Proline-Based Boronic Acid Receptors for Chiral Recognition of Glucose

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KEYWORDS: proline, chiral recognition, monosaccharide, ^{1}H NMR, ^{19}F NMR

ABSTRACT: Chiral recognition remains a major challenge in the area of molecular receptor design. With this research we set out to explore the use of proline based receptors for chiral recognition. Importantly, the proline structure allows for the introduction of at least two different binding groups due to the availability of both an amine and carboxylic acid group. Here we report a proof-of-concept exploration into the chiral recognition of D-/L-glucose, as model chiral species which prefers to bind to at least two boronic acid groups. We evaluated several proline-based receptors incorporating two phenylboronic acid groups, respectively at the N- and C-termini of the amino acid residue, via amide bonds. We confirmed that the receptors exhibited chiral recognition using CD, ^{1}H NMR and ^{19}F NMR spectroscopy. Given the derivation diversity available, our strategy to use proline-based receptors for chiral recognition holds significant promise for extension to other chiral systems.

INTRODUCTION

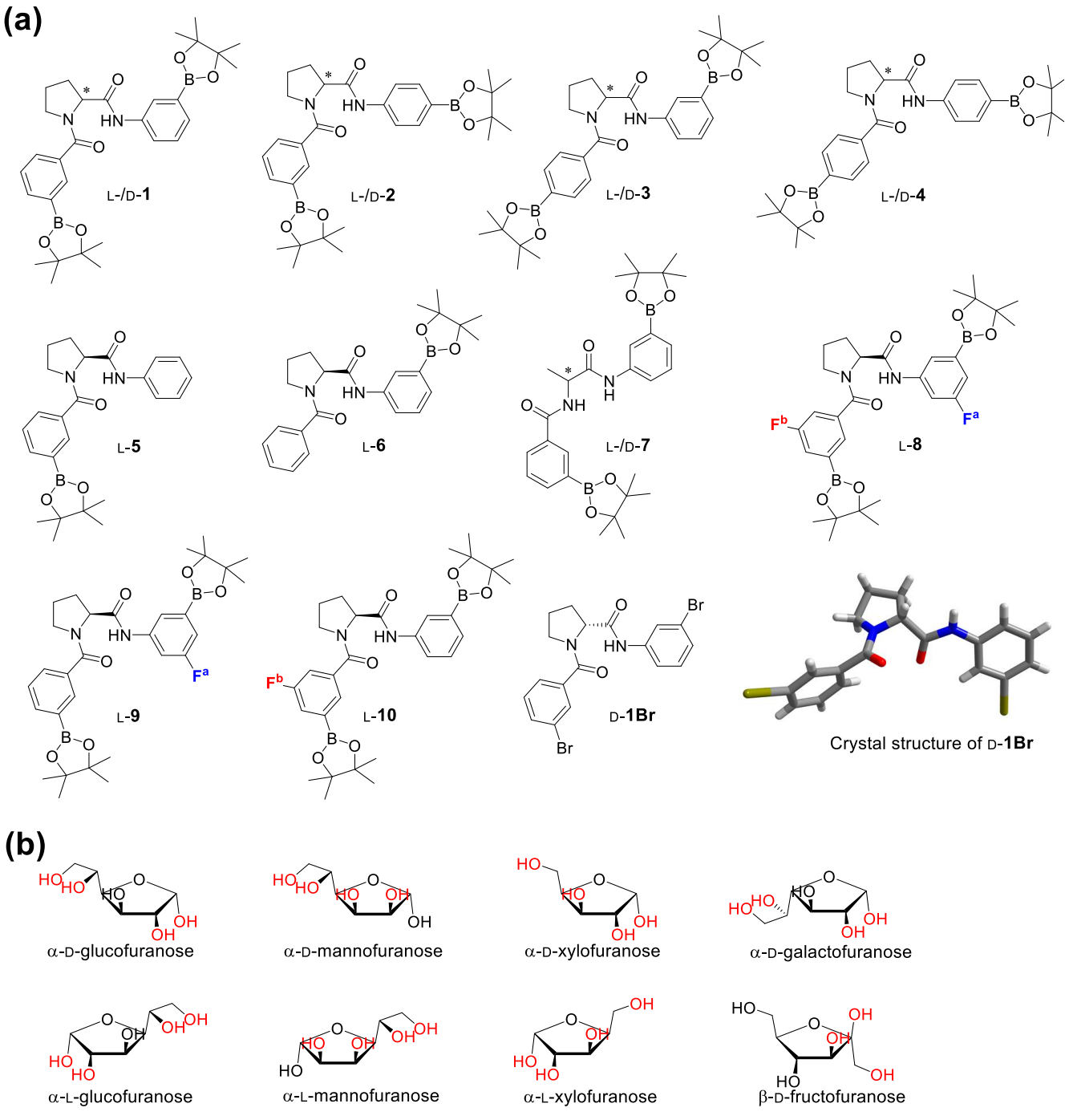
While molecular recognition and chiral sensing have seen tremendous developments,[1,2] chiral recognition remains a significant challenge. In many of the reported examples, 1,1'-binaphthol was the major structural framework that was derived into receptors bearing two identical binding groups and in the majority of the cases macrocyclic receptors are produced.[3-6] 1,1'-Binaphthol and proline are two of the major frameworks used for constructing asymmetric organocatalysts,[7-13] yet we noted that surprisingly much less attention has been paid to proline-based receptors for chiral recognition.[2,14-16] We therefore proposed that by using proline as a structural framework to construct receptors for chiral recognition could have several advantages, since it can contain at least two different binding groups at the N- and C-termini of the amino acid residue, the approach is simpler when compared to the 1,1'-binaphthol framework since its two reactive sites at 2,2'-positions, the -OHs, are the same in terms of reactivity and, subsequently, allows us to create receptors with larger structural diversity for a broader spectrum of chiral species. While the *cis*-/*trans*-conformation equilibrium of the proline residue,[17-19] in addition to its favorable cleft-shaped structure, can be employed to enhance chiral recognition.

Here we report our proof-of-concept exploration into the development of proline-based receptors for chiral recognition, which in general requires multiple interactions of the receptor with the chiral species, so that the receptor contains at least two binding groups to allow the chiral center(s) of the chiral species to be included within the interaction network. Our first model system was aimed at developing receptors for the chiral recognition of L-/D-glucose, which has been shown to prefer binding with diboronic acid derivatives.[20,21] Therefore, we designed diboronic acid derivatives of L-/D-proline, L-/D-**1** to **4** (Scheme 1a), which differ in the positions of the boronic acid groups on the phenyl rings at the N- and C-termini of proline residue. Their binding with L-/D-glucose was first investigated by circular dichroism (CD) spectroscopy, a powerful tool for chiral research.[22-26] Next fluorine atoms were introduced into the phenyl rings to facilitate the use of spectrally simpler ^{19}F NMR for receptor evaluation. Our results confirm that the proline-based receptors are indeed well suited towards chiral recognition.

