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Hot Paper

Carboranylphosphines: B9-Substituted Derivatives with Enhanced Reactivity for the Anchoring to Dendrimers

Max Milewski,^[a, b, c] Anne-Marie Caminade,^{*[b, c]} Sonia Mallet-Ladeira,^[b, c, d] Agustí Lledós,^[e] Peter Lönnecke,^[a] and Evamarie Hey-Hawkins^{*[a]}

Dedicated to Prof. Dr. Rinaldo Poli to acknowledge his tremendous work as coordinator of the Initial Training Network "Coordination Chemistry Inspires Molecular Catalysis" (CCIMC).

Several *ortho*-carboranes bearing a phenoxy or a phenylamino group in the B9 position were prepared employing various protection and deprotection strategies. Following established protocols, dendritic compounds were synthesized from a hexachlorocyclotriphosphazene or thiophosphoryl chloride core, and possible anchoring options for the B9-substituted *ortho*-carboranes were investigated experimentally and theoret-

ically (DFT). Furthermore, 1- or 1,2-phosphanyl-substituted carborane derivatives were obtained. The resulting diethyl-, diisopropyl-, di-*tert*-butyl-, diphenyl- or diethoxyphosphines bearing a tunable *ortho*-carborane moiety are intriguing ligands for future applications in homogeneous catalysis or the medicinal sector.

Introduction

Icosahedral *closo*-dicarbadodecaboranes (carboranes) have been a focus of interest of many research groups in the past years as building blocks for applications in medicinal chemistry,^[1–4] metal complexes,^[5–7] supramolecular assemblies, macrocyclic molecules,^[8] and luminescent materials.^[9,10] Important modifications of carboranes include functionalization of both, boron and carbon vertices, which are influenced by two fundamental electronic properties: the electron delocalization and the electron-withdrawing character of the skeletal carbon atoms.^[11] The latter causes an acidic character at the carbon-bound protons, thus facilitating their removal by bases. The acidity can be further adjusted by introducing electron-withdrawing or electron-donating substituents at the boron vertices.^[12] Substitution of the carbon-bound hydrogen atoms in carboranes by different heteroatoms such as carbon, nitrogen, oxygen, phosphorus, and sulfur already yielded a wide scope of PP,^[13–15] PN,^[16] PS,^[17] PC,^[18] and other ligands for transition metal complexes and catalytically active metals.^[19]

Especially, the easily accessible 1,2-bisphosphanyl-substituted carboranes (*ortho* isomers) are a family of versatile compounds with appealing features based on the carborane scaffold such as their adaptable C–C bond length, their electron-withdrawing effect, and the ability of hydridic B–H groups to engage in metal bonding.^[20] The carborane scaffold further enhances the stability of phosphines towards oxygen in contrast to alkyl- and aryl-substituted phosphines. Certain compounds such as 1,2-bis(chlorophosphino)-*ortho*-carborane, first reported in 1963,^[13] are even inert against the reaction with sulfur up to 200 °C.^[19] The aforementioned properties make carboranylphosphines promising ligands for metal complexes applied in homogeneous catalysis. However, the synthesis of homogeneous catalysts capable of selective and fast transformations, while being readily and quantitatively separated from reaction products, remains difficult.^[21,22] One commonly investigated method is the attachment of homogeneous catalysts to insoluble supports such as silica. Problems with this strategy include nonuniformity and partially unknown structures of heterogenized catalysts, mass transport limitations, usually

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reduced activity compared to their homogeneous counterparts, and metal leaching.^[22] Another approach is the attachment to soluble supports. Because of their well-defined design, macromolecules such as dendrimers offer precise management of a catalyst structure,^[22] and are soluble yet recoverable through nanofiltration or precipitation, depending on the organic solvent used.^[23] Furthermore, increasing local concentrations of catalytic sites positioned on the surface of dendrimers might result in dendritic effects with varying activity depending on the generation of dendrimer employed.^[24] Dendritic effects in catalysis can result in a variety of features, including easier recovery and reuse of dendritic catalysts. This might reduce metal complex leaching. To date, no carboranylphosphine-functionalized dendrimer has been reported, and only a few examples of monomeric carboranylphosphine catalysts are known.^[25–27]

However, not only catalytic applications should be considered. Bearing a large number of boron atoms, carboranes have been investigated as suitable building blocks for boron neutron capture therapy (BNCT).^[4,28] To date, the only cluster compound used in clinical trials is sodium mercaptoundecahydro-*closo*-dodecaborate.^[29] Thus, using hyperbranched macromolecules like dendrimers as scaffolds is an intriguing approach to boron-rich molecules. To the best of our knowledge, no dendrimers derived from $N_3P_3Cl_6$ or $P(S)Cl_3$ with carboranes as terminal functions have been reported.

