.)	T (˚C)	Yield (%)	
				3a	4a
1	-	-	r.t.	90[b]	-
2	-	-	10	85[b]	-
3	-	-	-10	Minor product[c]	-
4	-	-	-20	0[c]	-
5	50	-	-20	90[b]	-
6	-	2[d]	r.t.	90	0[b]
7	50	2[d]	r.t.	-	95[b]
8	50	2[d]	-20	-	85[b]

[a] Reagents: Amine **1** (0.1 mmol), aldehyde **2a** (0.1 mmol) and toluene (2 ml), 1 h.

[b] Determined by ^{1}H-NMR.

[c] Observed by TLC.

[d] $NaBH_4$, 1 h.

3. Reuse of Amberlyst 15

To screen the recyclability of the Amberlyst 15, two reactivation processes were applied to the material after reaction between **1** and **2a** at -20 ˚C (253 K; Table S1. Entry 8). In the first one, after separating the material from the reaction mixture, it was washed only with an organic solvent (CH_2Cl_2) and dried at room temperature. The second process includes a first wash with CH_2Cl_2, followed by HCl 1N (in water) and drying at 50 ˚C. Thus, if the used catalyst was reactivated firstly, the conversion drastically decreased after the first reuse. On the contrary, the second reactivation process allows maintaining the efficiency of the catalyst for at least three reuses (Fig. S1). The reduce activity of Amberlyst 15 is probably due to the presence of organic material on the surface, which is eliminated after acid treatment, thus recovering catalytic properties of the solid acid (Fig. S1, blue column, yield 78%).

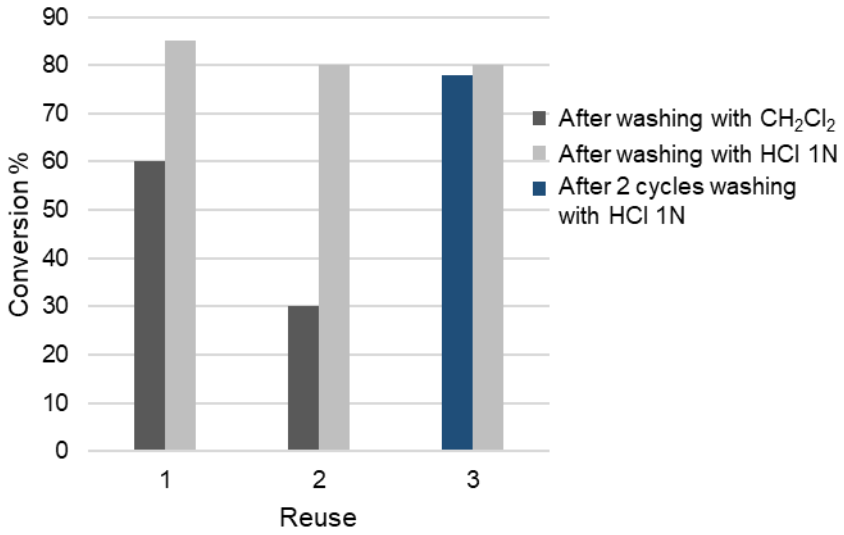


Figure S1. Reuse of Amberlyst 15 after reaction between **1** and **2a** at -20 ˚C.

To observe the stability of Amberlyst 15, FT-IR spectrum was performed before and after each reaction cycle. The FT-IR spectrum of Amberlyst 15 appeared to be the same before and after use (Fig. S2).

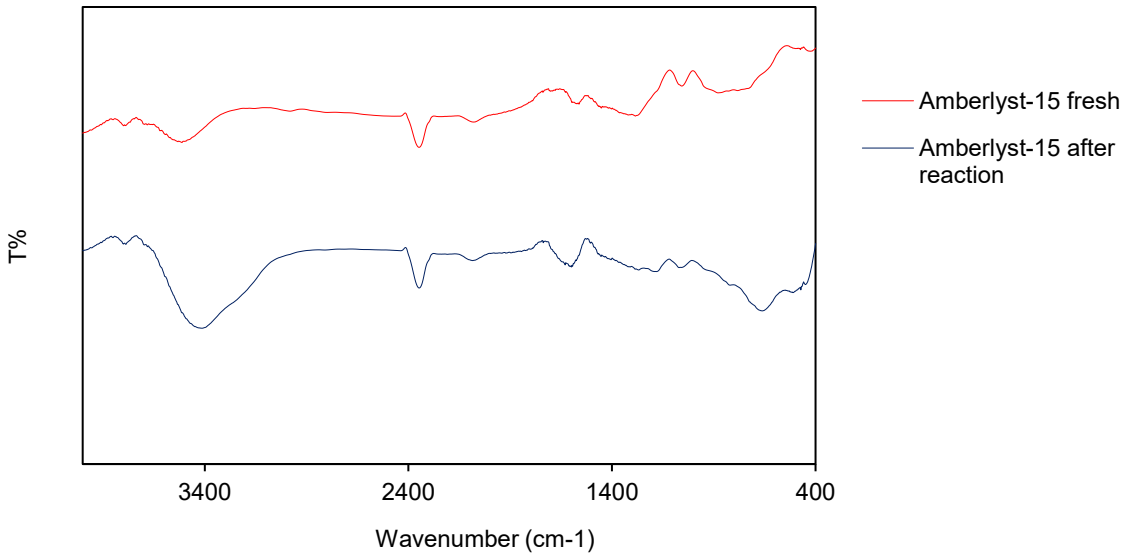
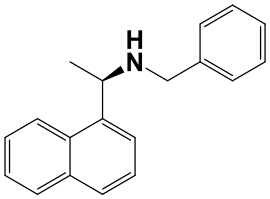


Figure S2. FT-IR of Amberlyst a) before and b) after reaction

4. Characterization of secondary amine products

(R)-N-benzyl-1-(naphthalen-1-yl)ethan-1-amine



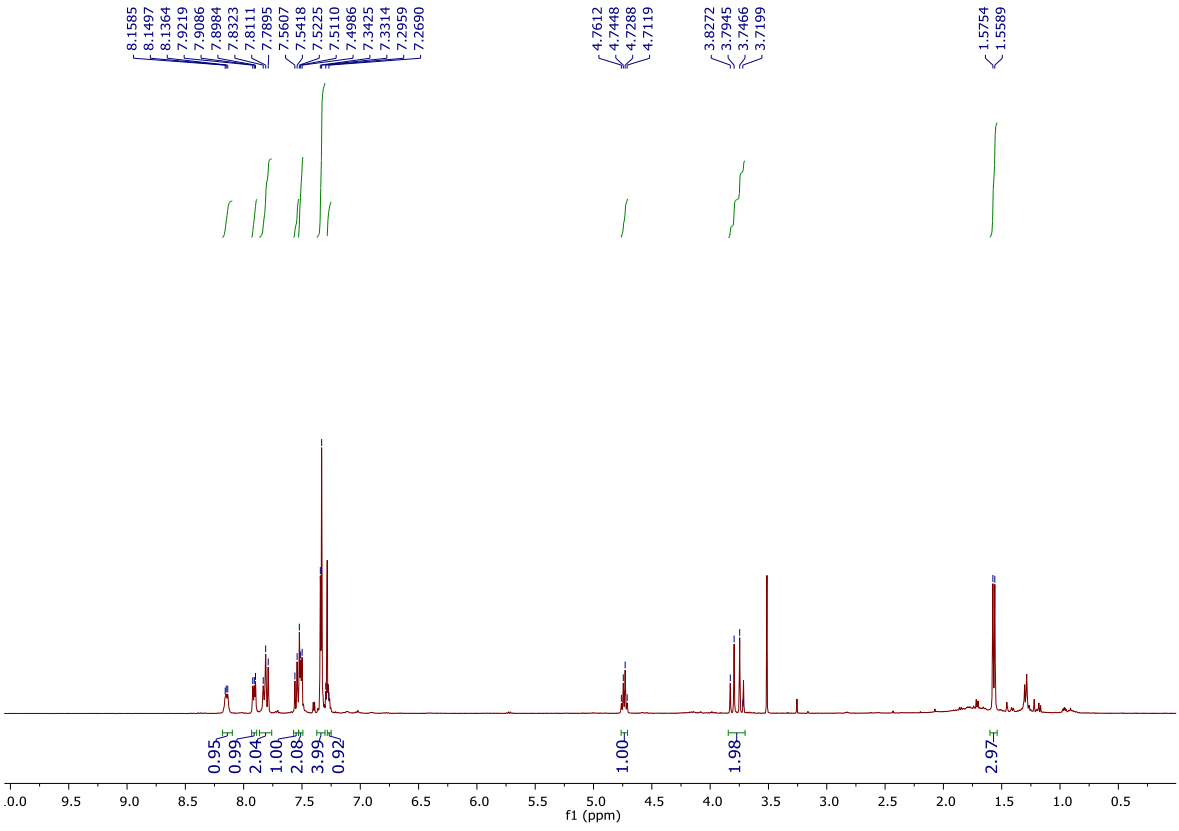
4a

Yellow oil, yield: 88%, ee: 91.4% (CHIRALPAK® IF column Reverse Phase, isocratic NH_4HCO_3 10mM pH= 8.6/IPA 50/50, 0.5 mL/min, retention time:53.9 min).

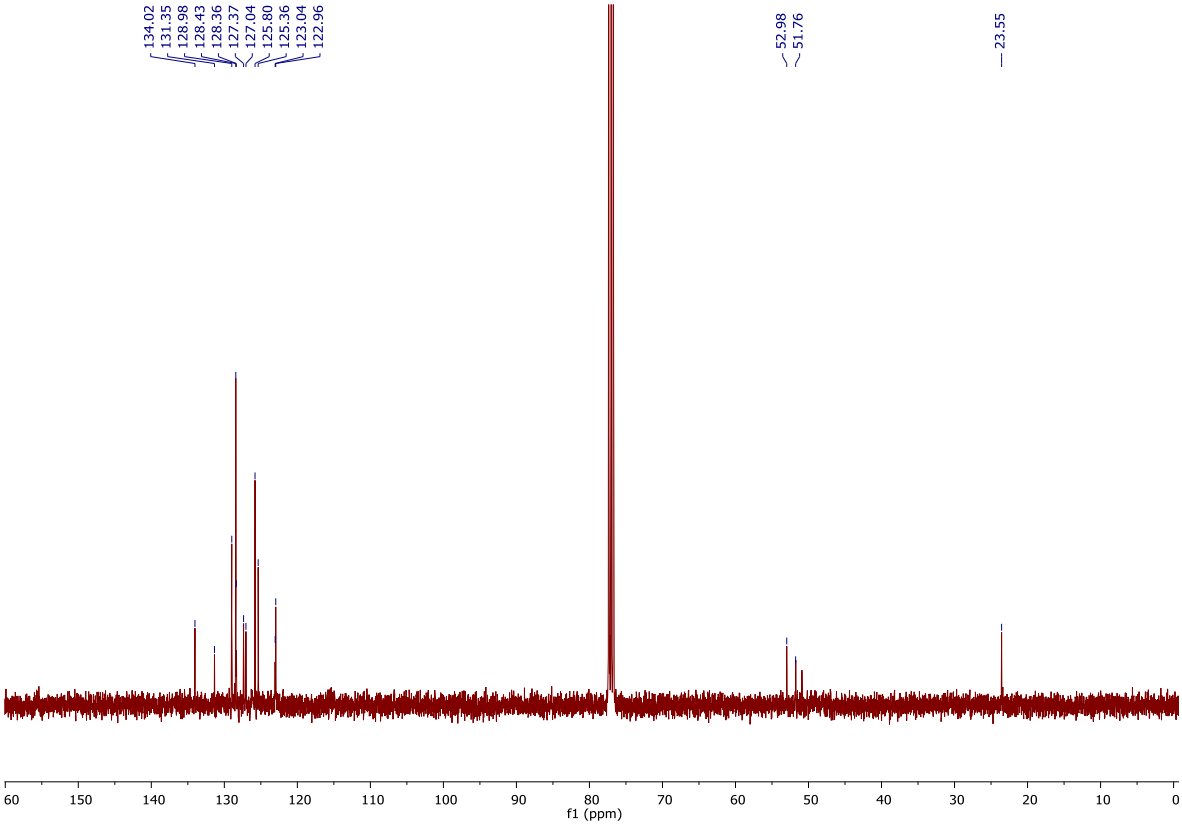
^{1}H NMR (400 MHz $CDCl_3$): δ = 8.14 (dd, *J*= 352, 8.84 Hz, 1H), 7.90 (dd, *J*=4.08, 9.4 Hz, 1H), 7.81 (t, *J*= 8.48 Hz, 2H), 7.54 (t, *J*= 7.56 Hz, 1H), 7.51 (dd, *J* = 4.96, 14.04 Hz, 2H), 7.33-7.34 (m, 4H), 7.26-7.29 (m, 1H), 4.73 (q, *J* = 6.56, 12.96 Hz, 1H), 3.77 (q, *J* = 13.08, 32.24 Hz, 2H), 1.56 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (104 MHz $CDCl_3$) : δ = 134.0, 131.3, 128.9, 128.4, 128.3, 127.4, 127.0, 125.8, 125.4, 123.0, 122.9, 52.9, 51.7, 23.5.

