Stable, crystalline, porous, covalent organic frameworks as a platform for chiral organocatalysts

Hong Xu, Jia Gao and Donglin Jiang*

The periodic layers and ordered nanochannels of covalent organic frameworks (COFs) make these materials viable open catalytic nanoreactors, but their low stability has precluded their practical implementation. Here we report the synthesis of a crystalline porous COF that is stable against water, strong acids and strong bases, and we demonstrate its utility as a material platform for structural design and functional development. We endowed a crystalline and porous imine-based COF with stability by incorporating methoxy groups into its pore walls to reinforce interlayer interactions. We subsequently converted the resulting achiral material into two distinct chiral organocatalysts, with the high crystallinity and porosity retained, by appending chiral centres and catalytically active sites on its channel walls. The COFs thus prepared combine catalytic activity, enantioselectivity and recyclability, which are attractive in heterogeneous organocatalysis, and were shown to promote asymmetric C-C bond formation in water under ambient conditions.

ovalent organic frameworks (COFs) are extended structures with periodic molecular orderings and inherent porosity¹⁻⁶. They are structurally predesignable using reticular chemistry and experimentally synthesized through reversible covalent bonds¹⁻⁶. COFs constitute an emerging class of crystalline polymer with a wide range of structures and potential applications. Owing to the reversible nature of their synthesis, currently these crystalline porous polymers can be prepared with only limited stability; the synthesis of a stable crystalline porous framework that is robust against harsh conditions and environments, such as humidity, acidity and basicity, remains a major issue that prevents their practical implementation. In this study, we report the synthesis of a crystalline porous COF that is stable in water, strong acids and strong bases, and we demonstrate its utility as a polymer platform for the design of chiral structures and the development of catalytic functions.

COFs with boroxine and boronate–ester linkages exhibit high crystallinities and porosities, but they are unstable in the presence of water or protic solvents because of the decomposition of their boronate or boroxine bonds^{7–12}. By contrast, COFs based on imine, hydrazone, triazine, phenazine and azine linkages show improved stability, but they usually have low crystallinities and limited porosities^{13–18}. Despite significant efforts in the synthesis of these materials, stability, crystallinity and porosity are rarely found together in a single COF material.

The stability of a two-dimensional (2D) COF originates from two factors: the bonding strength between components of the 2D layers and the interlayer force. The interlayer interactions play a key role in directing the formation of the layered stacking structure and, therefore, have significant effects on the crystallinity and porosity of the resulting COFs. In imine-linked COFs, the C=N bond is polarized to yield partially positively charged carbon and negatively charged nitrogen (Fig. 1a, inset). In a hexagonal 2D COF (Fig. 1), each macrocycle consists of 12 polarized C=N segments; the aggregation of a large number of charged groups causes electrostatic repulsion and destabilizes the layered structure, as predicted theoretically¹⁹. The introduction of new principles for the design of stable COFs is highly desired.

Here we address this issue by incorporating methoxy groups into the pore walls to reinforce the interlayer interactions for the synthesis of a new COF that combines outstanding stability with a high crystallinity and porosity. The COF is thermally stable up to 400 °C and retains its crystallinity and porosity even after treatments in boiling water, strong acids and strong bases. The COF has a Brunauer-Emmett-Teller (BET) surface area of 2,105 m² g⁻¹ and a Langmuir surface area of $3,336 \text{ m}^2 \text{ g}^{-1}$, which are the highest among 2D COFs reported to date^{4,7,20,21}. This COF combines stability, crystallinity and porosity and provides a material platform for the exploration of new structures and functions. It is compatible with post-synthetic functionalization while retaining the crystallinity and porosity of the framework. Modification of the walls converts the achiral COF into a chiral organocatalytic framework in which chiral centres and organocatalytic sites are anchored onto the walls of the open channels. We show that the chiral COFs function as metalfree heterogeneous catalysts for the acceleration of asymmetric Michael C-C formation reactions in water and exhibit high activities, enantioselectivities and recyclabilities.

Results

Design of stable COFs. We proposed a strategy to soften the polarization influence by delocalizing the lone pairs of electrondonating groups over the positively charged phenyl rings through resonance effects (Fig. 1a, inset). We developed a novel structure, TPB-DMTP-COF (TPB, triphenylbenzene; DMTP, dimethoxyterephthaldehyde), that possesses C3-TPB vertices and electrondonating (lone pairs on the oxygen) methoxy-substituted C_2 -phenyl edges (Fig. 1a). We investigated the crystal stacking energy of TPB-DMTP-COF and a control, TPB-TP-COF (TP, terephthaldehyde), that lacks methoxy groups (Supplementary Fig. 1)¹⁹. TPB-DMTP-COF has a crystal stacking energy of 106.862 kcal mol⁻¹, which is much higher than that of TPB-TP-COF (94.084 kcal mol⁻¹) (Supplementary Table 1). Therefore, introducing the two electrondonating methoxy groups to each phenyl edge delocalizes the two lone pairs from the oxygen atoms over the central phenyl ring, which reinforces the interlayer interactions and so stabilizes the COF and aids in its crystallization²².

