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Multivariate Metal-Organic Frameworks as Multifunctional Heterogeneous Asymmetric Catalysts for Sequential Reactions

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ABSTRACT: The search for versatile heterogeneous catalysts with multiple active sites for a broad of asymmetric transformations has long been of great interest, but it remains a formidable synthetic challenge. Here we demonstrate that multivariate metal-organic frameworks (MTV-MOFs) can be used as an excellent platform to engineer heterogeneous catalysts featuring multiple and cooperative active sites. An isostructural series of twofold interpenetrated MTV-MOFs that contain up to three different chiral metallosalen catalysts were constructed and used as efficient and recyclable heterogeneous catalysts for a variety of asymmetric sequential alkene epoxidation/epoxide ring-opening reactions. Interpenetration of the frameworks brings metallosalen units adjacent to each other, allowing cooperative activation, which results in improved efficiency and enantioselectivity over the sum of the individual parts. The fact that manipulation of molecular catalysts in MTV-MOFs can control the activities and selectivities would facilitate the design of novel multifunctional materials for enantioselective processes.

INTRODUCTION

The development of novel materials that can be used as versatile heterogeneous catalysts for various asymmetric transformations has long been of great interest in both academia and industry, but it poses a formidable synthetic challenge.[1,2] Metal-organic frameworks (MOFs) have attracted much attention for their high permanent porosity coupled with structural tunability[3] and they have shown potential for utility in gas adsorption,[4] smart sensors,[5] catalysis,[6] separation,[7] and others.[8] In particular, MOFs have provided great opportunities for heterogeneous catalysis,[6,9,10] especially for asymmetric catalysis because their local chiral environments can be generated through either constructing helical structures[11,12] or using optically active organic linkers.[12-14]Among the reported chiral MOF catalysts, the most efficient examples all contain isolated privileged chiral catalysts or ligands such as BINOL- and metallosalen-based derivatives, but they typically suffer from narrow substrate scope and limited types of reactions.[14,15] MOF catalysts with multiple active sites have been extensively studied for tandem/sequential transformations, targeting the maximization of spatial and temporal productivity with mobilization of minimum resources,[16] but chiral multifunctional MOF catalysts are far less explored. In fact, there are only two reports of MOF-based asymmetric sequential reactions.[15c,15d]

One of the recent MOF synthetic strategies has been centered on the fabrication of heterogeneity within order, which is capable of incorporating different synergistic functionalities into one crystalline network.[17] An appealing approach is the use of organic linkers with similar size and shape but distinct functionalities to build mixed-linker MOFs.[18] One of the exemplary examples is the successful fabrication of multivariate MOFs (MTV-MOFs), reported by Yaghi, in which up to eight different organic linkers were integrated into one single framework.[18a] The modular nature of MTV-MOF synthesis makes it possible to introduce two or more different chiral catalytic sites into one single MOF, which may promote a broad range of asymmetric tandem/sequential reactions.[10] Moreover, the cooperation among the disparate active centers in close proximity can allow access to improved efficiency and stereoselectivity over monocatalytic systems.[16] Notably, it is challenging to design and prepare heterogeneous catalysts featuring cooperative active sites as they spatially separated within the solid are usually difficult to cooperate.[19]

Metallosalen complexes are well-known privilege catalysts, as demonstrated by their successful application in many challenging asymmetric reactions.[20] For example, Jacobsen et al. have shown that chiral Co(salen) and Cr(salen) complexes are excellent catalysts for asymmetric ring opening (ARO) reactions of epoxides with different nucleophiles.[21] The epoxide ring opening reactions are believed to occur via a bimolecular activation process in which two catalyst molecules activate both the electrophile (epoxide) and nucleophile (eg. water or $TMSN_3$) cooperatively in the catalytic cycle. To improve such cooperativity, different types of supported catalysts using organic and inorganic supports have been developed.[22] Chiral MOFs based on M(salen)-derived bridging ligands, where M is Mn/Co/Fe/VO/Ru/Cu/Cr, were constructed.[15,23] The resultant M(salen)-MOFs have been demonstrated as heterogeneous asymmetric catalysts for epoxidation of olefins,[15a-d] aziridination of styrenes,[15e] cyclopropanation of olefins,[15f] hydrolytic kinetic resolution of epoxides,[15g] aminolysis of epoxides,[15h] cyanation of aldehydes[15i,j] and oxidation of sulfides.[15k] The synthesis of mixed-linker MOFs using multiple metallosalen-based linkers has not yet been explored.[15] Here we report the synthesis of a isostructrual family of chiral, porous and interpenetrating MTV-MOFs with strategically placed multiple and cooperative metallosalen active sites for asymmetric sequential alkene epoxidation/epoxide ring-opening reactions.

RESULTS AND DISCUSSION

Synthesis and characterization. All of the metallosalen-derived dicarboxylate ligands H_2L^M [M = Cu, VO, CrCl, MnCl, Fe(OAc) and Co(OAc)] were synthesized by reactions of N,N′-

bis(3-tert-butyl-5-(carboxyl)salicylide (H_4L) and corresponding metal salts in MeOH at room temperature, as shown in Figure 1A. The ester of $Me_2\mathbf{L}^{\mathbf{M}}$ was obtained in a way similar from the ester $H_2Me_2\mathbf{L}$ of $H_4\mathbf{L}$. Heating a mixture of $Zn(NO_3)_2\cdot 6H_2O$ and the carboxylic acid functionalized Cu(salen) ligand $H_2\mathbf{L}^{\mathbf{Cu}}$ at 80 °C in dimethylformamide (DMF) afforded dark blue crystals of $[Zn_4O(\mathbf{L}^{\mathbf{Cu}})_3]\cdot 5MeOH\cdot 2DMF$ ($\mathbf{1}^{\mathbf{Cu}}$) in 96% yield (Figure 1A). Single-crystal X-ray diffraction analysis of $\mathbf{1}^{\mathbf{Cu}}$ revealed a twofold interpenetrated network that crystallizes in the chiral cubic space group $F4_132$, with one $\mathbf{L}^{\mathbf{Cu}}$ ligand and two-thirds of the $Zn_4(\mu_4\text{-}O)$ cluster in the asymmetric unit. As expected, six bidentate carboxylate groups from six adjacent $\mathbf{L}^{\mathbf{Cu}}$ ligands coordinate to the four Zn ions to generate $[Zn_4(\mu_4\text{-}O)(\text{carboxylate})_6]$ building blocks, which connect $\mathbf{L}^{\mathbf{Cu}}$ ligands to give a 3D network of the pcu topology. Interpenetration of the 3D networks brings a pair of Cu(salen) units into close proximity with each other, with a Cu–Cu distance of about 8.2 Å (Figures 1B-1D), thereby generating an attractive scaffold for cooperative catalysis. $\mathbf{1}^{\mathbf{Cu}}$ possesses 3D inter-connected zigzag channels (Figure S4), with the largest channel dimensions of 7.1 ×7.1 $Å^2$ and a PLATON-calculated void space of 51%.[24]

