Synthesis of Boroxifen, A *Nido*-Carborane Analogue of Tamoxifen

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A *nido*-carborane analogue of tamoxifen, the widely employed breast cancer therapy agent, was prepared as an archetype of a potential new class of antiestrogen and boron neutron capture therapy agent in which the carborane is incorporated within the framework of the parent compound. The carborane was introduced through the reaction of 6,9-bis(acetonitrile)decaborane with a unique and highly conjugated ene-yne, which was prepared stereoselectively. NMR spectroscopy and a crystal structure of a key intermediate, the carborane analogue of chloro-tamoxifen, demonstrated the structural similarities between the tamoxifen carboranes and their corresponding phenyl analogues.

Introduction

Boron neutron capture therapy (BNCT) is a binary approach to cancer treatment originally proposed by Locher in 1936.[1] The daughters of the ^{10}B neutron-capture reaction [$^{10}B(n,\alpha)^{7}Li$] are high linear energy transfer (LET) particles which have a range in tissue approximately equal to the diameter of a single cell.[2] In addition, ^{10}B has a neutron capture cross-section that is far greater than the more abundant elements found in the body. Consequently, upon exposure to neutrons, cells that contain boron can be destroyed without causing irreparable harm to adjacent healthy tissue.[3]

It is generally accepted that between 10 and 30 μg of ^{10}B/g tumor is required for successful therapy;[4] however, this amount is reduced substantially if the neutron capture reaction takes place in or near the cell nucleus.[5] To this end, the estrogen receptor (ER), which is over-expressed on a number of different types of cancer cells, is an attractive target for the preparation of new BNCT agents. It is now known that ER−substrate complexes interacts directly with DNA, which, so long as the appropriate antagonist can be prepared, provides a means for selectively concentrating boron-10 in the nuclei of cancer cells.

Tamoxifen (**1**, Figure 1) is a drug in widespread use for the treatment of hormone dependent breast cancer.[6] Its principal mechanism of action is thought to be

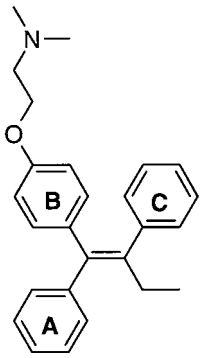

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Figure 1. Tamoxifen.

displacement of the growth hormone estradiol from the ER;[7] however, tamoxifen is also reported to target secondary receptor sites adding to its overall pharmacological effect.[8] A series of polyhedral borane cluster−tamoxifen conjugates, linked through the amino group of the B-ring side chain, were reported as a means to facilitate the delivery of boron to breast cancer cells.[9] The affinities of the carborane-based compounds for the estrogen receptor and their abilities to selectively concentrate boron in tumor cells, however, were not, to our knowledge, published.

The sensitivity of the amino group in tamoxifen to substitution,[10] and the fact that demethylation, followed by didemethylation of the side chain, is the principal tamoxifen metabolite in humans[11] (which could potentially result in premature release of boron cages prior to