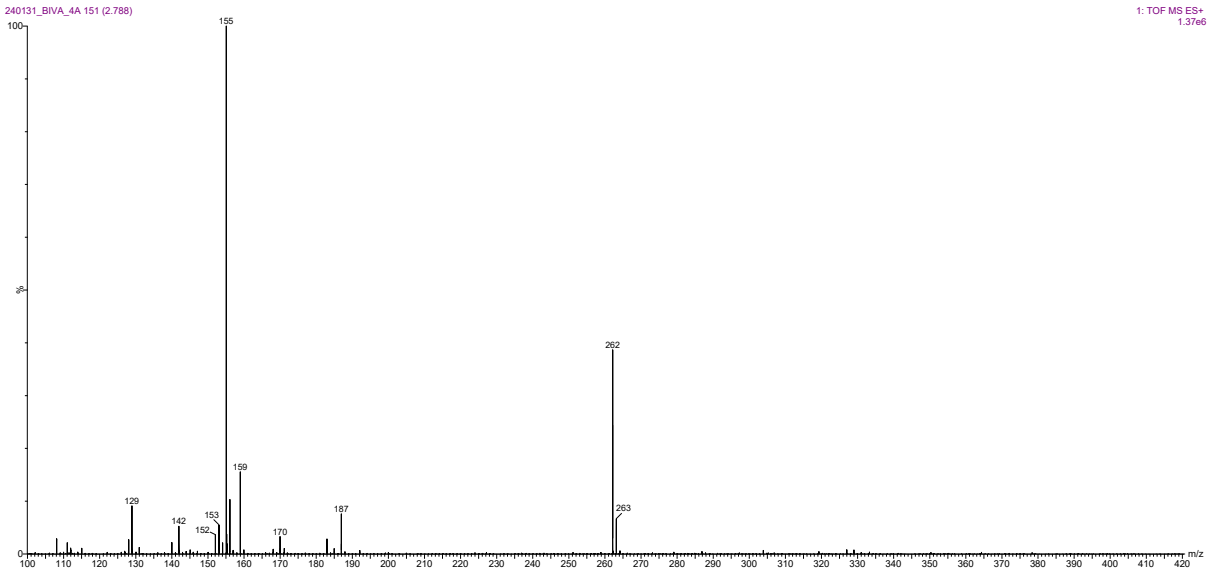
MS (ESI+) m/z: $[M + H]^+$ Calcd. for $C_{19}H_{19}N$ 261.37; Found 262.



^{1}H NMR of **4a**

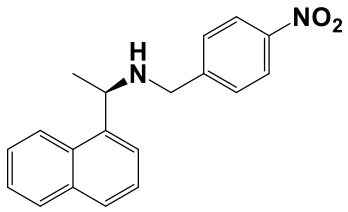


^{13}C NMR of **4a**



MS spectrum of **4a**

(R)-1-(naphthalen-1-yl)-N-(4-nitrobenzyl)ethan-1-amine



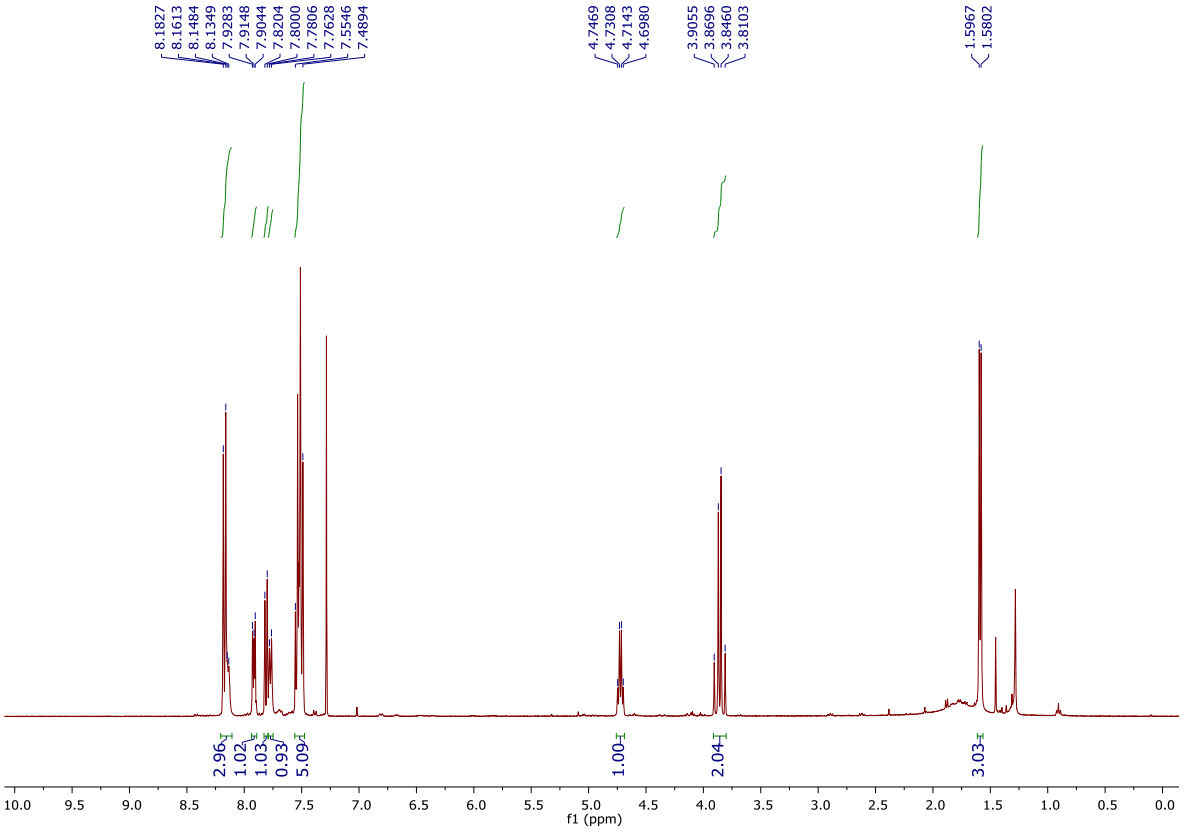
4b

White solid, yield: 92%, ee: 91.2% (CHIRALPAK® IF column Reverse Phase, isocratic NH_4HCO_3 10mM pH= 8.6/IPA 30/70, 0.5 mL/min, retention time:29.42 min).

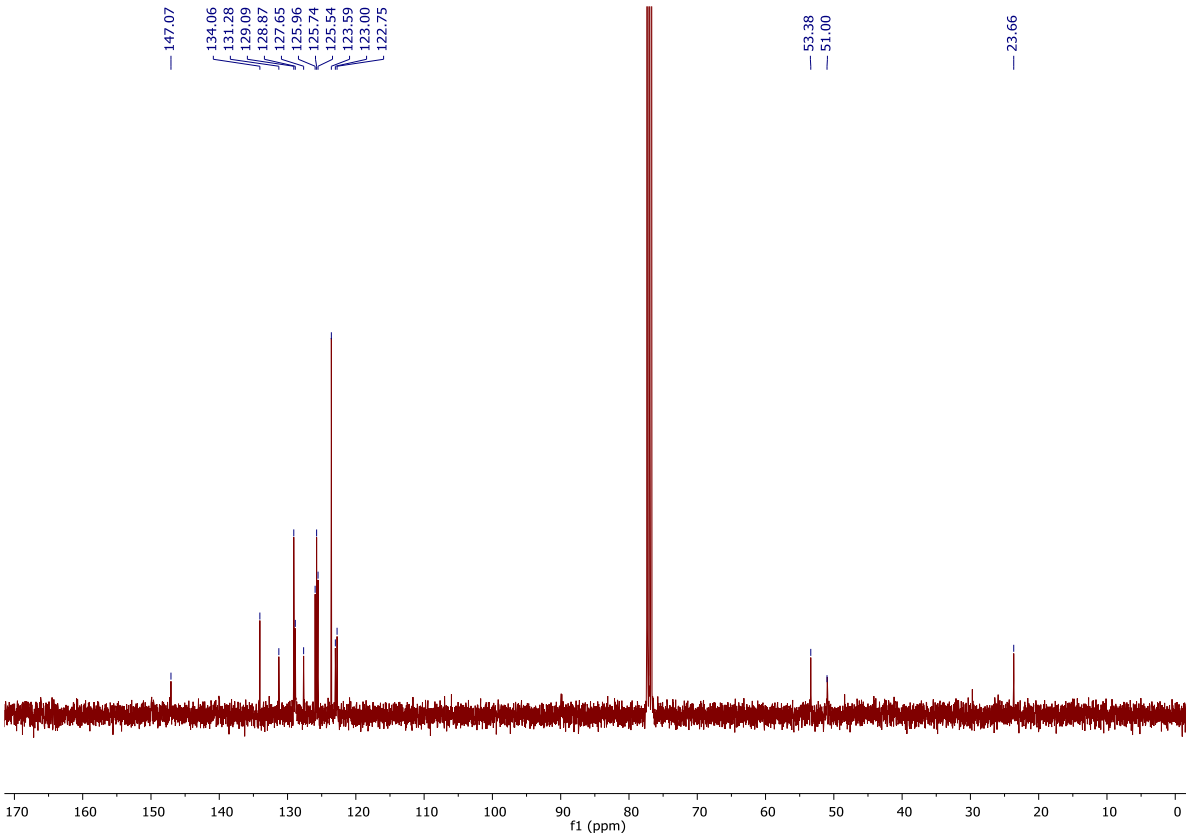
^{1}H NMR (400 MHz $CDCl_3$): δ = 8.17 (d, *J* = 8.56 Hz, 2H), 8.14 (d, *J* = 5.4 Hz, 1H), 7.91 (dd, *J* = 4.16, 9.56 Hz, 1H), 7.81 (d, *J* = 8.16 Hz, 1H), 7.77 (d, *J* = 7.12 Hz, 1H), 7.48-7.55 (m, 5H), 4.72 (q, *J* = 6.44, 13.04 Hz, 1H), 3.85 (q, *J* = 14.63, 23.8 Hz, 2H), 1.58 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (104 MHz $CDCl_3$) : δ = 147.0, 134.0, 131.3, 129.1, 128.9, 127.6, 125.9, 125.7, 1.25.5, 123.6, 123.0, 122.7, 53.4, 51.0, 23.6.

