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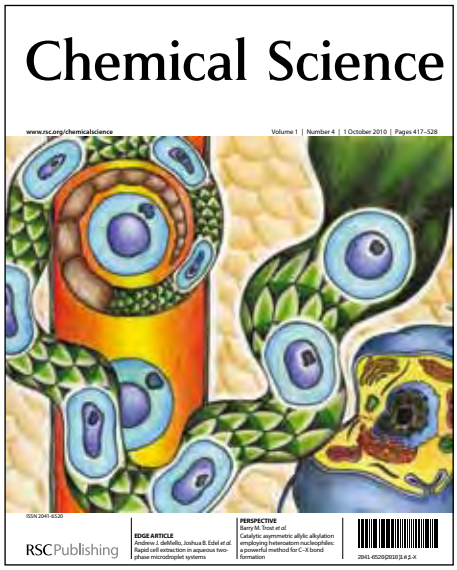

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Paper

Cavity Induced Enantioselectivity Reversal in A Chiral Metal-Organic Framework Brønsted Acid Catalyst

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A pair of highly porous chiral metal-organic frameworks (CMOFs **1** and **2**) were constructed from $[Cu_2(CO_2)_4]$ secondary building units (SBUs) and chiral 3,3',6,6'- or 4,4',6,6'-tetra(benzoate) ligands derived from 1,1'-binaphthyl-2,2'-phosphoric acid. Both **1** and **2** were active catalysts for Friedel-Crafts reactions between indole and imines. Interestingly, the **1**-catalyzed asymmetric reactions yielded the major enantiomers of the opposite chirality to those afforded by the corresponding homogeneous catalyst. Structural analyses and QM/MM calculations revealed that the flip of product handedness results from the chiral environment of CMOF-**1** cavity, similar to enzymatic catalysis in which the product stereo-selectivity is determined by the enzyme pocket.

The advancement of metal-organic frameworks (MOFs) in the past decade has afforded a wealth of enormously porous materials with tunable functional building blocks. [1] Such designer MOFs have been explored in many applications such as gas storage and separation,[2] chemical sensing,[3] biomedical imaging,[4] drug delivery,[5] and particularly heterogeneous catalysis.[6] Well-defined molecular asymmetric catalytic centers can be incorporated into MOF structures in a systematic fashion to yield single-site solid catalysts with activities and selectivities rivaling those of their homogeneous counterparts. For example, we and others have demonstrated highly stereoselective catalysis with chiral MOFs built from metal-based asymmetric catalysts such as Ti-BINOLate and metal-Salen complexes.[7] MOF-derived organocatalysts, including a MOF-based chiral Brønsted acid,[8] have also been shown recently to be capable of catalyzing enantioselective reactions.[9] In addition, chiral separations based on enantioselective interactions between substrate and chiral frameworks have been reported. [10]

All of the known MOF asymmetric catalysts rely on the intrinsic chiral environments of the active sites to exert stereo-control. On the other hand, the walls of the ordered cavities in MOF catalysts can in principle provide preferential secondary interactions between the substrate and the framework, leading to shape-, size-, chemo-, and enantio-selectivities that are not achievable in homogeneous systems. The pore wall surrounding the catalytic site in such a MOF can serve a similar function to the enzyme pocket in enzymatic catalysis.[11] In this work, chiral MOFs containing BINOL-based phosphoric acids were designed and used in heterogeneous Brønsted acid-catalyzed enantioselective Friedel-Crafts reactions between indole and imines. Interestingly, one of the MOF Brønsted acid catalysts gave the opposite enantioselectivity to that of the homogeneous control catalyst, as a result of the stereo-control by the MOF cavity as in enzymatic catalysis. Detailed structural analysis and Quantum Mechanics/Molecular Mechanics (QM/MM) calculations confirmed the origin of the enantio-differentiation reversal, supporting the first observation of enzyme-like stereo-control in chiral MOF catalyzed asymmetric reactions.

