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Boron NMR Probes

^{11}B NMR Probes of Copper(II): Finding and Implications of the Cu^{2+}-Promoted Decomposition of *ortho*-Carborane Derivatives

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Abstract: The development of noninvasive methodologies for the detection of d-block metal ions such as copper (Cu^{2+}), zinc (Zn^{2+}), and manganese (Mn^{2+}) is important for understanding their biological roles and relationship with diseases. We have been interested in the use of ^{11}B NMR probes for the detection of d-block metal ions, because ^{11}B is an ultratrace element in living systems. *o*-Carboranes, which consist of ten boron and two carbon atoms, have been applied to numerous drugs and biological active agents. In this work, we found that the *o*-carborane-pendant cyclens (L^3–L^5) (cyclen = 1,4,7,10-tetraazacyclododecane) are decomposed in the presence of Mn^{2+} or Cu^{2+} in aqueous solution at neutral pH, accompanied by the release of 4–9 equiv. of $B(OH)_3$. Furthermore, it was found that *o*-carborane derivatives that contain hydroxyl groups instead of a cyclen unit also undergo decomposition in the presence of Cu^{2+} and the corresponding complexes such as Cu(bpy) to afford 10 equiv. of $B(OH)_3$, as confirmed by ^{11}B NMR spectroscopic analysis and an azomethine-H assay. These reactions are applied to ^{11}B MRI (magnetic resonance imaging) probes for Cu^{2+}.

Introduction

Biologically relevant d-block metals, including copper (Cu^+ and Cu^{2+}), zinc (Zn^{2+}), and manganese (Mn^{2+}), play important roles in the physiological processes of living organisms.[1] For example, copper functions as a required cofactor for many enzymes such as tyrosinase, cytochrome c oxidase, and superoxide dismutase.[2] Current research indicates that the level of copper in the blood circulation, cells, and tissues are closely related to many diseases such as Menkes syndrome,[3] Willson's disease,[4] amyotrophic lateral sclerosis,[5] and Alzheimer's disease.[6] In addition, high levels of Cu^{2+} in the blood may induce cancer progression.[7] It was also reported that Mn^{2+} is associated with the development of Parkinson's disease and Willson's disease.[8] Zn^{2+} is known to be a crucial cofactor for Zn^{2+} enzymes and Zn^{2+}-containing proteins, and also functions as an intracellular second messenger, especially in neurons. Thus, the development of imaging probes for these d-block metals is important in terms of understanding their metabolism and roles in diseases and pathological events.[9]

A number of fluorescence-based probes for Cu^+,[10] Cu^{2+},[11] Mn^{2+},[12] Zn^{2+},[13] and Fe^{2+}[14] have been reported to date.[15] However, the fluorescence detection of these metal ions has limitations in term of the impermeability of emission through biological tissue. In contrast, magnetic resonance imaging (MRI) is considered to be a powerful technique for the detection of molecules and in the diagnosis of various diseases, because it is noninvasive and capable of producing three-dimensional images of opaque organisms with a high spatial and temporal resolution.[16] Nevertheless, progress in developing MRI probes of metal ions has been much slower than that of fluorescent sensors and they have mostly been limited to Gd^{3+}-based contrast agents that are used to observe changes in ^{1}H NMR signals.[17–21]

In this context, we have been interested in the possible use of ^{11}B NMR probes for the detection of d-block metal ions, because ^{11}B is an ultratrace element in living systems.[22] We previously reported on phenylboronic acid-pendant cyclen **1** (L^1) for the detection of d-block metals (cyclen = 1,4,7,10-tetraazacyclododecane).[23,24] The C–B bond of L^1 is cleaved upon the formation of metal complex **2** (ML^1) with d-block metals to give **3** (ML^2) and $B(OH)_3$ in aqueous solution at neutral pH (Scheme 1). Mechanistic studies strongly indicate that the cyclen unit of **1** forms stable complexes **2** with metal ions such as Zn^{2+}, $Cu^{+/2+}$, Ni^{2+}, Mn^{2+}, and Co^{3+} and produce a metal-bound OH^- ion, which then attacks the boron atom to promote C–B bond cleavage, resulting in the formation of **3** (ML^2) and 1 equiv. of $B(OH)_3$. Moreover, we succeeded in the *in-cell* ^{11}B NMR detection of Zn^{2+} in cultured Jurkat cells.

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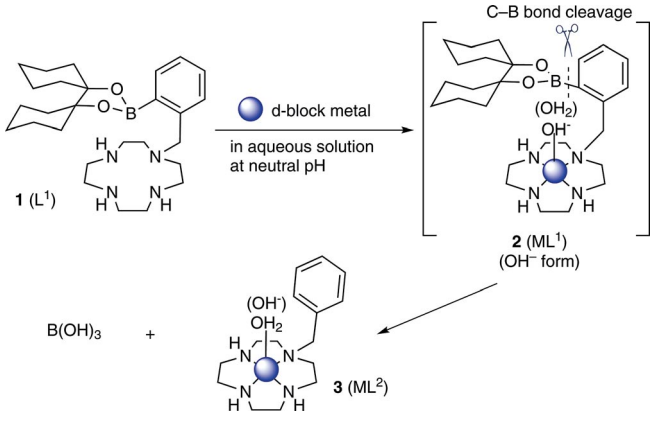
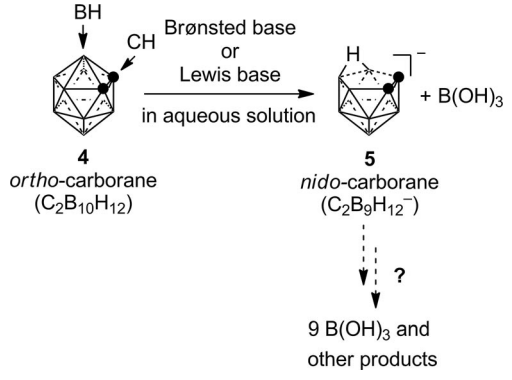


Scheme 1. Mechanism for the deboronation reaction of phenylboronic acid-pendant cyclen **1** by complexation with metal ions.

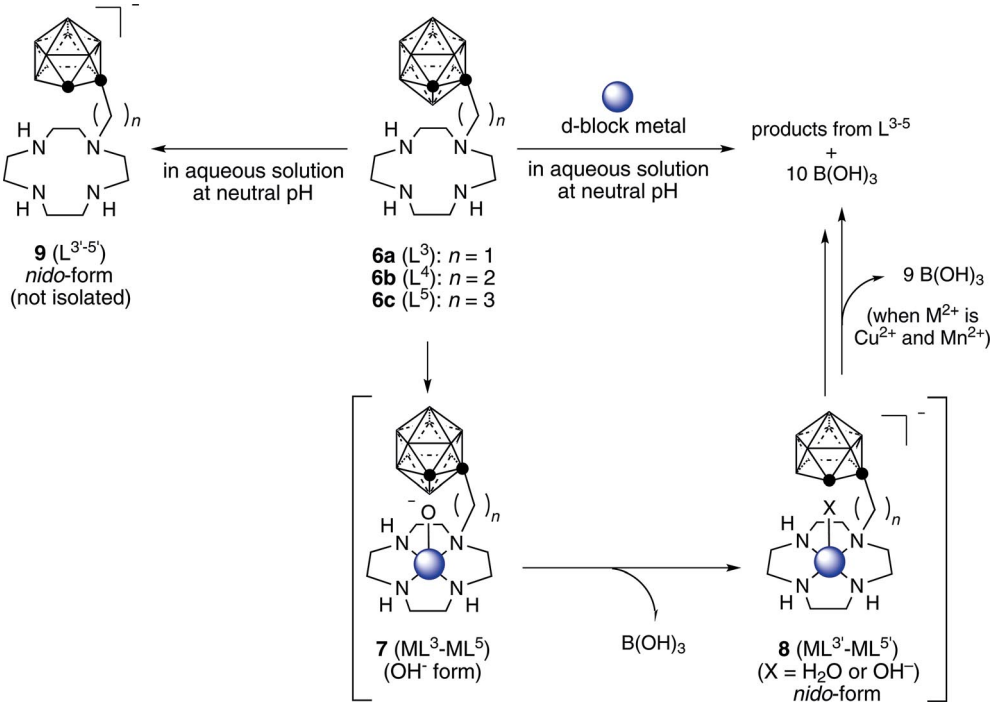


Scheme 2. Decomposition reaction of *o*-carborane **4** in the presence of Brønsted or Lewis base.

As an extension to the aforementioned work, we turned our attention to ^{11}B NMR (MRI) probes having the *o*-carborane (1,2-*closo*-dicarbadodecaborane) unit **4**, which is comprised of ten boron and two carbon atoms.[25] *o*-Carborane derivatives have been utilized as a hydrophobic pharmacophore, carbonic anhydrase (CA) inhibitors[26] and nuclear receptor ligands such as a vitamin D receptor (VDR),[27] androgen (AR) and estrogen receptor (ER),[28] and a retinoid receptor,[29] because of their remarkable chemical and thermal stability.[30] Carborane analogues have been proposed as potent agents for boron neutron capture therapy (BNCT).[31] It has been reported that **4** undergoes decomposition when treated with a Brønsted or Lewis base such as hydroxide, alkoxide, amine, fluoride and carbene to give the corresponding anionic *nido*-form **5** and 1 equiv. of $B(OH)_3$ (Scheme 2).[32] Although degradation of **5** has been reported under harsh conditions (acidic and high temperature),[33] it is generally believed that **5** undergoes very little further degradation under physiological conditions (in aqueous solution at neutral pH).[34]

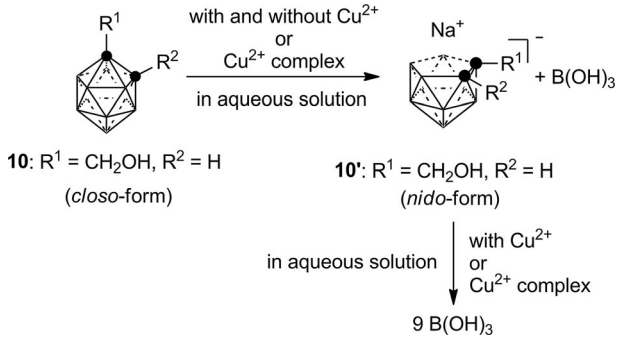
In this article, we report on the design and synthesis of *o*-carborane-pendant cyclens **6a**–**c** (L^3–L^5), in which an *o*-carborane unit is connected to cyclen through different linkers (C1–C3), as shown in Scheme 3. We expected that **6a**–**c** would form metal complexes **7** (ML^3–ML^5) with d-block metals, in which the metal-bound OH^- functions as a nucleophile to decompose their carborane units to afford the corresponding *nido*-form **8** or a further decomposed species, resulting in ^{11}B NMR spectral changes.

During the experiments, we observed that **6a**–**c** decompose to the corresponding *nido*-forms **8** (metal complex) and **9** (metal-free form) in both the presence and the absence of Zn^{2+}, Co^{2+}, Fe^{2+}, Ni^{2+}, Mn^{2+}, Pb^{2+}, and Ca^{2+} in aqueous solution at



Scheme 3. Decomposition reaction of *o*-carborane-pendant cyclen **6a**–**c**.

neutral pH. Interestingly, it was discovered that Cu^{2+} and Mn^{2+} accelerate the decomposition of *nido*-**8** to release 4–9 equiv. of $B(OH)_3$, as confirmed by ^{11}B NMR measurements and azomethine-H assays. Furthermore, we observed that *o*-carboranes possessing no cyclen unit **10** undergo complete decomposition and release ten $B(OH)_3$ in the presence of Cu^{2+} (Scheme 4). The results of the ligand screening of Cu^{2+}-mediated decomposition of **10** suggest that Cu^{2+} complexes with 2,2′-bipyridyl (bpy) and ethylenediamine (en) units accelerate this reaction at pH 5–10. Finally, applications of these findings to the ^{11}B MRI detection of Cu^{2+} are also reported.



Scheme 4. Decomposition reaction of *o*-carborane derivative **10**.

