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Selective Catalytic B−H Arylation of *o*-Carboanyl Aldehydes by a Transient Directing Strategy

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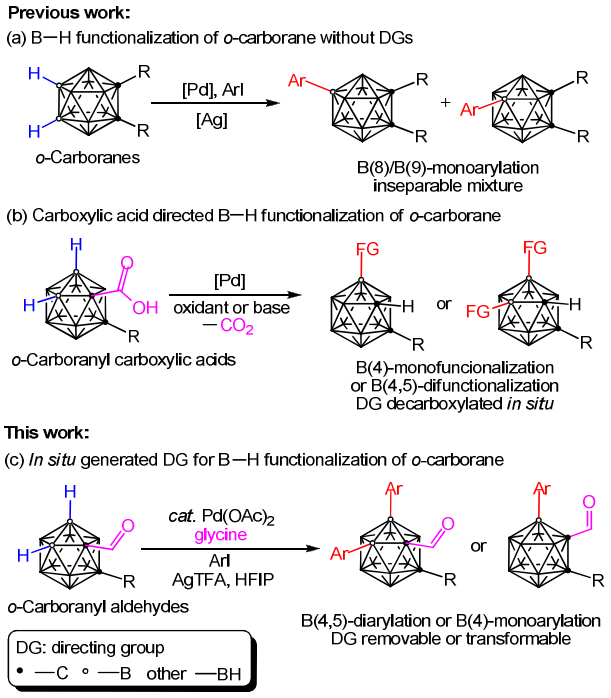
ABSTRACT: Carboranyl aldehydes are among the most useful synthons in derivatization of carboranes. However, compared to the utilization of carboranyl carboxylic acids in selective B−H bond functionalizations, the synthetic application of carboranyl aldehydes is limited due to the weakly coordinating nature of aldehyde group. Herein, the direct arylation of *o*-carboranyl aldehydes has been developed via Pd-catalyzed cage B−H bond functionalization. With the help of glycine to generate a directing group (DG) *in situ*, a series of cage B(4,5)-diarylated- and B(4)-monoarylated-*o*-carboranyl aldehydes were obtained in good to excellent yields with high selectivity. A wide range of functional groups are tolerated. The aldehyde group in the B−H arylated products could be readily removed or transformed into *o*-carboranyl methanol. A plausible catalytic cycle for B−H arylation was proposed based on control experiments and stoichiometric reactions, incluing the isolation of a key bicyclic palladium complex.

INTRODUCTION

Carboranes have been widely used for decades as attractive building blocks for the construction of unique ligands,[1] functional materials[2] and tunable pharmacophores[3] owing to their useful properties such as high stability, enriched boron content and delocalized three-dimensional aromaticity.[4] In order to broaden these applications, efficient methods for cage vertex (CH and BH) modifications are required to achieve vertex selectivity and diverse functionality. In the derivatization of carboranes, transitional-metal (TM) catalyzed B−H functionalization of carboranes has drawn increasing interests[5−7] since it provides an efficient tool for direct boron-carbon and boron-heteroatom bond constructions. However, there are two major challenges in this approach: the inert character of B−H bonds and site selectivity among multiple B−H bonds with similar chemical environment. To these points, directing group (DG) strategies have been employed to promote the reactivity and site selectivity in B−H functionalization. Up to date, carboxylic acid group (−COOH)[6] has been utilized as traceless DG in the B−H functionalization of *o*-carboranes (Scheme 1b). Apart from carboxylic acid, suitable DGs, robust for the B−H activation/functionalization and easily removable or transformable into diverse functional groups, are to be explored.

Carboranyl aldehydes have been exploited as valuable synthons for the synthesis of diversely decorated carboranes for material and biomedical applications.[8] Considering their functional diversity[8] and facile accessibility,[8b] carboranyl aldehydes may be competent functional substrates for cage B−H functionalization. However, in contrast to the superior directing power of carboxylic acids,[9] the carbonyl groups in aldehydes or ketones are less coordinative. The utility of these weakly coordinating DGs was limited in C−H functionalization[10] and elusive in B−H functionalization. To solve this problem, transient directing groups (DGs)[11] that can bind reversibly to the substrate and the metal center have been developed for the site-selective functionalization of inert C−H bonds in aldehydes and ketones.[11a−11d] This strategy avoids the additional steps for the installation and removal of the DGs.

Scheme 1. Transitional-metal Catalyzed B−H Functionalization of *o*-Carboranes.