Enantiopure *(R)*-3,3',6,6'-tetrakis(4-benzoic acid)-1,1'-binaphthyl phosphate ($\mathbf{L_1}H_4$) was synthesized by a Suzuki coupling between *(R)*-6,6'-dibromo-2,2'-diethoxy-3,3'-diiodo-1,1'-binaphthyl and 4-(methoxycarbonyl)phenylboronic acid, followed by acid catalyzed hydrolysis and phosphorylation. *(R)*-4,4',6,6'-tetrakis(4-benzoic acid)-1,1'-binaphthyl phosphate ($\mathbf{L_2}H_4$) was synthesized by phosphorylation of *(R)*-2,2'-dihydroxy-1,1'-binaphthyl-4,4',6,6'-tetrakis(4-benzoic acid)[7c] (supporting information). The ligands and new intermediate products were characterized by NMR spectroscopy and mass spectrometry. Single crystals of $[R\text{-}\mathbf{L_1}Cu_2(H_2O)_2]\cdot 21DMF\cdot 12H_2O$ (CMOF-**1**) and $[R\text{-}\mathbf{L_2}Cu_2(H_2O)_2]\cdot 27DMF\cdot 17H_2O$ (CMOF-**2**) were obtained by reacting $\mathbf{L_1}H_4$ and $\mathbf{L_2}H_4$ with $Cu(NO_3)_2\cdot 2.5H_2O$ in a DMF/H_2O solvent mixture at 80 °C for 2 days. The framework structures of **1** and **2** were established by single crystal X-ray crystallography.[12]

1 crystallizes in the orthorhombic *C222* space group. The asymmetric unit of **1** contains two $\mathbf{L_1}$ ligands of 1/2 and 1/4 occupancy and two Cu_2 paddle-wheels of 1/2 and 1/4 occupancy. The carboxylate groups from four adjacent $\mathbf{L_1}$ ligands coordinate to two Cu(II) centers to form $[Cu_2(carboxylate)_4]$ secondary building unit (SBU) which links $\mathbf{L_1}$ ligands to form a 4,4-connected 3D network of the hexagonal **pts** topology.[13] **1** exhibits enormous void space, comprising 80.8% of the total volume as calculated by PLATON. The number of solvent molecules (DMF and H_2O) in the channel was determined by a combination of ^{1}H NMR and thermogravimetric analysis (TGA) to give the complete formula of $[R\text{-}\mathbf{L_1}Cu_2(H_2O)_2]\cdot 21DMF\cdot 12H_2O$.

The largest dimensions of open channels in **1** measure 0.8×2.6 nm^2.

