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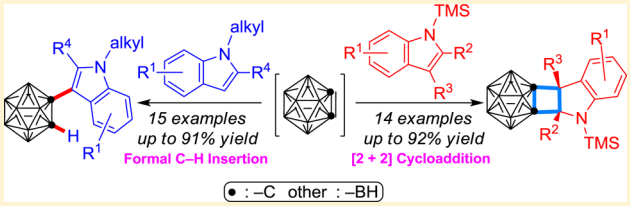
Dearomative [2 + 2] Cycloaddition and Formal C−H Insertion Reaction of *o*-Carboryne with Indoles: Synthesis of Carborane-Functionalized Heterocycles

Da Zhao, Jiji Zhang, and Zuowei Xie*

Department of Chemistry and State Key Laboratory of Synthetic Chemistry, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong, China

Supporting Information

ABSTRACT: *o*-Carboryne (1,2-dehydro-*o*-carborane) is a very useful synthon for the synthesis of a variety of carborane-functionalized heterocycles. Reaction of *o*-carboryne with *N*-protected indoles gave carborane-fused indolines if the protecting group was TMS via dearomative [2 + 2] cycloaddition or carboranyl indoles for *N*-alkyl ones through formal C−H insertion reaction. For *N*-aryl indoles, both reactions were observed, giving two products, in which the product ratio was dependent upon the nature of the substituents on the aryl rings. In general, electron-withdrawing substituents favor [2 + 2] cycloaddition, whereas electron-donating substituents promote a formal C−H insertion pathway. This reaction is also compatible with other heteroaromatics. Thus, a stepwise reaction mechanism was proposed to account for the experimental observations. These protocols offer general and efficient methods for the preparation of carborane-functionalized indoles and indolines as well as other heterocycles. The observed dearomative [2 + 2] cycloaddition represents the first example of indoles to undergo such reaction in the absence of transition metals or without UV irradiation. All new compounds were fully characterized by ^{1}H, ^{13}C, and ^{11}B NMR spectroscopy as well as HRMS spectrometry. Some were further confirmed by single-crystal X-ray analyses.



INTRODUCTION

Dearomatization reactions are important transformations of aromatic compounds as they lead directly to various cyclic or heterocyclic skeletons from structurally simple substrates.[1] In particular, due to the potent biological activities and pharmaceutical applications of indoline alkaloids, dearomatization of indoles has long been a subject of interest in synthetic chemistry.[1,2] Among those elegant dearomative strategies, dearomative cycloaddition of the indole molecules represents an attractive, straightforward, and atom-economic approach to indoline compounds.[3] It has been shown that indole can undergo [3 + 2],[3b−e,4] [4 + 2],[3f−i,5] and [5 + 2][6] cycloaddition reactions to generate cyclopenta[*b*]indoles, hydrocarbazoles, and cyclohepta[*b*]indoles, respectively. Despite great efforts in the dearomatization of indoles, there are only three reports on nonphotoinduced dearomative [2 + 2] cycloaddition of indoles.[7,8] To the best of our knowledge, transition-metal-free protocols to address cyclobuta-fused indoline frameworks are still absent in the literature.

On the other hand, direct C−H functionalization of heterocycles has received great attention due to the structural prevalence of substituted heterocycles in natural products, drugs, and other biologically active molecules.[9] In this regard, indole derivatives represent a system of particular interest and importance.[10] As a consequence, considerable efforts have been directed toward the development of mild, selective, and efficient methods for the functionalization of indole molecules, especially with regard to C−H bond activation based on transition-metal catalysis[11] and direct Friedel−Crafts alkylations as well as allylic alkylations.[11a,d,12]

In view of a growing interest in the applications of carborane-containing compounds in medicine,[13] materials science,[14] and organometallic/coordination chemistry,[15] the development of new methods for the synthesis of such class of molecules has received much attention. For instance, carborane derivatives bearing π substituents (aryl and heteroaryl) have shown interesting photophysical properties as light-emitting materials.[16] Additionally, carboranes containing a 5,6,7-trimethoxyindole unit are attractive DNA-binding boron sources for boron neutron capture therapy (BNCT).[17] Considering the unique properties of indoles and carboranes, carborane-functionalized indole or indolines may find applications in medicine and materials. Surprisingly, despite the considerable progress in carborane chemistry, straightforward and general synthesis of carborane-functionalized heterocycles such as indolinyl- or indolyl-*o*-carboranes still represents a very challenging task.[18] During our ongoing research on the functionalization of carboranes via 1,2-dehydro-*o*-carborane (*o*-carboryne) intermediate,[19] we found that *o*-carboryne reacted readily with *N*-protected indoles in two ways, in which the chemoselectivity of the reaction depended on the nature of *N*-protecting group of the indole substrates (Scheme 1). Herein, we report this new methodology, which provides an

