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Magnesium-mediated sp^3 C–H activation in cascade cyclization of 1-arylethynyl-2-alkyl-*o*-carboranes: efficient synthesis of carborane-fused cyclopentanes†

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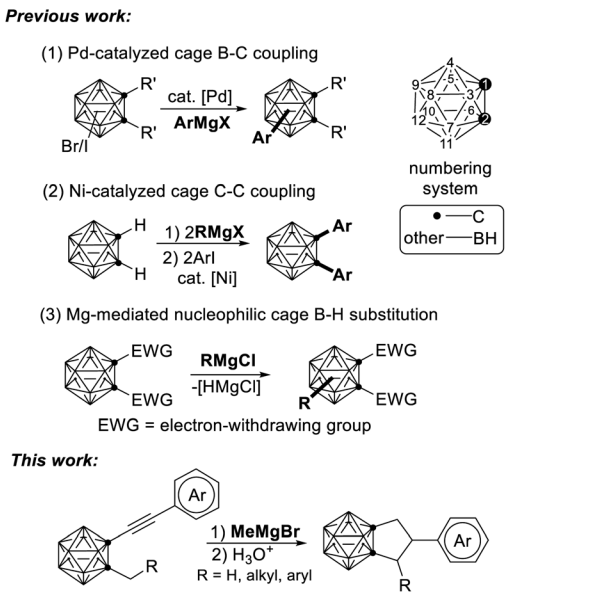
This work reports an unprecedented cascade cyclization of 1-arylethynyl-2-alkyl-*o*-carboranes promoted by magnesium-mediated sp^3 C–H activation. Treatment of 1-arylethynyl-2-alkyl-*o*-carboranes with MeMgBr gives a series of carborane-fused cyclopentanes in very good yields. Deuterium labelling and control experiments suggest that HMgBr, resulting *in situ* from the nucleophilic substitution of cage B–H bonds with Grignard reagent, initiates the reaction, in which magnesium-promoted intramolecular sp^3 C–H activation serves as a key step. This work not only offers a new route for the synthesis of carborane-fused cyclopentanes, but also sheds some light on Mg-mediated C–H activation and functionalization.

Introduction

Grignard reagents are a well-known class of C-nucleophiles and have been intensively used in organic synthesis for the formation of C–C bonds.[1] They have also been employed as coupling partners in the functionalization of carboranes, for example, in Pd-catalyzed cage B–C cross-coupling,[2] and Ni-catalyzed cage C–C cross-coupling[3] (Scheme 1). Very recently, we disclosed that Grignard reagents can activate the cage B–H bond in *o*-carboranes *via* nucleophilic cage BH substitution reaction for regioselective functionalization of *o*-carboranes.[4]

Carboranes, a class of carbon–boron molecular clusters, possess unique properties such as remarkable thermal and chemical stability, spherical geometry, and highly electron-delocalized hydrophobic surface.[5] These features have made carboranes useful functional blocks in materials,[6] organometallic/coordination chemistry,[7] boron neutron capture therapy agents,[8] pharmacophores,[9] and more.[10] To this end, functionalization of carboranes have attracted enormous research interest. Considerable progress has recently been made in selective functionalization of carboranes at either BH[5,11] or CH[5,12] vertices.

As an ongoing project in our laboratory, we studied the nucleophilic substitution reaction of 1-phenylethynyl-2-methyl-*o*-carborane (**1a**) with MeMgBr. No expected B(3,6)-dimethylated *o*-carborane was isolated, rather, an unprecedented compound **2a** was obtained from a mixture of polymethylated *o*-carboranes. Its ^{1}H coupled ^{11}B NMR spectrum indicated that **2a** is not a cage B-substituted species. The ^{13}C NMR spectrum showed the absence of the C≡C unit. Its ^{1}H NMR spectrum displayed a pentet at 4.05 ppm (1H), two double doublets at 2.89 ppm (2H) and 2.62 ppm (2H), respectively, in addition to phenyl protons. This compound was later unambiguously confirmed by single-crystal X-ray analysis to be 1,2-[$CH_2CH(Ph)CH_2$]-*o*-carborane



Scheme 1 Grignard reagents in the functionalization of *o*-carboranes.