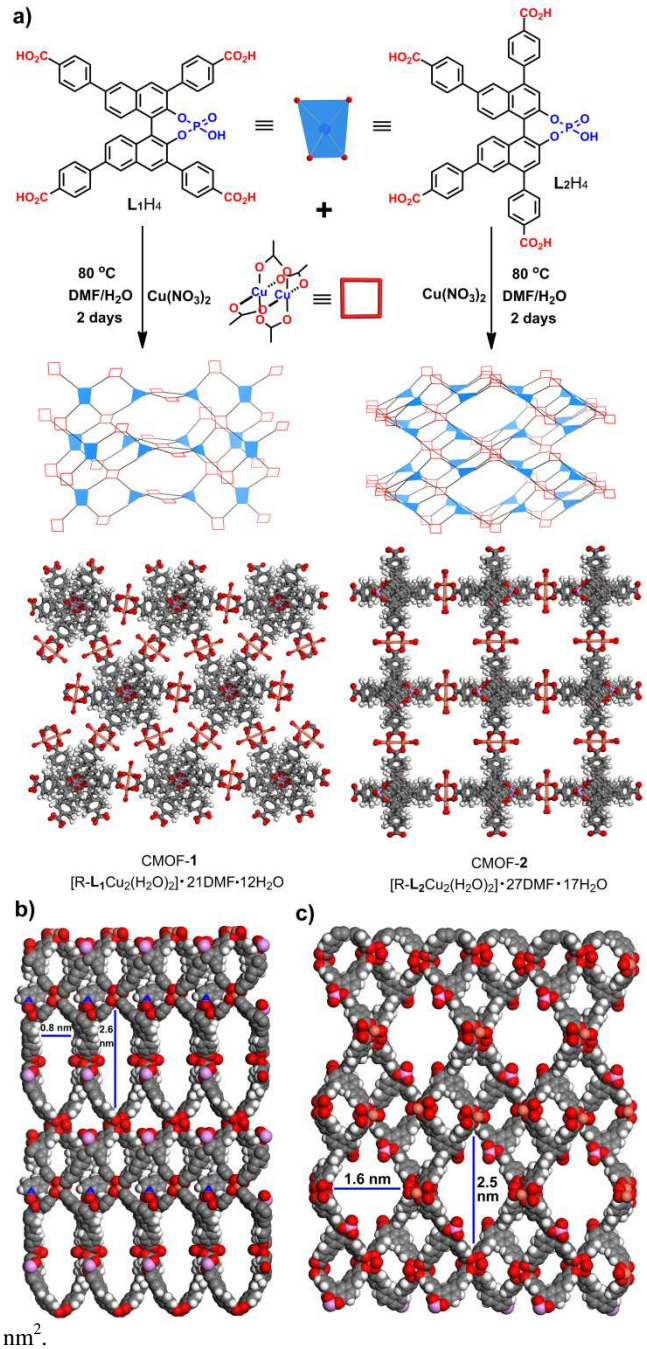


Figure 1. (a) Schematic showing the assembly of $\mathbf{L_1}$ and $\mathbf{L_2}$ ligands with [Cu_2(carboxylate)$_4$] SBUs to afford CMOF-**1** (left) and CMOF-**2** (right) of the 4,4-connected hexagonal **pts** (left) and new {4^3;6^2;8} (right) topology, respectively. (b) Space-filling model of **1** as viewed along the <110> direction, showing 2.6×0.8 nm^2 channels. (c) Space-filling model of **2** as viewed along <100> directions, showing 2.5×1.6 nm^2 channels.

2 shares the same [Cu_2(carboxylate)$_4$] SBUs as **1**, but forms a 4,4-connected 3D network of a slightly different topology (point symbol of the net {4^3; 6^2; 8}[14]), as a result of different orientations of the four carboxylate groups on the $\mathbf{L_2}$ ligand. **2** crystallizes in the tetragonal *I*4$_1$22 space group with one $\mathbf{L_2}$ ligand of ½ occupancy and one Cu_2 paddle-wheel of ½ occupancy in the asymmetric unit. **2** is isostructural to the previously reported isoreticular CMOF series that contain the BINOL functionality.[7c] **2** possesses even larger open channels than **1**, with dimensions of 1.6×2.5 nm^2. The void space in the structure was calculated by PLATON to be 85.9% of the total volume. The complete formula of **2** was determined to be [*R*-$\mathbf{L_2}Cu_2(H_2O)_2$]·27DMF·17H_2O by ^{1}H NMR and TGA.

Table 1. Key crystallographic data for CMOFs **1** and **2**

	1	**2**
Space group	*C*222	*I*4$_1$22
Cell volume (Å^3)	26172	43006
Framework density (g/cm^3)	0.365	0.304
Void space % calcd by PLATON	80.8	85.9
Largest channel dimensions (nm)	0.8×2.6	1.6×2.5
Solvent content wt%[a]	63.4	69.5
Dye uptake wt% [b]	123	174

[a]solvent content wt% was determined from the solvent weight loss in TGA. [b]BBR-250 (20 mg/mL in methanol) was used in the dye uptake experiments. The wt% dye uptake is defined as [(mass of adsorbed dye)/(mass of MOF framework)]*100.

High porosity is needed for asymmetric MOF catalysts in order to efficiently transport large reagent and product molecules through the open channels. Removal of solvent molecules from MOF channels can however result in significant framework distortion, preventing the accurate determination of their intrinsic porosity.[15] We recently demonstrated that a simple dye uptake assay can be used to reliably quantify the intrinsic porosity of CMOFs as well as to probe the capability of the open channels in transporting large molecules.[16] **1** and **2** uptake 123 wt% and 174 wt% of Brilliant Blue R-250, respectively, proving the accessibility of their open channels to large molecules. The higher dye uptake capacity of **2** than **1** is consistent with the different open channel sizes in their single crystal structures.