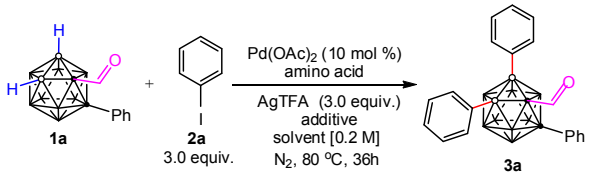
For example, Mo and Dong reported a Rh(I)-catalyzed α-C(sp^3)−H alkylation of ketones with olefins using a catalytic transient DG.[11d] Recently, Yu and co-workers described the catalytic C(sp^3)−H functionalization[11a] of *o*-alkyl benzaldehdes and ketones as well as C(sp^2)−H functionalization[11c] of benzaldehydes using transient DGs. In a very recent report, Ge

and coworkers reported the palladium-catalyzed C(sp^3)–H arylation of β-C–H bonds of aliphatic aldehydes with transient DGs.[11b]

Despite of these major advances, the utilizaiton of the transient directing strategy into the selective B–H functionalization of carboranes has not been reported so far. Herein, we describe the development of a Pd-catalyzed direct and site-selective arylation of cage B–H bonds of *o*-carboranyl aldehydes with aryl iodides, delivering B(4,5)-diarylated- and B(4)-monoarylated-*o*-carboranyl aldehydes in good to excellent yields (Scheme 1c). The aldehyde group is stable to tolerate the B–H activation/functionalization conditions and can be removed or transformed into other functional groups. In mechanistic studies, direct B–H activation has been observed at the B(4) site in Pd-*o*-carboranyl-imino complex.

RESULTS AND DISCUSSION

Table 1. Optimization of B(4,5)–H Diarylation of *o*-Carboranyl Aldehyde **1a**.[a]



entry	amino acid	solvent	additive	yield (%)[b]
1	0.5 eq glycine	DCE	/	n.d.
2	0.5 eq glycine	Toluene	/	n.d.
3	0.5 eq glycine	AcOH	/	messy
4	0.5 eq glycine	HFIP	/	27
5	0.3 eq glycine	HFIP	/	12
6	no glycine	HFIP	/	n.d.
7	0.5 eq glycine	HFIP	AcOH[c]	41
8	0.5 eq glycine	HFIP	3.0 eq H_2O	30
9	0.5 eq glycine	HFIP	1.0 eq TFA	55
10	**1.0 eq glycine**	HFIP	**1.0 eq TFA**	**75**
11[d]	1.0 eq glycine	HFIP	1.0 eq TFA	53
12	1.0 eq L-alanine	HFIP	1.0 eq TFA	65
13	1.0 eq L-valine	HFIP	1.0 eq TFA	54
14	*o*-aminophenol[e]	HFIP	1.0 eq TFA	55[f]
15[g]	1.0 eq glycine	HFIP	1.0 eq TFA	0

[a]Reaction conditions: **1a** (0.1 mmol), iodobenzene (**2a**) (3.0 equiv.), $Pd(OAc)_2$ (10 mol%), amino acid (0.3-1.0 equiv.), AgTFA (3.0 equiv.), solvent (0.5 mL), 80 °C, N_2 atmosphere, 36 h. [b]Isolated yield. [c]HFIP/AcOH (0.5 mL, v/v = 7/3) was used as solvent. [d]Sealed under air atmosphere. [e]1.0 eq of *o*-aminophenol used. [f]Isolated after workup with 3N HCl. [g]No $Pd(OAc)_2$. DCE: 1,2-dichloroethane. HFIP: hexafluoroisopropanol. TFA: trifluoroacetic acid. n.d. = not detected.

At the outset of our studies, we chose 1-CHO-2-Ph-*o*-$C_2B_{10}H_{10}$ **1a** as the model substrate and iodobenzene **2a** as the arylation reagent. To generate the DG *in situ*, amino acids were employed to form imine linkages with *o*-carboranyl aldehydes. After extensive experimental trials, we obtained the desired B(4,5)-diarylated product **3a** in 27% yield when the reaction was conducted in hexafluoroisopropanol (HFIP) with 10 mol% of $Pd(OAc)_2$, 0.5 equiv. of glycine, 3.0 equiv. of **2a** and 3.0 equiv. silver trifluoroacetate (AgTFA) under N_2 at 80 °C. (Table 1, entry 4 and Figure 1). The yield was slightly increased to 41% when a 7 : 3 mixture of HFIP and AcOH was used as the solvents (entry 7), whereas the use of H_2O as an additive led to no significant improvement (entry 8). We were pleased to find that the use of 1.0 equiv. of trifluoroacetic acid (TFA) as an additive can improve the yield to 55% (entry 9). Adjusting the stoichiometric amount of glycine led to the desired B(4,5)-diarylated product **3a** in 75% isolated yield without the formation of B(4)-monoarylated product (entry 10). The N_2 protection was necessary and decomposition of *o*-carboranyl aldehydes was observed when the reactions were sealed under air (entry 11). Other amino acids with side chains (L-alanine, L-valine, entry 12-13) did not have a marked effect on the efficiency of this transformation. Replacing glycine with 1.0 equiv. of *o*-aminophenol afforded **3a** in 55% yield (entry 14). Removing the $Pd(OAc)_2$ catalyst completely stopped the reaction (entry 15).