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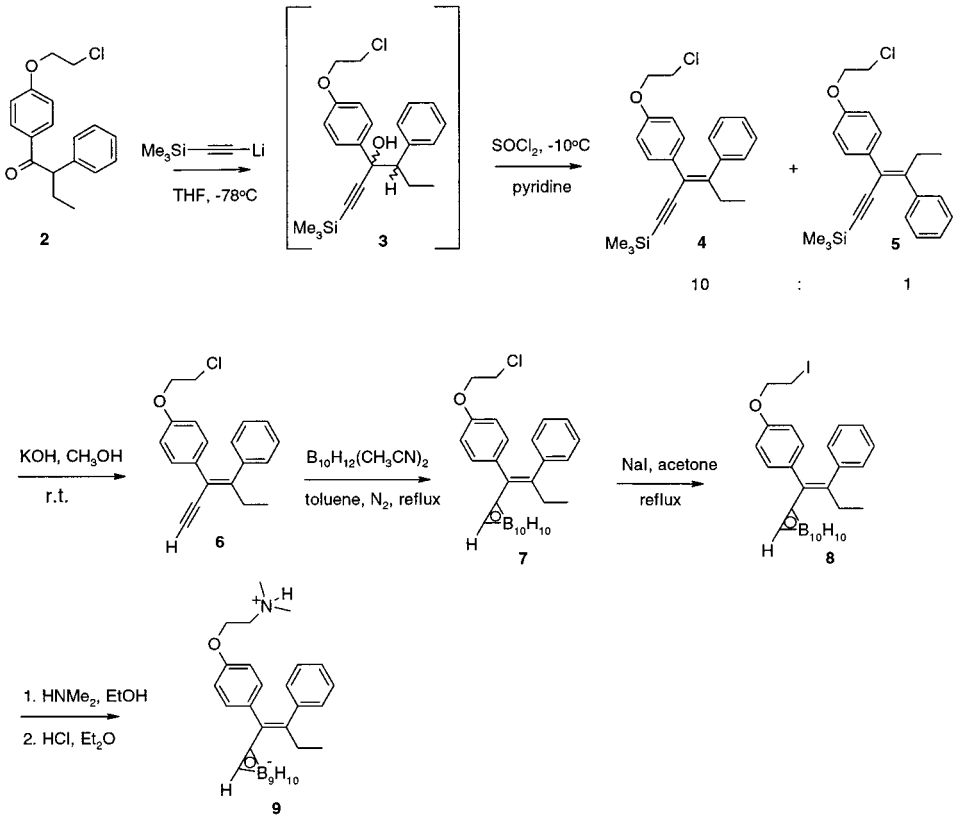
Scheme 1



their accumulation in tumor cells), may limit the efficacy of the reported compounds. An alternative approach is to substitute a carborane for one of the tamoxifen phenyl rings. Dicarba-*closo*-dodecarborane(12) (*o*-carborane), for example, occupies a volume similar to that for a rotating phenyl ring[12] and it exhibits a remarkable resistance to catabolism.[13] If a carborane were substituted for the appropriate phenyl ring, the product could mimic the selectivity of the parent compound while also delivering an appreciable number of boron-10 atoms per molecule to the nuclei of cancer cells. In the present paper we discuss the synthesis and structural characterization of a carborane analogue of tamoxifen, in which a *nido*-carborane $[HC_2B_9H_{10}]^-$ was incorporated in place of ring A. Numerous ring A derivatives, including those that hinder the rotation of the phenyl group, have been reported to retain affinity for the estrogen receptor.[14] Incorporation of the carborane should therefore have only a minimal impact on the compounds receptor specificity.[15] An added advantage of using a *nido*-carborane, which is more similar in terms of lipophilicity to a phenyl group than the corresponding *closo*-carborane,[16] is that it can be conveniently radiolabeled which will, in the future, facilitate the process of evaluating the compounds distribution in vivo.[17]

Results and Discussion

It has been well established that the geometric isomers of tamoxifen show significantly different biological activity. The *Z* isomer is antiestrogenic while its counterpart, the *E*-isomer, is estrogenic.[18] As a consequence, it is important that the synthesis of a carborane analogue of tamoxifen be stereoselective to avoid the possibility of promoting tumor growth via the unwanted isomer. Since carboranes are typically prepared from terminal alkynes, our retrosynthetic analysis identified compound **6** (Scheme 1) as the key synthetic intermediate.

