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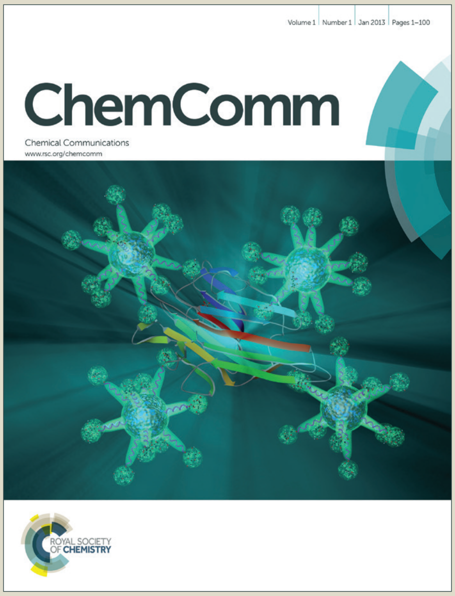

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Facile Synthesis of Magnetic Homochiral Metal-organic Frameworks for “Enantioselective Fishing”

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Abstract: Magnetic functionalized homochiral metal-organic frameworks (MOFs) were prepared and applied to efficiently enantioselective fishing of chiral drug intermediates. Under optimized conditions, the enantiomeric excess (*ee*) value as high as 85.2% was achieved for methyl phenyl sulfoxide (MPS) within 3 min.

Chirality, referring to the property of the object or system not identical to its mirror image, has been confirmed to be closely related to the origin of life.[1] In chemistry, chirality is used to describe molecules that lack of a symmetric plane. These chiral compounds, especially chiral drugs, often exhibit remarkably different effects in pharmacological activity, transport mechanism, metabolism pathway and toxicity. So obtaining enantiomeric pure compounds is extremely important, and it is still a big challenge nowadays because of the identical physical and chemical properties of enantiomers in the achiral environment. Hence, development of new materials for chiral separation has been a hot area in chemical and pharmaceutical fields.[2]

Metal-organic frameworks (MOFs), known as a subclass of the coordination polymers, are crystalline materials generated by the association of metal ions and organic ligands.[3] They have emerged as a promising type of materials for their potential applications in gas storage,[4] separation[5] and catalysis[6] due to their fascinating structures. In latest studies, some homochiral MOFs have been used for enantioselective separation with good performance, indicating the promising application of homochiral MOFs[7], such as direct enantioselective adsorption,[8] preparation chromatography,[9] gas chromatography,[10] liquid chromatography[11] and membrane separation.[12] Enantioseparation should be attributed to the interaction between the framework and racemic agents, such as hydrogen-bonding,[8d,17a] and the homochiral environment in the pores.[17b] Heere, as an alternative approach, we pay attention to the magnetization of homochiral MOF[13] and its application for enantioselective separation. Magnetic materials can be conveniently and fast separated from the medium by applying an external magnetic field.[14] In this work, for the first time, magnetic functionalized homochiral metal-organic frameworks (MOFs) were prepared by incorporation of magnetic iron oxide particles. This material showed good performance for enantioselective separation of MPS with *ee* value as high as ~85.2%.

A homochiral MOFs material, $[Zn_2(bdc)(L\text{-lac})(dmf)](DMF)$ (ZnBLD),[15] was selected for the preparation of magnetic homochiral MOFs via the reaction of Zn^{2+}, 1,4-benzenedicarboxylic acid and *L*-lactic acid. For preparing the magnetic homochiral MOFs, the incorporation of magnetic particles was a crucial factor.[14b] The reported ZnBLD was synthesized in Teflon-lined steel bombs under closed conditions without physical stirring, so It was difficult to form homogeneous composites of magnetic particles and homochiral MOFs by using this method[15]. To address this problem, we modified the synthesis approach of ZnBLD using a round-bottom flask in oil-bath with magnetic stirring (see ESI for details). Elemental analysis and powder X-ray diffraction (PXRD, Fig. S2 in ESI) demonstrated that the coordination numbers and skeleton structure were in consistent with the reported homochiral MOFs synthesized in Teflon-lined steel bombs. Whereas, the properties of the channel changed due to the modified synthesis method. Single crystal X-ray data for ZnBLD: $C_{36}H_{37}NO_{26}Zn_6$, $M\mathrm{r}=1291.89$, orthorhombic, $P2_12_12_1$, $a=8.0822(4)$, $b=20.8183(8)$, $c=30.8295(13)$ Å, $V=5187.3(4)$ Å ^{3}, $Z=4$, $T=293$K, $\rho_{\mathrm{calcd}}=1.417$g cm^{-3}, $R_1=0.0443$, $wR_2=0.1259$, GoF=1.083, Flack=0.08(4). CCDC-1033484 contains supplementary crystallographic data in detail.

