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Synthesis and Evaluation of Chiral Selectors with Multiple Hydrogen-Bonding Sites in the Macrocyclic Cavities

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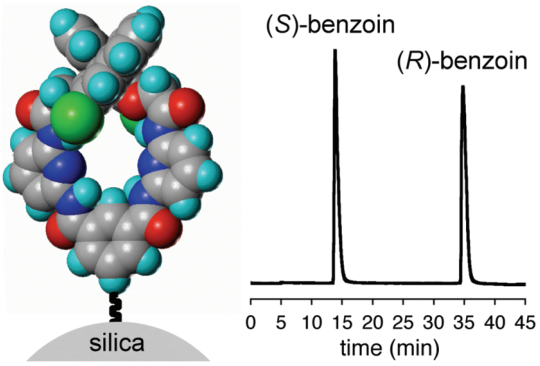

Chiral macrocycles with the hydrogen bond donor/acceptor sites in the cavity were synthesized and covalently bonded to silica gel to give chiral stationary phases (CSPs), which showed excellent abilities to resolve various chiral compounds including ketones, esters, carboxylic acids, sulfoxides, amines, amino acid derivatives, and metal complexes. The effect of the linker connecting the macrocyclic moiety to silica was examined, and a more electronegative substituent was found to be better. Various organic solvents could be used as the mobile phase to optimize the resolution efficiency of the CSPs. Although the separation factors (α) tended to decrease with an increase in the solvent polarity, remarkable solvent tolerance was also observed. In some cases, even MeCN and MeOH could be used for the complete resolution of enantiomers. The MM calculations suggested that the chiral recognition of $Co(acac)_3$ is achieved by a combination of steric interactions and hydrogen bonds between the carbonyl O atom coordinated to the Co atom and the macrocyclic amide NH groups. The attachment of substituents to the 3,3′-positions of the binaphthyl moiety improved chiral HPLC performance in some cases. In particular, **CSP-1d**, having the Br atoms, showed the best performance for several analytes.

Introduction

Chiral HPLC using a chiral column is a well-established method for the determination of the enantiomeric purity.[1] 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

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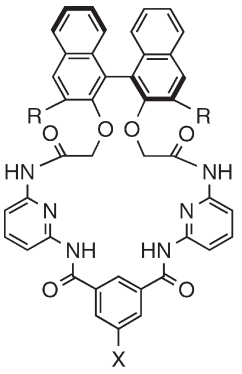
CHART 1



Chirabite-AR: R = H, X = NO_2

CSP-1a: R = H, X = $OCH_2CONH(CH_2)_3$-silica

CSP-1b: R = H, X = $CONH(CH_2)_3$-silica

CSP-1c: R = CO_2Me, X = $CONH(CH_2)_3$-silica

CSP-1d: R = Br, X = $CONH(CH_2)_3$-silica

CSP-1e: R = C_6H_5, X = $CONH(CH_2)_3$-silica

to silica gel.[1−8] A covalently immobilized CSP is preferred because the chromatographic conditions can be optimized by changing the mobile phases (solvents). Polysaccharides,[2] antibiotics,[3] cyclodextrins,[1d] crown ethers,[5] cyclophanes,[6,8] binaphthyls,[4,5a,8] and others[1,7] have been used as chiral selectors. Further advancement of chiral selectors will assist the research and development in academia and industry more powerfully.

Recently, we have reported that a synthetic macrocycle with multiple hydrogen-bonding sites in the cavity can function as an excellent chiral selector.[8] We expected that such a bifunctional host bearing both hydrogen-bond donor and acceptor sites could bind a wide range of compounds. Indeed, **CSP-1a**,**b** (Chart 1) could resolve a variety of chiral compounds not only in organic solvents but also in CO_2-based mobile phases.[8] The macrocyclic moiety of the chiral selector was originally developed as an NMR chiral solvating agent called Chirabite-AR (Chart 1),[9] where 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.[10] In view of these results, we prepared **CSP-1c**−**e** (Chart 1) as well to investigate the effect of the substituent at the 3,3′-positions of the binaphthyl moiety on chiral HPLC performance. Figure 1 illustrates the comparison of the size and shape of the macrocyclic moieties in **CSP-1**. Here we report the synthesis and evaluation of these macrocyclic chiral selectors.

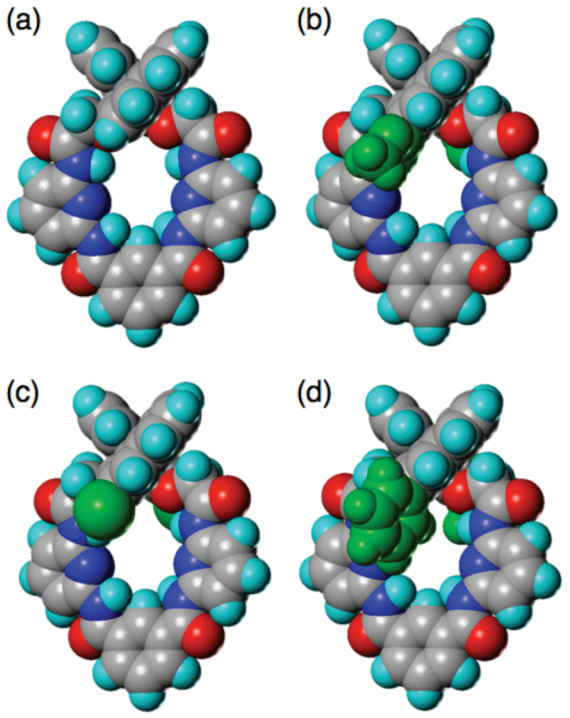


FIGURE 1. Chiral selectors in (a) **CSP-1a**,**b**, (b) **CSP-1c**, (c) **CSP-1d**, and (d) **CSP-1e**.

Results and Discussion

CSP-1a−**e** were synthesized as shown in Scheme 1. Binaphthols **2**−**5** were allowed to react with α-bromo esters to give ethers **6**−**9** (91−99%), which were then converted to acid chlorides **10**−**13**. The coupling of acid chlorides **10**−**13** with diamine **14** or **15** afforded macrocycles **16** and **19**−**22** in good yields (64−79%). The substituents at the 3,3′-positions of the binaphthyl moiety in **11**−**13** did not affect the yields of the cyclizations. The deprotection of the benzyl group in **16** (85%) followed by the attachment of the *tert*-butyl ester moiety to **17** gave **18** in 72% yield. The *tert*-butyl ester group in **18**−**22** was cleaved quantitatively by treatment with trifluoroacetic acid. The resulting acids were allowed to combine with 3-aminopropyl silica gel (Wakosil 5NH2, mean particle size 5 μm, mean pore size 12 nm, specific surface area 300 m^2/g) to give **CSP-1a**−**e**, which were packed in a stainless steel column

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SCHEME 1. Preparation of CSP-1