Seven mixed-crystal variants were obtained by varying the ratios of different ligands, as shown in Figure 1A. Crystals of the five binary MTV-MOFs ($\mathbf{1}^{\mathbf{CuV}}$, $\mathbf{1}^{\mathbf{CuMn}}$, $\mathbf{1}^{\mathbf{CuCr}}$, $\mathbf{1}^{\mathbf{CuFe}}$ and $\mathbf{1}^{\mathbf{CuCo}}$) were obtained by heating a 1:1 mixture of $H_2\mathbf{L}^{\mathbf{M}}$ [M = VO, CrCl, MnCl, Fe(OAc), Co(OAc)] and $H_2\mathbf{L}^{\mathbf{Cu}}$ with $Zn(NO_3)_2\cdot 6H_2O$ in DMF and MeOH at 80 °C. Crystal of the two ternary MTV-MOFs ($\mathbf{1}^{\mathbf{CuMnCr}}$ and $\mathbf{1}^{\mathbf{CuMnCo}}$) were obtained by heating a 1:1:1 mixture of one or two identical $H_2\mathbf{L}^{\mathbf{Cu}}$, $H_2\mathbf{L}^{\mathbf{Mn}}$ and $H_2\mathbf{L}^{\mathbf{M}}$ [M = CrCl and Co(OAc)] with $Zn(NO_3)_2\cdot 6H_2O$ in DMF and EtOH at 80 °C. The single-crystal X-ray diffraction data for these binary and ternary MOFs were a little weak, but their isostructural nature to $\mathbf{1}^{\mathbf{Cu}}$ could be well established by cell parameter determination and powder X-ray diffraction studies (Figures 2A and 2B). ICP-OES showed that molar ratios of $\mathbf{L}^{\mathbf{Cu}}/\mathbf{L}^{\mathbf{M}}$ in the binary frameworks are 2:1 for $\mathbf{1}^{\mathbf{CuV}}$ and $\mathbf{1}^{\mathbf{CuCo}}$, 3:1 for $\mathbf{1}^{\mathbf{CuCr}}$, and 4:1 for $\mathbf{1}^{\mathbf{CuMn}}$ and $\mathbf{1}^{\mathbf{CuFe}}$, respectively, and the molar ratios of both $\mathbf{1}^{\mathbf{CuMnCr}}$ and $\mathbf{1}^{\mathbf{CuMnCo}}$ are 2:1:1 in the ternary variants. The synthesis of these MTV-MOFs does not appear to be sensitive to the ligand feed ratios. For instance, varying the feed ratio of $H_2\mathbf{L}^{\mathbf{Cu}}/H_2\mathbf{L}^{\mathbf{Mn}}/H_2\mathbf{L}^{\mathbf{Cr}}$ from 1:1:1 to 2:1:1 and 3:1:1 did not change the composition of $\mathbf{1}^{\mathbf{MnCrCu}}$ at all. EDS analysis of individual single crystals further showed that these mixed-linker MOFs are truly mixed-component compounds rather than physical mixtures of homoleptic series (Figures 2C and 2D).

