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Chiral Recognition of Carboxylates by a Static Library of Thiourea Receptors with Amino Acid Arms

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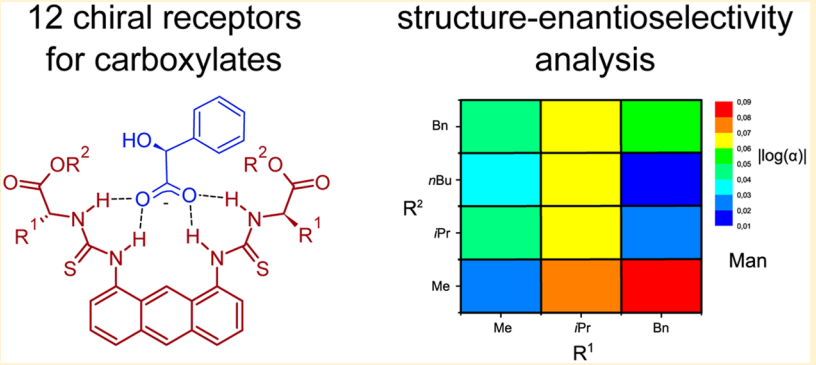
Supporting Information



ABSTRACT: Chiral recognition is based on a large network of very subtle interactions whose outcome is difficult to predict. A combinatorial approach is therefore the most suitable to search for the most efficient receptor and obtain a structure−enantioselectivity correlation. We synthesized a set of 12 receptors constructed with 1,9-diaminoantracene and α-amino acid esters, linked via thiourea groups. The association constants and enantioselectivities for the complexes with mandelate and *N*-acetylphenylalanine were determined by competitive NMR titrations. Association constants quite regularly depend on the substituents in the receptor structure, but the distribution of enantioselectivities across the library could not easily be rationalized.

1. INTRODUCTION

Chiral recognition is a phenomenon that relies on very subtle effects. The selectivities that have so far been obtained for artificial receptors, especially in the chiral recognition of carboxylates, are usually not very impressive, although many attempts have been made in the last 20 years.[1−40] At the same time, however, nature indicates that obtaining perfect enantioselectivity with high affinities is not impossible, not ruled out by some fundamental laws. Let the selectivity for (*S*)-naproxene in the human body be a representative example of such systems.[41]

One of the major problems in the development of receptors for chiral recognition is our inability to predict their enantioselectivity efficiency before their synthesis and tedious experiments are performed. It is the exception rather than the rule that the observed selectivity can easily be explained by a simple stereochemical model with just the total number of attractive and repulsive interactions rationalizing the chiral recognition.[42,43] It seems that it is the entropic rather than the enthalpic factor that controls the selectivity.[9] The entropy of binding is, however, extremely difficult to predict, especially when two compared complexes are in a diastereoisomeric relationship. This indicates that chiral recognition requires a large scope combinatorial approach. The usefulness of such an approach has already been shown in the field of chiral recognition of cations.[44]

2. RESULTS AND DISCUSSION

In this paper, we present our new[45] and more successful library of chiral anion receptors, which is, to the best of our knowledge, the most extensive ever investigated. Bisthioureidic receptors of type **1** are formally composed of 1,10-diaminoanthracene and two amino acid esters. The diaminoantharcene platform has already proved to be readily obtainable and its thiourea derivatives effectively bind carboxylates in polar solvents.[22] The application of amino acids has many advantages; e.g., they are readily available in enantiopure form with high diversity in their side chains and the possibility of modifying the C-terminus with various amines or alcohols. The N-terminus of the amino acid is used in the formation of thiourea moiety. We decided to employ the following amino acids: alanine (the smallest group), valine (bulky side chain), phenylalanine (aromatic group), and tryptophane (additional hydrogen bond donor). The C-termini of the chiral amino acids were modified into ester groups with methyl (small), isopropyl (bulky), *n*-butyl (long chain), and benzyl (aromatic) alcohols.

The synthesis of chiral receptors is outlined in Scheme 1 (path A). Bisisothiocyanate **4** was synthesized in three steps from dinitroantroquinone (**2**) following the literature.[46]

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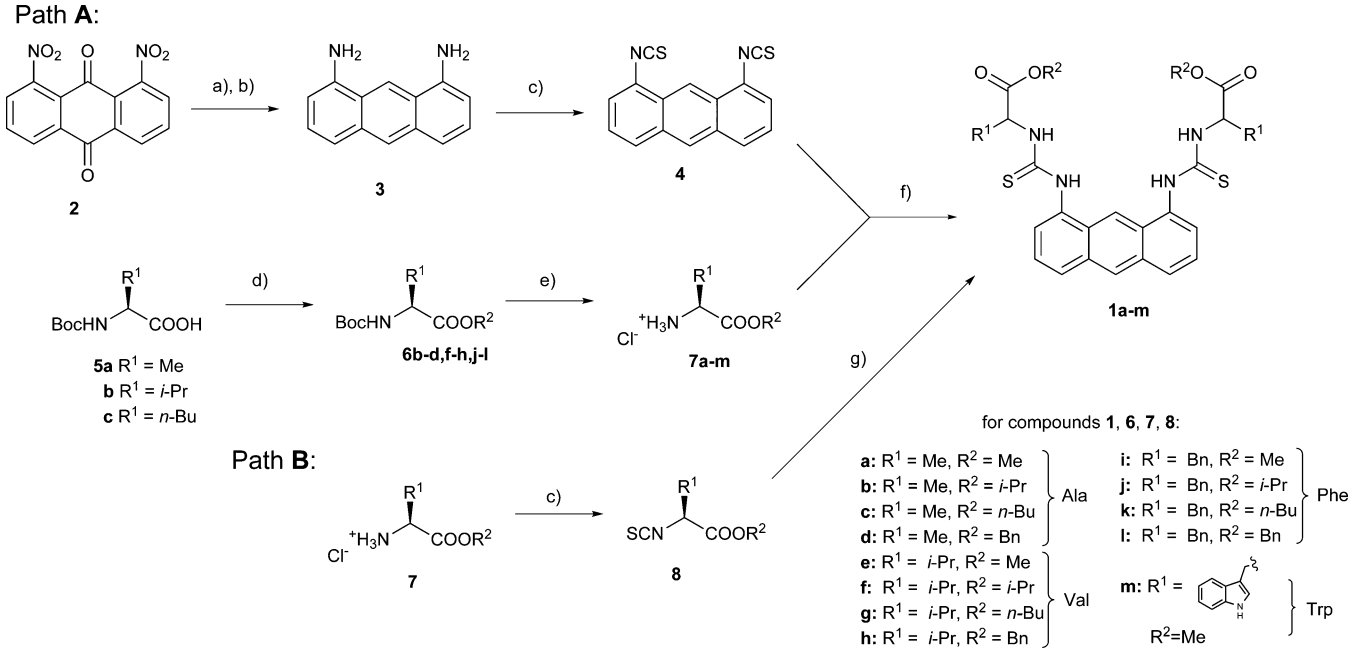
Scheme 1. Synthesis of Receptors 1 by Routes A and B

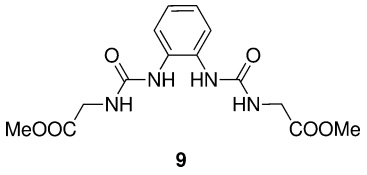


[a]Reagents and conditions: (a) Na_2S, iPrOH, reflux, 12 h; (b) $NaBH_4$, NaOH, iPrOH, reflux, 12 h; (c) thiophosgene, DCM/$NaHCO_3$(aq), rt, 30 min; (d) R^2OH, EDCI, DMAP, DCM, rt, 12 h; (e) 4 M HCl in dioxane, rt, 30 min; (f) DIPEA, DCM, 1 h; (g) **3**, DCM, rt, 2 h.

