Inorganic Chemistry

Article

Sequential Connection of Mutually Exclusive Catalytic Reactions by a Method Controlling the Presence of an MOF Catalyst: One-Pot Oxidation of Alcohols to Carboxylic Acids

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Cite This: https://dx.doi.org/10.1021/acs.inorgchem.0c02809			Read Online		
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ABSTRACT: A functionalized metal-organic framework (MOF) catalyst applied to the sequential one-pot oxidation of alcohols to carboxylic acids controls the presence of a heterogeneous catalyst. The conversion of alcohols to aldehydes was acquired through aerobic oxidation using a well-known amino-oxy radical-functionalized MOF. In the same flask, a simple filtration of the radical MOF with mild heating of the solution completely altered the reaction media, providing radical scavenger-free conditions suitable for the autoxidation of the aldehydes formed in the first step to carboxylic acids. The mutually exclusive radical-catalyzed aerobic oxidation (the first step with MOF) and radical-inhibited autoxidation (the second step without MOF) are sequentially achieved in a one-pot manner. Overall, we demonstrate a powerful and efficient method for the sequential oxidation of alcohols to carboxylic acids by employing a readily functionalizable heterogeneous MOF. In addition, our MOF in-and-out method can be utilized in an environmentally friendly way for the oxidation of alcohols to carboxylic acids of industrial and economic value with broad functional group tolerance, including 2,5-furandicarboxylic acid and 1,4-benzenedicarboxylic acid, with good yield and reusability. Furthermore, MOF-TEMPO, as an



antioxidative stabilizer, prevents the undesired oxidation of aldehydes, and the perfect "recoverability" of such a reactive MOF requires a re-evaluation of the advantages of MOFs from heterogeneity in catalytic and related applications.

INTRODUCTION

Metal-organic frameworks (MOFs) are emerging organicinorganic hybrid and porous materials for catalytic applications.¹⁻⁴ MOFs serve as an excellent platform for designing heterogeneous catalysts by combining molecular functional groups into solid-state materials because of their high porosity, stability, and tunability, and these heterogeneous catalysts have been utilized for a wide range of organic transformations.^{5–10} The metal cations or clusters on the node of MOFs could act as a Lewis acid catalytic site for organic transformations. In addition, the fine tunability of ligands allows the installation of active catalytic species such as metal complexes or radical moieties on the ligand struts of MOFs.⁹⁻¹³ Most importantly, a number of catalytic species could be strategically introduced into a single MOF through multifunctionalization or multivalent MOFs.¹⁴ The well-designed MOF-based catalysts and in-depth mechanistic investigations have been reported to afford catalysts that outcompete homogeneous catalysts under certain reactions.

MOF-based heterogeneous catalysts with more than two different catalytic sites could perform a sequential or a tandem organic transformation in a single pore.^{14–25} For example, the oxidation of alcohols to aldehydes and Knoevenagel condensation could be sequentially connected in a single MOF catalyst,²¹ and the epoxidation of alkenes followed by epoxide opening with various nucleophiles could be performed through a domino reaction type (Scheme 1).²³ The tandem reactions with

MOF-based heterogeneous catalysts, however, have been developed using the chemoselectivity of organic transformations. In previous studies, the catalytic species for Knoevenagel condensation did not impact the catalytic cycle of oxidation (the first step), and the catalytic species and mechanisms of aerobic oxidation have no effect on Knoevenagel condensation. At the same time, the catalytic system for epoxidation and ring-opening should not interfere with or damage the two reactions. Therefore, the mutually exclusive two or more catalytic reactions cannot be achieved by a single MOF even with multifunctionalization.

To connect two incompatible organic reactions following a mechanistic viewpoint, we focused on the excellent heterogeneity of MOFs with the ultimate tunability of organic ligands. Although radical-catalyzed reactions and radical-inhibited mechanisms cannot be connected or performed in a single pore, the catalytic MOF platform provides the perfect control of radicals (i.e., catalytically active species) via addition and removal for each transformation by filtration or centrifugation

Received: September 21, 2020







(b) Tandem reaction including epoxidation: Farha (2015), Cui (2017)



(c) Tandem reaction including oxidation of aldehydes: Cui (2018), Su (2019), Dong (2019)



(Scheme 1). In this case, the radical-catalyzed reaction as the first step is performed, and then the reaction medium is changed for autoxidation by removing the radical-functionalized MOFs. While this MOF in-and-out method (i.e., MOF catalyst "in" for the first step and MOF catalyst "out" for the second step) simply applies to the reaction procedures, two mutually exclusive

transformations can sequentially occur for efficient synthesis. In this work, for the first time, we report the MOF in-and-out method that originated from the heterogeneity with finetunability of MOFs and is not based on chemoselectivity, to the best of our knowledge.

