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Cooperative Catalysis in a Crystalline Framework with Templated Acid–Base Sites

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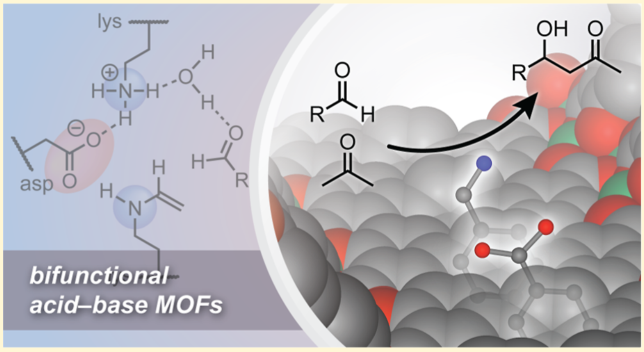

ABSTRACT: Nature uses weakly basic residues in conjunction with weakly acidic residues to catalyze challenging heterolytic bond transformations. Here, we show that these cooperative effects can be replicated in a metal–organic framework (MOF) containing bifunctional Brønsted acid–base sites. Using a templating strategy, we show that the colocalization of acid and base sites is key to catalytic activity. Specifically, a thermolabile cross-linker containing tertiary ester and tertiary carbamate linkages is used to tether carboxylic acid and benzylamine pairs in close proximity during framework synthesis. These templated materials are over 4-fold more active aldol condensation catalysts than nontemplated materials containing randomly distributed acid and base sites. Together, this work establishes MOFs as an exciting platform for cooperative acid–base catalysis that couples the advantages of heterogeneous catalysts with the structural precision of enzymes.

INTRODUCTION

In enzymes, multiple organic residues of moderate reactivity work together to facilitate heterolytic bond formation and cleavage under mild conditions. For example, class I aldolases use a combination of weakly acidic and basic residues to catalyze aldol condensation reactions (Figure 1a). Conserved lysine and aspartate residues work cooperatively to generate the key enamine intermediate, all within a tightly hydrogen-bonded network that facilitates proton transfer and circumvents high-energy charged species.[1−3]

These lessons from biology have gained renewed relevance in the context of biomass utilization. Active sites in which the reactivity of the whole is greater than the sum of the individual parts provide significant stability and selectivity advantages. Weakly reactive functional groups are more resistant to poisoning by contaminants and less prone to unselective substrate polymerization and fouling, two of the most common catalyst degradation pathways observed in biomass conversion technologies.[4,5]

Inspired by class I aldolases and other enzymes, bifunctional acid–base catalysts have been explored in multiple platforms, including small-molecule amino acid and peptide catalysts (Figure 1b),[6,7] functionalized organic polymers of both synthetic and biological origin (Figure 1c),[8−11] and amine-grafted silica (Figure 1d).[12−14] Clear cooperative effects have been observed in reactions relevant to biomass conversion, including the aldol condensation of biomass-derived methyl ketones into higher molecular weight biofuel precursors,[15] and the condensation of biomass-derived aldehydes (e.g., furfural, 5-hydroxymethylfurfural) into higher value products.[11,16]

Fully realizing the promise of enzyme-like cooperativity in a synthetic platform requires the ability to adjust active site parameters by as little as a few angstroms. In enzymes, the relative spatial rearrangement of amino acid residues is as critical to function as their number and identity. For example, lengthening the aspartate residue in a class I aldolase active site by just a single methylene unit dramatically reduces catalytic activity by over 40-fold.[1] This level of spatial precision is difficult, if not impossible, to replicate in supports such as amine-grafted mesoporous silica, where structural fidelity is fundamentally limited by the amorphous surface.

