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Scalable preparation and property investigation of a *cis*-cyclobutane-1,2-dicarboxylic acid from β-*trans*-cinnamic acid†

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Scalable synthesis of β-truxinic acid (CBDA-4) was accomplished by capturing and photodimerizing a metastable crystalline solid of *trans*-cinnamic acid. This synthetic approach builds a foundation for investigating the properties and applications of the useful diacid. The X-ray crystal structure of CBDA-4 was determined for the first time. The cyclobutane ring in CBDA-4 was cleaved upon heating, making it a promising building block for thermally recyclable/degradable materials.

Dicarboxylic acids have extensive applications in many different fields such as polymers, metal–organic materials, and medicines.[1] Compared to the widely-used diacids (*e.g.*, phthalic acid, succinic acid, and adipic acid), cyclobutanedicarboxylic acids (CBDAs) are unfamiliar to many researchers, especially those working in materials science.[2] CBDAs and their derivatives represent promising building blocks in materials mainly because they can be readily produced from commercially available starting materials, including many biobased chemicals, and have desired properties (*e.g.* cleavability). Recent studies have demonstrated that CBDAs can be used in producing both thermoplastics and thermosets with excellent properties.[3] In these polymers, CBDA served as either a diacid monomer or cross-linker. Fig. 1 shows two examples of CBDAs that have been used in polymer synthesis together with **CBDA-4**, (1*R*,2*S*,3*R*,4*S*)-*rel*-3,4-diphenyl-cyclobutane-1,2-dicarboxylic acid, which is the focus of this work. Just like **CBDA-2**, with its structural similarity to *o*-phthalic acid,[4] **CBDA-4** can be a useful building block with many applications in materials. Recently, studies have also shown that **CBDA-4** and its derivatives have antinociceptive activities,[5] and can be used as phthalate-free internal donors in Ziegler–Natta catalysts for propylene polymerization.[6] However, researchers have had to take a detour to make **CBDA-4** by first converting *trans*-cinnamic acid to its *p*-nitrophenyl ester or 1,3-trimethylene diester for photodimerization, and then hydrolyzing the ester dimer back to **CBDA-4.**[5–7] Even in a recent development using transition metal-catalyzed enantioselective synthesis of cyclobutane derivatives, **CBDA-4** was only a minor product.[8] Thus, a simple, reliable, and scalable preparation method for **CBDA-4** is highly desirable.

It has been known for about a century that both **CBDA-1** (also known as α-truxillic acid) and **CBDA-4** (also known as β-truxinic acid) can be synthesized from two polymorphs: α- and β-*trans*-cinnamic acid, respectively, in the solid state. However, it has also been documented that the metastable crystalline β-form (head-to-head packing) of *trans*-cinnamic acid readily transforms to the stable α-form (head-to-tail packing).[7b,9] The low energy barrier from the β-form to the α-form renders reliable synthesis of **CBDA-4** challenging, because only the β-form gives **CBDA-4** after photodimerization while the α-form leads to **CBDA-1**, which also explains the conflicting experimental results about **CBDA-4** synthesis in the literature.[9d,10]

Herein, we report a simple, dependable, and scalable preparation method for **CBDA-4** (Scheme 1). Commercially available *trans*-cinnamic acid (m.p.: 133 °C) was first melted and heated in an oven at 180 °C for 30 minutes. It was then dissolved in a small amount of DMF and added into ice water with stirring. Blacklight irradiation of the slurry mixture, which contained the metastable crystalline β-form of *trans*-cinnamic acid, led to the formation of **CBDA-4.** This procedure was repeated dozens of times at a 5 g scale and has been successfully extended to 1 g and 50 g scales. While the detailed procedure is included in the ESI,† it is worthwhile

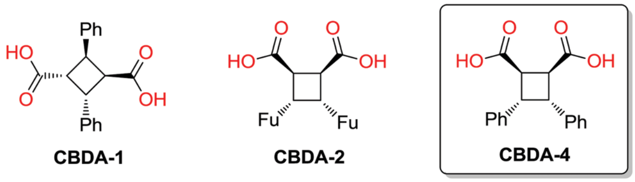

Fig. 1 Examples of CBDAs: *trans*-1,3-CBDA and *cis*-1,2-CBDA. The box highlights the focus of this work.