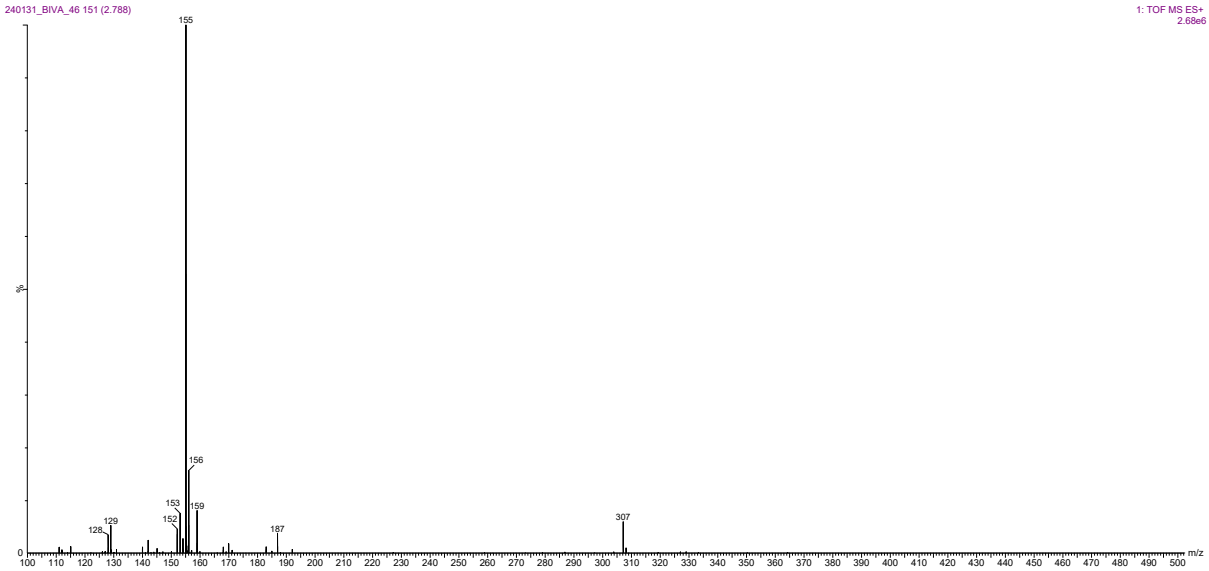
MS (ESI+) m/z: $[M + H]^+$ Calcd. for $C_{19}H_{18}N_2O_2$ 306.37; Found 307.



^{1}H NMR of **4b**



^{13}C NMR of **4b**



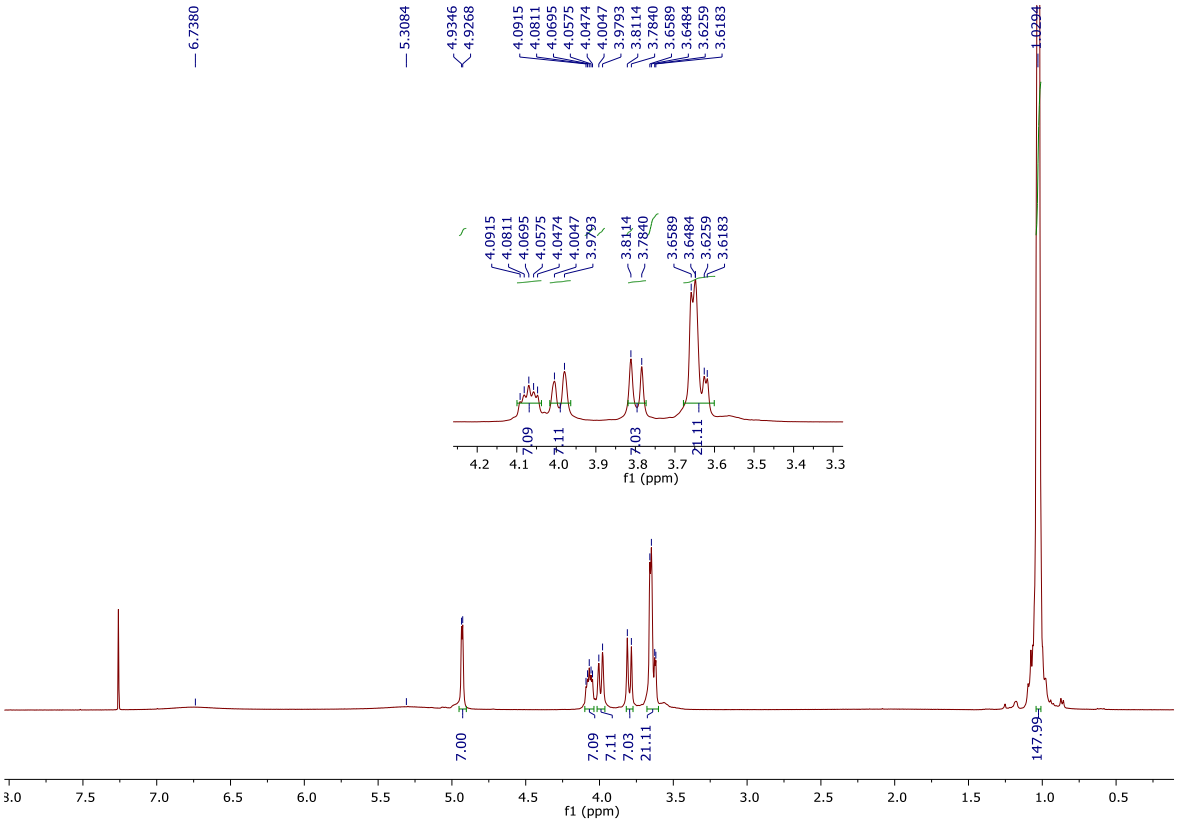
MS spectrum of **4b**

5. Synthesis and characterization of Heptakis(6-O-triisopropylsilyl)-β-cyclodextrin (TIPS-β-CD)

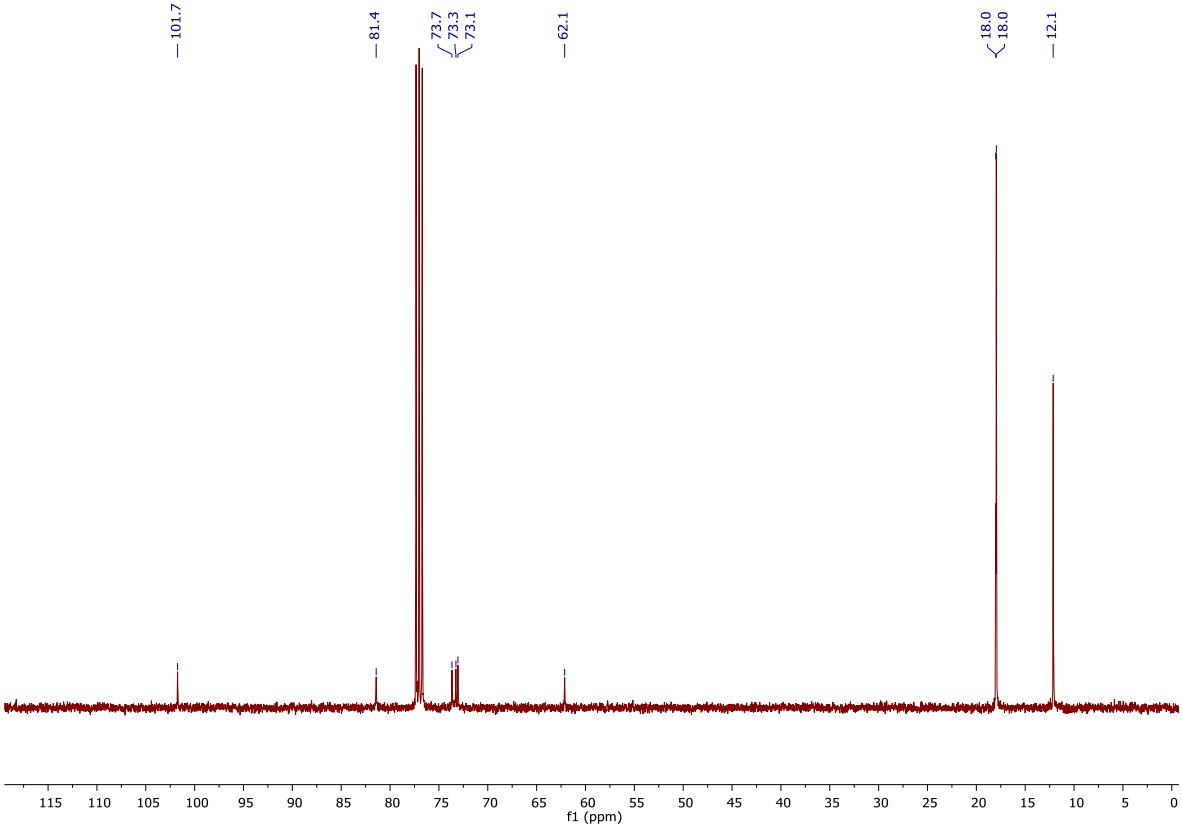
A mixture of β-cyclodextrin (0.8 mmol, 1 eq, 904 mg), imidazole (33.6 mmol, 42 eq, 2.23g), triisopropylsilylchloride (30.4 mmol, 38 eq, 5.86 g, 6 mL) and dry dimethylformamide (12 mL) was placed in a 20 ml microwave tube having a magnetic stirrer. The mixture, which was heated under microwave irradiation (70 °C) during 2 hours. The reaction mixture was extracted with ethyl acetate (150 mL) – water (150 mL), The resultant ethyl acetate solution was extracted with aqueous citric acid solution 10 % (150 mL and washed twice with brine (150 mL), and then was dried over anhydrous $NaSO_4$. After the solvent was removed in vacuo, the resulting solid was purified by silica gel column chromatography (85:15, *v*/*v* dichloromethane/methanol) to yield **TIPS-β-CD** as a white solid (1.15 g, 64%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.73 (s, 7OH), 5.30 (s, 7OH), 4.93 (d, 7H, J = 3.12 Hz, 7H), 4.06 (qu, *J*= 4.16, 8.8, 13.6, 17.64 Hz, 7H), 3.99 (br d, *J* = 10.16 Hz, 7H), 3.79 (br d, *J* = 10.96 Hz, 7H), 3.61-3.65 (m, 21H), 1.02 (s, 147H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 101.7, 81.4, 73.7, 73.3, 73.1, 62.1, 18.1, 18.0, 12.1; FT-IR (ATR): 3318, 2941, 2866, 1461, 1154, 1035, 881, 679 cm^{-1}.



^{1}H NMR of **TIPS-β-CD**



^{13}C NMR of **TIPS-β-CD**

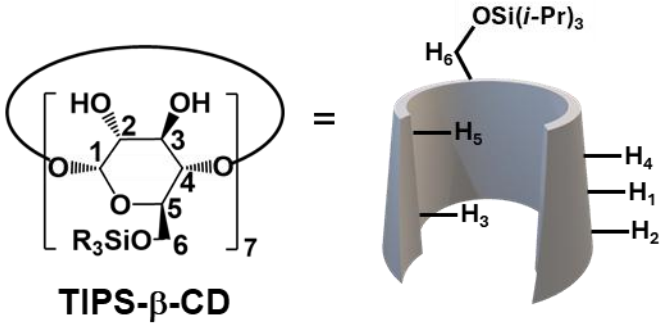
6. Binding of amine *(S)*-1 and *(R)*-1 by TIPS-β-CD

All NMR binding studies were performed in Toluene-d8 solution.

Titrations were performed to assess the binding of both amine enantiomers by **TIPS-β-CD.** Solvents and solutions were dispensed using Hamilton syringes, as appropriate; host or guest substance aliquots for addition to stock solutions were measured by mass (whether liquid or solid).