As shown in Fig. S1, the coordination number of Zn^{2+} is five. It is worth noting that one of the coordinated oxygen atoms comes from H_2O instead of DMF in this single crystal structure, which is different from the reported result.[8c] Chiral recognition functional pores formed by *L*- lactic ligand are interconnected and extend to three dimensional space.(Fig. 1) Enantioselective separation could be achieved by homochiral MOFs because of the chiral-recognition environment formed by chiral ligand and open chiral channels or cavities.[17] The diameter of the pores is roughly 4 Å. As the molecular volume of H_2O is much smaller than that of DMF, unit cell becomes smaller especially along *a* axis, which is consistent with the fitting results of PXRD (Fig. S3 in ESI). Overall, the homochiral environment is confined in a smaller space and effectively restrains nonspecific interaction, thus improving capture ability of chiral molecules. To some extent, the following experimental results exactly showed the improvement of the enantioselectivity.

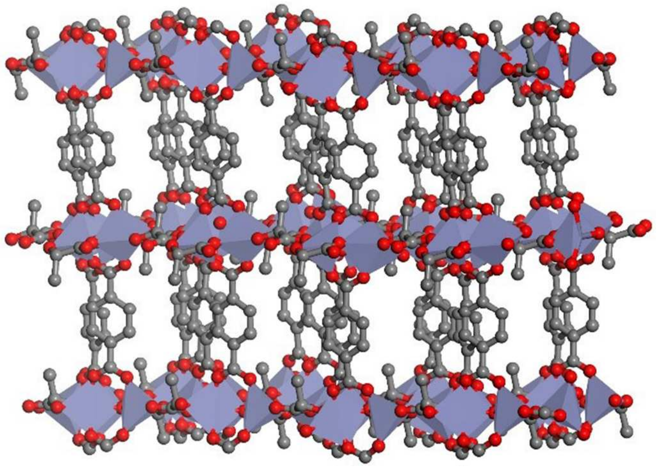


Figure 1. 3D framework of ZnBLD

Based on the successful synthesis of the ZnBLD using a round-bottom flask in oil-bath with magnetic stirring, we further synthesized a magnetic functionalized homochiral ZnBLD (Fe_3O_4@SiO_2-ZnBLD) (Fig. 2a). A certain amount of Fe_3O_4@SiO_2 particles were added into the DMF solution of $Zn(NO_3)_2$, 1,4-benzenedicarboxylic acid and *L*-lactic acid. And then the resulted mixture was sonicated, stirred and heated at 120 ºC for 24 h. The obtained solid was washed with DMF and ethanol before use. PXRD patterns of the Fe_3O_4@SiO_2-ZnBLD, Fe_3O_4@SiO_2 and ZnBLD were shown in Fig. 2b. Most of the diffraction peaks in PXRD patterns with the 2θ from 5 to 40 º for Fe_3O_4@SiO_2-ZnBLD composites were indexed to crystalline ZnBLD. The diffraction peaks in PXRD patterns with the 2θ from 50 to 70 º (shown in the black circle) were corresponding to Fe_3O_4@SiO_2 in the composites. The intensity of Fe_3O_4@SiO_2 was relatively low, which was due to the low contents of Fe_3O_4@SiO_2 in the composites. At the same time, the IR spectrum (Fig. S6 in ESI) of as-synthesized Fe_3O_4@SiO_2-ZnBLD composites contained the typical absorption features of Fe_3O_4@SiO_2 and ZnBLD. In addition, the energy dispersive X-ray (EDX) analysis (Fig. 2c) of the composites also revealed the presence of Fe, Si and Zn. The corresponding morphology was identified by scanning electron microscopy (SEM, Fig. 2d) and transmission electron microscopy (TEM, Fig. 2e) techniques. The SEM image revealed that the Fe_3O_4@SiO_2-ZnBLD composites were mainly rod-like with a size range of 10-15 μm and a diameter of ~1.5 μm. The TEM image demonstrated the presence of Fe_3O_4@SiO_2 nanoparticles. Compared with the TEM image of the Fe_3O_4@SiO_2 (Fig. S5 in ESI), although the distribution of Fe_3O_4@SiO_2 in ZnBLD was not very homogeneous, the formed composites clearly showed the embedded structures with Fe_3O_4@SiO_2 interspersed in ZnBLD. Besides, the magnetic measurements were conducted at room temperature to evaluate the magnetic behavior of the Fe_3O_4@SiO_2-ZnBLD. The saturated value of magnetization was measured to be 1.624 emu g^{-1} (Fig. 2f), revealing strong magnetic properties. When a magnet was placed near the glass bottle with the dispersing solution of Fe_3O_4@SiO_2-ZnBLD, the magnetic particles were immediately attracted toward the magnet (Fig. 2g), which directly demonstrating the convenient separation of Fe_3O_4@SiO_2-ZnBLD composites from liquids by means of an external magnetic field.

