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Palladium-Catalyzed Regioselective Intramolecular Coupling of *o*-Carborane with Aromatics via Direct Cage B−H Activation

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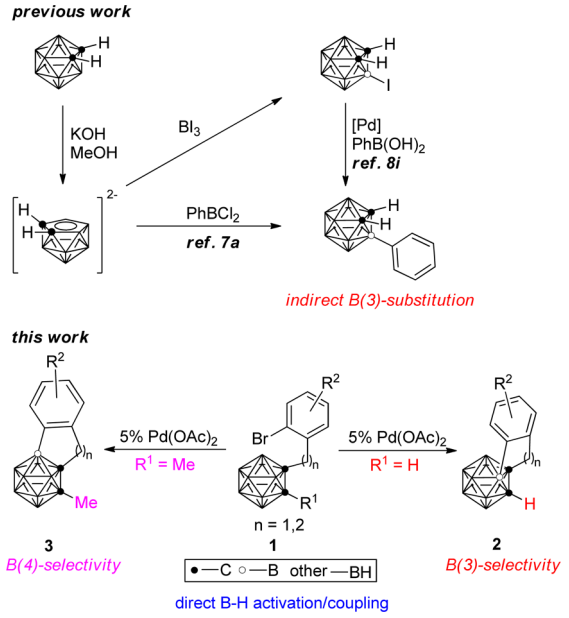
Supporting Information

ABSTRACT: Palladium-catalyzed intramolecular coupling of *o*-carborane with aromatics via direct cage B−H bond activation has been achieved, leading to the synthesis of a series of *o*-carborane-functionalized aromatics in high yields with excellent regioselectivity. In addition, the site selectivity can also be tuned by the substituents on cage carbon atom.

Carboranes, a class of three-dimensional relatives of benzene, are finding many applications in medicine as boron neutron capture therapy agents,[1] in supramolecular design/materials as building blocks,[2] and in coordination/organometallic chemistry as unique ligands,[3] which has received growing interest.[4] However, their unique structures make derivatization difficult, which results in a limited application scope. Thus, it is important and necessary to develop new methodologies for the functionalization of carboranes. Compared with cage carbon functionalization,[5] cage boron functionalization is very challenging due to much less reactive cage B−H over cage C−H bond and site-selectivity among ten cage B−H bonds.[6] The selective cage B−H activation is also more challenging than benzene C−H activation as the latter has only three reactive sites. It has been documented that the cage B(3,6) substitution can be achieved via capitation reaction of *nido*-$C_2B_9H_{11}^{2-}$ with RBX_2 (X = halides) (Scheme 1)[7] or transition metal-mediated cage B functionalization in a stoichiometric manner.[8] Selective electrophilic substitution at cage-(8,9,10,12) boron is also reported for some compounds.[9] Very recently, Ir-catalyzed selective cage-(4,7) boron alkenylation has been realized with the help of a directing group −COOH in our laboratory.[10]

On the other hand, the construction of π-conjugated systems including the *o*-carborane moiety for applications as light-emitting materials has recently received significant attention,[2d−h,11] in which carborane plays a crucial role. These molecules are often prepared using indirect methods (Scheme 1). It is obvious that a cross-coupling reaction of *o*-carborane with aromatics via direct cage B−H activation would be an ideal methodology for the synthesis of cage B-substituted aryl-*o*-carboranes. Inspired by transition metal catalyzed cross-coupling reaction of aryls via benzene C−H activation[12] and our earlier work on Zr/Ni comediated [2+2+1] cross-cyclotrimerization of carboryne, alkene, and 2-bromophenyltrimethylsilylacetylene for the preparation of C,C,B-substituted carborane-fused tricyclics,[13] we have developed the first Pd-catalyzed regioselective intramolecular coupling of *o*-carborane with phenyls via direct cage B−H activation. These new findings are reported in this Communication (Scheme 1).

Scheme 1. Synthesis of Phenyl-Substituted *o*-Carboranes



Compound 1-($CH_2C_6H_4$-*o*-Br)-*o*-$C_2B_{10}H_{11}$ (**1a**)[14] was chosen as the model substrate for initial screening. In the presence of 10 mol % of $Pd(OAc)_2$, 20 mol % of PPh_3, and 2 equiv of Cs_2CO_3 in THF at 60 °C, the corresponding coupling products 1,3-$CH_2C_6H_4$-*o*-$C_2B_{10}H_{10}$ (**2a**) and 1,4-$CH_2C_6H_4$-*o*-$C_2B_{10}H_{10}$ (**3a**) were obtained in 67% and 10% GC yields, respectively (entry 1, Table 1). We then screened various conditions, and the results are summarized in Table 1. Polar solvent CH_3CN gave the best result (entries 1−4, Table 1). On the other hand, though both monophosphines and bisphosphines could promote the catalytic reactions, tri(*o*-anisyl)phosphine offered the best yield of **2a** (entry 6, Table 1). Lower catalyst loading (5 mol %) resulted in a slightly decreased yield of **2a** (entry 12, Table 1). Screening of bases, temperatures, and palladium sources led to the optimal reaction conditions as shown in entry 12 of Table 1 (see Table S1 in the Supporting Information for details).