Results and Discussion

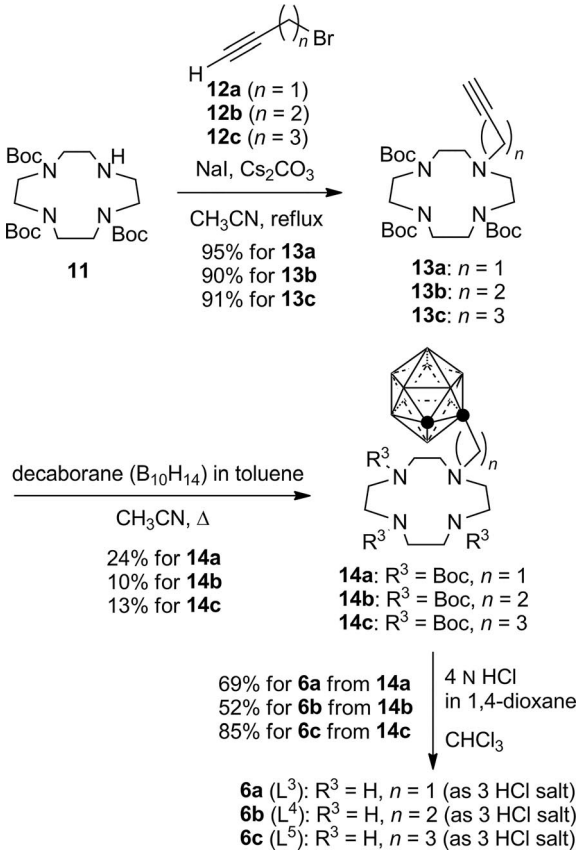
Synthesis of *o*-/*m*-Carborane Derivatives

The synthesis of *o*-carborane-pendant cyclen containing the C1–C3 linkers **6a**–**c** was carried out as shown in Scheme 5. The tri-Boc-1,4,7,10-tetraazacyclododecane (**12**)[35] was alkylated with 1-bromo-3-propyne (**13a**), 1-bromo-4-butyne (**13b**) and 1-bromo-5-hexyne (**13c**) to give **14a**–**c**, respectively. The reaction of **14a**–**c** with decaborane ($B_{10}H_{14}$) complex[36] followed by the deprotection of the Boc group with 4 N HCl in 1,4-dioxane gave **6a**–**c** (L^3–L^5) in moderate chemical yields.

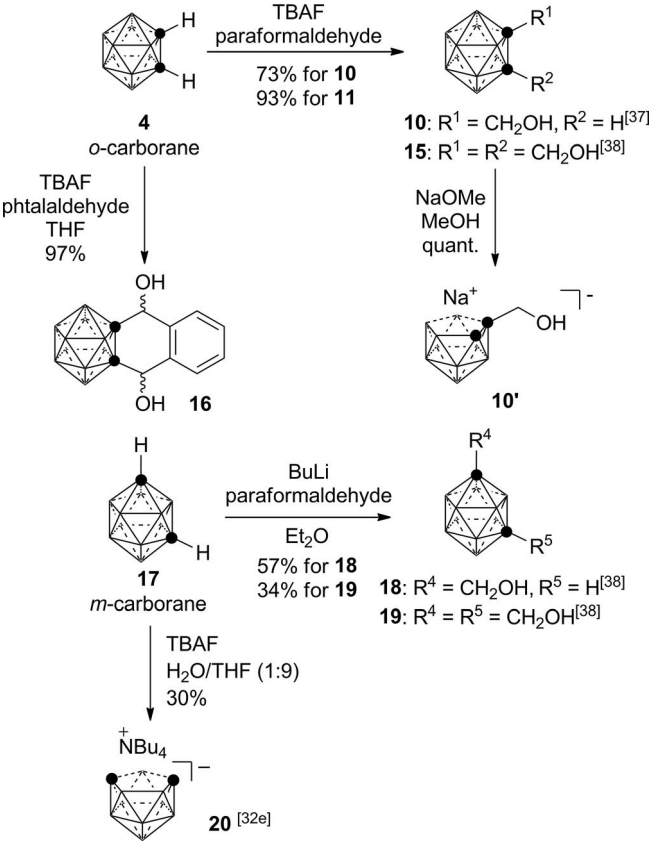
The *o*-carborane analogues **10**,[37] **15**,[38] and **16** were synthesized according to a reported method using tetrabutylammonium fluoride (TBAF) and an aldehyde (Scheme 6).[37] Deboronation reaction of **10** was achieved by treatment with sodium methoxide in MeOH to afford *nido*-form **10′**.[32i] The *m*-carborane **17** was treated with BuLi and paraformaldehyde in Et_2O to obtain **18** and **19**, as previously reported.[38] Deboronation of **17** was performed according to reported methods to afford the *nido*-*m*-carborane tetrabutylammonium salt **20**.[32e]

Decomposition Reaction of *o*-Carborane-Pendant Cyclen

The decomposition of **6a**–**c** in the presence of various d-block metals (Mn^{2+}, Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, and Cd^{2+}) was monitored by $^{11}B\{^1H\}$ NMR (^1H decoupled)[39] and azomethin-H assays.[40] Figure 1 displays changes in the $^{11}B\{^1H\}$ NMR spectra (128 MHz) of **6b** (10 mM) in the absence and presence of Zn^{2+}, Co^{2+}, Cu^{2+}, and Mn^{2+} (20 mM) in 0.5 M HEPES buffer (pH 7)/D_2O (4:1) at 50 °C. After incubation for 96 h in the absence of a metal ion, new ^{11}B NMR signals corresponding to $B(OH)_3$ (δ =



Scheme 5. Synthesis of *o*-carborane-pendant cyclen **6a**–**c**.



Scheme 6. Structure and synthetic scheme of carborane analogues.

ca. 20 ppm) and the anionic *nido*-form **9** (δ = –10 to –40 ppm) (Figure 1) were observed (Figure 1, a and b). Similar spectral changes were observed in the presence of Zn^{2+} and Co^{2+}, suggesting that 1 equiv. of $B(OH)_3$ and **8** was released (Figure 1, c and d). Interestingly, stronger ^{11}B NMR signals for $B(OH)_3$ were observed in the presence of Cu^{2+} and Mn^{2+} (Figure 1, e and f), albeit broad signals were observed in the case of with Mn^{2+}.

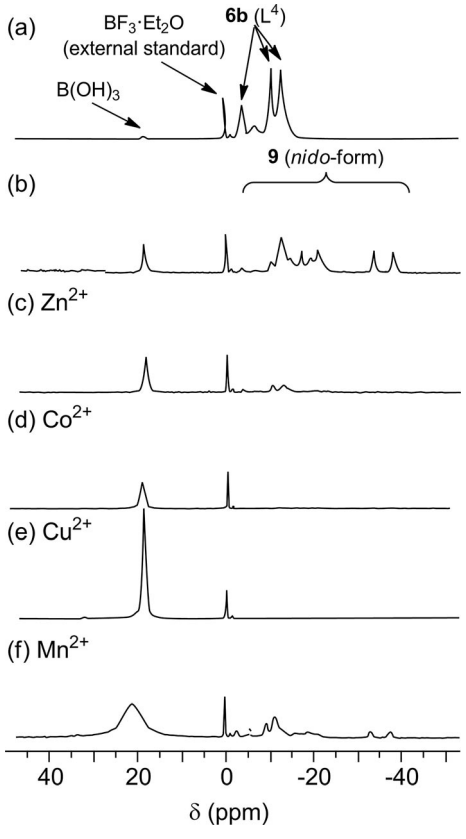


Figure 1. Change in ^{11}B {^1H} NMR spectra (128 MHz) of **6b** (10 mM) in the presence of d-block metals in 0.5 M HEPES buffer (pH 7)/D_2O (4:1) at 50 °C. (a) none, 0 h, (b) none, 96 h, (c) in the presence of Zn^{2+}, 96 h, (d) Co^{2+}, 96 h, (e) Cu^{2+}, 180 h, and (f) Mn^{2+}, 96 h ([metal ion] = 20 mM). A solution 10 % BF_3Et_2O in toluene was used as an external standard (see ref.[39] and Figure S1 in the Supporting Information).

The chemical yields of $B(OH)_3$ released from **6b** (10 mM) in HEPES (pH 7)/D_2O (4:1) at 50 °C in the absence and presence of Cu^{2+}, Mn^{2+}, Co^{2+}, and Zn^{2+} (20 mM) were also determined by azomethine-H assays.[40] It was found that **8** and about 4 equiv. of $B(OH)_3$ were released from one molecule of **6b** after incubation with $CuSO_4$ or $MnSO_4$ (20 mM) for 96 h (Figure 2). Furthermore, 9 equiv. of $B(OH)_3$ was produced after incubation with Cu^{2+} for 144 h. In contrast, only 1 equiv. of $B(OH)_3$ was released in the presence of Co^{2+} and Zn^{2+}. These results indicate that Cu^{2+} and Mn^{2+} induce the decomposition of the *o*-carborane unit of **6b** to produce not only the corresponding *nido*-form but also further decomposition products. As shown in Figure 3, the presence of Cu^{2+} and Mn^{2+} produces 4–9 equiv. of $B(OH)_3$, whereas other metals such as Zn^{2+} and Co^{2+} produce less than 1 equiv.

The results of the reaction of **6a**, **6b**, and **6c** (10 mM) with 2 equiv. of Cu^{2+} and Mn^{2+} (20 mM) in 0.5 M HEPES buffer (pH 7)/

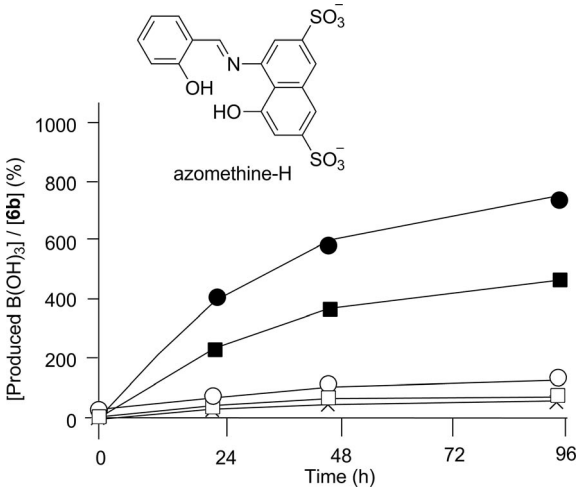


Figure 2. Results of azomethin-H assays of the decomposition reaction of **6b** (10 mM) in the absence (cross) and presence of Zn^{2+} (20 mM) (open squares), Cu^{2+} (20 mM) (closed circles), Co^{2+} (20 mM) (open circles), and Mn^{2+} (20 mM) (closed squares) in 0.5 M HEPES buffer (pH 7)/D_2O (4:1) at 50 °C. UV/Vis absorption spectra of azomethine-H in the presence of $B(OH)_3$ and those measured in the decomposition reaction of **6a** are shown in Figure S2 and Figure S3 in the Supporting Information, respectively.

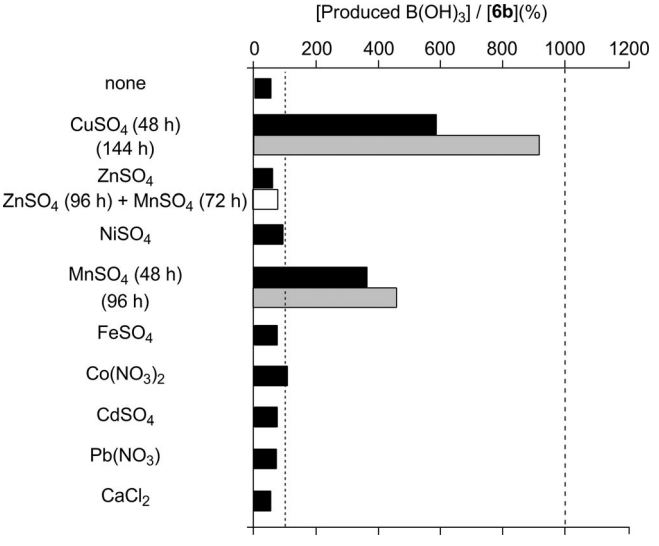


Figure 3. Chemical yields of $B(OH)_3$ produced from **6b** (10 mM) in the absence or presence of $CuSO_4$, $ZnSO_4$, $NiSO_4$, $MnSO_4$, $FeSO_4$, $Co(NO_3)_2$, $CdSO_4$, $Pb(NO_3)_2$, and $CaCl_2$ (20 mM) in 0.5 M HEPES buffer (pH 7)/D_2O (4:1) after incubation at 50 °C for 48 h (azomethine-H assay).

D_2O (4:1) at 50 °C are summarized in Figure 4. Although the reactivity of **6c** with Cu^{2+} is somewhat lower than that of **6a** and **6b**, all of the compounds decomposed to release 8–9 equiv. of $B(OH)_3$ (Figure 4, a). On the other hand, the chemical yields of $B(OH)_3$ released from **6a** and **6b** by Mn^{2+} reached a plateau at 4–6 equiv. after a 96 h incubation. These results show good agreement with the ^{11}B NMR spectra as shown in Figure S4 in the Supporting Information. Given that it was possible that Mn^{2+} might be oxidized during the reaction, 10 equiv. of DTT (dithiothreitol) and sodium ascorbate were added to the resulting mixture and the reaction was continued for 24 h. However, negligible acceleration was observed (data not shown).[41]

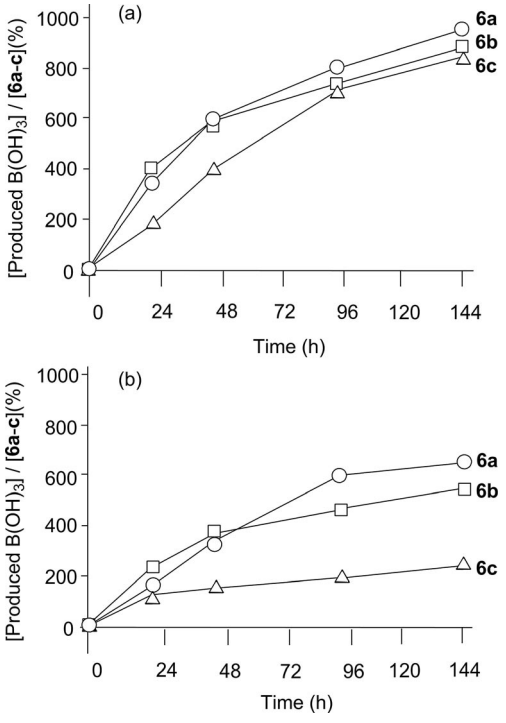


Figure 4. Comparison of the decomposition reaction of **6a** (open circles), **6b** (open squares), and **6c** (open triangles) with (a) Cu^{2+} and (b) Mn^{2+} in 0.5 M HEPES buffer (pH 7)/D_2O (4:1) at 50 °C (azomethine-H assay). [**6**] = 10 mM and [Cu^{2+} or Mn^{2+}] = 20 mM.

