J Incl Phenom Macrocycl Chem (2012) 74:41–55
DOI 10.1007/s10847-012-0136-6

REVIEW ARTICLE

Synthetic macrocyclic receptors in chiral analysis and separation

Tadashi Ema

Received: 4 November 2011 / Accepted: 24 February 2012 / Published online: 9 March 2012

Abstract Chiral synthetic macrocyclic receptors that can achieve chiral discrimination by NMR spectroscopy and/or chiral separation by HPLC are overviewed. Synthetic macrocycles introduced here include crown ethers, calixarenes/calixresorcinarenes/calixpyrroles, macrocyclic amides/amines, and porphyrins. These macrocyclic frameworks are advantageous because intermolecular interactions can take place effectively, such as the ion–dipole interactions in crown ethers, the CH/π and π–π interactions in calixarenes, hydrogen bonding and salt formation in macrocyclic amides and amines, and π–π stacking and metal coordination in porphyrins. Additional functional groups on the periphery of the macrocyclic platforms not only make the whole molecule chiral but also act as the interaction sites. Chiral macrocyclic receptors can show a high degree of chiral recognition/discrimination by using the peripheral functional groups as well as the macrocyclic skeletons (preorganization). Both hosts and guests are shown in the figures to quickly overview the molecular recognition scope of synthetic macrocyclic receptors in chiral analysis and separation.

Keywords Chiral discrimination · Chiral recognition · Chiral solvating agent · Chiral stationary phase · HPLC · NMR

This is a paper selected for "HGCS Japan Award of Excellence 2011".

T. Ema (✉)
Division of Chemistry and Biochemistry, Graduate School of Natural Science and Technology, Okayama University, Tsushima, Okayama 700-8530, Japan
e-mail: ema@cc.okayama-u.ac.jp

Introduction

Chirality is significant because chiral biomolecules such as proteins, nucleic acids, and carbohydrates play a central role in life, and chiral recognition is also inevitably important. In the field of analytical chemistry, chiral recognition/discrimination maintains an essential status at a high level [1–3]. Chiral analysis and separation with GC, HPLC, and NMR are the most popular techniques, and various chiral hosts have been developed for these purposes. However, there is much room for improvement, and more repertories of chiral hosts are needed to analyze and separate a wide variety of chiral compounds newly synthesized. The role that synthetic organic chemists can play in this field is very important because they can design, synthesize, and modify the chiral receptors.

The HPLC method with a chiral column for the determination of the enantiomeric purity is widely used [4–8]. In addition to the analytical utility, chiral HPLC also enables the preparative isolation of enantiomers. Recently, various types of chiral stationary phases (CSP) have been developed, where a chiral selector is covalently or noncovalently bound to silica gel. The former CSP is preferred because chromatographic conditions can be optimized by changing mobile phases (solvents). Various chiral selectors have been developed, but further advancement will assist research and development in academia and industry more powerfully.

The NMR method is also useful for chiral analysis because the enantiomeric purity can be determined quickly and economically [9, 10]. The enantiomeric purity can be determined by adding a chiral host, which is herein called chiral solvating agent (CSA), to a chiral compound in a small amount of deuterated solvent. In a rare but ideal case, a catalytic amount of reagent is enough for chiral discrimination in NMR. Obviously, CSAs have an advantage

over chiral derivatizing agents, which are used in excess for derivatization prior to analysis.

Here we would like to overview various types of synthetic macrocyclic receptors, such as crown ethers, calixarenes, porphyrins, and other macrocycles, which have been developed mainly for chiral analysis and separation, or which will be used for this purpose. Because excellent reviews and books that cover the related research areas have been published [1–10], we would like to introduce some of the recent achievements selectively. We focus on the macrocyclic structures because the functional groups can be arrayed and fixed (preorganized) well by the macrocyclic frameworks, which is advantageous to a high degree of chiral recognition/discrimination, and because synthetically challenging problems associated with the macrocyclization step are also involved.

Chiral crown ethers

Crown ethers are well-known and useful frameworks capable of binding amines in the form of ammonium salts. It was in the 1970s that Cram and co-workers first reported the optical resolution of amino acid derivatives by HPLC using chiral stationary phases (CSP) consisting of chiral crown ethers as chiral selectors [11]. Since then various attempts have been made to improve the performance of chiral columns of this type. Recently, there has been a strong demand for the resolution of chiral lipophilic amines in the pharmaceutical area [11]. It is therefore ideal to covalently attach the chiral selector to silica gel because normal mobile phases having good solubility can be used without leaching of the chiral selector. Chiral pseudo-18-crown-6 ethers **1** and **2** have been synthesized to achieve this aim (Fig. 1) [12–14]. CSP **1** needed trifluoroacetic acid as an acid additive for the protonation of amines, whereas CSP **2** did not need the acid additive because the phenolic OH group in **2** served as a good proton donor for amines. On the contrary, in the latter case, the addition of triethylamine to the eluent improved the separation. With respect to amines and amino alcohols such as **3**–**5**, CSP **2** exhibited much better performance than CSP **1**. The binding constants (K_a) of the corresponding model hosts in solution were determined by the NMR titration, and a good correlation was observed between the ratios of the K_a values for the two enantiomers and the separation factors, α, in chiral HPLC. As for amino acids **6**, on the other hand, CSP **1** showed better performance than CSP **2**; although peak broadening was observed for asparagine and arginine, other 18 amino acids were separated well by CSP **1**. CSP **1** was commercialized as Sumichiral OA-8000 in 2000.

The naked-eye discrimination of enantiomers on the basis of a color change is an interesting and challenging

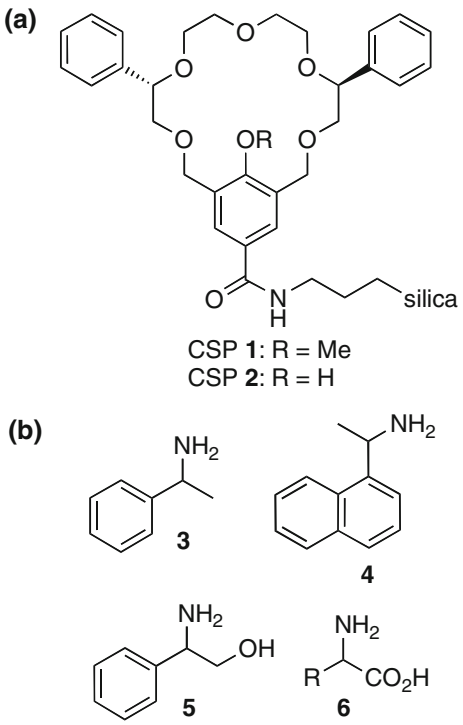


Fig. 1 **a** CSPs containing chiral crown ethers and **b** analytes

subject. Bifunctional receptors **7**–**10** bearing two crown ethers and a phenolphthalein skeleton were designed and synthesized for the detection of the absolute configuration and enantiomeric purity of chiral compounds based on a color change (Fig. 2) [15]. Chiral hosts **7**–**10** were mixed with each enantiomer of alanine derivatives **11**. As a result, enantioselective coloration was observed only under the specified conditions with **8** (Table 1). Complexation of (*S*,*S*,*S*,*S*)-**8** with (*R*)-**11** gave a brilliant pink color, whereas that of (*S*,*S*,*S*,*S*)-**8** with (*S*)-**11** led to almost no color development. The K_a values indicated that only host **8** showed high enantioselectivity ($K_a(R)/K_a(S) \sim 6$). Furthermore, when (*S*,*S*,*S*,*S*)-**8** was mixed with **11b** having different enantiomeric purities in a 1:1 ratio, a linear relationship was observed between the absorbance at 574 nm and the enantiomeric purity. The proposed mechanism of chiral recognition is given in Fig. 3. The two amino groups in **11** bridge the two crown ether rings in **8**, and the spatial relationship between the methyl groups at positions 7 and 11 in **8** and the methyl group in **11** determines the stability of the complex. (*S*)-**11** is likely to cause unfavorable steric interactions, showing a smaller binding constant, which is in agreement with the experimental results (Table 1). Moreover, this model can also explain the opposite enantiopreferences of hosts **8** and **9** for **11** (Table 1). The dianionic structure of **8** in Fig. 3 is considered to exhibit a pink color.

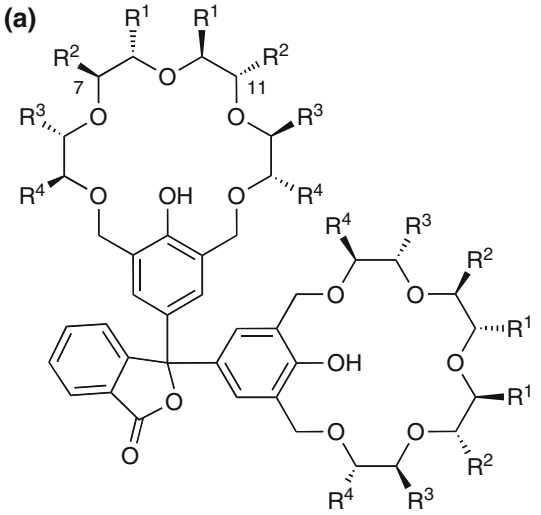


Fig. 2 **a** Bifunctional receptors and **b** guests

Table 1 Visual enantiomeric recognition of alanine derivatives by chiral crown ethers

Host	Guest	Binding constant[a]			Visual detection
		$K_a(R)$	$K_a(S)$	$K_a(R)/K_a(S)$	
(*S*,*S*,*S*,*S*)-**7**	**11a**	2,334	1,554	1.5	
(*S*,*S*,*S*,*S*)-**8**	**11a**	378	62	6.1	Yes
(*S*,*S*,*S*,*S*)-**9**	**11a**	148	328	0.45	
(*S*,*S*,*S*,*S*)-**10**	**11a**	262	214	1.2	
(*S*,*S*,*S*,*S*)-**7**	**11b**	2,224	1,437	1.5	
(*S*,*S*,*S*,*S*)-**8**	**11b**	366	65	5.6	Yes
(*S*,*S*,*S*,*S*)-**9**	**11b**	251	296	0.85	
(*S*,*S*,*S*,*S*)-**10**	**11b**	208	245	0.85	

