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Enantiomeric recognition of carboxylic anions by a library of neutral receptors derived from α-amino acids and *o*-phenylenediamine

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ABSTRACT

A library of eight neutral anion receptors consisting of α-amino acid esters attached to *o*-phenylenediamine by urea groups was synthesized and analysed in terms of capacity for chiral recognition of carboxylates. The NMR titrations revealed that the association constants of complexes consisting of a chiral guest and a chiral host are two orders of magnitude lower than those of achiral partners. Diverse substituents in the receptor structure modify both the affinities and enantioselectivities.

1. Introduction

Carboxylic acids are one of the most common and relevant types of organic molecules found in living organisms. The great majority of them are chiral, that is, the lactic, mandelic, tartaric, gluconic and above all α-amino acids. They are also frequently found in drugs, such as non-steroidal anti-inflammatory drugs (NSAI) (e.g., naproxen, ibuprofen, ketoprofen and baclofen), L-DOPA, many antibiotics (penicillin), etc. In most cases, each enantiomer of an acid possesses different biological activity.[1] It should be noted that carboxylic acids exist in their dissociated form at physiological pH. Therefore the supramolecular chemistry of acids resembling biological interactions should in fact be the chemistry of carboxylate anions. It is mainly the biological relevance of chiral carboxylates that makes their chiral recognition of prime importance.

Very little is known about the process of chiral recognition. Some models, for instance the three-point-binding model,[2] give us a general idea of the phenomenon but do not support any details on preferable receptor structures. Therefore, the most valuable method for examining chiral recognition remains evaluating a library of receptors with systematically varying structures. Analysis of such a library in terms of structure versus binding abilities may provide guidelines ref designing novel receptors.

Natural amino acids are very useful building blocks in the synthesis of such libraries. They are a readily available source of chirality, with side chains that vary in size, polarity and hydrogen bond acceptor/donor abilities. Moreover, both their C- and N-termini may be easily modified with a large range of moieties. Their amino group may, for example, be incorporated into an amide or urea group, which are potent hydrogen bond donors that are very useful in the anion binding process.[3–10]

In view of the above considerations we decided to synthesize and evaluate a family of C_2 symmetrical receptors where the amino acid moieties are bonded to the core unit by urea groups. Herein we report work using the simple and readily available *o*-phenylenediamine as the model core unit[11] (**1**, Fig. 1). Two urea groups in close proximity should allow high anion affinity while the amino acid side chains constitute the chiral environment for the guest. The amino acids, valine (R^1 = *i*Pr) and phenylalanine (R^1 = Bn), were used, as representatives of aliphatic and aromatic side chains, respectively. For the modification of the C-terminus (R^2), we used methyl, isopropyl, *n*-butyl, and benzyl alcohols representing the small, bulky, long chain, and aromatic groups, respectively. As model anions we decided to use mandelate (Man) and *N*-acetylphenylalanine (AcPhe) anions, both as tetrabutylammonium (TBA) salts.

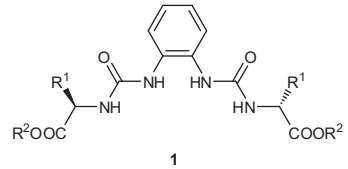

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Figure 1. General structure of urea type receptors.

2. Results and discussion

The synthesis of the receptors **1a**–**h** is outlined in Scheme 1. Commercially available hydrochlorides of methyl esters of amino acids **2a** and **2e** were reacted with triphosgene and the resulting

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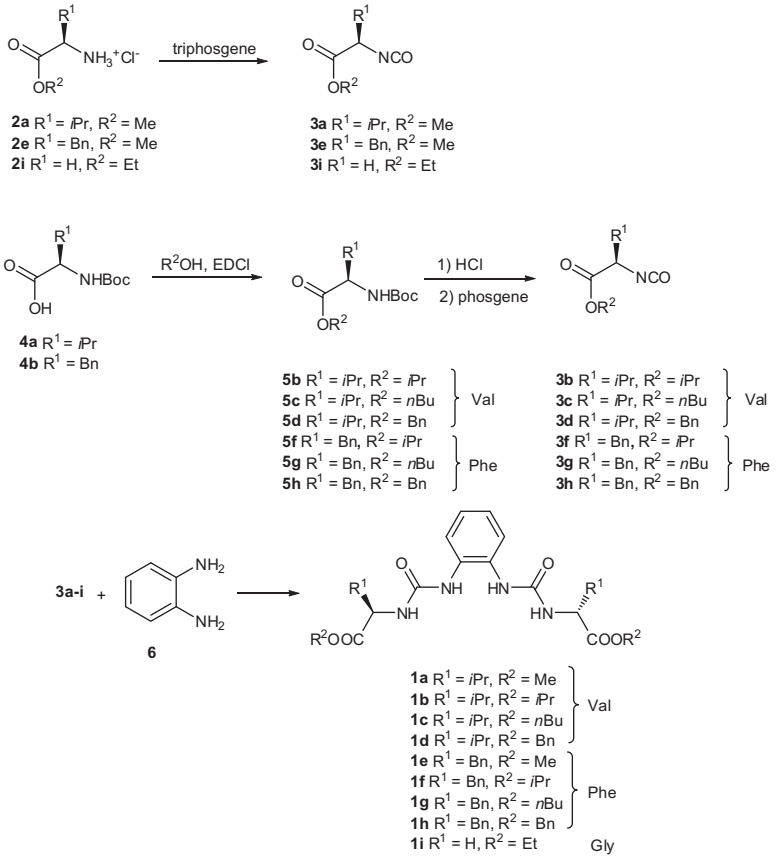
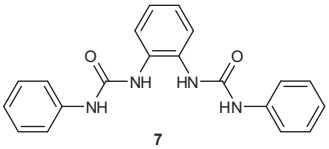


Scheme 1. Synthesis of receptors **1a**–**i**.

