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Solvent-Dependent Self-Discrimination of Bis(2-hydroxyphenyl)diamides

Akinobu Matsuzawa, Akihiro Nojiri, Naoya Kumagai,* and Masakatsu Shibasaki*[a]

Abstract: Solvent-dependent, self-discrimination of diamides is described. Mixing a solution of (*R*)-**1a** and (*S*)-**1a**, which are valine-derived, bis(2-hydroxyphenyl)diamide-bearing, multiple hydrogen-bonding modules, in dichloromethane immediately led to the formation of a thick suspension comprising a 1:1 heterochiral aggregate of **1a**. The solubility of heterochiral **1a** was substantially lower in halogenated solvents than in ethyl acetate. A perusal of racemic crystal structures obtained from chloroform and ethyl acetate revealed a significant difference in the crystal-packing pattern, which is likely to be the basis for the pronounced difference in solubility. Specific self-discrimination of **1a** in an ensemble of eight structurally related molecules showcased the specific aggregation through the hydrogen-bonding network of the bis(2-hydroxyphenyl)diamide framework. The low solubility of heterochiral **1a** in halogenated solvent was exploited to achieve high stereoselectivity in a catalytic asymmetric reaction by using a low enantiomeric excess sample of **1a**.

Keywords: aggregation · asymmetric catalysis · chiral resolution · molecular recognition · self-assembly · stacking interactions

Introduction

Since the pioneering work of Cram, Lehn, and Pedersen, supramolecular chemistry has produced a diverse array of assembled molecular architectures by harnessing various noncovalent inter- and intramolecular interactions.[1] Intensive research in this area has enhanced the understanding and development of molecular recognition and self-assembly processes, leading to the emergence of systems with functions that are molecular in basis.[2] For controlled integration of molecular architecture to exert a specific function, molecular recognition capabilities that enable high-fidelity, molecule-selective association from an ensemble of molecules are key. Nature deploys a number of molecular machineries, such as DNA, RNA, and proteins, to exert a myriad of functions that are initiated by precise molecular recognition, including the element of molecular chirality. Intense efforts to replicate similar molecular recognition processes in the laboratory have revealed various self-assembly systems.[3] The handedness of a molecule is a prominent factor in molecular differentiation, as exemplified by enantiomeric self-sorting (recognizing self)[4] and self-discriminating (recognizing opposite handedness) systems.[5] Heterochiral association of several proteinogenic amino acids has recently been documented in detail, and the behavior of the system was rationalized on the basis of ternary eutectic composition, which led to significant enantiomeric amplification of solution enantiomeric excess (*ee*) from a nearly racemic mixture of amino acids.[6–10] Sublimation of partially resolved compounds also causes enantiomeric amplification due to the differential vapor pressure of enantiopure samples and their mixtures.[11–13] These findings have been used to support a potential rationale for the evolution of homochirality in a prebiotic environment and are the subject of growing interest.[8,9,11–13] Herein, we report solvent-dependent self-discrimination of valine-derived bis(2-hydroxyphenyl)diamide **1a**, which harbors multiple hydrogen-bonding modules that exhibit extensive heterochiral aggregation of (*R*)-**1a** and (*S*)-**1a** to form a highly insoluble heterochiral precipitate from an ensemble of eight structurally related amides. X-ray crystallographic analyses provided clues to the origin of the strict heterochiral aggregation of **1a**. The high fidelity of the heterochiral aggregation allowed the generation of a solution composed of highly enantioenriched **1a** from an initial sample of 5–10% *ee*. The use of **1a** as a chiral ligand in combination with rare earth metals was exploited to produce a large, nonlinear effect in catalytic asymmetric reactions.

[a] A. Matsuzawa, A. Nojiri, N. Kumagai, M. Shibasaki
Graduate School of Pharmaceutical Sciences
The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku
Tokyo 113-0033 (Japan)
Fax: (+81) 3-5684-5206
E-mail: nkumagai@mol.f.u-tokyo.ac.jp
mshibasa@mol.f.u-tokyo.ac.jp

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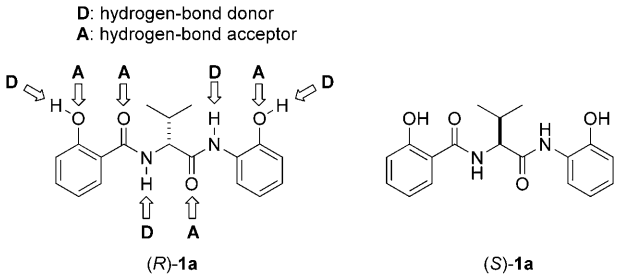