McCague et al. demonstrated that reasonable selectivity toward the desired tamoxifen isomer (*Z*) could be attained by reacting phenylmagnesium bromide with ketone **2** followed by subsequent elimination of the resultant alcohol under acidic conditions.[19] In our work, lithium (trimethylsilyl)acetylide was reacted with ketone **2** yielding a tertiary alcohol, which was immediately converted to the corresponding alkenes **4** and **5** using thionyl chloride in pyridine at −10 °C. Under these conditions, the E2 reaction was favored, and the selectivity for the *Z* versus the *E* isomer was 10:1. The residual *E* isomer was easily separated by column chromatography yielding **4** as a yellow oil. The TMS group of **4** was removed by treatment with potassium hydroxide in methanol and the product, **6**, isolated by column chromatography. The proposed stereochemistry of **6** was supported by NOE experiments, which demonstrated a strong enhancement between the protons of ring-B with the adjacent phenyl protons of ring-C.

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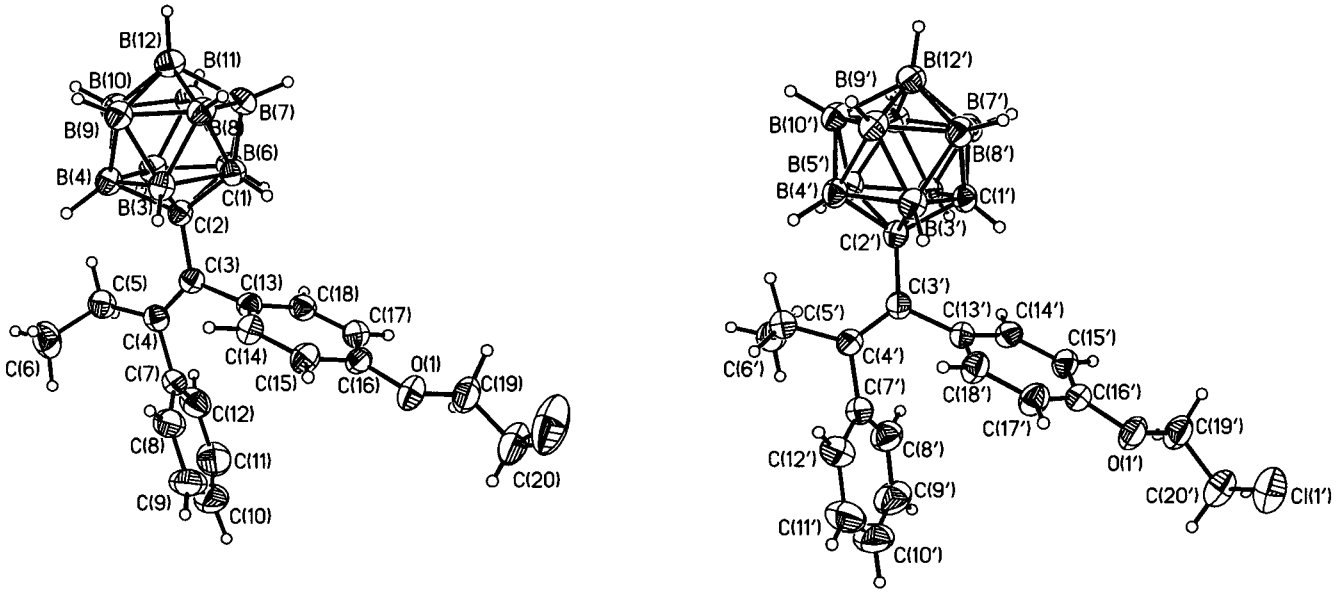

Molecule 1 **Molecule 2**

Figure 2. ORTEP diagrams of the two molecules (1 and 2) of compound **7** showing 50% thermal probability ellipsoids.

There are only a few reported examples of the synthesis of carboranes from ene-ynes,[20] the first being 1-isopropenylcarborane.[21] In our work, compound **7** was isolated in poor yield (10%) despite attempts to improve the yield by changing the nature of the Lewis base−decaborane complexes ($B_{10}H_{12}X_2$, X = CH_3CN, CH_3SCH_3) or the solvent systems (benzene, acetonitrile, toluene, acetonitrile−toluene mixtures) or by changing the ratio of alkyne to the decaborane adduct (1:1, 1:3, 1:10). The low yields may be attributable to the highly conjugated nature of the system, which reduces the reactivity of the alkyne toward formation of the carborane. Nevertheless, an appreciable quantity of **7** was isolated as X-ray quality crystals.

