



ChemComm

**Rapid Post-Synthetic Modification of Porous Coordination  
Cages with Copper-Catalyzed Click Chemistry**

Journal:	<i>ChemComm</i>
Manuscript ID	CC-COM-04-2023-002015.R2
Article Type:	Communication

SCHOLARONE™  
Manuscripts

## COMMUNICATION

## Rapid Post-Synthetic Modification of Porous Coordination Cages with Copper-Catalyzed Click Chemistry

Received 00th January 20xx,  
Accepted 00th January 20xx

Michael R. Dworzak,<sup>a,○</sup> Christine M. Montone,<sup>a,b,○</sup> Nicole I. Halaszynski,<sup>c</sup> Glenn P. A. Yap,<sup>a</sup>  
Christopher J. Kloxin,<sup>\*c,d</sup> and Eric D. Bloch<sup>\*a,b</sup>

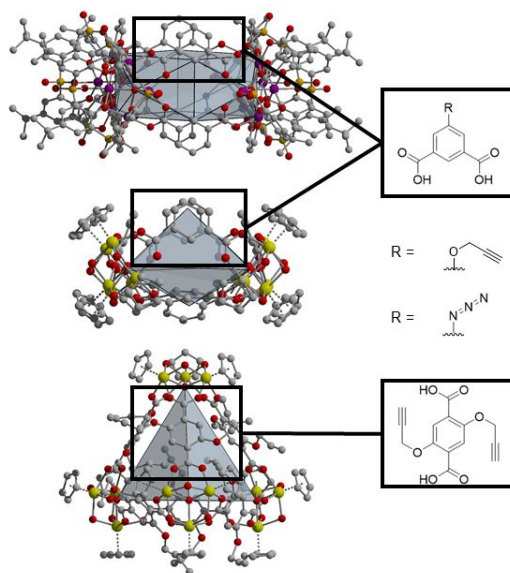
DOI: 10.1039/x0xx00000x

**Novel cobalt calixarene-capped and zirconium-based porous coordination cages were prepared with alkyne and azide functionality to leverage post-synthetic modification by click chemistry. While the calixarene-capped cages showed impressive stability when exposed to the most straightforward copper(I)-catalyzed alkyne–azide cycloaddition (CuAAC) reaction conditions with copper (II) sulfate and sodium ascorbate as the reducing agent, milder reaction conditions were necessary to perform analogous CuAAC reactions on zirconium-based cages. Reaction kinetics were monitored by IR spectroscopy, confirming rapid reaction times (< 3 hours).**

Porous hybrid materials, including metal-organic frameworks (MOFs) and porous coordination cages (cages), have been modified at either their organic bridging ligands or structural metal cations as a method to finely tune their properties.<sup>1,2</sup> These modifications can be used to incorporate targeted functionality to tune the porous hybrid material's phase, porosity, or in the case of cages, solubility.<sup>3</sup> Depending on the nature of the targeted functional group, it can be incorporated on the bridging ligand either prior to or after synthesis of the porous product. In cases where the functional group does not interfere with the MOF or cage synthesis, it is straightforward to modify the bridging ligand, where often only minor modifications to established synthesis protocols afford the desired phase. However, in many cases, post-synthetic modification of porous materials is necessary as some functional groups can interfere with product formation resulting in side products or alternative phases. In some cases, the organic functional group is not compatible with the conditions to afford the targeted MOF or cage.