The state-of-the-art approaches to stabilize COFs are based on the introduction of enol-keto tautomerizations or hydrogen-

Department of Materials Molecular Science, Institute for Molecular Science, National Institutes of Natural Sciences, 5-1 Higashiyama, Myodaiji, Okazaki 444-8787, Japan. *e-mail: jiang@ims.ac.jp



Figure 1 | Synthesis and structure of stable crystalline porous COFs. a, Synthesis of TPB-DMTP-COF through the condensation of DMTA (blue) and TAPB (black). Inset: The structure of the edge units of TPB-DMTP-COF and the resonance effect of the oxygen lone pairs that weaken the polarization of the C=N bonds and soften the interlayer repulsion in the COF. **b**, Graphic view of TPB-DMTP-COF (red, O; blue, N; grey, C; hydrogen is omitted for clarity). **c**, Synthesis of chiral COFs ([(S)-Py]_x-TPB-DMTP-COFs, *x* = 0.17, 0.34 and 0.50; blue, DMTA; black, TAPB; red, BPTA; green, (S)-Py sites) via channel-wall engineering using a three-component condensation followed by a click reaction.

bonding interactions to the COF skeletons^{15,23-25}. The keto-type COFs under alkaline conditions (6 M NaOH, three days) lose crystallinity because of the backward keto-to-enol conversion²⁵. The hydrogen-bonding COFs under acidic conditions (3 M HCl, one week) exhibit a decrease in surface area from 1,305 to 570 m² g⁻¹. Under alkaline conditions (3 M NaOH, one week), these COFs

show a weight loss of 70 wt% along with the loss of crystallinity and porosity²⁴. These examples demonstrate the best stability performance among the COFs reported to date and indicate the challenges faced in the synthesis of a COF material that is robust against acids and bases and simultaneously combines a high crystallinity and porosity.



Figure 2 | **Crystallinity, porosity and stability. a**, PXRD profiles of TPB-DMTP-COF. Experimentally observed (red), Pawley refined (green) and their difference (black), simulated using the AA stacking mode (blue) and the staggered AB stacking mode (orange). **b**, Unit cell of the AA stacking mode (O, red; N, blue; C, grey; H, white); **c**, Unit cell of the AB stacking mode (O, red; N, blue; C, grey; H, white; green, a further layer). **d**, Nitrogen-sorption isotherm curves measured at 77 K. **e**, Profiles of the pore size and pore-size distribution. **f**, Residue weight percentage of TPB-DMTP-COF after treatment for one week in different solvents.

Stability of COFs. Thermogravimetric analysis (TGA) revealed that TPB-DMTP-COF exhibited no weight loss under N₂ to 400 °C, whereas under O₂ it burned out completely above 340 °C (Supplementary Fig. 2a,b). To investigate the chemical stability of TPB-DMTP-COF, we dispersed TPB-DMTP-COF samples for one week in various solvents, including dimethylformamide (DMF), dimethylsulfoxide (DMSO), THF, MeOH, cyclohexanone, water (100 and 25 °C), aqueous HCl (12 M) and aqueous NaOH (14 M) solutions. Figure 2f presents the residue weight percentage of these COF samples. In water and the organic solvents examined, TPB-DMTP-COF exhibited almost no weight loss (<0.1 wt%). Under the ultraharsh conditions of a strong acid (12 M HCl (concentrated HCl)) and a strong base (14 M NaOH), the residual weight percentages were 85 and 92 wt%, respectively. Even on hydrolysis in boiling water for one week, the TPB-DMTP-COF retained 72 wt% of its original mass.

TPB-DMTP-COF retained its original crystalline structure, as indicated by the unchanged intensities and positions of the peaks in its powder X-ray diffraction (PXRD) profile on dispersion for one week in DMF, DMSO, THF, MeOH, cyclohexanone, water (100 and 25 °C), aqueous HCl (12 M) and aqueous NaOH (14 M) solutions (Fig. 2g). We evaluated the full-width at half-maximum (FWHM) values, which also suggested that these treated TPB-DMTP-COF samples retained their crystallinity (Supplementary Table 2). The BET surface areas were 2,081, 2,074 and 2,020 m² g⁻¹ for the COF samples treated for one week in boiling water, strong acid and strong base, respectively; these values are very close to that of the as-synthesized COF $(2,105 \text{ m}^2 \text{ g}^{-1})$ (Supplementary Fig. 3 and Supplementary Table 3)). Moreover, the infrared spectra confirmed that the chemical bonds were well preserved (Supplementary Fig. 4). To the best of our knowledge, this COF is the most stable among COFs reported to date (Supplementary Table 4)15,16,23-27. In contrast to TPB-DMTP-COF, TPB-TP-COF without methoxy groups on the walls exhibited a low chemical stability, which is indicated by the more-significant weight loss after treatment in acid, base or boiling water (Supplementary Fig. 5).

We further synthesized TPB-DHTP-COF (DHTP, dihydroxyterephthaldehyde) with phenol groups on the edge units that allow for the hydrogen-bonding O–H…N interactions between the OH units and imine groups (Supplementary Fig. 1)²⁴. TPB-DHTP-COF exhibited a low crystallinity (intensity = 11×10^3 counts per second (c.p.s.), FWHM = 0.672° (Supplementary Fig. 6)) and porosity (BET surface area = 849 m² g⁻¹ (Supplementary Fig. 7)). On treatment for one week in HCl (12 M), NaOH (14 M) or boiling water, TPB-DHTB-COF deteriorated in both crystallinity and porosity (Supplementary Figs 6 and 7 and Supplementary Table 3). Compared with TPB-DMTP-COF, TPB-DHTP-COF exhibited a worse π -stacking between the layers with a decreased crystal-stacking energy (103 kcal mol⁻¹ per unit cell (Supplementary Table 1)), which led to low crystallinity and stability.

Crystallinity and porosity. The PXRD pattern of TPB-DMTP-COF exhibited six prominent diffraction peaks, with the most-intensive one at 2.76° (FWHM = 0.39°) and the five other peaks at 4.82, 5.60, 7.42, 9.70 and 25.2°; these peaks were assigned to the (100), (110), (200), (210), (220) and (001) facets, respectively (Fig. 2a, red curve). The (100) signal is sharp compared with that of TPB-TP-COF under the same PXRD experimental conditions (qualitatively, 135×10^3 c.p.s. versus 1.7×10^3 c.p.s. in intensity (Supplementary Fig. 8)). Another feature is that the PXRD pattern contains more peaks than those for other imine-linked COFs. A density-functional tight-binding method, which included a Lennard-Jones dispersion, was used to simulate the optimum structures of TPB-DMTP-COF. Using the optimal monolayer structure, AA and staggered AB stacking modes were generated and optimized. In the stacked frameworks, TPB-DMTP-COF adopts the AA stacking mode of a space group of P6 with a = b = 37.2718 Å, interlayer distance (c) of 3.5215 Å, $\alpha = \beta = 90^{\circ}$ and $\gamma = 120^{\circ}$ (Fig. 2b and Supplementary Table 5). The simulated PXRD pattern of the AA stacking mode (Fig. 2a, blue curve) matched the experimental peak positions and intensities, whereas the staggered AB stacking mode (Fig. 2a, orange curve) did not reproduce the data (red curve). The staggered AB mode gave rise to a space group of *P*-3 with a = b = 36.6669 Å, c = 6.3984 Å, $\alpha = \beta = 90^{\circ}$ and $\gamma = 120^{\circ}$ (Supplementary Table 6), which, however, covers the pores of the neighbouring sheets (Fig. 2c).

