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Chiral porous metal-metallosalan frameworks are constructed from an unsymmetrical chiral pyridinecarboxylate ligand derived from Ti(salan) and are shown to be heterogeneous catalysts for asymmetric oxidation of thioethers to sulfoxides.

Metal–organic frameworks (MOFs) are crystalline porous hybrid solids composed of organic struts and inorganic nodes and have shown promise for a wide range of applications in diverse areas.¹ Unlike traditional inorganic materials, MOFs feature structural diversity and amenability to be designed with desired functionalities at the molecular level.² In particular, MOFs offer great potential in heterogeneous catalysis because of their advantages over other immobilized catalyst systems such as crystalline structures, with high catalyst loadings, more uniform, isolated and accessible active sites and enhanced catalytic activity in some cases by providing confined spaces for reactants.³ Incorporating chiral molecular catalysts into MOFs means they can be used for asymmetric catalysis,⁴ but there is still difficulty in making chiral MOF catalysts with stereoselectivity rivaling their homogeneous counterparts.^{2b,5}

Chiral salen ligands and their metal complexes have been widely applied in asymmetric synthesis,^{3b,c,6} but their reduced forms of salans that have increased ligand flexibility and stronger nitrogen donors are less studied.⁷ Herein we report the rational synthesis of two chiral porous MOFs built from a pyridinecarboxylate bridging ligand of Ti(salan) and show that they can be used as heterogeneous catalysts for the asymmetric oxidation of thioethers with aqueous H_2O_2 as an oxidant.

The unsymmetrical difunctionalized chiral salan ligand H_5L was prepared in four steps in an overall 72% yield from 3-*tert*butyl-5-(4-pyridyl)salicylaldehyde and 3-*tert*-butyl-5-formyl-4-hydroxybenzoic acid. Metalation of H_5L with Ti(OBu)₄ (1:1 molar ratio) in THF gave TiL(OBu)₂. Heating a mixture of TiL(OBu)₂ and CdBr₂·4H₂O or Zn(OAc)₂·2H₂O (2:1 molar ratio) in DMF and



Scheme 1 Synthesis of H₅L, metalloligand TiL(OBu)₂, 1 and 2.

Chiral microporous Ti(salan)-based metal-organic

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frameworks for asymmetric sulfoxidation⁺

MeOH or EtOH at 100 °C afforded single-crystals of $Cd_3(\mu_3$ -OH)Br[(TiLOMe)_2O]_2·3DMF·H_2O (1) or $Zn_3(\mu_3$ -OH)(OH)-[(TiLOEt)_2O]_2·3DMF (2) in good yields (Scheme 1). The products were stable in air and insoluble in water and common organic solvents, and were formulated on the basis of elemental analysis, IR and thermogravimetric analysis (TGA).

(*R*)-1 crystallizes in a chiral orthorhombic $P2_12_12$ space group.[‡] The basic building unit in 1 is a Ti₂L₂(µ₂-O) dimer built of TiL monomers. The dimetallic core consists of two six-coordinate octahedral Ti centers enclosed in the N₂O₂ pockets, binding one MeO⁻ anion and linked by one µ₂-O atom. In the dimer, the two pyridyl groups of TiL associate in parallel pointing towards the same direction, whereas the two carboxyl groups orient towards two different directions (Fig. 1a). The Ti₂L₂(µ₂-O) dimer acts as a tetradentate ligand and binds to three Cd₃O clusters using its two pyridyl groups and two carboxylate groups in a bidentate fashion. Of the two independent Cd ions in [Cd₃(µ₃-OH)Br(O₂C)₄], Cd1 is octahedrally coordinated by one µ₃-OH⁻ anion, one Br⁻ anion, two carboxylate oxygen atoms and two pyridyl groups of four Ti₂L₂(µ₂-O) dimers, and the Cd2 is octahedrally coordinated by one µ₃-OH⁻, one pyridyl group and four carboxylate oxygen atoms of three Ti₂L₂(µ₂-O).