We used the sequential one-pot oxidation reactions of alcohols to carboxylic acids in a method controlling the presence of MOF-TEMPO (TEMPO = (2,2,6,6-tetramethylpiperidin-1yl)oxyl) (the MOF in-and-out method). The MOF-catalyzed aerobic oxidation of alcohols to corresponding aldehydes is wellknown chemistry and is widely studied. A variety of strategies have been incorporated into MOFs to carry out aerobic oxidation, and they could be generally categorized as aminooxy-radical-containing MOFs,^{26–32} metal-cation-incorporated MOFs,^{33–38} and metal-nanoparticle-embedded MOFs.^{39–42} In particular, a zirconium-based UiO series of MOFs (UiO = University of Oslo) with TEMPO have been extensively studied with respect to aerobic oxidation.^{30,31} Zhaung and co-workers successfully developed an efficient aerobic oxidation of alcohols to aldehydes with MOF-TEMPO in the UiO-68 platform in the presence of O₂, and the synergic effect between Zr nodes of MOF and TEMPO was investigated.³⁰

Molecular dioxygen (O_2) is commonly utilized as the final oxidant for all the three types of MOF catalysts (Scheme 1), and water is produced as the only byproduct. However, the oxidation of alcohols to aldehydes has not been successful with most of the functionalized MOFs. Until now, the overoxidation of aldehydes to carboxylic acids by employing such MOF-based catalysts has not been reported. This is because the second step in oxidation, autoxidation, is inhibited by radicals such as TEMPO.43-Therefore, neither aerobic oxidation nor autoxidation can occur sequentially from alcohols to carboxylic acids in the same flask or in a single MOF pore. In the homogeneous system, the dehydrogenation and oxidation processes have been developed to convert alcohols to carboxylic acids with transition-metal systems^{47–50} and metal-free systems.^{51–53} It should be noted that the amino-oxy-radical-catalyzed aerobic oxidation of alcohols to carboxylic acids through iron-catalyzed reactions [the $Fe(NO_3)_3$ /TEMPO system and TEMPO-consumption process] and the electrochemical methods (with aminefunctionalized TEMPO) has been recently illustrated in the case of homogeneous catalysis.⁵⁴⁻⁶² Finally, a TEMPOfunctionalized polymer was also utilized for the oxidation of alcohols to carboxylic acids in mechanochemical systems.⁶³ This polymer-based catalyst, however, is the combinatorial system between TEMPO and another oxidant: Oxone. TEMPO is used in the aerobic oxidation of alcohols to aldehydes followed by the Oxone-catalyzed second oxidation to carboxylic acids. The catalysis is not able to be recycled without refilling Oxone.

To achieve selective transformation from alcohols to carboxylic acids using heterogeneous, well-known, TEMPOfunctionalized MOFs, our MOF in-and-out method was thoroughly investigated via optimization and control experiments. Research on the MOF-catalyzed oxidation of alcohols to carboxylic acids has been sluggish, relative to that of other available catalytic systems, due to multiple limitations, including the incorporation of the produced carboxylic acids into the structures of MOF catalysts,²⁷ the difficulty of controlling the selectivity, 64,65 the inhibition of overoxidation by amino-oxy radicals, $^{26-32}$ the detachment of oxy species from MOFs through N–O cleavage (by Fe catalysts), 66,67 the accumulation of salts in MOFs (by excess amounts of OCl sources), $^{60-62}$ and the narrow scope of aliphatic substrates.^{68,69} Indeed, we confirmed the facile recoverability of the MOF used for this study, which is a significant advantage of MOFs and has not received as much attention as their reusability in the literature. The deterrence of MOF-TEMPO to autoxidation was also verified to efficiently stabilize benzaldehyde in air as a practical

application of this study. Moreover, our MOF in-and-out method was demonstrated to cover a wide range of substrates producing products in relatively good yields as well as being recycled for up to eight cycles (for the step with the MOF).