Pawley refinement (Fig. 2a, green curve) provided a good match to the observed PXRD pattern, as indicated by the negligible difference between the simulated and experimental patterns (Fig. 2a, black curve). The Pawley refinement led to a space group of *P*6 with a = b = 37.1541 Å, c = 3.5378 Å, $\alpha = \beta = 90^{\circ}$ and $\gamma = 120^{\circ}$, and $R_{\rm P}$ and $R_{\rm WP}$ values of 2.02 and 4.37%, respectively (Supplementary Table 7). We further used the Rietveld refinement method reported for the imine-linked COFs²⁸ to refine our crystal structure of TPB-DMTP-COF, which resulted in a space group of *P*6 with a = b = 36.4594 Å, c = 3.5239 Å, $\alpha = \beta = 90^{\circ}$ and $\gamma = 120^{\circ}$, and $R_{\rm P}$ and $R_{\rm WP}$ values of 3.31 and 6.52%, respectively (Supplementary Table 8). The Rietveld refinement also reproduced the PXRD pattern well (Supplementary Fig. 9). These refinements indicated that the peak assignment of the PXRD pattern was correct.

Nitrogen-sorption isotherms of TPB-DMTP-COF measured at 77 K exhibited a rapid uptake at a low pressure of $P/P_0 < 0.1$, followed by a sharp step between $P/P_0 = 0.15$ and 0.25 (Fig. 2d, black curve). This sorption profile is best described as a type IV isotherm, which is characteristic of mesoporous materials. The BET and Langmuir surface areas were 2,105 and 3,336 m² g⁻¹, respectively. These surface areas are among the highest BET surface areas of 2D COFs^{4,7,20,21}. By contrast, TPB-TP-COF exhibited a BET surface area of only 16 m² g⁻¹ (Supplementary Fig. 10 and Supplementary Table 3). The pore size and volume of TPB-DMTP-COF were evaluated to be 3.26 nm and 1.28 cm³ g⁻¹, respectively. The theoretical surface area calculated using the AA stacking mode was 2,098 m² g⁻¹; the experimentally observed surface area is nearly identical to the theoretical one.

As shown above, TPB-DMTP-COF exhibits an outstanding stability and possesses high crystallinity and porosity. The introduction of electron-donating groups to the positively charged edges reinforces the interlayer interactions that exert a positive and significant effect on the stability, crystallinity and porosity. Such a robust open framework constitutes a useful material platform for structural design and functional exploration. High-resolution transmission electron microscopy of TPB-DMTP-COF enables the direct visualization of the hexagonal polygon textures and the stacking layer structures (Supplementary Fig. 11).

Chiral COFs engineered with organocatalytic sites on the walls. Intrigued by its high crystallinity and large mesoporous channels, we developed TPB-DMTP-COF into a catalytic chiral open framework by anchoring chiral centres and organocatalytic sites onto the channel walls via post-synthetic functionalization (Fig. 1c). The robust open-framework structure provides a benchmark sample to demonstrate the potential of COFs in asymmetric catalysis. We employed a three-component condensation system with 2,5-bis(2-propynyloxy)terephthalaldehyde (BPTA) and 2,5-dimethoxyterephthalaldehyde (DMTA) as edge units to synthesize the intermediate $[HC\equiv C]_x$ -TPB-DMTP-COFs (Fig. 1c), where x is the percentage of functional groups (either $[HC\equiv C]$ or, subsequently, (S)-Py moieties) as a fraction of the groups lining the pore walls (that is, including the nonfunctionalized OMe groups of DMTA and the functionalized [HC=C] or (S)-Py moieties), so that x = [BPTA]/([BPTA]+[DMTA]);x = 0, 0.17, 0.34 and 0.50. After a quantitative azide-ethynyl click reaction^{20,29}, the $[HC\equiv C]_x$ -TPB-DMTP-COFs were converted into chiral organocatalytic $[(S)-Py]_x$ -TPB-DMTP-COFs ((S)-Py), (S)-pyrrolidine) (Fig. 1c) in which chiral and catalytic (S)-Py sites were anchored onto the channel walls through triazole rings in a random manner. To estimate the real [HC≡C] contents



[(S)-Py]_{0.50}-TPB-DMTP-COF

Figure 3 | Channel-wall structure of the chiral organocatalytic COFs. The open structures of the chiral centres and the catalytic sites on the channel walls are shown for different COFs (O, red; N, blue; C, grey). The space between the catalytic sites is required for the face-on stacking of nitrostyrene over the catalytic sites and plays a role in controlling the activity of the catalysts.