Results and Discussion

We previously revealed that diamide **1a**, which has two aryloxide moieties and is prepared from valine through a chromatography-free process,[14a] can serve as a chiral ligand upon complexation with rare earth metals to facilitate asymmetric catalysts.[14] In the ^{1}H NMR spectrum of enantiopure (*S*)-**1a**, chemical shifts of not only NH and OH protons, but also aromatic CH protons, varied depending on the concentration of the sample;[15] this suggested that extensive intermolecular interaction of **1a** occurred, probably due to hydrogen-bonding interactions. In our continuing efforts to expand the utility of **1a**, we found that mixing a 0.1 M solution of (*R*)-**1a** and (*S*)-**1a** in dichloromethane immediately led to the formation of a thick suspension (Figure 1a). The development of the suspension from a 1:1 mixture of a diluted solution of (*R*)-**1a** and (*S*)-**1a** was monitored by using a turbidity meter, which revealed that the formation of the suspension was complete within 30 min even at 0.01 M.[15] The isolated insoluble material was a racemate of **1a** with a much higher melting point (172 °C) than enantiopure **1a** (123–124 °C), suggesting that it was not a conglomerate, but a racemic compound.[6] Formation of the insoluble heterochiral aggregation was dependent on the solvent used; halogenated solvents such as dichloromethane or chloroform immediately produced a suspension (Figure 1a), whereas the heterochiral solution in tetrahydrofuran, ethyl acetate, or methanol remained homogeneous after 3 h of stirring at 30 °C (Figure 1b).

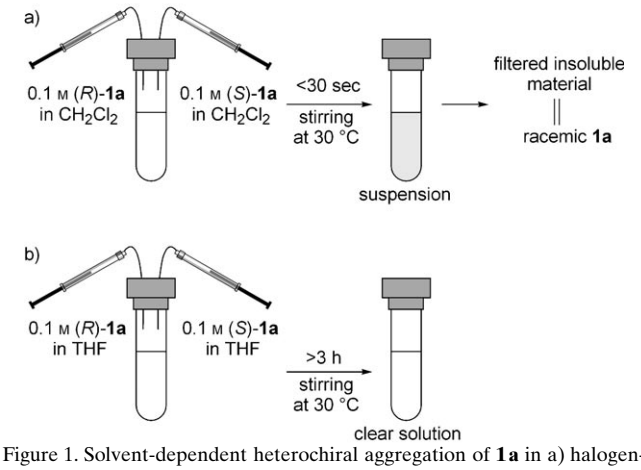


Figure 1. Solvent-dependent heterochiral aggregation of **1a** in a) halogenated solvent (CH_2Cl_2, $CHCl_3$) and b) in THF, AcOEt, or MeOH.

To delineate the origin of the preferential heterochiral aggregation of **1a** and its solvent-dependency, crystals of **1a** were grown under four different conditions: 1) enantiopure (*S*)-**1a** in dichloromethane, 2) enantiopure (*S*)-**1a** in ethyl acetate/*n*-pentane, 3) racemic **1a** in chloroform, and 4) racemic **1a** in ethyl acetate/*n*-pentane; each crystal was analyzed by X-ray crystallography. The crystal structures of enantiopure (*S*)-**1a** from the different solvent systems were not appreciably different.[16] In contrast, a marked difference in the packing pattern of (*S*)-**1a** and (*R*)-**1a** molecules was revealed in racemic crystals grown under the different solvent systems. As illustrated in Figure 2, from a racemic solution of **1a**, centrosymmetric cocrystals composed of (*R*)- and (*S*)-**1a** in a ratio of 1:1 were formed from either chloroform or ethyl acetate/*n*-pentane, confirming that **1a** formed a racemate. A regular zigzag alternating *S*/*R* array associated through hydrogen bonding was observed in the crystal structure of the racemate from chloroform (Figure 2a and b), which laterally associated with each other to form highly insoluble aggregates.[17] On the other hand, a perusal of the crystal structure of the racemate from ethyl acetate/*n*-pentane led to the identification of an alternating *SS*/*RR* array associated by hydrogen bonding (Figure 2c and d). The significant difference in the solubility of racemic **1a** in chloroform or ethyl acetate could be ascribed to the enhanced stability of the zigzag alternating *S*/*R* array formed in chloroform over the *SS*/*RR* counterpart formed in ethyl acetate/*n*-pentane. Amino acid residues are presumably not relevant to the heterochiral aggregation of **1a** in crystallographic analysis, implying that there is the potential to introduce specific functionality in this moiety to devise a functional assembly.