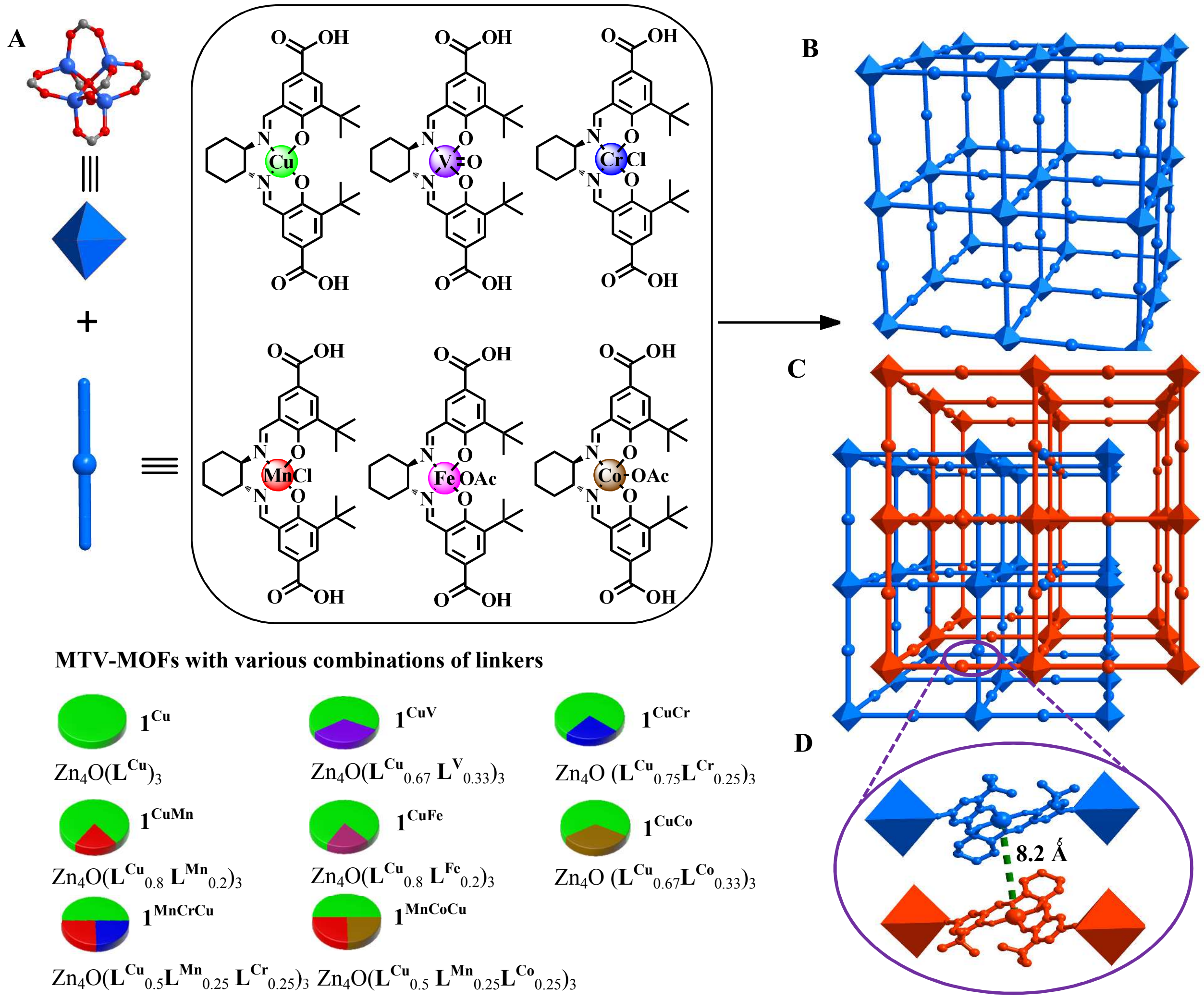


Figure 1. (**A**) Construction of MOF $\mathbf{1}^{\mathbf{Cu}}$ and corresponding MTV-MOFs $\mathbf{1}^{\mathbf{CuM}}$ and $\mathbf{1}^{\mathbf{CuMM'}}$ with different metallosalen linkers. (**B**) One 3D unit of MOF $\mathbf{1}^{\mathbf{CuM}}$. (**C**) Twofold interpenetrating $\mathbf{1}^{\mathbf{Cu}}$ (Red color indicates the interpenetrated 3D network). **(D)** Close-up view of two $\mathbf{L}^{\mathbf{Cu}}$ units brought into proximity to each other by twofold interpenetration.

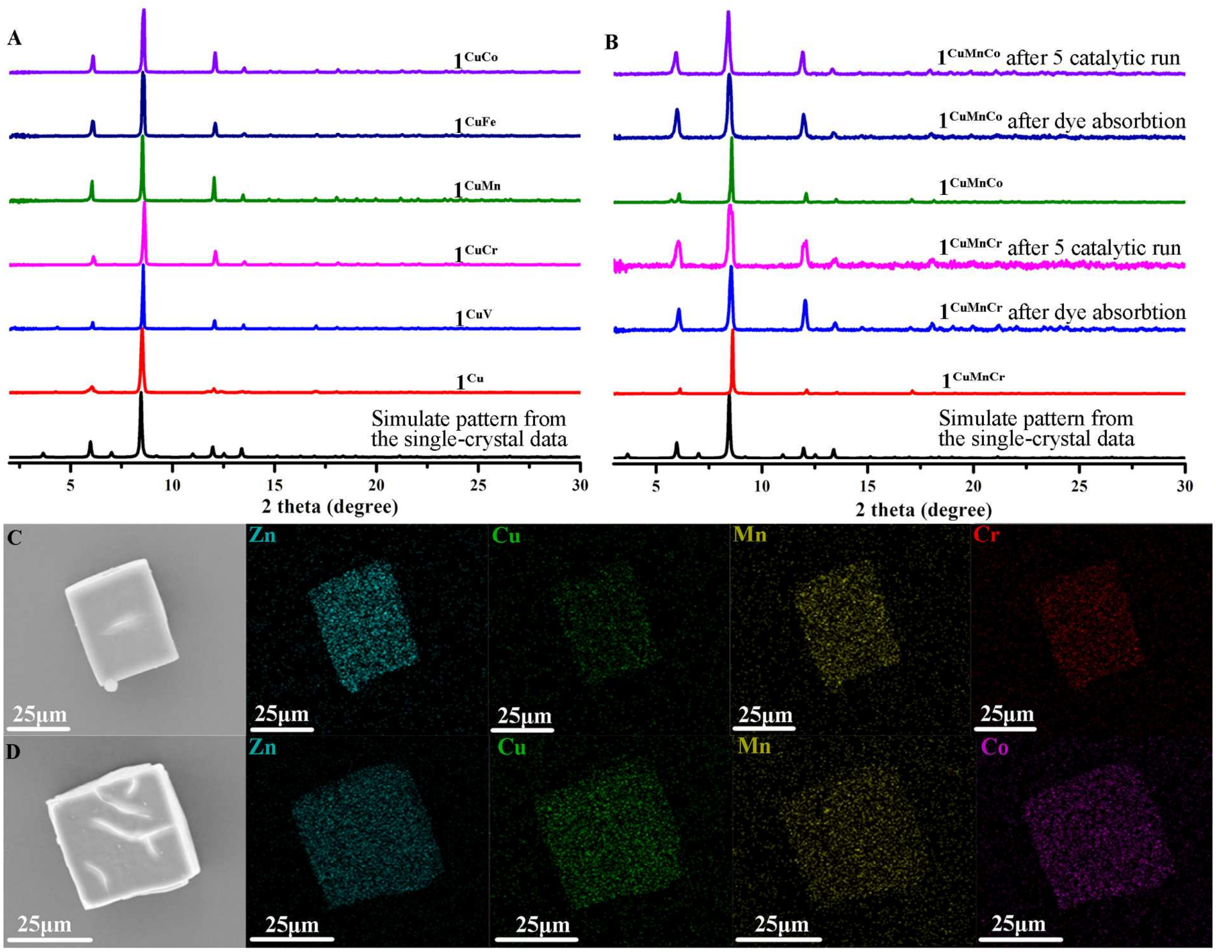
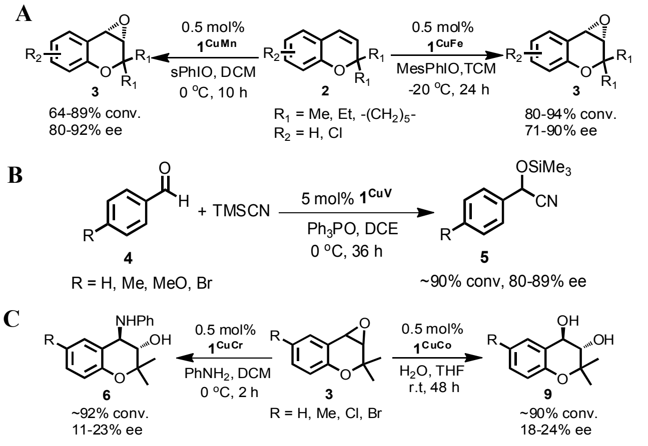


