MOF-derived metal oxide clusters in porous aluminosilicates: a catalyst design for the synthesis of bioactive aza-heterocycles

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Supporting Information Placeholder

ABSTRACT: Simple solid-state mixing and calcination of catalytic amounts of MOFs in the presence of aluminosilicates allows for the generation of active and robust supported metal oxide nanoparticles that catalyze C-C and C-N bond formations. The proposed Cu and Zn containing aluminosilicates outperform state-of-the-art solid catalysts for the synthesis of various aza-heterocycles under mild and heterogeneous conditions, exhibiting the highest TOFs ever reported for cost-efficient and reusable CuO and ZnO active sites.

KEYWORDS: metal oxides, MOFs, organic synthesis, N-heterocycles, heterogeneous catalysis, aluminosilicates.

New strategies are needed to improve the activity and selectivity of MOF catalysts in industrial synthesis of organic molecules. In our group, we have recently designed reusable and heterogeneous catalytically active metal sites in MOFs as an eco-friendly alternative to traditional homogeneous organic catalysts.¹ Full coordination of the metal sites and/or poor accessibility of the inner active sites in the crystal are the main challenges to improve its catalytic activity in comparison with homogeneous catalysts. Although the generation of active defects in highly stable frameworks, like UiO-66 with its normally 8-coordinated Zr^{4+} , partially solves the problem,^{1b,c} an excessive amount of defects compromises the stability of the framework, especially for more labile MOFs with tetrahedrally coordinated Zn^{2+} or Cu^{2+} metals.²

Alternatively, it is possible to thermally decompose these bulk MOFs into high performance carbons³ or metal catalysts.⁴ With the aim of decreasing the cost of such MOF derived catalysts, lower amounts of MOF are proposed here as precursor of metal oxide catalytic species on inexpensive and robust aluminosilicates (~1 wt.% MOF with respect to the aluminosilicate). The excellent dispersion of the metal-oxo clusters in the MOF precursor (spaced by the organic linker in the extended framework) and the very low MOF loading, produce well-dispersed nanoparticles after thermal decomposition of the linker with respect to the use of discrete molecular species, such as acetate salts or preformed metal nanoparticles in a porous zeolite support (Fig. 1, top).⁵ Despite the widespread use of supported metal oxide nanoparticles in the synthesis of bulk chemicals and petrochemicals (selective oxidations, NH_3 and MeOH synthesis, etc.), their application in the production of fine chemicals and pharmaceuticals has been largely overlooked, due to their smaller production scale.⁶ However, it is necessary to develop alternative strategies to selectively modify important bio-active scaffolds in a clean and efficient manner, avoiding the waste generated during the steps of purification of pharmaceutically interesting compounds.

Figure 1. Pharmaceutically interesting scaffolds obtained using well-dispersed MOF derived metal oxides within porous H-USY.

The new general methodology presented here is based on the solvent-free grinding and co-calcination of catalytic amounts of MOFs (HKUST-1 or MOF-5) with aluminosilicates (USY or MCM-41). This solid-state synthesis allows to generate MOF derived non-precious metal oxide nanoparticles as catalysts in C-C (alkynylation, alkylation, aldol condensation, hetero-Diels-Alder) and C-N (amination) bond formations to make propargylamine, (spiro)(ox)indole and quinoline derivatives (Fig. 1, bottom),⁷ with the highest TOFs ever reported for simple $H^+/Zn/CuO$ active sites. The MOF derived metal oxide MO in the H-USY zeolite used as support is abbreviated in this work as “ $MO_{MOF}Y_w$ ”, where M is Zn or Cu and w indicates the weight percentage (A, B, C) of metal in each sample (see Tables S1-S2). For comparison purposes, zinc or copper acetates as precursors of metal oxides “ $MO_{Ac}Y_w$ ” were employed, following a similar synthetic procedure (see supporting information for details).

On the one hand, X-ray diffraction (XRD) patterns of the $CuO_{MOF}Y_C$ and $ZnO_{MOF}Y_C$ catalysts, which contain the higher metal loading, indicate that the zeolite structure is maintained after its co-calcination with the MOF (at 550 °C in air for 4 h). Diffraction peaks of the MOF precursor vanish; new peaks appear corresponding to the CuO or ZnO phases around 20 ~ 30-40 degrees (see Fig. 2a). N_2 physisorption suggests some decrease of the H-USY porosity due to MOF derived metal oxide species since the microporous volume (obtained by t -plot) of the starting zeolite decreases from 0.28 cm³g⁻¹ to 0.25 cm³g⁻¹ after calcining the MOFs in the presence of the H-USY support, as well as its surface area (see Fig. 2b and Table S3). Temperature

Figure 2. (a) XRD, (b) N₂ physisorption, (c) NH₃-TPD (left) and XAS (right) of the MOF derived metal oxide on H-USY support.

programmed NH₃ desorption (NH₃-TPD) experiments show the higher strength of the acid sites in the H-USY support with respect to those in the acid mesoporous silica H-MCM-41(Al). The incorporation of MOF derived metal oxide slightly decreases the number of acid sites (H⁺) and affects their strength distribution (see left part of Fig. 2c). Finally, X-ray Absorption Spectroscopy (XAS) indicates that the Cu active sites are in the form of CuO (see right part of Fig. 2c).