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† Electronic supplementary information (ESI) available: Experimental details, characterization and properties of β-*trans*-CA and CBDA-4. CCDC 1857653. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8cc08017h

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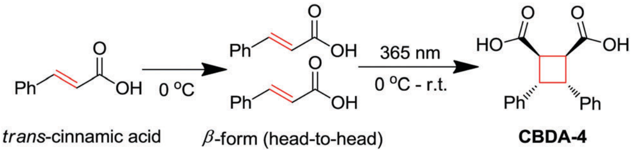


Scheme 1 The facile and scalable preparation of **CBDA-4**.

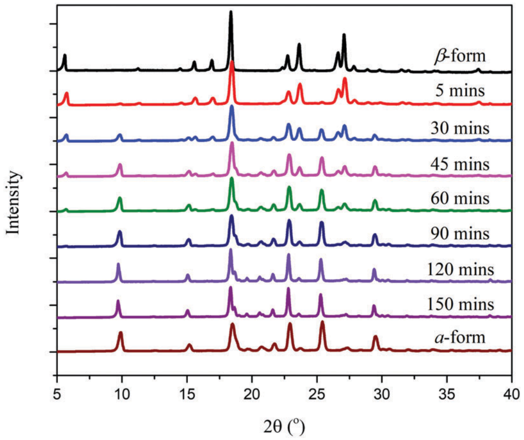


Fig. 2 The phase transformation of β- to α-*trans*-cinnamic acid at 50 °C. The β-form was prepared by precipitating a 5 mL DMF solution of 5 g of *trans*-cinnamic acid in 240 mL of ice water.

to mention here that skipping the step of melting and heating *trans*-cinnamic acid could lead to the formation of **CBDA-1**. It is also important to add the cinnamic acid/DMF solution directly into the ice-water solution, rather than on the top of the ice floating on the water, to avoid formation of any seeds of the stable α-*trans*-cinnamic acid. Otherwise, this could also lead to the formation of **CBDA-1** after photoreaction.[3b]

Powder X-ray diffraction (PXRD) analysis confirmed the ''head-to-head'' β-form of *trans*-cinnamic acid precipitated from the ice-water solution, since its powder pattern was nearly identical to the simulated pattern generated from the single-crystal diffraction data (ESI,† Fig. S8).[9b] Grinding should be avoided when preparing the sample for PXRD because it can easily turn the metastable β-*trans*-cinnamic acid into the stable α form. A knife can be used to gently cut the precipitate into smaller particles for PXRD experimentation if necessary.

The phase transformation from β- to α-*trans*-cinnamic acid was studied by PXRD and DSC. β-Form powder was heated to 50 °C and scanned after different time periods. The results illustrated that the β-form steadily converts to the α-form in 2.5 h. The characteristic peaks of β-*trans*-cinnamic acid at 5.6°, 15.6°, 16.9°, 23.6°, 26.6°, and 27.0° faded gradually upon heating, while new peaks appeared at 9.8°, 15.1°, 18.5°, 21.8°, 25.4°, and 29.5°, which were attributed to α-*trans*-cinnamic acid (Fig. 2). It is important to point out that the transformation rate depends on the size of the crystals, with smaller crystals having a faster rate.[9c] The easy transformation from β- to α-form might explain why the two polymorphs had almost the same melting ranges (133.5–134.4 °C for the α-form and 133.2–134.0 °C for the β-form) and DSC curves (ESI,† Fig. S9), because part of the metastable β-*trans*-cinnamic acid was converted to the stable α-form during the heating process while the melting point or DSC curve was being measured.[9a]