RESULTS AND DISCUSSION

Absorption spectra of the four receptors of L-configuration, L-**1** to L-**4**, were studied in optimized media consisting of 1:1 (v/v) MeOH/0.05 M pH 10.0 NH_4Cl-$NH_3{\cdot}H_2O$ buffer (Fig. S1). Despite the difference in the substitution positions of the two boronic acid groups, L-**1** to L-**4** all exhibit a major absorption around 245 nm with molar extinction coefficients of magnitude 10^4 M^{-1} cm^{-1}, indicative of the π-π^* nature of the transition of the phenylboronic acid chromophores (Fig. S2). Similar observations were made with D-**1** to D-**4** (Fig. S3). Much to our delight, L-**1** to L-**4** all exhibited CD signals at the absorption wavelength (Fig. S2), suggesting that the chirality of

Scheme1. (a) Chemical structures of stereoisomers of 1 to 10 and D-1Br investigated, and crystal structure of the intermediate D-1Br. L-5 and L-6, are monophenylboronic acid control compounds of L-1; L-/D-7 are alanine counterparts of L-/D-1. compounds L-8 to L-10 are fluorine-substituted L-1; The two boronic acid groups in 1-4 are substituted at the phenyl rings respectively at (L-/D-1) *m,m'*-, (L-/D-2) *p,p'*-, (L-/D-3) *p,m'*-, and (L-/D-4) *p,p'*-positions; fluorine atoms are introduced into the phenyl rings at different positions in L-8 to L-10 and are labelled as F^a and F^b, respectively; "*" on the structures highlights the chiral carbon. (b) Structures of the tested monosaccharide.



the proline residue is transferred to the achiral phenylboronic acid chromophores. This was supported by the mirror-imaged CD spectra of the corresponding D-enantiomers D-**1** to D-**4** (Fig. S4). Therefore, the structural advantage of the cleft-shaped proline residue in rendering the binding sites chiral was fully demonstrated.

We next evaluated the interactions of receptors L-/D-**1** to **4** with L-/D-glucose via absorption and CD titrations. Fig. 1a-d shows the absorption and CD spectral traces of L-**1** upon addition of L- and D-glucose, respectively. Both the absorption and CD spectral responses of L-**1** toward L-glucose are much more dramatic than those to D-glucose, in the latter cases the spectral variations are minor (Fig. 1b, d). Likewise, D-**1** exhibits chiral recognition toward D-glucose (Fig. 1e-h), while the CD spectral traces show mirror-image profiles for L-**1**/L-glucose and D-**1**/D-glucose (Fig. S5). The chiral recognition is therefore driven by the intrinsic chirality of the proline residue. The observation of an isosbestic point at 258 nm in the absorption titration profiles of L-**1** with L-glucose (Fig. 1a) suggests the

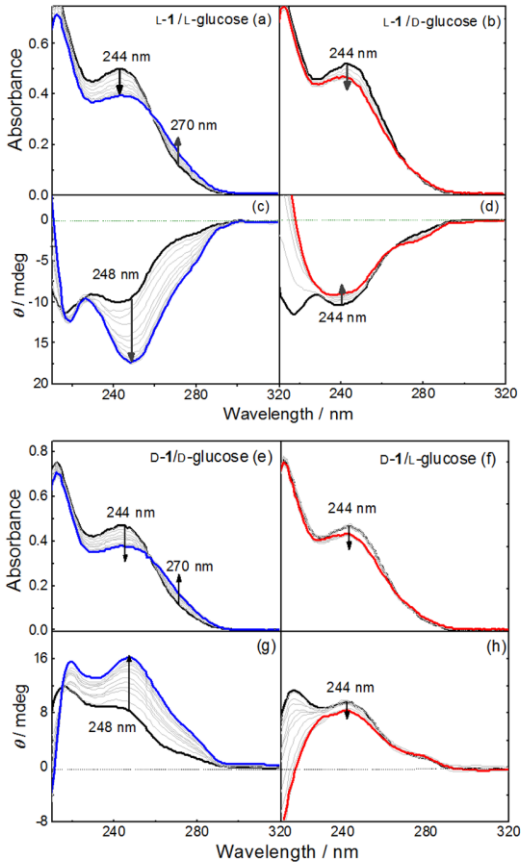


Figure 1. Absorption (a, b, e, f) and CD (c, d, g, h) spectra of L-**1** (a-d) and D-**1** (e-h) in the presence of L- or D-glucose in 1:1 (v/v) MeOH/0.05 M pH 10.0 NH_4Cl-NH_3·H_2O buffer. [L-**1**] = [D-**1**] = 30 μM, [glucose] = 0 - 6 mM.

formation of a boronate of defined composition. This is significant since there are two boronic acid groups in L-**1** and there are two *cis*-diol moieties in α-L-furanoglucose (Scheme 1b) which can interact. Job plot experiments under total concentrations of o.5 mM and 1.0 mM both indicated a 1:1 stoichiometry between L-**1** and L-glucose (Fig. S6).[27,28] Mass spectrometry provided direct evidence for the 1:1 interaction. A mixture of L-**1** (3 mg) and 200 equivalents of L-glucose incubated in 1:1 (v/v) MeOH/0.05 M pH 10.0 NH_3-NH_4Cl buffer for 3 hr afforded a distinct peak at m/z 491.1795 (Fig. S7), which corresponds to the 1:1 cyclic diboronate of calculated *m/z* 491.1719 for $C_{24}H_{24}B_2N_2O_8$ ($[M+H]^+$). Control compounds of L-**1**, L-**5** and L-**6** (Scheme 1a) that bear only one phenylboronic acid group were found to show very small spectral responses toward L-/D-glucose (Fig. S8 and S9). We therefore propose that a two-point interaction occurs between L-**1** and L-glucose and that each phenylboronic acid group in L-**1** interacts with a *cis*-diol moiety in L-glucose, leading to a cyclic boronate, likely in a cooperative manner. A substantial increase in the CD signal of L-**1** upon interaction with L-glucose supports this conclusion since it suggests a rigid conformation of the formed boronate.