(x value) in $[HC\equiv C]_x$ -TPB-DMTP-COFs, we plotted two standard curves (Supplementary Fig. 12) based on the characteristic stretching bands of a C=C bond at 2,120 cm⁻¹ and C≡C-H bond at 3,300 cm⁻¹ using [HC≡C]_{1.0}-TPB-DMTP-COF (equivalent to TPB-BPTP-COF (BPTP, bis(2-propynyloxy) terephthaldehyde; for the structure see Supplementary Fig. 1)) as the standard. From the standard curves, the x values were evaluated to be 0.17, 0.342 and 0.496, based on the bands at $2,120 \text{ cm}^{-1}$, and 0.173, 0.334 and 0.512, based on the bands at $3,300 \text{ cm}^{-1}$ for [HC≡C]_{0.17}-TPB-DMTP-COF, [HC≡C]_{0.34}-TPB-DMTP-COF and [HC≡C]_{0.50}-TPB-DMTP-COF, respectively (Supplementary Table 9). On the quantitative click reactions, the characteristic bands of the C=C-H units at 2,120 and 3,300 cm⁻¹ disappeared. Moreover, the clicked (S)-Py-triazole units consisted of four nitrogen atoms, which greatly enhanced the nitrogen content of the resulting $[(S)-Py]_{x}$ -TPB-DMTP-COFs. The x values based on the nitrogen-content increment were evaluated to be 0.18, 0.33 and 0.51 for [(S)-Py]_{0.17}-TPB-DMTP-COF, [(S)-Py]_{0.34}-TPB-DMTP-COF and [(S)-Py]_{0.50}-TPB-DMTP-COF, respectively (Supplementary Table 10). In these COFs, each hexagonal macrocycle contains one, two or three (S)-Py units on average, respectively (Fig. 1c). Figure 3 shows the structures of the channel walls with chiral organocatalytic sites. The organocatalytic sites are integrated into the walls and form catalytic nanospaces of different sizes (Fig. 3). The $[HC\equiv C]_x$ -TPB-DMTP-COFs and $[(S)-Py]_x$ -TPB-DMTP-COFs



Figure 4 | Crystallinity and porosity of chiral COFs. a, PXRD patterns of $[(S)-Py]_{0.17}$ -TPB-DMTP-COF (red curve) and of $[HC\equivC]_{0.17}$ -TPB-DMTP-COF (black curve). The chiral $[(S)-Py]_{0.17}$ -TPB-DMTP-COF retains a high crystallinity. **b**, Nitrogen-sorption isotherm curves of $[(S)-Py]_{0.17}$ -TPB-DMTP-COFs (red curve, x = 0.17; blue curve, x = 0.34; purple curve, x = 0.50) measured at 77 K. **c-e**, Profiles of the pore size (spheres) and pore-size distribution (solid lines) of $[(S)-Py]_{0.17}$ -TPB-DMTP-COF (**c**), $[(S)-Py]_{0.34}$ -TPB-DMTP-COF (**d**) and $[(S)-Py]_{0.50}$ -TPB-DMTP-COF (**e**). The chiral COFs exhibit one type of mesopore.

were unambiguously characterized using various analytical methods (Supplementary Figs 13–17 and Supplementary Tables 3 and 10). To investigate the possibility of Cu residues in $[(S)-Py]_x$ -TPB-DMTP-COFs, we conducted inductively coupled plasma atomic emission spectroscopy (ICP-AES) and observed that the content of Cu was as low as 0.004–0.009 wt% (Supplementary Table 11). TGA measurements under O₂ also revealed that these $[(S)-Py]_x$ -TPB-DMTP-COFs burned out without residues (Supplementary Fig. 2).

The PXRD profiles of the $[(S)-Py]_x$ -TPB-DMTP-COFs (Fig. 4a, red curve) showed diffraction patterns that were identical to that of $[HC\equiv C]_{0.17}$ -TPB-DMTP-COF (black curve), which indicates that the lattice structure was not affected by the chiral catalytic sites on the walls of the pores. $[(S)-Py]_x$ -TPB-DMTP-COFs are highly porous materials, as revealed by nitrogen-sorption isotherm measurements (Fig. 4b). The BET surface areas of $[(S)-Py]_{0.17}$ -TPB-DMTP-COF, $[(S)-Py]_{0.34}$ -TPB-DMTP-COF and $[(S)-Py]_{0.50}$ -TPB-DMTP-COF were 1,970, 1,802 and 1,612 m² g⁻¹, whereas their Langmuir surface areas were 3,059, 2,812 and 2,300 m² g⁻¹, respectively (Supplementary Table 3). Their pore sizes were 3.07, 2.95 and 2.86 nm, and their pore volumes were 1.13, 1.04 and 0.83 cm³ g⁻¹, respectively (Supplementary Fig. 18). Profiles of the pore-size distribution revealed the presence of only one type of mesopore (Fig. 4c–e).

To evaluate the stability of the COFs with catalytic sites on the walls, we treated $[(S)-Py]_{0.17}$ -TPB-DMTP-COF in different solvents, including DMF, DMSO, THF, MeOH, cyclohexanone, water (100 and 25 °C), aqueous HCl (12 M) and aqueous NaOH (14 M) solutions, under otherwise identical conditions to those for TPB-DMTP-COF.

[(S)-Py]_{0.17}-TPB-DMTP-COF retained its crystalline structure, as evidenced by the unchanged intensities, FWHM values and positions of the peaks in the PXRD profiles (Supplementary Fig. 19 and Supplementary Table 2). The BET surface areas were 1,924, 1,956 and 1,971 m² g⁻¹ on treatment for one week in boiling water, HCl (12 M) and NaOH (14 M), respectively; these values are close to that of the as-synthesized $[(S)-Py]_{0.17}$ -TPB-DMTP-COF (1,970 m² g⁻¹ (Supplementary Fig. 20 and Supplementary Table 3)).

Heterogeneous asymmetric organocatalysis. Organocatalysis in homogeneous systems is problematic because of the difficulty of separating expensive catalysts for repeated use^{30–34}. The development of immobilized, easily recoverable and reusable catalysts appears to be one of the most-promising strategies for overcoming these problems. Most heterogeneous organocatalysts are based on linear polymer supports; however, such catalysts exhibit low activities as a result of inefficient access to the catalytic sites^{32–34}. To overcome this issue, crystalline metal–organic framework (MOF)-based organocatalysts have been developed^{35–37}. However, their stabilities, small pore sizes, enantioselectivities and diastereoselectivities need to be improved.

