pubs.acs.org/JACS

# Rational Construction of an Artificial Binuclear Copper Monooxygenase in a Metal–Organic Framework

Xuanyu Feng,<sup>†</sup> Yang Song,<sup>†</sup> Justin S. Chen, Ziwan Xu, Soren J. Dunn, and Wenbin Lin\*

Cite This: J. Am. Chem. Soc. 2021, 143, 1107–1118



ACCESS Metrics & More	cle Recommendations s Supporting Information
-----------------------	--

**ABSTRACT:** Artificial enzymatic systems are extensively studied to mimic the structures and functions of their natural counterparts. However, there remains a significant gap between structural modeling and catalytic activity in these artificial systems. Herein we report a novel strategy for the construction of an artificial binuclear copper monooxygenase starting from a Ti metal–organic framework (MOF). The deprotonation of the hydroxide groups on the secondary building units (SBUs) of MIL-125(Ti) (MIL = Matériaux de l'Institut Lavoisier) allows for the metalation of the SBUs with closely spaced Cu<sup>I</sup> pairs, which are oxidized by molecular O<sub>2</sub> to afford the Cu<sup>II</sup><sub>2</sub>( $\mu_2$ -OH)<sub>2</sub> cofactor in the MOF-based artificial binuclear monooxygenase Ti<sub>8</sub>-Cu<sub>2</sub>. An artificial mononuclear Cu monooxygenase Ti<sub>8</sub>-Cu<sub>1</sub> was also prepared for comparison. The



MOF-based monooxygenases were characterized by a combination of thermogravimetric analysis, inductively coupled plasma-mass spectrometry, X-ray absorption spectroscopy, Fourier-transform infrared spectroscopy, and UV-vis spectroscopy. In the presence of coreductants,  $Ti_8-Cu_2$  exhibited outstanding catalytic activity toward a wide range of monooxygenation processes, including epoxidation, hydroxylation, Baeyer–Villiger oxidation, and sulfoxidation, with turnover numbers of up to 3450.  $Ti_8-Cu_2$  showed a turnover frequency at least 17 times higher than that of  $Ti_8-Cu_1$ . Density functional theory calculations revealed  $O_2$  activation as the rate-limiting step in the monooxygenation processes. Computational studies further showed that the  $Cu_2$  sites in  $Ti_8-Cu_2$ cooperatively stabilized the  $Cu-O_2$  adduct for O-O bond cleavage with 6.6 kcal/mol smaller free energy increase than that of the mononuclear Cu sites in  $Ti_8-Cu_1$ , accounting for the significantly higher catalytic activity of  $Ti_8-Cu_2$  over  $Ti_8-Cu_1$ .

# INTRODUCTION

Natural enzymes have evolved over millions of years to provide extremely powerful catalysts toward a variety of reactions with excellent activities under mild conditions and exquisite substrate specificity and product selectivity.<sup>1-4</sup> However, the practical use of natural enzymes in synthetic chemistry faces many challenges, including long-term stability, sensitivity to reaction conditions, and the difficulty in enzyme recovery and reuse.<sup>5-7</sup> Artificial enzymes with active metal or organic cofactors have been constructed to mimic the catalytic functions of natural enzymes,<sup>8-17</sup> showing promise in many catalytic transformations.<sup>11,18-21</sup> In-depth studies of these biomimetic artificial systems have in return provided important insights into natural enzymes.

Among the diverse family of natural enzymes, monooxygenases (EC 1.13.*x.x* and EC 1.14.*x.x*) insert one oxygen atom from molecular oxygen (O<sub>2</sub>) into organic substrates.<sup>22–24</sup> Monooxygenases with heme-, flavin-, copper-, nonheme iron-, or other cofactors efficiently catalyze a wide range of important oxidative processes, including hydroxylation, epoxidation, Baeyer–Villiger oxidation, sulfoxidation, and others.<sup>25–28</sup> In particular, natural monooxygenases with multicentered cofactors such as soluble methane monooxygenase (Fe–Fe),<sup>29</sup> catechol oxidase (Cu-Cu),<sup>30</sup> and tyrosinase  $(Cu-Cu)^{31,32}$  efficiently undergo multielectron processes through redox cooperativity to activate O<sub>2</sub> and oxidize organic substrates. Owing to the importance of direct activation of O<sub>2</sub> as a sustainable and inexpensive oxidant,<sup>33-37</sup> many artificial monooxygenases with heme- or flavin-derived cofactors have been developed but exhibit modest catalytic activity and substrate/product selectivity. In contrast, few artificial monooxygenases with binuclear cofactors have been studied and they exhibited limited catalytic activities.<sup>35,38-44</sup> We hypothesized that artificial binuclear monooxygenases with well-defined active sites and high monooxygenation activities can be rationally designed based on crystalline and porous metal–organic frameworks (MOFs) by taking advantage of recent advances in MOF biomimicry (Figure 1).<sup>45-52</sup>

Received: November 13, 2020 Published: January 7, 2021







**Figure 1.**  $Cu_2$  active sites with  $O_2$  bonding in (a) the natural enzyme tyrosinase (PDB code: 1WX2) and (b) the MOF-based artificial enzyme  $Ti_8$ - $Cu_2$  (this work).

Constructed from metal-oxo secondary building units (SBUs) and organic linkers, MOFs have been used to precisely install molecular functionalities with good spatial control.53-The uniform SBUs of MOFs allow the installation of molecularly precise mono- or multimetallic species as efficient cofactors,65 <sup>74</sup> while the uniform MOF pores and channels provide structurally defined microenvironments to confer substrate/product selectivities.<sup>75-82</sup> As an important class of heterogeneous catalysts, MOFs have robust structures and active sites and can be readily recovered and reused for multiple rounds of catalytic reactions.<sup>83-86</sup> Herein we report the rational design of a binuclear copper cofactor in a Ti-MOF (MIL-125) as an efficient artificial monooxygenase for the first time. The MOF-based artificial enzyme, Ti8-Cu2, displayed outstanding reactivity with turnover numbers (TONs) of up to 3450 toward a wide range of important monooxygenation processes, including epoxidation, hydroxylation, Baeyer-Villiger oxidation, and sulfoxidation. Ti8-Cu2 showed excellent stability and could be readily recycled and reused. Spectroscopic studies and computational results revealed the vital role of cooperativity between binuclear Cu centers in the O<sub>2</sub> activation process.

# RESULTS AND DISCUSSION

Synthesis and Characterization of MOF-Based Artificial Monooxygenases. We used the  $Ti_8(\mu_2-O)_8(\mu_2-OH)_4$ SBUs of MIL-125(Ti),  $Ti_8-OH$ , to support mononuclear and binuclear Cu cofactors as artificial monooxygenases. Each SBU of  $Ti_8-OH$  features four bridging hydroxides pointing to the center, along with eight adjacent bridging oxo groups. The precisely positioned bridging hydroxides were deprotonated to provide a hydrophilic binding pocket for reactive mononuclear or binuclear Cu species, while the small cavity in the SBU with a diameter of 5-6 Å brought the two Cu centers together via bridging hydroxide or oxo ligands to form redox-active cofactors for catalytic transformations.

Ti<sub>8</sub>-OH was synthesized through solvothermal reactions between  $Ti(O^{i}Pr)_{4}$  (<sup>i</sup>Pr = isopropyl) and H<sub>2</sub>BDC (terephthalic acid) based on a modified literature procedure.<sup>87</sup> Binuclear Cu species were installed on the SBUs of Tig-OH to afford the precatalyst Ti<sub>8</sub>-Cu<sub>2</sub>-pre through deprotonation of the hydroxides by LiCH<sub>2</sub>Si(CH<sub>3</sub>)<sub>3</sub> followed by metalation with excess  $Cu(CH_3CN)_4(BF_4)$ . Ti<sub>8</sub>-Cu<sub>2</sub>-pre was oxidized by bubbling O<sub>2</sub> through a MOF suspension in CH<sub>3</sub>CN to afford the binuclear artificial monooxygenase  $Ti_8$ -Cu<sub>2</sub> with Cu<sup>II</sup><sub>2</sub>( $\mu_2$ -OH)<sub>2</sub> cofactors (Figure 2c). Inductively coupled plasma-mass spectrometry (ICP-MS) analysis showed that Ti<sub>8</sub>-Cu<sub>2</sub>-pre and Ti<sub>8</sub>-Cu<sub>2</sub> had 2.0 and 1.95 Cu centers per SBU, suggesting complete metalation on all SBUs. By controlling the equivalent of Cu salts during the metalation process, Ti8-Cu1 with mononuclear Cu site was also synthesized. ICP-MS analysis showed the presence of 0.3 Cu per Ti<sub>8</sub> node in Ti<sub>8</sub>-Cu<sub>1</sub> to ensure the formation of mononuclear Cu species only.

