NOVEL ADDITION AND [3+2] CYCLOADDITION REACTIONS OF STANNYL- AND SILYL-*ortho*-CARBORANES TO CARBONYL COMPOUNDS

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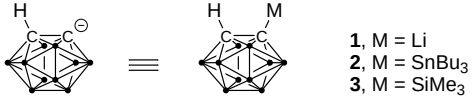
This paper is dedicated to Dr Stanislav Heřmánek on the occasion of his 70th birthday in recognition of his outstanding contributions to the areas of borane chemistry and NMR spectroscopy.

Stannyl- and silyl-*ortho*-carboranes serve as an *ortho*-carborane carbanion equivalents in the addition reaction to aldehydes. The reaction of (tributylstannyl)-*ortho*-carborane **2** with aldehydes **4** in the presence of palladium(0) catalysts gave the corresponding (*ortho*-carboranyl) carbinols **5** in good to high yields. The reaction of (trimethylsilyl)-*ortho*-carborane **3** with aldehydes **4** in the presence of tetrabutylammonium fluoride (TBAF) gave the corresponding (*ortho*-carboranyl) carbinols **5** in high yields. Furthermore, (trimethylsilyl)-*ortho*-carborane **3** underwent a facile [3+2] annulation reaction with various α,β-unsaturated enals and enones in the presence of tetrabutylammonium fluoride, giving the corresponding five-membered carboracyclic products **14** in good to high yields.

Key words: Additions; *ortho*-Carborane; Palladium catalysis; Carbonyl compounds; [3+2] Annulations; Carboranes; Stannanes; Silanes; Boron Neutron Capture Therapy.

The addition of carboranes to electrophiles is one of the most important reactions to synthesize carboranes containing organic functional groups, which are useful as multifunctional molecules for materials science[1] and/or as boron carriers for boron neutron capture therapy[2]. Lithiocarborane **1**, which is readily prepared from butyllithium and *ortho*-carborane, is widely utilized for the C–C bond formation between various functional groups and carboranes[3,4]. It is necessary to develop the addition reaction of *ortho*-carboranes, which proceeds under essentially neutral conditions, in order to synthesize biologically active functionalized molecules sensitive to strong basic or acidic conditions. We succeeded to synthesize tributylstannyl-*ortho*-carborane **2** (ref.[5]) and trimethylsilyl-*ortho*-carborane **3**

(refs[6,7]) which are considered to be an *ortho*-carborane carbanion equivalent. In this paper, we report novel reactions of the *ortho*-carborane derivatives; tributylstannyl-*ortho*-carborane **2** underwent the addition reaction to aldehydes **4** in the presence of palladium(0) catalysts, giving the corresponding *ortho*-carboranyl carbinols **5** in good to high yields[5] (Scheme 1). The reaction of trimethylsilyl-*ortho*-carborane **3** with aldehydes **4** proceeded very smoothly in the presence of tetrabutylammonium fluoride (TBAF) at room temperature to give the corresponding *ortho*-carboranyl carbinols **5** in high yields[6] (Scheme 4). Trimethylsilyl-*ortho*-carborane **3** underwent a facile annulation reaction with various α,β-unsaturated enals and enones in the presence of aqueous TBAF, giving the corresponding cyclopentane-fused carboranes **14** in good to high yields[7] (Scheme 6).



1, M = Li
2, M = $SnBu_3$
3, M = $SiMe_3$

• = BH

EXPERIMENTAL

General Information

^1H and ^{13}C NMR spectra were recorded on a Jeol GSX-270 spectrometer. The chemical shifts are reported in δ units relative to internal tetramethylsilane, coupling constants *J* in Hz. IR spectra were recorded on a Shimadzu FTIR-8200A spectrometer (in cm^{-1}). High-resolution mass spectra were recorded on a Jeol JMS-HX110. Most commercially supplied chemicals were distilled and stored over molecular sieves.

The Synthesis of (Tributylstannyl)-*ortho*-carborane (**2**)

To a solution of *ortho*-carborane (0.72 g, 5 mmol) in dry THF (50 ml) at –78 °C was added a 1.6 M solution of n-BuLi in hexane (3.13 ml, 5 mmol) dropwise with stirring. The mixture was then stirred for 30 min at –78 °C and tributyltin chloride was added dropwise. The solution was stirred for 1 h and then warmed to ambient temperature. The reaction was quenched with water and the mixture was extracted with ether, dried over anhydrous magnesium sulfate and concentrated. Purification by short column chromatography on silica gel with hexane as an eluent afforded **2** as a colorless solid in quantitative yield. IR (KBr): 3 430, 2 960, 2 930, 2 850, 2 580, 1 620, 1 460, 1 375, 1 070, 1 020. ^1H NMR ($CDCl_3$): 3.23 (bs, 1 H); 1.50 (m, 6 H); 1.34 (m, 6 H); 1.10 (m, 6 H); 0.92 (t, *J* = 7.0, 9 H). ^{13}C NMR ($CDCl_3$): 61.9, 59.2, 28.4, 27.2, 13.5, 11.9. ^{119}Sn NMR ($CDCl_3$): 22.83. MS (EI), *m/z*: 432 (M^+), 375 (M^+ – Bu), 318 (M^+ – Bu_2), 261 (M^+ – Bu_3). HRMS (EI): calculated for $C_{14}H_{37}B_{10}Sn$: *m/z* 435.2848; found: *m/z* 435.2836.

Addition of Tributylstannyl-*ortho*-carborane (**2**) to Aldehydes **4**

The reaction of **2** with 4-nitrobenzaldehyde **4c** is representative. To a dry THF (2 ml) solution of **2** (100 mg, 0.24 mmol) and **4c** (28 mg, 0.19 mmol) were added $Pd_2(dba)_3 \cdot CHCl_3$ (42 mg, 0.04 mmol) and (diphenylphosphino)ethane (dppe) (32 mg, 0.08 mmol) under Ar. The mixture was refluxed for 1 h and the progress of the reaction was monitored by TLC. The solvent was removed *in vacuo*, and the product was purified with silica gel column chromatography using hexane–ethyl acetate (4 : 1) as an eluent. The adduct **5c** was obtained in ≈100% yield (55 mg, 0.19 mmol). ^{1}H NMR investigation of the crude product indicated formation of the Bu_3Sn derivative of the adduct. Accordingly the hydrolysis of the O–Sn bond took place during the work-up process.

The Preparation of (Trimethylsilyl)-*ortho*-carborane **3**

To a solution of *ortho*-carborane (0.72 g, 5 mmol) in dry THF (50 ml) at –78 °C was added a 1.6 M solution of n-BuLi in hexane (3.13 ml, 5 mmol) dropwise with stirring. The mixture was stirred for 30 min at –78 °C and trimethylsilyl chloride was added dropwise. The solution was stirred for 1 h and then warmed to ambient temperature. The reaction was quenched with water and the mixture was extracted with ether, dried over anhydrous magnesium sulfate and concentrated. Purification by short column chromatography on silica gel with hexane as an eluent afforded **3** as a white solid in 86% yield (0.93 g, 4.3 mmol). In this case, bis(trimethylsilyl) substituted carborane was not obtained. The use of diluted solution of lithium carborane is essential to obtain the monosilyl substituted carborane derivative[8].