Decomposition Reaction of *o*- and *m*-Carborane Derivatives by Metal Ions

To examine the effect of the cyclen unit on the decomposition reaction of **6a–c**, *o*-carborane derivatives **10** and **11** (10 mM) containing a hydroxymethyl group were treated with a selection of metals. Given that neutral pH (pH 7) was not appropriate for following the reactions because of the formation of precipitates, the reaction was carried out at pH 4. As shown in the ^{11}B NMR spectra presented in Figure 5, the *closo*-form of **10** decomposes to give the *nido*-form **10′** and 1 equiv. of $B(OH)_3$ after 96 h in the absence of metal (Figure 5, a and b). In contrast, Cu^{2+} accelerates the decomposition of **10** to afford 10 equiv. of $B(OH)_3$ (Figure 5, c–f). It should be noted that ^{11}B signals of *nido*-form **10′** and $B(OH)_3$ were observed in the $^{11}B\{^1H\}$ NMR spectra of the reaction mixture with Cu^{2+} (Figure 5, c–e).

The ^{11}B NMR spectra recorded in the presence of Pb^{2+}, Zn^{2+}, Co^{2+}, and Mn^{2+} shown in Figure 5 (g–j) are almost identical to that of *nido*-**10′** (Figure 5, b). These data suggest that the *o*-carborane unit in **10** initially decomposes to the corresponding *nido*-form **10′** and that abstraction of the next boron atom may trigger the complete decomposition of *nido*-**10′**.

The effect of pH, the number of equivalents of Cu^{2+}, and reaction temperature was examined (the pH of each reaction mixture was adjusted at 25 °C). As displayed in Figure 6, 9–10 equiv. of $B(OH)_3$ (900–1000 % yields based on **10**) were released from **10** (10 mM) after incubation with $CuSO_4$ (10 mM) for 48 h at pH 4–5, but only 4–6 equiv. of $B(OH)_3$ were produced at pH >6. Interestingly, the decomposition of **10** (10 mM) was

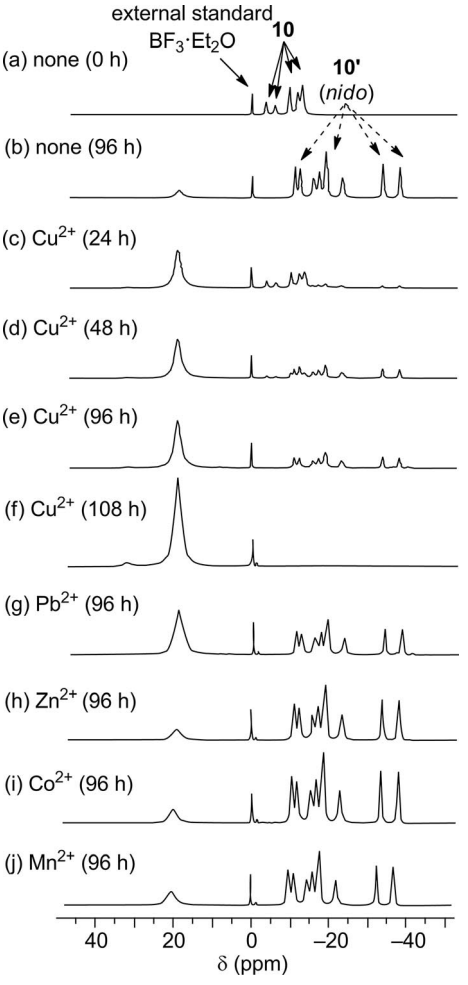


Figure 5. Change in $^{11}B\{^1H\}$ NMR spectra (128 MHz) of **10** (10 mM) in 0.5 M acetate buffer (pH 4)/DMSO/D_2O (3:5:2), 50 °C, after incubation for (a) 0 h and (b) 96 h in the absence of Cu^{2+} and after (c) 24 h, (d) 48 h, (e) 96 h, and (f) 108 h in the presence of Cu^{2+} (20 mM), and after 96 h in the presence of (g) Pb^{2+}, (h) Zn^{2+}, (i) Co^{2+}, and (j) Mn^{2+}.

observed to occur in the presence of a catalytic amount of Cu^{2+} (0.1 equiv.), although the reaction was slower than that in the presence of 1–10 equiv. of Cu^{2+} (Figure S5a in the Supporting Information). The reaction rate at 37 °C was also slower than at

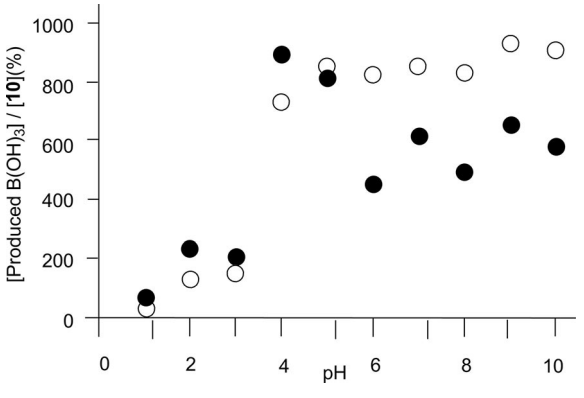


Figure 6. The decomposition reaction of **10** (10 mM) in the presence of $CuSO_4$ (closed circles) or Cu(bpy) (open circles) at 50 °C and various pH at 48 h ([Cu^{2+} or Cu(bpy)] = 10 mM) (azomethine-H assay).

50 °C, but ca. 10 equiv. of $B(OH)_3$ were released after incubation for 96 h (Figure S5b in the Supporting Information). The results using the Cu(bpy) complex (bpy = 2,2′-bipyridine) plotted with open circles are discussed below.

The effect of different Cu^{2+} salts and other metal ions (10 mM) such as Zn^{2+}, Ni^{2+}, Mn^{2+}, $Fe^{2+/3+}$, Co^{2+}, Cd^{2+}, Ca^{2+}, and Pb^{2+} on the decomposition of **10** (10 mM), as followed by an azomethin-H assay, is shown in Figure 7. The results imply that Zn^{2+}, Ni^{2+}, Mn^{2+}, $Fe^{2+/3+}$, Co^{2+}, Cd^{2+}, and Ca^{2+} do not cause the decomposition of *nido*-**10′**, whereas Pb^{2+} and Cu^{2+} [$CuSO_4$, $Cu(NO_3)_2$, $Cu(OAc)_2$ and $Cu(ClO_4)_2$] accelerate the decomposition of *nido*-**10′** to release 4–10 equiv. of $B(OH)_3$. The decomposition in the presence of CuI and CuI with sodium ascorbate was slower than with Cu^{2+}. Interestingly, the addition of Cu^{2+} to *nido*-**10′**, which had been produced by Zn^{2+}, Ni^{2+}, or Mn^{2+}, permitted decomposition to restart. These data support our previous hypothesis that the decomposition reaction of **10** proceeds via the *nido*-form **10′**.

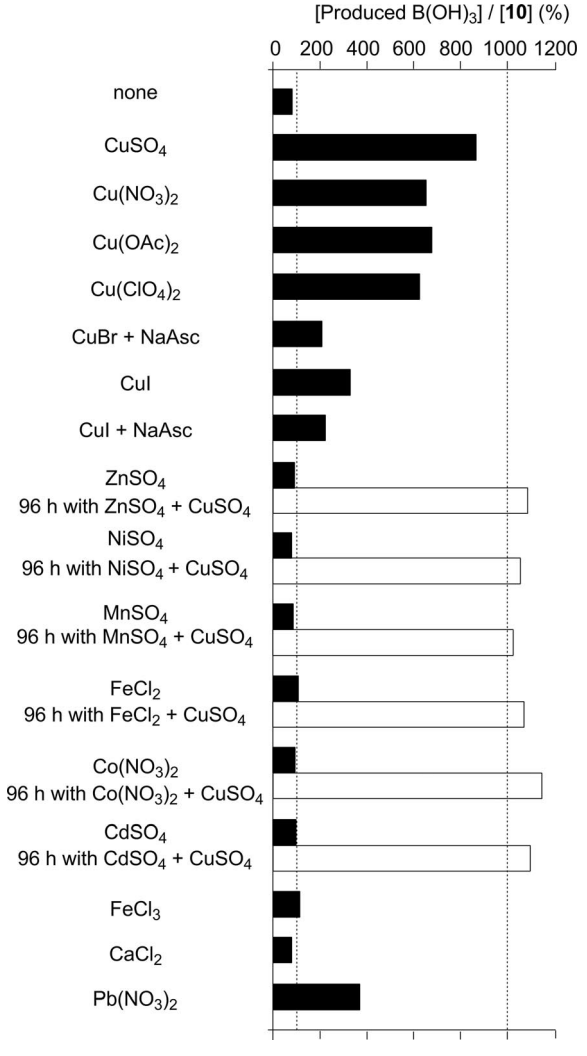


Figure 7. Effect of metal cations on the decomposition reaction of **10** (10 mM) with 2.0 equiv. of $CuSO_4$, $Cu(NO_3)_2$, $Cu(OAc)_2$, $Cu(ClO_4)_2$, CuI (with or without a reducing agent), $FeCl_3$, $CaCl_2$, and $Pb(NO_3)_2$ (20 mM) in 0.5 M acetate buffer (pH 4)/DMSO/D_2O (3:5:2), 2.0 equiv. of $ZnSO_4$, $NiSO_4$, $MnSO_4$, $FeCl_2$, $Co(NO_3)_2$, and $CdSO_4$ (20 mM) in 0.5 M acetate buffer (pH 4)/DMSO (1:1) at 48 h (black bar) ([metal salts] = 20 mM) then 1.0 equiv. of $CuSO_4$ was added (white bar) (azomethine-H assay). NaAsc refers to sodium ascorbate.

The decomposition of various *o*-carborane derivatives (**4**, **10**, **11**, and **16**) and *m*-carborane derivatives (**17**, **18**, **19**, and **20**) with Cu^{2+} was also examined. As shown in Figure 8, more than 6 equiv. of $B(OH)_3$ were released after incubation for 48 h from each *o*-carborane derivative, although the reaction rates differed.