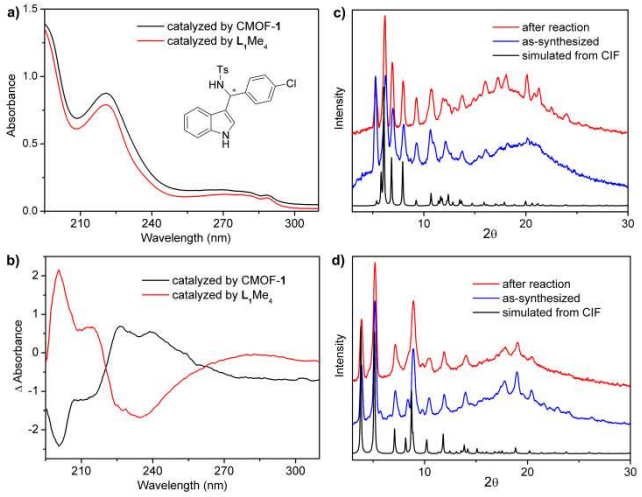


Figure 2. UV-Vis absorption (a) and CD (b) spectra of asymmetric Friedel-Crafts products **6b** from reactions catalyzed by **1** (black) and $\mathbf{L_1}Me_4$ (red). PXRD patterns of **1** (c) and **2** (d): simulated from CIF (black), as-synthesized (blue) and after catalytic reaction (red).

The catalytic activity of the chiral $\mathbf{L_1}$ building block was first evaluated using the ligand methyl ester $\mathbf{L_1}Me_4$ as the catalyst in asymmetric Friedel-Crafts reaction between indole and (*E*)-N-benzylidenebenzenesulfonamide **3a** (Table 2, entry 6). BINOL-derived chiral phosphoric acids have received considerable

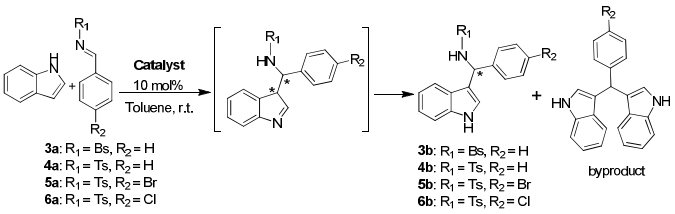
attention from synthetic chemists recently,[17] and have been used to catalyze a wide range of asymmetric organic transformations including Friedel-Crafts reactions.[18] Although two chiral centers are created in the C-C bond formation step, one of them is removed during the subsequent 1,3-hydrogen shift rearrangement, leading to only one pair of enantiomers (Table 2). At 10 mol% catalyst loading, N-[(1H-indol-3yl)(phenyl)methyl]-benzenesulfonamide (**3b**) was obtained in 75% yield and 72% e.e. in favor of the (*S*)-enantiomer after one day of reaction, consistent with previously reported results with chiral 3,3'-substituted-1,1'-binaphthyl phosphoric acid as catalysts.[18b] An achiral byproduct aryl(bisindolyl)methane was also formed due to amine elimination and addition of another indole following the first Friedel-Crafts reaction.[19] The reaction between indole and **5a** catalyzed by $\mathbf{L_1}Me_4$ gives 21% of the aryl(bisindolyl)methane byproduct vs. 75% of the product **5b**. Catalytic activity of **1** was then tested under similar conditions. To our surprise, the Friedel-Crafts reaction between indole and **3a** with the CMOF-**1** catalyst gave the (*R*)-**3b** as the major product (Table 2, entry 1). We further examined the asymmetric Friedel-Crafts reactions between indole and a range of imine substrates (Table 2) catalyzed by **1** (entries 3-5) and $\mathbf{L_1}Me_4$ (entries 7-9). In all cases, the heterogeneous CMOF-**1** catalyst produced the (*R*)-products as the major enantiomers with e.e. values ranging from 29 to 44%. while the molecular $\mathbf{L_1}Me_4$ catalyst yields the (S)-enatiomers as the major products. Circular dichroism (CD) spectra for the products obtained from **1**- and $\mathbf{L_1}Me_4$-catalyzed reactions are mirror images of each other, confirming that the major products from the MOF vs. mono-molecular catalytic systems have different chiralities (Figure 2b).

