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Enantioselective Diels–Alder reaction in the confined space of homochiral metal–organic frameworks†

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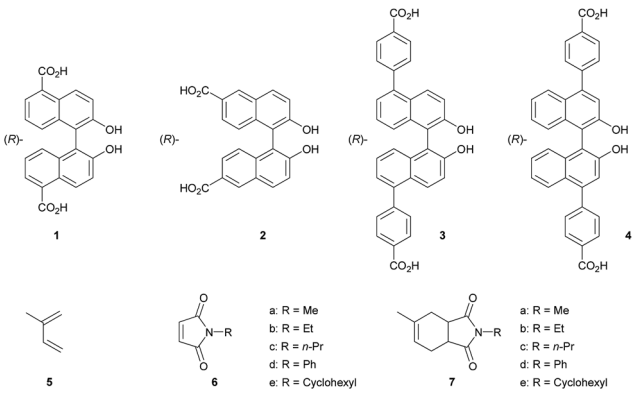
A novel homochiral porous metal–organic framework (MOF) has been synthesized using (*R*)-2,2′-dihydroxy-1,1′-binaphthyl-4,4′-dibenzoic acid as the chiral ligand. This MOF acts as an effective heterogeneous catalyst for the enantioselective Diels–Alder reaction between isoprene and *N*-ethyl maleimide.

Porous metal–organic frameworks (MOFs) with high surface areas and thermal stabilities have attracted much attention recently owing to their versatile applications in storage,[1] separation,[2] sensing,[3] and catalysis.[4] In particular, chiral MOFs, which are assembled using chiral organic ligands and metal ions, are of interest for applications in enantioselective separation and catalysis that are important for the pharmaceutical industry. Some homochiral MOFs and their applications in enantioselective reactions and separation have been described in the literature,[5] but there has been limited success until now. We have previously reported the synthesis of homochiral (*R*)-**MOF-1** using chiral ligand **1**, as well as its application in the asymmetric aminolysis[6] and alcoholysis[7] of epoxides, and in the asymmetric sulfoxidation[8] of sulfides using aqueous H_2O_2. We have also reported the efficient HPLC enantioseparation of several racemates using homochiral (*R*)-**MOF-2** (prepared from chiral ligand **2**) as the chiral stationary phase.[9]

The [4 + 2] cycloaddition reaction between a diene and a dienophile, known as the Diels–Alder reaction, is one of the most powerful methods for C–C bond construction in synthetic organic chemistry.[10] In particular, asymmetric catalytic variants of this reaction have received much attention, owing to their ability to rapidly provide enantioenriched carbocycles from simple substrates.[11] Chiral MOFs are promising candidates for these asymmetric Diels–Alder reactions because they can encapsulate the reactants and organize them in a confined chiral space that contains Lewis acidic metal sites. However, there has been only two reports on MOF-catalyzed heterogeneous Diels–Alder reactions; however, these were not enantioselective.[12] Herein, we report the synthesis of novel homochiral (*R*)-**MOF-4** and its successful application as a heterogeneous catalyst in the enantioselective Diels–Alder reaction between isoprene and *N*-ethyl maleimide.



Chiral organic ligand **4** was synthesized by Suzuki cross-coupling of 4-methoxycarbonyl phenylboronic acid and (*R*)-4,4′-dibromo-2,2′-diacetyl-1,1′-binaphthyl (prepared from (*R*)-4,4′-dibromo-2,2′-dihydroxy-1,1′-binaphthyl),[13] followed by hydrolysis and acidification. (*R*)-**MOF-4** was obtained as green prisms after a solvothermal reaction of chiral organic linker **4** and $Cu(NO_3)_2\ 3H_2O$ in a mixed solvent (DMF–H_2O) at 55 °C for 4 days. The structure was characterized by IR spectroscopy, thermogravimetric analysis, and single crystal X-ray diffraction. The structure was characterized by IR spectroscopy (Fig. S1†), thermogravimetric analysis (Fig. S2†), solid CD spectroscopy (Fig. S3†), powder (Fig. S4†) and single crystal X-ray diffraction. X-ray diffraction analysis reveals that (*R*)-**MOF-4** crystallizes in