RESULTS AND DISCUSSION

Screening of Catalytic Conditions and Control Experiments. We rationally selected a well-known, simple, stable zirconium-based UiO-68-TEMPO (MOF-TEMPO, Scheme 2)





as a TEMPO-functionalized MOF catalyst and tert-butyl nitrite (TBN) to design our method for continuous two-step oxidation processes from alcohols to carboxylic acids.^{30,31} The main ligand, TPDC-TEMPO (TPDC = *p*-terphenyl-4,4["]-dicarboxylic acid), and MOF-TEMPO (from the reaction with $ZrCl_4$) were prepared by previously reported procedures with minor modifications, as illustrated in Scheme 2.^{30,31} MOF-TEMPO as the main MOF catalyst was obtained by isolating pale-pink octahedral crystals. The structure of MOF-TEMPO was confirmed by powder X-ray diffraction (PXRD) patterns (Figure S1). The TEMPO functionality in MOF was characterized by ¹H nuclear magnetic resonance (NMR) spectroscopy after acid digestion (Figure S2). Finally, N₂ adsorption/desorption experiments were conducted to determine the porosity and surface area of MOF-TEMPO (Figure S3). The BET (Brunauer-Emmett-Teller) surface area was calculated to be $871 \text{ m}^2/\text{g}$, and the pore size distribution analysis through the NLDFT (nonlock density functional theory)⁷⁰ model displayed 12 and 15 Å for the main contributions (Figure S3). Since the TEMPO moiety connected to an amide group is quite large, the surface area and the pore size were decreased, compared to those of pristine UiO-68 (2143 m²/g for the BET surface area and 16.4 to 17.7 Å for the pore size).⁷

As the first step, the aerobic oxidation of benzyl alcohol (1a) to benzaldehyde (2a) was first optimized through a combination of MOF-TEMPO and TBN, as summarized in Table 1 (entries 1-3). No significant conversion of 1a to 2a was observed by MOF-TEMPO or TBN alone in acetonitrile (CH₃CN) under an O2 atmosphere. When both MOF-TEMPO and TBN were introduced into the reaction solution (entry 4), 1a was nearly fully oxidized to 2a at room temperature within 2 h. Notably, in the presence of MOF-TEMPO, the overoxidation of 2a to benzoic acid (3a) was not indicated under any conditions, as confirmed by TLC (thin-layer chromatography), GC (gas chromatography), and ¹H NMR spectroscopy (Table 1, entry 4 and Table S1, entry 5). It should be noted that 3a was not produced in the previous study for the aerobic oxidation of 1a to 2a by elevating the temperature to 80 °C under the same catalytic condition (UiO-68-TEMPO and TBN).³⁰ As mentioned earlier, the optimized conditions involve two steps: (i) 2a

Table 1. Optimization of the Reaction Conditions^a



^{*a*}Reaction conditions: **1a** (0.5 mmol, 54 mg), MOF-TEMPO (0.025 mmol, 16 mg), TBN (0.1 mmol), and solvent (1 mL) were used. The reaction was stirred under an O_2 balloon at 25 °C for 2 h, followed by the filtration of MOF-TEMPO and additional stirring under an O_2 balloon at 80 °C for 10 h. ^{*b*}O = used; X = not used. ^{*c*}GC conversion; n.r. = no reaction. ^{*d*}No MOF-TEMPO filtration. ^{*c*}After the filtration of MOF-TEMPO, the reaction was stirred under an O_2 balloon at 60 °C for 10 h. ^{*f*}Isolated yield (%).

was first generated by performing the first step at 25 °C for 2 h; (ii) after MOF-TEMPO was easily separated by centrifugation, 3a was acquired in the second step by heating the reaction mixture to 80 °C. Interestingly, MOF-TEMPO was recovered after oxidation of the alcohol to the aldehyde, and an approximately quantitative amount of 3a was obtained (entry 6) via oxidation of **2a** in the presence of O_2 at 80 °C for 10 h. The conversion of 2a to 3a was sensitive to the variation in the reaction temperature (Table 1, entries 5 and 6 and Table S1, entries 1–4). On the basis of the boiling point of CH₃CN, 80 °C was appropriate for autoxidation (Table 1, entry 6). The nature of the solvent substantially influenced the outcome of the autoxidation of the aldehyde to the carboxylic acid. For example, when 1,2-dichloroethane (1,2-DCE) was used instead of CH₃CN, the conversion was lowered (83%; Table S1, entry 6). Additionally, other solvents such as ethyl acetate, toluene, water, and 1,4-dioxane were not effective for the oxidation of 1a to 2a, along with no formation of 3a (Table S1, entries 7-10). In addition to the transformation of 2a to 3a, the autoxidation reaction of 2a to 3a was significantly affected by the solvents (Table S2, entries 4-8).

