Aminoalkyl carboranes are anticipated to be valuable synthons toward the synthesis of bifunctionalized carboranes. However, direct cage boron derivation of these carborane derivatives has not been solved. Herein, the reversible conversion of catalytically infeasible o-carboranyl methylamines (1-CH$_2$NH$_2$-o-carboranes) into bidentate imines initiates Pd-mediated cage B–H activation. As a result, an amine coordinated bicyclic Pd(II) complex (3) has been isolated and proven to be the catalytically active intermediate for highly site-selective B–H diarylation of o-carboranyl methylamines. Using glyoxylic acid as an inexpensive and commercially available transient directing reagent, a wide range of cage B(4,5)-diarylated free primary o-carboranyl methylamines were prepared in good to excellent yields with the avoidance of the pre-installation and removal of a directing group. This method provides easy access to cage boron functionalized o-carboranyl methylamines with potential for application in pharmaceuticals.

**Scheme 1** Direct cage boron derivation of o-carborane leading to unfunctionalized or bifunctionalized carboranes.
aminomethyl-o-carboranes (also termed as o-carboranyl methylamines and 1-CH₃NH₂-o-carboranes) by using glyoxylic acid or salicylaldehyde as the catalytic and transient directing groups. A wide array of B(4,5)-diarylated o-carboranyl methylamines were prepared as free primary amines without protection or deprotection steps. In addition, a bicyclic palladium complex (3) has been isolated featuring o-carboranyl methylamine as an internal ligand and proven to be the catalytically active intermediate. Importantly, direct C–H functionalization of organic amines has been realized by using a transient directing strategy or a steric tethering approach; cage B–H functionalization of o-carboranyl carboxylic acids has been reported by Xie and co-workers, where the carboxylic acid group serves as a traceless directing group (DG) (Scheme 1a); o-carboranyl aldehydes have also been utilized, by us, as suitable substrates for cage boron derivation with a transient DG (Scheme 1b). Our present work (Scheme 1c) constitutes the first study of cage B–H functionalization of aminoboranyl carboranes, which affords bifunctionalized carboranes with both aryl and amino groups in one molecule.

Results and discussion

Initial studies involved the investigation of Pd-mediated selective B–H activation of 1-phenyl-o-carboranyl-2-methyamine 1a. Treatment of 1a with PdX₂ (X = Cl or OAc) led to bis(amine) Pd(n) complexes which was characterized (Schemes 2 and S4†) and found to be unreactive for the cage B–H activation process. Three component reaction of 1a with salicylaldehyde (L1) and Pd(OAc)₂ in toluene at 25 °C afforded a new palladium complex 3 in 35% yield (Scheme 2). Alternatively, condensation of 1a with L1 delivered o-carboranyl methylaldimine 2, followed by sequential treatment with 1.0 equiv. of Pd[OAc]₂ and 1a also gave rise to 3. In solution, as indicated by the ¹H NMR spectrum, 3 exhibits typically two types of CH₂ signals with the coupling of homocarbon hydrogens for each (Scheme 2, δ = 4.04 and 3.53 ppm for H8A and H8B, JH₂-H₂ = 15 Hz; δ = 3.42 and 3.40 ppm for H25A and H25B, JH₂-H₂ = 6 Hz). These results shed light on the ring annulation to form a five-membered B–C–C–N–Pd palladacycle after B–H activation, which is consistent with a single-crystal X-ray analysis in the solid state. Interestingly, here o-carboranyl methylamine 1a plays a dual role in Pd-mediated B–H activation: (1) it acts as a substrate to form a 5,6-fused palladacycle through Pd–B bond formation (B₄–Pd1 2.009(14) Å), and (2) it acts as a ligand to furnish a four coordinated Pd(n) core with a square planar configuration.

In the current reaction, cage B–H activation was initiated by the dehydration of 1a with salicylaldehyde to produce a bidentate imine/hydroxyl directing group, followed by treatment with Pd(n) acetate to furnish a proximity-driven B–H palladation process. It is noteworthy that there have been pioneer reports in which some organic imines are utilized as transient directing groups for direct C–H bond functionalization of primary amines. However, reported examples of such a mechanism for inert C–H activation are proposed based on indirect evidence where the model intermediates have been isolated with the aid of an external ligand. Herein, complex 3 is formed with the aid of an internal ligand and it can mimic the real catalytic reaction conditions in which excess substrate (o-carboranyl methylamine) is present.