Although there are some challenges and limitations in the post-synthetic modification of MOFs, such as difficulties in assessing the extent or homogeneity of modification, it has

been widely reported for numerous families of MOFs where a variety of functional groups have been installed to tune material properties.<sup>4</sup> These methods have also been explored and successfully leveraged to tune porous coordination cages where both metal- and ligand-based chemistry has been targeted.<sup>5</sup> Given the molecular nature of these adsorbents, there are unique challenges and opportunities for their functionalization as homogeneous modifications can be used to alter their structures. Strategies for the post-synthetic modification of cages<sup>6,7</sup> have included both covalent coordination chemistry and non-covalent post-synthetic modifications.<sup>8,9,10</sup> Previous work conducted by our lab has shown that post-synthetic modification can allow for tuning solubility, crystallinity, or porosity.<sup>11,12</sup>



**Fig. 1** Single crystal XRD structural depictions of cages utilized in click reactions. A cobalt-based calixarene capped cage with eight azide (Co-N<sub>3</sub>) or alkyne-functionalized (Co-ppgy) isophthalic acid ligands (top), a box-shaped zirconium-based cage with six azide (Zr(5-N<sub>3</sub>)) or alkyne-functionalized (Zr(5-ppgy)) isophthalic acid ligands (center), and (bottom) the tetrahedral zirconium-based cage with six dialkyne terephthalic acid ligands (Zr(2,5-dippgy)).

Click chemistry is a particularly appealing tool for post-synthetic modification of cages due to the rapid and selective nature of this class of covalent reactions. There are several types of click reactions that are widely employed in synthetic

<sup>a</sup> Department of Chemistry and Biochemistry, University of Delaware, Newark, Delaware 19716, United States.

<sup>b</sup> Department of Chemistry, Indiana University, Bloomington, Indiana 47405, United States

<sup>c</sup> Department of Materials Science and Engineering, University of Delaware, Newark, Delaware 19716, United States

<sup>d</sup> Department of Chemical and Biomolecular Engineering, University of Delaware, Newark, Delaware 19716, United States

<sup>○</sup> These authors contributed equally and are joint first authors.

† Electronic Supplementary Information (ESI) available: adsorption isotherms, crystallographic information, spectroscopic data. See DOI: 10.1039/x0xx00000x

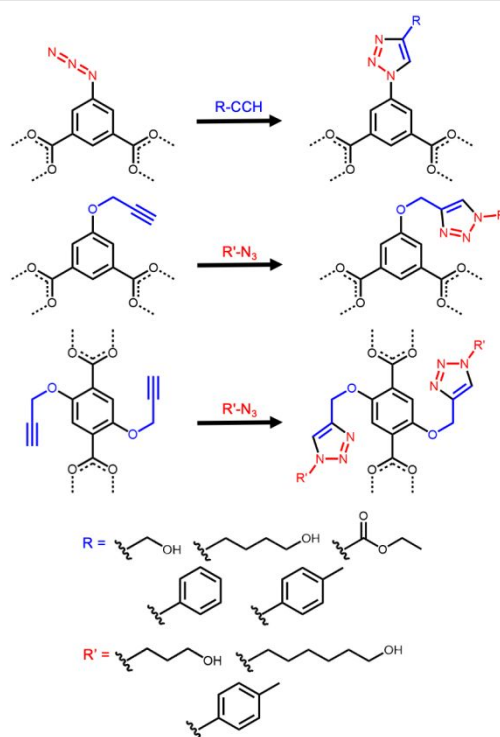
chemistry, including copper-catalyzed alkyne-azide cycloadditions,<sup>13</sup> Diels-Alder cycloadditions,<sup>14</sup> TCO-tetrazine ligation,<sup>15</sup> thiol-ene,<sup>16</sup> thiol-Michael,<sup>17,18</sup> and others. As such, click reactions have been employed for the modification of alkyne- or azide- functionalized MOFs,<sup>19,20,21,22,23,24</sup> with limited work investigating the utility of this class of reactions with cages.<sup>25,26,27,28</sup>

In this work, we focused on the copper(I)-catalyzed 1,3-cycloaddition between a terminal alkyne and azide to yield a 1,2,3-triazole.<sup>29</sup> This reaction is commonly carried out using a Cu(II) source, such as copper sulfate, which is reduced to Cu(I) using a reducing agent. There are alternatives to this method however, where directly utilizing Cu(I)<sup>30</sup> or direct photo-reduction of Cu(II) to Cu(I),<sup>31</sup> or using a radical photoinitiator.<sup>32</sup>

