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Simple, High-Yield Methods for the Synthesis of Aldehydes Directly from *o*-, *m*-, and *p*-Carborane and Their Further Conversions

Paola Dozzo, Ramesh A. Kasar,† and Stephen B. Kahl*

Department of Pharmaceutical Chemistry, University of California, San Francisco, San Francisco, California 94143-0446

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Aldehydes have long served as important building blocks for synthetic chemists, and carboranyl aldehydes are no exception. Recent literature reports, for example, illustrate their application as intermediates in biomedicine, materials science, and basic organic chemistry. We report here new methods for the single-step preparation of *C*-monoformyl and *C*,*C*-diformyl derivatives directly from *o*-, *m*-, and *p*-carborane, as well as improved synthetic routes to homologated carboranyl aldehydes. Additionally, reductive amination is used to transform these aldehydes into a series of 2° amines of α-amino acid esters.

Introduction

Aldehydes are among the most useful synthons in the chemist's toolbox, and new, high-yield methods for their synthesis are always welcome. A review of the literature demonstrates that carboranyl aldehydes have been versatile building blocks in the synthesis of compounds with applications in biomedicine, materials science, and basic organic chemistry of carboranes. However, there have been relatively few convenient synthetic methods for carboranyl aldehydes. The most versatile method for preparing the *C*-monoformyl derivatives is Rosenmund reduction of the acid chlorides, which unfortunately requires prior derivatization of the carborane cage and generally proceeds with poor (<25%) overall yield.[1,2] Ozonolysis of vinyl-*o*-carborane[3,4] and Swern oxidation of (hydroxymethyl)-*o*- and *m*-carborane[5] have also been used for this purpose, with similar results and drawbacks. There are no reported methods for the direct conversion the *o*-, *m*-, and *p*-$B_{10}C_2$ isomeric carboranes directly into their *C*-formyl derivatives. Similarly, *C*,*C*-diformyl-*m*-carborane has been prepared by Rosenmund reduction of the corresponding diacid chloride[6] and by Swern oxidation of the bis(hydroxymethyl) compound,[5] both of which require several steps and lead to reduced overall yields. Neither the diformyl *o*- nor *p*-carboranes have previously been reported. Preparations of homologous aldehydes, such as *o*-carboranylethanal and *o*-carboranylpropenal, have been reported using lithiation, followed by reaction of protected bromoaldehydes,[7,8] oxidation of 2-carboranylethanol,[9] and acetylene/decaborane reactions,[10] but in each case with poor overall yields. Because we were interested in several homologous and isomeric carboranyl aldehydes in our preparation of compounds for boron neutron capture therapy (BNCT) and matrix metalloprotease (MMP) inhibitors, we sought to develop new methodologies to more conveniently provide these starting materials. We report herein a general, high-yield method for the preparation of the three isomeric *C*-monoformyl compounds, which is also applicable to the synthesis of the *C*,*C*-diformyl derivatives of *m*- and *p*-carborane. We also report the synthesis of two aldehyde homologues of *C*-formyl-*o*-carborane. Last, we illustrate the chemistries of these homologous aldehydes by reductive amination of several into their amino acid amine analogues.

* To whom correspondence should be addressed. E-mail: sbkahl@itsa.ucsf.edu. Fax: 415-476-0688.

† Current address: ICOS, 2023 120th Avenue NE, Bellevue, WA 98005.

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Experimental Section

o-, *m*-, and *p*-carborane were purchased from Katchem Ltd. (Prague, Czech Republic) and sublimed prior to use. Other starting materials were purchased from Aldrich Chemical Co. and were not generally purified prior to use. Solvents were purchased from Fisher Chemical Co. and were dried prior to use using standard techniques. All reactions were followed by thin-layer chromatography carried out on silica gel 60 F_{254} plates (EM Science). Reported isolated yields are unoptimized. For purity tests of all compounds, a single spot (visualized by UV light and palladium chloride staining) was obtained. Silica gel 60 GEDURAN (40−63 μM) was used for flash chromatographic separation. Solutions were dried over Na_2SO_4 or $MgSO_4$ and concentrated using a Büchi rotary evaporator under house vacuum. Melting points (Pyrex capillary) were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a 400-MHz Varian Inova spectrometer and are reported in parts per million (ppm) relative to tetramethylsilane (1%) as an internal standard. Fourier transform infrared spectra were recorded on a Nicolet 5DX spectrometer using KBr pellets unless otherwise specified. Mass spectra were obtained on PE-Biosystems Mariner and VG70 instruments. Elemental analyses were performed by the Microanalytical Laboratory, Department of Chemistry, University of California, Berkeley, Berkeley, CA. Reported yields are isolated yields and are unoptimized.