Powdered X-ray diffraction (PXRD) studies showed that crystallinity of the MOF was retained throughout the metalation and oxidation processes (Figure 2d). Transmission electron microscopy (TEM) and scanning electron microscope (SEM) indicated that **Ti**<sub>8</sub>-**Cu**<sub>2</sub> maintained the disk-like morphology of **Ti**<sub>8</sub>-**OH** of ~1  $\mu$ m in diameter and ~0.4  $\mu$ m in thickness (Figures 2f, S3, S4). Installation of Cu centers reduced the Brunauer–Emmett–Teller (BET) surface area from 1520 m<sup>2</sup>/g for **Ti**<sub>8</sub>-**Cu**<sub>2</sub>, respectively (Figure 2e), while the pore sizes and volumes remained similar (Figure S5). Thermal gravimetric analysis (TGA) results supported the formulations of Ti<sub>8</sub>( $\mu_2$ -O)<sub>8</sub>[Cu( $\mu_2$ -O)\_2( $\mu_2$ -OH)]<sub>2</sub>(BDC)<sub>6</sub>Li<sub>2</sub> for **Ti**<sub>8</sub>-**Cu**<sub>2</sub>-**pre** and **Ti**<sub>8</sub>-**Cu**<sub>2</sub>.

**Olefin Epoxidation Catalyzed by MOF-Based Artificial Monooxygenases.** Natural monooxygenases efficiently transfer one oxygen from O<sub>2</sub> to form the mono-oxygenated product with the concomitant oxidation of coreductants such as NAD(P)H (NAD = nicotinamide adenine dinucleotide, NADP = nicotinamide adenine dinucleotide phosphate) and ascorbate in a four-electron process.<sup>88,89</sup> With binuclear Cu cofactors, MOF-based artificial monooxygenase  $Ti_8-Cu_2$ displayed excellent catalytic activity toward a broad range of monooxygenation reactions with O<sub>2</sub> as the oxygen source.

Ti<sub>8</sub>-Cu<sub>2</sub> effectively catalyzed epoxidation of olefins to afford epoxides. We used cyclohexene as a model substrate to screen the conditions for epoxidation reactions. In the presence of 0.2 mol % Ti8-Cu2, treatment of cyclohexene with 2 equiv of isobutyraldehyde as the coreductant in 1,2-dichloroethane (DCE) under atmospheric  $O_2$  at room temperature afforded cyclohexene oxide in 84% yield along with a small amount of hydroxylation products 2-cyclohexen-1-ol and 2-cyclohexen-1one (13% in total). The reaction also proceeded under ambient air to afford cyclohexene oxide in 77% yield (entry 3, Table 1). The absence of Ti8-Cu2, O2, or coreductant shut down the monooxygenation reaction, affording no or negligible amount of cyclohexene oxide (entries 4-6, Table 1). Replacement of Ti8-Cu2 by homogeneous control, CuCl2, afforded cyclohexene oxide in 7% yield (entries 8 and 9, Table 1), demonstrating the important role of Cu coordination to the SBU in the monooxygenation activity.

The reaction conditions were further screened with  $Ti_8$ - $Cu_2$ catalyzed epoxidation of cyclohexene. First, several solvents

Article



Figure 2. (a) Synthetic scheme of the MOF-based artificial monooxygenase  $Ti_8-Cu_2$  (Ti: light gray; O: red; C: gray). (b) SBU distribution and channel structure of the Ti MOF  $Ti_8-OH$ . (c) Installation of  $Cu^1$  centers and subsequent treatment with O<sub>2</sub> to afford  $Ti_8-Cu_2$ . (d) PXRD patterns of  $Ti_8-OH$  (blue),  $Ti_8-Cu_2$ -pre (gray),  $Ti_8-Cu_2$  (red), and the recovered  $Ti_8-Cu_2$  after reaction (AR, purple) along with the simulated pattern of MIL-125(Ti) (black). (e) Nitrogen sorption isotherms of  $Ti_8-OH$  (blue),  $Ti_8-Cu_2$  (red). (f) TEM image of  $Ti_8-Cu_2$ .

with different polarities and coordination abilities were tested (Table S5). Polar solvents such as DCE, dichloromethane, and trifluorotoluene displayed better monooxygenation performance than nonpolar solvents such as *n*-hexane. Notably, coordinating solvent, e.g. tetrahydrofuran (THF), led to a poor monooxygenation result, probably due to the strong solvent coordination to the Cu sites. Second, the effects of coreductants were also studied. Isobutyraldehyde, cyclohexanecarbaldehyde, and L-ascorbic acid showed 97%, 46%, and 5% conversions, respectively. Other electron donors such as 1,3-dimethyl-2-phenyl-2,3-dihydro-1*H*-benzo[*d*]imidazole (BIH), N-benzyl-1,4-dihydronicotinamide (BNAH), and tetrahydroxy-1,4-quinone did not work (Table S4). Third, the effects of isobutyraldehyde concentration and equivalents on the epoxidation reaction were examined. When the amount of isobutyraldehyde increased from 1 to 10 equiv, the selectivity of the epoxidation product over the hydroxylation

products improved from 75% to >99%. However, the highest epoxidation yield was achieved when 2 equiv of isobutyraldehyde were used (Figure S11). An excess amount of coreductant likely accelerates the regeneration of  $Cu_2(\mu$ -O) active species to suppress hydroxylation products, but coreductant also competes with substrate oxidation to decrease the yield of monooxygenation products.

The reactivity difference between a binuclear Cu cofactor and a mononuclear Cu cofactor was studied using  $Ti_8-Cu_2$  and  $Ti_8-Cu_1$  as catalysts. As shown in Figure 3a, the timedependent curves showed that  $Ti_8-Cu_2$  catalyzed cyclohexene monooxygenation efficiently within the first few hours with an initial turnover frequency (TOF) of 175 h<sup>-1</sup> and a high conversion of 97% in 24 h. In contrast,  $Ti_8-Cu_1$  showed a much slower reaction rate with an initial TOF of 10 h<sup>-1</sup> and a conversion of 43% in 24 h. This result shows the important role of binuclear Cu cofactors in the artificial monooxygenase.

# Table 1. Epoxidation of Cyclohexene Catalyzed by Ti<sub>8</sub>-Cu<sub>2</sub> and Homogeneous Controls



"Reactions were conducted with 0.25 mmol of cyclohexene in 2.0 mL of DCE. The reaction mixture was stirred at room temperature with a balloon of  $O_2$ , air, or  $N_2$ , and the conversions were determined by GC-MS analysis. Isobutyraldehyde was used as the coreductant. "Ti<sub>8</sub>-OH (1.0 mg) was used.

We next examined the substrate scope for Ti8-Cu2-catalyzed olefin epoxidation reactions. At 0.2 mol % of Ti8-Cu2, various alkenes were smoothly converted to their corresponding epoxides in the presence of isobutyraldehyde under atmospheric O2. Excellent yields of epoxides were obtained with cyclic alkenes bearing different substituents (entries 1-4, Table 2). Exclusive epoxidation selectivity was observed for reactive cyclic olefinic bonds in limonene and 3-carene (entries 5 and 6, Table 2). Noncyclic alkenes, including styrene derivatives (entries 7 and 8, Table 2) and linear-chain alkenes (entries 9 and 10, Table 2), also underwent epoxidation to afford epoxides in good to excellent yields. Internal alkenes displayed reactivity higher than that of terminal alkenes, likely due to the more electron-rich nature of internal alkenes. As a heterogeneous catalyst, Ti8-Cu2 was recycled by simple filtration from the reaction mixture and used in five consecutive runs of cyclohexene epoxidation. No significant reactivity drop was observed throughout the recycling experiments, demonstrating the stability of MOF-based artificial monooxygenase under oxygenation reaction conditions (Figure 3b).

Other Monooxygenation Reactions Catalyzed by MOF-Based Artificial Monooxygenases. Encouraged by excellent epoxidation activities of Ti8-Cu2, we examined the use of Ti<sub>8</sub>-Cu<sub>2</sub> in other monooxygenation reactions. Direct hydroxylation of alkanes under mild conditions provides an attractive strategy to construct valuable alcoholic feedstocks which can also be further oxidized to carbonyl compounds.<sup>90,91</sup> Ti8-Cu2 displayed excellent reactivity toward hydroxylation of benzylic substrates and further alcohol oxidation to carbonyl compounds. At 0.5 mol % of Ti<sub>8</sub>-Cu<sub>2</sub>, indane was efficiently converted into 1-indanol (8%) and 1-indanone (61%) under atmospheric O<sub>2</sub> at room temperature in 24 h. Elongating the reaction time to 48 h increased the yield of 1-indanone to 87% while reducing the yield of 1-indanol to <1%, which suggests sequential hydroxylation and oxidation to ketones (entry 11, Table 2). Several other substrates bearing benzylic C–H bonds including tetralin, phthalane, isochromane, and (methoxymethyl)benzene were successfully converted to corresponding ketones, lactones, and esters in good to excellent yields (entries 12-15, Table 2). The more difficult substrate ethylbenzene was oxidized to form acetophenone in 46% yield (entry 16, Table 2).

