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# Synthesis and biological evaluation of *meta*-carborane-containing phenoxyacetanilides as inhibitors of hypoxia-inducible factor (HIF)-1 transcriptional activity

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Dedicated to Professor Russell N. Grimes on the occasion of his 80th anniversary.

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ABSTRACT

*meta*-Carboranylphenoxyacetanilides were synthesized by copper catalyzed coupling reaction of *meta*-carborane and phenyl iodides. The synthesized compounds were evaluated for their ability to inhibit hypoxia-induced HIF-1 transcriptional activity using a cell-based reporter gene assay. Among the compounds synthesized, *meta*-carborane containing phenoxyanilides **2d** and **2h**, which have an isobutyl group on *meta*-carborane, exhibited significant inhibition of hypoxia-induced HIF-1 transcriptional activity toward HeLa cell-based reporter gene assay with the $IC_{50}$ values of 0.73 and 0.55 μM, respectively.


## 1. Introduction

Recently much attention has been focused on carboranes as pharmacophores in pharmaceutical drug design [1,2]. Especially dicarba-*closo*-dodecaboranes, having three isomers: 1,2-, 1,7-, and 1,12-dicarba-*closo*-dodecaboraneare referred to as *ortho*-, *meta*- and *para*-carbaborane, are extremely hydrophobic and regarded stable under chemical and physical conditions [3]. The van der Waals volume of these carboranes is a range of from 141 to 148 $Å^3$ and the volume is compatible to that of adamantane (136 $Å^3$) and almost twice the volume of benzene [1,4]. Carboranes have been widely used as boron sources for boron neutron capture therapy (BNCT) agents [5–7]. The first attempts to use carboranes as a pharmacophore have been initiated by Endo and coworkers, who introduced the 1-(4-hydroxyphenyl)carborane core as a steroidal framework [8,9]. Since their reports, various compounds have been synthesized based on the carborane pharmacophore strategy including folic acid analogs [10], antifolates [11], flufenamic acid and diflunisal analogs [12], aspirin and indomethacin analogs [13,14], nicotinamide phosphoribosyltranferase inhibitors [15], carbonic anhydrase inhibitors [16], purinergic $P2X_7$ receptor antagonists [17], combretastatin analogs [18], and manassantin analogs [19].

We recently reported *ortho*-carborane-containing hypoxia inducible factor (HIF)-1α inhibitors (1a–c) [20–22] that were synthesized based on the corresponding adamantane derivative LW6 (Fig. 1) [23,24]. HIF-1α is a transcription factor that regulates angiogenesis, invasion, metastasis, glucose uptake, and cell survival during cancer development [25–28]. Although HIF-1α undergoes an oxygen-dependent degradation under aerobic conditions, it is stabilized and translocate into the nucleus to form a heterodimeric complex with a constitutively expressed subunit HIF-1β. This α/β heterodimeric complex binds to specific nucleotide sequences (hypoxia response elements) with co-activators, such as p300 and CBP to activate various hypoxia responsive genes and overexpression of HIF-1α is associated with poor prognosis and resistance to treatment of cancer patients [29]. Therefore, HIF-1α is considered to be one of the potential targets for antitumor agents [30]. Previously, we examined the effects of substituents at a R2 group on HIF-1 transcriptional activity and found that an ethyl group (1b) was the most suitable for the inhibitory activity of HIF-1

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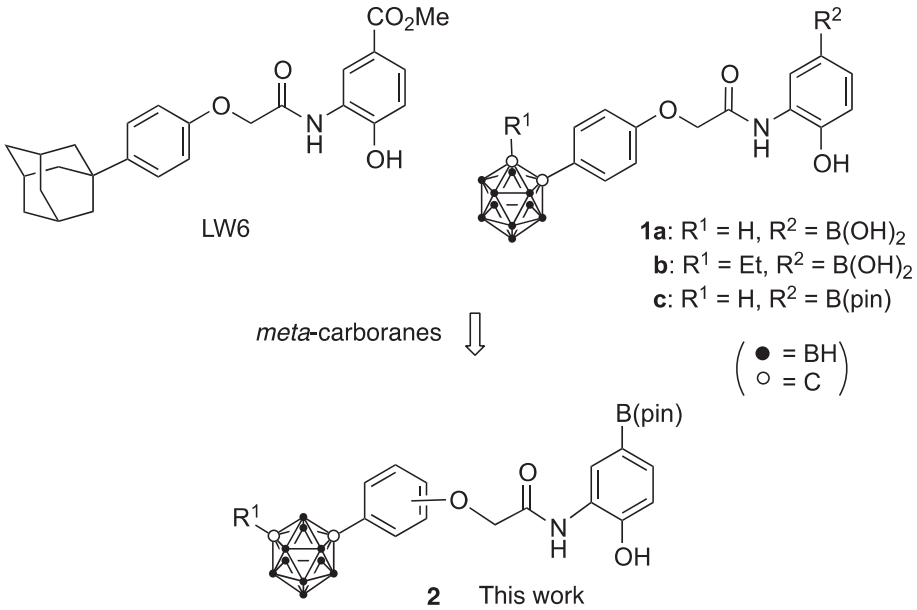



**Fig. 1.** Design of *meta*-carborane containing phenoxyacetanilides **2** based on the structures of LW6 and *ortho*-carborane derivatives **1**.

transcription [22]. In this paper, we synthesized *meta*-carboranylphenoxyacetanilides and evaluated their inhibitory effects on HIF-1 transcriptional activity.

