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Communication

Ir-Catalyzed Selective B(3)-H Amination of *o*-Carboranes with NH_3

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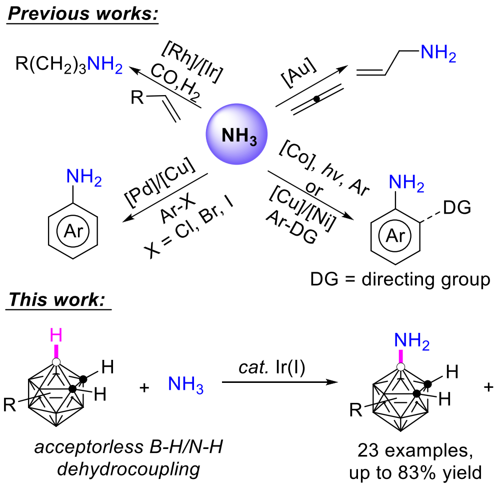
ABSTRACT: Ammonia gas, NH_3, is a cheap and widely used industrial feedstock, which has received tremendous research interests in its functionalization. This work reports a breakthrough in catalytic selective cage B(3)-H amination of *o*-carboranes with NH_3 via Ir-catalyzed B-H/N-H dehydrocoupling, offering convenient and efficient access to a series of 3-NH_2-*o*-carborane derivatives in moderate to high isolated yields with a broad substrate scope. The employment of readily available NH_3 gas as the aminating reagent with H_2 as the sole byproduct endows the protocol economy, practicability, and environmental friendliness. A plausible reaction mechanism is proposed on the basis of control experiments.

Ammonia gas, NH_3, is a cheap and widely used industrial feedstock, serving as the versatile building block in pharmaceutical and many other commercial products. Direct transformation of NH_3 gas to value-added organic molecules has been a persistent goal, though accompanied by considerable challenges such as the deactivation of the catalyst after forming stable Werner ammine complexes and high strength of the N−H bond (107 kcal/mol).[1] Despite these difficulties, several strategies for NH_3 functionalization have been developed including classic ammonia oxidation,[2] hydroaminomethylation,[3] reductive amination,[4] hydroamination,[5] and cross-coupling of aryl halides with ammonia.[6] Recently, straightforward C-H amination with NH_3[7] has also been realized via photoredox catalysis[7b] or directing-group-guided transition-metal catalysis.[7c,d] In spite of these achievements, acceptorless dehydrogenative NH_3 functionalization remains less investigated (Scheme 1).

As an ongoing project in our laboratory,[8a] we are very interested in developing a strategy for direct functionalization of NH_3 with *o*-carboranes. The extraordinary properties of carboranes[9] including icosahedral geometry, three-dimensional aromaticity, and inherent robustness endow them a wide range of applications,[10] yet make their functionalization quite challenging. In view of the considerable progress recently made in transition-metal-catalyzed vertex-specific functionalization of carboranes,[8,11,12] we hypothesized that acceptorless dehydrogenative cross-coupling between NH_3 and carborane would provide facile access to the desired aminocarborane derivatives. These compounds can only be synthesized through a reduction-nucleophilic amination−oxidation process with the risk of explosion or a tandem route including transition-metal-catalyzed B-H amination and subsequent deprotection.[11d,13] In sharp contrast to the strong coordination of NH_3 to BH_3 in amine-borane adducts,[14] no significant interactions between NH_3 and carborane exist, increasing the difficulty of the proposed dehydrogenative cross-coupling. After many attempts, a breakthrough of regioselective and straightforward cage B-H amination of *o*-carborane with NH_3 has been attained by means of Ir-catalyzed B-H/N-H dehydrocoupling with H_2 as the sole byproduct. These results are reported in this Communication (Scheme 1).