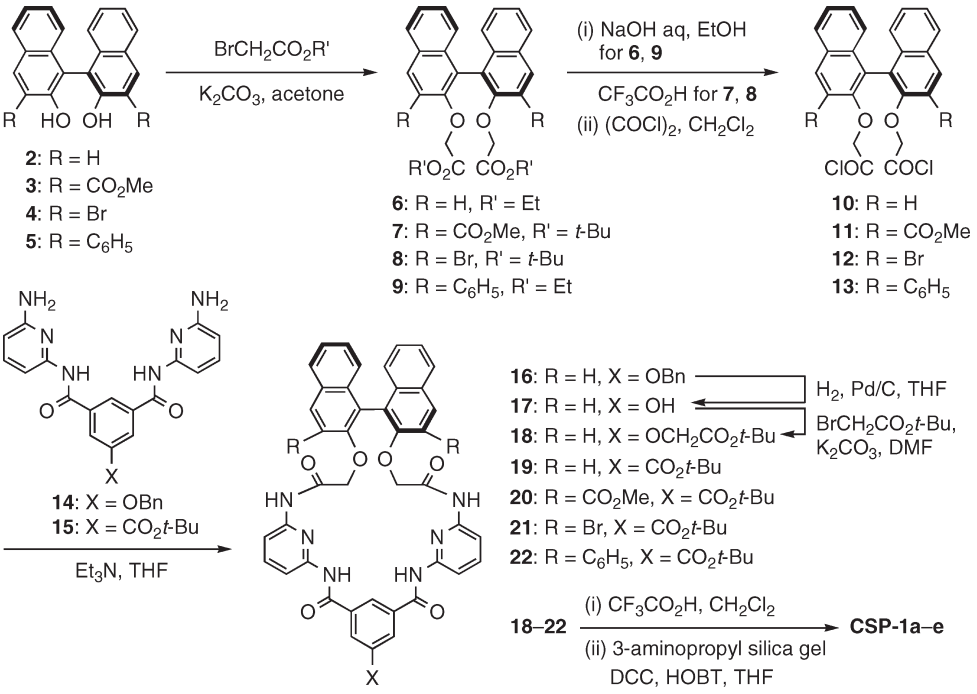
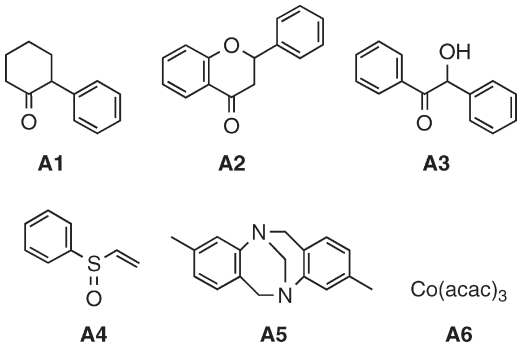


CHART 2



(∅ 0.46 × 25 cm) after the coverage of the macrocycle on silica had been adjusted to 0.17−0.19 mmol/g as determined by elemental analysis. The abilities of **CSP-1a**−**e** to resolve chiral analytes **A1**−**A6** (Chart 2) were then evaluated by HPLC. Four eluents were examined: hexane/*i*-PrOH (eluent I), hexane/$CHCl_3$ (eluent II), MeCN (eluent III), and MeOH (eluent IV). The chromatographic results are summarized in Table 1, and all of the chromatograms are given in the Supporting Information, among which the best chromatograms for **A1**−**A6** are shown in Figure 2. Figure 3 compares the separation factors (α), taken from Table 1, for the resolution of **A1**−**A6** on **CSP-1b**−**e** using eluents I and II.

Comparisons between **CSP-1a** and **CSP-1b** indicate that the α values are slightly larger for **CSP-1b** than for **CSP-1a** in most cases (Table 1). This difference results from the linker moiety; a more electronegative substituent (X in Chart 1) can enhance the hydrogen-bond donor ability of the lower amide groups in the macrocycle, which may be an important factor in enantioselective binding as is the case for Chirabite-AR.[9b] In the previous study, we demonstrated that the NO_2 group in Chirabite-AR enhanced not only the binding ability but also the degree of enantioselectivity.[9b] On the other hand, we consider that rigidity or flexibility of the linker is a less important factor in this case. We employed the amide linker for further investigations.

Remarkable solvent tolerance was observed although the α values had a tendency to decrease with an increase in the solvent polarity (Table 1). For example, **CSP-1b** completely resolved benzoin (**A3**) and $Co(acac)_3$ (**A6**) even in MeCN, and **A3** was completely resolved even in MeOH. These results were unexpected because the ability of Chirabite-AR to discriminate between enantiomers via NMR deteriorated in $CDCl_3$ solutions containing methanol-d_4 or in acetone-d_6.[9b] In this study, we determined the binding constants (K_a) of the relevant host **19** for (*R*)- and (*S*)-**A3** in $CDCl_3$ to be 228 and 14 M^{-1}, respectively, by means of NMR titrations (Table 2),[11,12] while we confirmed that the elution order on **CSP-1b** was (*S*)-**A3** followed by (*R*)-**A3** in all the eluents. The fact that (*R*)-**A3**, having a higher affinity for the (*R*)-host, eluted more slowly in all cases suggests that the hydrogen bonds are formed in the macrocyclic cavity of **CSP-1b** even in the polar solvents and that they are stronger at the surface of silica than in solution. Tröger base (**A5**) is unique in that MeCN was the best eluent (Figure 2e);

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TABLE 1. Chromatographic Data for the Resolution of Racemic Compounds on CSP-1[a]

		separation factor α[b] (peak separation)[c]			
CSP	analyte	eluent I	eluent II	eluent III	eluent IV
CSP-1a	**A1**	1.14 (B)	1.31 (B)	1.00 (C)	1.00 (C)
CSP-1b	**A1**	1.15 (A)	1.44 (A)	1.26 (C)	1.00 (C)
CSP-1c	**A1**	1.00 (C)	1.00 (C)	1.00 (C)	1.79 (B)
CSP-1d	**A1**	1.28 (A)	1.47 (A)	1.88 (B)	1.00 (C)
CSP-1e	**A1**	1.00 (C)	1.00 (C)	1.00 (C)	1.00 (C)
CSP-1a	**A2**	1.07 (B)	1.07 (C)	1.00 (C)	1.00 (C)
CSP-1b	**A2**	1.09 (B)	1.07 (B)	1.00 (C)	1.06 (C)
CSP-1c	**A2**	1.00 (C)	1.00 (C)	1.00 (C)	1.00 (C)
CSP-1d	**A2**	1.06 (B)	1.05 (B)	1.00 (C)	1.00 (C)
CSP-1e	**A2**	1.00 (C)	1.00 (C)	1.00 (C)	1.00 (C)
CSP-1a	**A3**	1.87 (A)	2.26 (A)	2.19 (A)	1.54 (B)
CSP-1b	**A3**	1.83 (A)	2.43 (A)	2.38 (A)	1.70 (A)
CSP-1c	**A3**	1.00 (C)	1.18 (B)	1.00 (C)	1.00 (C)
CSP-1d	**A3**	2.41 (A)	2.96 (A)	7.12 (A)	2.13 (A)
CSP-1e	**A3**	2.17 (A)	2.19 (A)	3.12 (B)	1.00 (C)
CSP-1a	**A4**	1.00 (C)	1.24 (B)	1.17 (B)	1.00 (C)
CSP-1b	**A4**	1.06 (B)	1.51 (A)	1.04 (C)	1.08 (C)
CSP-1c	**A4**	1.19 (A)	1.29 (A)	1.00 (C)	1.00 (C)
CSP-1d	**A4**	1.77 (A)	2.35 (A)	2.66 (A)	1.91 (B)
CSP-1e	**A4**	1.39 (A)	1.60 (A)	1.92 (B)	1.00 (C)
CSP-1a	**A5**	1.00 (C)	1.00 (C)	1.37 (B)	1.00 (C)
CSP-1b	**A5**	1.08 (B)	1.08 (B)	1.25 (B)	1.00 (C)
CSP-1c	**A5**	1.00 (C)	1.00 (C)	1.00 (C)	1.00 (C)
CSP-1d	**A5**	1.00 (C)	1.00 (C)	1.13 (B)	1.00 (C)
CSP-1e	**A5**	1.00 (C)	1.00 (C)	1.00 (C)	1.00 (C)
CSP-1a	**A6**	1.57 (B)	1.50 (B)	1.61 (B)	1.00 (C)
CSP-1b	**A6**	1.75 (A)	1.67 (A)	1.61 (A)	1.20 (B)
CSP-1c	**A6**	1.19 (B)	1.00 (C)	1.00 (C)	1.00 (C)
CSP-1d	**A6**	1.75 (A)	1.21 (B)	2.29 (A)	1.00 (C)
CSP-1e	**A6**	1.67 (A)	1.00 (C)	5.00 (B)[d]	1.00 (C)

[a] **CSP-1** packed in a stainless steel column (∅ 0.46 × 25 cm) was used for HPLC: flow rate 1.0 mL/min (0.4 mL/min for **CSP-1e**/eluent III), detection 254 nm (225 nm for **A1**), 25 °C, eluent I = hexane/*i*-PrOH (9:1), eluent II = hexane/$CHCl_3$ (for the composition, see the Supporting Information), eluent III = MeCN, eluent IV = MeOH. [b] Calculated from k_2'/k_1', where $k_1' = (t_1 - t_0)/t_0$ and $k_2' = (t_2 - t_0)/t_0$. The retention times for the faster and slower moving enantiomers are designated as t_1 and t_2, respectively, and that for 1,3,5-tri-*tert*-butylbenzene used as a void volume marker is designated as t_0. [c] A = complete or almost complete separation, B = partial separation, C = little or no separation. [d] This α value is not reliable because the retention time was very short.

eluents I and II, which are more hydrophobic, were ineffective (Table 1). Although the reason why MeCN was much better is unknown, this is a good example indicating that the resolution efficiency of CSP can be optimized just by changing the eluent, which is important from a practical viewpoint.