Compound **4** was purified by crystallization and then reacted with an appropriate amino acid ester (**7**) to yield the receptors **1**. An alternative synthesis path was also tested (Scheme 1, path B); this employed the formation of isothiocyanates (**8**) derived from the amino acid ester and their reaction with diamine **3**. The second approach generally resulted in a better yield; however, it is less convenient in terms of library synthesis and increases the exposure to toxic thiophosgene.

The receptors were evaluated for their enantioselectivities toward two model chiral anions: (*R*/*S*)-mandelate (Man) and *N*-acetyl-D/L-phenylalanine (AcPhe) used as tetrabutylammonium (TBA) salts. In the first step, the stoichiometry of the complexes was determined by analysis of direct ^{1}H NMR titrations and classical Job plots in MeCN-d_3. For the receptors containing alanine, valine, and phenylalanine (**1a**–**l**), the classical Job plot indicates a simple 1:1 stoichiometry, which is consistent with the titration curves (Figure 1a) and stochastic distribution of residuals. However, a closer look at the titration course of the tryptophane-based receptor **1m** indicates a more complex behavior (Figure 1b). The indole NH signal does not reach a plateau after 1 equiv of guest but continues to move downfield; similarly, the proton at position 9 in the anthracene moiety (green curve) switches its direction of movement after exceeding 1 equiv of anion. These observations indicate the subsequent formation of an HG_2 complex in the case of the tryptophan-containing host. This complex behavior is known to make the determination of association constants less reliable, and competitive methods cannot be applied. Thus, this receptor was excluded from further examination.

The association constants of the complexes with the model anions were determined in MeCN-d_3 by competitive NMR titration[2,45,47−50] using an achiral receptor **9** as an internal reference[45] (Figure 1c). This titration is insensitive to concentration errors and is a far more accurate and precise method. Enantioselectivities ($\alpha = K_S/K_R$ or K_L/K_D) were then calculated for each receptor−anion pair (Tables 1 and 2).



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K_a values exhibited dependence on the R^1 and R^2 groups. A comparison of various R^1 moieties was performed with scaled $K' = K/(K\ (R^1 = Me))$ (for constant R^2 and a given anion); the values are presented in Figure 2a and compared with Taft's steric parameters.[51,52] The highest K_a's were observed for the valine based receptors (**1e**–**h**) with $K' = 2.33$–2.91, although they possess the bulkiest *i*-Pr substituent (E_S= −0.47). The phenylalanine-based receptors (**1i**–**l**) exhibit affinities ca. half as high ($K' = 0.50$–0.76, $E_S = -0.38$) as those in the alanine series (**1a**–**d**, $E_S = 0$ by definition). This trend indicates that the bulky substituents may not only block the entrance to the binding pocket between the thiourea groups but also, in certain cases, help to preorganize the receptor to a conformation suitable for carboxylate binding. In the case of R^1 = *i*-Pr, the preorganization effect predominates, while benzyl groups mainly limit the availability of the binding pocket. A similar substituent effect analysis was performed for R^2 groups ($K'' = K/(K\ (R^2 = Me))$, Figure 2b), and we found this influence substantially weaker. On average, the K_a changes in the following order: *i*-Pr < *n*-Bu < Bn ≈ Me. Apart from benzyl, the remaining three groups qualitatively follow the Taft steric parameters as depicted in the graph. The presence of a benzyl group in the ester moiety increases the binding affinities most probably by receptor preorganization. The aforementioned observations are consistent with our recent results for receptors of similar structure.[45]

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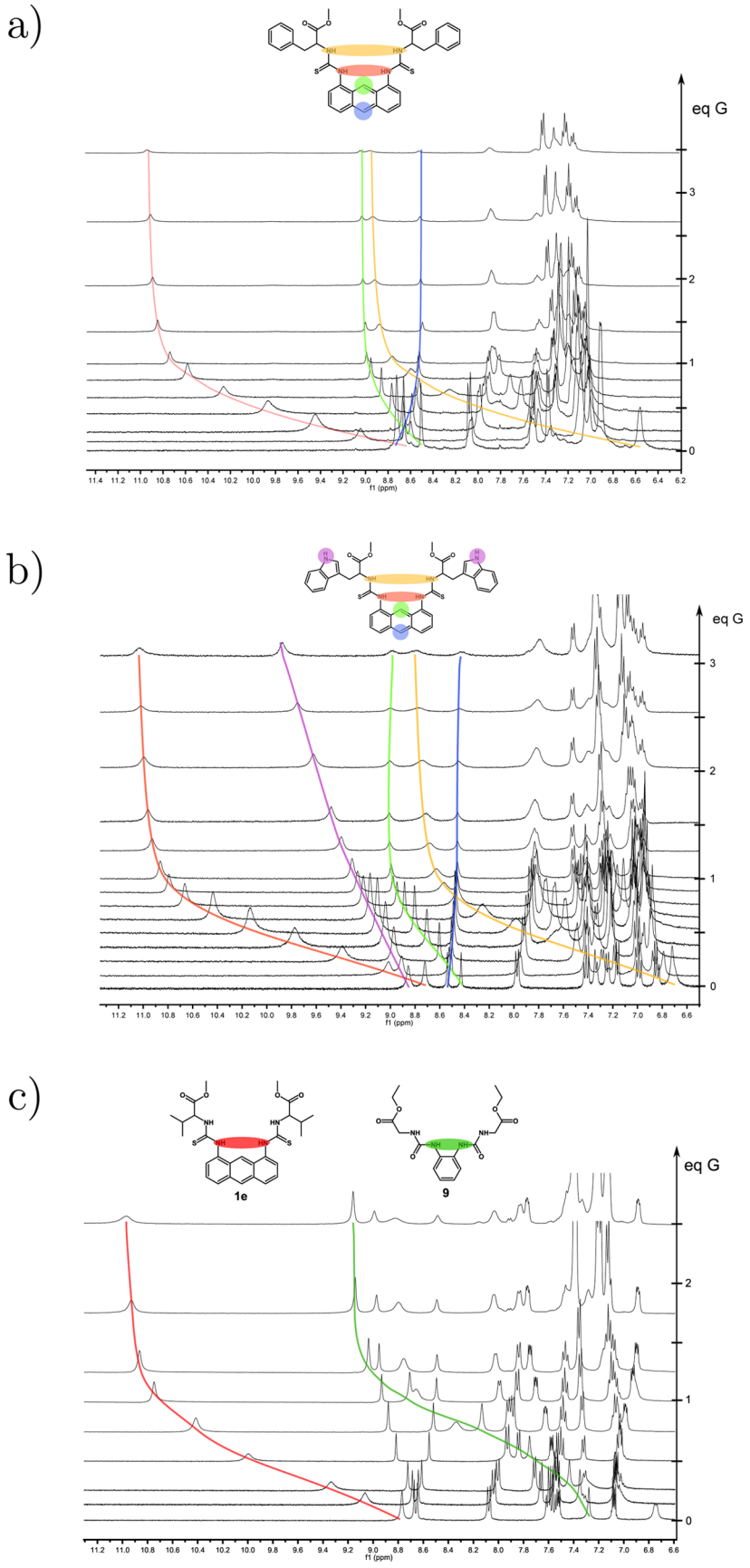

Figure 1. (a) NMR titration of **1i** indicating 1:1 stoichiometry, (b) NMR titration of **1m** with (*S*)-Man indicating the formation of an HG_2 complex, (c) an example of competitive titration of **1e** and **9** with (*S*)-Man, the equivalents of guests calculated against the sum of the two hosts. All measurements in MeCN-d_3, 303 K, anions used as TBA salts.

