JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

Strain-Promoted "Click" Modification of a Mesoporous Metal–Organic Framework

Chong Liu, Tao Li, and Nathaniel L. Rosi*

Department of Chemistry, University of Pittsburgh, 219 Parkman Avenue, Pittsburgh, Pennsylvania 15260, United States

Supporting Information

ABSTRACT: Strain-promoted "click" chemistry is used to post-synthetically modify the pore walls of azide-functionalized mesoporous **bio-MOF-100** (N_3**-bio-MOF-100**). The reactions proceed in high yield and produce no byproduct. This new method was used to introduce various functional groups into the MOF mesopores, including succinimidyl ester bioconjugation moieties that allow for straightforward coupling of biomolecules to the pore walls.

Microporous metal–organic frameworks (MOFs) have emerged as potential centerpiece materials for various applications in fields ranging from energy to medicine.[1] Their signature attributes include permanent porosity, periodicity, and structural diversity. Moreover, their pores can be decorated with functional groups or small molecules via the use of functionalized linkers or post-synthetic framework modification (PSM).[2] Ultimately, however, their pore diameter (≤2 nm) will limit the size and complexity of molecules that can be incorporated into the framework.

Mesoporous MOFs[3] having continuous mesoporous channels can serve as periodic scaffolds for organizing large and complex molecules, thus enabling the creation of periodic porous materials with unprecedented levels of pore complexity.[4] The straightforward introduction of increasing levels of functional diversity and complexity into MOF mesopore environments, beyond that which is currently possible for microporous MOFs, will lead to a step change in the overall application scope of MOF materials.

Facile incorporation of diverse molecular complexity into mesopore environments requires post-synthetic pore modification strategies. An ideal strategy would enable covalent pore modification with a variety of species ranging from simple organic molecules and catalysts to nanoparticles and complex biomolecules. Moreover, the synthetic approach should (1) be highly efficient under mild conditions; (2) be "clean", in that it should not yield byproduct or require input of additional reagents or catalysts; (3) not impact the structural integrity of the scaffold MOF; and (4) be orthogonal to a wide range of possible functional groups that one might choose to introduce. To our knowledge, no reported MOF PSM strategy meets all of these criteria. In fact, the most common methods either require catalysts (e.g., Cu^+ for the Huisgen cycloaddition),[5] produce byproduct (e.g., H_2O or HCl),[6] or require the removal of protecting groups to unmask the desired functional moieties;[7] in some cases, these reagents and byproducts can cause degradation of the scaffold MOF. It should be noted that Diels–Alder-based PSM[8] reactions have been reported and these important and useful strategies yield either no byproduct or simply N_2 gas. In some cases, however, these reactions require either a large excess of reagent (dienophile[8b]), long reaction times (two[8a] or seven[8b] days), or elevated temperatures.[8]

To find a PSM method that addresses all of the criteria outlined above, we examined the bioorthogonal chemistry literature.[9] From our search, we identified strain-promoted "click" chemistry reactions based on cyclooctyne derivatives that (1) proceed efficiently under mild conditions; (2) require no Cu^+ catalyst; and (3) yield no byproduct.[10] Based on the success of these reactions in the innocent modification of biological systems, we reasoned that they could serve as ideal platform reactions for a new universal pore modification strategy. Such a strategy should allow for the straightforward introduction of diverse molecules and functional groups into MOF pores. Further, we note that the size of typical cyclooctyne derivatives would make this strategy most useful for mesopore PSM.

We chose azide-modified mesoporous **bio-MOF-100** (Figure 1A) as the scaffold MOF for this study. **Bio-MOF-100**[11] is a permanently mesoporous material consisting of metal-adeninate tetrahedral building blocks connected together through biphenyldicarboxylate linkers into an open augmented **lcs** network.[12] Large interconnected channels run along [110], [101], and [011], which allow for the unimpeded diffusion of large molecules. To prepare the azide-modified version of **bio-MOF-100** (N_3**-bio-MOF-100**), we replaced biphenyldicarboxylic acid in our synthesis with 2-azidobiphenyldicarboxylic acid.[13] Powder X-ray diffraction (PXRD) was used to confirm that the product material was isostructural to **bio-MOF-100** (Figure 1B) and elemental analysis (Supporting Information) of a dried product sample was used to determine the composition: $Zn_8(Ad)_4(N_3\text{-BPDC})_6O_2\cdot 2(Me_2NH_2)\cdot 6.25(CH_2Cl_2)$ (Ad = adeninate; N_3-BPDC = 2-azidobiphenyldicarboxylate). Since three N_3-BPDC linkers connect neighboring zinc–adeninate building units together, the mesopores of the structure are densely decorated with azide groups (Figures 1A and S2), an aspect that should allow for dense coverage of desired functional molecules after PSM.

