Supplementary Information

Chiral Tandem Modifiers: Highly Efficient Cinchonidine-Derivative Modifiers at Low Concentrations for the Enantioselective Hydrogenation of (*E*)-2,3-Diphenylpropenoic acid over Pd/C

Takuya Mameda, Mio Shimogaki, Yasuaki Okamoto,* Takashi Sugimura*

Graduate School of Material Science, University of Hyogo, Kohto, Kamigori, Hyogo 678-1297, Japan

Supplementary Figures

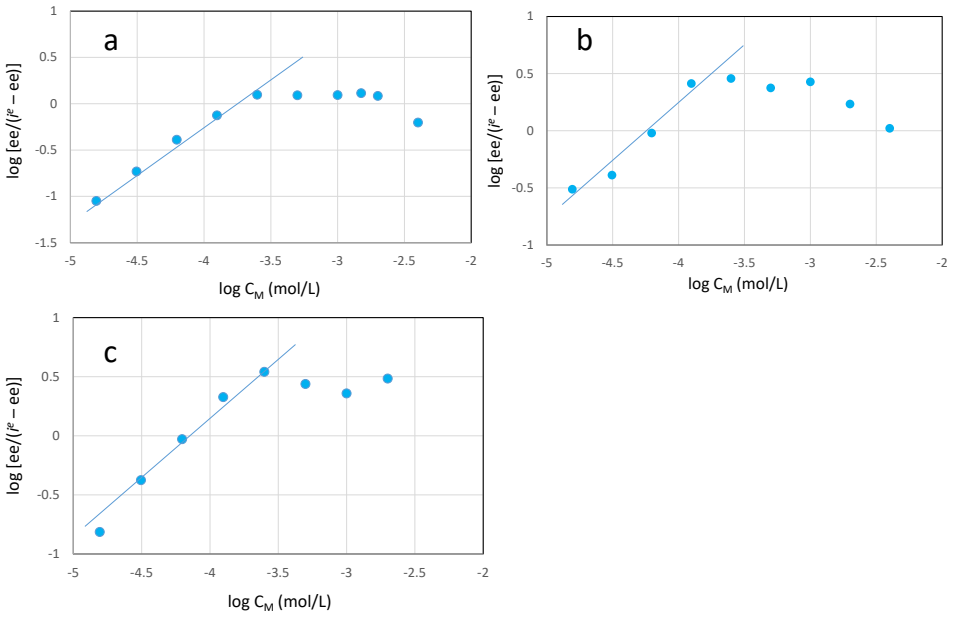

Figure S1. Correlation between log [ee/(i^e –ee)] and log C_M for (a) C2-Q2, (b) C6-Q2, and (c) C18-Q2. The slope of the linear line in the plot is set to unity according to eqn. (6). The values of i^e and log β obtained from the analysis are listed in Table 1.

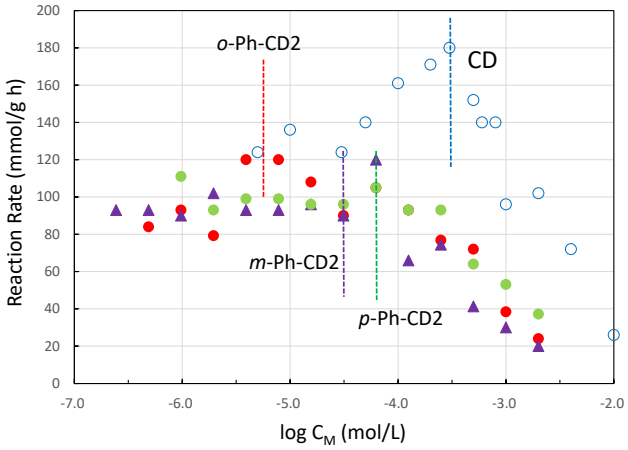

Figure S2. The initial reaction rates of the PCA hydrogenation over Pd/C modified with *o*-Ph-CD2 (●), *m*-Ph-CD2 (▲), and *p*-Ph-CD2 (●) as a function of log C_M. The initial reaction rate of CD-Pd/C (○) is shown for comparison.[53] The dotted vertical line indicates plausible log C_M* for each modifier.