The photoreaction was started at 0 °C when the β-*trans*-cinnamic acid precipitated from the ice-water solution. It was fine to allow the reaction mixture to warm up to room temperature gradually once the ice in the mixture had melted. Irradiating with blacklight was continued until the dimerization had completed. The photodimerization was performed using residential blacklights, which represent an ECO-UV irradiation source.[11] Regular lab glassware (*e.g.*, round-bottom flask, beaker, and Erlenmeyer flask) were used for the photoreaction because about 90% of the blacklight is transmitted through the glass.[12] The completion of dimerization was indicated in FT-IR spectra by the disappearance of the bands at 1627 cm^{-1} (C=C, stretching) and 976 cm^{-1} (C=C–H, out of plane bending), and shifting of the band at 1671 cm^{-1} (C=O, stretching) to 1697 cm^{-1}.[12,13] Subsequently, the mixture was filtered and washed with a small amount of ethanol to give a white powder, which was confirmed as **CBDA-4** by NMR. In the ^{1}H NMR spectrum of **CBDA-4**, two new doublets (δ: 4.22 and 3.82 ppm) appeared compared with the spectrum of cinnamic acid, which corresponded to the cyclobutane ring in **CBDA-4** with mirror symmetry (Fig. 3). The ^{1}H NMR of **CBDA-1** is also included in Fig. 3 for comparison. The two doublet-of-doublets peaks around 4.30 and 3.83 ppm are consistent with the center symmetry of **CBDA-1**.[12,13b,c]

Plate-shaped single crystals of **CBDA-4** were obtained in acetonitrile solution containing a tiny amount of acetic acid at room temperature. The X-ray single crystal structure of **CBDA-4** was reported for the first time (Fig. 4). The crystal structure revealed the orientation of the adjacent 1,2-dicarboxylic groups on the cyclobutane ring, showing its structural similarity to *o*-phthalic acid and its potential to serve as a diacid building block in materials.[3a,4b] The cyclobutane ring in **CBDA-4** adopts a 20° puckered conformation in the solid state, which is different from the planar cyclobutane ring of **CBDA-1** in its crystal.[3b,12,13c] The angles in the cyclobutane ring are 87.82(9), 88.21(9), 87.68(9), and 88.80(9)°, which indicate the ring strain in the structure. In addition, it was shown that a supramolecular helix self-assembles along the *b* axis *via*

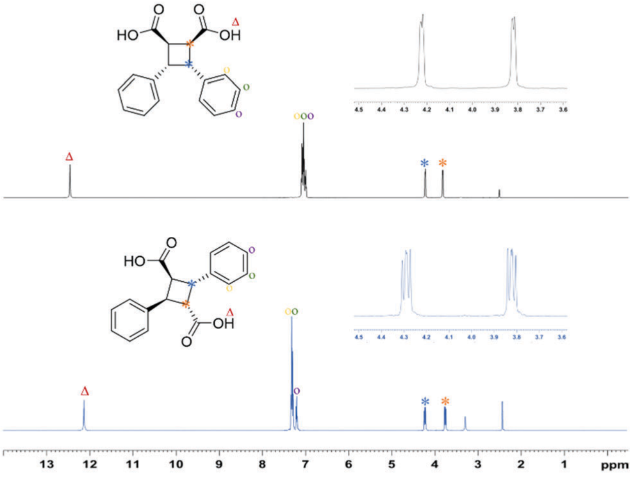


Fig. 3 Comparison of the ^{1}H NMR spectra of **CBDA-4** (top) and **CBDA-1** (bottom) collected in DMSO-d_6. Insets are magnified range from 3.6 to 4.5 ppm.

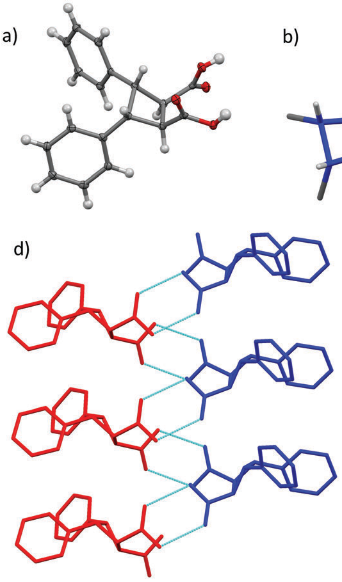


Fig. 4 X-ray structure of **CBDA-4**: (a) X-ray single crystal structure in Oak Ridge Thermal Ellipsoid Plot (ORTEP) representing at 50% electron density. (b) Cyclobutane-1,2-diacid moiety in **CBDA-4** with inner angle 87–88°. The cyclobutane ring is highlighted in blue for clarity. (c) Cyclobutane moiety adopted 20° puckered conformation. (d) Front view and side view of supramolecular helix *via* hydrogen bonds. Hydrogens are omitted in all three images. The phenyl group and half of the cyclobutane ring are omitted in the last two images for clarity.

