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Controlled Self-Assembly of Multiple Diastereomeric Macrocyclic Boronic Esters Composed of Two Chiral Units

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Supporting Information

ABSTRACT: Controlled construction of four out of five diastereomers of macrocyclic boronic ester was achieved in high yield by utilizing the self-assembly of two chiral components with the proper choice of reaction conditions. Three diastereomers could be constructed as enantiopure forms by properly changing the chirality combination between the two building blocks. Furthermore, the methodology could be applicable to the three-component self-assembly of enantiopure macrocyclic boronic esters having two different diboronic acid moieties.

Self-assembly of chiral, discrete structures based on the reversible metal−ligand coordination[1] or covalent bond formation[2,3] is becoming a powerful tool for the construction of functional architectures, which often exhibit characteristic properties that could not be attained by achiral, small organic molecules.[4−6] A majority of reported examples have been limited to the systems which could afford one enantiopure architecture selectively from a set of component molecules.[4−8] As for the self-assembly of chiral but racemic architectures, highly diastereoselective systems have been realized in which a single, racemic compound is employed as one of the component molecules,[9−12] whereas the self-assembly from two chiral, racemic components has not been explored probably due to the apparent difficulty in controlling the assembly process where the possible diastereomers increases considerably.[13,14] Therefore, the development of a new system, which enables the selective self-assembly of diverse enantiomeric architectures from the same set of component molecules, is highly desirable for the further growth of this field. Herein, we performed an extensive study on the self-assembly from two chiral components: indacene-type chiral bis(1,2-diol) **1** and chiral binaphthyl diboronic acid **2**, which led to the establishment of the prominent methodology for the divergent self-assembly of chiral architectures.

Bis(1,2-diol) **1** was used as one building block since we have already found that the diastereoselective self-assembly of racemic discrete boronic esters was possible by utilizing reversible boronic ester formation[3d] of racemic **1** with achiral di- or triboronic acid.[11e−g] In the previous cases, there were only two possible diastereomers (homo- and heterochiral isomers) for each 2:2, 3:3, and 3:2 complex of two components (abbreviated as [2 + 2], [3 + 3], and [3 + 2]). In contrast, by introducing another chiral component, diboronic acid **2**, the number of possible diastereomers becomes five for [2 + 2], which makes the selective construction of each diastereomer increasingly difficult.

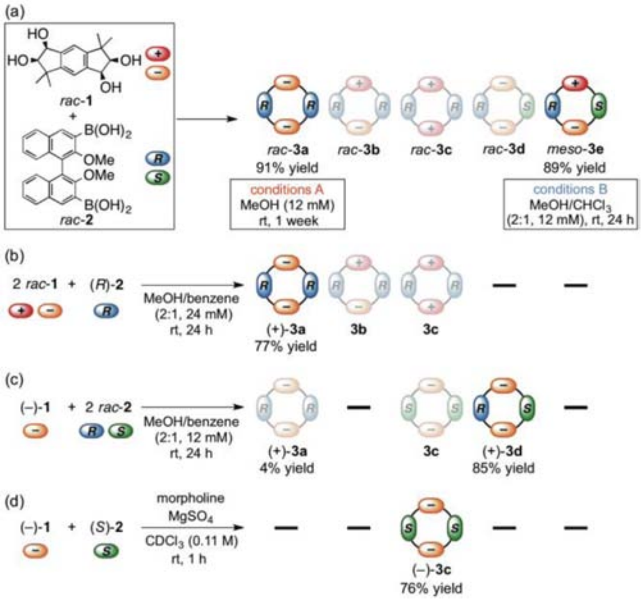

Figure 1. Controlled self-assembly of four diastereomers **3a**, **3c**, **3d**, and **3e**. (a) Self-assembly of *rac*-**3a** (conditions A) and *meso*-**3e** (conditions B) from *rac*-**1** and *rac*-**2**. Possible five diastereomers of [**2** + **2**] are shown. One enantiomer of each diastereomer is shown except *meso*-compound **3e**. (b) Self-assembly of (+)-**3a** from *rac*-**1** (2 mol. amt.) and (*R*)-**2**. Possible three enantiopure diastereomers of [**2** + **2**] are shown. (c) Self-assembly of (+)-**3d** from (−)-**1** and *rac*-**2** (2 mol. amt.). Possible three enantiopure diastereomers of [**2** + **2**] are shown. (d) Self-assembly of (−)-**3c** from (−)-**1** and (*S*)-**2**.

