Journal of Organometallic Chemistry 694 (2009) 1646–1651

Contents lists available at ScienceDirect

Journal of Organometallic Chemistry

journal homepage: www.elsevier.com/locate/jorganchem

Magnesium-assisted intramolecular demethylation utilizing carborane C–H geometry

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ARTICLE INFO

Article history:
Received 3 October 2008
Received in revised form 19 November 2008
Accepted 19 November 2008
Available online 30 November 2008

Keywords:
Carborane
Hydrogen bond
Demethylation
Grignard reagent

ABSTRACT

A novel type of demethylation reaction was designed in the Pd-catalyzed coupling reaction of iodocarboranes with several Grignard reagents, $CH_3OPhMgBr$. 3-Iodo-*o*-carborane **1** reacted with 2-$CH_3OPhMgBr$ to afford the corresponding phenol compound **4b** in 78% yield. However, when compound **1** was reacted with the other Grignard reagents, the corresponding methoxyl compounds **5a** and **6a** were obtained in excellent yields. 2-Iodo-*p*-carborane **3** reacted with 2-$CH_3OPhMgBr$ to afford the corresponding phenol **8b** in 50% yield and the methoxyl compound **8a** in 41% yield. The carborane C–H geometry, which can form an intramolecular C–H···O hydrogen bonding, seems to be an important factor in the demethylation process. To examine the mechanism of the demethylation, compounds **1** and **4a** were treated with CH_3MgBr and quenched with D_2O. While the two C–Hs of compound **1** were completely deuterated, compound **4a** showed a replacement of one C–H with C–D. Therefore, we propose a mechanism involving intramolecular C–Mg···O interaction instead of intramolecular C–H···O interaction, via the generation of 3-iodo-*o*-carboranyl$(MgBr)_2$, **11**. Since it is also possible to replace the C–Hs with various metals other than Mg, new applications of carboranes in coordination and metal catalyst chemistry can be expected.

1. Introduction

Applications of dicarba-*closo*-dodecaborane (carborane) as a building block for bioactive compounds, supramolecular assemblies, metal complexes, and macrocyclic molecules have recently been addressed by many researchers [1]. Carborane is an icosahedral structure and each vertex bears a hydrogen atom. It has high hydrophobicity, which is similar to that of hydrocarbons, and shows strong hydrophobic interactions with various molecules [2]. Furthermore, the C–H hydrogens (C–Hs) of carborane are highly acidic because of the electron-deficient nature of the carborane cage: the pK_a values reported for ortho-, meta- and para-carborane are 22.0, 25.6 and 26.8, respectively [3]. Therefore, the C–Hs have the potential for hydrogen bond (H-bond) formation. These contrasting features, i.e., high hydrophobicity and H-bonding ability, both favor strong intramolecular and intermolecular interactions. Thus, supramolecular assemblies utilizing carborane are expected to be generated through hydrophobic interaction and H-bonding via the acidic C–H vertices. The C–Hs interact with various substituents [4], such as halogens [5], π-rich systems [6] and H-bond acceptors [7] in the solid state. On the other hand, we are interested in the interactions of the C–Hs in solution and recently reported that C–H of *o*-carborane forms an intramolecular H-bond with the oxygen atom of a methoxyl (OCH_3) group in the solid and solution states [8]. We have also reported a proton-driven molecular switch based on C–H···O interaction of *p*-carborane in solution (Chart 1) [9]. In view of the coordinating ability of the C–H to oxygen, we focused on 3-substituted *o*-carborane, because *o*-carborane C–H is the most acidic among the carborane isomers and there are two acidic C–Hs. 3-Iodo-*o*-carborane (**1**) [10] reacts with a variety of Grignard reagents in the presence of Pd catalyst to afford 3-substituted *o*-carborane in high yield [11].

Vast numbers of natural products contain a phenolic hydroxyl (OH) group(s). In developing a synthesis of any phenol-containing product, protection is often mandatory to prevent reaction with oxidizing agents and electrophiles, or reaction of the nucleophilic phenoxide ion with even mild alkylating and acylating agents. Ethers are among the most widely used protective groups for phenol in organic synthesis. Methyl ether is the simplest and most robust, and can be formed and removed under a wide variety of conditions [12]. In the mechanism of demethylation, the most important step is the activation of the oxygen atom in the ether bond by strong interaction with a Lewis or Brønsted acid [13]. It is also possible to conduct demethylation with Grignard reagent, CH_3MgI [14]. Since the mechanism involves activation of oxygen atom by coordination of magnesium and nucleophilic attack on the carbon atom of the methyl group by I^- as a soft base, the reaction hardly progresses with Grignard reagents such as CH_3MgBr, unless there is additional activation of the oxygen atom [15].

Based upon the carborane C–H geometry, we designed a novel type of demethylation utilizing the Pd-catalyzed coupling reaction

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doi:10.1016/j.jorganchem.2008.11.044

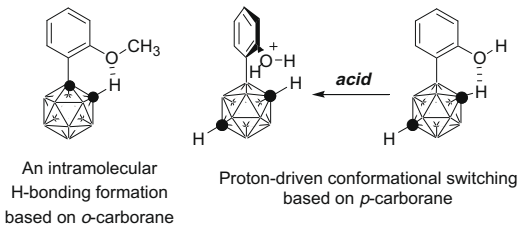


Chart 1. Intramolecular C–H···O interactions based on *o*-carborane and *p*-carborane C–Hs in solution.

of 3-iodo-*o*-carborane (**1**) with 2-methoxyphenylmagnesium bromide (2-$CH_3OPhMgBr$), anticipating that strong coordination of the C–Hs with oxygen atom of the OCH_3 group of the corresponding methoxyphenyl compound **4a** would assist the demethylation during the coupling reaction to afford the corresponding compound **4b** (Scheme 1). In this paper, we describe Pd-catalyzed coupling reactions of 3-iodo-*o*-carboranes (**1**), 9-iodo-*o*-carborane (**2**) [16] and 2-iodo-*p*-carborane (**3**) [17] with isomers of $CH_3OPhMgBr$ (Scheme 2). We expected that intramolecular C–H···O interaction would play an important role in the reaction mechanism of this novel type of demethylation.

