A Simple Method for the Determination of Enantiomeric Excess and Identity of Chiral Carboxylic Acids

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Supporting Information

Materials and Methods

All reagents and solvents were purchased from commercial sources and used as received. **PBA**, **BMA**, **PCA**, **BPA**, and **CMA** were purchased from Sigma Aldrich, while PPA, and AMA were purchased from TCI. Circular dichroism measurements were preformed at 25°C on a JASCO J-815 spectropolarimeter, using Starna Type 21 1 cm quartz cuvette. The program used to carry out linear discriminant analysis (LDA) was XLSTAT 2011.

Experimental

*Synthesis of Host **1***:[1]

BQPA was prepared according to literature procedure[2] and dissolved (0.196g, 0.5 mmol) in 10 mL dry MeOH. To this stirred solution, $Cu(ClO_4)_2$ (0.185g, 0.5 mmol) dissolved in 5 mL dry MeOH was added dropwise. This green solution was stirred for 10 mins. A light blue precipitate formed upon addition of Et_2O (45 mL). This solution was stirred for 1 hour, and subsequently collected by vacuum filtration. A total of 0.234 g

product were collected, for an isolated yield of 71.9%. ESI MS: m/z 453.33 (Cu^{+}BQPA); calculated 453.11.

CD Titrations:

a) Buffer solution

The default buffer solution was prepared by degassing acetonitrile and water via sonicating for 1 hour. 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES, 4.76g, 20 mmol) was dissolved in MeCN:H_2O (3:1, 900 mL). The pH of the solution was adjusted to 7.4 by addition of NaOH (2M). This solution was filtered, and diluted to 1L with MeCN:H_2O (3:1).

b) **PBA** Binding

A stock solution of the host was made by dissolving **1** (74.58 mg, 0.114 mmol) in 10 mL default buffer. To prepare the **PBA** stock solutions, the corresponding enantiomer (7.78 μL, 0.05 mmol) was dissolved to 10 mL with the default buffer. Each point on the titration was a separate solution, containing host **1** (43.78 μL, 0.5 mM) and the indicated amount of guest (0-2 mM) diluted to 1 mL. The titration was performed in this manner due to the small volume that the CD cuvette holds (400 μL), as well as the inability to stir the contents of the cuvette.

c) **PCA** Binding

Stock solutions of the guest were made by dissolving either (*R*)-**PCA** (11.64 mg, 0.051 mmol), or (*S*)-**PCA** (11.27 mg, 0.049 mmol) to 10 mL in default buffer. Each

point on the titration was a separate solution, containing host **1** (43.78 μL, 0.5 mM) and the indicated amount of guest (0-2 mM) diluted to 1 mL. The titration was performed in this manner due to the small volume that the CD cuvette holds (400 μL), as well as the inability to stir the contents of the cuvette.

