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Regioselective Insertion of Carborynes into Ethereal C−H Bond: Facile Synthesis of α-Carboranylated Ethers

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Supporting Information

ABSTRACT: Carborynes can exist in two resonance forms, bonding form vs biradical form. The biradical form can be readily generated via the elimination of LiI from 1-iodo-*n*-lithio-1,*n*-$C_2B_{10}H_{10}$ (n = 2, 7) under UV irradiation. They can undergo α-C−H bond insertion with aliphatic ethers, affording α-carboranylated ethers in excellent regioselectivity at room temperature. This serves as a new methodology for the generation of a series of functionalized carboranes bearing alkoxy units.

Selective radical cleavage of relatively unreactive C−H bonds has received considerable attention from the chemical community due to increasing interest in C−H bond functionalization.[1−4] Ethers are among the most attractive substrates for this purpose because of the susceptibility to hydrogen abstraction of their α-C−H bonds, which makes the regioselective chemical transformations possible.[2] *o*-Carboryne (1,2-dehydro-*o*-carborane) (**3a**), a very reactive intermediate reported first in 1990,[5] reacts readily with alkenes, dienes, alkynes, benzene or polycyclic aromatics in [2 + 2], [4 + 2] cycloaddition and ene-reaction patterns,[6] similar to that of benzyne.[7] It can be generated in situ from either 1-Br-2-Li-1,2-$C_2B_{10}H_{10}$[5] or 1-Me_3Si-2-[IPh(OAc)]-1,2-$C_2B_{10}H_{10}$.[8] Recently, we reported a more efficient precursor 1-I-2-Li-1,2-$C_2B_{10}H_{10}$ (**2a**), readily prepared from *o*-carborane (**1a**), for the production of **3a**.[9a,10] Our previous work showed that *o*-carboryne can formally insert into the C−C bond of aromatic rings bearing alkoxy groups to form cyclooctatetraenocarboranes **4** (Scheme 1).[10] However, the substrate anisoles were employed as solvent in the reactions. In the search for an appropriate solvent for such reactions, α-carboranylated ether **6aa** was unprecedentedly isolated in very high yield when the reaction was carried out in diethyl ether. It seems that *o*-carboryne favors insertion into the ethereal α-C−H bond rather than the C−O bond, in a different manner from that of benzyne (Scheme 1).[11] These new findings are reported in this communication.

Treatment of **2a** with anisole in diethyl ether at 60 °C overnight gave, after workup, only the unexpected C−H bond insertion product **6aa** as shown by ^{1}H NMR and GC−MS analyses. In the absence of anisole, the reaction also proceeded very well, affording **6aa** at 60 °C or even at rt in 80% isolated yield (Table 1, entries 1, 2). Surprisingly, when the reaction was performed in the dark, the consumption of **2a** in diethyl ether was dramatically suppressed and the reaction was incomplete in 24 h at rt or even 60 °C (Table 1, entries 3 and 4). To gain some insight into the reaction, a UV−visible absorption spectrum of the reaction solution was obtained.[12] It was found that the solution exhibited three major absorption bands: a very strong absorption near 230 nm, a strong absorption near 280 nm, and a mediate absorption near 350 nm, all of which were in UV region. Thus, it is rational to assume that a small amount of UV light emitted from the fluorescent lamps may play an important role in this process.[13] The higher yields obtained from the reactions under UV irradiation (365 or 254 nm) also supported this assumption (Table 1, entries 5 and 6).[14] It was noteworthy that 1-Br-2-Li-1,2-$C_2B_{10}H_{10}$ was stable for 24 h in Et_2O at room temperature under UV irradiation (Table 1, entry 7).[12]

Direct α-carboranylation of various ethers with *o*-carboryne **3a** was explored (Table 2). Similar to diethyl ether **5a**, symmetrical primary ethers **5b−d** also worked well with decreased yields from the Et to *n*-Bu group, which may be caused by the increasing steric hindrance of ethers (Table 2, entries 1−3). Such steric effect was also reflected on the regioselectivity in the reaction of unsymmetrical primary ether **5d**. It was noted that yields obtained from reactions under UV irradiation were higher than those under fluorescent light irradiation. For unsymmetrical *n*-butyl methyl ether **5e**, an evident preference for secondary C−H bond cleavage over methyl C−H bond cleavage was observed (Table 2, entry 5). It is consistent with the stability of the resulting ethereal radicals.[2a,d,15] Similar regioselectivity trend was also found in the reaction of DME **5f**. Notably, 1,2-disubstituted carboranes **8af** were isolated in 15% yield (Table 2, entry 6). In the case of methyl *tert*-butyl ether **5g**, UV irradiation was necessary to accelerate the reaction and to increase the yield (Table 2, entry 7). No productive results were obtained for ethers containing secondary alkyl groups (Table 2, entries 8 and 9). *o*-Carborane was predominantly regenerated when **2a** was completely consumed in these ethers. For cyclic ethers, the reaction was much dependent on the ring size due to steric effects (Table 2, entries 10−12).[15] For example, a good total yield was obtained for THF **5j** in both conditions, but only 23% and 5% of desired products were isolated, respectively, for THP **5k** and 1,4-dioxane **5l** even under UV irradiation. Similar to **5f**, 1,2-disubstituted carboranes **8aj** were also isolated with a *meso*:*rac* ratio of 44:56. In contrast, the precursor **2a** was stable at room temperature in anisole, the semiaromatic ether, under UV irradiation.

