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Catalytic regioselective 3,4-difunctionalization of 3-iodo-*o*-carborane *via* Pd migration†

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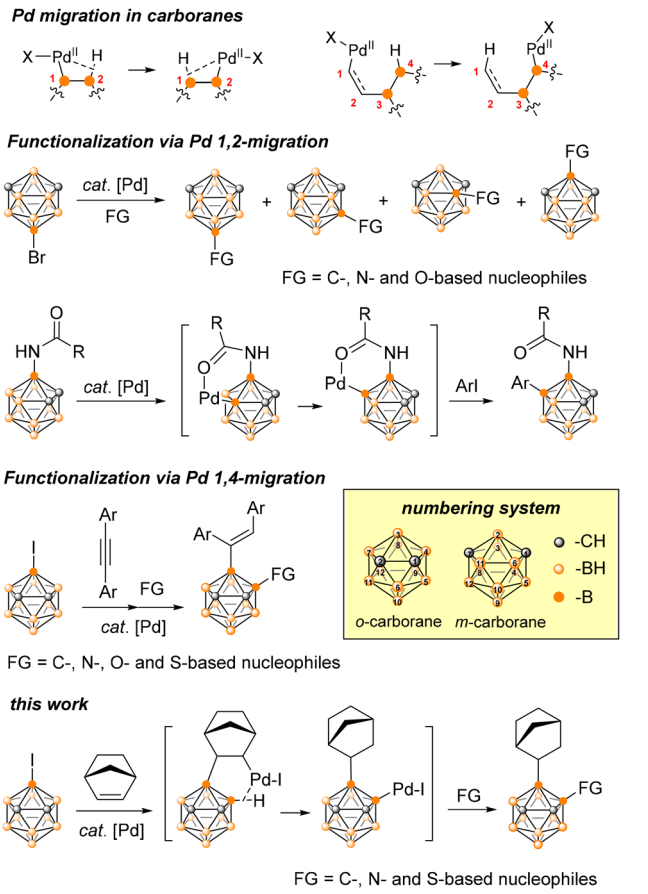
A Pd-catalyzed one-pot regioselective difunctionalization of 3-iodo-*o*-carborane has been achieved for the synthesis of a wide variety of 3-alkyl-4-Nu-*o*-carboranes (Nu = aryl, alkyl, amino, or thio groups) in moderate to excellent yields. This protocol combines the sequential activation of cage B(3)–I and B(4)–H bonds *via* Pd 1,4-migration.

Carboranes represent a unique class of polyhedral boron hydrides in which one or more BH vertices are replaced by CH units.[1] These molecules exhibit distinctive structural characteristics, including nearly spherical geometry and extensive three-dimensional electron delocalization, rendering them valuable building blocks for applications ranging from advanced materials to pharmaceuticals.[2,3] Although transition metal-catalyzed regioselective B–H functionalization of carboranes has witnessed remarkable progress, enabling access to structurally diverse derivatives that cannot be generated by other conventional methods,[4] there remains significant interest in developing efficient, versatile methodologies for the synthesis of difunctionalized carboranes bearing different substituents.[5] The metal migration strategy is a promising approach, which enables B–H functionalization at cage positions distinct from the initial site of bond activation.[6,7] In this context, the 1,2-metal migration strategy was first used in 2017 by the Spokoyny group, who reported sequential cage-walking during Pd-catalyzed B–Br/B–H activation of 9-Br-*m*-carborane, affording functionalization at B(2), B(4), B(5), and B(9) positions.[8] Our group subsequently disclosed an acylamino-directed Pd cage-walking process from B(4) to B(8) in *o*-carboranes, enabling selective B(8)-arylation.[9] On the other hand, B–I functionalization followed by 1,4-Pd migration can offer difunctionalized *o*-carborane in a one-pot reaction. We reported a Pd-catalyzed alkenylation-iodine migration cascade reaction of 3-iodo-*o*-carboranes with alkynes, which combines



Scheme 1 Carborane functionalization *via* Pd migration.