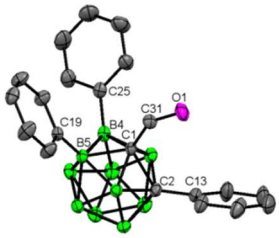
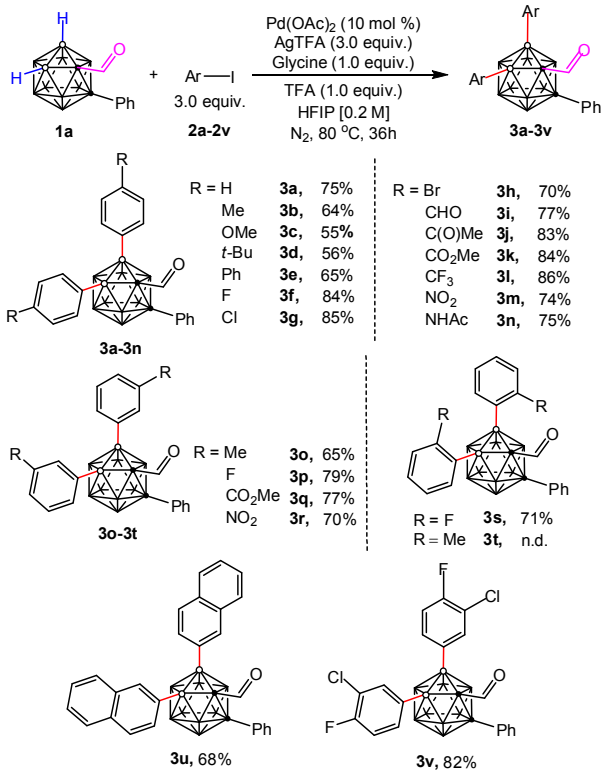


Figure 1. Molecular structure of **3a** (ellipsoids at 30% probability and H atoms omitted for clarity). Selected bond distances [Å]: C1–C2 1.712(2), B4–B5 1.812(3), B4–C25 1.571(3), B5–C19 1.576(2), C31–O1 1.1741(19).

Table 2. Substrate Scope of Aryl Iodide Coupling Partners.[a,b]



[a]Reaction conditions: **1a** (0.1 mmol), Ar–I (0.3 mmol), $Pd(OAc)_2$ (10 mol%), glycine (1.0 equiv.), AgTFA (3.0 equiv.), TFA (1.0 equiv.), HFIP (0.5 mL), 80 °C, N_2 atmosphere, 36 h. [b]Isolated yield. n.d. = not detected.

The substrate scope of aryl iodides **2** was further investigated. In general, electron-withdrawing group on the phenyl ring offered higher yields of **3** than did electron-donating substituents (Table 2). Remarkably, this reaction was well compatible with many functional groups at the *para*- and *meta*-positions of the aryl iodide coupling partners, such as -CHO (**3i**), -C(O)Me (**3j**), -CO_2Me (**3k**), -NHAc (**3n**), -NO_2 (**3m** and **3r**), furnishing the desired products in good to excellent yields. It is worth noting that although *ortho*-C−H functionalization of benzaldehydes using transient DGs has been recently published,[11c] *ortho*-C−H functionalization of 4-iodobenzaldehyde (**2i**) was not observed in current B−H functionalization system. Furthermore, halogen (fluoro, chloro or bromo)-substituted phenyl iodides were also applicable to generate the diarylated products (**3f-3h, 3p, 3s** and **3v**). In addition, substrate **2s** bearing an *ortho*-fluoro gave the desired product **3s** in a slightly decreased yield whereas sterically hindered 2-methyl iodobenzene (**2t**) failed to deliver the di-arylated product (**3t**). Instead, B(4)-mono-arylated product was isolated in 70% yield. Isolation of carboranyl aldehyde products proved to be feasible after a simple workup without further tactics to remove the DGs.

