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A General Thermolabile Protecting Group Strategy for Organocatalytic Metal−Organic Frameworks

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Supporting Information

ABSTRACT: We present a general strategy for incorporating organocatalytic moieties into metal−organic frameworks (MOFs). The organocatalytic units are protected by a thermolabile protecting group during MOF synthesis and then unveiled by a simple postsynthetic heating step. The strategy is exemplified using a thermolabile *tert*-butoxycarbonyl (Boc) protecting group for a proline moiety, the removal of which endows the resulting cubic zinc(II) IRMOF with catalytic activity for asymmetric aldol reactions. The bulky Boc groups also prevent framework interpenetration, producing open MOFs that can admit relatively large substrates.

Because of their porous and tunable nature, metal−organic frameworks (MOFs) show promise as heterogeneous catalysts.[1] A variety of structural features can engender catalytic activity in MOFs, such as open metal sites at framework nodes,[2] which often have unique coordination environments, and metal-centered catalytic units that are integrated into the ligand struts.[3,4]

We are interested in the development of a third mode of catalytic activity, *organocatalytic MOFs*, where organic functional groups appended to the framework provide specific sites for catalysis. This approach is motivated by the observation that the catalytic activity of many organocatalysts arises from small, discrete moieties such as pyrrolidine, urea, or phosphonic acid groups.[5] It has been demonstrated that these functional groups can be immobilized on various supports (e.g., polymers, dendrimers, or silica) to produce recoverable and recyclable catalysts.[6] In the case of MOFs, there have been surprisingly few deliberate attempts to integrate organocatalytic moieties.[7] Recently, postsynthetic modification reactions have been employed to introduce carboxylic acid groups into MOFs, which mimic known Brønsted acid catalysts for the methanolysis of epoxides.[8] To exploit the well-recognized catalytic activity of pyrrolidines, proline- and pyrrolidine-based ligands have been incorporated into MOFs.[9] A method of generating free carboxylic acid groups in aspartate-based MOFs has also been reported.[10] Frameworks derived from proline itself were also investigated, but organocatalytic activity was precluded by protonation of the proline nitrogen atom.[11]

As suggested by this last case, one reason for the paucity of examples of organocatalytic units in MOFs may be the fact that they can be chemically transformed under the conditions of MOF synthesis, for example by (de)protonation or coordination to metal ions. In addition to inhibiting catalysis, these changes may also prevent the growth of MOF crystals. We herein present a strategy designed to mitigate these undesired processes and provide a general method for the incorporation of organocatalytic groups into MOFs. This strategy builds on our recent demonstration of a new type of postsynthetic modification of MOFs involving the transformation of a bulky *tert*-butoxycarbonyl (Boc) group appended to a ligand skeleton into small, gaseous fragments by simple heating.[12] The Boc unit suppresses framework catenation (interpenetration) during the assembly of the MOF, and its expulsion both increases the pore volume of the framework and reveals an amino functional group.

Scheme 1 outlines how we envisaged the application of this methodology to the surreptitious incorporation into MOFs of proline groups designed to be specific sites for catalysis. Building on the fact that biphenyl-4,4′-dicarboxylic acid ligands, including those substituted at the 2 and/or 2′ positions, react with zinc(II) to form MOFs with cubic topologies,[12,13] we designed H_2**1** as a building block for IRMOF-Pro-Boc. The designation IRMOF denotes the "isoreticular"[14] nature of this family of cubic frameworks. The proline unit of ligand **1** is protected by a Boc group, which prevents its protonation or coordination to zinc(II) under the conditions of MOF synthesis. Further, the bulky nature of the Boc unit should discourage framework interpretation, resulting in the production of an open MOF. In a subsequent step, deprotection of the proline can be triggered by simple heating[15] to generate IRMOF-Pro in a single-crystal-to-single-crystal (SCSC) fashion. Importantly, this approach ensures that (i) IRMOF-Pro exhibits an open structure with contiguous channels that can admit reasonably large substrates and (ii) there is significant void space in the vicinity of the proline motifs, thus freeing them to interact with incoming molecules.

