This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this *Accepted Manuscript* with the edited and formatted *Advance Article* as soon as it is available.

You can find more information about *Accepted Manuscripts* in the **Information for Authors**.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard **Terms & Conditions** and the **Ethical guidelines** still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.

ChemComm

Dynamic Article Links ▶

COMMUNICATION

Dynamic covalent assembly of tribenzotriquinacences into molecular cubes†

Stefanie Klotzbach[a]**, Thorsten Scherpf and Florian Beuerle***[a]

Molecular cubes constructed from catechol-functionalized tribenzotriquinacenes and 1,4-phenylene diboronic acids were synthesized in a one-pot procedure by crosslinking of 20 individual components through a dynamic covalent approach.
10 **Structural identity of the nanocubes was confirmed by mass spectrometry and ^{1}H-NMR spectroscopy.**

The formation of monodisperse molecular structures with ever increasing complexity is an ongoing desire in synthetic chemistry. Molecular cage compounds are intriguing examples
15 for suchlike systems with dimensions in the nanometer regime. Over the last decades, hybrid systems assembled via metal coordination of appropriate organic linker molecules have been presented in large variety.[1] However, reports on solely organic cages are far more limited in numbers since tedious multiple step
20 synthesis hamper the efficient formation of highly complex systems. To circumvent these drawbacks, the concept of *dynamic covalent chemistry*[2] offers the possibility of performing multiple reaction steps under reversible conditions giving easy access to complex structures under thermodynamic control. The most
25 prominent reactions in this regard are the formation of imines[3] and boronate esters[4] from aldehydes and amines or boronic acids and 1,2-diols, respectively. Based on this approach, numerous examples of organic cage compounds have been presented in the literature in recent years.[5] Potential applications can be found in
30 the fields of host-guest chemistry[6] or porous materials[7] with reported BET surface areas of up to 3758 m^2g^{-1} for organic cages in the solid state.[8] However, it is still challenging to obtain permanent porous materials and only a few examples of processing cage molecules into devices such as quartz
35 microbalances[9] or macroscopic inorganic porous beads[10] have been reported. Since it was shown theoretically that any equilibrium states of dynamic molecular assemblies possess preferentially the highest possible symmetry,[11] formation of Archimedean or Platonic solids should be preferred and as a
40 matter of fact, solely organic representatives of tetrahedron,[12] cube,[13] octahedron[14] or cuboctahedron[8,15] were synthesized in the last decade. The factual shape of the cage is thereby encoded in the molecular symmetry of the implemented subunits. For instance, co-assembly of tritopic and ditopic building blocks in a
45 2:3 ratio is expected to yield either cuboctahedra (planar tritopic and ditopic molecules with tetrahedral angles) or cubes for trigonal corner units and linear ditopic struts. In contrast to the rich chemistry of octahedral metal complexes resulting in

numerous examples for metal-organic systems,[16] the chiral cubes
50 synthesized by Xu and Warmuth[13] from aldehyde-functionalized cyclotriveratrylenes and linear diamines are the only reported case for cubic organic cage compounds so far. The actual absence of further examples is most likely due to the lack of suitable organic building blocks featuring the required rectangular
55 arrangement of three functional units. One rare example for such a molecular framework is the tribenzotriquinacene (TBTQ) scaffold possessing three condensed indane moieties. After being introduced by Kuck,[17] functionalized TBTQ derivatives have been recently implemented into fullerene receptors,[18] micro-
60 porous polymers[19] or mimics for odd-membered ring-defects in graphenes.[20] However, despite the favourable rigid arrangement of up to three functional sites, there is only one reported example of a TBTQ-based cage compound[21] and surprisingly, no attempts have yet been made to incorporate such derivatives as corner
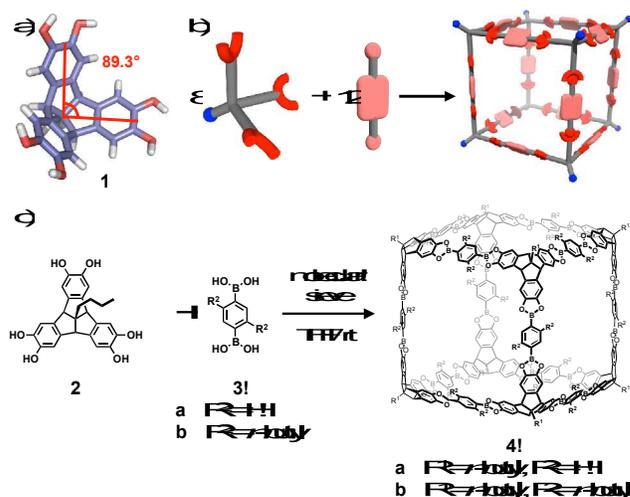65 units into covalent organic cages with cubic symmetry.

