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Synthesis of *Ortho*- and *Meta*-Re(I)-Metallocarboranes in Water

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A series of metallocarboranes of the types *rac*-$[M(CO)_3(\eta^5\text{-}7\text{-}R\text{-}7,8\text{-}C_2B_9H_{11})]^-$, *rac*-$[M(CO)_3(\eta^5\text{-}7\text{-}R\text{-}8\text{-}R'\text{-}7,8\text{-}C_2B_9H_{11})]^-$, and *rac*-$[M(CO)_3(\eta^5\text{-}7\text{-}R\text{-}7,9\text{-}C_2B_9H_{11})]^-$ (M = Re) were prepared by reacting $[NEt_4]_2[Re(CO)_3Br_3]$ or $[Re(CO)_3(OH_2)_3]Br$ with the corresponding carboranes in the presence of aqueous solutions of either alkali metal or tetraalkylammonium fluoride salts. Carborane derivatives that were investigated included those containing pyridine, amino, carboxylic acid, carbohydrate, and aryl substituents. During the course of the research, it was discovered that Re metallocarboranes can be prepared directly from the respective closo-clusters under similar reaction conditions used with nido-carboranes. Reaction yields ranged from modest to excellent depending on the carborane isomer and the nature of the cage substituent(s). A crystal structure of an amine-substituted Re metallocarborane was obtained where the complex crystallized in the orthorhombic space group $P2_12_12_1$ with $a = 8.982(2)$ Å, $b = 11.563(3)$ Å, $c = 16.811(4)$ Å, $\alpha = \beta = \gamma = 90°$, $V = 1746.1(7)$ Å^3, $Z = 4$, and R1 = 0.0684.

Introduction

There has been a significant amount of interest in using organometallic synthons to design molecular radioimaging and therapy agents.[1] The synthesis of organometallic complexes of radiometals, however, is exceptionally challenging because reactions must be carried out in water at extremely low concentrations of the metal. These requirements complicate the use of traditional organometallic ligands such as cyclopentadienide, which are often insoluble in water and require the use of aggressive reaction conditions to afford good yields of the desired product.

A number of creative strategies for the preparation of organometallic complexes of ^{99m}Tc, the most widely used radionuclide in diagnostic medicine,[2] have been developed. The primary target has been $Cp^{99m}Tc(CO)_3$, which was first prepared by Wenzel et al. using a ligand-transfer reaction performed in organic solvents.[3] This method has been improved upon by others[4] but still requires the use of harsh reaction conditions and organic solvents. More recently, Alberto and co-workers showed that introduction of an electron-withdrawing acetyl (Ac) substituent on Cp facilitated direct synthesis of $AcCp^{99m}Tc(CO)_3$ in aqueous solutions from $[^{99m}Tc(CO)_3(H_2O)_3]^+$.[5] This Tc(I) precursor is attractive because it can be prepared from $^{99m}TcO_4^-$,[6] which is the starting material used in all technetium-labeling reactions, using a commercially available kit.

An alternative to cyclopentadienide-type ligands are carboranes including both $C_2B_4^-$ type ligands[7] and derivatives of dicarba-closo-dodecaboranes. Carboranes of the type *nido*-$[C_2B_9H_{11}]^{2-}$, which are the focus of the study presented, are particularly attractive because, along with being formally

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isolobal to Cp^-, they are capable of forming metal complexes in both organic and aqueous solutions.[8] These ligands can be prepared bearing a wide range of different functional groups at one or more of the carbon and/or boron vertexes using straightforward synthetic procedures.[9] This confers a tremendous amount of flexibility when developing bioconjugation/targeting strategies.[10]

The most common methods used to prepare metallocarboranes are not suitable for the preparation of radiopharmaceuticals because they involve the use of strong bases (NaH, *n*-BuLi, etc.) and anhydrous reaction conditions.[11] It is possible to use concentrated solutions of sodium hydroxide in water to prepare metallocarboranes[12] and radiometallocarboranes;[13] however, we found that attempts to prepare Re and ^{99}Tc carborane complexes from $[M(CO)_3Br_3]^{2-}$ or $[M(CO)_3(OH_2)_3]^+$ under these conditions resulted in the formation of metal clusters.[14] By replacing strong bases with potassium fluoride, our group showed that Re and Tc metallocarboranes can be prepared in good yield in water and that the amount of metal cluster byproducts was significantly reduced.[15] A further benefit of this approach is that the mildly basic conditions are much more amenable to the synthesis of metallocarboranes bearing base-sensitive biomolecules as targeting agents. Herein, we report a further exploration of the general utility of the fluoride method for the synthesis of Re carborane complexes using a range of different carborane derivatives.

Experimental Section

Commercial reagents, unless otherwise stated, were obtained from Aldrich Chemical Co. and used as supplied. Decaborane and meta-carborane were purchased from Dexsil Corp. (Hamden, CT). CO_2(g), which was generated by sublimation of CO_2(s), was passed through a column of Drierite prior to its addition to a reaction. Hydrazine derivatives were visualized using a ninhydrin solution, which consisted of 0.3% of ninhydrin in *n*-butanol containing 3% acetic acid. $[NEt_4]_2[Re(CO)_3Br_3]$[16] and 1-(3′-chloropropyl)-1,2-dicarba-*closo*-dodecaborane[17] were prepared following literature procedures. Analytical TLCs were performed on silica gel 60-F_{254} (Merck), and boron compounds were visualized with 0.1% $PdCl_2$ in hydrochloric acid (3.0 M), which upon heating gave dark brown spots. Silicycle silica gel and silica gel with gypsum (70−230 Mesh) were used for flash column chromatography and preparative TLC, respectively.

NMR spectroscopy was performed on Bruker Avance AV200, AV300, DRX500, and AV600 spectrometers at ambient temperatures. The chemical shifts (δ) for ^{1}H and ^{13}C were recorded relative to residual solvent peaks as internal standards or through reference to trimethylsilane (TMS). $BF_3{\cdot}Et_2O$ was used as the reference standard for all ^{11}B experiments. Fourier transform IR spectra (KBr) were recorded on a Bio-Rad FTS-40 FTIR spectrometer. Electrospray ionization (ESI) mass spectrometry experiments were performed on a Micromass Quattro Ultima instrument where samples were dissolved in 1:1 CH_3OH/H_2O or 1:1 CH_3CN/H_2O mixtures. High-resolution MS was obtained using FAB MS and/or a Waters-Micromass Q-TOF Ultima Global instrument. Elemental analysis of the metallocarboranes was not performed as it gives inconsistent results for these types of compounds, which is likely due to boron carbide formation.[18] Consequently, reproductions of relevant spectra are given in the Supporting Information as evidence of purity. HPLC experiments were performed on a Varian Prostar Model 230 instrument, fitted with a Varian Pro Star model 330 PDA detector, and the wavelength for detection was set at $\lambda = 254$ nm. A Varian Dynamax (L × ID = 250 mm × 4.6 mm) or MicroSorb-MV (300 mm × 5μm) C18 columns were used along with two elution protocols: (Method A) solvent A = 0.1% CF_3CO_2H in H_2O, solvent B = 0.1% CF_3CO_2H in CH_3CN. Gradient elution, 0−3 min, 100% A to 95% A; 3−6 min, 75% A; 6−9 min, 66% A; 9−20 min, 0% A; 20−22 min, 0% A; 22−24 min, 95% A; 24−25 min, 100% A. Method B used the same gradient as Method A; however, solvent A was H_2O and solvent B was CH_3CN. The flow rate for all methods was set at 1 mL/min.

X-Ray Crystallography. X-ray diffraction data for compound **9** were collected on a single-crystal grown from a CH_3OH/CH_2Cl_2 mixture (1:1 v/v) (0.07 × 0.06 × 0.01 mm^3). Data were collected on a p4 Bruker diffractometer fitted with a rotating anode, a Bruker SMART-1K CCD (charge coupled device) area detector, and an Oxford Cryostream cooling system. Diffraction data were collected using the program SMART with graphite-monochromated Mo K_α X-radiation ($\lambda = 0.71073$ Å) and a single crystal of **9** mounted on the tip of a glass fiber. The crystal-to-detector distance was 4.987 cm. Initially, accurate unit cell parameters were determined at 173 K with better than 0.9 Å resolution from a least-squares fit of the strong reflections, collected by a 12° scan in 40 frames using the SMART software. Data were obtained from a chosen number of centered reflections of the setting angles (χ, ϕ, and 2θ) in reciprocal space with truncation of the data ($2\theta = 48°$), using least squares, due to disorder in the high angle reflections. Data reduction was carried out using the SAINT program applying polarization and Lorentz corrections to the integrated diffraction spots. The raw