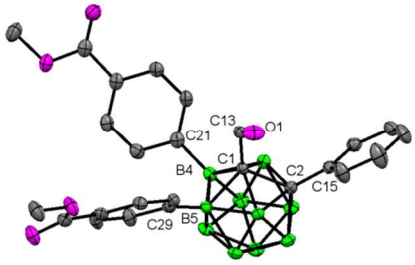
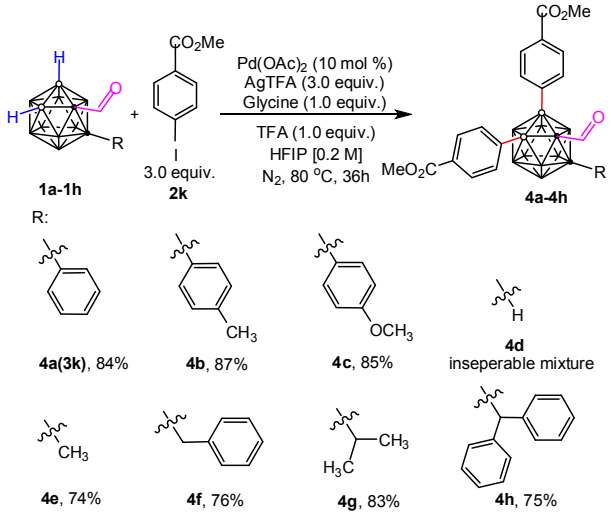


Figure 2. Molecular structure of **3k** (ellipsoids at 50% probability and H atoms omitted for clarity). Selected bond distances [Å]: C1–C2 1.715(2), B4–C21 1.583(3), B5–C29 1.584(2), C1–C13 1.522(2), C13–O1 1.1860(19).

Table 3. Substrate Scope of *o*-Carboranyl Aldehyde Coupling Partners.[a,b]

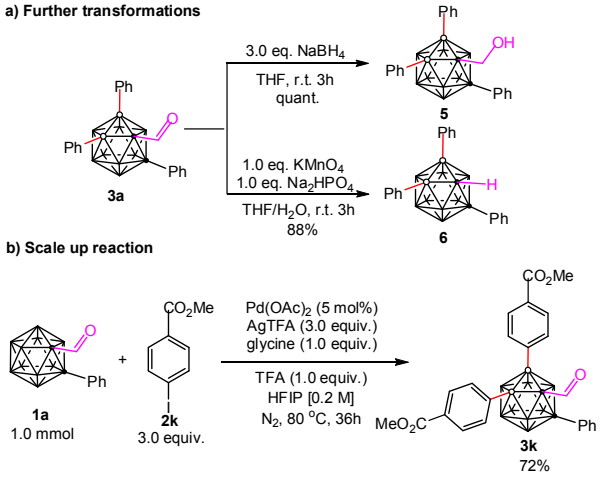


[a]Reaction conditions: **1a-1h** (0.1 mmol), **2k** (0.3 mmol), $Pd(OAc)_2$ (10 mol%), glycine (1.0 equiv.), AgTFA (3.0 equiv.), TFA (1.0 equiv.), HFIP (0.5 mL), 80 °C, N_2 atmosphere, 36 h. [b]Isolated yield.

The scope of *o*-carboranyl aldehydes with different carbon substitution was next explored using methyl 4-iodobenzoate **2k** as the arylation reagent (Table 3). For aryl substituents, products **4b** and **4c** were obtained in 87% and 85% isolated yields, whereas 1-CHO-*o*-$C_2B_{10}H_{11}$ (**1d**) afforded an inseparable mixture (for details, see SI-Scheme S3). For this case, the vertex substitution of the byproducts most probably occurred at the B(3)/B(6) position since all of the B−H bonds at B(3)/B(4)/B(5)/B(6) positions possess the closest proximity to the DGs.[13] We postulated that the steric effect of the substituents at the cage carbon atom may contribute to the B(4)/B(5)-selectivity. As expected, when R = methyl, benzyl, isopropyl and diphenylmethyl groups, products **4e-4h** were isolated as single regio-isomers in good yields (74-83%). Compounds **3** and **4** were fully characterized by ^{1}H, ^{11}B, and ^{13}C NMR spectroscopy, infrared (IR) spectrum and high resolution mass spectrometry (HRMS). The structures of **3a** and **3k** were further confirmed by single-crystal X-ray analysis (Figures 1 and 2).

The aldehyde group in *o*-carboranyl aldehyde can be readily removed or transformed into other functional groups. As demonstrated in Scheme 2a, B(4,5)-diarylated *o*-carboranyl aldehyde **3a** could be quantitatively reduced to *o*-carboranyl methanol **5** in the presence of $NaBH_4$ at ambient temperature. It is noteworthy that carboranyl methanols are also valuable synthons[14] in the derivation of carboranes. In addition, $KMnO_4$-mediated oxidation of **3a**, followed by *in situ* decarboxylation led to removal of the aldehyde group, as shown in **6**. Furthermore, when the reaction was scaled up to 1.0 mmol, the B(4,5)-diarylated product **3k** was isolated in 72% yield with a catalyst loading of 5 mol% (Scheme 2b).