[a] In MeOH at 15 °C

Chiral calixarenes, calix[4]resorcinarenes, and calix[4]pyrroles

Chiral calixarenes have great potential in chemical, analytical, biological, and material fields. This is due to their unique structures that can be used as a binding cleft and a molecular scaffold. Chiral receptor **12** has been constructed

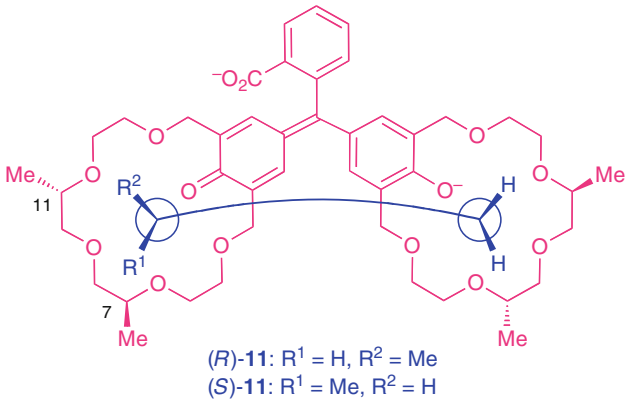


Fig. 3 Mechanism of chiral recognition of **11** by **8**

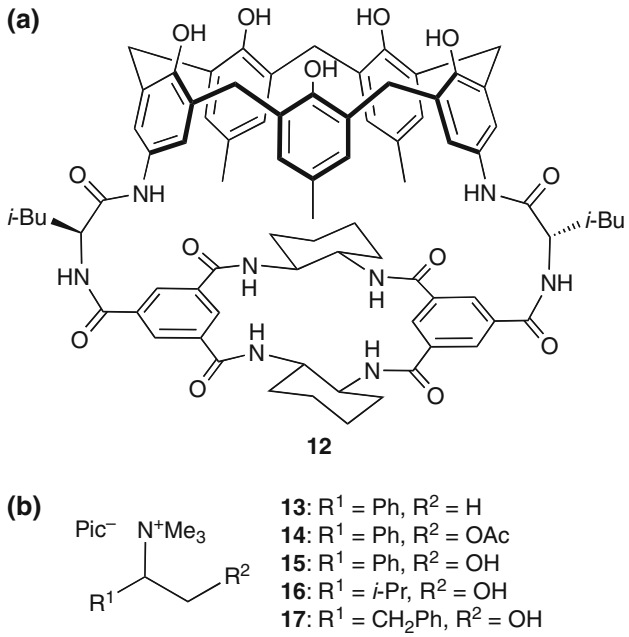


Fig. 4 **a** Chiral calix[5]arene-based receptor and **b** ammonium guests

by combining the calix[5]arene, which has a larger cavity than the calix[4]arene, with the chiral macrocycle (Fig. 4) [16]. The π-basic calix[5]arene cavity can accommodate a cationic guest via van der Waals, cation/π, and CH/π interactions, while the chiral macrocyclic moiety has the amide groups that can serve as the hydrogen-bonding sites. Interestingly, a dissymmetric distortion in the calix[5]arene cavity can be brought about by linking with the chiral macrocycle. Various chiral ammonium salts, such as **13**–**17**, were tested for enantioselective binding. The K_a values are summarized in Table 2. It should be noted that simple ammonium salt **13** with no hydrogen-bonding sites was enantioselectively encapsulated by **12** with an enantioselectivity of 2.0, which was achieved by the shape recognition via the weak interactions such as cation/π and CH/π. Furthermore, **12** showed higher affinity for **14** and **15** than

Table 2 Binding constants of **12** for **13–17**

Guest	K_a	*R*:*S*
(*R*)-**13**	2,400	1:2.0
(*S*)-**13**	4,900	
(*R*)-**14**	9,800	1:1.5
(*S*)-**14**	15,000	
(*R*)-**15**	12,000	1:1.4
(*S*)-**15**	17,000	
(*R*)-**16**	21,000	2.4:1
(*S*)-**16**	8,600	
(*R*)-**17**	26,000	3.7:1
(*S*)-**17**	7,100	

In $CHCl_3$ at 20 °C

for **13**, which was due to an additional hydrogen bond. The ^{1}H NMR signals for the isopropyl group of the two enantiomers of **16** appeared at different chemical shifts below 0 ppm upon complexation with **12**; MM calculations indicated that the ammonium and isopropyl groups of **16** were located in a shielded region of the five phenolic rings of the calix[5]arene. The enantioselectivity of **12** for **17** was the highest, which was ascribed to an additional π–π stacking interaction.

There are two ways of making chiral calixarenes: one is to simply attach a chiral molecule to the achiral calixarene moiety, and the other is to introduce substituents to the rim of the calixarene in a chiral manner. In the latter case, "inherently chiral" calixarenes can be created. Two typical examples are given in Fig. 5. Calix[4]arene **18** is furnished with chiral amino naphthol [17], while **19** is inherently chiral because of the substitution pattern [18, 19]. Both receptors have the amino group as a binding site for carboxylic acid, and the ^{1}H NMR signal for the benzylic proton of mandelic acid **20** was resolved by addition of 1 equiv of **18** ($\Delta\Delta\delta = 0.042$ ppm) and **19** ($\Delta\Delta\delta = 0.03$ ppm) in $CDCl_3$. Carboxylic acids **21–24** were also discriminated by **18** and its derivatives. The K_a value for (+)-**19** toward (*S*)-**20** (3.5×10^5 M^{-1}) was 2.2 times larger than that toward (*R*)-**20** (1.6×10^5 M^{-1}). Interestingly, **19** could also be used as an organocatalyst for the asymmetric Michael addition although enantioselectivity was modest (up to 16% ee).

Since many pharmaceutical compounds are designed to have good solubility in water, it is important to develop water-soluble chiral solvating agents. However, there are only a few water-soluble chiral synthetic receptors used for this purpose. A water-soluble calix[4]resorcinarene was prepared by the condensation of resorcinol with aldehyde bearing the sulfo group, and subsequent functionalization with optically pure proline derivatives under Mannich conditions gave chiral water-soluble calix[4]resorcinarenes

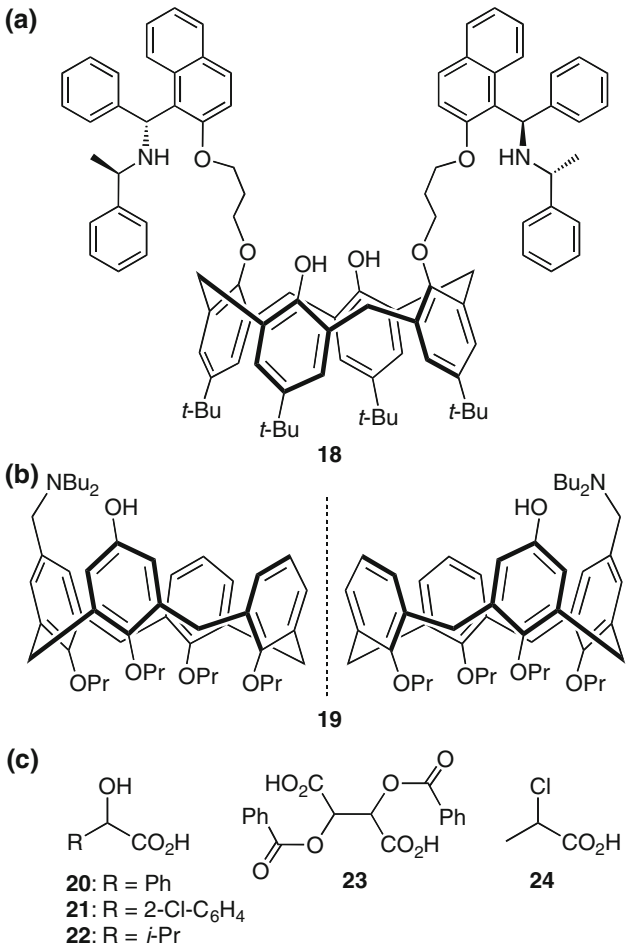


Fig. 5 **a** Chiral calix[4]arene, **b** inherently chiral calix[4]arene, and **c** carboxylic acid guests

such as **25–29** (Fig. 6) [20–23]. These hosts are considered to take a cone conformation, forming a cavity capable of accommodating guests with an aromatic ring. Job plots indicated 1:1 host–guest complexation in D_2O. Although **25** was the best host for **30**, either **27** or **28** usually showed the best performance in chiral discrimination in NMR [21, 22]. For example, host **28** exhibited the best enantiomeric discrimination for **31** and **32**, while host **27** was the best reagent for **33–35**. The dipole–dipole interactions around the hydroxy group at the 3- or 4-position in the pyrrolidine ring of **28** and **27** are proposed to be important for chiral discrimination. More recently, host **29** has been reported to be suitable for simple amines such as 1-phenylethylamine [23].

