

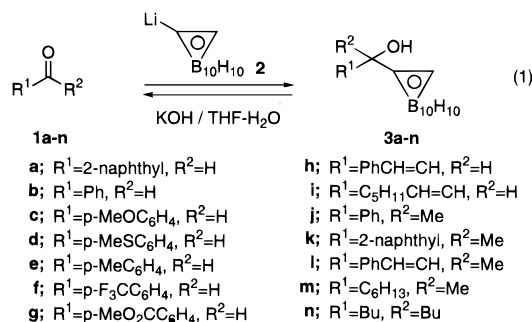
o-Carborane as a Novel Protective Group for Aldehydes and Ketones

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It is widely accepted that acetals and ketals are very useful as protective groups for aldehydes and ketones.^{1,2} The protective groups are readily cleaved by acid hydrolysis and Lewis acid coordination. The latter property is a drawback of these protective groups in the case of a Lewis acid-mediated reaction.³ We wish to report that the functionalized *o*-carboranyl methanols **3**, which can be prepared easily by the addition of lithiocarborane **2** to carbonyl compounds **1**,⁴ are very stable under aqueous protic acid and Lewis acid conditions and are readily cleaved under basic conditions to produce the corresponding carbonyl compounds **1** and *o*-carborane (eq 1).



Conditions used to cleave *o*-carborane from 1-carboranyl-2-naphthylmethanol **3a** are shown in Table 1. We examined several bases, such as NaOMe, pyridine, *n*-BuLi, and *t*-BuOK, but we found that KOH was the most suitable for this cleavage. The use of excess (3.0 equiv) and 1.1 equiv of KOH in THF gave **1** in fair to good yields (entries 1 and 2). It was found that even a catalytic amount of KOH was enough to induce the cleavage of *o*-carborane (entry 3). Small amounts of 2-naphthylmethanol were obtained as byproduct in entries 1–3. However, the presence of small amounts of water in the THF prevented formation of the byproduct (entries 4 and 5), and the best result was obtained by using 0.15 equiv of KOH in THF/H₂O (100/1) as a solvent (entry 4). Under these conditions, *o*-carborane was recovered in high yields (76% isolated yield in entry 4).⁵ Accordingly, recycling of *o*-carborane is possible.⁶

Having established optimum conditions for the decarboronylation of **3a**, we next applied this procedure to

Table 1. The Decarboronylation of 1-Carboranyl-2-naphthylmethanol **3a Promoted by KOH at Room Temperature**

entry	amount (equiv) of KOH	solvent	yield ^a of 1 (%)
1	3.0	THF	38 ^b
2	1.1	THF	58 ^b
3	0.15	THF	57 ^b
4	0.15	THF/H ₂ O (100/1)	92
5	0.15	THF/H ₂ O (10/1)	60

^a Yields were determined by GC analysis using hexadecane as an internal standard. ^b Reduced product (2-naphthylmethanol) was also produced in 8% (entry 1), 17% (entry 2), and 14% (entry 3) yield, respectively.

Table 2. The Decarboronylation of Various *o*-Carboranyl methanols **3 Promoted by a Catalytic Amount of KOH in THF/H₂O (100/1)**

entry	aldehyde and ketone 1	carboranyl methanol 3	time (d)	yield ^a (%) (isolated yield) ^b
1	1a	3a	2	92 ^c (85)
2	1b	3b	3	84 ^c
3	1c	3c	1	88
4	1d	3d	1	74
5	1e	3e	3	70
6	1f	3f	2	75 ^c
7	1g	3g	2	74
8	1h	3h	2	86 (74)
9	1i	3i	2	62
10	1j	3j	2	78
11	1k	3k	3	83 (66)
12	1l	3l	2	93
13	1m	3m	2	92 ^d
14	1n	3n	2	97

^a Yields were determined by ¹H NMR using *p*-xylene as an internal standard. ^b In some cases, the products were isolated by using silica gel column chromatography and the isolated yields are shown in parenthesis. ^c Yields were determined by GC analysis using hexadecane as an internal standard. ^d NaOH (0.15 equiv) was used instead of KOH.

various carboranyl methanols **3b–n** (Table 2). The decarboronylation of **3b** proceeded smoothly to give benzaldehyde **1b** in 84% yield (entry 2). Other aromatic aldehyde derivatives **3c–g** bearing either an electron-donating or an electron-withdrawing group gave the corresponding aldehydes in good yields (entries 3–7). Not only aromatic aldehydes but also α,β -unsaturated aldehydes **1h** and **1i** were obtained in good to high yields from the corresponding carboranyl methanols **3h** and **3i** (entries 8 and 9). In the case of di-substituted carboranyl methanols **3j–n**, the cleavage reaction proceeded smoothly to give the corresponding ketones **1j–n** in good to high yields (entries 10–14). The carboranyl methanols **3** were very stable under strong acid or Lewis acid conditions.⁷

A representative procedure is as follows. **A. Formation (1a → 3a).** To a solution of *o*-carborane (720 mg, 5

(1) *Protective Groups in Organic Synthesis*; Greene, T. W., Wuts, P. G. M., Ed.; John Wiley: New York, 1991; pp 175–223.