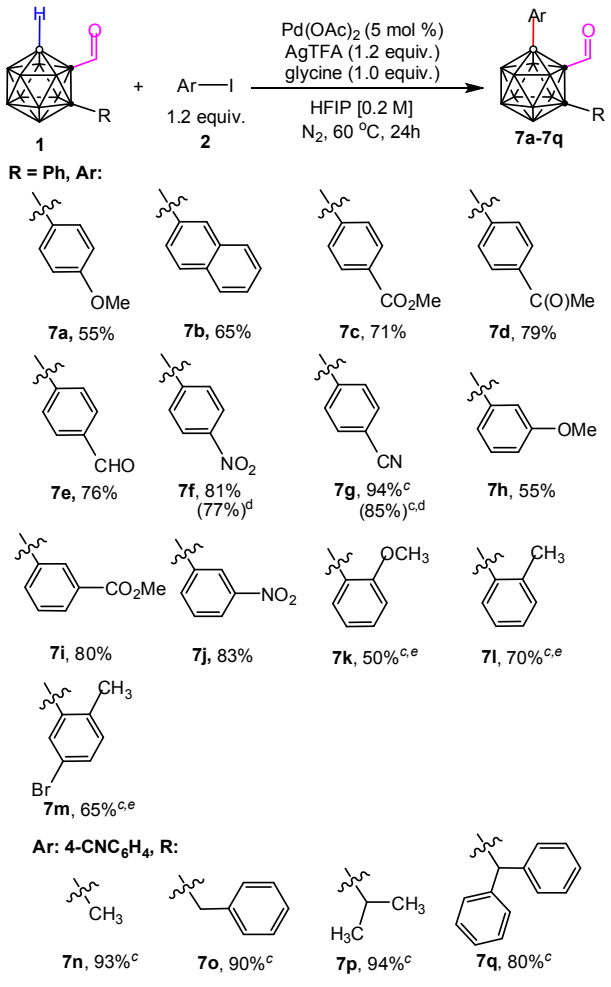
Scheme 2. Further Transformations and Scale-up Reaction.



Based on the established progress for B(4,5)-diarylation, we also extended our efforts to investigate the catalytic B−H monoarylation of *o*-carboranes, which was also very challanging.[6d,6h] Thus far, stoichiometric Pd-mediated B(4)−H monoarylation[6d] and catalytic B(8)/B(9)−H monoarylation have been achieved,[6h] of which the latter was afforded in an inseparable mixture of B(8)/B(9)-aryl-*o*-carboranes. Herein, stoichiometric control (1.2 equiv.) of aryl iodides and AgTFA in Pd-catalyzed B(4)−H monoarylation of **1a** led to the isolation of B(4)-monoarylated product **7a-7q** in 55-94% yields (Table 4). We found that both electronic and steric factors of aryl iodides played crucial roles in the formation of **7a-7q**. Generally, aryl

iodides with an electron-donating group react faster than those with an electron-withdrawing group, albeit with decreased yields. The byproducts were confirmed as the B(4,5)-diarylated species. The B(4)-selectivity was incredibly increased when the aryl iodides containing a strong electron-withdrawing group (-NO_2, -CN) were used, delivering **7f, 7g, 7j, 7n-7q** in 81-94% yields. When the reactions were scaled up to 1.0 mol, comparable isolated yields were obtained for **7f** and **7g**. Interestingly, when 2-methyl iodobenzenes bearing sterically hindered 2-tolyl group were used, the desired B(4)-monoarylated products **7l-7m** could been obtained in 65-70% yields. Since 2-methyl iodobenzene (**2t**) cannot deliver the B(4,5)-diarylated compound (**3t**), the steric effect of the methyl group probably inhibit the reactivity in the second round sequence of B−H functionalization based on B(4)-monoarylated compound **7l**. The substrate scope in Table 4 illustrated that both steric and electronic effect can be used to control the B(4)-monoselectivity in B−H functionalization of *o*-carboranes. Compounds **7a-7q** were fully characterized by NMR, IR spectrometry and HRMS. The molecular structure of **7g** was confirmed by single-crystal X-ray analysis (Figure 3).

Table 4. Synthesis of Cage B(4)-monoarylated *o*-Carboranyl Aldehydes **7a-7q** .[a,b]



[a]Reaction conditions: **1a** (0.1 mmol), Ar−I (1.2 equiv.), $Pd(OAc)_2$ (5 mol%), glycine (1.0 equiv.), AgTFA (1.2 equiv.), HFIP (0.5 mL), 60 °C, N_2 atmosphere, 24 h. [b]Isolated yield. [c]heated at 80 °C. [d]Reactions conducted at 1.0 mmol scale. [e]using 10 mol% of $Pd(OAc)_2$.