Interestingly, six adjacent $[Cd_3OBr(O_2C)_4]$ clusters that are related by C_2 symmetry and linked by eight Ti₂L₂(μ_2 -O) units encapsulate a

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Fig. 1 Structure of **1** showing (a) the coordination environment of the Ti₂L₂(μ_2 -O) building unit (H atoms are omitted for clarity), atoms labelled gray, carbon; green, titanium; red, oxygen; blue, nitrogen; (b) the cavity encapsulated by six trinuclear [Cd₃(μ_3 -OH)Br(O₂C)₄] clusters (the cavity is shown as a colored sphere and the Cd atoms are shown as green polyhedra) and space-filling representations of (c) a 1D channel of 0.78 × 0.54 nm along the *b* direction.

distorted octahedral cage. The cage has an irregular open cavity with a maximum inner width of ~1.7 nm (considering van der Waals radii) (Fig. 1b and Fig. S6, ESI†). The irregular apertures on the faces have a diagonal distance of ~0.78 × 0.54 nm or ~0.65 × 0.41 nm (Fig. 1c). Sharing of the narrow windows with neighboring cages leads to multidirectional zig-zag channels in the framework that are occupied by DMF, water and MeOH guest molecules. **1** is a rare example of MOFs decorated with chiral NH functionalities,^{1d} which are accessible to guest molecules and are beneficial for enantio-selective processes.

2 is isostructural to 1 and adopts a similar porous 3D network structure that is built from (TiL)₂O(OEt)₂ and [Zn₃O(OH)(O₂C)₄] units. The framework has open channels of ~0.78 × 0.54 nm along the *b*-axis and ~0.65 × 0.41 nm along the *c*-axis. Calculations using PLATON show that both 1 and 2 have about ~45.4% of the total volume available for guest inclusion.⁸

Solid-state circular dichroism (CD) spectra of **1** and **2** made from *R* and *S* enantiomers of the H_5L ligand are mirror images of each other, which indicate their enantiomeric nature (Fig. S9, ESI[†]).

TGA revealed that the included guest molecules could be readily released in the temperature range from 80 to 200 °C and the frameworks are stable up to ~315 °C. The phase purity of them was supported by the powder X-ray diffraction (XRD) patterns of the bulk samples, which are consistent with the calculated patterns. The N₂ sorption measurements of their apohost samples at 77 K showed only surface adsorption (Fig. S13, ESI†), although the theoretical values are expected to be 1650.87 m² g^{-1.9}

The presence of chiral TiL units in 1 prompted us to explore its utilization as a heterogeneous catalyst for oxidation of thioethers to sulfoxides.¹⁰ Optically active sulfoxides are important chiral auxiliaries as well as valuable intermediates in organic synthesis for many pharmaceuticals and biologically active compounds.¹¹ The oxidation reactions were conducted in acetone at 0 °C using 30% aqueous H2O2 (1.15 equiv.) as the oxidant. 1.12 mol% loading of (R)-1 afforded 54-90% conversions and 23-62% ee of the produced sulfoxides with 77-99% chemoselectivities after 16 h for the sulfides bearing both electron-rich and electron-poor species (Table 1). However, introduction of a strong electron-withdrawing -NO₂ group into the phenyl ring of the substrate led to slightly lower conversion of 60% (Table 1, entry 7). Compared with PhSMe, the sulfoxidation of methyl p-tolyl sulfide gave comparable conversion and chemoselectivity, but the product showed higher enantioselectivity. When the methyl group in PhSMe was substituted with isopropyl, the oxidation reaction still gave a conversion of 84%, but for a bulkier group like benzyl, the conversion was decreased to 54%, probably due to the slow mass-diffusion of the bulky substrate in the porous media (Table 1, entries 10 and 11). Under otherwise identical conditions, we have also examined the catalytic activities of MOF 2 for oxidation of sulfides, but the products showed lower enantioselectivities and chemoselectivities than those obtained using (R)-1. For example, oxidation of thioanisole and methyl p-tolyl sulfide gave sulfoxides with 20 and 41% ee and 82 and 83% chemoselectivities, respectively. (S)-1 exhibits catalytic performances closer to those of (R)-1, as evidenced by the oxidation of thioanisole and methyl p-tolyl sulfide (Table 1, entries 2 and 5).