isocyanates **3a** and **3e** were distilled under reduced pressure before reaction with *o*-phenylenediamine, to yield receptors **1a** and **1e**. Two Boc protected amino acids **4a** and **4e** were esterified with isopropyl, *n*-butyl and benzyl alcohols in the presence of 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDCI) and 4-(dimethylamino)pyridine (DMAP) to afford products **5b**–**d**, **5f**–**h** in good yields.[12] The amino group was then deprotected and transformed into an isocyanate with phosgene;[13] the two-step sequence proceeded quantitatively and isocyanates **3b**–**d**, **3f**–**h** were used without further purification. The isocyanates were reacted with *o*-phenylenediamine (*o*DAB) to produce the respective receptors in moderate yields. The final products were purified by flash chromatography and crystallized. Additionally, two receptors D-**1e** and D-**1f** were synthesized by following two paths starting from D-phenylalanine methyl ester hydrochloride and Boc-D-phenylalanine, respectively. The racemic mixtures, obtained by mixing the pairs of enantiomeric receptors, were successfully resolved using chiral HPLC and the enantiomeric purities of the representative receptors **1e** and **1f** were determined to be >99% ee. An alternative synthetic pathway, that would be more useful in the synthesis of multiple analogues was tested. Ester **1a** was hydrolysed to a corresponding diacid, which we attempted to transform into another ester; however, the standard reaction of EDCI and the appropriate alcohol failed.

An achiral model compound was synthesized according to the literature.[11]



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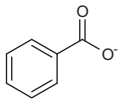
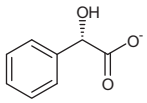
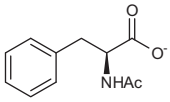
In our preliminary studies we decided to compare the binding affinities of the chiral receptors with an achiral receptor equipped with phenyl groups in the side arms, which are typical for studies in the field of achiral anions. One of the chiral receptors **1a**, achiral **1i**, and the model achiral receptor **7** were titrated with benzoate (BzO), (*S*)-mandelate, and *N*-acetyl-L-phenylalanine as tetrabutylammonium salts in DMSO-d_6 + 0.5% H_2O[‡] (Table 1). For all receptors, the association constants of the complexes increase in the following order: Man, AcPhe, and BzO, which reflects the electron densities in the carboxylate group and is consistent with other reports.[14,15] Similarly, for all guests employed, amino acid based receptors **1a**, **1e** exhibit lower affinities. This indicates that aliphatic side chains result in a reduction of anion affinities due to changes in electron density in the urea groups.[16,17] When changing from achiral benzoate to chiral Man and AcPhe anions the association constants for complexes with all receptors decreased but the complexes with chiral receptor **1a** are mostly affected. This effect must be attributed to the steric effects; both the host and guest in the Man-**1a** or AcPhe-**1a** pairs are quite bulky and exhibit repulsive interactions between their side-chains. Overall, the association constant of the complex of chiral receptor **1a** with the mandelate, the model chiral guest is nearly two orders of magnitude lower than the K_a of the achiral receptor achiral with the model chiral benzoate. These titrations show that examination of chiral recognition requires that the most effective receptor architectures developed so far should be employed, otherwise no binding may occur in competitive solvents.

Due to the low association constant for the (*S*)-Man **1a** complex in DMSO (K_a = 29 M^{-1}) we decided to use a less competitive solvent, acetonitrile, which is another standard solvent in the field

‡ 0.5% water content is used for standardisation of measurements in hygroscopic DMSO.

Table 1
Comparison of the binding affinities of achiral and chiral receptors towards achiral and chiral anions[a]

Anion	Receptor 7	Receptor 1i	Receptor 1a
	1300[b]	325	605
	152	21	29
	890	145	198

[b] Ref. 11.
[a] Association constants (M^{-1}) determined by ^1H NMR titrations in DMSO-d_6 + 0.5% H_2O (298K, errors estimated to be ±10%, anions used as TBA salts).

of anion binding. The association constant was found to be ~7000 M^{-1}. In both solvents the stoichiometry of the complexes with all carboxylates was 1:1, as indicated by the Job plots and stochastic distribution of residuals.

Regardless of the level of the association constants, they must be determined with the highest possible precision since the ratio of (*R*)- and (*S*)-guest association constants (K_R/K_S) rarely exceeds 2.[18] We decided to employ the competitive titration method,[19] which is insensitive to the errors in concentrations and gives more accurate results. We tried to determine the enantioselectivity ($\alpha = K_S/K_R$) in a single experiment by titration of a racemic mixture of anionic guest with a homochiral receptor.[20–23] The addition of a receptor resulted in a shift of signals of the anions, but the splitting of the signals of the enantiomers was too small for all of the receptors tested. We therefore determined the relative association constants using an achiral receptor **1i**. Mixtures of the given chiral receptor and the achiral reference were titrated with a homochiral TBA salt. The ratio of the two relative association constants gave the enantioselectivity α:

$$K_S^{rel} = \frac{K_S}{K^{ref}} \quad (1)$$

$$K_R^{rel} = \frac{K_R}{K^{ref}} \quad (2)$$

$$\frac{K_S^{rel}}{K_R^{rel}} = \alpha \quad (3)$$

We determined the K^{ref} for **1f** with Man and AcPhe by UV–Vis titration, and used these values to recalculate the relative association constants of chiral receptors into absolute ones (Tables 2 and 3). The K_a values for **1a**–**h** with Man are in the range of 0.76–1.1 × 10^4 M^{-1}, while with the AcPhe anion the values are on average eight times higher: 6.2–9.1 × 10^4 M^{-1}. The distribution of association constants among the family of receptors **1**, presented in Figure 2, indicate the moderate influence of the R^1 and R^2 groups on the anion binding affinity. The valine based receptors **a**–**d**

Table 2
Association constants and selectivities of receptors **1a**–**h** with mandelates