Because the self-discrimination of **1a** appeared to originate from the hydrogen-bonding network connecting the characteristic bis(2-hydroxyphenyl)diamide framework, we next directed our attention toward the possibility of inducing the specific aggregation of (*S*)-**1a** and (*R*)-**1a** in an ensemble of structurally related molecules **1a**–**g** (Scheme 1). The monoester analogue **1b**, bearing a salicylate moiety instead of salicylamide, did not form an insoluble heterochiral aggregate of **1b** upon mixing (*R*)-**1b** and (*S*)-**1b** in dichloromethane, indicating that the diamide substructure of the α-amino acid is crucial for the construction of the *S*/*R* alternating array found in the heterochiral aggregate of **1a** (Figure 2a). Therefore, along with (*R*)-**1b** and (*S*)-**1b**, another ester analogue (*S*)-**1c**, deoxy analogues (*S*)-**1d** and (*S*)-**1e**, and analogues (*S*)-**1f** and (*S*)-**1g** with an appended methylene group, were prepared and submitted to the same conditions used for the self-discrimination of **1a** in the presence of the closely related sets of different molecules (Figure 3). In contrast to the formation of heterochiral aggregation in the mixed solution of (*R*)-**1a** and (*S*)-**1a** in dichloromethane, combinations of either (*R*)-**1a**/(*S*)-**1b**, (*R*)-**1a**/(*S*)-**1c**, (*R*)-**1a**/(*S*)-**1d**, (*R*)-**1a**/(*S*)-**1e**, (*R*)-**1a**/(*S*)-**1f**, or (*R*)-**1a**/(*S*)-**1g** under identical conditions did not form a precipitate, validating

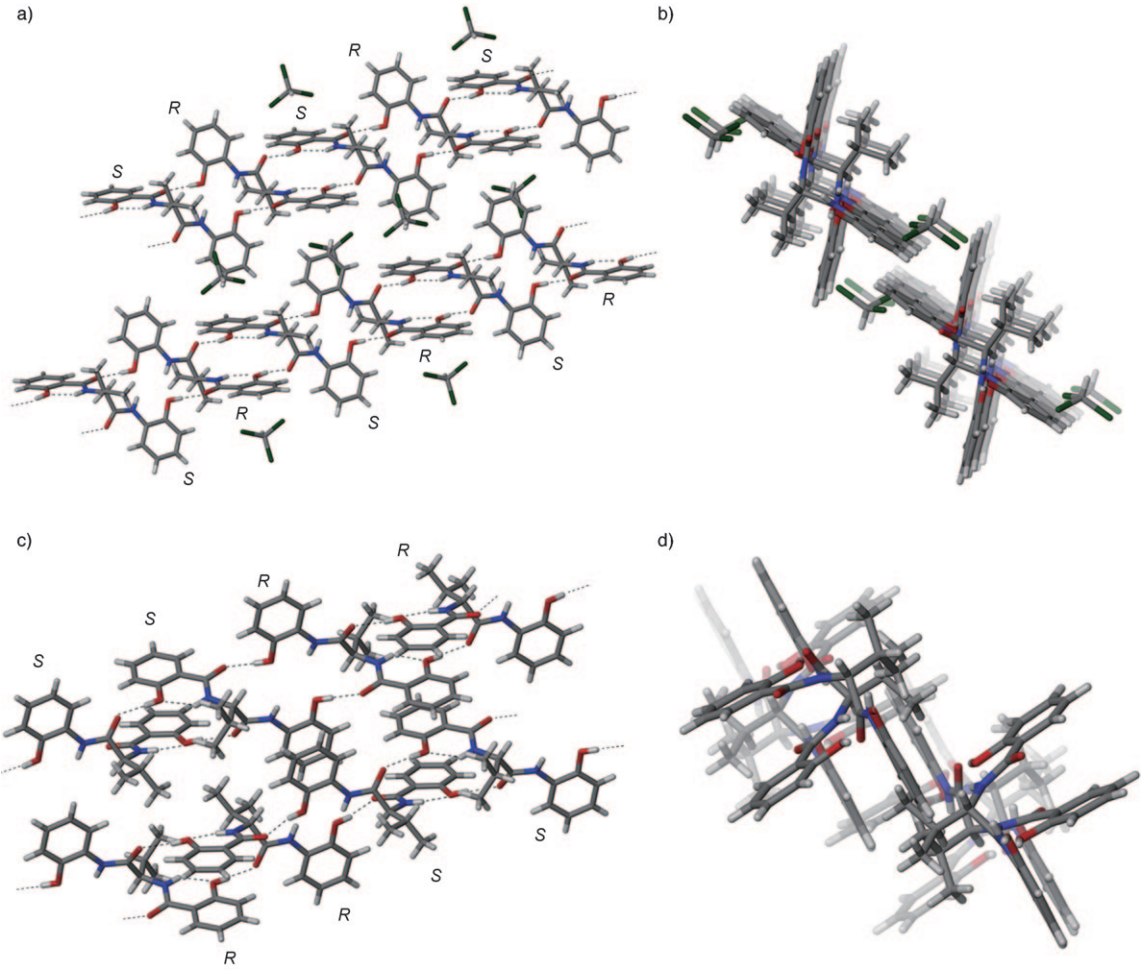
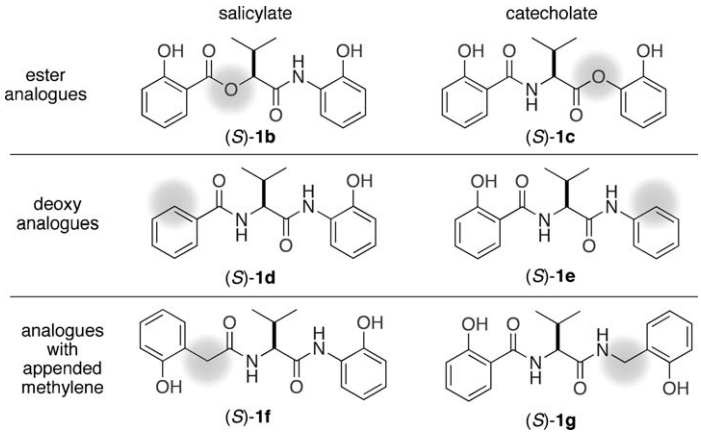