Table 1	Catalytic oxida	ation of sulfides by 1 ^a
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$R_{1} \xrightarrow{S} R_{2} \xrightarrow{Cat.} \\ \xrightarrow{1.15 \text{ equiv. } 30\% \text{ H}_{2}\text{O}_{2}}_{CH_{3}\text{COCH}_{3}, 273 \text{ K}} \xrightarrow{R_{2}} S \xrightarrow{R_{1}} + \xrightarrow{R_{1}} R_{1} \xrightarrow{S} R_{2}$							
Cat. ^b	R ₁	R_2	Conv. ^{d} (%)	ee^{e} (%)	Select. ^{f} (%)		
<i>R</i> -1	C_6H_4	Ме	89	23	84		
S-1	C_6H_4	Me	90	24	85		
<i>R</i> -TiL	C_6H_4	Me	94	8	64		
R-1	p-MeC ₆ H ₄	Me	90	46	87		
S-1	p-MeC ₆ H ₄	Me	89	43	86		
R-TiL	p-MeC ₆ H ₄	Me	93	12	59		
<i>R</i> -1	p-NO ₂ C ₆ H ₄	Me	60	50	77		
<i>R</i> -1	p-OMeC ₆ H ₄	Me	88	52	81		
<i>R</i> -1	2-Naphthyl	Me	68	62	88		
<i>R</i> -1	C_6H_4	Isopropyl	84	50	99		
<i>R</i> -1	C_6H_4	Benzyl	54	48	93		
<i>R</i> -TiL	C_6H_4	Benzyl	87	10	58		
R-1	2-Naphthyl	Benzyl	<5	_	70		
$R\text{-}\mathrm{Ti}\mathbf{L}$	2-Naphthyl	Benzyl	88	_	68		
	R Cat. ^b <i>R</i> -1 <i>S</i> -1 <i>R</i> -TiL <i>R</i> -1 <i>R</i> -1	$\begin{array}{c c} R_{1} & \stackrel{S}{\longrightarrow} R_{2} & {1.15 \text{ e}} \\ & & Ch_{3}c \\ \hline Cat.^{b} & R_{1} \\ \hline \\ \hline R-1 & C_{6}H_{4} \\ \hline S-1 & C_{6}H_{4} \\ \hline R-TiL & C_{6}H_{4} \\ \hline R-1 & p-MeC_{6}H_{4} \\ \hline R-1 & p-MeC_{6}H_{4} \\ \hline R-1 & p-MeC_{6}H_{4} \\ \hline R-1 & p-OMeC_{6}H_{4} \\ \hline R-1 & p-OMeC_{6}H_{4} \\ \hline R-1 & 2-Naphthyl \\ \hline R-1 & C_{6}H_{4} \\ \hline R-1 & C_{6}H_{4} \\ \hline R-1 & 2-Naphthyl \\ $	$ \begin{array}{c c} & Cat. \\ \hline R_1 & S_R_2 & Cat. \\ \hline 1.15 \ equiv. \ 30\% \ H_2 \\ CH_3COCH_3, \ 273 \\ \hline Cat.^b & R_1 & R_2 \\ \hline \\ \hline R-1 & C_6H_4 & Me \\ \hline S-1 & C_6H_4 & Me \\ \hline R-TiL & C_6H_4 & Me \\ \hline R-TiL & p-MeC_6H_4 & Me \\ \hline R-1 & p-MeC_6H_4 & Me \\ \hline R-1 & p-NO_2C_6H_4 & Me \\ \hline R-1 & p-OMeC_6H_4 & Me \\ \hline R-1 & p-OMeC_6H_4 & Me \\ \hline R-1 & 2-Naphthyl & Me \\ \hline R-1 & C_6H_4 & Benzyl \\ \hline R-TiL & 2-Naphthyl & Benzyl \\ \hline R-TiL & 2-Naphthyl & Benzyl \\ \hline R-TiL & 2-Naphthyl & Benzyl \\ \hline \end{array}$	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	$\begin{array}{c c c c c c c c c c c c c c c c c c c $		

^{*a*} For reaction details see experimental section. ^{*b*} 1.12 mol% loading of 1 based on sulfide. ^{*c*} Reaction time: 6 h; catalysis loading: 4.5 mol% (based on the same TiL loading as that of the heterogenous system). ^{*d*} Calculated as ([sulfone] + [sulfoxide])/([sulfide] + [sulfoxide] + [sulfone]) × 100. ^{*e*} e determined by HPLC. ^{*f*} Calculated as [sulfoxide]/([sulfoxide] + [sulfone]) × 100.