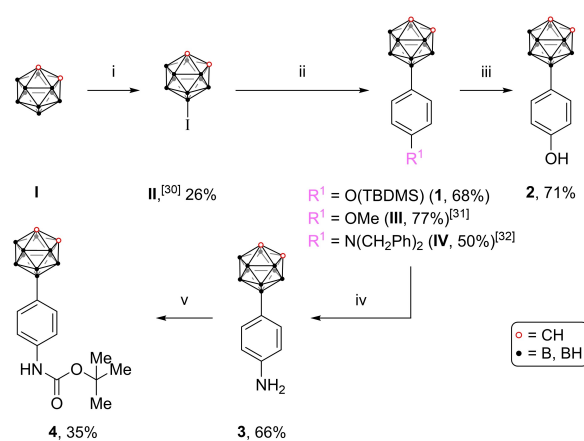
In this work, we present the synthesis of novel B9-functionalized *ortho*-carboranes as well as 1- or 1,2-phosphanyl-substituted *ortho*-carboranes. Furthermore, the grafting of these monomers to dendritic compounds was investigated experimentally and by DFT simulations.

Results and Discussion

Synthesis

Starting from commercially available *ortho*-carborane (I), 9-iodo-*ortho*-carborane (II) was prepared according to the literature.^[30] In the next step, different organomagnesium halides were reacted with II to yield the B9-substituted carboranes 1–4 as well as III^[31] and IV^[32] according to published protocols (see Scheme 1).^[33] The TBDMS (TBDMS = *tert*-butyldimethylsilyl) and the dibenzyl protecting groups were introduced prior to the formation of the Grignard reagents to avoid unwanted side reactions of the hydroxy or amine function.^[34–36] Excluding elemental iodine during the synthesis of the Grignard reagents increased the yields of the B9-substituted carboranes significantly.

After the Pd-catalyzed coupling (ii in Scheme 1), compounds 1 and IV were deprotected using different strategies to make them suitable candidates for further modifications ($R^1 = OH$ (2) or NH_2 (3)). A phenoxy or a phenylamino group is necessary for grafting to different macromolecules as demonstrated by Caminade and co-workers.^[37] The methoxyphenyl substituent in III mimics the phenoxy linker needed in immobilization

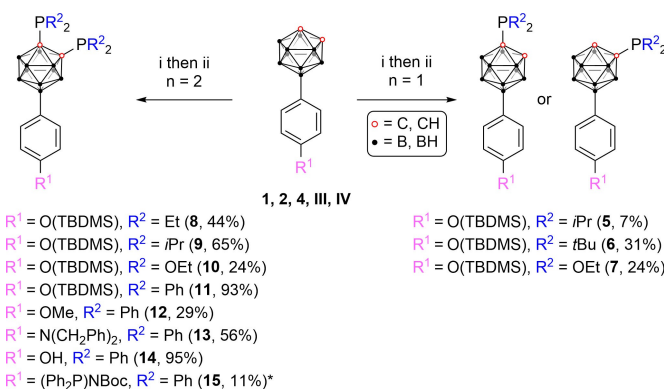


Scheme 1. Synthesis of B9-substituted *ortho*-carboranes. (i) I_2 , HNO_3/H_2SO_4 , $AcOH$, $80^\circ C$, 18 h; (ii) $p-R^1C_6H_4-MgBr$, $[PdCl_2(PPh_3)_2]$, for **1**: THF/ Et_2O , $0^\circ C$, 66 h, for **III**: THF, rt, 120 h,^[31] for **IV**: THF, rt, 2 d,^[32]; (iii) **2** is formed as by-product during the synthesis of **1** ($LiCl$, THF, rt, 2 d) or was prepared from **III** and HBr (33%), $AcOH$, ΔT , 24 h; (iv) Pd/C (5%), H_2 (20 bar), THF, rt, 96 h; (v) Boc_2O , THF, rt, 14 h. See Supporting Information for detailed conditions.

reactions. It can be considered as the monomeric equivalent of the carboranyl-substituted dendrimers.

In the following step, carboranylmono- (5–7) and bisphosphines (8–15) were prepared according to the synthetic pathway described by Alexander and Schroeder,^[13] employing the lithiation of the carborane derivatives **1**, **2**, **4**, **III**, and **IV**, followed by treatment with the corresponding chlorophosphines or -phosphite (Scheme 2). Carboranylmonophosphines 5–7 were formed as by-products in the synthesis of the carboranylbisphosphines 8–15 and isolated in low to moderate yields.