In targeting cages for post-synthetic modification with click-type reactions we sought materials with previously demonstrated stability under a relatively wide range of conditions. Both cyclopentadienyl-capped zirconium cages and calixarene-capped cobalt cages are promising candidates for post-synthetic modification as they are stable in the temperature and solvent conditions of interest, and present in various geometries depending on the angle between carboxylate groups in their ditopic linkers.<sup>33,34,35</sup> In the case of zirconium cages, we prepared three novel structures containing six bridging ligands and four vertices. Two of these based on isophthalic acid analogues, 5-azido isophthalic acid (5-N<sub>3</sub>-bdc) and 5-propargyl isophthalic acid (5-propargyl-bdc) adopt what has previously been described as “window” geometries (Figure 1).<sup>34</sup> The remaining cage uses 2,5-dipropargyl terephthalic acid as a bridging ligand, creating a tetrahedral cage (Figure 1).<sup>33,36</sup> The synthesis of these cages is straightforward and involves the solvothermal reaction of bis(cyclopentadienyl)zirconium(IV) dichloride and respective isophthalic/terephthalic derivatives in *N,N*-dimethylformamide (DMF). Crystalline material formed during heating and was washed with DMF and CHCl<sub>3</sub>. These cages are typically characterized with UPLC-mass spectrometry – as three distinct peaks are discernible for each cage, corresponding to the 4+, 3+, and 2+ *M/Z* fragments. IR was then used to verify the presence of the indicated functional group, azide or alkyne, and proton NMR is used to verify the composition of cage, as these zirconium-based materials are diamagnetic and clearly reveal the ligand composition. These two geometries/architectures are isorecticular in that they both contain four zirconocene-based caps bridged by six carboxylate-based ligands; however, the isophthalic acid-based ligands afford a single click-accessible functional group per ligand, where the chosen dialkyne-functionalized terephthalic acid-based ligand affords two click-accessible functional groups per ligand.

In an analogous manner the synthesis of calixarene-capped cobalt cages involves the solvothermal reaction of *p*-tert-butylsulfonycalix[4]arene (sc4a), Co(NO<sub>3</sub>)<sub>2</sub>·6H<sub>2</sub>O, and respective isophthalic acid derivatives in DMF. Although a variety of cage geometries can be isolated depending on the nature of bridging ligands used, we targeted the so-called Type-III structures based on isophthalic acid given our previous experience in the synthesis and

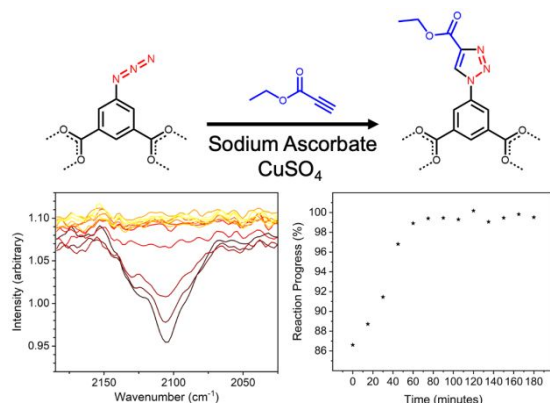
characterization of these cages and the fact that the 5-positions of the eight isophthalic acid ligands in these structures are relatively accessible and should be amenable to post-synthetic modification when a functional group or reaction site is present.<sup>35</sup> 5-propargyl-bdc (ppgy) and 5-N<sub>3</sub>-bdc (N<sub>3</sub>) afford two novel structures, Co-ppgy and Co-N<sub>3</sub>, respectively. These calixarene-capped cages are structurally similar, as confirmed by single crystal X-ray diffraction. Four of the functional groups on the cages point up from the plane of the sc4a units while the other 4 groups point down (Figure 1). While mass spectrometry can be used reliably when characterizing zirconium-based cages, it has proven to be a challenging technique to use for this cage. <sup>1</sup>H NMR can be used to confirm the composition of each cage, however, due to the paramagnetism of these Co(II) cages, digestion of the materials using deuterated acid was necessary to obtain interpretable, quantitative spectra. Additionally, IR and UV-Vis were further employed to confirm the retention of cage structure before and after click reactions, and before and after activation for gas adsorption studies.