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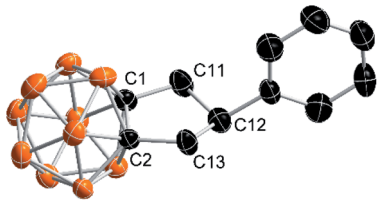


Fig. 1 Molecular structure of **2a** with the thermal ellipsoids shown at 50% probability level (all H atoms are omitted for clarity). Selected bond distance (Å) and angels (°): C(1)–C(2) 1.641(2), C(2)–C(13) 1.519(3), C(13)–C(12) 1.569(3), C(12)–C(11) 1.566(3), C(11)–C(1) 1.512(3); C(1)–C(2)–C(13) 106.9(2), C(2)–C(13)–C(12) 106.3(2), C(13)–C(12)–C(11) 107.1(2), C(1)–C(11)–C(12) 106.9(2), C(11)–C(1)–C(2) 106.8(2).

(**2a**; Fig. 1). This result indicates clearly that the alkyne unit –C≡C– in **1a** has been completely reduced to the alkyl by addition of three H atoms, forming a C–C single bond. To address the reaction pathway of this unprecedented Mg-mediated cyclization, we studied this reaction in detail and the results are presented in this article.

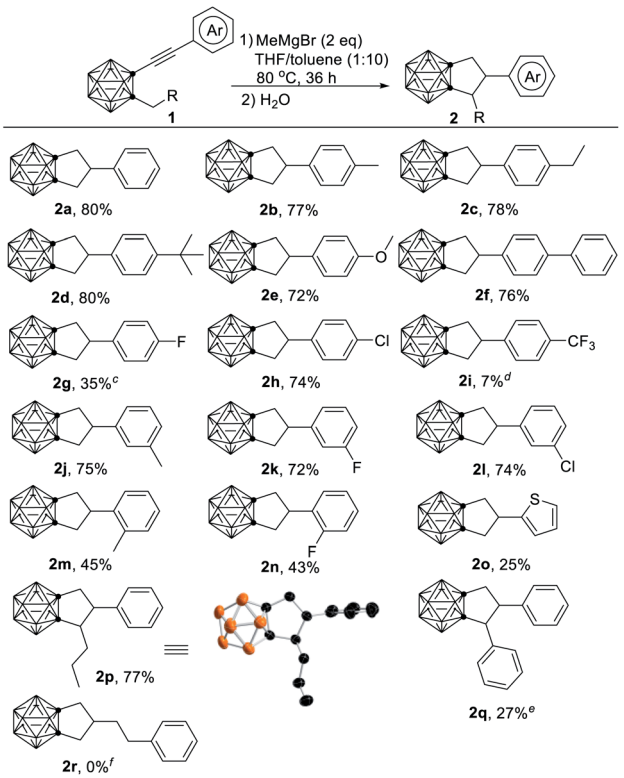
Results and discussion

We first optimized the reaction conditions for the formation of **2a**. Treatment of **1a** with 2 equiv. of MeMgBr in a mixed solvent of THF/toluene (1/10 in v/v) at 80 °C for 36 h gave **2a** in 80% isolated yield (entry 1, Table S1†). Replacement of MeMgBr with other Grignard reagents or organic lithium reagents led to a dramatically decreased yield of **2a** (entries 2–4, Table S1†). Screening of the reaction time, solvents and amount of MeMgBr did not offer better results (entries 5–8, Table S1†).