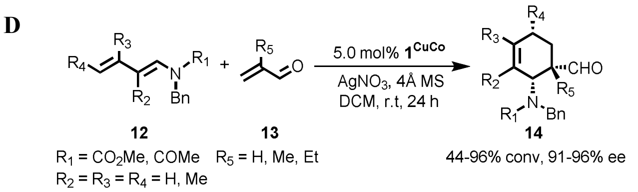
Figure 2. (A, B) PXRD patterns of the as-prepared MTV-MOFs and SEM images and EDS mappings of (C) $\mathbf{1}^{CuMnCr}$ and (D) $\mathbf{1}^{CuMnCo}$

All of the eight MOFs are stable in air and common organic solvents. TGA indicates that these frameworks are stable up to ~400 °C. Solid-state circular dichroism (CD) spectra of them constructed from (*R*)- or (*S*)-enantiomers of $H_2\mathbf{L}^{M}$ are mirror images of each other, demonstrating their enantiomeric nature. The permanent porosity of these MOFs has been confirmed by CO_2 adsorption experiments, and all of them displayed typical type-I gas sorption isotherms, with BET (Brunauer-Emmett-Teller) surface areas ranging from 172 to 219 m^2/g. The uptake of bulky dye molecules by MOFs has recently been utilized to assess their substrate-accessible pore volumes in solution.[15b] These MOFs could adsorb about 1.2 Rhodamine 6G molecules (R6G, ca. 1.4 nm × 1.6 nm in size) per formula unit in solution and the inclusion crystal displayed almost the same PXRD pattern as the pristine sample (Figure 2A), indicating the maintenance of porosity and structural integrity of them in solution.

Asymmetric catalysis. We first studied the catalytic performance of the binary MTV-MOFs (*R*)-$\mathbf{1}^{CuM}$. Both $\mathbf{1}^{CuMn}$ and $\mathbf{1}^{CuFe}$ are effective catalysts for asymmetric epoxidation of alkenes, affording up to 92% and 90% ee of the epoxides, respectively (Figure 3A, Table S3).[15a-d,25] $\mathbf{1}^{CuFe}$ can also catalyze oxidation of sulfides to sulfoxides with up to 53% ee (Table S4). After oxidation of V(IV) to V(V) with *m*-CPBA, $\mathbf{1}^{CuV}$ was an active catalyst for cyanosilylation of aldehydes with Me_3SiCN, affording the cyanohydrins silyl ethers with 80-89% ee (Figure 3B, Table S5).[15i,15j] $\mathbf{1}^{CuCr}$ can catalyze aminolysis of *trans*-stilbene oxide with anilines, providing the amino alcohols with up to 99% ee of the product (Table S6).[15h] However, For 2, 2-dimethyl benzopyran oxides, only 11-23% ee of the product were obtained (Figure 3C, Table S7).

Figure 3. **Asymmetric reactions catalyzed by the binary MOFs**





1^{CuCo} catalyzed hydrolysis of epoxides such as styrene oxide and 2, 2-dimethyl benzopyran oxide, yielding good conversions and no ee values of the products (Figure 3C, Table S8). Interestingly, (*R*)-**1**^{CuCo} was an excellent catalyst for Diels-Alder reaction of 1-aminosubstituted butadienes and α-substituted acroleins, affording 88-94% ee of the cycloadducts (Figure 3D, Table S9).[15h]

When (*R*)-**1**^{Cu} was used as the catalyst, only a trace of products was detected in epoxidation of 2, 2-dimethyl-2*H*-chromene, hydrolysis or aminolysis of epoxide, cyanation of benzaldehyde, under otherwise identical conditions. It suggests that the M(salen) (M = Mn, Fe, Co, Cr or V) moieties, instead of Cu(salen) and $Zn_4O(O_2CR)$ in these the binary MOFs, are the active sites for the examined reactions. However, the ligand Cu**L** is crucial for the formation of the twofold interpenetrating. Great attempts have been made to crystallize the similar framework without Cu**L**, but failed.

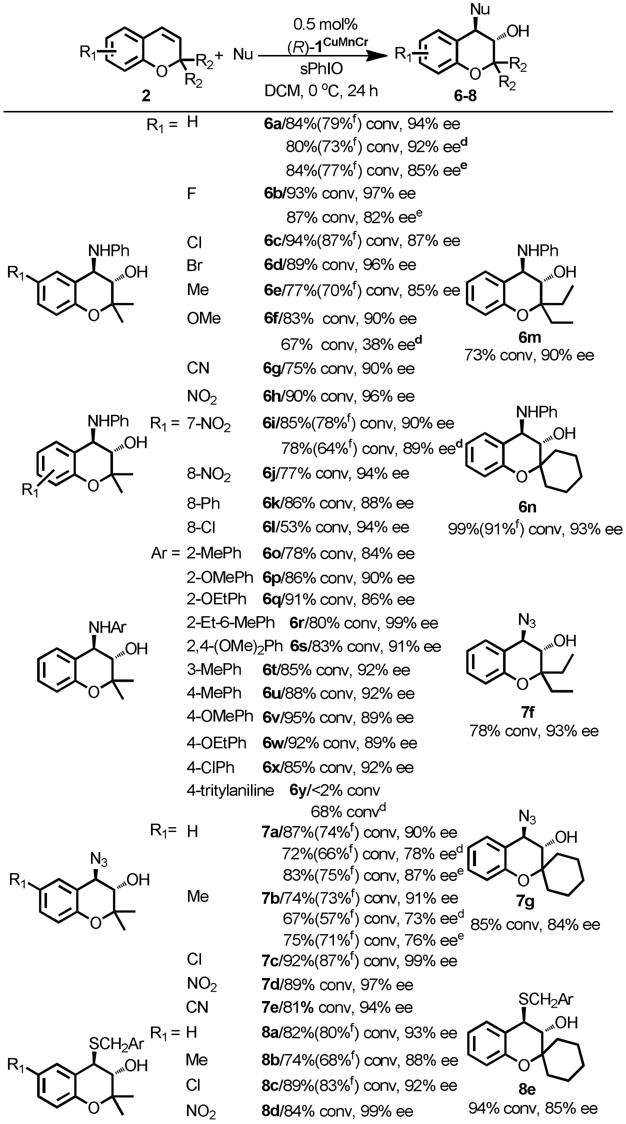
Having established that the Mn^{3+} centers in **1**^{CuMn} can promote epoxidation of alkenes and the Cr^{3+} (or Co^{3+}) centers in **1**^{CuCr} (or **1**^{CuCo}) can promote ring opening of epoxides, we decided to combine the different catalytic metal centers in one ternary MOF to catalyze sequential reactions initiated by epoxidation of alkene followed by ring opening reactions of epoxide to afford the targeted products. Indeed, both (*R*)-**1**$^{CuMnCr\ and}$ (*R*)-**1**^{CuMnCo} can promoted epoxidation of catalyzed 2, 2-dimethyl-2*H*-chromene and its derivatives, giving good conversions and enantioselectivities (Table S13, Figure S12). As expected, they can efficiently promote ring opening of epoxide with aniline and water, respectively, affording 23% and 20% ee.

