Carborane functionalized pyrroles and porphyrins *via* the Suzuki cross-coupling reaction†

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A new route to carboranylated pyrroles and porphyrins is reported which involves the Suzuki coupling of readily available bromo- and boronic acid-pyrroles and bromoporphyrins with functionalized carboranes; the X-ray structures of two targeted products are presented and discussed.

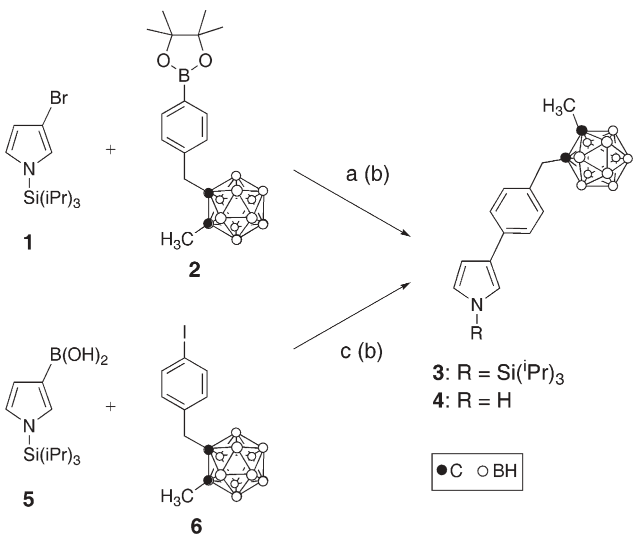
Boron-containing molecules have been of interest for some time because they have wide applications in medicine[1,2] and in materials science.[3,4] Carborane-containing porphyrins are particularly promising boron neutron capture therapy (BNCT) agents because of their selectivity for tumor tissue, their ability to deliver therapeutic boron concentrations, and their persistence within tumors.[5] Pyrroles substituted at the 3- or 4-position with a carborane group are key building blocks in the synthesis of β-carboranylporphyrins,[6] and of conducting polypyrroles with increased overoxidation resistance compared with unsubstituted polypyrroles.[7] In several of the porphyrin–carborane constructs under investigation, the carboranes are linked to the porphyrin through heteroatoms that are potentially labile *in vivo*.[5] We have previously reported the synthesis of carbon–carbon linked carboranylporphyrins from either carboranyl-substituted aldehydes[8–11] or pyrroles,[6,7,12] and these compounds are already showing promise as BNCT drugs. However, the synthetic routes to these molecules are generally long, especially for unsymmetrical porphyrins; for example, 3-substituted carboranylpyrroles required six steps for their syntheses from commercially available precursors.[6,7]

The efficient and regioselective brominations of pyrrole and the β-positions of tetraarylporphyrins have been reported,[13,14] making possible the selective modification of pyrrole and porphyrin macrocycles *via* metal-catalyzed cross-coupling reactions.[15,16] The Suzuki coupling reaction[17] is particularly suitable for the introduction of a variety of groups at the periphery of porphyrins and pyrroles by way of the coupling of halo-substituted precursors with the corresponding boronic acids or esters.[15,18] Herein, we report the efficient syntheses of carborane-functionalized pyrroles and porphyrins using Suzuki coupling reactions.[19]

Palladium(0)-mediated coupling of commercially available 3-bromopyrrole **1** with the carboranyl boronic ester **2** in the presence of $NaHCO_3$ gave the target pyrrole **4** in 18% yield, after *in situ* deprotection of **3** using tetrabutylammonium fluoride (Scheme 1). The boronic ester **2** was obtained in 91% yield by the reaction of the corresponding commercially available bromomethylboronic ester with the lithium anion of 1-methyl-*o*-carborane.[8] The yield of the coupling reaction was dependent on the solvent and base used. Lower yields of pyrrole **3** were obtained when the reaction was performed in anhydrous toluene using a base such as Na_2CO_3 or K_2CO_3, because of the instability of the starting pyrrole under these conditions; base-induced cleavage of the N-protecting group and polymerization of the resulting bromopyrrole gave undesirable polypyrrolic side products. Using a similar synthetic strategy, a 3,4-dicarboranylpyrrole was also prepared in 32% yield from commercially available 1-(triisopropyl)-3,4-dibromopyrrole and boronic ester **2**.

In a more efficient synthetic approach, pyrrole **3** was obtained in 89% yield from the coupling reaction between commercially available pyrrole-3-boronic acid **5** and carboranylphenyl iodide **6** (Scheme 1). Compound **6** was obtained in 79% yield from the reaction of bromomethylphenyl iodide with the lithium anion of 1-methyl-*o*-carborane.[8] Carboranylpyrrole **3** was characterized by NMR and MS spectra (see ESI).† The structure of **3** was further confirmed by X-ray crystallography (Fig. 1). The Si–N distance is 1.779(2) Å, and the pyrrole ring is not quite coplanar with the phenyl ring, forming a dihedral angle of 6.1(7)° with it.