To ensure accuracy, each stage in titrations was made up in a separate clean NMR tube, from stock solutions of **TIPS-β-CD** and the relevant amine. In each tube, a constant concentration of 0.005 M **TIPS-β-CD** was present. Relevant amounts of host (300 µl of 0.01 M solution) and stock guest solutions were used to reach the requisite concentration (0 to 60 eq); at higher guest additions (11.6 to 60.0 eq) a 1.00 M guest solution was used; at lower guest additions (0 to 10 eq) a 0.1 M guest solution was used, to ensure accurate dispensing. Each tube was made up to a constant volume of 600 µl using unadulterated solvent. ^{1}H spectra were acquired together, each comprising 160 scans, at room temperature (298 K). Spectra are shown in Figure S4 and Figure S5, below.

Spectra were processed using MestReNova v14.3.2-32681. A constant chemical shift of residual toluene proton at *ca.* 2.12 ppm was ensured. Chemical shifts were extracted using the peak picking tool in GSD mode, with the maximum number of fitting cycles available; where multiples were not recognised symmetrically, they were merged consistently to ensure consistent assessment of chemical shift. Binding isotherms were fit using Bindfit (sequential 2:1 NMR model; L-BFGS-B method; see "Notes on binding model and comparison to literature" for rationale of model choice) to estimate first (K_{11}) and second (K_{12}) binding constants, using the chemical shift of protons H_1, H_3, $H_{6(A)}$ and $H_{6(B)}$, where protons were labelled as set out below:



TIPS-β-CD

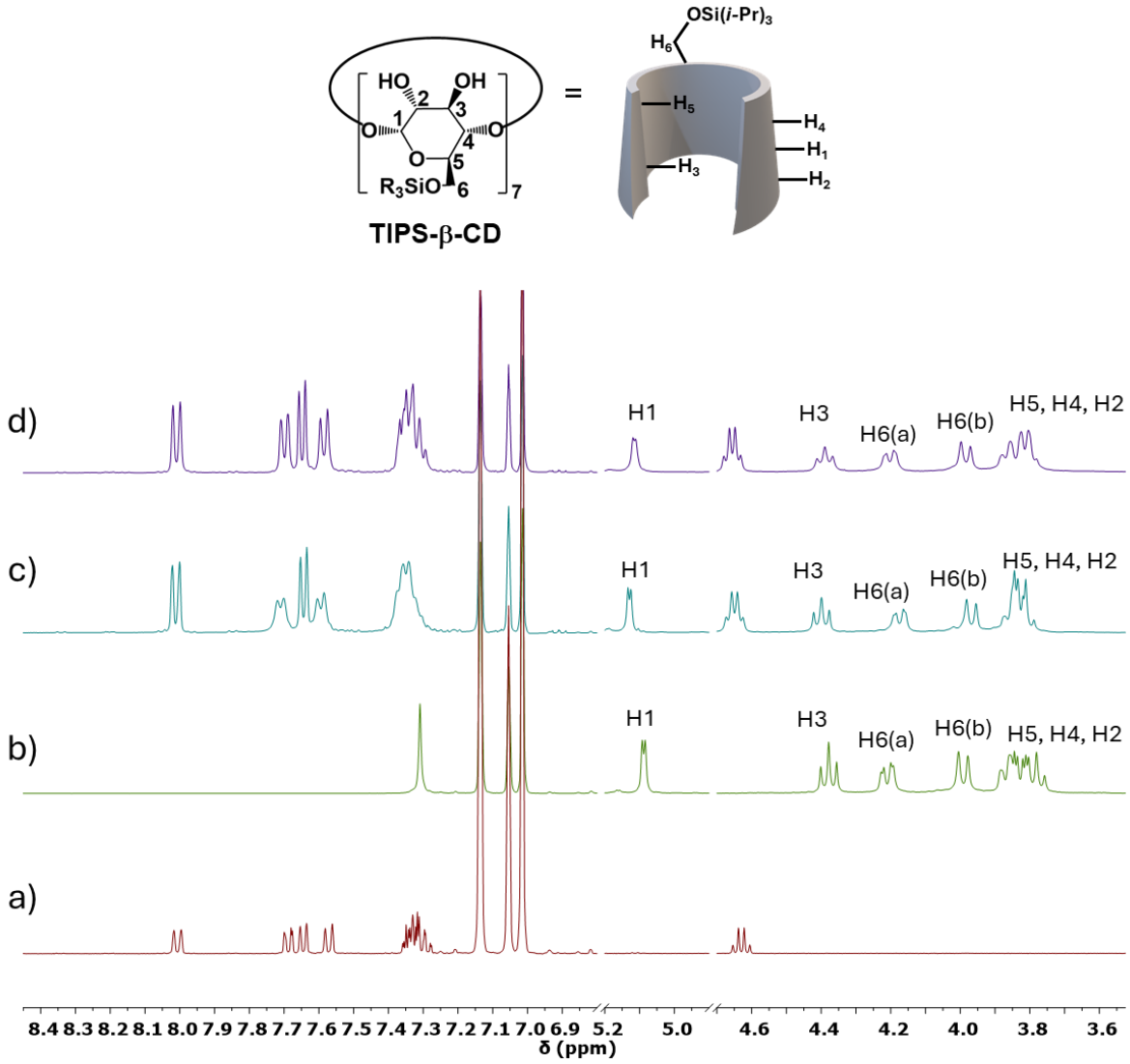


Fig S3. ^{1}H spectra of a) **(*S/R*)-1**, b) **TIPS-β-CD**, c) 1:1 mix of **(*S*)-1** + **TIPS-β-CD** and d) 1:1 mix of **(*R*)-1** + **TIPS-β-CD** in d_8-toluene [all at 298 K]. Assignment of important **TIPS-β-CD** resonance labelled.

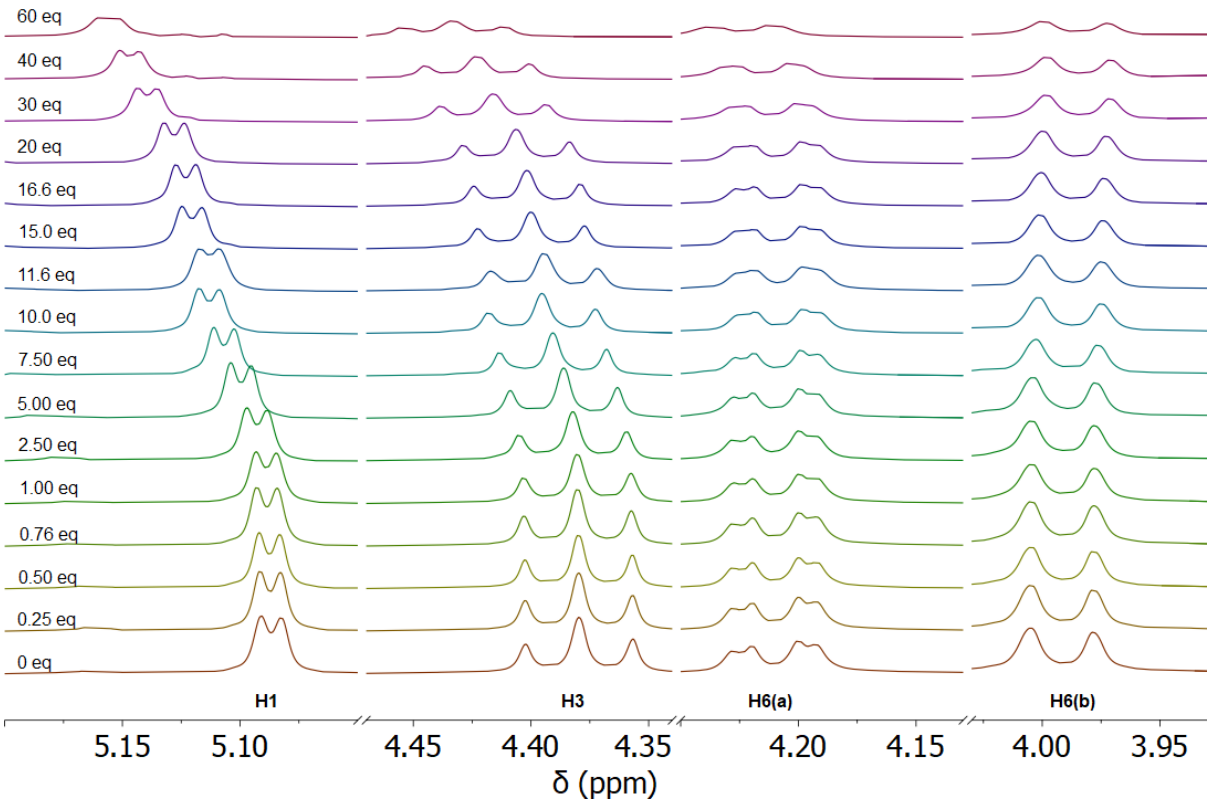


Fig S4. ^{1}H spectra of **TIPS-β-CD** (0.005 M) in d_8-toluene on addition of ***(S)*-1**, at 298 K (equivalents of ***(S)*-1** added noted to the left of spectra).

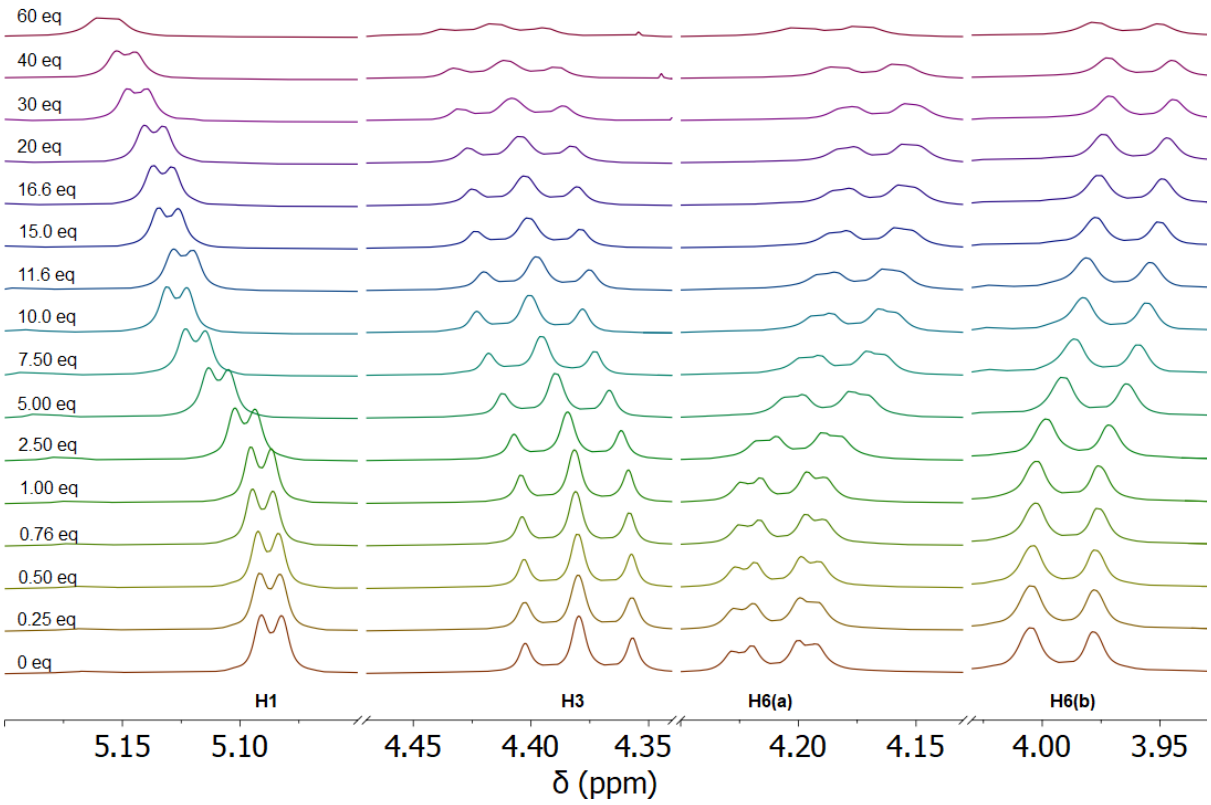


Fig S5. ^{1}H spectra of **TIPS-β-CD** (0.005 M) in d_8-toluene on addition of ***(R)*-1**, at 298 K. (equivalents of ***(R)*-1** added noted to the left of spectra)

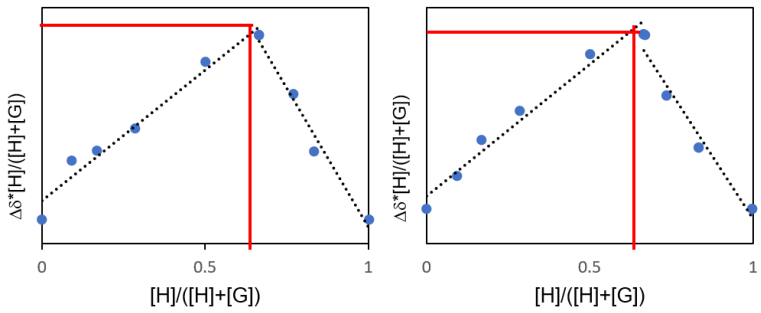


Fig S6. Jobs Plot of proton H1 of **TIPS-β-CD** host (**H**) at room temp (298 K) in d_8-toluene on addition of guests (**G**), ***(S)*-1** (left) and ***(R)*-1** (right).