Self-assembly of bis(1,2-diol) **1** and binaphthyl diboronic acid **2** was examined with four types of chirality combinations between **1** and **2** (Figure 1). Initially, both racemic **1** and **2** were used for the self-assembly (Figure 1a). When equimolar amounts of *rac*-**1** and *rac*-**2** were mixed in MeOH at room temperature, a precipitate immediately began to form in the reaction mixture. Although ^{1}H NMR spectrum of the precipitate collected after 5 min by filtration exhibited the existence of a complex mixture of oligomeric boronic esters, the ratio of a macrocyclic boronic ester gradually increased with time. A single, thermodynamically stable product was obtained

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in 91% yield after stirring for 1 week [Figure 1a, conditions A, Table S1 in the Supporting Information (SI)]. Formation of [2 + 2] was indicated by FAB-MS analysis of the precipitate. Although there were five possible diastereomers **3a**−**3e** for [2 + 2], the precipitate exhibited a simple ^{1}H NMR spectrum, in which only one set of signals was observed for each proton (Figure 2a). X-ray crystallographic analysis of the single crystal obtained by the recrystallization of the precipitate revealed that the crystal was a racemic crystal, which consisted of both enantiomers of **3a** composed of the same enantiomers of both **1** and **2** (Figure 3b). The diastereoselectivity of the precipitate was dramatically changed when the same components were mixed in methanol/chloroform (2:1) mixed solvent system (Figure 1a, conditions B, Tables S2 and S3 in the SI). The ^{1}H NMR spectrum of the precipitate exhibited two kinds of signal for all protons, indicating the formation of another macrocyclic boronic ester in 89% yield (Figure 2b). The structure could be determined by X-ray analysis of its single crystal as *meso*-**3e** composed of the different enantiomers of both **1** and **2** (Figure 3c). Thus, two diastereomers of [2 + 2], *rac*-**3a** and *meso*-**3e**, could be selectively constructed and precipitated out in high yields from *rac*-**1** and *rac*-**2** simply by changing the reaction solvent. Powder X-ray diffraction (PXRD) analysis of the precipitates revealed that the precipitates of *rac*-**3a** and *meso*-**3e** were amorphous solid and aggregates of microcrystals, respectively (Figure S5a in the SI). Therefore, the dramatic change in the diastereoselectivity should be attributed to the solvent-induced diastereoselective crystallization of *meso*-**3e** similar to our previously reported crystallization-induced selective self-assembly of boronic esters.[11e−g,15,16] To further confirm the role of the cosolvent, dynamic nature of the product was explored. When *rac*-**3a** was refluxed in methanol/chloroform (1:2) mixed solvent system,[17] *rac*-**3a** was cleanly converted to *meso*-**3e** in 97% yield (Figure S1 in the SI).[18]