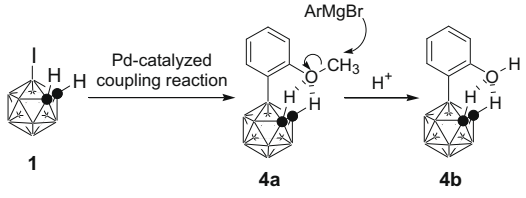
2. Results and discussion

2.1. Pd-catalyzed coupling reaction of iodocarboranes with isomers of $CH_3OPhMgBr$

Pd-catalyzed coupling reactions were performed as follows: A solution of iodocarborane, Grignard reagent (8.5 equiv.) generated from Mg and bromoanisole in THF, $Pd(PPh_3)_2Cl_2$ (10 mol%) and CuI (10 mol%) in THF was refluxed for 34 h (Scheme 2) [11]. Yields of products are shown in Table 1. Interestingly, the reaction of 3-iodo-*o*-carborane (**1**) with 2-$CH_3OPhMgBr$ afforded **4b** as a major product in 78% yield and *C*-methylated phenol (**4c**) as a minor product in 10% yield (Chart 2); none of **4a** was obtained (entry 1). When the amount of Grignard reagent was reduced (4.0 equiv.), the yield of **4b** markedly decreased, and **4a** was isolated as a major product in 56% yield (entry 2). After quenching for 24 h, compounds **4a** and **4b** were isolated in 34% and 25% yields, respectively (entry 3). On the other hand, 3-$CH_3OPhMgBr$ and 4-$CH_3OPhMgBr$ reacted with **1** to afford only the corresponding methyl ether products **5a** and **6a** in excellent yields (entries 4 and 5).

To investigate whether the demethylation is caused by 2-$CH_3OPhMgBr$, the reaction of 9-iodo-*o*-carborane (**2**), which has an iodine atom apart from the C–Hs, with 2-$CH_3OPhMgBr$ was performed, and afforded the corresponding methyl ether product (**7a**) in 95% yield (entry 6). This result shows that the demethylation is not caused by an effect of 2-$CH_3OPhMgBr$, but involves a synergistic effect between **1** and 2-$CH_3OPhMgBr$. Thus, we speculated that the demethylation process was related to an intramolecular C–H···O interaction in the products, because only compounds **4a** or **4b** among these products can have an intramolecular C–H···O interaction between C–H and the OCH_3 or OH group.

Next, the reactions of 2-iodo-*p*-carborane (**3**) with isomers of $CH_3OPhMgBr$ were performed to further evaluate the relationship between intramolecular C–H···O interaction and demethylation. The reaction of **3** with 2-$CH_3OPhMgBr$ gave a mixture of methyl ether (**8a**) and demethylated product (**8b**) in 41% and 50% yields, respectively (entry 7). The demethylation rate of **8a** was clearly slow as compared with that of 3-(2-methoxyphenyl)-*o*-carborane (**4a**). When the amount of Grignard reagent was decreased from 8.5 equiv. to 3.1 equiv. in the reaction of **3** with 2-$CH_3OPhMgBr$, the methyl ether product **8a** was afforded in 94% yield and none of the phenol **8b** was obtained (entry 8). Compound **3** was also reacted with 3-$CH_3OPhMgBr$ or 4-$CH_3OPhMgBr$ to give the corresponding methyl ether products **9a** and **10a** in 82% or 90% yields, respectively (entries 9 and 10). The phenol was not formed, because H-bond formation can not occur between **3** and these Grignard reagents. It seems that phenol formation depends on the number of C–Hs available to interact intramolecularly with the oxygen atom of the OCH_3 group.



Scheme 1. Pd-catalyzed coupling reaction of 3-iodo-*o*-carborane with 2-$CH_3OPhMgBr$ and consecutive demethylation assisted by intramolecular C–H···O interaction.

