Asymmetric catalysis mediated by a mirror symmetry-broken helical nanoribbon

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Although chirality has been recognized as an essential entity for life, it still remains a big mystery how the homochirality in nature emerged in essential biomolecules. Certain achiral motifs are known to assemble into chiral nanostructures. In rare cases, their absolute geometries are enantiomerically biased by mirror symmetry breaking. Here we report the first example of asymmetric catalysis by using a mirror symmetry-broken helical nanoribbon as the ligand. We obtain this helical nanoribbon from a benzoic acid appended achiral benzene-1,3,5-tricarboxamide by its helical supramolecular assembly and employ it for the Cu2+-catalyzed Diels–Alder reaction. By thorough optimization of the reaction (conversion: >99%, turnover number: ~90), the enantiomeric excess eventually reaches 46% (major/minor enantiomers = 73/27). We also confirm that the helical nanoribbon indeed carries helically twisted binding sites for Cu2+. Our achievement may provide the fundamental breakthrough for producing optically active molecules from a mixture of totally achiral motifs.
Chirality has been recognized as an essential entity for life. However, it still remains a big mystery how the homochirality in nature emerged in essential biomolecules, such as sugars and amino acids

Certain achiral molecules are known to form crystals adopting a chiral geometry, which usually form as a conglomerate, i.e., a racemic mixture of enantiomorphous crystals. Post chemical transformation of such geometrically chiral single crystals may afford enantiomerically enriched products. This is one of the typical approaches to absolute asymmetric synthesis; which has attracted long-term attention since the time of Pasteur. If mirror symmetry breaking occurs in the crystallization of achiral compounds, a mixture of unequal numbers of enantiomorphous crystals forms. For example, Kondapudi et al. reported that stirred crystallization is often effective to induce mirror symmetry breaking, leading to a high enantiomeric excess (ee) of the resulting crystal. Notably, Viedma et al. later demonstrated that continuous grinding of a slurry of a racemic mixture of enantiomorphic crystals could cause its deracemization to produce an enantiopure product (Viedma ripening).

Especially, Blackmond and coworkers for the first time experimentally supported a hypothesis of the emergence of solid-phase homochirality from racemic conglomerates composed of rapidly racemizing enantiomers. Tsogoeva and coworkers achieved a complete deracemization (100% ee) of an asymmetric reaction product by combining its reversible asymmetric reaction and physical grinding of crystals involved. Nevertheless, an even more challenging subject to tackle is how one can amplify the enantiomeric bias generated as a consequence of mirror symmetry breaking. In 2008, Soai and coworkers employed such a mirror symmetry-broken crystalline mixture of cytosine as a chiral auxiliary for the enantioselective addition reaction between diisopropylzinc and pyrimidine-5-carbaldehyde. Although the range of eligible substrates is highly limited, this reaction is well-known for amplifying the enantiomeric bias in an autocatalytic manner.

Some covalent helical polymers and their noncovalent analogues, prepared from certain chiral monomers, are known to serve as chiral ligands for asymmetric catalysis. Sugino and coworkers have developed a series of helical poly(quinoxaline-2,3-diy) copolymers bearing metal-binding phosphate pendants as chiral ligands for several palladium-catalyzed asymmetric reactions. Examples of noncovalent helical supramolecular assemblies include hydrogen-bonded helical stacks of chiral benzene-1,3,5-tricarboxamide (BTA) derivatives. In our previous paper, we reported that an achiral BTA motif that was appended with an ethyl cinnamate group in each of its three side chains self-assembled into helical nanoribbons, where mirror symmetry breaking occurred under certain conditions to form a mixture of unequal numbers of right-handed (P) and left-handed (M) helical nanoribbons. We envisioned that such mirror symmetry-broken supramolecular assemblies might mediate asymmetric reactions if they are properly designed to accommodate catalytically active transition metal ions.

