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Supplementary Table 1: Crystallographic data, experimental conditions for powder X-ray data collection and results of the Rietveld analysis of PCN-333(Al)

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Supplementary Table 2: Crystallographic data, experimental conditions for X-ray data collection and results of the Rietveld analysis of PCN-332(Fe).

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Supplementary Methods:

Materials and Instrumentation:

Horseradish peroxidase (HRP), N, N-dimethylformamide (DMF), N, N-diethylformamide (DEF), Acetone, 1,3,5-Trichlorobenzene, AlCl₃, FeCl₃, VCl₃, ScCl₃.6H₂O, In(NO₃)₃.xH₂O, CHCl₃ were purchased from Alfa Aesar. Cytochrome C from bovine heart (Cyt c) and Microperoxidase sodium salt (MP-11) were purchased from Sigma Aldrich. All commercial chemicals were used without further purification unless otherwise mentioned. Synchrotron powder X-ray diffraction (PXRD) was carried out with Bruker D8-Discover diffractometer equipped with a Mo sealed tube (λ = 0.72959) on the beamline 17-BM at the Advanced Photon Source, Argonne National Laboratory. Other PXRD experiments were carried out on a BRUKER D8-Focus Bragg-Brentano X-ray powder Diffractometer equipped with a Cu sealed tube (λ = 1.54178) at 40 kV and 40 mA. HRTEM was performed on a JEOL JEM-2100F microscope at 200 kV equipped with a field emission gun. Thermogravimetric analyses (TGA) were carried out on a Shimadzu TGA-50 thermal analyzer from room temperature to 600 °C at a ramp rate of 2 °C/min in a flowing nitrogen atmosphere. Nuclear magnetic resonance (NMR) data were collected on a Mercury 300 spectrometer. Gas sorption measurements were conducted at different temperatures using a Micrometritics ASAP 2020 system. TEM-EDX mapping was performed on a TECNAI F20 Super-Twin transmission electron microscope (TEM) fitted with an EDAX instruments ultrathin window energy dispersive X-ray spectroscopy (EDX) detector. The microscope was operated at 200 keV and elemental maps were collected in a nanoprobe mode. Benzo-(1,2;3,4;5,6)-tris(thiophene-2'-carboxylic acid) (H₃BTTC) and 4,4′,4′′-s-triazine-2,4,6-triyl-tribenzoic acid (H₃TATB) are synthesized according to the reported methods ⁶,⁷.
Structure refinement of PCN-332 and PCN-333 by synchrotron PXRD:

The structure models of PCN-333 and PCN-332 were built by Materials Studio 6.0 [s4] based on the isoreticular structure of MIL-100 according to the space group and unit cell parameters obtained from PXRD, rotation electron diffraction (RED) and HRTEM. The structure models of PCN-333(Al) and PCN-332(Fe) were refined by Rietveld refinement using Topas Academic version 4.1, with soft restraints for the M–O bond distances and rigid body for the ligands. The guest species in the cages could not be located owing to their partial occupancies and low symmetry. Instead, 20 oxygen atoms were added at random positions inside the pores to compensate for the contributions of the guest species, and refined subsequently.

In house powder X-ray diffraction patterns of PCN-332 and PCN-333:

Sample preparation: The precipitate was washed twice with fresh DMF and then three times by acetone. After that, these samples were dried at 85 °C in the oven. The following data was collected on an in-house diffractometer with Cu Kα radiation (λ=1.54178 Å).

SEM and TEM studies of PCN-332 and PCN-333:

SEM analysis for PCN-333 and PCN-332: SEM Images were taken on an FEI Quanta 600 FE-SEM equipped with a Schottky field emission gun capable of producing high-resolution images at low-vacuum. The SEM was equipped with a motorized x-y-z-tilt-rotate stage, providing a movement range of x, y = 150 mm and z = 65 mm, and a tilt range of +70° to −5°.
Rotation electron diffraction (RED) and HRTEM combined with crystallography image processing for PCN-333(Al): Samples for TEM observations were dispersed in acetone and treated by ultra-sonication for 5 minutes. A droplet of the suspension was transferred onto a carbon-coated copper grid.