the intermolecular hydrogen bonding between carboxylic acid groups ($O_{C=O}\cdots O_{OH}$ = 2.680(2)–2.694(2) Å, Fig. 4d), showing the potential of **CBDA-4** in preparing supramolecular materials such as hydrogen-bonded organic frameworks (HOFs)[14] and metal–organic materials (MOMs).[15]

The preparative method used readily provided us with pure **CBDA-4** to study its properties. The **CBDA-4** samples were treated with either 6 M NaOH or 6 M HCl aqueous solution at 100 °C for 12 h. After workup, ^{1}H and ^{13}C NMR spectra of the recovered samples showed no change compared to the original spectra of **CBDA-4**, which suggested the cyclobutane ring is stable under base or acid conditions. Thermogravimetric analysis (TGA) showed no obvious weight loss below 200 °C and 5% weight loss around 250 °C (Fig. S11, ESI†). The derivation exhibited the temperature of maximum weight loss for **CBDA-4** as 319 °C. In differential scanning calorimetry (DSC) analysis, no change was observed below the melting point of **CBDA-4** around 208 °C (Fig. 5). Both TGA and DSC suggested that **CBDA-4** is stable at temperature of at least 200 °C, which indicates that its thermostability is suitable for many potential applications. Despite the ring strain of the cyclobutane, **CBDA-4** is reasonably stable, presumably due to the fact that the [2+2] photocyclization and corresponding reverse reaction are generally thermally forbidden,[16] which means a high thermal energy barrier has to be overcome to break the four-membered ring once it is formed by photoreaction.

It was exciting to see a 2nd endothermic peak appear around 280 °C in the DSC curve of **CBDA-4** shown in Fig. 5. The sample was cooled down to 30 °C after heating it at 300 °C for 5 min.

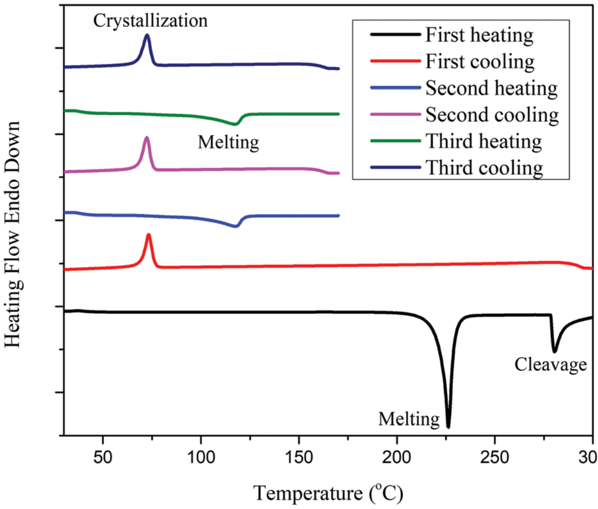


Fig. 5 DSC curve recorded with a heating rate of 20 °C min^{-1} under N_2 atmosphere.

During the subsequent 2nd and 3rd heating–cooling cycles, the sample was heated and cooled again under the same conditions from 30 °C to 170 °C. A new endothermic peak appeared repeatedly around the melting point of *trans*-cinnamic acid in the 2nd and 3rd heating–cooling cycles, showing the possibility of thermal cleavage of the **CBDA-4** at high temperature. To figure out what exactly happened to **CBDA-4** around 280 °C, a sample of **CBDA-4** was added to a test tube and heated to 300 °C under argon protection in a sand bath for 15 min. During this process, colourless crystals were formed on the test tube walls which were analyzed by NMR. In the ^{1}H NMR spectrum, it was found that the peaks around 4.22 and 3.82 ppm disappeared and two new doublet peaks showed up at 7.58 and 6.52 ppm, which indicated double bond formation. The ^{1}H NMR spectrum was identical to that of *trans*-cinnamic acid (Fig. 6). Based on this observation, it was confirmed that the photocycloaddition of *trans*-cinnamic acid to form **CBDA-4** can be reversed by thermocleavage (Scheme 2). Although it is known that cyclobutane rings can be cleaved by using deep UV,[17] there have been only a few reports on cleavage of the four-membered ring with heat,[18] and the potential application of the thermocleavage in recyclable or degradable materials has not been realized. This discovery reveals a facile and scalable way to degrade the diacid **CBDA-4** thermally at the end of its life as a polymer building block.

