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Versatile Launch Pad for Facile Functionalization of Cavitands

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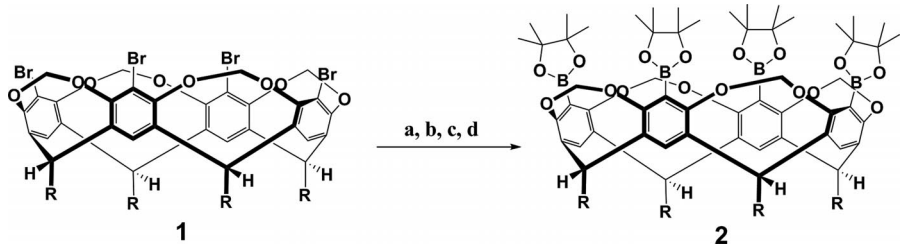
Suzuki–Miyaura cross-coupling reactions have been utilized for the derivatization of the upper-rim of cavitands, but unfortunately, only a relatively small number of suitable, inexpensive boronic acids are available. Herein, we report the synthesis and structure determination of a tetraboronic pinacolyl ester functionalized cavitand, which has been successfully employed in high-yielding coupling reactions with iodoarenes covering a range of functional groups, thereby demonstrating the versatility and chemoselectivity of this platform.

Introduction

Carbon–carbon bond formation, utilizing a palladium catalyst, is a well-known and versatile synthetic process in organic chemistry.[1] More specifically, the Suzuki–Miyaura reaction, where a palladium species catalyzes the coupling of organic halides or triflates with organoboronic acids or esters, is arguably one of the most useful and important of such reactions.[2,3] There are several reasons for its diversity and wide acceptance: (1) It is tolerable to a large variety of electron-donating and electron-withdrawing functional groups. (2) It utilizes mild reaction conditions (i.e., 25–70 °C), low catalyst loading, and dried solvents are not necessary. (3) Many boronic acids/esters are stable over long periods of time.[3] In short, this reaction is highly efficient and, consequently, has been employed extensively in the synthesis of natural products,[4] potential drug candidates,[5] and a range of functional materials.[6]

Within the last few years, the Suzuki–Miyaura reaction has also been utilized in the synthesis of functionalized resorcinarene-based cavitand receptor molecules[7] by cross-coupling of a substituted (e.g., pyridyl, benzonitrile, or methoxyphenyl) arylboronic acid or ester with a tetrahalogenated (I or Br) cavitand. The only reported exception involved coupling of a tetraboronic acid cavitand to 3-bromopyridine, albeit in low yields (ca. 20%).[7l]

The limited range of functional groups that has been successfully appended to cavitands can be attributed in part to the fact that a relatively small number of suitable, inexpensive boronic acids and esters are commercially available for cross-coupling. Moreover, arylboronic acids are often synthesized by low-temperature transmetalation reactions and can be difficult to isolate. In addition, effective coupling of tetrahalogenated cavitands to arylboronic acid or esters demands careful and time-consuming optimization of reaction conditions (e.g., change of base, catalyst, ligand, etc.) depending on the type of arylboronic acid or ester used.[7] Sometimes, coupling reactions with tetrahalogenated cavitands yields multisubstituted and multi-"protio"-cavitands as byproducts, causing tedious chromatographic separations and very low yields.[8]



Scheme 1. Synthetic route to tetraboronic pinacolyl ester cavitand **2**. Reagents and conditions: (a) *n*BuLi, THF, –78 °C; (b) $B(OMe)_3$, –78 °C to r.t.; (c) H^+/H_2O; (d) pinacol, $MgSO_4$, DCM.

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Against this background, we sought to design a more stable (compared to its boronic acid counterpart) tetraboronic ester cavitand counterpart,[9] and herein, we present a facile synthetic procedure for the construction of tetraboronic pinacolyl ester functionalized cavitand **2**

(Scheme 1) and demonstrate that it can be coupled successfully to a variety of iodoarenes under Suzuki–Miyaura conditions. Thus, this new tetraboronic pinacolyl ester cavitand represents a versatile and efficient synthetic platform that can provide a gateway to the successful and facile preparation of a much wider selection of chemically and structurally functionalized cavitands of interest to a broad range of synthetic and materials chemists.

