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Cage-Walking: Vertex Differentiation by Palladium-Catalyzed Isomerization of B(9)-Bromo-*meta*-Carborane

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Supporting Information

ABSTRACT: We report the first observed Pd-catalyzed isomerization ("cage-walking") of B(9)-bromo-*meta*-carborane during Pd-catalyzed cross-coupling, which enables the formation of B−O and B−N bonds at all boron vertices (B(2), B(4), B(5), and B(9)) of *meta*-carborane. Experimental and theoretical studies suggest this isomerization mechanism is strongly influenced by the steric crowding at the Pd catalyst by either a biaryl phosphine ligand and/or substrate. Ultimately, this "cage-walking" process provides a unique pathway to preferentially introduce functional groups at the B(2) vertex using B(9)-bromo-*meta*-carborane as the sole starting material through substrate control.

Isomerization mechanisms such as chain-walking via β-hydride elimination/reinsertion and aryne-based rearrangements (Figure 1A) are ubiquitous in metal-catalyzed transformations of organic molecules.[1,2] Through judicious choice of catalyst design, these mechanistic pathways can be biased to form specific regioisomers. Thus, metal-catalyzed isomerization control can provide a means of incorporating functional groups in molecules at positions remote from where initial bond activation occurs.[1−3]

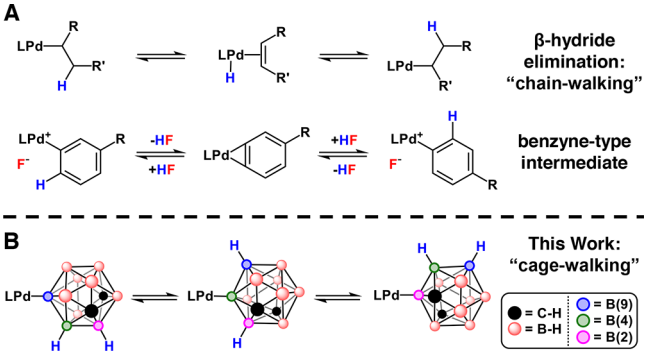

Figure 1. (A) Pd-catalyzed olefin isomerization through β-hydride elimination and arene regioisomer formation through a proposed benzyne intermediate. (B) Pd-catalyzed isomerization of *meta*-carboranyl through "cage-walking".

Boron clusters are unique molecular scaffolds that feature three-dimensional (3D) electronic delocalization.[4] Specifically, in the case of icosahedral carboranes ($C_2B_{10}H_{12}$) this delocalization is nonuniform.[5] This charge distribution makes carboranes an interesting alternative to classical carbon-based structural building blocks such as aryl and alkyl groups.[6] Because of their inherent robustness, carboranes can be promising molecular building blocks for applications ranging from pharmacophores to photoactive materials.[7] Ultimately, vertex-specific functionalization routes (vertex differentiation) are critical for constructing carborane-containing molecules and materials.[7,8]

Recent developments in carborane functionalization have relied on several metal-catalyzed routes, including B−H activation (either directed or undirected) and cross-coupling of halogenated carborane electrophiles at both C and B vertices.[8,9] Even so, these approaches provide limited access to rational, vertex-specific B−H functionalization. Surprisingly, metal-catalyzed isomerization reactivity commonly observed with classical organic substrates (vide supra) has never been reported for any boron cluster systems, including carboranes. Herein we disclose our discovery of a Pd-catalyzed activation of B(9)-bromo-*meta*-carborane (**Br−B(9)**), which can undergo subsequent "cage-walking", leading to the formation of B(2)-, B(4)-, B(5)-, and B(9)-functionalized clusters in the presence of a suitable nucleophile (Figure 1B).