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Table 1. Association Constants (M^{-1}) and Enantioselectivities (α) of Receptors 1 with Man[a]

receptor			K_a		α
	R^1	R^2	*S*	*R*	K_R/K_S
1a	Me	Me	$1.36 \times 10^4 \pm 7.0$ (%)	$1.44 \times 10^4 \pm 3.5$ (%)	1.06 ± 7.8 (%)
1b	Me	*i*-Pr	$1.00 \times 10^4 \pm 2.9$ (%)	$1.13 \times 10^4 \pm 3.3$ (%)	1.12 ± 4.4 (%)
1c	Me	*n*-Bu	$1.15 \times 10^4 \pm 2.4$ (%)	$1.26 \times 10^4 \pm 1.3$ (%)	1.09 ± 2.7 (%)
1d	Me	Bn	$1.20 \times 10^4 \pm 4.0$ (%)	$1.34 \times 10^4 \pm 3.5$ (%)	1.12 ± 5.3 (%)
1e	*i*-Pr	Me	$3.21 \times 10^4 \pm 4.2$ (%)	$3.82 \times 10^4 \pm 1.7$ (%)	1.19 ± 4.5 (%)
1f	*i*-Pr	*i*-Pr	$2.07 \times 10^4 \pm 4.5$ (%)	$2.43 \times 10^4 \pm 1.1$ (%)	1.18 ± 4.7 (%)
1g	*i*-Pr	*n*-Bu	$2.68 \times 10^4 \pm 8.3$ (%)	$3.10 \times 10^4 \pm 7.7$ (%)	1.16 ± 11 (%)
1h	*i*-Pr	Bn	$3.16 \times 10^4 \pm 3.6$ (%)	$3.66 \times 10^4 \pm 1.4$ (%)	1.16 ± 3.9 (%)
1i	Bn	Me	$6.64 \times 10^3 \pm 5.5$ (%)	$8.11 \times 10^3 \pm 5.9$ (%)	1.22 ± 8.1 (%)
1i	Bn	*i*-Pr	$5.90 \times 10^3 \pm 3.8$ (%)	$6.32 \times 10^3 \pm 5.4$ (%)	1.08 ± 6.6 (%)
1k	Bn	*n*-Bu	$6.06 \times 10^3 \pm 3.4$ (%)	$6.32 \times 10^3 \pm 5.4$ (%)	1.04 ± 6.4 (%)
1l	Bn	Bn	$7.36 \times 10^3 \pm 6.0$ (%)	$8.35 \times 10^3 \pm 4.5$ (%)	1.14 ± 7.5 (%)

[a]Competitive NMR titration in MeCN-d_3, 303 K.

Table 2. Association Constants (M^{-1}) and Enantioselectivities (α) of Receptors 1 with AcPhe[a]

receptor			K_a		α
	R^1	R^2	D	L	K_L/K_D
1a	Me	Me	$1.48 \times 10^5 \pm 1.9$ (%)	$1.58 \times 10^5 \pm 2.8$ (%)	1.06 ± 3.4 (%)
1b	Me	*i*-Pr	$1.14 \times 10^5 \pm 1.7$ (%)	$1.22 \times 10^5 \pm 2.0$ (%)	1.07 ± 2.6 (%)
1c	Me	*n*-Bu	$1.37 \times 10^5 \pm 2.8$ (%)	$1.47 \times 10^5 \pm 1.6$ (%)	1.08 ± 3.2 (%)
1d	Me	Bn	$1.42 \times 10^5 \pm 3.2$ (%)	$1.48 \times 10^5 \pm 3.7$ (%)	1.04 ± 4.9 (%)
1e	*i*-Pr	Me	$4.02 \times 10^5 \pm 3.8$ (%)	$3.90 \times 10^5 \pm 6.3$ (%)	0.97 ± 7.4 (%)
1f	*i*-Pr	*i*-Pr	$2.90 \times 10^5 \pm 4.2$ (%)	$2.91 \times 10^5 \pm 3.2$ (%)	1.00 ± 5.3 (%)
1g	*i*-Pr	*n*-Bu	$3.78 \times 10^5 \pm 2.2$ (%)	$3.45 \times 10^5 \pm 4.9$ (%)	0.91 ± 5.4 (%)
1h	*i*-Pr	Bn	$4.13 \times 10^5 \pm 2.8$ (%)	$4.15 \times 10^5 \pm 2.8$ (%)	1.01 ± 4.0 (%)
1i	Bn	Me	$8.36 \times 10^4 \pm 1.8$ (%)	$8.45 \times 10^4 \pm 4.2$ (%)	1.01 ± 4.6 (%)
1i	Bn	*i*-Pr	$6.88 \times 10^4 \pm 4.0$ (%)	$7.04 \times 10^4 \pm 1.5$ (%)	1.02 ± 4.3 (%)
1k	Bn	*n*-Bu	$7.61 \times 10^4 \pm 1.7$ (%)	$7.91 \times 10^4 \pm 3.5$ (%)	1.04 ± 3.9 (%)
1l	Bn	Bn	$1.08 \times 10^5 \pm 5.5$ (%)	$1.11 \times 10^5 \pm 4.00$ (%)	1.02 ± 6.8 (%)

[a]Competitive NMR titration in MeCN-d_3, 303 K.

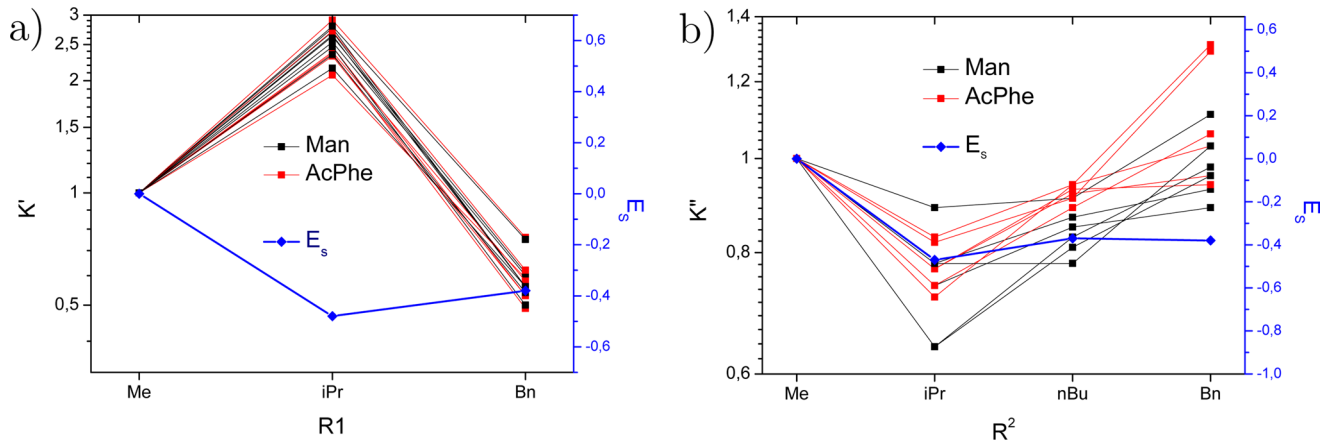

Figure 2. (a, b) Correlation between anion affinities and R^1 (a) or R^2 groups (b). Left vertical axis (K' or K'') is on a logarithmic scale; right vertical axis corresponds to E_S.