Given the importance of structural precision, we envisioned the use of metal–organic frameworks (MOFs) as a new platform for the construction of bifunctional acid–base active sites (Figure 1e). The synthesis of Brønsted acid–base MOFs has received far less attention than its closely related counterpart, bifunctional Lewis acid–base MOFs.[17,18] While several examples of frameworks jointly functionalized with amine and sulfonic acid groups have been reported,[19,20] only a few previous studies have demonstrated the colocalization of carboxylic acids and amines in a single MOF pore.[21,22] To our knowledge, only one previous report was able to install the acid

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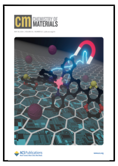

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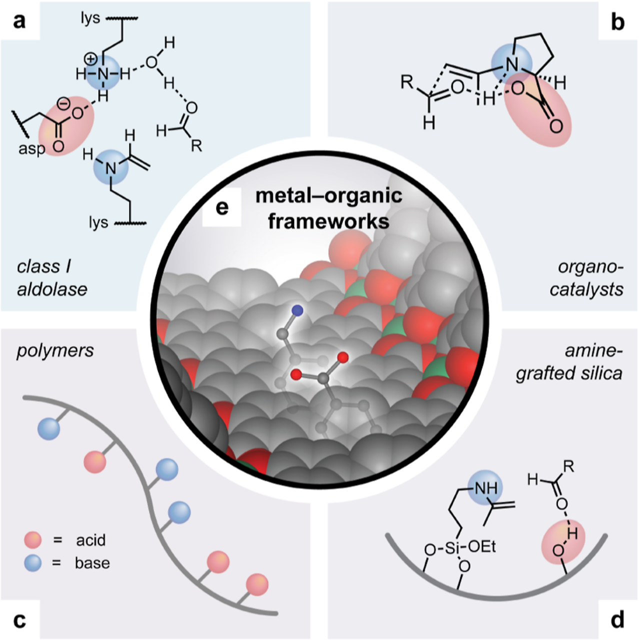


Figure 1. Overview of bifunctional acid−base catalysts for aldol condensation reactions, including (a) class I aldolase enzymes, (b) small-molecule organocatalysts, (c) acid−base functionalized polymers, (d) amine-grafted mesoporous silica, and (e) MOFs (this work). The structures in (a−d) are based on figures from refs 3, 6, 10 and 13.

and base pairs in a single predefined arrangement,[22] rather than randomly distributed throughout the framework structure. In this prior work, the functional groups were postsynthetically incorporated in a single crystal-to-single crystal fashion using sequential linker installation. As this technique is specific to PCN-700, a zirconium-based framework containing an ordered array of missing linkers,[23] this approach cannot be extended to other MOF structure types.

Here, we report a general strategy to template bifunctional acid−base sites in MOF pores. Using a mesoporous magnesium-based framework with ∼3 nm pore channels, we show how carboxylic acid and benzylamine functional groups can be installed pairwise in a single configuration less than 7 Å apart. Relative to nontemplated materials containing randomly distributed acid and base sites, the templated catalysts are over 4-fold and 2-fold more active for aldol condensation reactions with 4-nitrobenzaldehyde and furfural, respectively. Finally, the catalysts are stable and show no loss in activity or structural degradation after multiple cycles. Together, this work establishes MOFs as an exciting platform for cooperative acid−base catalysis that balances the advantages of heterogeneous catalysts with the precision of enzymes.

Framework Synthesis and Characterization. Our group has recently shown that thermolabile cross-linkers can be used to template pairs of functional groups in MOF pores at specific relative distances and orientations.[24,25] For example, we have used tertiary ester and tertiary carbamate-based cross-linkers to template pairs of carboxylic acids and pairs of amines in the terphenyl-expanded MOF-74 framework, also known as Mg_2dotpdc (dotpdc^{4-} = 4,4″-dioxido-[1,1′:4′,1″-terphenyl]-3,3″-dicarboxylate) (Figure 2a). This framework contains large, one-dimensional hexagonal channels (∼3 nm) framed by tightly packed ligand struts (∼7 Å apart).[26−28] Mg_2dotpdc (abbreviated **1**) and other frameworks with similar 1D channels[29,30] are attractive supports for bifunctional catalysis as they provide large pore diameters while still maintaining short distances between adjacent ligands.

