Carboryne Amination

Deutsche Ausgabe: DOI: 10.1002/ange.201507952
Internationale Ausgabe: DOI: 10.1002/anie.201507952

Facile Synthesis of *N*-Carboranyl Amines through an *ortho*-Carboryne Intermediate

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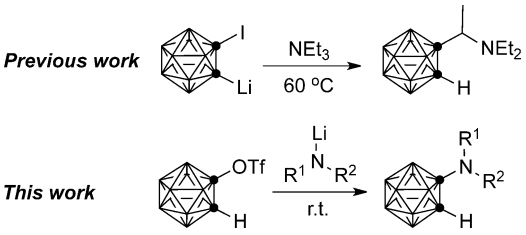
Abstract: *The efficient o-carboryne precursor 1-Li-2-OTf-o-$C_2B_{10}H_{10}$ reacts with lithium amides at room temperature to give a series of N-carboranyl amines in moderate to high isolated yields. This reaction is compatible with a broad substrate scope from primary to secondary, alkyl to aryl amines. The reaction mechanism is also proposed on the basis of experimental results and DFT calculations. This represents the first general and efficient method for the synthesis of 1-NR^1R^2-o-carboranes.*



Scheme 1. Reaction of *o*-carboryne with amines.

Amine derivatives are ubiquitous in biology and very important functional units in medicinal chemistry, which can be generally synthesized by alkylation of ammonia or amines, reduction of nitriles, azides, or imines, and hydroamination of alkenes or alkynes.[1] On the other hand, a growing interest has been directed toward the synthesis of *o*-carborane derivatives bearing organic nitrogen groups owing to their potential applications in medicinal chemistry[2] and catalysis.[3] For example, carborane-amino acid or -nucleoside combinations serve as excellent candidates for cancer treatment in boron neutron capture therapy (BNCT).[2b–e,4] Moreover, aminoalkyl-*o*-carboranes have been extensively employed as ligands for transition metal complexes.[3,5] Despite the recent advances in carborane chemistry, the straightforward and general synthesis of amino-*o*-carboranes, in particular, 1-R_2N-*o*-carboranes, still represents a very challenging project.[6]

It has been documented that 1-NH_2-*o*-$C_2B_{10}H_{11}$ can be prepared by reduction of azido- or nitroso-*o*-carborane or by Curtius rearrangement of the carboranyl amide.[7–9] However, unlike organic amines, 1-NH_2-*o*-carborane does not undergo alkylation/arylation to give the corresponding 1-RNH-*o*-carborane or 1-R_2N-*o*-carborane.[10] Unfortunately, there are no other convenient methods to prepare these amines.[6,11]

Very recently, we reported that *o*-carboryne,[12] generated in situ from 1-iodo-2-lithio-*o*-carborane, can undergo α-C–H bond insertion with tertiary amines, affording α-carboranylated amines (Scheme 1).[13] However, the reaction of 1-iodo-2-lithio-*o*-carborane with secondary amine gave a mixture of α-carboranylated amine and 1-R_2N-*o*-carborane because heating was necessary to promote the formation of *o*-carboryne through the elimination of LiI.[13] To avoid the α-C–H bond insertion, lowering the reaction temperature is crucial and *o*-carboryne should be generated at lower temperatures. Thus, a better leaving group than iodo is required to facilitate the elimination of salt, generating the *o*-carboryne intermediate. In view of benzyne chemistry,[14] it is believed that OTf is an appropriate leaving group. Subsequently, 1-OTf-*o*-$C_2B_{10}H_{11}$ (**1a**) was prepared according to previous procedures.[7d] Herein, we report that compound **1a** can, indeed, react with $LiNR_2$ or LiNHR to afford the desired 1-R_2N-*o*-$C_2B_{10}H_{11}$/1-RHN-*o*-$C_2B_{10}H_{11}$ in very good yields (Scheme 1).