In summary, a simple, reliable, and scalable preparation approach for **CBDA-4** has been developed, which offers a direct and facile way to access this versatile diacid building block from a commercially-available starting material. Synthesis of different useful targets (*e.g.*, **CBDA-1** and **CBDA-4**) from the same starting materials just by changing the crystallization/precipitation conditions is challenging, but appealing due to its potential ability to be highly useful, environmentally efficient and economically plausible. The synthetic strategy and tricks that are employed in capturing and photodimerizing a metastable crystalline solid of *trans*-cinnamic acid at low temperature might be utilized for

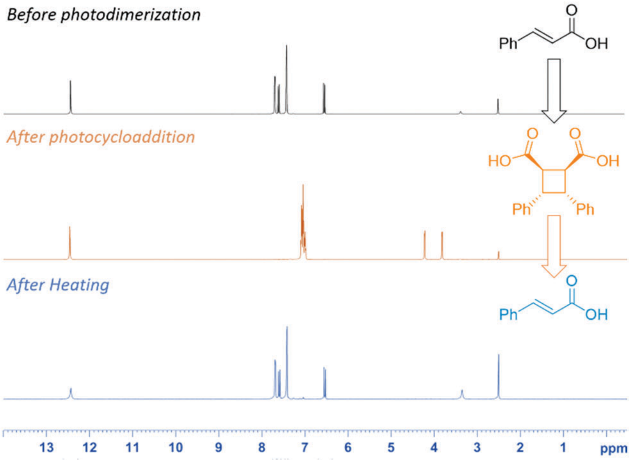
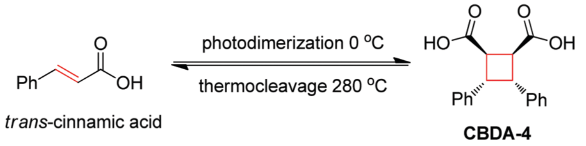


Fig. 6 ^{1}H NMR of *trans*-cinnamic acid before and after photodimerization and after heating. ^{1}H NMR was performed in DMSO-d_6.



Scheme 2 Photodimerization and thermocleavage exploration of **CBDA-4**.

producing other useful targets from starting materials with polymorphs. The single crystal structure of **CBDA-4** was reported for the first time, confirming the orientation of the two carboxylic acid groups, and the stability tests showed its potential as a diacid building block with a variety of applications. The thermal cleavage of **CBDA-4** discovered in this study might open a new gate for making thermally recyclable and/or degradable materials, such as sustainable polymers, as plastic wastes are causing severe environmental tribulations both on land and in the ocean.[19]

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Conflicts of interest

There are no conflicts to declare.

Notes and references

1 (*a*) B. Cornils and P. Lappe, *Dicarboxylic Acids, Aliphatic, Ullmann's encyclopedia of industrial chemistry*, Wiley-VCH, Weinheim, 2014; (*b*) U. Edlund and A. C. Albertsson, *Adv. Drug Delivery Rev.*, 2003, **55**, 585–609; (*c*) N. Stock and S. Biswas, *Chem. Rev.*, 2012, **112**, 933–969; (*d*) C. S. Kovash, E. Pavlacky, S. Selvakumar, M. P. Sibi and D. C. Webster, *ChemSusChem*, 2014, **7**, 2289–2294.