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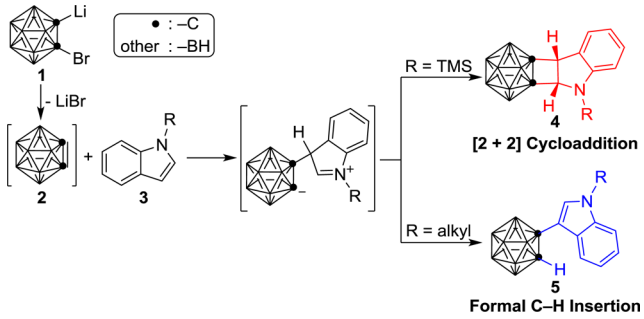
efficient, chemoselective, and highly controllable synthesis of carboranyl-substituted indoles and indolines.

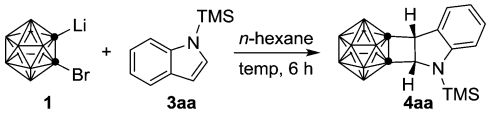
Scheme 1. Reaction of *o*-Carboryne with Indoles



RESULTS AND DISCUSSION

[2 + 2] Dearomative Cycloaddition. Our investigations began with the reaction of *o*-carboryne (**2**) with *N*-TMS indole **3aa**, and the results are compiled in Table 1. Treatment of 1-Br-2-Li-*o*-$C_2B_{10}H_{10}$ (**1**) (prepared in situ by mixing a 1:1 molar ratio of 1,2-Li_2-*o*-$C_2B_{10}H_{10}$ with 1,2-Br_2-*o*-$C_2B_{10}H_{10}$ in *n*-hexane)[20] with 5 equiv of 1-TMS-1*H*-indole (**3aa**) in *n*-hexane at 60 °C for 6 h gave [2 + 2] cycloadduct **4aa** in 81% isolated yield (Table 1, entry 1). Lowering the amount of **3aa** to 2.0 and 1.1 equiv showed no obvious changes in the isolated yield of **4aa** (Table 1, entries 1–3). Increasing the reaction temperature to 80 °C did not improve the yield (Table 1, entry 4). However, heating was necessary for this reaction as only a trace amount of **4aa** was formed after prolonged reaction at room temperature (Table 1, entry 6).

Table 1. Optimization of Reaction Conditions[a]

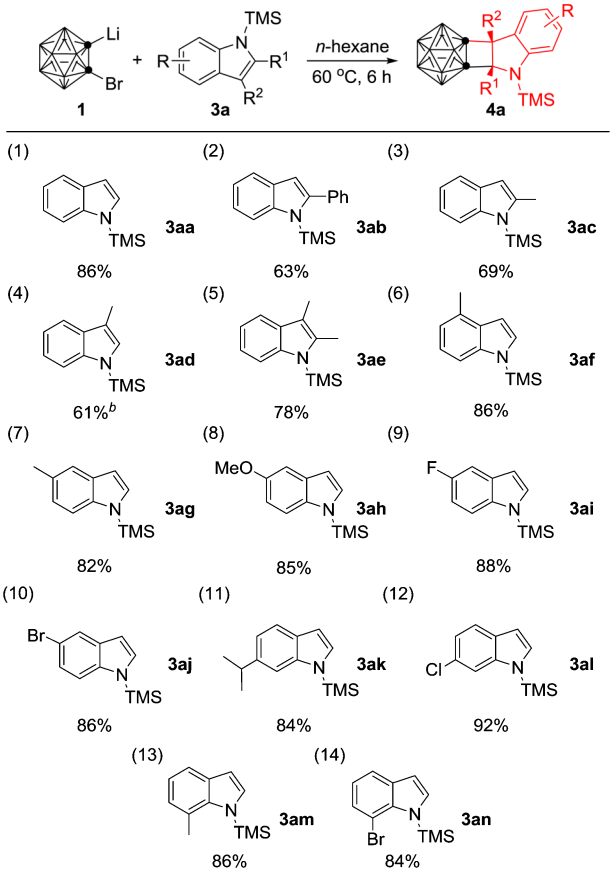


entry	**3aa** (equiv)	temp (°C)	**4aa** (%)[b]
1	5.0	60	81
2	2.0	60	87
3	**1.1**	**60**	**86**
4	1.1	80	78
5	1.1	40	38
6[c]	1.1	25	trace

[a]Reaction conditions: **1** (1.0 mmol), indole **3aa** (1.1, 2.0, or 5.0 mmol) in *n*-hexane (10 mL), 60 °C, 6 h, TMS = trimethylsilyl. [b]Isolated yields. [c]Stirred for 24 h.