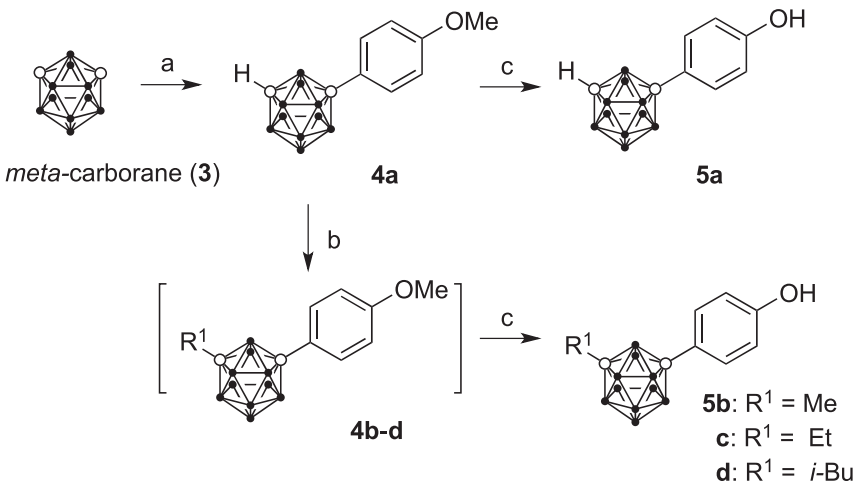
## 2. Results and discussions

### 2.1. Chemistry

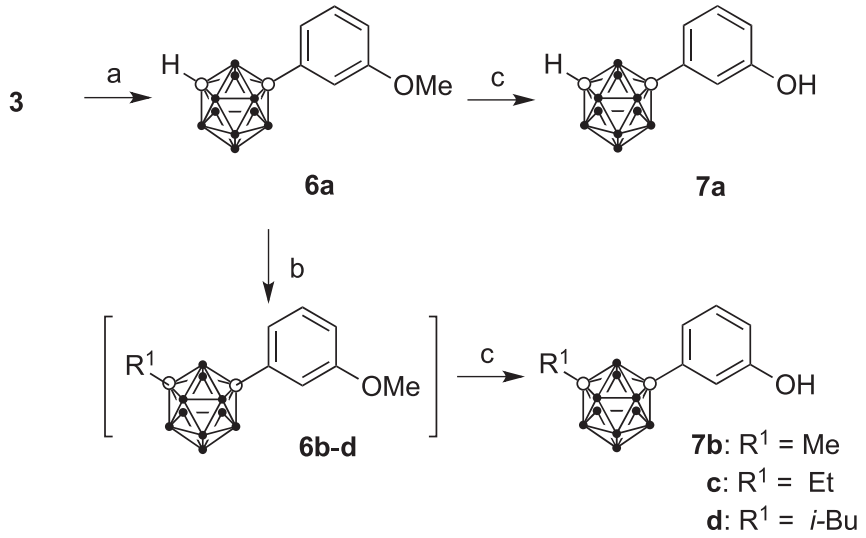
We first synthesized 1-(4-hydroxyphenyl)-*meta*-carboranes as shown in Scheme 1. The *C*-arylation of *meta*-carborane through its copper derivative was developed by Wade and coworkers [31]. *meta*-Carborane **3** was treated with *n*-BuLi in dimethoxyethane (DME) at 0 °C to give the corresponding lithiated carborane, which reacted with CuCl to generate the *C*-copper derivative of *meta*-carborane. Coupling reaction of the copper derivative with 4-iodoanisole proceeded in the presence of pyridine under refluxed conditions to give 1-(4-methoxyphenyl)-*meta*-carborane **4a** [8]. The methoxy group of **4a** was deprotected by boron tribromide to give 1-(4-hydroxyphenyl)-*meta*-carborane **5** [8] in 91% yield. Di-substituted *meta*-carboranes **5b**–**d** were also synthesized from **4a**. Lithiation of **4a** with *n*-BuLi proceeded in tetrahydrofuran (THF) at −10 °C and the resulting lithiated carborane reacted with alkyl iodides to give the corresponding di-substituted *meta*-carboranes **4b**–**d**. Deprotection of a methoxy group on **4b**–**d** was carried out using boron tribromide to give 1-alkyl-7-(4-hydroxyphenyl)-*meta*-carboranes **5b**–**d** in 40–74% yields in two steps.

We next synthesized 1-(3-hydroxyphenyl)-*meta*-carboranes in a similar manner to the synthesis of 1-(4-hydroxyphenyl)-*meta*-carboranes. As shown in Scheme 2, *C*-arylation of *meta*-carborane **3** with 3-iodoanisole proceeded in the presence of CuCl and pyridine to give 1-(3-methoxyphenyl)-*meta*-carborane **6a** [9], which was converted to the phenoxy derivatives **7a** [9] or **7b**–**d** through di-substituted *meta*-carboranes **6b**–**d**.

Scheme 3 shows the synthesis of *meta*-carboranylphenoxyacetanilides **2a**–**h**. The pinacol ester of boronic acid moiety was introduced into 4-bromo-2-nitrophenol benzyl ether **8** by the Suzuki-Miyaura diboron coupling and the resulting phenyl boronic ester **9** was converted to the corresponding aniline **10** under the




**Scheme 1.** Reagents and conditions: (a) (i) *n*-BuLi, DME, 0 °C, 30 min, (ii) CuCl, r.t.,1.5 h, (iii) 4-iodoanisole, pyridine, reflux, 48 h, 26%; (b) (i) *n*-BuLi, THF, −10 °C, 30 min, (ii) $R^1I$, −10 °C, 1.5 h; (c) $BBr_3$, $CH_2Cl_2$, r.t., overnight, 40–91%.