We next prepared methyl 4-(11,12-didehydrodibenzo[*b*,*f*]-azocin-5(6*H*)-yl)-4-oxobutanoate (**1**) and *N*-dodecanoyl-5,6-dihydro-11,12-didehydrodibenzo[*b*,*f*]azocine (**2**), using a

Received: August 3, 2012
Published: October 31, 2012

dx.doi.org/10.1021/ja307713q | *J. Am. Chem. Soc.* 2012, 134, 18886–18888

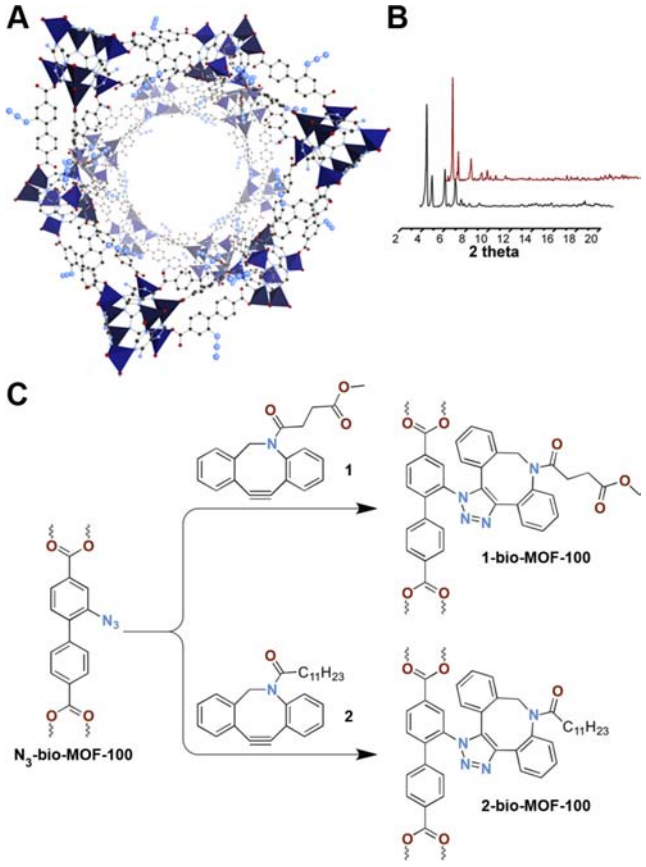

Figure 1. (A) Perspective view of an azide-decorated channel in **N_3-bio-MOF-100**. This image was generated from the single-crystal X-ray diffraction data for **bio-MOF-100**; Zn^{2+}, dark blue tetrahedra; O, dark red spheres; N, light blue spheres; C, dark gray spheres; H atoms omitted for clarity. (B) PXRD pattern for **bio-MOF-100** (black) and **N_3-bio-MOF-100** (dark red). (C) Synthetic scheme for the strain-promoted "click" modification of **N_3-bio-MOF-100** with **1** and **2**.

