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Boosting Chemical Stability, Catalytic Activity and Enantioselectivity of Metal-Organic Frameworks for Batch and Flow Reactions

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Supporting Information

ABSTRACT: A key challenge in heterogeneous catalysis is the design and synthesis of heterogeneous catalysts featuring high catalytic activity, selectivity and recyclability. Here we demonstrate that high-performance heterogeneous asymmetric catalysts can be engineered from a metal-organic framework (MOF) platform by using a ligand design strategy. Three porous chiral MOFs with the framework formula $[Mn_2\mathbf{L}(H_2O)_2]$ are prepared from enantiopure phosphono-carboxylate ligands of 1,1'-biphenol that are functionalized with 3,5-bis(trifluoromethyl)-, bismethyl- and bisfluoro-phenyl substituents at the 3,3'-position. For the first time, we show that not only chemical stability but also catalytic activity and stereoselectivity of the MOFs can be tuned by modifying the ligand structures. Particularly, the MOF incorporated with $-CF_3$ groups on the pore walls exhibits enhanced tolerance to water, weak acid and base compared with the MOFs with -F and -Me groups. Under both batch and flow reaction systems, the CF_3-containing MOF demonstrated excellent reactivity, selectivity and recyclability, affording high yields and enantioselectivities for alkylations of indoles and pyrrole with a range of ketoesters or nitroalkenes. In contrast, the corresponding homogeneous catalysts gave low enantioselectivity in catalyzing the tested reactions.

INTRODUCTION

Heterogeneous catalysts play an indispensible role in industrial processes used to produce many essential chemicals and fuels.[1] Activity and selectivity in heterogeneous catalysis are highly determined by the local environment and electronic structure of active sites. However, the multiplicity and intractability of active sites often observed in conventional solid catalysts complicate structure/performance-based control over reactivity and selectivity.[1,2] Metal−organic frameworks (MOFs), have attracted increasing interest in recent years as a new family of porous crystalline hybrid materials for various applications.[3] In light of their well-defined yet tunable structures and high porosities, MOFs provide an attractive platform for designing single-site solid catalysts for organic reactions,[4-6] especially for asymmetric transformations,[7] which afford enantiopure products of both fundamental and practical interest still catalyzed by homogeneous catalysts.[8] A growing number of examples utilize MOFs for asymmetric catalysis,[9-11] with the majority of work installing privileged chiral catalysts into organic linkers, but most of them suffer from low to mild selectivity and narrow substrate scope.[10,11] It remains challenging to tune the chiral environment and chemical properties around active sites in a MOF to control reactivity and exert stereoselectivity in reactions.[7,12] Another major challenge facing MOF catalysts is their typically low stability to humid and harsh reaction conditions,[13] limiting their use in practical catalytic processes particularly under flow reaction systems that are commonly employed in industries.[1b,5a] To address such issue, in this work we illustrated a ligand design strategy for producing advanced asymmetric MOF catalysts.

Organic ligands with different steric and electronic properties are known to play an important role in metal–ligand bonding as well as structures of transition metal complexes.[14] Different ligands can control reactivity and selectivity in homogeneous metal-catalyzed organic reactions, but the ligand effects on MOF-based catalysis have rarely been explored.[15] The use of bulky hydrophobic organic linkers or strong metal–ligand bonds has been explored to enhance the chemical stability of MOFs.[16] Herein we demonstrated for the first time that the ligands themselves can be used to tune the chemical stability, catalytic activity and seteroselectivity of MOF catalysts simultaneously. To illustrate this concept, we focus on the ligands of chiral phosphoric acids derived from axially biaryl diols considering that they are powerful Brønsted acid or Leiws acid/Brønsted base catalysts in homogeneous asymmetric reactions, especially those involving imines such as Mannich, amination, Pictet-Spengler, aza-Diels-Alder and aza-ene reactions.[17] Tetracarboxylate ligands derived from chiral 1,1'-biphenol-derived phosphoric acids that are functionalized with 3,5-bis(trifluoromethyl)phenyl, 3,5-bismethylphenyl or 3,5-bisfluorophenyl substituents at the 3,3'-position were therefore designed for MOF construction. The carboxylate and phosphonate groups can be linked by metal ions to form networks involving metal nodes as chiral Lewis acids, whereas the 3,3'-substituents can exert stereochemical and electronic control over catalytic transformations. Three chiral MOFs are built from $H_5\mathbf{L}^1$, $H_5\mathbf{L}^2$ or $H_5\mathbf{L}^3$ and dimanganese units (Figure 1) that can catalyze Friedel-Crafts (F-C) alkylations of indoles and -pyrrole. Dramatic enhancement in the stability, reactivity and enantioselectivity was observed for the CF_3-containing MOF when compared to the F- and CH_3-containing analogs. The highly asymmetric F-C alkylation of indoles was also successfully achieved under continuous-flow conditions using the MOF as self-supported catalyst, which is barely reported for heterogeneous asymmetric catalysis.[1b,5a]