The elegant work of Drueckhammer *et al.*[21] determined that in order to achieve strong binding with glucose the two boronic acid groups should be appropriately positioned. Therefore, we expected that the four receptors with different boronic acid positioning would display differential binding towards glucose. Comparative assays using CD signaling (Fig. S10) confirms that L-/D-**1** exhibit the highest chiral recognition between the L-/D-enantiomers of glucose amongst receptors **1**-**4**. L-**4**, despite being less capable, showed chiral recognition towards L-glucose. Unlike the other receptors, L-**2** exhibited a significant response in its CD at 244 nm toward L-glucose (Fig. S10c), while a distinct band at 255 nm was discovered in the presence of D-glucose (Fig. S10d). No significant

Table 1. Binding constants of receptors 1-4 with L-/D-glucose.[a]

Receptor	K_a ± sd, 10^3 M^{-1}	
	L-glucose	D-glucose
L-**1** (*m,m'*-)	6.72 ± 0.66	0.85 ± 0.09
D-**1** (*m,m'*-)	0.62 ± 0.08	5.42 ± 0.55
L-**2** (*m,p'*-)	4.01 ± 0.23	3.36 ± 0.27
D-**2** (*m,p'*-)	3.56 ± 0.32	3.52 ± 0.93
L-**3** (*p,m'*-)	–[b]	0.48 ± 0.07
D-**3** (*p,m'*-)	0.68 ± 0.22	–[b]
L-**4** (*p,p'*-)	0.51 ± 0.08	–[b]
D-**4** (*p,p'*-)	0.64 ± 0.11	1.0 ± 0.11

[a] Binding constants (K_a) were obtained by nonlinear fitting of the CD signal as a function of glucose concentration assuming a 1:1 stoichiometry. [Receptor] = 30 μM, T = 298 K. [b] Due to minor changes in CD spectra accurate K_a values could not be fitted.

change in the CD spectrum of L-**3** was observed upon the addition of L-glucose (Fig. S10e), while a weak CD signal was observed in the presence of D-glucose (Fig. S10f). The binding constants (K_a) obtained using nonlinear fitting for a 1:1 binding[27] of the CD data are listed in Table 1, which indicates that the L-**1**/L-glucose and D-**1**/D-glucose binding of K_a (5 - 7) × 10^3 M^{-1} (Table 1) is stronger than that of the L-**1**/D-glucose and D-**1**/L-glucose of K_a (0.6 – 0.9) × 10^3 M^{-1} (For titration curves see Fig. S11 and S12), indicating the chiral recognition of L-**1** towards L-glucose and D-**1** towards D-glucose.

Chiral recognition of receptor L-**1** was also examined for other monosaccharides, such as D-/L-mannose, D-/L-xylose and

D-galactose that bear two sets of *cis*-diols yet of different distance or relative orientation, or D-fructose that bears only one set of *cis*-diol (Scheme 1b). No significant changes in the CD spectra were observed (Fig. S19 and S20), suggesting weak interaction occurred and the chiral recognition was not significant. This means that the ability of the proline-based receptor L-**1** for chiral recognition of L- over D-glucose is highly selective.

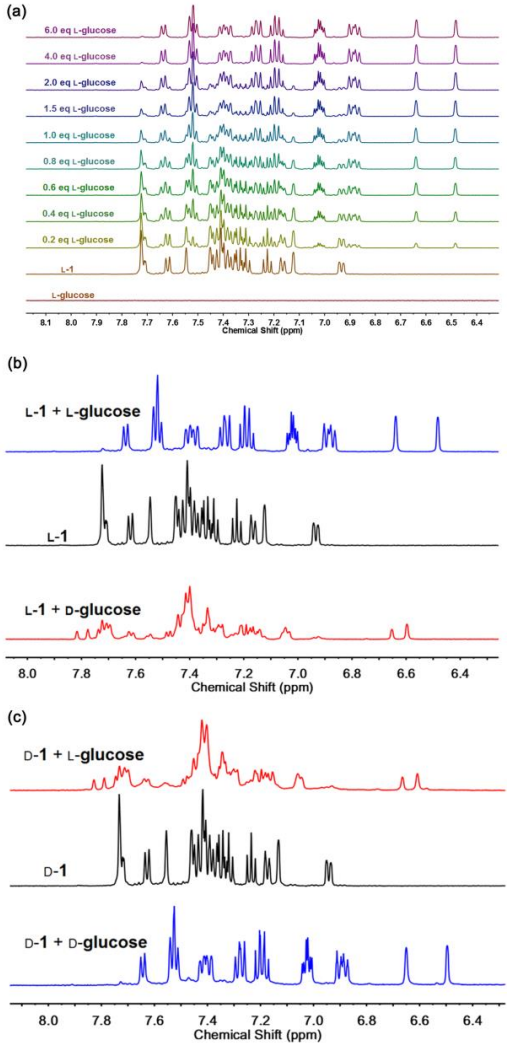


Figure 2. Chiral recognition for glucose by ^{1}H NMR signalling. Partial ^{1}H NMR spectra of L-**1** upon addition of L-glucose (a), and L-**1** (b) and D-**1** (c) in the presence of 6 eq L-glucose and D-glucose, respectively, in pH 9 NH_3-NH_4Cl buffer in D_2O. [**1**] = 5 mM; [NH_4Cl] + [NH_3] = 50 mM.

For understanding the binding of **1** with glucose, we performed ^{1}H NMR titrations. The resonances of protons on the aromatic ring (Fig. 2a) and the proline methylene region (δ 2.0-2.5 ppm, Fig. S21) of L-**1** in D_2O buffer changed significantly upon addition of L-glucose. In particular, the resonances of the aromatic protons become well-resolved in the presence of 1 eq or more of L-glucose, indicating thatL-**1** binds tightly with L-glucose to generate a rigid structure,[29] in agreement with the appearance of an isosbestic point in the absorption spectral evolution and adramatic change in CD signal (Fig. 1a, c). These observations support the two-point interaction mode for L-**1** with L-glucose. Meanwhile, the signals of the methylene protons at 2.50 ppm disappear and new signals at 2.45 ppm appear (Fig. S21), indicating a shift of the conformation equilibrium of L-**1** towards the *cis*-conformer upon the formation of the L-**1**/L-glucose boronates. A similar observation was made for the resonance around 2 ppm in that an enhancement of the resonances at around 2.10 ppm is accompanied by the disappearance of resonances at 1.95 ppm. Upon addition of D-glucose, however, resonances of the aromatic protons of L-**1** became irregular and broad (Fig. 2b and S22). This is indicative of a weaker and loose interaction for L-**1** with D-glucose. The ^{1}H NMR titrations therefore confirmed that the chiral recognition of L-**1** towards L-glucose results from the formation of the 1:1 cyclic diboronate complex via a two-point interaction (Fig. 3). This was further supported by the fact that the ^{1}H NMR profiles remain unchanged when the titrations were performed at dilutting concentrations of L-**1** of 4, 3, 2, 1, 0.5, 0.1 and 0.05 mM with 6 eq of L-glucose (Fig. S23). Likewise the chiral recognition of D-**1** for D-glucose over L-glucose was demonstrated in Fig. 2c, contrasting the well-resolved ^{1}H NMR of D-**1**/D-glucose boronate complex with the irregular and blurred ^{1}H NMR of D-**1**/L-glucose boronate complex. According to ^{1}H NMR data, the *trans*- to *cis*-conformation ratio is *ca*. 1.3 in L-**1**, which dropped slightly to 1.0 in the L-**1**/L-glucose boronate (Fig. S24).