Herein, we report the first example of asymmetric catalysis realized by using a mirror symmetry-broken helical supramolecular assembly of an achiral BTA motif as the ligand (Fig. 1). The achiral BTA derivative carries a benzoic acid group in each of its three arms for chelating a Cu$^2+$ ion that can catalyze the Diels–Alder cycloaddition reaction between aza-chalone and cyclopentadiene. The enantiomeric excess of the reaction reaches 46% (conversion: >99%, turnover number: ~90).

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**Fig. 1** Mirror symmetry breaking of helical supramolecular nanoribbons for asymmetric catalysis. **a, b** Molecular structure of the achiral BTA$^{3+}$ monomer and schematic representation of the preparation of helical PBTABA$^{3+}$ nanoribbons with either ($P$)- or ($M$)-dominant helical handedness by applying rotary stirring during the cooling process of a DMF/water solution of BTA$^{3+}$. **c** Diels–Alder cycloaddition reaction between aza-chalone and cyclopentadiene catalyzed by Cu$^{2+}$ in combination with PBTABA$^{3+}$ or PBTABA$^{3+}$. The reaction affords the endo isomer preferentially (~90%). The ($S$)-endo and ($R$)-endo enantiomers were obtained preferentially when ($P$)-PBTABA$^{3+}$ and ($M$)-PBTABA$^{3+}$ were used, respectively.
Results

Mirror symmetry breaking of helical nanoribbons. BTA\textsuperscript{BA} was synthesized and unambiguously characterized (see Supplementary Methods, Supplementary Figs. 1–6). Analogous to previous examples\textsuperscript{41,42,55}, BTA\textsuperscript{BA} self-assembled into PBTABA, a supramolecular helical nanoribbon (Fig. 1b). We found that this self-assembly event proceeds with mirror symmetry breaking to afford either (P)-dominant PBTABA ((–)-PBTABA) or (M)-dominant PBTABA ((+)-PBTABA) (Fig. 1b) under physical agitation generated by magnetic rotary stirring. The method for the preparation of mirror symmetry-broken PBTABA is slightly complicated as described below (Fig. 2) but quite analogous to that reported in our previous paper\textsuperscript{42}. Water (0.3 mL) was added to a N,N-dimethylformamide (DMF, 0.7 mL) solution of BTA\textsuperscript{BA} (3 mg, 5.3 × 10\textsuperscript{-6} mol) in a 5-mL cylindrical glass vial (Fig. 2a), whereupon the mixture, when allowed to stand at 25 °C for 2 h, underwent physical gelation (Fig. 2b and Supplementary Tables 1 and 2). The gel was heated at 100 °C for 3 min, and the resultant homogeneous solution (Fig. 2c) was allowed to cool to 25 °C with magnetic rotary stirring (1200 rpm) for 40 min, yielding a white suspension (Fig. 2d, e), which turned out to be optically active (see below). This result was highly reproducible (Supplementary Fig. 7), except that the sign of the circular dichroism (CD) activity at 316 nm of the resultant suspension was either negative ((–)-PBTABA) or positive ((+)-PBTABA) stochastically (see below). Although the CD sign was independent of the direction of rotary stirring (Supplementary Fig. 7), a stable CD activity, once emerged, lasted without fading unless the suspension was heated to transform into a homogeneous solution. Note that, as demonstrated for the suspension of (–)-PBTABA in Supplementary Fig. 8, its CD spectrum was barely contaminated with a spectral artifact due to linear dichroism (LD). Next, an aliquot of the suspension was taken out from the glass vial and cast on a silicon wafer for air-drying, followed by evacuation under reduced pressure. Scanning electron microscopy (SEM) of the resulting specimens revealed that (–)-PBTABA consisted mostly of (P)-helical nanoribbons (Fig. 2d), whereas (M)-helical nanoribbons were dominant in (+)-PBTABA (Fig. 2e). The gel (Fig. 2b) was CD-silent (Supplementary Figs. 9 and 10). Consistently, its cross-linked 3D network appeared to be composed of equal numbers of (P)- and (M)-helical nanoribbons (Fig. 2b). The same held true when a clear, hot solution of BTA\textsuperscript{BA} (Fig. 2c) was allowed to cool to 25 °C without rotary stirring (Fig. 2f and Supplementary Fig. 11). Not only magnetic rotary stirring but also mechanical rotary stirring using an overhead stirrer, vortex mixing, and even sonication resulted in the formation of a CD-active suspension of (–)-PBTABA or (+)-PBTABA (Supplementary Fig. 12). Interestingly, an ethyl ester derivative of BTA\textsuperscript{BA} did not assemble into helical nanoribbons under otherwise identical conditions to those for BTA\textsuperscript{BA} (Supplementary Fig. 13), suggesting that the peripheral carboxylic acid groups of BTA\textsuperscript{BA} play a critical role in its helical assembly. Fourier transform infrared (FT-IR) spectroscopy of a xerogel of PBTABA, dried under reduced pressure, showed small vibrational bands at 2665 and 2543 cm\textsuperscript{-1} (Supplementary Fig. 14), which are characteristic of the OH stretching vibrations due to hydrogen-bonded dimers of carboxylic acids. Two bands at 3311 and 1654 cm\textsuperscript{-1}, assignable