Anions are ubiquitous in life and environment and are important targets for drug development, diagnosis, environmental remediation, and catalysis. A variety of receptors for anionic species have therefore been developed. Calix[4]pyrrole is an attractive platform for the binding of anions such as halide, phosphate, and carboxylate. The BINOL-strapped calix[4]pyrrole **36** was prepared in three

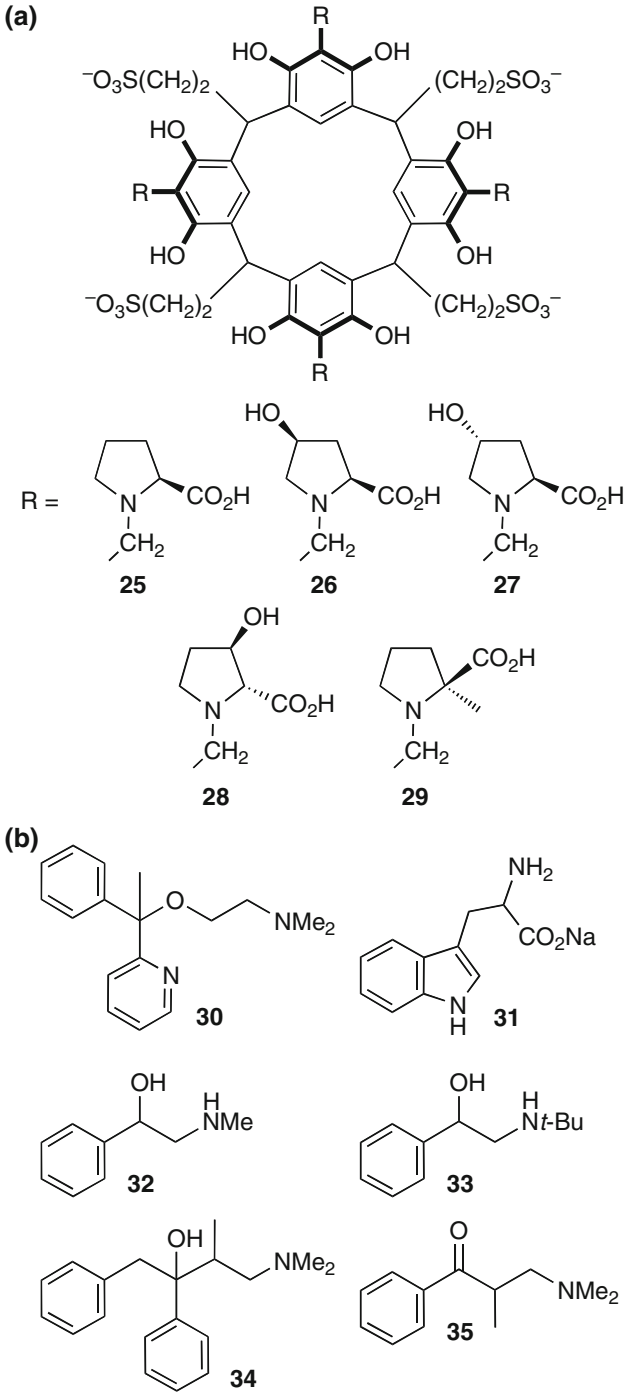


Fig. 6 **a** Water-soluble chiral calix[4]resorcinarenes and **b** guests

steps from BINOL, and chiral recognition of **36** toward 2-phenylbutyrate anion **37** (tetrabutylammonium salt) was studied (Fig. 7) [24]. The K_a values for (*S*)-**36** toward (*R*)- and (*S*)-**37** in dry acetonitrile were determined to be 9.8×10^3 and 1.0×10^5 M^{-1}, respectively, by isothermal titration calorimetry (ITC). This enantioselective binding corresponds to an energetic difference of 1.38 kcal/mol. The proposed binding modes are shown in Fig. 8. The

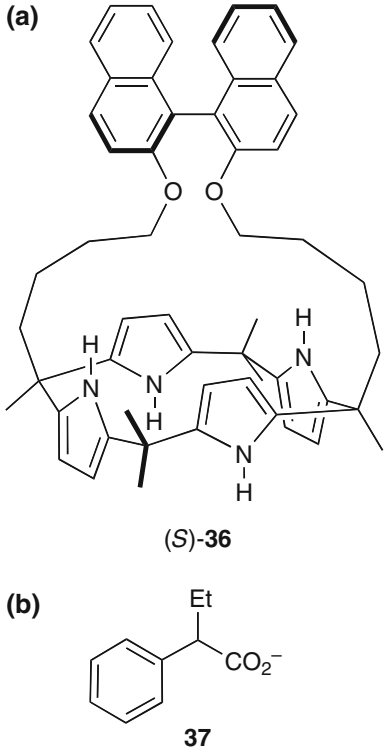


Fig. 7 **a** BINOL-strapped calix[4]pyrrole and **b** anionic guest

carboxylate anion of **37** is hydrogen bonded with the NH groups of **36**. The higher affinity of (*S*)-**36** for (*S*)-**37** is probably due to the favorable π–π interactions between the naphthyl group in (*S*)-**36** and the phenyl group in (*S*)-**37**, while the lower affinity of (*S*)-**36** for (*R*)-**37** is likely to be caused by the unfavorable steric interactions between (*S*)-**36** and the phenyl group in (*R*)-**37**. This was supported by density functional theory (DFT) calculations.

Chiral macrocyclic amides and amines

To find practical utility in analytical chemistry, the comprehensive performance becomes important, which includes versatility, signal sharpness, high splitting ability, high sensitivity, wide detection window, and synthetic accessibility. Well-designed receptors might meet these requirements. Among them, however, versatility is a difficult aspect for chiral hosts because specific binding is required for enantioselectivity, whereas nonspecific binding is needed to broaden the range of analytes. Obviously, there are no perfect answers. Nevertheless, efforts have been made to meet this requirement as much as possible. Chiral receptors bearing both hydrogen-bond donor and acceptor sites are expected to bind a wide range of compounds. In this respect, 2,6-diacylaminopyridine is a promising binding unit. A macrocyclic structure will

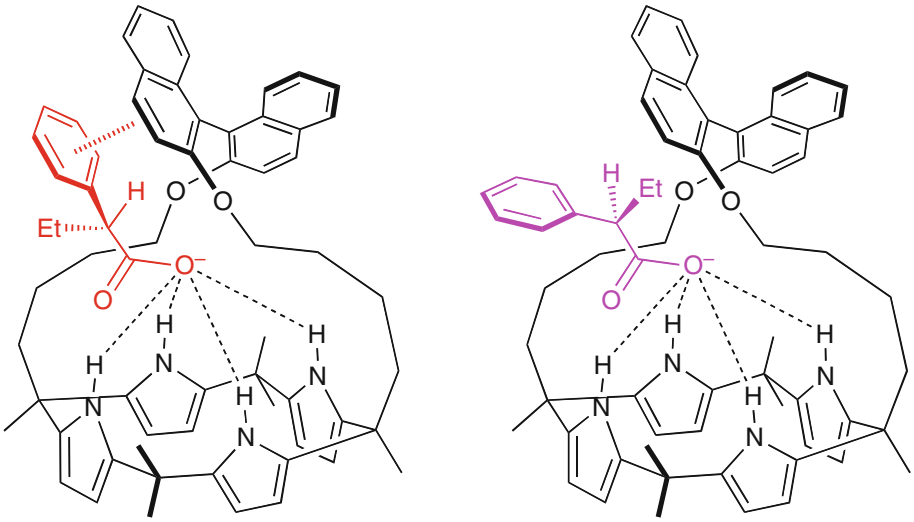


Fig. 8 Mechanism of chiral recognition

preorganize the disposition of the functional groups, providing effective binding sites. This concept led to the creation of chiral macrocycle **38** (Fig. 9), which was found to be an extremely versatile reagent that is effective for a wide range of chiral compounds such as carboxylic acid, oxazolidinone, carbonate, lactone, alcohol, sulfoxide, sulfoximine, sulfinamide, isocyanate, and epoxide compounds [25–27]. NMR signals for the enantiomers of **20** and **39**–**49** were well split upon complexation with host **38**. In a case, CSA **38** showed very high sensitivity; only 5 mol% (69 μg, 0.15 mM) of **38** was enough for the complete splitting of the enantiomeric signals of sulfoxide **45** (Fig. 9c). The reagent **38** could be used to determine the enantiomeric purity of a variety of chiral compounds and is commercialized as Chirabite-AR. The K_a values of **38** for several guests are summarized in Table 3. The reagent **38** has a good ability to recognize the chirality of the guests. For example, the K_a values for (*S*)-**45** and (*S*)-**46** are 4.3- and 4.9-fold higher, respectively, than those for (*R*)-**45** and (*R*)-**46**, the latter of which amounts to an energetic difference of -0.93 kcal mol^{-1}.

Although host **38** was originally developed as a CSA for NMR, it was later applied to a CSP for HPLC as well [28, 29]. We expected that the size and shape of the chiral cavity of the macrocyclic receptor could be tuned by alteration of the binaphthyl moiety to improve the chiral recognition ability. To investigate the effect of the substituent at the 3,3′-positions of the binaphthyl moiety on chiral HPLC performance, CSPs **50**–**53** (Fig. 10) were prepared. The carboxyl group attached to the macrocyclic moiety was combined with 3-aminopropyl silica gel to give CSPs **50**–**53**, which were then packed in a stainless steel column. Figure 11 illustrates the comparison of the size and shape of the macrocyclic moieties. Interestingly, extensive screening of CSPs **50**–**53** using **54**–**59** indicated that either CSP **50** or CSP **52** always showed the best HPLC performance. Eventually, nine analytes (**20**, **54**, **56**, **57**, **59**–**61**, **63**, and **64**) were baseline resolved, and the others (**55**, **58**, and **62**) resulted in partial resolution. In particular, CSP **52**, having the Br atoms, showed the best results for **54**, **56**, **57**, **62**, and **64**. HPLC chromatograms for **56** are shown in Fig. 11 as a representative example. Such wide scope (versatility) is achieved by the multiple hydrogen-bonding sites, while chiral recognition results from the orthogonal orientation of the binaphthyl moiety relative to the binding domain (lower segment), as can be seen in Fig. 11 [26]. It should also be noted that chiral compounds could be resolved not only in organic solvents but also in CO_2-based mobile phases [28].

It is known that in some cases, good chiral selectors in CSPs can be used as good CSAs, and vice versa. Based on CSP **65** consisting of (1*R*,2*R*)-1,2-diphenylethylenediamine and CSP **66** consisting of (1*R*,2*R*)-1,2-diaminocyclohexane, new $CDCl_3$-soluble CSAs **67** and **68** were prepared (Fig. 12) [30]. Several guests **69**–**77** were then analyzed by ^{1}H NMR. In the presence of the CSA, the aromatic or NH protons of the guests underwent splitting. CSP **65** had been known to be more efficient than CSP **66**, while in this study, CSA **67** was found to be superior to CSA **68**. The signal splitting increased with a decrease in temperature. The K_a values were determined by the DOSY technique as well as the traditional NMR titration. The ratios of the K_a values of CSA **67** for the enantiomers of **72** were about 2.