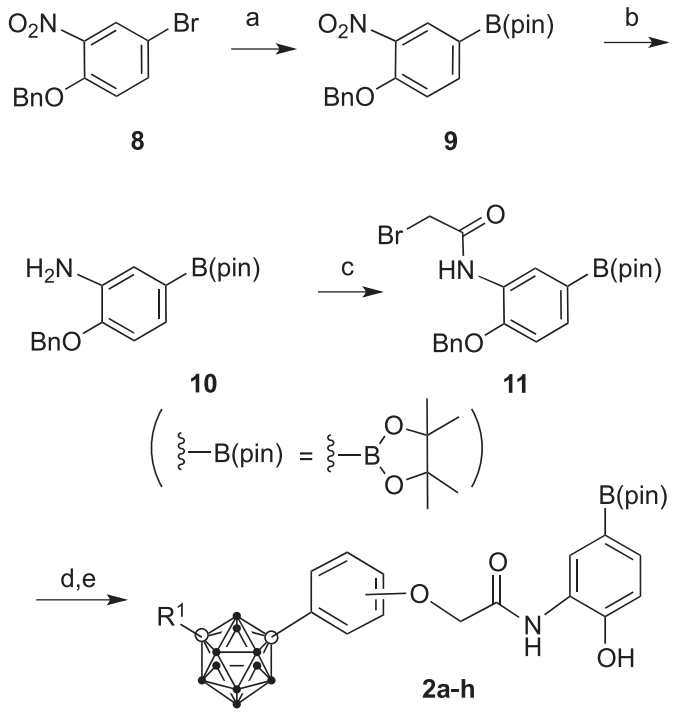



**Scheme 2.** Reagents and conditions: (a) (i) *n*-BuLi, DME, 0 °C, 30 min, (ii) CuCl, r.t.,1.5 h, (iii) 3-iodoanisole, pyridine, reflux, 48 h, 28%; (b) (i) *n*-BuLi, THF, −10 °C, 30 min, (ii) $R^1I$, 1.5 h; (c) $BBr_3$, $CH_2Cl_2$, r.t., overnight, 55–96%.

reductive conditions. Acylation of **10** with bromoacetyl bromide gave bromacetylanilide **11** [22]. Alkylation of 1-(4-hydroxyphenyl)-*meta*-carboranes **5a**–**d** and 1-(3-hydroxyphenyl)-*meta*-carboranes **7a**–**d** with bromacetylanilide **11** proceeded in THF at room temperature under basic conditions and the benzyl group of the resulting phenoxy ethers was deprotected by hydrogenesis to give the *meta*-carboranylphenoxyacetanilides **2a**–**h**.

### 2.2. Biological evaluation

The synthesized *meta*-carboranylphenoxyacetanilides **2a**–**h** were tested for their ability to inhibit hypoxia-induced HIF-1 transcriptional activity in HeLa cells under hypoxia (1% oxygen) using dual luciferase reporter gene assay expressing hypoxia response element (HRE)-dependent firefly luciferase reporter construct (HRE-Luc) and constitutively expressing CMV-driven renilla luciferase reporter [32]. The compound concentrations required to inhibit the hypoxia-induced HIF-1 transcriptional activity by 50% ($IC_{50}$) were summarized in Table 1. Although the previously reported phenoxyacetanilide **1a** [20] showed potent inhibitory activity ($IC_{50}$ = 4.10 μM), the corresponding pinacol ester **1c** was more potent ($IC_{50}$ = 2.72 μM). Since the pinacol ester derivatives were easy for purification and stable in a DMSO solution, the pinacol esters of *meta*-carborane derivatives were evaluated for their ability to inhibit hypoxia-induced HIF-1 transcriptional activity. The *meta*-carborane derivative **2a** showed the similar inhibitory activity to its *ortho*-derivative **1c** ($IC_{50}$ = 2.28 μM). Substituents of the $R^1$ group, such as methyl (**2b**), ethyl (**2c**), and *i*-butyl (**2d**) groups, affected the inhibitory potency against the hypoxia-induced HIF-1 transcription and the $IC_{50}$ values were 1.52, 0.83, and 0.73 μM, respectively. Next, inhibitory potency of 1-(3-hydroxyphenyl)-*meta*-carborane derivatives **2e**-**h** were evaluated. Compound **2e**, which has no substituent at the $R^1$ group, exhibited the $IC_{50}$ of 4.80 μM, whereas the sterically larger substituents of the $R^1$ group, such as methyl (**2f**), ethyl (**2g**), and *i*-butyl (**2h**) groups, increased their inhibitory activity. Especially, *i*-butyl-substituted *meta*-carboranylphenoxyacetanilide **2h** exhibited significant inhibitory activity against the hypoxia-induced HIF-1 transcription and the $IC_{50}$ was 0.55 μM.




**Scheme 3.** Reagents and conditions: (a) pinacolatodiboron, $PdCl_2$, dppf, AcOK, dioxane, reflux, overnight, 91%; (b) Fe, $NH_4Cl$, EtOH–$H_2O$, reflux, 2 h, 60%; (c) bromoacetyl bromide, pyridine, DMAP, r.t., overnight, 90%; (d) **5** or **7**, NaH, THF, r.t., 2 h; (e) $H_2$, Pd/C, MeOH-THF, r.t., overnight.

## 3. Conclusions

We succeeded in synthesis of *meta*-carborane containing phenoxyacetanilides **2** based on the structures of LW6 and *ortho*-carborane derivatives **1**. The *C*-arylation of *meta*-carborane through its copper derivative developed by Wade and coworkers is a key for the synthesis of **2**, although the yields were not satisfactory (26–28%). The effect of compounds **1** and **2** on hypoxia-induced HIF-1 transcriptional activity was examined using a cell-based dual luciferase reporter gene assay in HeLa cells under hypoxia. Among the compounds synthesized, *meta*-carborane containing phenoxyanilides **2d** and **2h** exhibited significant inhibitory activity toward hypoxia-induced HIF-1 transcription with the $IC_{50}$ values of

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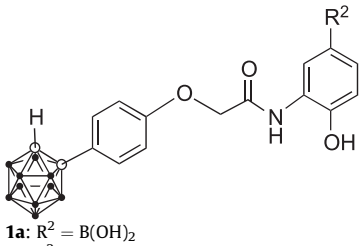
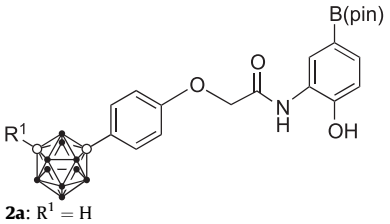
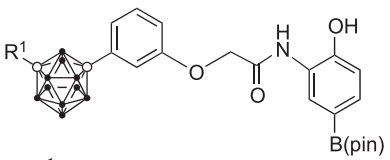
**Table 1**
Inhibition of HIF-1 transcriptional activity on HeLa cell-based HRE and CMV dual luciferase assay[a].