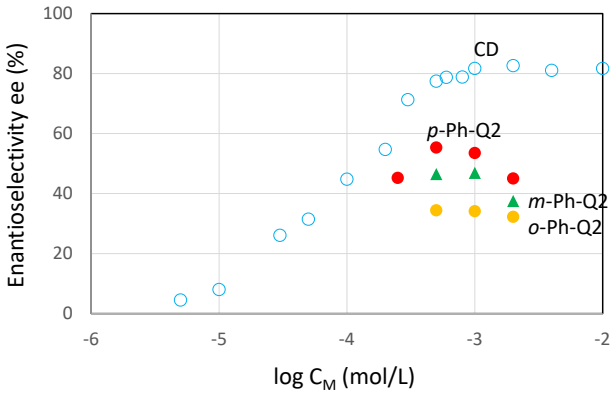

Figure S3. Enantioselectivity, as expressed by ee %, as a function of log C_M for the asymmetric hydrogenation of PCA over Pd/C modified with *o*-Ph-Q2 (●), *m*-Ph-Q2 (▲), and *p*-Ph-Q2 (●). The enantioselectivity of CD-Pd/C (○) is cited from the previous study[53] for comparison.

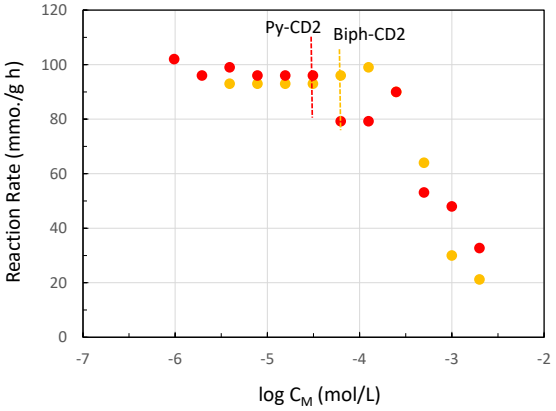

Figure S4. The initial reaction rates of the PCA hydrogenation over Pd/C modified with Py-CD2 (●) and Biph-CD2 (●) as a function of log C_M. The dotted vertical line indicates plausible log C_M* for each modifier.

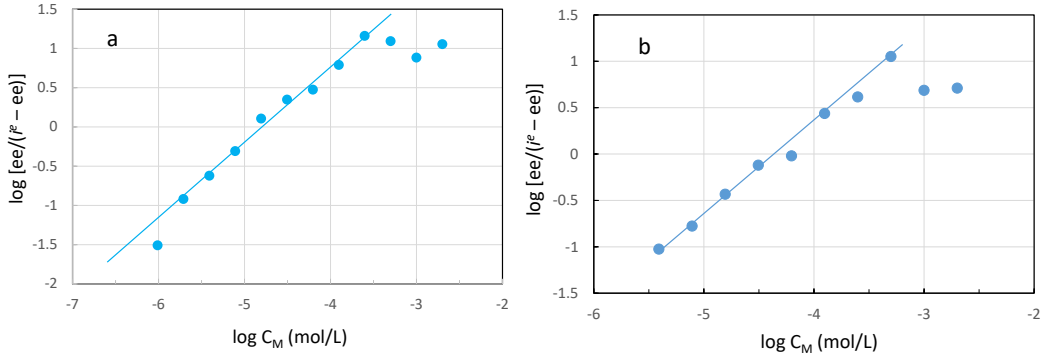

Figure S5. Correlation between log [ee/(i^e –ee)] and log C_M for (a) Py-Q2 and (b) Biph-Q2. The slope of the linear line in the plot is set to unity according to eqn. (6). The values of i^e and log β obtained from the analysis are listed in Table 2.

