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Transition Metal Catalyzed Direct Amination of Cage B(4)–H Bond in *o*-Carboranes: Synthesis of Tertiary, Secondary and Primary *o*-Carboranyl Amines

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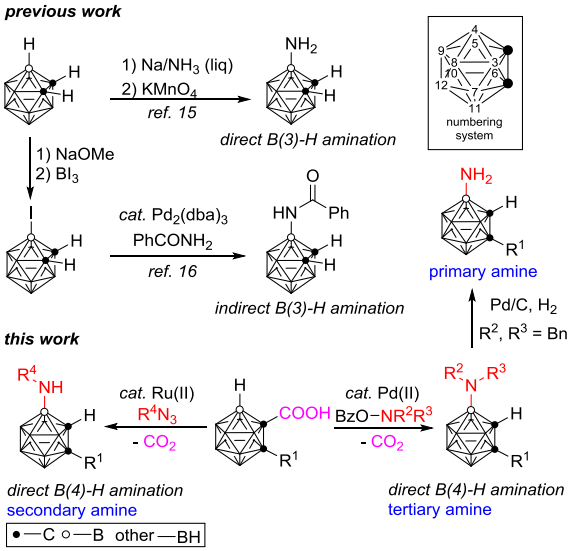
Supporting Information Placeholder

ABSTRACT: Transition metal catalyzed regioselective amination of cage B(4)-H bond in *o*-carboranes has been achieved for the first time using *O*-benzoyl hydroxylamines or organic azides as the amination reagents, leading to the preparation of a series of tertiary and secondary carboranyl amines. Both amination reactions proceeded under mild conditions without the addition of any external oxidants. Hydrogenolysis of the resultant product 4-N(CH_2Ph)$_2$-*o*-carborane afforded primary carboranyl amine, 4-amino-*o*-carborane, in quantitative yield.

Carboranes, a class of three-dimensional relatives of benzene, have proved as useful basic units in boron neutron capture therapy agents,[1] in supramolecular design/materials,[2] and in coordination/organometallic chemistry.[3] Thus, functionalization of carboranes has received a growing interest. A number of methods have been developed for the functionalization of cage CH and BH vertices.[4] In general, cage C–H activation/functionalization is relatively easier to be achieved than that of B–H ones as the cage CH proton is acidic (pK_a ~ 23).[5] We and other groups have taken up the challenge to develop transition metal catalyzed direct cage B–H functionalization.[6-8] With the help of a carboxylic acid directing group, catalytic cage B(4)-alkenylation,[6c] B(4,5)-dialkenylation,[6e] B(4,5)-diarylation,[6f] B(4)-alkynylation,[6g] and B(4)-hydroxylation[6i] have been achieved. These results indicate that the weakly coordinating directing group –COOH not only plays a key role in regioselectivity and mono-/di-selectivity of the reactions, but also is removable after the reaction. We also note that a key intermediate bearing five-membered metallacycle MBCCO is involved in the aforementioned catalytic cycles. Such intermediate may react with amination reagents to realize the direct amination of cage B–H bond.

Carborane derivatives containing organic nitrogen groups have received much attention due to their potential applications in medicinal chemistry[9] and catalysis.[10] For example, carborane-amino acid or -nucleoside combinations serve as excellent candidates for cancer treatment in boron neutron capture therapy (BNCT).[9,11] Moreover, aminoalkyl-*o*-carboranes have been extensively employed as ligands for transition metal complexes.[12] Despite the recent advances in carborane chemistry, straightforward and general synthesis of cage B-aminated-*o*-carboranes is rather limited.[3b,4,13,14] For instance, 3-NH_2-*o*-$C_2B_{10}H_{11}$ is prepared by the reduction of *o*-carborane with Na in liquid NH_3, followed by oxidation with $KMnO_4$. Such reaction has the risk of fire and explosion.[15] Recently, the synthesis of B(3)/B(9)-aminated-*o*-carboranes has been reported through a Pd-catalyzed Buchwald-Hartwig amination of B(3)/B(9)-iodo-*o*-carboranes (Scheme 1) or B(3)-bromo-*o*-carborane.[16] However, transition metal catalyzed direct cage B–H amination remains elusive.[4,13]