2 (*a*) G.-L. Ma, J. Xiong, G.-X. Yang, L.-L. Pan, C.-L. Hu, W. Wang, H. Fan, Q.-H. Zhao, H.-Y. Zhang and J.-F. Hu, *J. Nat. Prod.*, 2016, **79**, 1354–1364; (*b*) A. Sokolova, A. Pavlova, N. Komarova, O. Ardashov, A. Shernyukov, Y. Gatilov, O. Yarovaya, T. y. Tolstikova and N. Salakhutdinov, *Med. Chem. Res.*, 2016, **25**, 1608–1615; (*c*) J. Zhao, S. Gou and F. Liu, *Chem. – Eur. J.*, 2014, **20**, 15216–15225.

3 (*a*) Z. D. Wang, Q. Elliott, Z. Wang, R. A. Setien, J. Puttkammer, A. Ugrinov, J. Lee, D. C. Webster and Q. R. Chu, *ACS Sustainable Chem. Eng.*, 2018, **6**, 8136–8141; (*b*) Z. Wang, B. Miller, M. Mabin, R. Shahni, Z. D. Wang, A. Ugrinov and Q. R. Chu, *Sci. Rep.*, 2017, **7**, 13704.

4 (*a*) P. M. Lorz, F. K. Towae, W. Enke, R. Jäckh, N. Bhargava and W. Hillesheim, *Ullmann's encyclopedia of industrial chemistry*, Wiley-VCH Verlag GmbH & Co. KGaA, 2007; (*b*) V. V. Zhurov and A. A. Pinkerton, *Cryst. Growth Des.*, 2014, **14**, 5685–5691.

5 (*a*) Y.-M. Chi, M. Nakamura, X.-Y. Zhao, T. Yoshizawa, W.-M. Yan, F. Hashimoto, J. Kinjo, T. Nohara and S. Sakurada, *Biol. Pharm. Bull.*, 2006, **29**, 580–584; (*b*) A. Matta, P. Chammingkwan, B. K. Singh, M. Terano, T. Kaneko and T. Taniike, *Appl. Catal., A*, 2018, **554**, 80–87.

6 A. Matta, P. Chammingkwan, B. K. Singh, M. Terano, T. Kaneko and T. Taniike, *Appl. Catal., A*, 2018, **554**, 80–87.

7 (*a*) N. Tadatomi, T. Eiji, M. Takatoshi and I. Takashi, *Bull. Chem. Soc. Jpn.*, 1985, **58**, 3399–3400; (*b*) M. Freedman, Y. Mohadger, J. Rennert, S. Soloway and I. Waltcher, *Org. Prep. Proced. Int.*, 1969, **1**, 267–269.

8 (*a*) S. K. Pagire, A. Hossain, L. Traub, S. Kerres and O. Reiser, *Chem. Commun.*, 2017, **53**, 12072–12075; (*b*) T. Lei, C. Zhou, M. Y. Huang, L. M. Zhao, B. Yang, C. Ye, H. Xiao, Q. Y. Meng, V. Ramamurthy, C. H. Tung and L. Z. Wu, *Angew. Chem., Int. Ed.*, 2017, **56**, 15407–15410.

9 (*a*) I. Fonseca, S. E. Hayes, B. Blumich and M. Bertmer, *Phys. Chem. Chem. Phys.*, 2008, **10**, 5898–5907; (*b*) I. Abdelmoty, V. Buchholz, L. Di, C. Guo, K. Kowitz, V. Enkelmann, G. Wegner and B. M. Foxman, *Cryst. Growth Des.*, 2005, **5**, 2210–2217; (*c*) M. D. Cohen, G. M. J. Schmidt and F. I. Sonntag, *J. Chem. Soc.*, 1964, 2000–2013; (*d*) G. M. J. Schmidt, *J. Chem. Soc.*, 1964, 2014–2021.