RESULTS AND DISCUSSION

Synthesis and Characterization. The ligands $H_5\mathbf{L}^1$, $H_5\mathbf{L}^2$ and $H_5\mathbf{L}^3$ were prepared from (*R*)- or (*S*)-6,6'-dimethyl-3,3'-di-*tert*-

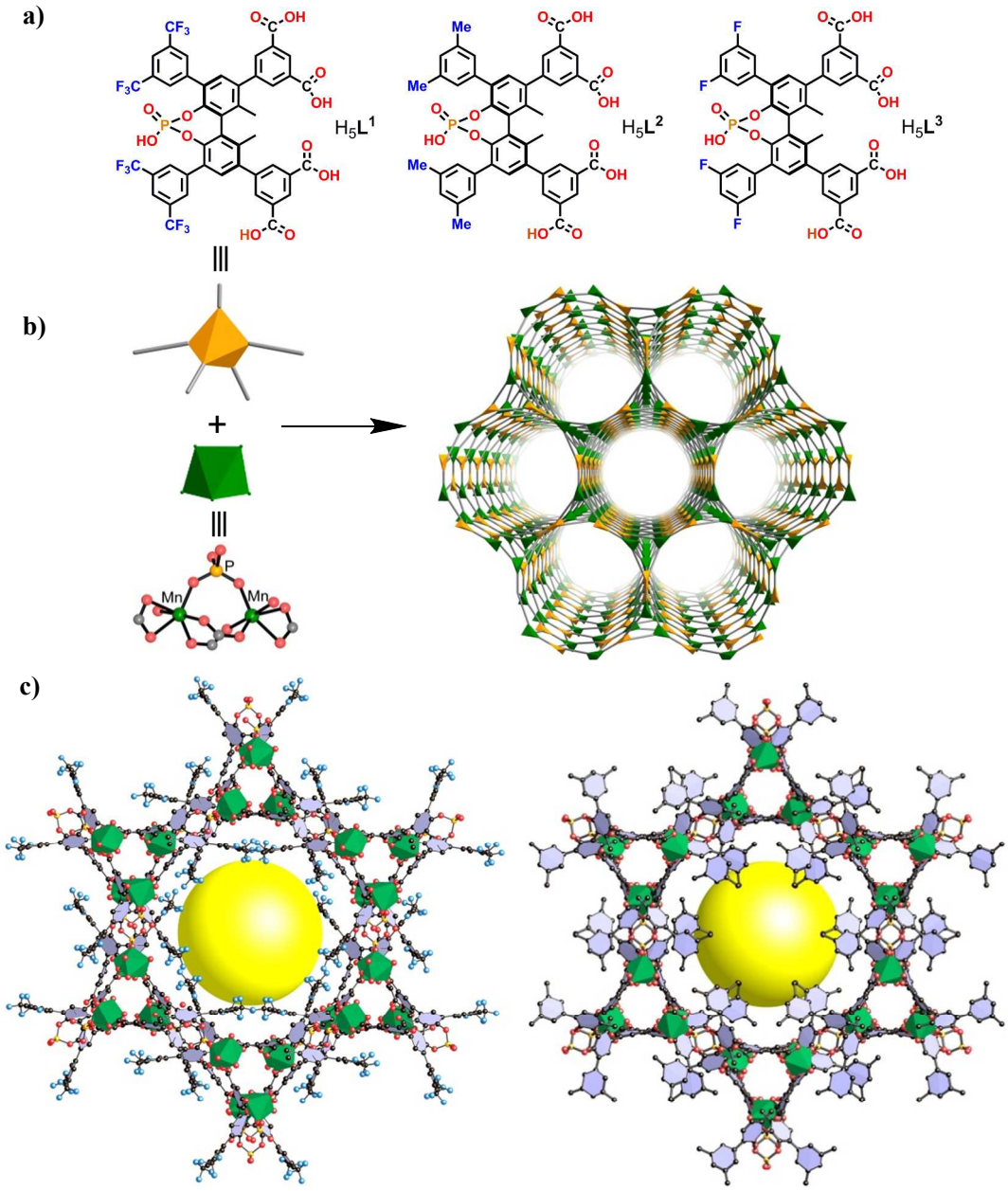


Figure 1. (a) Structures of the organic ligands $H_5\mathbf{L}^1$-$H_5\mathbf{L}^3$. (b) Construction of MOFs **1-3** from dimeric $[Mn_2(CO_2)_4(PO_4)(H_2O)_2]$ linked by $H_5\mathbf{L}$ to give 3D networks with the **fns** topology. (c) Framework structures of **1** and **2** with open channels in diameters of ~2.5 × 2.5 nm^2 and ~0.68 × 0.68 nm^2 along the *c*-axis (Mn, green polyhedra; O, red; P, yellow; C, black; F, light blue. H atoms are omitted for clarity).

butyl-5,5'-di(3,5-bis(methoxycarbonyl))phenyl-1,1'-biphenyl-2,2'-diol[18] in five steps in 34%, 47% and 32% overall yields, respectively. Heating $MnCl_2{\cdot}4H_2O$ and $H_5\mathbf{L}^1$, $H_5\mathbf{L}^2$ or $H_5\mathbf{L}^3$ in a mixed solvent containing dimethylacetamide (DMA) at 100 °C afforded colorless crystals of $[Me_2NH_2][Mn_2(\mathbf{L}^1)(H_2O)_2]{\cdot}2H_2O{\cdot}2DMA$ (**1**), $[Me_2NH_2][Mn_2(\mathbf{L}^2)(H_2O)_2]{\cdot}2H_2O{\cdot}3DMA$ (**2**) or $[Me_2NH_2][Mn_2(\mathbf{L}^3)(H_2O)_2]{\cdot}2H_2O{\cdot}3DMA$ (**3**). The products were stable in air and insoluble in water and common organic solvents. They were formulated based on elemental analysis, IR spectra, and thermogravimetric analysis (TGA). The phase purity of the bulk samples was established by comparison of their observed and simulated powder X-ray diffraction (PXRD) patterns.