 ${\bf Ti_8}\text{-}{\bf Cu_2}$  also displayed high activities toward Baeyer–Villiger reaction and oxidation of thioethers. Specifically,  ${\bf Ti_8}\text{-}{\bf Cu_2}$  (0.2 mol %) catalyzed Baeyer–Villiger oxidation of 3-phenyl-cyclobutanone with O<sub>2</sub> as oxidant to afford 4-phenyloxolan-2-one in 70% yield within 48 h (entry 17, Table 2).  ${\bf Ti_8}\text{-}{\bf Cu_2}$  catalyzed the oxidation of thioanisole to methyl phenyl sulfoxide in 95% yield under atmospheric O<sub>2</sub> in 72 h (entry 18, Table 2). These results indicate the effectiveness of MOF-based artificial monooxygenases in producing valuable chemical feedstocks with O<sub>2</sub> as oxidant under mild reaction conditions.

Identification of the Cu Cofactors. We used Cu K-edge X-ray absorption near-edge structure (XANES) and extended X-ray absorption fine structure (EXAFS) spectroscopies to study the Cu cofactors in MOF-based monooxygenases. The oxidation states of Cu centers in Ti<sub>8</sub>-Cu<sub>2</sub>-pre and Ti<sub>8</sub>-Cu<sub>2</sub> were determined by comparing the pre-edge features of their normalized XANES spectra to those of Cu<sub>2</sub>O and CuO (Figure 4a). While Ti<sub>8</sub>-Cu<sub>2</sub>-pre showed a similar pre-edge peak corresponding to the spin-allowed 1s  $\rightarrow$  4p electronic transition at 8982–8984 eV to Cu<sup>I</sup><sub>2</sub>O<sub>2</sub><sup>92,93</sup> Ti<sub>8</sub>-Cu<sub>2</sub> exhibited a similar pre-edge peak attributed to the dipole-forbidden  $\mathrm{Cu}^{\mathrm{II}}$ 1s  $\rightarrow$  3d electronic transition at 8977–8979 eV to Cu<sup>II</sup>O.<sup>94,95</sup> This pre-edge feature of  $Ti_8$ - $Cu_2$  also suggests an octahedral symmetry for Cu<sup>II</sup> centers.<sup>96</sup> Additionally, Ti<sub>8</sub>-Cu<sub>2</sub> showed a shoulder peak at 8989 eV which is assigned to  $Cu^{II}$  1s  $\rightarrow$  4p + L shakedown transition.<sup>97,98</sup> The XANES studies thus indicate that the Cu centers in Ti<sub>8</sub>-Cu<sub>2</sub>-pre adopt +1 oxidation state while the Cu centers in Ti8-Cu2 exhibit +2 oxidation state.

Density functional theory (DFT) calculations were performed using the B3LYP functional to determine Cu coordination environments in  $Ti_8$ -Cu<sub>2</sub>-pre and  $Ti_8$ -Cu<sub>2</sub>. DFT optimization of  $Ti_8$ -Cu<sub>2</sub>-pre converged at a structure with two tetrahedral Cu<sup>I</sup> centers slightly above and below the plane of the  $Ti_8$  node. Each Cu<sup>I</sup> center coordinates to two anionic



Figure 3. (a) Time-dependent curves of cyclohexene epoxidation catalyzed by MOF-based artificial monooxygenases with a binuclear Cu cofactor ( $Ti_8$ - $Cu_2$ ) or a mononuclear Cu cofactor ( $Ti_8$ - $Cu_1$ ) and without a cofactor ( $Ti_8$ -OH). (b) Recycle and reuse of  $Ti_8$ - $Cu_2$  catalyst in the epoxidation of cyclohexene.

bridging-oxo ( $\mu_2$ -O<sup>-</sup>) groups, one neutral bridging-oxo ( $\mu_2$ -O) group, and one CH<sub>3</sub>CN molecule in a distorted tetrahedral geometry. The distances of Cu-( $\mu_2$ -O<sup>-</sup>), Cu-( $\mu_2$ -O), and Cu-N were 2.13/2.15. 2.23, and 1.95 Å, respectively. DFT optimization of **Ti**<sub>8</sub>-**Cu**<sub>2</sub> converged on a Cu<sup>II</sup><sub>2</sub>( $\mu_2$ -OH)<sub>2</sub> structure with two Cu<sup>II</sup> centers in the plane of the Ti<sub>8</sub> node. Each Cu<sup>II</sup> center adopted octahedral geometry by coordinating to two anionic bridging-oxo ( $\mu_2$ -O<sup>-</sup>) groups in the axial positions as well as two neutral bridging-oxo ( $\mu_2$ -O) groups and two bridging  $\mu_2$ -OH groups in the equatorial positions. The Cu-O distances were 2.12, 2.45, and 2.03 Å for the Cu( $\mu_2$ -O<sup>-</sup>), Cu( $\mu_2$ -O), and Cu( $\mu_2$ -OH) moieties, respectively.

EXAFS analyses were performed to determine the local structures of Cu cofactors. We first compared the  $k^2$ -weighted  $\chi(R)$  spectra of Ti<sub>8</sub>-Cu<sub>2</sub>-pre, Ti<sub>8</sub>-Cu<sub>2</sub>, and Ti<sub>8</sub>-Cu<sub>1</sub>. No signals attributable to Cu nanoparticle or CuO are present in these EXAFS spectra. Ti<sub>8</sub>-Cu<sub>2</sub> and Ti<sub>8</sub>-Cu<sub>2</sub>-pre showed characteristic Cu–Cu single scattering signals at R  $\approx 2.58$  and 2.73 Å,

respectively (Figure 4b), consistent with the existence of Cu<sub>2</sub> species in both  $Ti_8-Cu_2$ -pre and  $Ti_8-Cu_2$ . In contrast, no Cu– Cu single scattering signal was present in the EXAFS spectrum of  $Ti_8-Cu_1$ , consistent with the mononuclear Cu species. Furthermore,  $Ti_8-Cu_2$  showed stronger Cu–Cu single scattering signal than  $Ti_8-Cu_2$ -pre, suggesting more intense interactions between two Cu<sup>II</sup> centers in  $Ti_8-Cu_2$  due to the bridging of the Cu centers by two  $\mu_2$ -OH groups after oxidation. This result matches the distance trend observed in DFT-optimized structures with Cu–Cu distances of 2.86 and 2.74 Å for  $Ti_8-Cu_2$ -pre and  $Ti_8-Cu_2$ , respectively.

We further fitted the Cu-EXAFS spectra using DFToptimized structure models (Figure 4c). For  $Ti_8-Cu_2$ , Cu–O single scattering pathways contributed most to the first and second peaks of the Cu K-edge EXAFS spectrum to afford Cu–O distances of 2.00, 2.20, and 1.91 Å for a Cu–( $\mu_2$ -O<sup>-</sup>), Cu–( $\mu_2$ -O), and Cu–( $\mu_2$ -OH) species, respectively. The third peak came mainly from the contribution of Cu–Cu interaction with a Cu–Cu distance of 2.80 Å, which agrees well with the calculated distance of 2.74 Å. Similarly, the first and second peaks of  $Ti_8$ -Cu<sub>2</sub>-pre were attributed to Cu–O interactions from ( $\mu_2$ -O<sup>-</sup>), ( $\mu_2$ -O), and N, while the weak third peak was mainly assigned to Cu–Cu interactions. These EXAFS results are consistent with those reported in the literature.<sup>99,100</sup>

Fourier-transform infrared (FT-IR) spectroscopy and UV– vis spectroscopy supported the generation of Cu cofactors in the MOFs. As shown in Figure 4d, **Ti<sub>8</sub>-OH**, **Ti<sub>8</sub>-Cu<sub>2</sub>-pre**, and **Ti<sub>8</sub>-Cu<sub>2</sub>** displayed similar carbonyl stretching at ~1550 cm<sup>-1</sup> and C<sub>sp2</sub>–H stretching at ~3000 cm<sup>-1</sup>, but only **Ti<sub>8</sub>-OH** showed a shoulder peak at 3645 cm<sup>-1</sup> attributable to the O–H stretching of Ti( $\mu_2$ -OH)Ti species.<sup>101</sup> This peak disappeared after deprotonation and metalation with Cu in **Ti<sub>8</sub>-Cu<sub>2</sub>-pre** and **Ti<sub>8</sub>-Cu<sub>2</sub>**. Interestingly, a new sharp peak at 3670 cm<sup>-1</sup> appeared in **Ti<sub>8</sub>-Cu<sub>2</sub>**, which is assigned to the O–H stretching of the Cu( $\mu_2$ -OH)Cu species.<sup>102,103</sup> UV–vis spectra were also taken on the MOF systems (Figure S10). While **Ti<sub>8</sub>-OH** displayed UV absorption at ~300 nm characteristic of Ti–O charge transfer (CT),<sup>104,105</sup> **Ti<sub>8</sub>-Cu<sub>2</sub>-pre** and **Ti<sub>8</sub>-Cu<sub>2</sub>** showed new bands at 330 and 355 nm, respectively. These bands are assigned to Cu<sup>1</sup>–O and Cu<sup>II</sup>–O CT absorptions, respectively.<sup>106</sup>

**Energy Profiles of Monooxygenation Processes.** DFT calculations with the B3LYP functional were conducted on SBU-supported Cu cofactors to gain insight into dioxygen activation and substrate oxidation by the MOF-based monooxygenases and to understand the drastic reactivity difference between Ti<sub>8</sub>-Cu<sub>2</sub> and Ti<sub>8</sub>-Cu<sub>1</sub>. Significant efforts have been made to study O<sub>2</sub> activation and utilization by the active Cu centers in natural and artificial Cu-based monooxygenases. Spectroscopic and computational evidence strongly suggested Cu-oxo species as the key intermediates in the monooxygenation process.<sup>36,40,107–109</sup> We propose Cu<sub>2</sub>( $\mu_2$ -O)<sub>2</sub> and Cu-oxo species as the active catalysts for the monooxygenation processes catalyzed by Ti<sub>8</sub>-Cu<sub>2</sub> and Ti<sub>8</sub>-Cu<sub>1</sub>, respectively (Figure 5).