Addition of (Trimethylsilyl)-*ortho*-carborane **3** to Aldehydes **4**

The following procedure for the reaction of trimethylsilyl-*ortho*-carborane **3** with 4-cyanobenzaldehyde **4l** in the presence of tetrabutylammonium fluoride (Bu_4NF) is representative. To a solution of (trimethylsilyl)-*ortho*-carborane **3** (0.22 g, 1 mmol) and 4-cyanobenzaldehyde **4l** (0.13 g, 1 mmol) in THF (5 ml) was added a solution of Bu_4NF in 1 M THF (1 ml) at room temperature and the mixture was stirred for 1 h. The reaction mixture was diluted with ether (20 ml), washed with water (2 × 5 ml) and dried over anhydrous magnesium sulfate. The solvent was evaporated and the residue was purified by column chromatography on silica gel with hexane–ethyl acetate (2 : 1) as an eluent to afford essentially pure 4-[(*ortho*-carbonyl)hydroxymethyl]benzonitrile **5l** (0.23 g, 82%).

(ortho-Carboranyl)phenylmethanol (**5a**). Colorless solid; m.p. 70 °C. IR (KBr): 3 550, 3 100, 2 550, 1 490, 1 460, 1 100, 1 040, 770, 710. ^{1}H NMR ($CDCl_3$): 7.36 (m, 5 H); 5.27 (d, *J* = 3.5, 1 H); 3.81 (bs, 1 H); 2.56 (d, *J* = 3.5, 1 H). MS (EI), *m/z*: 250 (M^+), 233 (M^+ – OH), 108 (M^+ – carborane), 77 (Ar). Analysis: for $C_9H_{18}B_{10}O$ (250.4) calculated: 43.18% C, 7.25% H; found: 42.98% C, 7.09% H.

(4-Bromophenyl)(ortho-carboranyl)methanol (**5b**). White solid; m.p. 70–71 °C. IR ($CHCl_3$): 3 600, 3 500–3 150, 3 050, 2 570, 1 600, 1 480, 1 400, 1 090, 1 070, 1 010. ^{1}H NMR ($CDCl_3$): 7.54 (d, *J* = 8.5, 2 H); 7.22 (d, *J* = 8.5, 2 H); 5.25 (d, *J* = 3.5, 1 H); 3.88 (bs, 1 H); 2.61 (d, *J* = 3.5, 1 H). MS (EI), *m/z*: 329 (M^+), 249 (M^+ – Br), 157 (BrPh), 143 (carborane). HRMS (EI): calculated for $C_9H_{17}B_{10}BrO$: *m/z* 330.1393; found: *m/z* 330.1405.

(ortho-Carboranyl)(4-nitrophenyl)methanol (**5c**). White needles; m.p. 177 °C. IR (KBr): 3 650–3 120, 3 100, 2 600, 1 610, 1 520, 1 350, 1 100, 1 010. ^{1}H NMR ($CDCl_3$): 8.27 (d, *J* = 8.8, 2 H); 7.55 (d, *J* = 8.8, 2 H); 5.40 (d, *J* = 4.0, 1 H); 4.03 (bs, 1 H); 2.85 (d, *J* = 4.0, 1 H). MS

(EI), *m/z*: 295 (M^+), 278 (M^+ – OH), 247 (M^+ – NO_2), 230 (M^+ – OH – NO_2), 173 (M^+ – NO_2Ar). HRMS (EI): calculated for $C_9H_{17}B_{10}NO_3$: *m/z* 297.2139; found: *m/z* 297.2138.

(ortho-Carboranyl)(4-tolyl)methanol (**5d**). Liquid. IR ($CHCl_3$): 3 600, 3 500–3 150, 3 150–2 800, 2 570, 1 730, 1 650, 1 610, 1 095, 1 010, 900. ^{1}H NMR ($CDCl_3$): 7.20 (s, 4 H); 5.23 (d, *J* = 3.0, 1 H); 3.77 (bs, 1 H); 2.51 (d, *J* = 3.0, 1 H); 2.37 (s, 3 H). MS (EI), *m/z*: 264 (M^+), 143 (carborane), 121 (M^+ – carborane), 93 (MePh). HRMS (EI): calculated for $C_{10}H_{20}B_{10}O$: *m/z* 266.2445; found: *m/z* 266.2448.

(ortho-Carboranyl)(4-methoxyphenyl)methanol (**5e**). White crystals; m.p. 111 °C. IR ($CHCl_3$): 3 600, 3 500–3 150, 3 150–2 850, 2 840, 2 570, 1 610, 1 500, 1 300, 1 220, 1 170, 1 090, 1 030. ^{1}H NMR ($CDCl_3$): 7.25 (d, *J* = 9.0, 2 H); 6.91 (d, *J* = 9.0, 2 H); 5.22 (d, *J* = 3.0, 1 H); 3.83 (s, 3 H); 3.78 (bs, 1 H); 2.48 (d, *J* = 3.0, 1 H). MS (EI), *m/z*: 280 (M^+), 264 (M^+ – OH), 121 (MeOPhC), 109 (MeOPh), 94 (OPh), 77 (Ph). HRMS (EI): calculated for $C_{10}H_{20}B_{10}O_2$: *m/z* 282.2394; found: *m/z* 282.2395. Analysis: for $C_{10}H_{20}B_{10}O_2$ (280.4) calculated: 42.80% C, 7.19% H; found: 42.20% C, 6.95% H.

1-(ortho-Carboranyl)-3-phenylpropan-1-ol (**5f**). Liquid. IR ($CHCl_3$): 3 600, 3 500–3 150, 3 100, 2 940, 2 860, 2 600, 1 600, 1 500, 1 460, 1 390, 1 100, 1 060, 1 020. ^{1}H NMR ($CDCl_3$): 7.34–7.16 (m, 5 H); 4.02 (m, 3 H); 2.87 (m, 1 H); 2.67 (m, 1 H); 2.10 (m, 2 H); 1.77 (m, 1 H). MS (EI), *m/z*: 278 (M^+), 261 (M^+ – OH). HRMS (EI): calculated for $C_{11}H_{22}B_{10}O$: *m/z* 280.2601; found: *m/z* 280.2603.