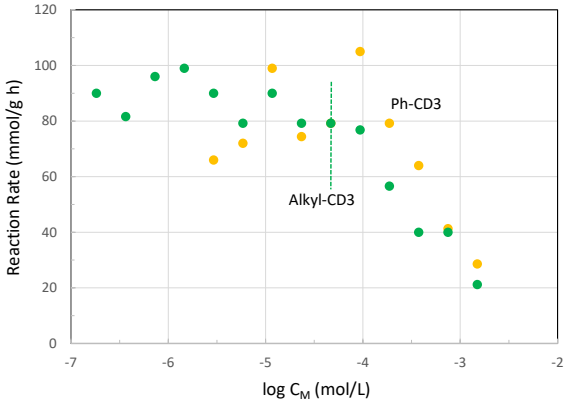

Figure S6. The initial reaction rates of the PCA hydrogenation over Pd/C modified with Alkyl-CD3 (●) and Ph-CD3 (●) as a function of log C_M. The dotted vertical line indicates plausible log C_M* for Alkyl-CD3.

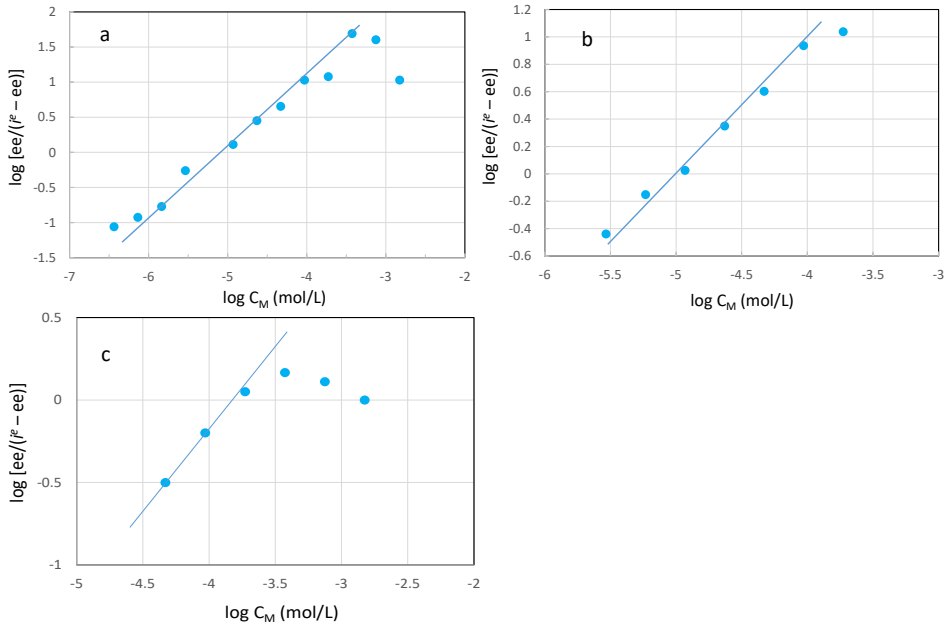

Figure S7. Correlation between log [ee/(i^e –ee)] and log C_M for (a) Alkyl-CD3, (b) Ph-CD3, and (c) Ph-Q3. The slope of the linear line in the plot is set to unity according to eqn. (6). The values of i^e and log β obtained from the analysis are listed in Table 3.

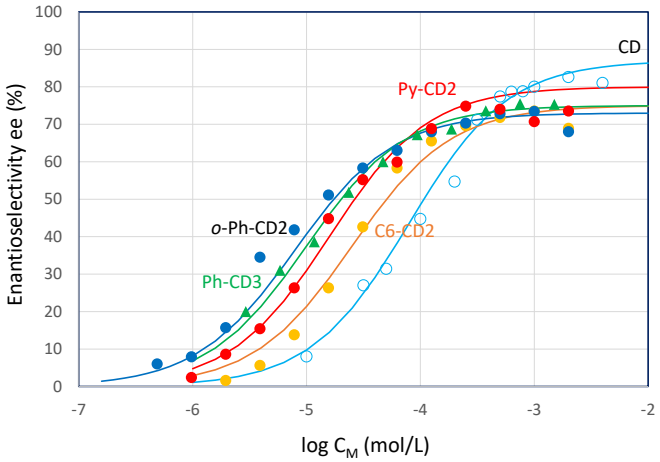

Figure S8. Enantioselectivity, as expressed by ee %, as a function of log C_M for the asymmetric hydrogenation of PCA over Pd/C modified with *o*-Ph-CD2 (●), Ph-CD3 (▲), Py-CD2 (●), and C6-CD2 (●). The enantioselectivity of CD-Pd/C (○) is cited from the previous study[53] for comparison.