Figure 2. Partial structure of *S*/*R* alternating array of the racemic crystal of **1a** obtained from $CHCl_3$ (a and b) and that of *SS*/*RR* alternating array of the racemic crystal of **1a** obtained from ethyl acetate/*n*-pentane (c and d). Side view of the array of each crystal showing hydrogen bond network with dashed line (a and c). Top view of the array of each crystal (b and d). Carbon: dark gray; hydrogen: light gray; nitrogen: blue; oxygen: red; chlorine: green. Dotted line represents hydrogen bonds.



Scheme 1. Structurally related bis(2-hydroxyphenyl)amide entities **1b**–**g**.

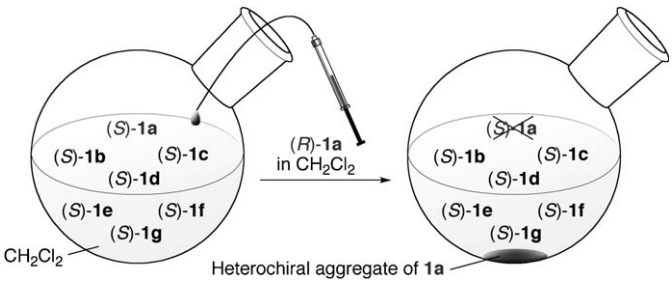


Figure 3. Self-discrimination of **1a** in an ensemble of eight structurally related molecules.

the specific association of (*R*)-**1a** and (*S*)-**1a**.[15] Upon addition of a 0.1 M solution of (*R*)-**1a** (500 μL, 50 μmol) in dichloromethane to a mixed solution of (*S*)-**1a**, (*S*)-**1b**, (*S*)-**1c**, (*S*)-**1d**, (*S*)-**1e**, (*S*)-**1f**, and (*S*)-**1g** (49±1 μmol each) in dichloromethane—to develop an ensemble of eight molecules in equimolar amounts (Figure 4 blue bars)—the solution gradually became a thick suspension. After stirring for 48 h at (25±1) °C, the suspension was filtered off and the filtered insoluble material was analyzed by HPLC.[15] The insoluble material was comprised of significant amounts of (*S*)-**1a** and (*R*)-**1a** in an almost 1:1 ratio, with only trace amounts of other species, indicating a high fidelity for the self-discrimi-