1-(ortho-Carboranyl)-2-phenylpropan-1-ol (**5g**). Liquid. IR ($CHCl_3$): 3 600, 3 500–3 200, 3 160, 2 600, 2 250, 1 820, 1 800, 1 640, 1 460, 1 380, 1 100. ^{1}H NMR: 7.37–7.21 (m, 5 H). Major isomer: 4.30 (dd, *J* = 7.0, 2.0, 1 H); 3.98 (bs, 1 H); 3.20 (dt, *J* = 7.0, 2.0, 1 H); 2.17 (d, *J* = 7.0, 1 H); 1.36 (d, *J* = 7.0, 3 H). Minor isomer: 4.26 (bs, 1 H); 4.11 (dd, *J* = 8.0, 3.5, 1 H); 3.01 (m, 1 H); 1.78 (d, *J* = 3.5, 1 H); 1.43 (d, *J* = 7.0, 1 H). MS (EI), *m/z*: 278 (M^+), 261 (M^+ – OH), 172 (M^+ – PhCHMe), 143 (carborane), 105 (PhCHMe). HRMS (EI): calculated for $C_{11}H_{22}B_{10}O$: *m/z* 280.2601; found *m/z* 280.2608.

1-(ortho-Carboranyl)pentan-1-ol (**5h**). Colorless needles. IR (KBr): 3 650–3 100, 2 950, 2 930, 2 850, 2 560, 1 620, 1 460, 1 120, 1 070, 1 010. ^{1}H NMR: 4.04 (m, 2 H); 1.97 (d, *J* = 7.0, 1 H); 1.76 (m, 1 H); 1.60–1.20 (m, 5 H); 0.92 (t, *J* = 7.0, 3 H). MS (EI), *m/z*: 230 (M^+), 212 (M^+ – H – OH), 197 (M^+ – H – OH – Me), 182 (M^+ – H – OH – C_2H_5), 172 (M^+ – H – C_3H_7), 155 (M^+ – H – C_3H_7OH), 142 (carborane). HRMS (EI): calculated for $C_7H_{22}B_{10}O$: *m/z* 232.2601; found: *m/z* 232.2609.

1-(ortho-Carboranyl)-2-methylpropan-1-ol (**5i**). Colorless crystals; m.p. 79 °C. IR ($CHCl_3$): 3 150–2 900, 2 600, 1 740, 1 020. ^{1}H NMR ($CDCl_3$): 4.04 (bs, 1 H); 3.96 (dd, *J* = 8.0, 2.5, 1 H); 2.08 (m, 1 H); 1.98 (d, *J* = 8.0, 1 H); 1.05 (d, *J* = 7.0, 3 H); 0.97 (d, *J* = 6.5, 3 H). MS (EI), *m/z*: 215 (M^+ – H), 200 (M^+ – H – Me), 172 (M^+ – H – iPr). HRMS (EI): calculated for $C_6H_{19}B_{10}O$: *m/z* 217.2366; found: *m/z* 217.2401. Analysis: for $C_6H_{20}B_{10}O$ (216.3) calculated: 33.31% C, 9.32% H; found: 33.14% C, 8.86% H.

(ortho-Carboranyl)cyclohexylmethanol (**5j**). Colorless crystals. IR (KBr): 3 700–3 250, 3 060, 2 570, 1 620, 1 210, 1 140, 1 030, 1 010. ^{1}H NMR ($CDCl_3$): 4.05 (bs, 1 H); 3.90 (dd, *J* = 8.1, 2.7, 1 H); 2.02 (d, *J* = 8.1, 1 H); 1.88–1.01 (m, 11 H). MS (EI), *m/z*: 256 (M^+), 143 (carborane), 113 (M^+ – carborane), 95 (cHex – CH), 83 (cHex). HRMS (EI): calculated for $C_9H_{24}B_{10}O$: *m/z* 258.2758; found: *m/z* 258.2758.

trans-1-(ortho-Carboranyl)-3-phenylprop-2-en-1-ol (**5k**). Liquid. IR (CCl_4): 3 590, 3 500–3 200, 3 060, 2 560, 1 930, 1 640, 1 480, 1 440, 1 360, 1 180, 1 080, 1 000, 950. ^{1}H NMR ($CDCl_3$): 7.43–7.28 (m, 5 H); 6.63 (d, *J* = 15.0, 1 H); 6.09 (dd, *J* = 15.0, 7.5, 1 H); 4.77 (dd, *J* = 7.5, 4.0,

1 H); 4.07 (bs, 1 H); 2.24 (d, *J* = 4.0, 1 H). MS (EI), *m/z*: 276 (M^+), 143 (carborane), 133 (M^+ – carborane). HRMS (EI): calculated for $C_{11}H_{20}B_{10}O$: *m/z* 278.2445; found: *m/z* 278.2446.

4-[(ortho-Carboranyl)hydroxymethyl]benzonitrile (**5l**). White solid. IR (KBr): 2 580, 2 240. ^{1}H NMR ($CDCl_3$): 7.56 (q, *J* = 8.0, 4 H); 5.33 (d, *J* = 4.0, 1 H); 4.06 (bs, 1 H); 3.17 (d, *J* = 4.0, 1 H). ^{13}C NMR ($CDCl_3$): 143.8, 132.4, 127.6, 118.1, 113.1, 73.9, 67.8, 58.9. Analysis: for $C_{10}H_{17}NB_{10}O$ (275.4) calculated: 43.62% C, 6.22% H, 5.09% N; found: 43.77% C, 6.08% H, 5.15% N.

Methyl 4-[(ortho-carboranyl)hydroxymethyl]benzoate (**5m**). White solid. IR (KBr): 3 404, 2 580. ^{1}H NMR ($CDCl_3$): 7.72 (q, *J* = 8.0, 4 H); 5.31 (d, *J* = 4.0, 1 H); 4.91 (s, 3 H); 3.53 (d, *J* = 4.0, 1 H). ^{13}C NMR ($CDCl_3$): 166.6, 143.5, 131.1, 129.8, 126.8, 74.4, 67.9, 59.0. Analysis: for $C_{11}H_{20}B_{10}O_3$ (308.4) calculated: 42.84% C, 6.54% H; found: 42.81% C, 6.49% H.

Pentavalent stannyl-ortho-carborane (**9**). IR (KBr): 3 450, 2 960, 2 930, 2 870, 2 580, 2 550, 1 460, 1 280, 1 200, 1 075, 1 020. ^{1}H NMR ($CDCl_3$): 3.10 (bs, 1 H); 2.39 (t, *J* = 5.3, 6 H); 1.74 (m, 6 H); 0.93 (t, *J* = 5.3, 6 H). ^{13}C NMR ($CDCl_3$): 69.3, 60.3, 55.3, 23.8, 8.03. ^{119}Sn NMR ($CDCl_3$): –33.9. MS (EI), *m/z*: 401 (M^+), 260 (M^+ – carborane).

4-(5-Oxohex-1-en-1-yl)benzaldehyde (**11**)

This compound was synthesized *via* Heck reaction of 4-bromobenzaldehyde and hex-5-en-2-one, which was prepared by the literature procedure[9]. Colorless oil. IR (KBr): 2 922, 2 841, 1 691, 1 600, 1 566, 1 366, 1 164, 914, 742. ^{1}H NMR ($CDCl_3$): 10.04 (s, 1 H); 7.89 (d, *J* = 7.2, 2 H); 7.56 (d, *J* = 7.2, 2 H); 6.52 (d, *J* = 15.0, 1 H); 6.47 (dt, *J* = 15.0, 5.5, 1 H); 2.73 (t, *J* = 6.0, 2 H); 2.62 (dt, *J* = 5.5, 6.0, 2 H); 2.26 (s, 3 H). ^{13}C NMR ($CDCl_3$): 207.08, 191.15, 143.12, 134.68, 132.72, 129.64, 129.38, 126.07, 42.16, 29.49, 26.69. HRMS (FAB): calculated for $C_{13}H_{14}O_2$: *m/z* 202.0994; found: *m/z* 202.0993.