Receptor			Association constant K_a (M^{-1})		Selectivity
1	R^1	R^2	(*S*)-Man	(*R*)-Man	α
a	*i*Pr	Me	1.13 × 10^4±2,8%	1.13 × 10^4±2,2%	1.00±3,6%
b	*i*Pr	*i*Pr	8.36 × 10^3±2,1%	8.28 × 10^3±1,5%	1.01±2,6%
c	*i*Pr	*n*Bu	9.21 × 10^3±1,8%	9.27 × 10^3±2,7%	1.00±3,2%
d	*i*Pr	Bn	1.03 × 10^4±3,3%	1.06 × 10^4±2,2%	0.98±4,0%
e	Bn	Me	8.66 × 10^3±2,0%	9.21 × 10^3±2,5%	0.94±3,2%
f	Bn	*i*Pr	7.74 × 10^3±4,0%	7.85 × 10^3±3,6%	0.99±5,5%
g	Bn	*n*Bu	7.94 × 10^3±2,5%	8.42 × 10^3±3,0%	0.94±3,9%
h	Bn	Bn	9.13 × 10^3±6,0%	9.61 × 10^3±5,0%	0.95±7,8%

Table 3
Association constants and selectivities of receptors with *N*-acetylphenylalanine anions

Receptor			Association constant K_a (M^{-1})		Selectivity
1	R^1	R^2	D-AcPhe	L-AcPhe	α
a	*i*Pr	Me	8.98 × 10^4±2,0%	9.37 × 10^4±2,6%	0.96±3,3%
b	*i*Pr	*i*Pr	6.86 × 10^4±2,5%	7.33 × 10^4±2,7%	0.94±3,7%
c	*i*Pr	*n*Bu	7.79 × 10^4±2,5%	8.38 × 10^4±2,6%	0.93±3,6%
d	*i*Pr	Bn	8.45 × 10^4±3,0%	7.99 × 10^4±1,8%	1.06±3,5%
e	Bn	Me	8.32 × 10^4±3,3%	7.72 × 10^4±2,2%	1.09±4,0%
f	Bn	*i*Pr	6.52 × 10^4±4,8%	6.27 × 10^4±1,7%	1.05±5,0%
g	Bn	*n*Bu	7.52 × 10^4±2,7%	7.23 × 10^4±2,3%	1.04±3,5%
h	Bn	Bn	8.12 × 10^4±3,5%	8.05 × 10^4±1,8%	1.00±3,9%

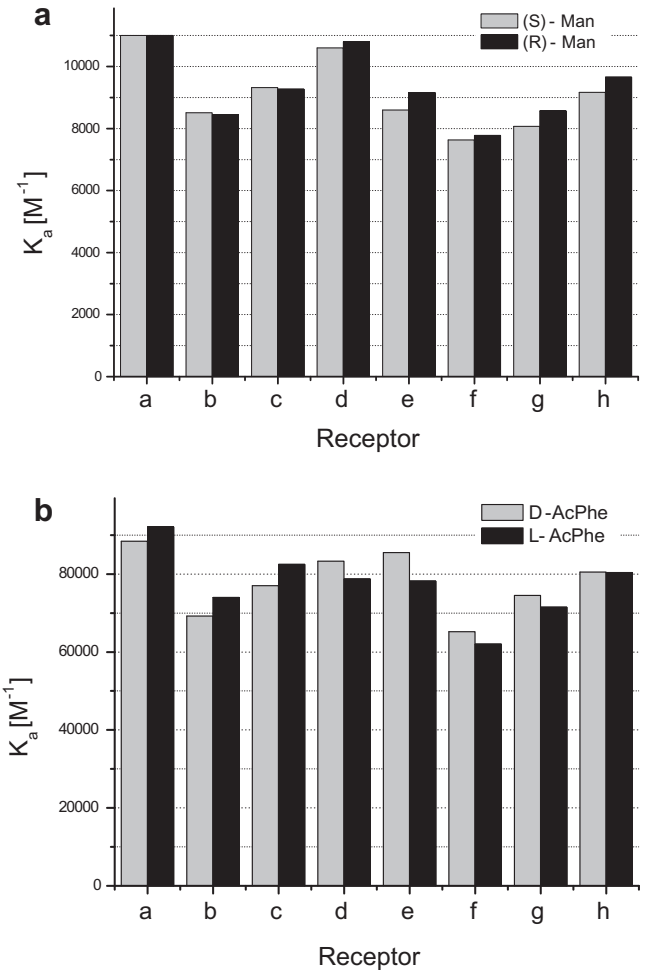


Figure 2. Graphical comparison of association constants of receptors **1** with (a) mandelate, and (b) *N*-acetylphenylalanine enantiomers.

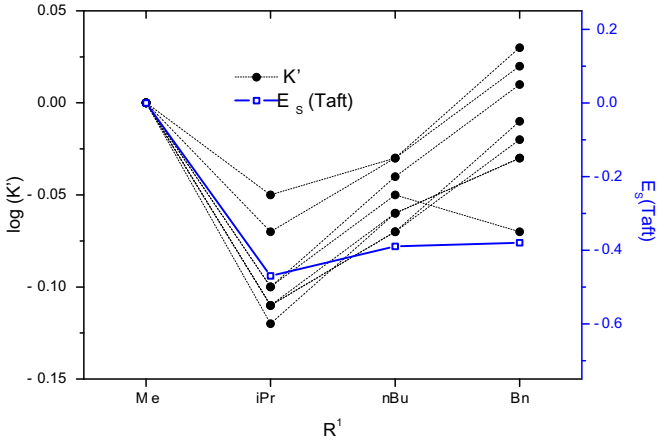


Figure 3. Distribution of reduced association constants (K', left axis) and their comparison with Taft steric parameters (E_S, right axis).

