**B–N, B–O, and B–CN Bond Formation via Palladium-Catalyzed Cross-Coupling of B-Bromo-Carboranes**

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**Supporting Information**

**ABSTRACT:** Carboranes are boron-rich molecules that can be functionalized through metal-catalyzed cross-coupling. Here, for the first time, we report the use of bromo-carboranes in palladium-catalyzed cross-coupling for efficient B–N, B–O, and unprecedented B–CN bond formation. In many cases bromo-carboranes outperform the traditionally utilized iodo-carborane species. This marked difference in reactivity is leveraged to circumvent multistep functionalization by directly coupling small nucleophiles (-OH, -NH₂, and -CN) and multiple functional groups onto the boron-rich clusters.

Cosahedral carboranes are boron-rich molecular clusters that are often described as three-dimensional (3D) analogs to benzene.¹ Their unique delocalized 3D aromatic bonding, high stability, and potential for site-selective functionalization make them attractive building blocks for tunable pharmacophores, unique ligand scaffolds, and building blocks for materials applications.² Further development of these and other applications with carboranes requires efficient methods for cluster synthesis and functionalization, where ultimately each individual vertex can be specifically addressed.¹

Over the past 50 years, palladium-catalyzed cross-coupling has emerged as a powerful synthetic method for creating new molecules.³ In particular, the emergence of designer ligands (beyond PPh₃) for Pd-catalyzed cross-coupling dramatically expanded the scope of electrophile substrates beyond aryl iodides.⁴ These new catalyst systems demonstrated a clear ability to cross-couple aryl-bromides and aryl-chlorides, thereby facilitating transformations of synthetically challenging substrates. Among existing ligand platforms, biaryl phosphine ligands significantly increased the efficacy of Pd-catalyzed C–C, C–N, and C–O bond formation.⁴

Despite these advances in catalyst design for aromatic substrates, effective methodologies for metal-catalyzed B–N, B–O and B–C cross-coupling in carboranes are lacking. In fact, only B-iodo-carboranes have been used in Pd-catalyzed cross-coupling thus far.⁵ Yet, analogy between carboranes and arenes provides a clear hypothesis that other B-functionalized electrophiles, beyond B-iodo-carboranes, may be competent cross-coupling partners. Here we report our discovery validating this hypothesis by demonstrating for the first time that B-bromo-carboranes can be efficient electrophiles for B–N, B–O, and B–CN bond formation in Pd-catalyzed cross-coupling. Furthermore, we show conditions where these B-bromo-carboranes are superior to the iodinated congeners enabling the synthesis of previously inaccessible B-substituted carboranes. This chemistry is furthermore attractive given the greater synthetic accessibility of B-bromo-carboranes compared to their iodo-based congeners (see SI).³

Hawthorne and co-workers recently reported Pd-catalyzed amidation of 9-I-carborane (I-mCB) utilizing the biaryl phosphine ligand DavePhos (L₁, Figure 1).⁵h To test our hypothesis, we replaced I-mCB with the bromo-carborane congener, 9-Br-m-carborane (Br-mCB), as a substrate under the reported cross-coupling conditions. However, our initial attempts at cross-coupling trifluoroacetamide with Br-mCB proved unsuccessful. Rapid formation of Pd metal was observed without any consumption of Br-mCB. We postulated that the Pd(0) precursor (Pd₂dba₃, dba = dibenzylideneacetone) was not efficiently forming the catalytically active species [L₁Pd⁶]. To resolve this issue, we employed a commercially available Pd(II) precatalyst (Figure 1B inset), which has been previously shown to dramatically improve catalytic activity across a large pool of aryl-based substrates and catalytic conditions.⁷ Importantly, this change tremendously improved the catalytic conversion of Br-mCB producing 1a in nearly quantitative conversion within 2 h (Figure 1A). This discovery demonstrates for the first time that one can efficiently activate a relatively inert B–Br bond in a carborane with electron-rich Pd-based species supported by a biaryl phosphine ligand (Figure 1B).

This example demonstrates the potential competence of Br-mCB toward cross-coupling (Figure 1B), which does not have any literature precedent. This advance was also appealing given that Br-mCB can be synthesized in a fraction of the time (1 h) that is required for the synthesis of I-mCB (1 day). We therefore investigated the scope of Pd-catalyzed cross-coupling...
of Br-mCB with other nucleophiles utilizing biaryl-ligand containing precatalysts.

To further probe the scope of B−N bond formation using Br-mCB, we evaluated several conditions and substrates for Pd-catalyzed amination. Using morpholine as a substrate (2a, Figure 2), we evaluated the cross-coupling efficiency of three precatalysts featuring L1, SPhos (L2), and XPhos (L3) ligands (see SI). For this transformation, L2 afforded complete consumption of Br-mCB and a high amount of B−N coupling product 2a as determined by GC-MS analysis. Evaluation of various bases indicated the superior performance of K’BuO for forming 2a. Importantly, Br-mCB showed superior cross-coupling efficiency compared to I-mCB for the formation of 2a (Figure 2A). Using these optimized conditions, cross-coupling of Br-mCB proceeds with primary, secondary, aromatic, and heterocyclic amines in nearly quantitative conversion affording the corresponding B−N compounds (2b−2e, Figure 2B and SI).

In general, cross-coupling using unprotected nitrogen-rich heterocyclic substrates is known to be challenging.8c Amination of halocarboranes has only been shown on the 2-I-carborane, which is a significantly more reactive substrate than Br-mCB.7 The cross-coupling methodology we developed addresses this issue for the first time in the context of m-carborane chemistry since, to the best of our knowledge, 2e represents the first product resulting from the direct cross-coupling of an unprotected five-membered heterocycle with a B-halo-m-carborane.

