Communication

Regioselective Nucleophilic Alkylation/Arylation of B-H Bonds in o-Carboranes: An Alternative Method for Selective Cage Boron Functionalization

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Regioselective Nucleophilic Alkylation/Arylation of B-H Bonds in *o*-Carboranes: An Alternative Method for Selective Cage Boron Functionalization

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Supporting Information Placeholder

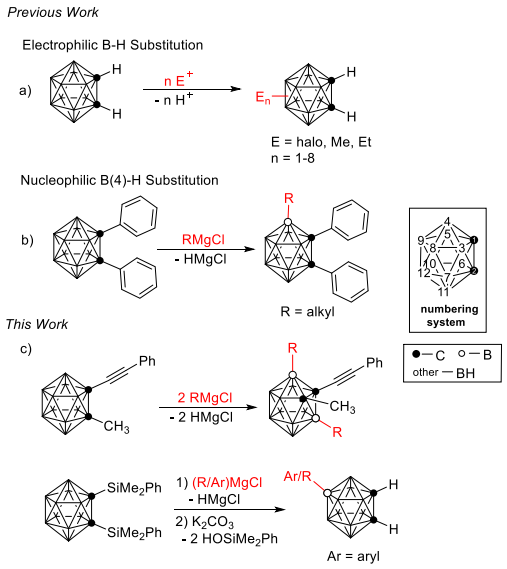
ABSTRACT: A new protocol for regioselective nucleophilic cage B-H substitution in *o*-carboranes has been proposed, which is complementary to the strategies of transition metal catalysis and electrophilic substitution. Magnesium-mediated site-selective nucleophilic cage B(3,6)-H and B(9)-H substitution reactions of *o*-carboranes give a series of B(3,6)-dialkylated and B(9)-alkylated/arylated *o*-carboranes in high yields. Both steric and electronic factors of cage C-substituents play crucial roles in controlling the site-selectivity.

Carboranes are carbon-boron molecular clusters with 3-D aromaticity (σ-aromaticity),[1] which are often viewed as analogs to 2-D benzenes (π-aromaticity).[2] They share some common features of aromatic molecules such as thermal stability and ability to undergo electrophilic substitution reactions. Strong electrophile E^+ attacks preferentially B-H vertices most distant from the cage carbon atoms in icosahedral framework, leading to the formation of new B-E bond(s) and releasing of H^+ (Scheme 1a).[1a,3] Such reaction proceeds stepwise in the order B(9,12)-H > B(8,10)-H > B(4,5,7,11)-H >> B(3,6)-H, which corresponds to the charge distribution of the cage (see Scheme 1 for numbering system).[4] It is noted that the degree of substitution in the aforementioned electrophilic reactions has hardly been controlled owing to electronic effects.[1a,3] However, in the case of transition metal electrophiles, selective cage B-H metalation has been achieved via tuning the bulkiness of the coordinating ligands and/or directing group strategy, which has led to the development of catalytic selective functionalization of cage B-H vertices.[5,6]

On the other hand, similar to nucleophilic benzene C-H substitution,[7] nucleophilic B-H substitution in *o*-carboranes was unknown till our recent publication (Scheme 1b).[8] Generally, strong nucleophiles such as MeO^- and F^- first attack the most electron-deficient cage B(3) that is bonded to both cage carbon atoms, followed by an attack of the second equivalent of the nucleophile on the same boron atom to remove one B-H vertex from *o*-carborane framework, leading to the formation of dicarbollide ion [*nido*-$C_2B_9H_{11}^{2-}$],[9] the most popular inorganic π ligand.[10] We thought that nucleophilic cage B-H substitution could be achieved if the second attack of the nucleophile could be blocked and the departure of H^- from the cage boron could be promoted by a hydride abstractor. Our recent proof-of-concept study shows that the replacement of two C-H vertices with two C-Ph ones in *o*-carborane enables regioselective nucleophilic B(4)-H substitution with Grignard reagents RMgX for the first time (Scheme 1b).[8]

In such a nucleophilic cage B(4)-H substitution reaction, the presence of two aryl groups on two cage carbon atoms is vital to decrease the electron density on B(4)-H vertex and to prevent the most electron-deficient B(3)-H one from being attacked by the nucleophiles. These results indicate the huge impact of cage C-substituents on nucleophilic cage B-H substitution reactions, suggesting that selective nucleophilic cage B-H substitution among ten B-H vertices may be achieved by tuning electronic/steric properties of two cage C-substituents. In this Communication, we report organomagnesium-mediated regioselective nucleophilic alkylation/arylation of *o*-carboranes at the most electron deficient B(3,6) positions or at the most electron-rich B(9,12) sites (Scheme 1c).