DFT optimized structure of the *trans*-L-**1** is slightly (3.61 kJ mol^{-1}) more stable than the *cis*-conformer (Fig. S25a), which agrees with the observed *trans*-/*cis*-ratio of 1.3 in solution (Fig. 3). This was also supported by the crystal structure of the bromide precursor of D-**1**, D-**1Br** of the *trans*-conformation (Scheme 1a and Fig. S26) and the similar CD profiles of D-**1Br** and D-**1** (Fig. S27). Moreover, the optimized structures indicate that the boronates of both *trans*- and *cis*-forms of L-**1** are more stable than the corresponding L-**1**/D-glucose boronates, again showing the favored interactions of L-**1** with L-glucose against D-glucose (Fig. S28 and S29). It should be pointed out that the two-point binding of L-**1** with D-glucose was only assumed for the purpose of calculations, it actually did not exist as revealed by their huge energy difference and the irregular ^{1}H NMR spectrum (Fig. 2b). Calculations showed that the optimized boronate of L-glucose of *cis*-form L-**1** is more stable than that of the *trans*-form L-**1** (Fig. S25b), which explained the lowered ratio of the L-glucose boronates of *trans*- to *cis*-L-**1**, being 1.0, compared to that (1.3) of the *trans*- to *cis*- L-**1** (Fig. 2 and 3).

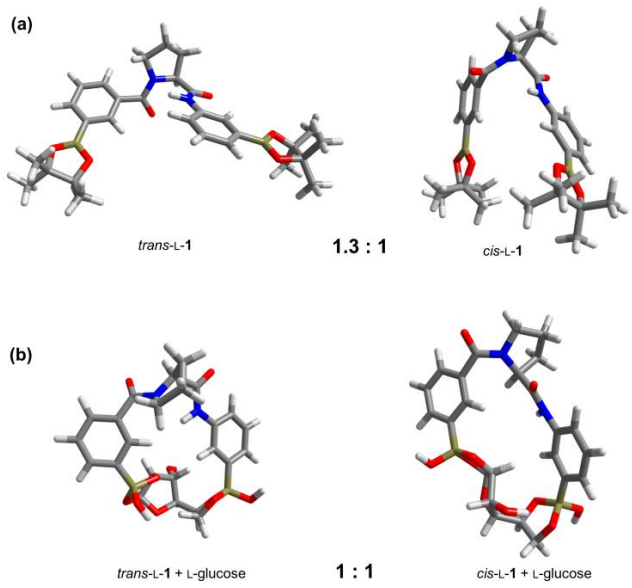


Figure 3. DFT-optimized structures of *trans*- and *cis*-L-**1** (a) and the corresponding boronates with L-glucose (b) in H_2O at B3LYP/6-31G* level. The ratio of *trans*- to *cis*-conformation were calculated from ^{1}H NMR data given in Figure S24.

By using the more flexible alanine counterparts of L-/D-**1**, L-/D-**7** (Scheme 1a), we found that their absorption, CD, and ^{1}H NMR did not change much in the presence of L- or D-glucose (Fig. S30-S32). These observations pointed to the important contribution of the rigidity of the proline residue in **1** for the chiral recognition of L-/D-glucose.[17,19,30,31]

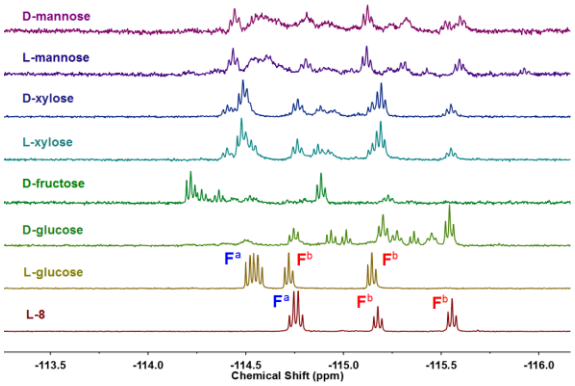


Figure 4. ^{19}F NMR spectra of L-**8** in the presence of given monosaccharide in pH 9.0 buffer in D_2O. [L-**8**] = 5 mM, [saccharide] = 30 mM.

In order to establish the potential utility of the proline-based structural framework, we introduced fluorine atoms into the phenylboronic acid moieties so that the spectrally simpler ^{19}F NMR[32-36] might be employed to evaluate the chiral recognition. Fluorine-containing receptors L-**8** to L-**10** (Scheme 1a) that correspond to L-**1** were synthesized. Three sets of ^{19}F NMR signals were observed for L-**8** and were assigned to F^a and F^b on the two aromatic rings respectively (Scheme 1a), by referring to the ^{19}F NMR spectra of L-**9** and L-**10** (Fig. S33). Indeed, the ^{19}F NMR spectra of L-**8**, L-**9**, and L-**10** are much simpler than the ^{1}H NMR spectrum of L-**1** (Fig. 2a). ^{19}F NMR spectra of L-**8** and the complex formed on the addition of 6 equivalents of D-/L- monosaccharides are shown in Figure 4. Only with L-glucose, the ^{19}F NMR of L-**8** appeared as a well-resolved pattern, suggesting that L-**8** and L-glucose forms a stable boronate of defined stoichiometry. This demonstrates the chiral recognition of L-**8** for L-glucose, a conclusion that was also made for its analogue L-**1** with L-glucose shown by the ^{1}H NMR and CD analyses. Again, the chiral recognition was observed for L-glucose, but not the other monosaccharides despite subtle differences in terms of the distance and relative orientation of the two sets of *cis*-diols (Fig. 1b). The ratios of the *trans*- to *cis*-conformation of free L-**8** and L-**8**/L-glucose boronate are 1.3 and 1.0, respectively, calculated from the ^{19}F NMR data (Fig. S34), close to those of L-**1** and its L-glucose boronate obtained from ^{1}H NMR data. Similar observations were found for L-**9** and L-**10** in their ^{19}F NMR response toward L-glucose, producing well-resolved spectra (Fig. S35-S39). ^{19}F NMR titrations also allowed the L-/D-glucose binding constants of L-**8** and L-**10** to be evaluated as $(2.5 \pm 0.3) \times 10^3$ M^{-1}/$(0.4 \pm 0.09) \times 10^3$ M^{-1} and $(1.9 \pm 0.4) \times 10^3$ M^{-1}/$(0.3 \pm 0.04) \times 10^3$ M^{-1} (Table S2), respectively. Meanwhile, substantial changes in the absorption and CD spectra of L-**8**, L-**9**, and L-**10** (Fig. S40-S42) allowed the binding constants with L-glucose to be evaluated as $(3.62 \pm 0.17) \times 10^3$ M^{-1}, $(5.67 \pm 0.28) \times 10^3$ M^{-1}, and $(3.48 \pm 0.15) \times 10^3$ M^{-1}(see Fig. S43-S45, Table S3), respectively, comparable to those obtained from ^{19}F NMR titrations.