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Table 1. Crystal and Structure Refinement Data for **9**

empirical formula	$C_{10}H_{23}B_9NO_3Re$	
fw	488.78	
temp	173(2) K	
wavelength	0.71073 Å	
cryst syst	orthorhombic	
space group	$P2_12_12_1$	
unit cell dimensions	$a = 8.982(2)$ Å	$\alpha = 90°$
	$b = 11.563(3)$ Å	$\beta = 90°$
	$c = 16.811(4)$ Å	$\gamma = 90°$
V	1746.1(7) Å^3	
Z	4	
density (calcd)	1.859 Mg/m^3	
absorption coefficient	6.966 mm^{-1}	
$F(000)$	936	
cryst size	0.07 × 0.06 × 0.01 mm^3	
θ range for data collection	2.14−24.00°	
index ranges	$-10 \le h \le 9$, $-13 \le k \le 13$, $-19 \le l \le 19$	
reflns collected	11 192	
independent reflns	2709 [R(int) = 0.1363]	
completeness to $\theta = 24.00°$	99.2%	
absorption correction	semiempirical based on equivalents	
refinement method	full-matrix least-squares on F^2	
data/restraints/params	2709/39/138	
GOF on F	21.102	
final R indices [$I > 2\Sigma(I)$]	R1 = 0.0684, wR2 = 0.0896	
R indices (all data)	R1 = 0.0982, wR2 = 0.0959	
absolute structure param	0.01(3)	
extinction coefficient	0.00076(15)	
largest diff. peak and hole	1.929 and −2.593 e·Å^{-3}	

frame data and the structure were solved from direct methods and refined by full-matrix least squares on F^2 using the Bruker SHELXTL PLUS package. Corrections were made for decay, and an empirical absorption correction was made with the SADABS program on the basis of redundant reflections. Additionally, after completion of data collection, the first 50 frames were re-acquired for the improvement of the decay correction. All non-hydrogen atoms were refined with anisotropic atomic displacement parameters giving rise to the prescribed $R1$ values, except for the carbonyl atoms (C_1, C_2, C_3, O_1, O_2, and O_3), which were refined isotropically due to positional disorder. All hydrogen atoms were assigned on the basis of the difference map and added as fixed contributors at calculated points with isotropic thermal parameters based on their respective carbon atoms. Crystallographic data are presented in Table 1.

Synthesis of Compound 2. Compound **1** (0.21 g, 0.98 mmol) and tetraethylammonium fluoride (TEAF) (0.82 g, 4.91 mmol) were combined and suspended in wet THF (10 mL) at room temperature. The suspension was heated to 80 °C for 14 h and subsequently cooled to room temperature. After the crude solution was concentrated to a yellow oil, the mixture was taken up in ethyl acetate (30 mL) and extracted with 1.0 M HCl (3 × 20 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered, and concentrated to an oily residue. The product was purified by flash chromatography on silica gel (gradient elution: 5:95 CH_3OH/CH_2Cl_2 to 15:85 CH_3OH/CH_2Cl_2). The product, an oil, was resuspended in ddH_2O (5 mL) and lyophilized at −80 °C to yield a cream-colored solid (0.21 g, 64%). TLC R_f (85:15 CH_2Cl_2/CH_3OH + 0.1% AcOH) = 0.82; ^{1}H NMR (200 MHz, CD_3OD): δ 0−2.5 (bm, BH), 1.54 (t, $^3J = 4.5$ Hz, CH_3), 1.82 (m, CH_2), 2.35 (m, CH_2), 3.63 (q, $^3J = 7.0$ Hz, CH_3); $^{13}C\{^1H\}$ NMR (50.3 MHz, CD_3OD): δ 18.14, 36.10, 38.83, 58.14, 181.26; $^{11}B\{^1H\}$ NMR (192.54 MHz, CD_3OD): δ −11.82, −14.03, −18.48, −22.21, −33.95, −37.84; FTIR (KBr, cm^{-1}): ν 3390, 2918, 2524, 1700; HRMS (ESI-Q-TOF): Calcd for $B_9C_5H_{15}O_2$: 206.2028. Found: 206.2055.

Synthesis of Compound 3. Method A. Compound **2** (0.130 g, 0.387 mmol) and $[NEt_4]_2[Re(CO)_3Br_3]$ (0.328 g, 0.426 mmol) were combined in a 10 mL penicillin vial, which was subsequently sealed with a rubber septum and aluminum cap and then flushed with N_2-(g) for 10 min. A solution (2.5 mL) containing 500 mM TEAF-(aq)/absolute EtOH (4:1 v/v) was added and the resultant heterogeneous suspension heated to 100 °C. After 19 h, the reaction was allowed to cool to room temperature and the mixture acidified by the addition of 12 M HCl (100 μL). A solution (66:34 v/v) solution of CH_3CN/ddH_2O (2.0 mL) was added and the crude product separated from excess TEAF by size-exclusion chromatography using Sephadex-G25 resin (10 g, 100−300 μm, 100−5000 MW). After 1 mL fractions were collected, the desired product was purified by flash column chromatography through silica gel (gradient elution: 95:5 CH_2Cl_2/CH_3OH to 90:10 CH_2Cl_2/CH_3OH) yielding a cream-colored solid after concentration under reduced pressure (0.142 g, 61%).

Method B (Direct Synthesis from the closo Isomer). Compound **1** (0.050 g, 0.231 mmol) and $[NEt_4]_2[Re(CO)_3Br_3]$ (0.196 g, 0.254 mmol) were combined in a 10 mL penicillin vial, sealed with rubber septum and aluminum cap and then flushed with N_2-(g) for 10 min. A solution containing 500 mM TEAF(aq)/absolute EtOH (9:1 v/v) was added (1.0 mL), and the resultant suspension heated to 100 °C. After 30 h, the heat was removed and the mixture acidified by the addition of 12 M HCl. CH_3CN was subsequently added (1.0 mL), and the vial vigorously shaken for 5 min. The mixture was frozen at −5 °C overnight in a freezer, resulting in a biphasic mixture with the organic layer portioned on top of the frozen aqueous layer. The organic layer was decanted and concentrated, yielding a brown viscous oil. The product was isolated by flash column chromatography through silica gel (gradient elution: 95:5 CH_2Cl_2/CH_3OH to 90:10 CH_2Cl_2/CH_3OH) as a cream-colored solid upon concentration under reduced pressure (0.098 g, 70%). TLC R_f (4:1 CH_2Cl_2/CH_3OH) = 0.44; mp > 140 °C (dec); ^{1}H NMR (300.13 MHz, acetone-d_6): δ 1.15 (m, CH_3), 1.81 (m, CH_2), 2.33 (m, CH_2), 3.23 (t, CH_3); $^{13}C\{^1H\}$ NMR (151 MHz, acetone-d_6): δ 7.59, 29.04, 35.27, 36.50, 37.03, 42.44, 46.21, 53.25, 176.89, 199.81, 200.66; $^{11}B\{^1H\}$ NMR (160.5 MHz, acetone-d_6): δ 18.82, −5.79, −8.13, −10.46, −11.87, −18.56, −20.02, −22.17; FTIR (KBr, cm^{-1}): ν 2542, 1998, 1893; HRMS (ESI-Q-TOF): Calcd for $B_9C_8H_{15}O_5Re$: 474.7085. Found: 475.1302.

Synthesis of Compound 5. Compound **4** (0.100 g, 0.426 mmol) was combined with potassium hydroxide (100 mg, 1.42 mmol) and dissolved in absolute ethanol (2.5 mL). The reaction mixture was heated at reflux for 24 h, the temperature lowered to room temperature, and CO_2(g) passed through the solution, resulting in the formation of a thick white precipitate. The heterogeneous mixture was filtered, and the clear, colorless eluent concentrated in vacuo, giving a viscous, opaque oil. The crude oil was dissolved in distilled, deionized water (3 mL) and lyophilized, giving the product as a white solid (>99%). TLC R_f (22% MeOH in CH_2Cl_2) = 0.56; mp > 225°C (dec); ^{1}H NMR (600 MHz, CD_3OD): δ 8.37 (d, $J = 4.59$, 1H, H-5), 7.71 (m, 1H, H-3), 7.25 (d, $J = 7.51$, 1H, H-2), 7.14 (m, 1H, H-4), 3.68 (bs, carborane CH), 3.036 (AB, J = −15.3, 1H, CH_2), 2.78 (AB, 1H, CH_2), 0−2.7 (br m, BH); $^{13}C\{^1H\}$NMR (151 MHz, CD_3OD): δ 162.0, 146.53, 136.49, 123.22, 120.63, 57.9, 46.53, 44.90; $^{11}B\{^1H\}$ NMR (160.5 MHz, CD_3OD): δ −8.89, −9.96, −11.96, −14.40, −17.29, −18.25, −19.90, −31.86, −35.44; FTIR (KBr, cm^{-1}): ν 2990, 2940, 2517, 1749; HRMS (ESMS-QTOF) calcd for $C_8H_{17}B_9N$: 225.2241. Found: 225.2246.