There were two independent molecules of **7** in the unit cell (Figure 2), both with the expected *Z*-geometry.[22] The major difference between the two molecules was the orientation of the ethyl groups (tortional angles for molecules 1 and 2 are −122.7° and 112.1°, respectively). The molecules, like tamoxifen itself, adopt a propeller-like structure, which is important if the derivatives are to retain affinity for the estrogen receptor.[23] The dihedral angles between the planes defined by the phenyl rings (B and C) and the alkene bond demonstrate that the B-ring in molecule 1 is nearly perpendicular to the alkene plane. The second molecule has a slightly different orientation, which is most likely a result of solid-state packing effects. The angles between the planes are significantly larger that those of tamoxifen itself (approximately 54°) which can possibly be ascribed to the size of the carborane and the fact that there appears to be a preference for the orientation of the carborane C−H group to point toward the open face of ring-B.[24] Contrastingly, the dihedral angles between the planes defined by the B and C rings in both molecules are nearly identical to that for tamoxifen.

Table 1. Selected Bond Lengths [Å] for Compound 7

molecule **1**		molecule **2**	
C(3)−C(4)	1.353(3)	C(3′)-C(4′)	1.347(3)
C(2)−C(3)	1.518(3)	C(2′)-C(3′)	1.524(3)
C(4)−C(7)	1.506(3)	C(4′)-C(7′)	1.498(3)
C(1)−C(2)	1.674(3)	C(1′)-C(2′)	1.657(3)
C(2)−B(5)	1.712(3)	C(2′)-B(5′)	1.709(3)
C(2)−B(4)	1.717(3)	C(2′)-B(4′)	1.724(3)
C(2)−B(3)	1.741(3)	C(2′)-B(3′)	1.749(3)
C(2)−B(6)	1.746(3)	C(2′)-B(6′)	1.732(4)
C(1)−B(8)	1.692(4)	C(1′)-B(8′)	1.696(4)
C(1)−B(7)	1.692(4)	C(1′)-B(7′)	1.683(4)
C(1)−B(3)	1.707(4)	C(1′)-B(3′)	1.704(4)
C(1)−B(6)	1.709(3)	C(1′)-B(6′)	1.710(3)

The boron−carbon lengths in the carborane cage ranged from 1.692(4) Å to 1.746(3) Å (average = 1.714(3) Å) in molecule 1 and 1.683(4) Å to 1.749(3) Å (average =1.713(4) Å) in molecule 2 (Table 1). The boron−boron bond distances in both molecules ranged from 1.763(4) Å to 1.790(4) Å. These distances are within the normal range for a carborane.[25] The alkene carbon−carbon distances (C(3) to C(4) and C(3′) to C(4′)) were 1.353(3) Å for molecule 1 and 1.347(3) Å for molecule 2, while the alkene−carborane carbon distances (C(2)−C(3) and C(2′)−C(3′)) were 1.518(3) Å and 1.524(3) Å for molecules 1 and 2, respectively. Both of these bond distances are similar

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to the corresponding bond lengths in tamoxifen (1.34 Å, 1.50 Å).[26]

The synthesis of compound **9** was accomplished by reacting compound **8**, which was prepared from the chloro analogue using a Finkelstein reaction,[27] with dimethylamine in ethanol. These conditions, as expected, resulted in the liberation of hydrogen gas as the *closo*-carborane was converted to the corresponding *nido* species.[28] The tamoxifen analogue was initially isolated as the tetra-*n*-butylammonium salt, but we found that the internal salt, **9**, demonstrated superior stability and increased solubility in aqueous media.