A Michael addition is a typical organocatalytic reaction, is one of the basic C–C bond formation reactions and provides a powerful synthetic tool for the formation of synthons of many important natural and biologically active products^{31,38,39}. Typically, Michael reactions are conducted in organic solvents or in mixed organic–aqueous solutions; the use of neat water as a solvent is particularly attractive from the environmental and economic

Entry	Catalyst	Time (h)	Conversion (%)	Yield (%)	e.e. (%)	d.r.
1	[(S)-Py] _{0.17} -TPB-DMTP-COF	12	100	95	92	90/10
2	[(S)-Py] _{0.34} -TPB-DMTP-COF	17	100	93	91	90/10
3	[(S)-Py] _{0.50} -TPB-DMTP-COF	34	100	95	89	88/12
4	Free (S)-Py-containing moiety, ((S)-1-(pyrrolidin-2-yl)methyl)- 4-phenoxymethyl-triazole	22	100	96	92	91/9
5	[(S)-Py] _{0.25} -H ₂ P-COF*	36	-	-	-	-

Reaction scheme: see Figure 5, top, with R = H; *No reaction.

points of view. The high catalytic activity of $[(S)-Py]_x$ -TPB-DMTP-COFs allows Michael reactions to be conducted in neat water at 25 °C and 1 bar. The insolubility of the $[(S)-Py]_x$ -TPB-DMTP-COFs gives rise to heterogeneous systems that have outstanding catalytic activities.

The Michael reaction of cyclohexanone and β-nitrostyrene proceeded cleanly and smoothly and achieved 100% conversion in 12 hours with enantioselectivity (e.e.) and diastereoselectivity (d.r.) values of 92% and 90/10, respectively (Table 1, entry 1). The molecular catalyst (S)-Py with the same catalytic structure (Table 1, entry 4) was used as a control and required a much longer reaction time of 22 hours. The reduced reaction time suggests that [(S)-Py]_{0.17}-TPB-DMTP-COF exhibits an enhanced catalytic activity; the open channels can accumulate the reactants from the water phase and promote the reactions in the confined nanopore space. The similarities in the enantioselectivity and diastereoselectivity between [(S)-Py]_{0.17}-TPB-DMTP-COF and (S)-Py indicate that the chiral catalytic sites on the channel walls retained both enantiocontrol and diastereocontrol. To investigate the effect of Cu species on the reaction, we conducted the following control experiments (Supplementary Table 12). (1) The Cu powder, CuI and CuSO₄·5H₂O were utilized separately as catalysts for the above reaction under otherwise identical conditions; these Cu species did not yield any products. (2) The Cu powder, CuI and CuSO₄·5H₂O in the presence of TPB-DMTP-COF were utilized separately for the above reaction; these systems again did not yield any products. (3) The Cu powder, CuI and CuSO₄·5H₂O in the presence of [(S)-Py]_{0.17}-TPB-DMTP-COF were utilized separately for the reaction; [(S)-Py]_{0.17}-TPB-DMTP-COF retained its original catalytic activity, irrespective of the addition of the Cu species. These results revealed that the Cu species did not affect the catalytic reactions. Supplementary Table 13 summarizes the heterogeneous organocatalysis reported to date for the Michael and aldol reactions. The majority of the heterogeneous catalysts are active for only aldol reactions that utilize small and highly active reactants. The large pore sizes and high activities render the COFs able to catalyse Michael reactions; to the best of our knowledge, this COF is the first example of a heterogeneous catalyst based on a crystalline porous material, including mesoporous silica, MOFs and COFs, for the activation of low-activity ketones in Michael reactions.

We observed that the densities of the chiral catalytic sites significantly affected the reaction rate. $[(S)-Py]_{0.34}$ -TPB-DMTP-COF and $[(S)-Py]_{0.50}$ -TPB-DMTP-COF required long reaction times of 17 and 34 hours, respectively (Table 1, entries 2 and 3). The prolonged reaction time suggests that the high density of catalytic sites on the channel walls causes these sites to overlap with each other and results in an inefficient utilization of them; the catalysis requires a face-on attack by nitrostyrenes at the catalytic sites (Fig. 3). The pore size is also important for the Michael reaction; as the pore size decreased to the microporous range, the Michael reactions were suppressed severely. For example, the microporous $[(S)-Py]_{0.25}$ -H₂P-COF with catalytic species identical to those of $[(S)-Py]_{0.17}$ -TPB-DMTP-COF exhibited a low activity for the Michael reaction with nearly negligible products after 36 hours (Table 1, entry 5).

Discussion

We investigated different reactants to illustrate the generality of the catalyst (Fig. 5). We used β -nitrostyrene compounds with different substituents on their phenyl ring for the Michael reaction. The *ortho*-chlorosubstituted β -nitrostyrene exhibited the highest activity among the series; the conversion reached 100% in six hours, with e.e. and d.r. values of 94% and 97/3, respectively. High activities were achieved for activated β -nitrostyrenes, for example, 4-bromo- β -nitrostyrene and 4-chloro- β -nitrostyrene. The reactions were completed in 12 and 10 hours, respectively. The reaction of deactivated 4-methyl- β -nitrostyrene was completed in 16 hours and reached e.e. and d.r. values of 93% and 92/8, respectively. The best selectivity was achieved for 4-methoxyl- β -nitrostyrene with 96% e.e. and 94/6 d.r. in 26 hours.