Deprotection of the hydroxyl and amino groups was then attempted. Deprotection of **13** to obtain the free phenylamino carboranylphosphine failed despite several attempts applying known hydrogenation methods (Pd/C , $NH_4(HCOO)$; Pd/C , H_2).^[38,39] Unfortunately, the substitution reaction with *tert*-butyloxycarbonyl (Boc)-protected carborane **4** always resulted in the triphosphanylated product **15**, even when only two



Scheme 2. Synthesis of B9-substituted carboranylphosphines. (i) n ($n = 1, 2$) $n-BuLi$, Et_2O or THF, $-78^\circ C$ to rt; (ii) n ($n = 1, 2$) PR^2_2Cl , Et_2O or THF, $-78^\circ C/0^\circ C$ to rt. *The NH group in **4** was also substituted by PPh_2 . See Supporting Information for detailed conditions.

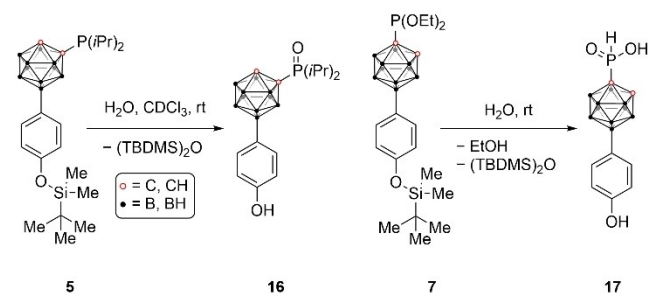
Table 1. Influence of the choice of phosphorus substituents on the pattern and the $^{31}\text{P}\{^1\text{H}\}$ NMR chemical shifts [ppm] of carboranylmono- and bisphosphines as well as of the respective chlorophosphines (J_{pp} coupling constant in Hz).					
Compound	$^{31}\text{P}\{^1\text{H}\}^{\text{[a]}}$	Compound	$^{31}\text{P}\{^1\text{H}\}^{\text{[a]}}$	Compound	$^{31}\text{P}\{^1\text{H}\}^{\text{[a]}}$
$\text{Ph}_2\text{PCl}^{\text{[b]}}$	81.8	11	7.3, 5.9 (d, 123)	$\text{Ph}_3\text{P}^{\text{[41]}}$	−6
12	7.1, 5.4 (d, 122)	13	7.2, 5.4 (d, 123)	14	7.2, 5.5 (d, 123)
15	58.5 (P–N), 7.0, 5.5 (d, 122)	8	4.9, 3.1 (d, 120)	$\text{Et}_3\text{P}^{\text{[42]}}$	−20
$\text{Et}_2\text{PCl}^{\text{[40]}}$	117.7	9	32.3, 30.2 (d, 107)	$i\text{-Pr}_3\text{P}^{\text{[42]}}$	19
$i\text{-Pr}_2\text{PCl}^{\text{[b]}}$	133.8	6	94.3, 92.1 (5:4)	$t\text{-Bu}_3\text{P}^{\text{[41]}}$	63
$t\text{-Bu}_2\text{PCl}^{\text{[b]}}$	146.6	10	151.6, 149.9 (d, 136)	$\text{P}(\text{OEt})_3^{\text{[43]}}$	138
$\text{P}(\text{OEt})_2\text{Cl}^{\text{[b]}}$	166.4	7			152.8, 151.7 (1:1)
5	58.6, 58.1 (1:1)				

[a] In CDCl_3 at 25 °C. [b] Experimentally measured.

equivalents of $n\text{-BuLi}$ and chlorodiphenylphosphine were employed. The monophosphines 5 and 7 were hydrolyzed or oxidized over time forming 16 and 17, respectively (Scheme 3).

Characterization

Compared to the respective chlorophosphines,^[40] the $^{31}\text{P}\{^1\text{H}\}$ NMR signals of the carboranylmono- and bisphosphines 5–15 are shifted to higher field (Table 1). However, compared to the ^{31}P resonances of the trialkyl- and triarylphosphines,^[41,42] the signals of the carboranylmono- and bisphosphines are shifted downfield. This indicates that the 1,2-*closo*-carboranyl group displays a strong electron-acceptor character, stronger than hydrocarbons.^[44,45] Interestingly, the $^{31}\text{P}\{^1\text{H}\}$ NMR spectra of the carboranyl bis(diphenyl)phosphines 11–15 differ only slightly, which indicates that there is almost no influence of the substituents in the B9 position on the electron density around the phosphorus atoms.



Scheme 3. Decomposition of monophosphines 5 and 7 after exposure to air for several months.

Most of the compounds were obtained as single crystals and analyzed by single crystal X-ray diffraction (XRD) analysis (Figures 1–3).