Recently we reported the Pd-catalyzed cross-coupling of **Br−B(9)** to generate B(9)−O and B(9)−N bonds with a wide range of substrates.[9] This cross-coupling relied on biaryl phosphine ligands to generate monoligated palladium(0) species ([**LPd**]) capable of undergoing oxidative addition into the B−Br bond of **Br−B(9)**. To our surprise, during the course of subsequent investigations, when the DavePhos (**L1**) or SPhos (**L2**) ligand was replaced with the bulkier XPhos

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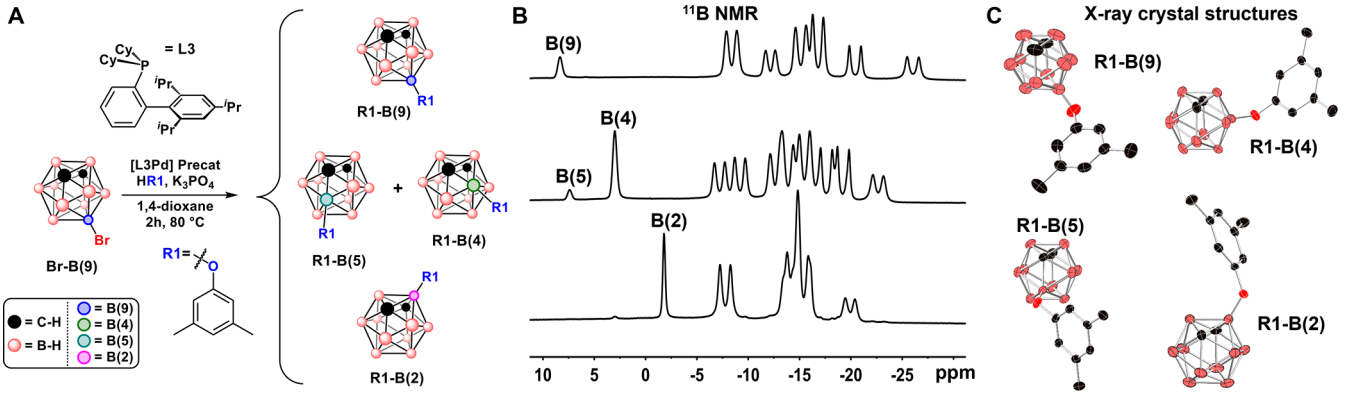

Figure 2. (A) Reaction conditions that result in the formation of **R1**-*meta*-carborane regioisomers. (B) ^{11}B NMR spectra of the isolated regioisomers. Singlet resonances (no ^{11}B−^{1}H coupling) corresponding to the B−O-bonded vertex are labeled; all other resonances correspond to doublet resonances arising from ^{11}B−^{1}H couplings. (C) Single-crystal X-ray structures of **R1-B(*n*)**, *n* = 2, 4, 5, 9 (ellipsoids drawn at 50% probability and H atoms omitted for clarity).

congener (**L3**) in the presence of alcohol or amine substrates, we consistently observed not one but rather three distinct peaks with identical *m*/*z* by gas chromatography−mass spectrometry (GC−MS). For example, using 3,5-dimethylphenol (**R1**) as a cross-coupling partner with **Br−B(9)**, we observed several products with identical *m*/*z* (see the Supporting Information (SI)). Upon chromatographic separation of the reaction mixture on silica gel, we identified four distinct **R1**-carborane compounds by ^{11}B, ^{1}H, and ^{13}C NMR spectroscopy (Figure 2).

The isolated carborane-containing molecules show a distinct downfield singlet in the ^{11}B NMR spectrum corresponding to **R1** bound at a B(2), B(4), B(5), or B(9) vertex of *meta*-carborane (**R1−B(2)**, **R1−B(4)**, **R1−B(5)**, and **R1−B(9)**, respectively). Although we were unable to chromatographically separate **R1−B(5)** and **R1−B(4)**, we identified the isomer ratio as 15:85 by ^{11}B and ^{1}H NMR spectroscopy: **R1−B(4)** is C_1-symmetric, resulting in 10 ^{11}B NMR resonances (one singlet and nine doublets), whereas **R1−B(5)** contains a mirror plane, resulting in six ^{11}B NMR resonances (one singlet and five doublets). Thus, the more intense singlet at ∼3 ppm (Figure 2B) is assigned to the dominant pattern of **R1−B(4)**. Similarly, two sets of ^{1}H and ^{13}C NMR resonances corresponding to **R1−B(5)** and **R1−B(4)** were observed in a 15:85 signal ratio for the CH aromatic and aliphatic regions, respectively (see the SI). These structural assignments are further supported by single-crystal X-ray diffraction studies of the four regioisomers (Figure 2C). Interestingly, **R1−B(4)** is the only monofunctionalized *meta*-carborane regioisomer that exhibits chirality. **R1−B(4)** crystallized as two distinct polymorphs, with both polymorphs containing equal amounts of the two enantiomers in the unit cell. Chiral HPLC analysis further supports the presence of two **R1−B(4)** enantiomers in the isolated mixture (Figure S12).