Single-crystal X-ray diffraction showed that **1** crystallizes in the hexagonal chiral space group $P6_122$. The Mn ion adopts a distorted octahedral geometry by binding to one water and five oxygen atoms from two bidentate and one chelated carboxylate groups and one bidentate/bridging phosphonate group. Two neighboring Mn ions are linked by two carboxylate groups and one phosphate group to form a dimanganese unit. The ligand exhibits an *exo*-heptadentate coordination fashion, binding to seven Mn ions of five $[Mn_2]$ units *via* four carboxylate groups and one phosphonate group. Along the *c*-axis, adjacent dimetal cores are linked by $\mathbf{L}^1$ to generate a left-handed 3_1 helix, leading to a tube with an opening of 0.68 × 0.68 nm^2. As shown in Figure 1, such helical metal-carboxylate chains are linked by phosphonate groups of $\mathbf{L}^1$ from other chains, which run around a 6_1 axis with a pitch of 23.2001(4) Å, to give a 3D network with 1D hexagonal channels. The channels have an opening size of 2.49 × 2.49 nm^2 (measured from van der Waals surfaces) and are periodically decorated with $[Mn_2]$ units with coordinating water pointing outwards. With respect to the topology, **1** has one vertex, represented by the $[Mn_2(CO_2)_4(PO_4)(H_2O)_2]$ unit and one bent edge (linker) leading to a 5-c net with the **fns** topology (Figure 1b).