The Suzuki cross-coupling reaction of tetrabromoporphyrin **7**[20] with boronic ester **2** using either toluene or THF–water as the solvent and K_2CO_3 as the base, gave the target porphyrin **9** in only 15% yield. Several debrominated porphyrin by-products were



Scheme 1 Reaction conditions: (a) $Pd(PPh_3)_4$, toluene–methanol 5 : 1, $NaHCO_3$, 19%; (b) Bu_4NF, THF, 0 °C, 95%; (c) $Pd(PPh_3)_4$, toluene–methanol 5 : 1, Na_2CO_3, 89%.

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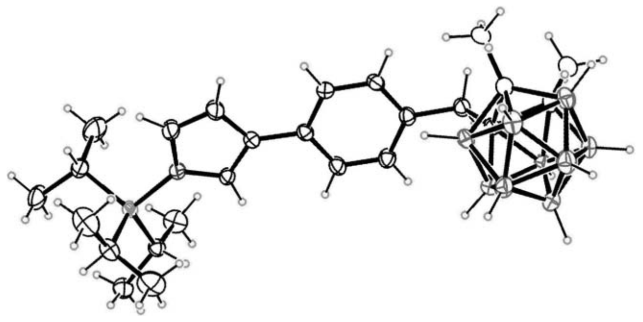


Fig. 1 X-Ray crystal structure of carboranylpyrrole **3** with 50% ellipsoids.

obtained from this reaction; for example tricarboranylporphyrin **10**, a rare example of a β-trifunctionalized porphyrin, was isolated in 15% yield. Dehalogenation is a common occurrence in metal-catalyzed cross-coupling reactions, particularly when there is steric hindrance in the starting material. A similar debrominated product was recently reported from the reaction of 1,6,7,12-tetrabromoperylene bis-imide with phenylboronic acid under Suzuki coupling conditions.[22]

In order to increase the reactivity of **2** in the Suzuki cross-coupling reaction and to decrease the steric hindrance caused by the boronic ester in the reaction transition state, boronic ester **2** was hydrolysed using sodium periodate followed by 2N HCl, giving boronic acid **8** in 81% yield.[21] The coupling reaction of porphyrin **7** with **8** (10 equiv) in anhydrous toluene and in the presence of $Pd(PPh_3)_4$ (0.2 equiv) and of anhydrous K_2CO_3 (20 equiv) gave tetracarboranylporphyrin **9** in 78% yield (Scheme 2), along with 14% of porphyrin **10** and trace amounts of other debrominated side products (see ESI for a detailed experimental procedure).† Porphyrins **9** and **10** were characterized by MS, ^{1}H-NMR and by UV-vis spectroscopy (see ESI).† Molecular ion peaks were observed at 1601.2177 and 1354.9814 by high resolution ESI for porphyrins **9** and **10**, respectively. While porphyrin **9** has a simplified ^{1}H-NMR spectrum with singlet peaks for the four β-pyrrolic protons (8.24 ppm) and the carborane methyl groups (2.05 ppm), that of porphyrin **10** is more complex, showing multiple resonances for the β-pyrrolic, phenyl and carborane protons.

Crystals of the porphyrin **9**, as the dicationic bis-trifluoroacetate salt, were grown from dichloromethane–methanol. The structure of the dication is shown in Fig. 2. It has a saddle conformation, with the N–H groups pointing alternately up and down. Opposite pyrrole planes form dihedral angles of 67.5(2) and 69.7(2)°, while adjacent pyrrole planes form smaller dihedral angles, in the range 41.7(2)–51.7(2)°. This conformation allows the four N–H hydrogen atoms to avoid unfavorable contacts in the center of the porphyrin ring, and to form hydrogen bonds to trifluoroacetate anions, one above the porphyrin and one below. The N···O distances in these four hydrogen bonds are in the range 2.733(9)–2.848(8) Å.

Similarly, the β-octacarboranyl-tetraphenylporphyrin **11** was obtained from the reaction of Ni(II)–β-octabromo-tetraphenylporphyrin[23] with excess of the boronic acid **8** in 18% yield after purification by preparative TLC. Free-base β-octabromo-tetraphenylporphyrin failed to react to give the target porphyrin under the Suzuki coupling conditions. The Ni(II)–porphyrin **11** gave a molecular ion peak at 2643.8 by MALDI-TOF MS and characteristic ^{1}H-NMR signals consistent with those previously reported for β-octasubstituted porphyrins.[24] The UV-vis spectra of carboranylporphyrins **9**, **10** and **11** show, as expected, red-shifted Soret and Q bands compared with *meso*-tetraphenylporphyrin, thus reflecting the distortion from planarity of the peripherally substituted porphyrin rings.