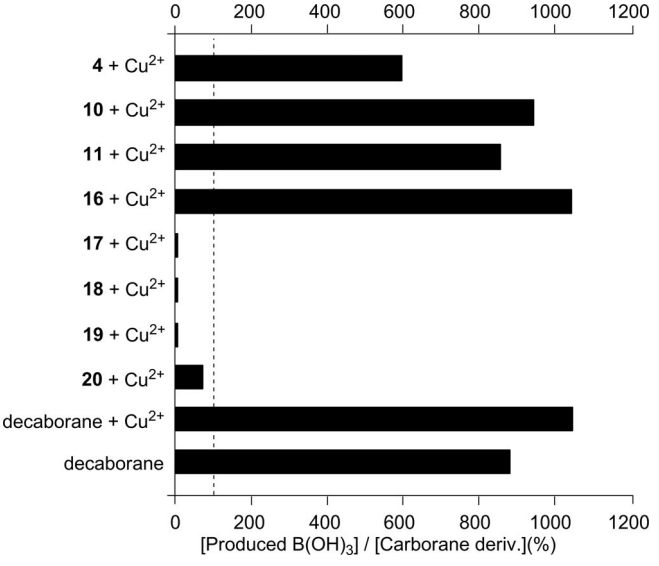


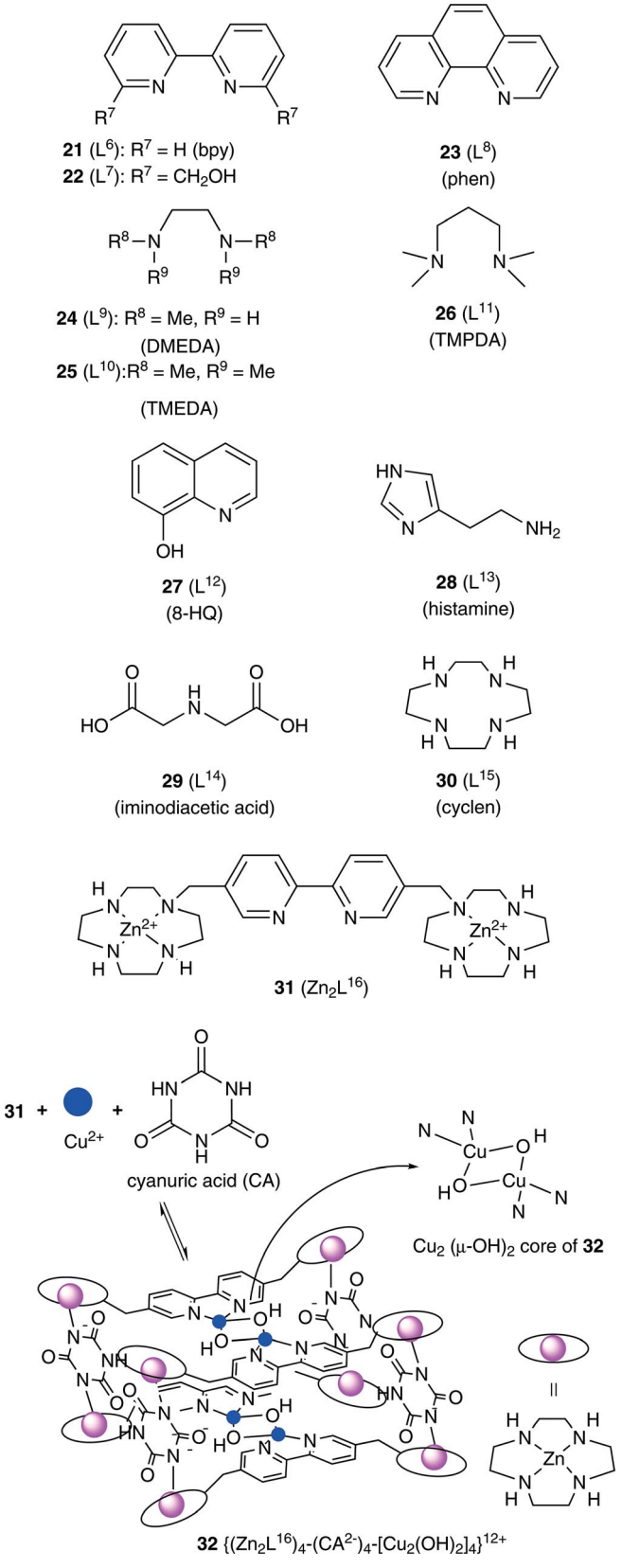
Figure 8. Decomposition reaction of carborane derivatives. Each carborane derivative (10 mM) was reacted in the presence of $CuSO_4$ (10 mM) in 0.5 M acetate buffer (pH 4)/DMSO (1:1 for **4**, **10**, **11**, **19**, and **20**, 7:3 for **16** and **18**, 6:4 for **17**) at 50 °C for 48 h (the reaction of decaborane was conducted for 24 h) (azomethine-H assay).

On the other hand, the decomposition of the *m*-carborane derivatives (**17**, **18**, **19**, and **20**) after 48 h was negligible. In comparison, decaborane ($B_{10}H_{14}$) (10 mM) in 0.5 M acetate buffer (pH 4)/dimethyl sulfoxide (DMSO) (1:1) completely decomposed to give 10 equiv. of $B(OH)_3$ after incubation with and without Cu^{2+} (10 mM) at 50 °C for 24 h (Figure 8 and Figure S6 in the Supporting Information), as previously reported.[42]

Effect of Ligands and Additives on Decomposition Reactions of 10

The effect of chelators on the Cu^{2+}-induced decomposition of **10** was examined. We used several copper ligands such as 2,2′-bipyridine (bpy) **21** (L^6), 6,6′-bis(hydroxymethyl)-2,2′-bipyridine [6,6′-bis(hydroxymethyl)bpy] **22** (L^7),[43] 1,10-phenanthroline (phen) **23** (L^8), *N*,*N*′-dimethylethylendiamine (DMEDA) **24** (L^9) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) **25** (L^{10}), *N*,*N*,*N*′,*N*′-tetramethylpropane-1,3-diamine (TMPDA) **26** (L^{11}), 8-quinolinol **27** (L^{12}), histamine **28** (L^{13}), iminodiacetic acid **29** (L^{14}), cyclen **30** (L^{15}), bis(Zn^{2+}-cyclen) containing a bpy linker **31** (Zn_2L^{16}), and 4:4:4 supramolecular catalyst **32** {$(Zn_2L^{16})_4$-

$(CA^{2-})_4$-$[Cu_2(OH)_2]_4\}^{12+}$, which was previously reported to function as an artificial phosphatase[44] (Scheme 7). As summarized in Figure 9a, Cu(bpy) (CuL^6), Cu[6,6′-bis(hydroxymethyl)bpy] (CuL^7), Cu(phen) (CuL^8), Cu(DMEDA) (CuL^9), Cu(TMEDA) (CuL^{10}), Cu(TMPDA) (CuL^{11}), Cu[H_{-1}(8-HQ)] ($CuH_{-1}L^{12}$), Cu(histamine) (CuL^{13}), Cu(ZnL^{16}), and **32** gave almost the same or better yields than ligand-free Cu^{2+} in 0.5 M HEPES (pH 7)/DMSO (1:1), whereas the Cu(imino diacetic acid) [Cu($H_{-2}L^{14}$)] and Cu^{2+}-cyclen complex (CuL^{15}) showed lower activity. It should also be reiterated that the decomposition of **10** proceeds at pH 5–10 in the presence of a Cu(bpy) complex (Figure 6, open circles). These results could be explained by higher Lewis acidity of Cu^{2+} in these complexes than that of ligand-free Cu^{2+}.[24a–24d]



Scheme 7. Structures of various ligands and additives.

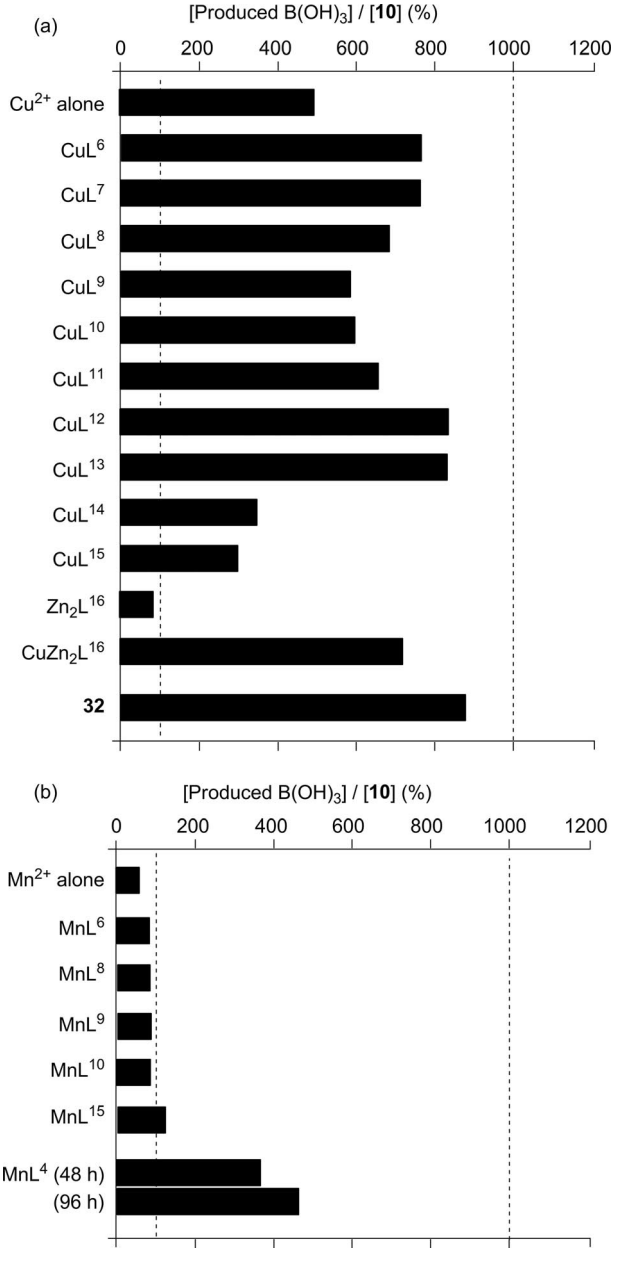


Figure 9. Effect of metal ligands on the decomposition reaction of **10** (10 mM) in the presence of (a) $CuSO_4$ (10 mM) or (b) $MnSO_4$ (10 mM) with metal ligands (10 mM) listed in Scheme 7 in 0.5 M HEPES (pH 7)/DMSO (1:1) (azomethine-H assay). In (b), L^4 was treated with $CuSO_4$ (20 mM) or $MnSO_4$ (20 mM) in 0.5 M HEPES (pH 7)/D_2O (4:1) at 50 °C (after reaction for 48 h).

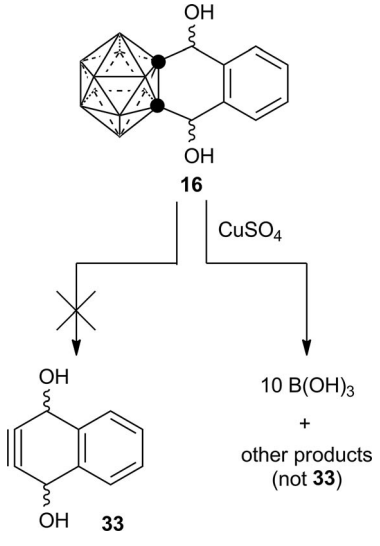
On the other hand, these ligands improved the reactivity of Mn^{2+} very little (Figure 9, b). These data indicate that the decomposition of **6a**–**c** proceeds only in an intramolecular manner (through complexation with Mn^{2+}) rather than by an intermolecular mechanism.

The effect of the stoichiometry between Cu^{2+} and ligands including **21** (L^6), **22** (L^7), **25** (L^{10}), and **27** (L^{12}) on the decomposition of **10** was also assessed. As shown in Figure S7 in the Supporting Information, the decomposition of **10** (10 mM) by Cu^{2+} (10 mM) was accelerated in the presence of 0.5 and 1 equiv. of **21** (L^6), **22** (L^7), and **27** (L^{12}), whereas the addition of 2 equiv. of these ligands resulted in lower yields. On the other hand, the loss of activity was only slightly improved by **22** (L^7), which likely forms a 1:1 CuL^7 complex, due to the steric effect of the substituent at the 6- and 6′-positions. Additionally, **25** (L^{10}) had little effect on the reactivity of Cu^{2+}, even when 2 equiv. was used. These data indicate that a 1:1 complex would be more active for the decomposition of *o*-carborane than a 2:1 complex.

The effect of oxidants and the reaction product $[B(OH)_3]$ on the decomposition of **10** was also examined. As summarized in Figure S8 in the Supporting Information, the catalytic activity of Cu(bpy) (10 mM, CuL^6) was not inhibited in the presence of an excess amount (10 equiv.) of $B(OH)_3$ and glycerol[45] in trapping the $B(OH)_3$ produced by the decomposition of **10**, suggesting that inhibition by $B(OH)_3$ is negligible. The addition of the weak oxidant TBHP had no effect on decomposition rate, despite the fact that the strong oxidant H_2O_2 strongly inhibits the decomposition of **10**, suggesting that a redox reaction is involved in the decomposition of *o*-carboranes.

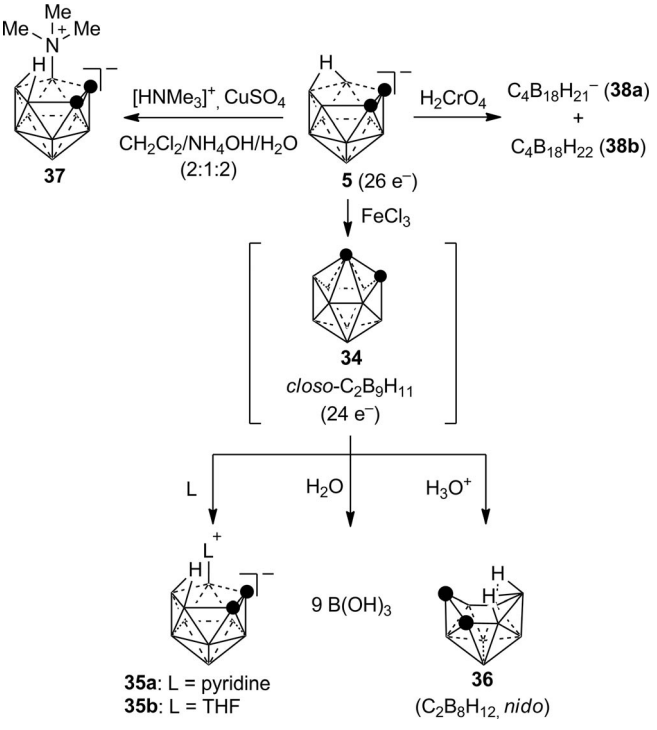
Mechanistic Studies of the Decomposition Reaction of *o*-Carborane Derivatives

We initially assumed that the products of the full decomposition of **10** would be alkyne derivatives, resulting from the loss of 10 boron atoms (Scheme 8), because the *o*-carborane units of **6a**–**c** were constructed from the corresponding alkyne in the synthesis of intermediates **13a**–**c** (Scheme 5). Based on this assumption, it was assumed that **16** would not undergo complete decomposition and that the reaction would stop at some intermediates, because these cyclic alkyne products would not be formed due to their highly strained structures. However, **16** underwent nearly complete decomposition, as shown in Figure 8, suggesting that the intermediates or final products of the substrates are not alkynes such as **33**. Based on these results, further characterization study of decomposition product is ongoing.