To extend our templating strategy to bifunctional acid−base sites, we designed a new nonsymmetric cross-linked ligand dimer, abbreviated **H_8XL-AB**, which incorporates a tertiary ester linkage on one end and a tertiary carbamate linkage on the other. The two halves of the dimeric ligand are bridged by a short alkyl chain (Figure 2b, see Supporting Information for synthetic details). After framework synthesis, thermal cleavage of the tertiary ester and carbamate groups should lead to bifunctional carboxylic acid and benzylamine pairs positioned on adjacent ligands roughly 7 Å apart (Figure 2c).

The synthesis of the cross-linked Mg_2dotpdc framework, abbreviated **1-crosslinked**, was achieved by heating a mixture of the unfunctionalized ligand H_4dotpdc (0.875 equiv), cross-linked ligand dimer **H_8XL-AB** (0.125 equiv), and $Mg(NO_3)_2 \cdot 6H_2O$ (2.50 equiv) in a mixture of DMF and MeOH. After 3 h, a microcrystalline powder consistent with the Mg_2dotpdc

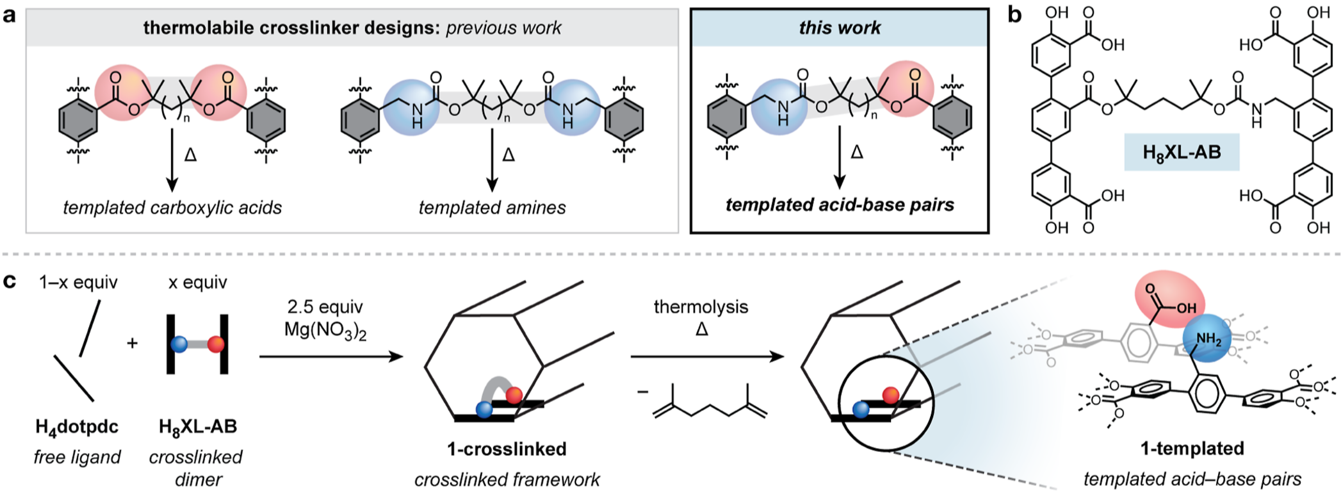


Figure 2. (a) Previous work on templating carboxylic acids and amines pairs (left) and templated acid−base pairs in this work (right). (b) Structure of the nonsymmetric cross-linker featuring a tertiary ester and tertiary carbamate linkage. (c) Overview of our templating strategy where the nonsymmetric cross-linker, **H_8XL-AB**, is used to templated acid−base pairs.

structure was obtained (Figure 3a). Digestion ^{1}H NMR analysis was used to quantify the framework composition and ensure no premature cross-linker degradation occurred during framework synthesis. We obtained a framework in which 24% of the ligands are cross-linked, which is slightly higher than the expected incorporation of ~22% based on the ratio of the starting ligands (Figures S9 and S10). The presence of the cross-linker peaks in the NMR (0.9−1.6 ppm) confirmed that no cross-linker degradation occurs under these conditions.