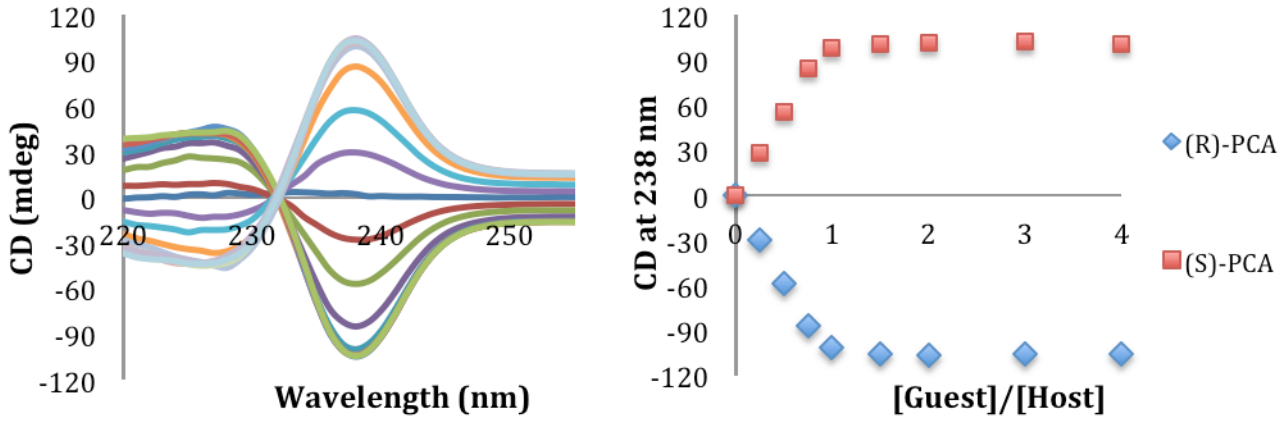

Figure S1. Left: CD spectra of host **1** (0.5 mM) upon addition of each enantiomer of **PBA** (0-2 mM) in default buffer. Right: Change in CD signal at 238 nm recorded for this titration.

d) **PPA** Binding

Stock solutions of the guest were made by independently dissolving each enantiomer of **PPA** (7.0 μL, 0.05 mmol) in 10 mL of default buffer. Each point on the titration was a separate solution, containing host **1** (43.78 μL, 0.5 mM) and the indicated amount of guest (0-2 mM) diluted to 1 mL. The titration was performed in this manner

due to the small volume that the CD cuvette holds (400 μL), as well as the inability to stir the contents of the cuvette.

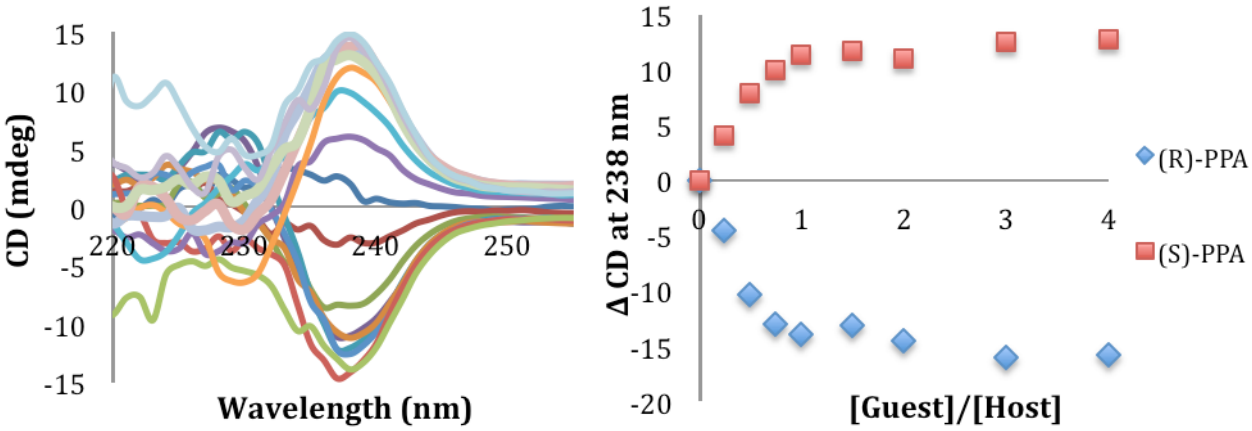

Figure S2. Left: CD spectra of host **1** (0.5 mM) upon addition of each enantiomer of **PPA** (0-2 mM) in default buffer. Right: Change in CD signal at 238 nm recorded for this titration.

e) **BPA** Binding

Stock solutions of the guest were made by independently dissolving each enantiomer of **BPA** (4.52 μL, 0.05 mmol) in 10 mL of default buffer. Each point on the titration was a separate solution, containing host **1** (43.78 μL, 0.5 mM) and the indicated amount of guest (0-2 mM) diluted to 1 mL. The titration was performed in this manner due to the small volume that the CD cuvette holds (400 μL), as well as the inability to stir the contents of the cuvette.

