Regioselective B(3,4)–H arylation of o-carboranes by weak amide coordination at room temperature†

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Palladium-catalyzed regioselective di- or mono-arylation of o-carboranes was achieved using weakly coordinating amides at room temperature. Therefore, a series of B(3,4)-diarylated and B(3)-monoarylated o-carboranes anchored with valuable functional groups were accessed for the first time. This strategy provided an efficient approach for the selective activation of B(3,4)–H bonds for regioselective functionalizations of o-carboranes.

Scheme 1 Chelation-assisted transition metal-catalyzed cage B–H activation of o-carboranes.
alternatives to traditional cross-coupling reactions.19 Within our program on sustainable C–H activation,20 we have now devised a protocol for unprecedented cage B–H arylation of o-carboranes with weak amide assistance, on which we report herein. Notable features of our findings include (a) transition metal-catalyzed room temperature B–H functionalization, (b) high levels of positional control, delivering B(3,4)-diarylated and B(3)-monoarylated o-carboranes, and (c) mechanistic insights from DFT computation providing strong support for selective B–H arylation (Scheme 1d).

We initiated our studies by probing various reaction conditions for the envisioned palladium-catalyzed B–H arylation of o-carborane amide 1a with 1-iodo-4-methylbenzene (2a) at room temperature (Tables 1 and S1†). We were delighted to observe that the unexpected B(3,4)-di-arylated product 3aa was obtained in 59% yield in the presence of 10 mol% Pd(OAc)2 and 2 equiv. of AgTFA, when HFIP was employed as the solvent, which proved to be the optimal choice (entries 1–5).21 Control experiments confirmed the essential role of the palladium catalyst and silver additive (entries 6–7). Further optimization revealed that AgOAc, Ag2O, K2HPO4, and Na2CO3 failed to show any beneficial effect (entries 8–11). Increasing the reaction temperature fell short in improving the performance (entries 12 and 13). The replacement of the amide group in substrate 1a with a carboxylic acid, aldehyde, ketone, or ester group failed to afford the desired arylation product (see the ESI†). We were pleased to find that the use of 1.0 equiv. of trifluoroacetic acid (TFA) as an additive improved the yield to 71% (entry 14). To our delight, replacing the silver additive with Ag2CO3 resulted in the

![Table 1](image)

| Entry | Additive | Solvent | Yield of 3aa/% | Yield of 4aa/% |
|-------|----------|---------|---------------|---------------|
| 1     | AgTFA    | PhMe    | 0             | 0             |
| 2     | AgTFA    | DCE     | 0             | 0             |
| 3     | AgTFA    | 1,4-Dioxane | 0             | 0             |
| 4     | AgTFA    | TFE     | 21            | 3             |
| 5     | AgTFA    | HFIP    | 59            | 4             |
| 6     | AgTFA    | —       | 0             | 0             |
| 7     | AgOAc    | HFIP    | 5             | <3            |
| 8     | Ag2O     | HFIP    | <3            | <3            |
| 9     | K2HPO4   | HFIP    | 0             | 0             |
| 10    | Na2CO3   | HFIP    | 0             | 0             |
| 11    | AgTFA    | HFIP    | 53            | 4             |
| 12    | AgTFA    | HFIP    | 42            | 3             |
| 13    | AgTFA    | HFIP    | 71            | <3            |
| 14    | AgTFA    | HFIP    | 9             | 34            |
| 15    | Ag2CO3   | HFIP    | 55            | 6             |
| 16    | Ag2CO3   | HFIP    | 5             | 55            |

* Reaction conditions: 1a (0.20 mmol), 2a (0.48 mmol), Pd(OAc)2 (10 mol%), additive (0.48 mmol), solvent (0.50 mL), 25 °C, 16 h, and isolated yield. † Without Pd(OAc)2. ‡ At 40 °C. § At 60 °C. ¶ TFA (0.2 mmol) was added. # 1a (0.20 mmol), 2a (0.24 mmol), Pd(OAc)2 (5.0 mol%), and Ag2CO3 (0.24 mmol). ‖ 2a was added in three portions every 4 h. DCE = dichloroethane, TFE = 2,2,2-trifluoroethanol, HFIP = hexafluorisopropanol, and TFA = trifluoroacetic acid.

![Scheme 2](image)

Scheme 2 Cage B(3,4)–H di-arylation of o-carboranes.

![Scheme 3](image)

Scheme 3 Effect of substituents on B–H diarylation. *At 50 °C.
formation of B(3)–H mono-arylation product 4aa as the major product (entries 15–16).