Results and Discussion

The synthesis of **2** was achieved in 50% yield by following a modified procedure.[10] It should be noted that in the reported case, the goal was to only convert two of the four bromine atoms into the pinacolyl boronate derivative. In our case, *C*-pentyltetrabromo cavitand[11] **1** (carefully dried by using Sherburn's procedure[12]) was allowed to react with *n*-butyllithium (4.6 equiv.) at –78 °C for 0.5 h, resulting in a fourfold lithium–halogen exchange. To this was added trimethoxyborane (6 equiv.), and the reaction was allowed to reach room temperature after 0.5 h. The mixture was acidified with hydrochloric acid, producing the tetraboronic acid cavitand, which was then converted into the desired tetraboronic pinacolyl ester cavitand **2** by addition of an excess amount of pinacol and magnesium sulfate (Scheme 1). Purification was carried out by dissolving the reaction mixture in dichloromethane and adding an excess amount of acetone, resulting in the formation of a white precipitate.

Crystals of **2**, suitable for single-crystal X-ray diffraction, were grown from a saturated hexanes/dichloromethane solution by slow evaporation at room temperature over 3 d.[13] Structure determination of **2** shows one tetraboronic pinacolyl ester cavitand and two molecules of hexane in the asymmetric unit (Figure 1).

Furthermore, one hexane molecule resides within the upper-cavity, whereas a second solvent molecule resides outside the cavitand, filling space within the crystalline lattice. The presence of an alkyl group inside the cavity is akin to what has been observed in other cavitand structures, where

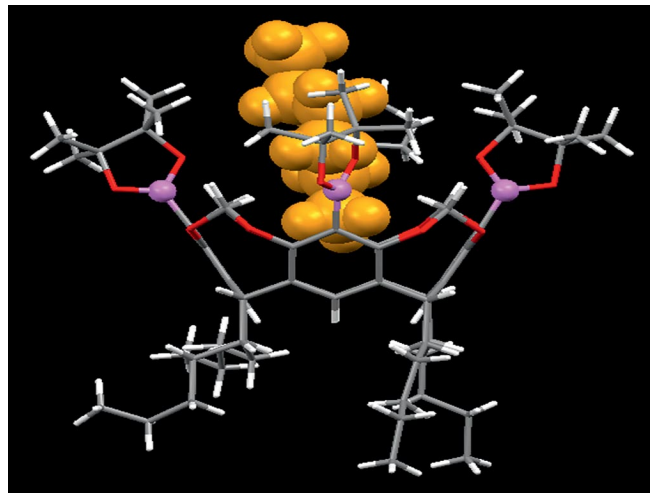
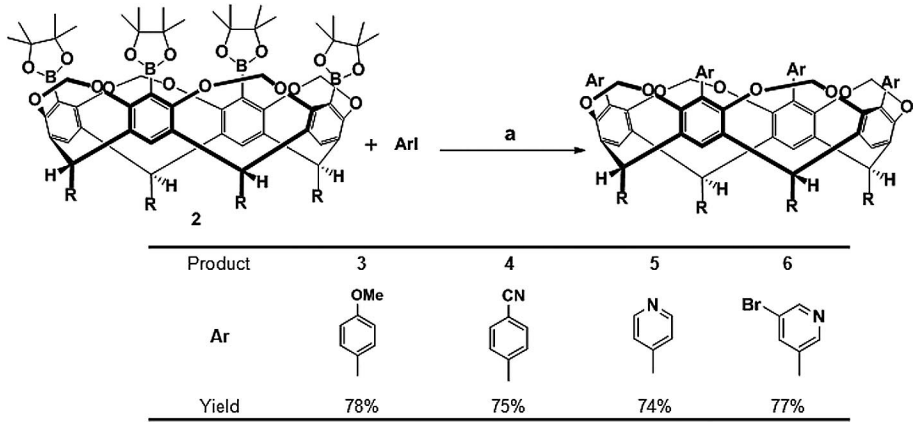