2.2. Deuteration of the C–Hs in the presence of Grignard reagent and a possible reaction mechanism

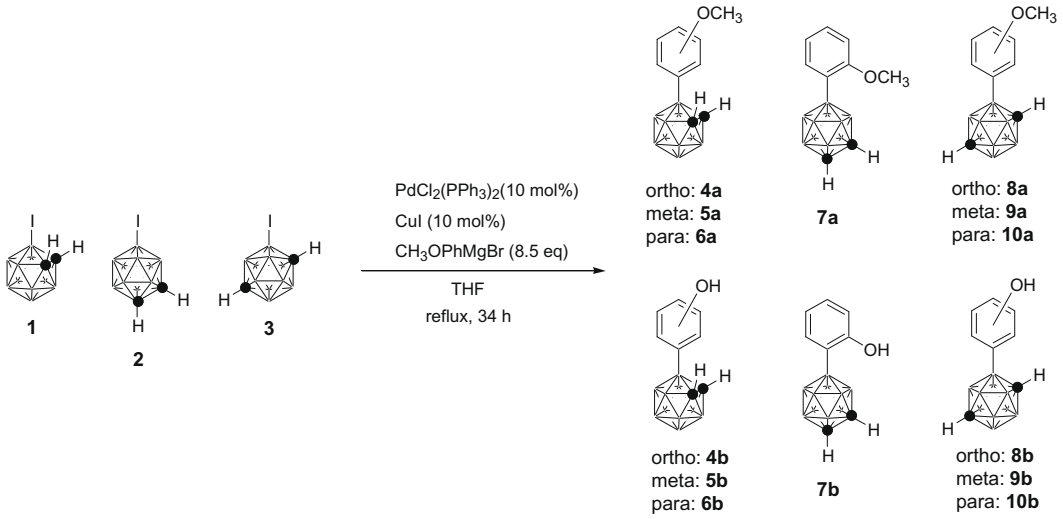
The C–Hs were easily deprotonated with various Grignard reagents to generate carborane *C*–magnesium (C–Mg) halide species. Thus, the demethylation in this system would be facilitated by C–Mg···O interaction as well as by C–H···O interaction. There are three possible mechanisms for the demethylation of **4a** with Grignard reagent (Scheme 3).

First, the demethylation of **4a** with methylmagnesium bromide (CH_3MgBr) was examined under the same conditions as used for the coupling reaction; [**4a**] = 0.15 M in THF, CH_3MgBr (8.5 equiv.), reflux for 34 h (Method A; Scheme 4). Although the corresponding phenol **4b** was obtained in 20% yield, **4a** was recovered in 48% yield. In addition, *C*-methylated compounds **4c** and **4d** were isolated in 13% and 15% yield, respectively. Next, we examined the participation of Pd and Cu catalysts in the demethylation process. When 10 mol% of $PdCl_2(PPh_3)_2$ and 10 mol% of CuI were added to the reaction mixture, or 2-$CH_3OPhMgBr$ was used instead of CH_3MgBr, there were no significant change in the yields of the products: compounds **4a**–**4d** were isolated in 49%, 22%, 11% and 15% yields, respectively (Method B; Scheme 4). Pd and Cu catalysts had no influence on the demethylation, and efficient demethylation of **4a** was not obtained under these conditions compared to those of entry 1 in Table 1. Why was the demethylation efficiently accelerated by the Pd-catalyzed coupling reaction of **1** with Grignard reagent?

To answer this question, we deuterated the C–Hs by quenching with cold deuterated water (D_2O) after the treatment of **4a** with CH_3MgBr (8.5 equiv.) under reflux for 2.5 h. Interestingly, only one C–H of **4a** was found to have been converted to C–D when the replacement efficiency was evaluated by means of integration of the C–H signals in the NMR spectrum (Fig. 1). This result indicates that one of the two C–Hs was deprotonated with CH_3MgBr and converted to C–MgBr.

On the other hand, when compound **1** was treated with CH_3MgBr (8.5 equiv.) under the same conditions, both C–Hs were completely converted to C–Ds. The C–Hs of **1** disappeared without any change of the carborane B–H peaks in the NMR spectra (Fig. 2). This result means that both C–Hs were converted to C–MgBr.

From the results of demethylation with CH_3MgBr and the deuteration studies, it seems that the number of C–Hs replaced with C–MgBr is correlated with the yield of phenols. In addition, the reaction of **3** with 2-$CH_3OPhMgBr$ to afford a mixture of **8a** and

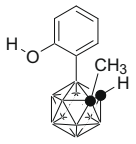


Scheme 2. Pd-catalyzed coupling reactions of iodocarboranes with $CH_3OPhMgBr$.

Table 1
Pd-catalyzed coupling reaction of iodocarborane with Grignard reagent.

Entry	Starting material		Grignard reagent	Yield of product (%)[b]	
				Methoxyl (CH_2OPh)	Hydroxyl (HOPh)
1	3-Iodo-*o*-carborane	1	2-$CH_3OPhMgBr$	0(**4a**)	78 (**4b**)[c]
2		1	2-$CH_3OPhMgBr$	56 (**4a**)	6 (**4b**)[d]
3		1	2-$CH_3OPhMgBr$	34 (**4a**)	25 (**4b**)[e]
4		1	3-$CH_3OPhMgBr$	99 (**5a**)	0 (**5b**)
5		1	4-$CH_3OPhMgBr$	98 (**6a**)	0 (**6b**)
6	9-Iodo-*o*-carborane	2	2-$CH_3OPhMgBr$	95 (**7a**)	0 (**7b**)
7	2-Iodo-*p*-carborane	3	2-$CH_3OPhMgBr$	41 (**8a**)	50 (**8b**)
8		3	2-$CH_3OPhMgBr$	94 (**8a**)	0 (**8b**)[f]
9		3	3-$CH_3OPhMgBr$	82 (**9a**)	0 (**9b**)
10		3	4-$CH_3OPhMgBr$	90 (**10a**)	0 (**10b**)

Reactions condition: [substrate] = 0.15 M in THF, Grignard reagent (8.5 equiv.), $Pd(PPh_3)_2Cl_2$ (10 mol%), CuI (10 mol%), reflux for 34 h.
[b] Yield of isolated product.
[c] *C*-methyl compound (**4c**) was isolated in 10% yield.
[d] Grignard reagent (4.0 equiv.).
[e] *Reaction time*: 24 h.
[f] *Reaction conditions*: 2-$CH_3OPhMgBr$ (3.1 equiv.), 9 h.