Kinetic studies were conducted throughout the entire reaction region between 0 and 100% conversion, with each experiment performed at least in duplicate. The average conversions were used for the kinetic evaluations. The decrease in the concentration of *trans*-2-chloro- β -nitrostyrene and increase in the concentration of the product were straightforward, and the catalytic reactions proceeded smoothly (Supplementary Fig. 21). The reactions exhibited apparent first-order behaviour with respect to the concentration of *trans*-2-chloro- β -nitrostyrene (Supplementary Fig. 22). The calculated rate constant and lifetime ($t_{1/2}$) were 0.78 per hour and



Figure 5 | Scope of reactants. Different β -nitrostyrene derivatives investigated for the Michael reactions catalysed with chiral COFs, their products, e.e. yields and d.r. values (red, cyclohexanone; green, newly formed C-C bond; blue, nitrostyrene derivatives). R, substituent H, Cl, Br, Me or OMe.

Table 2 C	Cycling test o	of [(S)-Py] _{0.17} -	TPB-DMTP-COF	[:] catalyst for	the Michael	reaction.
-------------	----------------	-------------------------------	--------------	---------------------------	-------------	-----------

Cycle number	Time (h)	Conversion (%)	Yield (%)	e.e. (%)	d.r.	RY (wt%)*
1	6	100	95	94	97/3	>99
2	7	100	93	94	97/3	>99
3	9	100	94	94	97/3	>99
4	11	100	92	94	97/3	>99
5	13	100	92	93	97/3	>99

Reaction scheme: see Figure 5, top, with R = CI in ortho position; *Recovery yield (RY) of the catalyst.

0.9 hours, respectively. A plausible explanation for the observed first-order rate may involve the quick addition of cyclohexanone to the pyrrolidine catalyst to form an enamine intermediate, followed by the face-on-face addition of the styrene substrate to the enamine intermediate as the rate-determining step, with a subsequent rapid hydrolysis to yield the corresponding products. The observed (2S,1R) absolute configuration of the major *syn* Michael adduct, determined from a literature comparison of the HPLC elution order, is consistent with the transient state of the nitrostyrene to attack the *re*-face of the enamine⁴⁰.

A long catalyst lifetime and the capability of repeated use are important for useful applications. [(S)-Py]x-TPB-DMTP-COFs were separated easily from the reaction mixture and recovered; filtration and rinsing with solvents refreshed the catalyst for the next round of use. [(S)-Py]_{0.17}-TPB-DMTP-COF at 10 mol% loading in the first round was subsequently subjected to repeated use in water at 25 °C. [(S)-Py]_{0.17}-TPB-DMTP-COF retained its activity, enantioselectivity and diastereoselectivity after five cycles (Table 2). The extended reaction time required with increased cycle number is probably related to the side reactions of the pyrrolidine catalytic sites, as reported in the literature⁴¹. Various analytical methods revealed that [(S)-Py]_{0.17}-TPB-DMTP-COF retained its crystallinity and porosity (Supplementary Figs 23-25 and Supplementary Table 3). Typically, organocatalysts based on MOFs³⁵⁻³⁷ and porous organic polymers⁴² have exhibited drastically decreased activities that demand a much longer reaction time per cycle (Supplementary Table 13). Combining all of the above catalytic features, the chiral COFs function as high-performance heterogeneous catalysts for asymmetric transformations.

Conclusion

In summary, we have developed a mesoporous COF that combines stability, crystallinity and porosity by reinforcing the interlayer interactions between the 2D layers. The COF's skeleton is compatible with post-synthetic functionalization with its crystallinity and porosity retained; engineering the channel walls with chiral centres and organocatalytic species resulted in the development of two distinct chiral COFs in a simple yet controlled manner. The resulting crystalline metal-free catalysts display activity, enantioselectivity, recyclability and environmental benignity—a set of characteristics that has remained challenging to engineer together in heterogeneous organocatalysis. Our strategy may thus facilitate the design of COFs in which the combination of stability, crystallinity and porosity would be of use for a variety of functions and applications.

Methods

TPB-DMTP-COF. An *o*-dichlorobenzene (*o*-DCB)/*n*-BuOH (0.5/0.5 ml) mixture of 1,3,5-tri-(4-aminophenyl)benzene (TAPB) (0.080 mmol, 28.1 mg) and DMTA (0.120 mmol, 23.3 mg) in the presence of an acetic-acid catalyst (6 M, 0.1 ml) in a Pyrex tube (10 ml) was degassed via three freeze-pump-thaw cycles. The tube was flame sealed and heated at 120 °C for three days. The precipitate was collected via centrifugation, washed six times with THF and then subjected to Soxhlet extraction with THF as the solvent for one day to remove the trapped guest molecules. The powder was collected and dried at 120 °C under vacuum overnight to produce TPB-DMTP-COF in an isolated yield of 81%.

[HC≡C]_x-TPB-DMTP-COFs. *o*-DCB/*n*-BuOH (0.5/0.5 ml) mixtures of TAPB (0.080 mmol, 28.1 mg) and DMTA/BPTA (a total of 0.120 mmol) at different molar ratios of 5/1, 4/2, 3/3 and 0/1 in the presence of an acetic-acid catalyst (6 M, 0.1 ml) in a Pyrex tube (10 ml) were degassed via three freeze–pump–thaw cycles. The tubes were sealed off by flame and heated at 120 °C for three days. The precipitates were collected via centrifugation, washed six times with THF and then subjected to Soxhlet extraction with THF as the solvent for one day to remove the trapped guest molecules. The powders were collected and dried at 120 °C under vacuum overnight to produce the corresponding [HC≡C]_{0.17}-TPB-DMTP-COF, [HC≡C]_{0.34}-TPB-DMTP-COF, [HC≡C]_{0.50}-TPB-DMTP-COF and [HC≡C]_{1.0}-TPB-DMTP-COF (equivalent to TPB-BPTP-COF) in the isolated yields of 80, 79, 81 and 81%, respectively.