Figure 1. Side view of the host–guest complex in the crystal structure of **2**. The disordered atoms around one boronic pinacolyl ester and the exterior solvent molecule have been omitted for clarity. Boron atoms are shown as light-pink spheres and the interior hexane molecule is shown in orange.[16]

the "leg" of one cavitand is inserted into the cavity of a neighboring host molecule.[14] This type of interaction has recently been used for designing supramolecular polymers having cavity-bearing moieties.[15] All four pinacolyl ester groups are oriented perpendicularly with respect to the phenyl group to which they are connected, presumably due to oxygen–oxygen repulsion between neighboring bridging ether groups.

In order to successfully couple **2** to different representative haloarenes, we had to identify the optimum reaction conditions that result in versatile and facile tetrafunctionalization on the upper-rim of the cavitand. Our choice of suitable haloarenes was based on two criteria: (1) the haloarenes should represent different classes of functional groups to establish the versatility of this system and (2) the end product, the resulting tetrafunctionalized cavitand, should have obvious applications and utility in host–guest chemistry.



Scheme 2. Synthetic route to tetraboronic pinacolyl ester cavitand **2**. Reagents and conditions: (a) $Pd_2(dba)_3$, Ag_2CO_3, PPh_3, THF, r.t., dark, 72 h.

We chose 4-iodoanisole as a representative of arenes bearing an electron-donating group. The targeted product, tetra-4-methoxyphenyl cavitand, is – upon deprotection – an important precursor for the construction of heteromeric capsules.[17] Consequently, **2** was allowed to react at room temperature with 4-iodoanisole (5 equiv.), $Pd_2(dba)_3$ as a catalyst, Ag_2CO_3 as a base, and PPh_3 as a ligand in THF (18 M) to give the tetra-4-methoxyphenyl cavitand (Scheme 2, **3**).[18,19]

The ^1H NMR spectrum of **3** clearly shows that only the desired tetra-4-methoxyphenyl cavitand product is formed with no unreacted starting material present (Figure 2).

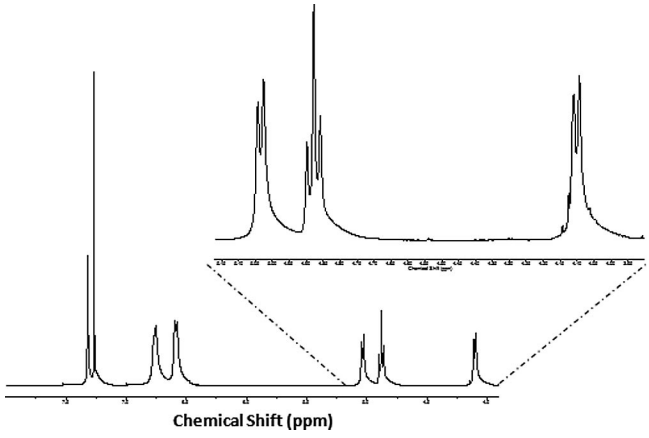


Figure 2. Partial ^1H NMR spectrum ($CDCl_3$) of cavitand **3** (δ = 3.8 to 8 ppm region). Magnified region shown for corresponding bridging protons of **3**.

Furthermore, we have characterized product **3** by high-resolution TOF (time of flight) mass spectrometry (Figure 3), and we only observed the molecular ion peaks corresponding to the desired product.