We commenced our studies by screening for a suitable base for the reaction of **1a** with *n*Bu_2NH. Slow addition of 1 equivalent of *n*BuLi to a 1:1 mixture of **1a** and *n*Bu_2NH in cyclohexane at room temperature for 10 min with stirring gave 1-*n*Bu_2N-*o*-$C_2B_{10}H_{11}$ (**3b**), *o*-carborane, and 1-*n*Bu-*o*-$C_2B_{10}H_{11}$ in a ratio of 65:16:19 as determined by GC analyses, where 1-*n*Bu-*o*-$C_2B_{10}H_{11}$ was likely generated from the side reaction of *o*-carboryne with *n*BuLi (see below).[15] To avoid the formation of byproduct 1-*n*Bu-*o*-$C_2B_{10}H_{11}$, various bases such as KH, NaH, *t*BuOK, and *n*Bu_2NLi were examined (Supporting Information, Table S1). The results suggested that in situ generated *n*Bu_2NLi afforded **3b** in >90% GC yield in 10 min. Lowering the reaction temperature to −30 °C, or increasing the amount of *n*Bu_2NLi to 2 equivalents, did not improve the yield of **3b**. Donor solvents such as Et_2O and THF led to the deboration reaction.[16] On the other hand, toluene resulted in the formation of Diels–Alder reaction byproducts.[17]

After the identification of the optimal reaction conditions ($LiNR_2$, cyclohexane, room temperature, 10 min), the substrate scope was examined. The results were compiled in Table 1, which showed that this amination reaction is compatible with a wide range of amines from aliphatic to

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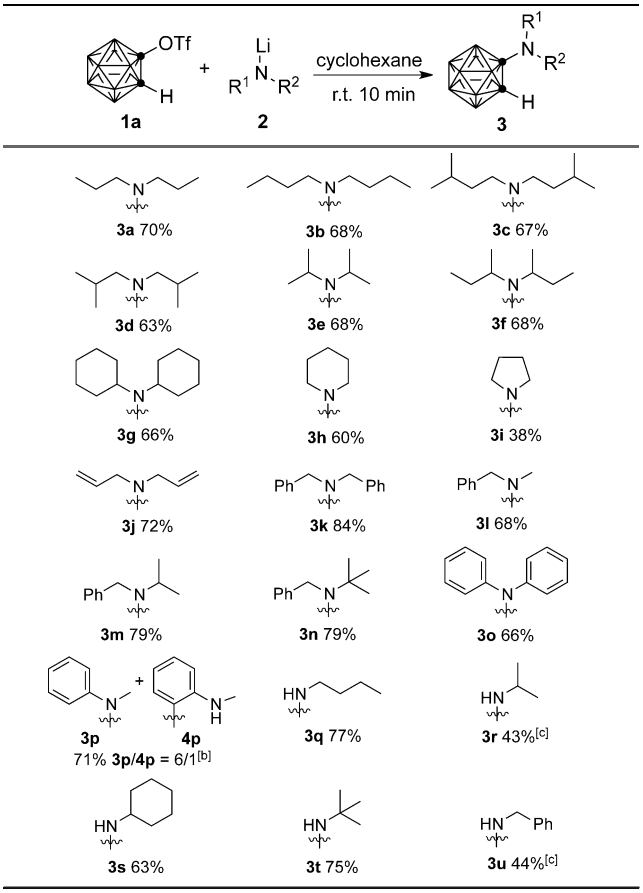
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201507952.