Scheme 1. Cage B-H Substitution Reactions

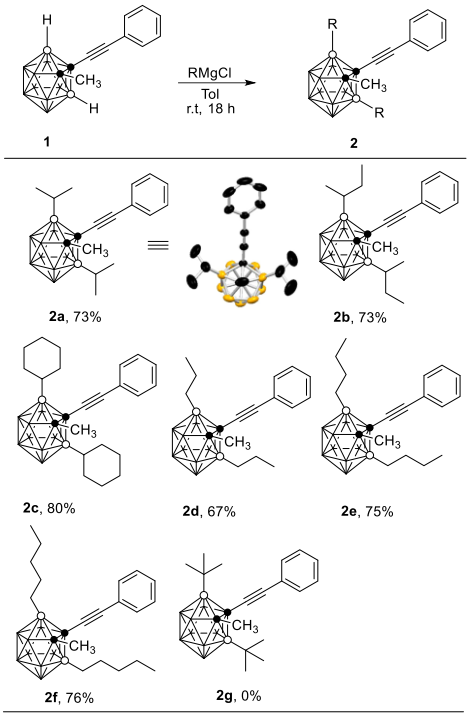


Our investigation began with the functionalization at the most electron-deficient B(3,6) sites. Though B(3,6)-H bonds are the most susceptible to nucleophilic attack by hard nucleophiles such as MeO^- and F^-, they do not react with soft nucleophiles such as Grignard reagents and organolithium compounds. Previous work indicates that aryls on cage carbons can sterically block B(3,6) positions. Thus, electron-withdrawing yet sterically less bulky cage C-substituents are desired. In this regard, acetylene is an appropriate moiety. Unfortunately, many attempts to prepare 1,2-$(C{\equiv}CR)_2$-*o*-carborane failed. We then prepared 1-methyl-2-phenylethynyl-*o*-carborane (**1a**) as the model substrate. Reaction of **1a** with 1 equiv of isopropyl magnesium chloride at room temperature in toluene for 18 h gave 1-methyl-2-phenylethynyl-3,6-diisopropyl-*o*-carborane (**2a**) in 21% GC yield (entry 1, Table S1 in the SI). If the amount

of ^{i}PrMgCl was increased to 2.1 equiv, **2a** was generated in quantitative GC yield (73% isolated yield; entry 3, Table S1).

With the optimal reaction conditions in hand, we explored the substrate scope and the results were summarized in Table 1. Both primary and secondary alkyl magnesium chlorides underwent smoothly such nucleophilic substitution reaction to give 1-methyl-2-phenylethynyl-3,6-dialkyl-*o*-carboranes (**2**) in good to high yields. No reaction with ^{t}BuMgCl was observed, probably due to steric reasons. It is noteworthy that these 3,6-dialkylated *o*-carboranes may only be prepared using deboronation-capitation-deboronation-capitation method.[1a,11] Transition metal catalyzed cross-coupling methodology is not feasible for the synthesis of cage B-alkylated *o*-carboranes owing to facile β-hydrogen elimination reactions. Electrophilic B-H substitution does not proceed at B(3,6)-H vertices.[1a,3] Thus, nucleophilic B-H substitution provides a complementary method for convenient synthesis of 3,6-dialkyl-*o*-carboranes.

Table 1. Synthesis of 3,6-Dialkylated *o*-Carboranes[a]



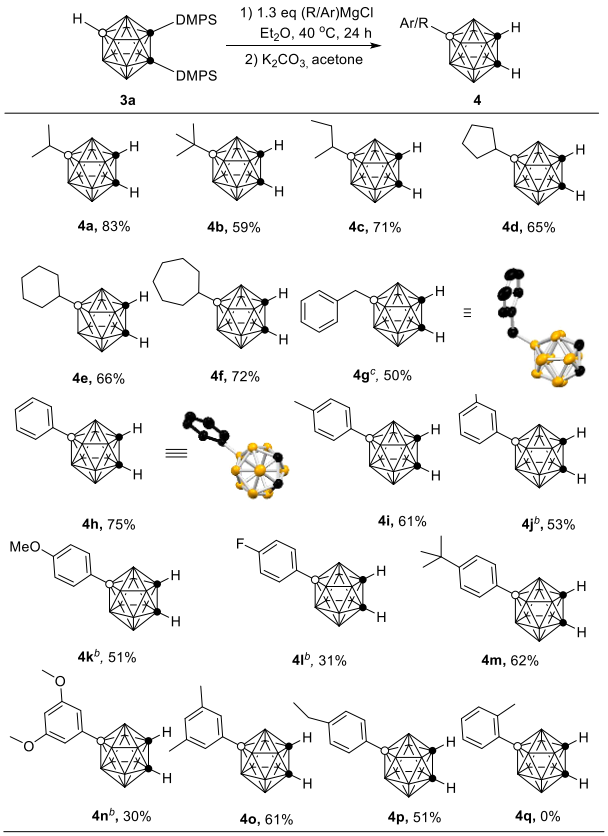
[a]Isolated yields.