Moderate yields of the reactions catalyzed by **1** are due to formation of the byproducts aryl(bisindolyl)methane. The reaction between indole and **5a** catalyzed by **1** gives 39% of the byproduct vs. 42% of the product **5b**. The byproduct was formed from amine elimination and indole addition of **5b**, as verified by a reaction between **5b** and indole catalyzed by **1**, which gives 31% conversion of racemic **5b** to the byproduct under the same reaction condition as in other catalytic tests. The remaining **5b** after this test exhibits zero e.e. value, proving that the amine elimination reaction is not enantioselective. The **1**-catalyzed Friedel-Crafts reactions are thus enantioselective. The MOF catalyzed reaction gives higher amount of byproduct as compared to that of the mono-molecular catalyst, presumely due to trapping of the Friedel-Crafts reaction products inside the cavity for further transformation.

As expected, the 4,4',6,6'-tetrabenzyl-BINOL derived $\mathbf{L_2}Me_4$ catalyst is less enantioselective than the 3,3',6,6'-tetrabenzyl-BINOL derived $\mathbf{L_1}Me_4$ catalyst in asymmetric Friedel-Crafts reactions (Table 2, entries 15-18), as a result of different steric effects of the benzyl groups on 3,3' positions vs. 4,4' positions of the binaphthyl rings. Consistent with this, **2** gave much lower e.e.'s than that given by **1** in the asymmetric catalysis (entries 10, 12-14). Both **2** and $\mathbf{L_2}Me_4$ gave the (R)-products as the major enantiomers, indicating the absence of the stereo-control by the framework wall in **2**-catalyzed reactions.

To evaluate the contributions from the non-enantioselective background Friedel-Crafts reactions catalyzed by Cu_2(carboxylate)$_4$ SBUs of **1**, we also synthesized CMOF-**3** using the corresponding BINOL-derived ligand *(R)*-2,2'-diethoxy-1,1'-binaphthyl-3,3',6,6'-tetrakis(4-benzoic acid) ($\mathbf{L_3}H_4$, see supporting information) that does not contain the phosphoric acid group but has ethyl protected naphthol groups. **3** has a formula of ([*R*-$\mathbf{L_3}Cu_2(H_2O)_2$]·21DEF·6H_2O) and is similar to the structure of **1** with the [Cu_2(carboxylate)$_4$] SBUs and the $\mathbf{L_3}$ ligands. **3** adopts the **pts** topology, and possesses 80% of void volume as calculated by PLATON, with 1.4×1.4 nm square channels running along <100> directions and 2.6×1.4 nm channels running along <001> directions. **3** catalyzed the reaction of indole with **4a**, **5a** and **6a** to give the racemic Friedel-Crafts products **4b**, **5b**, and **6b** in 27%, 42%, and 32% yields, respectively. No aryl(bisindolyl)methane byproducts were observed in the **3**-catalzyed reactions. The lack of enantioselectivity in the Cu_2(carboxylate)$_4$ SBU catalyzed reaction is consistent with less defined chiral environment around the SBU in the structure. This control experiment not only supports the involvement of phosphoric acid reaction center in the catalysis because of the observation of chiral products, but also explains relatively modest e.e. values (29 – 44%) observed for **1**-catalyzed Friedel-Crafts reactions as a result of the non-enantioselective background reactions catalyzed by the [Cu_2(carboxylate)$_4$] SBUs.