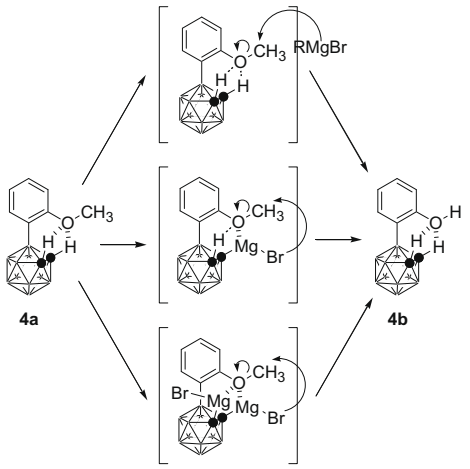
4c

Chart 2. The structure of **4c**.

8b can be explained by the replacement of one C–H of **3** with C–MgBr (entry 7; Table 1). It seems likely that C–MgBr interacts with OCH_3 through a C–Mg···O interaction. Therefore, we concluded that the demethylation was mainly caused by C–Mg···O interaction and depended upon the number of C–Mg···O interactions.

A plausible mechanism for the demethylation process is illustrated in Scheme 5. Compound **1** reacts with an excess of 2-$CH_3OPhMgBr$ to generate *o*-carboranyl$(MgBr)_2$ (**11**), followed by Pd-catalyzed coupling to afford 3-(2-CH_3OPh)-*o*-carboranyl$(MgBr)_2$ (**12**), in which intramolecular C–Mg···O interactions might activate the oxygen atom of the methoxyl group. Bromide anion (Br^-) attacks at the backside of the carbon atom of the methoxyl group in compound **12** to afford intermediate **13** with elimination of CH_3Br. Finally, compound **13** is quenched with H_3O^+ to afford the demethylated compound **4b** and with CH_3Br generated within the system to afford compound **4c** as a by-product.

The dual activation process of the OCH_3 with two C–Mg is the key to efficient demethylation. The spherical structure of the carborane cage plays an important role in the demethylation, as well as intramolecular C–H···O and C–Mg···O interactions. That is, the three-dimensionally fixed geometry of carborane C–Hs, which can form intramolecular H-bonds, makes it possible for the demethylation to accompany the Pd-catalyzed coupling reaction. This reaction appears to have great potential, because the carborane C–Hs can be replaced with various metals, thereby opening up new fields in metal coordination chemistry.



Scheme 3. Possible demethylation mechanisms involving C–Mg···O or C–H···O interaction.

3. Conclusion

We found a novel type of demethylation reaction that accompanies the Pd-catalyzed coupling reaction of **1** and **3** with 2-CH_3OPhMgBr. Compounds **1** and **3** reacted with 2-CH_3OPhMgBr to afford the corresponding phenol compounds **4b** and **8b** in 78% and 50% yield, respectively. We propose a mechanism involving intramolecular C–Mg···O interaction instead of intramolecular C–H···O interaction, based on the results of deuteration studies with compounds **1** and **4a**. Since it is possible to replace the C–Hs with various metals, novel intermolecular interactions in solution may become available in coordination chemistry.

4. Experimental

4.1. General

Melting points were determined with a Yanaco micro melting point apparatus and were not corrected. ^{1}H NMR, ^{13}C NMR and ^{10}B NMR spectra were recorded with JEOL JNM-EX-270, JNM-LA-400 and JNM-LA-600 spectrometers. Chemical shifts for ^{1}H NMR spectra were referenced to tetramethylsilane (0.0 ppm) as an internal standard. Chemical shifts for ^{13}C NMR spectra were referenced to residual ^{13}C present in deuterated solvents. Chemical shift values for ^{11}B spectra were referenced to external $BF_3 \cdot OEt_2$ (0.0 ppm with negative values upfield). The splitting patterns are designated as follows: s (singlet), d (doublet), t (triplet), and m (multiplet). Mass spectra were recorded on a JEOL JMS-DX-303 spectrometer. Elemental analyses were performed with a Perkin–Elmer 2400 CHN analyzer.

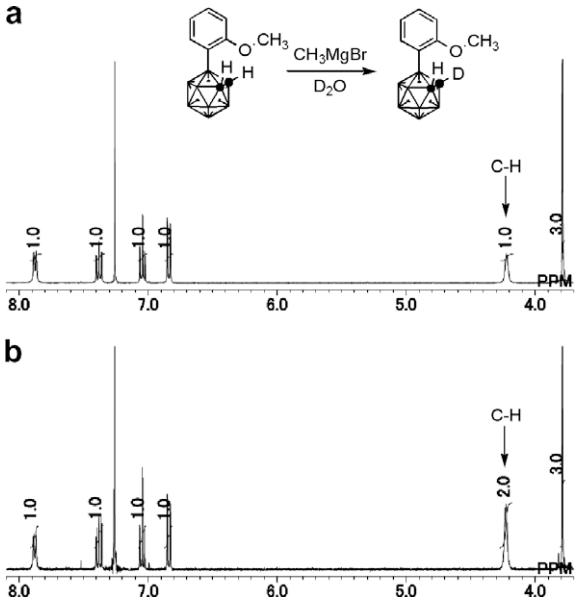


Fig. 1. NMR spectra of **4a** and the deuteration product. Spectra (a) and (b) are those of the deuterated product and compound **4a** in $CDCl_3$ at 25 °C, respectively.