Rotation electron diffraction (RED)

Recently we developed software-based rotation electron diffraction (RED) method for automated collection and processing of three-dimensional (3D) electron diffraction data [S1, S2]. The RED data collection software combines electron beam tilts at a fine step (0.05–0.20°) with goniometer tilts at a coarse step (2.0–3.0°) around a common tilt axis. More than 1000 electron diffraction (ED) frames can be collected in less than one hour from an arbitrarily oriented crystal at different combinations of beam tilt and goniometer tilt. The RED data processing software processes the three-dimensional ED data, which includes shift correction of the ED frames, peak hunting for diffraction spots in individual ED frames and identification of these diffraction spots as reflections in three dimensions. A three-dimensional reciprocal lattice is reconstructed from the ED frames, and the unit cell parameters are determined from the positions of reflections in three-dimensional reciprocal space.

3D RED data of PCN-333(Al) was collected at 200 kV using the RED data collection software [S2] on a JEOL JEM2100 TEM. A single-tilt tomography sample holder was used for the data collection, which allows a tilt range from -70° to +70° in the TEM. ED frames were recorded on a 12-bit Gatan ES500W Erlangshen camera side-mounted at a 35 mm port. The electron beam was fully spread and covered the whole phosphorus screen. The aperture used for RED data collection was about 1.6 μm in diameter. The ED frames were acquired in selected area electron diffraction mode, and after each goniometer tilt, the position of the crystal was
tracked in image mode. The step of the beam tilt was 0.60° and the step of the goniometer tilt was 2.0°. The exposure time was 0.8 s per ED frame. 215 ED frames were collected within 15 minutes, covering a tilt range from -47.78° to 39.14°. The three-dimensional reciprocal lattice of **PCN-333(Al)** (Supplementary Figure 19) was reconstructed from the ED frames using the RED – data processing software package [S2]. As the sample was very beam sensitive, the diffraction intensity and resolution dropped quickly during the data collection. Totally, 515 reflections within the resolution of 5 Å were collected. The reconstructed 3D reciprocal lattice from the RED data shows that **PCN-333(Al)** is F-centered and the unit cell parameters determined from the RED data are $a = 120$ Å, $b = 121$ Å, $c = 122$ Å, $\alpha = 91.0^\circ$, $\beta = 92.1^\circ$, $\gamma = 91.7^\circ$.

The unit cell parameters obtained from the RED data ($a \approx 121$ Å) are slightly smaller than that from PXRD ($a = 126.42(3)$ Å). Many factors, such as the alignment of the TEM, sample height, camera length calibration and distortions caused by CCD camera and lenses, may affect the accuracy of the unit cell parameters determined by electron diffraction. The accuracy of unit cell determined by ED is usually within 2–3%. In the case of **PCN-333(Al)**, the sample was very beam sensitive and the resolution was low (5 Å). The low resolution data also decreases the accuracy of the unit cell determination. In addition, the guest molecules/ions inside the pores may be removed or decomposed under vacuum or electron beam, which could cause changes of unit cell parameters. Therefore, the errors in unit cell determination of **PCN-333(Al)** may be larger than 3%.

Considering that the $a$, $b$ and $c$ parameters are very similar (differ by 1.7%), and $\alpha$, $\beta$ and $\gamma$ angles are close to 90°, the crystal system of **PCN-333(Al)** is likely to be cubic. This is also in agreement with the octahedral morphology of **PCN-333(Al)** observed by SEM. The reflection conditions deduced from the RED data are $hkl$: $h+k = 2n$, $h+l = 2n$, $k+l = 2n$; $hk0$: $h+k = 4n$ and $h$, $k = 2n$; $hhl$: $h+l = 2n$; $h00$: $h = 4n$. This gave the following two possible space groups: $Fd-3$ and $Fd-3m$. 
Because the RED data is three-dimensional and the diffraction peaks do not overlap, RED provides more information than powder X-ray diffraction. However, due to the low data resolution and the radiation damage of the sample, we are not able to solve the structure from RED data. Therefore, we compared the RED data with the electron diffraction data simulated from the structure model. As the RED data only covered 86° of reciprocal space, the cubic symmetry \((m-3m)\) was applied to generate the symmetry-related missing reflections from the RED data. The \(hk0, hk1, hk2,\) and \(hk3\) planes from the RED data and simulated electron diffraction data from structure model are shown in Supplementary Figure 20. The intensity distribution of the RED data and those simulated from the structure model is quite similar, except for some axial \(h00\) reflections and very low angle reflections. The differences in intensities are caused by radiation damage and dynamical effects, because the crystal is rather thick (ca 1 µm, see Supplementary Figure 19A).