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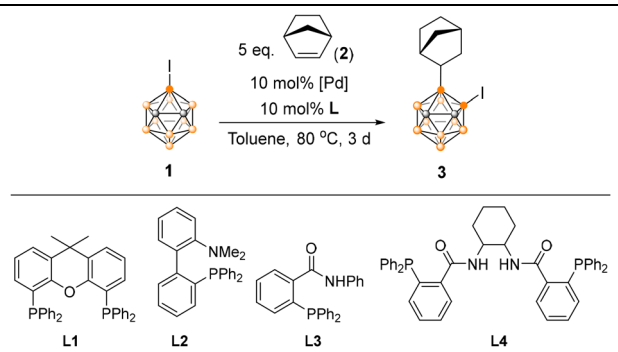
the sequential activation of cage B–I and B–H bonds *via* Pd 1,4-migration with excellent regioselectivity (Scheme 1).[10] This prompted us to investigate whether alkenes could be employed to achieve regioselective B(3)-alkylation and B(4)-functionalization *via* a similar Pd 1,4-migration pathway (Scheme 1).[11] The results of our investigation are presented in this Communication.

We first evaluated the feasibility of B(3)-alkylation and iodine migration in the reaction of 3-iodo-*o*-carborane (**1**) with alkenes. Norbornene (**2**) was selected as the model substrate to suppress β-hydride elimination during the alkylation process. In the presence of 10 mol% $Pd(dba)_2$ and 10 mol% PPh_3, treatment of **1** with 5.0 equivalents of **2** in toluene at 80 °C for 3 days afforded 3-(2-norbornyl)-4-iodo-*o*-carborane (**3**) in 46% yield (Table 1, entry 1). Other monodentate phosphine ligands such as PCy_3 and PPh_2Cy failed to produce **3** (Table 1, entries 2 and 3), while PPh_2Py led to a slightly improved yield of 53% (Table 1, entry 4). Bidentate ligands DPPB and DPPF afforded low yields (Table 1, entries 5 and 6), and bisphosphine **L1** deactivated the catalyst entirely (Table 1, entry 7). The use of PhDavePhos (**L2**) gave a 16% yield (Table 1, entry 8), whereas the phosphine-amide ligand **L3** significantly enhanced reaction efficiency (Table 1, entry 9). In addition, bisphosphine-amide ligand **L4** enabled the formation of **3** in 92% yield with excellent regioselectivity (Table 1, entry 10). Screening of other Pd(0) catalysts did not yield better results, while Pd(II) was not suitable for this reaction (Table 1, entries 11, 12, 14 and 15). In the case of $Pd(OAc)_2$, the reaction can be initiated by reactive Pd(0) species generated *in situ* through reduction of Pd(II) by the phosphine ligand (Table 1, entry 13).[12] Reducing the catalyst or ligand loading or decreasing the amount of **2** led to diminished yields (Table 1, entries 16–18). Notably, no reactivity was observed with other alkenes, such as cyclohexene, 1-hexene, styrene, methyl acrylate, or 2-vinylpyridine, likely due to the unique ring strain and high reactivity of norbornene.

Table 1 Optimization of reaction conditions for Pd-catalyzed alkylation with iodine migration[a]



Entry	L	[Pd]	Yield[b] (%)
1	PPh_3	$Pd(dba)_2$	46
2	PCy_3	$Pd(dba)_2$	Messy
3	PPh_2Cy	$Pd(dba)_2$	Messy
4	PPh_2Py	$Pd(dba)_2$	53
5	DPPB	$Pd(dba)_2$	27
6	DPPF	$Pd(dba)_2$	13
7	**L1**	$Pd(dba)_2$	N.R.
8	**L2**	$Pd(dba)_2$	16
9	**L3**	$Pd(dba)_2$	72
10	**L4**	$Pd(dba)_2$	92
11	**L4**	$Pd_2(dba)_3$[c]	69
12	**L4**	$Pd(PPh_3)_4$	53
13	**L4**	$Pd(OAc)_2$	56
14	**L4**	$PdCl_2(PPh_3)_2$	N.R.
15	**L4**	$[Pd(Allyl)_2Cl]_2$	N.R.
16[d]	**L4**	$Pd(dba)_2$	80
17[e]	**L4**	$Pd(dba)_2$	42
18[f]	**L4**	$Pd(dba)_2$	72

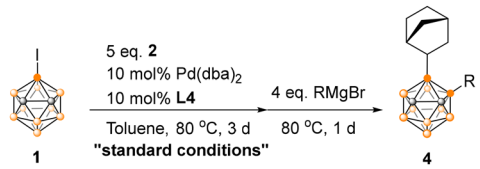
[a] Reactions were conducted on a 0.2 mmol scale of **1** in 2.0 mL of toluene; DPPB = 1,4-bis(diphenylphosphino)butane; DPPF = 1,1′-bis (diphenylphosphino)ferrocene. [b] Yield determined by ^1H NMR using 1,1,2,2-tetrachloroethane as the internal standard. [c] 5 mol% $Pd_2(dba)_3$. [d] 5 mol% $Pd(dba)_2$. [e] 5 mol% **L4**. [f] 4 equiv. of **2**.