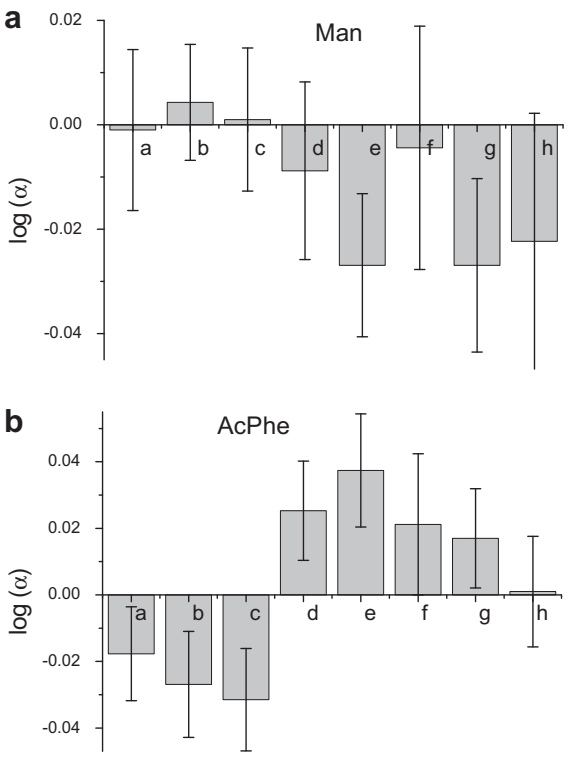


Figure 4. Plots of enantioselectivities of receptors **1a–h** with (a) mandelate, and (b) *N*-acetylphenylalanine.

exhibit slightly higher binding affinities for both anions tested compared to the phenylalanine based receptors **e–h** with the same R^2 moiety. The isopropyl group is more bulky then the benzyl one according to the Taft steric parameters[24,25] E_S (−0.47 and −0.38, respectively); therefore an opposite observation was expected. The dependence of the association constant on the R^2 moiety is also visible and is consistent for both R^1 groups and both anions; the K_a values increase in the following order: *i*Pr < *n*Bu < Bn < Me. The reduced association constants ($K' = K/K_{R^2=Me}$) are in a qualitative correlation with Taft steric parameters (E_S) (Fig. 3), except for the benzyl moieties, which seem to increase the affinity towards the model anions by either by preorganisation of receptor structure (entropy) or by additional π–π attractive interactions (enthalpy).

The enantioselectivities of the receptor family towards both anions tested were low. The highest observed value was 1.09 for **1d** with the AcPhe anion; the most successful receptor for mandelate was **1e**. The distribution of selectivities among the receptors is stochastic (Fig. 4); it is therefore impossible to perform a structure–enantioselectivity correlation. A preference for the (*R*)-mandelate can be observed among the library, however the magnitude of the selectivity cannot be rationalised. In the case of AcPhe guests, the selectivity distribution is more complicated; receptors **1a–c** exhibit a preference for L-AcPhe, while receptors **1d–g** bind D-AcPhe anion more strongly (**1h** showed no selectivity). Hosts **1e**,**f** were successful in the chiral recognition of both model anions. In neither case was the presence of a specific R^1 or R^2 group responsible for the observed selectivity. Only a proper combination of the two groups may result in the desired properties.

3. Conclusion

Herein we have proven that supramolecular complexes with chiral components are less stable compared to achiral receptors and typical achiral guests, which makes the investigation of chiral recognition even more demanding. We have synthesised a series of eight receptors **1**, which proved successful in the chiral recognition of two model carboxylates. This small combinatorial study indicates that there are no preferable substituents, whose application will result in high selectivity. Preparing an efficient receptor requires a fine tuning of its side arms, including both amino acid and its

C-terminus. So far no generalisation on the structure—chiral recognition correlation can be made. It is very likely that only a large-scale combinatorial approach will result in efficient receptors and guidelines on their preferable structures. This work demonstrates that a variety of esters of amino acids can be easily synthesized and transformed into urea type receptors via the corresponding isocyanates. Many core units known to bind anions efficiently are also bisamines.[16,26–28] We plan to employ them with amino acid side chains in the future investigations of the chiral recognition of carboxylates.

4. Experimental

4.1. Syntheses: General remarks

All reagents and solvents were of purest p.a. quality. Dichloromethane for reactions with EDCI or isocyanates was distilled over CaH_2. Column chromatography was performed with silica gel 60 (60–230 mesh).

4.1.1. Synthesis of esters 5b–d,f–h: general procedure

To a solution of Boc protected amino acid (10 mmol) in dichloromethane (50 mL) at 0 °C was added the appropriate alcohol (20 mmol) followed by EDCI (11 mmol) and DMAP (1 mmol). The mixture was allowed to reach room temperature and was stirred for 12 h. It was then concentrated to ca. 20 mL on a rotary evaporator. Ethyl acetate (80 mL) was added, and the organic phase was washed with 10% $NaHSO_4$ (2 × 50 mL), saturated $NaHCO_3$ (2 × 50 mL) and brine (20 mL). The organic phase was then dried over magnesium sulfate and concentrated. Isopropyl and *n*-butyl esters were sufficiently pure enough to be used in the next step, while benzyl esters **5d**,**h** were purified by chromatography (silica gel, hexanes/ethyl acetate 7:3) to remove the excess of benzyl alcohol.

Boc-Val-OiPr ***5b****:* colourless oil (1.92 g, 74%), δ_H (500 MHz, DMSO) 7.06 (1H, d, *J* = 8.0 Hz), 4.91 (1H, sept, *J* = 6.4 Hz), 3.84–3.63 (1H, m), 2.13–1.83 (1H, m), 1.39 (9H, s), 1.19 (3H, d, *J* = 6.3 Hz), 1.17 (3H, d, *J* = 6.2 Hz), 0.87 (6H, d, *J* = 6.7 Hz); δ_C (126 MHz, DMSO) 171.4, 155.7, 78.1, 67.5, 59.5, 29.5, 28.2, 21.6, 21.5, 18.9, 18.3. HRMS (ESI, $[M+Na]^+$): calc for ($C_{13}H_{25}NO_4$+Na^+) 282.16758, found: 282.16777, $[\alpha]_D^{20}$ = −34.8 (*c* 1.2, MeOH).

Boc-Val-OnBu ***5c****:* colourless oil (2.02 g, 74%), δ_H (500 MHz, DMSO) 7.11 (1H, d, *J* = 8.2 Hz), 4.11–3.97 (2H, m), 3.81 (1H, dd, *J* = 8.2, 6.7 Hz), 2.00 (1H, oct, *J* = 6.7 Hz), 1.63–1.45 (2H, m), 1.38 (9H, s), 1.38–1.28 (2H, m), 0.95–0.79 (9H, m); δ_C (126 MHz, DMSO) 172.0, 155.7, 78.1, 63.8, 59.5, 30.2, 29.5, 28.2, 19.0, 18.6, 18.4, 13.5. HRMS (ESI, $[M+Na]^+$): calcd for ($C_{14}H_{27}NO_4$+Na^+): 296.18323, found: 296.18332, $[\alpha]_D^{20}$ = −29.2 (*c* 1.82, MeOH).