The synthesis of (*S*)-H_2**1** was achieved in two steps via the reaction of *N*-Boc-L-proline and dimethyl 2-aminobiphenyl-4,4′-dicarboxylate. Chiral HPLC established that the amide coupling reaction resulted in only a minor degree of racemization, with the enantiomeric excess (ee) of (*S*)-H_2**1** found to be 94%. In accord with related literature results,[12,13] the solvothermal reaction of (*S*)-H_2**1** with $Zn(NO_3)_2$ in *N*,*N*-diethylformamide (DEF) produced well-faceted, colorless, cubic crystals of IRMOF-Pro-Boc (Scheme 1). Analysis by X-ray crystallography demonstrated that

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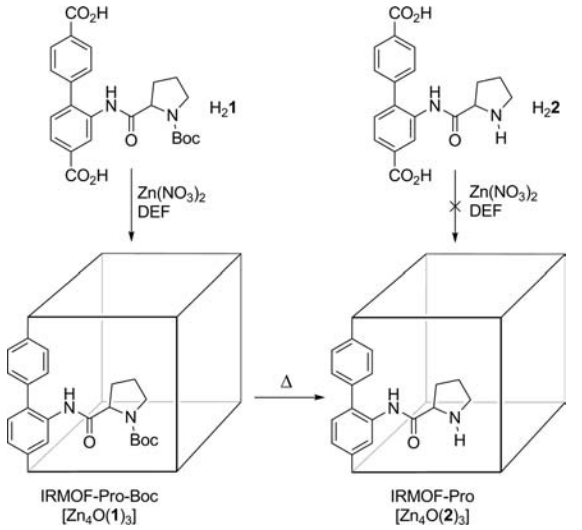
Scheme 1. Conversion of Ligand $H_2$1 to a Cubic Metal–Organic Framework, IRMOF-Pro-Boc ($[Zn_4O(1)_3]$), Followed by Thermolytic Expulsion of the Boc Moiety To Generate IRMOF-Pro ($[Zn_4O(2)_3]$); Isobutylene and CO_2 Are Produced as Side Products in This Step



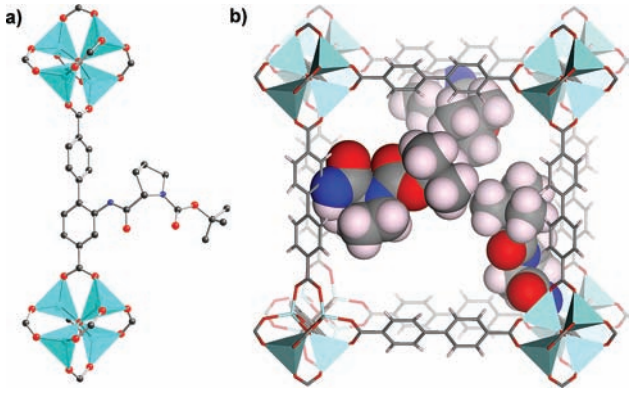


Figure 1. Structure of IRMOF-Pro-Boc as determined by X-ray crystallography. (a) Ligand strut and Zn_4O nodes. Gray = C; red = O; blue = N; turquoise = Zn. Hydrogen atoms have been omitted for clarity. (b) Typical cubic repeating unit. One set of the statistically disordered *N*-Boc-proline side chains is shown.

the structure closely resembles other members of the IRMOF series; the stoichiometry is $[Zn_4O((S)\text{-}\mathbf{1})_3]$, and a framework with cubic topology is built up by linking of Zn_4O nodes by the divergent carboxyl groups of ligand **1** (Figure 1). Because of the steric bulk of the *N*-Boc-proline side arm, the MOF adopts an open, noninterpenetrated structure.

Strong diffraction from the rigid, highly ordered cubic lattice comprising the Zn_4O nodes and the biphenyl ligand skeletons generated a reciprocal lattice that was most consistent with the cubic space group $P\bar{4}3m$ [lattice constant = 17.1625(19) Å]. The statistical disordering of the *N*-Boc-proline groups over four sites mitigated against their identification in the Fourier difference map, so they were placed in calculated positions to complete the refinement.[16]

The phase purity of IRMOF-Pro-Boc was established by powder X-ray diffraction (XRD), where the observed diffraction

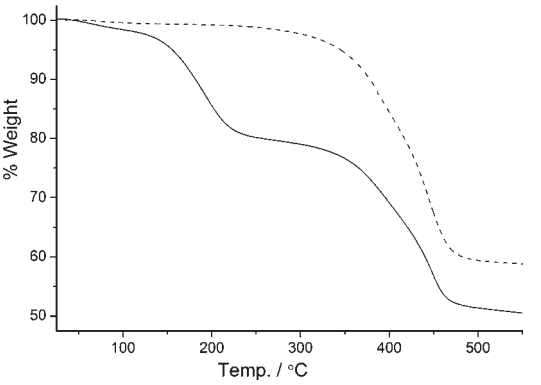


Figure 2. Thermogravimetrograms of IRMOF-Pro-Boc under N_2. The dashed curve was recorded after the sample was preheated to 250 °C. The heating rate was 5 °C/min.