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† Electronic supplementary information (ESI) available: Synthesis of (*R*)-MOF-4, catalytic Diels–Alder reactions, IR, CD, TG spectra and HPLC chromatographic data, XRD data. CCDC 1483410. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6ra23740a

the trigonal space group *R*32 (hexagonal axes).‡ Asymmetric unit of (*R*)-**MOF-4** consists of di-copper(II) cations, two anionic ligands **4**, three molecules of *N*-methylformamide (including two disordered between two positions with *ca.* 0.64 : 0.36 occupancy) and one molecule of methanol. As expected, metal–organic framework is organized around di-copper(II) ions as quasi square-planar network (Fig. 1). It contains one well localized DMF molecule that is H-bonded to one of the hydroxy groups of the ligand and two disordered DMF molecules that are coordinated in axial positions of both Cu(II) atoms. In contrast to previously reported relatively porous interpenetrating homochiral (*R*)-**MOF-3**,[12b] in the present case *ca.* 88% of crystal volume is occupied by already localized (*R*)-**MOF-4** and DMF molecules (Fig. 2). As seen in Fig. 1, crystals contain discrete voids of approximately 4.6 Å radius that are not arranged in tunnels pointing across the whole crystals. However, when all solvent molecules present in crystal are removed another channel like of a 2.4 Å radius are formed around catalytic centres that may afford crystal penetration by relatively small linear organic molecules (Fig. 1, bottom part). In this case about 50.1% of the crystal volume is accessible. Therefore, one might assume that enantioselection may take place inside of an internal empty larger chiral cavity generated by evacuation of included DMF solvents. Thus the reaction of relatively small reactant may occur in the cavity.

Crystalline evacuated (*R*)-**MOF-4** exhibited excellent catalytic activity in the asymmetric Diels–Alder reaction between isoprene and *N*-ethyl maleimide when used as a heterogeneous catalyst. When isoprene **5** and *N*-ethyl maleimide **6b** were stirred in various solvents in the presence of evacuated (*R*)-**MOF-4** at 20 °C for 24 h, optically active adduct **7b** was formed in the yields shown in Table 1. When the reaction was carried out in AcOEt or cyclohexane, relatively higher enantioselectivities (71% ee and 63% ee, respectively) were obtained (Table 1, entries 4 and 7). In contrast, reactions in EtOH, i-PrOH, $CHCl_3$, toluene, and *n*-hexane resulted in lower enantioselectivities (Table 1, entries 2, 3, 5–8), and only the racemic product was isolated when the reaction was performed in MeOH (Table 1, entry 1).

Next, we examined the effect of reaction temperature (Table 2), and the best result (81% yield, 75% ee) was obtained when the reaction was carried out at 0 °C for 48 h (Table 2, entry 2). The enantioselectivity of the reaction decreased at elevated temperatures (entries 4–6).

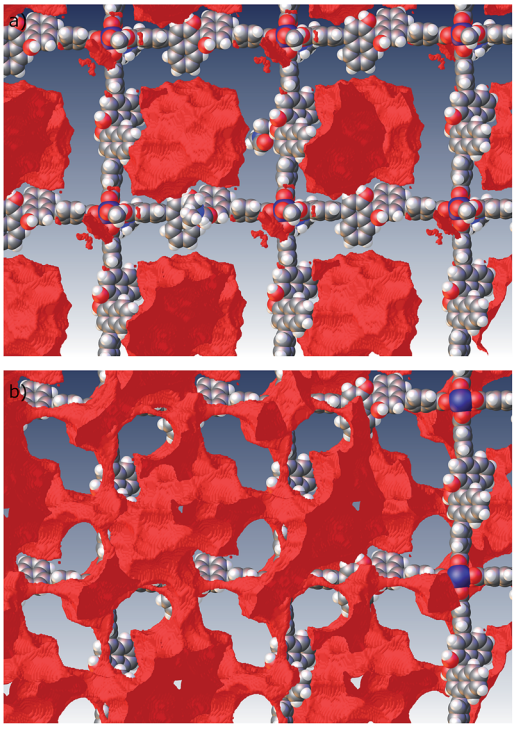


Fig. 1 2D coordination polyhedron of (*R*)-MOF-**4** showing coordination of di-copper(II) ion by a chiral ligand **4** and presence of discrete void spaces in case when DMF/MeOH molecules localized in X-ray studies are present (upper figure) and when they were all removed (bottom figure).