Macrocyclic amide receptors **78** and **79** were designed for the chiral recognition of naproxen tetraethylammonium salt **80** (Fig. 13) [31]. It is described that various chiral hosts reported before exhibited enantioselectivity lower than 1.3 (K_a ratio) in solution or 2.25 (α value) in CSP. This

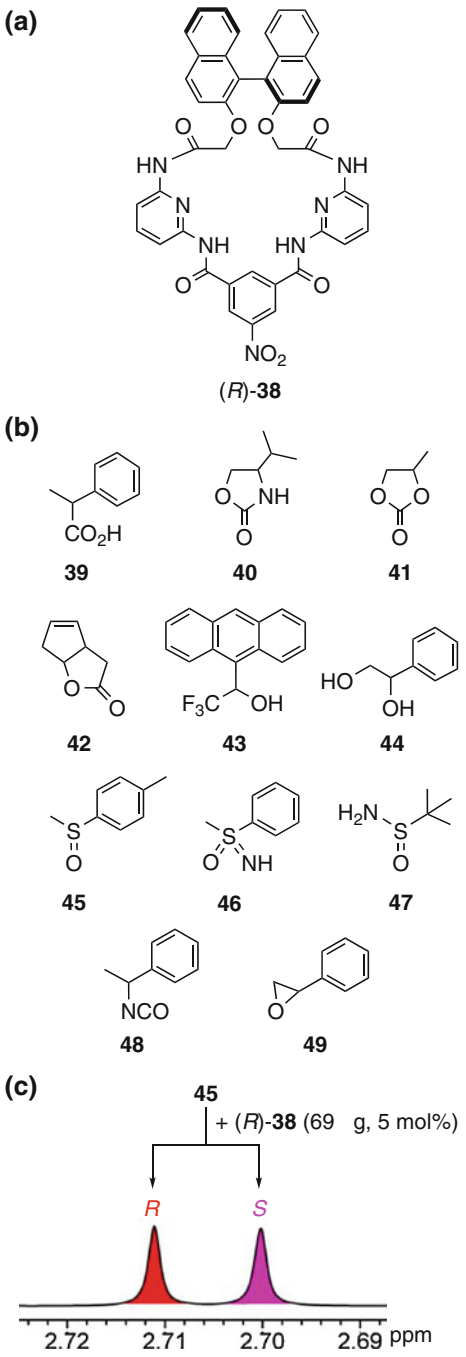


Fig. 9 **a** Chiral macrocyclic host with multiple hydrogen-bonding sites in the cavity and **b** various guests. **c** 600 MHz ^{1}H NMR of *rac*-**45** (277 μg, 3 mM) in the presence of (*R*)-**38** (69 μg, 5 mol%) in $CDCl_3$ (0.6 mL) at 22 °C

difficulty is probably due to a small difference in size between the methyl group and the hydrogen atom. On the other hand, **78** and **79** showed the enantioselectivity factors of 1.2 and 7.2, respectively, as determined by the competitive experiments in DMSO-d_6. ^{1}H NMR spectra showed the signal splitting upon the diastereomeric

Table 3 Binding constants and chiral recognition energies between (*R*)-**38** and guests

Guest	K_a	$\Delta\Delta G^{oa}$
(*R*)-**39**	1670	−0.35
(*S*)-**39**	3050	
(*R*)-**40**	510	+0.35
(*S*)-**40**	280	
(1*R*,5*S*)-**42**	51	+0.26
(1*S*,5*R*)-**42**	33	
(*R*)-**45**	610	−0.85
(*S*)-**45**	2600	
(*R*)-**46**	170	−0.93
(*S*)-**46**	830	

In $CDCl_3$ at 22 °C

[a] Chiral recognition energy calculated from $-RT\ln\{K_a(S)/K_a(R)\}$. In kcal mol^{-1}

complexation. The higher enantioselectivity of **79** is ascribed to the methyl groups at the *ortho* positions of the phenyl groups in **79**, one of which seems to be directed toward the stereogenic center of the bound guest molecule. Although the optical resolution of **78** and **79** was not yet done, MM calculations predicted the (*R*,*R*)-**79**–(*S*)-**80** complex to be more stable, which is due to the four hydrogen bonds of the carboxylate anion in the binding cleft and to the methyl–methyl interactions, as shown in Fig. 14.

Based on the general trend that amines can form tight complexes with acids, macrocyclic amines **81**–**86** were used as chiral receptors for carboxylic acids (Fig. 15) [32, 33]. They were prepared in two steps from chiral amine, dialdehyde, and 2-naphthol. Starting from (*S*)-1-phenylethylamine or (*S*)-1-(2-naphthyl)ethylamine, **81**–**86** with the (*S*,*S*,*S*,*S*)-configuration were obtained. Despite the similar structures of **81**–**86**, the chiral discrimination abilities toward mandelic acid **20** were found to be different; CSAs **81** and **82** were superior to others. A non-macrocyclic analog (not shown) was ineffective. Therefore, the bridging pyridine ring, the *m*-phenylene spacer, and the secondary amino group are important for the chiral discrimination function. CSAs **81** and **82** showed the chemical shift nonequivalences ($\Delta\Delta\delta$) for various carboxylic acids **20**, **21**, **39**, and **87**–**103**. Job plots indicated that **81** or **82** forms a complex with **20** in a 1:2 ratio, which suggests that two molecules of **20** interacts with the two amino groups in **81** or **82**. In addition, carboxylic acids having hydrogen-bond donor at the α-position, such as OH and NHAc, were resolved well, which suggests an additional hydrogen bond between the hydrogen-bond donor at the α-position of the guest and the pyridyl nitrogen atom of the host. It is also reported that **81** and **82** acted as good CSAs for phosphinic, phosphonic, and phosphoric acids [34].

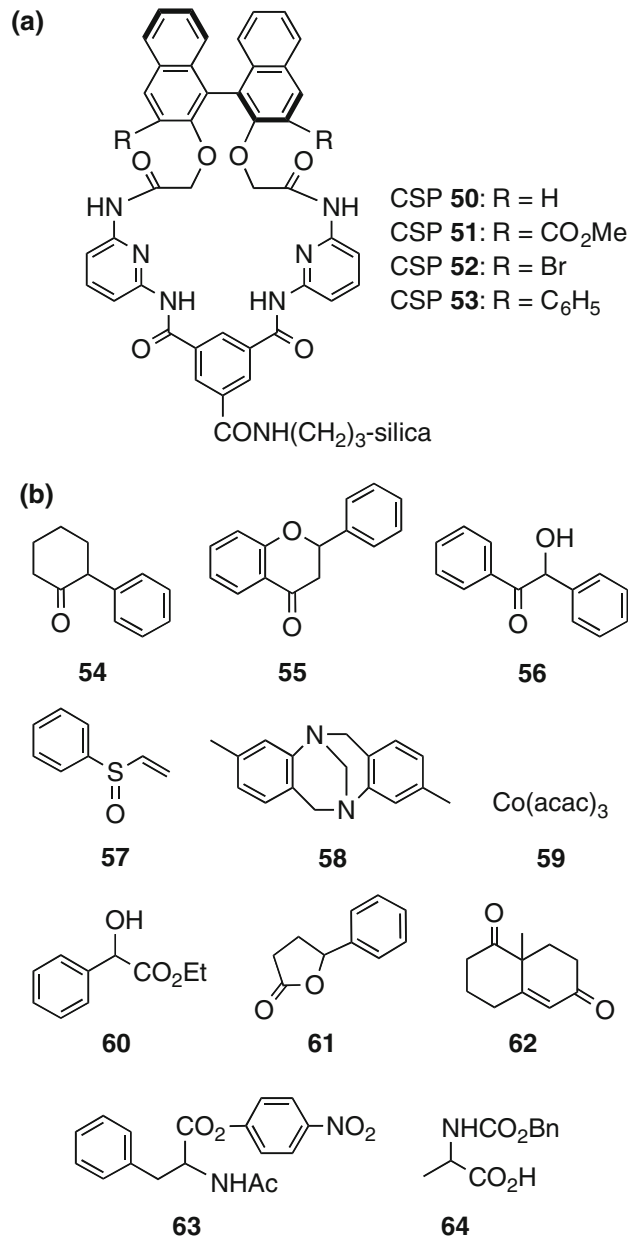


Fig. 10 **a** Chiral selectors for HPLC and **b** various guests

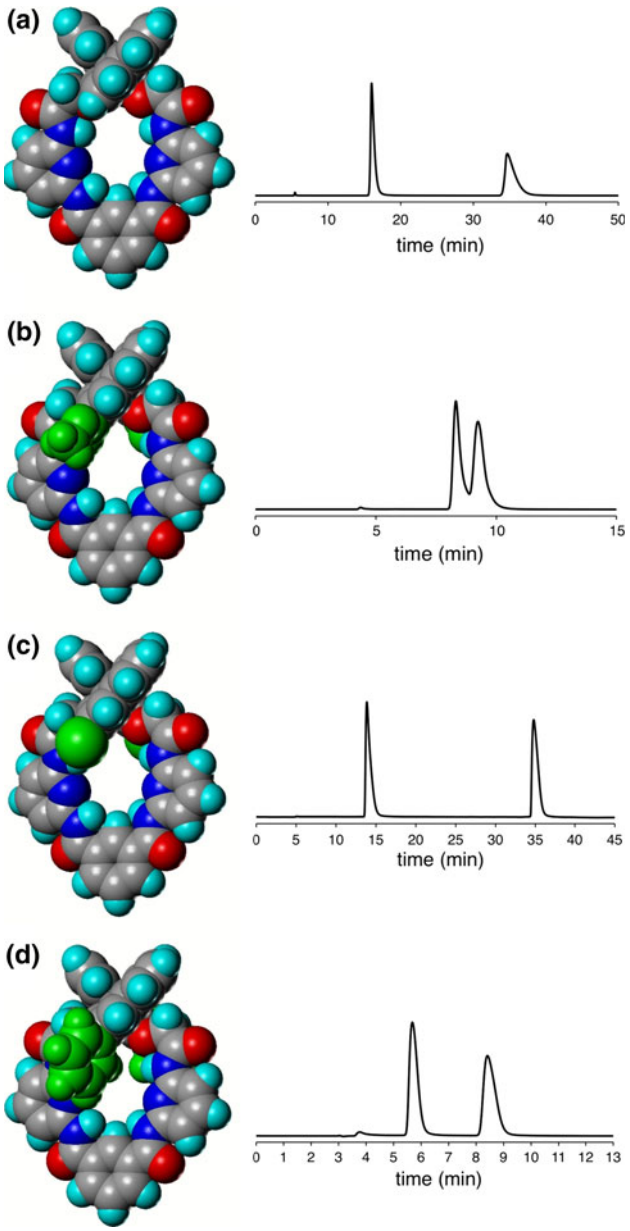
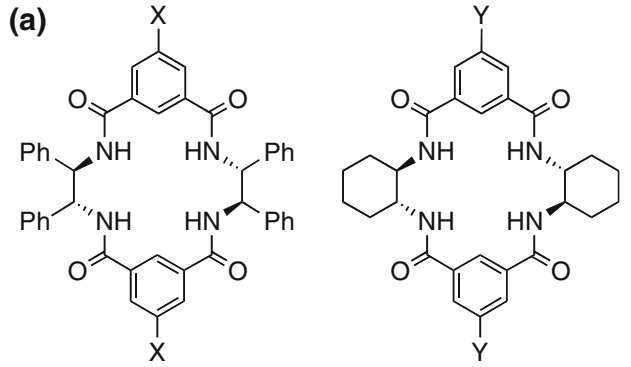