**Fig. 2** Generalized scheme of the post-synthetic modification of cages using copper-catalyzed alkyne-azide click chemistry depicting reactions of alkyne or azide cage ligands with alkyne or azide small molecules.

With two families of azide- and alkyne-functionalized cages in hand, we turned to copper catalyzed click modification with an array of functional groups, including aryl, ester, and alkyl alcohol groups. Specifically, we utilized propargyl alcohol, ethynyl toluene, 5-hexyn-1-ol, ethyl propiolate, and phenylacetylene in combination with azide-functionalized cages and *p*-azide toluene, 3-azido 1-propanol, and 6-azidohexanol for the alkyne-functionalized cages (Figure 2). We employed well-known CuAAC conditions where a precatalyst (hydrated copper(II) sulfate) is reduced to the active copper(I) catalyst by sodium ascorbate under

solvothermal conditions. Each reaction was conducted at 65 °C without stirring in sealed, 20 mL scintillation vials. After 12 hours, significant copper(0) had precipitated from the otherwise homogeneous reaction mixture. Reactions were filtered and diethyl ether added to precipitate product material. After collection of cage products via centrifuge, each was dried under reduced pressure before characterization by <sup>1</sup>H NMR, IR spectroscopy, UV-Vis, TGA, and N<sub>2</sub> gas adsorption analysis. These methods confirm the persistence of the calixarene-capped cage in these reaction conditions, but mass spectrometry suggests the zirconium-based cages decompose in the presence of copper(II) and ascorbic acid.



Reagent	Abbrev.	Cage	% Conv.
	N <sub>3</sub> Tol	Zr(5-ppgy)	67
		Zr(2,5-dippgy)	100
	3AP	Co-ppgy	92
		Zr(5-ppgy)	83
		Zr(2,5-dippgy)	100
	6AH	Co-ppgy	86
		Zr(5-ppgy)	<33
		Zr(2,5-dippgy)	<50
	EtTol	Zr(5-N <sub>3</sub> )	83
	PA	Co-N <sub>3</sub>	100
	6OH	Zr(5-N <sub>3</sub> )	83
	PrOH	Co-N <sub>3</sub>	100
		Zr(5-N <sub>3</sub> )	100
	EP	Co-N <sub>3</sub>	100

**Fig. 3 (Top)** Example of kinetics data gathered during the CuAAC reaction of Co-N<sub>3</sub> cage with ethyl propiolate. The characteristic azide IR stretch near 2100 cm<sup>-1</sup> was monitored (left) throughout the reaction and (right) the transmission was plotted against the reaction time, showing rapid conversion of azide/alkyne to triazole. **(Bottom)** Table including reagents and their abbreviations used in click reactions with corresponding cages as well as associated conversions after being allowed to react for 1 hour at 60 °C for cobalt-based cages (CuAAC), and 3 hours at room temperature for zirconium-based cages (Cu(I) catalyzed) as determined by <sup>1</sup>H NMR.

As the carboxylate-based reductant used under typical click conditions likely contributes to the decomposition of zirconium-based cages over the course of a reaction, we targeted copper(I) salt as the active catalyst. For this, we prepared fresh solutions of CuI in anhydrous acetonitrile under air-free conditions prior to each reaction. Transfer of the solution from an air free vessel to the reaction flask was conducted by injection into a sparged solution of cage, the

click-relevant molecule, and triethylamine. When zirconium cages were subjected to these reaction conditions without the addition of a small molecule reactant, the resulting mass spectrum (Figure S99) indicates the three characteristic M/Z peaks, signifying that the cage can withstand these reaction conditions. IR spectroscopy was used to monitor the click reaction kinetics in the cobalt and zirconium azide functionalized cage reactions (Figure 3). Reaction monitoring was accomplished by removing a small aliquot from an ongoing reaction and precipitating the cage material with diethyl ether. The solid was then analysed with IR spectroscopy and the intensity of the azide stretch was compared to that of the unreacted starting cage. As expected, these experiments confirmed that modification of cages is extremely rapid under these conditions and, although the reactions were not quantitative in all cases, likely a result of the close proximity of functional groups on the periphery of these cages, the reaction progress was complete after less than one hour at 65 °C or three hours at 35 °C.