Enantioselectivities for the two model anions are presented in Tables 1 and 2 and Figure 3. All of the receptors studied exhibit consistent preference for the (*R*)-Man, while the selectivities of the AcPhe enantiomers have a more complex distribution—alanine and phenylalanine receptors (**1a**–**d**,**i**–**k**) bind L-AcPhe more strongly, while valine-based receptors (**1e** and **1g**) possess a reverse selectivity. Several receptors (**1b**,**c**,**g**) were found to be quite successful in chiral recognition of both guests. The distributions of selectivities may seem stochastic for the two model anions, but a graphical analysis of the selectivity vs R^1 and R^2 substituents presented in Figure 2e,f facilitates the observation of some trends. For a mandelate guest, R^1 = *i*-Pr (Val) results in the best chiral recognition properties (all $|\log(\alpha)| > 0.6$), and R^2 = Me gives the best results for R^1 = *i*-Pr or Bn. In the case of the AcPhe anion, the receptors incorporating alanine (R^1 = Me) are

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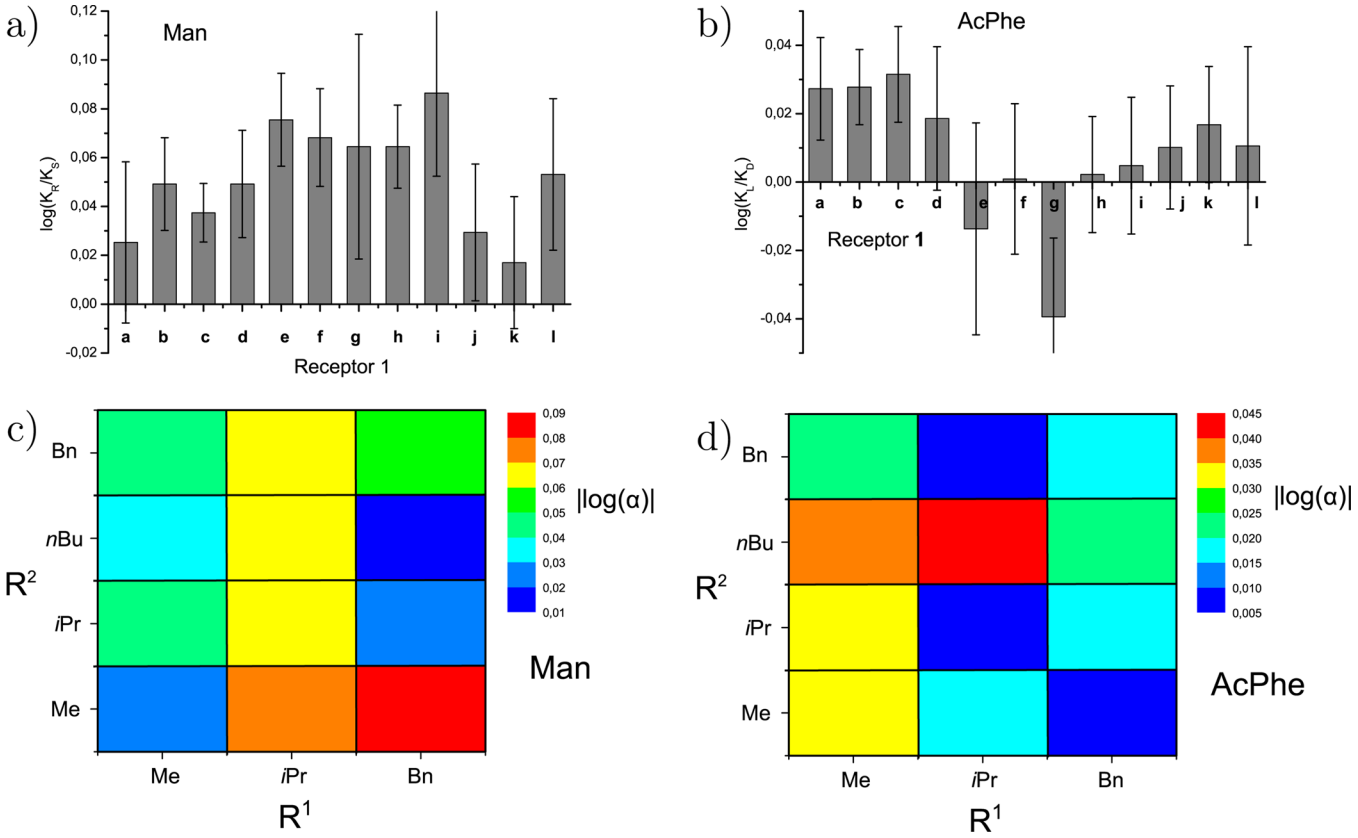
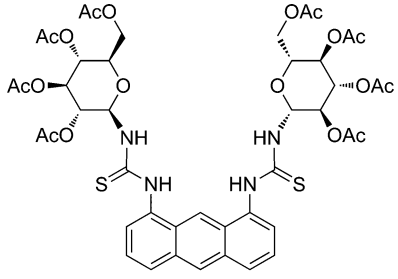


Figure 3. (a, b) Distributions of enantioselectivities (log(α)) of receptors **1** with Man and AcPhe, respectively. (c, d) Graphical analysis of influence of R^1, R^2 on enantioselectivities (|log(α)|) with Man and AcPhe anions, respectively.

slightly more effective, and R^2 = *n*-Bu is preferable across the series. Each guest exhibits a different preference for receptor structure. The highest observed selectivities are K_R/K_S = 1.22 for **1e** with Man and K_D/K_L = 1.10 for **1g** with AcPhe. Both results did not appear at the intersection of the most promising R^1 and R^2 groups but emerged for receptors with different substituents. These observations indicate that some global analyses can be performed; however, the highest enantioselectivities are the consequences of a unique, nonadditive match between the substituents.

The level of enantioselectivity in our receptors seems quite low, especially when compared to the results reported by Kim et al.[22] In the cited paper, the authors describe receptor **10**, decorated with glucose derivatives, which is based on the same 1,8-diaminoanthracene platform as our hosts of type **1**. Receptor **10** was tested with a set of Boc- or DNB-protected α-amino acid anions by fluorometic titration. The reported enantioselectivities reach values up to 10. Concerned about the dissonance between the results by Kim et al. and ours, we decided, in the first step, to check receptor **10** in chiral recognition of our model carboxylates. The enantioselectivities determined by NMR competitive titrations are 1.02 and 1.06 for Man and AcPhe, respectively, which are comparable with the results for our receptors **1a**–**l**. Significantly higher enantioselectivities reported by Kim et al. for Boc- and DNB-amino acids suggested that both Man and AcPhe may be particularly difficult guests in obtaining high chiral recognition. We therefore decided to confirm some of the enantioselectivities reported by Kim et al. by our competitive titration method. According to our results, the selected α values are far lower: 1.3 instead of 5.5 and 1.2 insted of 4.3 for BocAla and BocVal, respectively (Table 3). We have further confirmed these results by UV–vis titration. However, when we performed titration under fluorometric control, as in the cited paper, we found that fitting the data is quite difficult due to complex mechanism of fluorescence quenching (see the Supporting Information for details). In this case Benesi–Hildebrand linearization[53] cannot be applied, which is the

Table 3. Enantioselectivities of Receptor 10 Determined by Various Methods



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guest	enantioselectivity $\alpha = K_D/K_L$		
	fluorometric titration by Kim et al.	NMR competitive titration	UV–vis titration
Man		1.02	
AcPhe		1.06	
Boc-Ala	5.5	1.31	1.40
Boc-Val	4.3	1.22	1.02
Boc-Phe	1.2	1.18	

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main reason for the false results obtained by Kim et al. In view of these facts, all values of association constants and enantioselectivities reported in that paper are doubtful.