CSP-1b showed the best HPLC performance for **A3** (Table 1), and the relevant host **19** exhibited highly enantioselective binding for **A3** ($K_a(R)/K_a(S) = 16$) as described above (Table 2). Because this selectivity factor was much higher than those reported previously,[9] we examined the molecular recognition mode in the **19**−**A3** complex by ^{1}H NMR. When **19** and (*R*)-**A3** were mixed in a 1:1 ratio, the NH signal of **19** and the OH signal of (*R*)-**A3** shifted downfield by 0.49 and 1.13 ppm, respectively (Figure 4a−c). On the other hand, when **19** and (*S*)-**A3** were mixed in a 1:1 ratio, the NH signal of **19** and the OH signal of (*S*)-**A3** shifted downfield only by 0.22 and 0.53 ppm, respectively (not shown). It is therefore likely that (*R*)-**A3** is bound to **19** via the three hydrogen bonds as shown in Figure 4d, while unfavorable steric interactions between **19** and (*S*)-**A3** weakens the hydrogen bonding, leading to the highly enantioselective binding.[12] We expect that this macrocyclic host has a good ability to recognize the chirality of other α-hydroxy ketones.

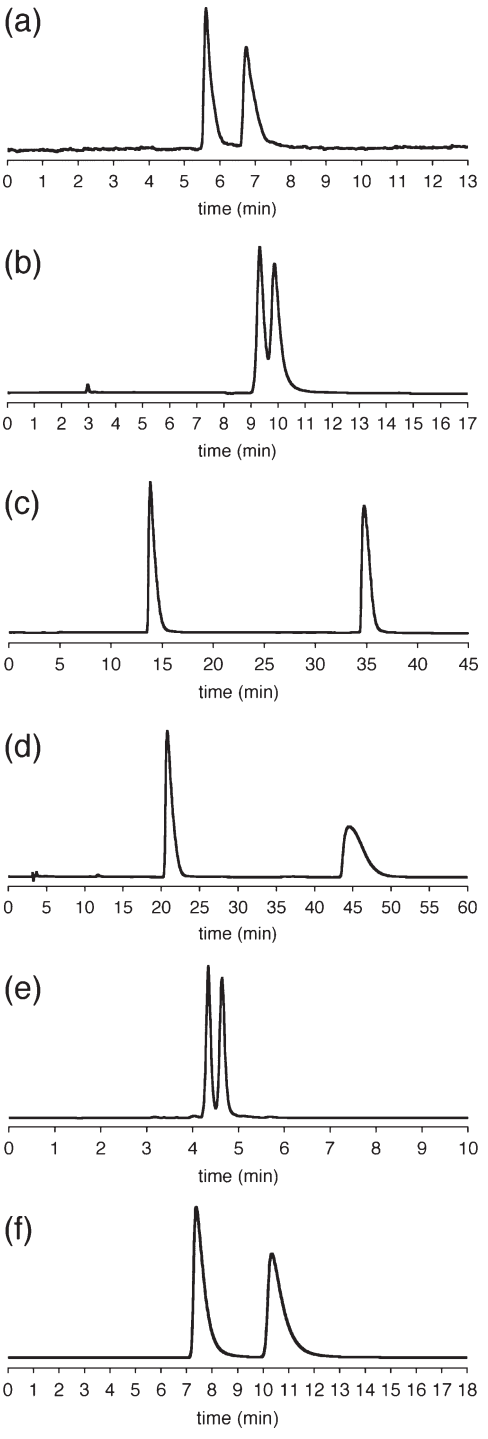


FIGURE 2. Chromatographic resolution of (a) **A1** on **CSP-1d** (eluent II), (b) **A2** on **CSP-1b** (eluent I), (c) **A3** on **CSP-1d** (eluent II), (d) **A4** on **CSP-1d** (eluent II), (e) **A5** on **CSP-1b** (eluent III), and (f) **A6** on **CSP-1b** (eluent II). For the detailed analytical conditions, see the Supporting Information.

Intriguing results were obtained for **A6**, which happened to be used as one of our standard samples for the CSP assay.[13] We did not expect such successful separation of

(13) Several CSPs have been reported to be effective for the resolution of **A6**. For example, see refs 1b and 2e. In ref 2e, it is mentioned that **A6** is usually rather difficult to resolve on commercially available columns.

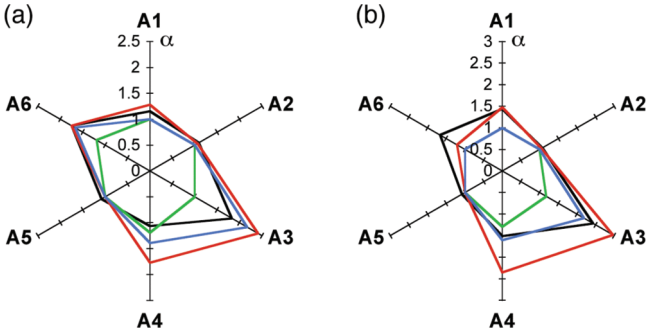


FIGURE 3. Comparison of the α values for the resolution of **A1**−**A6** on **CSP-1b**−**e** using (a) eluent I and (b) eluent II. The data are taken from Table 1. The values for **CSP-1b**, **CSP-1c**, **CSP-1d**, and **CSP-1e** are shown in black, green, red, and blue, respectively.

TABLE 2. Binding Constants of 19−22 for A3 and Enantioselectivity

	K_a (M^{-1})[a]		enantioselectivity	
host	(*R*)-**A3**	(*S*)-**A3**	$K_a(R)/K_a(S)$	α[b]
19	228	14	16	2.43
20	33	5	7	1.18
21	127	8	16	2.96
22	83	7	12	2.19

[a]In $CDCl_3$ at 22 °C. The K_a values were calculated by the nonlinear least-squares method. The standard deviations are given in the Supporting Information. [b]Separation factors for **CSP-1b**−**e** are taken from Table 1.

the metal complex before HPLC evaluation (Figure 2f). Because the chiral recognition mechanism previously proposed for Chirabite-AR could not be applied directly to **A6**, we performed MM calculations on the complexes between the macrocyclic moiety of **CSP-1b** and Λ- or Δ-**A6**. The optimized structures are shown in Figure 5. In both cases, interestingly, the methyl group of the acetylacetonate ligand penetrates through the macrocyclic cavity, which is necessary for attractive interactions to take place, and the carbonyl O atom coordinated to the Co atom is hydrogen bonded with the two amide NH groups in the macrocyclic cavity. Although the origin of enantioselectivity is unclear from the two optimized structures, the complex of the macrocycle with Δ-**A6** is apparently destabilized by ca. 1.9 kcal/mol relative to that with Λ-**A6**. It is likely that the former is less stable because of unfavorable steric interactions. Based on the computational calculations, we predicted that Δ-**A6**, which was postulated to have a lower affinity for the (*R*)-host, would elute first. Indeed, this prediction was found to be correct by eluting optically active **A6** that had been prepared by chiral HPLC and characterized by CD spectra (Supporting Information).[14]

Synthetic chiral selectors are attractive because the structures can be altered and tuned easily. The variation in the size and shape of the macrocyclic cavity in **CSP-1b**−**e** (Figure 1) prompted us to examine chiral HPLC performance. As shown in Figure 2, **A1**, **A3**, and **A4** were best resolved by **CSP-1d**, whereas **A2** and **A5** were best resolved by **CSP-1b**, the unsubstituted CSP. Although **CSP-1b** and **CSP-1d** had comparable capacities to resolve **A6**, the former was slightly better. Clearly, the attachment of a substituent had a beneficial effect on the HPLC performance in several cases. In particular, attaching the Br atoms (**CSP-1d**) produced dramatic improvement in the resolution of **A4** (Table 1 and Figure 3); the α values for **CSP-1d** toward **A4** were much greater than those for **CSP-1b**. Interestingly, **CSP-1d** was superior to **CSP-1e** in all cases. Unexpectedly, **CSP-1c**, having the methoxycarbonyl group as the substituent, showed very poor performance (Table 1 and Figure 3).