![Fig. 2 Procedures for the preparation of mirror symmetry-broken helical PBTABA nanoribbons. a Photograph of a DMF (0.7 mL) solution of BTA\textsuperscript{BA} (3 mg, 5.3 × 10\textsuperscript{-6} mol). b Photograph of a CD-silent gel of PBTABA ([PBTABA] = 5.3 mM) formed in DMF/water (7/3, v/v; 1 mL) and SEM image of its air-dried specimen. The gel can be prepared via an antisolvent method through direct addition of water (poor solvent) into a DMF (good solvent) solution of BTA\textsuperscript{BA} without magnetic rotary stirring. c Photograph of a DMF/water (7/3, v/v; 1 mL) solution of BTA\textsuperscript{BA} (5.3 mM) after heating at 100 °C for 3 min. d, e Typical photographs of CD-active DMF/water (7/3, v/v; 1 mL) suspensions of PBTABA ([PBTABA] = 5.3 mM) and SEM images of their air-dried specimens. The suspensions of (–)-PBTABA and (+)-PBTABA display mirror-image CD spectra of one another (Fig. 4b). They can be prepared by natural cooling of a clear, hot DMF/water (7/3, v/v; 1 mL) solution of BTA\textsuperscript{BA} (5.3 mM) with magnetic rotary stirring at 1200 rpm for 40 min. f Photograph of a CD-silent precipitate of PBTABA ([PBTABA] = 5.3 mM) in DMF/water (7/3, v/v; 1 mL) and SEM image of its air-dried specimen. This precipitate can be prepared by natural cooling of a clear, hot DMF/water (7/3, v/v; 1 mL) solution of BTA\textsuperscript{BA} (5.3 mM) without magnetic rotary stirring.](https://doi.org/10.1038/s41467-019-11840-3)
to the stretching vibrations of hydrogen-bonded amide NH and C–O groups, respectively, were also found. We found that BTA\textsuperscript{BA} is quite soluble in DMF, where it showed a much sharper absorption band at 290 nm (Supplementary Fig. 15) than its self-assembled state ([BTA\textsuperscript{BA}]) = 5.3 mM) in the gel formed in DMF/water (7/3, v/v, Fig. 2b). Compared with the DMF solution of BTA\textsuperscript{BA}, the gel was much more luminescent (~300 times) at 447 nm upon excitation at 290 nm (Supplementary Fig. 16), suggesting that the BTA\textsuperscript{BA} units in the gel network are located in a highly congested environment. Further to note, a DMF/water suspension of PBTABA (Fig. 2d/e) was silent in polarized optical microscopy (Supplementary Fig. 17), and a wet sample of PBTABA isolated by centrifugation of its suspension showed no X-ray diffraction (Supplementary Fig. 18). These results allow us to conclude that PBTABA is a noncrystalline material.