To further assess the generality of this isomerization process, we examined three biaryl phosphine ligands and several substrates to generate B−O- and B−N-bound carborane regioisomers (Figure 3). Consistent with our previous report, [**L1Pd**] and [**L2Pd**] generate B(9) isomers almost exclusively with O- and N-based nucleophiles.[9] However, [**L3Pd**] generates appreciable amounts of regioisomers under the same conditions. Noteworthy was the presence of bromo-*meta*-carborane regioisomers when the cross-coupling reactions were stopped early, indicating that isomerization of **Br−B(9)** occurs in addition to the cross-coupling reaction. Furthermore, **Br−B(9)** forms bromo-*meta*-carborane isomers in the presence

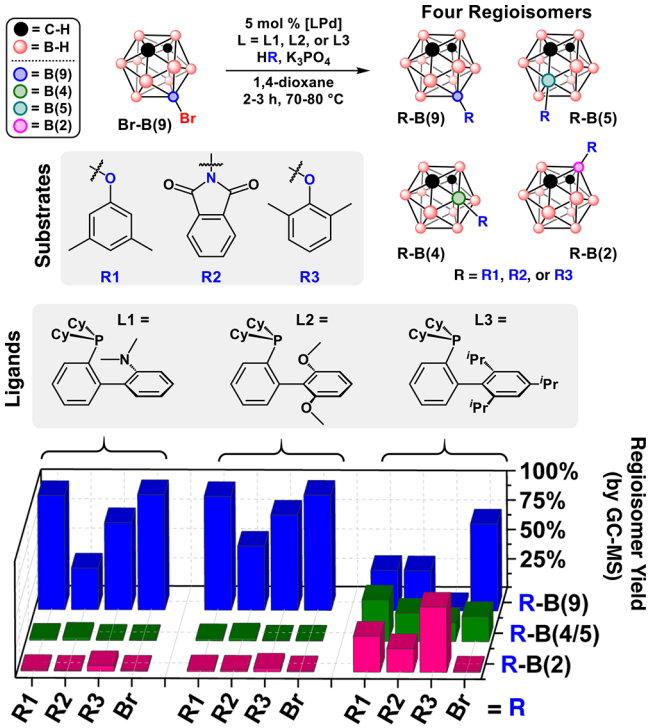

Figure 3. Reaction conditions for forming B-functionalized *meta*-carborane isomers using different substrates (**R1−R3**) and biaryl phosphine ligands (**L1−L3**). Yields were obtained by GC−MS. See the SI for full experimental conditions.

of [**L3Pd**] precatalyst and triethylamine, implying that isomerization can occur prior to transmetalation of a cross-coupling partner and subsequent reductive elimination of the B-functionalized *meta*-carborane. Hence, this metal-catalyzed isomerization may provide a convenient pathway to B(2)-, B(4)-, and B(5)-functionalized *meta*-carborane species that circumvents laborious and often low-yielding protocols such as deboronation/capitation or thermal isomerization strategies.[10,11]

Since bromo-*meta*-carboranyl isomerization can occur before all of the carborane regioisomers are depleted by cross-coupling (vide supra), we hypothesized that the isomerization process might operate separately from the main cross-coupling cycle. To further explore the isomerization mechanics, we attempted