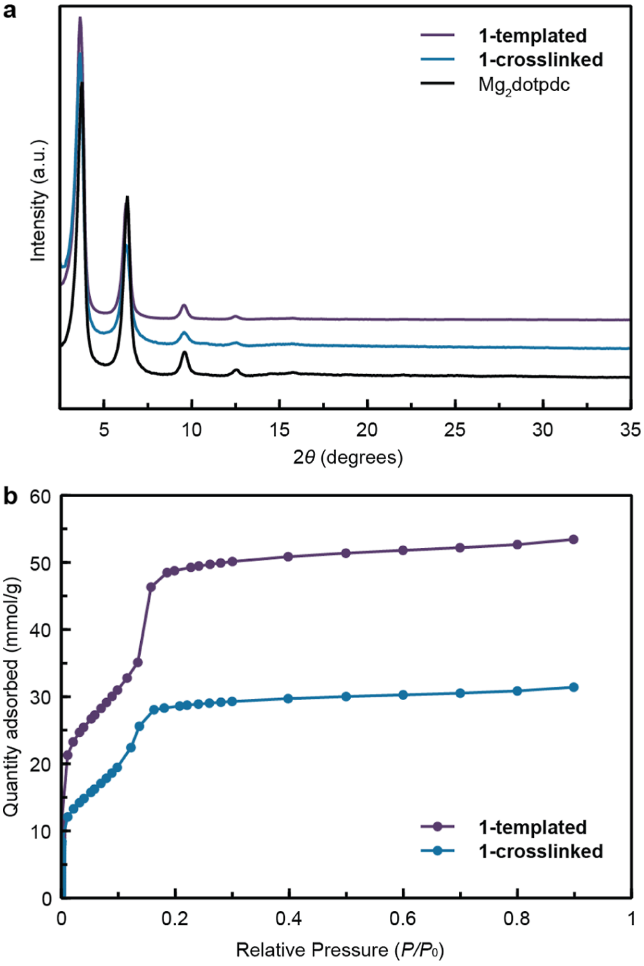


Figure 3. (a) PXRD data of Mg_2dotpdc, **1-crosslinked**, and **1-templated** and (b) 77 K nitrogen adsorption data for **1-crosslinked** and **1-templated**.

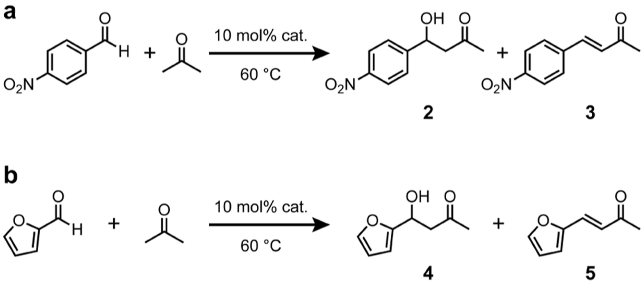
While there have been reports of separate tertiary carbamate[27,31] or tertiary ester[24] thermolysis in MOFs, prior to this work, the simultaneous cleavage of both groups within a single framework was not known. Excitingly, upon microwave heating at 230 °C, the mixed tertiary ester/carbamate cross-linker in **1-crosslinked** could be cleanly removed to generate **1-templated**, a framework containing acid and base pairs. Experimentally, we have found that the primary amines in **1-templated** have heightened oxidative sensitivity due to the presence of neighboring acidic groups, and the microwave reaction must be done using samples that have been rigorously sparged and sealed under N_2.