Boc-Val-OBn ***5d****:* colourless oil (1.41 g, 46%), δ_H (600 MHz, DMSO) 7.40–7.29 (5H, m), 7.21 (1H, d, *J* = 8.0 Hz), 5.16 (1H, d, *J* = 12.5 Hz), 5.09 (1H, d, *J* = 12.5 Hz), 3.88 (1H, dd, *J* = 8.0, 6.7 Hz), 2.02 (1H, oct, *J* = 6.8 Hz), 1.38 (9H, s), 0.86 (3H, d, *J* = 6.8 Hz), 0.85 (3H, d, *J* = 6.8 Hz); δ_C (151 MHz, DMSO) 171.9, 155.8, 142.5, 136.0, 128.3, 128.0, 127.9, 127.6, 126.6, 126.4, 78.2, 65.7, 62.9, 59.5, 29.6, 28.2, 19.0, 18.4. HRMS (ESI, $[M+Na]^+$): calcd for ($C_{17}H_{25}NO_4$+Na^+): 330.16758, found: 330.16895, $[\alpha]_D^{20}$ = −31.8 (*c* 1.1, MeOH) (Lit.:[29] −29.7).

Boc-Phe-OiPr ***5f****:* colourless oil (1.96 g, 64%) δ_H (600 MHz, DMSO) 7.80–7.04 (6H, m), 4.86 (1H, sept, *J* = 6.2 Hz), 4.08 (1H, ddd, *J* = 9.3, 8.1, 5.8 Hz), 2.95 (1H, dd, *J* = 13.7, 5.6 Hz), 2.86 (1H, dd, *J* = 13.5, 9.8 Hz), 1.34 (9H, s), 1.17 (3H, d, *J* = 6.2 Hz), 1.08 (3H, d, *J* = 6.2 Hz); δ_C (151 MHz, DMSO) 171.5, 155.3, 137.6, 129.1, 128.1, 126.4, 78.2, 67.8, 55.5, 36.4, 28.1, 21.5, 21.3; HRMS (ESI, $[M+Na]^+$): calcd for ($C_{17}H_{25}NO_4$+Na^+): 330.16758, found: 330.16722, $[\alpha]_D^{20}$ = −5.1 (*c* 1.1, MeOH).

Boc-Phe-OnBu ***5g****:* colourless oil (2.02 g, 63%), δ_H (500 MHz, DMSO) 7.37–7.16 (6H, m), 4.15 (1H, ddd, *J* = 9.5, 8.5, 5.6 Hz), 4.08–3.93 (2H, m), 2.97 (1H, dd, *J* = 13.7, 5.6 Hz), 2.87 (1H, dd, *J* = 13.7, 9.5 Hz), 1.54–1.39 (2H, m), 1.32 (9H, s), 1.31–1.17 (2H, m), 0.85 (3H, t, *J* = 7.4 Hz); δ_C (126 MHz, DMSO) 172.1, 155.3, 137.6, 129.0, 128.1, 126.4, 78.2, 64.0, 55.3, 36.5, 30.1, 28.1, 18.5, 13.5; HRMS (ESI, $[M+Na]^+$): calcd for ($C_{18}H_{27}NO_4$+Na^+) 344.18323, found: 344.18309, $[\alpha]_D^{20}$ = −7.55 (*c* 1.46, MeOH).

Boc-Phe-OBn ***5h****:* white crystals (1.98 g, 56%), mp 64–65 °C (Lit.[30] 62–63 °C), δ_H (600 MHz, DMSO) 7.54–7.01 (11H, m), 5.10 (2H, s), 4.22 (1H, ddd, *J* = 9.8, 8.1, 5.5 Hz), 3.01 (1H, dd, *J* = 13.7, 5.4 Hz), 2.90 (1H, dd, *J* = 13.7, 9.9 Hz), 1.32 (9H, s). δ_C (151 MHz, DMSO) 172.0, 155.4, 137.5, 135.8, 129.1, 128.3, 128.2, 128.0, 127.7, 126.4, 78.3, 65.9, 55.4, 36.3, 28.1. HRMS (ESI, $[M+Na]^+$): calcd for ($C_{21}H_{25}NO_4$+Na^+) 378.16758, found: 378.16725, $[\alpha]_D^{20}$ = −11.6 (*c* 1.06, MeOH) (Lit.[29] −10).

4.1.2. Synthesis of receptors 1a,e

Caution: All operations with triphosgene should be carried in a well ventilated hood, and the rotary evaporator should be equipped with a water jet pump to adsorb the gaseous phosgene.

Amino acid methyl ester hydrochloride (20 mmol) was suspended in toluene (50 mL), after which triphosgene (1.32 g, 13.3 mmol) was added and the well stirred mixture was heated at reflux. HCl evolving through the top of the condenser was trapped in water. After 3 h of reflux, the solution was evaporated on a rotary evaporator and the crude isocyanate was purified by distillation under reduced pressure (89 °C/4 torr for Val and 115 °C/4 torr for Phe). Yield 80% (Val), 84% (Phe). The pure isocyanate (15 mmol) was dissolved in dichloromethane (20 mL) and *o*-phenylenediamine (540 mg, 5 mmol) was added. The mixture was stirred for 24 h. If some precipitate was formed, dichloromethane was added to dissolve it, and the solution was directly poured onto the top of a chromatographic column (silica gel). The chromatography proceeded with 5–10% acetone in dichloromethane as the eluent. The product was then dissolved in a minimal volume of hot acetone, after which the same volume of water was added and acetone was slowly removed on a rotary evaporator to yield a white powder which was filtered off and dried in vacuo.