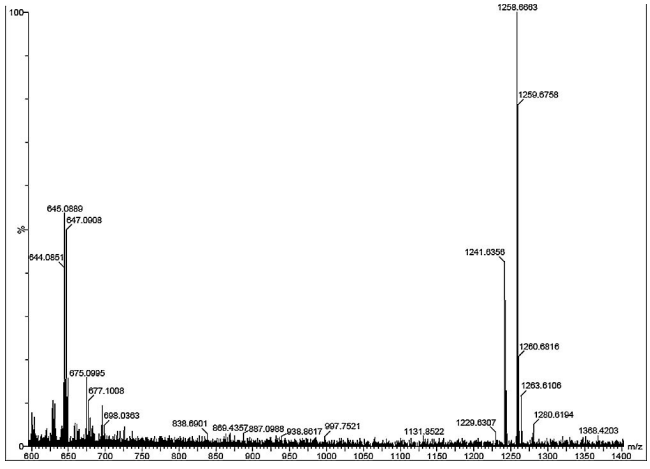


Figure 3. High-resolution TOF mass spectrum of **3** showing molecular ion peaks corresponding to $[M + H]^+$ (m/z = 1241.6) and $[M + NH_4]^+$ (m/z = 1258.6).

Our next goal was to couple **2** to an iodoarene bearing an electron-withdrawing group. We chose 4-iodobenzonitrile as a haloarene because the target product, tetra-4-cyanophenyl cavitand **4**, can be employed in the construction of a variety of homo- and heterocavitand metal cages.[7d,20] Using the coupling protocol outlined for the synthesis of **3**, we were successful in tetracoupling 4-iodobenzonitrile to precursor **2** (Scheme 2, **4**).

Cavitands bearing heterocyclic moieties on the upper-rim are of great interest in the assembly of noncovalent capsules,[17] as multidentate ligands for coordination complexes,[7d] and as well in systematic co-crystal studies.[14,21] We therefore treated **2** with 4-iodopyridine to yield the desired tetrapyridyl cavitand **5** (Scheme 2).

Finally, we wanted to determine if this platform could display chemoselective coupling to arenes bearing both iodo and bromo substituents. We chose 3-bromo-5-iodopyridine as a representative substrate because the desired tetrafunctionalized product would have active nitrogen atoms capable of forming coordination cages with metals and could be used to assemble noncovalent capsules (bulky bromide group at the 3-position should aid pyridyl nitrogen atoms to orient upward, facilitating capsule formation). Using our coupling protocol with **2** and 3-bromo-5-iodopyridine, we achieved complete selective cross-coupling at the iodo substituent, and no reaction was observed with the bromo functional group, yielding desired tetra(3-bromopyridyl)cavitand **6** (Scheme 2).

Conclusions

We have described the design, synthesis, and structural characterization of a tetraboronic pinacolyl ester cavitand that can be prepared in good yields. High-yielding Suzuki–Miyaura coupling reactions of **2** to iodoarenes covering a range of functional groups shows the robustness and versatility of this tetraboronic ester cavitand, making it a "launch pad" for the synthesis of many new cavitands in a facile manner. The presented coupling protocol of **2** has many advantages compared to conventional routes, such as no byproduct formation, no need of tedious chromatographic separation, and highly improved economical efficiency due to the need of fewer equivalents of inexpensive iodoarenes compared to their expensive boronic acid/ester counterparts (which also need to be used in 8–10-fold excess). It is also notable that so far no examples of cavitand cross-coupling with successful chemoselectivity have been reported, which opens new avenues for designing and synthesizing macrocycles. The depth and electronic nature of the interior of the cavitand can be readily altered through the suitable choice of haloarene, and new molecular capsules can also be envisioned in a straightforward manner.

Experimental Section

***C*-Pentyltetraboronic Acid Dipinacolyl Ester (2):** *C*-Pentyltetrabromocavitand **1** (1.00 g, 0.883 mmol) was dissolved in dry tetrahydrofuran (10 mL), and then the solution was evaporated and dried at 100 °C (0.1 Torr) for 2 h under an argon atmosphere. This procedure was repeated twice. The resulting cavitand was dissolved in dry tetrahydrofuran (70 mL) and cooled to –78 °C (dry ice/acet-