Table 1: Synthesis of 1-R^1R^2N-*o*-$C_2B_{10}H_{11}$.[a]



[a] Lithium amides were prepared in situ by the reaction of the corresponding amines (1.1 equiv) with *n*BuLi (1.1 equiv) in cyclohexane at room temperature. Yields of isolated products are given. [b] Determined by ^{1}H NMR spectrum. [c] Low yield resulted from the high volatility of product.

aromatic, primary to secondary, cyclic to acyclic amines. Dialkyl amides gave **3a**-**h** in 60–70% yields of isolated products, except for that of **3i** (38%). The lower yield may be ascribed to the stronger nucleophilicity of $LiNC_4H_8$, leading to partial deboration of the cage. Diallylamide, various benzylamides, and diphenylamide afforded the corresponding products **3j**–**o** in 66-84% yields. For *N*-methylaniline, the major amination product **3p** as well as the arylation byproduct **4p** were isolated with a molar ratio of 6/1. This may be rationalized by *o*-carboryne insertion into the C(sp^2)–Li bond that exists in the resonance hybrid of aniline lithium salt, which was observed in the benzyne system.[18] The above amination reaction also proceeded well with primary amides to generate the corresponding amination products **3q**–**u** in moderate to very good yields. Unfortunately, no reaction was observed with $LiNH_2$ in cyclohexane probably owing to solubility reasons, while addition of Et_2O or THF led to the deboration of the cage.

Compounds **3** were fully characterized by ^{1}H, ^{13}C, and ^{11}B NMR spectroscopy, as well as elemental analyses or high-resolution mass spectrometry.[19] The chemical shift of cage CH proton in **3** was observed in the range of 3.67–4.02 ppm, which was shifted downfield compared with that of 3.55 ppm observed in *o*-carborane. On the other hand, the N-bonded cage carbon showed a broad signal at about 108 ppm for **3a**–**p** and 95 ppm for **3q**–**u**, whereas another cage carbon was found at about 70 ppm, suggesting the presence of an *exo* C_{cage}=N bonding character.[6,10,20]

The molecular structures of **3e**, **3g**, and **3o** were further confirmed by single-crystal X-ray analyses (representative structures shown in Figure 1).[21] It is clear that the N atom

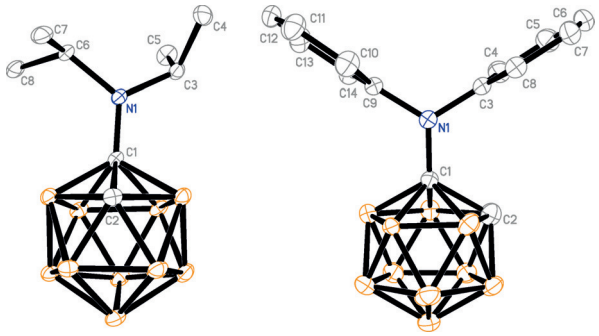
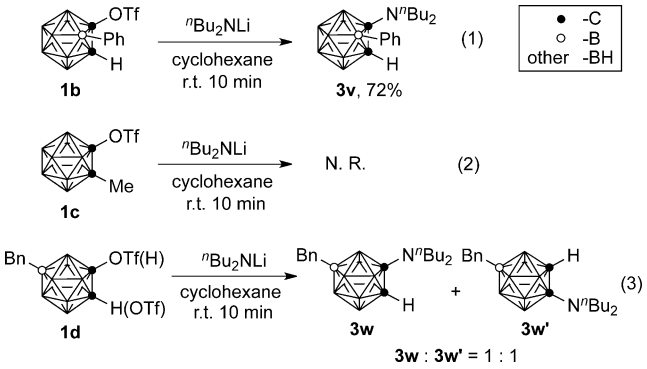


Figure 1. Molecular structures of **3e** (left) and **3o** (right). Selected bond distances [Å] and angles [°]. For **3e**: C(1)-N(1) 1.369(2) Å, C(1)-C(2) 1.890(2) Å, N(1)-C(3) 1.481(2) Å, N(1)-C(6) 1.486(2) Å, C(1)-N-(1)-C(3) 119.2 (1)°, C(1)-N(1)-C(6) 124.5(2)°, C(3)-N(1)-C(6) 116.1-(1)°; for **3o**: C(1)-N(1) 1.402(3) Å, C(1)-C(2) 1.698(4) Å, N(1)-C(3) 1.441(3) Å, N(1)-C(9) 1.440(3) Å, C(1)-N(1)-C(3) 119.6(2)°, C(1)-N(1)-C(9) 122.5(2)°, C(3)-N(1)-C(9) 116.6(2)°.