A survey of the CSD (Cambridge Structural Database, version 5.43, November 2021) was performed with ConQuest[®] (version 2022.2.0) and bond lengths of selected carboranylphosphines and substituted *ortho*-carboranes were obtained.^[46,47] The C1–C2 ($\text{C}_{\text{Cluster}}\text{--C}_{\text{Cluster}}$) bond lengths of the carboranylphosphines compare well with other known compounds (1.727(46) Å).^[46,47] Compared to the C-unsubstituted and C-monosubstituted carboranes, which also show C1–C2 ($\text{C}_{\text{Cluster}}\text{--C}_{\text{Cluster}}$) distances in the same range as already reported

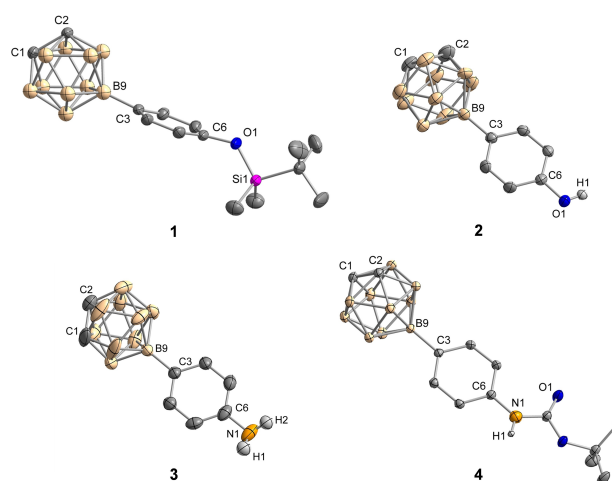


Figure 1. Molecular structures of carboranes 1–4 in the solid state with thermal ellipsoids drawn at the 50% probability level. Hydrogen atoms other than OH and NH are omitted for clarity. Selected bond lengths [Å] of 1: C1–C2 1.620(3); 2: C1–C2 1.623(3); 3: C1–C2 1.596(4); 4: C1–C2 1.625(1).

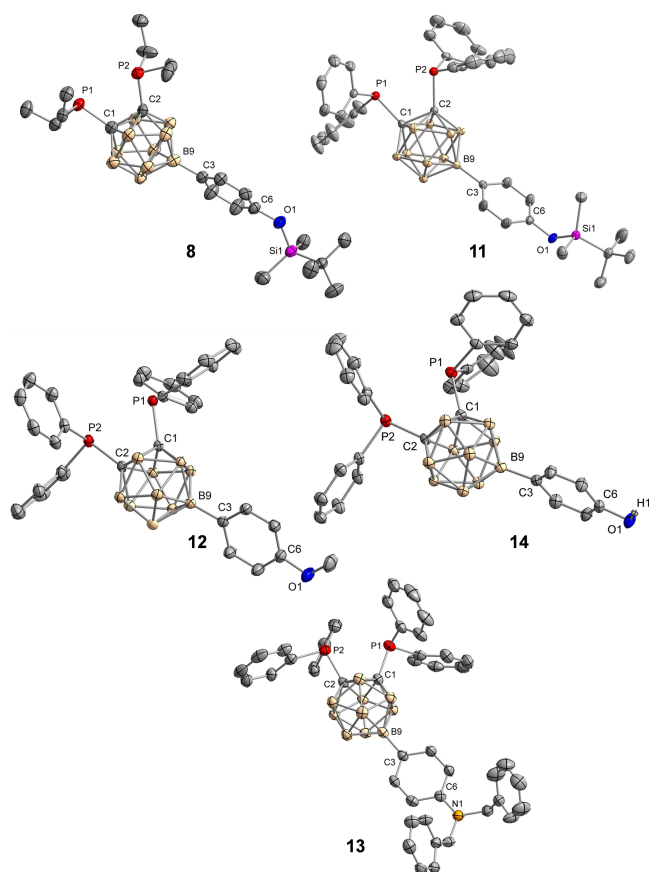


Figure 2. Molecular structures of carboranylphosphines **8** and **11–14** in the solid state with thermal ellipsoids drawn at the 50% probability level. Hydrogen atoms other than OH in **14** are omitted for clarity. Selected bond lengths [Å] of **8**: C1–C2 1.717(10), mean P–C 1.879(1), P1...P2 3.280(2); **11**: C1–C2 1.717(3), mean P–C 1.882(7), P1...P2 3.195(8); **12**: C1–C2 1.717(3), mean P–C 1.881(7), P1...P2 3.224(7); **13**: C1–C2 1.716(2), mean P–C 1.883(7), P1...P2 3.130(1); **14**: C1–C2 1.706(3), mean P–C 1.883(2), P1...P2 3.1827(9).