Chemical Data of the tandem modifiers

The ^{1}H-NMR and high resolution mass spectrometry data of the tandem modifiers synthesized in the present study are compiled here. The symbols of the tandem modifiers employed in Schemes 3-8 are used for simplicity.

Proton NMR spectra were measured on a JEOL JNM-ECZ600R spectrometer as solutions in $CDCl_3$. Proton NMR spectra were recorded using the residual $CHCl_3$ as internal reference (7.24 ppm). Data were reported as follow: chemical shifts, integration, multiplicity (s = singlet, d = doublet, t = triplet, ddd = doublet of doublet of doublet, dd = doublet of doublet, td = triplet of doublet, m = multiplet, and br = broad), coupling constants (Hz), and assignment. High performance liquid chromatography (HPLC) was performed on a HPLC system containing of the following: pump, Jasco PU-2080 Plus; detector, Jasco UV-2075 Plus; column, Daicel CHIRALPAK IC-3 4.6 mm × 25 cm column. High-resolution mass spectra (HRMS) were measured on Thermo SCIENTIFIC Exactive Plus.

Scheme 3

C2-CD2

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7.6 Hz, 2H), 8.02 (d, *J* = 7.6 Hz, 2H), 7.64 (t, *J* = 7.6 Hz, 2H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.10 (s, 2H), 5.66 (dt, *J* = 17.2, 9.0 Hz, 2H), 5.46–5.41 (m, 2H), 4.92 (d, *J* = 17.2 Hz, 2H), 4.90 (d, *J* = 9.0 Hz, 2H), 3.56–3.44 (m, 4H), 3.26–3.12 (m, 2H), 3.10–2.98 (m, 4H), 2.61–2.53 (m, 2H), 2.51–2.41 (m, 2H), 2.27–2.17 (m, 2H), 1.74–1.33 (m, 10H); HRMS (ESI) *m*/*z* calcd for $C_{40}H_{47}N_4O_2^+$ ($[M + H]^+$) 615.3694, found: *m*/*z*: 615.3688.

C6-CD2

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.15–8.03 (br, 2H), 8.00 (d, *J* = 7.6 Hz, 2H), 7.60 (t, *J* = 7.6 Hz, 2H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.42 (d, *J* = 7.6 Hz, 2H), 5.71 (dt, *J* = 17.2, 9.0 Hz, 2H), 5.66–5.57 (m, 2H), 4.93 (d, *J* = 17.2 Hz, 2H), 4.88 (d, *J* = 10.3 Hz, 2H), 3.57–3.42 (m, 2H), 3.23–3.10 (m, 2H), 3.06 (dd, *J* = 14.5, 11.7 Hz, 2H), 2.72–2.51 (m, 8H), 2.28–2.18 (m, 2H), 1.86–1.35 (m, 18H); HRMS (ESI) *m*/*z* calcd for $C_{44}H_{55}N_4O_2^+$ ($[M + H]^+$) 671.4320, found: *m*/*z*: 671.4320.

C7-CD2

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.3 Hz, 2H), 7.66 (d, *J* = 8.3 Hz, 2H), 7.57 (s, 2H), 7.20 (t, *J* = 8.3 Hz, 2H), 6.95 (t, *J* = 8.3 Hz, 2H), 6.35 (s, 2H), 6.24–6.07 (br, 2H), 5.50 (ddd, *J* = 17.2, 11.0, 6.9 Hz, 2H), 4.96 (d, *J* = 17.2 Hz, 2H), 4.96 (d, *J* = 11.0 Hz, 2H), 4.48–4.37 (m, 2H), 3.42 (t, *J* = 12.4

Hz, 2H), 3.28 (t, *J* = 9.0 Hz, 2H), 3.13–2.99 (m, 4H), 2.90 (t, *J* = 7.6 Hz, 4H), 2.68–2.57 (m, 2H), 2.22–1.96 (m, 6H), 1.88–1.71 (m, 6H), 1.50–1.25 (m, 8H); HRMS (ESI) *m*/*z* calcd for $C_{45}H_{57}N_4O_2^+$ ([M + H]$^+$) 685.4476, found: *m*/*z*: 685.4464.