CONCLUSIONS

In conclusion, we have successfully developed proline based receptors for chiral recognition. Highly efficient and selective chiral recognition was demonstrated for L-/D-glucose using the designed diboronic acid *meta*-substituted derivatives of rigid L-/D-proline constructed using amide bonds at both the N- and C-termini of the proline residue. The limited conformational flexibility of the receptor molecule, thanks to the conformational character of the proline residue, was shown to be locked within the formed of 1:1 cyclic diboronates with glucose using two-points of interaction. ^{1}H NMR clearly displays the conformational change in the receptor molecule upon interaction with glucose since the formed boronate produces well-resolved NMR spectra. The strategy has been successfully extended by the introduction of fluorine atoms onto the phenyl rings of receptor L-**1** thus enabling the use of spectrally simpler ^{19}F NMR to determine the chiral recognition of L-**8**, L-**9**, or L-**10** with L-glucose. The strategy of using the proline residue to build receptors for chiral recognition is expected to be of general utility, since suitable combinations of binding sites can be introduced stepwise to the N- and C-termini of the proline residue. We are currently exploring the use of different receptors in order to develop a number of chiral receptors using this modular approach, preliminary work on chiral recognition of L-/D-Dopa appears to be promising.

EXPERIMENTAL SECTION

General Experimental Information. All reagents were purchased from commercial sources and were used without further purification. Solvents for spectral titrations were deionized water and redistilled MeOH.

Details of the synthesis of **1** to **10** are given in the Supporting Information (SI) together with full characterization by ^{1}H NMR, ^{13}C NMR, and HRMS. Flash chromatography was carried out on silica gel (230−400 mesh). ^{1}H NMR and ^{13}C NMR spectra ($CDCl_3$ or CD_3CN) were recorded on Bruker

AV500MHz, AV600MHz or AV850MHz spectrometer; highre solution mass spectra (HRMS) were acquired on Bruker En Apex ultra 7.0 TFT-MS spectrometer. The melting point range was recorded by Melting Point M-560. Circular dichroism (CD) spectra were obtained on Jasco J-810 or Biologic spectrometer. Absorption spectra were obtained on Thermo Evolution 300 spectrometer with a 1 cm standard quartz cell. Job plot was obtained from absorption measurements of 11 solutions with fixed total concentration of L-**1** and L-glucose at 0.5 mM and 1 mM respectively.

Absorption and CD spectral measurements were carried out using a stock solution of **1** of 2 mM in MeOH, which was diluted with 1:1 (v/v) MeOH/0.05 M pH 10.0 NH_4Cl buffer to afford the desired concentration of **1** at 30 μM, to which 0 - 6 mM of L-glucose and D-glucose or other guest species were added and recorded CD and UV spectra after 30 min.

^1H NMR and ^{19}F NMR spectral measurements were recorded using a stock solution of **1** of 5 mM in D_2O and adjusted the pH reach to 9 by NH_4Cl and NaOD. L-/D-glucose and other monosaccharides were dissolved in D_2O to obtained 0.1 M concentrated solutions. Then 0 - 30 mM (0 - 6 equivalent) of L- or D-glucose was added to solution **1** respectively, the mixture was incubated at 27 °C, after 30 min, the ^1H NMR and ^{19}F NMR spectra were recorded using Bruker AV500MHz or AV600MHz spectrometer.

General Procedure for Preparation of Proline based Receptors.

General Procedure for the (a). Boc-L-proline (2.15 g, 10 mmol) was dissolved in dichloromethane under stirring in ice bath, to which trimethylamine (2.5 mL) and isobutyl chloroformate (1.7 mL, 13 mmol) were added. The mixture was kept in ice-bath for 30 min. 3-Bromobenzenamine (1.09 mL, 10 mmol) was next added dropwise and the solution was stirred at room temperature overnight. Solvent was removed in vacuo to lead to a crude mixture solid. This solid was washed with water, and the residue was washed with petroleum ether/EtOAc (8/1, v/v) (4 × 10 mL) to afford a white solid **a** (2.740 g, 74%), mp 211-212 °C. ^1H NMR (850 MHz, $CDCl_3$) δ (ppm) 9.65 (s, 1H), 7.82 (s, 1H), 7.34 (s, 1H), 7.14 (d, J = 41.8 Hz, 2H), 4.47 (s, 1H), 3.39 (d, J = 74.6 Hz, 2H), 2.50 (s, 1H), 2.06 - 1.84 (m, 3H), 1.51 (s, 9H). $^{13}C\{^1H\}$ NMR (214 MHz, $CDCl_3$) δ (ppm) 170.1, 156.7, 139.7, 130.1, 126.7, 122.5, 118.0, 81.1, 60.5, 47.3, 28.4, 27.2, 24.6. HRMS (FTICR MS ESI$^+$) $[M+Na]^+$ calcd for $C_{16}H_{21}NaBrN_2O_3$: 391.0628, found 391.0628.

Boc Deprotection (b). a (2 g, 5.4 mmol) was dissolved in 20 mL methylene dichloride. Then TFA (8 mL) was added to the mixed solution dropwise followed by stirring at room temperature for 2 h. Solvent was removed under reduced pressure to yield a white solid.

General Procedure for the (c). *m*-Bromobenzoic acid (1.21 g, 6 mmol) in dichloromethane (10 mL) was stirred at 0 °C, to which HOBt (1.05 g, 7.8 mmol), EDCI (1.72 g, 9 mmol), trimethylamine (5 mL, 36 mmol) were added and the resultant mixture was stirred at this temperature for 30 min. To this mixture was added dropwise the above white solid product dissolved in dichloromethane, which was allowed to react at room temperature overnight. The mixture was washed with 0.1 M HCl (3 × 10 mL), saturated sodium bicarbonate solution (3 × 10 mL), saturated sodium chloride solution (3 × 10 mL) respectively, and the organic layer was dried with anhydrous Na_2SO_4. The solution was evaporated to afford a crude oil. After washing with the mixed solvent of petroleum ether/EtOAc (5/1, v/v) (4 × 10 mL) to afforded a white solid **c** (1.970 g, 80.7 %), mp 220-221 °C. ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) δ 9.61 (s, 1H), 7.82 (s, 1H), 7.71 (s, 1H), 7.61 (d, J = 7.6 Hz, 1H), 7.49 (d, J = 7.0 Hz, 1H), 7.32 (dd, J = 16.2, 7.8 Hz, 2H), 7.14 (d, J = 7.4 Hz, 1H), 7.06 (t, J = 7.6 Hz, 1H), 4.93 (s, 1H), 3.58 (d, J = 42.9 Hz, 2H), 2.50 (s, 1H), 2.14 (s, 2H), 1.91 (s, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ (ppm) 169.9, 169.1, 139.4, 137.7, 133.6, 130.2 130.16 , 130.0, 126.9, 125.7, 122.6, 122.5, 122.5, 118.1, 61.1, 50.7, 27.5, 25.4. HRMS (FTICR MS ESI$^+$) $[M+Na]^+$ calcd for $C_{18}H_{16}NaBr_2N_2O_2$: 472.9471, found 472.9475.