Scheme 1. Catalytic Strategies for NH_3 Functionalization



Commercially available *o*-carborane and NH_3 were chosen as the model coupling partners to evaluate the feasibility of B-H/N-H dehydrocoupling. In the presence of an Ir(I) catalyst and phosphine ligand, the reaction of *o*-carborane with NH_3 in THF at 110 °C (bath temperature) for 12 h afforded only a trace amount of the product 3-NH_2-*o*-carborane **3a** detected by gas chromatography mass spectrometry (GC-MS) (entry 1, Table 1). Screening of phosphine ligands proved PCy_3 was the optimal choice, generating **3a** in 40% isolated yield (entries 1−4, Table 1 and Table S1 in the SI). Other solvents offered reduced yields of **3a** (entries 5−7, Table 1 and Table S2 in the

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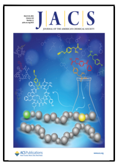

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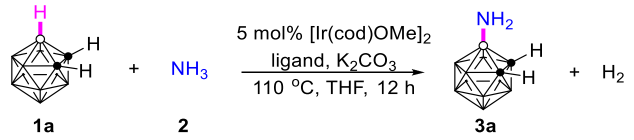
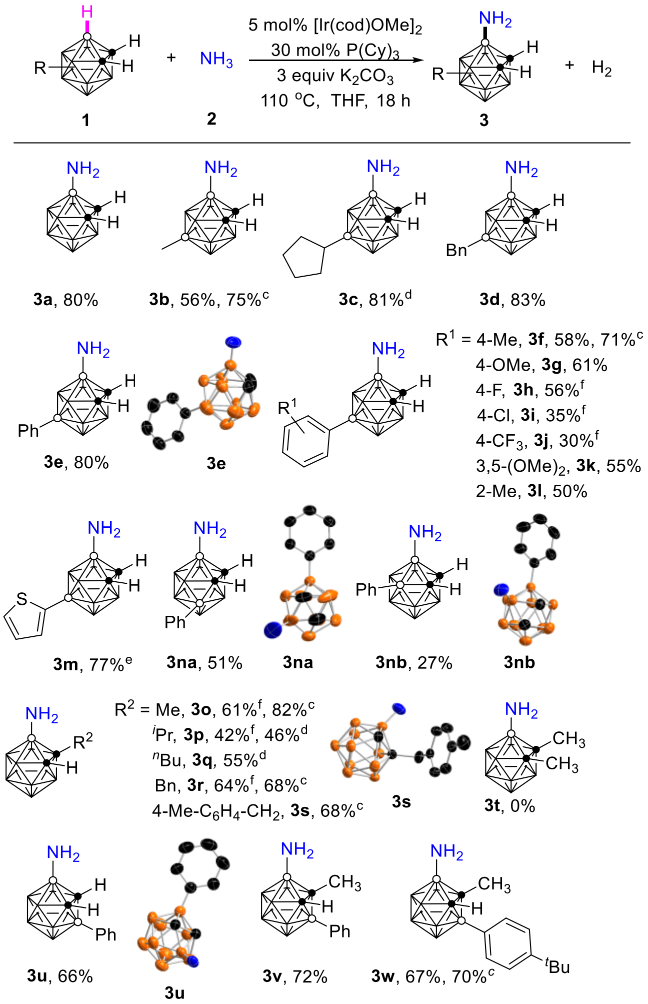
Table 1. Optimization of Reaction Conditions[a]



entry	ligand (mol %)	K_2CO_3 (equiv)	**3a** (%)
1	P(*o*-tol)$_3$ (20)	-	trace
2	P(Cy)$_3$ (20)	-	40
3	XPhos (20)	-	trace
4	P(^{t}Bu)$_3$ (20)	-	trace
5[b]	P(Cy)$_3$ (20)	-	N. R.
6[c]	P(Cy)$_3$ (20)	-	19
7[d]	P(Cy)$_3$ (20)	-	N. R.
8	P(Cy)$_3$ (20)	2	70
9	P(Cy)$_3$ (20)	3	71
10	P(Cy)$_3$ (20)	4	63
11	P(Cy)$_3$ (30)	2	69
12	P(Cy)$_3$ (30)	3	76
13	P(Cy)$_3$ (40)	3	71
14[e]	P(Cy)$_3$ (30)	3	80
15[f]	P(Cy)$_3$ (30)	3	59
16[g]	P(Cy)$_3$ (30)	3	66
17[h]	P(Cy)$_3$ (15)	3	56