C8-CD2

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.6 Hz, 2H), 7.65 (d, *J* = 7.6 Hz, 2H), 7.57 (s, 2H), 7.19 (t, *J* = 7.6 Hz, 2H), 6.92 (t, *J* = 7.6 Hz, 2H), 6.38–6.27 (m, 2H), 5.48 (ddd, *J* = 17.2, 10.3, 7.6 Hz, 2H), 4.95 (d, *J* = 17.2 Hz, 2H), 4.94 (d, *J* = 10.3 Hz, 2H), 4.50–4.33 (m, 2H), 3.46–3.20 (m, 4H), 3.14–2.85 (m, 6H), 2.65–2.58 (m, 2H), 2.24–1.54 (m, 12H), 1.46–0.88 (m, 12H); HRMS (ESI) *m*/*z* calcd for $C_{46}H_{59}N_4O_2^+$ ([M + H]$^+$) 699.4633, found: *m*/*z*: 699.4634.

C14-CD2

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.6 Hz, 2H), 7.66 (d, *J* = 7.6 Hz, 2H), 7.56 (s, 2H), 7.20 (t, *J* = 7.6 Hz, 2H), 6.88 (t, *J* = 7.6 Hz, 2H), 6.35–6.28 (m, 2H), 5.48 (ddd, *J* = 17.2, 9.6, 6.9 Hz, 2H), 4.95 (d, *J* = 17.2 Hz, 2H), 4.95 (d, *J* = 9.6 Hz, 2H), 4.54–4.42 (m, 2H), 3.41 (t, *J* = 12.4 Hz, 2H), 3.29 (t, *J* = 8.3 Hz, 2H), 3.09–2.97 (m, 4H), 2.88 (t, *J* = 8.3 Hz, 2H), 2.67–2.58 (m, 2H), 2.26–2.15 (m, 2H), 2.15–2.04 (m, 2H), 2.02–1.97 (m, 2H), 1.82–1.71 (m, 6H), 1.44–1.12 (m, 24H); HRMS (ESI) *m*/*z* calcd for $C_{52}H_{71}N_4O_2^+$ ([M + H]$^+$) 783.5572, found: *m*/*z*: 783.5569.

Scheme 4

C2-Q2

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.85 (d, *J* = 4.1 Hz, 2H), 8.07 (d, *J* = 8.3 Hz, 2H), 7.96 (d, *J* = 8.3 Hz, 2H), 7.63 (t, *J* = 8.3 Hz, 2H), 7.56 (d, *J* = 4.1 Hz, 2H), 7.38 (t, *J* = 8.3 Hz, 2H), 5.67–5.62 (m, 2H), 4.04 (dt, *J* = 11.0, 6.2 Hz, 2H), 3.97 (dt, *J* = 11.0, 6.2 Hz, 2H), 3.59–3.30 (m, 4H), 3.14–3.02 (m, 4H), 2.68–2.38 (m, 8H), 1.93–1.35 (m, 14H); HRMS (ESI) *m*/*z* calcd for $C_{42}H_{51}N_4O_6^+$ ([M + H]$^+$) 707.3803, found: *m*/*z*: 707.3797.

C6-Q2

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.70 (d, *J* = 4.1 Hz, 2H), 7.96 (d, *J* = 8.3 Hz, 2H), 7.90 (d, *J* = 8.3 Hz, 2H), 7.55 (d, *J* = 4.1 Hz, 2H), 7.52 (t, *J* = 8.3 Hz, 2H), 7.23 (t, *J* = 8.3 Hz, 2H), 5.80–5.70 (m, 2H), 3.90 (t, *J* = 6.9 Hz, 4H), 3.67–3.52 (m, 2H), 3.02 (t, *J* = 11.0 Hz, 4H), 2.62–2.49 (m, 2H), 2.44–2.31 (m, 2H), 2.17 (t, *J* = 6.9 Hz, 4H), 1.88–1.67 (m, 6H), 1.65–1.57 (m, 2H), 1.53–1.15 (m, 16H); HRMS (ESI) *m*/*z* calcd for $C_{46}H_{59}N_4O_6^+$ ([M + H]$^+$) 763.4429, found: *m*/*z*: 763.4429.