When a clear, hot solution of BTA\textsuperscript{BA} (Fig. 2c) in DMF/water (7/3, v/v) was allowed to cool to 25 °C with continuous rotary stirring, the absorption dissymmetry factor (\(\Delta_{\text{abs}}\)) of the resulting suspension, evaluated from the CD intensity relative to the absorbance at 316 nm, gradually increased with the stirring time and then leveled off in 40 min at 2.2 \(\times\) 10\(^{-2}\) (Supplementary Fig. 19). We noticed that faster stirring resulted in the emergence of a larger CD intensity at 316 nm (Supplementary Fig. 20). Rotary stirring of the CD-silent gel did not induce any CD band (Supplementary Fig. 21), indicating that physical agitation such as rotary stirring does not affect the helical handedness of the PBTABA nanoribbons once formed. From these observations, we proposed a mechanism for the formation of the (P)- or (M)-dominant helical nanoribbons from BTA\textsuperscript{BA} as follows: BTA\textsuperscript{BA} self-assembles into (P)- and (M)-helical short 1D aggregates (primary nucleation). Such aggregates grow up to longer (P)- and (M)-helical nanoribbons, respectively. By physical agitation, the long helical nanoribbons preferentially break up into numerous short aggregates with the same handedness (secondary nucleation). In the resulting nonequilibrated state, once the mirror symmetry of the PBTABA nanoribbon is broken as a consequence of stochastic fluctuation, a small chiral bias thus generated can be amplified through repeated cycles of the secondary nucleation, as proposed for the mechanism of chiral amplification via thermal cycling or attrition in conglomerate crystal systems\(^9\)-\(^11\). Accordingly, the addition of (P)-dominant PBTABA as a seed into a DMF/water (7/3, v/v; 1 mL) solution of BTA\textsuperscript{BA} (5.3 mM) before rotary stirring always resulted in the formation of a suspension of (P)-dominant PBTABA with a negative CD band at 316 nm (Supplementary Fig. 22).

Asymmetric catalysis. Previously, groups of Engberts\(^56,57\) and Roelfes\(^25,27\) reported highly enantioselective Cu\textsuperscript{2+}-catalyzed Diels–Alder reactions between aza-chalcone and cyclopentadiene using amino acids and DNA as the chiral mediators, respectively. Inspired by these successful examples, we chose the same reaction to investigate a possibility of mirror symmetry-broken PBTABA nanoribbons as a chiral ligand. Typically, Cu\textsuperscript{2+}-coordinated (−)-PBTABA or (+)-PBTABA ((Cu\textsuperscript{2+})/[BTA\textsuperscript{BA}] = 1.0%), employed as a catalyst for the Diels–Alder reaction (Fig. 3a), was prepared by mixing an aqueous solution of Cu(NO\textsubscript{3})\textsubscript{2} (4.1 mM, 13 µL) and a DMF/water (7/3, v/v; 1 mL) suspension of (−)-PBTABA or (+)-PBTABA ([BTA\textsuperscript{BA}] = 5.3 mM, Fig. 2d, e) at 25 °C for 1 h. The luminescence of PBTABA was quenched upon being mixed with Cu(NO\textsubscript{3})\textsubscript{2} (Supplementary Fig. 23), suggesting that PBTABA accommodates Cu\textsuperscript{2+} presumably at the peripheral carboxylate units. As observed by SEM and CD spectroscopy, PBTABA maintained its helical nanoribbon structure even after being mixed with Cu\textsuperscript{2+} (Supplementary Fig. 24). For the Diels–Alder reaction, an acetonitrile (40 µL) solution of azachalcone (1 mg) and freshly distilled cyclopentadiene (40 µL) were successively added to a DMF/water (7/3, v/v) suspension of (−)-PBTABA/Cu\textsuperscript{2+} or (+)-PBTABA/Cu\textsuperscript{2+}, and the mixture was stirred at 25 °C. After 36 h, the reaction mixture was extracted with ethyl acetate (0.5 mL), and an organic extract, after being evaporated to dryness, was subjected to chiral high performance liquid chromatography (HPLC), where the endo isomer was revealed to be the major product (−90%, conversion: >99%, turnover number: ~90, Fig. 3b, c). Of particular interest, (−)-PBTABA/Cu\textsuperscript{2+} (Fig. 2d) and (+)-PBTABA/Cu\textsuperscript{2+} (Fig. 2e) preferentially afforded the enantiomers of (S)-endo (Fig. 3b) and (R)-endo (Fig. 3c), respectively. We conducted a total of 76 runs of the Diels–Alder reaction using 76 different batches of (−)-PBTABA/Cu\textsuperscript{2+} and (+)-PBTABA/Cu\textsuperscript{2+} under the conditions described above and confirmed that this stereochemical correlation between the catalyst and product was perfectly reproduced (Fig. 3d and Supplementary Table 3). However, there is no clear correlation between the CD intensities of the catalyst and enantiomeric excess values of the product (Supplementary Fig. 25). We confirmed that the nanoribbons of PBTABA after the reaction were shorter than those before the reaction (Supplementary Fig. 26). However, the ee value of the endo isomer did not substantially change with the reaction time (Supplementary Fig. 27). In sharp contrast, repeated usage of the catalyst, isolated each time via centrifugation from the reaction mixture, resulted in lowering of the enantiomeric excess of the product (Supplementary Table 4). Meanwhile, CD-silent PBTABA/Cu\textsuperscript{2+} nanoribbons (Fig. 2b) also catalyzed the Diels–Alder reaction. However, as expected, the reaction was not enantioselective (Supplementary Fig. 28), as in the case where PBTABA was not employed for the Cu\textsuperscript{2+}-catalyzed Diels–Alder reaction (Supplementary Fig. 29).