We first determined the energy profiles of O<sub>2</sub> activation processes on **Ti**<sub>8</sub>-**Cu**<sub>2</sub> and **Ti**<sub>8</sub>-**Cu**<sub>1</sub>. O<sub>2</sub> activation by **Ti**<sub>8</sub>-**Cu**<sub>2</sub> starts with the coordination of O<sub>2</sub> to the reduced (Cu<sup>1</sup>)<sub>2</sub> complex (IN-1) with an  $\eta^1$ -end-on mode to form a Cu<sup>II</sup>( $\eta^1, \mu_2$ -O<sub>2</sub>)Cu adduct (IN-2). IN-2 then transforms into a Cu( $\eta^2, \mu_2$ -O<sub>2</sub>)Cu adduct (IN-3). The cleavage of the O–O bond affords the highly active Cu<sup>III</sup><sub>2</sub>( $\mu_2$ -O)<sub>2</sub> intermediate (IN-4). For O<sub>2</sub> activation on **Ti**<sub>8</sub>-**Cu**<sub>1</sub>, O<sub>2</sub> first coordinates with Cu<sup>I</sup> (IN-5) to

Entry	Substrate	Catalyst Load- ing	Product	Conv. (Yield)	TON	Entry	Substrate	Catalyst Loading	Product	Yield	TON
1	$\bigcirc$	0.2 mol%	<b>○</b>	97% (84%)	420	10	Etn-C <sub>4</sub> H <sub>10</sub>	0.2 mol%	O Et n-C <sub>4</sub> H <sub>10</sub>	90% trans:cis 83:7	450
2	$\bigcirc$	0.2 mol%		97% (92%)	460	11		0.5 mol%		87%	174
3	À	0.2 mol%		95% (92%)	460	12	-	0.2 mol%		86%	430
4	$\bigcup$	0.2 mol%	0	100% (81%)	405	13		0.5 mol%	<b>○</b>	94%	188
5	$\times$	0.2 mol%		89% (89%)	445	14		0.5 mol%		81%	162
6		0.2 mol%		90% (90%)	450	15	<u> </u>	0.5 mol%	<b>0</b>	68%	136
7		0.2 mol%		76% (70%)	350	16	-	0.5 mol%		46%	92
8	$\bigcirc$	0.2 mol%		100% (88%)	440	17		0.2 mol%		70%	350
9	n-C <sub>5</sub> H <sub>12</sub>	0.2 mol%	n-C <sub>5</sub> H <sub>12</sub>	50% (50%)	250	18	<u> </u>	0.2 mol%	S S	95%	475

#### Table 2. Ti<sub>8</sub>-Cu<sub>2</sub>-Catalyzed Monooxygenation Reactions

<sup>*a*</sup>Reactions were conducted with 0.25 mmol of substrate in 2.0 mL of DCE solvent. The reaction mixture was stirred at room temperature with an  $O_2$  balloon. Isobutyraldehyde (2 equiv) was applied as coreductant. The conversions were determined by GC-MS analysis.

form an  $\eta^1$ -O<sub>2</sub>-adduct (IN-6), which is further activated via a one-electron and one-proton  $(1e^{-}/1H^{+})$  process (provided by the coreductant) to form a Cu<sup>II</sup>-OOH intermediate (IN-7). IN-7 loses one H<sub>2</sub>O to afford the active Cu<sup>III</sup>=O species (IN-8) via another  $1e^{-}/1H^{+}$  process. Calculations of the free energies of these key intermediates revealed total free energy increases of +47.7 kcal/mol for O2 activation in Ti8-Cu2 to access IN-4 and +54.3 kcal/mol for O2 activation in Ti8-Cu1 to access IN-8. Although the cleavage of O-O bond in Ti8-Cu1 features a lower barrier (IN-7 to IN-8, 23.6 kcal/mol) than in Ti<sub>8</sub>-Cu<sub>2</sub> (IN-3 to IN-4, 32.8 kcal/mol) with the assistance of the coreductant, the significant stabilization of the dioxygen species by the Cu<sub>2</sub> species leads to a smaller free energy increase for the overall transformation by 6.6 kcal/mol. Such a difference indicates an easier O2 activation process on the binuclear Cu site than the mononuclear Cu site.

DFT studies were also performed on the monooxygenation processes starting from the active Cu-oxo intermediates in  $Ti_8$ - $Cu_2$  and  $Ti_8$ - $Cu_1$ . The hydroxylation of toluene to afford benzyl alcohol was selected as a model reaction. Typically, hydroxylation of C–H bonds on Cu-oxo species is initiated by

the hydrogen atom abstraction (HAA) from the substrate by the Cu-oxo species to form the Cu-hydroxo species and the carbon radical, followed by a radical rebound step to construct the C-O bond between the carbon radical and Cu-bonded hydroxide. Figure 6 shows the key intermediates and transition states during the hydroxylation processes. The hydroxylation processes on both Ti<sub>8</sub>-Cu<sub>2</sub> and Ti<sub>8</sub>-Cu<sub>1</sub> are highly exothermic and spontaneous with small activation barriers. Specifically, the binuclear Cu cofactor featured a +4.2 kcal/mol activation barrier for the HAA step and a +1.9 kcal/mol barrier for the radical rebound to form the benzyl alcohol product. For the mononuclear Cu cofactor, a +2.6 kcal/mol activation barrier is calculated for the HAA step and a +9.2 kcal/mol barrier for the radical rebound step. Both processes are driven by the highly reactive nature of the Cu-oxo species (IN-4 and IN-8) and the formation of strong C–O bonds.

The DFT results suggest the O<sub>2</sub> activation as the ratelimiting step in the monooxygenation processes catalyzed by both  $Ti_8$ - $Cu_2$  and  $Ti_8$ - $Cu_1$ . Subsequent substrate oxidation processes by the active Cu-oxo species proceed spontaneously. Importantly, the Cu<sub>2</sub> sites in  $Ti_8$ - $Cu_2$  cooperatively stabilize



Figure 4. (a) Normalized Cu-XANES spectra of  $Ti_8$ - $Cu_2$ -pre,  $Ti_8$ - $Cu_2$ , and reference compounds. The inset shows the pre-edge feature at 8973–8982 eV corresponding to the  $1s \rightarrow 3d$  electronic transition for  $Cu^{II}$ . (b)  $k^2$ -weighted Cu-EXAFS  $\chi(R)$  spectra of  $Ti_8$ - $Cu_2$ -pre,  $Ti_8$ - $Cu_2$ , and  $Ti_8$ - $Cu_1$ . SS = single scattering. (c) EXAFS spectra and fits in R-space (within the gray lines) at the Cu K-edge of  $Ti_8$ - $Cu_2$  with the magnitude (open circles, red) and real components (open squares, blue) of the Fourier transforms (FT). (d) FT-IR spectra of  $Ti_8$ -OH (blue),  $Ti_8$ - $Cu_2$ -pre (black), and  $Ti_8$ - $Cu_2$  (red). (e) Structural models of  $Ti_8$ - $Cu_1$  (left),  $Ti_8$ - $Cu_2$ -pre (middle), and  $Ti_8$ - $Cu_2$  (right) with the Cu–Cu distances from DFT optimization and EXAFS fitting.



Figure 5. (a, b) Monooxygenation processes on (a) the mononuclear Cu cofactor in  $Ti_8$ - $Cu_1$  and (b) the binuclear Cu cofactor in  $Ti_8$ - $Cu_2$ . (c) Energy profiles of the O<sub>2</sub> activation processes on  $Ti_8$ - $Cu_1$  (top) and  $Ti_8$ - $Cu_2$  (bottom).

the Cu-dioxygen adduct for O-O bond cleavage, leading to a smaller free energy increase for the dioxygen activation than

the mononuclear Cu sites in Ti<sub>8</sub>-Cu<sub>1</sub>. Although several factors, including substrate/product diffusions, MOF channels, and Cu



Figure 6. Energy profiles of the hydroxylation processes on  $Ti_8$ -Cu<sub>1</sub> (up) and  $Ti_8$ -Cu<sub>2</sub> (bottom).

cofactor concentrations, contributed to the monooxygenation reactivities, the 6.6 kcal/mol difference in  $\Delta G$  values rationalized the significantly higher catalytic activity of Ti<sub>8</sub>-Cu<sub>2</sub> over Ti<sub>8</sub>-Cu<sub>1</sub>.