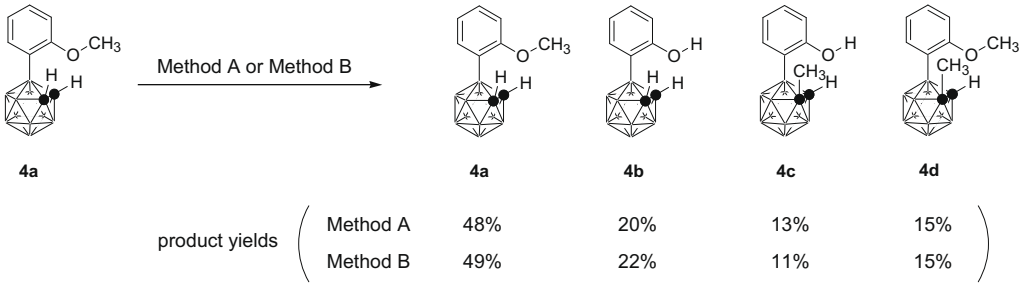
4.2. Materials

Unless otherwise noted, the reagents and solvents were purchased from Aldrich Chemical Co., Kanto Chemicals, Tokyo Kasei, or Wako Chemicals, Inc. and were used as received. Carboranes were purchased from Katchem s.r.o. (Prague, Czech Republic). 3-Iodo-*o*-carborane (**1**), 9-iodo-*o*-carborane (**2**) and 2-iodo-*p*-carborane (**3**) were synthesized according to the literature [10,16,17].

4.3. Pd-catalyzed coupling of iodocarboranes with Grignard reagent

A solution of 1.70 M Grignard reagent (10 mL, 17.0 mmol), which was freshly prepared from magnesium turnings and a tiny quantity of I_2 with the corresponding bromoanisole in dry THF, was added dropwise to a stirred dry THF solution (3.0 mL) of iodocarborane (540 mg, 2.0 mmol), $Pd(PPh_3)_2Cl_2$ (140 mg, 0.2 mmol) and CuI (38 mg, 0.2 mmol) under an Ar atmosphere. The mixture was refluxed, and then excess Grignard reagent was quenched by the slow addition of a dilute HCl solution. The mixture was extracted with AcOEt and the organic phase was washed with water, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography. Yields are shown in Table 1.

*Compound **4a***: Colorless needles (*n*-hexane-CH_2Cl_2). M.p. 105.0–106.0 °C. ^{1}H NMR (396 MHz, $CDCl_3$) δ (ppm) 1.3–3.2 (brm, 9H, carborane B–H), 3.79 (s, 3H, OCH_3), 4.23 (brs, 2H, carborane C–H), 6.84 (d, J = 8.2 Hz, 1H, Ar), 7.04 (dt, J = 1.0 Hz, 7.2 Hz, 1H, Ar), 7.38 (ddd,



Scheme 4. Demethylation of **4a** with CH_3MgBr. *Conditions*: Method A: [substrate] = 0.15 M in THF, CH_3MgBr (8.5 equiv.), reflux for 34 h; Method B: [substrate] = 0.15 M in THF, CH_3MgBr (8.5 equiv.), $Pd(PPh_3)_2Cl_2$ (10 mol%), CuI (10 mol%), reflux for 34 h.

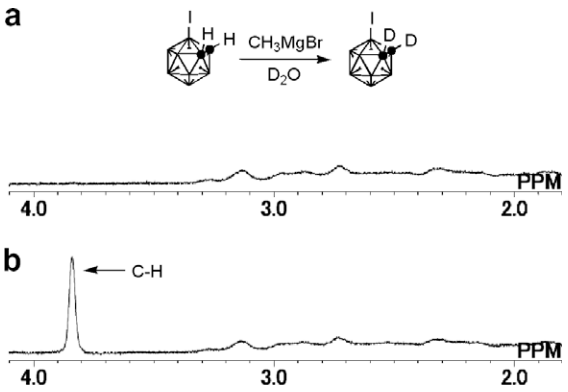


Fig. 2. NMR spectra of **1** and the deuteration product. Spectra (a) and (b) are those of the deuterated product and compound **1** in $CDCl_3$ at 25 °C, respectively.

J = 1.8 Hz, 7.4 Hz, 8.3 Hz, 1H, Ar), 7.88 (dd, *J* = 1.0 Hz, 7.2 Hz, 1H, Ar). ^{13}C NMR (99 MHz, $CDCl_3$) δ (ppm) 55.16 (OCH_3), 55.76 (carborane), 109.91 (Ar), 121.34 (Ar), 131.06 (Ar), 138.44 (Ar), 161.12 (Ar). MS (EI) *m/z* 250 (M^+, 100%). HRMS Calcd. for $C_9H_{18}B_{10}O$: 250.2365. Found: 250.2360.

Compound ***4b***: Colorless needles (*n*-hexane-CH_2Cl_2). M.p. 160.0–162.0 °C. ^{1}H NMR (396 MHz, $CDCl_3$) δ (ppm) 1.2–3.2 (brm, 9H, carborane B–H), 4.29 (brs, 2H, carborane C–H), 4.98 (s, 1H, OH), 6.67 (dd, *J* = 1.0 Hz, 7.2 Hz, 1H, Ar), 7.02 (dt, *J* = 1.0 Hz, 7.7 Hz, 1H, Ar), 7.27 (dt, *J* = 1.9 Hz, 7.7 Hz, 1H, Ar), 7.83 (d, *J* = 6.8 Hz, 1H, Ar). ^{13}C NMR (99 MHz, $CDCl_3$) δ (ppm) 55.94 (carborane), 114.91 (Ar), 121.57 (Ar), 130.96 (Ar), 138.29 (Ar), 157.19 (Ar). MS (EI) *m/z* 236 (M^+, 100%). HRMS Calcd. for $C_8H_{16}B_{10}O$: 236.2208. Found: 236.2209.