To identify the sequential oxidation better, a series of control experiments were conducted, as shown in Scheme 3. The presence of homogeneous or heterogeneous TEMPO species notably suppressed the generation of carbonyl compound 3a (Scheme 3a,c), implying that the autoxidation as the second step was inhibited by an additional radical species or a solid catalyst in solution. Furthermore, as depicted in Scheme 3d,e, the presence of MOF-TEMPO was altered for direct comparison. First, when the conversion of 1a to 2a was completed and the second step was carried out by recovering MOF-TEMPO, a conversion rate of 52% to 3a was formed after 4 h. Not surprisingly, upon reintroduction of MOF-TEMPO into the reaction, the conversion was stopped (after both 6 and 8 h, 51%). Again, the formation of 3a was increased after 10, 12, and 14 h (72, 87, and 96%, respectively) by removing MOF-TEMPO from the reaction.

As displayed in Scheme 4a, **3a** was not produced when the first step was not completed by the indication of the remaining **1a** (Scheme 4a). This result is consistent with the observation that Scheme 3. Control Experiments (I) to Identify the Involvement of the Radical Species in the Second Step^{*a*}



^an.d., not detected.





1a can quench free radicals that are involved in autoxidation.⁷³ Basically, the full conversion of alcohols to aldehydes is required for the efficient second step. In addition, *tert*-butyl alcohol (*t*-BuOH) generated as a byproduct of TBN, as shown in Scheme 4b, did not inhibit the radical reaction, as expected because it is a tertiary alcohol.⁷³ Finally, the requirement of O₂ in the second step was verified by conducting the reaction under an N₂ atmosphere (Scheme 4c,d). In the absence of O₂, the aldehyde was not oxidized to the carboxylic acid, confirming that such a conversion occurs through autoxidation.

Substrate Scope for Sequential One-Pot Oxidation. Our MOF in-and-out method involved in controlling the presence of MOF-TEMPO was tested for the sequential one-pot oxidation of diverse substrates. Under our optimized conditions, the conversion of alcohols to aldehydes (first step) was monitored by TLC. When alcohols were completely transformed to aldehydes, MOF-TEMPO was removed and the second step was conducted. As illustrated in Scheme 5,

Scheme 5. Substrate Scope Tested for Producing Various Carboxylic Acids via Our MOF in-and-out Method



substituted benzyl alcohols with a wide range of functional groups, heterocyclic alcohols, and aliphatic alcohols underwent two-step oxidation to yield the desired carboxylic acids. Using benzyl alcohols with distinct electronic (1a, 1b, 1e-1h, 1I, and 1p) and steric (1c, 1d, 1i, and 1j) properties, the corresponding benzoic acids were obtained in very good to excellent yields (83–99%). Unfortunately, functional moieties, including different halogens (3k), amines (3m), and boronic esters (3n), resulted in relatively moderate yields (50–65%).

It should be emphasized that the production of boronic estersubstituted benzoic acid (**3n**) through sequential oxidation reactions of **1n** is very important. Compound **3n** is not easily generated via traditional oxidation reactions using strong oxidants because the C–B bond is fragile.⁷⁴ In addition, terephthalic acid (**3o**), which is a representative ligand for general MOFs and is industrially useful, was obtained in 81% yield upon oxidation of 1,4-benzenedimethanol (**1o**) at para positions. Given that the efficiency of the autoxidation of heterocyclic aldehydes was not good under our optimized conditions, these substrates were prepared under modified conditions where the solvent was changed from CH₃CN to 1,4-