one bath) under a dinitrogen atmosphere. To this solution was added *n*-butyllithium (1.6 M in hexanes, 2.54 mL, 4.06 mmol) dropwise over 10 min, and the mixture was stirred for an additional 0.5 h. Trimethoxyborane (0.60 mL, 5.3 mmol) was added dropwise over 10 min, and the resulting solution was stirred at –78 °C for 0.5 h, at which time the dry ice/acetone bath was removed, and the reaction mixture was allowed to reach room temperature. Upon reaching room temperature, the mixture was quenched with a 1 M hydrochloric acid solution (100 mL) and stirred for 0.5 h. The mixture was extracted with dichloromethane (3 × 100 mL), and the organic portions were collected and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was dissolved in dichloromethane (100 mL). Excess amounts of pinacol (750 mg, 6.30 mmol) and magnesium sulfate (2.25 g) were added to the mixture, which was stirred for 12 h and then filtered and dried via a rotary evaporator. The residue was dissolved in dichloromethane and added to a beaker of acetone, which was left on the rotary evaporator until the dichloromethane was completely removed; precipitation of the product was induced by using acetone and the product was filtered off resulting in pure product **1** (570 mg, 50%). The product can be recrystallized from dichloromethane/ethyl acetate/hexane (1:1:1). M.p. >280 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.10 (s, 4 H), 5.59 (d, J = 6.8 Hz, 4 H), 4.75 (t, J = 7.2 Hz, 4 H), 4.54 (d, J = 7.6 Hz, 4 H), 2.17–2.15 (m, 8 H), 1.40–1.29 (m, 72 H), 0.90–0.88 (m, 12 H) ppm. ^{13}C NMR (200 MHz, $CDCl_3$): δ = 157.72, 137.77, 122.37, 99.42, 83.53, 36.11, 31.91, 30.89, 29.88, 27.54, 24.70, 22.65, 14.02 ppm. IR: $\tilde{\nu}$ = 2977, 2931, 1705, 1592, 1442, 1358, 1316, 1145, 978, 851, 582 cm^{-1}. MS (MALDI-TOF/TOF): m/z = 1343.75 [**2** + Na]$^+$. $C_{76}H_{108}B_4O_{16}$ (1320.91): calcd. C 69.11, H 8.24; found C 69.24 H 8.44.

General Procedure for the Coupling Reaction: An oven-dried round-bottom flask was placed under an argon atmosphere and charged with **1** (100 mg; 75.7 μmol), iodoarene (378 μmol, 5 mol equiv.), silver carbonate (608 μmol, 8.0 mol equiv.), tris(dibenzylideneacetone)dipalladium(0) (36 μmol, 0.12 mol equiv.), and triphenylphosphane (151 μmol, 2 mol equiv.). The flask was evacuated and refilled with dinitrogen three times then dry tetrahydrofuran (5 mL) was added. The reaction mixture was stirred at room temperature in the dark for 72 h then filtered through a short plug of Celite, washed with chloroform (3×), and the solvent was evaporated to afford the crude product, which was purified by column chromatography (SiO_2).

3: This compound was synthesized by using the general coupling procedure with 4-iodoanisole as iodoarene. The crude product was purified by column chromatography (100 g of silica; hexane/ethyl acetate, 10:0 → 8:2) to give **3** (73 mg, 78%). M.p. >280 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (s, 4 H), 6.76 (d, J = 8 Hz, 8 H), 6.59 (d, J = 8 Hz, 8 H), 5.03 (d, J = 4 Hz, 4 H), 4.88 (t, J = 8 Hz, 4 H), 4.10 (d, J = 4 Hz, 4 H),3.00 (br. s, 8 H), 2.40–2.33 (m, 8 H), 1.50–1.38 (m, 24 H), 0.97 (t, J = 8 Hz, 12 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 158.26, 152.84, 138.46, 130.90, 129.73, 125.84, 119.48, 113.15, 99.88, 75.03, 37.12, 32.03, 27.63, 24.81, 22.71, 14.17 ppm. IR: $\tilde{\nu}$ = 3403, 2927, 1611, 1514, 1447, 1244, 1156, 1110, 1018, 973, 949, 827, 805, 673 cm^{-1}. MS (ESI-TOF): m/z = 1241.6 [M + H]$^+$, 1258.6 [M + NH_4]$^+$.