Synthesis of Compound 6. Compound **5** (11.4 mg, 0.044 mmol) and $[NEt_4]_2[Re(CO)_3Br_3]$ (32 mg, 0.042 mmol) were combined and dissolved in 100 mM aqueous potassium fluoride (2 mL), and the mixture heated to reflux for 24 h. Upon the mixture being cooled

to room temperature, the pH was adjusted using 0.1 M HCl (final pH ~1) and the mixture extracted with CH_2Cl_2 (3 × 10 mL). All organic portions were combined, dried over sodium sulfate, and the solvent removed by rotary evaporation, giving pure **6** (19 mg, 85%) as an off-white semisolid. No further purification was required. TLC R_f (18% MeOH in CH_2Cl_2) = 0.05; ^{1}H NMR (600 MHz, CD_3OD): δ 8.57 (d, H-5), 7.91 (m, 1H, H-3), 7.41 (m, 2H, H-2, H-4), 3.69 (bs, carborane CH), 3.31 (m, CH_2), 2.1−1.01 (bm, BH); ^{13}C{^{1}H} NMR (50.3 MHz, CD_3OD): δ 199.90, 155.32, 146.38, 142.49, 130.32, 126.43, 50.37, 45.17, 29.25; ^{11}B{^{1}H}NMR (192.54 MHz, CD_3OD) δ −7.88, −11.44, −14.11, −16.77, −18.20, −19.96; IR (KBr, cm^{-1}): ν 2546, 1993, 1885, 1626; HRMS (ESMS-QTOF) Calcd for $C_{11}H_{16}O_3B_9NRe$: 494.1581. Found: 494.1584.

Synthesis of Compound 7. 1-(3′-Chloropropyl)-1,2-dicarba-*closo*-dodecaborane (1.23 g, 5.57 mmol) and sodium iodide (1.67 g, 11.14 mmol) were combined in dry acetone (150 mL) under nitrogen and heated to reflux for 22 h. A precipitate appeared, which, upon completion of the reaction, was collected by filtration through a medium-porosity fritted funnel. The residue was washed with diethyl ether (3 × 25 mL), and all organic fractions pooled and concentrated under reduced pressure, giving an off-white solid. The solid was subsequently dissolved in diethyl ether (25 mL), which was extracted with 0.1 M sodium thiosulfate (2 × 25 mL). The aqueous layer was further extracted with ether (2 × 20 mL), and the organic fractions combined, dried over Na_2SO_4, filtered, and the filtrate concentrated to dryness under reduced pressure, yielding a white solid. The product was purified by flash column chromatography (isocratic elution: 100% $CHCl_3$) through silica gel to give a white solid (1.42 g, 81%). TLC R_f ($CHCl_3$) = 0.56; ^{1}H NMR (200.13 MHz, $CDCl_3$): δ 0.8−3.6 (bm, BH), 1.91 (m, CH_2), 2.33 (m, CH_2), 3.08 (t, CH_2), 3.51 (bs, carborane CH); ^{13}C{^{1}H} NMR (50.3 MHz, $CDCl_3$): δ 3.61, 32.33, 38.84, 61.50, 73.77; ^{11}B-{^{1}H} NMR (160.5 MHz, $CDCl_3$): δ −2.65, −6.05, −9.64, −12.12, −12.52, −13.46; FTIR (KBr, cm^{-1}): ν 2959, 2591; MS (EI): m/z = 312 $[M]^{\cdot+}$, 183 $[M - I]^+$.

Synthesis of Compound 8. Compound **7** (0.27 g, 0.87 mmol) was dissolved in a solution of 33% dimethylamine in ethanol (5.0 mL, 84.9 mmol). The mixture was stirred at room temperature under N_2(g) for 10 min and subsequently heated to reflux overnight. After cooling to room temperature, the orange homogeneous solution was concentrated to dryness under reduced pressure, yielding a deep orange solid. The solid was layered in methanol (5 mL), yielding a heterogeneous suspension, whereupon the product appeared as an insoluble white precipitate. Decantation of the orange solution and repeated washes of the resultant precipitate with cold methanol (3 × 5 mL) gave a cream-colored solid (0.11 g, 58%). TLC R_f (95:5 CH_2Cl_2/CH_3OH) = 0.22; ^{1}H NMR (600.13 MHz, DMSO-d_6): δ 0.0−2.5 (bm, BH), 1.56 (m, CH_2), 1.68 (bs, carborane C−H), 2.72 (s, NCH_3), 2.92 (m, CH_2), 3.33 (m, CH_2), 9.25 (s, NH); ^{13}C-{^{1}H} NMR (150.5 MHz, DMSO-d_6): δ 25.68, 35.51, 42.33, 56.39, 73.77; ^{11}B{^{1}H} NMR (192.5 MHz, DMSO-d_6): δ −11.26, −14.08, −16.67, −18.97, −21.83, −33.33, −37.24; FTIR (KBr, cm^{-1}): ν 3423, 3152, 2959, 2929, 2522; HRMS (FAB, positive ion): Calcd for $B_9C_7H_{24}N$: 219.5723. Found: 219.1606.

Synthesis of Compound 9. Compound **8** (0.070 g, 0.32 mmol) and $[NEt_4]_2[Re(CO)_3Br_3]$ (0.27 g, 0.35 mmol) were suspended in 500 mM aqueous KF (3.0 mL) under Ar, and the temperature raised to 100 °C. After 13 h, the reaction was cooled to room temperature and the pH adjusted to 3 by the dropwise addition of 1 M HCl. The suspension was passed through a fritted funnel containing Celite, which was washed with ethyl acetate (3 × 5 mL). Concentration of the orange-brown filtrate under reduced pressure gave a similarly colored solid, which was purified by flash column chromatography through silica gel (gradient elution: 95:5 CH_2Cl_2/CH_3OH to 85:15 CH_2Cl_2/CH_3OH) (0.11 g, 72%). TLC R_f (85:15 CH_2Cl_2/CH_3OH + 0.1% AcOH) = 0.33; ^{1}H NMR (600.13 MHz, acetone-d_6): δ -0.21−2.4 (bm, BH), 1.53 (m, ^3J = 6.0 Hz, CH_2), 1.60 (bs, carborane CH), 1.68 (m, ^3J = 6.6 Hz, CH_2), 1.94 (m, ^3J = 3.2 Hz, CH_2), 3.18 (d, ^3J = 5.2 Hz, CH_3), 3.29 (m, ^3J = 7.2 Hz, CH_2), 5.70 (bs, NH); ^{13}C{^{1}H} NMR (150.92 MHz, acetone-d_6): δ 26.92, 36.67, 44.14, 46.25, 59.41, 199.70, 200.40; ^{11}B{^{1}H} NMR (160.46 MHz, acetone-d_6): δ -10.22, −10.75, −13.37, −15.26, −18.69, −21.04, −32.53, −36.43; FTIR (KBr, cm^{-1}): ν 2526, 2005, 1899; HRMS (EI) Calcd for $B_9C_{10}H_{23}NO_3Re$: 488.8026. Found: 489.2075.

Synthesis of Compound 11a. Compound **10** (0.506 g, 1.00 mmol) and KOH (1.2 g, 22 mmol,) were dissolved in absolute ethanol (20 mL), and the mixture heated to reflux overnight. The reaction was cooled to room temperature, and the excess KOH was precipitated as K_2CO_3 by passing a stream of CO_2 gas through the solution. The solid was removed by filtration, and the residue washed with cold ethanol (20 mL). The combined filtrates were concentrated under reduced pressure, yielding a white solid, which was dissolved in distilled water, and the pH adjusted to approximately 4 by the dropwise addition of 1 M HCl. The solution was again concentrated to a white solid by rotary evaporation. The product was purified by silica gel column chromatography using a gradient of 50−70% acetone in CH_2Cl_2. A white solid was obtained by evaporating ether solutions of the product fraction. Yield: 83% (0.3 g). TLC R_f (25% CH_3OH/CH_2Cl_2) = 0.38; ^{1}H NMR (500 MHz, CD_3OD): δ 4.51 (d, H-1, $^3J_{1,2}$ = 7.8 Hz), 4.41 (d, H-1′,$^3J_{1',2'}$ = 7.8 Hz), 4.01 (d, 1H, OC*H*$_2$C$_{cage}$C$_{cage}$H, $^2J_{7a,7b}$ = − 10.9 Hz, H-7a), 4.01 (2dd, H-6a,6a′), 3.88 (d, 1H, $^2J_{7a'}$,7b′ = −10.7 Hz, H-7a′), 3.86 (2dd, H-6b,6b′), 3.77 (d, H-7b′), 3.64 (d, H-7b), 3.54−3.48 (m, H-3,3′, H-4,4′), 3.40 (m, H-5,5′), 3.34 (m, H-2,2′), 2.07 (br s, $OCH_2C_{cage}C_{cage}H$, H-9,9′), 2.14−0.30 (br, m, B−H), −2.5 (br, B−H−B); ^{13}C NMR (126 MHz, CD_3OD): δ 103.41, 103.01 (C-1,1′), 78.46 (C-7,7′), 77.12, 77.01 (C-3,3′), 77.84, 77.74 (C-5,5′), 75.16 (C-2,2′), 71.55 (C-4,4′), 62.51 (C-6,6′); ^{11}B NMR (160 MHz, CD_3OD): δ −10.83, −16.72, −21.87, −33.02, −37.50; IR (KBr, cm^{-1}): ν 3429, 2526; HRMS (EI): Calcd for $C_9H_{24}B_9O_6$: 326.2455. Found: 326.2452.