Complex 3 is reactive for further transformations. For example, ligand exchange of 3 with PPh₃ delivered 4 in

Scheme 2 Synthesis of bicyclic palladium complex 3 through palladium-mediated B–H activation and its further transformations including ligand exchange and subsequent diarylation. †Isolated yields based on o-carboranyl methylamine.
quantitative yield. Stoichiometric reaction of 3 with 5.0 equiv. of iodobenzene and AgTFA in HFIP at 80 °C afforded two B(4,5)-diarylated species which were identified as salicyldimine and trifluoroacetamide in moderate yields. Compound 6 could be converted to its free amine 7 under basic and moisture conditions. Compounds 5–7 were fully characterized by NMR spectroscopy, infrared spectroscopy (IR) and high resolution mass spectrometry (HRMS). The structure of 6 was further confirmed by single-crystal X-ray diffraction analysis (Scheme 2).

The catalytic performance of 3 and 4 has been evaluated. We found that the addition of 3.0 equiv. of AcOH and H2O for each complex is most likely involved in the catalytic cycle. Interestingly, between mentioned species is depicted in Scheme 3b. Dehydration a proposed reaction pathway for the formation of the above-diarylated species which were identified as salicyldimine and trifluoroacetamide 6 in moderate yields. Compound 6 could be converted to its free amine 7 under basic and moisture conditions. Compounds 5–7 were fully characterized by NMR spectroscopy, infrared spectroscopy (IR) and high resolution mass spectrometry (HRMS). The structure of 6 was further confirmed by single-crystal X-ray diffraction analysis (Scheme 2).

The catalytic performance of 3 and 4 has been evaluated and found that the addition of 3.0 equiv. of AcOH and H2O for each was essential for catalytic reactions (Table S1). Using complex 3 as a catalyst (10 mol%) under catalytic conditions (Scheme 3a) afforded B–H diarylated product 7 in 64% yield. Thus, complex 3 is most likely involved in the catalytic cycle. Interestingly, complex 4, a PPh3 adduct, also exhibited catalytic activity, albeit with decreased efficiency. On the basis of the above results, we propose a reaction pathway for the formation of the above-mentioned species as depicted in Scheme 3b. Dehydration between 1a and L1 forms 2 which can subsequently replace the acetate of Pd(OAc)2 to afford A. Then, B–H activation occurs at the B(4) site to yield a bicyclic palladium intermediate B. Oxidative addition of B with 1.0 equiv. of PhI affords a Pd(IV) intermediate C, followed by reductive elimination to generate D.

Then iodide abstraction with AgTFA leads to F, before the repetition of a similar tandem sequence at the B(5) site to deliver G. Iodide abstraction and protonation gives rise to B(4,5)-diarylated salicyldimine 5, followed by hydrolysis to furnish the free amine 7 with release of the Pd catalyst and salicylaldehyde. It is noteworthy that o-carboranyl methylamines (1a or 7) can stabilize the Pd-involved intermediates through H2N → Pd coordination, for example, the combination of 1a and B can produce 3.

Considering the importance of a directing ligand for selective cage B–H activation, we continued our investigation of palladium-catalyzed B–H diarylation of 1a with iodobenzene with focus on ligand screening (Table 1). Gratifyingly, either salicylaldehyde (L1) or 3,5-di-tert-butylishalicylaldehyde (L3) can afford the desired product 7 in 70% and 67% yields, respectively. Utilizing 3,5-dichlorosalicylaldehyde (L2) with electron-withdrawing groups reduced the yield. Pyridine-based ligands (L4 and L5) led to decomposition of 1a. The reaction could be performed with glyoxylic acid monohydrate (L6) in 85% yield whereas the yield was decreased with 2-oxopropanoic (L7) or phenylglyoxylic acid (L8), indicating the importance of an aldehyde moiety. In the absence of ligands, no reaction was observed, demonstrating the necessity of a transient DG for B–H activation (Table S1, entry 8). Neither benzaldehyde (L9) nor butyraldehyde (L10) was reactive, which again shows the importance of bidentate chelation of imine and hydroxymethyl moieties.