Fig. 11 Chiral selectors in **a** CSP **50**, **b** CSP **51**, **c** CSP **52**, and **d** CSP **53**, together with their HPLC chromatograms for **56**: flow rate 1.0 mL/min, detection 254 nm, 25 °C, hexane/$CHCl_3$ (7:3 for CSP **50**–**52** and 1:1 for CSP **53**)

Macrocyclic amine **104** was synthesized via the dynamic formation of the corresponding imine at equilibrium, where Ba^{2+} was used as a template to increase the yield, followed by reduction (Fig. 16) [35, 36]. The four amino groups would form the salts with carboxylic acids, while the two pyridine rings would have additional interactions, such as hydrogen bonding, solvophobic, and π–π stacking interactions, causing the anisotropic effect. Macrocycle **104** was tested for the CSA activity toward carboxylic acids **20**, **39**, **87**, **88**, **93**, and **105**–**108**. In the case of the acids with a heteroatom at the α-position, the signal for the proton attached to the stereocenter was baseline resolved in $CDCl_3$. The signal for the methoxy group at the α-position was also split. In most cases, the amount of **104** necessary for the signal splitting was less than 1 equiv of the acid; the largest signal separation was observed when host and guest were mixed in a 1:4 ratio. Job plots indicated 1:4 host–guest complexation. Macrocycle **104** was also used as a water-soluble receptor for malate **109**, for which 1:1 complexation was observed, and the K_a ratios ($K_a(S)/K_a(R)$) reached ca. 12 [37].

trans-1,2-Diaminocyclohexane is a useful chiral unit, from which a series of macrocyclic amines **110**–**114** were prepared (Fig. 17) [38–40]. Trianglamines **110** and **111**



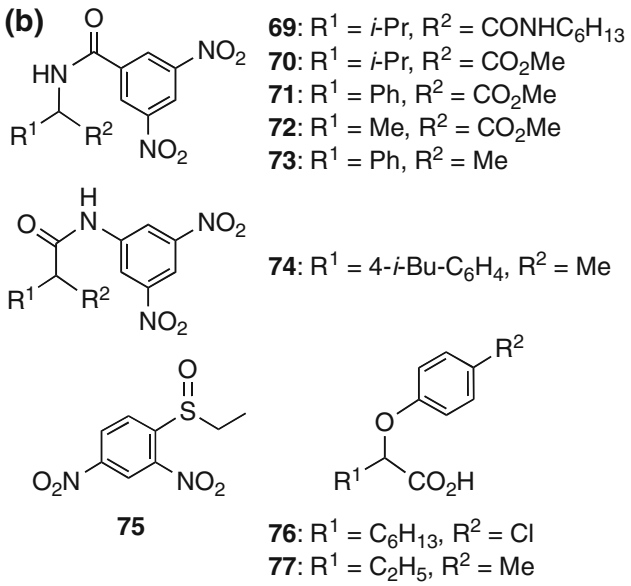


Fig. 12 **a** Macrocyclic CSPs and CSAs and **b** guests

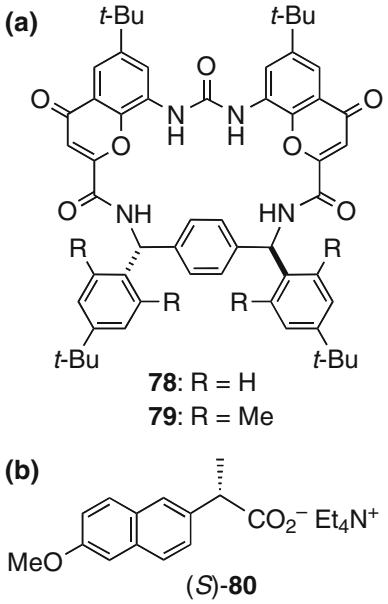


Fig. 13 **a** Macrocyclic amide receptor and **b** guest

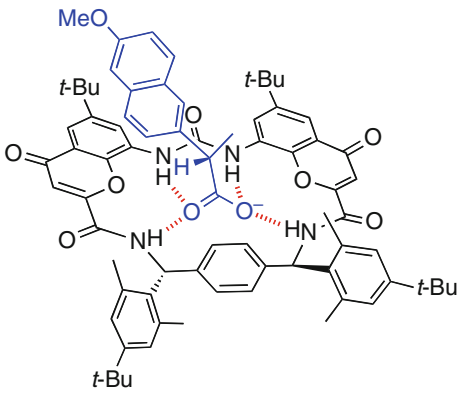


Fig. 14 The more favorable (*R*,*R*)-**79**–(*S*)-**80** complex predicted by MM calculations

showed the CSA activity toward secondary alcohols **115**–**124**. Interestingly, **110** exhibited a higher ability than **111** in most cases. Both the amino groups and the macrocyclic framework in **110** are important because neither the corresponding imine nor a non-macrocyclic analog (not shown) were effective. Job plots indicated that **110** forms a 1:1 complex with (*R*)- or (*S*)-**123**, while **111** forms a 2:1 complex with (*R*)- or (*S*)-**123**. On the other hand, **112**–**114** could be used as CSAs for various carboxylic acids. Among them, the comparison between rhombamines **113** and **114** is intriguing; the chiral discrimination ability of **113** was higher than that of **114** in most cases. Job plots indicated that **113** forms a 1:4 complex with (*R*)- or (*S*)-**20**. The NOESY spectra for a mixture of (*R*)-**20** and 0.25 equiv of (*R*)-**113** showed a cross peak between the signal for the proton attached to the asymmetric carbon of (*R*)-**20** and that for the aromatic proton of (*R*)-**113**, suggesting that a CH/π interaction takes place in addition to the major acid–base interaction.

Chiral porphyrins

Porphyrins are unique macrocyclic tetrapyrroles, which have (i) a large π-surface suitable for π–π stacking, (ii) a metal center as a coordination site (in metalloporphyrins), and (iii) a great ring-current effect [41]. Chiral diporphyrin receptor **125** with a chiral cavity, shown in Fig. 18, was designed as follows: two porphyrins were disposed in parallel at a distance of ca. 7 Å suitable for the intercalation of aromatic guests, and BINOL was used as a chiral spacer to link the two porphyrins [42, 43]. MM calculations