(2) Stork, G.; Maldonado, L. *J. Am. Chem. Soc.* **1971**, *93*, 5286. Evans, D. A.; Hoffman, J. M.; Truesdale, L. K. *J. Am. Chem. Soc.* **1973**, *95*, 5822. Hiyama, T.; Oishi, H.; Saimoto, H. *Tetrahedron Lett.* **1985**, *26*, 2459. Also see ref 1.

(3) On the other hand, the latter property can become an advantage of the protecting group. Very high asymmetric induction is accomplished by the Lewis acid-mediated reactions of chiral acetals: Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 817. Johnson, W. S.; Elliott, R.; Elliott, D. *J. Am. Chem. Soc.* **1983**, *105*, 2904. Johnson, W. S.; Edington, C.; Elliott, J. D.; Silverman, I. R. *J. Am. Chem. Soc.* **1984**, *106*, 7588. Yamamoto, Y.; Nishii, S.; Yamada, J. *J. Am. Chem. Soc.* **1986**, *108*, 7116. Also see the recent review: *Comprehensive Organic Synthesis*; Schreiber, S. L., Ed.; Pergamon Press: Oxford, 1991; Vol. 1, pp 325–354.

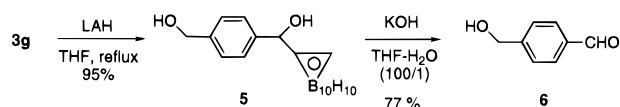
(4) It was reported that generation of monolithiocarborane **2** by treating *o*-carborane with *n*-BuLi was accompanied by dilithiocarborane formation due to the disproportionation reaction of **2** (see Gome, F. A.; Johnson, S. E.; Hawthorne, M. F. *J. Am. Chem. Soc.* **1991**, *113*, 5915). However, we have found that the redistribution reaction can be avoided by carrying out the lithiation of *o*-carborane under controlled conditions (see a representative example in text).

(5) *o*-Carborane (*closo*) is converted to *nido-*o**-carborane by treatment with bases. However, under the cleavage conditions, the *closo* framework was stable to KOH.

(6) Other attractive points of this protective group are that protected aldehydes and ketones **3** are readily crystallized and stable to air, moisture, and acids.

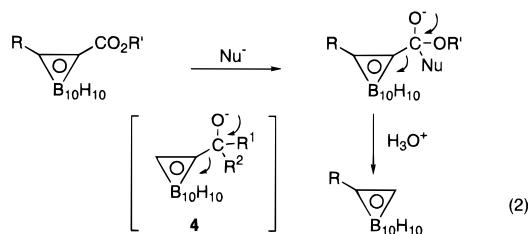
(7) When benzaldehyde dimethyl acetal was treated with TiCl₄ (2 equiv) in dichloromethane, benzaldehyde **1b** was obtained in 82% yield. However, treatment of **3b** with aqueous HCl (1 N) or TiCl₄ (2 equiv) for 2 days gave no benzaldehyde, but **3b** was recovered quantitatively.

Scheme 1



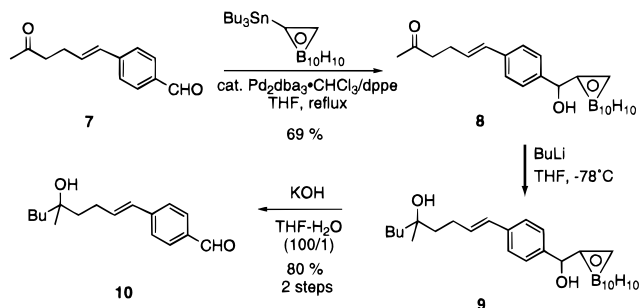
mmol) in dry THF (50 mL) at -78°C was added *n*-BuLi (3.1 mL, 1.6 M in hexane) dropwise with stirring. The mixture was stirred for 30 min at -78°C , and **1a** (859 mg, 5.5 mmol) was added. The solution was stirred for 1 h and then warmed to rt. After being quenched with water, the mixture was extracted with ether and dried over anhydrous MgSO₄. Evaporation of the solvents followed by purification using silica gel column chromatography (hexane:ethyl acetate = 5:1) afforded **3a** (1.29 g, 4.3 mmol, 86%).⁸ In no case was disubstituted carborane obtained. The use of dilute solutions of lithium carborane (~ 0.1 M) is essential to obtain selectively the monosubstituted carborane derivatives. Furthermore, in the addition of **2** to aldehyde **1g**, carboranymethanol **3g** was obtained chemoselectively in 95% yield under the same conditions (entry 7). **B. Cleavage (3a \rightarrow 1a).** To a THF/H₂O (100/1, 9 mL) solution of **3a** (274 mg, 0.91 mmol) was added KOH (7.7 mg, 0.136 mmol, 0.15 equiv) at rt and the mixture was stirred for 2 days. The reaction was quenched with NH₄Cl (aq). The mixture was extracted with ether, dried over anhydrous magnesium sulfate, and concentrated. Purification by silica gel column chromatography with hexane/ethyl acetate (10:1) gave the corresponding aldehyde **1a** (121 mg, 0.775 mmol, 85%, 92% by GC) first and then *o*-carborane (100 mg, 0.69 mmol, 76%).

