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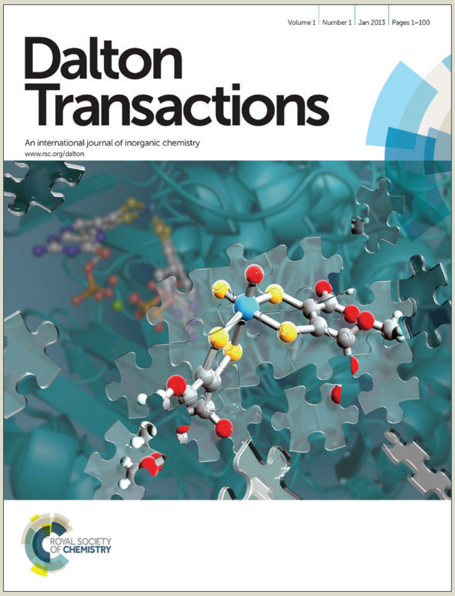

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Chiral Environment of Catalytic Sites in the Chiral Metal-Organic Frameworks

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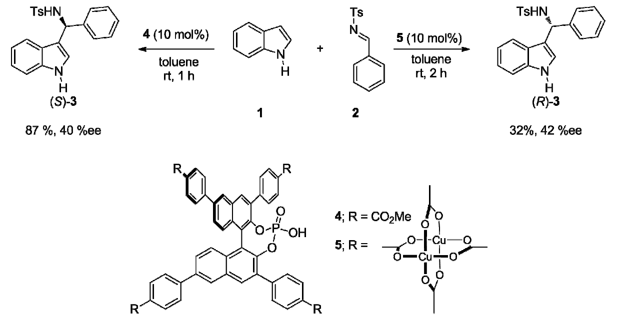
Chiral metal-organic frameworks are considered a useful platform in heterogeneous catalysis for enantioselective chemical transformations. However, it has been observed that the enantioselectivity is sensitive to the site at which the reaction takes place, even in a single crystal, since the chiral environment of the catalytic site varies according to its location; e.g., that of the surface is anisotropic whereas that of the interior is isotropic.

Impressive progress has been made in the development of heterogeneous catalysts based on metal-organic frameworks (MOFs), including chiral MOFs for the enantioselective reactions.[1,2] Several reports on MOFs for catalysis has been reported by us[2] and others.[3] However, it is still unclear to date the catalytic sites in these materials (surface vs open metal sites in MOF). In order to design a better enantioselective catalys, based on MOFs, it is necessary to understand whether the catalytic reactions are taking place at the surface of the crystals leaving the active sites inside the MOF untouchedor the reactions taking place at the active sites inside the MOF. If the reaction is taking place at the surface, the use of MOFs as heterogeneous catalysts would be seriously undermined. As a result it is difficult to highlight the true advantages of MOF-based heterogeneous catalysts over conventional embedded catalysts on solid supports.[3]

The location of the reactive sites is an important aspect when enantioselective reactions are mediated by a chiral MOF. In this context, the chiral environments in MOFs are not necessarily identical to those homogeneous counterparts, although the basic skeleton and absolute configuration of the ligands in both cases is essentially the same. Lin and co-workers presented an example to illustrate this concept through a Friedel-Crafts reaction of indole, **1** with *N*-tosyl imine **2** to produce **3** (Scheme 1). The reaction with the homogeneous catalyst **4** provided the product (*S*)-**3** as the major optical isomer, whereas the chiral MOF catalyst **5** yielded the antipode, (*R*)-**3**, as the major isomer, despite both skeletons having the same absolute configuration (Scheme 1).[1h] It implies that the chiral environment of the cavities in the MOF must be different to that the predicted based on the homogeneous catalyst.



Scheme 1. Comparison of the enantioselectivity by a homogeneous chiral catalyst and a MOF based heterogeneous chiral catalyst.

Furthermore, chiral environments of the catalytic sites even in a single MOF crystal, would vary depending on the location of the cavities. As shown in Figure 1, the chiral environment of the reaction site on the surface is anisotropic, whereas that inside the crystal is isotropic, much like a sphere enclosed by uniform surroundings. The cavity inside more closely resembles the homogeneous system. Thus, it is expected that the optical purity of the products would vary depending on the location at which the reaction takes place. The obsereved optical purity of overall product may be an average value of the ensemble of product fractions originated from various locations. Prior to further studies, the diffusion pattern of the substrate was exemplified using the two-photon fluorescence microscopy (TPM) method we have developed.[4] The (*R*)-**KUMOF-1**, obtained under the routine solvothermal reaction conditions that we employed previously,[2] and Zn/(*R*)-**KUMOF-1**, prepared by addition of dimethylzinc to (*R*)-**KUMOF-1** (Figure 2c). Both MOFswere incubated with a dye, pyrene-1-carbaldehyde, **6** at room temperature. Penetration of the dye into the MOF crystals was monitored by TPM at various time intervals. The penetration of dye into (*R*)-**KUMOF-1** was smooth. As the incubation time lengthened, more dye gradually diffused into the crystal until it was evenly saturated. On the other hand, the diffusion pattern in the case of Zn/(*R*)-**KUMOF-1** exhibited slightly different features. The dye initially accumulated on the shallow layer due to a strong interaction between the carbonyl group of **6** and biphenoxy-zinc(II) of the framework. As a result, the channel would shrink and further diffusion of more dye molecules could be substantially hindered. However, the passageway, even with obstruction of the channel by **6**, would still be roomy enough to accommodate

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additional incoming dyes. Thus, the dye is eventually uniformly distributed inside, but a heavy localization of **6** on the boundary was detected. Thus, it is reasonable to assume that the aldehyde substrates diffuse into the crystals in the same manner.

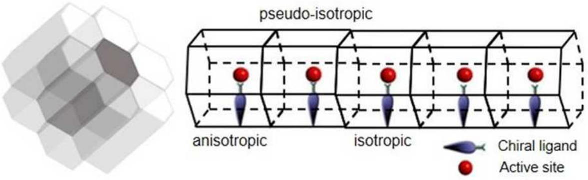


Figure 1. Chiral environments of cavities in the chiral MOF crystal

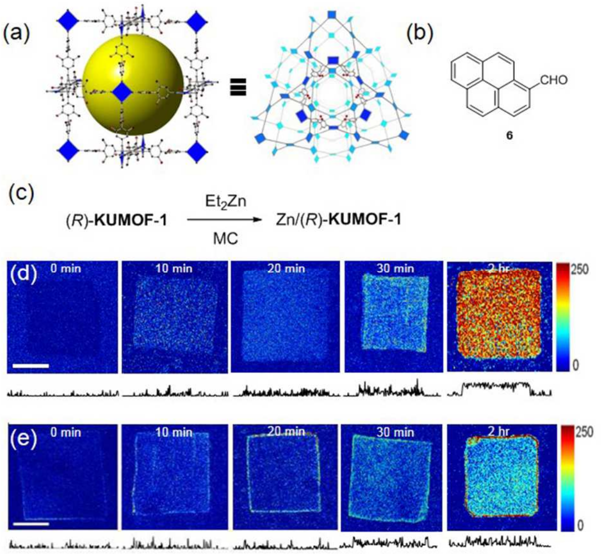
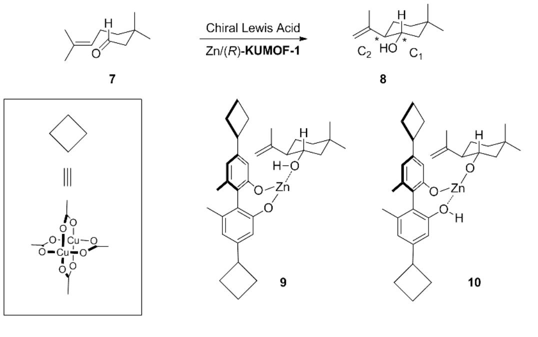


Figure 2. (a) (*R*)-**KUMOF-1**, (b) pyrene-1-carbaldehyde, **6**, (c) preparation of Zn/(*R*)-**KUMOF-1**, (d) incubation of (*R*)-**KUMOF-1** with **6**, (e) incubation of Zn/(*R*)-**KUMOF-1** with **6**

With this information in hand, it was envisioned that, if a stoichiometric reaction in which the product remained at the location where it was formed is employed, it may be possible to correlate the contribution of the product at each location to the optical purity of the overall product. In this regard, a stoichiometric enantioselective carbonyl-ene reaction of **7**, promoted by Zn/(*R*)-**KUMOF-1**, was chosen (Scheme 2, See ESI).[2,5] This benchmark stoichiometric reaction would allow us to identify the origin of each product because, after the reaction, the product, **9** or **10**, would remain in the position at which the reaction had taken place(Scheme 2). First, four identical reactions were set up; each was charged with **7** (15 mg, 0.089 mmol) and Zn/(*R*)-**KUMOF-1** (102 mg, 0.27 mmol, 3 equiv of active sites to the substrate)† in CH_2Cl_2 (0.1 mL) and the reaction was then performed with mild shaking to allow the catalyst crystals to remain intact. The reactions were quenched after different time intervals by filtration of the crystals from the reaction mixture. Then the crystals were dismantled by treatment with aqueous acidic solution (6 *N* HCl) and the resultant products were harvested as described previously.[2,5,6]

With a shorter reaction time the optical purity of the product would be expected to primarily reflect the anisotropic chiral environment, since most substrates were trapped only in the cavities on the shallow layer of the crystals. As the reaction time is extended, more substrate could penetrate deeper to find free reaction sites. Thus, more products would be obtained from the isotropic environment and would contribute to the optical purity of the overall product (Table 1). The products obtained from the reaction quenched after 1 h, at which most of the unreacted starting materials remained in the solution, afforded **8** in 11% yield, but its optical purity was approximately zero. From the second reaction vessel, quenched after 2 h, **8** was obtained in 30 % yield with a marginal, but significant, stereoselectivity (10 % ee). The third reaction, quenched after 3.5 h, provided **8** in 62 % yield with a further improved optical purity of 24 % ee. Finally, the reaction mixture was allowed to react to completion over 12 h. The chemical yield and optical purity of the overall product was improved to 92 % and 50 % ee, respectively.



Scheme 2. Carbonyl-ene reaction mediated by Zn/(*R*)-**KUMOF-1**

Table 1. Optical purity dependency on the degree of reaction progress

entry	*t* (h)	yield (%)[a]	Ee (%)[b]
1	1	11	0
2	2	30	10
3	3.5	62	24
4	12	92	50

a. Reaction condition; All the reactions were carried out at 0°C in dichloromethane using 3 equivalent Zn/(*R*)-**KUMOF-1**. b. Absolute configuration of the major isomer is ($S(C_1)$, $R(C2)$).

Table 2. Optical purity dependency on the substrate amount

entry	Eq of 7	*t* (h)	yield (%)	Ee (%)
1	0.033	12	91	0
2	0.067	12	90	17
3	0.33	12	89	50

a. Reaction condition; All the reactions were carried out at 0°C in dichloromethane. b. Absolute configuration of the major isomer is ($S(C_1)$, $R(C2)$).

It is noteworthy that the optical purity of the overall product linearly increased with increasing reaction time and that the absolute configuration of the major product is ($S(C_1)$, $R(C_2)$), which remained the same. These points can be accounted for as follows: the optical purity of the overall product improved significantly with the increasing ratio of product obtained from the internal cavities, which are likely to act as homogeneous catalysts due to their chiral environment. Nonetheless, a general conclusion cannot be made on which location provides the better chiral environment, although in this case isotropic chiral bias provides the better chiral environment.

A set of reactions with different amounts of substrate was performed (see ESI).[7] Each reaction vessel was charged with the same amount of the MOF-based catalyst,† and with 0.033, 0.067, and 0.33 equiv of substrate, respectively. All the reactions were allowed to proceed to completion and the crystals were then treated as usual (Table 2). The optical purity of the overall product dramatically improved as the amount of substrate increased to afford 0, 17, and 50% ee with 0.033, 0.067, and 0.33 equiv of **7**, respectively. Once again, as the

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amount of substrate increased, the share of product obtained from the interior increased.

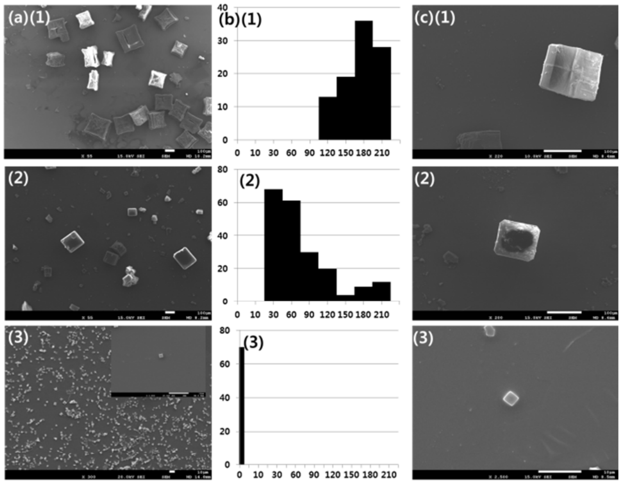

Figure 3. SEM images of various crystals (a) (1) (*R*)-**KUMOF-1**(1); after collection by filtration of (*R*)-**KUMOF-1**(2) through the glass filter (50 μm) (2) (*R*)-**KUMOF-1**(2); as synthesized by solvothermal method, (3) (*R*)-**KUMOF-1**(3); as synthesized in microwave reactor, (b) Distibution of crystal size in a given batch (1) (*R*)-**KUMOF-1**(1), (2) (*R*)-**KUMOF-1**(2), (3) (*R*)-**KUMOF-1**(3), (c) SEM images of crystals recovered after the reaction; (1) (*R*)-**KUMOF-1**(1), (2) (*R*)-**KUMOF-1**(2), (3) (*R*)-**KUMOF-1**(3).

Table 3. The carbonyl-ene reaction of 7 with MOF-based reagents bearing various crystal size.

	8		
	t (h)	yield^a (%)	ee (%)
Zn/(*R*)-**KUMOF-1**(1)	12	92	70
Zn/(*R*)-**KUMOF-1**(2)	12	89	50
Zn/(*R*)-**KUMOF-1**(3)	12	91	0

a.Reaction condition; All the reactions were carried out at 0°C in dichloromethane using 3 equivalent of Zn/(*R*)-**KUMOF-1**. b. Absolute configuration of the major isomer is (*S*(C_1), *R*(C2)).

Subsequently, we attempted to examine the influence of the crystal size. Since the ratio of surface area to total volume is inversely proportional to the crystal size, the contribution of the product obtained from the surface to the overall optical purity would become more substantial as the crystal size decreased. If the reaction was catalytic and progressed primarily on the surface, it is expected that the increasing surface area would increase the reaction rate – i.e. a higher reaction rate would be observed as the surface area increased by reducing the crystal size. In addition, the products obtained from the anisotropic environment would be dominant and would determine the optical purity of overall product.

Three batches of crystals according to the crystal size were prepared (see supporting information). (*R*)-**KUMOF-1** crystals used in the previous studies as synthesized from the conventional solvothermal method, designated as (*R*)-**KUMOF-1**(2),† had crystal size ranging from 10 μm to a few hundred μm. (*R*)-**KUMOF-1**(1), consisted of crystals larger than 50 μm on side, was collected from (*R*)-**KUMOF-1**(2) by filtration through glass filter (50 μm) (Fig. S1). Meantime, the micron size crystals, denoted as (*R*)-**KUMOF-1**(3), whose size is uniformly in a few μm range, were synthesized with an aid of microwave reactor.[7] All kinds of crystals were confirmed to be identical, except the size (Figure S2 - S4), by XRD, SEM, TGA etc.

Since it is important that the shape of the catalyst crystals remains unaffected during the reaction, the reactions were carried out by mild shaking and then the shape of the crystals were re-examined before and after the reaction. As shown in Figure 3c, the cubic shape of the crystals persisted even after prolonged shaking, albeit not perfect. All three forms of crystal promoted the reaction with unremarkable activity and the difference in reaction rate was not noticeable either; the reactions were complete in 12 h to provide **8** in 90% yield by Zn/(*R*)-**KUMOF-1**(1), 88% yield by (2), and 90 % by (3), respectively (Table 3). However, as expected, the optical purity of the product dramatically increased as the crystal size increased, 70% ee by (1), 50 %ee by (2), and 0 %ee by (3). In other words, as more of the reaction takes place internally, where the chiral bias is isotropic or pseudoisotropic, the optical purity of the overall product improved considerably.

Although the chiral metal-organic frameworks are considered as a useful platform of heterogeneous catalyst for the enantioselective chemical transformation, it seems to be overlooked that the chiral MOF is merely an ensemble of cavities bearing diverse chiral environments. Since the chiral environment of cavities is not uniform and varies according to their location; e.g. that of surface is anisotropic whereas that of the inside isotropic, the exact location of the reaction would be critical to the overall optical purity of the product. The previous catalytic reactions exhibiting high enantioselectivity might happen to be the very special where even the cavities on surface have sufficient chiral bias to discriminate efficiently. In general, the reaction must be manipulated to limit the reaction sites only on the uniform chiral environment to obtain the consistent result. However, this task can hardly be done.

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6. Details are described in the reference 2. As the reaction progressed and even after complete disappearance of **7**, product **8** did not appear in the solution; eventually, neither **7** nor **8** were detected on TLC. This indicated that the product **8** was entrapped somehow in Zn/(*S*)-**KUMOF-1**, and therefore, **8** could be released from the crystals only after catalyst crystals were dismantled by a treatment with an aqueous HCl (6 *N*) solution. It was suggested that **8** was bound to the Zn ion centers in the MOF even after the chemical transformation was completed, lingering there and thus blocking another catalytic cycle, since the product **8** has alcohol group, and their coordinating ability to zinc ion is presumably much stronger than the carbonyl of **7**,. This explains the need for more than a stoichiometric amount of the catalyst for completing the transformation with reasonable enantioselectivity to determine the stereoselectivity depending on the locatrion of reaction sites.
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