



Magnesium-assisted intramolecular demethylation utilizing carborane C–H geometry

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ABSTRACT

A novel type of demethylation reaction was designed in the Pd-catalyzed coupling reaction of iodocarboranes with several Grignard reagents, $\text{CH}_3\text{OPhMgBr}$. 3-Iodo-*o*-carborane **1** reacted with 2- $\text{CH}_3\text{OPhMgBr}$ 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- $\text{CH}_3\text{OPhMgBr}$ 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 $\cdots$ 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 $\cdots$ O interaction instead of intramolecular C–H $\cdots$ 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.

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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 $\cdots$ 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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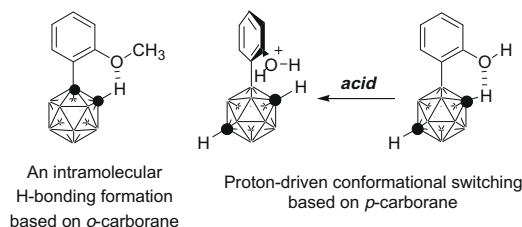


Chart 1. Intramolecular C–H...O interactions based on *o*-carborane and *p*-carborane C–Hs in solution.

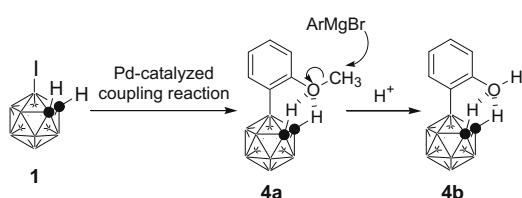
of 3-iodo-*o*-carborane (**1**) with 2-methoxyphenylmagnesium bromide (2-CH₃OPhMgBr), anticipating that strong coordination of the C–Hs with oxygen atom of the OCH₃ group of the corresponding methoxyphenyl compound **4a** would assist the demethylation during the coupling reaction to afford the corresponding 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 CH₃OPhMgBr (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 CH₃OPhMgBr

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(PPh₃)₂Cl₂ (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-CH₃OPhMgBr 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-CH₃OPhMgBr and 4-CH₃OPhMgBr 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-CH₃OPhMgBr, the reaction of 9-iodo-*o*-carborane (**2**), which has an iodine atom apart from the C–Hs, with 2-CH₃OPhMgBr 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-CH₃OPhMgBr, but involves a synergistic effect between **1** and 2-CH₃OPhMgBr. Thus, we speculated that the demethylation process was related to an intramolecular C–H...O interaction in the products, because only compounds **4a** or



Scheme 1. Pd-catalyzed coupling reaction of 3-iodo-*o*-carborane with 2-CH₃OPhMgBr and consecutive demethylation assisted by intramolecular C–H...O interaction.

4b among these products can have an intramolecular C–H...O interaction between C–H and the OCH₃ or OH group.

Next, the reactions of 2-iodo-*p*-carborane (**3**) with isomers of CH₃OPhMgBr were performed to further evaluate the relationship between intramolecular C–H...O interaction and demethylation. The reaction of **3** with 2-CH₃OPhMgBr 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-CH₃OPhMgBr, 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-CH₃OPhMgBr or 4-CH₃OPhMgBr 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 OCH₃ group.

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 (CH₃MgBr) was examined under the same conditions as used for the coupling reaction; [**4a**] = 0.15 M in THF, CH₃MgBr (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 PdCl₂(PPh₃)₂ and 10 mol% of CuI were added to the reaction mixture, or 2-CH₃OPhMgBr was used instead of CH₃MgBr, 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 (D₂O) after the treatment of **4a** with CH₃MgBr (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 CH₃MgBr and converted to C–MgBr.

On the other hand, when compound **1** was treated with CH₃MgBr (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 CH₃MgBr 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-CH₃OPhMgBr to afford a mixture of **8a** and

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