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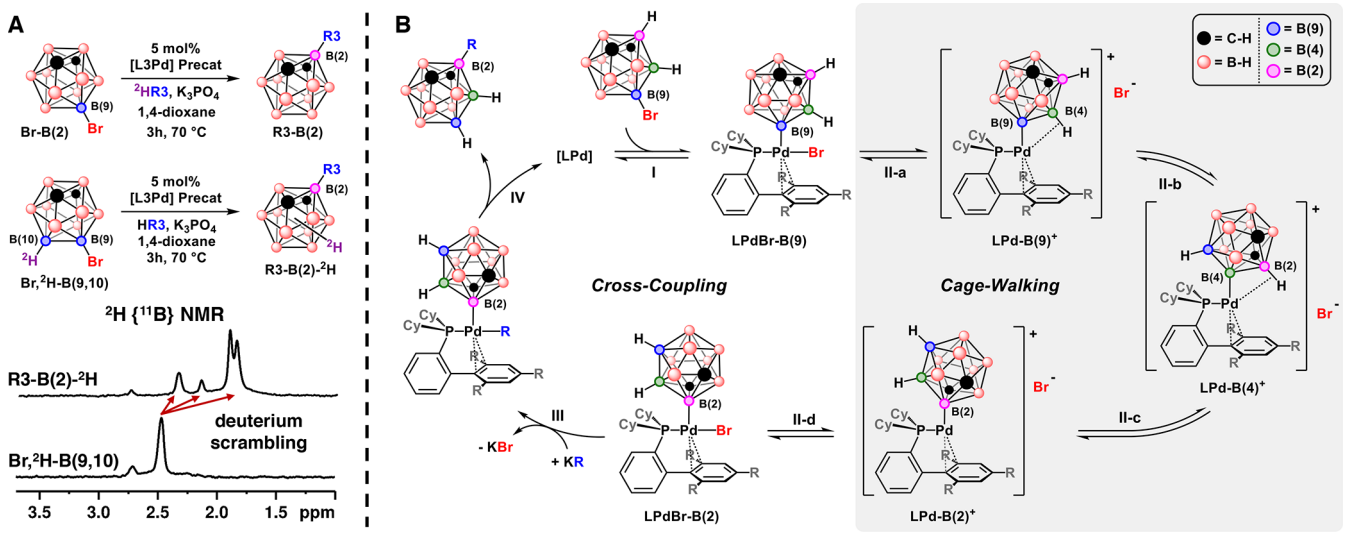

Figure 4. (A) Deuterium labeling experiments. The resonance at 2.7 ppm is present from polydeuterated **Br−B(9)**. See the SI for full experimental details. (B) Proposed metal-catalyzed isomerization of bromo-*meta*-carborane through a "cage-walking" mechanism: (I) oxidative addition; (II-a) bromide dissociation; (II-b, II-c) "cage-walking"; (II-d) bromide association; (III) transmetalation; (IV) reductive elimination.

to inhibit transmetalation by increasing the steric bulk of the cross-coupling partner, thereby allowing the active catalyst species to operate in the isomerization pathway for a longer time (Figure 4, step II). Indeed, cross-coupling reactions using bulky **L3** and sterically congested 2,6-dimethylphenol (**R3**) yielded **R3−B(2)** as the major product (Figure 3). As a control experiment, equimolar amounts of 3,5-dimethylphenol (**R1**) and 2,4,6-trimethylphenol (**R3′**, a variant of **R3** to permit separation of the products by GC−MS) were reacted with **Br−B(9)** in the presence of [**L3Pd**] and K_3PO_4 in 1,4-dioxane at 80 °C (Figures S5 and S6). GC−MS analysis of the reaction mixture showed complete consumption of **Br−B(9)** with **R1**-*meta*-carborane isomers as the major products, suggesting that the size of the nucleophile is linked to the rate of product formation. Since oxidative addition is likely rapid in this process,[12] it appears that by decreasing the rate of transmetalation and/or reductive elimination one can increase the yield of the B(2) regioisomer (Figure 4B). This type of Pd-catalyzed remote vertex functionalization is unprecedented and demonstrates the utility of a metal-catalyzed route to *meta*-carborane vertex differentiation. Importantly, it contrasts with known thermal rearrangements that are limited to thermally resistant functional groups (above 300 °C) and produce isomer mixtures with B(2) substituted *meta*-carboranes as the minor product.[11]