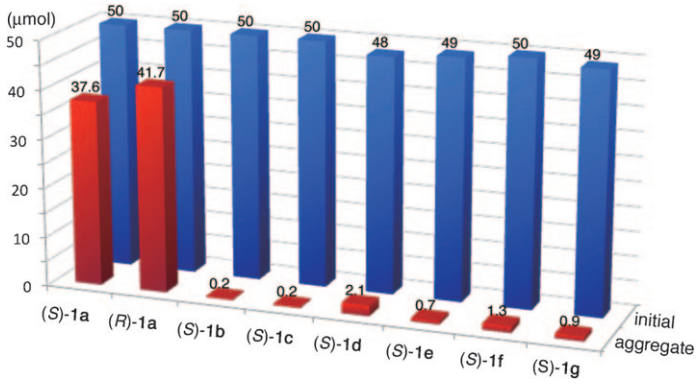


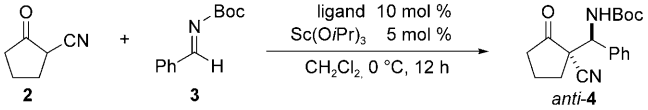
Figure 4. Comparison of the amount of each molecule in the ensemble before and after the self-discrimination. Blue: initial amount of each molecule. Red: amount of each molecule after self-discrimination of (*R*)-**1a** and (*S*)-**1a** from the ensemble of 8 molecules.

nation of **1a** (Figure 4, red bars).[18] The fact that (*R*)-**1a** did not form an aggregation with either (*S*)-**1f** or (*S*)-**1g** provided further evidence that both the diamide substructure and the location of the aryloxide functionalities were the dominant factors involved in the heterochiral aggregation.

The 1:1 heterochiral aggregation of **1a**, with much lower solubility than that of enantiopure **1a** in halogenated solvents, produced a strong asymmetric amplification of the solution *ee* value from an initial sample of **1a** with low *ee* value.[19] Whereas a heterochiral mixture of **1a** in ethyl acetate, which was prepared by mixing 0.1 M (*R*)- and (*S*)-**1a** solution in ethyl acetate, never formed a suspension, an identical mixture in dichloromethane rapidly formed a precipitate of heterochiral aggregate and the *ee* value of **1a** remaining in the solution was substantially amplified (Figure 5).[15] From an initial *ee* value of 4.0%, a dichloromethane/*n*-hexane binary solvent system enhanced the solubility ratio ([racemic **1a**]/[enantiopure **1a**]) and the solution *ee* value reached 91.2% after 30 min of stirring at room temperature.

Because **1a** enables asymmetric catalysts upon complexation with rare earth metals,[14] we then proceeded to demonstrate the large nonlinear effect in catalytic asymmetric reactions.[19] Both **1a** and salicyl ester analogue **1b** served as suitable ligands in combination with $Sc(OiPr)_3$ in a catalytic asymmetric Mannich-type reaction[20] of 2-cyanocyclopentanone (**2**) and *N*-Boc imine **3** in dichloromethane, to afford the corresponding product **4** with high *anti*-selectivity and *ee* value (Table 1).[14d] Self-discrimination/enantiomeric amplification in solution and a large nonlinear effect were anticipated for the Mannich-type reaction with a low *ee* sample of **1a**, whereas a low *ee* sample of **1b** was anticipated to give a nearly racemic product. When a sample of (*S*)-**1a** with 10% *ee* was stirred in dichloromethane/*n*-hexane for 30 min, a thick suspension developed. Subsequent addition of $Sc(OiPr)_3$, **2** and **3** at −20°C afforded **4** in 93% yield with an *anti*/*syn* ratio of 93:7, and 91% *ee* (*anti*); the reaction thus exhibited a stereoselectivity comparable to that obtained from enantiopure (*S*)-**1a** (Scheme 2a vs. Table 1, entry 1). On the other hand, the heterochiral aggregation of the ester analogue **1b** did not occur with a 10% *ee* heterochiral mixture of (*S*)-**1b** in dichloromethane/*n*-hexane, and a subsequent Mannich-type reaction gave nearly racemic **4** (Scheme 2 b vs. Table 1, entry 2). Enantiomeric amplification of **1a** enabled other catalytic asymmetric reactions to be performed from a low *ee* value sample of **1a** after filtration of heterochiral aggregates and solvent exchange. The diastereoselectivity was switched in the Mannich-type reaction of the same set of substrates in combination with **1a** and $Er(OiPr)_3$ in ether solvent.[14d] Thus, filtration and solvent exchange of the 10% *ee* sample of **1a** in dichloromethane/*n*-hexane, followed by the addition of $Er(OiPr)_3$, **2**, and **3**, afforded *syn*-**4** in excellent yield and stereoselectivity (Scheme 3a). A similar procedure could be applied to the catalytic asymmetric amination[21] of α-ethoxycarbonyl amide **5** with di-*tert*-butyl azodicarboxylate, which was promoted by a ternary catalytic system of $La(NO_3)_3{\cdot}6H_2O$, **1a**, and H-L-Val-O*t*Bu,[14e] providing the corresponding amination product with a tetrasubstituted carbon in optically pure form from a 5% *ee* sample of **1a** (Scheme 3b).