This finding indicates that obtaining a high level of enantiodiscrimination in the supramolecular chemistry of carboxylates is not very common, and some results that act as the *gold standard* are actually experimental artifacts. It is worth mentioning here that from the point of view of modern chiral stationary phases in HPLC or GC the selectivity at a level of 1.1 is not only sufficient but even optimal.[43] Most of the receptors **1a–l** exhibit enantioselectivity of the model carboxylates close to this optimal level.

3. CONCLUSIONS

The library of thiourea receptors **1** was easily synthesized in a convergent mode. A tryptophan-based receptor, equipped with an additional hydrogen bond donor, binds carboxylates with a complex HG + HG_2 stoichiometry, while other receptors form 1:1 complexes exclusively. The amino acid side chains (R^1) strongly influence binding affinities either by receptor preorganization or by hindering the thiourea groups. This library exhibits modest enantioselectivity values which depend on both R^1 and R^2 groups. Although some regularity in the structure–enantioselectivity relationship was found, the influences of the substituents were determined not to be simply additive. The enantioselectivity values are in the range of 1.0–1.22, which is quite consistent with results obtained in our group for similar receptors.[36] We also proved that the very high enantioselectivities obtained by Kim et al. for receptor **10** are artifacts resulting from misuse of the Benesi–Hildebrand approximation, and the real selectivity values are close to those obtained by us.

4. EXPERIMENTAL SECTION

Dichloromethane used in the syntheses was distilled over CaH_2. The reactions were carried under Ar. Preparative chromatography was performed with silica gel (silicagel 60, 230–400 mesh); typically, a 40-fold mass excess of gel was used. Abbreviations of the signal multiplicity in the signal listing: s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; sext, sextet; sept, septet; m, complex multiplet; bs, broad signal. HRMS measurements were performed with ESI ionization and TOF analyzer. Optical rotations (O.R.) were measured in 10 cm cuvettes, and $[\alpha]_D^{20}$ values are given in deg cm^3 dm^{-1} g^{-1}.

Methyl ester hydrochlorides **7a,e,i,m** are commercially available. Synthesis of other esters was performed as described previously.[45]

Boc-L-AlaOiPr, 6b. Colorless oil. Yield: 3.23 g (70%). ^{1}HNMR (400 MHz, DMSO-d_6) δ: 7.22 (1 H, d, J = 7.2 Hz); 4.87 (1 H, sept, J = 6.3 Hz); 3.90 (1 H, p, J = 7.3 Hz); 1.37 (s, 9 H); 1.24–1.12 (m, 9 H). ^{13}CNMR (100 MHz, DMSO-d_6) δ: 172.6; 155.3; 78.0; 67.6; 49.2; 28.2; 21.6; 21.5; 16.7. HRMS: calcd for $C_{11}H_{21}NO_4$ + Na 254.13628, found 254.1368. O.R.: $[\alpha_D^{20}]$ = −31.0 (c = 1, MeOH).

Boc-L-AlaOnBu, 6c. Colorless oil. Yield: 4.02 g (82%). ^{1}HNMR (400 MHz, DMSO-d_6) δ: 7.25 (1 H, d, J = 7.3 Hz); 4.12–3.92 (m, 3 H); 1.59–1.48 (m, 2 H); 1.44–1.28 (m, 11 H); 1.22 (3 H, d, J = 7.3 Hz); 0.87 (3 H, t, J = 7.4 Hz). ^{13}CNMR (100 MHz, DMSO-d_6) δ: 173.2; 155.3; 78.1; 63.9; 49.1; 30.2; 28.2; 18.6; 16.8; 13.5. HRMS: $C_{12}H_{23}NO_4$ + Na 268.15193, found 268.1503. O.R.: $[\alpha]_D^{20}$ = −35.7 (c = 1.09, MeOH) (lit.:[54] $[\alpha]_D^{20}$ = −41).

Boc-L-AlaOBn, 6d. Colorless oil. Yield: 2.95 g (53%). ^{1}HNMR (400 MHz, DMSO-d_6) δ: 7.40–7.30 (m, 1 H); 5.15 (1 H, d, J = 12.7 Hz); 5.08 (1 H, d, J = 12.7 Hz); 4.07 (1 H, quint, J = 7.3 Hz); 1.37 (s, 2 H); 1.26 (1 H, d, J = 7.5 Hz). ^{13}CNMR (100 MHz, DMSO-d_6) δ: 173.0; 155.3; 136.1; 128.4; 128.0; 127.7; 78.2; 65.8; 49.2; 28.2; 16.8. HRMS: calcd for $C_{15}H_{21}NO_4$ + Na 302.13628, found 302.1381. O.R.: $[\alpha]_D^{20}$ = 33.6 (c = 1.26, MeOH).

General Procedure for Boc Deprotection. Boc-amino ester **6** (3 mmol) was dissolved in 4 M HCl in dioxane (15 mL) and stirred for 2 h at rt. The mixture was concentrated on a rotary evaporator to yield a white solid. The reaction proceeds quantitatively, and the product–amino acid ester hydrochloride is pure enough for the next step.

General Procedure for the Synthesis of Receptors 1, Path A. Amino acid ester hydrochloride **7** (3 mmol) was dissolved in DCM and DIPEA (0.85 mL, 5 mmol), 1,8-diisothiocyanoantracene **4** (292 mg, 1 mmol) was added, and the reaction was carried out for 2 h at rt. The mixture was then directly subjected to chromatography, and the receptors were eluted with 2–4% acetone in DCM. The product was further purified by dissolving in minimum amount of DCM and titruated with hexane. The yellow (or beige) precipitate was filtered off and dried in vacuo.

General Procedure for the Synthesis of Receptors 1, Path B. This procedure involves very toxic thiophosgene, and the reaction should be carried with caution under a well-ventilated hood. Amino acid ester hydrochloride **7** (3 mmol) was dissolved in DCM (30 mL), and a satd solution of $NaHCO_3$ (30 mL) was added to the flask. Thiophosgene (6 mmol) was added into the DCM phase, and the mixture was stirred intensively for 30 min at room temperature. Phases were separated, the aqueous phase was extracted with DCM, and combined organic phases were dried over sodium sulfate. The drying agent was filtered off, and the solution was concentrated on a rotary evaporator (equipped with water jet pump to neutralize the thiophosgene vapors in water). The obtained isocyanate was dissolved in DCM, and amine **3** (1 mmol) was added. The reaction was carried out at rt for 1 h, and the product was purified as in path A. Figure 4 shows the numbering scheme of protons in **1**.

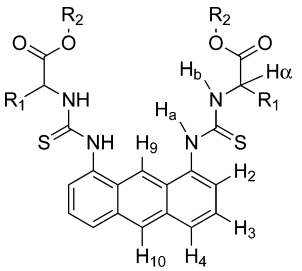

Figure 4. Numbering scheme of protons in receptors **1**.