To investigate the origin of this substituent effect, we selected **A3**, which was the most sensitive to the substituent of the chiral selector, and determined the K_a values of **19**−**22** for **A3** in $CDCl_3$. Table 2 indicates that the K_a values for each enantiomer of **A3** decrease in the following order: **19** > **21** > **22** > **20**. This order

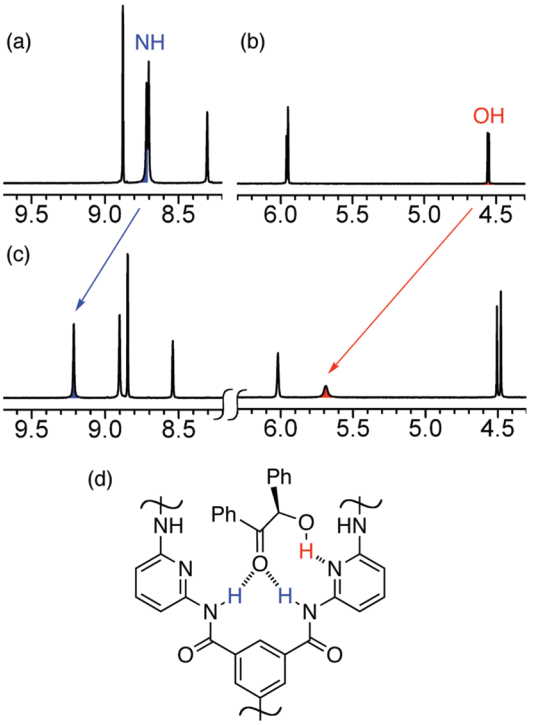


FIGURE 4. Selected regions of ^1H NMR spectra of (a) **19**, (b) (*R*)-**A3**, and (c) a 1:1 mixture of **19** and (*R*)-**A3** in $CDCl_3$ at 22 °C. (d) Plausible hydrogen bonds in the complex of **19** with (*R*)-**A3**.

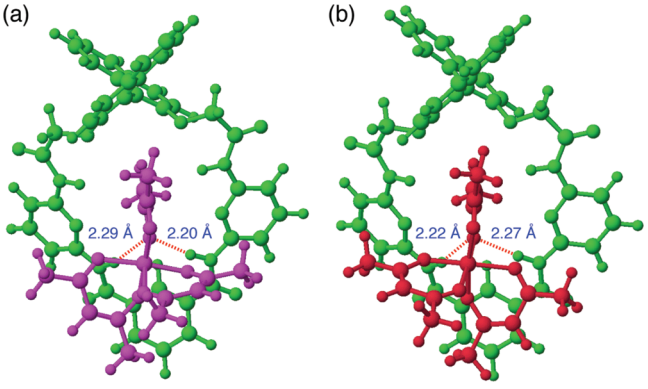
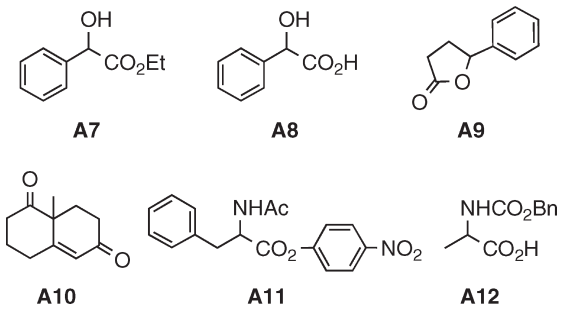


FIGURE 5. Optimized structures for the complexes between the macrocyclic moiety of **CSP-1b** and (a) Λ-**A6** and (b) Δ-**A6**. The macrocyclic moiety is shown in green, and Λ-**A6** and Δ-**A6** are shown in magenta and red, respectively. The geometries were optimized by MM3 calculations with CAChe WorkSystem Pro ver. 5.02 (Fujitsu).

(14) (a) Von Dreele, R. B.; Fay, R. C. *J. Am. Chem. Soc.* **1971**, *93*, 4936–4938. (b) Jonás, I.; Nordén, B. *Inorg. Nucl. Chem. Lett.* **1976**, *12*, 43–47.

CHART 3



seems to reflect the degree of steric hindrance caused by the substituent of the host. Although the postulate that the methoxycarbonyl group is more bulky than the phenyl group is unusual, the former may be solvated more tightly. Importantly, a bulky substituent of the host reduced binding affinity for (*R*)-**A3** considerably, probably by a steric repulsion deteriorating the ideal hydrogen bonds shown in Figure 4d. In particular, the methoxycarbonyl and phenyl groups hindered the binding of (*R*)-**A3** rather than that of (*S*)-**A3**, which resulted in a drop in chiral recognition ability of **20** and **22**, respectively. We suppose that the same event occurred on **CSP-1c** and **CSP-1e**. Although the separation factor of **A3** was greater on **CSP-1d** ($\alpha = 2.96$) than on **CSP-1b** ($\alpha = 2.43$), this trend could not be seen for the corresponding hosts **21** and **19**, both of which showed comparable enantioselectivity for **A3** ($K_a(R)/K_a(S) = 16$, Table 2). This discrepancy might be due to the difference in the solvent used in the NMR titration ($CDCl_3$) and the HPLC analysis (hexane/$CHCl_3$ (7:3)).

We further characterized the two best CSPs, **CSP-1b** and **CSP-1d**, by eluting other chiral compounds **A7**−**A12** (Chart 3). The chromatograms for the resolution of **A7**−**A12** on **CSP-1b** or **CSP-1d** are shown in Figure 6. The compounds **A7**−**A9** and **A11** were better resolved by **CSP-1b**, while **A10** and **A12** were resolved more efficiently by **CSP-1d**. In view of the remarkable resolution of α-hydroxy ketone **A3** (Table 1 and Figure 2), we examined α-hydroxy ester **A7** and α-hydroxy acid **A8**. As a result, both of them were resolved very successfully (Figure 6a,b). In addition, lactone **A9** and diketone (Wieland−Miescher ketone) **A10** were also resolved well (Figure 6c,d), the latter of which is an important chiral building block that has been used in the total synthesis of more than 50 natural products including taxol.[15] Successful resolution of amino acid derivatives **A11** and **A12** (Figure 6e,f) convinced us of the excellence of **CSP-1b** and **CSP-1d**. Figure 6 also indicates that they are useful for the resolution of carboxylic acids such as **A8** and **A12**.