Removal of the cross-linker is evident in the ^{1}H NMR of digested samples, which shows full disappearance of the cross-linker and the emergence of peaks associated with the carboxylic acid and benzylamine-functionalized ligands (abbreviated H_4dotpdc-CO_2H and H_4dotpdc-CH_2NH_2, Figures S12 and S13). Together, the sum of H_4dotpdc-CO_2H (12%) and H_4dotpdc-CH_2NH_2 (10%) in the templated sample is roughly consistent with the number of cross-linked ligands in **1-crosslinked** (24%). We attribute the slight discrepancy (~2%) to the partial oxidation of the benzylamines during thermolysis. Carrying out the microwave reaction under air, rather than N_2, further reduces the H_4dotpdc-CH_2NH_2 percentage and introduces new features associated with aldehyde functional groups, supporting this hypothesis (Figure S14).

No structural degradation following thermal treatment is observed, as is evident by the powder X-ray diffraction (PXRD) patterns (Figure 3a). A large increase in the Brunauer−Emmett−Teller (BET) surface area is observed, from 2130 m^2/g in **1-crosslinked** to 2730 m^2/g in **1-templated** (Figure 3b). This latter value is within the range of previously reported surface areas for unfunctionalized Mg_2dotpdc (2440−3100 m^2/g), consistent with full removal of the cross-linker.[24,26,28]

Cooperative Aldol Condensation. We next probed the ability of our templated frameworks to catalyze aldol condensation reactions (Scheme 1). We hypothesized that the amine could form a nucleophilic enamine intermediate, while the acid could participate in hydrogen bonding and electrophilic activation of the aldehyde partner. Similar mechanisms have been shown in other bifunctional acid−base catalysts (Figure 1).[6,32]

Scheme 1. Aldol Condensation Reactions with Acetone and (a) 4-Nitrobenzaldehyde and (b) Furfural



To provide unambiguous evidence of acid−base cooperativity, we synthesized four control frameworks: (1) **1-nontemplated**, a framework in which the acid and base groups are present in similar concentrations but are randomly distributed throughout the pores; (2) **1-CH_2NH_2**, a framework containing only amine groups; (3) **1-COOH**, a framework containing only carboxylic acid groups; and (4) **Mg_2dotpdc**, the bare framework containing no functional groups.

To synthesize the nontemplated framework, we heated a mixture of H_4dotpdc-CO_2tBu (0.100 equiv), H_4dotpdc-CH_2NHBoc (0.100 equiv), H_4dotpdc (0.800 equiv), and $Mg(NO_3)_2 \cdot 6H_2O$ (2.50 equiv) in DMF and MeOH for 3 h. PXRD and ^{1}H NMR digestion studies confirmed that the resulting framework, which contains protected carboxylic acid and benzylamine groups, adopts the desired Mg_2dotpdc structure (Figure S15) with the expected functional group loading (~10% of each group, Figures S16 and S17). The *tert*-butyl ester and carbamates in this framework were removed via microwave thermolysis to reveal **1-nontemplated** (Figures S19 and S20). Like the templated framework, a large increase in

BET surface area from 2440 to 2780 m^2/g was observed upon thermolysis and removal of the protecting groups (Figure S21). The control frameworks **1-CH_2NH_2** and **1-COOH** were synthesized in a similar fashion but with functional group loadings of ~10 mol %.

Given how differences in particle size and internal mass transport limitations can obscure intrinsic differences in catalytic activity, scanning electron microscopy (SEM) studies were carried out to confirm that all frameworks have similar morphologies. An average length of 0.307 ± 0.148 μm and an average diameter of 0.060 ± 0.018 μm were observed for **1-templated**, while an average length of 0.338 ± 0.139 μm and an average diameter of 0.077 ± 0.025 μm were obtained for **1-nontemplated** (Figures S23 and S24). These lengths and diameters are all within error of each other, confirming that the use of cross-linked ligand dimers at these concentrations has little impact on the resulting framework morphology. Together, these analyses confirm that all frameworks are identical in terms of their overall structure, surface area, and particle morphology and differ only in their functional group content and spatial distribution.