[(*S*)-**Py**]_{*x*}-**TPB-DMTP-COFs**. (*S*)-2-(azidomethyl)pyrrolidine (toluene solution, 1 M, 60 µl) was added to a THF/water (2.1/0.7 ml) mixture of $[HC≡C]_{0.17}$ -TPB-DMTP-COF (65 mg) in the presence of CuI (6 mg) and *N*,*N*-diisopropylethylamine (THF solution, 1 M, 108 µl) in a flask (25 ml). The flask was degassed via three freeze-pump-thaw cycles and the mixture was stirred at room temperature for four hours. The precipitate was collected via centrifugation, washed five times with THF and acetonitrile, and dried at room temperature under vacuum to produce [(*S*)-Py]_{0.17}-TPB-DMTP-COF as a dark-green solid in quantitative yield. The ethynyl groups quantitatively reacted with the azide units, as shown by infrared spectroscopy. A click reaction of $[HC≡C]_x$ -TPB-DMTP-COFs (*x* = 34 and 50) with (*S*)-2-(azidomethyl)pyrrolidine was conducted to produce [(*S*)-Py]_*x*-TPB-DMTP-COFs (*x* = 34 and 50) in quantitative yield according to this method under otherwise identical conditions.

Stability test. The COF samples (10 mg) were kept for seven days in 1 ml of DMF, DMSO, THF, cyclohexanone, MeOH, HCl (12 M, equivalent to concentrated HCl), NaOH (14 M), water (25 °C) or boiling water (100 °C). The samples were washed with THF (for samples treated in organic solvents) or water (for samples treated in aqueous solutions), dried under vacuum at 120 °C for 12 hours and subjected to PXRD, infrared spectroscopy and nitrogen-sorption isotherm measurements.

Asymmetric Michael reactions. Cyclohexanone (2 mmol), nitrostyrene (0.1 mmol), benzoic acid (0.025 mmol) and *N*,*N*-diisopropylethylamine (water suspension, 0.5 M, 32 μ l) were added to a water (0.4 ml) suspension of the [(S)-Py]_x-TPB-DMTP-COFs catalyst (0.01 mmol). The mixture was stirred at room temperature until 100% conversion was reached. After the addition of EtOH (5 ml), the organic layer was removed via centrifugation. The catalyst was washed with EtOH (5 ml twice) and ethyl acetate (5 ml three times), and the organic layers were combined and concentrated under reduced pressure. ¹H NMR spectroscopy was used to determine the d.r. The e.e. was determined using HPLC on a chiral-phase Chiralpak AD-H column.

Cycle use of the catalyst. $[(S)-Py]_{0.17}$ -TPB-DMTP-COF was recovered via centrifugation, washed with ethyl acetate and a mixture of triethylamine/ethanol (5% by volume) to remove any products and dried under vacuum for use in the next reaction cycle.

Received 13 June 2015; accepted 13 August 2015; published online 21 September 2015

References

- Feng, X., Ding, X. & Jiang, D. Covalent organic frameworks. *Chem. Soc. Rev.* 41, 6010–6022 (2012).
- Ding, S. Y. & Wang, W. Covalent organic frameworks (COFs): from design to applications. *Chem. Soc. Rev.* 42, 548–568 (2013).
- Cote, A. P. et al. Porous, crystalline, covalent organic frameworks. Science 310, 1166–1170 (2005).
- Tilford, R. W., Gemmill, W. R., zur Loye, H. C. & Lavigne, J. J. Facile synthesis of a highly crystalline, covalently linked porous boronate network. *Chem. Mater.* 18, 5296–5301 (2006).
- 5. Belowich, M. E. & Stoddart, J. F. Dynamic imine chemistry. *Chem. Soc. Rev.* **41**, 2003–2024 (2012).
- Xiang, Z. H., Cao, D. P. & Dai, L. M. Well-defined two dimensional covalent organic polymers: rational design, controlled syntheses, and potential applications. *Polym. Chem.* 6, 1896–1911 (2015).

NATURE CHEMISTRY DOI: 10.1038/NCHEM.2352

- Cote, A. P., El-Kaderi, H. M., Furukawa, H., Hunt, J. R. & Yaghi, O. M. Reticular synthesis of microporous and mesoporous 2D covalent organic frameworks. *J. Am. Chem. Soc.* 129, 12914–12915 (2007).
- Wan, S., Guo, J., Kim, J., Ihee, H. & Jiang, D. A belt-shaped, blue luminescent, and semiconducting covalent organic framework. *Angew. Chem. Int. Ed.* 47, 8826–8830 (2008).
- Tilford, R. W., Mugavero, S. J., Pellechia, P. J. & Lavigne, J. J. Tailoring microporosity in covalent organic frameworks. *Adv. Mater.* 20, 2741–2746 (2008).
- Wan, S., Guo, J., Kim, J., Ihee, H. & Jiang, D. A photoconductive covalent organic framework: self-condensed arene cubes composed of eclipsed 2D polypyrene sheets for photocurrent generation. *Angew. Chem. Int. Ed.* 48, 5439–5442 (2009).
- Campbell, N. L., Clowes, R., Ritchie, L. K. & Cooper, A. I. Rapid microwave synthesis and purification of porous covalent organic frameworks. *Chem. Mater.* 21, 204–206 (2009).
- Spitler, E. L. & Dichtel, W. R. Lewis acid-catalysed formation of two-dimensional phthalocyanine covalent organic frameworks. *Nature Chem.* 2, 672–677 (2010).
- 13. Wan, S. *et al.* Covalent organic frameworks with high charge carrier mobility. *Chem. Mater.* **23**, 4094–4097 (2011).
- Uribe-Romo, F. J., Doonan, C. J., Furukawa, H., Oisaki, K. & Yaghi, O. M. Crystalline covalent organic frameworks with hydrazone linkages. *J. Am. Chem.* Soc. 133, 11478–11481 (2011).
- 15. Kandambeth, S. *et al.* Construction of crystalline 2D covalent organic frameworks with remarkable chemical (acid/base) stability via a combined reversible and irreversible route. *J. Am. Chem. Soc.* **134**, 19524–19527 (2012).
- Dalapati, S. *et al.* An azine-linked covalent organic framework. J. Am. Chem. Soc. 135, 17310–17313 (2013).
- Kuhn, P., Antonietti, M. & Thomas, A. Porous, covalent triazine-based frameworks prepared by ionothermal synthesis. *Angew. Chem. Int. Ed.* 47, 3450–3453 (2008).
- Guo, J. *et al.* Conjugated organic framework with three-dimensionally ordered stable structure and delocalized π clouds. *Nature Commun.* 4, 2736 (2013).
- 19. Lukose, B., Kuc, A. & Heine, T. The structure of layered covalent-organic frameworks. *Chem. Eur. J.* 17, 2388–2392 (2011).
- Nagai, A. et al. Pore surface engineering in covalent organic frameworks. Nature Commun. 2, 536 (2011).
- Dogru, M., Sonnauer, A., Gavryushin, A., Knochel, P. & Bein, T. A covalent organic framework with 4 nm open pores. *Chem. Commun.* 47, 1707–1709 (2011).
- 22. Chen, X., Addicoat, M., Irle, S., Nagai, A. & Jiang, D. Control of crystallinity and porosity of covalent organic frameworks by managing interlayer interactions based on self-complementary π-electronic force. J. Am. Chem. Soc. 135, 546–549 (2013).
- 23. Biswal, B. P. *et al.* Mechanochemical synthesis of chemically stable isoreticular covalent organic frameworks. *J. Am. Chem. Soc.* **135**, 5328–5331 (2013).
- Kandambeth, S. *et al.* Enhancement of chemical stability and crystallinity in porphyrin-containing covalent organic frameworks by intramolecular hydrogen bonds. *Angew. Chem. Int. Ed.* 52, 13052–13056 (2013).
- Chandra, S. et al. Phosphoric acid loaded azo-based covalent organic framework for proton conduction. J. Am. Chem. Soc. 136, 6570–6573 (2014).
- Du, Y. *et al.* Experimental and computational studies of pyridine-assisted postsynthesis modified air stable covalent-organic frameworks. *Chem. Commun.* 48, 4606–4608 (2012).

