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Asymmetric Transformation Driven by Confinement and Self-Release in Single-Layered Porous Nanosheets

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Abstract: Reported here is the use of single-layered, chiral porous sheets with induced pore chirality for repeatable asymmetric transformations and self-separation without the need for chiral catalysts or chiral auxiliaries. The asymmetric induction is driven by chiral fixation of absorbed achiral substrates inside the chiral pores for transformation into enantiopure products with enantioselectivities of greater than 99% ee. When the conversion is completed, the products are spontaneously separated out of the pores, enabling the porous sheets to perform repeated cycles of converting achiral substrates into chiral products for release without compromising pore performance. Confinement of achiral substrates into two-dimensional chiral porous materials provides access to a highly efficient alternative to current asymmetric synthesis methodologies.

Introduction

Asymmetric induction in chemical transformations has enormous impact on the advancement of nanotechnology and drug discovery.^[1,2] However, the use of chiral catalysts suffers from energy intensive processes such as high cost, difficult recovery, and laborious separations. Although the confinement in chiral spaces can render reactions enantioselective without the help of chiral catalysts, it is hampered by a lack of generality and insufficient enantiomeric purity.^[3–6] The selfassembly of pore units into an extended nanostructure can offer a necessary condition for chiral transformations under confinement.^[7–11] Nevertheless, most of the porous nanostructures are far from the internal cavities with chiral environments required to guide precise asymmetric fixation for clean chiral transformation.^[12–14] Here we report that chiral porous nanosheets are able to perform clean asym-

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metric transformation (>99% ee) of absorbed achiral substrates without the use of chiral catalysts or chiral auxiliaries. When the conversion is completed, the products are spontaneously separated out of the nanosheets, enabling the sheets to perform repeated cycles of converting achiral substrates to release as chiral products.

We envisioned that a single layer porous structure with uniformly discrete cavities would precisely confine all entrapped achiral substrates to the chiral spaces to induce a fixed spatial orientation for exposure of their preferential face to a reagent, because all the pores maintain the structural integrity of individual pores without pore blocks and pore to pore connections caused by layer stackings.^[14–19] Thus, the precise confinement of achiral substrates inside the chiral cavities of the 2D pore assembly would lead to highly efficient asymmetric transformations.

Results and Discussion

Construction of Single-Layered Porous Nanosheets with Induced Chiral Pores

To explore the asymmetric induction in chemical transformations purely by confining achiral substrates to a chiral space, we used a single-layered porous sheet assembly containing only achiral building blocks in which the chiral environment of the pores is induced by a memory effect using a chiral template, (S)- or (R)-2,2'-dimethoxy- 1,1'binaphthyl (**BD**; Figure 1 a).^[20] The homochiral porous sheet structures form from the self-assembly of an achiral macrocycle amphiphile, 1 (Figure 1a and Figures S1 and S2 in the Supporting Information), thereby a lack of chiral moieties in its assembly. The primary pore structure of the sheets consists of a paired macrocycle dimer with opposing dendritic chains at the aromatic basal planes. Our earlier study showed that the aromatic plane of 1 adopts a nonplanar conformation which leads the paired aromatic macrocycles to be rotationally offset from each other with a certain twist angle.^[19] In the absence of the chiral template, a twist stack of the nonplanar macrocycle generates a racemic mixture of P- and M-stacked pores in methanol, resulting in circular dichroism (CD)-silent, racemic sheet structures (Figure 2a). In contrast, the selfassembly in the presence of a chiral template generates homochiral porous sheet structures (Figure 2a and Figure S3). When 1 equivalent of (S)-BD as a chiral template was added to the methanol solution of 1, the solution exhibited a near maximum CD signal in the absorption range



Figure 1. Homochiral porous nanosheet for asymmetric transformation and self-separation. a) Molecular structure of host amphiphile 1 and guest (*S*)- or (*R*)-2,2'-dimethoxy-1,1'binaphthyl (BD). The pore chirality of the dimers is induced by memory effect of (*S*)-BD (*P*-stacked pore) and (*R*)-BD (*M*-stacked pore), respectively, which laterally assemble into a \approx 3 nm thick 2D porous sheet structure in MeOH. b) A homochiral porous sheet as a chiral transformer that changes achiral substrates to self-release as chiral products. c) Fixation-driven chiral transformation of the hydride reduction of a ketone and the chiral macrocyclization of a linear substrate in the presence of triflic acid inside the chiral pores of the 2D homochiral porous sheets at room temperature in MeOH.