Scheme 1. Synthetic Routes to Cage B-Aminated-*o*-Carboranes

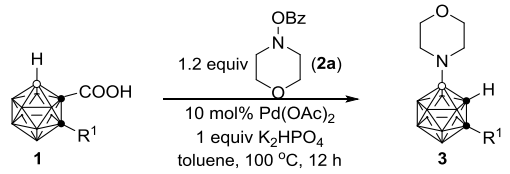


Inspired by the recent achievements in catalytic C-H amination[17] and the unique role of weakly coordinating carboxylic ligand in regioselective activation of cage B-H bond,[6c,e,f,g,i] we have developed two efficient methods for direct and regioselective amination of *o*-carboranes using *O*-benzoyl hydroxylamines and organic azides as the amino

sources, respectively. These new findings are reported in this communication (Scheme 1).

The optimization of reaction conditions was summarized in Table S1 of the Supporting Information. Our initial reaction of 1-COOH-2-CH_3-$C_2B_{10}H_{10}$ (**1a**) with *O*-benzoyl hydroxylmorpholine (**2a**) in the presence of 10 mol % $Pd(OAc)_2$ and 2 equiv of AgOAc in toluene at 110 °C for 12 h gave no desired amination product (entry 1, Table S1). The addition of 2 equiv of K_2HPO_4 offered the B(4)-aminated-*o*-carborane **3a** in 49% GC yield, whereas 2 equiv of KOAc only led to a trace amount of **3a** (entries 2-3, Table S1). Lowering the loading of K_2HPO_4 to 1 equiv and the reaction temperature to 100 °C afforded higher yields of **3a** (entries 4-5, Table S1). It was later found that the amination reaction proceeded well in the absence of AgOAc, giving **3a** in 93% GC yield (entries 6-7, Table S1). Lowering the catalyst loading to 5% led to a decreased yield of **3a** (entry 9, Table S1). In view of the yield of **3a**, entry 7 in Table S1 was chosen as the optimal reaction conditions.

Table 1. Synthesis of B(4)-Morpholinated-*o*-Carboranes[a]

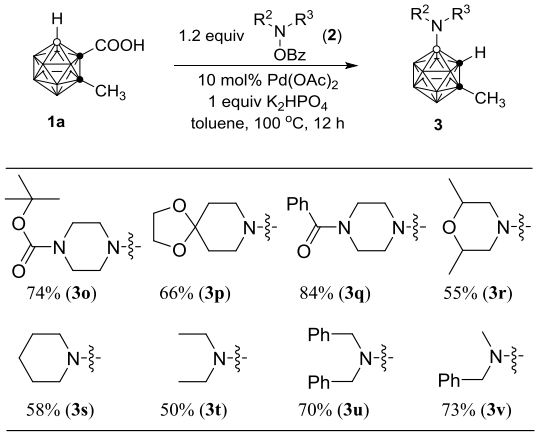


entry	R^1	yield (%)[b]
1	Me	79 (**3a**)
2	Et	72 (**3b**)
3	^{n}Bu	71 (**3c**)
4	^{i}Pr	52 (**3d**)
5	TMS	53 (**3e**)[c]
6	H	46 (**3e**)
7	benzyl	68 (**3g**)
8	4-CH_3-benzyl	74 (**3h**)
9	4-Cl-benzyl	73 (**3i**)
10	4-F-benzyl	71 (**3j**)
11	4-OMe-benzyl	78 (**3k**)
12	3-CH_3-benzyl	70 (**3l**)
13	styryl	48 (**3m**)
14	4-CH_3-styryl	58 (**3n**)

[a] Reactions were conducted on 0.2 mmol scale in 5 mL of toluene in a closed flask. [b] Yield of isolated products. [c] TMS was removed after work up.

Subsequently, a variety of B(4)-morpholinated-*o*-carborane derivatives were synthesized under the optimal reaction conditions. Effects of cage carbon substituents R^1 on the reaction results were examined. Both liner alkyl and benzyl substituents gave the B(4)-aminated products **3** in 68-79% isolated yields (entries 1-3 and 7-12, Table 1). No obvious electronic effects were observed (entries 7-12, Table 1). However, branch alkyl, TMS and styryl groups led to the decreased yields of **3** (entries 4-5 and 13-14, Table 1). If R^1 = H, the corresponding product **3e** was isolated in 46% yield (entry 6, Table 1). Substrate scope of other *O*-benzoyl hydroxylamines was also evaluated. To our delight, a variety of alkylamine moieties were readily introduced to the cage B(4) position by simply treatment of **1a** with various *O*-benzoyl hydroxylamines, giving **3o**-**3v** in moderate to high isolated yields (Table 2).