We first evaluated the ability of each framework to catalyze the aldol reaction between 4-nitrobenzaldehyde and acetone to yield products **2** and **3** (Scheme 1a). This reaction has been widely used to benchmark heterogeneous bifunctional acid−base catalysts.[11−14] Initial control experiments using the unfunctionalized Mg_2dotpdc framework revealed highly variable background reactivity. We hypothesized that the coordinatively unsaturated magnesium sites in the framework may be acting as Lewis acid catalysts, with activity that is highly sensitive to the presence of trace water. Indeed, this background reaction was nearly completely quenched upon the addition of a small amount of water (2 vol %) in the solvent mixture (Table 1). Given these results, we adopted 2 vol % water in acetone as our default solvent for all subsequent catalytic runs.

Table 1. Catalytic Performance of Frameworks for the Aldol Condensation of 4-Nitrobenzaldehyde and Acetone[a]

framework	conversion (%)[e]
none	n.r.
Mg_2dotpdc[b]	4
1-crosslinked[c]	4
1-COOH[d]	16
1-CH_2NH_2[c]	19
1-nontemplated[c]	41
1-templated[c]	82

[a] All reactions were heated at 60 °C for 5 h in a water/acetone (2% v/v) with 0.05 M 4-nitrobenzaldehyde and 0.025 M of the internal standard 1,3,5-trimethoxybenzene. [b] Catalyst loading: 30 mg. [c] Catalyst loading: 10 mol % (based on benzylamine content). [d] Catalyst loading: 10 mol % (based on carboxylic acid content). [e] Determined by ^{1}H NMR analysis.

We next compared the performance of each framework by monitoring substrate conversion after 5 h at 60 °C. The results, which are summarized in Table 1, show that **1-templated** achieves the highest conversion under these conditions (82%), followed by **1-nontemplated** with 41% conversion. Both frameworks outperform the monofunctionalized **1-COOH** and **1-CH_2NH_2**, which achieve only 16 and 19% conversion, respectively. Low catalytic activity (4% conversion) was also observed when **1-crosslinked** was used as a catalyst. These initial catalyst screenings provide strong evidence that not only is the presence of both acid and base critical to activity but also their spatial distribution.

To gain greater insight into the catalytic performance of **1-templated** and **1-nontemplated**, we monitored the kinetics of each reaction to obtain initial rates. Using the same conditions as before, time points ranging from 10 min to 8 h were collected in triplicate. At low conversion (<10%), initial turnover frequency values of 6.26 and 1.49 h^{-1} were obtained for **1-templated** and **1-nontemplated**, respectively, indicating that the templated framework is over 4-fold more active than the nontemplated framework (Figure 4a). Both catalysts are highly selective for the addition product **2** over the dehydrated product **3**. After 8 h, **1-templated** achieves 95% conversion (10:1 ratio of **2**:**3**), whereas **1-nontemplated** achieves 57% conversion (23:1 ratio of **2**:**3**). Both catalysts retain crystallinity over the 8 h period (Figure S25), and digestion ^{1}H NMR of the frameworks confirms that both catalysts maintain the same functional group composition (Figures S26 and S27).