The IR spectrum of compound **9** exhibits a strong B−H stretch at 2514 cm^{-1}, which is shifted from the corresponding stretch in the *closo*-carborane **7** (2579 cm^{-1}) but within the range expected for a *nido*-carborane. The major peak in the electrospray mass spectrum of compound **9** was that of the molecular ion. The parent peak displayed the expected isotopic distribution. The ^{11}B NMR spectrum of **9** was more complex than that for **7**, which is consistent with the loss of symmetry upon degradation of the carborane cage. The ^{1}H-decoupled spectrum for **9** consisted of resonances ranging between −7.90 and −35.20 ppm occurring in a 1:1:1:2:1:1:1:1 ratio. The resonance at −31.58 ppm, in the coupled spectrum, demonstrated coupling to the bridging hydrogen atom. The ^{11}B NMR spectrum of compound **7** exhibited a 1:2:1:1:1 pattern which is typical for monosubstituted *closo*-carboranes.[29] Reversed phase HPLC analysis of compound **9** under several different solvent conditions exhibited only one peak. The two possible diastereomers of **9**, which form upon conversion of the *closo*-carborane to its *nido* counterpart, could not be resolved on the HPLC and were only somewhat visible in the ^{1}H NMR spectra at 500 MHz.

^{1}H NMR experiments indicated that compounds **7** and **9** behave, in solution, like tamoxifen. The allylic protons, for example, were found to be equivalent, suggesting that, at room temperature, compounds **7** and **9** do not exist as discrete atropisomers.[30] Furthermore, the protons on the B-rings in both compounds **7** and **9** appear as AA′BB′ systems, which is identical to that for tamoxifen. The NMR evidence appears to suggest that substitution of ring A with a carborane cage does not significantly alter the range of possible orientations of the B and C rings in solution at room temperature to any greater extent than if ring A was a phenyl group.

E/*Z* isomerization in derivatives and metabolites of tamoxifen is often a major problem because of the differing types (estrogenic versus antiestrogenic) and levels of activities of the two isomers. As a consequence of the highly conjugated systems, 4-hydroxytamoxifen derivatives and metabolites undergo facile isomer interconversion by radical processes.[31] Similarly, ferrocifen, a ferrocenyl derivative of tamoxifen,[32] because of the additional stabilization provided by the iron moiety, undergoes facile isomerization via a cationic mechanism. In contrast, carboranes, like those in compound **7**, will resist radical and cation formation at the carbon atom adjacent to the carborane because of the electron deficient nature of the cluster.[33] Consequently, introduction of a carborane unit will not only preclude catabolism on the carborane cage, but it should impede the process of isomer interconversion. Experiments to verify this hypothesis are currently underway.

Conclusion

The product of this research is an archetype of a potential new class of antiestrogens and BNCT agents in which the carborane was incorporated into the structure of tamoxifen in place of ring-A. The reported synthetic approach yielded a carborane−tamoxifen derivative with the appropriate stereochemistry as shown by X-ray crystallography. The antiestrogenic activity of the reported compounds along with their ability to selectively deliver boron to hormonally responsive cancer cells is currently being evaluated and will be reported in due course.

Experimental Section

General Procedures. Analytical TLC was performed on silica gel 60-F_{254} (Merck) with detection by long wavelength ultraviolet light. HPLC experiments were performed on a Varian ProStar HPLC system fitted with a PDA detector and a C-18 reversed phase column. Gradients of acetonitrile and distilled deionized water were used as the mobile phase. NMR spectra (^{1}H, ^{13}C, ^{11}B) were recorded on Bruker Avance DRX-500, AV300, and AC-200 spectrometers. The X-ray structure was collected using Mo Kα radiation on a Siemens rotating anode instrumented fitted with a CCD detector. Electrospray mass spectrometry (ESMS) was performed on a Fisons Platform quadrupole instrument where samples were dissolved in 50/50 CH_3CN/H_2O. Electron impact (EIMS) and chemical ionization (CIMS) mass spectra were measured at 70 eV with a source temperature of 200 °C on a VG Instruments analytical ZAB-E mass spectrometer equipped with a VG11-250 data system. For CIMS, NH_3 was used as the ionizing agent. IR spectra were run on a Bio-Rad FTS-40 FT FTIR spectrometer. For IR data, s refers to strong, m refers to medium, and w refers to weak stretches. Microanalyses were performed by Guelph Chemical Laboratories (Guelph, Ontario, Canada).