The supported CuO_{MOF}Y metal oxide samples were employed as catalysts in C-C (alkynylation) and C-N (amination) bond forming reactions involving a multicomponent reaction between alkyne, aldehyde and amine groups, a green process for the synthesis of bio-active propargylamines.⁸ Copper catalysts have been traditionally employed due to their low cost and toxicity, especially when immobilized in a solid support.⁹ The CuO_{MOF}Y_A proposed here (having only 0.9 wt.% Cu) compares very favorably to literature data of benchmark copper oxide or Cu-MOFs,^{9a,b} copper on mesoporous silica,^{9c,d} or copper nanoparticles on zeolite NaY (see Table S5).^{9e} Other amines, such as morpholine and pyrrolidine, also produce the corresponding propargylamines **1a-c** in good yields using the novel CuO_{MOF}Y_A catalytic system (see Table S9). In our hands, the turnover frequency (TOF) of the well-dispersed copper active sites in CuO_{MOF}Y, is one order of magnitude higher than those present in bulk copper oxide derived from the MOF (CuO_{MOF}) and starting Cu-MOF material (see Fig. 3a). Moreover, using the calcined MOF instead of the intact one facilitates the regeneration of the spent CuO_{MOF}Y catalyst after reaction, by a simple thermal treatment in order to remove the reactants that otherwise remain adsorbed in the microporous zeolite for subsequent reuses (see Fig. 2b and Fig. S4-S6). On the contrary, the limited thermal stability of MOF powders only allows regeneration by washing, which is associated with large volumes of organic solvents and compromises the stability of the MOF.

Figure 3. Catalytic performance of CuO containing aluminosilicates and MOFs in the synthesis of propargylamine **1** (a) and quinoline **2** (b). Left: MOF derived CuO on different supports. Right: MOF (blue) vs. Cu(OAc)₂ (red) derived CuO at increasing metal loadings (A < B < C) on H-USY (see Table S1).

The higher TOFs obtained using the H-USY zeolite with strong acidity (CBV 720) as support of the CuO active sites with respect to lower Si/Al ratio (from 15 to 2.5, named as CBV 400 in Fig. 3) alludes to the fact that the acidity of the support favors the A3 reaction (see left part of Fig. 4).¹⁰ An important role of the acidity is to promote a very high dispersion of the CuO clusters, maybe due to some re-protonation of the MOF linkers (during the catalyst preparation in the presence of acidic supports) and relocation of the Cu²⁺ cations partially compensated by the oxide anions of the CuO clusters and zeolite. The catalytic activity of the bifunctional CuO/H⁺ sites on the microporous H-USY zeolite or mesoporous H-MCM-41(Al) is higher than that obtained when using non-acidic mesoporous or amorphous silica supports (see Fig. 3a). The same trend is observed for reactions where the acidity of the support plays a major role, such as the Friedländer condensation of 2-aminobenzophenone with acetylacetone (see Fig. 3b and Fig. S7).¹¹ In this case, the TOFs obtained with copper oxide containing MCM-41 catalyst, bulk Cu₃(BTC)₂ or pure CuO derived from this MOF (by calcining it in bulk) are far below from those obtained when CuO is dispersed via co-calcination in acid supports such as H-USY or H-MCM-41(Al). For both reactions, the use of the CuBTC as precursor of CuO active species instead of traditional Cu(OAc)₂ remarkably improves the catalytic activity of the copper containing zeolite.

Faujasite zeolites were also described as acid catalysts in the Friedel-Crafts alkylation at the C-3 of the electron rich indole, using alcohols or electron deficient alkenes such as

Figure 4. Proposed mechanism for the synthesis of propargylamines **1** and substituted indoles **3** using the bifunctional MOF/H⁺ Cu₂(OH)₂(CO₃)₂·xH₂O and Zn₂(OH)₂(CO₃)₂·xH₂O heterogeneous catalysts.