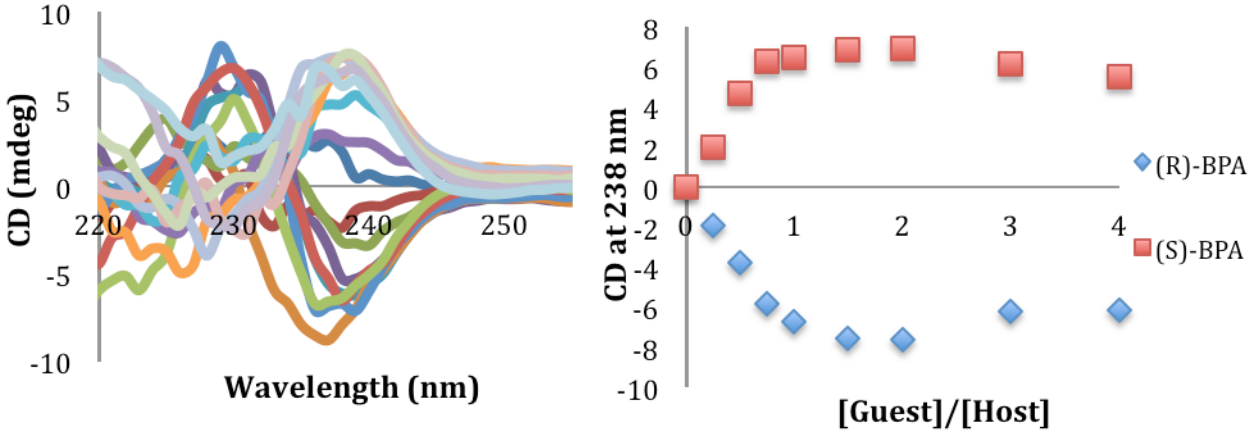

Figure S3. Left: CD spectra of host **1** (0.5 mM) upon addition of each enantiomer of **BPA** (0-2 mM) in default buffer. Right: Change in CD signal at 238 nm recorded for this titration.

f) **CMA** Binding

Stock solutions of the guest were made by independently dissolving each enantiomer of **CMA** (5.97 μL, 0.05 mmol) in 10 mL of default buffer. Each point on the titration was a separate solution, containing host **1** (43.78 μL, 0.5 mM) and the indicated amount of guest (0-2 mM) diluted to 1 mL. The titration was performed in this manner due to the small volume that the CD cuvette holds (400 μL), as well as the inability to stir the contents of the cuvette.

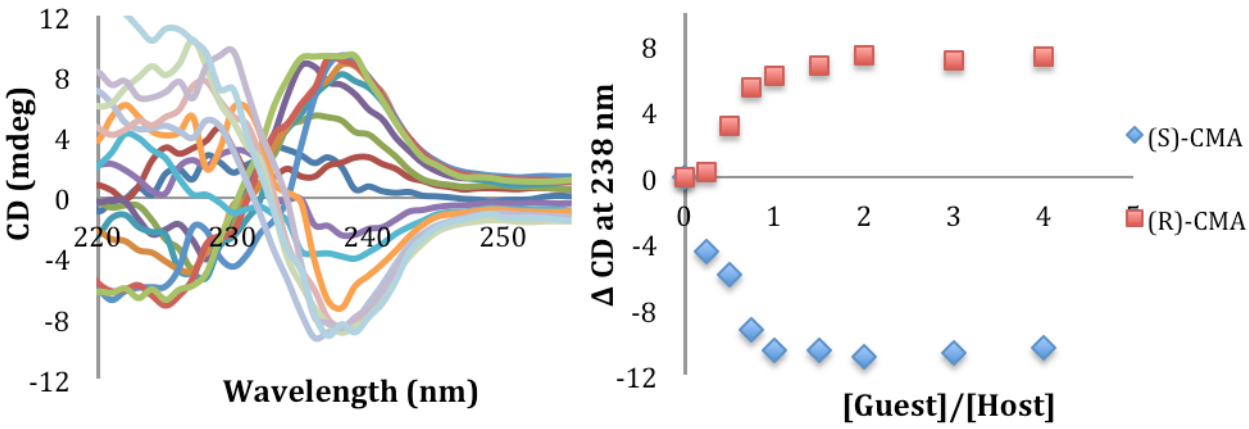

Figure S4. Left: CD spectra of host **1** (0.5 mM) upon addition of each enantiomer of **CMA** (0-2 mM) in default buffer. Right: Change in CD signal at 238 nm recorded for this titration.