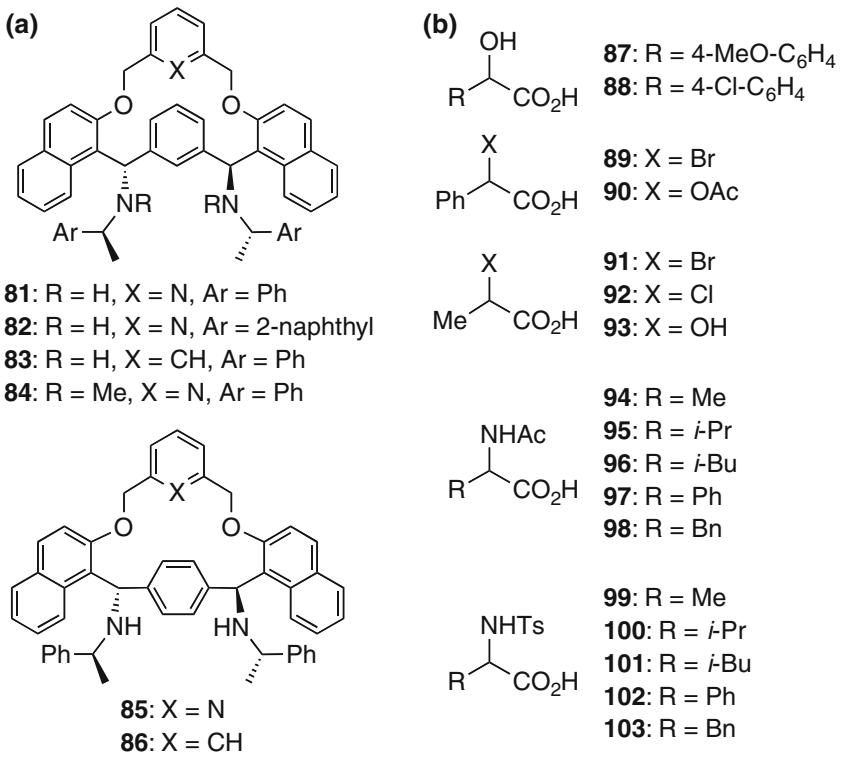


Fig. 15 **a** Macrocyclic amine receptors and **b** carboxylic acid guests

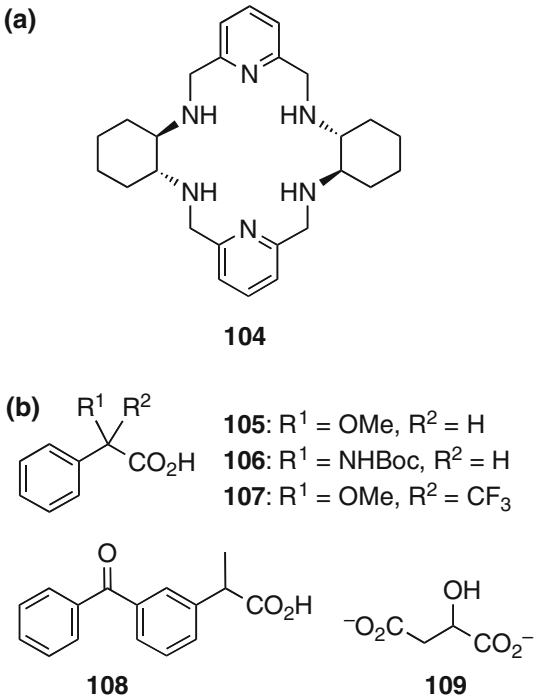


Fig. 16 **a** Macrocyclic amine receptor and **b** carboxylic acid guests

indicated that the two porphyrins are arranged in an offset face-to-face geometry with an interplanar distance of 5.8–7.2 Å (Fig. 19). No aliphatic hydrocarbon groups, which may interfere with the NMR signals for the guests, are used in **125**. Despite such a large but sophisticated structure, **125** could be prepared only in five steps from pyrrole. NMR or UV–Vis titration demonstrated the good affinity of **125** for electron-deficient aromatic guests; for example, $K_a = 1850$ and $42.9\ M^{-1}$ for **126** and **127**, respectively, in chloroform, as shown in Table 4. MM calculations indicated that an aromatic guest molecule, such as **126** and **127**, can be nicely included as represented by Fig. 19. Interestingly, **125** functioned as a naked-eye sensor for explosive **126**; a dark-red solution of **125** in $CHCl_3$ turned into a colloidal suspension upon addition of **126**, while fluorescence of **125** was quenched by complexation with **126**, both of which were visible with the naked eye. Despite modest binding constants for dinitrobenzene derivatives, receptor **125** exhibited the CSA function for chiral compounds **73** and **128**–**130**. As shown in Table 4, the K_a values of **125** for **128** were very small ($K_a = 4.2\ M^{-1}$ for (*R*)-**128** and $K_a = 1.2\ M^{-1}$ for (*S*)-**128**), which suggests that **128** is sterically more hindered than the corresponding methyl ester **127**. It is surprising that the CSA function of **125** toward **128** is based on such weak binding, even if the degree of enantioselectivity is moderate ($K_a(R)/K_a(S) = 3.5$). This is the first example of arraying two porphyrins in a parallel but chiral manner at a distance suitable for sandwiching aromatic molecules and is a rare example of a chiral receptor showing chiral recognition/discrimination using the π–π stacking interaction as a sole driving force of complexation.

Carbon clusters, such as fullerenes and carbon nanotubes, are hollow spherical, ellipsoidal, or tubular

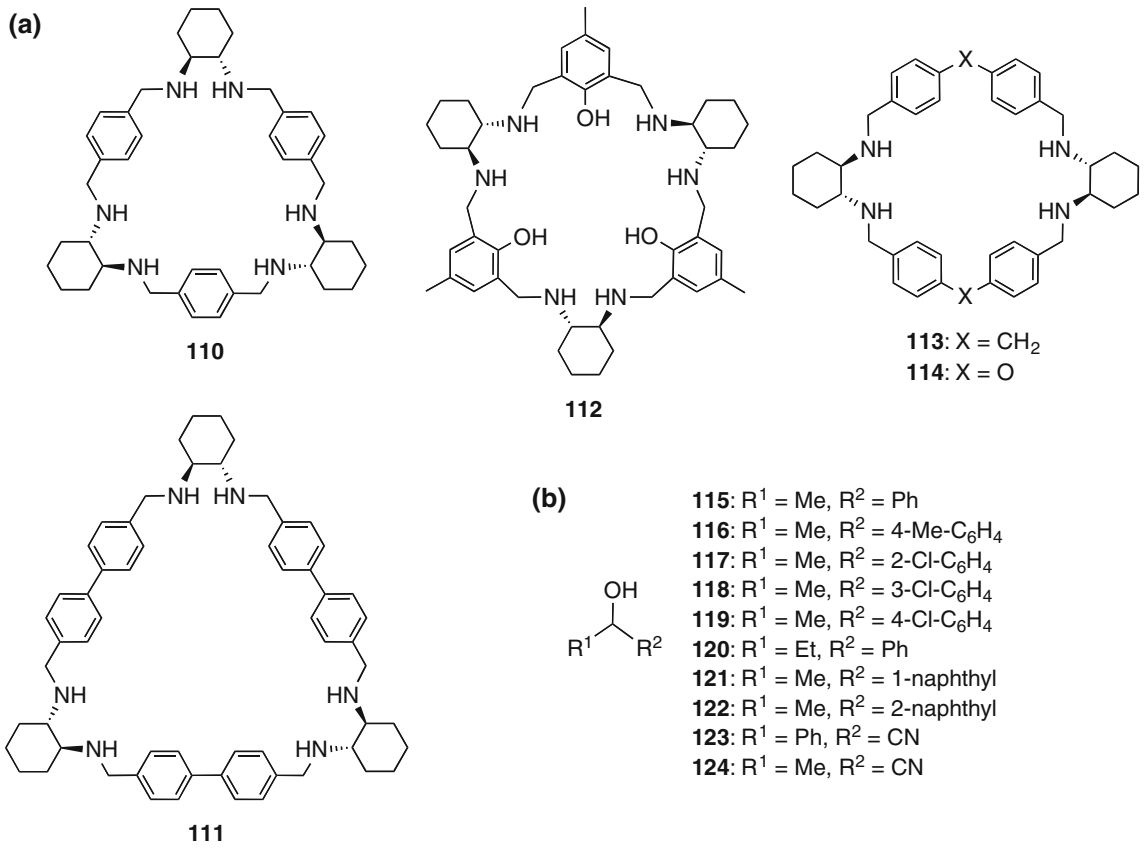


Fig. 17 **a** Macrocyclic amine receptors and **b** secondary alcohol guests

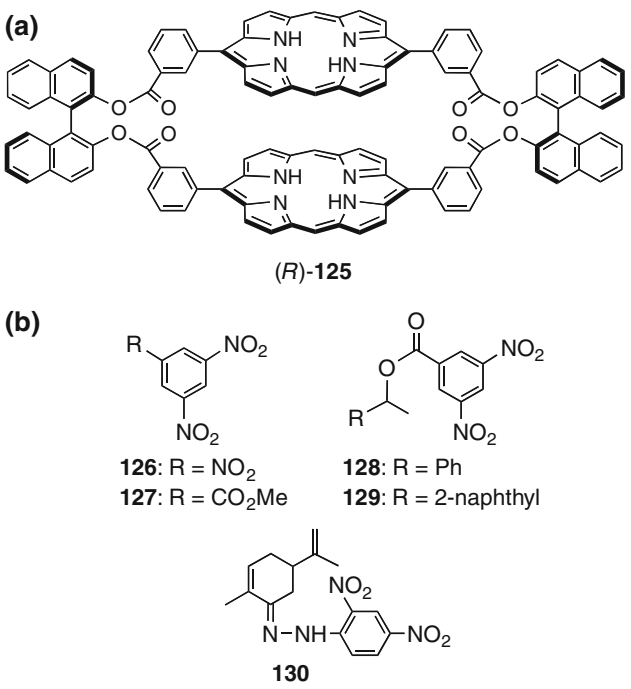


Fig. 18 **a** Chiral diporphyrin receptor and **b** nitroaromatic guests

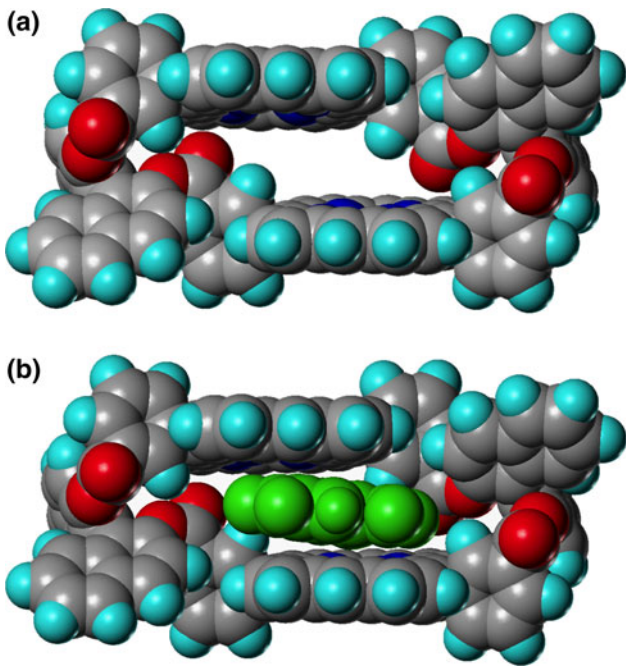


Fig. 19 Optimized structures of **a** **125** and **b** a **125**–**126** inclusion complex

Table 4 Binding constants of (*R*)-**125** for aromatic guests

Guest	K_a	$\Delta G^{\circ a}$
126	1850	–4.5
127	42.9	–2.2
(*R*)-**128**	4.2	–0.8
(*S*)-**128**	1.2	–0.1

In $CDCl_3$ or $CHCl_3$ at 25 °C

[a] Calculated from $\Delta G^{\circ} = -RT \ln K_a$. In kcal mol^{-1}

molecules composed of only carbon. Interestingly, some of them are chiral [44]. Because unsubstituted chiral carbon clusters have no functional groups but a distorted π-electronic surface, the chiral recognition of chiral carbon clusters is extremely difficult. For the enantioselective binding of C_{76}, the smallest chiral fullerene homolog, host **131** with a *meso*-diaryl-β-octaethylporphyrin unit and the *N*-substituted counterpart was designed (Fig. 20) [45]. The former is an electron-rich (π-basic) unit, and the latter is a more π-basic, distorted unit having planar chirality. The spectroscopic titration indicated that the affinity of (±)-**131** for (±)-C_{76} in toluene was very high ($K_a = 5.5 \times 10^6\ M^{-1}$ at 20 °C). The optical resolution of C_{76} was carried out by mixing (+)-**131** with (±)-C_{76} in toluene in a 1:10 molar ratio followed by size exclusion chromatography. The first fraction containing the inclusion complex was collected and then chromatographed on silica gel, which released (−)-C_{76} with 7.1% ee. This host **131** has great potential in chiral HPLC for the optical resolution of chiral fullerenes. The chiral discrimination of C_{76} in NMR was also achieved by host **131** and other derivatives; a *meso*-H signal of (±)-**131** split into two singlet peaks upon complexation with (±)-C_{76} in toluene-d_8 at 20 °C [45, 46].