Table 2. Enantioselective Friedel-Crafts Reactions of Indole with N-Sulfonyl Aldimines



Entry	Catalyst	imine	Time (d)	Yield (%)[a]	ee (%)[b]	Major enantiomer

1	CMOF-**1**	**3a**	2	39	42	(*R*)-**3b**
2[c]	CMOF-**1**	**3a**	2	38	39	(*R*)-**3b**
3	CMOF-**1**	**4a**	2	32	44	(*R*)-**4b**
4	CMOF-**1**	**5a**	2	42	40	(*R*)-**5b**
5	CMOF-**1**	**6a**	2	45	29	(*R*)-**6b**
6	**L**$_1$-Me$_4$	**3a**	1	75	72	(*S*)-**3b**
7	**L**$_1$-Me$_4$	**4a**	1	87	40	(*S*)-**4b**
8	**L**$_1$-Me$_4$	**5a**	1	75	89	(*S*)-**5b**
9	**L**$_1$-Me$_4$	**6a**	1	83	58	(*S*)-**6b**
10	CMOF-**2**	**3a**	2	37	7	(*R*)-**3b**
11[c]	CMOF-**2**	**3a**	2	33	7	(*R*)-**3b**
12	CMOF-**2**	**4a**	2	40	6	(*R*)-**4b**
13	CMOF-**2**	**5a**	2	26	20	(*R*)-**5b**
14	CMOF-**2**	**6a**	2	20	14	(*R*)-**6b**
15	**L**$_2$-Me$_4$	**3a**	1	77	8	(*R*)-**3b**
16	**L**$_2$-Me$_4$	**4a**	1	58	18	(*R*)-**4b**
17	**L**$_2$-Me$_4$	**5a**	1	74	11	(*R*)-**5b**
18	**L**$_2$-Me$_4$	**6a**	1	75	5	(*R*)-**6b**

[a]Isolated yields. [b]Determined by chiral HPLC analysis (Chiralcel OD-H). [c]Recycling of **1** and **2** for the Friedel-Crafts Reaction.

We have also examined the recyclability of **1** and **2** for the asymmetric Friedel-Crafts reactions. As shown in Table 2 (entries 2 and 11), CMOFs were readily recovered from the catalytic reaction via centrifugation and the recovered catalysts showed similar yields and e.e's as those of the as-synthesized CMOFs. Furthermore, the solid catalysts recovered from the catalytic Friedel-Crafts reactions exhibited the same PXRD patterns as that of the pristine solids of **1** and **2** (Figures 2c and 2d), unambiguously supporting the stability of the CMOF frameworks during the catalytic reactions.

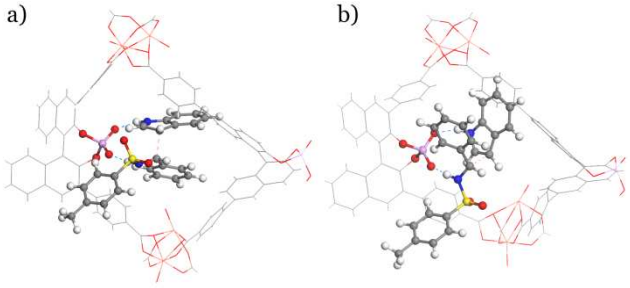
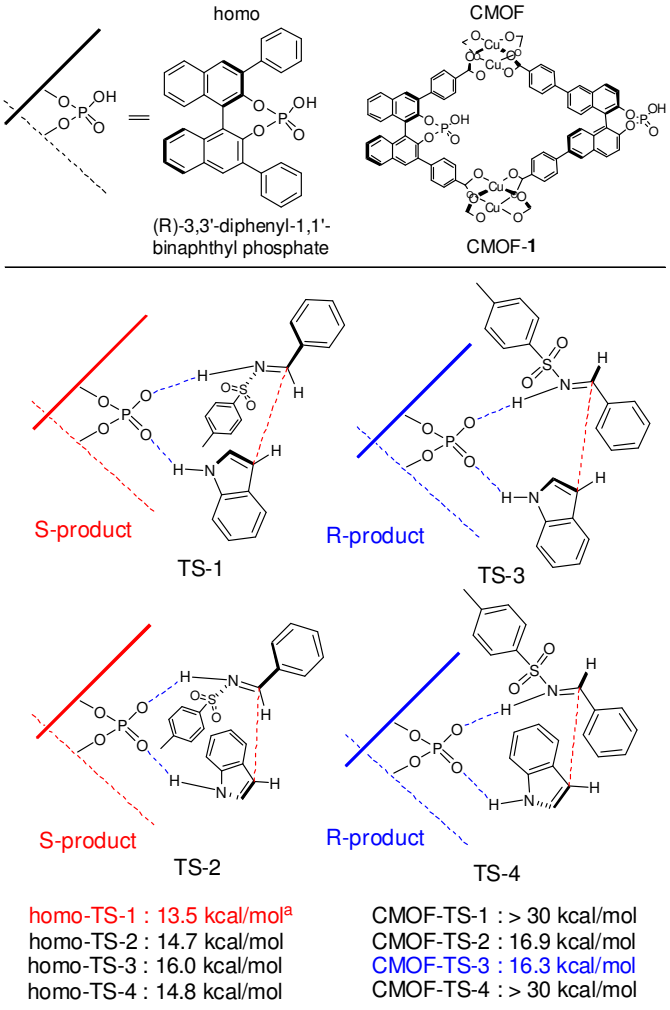