1a. Yellow powder. Yield: 174 mg (35%). Mp: 164–165 °C.^{1}HNMR (MHz, DMSO-d_6) δ: 9.90 (s, 2 H, H_a); 8.67 (1 H, s, J = 5.1 Hz, H_{10}); 8.66 (s, 1 H); 8.10 (2 H, d, J = 7.3 Hz, H_2); 8.02 (2 H, d, J = 8.4 Hz, H_4); 7.60 (2 H, d, J = 7.0 Hz, H_b); 7.58–7.51 (m, 2 H, H_3); 5.03 (2 H, p, J = 7.3 Hz, H_α); 3.67 (s, 6 H, R_2); 1.39 (6 H, d, J = 7.3 Hz, R_1). ^{13}CNMR (MHz, DMSO-d_6) δ: 182.0; 173.0; 134.8; 132.0; 127.8; 127.0; 126.4; 125.4; 123.8; 116.6; 52.6; 51.9; 17.4. HRMS: calcd for $C_{24}H_{26}NO_4S_2$ + H 499.1454, found 499.1447. Anal. Calcd for $C_{24}H_{26}N_4O_4S_2$: C, 57.81; H, 5.26; N, 11.24, S, 12.86. Found: C, 57.91; H, 5.25; N, 11.13; S, 12.76. O.R.: $[\alpha]_D^{20}$ = −110.24 (c = 0.37, DCM).

1b. Beige powder. Yield: 122 mg (22%). Mp: 204–206 °C. ^{1}HNMR (500 MHz, DMSO-d_6) δ: 9.92 (s, 2 H, H_a); 8.68 (s, 2 H, H_{10} + H_9); 8.02 (4 H, m, H_2 + H_4); 7.62 (2 H, d, J = 7.1 HzH_b); 7.59–7.50 (m, 2 HH_3); 5.48–4.65 (m, 4 H, H_α + R_2); 1.37 (6 H, d, J = 7.2 Hz, R_2); 1.23 (6 H, d, J = 6.4 Hz, R_2); 1.21 (6 H, d, J = 6.4 Hz, R_1). ^{13}CNMR (126 MHz, DMSO-d_6) δ: 182.0; 172.0; 134.8; 132.0; 127.8; 127.0; 126.3; 125.4; 123.7; 116.6; 68.1; 52.8; 21.5; 21.4; 17.5. HRMS: calcd for $C_{28}H_{34}N_4O_4S_2$ + H 499.1454, 555.2095, found 555.2100. Anal. Calcd for $C_{28}H_{34}N_4O_4S_2$: C, 60.62; H, 6.18; N, 10.10; S, 11.56. Found: C, 60.44; H, 6.21; N, 10.02; S, 11.47. O.R.: $[\alpha]_D^{20}$ = −106 (c = 0.503, DCM).

1c. Beige powder. Yield: 163 mg (28%). Mp: 165–168 °C. ^{1}HNMR (500 MHz, DMSO-d_6) δ: 9.95 (s, 2 H, H_a), 8.68 (s, 1 H, H_{10}); 8.67 (s, 1 H, H_9); 8.06 (2 H, d, J = 7.3 Hz, H_2); 8.02 (2 H, d, J = 8.5 Hz, H_4); 7.60 (2 H, d, J = 7.0 Hz, H_b); 7.58–7.50 (m, 2 H,

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H_3); 5.00 (2 H, p, J = 7.2 Hz, H_α); 4.19−4.05 (m, 4 H, R_2); 1.67−1.50 (m, 4 H, R_2); 1.45−1.24 (m, 10 H, R_2); 0.89 (6 H, t, J = 7.4 Hz, R_1). ^{13}CNMR (126 MHz, DMSO-d_6) δ: 182.0; 172.6; 134.8; 132.1; 127.8; 127.1; 126.4; 125.4; 123.8; 116.7; 64.2; 52.8; 30.1; 18.6; 17.5; 13.5. HRMS: calcd for $C_{30}H_{38}N_4O_4S_2$ + H 583.2413, found 583.2406. Anal. Calcd for $C_{30}H_{38}N_4O_4S_2$: C, 61.83; H, 6.57; N, 9.61; S, 11.00. Found: C, 61.97; H, 6.51; N, 9.48; S, 10.91. O.R.: $[\alpha]_D^{20}$ = −83.3 (c = 0.475, DCM).

1d. Yellow powder. Yield: 240 mg (37%). Mp: 99−101 °C. ^{1}HNMR (500 MHz, DMSO-d_6) δ: 9.93 (s, 2 H, H_a); 8.68 (s, 1 H, H_{10}); 8.67 (s, 1 H, H_9); 8.15 (2 H, d, J = 7.3 Hz, H_2); 8.01 (2 H, d, J = 8.4 Hz, H_4); 7.56 (2 H, d, J = 6.9 Hz, H_b); 7.53−7.46 (m, 2 H, H_3); 7.45−7.28 (m, 10 H, R_2); 5.17 (4 H, s, R_2); 5.14−4.95 (m, 2 H, H_α); 1.40 (6 H, d, J = 7.2 Hz, R_1). ^{13}CNMR (126 MHz, DMSO-d_6) δ: 182.5; 172.9; 136.4; 135.3; 132.5; 128.9; 128.5; 128.3; 128.3; 127.5; 126.9; 125.9; 124.2; 117.1; 66.5; 53.4; 17.8. HRMS: calcd for $C_{36}H_{34}N_4O_4S_2$ + H 651.2100, found 651.2100. Anal. Calcd for $C_{36}H_{34}N_4O_4S_2$: C, 66.44; H, 5.27; N, 8.61; S, 9.85. Found: C, 66.45; H, 5.36; N, 8.34; S, 9.70. O.R.: $[\alpha]_D^{20}$ = −89.45 (c = 0.45; DCM).

1e. Yellow powder. Yield: 250 mg (45%). Mp: 177−179 °C. ^{1}HNMR (500 MHz, DMSO-d_6) δ: 10.05 (s, 2 H, H_a); 8.73 (s, 1 H, H_{10}); 8.68 (s, 1 H, H_9); 8.08 (2 H, d, J = 7.6 Hz, H_4); 7.99 (2 H, d, J = 8.5 Hz, H_2); 7.80 (2 H, d, J = 7.0 Hz, H_b); 7.54 (2 H, t, J = 7.8 Hz, H_3); 4.95 (2 H, dd, J = 7.6; 5.3 Hz, H_α); 3.70 (s, 6 H); 2.26−2.15 (m, 2 H); 0.98 (12 H, s, J = 6.7 Hz). ^{13}CNMR (126 MHz, DMSO-d_6) δ: 182.7; 171.9; 134.9; 131.9; 127.5; 127.3; 125.9; 125.2; 123.4; 115.4; 62.0; 51.7; 30.6; 18.7; 18.5. HRMS: calcd for $C_{28}H_{34}N_4O_4S_2$ 555.2100, found 555.2096. Anal. Calcd for $C_{28}H_{34}N_4O_4S_2$: C, 60.62; H, 6.18; N, 10.10; S, 11.56. Found: C, 60.55; H, 6.09; N, 9.95; S, 11.62. O.R.: $[\alpha]_D^{20}$ = −220 (c = 0.55; DCM).