4.1.3. Synthesis of receptors 1b–d,f–h,i: general procedure

Caution: All operations with phosgene should be carried in a well ventilated hood, and the rotary evaporator should be equipped with a water jet pump to adsorb the gaseous phosgene in water.

The appropriate Boc protected amino acid ester (6 mmol) was dissolved in 4 M HCl in dioxane (10 mL) and stirred for 2 h at rt. It was then concentrated, and deprotected hydrochloride was suspended in dichloromethane (20 mL), cooled to 0 °C. Next, 10% aqueous $NaHCO_3$ (20 mL) was added and the phases were stirred vigorously. After complete dissolution of the starting material, the stirring was stopped and phosgene (1.93 M solution in toluene, 6 mL) was added. Stirring was continued at 0 °C for 10 min. The phases were separated in a separatory funnel and the water phase was further extracted with dichloromethane (10 mL). The combined organic phases were dried over $MgSO_4$, and concentrated on a rotary evaporator. The resulting isocyanate was dissolved in dichloromethane and *o*-phenylenediamine (2 mmol) was added. The mixture was stirred for 24 h. If some precipitate was formed, hot dichloromethane was added until the solution was clear. The solution was then poured onto the top of a chromatographic column (silica gel), and the chromatography proceeded with 5–10% acetone in dichloromethane as the eluent. The product was then dissolved in the minimal volume of hot acetone, after which the same volume of water was added and acetone was slowly removed on a rotary evaporator to yield a white powder which was filtered and dried in vacuo.

Compound **1a** white powder (717 mg, 85%), mp 152–155 °C, δ_H (500 MHz, DMSO) 7.92 (2H, s), 7.51 (2H, dd, *J* = 5.9, 3.6 Hz), 6.97

(2H, dd, J = 6.0, 3.5 Hz), 6.91 (2H, d, J = 8.3 Hz), 4.17 (2H, dd, J = 8.2, 5.6 Hz), 3.66 (6H, s), 2.05 (2H, oct, J = 7.0 Hz), 0.92 (6H, d, J = 7.0 Hz), 0.90 (6H, d, J = 7.0 Hz); δ_C (126 MHz, DMSO) 172.8, 155.7, 131.1, 123.3, 123.2, 57.9, 51.6, 30.5, 19.0, 18.0. HRMS (ESI, $[M+Na]^+$): calc for ($C_{20}H_{30}N_4O_6$+Na^+) 445.205207, found: 445.205210, $[\alpha]_D^{20}$ = −2.8 (c 0.5, MeCN).

Compound **1b** white powder (411 mg, 43%), mp 120–123 °C; δ_H (500 MHz, DMSO) 7.96 (2H, s), 7.57–7.44 (2H, m), 6.99–6.93 (2H, m), 6.84 (2H, d, J = 8.4 Hz), 4.95 (2H, sept, J = 6.3 Hz), 4.11 (2H, dd, J = 8.4, 5.3 Hz), 2.05 (2H, td, J = 13.7, 6.8 Hz), 1.25–1.19 (12H, m), 0.93 (6H, s, J = 6.8 Hz), 0.90 (6H, d, J = 6.9 Hz); δ_C (126 MHz, DMSO) 171.7, 155.7, 131.1, 123.2, 123.2, 67.8, 57.9, 30.5, 21.6, 21.6, 18.9, 17.9. HRMS (ESI, $[M+Na]^+$): calcd for ($C_{24}H_{38}N_4O_6$+Na^+) 501.26836, found: 501.26922, $[\alpha]_D^{20}$ = −9.1 (c 0.5, MeCN).

Compound **1c** white powder (405 mg, 40%), mp 134–136 °C, δ_H (500 MHz, DMSO) 7.93 (2H, s), 7.51 (2H, dd, J = 5.7, 3.6 Hz), 6.97 (2H, dd, J = 5.8, 3.6 Hz), 6.87 (2H, d, J = 8.3 Hz), 4.29–3.91 (6H, m), 2.05 (2H, oct, J = 6.3 Hz), 1.69–1.46 (4H, m), 1.47–1.25 (4H, m), 1.02–0.79 (18H, m); δ_C (126 MHz, DMSO) 172.3, 155.7, 131.1, 123.3, 64.0, 57.9, 30.5, 30.2, 19.0, 18.6, 18.0, 13.5. HRMS (ESI, $[M+Na]^+$): calcd for ($C_{26}H_{42}N_4O_6$+Na^+): 529.29966, found: 529.30038, $[\alpha]_D^{20}$ = +1.6 (c 0.5, MeCN).

Compound **1d** white powder (367 mg, 32%), mp 150–152 °C, δ_H (600 MHz, DMSO) 7.97 (2H, s), 7.50 (2H, dd, J = 5.9, 3.6 Hz), 7.44–7.30 (10H, m), 6.97 (2H, dd, J = 6.0, 3.6 Hz), 6.93 (2H, d, J = 8.3 Hz), 5.19 (2H, d, J = 12.4 Hz), 5.13 (2H, d, J = 12.4 Hz), 4.21 (2H, dd, J = 8.3, 5.4 Hz), 2.07 (2H, d, J = 6.8 Hz), 0.91 (6H, d, J = 6.8 Hz), 0.88 (6H, d, J = 6.8 Hz); δ_C (151 MHz, DMSO) 172.2, 155.8, 135.9, 131.1, 128.4, 128.1, 128.1, 123.3, 123.2, 109.5, 65.9, 58.0, 30.4, 19.0, 17.9. HRMS (ESI, $[M+Na]^+$): calcd for ($C_{32}H_{38}N_4O_6$+Na^+) 597.26835, found: 597.26448, $[\alpha]_D^{20}$ = +2.0 (c 0.45, MeCN).