***C*-Formyl-*o*-carborane (1).** To a stirring solution of *o*-carborane (1.00 g, 6.94 mmol) in diethyl ether (95 mL) at −78 °C was added *n*-BuLi (4.76 mL, 7.7 mmol, 1.6 M in hexanes) over 20 min, and stirring was continued for another 2.5 h at the same temperature. Methyl formate (1.5 mL, excess) was added to the reaction mixture, and stirring was continued for an additional 2 h. The reaction was quenched with dilute HCl (4%, 20 mL) at −78 °C and warmed to room temperature. Excess ether was removed on a rotary evaporator at room temperature. Water (30 mL) was added to the reaction product. The desired product was extracted from the resulting oil with hexanes (4 × 150 mL), and the combined extracts were dried and concentrated. Purification of the crude product on silica gel using hexane afforded the desired *C*-formyl-*o*-carborane **1** (1.130 g, 6.590 mmol, 95%): mp 207−209 °C (sealed tube) (lit.[1] mp 208−209 °C); IR (KBr, cm^{-1}) 3067, 2598, 1740; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.20−3.60 (bm, 10H), 4.05 (s, 1H), 9.27 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 54.1, 74.4, 184.1; LRMS (*m*/*z*) 172.2, 142.2, 124.1, and 112.1; HRMS calcd for $C_3H_{11}{}^{10}B_2{}^{11}B_8O$ ([M−H]$^+$) 171.1813, found 171.1810.

***C*-Formyl-*m*-carborane (2).** This isomer was prepared similarly to **1** in 90% yield: mp 209−210 °C (sealed tube) (lit.[1] mp 213-214 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20−3.70 (bm, 10H), 3.04 (s, 1H), 9.02 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.6, 79.5, 186.6; HRMS calcd for $C_3H_{11}{}^{10}B_2{}^{11}B_8O$ ([M−H]$^+$) 171.1813, found 171.1814.

C-Formyl-*p*-carborane (3). This isomer was prepared similarly to **1** in 60% yield: mp 193−200 °C (sealed tube) (lit.[2] mp 208.5−210 °C); IR (NaCl plate, cm^{-1}) 3118, 2612, 1736; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45−2.80 (bm, 10H), 2.86 (s, 1H), 8.71 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 64.1, 84.0, 185.9; HRMS calcd for $C_3H_{12}{}^{10}B_2{}^{11}B_8O$ (M$^+$) 172.1891, found 172.1893.

***C,C*-Diformyl-*p*-carborane (4).** To a stirring solution of *p*-carborane (0.170 g, 1.18 mmol) in Et_2O (10 mL) at 0 °C was slowly added *n*-BuLi (1.66 mL, 2.65 mmol). The reaction was stirred for 30 min at 0 °C, followed by 45 min at room temperature. The reaction mixture was cooled to −40 °C with dry ice, and methyl formate (0.370 mL, 6.03 mmol) was slowly added. The reaction was allowed to warm to room temperature and stirred overnight. It was then cooled to 0 °C and quenched with dilute HCl (3 mL). Excess ether was removed under reduced pressure, and the aqueous layer was extracted with hexanes (3 × 10 mL). The combined organic layers were dried over $MgSO_4$. Filtration and evaporation gave a crude product, which was purified by flash chromatography (silica gel/10−25% Et_2O in hexanes) to yield the desired dialdehyde **4** as a white solid (0.106 g, 0.533 mmol, 45%): mp 75−78 °C; IR (NaCl plate, cm^{-1}) 2840, 2614, 1734; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52−3.38 (bm, 10H), 8.75 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 84.5, 185.4; HRMS calcd for $C_4H_{12}{}^{10}B_2{}^{11}B_8O_2$ (M$^+$) 200.1840, found 200.1834. Anal. Calcd for $C_4H_{12}B_{10}O_2$: C, 23.99; H, 6.04. Found: C, 23.79; H, 6.18.