g) Guest repetitions

A different sample was prepared for each enantiomer of all of the guests studied. The sample was comprised of host **1** (43.78 μL, 0.5 mM) and two equivalents of the guest (1.0 mM) dissolved in 1 mL of the default butter. After the data was collected, it was input into the LDA program to perform the pattern recognition.

Analysis of Unknown Samples

a) **PBA**

The CD signal at 238 nm was plotted against the *ee* value of **PBA**, as determined by mixing different amounts of each enantiomer. A total of 2 equivalents of **PCA** (1.0

mM) were added relative to host **1** (43.78 μL, 0.5 mM). A linear trendline was fit to the data, and the equation for this line, as well as correlation, are reported on the graph. The CD spectrum for eight unknown samples were recorded at the same concentration of guest added as in the calibration curve. The *ee* values for the unknown samples were then determined by inputing the CD spectrum as the y-value in the best-fit trendline. The results are displayed in **Table S6**.

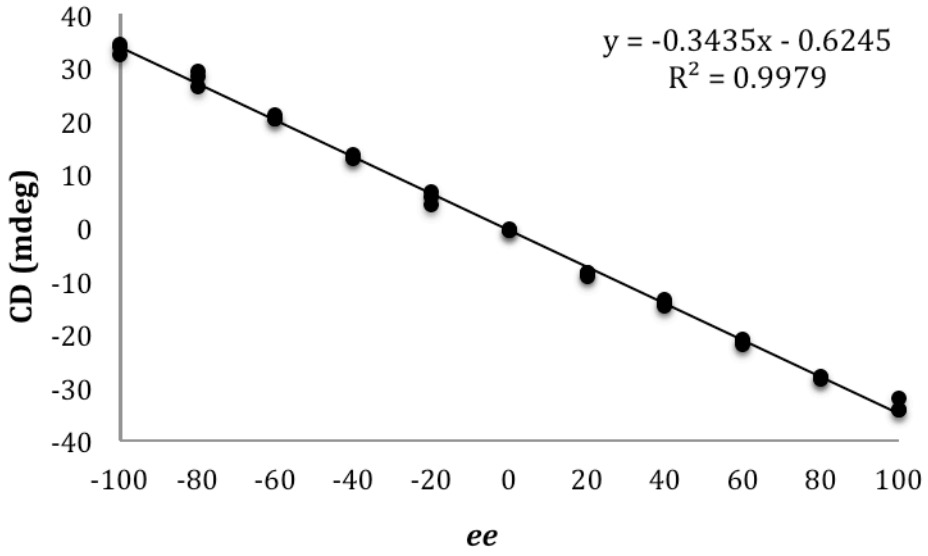

Figure S5. Graph relating the *ee* values of samples to the CD signals that were recorded. A value of 100% *ee* corresponds to 100% *R*, while a value of -100% *ee* corresponds to 100% *S*.

Entry	CD at 238 nm (mdeg)	Calc. *ee*	Actual *ee*	Error
1	-2.78	6.3	7	0.7%
2	-16.9	47.3	43	4.3%
3	30.0	-89.1	-85	4.1%
4	6.3	-20.1	-18	2.1%
5	-32.4	92.5	97	4.5%
6	10.7	-33.0	-31	2.0%
7	20.8	-62.4	-59	3.4%
8	-27.5	78.3	74	4.3%

Table S6. Results of analysis of the eight unknown samples. The average absolute error was determined to be 3.2% for these eight unknowns.

b) **PCA**

The CD signal at 238 nm was plotted against the *ee* value of **PCA**, as determined by mixing different amounts of each enantiomer. A total of 2 equivalents of **PCA** (1.0 mM) were added relative to host **1** (43.78 μL, 0.5 mM). A linear trendline was fit to the data, and the equation for this line, as well as correlation, are reported on the graph. The CD spectrum for eight unknown samples were recorded at the same concentration of guest added as in the calibration curve. The *ee* values for the unknown samples were then determined by inputing the CD spectrum as the y-value in the best-fit trendline. The results are displayed in **Table S8**.