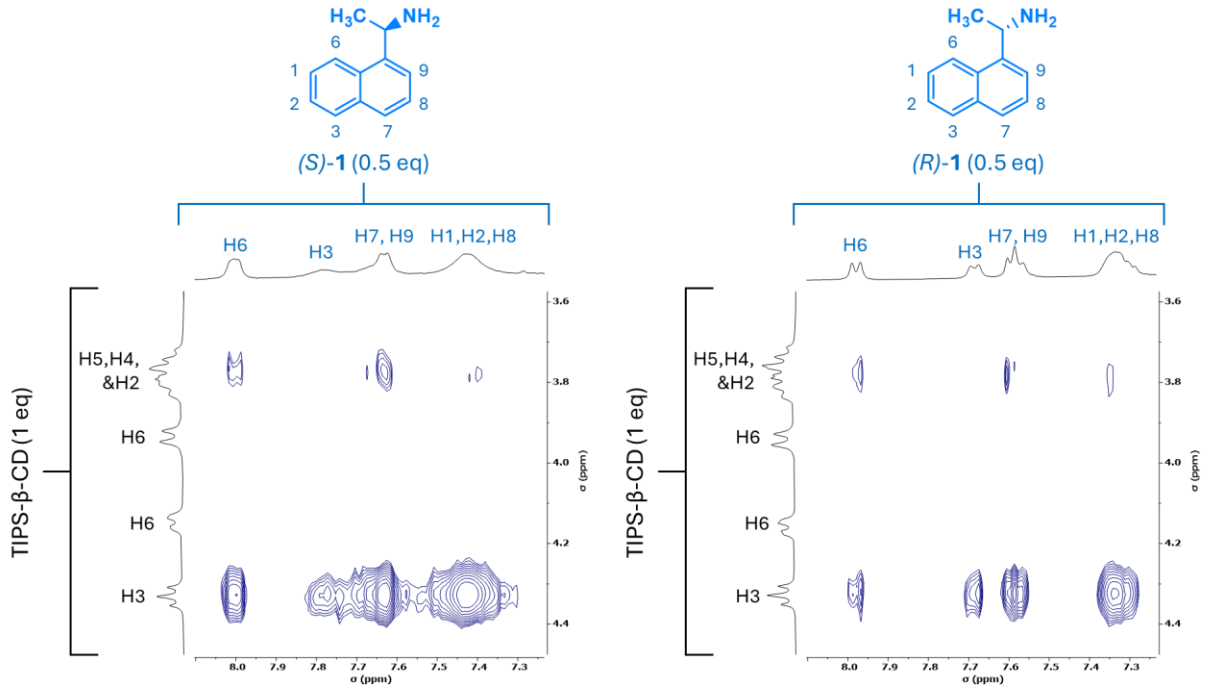


Fig. S7. Rotating Frame Overhauser Effect Spectroscopy (ROESY) spectra of **TIPS-β-CD** mixed with (left) **(*S*)-1**, and (right) **(*R*)-1**, in toluene-d8 at room temp (298 K). Interactions observable between the aromatic protons of **1** (labelled light blue), and H-3 and H-5 of **TIPS-β-CD**, showing amine **1** inclusion into **TIPS-β-CD** (host). Interactions with **(*S*)-1** are somewhat more intense.

Notes on binding model and comparison to literature:

All previously-observed binding for these host/guest combinations (binding in other solvents) [Kida *et al*., 10.1021/ja312367k] follow a 2:1 binding stoichiometry, schematically illustrated in Fig 3b. Jobs Plots in our solvent, toluene (Fig S3), concur. We note, however, that direct comparison to literature values (binding in other solvents) are not appropriate, since published binding constants are calculated using an unorthodox concerted (one step) 2:1 binding model as follows:

$$2\mathbf{H} + \mathbf{G} \leftrightharpoons \mathbf{G@H_2}$$

Observing chemical shift changes at multiple host protons (Figure 3), we did not find exclusively monotonic responses, and this is inconsistent with the concerted 2:1 binding model. [Kida *et al*., 10.1021/ja312367k] Furthermore, cooling to -20 °C (Figure S8), we found direct evidence of a two-step process: slow guest exchange for the second binding of **(S)-1** (K_{12}), and fast exchange for a first binding step (K_{11}).

As a result, we applied a stepwise 2:1 model (2:1 NMR model, Bindfit) to model binding as follows:

$$2\mathbf{H} + \mathbf{G} \leftrightharpoons \mathbf{G@H} + \mathbf{H} \leftrightharpoons \mathbf{G@H_2}$$

Estimating 2:1 Binding of *(S)*-1 by TIPS-β-CD:

Spectra are shown in Figure S4, below, and change in selected. Simultaneous fitting of chemical shift changes of H1, H3, H6(A) and H6(B) on titration is shown in Figure 3 (at 298 K).

K_{11} estimated as 0.213 M^{-1} (+/- 2.74%)

K_{12} estimated as 1999.9 M^{-1} (+/- 0.74%)

$\beta \approx 426\ M^{-2}$

Estimating 2:1 Binding of *(R)*-1 by TIPS-β-CD:

Spectra are shown in Figure S5, below, and change in selected. Simultaneous fitting of chemical shift changes of H1, H3, H6(A) and H6(B) on titration is shown in Figure 3 (at 298 K).

K_{11} estimated as 0.0805 M^{-1} (+/- 1.72%)

K_{12} estimated as 1219.9 M^{-1} (+/- 0.41%)

$\beta \approx 98\ M^{-2}$

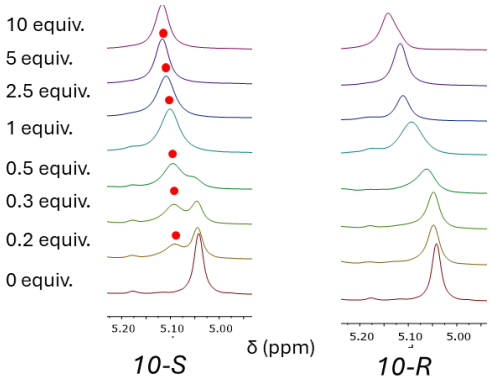


Fig S8. ^{1}H spectra of proton H1 of **TIPS-β-CD** in d_8-toluene on addition of ***(S)*-1** (left) and ***(R)*-1** (right) at -20 °C (253 K). *[Note line broadening is observed in all resonance at low temperature in d_8-toluene (See Fig S9 and S10), including residual aromatic toluene resonances.]*

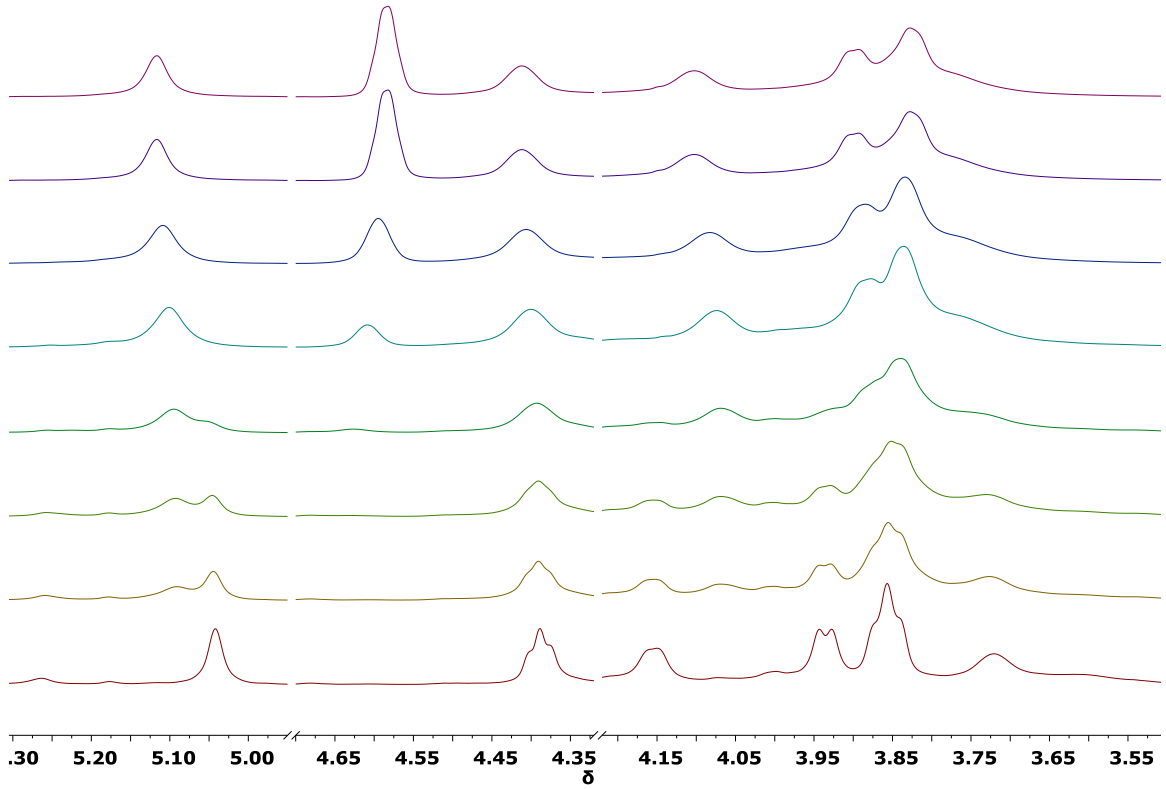


Fig S9. ^{1}H spectra of **TIPS-β-CD** (0.005 M) in d_8-toluene on addition of ***(S)*-1** at -20 °C (253 K).