| Compound | $IC_{50}$ (μM) | ± SD |
|---|---|---|
|  | | |
| **1a**: $R^2 = B(OH)_2$ | 4.10 | 0.91 |
| **1c**: $R^2 = B(pin)$ | 2.72 | 0.36 |
|  | | |
| **2a**: $R^1 = H$ | 2.28 | 0.52 |
| **2b**: $R^1 = Me$ | 1.52 | 0.32 |
| **2c**: $R^1 = Et$ | 0.83 | 0.12 |
| **2d**: $R^1 = i$-Bu | 0.73 | 0.01 |
|  | | |
| **2e**: $R^1 = H$ | 4.80 | 0.80 |
| **2f**: $R^1 = Me$ | 1.34 | 0.29 |
| **2g**: $R^1 = Et$ | 1.29 | 0.44 |
| **2h**: $R^1 = i$-Bu | 0.55 | 0.03 |

[a] The drug concentration required to inhibit the relative light units by 50% ($IC_{50}$) was determined from semi-logarithmic dose–response plots and the results represent means ± standard deviation (SD) of triplicate samples.

0.73 and 0.55 μM, respectively. These compounds are more potent than *ortho*-carboranylphenoxyacetanilides (**1a**–**c**) that were previously synthesized. Both compounds have an isobutyl group substituted at $R^1$ position of *meta*-carborane, revealing that a sterically bulky group is essential for their significant inhibitory potency.

## 4. Experimental section

### 4.1. General procedures

All reactions were carried out under nitrogen atmosphere using standard Schlenk techniques. Most chemicals and solvents were analytical grade and used without further purification. $^1H$ NMR and $^{13}C$ NMR spectra were recorded on a Bruker biospin AVANCE III HD500 (500 MHz) spectrometer. Tetramethylsilane ($\delta$ 0.00) was used as internal standard for $^1H$ NMR. $^{13}C$ NMR was referenced to the residual solvent ($CDCl_3$, $\delta$ 77.0). IR spectra were measured on a JASCO FT/IR-4100 spectrophotometer. Melting points were determined with a As one ATM-01 melting point apparatus. High-resolution mass spectra were measured on a Bruker microTOF II spectrometer. Analytical thin layer chromatography (TLC) was performed on a glass plates (Merck Kieselgel 60 $F_{254}$, layer thickness 0.2 mm). Visualization was accompanied by UV light (254 nm), $I_2$ and $KMnO_4$. Column chromatography was performed on silica gel (FUJI SILYSIA CHEMICAL LTD. silica gel PSQ 60B). Compounds **4a**, **5a**, **6a**, **7a** have been already reported, thus identified by comparison with the reported $^1H$ NMR spectral data [8,9].

### 4.2. Synthesis of 1-(4-methoxyphenyl)-1,7-dicarba-closo-dodecaborane *4a*

To a solution of *meta*-carborane **3** (4.78 g, 33 mmol) in 150 mL of dry ethylene glycol dimethyl ether (DME) was added a 1.6 M solution of *n*-BuLi in *n*-hexane (20.6 mL, 33 mmol) dropwise at 0 °C under $N_2$. After the mixture was stirred for 30 min, CuCl (5.94 g, 60 mmol) was added. The mixture was further stirred at room temperature for 1.5 h. Pyridine (21 mL) and 4-iodoanisole (7.02 g, 30 mmol) were added and the resulting mixture was refluxed for 48 h. After the removal of the solvent with a rotary evaporator under reduced pressure, the residue was diluted with water and extracted three times with ethyl acetate. The combined organic layer was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography using hexane/AcOEt (100:1) as an eluent to give **4a** (1.93 g, 26%) as a colorless solid: $^1H$ NMR (500 MHz; $CDCl_3$): $\delta$ 7.33 (d, $J = 9.0$ Hz, 2H), 6.76 (d, $J = 9.0$ Hz, 2H), 3.78 (s, 1H), 3.04 (s, 1H).

### 4.3. Synthesis of 1-(4-hydroxyphenyl)-1,7-dicarba-closo-dodecaborane *5a*

Compound **4a** (500.6 mg, 2 mmol) was dissolved in $CH_2Cl_2$ solution (10 mL), and a 1.0 M solution of $BBr_3$ in $CH_2Cl_2$ (6 mL, 6 mmol) was added to the solution dropwise at 0 °C under $N_2$. The resulting mixture was stirred overnight at room temperature. The reaction was quenched by water and the mixture was extracted three times with ethyl acetate. The combined organic layer was

washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography with hexane/$CH_2Cl_2$ (2:1) to give **5a** (429.5 mg, 91%) as a colorless solid: $^1$H NMR (500 MHz; $CDCl_3$): $\delta$ 7.29 (d, $J$ = 9.0 Hz, 2H), 6.69 (d, $J$ = 9.0 Hz, 2H), 4.90 (s, 1H), 3.04 (s, 1H).

### 4.4. General procedure for synthesis of carboranylphenols **5b–d**

To a solution of carboranylanisole **4a** (500.6 mg, 2 mmol) in 15 mL of dry THF was added a 1.6 M solution of *n*-BuLi in *n*-hexane (1.9 mL, 3 mmol) dropwise at −10 °C under $N_2$. After the mixture was stirred for 30 min at −10 °C, alkyl iodide (3 mmol) was added to the reaction media. The reaction mixture was continuously stirred for 1.5 h and then the reaction was quenched by saturated NH4Cl aqueous solution. The mixture was extracted three times with ethyl acetate and the combined organic layer was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and concentrated. The resulting crude products **4b–d** was subsequently dissolved in $CH_2Cl_2$ solution (10 mL), and a 1.0 M solution of $BBr_3$ in $CH_2Cl_2$ (6 mL, 6 mmol) was added dropwise at 0 °C. The mixture was stirred overnight at room temperature. The reaction was quenched by water and the mixture was extracted three times with ethyl acetate. The combined organic layer was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography with hexane/$CH_2Cl_2$ (2:1) to give **5b–d** as a colorless solid.