associated with the aromatic macrocycle of **1** (Figures 2b and c and Figure S4), indicating that the chiral guest drives the stacked macrocycle dimers to adopt the twisted conformation with a clockwise rotation because the strong hydrophobic and π - π interactions between the macrocycle dimer and the chiral guest lead the chiral information to transfer into the dimeric

pore, giving rise to a P-stacked chiral superstructure.^[19] After removal of the chiral template by centrifugation (Figure 2d and Figure S5), the global homochiral packing can be trapped, revealing a chiral memory effect.^[21,22] This was confirmed by CD measurements after complete removal of the chiral guest, which showed that the CD intensity remains unchanged (Figure 2e and Figures S6 and S7). Importantly, the induced chirality of the porous sheet structures is very stable, as illustrated by retaining the CD intensity for at least several months (Figure S8). This stability in chirality is attributed to high rotational restriction in the stacked dimer of the nonplanar macrocycle. The twist angle of the chiral dimer was measured to be 30° using 2D-NMR with rotating frame nuclear Overhauser effect (ROE; Figures S9 and S10). After removal of the chiral guest, cryogenic transmission electron microscopy (cryo-TEM) showed that isolated sheet objects, in lateral dimensions ranging from submicro- to several micrometers are retained, indicating that the sheets are robust and free existence in bulk solution (Figure 2 f). TEM experiments with cast films revealed flat 2D structures (Figure 2g), consistent with the cryo-TEM results. Atomic force microscopy (AFM) analysis showed that the sheets are very flat and uniform with a thickness of 3.0 nm (Figure 2h). Considering the molecular size of 1, this thickness implies that the primary structure consists of 2 molecules in which the aromatic macrocycles face one another (Figure 1a). This was further confirmed by topochemical polymerization of the sheet solution, which produced a pure dimer with a lack of any higher-molecular-weight fractions (Figure S11). This result demonstrates that the dimeric chiral pores created by a chiral memory effect laterally associate into a single-layered homochiral porous sheet structures. The porous sheets derived from (R)-BD exhibit opposite CD signals with a perfect mirror image relationship (Figures 2a and e), indicating that the chirality of the template is transferred to the self-assembly of the macrocycles.

Chiral Reduction in the Homochiral Porous Nanosheets

We envisioned that the pores with a chiral cavity can entrap prochiral ketone substrates with a fixed spatial orientation in a confined chiral space.^[9,23] The preferred spatial orientation of one face over the other toward a nucleophile would lead to the asymmetric transformation of achiral molecules. To corroborate the capability of the homochiral porous sheets for enantioselective transformation of achiral molecules, 4-acetylbiphenyl (S1) was selected as a prochiral substrate (Figure 3a). Titration experiments showed that one pore includes 2 substrate molecules with 96% uptake of the pores (Figures S12 and S13). It is worth noting that the CD signal of the sheets remains unchanged even after inclusion of the substrate (Figure S14), demonstrating that the dimeric macrocycle with a chiral cavity retains a fixed conformation, even with guest inclusion. 2-Acetyl-6-methoxynaphthalene (S2), similar size to S1, can be also entrapped by the porous sheet with 96% uptake. In great contrast, the sheets do not exhibit any apparent inclusion activity for the smaller aromatic derivatives such as 4-t-butyl



Figure 2. The homochiral porous nanosheets induced by chiral memory and their structural characterization. a) CD spectra of $1 (91 \mu M) - (S) - BD$ (91 μM ; red solid line), $1 (91 \mu M) - (R) - BD$ (91 μM ; dark blue solid line), $1 (91 \mu M)$; black dashed line) and (S) - BD (91 μM ; light blue solid line) in methanol solution. b) CD spectra of $1 (91 \mu M)$ with different equivalents of (S)-BD in methanol solution. c) CD intensity at 306 nm of 1 with different equivalents of (S)-BD. Trend lines from (S)-BD indicate the formation of a 2/1 inclusion complex with chiral pores. d) Partial ¹H NMR spectra of 1 (2.74 mM) with (S)-BD (2.74 mM) and after remove (S)-BD (2.74 mM) by centrifugation in [D₄]MeOH/[D₈]THF (3:2 vol/vol). The proton peaks associated with (S)-BD disappear after centrifugation, indicative of the complete removal of (S)-BD from 1P. e) CD spectra of $1P (91 \mu M)$ and $1M (91 \mu M)$ after removal of (S)-BD and (R)-BD, respectively. (f and g) Cryo-TEM image (f) and negatively-stained TEM image (g) of $1P (91 \mu M)$ in methanol solution. h) AFM height image of sheets on mica. The sample film was dropcasted from $1P (91 \mu M)$ in methanol solution. The cross-sectional profiles (top) is taken along the white line.

acetophenone (S3) and 4-methoxy acetophenone (S4), indicative of size selectivity (Figure S12).