The evaluation of proposed sequential transformation began with exposure of 2, 2-dimethyl-2*H*-chromene (**2a**) to oxidant 2-(tertbutylsulfonyl)iodosylbenzene (*s*PhIO) and (*R*)-**1**^{CuMnCr} firstly, and aniline as a nucleophile. After screening a series of solvents, different catalyst loading and temperature conditions, the sequential reaction was carried out with 0.5 mol% **1**^{CuMnCr} in the presence of 1.1 equiv of sPhIO in CH_2Cl_2 at 0 °C. It's essential to add the oxidant for several times at 15 min intervals, which can significantly improve the conversion of epoxide, and the aniline was added after epoxidation. Under the optimized conditions, only one pair of enantiomers out of all possible four pairs was observed, and the amino alcohol **6a** was obtained in 85% conversion with 94% ee.

Subsequently, we examined the substrate scope with respect to alkenes. As shown in Figure 4, 2, 2-dimethyl-2H-chromene bearing various functional groups proceeded efficiently to give the corresponding amino alcohols (**6b-n**) in good conversions with excellent enantioselectivities. Electron-withdrawing groups substituted alkenes showed better enantioselectivities, and the conversion was affected by the position of the groups. For instance, compared with **6c** and **6h**, the conversion of **6j** and **6l** decreased obviously. While the relatively bulky diethyl and cyclohexyl groups at the 2-position did not hamper the reactivity and enantioselectivity at all (**6m**, **6n**). The reaction scope with respect to diverse anilines was also examined (Figure 4, **6o-6x**). Anilines with electron-donating or electron-withdrawing groups attached to the aromatic ring could undergo the desired transformation to afford the targeted amino alcohols with satisfactory conversions (78-95%) and excellent enantioselectivity (86-96%). Different substituent positions on anilines had little influence on both of the conversion and selectivity, and dialkyl- or dialkoxy-substituted anilines could also be tolerated in the transformation (**6r, 6s**). Notably, very hindered aniline such as 4-tritylaniline proved to be a challenging nucleophile for **1**^{CuMnCr}-catalyzed sequential reaction of 2, 2-dimethyl-2H-chromene and little conversion was observed (Figure 4, **6y**). Whereas the corresponding homogeneous catalysts still afforded 68% conversion, indicating that the bulky substrate could not diffuse into the MOF catalyst efficiently and the catalysis may mainly occur inside the framework.

To further showcase the generality of this synthetic protocol, we employed different nucleophiles including trimethylsilylazide ($TMSN_3$) and benzyl mercaptan derivatives in this sequential transformation (Figure 4). (*R*)-**1**^{CuMnCr} catalyzed the reaction of diverse alkenes with sPhIO as oxidant followed by $TMSN_3$ proceeded smoothly, giving rise to the corresponding azido alcohols (upon TFA-mediated elimination of the TMS group) in 74-92% conversions with 84-99% ee (**7a-7g**). In a similar fashion, the variation with benzyl mercaptan derivatives was also accompanied by satisfactory conversions (74-94%) and good to high enantioselectivities (86-99% ee) (**8a-8e**).

Figure 4. Sequential asymmetric epoxidation/ring-opening reactions of alkenes catalyzed by **1**^{CuMnCr}.[a-c]



[a]For reaction details see experimental section in SI. Nu = aniline, $TMSN_3$, and $ArCH_2SH$ for **6-8**, respectively, CF_3CO_2H was used in subsequent reaction work-up for **7**. [b]Conversions were calculated by ^1H NMR. [c]ee

values were determined by HPLC. [d]Catalyzed by 0.375 mol% loading of a 1:1 mixture of Me$_2$**L**$^{\mathrm{MnCl}}$ and Me$_2$**L**$^{\mathrm{CrCl}}$. [e]Catalyzed by mixture of 0.625 mol% loading of **1**$^{\mathrm{CuMn}}$ and 0.5 mol% loading of **1**$^{\mathrm{CuCr}}$. [f]Isolate yield.

To exam the confinement effect of a MOF on metallosalen, the catalytic performances of a 1:1 mixture of (*R*)-Me$_2$**L**$^{\mathrm{MnCl}}$ and (*R*)-Me$_2$**L**$^{\mathrm{CrCl}}$ (the same M(salen) loading as the heterogeneous system) was tested (Figure 4, **6a 6f**, **6i, 7a** and **7b**). Under identical conditions, the homogeneous system afforded the products **6a**, **6f**, **6i, 7a and 7b** in 80%, 67%, 78%, 72% and 67% conversions with 92%, 38%, 89%, 78% and 73% ee, respectively. Obviously, the MTV-MOF catalyst displayed higher activities and enantioselectivities than the homogeneous mixture. We further compared the activities of **1**$^{\mathrm{CuMnCr}}$ and the homogeneous mixture for the ARO of epoxide **2a** with TMSN$_3$ at a low catalyst loading. As shown in Table 1 and Figures S13a, b, the difference in catalytic activity and selectivity became larger as the catalyst loading decreased. Specially, when the loading was from 0.05 mol% to 0.01 mol%, **1**$^{\mathrm{CuMnCr}}$ was able to afford 15% conversion with 35% ee, whereas the homogeneous control could not promote the reaction at all. The enantioselectivity is low on low MOF loadings, probably due to that the conversion of catalytic sites into less selective species in very dilute solutions. When isostructural MTV-MOF **1**$^{\mathrm{CuMnCo}}$ was used, no targeted product was observed, highlighting the contribution from Cr(salen) units. Taken together, the above results indicate that the **1**$^{\mathrm{CuMnCr}}$-catalyzed ARO reaction involves a cooperative mechanism: Cr(salen) serves as a Lewis acid to activate the epoxide while the adjacent M(salen) (M = Cr, Mn or Cu) coordinates to TMSN$_3$ to make it more nucleophilic (Figure S14). The activated TMSN$_3$ attacks the activated epoxide to afford the azido silyl ether, which is hydrolyzed by TFA to give the final product. For the **1**$^{\mathrm{CuMnCr}}$ system, two metal centers close to each other were relatively fixed, and so a quasi-linear relationship was observed for conversions at low catalyst loadings (Figure 5A).[20] For the homogeneous system, the possibility of two metallosalen species meeting each other decreased at a low concentration, thereby leading to a dramatic drop in or complete loss of the activity.