Conclusions

We have designed and synthesized chiral macrocycles with multiple hydrogen-bonding sites in the cavity. We expected that bifunctional hosts bearing both hydrogen-bond donor and acceptor sites could bind a wide range of compounds. Indeed, the macrocycles covalently immobilized on silica gel functioned as excellent chiral selectors for a variety of chiral compounds including ketones, esters, carboxylic acids, sulfoxides, amines, amino acid derivatives, and metal complexes. By changing the structure of the chiral selector and the mobile phase, nine analytes (**A1**, **A3**, **A4**, **A6**−**A9**, **A11**, and **A12**) were baseline resolved, and the others (**A2**, **A5**, and **A10**) resulted in partial resolution. The effect of the linker connecting the macrocyclic moiety to silica was examined, and a more electronegative substituent was found to be better. Although the separation factors (α) tended to decrease with an increase in the solvent polarity, remarkable

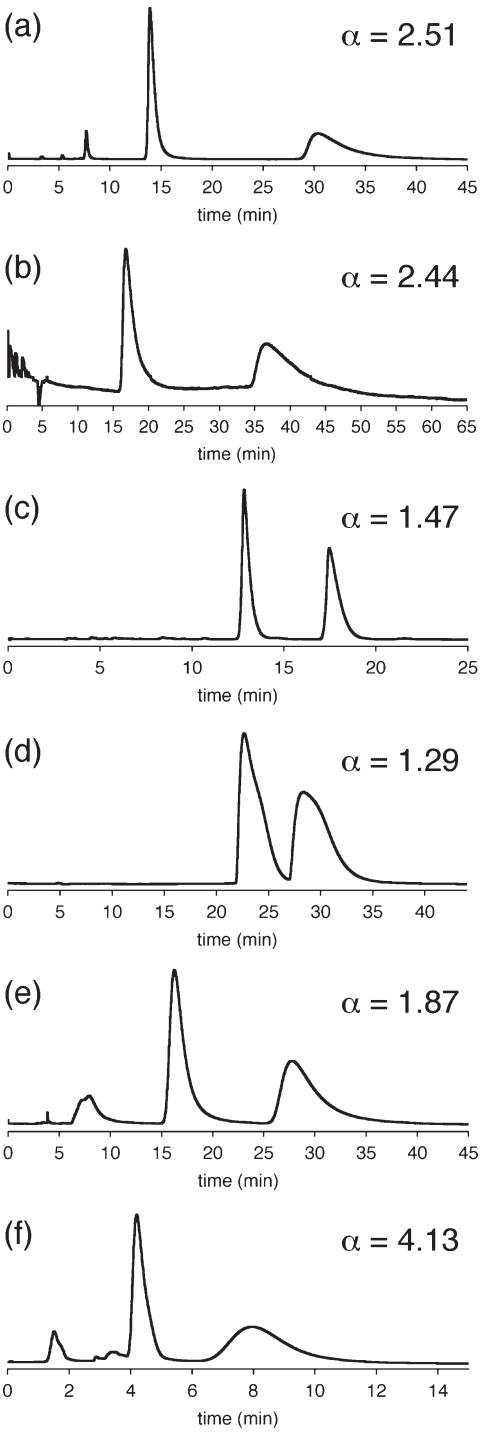


FIGURE 6. Chromatographic resolution of (a) **A7** on **CSP-1b** (hexane/*i*-PrOH (9:1)), (b) **A8** on **CSP-1b** (hexane/*i*-PrOH/CF_3CO_2H (80:20:0.1)), (c) **A9** on **CSP-1b** (hexane/$CHCl_3$ (7:3)), (d) **A10** on **CSP-1d** (hexane/*i*-PrOH/CF_3CO_2H (90:10:0.1)), (e) **A11** on **CSP-1b** (hexane/*i*-PrOH (6:4)), and (f) **A12** on **CSP-1d** (hexane/EtOH/CF_3CO_2H (25:75:0.1)). Flow rate 1.0 mL/min, detection 254 nm, 25 °C.

(15) Bui, T.; Barbas, C. F., III. *Tetrahedron Lett.* **2000**, *41*, 6951–6954.

solvent tolerance was also observed. The MM calculations suggested that the chiral recognition of $Co(acac)_3$ is achieved by a combination of steric interactions and hydrogen bonds between the carbonyl O atom coordinated to the Co atom and the macrocyclic amide NH groups. The attachment of the substituents to the 3,3′-positions of the binaphthyl moiety improved chiral HPLC performance in some cases. In particular, **CSP-1d**, having the Br atoms, showed the best results for **A1**, **A3**, **A4**, **A10**, and **A12**. We expect that the ability of these synthetic chiral selectors will be further improved by structural alteration in the future.

Experimental Section

General Methods. (*R*)-1,1′-Bi-2-naphthol ((*R*)-**2**), (*R*)-2,2′-dihydroxy-3,3′-bis(methoxycarbonyl)-1,1′-binaphthyl ((*R*)-**3**), and (*R*)-3,3′-dibromo-2,2′-dihydroxy-1,1′-binaphthyl ((*R*)-**4**) were purchased. (*R*)-2,2′-Dihydroxy-3,3′-diphenyl-1,1′-binaphthyl ((*R*)-**5**),[16] (*R*)-2,2′-bis[(ethoxycarbonyl)methoxy]-1,1′-binaphthyl ((*R*)-**6**),[9] (*R*)-2,2′-bis[(*tert*-butoxycarbonyl)methoxy]-3,3′-bis(methoxycarbonyl)-1,1′-binaphthyl ((*R*)-**7**),[10] *N*,*N*′-bis(6-amino-2-pyridinyl)-5-benzyloxy-1,3-benzenedicarboxamide (**14**),[8] and *N*,*N*′-bis(6-amino-2-pyridinyl)-5-*tert*-butoxycarbonyl-1,3-benzenedicarboxamide (**15**)[8] were prepared according to the literature, and they were characterized by ^{1}H NMR.

Chiral Macrocycle (*R*)-16. To a solution of (*R*)-**6** (1.27 g, 2.77 mmol) in EtOH (6 mL) was added 33% NaOH (6 mL), and the solution was heated at reflux for 38 h. After removal of EtOH, the mixture was acidified with concd HCl. The white precipitate formed was filtered and dried in vacuo. To a suspension of diacid (360 mg, 0.89 mmol) in dry CH_2Cl_2 (56 mL) were added $(COCl)_2$ (0.60 mL, 6.9 mmol) and DMF (1 drop). The mixture was stirred at room temperature for 4 h. The volatiles were removed by rotary evaporation, and the residue was dried in vacuo for 3 h. The obtained acid chloride (*R*)-**10** was used without further purification.[9] A solution of (*R*)-**10** (785 mg, 1.79 mmol) in dry THF (180 mL) and a solution of **14** (654 mg, 1.44 mmol) and Et_3N (0.40 mL, 2.9 mmol) in dry THF (180 mL) were added dropwise simultaneously to dry THF (120 mL) at room temperature with vigorous stirring over 3.5 h. The mixture was stirred for an additional 10 h, and the volatiles were removed by rotary evaporation. The solid residue was dissolved in CH_2Cl_2, and the solution was washed with saturated aqueous $NaHCO_3$ (40 mL), dried over Na_2SO_4, and concentrated. The product was purified by silica gel column chromatography (CH_2Cl_2/THF (20:1)). Recrystallization from CH_2Cl_2 afforded (*R*)-**16** as white crystals (753 mg, 64%): mp 206 °C; $[\alpha]^{30}_D$ +220 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 4.27 (d, J = 15.9 Hz, 2H), 4.51 (d, J = 15.9 Hz, 2H), 5.20 (s, 2H), 7.29 (d, J = 8.1 Hz, 2H), 7.33−7.49 (m, 11H), 7.78 (t, J = 8.3 Hz, 2H), 7.909−7.911 (m, 3H), 7.93 (d, J = 8.1 Hz, 2H), 7.96 (d, J = 8.3 Hz, 2H), 8.04 (d, J = 8.4 Hz, 2H), 8.15 (d, J = 8.3 Hz, 2H), 8.70 (s, 2H), 8.86 (s, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 70.5, 73.0, 109.9, 110.2, 115.1, 119.0, 119.2, 123.0, 125.2, 125.6, 127.3, 127.5, 128.3, 128.4, 128.7, 130.9, 131.1, 133.4, 135.2, 135.8, 141.3, 148.5, 149.5, 154.1, 160.3, 163.3, 167.4; IR (KBr) 3387, 3055, 1697, 1589, 1512, 1450, 1312, 1242, 1211, 1150, 1049, 802 cm^{-1}; HRMS (ESI-IT-TOF, MeCN) calcd for $C_{49}H_{36}N_6O_7Na$ 843.2538, found 843.2550 (M + Na).