- Ding, S. Y. *et al.* Construction of covalent organic framework for catalysis: Pd/COF-LZU1 in Suzuki–Miyaura coupling reaction. *J. Am. Chem. Soc.* 133, 19816–19822 (2011).
- Rabbani, M. G. *et al.* A 2D mesoporous imine-linked covalent organic framework for high pressure gas storage applications. *Chem. Eur. J.* **19**, 3324–3328 (2013).
- Xu, H. et al. Catalytic covalent organic frameworks via pore surface engineering. Chem. Commun. 50, 1292–1294 (2014).
- MacMillan, D. W. The advent and development of organocatalysis. *Nature* 455, 304–308 (2008).
- List, B. Proline-catalyzed asymmetric reactions. *Tetrahedron* 58, 5573–5590 (2002).
 Benaglia, M., Puglisi, A. & Cozzi, F. Polymer-supported organic catalysts. *Chem.*
- Bendgin, J., 1 dans, 1 de Course 1 : 1 of milet supported organic entrysis. *Onem Rev.* 103, 3401–3429 (2003).
 Lee, J. *et al.* Metal–organic framework materials as catalysts. *Chem. Soc. Rev.*
- Lee, J. et al. Metal-organic framework materials as catalysts. Chem. Soc. Rev. 38, 1450–1459 (2009).
- Yoon, M., Srirambalaji, R. & Kim, K. Homochiral metal–organic frameworks for asymmetric heterogeneous catalysis. *Chem. Rev.* 112, 1196–1231 (2012).
- Banerjee, M. *et al.* Postsynthetic modification switches an achiral framework to catalytically active homochiral metal–organic porous materials. *J. Am. Chem. Soc.* 131, 7524–7525 (2009).
- Dang, D., Wu, P., He, C., Xie, Z. & Duan, C. Homochiral metal–organic frameworks for heterogeneous asymmetric catalysis. J. Am. Chem. Soc. 132, 14321–14323 (2010).
- Lun, D. J., Waterhouse, G. I. & Telfer, S. G. A general thermolabile protecting group strategy for organocatalytic metal–organic frameworks. *J. Am. Chem. Soc.* 133, 5806–5809 (2011).
- Notz, W., Tanaka, F. & Barbas, C. F. III. Enamine-based organocatalysis with proline and diamines: the development of direct catalytic asymmetric aldol, Mannich, Michael, and Diels–Alder reactions. *Acc. Chem. Res.* 37, 580–591 (2004).
- Berner, O. M., Tedeschi, L. & Enders, D. Asymmetric Michael additions to nitroalkenes. *Eur. J. Org. Chem.* 2002, 1877–1894 (2002).
- Bock, D. A., Lehmann, C. W. & List, B. Crystal structures of proline-derived enamines. Proc. Natl Acad. Sci. USA 107, 20636–20641 (2010).
- Luo, S., Li, J., Zhang, L., Xu, H. & Cheng, J. P. Noncovalently supported heterogeneous chiral amine catalysts for asymmetric direct aldol and Michael addition reactions. *Chem. Eur. J.* 14, 1273–1281 (2008).
- Wang, C. A. *et al.* 'Bottom-up' embedding of the Jorgensen–Hayashi catalyst into a chiral porous polymer for highly efficient heterogeneous asymmetric organocatalysis. *Chem. Eur. J.* 18, 6718–6723 (2012).

Acknowledgements

D.J. acknowledges the support of a Grant-in-Aid for Scientific Research (A) (24245030) from the Ministry of Education, Culture, Sports, Science and Technology of Japan (MEXT).

Author contributions

D.J. conceived the project, designed the experiments and provided funding. H.X. conducted the experiments and J.G. performed computational calculations. D.J. and H.X. wrote the manuscript.

Additional information

Supplementary information is available in the online version of the paper. Reprints and permissions information is available online at www.nature.com/reprints. Correspondence and requests for materials should be addressed to D.J.

Competing financial interests

The authors declare no competing financial interests.