[a] Reactions were conducted on a 0.1 mmol scale in 6 mL of THF in a 200 mL closed flask with 1.5 atm of NH_3, XPhos = 2-dicyclohexylphosphino-2,4,6′-triisopropylbiphenyl, yield of isolated products. [b] Toluene instead of THF. [c] DME instead of THF. [d] 1,4-Dioxane instead of THF. [e] 18 h instead of 12 h. [f] 24 h instead of 12 h; the lower yield was due to deboronation. [g] $[Ir(cod)Cl]_2$ instead of $[Ir(cod)OMe]_2$. [h] $[Ir(cod)OMe]_2$ (2.5 mol %) was employed.

Table 2. Synthesis of B(3)-amino-*o*-carboranes[a,b]



[a] Reactions were conducted on a 0.1 mmol scale. [b] Yield of isolated products. [c] 24 h instead of 18 h. [d] 40 h instead of 18 h. [e] 8 h instead of 18 h. [f] 12 h instead of 18 h.

SI). It was later found that the addition of base promoted such B-H/N-H dehydrocoupling, and the use of 3.0 equiv of K_2CO_3 increased the yield of **3a** to 71% (entries 8–10, Table 1 and Table S3 in the SI). Further optimization of the phosphine loading indicated 30 mol % was the best, resulting in **3a** in 76% isolated yield (entries 9, 12, and 13, Table 1). A longer reaction time (18 h) further improved the yield of **3a** to 80% (entry 14, Table 1). However, a prolonged reaction time (24 h) led to a lower yield of **3a** due to the deboronation (entry 15, Table 1). The employment of $[Ir(cod)Cl]_2$ resulted in a drop of yield to 66% (entry 16, Table 1). In view of the yield of **3a**, entry 14 in Table 1 was chosen as the optimal reaction conditions.

Various cage C- or B-substituted *o*-carboranes were subsequently examined for this Ir-catalyzed B-H/N-H dehydrocoupling, and results were compiled in Table 2. A wide range of substituents including alkyl, aryl, and benzyl at the B(9) position were compatible with this reaction, leading to the corresponding B(3)-amino-*o*-carborane derivatives in moderate to high isolated yields (**3a**-**3m**). Electron-donating groups generally offered higher yields than the electron-deficient ones (**3f**-**3j**). The thiophene-containing substrate worked well, affording the aminated product **3m** in 77% isolated yield. 4-Ph-*o*-carborane afforded two regioisomers 6-NH_2-4-Ph-*o*-carborane (**3na**) and 3-NH_2-4-Ph-*o*-carborane (**3nb**) in 51 and 27% isolated yields, respectively. Various substituents at cage C were also tolerated, and the corresponding products **3o**-**3s** were isolated in 46–82% yields. The more steric demanding substituents at the cage C atom provided the relatively lower yields (**3a** vs **3o** vs **3p**). The use of 1,2-Me_2-*o*-carborane led to no reaction (**3t**). Cage B(3)-substituted carboranes reacted with NH_3 smoothly to generate the target 6-amino-*o*-carboranes in 66–72% isolated yields (**3u**-**3w**).

Compounds **3** were fully characterized by ^1H, ^{13}C, ^{19}F, and ^{11}B NMR spectroscopy as well as high-resolution mass spectrometry. The molecular structures of **3e**, **3na**, **3nb**, **3s**, and **3u** were further confirmed by single-crystal X-ray analyses.