Chiral Macrocycle (*R*)-17. To a solution of macrocycle (*R*)-**16** (910 mg, 1.11 mmol) in dry THF (42 mL) was added 10% Pd/C (203 mg), and the mixture was stirred under H_2 at room temperature for 22 h. The mixture was filtered through Celite and concentrated. Recrystallization from acetone afforded (*R*)-**17** as a white solid (687 mg, 85%): mp 233 °C dec; $[\alpha]^{29}_D$ +262 (*c* 1.01, THF); ^{1}H NMR (acetone-d_6, 600 MHz, 40 °C) δ 4.40 (d, J = 15.6 Hz, 2H), 4.80 (d, J = 15.6 Hz, 2H), 7.44−7.51 (m, 6H), 7.72 (d, J = 1.8 Hz, 2H), 7.76 (d, J = 9.0 Hz, 2H), 7.80 (d, J = 8.0 Hz, 2H), 7.83 (t, J = 8.0 Hz, 2H), 8.02 (d, J = 7.5 Hz, 2H), 8.14 (dd, J = 1.2, 8.0 Hz, 2H), 8.17 (d, J = 9.0 Hz, 2H), 8.45 (s, 1H), 8.62 (s, 2H), 9.09 (s, 1H), 9.65 (s, 2H); ^{13}C NMR (acetone-d_6, 150 MHz) δ 73.5, 109.6, 110.0, 117.5, 119.7, 120.0, 123.2, 126.1, 126.4, 127.8, 129.2, 131.6, 131.8, 134.5, 136.4, 141.7, 149.9, 151.5, 155.3, 159.4, 164.9, 167.8; IR (KBr) 3379, 3063, 1697, 1589, 1528, 1450, 1319, 1242, 1211, 1157, 1065, 802 cm^{-1}; HRMS (ESI-IT-TOF, MeCN) calcd for $C_{42}H_{30}N_6O_7Na$ 753.2068, found 753.2065 (M + Na).

Chiral Macrocycle (*R*)-18. A mixture of (*R*)-**17** (698 mg, 0.955 mmol), *tert*-butyl bromoacetate (0.17 mL, 1.2 mmol), and K_2CO_3 (147 mg, 1.06 mmol) in dry DMF (3.3 mL) was heated under N_2 at 80 °C for 17.5 h. The mixture was filtered and concentrated. Purification by silica gel column chromatography (CH_2Cl_2/THF (30:1)) afforded (*R*)-**18** as a white solid (578 mg, 72%): mp 244 °C dec; $[\alpha]^{25}_D$ +211 (*c* 1.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.50 (s, 9H), 4.28 (d, J = 16.2 Hz, 2H), 4.52 (d, J = 16.2 Hz, 2H), 4.66 (s, 2H), 7.29 (d, J = 8.1 Hz, 2H), 7.38 (dt, J = 1.3, 8.1 Hz, 2H), 7.44 (d, J = 9.3 Hz, 2H), 7.47 (dt, J = 1.3, 8.1 Hz, 2H), 7.79 (t, J = 7.8 Hz, 2H), 7.82 (s, 2H), 7.90 (br s, 1H), 7.93 (d, J = 8.1 Hz, 2H), 7.96 (d, J = 7.8 Hz, 2H), 8.02 (d, J = 9.3 Hz, 2H), 8.14 (d, J = 7.8 Hz, 2H), 8.76 (s, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 28.0, 65.7, 72.9, 82.9, 109.9, 110.2, 115.8, 118.7, 119.1, 122.9, 125.2, 125.5, 127.2, 128.4, 130.9, 131.0, 133.4, 135.2, 141.3, 148.4, 149.4, 154.1, 159.5, 163.0, 167.2, 167.4; IR (KBr) 3391, 3059, 1686, 1585, 1520, 1454, 1315, 1242, 1157, 1080, 802 cm^{-1}; HRMS (ESI-IT-TOF, MeCN) calcd for $C_{48}H_{40}N_6O_9Na$ 867.2749, found 867.2741 (M + Na).

Chiral Stationary Phase CSP-1a. A solution of (*R*)-**18** (1.38 g, 1.63 mmol) in CF_3CO_2H (2.5 mL, 32 mmol) and dry CH_2Cl_2 (1 mL) was stirred under N_2 at room temperature for 13 h. The mixture was concentrated in vacuo to give the corresponding macrocyclic carboxylic acid. A solution of the macrocyclic carboxylic acid (1.29 g, 1.63 mmol) in dry DMF (4.5 mL) and dry THF (10 mL), 1,3-dicyclohexylcarbodiimide (DCC) (510 mg, 2.47 mmol), and 1-hydroxybenzotriazole (HOBT) (340 mg, 2.52 mmol) were added to 3-aminopropyl silica gel (2.51 g, mean particle size 5 μm, mean pore size 12 nm, specific surface area 300 m^2/g) that had been dried in vacuo at 150 °C for 4.5 h and cooled to room temperature under N_2 in advance. The mixture was stirred with a mechanical stirrer at room temperature for 48 h. DCC (510 mg, 2.47 mmol), HOBT (340 mg, 2.52 mmol) and acetic acid (0.26 mL, 4.5 mmol) were added, and the mixture was stirred for an additional 24 h. The mixture was filtered, washed with THF, EtOH, and then hot EtOH, and dried in vacuo to afford **CSP-1a** as a pale green powder.

Chiral Macrocycle (*R*)-19. A solution of (*R*)-**10** (785 mg, 1.79 mmol) in dry THF (180 mL) and a solution of **15** (647 mg, 1.44 mmol) and Et_3N (0.45 mL, 3.2 mmol) in dry THF (180 mL) were added dropwise simultaneously to dry THF (120 mL) at room temperature with vigorous stirring over 4.5 h. The mixture was stirred for an additional 11 h, and the volatiles were removed by rotary evaporation. The solid residue was dissolved in CH_2Cl_2, and the solution was washed with brine, dried over Na_2SO_4, and concentrated. The product was purified by silica gel column chromatography (CH_2Cl_2/THF (30:1)) to give (*R*)-**19** as a white solid (864 mg, 74%): mp 266 °C dec; $[\alpha]^{22}_D$ +182 (*c* 1.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.63 (s, 9H), 4.28 (d, J = 16.2 Hz, 2H), 4.53 (d, J = 16.2 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 7.39 (dt, J = 1.1, 8.0 Hz, 2H), 7.43 (d, J = 9.0 Hz, 2H), 7.47 (dt, J = 1.1, 8.0 Hz, 2H), 7.78 (t, J = 8.0 Hz, 2H), 7.91−7.93 (m, 4H), 7.99 (d, J = 9.0 Hz, 2H), 8.15 (d, J = 8.0 Hz, 2H), 8.41 (s, 1H), 8.72 (s, 2H), 8.87 (d, J = 1.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 28.1, 72.7, 82.4, 110.0, 110.4, 118.9, 122.8, 125.1, 125.6, 126.7, 127.3, 128.4, 130.8,

(16) Simonsen, K. B.; Gothelf, K. V.; Jørgensen, K. A. *J. Org. Chem.* **1998**, *63*, 7536–7538.

131.0, 133.3, 133.4, 133.9, 134.5, 141.1, 148.2, 149.4, 153.9, 163.0, 163.7, 167.4; IR (KBr) 3395, 3055, 1701, 1585, 1508, 1454, 1292, 1246, 1157, 1080, 802 cm^{-1}; HRMS (ESI-IT-TOF, MeCN) calcd for $C_{47}H_{38}N_6O_8Na$ 837.2643, found 837.2605 (M + Na).

Chiral Stationary Phase CSP-1b. A solution of (*R*)-**19** (542 mg, 0.665 mmol) in CF_3CO_2H (1.1 mL, 14 mmol) and dry CH_2Cl_2 (0.5 mL) was stirred under N_2 at room temperature for 4.5 h. The mixture was concentrated in vacuo to give the corresponding macrocyclic carboxylic acid. A solution of the macrocyclic carboxylic acid (1.11 g, 1.46 mmol) in dry DMF (3.5 mL) and dry THF (9.5 mL), DCC (459 mg, 2.23 mmol) and HOBT (301 mg, 2.23 mmol) were added to 3-aminopropyl silica gel (2.99 g) that had been dried in vacuo at 150 °C for 4 h and cooled to room temperature under N_2 in advance. The mixture was stirred with a mechanical stirrer at room temperature for 48 h. DCC (463 mg, 2.25 mmol), HOBT (302 mg, 2.23 mmol), and acetic acid (0.23 mL, 4.0 mmol) were added, and the mixture was stirred for an additional 24 h. The mixture was filtered, washed with THF, EtOH, and then hot EtOH, and dried in vacuo to afford **CSP-1b** as a white powder.