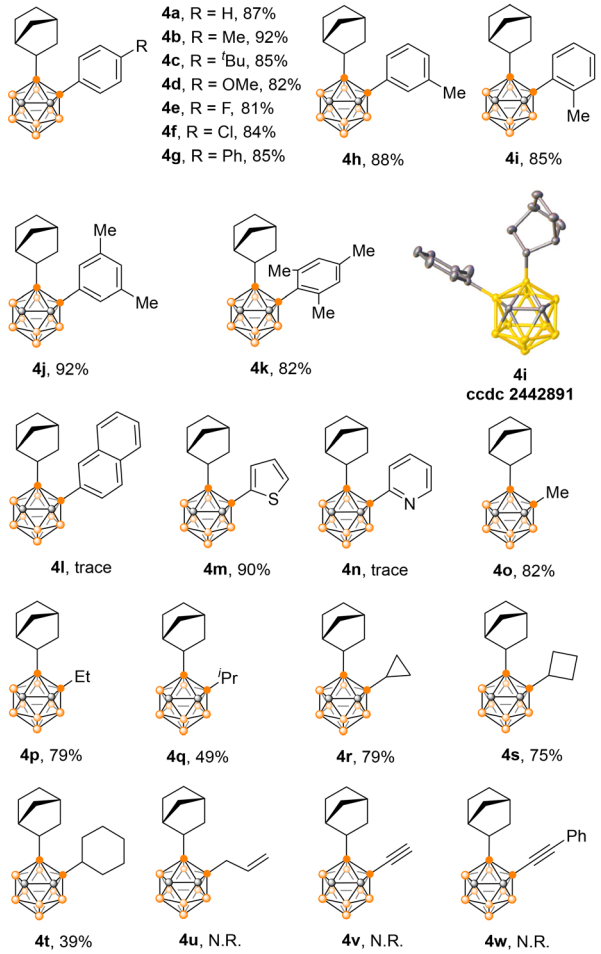
Subsequently, the scope of the one-pot difunctionalization process was explored under the optimized conditions through Pd-catalyzed cage B–C coupling reactions of 3-iodo-*o*-carborane with Grignard reagents (Table 2).[13] It was found that this method was quite general and a range of aryl Grignard reagents delivered the desired products **4a–4k** in 81–92% yields, regardless of their electronic nature. The sterically demanding 2,6-dimethylphenyl Grignard reagent furnished the corresponding **4k** in 82% yield, though 2-naphthyl Grignard reagents were incompatible. For substrates bearing heteroaryls, 2-thienyl successfully afforded **4m** in 90% yield, while no coupling reaction occurred with 2-pyridyl substrates, likely due to nitrogen coordination inhibiting Pd catalysis. A variety of alkyl Grignard reagents also reacted to afford **4o–4t** in 39–82% yields. Lower yields for **4q** and **4t** were attributed to β-H elimination, generating 3-(2-norbornyl)-*o*-carborane as a byproduct. Allyl and alkynyl Grignard reagents failed to react under the optimized conditions due to lower nucleophilicity.

Given the utility of iodinated carboranes as key intermediates for boron vertex derivatization with the efficient construction of B–heteroatom bonds,[14] we next examined the use of arylamino Grignard reagents for constructing B–N bonds (Scheme 2). One-pot reactions with phenylamino Grignard reagents afforded the difunctionalized product **5a** in 64% yield. A series of substituted arylamino magnesium bromides bearing either electron-donating or -withdrawing groups were well tolerated, affording the corresponding **5b–g** in 55%–68% isolated yields. Increasing steric hindrance on the aryl ring led to a reduced yield of **5h**. Attempts to use alkylamino Grignard reagents resulted in complex mixtures.

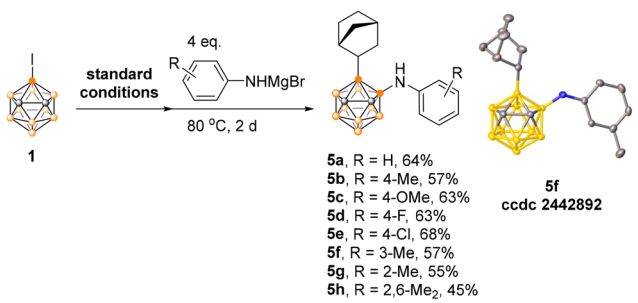
After examining the one-pot B(3)-alkylation and B(4) cross-coupling reaction of 3-iodo-*o*-carborane and norbornene with Grignard reagents, we then evaluated the reactivity of sodium mercaptides as nucleophiles (Scheme 3). Reactions with these sulfur-based nucleophiles yielded B(4)-alkylthio derivatives **6a–6c** in moderate to good yields. Sodium thiophenolate afforded **6d** in 74% yield, while substrates bearing electron-donating (–OMe) or electron-withdrawing (–F) groups on the aryl ring