C18-Q2

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.69 (d, *J* = 4.1 Hz, 2H), 7.99 (d, *J* = 8.3 Hz, 2H), 7.87 (d, *J* = 8.3 Hz,

2H), 7.56 (t, *J* = 8.3 Hz, 2H), 7.54 (d, *J* = 4.1 Hz, 2H), 7.23 (t, *J* = 8.3 Hz, 2H), 5.68–5.61 (m, 2H), 3.92 (t, *J* = 6.2 Hz, 4H), 3.58–3.48 (m, 2H), 2.99 (t, *J* = 11.0 Hz, 4H), 2.56–2.48 (m, 2H), 2.39–2.31 (m, 2H), 2.19 (t, *J* = 7.6 Hz, 4H), 1.83–1.67 (m, 6H), 1.62–1.13 (m, 42H); HRMS (ESI) *m*/*z* calcd for $C_{58}H_{83}N_4O_6^+$ ([M + H]$^+$) 931.6307, found: *m*/*z*: 931.6298.

Scheme 5

***o*-Ph-CD2**

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.3 Hz, 2H), 8.01 (d, *J* = 8.3 Hz, 2H), 7.60 (t, *J* = 8.3 Hz, 2H), 7.44 (t, *J* = 8.3 Hz, 2H), 7.35–7.27 (m, 2H), 7.16–7.10 (m, 2H), 7.09–7.04 (m, 2H), 5.68–5.55 (m, 4H), 4.90 (d, *J* = 17.2 Hz, 2H), 4.86 (d, *J* = 11.0 Hz, 2H), 3.50–3.36 (m, 2H), 3.25–2.97 (m, 12H), 2.68–2.51 (m, 4H), 2.27–2.18 (m, 2H), 1.77–1.49 (m, 6H), 1.48–1.35 (m, 4H); HRMS (ESI) *m*/*z* calcd for $C_{48}H_{55}N_4O_2^+$ ([M + H]$^+$) 719.4320, found: *m*/*z*: 719.4318.

***m*-Ph-CD2**

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.6 Hz, 2H), 8.00 (d, *J* = 7.6 Hz, 2H), 7.58 (t, *J* = 7.6 Hz, 2H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.27 (s, 2H), 7.00 (t, *J* = 7.6 Hz, 1H), 6.85 (d, *J* = 7.6 Hz, 2H), 6.68 (s, 1H), 5.74–5.67 (m, 2H), 5.64 (ddd, *J* = 17.2, 10.3, 7.6 Hz, 2H), 4.91 (d, *J* = 17.2 Hz, 2H), 4.86 (d, *J* = 10.3 Hz, 2H), 3.65–3.49 (m, 2H), 3.15–2.87 (m, 12H), 2.71–2.55 (m, 4H), 2.29–2.20 (m, 2H), 1.82–1.68 (m, 6H), 1.49–1.39 (m, 2H), 1.35–1.26 (m, 2H); HRMS (ESI) *m*/*z* calcd for $C_{48}H_{55}N_4O_2^+$ ([M + H]$^+$) 719.4320, found: *m*/*z*: 719.4319.

***p*-Ph-CD2**

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.6 Hz, 2H), 7.97 (d, *J* = 7.6 Hz, 2H), 7.62 (t, *J* = 7.6 Hz, 2H), 7.48–7.40 (m, 2H), 7.27 (s, 2H), 7.07–7.02 (m, 4H), 5.69 (ddd, *J* = 17.2, 10.3, 7.6 Hz, 2H), 5.65–5.56 (m, 2H), 4.94 (d, *J* = 17.2 Hz, 2H), 4.91 (d, *J* = 10.3 Hz, 2H), 3.52–3.39 (m, 2H), 3.25 (t, *J* = 7.6 Hz, 4H), 3.17–3.04 (m, 8H), 2.75–2.62 (m, 4H), 2.32–2.23 (m, 2H), 1.85–1.39 (m, 10H); HRMS (ESI) *m*/*z* calcd for $C_{48}H_{55}N_4O_2^+$ ([M + H]$^+$) 719.4320, found: *m*/*z*: 719.4321.