Under the optimal reaction conditions (Table 1, entry 3), a broad array of *N*-TMS-substituted indoles underwent [2 + 2] cycloaddition with *o*-carboryne, producing carborane-fused indolines in 61–92% yields (Table 2). For instance, the C2,C3-carborane-fused indoline **4ab** and **4ac** were obtained in good yields for 2-phenyl- and 2-Me-substituted *N*-TMS-1*H*-indole **3ab** and **3ac** (Table 2, entries 2 and 3). For indole **3ad** featuring a methyl group at the C3 position, in addition to the major [2 + 2] cycloadduct **4ad**, an ene product (see Scheme 4, eq 5)[21] was isolated in 24% yield (Table 2, entry 4). In contrast, only the [2 + 2] cycloadduct was obtained in 78% isolated yield, and the formation of the undesired ene product was suppressed for C2,C3-disubstituted indole **3ae** (Table 2, entry 5). Both electron-withdrawing (F, Cl, Br, Ph) and electron-donating (Me, OMe, *i*Pr) benzenoid substituents were well tolerated in this reaction (Table 2, entries 6–14).

Table 2. Substrate Scope for [2 + 2] Cycloaddition of *N*-TMS Indoles[a]



[a]Reaction conditions: **1** (1.0 mmol), indole **3a** (1.1 mmol) in *n*-hexane (10 mL), 60 °C, 6 h. Yields of isolated products were given. [b]Ene reaction product was also isolated in 24% yield (see Scheme 4, eq 5).

Effects of *N*-Substituents. Interestingly, as shown in Table 3, the electronic and steric properties of the *N*-substituents have a dramatic influence in controlling the chemoselectivity of the reactions. For instance, a significant steric effect was observed for *N*-silyl indoles. *N*-(*tert*-Butyldimethylsilyl) indole **3b** gave both [2 + 2] cycloadduct **4b** in 33% yield and formal C–H insertion product[22] **5b** in 42% yield. The [2 + 2] cycloaddition was completely inhibited for a more bulky triisopropylsilyl (TIPS) group (Table 3, entries 2 and 3) likely due to the interactions between the hydrogen atoms of the TIPS and indoline moiety (see Figure S6 in the Supporting Information). For unprotected 1*H*-indole **3d**, an equimolar reaction gave only acid–base reaction product, 1-Br-*o*-$C_2B_{10}H_{11}$ (pK_a values 21.0 for **3d** versus ~23 for *o*-carborane).[10a,18a] The desired 3-carboranyl-1*H*-indole **5d** was isolated in 30% yield (60% based on recovered starting material) when 0.5 equiv of **3d** was used (Table 3, entry 4). The corresponding formal C–H insertion products were obtained in very high yields with excellent regioselectivity for *N*-alkyl indoles (alkyl = methyl, allyl, benzyl) (Table 3, entries 5–7).

For *N*-aryl indoles, both the formal C–H insertion product and the [2 + 2] cycloaddition product were formed (Table 3,

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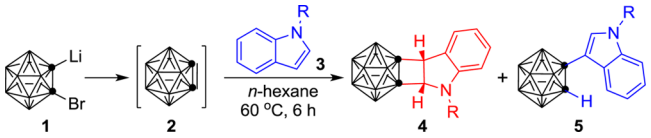
Table 3. Effects of *N*-Substituents[a]



entry	R	4 (%)[b]	5 (%)[b]
1	**Me_3Si (3aa)**	**86**	
2	*t*$BuMe_2Si$ (**3b**)	33	42
3	*i*Pr_3Si (**3c**)		83
4[c]	H (**3d**)		30
5	**Me (3ea)**		**85**
6	allyl (**3f**)		85
7	$C_6H_5CH_2$ (**3g**)		78
8	Ph (**3h**)	39	38
9	4-$MeOC_6H_4$ (**3i**)	30	45
10	4-FC_6H_4 (**3j**)	43	30

[a]Reaction conditions: **1** (1.0 mmol), indole **3** (1.1 mmol) in *n*-hexane (10 mL), 60 °C, 6 h. [b]Isolated yields. [c]A 0.5 equiv amount of **3d** was used.