***C,C*-Diformyl-*m*-carborane (5).** This isomer was prepared similarly to **4** in 51% yield: mp 158 °C (lit. mp 162 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90−3.95 (bm, 10H), 9.02 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 78.6, 184.7; HRMS calcd for $C_4H_{12}{}^{10}B_2{}^{11}B_8O_2$ (M$^+$) 200.1840, found 200.1844.

***o*-Carborane Dimethoxy Acetal (7).** To a stirred solution of *o*-carborane (0.300 g, 2.08 mmol) in dry diethyl ether (10 mL) at room temperature was slowly added *n*-BuLi (1.6 M in hexanes, 3.00 mL, 4.78 mmol). The reaction mixture was stirred for 1 h after the addition was complete and then cooled to −78 °C, and excess methyl formate was added (0.31 mL, 4.99 mmol). After 2 h, the reaction was quenched with dilute aqueous HCl (10 mL). Excess ether was removed under reduced pressure, the aqueous layer was extracted with hexanes (3 × 10 mL), and the combined organic layers were dried over $MgSO_4$. Filtration and evaporation gave the crude product containing **6**, which was not purified further: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.50−3.00 (bm, 10H), 3.46 (s, 3H), 3.80 (s, 1H), 5.27 (m, 1H), 5.70 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 57.8, 79.1, 79.9, 97.5, 103.7; HRMS calcd for $C_5H_{15}{}^{10}B_2{}^{11}B_8O_3$ ([M−H]$^+$) 231.2024, found 231.2031.

To a stirred solution of acetal **6** in methanol (5 mL) was added an aqueous solution of TsOH (0.440 g, 2.34 mmol in 2 mL of H_2O), and the mixture was heated to reflux for 24 h. Excess solvent was removed under pressure. The crude product was dissolved in EtOAc, washed with saturated aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. Filtration and evaporation gave a crude material that was purified by flash chromatography [9:1 silica gel−hexanes/ethyl acetate and then 4:1 (v/v)] to yield the dimethoxy acetal **7** (0.160 g, 0.680 mmol, 32% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20−3.20 (bm, 10H), 3.45 (s, 6H), 5.21 (d, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 57.4, 78.7, 103.6; HRMS calcd for $C_6H_{17}{}^{10}B_2{}^{11}B_8O_3$ ([M−H]$^+$) 245.2181, found 245.2190.

2-(*o*-Carboranyl)ethanal (9). *o*-Carborane (1.00 g, 6.94 mmol) was dissolved in ether (950 mL) at room temperature in a dry 1-L round-bottomed flask equipped with a magnetic stir bar and cooled to −78 °C under an argon atmosphere. To the stirred solution of *o*-carborane was slowly added *n*-BuLi (5.0 mL, 8.0 mmol, 1.6 M in hexanes) over 20 min, and stirring was continued for another 20 min at the same temperature. Methyl bromoacetaldehyde dimethyl acetal (1.20 g, 7.00 mmol) in ether (10 mL) was added to the reaction mixture, and stirring was continued for an additional 48 h at room temperature. Excess ether was removed under reduced pressure. The crude product was extracted with ethyl acetate (2 × 200 mL), dried over $MgSO_4$, and concentrated. The crude product **8** was taken to the deprotection step without further purification. It was dissolved in 80% formic acid and stirred overnight. Excess formic acid was removed in vacuo, and the crude aldehyde product was purified on neutral alumina using hexane elution to afford aldehyde **9** (0.98 g, 5.27 mmol, 76%): mp 92−94 °C (lit.[4] mp 93−95 °C); IR (KBr, cm^{-1}) 3062, 2592, 1730; ^{1}H NMR ($CDCl_3$,

400 MHz) 1.25−3.10 (bm, 10H), 3.26 (d, 2H), 4.13 (s, 1H), 9.56 (t, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 48.2, 54.4, 60.0, 194.3; HRMS calcd for $C_4H_{13}{}^{10}B_2{}^{11}B_8O$ ($[M-H]^+$) 185.1969, found 185.1973.