We attribute this difference in reactivity between "cage-walking" (when using **L3**) and cross-coupling exclusively at the B(9) vertex (when using **L1**/**L2**) to steric crowding at the Pd center. The combination of a sterically demanding ligand and nucleophile appears to inhibit transmetalation,[13] allowing the catalyst to operate through several "cage-walking" steps before re-entering the traditional cross-coupling cycle (vide supra). On the basis of these observations, we propose a Pd-catalyzed "cage-walking" mechanism for isomerization of **Br−B(9)** (Figure 4B). Beginning with the oxidative addition complex [**LPdBr−B(9)**], an open Pd(II) coordination site is generated by bromide dissociation[2d] (Figure 4, step II-a) to form [**LPd−B(9)**]$^+$. Consistent with this hypothesis, cross-coupling experiments between **Br−B(9)** and **R3** in the presence of tetrabutylammonium bromide show decreased **Br−B(9)** consumption and decreased formation of **R3**-*meta*-carborane (Figure S7). These experiments suggest that bromide dissociation is an important step in the overall cross-coupling process.[14] After bromide dissociation, two possible "cage-walking" pathways were envisioned for the formally cationic [**LPd−B(9)**]$^+$: (1) deprotonation of an adjacent B−H vertex to form a B(4),B(9)-bound carborane species that isomerizes upon reprotonation to form [**LPd−B(4)**]$^+$ (Figure S9) and (2) a Pd-mediated B−H activation that leads to an intramolecular β-hydride shift (Figure S10). Deuterium labeling experiments in which 2,6-$Me_2C_6H_4OD$ was used as the nucleophile did not result in deuterium incorporation at any B−H vertex, as judged by GC−MS and ^{2}H and ^{11}B NMR spectroscopy, likely ruling out isomerization pathway 1. However, with the deuterated congener of **Br−B(9)**, 9-Br-10-D-*meta*-$C_2B_{10}H_{10}$, and 2,6-$Me_2C_6H_4OH$ as the nucleophile, we observed five B−^{2}H resonances in the ^{2}H{^{11}B} NMR spectrum of **R3−B(2)**, indicating deuterium scrambling across the carborane B−H framework (Figure 4A). We postulate that this β-hydride shift exchanges the B(10) deuterium with an adjacent B(5) proton and enables "cage-walking" to form [**LPd−B(4)**]$^+$ (Figure 4B, step II-b). The "cage-walking" process can occur again to generate [**LPd−B(2)**]$^+$ (Figure 4B, step II-c). Similar reports of metal-catalyzed carborane B−H activation processes have been reported;[8,15,16] however, they are limited to B−H vertices adjacent to carborane-bound directing groups, whereas the presently reported "cage-walking" accesses all of the *meta*-carborane B−H vertices from one starting point in a diversity-oriented fashion.

Through the "cage-walking" process, the carboranyl fragment eventually binds the Pd center through the most electron-deficient boron vertex, B(2), resulting in a more electrophilic Pd center that can overcome the steric repulsion between the cationic [**LPd−B(2)**]$^+$ and the anionic cross-coupling partner. Density functional theory (DFT) calculations (B3LYP/LANL2DZ 6-31G* and M06/SDD/6-311++G**, SMD(1,4-dioxane)) on [**LPd−B(9)**]$^+$, [**LPd−B(4)**]$^+$, and [**LPd−B(2)**]$^+$ indicate that [**LPd−B(2)**]$^+$ has the most cationic Pd center, which likely results in a lower transmetalation barrier due to a stronger electrostatic attraction between the Pd center and the

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phenoxide nucleophile (Figures S13–S16). Furthermore, the ΔG of B–O and B–N bond formation decreases accordingly, B(9) > B(5) ~ B(4) > B(2), for the cross-coupling between **Br–B(9)** and **R1–R3**. Similar electronic effects of substrate and ligand were observed in Pd-catalyzed aryl halide cross-coupling.[17]

In summary, we have discovered the first example of metal-catalyzed isomerization ("cage-walking") of *meta*-carboranyl fragment. The isomerization process appears to operate in conjunction with a classical cross-coupling mechanism, leading to a distribution of carborane regioisomers. The rate of cross-coupling relative to "cage-walking" can be adjusted to achieve selective B-vertex functionalization. We have demonstrated this selectivity by controlling the steric crowding at the Pd center by appropriate choice of catalyst ligand and cross-coupling substrate. Preliminary studies have shown that this "cage-walking" strategy can be applied to carborane B(2)–C_{aryl} bond formation using an arylboronic acid (Figure S17). Overall, this approach provides a unique pathway to vertex differentiation of boron clusters.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b04080.

Full procedures and additional data (PDF)
Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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