With the optimized reaction conditions in hand, we probed the scope of the B–H di-arylation of o-carboranes 1a with different aryl iodides 2 (Scheme 2). The versatility of the room temperature B(3,4)–H di-arylation was reflected by tolerating valuable functional groups, including bromo, chloro, and enolizable ketone substituents. The connectivity of the products 3aa and 3ab was unambiguously verified by X-ray single crystal diffraction analysis.22

Next, we explored the effect exerted by the N-substituent at the amide moiety (Scheme 3). Tertiary amides 1b–1f proved to be suitable substrates with optimal results being accomplished with substrate 1a. The effect of varying the cage carbon substituents R1 on the reaction’s outcome was also probed, and both aryl and alkyl substituents gave the B–H arylation products and the molecular structures of the products 3dd, 3ea and 3fa were fully established by single-crystal X-ray diffraction.

The robustness of the palladium-catalyzed B–H functionalization was subsequently investigated for the challenging catalytic B–H monoaarylation of o-carboranes (Scheme 4). The B(3)–H monoaarylation, as confirmed by single-crystal X-ray diffraction analysis of products 4aa and 4ai, proceeded smoothly with valuable functional groups, featuring aldehyde and nitro substituents, which should prove invaluable for further late-stage manipulation.

To elucidate the palladium catalysts’ working mode, a series of experiments was performed. The reactions in the presence of TEMPO or 1,4-cyclohexadiene produced the desired product 3aa, which indicates that the present B–H arylation is less likely to operate via radical intermediates (Scheme 5a). The palladium catalysis carried out in the dark performed efficiently (Scheme 5b). Compound 4aa could be converted to di-arylation product

![Scheme 4 Cage B(3)–H monoaarylation of o-carboranes.](image)

![Fig. 1 Computed relative Gibbs free energies in kcal mol$^{-1}$ and the optimized geometries of the transition states involved in the B–H activation at the PBE0-D3(BJ)/def2-TZVP+SMD(HFIP)//TPSS-D3(BJ)/ def2-SVP level of theory. (a) First B–H activation transition states at the B3 and B4 positions. (b) Second B–H activation transition states at the B4 and B6 positions. Irrelevant hydrogen atoms in the transition states are omitted for clarity and the bond lengths are given in Å.](image)
3aa with high efficiency, indicating that 4aa is an intermediate for the formation of the diarylated cage 3aa (Scheme 5c).

To further understand the catalyst mode of action, we studied the site-selectivity of the o-carborane B–H activation for the first B–H activation at the B3 versus B4 position and for the second B–H activation at the B4 versus B6 position using density functional theory (DFT) at the PBE0-D3(BJ)/def2-TZVP+SMD(HFIP)//TPSS-D3(BJ)/def2-SVP level of theory (Fig. 1). Our computational studies show that the B3 position is 5.8 kcal mol$^{-1}$ more favorable than the B4 position for the first B–H activation, while the B4 position is 3.4 kcal mol$^{-1}$ more favorable than the B6 position for the second B–H activation. It is noteworthy that here the interaction between AgTFA and a cationic palladium(n) complex was the key to success, being in good agreement with our experimental results (for more details, see the ESI†).

A plausible reaction mechanism is proposed which commences with an organometallic B(3)–H activation of 1a with weak assistance of the amide group and assistance by AgTFA to form the cationic intermediate I (Scheme 6). Oxidative addition of the aryl iodide 2 affords the proposed cationic palladium(n) intermediate II, followed by reductive elimination to give the B(3)-mono-arylation product 4aa. Subsequent B(4)-arylation occurs assisted by the weakly coordinating amide to generate the B(3,4)-di-arylation product 3aa. Due to the innate higher reactivity of the B(4)–H bond in intermediate 4aa – which is inherently higher than that of the B(6)–H bond – the B(3,6)-di-arylation product is not formed.

In summary, room temperature palladium-catalyzed direct arylations at cage B(3,4) positions in o-carboranes have been achieved with the aid of weakly coordinating, synthetically useful amides. Thus, palladium-catalyzed B–H activations enable the assembly of a wealth of arylated o-carboranes. This method features high site-selectivity, high tolerance for functional groups, and mild reaction conditions, thereby offering a platform for the design and synthesis of boron-substituted o-carboranes. Our findings offer a facile strategy for selective activations of B(3,4)–H bonds, which will be instrumental for future design of optoelectronics, nanomaterials, and boron neutron capture therapy agents.

**Conflicts of interest**

There are no conflicts to declare.

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