Single-walled carbon nanotubes (SWNTs) are promising materials. However, the as-prepared SWNT sample is a mixture of different structures that vary in length, diameter, and chirality. Because the optical, electrical, and mechanical properties of SWNTs are determined by their structures, the

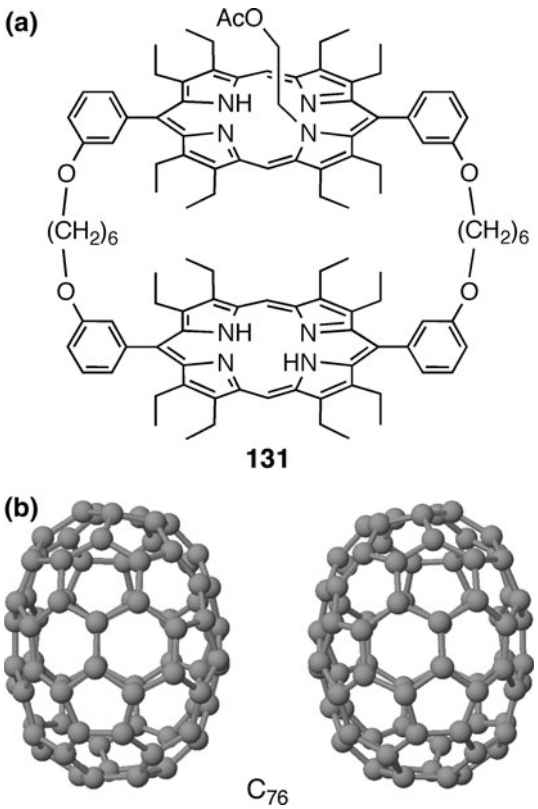


Fig. 20 **a** Chiral diporphyrin receptor and **b** both enantiomers of C_{76}

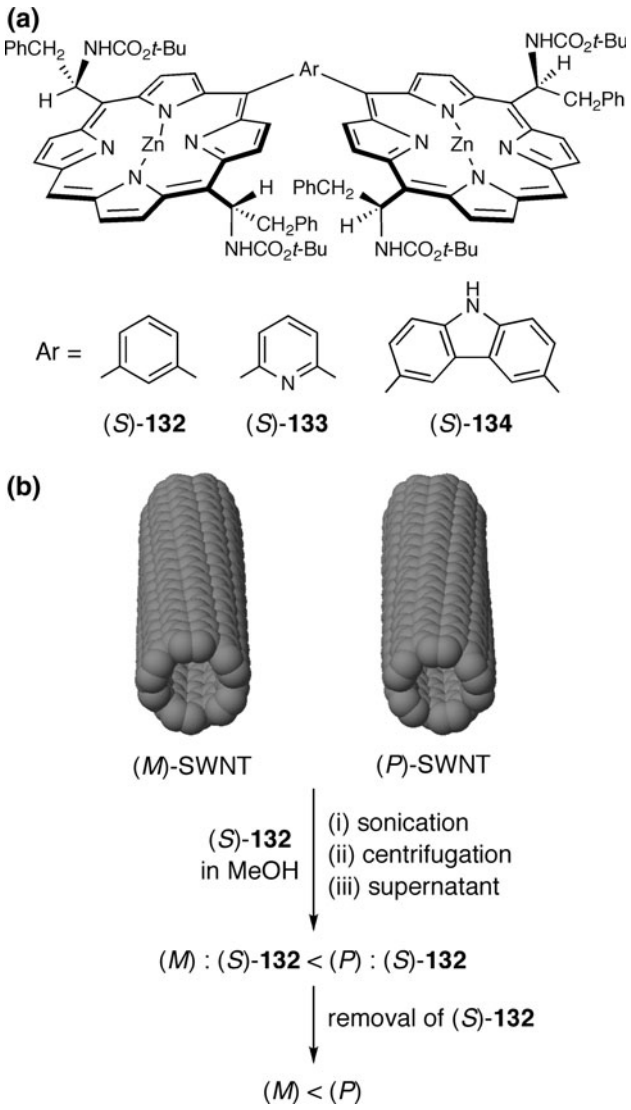


Fig. 21 **a** Chiral nanotweezers. **b** Enantioselective extraction of SWNTs with (*S*)-**132**. Although only the most abundant isomer called (6,5)-SWNT is shown, other isomers called (7,5)-, (7,6)-, (8,4)-, and (8,3)-SWNTs, which differ in the roll-up angle and diameter, were also extracted enantioselectively at the same time

method for the preparation of a uniform material is required [47]. To recognize the left- and right-handed helical sense ((*M*)- and (*P*)-enantiomers) of SWNTs, a chiral gable-type diporphyrin **132** was designed and synthesized (Fig. 21) [48]. If the two enantiomers of SWNTs are bound by (*S*)-**132** with unequal stability, the SWNTs may be resolved. In fact, the enantioselective extraction of the SWNTs with (*S*)-**132** followed by removal of (*S*)-**132** gave optically enriched SWNTs for the first time (Fig. 21). The geometries of the complexes between (*S*)-**132** and (*M*)- or (*P*)-SWNT were optimized by MM calculations. The two porphyrin rings in (*S*)-**132** fit nicely to the curved surface of the SWNTs via π–π stacking interactions. Additional π–π stacking interactions took place between three phenyl rings in (*S*)-**132** and the SWNT surface at a distance of 3.4 Å. In addition, a CH/π interaction was also observed between a hydrogen atom of the benzene ring bridging the two porphyrins in (*S*)-**132** and the SWNT surface at a distance of 2.8 Å. These interactions are proposed to discriminate the helical sense of the SWNTs. The complex between (*S*)-**132** and (*P*)-SWNT was more stable by −0.32 kcal/mol than that between (*S*)-**132** and (*M*)-SWNT, which agrees qualitatively with the experimental results. Interestingly, as compared with the 1,3-phenylene-bridged diporphyrin **132**, the 2,6-pyridylene-bridged counterpart **133** showed the improved ability in the chiral recognition and extraction of the SWNTs [49]. On the other hand, the 3,6-carbazolylene-bridged diporphyrin **134** enhanced both abundance and optical purity of the other SWNT isomer that slightly differs in the roll-up angle and diameter [50].

Conclusions

Here we overviewed synthetic chiral macrocyclic receptors. Synthetic receptors have an advantage of design flexibility, and macrocyclic structures not only provide binding sites but also function as scaffolds for the construction of chiral spaces. Various intermolecular interactions can take place around the macrocyclic frameworks, such as the ion–dipole interactions in crown ethers, the CH/π and π–π interactions in calixarenes, hydrogen bonding and salt formation in macrocyclic amides and amines, and π–π stacking and metal coordination in porphyrins. Additional functional groups on the periphery of the macrocyclic platforms can also act as the interaction sites. Accordingly, chiral macrocyclic receptors can show a high degree of chiral recognition/discrimination based on the functional groups that are arrayed and fixed in appropriate positions (preorganization). Optical resolution by HPLC is based on enantioselective binding (chiral recognition), while chiral discrimination in NMR results from the differential anisotropic effect and the differential stability (enantioselective binding). Although the principle of chiral HPLC is different from that of chiral NMR, both of them require excellent chiral receptors. The performance of chiral receptors strongly depends on their molecular structures. Obviously, simple but intelligent receptors will contribute to the practical application to CSP and CSA. In addition, complex but sophisticated receptors capable of displaying an extraordinary level of functions need to be pursued at the same time. In the latter case, we need to take full advantage of the cooperative multiple interactions as can be seen in enzymes or antibodies, which can sustain life based on high affinity and enantioselectivity for the transition- or ground-state structures. Much effort will be needed to achieve such a high level. Although there are excellent non-macrocyclic receptors, they are not included here. Some of the synthetic receptors introduced here, their derivatives, and new receptors will play an important role in the field of chiral analysis and separation.

Acknowledgments The author thanks the organizing committee of Association of Research for Host–Guest and Supramolecular Chemistry (Japan) for giving him "HGCS Japan Award of Excellence 2011" and the opportunity of writing this review. The author is grateful to Professors Takashi Sakai and Toshinobu Korenaga (Okayama University) for their valuable suggestions and discussions. The author also thanks all of the collaborators. His works were partly supported by Grant for Research for Promoting Technological Seeds from Japan Science and Technology Agency (JST), Okayama Foundation for Science and Technology, and Daicel Chemical Industries.

References

1. Tsukamoto, M., Kagan, H.B.: Recent advances in the measurement of enantiomeric excesses. Adv. Synth. Catal. **344**, 453–463 (2002)
2. Anslyn, E.V.: Supramolecular analytical chemistry. J. Org. Chem. **72**, 687–699 (2007)
3. Pu, L.: Enantioselective fluorescent sensors: a tale of BINOL. Acc. Chem. Res. **45**, 150–163 (2012)
4. Pirkle, W.H., Pochapsky, T.C.: Considerations of chiral recognition relevant to the liquid chromatographic separation of enantiomers. Chem. Rev. **89**, 347–362 (1989)
5. Okamoto, Y., Yashima, E.: Polysaccharide derivatives for chromatographic separation of enantiomers. Angew. Chem. Int. Ed. **37**, 1020–1043 (1998)
6. Gasparrini, F., Misiti, D., Villani, C.: High-performance liquid chromatography chiral stationary phases based on low-molecular-mass selectors. J. Chromatogr. A **906**, 35–50 (2001)
7. Tachibana, K., Ohnishi, A.: Reversed-phase liquid chromatographic separation of enantiomers on polysaccharide type chiral stationary phases. J. Chromatogr. A **906**, 127–154 (2001)
8. Gübitz, G., Schmid, M.G. (eds.): Chiral Separations: Methods and Protocols. Humana, Totowa (2004)
9. Parker, D.: NMR determination of enantiomeric purity. Chem. Rev. **91**, 1441–1457 (1991)
10. Wenzel, T.J.: Discrimination of chiral compounds using NMR spectroscopy. Wiley, New Jersey (2007)
11. Sousa, L.R., Sogah, G.D.Y., Hoffman, D.H., Cram, D.J.: Host–guest complexation. 12. Total optical resolution of amine and