To study the confinement effect of the chiral MOF, the catalytic performance of the monomer TiL(OBu)2 was also studied. Thioanisole, methyl p-tolyl sulfide and phenyl benzyl sulfide were oxidized by aqueous H₂O₂ with 4.5 mol% TiL(OBu)₂ as the catalyst (the same TiL loading as that of the heterogenous system). The conversions are obviously higher than those of the corresponding heterogeneous systems after 6 h, which afforded 8, 12 and 10% ee for sulfoxides with 64, 59 and 58% chemoselectivities, respectively (Table 1, entries 3, 6 and 12). Therefore, the TiL-containing framework displayed obviously enhanced enantioselectivities and chemoselectivities with respect to its homogeneous catalyst, although the heterogeneous reaction needs a longer time for diffusion of species into the porous structure. A careful examination of the crystal structure of 1 reveals that the channel surfaces are uniformly lined with chiral $Ti_2L_2(\mu_2-O)$ units with Ti sites pointing to the open channels, and the shortest Ti-Ti distance of adjacent surfaces in a channel is 3.599 Å (Fig. S5, ESI⁺). The increased enantioselectivity and chemoselectivities may arise from geometrical constraints imposed by the unique chiral micro-environments around the site-isolated Ti centers, which may effectively restrict molecular motion, leading to efficient enantiodiscrimination.^{3c,12} The turnover frequency (TOF) of (R)-1 and (R)-TiL is 1.24 and 3.50, 1.26 and 3.46, and 0.75 and 3.24 h⁻¹, respectively, for oxidation of thioanisole, methyl *p*-tolyl sulfide, and phenyl benzyl sulfide; the lower TOF of (R)-1 is probably due to the diffusion of substrates in the porous structure, which makes the access of the substrate to the active site slow.

To probe whether oxidation of the sulfides occurs inside the chiral pores or on the surface of the solid framework catalyst, a more sterically bulky substrate, benzyl 2-naphthyl sulfide, was subjected to the oxidation conditions. Less than 5% conversion was observed when catalyzed by (R)-1 after 16 h, which was much lower than 88% conversion obtained using the homogeneous TiL catalyst within 6 h (Table 1, entries 13 and 14). This result suggests that the bulky substrate cannot access the catalytic Ti sites in the porous structure due to its large diameter and so the oxidation reaction indeed occurs within the chiral MOF. This point is also supported by the fact that ground and unground particles of (R)-1 exhibited similar catalytic performance in oxidation of methyl p-tolyl sulfide (91% vs. 90% and 44% vs. 46%, conversions and enantioselectivities after 16 hours, respectively).

The heterogeneity of the MOF catalyst was also examined. The supernatant obtained from the oxidation of methyl p-tolyl sulfide after filtration through a regular filter did not afford any additional oxidation product. To evaluate the stability of the solid catalysts, we investigated recycled and reused (R)-1 in the sulfoxidation of methyl p-tolyl sulfide. Upon completion of the reaction, catalyst 1 could be recovered in quantitative yield and used repeatedly without significantly degrading the catalytic performance for the following three runs (conversions $\sim 90\%$ and 46, 42, 44 and 43% ee for 1-4 runs, respectively). PXRD showed that the recycled catalyst retained crystallinity after four runs, although the structure got distorted. Inductively coupled plasma optical emission spectrometry (ICP-OES) analysis of the product solution indicated little loss of the metal ions (~ 2 ppm for Cd and 6 ppm for Ti) from the structure, either as molecular species or as particles too small to be removed by filtration through Celite.

In conclusion, we have synthesized two microporous 3D MOFs utilizing a pyridine- and carboxylic acid-functionalized Ti(salan) ligand. The frameworks were shown to be heterogeneous catalysts for asymmetric oxidation of thioethers to sulfoxides, with improved enantioselectivity relative to the homogeneous catalyst. The ready tunability of such a modular approach based on chiral metallosalans promises to lead to a variety of framework materials with novel enantioselective functions.

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Notes and references

‡ Crystallographic data for 1: M = 3427.85, orthorhombic, space group $P2_{12}_{12}$, a = 34.4419(13) Å, b = 16.7622(8) Å, c = 18.4473(8) Å, V = 10650.0(8) Å³, Z = 2, $D_c = 1.069$ Mg m⁻³, F(000) = 3522, 11722 unique $(R_{int} = 0.0894)$, $R_1 = 0.0794$, w $R_2 = 0.1873$ $[I > 2\sigma(I)]$, GOF = 1.074, Flack parameter = 0.005(12). 2: M = 3246.95, orthorhombic, space group $P2_{12}_{12}$, a = 34.0597(5) Å, b = 16.9014(2) Å, c = 18.3315(3) Å, V = 10552.6(3) Å³, Z = 2, $D_c = 1.022$ Mg m⁻³, F(000) = 3392, 12 261 unique $(R_{int} = 0.0391)$, $R_1 = 0.0984$, w $R_2 = 0.2573$ $[I > 2\sigma(I)]$, GOF = 1.084, Flack parameter = 0.031(13). CCDC 936226 and 936227.

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