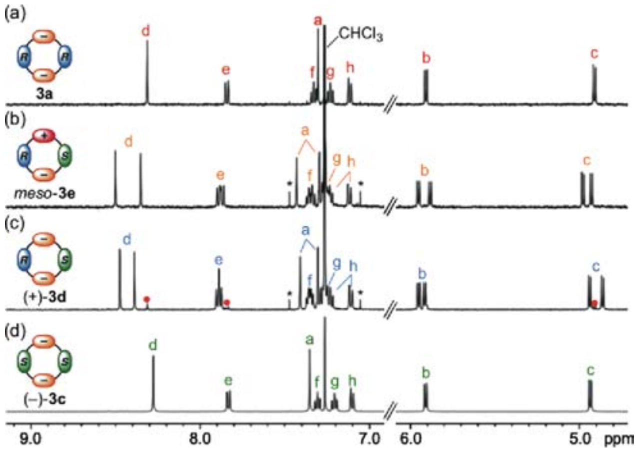

Figure 2. Partial ^{1}H NMR spectra (500 MHz) of four diastereomers (in CDCl$_3$, rt). (a) Partial ^{1}H NMR spectrum of **3a** obtained in Figure 1a (conditions A) and Figure 1b. (b) Partial ^{1}H NMR spectrum of *meso*-**3e** obtained in Figure 1a (conditions B). (c) Partial ^{1}H NMR spectrum of (+)-**3d** obtained in Figure 1c. The trace signals marked with the red circle correspond to (+)-**3a** (other signals are overlapped). (d) Partial ^{1}H NMR spectrum of (−)-**3c** obtained in Figure 1d. The proton assignments of these spectra correspond to the labels shown in Figure 3a.

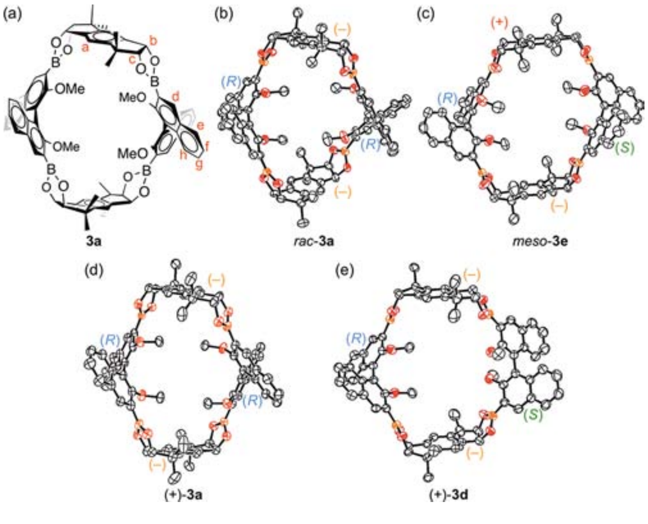

Figure 3. Chemical and X-ray structure of macrocyclic boronic esters. (a) Chemical structure of **3a**. The labels (a−h) correspond to the assignment of ^{1}H NMR signals in Figure 2. (b−e) ORTEP structures of *rac*-**3a** (b), *meso*-**3e** (c), (+)-**3a** (d), and (+)-**3d** (e) with thermal ellipsoids shown at 30% (b,d) or 50% (c,e) probability (C = black, O = red, B = orange). All hydrogen atoms and solvents are omitted for clarity.

Next, the selective self-assembly of enantiopure diastereomers was examined by changing the chirality combinations of two components, wherein at least one component was employed as an enantiopure form. Enantiopure (+)-**3a** could be constructed as precipitate in 77% yield when (*R*)-**2** (>99% ee) was mixed with 2 molar amounts of *rac*-**1** in methanol/benzene mixed solvent system (Figure 1b, Tables S4−S7 in the SI).[19] The structure of (+)-**3a** was confirmed by X-ray analysis (Figure 3d). It should be noted that the optical resolution of *rac*-**1** occurred during the self-assembly process[14] and other possible diastereomers **3b** and **3c** were not formed at all. Enantiopure (−)-**1** could be isolated in quantitative yield after (+)-**3a** was treated with 30% aqueous H_2O_2 solution. Enantioenriched (+)-**1** was also obtained from the filtrate (Figure S3 in the SI).

Another enantiopure diastereomer (+)-**3d** was obtained as precipitate in 85% yield by the self-assembly of (−)-**1** and *rac*-**2** (2 mol. amt.) in methanol/benzene (2:1) mixed solvent system (Figure 1c).[16,19] Although a trace amount of (+)-**3a** was detected in the ^{1}H NMR spectrum of the precipitate, the major compound was another boronic ester (Figure 2c), the structure of which was confirmed by X-ray analysis to be (+)-**3d** composed of the same enantiomers of **1** and the different enantiomers of **2** (Figure 3e).