The resulting NMR spectra from the 14 cage click reactions of both cobalt- and zirconium-based cages show peaks in the aromatic region corresponding to protons present on either isophthalic acid (2:1 integration) or terephthalic acid (1:1:1 integration) as was observed in <sup>1</sup>H NMR spectra of the parent cages. In addition, the presence of a peak corresponding to the proton of the newly formed triazole ring was observed at a further downfield shift than the isophthalic/terephthalic acid proton peaks at a near quantitative integration. Depending on the cage and azide or alkyne reagent used, we observed varying levels of conversion from < 33 % in the case of the monofunctionalized zirconium alkyne cage to quantitative conversion for many of the cobalt cage reactions (Figure 3).

Further probing of how click reactions change the properties of the cage, gas adsorption measurements were conducted. Porosity of the clicked cage materials to N<sub>2</sub> was probed and showed that while the starting cobalt cages, Co-ppgy and Co-N<sub>3</sub> exhibited no porosity to N<sub>2</sub>, product cages displayed significant porosity. In the case of the clicked PPCs derived from Co-ppgy, both Co-ppgy-3AP and Co-ppgy-6AH exhibited significant porosity to N<sub>2</sub> with peak uptakes of 8.1 mmol/g and 9.2 mmol/g respectively near P/P<sub>0</sub> = 0.90 (Figures S76 and S80). It is important to note that the N<sub>2</sub> adsorptive plot for this material adopts a Type II isotherm shape which explains the relatively low Langmuir (BET) surface area values of 426 (221) m<sup>2</sup>/g and 613 (196) m<sup>2</sup>/g for the respective materials.

The cobalt-based cages also display Type II isotherms, again indicating that installation of functional groups into these systems significantly alters cage packing in the solid state. Co-N<sub>3</sub>-PrOH does exhibit a significantly lower N<sub>2</sub> uptake than Co-N<sub>3</sub>-EP and Co-N<sub>3</sub>-PA, with uptakes of 1.25 mmol/g compared to 7.5 mmol/g and 5.4 mmol/g, respectively (Figures S84, S88, and S92). Similar to the previous set of cages derived from Co-ppgy, relatively low BET surface areas are observed for these materials when considering their peak uptake due to the Type II isotherm shape observed. Co-N<sub>3</sub>-PrOH, Co-N<sub>3</sub>-EP,

and Co-N<sub>3</sub>-PA exhibit N<sub>2</sub> BET surface areas of 37 m<sup>2</sup>/g, 179 m<sup>2</sup>/g, and 221 m<sup>2</sup>/g, respectively.

While parent cages Co-ppgy and Co-N<sub>3</sub> showed no porosity to N<sub>2</sub>, they are however porous to CO<sub>2</sub>, exhibiting uptakes of 7.13 mmol/g and 4.37 mmol/g and Langmuir (BET) surface areas of 902 (308) m<sup>2</sup>/g and 491 (240) m<sup>2</sup>/g, respectively. While these materials gained porosity to N<sub>2</sub> after undergoing click reactions with various substrates, CO<sub>2</sub> accessible surface areas decreased upon modification. Co-ppgy-3AP had a CO<sub>2</sub> uptake of 2.73 mmol/g and a surface area of 310 (153) m<sup>2</sup>/g. Co-ppgy-6AH showed a similar decrease in porosity with an uptake of 2.46 mmol/g and a surface area of 287 (126) m<sup>2</sup>/g. Meanwhile, Co-N<sub>3</sub>-PrOH, Co-N<sub>3</sub>-EP, and Co-N<sub>3</sub>-PA also seemed to suffer a decrease in porosity albeit to a significantly lesser degree compared to the parent material. Each material had an uptake of 1.78 mmol/g, 2.11 g/mol, and 2.30 mmol/g respectively while maintaining surface areas of 196 (127) m<sup>2</sup>/g, 240 (117) m<sup>2</sup>/g, and 263 (125) m<sup>2</sup>/g respectively.