Synthesis of Compound 11b. Compound **11a** (0.103 g, 0.282 mmol) was dissolved in distilled, deionized water (1 mL) and placed in a water/ice bath. Tetraethylammonium bromide in water (2.0 M; 141 μL, 0.282 mmol) was added, whereupon a white precipitate formed. After the precipitate was allowed to congeal, the solid was collected by vacuum filtration and dried using a lyophilizer. The product (0.075 g, 58%) was a white solid. TLC R_f (25% CH_3OH/CH_2Cl_2) = 0.54; ^{1}H NMR (500 MHz, acetone-d_6): δ 4.35 (d, 1H, H-1, $^3J_{1,2}$ = 7.8 Hz), 4.25 (d, 1H, H-1′, $^3J_{1',2'}$ = 7.8 Hz), 3.84 (d, 1H, OC*H*HC$_{cage}$C$_{cage}$H, H-7a, $^2J_{7a,7b}$ = −10.9 Hz), 3.81 (2dd, 2H, H-6a, 6a′), 3.70 (d, 1H, OC*H*HC$_{cage}$C$_{cage}$H, H-7a′, $^2J_{7a'}$,7b′ = −10.7 Hz), 3.71 (2dd, 2H, H-6b, 6b′), 3.59 (d, 1H, OCH*H*C$_{cage}$C$_{cage}$H, H-7b′), 3.49−3.40 (m, 3H, H-3,3′, OCH*H*C$_{cage}$C$_{cage}$H, H-7b), 3.46 (q, 8H, $(CH_3CH_2)_4N^+$, ^3J = Hz), 3.40 (m, 2H, H-4,4′), 3.26 (m, 2H, H-5,5′), 3.20 (m, 2H, H-2,2′), 1.90 (br s, 2H, $OCH_2C_{cage}C_{cage}H$, H-8,8′), 1.39 (tt, 12H, $(CH_3CH_2)_4N^+$); ^{13}C NMR (126 MHz, acetone-d_6): δ 103.07 (C-1), 102.58 (C-1′), 77.96, 77.85 (OCH_2-$C_{cage}C_{cage}$H, C-7,7′), 77.43, 77.37 (C-3,3′), 77.28, 77.20 (C-5,5′), 74.85 (C-2,2′), 71.61 (C-4,4′), 62.70 (C-6,6′), 53.12 ($(CH_3CH_2)_4N^+$), 7.76 ($(CH_3CH_2)_4N^+$); ^{11}B NMR (160 MHz, acetone-d_6): −8.86, −15.99, −21.01, −31.52, −35.85; FTIR (KBr, cm^{-1}): ν 3417 (s, br, O−H), 2526 (s, B−H); HRMS (EI): Calcd for $C_9H_{24}B_9O_6$: 326.2455. Found: 326.2462

Synthesis of Compound 12. Compound **11b** (0.21 g, 0.46 mmol), TEAF (0.35 g, 2.32 mmol), and $[NEt_4]_2[Re(CO)_3Br_3]$ (0.432 g, 5.61 mmol) were dissolved in distilled water (10 mL), and the mixture heated to reflux for 7 days. Analytical HPLC indicated complete consumption of the starting material, and LC-MS indicated that the major peak in the chromatogram corresponded to the target mass. Semipreparative HPLC (80:20 to 54:46 H_2O: AcN, $t = 20$ min) was used to isolate the product. Yield: 45 mg (16%); ^{1}H NMR (600 MHz, CD_3CN): δ 4.19 (d, 1H, $^3J_{1,2} = 7.6$ Hz, H-1), 3.90 (2d, 2H, $^2J_{7a,7b} = -10.8$ Hz, H-7a), 3.69 (dd, 1H, $^2J_{6a,6b} = -11.5$ Hz, H-6a), 3.56 (m, 2H, H-6b, 7b), 3.28 (pt, 1H, H-3), 3.22 (pt, 1H, H-4), 3.16 (q, m, NCH_2CH_3, H-5), 3.11 (pt, 1H, H-2), 1.81 (br s, 1H, $OCH_2C_{cage}C_{cage}H$, H-9), 1.21 (t, NCH_2CH_3); ^{13}C NMR (151 MHz, CD_3CN): δ 200.39 (C≡O), 103.68 (C-1), 77.43 (C-3), 77.19 (C-5), 75.82 (C-7), 74.74 (C-4), 62.72 (C-6), 53.06 (NCH_2CH_3), 7.67 (NCH_2CH_3); ^{11}B{^{1}H} NMR (192 MHz, CD_3CN): δ -5.82, −7.65, −8.78, −11.62, −18.35, −19.55, −20.13; FTIR (KBr, cm^{-1}): ν 3425, 2537, 1999, 1898; HRMS (ES-QTOF): Calcd for $C_{12}H_{23}B_9O_9Re$: 595.1794. Found: 595.1785.

Synthesis of Compound 14. Aqueous sodium fluoride (500 mM, 5 mL) was added to compound **13** (50 mg, 0.21 mmol) along with 3 equiv of $[Re(CO)_3(OH_2)_3]Br$ (258 mg, 0.62 mmol), and the mixture heated to reflux for 2 days. After the reaction was allowed to cool to room temperature, the mixture was acidified with 10 M HCl (5 mL). The solution was subsequently diluted with acetonitrile (10 mL) and cooled at −10 °C until the organic layer separated. The acetonitrile layer was removed by pipet and concentrated under reduced pressure. The product was isolated by silica gel chromatography (5% methanol/chloroform) as a dark brown oil (70 mg, 51%). TLC R_f (10% methanol/chloroform) = 0.15; ^{1}H NMR (600 MHz, CD_3OD): δ 7.58 (d, 1H, H-aryl), 7.38 (d, 1H, H-aryl), 7.15 (m, 1H, H-aryl), 7.066 (d, $J = 7.8$ Hz, 1H, H-aryl), 6.98 (t, $J = 7.8$ Hz, 1H, H-aryl), 6.91 (d, $J = 15$ Hz, 1H, H-aryl), 6.84 (t, $J = 7.8$ Hz, 1H, H-aryl), 6.59 (d, $J = 12.2$ Hz, 1H, H-aryl), 6.43 (d, $J = 8.4$ Hz, 1H, H-aryl); ^{13}C{^{1}H} NMR (151 MHz, CD_3OD): δ 206.01, 156.85, 154.73, 149.24, 144.42, 140.88, 135.56, 132.36, 130.66, 129.71, 128.20, 127.81, 127.22, 126.58, 125.71, 124.88, 114.57, 114.07, 58.54, 58.38, 57.11, 56.85; ^{11}B{^{1}H} NMR (160 MHz, CD_3OD): δ −9.04, −11.61, −15.80, −19.57, −20.46, −21.93; FTIR (KBr, cm^{-1}): ν 3440, 2557, 2001, 1900, 1615, 1513; ESMS (negative ion): 571.2 $[M]^-$.

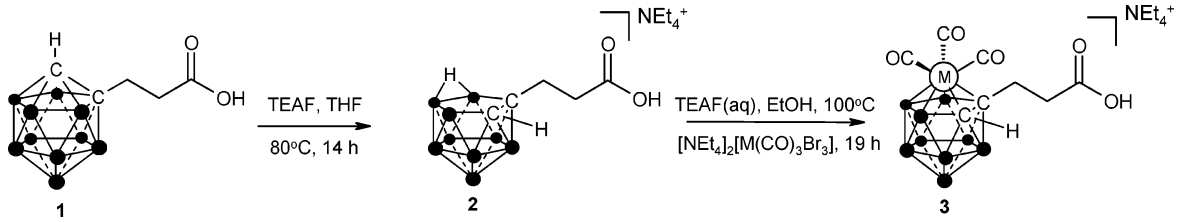
Synthesis of Compound 16. *n*-BuLi (2.77 mL, 6.93 mmol; 2.5 M in hexanes) was added dropwise to a rapidly stirring solution of 1,7-dicarba-*closo*-dodecaborane (1.0 g, 6.93 mmol) in dry diethyl ether (125 mL) at −10 °C under a nitrogen atmosphere. The reaction mixture, which was maintained at −10 °C for 45 min, was subsequently added dropwise over 15 min to a stirring solution of methyl-3-bromopropionate (823 μL, 1.27 g, 7.63 mmol) in dry diethyl ether (125 mL) at −10 °C under nitrogen. The temperature was maintained for an additional 30 min at −10 °C and then brought to reflux. After 2.5 h, the crude reaction was concentrated under reduced pressure, yielding a viscous oil, which was resuspended in diethyl ether (75 mL) and extracted with acidified brine (pH = 0.1; 3 × 75 mL). The organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure giving a pale yellow oil, and the target was isolated by silica gel chromatography (gradient elution: 5% ethyl acetate to 10% ethyl acetate in hexanes). The desired product was recrystalized from a solution of CH_3CN/acetone (6:1) yielding a powdery white solid (0.76 g, 46%). TLC R_f (5:95 EtOAc/hexanes) = 0.13; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.0−3.0 (bm, BH), 1.73 (m, CH_2), 2.44 (m, CH_2) 2.89 (s, CH_3), 3.52 (bs, carborane CH); ^{13}C{^{1}H} NMR (50.3 MHz, $CDCl_3$): δ 28.04, 34.05, 41.56, 41.96, 80.53, 173.93; ^{11}B{^{1}H} NMR (96.3 MHz, $CDCl_3$): δ −7.08, −10.93, −13.72, −17.41; FTIR (KBr, cm^{-1}): ν 3067, 2603, 1728; MS (ESMS): 273.3 $[M + K]^+$.