4: This compound was synthesized by using the general coupling procedure with 4-iodobenzonitrile as iodoarene. The crude product was purified by column chromatography (100 g of silica; chloroform/ethyl acetate, 8:2) to give **4** (69 mg, 75%). M.p. >280 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (d, J = 8 Hz 8 H), 7.38 (s, 4 H), 7.17 (d, J = 8 Hz, 8 H), 5.25 (d, J = 8 Hz, 4 H), 4.83 (t, J = 8 Hz, 4 H), 4.20 (d, J = 4 Hz, 4 H), 2.40–2.33 (m, 8 H), 1.50–1.38 (m, 24 H), 0.97 (t, J = 8 Hz, 12 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 152.25, 138.59, 131.70, 130.80, 127.69, 120.86, 118.52, 111.27, 100.43, 37.06, 31.98, 27.59, 22.67, 14.12 ppm. IR: $\tilde{\nu}$ = 2925, 2226, 1608, 1447, 1157, 1082, 971, 839, 805, 740, 692 cm^{-1}. MS (ESI-TOF): m/z = 1265.5 [M + CH_2O_2 – H]$^+$.

5: This compound was synthesized by using the general coupling procedure with 4-iodopyridine as iodoarene. The crude product was purified by column chromatography (100 g of silica; ethyl acetate/ethanol, 1:1 + 3% triethylamine) to give **5** (63 mg, 74%). M.p. >280 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.59 (d, J = 6.0 Hz, 8 H), 7.37 (s, 4 H), 6.98 (d, J = 6 Hz, 8 H), 5.29 (d, J = 6 Hz, 4 H), 4.84 (t, J = 8 Hz, 4 H), 4.23 (d, J = 8.0 Hz, 4 H), 2.34 (m, 8 H), 1.46 (m, 24 H), 0.96 (t, J = 7 Hz, 12 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 152.17, 149.46, 142.02, 138.00, 126.83, 124.91, 120.85, 100.39, 43.23, 37.01, 31.99, 30.24, 27.58, 22.68, 14.14 ppm. IR: $\tilde{\nu}$ = 2929, 2859, 1583, 1450, 1408, 1160, 1084, 975, 716 cm^{-1}. MS (ESI-TOF): m/z = 1125.5 [M + H]$^+$.

6: This compound was synthesized by using the general coupling procedure with 3-bromo-5-iodopyridine as iodoarene. The crude product was purified by column chromatography (100 g of silica; ethyl acetate/ethanol, 8:2) to give **6** (84 mg, 77%). M.p. >280 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.59 (d, J = 2.0 Hz, 4 H), 8.14 (s, 4 H), 7.62 (t, J = 2 Hz, 4 H), 7.37 (s, 4 H), 5.38 (d, J = 8 Hz, 4 H), 4.83 (t, J = 8 Hz, 4 H), 4.21 (d, J = 4.0 Hz, 4 H), 2.34 (m, 8 H), 1.46 (m, 24 H), 0.96 (t, J = 6 Hz, 12 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 152.53, 149.59, 147.88, 140.28, 138.56, 130.93, 124.48, 121.05, 37.03, 31.97, 30.21, 27.57, 22.67, 14.12 ppm. IR: $\tilde{\nu}$ = 2921, 2850, 1583, 1459, 1400, 1299, 1259, 1177, 1080, 1013, 970, 732 cm^{-1}. MS (ESI-TOF): m/z = 1441.3 [M + H]$^+$.

Supporting Information (see footnote on the first page of this article): Detailed experimental procedures and characterization of compounds **2**–**5** along with crystallographic data for **2** (CCDC-647956 contains the supplementary crystallographic data for this paper; these data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif).

Acknowledgments

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