Cage *B*-substituents such as phenyl, halo, and methyl groups were well tolerated for this reaction (Table 3). Two

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Scheme 1. Reaction of Reactive Intermediates with Ethers

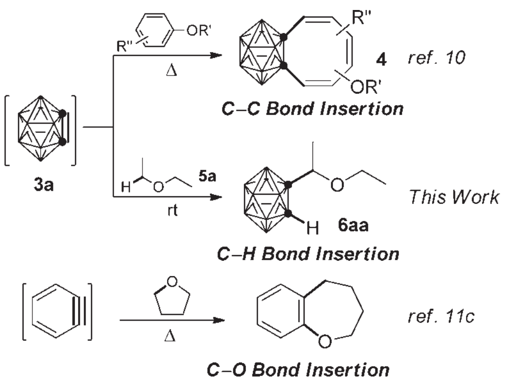
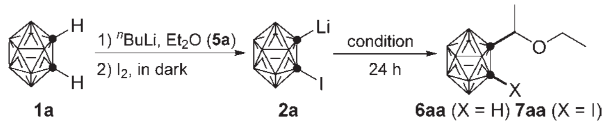


Table 1. Screening of Reaction Conditions

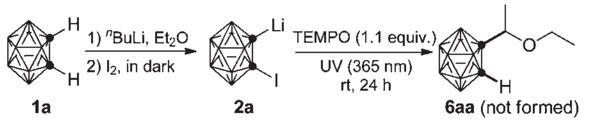


entry	condition	6aa (%)[a]
1	fluorescent lamp, 60 °C	80
2	fluorescent lamp, rt	80
3	in the dark, rt	12 (2)[b]
4	in the dark, 60 °C	35 (6)[b]
5	UV lamp (365 nm), rt	85
6	UV lamp (254 nm), rt	85
7[c]	UV lamp (365 nm), rt	N. R.

[a] Isolated yield. Yield in parentheses refers to **7aa**. [b] **2a** was not completely consumed. [c] Replacement of **2a** by its bromo analogue.

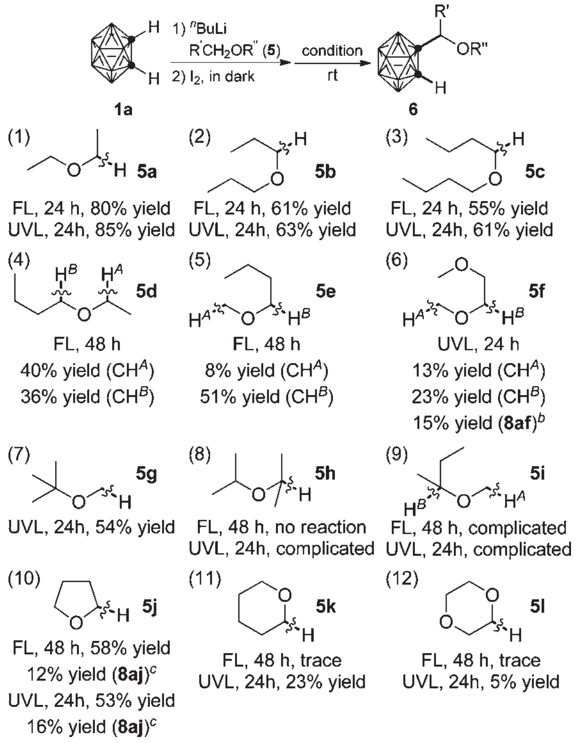
diastereoisomers were formed in a 1:1 ratio for 3-substituted carboranes (entries 1–2). It is noted that electronic factor plays an evident role in the regioselectivity for 9-substituted carboranes in view of the results from entries 3 and 4.[16] Electronic effects also show dramatic influence on the product yields. For example, 4,5,7,8,9,10,11,12-octamethyl carboranylated ether **6ha** was isolated in as low as 35% yield, while 9,12-dimethyl carboranylated ether **6ga** was obtained in an excellent yield.

To gain some insight into the reaction pathway, a radical scavenger, 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), was added to the reaction system (eq 1).