Synthesis of Compound 17. Compound **16** (0.050 g, 0.217 mmol) and $[NEt_4]_2[Re(CO)_3Br_3]$ (0.184 g, 0.234 mmol) were combined in a 10 mL penicillin vial, sealed with a rubber septum and aluminum cap and then flushed with N_2(g) for 10 min. A solution containing 500 mM TEAF(aq)/absolute EtOH (9:1 v/v) was added (1.0 mL), and the resultant suspension heated to 100 °C. After 22 h, the heat was removed and the mixture acidified by the addition of 12 M HCl. CH_3CN was subsequently added (1.0 mL), and the vial vigorously shaken for 5 min. The mixture was frozen at −5 °C overnight in a freezer, resulting in a biphasic mixture with the organic layer portioned on top of the frozen aqueous layer. The organic layer was decanted and concentrated, yielding a brown viscous oil. The product was isolated by flash column chromatography through silica gel (gradient elution: CH_2Cl_2 to 90:10 CH_2Cl_2/CH_3OH) as a cream-colored solid (0.061 g, 57%). TLC R_f (85:15 CH_2Cl_2/CH_3OH + 0.1% AcOH) = 0.44; ^{1}H NMR (500.13 MHz, 5:1 CD_3OD- acetone-d_6): δ 1.0−3.0 (b, BH), 1.39 (t, $^3J = 5.8$ Hz, CH_3), 1.74 (bs, carborane CH), 2.09, 2.22 (t, CH_2), 2.33, 2.39 (m, CH_2) 3.48 (q, $^3J = 7.2$ Hz, NCH_2); ^{13}C{^{1}H} NMR (125.77 MHz, acetone-d_6): δ 7.47, 33.37, 37.59, 52.77, 53.69, 85.31, 172.73, 200.38; ^{11}B{^{1}H} NMR (160.46 MHz, CD_3OD): δ -6.68, −10.81, −13.06, −16.51, −18.44, −22.05; FTIR (KBr, cm^{-1}): ν 2032, 1915; HRMS (ESI-Q-TOF): Calcd for $B_9C_9H_{14}O_5Re$: 475.1370. Found: 475.1404.

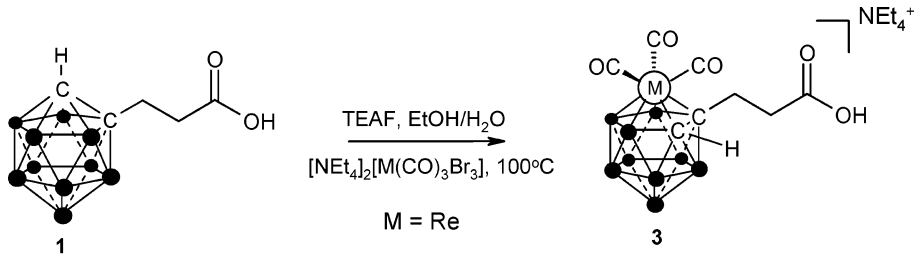
Synthesis of Compound 18. *n*-BuLi (2.77 mL, 6.93 mmol, 2.5 M in hexanes) was added dropwise to a rapidly stirring solution of meta-carborane (1.0 g, 6.93 mmol) in dry diethyl ether (125 mL) at −10 °C under a nitrogen atmosphere. The reaction mixture, which was maintained at −10 °C for 45 min, was subsequently added dropwise over 15 min to a solution of dibenzylazodicarboxylate (DBzAD) (2.30 g, 7.7 mmol) in dry diethyl ether (125 mL) at −10 °C under nitrogen. The reaction was stirred for 1 h, whereupon it was heated to reflux 2.5 h. After cooling to room temperature, the reaction was concentrated under reduced pressure, yielding a viscous oil, which was taken up in ethyl acetate (75 mL) and washed with 1.0 M HCl (3 × 75 mL). The organic layer was dried over $MgSO_4$, and the solvent removed under reduced pressure to yield a viscous oil, which was purified by chromatography on silica gel (isocratic elution: 1:4 Et_2O/p.Et_2O) giving the final product as a white solid (1.81 g, 59%). TLC R_f (3:7 Et_2O/p.Et_2O) = 0.40; mp = 101−104 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 0.9−3.3 (bm, BH), 2.88 (s, CH), 5.07−5.09 (m, CH_2), 6.65 (bs, NH), 7.18−7.30 (m, C_6H_5); ^{13}C{^{1}H} NMR (50.3 MHz, acetone-d_6): δ 35.49, 52.88, 68.20, 69.25, 128.25, 128.57, 134.69, 152.85, 155.01; ^{11}B{^{1}H} NMR (96.3 MHz, $CDCl_3$): δ −5.60, −11.45, −12.90, −15.65; FTIR (KBr): ν 3310, 3053, 2632, 1745; HRMS (ESI-Q-TOF): Calcd for $C_{18}B_{10}H_{26}N_2O_4$: 442.1265. Found: 441.1297.

Synthesis of Compound 19. Compound **18** (0.10 g, 0.23 mmol) and TEAF (0.15 g, 0.90 mmol) were suspended in wet THF (2.3 mL), and the mixture heated to 80 °C for 18 h. The mixture was subsequently cooled to room temperature, concentrated to dryness, and purified by flash chromatography with silica gel (isocratic elution: 1:9 CH_3OH/CH_2Cl_2), to give the desired product as a flaky cream-colored solid (0.124 g, 98%). TLC R_f (85:15 CH_2Cl_2/CH_3OH + 0.1% AcOH) = 0.48; ^{1}H NMR (300.13 MHz, acetone-d_6): δ 0.5−2.5 (bm BH), 1.30 (m, CH_3), 3.34 (m, CH_2), 3.65 (s, NH), 5.11 (m, CH_2), 7.26(m, C_6H_5); ^{13}C{^{1}H} NMR (50.3 MHz, acetone-d_6,): δ 7.55, 15.46, 49.73, 52.80, 65.94, 66.69, 66.98, 67.54, 127.72, 128.09, 128.32, 128.45, 128.86, 129.01, 137.76, 137.96, 156.18, 157.20; ^{11}B{^{1}H} NMR (96.3 MHz, acetone-d_6): δ 19.65, 18.93, -2.85, −7.07, −20.43, −23.28, −34.13, −37.72; FTIR (KBr, cm^{-1}):

Scheme 1



Scheme 2



ν 3364, 3002, 2535, 1755, 1706; HRMS (ESI-Q-TOF): Calcd for $C_{19}B_{10}H_{26}N_2O_6$: 432.2780. Found: 432.2782.

Results and Discussion

One of the limitations of the fluoride-based approach for preparing rhenacarboranes that we reported previously is that the products were formed as a mixture of different salts. This is a consequence of the fact that the Re(I) starting material was used as the $[NEt_4]^+$ salt, which was reacted with the potassium salts of fluoride and the nido-carborane ligand. Traditional ion-exchange procedures were not particularly effective at producing the final product with a single counterion, and it often resulted in a significant loss of product due to absorption on the resin. Tedious fractionation following column chromatography was somewhat effective at producing batches of compound containing single counterions, although this approach compromised the overall yield.

To mitigate the mixed-counterion problem, the complexation reaction we reported previously was repeated using an aqueous solution of tetraethylammonium fluoride (TEAF) in place of KF and the NEt_4^+ salt of **2** (Scheme 1). To prepare the appropriate nido-carborane salt, compound **1** was treated with TEAF in wet THF following the methodology developed by Fox et al.[19] Compound **2** was isolated in 64% yield following chromatographic purification, which was needed to remove unreacted starting material. Compound **2** was subsequently reacted with $[NEt_4]_2[Re(CO)_3Br_3]$ in a 500 mM solution of TEAF in water/EtOH, and the mixture heated to reflux. After approximately 19 h, the product, compound **3**, was isolated in 61% yield.

The characterization data for **3** were consistent with our previously reported results, with the only changes being associated with the different counterions. Maintaining a single counterion improved the isolated yield, and it demonstrated that the Re-carborane complexes can be prepared in aqueous solution using different sources of fluoride ion.