Compound **1e** white powder (787 mg, 76%), mp 141–143 °C, δ_H (600 MHz, DMSO) 7.98 (2H, s), 7.47–7.40 (2H, m), 7.32–7.18 (10H, m), 6.99–6.94 (2H, m), 6.92 (2H, d, J = 7.8 Hz), 4.51 (2H, ddd, J = 13.6, 7.6, 5.7 Hz), 3.62 (6H, s), 3.04 (2H, dd, J = 13.8, 5.8 Hz), 2.97 (2H, dd, J = 13.6, 7.6 Hz); δ_H (151 MHz, DMSO) 172.7, 172.6, 155.3, 136.9, 131.0, 129.18, 129.15, 128.30, 128.25, 126.61, 126.54, 123.41, 123.36, 54.2, 51.8, 37.5; HRMS (ESI, $[M+Na]^+$): calcd for ($C_{28}H_{30}N_4O_6$+Na^+) 541.20576, found: 541.21088, $[\alpha]_D^{20}$ = +7.2 (c 0.45, MeCN).

Compound **1f** white powder (436 mg, 38%), mp 115–118 °C, δ_H (600 MHz, DMSO) 7.99 (2H, s), 7.45 (2H, dd, J = 5.8, 3.6 Hz), 7.29 (4H, t, J = 7.3 Hz), 7.26–7.19 (6H, m), 6.96 (2H, dd, J = 5.8, 3.6 Hz), 6.89 (2H, d, J = 7.7 Hz), 4.85 (2H, sept, J = 6.2 Hz), 4.45 (2H, dt, J = 7.7, 6.8 Hz), 2.99 (2H, s), 2.98 (2H, s), 1.16 (6H, d, J = 6.2 Hz), 1.08 (6H, d, J = 6.2 Hz); δ_C (151 MHz) 171.6, 155.3, 136.8, 131.1, 129.3, 128.2, 126.6, 123.4, 109.5, 68.0, 54.3, 37.7, 21.6, 21.4. HRMS (ESI, $[M+Na]^+$): calcd for ($C_{32}H_{38}N_4O_6$+Na^+) 597.26836, found: 597.26923, $[\alpha]_D^{20}$ = +16.3 (c 0.5, MeCN).

Compound **1g** white powder (481 mg, 40%), mp 123–126 °C, δ_H (600 MHz, DMSO) 7.99 (2H, s), 7.48–7.41 (2H, m), 7.29 (4H, t, J = 7.4 Hz), 7.25–7.19 (6H, m), 7.01–6.94 (2H, m), 6.91 (2H, d, J = 7.8 Hz), 4.49 (2H, q, J = 7.5 Hz), 4.05–3.97 (4H, m), 3.03–2.95 (4H, m), 1.51–1.44 (4H, m), 1.29–1.18 (4H, m), 0.85 (6H, t, J = 7.4 Hz); δ_C (151 MHz, DMSO) 172.2, 155.3, 136.8, 131.1, 129.2, 128.3, 126.6, 123.4, 64.1, 54.3, 37.7, 30.1, 18.5, 13.5; HRMS (ESI, $[M+Na]^+$): calcd for ($C_{34}H_{42}N_4O_6$+Na^+) 625.29966, found: 625.30061, $[\alpha]_D^{20}$ = +4.0 (c 0.5, MeCN).

Compound **1h** white powder (442 mg, 33%), mp 142–144 °C, δ_H (500 MHz, DMSO) 8.00 (2H, s), 7.47–7.12 (22H, m), 7.00–6.90 (4H, m), 5.10 (4H, s), 4.56 (2H, q, J = 7.0 Hz), 3.09–2.94 (4H, m). δ_C (126 MHz, DMSO) 172.0, 155.4, 136.7, 135.7, 131.0, 129.2, 128.4, 128.3, 128.1, 128.0, 126.6, 123.4, 123.4, 66.0, 54.3, 37.5. HRMS (ESI, $[M+Na]^+$): calcd for ($C_{40}H_{38}N_4O_6$+Na^+) 693.26835, found: 693.26955, $[\alpha]_D^{20}$ = −2.0 (c 0.5, MeCN).

Compound **1i** grey crystals, (357 mg, 65%), mp 146–147 °C, δ_H (400 MHz, CD_3CN) 7.57 (s, 2H); 7.35–7.33 (m, 2H); 7.11–7.03 (m, 2H); 5.85 (2H, t, J = 5.5 Hz); 4.14 (4H, q, J = 7.1 Hz); 3.86 (4H, d, J = 5.9 Hz); 1.22 (6H, t, J = 7.1 Hz). δ_C (100 MHz, CD_3CN) 170.5; 156.9; 130.8; 126.8; 119.7; 61.2; 43.5; 14.7, elemental analysis: calcd: C-52.45; H-6.05; N-15.29, found: C-52.32; H-6.25; N-14.76.

4.2. Competitive titration

Competitive titrations[19] were conducted in MeCN-d_3 (0.05% H_2O, Eurisotop, packed in a vial with a septum) on a mixture of chiral host (~0.01 m) and achiral reference **1i** (~0.005 M); the differences in concentrations enabled the unambiguous assignment of the signals. To this mixture, aliquots of homochiral guest solutions were added in several steps until $[G]_0 \approx [H] + [H^{ref}]$. Changes in the chemical shifts of the inner urea protons were followed. The ratio of the association constants were calculated according to the equation:

$$K^{rel} = \frac{K_H}{K_{ref}} = \frac{\frac{\Delta\delta_{ref}^{max}}{\Delta\delta_{ref}} - 1}{\frac{\Delta\delta_{H}^{max}}{\Delta\delta_{H}} - 1}$$

where $\Delta\delta^{max}$ corresponds to the chemical shift of the pure supermolecule (host fully saturated with guest). $\Delta\delta_{ref}^{max}$ values for both anions were determined by classical NMR titration. $\Delta\delta_H^{max}$ and K^{rel} were fitted to obtain the best match between calculated and experimental values by Origin® software[§] curve fitting algorithm:

$$\Delta\delta_H = \frac{K^{rel}\cdot\Delta\delta_H^{max}}{K^{rel} + \frac{\Delta\delta_{ref}^{max}}{\Delta\delta_{ref}} - 1}$$

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 that arise from errors in concentrations. Also the lower purity of the hosts and guest does not affect the results (if only the impurities do not significantly change the chemical shifts). The lowest error is obtained for data-points with $0.1 < \Delta\delta/\Delta\delta^{max} < 0.9$. The uncertainty of a single competitive titration was calculated by Origin fitting algorithm. The uncertainty of enantioselectivity was calculated according to the formula:

$$\Delta\alpha/\alpha = \sqrt{\left(\Delta K_S^{rel}/K_S^{rel}\right)^2 + \left(\Delta K_R^{rel}/K_R^{rel}\right)^2}.$$

4.3. HPLC analyses

Enantiomers of receptors **1e** and **1f** were resolved using AS-H (Daicel Chiralpak®, i.d. 4.6 mm, length 200 mm) column with an isocratic elution: 35% actone/65% n-hexane. t_R for **1e**: 6.85 min (L); 9.10 min (D); t_R for **1f** 3.90 min (L); 4.55 min (D).