Scheme 6

***o*-Ph-Q2**

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.62 (d, *J* = 4.1 Hz, 2H), 7.94 (d, *J* = 7.6 Hz, 2H), 7.88 (d, *J* = 7.6 Hz, 2H), 7.59–7.39 (m, 8H), 7.18 (t, *J* = 7.6 Hz, 2H), 5.72–5.58 (m, 2H), 4.06 (t, *J* = 6.2 Hz, 4H), 3.58–3.43 (m, 2H), 3.04–2.85 (m, 4H), 2.48–2.23 (m, 4H), 1.83–1.20 (m, 16H); HRMS (ESI) *m*/*z* calcd for $C_{46}H_{51}N_4O_6^+$ ([M + H]$^+$) 755.3803, found: *m*/*z*: 755.3800.

***m*-Ph-Q2**

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.62 (d, *J* = 4.1 Hz, 2H), 8.46 (s, 1H), 8.07 (d, *J* = 8.3 Hz, 2H), 7.93 (d, *J* = 8.3 Hz, 2H), 7.90 (d, *J* = 8.3 Hz, 2H), 7.54 (d, *J* = 4.1 Hz, 2H), 7.48 (t, *J* = 8.3 Hz, 2H), 7.41 (t, *J* = 8.3 Hz, 2H), 7.20 (t, *J* = 8.3 Hz, 2H), 5.77–5.68 (m, 2H), 4.26–4.06 (m, 4H), 3.70–3.48 (m, 2H), 3.06–2.94 (m, 4H), 2.54–2.30 (m, 4H), 2.00–1.26 (m, 16H); HRMS (ESI) *m*/*z* calcd for $C_{46}H_{51}N_4O_6^+$ ($[M + H]^+$) 755.3803, found: *m*/*z*: 755.3802.

***p*-Ph-Q2**

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.78 (d, *J* = 4.1 Hz, 2H), 8.03 (s, 4H), 7.99 (d, *J* = 8.3 Hz, 2H), 7.71 (d, *J* = 4.1 Hz, 2H), 7.67 (d, *J* = 8.3 Hz, 2H), 7.19 (t, *J* = 8.3 Hz, 2H), 6.84 (t, *J* = 8.3 Hz, 2H), 6.41–6.37 (m, 2H), 4.62–4.52 (m, 2H), 4.39–4.17 (m, 4H), 3.66–3.56 (m, 2H), 3.42–3.20 (m, 6H), 3.03–2.91 (m, 2H), 2.39–2.05 (m, 8H), 1.96–0.93 (m, 6H); HRMS (ESI) *m*/*z* calcd for $C_{46}H_{51}N_4O_6^+$ ($[M + H]^+$) 755.3803, found: *m*/*z*: 755.3801.

Scheme 7

Py-CD2

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.3 Hz, 2H), 7.85 (d, *J* = 8.3 Hz, 2H), 7.61 (s, 2H), 7.53 (t, *J* = 8.3 Hz, 2H), 7.41 (t, *J* = 8.3 Hz, 2H), 7.31 (t, *J* = 8.3 Hz, 1H), 6.81 (d, *J* = 8.3 Hz, 2H), 6.14–5.99 (m, 2H), 5.56 (ddd, *J* = 16.5, 9.6, 6.2 Hz, 2H), 4.91 (d, *J* = 16.5 Hz, 2H), 4.88 (d, *J* = 9.6 Hz, 2H), 3.88–3.73 (m, 2H), 3.24–2.97 (m, 12H), 2.82–2.72 (m, 2H), 2.68–2.53 (m, 2H), 2.42–2.27 (m, 2H), 1.92–1.74 (m, 6H), 1.56–1.44 (m, 2H), 1.28–1.18 (m, 2H); HRMS (ESI) *m*/*z* calcd for $C_{47}H_{54}N_5O_2^+$ ($[M + H]^+$) 720.4272, found: *m*/*z*: 720.4280.