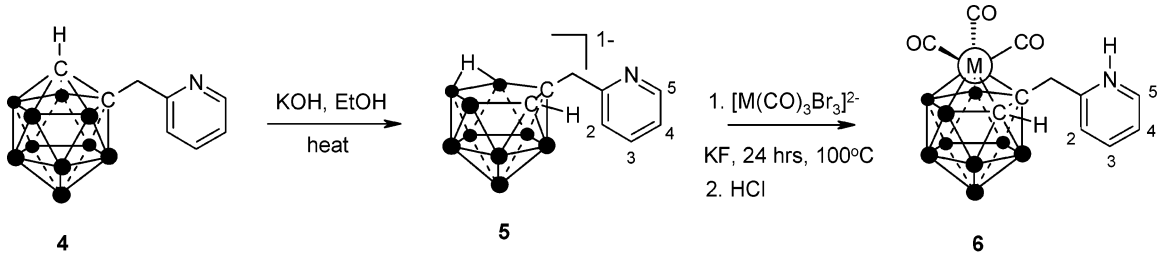
(19) Fox, M. A.; MacBride, H.; Wade, K. *Polyhedron* **1997**, *16*, 2499.

In light of the fact that fluoride can be used to degrade closo-carboranes to the corresponding nido-clusters and, as demonstrated above, to facilitate formation of the desired Re-carborane complexes, attempts were made to prepare the metal complexes directly from closo-carboranes. Reports of the direct formation of a metallocarborane from the corresponding closo-isomer are rare,[12] and there currently exists no method to carry out such a reaction in water. This approach would offer a number of advantages in that there would be a reduction in the number of steps necessary to prepare the desired complex and it would eliminate one of the counterions present in solution. To test the feasibility of this approach, compound **1** was combined with a slight excess of $[NEt_4]_2[Re(CO)_3Br_3]$ in a solution of 500 mM TEAF containing a small quantity of absolute ethanol which was needed to solubilize the closo-carborane (Scheme 2). The heterogeneous suspension was heated at 100 °C, and after 30 h, TLC indicated complete consumption of **1**. Extraction followed by chromatography led to isolation of the desired product in 70% yield.

The majority of the developmental work on the fluoride reaction was done using compounds **1** and **2** because of their reasonable solubility in water and because the pendant acid group provides a site for conjugating the metal complex to targeting molecules. With the fluoride-mediated complexation strategy in hand, the general utility of the methodology was investigated by attempting to prepare rhenium complexes of carboranes bearing a range of different substituents, including groups that could potentially be used as targeting vectors. In addition to varying the nature of the substituents, for certain reactions, a new Re(I) starting material, $[Re(CO)_3(OH_2)_3]Br$, recently reported by Zubieta et al., was employed.[20] The advantage of using this starting material in conjunction with reactions involving closo-carboranes is that the counterion for the metallocarborane is dictated by the source of fluoride ion (NaF, KF, or TEAF). Beyond facilitating the process of isolating the desired products (Na^+

(20) Lazarova, N.; James, S.; Babich, J.; Zubieta, J. *Inorg. Chem. Commun.* **2004**, *7*, 1023.

Scheme 3



and K^+ salts for RP-HPLC purification and TEA salts for silica gel column chromatography), this simple means of varying the counterion is helpful when attempting to prepare high-quality single crystals of novel metal complexes for X-ray diffraction studies.

To determine if substituents bearing good donor atoms would impact complexation yields, a pyridine-substituted carborane was prepared following a literature procedure.[21] Pyridines, which are excellent ligands for Re(I), have been used to construct a number of Re(I) and Tc(I) bifunctional chelators. Pyridine-substituted compounds have the added attraction that they can also be used to prepare piperidine derivatives as a means of targeting specific neuroreceptors. The nido-carborane **5** was reacted with $[NEt_4]_2[Re(CO)_3Br_3]$ in the presence of 100 mM KF, and the solution heated to reflux for 24 h. After the addition of HCl to form the internal salt, the product was isolated in excellent yield (85%) by extraction into dichloromethane (Scheme 3).

The MS of **6** is consistent with the formation of the η^5-rhenacarborane complex, as opposed to a compound in which Re is coordinated to the pyridine nitrogen. The ^{1}H NMR showed some minor shifts in the aromatic region of the NMR spectrum compared to that for the starting material, which is expected given the proximity of the pyridine ring to the carborane cage. The ^{1}H NMR did not show any evidence of the bridging H atom on the cluster, which further supports our hypothesis that metal complex resides on the carborane. The ^{11}B{^{1}H}NMR of **6** showed six peaks with some overlapping signals that are for the most part shifted to higher frequency compared to that of the starting material.

The higher yield of **6** with respect to the other Re-carborane complexes (vide infra) may be associated with the formation of a kinetic product involving coordination of the pyridyl group to rhenium, which helps prevent the formation of metal clusters. This is analogous to the addition of co-ligands to formulations for preparing Tc(V) complexes as a way of preventing the formation of TcO_2. A further advantage is gained if coordination to pyridine takes place initially in that the intermediate complex would situate the *fac*-$[Re(CO)_3]^+$ core in close proximity to the open C_2B_3 face of the cluster. Alternatively, the pyridine nitrogen may simply facilitate deprotonation of the bridging H atom during the complexation process. One clear practical advantage is the ability to form the internal salt of **6** which avoided problems associated with the presence of different counterions.

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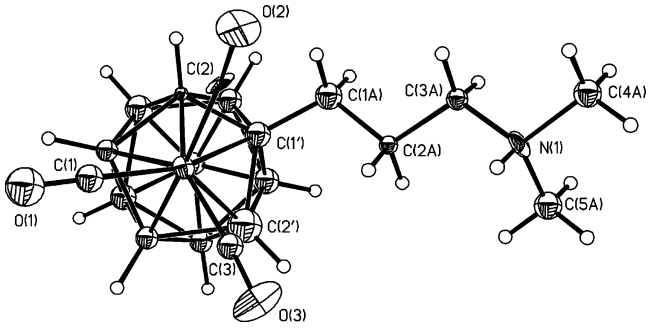

Figure 1. X-ray structure of **9** showing 30% thermal probability ellipsoids

A carborane bearing a pendent tertiary amine was also prepared, and the corresponding $[Re(CO)_3]^+$ complex generated. The target Re metallocarborane was prepared from the dimethylamino nido-carborane ligand **8**, which was synthesized in 58% yield by reacting the iodoalkyl-carborane **7** with an ethanolic solution of dimethylamine overnight at room temperature. Compound **8** and $[NEt_4]_2[Re(CO)_3Br_3]$ were then combined in 500 mM aqueous KF, and the resultant heterogeneous mixture heated to 100 °C. After 13 h, the product was isolated as an internal salt by adjusting the pH to 3 by the dropwise addition of HCl (Scheme 4). The product was subsequently purified by column chromatography through silica gel to give **9** in 72% yield.

The FTIR of **9** showed the characteristic C≡O stretches at 2005 and 1899 cm^{-1}, while the B−H stretch (2526 cm^{-1}) was not significantly shifted from that of the free ligand. The ^{1}H NMR revealed that the methylene protons directly adjacent to the cage are diastereotopic and appear as two distinct multiplets at 1.53 and 1.68 ppm. The protons in the methylene group adjacent to the amine in contrast are homotopic. The presence of the protonated amine is evident in that the *N*-methyl groups, which appear at 3.18 ppm, are split into a doublet from the adjacent N−H group. The amino N−H proton appears as a broad singlet at 5.70 ppm. Its identity was confirmed by adding a small quantity of CD_3-OD to the NMR sample, which caused the resonance to disappear due to exchange.

X-ray-quality crystals of **9** were obtained using a 1:1 (v/v) solution of dichloromethane and methanol. The structure exhibits the tripodal *fac*-$[Re(CO)_3]^+$ core with one CO ligand nearly eclipsing the carborane C−H bond in the solid state (Figure 1). The aliphatic chain almost completely bisects the OC−Re−CO bond angle and extends away from the carborane cage. The average Re−B bond distance is 2.322(14) Å, which is identical to the Re−C_{cage} distance

Table 2. Selected Bond Lengths and Angles for Compound **9**

Re(1)−C(3)	1.845(17)	C(1)−O(1)	1.168(17)
Re(1)−C(1)	1.907(16)	C(3)−O(3)	1.183(18)
Re(1)−C(2)	1.962(17)	C(2)−O(2)	1.115(17)
Re(1)−B(4)	2.275(17)	C(2′)−C(1′)	1.73(2)
Re(1)−B(7)	2.33(2)	C(1′)−C(1A)	1.54(2)
Re(1)−C(2′)	2.34(2)	C(3A)−N(1)	1.522(18)
Re(1)−C(1′)	2.348(19)	C(5A)−N(1)	1.497(19)
Re(1)−B(11)	2.361(19)	N(1)−C(4A)	1.489(18)
C(3)−Re(1)−C(1)	86.6(7)	O(3)−C(3)−Re(1)	176.4(15)
C(3)−Re(1)−C(2)	92.7(7)	O(2)−C(2)−Re(1)	174.2(14)
C(1)−Re(1)−C(2)	88.6(7)	C(1A)−C(1′)−C(2′)	124.1(15)
C(3)−Re(1)−C(2′)	82.2(7)	C(1A)−C(1′)−Re(1)	109.9(11)
C(1)−Re(1)−C(2′)	140.2(6)	C(2′)−C(1′)−Re(1)	68.1(10)
C(2)−Re(1)−C(2′)	129.8(7)	C(1′)−C(1A)−C(2A)	115.3(12)
C(3)−Re(1)−C(1′)	111.1(7)	C(2A)−C(3A)−N(1)	111.4(11)
C(1)−Re(1)−C(1′)	161.6(7)	C(4A)−N(1)−C(5A)	109.4(13)
C(2)−Re(1)−C(1′)	95.4(7)	C(4A)−N(1)−C(3A)	111.3(10)
C(2′)−Re(1)−C(1′)	43.4(6)	C(5A)−N(1)−C(3A)	111.3(12)
O(1)−C(1)−Re(1)	174.4(19)		

(2.32(14) Å). Crystallographic data for **9** are summarized in Tables 1 and 2.