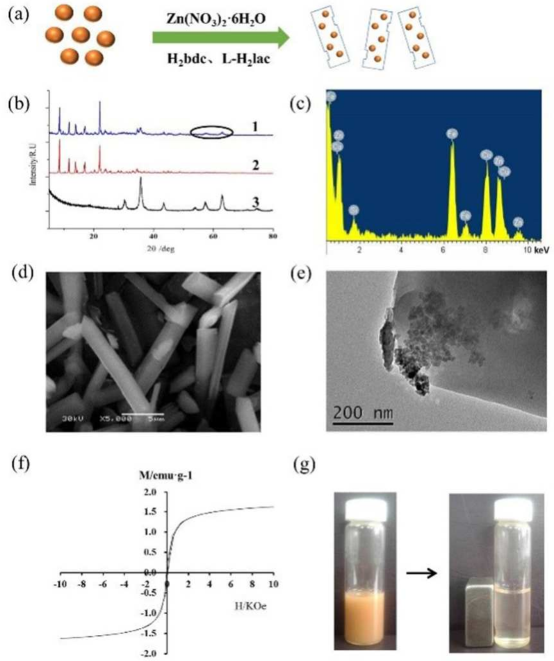


Figure 2. Synthesis and characterizations of Fe3O4@SiO2-ZnBLD composites. (a) Schematic diagram of synthesis approach; (b) PXRD patterns of Fe3O4@SiO2-ZnBLD (1), ZnBLD (2) and Fe3O4@SiO2 (3); (c) EDS result of Fe3O4@SiO2-ZnBLD; (d) SEM image of Fe3O4@SiO2-ZnBLD; (e) TEM image of Fe3O4@SiO2-ZnBLD; (f) Magnetization curve of Fe3O4@SiO2-ZnBLD; (g) Separation of Fe3O4@SiO2-ZnBLD from solution under an external magnetic field.