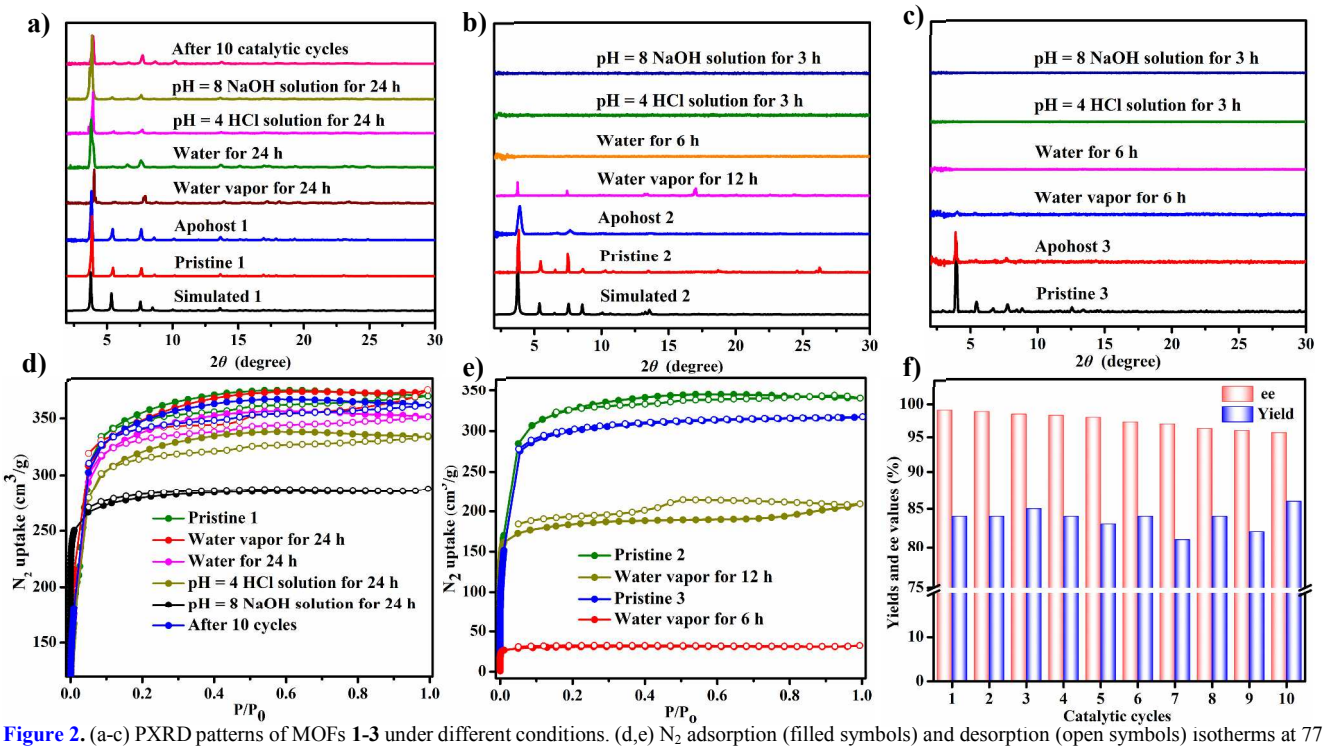


Figure 2. (a-c) PXRD patterns of MOFs **1-3** under different conditions. (d,e) N_2 adsorption (filled symbols) and desorption (open symbols) isotherms at 77 K. (f) Recycling tests of the MOF catalyst in the alkylation of *N*-methylindole with *α*-keto ester.

MOF **2** is isostructural to **1** and has a similar 3D network containing two kinds of 1D open channels in diameters of 2.54 × 2.54 nm^2 and 0.68 × 0.68 nm^2. Calculations using PLATON indicated that **1** and **2** have about 60 % and 66 % void volume available for guest inclusion.[19] The single-crystal X-ray diffraction data for **3** was extremely weak, but PXRD study established that it is isostructural to **1** and **2** (Figure 2c). Circular dichroism (CD) spectra of **1-3** made from *R* and *S* enantiomers of $H_5\mathbf{L}^1$, $H_5\mathbf{L}^2$ and $H_5\mathbf{L}^3$ are mirror images of each other, indicative of their enantiomeric nature (Figure S5). The MOFs were degassed under vacuum after being thoroughly soaked in methanol. Powder X-ray diffraction (PXRD) patterns of the activated samples were in good agreement with calculated patterns from their crystal data (Figures 2a-c), indicating that the frameworks remain intact after removal of guest solvent molecules. The permanent porosity was examined by N_2 adsorption measurements at 77 K. The Brunauer-Emmett-Teller (BET) surface areas were calculated to be 1118, 1029 and 925 m^2g^{-1}, for **1-3**, respectively. Dye uptake measurements showed that the open channels were retained in solution (Figure S7). X-ray photoelectron spectroscopy (XPS) showed the oxidation states of Mn in all three MOFs are +2 oxidation state (Figure S9).[20]

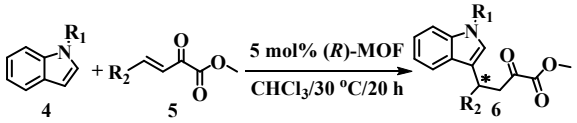
Chemical Stability. Like other phosphonate-MOFs, **1-3** showed excellent thermal stability. Thermogravimetric analysis (TGA) showed that guest molecules could be removed in the temperature range from 70 to 200 °C and the networks are thermally stable up to 380 °C (Figure S6).