# CONCLUSION

In this work, we demonstrated a novel strategy to construct an artificial monooxygenase,  $Ti_8$ - $Cu_2$ , starting from a Ti MOF following the blueprint of natural enzymes. The hydroxides of the MOF SBUs were deprotonated to support a pair of  $Cu^{I}$  precursors, which were treated with  $O_2$  to generate the  $Cu^{II}_2(\mu_2$ -OH)\_2 cofactors in the artificial enzymes. The SBU provided a precise binding pocket for the installation of

binuclear Cu cofactors to cooperatively activate  $O_2$ . The strong oxo ligating ligands and the reticular isolation of  $Cu_2$  cofactors in the MOF led to a robust artificial enzyme for monooxygenation reactions. **Ti**<sub>8</sub>-**Cu**<sub>2</sub> catalyzed a wide scope of monooxygenation reactions, including epoxidation, hydroxylation, Baeyer–Villiger oxidation, and sulfoxidation, with atmospheric  $O_2$  as the oxidant and isobutyraldehyde as the coreductant. **Ti**<sub>8</sub>-**Cu**<sub>2</sub> efficiently catalyzed the epoxidation of alkenes with TONs as high as 3450 and an initial TOF of 175 h<sup>-1</sup>, which was more than 17 times higher than the mononuclear analogue **Ti**<sub>8</sub>-**Cu**<sub>1</sub>. Computational studies revealed the  $O_2$  activation as the rate-limiting step in the monooxygenation processes catalyzed by both **Ti**<sub>8</sub>-**Cu**<sub>2</sub> and

 $Ti_8$ - $Cu_1$ . The  $Cu_2$  sites in  $Ti_8$ - $Cu_2$  cooperatively stabilize the Cu-dioxygen adduct for the O–O bond cleavage with a 6.6 kcal/mol lower free energy increase than the mononuclear Cu sites in  $Ti_8$ - $Cu_1$ , which accounts for the significantly higher catalytic activity of  $Ti_8$ - $Cu_2$  over  $Ti_8$ - $Cu_1$ . This work highlights the potential of MOFs in the construction of robust artificial enzymes with uniform and precise active sites and high catalytic activities.

# ASSOCIATED CONTENT

## **Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c11920.

Synthesis and characterization of Ti<sub>8</sub>-Cu<sub>2</sub>-pre, Ti<sub>8</sub>-Cu<sub>2</sub>, Ti<sub>8</sub>-Cu<sub>1</sub>; reaction procedures and characterization results of monooxygenation; DFT calculations (PDF)

#### AUTHOR INFORMATION

#### **Corresponding Author**

Wenbin Lin – Department of Chemistry, The University of Chicago, Chicago, Illinois 60637, United States;
orcid.org/0000-0001-7035-7759; Email: wenbinlin@ uchicago.edu

#### Authors

Xuanyu Feng – Department of Chemistry, The University of Chicago, Chicago, Illinois 60637, United States; orcid.org/0000-0003-1355-1445

Yang Song – Department of Chemistry, The University of Chicago, Chicago, Illinois 60637, United States; orcid.org/0000-0003-4212-8814

Justin S. Chen – Department of Chemistry, The University of Chicago, Chicago, Illinois 60637, United States; orcid.org/0000-0003-0192-3125

Ziwan Xu – Department of Chemistry, The University of Chicago, Chicago, Illinois 60637, United States

Soren J. Dunn – Department of Chemistry, The University of Chicago, Chicago, Illinois 60637, United States

Complete contact information is available at:

https://pubs.acs.org/10.1021/jacs.0c11920

#### **Author Contributions**

<sup>†</sup>X. Feng and Y. Song contributed equally to this work.

#### Notes

The authors declare no competing financial interest.

# ACKNOWLEDGMENTS

This work was supported by NSF and the University of Chicago. XAS analysis was performed at Beamline 10-BM, supported by the Materials Research Collaborative Access Team (MRCAT). Use of the Advanced Photon Source, an Office of Science User Facility operated for the U.S. DOE Office of Science by ANL, was supported by the U.S. DOE under contract no. DE-AC02-06CH11357.

# REFERENCES

(1) Wolfenden, R.; Snider, M. J. The Depth of Chemical Time and the Power of Enzymes as Catalysts. *Acc. Chem. Res.* **2001**, *34* (12), 938–945.

(2) Benkovic, S. J.; Hammes-Schiffer, S. A Perspective on Enzyme Catalysis. *Science* **2003**, *301* (5637), 1196.

(3) Bornscheuer, U. T.; Huisman, G. W.; Kazlauskas, R. J.; Lutz, S.; Moore, J. C.; Robins, K. Engineering the third wave of biocatalysis. *Nature* **2012**, 485 (7397), 185–194.

(4) Sheldon, R. A.; Woodley, J. M. Role of Biocatalysis in Sustainable Chemistry. *Chem. Rev.* 2018, 118 (2), 801–838.

(5) Daniel, R. M.; Dunn, R. V.; Finney, J. L.; Smith, J. C. The Role of Dynamics in Enzyme Activity. *Annu. Rev. Biophys. Biomol. Struct.* **2003**, 32 (1), 69–92.

(6) Iyer, P. V.; Ananthanarayan, L. Enzyme stability and stabilization—Aqueous and non-aqueous environment. *Process Biochem.* 2008, 43 (10), 1019–1032.

(7) DiCosimo, R.; McAuliffe, J.; Poulose, A. J.; Bohlmann, G. Industrial use of immobilized enzymes. *Chem. Soc. Rev.* **2013**, *42* (15), 6437–6474.

(8) Breslow, R.; Overman, L. E. "Artificial enzyme" combining a metal catalytic group and a hydrophobic binding cavity. *J. Am. Chem. Soc.* **1970**, *92* (4), 1075–1077.

(9) Breslow, R. Artificial enzymes. Science 1982, 218 (4572), 532.

(10) Breslow, R. Biomimetic Chemistry and Artificial Enzymes: Catalysis by Design. Acc. Chem. Res. 1995, 28 (3), 146-153.

(11) Murakami, Y.; Kikuchi, J.-i.; Hisaeda, Y.; Hayashida, O. Artificial Enzymes. *Chem. Rev.* **1996**, *96* (2), 721–758.

(12) Lin, Y.; Zhao, A.; Tao, Y.; Ren, J.; Qu, X. Ionic Liquid as an Efficient Modulator on Artificial Enzyme System: Toward the Realization of High-Temperature Catalytic Reactions. *J. Am. Chem. Soc.* **2013**, *135* (11), 4207–4210.

(13) Lin, Y.; Ren, J.; Qu, X. Catalytically Active Nanomaterials: A Promising Candidate for Artificial Enzymes. *Acc. Chem. Res.* 2014, 47 (4), 1097–1105.

(14) Raynal, M.; Ballester, P.; Vidal-Ferran, A.; van Leeuwen, P. W. N. M. Supramolecular catalysis. Part 2: artificial enzyme mimics. *Chem. Soc. Rev.* **2014**, *43* (5), 1734–1787.

(15) Cai, R.; Yang, D.; Peng, S.; Chen, X.; Huang, Y.; Liu, Y.; Hou, W.; Yang, S.; Liu, Z.; Tan, W. Single Nanoparticle to 3D Supercage: Framing for an Artificial Enzyme System. *J. Am. Chem. Soc.* **2015**, *137* (43), 13957–13963.

(16) Wu, J.; Wang, X.; Wang, Q.; Lou, Z.; Li, S.; Zhu, Y.; Qin, L.; Wei, H. Nanomaterials with enzyme-like characteristics (nanozymes): next-generation artificial enzymes (II). *Chem. Soc. Rev.* **2019**, *48* (4), 1004–1076.

(17) Ren, X.; Fasan, R. Synergistic catalysis in an artificial enzyme. *Nat. Catal.* **2020**, 3 (3), 184–185.

(18) Bjerre, J.; Rousseau, C.; Marinescu, L.; Bols, M. Artificial enzymes, "Chemzymes": current state and perspectives. *Appl. Microbiol. Biotechnol.* **2008**, *81* (1), 1–11.

(19) Dong, Z.; Luo, Q.; Liu, J. Artificial enzymes based on supramolecular scaffolds. *Chem. Soc. Rev.* **2012**, *41* (23), 7890–7908. (20) Wei, H.; Wang, E. Nanomaterials with enzyme-like characteristics (nanozymes): next-generation artificial enzymes. *Chem. Soc. Rev.* **2013**, *42* (14), 6060–6093.

(21) Schwizer, F.; Okamoto, Y.; Heinisch, T.; Gu, Y.; Pellizzoni, M. M.; Lebrun, V.; Reuter, R.; Köhler, V.; Lewis, J. C.; Ward, T. R. Artificial Metalloenzymes: Reaction Scope and Optimization Strategies. *Chem. Rev.* **2018**, *118* (1), 142–231.

(22) Burton, S. G. Oxidizing enzymes as biocatalysts. *Trends Biotechnol.* 2003, 21 (12), 543-549.

(23) Torres Pazmiño, D. E.; Winkler, M.; Glieder, A.; Fraaije, M. W. Monooxygenases as biocatalysts: Classification, mechanistic aspects and biotechnological applications. *J. Biotechnol.* **2010**, *146* (1), 9–24.