Scheme 8. Our initial assumption for the product of decomposition reaction.

Hawthorne and co-workers reported that the anionic *nido*-carborane **5** is oxidized by $FeCl_3$ and, when reacted with a Lewis base such as pyridine and tetrahydrofuran, gives the charge-compensated derivatives **35a** and **35b** (Scheme 9), respectively.[46a] In addition, they reported that **5** reacts with $FeCl_3$ in water and completely decomposes[33a] and that the oxidation of **5** by $FeCl_3$ under acidic conditions gives the neutral *nido*-carborane **36**.[46b] The results of a recent mechanistic study concluded that these reactions proceed via the unstable intermediate **34**.[47] On the other hand, Kudinov and co-workers reported on the oxidative reaction of **5** with NMe_3 using $CuSO_4$ in a two-phase system of CH_2Cl_2 and aqueous NH_3 solution to afford the charge-compensated compound **37**, suggesting that Cu^{2+} is capable of oxidizing **5** under basic conditions, unlike Fe^{3+}.[46c] Plešek and co-workers reported that **5** is converted into the *nido*-carborane dimer **38a** and **38b** in the presence of a strong oxidant such as chromic acid.[46d]



Scheme 9. Reported oxidation reaction of **5** with metal ions.

In our experiments described above, the formation of a brownish metal-like material, possibly Cu^0 or an alloy, was ob-

served (ca. 70–80 % of the copper was recovered based on the calculation as Cu^0, see Figure S9 in the Supporting Information). We therefore hypothesized that Cu^{2+} likely functions as an oxidant in the decomposition of *o*-carboranes (namely, Cu^{2+} is reduced to Cu^+ or Cu^0). To obtain evidence for this hypothesis, the redox potentials of **4**, **5**, **10′**, **20**, and CuL^6 were measured by cyclic voltammetry. As shown in Figure 10b, **5** (*nido*-form) exhibits two irreversible oxidation peaks at 0.57 and 0.87 V vs. Ag/AgCl, corresponding to the two-electron oxidation of the *nido*-anion, whereas **4** (*closo*-form) undergoes negligible levels of oxidation (Figure 10, a).[48a,48b] We assumed that these oxidation peaks correspond to an oxidative ring-closure reaction (**5**→**34** in Figure S10 in the Supporting Information) and further oxidation reaction of the *nido*-anion, respectively. The *C*-monoalkyl-substituted *nido*-carborane derivative **10′** shows two irreversible oxidation peaks at 0.51 and 0.83 V (Figure 10, c).[48b] The oxidation potentials of $(CuL^6)^{2+}$ (Figure 10, d, 0.67 V)[48c] and Fe^{3+} (Figure 10, e, 0.76 V) are more positive than the first oxidation peak of the *nido*-*o*-carborane derivatives (0.57 V for **5** and 0.51 V for **10′**), suggesting that Cu^{2+} is capable of oxidizing *nido*-$C_2B_9H_{12}^-$ to produce neutral *closo*-5,6-$C_2B_8H_{12}$ (**34**), similar to Fe^{3+}. Given that the oxidation potential of **34** (0.87 V) is more positive than Cu^{2+} (0.5–0.8 V), the next oxidation is very slow and the further oxidation of **34** is negligible (see the Supporting Information). On the other hand, the oxidation potentials of Mn^{2+} (0.45 V) and Zn^{2+} (–0.97 V) are more negative than those for the *nido*-*o*-carborane derivatives (Figure S11 in the Supporting Information), suggesting that these metals are not capable of oxidizing the *nido*-form. The results shown in Figure 10f implies that the *nido*-*m*-carborane **20**, which is not decomposed by Cu^{2+}, has a more positive oxidation potential (0.98 V) than that of **5**, suggesting that a relationship exists between oxidation potential and the Cu^{2+}-induced decomposition reaction.

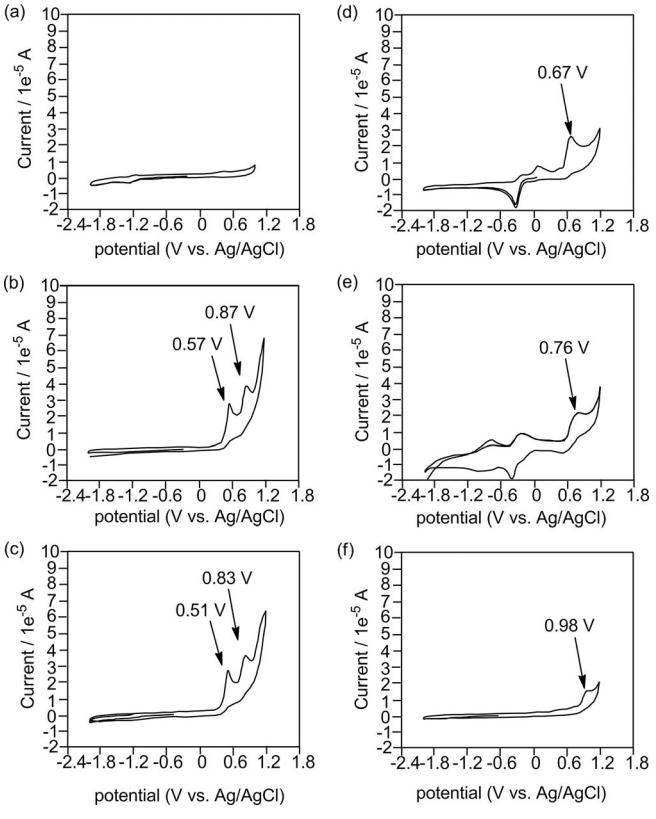
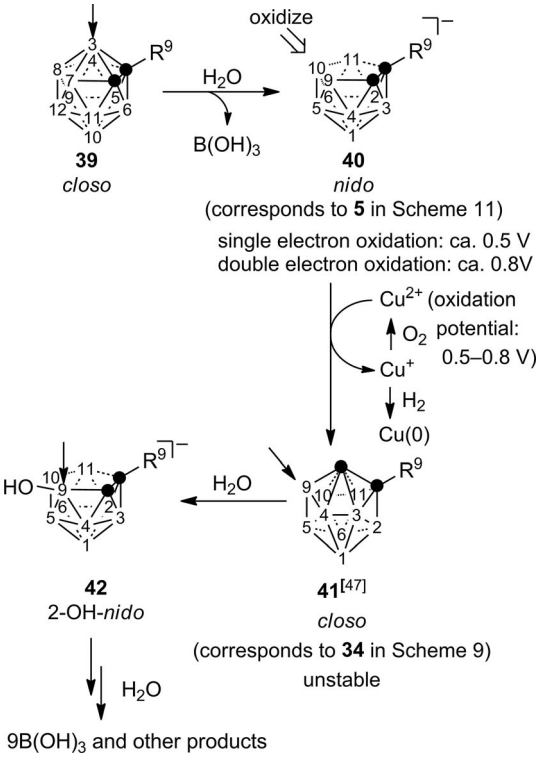


Figure 10. Cyclic voltammograms of (a) **4** (*closo*-form) (10 mM), (b) **5** (*nido*-form) (1 mM), (c) **10′** (*nido*-form) (1 mM), (d) CuL^6 (1 mM), (e) $FeCl_3$ (1 mM), and (f) **20** (*nido*-*m*-carborane) (1 mM) recorded in DMF solutions of tetrabutylammonium hexafluorophosphate (0.1 M) on a glassy carbon electrode (0.1 mV s^{-1}) starting on reduction (potentials vs. Ag/AgCl).

Based on these results and on DFT calculations of the *closo*- and *nido*-forms of *o*-carborane (Figure S12 in the Supporting Information), a reaction mechanism is proposed, as shown in Scheme 10. Initially, the *closo*-form **39** is deboronated by a nucleophile such as OH^- (metal-bound OH_2 or OH^-) and OMe^- at the electron positive B3 or B6 to afford the *nido*-form **40**. The latter is then oxidized by Cu^{2+} at the electronegative B10 of **40** and undergoes a ring-closure reaction to produce the *closo*-form **41**,[47] although the isolation and characterization of this product has yet to be studied.[49] The B2 atom of **41** is attacked by H_2O to produce the transient state **42**, which decomposes in the presence of OH^- to generate 9 equiv. of $B(OH)_3$ and other products.



Scheme 10. Proposed mechanism for the decomposition reaction (arrows indicate positively charged boron atoms, which are susceptible to attack by H_2O or OH^-).

Detection of Cu^{II} with ^{11}B MRI Based on Decomposition Reactions of *o*-Carborane Derivatives

The aforementioned results allowed us to conduct ^{11}B MRI experiments. Sample solutions of $B(OH)_3$ and *o*-carboranes were

prepared as shown in Figure 11, in which a smaller vial is nested in a larger vial. The solution in the inside vial (S_{in}) contains a solution of the *o*-carborane derivative **10** (1 mM) and the outside vial (S_{out}) contains $B(OH)_3$ (10 mM) with Cu(bpy) (1 mM) (the ratio of two-dimensional area of S_{in} and S_{out} is ca. 1:1.6). The ^{11}B atoms of $B(OH)_3$ and *o*-carborane can be irradiated separately because of their different chemical shifts, allowing these two different molecules to be detected separately. Namely, BF1 (the basic transmitter frequency) values for $B(OH)_3$ and **10** are ca. 128.392 and 128.387 MHz, respectively, as shown in Figure 11 (a-i and b-i, irradiation range: 5 kHz). In our initial experiments using spin echo sequence with TE (echo time) of 3.4 ms and TR (repetition time) of 200 ms, ^{11}B MRI signals of *o*-carboranes (**4** and **10**) were clearly observed (Figure 11, b-ii, and Figure S13 in the Supporting Information).[50] However, ^{11}B signals of $B(OH)_3$ were very weak, possibly due to shorter relaxation time of B atoms in $B(OH)_3$ (< 1 ms) than that in **10** and other *o*-carborane analogues (ca. 10 ms). Thus, we have used an ultra-short echo time (UTE) sequence with shorter TE and TR values (199 μs and 30 ms, respectively) than those of aforementioned spin echo sequence and succeeded in the selective detection of the ^{11}B signals of $B(OH)_3$, as shown in Figure 11 (a-ii).

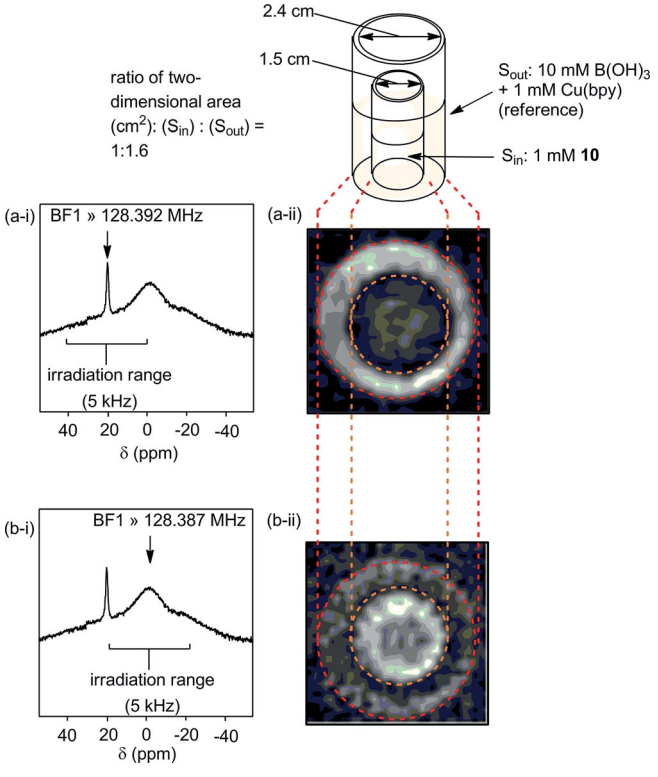


Figure 11. ^{11}B MRI images differentiating $B(OH)_3$ and **10**. Curves (a-i) and (b-i) show typical ^{11}B NMR spectra of solutions in two vials [inside vial contains 1 mM **10** and outside contains 10 mM $B(OH)_3$]. Images (a-ii) and (b-ii) show ^{11}B MRI of the inside vial (S_{in}) containing 1 mM **10** and the outside vial (S_{out}) including 10 mM $B(OH)_3$ + 1 mM Cu(bpy) (CuL^6). BF1 values for $B(OH)_3$ and **10** are ca. 128.392 MHz (a-i) and ca. 128.387 MHz (b-i), respectively (irradiation range = 5 kHz). Both ^{11}B NMR images are acquired by using a two-dimensional ultra-short echo time sequence (UTE2D) with TE = 199 μs and TR = 30 ms.