We attempted to optimize the conditions for the Diels–Alder reaction. First, we varied [Cu\textsuperscript{2+}] versus [BTA\textsuperscript{BA}] and found that the ee value of the endo isomer reached a maximum at [Cu\textsuperscript{2+}]/[BTA\textsuperscript{BA}] = 1.0% (Fig. 3e). When [Cu\textsuperscript{2+}]/[BTA\textsuperscript{BA}] exceeded 1.0%, the ee value of the endo isomer dropped, most likely because of a possible increase in the amount of Cu\textsuperscript{2+} unanchored to the helical PBTABA nanoribbons. A strong base such as NaOH is expected to deprotonate the benzoic acid groups of PBTABA to promote the anchoring of Cu\textsuperscript{2+} onto the helical PBTABA nanoribbons\(^36\). In fact, as shown in Fig. 3f, the addition of NaOH to the reaction system resulted in a considerable enhancement of the enantioselectivity of the reaction, where an average ee value of >40% was realized at [NaOH]/[BTA\textsuperscript{BA}] = 50% with the highest ee value of 46% (major/minor enantiomers = 73/27; Supplementary Fig. 30).

Chirality transfer via electrostatic interaction. We explored the stereochemical environment of the cation-binding sites in the helical PBTABA nanoribbon by using a cationic fluorescent dye, methylene blue (MB, Fig. 4a). When an aqueous solution of MB (21.2 mM, 50 µL) was added to a DMF/water (7/3, v/v; 1 mL) suspension of mirror symmetry-broken (−)-PBTABA ([BTA\textsuperscript{BA}] = 5.3 mM, [MB]/[BTA\textsuperscript{BA}] = 20%), a broad positive CD band at 570–700 nm emerged (Fig. 4d and Supplementary Fig. 31). When (+)-PBTABA ([BTA\textsuperscript{BA}] = 5.3 mM) was employed instead of (−)-PBTABA for mixing with MB, the sign of the CD band at 570–700 nm was negative (Fig. 4d and Supplementary Fig. 31). Considering that MB has an absorption band at 570–700 nm (Supplementary Fig. 31), the CD bands in this region are silent in polarized optical microscopy (Supplementary Fig. 31), the CD bands in this region are silent in polarized optical microscopy (Supplementary Fig. 31), the CD bands in this region are silent in polarized optical microscopy (Supplementary Fig. 31), the CD bands in this region are silent in polarized optical microscopy (Supplementary Fig. 31), the CD bands in this region are silent in polarized optical microscopy (Supplementary Fig. 31).
Fig. 3 Enantioselective Diels–Alder reaction catalyzed by Cu²⁺-coordinated PBTA²⁺ nanoribbons. a) Diels–Alder reaction between aza-chalcone and cyclopentadiene catalyzed by (−)-PBTA²⁺/Cu²⁺ or (+)-PBTA²⁺/Cu²⁺, which preferentially affords the endo isomer (−90%). b) Chiral HPLC traces of the reaction mixtures in run No. 1 (b) and 34 (c) in (d). Symbols ee (S) and ee (R) represent enantiomeric excess (ee) values of the endo isomers with the dominance of their (S)-endo and (R)-endo enantiomers, respectively. d) Statistical ee values