General Procedure for L-1. c (1.97 g, 4.4 mmol), boric acid pinacol ester (3.35 g, 13.2 mmol) and KOAc (2.68 g, 26.4 mmol) in DMF was stirred under nitrogen at room temperature for 30 min. Then $Pd(dppf)Cl_2$ (0.2 g) was added. In nitrogen atmosphere, the mixture was stirred at 80 °C in oil bath for 24 h. After which the mixture was allowed to cool down and filtered. The filtrate was evaporated in vacuo to obtain a crude mixture solid. The target compound L-**1** was isolated by silica chromatography eluted by petroleum ether/ EtOAc (20/1 - 8/1, v/v) (0.800 g, 33 %), mp 210-221 °C. ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 9.48 (s, 1H), 7.94 (s, 1H), 7.87 (t, J = 6.9 Hz, 2H), 7.82 (s, 1H), 7.60 (d, J = 7.7 Hz, 1H), 7.51 (d, J = 7.2 Hz, 1H), 7.43 (t, J = 7.5 Hz, 1H), 7.32 (t, J = 7.7 Hz, 1H), 4.98 (dd, J = 7.8, 4.3 Hz, 1H), 3.53 (dtd, J = 17.4, 10.6, 7.0 Hz, 2H), 2.69 (dt, J = 11.3, 5.9 Hz, 1H), 2.11 (tt, J = 13.6, 6.9 Hz, 1H), 2.04 - 1.96 (m, 1H), 1.93 - 1.83 (m, 1H), 1.33 (d, J = 10.3 Hz, 24H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ (ppm) 172.1, 168.6, 137. 8, 136.6, 135.4, 133.2, 130.4, 129.8, 128.4, 127.9, 125.9, 122.8, 84.1, 83.8, 60.7, 50.6, 26.3, 25.4, 24.9. HRMS (FTICR MS ESI$^+$) $[M+Na]^+$ calcd for $C_{30}H_{40}NaB_2N_2O_6$: 569.2965, found 569.2976.

Compounds **1**-**10** were synthesized by the same procedures.

Compound D-**1**: White solid; 0.820 g, 34 % yield; mp 223-224 °C. ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 9.50 (s, 1H), 7.94 (s, 1H), 7.88 (d, J = 7.6 Hz, 2H), 7.82 (s, 1H), 7.60 (d, J = 7.6 Hz, 1H), 7.51 (d, J = 7.2 Hz, 1H), 7.43 (t, J = 7.5 Hz, 1H), 7.32 (t, J = 7.7 Hz, 1H), 4.99 (dd, J = 7.8, 4.3 Hz, 1H), 3.52 (dtd, J = 17.4, 10.6, 6.9 Hz, 2H), 2.70 (td, J = 11.8, 6.3 Hz, 1H), 2.17 - 2.06 (m, 1H), 2.04 - 1.96 (m, 1H), 1.93 - 1.82 (m, 1H), 1.33 (d, J = 10.9 Hz, 24H). $^{13}C\{^1H\}$ NMR (125 MHz, CD_3CN) δ (ppm) 171.3, 170.9, 139.3, 137.4, 136.7, 133.9, 130.7, 129.4, 128.8, 126.4, 123.6, 85.1, 84.9, 62.3, 51.2, 29.9, 26.1, 25.2. HRMS (FTICR MS ESI$^+$) $[M+H]^+$ calcd for $C_{30}H_{41}B_2N_2O_6$: 547.3145, found 547.3155.

Compound L-**2**: White solid; 0.780 g, 32 % yield; mp 147-148 °C. ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 9.43 (s, 1H), 7.97 - 7.72 (m, 4H), 7.51 (t, J = 7.5 Hz, 3H), 7.32 (t, J = 7.7 Hz, 1H), 4.98 (d, J = 2.9 Hz, 1H), 3.49 (dtd, J = 17.2, 10.6, 6.8 Hz, 2H), 2.68 (dd, J = 10.3, 5.0 Hz, 1H), 2.18 - 1.95 (m, 2H), 1.94 - 1.81 (m, 1H), 1.33 (d, J = 17.0 Hz, 24H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ (ppm) 170.7, 167.7, 137.3, 136.7, 133.8, 129.4, 127.4, 125.2, 124.8, 121.8, 83.1, 82.8, 59.7, 49.4, 25.5, 24.4, 23.8. HRMS (FTICR MS ESI$^+$) $[M+Na]^+$ calcd for $C_{30}H_{40}NaB_2N_2O_6$: 569.2965, found 569.2977.

Compound D-**2**. White solid; 0.805 g, 33 % yield; mp 151-152 °C. ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 9.42 (s, 1H), 7.85 (dd, J = 13.5, 7.3 Hz, 4H), 7.51 (t, J = 7.2 Hz, 3H), 7.32 (t, J = 7.7 Hz, 1H), 4.97 (dd, J = 7.9, 4.3 Hz, 1H), 3.49 (ddt, J =

45.7, 10.6, 6.9 Hz, 2H), 2.67 (td, J = 11.8, 6.2 Hz, 1H), 2.16 - 1.96 (m, 2H), 1.92 - 1.80 (m, 1H), 1.33 (d, J = 16.8 Hz, 24H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ (ppm) 172.0, 168.7, 138.5, 137.9, 134.9, 130.5, 128.5, 126.3, 126.0, 122.9, 84.3, 84.0, 60.8, 50.6, 26.5, 25.5, 25.0. HRMS (FTICR MS ESI$^+$) $[M+Na]^+$ calcd for $C_{30}H_{40}NaB_2N_2O_6$: 569.2965, found 569.2974.

Compound **L-3**. White solid; 0.793 g, 33 % yield; mp 232-233 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 9.72 (s, 1H), 7.93 (s, 1H), 7.88 (d, J = 7.4 Hz, 1H), 7.75 (d, J = 8.5 Hz, 2H), 7.59 (t, J = 7.0 Hz, 3H), 7.43 (t, J = 7.6 Hz, 1H), 4.99 (dd, J = 7.8, 4.1 Hz, 1H), 3.62 - 3.43 (m, 2H), 2.70 (dt, J = 11.6, 6.1 Hz, 1H), 2.15 - 1.95 (m, 2H), 1.87 (tt, J = 13.1, 6.7 Hz, 1H), 1.33 (d, J = 2.2 Hz, 24H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ (ppm) 172.2, 168.9, 141.0, 136.8, 135.8, 135.4, 133.2, 129.9, 128.0, 118.9, 84.2, 83.8, 60.9, 50.8, 26.5, 25.5, 25.0. HRMS (FTICR MS ESI$^+$) $[M+H]^+$ calcd for $C_{30}H_{41}B_2N_2O_6$: 547.3145, found 547.3158.

Compound **D-3**. White solid; 0.840 g, 35 % yield; mp 233-234 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 9.73 (s, 1H), 7.93 (s, 1H), 7.88 (d, J = 7.4 Hz, 1H), 7.75 (d, J = 8.4 Hz, 2H), 7.59 (t, J = 6.9 Hz, 3H), 7.43 (t, J = 7.5 Hz, 1H), 4.99 (dd, J = 7.9, 4.3 Hz, 1H), 3.53 (ddt, J = 49.9, 10.5, 6.8 Hz, 2H), 2.70 (dt, J = 11.6, 6.1 Hz, 1H), 2.05 (ddt, J = 47.4, 20.3, 7.3 Hz, 2H), 1.87 (tt, J = 12.7, 6.4 Hz, 1H), 1.33 (d, J = 2.1 Hz, 24H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ (ppm) 172.3, 168.9, 141.0, 136.8, 135.8, 135.4, 133.2, 129.9, 128.0, 118.9, 84.3, 83.8, 60.9, 50.8, 26.5, 25.5, 25.0. HRMS (FTICR MS ESI$^+$) $[M+H]^+$ calcd for $C_{30}H_{41}B_2N_2O_6$: 547.3145, found 547.3158.