To gain some insights into the reaction mechanism, several control experiments were performed (Scheme 2). It was expected that 1 equiv of H_2 should be generated as the byproduct during the reaction. Indeed, a significant peak at $\delta = 4.47$ ppm assignable to H_2 was observed in the ^1H NMR spectroscopy of the reaction mixture (see Figure S6 in the SI), which was further confirmed by gas chromatography thermal conductivity detector (GC-TCD) analyses (see Figure S7 in the SI).[15] The crucial role of the Ir(I) catalyst was proved by the control experiment shown in Scheme 2a, as no reaction was observed in the absence of $[Ir(cod)OMe]_2$. On the other hand, the yields for **3a** were gradually enhanced by increasing the loading of the Ir(I) catalyst in the absence of K_2CO_3 (Scheme 2b). Such a phenomenon may suggest the presence of catalyst poisoning by the product 3-amino-*o*-carborane. To test this hypothesis, product **3a** was added to the reaction

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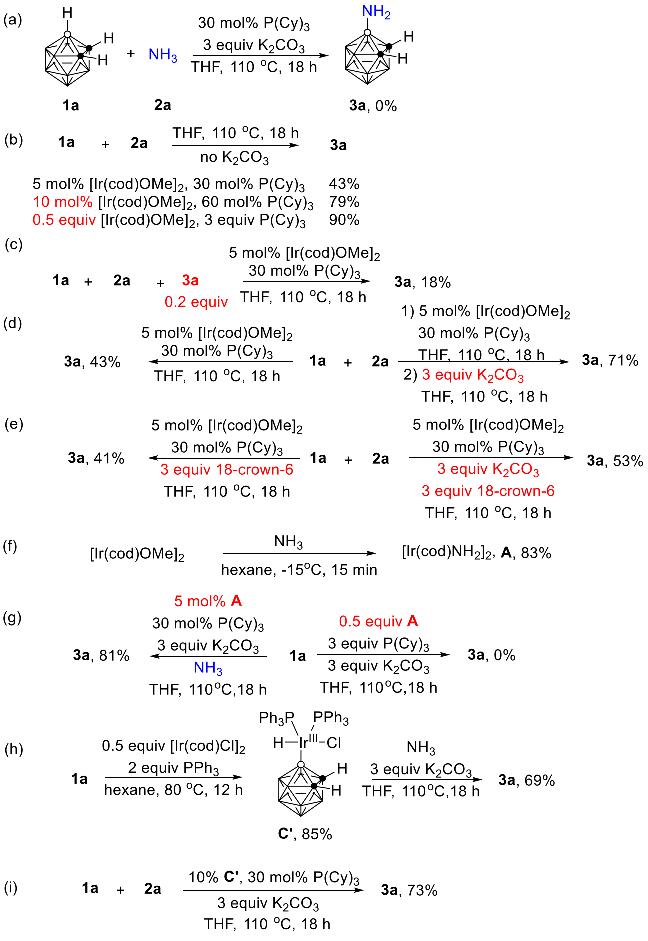
J. Am. Chem. Soc. 2021, 143, 4148−4153