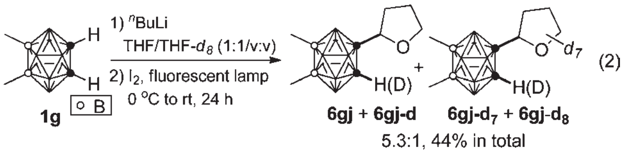


Not only was the formation of the desired product **6aa** completely suppressed, but also the iodo anion **2a** itself was surprisingly stabilized by TEMPO. This result suggested that a radical process was possibly involved in the initial step of the reaction. The aforementioned positive correlation between the nucleophilicity of the cage carbon and the observed regioselectivity (Table 3, entries 3 and 4) is in agreement with that found in common nucleophilic reactions. Meanwhile, the intermolecular primary kinetic isotope effect (KIE) experiments were also carried out under standard conditions (eq 2).[12]

Table 2. Reaction of Ethers with *o*-Carboryne[a]



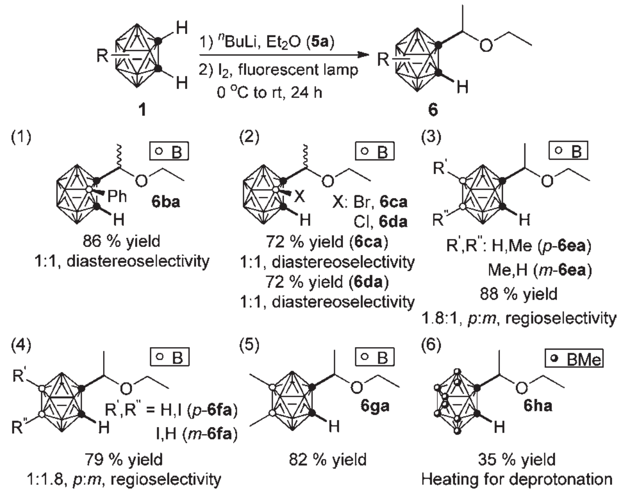
[a] FL stands for fluorescent lamp; UVL stands for UV lamp (365 nm). [b] For yield of each isomer, see SI. [c] *meso*:*rac* = 44:56.



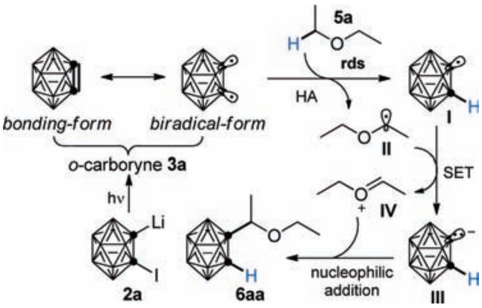
The results showed a k_H/k_D value of 5.3. Such a significant isotope effect revealed that the C–H bond cleavage was the rate-determining step.[2e,f] Competitive experiments in a mixed solvent of diethyl ether and toluene (1:1 in v/v) afforded the C–H bond insertion product **6aa** in 81% yield, and no [4 + 2] cycloaddition products were detected.[12] This result indicated that *o*-carboryne **3a** generated herein might not exist as the bonding form but rather as a biradical form, which prefers hydrogen abstraction instead of cycloaddition (Scheme 2).

On the basis of the above experimental results, a plausible mechanism is proposed in Scheme 2. UV irradiation promotes the elimination of LiI from **2a** giving the reactive intermediate *o*-carboryne **3a** that is best described as a resonance hybrid of both bonding and biradical forms. Such intermediate undergoes hydrogen abstraction (HA) with **5a** to generate radicals **I** and **II**, which is the rate-determining step. A following fast single-electron transfer (SET) between **I** and **II** produces carboranyl anion **III** and electrophile **IV**. Finally, the nucleophilic addition of **III** to **IV** yields the desired insertion product **6aa**.

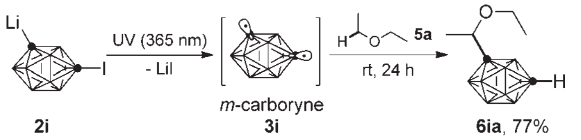
Table 3. Effects of Cage B-Substituents on α-Carboranylation



Scheme 2. Possible Pathway for Direct α-Carboranylation of Ethers



Scheme 3. Reaction of *m*-Carboryne 3i with Diethyl Ether



According to the proposed mechanism, we wondered if the unknown species *m*-carboryne **3i** could be generated in a similar manner (Scheme 3). A diethyl ether solution of **2i** under UV irradiation gave the α-carboranylation product **6ia** in 77% isolated yield (Scheme 3). It seems that both intra- and intermolecular elimination of LiI from precursors **2** are feasible. The former is easier than the latter, since **2i** is only partially consumed in 24 h under fluorescent light irradiation.[12]

In summary, this work suggests that carborynes can exist in two resonance forms, bonding form vs biradical form. Their reactivity patterns are dependent upon the nature of the substrates. They react with aromatics in the bonding form to give [4 + 2] and [2 + 2] cycloaddition products.[6,10] On the other hand, they undergo α-C—H bond insertion with aliphatic ethers in the biradical form, affording α-carboranylated ethers with excellent regioselectivity. This serves as a new methodology for the generation of a series of functionalized carboranes bearing alkoxy units.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Detailed experimental procedures, complete characterization data, and X-ray data in CIF format for (*R*,*R*)-**6ba**, *m*-**6fa**, and *meso*-**8aj**. This material is available free of charge via the Internet at http://pubs.acs.org.

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