Another combination of chirality, (−)-**1** and (*S*)-**2**, was also examined aiming at the construction of the third enantiopure diastereomer **3c** (Figure 1d). Although complex mixtures of oligomeric boronic esters were obtained as precipitates when the two components were mixed in methanol solution with various additives (Tables S9−S11 and Figure S2 in the SI), further investigation finally revealed that (−)-**3c** could be constructed as a predominant compound in CDCl$_3$ solution (not as precipitate) when morpholine (5 mol. amt.) and MgSO$_4$ (4 mol. amt.) were added to the mixture of (−)-**1** and (*S*)-**2**. After removing MgSO$_4$ by filtration, the filtrate was purified by gel permeation chromatography to give (−)-**3c** in 76% yield, which exhibited a simple ^{1}H NMR spectrum (Figure 2d). FAB-MS and DOSY NMR analysis of the product supported the formation of [2 + 2] (Figure S4 in the SI).

As shown in Figure 1a,c, the selective construction of the macrocyclic boronic esters (+)-**3d** and *meso*-**3e** composed of the different enantiomers of the boronic acid **2** was realized by utilizing the chiral discrimination feature in the assembly process. The methodology was then applied to the construction of unsymmetrical enantiopure macrocyclic boronic esters, which have different boronic acid units with different chiralities. Generally, the incorporation of two building blocks with the same functional group into one discrete structure is difficult to achieve in the reversible covalent bond-based self-assembly, and the reported examples are limited to achiral systems.[20] When each 0.5 molar amount of (*S*)-dimethoxy diboronic acid **2** and (*R*)-diethoxy diboronic acid **4** were mixed with (−)-**1** in methanol/THF (2:1) mixed solvent system at room temperature for 24 h, a macrocyclic boronic ester was obtained as a precipitate in high selectivity (Figure 4a, conditions A, and Table S12 in the SI). The incorporation of different boronic acid units was supported by ^{1}H NMR spectrum, which exhibited the existence of both methoxy and ethoxy groups (Figure 4b, top). Signals of other protons were similar to those of (+)-**3d**. X-ray crystallographic analysis confirmed the formation of the desired structure (+)-**5a** (Figure S10 in the SI). Similarly, (−)-**5b** could be constructed by three-component self-assembly from *rac*-**1**, (*S*)-**2** (0.5 mol. amt.), and (*R*)-**4** (0.5 mol. amt.) in methanol/chloroform (2:1) at room temperature for 24 h (89% yield, Figure 4a, conditions B, and Table S13 in the SI). All protons of each bis(1,2-diol) and diboronic acid unit were observed independently in ^{1}H NMR spectrum of the product, indicating the formation of unsymmetrical structure (Figure 4b, bottom). The structure of (−)-**5b** could also be confirmed by X-ray crystallographic analysis (Figure S11 in the SI). Note that **5b**, constructed from *rac*-**1** with quasi-racemate (*S*)-**2** and (*R*)-**4**, is a chiral compound owing to the incorporation of different boronic acid units, although **3e**, constructed from *rac*-**1** with *rac*-**2**, is *meso*-compound.