3-(*o*-Carboranyl)propenal (11). *o*-Carborane (1.00 g, 6.94 mmol) was dissolved in ether (950 mL) at room temperature in a dry 1-L round-bottomed flask equipped with a magnetic stir bar and cooled to −78 °C under an argon atmosphere. To the stirred solution of *o*-carborane was slowly added *n*-BuLi (5.0 mL, 8.0 mmol, 1.6 M in hexanes) over 20 min, and stirring was continued for another 20 min at the same temperature. 2-(2-bromoethyl)-1,3-dioxolane (1.30 g, 7.10 mmol) in ether (1.0 mL) was added to the reaction mixture, and stirring was continued for an additional 48 h at room temperature. Excess ether was removed under reduced pressure, and the crude product was purified on silica gel using hexane to give the intermediate protected acetal **10** (1.15 g, 4.71 mmol, 68% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20−3.20 (bm, 10H), 1.79−1.84 (m, 2H), 2.32 (t, 2H), 3.56 (s, 1H), 3.81 (t, 2H), 3.89 (t, 2H), 4.79 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.0, 33.3, 61.6, 65.1, 65.4, 74.9, 102.5; HRMS calcd for $C_7H_{19}{}^{10}B_2{}^{11}B_8O_2$ ($[M-H]^+$) 243.2388, found 243.2384.

To provide aldehyde **11**, an aqueous solution of *p*-TsOH (0.06 g, 0.33 mmol in 1 mL of H_2O) was added to a stirred solution of acetal **10** (0.07 g, 0.27 mmol) in acetone (4 mL), and the reaction mixture was refluxed for 2 days. The excess solvent was removed under pressure. Aqueous $NaHCO_3$ was then added, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. Filtration and evaporation gave a crude product, which was purified by flash chromatography (silica gel/10−20% ethyl acetate in hexanes) to yield the desired aldehyde **11** (0.040 g, 0.18 mmol, 68%): mp 80−83 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20−3.40 (bm, 10H), 2.52−2.55 (m, 2H), 2.71−2.75 (m, 2H), 3.67 (s, 1H), 9.71 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.2, 43.2, 61.9, 65.3, 198.9; HRMS calcd for $C_5H_{15}{}^{10}B_2{}^{11}B_8O$ ($[M-H]^+$) 199.2126, found 199.2126.

***o*-Carboranylenamine of D-Leucine Methyl Ester (12). 1** (1.50 g, 8.71 mmol) and D-leucine methyl ester hydrochloride (1.40 g, 9.60 mmol) in dry toluene (150 mL) were refluxed with azeotropic distillation of water for 18 h. The excess toluene was removed under reduced pressure. The product was dissolved in hexane and washed with water, dried over $MgSO_4$, and concentrated to give enamine **12** (2.35 g, 7.864 mmol, 90%): IR (KBr, cm^{-1}) 3067, 2578, 1740; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.84 (d, 3H), 0.92 (d, 3H), 1.40 (m, 1H), 1.20−3.20 (bm, 10H), 1.69 (m, 2H), 3.71 (s, 3H), 3.99 (t, 1H), 4.33 (s, 1H), 7.62 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 23.2, 24.6, 41.6, 52.5, 56.5, 69.0, 72.1, 155.9, 171.3; HRMS calcd for $C_{10}H_{24}{}^{10}B_2{}^{11}B_8NO_2$ (M^+) 298.2810, found 298.2811.

***o*-Carboranylmethylamine of D-Leucine Methyl Ester (13).** Sodium cyanoborohydride (400 mg, 6.36 mmol) was added to a stirred solution of enamine **12** (0.700 g, 2.31 mmol) in a THF/acetic acid mixture (1:1, 15 mL) at 0 °C. The mixture was stirred for 6 h at room temperature. Excess solvent was removed under reduced pressure. Water (50 mL) was added to the crude product and the mixture extracted with CH_2Cl_2 (4 × 50 mL). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The product was purified on a silica gel column and eluted with CH_2Cl_2 to afford amine **13** (0.510, 1.699 mmol, 73%): IR (KBr, cm^{-1}) 3070, 2589, 1733; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.90 (d, 3H), 0.94 (d, 3H), 1.50 (m, 2H), 1.65 (m, 1H), 1.20−3.10 (bm 10H), 2.95 (d, 1H), 3.20 (dd, 1H), 3.45 (d, 1H), 3.73 (s, 3H), 4.15 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.7, 22.8, 24.8, 42.4, 52.0, 52.4, 57.6, 60.5, 74.9, 175.3; HRMS calcd for $C_{10}H_{27}{}^{10}B_2{}^{11}B_8NO_2$ (M^+) 301.3045, found 301.3047.