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References

1. Reddy, I.; Mehvar, R. *Chirality in Drug Design and Development*; Taylor & Francis, 2004.
2. Pirkle, W. H.; Pochapsky, T. C. *Chem. Rev.* **1989**, *89*, 347–362.
3. Kyne, G. M.; Light, M. E.; Hursthouse, M. B.; Mendoza, J. D.; Kilburn, J. D. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1258–1263.

§ OriginPro 8, OriginLab Corporation, Northampton, MA, USA.

4. Xu, K.-X.; He, Y.-B.; Qin, H.-J.; Qing, G.-Y.; Liu, S.-Y. *Tetrahedron: Asymmetry* **2005**, *16*, 3042–3048.
5. Qing, G.-Y.; He, Y.-B.; Zhao, Y.; Hu, C.-G.; Liu, S.-Y.; Yang, X. *Eur. J. Org. Chem.* **2006**, 1574–1580.
6. Qin, H.; He, Y.; Qing, G.; Hu, C.; Yang, X. *Tetrahedron: Asymmetry* **2006**, *17*, 2143–2148.
7. Yakovenko, A. V.; Boyko, V. I.; Kalchenko, V. I.; Baldini, L.; Casnati, A.; Sansone, F.; Ungaro, R. *J. Org. Chem.* **2007**, *72*, 3223–3231.
8. Qing, G.-Y.; Sun, T.-L.; Wang, F.; He, Y.-B.; Yang, X. *Eur. J. Org. Chem.* **2009**, 841–849.
9. Bois, J.; Bonnamour, I.; Duchamp, C.; Parrot-Lopez, H.; Darbost, U.; Felix, C. *New J. Chem.* **2009**, *33*, 2128.
10. Huang, X.-H.; He, Y.-B.; Hu, C.-G.; Chen, Z.-H. *J. Fluoresc.* **2009**, *19*, 97–104.
11. Brooks, S. J.; Gale, P. A.; Light, M. E. *Chem. Commun. (Camb.)* **2005**, 4696–4698.
12. Dhaon, M. K.; Olsen, R. K.; Ramasamy, K. *J. Org. Chem.* **1982**, *47*, 1962–1965.
13. Nowick, J. S.; Holmes, D. L.; Noronha, G.; Smith, E. M.; Nguyen, T. M.; Huang, S.-L. *J. Org. Chem.* **1996**, *61*, 3929–3934.
14. Liu, S. Y.; Law, K. Y.; He, Y. B.; Chan, W. H. *Tetrahedron Lett.* **2006**, *47*, 7857–7860.
15. Kormos, A.; Ḿocźar, I.; Ṕal, D.; Baranyai, P.; Kupai, J.; Ťoth, K.; Huszthy, P. *Tetrahedron: Asymmetry* **2013**, *24*, 62–65.
16. Dydio, P.; Zieliski, T.; Jurczak, J. *Org. Lett.* **2010**, *12*, 1076–1078.
17. Jurczak, J.; Chmielewski, M. J.; Dydio, P.; Lichosyt, D.; Ulatowski, F.; Zieliski, T. *Pure Appl. Chem.* **2011**, *83*, 1543–1554.
18. Stibor, I.; Zlatušková, P. *Top. Curr. Chem.* **2005**, *255*, 307–341.
19. Whitlock, B. J.; Whitlock, H. W. *J. Am. Chem. Soc.* **1990**, *112*, 3910–3915.
20. Hernández, J.; Almaraz, M.; Raposo, C.; Martín, M.; Lithgow, A.; Crego, M.; Caballero, C.; Morán, J. R. *Tetrahedron Lett.* **1998**, *39*, 7401–7404.
21. Martín, M.; Raposo, C.; Oliva, A. I.; Simón, L.; Caballero, C.; Morán, J. R. *Chem. Lett.* **2000**, 718–719.
22. Pérez, E. M.; Oliva, A. I.; Hernández, J. V.; Simón, L.; Morán, J. R.; Sanz, F. *Tetrahedron Lett.* **2001**, *42*, 5853–5856.
23. Gonzalez, S.; Pelaez, R.; Sanz, F.; Jiménez, M. B.; Morán, J. R.; Caballero, M. C. *Org. Lett.* **2006**, *8*, 4679–4682.
24. Taft, R. W. *J. Am. Chem. Soc.* **1952**, *74*, 2729–2732.
25. Taft, R. W. *J. Am. Chem. Soc.* **1953**, *75*, 4538–4539.
26. Chmielewski, M.; Jurczak, J. *Tetrahedron Lett.* **2004**, *45*, 6007–6010.
27. Kim, Y. K.; Lee, H. N.; Singh, N. J.; Choi, H. J.; Xue, J. Y.; Kim, K. S.; Yoon, J.; Hyun, M. H. *J. Org. Chem.* **2008**, *73*, 301–304.
28. Hamankiewicz, P.; Granda, J. M.; Jurczak, J. *Tetrahedron Lett.* **2013**, *54*, 5608–5611.
29. Kim, S.; Lee, J. I.; Kim, Y. C. *J. Org. Chem.* **1985**, *50*, 560–565.
30. Jackson, R. F. W.; Wishart, N.; Wood, A.; James, K.; Wythes, M. J. *J. Org. Chem.* **1992**, *57*, 3397–3404.