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

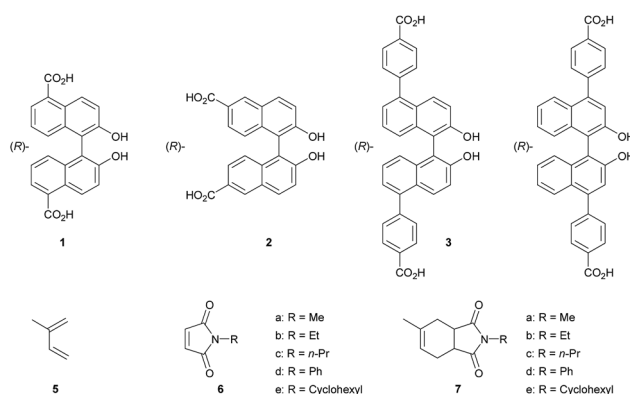
Koichi Tanaka,^{*a} Shohei Nagase,^a Taku Anami,^a Michał Wierzbicki^b
and Zofia Urbanczyk-Lipkowska^b

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 aminolysis⁶ and alcoholysis⁷ of epoxides, and in the asymmetric sulfoxidation⁸ of sulfides using aqueous H₂O₂. 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(NO₃)₂·3H₂O in a mixed solvent (DMF–H₂O) 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

^aDepartment of Chemistry and Materials Engineering, Faculty of Chemistry, Materials and Bioengineering, Kansai University, Suita, Osaka 564-8680, Japan. E-mail: ktanaka@kansai-u.ac.jp; Fax: +81-06-6368-0861; Tel: +81-06-6368-0861

^bInstitute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warszawa, Poland. E-mail: ocryst@icho.edu.pl; Fax: +48 22 6326681; Tel: +48 22 3432207

† 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 $R32$ (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

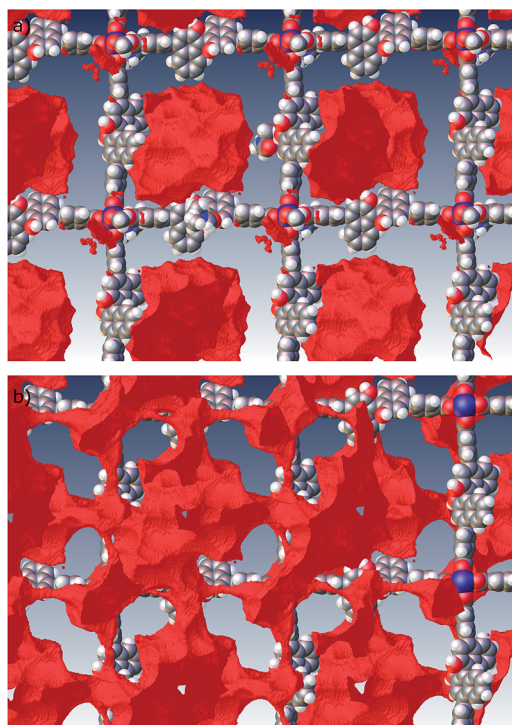


Fig. 1 2D coordination polyhedron of (*R*)-**MOF-4** showing coordination of di-copper(II) ion by a chiral ligand **4** and presence of discrete void spaces in case when DMF/MeOH molecules localized in X-ray studies are present (upper figure) and when they were all removed (bottom figure).

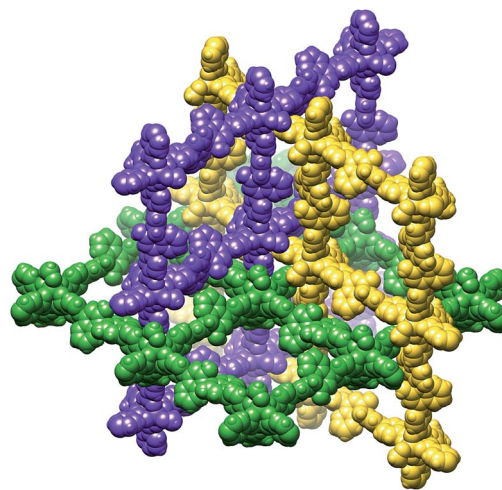
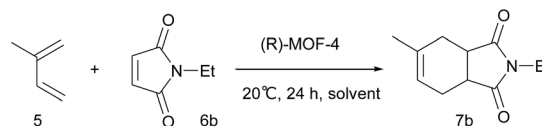


Fig. 2 Interwoven network of (*R*)-**MOF-4** showing viewed down triple symmetry.

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, CHCl₃, 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).