Fig. 1 a) PM6-minimized[22] model of **1** as a tritopic building block with an orthogonal arrangement of the peripheral catechol units; b) Formation of molecular cubes after reaction of eight tritopic corner units and twelve
70 ditopic linear spacer units under dynamic covalent conditions; c) Synthesis of molecular cubes **4** from TBTQ derivative **2** and diboronic acids **3** in THF under water removing conditions.

Herein, we report on the synthesis of novel metal-free molecular cubes utilizing the formation of 24 boronate esters by
75 crosslinking of catechol-functionalized tribenzotriquinacenes and 1,4-phenylene diboronic acids in a one-pot reaction.

Hexahydroxy TBTQ **1** has been recently used as a precursor for microporous polymers[19] and based on the PM6-minimized[22] model in Fig. 1, an angle of 89.3° could be calculated between two catechol units each indicating an almost rectangular orientation of the three indane moieties with respect to each other. As a matter of fact, this spatial arrangement of its functional groups identifies **1** as a well-suited precursor for the formation of molecular cubes via boronate ester formation with linear boronic acids. We therefore investigated the reaction of **1** with 1,4-phenylene diboronic acid **3a** in a 2:3 molecular ratio in various solvents and under different reaction conditions. However, in all cases either no reaction occured or rapid precipitation of presumably oligomeric side products was observed probably due to low solubility of either the starting materials or the formed reaction intermediates.

Most promising results were obtained in THF solution at room temperature, indicating an equilibrium of unreacted **1** and one- to threefold boronate esters as detected by monitoring the reaction progress with ^{1}H-NMR spectroscopy. Addition of 4Å molecular sieve shifted the equilibrium significantly towards higher condensation products, yet, primarily resulted in precipitation of an insoluble material, which could not be further characterized. Since it was assumed that successful cage formation was mainly prevented due to solubility issues of the small-size reaction intermediates, we modified the apical position of the TBTQ moiety by introducing a butyl chain in **2** (see ESI† for synthetic procedures and characterization details) in order to enhance the solubility of both the starting material and oligomeric condensation products. Analogous to **1**, reaction of **2** and **3a** in a 2:3 molecular ratio in THF at room temperature resulted in an equilibrium of unreacted **2** and mono- to trisboronate esters as monitored by ^{1}H-NMR spectroscopy for the TBTQ methine protons (see Fig. S11 ESI†).
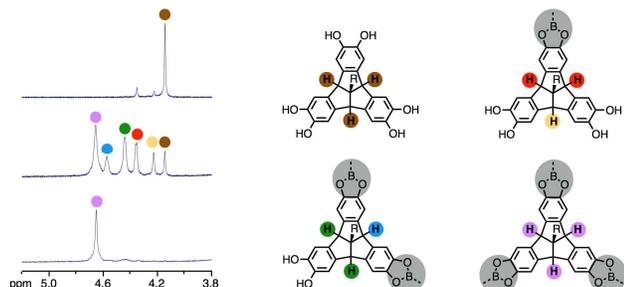

Fig. 2 ^{1}H-NMR monitoring (THF-d8, 400 MHz, rt) of methine protons for reaction of **2** and **3b** in a 2:3 molecular ratio (top: start of reaction, middle: after one day, bottom: after five days). .