10 H. I. Bernstein and W. C. Quimby, *J. Am. Chem. Soc.*, 1943, **65**, 1845–1846.

11 ECO-UV is an abbreviation for energy-efficient, cost-effective, and operator-friendly UV.

12 K. Randazzo, Z. Wang, Z. D. Wang, J. Butz and Q. R. Chu, *ACS Sustainable Chem. Eng.*, 2016, **4**, 5053–5059.

13 (*a*) S. d'Agostino, E. Boanini, D. Braga and F. Grepioni, *Cryst. Growth Des.*, 2018, **18**, 2510–2517; (*b*) S. d'Agostino, F. Spinelli, E. Boanini, D. Braga and F. Grepioni, *Chem. Commun.*, 2016, **52**, 1899–1902; (*c*) Z. Wang, K. Randazzo, X. Hou, J. Simpson, J. Struppe, A. Ugrinov, B. Kastern, E. Wysocki and Q. R. Chu, *Macromolecules*, 2015, **48**, 2894–2900; (*d*) Z. Wang, B. Miller, J. Butz, K. Randazzo, Z. D. Wang and Q. R. Chu, *Angew. Chem., Int. Ed.*, 2017, **56**, 12155–12159; (*e*) Z. Wang, B. Kastern, K. Randazzo, A. Ugrinov, J. Butz, D. W. Seals, M. P. Sibi and Q. R. Chu, *Green Chem.*, 2015, **17**, 4720–4724.

14 (*a*) J. D. Wuest, *Chem. Commun.*, 2005, 5830–5837; (*b*) A. I. Cooper, *Angew. Chem., Int. Ed.*, 2012, **51**, 7892–7894; (*c*) X. Hou, Z. Wang, M. Overby, A. Ugrinov, C. Oian, R. Singh and Q. R. Chu, *Chem. Commun.*, 2014, **50**, 5209–5211.

15 (*a*) S. R. Batten, *Coordination Polymers: Design, Analysis and Application*, RSC Publishing, 2008; (*b*) A. Schoedel, M. Li, D. Li, M. O'Keeffe and O. M. Yaghi, *Chem. Rev.*, 2016, **116**, 12466–12535; (*c*) Q. Chu, A. J. E. Duncan, G. S. Papaefstathiou, T. D. Hamilton, M. B. J. Atkinson, S. V. S. Mariappan and L. R. MacGillivray, *J. Am. Chem. Soc.*, 2018, **140**, 4940–4944; (*d*) I. E. Claassens, V. I. Nikolayenko, D. A. Haynes and L. J. Barbour, *Angew. Chem., Int. Ed.*, 2018, **57**, 15563–15566.

16 R. Hoffmann and R. B. Woodward, *Science*, 1970, **167**, 825–831.

17 (*a*) D. Tunc, C. Le Coz, M. Alexandre, P. Desbois, P. Lecomte and S. Carlotti, *Macromolecules*, 2014, **47**, 8247–8254; (*b*) A. Lendlein, H. Jiang, O. Jünger and R. Langer, *Nature*, 2005, **434**, 879; (*c*) C.-M. Chung, Y.-S. Roh, S.-Y. Cho and J.-G. Kim, *Chem. Mater.*, 2004, **16**, 3982–3984.

18 (*a*) I.-H. Park, A. Chanthapally, Z. Zhang, S. S. Lee, M. J. Zaworotko and J. J. Vittal, *Angew. Chem., Int. Ed.*, 2014, **53**, 414–419; (*b*) C. Anjana, K. G. Kumar, Q. Kang, T. G. Kheng, G. Song and J. J. Vittal, *Chem. – Eur. J.*, 2012, **18**, 7869–7877; (*c*) J. W. Chung, Y. You, H. S. Huh, B.-K. An, S.-J. Yoon, S. H. Kim, S. W. Lee and S. Y. Park, *J. Am. Chem. Soc.*, 2009, **131**, 8163–8172; (*d*) N. Kathleen, E. Volker, W. Gerhard and K. B. Wagener, *Angew. Chem., Int. Ed.*, 1993, **32**, 1614–1616.

19 (*a*) S. Lemonick, *Chem. Eng. News*, 2018, **96**, 24–25; (*b*) J.-B. Zhu, E. M. Watson, J. Tang and E. Y.-X. Chen, *Science*, 2018, **360**, 398–403; (*c*) C. Isola, H. L. Sieverding, R. Raghunathan, M. P. Sibi, D. C. Webster, J. Sivaguru and J. J. Stone, *J. Cleaner Prod.*, 2017, **142**(4), 2935–2944.