(1.630(35) Å for C-unsubstituted,^[46,47] and 1.660(19) Å for 1-PR₂-*ortho*-carboranes),^[46,47] a significant increase of the bond length can be observed in the disubstituted compounds (**1**: 1.620(3) Å vs. **8**: 1.716(2) Å) due to the electronic and steric influence of the substituents on the P atoms. As reported in literature, phosphorus atoms convey a unique tunability to the C_{Cluster}–C_{Cluster} distance.^[19]

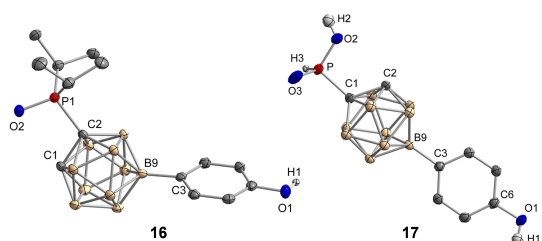


Figure 3. Molecular structures of carboranylphosphines **16** and **17** in the solid state with thermal ellipsoids drawn at the 50% probability level. Hydrogen atoms other than OH and PH are omitted for clarity. Selected bond lengths [Å] of **16**: C1–C2 1.657(3), C2–P 1.867(3); **17**: C1–C2 1.641(2), C1–P 1.825(2).

The mean C–P bond lengths of the carboranylphosphines (C–P between 1.879(1) Å for **8** and 1.883(7) Å for **13**) compare well with other carboranylphosphines (1.898(17) Å).^[46,47] The same is true for the P...P distances (literature: 3.295(15) Å).^[46,47] The obtained results show that there is only a marginal influence of different substituents in the B9 position on the C1–C2 and C–P bond lengths, but, as expected, there is a big influence of the substituents at the phosphorus atom. It should therefore be possible to employ these compounds in metal complexation reactions as was already shown for 1,2-diphenylphosphino-*ortho*-carborane.^[6]

Grafting to Monomers and Dendrimers

The grafting of compounds **2** and **14**, bearing appropriate functionalities for an attachment to different macromolecules, was investigated theoretically and experimentally with various dendritic phosphorus-containing compounds (Figure 4).^[48,49] Such family of dendrimers possess many properties in different fields such as catalysis,^[50] nanomaterials,^[51] and above all nanomedicine,^[52] depending on the type of the terminal (surface) functions. The dendrimer **VIII** was synthesized applying well-known procedures.^[49]

Before starting the synthetic work, DFT calculations (see Supporting Information) were carried out to establish the mechanism of the substitution process of one equivalent of **2** on the hexachlorocyclotriphosphazene core **VI** (Figure 4). The investigation started with the optimization of the deprotonated starting material **2*** and product **G01**, showing greater stability of **G01** by 31.1 kcal mol^{−1} relative to the starting material **VI**. The reaction proceeds similar to an S_N2, with the nucleophilic phenolate **2*** approaching the electrophilic phosphorus center opposite to the leaving group Cl[−], as is also supported by an O–P–Cl angle of 178.3° and a change in geometry from tetrahedral to trigonal-bipyramidal in the transition state (TS) (Scheme 4).^[53,54]

Furthermore, the products of multiple substitution reactions of **VI** with **2*** were optimized to computationally check the stability of such products. Even the sixfold substitution of **VI**