**High resolution transmission electron microscopy (HRTEM)**

High-resolution transmission electron microscopy (HRTEM) of **PCN-333(Al)** sample was performed on a JEOL JEM-2100F microscope equipped with a field emission gun operated at 200 kV. The images were recorded on a Gatan Ultrascan 1000 2k × 2k CCD camera. Since **PCN-333(Al)** was extremely electron beam sensitive, electron beam damage to the specimen was minimized as much as possible by using an electron dose of 70 electrons/(nm²·s) and an exposure time of 2 seconds. Supplementary Figure 21 shows an HRTEM image of **PCN-333(Al)** taken along the \([111]\) direction. Highly-ordered mesopores in a honeycomb arrangement can be observed throughout the entire image, which indicates the high crystallinity of **PCN-333(Al)**.
One of the most important advantages of HRTEM is that the crystallographic structure factor phase information can be obtained from the Fourier transform of the HRTEM image [S3]. The phase information is important for symmetry determination and essential for structure determination. Amplitudes and phases for all observed reflections were extracted from the Fourier transform of HRTEM image (Supplementary Figure 20D). The space groups $Fd-3$ and $Fd-3m$ give the projection symmetries of $p6$ and $p6mm$, respectively along the [111] direction. The corresponding phase errors $\phi_{res}$ are 21.0° for $p6$ and 18.8° for $p6mm$, as determined by crystallographic image processing using the program CRISP [S3]. The similar phase errors indicate that the projection symmetry of the PCN-333(Al) crystal can be the highest symmetry $p6mm$. The Fourier transform in Supplementary Figure 20D also shows the $6mm$ symmetry. Thus, the projection symmetry of PCN-333(Al) should be $p6mm$ and the only possible space group is $Fd-3m$.

The projection symmetry $p6mm$ was imposed on the experimental amplitudes and phases of the reflections extracted from the HRTEM image ($d > 14$ Å). A 2D map was calculated by an inverse Fourier transformation from the amplitudes and phases (Supplementary Figure 20E). Due to the beam damage of the sample, and the damping effect of the objective lens (contrast transfer function), the amplitudes from the Fourier transform of HRTEM image were attenuated. Thus, we replaced the amplitudes by those from PXRD, and the corresponding projected potential map is shown in Supplementary Figure 20F, which is quite similar to the one calculated by using the amplitudes and the phases from the final structure model (Supplementary Figure 20G). This further confirms that the structure model is correct.
**Porosity measurement for PCN-332 and PCN-333:**

Sample preparation: The precipitate was washed twice with fresh DMF and then three times by acetone. After that, these samples were dried at 85 °C in the oven. The samples were then dried again at 150 °C for 12 h by using the ‘outgas’ function of the sorption instrument prior to gas adsorption/desorption measurement.

**Thermogravimetric Analysis:**

See in Supplementary Figure 32-39.

**Theoretical protein uptake estimation:**

In each unit cell of PCN-333, there are eight of A-cages (5.5 nm) and 16 of B-cages (4.2 nm).

The volume of each unit cell = (126 Å)³ = 2.000376×10⁻¹⁸ cm³.

The density of **PCN-333(Al)** = 0.2299 g/cm³

So the mass of each unit cell = ρ×V

= 0.2299 g/cm³×2.00376×10⁻¹⁸ cm³

= 0.45989×10⁻¹⁸ g

Therefore, the total number of unit cells per gram of **PCN-333(Al)** is:

\[
1/(0.45989\times10^{-18}) = 2.17443\times10^{18}
\]

And the A-cage in each gram of **PCN-333(Al)** = 2.17443×10^{18}×8
B-cage in each gram of PCN-333(Al) = 3.47909×10^{19}

= 5.777×10^{-5} \text{ mol}

For cytochrome c, MW = 12000, so the maximum loading is 12000×(2.888×10^{-5})×3 = 1.039 \text{ g/g}.