The scope of the aryl iodides and o-carboranyl methylamines was further investigated by the use of the cheap DG (L6) (Table 2). Alkyl, phenyl, alkoxy, trifluoromethyl, alkoxycarbonyl and acetyl substituted aryl iodides were well tolerated in this process, furnishing the B(4,5)-diarylated o-carboranyl methylamines (7–14 and 19–22) in good to excellent yields with high site-selectivity (Table 2). Halogenated (fluoro, chloro or bromo) aryl iodides were also found to be viable (15–18). Unfortunately, B(4,5)-diarylation for ortho-iodotoluene was not compatible under the current conditions, presumably due to the steric effect of the 2-tolyl group. In addition, C-aryl, -alkyl or -z-methyl substituted o-carboranyl methylamines were effective substrates, providing the corresponding B(4,5)-diarylated

![Scheme 3](image)

**Scheme 3** (a) Catalytic performance of 3 and 4 in cage B–H diarylation. (b) A plausible reaction mechanism.

**Table 1** Evaluation of the transient DGs**

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Yield (%)</th>
</tr>
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<tbody>
<tr>
<td>L1</td>
<td>70%</td>
</tr>
<tr>
<td>L2</td>
<td>31%</td>
</tr>
<tr>
<td>L3</td>
<td>67%</td>
</tr>
<tr>
<td>L4</td>
<td>n.d.</td>
</tr>
<tr>
<td>L5</td>
<td>n.d.</td>
</tr>
<tr>
<td>L6</td>
<td>85%</td>
</tr>
<tr>
<td>L7</td>
<td>51%</td>
</tr>
<tr>
<td>L8</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

*Conditions: 1a (0.1 mmol), iodobenzene (0.3 mmol), Pd(OAc)2 (10 mol%), ligands (20 mol%), AgTFA (0.3 mmol), AcOH (0.3 mmol), H2O (0.3 mmol), HFIP (0.5 mL), 80 °C, N2 atmosphere, 12 h.*

*Isolated yield. **1a** was decomposed. *Optimal conditions. n.d.: desired product not detected.*
products in synthetically satisfactory yields (23–29). However, 1-CH$_2$NH$_2$-o-C$_2$B$_{10}$H$_{11}$ without a substituent at the carbon vertex afforded an inseparable mixture. These observations suggested that the substitution at the carbon site can contribute to B(4)/B(5)-selectivity, which was consistent with our previous reports. The α-dimethyl substituent also gave rise to B(4,5)-diarylated α-carborane (30) with an in situ removal of the methylamine group via C$_{cage}$–C bond cleavage. After treatment...
with Na2CO3 in THF/H2O, non-protected primary amines could be obtained without the need for further tactics to remove the DGs. All of the new compounds (7–29) were fully characterized by 1H, 13C, and 15N NMR spectroscopy, IR and HRMS. The structures of 10, 17 and 28 were further confirmed by single-crystal X-ray diffraction analysis (Fig. 1).

The substrates (aminomethyl-o-carboranes) used in this study are stable under the current catalytic conditions and can be readily transformed into other derivatives. As demonstrated in Scheme 4a, B(4,5)-diarylated o-carboranyl methylamine 7 could be readily converted to its Boc, Fmoc or tosyl amide derivatives (31–33) in excellent yields. In addition, attachment of the sulfamide moiety by using transamination between 7 and sulfamide gave rise to 34 in 84% yield (Scheme 4a). Since three-dimensional carboranyl sulfamides are promising inhibitors for carbonic anhydrase isozymes,34 the cage B–H activation strategy on carboranyl methylamines would be beneficial to the structure-based design of these specific inhibitors. The structure of 34 was determined by X-ray diffraction analysis (Fig. 2). Furthermore, when the reaction of 1a and 4-bromo-1-iodobenzene was scaled up to 1.0 mmol, the B(4,5)-diarylated product 17 was isolated in 60% yield after silica chromatography (Scheme 4b).

**Conclusions**

In conclusion, we have developed aminomethyl-o-carboranes as ideal candidates for cage B–H activation reaction. This reaction demonstrates high site-selectivity for B(4,5)-diarylation at the carboranyl unit, as well as good functional group compatibility. In the presence of salicylaldehyde, the bidentate nature of the in situ generated imine-hydroxyl ligand favours the formation of a bicyclic palladium complex (3) featuring cage B–H activation at the B(4) site. With o-carboranyl methylamine as an internal ligand, a bicyclic palladium complex (3) has been isolated and proven to be the catalytically active intermediate for catalytic B–H diarylation. Through the use of glyoxalic acid as an inexpensive and transient directing agent, a series of B(4,5)-diarylated free primary o-carboranyl methylamines were obtained without further tactics to install and remove the DGs. Considering the importance of aminoaalkyl carboranes in biological systems, the methodology reported here will be beneficial to the synthesis of bifunctionalized carboranes for drug discovery.

**Conflicts of interest**

There are no conflicts to declare.

**Acknowledgements**

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**Notes and references**