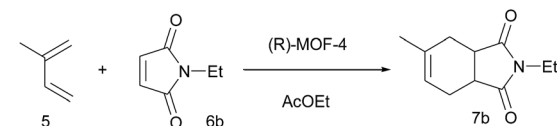
Table 1 Effect of solvent on the asymmetric Diels–Alder reactions of isoprene and *N*-ethyl maleimide



Entry	Solvent	Yield (%)	ee ^a (%)
1	MeOH	43	0
2	EtOH	66	21
3	<i>i</i> -PrOH	87	33
4	AcOEt	49	71
5	CHCl ₃	85	13
6	Toluene	77	21
7	Cyclohexane	59	63
8	<i>n</i> -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**.

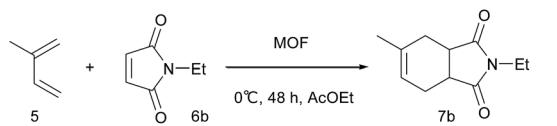
The catalytic performances of (*R*)-**MOF-1**, (*R*)-**MOF-2**, and (*R*)-**MOF-3** in the asymmetric Diels–Alder reaction between isoprene and *N*-ethyl maleimide were compared with that of (*R*)-**MOF-4**. (*R*)-**MOF-1** and (*R*)-**MOF-2** afforded the optically active products with 5% ee and 25% 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,

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	<i>n</i> -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.

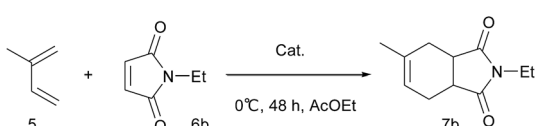
Table 4 Asymmetric Diels–Alder reactions of isoprene and *N*-ethyl maleimide catalyzed by various chiral MOFs


Entry	MOF	Yield (%)	ee ^a (%)
1	None	10	0
2	(<i>R</i>)- MOF-1	12	5
3	(<i>R</i>)- MOF-2	15	25
4	(<i>R</i>)- MOF-3	11	0
5	(<i>R</i>)- 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.

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. Bulky 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 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	(<i>R</i>)-BINOL	21	0
4	Cu(OAc) ₂ + (<i>R</i>)-BINOL	10	0
5	(<i>R</i>)- 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, $\beta = 120.0^\circ$, $V = 39\,517(14)$ Å³, $F(000) = 13\,302$, $d_{\text{exp}} = 1.328(4)$ and $d_{\text{calc}} = 1.079$ Mg m⁻³, trigonal; space group R32 (No. 155), $Z = 18$, μ (MoK α) = 0.541 cm⁻¹, $\lambda = 0.6888$ Å, $T = 100(2)$ K, 137 923 reflections measured, 17 540 unique ($R_{\text{int}} = 0.0292$), final $R_1 = 0.0732$, $wR_2 = 0.2230$, for 16 757 observed reflections with $I > 2\sigma(I)$; GOF = 1.041. CCDC: 1483410.