These results allowed us to monitor decomposition of **10** by ^{11}B MRI. As shown in Figure 12, the solution in the inside vial contains a solution of **10** (1 mM) in 0.5 M HEPES buffer (pH 7)/DMSO (1:1) after incubation with $CuSO_4$ (10 mM) and **21** (10 mM) at 50 °C for 0, 48, and 96 h. As shown in Figure 12 (a–c), the brightness of the inside sample increased in proportion to the progress of the decomposition reaction. After 96 h, the inside sample could be detected as well as the outside reference, indicating that **10** had decomposed and nearly 10 equiv. of $B(OH)_3$ had been released.[51]

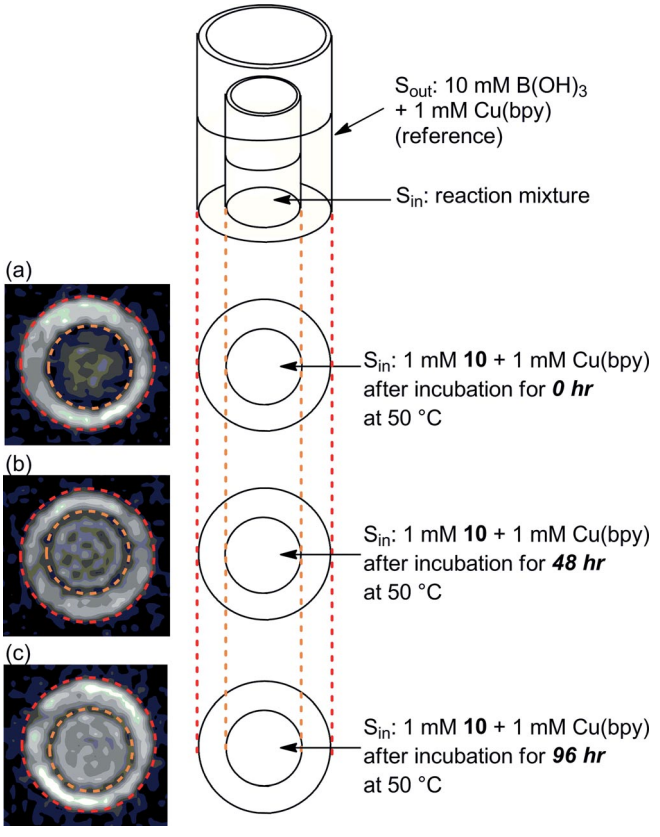


Figure 12. The decomposition of **10** was monitored by ^{11}B MRI. S_{in}: 1 mM **10** + 1 mM Cu(bpy) after incubation for (a) 0 h, (b) 48 h, and (c) 96 h. S_{out}: 10 mM $B(OH)_3$ + 1 mM Cu(bpy) (as a reference). Both ^{11}B NMR images were acquired by using a two-dimensional ultra-short echo time sequence (UTE2D) with BF1 values of ca. 128.392 MHz, TE = 199 μs and TR = 30 ms.

We then observed change in ^{11}B MRI at several concentrations of Cu^{2+} (10, 5, 2.5, and 1.25 mM) in the presence of **21** (bpy) (10 mM) for 96 h in 0.5 M HEPES buffer (pH 7)/DMSO (1:1). As summarized in Figure 13, the brightness of the inside sample increased in a Cu^{2+} concentration dependent manner. These results were also supported by azomethine-H assays (Figure S15 in the Supporting Information).

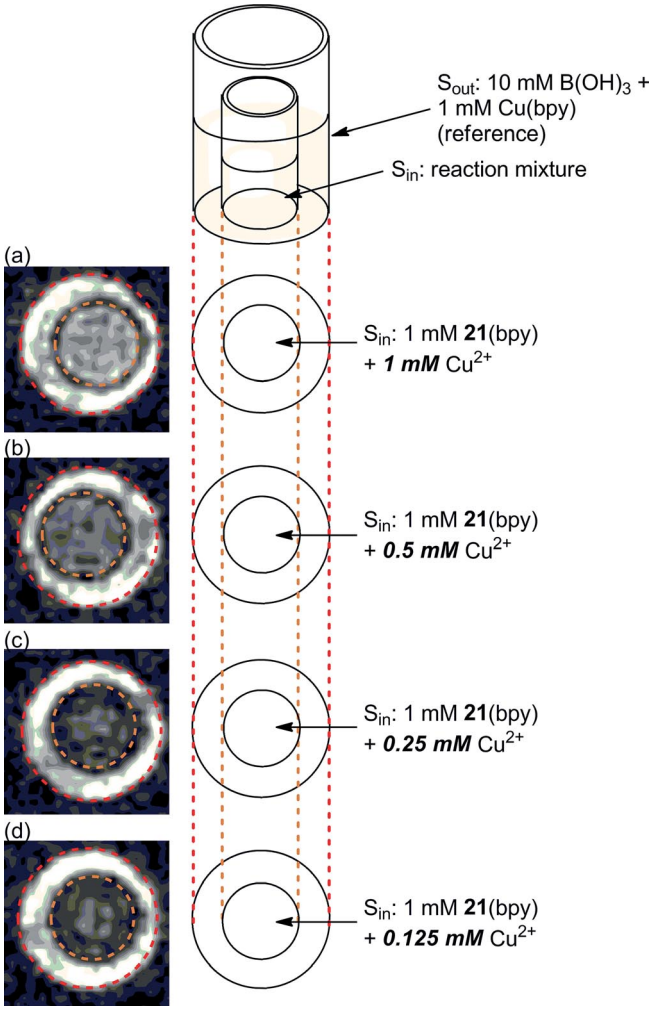


Figure 13. Change in ^{11}B MRI of 1 mM **10** at [Cu^{2+}] of (a) 1 mM, (b) 0.5 mM, (c) 0.25 mM, and (d) 0.125 mM. S_{in}: 1 mM **10** + 0.125–1 mM Cu^{2+} + 1 mM **21**(bpy) in 0.5 M HEPES buffer (pH 7)/DMSO (1:1) after incubation for 96 h at 50 °C. S_{out}: 10 mM $B(OH)_3$ + 1 mM Cu^{2+} + 1 mM **21**(bpy) (as a reference). Both ^{11}B NMR images were acquired by using a two-dimensional ultra-short echo time sequence (UTE2D) with BF1 values ca. 128.392 MHz, TE = 199 μs and TR = 30 ms.

Conclusions

We report on the degradation of *o*-carborane-pendant cyclens (**6a**, **6b**, and **6c**) to release ca. 4 equiv. of $B(OH)_3$ in the presence of Mn^{2+} and 8–9 equiv. of $B(OH)_3$ in the presence of Cu^{2+}. It was also discovered that *o*-carborane derivatives **10** and **11**, having a hydroxyl group, are completely decomposed by Cu^{2+} in the presence of Cu^{2+} or a Cu^{2+} complex such as Cu(bpy) (CuL^6) and Cu(phen) (CuL^8) to release 10 equiv. of $B(OH)_3$. Mechanistic studies indicate that the *closo*-form of *o*-carborane derivatives are converted into the corresponding *nido*-forms and that further decomposition reactions are triggered by the single-electron oxidation by Cu^{2+}. To our knowledge, this represents the first report dealing with the complete decomposition of *o*-carborane derivatives by Cu^{2+} under physiological conditions. Finally, the ^{11}B MRI detection of $B(OH)_3$ released from **10** (and **6a**, **6b**) in the presence of Cu^{2+} is reported.

We believe that these results provide useful information regarding the fundamental chemistry of *o*-carboranes and boron-containing drugs, and for the design and synthesis of ^{11}B MRI (NMR) probes and related materials.

Experimental Section

General Information: *o*-Carborane was purchased from Sigma–Aldrich and Katchem Ltd and organic solvents for spectroscopic analysis were purchased from Wako Chemicals Co., Ltd. $ZnSO_4 \cdot 7H_2O$ and $NiSO_4 \cdot 6H_2O$ were purchased from Yoneyama Chemical Industry Co. Ltd. $Zn(NO_3)_2 \cdot 6H_2O$ and $Cd(NO_3)_2 \cdot 4H_2O$, $Co(NO_3)_2 \cdot 6H_2O$, $FeSO_4 \cdot 7H_2O$ were purchased from Kanto Chemical Co. Ltd. $FeCl_2 \cdot 4H_2O$, $Cu(NO_3)_2 \cdot 3H_2O$ and CuBr was purchased from Wako Pure Chemical Industries, Ltd. Anhydrous $CaCl_2$, $Pb(NO_3)_2$, $CuSO_4 \cdot 5H_2O$ and CuI were obtained from Nacalai Tesque, Inc. and $MnSO_4 \cdot H_2O$, $Cu(CH_3COO)_2 \cdot H_2O$ and $Cu(ClO_4)_2 \cdot 6H_2O$ were purchased from Sigma–Aldrich Co. Azomethine-H reagent was purchased from Dojindo. Acetonitrile (CH_3CN) was distilled from calcium hydride prior to use. All aqueous solutions were prepared by using deionized and distilled water. The Good's buffer reagents (Dojindo) were obtained from commercial sources: MES (2-morpholinoethanesulfonic acid, pK_a = 4.8), HEPES [*N*-(2-hydroxyethyl)piperazine-*N*′-2-ethanesulfonic acid, pK_a = 7.5], EPPS [*N*-(2-hydroxyethyl)piperazine-*N*′-3-propanesulfonic acid, pK_a = 8.0], CHES [2-(cyclohexylamino)ethanesulfonic acid, pK_a = 9.5], CAPS [3-(cyclohexylamino)propanesulfonic acid, pK_a = 10.4]. Buffer solutions (KCl/HCl, pH 1 and pH 2; K-Cl/HCl, pH 3; acetic acid/sodium acetate, pH 4 and pH 5; MES, pH 6; HEPES, pH 7; EPPS, pH 8; CHES, pH 9; CAPS, pH 10) were used. All other reagents and solvents were of the highest commercial quality available and were used without further purification, unless otherwise noted. Melting points were measured with a YANACO Micro Melting Point Apparatus and are uncorrected. IR spectra were recorded with a JASCO FTIR-410 and a PerkinElmer Spectrum100 spectrophotometer at room temperature. ^1H (400 MHz), ^{13}C (100 MHz), and ^{11}B (128 MHz) NMR spectra were recorded with a JEOL Lambda 400 spectrometer. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded with a JEOL Always 300 spectrometer. Chemical shifts (δ) in $CDCl_3$ were determined relative to an internal reference of tetramethylsilane (TMS) for ^1H NMR and $CDCl_3$ for ^{13}C NMR spectroscopy. The sodium salt of 3-(trimethylsilyl)propionic-2,2,3,3-d_4 acid (TSP) was used as an external reference for ^1H NMR and 1,4-dioxane for ^{13}C NMR measurements in D_2O. ^{11}B NMR spectra were measured in a quartz NMR tube by using boron trifluoride diethyl ether complex in $CDCl_3$ as an external reference (δ = 0 ppm). Elemental analyses were performed with a Perkin–Elmer CHN 2400 analyzer. Electrospray ionization (ESI) mass spectra were recorded with a JEOL JMS-SX102A and Varian 910-MS. Thin-layer chromatography (TLC) was performed using Merck Silica 5554 (silica gel) TLC plates. Silica gel column chromatography was performed using Fuji Silysia Chemical FL-100D. Density functional theory (DFT) calculations were also performed by using the Gaussian 09 program (B3LYP, the 6-31G basis set.) Compound **5**, **10**, **15**, **18**, **19**, and **20** were prepared according to the reported methods.[38,39,32e]

1-(Prop-2-yn-1-yl)-4,7,10-tris(*tert*-butyloxycarbonyl)-1,4,7,10-tetraazacyclododecane (13a): A mixture of 3-Boc-cyclen **11**[36] (900 mg, 1.90 mmol), propargyl bromide **12a** (272 mg, 2.29 mmol), and Na_2CO_3 (403 mg, 3.80 mmol) in CH_3CN (25 mL) was heated to reflux for 16 h. After filtration through a Celite pad, the filtrate was evaporated and purified by silica gel column chromatography (hexane/EtOAc, 1:1) to afford **13a** (922 mg, 95 %) as a colorless amor-

phous solid. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.20–3.60 (m, 14 H), 2.77 (br. s, 4 H), 2.19 (s, 1 H), 1.47 (s, 9 H), 1.45 (s, 18 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 155.80, 155.50, 155.07, 79.49, 79.27, 79.07, 73.51, 54.68 (br), 54.11, 53.03, 49.63, 48.95 (br), 47.67, 47.48, 46.85, 46.33, 28.54, 28.33, 28.28 ppm. IR (ATR): $\tilde{\nu}$ = 630, 757, 772, 1104, 1152, 1247, 1363, 1412, 1458, 1679, 2932, 2976 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{26}H_{46}N_4O_6$ + H^+ [M + H^+] 511.3490; found 511.3486.