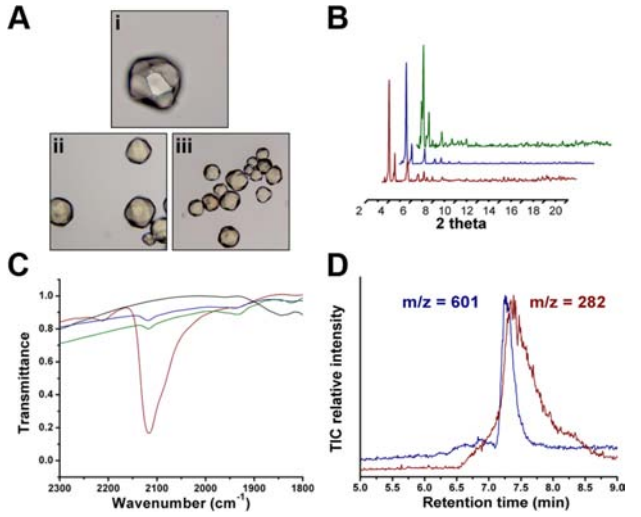

Figure 2. (A) Light microscopy images of reactant **N_3-bio-MOF-100** (i) and products **1-bio-MOF-100** (ii) and **2-bio-MOF-100** (iii). (B) PXRD patterns of reactant **N_3-bio-MOF-100** and products **1-bio-MOF-100**, and **2-bio-MOF-100**. (C) FTIR spectra showing the absence of an N_3 stretch for **bio-MOF-100**, the strong N_3 stretch for reactant **N_3-bio-MOF-100**, and the comparatively weak N_3 stretches for products **1-bio-MOF-100** and **2-bio-MOF-100**. (D) LCMS negative-mode total ion current plots for dissolved reactant **N_3-bio-MOF-100** and product **1-bio-MOF-100**. For all data: **bio-MOF-100**, black; **N_3-bio-MOF-100**, dark red; **1-bio-MOF-100**, blue; and **2-bio-MOF-100**, green.

modified synthetic pathway,[14] for our initial proof-of-principle PSM studies (Figure 1C). We thoroughly washed a MOF sample with dimethylformamide followed by dichloromethane (DCM) and then stored the sample in DCM prior to reaction. A solution containing 1 equivalent (i.e., 1 alkyne per every 1 azide in MOF sample) of either **1** or **2** in DCM was added to separate vials containing samples of solid DCM-exchanged **N_3-bio-MOF-100**, and these mixtures were allowed to stand overnight at room temperature. The following day, the supernatants were removed and the MOF crystals were thoroughly washed with DCM to remove any unreacted **1** or **2**.

Light microscopy images (Figures 2A and S18−S20) provide visual proof that the modified **bio-MOF-100** crystals remain intact throughout the PSM reaction, and PXRD patterns of the product materials indicate retention of crystallinity (Figure 2B). Fourier-transform infrared (FTIR) spectroscopy (Figure 2C) revealed that the strain-promoted "click" PSM procedure, in both cases, was nearly quantitative because the azide stretch (2116 cm^{-1}) present for the reactant MOF was nearly absent in the product MOF. Comparison of the thermogravimetric analysis data for **N_3-bio-MOF-100** to those for both **1-bio-MOF-100** and **2-bio-MOF-100** reveals a significant decrease in the amount of included solvent (Figure S8). To further study the yield of the PSM reaction, we dissolved the product MOFs in dilute HCl/acetonitrile and analyzed the resulting solution using liquid chromatography coupled with mass spectrometry (LCMS). For both samples, the negative mode total ion current plots obtained from this analysis show peaks for the "click"-modified biphenyldicarboxylic acid molecules (Figures 2D and S7); the peak associated with 2-azidobiphenyldicarboxylic acid (m/z = 282) was nearly absent in both samples. Finally, we compared the efficiency of this new strain-promoted "click" PSM methodology to the established Cu-catalyzed "click" PSM methods.[5d−f] In short, a sample of **N_3-bio-MOF-100** was reacted with 2 equivalents of 1-hexyne (i.e., 2 hexynes per every 1 azide in MOF sample) in the presence of CuI catalyst. An FTIR spectrum of the product revealed a significant azide stretch (Figure S9). Therefore, we next performed the Cu-catalyzed reaction with 50 equivalents of 1-hexyne; in this case, FTIR confirmed complete consumption of the azide (Figure S9), which is in agreement with previous PSM studies.[5f] The Cu-catalyzed approach requires a large excess of alkyne to achieve levels of conversion that are comparable to those achieved via the strain-mediated approach, which only requires 1 equivalent of alkyne.