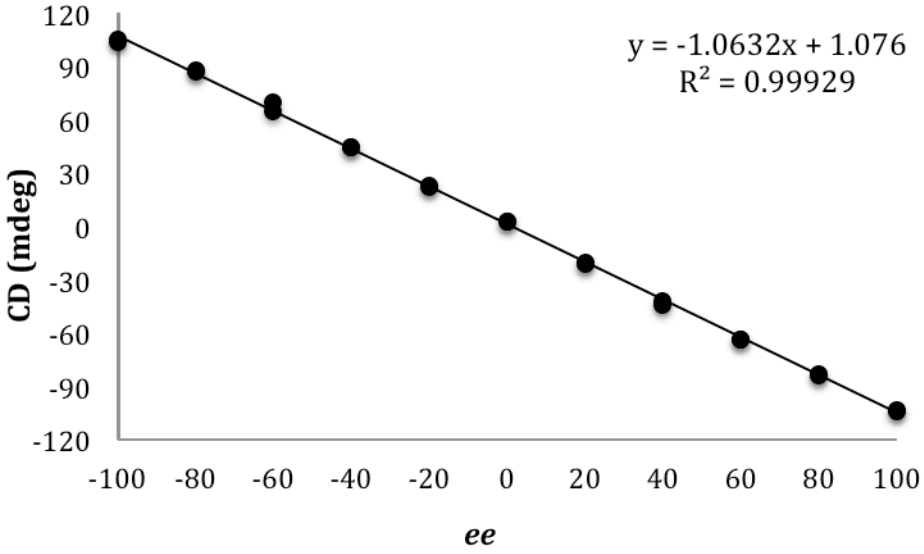

Figure S7. Graph relating the *ee* values of samples to the CD signals that were recorded. A value of 100% *ee* corresponds to 100% *R*, while a value of -100% *ee* corresponds to 100% *S*.

Entry	CD at 238 nm (mdeg)	Calc. *ee*	Actual *ee*	Error
1	89.2	-82.9	-88	5.1%
2	-27.1	26.5	27	0.5%
3	34.5	-31.4	-31	0.4%
4	17.0	-15.0	-12	3.0%
5	-92.5	88.0	92.0	4.0%
6	-3.1	3.9	4	0.1%
7	-65.1	62.2	63.0	0.8%
8	52.8	-48.7	-49	0.3%

Table S8. Results of analysis of the eight unknown samples. The average absolute error was determined to be 1.8% for these eight unknowns.

b) **PPA**

The CD signal at 238 nm was plotted against the *ee* value of **PPA**, as determined by mixing different amounts of each enantiomer. A total of 2 equivalents of **PPA** (1.0 mM) were added relative to host **1** (43.78 μL, 0.5 mM). A linear trendline was fit to the data, and the equation for this line, as well as correlation, are reported on the graph. The CD spectrum for eight unknown samples were recorded at the same concentration of guest added as in the calibration curve. The *ee* values for the unknown samples were then determined by inputing the CD spectrum as the y-value in the best-fit trendline. The results are displayed in **Table S10**.