#### 4.4.1. 1-Methyl-7-(4-hydroxyphenyl)-1,7-dicarba-closo-dodecaborane **5b**

Compound **5b** was synthesized using methyl iodide (0.19 mL, 3 mmol) in 74% yield (370.2 mg) as a colorless solid: mp. 127–128 °C ($CH_2Cl_2$/Hexane); $^1$H NMR (500 MHz; $CDCl_3$): $\delta$ 7.28 (d, $J$ = 8.5 Hz, 2H), 6.68 (d, $J$ = 8.5 Hz, 2H), 5.12 (s, 1H), 1.76 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 155.7, 129.2, 128.0, 115.0, 78.4, 70.6, 24.6; IR (NaCl) 3302, 2976, 2596, 1518, 1180 cm$^{-1}$; HRMS (ESI) $m/z$ Calcd for $C_9H_{17}B_{10}O$ $[M-H]^+$: 249.2282. Found: 249.2278.

#### 4.4.2. 1-Ethyl-7-(4-hydroxyphenyl)-1,7-dicarba-closo-dodecaborane **5c**

Compound **5c** was synthesized using ethyl iodide (0.24 mL, 3 mmol) in 40% yield (214.8 mg) as a colorless solid: mp. 94–95 °C ($CH_2Cl_2$/Hexane); $^1$H NMR (500 MHz; $CDCl_3$): $\delta$ 7.28 (d, $J$ = 9.0 Hz, 2H), 6.68 (d, $J$ = 9.0 Hz, 2H), 5.04 (s, 1H), 2.05 (q, $J$ = 7.5 Hz, 2H), 1.00 (t, $J$ = 7.5 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 155.7, 129.2, 128.1, 115.0, 77.5, 30.5, 14.2; IR (NaCl) 3277, 2599, 1516, 1244 cm$^{-1}$; HRMS (ESI) $m/z$ Calcd for $C_{10}H_{19}B_{10}O$ $[M-H]^+$: 263.2439. Found: 263.2434.

#### 4.4.3. 1-Isobutyl-7-(4-hydroxyphenyl)-1,7-dicarba-closo-dodecaborane **5d**

Compound **5d** was synthesized using isobutyl iodide (0.35 mL, 3 mmol) in 70% yield (410.0 mg) as a colorless solid: Mp. 97–98 °C ($CH_2Cl_2$/Hexane); $^1$H -NMR (500 MHz; $CDCl_3$): $\delta$ 7.27 (d, $J$ = 9.0 Hz, 2H), 6.67 (d, $J$ = 9.0 Hz, 2H), 5.40 (s, 1H), 1.90 (d, $J$ = 6.0 Hz, 2H), 1.66–1.74 (m, 1H), 0.91 (d, $J$ = 6.5 Hz, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 155.5, 129.2, 128.2, 115.0, 77.6, 75.9, 45.9, 32.0, 23.3; IR (NaCl) 3310, 2959, 2936, 2594, 1516, 1232, 841 cm$^{-1}$; HRMS (ESI) $m/z$ Calcd for $C_{12}H_{23}B_{10}O$ $[M-H]^+$: 291.2753. Found: 291.2748.

### 4.5. Synthesis of 1-(3-methoxyphenyl)-1,7-dicarba-closo-dodecaborane **6a**

Compound **6a** was synthesized from *meta*-carborane **3** (4.78 g, 33 mmol) and 3-iodoanisole (7.02 g, 30 mmol) using the procedure described for **4a** to give **6a** (1.63 g, 28%) as a colorless solid: $^1$H NMR (500 MHz; $CDCl_3$): $\delta$ 7.15 (t, $J$ = 8.0 Hz, 1H), 7.01 (dd, $J$ = 8.0 Hz, 1.0 Hz, 1H), 6.97 (t, $J$ = 2.0 Hz, 1H), 6.82 (dd, $J$ = 8.0 Hz, 2.0 Hz, 1H), 3.78 (s, 3H), 3.03 (s, 1H).

#### 4.5.1. Synthesis of 1-(3-hydroxyphenyl)-1,7-dicarba-closo-dodecaborane **7a**

Compound **7a** was synthesized from **6a** (500.6 mg, 2 mmol) using the procedure described for **5a** to give **7a** (453.1 mg, 96%) as a colorless solid: $^1$H NMR (500 MHz; $CDCl_3$): $\delta$ 7.11 (t, $J$ = 8.0 Hz, 1H), 7.00 (d, $J$ = 8.0 Hz, 1H), 6.91 (t, $J$ = 2.0 Hz, 1H), 6.76 (dd, $J$ = 8.0 Hz, 2.0 Hz, 1H), 5.03 (s, 1H), 3.04 (s, 1H).

#### 4.5.2. Synthesis of 1-methyl-7-(3-hydroxyphenyl)-1,7-dicarba-closo-dodecaborane **7b**

Compound **7b** was synthesized from **6a** (500.6 mg, 2 mmol) and methyl iodide (0.19 mL, 3 mmol) using the procedure described for **5b** to give **7b** (279.2 mg, 56%) as a colorless solid: Mp. 79–80 °C ($CH_2Cl_2$/Hexane); $^1$H- NMR (500 MHz; $CDCl_3$): $\delta$ 7.10 (t, $J$ = 8.0 Hz, 1H), 6.99 (d, $J$ = 8.0 Hz, 1H), 6.91 (t, $J$ = 2.0 Hz, 1H), 6.75 (dd, $J$ = 8.0 Hz, 2.0 Hz, 1H), 5.49 (s, 1H), 1.75 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 155.0, 136.9, 129.5, 120.4, 115.6, 115.2, 78.1, 70.6,53.4, 24.6; IR (NaCl) 3347, 2941, 2598, 1600, 1589, 1493, 1447, 1283, 1189 cm$^{-1}$; HRMS (ESI) $m/z$ Calcd for $C_9H_{17}B_{10}O$ $[M-H]^+$: 249.2282. Found: 249.2289.