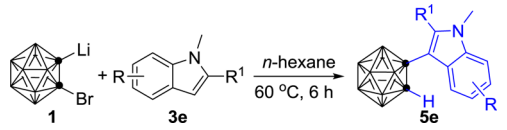
entries 8−10). A fluoro substituent at the para position of the phenyl ring increased the molar ratio of [2 + 2] cycloadduct over the formal C−H insertion product to 1.4, while a 4-methoxy substituent decreased such ratio to 0.7. The above results indicate that the [2 + 2] cycloaddition reaction is more favored if the protecting group on the nitrogen is electron deficient, which may shed some light on the reaction mechanism (vide infra). Many attempts to utilize other *N*-protected (e.g., protecting group = $SO_2C_6H_4CH_3$, $CO_2(CH_3)_3$, $COCH_3$) indoles failed due probably to the side reactions of the protecting group with precursor **1**. These results indicate the synthetic potential of these two reactions since carboranyl-substituted indoles and indolines that were unable to be constructed before can now be synthesized in an efficient and highly controlled manner by utilizing different *N*-protecting groups (alkyl or TMS).

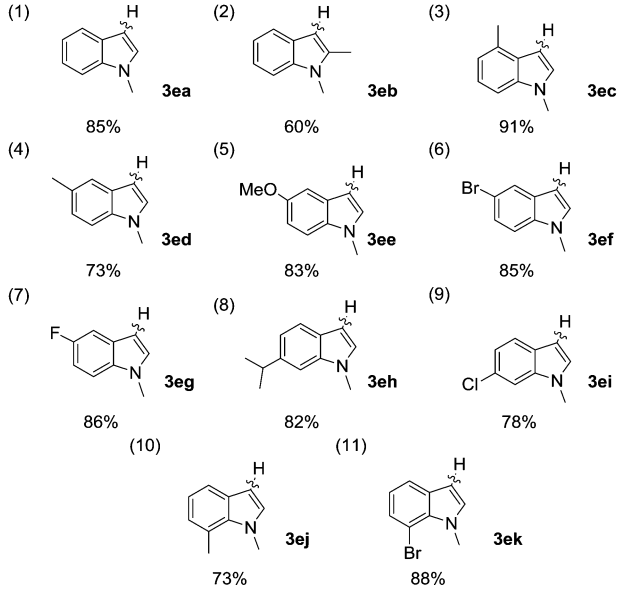
Formal C−H Insertion. We then investigated the substrate scope with a variety of *N*-methyl-protected indole derivatives for the synthesis of carboranyl-substituted indoles, and the results are compiled in Table 4. Both electron-withdrawing (F, Cl, Br) and electron-donating (Me, iPr, OMe) groups on the indole ring were well tolerated, producing the corresponding C3-carboranylindoles **5ea**−**5ek** in 60−91% yields. Notably, the halogen substituents can be used for further synthetic elaboration.

This reaction is also compatible with other *N*-heterocycles, providing a general and straightforward approach for carboranyl heterocycles (Table 5). It is noted that the construction of such molecules often involves multistep synthesis as reported in the literature.[23] Compounds 1-methyl-1*H*-benzimidazole **6a**, benzoxazole **6b**, and benzothiazole **6c** afforded the corresponding C2-carboranylated heterocycles in moderate isolated yields (Table 5, entries 1−3). Both C2 and C3 carboranylated products with a molar ratio of 1:1.5 were isolated in 80% yield for *N*-methyl-1*H*-pyrrole **6d** (Table 5, entry 4). The reaction of 4,5-dimethylthiazole **6e** proceeded smoothly to give C2-carboranylated product in 87% yield, whereas quinoline **6f** was a poor substrate as only 40% of the desired product was obtained (Table 5, entries 5−6).