Materials. All commercial reagents were used as supplied with the following exceptions: THF was distilled from sodium and benzophenone, pyridine was distilled from potassium hydroxide, toluene was distilled from calcium hydride, and acetone was distilled from potassium carbonate. Decaborane was purchased from Boron Biologicals and used as received. Compound **2** was prepared by following literature procedures.[19]

3-(4-(2-Chloroethoxy)phenyl)-4-phenylhex-3-ene-1-(2-trimethylsilylacetylene) (4). Four equal portions of fresh *n*-butyllithium (80 mL, 1.6 M hexanes) were added to (trimethylsilyl)acetylene (18 mL, 0.13 mol) in dry THF (100 mL), which had been previously cooled to −78 °C under a nitrogen atmosphere. After five min, compound **2** (33 g, 0.11 mol) dissolved in dry THF (50 mL) was added dropwise. The reaction was allowed to warm to room temperature overnight. Saturated ammonium chloride (20 mL) was slowly added to the reaction followed by distilled water (100 mL) and the resulting solution extracted with ether (4 × 100 mL). The organic fractions were combined, dried over sodium sulfate, and filtered through a fritted funnel, and the filtrate was

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(33) Compounds **7** and **9** showed no evidence of degradation or isomer interconversion in solution or in the solid state when left at room temperature for an extended period of time.

evaporated to dryness. The resulting yellow oil was dissolved in a mixture of freshly distilled pyridine (50 mL) and ether (50 mL) and cooled to 0 °C under nitrogen. Thionyl chloride (16 mL) was added dropwise over 5 min. The reaction was allowed warm to room temperature overnight whereupon distilled water (100 mL) was added slowly while cooling the solution over ice. Aqueous HCl (1 M, 100 mL) was added, and the layers were separated. The dark aqueous layer was extracted with ether (3 × 200 mL) and combined with the original organic fraction. The organic solution was further extracted with 1 M HCl (3 × 100 mL) and dried over sodium sulfate and the solvent evaporated leaving an orange/red oil. The product, a yellow oil (27.2 g, 65%), was isolated by column chromatography (100% hexanes on silica). TLC (70:30 v/v hexanes−ether): R_f 0.71; IR (NaCl, cm^{-1}): ν 2967(s), 2929(m), 2134 (s), 1608(s); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.14−6.60 (m, 9H), 4.11 (t, 2H), 3.72 (t, ^3J = 6.0 Hz, 3H), 2.89 (q, 2H), 1.03 (t, ^3J = 7.4 Hz, 3H), 0.24 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 152.41, 147.77, 136.42, 126.73, 125.82, 124.30, 123.71, 122.53, 115.04, 109.47, 101.49, 94.16, 63.53, 37.49, 27.09, 7.96; MS (EI): *m*/*z* calcd for $C_{23}H_{27}OSiCl$, 382.153, found 382.152.