Table 1.



Entry	Ligand	Yield [%]	*anti*/*syn*	*ee* [%]
1	(*S*)-**1a**	90	94:6	94
2	(*S*)-**1b**	93	89:11	93

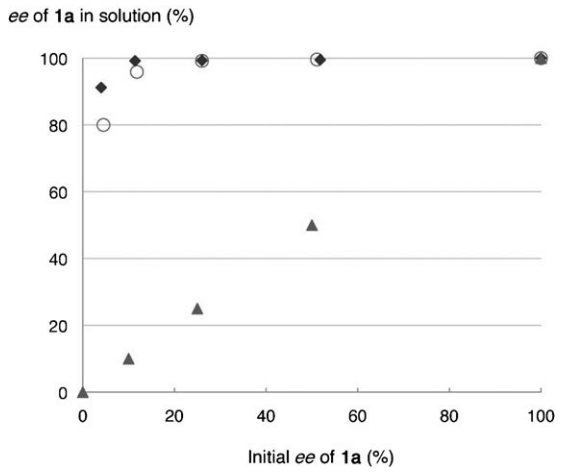
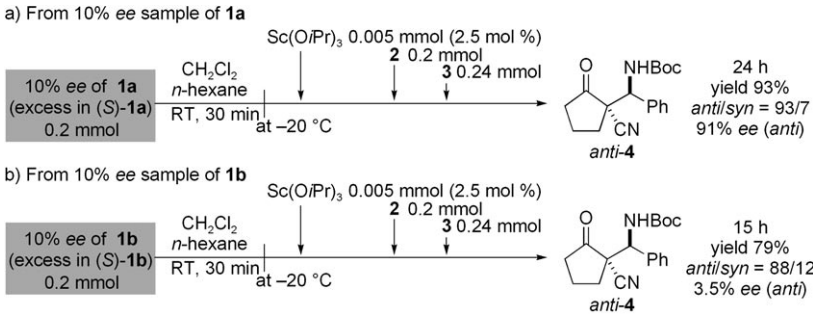


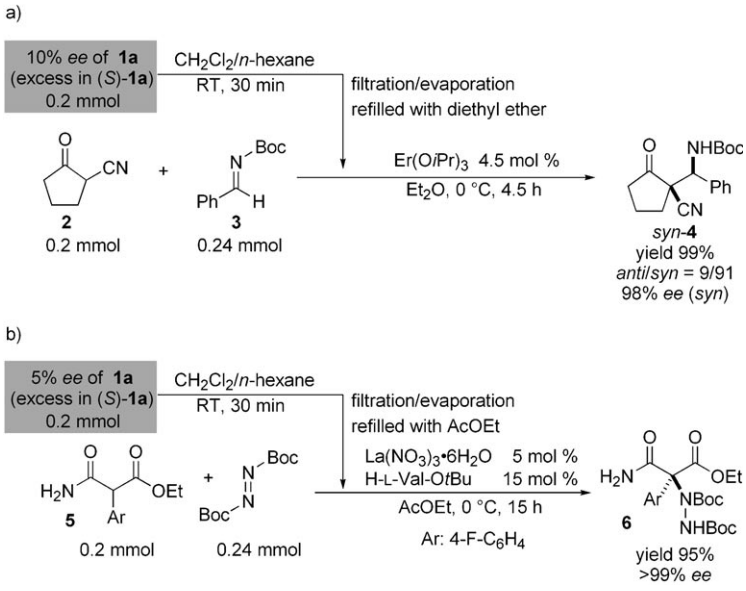
Figure 5. Plot of solution *ee* of **1a** versus initial heterochiral mixture of **1a** in CH_2Cl_2 (○), CH_2Cl_2/*n*-hexane (◆), and AcOEt (▲).