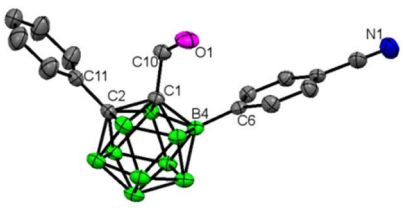
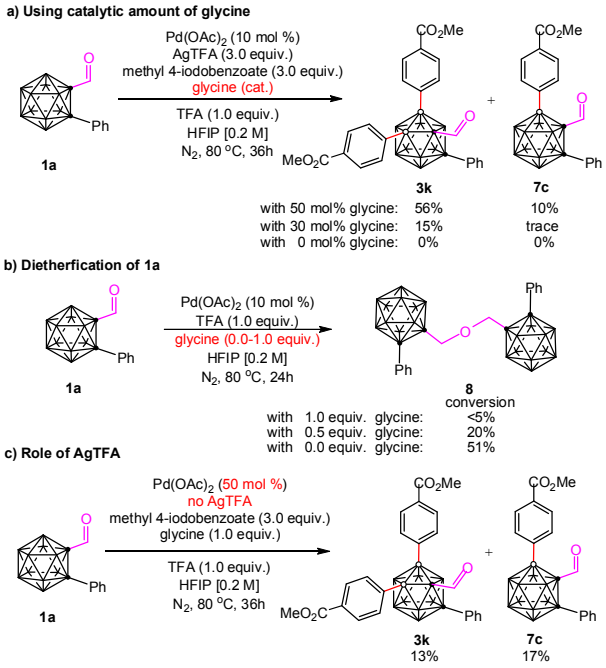


Figure 3. Molecular structure of **7g.** (ellipsoids at 50% probability and H atoms omitted for clarity) Selected bond distances [Å]: C1–C2 1.690(3), C1–B4 1.724(4), B4–C6 1.574(4), C1–C10 1.509(6), C10–O1 1.187(10).

Scheme 3. Control Experiments.



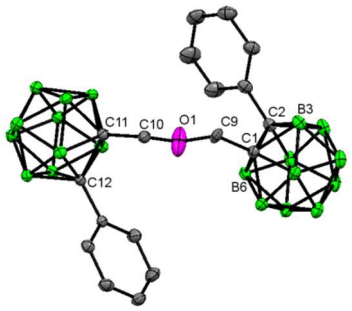
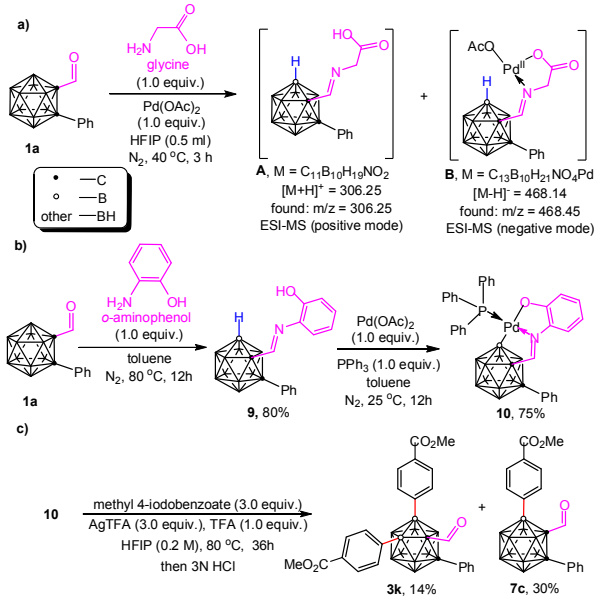


Figure 4. Molecular structure of **8.** (ellipsoids at 30% probability and H atoms omitted for clarity) Selected bond distances [Å] and angles [°]: C1–C2 1.687(3), C11–C12 1.697(3), C1–C9 1.504(3), C10–C11 1.501(3), C10–O1 1.354(3), C9–O1 1.329(3), C9–O1–C10 119.2(2).

To gain insights into the reaction mechanisms, control experiments were conducted. In contrast to the organic phenyl or aliphatic aldehydes that can use a catalytic transient ligand to achieve C−H functionalization,[11a–11c] in the case of *o*-carboranyl aldehyde, the use of a catalytic amount (50-30 mol%) of glycine led to decreased yields of **3k** and **7c** (Scheme 3a). When the reaction was conducted without glycine, no desired products were observed and considerable con-