Compound **L-4**. White solid; 0.823 g, 34 % yield; mp 296-297 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 9.65 (s, 1H), 7.86 (d, J = 8.0 Hz, 2H), 7.75 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H), 7.49 (d, J = 8.0 Hz, 2H), 4.98 (dd, J = 8.0, 4.3 Hz, 1H), 3.49 (ddt, J = 39.4, 10.7, 6.8 Hz, 2H), 2.69 (dt, J = 17.2, 6.1 Hz, 1H), 2.16 - 1.95 (m, 2H), 1.87 (tt, J = 12.5, 6.3 Hz, 1H), 1.34 (d, J = 10.1 Hz, 24H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ (ppm) 172.0, 168.9, 141.0, 138.3, 135.8, 134.9, 131.7, 126.3, 121.3, 118.8, 84.2, 83.8, 60.9, 50.6, 26.6, 25.5, 25.0. HRMS (FTICR MS ESI$^+$) $[M+H]^+$ calcd for $C_{30}H_{41}B_2N_2O_6$: 547.3145, found 547.3159.

Compound **D-4**. White solid; 0.770 g, 32 % yield; mp 300-301 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 9.67 (s, 1H), 7.86 (d, J = 7.3 Hz, 2H), 7.75 (d, J = 7.8 Hz, 2H), 7.58 (d, J = 7.8 Hz, 2H), 7.49 (d, J = 7.4 Hz, 2H), 4.99 (dd, J = 5.4, 2.5 Hz, 1H), 3.49 (dq, J = 23.1, 8.4 Hz, 2H), 2.69 (dd, J = 10.0, 5.1 Hz, 1H), 2.17 - 1.94 (m, 2H), 1.93 - 1.80 (m, 1H), 1.34 (d, J = 10.0 Hz, 24H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ (ppm) 172.2, 168.7, 141.1, 138.4, 135.9, 135.0, 131.9, 126.3, 121.5, 118.9, 84.3, 83.8, 60.9, 50.6, 26.3, 25.5, 25.0. HRMS (FTICR MS ESI$^+$) $[M+Na]^+$ calcd for $C_{30}H_{40}NaB_2N_2O_6$: 569.2965, found 569.2982.

Compound **L-5**. White solid; 0.910 g, 43 % yield; mp 214-215 °C. ^{1}H NMR (850 MHz, $CDCl_3$) δ (ppm) 9.62 (s, 1H), 7.96 (s, 1H), 7.91 (d, J = 7.3 Hz, 1H), 7.62 (d, J = 7.6 Hz, 1H), 7.59 (d, J = 7.9 Hz, 2H), 7.46 (t, J = 7.5 Hz, 1H), 7.32 (t, J = 7.8 Hz, 2H), 7.10 (t, J = 7.2 Hz, 1H), 5.01 (dd, J = 7.8, 4.4 Hz, 1H), 3.56 (ddt, J = 84.3, 10.6, 6.9 Hz, 2H), 2.71 (td, J = 11.9, 6.3 Hz, 1H), 2.19 - 1.86 (m, 3H), 1.36 (s, 12H). $^{13}C\{^{1}H\}$ NMR (214 MHz, $CDCl_3$) δ (ppm) 171.9, 168.9, 138.3, 136.7, 135.4, 133.1, 129.8, 128.8, 127.9, 123.9, 119.8, 84.1, 60.8, 50.6, 26.8, 25.4, 24.6. HRMS (FTICR MS ESI$^+$) $[M+Na]^+$ calcd for $C_{24}H_{29}NaBN_2O_4$: 443.2113, found 443.2114.

Compound **L-6**. White solid; 0.830 g, 39 % yield; mp 212-213 °C. ^{1}H NMR (850 MHz, $CDCl_3$) δ (ppm) 9.44 (s, 1H), 7.89 (d, J = 6.9 Hz, 1H), 7.85 (s, 1H), 7.55 (t, J = 7.4 Hz, 3H), 7.51 - 7.47 (m, 1H), 7.46 (t, J = 6.7 Hz, 2H), 7.35 (t, J = 7.4 Hz, 1H), 5.02 (s, 1H), 3.57 (d, J = 54.8 Hz, 2H), 2.72 (s, 1H), 2.22 - 2.01 (m, 2H), 1.91 (s, 1H), 1.34 (s, 12H). $^{13}C\{^{1}H\}$ NMR (214 MHz, $CDCl_3$) δ (ppm) 171.9, 168.8, 137.8, 135.9, 130.5, 130.4, 128.5, 128.4, 127.2, 125.9, 122.8, 83.9, 60.7, 50.6, 26.5, 25.5, 24.9, 24.9. HRMS (FTICR MS ESI$^+$) $[M+Na]^+$ calcd for $C_{24}H_{29}NaBN_2O_4$: 443.2113, found 443.2115.

Compound **L-7**: White solid; 0.520 g, 53 % yield; mp 134-135 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 9.12 (s, 1H), 8.21 (s, 1H), 8.03 (d, J = 7.7 Hz, 1H), 7.98 (d, J = 7.3 Hz, 1H), 7.95 (s, 1H), 7.80 (d, J = 7.7 Hz, 1H), 7.56 (d, J = 7.2 Hz, 1H), 7.49 (t, J = 7.6 Hz, 1H), 7.34 (t, J = 7.7 Hz, 1H), 7.18 (d, J = 7.1 Hz, 1H), 5.10 (dd, J = 13.9, 6.8 Hz, 1H), 1.66 (d, J = 6.9 Hz, 3H), 1.36 (d, J = 22.5 Hz, 24H). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ (ppm) 170.7, 167.8, 138.4, 137.5, 133.0, 132.8, 130.84, 130.7, 128.5, 128.4, 126.2, 123.3, 84.3, 84.0, 50.3, 25.0, 24.99, 24.98, 24.96, 18.7. HRMS (FTICR MS ESI$^+$) $[M+Na]^+$ calcd for $C_{28}H_{38}NaB_2N_2O_6$: 543.2808, found 543.2803.