1f. Yellow powder. Yield: 183 mg (30%). Mp: 200−204 °C. ^{1}HNMR (500 MHz, DMSO-d_6) δ: 10.08 (s, 2 H, H_a); 8.74 (s, 1 H, H_{10}); 8.68 (s, 1 H, H_9); 8.06−7.86 (m, 4 H, H_2 + H_4); 7.81 (2 H, d, J = 7.1 Hz, H_b); 7.54 (2 H, t, J = 7.8 Hz), H_3; 5.07−4.92 (m, 2 H, R_2); 4.88 (2 H, dd, J = 7.7; 5.0 Hz, H_α); 2.31−2.15 (m, 2 H, R_1); 1.24 (6 H, d, J = 6.6 Hz, R_2); 1.23 (6 H, d, J = 6.8 Hz, R_2); 1.00−0.93 (12 H, m, J = 6.7 Hz, R_1). ^{13}CNMR (126 MHz, DMSO-d_6) δ: 182.5; 170.7; 134.9; 131.9; 127.5; 127.3; 125.8; 125.2; 123.3; 115.4; 68.1; 61.9; 30.6; 21.6; 21.5; 18.58; 18.58. HRMS: calcd for $C_{32}H_{42}N_4O_4S_2$ + H 611.2726, found 611.2733. Anal. Calcd for $C_{32}H_{42}N_4O_4S_2$: C, 62.92; H, 6.93; N, 9.17; S, 10.50. Found: C, 63.08; H, 7.00; N, 9.16; S, 10.56. O.R.: $[\alpha]_D^{20}$ = −159.5 (c = 0.485; DCM).

1g. Yellow powder. Yield: 185 mg (29%). Mp: 173−175 °C. ^{1}HNMR (500 MHz, DMSO-d_6) δ: 10.07 (s, 2 H, H_a); 8.73 (s, 1 H, H_{10}); 8.68 (s, 1 H, H_9); 8.07−7.92 (m, 4 H, H_2 + H_4); 7.80 (2 H, d, J = 7.1 Hz, H_b); 7.54 (2 H, t, J = 7.8 Hz, H_3); 4.93 (2 H, dd, J = 7.8; 5.2 Hz, H_α); 4.29−3.90 (m, 4 H, R_2); 2.27−2.14 (m, 2 H, R_1); 1.74−1.52 (m, 4 H, R_2); 1.41−1.32 (m, 4 H, R_2); 0.97 (12 H, d, J = 6.9 Hz, R_1); 0.90 (6 H, t, J = 7.4 Hz, R_2). ^{13}CNMR (126 MHz, DMSO-d_6) δ: 182.6; 171.3; 134.8; 131.9; 127.5; 127.3; 125.8; 125.2; 123.3; 115.4; 64.1; 62.0; 30.6; 30.1; 18.7; 18.6; 18.4; 13.4. HRMS: calcd for $C_{34}H_{46}N_4O_4S_2$ + H 639.3027, found 639.3050. Anal. Calcd for $C_{34}H_{46}N_4O_4S_2$: C, 63.92; H, 7.26; N, 8.77; S, 10.04. Found: C, 63.65; H, 7.06; N, 8.68; S, 10.15. O.R.: $[\alpha]_D^{20}$ = −172.0 (c = 0.62; DCM).

1h. Yellow powder. Yield: 148 mg (21%). Mp: 153−156 °C. ^{1}HNMR (500 MHz, DMSO-d_6) δ: 10.08 (s, 2 H, H_a); 8.73 (s, 1 H, H_{10}); 8.68 (s, 1 H, H_9); 8.08 (2 H, d, J = 7.7 Hz, H_2); 7.99 (2 H, d, J = 8.5 Hz, H_4); 7.79 (2 H, d, J = 7.0 Hz, H_b); 7.63−7.48 (m, 2 H, H_3); 7.48−7.30 (m, 10 H, R_2); 5.22 (2 H, d, J = 12.4 Hz, R_2); 5.17 (2 H, d, J = 12.4 Hz, R_2); 4.98 (2 H, dd, J = 7.7; 5.2 Hz, H_α); 2.27−2.15 (m, 2 H, R_1); 0.96 (6 H, d, J = 7.1 Hz, R_1); 0.94 (6 H, d, J = 7.1 Hz, R_1). ^{13}CNMR (126 MHz, DMSO-d_6) δ: 182.7; 171.2; 135.8; 134.8; 131.9; 128.4; 128.09; 128.05; 127.5; 127.3; 127.1; 125.8; 125.2; 123.3; 115.5; 66.0; 62.1; 30.6; 18.7; 18.4. HRMS: calcd for $C_{40}H_{42}N_4O_4S_2$ + H 707.2726, found 707.2706. Anal. Calcd for $C_{40}H_{42}N_4O_4S_2$: C, 67.96; H, 5.99; N, 7.93; S, 9.07. Found: C, 67.90; H, 6.07; N, 7.92; S, 9.05. O.R.: $[\alpha]_D^{20}$ = −141 (c = 0.5; DCM).

1i. Yellow powder. Yield: 292 mg (45%). Mp: 107−110 °C. ^{1}HNMR (500 MHz, DMSO-d_6) δ: 10.05 (s, 2 H, H_a); 8.71 (s, 1 H, H_{10}); 8.70 (s, 1 H, H_9); 8.02 (2 H, d, J = 8.5 Hz, H_2); 7.89 (2 H, d, J = 7.7 Hz, H_b); 7.57−7.45 (m, 2 H, R_1); 7.41 (2 H, d, J = 7.0 Hz, H_4); 7.37−7.08 (m, 10 H, H_3 + R_1); 5.60−4.90 (m, 2 H, H_α); 3.69(s, 6 H, R_2); 3.17−3.08 (m, 4 H, R_1). ^{13}CNMR (126 MHz, DMSO-d_6) δ: 182.1; 171.7; 136.5; 134.6; 132.1; 129.2; 128.3; 127.8; 127.2; 126.6; 126.5; 125.4; 123.8; 116.5; 58.3; 51.9; 37.1. HRMS: calcd for $C_{36}H_{34}N_4O_4S_2$ + H 651.2100, found 651.2087. Anal. Calcd for $C_{36}H_{34}N_4O_4S_2$: C, 66.44; H, 5.27; N, 8.61; S, 9.85. Found: C, 66.49; H, 5.54; N, 8.35; S, 9.75. O.R.: $[\alpha_D^{20}]$ = −168.3 (c = 0.485; DCM).

1j. Yellow powder. Yield: 177 mg (25%). Mp: 101−103 °C. ^{1}HNMR (500 MHz, DMSO-d_6) δ: 10.07 (s, 2 H, H_a); 8.73 (s, 1 H, H_{10}); 8.70 (s, 1 H, H_9); 8.03 (2 H, d, J = 7.6 Hz H_2); 7.80 (2 H, d, J = 7.9 Hz, H_4); 7.55−7.47 (m, 4 H, H_4 + R_1); 7.40−7.09 (m, 10 H, H_3 + R_1); 5.25−5.17 (m, 2 H, R_2); 4.96−4.75 (m, 2 H, H_α); 3.17 (2 H, dd, J = 13.5; 5.9 Hz, R_1); 3.09 (2 H, dd, J = 13.5; 7.1 Hz, R_1); 1.13 (6 H, d, J = 6.2 Hz, R_2); 1.05 (6 H, d, J = 6.2 Hz, R_2). ^{13}CNMR (126 MHz, DMSO-d_6) δ: 181.9; 170.6; 136.5; 134.6; 132.1; 129.2; 128.3; 127.8; 127.2; 126.6; 126.5; 125.4; 123.8; 116.5; 68.3; 58.2; 37.2; 21.4; 21.3. HRMS: calcd for $C_{40}H_{42}N_4O_4S_2$ + H 707.2726, found 707.2726. Anal. Calcd for $C_{40}H_{42}N_4O_4S_2$: C, 67.96; H, 5.99; N, 7.93; S, 9.07. Found: C, 67.74; C, 6.17; N, 7.83; S, 9.16. O.R.: $[\alpha]_D^{20}$ = −129.3 (c = 0.55; DCM).