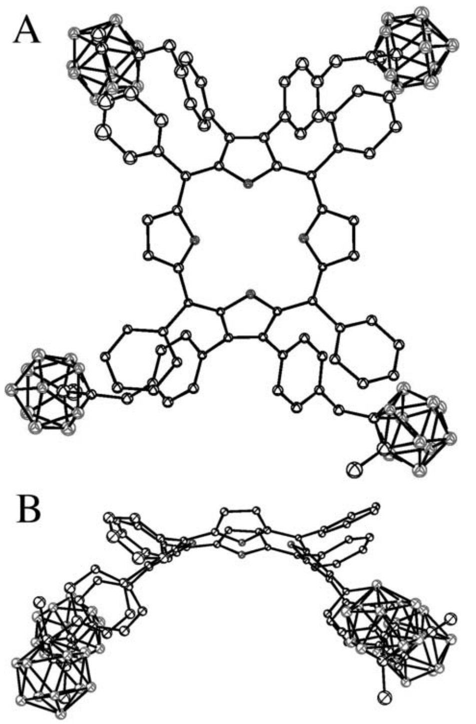
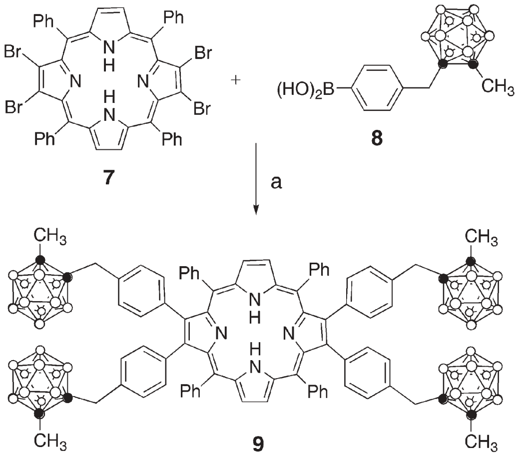
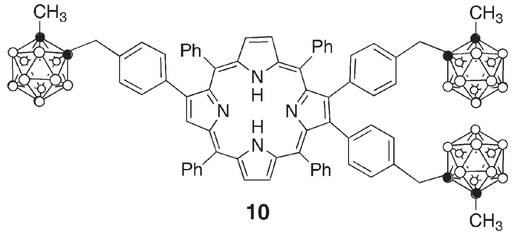


Fig. 2 X-Ray crystal structure of porphyrin **9**, A, top view; B, end-on view showing saddled conformation. Hydrogen atoms are omitted for clarity.

In summary, we have developed a new expeditious route to carborane-substituted pyrroles and porphyrins from readily available starting materials. These compounds contain hydrolytically-stable carbon–carbon bonds between the carborane and pyrrole or porphyrin moieties, and are expected to find



Scheme 2 Reaction conditions: (a) $Pd(PPh_3)_4$, toluene, K_2CO_3, 78%.



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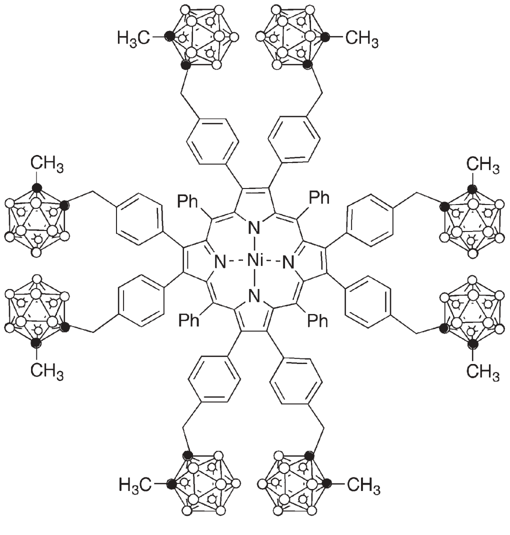

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applications as delivery agents for BNCT of tumors and/or as conducting and catalytic materials.

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Notes and references

‡ *Crystal data*: for **3** at 115 K: $C_{23}H_{43}B_{10}NSi$, orthorhombic, space group *Pbca*, $a = 18.875(2)$, $b = 10.6604(10)$, $c = 28.891(3)$ Å, $V = 5813.3(10)$ Å^3, $Z = 8$, 38536 reflections collected with $\theta < 26.0°$ (MoKα), 5706 unique; $R_1 = 0.057$, $wR_2 = 0.146$ refined on F^2. The carborane exhibits a rotational disorder, in which the methyl group occupies two alternate orientations with approximately equal occupancy, CCDC 614469. For the porphyrin trifluoroacetate salt **9** at 115 K: $[C_{84}H_{104}B_{40}N_4](C_2F_3O_2)_2 \cdot CH_2Cl_2 \cdot CH_3OH$, monoclinic, space group $P2_1/c$, $a = 13.618(3)$, $b = 33.525(6)$, $c = 23.329(5)$ Å, $\beta = 103.989(6)°$, $V = 10335(4)$ Å^3, $Z = 4$, 38 494 reflections collected with $\theta < 22.0°$ (MoKα), 12 547 unique; $R_1 = 0.134$, $wR_2 = 0.407$ refined on F^2. Both independent trifluoroacetate anions exhibit disorder, CCDC 614470. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b611571c

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