Equilibrium state is reached after several minutes and no further changes were observed even over the course of several days. However, addition of 4Å molecular sieve led to precipitation of a microcrystalline material (see Fig. S12 ESI†) after several hours and MALDI TOF-MS of the reaction mixture (see Fig. S13 ESI†) showed one peak at m/z = 4584 as the dominant signal which correlates exactly to the molecular mass of the desired organic cube **4a** (see Fig 1c). After filtration, the measured elemental analysis of the precipitate is in good agreement to a calculated one for **4a** assuming the isolation of cube **4a** in 53% yield. Unfortunately, the obtained crystals were either to small or tended to grow in bigger agglomerates so that we were not able to

determine the structure by X-ray diffraction. Since the obtained solid material was virtually insoluble in most organic solvents, with the exception of methanol where cleavage of the boronic esters occurred and starting materials **2** and **3a** were recovered in a 2:3 ratio (see Fig. S15 ESI†), all attempts to recrystallize the reaction product also failed. However, MALDI TOF-MS under solvent-free conditions of the precipitate showed the molecular ion peak of **4a** at m/z = 4584.49 as the only signal (see Fig. 3b).
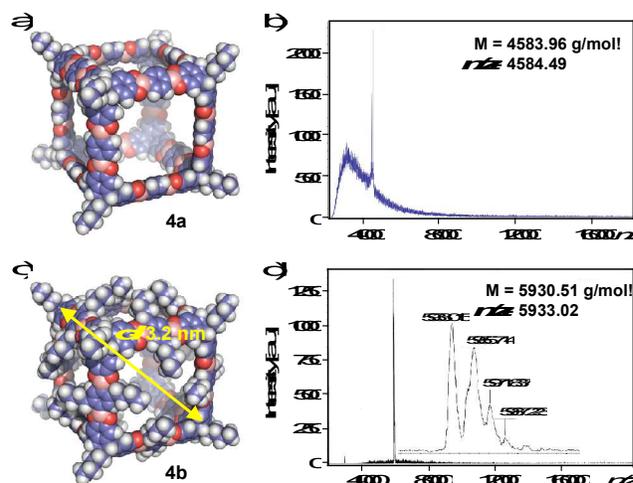

Fig. 3 a) PM6-minimized[19] model of molecular cube **4a** with non-functionalized spacer units **3a**; MALDI-TOF MS (TCNQ, solvent free, molecular ratio **4a**:**matrix** 1:500) of **4a** in the solid state; c) PM6-mini-mized[20] model of molecular cube **4b** with spacer units **3b** containing butyl chains as solubilizing groups; d) MALDI-TOF MS (DCTB, CHCl3) of **4b**.

In order to enhance the solubility of the molecular cages and to definitely prove the structural assignment as cubes with O_h symmetry, we synthesized phenylene diboronic acid **3b** with two butyl chains as additional solubilizing groups (see ESI† for synthetic procedures and characterization details). Again, mixing of **2** and **3b** in a 2:3 ratio in THF-d8 resulted in an equilibrium of several reaction intermediates, whereas subsequent addition of 4Å molecular sieve led to quantitative conversion to a highly symmetrical product after five days as indicated by NMR analysis (see Fig. 2 and Fig. S18 ESI†). The reaction product could be precipitated with hexane and redissolved in CHCl3, a solvent in which both precursors are completely insoluble. Subsequent filtration, removal of the solvent and drying in high vacuum gave cube **4b** in 94% yield. Fig. 3d shows the MALDI TOF mass spectrum of a CHCl3 solution revealing the formation of cube **4b** as the only detectable species. As depicted in Fig. 4, ^{1}H NMR spectroscopy shows only one set of signals for the individual protons indicating the high symmetry of the structure. Therefore, the successful formation of O_h symmetrical molecular cubes **4b** is the only plausible conclusion in accordance with both MS and ^{1}H-NMR results. DOSY NMR spectroscopy of **4b** showed all relevant signals with the same diffusion coefficient (see Fig. S20 ESI†) and from that we could calculate a diameter for the cage of 3.3 nm via the Stokes-Einstein equation. This finding is in good agreement with an PM6-optimized model[22] of **4b** exhibiting a diagonal corner-to-corner distance of 3.2 nm (see Fig. 3c). Altogether, these analytical findings are proofing evidence for the efficient formation of molecular cubes **4b**.
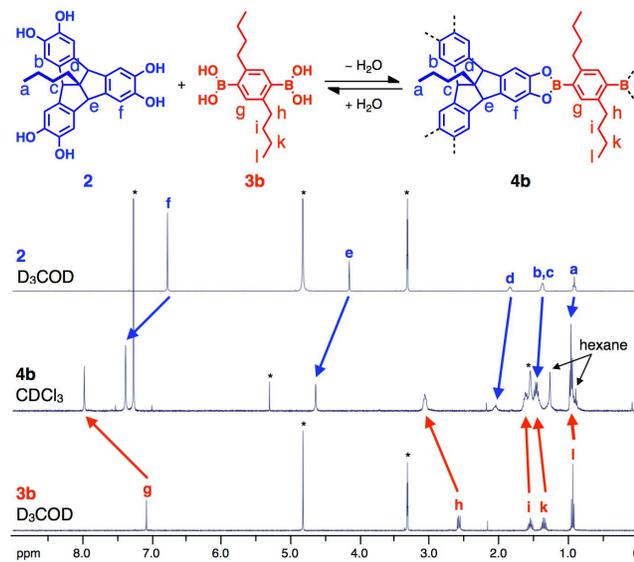
Fig. 4 ^{1}H-NMR spectra (400 MHz, rt) of tritopic building block **2** (D$_3$COD, top), linear linker **3b** (D$_3$COD, bottom) and molecular cube **4b** (CDCl$_3$, middle); * indicates residual solvent peaks.