- (a) K. S. Suslick, P. Bhyrappa, J. H. Chou, M. E. Kosal, S. Nakagaki, D. W. Smithenry and S. R. Wilson, *Acc. Chem. Res.*, 2005, **38**, 283–291; (b) L. J. Murray, M. Dinca and J. R. Long, *Chem. Soc. Rev.*, 2009, **38**, 1294–1314; (c) A. Phan, C. J. Doonan, F. J. Uribe-Romo, C. B. Knobler, M. O’Keeffe and O. M. Yaghi, *Acc. Chem. Res.*, 2010, **43**, 58–67; (d) K. Sumida, D. L. Rogow, J. A. Mason, T. M. McDonald, E. D. Bloch, Z. R. Herm, T. Bae and J. R. Long, *Chem. Rev.*, 2012, **112**, 724–781; (e) B. Van de Voorde, B. Bueken, J. Denayer and D. De Vos, *Chem. Soc. Rev.*, 2014, **43**, 5766–5788.
- (a) B. Van de Voorde, B. Bueken, J. Denayer and D. De Vos, *Chem. Soc. Rev.*, 2014, **43**, 5766–5788; (b) S. R. Venna and M. A. Carreon, *Chem. Eng. Sci.*, 2015, **124**, 3–19; (c) W. Li, Y. Zhang, Q. Li and G. Zhang, *Chem. Eng. Sci.*, 2015, **135**, 232–257; (d) D. Banerjee, A. J. Cairns, J. Liu, R. K. Motkuri, S. K. Nune, C. A. Fernandez, R. Krishna, D. M. Strachan and P. K. Thallapally, *Acc. Chem. Res.*, 2015, **48**, 211–219; (e) L. Heinke, M. Tu, S. Wannapaiboon, R. Fischer and C. Woell, *Microporous Mesoporous Mater.*, 2015, **216**, 200–215.
- (a) L. E. Kreno, K. Leong, O. K. Farha, M. Allendorf, R. P. Van Duyne and J. T. Hupp, *Chem. Rev.*, 2012, **112**, 1105–1125; (b) D. Liu, K. Lu, C. Poon and W. Lin, *Inorg. Chem.*, 2014, **53**, 1916–1924.
- (a) J. Y. Lee, O. K. Farha, J. Roberts, K. A. Scheidt, B. T. Nguyen and J. T. Hupp, *Chem. Soc. Rev.*, 2009, **38**, 1450–1459; (b) L. Ma and W. Lin, *Top. Curr. Chem.*, 2010, **293**, 175–205; (c) M. Yoon, R. Srirambalaji and K. Kim, *Chem. Rev.*, 2012, **112**, 1196–1231; (d) J. M. Falkowski, S. Liu and W. Lin, *RSC Catal. Ser.*, 2013, **12**, 344–364; (e) A. Dhakshinamoorthy, M. Opanasenko, J. Cejka and H. Garcia, *Catal. Sci. Technol.*, 2013, **3**, 2509–2540; (f) J. Liu, L. Chen, H. Cui, J. Zhang, L. Zhang and C. Su, *Chem. Soc. Rev.*, 2014, **43**, 6011–6061; (g) A. H. Chughtai, N. Ahmad, H. A. Younus, A. Laypkov and F. Verpoort, *Chem. Soc. Rev.*, 2009, **38**, 1450–1459.
- (a) Y. Liu, W. Xuan and Y. Cui, *Adv. Mater.*, 2010, **22**, 4112–4135; (b) C. Wang, M. Zheng and W. Lin, *J. Phys. Chem. Lett.*, 2011, **2**, 1701–1709; (c) G. Nickerl, A. Henschel, R. Gruenker, K. Gedrich and S. Kaskel, *Chem. Ing. Tech.*, 2011, **83**, 90–103; (d) Z. Gu, C. Yang, N. Chang and X. Yan, *Acc. Chem. Res.*, 2012, **45**, 734–745; (e) J. M. Falkowski, S. Liu and W. Lin, *Isr. J. Chem.*, 2012, **52**, 591–603; (f) S. Regati, Y. He, M. Thimmaiah, P. Lia, S. Xiangb, B. Chen and J. C. Zhao, *Chem. Commun.*, 2013, **49**, 9836–9838; (g) P. Peluso, V. Mamane and S. Cossu, *J. Chromatogr. A*, 2014, **1363**, 11–26; (h) T. Duerinck and J. F. M. Denayer, *Chem. Eng. Sci.*, 2015, **124**, 179–187; (i) Y. Cui, B. Li, H. He, W. Zhou, B. Chen and G. Qian, *Acc. Chem. Res.*, 2016, **49**, 483–493.
- K. Tanaka, S. Oda and M. Shiro, *Chem. Commun.*, 2008, 820–822.
- (a) K. Tanaka and K. Otani, *New J. Chem.*, 2010, **34**, 2389–2391; (b) K. Tanaka, K. Otani, T. Murase, S. Nishihote and Z. Urbanczyk-Lipkowska, *Bull. Chem. Soc. Jpn.*, 2012, **85**, 709–714.
- K. Tanaka, K. Kubo, K. Iida, K. Otani, T. Murase, D. Yanamoto and M. Shiro, *Asian J. Org. Chem.*, 2013, **2**, 1055–1060.
- (a) K. Tanaka, T. Muraoka, D. Hirayama and A. Ohnishi, *Chem. Commun.*, 2012, **48**, 8577–8579; (b) K. Tanaka, Y. Kikumoto, N. Hota and H. Takahashi, *New J. Chem.*, 2014, **38**, 880–883; (c) K. Tanaka, N. Hotta, S. Nagasea and K. Yoza, *New J. Chem.*, 2016, **40**, 4891–4894; (d) K. Tanaka, T. Muraoka, Y. Otubo, H. Takahashi and A. Ohnishi, *RSC Adv.*, 2016, **6**, 21293–21301.
- J. Funel and S. Abele, *Angew. Chem., Int. Ed.*, 2013, **52**, 3822–3863.
- (a) E. J. Corey, *Angew. Chem., Int. Ed.*, 2002, **41**, 1650–1667; (b) M. Hatano and K. Ishihara, *Chem. Commun.*, 2012, **48**, 4273–4283.
- (a) B. Gole, A. K. Bar, A. Mallick, R. Banerjee and P. S. Mukherjee, *Chem. Commun.*, 2013, **49**, 7439–7441; (b) K. Tanaka, D. Yanamoto, K. Yoshimura, T. Anami and Z. Urbanczyk-Lipkowska, *CrystEngComm*, 2015, **17**, 1291–1295.
- M. W. A. MacLean, T. K. Wood, G. Wu, R. P. Lemieux and C. M. Crudden, *Chem. Mater.*, 2014, **26**, 5852–5859.