(24) Dong, J.; Fernández-Fueyo, E.; Hollmann, F.; Paul, C. E.; Pesic, M.; Schmidt, S.; Wang, Y.; Younes, S.; Zhang, W. Biocatalytic Oxidation Reactions: A Chemist's Perspective. *Angew. Chem., Int. Ed.* **2018**, 57 (30), 9238–9261.

(25) Bernhardt, R. Cytochromes P450 as versatile biocatalysts. J. Biotechnol. 2006, 124 (1), 128–145.

(26) van Berkel, W. J. H.; Kamerbeek, N. M.; Fraaije, M. W. Flavoprotein monooxygenases, a diverse class of oxidative biocatalysts. *J. Biotechnol.* **2006**, *124* (4), 670–689.

pubs.acs.org/JACS

(27) Solomon, E. I.; Heppner, D. E.; Johnston, E. M.; Ginsbach, J. W.; Cirera, J.; Qayyum, M.; Kieber-Emmons, M. T.; Kjaergaard, C. H.; Hadt, R. G.; Tian, L. Copper Active Sites in Biology. *Chem. Rev.* **2014**, *114* (7), 3659–3853.

(28) Wedde, S.; Biermann, M.; Choi, J. E.; Oike, K.; Zumbrägel, N.; Gröger, H. The Recent Developments of Enzymatic Oxidation. *Green Oxidation in Organic Synthesis* **2019**, 439–496.

(29) Ross, M. O.; Rosenzweig, A. C. A tale of two methane monooxygenases. *JBIC*, J. Biol. Inorg. Chem. 2017, 22 (2), 307-319.
(30) Eicken, C.; Krebs, B.; Sacchettini, J. C. Catechol oxidase —

structure and activity. *Curr. Opin. Struct. Biol.* **1999**, *9* (6), 677–683.

(31) Matoba, Y.; Kumagai, T.; Yamamoto, A.; Yoshitsu, H.; Sugiyama, M. Crystallographic evidence that the dinuclear copper center of tyrosinase is flexible during catalysis. *J. Biol. Chem.* **2006**, *281* (13), 8981–8990.

(32) Ramsden, C. A.; Riley, P. A. Tyrosinase: The four oxidation states of the active site and their relevance to enzymatic activation, oxidation and inactivation. Biorg. *Bioorg. Med. Chem.* **2014**, *22* (8), 2388–2395.

(33) Anastas, P. T.; Kirchhoff, M. M. Origins, Current Status, and Future Challenges of Green Chemistry. *Acc. Chem. Res.* **2002**, *35* (9), 686–694.

(34) Fukuzumi, S.; Lee, Y.-M.; Jung, J.; Nam, W. Thermal and photocatalytic oxidation of organic substrates by dioxygen with water as an electron source. *Green Chem.* **2018**, *20* (5), 948–963.

(35) Jasniewski, A. J.; Que, L. Dioxygen Activation by Nonheme Diiron Enzymes: Diverse Dioxygen Adducts, High-Valent Intermediates, and Related Model Complexes. *Chem. Rev.* **2018**, *118* (5), 2554–2592.

(36) Wu, P.; Fan, F.; Song, J.; Peng, W.; Liu, J.; Li, C.; Cao, Z.; Wang, B. Theory Demonstrated a "Coupled" Mechanism for  $O_2$  Activation and Substrate Hydroxylation by Binuclear Copper Monooxygenases. J. Am. Chem. Soc. **2019**, 141 (50), 19776–19789.

(37) Alamgholiloo, H.; Rostamnia, S.; Zhang, K.; Lee, T. H.; Lee, Y.-S.; Varma, R. S.; Jang, H. W.; Shokouhimehr, M. Boosting Aerobic Oxidation of Alcohols via Synergistic Effect between TEMPO and a Composite  $Fe_3O_4/Cu$ -BDC/GO Nanocatalyst. *ACS Omega* **2020**, 5 (10), 5182–5191.

(38) Karlin, K. D.; Hayes, J. C.; Gultneh, Y.; Cruse, R. W.; McKown, J. W.; Hutchinson, J. P.; Zubieta, J. Copper-mediated hydroxylation of an arene: model system for the action of copper monooxygenases. Structures of a binuclear copper(I) complex and its oxygenated product. J. Am. Chem. Soc. **1984**, 106 (7), 2121–2128.

(39) Ruiz, E.; Alemany, P.; Alvarez, S.; Cano, J. Structural Modeling and Magneto–Structural Correlations for Hydroxo-Bridged Copper-(II) Binuclear Complexes. *Inorg. Chem.* **1997**, *36* (17), *3683–3688*.

(40) Rolff, M.; Schottenheim, J.; Decker, H.; Tuczek, F. Copper $-O_2$  reactivity of tyrosinase models towards external monophenolic substrates: molecular mechanism and comparison with the enzyme. *Chem. Soc. Rev.* **2011**, *40* (7), 4077–4098.

(41) Citek, C.; Lin, B.-L.; Phelps, T. E.; Wasinger, E. C.; Stack, T. D. P. Primary Amine Stabilization of a Dicopper(III)  $Bis(\mu$ -oxo) Species: Modeling the Ligation in pMMO. *J. Am. Chem. Soc.* **2014**, *136* (41), 14405–14408.

(42) Serrano-Plana, J.; Garcia-Bosch, I.; Company, A.; Costas, M. Structural and Reactivity Models for Copper Oxygenases: Cooperative Effects and Novel Reactivities. *Acc. Chem. Res.* **2015**, *48* (8), 2397–2406.

(43) Cowley, R. E.; Tian, L.; Solomon, E. I. Mechanism of  $O_2$  activation and substrate hydroxylation in noncoupled binuclear copper monooxygenases. *Proc. Natl. Acad. Sci. U. S. A.* **2016**, *113* (43), 12035.

(44) Ali, G.; VanNatta, P. E.; Ramirez, D. A.; Light, K. M.; Kieber-Emmons, M. T. Thermodynamics of a  $\mu$ -oxo Dicopper(II) Complex for Hydrogen Atom Abstraction. *J. Am. Chem. Soc.* **2017**, *139* (51), 18448–18451.

(45) Meng, L.; Cheng, Q.; Kim, C.; Gao, W.-Y.; Wojtas, L.; Chen, Y.-S.; Zaworotko, M. J.; Zhang, X. P.; Ma, S. Crystal Engineering of a Microporous, Catalytically Active fcu Topology MOF Using a Custom-Designed Metalloporphyrin Linker. Angew. Chem., Int. Ed. 2012, 51 (40), 10082-10085.

(46) Pullen, S.; Fei, H.; Orthaber, A.; Cohen, S. M.; Ott, S. Enhanced Photochemical Hydrogen Production by a Molecular Diiron Catalyst Incorporated into a Metal–Organic Framework. *J. Am. Chem. Soc.* **2013**, *135* (45), 16997–17003.

(47) Liao, P.-Q.; Chen, H.; Zhou, D.-D.; Liu, S.-Y.; He, C.-T.; Rui, Z.; Ji, H.; Zhang, J.-P.; Chen, X.-M. Monodentate hydroxide as a super strong yet reversible active site for  $CO_2$  capture from high-humidity flue gas. *Energy Environ. Sci.* **2015**, 8 (3), 1011–1016.

(48) Nath, I.; Chakraborty, J.; Verpoort, F. Metal organic frameworks mimicking natural enzymes: a structural and functional analogy. *Chem. Soc. Rev.* 2016, 45 (15), 4127–4170.

(49) Bien, C. E.; Chen, K. K.; Chien, S.-C.; Reiner, B. R.; Lin, L.-C.; Wade, C. R.; Ho, W. S. W. Bioinspired Metal–Organic Framework for Trace  $CO_2$  Capture. J. Am. Chem. Soc. **2018**, 140 (40), 12662–12666.

(50) Wright, A. M.; Wu, Z.; Zhang, G.; Mancuso, J. L.; Comito, R. J.; Day, R. W.; Hendon, C. H.; Miller, J. T.; Dincă, M. A Structural Mimic of Carbonic Anhydrase in a Metal-Organic Framework. *Chem.* **2018**, *4* (12), 2894–2901.

(51) Baek, J.; Rungtaweevoranit, B.; Pei, X.; Park, M.; Fakra, S. C.; Liu, Y.-S.; Matheu, R.; Alshmimri, S. A.; Alshehri, S.; Trickett, C. A.; Somorjai, G. A.; Yaghi, O. M. Bioinspired Metal–Organic Framework Catalysts for Selective Methane Oxidation to Methanol. *J. Am. Chem. Soc.* **2018**, *140* (51), 18208–18216.

(52) Osadchii, D. Y.; Olivos-Suarez, A. I.; Szécsényi, Á.; Li, G.; Nasalevich, M. A.; Dugulan, I. A.; Crespo, P. S.; Hensen, E. J. M.; Veber, S. L.; Fedin, M. V.; Sankar, G.; Pidko, E. A.; Gascon, J. Isolated Fe Sites in Metal Organic Frameworks Catalyze the Direct Conversion of Methane to Methanol. *ACS Catal.* **2018**, *8* (6), 5542–5548.