Conclusion

We have studied the heterochiral aggregation of **1a**, which was developed as an effective amide-based chiral ligand in asymmetric catalysis. The solubility of heterochiral **1a** was



Scheme 2. Catalytic asymmetric Mannich-type reaction with a low *ee* sample of **1a** or **1b**.



Scheme 3. a) *syn*-Selective catalytic asymmetric Mannich-type reaction and b) catalytic asymmetric amination using a low *ee* sample of **1a**.

substantially lower in halogenated solvents compared with the high solubility in ethyl acetate. A perusal of racemic crystal structures obtained from chloroform and ethyl acetate revealed a significant difference in the crystal-packing pattern, which is likely to be the basis for the pronounced difference in solubility. Specific self-discrimination of **1a** in the ensemble of eight structurally related molecules showcased the specific aggregation through the hydrogen-bonding network of the bis(2-hydroxyphenyl)diamide framework. The low solubility of heterochiral **1a** in halogenated solvent was exploited to achieve high stereoselectivity in catalytic asymmetric reactions by using a low *ee* sample of **1a**. Future work will be dedicated to the introduction of functionalities to the amino acid components of the bis(2-hydroxyphenyl)-diamide framework, with the aim of developing a functional assembly.

Experimental Section

General procedure: Formation of the heterochiral aggregate and catalytic asymmetric reactions were performed in a 20 mL test tube with a Teflon-coated magnetic stirring bar. The test tubes were capped with a glass stopper for the formation of the heterochiral aggregation under ambient atmosphere. The test tubes were fitted with a three-way glass stopcock for asymmetric reactions under Ar atmosphere. All work-up and purification procedures were carried out with reagent-grade solvents under ambient atmosphere.

Heterochiral aggregation of 1a in CH_2Cl_2: A solution of (*R*)-**1a** (0.1 M, 1.0 mL, 0.10 mmol) in CH_2Cl_2 at 30 °C was added to a stirred solution of (*S*)-**1a** (32.8 mg, 0.10 mmol) in CH_2Cl_2 (0.1 M, 1.0 mL) in a 20 mL test tube. The resulting mixture immediately developed into a white suspension. The suspension was stirred at the same temperature for 30 min, then filtered through filter paper under reduced pressure and the insoluble solid material was washed with a small portion of CH_2Cl_2. The solid was dissolved in MeOH and submitted to HPLC analysis [Daicel CHIRALPAK AS-H column; 0.46×25 cm; eluent: *n*-hexane/2-propanol = 9:1; flow rate: 1.0 mL min^{-1}; detection at 254 nm; t_R = 8.1 min for (*S*)-**1a**, t_R = 17.9 min for (*R*)-**1a**]. The peak areas for (*S*)-**1a** and (*R*)-**1a** were identical, indicating that the insoluble solid was a 1:1 heterochiral mixture, which was revealed to be a racemate (contains both *S* and *R* compounds in a unit cell) by single-crystal X-ray crystallography. The filtered solid material was dried under vacuum for 5 h. The melting point (172 °C) was significantly higher than that of enantiopure **1a** (123–124 °C).