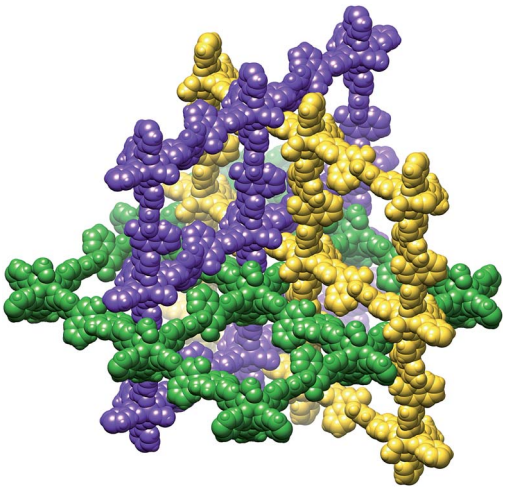
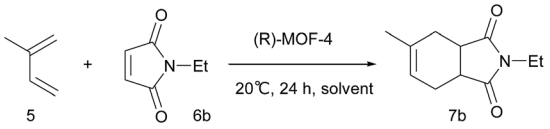


Fig. 2 Interwoven network of (*R*)-MOF-**4** showing viewed down triple symmetry.

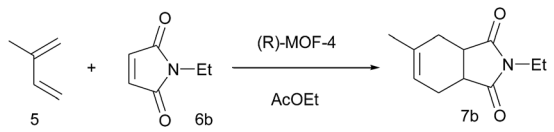
Table 1 Effect of solvent on the asymmetric Diels–Alder reactions of isoprene and *N*-ethyl maleimide



Entry	Solvent	Yield (%)	ee[a] (%)
1	MeOH	43	0
2	EtOH	66	21
3	i-PrOH	87	33
4	AcOEt	49	71
5	$CHCl_3$	85	13
6	Toluene	77	21
7	Cyclohexane	59	63
8	*n*-Hexane	80	31

[a] HPLC column: Chiralcel OB-H, eluent: hexane/i-PrOH = 90/10, flow rate: 0.2 mL min^{-1}, detection: UV 220 nm.

Table 2 Effect of temperature on the asymmetric Diels–Alder reactions of isoprene and *N*-ethyl maleimide



Entry	Temp (°C)	Time (h)	Yield (%)	ee[a] (%)
1	0	24	33	73
2	0	48	81	75
3	0	72	70	71
4	20	24	49	71
5	40	24	83	59
6	60	24	61	55

[a] HPLC column: Chiralcel OB-H, eluent: hexane/i-PrOH = 90/10, flow rate: 0.2 mL min^{-1}, detection: UV 220 nm.

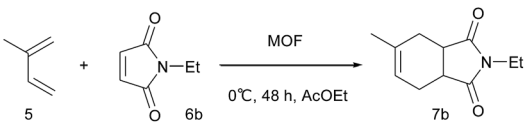
To explore this catalytic activity further, we used a variety of *N*-substituted maleimide derivatives (Table 3) as dienophiles. *N*-methyl maleimide **6a** showed lower reactivity and enantioselectivity than **6b** (Table 3, entry 1). Sterically bulky *N*-substituted maleimides **6c–6e** resulted in poor catalytic efficiency in terms of both product yield and enantioselectivity. This may be due to the weaker encapsulation of sterically bulky dienophiles in the chiral channels of (*R*)-**MOF-4**.

The catalytic performances of (*R*)-**MOF-1**, (*R*)-**MOF-2**, and (*R*)-**MOF-3** in the asymmetric Diels–Alder reaction between isoprene and *N*-ethyl maleimide were compared with that of (*R*)-**MOF-4**. (*R*)-**MOF-1** and (*R*)-**MOF-2** afforded the optically active products with 5% ee and 25% ee, respectively (Table 4, entries 1 and 2), whereas interpenetrating (*R*)-**MOF-3** gave low product yields and did not show enantioselectivity (Table 4, entry 3).