***m*-Carboranylenamine of D-Leucine Methyl Ester (14).** This compound was prepared similarly to **12** in 40% yield from aldehyde **2**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.73 (d, 3 H), 0.83 (d, 3 H), 1.35 (m, 1 H), 1.61−1.68 (m, 2 H), 1.12−3.17 (bm, 10H), 2.97 (s, 1 H), 3.62 (s, 3 H), 3.78−3.83 (m, 1 H), 7.29 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 23.2, 24.5, 41.4, 52.4, 55.5, 69.9, 75.2, 157.6, 171.7; HRMS calcd for $C_{10}H_{24}{}^{10}B_2{}^{11}B_8NO_2$ ($[M-H]^+$) 298.2810, found 298.2824.

***m*-Carboranylmethylamine of D-Leucine Methyl Ester (15).** Amine **15** was prepared from enamine **14** (61% yield) in a fashion similar to that of **13**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (d, 3H), 0.86 (d, 3H), 1.38−1.34 (m, 2H), 1.45 (bs, 1H), 1.74 (m, 1H), 1.60−3.00 (bm, 10H), 2.85 (s, 1H), 3.04 (d, 1H), 3.13 (t, 1H), 3.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.1, 23.0, 24.9, 42.6, 51.9, 52.6, 54.7, 60.2, 60.5, 175.9; HRMS calcd for $C_{10}H_{27}{}^{10}B_2{}^{11}B_8NO_2$ (M^+) 301.3045, found 301.3033.

***p*-Carboranylenamine of D-Leucine Methyl Ester (16).** Enamine **16** was prepared similarly to **12** in 15% yield from aldehyde **3**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.73 (d, 3H), 0.81 (d, 3H), 1.30−1.36 (m, 1H), 1.55−1.69 (m, 2H), 1.43−3.03 (bm, 10H), 2.74 (s, 1H), 3.63 (s, 3H), 3.69−3.73 (m, 1H), 7.06 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 23.3, 24.4, 41.3, 52.4, 61.4, 69.9, 73.6, 158.6, 171.8; HRMS-ESI calcd for $C_{10}H_{26}{}^{10}B_2{}^{11}B_8NO_2$ ($[M + H]^+$) 300.2967, found 300.2967.

***p*-Carboranylmethylamine of D-Leucine Methyl Ester (17).** Amine **17** was prepared from enamine **16** in 55% yield in a fashion similar to that of **13**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (d, 3H), 0.86 (d, 3H), 1.22 (m, 1H), 1.33 (t, 1H), 1.40−3.00 (bm, 10H), 1.54 (bs, 1H), 1.68−1.72 (m, 1H), 2.33 (d, 1H), 2.63 (s, 1H), 2.72 (d, 1H), 3.04 (t, 1H), 3.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.1, 23.0, 24.9, 42.6, 51.8, 54.1, 59.0, 60.1, 84.7, 176.0; HRMS calcd for $C_{10}H_{27}{}^{10}B_2{}^{11}B_8NO_2$ (M^+) 301.3045, found 301.3035.