Compounds **2** were characterized by ^{1}H, ^{13}C, and ^{11}B NMR spectroscopy as well as high-resolution mass spectrometry. Their ^{11}B NMR spectra exhibited a similar pattern of 2:1:1:3:3 spanning the range of -16 to 1 ppm with the substituted cage boron being observed at *ca.* 1 ppm as indicated by ^{1}H coupled ^{11}B NMR spectra. Single-crystal X-ray analyses of **2a** unambiguously confirm cage B(3,6) selectivity.

Having achieved nucleophilic B-H substitution at B(3,6) and B(4,5,7,11) sites,[8] we wondered if the nucleophilic B-H substitution could be realized at distal positions. This seems very challenging since (1) the electron density at B(8,9,10,12) positions is much higher than that of B(3,6) and B(4,5,7,11) vertices, and (2) the electronic properties of cage C-substituents have little impact on the distal B(8,9,10,12) sites in such σ-system. These analyses suggest that relatively electron-deficient B(3,4,5,6,7,11) vertices must be protected in order to achieve nucleophilic substitution at distal positions. With this in mind, we chose 1,2-$(TMS)_2$-*o*-carborane (TMS = Me_3Si) as the model substrate since (1) these groups can be easily removed after the reactions, releasing the two cage carbons for further functionalization, and (2) space-filling model indicates that B(3,4,5,6,7,11) vertices can be sterically protected by two TMS groups on cage carbons (*vide infra*).

We initially examined the reaction of 1,2-$(TMS)_2$-*o*-carborane with 1.2 equiv of ^{i}PrMgCl in Et_2O at 60 °C for 24 h, followed by desilylation in acetone via the addition of 10 equiv of K_2CO_3, which gave 9-^{i}Pr-*o*-carborane (**4a**) in 75% GC yield. We noted that the partial desilylation product was observed by GC before adding K_2CO_3, indicating that the C(cage)-$SiMe_3$ bonds were not so stable under the basic conditions. It has been documented that the stability of C-SiR_3 bond is closely related to steric hindrance of R substituents.[12] Thus, the effects of silyls on the nucleophilic substitution reactions were evaluated and the results were compiled in Table S2 in the SI.

Table 2. Synthesis of 9-(R/Ar)-*o*-carboranes[a]



[a]Isolated yield. [b]60 °C in toluene

It was found that 1,2-$(DMPS)_2$-*o*-carborane (**3a**; DMPS = dimethylphenylsilyl) afforded **4a** in 80% GC yield (entries 1-3, Table S2). Screening the amount of Grignard reagent indicated that 1.3 equiv offered the best result (entries 4-7, Table S2). Higher loadings led to the formation of disubstituted species (entries 6-7 Table S2). In view of the yield and selectivity of **4a**, the reaction conditions established in entry 5 in Table S2 were chosen as the optimal conditions.

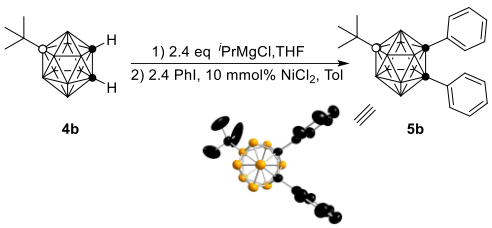
Under the above optimized reaction conditions, the substrate scope was examined, and the results were summarized in Table 2. It showed that both alkyl and aryl Grignard reagents

were compatible with the reaction, giving cage B(9)-substituted *o*-carboranes. Generally, alkyl Grignard reagents offered higher yields of **4** than those of aryl Grignard reagents. Heteroatom-containing Grignard reagents reacted slower and required higher temperature (60 °C) yet gave lower yields of **4** (**4k**, **4l** and **4n**), due probably to some interactions between these heteroatoms and Mg^{2+}. Sterically bulky tertiary carbon nucleophiles such as ^{t}BuMgCl offered a relatively lower yield of **4b**, whereas *o*-tolyl magnesium chloride failed to afford any product **4q**. On the other hand, CH_3MgBr generated an inseparable mixture of isomeric species.

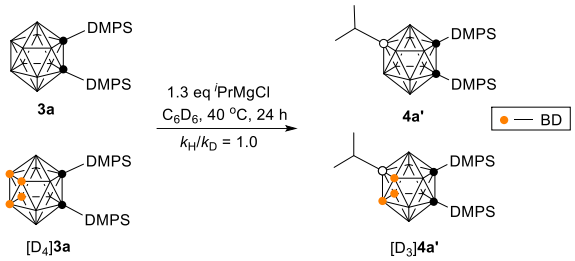
Compounds **4** were characterized by ^{1}H, ^{13}C, and ^{11}B NMR spectroscopy as well as high-resolution mass spectrometry. Their ^{11}B NMR spectra exhibited a similar pattern of 1:1:2:4:2 spanning the range of -16 to 11 ppm with the substituted cage boron being observed at *ca.* 11 ppm as indicated by ^{1}H coupled ^{11}B NMR spectra. The molecular structures of **4g** and **4h** were further confirmed by single-crystal X-ray analyses.

