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Palladium catalyzed selective mono-arylation of o-carboranes via B-H activation

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A palladium catalyzed selective mono-arylation of *o*-carboranes with aryl iodides has been developed, and a series of B(8)/B(9)-Ar-*o*-carboranes anchored with active groups have been synthesized with moderate to good yield as well as good selectivity. The mechanism involving a Pd^{II} catalyzed electrophilic B-H activation was also proposed.

Carboranes are a class of boron hydride cluster with threedimensional aromaticity, which have extensive applications in boron neutron capture therapy (BNCT),¹ supramolecular chemistry² and coordination chemistry.³ Thus, regioselective synthesis of carbon and boron functionalized carboranes has been an attractive subject as their importance in diverse applications. In the past decades, the carbon functionalization of carboranes including transition metal mediated/catalyzed method has been well developed.⁴ On the contrary, the boron functionalization of carboranes with regioselectivity is more challenge because of the slight difference in reactivity among the 10 B-H bonds, thus led the boron functionalization more complicated than that of carbon. ⁵ The typical method for regioselective synthesis of boron-substituted carboranes developed by Jones Jr. and Hawthorne is based on boron-halogenated carboranes.⁶ Due to low activity of the boron-halogen bonds, the subsequent coupling with Grignard reagent proceeds sluggishly and has limited application values in synthetic chemistry. Therefore, the development of new approach, especially with selective mode, for the boron functionalization of carboranes is eagerly desired but still a challenging subject.

To synthesize boron-substituted carboranes, transition metal catalyzed direct functionalization via B-H activation would be an ideal approach, which would avoid the pre-functionalization of carboranes and generate of versatile carborane derivatives for their diverse applications. Although selective B-H activation of *o*-carboranes has been found in transition metal complex by forming B-M (M = transition metal) bonds,⁷ utilization of selective B-H activation for the

synthesis of boron functionalized o-carboranes with regioselectivity has been rarely reported.^{8, sb}

For o-carboranes, molecular orbital calculation indicates the B(8, 9, 10,12) owned higher negative charge density than other boron atoms, which led them favour to take electrophilic reaction.9 However, the four boron atoms of B(8, 9, 10,12) are not full equally, among them, B(9) and B(12), B(8) and B(10) are equivalence, respectively. Additionally, B(9,12) possess slight higher negative charge density than that of B(8,10), hence, the electrophilic reaction of B(9,12) showed prior to that of B(8,10).¹⁰ Based on the three-dimensional aromaticity of o-carboranes and transition metal catalyzed direct C-H functionalization of arenes, we envisioned that if o-carboranes would display similar chemical reactivity to that of arenes to coupling with organic partners via B-H activation, and if we can distinguish the slight difference in reactivity of B(9,12) and B(8,10) to achieve their selective mono-functionalization. With this idea in mind and our recent research interest in boron cluster chemistry,¹¹ we found that the selective mono-arylation of B(8) and B(9) could be realized by palladium catalyzed direct functionalization of B-H bond with aryl iodides.¹² Herein, we are pleased to present our results.

To initial of our research, *o*-carborane (**1a**) and iodobenzene were selected to screening conditions and the results were summarized in Table **1**. Extensive investigation indicated palladium salts were suitable for the coupling reaction. Pioneering work has demonstrated the capture of iodide by silver salt is crucial in palladium catalyzed direct arylation of arenes with iodobenzene.³³ Therefore, various silver salts were examined. With Ag₂O as additive, the coupling product **2a** could be obtained in only 5% yield (entry **1**, Table **1**). The yield was slightly increased with AgOAc (entry 2). To our delight, when Ag₂CO₃ was used, the yield was enhanced to 36% (entry 3), and the arylation was selective on B(8) and B(9) with a ratio of **1**:8.¹⁴ Control experiments demonstrated that Pd(OAc)₂ and Ag₂CO₃ were essential for this coupling reaction, the reaction could not proceed at all without Pd(OAc)₂ or Cs₂CO₃ instead (entries 4-5). When the reaction was conducted in dioxane and toluene, the corresponding product

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^{*a*} All reactions were carried on 0.25 mmol **1a** or **1b**, 0.025 mmol catalyst, 0.75 mmol iodobenzene, 0.50 mmol additive and 1 mL solvent at 60°C for 48h under argon atmosphere. ^{*b*} Isolated yields. ^{*c*} DCE: 1,2-dichloroethane. ^{*d*} The ratio of arylation on B(8)/B(9) was 1:8 and determined by GC-MS. ^{*e*} The ratio of arylation on B(8)/B(9) was 1:1.6.

was afforded in 12% and 24% yields, respectively (entries 6-7). The palladium source was also examined, the catalytic efficiency of

 $Pd(PPh_3)_2Cl_2$ and $Pd(dppf)_2Cl_2$ behaved lower activity than that of $Pd(OAc)_2$ (entries 8-9). When 1, 2-dimethyl-o-carborane (1b) was employed, the coupling product **2b** was obtained with 82% yield (entry 10), and the structure of B(9)-Ph-1,2-dimethyl-o-carborane was confirmed by X-ray crystallographic analysis (Figure S1, ESI).¹⁵ The similar phenomenon of prominent yield enhancement has also been found in fluorination of *o*-carboranes.^{8b,16} It is worth noting that we have not detected poly-arylated *o*-carboranes.