Figure 3. Optimized transition states of CMOF-**1** catalyzed Friedel-Crafts reaction between indole and **4a**. (a) CMOF-TS-2, leading to the *S*-product. (b) CMOF-TS-3, leading to the *R*-product.

QM/MM calculations on the reaction between indole and imine **4a** provide further insights into the origin of the flip of enantioselectivity of **1** vs. **L**$_1$Me$_4$.[20] Density functional theory at the B3LYP/6-311G(d) level[21] was employed to calculate the transition state barrier heights for the four possible intermediates with *(R)*-3,3'-diphenyl-1,1'-binaphthyl phosphoric acid as a homogeneous catalyst model (homo-TS-1 to 4, Scheme 1). Solvation was considered in the calculations using conductor-like polarizable continuum model (CPCM).[22] The TS-1 pathway tends to be kinetically preferred, leading to the *S*-product as the major enantiomer with a calculated ee of 80%, very close to the experimental value of 73% ee.[18b]



Scheme 1. QM / MM calculations of transition state energy barriers in homogeneous / CMOF catalytic systems

To simulate the cavity environment in **1**, one repeating unit of **1** was taken into account (Scheme 1) and treated with the semiempirical approach PM6.[23] Density functional theory at the same level as the homogeneous system was applied to the catalytic center and reactants with the CPCM solvation model. As a result of the steric interference from the cavity in **1**, the pathways towards two out of the four possible Friedel-Crafts products in **1** were effectively blocked (CMOF-TS-1 and CMOF-TS-4) with estimated activation barriers of >30 kcal/mol. In contrast to the homogeneous case, the relative order of energy levels of the remaining two transition states CMOF-TS-2/3 favoured the *R*-product as the major enantiomer with a calculated ee of 47%. This calculated ee value is very close to the experimental result (42%, Table 2 entry 1). QM/MM calculations

thus revealed different reaction pathways between **1**- and $\mathbf{L_1}Me_4$-catalyzed reactions as a result of the preferential interactions between substrates and cavity walls in **1**. The preferred pathway involving TS-1 in the homogenous reaction is totally blocked in the **1**-catalyzed reaction; instead, the preferred pathway for the **1**-catalyzed reaction involves TS-3 which has the highest energy barrier in the homogeneous reactions.

In summary, a pair of highly porous chiral MOFs were built from enantiopure BINOL phosphoric acid derived ligands and Cu_2(carboxylate)$_4$ SBUs. In the catalytic asymmetric Friedel-Crafts reactions between indole and imines, CMOF-**1** gave the major product with opposite chirality compared to that obtained from the corresponding homogeneous catalyst. By structural analyses and QM/MM calculations, we demonstrated that the flip of handedness originates from the chiral environment of the MOF cavity, resembling the stereo-control of the enzyme pocket in enzymatic catalysis. Future efforts will be devoted to designing CMOFs containing both chiral cavity for enzyme-like stereo-control and larger open channels for substrate and product transport[24] in order to design highly active and selective MOF catalysts for organic transformations.

Notes and references

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