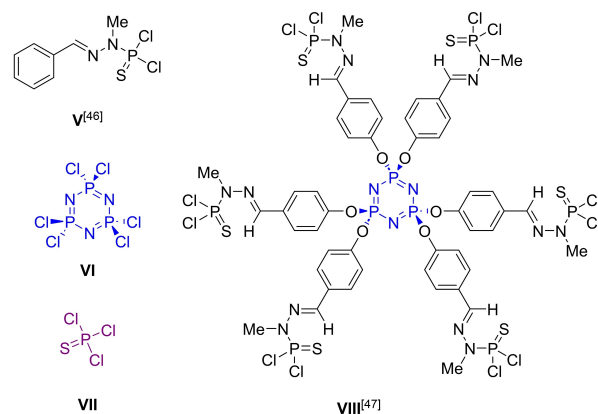
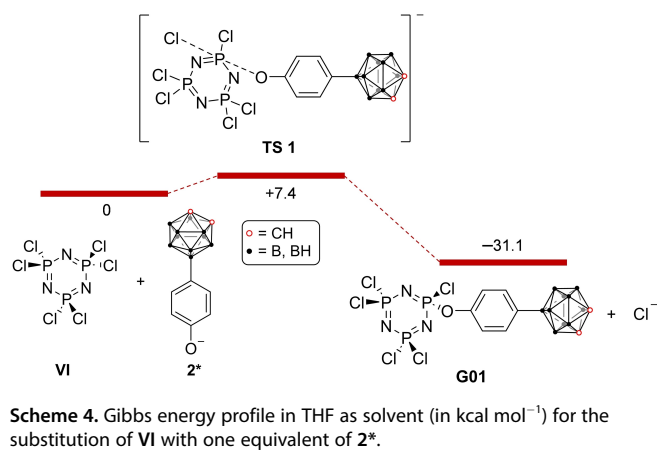
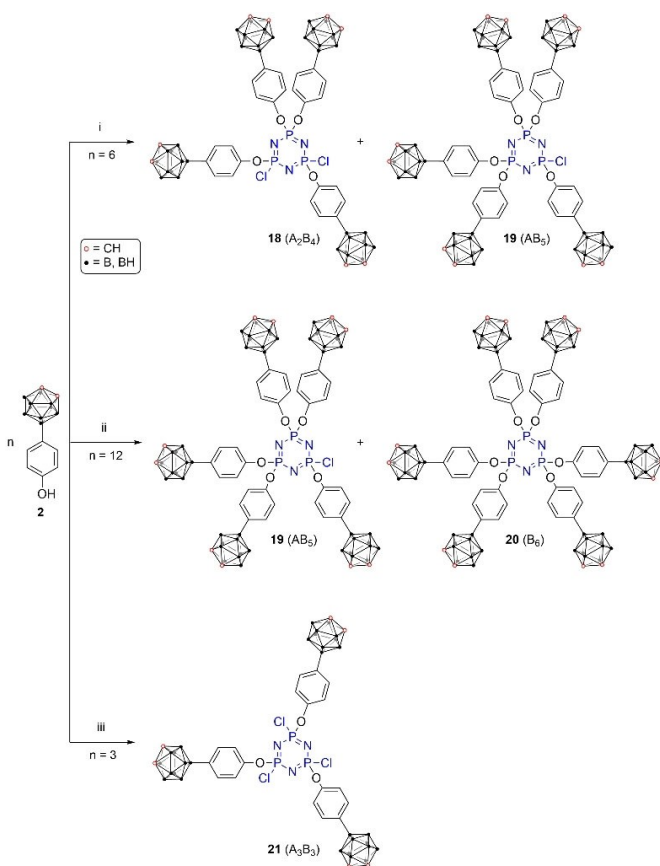


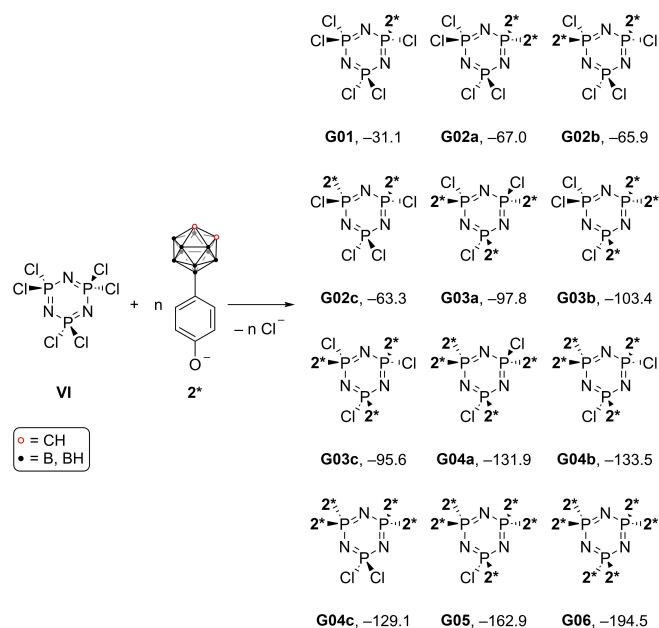
Figure 4. Different scaffolds tested for grafting reactions with carborane derivative **2** and carboranylphosphine **14**.



results in a product with greater stability (by 194.5 kcal mol⁻¹) than the starting material VI (Scheme 5). The energy difference of various substitution patterns was found to be relatively small. With differences between the diastereomers of 1.1 kcal mol⁻¹ (range of van der Waals interactions,^[55] less than the rotation barrier in ethane)^[56] up to 7.8 kcal mol⁻¹ (range of hydrogen



Scheme 6. Reaction of different equivalents of 2 with N₃P₃Cl₆ (VI). (i) VI, K₂CO₃, acetone, 40 °C for 120 h then rt for 72 h; (ii) VI, Cs₂CO₃, THF, rt, 25 d; (iii) VI, K₂CO₃, acetone, rt, 72 h. See Supporting Information for detailed conditions. All compounds were analyzed by NMR spectroscopy and ESI-MS.