To corroborate the fixed chiral orientation of the prochiral substrates inside the chiral cavities, vibrational CD (VCD) experiments were performed with **S1**. When the substrate is entrapped inside the hollow cavities of the sheets with *P*-stacked pores (Figure 3b and Figures S15–S17), the VCD spectrum showed a negative signal in the carbonyl stretching IR region at 1680 cm⁻¹ (Figure 3c and Figure S18), demonstrating that the pores entrap the prochiral substrate to fix a preferential chiral conformer. The enantiomeric sheets based on *M*-stacked pores lead to a mirror-imaged VCD signal, indicating that the pore chirality communicates with the prochiral substrate to fit into the chiral environment. The fixed spatial orientation of prochiral ketones would allow

preferential exposure of one face over the opposite face of the carbonyl group to a nucleophile for an enantioselective reaction (Figure 3d). To corroborate the asymmetric induction in chemical transformation, we added NaBH₄ to the methanol solution of **1** based on *P*-stacked pores containing **S1** at room temperature. Remarkably, the homochiral porous sheets perform quantitative reduction of the ketone substrate within 50 min at room temperature to yield a pure one enantiomer with enantiomeric excess (*ee*) of >99% (Figure 4a and Figure S19). Molecular dynamics (MD) calculations showed that the phenyl group of **S1** in **1P** adopts clockwise rotation with respect to a carbonyl axis, generating less hindered *si* face than *re* face, thereby producing the (*R*)-alcohol (Figure S20), which explains the observed enantiose-lectivity. For a control experiment, we performed an identical



Figure 3. Fixed chiral orientation of prochiral substrates inside chiral cavities. a) Chemical structure of prochiral ketone guests **S1–S4**. b) 1D NOE spectrum from **1P** (2.74 mM)-**S1** (2.74 mM) in $[D_4]MeOH/[D_8]THF$ (3:2, vol/vol). Irradiation at 7.849 ppm (H_g peak) induced NOE peaks at 7.790–7.806 ppm. c) VCD and IR spectra of **1M–S1** (red line) and **1P–S1** (blue line) in the presence of **S1** (1 equivalent) recorded as KBr pellets after normalization of the peak intensities. The induced VCD peak at 1679 cm⁻¹ shows complete mirror image, indicative chiral conformer formed of **S1** in **1M** and **1P**. d) Schematic representation of the fixed chiral conformer and mechanism of asymmetric reduction of **S1** in *P* pore.

reduction of S1 in the absence of the porous sheets (Figure S21). The reaction yielded only a racemic product as expected, indicating that the confinement of the ketone substrate inside the chiral space induces highly efficient asymmetric conversion. S2 based on a naphthalene group also undergoes nearly perfect asymmetric conversion in an identical reaction condition (Figures S22 and S23). Notably, when the reduction is completed, both the chiral products are spontaneously released out of the porous materials because the ketone substrate is converted into a more polar hydroxy product (Figure 4b). After removal of the released products using a Sephadex column, analytical high-performance liquid chromatography (HPLC) measurements of the solutions showed a complete lack of the substrate and product, demonstrating that reduction leads the substrates to spontaneously release out of the internal cavities, which was further confirmed by NMR (Figure 4c and Figures S24 and S25) and fluorescence measurements (Figure S26). The self-release of the enantiomeric product allows the porous sheets to perform consecutive cycles of binding carbonyl substrates to release as enantiomeric products without compromising the pore performance in both uptake capacity and asymmetric conversion (Figure 4d and Figures S19 and S27).

Chiral Macrocyclization under Confinement in Porous Sheets

We considered that the concept of asymmetric induction under confinement can be extended to perform enantioselective macrocyclization which is a crucial step for drug