(53) Lee, J.; Farha, O. K.; Roberts, J.; Scheidt, K. A.; Nguyen, S. T.; Hupp, J. T. Metal–organic framework materials as catalysts. *Chem. Soc. Rev.* **2009**, 38 (5), 1450–1459.

(54) Yoon, M.; Srirambalaji, R.; Kim, K. Homochiral Metal– Organic Frameworks for Asymmetric Heterogeneous Catalysis. *Chem. Rev.* **2012**, *112* (2), 1196–1231.

(55) Cohen, S. M. Postsynthetic Methods for the Functionalization of Metal–Organic Frameworks. *Chem. Rev.* **2012**, *112* (2), 970–1000.

(56) Furukawa, H.; Cordova, K. E.; O'Keeffe, M.; Yaghi, O. M. The Chemistry and Applications of Metal-Organic Frameworks. *Science* **2013**, *341* (6149), 1230444.

(57) Liu, J.; Chen, L.; Cui, H.; Zhang, J.; Zhang, L.; Su, C.-Y. Applications of metal-organic frameworks in heterogeneous supramolecular catalysis. *Chem. Soc. Rev.* **2014**, 43 (16), 6011–6061.

(58) Zhao, M.; Ou, S.; Wu, C.-D. Porous Metal–Organic Frameworks for Heterogeneous Biomimetic Catalysis. *Acc. Chem. Res.* **2014**, *47* (4), 1199–1207.

(59) Cui, Y.; Li, B.; He, H.; Zhou, W.; Chen, B.; Qian, G. Metal– Organic Frameworks as Platforms for Functional Materials. *Acc. Chem. Res.* **2016**, 49 (3), 483–493.

(60) Huang, Y.-B.; Liang, J.; Wang, X.-S.; Cao, R. Multifunctional metal-organic framework catalysts: synergistic catalysis and tandem reactions. *Chem. Soc. Rev.* **2017**, *46* (1), 126–157.

(61) Dhakshinamoorthy, A.; Li, Z.; Garcia, H. Catalysis and photocatalysis by metal organic frameworks. *Chem. Soc. Rev.* 2018, 47 (22), 8134–8172.

(62) Xiao, J.-D.; Jiang, H.-L. Metal–Organic Frameworks for Photocatalysis and Photothermal Catalysis. *Acc. Chem. Res.* 2019, 52 (2), 356–366.

(63) Wei, Y.-S.; Zhang, M.; Zou, R.; Xu, Q. Metal–Organic Framework-Based Catalysts with Single Metal Sites. *Chem. Rev.* 2020, 120 (21), 12089–12174.

(64) Feng, L.; Wang, K.-Y.; Willman, J.; Zhou, H.-C. Hierarchy in Metal–Organic Frameworks. *ACS Cent. Sci.* **2020**, *6* (3), 359–367.

(65) Nguyen, H. G. T.; Schweitzer, N. M.; Chang, C.-Y.; Drake, T. L.; So, M. C.; Stair, P. C.; Farha, O. K.; Hupp, J. T.; Nguyen, S. T. Vanadium-Node-Functionalized UiO-66: A Thermally Stable MOF-

Supported Catalyst for the Gas-Phase Oxidative Dehydrogenation of Cyclohexene. ACS Catal. 2014, 4 (8), 2496–2500.

(66) Beyzavi, M. H.; Vermeulen, N. A.; Howarth, A. J.; Tussupbayev, S.; League, A. B.; Schweitzer, N. M.; Gallagher, J. R.; Platero-Prats, A. E.; Hafezi, N.; Sarjeant, A. A.; Miller, J. T.; Chapman, K. W.; Stoddart, J. F.; Cramer, C. J.; Hupp, J. T.; Farha, O. K. A Hafnium-Based Metal–Organic Framework as a Nature-Inspired Tandem Reaction Catalyst. *J. Am. Chem. Soc.* **2015**, *137* (42), 13624– 13631.

(67) Chen, Y.-Z.; Zhou, Y.-X.; Wang, H.; Lu, J.; Uchida, T.; Xu, Q.; Yu, S.-H.; Jiang, H.-L. Multifunctional PdAg@MIL-101 for One-Pot Cascade Reactions: Combination of Host–Guest Cooperation and Bimetallic Synergy in Catalysis. *ACS Catal.* **2015**, *5* (4), 2062–2069.

(68) Manna, K.; Ji, P.; Lin, Z.; Greene, F. X.; Urban, A.; Thacker, N. C.; Lin, W. Chemoselective single-site Earth-abundant metal catalysts at metal–organic framework nodes. *Nat. Commun.* **2016**, 7 (1), 12610.

(69) Kalmutzki, M. J.; Hanikel, N.; Yaghi, O. M. Secondary building units as the turning point in the development of the reticular chemistry of MOFs. *Sci. Adv.* **2018**, *4* (10), eaat9180.

(70) Feng, X.; Song, Y.; Lin, W. Transforming Hydroxide-Containing Metal–Organic Framework Nodes for Transition Metal Catalysis. *Trends Chem.* **2020**, *2* (11), 965–979.

(71) Syed, Z. H.; Sha, F.; Zhang, X.; Kaphan, D. M.; Delferro, M.; Farha, O. K. Metal–Organic Framework Nodes as a Supporting Platform for Tailoring the Activity of Metal Catalysts. *ACS Catal.* **2020**, *10* (19), 11556–11566.

(72) Bour, J. R.; Wright, A. M.; He, X.; Dincă, M. Bioinspired chemistry at MOF secondary building units. *Chem. Sci.* 2020, 11 (7), 1728–1737.

(73) Song, Y.; Feng, X.; Chen, J. S.; Brzezinski, C.; Xu, Z.; Lin, W. Multistep Engineering of Synergistic Catalysts in a Metal–Organic Framework for Tandem C–O Bond Cleavage. *J. Am. Chem. Soc.* **2020**, 142 (10), 4872–4882.

(74) Alamgholiloo, H.; Zhang, S.; Ahadi, A.; Rostamnia, S.; Banaei, R.; Li, Z.; Liu, X.; Shokouhimehr, M. Synthesis of bimetallic 4-PySI-Pd@Cu(BDC) via open metal site Cu-MOF: Effect of metal and support of Pd@Cu-MOFs in  $H_2$  generation from formic acid. *Mol. Catal.* **2019**, *467*, 30–37.

(75) Juan-Alcañiz, J.; Gascon, J.; Kapteijn, F. Metal-organic frameworks as scaffolds for the encapsulation of active species: state of the art and future perspectives. *J. Mater. Chem.* **2012**, *22* (20), 10102–10118.

(76) Zhao, M.; Yuan, K.; Wang, Y.; Li, G.; Guo, J.; Gu, L.; Hu, W.; Zhao, H.; Tang, Z. Metal–organic frameworks as selectivity regulators for hydrogenation reactions. *Nature* **2016**, *539* (7627), 76–80.

(77) Chen, L.; Luque, R.; Li, Y. Controllable design of tunable nanostructures inside metal-organic frameworks. *Chem. Soc. Rev.* **2017**, *46* (15), 4614–4630.

(78) Liu, L.; Zhou, T.-Y.; Telfer, S. G. Modulating the Performance of an Asymmetric Organocatalyst by Tuning Its Spatial Environment in a Metal–Organic Framework. *J. Am. Chem. Soc.* **2017**, *139* (39), 13936–13943.

(79) Feng, L.; Yuan, S.; Zhang, L.-L.; Tan, K.; Li, J.-L.; Kirchon, A.; Liu, L.-M.; Zhang, P.; Han, Y.; Chabal, Y. J.; Zhou, H.-C. Creating Hierarchical Pores by Controlled Linker Thermolysis in Multivariate Metal–Organic Frameworks. *J. Am. Chem. Soc.* **2018**, *140* (6), 2363– 2372.

(80) Huxley, M. T.; Burgun, A.; Ghodrati, H.; Coghlan, C. J.; Lemieux, A.; Champness, N. R.; Huang, D. M.; Doonan, C. J.; Sumby, C. J. Protecting-Group-Free Site-Selective Reactions in a Metal– Organic Framework Reaction Vessel. *J. Am. Chem. Soc.* **2018**, *140* (20), 6416–6425.

(81) Liu, Y.; Shen, Y.; Zhang, W.; Weng, J.; Zhao, M.; Zhu, T.; Chi, Y. R.; Yang, Y.; Zhang, H.; Huo, F. Engineering channels of metal– organic frameworks to enhance catalytic selectivity. *Chem. Commun.* **2019**, 55 (78), 11770–11773.

(82) Bauer, G.; Ongari, D.; Tiana, D.; Gäumann, P.; Rohrbach, T.; Pareras, G.; Tarik, M.; Smit, B.; Ranocchiari, M. Metal-organic frameworks as kinetic modulators for branched selectivity in hydroformylation. *Nat. Commun.* **2020**, *11* (1), 1059.

(83) Hong, K.; Sajjadi, M.; Suh, J. M.; Zhang, K.; Nasrollahzadeh, M.; Jang, H. W.; Varma, R. S.; Shokouhimehr, M. Palladium Nanoparticles on Assorted Nanostructured Supports: Applications for Suzuki, Heck, and Sonogashira Cross-Coupling Reactions. *ACS Appl. Nano Mater.* **2020**, *3* (3), 2070–2103.