6{4-[(*ortho*-Carboranyl)hydroxymethyl]phenyl}hex-5-en-2-one (**12**)

A solution of **11** (161 mg, 0.80 mmol), (tributylstannyl)-*ortho*-carborane **2** (442 mg, 0.96 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (167 mg, 0.16 mmol), and bis(diphenylphosphino)ethane (126 mg, 0.32 mmol) in dry THF (5 ml) was stirred under reflux for 4 h. Evaporation of the solvent followed by purification using silica gel column chromatography (hexane–ethyl acetate, 5 : 1) afforded **12** (191 mg, 0.55 mmol, 69%) as a yellow oil. IR (KBr): 3 583, 3 392, 3 084, 3 030, 2 956, 2 922, 2 576, 1 701, 1 363, 1 087, 1 047. ^{1}H NMR ($CDCl_3$): 7.44 (d, *J* = 8.0, 2 H); 7.34 (d, *J* = 8.0, 2 H); 6.50 (d, *J* = 16.0, 1 H); 6.33 (dt, *J* = 16.0, 6.5, 1 H); 5.33 (d, *J* = 3.0, 1 H), 3.91 (s, 1 H); 3.31 (d, *J* = 3.0, 1 H); 2.73 (t, *J* = 7.0, 2 H); 2.58 (dt, *J* = 7.0, 6.5, 2 H); 2.27 (s, 3 H). ^{13}C NMR ($CDCl_3$): 208.7, 138.5, 137.3, 130.1, 129.9, 126.8, 126.1, 78.76, 74.64, 59.23, 42.93, 29.95, 26.98.

[3+2] Annulation of Silyl-*ortho*-carborane **3** to α,β-Unsaturated Carbonyl Compounds **13**

The following procedure is representative. To a solution of trimethylsilyl-*ortho*-carborane **3** (216 mg, 1 mmol) and crotonaldehyde **13a** (77 mg, 1.1 mmol) in THF (10 ml), a 1 M solution of Bu_4NF in THF (3 ml) was added at room temperature and the mixture was stirred for 10 min. The reaction mixture was diluted with ether (20 ml), washed with water (2 × 5 ml) and dried over anhydrous magnesium sulfate. The solvent was evaporated and the residue was purified by column chromatography on silica gel with hexane–ethyl acetate (10 : 1) as eluent to afford the essentially pure cyclic product **14a** in 83% yield.

15-Methylcyclopenta[1,2]dicarba-closo-dodecarboran(12)-13-ol (**14a**). White solid. IR (KBr): 3 325, 2 976, 2 586, 1 458, 1 384, 1 342, 1 166, 731. ^{1}H NMR ($CDCl_3$): 4.71 (m, 1 H); 2.82 (m, 2 H); 2.22 (d, *J* = 7.0, 1 H); 1.70 (m, 1 H); 1.16 (d, *J* = 5.1, 3 H). Analysis: for $C_6H_{18}B_{10}O$ (214.3) calculated: 33.63% C, 8.47% H; found: 33.98% C, 8.41% H.

14-Methylcyclopenta[1,2]dicarba-closo-dodecarboran(12)-13-ol (**14b**). White solid. IR (CCl_4): 3 583, 3 363, 2 970, 2 588, 665. ^{1}H NMR ($CDCl_3$): 4.30 (dd, *J* = 7.8, 5.9, 1 H); 2.48–2.70 (m, 2 H); 2.23 (d, *J* = 5.9, 1 H); 2.05 (m, 1 H); 1.20 (d, *J* = 7.8, 3 H). Analysis: for $C_6H_{18}B_{10}O$ (214.3) calculated: 33.63% C, 8.47% H; found: 33.36% C, 8.47% H.

15,15-Dimethylcyclopenta[1,2]dicarba-closo-dodecarboran(12)-13-ol (**14c**). White solid. IR (KBr): 3 367, 2 978, 2 596, 1 334, 1 074. ^{1}H NMR ($CDCl_3$): 4.67 (ddd, *J* = 8.0, 5.1, 5.0, 1 H); 2.54 (dd, *J* = 14.8, 8.0, 2 H); 2.18 (d, *J* = 5.0, 1 H); 2.02 (dd, *J* = 14.8, 5.1, 1 H); 1.37 (d, *J* = 5.0, 3 H); 1.32 (d, *J* = 5.0, 3 H). HRMS (EI): calculated for $C_7H_{20}B_{10}O$: *m/z* 230.2445; found: *m/z* 230.2443. Analysis: for $C_7H_{20}B_{10}O$ (228.3) calculated: 36.82% C, 8.83% H; found: 36.45% C, 8.95% H.

14-Methyl-15-phenylcyclopenta[1,2]dicarba-closo-dodecarboran(12)-13-ol (**14d**). White solid. IR (CCl_4): 3 853, 3 448, 3 066, 2 968, 2 588, 1 498, 1 149. ^{1}H NMR ($CDCl_3$): diastereoisomer ratio was 61/39, major isomer: 7.43–7.23 (m, 5 H); 4.43 (dd, *J* = 7.5, 5.5, 1 H); 3.53 (d, *J* = 10.5, 1 H); 2.67–2.83 (m, 1 H); 2.43 (d, *J* = 5.5, 1 H); 1.14 (d, *J* = 8.0, 3 H); minor isomer: 7.43–7.23 (m, 5 H); 4.67 (dd, *J* = 7.5, 5.5, 1 H); 3.61 (d, *J* = 10.5, 1 H); 3.06–3.20 (m, 1 H); 2.25 (d, *J* = 5.5, 1 H); 0.98 (d, *J* = 7.9, 3 H). Analysis: for $C_{12}H_{22}B_{10}O$ (290.4) calculated: 49.63% C, 7.64% H, found: 49.34% C, 7.60% H.

15-Phenylcyclopenta[1,2]dicarba-closo-dodecarboran(12)-13-ol (**14e**). White solid. IR (CCl_4): 3 583, 3 413, 2 586, 1 748, 1 074, 794. ^{1}H NMR ($CDCl_3$): diastereoisomer ratio was 56/44, major isomer: 7.15–7.34 (m, 5 H); 4.82 (m, 1 H); 4.16 (dd, *J* = 9.5, 9.0, 1 H); 2.83–3.05 (m, 1 H); 2.39–2.53 (m, 1 H); 2.10 (d, *J* = 3.0, 1 H); minor isomer: 7.15–7.34 (m, 5 H); 4.82 (m, 1 H); 3.92 (dd, *J* = 9.0, 8.5, 1 H); 2.83–3.05 (m, 1 H); 2.39–2.53 (m, 1 H); 2.10 (d, *J* = 3.0, 1 H). HRMS (EI): calculated for $C_{11}H_{20}B_{10}O$: *m/z* 278.2447; found: *m/z* 278.2452.