Biph-CD2

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.6 Hz, 2H), 7.91 (d, *J* = 7.6 Hz, 2H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.40 (d, *J* = 7.6 Hz, 4H), 7.32 (s, 2H), 7.19 (d, *J* = 7.6 Hz, 6H), 6.17–6.07 (m, 2H), 5.48 (ddd, *J* = 17.2, 9.6, 7.6 Hz, 2H), 4.90 (d, *J* = 17.2 Hz, 2H), 4.90 (d, *J* = 9.6 Hz, 2H), 4.05–3.92 (m, 2H), 3.32–3.26 (m, 6H), 3.23–3.10 (m, 6H), 2.94–2.81 (m, 4H), 2.47–2.34 (m, 2H), 2.01–1.52 (m, 8H), 1.29–1.15 (m, 2H); HRMS (ESI) *m*/*z* calcd for $C_{54}H_{59}N_4O_2^+$ ($[M + H]^+$) 795.4633, found: *m*/*z*: 795.4630.

Scheme 8

Ph-CD3

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.14 (d, *J* = 7.6 Hz, 3H), 7.98 (d, *J* = 7.6 Hz, 3H), 7.56 (t, *J* = 7.6 Hz, 3H), 7.40 (t, *J* = 7.6 Hz, 3H), 7.33 (s, 3H), 6.58 (s, 3H), 5.98–5.77 (m, 3H), 5.66 (ddd, *J* = 17.2, 9.6, 7.6 Hz, 3H), 4.95 (d, *J* = 17.2 Hz, 3H), 4.91 (d, *J* = 9.6 Hz, 3H), 3.79–3.58 (m, 3H), 3.22–3.12 (m, 6H), 3.00–2.93 (m, 6H), 2.88–2.69 (m, 12H), 2.43–2.29 (m, 3H), 1.91–1.72 (m, 9H), 1.60–1.38 (m, 6H); HRMS (ESI) *m*/*z* calcd for $C_{69}H_{79}N_6O_3^+$ ($[M + H]^+$) 1039.6208, found: *m*/*z*: 1039.6212.

Alkyl-CD3

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.6 Hz, 3H), 7.96 (d, *J* = 7.6 Hz, 3H), 7.55 (t, *J* = 7.6 Hz, 3H), 7.47 (s, 3H), 7.39 (t, *J* = 7.6 Hz, 3H), 5.87–5.71 (m, 3H), 5.64 (ddd, *J* = 17.2, 9.6, 7.6 Hz, 3H), 4.91 (d, *J* = 17.2 Hz, 3H), 4.88 (d, *J* = 9.6 Hz, 3H), 3.59–3.41 (m, 3H), 3.20–2.99 (m, 6H), 2.90–2.48 (m, 12H), 2.31–2.17 (m, 3H), 1.88–1.09 (m, 28H); HRMS (ESI) *m*/*z* calcd for $C_{67}H_{83}N_6O_3^+$ ([M + H]$^+$) 1019.6521, found: *m*/*z*: 1019.6526.

Ph-Q3

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.80 (d, *J* = 4.1 Hz, 3H), 8.02 (d, *J* = 8.3 Hz, 3H), 7.97 (d, *J* = 8.3 Hz, 3H), 7.58 (t, *J* = 8.3 Hz, 3H), 7.54 (d, *J* = 4.1 Hz, 3H), 7.33 (t, *J* = 8.3 Hz, 3H), 7.01 (s, 3H), 5.75–5.64 (m, 3H), 4.03–3.89 (m, 6H), 3.55–3.47 (m, 6H), 3.17–2.98 (m, 6H), 2.68–2.54 (m, 3H), 2.43–2.32 (m, 3H), 2.01–1.32 (m, 27H); HRMS (ESI) *m*/*z* calcd for $C_{69}H_{79}N_6O_9^+$ ([M + H]$^+$) 1135.5903, found: *m*/*z*: 1135.5892.