To further understand the cooperative catalysis, we compared the catalytic performances of (*R*)-**1**$^{\mathrm{CuMnCr}}$ and a mixture of (*R*)-**1**$^{\mathrm{CuMn}}$ and (*R*)-**1**$^{\mathrm{CuCr}}$ (the same M(salen) loading as (*R*)-**1**$^{\mathrm{CuMnCr}}$). At 0.5 mol% loading, **1**$^{\mathrm{CuMnCr}}$ gave similar catalytic activity and enantioselectivity to the hybrid catalyst (Figure 4, **6a**, **6b**, **7a** and **7b)**. When the catalyst loading was decreased, **1**$^{\mathrm{CuMnCr}}$ showed increasingly higher activity and enantioselectivity than the hybrid system, as shown in Table 1. Like **1**$^{\mathrm{CuMnCr}}$, the hybrid catalyst remained active even at 0.01 mol% loading, suggesting the bimetallic activation mechanism. The different catalytic behaviors showed that the ternary framework was not a simple addition of two binary ones, and embedding Mn(salen) and Cr(salen) catalysts into a single network may generate complex cooperative effects to improve the catalytic performances. It should be noted that, in comparison with **1**$^{\mathrm{CuMnCr}}$, the cost of the materials is considerable in the hybrid case, and the intrinsically high Zn and Cu contents and organic ligands of the MOFs are not really valorized.

We have demonstrated the heterogeneous nature of the ternary catalyst system. First, after the catalyst was removed during the reaction, no increase in the formation of epoxide (before aniline added) or amino alcohol was detected. Second, the inductively coupled plasma (ICP) analysis of the filtrate after the reaction revealed almost no leaching of Mn and Cr ions. Third, the framework catalyst has the potential of efficient recycling for at least five times without much loss of catalytic activity and enantioselectivity ((>83% conversions and 94%, 92%, 93%, 91% and 90% ee for 1−5 runs, Tables S15 and S16). Moreover, the recovered solid catalyst retained structural intact and crystallinity, as proved by PXRD (Figure 2B).

Figure 5. Plot of conversion *vs.* catalyst loading

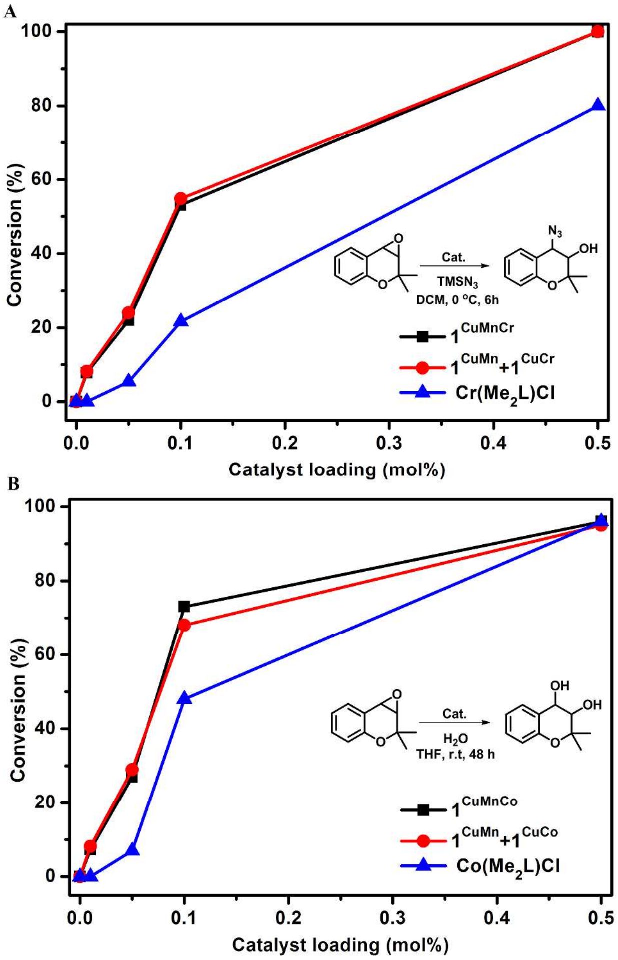
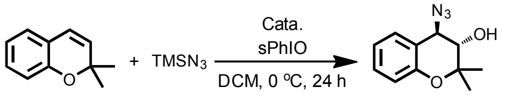


Table 1. Sequential epoxidation/ring-opening reactions of alkene with TMSN$_3$ catalyzed by (*R*)-**1**$^{\mathrm{CuMnCr}}$ and related catalysts at different catalyst loadings.[a-c]

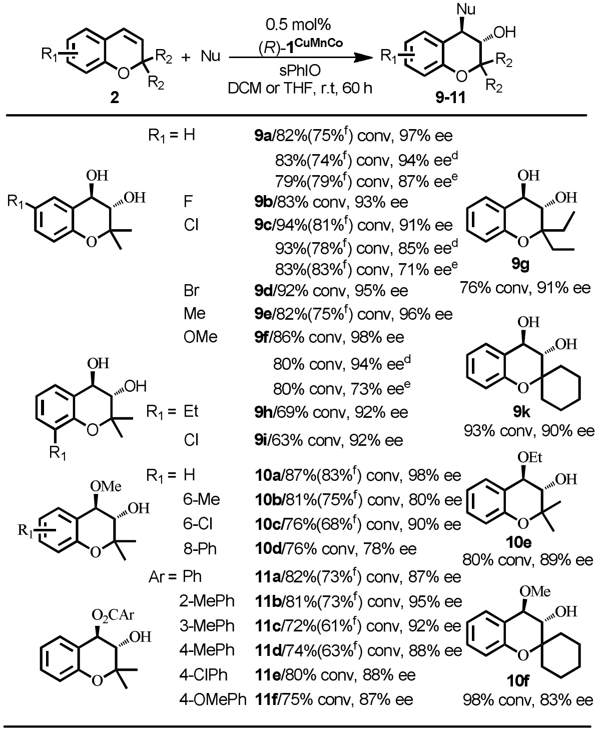


	1$^{\mathrm{CuMnCr}}$		**1**$^{\mathrm{CuMn}}$ + **1**$^{\mathrm{CuCr}}$[d]		**homo**[e]	
loading (mol%)[f]	Conv. (%)	ee (%)	Conv. (%)	ee (%)	Conv. (%)	ee (%)
0.5	84	87	83	87	72	78
0.1	72	76	67	66	58	67
0.05	51	58	49	30	13	41
0.01	15	35	13	6	trace	n.d.