For horseradish peroxidase, MW = 44000, so the maximum loading is 44000×(2.888×10^{-5}) = 1.27 \text{ g/g}.

**Enzyme loading process for PCN-333(Al) (compared with SBA-15):**

The enzyme solutions (with different concentrations) were incubated with as-synthesized PCN-333(Al) (5 mg) at 28 °C and gently shaken for 40 min. The resulted enzyme loaded PCN-333(Al) was then centrifuged and the supernatant was carefully removed for UV-vis measurement. The absorption of the soret band was proportional to the concentration of enzyme according to the Beer-Lambert Law. The loading amount of enzymes was calculated by measuring the concentration of enzymes in the supernatant and then subtracting from the free-enzyme amount added in the beginning of experiment. The enzyme uptake reached the saturation in 40 min since no more change on the soret band of supernatant was observed. The soret band was 403 nm for HRP, 409 nm for cytochrome C and 399 nm for MP-11. The mole absorption coefficient was determined by preparing four different concentrations to derive a standard curve which gave ε = 4.287×10^{5} \text{ M}^{-1}\text{ cm}^{-1} for HRP, 8.66×10^{4} \text{ M}^{-1}\text{ cm}^{-1} and 8.31×10^{4} \text{ M}^{-1}\text{ cm}^{-1} for MP-11. The immobilized enzyme particles need to be washed with water several times and stored at 0 °C before use.

**PXRD of PCN-333(Al) after enzyme loading:**

See in Supplementary Figure 40-45.

**Thermogravimetry analysis of PCN-333(Al) and the compounds after enzyme loading:**

See in Supplementary Figure 46-49.

**Spectroscopy studies of PCN-333(Al) and the compounds after enzyme loading:**
The kinetic studies on PCN-333(Al) immobilized enzyme and free enzyme

The HRP/H₂O₂ catalyzed oxidation of OPD can lead to the formation of 2,3-diaminophenazine (DAP), so the activity of HRP can be measured by monitoring the rate of reaction product formation spectrophotometrically at 418 nm using the reported molar absorption coefficient of 1.67×10⁴ M⁻¹cm⁻¹. Cytochrome C and Microperoxidase 11 can catalyze the oxidation of 2-2’-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS) in the presence of H₂O₂ and determine the activity of enzyme by monitoring the absorbance of soret band at 418 nm with reported molar absorption coefficient of 3.6×10⁴ M⁻¹cm⁻¹. The concentration of H₂O₂ was determined spectrophotometrically at 240 nm with ε = 43.6 M⁻¹cm⁻¹ [S5]. Kinetic measurements were carried out in time course mode by monitoring the absorbance change at 418 nm for OPD and ABTS. The Michealis-Menten equation (eqs. 1) was used for enzyme kinetics.

\[ V_0 = \frac{V_{\text{max}} [S]}{K_m + [S]} \]  

(eqns. 1)

Here, \( V_0 \) is the initial catalytic rate, \( V_{\text{max}} \) is the maximum rate conversion, which is obtained when the catalytic sites on the enzyme are saturated with substrate. \([S]\) is the substrate concentration and \( K_m \) is the apparent Michealis-Menten constant. The \( K_m \) and \( V_{\text{max}} \) values can be estimated using the least squares non-linear regression to fit the plot of \( V \) vs \([S]\) to the Michealis-Menten equation.
General procedure: The PCN-333(Al) immobilized enzyme (2.5 mg enzyme containing) were dispended in 100 ml water in advance. The reactions were conducted in the 3ml cuvette directly. The substrate and enzyme solution were added to buffer followed with the addition of H₂O₂. After a quick shaking, the cuvette was put in the UV sample holder as quickly as possible. Typically this process need two seconds on average. The data were collected using the kinetic mode and the plots of absorbance to time (mentioned as Time course in supporting information) were obtained. The background need to be scanned before data collection with addition of DI water instead of H₂O₂.

The kinetic studies on PCN-333(Al) immobilized HRP and free HRP:
See in Supplementary Figure 55-58.

The kinetic studies on PCN-333(Al) immobilized and free Cyt C:
See in Supplementary Figure 59-62.

The kinetic studies on PCN-333(Al) immobilized and free MP-11:
See in Supplementary Figure 63-66.