3-(4-(2-Chloroethoxy)phenyl)-4-phenylhex-3-ene-1-yne (6). To compound **4** (26.5 g, 69.1 mmol), dissolved in absolute methanol (200 mL), was added potassium hydroxide (4.26 g, 76.0 mmol). The reaction was maintained at ambient temperature overnight under nitrogen. After the addition of distilled water (100 mL), the mixture was extracted with ether (3 × 50 mL). The organic fractions were pooled, dried over sodium sulfate, and gravity-filtered, and the solvent was removed by rotary evaporation leaving a yellow-colored solid. The product was initially purified by flash silica gel chromatography (4% ether in petroleum ether) followed by recrystallization from petroleum ether: a colorless solid (15.62 g, 73%), mp 53−55 °C; TLC (8% ether:hexanes): R_f 0.59; IR (CH_2Cl_2, cm^{-1}): ν 3301(m), 3055(m), 2974(m), 2935(w), 2874(w), 1607(m), 1508(s); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.16−6.64 (m, 9H), 4.12 (t, ^3J = 6.0 Hz, 2H), 3.73 (t, 2H), 3.29 (s, 1H), 2.91 (q, ^3J = 7.5 Hz, 2H), 1.03 (t, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 156.76, 152.49, 140.37, 131.63, 130.93, 128.96, 128.01, 126.90, 118.24, 113.82, 84.24, 81.38, 67.80, 41.77, 31.16, 12.40; MS (EI): *m*/*z* calcd for $C_{20}H_{19}OCl$, 310.114, found 310.112. Anal. Calcd for $C_{20}H_{19}OCl$: C, 77.29; H, 6.16. Found: C, 77.66; H, 6.34.

***Z*-1-(1,2-Dicarba-*closo*-dodecaboranyl)-1-(4-(2-chloroethoxy)phenyl)-2-phenylbut-1-ene (7).** Compound **6** (14.43 g, 46.43 mmol) was added as a solid to dry toluene (150 mL) under nitrogen. 6,9-Bis(acetonitrile)decaborane (10.31 g, 51.07 mmol) was added in one portion. The reaction mixture was brought to reflux and monitored by TLC and IR spectroscopy. After 24 h, the solvent was removed by rotary evaporation leaving a yellow-colored oil. The oil was dissolved in CH_2Cl_2 (100 mL) and extracted with 0.1 N NaOH (3 × 50 mL). The aqueous fractions were pooled and further extracted with CH_2Cl_2 (3 × 50 mL). All organic fractions were combined and dried over sodium sulfate and gravity-filtered. The solvent was removed by rotary evaporation leaving a yellow solid. The crude product was purified by silica gel chromatography (4% ether in petroleum ether) and the resulting solid recrystallized from petroleum ether resulting in X-ray quality crystals (2.0 g, 10%). The compound showed: mp 55−57 °C; TLC (8% Ether: Hexanes): R_f 0.50; IR (CH_2Cl_2, cm^{-1}): ν 3303(m), 3055(m), 2970(m), 2935(m), 2579(s), 1607(s); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.16−6.64 (m, Ar−H), 4.09 (t, ^3J = 6.0 Hz, 2H, OCH_2,), 3.71 (t, 2H, CH_2Cl), 3.13 (s, 1H, CH), 2.92 (q, ^3J = 7.5 Hz, 2H, CH_2CH_3,), 0.91 (t, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 157.14, 151.13, 142.40, 132.73, 131.73, 128.99, 128.24, 127.39, 126.00, 114.24, 67.82, 62.98, 41.67, 27.49, 12.56; ^{11}B NMR (96 MHz, $CDCl_3$): δ −3.51, −8.99, −12.67, −13.95; MS (EI): *m*/*z* calcd for $C_{20}H_{29}B_{10}OCl$, 429.290, found 429.292. Anal. Calcd for $C_{20}H_{29}B_{10}OCl$: C, 55.81; H, 6.74. Found: C, 55.78; H, 6.36.