We also performed control experiments to study the confinement effect of (*R*)-**MOF-4** on the catalyst. When the reaction was performed using $Cu(OAc)_2$ as the catalyst, cycloaddition product *rac*-**7b** was obtained in 25% yield (Table 5, entry 2). When the reaction was performed using (*R*)-1,1′-bi-2-naphthol (BINOL), *rac*-**7b** was obtained in 21% yield (Table 5, entry 3). With a combination of (*R*)-BINOL and $Cu(OAc)_2$ as the catalyst, the reaction proceeded with similar efficiency, affording *rac*-**7b** in 10% yield (Table 4, entry 4), which is comparable to that for the reaction without any catalyst (Table 4, entry 1). The catalyst was separated by filtration and washed several times with methanol. The recovered catalyst can be used for further catalytic cycles.

In summary, the synthesis and structural elucidation of a novel extended homochiral MOF, (*R*)-**MOF-4** with a non-interpenetrating framework were successfully achieved. With the free void space of homochiral (*R*)-**MOF-4**, it is reasonable to assume that the reactions occur inside its chiral pores. Obtained (*R*)-**MOF-4** exhibited excellent catalytic activity as a heterogeneous catalyst in the asymmetric Diels–Alder reaction between isoprene and *N*-ethyl maleimide. Balky reactants have been shown to have lower reactivity and enantioselectivity due to their weaker interaction with the chiral MOF. Further study of the mechanism and scope of this reaction is now underway.

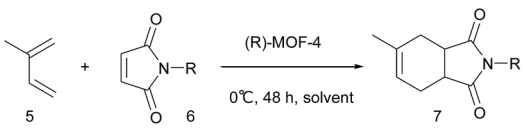
Table 4 Asymmetric Diels–Alder reactions of isoprene and *N*-ethyl maleimide catalyzed by various chiral MOFs



Entry	MOF	Yield (%)	ee[a] (%)
1	None	10	0
2	(*R*)-**MOF-1**	12	5
3	(*R*)-**MOF-2**	15	25
4	(*R*)-**MOF-3**	11	0
5	(*R*)-**MOF-4**	81	75

[a] HPLC column: Chiralcel OB-H, eluent: hexane/i-PrOH = 90/10, flow rate: 0.2 mL min^{-1}, detection: UV 220 nm.

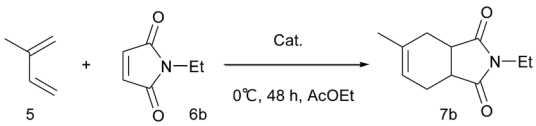
Table 3 Asymmetric Diels–Alder reactions of isoprene and *N*-substituted maleimide



Entry	R	Solvent	Yield (%)	ee[a] (%)
1	Me	AcOEt	37	37
2	Et	AcOEt	81	75
3	*n*-Pr	AcOEt	11	5
4	Ph	AcOEt	17	7
5	Cyclohexyl	AcOEt	18	0

[a] HPLC column: Chiralcel OB-H, eluent: hexane/i-PrOH = 90/10, flow rate: 0.2 mL min^{-1}, detection: UV 220 nm.

Table 5 Control experiment of Diels–Alder reactions of isoprene and *N*-ethyl maleimide



Entry	Cat.	Yield (%)	ee[a] (%)
1	None	10	0
2	$Cu(OAc)_2$	25	0
3	(*R*)-BINOL	21	0
4	$Cu(OAc)_2$ + (*R*)-BINOL	10	0
5	(*R*)-**MOF-4**	81	75

[a] HPLC column: Chiralcel OB-H, eluent: hexane/i-PrOH = 90/10, flow rate: 0.2 mL min^{-1}, detection: UV 220 nm.

Acknowledgements

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Notes and references

‡ Crystal data for (*R*)-**MOF-4**: $C_{78}H_{64}Cu_2N_3O_{16}$, MW = 1426.40, $a = b = 33.835(5)$, $c = 39.859(8)$ Å, $\beta = 120.0°$, $V = 39\,517(14)$ Å^3, $F(000) = 13\,302$, $d_{exp} = 1.328(4)$ and $d_{calc} = 1.079$ Mg m^{-3}, trigonal; space group *R*32 (No. 155), $Z = 18$, μ (MoKα) = 0.541 cm^{-1}, $\lambda = 0.6888$ Å, $T = 100(2)$ K, 137 923 reflections measured, 17 540 unique ($R_{int} = 0.0292$), final $R_1 = 0.0732$, w$R_2 = 0.2230$, for 16 757 observed reflections with $I > 2\sigma(I)$; GOF = 1.041. CCDC: 1483410.

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