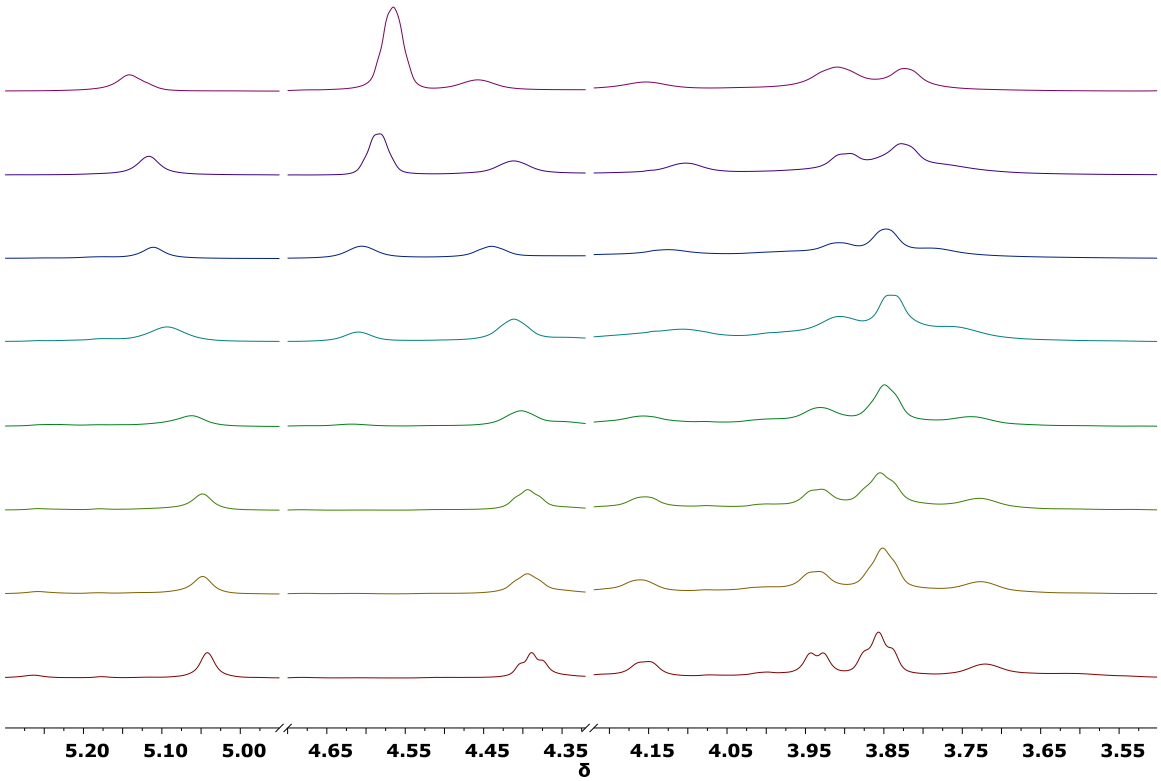
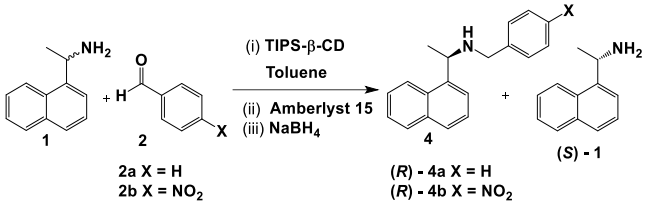


Fig S10. ^{1}H spectra of **TIPS-β-CD** (0.005 M) in d_8-toluene on addition of ***(R)*-1** at -20 °C (253 K).

7. SPG-Mediated Kinetic Resolution in Model Reaction

Table S2. Catalyst screening and reaction conditions optimisation. [a]

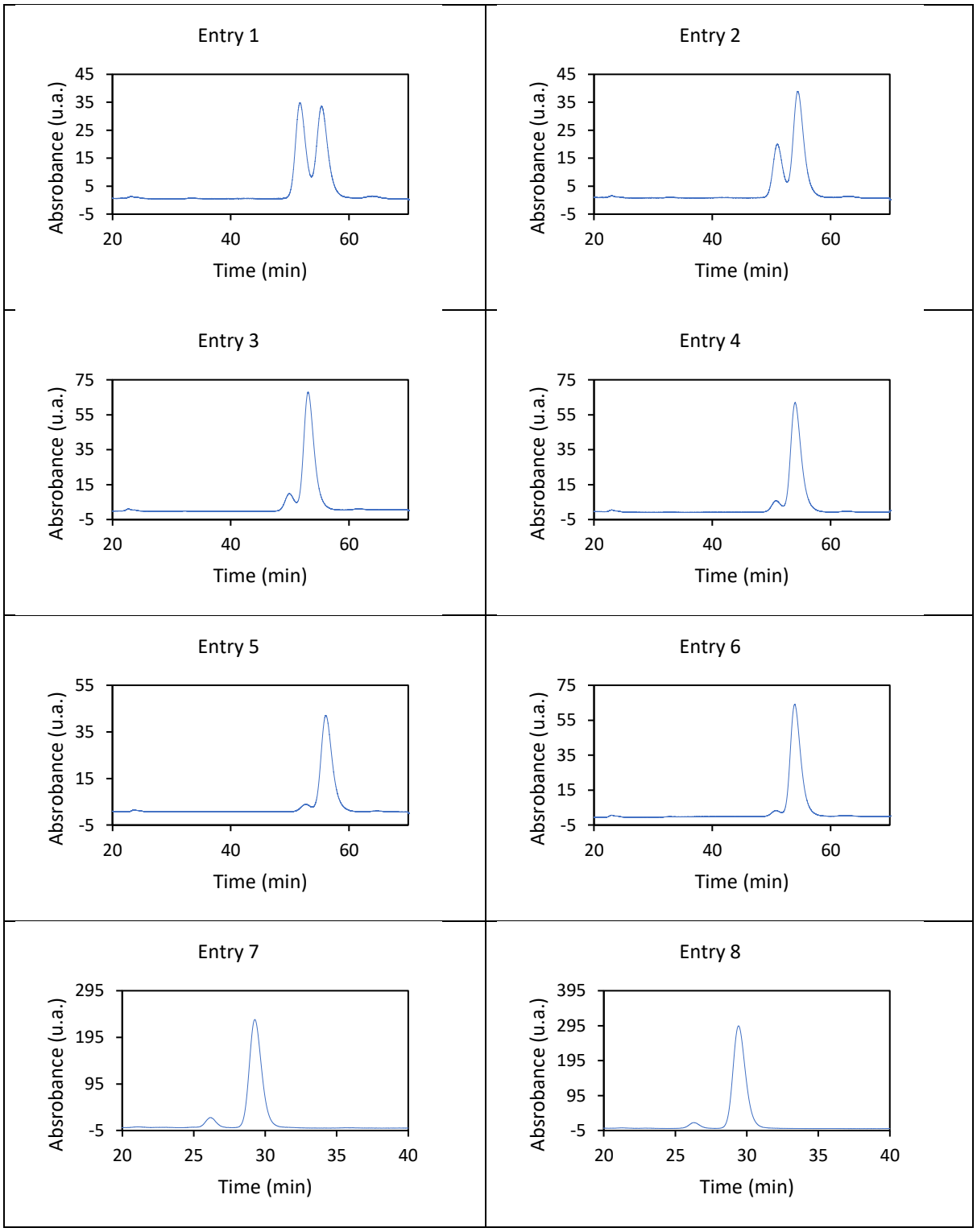


Entry	Aldehyde	Equiv.	T (˚C)	Conv. (%)[b]	ee (%)[b]
1	**2a**	0.5	r.t.	90	3.6
2	**2a**	0.5	10	82	38
3	**2a**	0.5	0	80	78
4	**2a**	0.5	-10	80	84
5	**2a**	0.5	-20	78	90
6	**2a**	0.2	-20	80	91
7	**2b**	0.2	-10	81	86
8	**2b**	0.2	-20	82	91

[a] Reagents: [(i) amine **1** (0.1 mmol), aldehyde **2a** (0.05 mmol), TIPS-β-CD (0.4 mmol) and toluene (2 mL), 15 min. (ii) Amberlyst 15 (50% mmol), 1 h. (iii) $NaBH_4$ (0.20 mmol), 1h.

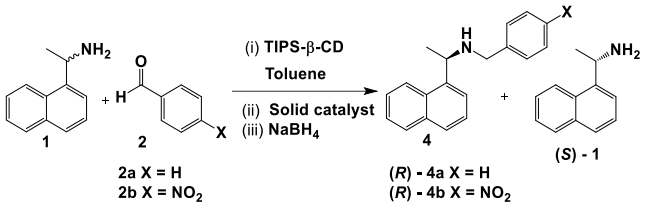
[b] The conversion of **2a**/**2b** and % *ee* of products **4a**/**4b** was determined by HPLC (see chromatograms below).

Chromatograms of **Table S2.** Catalyst screening and reaction conditions optimisation.



8. Modular Substitution Of Catalyst

Table S3. Assessing effect of modular substitution of solid catalysts on system selectivity.[a]



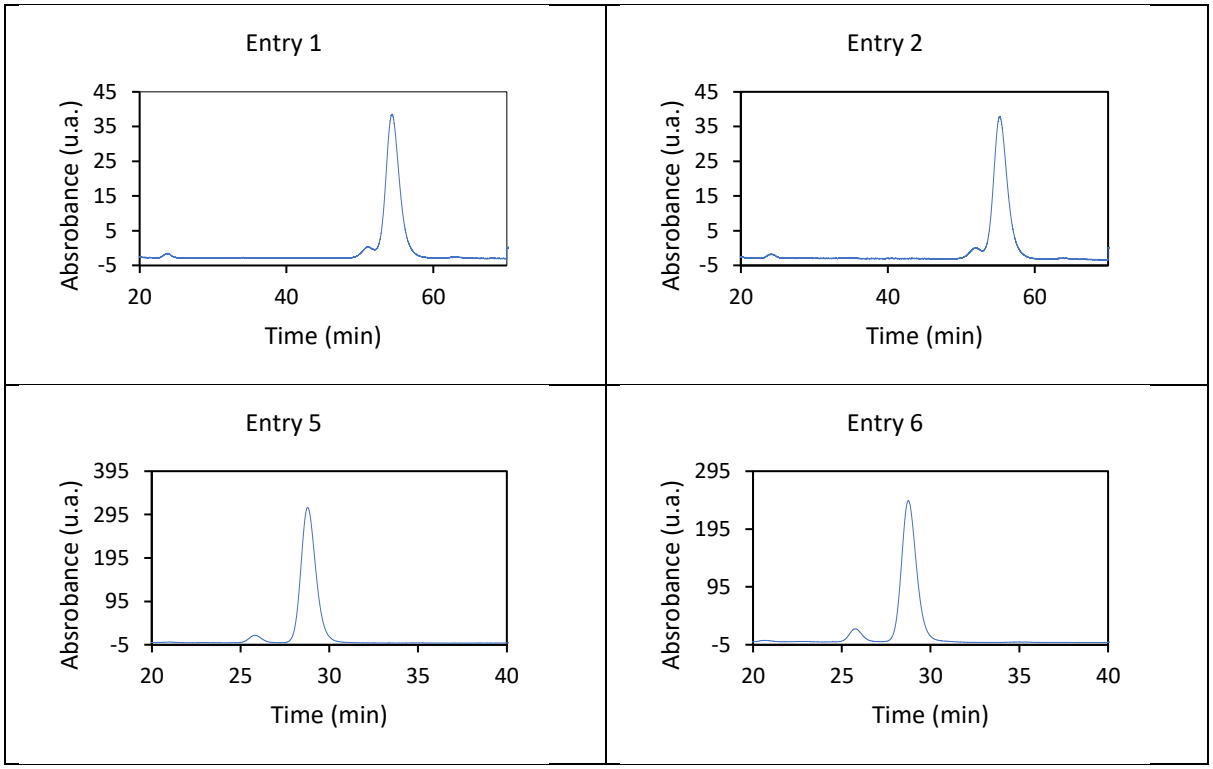
2a X = H
2b X = NO_2

(*R*) - 4a X = H
(*R*) - 4b X = NO_2

Entry	Aldehyde	Solid acid catalyst	Conv (%)[b]	ee (%)[b]
1	**2a**	Graphene oxide	28	88
2	**2a**	Montmorillonite	20	88
3	**2a**	MCM-41		-
4	**2a**	SiO_2		-
5	**2b**	Graphene oxide	30	92
6	**2b**	Montmorillonite	22	85
7	**2b**	MCM-41		-
8	**2b**	SiO_2		-

[a] Reagents: Amine **1** (0.1 mmol), aldehyde **2a** or **2b** (0.05 or 0.02 mmol), TIPS-β-CD (0.4 mmol) and toluene (2 mL), 15 min. Then, solid acid (50% mmol), 1 h. Finally, $NaBH_4$ (0.20 mmol), 1h at 20 ˚C. [b] The conversion of **2a** or **2b** and ee were determined by HPLC. (see chromatograms below)

Chromatograms of **Table S3.** Assessing effect of modular substitution of solid catalysts on system selectivity.