of the endo isomers obtained when (−)-PBTA²⁺/Cu²⁺ and (+)-PBTA²⁺/Cu²⁺, which preferentially afford the endo isomer (~90%), are used as the catalysts. e) Effects of [Cu²⁺]/[BTA²⁺] on the ee values of the endo isomers obtained at 25 °C with (−)-PBTA²⁺/Cu²⁺ or (+)-PBTA²⁺/Cu²⁺. f) Effects of [NaOH]/[BTA²⁺] on the ee values of the endo isomers obtained at 25 °C with (−)-PBTA²⁺/Cu²⁺ or (+)-PBTA²⁺/Cu²⁺ at [Cu²⁺]/[BTA²⁺] = 1.0%, where NaOH was added to the suspensions of (−)-PBTA²⁺ or (+)-PBTA²⁺ prior to the addition of Cu(NO₃)₂. Error bars represent the standard deviation. Source data are provided as a Source Data file.

Discussion
All of these results allow us to conclude that a mirror symmetry-broken helical supramolecular nanoribbon composed of an...
achiral monomer can serve as a chiral ligand for mediating enantioselective catalysis. Although the noncrystalline nature of PBTABA (Supplementary Figs. 17 and 18) does not permit elucidation of its molecular packing, the successful CPL observation from MB in Fig. 4e suggests that the catalytic site having a Cu2+ ion is chiral. As for the modest enantioselectivity of the reaction, we assume that this is due to the helical nanoribbon structure, which is formed by rolling up of a rather planer, sheet structure. It is likely that the catalytic sites located on such a gently curved surface cannot efficiently bias the stereochemical course of the reaction. We also noted that the mirror symmetry-broken helical nanoribbons of PBTABA display intense electronic CD (Δε = 570 L mol⁻¹ cm⁻¹). This is very rare, but some helicene nanoribbons are known to show such an amplification of their molecular packing, the successful CPL observation via chiroptical CD (mdeg) amplification was performed on a Rigaku D/Max-2500 X-ray diffractometer (Japan) with Cu Ka radiation (λ = 1.5406 Å), which was operated at a voltage of 40 kV and a current of 200 mA. Polarized optical microscopy (POM) was performed using a Leica DM2500 upright materials microscope. Chiral HPLC was performed using a Waters 1525 HPLC system with a Daicel Chiralcel® OD-H column.

**Data availability**

The data source underlying Fig. 3b–d and 4b–e and Supplementary Figs. 1–11, 12a, e, h, 14–16, 18–21, 23, 24b, 25 and 27–32 are provided as a Source Data file via figshare (DOI: 10.6084/m9.figshare.8940404).

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Author contributions
Z.S., T.A., and M.L. conceived the project. Z.S., Y.S., T.W., J.J., K.O., T.A., and M.L. designed experiments. Z.S., Y.S., J.J., Y.M., and Y.J. performed and interpreted the experiments. Z.S., T.W., K.O., T.A., and M.L. contributed to the writing and editing of the paper. All the authors discussed the results and commented on the paper. Z.S., T.W., K.O., T.A., and M.L. directed the research.

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