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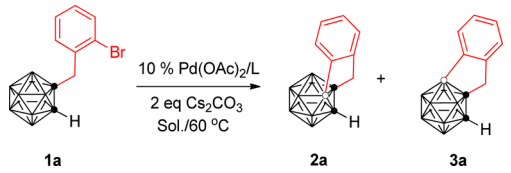
Table 1. Optimization of Reaction Conditions[a]



1a 2a 3a

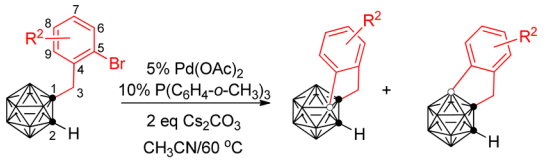
entry	ligand L	solvent	2a/3a (%)[b]
1	20 mol % PPh_3	THF	67/10
2	20 mol % PPh_3	toluene	49/13
3	20 mol % PPh_3	DME	68/10
4	20 mol % PPh_3	CH_3CN	78/13
5	20 mol % PCy_3	CH_3CN	74/10
6	20 mol % $P(C_6H_4$-*o*-$OMe)_3$	CH_3CN	85/12
7	10 mol % dppe	CH_3CN	72/6
8	10 mol % dppp	CH_3CN	68/6
9	10 mol % dppb	CH_3CN	70/8
10	10 mol % dppf	CH_3CN	73/9
11	10 mol % Xantphos	CH_3CN	75/7
12[c]	10 mol % $P(C_6H_4$-*o*-$OMe)_3$	CH_3CN	81/13

[a]Reactions were conducted at 0.05 mmol scale in 0.5 mL of solvent in a sealed flask; dppe = 1,2-bis(diphenylphosphino)ethane; dppp = 1,3-bis(diphenylphosphino)propane; dppb = 1,4-bis(diphenylphosphino)-butane; dppf = 1,1′-bis(diphenylphosphino)ferrocene; Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene. [b]GC yields. [c]5 mol % $Pd(OAc)_2$ was used.

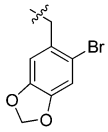
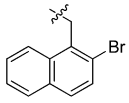
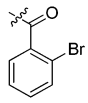
Under such optimized reaction conditions, the substrate scope was then examined, and the results were compiled in Table 2. The coupling efficiency was very high regardless of substituents on the phenyl ring. In general, electron-donating groups gave a relatively higher molar ratio of **2**/**3** than that of electron-withdrawing groups (entries 2−5 vs 6−7, Table 2). Such coupling reaction was tolerant of various functional groups and compatible with other aromatic moieties. Substrate **1i** with a naphthyl substituent proceeded smoothly to afford the desired product **2i** and **3i** in 71% and 14% isolated yields (entry 9, Table 2). Heteroaromatic thiophene compound **1j** afforded the coupling species **2j** and **3j** in relatively low yields (entry 10, Table 2). When *o*-bromobenzoylcarborane **1k** was used as the substrate, the target products **2k** and **3k** were isolated in 49% and 12% yields (entry 11, Table 2).

The previous results showed that both cage B(3)/B(4)-substituted products were generated during the coupling reaction with cage B(3) species being the major one. Since B(3) is bonded to both cage carbon atoms, the introduction of a substituent onto another cage carbon may block the activation of cage B(3)-H, thus increasing the site selectivity. With this in mind, a methyl group was introduced to the cage C(2). Under the optimal reaction condition (entry 12, Table 1), the resultant compound **1l** gave the corresponding coupling product **3l** with cage B(4) selectivity as a sole species in 81% isolated yield (entry 1, Table 3). A variety of substituted aromatics including thiophene were examined, affording the desired products in >72% isolated yields with excellent cage-(4) boron selectivity (entries 2−7, Table 3). Other cage C(2) protected substrates **1s** and **1t** generated the coupling products **3s** and **3t** in 78% and 83% isolated yields (entries 8 and 9, Table 3). If the linkage between the cage and phenyl was changed from $-CH_2$ to *cis*-CH=CH, the resultant 1-(*cis*-CH=CH-C_6H_4-*o*-Br)-1,2-$C_2B_{10}H_{11}$ (**1u**) and 1-(*cis*-CH=CH-C_6H_4-*o*-Br)-2-CH_3-1,2-$C_2B_{10}H_{10}$ (**1v**) underwent a similar

Table 2. Synthesis of B(3)/B(4)-Substituted Carboranes[a]