The chemical stability of the three MOFs was examined by PXRD and N_2 sorption on samples exposed to harsh humid conditions. **1-3** showed quite different chemical stabilities. After **1** was immersed in water vapor, water, weak acid (pH = 4 HCl solution) and base (pH = 8 NaOH solution) for 24 h, respectively, PXRD studies revealed no significant changes in the diffraction patterns. The as-treated samples have BET surface areas of 1102, 1063, 1009 and 854 m^2g^{-1}, respectively, further confirming the framework stability and permanent porosity (Figure 2a, 2d). **1** retained its original structure in pH = 8 NaOH solution, but gave a slightly decreased crystallinity. A small decrease in signal-to-noise ratio and an obvious decrease in the surface area indicate just partial structural collapse upon treatment. **2** maintained stability after being exposed to water vapor for 12 h, but gave an obvious decreased BET surface area (568 m^2g^{-1}). In contrast, **3** lost crystallinity after exposure to water vapor only for 6 hours. Moreover, both **2** and **3** got amorphous or partly decomposed after being soaked in water for 6 h and in aqueous HCl solution (pH = 4) and aqueous NaOH solution (pH = 8) for less than 3 h (Figure 2b, 2c). It should be noted that all the three MOFs retained good crystallinity after immersion in common organic solvents such as methanol and toluene for two weeks. The above results revealed the chemical stability of the three MOFs increased in the order **1** > **2** > **3**, consistent with the increase in the sizes of the bulky phenyl substituents at the 3,3'-position of the 1,1'-biphenol ligands. It is likely that the stronger water repelling property of trifluoromethyl groups may strongly promote the tolerance of the MOF platform toward water and even acidic and alkaline media.[13,16a-c]

Heterogeneous Asymmetric Catalysis. The presence of large channels and potential Lewis acid metal sites in the three MOFs prompted us to evaluate their catalytic activities. All of them were found to be capable of catalyzing F−C alkylations of indoles and pyrrole, but **1** gave much higher reactivity and stereoselectivity than **2** and **3**. The F-C reactions provide direct access to optical active indole and pyrrole scaffolds, which are common structural motifs used in a range of natural products and pharmaceuticals.[21]

After screening various reaction conditions including catalyst loading, reaction time and temperature (Table S4), we found that, at 5 mol% loading, **1** catalyzed the addition of *N*-methylindole to (*E*)-methyl 2-oxo-4-phenylbut-3-enoate to give the 1,4-addition product in 91% yield and 96% ee in $CHCl_3$ at 30 °C after 20 h (Table 1, entry 1). A variety of *β,γ*-unsaturated *α*-keto esters with various electronic properties

Table 1. Enantioselective Friedel-Crafts alkylation of indoles with *β,γ*-unsaturated *α*-keto esters.[a]



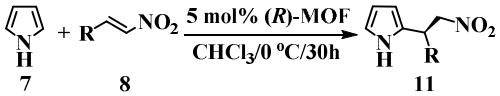
entry	MOF	R_1	R_2	yield (%)[b]	ee (%)[c]
1	1	Me	Ph	91 (33)[d]	96 (42)[d]
2	1	Me	4-Me-Ph	88 (<5)[d]	99 (n.d.)[d]
3	1	Me	4-NO_2-Ph	86 (13)[d]	98 (23)[d]
4	1	Me	2-thienyl	88 (43)[d]	96 (8)[d]
5	2	Me	Ph	81	61
6	2	Me	4-Me-Ph	73	55
7	2	Me	4-NO_2-Ph	77	69
8	2	Me	2-thienyl	82	74
9	3	Me	Ph	80	71
10	3	Me	4-Me-Ph	84	73
11	3	Me	4-NO_2-Ph	79	85
12	3	Me	2-thienyl	83	81
13	1	Me	4-Cl-Ph	88	95
14	1	Me	4-Br-Ph	84	99.1
15	1	Me	4-F-Ph	85	99.9
16	1	Me	2-F-Ph	85	96
17	1	Me	4-OMe-Ph	90	95
18	1	Me	4-CN-Ph	89	98
19	1	Me	4-CO_2Me-Ph	91	98
20	1	Me	4-CF_3-Ph	95	99.7
21	1	Bn	Ph	85	91
22	1	Me	2-naphthyl	86	95
23	1	Me	BBP[e]	< 5 (32)[d]	n.d. (n.d.)[d]