[a] For reaction details, see Experimental section. [b]Conversions were calculated by ^{1}H NMR. [c]ee values were determined by HPLC. [d]a 1:1 mixture. [e]Homo = a 1:1 mixture of Me$_2$**L**$^{\mathrm{Mn}}$ and Me$_2$**L**$^{\mathrm{Cr}}$. [f]The same catalyst loadings of Mn(salen) and Cr(salen) as **1**$^{\mathrm{CuMnCr}}$ for the hybrid mixture.

(*R*)-$\mathbf{1}^{\mathbf{CuMnCo}}$ could serve as a heterogeneous catalyst for epoxidation of alkene followed by enantioselective hydrolysis of epoxide to afford diols. Catalytic epoxidation of 2, 2-dimethyl benzopyran derivatives and subsequent ring-opening reactions using 0.5 mol% loading of $\mathbf{1}^{\mathbf{CuMnCo}}$ as the catalyst were performed in mixed solvents of THF and water (Figure 6). For 2, 2-dimethyl-2*H*-chromene bearing various substituents, from electron-rich to electron-deficient, on the phenyl moiety, the sequential reaction proceeded smoothly to give corresponding 1, 2-diols with good conversions (63-94%) and excellent enantioselectivities (90-98%). Again, in each case, only one pair of enantiomers out of all possible four pairs was observed. The ring-opening products with high ee values are obtained from the epoxides with moderate enantioselectivities that were produced by $\mathbf{1}^{\mathbf{CuMnCo}}$-catalyzed epoxidation of alkenes, showing that the ring-opening reaction is of high stereoselectivity.

Figure 6. Sequential asymmetric epoxidation/ring-opening reactions of alkenes catalyzed by (*R*)-$\mathbf{1}^{\mathbf{CuMnCo}}$.[a-c]

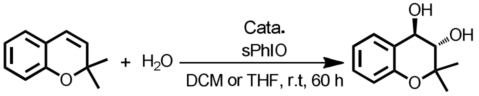


[a]For reaction details see experimental section in SI. Nu = H_2O, alcohol and $ArCO_2H$ for **9-11**, respectively. [b]Conversions were calculated by ^1H NMR. [c]ee values were determined by HPLC. [d]Catalyzed by 0.375 mol% loading of a 1:1 mixture of $Me_2\mathbf{L}^{\mathbf{Mn}}$ and $Me_2\mathbf{L}^{\mathbf{Co}}$. [e]Catalyzed by mixture of 0.625 mol% loading of $\mathbf{1}^{\mathbf{CuMn}}$ and 0.375 mol % loading of $\mathbf{1}^{\mathbf{CuCo}}$. [f]Isolate yield.

We have also found that (*R*)-$\mathbf{1}^{\mathbf{CuMnCo}}$ catalyzed the sequential epoxidation/ring-opening reactions of 2, 2-dimethyl-2*H*-chromene derivatives with methanol or ethanol acted as nucleophiles was found to proceed well, with corresponding products afforded in moderate to high conversions with up to 97% ee (Figure 6, **10a-10d**). Importantly, a variety of benzoic acid derivatives even including *o*-, *m*-, *p*-toluic acid, anisic acid were also efficiently transferred, affording **11a-11f** with satisfying conversions and enantioselectivities.

Several tests also demonstrated the heterogeneous nature of $\mathbf{1}^{\mathbf{CuMnCo}}$ in the sequential alkene epoxidation/epoxide ring-opening reactions. The solid catalyst can also be recycled and reused with negligible loss of efficiency and enantioselectivity (Tables S17, S18), and the recovered catalyst retained crystallinity and structural intact (Figure 2B).

Table 2. Sequential epoxidation/ring-opening reactions of alkene with H_2O catalyzed by (*R*)-$\mathbf{1}^{\mathbf{CuMnCo}}$ and related catalysts at different catalyst loadings.[a-c]



	$\mathbf{1}^{\mathbf{CuMnCo}}$		$\mathbf{1}^{\mathbf{CuMn}} + \mathbf{1}^{\mathbf{CuCo}}$[d]		**Homo**[e]	
loading[f] (mol%)	Conv. (%)	ee (%)	Conv. (%)	ee (%)	Conv. (%)	ee (%)
0.5	82	97	80	87	83	94
0.1	63	83	55	76	47	66
0.05	43	64	31	58	16	49
0.01	14	33	8	21	trace	n.d.

[a]For reaction details, see Experimental section. [b]Conversions were calculated by ^1H NMR. [c]ee values were determined by HPLC. [d]a 1:1 mixture. [e]Homo = a 1:1 mixture of $Me_2\mathbf{L}^{\mathbf{MnCl}}$ and $Me_2\mathbf{L}^{\mathbf{CoOAc}}$. [f]The same catalyst loadings of Mn(salen) and Co(salen) as $\mathbf{1}^{\mathbf{CuMnCo}}$ for the hybrid mixture.

Cooperative effects between different M(salen) units in the $\mathbf{1}^{\mathbf{CuMnCo}}$-catalyzed sequential epoxidation/ring-opening reactions of alkenes were also observed. For example, $\mathbf{1}^{\mathbf{CuMnCo}}$ exhibited slightly higher activities and stereoselectivities than the homogeneous control in producing **9a**, **9c** and **9f**. The catalytic difference became larger as the catalyst loading was decreased (Table 2, Figure S13c, d). Especially, at very low catalyst loadings (0.01-0.05 mol%), $\mathbf{1}^{\mathbf{CuMnCo}}$ and the mixture of $\mathbf{1}^{\mathbf{CuMn}}$ and $\mathbf{1}^{\mathbf{CuCo}}$ remained active and displayed a nearly linear relationship between conversions and loadings (Figure 5B), while the homogeneous counterpart mixture showed negligible activity. Again, these findings indicated that the reaction involved two M(salen) complexes including at least one Co(salen) to allow cooperative activation (Figure S14). $\mathbf{1}^{\mathbf{CuMnCo}}$ gave higher ee than the hybrid catalyst, further highlighting the intriguing confinement effect of MTV-MOF-based catalysis.