Due to the microcrystallinity of **4a**, we investigated the potential porosity of the solid material. After redissolving the precipitate in MeOH, 0.9 equivalents of THF remained in the product (see Fig. S22 ESI†) even after drying for 24 hours at 50 °C in high vacuum. Thermogravimetric analysis of the dried solid revealed a weight loss of 11.5% between 100–200 °C (see Fig. S21 ESI†). This result was attributed to the removal of eight THF molecules per molecular cube **4a** being in very good agreement with the amount of encapsulated THF determined by ^{1}H-NMR. However, gas sorption measurements after washing the precipitate with dry THF and drying under high vaccum at 100 °C for 20 hours showed no significant porosity of the material. This findings indicate either kinetic hindrance of gas absorption or a structural collapse of the cubes after desolvation, a fact which is often observed for organic cage molecules.[7c] In ongoing work, we will adress these issues and look for alternative activation protocols in order to preserve porosity of suchlike materials and gain more insight into the inner surfaces of the cubes.

In conclusion, we were able to synthesize molecular cubes **4a** and **4b** through the concerted formation of 24 boronate esters in a [8+12] cocondensation of twenty small molecule precursors in a dynamic covalent approach. These cage compounds are the first examples for purely organic cubes with the highest possible cubic symmetry O_h. Due to the easy and modifiable synthesis of TBTQ precursors **2** and linear diboronic acids **3**, this strategy will give access to a whole new family of structurally related cubic organic cage molecules and starting from lower symmetry analogues of the corner units also cuboid cages can be envisaged. Currently, we are working on the synthesis and characterization of modified cubes and cuboids in order to test the scope and potential of this synthetic approach for dynamic covalent cube formation.

Notes and references

^{a} Universität Würzburg, Institut für Organische Chemie & Center for Nanosystems Chemistry (CNC), Am Hubland, 97074 Würzburg, Germany. Fax: +49 931 3187348; Tel: +49 931 3183603; E-mail: florian.beuerle@uni-wuerzburg.de

† Electronic Supplementary Information (ESI) available: Experimental procedures and spectral data for all new compounds, TGA for cube **4a**, DOSY NMR for cube **4b**. See DOI: 10.1039/b000000x/