To eliminate any ambiguities of site-selectivity, compound **4b** was converted to **5b** using Ni-catalyzed cage C-arylation method (Scheme 2).[13] Single-crystal X-ray analyses of **5b** unambiguously confirmed the cage B(9) selectivity.

Scheme 2. Synthesis of 5b



Scheme 3. Kinetic Isotope Effect



To gain some insight into the reaction pathway, several control experiments were carried out. Treatment of **3a** with 1.3 equiv of ^{i}PrMgCl in the presence of 1,1-diphenylethylene gave **4a** in 75% yield under standard reaction conditions.[14] No change was observed if the reaction ran in dark. These results suggested that the above B(9)-functionalization reaction may not involve a radical pathway. On the other hand, the formation of H_2 at 4.5 ppm was observed in the ^{1}H NMR spectrum of the hydrolysis product from the reaction of **3a** with ^{i}PrMgCl (see Figure S5 in the SI), which was further confirmed by GC-TCD analysis. Such H_2 was considered to originate from the hydrolysis of the resultant MgHCl.[7] Furthermore, parallel reactions of **3a** and [D_4]**3a** under the standard reaction conditions (Scheme 3) gave a KIE value of 1.0 by comparison of their reaction rates. This result suggested that the B-H bond-breaking may not be involved in the rate-determining step (see Figure S6).

To understand the site-selectivity at B(9), density functional theory (DFT) calculations were performed at the B3LYP/6-311++G(d,p) level of theory[15] for 1,2-$C_2B_{10}H_{12}$, 1-Me-2-(C≡CPh)-1,2-$C_2B_{10}H_{10}$ (**1a**), 1,2-Ph_2-1,2-$C_2B_{10}H_{10}$, 1,2-$(DMPS)_2$-1,2-$C_2B_{10}H_{10}$ (**3a**), and 1,2-$(TMS)_2$-1,2-$C_2B_{10}H_{10}$ (**3c**). The space-filling models of the optimized structures of both **3a** and **3c** clearly show that B(3,4,5,6,7,11)-H vertices are sterically blocked by two silyl groups and only B(8,9,10,12)-H ones are accessible by nucleophiles (see Figure S7 in the SI).

On the other hand, NBO (natural bond orbital) analyses show that (1) the impact of electronic effects of cage C-substituents on the vertex charge follows the order: C(1,2) > B(3,6) > B(4,5,7,11) > B(8,9,10,12) (see Table S3 in the SI) , and (2) the calculated charge of the B(9/12)-H vertex (*ca.* -0.06) in all compounds aforementioned regardless of cage C-substituents is less negative than that of B(8/10)-H one (*ca.* -0.08), indicating that B(9/12)-H vertex is more susceptible to nucleophilic attack than B(8,10)-H one.

On the basis of above analyses, it is rational to suggest that the B(9)-selectivity in the current organomagnesium-mediated nucleophilic substitution reaction is controlled by both steric and electronic factors of the cage C-substituents. The NBO analyses also indicate that the vertex charge of B(3,6)-H in 1-Me-2-(C≡CPh)-1,2-$C_2B_{10}H_{10}$ (**1a**) is calculated to be +0.241, which is more electron-deficient than that of B(3,6)-H one (+0.214) in *o*-carborane (see Table S3 in the SI). This offers an explanation on why **1a** reacts well with Grignard reagents whereas *o*-carborane does not.

In summary, a new protocol for regioselective nucleophilic cage B-H substitution in *o*-carboranes has been proposed and validated: (1) for B(3,6)-H nucleophilic substitution, less bulky electron-withdrawing substituents on cage carbons is necessary, (2) for B(4,5,7,11)-H nucleophilic substitution, an appropriate size of electron-withdrawing substituents (such as aryls) on both cage carbons are required,[8] and (3) for B(9,12)-H nucleophilic substitution, very sterically hindered groups (such as silyls) on both cage carbons are needed to block B(3,4,5,6,7,11)-H vertices. This transition-metal-free strategy is complementary to those of transition metal-catalyzed regioselective functionalization of *o*-carboranes,[5] and electrophilic substitution reactions,[1a,3] enabling the facile synthesis of cage B-alkylated/arylated carboranes in a regioselective and controlled manner. This work opens a new window to the controlled functionalization of boron clusters.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, characterization of the products (PDF), and crystal structures (CIF)

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Notes

The authors declare no competing financial interests.

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Graphic Abstract