Figure 4. Asymmetric reduction of prochiral aromatic ketones inside homochiral pores. a) Time-dependent HPLC conversion of **S1** (91 μM) with **1P** (91 μM) in the presence of NaBH₄ in methanol solution. Inset: HPLC spectra of **S1** reduction in the presence and absence of **1P** in methanol solution. b) Time-dependent substrate amount remaining in the homochiral porous nanosheets of **1P** in the presence (orange) and absence (violet) of NaBH₄. c) Time-dependent 1D NOE spectra from **1P** (2.74 mM)-**S1** (2.74 mM) in the presence of NaBH₄ in methanol*d*₄/[D₈]THF (3:2, vol/vol). Irradiation at 7.666–7.692 ppm (H_c peak) induced NOE peaks at 7.624–7.643 ppm (H₃). The induced NOE correlations of H_c-H₃ gradually disappear with time, indicative of the self-release of **P1** from pores. d) Time-dependent HPLC conversions of **S1** (91 μM) with **1P** (91 μM) in the presence of NaBH₄ with repeated cycles.

discovery and nanomedicine.^[24] To date, however, it remains an enormous challenge because of additional requirement for a linear precursor to adopt an entropically disfavored, preorganized conformation.^[25] As a result, the traditional synthetic methodologies for asymmetric macrocyclization are still far from perfect.^[26] One approach to overcome this difficulty is to entrap a linear precursor inside a uniformly discrete chiral space.^[27,28] Our 2D porous sheets with uniformly discrete internal cavities are well fit for a linear precursor to adopt a folded conformation, a favorable shape for cyclization. Moreover, the chiral environment of the pores is able to provide asymmetric induction in cyclization because the chiral information of the pore interior can be transferred into a linear precursor through stereoselective couplings. To explore the capability of the porous nanosheets for asymmetric macrocyclization and the generality of the chiral induction, a linear substrate based on an α,β -unsaturated carbonyl group and an indole moiety (S5-6) was selected because its estimated size in a folded conformation is compatible with the internal cavity (Figure 5a and Figures S28 and S29). Titration experiments showed that each pore is occupied by a single **S5-6** molecule with greater than 98% uptake (Figure 6b and Figures S30 and S31), indicative of near perfect fit between the internal cavity and the substrate



Figure 5. Folded conformation of linear substrates inside confined homochiral pores. a) Chemical structure of hydrophobic linear substrate **S5-6** for Michael reaction. 1D NOE spectra from **1P** (2.74 mM)-**S5-6** (1.37 mM) in $[D_4]MeOH/[D_8]THF$ (3:2, vol/vol). Irradiation at 7.662–7.688 ppm (H_c peak) induced NOE peaks at 7.692 ppm and 7.596 ppm. Irradiation at 7.048–7.053 ppm (H₁₁ peak) induced NOE peaks at 6.988–7.011 ppm, indicative formation of the folded structure between unsaturated carbonyl segment and indole moiety of **S5-6**. b) CD spectra of **1P** (91 μ M)-**S5-6** (46 μ M; red line), **1M** (91 μ M)-**S5-6** (46 μ M; blue line) in methanol solution. The wavelength range shaded by green color corresponds to the substrates. c) Top and side views of MD simulation of **S5-6** trapped in **1P**. d) Schematic representation of the fixed chiral conformer of **S5-6** in **1P**.



Figure 6. Enantioselective macrocyclization inside homochiral pores. a) Time-dependent HPLC conversion of **S5-6** (46 μ M) with triflic acid (0.46 μ M) for cyclization in the presence of **1P** (91 μ M) in methanol solution. b) Uptake, conversion and enantioselectivity of cyclization from **1P** (91 μ M) and **1M** (91 μ M) with different guest molecules. c) Time-dependent substrate amount remaining in the homochiral porous nanosheets of **1P** in the presence (orange) and absence (violet) of triflic acid. d) Time-dependent HPLC conversions of **S5-6** (46 μ M) with **1P** in the presence of triflic acid (0.46 μ M) with repeated cycles.