To verify the catalytic cooperativity between the Co^{3+} and M^{n+} (M = Co or Mn) sites in $\mathbf{1}^{\mathbf{CuMnCo}}$, the MOF $Zn_4O[Co\mathbf{L}(OAc)]_3$[26] was tested for hydrolysis of epoxide. The Co(salen)-MOF has a non-interpenetrated porous 3D framework with the largest 1D open channels of 1.2 nm. The shortest Co-Co distance of 13.0 Å is too large for the adjacent Co sites to cooperatively activate both epoxide and water in the pores. Because of its larger channels, which can enable faster diffusion of substrates and products, Co(salen)-MOF is expected to have a high catalytic activity in epoxide hydrolysis if a monometallic activation pathway was dominant. However, the Co(salen)-MOF system only gave 37% conversion when subjected to a 60 h reaction with 2, 2-dimethyl-2*H*-chromene at 0.5 mol % loading. In addition, no substantial catalytic activity was observed when the isostructural $\mathbf{1}^{\mathbf{CuMnCr}}$ was subjected to the same reaction, confirming the contribution from Co(salen) units. These results show that the epoxide hydrolysis activity is specific to $\mathbf{1}^{\mathbf{CuMnCo}}$, where the unique combination of Co(salen) and the adjacent M(salen) sites of the MTV-MOF is required for cooperative catalysis.

Chiral 1,2-functionalized *β*-hydroxy compounds are an important class of intermediates for the synthesis of both synthetic pharmaceuticals and naturally occurring substances.[21a] Although lots of catalyst systems having been developed for their synthesis, most of them are restricted to only epoxide ring-opening reactions.[27] With regard to achieving atom efficiency and selectivity, sequential/tandem chromene epoxidation/epoxide ring-opening to 1,2-functionalized β-hydroxy compounds remains a challenge.[28] Notably, two MOFs were examined for sequential transformation alkenes to 1,2-azido alcohol by using the enantiopure Mn(salen) and achiral metal cluster active sites, respectively, with much low activity and stereoselectivity (81-86% ee and 41-57% conversions) than the present MTV-MOFs.[15c] In contrast, our MTV-MOFs represent a general catalyst system, capable of efficiently transforming alkenes of varied geometric and electronic natures to 1,2-functionalized *β*-hydroxy molecules with good to high stereoselectivity. However, it should be noted that the MTV-MOF systems are very selective. Other alkenes such as styrene, *trans*-stilbene and allyl phenyl ether, can also be readily converted into 1,2-functionalized β-hydroxy molecules, but with no enantioselectvities, while indene and 1,2-dihydronaphthalene can give low to moderate ee values. (Table S10). Nevertheless, this work demonstrated the potential utility of MTV-MOFs with multiple and coorperative active sites in the efficient preparation of complex molecules with high regio- and stereo-controls.

CONCLUSIONS

In summary, we have designed and synthesized an isostructural family of chiral porous MTV-MOFs by controlling incorporation of one, two or three different enantiopure metallosalen-based linkers. The afforded ternary MTV-MOFs are efficient and recyclable heterogeneous asymmetric catalysts for a broad scope of important asymmetric sequential alkene epoxidation/epoxide ring-opening reactions. The twofold interpenetration of the frameworks brings catalytically active M(salen) units into a dense arrangement and close proximity that allow bimetallic cooperative activation, leading to improved chemical activity and enantioselectivity compared with the hybrid mixture of the individual catalytic components or the binary MOFs. This work therefore advances MTV-MOF as a new platform for asymmetric tandem/sequential catalysis in a variety of syntheses and provides a new strategy for preparing multifunctional heterogeneous catalysts.

EXPERIMENTAL SECTION

Materials and general procedures. All reagents and solvents used in these studies are commercially available and used without further purification. Elemental analyses were performed with an EA1110 CHNS-0 CE elemental analyzer. The IR (KBr pellet) spectra were recorded (400-4000 cm^{-1} region) on a Nicolet Magna 750 FT-IR spectrometer. The CD spectra were recorded on a J-800 spectropolarimeter (Jasco, Japan). Thermogravimetric analyses (TGA) were carried out in an air atmosphere with a heating rate of 10 ^{o}C/min on a STA449C integration thermal analyzer. Powder X-ray diffraction (PXRD) data were collected on a DMAX2500 diffractometer using Cu-Kα radiation. The calculated PXRD patterns were produced using the SHELXTL-XPOW program and single crystal reflection data. The NMR experiments were carried out on a MERCURYplus 400 spectrometer operating at resonance frequencies of 400 MHz. Electrospray ionization mass spectra (ESI-MS) were recorded on a Finnigan LCQ mass spectrometer using dichloromethane-methanol as mobile phase. ICP-OES was performed on Optima 7300DV ICP-OES (Perkin Elmer Coporation, USA). Analytical high performance liquid chromatography (HPLC) was performed on a LC-2010HAT HPLC with UV detection at 200 or 254 nm. Analytical CHIRALCEL OD-H, AD-H, AS-H and OJ-H column (4.6 mm × 25 cm) from Daicel were used. The CO_2 adsorption isotherms were recorded at 273K by using a micromeritics ASAP 2020 surface area and porosity analyzer. Before the adsorption measurement, the samples were activated at 80 ^{o}C under vacuum (< 10^{-3} torr) for 4 h. Scanning Electron Microscopy (SEM) imagings were performed on a NOVA NanoSEM 230 instrument equipped with an energy dispersive spectroscopy (EDS) detector. X-ray photoelectron spectroscopy (XPS) were recorded on a AXIS Ultra DLD surface analysis instrument.

Single-Crystal X-ray Diffraction. Single-crystal XRD data for compound **1**$^{\mathbf{Cu}}$ was collected on a Bruker SMART Apex II CCD-based X-ray diffractometer with Cu-Kα radiation (λ = 1.54178 Å) at 296 K. We have collected about several datasets for **1**$^{\mathbf{Cu}}$ using Cu-Kα radiation. Among the several datasets, the best dataset was used for structure solution and refinement. The empirical absorption correction was applied by using the SADABS program (G. M. Sheldrick, SADABS, program for empirical absorption correction of area detector data; University of Göttingen, Göttingen, Germany, 1996). The structure was solved using direct method, and refined by full-matrix least-squares on F^2 (G. M. Sheldrick, SHELXTL97, program for crystal structure refinement, University of Göttingen, Germany, 1997). In the structure, the all non-H atoms were refined anisotropically. Contributions to scattering due to these highly disordered solvent molecules were removed using the SQUEEZE routine of PLATON. The structure was then refined again using the data generated. Crystal data and details of the data collection are given in Table S1, while the selected bond distances and angles are presented in Tables S2.

ASSOCIATED CONTENT

Supporting Information.

Details on experimental procedures, X-ray crystallographic data, supporting figures, reaction procedures and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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Graphic Content