A number of carbohydrate-derived carboranes have been prepared for use in boron neutron capture therapy (BNCT) as a means of increasing the solubility of the cluster in aqueous media.[22] Carbohydrates are attractive not only as hydrophilic prosthetic groups but also as targeting vectors. An ^{18}F-labeled analogue of glucose (^{18}F-FDG), for example, is routinely used to detect sites of increased glucose metabolism using positron emission tomography (PET).[23] To determine if the fluoride-mediated complexation reaction could be used to prepare organometallic−carbohydrate complexes, a carborane−glucose derivative in which the cluster is linked to the C1 position was prepared and reacted with the $Re(CO)_3^+$ core (Scheme 5).

Compound **10**, which was prepared following literature methods,[24] was converted to the corresponding nido-caborane as both the potassium and TEA salts. Formation of the potassium salt involved treating compound **10** with KOH in ethanol and heating the mixture to reflux for 12 h. This method also resulted in the simultaneous deprotection of the acetate esters on C-2, 3, 4, and 6. The nido-carboranyl glucose derivative **11a** could then be extracted into methanol, ethanol, acetone, or tetrahydrofuran, thereby separating the product from residual salts. Further purification was accomplished using silica gel column chromatography and the desired product, **11a**, was obtained as a glassy solid in 83% yield.

The ^{1}H NMR of **11a** showed the existence of two diastereomers, which arise as a consequence of the fact that during degradation of monosubstituted ortho-carboranes two enantiomers (diastereomers in the case of **11a**) are formed. Two distinct signals for the anomeric proton were detected at 4.51 and 4.41 ppm, while two pairs of doublets arising from the protons of the C-1 substituent group were also observed. The formation of the nido-carborane was evident in that there was a broad signal at −2.5 ppm which is associated with the hydrogen atom that is bound to the open C_2B_3 face of the nido-carborane cage. The ^{13}C NMR spectrum of **11a** also indicated a mixture of diastereomers. For instance, there were two signals associated with the anomeric carbon atom at 103.41 and 103.01 ppm and pairs of signals corresponding to the C-3 and C-5 carbon atoms.

Compound **11a** and $[NEt_4]_2[Re(CO)_3Br_3]$ were combined in 1.0 M aqueous KF, and the reaction mixture heated to reflux for 24 h. The mass spectrum showed the presence of the ligand mass and the target mass, plus some rhenium cluster species which appeared at $m/z = 590$ and 633, and at 878. Reduction of the concentration of KF to 0.1 M in subsequent reactions appeared to eliminate these undesired products; however, LC-MS analysis as a function of time showed only very small quantities of the product after 48 h. After a period of 7 days, the peak corresponding to the starting material had diminished almost completely, while the peak corresponding to **12** increased accordingly. The reaction lead to the formation of K^+ and NEt_4^+ salts of the desired complex, which were unfortunately inseparable. To simplify purification, the NEt_4^+ salt (**11b**) was prepared and the reaction repeated using TEAF as the base. Semipreparative HPLC was employed to isolate pure **12** in 16% yield. The low yield of the target was somewhat surprising given that the analytical HPLC of the crude reaction mixture indicated a much higher yield than what was actually isolated.

The IR spectrum of **12** featured the characteristic O−H stretch at 3425 cm^{-1}, B−H stretches at 2537 cm^{-1}, and C≡O stretches at 1999 and 1898 cm^{-1}. The electrospray mass spectrum of the purified product showed the target mass with an isotopic distribution characteristic of a ReB_9 cluster. The ^{1}H and ^{13}C NMR spectra, interestingly, appeared to indicate the formation of unequal amounts of the two diastereomers of **12**. The anomeric doublets at 4.28 and 4.19 ppm for example appeared with integration ratios of approximately 10:1 in favor of the lower-frequency signal. The ^{11}B{^{1}H} NMR spectrum of **12** showed seven signals, which appeared at −5.82, −7.65, −8.78, −11.62, −18.35, −19.55, and −20.13 ppm, with the peaks at −8.78 and −11.62 ppm consisting of two overlapping signals. The signals in the ^{11}B-{^{1}H} spectrum for **12** were shifted to higher frequency versus those in **11b**.

The long reaction time needed to achieve reasonable yields of **12** could be the result of the formation of an intermediate

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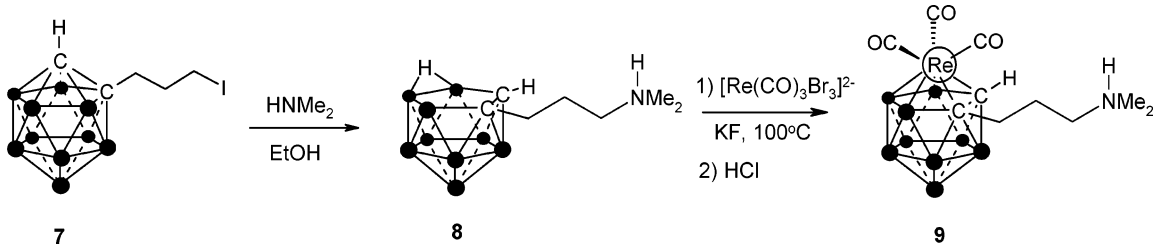
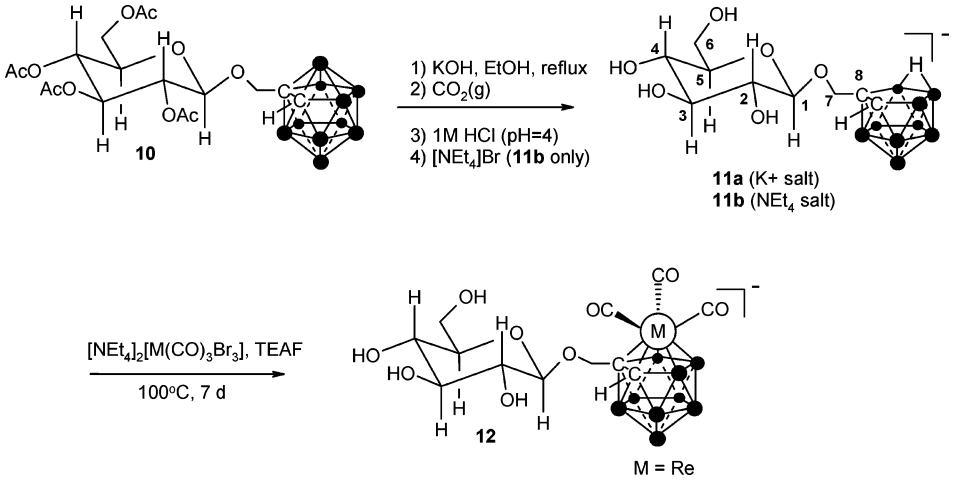
Scheme 4



Scheme 5

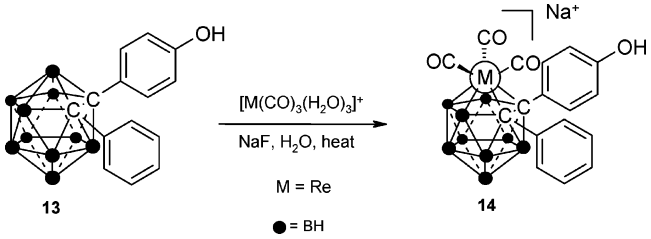


complex between the rhenium tricarbonyl core and multiple glucose hydroxyl groups. It is reasonable to expect that the product(s) of the rhenium core and the glucose hydroxyl groups would form at a rate that is faster than the formation of the metallocarborane. Separate attempts to isolate a Re-glucose complex, however, were unsuccessful. With respect to the observed isomer ratio, stereoselectivity in the complexation reaction is improbable. It is more likely that one isomer was enriched during HPLC purification.

One of the attractive features of carboranes is that they can be derivatized at both of the cage carbon atoms selectively as a means of preparing unique targeting agents. Endo et al. have utilized this feature to prepare a series of diphenyl-substituted carboranes as estrogen agonists and antagonists.[25] The metallocarborane complexes of related analogues could serve as a novel class of inorganic antiestrogens[26] or as radiotracers for imaging estrogen receptor positive tumors.[27] One important consideration for disubstituted derivatives is that the steric hindrance could reduce the yields of the Re complexes. As a consequence, a model compound was prepared and its reactivity toward complexation with the $[Re(CO)_3]^+$ core investigated.