1-(1,2-Dicarbadodecaboranyl)methyl-4,7,10-tris(*tert*-butyloxycarbonyl)-1,4,7,10-tetraazacyclododecane (14a): To a solution of $B_{10}H_{14}$ (42.8 mg, 0.35 mmol) in toluene (2 mL) was added CH_3CN (0.33 mL) and **13a** (185 mg, 0.35 mmol) and the reaction mixture was heated at 80–90 °C for 11 h. After evaporation, the resulting residue was purified by silica gel column chromatography (hexane/EtOAc, 5:1) to afford **14a** (53.6 mg, 24 %) as a colorless amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 4.51 (br. s, 1 H), 3.10–3.60 (m, 14 H), 2.70 (br. s, 1 H), 1.46 (s, 27 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 156.34, 155.80, 80.29, 80.08, 74.28, 59.53 (br), 53.98 (br), 50.04 (br), 49.45 (br), 46.20 (br), 28.51 ppm. ^{11}B{^{1}H} NMR (128 MHz, $CDCl_3$, 25 °C, BF_3·Et_2O): δ = –2.2, –5.1, –10.0, –11.8 ppm. IR (ATR): $\tilde{\nu}$ = 755, 773, 1248, 1365, 1414, 1457, 1680, 2587, 2933, 2978 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{26}H_{56}B_{10}N_4O_6$ + H^+ [M + H^+] 629.5287; found 629.5288.

1-(1,2-Dicarbadodecaboranyl)methyl-1,4,7,10-tetraazacyclododecane Hydrochloride Salt (6a): To a MeOH solution (6 mL) of **14a** (120 mg, 0.19 mmol) was added 4 N HCl/dioxane (6 mL) at room temperature and the reaction mixture was stirred for 2 h. After evaporation, the resulting residue was washed with $CHCl_3$ to give **6a** (56.4 mg, 69 %) as a colorless solid; m.p. 239–243 °C (dec.). ^{1}H NMR (300 MHz, D_2O, 25 °C, TSP): δ = 4.50 (br. s, 1 H), 3.61 (s, 1 H), 3.15–3.30 (m, 12 H), 3.01 (m, 4 H) ppm. ^{13}C NMR [75 MHz, D_2O, 25 °C, 1,4-dioxane (external reference)]: δ = 74.42, 63.23, 58.70, 48.79, 45.19, 43.92, 43.04, 42.01 ppm. ^{11}B{^{1}H} NMR (128 MHz, D_2O, 25 °C, BF_3·Et_2O): δ = –0.4, –2.5, –6.9, –9.9 ppm. IR (KBr): $\tilde{\nu}$ = 718, 1075, 1083, 1098, 1377, 1442, 1450, 1584, 1651, 2351, 2428, 2559, 2572, 2584, 2594, 2606, 2626, 2964, 3006, 3047, 3293, 3385 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{11}H_{32}N_4B_{10}$ + H^+ [M + H^+] 329.3705; found 329.3707. $C_{11}H_{35}B_{10}Cl_3N_4$·$2H_2O$: calcd. C 27.88, H 8.30, N 11.82; found C 28.28, H 8.29, N 11.87.

1-(3-Butynyl)-4,7,10-tris(*tert*-butyloxycarbonyl)-1,4,7,10-tetraazacyclododecane (13b): A mixture of **11** (1.0 g, 2.1 mmol), 4-bromo-1-butyne **12b** (1.4 g, 10.6 mmol), NaI (3.8 g, 25.3 mmol) and Cs_2CO_3 (825 mg, 2.5 mmol) in CH_3CN (33 mL) was heated to reflux for 44 h. After filtration through a Celite pad, the filtrate was evaporated and the residue was purified by silica gel column chromatography (hexane/EtOAc, 1:1) to afford **13b** (1.1 g, 90 %) as a colorless amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.20–3.60 (br, 12 H), 2.87 (t, *J* = 7.4 Hz, 2 H), 2.62–2.78 (br, 4 H), 2.34 (td, *J* = 2.5, 7.5 Hz, 2 H), 1.98 (t, *J* = 2.6 Hz, 1 H), 1.47 (s, 1 H), 1.45 (s, 18 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 157.39, 157.18, 157.00, 137.43, 137.05, 136.70, 134.59, 133.91, 133.29, 132.70, 128.38, 80.73, 57.91 (br), 56.56 (br), 50.76 (br), 48.50, 48.23, 29.09, 28.86 ppm. IR (ATR): $\tilde{\nu}$ = 630, 757, 772, 1104, 1152, 1247, 1363, 1412, 1458, 1679, 2932, 2976 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{27}H_{48}N_4O_6$ + H^+ [M + H^+] 525.3647; found 525.3645.

1-(1,2-Dicarbadodecaboranyl)ethyl-4,7,10-tris(*tert*-butyloxycarbonyl)-1,4,7,10-tetraazacyclododecane (14b): To a solution of $B_{10}H_{14}$ (229 mg, 1.87 mmol) in toluene (3 mL) was added CH_3CN (1.73 mL) and **13b** (981 mg, 1.87 mmol). The resulting solution was heated 80–90 °C for 24 h. After evaporation, the resulting residue was purified by silica gel column chromatography (hexane/EtOAc, 5:1) to afford **14b** (122 mg, 10 %) as a colorless amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.95 (br s, 1 H), 2.50–2.72 (br, 12 H), 2.31 (t, *J* = 8.1 Hz, 2 H), 1.46 (s, 9 H), 1.45 (s, 18 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 134.52, 133.41, 133.30, 131.94, 128.77–128.99 (m), 128.04–128.21 (m), 66.73–67.66 (m), 57.20–57.69 (m), 48.34–48.64 (m), 43.95–44.33 (m), 41.81–42.22 (m) ppm; ^{11}B{^{1}H} NMR (128 MHz, $CDCl_3$, 25 °C, BF_3·Et_2O): δ = –1.8, –5.1, –9.1, –11.3 (br s) ppm. IR (ATR): $\tilde{\nu}$ = 758, 772, 1110, 1152, 1247, 1365, 1414, 1457, 1675, 2587, 2932, 2976 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{27}H_{58}B_{10}N_4O_2$ + H^+ [M + H^+] 643.5443; found 643.5432.

1-(1,2-Dicarbadodecaboranyl)ethyl-1,4,7,10-tetraazacyclododecane Hydrochloride Salt (6b): To a $CHCl_3$ solution (1 mL) of **14b** (24 mg, 0.0382 mmol) was added 4 N HCl/dioxane (1 mL) at room temperature and the reaction mixture was stirred for 2 h. After evaporation, the resulting residue was reprecipitated from hexane/$CHCl_3$/MeOH to give **6b** (8.9 mg, 52 %) as a colorless solid, which was determined to be the 3HCl salt by elemental analysis, m.p. 234–240 °C (dec.). ^{1}H NMR (300 MHz, D_2O, 25 °C, TSP): δ = 4.42 (br s, 1 H), 3.65–3.90 (m, 2 H), 3.10–3.30 (m, 7 H), 2.75–3.05 (m, 9 H), 2.48–2.60 (m, 2 H) ppm. ^{13}C NMR [75 MHz, D_2O, 25 °C, 1,4-dioxane (external reference)]: δ = 73.91, 67.75, 63.59, 51.44, 47.50, 44.96, 42.57, 42.12, 30.83 ppm. ^{11}B{^{1}H} NMR (128 MHz, D_2O, 25 °C, BF_3·Et_2O): δ = –2.8, –5.7, –9.4, –11.7 ppm. IR (KBr): $\tilde{\nu}$ = 722, 960, 1017, 1072, 1448, 1577, 1613, 2575, 2970, 3381 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{15}H_{27}B_{10}N_4O_2$ + H^+ [M + H^+] 306.2339; found 306.2336. $C_{12}H_{37}B_{10}Cl_3N_4$ (451.91): calcd. C 31.89, H 8.25, N 12.40; found C 31.65, H 8.57, N 12.76.

1-(3-Pentynyl)-4,7,10-tris(*tert*-butyloxycarbonyl)-1,4,7,10-tetraazacyclododecane (13c): A mixture of **11** (1 g, 2.11 mmol), 5-chloro-1-propyne **12c** (2.16 g, 21.1 mmol), NaI (3.80 g, 25.3 mmol) and Cs_2CO_3 (687 mg, 2.11 mmol) in CH_3CN (5 mL) was heated to reflux for 4 d. After filtration through a Celite pad, the filtrate was evaporated and the residue purified by silica gel column chromatography (hexane/EtOAc, 3:1) to afford **13c** (1.04 g, 91 %) as a colorless amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.20–3.62 (br, 12 H), 2.68–2.74 (m, 6 H), 2.19 (td, *J* = 2.6, 7.0 Hz, 2 H), 1.96 (t, *J* = 2.6 Hz, 1 H), 1.62–1.78 (m, 4 H), 1.47 (s, 9 H), 1.45 (s, 18 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 156.00, 155.58, 155.28, 83.64, 79.36, 79.13, 68.71, 54.80, 53.60, 51.37, 49.86, 48.11 (br), 47.83 (br), 47.48 (br), 28.57, 28.39, 22.94, 16.55 ppm. IR (ATR): $\tilde{\nu}$ = 772, 1104, 1151, 1248, 1363, 1413, 1459, 1681, 2933, 2975 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{28}H_{50}N_4O_6$ + H^+ [M + H^+] 539.3803; found 539.3798.

1-(1,2-Dicarbadodecaboranyl)propyl-4,7,10-tris(*tert*-butyloxycarbonyl)-1,4,7,10-tetraazacyclododecane (14c): To a solution of $B_{10}H_{14}$ (227 mg, 1.86 mmol) in toluene (10 mL) was added CH_3CN (2 mL) and **13c** (1.0 g, 1.86 mmol). The resulting solution was heated at 80–90 °C for 14 h. After evaporation, the resulting residue was purified by silica gel column chromatography (hexane/EtOAc, 5:1) to afford **14c** (122 mg, 13 %) as a colorless amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.64 (br s, 1 H), 3.18–3.48 (br, 12 H), 2.38–2.62 (br, 8 H), 2.10–2.22 (br, 2 H), 1.45 (s, 9 H), 1.44 (s, 18 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 156.19, 155.78, 155.42, 79.71, 79.56, 75.21, 61.38, 54.80 (br), 53.91 (br), 51.44 (br), 49.87 (br), 48.37 (br), 47.79 (br), 35.90, 28.63, 28.51, 24.90 ppm. ^{11}B{^{1}H} NMR (128 MHz, $CDCl_3$/BF_3·Et_2O): δ = –2.5, –5.9, –9.4, –11.7 ppm. IR (ATR): $\tilde{\nu}$ = 772, 1153, 1249, 1365, 1414, 1458, 1674, 2589, 2932, 2976 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{28}H_{60}B_{10}N_4O_2$ + H^+ [M + H^+] 657.5600; found 657.5598.

1-(1,2-Dicarbadodecaboranyl)propyl-1,4,7,10-tetraazacyclododecane Hydrochloride Salt (6c): To a MeOH solution (3 mL) of **14c** (61.3 mg, 0.093 mmol) was added 4 N HCl/dioxane (3 mL) at room temperature, and the reaction mixture was stirred for 3.5 h. After

evaporation, the resulting residue was washed with $CHCl_3$ to give **6c** (37 mg, 85 %) as a colorless solid, which was determined to be the 3HCl salt by elemental analysis, m.p. 239–243 °C (dec.). ^{1}H NMR (300 MHz, D_2O, 25 °C, TSP): δ = 4.40 (br s, 1 H), 2.98–3.26 (br m, 16 H), 2.72 (t, J = 8.1 Hz, 2 H), 2.30 (t, J = 8.4 Hz, 2 H), 1.78–1.82 (m, 2 H) ppm. ^{13}C NMR [75 MHz, D_2O, 25 °C, 1,4-dioxane(external reference)]: δ = 65.58, 52.79, 41.59, 38.00, 34.12, 32.20, 32.12, 24.58, 13.19 ppm. ^{11}B{^{1}H} NMR (128 MHz, D_2O, 25 °C, BF_3·Et_2O): δ = –3.2, –6.4, –9.8, –11.7 ppm. IR (KBr): $\tilde{\nu}$ = 722, 1021, 1381, 1445, 1458, 1473, 1575, 2568, 3231, 3400, 3473 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{13}H_{36}B_{10}N_4$ + H^+ [M + H^+] 357.4018; found 357.4016. $C_{13}H_{39}B_{10}Cl_3N_4$·1/3,$CHCl_3$·1/3$CH_3OH$: calcd. C 31.79, H 7.94, N 10.85; found C 31.84, H 7.95, N 10.48.