dioxane. As shown in Scheme 5, sequential oxidation reactions of 2-furanmethanol (1q), 2-thiophenemethanol (1s), and 3thiophenemethanol (1t) were performed by forming the corresponding carboxylate acids in good to excellent yields (80-90%). Biomass-derived 5-(hydroxymethyl)furfural (1r, HMF) was tested to be oxidized to 2,5-furandicarboxylic acid (3r, FDCA), which has been the subject of many studies in both homogeneous and heterogeneous catalysis. Notably, the oxidation of 1r at para positions occurred, and 2,5-furandicarboxylic acid (3r) was generated in 88% yield.⁷⁵ These overall observations regarding the substrate scope highlight that our MOF in-and-out method is useful for producing a variety of carboxylic acids. Finally, the substrate scope was extended to aliphatic alcohols by changing the solvent from CH₃CN to ethyl acetate. The conversion from alcohols to carboxylic acids was observed in both CH₃CN and ethyl acetate. Note that the system using ethyl acetate achieved full conversion in a shorter time, relative to that using CH₂CN, 1-Hexanol (1u) and 1dodecanol (1w) were oxidized by our method affording the desired hexanoic acid (3u) and dodecanoic acid (3w) (89 and 92%, respectively). In our previous study, the reactivity of the TEMPO species onto the surface of MOFs was intensively studied.³⁴ Since the present MOF-TEMPO has active TEMPO species on the surface, the substrate size discrimination with large substrates was not attempted in this MOF in-and-out method for the synthesis of carboxylic acids.

Mechanistic Studies Employing ¹H NMR and EPR Spectroscopy. To identify the involvement of TBN in the sequential oxidation reactions, we performed in situ NMR studies in CD_3CN , as depicted in Figure 1. We first found that



Figure 1. In situ NMR studies of the second step. Experimental conditions: [1a] = 0.25 M, [MOF-TEMPO] = 12.5 mM, [TBN] = 50 mM, and CD_3CN .

TBN could form *t*-BuOH (after 0 h, \bigtriangledown , Figure 1) in the first step. Upon performing the second step, a new peak in the aliphatic region was shown (\blacktriangledown , Figure 1). The intensity of the new peak (\blacktriangledown) increased as the reaction progressed, and this peak in the ¹H NMR was not assigned to any known, *tert*-butoxide-related compounds such as peroxides (Figure S4). As expected, it was difficult to confirm the exact structure due to the

unstable behavior of NO_x)⁷⁶ but in situ ¹H NMR and GC–MS analyses indicated the molecular species carrying the fragments of *tert*-butyl and N_xO_x (Figures S4–S6). The peak (\checkmark) was observed only by elevating the reaction temperature, and the second oxidation was initiated at 80 °C. Thus, both TBN and the radical-terminating step could be activated by heating, and *t*-BuON_xO_x may be monitored by ¹H NMR. Regardless of the change in the behavior of TBN, we detected 2a (\diamondsuit) and 3a (\blacklozenge) when the reactions proceeded, and the peaks corresponding to the expected byproducts such as peroxybenzoic acid were not observed.

To determine the presence of active radical species at room temperature as well as their elimination at 80 °C, additional studies were conducted. The experiments with an NHC (Nheterocyclic carbene) ligand, published by Lee and coworkers,⁷⁷ for trapping active radical species from TBN in the second step were performed by employing EPR (electron paramagnetic resonance) and NMR spectroscopy, as presented in Figures S7 and S8. The ¹H NMR studies confirmed that NHC captured radicals and generated paramagnetic species when TBN derivatives were exposed to O_2 at 25 °C. When the TBN derivative was exposed at 80 °C (the thermal treatment for the second step), NHC showed inherent signals in both ¹H NMR and EPR. The EPR studies verified that TBN derivatives maintained their radical character (expected for NHC-NO species) when being exposed to O_2 at room temperature, and radical-free conditions from TBN derivatives could be obtained at an elevated temperature of 80 °C. The observations of a chemical shift in ¹H NMR and distinct EPR signals by changing the temperature, along with multiple control experiments (Schemes 3 and 4), demonstrated that active radical species in the reaction without MOF-TEMPO could be eliminated by thermal activation. This alteration of the reaction environment allowed the second step (the autoxidation of aldehydes to carboxylic acids).

Scheme 6. Proposed Mechanisms for Sequential Oxidation Reactions by Controlling the Presence of MOF-TEMPO



On the basis of the overall experimental results and previous reports,^{78–86} Scheme 6 illustrates the proposed mechanisms for the sequential one-pot oxidation reactions. Controlling the presence of MOF-TEMPO is a critical factor in achieving such oxidation reactions. TBN or TBN derivatives do not affect the autoxidation in the second step after thermal treatment. As the first step with MOF-TEMPO, the aerobic oxidation of alcohols to aldehydes is in general thought to proceed via two previously reported cooperative redox cycles: the oxidation cycle of an external oxidant and the NO cycle associated with O_2 and water.⁶⁹ After MOF-TEMPO is removed, the remaining TBN naturally decomposes or becomes inactive adducts at 80 °C (Scheme S1),⁷⁶ which provides radical-free conditions for the

next step. Finally, the aldehydes produced from the first step are oxidized to their corresponding carboxylic acids through autoxidation.^{73,87–91}

