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Synthesis of quadruped-shaped polyfunctionalized *o*-carborane synthons†

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***o*-Carborane derivatives with precisely defined patterns of substitution have been prepared from 8,9,10,12-I_4-1,2-*closo*-$C_2B_{10}H_8$ by replacing the iodine atoms, bonded to four adjacent boron vertices in the cluster, with allyl, and subsequently 3-hydroxypropyl groups. The resulting structures, comprising four pendant arms and two reactive vertices located on opposite sides of a central *o*-carborane core, can be envisaged as versatile precursors for dendritic growth.**

Carboranes are molecules with unique structural features due to their rigid geometry and rich derivative chemistry, which make them of great interest as building blocks for macromolecular or supramolecular entities.[1] Of particular interest is the generation of dendrimers of high boron content, given their potential use in boron neutron capture therapy (BNCT).[2] This has been usually achieved by tethering boron cluster units to the periphery of dendritic compounds or precursors.[3] In addition, globular dendrimers with twelve identical branches appending from a central icosahedral *closo*-borane cluster (closomers) have been produced.[4] Nevertheless, much less attention has been paid to carboranes as cores or focal points for dendrimer growth, despite their possibilities for multiple and versatile functionalisation. In this regard, we have recently reported the synthesis of dendrons where *o*-carborane cluster carbon atoms are located at the focal points.[5] Subsequently, we became interested in exploring similar molecular construction from the boron vertices of the cluster.

Derivatization reactions on the *o*-carborane cluster (1,2-*closo*-$C_2B_{10}H_{12}$, **1**) can be executed on either carbon or boron vertices.[6] In most of the occasions these transformations are carried out through the carbon atoms, whereas the chemistry of boron-substituted *o*-carboranes is relatively underdeveloped. This is somewhat surprising, because B–H vertices in *o*-carboranes exhibit electrophilic substitution chemistry in many ways reminiscent of arenes.[7] Furthermore, boron vertices react at different rates depending on their position in the cluster,[8] which may enable an accurate control of the degree and regioselectivity of substitution, while maintaining the integrity of the underlying geometry.

A useful and general method for the functionalization of *o*-carboranes through their boron atoms is electrophilic iodination followed by Kumada cross-coupling reaction that allows the introduction of organic moieties. This has led to mono- and disubstituted compounds, starting from 9-I-1,2-*closo*-$C_2B_{10}H_{11}$, 9,12-I_2-1,2-*closo*-$C_2B_{10}H_{10}$, 3-I-1,2-*closo*-$C_2B_{10}H_{11}$ or 3,6-I_2-1,2-*closo*-$C_2B_{10}H_{10}$,[9] but, as we are aware, never to a higher degree of substitution. Recently, we reported on the regioselective synthesis of 8,9,10,12-I_4-1,2-*closo*-$C_2B_{10}H_8$ (**2**),[10] where the four B–I vertices reside at the compacted adjacent positions antipodal to the two carbon atoms. By substitution of iodine with the appropriate organic groups, the *o*-carborane cluster can be envisaged as a robust dendritic core for multiple and diverse types of ramifications, as illustrated in Fig. 1. Four arms may be densely appended to the cluster through four boron vertices located at a compact area of the cluster, whilst the two C–H vertices occupying the two positions furthest away from them remain ready for further functionalization or complexation. These prospects prompted us to study the reactivity of **2** in order to create polyfunctionalized quadruped-shaped synthons. Here, we report on the synthesis of such structures, which may offer a unique platform for the construction of large molecules with full control over the position of the substituents.

In the present study, the boron tetraiodinated *o*-carborane (**2**) has been chosen as the platform to prepare multiple regioselective derivatives with different patterns of substitution (Scheme 1). It was our main target to elucidate if the four highly crowded iodine atoms in a compact region of the boron cluster could be replaced. To achieve so, the cross-coupling reaction on **2** with Grignard reagents in the presence of Pd(II)

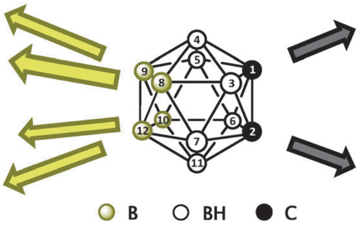

Fig. 1 Vertex numbering in *o*-carborane and schematic representation of its functionalization on boron (four-fold) and carbon (two-fold) resulting in quadruped-shaped clusters. The arrows represent possible directions for dendritic growth.