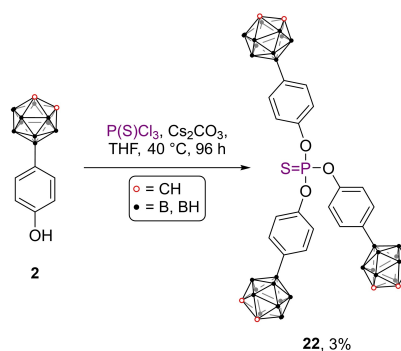
Scheme 5. Computed Gibbs energy values in THF as solvent (in kcal mol⁻¹) for the substitution of VI with n equivalents of 2* relative to the starting material VI.

bonding)^[57] it is evident that no diastereomer is preferentially formed during the reaction.

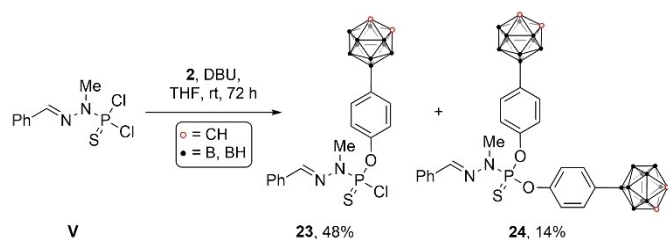
As calculations support the possibility of multiple substitutions of chlorides in VI by phenoxide 2*, we experimentally checked this hypothesis (Scheme 6).

Depending on the amount of 2 used, different dendrimers, varying from a threefold (21, A₃B₃) to a sixfold substitution (20, B₆) could be obtained. The substitution of only one Cl per phosphorus atom yielded 21 almost quantitatively, albeit as a mixture of isomers. However, neither 18 nor 19 and 20 could be purified successfully.

With thiophosphoryl chloride (VII), a threefold substitution was possible, but the product 22 was isolated only in very low yield (Scheme 7), as deboronation occurred with base yielding various *nido*-carborane species (observed by ¹¹B{¹H} NMR spectroscopy). The subsequent chromatographic purification decreased the yield further. The ³¹P{¹H} NMR spectrum only



Scheme 7. Synthesis of the triply substituted derivative 22 of VII using four equivalents of 2. See Supporting Information for detailed conditions.



Scheme 8. Reaction of model compound **V** with 2.1 equivalents of **2**. DBU = 1,8-diazabicyclo[2.4.0]undec-7-ene. See Supporting Information for detailed conditions.

showed one signal at 52.3 ppm which is downfield-shifted compared to $P(S)Cl_3$ (28.6 ppm), corresponding to a trisubstitution. The experimental result agrees with the theoretically (DFT) predicted increased stability (90.4 kcal mol⁻¹) of the trisubstituted product **22** over the mono- (33.5 kcal mol⁻¹) and disubstituted (64.6 kcal mol⁻¹) derivatives compared to the starting material **VII**.

Compound **V** with a $P(S)Cl_2$ function was tested as a model for complex dendrimer **VIII** to obtain further information about the possible substitution on the phosphorus atom. Under the conditions used, a complete conversion to the twofold substituted compound **24** was not observed (14% yield, Scheme 8). This could be due to the slight excess of **2** used in this reaction.

Similar experiments were performed with the first generation of the phosphorus-containing dendrimer **VIII** (Scheme 9).

For reaction (i), the ³¹P{¹H} NMR spectrum showed three broad signals at 68.8, 61.9, and 8.1 ppm indicating three different phosphorus atoms in the formed compound. The typical pattern for carborane species could be further observed

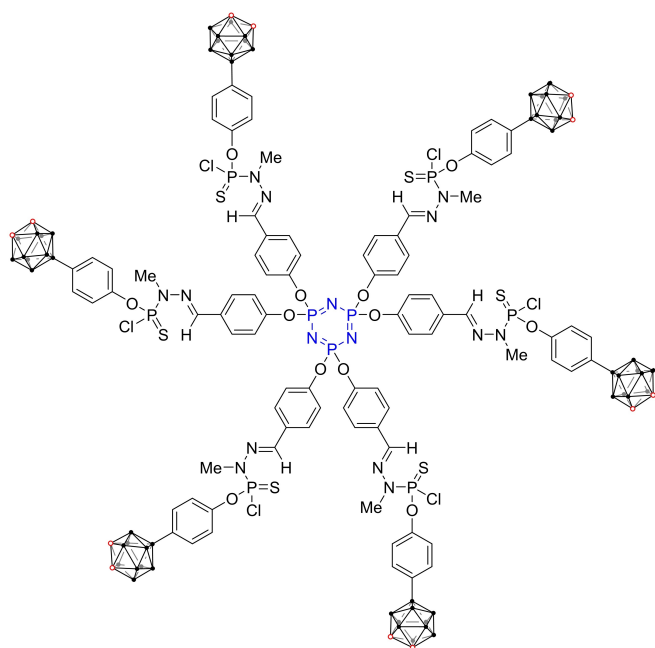
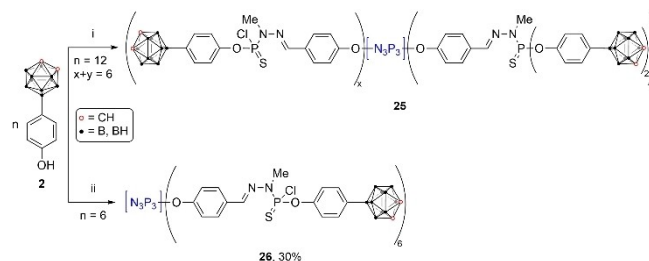