To summarize, these proof-of-principle studies demonstrate that strain-promoted "click" reactions in mesoporous **N_3-bio-MOF-100** samples proceed nearly quantitatively under ambient conditions and do not impact the structural integrity of the MOF. These reactions proceed more efficiently than their Cu-catalyzed counterparts and they also have the added benefit of being free of byproduct (e.g., Cu^+, H_2O, or HCl, for example). It is important to realize that **1**, with its ester functionality, can easily be modified with other molecules and functional groups; therefore, **1** is an ideal platform molecule for this straightforward PSM methodology. In addition, we note that a variety of other strained alkynes are commercially available, which should allow for the broad application of this strategy.

dx.doi.org/10.1021/ja307713q | J. Am. Chem. Soc. 2012, 134, 18886−18888

To exploit the versatility of **1** and to explore the scope of this PSM methodology, we prepared **3**, a succinimide-modified version of **1** that is ideal for coupling to primary amines, such as those at the N-terminus of peptides. Reaction of **3** with **N_3-bio-MOF-100** yields the succinimide-decorated product MOF. Soaking this MOF in a solution of di-L-phenylalanine, a bulky dipeptide, yields **Phe_2-bio-MOF-100** with di-L-phenylalanine peptides anchored to its channel walls (Figure 3; section 8 of Supporting Information). In principle, this straightforward bioconjugation strategy could be used to tether other peptides, proteins (including enzymes), or aminated nucleic acids and biomolecules, polymers, dyes, and nanoparticles to the internal surface of a mesoporous MOF.

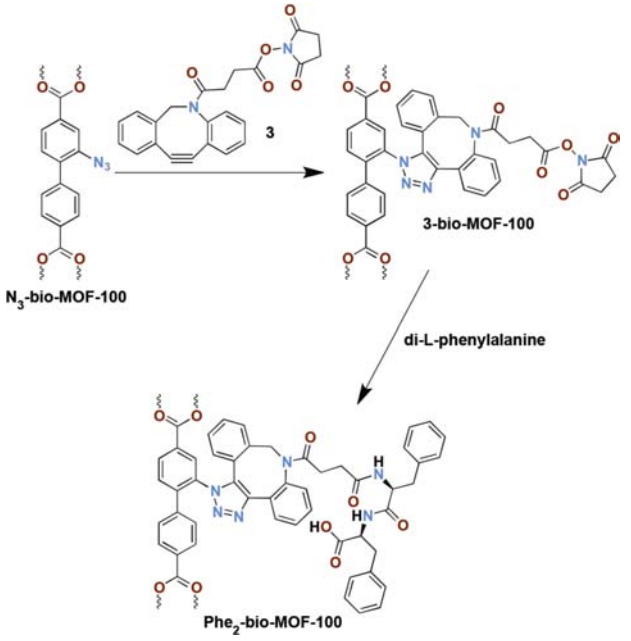

Figure 3. Scheme for the strain-promoted "click" introduction of succinimidyl ester groups into **bio-MOF-100** and the subsequent bioconjugation of the Phe_2 peptide.

■ ASSOCIATED CONTENT

Supporting Information

Synthetic details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

nrosi@pitt.edu

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Funding for this work was provided by the University of Pittsburgh. The authors thank the Petersen NanoFabrication and Characterization Facilty for provision of access to PXRD and FTIR instrumentation. C.L. acknowledges the University of Pittsburgh Dietrich School of Arts and Sciences for funding through an Arts and Sciences Fellowship.

■ REFERENCES

(1) The diverse chemistry of MOFs is detailed in various reviews within the following special issues: (a) Long, J. R.; Yaghi, O. M. *Chem. Soc. Rev.* **2009**, *38*, 1213. (b) Zhou, H. C.; Long, J. R.; Yaghi, O. M. *Chem. Rev.* **2012**, *112*, 673.

(2) Cohen, S. M. *Chem. Rev.* **2012**, *112*, 970.

(3) (a) Fang, Q.-R.; Makal, T. A.; Young, M. D.; Zhou, H.-C. *Comments Inorg. Chem.* **2010**, *31*, 165. (b) Xuan, W.; Zhu, C.; Liu, Y.; Cui, Y. *Chem. Soc. Rev.* **2012**, *41*, 1677.

(4) (a) Suzuki, K.; Kawano, M.; Sato, S.; Fujita, M. *J. Am. Chem. Soc.* **2007**, *129*, 10652. (b) Deng, H.; Grunder, S.; Cordova, K. E.; Valente, C.; Furukawa, H.; Hmadeh, M.; Gandara, F.; Whalley, A. C.; Liu, Z.; Asahina, S.; Kazumori, H.; O'Keeffe, M.; Terasaki, O.; Stoddart, J. F.; Yaghi, O. M. *Science* **2012**, *336*, 1018.