This work described the covalent modification of porous coordination cages with copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) click reactions. Although this strategy proved to be a viable method for the rapid modification of the porous molecules discussed here, care must be taken to ensure the parent cage materials are compatible with the reaction conditions used for this transformation. Although calixarene-capped cages display the requisite stability for modification under more classical conditions, zirconium cages are unstable in the presence of sodium ascorbate which is a common reductant employed in conjunction with the copper(II) salt used in CuAAC reactions, and reaction conditions must be modified by directly using Cu(I) to achieve conversion of products.

This research was supported by the National Science Foundation (NSF) through the University of Delaware Materials Research and Engineering Center, DMR-2011824-The Center for Hybrid, Active, and Responsive Materials (CHARM). Conflicts of interest  
There are no conflicts to declare.

## References

- 1 A. M. Antonio, K. J. Korman, M. M. Deegan, G. A. Taggart, G. P. A. Yap and E. D. Bloch, *Inorg. Chem.* 2022, **61**, 4609–4617.
- 2 G. E. Cmarik, M. Kim, S. M. Cohen and K. S. Walton, *Langmuir* 2012, **28**, 15606–15613.
- 3 M. M. Deegan, R. Bhattacharjee, S. Caratzoulas and E. D. Bloch, *Inorg. Chem.* 2021, **60**, 7044–7050.
- 4 Z. Yin, S. Wan, J. Yang, M. Kurmoo and M.-H. Zeng, *Coord. Chem. Rev.* 2019, **378**, 500–512.
- 5 A. Carné-Sánchez, J. Albalad, T. Grancha, I. Imaz, J. Juanhuix, P. Larpent, S. Furukawa and D. Maspoch, *J. Am. Chem. Soc.* 2019, **141**, 4094–4102.
- 6 D. A. Roberts, B. S. Pilgrim and J. R. Nitschke, *Chem. Soc. Rev.* 2018, **47**, 626–644.
- 7 J. Liu, Z. Wang, P. Cheng, M. J. Zaworotko, Y. Chen and Z. Zhang, *Nat. Rev. Chem.* 2022, **6**, 339–356.
- 8 A. Legrand, L.-H. Liu, P. Royla, T. Aoyama, G. A. Craig, A. Carné-Sánchez, K. Urayama, J. J. Weigand, C.-H. Lin and S. Furukawa, *J. Am. Chem. Soc.* 2021, **143**, 3562–3570.
- 9 Z. Wang, G. A. Craig, A. Legrand, F. Haase, S. Minami, K. Urayama and S. Furukawa, *Chem. – Asian J.* 2021, **16**, 1092–1100.
- 10 S. K. Samanta, D. Moncelet, V. Briken and L. Isaacs, *J. Am. Chem. Soc.* 2016, **138**, 14488–14496.
- 11 G. A. Taggart, A. M. Antonio, G. R. Lorzing, G. P. A. Yap and E. D. Bloch, *ACS Appl. Mater. Interfaces* 2020, **12**, 24913–24919.
- 12 M. M. Deegan and E. D. Bloch, *Dalton Trans.* 2021, **50**, 3127–3131.
- 13 V. V. Rostovtsev, L. G. Green, V. V. Fokin and K. B. Sharpless, *Angew. Chem. Int. Ed.* 2002, **41**, 2596–2599.