Figure 5. Structure of dendrimer **26**.



Scheme 9. Reaction of different equivalents of **2** ($n = 6$ or 12) with first generation dendrimer **VIII**. (i) **VIII**, Cs_2CO_3 , THF, rt for 72 h then 40 °C for 23 h; (ii) **VIII**, Cs_2CO_3 , THF, rt for 72 h then 40 °C for 23 h. See Supporting Information for detailed conditions.

in the HRMS (ESI⁺) in the range of m/z 1000 to 5000. The ¹H NMR signals are also broad due to the mixture of isomers; thus, no conclusive information about the distribution of **2** at the different branches could be obtained.

In the second reaction (ii), only half of the PCl_2 functions were substituted to avoid possible steric problems. The ³¹P{¹H} NMR spectrum showed only two signals at 67.7 and 8.4 ppm; the number of protons found in the ¹H NMR spectrum also hints at the successful formation of **26** (Figure 5).

With the knowledge obtained for the non-phosphorylated compounds, the more precious carboranylphosphine **14** was employed next in the coupling reaction. Preliminary experiments already indicated an instability of the labile C–P bonds towards the alkali metal carbonates used as bases for the deprotonation of the phenolic moiety. Various inorganic and organic bases were tested, and DBU was identified as suitable candidate, yielding the desired phenolate of carboranylphosphine **14** without decomposition (reaction followed by ³¹P{¹H} NMR spectroscopy). Following reactions with **V–VIII** were, however, not successful. In the reaction with **VI**, the steric bulk and electronic properties of the phosphanyl groups hindered the formation of a sixfold substituted dendrimer. Instead, the known dimer $(PhPCl)_2$,^[58] as well as various by-products which could not be fully characterized were observed.

Conclusion and Outlook

We have demonstrated the syntheses of B9-substituted carboranes (**1–4**) and carboranylphosphines (**8–15**) in acceptable yields. Utilizing different protection and deprotection strategies, suitable building blocks with enhanced reactivity for further grafting to different cores, namely **V** to **VIII**, were prepared. Despite the lack of fully carboranylphosphine-substituted compounds, several carborane-substituted dendrimers were obtained. However, the separation of differently carborane-substituted dendrimers is challenging.

The potentially bidentate carboranylbisphosphines themselves, however, appear to be suitable ligands for metal complexes employed in homogeneous catalysis.^[39]

Furthermore, the selective grafting of a single carborane moiety per $P(S)Cl_2$ function in **VIII** opens the way to introducing additional functionalities by replacing the remaining Cl, for

instance, with water-solubilizing functions, in view of biological experiments.^[4]

X-ray crystallography

CCDC-2300964 (1), CCDC-2300965 (2), CCDC-2300966 (3), CCDC-2300967 (4), CCDC-2303300 (8), CCDC-2300968 (11), CCDC-2300969 (12), CCDC-2300970 (13), CCDC-2300971 (14), CCDC-2303301 (16), and CCDC-2303302 (17) contain 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.

Supporting Information

Supporting information available: Experimental details, NMR spectra, computational methods, absolute energies of all calculated species and their Cartesian coordinates, crystallographic characterization, and tables containing a compilation of C–C bond distances from The Cambridge Crystallographic Data Centre.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: Carboranes · Dendrimers · Phosphines · Phosphanylation · Substituent effects

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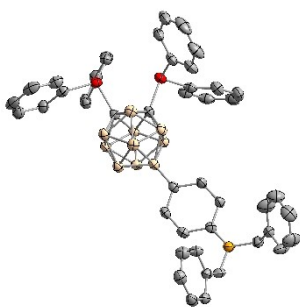
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RESEARCH ARTICLE

Several *ortho*-carboranes functionalized in the B9 position were prepared and grafted to phosphorus dendritic compounds. 1- or 1,2-phosphanyl-substituted carboranes were also synthesized for eventual applications in catalysis or the medicinal sector.



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Carboranylphosphines: B9-Substituted Derivatives with Enhanced Reactivity for the Anchoring to Dendrimers