Compound ***4c***: Colorless needles (CH_3OH-H_2O). M.p. 110.0–113.0 °C. ^{1}H NMR (396 MHz, $CDCl_3$) δ (ppm) 1.5–3.2 (brm, 9H, carborane B–H), 1.81 (s, 3H, CH_3), 4.71 (brs, 1H, carborane C–H), 4.98 (s, 1H, OH), 6.70 (d, *J* = 8.2 Hz, 1H, Ar), 7.04 (dt, *J* = 1.0 Hz, 7.2 Hz, 1H, Ar), 7.29 (dt, *J* = 1.9 Hz, 7.7 Hz, 1H, Ar), 7.76 (d, *J* = 7.2 Hz, 1H, Ar). ^{13}C NMR (99 MHz, $CDCl_3$) δ (ppm) 23.60 (CH_3), 62.11 (carborane), 70.75 (carborane), 115.23 (Ar), 121.50 (Ar), 131.10 (Ar), 139.18 (Ar), 157.87 (Ar). MS (EI) *m/z* 250 (M^+, 100%). HRMS Calcd. for $C_9H_{18}B_{10}O$: 250.2365. Found: 250.2360.

Compound ***5a***: Colorless leafs (*n*-hexane-CH_2Cl_2). 76.0–77.0 °C. ^{1}H NMR (396 MHz, $CDCl_3$) δ (ppm) 1.5–3.2 (brm, 9H, carborane B–H), 3.70 (brs, 2H, carborane C–H), 3.83 (s, 3H, OCH_3), 6.95 (dd, *J* = 2.2 Hz, 8.8 Hz, 1H, Ar), 7.13–7.15 (m, 2H, Ar), 7.29 (t, *J* = 7.7 Hz, 1H, Ar). ^{13}C NMR (99 MHz, $CDCl_3$) δ (ppm) 55.24 (OCH_3), 56.64 (carborane), 114.83 (Ar), 119.15 (Ar), 125.12 (Ar), 129.50 (Ar), 159.28 (Ar). MS (EI) *m/z* 250 (M^+, 100%). HRMS Calcd. for $C_9H_{18}B_{10}O$: 250.2365. Found: 250.2349.

Compound ***6a***: Colorless needles (*n*-hexane-CH_2Cl_2). 94.0–94.5 °C. ^{1}H NMR (396 MHz, $CDCl_3$) δ (ppm) 1.7–3.1 (brm, 9H, carborane B–H), 3.67 (brs, 2H, carborane C–H), 3.82 (s, 3H, OCH_3), 6.90 (d, *J* = 8.7 Hz, 2H, Ar), 7.52 (d, *J* = 8.7 Hz, 2H, Ar). ^{13}C NMR (99 MHz, $CDCl_3$) δ (ppm) 55.20 (OCH_3), 56.69 (carborane), 113.90 (Ar), 134.50 (Ar), 160.99 (Ar). MS (EI) *m/z* 250 (M^+, 100%). HRMS Calcd. for $C_9H_{18}B_{10}O$: 250.2365. Found: 250.2356.

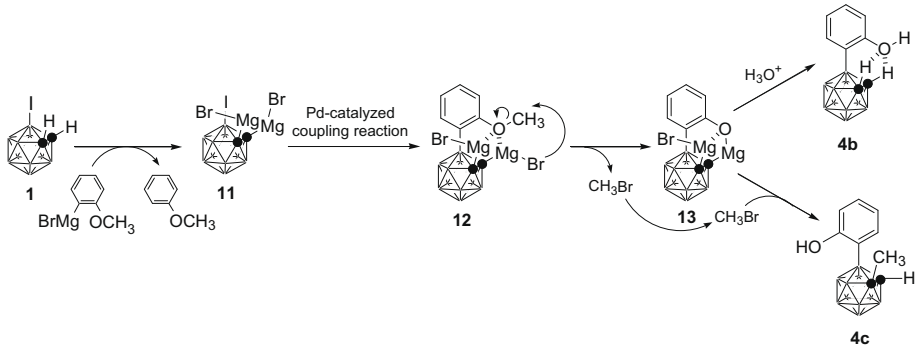
Compound ***7a***: Colorless prisms (*n*-hexane-CH_2Cl_2). 135.0–136.0 °C. ^{1}H NMR (396 MHz, $CDCl_3$) δ (ppm) 1.6–3.2 (brm, 9H, carborane B–H), 3.52 (brs, 1H, carborane C–H), 3.56 (brs, 1H, carborane C–H), 3.75 (s, 3H, OCH_3), 6.77 (d, *J* = 8.7 Hz, 1H, Ar), 6.86 (dt, *J* = 1.0 Hz, 7.2 Hz, 1H, Ar), 7.20 (dt, *J* = 1.9 Hz, 7.7 Hz, 1H, Ar), 7.36 (d, *J* = 6.8 Hz, 1H, Ar). ^{13}C NMR (99 MHz, $CDCl_3$) δ (ppm) 49.95 (OCH_3), 52.91 (carborane), 55.05 (carborane), 110.43 (Ar), 120.18 (Ar), 128.96 (Ar), 135.94 (Ar), 161.53 (Ar). MS (EI) *m/z* 250 (M^+, 100%). HRMS Calcd. for $C_9H_{18}B_{10}O$: 250.2365. Found: 250.2360.