Table 2. Scope of *O*-Benzoyl Hydroxylamine Substrates[a,b]



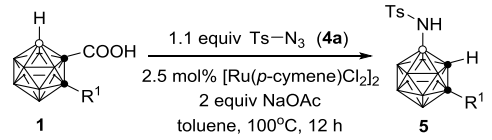
[a] Reactions were conducted on 0.2 mmol scale in 5 mL of toluene in a closed flask. [b] Yield of isolated products.

The aforementioned direct catalytic B-H amination gave tertiary carboranyl amines. We wondered if primary amido groups could be introduced to the cage B(4) position using organic azides as the amination reagents. The results showed that replacement of *O*-benzoyl hydroxylamine with tosyl azide in the aforementioned optimal reaction conditions did not give any target product (entry 1, Table S2 in the SI). Inspired by Rh- or Ru-promoted cage B-H activation[6h,6j,7c,7f] and Rh- or Ru-catalyzed C-N bond forming reactions using organic azides as reagents,[17b] we then screened these transition metals as the catalysts. $[Cp^*RhCl_2]_2$ only afforded the aminated product 4-TsNH-2-CH_3-$C_2B_{10}H_{10}$ (**5a**) in 12% yield (entry 2, Table S2). To our delight, in the presence of 2.5 mol % $[Ru(p\text{-cymene})Cl_2]_2$ and 2 equiv of NaOAc, reaction of **1a** with TsN_3 in toluene at 100 °C for 12 h gave the desired amination product **5a** in 95% GC yield (entry 10, Table S2). Further screening of bases and reaction temperatures did not offer better results. Thus, entry 10 in Table S2 was chosen as the optimal reaction conditions.

Under the above optimized reaction conditions, the scope of such amination was investigated. A variety of alkyl and benzyl substituents at the cage C(2) position gave the amination products **5** in very good to excellent isolated yields, and no obvious electronic effects were observed (entries 1-3 and 5-9, Table 3). Compound **1e** (R^1 = TMS) afforded the corresponding product **5d** in a good yield of 67% (entry 4, Table 3). In addition, the scope of sulfonyl azides was also examined (Table 4). Arylsulfonyl azides reacted smoothly regardless of the substituents on the phenyl ring, giving **5j**-**5o** in > 80% isolated yields. Benzylsulfonyl azide worked equally well, whereas butylsulfonyl azide resulted in relatively lower isolated yield of 72% (**5p** and **5q** in Table 4). These results show that Ru-catalyzed direct cage B-H amination is generally more efficient than Pd-catalyzed one

in view of the isolated yields of amination products **3** and **5** (Tables 1 and 2 vs Tables 3 and 4).

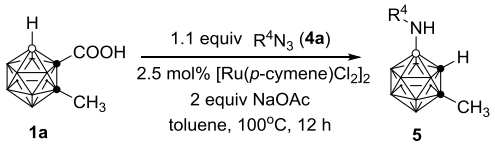
Table 3. Synthesis of B(4)-Aminated-*o*-Carboranes Using Tosyl Azide[a]

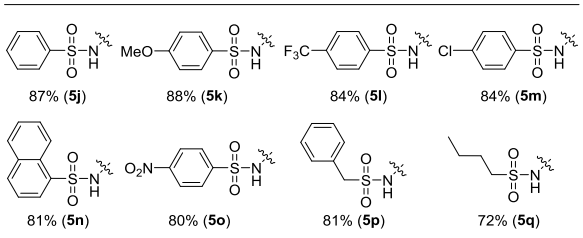


entry	R^1	yield (%)[b]
1	Me	90 (**5a**)
2	Et	88 (**5b**)
3	^{i}Pr	85 (**5c**)
4	TMS	67 (**5d**)[c]
5	benzyl	91 (**5e**)
6	4-CH_3-benzyl	84 (**5f**)
7	4-Cl-benzyl	94 (**5g**)
8	4-OMe-benzyl	93 (**5h**)
9		92 (**5i**)

[a] Reactions were conducted on 0.2 mmol scale in 5 mL of toluene in a closed flask. [b] Yield of isolated products. [c] TMS was removed after work up.