Measurement of the enzymatic activity of immobilized enzyme and free enzyme

The specific activity (U) was defined as the number of millimoles of substrate oxidized by one milligram of enzyme in 1 min at the described condition.

The specific activities for PCN-333(Al) immobilized HRP and free HRP were measured with 4 mM ABTS, 3.3 mM H₂O₂, 0.010 μM enzyme in 3 ml water at 25 °C. The specific activity for PCN-333(Al) immobilized Cyt C was measured with 2 mM ABTS, 1 mM H₂O₂, 0.48 μM immobilized enzyme in 3 ml water at 25 °C. The specific activity for free Cyt C was measured with 2 mM ABTS, 1 mM H₂O₂, 0.81 μM free enzyme in 3 ml water at 25 °C. The specific activity for PCN-333(Al) immobilized MP-11 was measured with 2 mM ABTS, 1 mM H₂O₂, 0.32 μM immobilized enzyme in 3 ml water at 25 °C. The specific activity for free MP-11 was
measured with 2 mM ABTS, 1 mM H₂O₂, 0.27 μM free enzyme in 3ml water at 25 °C. The specific activities in different solvents for immobilized HRP and free HRP were measured with 2 mM OPD, 0.67 mM H₂O₂, 0.46 μM enzyme in a 3 ml mixture of organic solvent : water = 1 : 1 at 25 °C.

**Enzyme recycling**

For the recycling studies with **PCN-333(Al)** immobilized HPR, the reaction was performed with 2.2 mg particle (1 mg HRP content), 0.86 mM OPD, 0.72 mM H₂O₂ in 41.5 mL of 0.1 M citric acid-sodium citrate buffer at pH = 6 and room temperature. After reaction, the mixture was centrifuged and the supernatant was separated. The resulting solid was washed twice with water to remove any soluble residue. The recovered enzyme was used for the next reaction with adding the same amount of substrate, buffer and H₂O₂. The procedure was repeated 5 times as describe above. The relative activity was calculated as a ratio of reused enzyme activity and enzyme activity used for the first time.

For other immobilized enzyme recycling activity, the reaction mixture contained: 8 mg particle (0.8 mg HRP content), 0.86 mM OPD, 0.72 mM H₂O₂ in 41.5 mL of 0.1 M citric acid-sodium citrate buffer at pH = 6 for SBA-15 immobilized HRP; 3mg particle (1 mg Cyt C content), 0.16 mM ABTS, 0.56 mM H₂O₂ in 45 mL of 0.1 M citric acid-sodium citrate buffer at pH = 6 for **PCN-333(Al)** immobilized Cyt C; 11 mg particle (1 mg Cyt C content), 0.1 mM ABTS, 0.66 mM H₂O₂ in 45 mL of 0.1 M citric acid-sodium citrate buffer at pH = 6 for SBA-15 immobilized Cyt C; 3 mg particle (1 mg Cyt C content), 2 mM ABTS, 1 mM H₂O₂ in 45 mL of 0.1 M citric acid-sodium citrate buffer at pH = 6 for **PCN-333(Al)** immobilized MP-11; 10.8 mg particle (0.8
mg Cyt C content), 2 mM ABTS, 1 mM H₂O₂ in 45 mL of 0.1 M citric acid-sodium citrate buffer at pH = 6 for PCN-333(Al) immobilized MP-11.

**The leaching test of PCN-333(Al) immobilized enzyme and SBA-15 immobilized enzyme**

The PCN-333(Al) immobilized HRP particles (3 mg, contains HRP 1.55 mg) and SBA-15 immobilized HRP particles (5.8 mg, contains HRP 0.8 mg) were dispersed in 3mL of water and then equilibrated for 5 hours prior to centrifugation. The supernatant was monitored by UV-vis to determine the concentration. After that, the supernatant was re-dispersed with immobilized enzyme particles and allowed to equilibrate for a longer time. The procedure was repeated until the total equilibrium time reached 38 hours. The leaching tests for PCN-333(Al) immobilized Cyt C and MP-11 as well as immobilized SBA-15 enzymes were conducted through the same method. The relative concentration was calculated as the ratio of the initial enzyme content in supports and the supernatant concentration in solution after required immersion time.
Supplementary References: