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# Identification of Reaction Sites on Metal-Organic Framework-Based Asymmetric Catalysts for Carbonyl-Ene Reactions

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## Abstract

The characteristics of catalytic sites in metal-organic framework (MOF)-based catalysts could be approximately classified by their location, i.e., the inside of the pore and/or on the surface of the crystal. This classification of catalytic sites in a single MOF crystal has been widely overlooked. Particularly, in a chiral MOF, the environment of any specific reaction site will vary depending on its location. Thus, pin-pointing the reaction site for a MOF-based heterogeneous catalyst is an intriguing issue. In this study, the active site of a MOF-based catalyst is revealed after a thorough investigation comparing substrate size versus reaction rate for two distinct mechanisms of carbonyl-ene reactions.

Both Zn-mediated stoichiometric carbonyl-ene reactions and Ti-catalyzed carbonyl-ene reactions were performed separately and compared using homogeneous and heterogeneous media. These results could provide a clear answer to the question of locating the reaction sites within the MOF. Through this work, it became evident that the entire MOF crystal is effective, however, the inside of the pore is an important contributor to having chirality control in the stoichiometric reaction. In addition, for a catalytic reaction, our findings suggest that the substrate size is mostly irrelevant as catalysis can simply take place on the surface of the crystals. Thus, the comparison of the reaction rate and substrate size may not be a valid method to ascertain whether a reaction occurs inside the MOF or on its surface. This conclusion is further supported by the effect of particle size on the reaction efficiency and the enantioselectivity along with visualization of the guest-accessible space using two-photon fluorescence microscopy.

KEYWORDS Heterogeneous catalysts; Metal-organic frameworks; Carbonyl-ene reaction; Twophoton fluorescence microscopy; Size selectivity; Enantiomeric excess

## Introduction

Metal-organic frameworks (MOFs), also known as porous coordination polymers (PCPs), have been at the forefront of research during the last decade as a new type of porous material for storage, separation, and catalytic applications. Because MOFs provide tunable, three-

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dimensional architectures that are ideal for controlling the environment of a catalyst, a significant amount of work has been done in the area of enantioselective catalytic reactions using chiral MOFs.<sup>1–19</sup> However, the identity of the reaction sites in MOF-based catalysts is still under debate.

Thiele observed that if the reaction rate is faster than the diffusion rate, then diffusion forces push the product away from the reaction sites on the surface in porous material-based catalysts.<sup>20</sup> Thus, only the surface of the heterogeneous catalyst would be involved in the reactions. In discussions concerning MOF-based catalysts, this point has been widely overlooked, although a few reports dealing with this subject have appeared in the literature.<sup>21–23</sup>

The localization of reactions on the surface of a porous material poses a serious challenge to the legitimacy of the MOF-catalyst approach. The legitimacy is related to a question regarding the real advantages of using MOF-based catalysts in place of conventional heterogeneous catalysts that are typically obtained by the immobilization of discrete catalytic species on a solid support.<sup>24</sup> Recently, two-dimensional metal-organic materials (e.g., metal-organic nanosheets) have been used as heterogeneous catalytic platforms with full surface utilization and reduced diffusion issues.<sup>25–28</sup> Another issue related to the identification of reaction sites is more critical if the catalysis considers enantioselective reactions. Because the chiral environment of each cavity varies according to its location in the MOF crystal, the overall stereoselectivity of the reaction will greatly depend on the location where the reaction occurs.<sup>29</sup>

Furthermore, the role of the cavity size in porous materials and the resultant discrimination of substrates by their size, which is a frequently cited advantage of MOF-based catalysis, have been overemphasized.<sup>24</sup> A significant number of previous reports have used open framework structures after introducing a bulkier catalytic species to promote the reaction.<sup>2,9,12</sup> This

introduction of the catalytic species substantially reduces the void space in the crystals, and as a result, the composite becomes unable to accommodate the entire substrate within its crystal. Thus, the benefit of using MOFs to discriminate between different substrates by the cavity size should be scrutinized.

In response to this issue, researchers have attempted to provide support for the notion that reactions occur inside the crystals by comparing the reaction rates of different substrate sizes. The presence of a threshold point (i.e., the reaction rate sharply decreases as the substrate size increases) has been considered to be strong evidence of reactions occurring inside the MOF channels. However, if the reactions are catalytic, then this argument has limitations. Furthermore, the argument is inappropriate in many cases because the threshold point often exceeds the cavity size. As is clearly seen in some reports,<sup>9,12</sup> substrates apparently larger than the cavities or channels in the MOFs were easily converted into their corresponding products. Such substrates underwent the reaction provided that the reacting functionality of the substrate could make contact with a catalytic site on the surface of the crystals.<sup>20</sup> In other words, the substrates did not necessarily diffuse into the interior of the MOF crystal to undergo catalysis. Therefore, the cavity size was not directly related to the threshold point.

The identification of reaction sites in MOF catalysts for a given reaction is foundational and important. The Lewis-acid-promoted carbonyl-ene reaction of 3-methylgeranial and its congeners (1) to produce cyclic terpenoid analogs (2) was chosen as a reference reaction (Figure 1). This reaction can be facilitated either stoichiometrically with a reagent (e.g., Zn/(S)-KUMOF-1, KUMOF = Korea University MOF) or catalytically with a catalyst (e.g., Ti/(S)-KUMOF-1). Both reagents and catalysts have been previously reported for MOF-based

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carbonyl-ene reactions.<sup>6</sup> These two characteristic reactions provide us with a method for identification of the reaction sites based on the nature of the reaction.

The reaction of **1a** (the smallest substrate in the family) employs more than a stoichiometric amount of reagent Zn/(S)-KUMOF and has been previously used to demonstrate that the reaction must utilize all the reaction sites inside the crystal.<sup>6</sup> Further studies using larger substrates have been suggested to determine the threshold point for this stoichiometric reaction. However, this reaction was the only one tested at that time for this system. This determination is more interesting for the catalytic reaction than the previous stoichiometric reaction because this issue is a subject of real concern for the catalytic reaction. With this preface, the present study compared the reaction rate as a function of substrate size using two kinds of MOFs to directly between two distinct reaction mechanisms (Zn/(S)-KUMOF-1 for the stoichiometric reaction and Ti/(S)-KUMOF-1 for the catalytic reaction).<sup>6,30,31</sup>

Two-photon fluorescence microscopy (TPM) has been used to approximately, but decisively, determine and visualize the guest-accessible volume of the channels after the postsynthetic introduction of reaction sites to the MOF (i.e., (*S*)- or (*R*)-**KUMOF-1**, Zn/(S)-**KUMOF-1**, and Ti/(*S*)-**KUMOF-1**) and the substrate diffusion pattern into the modified MOF crystal, which together make it possible to better understand the situation.<sup>2</sup>



Figure 1. Four types of catalytic-enantioselective carbonyl-ene reactions in this study.

## Experimental

## 2.1 General considerations (materials and instrumentation)

All materials were obtained from Aldrich and TCI, and used without further purification, unless otherwise noted. Anhydrous solvents were obtained by distillation over calcium hydride (dichloromethane, toluene) or sodium/benzophenone (Et<sub>2</sub>O, THF). Chromatographic purification of products was accomplished by flash chromatography using Merck silica gel 60 (230-400 mesh) with an appropriate mixture of hexane and ethyl acetate as eluent. Gas chromatography analyses were performed using an Acme 6000 series system equipped with a flame ionization detector (FID). High-performance liquid chromatography was conducted using a Jasco LC-1500 Series HPLC system with an ultraviolet detector at 254 nm.

## 2.2 Preparation of substrates

The synthetic routes to **1a**, **1b**, and **1c** (Scheme S1) along with all relevant experimental details are given in the supplementary information.

## 2.3 Preparation of MOF catalysts

2.3.1 Preparation of (S)-KUMOF-1: A reaction mixture in a small vial (4 mL) was prepared by dissolving Cu(NO<sub>3</sub>)<sub>2</sub>·3H<sub>2</sub>O (7.2 mg, 0.030 mmol) and (S)-2,2'-dihydroxy-6,6'-dimethyl-[1,1'biphenyl]-4,4'-dicarboxylic acid (9 mg, 0.030 mmol)<sup>6</sup> in *N*,*N*-diethylformamide (DEF)/MeOH (1.5 mL/1.5 mL). This vial was sealed with a perforated cap and placed in a larger (20 mL capacity) vial filled with *N*,*N*-dimethylaniline (1.0 mL). The tightly-capped larger vial was placed in an oven at 65 °C for 1 day. Blue cubic crystals were obtained in 35% yield based on the ligand used. The crystals were separated and rinsed with DEF/MeOH (3 mL/3 mL) three times. Characterization and rigorous crystal structure determination of (*S*)-KUMOF-1 were reported in a previous paper.<sup>6</sup>

2.3.2 Preparation of Zn/(S)-KUMOF-1 and confirmation of hydrogen-metal exchange by determination of Zn/Cu ratio: Dimethylzinc (0.4 mL, 2 M in dichloromethane, 0.81 mmol) was added to a suspension of solvent exchanged (S)-KUMOF-1 (102 mg, 0.27 mmol) in dichloromethane (2 mL) at -78 °C, and the solution was shaken for 3 h at this temperature. The supernatant was decanted and the resultant Zn/(S)-KUMOF-1 was washed with cold dichloromethane several times. Inductively coupled plasma atomic emission spectroscopy (ICP-

AES) was performed after complete removal of dichloromethane by drying under vacuum for 1 day (Table 1).

Table 1. Concentration of elements in Zn/(S)-KUMOF-1

Element	amount (ppm (µmol))
Cu	129200 (2033)
Zn	135100 (2066)

2.3.3 Preparation of Ti/(S)-KUMOF-1 and confirmation of hydrogen-metal exchange by determination of Ti/Cu ratio: A mixture of (S)-KUMOF-1 (24 mg, 0.063 mmol) and Ti(O-*i*Pr)<sub>4</sub> (0.2 mL, 1 M in toluene, 0.20 mmol) in toluene (1.5 mL) was shaken for 5 h at 25 °C. The resultant crystals were washed with cold toluene several times. The Ti(IV) loading in Ti/(S)-KUMOF-1 was determined by ICP-AES after complete removal of toluene by drying under vacuum for 1 day (Table 2).

 Table 2. Concentration of elements in Ti/(S)-KUMOF-1

Element	amount (ppm (µmol))
Cu	173000 (2722)
Ti	173600 (3625)

2.4 Assessment of channel size

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2.4.1 Incubation of MOFs with pyrene-1-carbaldehyde (A): MOF crystals (roughly 4 mg) were immersed in a stock solution of A in DMF (1.0 mL of a 0.05 M solution) at room temperature for 2 h (Figure S1).

2.4.2 Measurement of TPM images: The incubated crystals were placed on Paratone-N oil, which was applied to a glass slide prior to placement of crystals, and then the wet crystals were blotted dry with tissue paper. Prior to TPM measurement, suitable crystals (75-100 µm in size) were screened using wide-field fluorescence and white-light transmission microscopes. The spatial distribution of dyes inside the selected MOFs was imaged with a two-photon confocal microscope (Leica TCS SP2) equipped with a femtosecond laser (Chameleon, Coherent Inc.,  $\lambda =$ 750 nm, 200 fs, 10 mW) and an objective lens (NA 0.5, HC PL Fluotar 20x). By carefully adjusting the position of the focal plane, we were able to obtain cross-sectional fluorescence images from the center of the crystals, which reflected the local concentration of dyes. An internal photomultiplier tube (PMT2) was used to collect the signals into 8 bits unsigned 512  $\times$ 512-pixel images at a scan speed of 400 Hz. Compared with the more conventional one-photon fluorescence microscopy technique, two-photon microscopy with a near-infrared light source (750 nm) does not suffer significantly from the attenuation of excitation light, allowing more reliable information on the 2-dimensional distribution of dyes to be obtained. Full images of the dye diffusion patterns with time are displayed in the supporting information (Figures S2-S7).

## 2.5 Carbonyl-ene reaction

2.5.1 General procedure of the homogeneous carbonyl-ene reaction by Zn/(R)-3: A mixture of (*R*)-3 (BINOL, 0.089 mmol) and 1 M ZnEt<sub>2</sub> in hexane (0.27 mL) was stirred at -78 °C for 1 h.

The solution was warmed to 0 °C, and **1** (0.089 mmol) in dichloromethane (1.5 mL) was added. The reaction mixture was stirred for a further 3.5 h at 0 °C, quenched with an aqueous solution of 6 *N* HCl (3 mL), and extracted with dichloromethane (3 mL  $\times$  3). The combined organic layer was washed with sodium bicarbonate (3 mL  $\times$  3) and brine (3 mL  $\times$  3). The organic layer was concentrated under reduced pressure to give the crude product, which was purified by flash chromatography (*n*-hexane/ethyl acetate 19:1) to give **2** as pale-yellow oil.

2.5.2 Preparation of Mosher esters of 4 and ee determination: Compound 2 was treated with (S)-(-)- $\alpha$ -methoxy- $\alpha$ -trifluoromethylphenylacetyl chloride ((S)-(-)-MTPA-Cl) and pyridine in dichloromethane to give its Mosher ester 4 as a diastereomeric mixture that could be subjected to gas chromatography for determining optical purity (Scheme S2).

### 2.5.3 Heterogeneous carbonyl-ene reaction of 1s by Zn/(S)-KUMOF-1

2.5.3.1 Determination of amount of chiral catalyst, (S)-KUMOF-1: The mole number of catalytic sites was calculated based on the assumption that one catalytic site is present in a Cu and (S)-2,2'-dihydroxy-6,6'-dimethyl-[1,1'-biphenyl]-4,4'-dicarboxylic acid ligand pair.

2.5.3.2 General procedure for the carbonyl-ene reaction of 1 by Zn/(S)-KUMOF-1: A solution of 1 (0.089 mmol, in dichloromethane 0.1 mL) was added to a suspension of Zn/(S)-KUMOF-1 (102 mg, 0.27 mmol) in dichloromethane (2 mL) at -78 °C. The reaction mixture was warmed to 0 °C, and stirred for 3.5 h at this temperature. The reaction mixture was then quenched with an aqueous solution of 6 *N* HCl (3 mL) and the resultant mixture was filtered through Celite. The

filtrate was concentrated *in vacuo* and the residue was purified by flash chromatography (*n*-hexane/ethyl acetate 5:1) to give **2** as a pale-yellow oil. The enantiomeric excess (ee) of **2** was determined as the de of **4** after transformation of **2** to **4** as previously described (Figures S8-S11). **2a** was obtained in 92% yield in 3.5 h at 0 °C. The diastereomeric ratio of the MTPA esters of **2a** was measured to be 75:25 (50% ee). **2b** was obtained in 52% yield in 3.5 h at 0 °C. The diastereomeric ratio of the MTPA esters of **2b** was measured to be 52.5:47.5 (5% ee).

2.5.4 General procedure for the homogeneous carbonyl-ene reaction by Ti/(R)-3: A mixture of (R)-3 (BINOL, 0.015 mmol) and 1 M Ti(O-iPr)<sub>4</sub> in dichloromethane (15  $\mu$ L) was stirred at room temperature for 1 h. The red-brown mixture was cooled to 0 °C, and 1 (0.3 mmol) in dichloromethane (1.5 mL) was added. The reaction mixture was stirred for 12 h at this temperature. The resulting solution was filtered through a pad of Celite and the filtrate was extracted with dichloromethane (3 mL × 3) and washed with sodium bicarbonate (3 mL × 3). The extract was evaporated under reduced pressure to give the crude product, which was purified by flash chromatography (*n*-hexane/ethyl acetate 19:1) to give 2. The ee of 2 was determined as the de of 4 after the transformation of 2 to 4. 2a was obtained in 90% yield. The diastereomeric ratio of the MTPA esters (4a) of 2a was measured to be 70.5:29.5 (41% ee). 2b was obtained in 92% yield. The diastereomeric ratio of the MTPA esters (4c) of 2c was measured to be 60:40 (20% ee).

2.5.5 General procedure for the carbonyl-ene reaction of 1 by Ti/(S)-KUMOF-1: A solution of
1 (0.29 mmol, in dichloromethane, 0.1 mL) was added to a suspension of Ti/(S)-KUMOF-1 (12

mg, 0.029 mmol) in dichloromethane (1 mL) at 0 °C. The reaction mixture was shaken for 36 h at this temperature, then the supernatant was collected and the resultant crystalline materials were washed with dichloromethane. Collection of the supernatant was repeated twice. The combined organic layer was concentrated *in vacuo* and the residue was purified by flash chromatography (*n*-hexane/ethyl acetate 5:1) to give **2**. The ee of **2** was determined as the de of **4** after the transformation of **2** to **4** (Figures S8-S11). **2a** was obtained in 85% yield. The diastereomeric ratio of the MTPA esters (**4a**) of **2a** was measured to be 61.5:38.5 (24% ee). **2b** was measured to be 53.5:46.5 (7% ee). **2c** was obtained in 83% yield. The diastereomeric ratio of the MTPA esters (**4c**) of **2c** was measured to be 50:50 (0% ee).

2.5.6 Carbonyl-ene reaction of 1d by Zn/(S)-KUMOF-1: To a suspension of (S)-KUMOF-1 (102 mg, 0.27 mmol) in toluene (2 mL), dimethylzinc (0.4 mL, 2 M in dichloromethane, 0.80 mmol) was added at 0 °C. The resultant mixture was shaken for 3 h at this temperature. Compound 1d (25 mg, 0.089 mmol) in toluene (0.1 mL) was added to this mixture at -78 °C (for the preparation of compound 1d, see Supporting Information, Scheme S3). The reaction mixture was warmed to 0 °C and shaken for 36 h at this temperature, and then quenched with an aqueous solution of 6 *N* HCl (3 mL). The resultant mixture was filtered through Celite. The filtrate was concentrated *in vacuo* and the residue was purified by flash chromatography (*n*-hexane/ethyl acetate 1:1) to give 2d (13.8 mg, 9% yield, Scheme S4). The ee was determined as 0% by HPLC (Figure S13 and Table S1)

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2.5.7 Carbonyl-ene Reaction of 1d by Ti/(S)-KUMOF-1: A mixture of (S)-KUMOF-1 (24 mg, 0.063 mmol) and Ti(O-*i*Pr)<sub>4</sub> (0.3 mL, 1.0 M in dichloromethane 0.3 mmol) in toluene (1.5 mL) was shaken for 10 h at 25 °C. The Ti/(S)-KUMOF-1 was collected by centrifugation and washed five times with dichloromethane (1.5 mL). To the Ti/(S)-KUMOF-1 (12 mg, 0.029 mmol) in toluene (1 mL) 1d (78 mg, 0.29 mmol) in toluene (0.1 mL) was added at 0 °C. The reaction mixture was shaken for 36 h at this temperature. The supernatant was then collected and the resultant crystalline materials were washed with ethyl acetate. The collection of the supernatant was repeated two more times. The combined organic layer was concentrated *in vacuo* and the residue was purified by flash chromatography (*n*-hexane/ethyl acetate 1:1) to give 2d (56 mg, 72% yield, Scheme S4). The ee of 2d was determined to be 0% by HPLC (Figure S14 and Table S2).

## **Results and Discussion**

3.1 A stoichiometric and homogeneous carbonyl-ene reaction of 1 by Zn catalysts (Lewis cat I, Zn/(R)-3)

A homogeneous reaction requiring an excess of Lewis acids (up to 6 equiv.) was first studied to understand the reactivity and nature of the catalyst. This enantioselective carbonyl-ene reaction was promoted by Zn/(R)-3, which was obtained by mixing (*R*)-binol 3 and dimethylzinc. This reaction was initially considered to be catalytic; however, more than the stoichiometric amount of Lewis acid was required to obtain acceptable results.<sup>30,31</sup> Even with a stoichiometric amount of the reagent, the reaction often stops halfway to completion (77% yield with a 1.5 equiv. of Zn/(R)–3), and the stereoselectivity is unsatisfactory (52% ee with 1.5 equiv. of Zn/(R)–3). Six equivalents of Zn/(R)–3 are necessary to achieve both good yields (87%) and high stereoselectivity (85% ee) of **2a** (Table 3).

The rationale for a large excess of the Zn reagent to obtain higher yields and stereoselectivity is as follows: It suggests that the alkoxy group of product **2** binds to the Zn(II) center after the chemical transformation is complete because the alkoxy group binds better to metals than a carbonyl group (**I**, **II**, and **III** in Scheme S5). This newly formed Zn alkoxide **III** can also act as a catalyst and can compete with Zn/(*R*)-**3** for the next reaction. The catalytic cycle by **III** produces **2** with significantly lower stereoselectivity (Scheme S5). The use of excess Zn/(*R*)-**3** alleviates this unfavorable competition (**IV** and **V** in Scheme S5). The presence of a substantial excess of Zn/(*R*)-**3** increases the chance of reaction with the preferred catalyst. Thus, the requirement of a large excess of Zn/(*R*)-**3** for this carbonyl-ene reaction is due to minimizing suicide inhibition; a distinct weakness of this reaction system from a pragmatic point of view (Scheme S5). As mentioned earlier, this setup (i.e., the requirement of excessive reagent) has been previously used to support the assertion that all the cavities in the MOF catalyst are reaction sites.<sup>6</sup>

Table 3. Dependence of the reaction efficiency on the amount of reagent used



1	0.2	2	20	10
2	1.5	2	77	52
3	3	1	86	80
4	6	1	87	85

<sup>*a*</sup>The ee of 2a was determined as the dextrose equivalent (de) of its corresponding 4a for practical reasons

Next, we investigated the reaction efficiency in terms of the substrate size in homogeneous reactions with an excess of Zn/(R)-3. All the tested substrates (1a - 1c) afforded their corresponding products 2 in 1 h with equally high yields and stereoselectivities, regardless of the substituent size: 87% (82% ee) for 2a, 82% (88% ee) for 2b, and 85% (87% ee) for 2c (Table 4). There is no significant difference in the reaction rate depending on the substrate size for the stoichiometric-homogeneous reaction (Lewis Acid Cat I in Figure 1).

**Table 4**. Enantioselective carbonyl-ene reaction of 1 by Zn/(R)-3



<sup>*a*</sup>The ee of **2** was determined as the de of its corresponding **4**.

3.2 A stoichiometric and heterogeneous carbonyl-ene reaction of 1 by Zn catalysts (Lewis cat II, Zn/(S)-KUMOF-1)

To explore the corresponding heterogeneous enantioselective carbonyl-ene reaction using MOF-based catalysts, (*S*)-**KUMOF-1** was selected as a platform. This platform was obtained from coordination between (*S*)-2,2'-dihydroxy-6,6'-dimethyl-[1,1'-biphenyl]-4,4'-dicarboxylic acid and Cu(II). (*S*)-**KUMOF-1** has a NbO-type network topology with a noninterpenetrating framework.<sup>6</sup> The void space of (*S*)-**KUMOF-1** is substantial; the diagonal interatomic distances between the three sets of opposite water oxygen atoms on Cu(II) of the secondary binding unit are 23.16 Å; therefore, an imaginary  $2 \times 2 \times 2$  nm<sup>3</sup> cube can exist within the van der Waals surfaces of the coordinating water molecules (Figure S5). This is one of the largest void spaces available among the known chiral MOFs. (*S*)-**KUMOF-1** also provides a large hexagonal channel with a free aperture diameter of 1.69 nm along the [111] direction.<sup>6</sup>

Zn/(S)-KUMOF-1 was prepared by treating (*S*)-KUMOF-1 with dimethyl zinc, as previously described. The identity of Zn/(S)-KUMOF-1 was confirmed with various spectroscopic techniques.<sup>6</sup> Particularly, the 1.01 Zn/Cu ratio was measured by ICP-AES (Table 1), which suggests a stoichiometric exchange of the phenolic protons in the MOF ligand with Zn(II) ions.

Next, the guest-accessible volume of MOFs after modification (i.e., Zn-metalation) was evaluated by two-photon fluorescence confocal microscopy.<sup>32</sup> Pyrene-1-carbaldehyde (**A**) was employed as a reference dye to assess whether the MOF can accommodate the dye in the channels (Table S3) because its size ( $10.4 \times 8.2 \times 2.8 \text{ Å}^3$ ) is comparable to that of products **2a** ( $7.8 \times 6.0 \times 5.2 \text{ Å}^3$ ) and **2b** ( $13.5 \times 6.3 \times 6.0 \text{ Å}^3$ ) (Table S4). The diffusion rates of the dye into (*S*)-**KUMOF-1** and Zn/(*S*)-**KUMOF-1** crystals were approximately determined by monitoring

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the intensity of dye-dependent fluorescence from the crystals at regular intervals. As illustrated in Figure S5(d), the dye gradually diffuses into (*S*)-**KUMOF-1** with increasing incubation time, and the crystals are uniformly saturated with dye after 2 h. Bright fluorescence is detected uniformly at the center of the Zn/(*S*)-**KUMOF-1** crystal after incubation with dye for 2 h (Figure S5(e)). This comparison clearly suggests that there is still plenty of room in Zn/(*S*)-**KUMOF-1** for the diffusion of guest molecules. The amount of dye entrapped by Zn/(*S*)-**KUMOF-1** was determined to be 325 mg/g (dye/MOF), which is slightly lower than the amount trapped by free (*S*)-**KUMOF-1** (575 mg/g, dye/MOF). The localization of dye near the surface of Zn/(*S*)-**KUMOF-1** is apparent, whereas the distribution of dye is uniform in pristine (*S*)-**KUMOF-1**. This observation may be explained by the stronger binding of the carbonyl compound dye **A** to Zn(II) in Zn/(*S*)-**KUMOF-1**. Further diffusion of the dye is significantly inhibited by the presence of previously bound dye molecules. Finally, the aperture diameter of the channel after the introduction of Zn(II) is calculated to be 11.97 Å (Figure S5(f)), which is still adequate for the access of substrates.

Carbonyl-ene reactions of **1** with heterogeneous reagents (or catalysts) were investigated (Table 5). While untreated, pristine (*S*)-**KUMOF-1** does not initiate the reaction;<sup>6</sup> **1a** (0.045 M) satisfactorily undergoes the reaction in the presence of Zn/(S)-**KUMOF-1**, giving product **2a** with a 92% yield with 50% ee. However, at least 3 equiv. of reagent is required for a complete reaction.<sup>6</sup> Notably, as the reaction progresses, and even after the complete disappearance of **1a** from the solution, product **2a** is not detected in the solution. Eventually, neither **1a** nor **2a** are detected in the reaction mixture. Product **2a** is obtained only after dismantling the MOF crystals by treating them with aqueous HCl (6 *N*) solution. This finding suggests that product **2a** is completely entrapped in the MOF pores and remains there during the reaction. Due to the

necessary destruction of the Zn/(S)-KUMOF-1 crystal for reactivity and selectivity characterization, no recycling test was attempted for the heterogeneous-stoichiometric reactions. Although the carbonyl-ene reaction could occur on the surface of MOF crystals, we believe the portion of the reaction that occurred in that manner is not significant because the yield for the substrate decreases with increasing substrate size. Additionally, the largest substrate 1c showed almost no conversion until 20 h after reaction (Table 5). Because an approximate calculation indicates that the surface/volume ratio is far lower than 1% (Table S5), it is safe to speculate that the MOF crystals accommodate all the substrates as some form of the product.

Table 5.	Enantiose	lective c	carbonyl	-ene reac	tion o	f 1	by Zn	(S)	-KUN	<b>MO</b>	F-1
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	R Zn/(S)- <b>KUMO</b> CH <sub>2</sub> Cl <sub>2</sub> , 0 °(		H R	a; R = H b; R = 32 c; R = 32 c; R = 32
entry	substrate	t (h)	yield (	$(\%)$ ee $(\%)^a$
1	1a	3.5	92	50
2	1b	3.5	52	5
3	1c	20	NR <sup>b</sup>	NA <sup>c</sup>

<sup>*a*</sup>The ee of **2** was determined as the de of its corresponding **4**; <sup>*b*</sup>NR: no reaction, under the detection limit; <sup>*c*</sup>NA: not applicable.

There is a distinct difference in the reaction rate as the substrate size increases. The reaction of **1b** is halted halfway, even with a prolonged reaction time (3.5 h), giving rise to **2b** with a 52% yield and a negligible stereoselectivity (5%). Furthermore, **1c** does not react at all. The presence of **2a** in the catalytic site would naturally reduce the free passage of new substrates. However, the blockage caused by the presence of **2a** is still passable by smaller **1a** molecules (Scheme

1(a)) due to the relatively small size of **2a** ( $7.8 \times 6.0 \times 5.2$  Å<sup>3</sup>) compared to **1a**. As the substrate size increases, the blockage becomes more significant. The free space in the channels is significantly reduced, and the incoming substrates are too large to penetrate the smaller channels. Thus, there is considerable difficulty for the incoming substrates to penetrate and diffuse into the MOF to reach the free catalytic sites. Although **1b** and **2b** are larger than **1a** and **2a**, **2b** is not sufficiently large to obstruct the whole channel (Scheme 1(b)). Thus, the reaction of **1b** ( $13.5 \times 6.3 \times 6.0$  Å<sup>3</sup>) gives **2b** in 52% yield, but the stereoselectivity of **2b** was substantially diminished to 5% ee. However, **1c** is completely resistant to the reaction under the same conditions. Once a very small amount of **2c** ( $17.8 \times 6.7 \times 6.5$  Å<sup>3</sup>) forms and remains at the metal centers on the surface, it completely covers the channels and prevents further reaction between the remaining substrate **1c** and catalytic sites located inside the MOF (Table 5 and Scheme 1(c)). This reaction is supposed to utilize all the reaction sites; therefore, once a reaction site on the surface of the MOF participates in the reaction, it substantially blocks the channel and exhibits a clear discrimination of the substrates by their size by preventing access to available catalytic sites.

Scheme 1. Diagrams illustrating the blockage of channels by the products. Molecules in green are products bound to the metal center, and molecules in pink are substrates to be reacted. For the reaction by Zn/(S)-KUMOF-1, (a) 1a can penetrate into the MOF without significant obstruction by 2a. (b) 1b is blocked by the presence of 2b in the channel but still manages to diffuse into the MOF. (c) Access of 1c is completely blocked because of the initially formed 2c, which covers the whole channel and blocks it completely



From a previous study and the results mentioned above, it is evident that the chiral environment of catalytic sites on the surface is not as effective as those inside the crystals in terms of enantioselectivity.<sup>29</sup> The effect of particle size on the reaction efficiency and stereoselectivity was investigated to verify the reaction sites in the stoichiometric-heterogeneous Zn/(S)-KUMOF-1 case. Three different sizes of Zn/(S)-KUMOF-1 were prepared; Zn/(S)-**KUMOF-1-**(L) with a particle size of >100  $\mu$ m, Zn/(S)-**KUMOF-1-**(M) with a particle size of >20  $\mu$ m, and Zn/(S)-KUMOF-1-(S) with a particle size of <1  $\mu$ m. We hypothesized that a larger particle utilizes more of the inside catalytic sites for the carbonyl-ene reaction and will display higher stereoselectivity than a small particle. Under the same reaction conditions by catalyst loading (by weight), Zn/(S)-KUMOF-1-(S) has more surface catalytic sites than Zn/(S)-**KUMOF-1-**(M) or Zn/(S)-**KUMOF-1-**(L) and we expected a proportionate difference in ee. While the reaction efficiency was almost identical for all three cases, the ee value dramatically decreased with particle size (Table 6).<sup>29</sup> This particle size control experiment clearly demonstrates again the identification of reaction sites (inside of the pore) of the enantioselective, stoichiometric-heterogeneous Zn/(S)-KUMOF-1 (Lewis Acid Cat II in Figure 1).

**Table 6.** Particle size effect on the carbonyl-ene reaction of 1 by Zn/(S)-KUMOF-1



<sup>*a*</sup>The ee of **2** was determined as the de of its corresponding **4**.

3.3 A catalytic and homogeneous carbonyl-ene reaction of 1 by Ti catalysts (Lewis cat III, Ti/(R)-3)

In parallel with the above study, a truly catalytic carbonyl-ene reaction by Ti/(S)-KUMOF-1 was studied, which represents the case where the reaction could take place entirely on the surface of the crystal. First, a catalytic-homogeneous version of the carbonyl-ene reaction was performed (Table 7). The enantioselective carbonyl-ene reaction of 1 by Ti/(R)-3 proceeds uneventfully, even though the stereoselectivities are uniformly lower than those from the reaction by Zn/(R)-3 (Tables 4 and 7).

As shown by the results summarized in Table 7, the reaction of all the substrates proceeds smoothly, regardless of the substrate size. **1a** provides **2a** in high yield (90%) and somewhat lower stereoselectivity (41% ee). **1b** and **1c** give rise to **2b** in 92% yield with a 43% ee and **2c** in 86% yield with a 20% ee, respectively (Table 7). There is no considerable discrimination by substrate size in terms of the reaction efficiency.

Table 7. Enantioselective carbonyl-ene reaction catalyzed by Ti/(R)-3

	$\begin{array}{c} \text{Ti}(R)-3\\ \hline \text{CH}_2\text{Cl}_2, 0 \ ^{\circ}\text{C}\\ 12 \text{ h} \end{array}$	PH OH 2	a; R = H b; R = 52 c; R = 52
entry	substrate	yield (%	$(6)$ ee $(\%)^a$
1	1a	90	41
2	1b	92	43
3	1 <b>c</b>	86	20

<sup>*a*</sup>The ee of **2** was determined as the de of its corresponding **4**.

3.4 A catalytic and heterogeneous carbonyl-ene reaction of **1** by Ti catalysts (Lewis cat IV, Ti/(S)-**KUMOF-1**)

Ti/(*S*)-**KUMOF-1** was prepared by mixing pristine (*S*)-**KUMOF-1** with excess Ti(O-*i*Pr)<sub>4</sub>, as previously described.<sup>6</sup> This catalyst exhibited somewhat different characteristics from Zn/(*S*)-**KUMOF-1**. The Ti/Cu ratio of Ti/(*S*)-**KUMOF-1** was measured to be 1.30-1.80 by ICP-AES (Table 2), even after extensive washings. The ratio is constantly slightly higher than the expected value of 1.0, which indicates that a substantial amount of free Ti(O-*i*Pr)<sub>4</sub> is tightly entrapped.

The amount of entrapped dye in the TPM experiment with Ti/(S)-KUMOF-1 is determined to be 60 mg/g (dye/MOF), which is substantially lower than in the case with Zn/(S)-KUMOF-1. In addition, most of the entrapped dye is localized on the surface of the MOF crystal and more visibly than in the case of Zn/(S)-KUMOF-1, as shown in the TPM image (Figure S7(b)). These observations suggest that the titanium species ( $Ti(O-iPr)_2$ ) attached to the frame occupies or blocks a considerable portion of the channels and significantly inhibits the diffusion of other dye molecules. Additionally, it is possible that a substantial amount of extra  $Ti(O-iPr)_4$  fills the cavity

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inside the MOF, probably as a dimeric titanium species, and remains there. Considering these effects, it is apparent that there is little room for the guest substrates inside the MOF, indicating the plugging of the channel and explaining the difficulty in the penetration of the substrate into the center of the crystal.<sup>32</sup> The aperture of the channel of Ti/(*S*)-**KUMOF-1** is calculated to be 5.73 Å (Figure S7(c)), providing little chance for any substrate to penetrate into the channels; even the smallest **1a**. Thus, the entrapped titanium species would most likely not be involved in the catalytic cycle of the carbonyl-ene reaction, and the pores are blocked, ensuring that only surface catalysis is occurring.

Nonetheless, in contrast to the case with Zn/(S)-KUMOF-1, all reactions with 1a - 1c proceeded smoothly to give the corresponding products 2a - 2c. There is no difference in the reaction efficiency with different substrate sizes under the reaction conditions when using Ti/(S)-KUMOF-1, although the reactions require a prolonged reaction time for completion (36 h). The results of the heterogeneous catalytic reactions are summarized in Table 8. All the tested substrates (1a - 1c) smoothly undergo the reaction to afford the corresponding products. In contrast to Zn/(S)-KUMOF-1, there is no substrate discrimination. 1a is transformed into 2a with an 85% yield and a 24% ee, 1b is transformed into 2b with an 89% yield and a 7% ee, and 1c is transformed into 2c with an 83% yield and a negligible stereoselectivity (~0% ee) (Table 8).





entry	substrate	product obtained from solution		product obtai	ned from MOF
		yield (%)	ee (%) <sup>a</sup>	yield (%)	ee (%)
1	1a	85	24	2.8	NA <sup>b</sup>
2	1b	89	7	0.7	$NA^b$
3	1c	83	0	0.2	$NA^b$

<sup>*a*</sup>The ee of **2** was determined as the de of its corresponding **4**; <sup>*b*</sup>NA: not applicable.

These results have many interesting implications. First, all the reacting substrates do not necessarily penetrate the crystal to be reacted. In other words, all the reactions take place only on the surface of the crystals, rather than inside the crystals. Contrary to the case with Zn/(S)-**KUMOF-1**, the products obtained at the catalytic site leave the site immediately after the completion of the transformation. The catalytic sites, particularly those on the surface, would be regenerated and available for the next reaction of the incoming substrates immediately (Scheme 2). Thus, the reaction of substrates, even those too large to enter the crystals, could also take place on the surface of crystals. One side of the cavity on the very first layer is potentially open depending on crystallization; thus, the section of a substrate not participating in the reaction can be positioned outside of the crystal, extending toward the solvent. Therefore, as long as the reacting functionality of the molecule reaches a catalytic site, the reaction can proceed without difficulty. This notion is further confirmed by determining the amount of substrate 1 or product 2 trapped inside Ti/(S)-KUMOF-1 after the reaction is complete. Only 2.8% of product 2a is recovered from the MOF crystals for the reaction with 1a. Conversely, only traces of products 2b and 2c are recovered from the reaction with 1b and 1c because they cannot be entrapped at all (Tables 8, S6-S8, and Figures S15-S17). Second, it may also be inferred that only a limited

number of catalytic sites among all available sites are utilized, and the reaction time required for completion is prolonged. Lastly, the reusability of Ti/(S)-KUMOF-1 was studied for the carbonyl-ene reaction with 1a. The reactivity was not changed by recycling (88% for the first cycle and 86% for the second cycle), and the morphology was completely retained after recycling, as confirmed by optical microscopy images and scanning electron microscopy (SEM) images (Figure S18). Finally, a filtration experiment was performed to confirm the heterogeneity of the reaction with the recycled sample. When the Ti/(S)-KUMOF-1 catalyst was removed by filtration at 6 h, the reaction completely stopped with a 52.2% yield (Figure S19) indicating that there is no free-floating homogeneous catalyst in solution.

Scheme 2. Illustration of the situation with Ti/(S)-KUMOF-1. (a)-(c) After the completion of the reaction, (d) the newly formed 2 leaves the reaction center to yield the site to new incoming substrates 1



3.5 Visualization of reactions on the surface of the crystals

In a number of previous reports, the MOFs investigated have cavities or channels intrinsically too small to accommodate the entire molecule.<sup>10,13</sup> It is reasonable to suggest that only the very first layer of the MOF cavities could be utilized for these reactions by trapping a section of the

substrate. In addition, the inferior stereoselectivity observed is also understandable because the chirality bias based on the pore environment is diminished on the surface.<sup>29</sup> More convincing evidence for this situation is obtained from the reaction with the dye-containing substrate **1d** and the observed image by TPM (for the preparation of **1d**, see the supporting information, Schemes S3 and S4). The reaction of **1d** by Zn/(*S*)-**KUMOF-1** stops at an early stage. Only a trace amount of **1d** is reacted, and the resultant product **2d** remains on the surface of the catalyst crystal. Thus, **2d** residing on the surface prevents the diffusion of other substrates (**1d**) into the crystal and makes the reaction stop once the exposed channels are covered. After the dismantling of the crystal, **2d** is harvested with a 9% yield and negligible stereoselectivity (Figure S13 and Table S1). Conversely, with Ti/(*S*)-**KUMOF-1**, the reaction of **1d** is completed within 36 h to provide **2d** with a 72% yield (0% ee) from the solution (Figure S14 and Table S2). No **2d** accumulates on the catalyst crystals (Table 9 and Figure 2).

Table 9. Carbonyl-ene reaction with 1d by Zn/(S)-KUMOF-1 and Ti/(S)-KUMOF-1

	O <sub>2</sub> N.	1d	H condition toluene	0 <sub>2</sub> N	O OH		
	Reaction condition			product	obtained	product	obtained
entry				from solut	tion	from MOI	[1
	reagent	time (h)	temp (°C)	yield (%)	ee (%)	yield (%)	ee (%)
1	Zn/(S)-KUMOF-1	12	0	NR <sup>a</sup>	NΔb	9	0
	(3 equiv.)	12	v		1 1/2 1	,	v
2	Ti/( <i>S</i> )- <b>KUMOF-1</b>	36	RT	72	0	NR <sup>a</sup>	NA <sup>b</sup>

(10 mol%)<sup>*a*</sup>NR: no reaction, under the detection limit; <sup>*b*</sup>NA: not applicable. (b) (a) Ti/(S)-KUMOF-1 2d (72 %yield) Zn/(S)-KUMOF-1 (1) (1) 1d 1d 2d (9 %yield) (2)(2)

Figure 2. (a) (1) Carbonyl-ene reaction by Zn/(S)-KUMOF-1, showing that dyes are heavily localized on the surface of the crystal. (2) The TPM image of Zn/(S)-KUMOF-1 after the reaction. (b) (1) Carbonyl-ene reaction by Ti/(S)-KUMOF-1. (2) The TPM image of Ti/(S)-KUMOF-1 after the reaction, which shows that the fluorescence from the dyes is detected only in the surrounding solution, not from the crystal (red line: crystal boundary, scale bar =  $50 \mu m$ ).

## Conclusion

The reaction sites of MOF-based catalysts were investigated and vary according to the nature of the reaction with two representative examples. A reaction requiring more than a stoichiometric amount of Zn/(S)-KUMOF-1 must utilize all available reaction sites inside the MOF; thus, there is a clear distinction in reaction efficiency depending on the substrate size. In contrast, a catalytic reaction by Ti/(S)-KUMOF-1 does not exhibit discrimination of the substrate based on its size because most reactions take place on the crystal surface. The substrates do not necessarily diffuse into the center of the crystals because the proximal catalytic sites residing on the surface

are constantly being regenerated. This detail has been potentially overlooked in the literature when identifying the causes of MOF-based product selectivity.

Therefore, as long as the reactions being examined are catalytic, the comparison of reaction rates vs. substrate size could be carefully utilized to discuss whether the reactions take place inside the MOF or on the surface, and these comparisons should not be used to support the claim that reactions occur inside the channels of the MOF crystals.

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## **Author Contributions**

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

## ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publication website at DOI:

Additional figures, synthetic procedures, crystal image data, UV data, characterization data for organic compounds (PDF)

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