MPS enantiomers can be used as both efficient synthetic auxiliaries and valuable pharmaceuticals, therefore, obtaining enantiomeric pure MPS is rather important[16]. Here, Fe_3O_4@SiO_2-ZnBLD composites were expected to select a single enantiomer from the racemic MPS solution and achieve the convenient separation of Fe_3O_4@SiO_2-ZnBLD-enantiomer complexes from the solution using an external magnet. This process can be vividly called as "enantioselective fishing", just as shown in Fig. 3a. Fe_3O_4@SiO_2-ZnBLD and racemic solution of MPS (final concentration is 0.1 mg/mL) were added into a vial, shaken with a vortex mixer at room temperature and then the Fe_3O_4@ SiO_2-BLD- enantiomer complexes were collected using a magnet. The collected Fe_3O_4@SiO_2-ZnBLD-enantiomer complexes were washed with methanol in order to retrieve the separated enantiomer and the enantiomeric composition of the separated enantiomer was analyzed by HPLC (Agilent Technology, USA) with a CHIRAlCEL OD-3 column (4.6 x150 mm, 3 µm, Daicel, Japan). Systematic optimization of the operation parameters was done to improve the enantioselective ability of Fe_3O_4@SiO_2-ZnBLD, including extraction solvent, extraction time and washing time (Fig. 3b). The results demonstrated that different extraction solvent had significant influence on the *ee* value. Among them, acetonitrile was much better than other solvents and gave the highest *ee* value. When the extraction time and washing time changed from 1 min to 15 min, the *ee* value almost kept constant, which demonstrated the fast adsorption and desorption equilibrium between the Fe_3O_4@SiO_2-ZnBLD and the racemic solution of MPS. After the systematic optimization, acetonitrile was selected as the extraction solvent, and 1 min was used as the extraction and washing time. Therefore, benefitting from the convenient and fast magnetic separation, the whole enantioselective adsorption process can be completed in no more than 3 min, which was much efficient than the conventional centrifugation and adsorption approach consuming more than 16 h.[9, 11c, 15] Additionally, Fe_3O_4@SiO_2-ZnBLD composites showed much higher preference for the (*S*)-enantiomer over the (*R*)-enantiomer due to the *L*-lactic acid in the homochiral MOF[9, 15]. It was worth mentioning that the *ee* value was as high as 85.2%, which was much higher than the reported results of ~60%.[11c, 14a, 15] And the adsorption amount of (*S*)-MPS could reach up to 86.5 µg/mg. After washed by methanol, the collected Fe_3O_4@SiO_2-ZnBLD can be reused for at last six times with the high *ee* value of 80% (Fig. S7 in ESI).

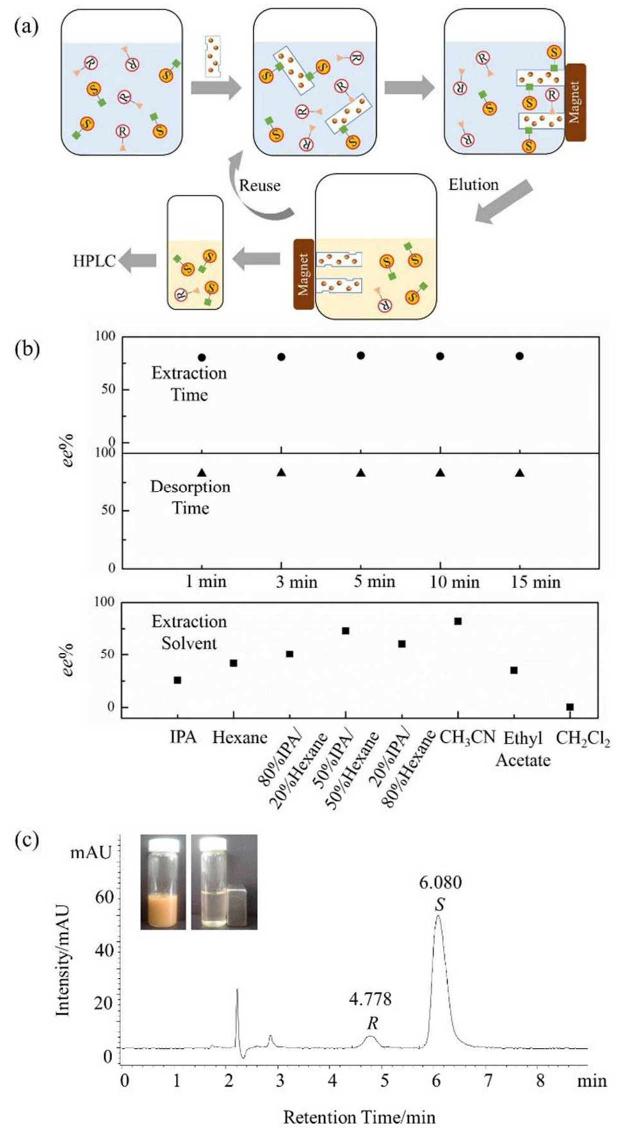
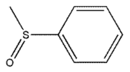
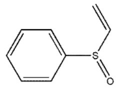
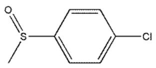


Figure 3. "Enantioselective fishing" process using Fe_3O_4@SiO_2-ZnBLD. (a) Schematic diagram; (b) Optimization of operation parameters; (c) Optimized result for methyl phenyl sulfoxide.