8-(Hydroxymethyl)-7,8-dicarbaundecaborate(2$^-$) Sodium Salt (10′): To a MeOH solution (3 mL) of **10** (43.5 mg, 0.25 mmol) was added NaOMe (27 mg, 2 equiv.) at room temperature and the reaction mixture was stirred and heated to reflux for 18.5 h. After cooling the reaction mixture, solvent was removed in vacuo and the residue was dissolved in acetone and precipitation was removed by filtration. After filtration, the filtrate was evaporated and the residue was purified by silica gel column chromatography ($CHCl_3$/MeOH, 4:1) to afford **10′** (41 mg, 88 %) as an amorphous mass. ^{1}H NMR (400 MHz, CD_3OD, 25 °C, TMS): δ = 4.637 (s, 1 H), 3.72 (d, J = 11.2 Hz, 1 H), 2.53 to –0.36 (br. m, 9 H), –2.65 (br, 1 H) ppm. ^{13}C NMR (100 MHz, CD_3OD, 25 °C, TMS): δ = 70.61, 62.40–61.43 (m), 46.63–45.55 (m) ppm. ^{11}B{^{1}H} NMR (128 MHz, CD_3OD, 25 °C, BF_3·Et_2O): δ = –10.4, –11.4, –14.8, –17.3, –18.4, –22.1, –33.0, –37.4 ppm. IR (ATR): $\tilde{\nu}$ = 1007, 1088, 1153, 1226, 1273, 1348, 1391, 1461, 1615, 1714, 2505, 2850, 2889, 2925, 2950, 3557 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_3H_{15}B_9ONa$ – Na^+ [M – Na^+] 165.1882; found 165.1883.

Compound 16: To a solution of **5** (200 mg, 1.39 mmol) and phthalaldehyde (203 mg, 1.51 mmol) in THF (6.88 mL) was added tetrabutylammonium fluoride (1.0 M in THF, 4.17 mL) under Ar atmosphere, and the mixture was stirred at room temperature for 30 min. The reaction was quenched with saturated aqueous NH_4Cl, and the mixture was extracted with diethyl ether, washed with brine, and dried with anhydrous Na_2SO_4. After filtration, the filtrate was evaporated and the residue was purified by silica gel column chromatography (hexane/EtOAc, 3:1) to afford **16** (376 mg, 97 %) as a white solid. For characterization of the diastereomer by NMR analysis, **16** (50 mg) was purified by HPLC (H_2O/MeOH, 50:50 to 0:100 in 30 min, column: senshu pak PEGASIL ODS) to afford **16a** (t_R = 19 min, 22.1 mg) and **16b** (t_R = 21 min, 18.1 mg) as a white solid.

Compound 16a: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.50 (dd, J = 5.4 Hz, 2 H), 7.38 (dd, J = 5.8 Hz, 2 H), 5.24 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 132.83 (2 C), 129.63 (2 C), 128.35 (2 C), 69.82 (2 C), 50.91 (2 C) ppm; ^{11}B{^{1}H} NMR (128 MHz, $CDCl_3$, 25 °C, BF_3·Et_2O): δ = –4.0, –10.0, –12.0 ppm.

Compound 16b: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.48 (dd, J = 5.8 Hz, 2 H), 7.37 (dd, J = 6.2 Hz, 2 H), 5.20 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 132.79 (2 C), 129.65 (2 C), 128.36 (2 C), 69.83 (2 C), 58.12 (2 C) ppm; ^{11}B{^{1}H} NMR (128 MHz, D_2O, 25 °C, BF_3·Et_2O): δ = –3.9, –9.9, –12.0 ppm. IR (ATR): $\tilde{\nu}$ = 764, 1013, 2561, 2573, 2599, 2622, 3251, 3374 cm^{-1}. HRMS (FAB): *m/z* calcd. for $C_{10}H_{18}B_{10}O_2$ + H^+ [M + H^+] 280.2237; found 280.2246.

General Procedure for Detection of d-Block Metal Ions with ^{11}B NMR Spectroscopy: (Figures 1 and 5). Sample solutions of *o*-carborane-pendant cyclens **6a**–**c** (12.5 mM) in 0.5 M HEPES buffer (pH 7; 0.8 mL) were prepared and each was mixed with a solution (0.2 mL) of a metal salt in D_2O ([metal salt] = 100 mM). For *o*-carborane **10**, having a hydroxymethyl group, its solution (0.1 mL) in DMSO (100 mM) was mixed with 0.7 mL of DMSO/0.5 M acetate buffer (pH 4; 4:3), and the solution was then added to a solution (0.2 mL) of the metal salt in D_2O ([metal salt] = 100 mM). These resulting mixtures were incubated in screw-top vials at the given temperature and for the given time. An aliquot of the reaction mixture (0.66 mL) was placed into a quartz NMR tube and analyzed by ^{11}B NMR spectroscopy (128 MHz) with a sweep width of 38022 Hz, 4096 data points, a 45° pulse width, a 0.16 second recycle time, and 2850 scans. Each spectrum was processed with 4.6 Hz line-broadening using BF_3·Et_2O in $CDCl_3$ as an external reference (δ = 0 ppm) (see Figure S1 in the Supporting Information).

Azomethin-H Assay for the Decomposition of Carborane Derivatives by Metal Ions: See Figures 2, 3, 4, 6, 7, 8, and 9.[40]

Preparation of Reaction Samples (Solution A): For *o*-carborane-pendant cyclen **6a**–**c**, solutions (0.8 mL) of each compound in 0.5 M HEPES buffer (pH 7) were prepared ([**6a**–**c**] = 12.5 mM) and mixed with a solution (0.2 mL) of the metal salt (100 mM) in water. For *o*- or *m*-carborane derivatives (**4**, **10**, **11**, **16**, **17**, **18**, **19**, and **20**), solutions (0.9 mL) of each compound in DMSO/buffer (5:4 for **4**, **10**, **11**, **17**, **18**, **19**, and **20**; 7:2 for **16**) ([**4**, **10**, **11**, **16**, **17**, **18**, **19**, and **20**] = 11.1 mM) were prepared, to which a solution (0.1 mL) of the metal salt in water were added ([metal salt] = 1, 5, 10, 100 mM). These mixtures were incubated at 37 or 50 °C in a screw-top vial for the decomposition reaction. An aliquot (20 μL) of the reaction mixture (solution A) was taken at given reaction times (after 0, 12, 24, 48, 96 and 144 h), in which concentrations of $B(OH)_3$ produced by the decomposition reaction of carborane derivatives were determined according to the following procedure.

Preparation of Ammonium Acetate Buffer Solution (Solution B): Ammonium acetate [$(NH_4)OAc$, 1.87 mol, 100 g] was dissolved in water (ca. 80 mL), to which EDTA (400 mg, 1.37 mmol) and anhydrous citric acid (366 mg, 1.9 mmol) had been added. Then, H_3PO_4 [2 mL, 85 % (w/w), 38.6 mmol] and H_2SO_4 [6 mL, 96 % (w/w), 113 mmol] were added dropwise to a solution of $(NH_4)OAc$, EDTA and citric acid with gentle stirring and warming at 50–70 °C to dissolve the reagents, and the solution was then made up to 100 mL with water to prepare solution B [containing 18.7 M $(NH_4)OAc$, 13.7 mM EDTA, 19 mM citric acid, 386 mM H_3PO_4, and 1.13 M H_2SO_4].

Preparation of Azomethine-H Stock Solution (Solution C). Azomethine-H (1 g, 2.3 mmol) and ascorbic acid (3 g, 17 mmol) were dissolved in water (100 mL). The resulting azomethine-H solution (containing 23 mM azomethine-H and 170 mM ascorbic acid) was mixed with an equal volume of solution B (typically, 15 mL + 15 mL) to prepare solution C [containing 9.4 M $(NH_4)OAc$, 6.9 mM EDTA, 9.5 mM citric acid, 193 mM H_3PO_4, 551 mM H_2SO_4, 170 mM ascorbic acid and 23 mM azomethine-H].

Preparation of Standard Solution (Solution D): Standard solutions of $B(OH)_3$ in water (4, 2, 1 mg/L) were prepared for preparing a standard (working) curve (32, 16, 8.1 μM).

Procedure of Azomethine-H Assay: For the measurement of the blank solution, 2 mL of the azomethine-H solution (solution C) was mixed with 8 mL of water (solution E, 10 mL in total). For the measurement of the standard solution of $B(OH)_3$, 5 mL of standard solution of $B(OH)_3$ (solution D) were mixed with 3 mL of water and 2 mL of the azomethine-H solution (solution C) to obtain solution F (10 mL in total). For the measurement of the decomposition reaction mixture of carborane derivatives, 10 μL of reaction mixture (from 20 μL of solution A) was made up to 10 mL with water (solution G). From solution G, 2 mL was removed and 2 mL of the azomethine-H solution (solution C) was added to prepare sample solutions

for analysis (solution H, 10 mL in total). After standing for 1 h, the absorbance at 412 nm of standard solution (solution F) and a sample solution (solution H) were measured by using absorbance of a blank solution (solution E) as a baseline. It is strongly recommended to prepare standard solutions {solution F, in which $[B(OH)_3]$ = 8.1, 16 and 32 μM} and measure their UV/Vis spectra to make a working curve, immediately before the measurement of the sample solutions in all the experiments. Typical UV/Vis spectra of standard solution of $B(OH)_3$ are shown in Figure S2a in the Supporting Information ($\varepsilon_{415} = 1.01 \times 10^4$ M^{-1} cm^{-1}). Concentrations of $B(OH)_3$ in sample solutions (solution H) were determined based on the standard curve, which was obtained from standard $B(OH)_3$ solutions (Figure S2b in the Supporting Information).

Cyclic Voltammetry of Carborane Derivatives and Metal Ions: (Figure 10) Cyclic voltammetry measurements were performed with a BAS model 660A electrochemical analyzer at room temperature in DMF containing 0.1 M nBu$_4$N(PF$_6$) as the supporting electrolyte in a standard one-component cell equipped with 3-mm outer diameter glassy carbon working electrode, and a platinum wire counter electrode, the Ag/AgCl-referenced electrode (Ag/AgCl in MeCN containing 0.01 M $AgNO_3$ and 0.1 M nBu$_4$NPF$_6$). All solutions were deoxygenated by bubbling with argon for at least 10 min, immediately before the measurement.

Magnetic Resonance Imaging of Probes in the Presence of Cu^{II} and Mn^{II}: (Figure 11) A solution (1 mL) of **10** (10 mM), bpy (10 mM) and $CuSO_4{\cdot}5H_2O$ (10 mM) in DMSO/0.5 M HEPES buffer (pH 7; 1:1) was incubated at 50 °C in a screw-capped vial. After incubation for a given time (24, 48 and 96 h), the solutions were diluted with 9 mL of HEPES buffer (0.5 M, pH 7) (10 mL in total). A solution of $B(OH)_3$ (10 mM), Cu^{2+} ($CuSO_4{\cdot}5H_2O$) (1 mM) and **26** (1 mM) in DMSO/0.5 M HEPES buffer (pH 7; 5:95) was prepared as reference solution. NMR imaging experiments were performed with a 9.4 T Avance I Micro-Imaging system (Bruker BioSpin, Rheinstetten, Germany) with a Micro2.5 gradient coil and ^{1}H/^{11}B dual tuned RF coil (dia. 25 mm). ^{11}B NMR images were acquired by a two dimensional ultra-short echo time sequence (UTE2D) with the following parameters: TE = 199 μs, TR = 30 ms, flip angle: 60°, matrix size: 64 × 64, FOV = 60 × 60 mm, slice thickness: 20 mm, number of projection: 202. The scan time was 16 min.

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chemical shifts of ^{11}B NMR signals of $B(OH)_3$ produced from *o*-carborane derivatives accurately in all the decomposition reactions and the second is to determine the concentrations of $B(OH)_3$ produced by decomposition of *o*-carborane based on the amount (concentration) of $BF_3{\cdot}Et_2O$ solution (the same reference sample was used throughout the decomposition reactions of each substrate). An illustration of NMR samples used in this work is shown in Figure S1 in the Supporting Information. For the references of ^{11}B NMR of boron-containing compounds in which $BF_3{\cdot}Et_2O$ was used as an external reference, see: a) R. Otero, S. Seoane, R. Sigüeiro, A. Y. Belorusova, M. A. Maestro, R. Pérez-Fernández, N. Rochei, A. Mourino, *Chem. Sci.* **2016**, *7*, 1033–1037; b) S. Krupski, G. Kehr, C. G. Daniliuc, G. Erker, *Dalton Trans.* **2016**, DOI: 10.1039/C5DT03879K.

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[50] ^{11}B MRI images differentiating $B(OH)_3$ and *o*-carborane **4** is shown in Figure S13 in the Supporting Information. These ^{11}B NMR images were acquired by using spin echo sequence with TE = 3.4 ms and TR = 200 ms.

[51] Changes, in: the ^{11}B MRI of **6a**, **6b** and **10** and a detailed explanation are presented in Figure S14 in the Supporting Information.

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