(5) (a) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565. (b) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596. (c) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057. (d) Goto, Y.; Sato, H.; Shinkai, S.; Sada, K. *J. Am. Chem. Soc.* **2008**, *130*, 14354. (e) Gadzikwa, T.; Lu, G.; Stern, C. L.; Wilson, S. R.; Hupp, J. T.; Nguyen, S. T. *Chem. Commun.* **2008**, 5493. (f) Savonnet, M.; Bazer-Bachi, D.; Bats, N.; Perez-Pellitero, J.; Jeanneau, E.; Lecocq, V.; Pinel, C.; Farrusseng, D. *J. Am. Chem. Soc.* **2010**, *132*, 4518.

(6) (a) Wang, Z. C.; Cohen, S. M. *J. Am. Chem. Soc.* **2007**, *129*, 12368. (b) Ingleson, M. J.; Barrio, J. P.; Guilbaud, J. B.; Khimyak, Y. Z.; Rosseinsky, M. J. *Chem. Commun.* **2008**, 2680. (c) Morris, W.; Doonan, C. J.; Furukawa, H.; Banerjee, R.; Yaghi, O. M. *J. Am. Chem. Soc.* **2008**, *130*, 12626. (d) Savonnet, M.; Aguado, S.; Ravon, U.; Bazer-Bachi, D.; Lecocq, V.; Bats, N.; Pinel, C.; Farrusseng, D. *Green Chem.* **2009**, *11*, 1729.

(7) (a) Deshpande, R. K.; Minnaar, J. L.; Telfer, S. G. A *Angew. Chem., Int. Ed.* **2010**, *49*, 4598. (b) Deshpande, R. K.; Waterhouse, G. I.; Jameson, G. B.; Telfer, S. G. *Chem. Commun.* **2012**, *48*, 1574. (c) Tanabe, K. K.; Allen, C. A.; Cohen, S. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 9730.

(8) (a) Chen, C.; Allen, C. A.; Cohen, S. M. *Inorg. Chem.* **2011**, *50*, 10534. (b) Roy, P.; Schaate, A.; Behrens, P.; Godt, A. *Chem. Eur. J.* **2012**, *18*, 6979.

(9) (a) Sletten, E. M.; Bertozzi, C. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 6974. (b) Jewett, J. C.; Bertozzi, C. R. *Chem. Soc. Rev.* **2010**, *39*, 1272. (c) Sletten, E. M.; Bertozzi, C. R. *Acc. Chem. Res.* **2011**, *44*, 666.

(10) (a) Baskin, J. M.; Prescher, J. A.; Laughlin, S. T.; Agard, N. J.; Chang, P. V.; Miller, I. A.; Lo, A.; Codelli, J. A.; Bertozzi, C. R. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 16793. (b) Debets, M. F.; van Berkel, S. S.; Schoffelen, S.; Rutjes, F. P.; van Hest, J. C.; van Delft, F. L. *Chem. Commun.* **2010**, *46*, 97.

(11) An, J.; Farha, O. K.; Hupp, J. T.; Pohl, E.; Yeh, J. I.; Rosi, N. L. *Nat. Commun.* **2012**, *3*, 604.

(12) Friedrichs, O. D.; O'Keeffe, M. O.; Yaghi, O. M. *Acta Crystallogr., Sect. A* **2003**, *59*, 515.

(13) (a) Olkhovik, V. K.; Vasilevskii, D. A.; Pap, A. A.; Kalechyts, G. V.; Matveienko, Y. V.; Baran, A. G.; Halinouski, N. A.; Petushok, V. G. *ARKIVOC* **2008**, 69. (b) Ol'khovik, V. K.; Pap, A. A.; Vasilevskii, V. A.; Galinovskii, N. A.; Tereshko, S. N. *Russ. J. Org. Chem.* **2008**, *44*, 1172. (c) Sato, H.; Matsuda, R.; Sugimoto, K.; Takata, M.; Kitagawa, S. *Nat. Mater.* **2010**, *9*, 661.

(14) (a) Campbell-Verduyn, L. S.; Mirfeizi, L.; Schoonen, A. K.; Dierckx, R. A.; Elsinga, P. H.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 11117. (b) Cho, H.; Iwama, Y.; Sugimoto, K.; Mori, S.; Tokuyama, H. *J. Org. Chem.* **2010**, *75*, 627.