Compound **D-7**. White solid; 0.600 g, 56 % yield; mp 132-133 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 9.10 (s, 1H), 8.21 (s, 1H), 8.03 (d, J = 7.8 Hz, 1H), 7.98 (d, J = 7.3 Hz, 1H), 7.94 (s, 1H), 7.81 (d, J = 7.9 Hz, 1H), 7.56 (d, J = 7.3 Hz, 1H), 7.53 - 7.44 (m, 1H), 7.34 (t, J = 7.7 Hz, 1H), 7.15 (dd, J = 22.6, 7.4 Hz, 1H), 5.43 - 4.84 (m, 1H), 1.66 (d, J = 6.9 Hz, 3H), 1.36 (d, J = 22.5 Hz, 24H). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ (ppm) 170.7, 167.8, 138.4, 137.5, 133.0, 132.7, 130.8, 130.7, 128.6, 128.4, 126.2, 123.3, 84.3, 84.0, 50.3, 25.0, 24.99, 24.98, 24.96, 18.7. HRMS (FTICR MS ESI$^+$) $[M+Na]^+$ calcd for $C_{28}H_{38}NaB_2N_2O_6$: 543.2808, found 543.2816.

Compound **L-8**. White solid; 0.430 g, 49 % yield; mp 182-183 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 9.55 (s, 1H), 7.84 (d, J = 11.0 Hz, 1H), 7.70 (s, 1H), 7.56 (dd, J = 8.6, 2.3 Hz, 1H), 7.43 (s, 1H), 7.31 (d, J = 8.7 Hz, 1H), 7.19 (dd, J = 8.4, 2.2 Hz, 1H), 4.94 (dd, J = 7.9, 4.4 Hz, 1H), 3.59 (dt, J = 10.6, 6.8 Hz, 1H), 3.47 (dt, J = 10.7, 7.0 Hz, 1H), 2.68 (td, J = 12.0, 6.3 Hz, 1H), 2.12 (dq, J = 14.1, 7.1 Hz, 1H), 2.01 (dt, J = 15.1, 7.5 Hz, 1H), 1.95 - 1.85 (m, 1H), 1.32 (d, J = 11.6 Hz, 24H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ (ppm) 170.7, 168.5, 163.5, 163.0, 161.8, 161.4, 139.3, 139.2, 137.31, 137.27, 128.8, 123.2, 123.1, 121.2, 117.1, 117.0, 116.4, 116.2, 110.2, 110.0, 84.5, 84.2, 60.9, 50.6, 26.3, 25.4, 24.9, 24.8. HRMS (FTICR MS ESI$^+$) $[M+Na]^+$ calcd for $C_{30}H_{38}NaB_2F_2N_2O_6$: 605.2776, found 605.2787.

Compound **L-9**. White solid; 0.420 g, 52 % yield; mp 216-217 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 9.72 (s, 1H), 7.94 (s, 1H), 7.88 (d, J = 7.3 Hz, 1H), 7.84 (d, J = 11.0 Hz, 1H), 7.60 (d, J = 7.6 Hz, 1H), 7.44 (t, J = 7.5 Hz, 2H), 7.21 - 7.15 (m, 1H), 4.97 (dd, J = 7.9, 4.4 Hz, 1H), 3.65 - 3.53 (m, 1H), 3.52 - 3.41 (m, 1H), 2.68 (td, J = 11.5, 6.0 Hz, 1H), 2.10 (dq, J = 20.1, 6.7 Hz, 1H), 2.00 (dt, J = 20.4, 7.5 Hz, 1H), 1.95 - 1.82 (m, 1H), 1.32 (d, J = 15.3 Hz, 24H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ (ppm) 172.3, 168.7, 163.5, 161.8, 139.4, 139.3,

136.7, 135.2, 133.1, 129.8, 127.9, 121.2, 116.3, 116.1, 110.2, 110.0 (d, J = 20.5 Hz), 84.2, 84.1, 60.7, 50.7, 26.1, 25.4, 25.0, 24.9, 24.8. HRMS (FTICR MS ESI$^+$) [M+Na]$^+$ calcd for $C_{30}H_{39}NaB_2FN_2O_6$: 587.2870, found 587.2876.

Compound **L-10**. White solid; 0.500 g, 44 % yield; mp 181-182 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 9.33 (s, 1H), 7.86 (d, J = 8.1 Hz, 1H), 7.81 (s, 1H), 7.71 (s, 1H), 7.55 (d, J = 7.2 Hz, 1H), 7.52 (d, J = 7.2 Hz, 1H), 7.32 (dd, J = 13.3, 6.2 Hz, 2H), 4.95 (s, 1H), 3.58 (dd, J = 11.8, 5.2 Hz, 1H), 3.52 - 3.42 (m, 1H), 2.68 (d, J = 5.5 Hz, 1H), 2.18 - 2.08 (m, 1H), 2.02 (dd, J = 12.8, 7.1 Hz, 1H), 1.90 (dd, J = 12.4, 6.3 Hz, 1H), 1.33 (d, J = 7.5 Hz, 24H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ (ppm) 170.6, 168.4, 163.0, 161.4, 137.7, 137.5, 137.4, 130.5, 128.8, 128.4, 125.9, 123.1, 123.0, 122.8, 84.5, 83.9, 60.8, 50.6, 26.4, 25.5, 24.88, 24.85. HRMS (FTICR MS ESI$^+$) [M+Na]$^+$ calcd for $C_{30}H_{39}NaB_2FN_2O_6$: 587.2870, found 587.2876.

Compound **D-1Br**. White solid; 1.988 g, 81.5 %, mp 223-224 °C. ^{1}H NMR (500 MHz, CDCl3) δ (ppm) 9.63 (s, 1H), 7.82 (s, 1H), 7.70 (s, 1H), 7.62 (t, J = 13.4 Hz, 1H), 7.47 (t, J = 10.3 Hz, 1H), 7.31 (dd, J = 16.4, 8.2 Hz, 2H), 7.14 (d, J = 7.9 Hz, 1H), 7.06 (t, J = 8.0 Hz, 1H), 5.00-4.87 (m, 1H), 3.62 (dd, *J* = 11.4, 5.7 Hz, 1H), 3.57-3.47 (m, 1H), 2.57-2.42 (m, 1H), 2.26-2.07 (m, 2H), 1.93 (ddd, J = 18.3, 14.6, 5.9 Hz, 1H). ^{13}C NMR (125 MHz, CDCl3) δ (ppm) 169.8, 169.0, 139.4, 137.7, 133.6, 130.2, 130.2, 130.0, 126.9, 125.7, 122.7, 122.5, 122.5, 118.0, 61.1, 50.7, 27.4, 25.4. HRMS (FTICR MS ESI$^+$) [M+Na]+ calcd for $C_{18}H_{16}NaBr_2N_2O_2$: 472.9471, found 472.9477.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS publications website.
Synthesis; absorption and CD titration curves; ^{19}F NMR spectral titration profiles; ^{1}H, ^{13}C NMR and HRMS spectra of 1-10, computational data and others (PDF). Crystallographic information for D-**1Br** (CCDC 1574044) (CIF)

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Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

We thank Professor Eric V. Anslyn of the University of Texas at Austin for useful discussion. We are grateful for the financial support from the NSF of China (grants 21435003, 91427304, 21521004, and J1310024), the Ministry of Education of China (grant IRT13036) and the NSFC RS Joint Project (grant 21311130122).

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