Chiral Macrocycle (*R*)-20. A solution of (*R*)-**7** (1.00 g, 1.59 mmol) in CF_3CO_2H (4.4 mL, 57 mmol) was stirred at room temperature for 8 h. The solution was concentrated and dried in vacuo to give the corresponding diacid as a white solid. To a suspension of diacid (3.01 g, 5.81 mmol) in dry CH_2Cl_2 (300 mL) were added $(COCl)_2$ (5.4 mL, 63 mmol) and DMF (3 drops). The mixture was stirred at room temperature for 18 h. The volatiles were removed by rotary evaporation, and the residue was dried in vacuo for 3 h. The obtained acid chloride (*R*)-**11** was used without further purification.[10] A solution of (*R*)-**11** (3.22 g, 5.80 mmol) in dry THF (200 mL) and a solution of **15** (2.40 g, 5.35 mmol) and Et_3N (1.5 mL, 11 mmol) in dry THF (200 mL) were added dropwise simultaneously to dry THF (240 mL) at room temperature with vigorous stirring over 4 h. The mixture was stirred for an additional 15 h, and the volatiles were removed by rotary evaporation. The solid residue was dissolved in CH_2Cl_2, and the solution was washed with brine, dried over Na_2SO_4, and concentrated. Purification by silica gel column chromatography (CH_2Cl_2/THF (30:1)) afforded (*R*)-**20** as a white solid (3.47 g, 70%): mp 278 °C dec; $[\alpha]^{28}_D$ +137 (*c* 0.964, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz) δ 1.63 (s, 9H), 3.64 (d, *J* = 14.7 Hz, 2H), 3.90 (s, 6H), 4.16 (d, *J* = 14.7 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 7.48 (t, *J* = 8.1 Hz, 2H), 7.58 (t, *J* = 8.1 Hz, 2H), 7.78 (t, *J* = 7.8 Hz, 2H), 7.92 (d, *J* = 7.8 Hz, 2H), 8.04 (d, *J* = 8.1 Hz, 2H), 8.13 (d, *J* = 7.8 Hz, 2H), 8.70 (s, 1H), 8.74 (s, 2H), 8.87 (d, *J* = 1.8 Hz, 2H), 9.03 (s, 2H), 9.21 (br s, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 28.0, 52.8, 73.1, 82.2, 109.5, 109.7, 122.6, 125.0, 126.4, 126.8, 127.3, 129.8, 129.9, 132.9, 133.8, 134.2, 135.3, 135.4, 140.9, 148.6, 149.4, 151.7, 163.1, 163.5, 165.7, 166.3; IR (KBr) 3391, 3059, 2978, 2955, 1720, 1701, 1585, 1520, 1454, 1300, 1242, 1219, 1153, 1072, 799, 752, 725 cm^{-1}; HRMS (ESI-IT-TOF, MeCN) calcd for $C_{51}H_{42}N_6O_{12}Na$ 953.2753, found 953.2766 (M + Na).

Chiral Stationary Phase CSP-1c. A solution of (*R*)-**20** (2.60 g, 2.79 mmol) in CF_3CO_2H (6.0 mL, 78 mmol) was stirred under N_2 at room temperature for 19 h. The mixture was concentrated in vacuo to give the corresponding macrocyclic carboxylic acid. A solution of the macrocyclic carboxylic acid (2.77 g, 3.17 mmol) in dry CH_2Cl_2 (10 mL) and dry THF (10 mL), DCC (988 mg, 4.79 mmol), and HOBT (642 mg, 4.75 mmol) were added to 3-aminopropyl silica gel (3.19 g) that had been dried in vacuo at 150 °C for 4 h and cooled to room temperature under N_2 in advance. The mixture was stirred with a mechanical stirrer at room temperature for 48 h. DCC (989 mg, 4.79 mmol), HOBT (641 mg, 4.74 mmol), and acetic acid (0.48 mL, 8.4 mmol) were added, and the mixture was stirred for an additional 24 h. The mixture was filtered, washed with THF, EtOH, and then hot EtOH, and dried in vacuo to afford **CSP-1c** as a white powder.

(*R*)-3,3′-Dibromo-2,2′-bis[(*tert*-butoxycarbonyl)methoxy]-1,1′-binaphthyl ((*R*)-8). A mixture of (*R*)-**4** (4.07 g, 9.16 mmol), *tert*-butyl bromoacetate (3.0 mL, 20 mmol), and K_2CO_3 (2.78 g, 20.1 mmol) in acetone (135 mL) was heated at reflux for 17 h under N_2. The mixture was filtered and concentrated. The product was purified by silica gel column chromatography (hexane/EtOAc (5:1)) to give (*R*)-**8** as a white solid (6.12 g, 99%): mp 120 °C; $[\alpha]^{26}_D$ −3.30 (*c* 0.940, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz) δ 1.27 (s, 18H), 4.16 (d, *J* = 15.3 Hz, 2H), 4.54 (d, *J* = 15.3 Hz, 2H), 7.02 (d, *J* = 8.4 Hz, 2H), 7.25−7.28 (m, 2H), 7.43 (t, *J* = 8.4 Hz, 2H), 7.80 (d, *J* = 8.4 Hz, 2H), 8.24 (s, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 27.8, 70.4, 81.5, 117.0, 125.7, 126.1, 126.5, 127.1, 131.6, 132.8, 133.0, 151.3, 167.1; IR (KBr) 3067, 2982, 2928, 1755, 1728, 1497, 1447, 1393, 1366, 1219, 1146, 1065, 752 cm^{-1}; HRMS (ESI-IT-TOF, MeCN) calcd for $C_{32}H_{32}Br_2O_6Na$ 695.0443, found 695.0420 (M + Na).

Chiral Macrocycle (*R*)-21. A solution of (*R*)-**8** (5.48 g, 8.15 mmol) in CF_3CO_2H (13 mL, 169 mmol) was stirred at room temperature for 18 h. The solution was concentrated and dried in vacuo to give the corresponding diacid as a white solid. To a suspension of diacid (4.39 g, 7.84 mmol) in dry CH_2Cl_2 (450 mL) were added $(COCl)_2$ (7.0 mL, 82 mmol) and DMF (3 drops). The mixture was stirred at room temperature for 18 h. The volatiles were removed by rotary evaporation, and the residue was dried in vacuo for 3 h. The obtained acid chloride (*R*)-**12** was used without further purification. A solution of (*R*)-**12** (4.68 g, 7.84 mmol) in dry THF (250 mL) and a solution of **15** (3.28 g, 7.31 mmol) and Et_3N (2.1 mL, 15 mmol) in dry THF (250 mL) were added dropwise simultaneously to dry THF (300 mL) at room temperature with vigorous stirring over 4 h. The mixture was stirred for an additional 15 h, and the volatiles were removed by rotary evaporation. The solid residue was dissolved in CH_2Cl_2, and the solution was washed with brine, dried over Na_2SO_4, and concentrated. Purification by silica gel column chromatography (CH_2Cl_2/THF (20:1)) afforded (*R*)-**21** as a white solid (5.36 g, 75%): mp 282 °C dec; $[\alpha]^{30}_D$ +179 (*c* 0.994, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz) δ 1.63 (s, 9H), 3.73 (d, *J* = 15.3 Hz, 2H), 4.27 (d, *J* = 15.3 Hz, 2H), 7.13 (d, *J* = 7.8 Hz, 2H), 7.40 (t, *J* = 7.8 Hz, 2H), 7.54 (t, *J* = 7.8 Hz, 2H), 7.80 (t, *J* = 7.8 Hz, 2H), 7.89 (d, *J* = 7.8 Hz, 2H), 7.94 (d, *J* = 7.8 Hz, 2H), 8.15 (d, *J* = 7.8 Hz, 2H), 8.33 (s, 2H), 8.52 (s, 1H), 8.88 (s, 2H), 8.89 (d, *J* = 1.8 Hz, 2H), 8.95 (s, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 28.0, 71.7, 82.4, 109.7, 109.9, 116.1, 125.2, 126.6, 126.7, 127.1, 127.7, 128.1, 131.9, 132.4, 133.1, 133.7, 133.9, 134.3, 141.1, 148.5, 149.2, 149.5, 163.1, 163.2, 165.7; IR (KBr) 3391, 3260, 3059, 2978, 2916, 1717, 1693, 1670, 1585, 1523, 1454, 1312, 1292, 1246, 1153, 1057, 802, 725 cm^{-1}; HRMS (ESI-IT-TOF, MeCN) calcd for $C_{47}H_{36}N_6O_8Br_2Na$ 995.0839, found 995.0848 (M + Na).