[a]Reaction conditions: MOF (5 mol %), **4** (0.20 mmol) and **5** (0.10 mmol), $CHCl_3$ (1 mL), 30 °C, 20 h. [b]isolated yield. [c]ee was Determined by HPLC analysis. The absolute configurations of the products in entries 1, 2, 5, 6, 9, 10, 13, 14, 17, 21 and 22 were assigned as *S* by comparing their HPLC profiles and optical rotation with those reported in literature.[22c,22e] Those of the other products were assigned by analogy. [d]a 1:1 mixture of $MnCl_2{\cdot}4H_2O$ and (*R*)-$Me_4\mathbf{L}^1$ (5 mol% loading) was used as a catalyst. [e]BBP = 3,5-bis(benzyloxy)phenyl.

and different ring sizes were subjected to the catalytic reactions with *N*-methyl or *N*-benzyl indole and gave the corresponding products in 84-95% yields and with 91-99.9% ee (Table 1, entries 1-4 and 13-22). In all cases, only the 1,4-addition products were obtained and none of the products from a potentially competitive 1,2-addition pathway was observed. Under identical conditions, MOFs **2** and **3** can also catalyze the addition of *N*-methylindole to *α*-keto esters, providing 73-82% and 79-84% yields and 55-74% and 71-85% ee of the products, respectively, which are about 6-15%, 4-11%, 22-44% and 13-26% lower than those obtained with **1**. It can be concluded that the nature of the substituents at the 3,3'-positions of the biphenyl unit plays an important role in the catalytic performances of the MOFs. Specifically, *ortho*-disubstitution of the aromatic ring with highly electron-withdrawing -CF_3 groups leads to great increase in both steric bulk and Lewis acidity of metal ions, thereby resulting in dramatic enhancement of the reaction rate and the level of asymmetric induction.[17a]

To evaluate the contribution of the frameworks to the asymmetric catalysis, we tested the catalytic activities of molecular metal phosphonates. Controlled experiments were performed for the homogeneous catalyst of metal phosphonate of $Me_4\mathbf{L}^1$ (5 mol% loading) under identical conditions, which afforded much lower yields and enantioselectivties for the desired products from the alkylation reactions of indoles as compared with **1** (Table 1, entries 1-4). To further exclude the possibility that $MnCl_2$ worked as a Lewis acid toward the catalytic alkylation of indoles, we used only (*R*)-$H_5\mathbf{L}^1$ and its ester in the absence of $MnCl_2$ to perform the control experiments. Trace amount of the desired addition products was obtain, when only (*R*)-$Me_4\mathbf{L}^1$ was used as catalyst. However, the products were produced in 54-88% yield but with no enantioselectivity when only (*R*)-$H_5\mathbf{L}^1$ was used (Table S6). These results are indicative of that chiral phosphono-carboxylate groups of 1,1'-biphenol, together with the metal ions and phenyl rings create a chiral microenvironment in the MOFs, which should be responsible for the observed high catalytic activity and selectivity, by concentrating reactants and generating additional steric and electronic effects around the metal active sites. Albeit there have been described numerous acid catalyzed additions of aromatic systems to unsaturated carbonyl compounds, it remains underexplored for the stereoselective variants.[21a,22] There are only very few chiral metal phosphates having been studied for alkylation of indoles with unsaturated *α*-keto esters.[21] High setereo- and regioselectivity are noteworthy features of our **1**-based protocol, which are even among the highest values reported for homogeneous metal-/organo-based catalysts (Table S8.[22c,22e]

Table 2. Enantioselective Friedel-Crafts Reaction of Pyrrole with Nitroalkenes.[a]



entry	R	MOF	yield (%)[b]	ee (%)[c]
1	Ph	1	87 (65)[d]	97 (3)[d]
2	4-Br-Ph	1	90 (73)[d]	94 (3)[d]
3	4-OMe-Ph	1	84 (61)[d]	92 (21)[d]
4	2-thienyl	1	86 (53)[d]	84 (9)[d]
5	Ph	2	89	65
6	4-Br-Ph	2	93	35
7	4-OMe-Ph	2	87	14
8	2-thienyl	2	79	47
9	Ph	3	85	70
10	4-Br-Ph	3	89	67
11	4-OMe-Ph	3	85	62
12	2-thienyl	3	82	54