(84) Zhang, K.; Cha, J. H.; Jeon, S. Y.; Kirlikovali, K. O.; Ostadhassan, M.; Rasouli, V.; Farha, O. K.; Jang, H. W.; Varma, R. S.; Shokouhimehr, M. Pd modified prussian blue frameworks: Multiple electron transfer pathways for improving catalytic activity toward hydrogenation of nitroaromatics. *Mol. Catal.* **2020**, *492*, 110967.

(85) Cao, C.-S.; Shi, Y.; Xu, H.; Zhao, B. A multifunctional MOF as a recyclable catalyst for the fixation of  $CO_2$  with aziridines or epoxides and as a luminescent probe of Cr(VI). *Dalton Trans.* **2018**, 47 (13), 4545–4553.

(86) Fei, H.; Shin, J.; Meng, Y. S.; Adelhardt, M.; Sutter, J.; Meyer, K.; Cohen, S. M. Reusable Oxidation Catalysis Using Metal-Monocatecholato Species in a Robust Metal–Organic Framework. J. Am. Chem. Soc. **2014**, *136* (13), 4965–4973.

(87) Dan-Hardi, M.; Serre, C.; Frot, T.; Rozes, L.; Maurin, G.; Sanchez, C.; Férey, G. A New Photoactive Crystalline Highly Porous Titanium(IV) Dicarboxylate. *J. Am. Chem. Soc.* **2009**, *131* (31), 10857–10859.

(88) Sono, M.; Roach, M. P.; Coulter, E. D.; Dawson, J. H. Heme-Containing Oxygenases. *Chem. Rev.* **1996**, *96* (7), 2841–2888.

(89) Blain, I.; Slama, P.; Giorgi, M.; Tron, T.; Réglier, M. Coppercontaining monooxygenases: enzymatic and biomimetic studies of the O-atom transfer catalysis. *Rev. Mol. Biotechnol.* **2002**, *90* (2), 95–112.

(90) Punniyamurthy, T.; Velusamy, S.; Iqbal, J. Recent Advances in Transition Metal Catalyzed Oxidation of Organic Substrates with Molecular Oxygen. *Chem. Rev.* **2005**, *105* (6), 2329–2364.

(91) Parmeggiani, C.; Cardona, F. Transition metal based catalysts in the aerobic oxidation of alcohols. *Green Chem.* **2012**, *14* (3), 547–564.

(92) Fulton, J. L.; Hoffmann, M. M.; Darab, J. G.; Palmer, B. J.; Stern, E. A. Copper(I) and Copper(II) Coordination Structure under Hydrothermal Conditions at 325 °C: An X-ray Absorption Fine Structure and Molecular Dynamics Study. J. Phys. Chem. A 2000, 104 (49), 11651–11663.

(93) Groothaert, M. H.; van Bokhoven, J. A.; Battiston, A. A.; Weckhuysen, B. M.; Schoonheydt, R. A.  $Bis(\mu$ -oxo)dicopper in Cu-ZSM-5 and Its Role in the Decomposition of NO: A Combined in Situ XAFS, UV–Vis–Near-IR, and Kinetic Study. *J. Am. Chem. Soc.* **2003**, 125 (25), 7629–7640.

(94) Kau, L. S.; Spira-Solomon, D. J.; Penner-Hahn, J. E.; Hodgson, K. O.; Solomon, E. I. X-ray absorption edge determination of the oxidation state and coordination number of copper. Application to the type 3 site in Rhus vernicifera laccase and its reaction with oxygen. *J. Am. Chem. Soc.* **1987**, *109* (21), 6433–6442.

(95) Deka, U.; Juhin, A.; Eilertsen, E. A.; Emerich, H.; Green, M. A.; Korhonen, S. T.; Weckhuysen, B. M.; Beale, A. M. Confirmation of Isolated Cu<sup>2+</sup> Ions in SSZ-13 Zeolite as Active Sites in NH3-Selective Catalytic Reduction. *J. Phys. Chem. C* **2012**, *116* (7), 4809–4818.

(96) Ikuno, T.; Zheng, J.; Vjunov, A.; Sanchez-Sanchez, M.; Ortuño, M. A.; Pahls, D. R.; Fulton, J. L.; Camaioni, D. M.; Li, Z.; Ray, D.; Mehdi, B. L.; Browning, N. D.; Farha, O. K.; Hupp, J. T.; Cramer, C. J.; Gagliardi, L.; Lercher, J. A. Methane Oxidation to Methanol Catalyzed by Cu-Oxo Clusters Stabilized in NU-1000 Metal–Organic Framework. J. Am. Chem. Soc. **2017**, *139* (30), 10294–10301.

(97) Kau, L. S.; Hodgson, K. O.; Solomon, E. I. X-ray absorption edge and EXAFS study of the copper sites in zinc oxide methanol synthesis catalysts. *J. Am. Chem. Soc.* **1989**, *111* (18), 7103–7109.

(98) Shadle, S. E.; Penner-Hahn, J. E.; Schugar, H. J.; Hedman, B.; Hodgson, K. O.; Solomon, E. I. X-ray absorption spectroscopic studies of the blue copper site: metal and ligand K-edge studies to probe the origin of the EPR hyperfine splitting in plastocyanin. *J. Am. Chem. Soc.* **1993**, *115* (2), 767–776.

Article

(99) Handley, D. A.; Hitchcock, P. B.; Lee, T. H.; Leigh, G. J. Copper(II) adducts with N,N,N',N'-tetramethylethane-1,2-diamine and attempts to prepare trinuclear derivatives. *Inorg. Chim. Acta* **2001**, *316* (1), 59–64.

(100) Zheng, J.; Ye, J.; Ortuño, M. A.; Fulton, J. L.; Gutiérrez, O. Y.; Camaioni, D. M.; Motkuri, R. K.; Li, Z.; Webber, T. E.; Mehdi, B. L.; Browning, N. D.; Penn, R. L.; Farha, O. K.; Hupp, J. T.; Truhlar, D. G.; Cramer, C. J.; Lercher, J. A. Selective Methane Oxidation to Methanol on Cu-Oxo Dimers Stabilized by Zirconia Nodes of an NU-1000 Metal–Organic Framework. J. Am. Chem. Soc. **2019**, 141 (23), 9292–9304.

(101) Primet, M.; Pichat, P.; Mathieu, M. V. Infrared study of the surface of titanium dioxides. I. Hydroxyl groups. *J. Phys. Chem.* **1971**, 75 (9), 1216–1220.

(102) Giordanino, F.; Vennestrøm, P. N. R.; Lundegaard, L. F.; Stappen, F. N.; Mossin, S.; Beato, P.; Bordiga, S.; Lamberti, C. Characterization of Cu-exchanged SSZ-13: a comparative FTIR, UV-Vis, and EPR study with Cu-ZSM-5 and Cu- $\beta$  with similar Si/Al and Cu/Al ratios. *Dalton Trans.* **2013**, *42* (35), 12741–12761.

(103) Borfecchia, E.; Lomachenko, K. A.; Giordanino, F.; Falsig, H.; Beato, P.; Soldatov, A. V.; Bordiga, S.; Lamberti, C. Revisiting the nature of Cu sites in the activated Cu-SSZ-13 catalyst for SCR reaction. *Chem. Sci.* **2015**, *6* (1), 548–563.

(104) Fu, Y.; Sun, D.; Chen, Y.; Huang, R.; Ding, Z.; Fu, X.; Li, Z. An Amine-Functionalized Titanium Metal–Organic Framework Photocatalyst with Visible-Light-Induced Activity for CO2 Reduction. *Angew. Chem., Int. Ed.* **2012**, *51* (14), 3364–3367.

(105) Zhang, R.; Li, G.; Zhang, Y. Photochemical synthesis of CdS-MIL-125(Ti) with enhanced visible light photocatalytic performance for the selective oxidation of benzyl alcohol to benzaldehyde. *Photochem. Photobiol. Sci.* **2017**, *16* (6), 996–1002.

(106) Singh, L.; Rekha, P.; Chand, S. Cu-impregnated zeolite Y as highly active and stable heterogeneous Fenton-like catalyst for degradation of Congo red dye. *Sep. Purif. Technol.* **2016**, *170*, 321–336.

(107) Mirica, L. M.; Ottenwaelder, X.; Stack, T. D. P. Structure and Spectroscopy of Copper–Dioxygen Complexes. *Chem. Rev.* **2004**, *104* (2), 1013–1046.

(108) Woertink, J. S.; Smeets, P. J.; Groothaert, M. H.; Vance, M. A.; Sels, B. F.; Schoonheydt, R. A.; Solomon, E. I. A  $[Cu_2O]^{2+}$  core in Cu-ZSM-5, the active site in the oxidation of methane to methanol. *Proc. Natl. Acad. Sci. U. S. A.* **2009**, *106* (45), 18908.

(109) Mahyuddin, M. H.; Shiota, Y.; Staykov, A.; Yoshizawa, K. Theoretical Overview of Methane Hydroxylation by Copper–Oxygen Species in Enzymatic and Zeolitic Catalysts. *Acc. Chem. Res.* **2018**, *51* (10), 2382–2390.