1k. Yellow powder. Yield: 257 mg (35%). Mp: 71−75 °C. ^{1}HNMR (500 MHz, DMSO-d_6) δ: 10.07 (s, 2 H, H_a); 8.72 (s, 1 H, H_{10}); 8.70 (s, 1 H, H_9); 8.03 (2 H, d, J = 8.5 Hz, H_2); 7.82 (2 H, d, J = 7.6 Hz, H_4); 7.56−7.48 (m, 2 H, R_1); 7.45 (2 H, d, J = 7.0 Hz, H_b); 7.30−7.17 (m, 6 H, R_1); 7.13 (4 H, m, H_3 + R_1); 5.30−5.23 (m, 2 H, H_α); 4.04−3.92 (m, 4 H, R_2); 3.16 (2 H, dd, J = 13.8; 6.2 Hz, R_1); 3.09 (2 H, dd, J = 13.6; 6.9 Hz, R_1); 1.49−1.40 (m, 4 H, R_2); 1.25−1.16 (m, 4 H, R_2); 0.82 (6 H, t, J = 7.4 Hz, R_2). ^{13}CNMR (126 MHz, DMSO-d_6) δ: 182.4; 171.7; 136.9; 135.1; 132.5; 129.6; 128.7; 128.2; 127.7; 127.1; 127.0; 125.8; 124.3; 117.0; 64.8; 58.8; 37.7; 30.4; 18.9; 14.0. HRMS: calcd for $C_{42}H_{46}N_4O_4S_2$ + H 735.3039, found: 735.3034. Anal. Calcd for $C_{42}H_{46}N_4O_4S_2$: C, 68.64; H, 6.31; N, 7.62; S, 8.73. Found: C, 68.45; H, 6.50; N, 7.54; S, 8.80. O.R.: $[\alpha]_D^{20}$ = 136.9 (c = 0.55; DCM).

1l. Yellow powder. Yield: 297 mg (37%). Mp: 99−101 °C. ^{1}HNMR (500 MHz, DMSO-d_6) δ: 10.05 (s, 2 H, H_a); 8.71 (s, 1 H, H_{10}); 8.70 (s, 1 H, H_9); 8.02 (2 H, d, J = 8.5 Hz, H_2); 7.89 (2 H, d, J = 7.7 Hz, H_b); 7.57−7.45 (m, 2 H, R_1); 7.41 (2 H, d, J = 7.0 Hz, H_4); 7.37−7.08 (m, 10 H, H_3 + R_1); 5.22 (2 H, d, J = 12.4 Hz, R_2); 5.17 (2 H, d, J = 12.4 Hz, R_2); 5.10−4.90 (m, 2 H, H_α); 3.69(s, 6 H, R_2); 3.17−3.08 (m, 4 H, R_1). ^{13}CNMR (100 MHz, DMSO-d_6) δ: 181.8; 171.6; 137.7; 137.1; 135.6; 135.4; 129.4; 129.1; 128.3; 128.2; 127.2; 124.6; 123.4; 120.4; 119.7; 116.2; 66.7; 55.8; 37.6. HRMS: calcd for $C_{48}H_{42}n_4O_4S_2$ + H 803.2726, found 803.2715. O.R.: $[\alpha]_D^{20}$ = −149.8 (c = 0.46; DCM).

1m. Yellow powder. Yield: 240 mg (37%). Mp: 154−157 °C. ^{1}HNMR (500 MHz, DMSO-d_6) δ: 10.87 (s, 2 H, H_a); 10.07 (s, 2 H, R_1); 8.74 (s, 1 H, H_{10}); 8.68 (s, 1 H, H_9); 8.00 (2 H, d, J = 7.7 Hz, H_b); 7.84 (2 H, d, J = 6.5 Hz, H_4); 7.53−7.40 (m, 6 H, R_1 + H_3); 7.34 (2 H, d, J = 8.0 Hz); 7.12−6.98 (m, 4 H, R_1); 6.93 (2 H, t, J = 7.3 Hz, R_1); 5.37−5.28 (m, 2 H_α); 3.31 (s, 4 H, R_1). ^{13}CNMR (126 MHz, DMSO-d_6) δ: 181.9; 172.1; 136.0; 134.7; 132.0; 127.7; 127.2; 127.1; 126.3; 125.3; 123.9; 123.6; 121.0; 118.4; 118.1; 116.4; 111.4; 108.6; 57.8; 51.9; 27.2. HRMS: calcd for $C_{40}H_{36}N_4O_4S_2$ + H 729.2318, found 729.2315. Anal. Calcd for $C_{40}H_{36}N_6O_4S_2$: C, 65.91; H, 4.98; N, 11.53; S, 8.80. Found: C, 65.00; H, 5.15; N, 11.14; S, 8.63.

Competitive titrations[47] were conducted in MeCN-d_3 (0.05% H_2O, Eurisotop, packed in vial with septum) on a mixture of chiral host (~0.01 M) and achiral reference **9** (~0.005 M); the differences in concentrations enabled unambiguous assignment of signals. To this mixture were added aliquots of solution of homochiral guest in

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several steps until $[G]_0 \approx [H] + [H^{ref}]$. Changes in chemical shifts of inner urea protons were followed. Ratios of association constants were calculated according to the equation

$$K^{rel} = \frac{K_H}{K_{ref}} = \frac{\frac{\Delta\delta_{ref}^{max}}{\Delta\delta_{ref}} - 1}{\frac{\Delta\delta_H^{max}}{\Delta\delta_H} - 1} \quad (1)$$

where $\Delta\delta^{max}$ correspond to chemical shift of the pure supermolecule (host fully saturated with guest). $\Delta\delta_{ref}^{max}$ values for the complexes of the achiral receptor with both anions were determined in separate experiments, by classical NMR titration. Two parameters: $\Delta\delta_H^{max}$ and K^{rel} were fitted to obtain the best match between calculated and experimental values by Origin software (OriginPro 8, OriginLab Corp., Northampton, MA) curve-fitting algorithm:

$$\Delta\delta_H = \frac{K^{rel}\Delta\delta_H^{max}}{K^{rel} + \frac{\Delta\delta_{ref}^{max}}{\Delta\delta_{ref}} - 1} \quad (2)$$

The latter equation does not include any variable referring to the concentrations of the reagents; therefore, mixtures of any (even unknown) compositions may be used. This eliminates the common errors arising from errors in concentrations. In addition, lower purity of hosts and guest does not affect the results (only if the impurities do not significantly change the chemical shifts). Lowest error is obtained for data points with $0.1 < \Delta\delta/\Delta\delta^{max} < 0.9$. Uncertainty of the single competitive titration was calculated by an Origin fitting algorithm (asymptotic error). The uncertainty of enantioselectivity was calculated according to the following formula: $\Delta\alpha/\alpha = ((\Delta K_S^{rel}/K_S^{rel})^2 + (\Delta K_R^{rel}/K_R^{rel})^2)^{1/2}$.

■ ASSOCIATED CONTENT

Supporting Information

Titration plots and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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