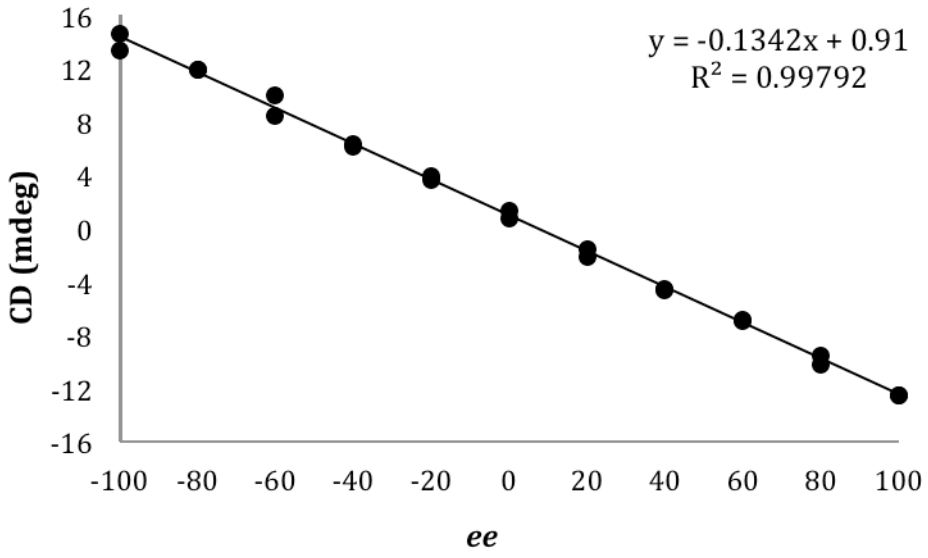

Figure S9. Graph relating the *ee* values of samples to the CD signals that were recorded. A value of 100% *ee* corresponds to 100% *R*, while a value of -100% *ee* corresponds to 100% *S*.

Entry	CD at 238 nm (mdeg)	Calc. *ee*	Actual *ee*	Error
1	2.8	-14.2	-19	4.8%
2	12.6	-86.9	-90	3.1%
3	-7.8	65.1	59	6.1
4	-0.6	11.4	10	1.4%
5	10.4	-70.5	-71	0.5%
6	-10.3	83.3	84	0.7%
7	6.2	-39.1	-43	3.9%
8	-0.4	9.5	22	12.5%

Table S10. Results of analysis of the eight unknown samples. The average absolute error was determined to be 4.1% for these eight unknowns.

Creation of Newman projection:

For this Newman projection, the molecule is viewed down the N-Cu bond, looking towards the location of the bound guest (**Figure S11**). The nitrogen in the foreground is the tertiary amine nitrogen, while the circle in the projection represents the carbon stereocenter on the bound carboxylate guest. The groups are oriented around this stereocenter to give the (*R*)- or (*S*)- designation by CIP rules, and the molecules twists to accommodate the sterics of the groups.

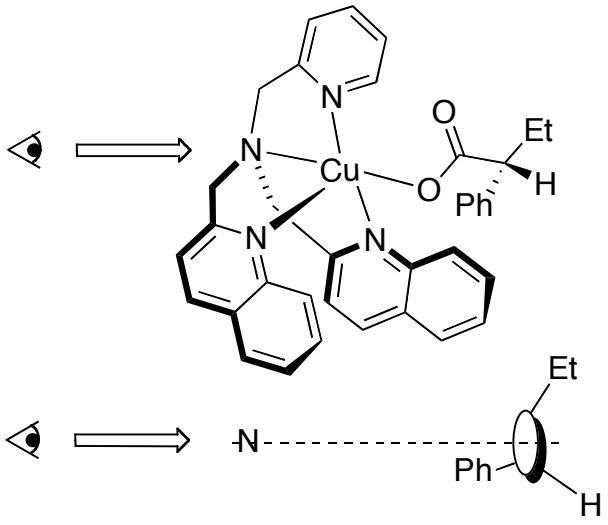

Figure S11. Schematic representation for the construction of Newman projections that explain the sign of the observed CD signal.

References:

(1) Canary, J. W.; Holmes, A. E.; Liu, J. *Enantiomer,* **2001**, *6*, 181.

(2) Karlin, K. D.; Wei, N.; Jung, B.; Kaderli, S.; Niklaus, P.; Zuberbuehler, A. D. *J. Am. Chem. Soc.* **1993**, *115*, 9506-9514.