Compound ***8a***: Colorless prisms (*n*-hexane). M.p. 84.5–85.0 °C. ^{1}H NMR (396 MHz, $CDCl_3$) δ (ppm) 1.2–3.4 (brm, 9H, carborane B–H), 2.79 (brs, 1H, carborane C–H), 3.69 (brs, 1H, carborane C–H), 3.72 (s, 3H, OCH_3), 6.81 (d, *J* = 8.2 Hz, 1H, Ar), 6.97 (dt, *J* = 1.0 Hz, 7.5 Hz, 1H, Ar), 7.30 (ddd, *J* = 1.9 Hz, 7.4 Hz, 8.3 Hz, 1H, Ar), 7.67 (d, *J* = 6.8 Hz, 1H, Ar). ^{13}C NMR (68 MHz, $CDCl_3$) δ (ppm) 55.0 (OCH_3), 61.7 (carborane), 65.4 (carborane), 110.2 (Ar), 120.6 (Ar), 129.7 (Ar), 136.0 (Ar), 161.8 (Ar). MS (EI) *m/z* 250 (M^+, 100%). Anal. Calc. for $C_9H_{18}B_{10}$: C, 43.18; H, 7.25. Found: C, 43.04; H, 7.16%.

Compound ***8b***: Colorless leafs (*n*-hexane-CH_2Cl_2). M.p. 112.0–113.0 °C. ^{1}H NMR (396 MHz, $CDCl_3$) δ (ppm) 1.5–3.3 (brm, 9H, carborane B–H), 2.84 (brs, 1H, carborane C–H), 3.66 (brs, 1H, carborane C–H), 4.91 (brs, 1H, OH), 6.68 (dd, *J* = 1.0 Hz, 8.2 Hz, 1H, Ar), 6.93 (dt, *J* = 1.0 Hz, 7.2 Hz, 1H, Ar), 7.20 (dt, *J* = 1.5 Hz, 7.2 Hz, 1H, Ar), 7.57 (d, *J* = 7.6 Hz, 1H, Ar). ^{13}C NMR (68 MHz, $CDCl_3$) δ (ppm) 62.2 (carborane), 65.7 (carborane), 115.3 (Ar), 120.7 (Ar), 129.8 (Ar), 136.1 (Ar), 158.1 (Ar). MS (EI) *m/z* 236 (M^+, 100%). Anal. Calc. for $C_8H_{16}B_{10}$: C, 40.66; H, 6.82. Found: C, 40.90; H, 6.97%.

Compound ***9a***: Colorless oil. ^{1}H NMR (396 MHz, $CDCl_3$) δ (ppm) 1.2–2.8 (brm, 9H, carborane B–H), 2.89 (brs, 1H, carborane C–H), 3.07 (brs, 1H, carborane C–H), 3.82 (s, 3H, OCH_3), 6.87 (ddd, *J* = 1.0 Hz, 2.4 Hz, 8.2 Hz, 1H, Ar), 7.09 (s, 1H, Ar), 7.11 (d, *J* = 7.2 Hz, 1H, Ar), 7.23 (t, *J* = 7.7 Hz, 1H, Ar). ^{13}C NMR (99 MHz, $CDCl_3$) δ (ppm) 55.10 (OCH_3), 63.52 (carborane), 65.40 (carborane), 113.48 (Ar), 119.15 (Ar), 125.62 (Ar), 128.96 (Ar), 158.95 (Ar). MS (EI) *m/z* 250 (M^+, 100%). HRMS Calcd. for $C_9H_{18}B_{10}O$: 250.2365. Found: 250.2352.

Compound ***10a***: Colorless leafs (*n*-hexane-CH_2Cl_2). M.p. 101.0–101.5 °C. ^{1}H NMR (396 MHz, $CDCl_3$) δ (ppm) 1.3–3.2 (brm, 9H, carborane B–H), 2.89 (brs, 1H, carborane C–H), 3.03 (brs, 1H, carborane C–H), 3.81 (s, 3H, OCH_3), 6.86 (d, *J* = 8.7 Hz, 2H, Ar), 7.47 (d, *J* = 8.2 Hz, 2H, Ar). ^{13}C NMR (99 MHz, $CDCl_3$) δ (ppm) 55.10 (OCH_3), 63.66 (carborane), 65.77 (carborane), 113.46 (Ar), 134.69



Scheme 5. A plausible demethylation mechanism in the Pd-catalyzed coupling reaction of **1** with 2-CH_3OPhMgBr.

(Ar), 160.07 (Ar). MS (EI) *m/z* 250 (M^+, 100%). HRMS Calcd. for $C_9H_{18}B_{10}O$: 250.2365. Found: 250.2352.

4.4. Dealkylation study of *4a* with CH_3MgBr

A solution of 3.0 M CH_3MgBr in ether (1.13 mL, 8.5 mmol) was added dropwise to a stirred dry THF solution (2.7 mL) of **4a** (100 mg, 0.4 mmol) under an Ar atmosphere. The mixture was refluxed for 34 h, and then the excess Grignard reagent was quenched by the slow addition of a dilute HCl solution. The mixture was extracted with AcOEt and the organic phase was washed with water, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography with 8:1 to 3:1 *n*-hexane:AcOEt to give 48 mg (48%) of **4a**, 19 mg (20%) of **4b**, 13 mg (13%) of **4c** and 16 mg (15%) of **4d**.