adopts the trigonal planar geometry with the total sum of three angles around the N atom being 360°. The C(1)–N(1) distances of 1.369(2) Å in **3e** and 1.372(2) Å in **3g**, are significantly shorter than the C–N single bond distances in amines (typically ca. 1.47 Å), and slightly shorter than that of 1.392(3) Å in 1-Ph-2-NH_2-*o*-$C_2B_{10}H_{10}$,[10] and 1.423(3) Å observed in 1-HONH-*o*-$C_2B_{10}H_{11}$.[7f] On the other hand, the C(1)–N(1) distance of 1.402(3) Å in **3o** is longer than those in **3e** and **3g**, which can be attributed to the electron-withdrawing nature of the phenyl rings.[22] The C(1)–C(2) distances of 1.890(2) Å in **3e**, 1.852(2) Å in **3g**, 1.767(3) Å in 1-Ph-2-NH_2-*o*-$C_2B_{10}H_{10}$,[10] and 1.737(3) Å in 1-HONH-*o*-$C_2B_{10}H_{11}$[7f] are much longer than that of 1.698(4) Å in **3o** and 1.63 Å in *o*-carborane. These data suggest that the short C(1)–N(1) distances are associated with the longer C(1)–C(2) bonds, implying again the presence of *exo* C(1)=N(1) π bonding.[20]

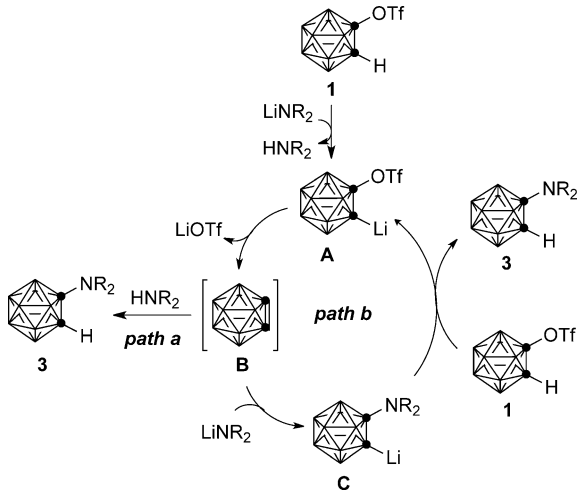
To gain some insight into the reaction pathway, 3-Ph-1-OTf-*o*-$C_2B_{10}H_{10}$ (**1b**), 2-Me-1-OTf-*o*-$C_2B_{10}H_{10}$ (**1c**), and 9/12-Bn-1-OTf-*o*-$C_2B_{10}H_{10}$ (**1d**, Bn = CH_2Ph) were synthesized and subjected to the amination reaction. The reaction proceeded smoothly with **1b** to afford 1-*n*Bu_2N-3-Ph-*o*-$C_2B_{10}H_{10}$ (**3v**) in 72% yield, suggesting little influence of the B(3)–Ph substituent on the amination [Scheme 2, Eq. (1)]. No reaction was observed when **1c** was treated with $LiNBu^n_2$, ruling out the possibility of direct nucleophilic substitution reactions [Scheme 2, Eq. (2)]. On the other hand, a 1:1 mixture of 1-*n*Bu_2N-9-Bn-*o*-$C_2B_{10}H_{10}$ (**3w**) and 1-*n*Bu_2N-12-Bn-*o*-$C_2B_{10}H_{10}$ (**3w′**) was observed by ^{1}H NMR spectroscopy and GC-MS from the reaction of $LiNBu^n_2$ with a single



Scheme 2. Control experiments.

isomer of either 9-Bn-1-OTf-*o*-$C_2B_{10}H_{10}$ or 12-Bn-1-OTf-*o*-$C_2B_{10}H_{10}$, whose structure was unable to be confirmed by NMR [Scheme 2, Eq. (3)]. These results clearly indicate that an *o*-carboryne intermediate is involved in the above amination process.