13-Methylcyclopenta[1,2]dicarba-closo-dodecaboran(12)-13-ol (**14f**). White solid. IR (KBr): 3 583, 3 467, 2 991, 2 956, 2 592, 1 452, 1 379. ^{1}H NMR ($CDCl_3$): 2.33–2.63 (m, 4 H); 2.08 (s, 1 H); 1.62 (s, 1 H). Analysis: for $C_6H_{18}B_{10}O$ (214.3) calculated: 33.63% C, 8.47% H; found: 33.50% C, 8.81% H.

13,15-Dimethylcyclopenta[1,2]dicarba-closo-dodecaboran(12)-13-ol (**14**g). White solid. IR (KBr): 3 565, 3 487, 2 856, 2 594, 1 452, 1 385. ^{1}H NMR ($CDCl_3$): 3.08–2.93 (m, 1 H); 2.45 (dd, *J* = 14.5, 7.7, 1 H); 2.05 (s, 1 H); 1.95 (dd, *J* = 14.5, 10.0, 1 H); 1.55 (s, 3 H); 1.11 (d, *J* = 6.5, 3 H). Analysis: for $C_7H_{20}B_{10}O$ (228.3) calculated: 36.82% C, 8.83% H; found: 36.81% C, 8.85% H.

13-Methyl-15-phenylcyclopenta[1,2]dicarba-closo-dodecaboran(12)-13-ol (**14h**). White solid. IR (CCl_4): 3 583, 3 467, 2 580, 2 310, 2 343, 665. ^{1}H NMR ($CDCl_3$): 7.24–7.41 (m, 5 H); 4.21 (dd, *J* = 10.5, 8.0, 1 H); 2.75 (dd, *J* = 14.0, 10.5, 1 H); 2.67 (dd, *J* = 14.0, 8.0, 1 H); 2.13 (s, 1 H); 1.69 (s, 1 H). Analysis: for $C_{12}H_{22}B_{10}O$ (290.4) calculated: 49.63% C, 7.64% H; found: 49.57% C, 7.28% H.

3-(ortho-Carboranyl)cyclohexanone (**15**). Yellow liquid. IR (neat): 3 781, 3 085, 3 060, 2 933, 2 586, 1 716. ^{1}H NMR ($CDCl_3$): 3.66 (s, 1 H); 1.20–2.66 (m, 9 H). HRMS (EI): calculated for $C_8H_{20}B_{10}O$: *m/z* 242.2445; found: *m/z* 242.2452.

Synthesis of the *ortho*-Carboranyl-azulene Conjugate **23**

A mixture of the formylazulene **22** (40 mg, 0.16 mmol), (tributylstannyl)-*ortho*-carborane **2** (101 mg, 0.23 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (32 mg, 0.031 mmol), and 1,4-bis(diphenylphosphino)butane (dppb) (26 mg, 0.062 mmol) was dissolved in THF (1.5 ml) under Ar and stirred for 14 h under reflux. The solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel (hexane–ethyl acetate, 5 : 1) to give **23** (32 mg, 0.081 mmol, 52%) as violet needles, m.p. 203 °C. IR (KBr): 3 610, 2 579, 2 350, 2 330, 1 670, 1 654, 1 649, 1 453, 1 229, 777. ^{1}H NMR ($CDCl_3$): 9.78 (d, *J* = 2.0, 1 H); 8.38 (dd, *J* = 10.0, 2.0, 1 H); 8.31 (s, 1 H); 7.84 (dd, *J* = 10.0, 2.0, 1 H); 7.50 (dd, *J* = 10.0, 1 H); 5.92 (d, *J* = 3.0, 1 H); 4.00 (bs, 1 H); 3.94 (s, 3 H); 3.25 (m, 1 H); 2.80 (d, *J* = 3.0, 1 H); 1.43 (d, *J* = 7.0, 6 H). Analysis: for $C_{18}H_{28}B_{10}O_3$ (400.5) calculated: 53.98% C, 7.05% H; found: 54.12% C, 6.77% H.

RESULTS AND DISCUSSION

*Addition of the Stannyl-ortho-carborane **2** to Aldehydes **4***

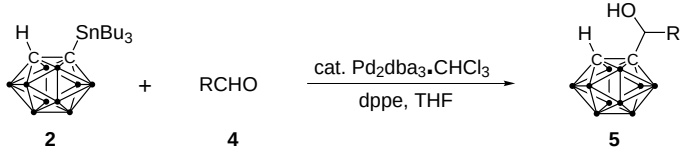
The results are summarized in Table I. The addition of (tributylstannyl)-*ortho*-carborane **2** to benzaldehyde **4a** (Scheme 1) proceeded very smoothly even at room temperature in the presence of $Pd_2(dba)_3 \cdot CHCl_3$/dppe catalyst (entry 1). The use of $Pd(PPh_3)_4$ and $PdCl_2(PPh_3)_2$ gave lower yields, and the use of $RhCl(PPh_3)_3$ and $RhH(CO)(PPh_3)_3$ afforded the adduct in *ca* 10% yield. No addition took place by the use of $NiBr_2(PPh_3)_2$ catalyst. Not only aromatic aldehydes (**4a**–**4e**) but also aliphatic aldehydes (**4f**–**4j**) and cinnamaldehyde **4k** underwent the addition reaction in good to high yields (entries 2–11). The addition to 2-phenylpropanal **4g** produced a 3 : 1 diastereoisomeric mixture of the adducts (entry 7).

*Mechanism of Palladium-Catalyzed Addition Reaction of Compound **2***

A mechanistic rationale, which accounts for this unprecedented addition reaction, is shown in Scheme 2. The oxidative insertion of Pd(0) into the C–Sn bond of **2** produces the Pd(II) intermediate **6**. The addition of **6** to aldehyde **4** affords **7**, which gives **8** and Pd(0) species *via* reductive elimination. In order to obtain a proof for the proposed mechanism, a 1 : 1 mixture of **2** and $Pd_2(dba)_3 \cdot CHCl_3$ in THF was kept at room temperature under Ar for 1 day, and quenched with H_2O. *ortho*-Carborane was obtained in essentially quantitative yield. Therefore, it is clear that **6** is formed by the oxidative insertion of Pd(0) into the C–Sn bond in the absence of aldehydes.