With the optimal reaction conditions (entry 1, Table S1†) in hand, we examined the substrate scope, and the results were summarized in Table 1. Both electron-donating and electron-withdrawing groups at *para* position of the phenyl ring except for *p*-F and *p*-CF_3 gave the corresponding carborane-fused cyclopentanes in 72–80% yields (**2a–2i**). For **1g** with *p*-F or **1i** with *p*-CF_3 on phenyl ring, the desired product **2g** or **2i** was isolated in 35% or 7% yield along with **1g**/**1i** being recovered in 47%/80% yield, whereas *m*-F substituted **1k** afforded **2k** in 72% yield. On the other hand, the cyclization of *ortho*-substituted substrates gave **2m** and **2n** in 43–45% yields because of steric reasons. Replacement of the methyl group at cage-C with *n*-butyl, the cyclization reaction occurred smoothly to generate **2p** in 77% yield. In contrast, the benzyl group at the cage-C lowered the cyclization efficiency, leading to **2q** in 27% yield along with 1-(PhCH=CH)-2-Bn-*o*-$C_2B_{10}H_{10}$ as the major product. No reaction was observed if Ph and –C≡C– was separated by a –CH_2CH_2– unit (**2r**), suggesting an important role of phenylacetylene moiety in the reaction. These results offer some hints into the reaction mechanism (*vide infra*).

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 4 : 1 : 2 : 1 : 2 spanning the range from −14 to −7 ppm. The

Table 1 Cyclization of 1-arylethynyl-2-alkyl-*o*-carboranes[a,b]

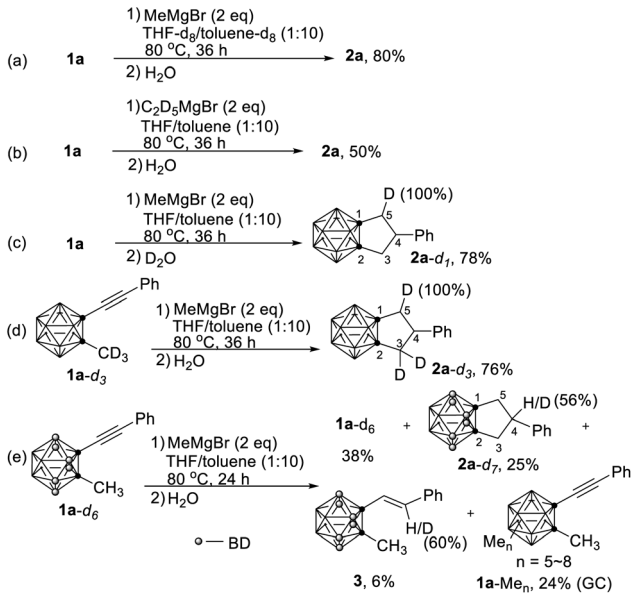


[a] Reactions were conducted on 0.1 mmol scale of **1** in a mixed solvent of THF/toluene (0.8 mL, 1/10 in v/v) in a closed flask at 80 °C for 36 h. [b] Isolated yields. [c] 47% starting material recovered. [d] 80% starting material recovered. [e] Reaction was conducted at 120 °C for 7 d. 1-(PhCH=CH)-2-Bn-*o*-$C_2B_{10}H_{10}$ was isolated in 60% yield. [f] 100% starting material recovered.

molecular structures of **2a** and **2p** have been further confirmed by single-crystal X-ray analyses.[13]

The most interesting part of this reaction is the reaction mechanism by which compounds **2** are formed. To figure out the sources of the three added H atoms in **2a**, several deuterium labelling experiments were carried out (Scheme 2). When the reaction was conducted in a mixed deuterated solvent (THF-d_8/toluene-d_8), **2a** was obtained without any D incorporation in 80% yield (Scheme 2a). Treatment of **1a** with fully deuterated ethyl magnesium bromide (C_2D_5MgBr)[14] gave **2a** in 50% yield without any incorporation of deuterium. These results clearly indicated that (1) the three added H atoms come from neither solvent nor Grignard reagent, and (2) ethyl magnesium bromide is less reactive than methyl magnesium bromide. If the reaction was quenched with D_2O, **2a**-d_1 was isolated in 78% yield with 100% D incorporation (Scheme 2c). On the other hand, reaction of 1-(PhC≡C)-2-CD_3-*o*-carborane (**1a**-d_3) with MeMgBr under the standard conditions, followed by quenching with H_2O, afforded **2a**-d_3 in 76% yield. Surprisingly, one of the methyl deuterium atoms migrated to C(5) with 100% D incorporation (Scheme 2d).