sumption of the starting material **1a** was detected. The utilization of 1.0 equiv. of glycine is not only essential for enabling B−H functionalization, but plays an important role in stabilizing the *o*-carboranyl aldehydes under catalytic conditions. Dietherification was observed when **1a** was treated with 10 mol% of $Pd(OAc)_2$ in the presence of 1.0 equiv. TFA at 80 °C (Scheme 3b). Compound **8** was isolated in moderate yield and characterized with NMR, HRMS as well as single-crystal X-ray analysis (Figure 4). Utilization of glycine (0.5 to 1.0 equiv.) significantly inhibited the dietherfication of **1a**. In addition, when **1a** was treated with 3.0 equiv. of methyl 4-iodobenzoate in the presence of 50 mol% of $Pd(OAc)_2$ and 1.0 equiv. of glycine in HFIP at 80 °C in the absence of AgTFA, both B(4,5)-diarylated product **3k** and B(4)-monoarylated **7c** were isolated in 13% and 17% yields, respectively (Scheme 3c). These outcomes suggest that stoichiometric amount of Pd^{II} does promote cage B−H mono- and di-arylation whereas Pd^{II} cannot catalyze this reaction in the absence of AgTFA.

Scheme 4. Stoichiometric Reactions Toward the Synthesis of Bicyclic Palldium Complexes and Their Subsequent Arylation.



In order to further elucidate the reaction mechanism, stoichiometric reaction of **1a** with $Pd(OAc)_2$ (1.0 equiv.) and glycine (1.0 equiv.) in HFIP at 40 °C lead to the detection of both intermediates **A** and **B** by ESI-MS analysis (Scheme 4a, **A**, m/z = 306.25, $[M+H]^+$, **B**, X = OAc, m/z = 468.45, $[M-H]^-$) (for details, see SI-Figure S6−S8). Although the observed intermediates **A** or **B** could not be isolated because of their instability, they were tentatively assigned to be imine-type intermediates before B−H activation (Scheme 4a). Decomposition of **B** was observed in solution and the carboranyl related specie was transformed to *o*-carboranyl methanol as a known compound (SI-Figure S8). To address the stability issue, *o*-aminophenol was selected based on the following considerations: 1) the presence of benzene ring can form p-π conjugation with the C=N bond and thus may stabilize the *o*-carboranyl imine species; 2) similar to the *α*-amino acid ligand, the imine moiety and the phenolic hydroxyl group in *o*-aminophenol ligand can form a five membered palladacycle for possible B−H activation; 3) condition screening indicated that *o*-aminophenol can also be used as transient directing ligand for the palladium catalyzed B−H arylation with *o*-carboranyl aldehyde (Table 1, entry 14). Treatment of **1a** with *o*-aminophenol in toluene at 80 °C led to the isolation of **9** in 80% yield (Scheme 4b). The reaction of **9** with stoichiometric amounts (1.0 equiv.) of $Pd(OAc)_2$ and PPh_3 at 25 °C gave rise to the bicyclic palladium complex **10** via direct B−H activation of the cage B−H bond. Limited examples for Pd(II)-mediated B−H activation have been previously documented in carboranyl based pincers or thioamide complexes.[15]

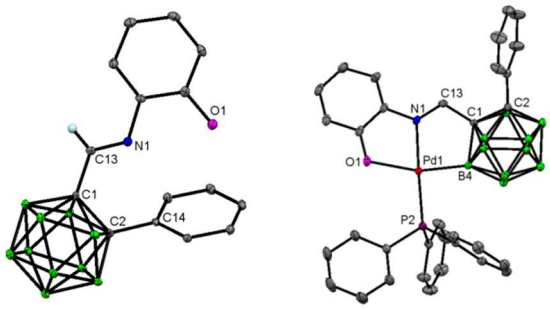
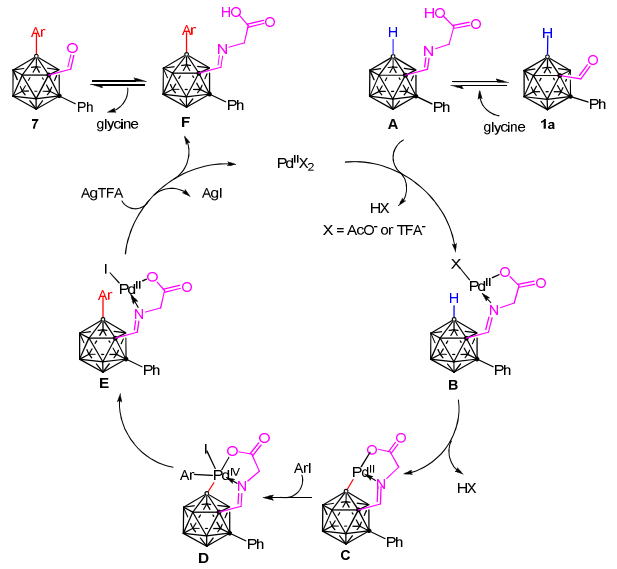


Figure 5. Molecular structures of **9** and **10.** (ellipsoids at 50% probability and H atoms partially omitted for clarity) Selected bond distances [Å] for **9**: C1–C2 1.695(4), C1–C13 1.493(4), C13–N1 1.264(4), C2–C14 1.507(4). Selected bond distances [Å] and angles [°] for **10**: C1–C2 1.676(4), C1–C13 1.472(4), C13–N1 1.278(4), N1–Pd1 2.086(2), O1–Pd1 2.142(2), B4–Pd1 2.042(3), P2–Pd1 2.2485(8), B4–Pd1–O1 163.20(11), N1–Pd1–P2 171.91(7).