1   T. Mitra, K. E. Jelfs, M. Schmidtmann, A. Ahmed, S. Y. Chong, D. J. Adams and A. I. Cooper, *Nat. Chem.*, 2013, **5**, 276–281.
2   M. Mastalerz, *Chem. Eur. J.*, 2012, **18**, 10082–10091.
3   (*a*) R. Chakrabarty, P. S. Mukherjee and P. J. Stang, *Chem. Rev.*, 2011, **111**, 6810–6918; (*b*) M. M. J. Smulders, I. A. Riddell, C. Browne and J. R. Nitschke, *Chem. Soc. Rev.*, 2013, **42**, 1728–1754.
4   (*a*) S. J. Rowan, S. J. Cantrill, G. R. L. Cousins, J. K. M. Sanders and J. F. Stoddart, *Angew. Chem. Int. Ed.*, 2002, **41**, 898–952; (*b*) Y. Jin, C. Yu, R. J. Denman and W. Zhang, *Chem. Soc. Rev.*, 2013, **42**, 6634–6654.
5   (*a*) C. D. Meyer, C. S. Joiner and J. F. Stoddart, *Chem. Soc. Rev.*, 2007, **36**, 1705–1723; (*b*) M. E. Belowich and J. F. Stoddart, *Chem. Soc. Rev.*, 2012, **41**, 2003–2024.
6   K. Severin, *Dalton Trans.*, 2009, 5254–5264.
7   (*a*) M. Mastalerz, *Angew. Chem. Int. Ed.*, 2010, **49**, 5042–5053; (*b*) N. M. Rue, J. Sun and R. Warmuth, *Isr. J. Chem.*, 2011, **51**, 743–768; (*c*) G. Zhang and M. Mastalerz, *Chem. Soc. Rev.*, 2014, DOI: 10.1039/c3cs60358j.
8   G. Zhang, O. Presly, F. White, I. M. Oppel and M. Mastalerz, *Angew. Chem. Int. Ed.*, 2014, **126**, 1516–1520.
9   M. Brutschy, M. W. Schneider, M. Mastalerz, S. R. Waldvogel, *Adv. Mater.,* 2012, **24**, 6049–6052.
10   T. Hasell, H. Zhang, A. I. Cooper, *Adv. Mater.*, 2012, **24**, 5732–5737.
11   S.-K. Lin, *J. Chem. Inf. Comput. Sci.*, 1996, **36**, 367–376.
12   For selected recent examples, see reviews in ref. 7 and: (*a*) T. Tozawa, J. T. A. Jones, S. Swamy, S. Jiang, D. J. Adams, S. Shakespeare, R. Clowes, D. Bradshaw, T. Hasell, S. Y. Chong, C. Tang, S. Thompson, J. Parker, A. Trewin, J. Bacsa, A. Slawin, A. Steiner and A. I. Cooper, *Nat. Mater.*, 2009, **8**, 973–978; (*b*) M. Mastalerz, M. W. Schneider, I. M. Oppel and O. Presly, *Angew. Chem. Int. Ed.*, 2011, **50**, 1046–1051.
13   D. Xu and R. Warmuth, *J. Am. Chem. Soc.*, 2008, **130**, 7520–7521.
14   X. Liu, Y. Liu, G. Li and R. Warmuth, *Angew. Chem. Int. Ed.*, 2006, **45**, 901–904.
15   P. Skowronek, B. Warzajtis, U. Rychlewska and J. Gawroński, *Chem. Commun.*, 2013, **49**, 2524–2526.
16   For example: W. Meng, B. Breiner, K. Rissanen, J. D. Thoburn, J. K. Clegg and J. R. Nitschke, *Angew. Chem. Int. Ed.*, 2011, **50**, 3479–3483.
17   D. Kuck, *Angew. Chem. Int. Ed.*, 1984, **23**, 508−509.
18   (*a*) S. Henne, B. Bredenkötter, A. A. Dehghan Baghi, R. Schmid and D. Volkmer, *Dalton Trans.*, 2012, **41**, 5995; (b) T. Wang, Z. Y. Li, A. L. Xie, X. J. Yao, X. P. Cao and D. Kuck, *J. Org. Chem.*, 2011, **76**, 3231−3238.
19   J. Vile, M. Carta, C. G. Bezzu and N. B. McKeown, *Polym. Chem.*, 2011, **2**, 2257–2260.
20   (*a*) E. U. Mughai and D. Kuck, *Chem. Commun.*, 2012, **48**, 8880–8882; (b) Y. Kirchwehm, A. Damme, T. Kupfer, H. Braunschweig and A. Krueger, *Chem. Commun.*, 2012, **48**, 1502–1504.
21   T. Wang, Y.-F. Zhang, Q.-Q. Hou, W.-R. Xu, X.-P. Cao, H.-F. Chow and D. Kuck, *J. Org. Chem.*, 2013, **78**, 1062–1069.
22   **Spartan'14**, Wavefunction, Inc., Irvine, CA, USA.