[a]Reaction conditions:**7** (0.40 mmol), **8** (0.20 mmol), MOF (5 mol %), $CHCl_3$ (1 mL), 0 °C, 30 h. [b]isolated yield. [c]ee was determined by HPLC analysis. The absolute configurations of the products were assigned as *R* by comparing their HPLC profiles and optical rotation with those reported in literature.[24a] [d]a 1:1 mixture of $MnCl_2{\cdot}4H_2O$ and (*R*)-$Me_4\mathbf{L}^1$ (5 mol% loading) was used as a catalyst.

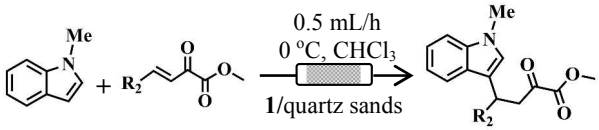
Under optimized conditions (Table S5), MOF **1** can also promote the asymmetric F-C alkylations of pyrrole and nitroalkenes. Specially, the reaction of *trans-β*-nitrostyrene with pyrrole catalyzed by 5 mol % loading of **1** gave the product in 87% isolated yield and with 97% ee in $CHCl_3$ at 0 °C after 30 h (Table 2, entry 1). Aryl-substituted nitroalkenes containing electro-donating and electro- withdrawing groups on the aromatic rings were tolerated, affording excellent to high yields and enantioselectivities (Table 2, entries 2-4). In all cases, **1** exhibited comparable catalytic activities to **2** and **3** but with 27-78% higher enantioselectivity (Table 2, entries 5-12). Moreover, the F-containing MOF **3** showed higher enantioselectivity than the Me-containing **2**. Controlled experiments showed that manganese phosphonate of $Me_4\mathbf{L}^1$ (5 mol% loading) gave much lower reactivity and stereoselectivity than the MOFs as well (Table 2, entries 1-4). In addition, in the absence of $MnCl_2$, the use of (*R*)-$Me_4\mathbf{L}^1$ or (*R*)-$H_5\mathbf{L}^1$ alone to promote the alkylation reactions afforded the products in 42-51%

yield with 0-12% ee or 60-71% yield with 0-6% ee (Table S7).

Despite their prevalence in biologically active compounds, asymmetric F-C alkylations of pyrroles, especially unprotected pyrroles are less explored, due to the relative instability of pyrroles towards acidic environments.[23] **1** provided mild reaction conditions by well-defined hydrophobic cavities to implement the pyrrole alkylation with stereoselectivities comparable to the results of binaphthyl phosphoric acids[24a] and their solid catalysts (Table S9).[24b]

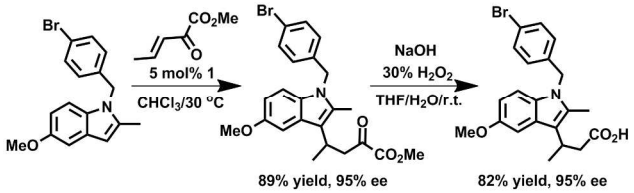
Several tests demonstrated that **1** was a heterogeneous and recyclable catalyst. Upon completion of the alkylation of *N*-methylindole with *α*-keto ester, **1** could be recovered by simple filtration and reused at least ten times without any loss of its activity, regio- and enantioselectivity (Figure 2f). After ten cycles, both the PXRD pattern and BET surface area (1094 m^2g^{-1}) of **1** remained almost the same as those of the pristine sample (Figures 2a and 2d). Moreover, a hot filtration test showed no indication of catalysis by leached homogeneous species. Inductively coupled plasma optical emission spectrometry (ICP-OES) analysis of the product solution indicated almost no loss of Mn ions (~0.001%) from the structure per cycle. To examine whether catalysis by **1** occurs mainly within the channels or instead on the exterior surface, a more sterically demanding substrate (*E*)-methyl-4-(3,5-bis(benzyloxy) -phenyl)-2-oxobut-3-enoate (BBP) was subjected to the reaction (Table 1, entry 23). Only less than 5% conversion was detected even after 48 h, much lower than 32% conversion was observed for manganese phosphonate of $Me_4\mathbf{L}^1$ as a homogeneous catalyst. When (*R*)-$Me_4\mathbf{L}^1$ or (*R*)-$H_5\mathbf{L}^1$ was employed, either no product or no selectivity was obtained (Table S6, entries 5 and 10). The extremely low conversion for the large substrate is consistent with hindered access to active Mn sites within the framework, indicating that catalysis does occur predominantly at the active sites within the inner pores. This point was also supported by the fact that ground and unground particles of **1** showed similar conversions (95% vs 97% in 20 h) in catalysis.