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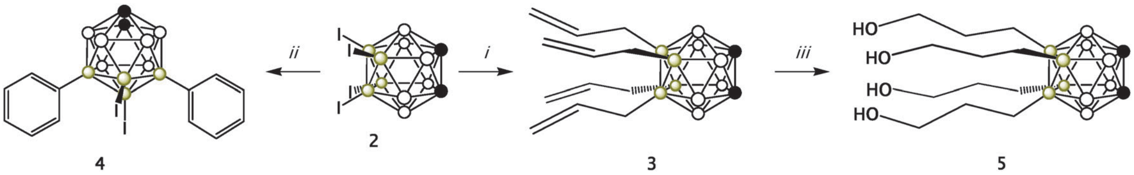
† Electronic supplementary information (ESI) available: Synthesis and characterization of **3–5** and crystallographic data of **4** and **5**. See DOI: 10.1039/c0cc05151a



Scheme 1 Derivatization reactions on **2**. i and ii: RMgCl, *cis*-[Pd(PPh$_3$)$_2$Cl$_2$] (cat.), CuI (cat.), THF, reflux (R = CH$_2$=CHCH$_2$ and C$_6$H$_5$ for i and ii, respectively); iii: (1) BH$_3$·THF, (2) H$_2$O$_2$, NaOH (aq.).

and Cu(I) catalysts was studied. Two types of Grignard reagents were used, phenylmagnesium and allylmagnesium chlorides. The first would produce a highly congested region in the *o*-carborane whereas the second would produce a more relaxed space and, in addition it could provide "free" ends for further reactions. Reaction of **2** with allylmagnesium chloride proceeded completely after several hours to give 8,9,10,12-$(CH_2{=}CHCH_2)_4$-1,2-*closo*-$C_2B_{10}H_8$ (**3**) as a colourless oil in high yields (see Scheme 1). The four-fold allylation of the *o*-carborane cluster in **3** was confirmed by multinuclear NMR and FT-IR spectroscopic techniques, mass spectrometry and elemental analysis. In contrast, when **2** was reacted with phenylmagnesium chloride, two iodine atoms were readily exchanged, but the coupling of a third phenyl ring into the cage was extremely slow, as observed by ^{11}B NMR monitoring. The resulting diiodo-diphenyl- mixed substituted *o*-carborane could be isolated and characterized by spectroscopy, although the positions of the iodine and phenyl substituents remained unclear. Crystals suitable for X-ray diffraction were grown from a chloroform/acetone solution.[11] Solution and refinement of the crystal structure unambiguously proved that the compound obtained was 8,10-Ph_2-9,12-I_2-1,2-*closo*-$C_2B_{10}H_8$ (**4**) (Fig. 2). The reason for the substitution being restricted to B(8,10) could be a steric one, since these B–I vertices are the furthest removed from each other in **2**, whereas the iodine atoms at B(9,12) lie at crowded positions. A similar observation was reported for the B-arylation of the [1-Ph-6,7,8,9,10-I_5-*closo*-1-CB_9H_4]$^-$ anion.[12] An interesting packing is observed in the crystal lattice of **4**, driven by $C_{cluster}$–H···π interactions, established between the $C_{cluster}$–H vertices and the centres of the phenyl ring planes (Fig. 3). Directed by such interactions, the molecules of **4** pack into infinite layers parallel to the crystallographic *ab* plane.

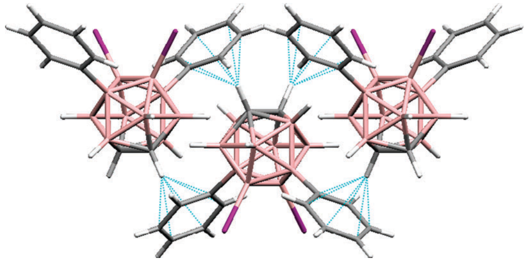


Fig. 3 A perspective of the molecular assembly through periodical $C_{cluster}$–H···π interactions in the crystal structure of **4**. White = H, pink = B, grey = C, purple = I. Contacts shorter than the sum of Van der Waals radii minus 0.1 Å are depicted as dashed blue lines.

Thus, the crystal structure of **4** clearly reflects the ability of $C_{cluster}$–H vertices in *o*-carboranes to participate in hydrogen bonding with aromatic π systems. As previously reported, these $C_{cluster}$–H···π interactions may serve as useful vectors in crystal engineering and supramolecular recognition.[1c,d,g,13] The terminal olefinic groups in **3** are free to perform further reactions on them. As a first approach to the development of these molecules, a hydroboration/oxidation reaction has been carried out to transform the four terminal double bonds to hydroxyl groups. BH$_3$·THF was used as the hydroborating agent. Subsequent oxidation was performed by treatment with H$_2$O$_2$ in a basic aqueous solution. After work up, a crystalline solid was obtained. Its spectroscopic characterisation revealed that the reaction had proceeded through specific anti-Markovnikov additions, yielding pure 8,9,10,12-$(HOCH_2CH_2CH_2)_4$-1,2-*closo*-$C_2B_{10}H_8$ (**5**), *i.e.* with all four hydroxyl groups at terminal positions (see Scheme 1).