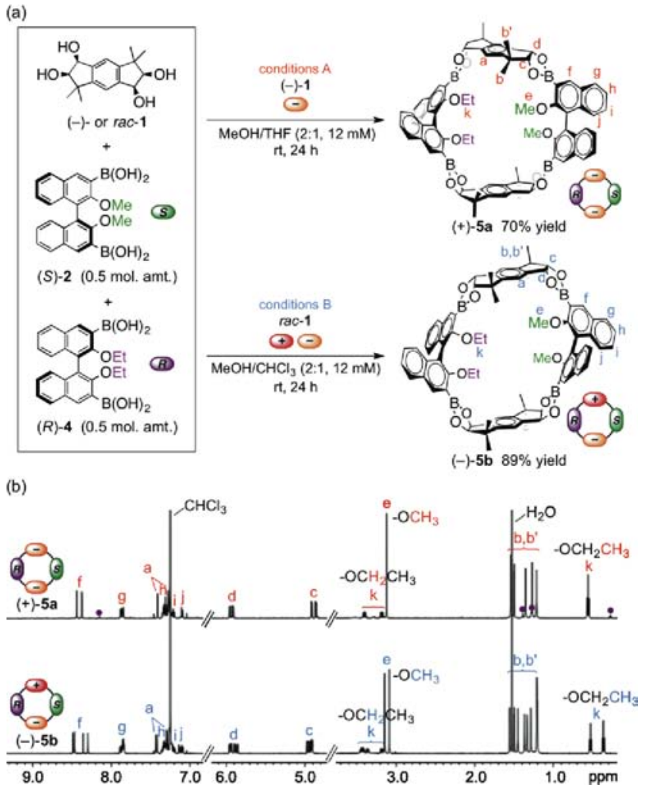

Figure 4. Three-component self-assembly of **5a** and **5b**. (a) Self-assembly of (+)-**5a** from (−)-**1**, (*S*)-**2**, and (*R*)-**4** (conditions A). Self-assembly of (−)-**5b** from *rac*-**1**, (*S*)-**2**, and (*R*)-**4** (conditions B). (b) ^{1}H NMR spectra (500 MHz) of (+)-**5a** (top) and (−)-**5b** (bottom) in CDCl$_3$ at room temperature. The proton assignments of these spectra correspond to the labels shown in panel a. The trace signals marked with the purple circle correspond to the 2:2 complex of (−)-**1** and (*R*)-**4** (other signals are overlapped or not detected).

In conclusion, we achieved controlled construction of four out of five diastereomers of macrocyclic boronic ester [**2** + **2**] in high yield by utilizing the self-assembly of two chiral components with the proper choice of reaction conditions. In particular, three diastereomers could be constructed as enantiopure forms by properly changing the chirality combination between the two building blocks. The construction of enantiopure architectures is highly desirable considering their applications. To the best of our knowledge, this is the first example that realized the construction of more than two enantiopure diastereomers of one discrete self-assembled structure. Moreover, the methodology also enabled another challenging task in the self-assembly of discrete molecules: incorporation of heterocomponents into one self-assembled structure. That is, enantiopure macrocyclic boronic esters, which consist of two different boronic acid units, could easily be constructed by using quasi-racemate. The basic concept of the methodology demonstrated here, that is, changing the chirality combination of two chiral components, would not be specific to the self-assembly based on boronic ester formation, thus should be applicable to other self-assembly systems to generate diverse enantiopure architectures. Further studies on the divergent self-assembly of enantiopure boronic esters from functional chiral boronic acids are now in progress.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Additional experimental details, characterization data of new compounds, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(16) The result of solubility measurement of each diastereomer indicated that the diastereoselective precipitation was not attributed to a simple solubility difference (Tables S14 and S15 in the SI).

(17) Higher amount of chloroform was used and the reaction was carried out under refluxing conditions so as to facilitate the conversion of *rac*-**3a** to *meso*-**3e** since *rac*-**3a** was recovered in 84% yield when *rac*-**3a** in methanol/chloroform (2:1) was stirred at room temperature for 24 h.

(18) Interestingly, *meso*-**3e** was not converted to *rac*-**3a** in refluxing methanol (Figure S1 in the SI). PXRD analysis of the recovered *meso*-**3e** showed the existence of a crystalline structure, which was not identical to the original precipitate of *meso*-**3e** obtained from methanol/chloroform (2:1) solution (Figure S5b in the SI). It is likely that the existence of the crystalline structure prevented the conversion of *meso*-**3e** to *rac*-**3a** although more detailed investigation is necessary.

(19) The major diastereomer in the precipitate was the thermodynamic product (Tables S7 and S8 in the SI). PXRD analysis of the precipitate exhibited the existence of a crystalline structure (Figure S5c in the SI).

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