Table 4. Scope of Sulfonyl Azide Substrates[a,b]



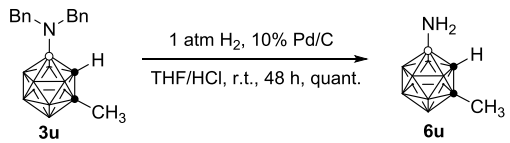


[a] Reactions were conducted on 0.2 mmol scale in 5 mL of toluene in a closed flask. [b] Yield of isolated products.

It was noteworthy that the benzyl groups in **3u** was easily removed through hydrogenolysis in the presence of 10 mol % Pd/C to afford quantitatively 4-amino-*o*-carborane **6u**, which may serve as a new precursor for cage B(4) functionalization of *o*-carboranes (Scheme 2).[18]

Compounds **3**, **5** and **6u** were fully characterized by ^{1}H, ^{13}C, and ^{11}B NMR spectroscopy as well as high-resolution mass spectrometry (see the SI for detail). The molecular structures of **3e**, **3o**, **3p**, **5a** and **5k** were further confirmed by single-crystal X-ray analyses (Figure S1-S5).

Scheme 2. Synthesis of 4-Amino-*o*-Carborane



To gain mechanistic insights into these B-H amination reactions, several control experiments were carried out. Under the optimal reaction conditions, **1a**, **4k** and norbornene were mixed in 1:1:1 molar ratio, giving an azacyclopropane **7** and **5k** in 43% and 51% yields, respectively (Scheme S1a in the SI), whereas only a trace amount of azacyclopropane **7** was detected by GC-MS in the absence of the Ru catalyst (Scheme S1b). These results suggest that a Ru-nitrene intermediate may be involved in the Ru-catalyzed amination.[17b] On the other hand, comparison of the reaction rates of **1a**-d_6 (1-COOH-2-Me-3,4,5,6,7,11-D_6-*o*-$C_2B_{10}H_4$) and **1a** under the optimal reaction conditions gave very small KIE values of k_H/k_D = 1.15 for Pd system and 0.96 for Ru one (Schemes S2 and 3), which indicates that the cyclometalation (B-H activation) step may not be involved in the rate-determining step. However, many attempts to isolate the five-membered cyclometalated intermediates failed. Based on the aforementioned experimental results and literature reports,[6,17] two plausible reaction mechanisms for Pd- and Ru-catalyzed direct cage B–H amination are proposed in Schemes S4 and 5, respectively (see the SI for detail).

In conclusion, we have developed two catalytic systems for regioselective and efficient direct amination of cage B(4)–H bond in *o*-carboranes, for the first time, using *O*-benzoyl hydroxylamines or organic azides as aminating agents, where –COOH acts as a traceless directing group. This work builds a toolbox for the preparation of previously inaccessible tertiary, secondary and primary *o*-carboranyl amines directly from *o*-carboranes, which might find applications in medicine, catalysis and materials.[1-3] These amination reactions have a broad substrate scope and are tolerant of functional groups, which offers useful references for selective C–H amination in organic compounds and B-H amination in other boron clusters.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, complete characterization data, NMR spectra, and X-ray data in CIF format for **3e, 3o, 3p, 5a** and **5k**. 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 interests.

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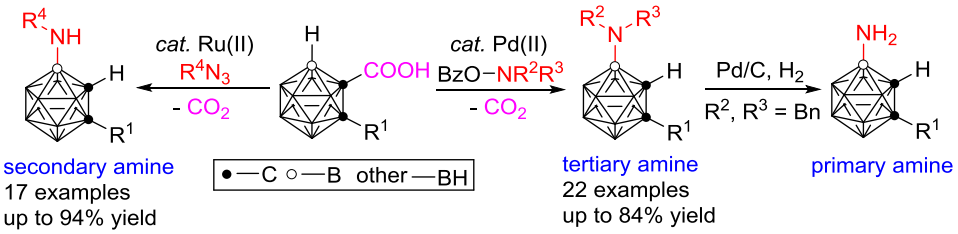
R4NH
H
R1
cat. Ru(II)
R4N3
- CO2
H
COOH
R1
cat. Pd(II)
BzO−NR2R3
- CO2
R2
N
R3
H
R1
Pd/C, H2
R2, R3 = Bn
NH2
H
R1
secondary amine
17 examples
up to 94% yield
●—C ○—B other—BH
tertiary amine
22 examples
up to 84% yield
primary amine