Complex **10** was fully characterized by multinuclear NMR spectroscopy, IR spectroscopy and HRMS. The molecular structure of **10** was determined by a single-crystal X-ray diffraction study. The X-ray structure of **10** exhibited a four coordinated Pd(II) center with a tortuous planar square configuration (Figure 5, B4–Pd1–O1 163.20(11)°, N1–Pd1–P2 171.91(7)°). The formation of a Pd–B bond (B4–Pd1 2.042(3) Å) was consistent with the fact that direct B−H activation occurred at the B(4) site in *o*-carboranyl-imino cyclic palladium complex. Furthermore, **10** reacted with 3.0 equiv. of methyl 4-iodobenzoate under arylation condition to generate the desired di- and mono-arylated products **3k** and **7c** in 14% and 30% yield, respectively (Scheme 4c).

Based on the aforementioned experimental results and related literature reports,[11b] a plausible reaction mechanism for B(4)–H arylation is proposed in Scheme 5. Condensation between *o*-carboranyl aldehyde **1a** and glycine leads to an imine-type intermediate **A**, followed by ligand exchanging with $Pd(OAc)_2$ to afford a palladium intermediate **B** before B−H activation at the B(4) site to yield intermediate **C**. Oxidative addition of the intermediate **C** with 1.0 equiv. of ArI affords a Pd(IV) intermediate **D**, followed by reductive elimination to generate intermediate **E**. Then iodide abstraction, protonation and hydrolysis give rise to the B(4)-monoarylated product **7** with release of the catalyst and glycine. In the presence of excess amount of aryl iodides and AgTFA (3.0 equiv.), the repetition of the similar tandem sequence gives rise to the B(4,5)-diarylated product **3** (see SI-Scheme S12 for detail).

Scheme 5. Proposed Reaction Mechanism for Pd-catalyzed B(4)−H Arylation of *o*-Carboranyl Aldehyde **1a**.



CONCLUSION

In conclusion, we have presented the palladium-catalyzed site-selective B−H arylation of *o*-carboranyl aldehydes using a transient directing group. Due to steric hinderance, *o*-carboranyl aldehydes with aryl- or alkyl- substituents at the cage carbon atom tend to functionalize the B(4)/B(5)−H bonds rather than B(3)/B(6)−H bonds. Both electron-rich and electron-deficient aromatic rings can be efficiently incorporated in a site-selective manner. This approach gave access to a series of B(4,5)-diarylated- and B(4)-monoarylated-*o*-carboranyl aldehydes, which were difficult to access in previous reports. Furthermore, the aldehyde group in the products can be conveniently removed or modified into other functional groups. With the help of *o*-aminophenol as the directing ligand, a key bicyclic palladium intermediate has been isolated and characterized, which strongly supports the proposed reaction mechanism. This work could have great potential for broad applications in catalysis and materials.

ASSOCIATED CONTENT

The Supporting Information containing experimental details, compound characterizations and X-ray data in CIF format for **3a**, **3k**, **7g**, **8**, **9**, **10** (CCDC number: 1538449-1538451, 1561202-1561204). This material is available free of charge on the ACS Publications website: http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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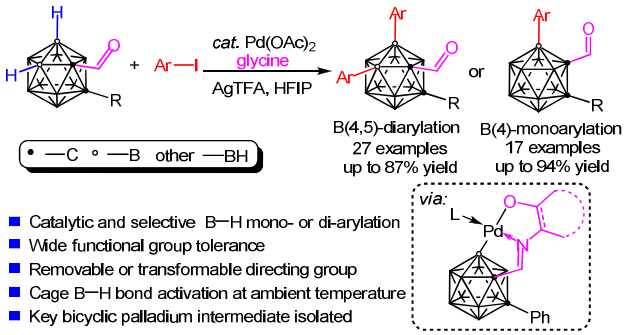

- Catalytic and selective B—H mono- or di-arylation
- Wide functional group tolerance
- Removable or transformable directing group
- Cage B—H bond activation at ambient temperature
- Key bicyclic palladium intermediate isolated