pattern closely matched that predicted from the single-crystal structure (Figure S6 in the Supporting Information). To determine the temperature at which the Boc groups could be expelled from IRMOF-Pro-Boc to generate IRMOF-Pro, we carried out thermogravimetric analysis (TGA) of this material. Significant weight loss was observed in the region 140–240 °C (Figure 2, solid curve) as a consequence of the thermolytic reaction shown in Scheme 1. Consistent with this analysis, when a sample was pretreated at 250 °C, this weight loss was not observed (dashed curve). Framework decomposition occurred above 350 °C.

With these results in hand, IRMOF-Pro-Boc was converted to IRMOF-Pro in a SCSC reaction by heating to 165 °C in *N*,*N*-dimethylformamide (DMF) using microwave irradiation. Complete expulsion of the Boc group was evidenced within a period of 4 h by ^{1}H NMR spectroscopy of the MOF crystals digested in dimethyl sulfoxide-d_6/DCl (Figure S4). Following thermolysis, the enantiopurity of the proline groups of ligand (*S*)-**2** in IRMOF-Pro was ascertained by chiral HPLC to be 80% ee. It thus appears that the thermolysis process results in the racemization of ~7% of the total number of proline groups. Lowering the thermolysis temperature to 150 °C led to only a marginal improvement in the ee.

IRMOF-Pro was further characterized by microanalysis, IR spectroscopy (see the Supporting Information), and XRD. Powder XRD demonstrated that the framework maintained crystallinity following the thermolysis reaction and that the cubic lattice was retained (Figure S6). This was corroborated by single-crystal XRD experiments, from which a lattice constant of 17.160(3) Å was deduced. A structural model could be satisfactorily refined against these data in the space group $P\bar{4}3m$ (Figure 3). The statistically disordered proline side chains were placed in calculated positions to complete the refinement.[15]

In previous work, we showed that 2-aminobiphenyl-4,4′-dicarboxylic acid does not produce a MOF under standard synthesis conditions, whereas MOF formation proceeds smoothly when the amino moiety is protected by a Boc group.[12] In this light, we attempted to prepare IRMOF-Pro directly from H_2**2**, but all attempts met with failure. We suspect that the exposed proline group interferes with MOF formation, perhaps as a consequence of the coordination of its nitrogen atom to zinc(II). This experiment also confirmed that the thermolysis of IRMOF-Pro-Boc to IRMOF-Pro takes place via an SCSC pathway, as ligand **2** cannot form IRMOF-Pro from solution.

The X-ray crystal structure of IRMOF-Pro established that this material is amenable to heterogeneous catalysis, as the proline units

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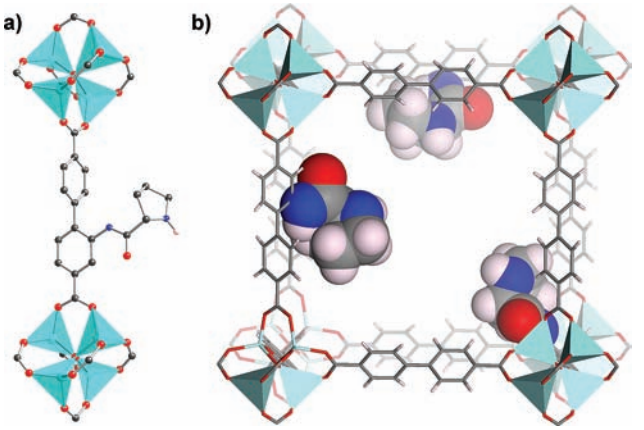

Figure 3. Structure of IRMOF-Pro as determined by X-ray crystallography. (a) Ligand strut and Zn_4O nodes. Gray = C; red = O; blue = N; turquoise = Zn. Most of the hydrogen atoms have been omitted for clarity. (b) Typical cubic repeating unit. One set of the statistically disordered proline side chains is shown.