The versatility of Br-mCB as a cross-coupling partner can be further seen from its efficient reactivity with challenging nucleophiles. For example, Br-mCB cross-couples with ammonia producing 2c (Figure 2B), whereas previously 2c could only be prepared by lengthy hydrolysis of 1a.8b Importantly, our method represents the first example of a direct cross-coupling leading to 2c and is enabled by the previously unrecognized reactivity of Br-mCB when using biaryl phosphine supported Pd-based catalysts.

During the course of our amination studies, we observed B−OH coupling with Br-mCB (2f, see SI) when nonanhydrous bases were used. This is remarkable, given that the only example of a Pd-catalyzed carborane B−O bond formation was reported on 2-I-p-carborane. Importantly, the I-mCB congener was previously deemed too unreactive.8d

Based on these observations, we developed a new cross-coupling protocol enabling the direct coupling of water, methanol, trifluoroethanol, and 3,5-dimethylphenol with Br-mCB (2f−2i, Figure 2C). This constitutes the first reported Pd-catalyzed cross-coupling leading to a B−O bond formation with m-carborane substrates. Significantly, a control reaction where I-mCB was used as a substrate led to a significantly lower conversion to 2i (Figure 2A). This Pd-catalyzed route is also superior to the existing method for forming related B−O compounds utilizing carborane B-halonium salts.8e Additionally, 2f can be readily converted to 2g by deprotonation with NaH and followed by treatment with MeI, demonstrating the added synthetic utility of 2f.
The versatility of Br-mCB cross-coupling with small nucleophiles led us to investigate B–CN bond formation. Cyanide is known to be a difficult cross-coupling partner in metal catalysis due to its propensity toward binding to catalytically active species, resulting in their deactivation.9-d Recently several groups reported efficient protocols for cyanation of aromatic substrates using K₄[Fe(CN)₆] as a mild cyanide source.9b,d Pd-catalyzed cyanation of mBr-mCB using K₄[Fe(CN)₆] with an L₃-based precatalyst led to the formation of 9-CN-m-carborane in a nearly quantitative conversion (3a, Figure 3A). This example represents the first direct cyanation of a halogenated derivative of dicarba-closo-dodecaborane. Importantly, cross-coupling activity of the I-mCB species under these conditions is dramatically diminished compared to Br-mCB (Figure 3A).

The ability to append multiple functional groups is crucial to developing carboranes for new and existing materials.2,10,11 While polyfunctionalization of arene-based electrophiles via cross-coupling is well-established, similar methods for carboranes are rare.5,10 Our methodology can be applied toward disubstitution cross-coupling chemistry. Specifically, 9,10-Br₂-m-carborane (4a) can be functionalized with two bulky 3,5-dimethylphenol substituents (4c, Figure 4). Interestingly, under B–OH cross-coupling conditions (vide supra), 4a undergoes exclusive monosubstitution to produce 4d.

In addition, given the pronounced orthogonal reactivity of B–Br versus B–I bonds in cross-coupling, our methodology can be used to heterofunctionalize mixed halo-carborane substrates. We leveraged the selectivity of PdCl₂(PPh₃)₂ for B–I bond functionalization to produce 9-Br-10-Et-m-carborane (4e) from 9-Br-10-I-m-carborane (4b, Figure 4 and SI).

Selective Pd-catalyzed cross-coupling of the B–Br moiety in 4e with L₂-containing precatalyst yields the heterofunctionalized 9-O-(3,5-Me₂C₆H₃)-10-Et-m-carborane (4f). This transformation represents the first metal-catalyzed B-heterofunctionalization of dicarba-closo-dodecaborane via cross-coupling demonstrating that B-Br-carboranes offer an additional pathway for multifunctionalization. These experiments also suggest that our methodology is amenable to sterically encumbered carborane-based electrophiles.

Ortho-carboranes are the most challenging substrates in cross-coupling methodologies, since these species undergo facile deboronation in the presence of nucleophiles.12 Our conditions are sufficiently mild and enable the cross-coupling of 3-Br-ortho-carborane (Br-oCB, see SI for details) with amine and alcohol substrates that are not strongly nucleophilic (5a–5b, Figure 5). Using 3-Br-ortho-carborane in this case is preferred, given its higher conversion efficiency and ease of preparation compared to the 3-1-o-carborane analogue.

In summary, we discovered that B-bromo-m-carboranes undergo efficient Pd-catalyzed B–N, B–O, and B–CN cross-coupling enabled by precatalysts featuring electron-rich biaryl phosphine ligands. The higher reactivity of Br-mCB likely stems from faster transmetalation (Figure 1B, step II) due to a weaker Pd–Br bond compared to Pd–I congener. This is consistent with previously observed trends in palladium-catalyzed transformations using aryl halide electrophiles and Pd-based catalysts supported by bulky electron-rich phosphine ligands.13,14 The use of B-bromo-carboranes allows direct access to previously unknown B-functionalizations of these clusters. In addition, judicious use of Pd-catalyst systems with either iodo- or bromo-functionalized carborane was used to access unprecedented heterofunctionalized species. This approach is also amenable to o-carborane, which is the most challenging carborane substrate. Notably, this cross-coupling chemistry is complementary to the recently developed efforts in directed B–H functionalization strategies15 and, if successfully
combined, may provide unprecedented densely functionalized carbane species. Further expansion of this methodology to other cross-coupling chemistry along with a full mechanistic investigation is currently underway in our laboratory.

**ASSOCIATED CONTENT**

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b05505.

Full procedures and other characterization data (PDF) Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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