Transformation of [2 + 2] Cycloadducts. The transformations of the [2 + 2] cycloadducts were examined. As

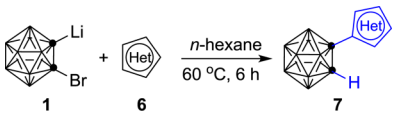
Table 4. Substrate Scope for Regioselective Carboranylation of *N*-Methyl Indoles[a]

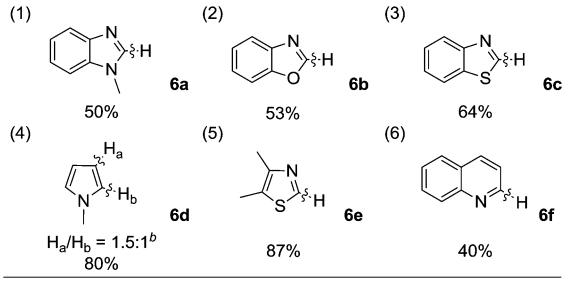




[a]Reaction conditions: **1** (1.0 mmol), indole **3e** (1.1 mmol) in *n*-hexane (10 mL), 60 °C, 6 h. Yields of isolated products were given.

Table 5. Substrate Scope for Regioselective Carboranylation of Heterocycles[a]





[a]Reaction conditions: **1** (1.0 mmol), *N*-heterocycle **6** (1.1 mmol) in *n*-hexane (10 mL), 60 °C, 6 h. Yields of isolated products were given. [b]Determined by ^{1}H NMR.

shown in Scheme 2, the [2 + 2] cycloadduct **4j** rearomatized to **5j** under thermal or acidic conditions.[24] For methoxyl-substituted cycloadduct **4ah**, this ring-opening process occurred more easily to give the rearomatized product (ring-opening product) upon treatment with silica gel. On the other hand, treatment of **4ah** or **4ac** with KF afforded the rearomatized product **5dh** or **5dc** in quantitative yield. For 3-methyl-substituted indoline **4ae**, no rearomatization product was observed; instead, a carboranyl-substituted indolenine **8** was generated in quantitative yield upon desilylation.

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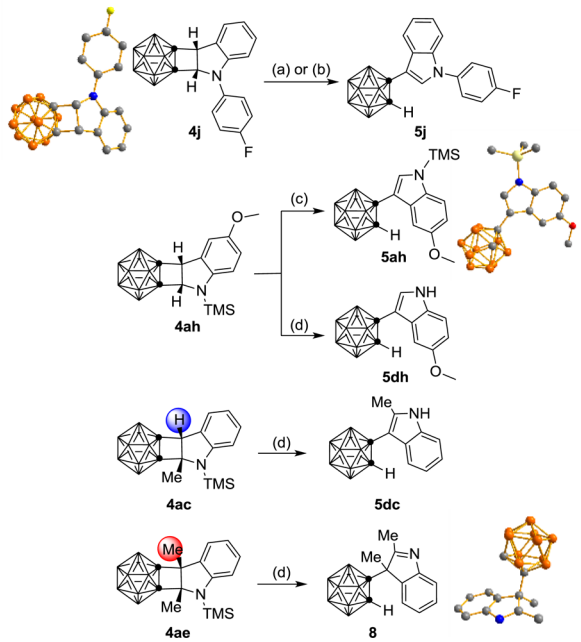
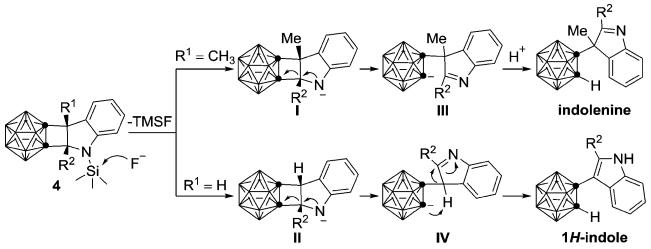
Scheme 2. Transformation of [2 + 2] Cycloadducts[a]



[a](a) 110 °C, Tol, 2 days, 77%; (b) $TsOH.H_2O$, 40 °C, DCM, 12 h, 66%; (c) SiO_2, 25 °C, *n*-hexane, 3 h, quant; (d) KF, 0 °C, H_2O/*n*-hexane, 0.5 h, quant.