Scheme 2. Aldol Reactions of Acetone and Cyclopentanone with 4-Nitrobenzaldehyde Catalyzed by IRMOF-Pro

line a continuous network of pores. The diameter of the windows between these pores ranges from ~5 to 10.5 Å (because of the variable location of the proline units). Free diffusion of large molecules into these pores was established experimentally using a merocyanine dye,[4,17] which showed uniform penetration into IRMOF-Pro crystals (Figure S7). Following activation by supercritical CO_2,[18] N_2 gas sorption experiments gave a Brunauer–Emmett–Teller (BET) surface area of 138 $m^2\ g^{-1}$ (Figure S8), which is lower than predicted on the basis of X-ray crystallography and indicates a degree of pore collapse upon desolvation. For optimal performance in catalysis, the above results led to the practice of keeping the MOF crystals suspended in solvent at all times.

To examine the catalytic ability of IRMOF-Pro, we employed aldol reactions that are known to be catalyzed by proline[19] and both unsupported[20] and supported[21] proline-based catalysts. Crystals of IRMOF-Pro were suspended in acetone, and 4-nitrobenzaldehyde was added. To our delight, the formation of the aldol product of these reactants, 4-hydroxy-4-(4-nitrophenyl)pentan-2-one (Scheme 2), was evident over the course of a few hours, and the aldehyde was completely consumed within 24 h (Table S1 in the Supporting Information). The ee of the aldol product was determined to be 29% by chiral HPLC analysis. We also found that the aldol reaction of cyclopentanone and 4-nitrobenzaldehyde to give hydroxy(4-nitrophenyl)methylcyclopentanone was also catalyzed by IRMOF-Pro. The diastereomeric ratio (dr) of the anti to the syn products was determined to be 75:25, with ee's of 14% for the anti isomer and 3% for the syn isomer.

A series of control experiments confirmed that intact IRMOF-Pro was responsible for the observed catalytic activity. First, removal of the solid catalyst by filtration partway through the reaction completely halted the consumption of the aldehyde. Second, IRMOF-Pro-Boc was completely inactive toward this conversion, demonstrating that the catalytic activity arises from the presence of unprotected pyrrolidine groups. Third, there was no evidence of dissolution of the crystals of IRMOF-Pro, and we found that both aldol reactions were catalyzed only very slowly by $Zn(NO_3)_2$, even at high loadings. Although H_2**2** also functioned as a catalyst for these reactions, different stereoselectivity patterns in comparison with IRMOF-Pro were observed (see the Supporting Information).

To test the recyclability of the IRMOF-Pro catalyst, we subjected it to three cycles of the aldol reaction with cyclopentanone. The reaction was driven to completion in each cycle, although diminished activity of the catalyst was evident from an increase in the required reaction time, which was correlated with a slight loss of long-range crystallinity (Figure S9).

Although the initial focus of this work was to develop thermolabile protecting groups for organocatalytic moieties rather than to discover a highly enantioselective catalyst, we did ponder why the enantioselectivities observed for the aldol reactions catalyzed by IRMOF-Pro were modest. In addition to the minor degree of racemization of the proline groups, this may be ascribed to a lack of organization in the reaction transition state as a consequence of several factors, including motion of the catalytic unit with respect to the framework, the large intraframework void space that allows the electrophile to approach either side of the intermediate enamine, and the absence of accessible hydrogen-bond donors on the catalytic unit.[22] Highly enantioselective small-molecule organocatalysts often allow for participation of both the proline nitrogen atom and its carboxyl group in the catalytic cycle. Our current efforts to produce second-generation catalysts that exhibit improved enantioselectivities are focused on thermolabile groups that enable this to occur within MOFs. Different MOF topologies are also being explored.

In summary, we have developed a general methodology for the introduction of organocatalytic groups into MOFs that exhibits several advantageous features: (1) it encompasses catalytically active groups that would otherwise disrupt MOF formation or be chemically altered under MOF synthesis conditions; (2) it ensures that there is vacant space around the catalytic unit, allowing it to interact with incoming substrates; and (3) bulky protective groups can preclude framework interpenetration, producing open networks. We expect that this strategy can be applied to virtually any MOF and a substantial number of organocatalytic functional groups.[15] A vast library of catalysts is thus potentially accessible, and structure–activity relationships may increase the performance of these materials to the point where they are viable and attractive catalysts for applications in synthetic chemistry.

■ ASSOCIATED CONTENT

Supporting Information. Full details of ligand and MOF synthesis and characterization, crystallography (including a CIF), dye uptake and gas sorption experiments, and catalysis reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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