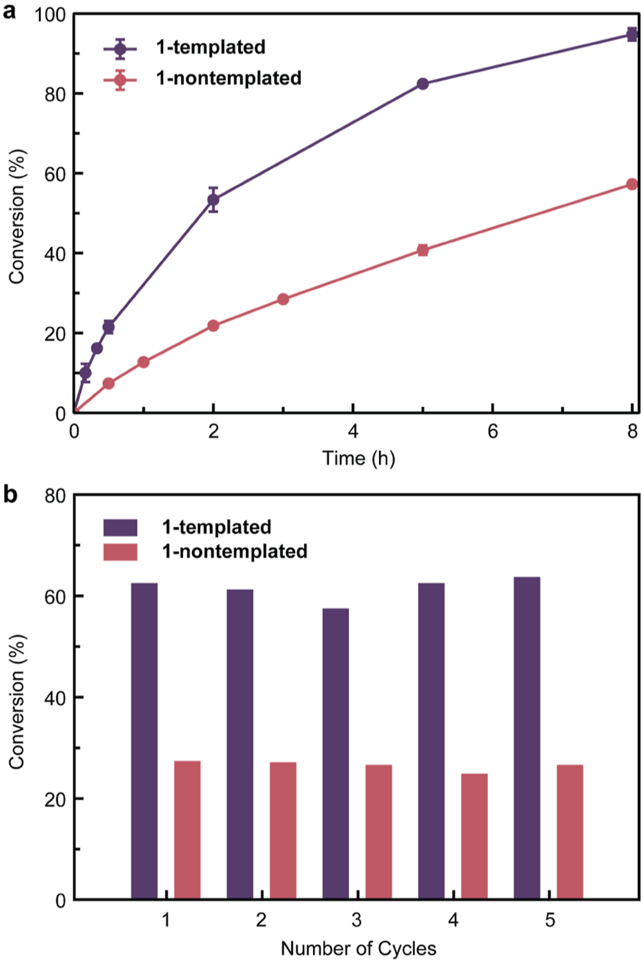


Figure 4. (a) Conversion of 4-nitrobenzaldehyde in the aldol reaction with acetone over 8 h for **1-templated** and **1-nontemplated** catalysts. (b) Conversion of 4-nitrobenzaldehyde using the same samples of **1-templated** and **1-nontemplated** catalysts for five cycles at 60 °C for 3 h.

To test the stability and recyclability of **1-templated** and **1-nontemplated**, we performed cycling studies under the same catalytic conditions. After 3 h, the materials were washed with acetone and resubjected to the reaction conditions (see Supporting Information). Both catalysts remain stable over five cycles, showing little variation in yields (Figure 4b), no loss in crystallinity (Figure S28), and no change in functional group composition (Figures S29 and S30).

In both frameworks, a small amount of 4-nitrobenzaldehyde is detected in the pores by ^{1}H NMR digestion studies even after rigorous washing with acetone. After one 8 h run, we detect 0.2−0.3 equiv of 4-nitrobenzaldehyde relative to the benzylamine loading (Figures S26 and S27). After five cycles, this value increased slightly to 0.4−0.6 equiv (Figures S29 and S30). We hypothesize that the aldehyde substrate may be reacting with our amines to form an off-cycle imine intermediate, which not only restricts access to the pores but also prevents the formation of the desired enamine. Substrate inhibition due to imine formation and pore clogging has been previously observed in primary amine-functionalized mesoporous silica and is especially pronounced when the pore diameters are less than 3 nm.[33] The formation of off-cycle imines may explain why the initial 4-fold difference in activity between **1-templated** and **1-nontemplated** appears to decrease over longer reaction times. Future work will explore the use of secondary amine sites, which are not able to form stable imines.

Excitingly, evidence of cooperative catalysis is also observed when furfural, a biomass-derived aldehyde, is used as a substrate. We tested the performance of **1-nontemplated** and **1-templated** for the reaction between furfural and acetone, and the reaction was monitored for 16 h at 60 °C (Scheme 1b). The results summarized in Table 2 show that **1-templated** is a more active catalyst for this reaction, achieving a conversion of 72% (1:1.5 ratio of **4**:**5**) compared to 34% conversion (2:1 ratio of **4**:**5**) from **1-nontemplated** (Figure S31). Both frameworks remain crystalline, indicating that they are stable over 16 h (Figure S32). These results, combined with the apparent stability over multiple cycles, demonstrate that MOFs with colocalized Brønsted acid and base groups serve as a promising catalyst for the conversion of biomass-derived aldehydes.

Table 2. Catalytic Performance of Frameworks for the Aldol Condensation of Furfural and Acetone[a]

framework	conversion (%)[c]
1-nontemplated[b]	34
1-templated[b]	72

[a] All reactions were heated at 60 °C for 16 h in water/acetone (2% v/v) with 0.05 M furfural and 0.025 M of the internal standard 1,3,5-trimethoxybenzene. [b] Catalyst loading: 10 mol % (based on benzylamine content). [c] Determined by ^{1}H NMR analysis.