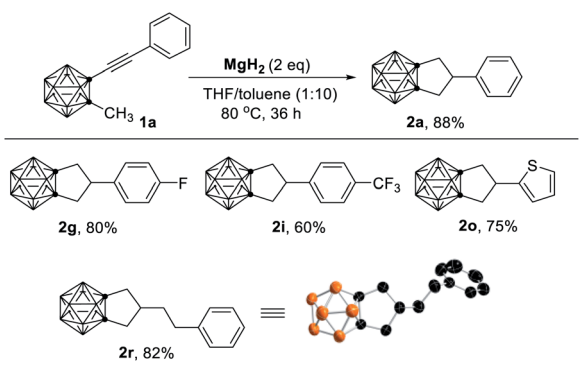
Having identified the sources of two out of three added hydrogen atoms in **2a**, the question then arises as to what is the



Scheme 2 Deuterium labelling experiments: (a) reaction run in deuterated solvents (THF-d_8/toluene-d_8). (b) Reaction of **1a** with C_2D_5MgBr. (c) Quenching of reaction by D_2O. (d) Reaction of 1-(PhC≡C)-2-CD_3-*o*-carborane (**1a**-d_3) with MeMgBr. (e) Reaction of 1-(PhC≡C)-2-CH_3-3,4,5,6,7,11-D_6-*o*-carborane (**1a**-d_6) with MeMgBr.

origin of the third added hydrogen in **2a**. We learnt from our previous work that HMgBr was generated as a by-product in the nucleophilic cage BH substitution of *o*-carboranes with RMgBr.[4] It was then assumed that the cage B–H may serve as H source for the third H atom. To verify this hypothesis, compound 1-(PhC≡C)-2-CH_3-3,4,5,6,7,11-D_6-*o*-carborane (**1a**-d_6) was synthesized. Treatment of **1a**-d_6 with MeMgBr under the standard conditions gave the corresponding product **2a**-d_7 in 25% yield with 56% D incorporation at C(4)-position (Scheme 2e). This result suggested that cage BH indeed served as H source *via* the formation of HMgBr, which was further supported by the observation of a mixture of multi-B-methylated *o*-carboranes **1a**-Me_n on GC-MS.

Table 2 Cyclization promoted by MgH_2[a,b]

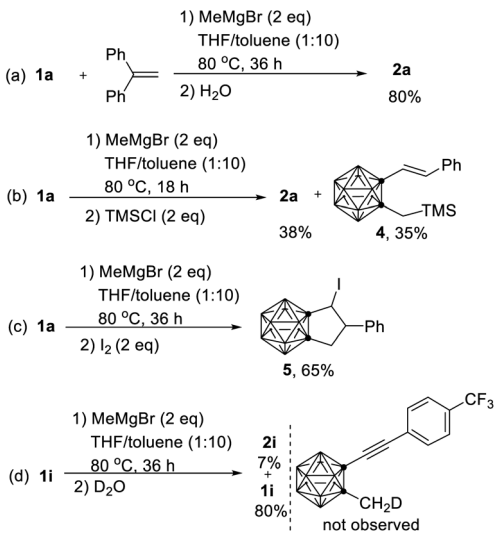


[a] Reactions were conducted on 0.1 mmol scale of **1** in a mixed solvent of THF and toluene (0.8 mL, 1/10 in v/v) in a closed flask at 80 °C for 36 h. [b] Isolated yields.