Applications of the MOF in-and-out Method: Recycling and the Antioxidative Effect. To confirm the applicability of our method of oxidizing alcohols to carboxylic acids of industrial and economic value in an environmentally friendly manner, we designed gram-scale reaction conditions. This testing can also verify the recovery and reusability of the MOF catalyst employed in this work. As shown in Figure 2, the



Figure 2. Recycling test of MOF-TEMPO for the sequential oxidation of benzyl alcohol to benzoic acid.

recovered MOF-TEMPO was used for at least eight additional cycles without the loss of its catalytic activity in the conversion of 1a to 2a. The autooxidation of 2a to 3a was successfully achieved under an O₂ atmosphere on the gram scale for each cycle. After each run for aerobic oxidation (the first step), the MOF-TEMPO solids were recovered by centrifugation, washed with organic solvents such as CH₃OH and CH₃CN, and dried to monitor their stability. The microscope and SEM (scanning electron microscope) images of MOF-TEMPO (before the reaction) after recovery showed no significant change in the morphology (Figure S9). Then, the recovered MOF-TEMPO solids were structurally analyzed by PXRD after several cycles, as compared to the original MOF-TEMPO. The PXRD patterns of the recovered MOF-TEMPO after one, three, four, five, and eight cycles, as depicted in Figure S10, indicated that the main peaks were retained, although the overall patterns were broadened. This analysis suggested that the structural integrity of MOF-TEMPO was relatively stable over several cycles. It should be noted that similar PXRD patterns after recovery were frequently observed with TEMPO-functionalized MOFs in the literature.^{31,36,92} After the eighth run, the conversion of the first step (aerobic oxidation) was slightly decreased (i.e., no full conversion of the alcohol to the aldehyde). Since the remaining alcohol can prevent the second step (autoxidation; Scheme 3), the recycling test was not carried out further.

As an opposite approach, the protective effect of MOF-TEMPO against the autoxidation of aldehydes to the corresponding carboxylic acids was evaluated. This application would be useful for keeping aldehydes relatively pure under ambient conditions. After the incubation of **2a** at 25 °C for 7 days in a scintillation vial without a cap, a total 45% conversion to **3a** was determined by ¹H NMR, as illustrated in Figure 3. In



Figure 3. ¹H NMR spectra and pictures obtained from testing the oxidation of benzaldehyde (top) with and (bottom) without MOF-TEMPO.

the optical observation, the massive colorless precipitates (**3a**) were detected after the incubation of **2a** without MOF-TEMPO. In contrast, the addition of 2 wt % MOF-TEMPO into the vial containing **2a** exhibited more than 99% purity of the compound under the same conditions. Moreover, the TEMPO ligand and Zr(IV) from MOF-TEMPO were not dissociated after the reactions, as confirmed by ¹H NMR and ICP-OES, respectively (Figure 3; inductively coupled plasma-atomic emission spectroscopy (ICP-OES)). Together, the applications of MOF-TEMPO shown in this study include the sequential two-step catalytic oxidation reactions and the stabilization of aldehydes against autoxidation. Such utilization is useful and practical because MOFs are perfectly heterogeneous and their structures and excellent stability can be fine-tuned through the functionalization of organic ligands.

EXPERIMENTAL SECTION

Preparation of MOF-TEMPO. TPDC-TEMPO (214 mg, 0.42 mmol), $ZrCl_4$ (96 mg, 0.42 mmol), and benzoic acid (BzOH, 760 mg, 6.2 mmol) were placed in a 250 mL roundbottomed flask with a magnetic stirring bar (3 mm × 6 mm), and the solid mixtures were fully dissolved in DMF (DMF = *N*,*N*-dimethylformamide, 16 mL). The mixture was stirred (300 rpm) at 120 °C in a heating mantle for 48 h and then cooled to room temperature. The pale-pink octahedral crystals were isolated by filtration and washed five times with fresh DMF (5 × 10 mL), washed five times with MeOH (5 × 10 mL), and washed five times with CH₃CN (5 × 10 mL). Then heating to 40 °C under vacuum for 12 h yielded the activated MOF-TEMPO.