Chiral Stationary Phase CSP-1d. A solution of (*R*)-**21** (4.56 g, 4.69 mmol) in CF_3CO_2H (11 mL, 143 mmol) was stirred under N_2 at room temperature for 16 h. The mixture was concentrated in vacuo to give the corresponding macrocyclic carboxylic acid. A solution of the macrocyclic carboxylic acid (2.00 g, 2.18 mmol) in dry CH_2Cl_2 (10 mL) and dry THF (10 mL), DCC (693 mg, 3.36 mmol), and HOBT (445 mg, 3.29 mmol) were added to 3-aminopropyl silica gel (3.06 g) that had been dried in vacuo at 150 °C for 4 h and cooled to room temperature under N_2 in advance. The mixture was stirred with a mechanical stirrer at room temperature for 48 h. DCC (672 mg, 3.26 mmol), HOBT (452 mg, 3.34 mmol) and acetic acid (0.34 mL, 5.9 mmol) were added, and the mixture was stirred for an additional 24 h. The mixture was filtered, washed with THF, EtOH, and then hot EtOH, and dried in vacuo to afford **CSP-1d** as a white powder.

(*R*)-2,2′-Bis[(ethoxycarbonyl)methoxy]-3,3′-diphenyl-1,1′-binaphthyl ((*R*)-9). A mixture of (*R*)-**5** (346 mg, 0.789 mmol), ethyl bromoacetate (0.21 mL, 1.9 mmol), and K_2CO_3 (277 mg, 2.00 mmol) in acetone (5 mL) was heated at reflux for 18 h under N_2. The mixture was filtered and concentrated. The product was purified by silica gel column chromatography (hexane/EtOAc (4:1)) to give

(*R*)-**9** as white crystals (452 mg, 94%): mp 54 °C; $[\alpha]^{29}_{D}$ −95.7 (*c* 0.987, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.94 (t, J = 7.2 Hz, 6H), 3.75 (q, J = 7.2 Hz, 4H), 3.82 (d, J = 15.6 Hz, 2H), 4.22 (d, J = 15.6 Hz, 2H), 7.19 (d, J = 8.1 Hz, 2H), 7.27 (t, J = 8.1 Hz, 2H), 7.37 (t, J = 8.1 Hz, 2H), 7.41−7.46 (m, 6H), 7.75 (d, J = 8.4 Hz, 4H), 7.91 (d, J = 8.1 Hz, 2H), 7.97 (s, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 13.8, 60.4, 69.6, 125.3, 125.67, 125.72, 126.6, 127.5, 128.0, 128.4, 129.4, 130.5, 131.0, 133.3, 134.7, 138.1, 152.5, 168.4; IR (KBr) 3055, 2980, 2907, 1761, 1732, 1495, 1418, 1188, 1069, 1026, 754, 700 cm^{-1}; HRMS (ESI-IT-TOF, MeCN) calcd for $C_{40}H_{34}O_6Na$ 633.2248, found 633.2220 (M + Na).

Chiral Macrocycle (*R*)-22. To a solution of (*R*)-**9** (222 mg, 0.364 mmol) in EtOH (2 mL) was added 10% NaOH (2 mL), and the solution was heated at reflux for 14 h. After removal of EtOH, the mixture was acidified with 10% HCl. The white precipitate formed was filtered and dried in vacuo. To a suspension of diacid (1.00 g, 1.80 mmol) in dry CH_2Cl_2 (110 mL) were added $(COCl)_2$ (1.6 mL, 19 mmol) and DMF (2 drops). The mixture was stirred at room temperature for 13 h. The volatiles were removed by rotary evaporation, and the residue was dried in vacuo for 5 h. The obtained acid chloride (*R*)-**13** was used without further purification. A solution of (*R*)-**13** (1.06 g, 1.80 mmol) in dry THF (60 mL) and a solution of **15** (768 mg, 1.71 mmol) and Et_3N (0.48 mL, 3.4 mmol) in dry THF (60 mL) were added dropwise simultaneously to dry THF (80 mL) at room temperature with vigorous stirring over 4.5 h. The mixture was stirred for an additional 13 h, and the volatiles were removed by rotary evaporation. The solid residue was dissolved in CH_2Cl_2, and the solution was washed with brine, dried over Na_2SO_4, and concentrated. The product was purified by silica gel column chromatography (CH_2Cl_2/THF (30:1)) to give (*R*)-**22** as a white solid (1.30 g, 79%): mp 276 °C dec; $[\alpha]^{31}_{D}$ +50.4 (*c* 0.973, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.65 (s, 9H), 3.72 (d, J = 15.0 Hz, 2H), 3.82 (d, J = 15.0 Hz, 2H), 7.20−7.23 (m, 4H), 7.36−7.39 (m, 6H), 7.52 (t, J = 7.8 Hz, 2H), 7.66−7.69 (m, 6H), 7.75 (t, J = 8.4 Hz, 2H), 7.96 (d, J = 8.4 Hz, 2H), 8.03 (s, 2H), 8.18 (d, J = 7.8 Hz, 2H), 8.42 (s, 2H), 8.92 (d, J = 1.2 Hz, 2H), 8.97 (s, 1H), 9.40 (s, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 28.0, 71.7, 82.4, 109.6, 109.8, 125.2, 125.6, 126.2, 127.3, 127.4, 127.9, 128.4, 128.6, 129.2, 131.2, 131.4, 132.91, 132.94, 134.0, 134.4, 134.6, 137.2, 141.1, 148.2, 149.5, 151.2, 163.1, 163.6, 166.0; IR (KBr) 3382, 3055, 2978, 2908, 1717, 1701, 1585, 1520, 1454, 1292, 1246, 1153, 1049, 802, 702 cm^{-1}; HRMS (ESI-IT-TOF, MeCN) calcd for $C_{59}H_{46}N_6O_8Na$ 989.3269, found 989.3274 (M + Na).

Chiral Stationary Phase CSP-1e. A solution of (*R*)-**22** (1.71 g, 1.77 mmol) in CF_3CO_2H (3.5 mL, 45 mmol) was stirred under N_2 at room temperature for 19 h. The mixture was concentrated in vacuo to give the corresponding macrocyclic carboxylic acid. A solution of the macrocyclic carboxylic acid (2.87 g, 3.15 mmol) in dry CH_2Cl_2 (10 mL) and dry THF (10 mL), DCC (986 mg, 4.78 mmol), and HOBT (645 mg, 4.77 mmol) were added to 3-aminopropyl silica gel (3.07 g) that had been dried in vacuo at 150 °C for 4 h and cooled to room temperature under N_2 in advance. The mixture was stirred with a mechanical stirrer at room temperature for 48 h. DCC (981 mg, 4.75 mmol), HOBT (641 mg, 4.74 mmol) and acetic acid (0.48 mL, 8.4 mmol) were added, and the mixture was stirred for an additional 24 h. The mixture was filtered, washed with THF, EtOH, and then hot EtOH, and dried in vacuo to afford **CSP-1e** as a white powder.

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Supporting Information Available: Determination of the coverage of the macrocycle on silica, preparative HPLC of **A6**, determination of the binding constants by NMR titrations, copies of NMR and chromatograms, and calculations of host−guest complexes. This material is available free of charge via the Internet at http://pubs.acs.org.