with a folded conformation. Considering that the end parts of **S5-6** are functionalized for a Michael reaction,^[29] the entrapment of the substrate inside the chiral confined space would promote asymmetric cyclization by adopting a spirally-folded conformation, which was confirmed by CD measurements and dynamic simulations (Figures 5b-d and Figure S32). Moreover, sequestering the substrate would prevent any possible intermolecular processes producing undesired linear oligomers. To corroborate the asymmetric cyclization inside the chiral cavities, we added a catalytic amount of triflic acid (1 mol% relative to \$5-6) to the methanol solution of 1 containing **S5-6** at room temperature.^[30] Remarkably, the 2D porous sheets perform clean macrocyclization of the linear substrate preventing undesired oligomerization. Upon addition of triflic acid, a single additional peak corresponding to a macrocycle product was identified in analytical HPLC of which the intensity increases gradually at the expense of S5-6 and then levels-off at 6 h (Figure 6 a and Figure S33), demonstrating that the reaction inside a confined space yields a pure macrocycle product with stoichiometric conversion, while preventing the formation of undesired linear oligomers. Notably, the cyclization proceeds with highly efficient asymmetric transformation to yield an enantiopure macrocycle (>99% ee), as traced by analytical HPLC using a chiral column (Figure 6b and Figure S34). The obtained profile shows only a single peak associated with the pure enantiomer of the macrocycle without any noticeable trace associated with the other enantiomer, demonstrating that the cyclization inside the fixed chiral space gives rise to precise asymmetric induction. For a control experiment with the identical Michael reaction of **S5-6** in the absence of the porous sheets showed that the reaction yielded only mixture products with low conversion of less than 27 % (Figure S34), demonstrating that the inclusion of the open chains inside the confined chiral space is essential, not only for quantitative cyclization, but also for perfect asymmetric transformation. The linear substrate based on a heptyl chain (S5-7), similar size to S5-6, can be also entrapped by the porous sheet with 97% uptake, generating enantiopure macrocycle (Figure 6b and Figure S35). In great contrast, the sheets are unable to perform chiral macrocyclization for the other linear substrates such as S5-4, S5-5, and S5-8 that are not fit into the pore (Figure S36), indicating that the pores are remarkably size selective and very stereospecific. This is further supported by precise control of enantiomeric excess (ee%) using different ratios of **1P** and **1M** (Figures S37 and S38).

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Notably, when the conversion is completed, the macrocycle product is spontaneously released out of the porous materials without applying any external forces such as shaking and stirring (Figure 6c and Figures S39 and S40). After removal of the macrocycle product by simple Sephadex filtrations, analytical HPLC measurements of the solution showed a complete lack of the cyclic product, demonstrating that converting into a macrocycle leads the substrate to spontaneously release out of the internal pores. This is in sharp contrast to the linear substrate which resides inside the pore during this period of time without any noticeable release (Figure 6c). The spontaneous release could be attributed to the size mismatch of the substrate with the fixed internal cavity by changing into a cyclic topology because macrocycle structures possess smaller hydrodynamic volumes in comparison to their linear counterparts as a consequence of a conformational constraint of cyclic chains.^[31]

Considering the spontaneous release of the macrocycle product, the porous nanosheet solution is able to perform a new cycle of binding substrates to convert into macrocycles and then release. Indeed, upon subsequent addition of **S5-6** into the solution after removal of the cyclic product, a new cycle of the substrate conversion undergoes without compromising the pore performance in both uptake and conversion efficiency (Figure 6d). The subsequent cycles showed that the porous sheet structures repeatedly perform full conversion with high optical purity of $\approx 99\%$ *ee* and complete release up to 3 cycles (Figure S41), demonstrating that the pores are highly stable without deterioration in their performance even after many cycles of binding the substrate for asymmetric conversion.

Conclusion

Our results demonstrate that homochiral porous sheet structures can perform highly efficient asymmetric conversion purely by confining achiral substrates to the chiral cavities without the use of chiral moieties or catalysts. Moreover, the near perfect chemical transformation of the substrates allows the porous nanosheet structures to spontaneously release as enantiopure products, thus enabling the regenerated porous sheets to carry out repeated cycles of binding achiral substrates to release as chiral products without deterioration in pore performance. Although significant progress has been achieved in asymmetric synthesis using a number of porous materials,^[32,33] most of them are based on chiral moieties or chiral catalysts. Remarkably, the entrapment of a linear precursor molecule for macrocyclization enables the sheet materials to carry out clean cyclization with extremely high enantioselectivity which is difficult with current synthetic methodologies.^[24,25] This is attributed that the single-layered 2D assembly enables all the pores to bind the linear substrate inside uniformly discrete chiral cavities to adopt a spiral conformation with a fixed spatial orientation, to facilitate clean asymmetric cyclization. After the spontaneous release of the macrocycle product, the regenerated porous sheets perform consecutive cycles of binding the substrate for asymmetric cyclization and spontaneous release (Figure 7), reminiscent of enzymatic action that changes an entrapped substrate to release as a product. We anticipate that such a purely geometric approach to asymmetric transformation will provide a new insight into chiral molecule foundry for diverse asymmetric conversions and self-separation of the desired chiral products on passing achiral substrates across their chiral cavities.

Detailed experimental procedures, compound characterizations, supporting data and movies are present in the Supporting Information.



Figure 7. Schematic representation of repeated cycles of entrapping linear substrate, chiral transformation, and spontaneous release as chiral macrocycle.

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Conflict of interest

The authors declare no conflict of interest.

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