Needless to say, the palladium catalyzed addition reaction between aldehydes and common organotins, such as Bu_4Sn, $C_6H_5SnBu_3$, and $CH_2{=}CHSnBu_3$,

did not take place. The ^{119}Sn chemical shifts of **2**, **9**, and **10** in $CDCl_3$ were δ 22.83, –33.9, and –35.4 ppm, respectively. Judging from the ^{119}Sn chemical shift data, the tin atoms of **9** and **10** are more negatively charged in comparison with the tin atom of **2**. No reaction took place between aldehydes and **9** in the presence of palladium catalysts. No oxidative insertion of Pd(0) into the C–Sn bond of **9** and **10** occurred. Accordingly, it seems that the presence of a less negative charge on the tin atom is essential for the oxidative insertion. Recently, the insertion mechanism of transition metal



2 **4** **5**

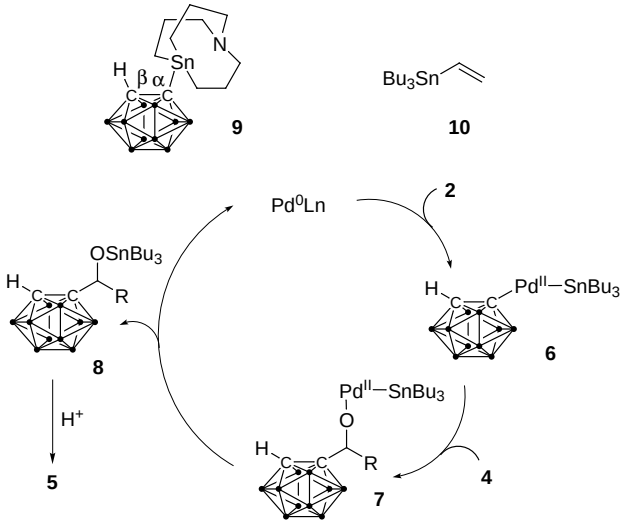
SCHEME 1

TABLE I
Palladium-catalyzed addition of (tributylstannyl)-*ortho*-carborane **2** to aldehydes **4**

Entry	Aldehyde		Reaction conditions		Product[a]	Yield %
	R	**4**	temperature	time		
1	C_6H_5CHO	**4a**	r.t.	1 d	**5a**	70
2	4-PhCHO	**4b**	reflux	1 h	**5b**	98
3	4-NO_2PhCHO	**4c**	reflux	2 h	**5c**	100
4	4-CH_3PhCHO	**4d**	reflux	1 h	**5d**	85
5	4-MeOPhCHO	**4e**	reflux	3 h	**5e**	99
6	$PhCH_2CH_2CHO$	**4f**	reflux	1 h	**5f**	97
7	$PhCH(CH_3)CHO$	**4g**	reflux	1 h	**5g**	63[b]
8	$CH_3(CH_2)_3$	**4h**	reflux	1 h	**5h**	74
9	$(CH_3)_2CH$	**4i**	50 °C	12 h	**5i**	65
10	cyclohexylCHO	**4j**	reflux	1 h	**5j**	96
11	PhCH=CHCHO	**4k**	reflux	4 h	**5k**	47[c]

[a] Isolated yield using silica gel column chromatography. [b] The diastereoisomer ratio was 3 : 1. [c] No 1,4-adduct was obtained.

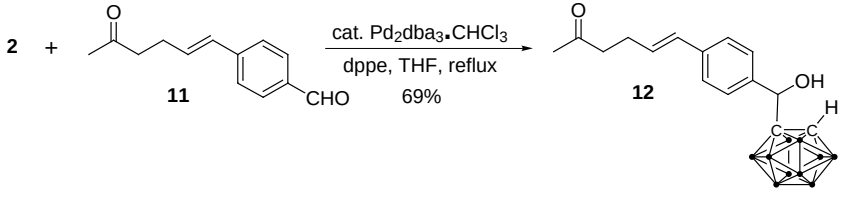
complexes into C–Sn bond of other organostannanes was also proposed in the palladium-catalyzed allylation of aldehydes[10] or carbon dioxide[11], and on the rhodium-catalyzed arylation of aldehydes[12].



SCHEME 2
Palladium-catalyzed carboranylation of aldehydes

*Chemoselective Addition of Stannyl-ortho-carborane **2** to Aldehyde **11***

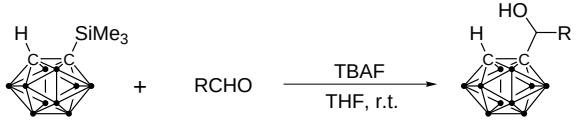
Next, we examined the addition reaction of stannyl-*ortho*-carborane **2** to the bifunctional substrate **11**, which contained an aldehyde and a ketone functions in the molecule (Scheme 3). The reaction of **2** with **11** proceeded smoothly in the presence of a catalytic amount of $Pd_2(dba)_3 \cdot CHCl_3$ (10 mole %)/dppe (20 mole %) in THF under reflux, giving the corresponding carbinol **12**, in which the aldehyde group of **11** reacted chemoselectively, in 69% yield. In the case of the reaction of *ortho*-lithiocarborane **1** with **11**, the chemoselective addition was not observed[13].



SCHEME 3

*Addition of Silyl-ortho-carborane **3** to Aldehydes **4***

Certain organosilanes can be considered as stable yet reactive carbanions which allow many unique fluoride-ion catalyzed carbon–carbon forming reactions under mild conditions[14]. The fluoride ion presumably attacks silicon atom and leads to the formation of pentacoordinated silicon containing anions which are implicated as reactive intermediates in these kind of reactions[15]. Silyl-*ortho*-carborane **3** also underwent fluoride ion-promoted reaction (Scheme 4). The results are summarized in Table II. The addition of (trimethylsilyl)-*ortho*-carborane **3** to benzaldehyde **4a** proceeded very smoothly in the presence of TBAF (1 equivalent), giving the corresponding carbinol **5a** in 98% yield. This reaction is also highly chemoselective. Thus, functional groups, such as nitro (**4c**), cyano (**4l**) and ester (**4m**), are tolerated and the reaction takes place exclusively at the aldehyde group (entries 2–4). Both aliphatic and aromatic aldehydes can be utilized for this reaction



3 **4** **5**

SCHEME 4

TABLE II
TBAF-Promoted addition of trimethylsilane **3** to aldehydes **4**[a]

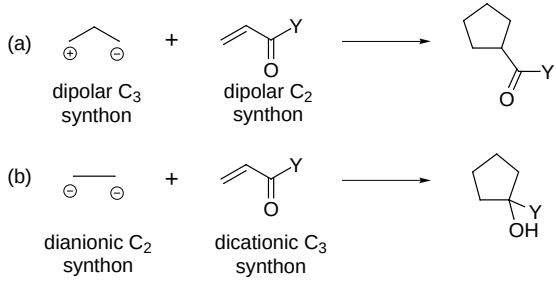
Entry	Aldehyde		Product	Yield[b], %
	R	**4**		
1	PhCHO	**4a**	**5a**	98
2	4-NO_2PhCHO	**4c**	**5c**	82
3	4-CNPhCHO	**4l**	**5l**	95
4	4-MeOOCPh	**4m**	**5m**	75
5	$CH_3(CH_2)$CHO	**4n**	**5n**	75
6	(CH_3)CHCHO	**4i**	**5i**	95
7	$(CH_3)_3$CCHO	**4o**	**5o**	0[c]

[a] All reactions were carried out at 25 °C for 1 h. [b] Isolated yield using silica gel column chromatography. [c] Quantitative formation of *ortho*-carborane.