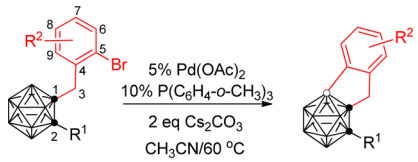


1 2 3

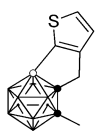
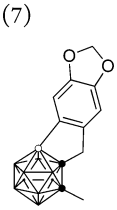
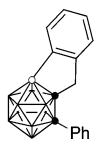
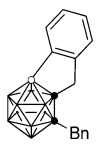
entry	R^2 (**1**)	isolated yield (%) **2**	**3**
1	H (**1a**)	69 (**2a**)	17 (**3a**)
2	8-F (**1b**)	64 (**2b**)	23 (**3b**)
3	7-F (**1c**)	66 (**2c**)	16 (**3c**)
4	6-F (**1d**)	64 (**2d**)	22 (**3d**)
5	8-CF_3 (**1e**)	56 (**2e**)	24 (**3e**)
6	8-OMe (**1f**)	64 (**2f**)	16 (**3f**)
7	7-Me (**1g**)	76 (**2g**)	18 (**3g**)
(8)	(9)	(10)	(11)
			
(**1h**)	(**1i**)	(**1j**)	(**1k**)
60% (**2h**) 14% (**3h**)	71% (**2i**) 14% (**3i**)	37% (**2j**) 29% (**3j**)	49% (**2k**) 12% (**3k**)

[a]Reactions were conducted at 0.5 mmol scale in a sealed flask.

Table 3. Synthesis of B(4)-Substituted Carboranes[a]



1 3

entry	R^1, R^2 (**1**)	isolated yield (%)
1	Me, H (**1l**)	81 (**3l**)
2	Me, 8-F (**1m**)	77 (**3m**)
3	Me, 6-F (**1n**)	88 (**3n**)
4	Me, 7-Me (**1o**)	72 (**3o**)
5	Me, 8-OMe (**1p**)	76 (**3p**)
(6)	(7) (8)	(9)
		 
73% (**3q**)	75% (**3r**)	78% (**3s**) 83% (**3t**)

[a]Reactions were conducted at 0.5 mmol scale in a sealed flask.

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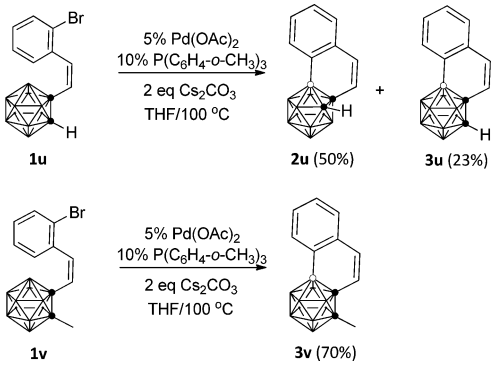
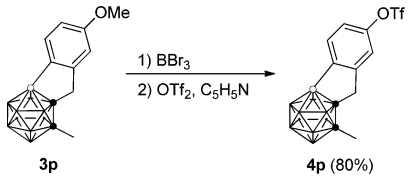
coupling reaction to give carborane-fused napthalene **2u**/**3u** and **3v** in 50%/23% and 70% isolated yields, respectively (Scheme 2). On the other hand, the -OMe group in **3p** was able to be conveniently converted to -OTf, which could be utilized for further synthetic elaborations (Scheme 3).

Scheme 2. Synthesis of Carborane-Fused Naphthalene



Scheme 3. Functional Group Transformation



Compounds **2** and **3** were fully characterized by ^{1}H, ^{13}C, and ^{11}B NMR spectroscopy as well as high-resolution mass spectrometry.[14] The molecular structures of **2a**, **3a**, and **3l** were further confirmed by single-crystal X-ray analyses. Figure 1 shows the representative structures of **2a** and **3l**.

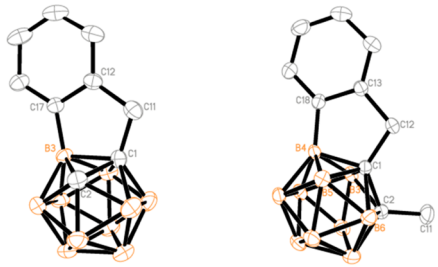


Figure 1. Molecular structures of **2a** (left) and **3l** (right).

A Pd(0)/Pd(II) catalytic process is proposed as the plausible mechanism. Oxidative addition of C(sp^2)-Br bond on Pd(0), followed by intramolecular electrophilic substitution on the cage-(3) or cage-(4) B−H gives a palladacycle[15] that undergoes reductive elimination to afford the final product and regenerate Pd(0).[13] Notably, cage C(2)-substituents can efficiently block the cage B(3)-H activation due to steric reasons, leading to the formation of cage-(4) boron substituted carboranes as the only products.

In summary, a regioselective and highly efficient Pd-catalyzed intramolecular cage-(3) or cage-(4) B−C(sp^2) coupling of carborane with aromatics has been achieved, leading to the synthesis of a series of cage B-aryl-*o*-carborane derivatives. This represents a new methodology for transition metal catalyzed coupling of carborane with aromatics via direct cage B−H activation, which can be used for the preparation of carborane-fused polycyclic aromatics for material application.[2,11] This work not only sheds some light on how to control selective cage B−H activation on different B−H vertices of carborane cage, but also offers useful references for selective aromatic C−H activation/functionalization in organic synthesis.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, complete characterization data, and X-ray data in CIF format for **2a**, **3a**, and **3l**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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