***Z*-1-(1,2-Dicarba-*closo*-dodecaboranyl)-1-(4-(2-iodoethoxy)phenyl)-2-phenyl-but-1-ene (8).** Compound **7** (200 mg, 0.46 mmol) was added to a dry round-bottom flask containing freshly distilled acetone (20 mL). Sodium iodide (350 mg, 2.34 mmol) was added and the reaction mixture brought to reflux for 2 days. The reaction was cooled and the solvent removed by rotary evaporation leaving a colorless solid, which was dissolved in methylene chloride and extracted with distilled water (2 × 25 mL). The organic layer was dried over sodium sulfate, gravity-filtered, and the solvent removed using a rotary evaporator. The crude iodide was purified by radial chromatography with 3% ether in petroleum ether: a colorless crystalline solid (156 mg, 65%), TLC (5% ether:petroleum ether): R_f 0.37; IR ($CHCl_3$, cm^{-1}): ν 3020(m), 2971(w), 2579(s); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.01−6.60 (m, 9H), 4.10 (t, ^3J = 6.6 Hz, 2H), 3.32 (t, 2H), 3.13 (s, 1H), 2.92 (q, ^3J = 7.3 Hz, 2H), 0.91 (t, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 156.86, 151.10, 142.38, 131.98,131.73, 128.95, 128.24, 127.39, 125.99, 114.31, 68.42, 62.96, 27.49, 12.59; ^{11}B NMR (160 MHz, $CDCl_3$): δ −3.50, −8.97, −12.67, −13.96; MS (EI): *m*/*z* observed boron distribution at 521 (20, $[M + 1]^+$); HRMS (EI): *m*/*z* calcd for $C_{18}H_{25}B_{10}$ (M-OCH_2CH_2I), 365.2929, found 365.2918.

***Z*-1-([3]-1,2-Dicarbadodecahydroundecarboranyl)-1-(4-(2-dimethylammonium-methoxy)phenyl)-2-phenylbut-1-ene Inner Salt (9).** The iodide **8** (136 mg, 0.261 mmol) was added to a dry round-bottom flask containing dimethylamine (10 mL, 30% solution in EtOH) whereupon gas evolution was noted. The reaction mixture was stirred at ambient temperature under nitrogen for 3 h. The excess amine was removed by rotary evaporation leaving a viscous yellow oil. The oil was triturated with ethereal HCl and allowed to stand at −10 °C for 48 h. The excess ether was removed by rotary evaporation leaving a yellow semisolid, which was subsequently dissolved in a minimal amount of CH_2Cl_2. The crude product was purified by radial chromatography (10% methanol in methylene chloride), yielding a colorless solid (21 mg, 19%): mp 260 °C (decomp); TLC (20% MeOH:CH_2Cl_2): R_f 0.53; IR (Nujol, cm^{-1}): ν 3119(m), 2963(m), 2927(m), 2854(w), 2752(w), 2514(s), 1603(m); ^{1}H NMR (300 MHz, CD_3CN): δ 7.03−6.58 (m, 9H, Ar−H); 4.12 (t, ^3J = 5.0 Hz, 2H, CH_2NMe_2); 3.39 (t, 2H, OCH_2); 2.83 (s, 6H, $N(CH_3)_2$); 2.55 (q, 2H, CH_2CH_3); 2.17 (s, 1H, CH); 0.92 (t, ^3J = 7.4 Hz, 3H, CH_3); ^{13}C NMR (50 MHz, CD_3CN): δ 154.99, 144.49, 143.58, 141.32, 137.14, 132.03, 129.65, 127.29, 125.36, 117.45, 112.32, 61.08, 57.04, 43.47, 28.84, 12.22; ^{11}B NMR (96 MHz, CD_3CN): δ −7.90, −10.47, −15.37, −18.36, −21.47, −31.58, −35.20; MS (-ES) *m*/*z*: observed boron distributions at 427 (100, [M]); HRMS (ESMS): *m*/*z* calcd for $C_{22}H_{36}B_9NO$, 430.371, found 430.374. Anal. Calcd for $C_{22}H_{36}B_9NO$: C, 61.92; H, 8.26. Found: C, 61.93; H, 8.96.

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Supporting Information Available: ^{1}H NMR assignments, ^{1}H and ^{13}C NMR spectra of compounds **7** and **9**, HPLC trace of compound **9** and crystallographic data for compound **7** (tables of crystallographic details, non-hydrogen coordinates, bond-distances and angles, anisotropic displacement parameters, hydrogen coordinates and packing diagrams). This material is available free of charge via the Internet at http://pubs.acs.org.

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