Compound ***4d***: Colorless needles (CH_3OH-H_2O). M.p. 103.0–104.0 °C. ^{1}H NMR (396 MHz, $CDCl_3$) δ (ppm) 1.5–3.2 (brm, 9H, carborane B–H), 1.75 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 4.63 (brs, 1H, carborane C–H), 6.88 (d, J = 8.7 Hz, 1H, Ar), 7.06 (t, J = 7.2 Hz, 1H, Ar), 7.40 (dt, J = 1.4 Hz, 7.8 Hz, 1H, Ar), 7.81 (d, J = 7.2 Hz, 1H, Ar). ^{13}C NMR (99 MHz, $CDCl_3$) δ (ppm) 23.60 (CH_3), 55.24 (OCH_3), 60.29 (carborane), 70.50 (carborane), 110.39 (Ar), 121.34 (Ar), 131.22 (Ar), 139.36 (Ar), 161.80 (Ar). MS (EI) *m/z* 264 (M^+, 100%). Anal. Calc. for $C_{10}H_{20}B_{10}O$: C, 45.43; H, 7.63. Found: C, 45.69; H, 7.75%.

4.5. Dealkylation study of *4a* with CH_3MgBr in the presence of Pd and Cu catalysts

A solution of 3.0 M of CH_3MgBr in ether (1.13 mL, 3.4 mmol) was added dropwise to a stirred dry THF solution (2.7 mL) of **4a** (100 mg, 0.4 mmol), $Pd(PPh_3)_2Cl_2$ (28 mg, 0.04 mmol) and CuI (8 mg, 0.04 mmol) under an Ar atmosphere. The mixture was refluxed for 34 h, and then the excess Grignard reagent was quenched by the slow addition of a dilute HCl solution. The mixture was extracted with AcOEt and the organic phase was washed with water, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography with 8:1 to 3:1 *n*-hexane:AcOEt to give 49 mg (49%) of **4a**, 21 mg (22%) of **4b**, 11 mg (11%) of **4c** and 16 mg (15%) of **4d**.

4.6. Deuteration studies of compounds *4a*

A solution of 3.0 M CH_3MgBr in ether (1.42 mL, 4.25 mmol) was added dropwise to a stirred dry THF solution (1.85 mL) of **4a** (125 mg, 0.5 mmol) under an Ar atmosphere. The mixture was refluxed for 3 h and poured into a cold D_2O solution. The mixture was extracted with AcOEt and the organic phase was washed with water, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography with 4:1 *n*-hexane:CH_2Cl_2 to give 116 mg (92%) of deuterated compound: Colorless needles (CH_2Cl_2-*n*-hexane). M.p. 105.5–106.5 °C. ^{1}H NMR (396 MHz, $CDCl_3$) δ (ppm) 1.4–3.2 (brm, 9H, carborane B–H), 3.79 (s, 3H, CH_3), 4.22 (brs, 1H, carborane C–H), 6.84 (d, J = 8.2 Hz, 1H, Ar), 7.05 (dt, J = 1.0 Hz, 7.2 Hz, 1H, Ar), 7.38 (ddd, J = 1.9 Hz, 7.4 Hz, 8.6 Hz, 1H, Ar), 7.88 (d, J = 7.2 Hz, 1H, Ar). ^{13}C NMR (99 MHz, $CDCl_3$) δ (ppm) 55.17 (OCH_3), 55.67 (carborane), 55.76 (carborane), 119.91 (Ar), 121.34 (Ar), 131.06 (Ar), 138.44 (Ar), 161.12 (Ar). MS (EI) *m/z* 251 (M^+, 100%). HRMS Calcd. for $C_9H_{17}DB_{10}O$: 251.2428. Found: 251.2421.

4.7. Deuteration studies of compounds *1*

A solution of 3.0 M CH_3MgBr in ether (1.42 mL, 4.25 mmol) was added dropwise to a stirred dry THF solution (1.85 mL) of **1** (135 mg, 0.5 mmol) under an Ar atmosphere. The mixture was refluxed for 3 h and poured into a cold D_2O solution at 0 °C. The mixture was extracted with AcOEt and the organic phase was washed with water, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography with 10:1 *n*-hexane:AcOEt to give 133 mg (98%) of deuterated compound: Colorless needles (*n*-hexane). M.p. 77.0–78.0 °C. ^{1}H NMR (396 MHz, $CDCl_3$) δ (ppm) 1.2–3.3 (brm, 9H, carborane B–H). ^{13}C NMR (99 MHz, $CDCl_3$) δ (ppm) not detected. ^{11}B NMR (127 MHz, $CDCl_3$) δ (ppm) −29.54 (1B), −13.19 (1B), −12.64 (2B), −111.23 (3B), 7.30 (1B), −1.43 (2B). MS (EI) *m/z* 272 (M^+, 100%). HRMS Calcd. for $C_2H_9D_2B_9I$: 272.1035. Found: 272. 1025.

Acknowledgements

This work was supported by Grants-in-Aid for Scientific Research (B) (No. 16390032 and 20390035) and by a Grant-in-Aid for Young Scientists (B) (No. 18790089) from the Ministry of Education, Culture, Sports, Sciences and Technology, Japan.

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