9. Reuse of TIPS-β-CD

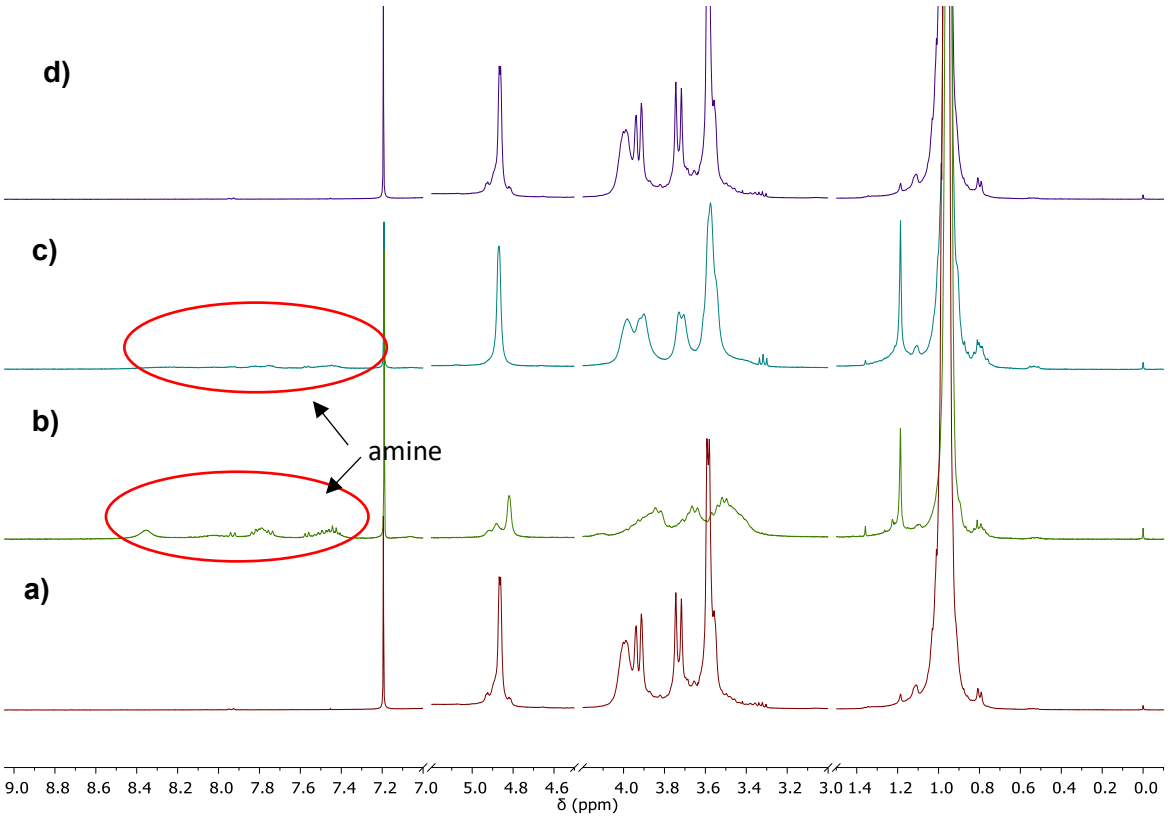
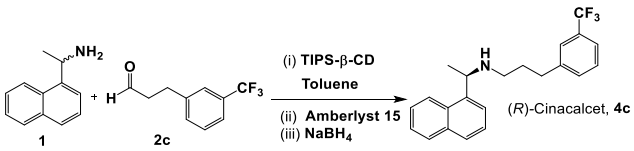


Fig S11. ^{1}H spectra (in d_8-toluene) of: a) fresh **TIPS-β-CD**, unused as SPG; b) **TIPS-β-CD** after the reaction; c) **TIPS-β-CD** after one extraction (ethyl acetate/HCl 1N in water), d) **TIPS-β-CD** after two extractions (ethyl acetate-HCl 1N in water).

10. SPG-Mediated Stereoselective Synthesis Of (R)-Cinacalcet

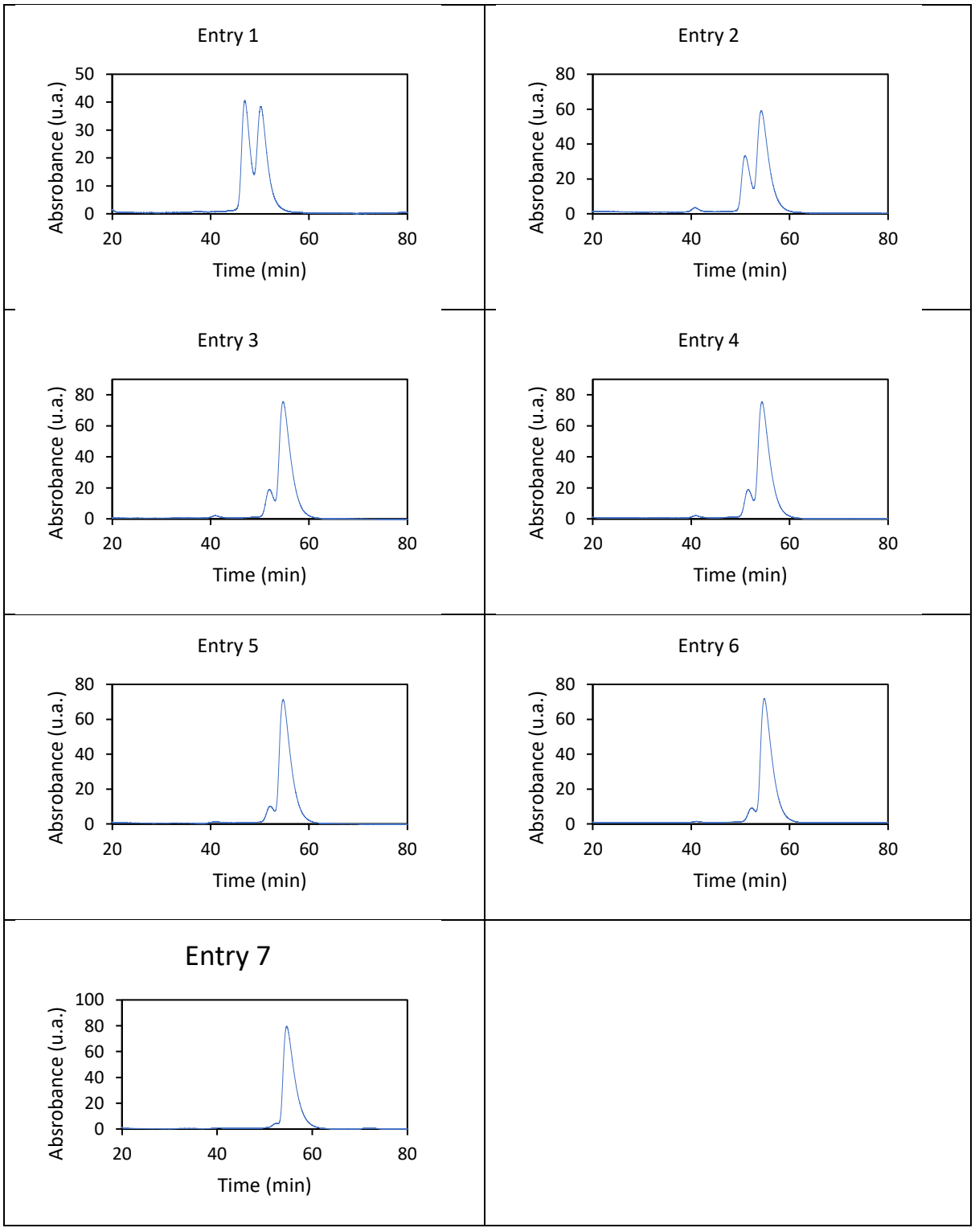
Table S4. Synthesis of cinacalcet under heterogenous conditions. [a]



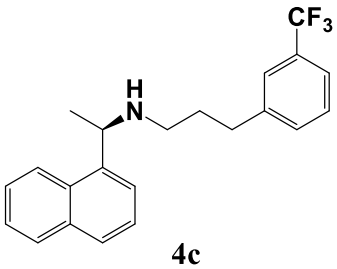
Entry	Aldehyde 2c Equiv.	T (˚C)	Conv. (%)[b]	ee (%)[b]
1	0.5	r.t.	91	2
2	0.5	10	90	40
3	0.5	0	88	70
4	0.5	-10	85	72
5	0.5	-20	80	85
6	0.2	-10	84	84
7	0.2	-20	80	94

[a] Reagents: Amine **1** (0.1 mmol), aldehyde **2c** (0.05 or 0.02 mmol), TIPS-β-CD (0.4 mmol) and toluene (2 mL), 15 min. Then, amberlyst 15 (50% mmol), 1 h. Finally, $NaBH_4$ (0.20 mmol), 1h. [b] The conversion of **2c** and ee were determined by HPLC. (see chromatograms below)

Chromatograms of Table S4. Synthesis of cinacalcet under heterogenous conditions.



(R)-Cinacalcet (4c)



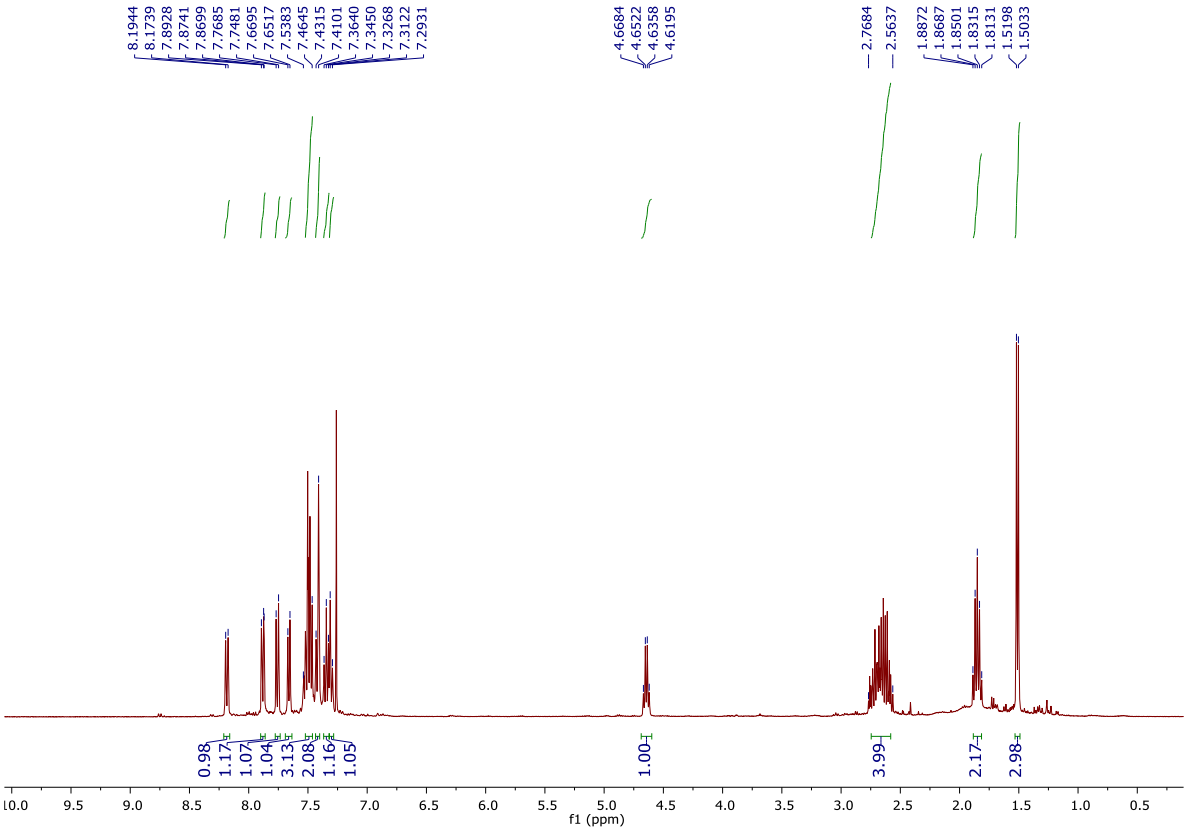
4c

Solid yellow, yield: 90%, ee: 93.7% (CHIRALPAK® IF column Reverse Phase, isocratic NH_4HCO_3 10mM pH= 8.6/IPA 45/55, 0.5 mL/min, retention time:50.23 min).