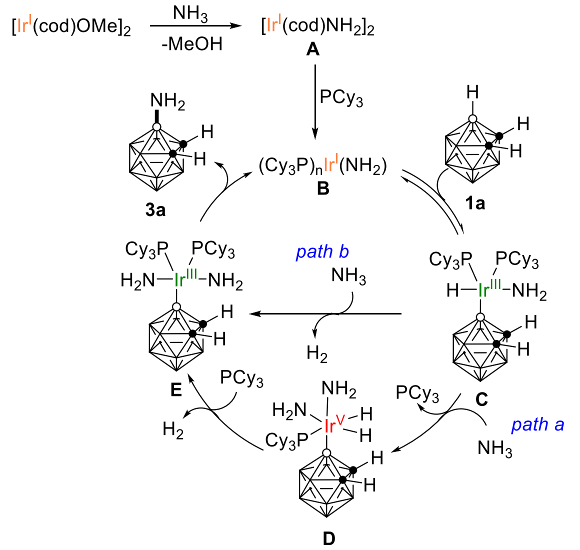
Scheme 2. Control Experiments



mixture, leading to an obvious drop of the yield of **3a** (Scheme 2c). In the absence of K_2CO_3, the reaction of *o*-carborane with NH_3 afforded **3a** in 43% yield, whereas the addition of K_2CO_3 led to **3a** in 71% yield (Scheme 2d). However, the addition of 3 equiv of 18-crown-6, a well-known K^+ trapper,[16] to the reaction system resulted in a big drop of the yield of **3a** to 53% (Scheme 2e). These results indicated that the trapping of K^+ by 18-crown-6 largely reduced the reaction efficiency, which suggested that the interactions between **3a** and K^+ might remove the poisoning effect from **3a**.

To obtain some information on the reaction intermediates, an iridium amide complex $[Ir(cod)NH_2]_2$ **A** was prepared in 83% yield from the reaction of $[Ir(cod)OMe]_2$ with NH_3 according to a literature report (Scheme 2f).[17a] **A** could catalyze the dehydrocoupling reaction under standard conditions to offer **3a** in 81% yield, whereas its stoichiometric reaction with *o*-carborane in the absence of NH_3 gave no target product (Scheme 2g). These results indicated that (1) **A** might be a precatalyst and (2) the corresponding Ir(III) intermediate **C** (Scheme 3) that resulted from the oxidative addition of **A** onto the B(3)-H bond in the presence of PCy_3 should not undergo reductive elimination to afford **3a** in the absence of NH_3. Many attempts to isolate the intermediate **C** were not successful. An alternative Ir(III) complex **C′** was then prepared according to a literature report (Scheme 2h).[17b] **C′** indeed catalyzed the cross-coupling efficiently to give **3a** in 73% yield (Scheme 2i), which is very comparable to the catalytic activity of $[Ir(cod)Cl]_2$ (entry 16, Table 1). In addition, the reaction of

Scheme 3. Proposed Reaction Mechanism



C′ with NH_3 also afforded the target product **3a** in 69% yield (Scheme 2h).

On the basis of the aforementioned experimental results and literature reports,[12c,17,18] a proposed reaction mechanism for catalytic selective B(3) amination is shown in Scheme 3. The reaction of $[Ir(cod)OMe]_2$ with NH_3 produces a dinuclear amino-bridged complex $[Ir(cod)NH_2]_2$ (**A**),[17a] which undergoes ligand exchange reaction with PCy_3 to give a monomeric active species $(Cy_3P)_nIr^INH_2$ (**B**) to start the catalytic cycle. The oxidative addition of **B** onto the most electron-deficient B(3)-H bond of *o*-carborane (**1a**) affords an Ir^{III} intermediate **C**.[12c,17b] Intermediate **C** undergoes an oxidative addition with NH_3 to generate another intermediate **D**.[12c,18] Reductive elimination of **D** gives the intermediate **E** and releases H_2 gas (path a). Alternatively, the acid−base reaction of **C** with NH_3 also affords **E** (path b).[12c,19] Another reductive elimination of **E** yields the final product **3a** and regenerates the Ir^I catalyst to complete the catalytic cycle.

In summary, a straightforward and efficient iridium-catalyzed dehydrogenative cross-coupling between *o*-carboranes and ammonia gas was achieved, leading to facile synthesis of a series of 3-NH_2-*o*-carboranes. This new protocol allows chemical-oxidant-free B-H/N-H dehydrocoupling and generates H_2 gas as the sole byproduct. This work not only opens up a new pathway for direct, efficient, and regioselective B-H amination of *o*-carboranes but also offers a valuable reference for organic C-H amination with NH_3.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c00593.

Experimental procedures and characterization of the products (PDF)

Accession Codes

CCDC 2056780−2056784 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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