The enantioselective performance of this Fe_3O_4@SiO_2-ZnBLD was further studied using other sulfoxides including vinyl phenyl sulfoxide and 4-chlorophenyl methyl sulfoxide, and the results were shown in Table 1. Apparently, corresponding *ee* values exhibited great difference among the three compounds due to the different substituents in molecules. Compared with MPS, the vinyl group in vinyl phenyl sulfoxide and -Cl in 4-chlorophenyl methyl sulfoxide had electron-withdrawing effect on the chiral center, which reduced the coordinating ability of the sulfoxides with Fe_3O_4@SiO_2-ZnBLD. Besides, the electron-withdrawing effect of -Cl in 4-chlorophenyl methyl sulfoxide was much bigger than that of vinyl in vinyl phenyl sulfoxide. Hence, the *ee* value gradually decreased from MPS to 4-chlorophenyl methyl sulfoxide. In other words, MPS had the most appropriate coordination with Fe_3O_4@SiO_2-ZnBLD and showed higher *ee* value than other sulfoxides. This results were in good accordance with previous report.[9]

Table 1. The enantioselective adsorption of model sulfoxides.

Entry	Name	Structure	*ee*	
			Fe_3O_4@SiO_2-ZnBLD	Fe_3O_4@SiO_2-ZnBDD
1	Phenyl methyl sulfoxide		85.2% in *S*-enantiomer	86.2% in *R*-enantiomer
2	Phenyl vinyl sulfoxide		76.7% in *S*-enantiomer	77.0% in *R*-enantiomer
3	4-Chlorophenyl methyl sulfoxide		29.0% in *S*-enantiomer	29.9% in *R*-enantiomer

As an alternative method, another magnetic homochiral MOFs, named as Fe_3O_4@SiO_2-ZnBDD, was synthesized using *D*-lactic acid as the chiral ligands. Fe_3O_4@SiO_2-ZnBDD composites were expected to select another enantiomer from the racemic MPS solution. The operation parameters were the same as before. Each methanol solution was also analyzed by HPLC (Agilent Technology, USA) with the CHIRAlCEL OD-3 column (4.6 x150 mm, 3 μm, Daicel, Japan). The enantiomer separation results were summarized in Table 1. Fe_3O_4@SiO_2-ZnBDD composited showed higher enantioselectivity for the (*R*)-enantiomer over the (*S*)-enantiomer due to the *D*-lactic acid in the homochiral MOF, and the *ee* value was as high as 86.2% (Fig. S8 in ESI). Furthermore, the trends of the enantioselectivity with the variation of the groups in the three sulfoxides were in consistent with those of Fe_3O_4@SiO_2-ZnBLD composites. All of these results demonstrated that we can realize convenient and efficient "enantioselective fishing" of MPS enantiomer using Fe_3O_4@SiO_2-ZnBLD or Fe_3O_4@SiO_2-ZnBDD composites.

Conclusions

In conclusion, we have demonstrated that Fe_3O_4@SiO_2 tagged to an appropriate homochiral ZnBLD or ZnBDD, can be utilized for "enantioselective fishing" of enantiomers in magnetic field. Benefitting from the magnetic separation, the whole process can be completed in 3 min. Fe_3O_4@SiO_2-ZnBLD and Fe_3O_4@SiO_2-ZnBDD composites showed much higher preference for the (*R*)-enantiomer or (*S*)-enantiomer with the *ee* value of 85.2% and 86.2%, respectively. After reuse for six times, the enantioselective ability kept almost constant and demonstrated the stability of these composites. Even though the complete separation of the two enantiomers was not achieved in this study, the convenience and efficiency of Fe_3O_4@SiO_2-ZnBLD and Fe_3O_4@SiO_2-ZnBDD made this approach promising in the enantiomer separation in the future.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [Experiment details, X-ray diffractogram, magnetization curve, TEM image, IR spectrum, recycle use and enantioselective ability]. See DOI: 10.1039/c000000x/

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