The aforementioned results show that the formation of 1*H*-indoles or indolenine is dependent on the C3 substituent of the indoline molecule (Scheme 3). When the substituent is

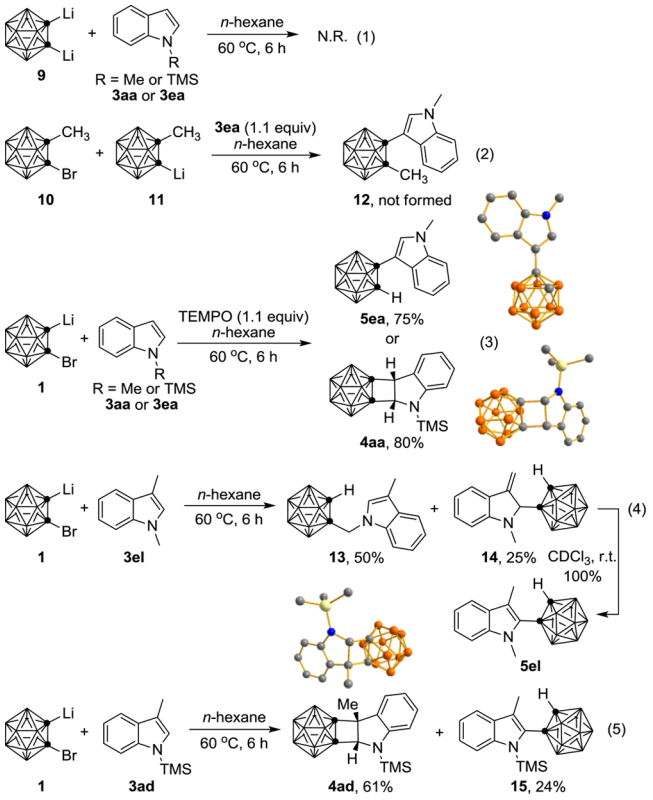
Scheme 3. Proposed Reaction Pathways for Desilylation of [2 + 2] Cycloadducts



hydrogen, carboranyl-1*H*-indole is produced through a ring-opening reaction followed by an intramolecular hydrogen transfer sequence. For C3-substituted indoline, desilylation affords the corresponding carboranyl-substituted indolenine as it cannot undergo rearomatization process. These results also indicate that the ring-opening or rearomatized product is favored when the electron density of the indole nitrogen is increased.

Mechanistic Study. To gain some insight into the reaction mechanism, several control experiments were conducted (Scheme 4). Neither the [2 + 2] cycloadduct **4aa** nor the insertion product **5ea** was detected from the reaction of 1,2-dilithio-*o*-carborane (**9**) with **3aa** or **3ea** (eq 1). Furthermore, no reaction occurred when **3ea** was added to a 1:1 molar ratio of 1-bromo-2-methyl-*o*-carborane (**10**) and 1-lithio-2-methyl-*o*-carborane (**11**) (eq 2). The above experiments may indicate the intermediacy of *o*-carboryne in these reactions. The desired product **4aa** or **5ea** was still obtained in 80% or 75% isolated yield in the presence of 1.1 equiv of a radical scavenger, 2,2,6,6-

Scheme 4. Control Experiments



tetramethylpiperidine-1-oxyl (TEMPO), which rules out the involvement of radical species (eq 3). When the C3 position of the indole derivative was blocked, for example, **3el**, the expected C2-carboranyl-substituted product **5el** was not initially observed in the crude reaction mixture. Instead, the formal sp^3 C−H insertion[22c] product **13** and ene reaction[21] product **14** were produced in 50% and 25% isolated yields. The latter (**14**) was then converted quantitatively to **5el** in $CDCl_3$ at room temperature after 6 h (eq 4).[24] These results not only indicate the involvement of *o*-carboryne intermediate in this reaction but also clarify that the C3 position of the indole ring is the initial reaction site for the formation of the formal C−H insertion product. On the other hand, the [2 + 2] cycloaddition was still the dominant pathway in the reaction of 1-TMS-3-methyl-1*H*-indole **3ad**, although minor ene product **15** was also observed (eq 5).

To determine the proton source of the formal C−H insertion reaction, a deuterium-labeled substrate **3ea-d$_1$** was subjected to the reaction (Scheme 5). Product **5ea-d$_1$** with 84% D incorporation at the cage C−H was obtained in 78% yield (eq 6). No deuterium-labeled product was observed when the reaction was either carried out in cyclohexane-d_{12} or quenched with D_2O (eqs 7 and 8).[24] These findings reveal that D (H) incorporated into the cage C−H comes from the indole substrate.