It is known that decarboxylation of *o*-carboranyl carboxylates is accomplished by sodium ethoxide,⁹ *n*-butyllithium,¹⁰ or potassium hydroxide,¹¹ giving the parent *o*-carboranes (eq 2).¹² In the present reaction, an ionic species **4** generated by treatment of **3** with KOH would undergo a facile cleavage reaction, since *o*-carborane is a reasonably good leaving group (as shown in eq 2).

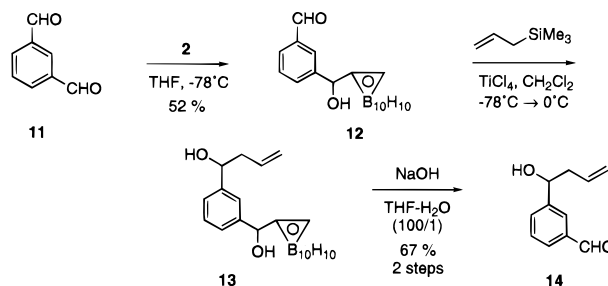


Next, we examined representative reactions of bifunctional molecules to demonstrate the synthetic utility of *o*-carborane as a protective group. The reduction of **3g** with lithium aluminum hydride in THF under reflux gave diol **5** in 95% yield (Scheme 1). Removal of *o*-

Scheme 2



Scheme 3



carborane from **5** proceeded very smoothly under the usual reaction conditions, giving the corresponding aldehyde **6**, in which the ester group of **1g** was reduced chemoselectively to the alcohol, in 77% yield.

Furthermore, chemoselective alkylation of a ketone group in the presence of an aldehyde was examined using bifunctional molecule **7**¹³ (Scheme 2). The chemoselective addition of *o*-carborane to the aldehyde group **7** was accomplished by the palladium-catalyzed reaction developed by our laboratory;¹⁴ the reaction of **7** with *o*-carboranyltributylstannane in the presence of a catalytic amount of Pd₂dba₃·CHCl₃ (10 mol %)/dppe (20 mol %) in THF under reflux gave the adduct **8** in 69% yield. The reaction of ketone **8** with BuLi (2 equiv) followed by the decarboranylation of **9** proceeded very smoothly, giving the corresponding aldehyde **10** in 80% yield in two steps from **8**.

The *o*-carborane protective group for aldehydes was also stable to Lewis acid-promoted allylation (Scheme 3). The TiCl₄-mediated reaction of allyltrimethylsilane with aldehyde **12**, which was prepared by the selective monoaddition of **2** to **11** (4 equiv), gave the homoallylic alcohol **13**. The decarboranylation of crude product **13** proceeded smoothly by treatment with NaOH (0.15 equiv) in THF-H₂O (100/1), giving the corresponding aldehyde **14** in 67% yield in two steps from **12**. In this case, the use of NaOH was more effective for the cleavage reaction than that of KOH.

Supporting Information Available: Full spectroscopic and analytical characterization of all new compounds (6 pages).

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(8) The ¹H NMR spectral data of **3a** are as follows: (CDCl₃) δ 7.87 (m, 3H), 7.78 (s, 1H), 7.54 (m, 2H), 7.45 (dd, *J* = 9.0, 2.0 Hz, 1H), 5.44 (d, *J* = 3.5 Hz, 1H), 3.84 (s, 1H), 2.72 (d, *J* = 3.5 Hz, 1H).

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(11) Zakharkin, L. I.; Chapovskii, Y. A.; Brattsev, V. A.; Stanko, V. I. *Zh. Obshch. Khim.* **1966**, 36, 878.

(12) *Carboranes* Grimes, R. N., Ed.; Academic Press: New York, 1970; pp 82–115.

(13) The bifunctional molecule **11** was synthesized via Heck reaction of *p*-bromobenzaldehyde and 5-hexen-2-one, which was prepared by the literature procedure: Buntin, S. A.; Heck, R. F. *Org. Synth.* **1993**, 61, 82.

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