(entries 1–4 *vs* entries 5,6). The reaction is sensitive to steric requirements and the protodesilylated product, *ortho*-carborane, was obtained exclusively in the case of pivalaldehyde **4o** (entry 7).

*[3+2] Annulation of Silyl-ortho-carborane **3** with Enals and Enones **13***

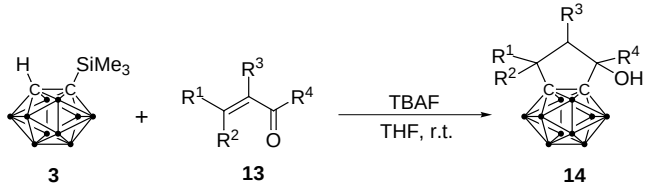
Next we examined the addition reaction to α,β-unsaturated enals and enones and found that silyl-*ortho*-carborane **3** underwent a [3+2] annulation reaction with conjugated carbonyl compounds **13**. The most efficient method for the construction of five-membered carbocyclic rings is [3+2] annulation processes[16]. Perhaps the most widely utilized strategy in this regard is one in which dipolar C_3 synthons are utilized in conjunction with electron-deficient olefins (dipolar C_2 synthons) to achieve [3+2] annulation[16–21] (Scheme 5). However, [3+2] annulation between dianionic C_2 synthons and dicationic C_3 synthons are less common than dipolar annula-



SCHEME 5
[3+2] Annulation of dipolar C_3 and C_2 building blocks (a) and of dianionic C_2 and dicationic C_3 building blocks (b)

tions[22]. The coupling of the 1,3-dihalides or β-haloesters with the doubly charged succinate anions[23] or tetra(ethoxycarbonyl)ethyl anions[24] has been investigated in the latter approach. We found that [3+2] annulation between dianionic C_2 synthons and α,β-unsaturated enals and enones (dicationic C_3 synthons) gives the corresponding five membered carbocycles (Scheme 5b). (Trimethylsilyl)-*ortho*-carborane (**3**) underwent a facile annulation reaction with various α,β-unsaturated carbonyl compounds in aqueous TBAF, giving the corresponding cyclopentane-fused carboranes **14** in good yields (Scheme 6).

The detailed results are summarized in Table III. The reaction of compound **3** with crotonaldehyde **13a** proceeded smoothly at 25 °C in the presence of three equivalents of TBAF, giving **14a** in 83% yield as a 58 : 42



SCHEME 6

TABLE III
[3+2] Annulation of silyl-*ortho*-carborane **3** with enones or enols **13**

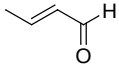
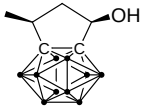
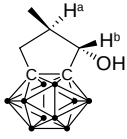
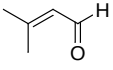
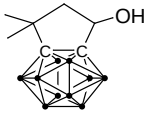
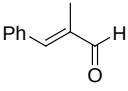
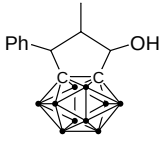
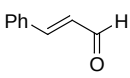
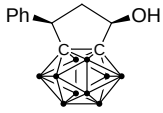
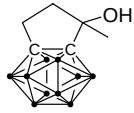
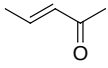
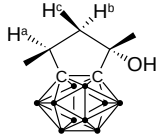
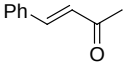
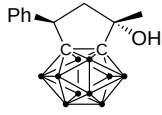
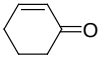
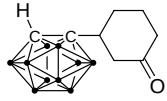
Entry	**13**		**14**[a]		Yield %	Ratio[b] (*syn/anti*)
1		**13a**		**14a**	83	52/48
2		**13b**		**14b**	48	17/83
3		**13c**		**14c**	77	–
4		**13d**		**14d**	81	ND[c]

TABLE III
(*Continued*)

Entry	**13**	**14**[a]	Yield %	Ratio[b] (*syn/anti*)
5	 **13e**	 **14e**	76[d]	56/44
6	 **13f**	 **14f**	74	–
7	 **13g**	 **14g**	52	40/60
8	 **13h**	 **14h**	35[e]	21/79
9	 **13i**	 **15**	39	–

[a] When the stereochemistry of **14** was determined unambiguously, that of a major isomer is shown in the column. [b] Diastereoisomer ratios were determined by ^{1}H NMR. The stereochemistry of the products was determined by X-ray analysis (**14a**), NOE measurement (**14b** and **14g**), or analogy with the stereochemistry of **14a** (**14e**) and **14g** (**14h**). [c] Three diastereoisomers were obtained with a ratio of 55/34/11. The stereochemistry of the diastereoisomers was not determined. [d] The reaction time was 35 min. [e] The reaction was sluggish and the product was obtained in 35% yield after 16 h.

mixture of *syn* and *anti* diastereoisomers (entry 1). The use of catalytic amounts of TBAF gave lower chemical yield. The *syn* configuration of a major diastereoisomer of **14a** was confirmed unambiguously by X-ray analysis (Fig. 1). The reaction of 2-methylprop-2-enal **13b** gave **14b** in 48% yield with a *syn/anti* ratio of 17/83 (entry 2). The stereochemistry of the major isomer of **14b** was determined by NOE experiments. NOEs were observed between CH_3 protons and H^b, but not between H^b and H^a, indicating that the configuration of the major isomer was *anti*. The stereochemistry of the minor isomer (*syn*) was also determined by NOE experiments. The yields in the reactions with 3-substituted aldehydes (**13a**, **13c**, **13d**, and **13e**) were higher than those with 3-unsubstituted aldehyde (**13b**), as shown in entries 1–5. Although the diastereosiomer ratio of **14d** was determined by 400 Hz ^{1}H NMR, the stereochemistries of those isomers were not determined. Even α,β-unsaturated ketones reacted with **3** under the same reaction conditions as above to afford the cyclic adducts in good to acceptable yields (entries 6–8). The reaction of (trimethylsilyl)-*ortho*-carborane **3** with **13g** gave **14g** in 52% yield with a *syn/anti* ratio of 40/60. NOEs were observed between H^a and H^b and between H^c and protons of CH_3 attached to CHOH of **14 g**, indicating that the configuration of the major isomer was *anti* (see **14g**). However, phenyl group at the γ-position of enone proved effective for higher diastereoselectivity (*syn/anti* = 21/79, entry 8), although the substituent groups at the γ-position of enals did not exert significant influence upon diastereoselectivity (entries 1 and 5). Cyclohexenone **13i**, which has a fixed *s-trans*-enone configuration, gave the corresponding 1,4-addition compound **15** in 39% yield instead of affording an expected annulation product (entry 9).