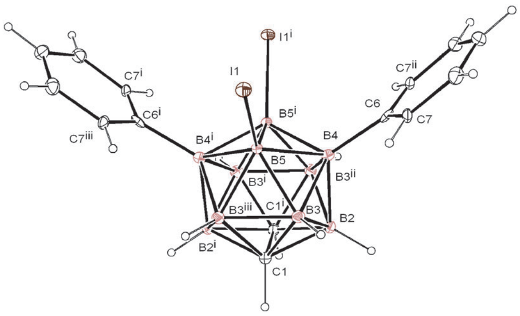


Fig. 2 Ortep drawing of **4** having crystallographic *mm* symmetry. Thermal displacement parameters are drawn at 30% level. Selected bond distances: C(1)–C(1^i) = 1.640(14), I(1)–B(5) = 2.177(8), B(4)–C(6) = 1.667(11) Å. Symmetry operations: i = $\frac{1}{2} - x, \frac{1}{2} - y, z$; ii = $\frac{1}{2} - y, \frac{1}{2} - x, z$; iii = y, x, z.

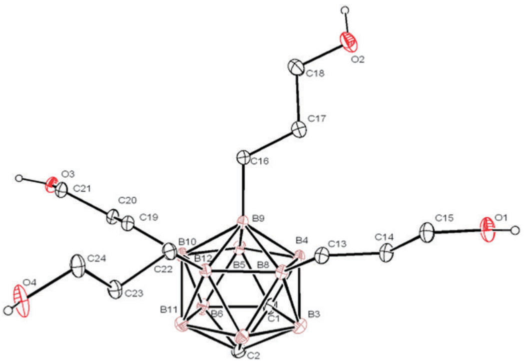


Fig. 4 Ortep drawing of **5**. Thermal displacement parameters are drawn at 30% level. Hydrogen atoms, except the hydroxyl hydrogens are omitted. Selected bond distances: C(1)–C(2) = 1.632(4), C(13)–B(8) = 1.593(4), C(16)–B(9) = 1.588(4),C(19)–B(10) = 1.584(4) and C(22)–B(12) = 1.591(4) Å.

No hindered hydroboranes were thus needed for the control of the regioselectivity. In addition, the crystal structure of **5** was determined by X-ray diffraction from samples grown by slow evaporation from an ethanol/water solution (Fig. 4).[14] A three-dimensional hydrogen bonded network involving all O–H and $C_{cluster}$–H units dominates the crystal lattice. In addition, the quadruped-like molecular structure displayed by **5** illustrates the unique four-fold armed array on the cluster. This anticipates a versatile chemistry for dendritic growth, given the availability of the four terminal hydroxyl groups for further elongation of the chains. Moreover, the $C_{cluster}$–H vertices on the rigid head remain ready for derivatization or supramolecular assembly. Work is underway to attain larger polyfunctionalized molecules from **5**.

The *o*-carborane cluster then provides a unique platform for the construction of highly dense multibranched molecules with a wide range of possibilities for derivatization. Derivatives of *o*-carborane with precise patterns of substitution can be prepared by judicious choice of the synthetic procedure. We have coupled four hydroxyl terminated arms onto a specific, compact area of the cluster occupied by four adjacent boron vertices, ultimately leading to a quadruped-shaped structure which might serve as a versatile dendritic precursor. The system also offers the possibility for uneven substitution, *e.g.*, 8,10-aryl$_2$-9,12-I$_2$-1,2-*closo*-$C_2B_{10}H_8$ in which the two iodine atoms are ready for substitution with less crowded substituents. Moreover, the $C_{cluster}$–H vertices on the rigid *o*-carborane head are available as further linking points for organic moieties, hydrogen bond acceptors, transition metals, nanoparticles or surfaces. The generation of diverse macromolecules and supramolecular assemblies constitutes a main focus for our current research and related advances will be reported in the near future.

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11 Crystal data for **4**. $C_{14}H_{18}B_{10}I_2$, M_r = 548.18, tetragonal, space group $P4_2/n$ c m (no. 138), $a = b = 9.7507(3)$, $c = 21.3372(8)$ Å, $\alpha = \beta = \gamma = 90°$, $V = 2028.66(12)$ Å^3, $T = 173(2)$ K, $Z = 4$, μ(Mo-K$_\alpha$) = 3.095 mm^{-1}, 10 054 reflections collected, 1080 unique reflections (R_{int} = 0.054) which were used in calculations. The final w$R(F^2)$ was 0.0765 (all data) and $R[F^2 > 2\sigma(F^2)]$ = 0.0359.

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14 Crystal data for **5**. $C_{14}H_{36}B_{10}O_4$, M_r = 376.53, monoclinic, space group $P2_1/n$ (no. 14), $a = 12.1257(5)$, $b = 14.7447(6)$, $c = 13.6855(5)$ Å, $\alpha = 90$, $\beta = 113.738(2)$, $\gamma = 90°$, $V = 2239.82(15)$ Å^3, $T = 173(2)$ K, $Z = 4$, μ(Mo-K$_\alpha$) = 0.068 mm^{-1}, 8518 reflections collected, 4395 unique reflections (R_{int} = 0.050) which were used in calculations. The final w$R(F^2)$ was 0.1835 (all data) and $R[F^2 > 2\sigma(F^2)]$ = 0.0746.