Table 2 Substrate scope[a,b]

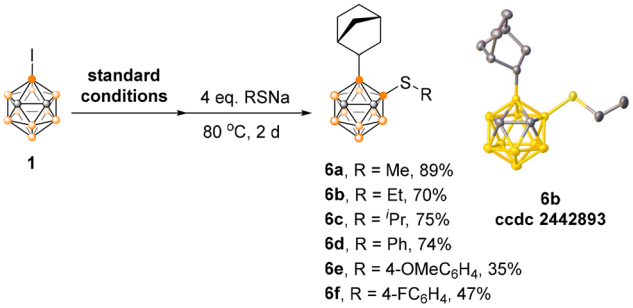




[a] Reactions were conducted on a 0.2 mmol scale in 2 mL of toluene. [b] Yield of the isolated product.



Scheme 2 One-pot construction of B(3)–C and B(4)–N bonds.

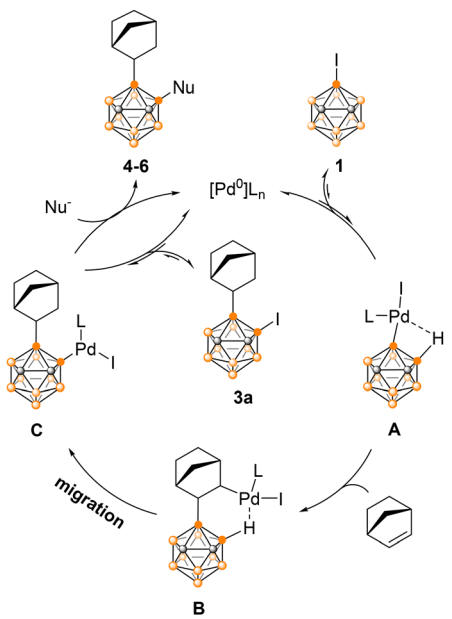


Scheme 3 One-pot construction of B(3)–C and B(4)–S bonds.

also proved compatible, affording **6e** and **6f** in 35% and 47% yields, respectively.

All products **3**, **4**, **5** and **6** were fully characterized by ^{1}H, ^{13}C, and ^{11}B NMR spectroscopy as well as high-resolution mass spectrometry. The molecular structures of **4i**, **5f** and **6b** were further confirmed by single-crystal X-ray analyses.

Based on our previous studies[10] and current observations, a plausible reaction mechanism is proposed in Scheme 4. The catalysis begins with oxidative addition of the B(3)–I bond in 3-iodo-*o*-carborane onto Pd(0), followed by norbornene insertion into the Pd–B bond to form a Pd(II) intermediate **B**. The subsequent 1,4-Pd migration from the alkyl carbon to the B(4) vertex furnishes intermediate **C**, which undergoes reductive elimination to deliver product **3** and regenerate Pd(0). Many attempts for the direct detection or characterization of the Pd–B intermediates failed.[15] In the presence of nucleophiles, transmetallation and a second reductive elimination afford the difunctionalized products **4**, **5**, or **6**, completing the catalytic cycle.



Scheme 4 Proposed reaction mechanism.

Conclusions

In summary, we have developed a Pd-catalyzed one-pot regioselective difunctionalization of 3-iodo-*o*-carborane *via* 1,4-Pd migration. This protocol enables the construction of a wide variety of 3-alkyl-4-Nu-*o*-carboranes (Nu = aryl, alkyl, amino, or thio groups) in moderate to excellent yields. The strategy integrates sequential B(3)–I and B(4)–H activation, followed by Pd-catalyzed B(4)–Nu bond formation, offering a powerful platform for diversifying *o*-carborane scaffolds.

Author contributions

Z. Q. and Z. X. directed and conceived this project. X. J. conducted the experiments. All authors discussed the results and wrote the manuscript.

Data availability

The data supporting this article have been included as part of the ESI.† Crystallographic data for **4i**, **5f** and **6b** have been deposited at the CCDC under deposition numbers 2442891 (**4i**), 2442892 (**5f**), and 2442893 (**6b**) and can be obtained from the CCDC *via* **https://www.ccdc.cam.ac.uk/structures/**.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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