β -nitrostyrene.^{1d, 12} For the last reaction, we have observed that commercial H-USY zeolite with Si/Al = 15 shows a higher initial reaction rate ($r_0 = 0.40$ h⁻¹) with respect to lower Si/Al = 2.5, i.e. weaker acid sites, $r_0 = 0.28$ h⁻¹, (see CBV720 and CBV400 in Fig. S8 and Table S7). With Cu₂(OH)₂(CO₃)₂·xH₂O, the initial reaction rate increases twofold with respect to the pure Faujasite acid support and the TOF_{Cu} is two orders of magnitude higher with respect to CuBTC: 104 vs. 5 h⁻¹ (see Fig. S8 and Table S7).^{1a, 13} Those findings indicate that the novel method of creating CuO active sites in acidic supports could be unique and generic for different catalytic reactions. To broaden the scope of this concept, we have also employed zinc MOFs as precursor of inexpensive and non-toxic ZnO acid-base sites on H-USY. This bifunctional system is an optimal catalyst for the Michael addition of indole to β -nitrostyrene (see right part of Fig. 4). The catalytic activity of the Zn sites is boosted when they are dispersed on the HY porous zeolite, especially for low metal loadings (1.4 wt.%), obtaining a TOF_{Zn} of 204 with respect to the 104 mol of indole converted per mol of copper sites and per hour in the Cu₂(OH)₂(CO₃)₂·xH₂O. Moreover, the Zn₂(OH)₂(CO₃)₂·xH₂O MOF derived heterogeneous catalytic approach remarkably outperform reported homogeneous Zn(OAc)₂ catalysts.¹⁴ The acid sites associated to Al in the H-USY or H-MCM-41(Al) supports (see NH₃-TPD in Fig. 2c), cooperatively interact with the supported and well-dispersed (~1 wt.%) CuO or ZnO nanoparticles and promote the nitro, carbonyl and alkyne activations involved in the C-C and C-N couplings shown in Figure 4.

Apart from propargylamines and indoles, oxindoles are interesting compounds that exhibit antitumor activity by inhibiting tyrosine kinase receptors, as occurs with the C-3 substituted indolin-2-one *Sunitinib*.¹⁵ This type of substituted oxindoles are currently prepared using harsh conditions and/or toxic reagents, i.e. KF/Al₂O₃ or piperidine, piperazine, NaOH in ethanol under reflux.¹⁶ When using the 1.2 wt.% loaded Zn₂(OH)₂(CO₃)₂·xH₂O it is possible to obtain the 3-benzyliden-2-oxindole **4** in high yields (90%) after only two hours of aldol condensation of benzaldehyde with oxindole, proving the good performance of these novel Zn containing zeolites in C-C bond forming Michael additions (see Fig. 4) and aldol condensations (see Fig. 5a). Other aliphatic aldehydes such as heptanaldehyde or the biomass derived furfural were successfully employed to functionalize the oxindole substrate (see Table S9). The use of H-MCM-41(Al) acid mesoporous support increases the Zn TOFs with respect to the use of microporous H-USY (CBV720) zeolite, non-acidic MCM-41 or amorphous silica. This indicates the importance of H⁺/ZnO acid-base sites, as well as a good dispersion and accessibility to the active sites.¹⁷ Finally, the aldol condensation/oxa-Diels-Alder reaction of isatin (1H-indole-2,3-dione) with an hetero diene such as an α,β -unsaturated ketone, was also studied in order to obtain pharmaceutically interesting spirooxindoles.¹⁸ A clear improvement in the final turnover number (TON_{Zn}) or moles of isatin converted to **5** per mol of Zn is obtained with the lowest loaded sample Zn₂(OH)₂(CO₃)₂·xH₂O (see Fig. 5b). As observed previously for the Cu containing catalysts, high-

er Zn MOF loadings, or the use of Zn(OAc)₂ precursor, pure or calcined MOF, results in the decrease of TOF_{Zn} and TON_{Zn} by 1-2 orders of magnitude (see Figure 5 and Table S10).

Figure 5. Catalytic performance of ZnO containing aluminosilicates and MOFs in the synthesis of substituted oxindoles **4** (a) or spirooxindoles **5** (b). Left: MOF derived ZnO on different supports. Right: MOF (blue) vs. Zn(OAc)₂ (red) derived ZnO at increasing metal loadings (A < B < C) on H-USY (see Table S2).

In conclusion, the methodology proposed allows for the eco-efficient solid-state synthesis of metal containing porous catalysts, producing more mechanically and chemically resistant materials in comparison with the starting MOFs, with a very low metal content (below 2 wt.%). No solvent is employed during the procedure; thus the solid-to-solid (MOF-zeolite) co-calcination synthesis can be easily scaled up without requiring filtration or washing steps. The solids were used as active and stable heterogeneous catalysts for a range of C-C (compounds **1-5**) and C-N (compounds **1** and **2**) bond formations in *N*-heterocyclic scaffolds, resulting in substituted propargylamines (**1**), quinolines (**2**), indoles (**3**), oxindoles (**4**) and spirooxindoles (**5**), outperforming state-of-the-art Cu and Zn supported catalysts and MOF benchmarks. The higher availability of this metal oxide sites when they are dispersed within the porous matrix with respect to bulk metal-oxide or metal-organic framework, results in a better activity (TOFs up to two orders of magnitude higher) and reusability (by simple calcination), compared to the pure MOF.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Kinetic experiments, characterization of the catalysts and reaction products.

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Notes

The authors declare no competing financial interests.

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SYNOPSIS TOC “Co-calcining MOFs with aluminosilicate hosts as a new path to uniquely active metal-oxide catalysts for eco-friendly C-C and C-N bond formations in *N*-heterocyclic scaffolds”