On the basis of the above experimental results, a plausible mechanism is proposed in Scheme 6. Elimination of LiBr from precursor **1** gives the reactive intermediate *o*-carboryne **2**. Electrophilic attack at the C3 position of *N*-protected indole **3** generates a zwitterionic intermediate **A**. **A** then undergoes either a proton shift to afford the formal insertion product **B** (path a) or an intramolecular nucleophilic addition to yield the [2 + 2] cycloaddition product **C** (path b). Pathway b is

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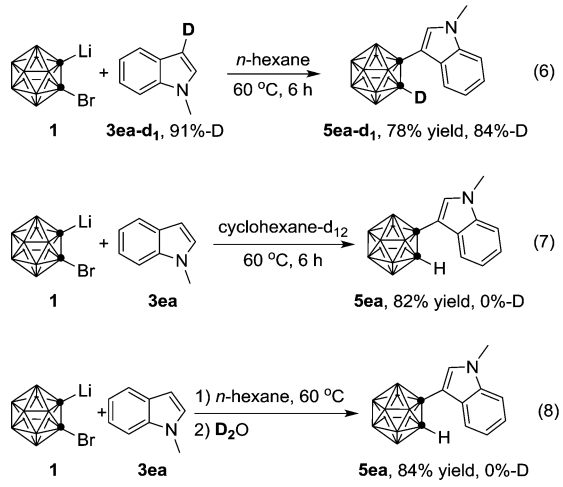
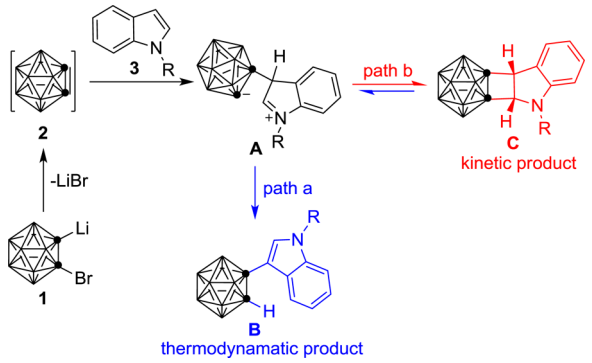
Scheme 5. Deuterium Experiments



Scheme 6. Proposed Reaction Pathways



reversible as evidenced by the thermal transformation of **4j** to **5j** (Scheme 2). The chemoselectivity of the reaction is dependent upon the nature of protecting group R. When R = alkyl groups, **B** is the sole product. When R = TMS group, **C** is the sole product. When R = aryl groups, both **B** and **C** are formed. Such **C**/**B** ratios increase if an electron-withdrawing substituent is introduced to the phenyl ring, which may be ascribed to the increased electrophilicity of C2 position in the intermediate **A**.[25]

CONCLUSIONS

This work demonstrates that *o*-carboryne can serve as a useful synthon for the incorporation of an *o*-carborane unit into heteroaromatic molecules. Reaction of *o*-carboryne with *N*-protected indoles goes two ways: dearomative [2 + 2] cycloaddition and formal C−H insertion reaction, dependent upon the nature of *N*-substituents, leading to the synthesis of a series of carborane-functionalized indoles and indolines in a controlled manner. For *N*-TMS indoles, only dearomative [2 + 2] cycloaddition products are isolated, while the formal C−H insertion species are the sole products for *N*-alkyl ones. On the other hand, both [2 + 2] cycloaddition products and formal C−H insertion products are isolated if *N*-substituents are aryls, in which the molar ratios of two products are determined by the electronic properties of the substituents on the phenyl ring. In general, electron-donating substituents on the N atom favor the formal C−H insertion reaction, whereas electron-withdrawing groups promote dearomative [2 + 2] cycloaddition. To account for theses experimental observations, a stepwise reaction mechanism is proposed.

It has been documented that indoles undergo [2 + 2] cycloaddition reaction under UV irradiation or in the presence of transition metals. However, there is no precedent for indoles to undergo [2 + 2] cycloaddition without UV irradiation or transition metals. Thus, this work represents the first example observed for indoles to have such [2 + 2] cycloaddition in the absence of transition metals or without light. The resultant carborane-functionalized heterocycles may find their applications in medicine[13,26] and materials science.[14,16,18b,27]

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, complete characterization data, and X-ray data in CIF format for **4aa, 4ab, 4ad, 4ag, 4am, 4h, 4j, 5ah, 5ea, 7c, 7da, 7f,** and **8**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b05426.

AUTHOR INFORMATION

Corresponding Author

*E-mail: zxie@cuhk.edu.hk

Notes

The authors declare no competing financial interest.

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