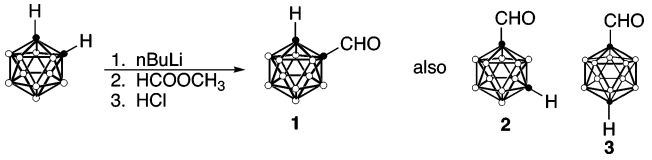
***o*-Carboranylethylamine of D-Leucine Methyl Ester (18).** This compound was prepared in 65% overall yield from carboranyl acetaldehyde **9** as above: IR (KBr, cm^{-1}) 3062, 2956, 2589, 1735; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.85 (d, 3H), 0.86 (d, 3H), 1.35 (m, 1H), 1.20−3.15 (bm, 10H), 1.61 (m, 2H), 2.30 (t, 2H), 2.49 (m, 2H), 2.26 (m, 2H), 3.14 (t, 1H), 3.64 (s, 3H), 4.21 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.8, 22.7, 24.8, 27.4, 42.5, 46.4, 51.5, 59.5, 60.4, 73.7, 175.6; HRMS calcd for $C_{11}H_{28}{}^{10}B_2{}^{11}B_8NO_2$ ($[M-H]^+$) 314.3123, found 314.3124.

***o*-Carboranylethylamine of D-Valine Methyl Ester (19).** This compound was prepared in 66% overall yield from carboranyl acetaldehyde **9** as above for **18**: IR (KBr, cm^{-1}) 3304, 3045, 2964, 2589, 1726; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (d, 3H), 0.92 (d, 3H), 1.86−1.92 (m, 1H), 2.35−2.39 (m, 2H), 2.46−2.51 (m, 1H), 2.81 (q, 1H), 2.92 (d, 1H), 1.40−2.98 (bm, 10H), 3.62−3.84 (m, 1H), 3.76 (s, 3H), 4.21 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.3, 19.4, 31.5, 37.5, 46.9, 51.6, 60.4, 67.1, 73.7, 174.9; HRMS calcd for $C_{10}H_{28}{}^{10}B_2{}^{11}B_8NO_2$ ($[M + H]^+$) 302.3123, found 302.3104.

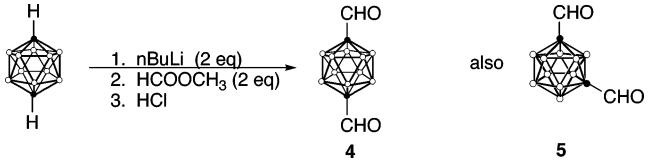
Results

Our preparative method for the *C*-formylcarborane isomers is illustrated in Scheme 1 for the ortho derivative (**1**). Although preparations of all three isomers of $B_{10}C_2$ *C*-formylcarboranes have previously been reported, all require prior derivatization of the carborane cage before conversion into their respective aldehydes. This simple procedure consistently results in isolated yields of **1** of >90% and similarly provides **2** in 90% yield and **3** in more than

Scheme 1



Scheme 2



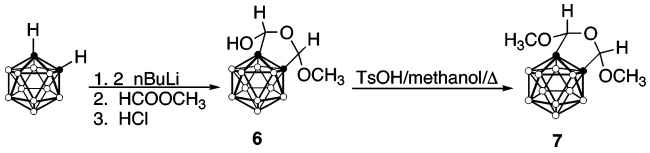
60% yield. In none of these cases did we observe any thin-layer chromatographic evidence for the presence of diformylated species in these reactions. This seems likely because of the low temperature and relatively high dilution conditions of the reactions.

The earliest method for the synthesis of **1** and **2** was Rosenmund reduction of their respective acid chlorides,[1] a method also later used to prepare the para isomer **3**.[2] This procedure obviously requires prior synthesis of the acid, conversion to the acid chloride, and then hydrogenation of the acyl halide for 16−18 h in boiling xylene using $Pd/BaSO_4$ or Pd/C as the catalyst. Yields of **1** and **2** from the acyl chlorides were 35−40% and 60%, respectively, while that of **3** was described as "almost quantitative". Ozonolysis of vinyl-*o*-carborane was also reported in 1967 and was claimed to provide the desired product in "practically quantitative" yield, although no experimental details were described.[3] Later, in 1982 a detailed ozonolysis method was published in which the yield of **1** was a more probable 71%.[4] More recently, Yang and Hawthorne have shown that Swern oxidation of (hydroxymethyl)-*o*-carborane affords **1** in 43% yield and a similar yield of **2** from (hydroxymethyl)-*m*-carborane.[5] In the latter report, the authors also note a private communication from Jones et al. by which they had prepared **1** in 85% yield by the Corey method of reaction with *N*-chlorosuccinimide and dimethyl sulfide.[11] Jones and co-workers have also reported a method for the preparation of the monoformyl-*m*-carborane compound by reaction of monolithio-*m*-carborane with diethylphenyl *o*-formate and subsequent unmasking of the aldehyde with refluxing glacial acetic acid/HCl in ∼86% overall yield.[5]