Table 2. Palladium catalyzed selective mono-arylation of o-carboranes with iodobenzene. ^{*a,b*}





Based on the optimized conditions, the scope of *o*-carboranes was then examined and the results were summarized in Table 2. As we can see, except *o*-carborane **1a**, C_{cage} -substituted *o*-carboranes were all compatible with this transformation, and gave the corresponding

coupling products with moderate to good yields (**2b-2e**). However, **1f** was very sluggish for this coupling and only generated trace amount of the expected product (**2f**). These results indicate the substituent groups on C_{cage} play an important role in the reaction as well as selectivity.

Table 3. Palladium catalyzed selective mono-arylation of 1, 2-Me₂-o-carborane with various aryl iodides. ^{*a,b*}



^{*a*} All reactions were carried on 0.25 mmol scale in 1 mL DCE for 48h at 60° C under argon atmosphere. ^{*b*} Isolated yields, the ratio of B(8) and B(9) isomers was determined by GC-MS is given in parentheses.



Figure 1. Crystal structure of 2q-B(9) (up) and 2q-B(8) (down)

From the aspect of aryl iodides, further investigations demonstrated this transformation has a broad substrate scope. Various substituent groups were compatible with this reaction with moderate to good yields (Table 3). Aryl iodides substituted with electron donating **JOMM ACCEDTEC**

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groups such as methoxyl, ethyoxyl and tert-butyl favored the transformation, and the expected products were isolated in good yields (2g, 2h, 2j, 2k). Halogenated iodobenzenes showed slightly lower reactivity and gave the desired products with moderated yields (21, 2n-2p). Importantly, bromide, chloride and fluoride substituents were all untouched, which offered an opportunity to further derivatization the products through transition metal catalyzed crosscouplings. Furthermore, aryl iodides decorated with electron withdrawing groups such as ethyl 4-iodobenzoate and 4iodoacetophenone were also tested, and the corresponding products were obtained with 51% and 43% yields, respectively (2q, 2r). Meanwhile, both isomers of 2q could be separated by column chromatography, and the structures were confirmed by X-ray crystallographic analysis.¹⁵ (Figure 1) Additionally, the steric hindrance of aryl iodides also has a large influence on the coupling. When 2-Iodoanisole and 1-Bromo-2-iodobenzene were subjected to the conditions, the coupling could not proceed at all (2i, 2m).

Comparing to the documented method, in which, large excess of Grignard reagents are required and has poor group tolerance, for synthesis of boron arylated carboranes by palladium catalyzed cross coupling of Grignard regents with iodocarboranes,^{100, 17-18} we can see this method offers an efficient and economical way for synthesis of 8(9)-aryl-o-carboranes with active groups.

Although the exact mechanism is not clear, based on the experiment results, a plausible mechanism was proposed as shown in Scheme 1. An electrophilic substitution of more nucleophilic B(g,12) and B(8,10)to Pd(OAc)₂ takes place first leading to intermediate I. Then, forming Pd^{IV} intermediate II by oxidation addition of iodobenzenes to I, after reductive elimination give rise to product and release III. Finally, regenerating the active Pd(OAc)₂ by cleavage of Pd-I bond by Ag₂CO₃. ^{8b, 19} We consider the ratio of regioisomers is reasonable in view of the preference of electrophilic reaction for B(9,12) over B(8,10), and the mono-arylation might ascribed to the steric hindrance of the aryl anchored on boron atom, the congested environment would hinder secondary arylation by forming transition state II.¹⁷



Scheme 1. Plausible mechanism for the Pd-catalyzed arylation of *o*-carboranes with aryl iodides.

Conclusions

In summary, we have developed a palladium catalyzed monoarylation of *o*-carboranes selectively at B(8) and B(9) under mild conditions, and a Pd(II) catalyzed electrophilic B-H activation was also proposed. A series of 8(9)-aryl-*o*-carboranes anchored with active groups have been synthesized with moderate to good yields. It offers an opportunity for further chemical transformation and diverse applications of B-substituted-*o*-carboranes in related fields. This work represents the first example in cross-coupling of boron hydride cluster with organic partner by direct B-H functionalization, which would be useful in the design of other coupling reactions of *o*-carboranes.

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Notes and references

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