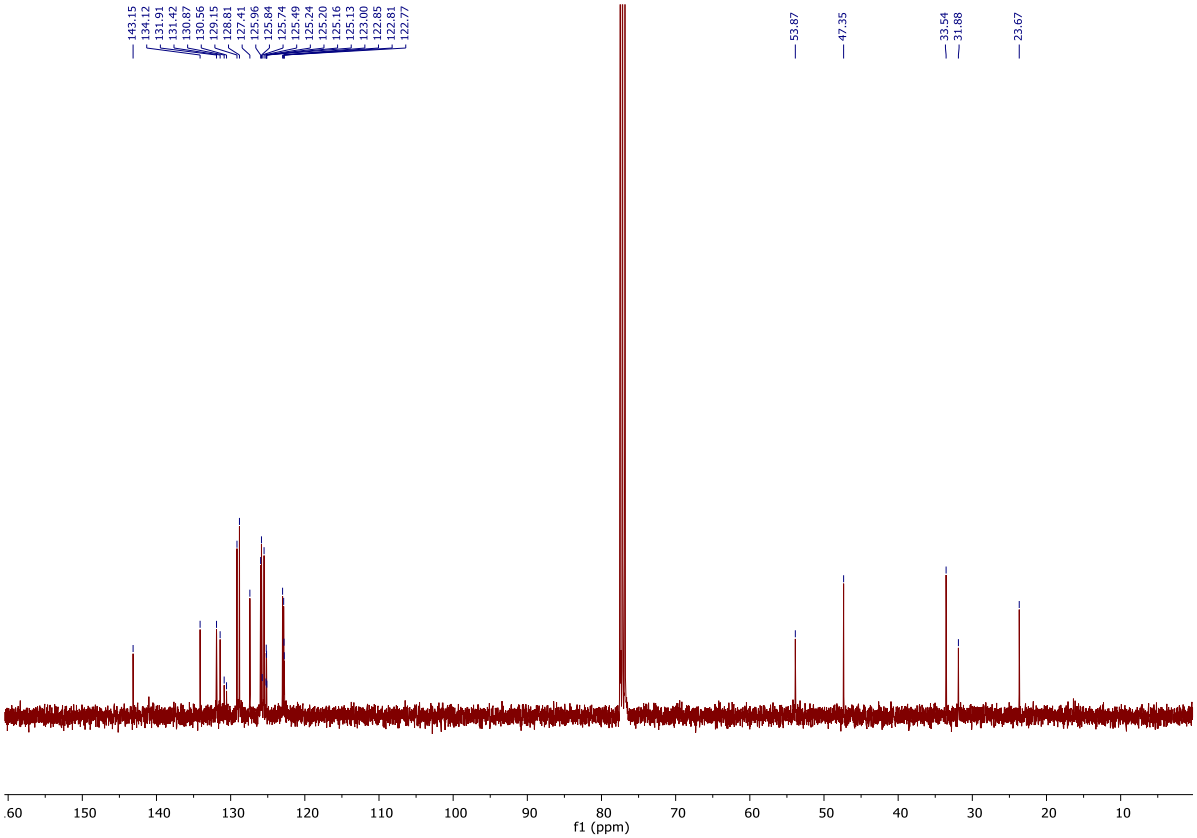
^{1}H NMR (400 MHz $CDCl_3$): δ = 8.18 (d, *J*=8.0 Hz, 1H), 7.88 (dd, *J*=1.68, 7.48 Hz, 1H), 7.75 (d, *J*=8.2 Hz, 1H), 7.65 (d, *J*=7.12 Hz, 1H), 7.46-7.53 (m, 3H), 7.42 (td, J = 8.56 Hz, 2H), 7.34 (t, J = 7.6 Hz, 1H), 7.30 (td, J = 7.64 Hz, 1H), 4.64 (q, J = 6.48, 13.04 Hz, 1H), 2.56-2.76 (m, 4H), 1.85 (qu, J = 7.40, 14.84 Hz, 2H), 1.51 (d, J = 6.6 Hz, 3H).

^{13}C NMR (104 MHz $CDCl_3$) : δ = 145.2, 134.1, 121.9, 131.4, 130.9, 130.6, 129.2, 128.8, 127.4, 126, 125.8, 125.7, 125.5, 125.2, 123, 122.8, 122.8, 53.9, 47.4, 33.5, 31.9, 23.7.

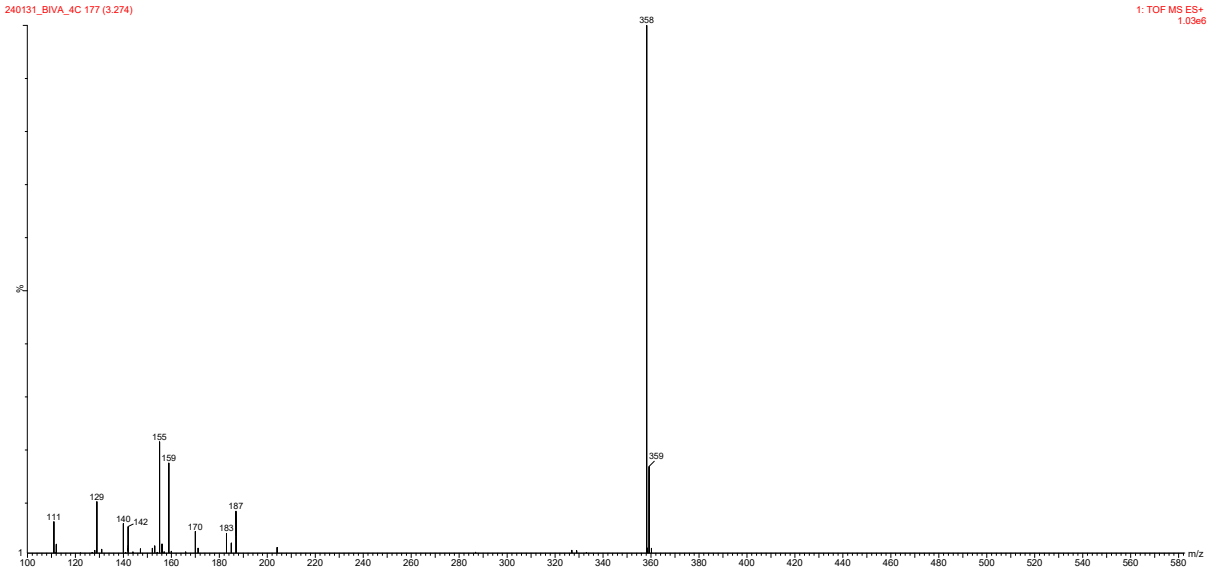
MS (ESI+) m/z: $[M + H]^+$ Calcd. for $C_{22}H_{22}F_3N$ 357.42; Found 358.



^{1}H NMR of **4c**



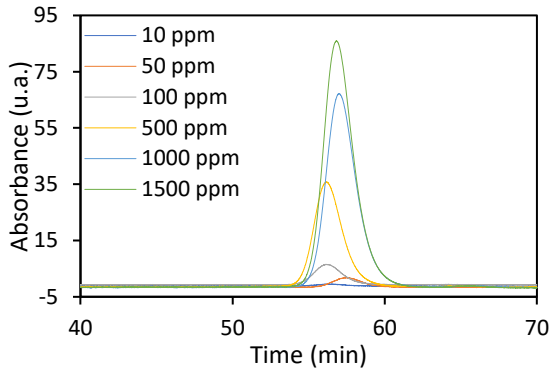
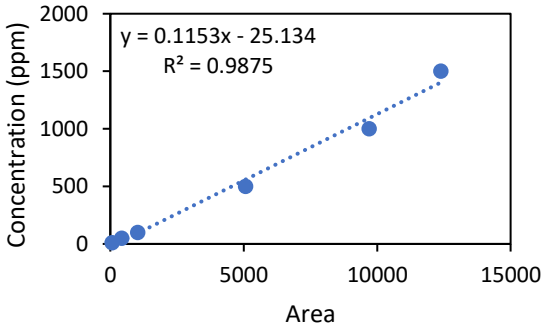
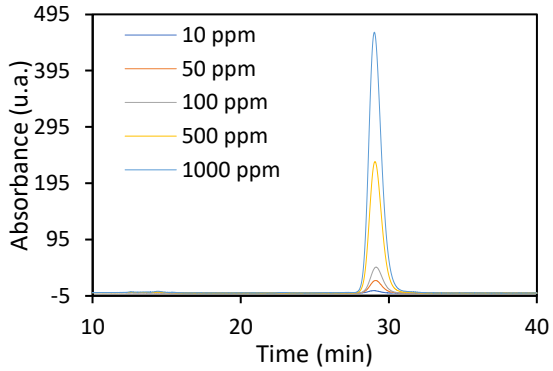
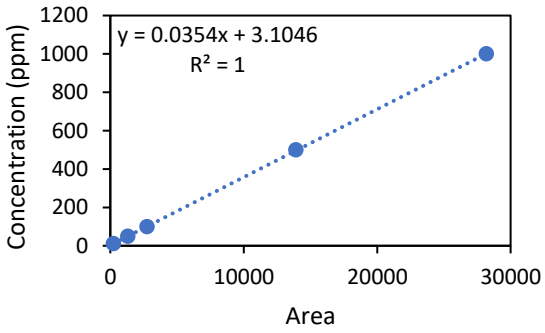
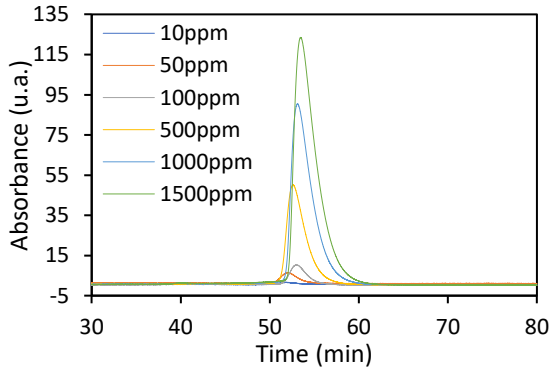
^{13}C NMR of **4c**



MS spectrum of **4c**

11. Chromatograms

Calibration curves

Chromatograms	Calibration Curve Enantiomer *R*
Compound **4a** 	Compound **4a** 
Compound **4b** 	Compound **4b** 
Compound **4c** 	Compound **4c**