amino ester salts by chromatography. J. Am. Chem. Soc. **100**, 4569–4576 (1978)
12. Hirose, K., Nakamura, T., Nishioka, R., Ueshige, T., Tobe, Y.: Preparation and evaluation of novel chiral stationary phases covalently bound with chiral pseudo-18-crown-6 ethers. Tetrahedron Lett. **44**, 1549–1551 (2003)
13. Hirose, K., Yongzhu, J., Nakamura, T., Nishioka, R., Ueshige, T., Tobe, Y.: Chiral stationary phase covalently bound with a chiral pseudo-18-crown-6 ether for enantiomer separation of amino compounds using a normal mobile phase. Chirality **17**, 142–148 (2005)
14. Yongzhu, J., Hirose, K., Nakamura, T., Nishioka, R., Ueshige, T., Tobe, Y.: Preparation and evaluation of a chiral stationary phase covalently bound with a chiral pseudo-18-crown-6 ether having a phenolic hydroxy group for enantiomer separation of amino compounds. J. Chromatogr. A **1129**, 201–207 (2006)
15. Tsubaki, K., Tanima, D., Nuruzzaman, M., Kusumoto, T., Fuji, K., Kawabata, T.: Visual enantiomeric recognition of amino acid derivatives in protic solvents. J. Org. Chem. **70**, 4609–4616 (2005)
16. Haino, T., Fukuoka, H., Iwamoto, H., Fukazawa, Y.: Synthesis and enantioselective recognition of a calix[5]arene-based chiral receptor. Supramol. Chem. **20**, 51–57 (2008)
17. Durmaz, M., Yilmaz, M., Sirit, A.: Synthesis of chiral calix[4]arenes bearing aminonaphthol moieties and their use in the enantiomeric recognition of carboxylic acids. Org. Biomol. Chem. **9**, 571–580 (2011)
18. Shirakawa, S., Moriyama, A., Shimizu, S.: Design of a novel inherently chiral calix[4]arene for chiral molecular recognition. Org. Lett. **9**, 3117–3119 (2007)
19. Shirakawa, S., Moriyama, A., Shimizu, S.: Synthesis, optical resolution and enantiomeric recognition ability of novel, inherently chiral calix[4]arenes: trial application to asymmetric reactions as organocatalysts. Eur. J. Org. Chem. 5957–5964 (2008)
20. Yanagihara, R., Tominaga, M., Aoyama, Y.: Chiral host–guest interaction. A water-soluble calix[4]resorcarene having L-proline moieties as a non-lanthanide chiral NMR shift reagent for chiral aromatic guests in water. J. Org. Chem. **59**, 6865–6867 (1994)
21. O'Farrell, C.M., Chudomel, J.M., Collins, J.M., Dignam, C.F., Wenzel, T.J.: Water-soluble calix[4]resorcinarenes with hydroxyproline groups as chiral NMR solvating agents. J. Org. Chem. **73**, 2843–2851 (2008)
22. Hagan, K.A., O'Farrell, C.M., Wenzel, T.J.: Water-soluble calix[4]resorcinarenes with hydroxyproline groups as chiral NMR solvating agents for phenyl- and pyridyl-containing compounds. Eur. J. Org. Chem. 4825–4832 (2009)
23. Pham, N.H., Wenzel, T.J.: A water-soluble calix[4]resorcinarene with α-methyl-L-prolinylmethyl groups as a chiral NMR solvating agent. J. Org. Chem. **76**, 986–989 (2011)
24. Miyaji, H., Hong, S.-J., Jeong, S.-D., Yoon, D.-W., Na, H.-K., Hong, J., Ham, S., Sessler, J.L., Lee, C.-H.: A binol-strapped calix[4]pyrrole as a model chirogenic receptor for the enantioselective recognition of carboxylate anions. Angew. Chem. Int. Ed. **46**, 2508–2511 (2007)
25. Ema, T., Tanida, D., Sakai, T.: Versatile and practical chiral shift reagent with hydrogen-bond donor/acceptor sites in a macrocyclic cavity. Org. Lett. **8**, 3773–3775 (2006)
26. Ema, T., Tanida, D., Sakai, T.: Versatile and practical macrocyclic reagent with multiple hydrogen-bonding sites for chiral discrimination in NMR. J. Am. Chem. Soc. **129**, 10591–10596 (2007)
27. Ema, T., Tanida, D., Hamada, K., Sakai, T.: Tuning the chiral cavity of macrocyclic receptor for chiral recognition and discrimination. J. Org. Chem. **73**, 9129–9132 (2008)
28. Ema, T., Tanida, D., Sugita, K., Sakai, T., Miyazawa, K., Ohnishi, A.: Chiral selector with multiple hydrogen-bonding sites in a macrocyclic cavity. Org. Lett. **10**, 2365–2368 (2008)
29. Ema, T., Hamada, K., Sugita, K., Nagata, Y., Sakai, T., Ohnishi, A.: Synthesis and evaluation of chiral selectors with multiple hydrogen-bonding sites in the macrocyclic cavities. J. Org. Chem. **75**, 4492–4500 (2010)
30. Uccello-Barretta, G., Balzano, F., Martinelli, J., Berni, M.-G., Villani, C., Gasparrini, F.: NMR enantiodiscrimination by cyclic tetraamidic chiral solvating agents. Tetrahedron Asymmetry **16**, 3746–3751 (2005)
31. González, S., Peláez, R., Sanz, F., Jiménez, M.B., Morán, J.R., Caballero, M.C.: Macrocyclic chiral receptors toward enantioselective recognition of naproxen. Org. Lett. **8**, 4679–4682 (2006)
32. Ma, F., Ai, L., Shen, X., Zhang, C.: New macrocyclic compound as chiral shift reagent for carboxylic acids. Org. Lett. **9**, 125–127 (2007)
33. Ma, F., Shen, X., Ming, X., Wang, J., Ou-Yang, J., Zhang, C.: The novel macrocyclic compounds as chiral solvating agents for determination of enantiomeric excess of carboxylic acids. Tetrahedron Asymmetry **19**, 1576–1586 (2008)
34. Ma, F., Shen, X., Ou-Yang, J., Deng, Z., Zhang, C.: Macrocyclic compounds as chiral solvating agents for phosphinic, phosphonic, and phosphoric acids. Tetrahedron Asymmetry **19**, 31–37 (2008)
35. González-Álvarez, A., Alfonso, I., Gotor, V.: An azamacrocyclic receptor as efficient polytopic chiral solvating agent for carboxylic acids. Tetrahedron Lett. **47**, 6397–6400 (2006)
36. Busto, E., González-Álvarez, A., Gotor-Fernández, V., Alfonso, I., Gotor, V.: Optically active macrocyclic hexaazapyridinophanes decorated at the periphery: synthesis and applications in the NMR enantiodiscrimination of carboxylic acids. Tetrahedron **66**, 6070–6077 (2010)
37. González-Álvarez, A., Alfonso, I., Díaz, P., García-España, E., Gotor, V.: A highly enantioselective abiotic receptor for malate dianion in aqueous solution. Chem. Commun. 1227–1229 (2006)
38. Tanaka, K., Fukuda, N., Fujiwara, T.: Trianglamine as a new chiral shift reagent for secondary alcohols. Tetrahedron Asymmetry **18**, 2657–2661 (2007)
39. Tanaka, K., Fukuda, N.: 'Calixarene-like' chiral amine macrocycles as novel chiral shift reagents for carboxylic acids. Tetrahedron Asymmetry **20**, 111–114 (2009)
40. Tanaka, K., Nakai, Y., Takahashi, H.: Efficient NMR chiral discrimination of carboxylic acids using rhombamine macrocycles as chiral shift reagent. Tetrahedron Asymmetry **22**, 178–184 (2011)
41. Ema, T., Ouchi, N., Doi, T., Korenaga, T., Sakai, T.: Highly sensitive chiral shift reagent bearing two zinc porphyrins. Org. Lett. **7**, 3985–3988 (2005)
42. Ema, T., Ura, N., Eguchi, K., Ise, Y., Sakai, T.: Chiral porphyrin dimer with a macrocyclic cavity for intercalation of aromatic guests. Chem. Commun. **47**, 6090–6092 (2011)
43. Ema, T., Ura, N., Eguchi, K., Sakai, T.: Molecular recognition of chiral diporphyrin receptor with a macrocyclic cavity for intercalation of aromatic compounds. Bull. Chem. Soc. Jpn. **85**, 101–109 (2012)
44. Simeonov, K.S., Amsharov, K.Y., Jansen, M.: Connectivity of the chiral D_2-symmetric isomer of C_{76} through a crystal-structure determination of $C_{76}Cl_{18}{\cdot}TiCl_4$. Angew. Chem. Int. Ed. **46**, 8419–8421 (2007)
45. Shoji, Y., Tashiro, K., Aida, T.: One-pot enantioselective extraction of chiral fullerene C_{76} using a cyclic host carrying an asymmetrically distorted, highly π-basic porphyrin module. J. Am. Chem. Soc. **132**, 5928–5929 (2010)
46. Shoji, Y., Tashiro, K., Aida, T.: Sensing of chiral fullerenes by a cyclic host with an asymmetrically distorted π-electronic component. J. Am. Chem. Soc. **128**, 10690–10691 (2006)
47. Komatsu, N.: Separation of nanocarbons by molecular recognition. J. Incl. Phenom. Macrocycl. Chem. **61**, 195–216 (2008)

48. Peng, X., Komatsu, N., Bhattacharya, S., Shimawaki, T., Aonuma, S., Kimura, T., Osuka, A.: Optically active single-walled carbon nanotubes. Nat. Nanotechnol. **2**, 361–365 (2007)
49. Peng, X., Komatsu, N., Kimura, T., Osuka, A.: Improved optical enrichment of SWNTs through extraction with chiral nanotweezers of 2,6-pyridylene-bridged diporphyrins. J. Am. Chem. Soc. **129**, 15947–15953 (2007)
50. Peng, X., Komatsu, N., Kimura, T., Osuka, A.: Simultaneous enrichments of optical purity and (n, m) abundance of SWNTs through extraction with 3,6-carbazolylene-bridged chiral diporphyrin nanotweezers. ACS Nano **2**, 2045–2050 (2008)