Self-discrimination of (*S*)-1a and (*R*)-1a in an ensemble of eight structurally related compounds in CH_2Cl_2: A test tube was charged with a solution containing a mixture of seven compounds (*S*)-**1a–g** in THF [2.65 mL, containing (*S*)-**1a** (50 μmol), (*S*)-**1b** (50 μmol), (*S*)-**1c** (50 μmol), (*S*)-**1d** (48 μmol), (*S*)-**1e** (49 μmol), (*S*)-**1f** (50 μmol), and (*S*)-**1g** (49 μmol)]; the concentration was determined by HPLC analysis with *N*-methylbenzamide as an internal standard. THF was removed under reduced pressure and the resulting residue was dried in vacuo for 30 min. Anhydrous CH_2Cl_2 (1000 μL) was added and the Teflon-coated magnetic stirring bar was placed into the test tube to give a solution of seven compounds in CH_2Cl_2. The test tube was immersed in an electronically controlled oil bath set at (25±1) °C with gentle stirring and a solution of (*R*)-**1a** (0.1 M, 500 μL, 50 mmol) in $CH_2Cl_2$was added to the stirred solution. A suspension gradually formed and the resulting suspension was stirred at the same temperature for 48 h. The suspension was filtered through a membrane filter with a syringe to give a filtrate sample. The test tube was rinsed with cooled (−78 °C) CH_2Cl_2 (1 mL) and the washing was filtered through the same membrane filter to collect all the insoluble material. The membrane filter was washed with cooled (−78 °C) CH_2Cl_2 (1 mL). Insoluble material in the membrane filter was eluted with THF (5 mL at RT, then 5 mL at 45 °C) to give an aggregate sample. The filtrate (100 mL aliquot was taken and submitted to HPLC analysis) and the aggregate samples were individually analyzed by HPLC with *N*-methylbenzamide (500 μL, concentration: 100 mg in 25 mL 2-propanol (IPA)) as an internal standard [Daicel CHIRALPAK IC column; 0.46×25 cm; eluent: *n*-hexane/MeOH = 60:1; flow rate: 1.0 mL min^{-1}; detection: 254 nm]. Retention times and calibration curves for the determination of the concentration of each compound are summarized in the Supporting Information.

***anti*-Selective catalytic asymmetric Mannich-type reaction with a 10 % *ee* sample of 1a in CH_2Cl_2/*n*-hexane**: Compounds (*S*)-**1a** in CH_2Cl_2 (1130 μL, 0.11 mmol, 0.976 M), (*R*)-**1a** in CH_2Cl_2 (940 μL, 0.090 mmol, 0.961 M), and anhydrous *n*-hexane (3.0 mL) were successively added, by using a syringe equipped with a stainless-steel needle at RT under an Ar atmosphere, to a flame-dried 20 mL test tube containing a Teflon-coated

magnetic stirring bar, giving a 10% *ee* mixture of **1a** (excess in *S* form). After stirring the resulting suspension at the same temperature for 30 min (heterochiral aggregation of **1a** occurred to give a white suspension), the test tube was immersed in an electronically controlled cooling bath at −20°C with 2-propanol as medium. Then, $Sc(OiPr)_3$ (25 μL, 5.0 μmol, 0.2 M in *n*-hexane), **2** (21 μL, 0.2 mmol), and **3** (49 μL, 0.24 mmol) at −20°C were added to the resulting suspension. After stirring at the same temperature for 20 h, 1 N aqueous HCl (1 mL) was added and the resulting mixture was extracted with diethyl ether. The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ and brine, and then dried over Na_2SO_4. After filtration, the organic solvent was removed under reduced pressure and the resulting residue was submitted to ^1H NMR spectroscopic analysis to determine the diastereomeric ratio [*anti*/*syn* = 93:7; integrated value of the peaks at $\delta = 4.98$ ppm (*syn*: −C*H*(Ph)NHBoc) and $\delta = 5.10$ ppm (*anti*: −C*H*(Ph)NHBoc)]. The crude mixture was purified by silica gel column chromatography (*n*-hexane/acetone = 10:1) to give Mannich product **4** (58.4 mg, 1.86 mmol, 93% yield). The *ee* value was determined by HPLC analysis [Daicel CHIRALPAK IC column; 0.46 × 25 cm; eluent: *n*-hexane/2-propanol = 9:1; detection at 254 nm; flow rate: 1.0 mL min^{-1}; $t_R = 21.8$ min (major), 26.8 min (minor); 91% *ee*].

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[17] In reference [8b], the authors provided a crystal structure of racemic proline incorporating a $CHCl_3$ molecule and proposed that this incorporation caused a significant enhancement of the eutectic *ee* value. For a more detailed study on the tuning of eutectic composition by achiral additives, see reference [8e].

[18] The amount of (*S*)-**1b**, (*S*)-**1c**, (*S*)-**1d**, (*S*)-**1e**, (*S*)-**1f**, and (*S*)-**1g** in the filtrate remained almost identical to the initial concentration, whereas the amount of (*S*)-**1a** and (*R*)-**1a** was significantly decreased. A small imbalance of the amount of (*S*)-**1a** and (*R*)-**1a** in the filtered insoluble material indicated that tiny amounts of (*R*)-**1a**/(*S*)-**1b**–**g** aggregates were formed.

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