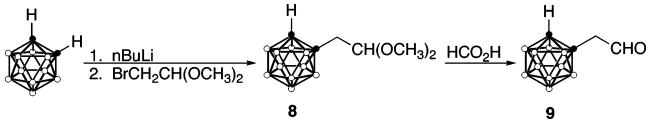
As shown in Scheme 2, the method is also applicable to the preparation of the previously unknown *C,C*-diformyl derivatives of **4** and **5**. **5** is the only one of the three isomeric dialdehydes that has previously been reported in the literature and was prepared in highest yield (80%) by Rosenmund reduction of the diacid chloride with triethylsilane on Pd/C.[7] Swern oxidation of bis(hydroxymethyl)-*m*-carborane smoothly provides the *m*-dialdehyde in 41% yield.[6] Our method provides this dialdehyde directly from *m*-carborane in 51% yield.

Application of the method to the preparation of the previously unknown ortho isomer (Scheme 3) gave unexpected results. Treatment of *o*-carborane with excess *n*-BuLi at ambient temperature, cooling to dry ice temperature, addition of excess methyl formate, and workup with dilute HCl gave the cyclic ether **6** in essentially quantitative yield. Mechanistically, the formation of **6** can be understood as resulting from the initial attack of the dilithiocarborane species on methyl *o*-formate to produce a monolithio, monoformyl intermediate, which again attacks another mole of the ester to give an intermediate oxyanion. This species presumably undergoes an intramolecular nucleophilic attack to form the oxyanion of the cyclic ether product, which is protonated on workup to form the isolated product **6**. When this compound was refluxed with *p*-toluenesulfonic acid in methanol, dimethoxy acetal **7** was formed. However, we were unable to convert this compound into the desired *C,C*-diformyl-*o*-carborane. Hawthorne has noted that Swern oxidation of bis(hydroxymethyl)-*o*-carborane also failed to produce the desired dialdehyde,[6] as did acid hydrolysis of bis(diethoxymethyl)-*o*-carborane.[7]

Scheme 3



Scheme 4



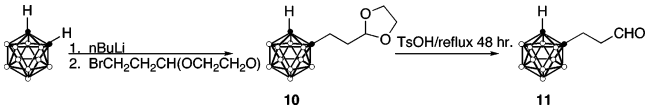
We next turned our attention to preparing a few of the *o*-carborane homologues of **1**. Scheme 4 demonstrates our successful approach to the synthesis of 2-(*o*-carboranyl) acetaldehyde. Low-temperature monolithiation of *o*-carborane followed by the addition of bromoacetaldehyde dimethyl acetal and workup provided acetal **8** as an oil, which was taken directly to the deprotection step without further purification. Conversion of the acetal into the desired aldehyde **9** was carried out in 80% formic acid at room temperature in an overall yield of 76%. This compound had been prepared previously in ∼50% yield using a similar procedure, but few experimental details or spectral characteristics were described in either case.[8] Rudolph et al. described a preparation of this aldehyde through pyridinium chlorochromate oxidation of 2-carboranylethanol, itself synthesized by methanolysis of the acetate ester.[9] No overall yield from decaborane was given for the presumably three-step process, but it is likely ≤30%.

Extension of a similar strategy to *o*-carboranylpropenal **11** was also successful. In this case, the intermediate cyclic acetal **10** was isolated and characterized (Scheme 5). The isolated yield in the first step was 68% and the second nearly quantitative, so the overall yield from *o*-carborane is again a respectable ∼65% or so. The only previous mention of

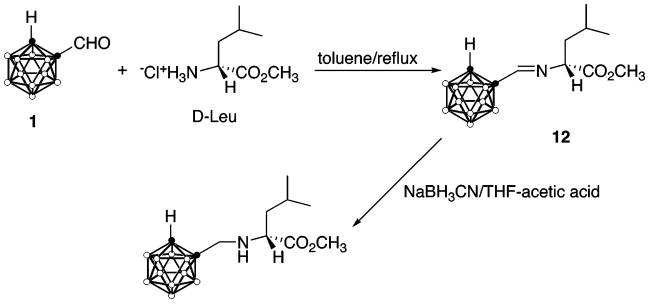
(11) Corey, E. J.; Kim, C. U. *J. Am. Chem. Soc.* **1972**, *94*, 7586.