Scheme 1. MOF 1-catalyzed F-C alkylations of *N*-methyl indole with *β,γ*-unsaturated *α*-ketoesters under continuous flow conditions.



89, 91, 92% yield and 94, 91, 94% ee for R = 4-MePh, 4-BrPh and 4-thienyl, respectively.

Scheme 2. MOF 1-catalyzed F-C alkylation for the synthesis of the COX-2 inhibitor



Encouraged by the outstanding recyclability of **1**, we decided to evaluate its catalytic performances on a fixed-bed reactor, which is commonly adapted in industry.[1b] The continuous flow reactions of *N*-methylindole and *α*-keto esters were performed in a stainless steel column filled with finely grounded **1** (0.4-5 μm) and quartz sands (Scheme 1). Under optimal flow conditions, a residence time of 12 h was required for complete conversion of *α*-keto esters to the addition product in 89-92% yield with 91-94% ee. In comparison with reactions in batch, the flow reactor of **1** gave a slightly increase in catalytic activity, but a slightly decrease in enantioselectivity. Substrate channelling may enable increased efficiencies and yields in reaction and diffusion processes, while the use of silica for packing reactor may lead to lower enantioselectivity, presumably *via* some unfavourable active sites. Given the large pore size of the MOF catalyst, the heat generated during the reaction in the fixed-bed reactor can be well dispersed to avoid the coke formation due to local over heating thus hindering the reaction, as widely observed in zeolite catalysts.[1b] This could be one of the advantages for MOF catalysts in fix-bed reactions, as also illustrated in a recent work.[5a]

The flow system can be reused at less seven times (each a 24 h cycle) successively, without any obvious loss in activity and selectivity. It is worth mentioning that the use of MOFs as heterogeneous catalysts for fixed-bed reactions, where zeolites have played a key role, has been less exploited;[4c,4d] to the best of our knowledge, this represents the first report of MOF-based heterogeneous asymmetric catalysts for continuous-flow reactions.[4] The durability compared favorably with the flow reactors packed with other MOFs and classic supports such as polymeric composites, carbon and silica.[4c,4d,25]

A demonstration of the utility of this MOF-catalyzed alkylation is presented in the synthesis of the optically enriched indolobutyric acid, a cyclooxygenase-2 (COX-2) inhibitor.[26] As outlined in Scheme 2, **1** loading at 5 mol% catalyzed alkylation of 1-(4-bromo-benzyl)-5-methoxy-2-methyl-1*H*-indole with *trans*-methyl crotonate followed by hydrolysis with NaOH and oxidation of the *α*-ketoacid moiety with H_2O_2 provides indolobutyric acid in 72% yield and with 95% ee over two steps. This ee value (95%) of COX-2 is higher than the obtained (up to 87% ee) with imidazolidinone organocatalysts.[26b]

CONCLUSIONS

We have demonstrated that the chemical stability, catalytic activity and enantioselectivity of chiral MOFs can be tuned simultaneously by changing ligand steric and electronic effects. Under both batch and flow reaction systems, the MOF with bulky electron-withdrawing 3,5-bis(trifluoromethyl) phenyl groups exhibited high reactivity and stereoselectivity and excellent stability and recyclability in asymmetric F-C alkylations of indoles and pyrroles, allowing easy access to a range of optically active indole and pyrrole derivatives. The synthetic utility of the MOF was shown in the synthesis of a COX-2 inhibitor. This work thus provides a new strategy for preparing heterogeneous catalysts combining high catalytic activity, selectivity and durability and would facilitate the design of novel functional materials for enantioselective processes. The use of MOF **1** as self-supported catalyst for continuous flow reactions represents an important step toward using MOFs in applications dealing with the pharmaceutical and fine chemical industries.

ASSOCIATED CONTENT

Supporting Information.
Experimental procedures and characterization data. 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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