- 14 H. C. Kolb, M. G. Finn and K. B. Sharpless, *Angew. Chem. Int. Ed.* 2001, **40**, 2004–2021.
- 15 A. Jemas, Y. Xie, J. E. Pigga, J. L. Caplan, C. W. am Ende and J. M. Fox, *J. Am. Chem. Soc.* 2022, **144**, 1647–1662.
- 16 C. E. Hoyle and C. N. Bowman, *Angew. Chem. Int. Ed.* 2010, **49**, 1540–1573.
- 17 C. E. Hoyle, A. B. Lowe and C. N. Bowman, *Chem. Soc. Rev.* 2010, **39**, 1355–1387.
- 18 S. Chatani, D. P. Nair and C. N. Bowman, *Polym. Chem.* 2013, **4**, 1048–1055.
- 19 Y. Goto, H. Sato, S. Shinkai and K. Sada, *J. Am. Chem. Soc.* 2008, **130**, 14354–14355.
- 20 U. Fluch, B. D. McCarthy and S. Ott, *Dalton Trans.* 2019, **48**, 45–49.
- 21 Q. Fu, K. Xie, S. Tan, J. M. Ren, Q. Zhao, P. A. Webley and G. G. Qiao, *Chem. Commun.* 2016, **52**, 12226–12229.
- 22 T. Gadzikwa, O. K. Farha, C. D. Malliakas, M. G. Kanatzidis, J. T. Hupp and S. T. Nguyen, *J. Am. Chem. Soc.* 2009, **131**, 13613–13615.
- 23 B. Gui, X. Meng, H. Xu, and C. Wang, *Chin. J. Chem.* 2016, **34**, 186–190.
- 24 H.-L. Jiang, D. Feng, T.-F. Liu, J.-R. Li and H.-C. Zhou, *J. Am. Chem. Soc.* 2012, **134**, 14690–14693.
- 25 N. J. Oldenhuis, K. P. Qin, S. Wang, H.-Z. Ye, E. A. Alt, A. P. Willard, T. Van Voorhis, S. L. Craig and J. A. Johnson, *Angew. Chem. Int. Ed.* 2020, **59**, 2784–2792.
- 26 D. Zhao, S. Tan, D. Yuan, W. Lu, Y. H. Rezenom, H. Jiang, L.-Q. Wang and H.-C. Zhou, *Adv. Mater.* 2011, **23**, 90–93.
- 27 S. K. Samanta, D. Moncelet, B. Vinciguerra, V. Briken and L. Isaacs, *Helv. Chim. Acta* 2018, **101**, e1800057.
- 28 N. Ahmad, H. A. Younus, A. H. Chughtai, K. Van Hecke, M. Danish, Z. Gaoke and F. Verpoort, *Sci. Rep.* 2017, **7**, 832.
- 29 M. Meldal and C. W. Tornøe, *Chem. Rev.* 2008, **108**, 2952–3015.
- 30 J. E. Hein, J. C. Tripp, L. B. Krasnova, K. B. Sharpless and V. V. Fokin, *Angew. Chem. Int. Ed.* 2009, **48**, 8018–8021.
- 31 M. A. Tasdelen and Y. Yagci, *Tetrahedron Lett.* 2010, **51**, 6945–6947.
- 32 B. J. Adzima, Y. Tao, C. J. Kloxin, C. A. DeForest, K. S. Anseth and C. N. Bowman, *Nat. Chem.* 2011, **3**, 256–259.
- 33 A. J. Gosselin, G. E. Decker, B. W. McNichols, J. E. Baumann, G. P. A. Yap, A. Sellinger and E. D. Bloch, *Chem. Mater.* 2020, **32**, 5872–5878.
- 34 S. Du, X. Yu, G. Liu, M. Zhou, E.-S. M. El-Sayed, Z. Ju, K. Su and D. Yuan, *Cryst Growth Des.* 2021, **21**, 692–697.
- 35 M. R. Dworzak, M. M. Deegan, G. P. A. Yap and E. D. Bloch, *Inorg. Chem.* 2021, **60**, 5607–5616.
- 36 G. Liu, Z. Ju, D. Yuan and M. Hong, *Inorg. Chem.* 2013, **52**, 13815–13817.