#### 4.5.3. 1-Ethyl-7-(3-hydroxyphenyl)-1,7-dicarba-closo-dodecaborane **7c**

Compound **7c** was synthesized from **6a** (500.6 mg, 2 mmol) and ethyl iodide (0.24 mL, 3 mmol) using the procedure described for **5c** to give **7c** (290.7 mg, 55%) as a colorless oil: $^1$H- NMR (500 MHz; $CDCl_3$): $\delta$ 7.10 (t, $J$ = 8.0 Hz, 1H), 7.00 (d, $J$ = 8.0 Hz, 1H), 6.91 (t, $J$ = 2.0 Hz, 1H), 6.75 (dd, $J$ = 8.0 Hz, 2.0 Hz, 1H), 5.30 (s, 1H), 2.04 (q, $J$ = 7.5 Hz, 2H), 1.00 (t, $J$ = 7.5 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 155.1, 137.0, 129.5, 120.5, 115.6, 115.2, 77.1, 30.4, 14.2; IR (NaCl) 3334, 2978, 2938, 2600, 1589, 1447, 1283, 1186 cm$^{-1}$; HRMS (ESI) $m/z$ Calcd for $C_{10}H_{19}B_{10}O$ $[M-H]^+$: 263.2439. Found: 263.2441.

#### 4.5.4. 1-Isobutyl-7-(3-Hydroxyphenyl)-1,7-dicarba-closo-dodecaborane **7d**

Compound **7d** was synthesized from **6a** (500.6 mg, 2 mmol) and isobutyl iodide (0.35 mL, 3 mmol) using the procedure described for **5d** to give **7d** (419.0 mg, 72%) as a colorless oil: $^1$H- NMR (500 MHz; $CDCl_3$): $\delta$ 7.10 (t, $J$ = 8.0 Hz, 1H), 7.00 (d, $J$ = 8.0 Hz, 1H), 6.91 (t, $J$ = 2.0 Hz, 1H), 6.75 (dd, $J$ = 8.0 Hz, 2.0 Hz, 1H), 5.53 (s, 1H), 1.89 (d, $J$ = 6.0 Hz, 2H), 1.66–1.73 (m, 1H), 0.91 (d, $J$ = 7.0 Hz, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 155.1, 137.0, 129.5, 120.5, 115.6, 115.2, 77.1, 30.4, 14.2; IR (NaCl) 3335, 2959, 2934, 2602, 1600, 1589, 1447, 1189 cm$^{-1}$; HRMS (ESI) $m/z$ Calcd for $C_{12}H_{23}B_{10}O$ $[M-H]^+$: 291.2753. Found: 291.2759.

### 4.6. General procedure for synthesis of **2a–h**

To a dry THF solution (10 mL) of carboranylphenols **5a–d** or **7a–d** (0.5 mmol) was added 60% NaH (30 mg, 0.75 mmol) at 0 °C under $N_2$, and the mixture was stirred for 30 min at room temperature. Then bromoacetanilide **11** (334.5 mg, 0.75 mmol) was added to the reaction media and let stirring continue for 2 h. The reaction was quenched by saturated NH4Cl aqueous solution and the mixture was extracted three times with ethyl acetate. The combined organic layer was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The resulting crude product was subsequently dissolved in MeOH/THF (6mL/2 mL) solution and 50% Pd/C was added. The mixture was

stirred overnight at room temperature under hydrogen atmosphere. The palladium catalysts were removed by Celite pad filtration and solvent was removed in vacuo, resulting residue was purified by silica gel column chromatography with hexane/ethyl acetate (2:1) give to **2a**–**h** as a colorless solid.

#### 4.6.1. 3-[(4-(1,7-Dicarba-closo-carboranyl)phenoxyacetylamino)-4-hydroxybenzene boronic acid pinacol ester **2a**

Compound **2a** was synthesized using **5a** (118.2 mg, 0.5 mmol) in 15% yield (56.4 mg) as a colorless solid: mp. 268–269 °C ($CH_2Cl_2$/Hexane); $^1$H NMR (500 MHz; $CDCl_3$): $\delta$ 9.36 (s, 1H), 8.46 (s, 1H), 7.62 (d, $J$ = 8.0 Hz, 1H), 7.42 (d, $J$ = 8.0 Hz, 2H), 7.41 (s, 1H), 7.05 (d, $J$ = 8.0 Hz, 1H), 6.88 (d, $J$ = 8.0 Hz, 2H), 4.65 (s, 2H), 3.08 (s, 1H), 1.34 (s, 12H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 167.6, 156.9, 151.8, 134.7, 129.8, 129.6, 129.0, 124.0, 120.0, 114.5, 83.9, 77.6, 67.0, 55.1, 24.8; IR (NaCl) 3372, 3056, 2979, 2923, 2604, 1664, 1562, 1509, 1353 cm$^{-1}$; HRMS (ESI) $m/z$ Calcd for $C_{22}H_{34}B_{11}NO_5Na$ $[M+Na]^+$: 534.3438. Found: 534.3439.

#### 4.6.2. 3-[(4-(1-Methyl-1,7-dicarba-closo-carboranyl) phenoxyacetylamino)-4-hydroxybenzene boronic acid pinacol ester **2b**

Compound **2b** was synthesized using **5b** (125.2 mg, 0.5 mmol) in 25% yield (56.6 mg) as a colorless solid: Mp. 252–253 °C ($CH_2Cl_2$/Hexane); $^1$H NMR (500 MHz; $CDCl_3$): $\delta$ 9.35 (s, 1H), 8.48 (s, 1H), 7.61 (dd, $J$ = 8.0 Hz, 1.5 Hz, 1H), 7.44 (d, $J$ = 1.0 Hz, 1H), 7.41 (d, $J$ = 9.0 Hz, 2H), 7.04 (d, $J$ = 9.0 Hz, 1H), 6.87 (d, $J$ = 9.0 Hz, 2H), 4.64 (s, 2H), 1.78 (s, 3H), 1.34 (s, 12H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 167.6, 156.8, 151.8, 134.7, 129.9, 129.6, 129.0, 124.0, 119.8, 114.5, 83.9, 77.9, 70.6, 67.0, 24.8, 24.7; IR (NaCl) 3384, 3254, 2978, 2925, 2597, 1510, 1358 cm$^{-1}$; HRMS (ESI) $m/z$ Calcd for $C_{23}H_{36}B_{11}NO_5Na$ $[M+Na]^+$: 548.3595. Found: 548.3592.