General Procedure for the MOF-TEMPO in-and-out Method. Alcohol reagent (0.25 mmol), MOF-TEMPO (8 mg, 0.0125 mmol), and CH₃CN (1 mL) were added to a scintillation vial. *tert*-Butyl nitrite (5 mg, 0.05 mmol) was added to the solution mixture, and then the mixture was stirred at 25 °C for 2–24 h under an O₂ balloon (1 atm). The reaction was monitored by TLC (thin-layer chromatography). When the conversion of alcohol to aldehyde was complete (by TLC monitoring), subsequently MOF-TEMPO was recovered from the reaction mixture by a syringe filter. Approximately 2 × 0.25 mL of solvent (mainly CH₃CN, 1,2-dichloroethane, or 1,4dioxane by a substrate) was used to prevent yield loss. Then the reaction mixture was stirred for the second step under an O₂ balloon (1 atm) at 80 °C for 10–24 h. After completion (monitored by TLC), the desired product was isolated by silica gel column chromatography with ethyl acetate and *n*-hexane.

CONCLUSIONS

The development of multifunctional MOF-based catalysts, especially for tandem or sequential organic transformations, is the important topic in heterogeneous catalysis. The finetunability of MOFs opens up many possibilities for tandem organic reactions in a single MOF pore; however, the combinations of organic transformations are limited to chemoselective reactions. Although various heterogeneous catalytic reactions directed by MOFs have been extensively studied with respect to the aerobic oxidation of alcohols to aldehydes, sequential two-step oxidation reactions from alcohols to carboxylic acids in an MOF platform remain very challenging. The two representative oxidations of organic molecules, the aerobic oxidation of alcohols to aldehydes, and the autoxidation of aldehydes to carboxylic acids cannot occur sequentially due to their distinct mechanistic cycles, and this discontinuity has been considered to be the benzaldehyde oxidation paradox in common organic chemistry laboratories.

To achieve such challenging sequential oxidation reactions without the consumption of catalytic TEMPO species, we developed the MOF in-and-out method on the basis of carefully analyzing the mechanisms of both the TEMPO-catalyzed aerobic oxidation of alcohols to aldehydes and the radicalinhibited autoxidation of aldehydes to carboxylic acids. The twostep oxidation of alcohols to carboxylic acids succeeded under mild conditions simply by managing the presence or absence of a heterogeneous MOF-TEMPO catalyst and radical species. Our MOF in-and-out method demonstrates a broad substrate scope and is easily utilized in industrially applicable gram-scale reactions. Additionally, the catalyst MOF-TEMPO can be recycled multiple times by maintaining its catalytic activity. It should be noted that previous homogeneous one-pot Fe-TEMPO and electrochemical methods for the oxidation of alcohols to carboxylic acids are not recyclable.

Our MOF in-and-out method also overcomes the incompatibility of MOF catalysts with carboxylic acids produced from the reactions. As the two main concerns regarding the compatibility of carboxylic acids with MOF catalysts, trapping carboxylic acids into the MOF pores and the additional coordination of carboxylic acids to the MOF nodes are much less relevant in our MOF in-and-out system than in previously reported studies. Furthermore, MOF-TEMPO used as a catalytic platform in this work highlights its recoverability from the solution because of the heterogeneous characteristics of MOFs. The recoverability of MOFs with excellent tunability and stability has not been fully revealed as a great advantage, compared to their reusability and reactivities in catalytic applications. Moreover, on the basis of mechanistic studies of MOF-TEMPO, this MOF catalyst is confirmed to be an excellent antioxidative stabilizer against the undesired oxidation of aldehydes in reagent containers of general laboratories.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.inorgchem.0c02809.

Additional figures, schemes, and characterization data for the obtained compounds (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was supported by the Basic Science Research Program (2019R1A2C4070584) and the Science Research Center (2016R1A5A1009405) through the National Research Foundation of Korea (NRF) funded by the Ministry of Science and ICT. S.K. was supported by the NRF Global Ph.D. Fellowship Program (2018H1A2A1062013) funded by the Ministry of Education. The EPR experiment was supported by the Institute for Basic Science (IBS-R010-D1) in Korea. We thank Prof. Eunsung Lee (POSTECH, Korea) and Prof. Jinho Kim (Incheon National University, Korea) for mechanistic discussions with EPR and radicals. We also thank Younghu Son and Prof. Minyoung Yoon (Kyungpook National University, Korea) for assistance with MOF characterization.

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