On the basis of the above experimental results and DFT calculations,[19] a plausible mechanism is proposed in Scheme 3. Lithiation of **1** by $LiNR_2$, followed by LiOTf



Scheme 3. Proposed reaction mechanism for carborane amination.

elimination, generates *o*-carboryne intermediate **B. B** undergoes N–H insertion with HNR_2 to directly give the amination product **3** (path a).[23] Alternatively, **B** can undergo N–Li insertion with $LiNR_2$ to afford **C**. Protonation of **C** by **1** releases product **3** and generates **A** to complete the reaction cycle. DFT calculations show that both pathways are exothermic, however, the addition of *o*-carboryne over N–Li bond (path b) is energetically more favorable than that of N–H bond (path a; see the Supporting Information).

In summary, a new carboryne precursor, 1-OTf-*o*-$C_2B_{10}H_{11}$ has been developed, which reacts with lithium amides to give a new class of *N*-carboranyl amines in moderate to very good yields with a broad substrate scope from primary to secondary, aryl to alkyl, and cyclic to acyclic amines. This represents the first general method for the synthesis of 1-R^1R^2N-*o*-carboranes. Mechanistic studies suggest that the *o*-carboryne intermediate is involved in this amination reaction.

Experimental Section

Typical procedure: To a cyclohexane solution (3 mL) of $LiNBu^n_2$ (0.55 mmol), prepared in situ from the reaction of *n*BuLi (0.35 mL, 1.6 M in hexane, 0.55 mmol) with $HNBu^n_2$ (**2b**; 71 mg, 0.55 mmol) at 0 °C, was added a cyclohexane solution (2 mL) of **1a** (146 mg, 0.50 mmol). The reaction mixture was stirred at room temperature for 10 min and then quenched with wet hexane. After removal of the solvents, the residue was subjected to flash column chromatography on silica gel (230–400 mesh) using *n*-hexane/Et_3N (100/1 in *v*/*v*) as eluent to give **3b** as a light yellow oil (92 mg, 68 %). ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 3.73$ (s, 1H; cage C*H*), 3.02 (t, $J = 7.5$ Hz, 4H; NCH_2), 1.42 (m, 4H), 1.24 (m, 4H; CH_2), 0.91 ppm (t, $J = 7.5$ Hz, 6H; CH_3). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): $\delta = 108.9$ (cage *C*-N), 72.8 (cage *C*H), 54.9 (N*C*H$_2$), 30.6, 19.9 (*C*H$_2$), 13.8 ppm (*C*H$_3$). ^{11}B{^{1}H} NMR ($CDCl_3$, 128 MHz): $\delta = -2.3$ (1B), −9.9 (1B), −11.2 (2B), −12.2 (2B), −13.1 ppm (4B). Analytical calculations for $C_{10}H_{29}B_{10}N$: C = 44.25; H = 10.77; N = 5.16. Found: C = 44.75; H = 10.73; N = 5.17.

Acknowledgements

This work was supported by grants from the National Basic Research Program of China (973 Program, Grant No. 2012CB821600), National Natural Sciences Foundation of China (No. 21372245 to Z.Q.), Shanghai Pujiang Program (No. 13PJ1410800 to Z.Q.), Youth Innovation Promotion Association CAS (No. 2014230 to Z.Q.), CAS-Croucher Funding Scheme, and NSFC/RGC Joint Research Scheme (N_CUHK442/14 to Z.X.). We thank Dr. Sunewang R. Wang for helpful discussion.

Keywords: addition reaction · amination · boron cluster · carborane · carboryne

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 1751–1754
Angew. Chem. **2016**, *128*, 1783–1786

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Received: August 25, 2015
Published online: October 16, 2015