(12) Luguya, R.; Jaquinod, L.; Fronczek, F. R.; Vicente, M. G. H.; Smith, K. M. *Tetrahedron* **2004**, *60*, 2757−2763.

Scheme 5



Scheme 6



this aldehyde in the literature is a report by Yamamoto and co-workers, which gave no experimental details but noted that the precursor ynals were prepared from decaborane and the corresponding acetylene derivative, a procedure not known for its particularly high yields.[10]

Once these aldehydes were in hand in significant quantities, we undertook an investigation of their reactivity. One of our projects involved the preparation of carborane-containing inhibitors of MMPs whose retrosynthetic analysis pointed to the need for secondary (carboranylmethyl)amino acid derivatives such as leucine derivative **13** (Scheme 6). Leucine was selected for this reaction because the isopropyl side chain provides moderate steric hindrance and gives a suitable test of the reaction conditions. It is also the side chain found by several authors to provide optimal activity in similar non-carboranyl MMP inhibitors. Less hindered amines react under these conditions equally well. Reflux of **1** with D-leucine methyl ester hydrochloride with azeotropic removal of water produced imine **12** in good yield (90%). This imine and other similar ones showed surprising resistance to reduction under a variety of standard reducing conditions, including sodium borohydride, sodium triacetoxyborohydride/EDC, sodium cyanoborohydride/EDC, and hydrogen over Pd−C but were successfully and cleanly reduced in high yield (73%) to the secondary amine **13** with sodium cyanoborohydride in a 1:1 THF/acetic acid mixture. This contrasts to the observations of Smith and co-workers who, after preparing an *o*-carboranyl(iminophenyl)porphyrin by reaction of **1** with the corresponding aniline derivative, reported successfully reducing a carboranylimine with sodium borohydride in THF at room temperature.[12] Similarly prepared were the *m*- and *p*-carboranylenamines **14** and **16** and the corresponding *m*- and *p*-carboranylamine derivatives

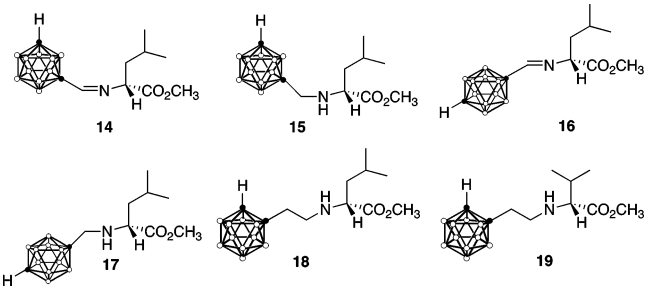


Figure 1. Other carboranyl aldehyde amino acid derivatives prepared.

15 and **17** (Figure 1). Using homologous aldehyde **9**, we also readily prepared the longer chain derivative leucine methyl ester **18**. To illustrate that steric hindrance by the amino acid side chain should not be a problem, we prepared *o*-carboranyl valine derivative **19**. These carboranyl amino acid derivatives may be potentially useful as boron delivery agents for BNCT, a possibility we are currently investigating.

Conclusions

Aldehyde derivatives of the $B_{10}C_2$ polyhedral carboranes continue to be of interest in the preparation of compounds for BNCT and other pharmaceutical applications, as well as in materials science and in fundamental organic chemistry, but methods for their synthesis directly from the parent carboranes have been essentially unavailable until now. We have found that low-temperature lithiation under relatively dilute conditions, followed by the addition of methyl formate, provides a clean, high-yield method for the preparation of all of the *C*-monoformyl and all but the ortho *C*,*C*-diformyl compounds. These are also shown to undergo reduction amination reactions with amino acid esters to give excellent yields of the N-substituted amino acid esters. Application of the low-temperature dilute lithiation conditions to suitably protected bromoaldehydes also provides high-yield methods for homologous carboranyl aldehydes.

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