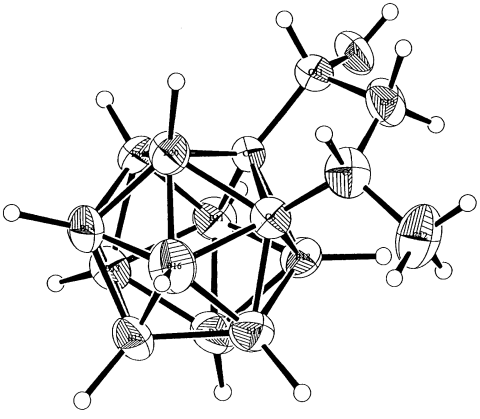
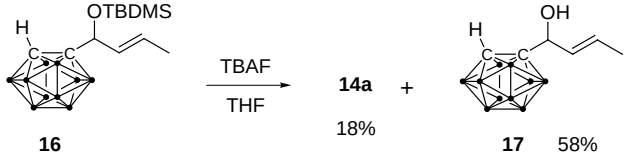


FIG. 1
The X-ray structure of **14a**

Mechanism of [3+2] Annulation

In order to clarify the mechanism of this unique annulation reaction, we monitored the reaction of compound **3** with cinnamaldehyde **13e** (Fig. 2). The reaction time is plotted on the horizontal axis and the yields of the products are plotted on the vertical. It is clear from Fig. 2 that, within a minute after the addition of TBAF, 1,2-adduct **5k** and the cyclic adduct **14e** were produced in 53 and 9% yields, respectively. The yield of **5k** gradually decreased as the reaction progressed while the yield of **14e** increased with time. After 30 min, the cyclic product **14e** was produced in 76% yield, the starting enal **13e** was consumed completely, and very small amounts of the 1,2-adduct **5k** were formed.

Based on this observation, it was thought that the [3+2] annulation would proceed through kinetically controlled 1,2-addition followed by the



SCHEME 7

cyclization process. Actually, when **16** was treated with TBAF, **14a** was obtained in 18% yield along with the formation of desilylated product **17** in 58% yield (Scheme 7). A possible mechanism for this unprecedented annulation reaction is shown in Scheme 8.

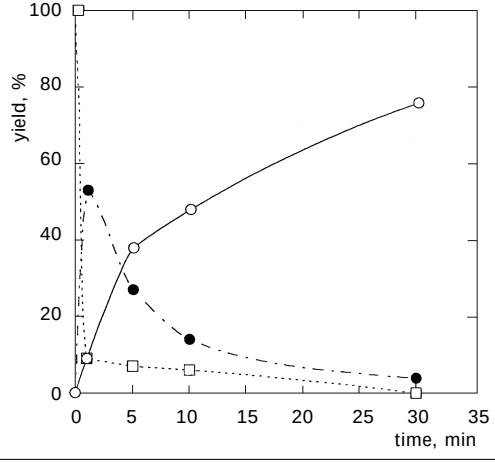
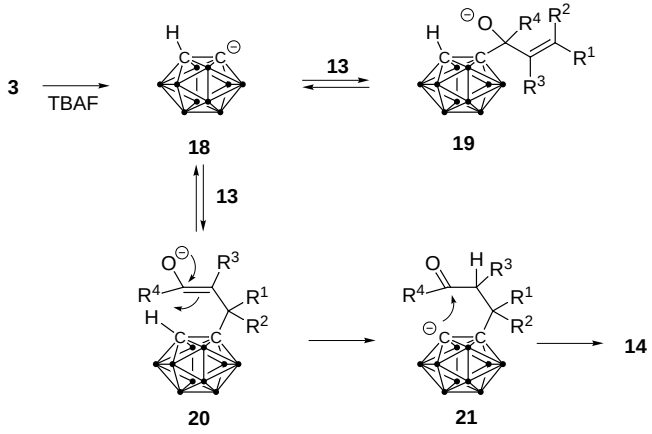


FIG. 2
Time dependence of concentration of **14e** (○) and **5k** (●) in the reaction of **3** and **13e** (❑) catalyzed by TBAF in THF. The amounts of product (%) were determined by ^{1}H NMR spectroscopy



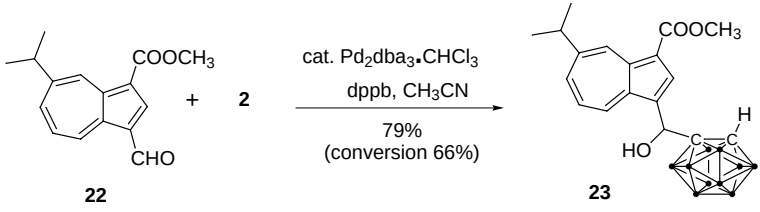
SCHEME 8

The reaction of **3** with TBAF gives an anionic intermediate **18**, which undergoes addition to **13** either in 1,2- or 1,4-manner to give the 1,2-adduct **19** or 1,4-adduct **20**, respectively. There exists an equilibrium between **19** and **20**, and the formation of **19** is a kinetically controlled process as is apparent from the results of Fig. 2. The thermodynamically favored **20** undergoes proton exchange to afford the *ortho*-carborane anion **21**, which gives **14** *via* an intramolecular ring closure[25]. In the case of cyclohexenone, the enolate generated by the 1,4-addition may abstract a proton from the carborane cage, but the carbonyl group cannot approach to the resulting carboranyl anion due to its steric requirement and thus no annulation took place with **13i**.

Application to the Synthesis of Carboranylazulenes for Boron Neutron Capture Therapy

Recently, much attention has been paid to the ^{10}B neutron capture therapy (BNCT), an alternative cancer therapy[2]. A key requirement for BNCT is to develop a new ^{10}B carrier that delivers adequate concentration of ^{10}B atoms to tumors. It has been reported that azulene derivatives, such as guaiazulene[26], an active component of the essential oil of the plant *Guaiacum officinalis* (ref.[27]), have biologically active properties such as anti-allergic, anti-inflammatory and anti-ulcer activities. We thought that the azulene moiety might be a good candidate for a ^{10}B carrier to deliver boron to tumor tissues because of known biological activity of azulenes[28]. The reaction of azulenecarbaldehyde **22** (ref.[29]) with *ortho*-lithiocarborane **1** resulted in

the destruction of the azulene skeleton. This result indicated that neutral condition are essential for introduction of *ortho*-carborane to the azulene moiety. Thus, we examined the addition of the stannyl-*ortho*- carborane **2** to the azulenecarbaldehyde **22** using several palladium catalysts and found that the use of 20 mole % of $Pd_2(dba)_3 \cdot CHCl_3$/2 dppb gave the corresponding carbinol **23** in 52% yield along with 34% yield of the recovered **22** (Scheme 9). The use of dppe or dppp (1,3-bis(diphenylphosphino)propane) as a ligand of palladium catalyst gave **23** in lower yields. On the other hand, the TBAF-promoted addition of the silyl- *ortho*-carborane **3** to azulenecarbaldehyde **22** gave a complex mixture of products.



22 **23**

SCHEME 9

We are actively investigating the scope and limitation of these novel addition reactions, which are synthetically useful for providing biologically active carborane derivatives for boron neutron capture therapy.

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