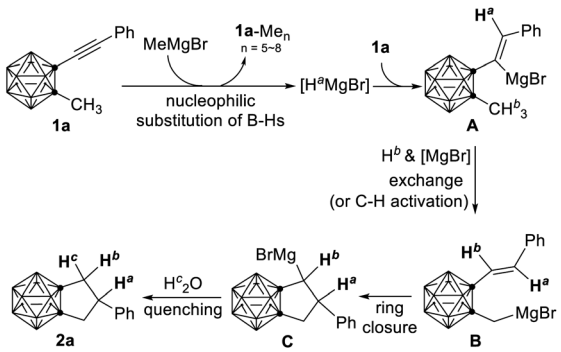
To further understand the role of HMgBr, the easily accessible MgH_2 (ref. 15) was selected as the reagent. Treatment of **1a** with 2 equiv. of MgH_2 in THF/toluene at 80 °C for 36 h afforded **2a** in 88% isolated yield (Table 2). Substrates that showed no or poor activity using MeMgBr as a reagent (**1g**, **1i**, **1o**, **1r** in Table 1) worked well in the reaction with MgH_2 to give the corresponding cyclization products (**2g**, **2i**, **2o**, **2r**) in 60–82% yields (Table 2). These results strongly indicated that HMgBr was essential for this cyclization reaction.

To gain more insight into the reaction pathway, additional control experiments were carried out (Scheme 3). Treatment of **1a** with MeMgBr in the presence of 2 equiv. of 1,1-diphenylethylene[16] under standard reaction conditions gave **2a** in 80% yield (Scheme 3a). No obvious change was observed when the reaction was run in the dark. These results suggested that the above cascade cyclization reaction may not involve a radical pathway. Quenching the reaction with TMSCl after 18 h generated a compound **4** in 35% isolated yield in addition to **2a** (38% yield) (Scheme 3b). On the other hand, compound **5** was isolated in 65% yield if the reaction was quenched by I_2 after 36 h (Scheme 3c). The isolation of **4** and **3** (Scheme 2e) shed some light on the reaction intermediates. Moreover, quenching the reaction of **1i** with MeMgBr after 36 h with D_2O led to the 80% recovery of **1i** without any D incorporation, suggesting that the cage C–CH_3 proton was not deprotonated by MeMgBr. This result was in agreement with the D-labelling experiments shown in Scheme 2d. If the cage C-CD_3 was deprotonated by MeMgBr, the D would not migrate to C(5) with 100% D incorporation in **2a**-d_3.

On the basis of the aforementioned results, a plausible mechanism was proposed in Scheme 4 in an example of **2a**. Multiple nucleophilic substitution reaction of cage B–H bonds in **1a** with MeMgBr leads to the formation of HMgBr and multi B-methylated carboranes **1a**-Me_n (Scheme 2e).[4] *trans*-Hydromagnesiation of the triple bond in **1a** furnishes an intermediate



Scheme 3 Control experiments: (a) reaction in the presence of 1,1-diphenylethylene. (b) Quenching reaction of **1a** by TMSCl. (c) Quenching reaction of **1a** by I_2. (d) Quenching reaction of **1i** by D_2O.



Scheme 4 Proposed reaction mechanism.

A (**3** in Scheme 2e).[17] The regioselectivity is controlled by the polarity of C≡C triple bond as carboranyl is a stronger electron-withdrawing group than phenyl. Intramolecular methyl proton–MgBr exchange in **A** proceeds to form **B** (Schemes 2d and 3b).[18,19] Intramolecular ring closure affords **C** (Schemes 2c and 3c). Quenching of **C** with water generates **2a**.

Conclusions

We report an unprecedented cascade cyclization of 1-arylethynyl-2-alkyl-*o*-carboranes with Grignard reagent for highly efficient synthesis of various carborane-fused cyclopentanes. On the basis of D-labelling and control experiments, a HMgBr-initiated reaction mechanism is proposed, in which the magnesium-mediated intramolecular sp^3 C–H activation serves as a key step. These results not only shed some light on magnesium-promoted C–H activation and functionalization, but also offer references for the design of cascade reactions.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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