#### 4.6.3. 3-[(4-(1-Ethyl-1,7-dicarba-closo-carboranyl) phenoxyacetylamino)-4-hydroxybenzene boronic acid pinacol ester **2c**

Compound **2c** was synthesized using **5c** (132.2 mg, 0.5 mmol) in 26% yield (60.3 mg) as a colorless solid: Mp. 225–226 °C ($CH_2Cl_2$/Hexane); $^1$H NMR (500 MHz; $CDCl_3$): $\delta$ 9.36 (s, 1H), 8.47 (s, 1H), 7.62 (dd, $J$ = 8.0 Hz, 1.0 Hz, 1H), 7.43 (s, 1H), 7.42 (d, $J$ = 9.0 Hz, 2H), 7.05 (d, $J$ = 8.0 Hz, 1H), 6.87 (d, $J$ = 9.0 Hz, 2H), 4.64 (s, 2H), 2.07 (q, $J$ = 7.5 Hz, 2H), 1.34 (s, 12H), 1.02 (t, $J$ = 7.5 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 167.6, 156.8, 151.8, 134.7, 130.0, 129.5, 129.0, 124.0, 119.9, 114.5, 83.9, 67.0, 30.5, 24.8, 14.3; IR (NaCl) 3386, 2978, 2600, 1607, 1510, 1354 cm$^{-1}$; HRMS (ESI) $m/z$ Calcd for $C_{24}H_{38}B_{11}NO_5Na$ $[M+Na]^+$: 562.3752. Found: 562.3760.

#### 4.6.4. 3-[(4-(1-Isobutyl-1,7-dicarba-closo-carboranyl) phenoxyacetylamino)-4-hydroxybenzene boronic acid pinacol ester **2d**

Compound **2d** was synthesized using **5d** (146.2 mg, 0.5 mmol) in 21% yield (51.8 mg) as a colorless solid: Mp. 190–191 °C ($CH_2Cl_2$/Hexane); $^1$H NMR (500 MHz; $CDCl_3$): $\delta$ 9.35 (s, 1H), 8.48 (s, 1H), 7.61 (dd, $J$ = 8.0 Hz, 1.5 Hz, 1H), 7.44 (d, $J$ = 1.5 Hz, 1H), 7.41 (d, $J$ = 9.0 Hz, 2H), 7.04 (d, $J$ = 8.0 Hz, 1H), 6.86 (d, $J$ = 9.0 Hz, 2H), 4.63 (s, 2H), 1.91 (d, $J$ = 6.0 Hz, 2H), 1.68–1.75 (m, 1H), 1.34 (s, 12H), 0.93 (d, $J$ = 6.5 Hz, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 167.6, 156.7, 151.7, 134.6, 130.0, 129.5, 129.0, 124.0, 119.9, 114.5, 83.9, 77.1, 67.0, 46.0,28.7, 24.8, 23.4; IR (NaCl) 3384, 3273, 2978, 2929, 2601, 1510, 1355 cm$^{-1}$; HRMS (ESI) $m/z$ Calcd for $C_{26}H_{42}B_{11}NO_5Na$ $[M+Na]^+$: 590.4066. Found: 590.4066.

#### 4.6.5. 3-[(3-(1,7-Dicarba-closo-carboranyl)phenoxyacetylamino)-4-hydroxybenzene boronic acid pinacol ester **2e**

Compound **2e** was synthesized using **7a** (118.2 mg, 0.5 mmol) in 15% yield (69.6 mg) as a colorless solid: Mp. 259–260 °C ($CH_2Cl_2$/Hexane); $^1$H- NMR (500 MHz; $CDCl_3$): $\delta$ 9.38 (s, 1H), 8.50 (s, 1H), 7.63 (dd, $J$ = 8.0 Hz, 1.0 Hz, 1H), 7.45 (d, $J$ = 1.5 Hz, 1H), 7.26 (t, $J$ = 8.0 Hz, 1H), 7.17 (d, $J$ = 8.0 Hz, 1H), 7.12 (t, $J$ = 2.0 Hz, 1H), 7.06 (d, $J$ = 8.0 Hz, 1H), 6.91 (dd, $J$ = 8.0 Hz, 2.0 Hz, 1H), 4.66 (s, 2H), 3.10 (s, 1H), 1.35 (s, 12H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 167.6, 156.3, 151.9, 137.2, 134.7, 130.0, 129.0, 124.0, 122.3, 120.0, 115.6, 114.2, 83.9, 77.5, 67.0, 55.1, 24.8; IR (NaCl) 3395, 3266, 2978, 2925, 2602, 1355 cm$^{-1}$; HRMS (ESI) $m/z$ Calcd for $C_{22}H_{34}B_{11}NO_5Na$ $[M+Na]^+$: 534.3438. Found: 534.3435.