Finally, we compared the performance of our templated MOF catalysts with amine-grafted mesoporous silica, one of the most well-studied bifunctional heterogeneous catalysts for aldol condensation reactions. Previous work on amine-grafted mesoporous silica has shown that more weakly acidic surface silanols ($pK_a \sim 7$) afford much stronger cooperative effects than surface-bound carboxylic acids ($pK_a \sim 5$).[13] Interestingly, the activity of our templated MOF catalyst is very similar to amine-functionalized mesoporous silica with 2 nm pores (see Table S1), despite the more acidic partner.[14] More rigorous studies are required to determine whether the same pK_a trends will be observed in framework materials as in mesoporous silica.

■ CONCLUSIONS

In summary, our work establishes a new route to achieve structurally unambiguous acid−base sites in a MOF. Significant cooperative effects are observed due to the colocalization of acid and base sites, with the templated materials catalyzing aldol condensation reactions up to 4-fold faster than nontemplated controls.

With the initial thermolabile cross-linker design now established, future catalyst modifications are limited only by our ability to synthesize slight variations of this underlying motif. Going forward, it should be straightforward to alter the identity of the templated functional groups to increase activity, such as changing the primary amine to a secondary amine. Work along this vein is under way. One can further imagine shortening the distance between acid−base pairs by replacing the benzylamine groups with a longer phenylethylamine, or, conversely, lengthening the distance by extending the cross-linker. As spatial precision is critical to harnessing cooperative interactions, we anticipate that these subtle adjustments will have dramatic effects on catalytic activity. Finally, given the orthogonal postsynthetic reactivity of carboxylic acids and amines, our templated sites can serve as a convenient and versatile entry point to more complex active sites, beyond simple acid−base pairs.

■ EXPERIMENTAL METHODS

General Materials and Methods. All ligand synthesis, framework synthesis, and framework thermolysis are described in detail in the Supporting Information. PXRD patterns were collected on a Bruker D2 PHASER benchtop diffractometer. Solution-phase NMR data were collected on Bruker AV300, AV301, GG500, or NEO500 instruments. Surface area and pore size distribution data were determined by N_2 adsorption measurements at 77 K on a Micromeritics 3Flex instrument. SEM images were collected on a Thermo Fisher Scientific Apreo-S with LoVac SEM with an operating voltage of 2 kV. All samples were prepared via drop casting from ethanol suspensions onto silicon wafers. Thermogravimetric analysis data were collected using a TA Instruments Q5000 analyzer. Samples were analyzed under N_2, heating to 500 °C at a rate of 10 °C min^{-1}.

Catalytic Testing. The aldol condensation reactions were performed by weighing out the MOF catalyst (10 mol %, based on amine or carboxylic acid content) into an 8.0 mL vial equipped with a stir bar. The MOF catalyst was suspended in 0.5 mL of a water/acetone (2% v/v) solution, briefly sonicated, and stirred at room temperature for 10 min. A stock solution of water/acetone (2% v/v) with 0.1 M 4-nitrobenzaldehyde or furfural and 0.05 M of the internal standard 1,3,5-trimethoxybenzene was prepared, and 0.5 mL of this solution was added to the reaction mixture. The reactions were sealed, placed onto a preheated aluminum block at 60 °C, and stirred at 1000 rpm. Time points were taken by removing the reaction from heat and immediately placing it into an ice bath. Once cooled down, the MOF catalyst was removed by centrifugation and washed with fresh acetone, and the solution was concentrated under vacuum and analyzed by ^{1}H NMR ($(CD_3)_2CO$).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.chemmater.4c00769.

Additional experimental details, synthetic procedures, and characterization data (PDF)

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Author Contributions

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

Notes

The authors declare no competing financial interest.

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