#### 4.6.6. 3-[(3-(1-Methyl-1,7-dicarba-closo-carboranyl) phenoxyacetylamino)-4-hydroxybenzene boronic acid pinacol ester **2f**

Compound **2f** was synthesized using **7b** (125.2 mg, 0.5 mmol) in 27% yield (61.2 mg) as a colorless solid: Mp. 233–234 °C ($CH_2Cl_2$/Hexane); $^1$H NMR (500 MHz; $CDCl_3$): $\delta$ 9.39 (s, 1H), 8.51 (s, 1H), 7.63 (dd, $J$ = 8.0 Hz, 1.5 Hz, 1H), 7.46 (d, $J$ = 1.5 Hz, 1H), 7.25 (t, $J$ = 8.0 Hz, 1H), 7.15 (d, $J$ = 8.0 Hz, 1H), 7.12 (t, $J$ = 2.0 Hz, 1H), 7.06 (d, $J$ = 8.5 Hz, 1H), 6.90 (dd, $J$ = 8.0 Hz, 2.0 Hz, 1H), 4.66 (s, 2H), 1.80 (s, 3H), 1.35 (s, 12H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 167.6, 156.3, 151.9, 137.4, 134.8, 129.9, 129.0, 124.0, 122.3, 120.0, 115.6, 114.1, 83.9, 77.8, 70.7, 67.0, 24.8, 24.7; IR (NaCl) 3382, 3092, 2977, 2598, 1659, 1555, 1354 cm$^{-1}$; HRMS (ESI) $m/z$ Calcd for $C_{23}H_{36}B_{11}NO_5Na$ $[M+Na]^+$: 548.3595. Found: 548.3594.

#### 4.6.7. 3-[(3-(1-Ethyl-1,7-dicarba-closo-carboranyl) phenoxyacetylamino)-4-hydroxybenzene boronic acid pinacol ester **2g**

Compound **2g** was synthesized using **7c** (132.2 mg, 0.5 mmol) in 22% yield (52.7 mg) as a colorless solid: Mp. 192–193 °C ($CH_2Cl_2$/Hexane); $^1$H NMR (500 MHz; $CDCl_3$): $\delta$ 9.38 (s, 1H), 8.52 (s, 1H), 7.62 (dd, $J$ = 8.0 Hz, 1.5 Hz, 1H), 7.47 (s, 1H), 7.25 (t, $J$ = 8.0 Hz, 1H), 7.15 (d, $J$ = 8.0 Hz, 1H), 7.12 (t, $J$ = 2.0 Hz, 1H), 7.05 (d, $J$ = 8.5 Hz, 1H), 6.90 (dd, $J$ = 8.0 Hz, 2.0 Hz, 1H), 4.65 (s, 2H), 2.08 (q, $J$ = 7.5 Hz, 2H), 1.35 (s, 12H), 1.03 (t, $J$ = 7.5 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 167.6, 156.3, 151.9, 137.4, 134.8, 129.9, 129.0, 124.0, 122.3, 120.0, 115.6, 114.1, 83.9, 77.8, 70.7, 67.0, 24.8, 24.7; IR (NaCl) 3391, 3260, 2978, 2919, 2599, 1543 cm$^{-1}$; HRMS (ESI) $m/z$ Calcd for $C_{24}H_{38}B_{11}NO_5Na$ $[M+Na]^+$: 562.3752. Found: 562.3753.

#### 4.6.8. 3-[(3-(1-Isobutyl-1,7-dicarba-closo-carboranyl) phenoxyacetylamino)-4-hydroxybenzene boronic acid pinacol ester **2h**

Compound **2h** was synthesized using **7d** (146.2 mg, 0.5 mmol) in 23% yield (56.4 mg) as a colorless solid: Mp. 170–171 °C ($CH_2Cl_2$/Hexane); $^1$H- NMR (500 MHz; $CDCl_3$): $\delta$ 9.38 (s, 1H), 8.52 (s, 1H), 7.62 (dd, $J$ = 8.0 Hz, 1.5 Hz, 1H), 7.46 (d, $J$ = 1.0 Hz, 1H), 7.25 (t, $J$ = 8.5 Hz, 1H), 7.15 (d, $J$ = 6.0 Hz, 1H), 7.11 (t, $J$ = 2.0 Hz, 1H), 7.05 (d, $J$ = 8.5 Hz, 1H), 6.90 (dd, $J$ = 8.0 Hz, 2.0 Hz, 1H), 4.65 (s, 2H), 1.93 (d, $J$ = 6.0 Hz, 2H), 1.69–1.76 (m, 1H), 0.93 (d, $J$ = 6.5 Hz, 6H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 167.6, 156.3, 151.9, 137.5, 134.7, 129.8, 129.0, 124.0, 122.3, 119.9, 115.6, 114.1, 83.9, 76.1, 67.0,46.0, 28.7, 24.9, 23.4; IR (NaCl) 3387, 3274, 2978, 2927, 2602, 1434, 1355 cm$^{-1}$; HRMS (ESI) $m/z$ Calcd for $C_{26}H_{42}B_{11}NO_5Na$ $[M+Na]^+$: 590.4066. Found: 590.4066.

### 4.7. Cell culture

Cells were cultured under 5% $CO_2$ at 37 °C in RPMI 1640 medium (Wako pure Pure Chemicals, Osaka, Japan) supplemented with 10% fetal bovine serum (FBS, HyClone, Logan, UT), 100 U/ml mL penicillin and 100 μg/ml mL streptomycin (Invitrogen, Carlsbad, CA). For subsequent experiments, the cells were seeded at a density of $2.5 \times 10^5$ cells/ml/well in a 12-well TC plate (Greiner Japan, Tokyo,

Japan), and incubated at 37 °C for 12 h. Hypoxic condition was achieved by replacing cells to 1% $O_2$, 95% $N_2$ and 5% $CO_2$ in a multigas incubator (Astec, Fukuoka, Japan).

### 4.8. HIF-1 transcriptional activity on HeLa cell-based HRE and CMV dual luciferase assay

HeLa cells expressing HRE-dependent firefly luciferase reporter construct (HRE-Luc) and constitutively expressing CMV-driven Renilla luciferase reporter with SureFECT Transfection Reagent were established with Cignal™ Lenti Reporter (SABiosciences, Frederick, MD) according to the manufacturer's instructions. The consensus sequence of HRE was 5′-TACGTGCT-3′ from the erythropoietin gene. Cells stably expressing the HRE-reporter gene were selected with puromycin. The cells were incubated for 12 h with or without drugs under the hypoxic condition (1% oxygen). After removal of the supernatant, the luciferase assay was performed using a Luciferase Assay System (Promega, Madison, WI) according to the manufacturer's instructions.

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