Compound **13** was prepared following literature procedures,[25] and the synthesis of the target metal complex **14**

Scheme 6



carried out directly from the closo carborane (Scheme 6). The reaction was performed at reflux using an excess of Re and 500 mM sodium fluoride. After 2 days, HPLC showed complete consumption of **13** with the target compound being the major product. Compound **14** was obtained via silica gel chromatography as a yellow oil in 51% yield.

The IR and mass spectra of the Re complex are consistent with the proposed structure of **14**. The ^{1}H NMR spectrum is relatively uncomplicated and shows that the each of the aromatic protons exist in a unique environment. In contrast, the ^{13}C NMR spectrum showed multiple environments for most carbon atoms. This is not unexpected as Welch et al. showed that from an orbital overlap perspective, the most favorable conformation of the aryl rings is parallel to the binding face of the carborane.[28] In diaryl carboranes, however, interaction between the rings prevents a parallel arrangement. As such, the rings can adopt multiple θ values between 5° and 40°, where θ is defined as the angle between the plane made by the ring and the plane defined by the two carbon vertexes and the bond to the substituent. Attempts

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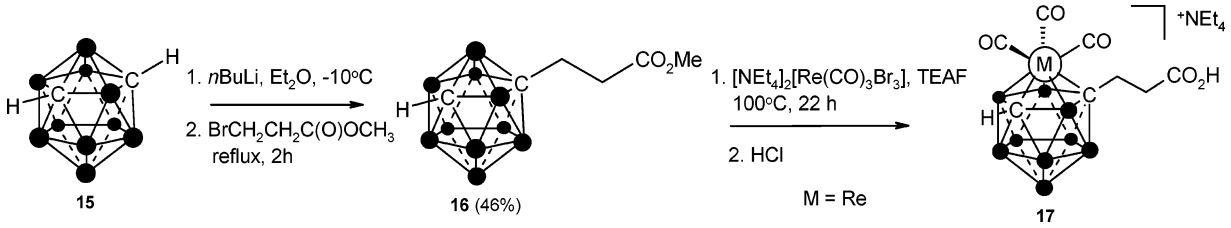
Scheme 7



are being made at present to measure the barrier(s) to rotation and to determine if there is any evidence of correlated motion.

There are three isomeric forms of dicarba-*closo*-dodecaborane, which differ in the relative positions of the carbon atoms in the cluster. Sandwich complexes of nido-carboranes derived from the ortho-isomer are widespread while analogous complexes derived from meta-carboranes are comparatively less common. Investigating complexation reactions with the meta isomer, [*nido*-7,9-$C_2B_9H_{12}$]$^-$ is important because the bonding face of the carborane has a smaller dipole than in the case of [*nido*-7,8-$C_2B_9H_{12}$]$^-$. This difference could result in more stable metal complexes and higher yields of the desired product. Furthermore, the different relative positions of the carbon atoms in the cluster offers a way to vary the spatial orientations of targeting entities attached to disubstituted carboranes in order to achieve favorable receptor binding interactions.

To determine if the fluoride-mediated reaction would work with the meta isomer, the ester **16** (Scheme 7) was prepared and reacted with the [Re(CO)$_3$]$^+$ core. Substituted meta-carboranes are prepared by deprotonating one of the CH vertexes of the cluster followed by treatment with an electrophile. In the example presented here, meta-carborane **15** was treated with *n*-BuLi followed by methyl-3-bromopropionate.[29] Compound **16** was purified by silica gel chromatography and recrystallization, giving the final product in 46% yield. The complexation reaction was carried out using the closo-isomer to allow for direct comparison to the synthesis of compound **3** (Scheme 2). Because saponification of **16** routinely led to a mixture of the closo and nido acids, the methyl ester itself was used for the complexation reaction. The Re complex was prepared successfully by heating the closo-carborane **16** with [NEt$_4$][Re(CO)$_3$Br$_3$] in a solution of 500 mM TEAF(aq)/absolute EtOH (9:1 v/v) at 100 °C for 22 h. The meta-rhenacarborane **17** was obtained as a brownish-colored solid in 57% yield after acid hydrolysis of the methyl ester using HCl(aq), which was done to facilitate direct comparison of the spectral data to that of compound **3**.

The IR spectrum of compound **17** was nearly identical to that of the ortho isomer with the primary difference being the position of the two C≡O stretches which appeared at 2032 and 1915 cm^{-1} in **17** versus 1998 and 1893 cm^{-1} for **3**. The ^{1}H NMR spectrum of **17** was also similar to compound **3** where the methylene protons directly adjacent to the carborane cage appeared as two sets of triplets at 2.22 and 2.09 ppm. The carborane C−H was a broad singlet at 1.74 ppm and the protons from the NEt$_4^+$ cation were visible as a characteristic quartet (3.48 ppm) and triplet (1.39 ppm). The ^{13}C{^{1}H} NMR spectrum of **17** showed a single resonance for the C≡O carbon atoms at 200.4 ppm which was not significantly shifted from that of the ortho analogue (199.9 ppm). As expected, the ^{11}B{^{1}H} NMR spectrum of **17** was significantly different than that for **3**. The difference in the chemical shift, particularly for the highest-field resonances for **3** in comparison to **17**, reflect the differences in the frontier molecular orbitals of the C_2B_3 bonding faces of the two carborane isomers.[30] We believe that the conversion of **16** to **17** is the first example of a direct metalation reaction of a closo-meta-carborane derivative carried out in water. The stability of the resulting complex, at least qualitatively, is comparable to that of the ortho analogue.

We recently reported a series of *C*-hydrazino-*C*-carboxy closo-carboranes derived from meta-carboranes as synthons that can be used to prepare targeted BNCT/BNCS agents and radiotracers.[31] The attraction to these ligands is that they can be conjugated to targeting agents via the acid group or the highly nucleophilic hydrazine. The hydrazine substituents can also be used to form metal complexes and hydrazone conjugates with analogy to HYNIC-type ligands.[32] On the basis of the work described above, it should now be possible to use these ligands to prepare organometallic amino acid analogues.

The initial target was the metal complex of a monosubstituted meta-carborane ligand (Scheme 8). A Cbz-protected hydrazine derivative of meta-carborane **18** was prepared using a modification of our published methodology for the Boc analogue. The Cbz protecting group was used in place of Boc groups, as we discovered that fluoride in the presence of Re(I) can facilitate deprotection of the *tert*-butylcarbamate,[33] even in water, which resulted in the formation of mixtures that included hydrazine−Re complexes. The Cbz-protected hydrazine carborane was subsequently degraded to the corresponding nido-carborane using TEAF in THF in excellent yield. Compound **19** was reacted with [NEt$_4$]$_2$[Re(CO)$_3$Br$_3$] in varying amounts of TEAF. IR and MS experiments before and after purification indicated

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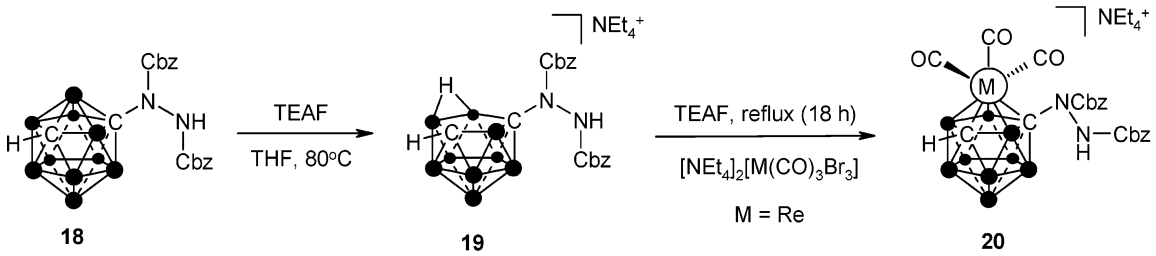
Scheme 8



18 19 20

the presence of the desired product. Unfortunately, despite repeated attempts which included the use of HPLC, compound **20** could not be obtained in sufficient purity. The impurity was likely a Re complex of the hydrazine ligands which had an R_f value similar to that of compound **20**.

From a mechanistic point of view, the fluoride reaction is somewhat perplexing. Fluoride ion in water is not sufficiently basic to remove the bridging hydrogen atom on nido-carboranes, which is necessary in order to form the dicarbollide dianion. In a simple NMR experiment, we observed that fluoride ion in D_2O did not cause the bridging H atom in nido ortho-carborane to exchange to any appreciable extent. The addition of $[NEt_4]_2[Re(CO)_3Br_3]$ did not promote exchange, which indicates that partial coordination of the metal to the open face of the carborane does not lead to a significant drop in the pK_a of the bridging hydrogen atom. From a series of ^{11}B NMR experiments, there was some evidence that the metal complex first coordinates to the carborane in an exopolyhedral fashion; a process which has been observed for a number of other metallocarboranes.[34] More detailed multi-NMR studies are currently underway to explore this process and to further elucidate the overall reaction mechanism. One important role of fluoride that is apparent is its ability to prevent premature degradation of the Re(I) starting material in water at elevated temperatures, thereby providing sufficient time for the desired complexation reaction to occur.

Conclusions

In summary, a new method for the synthesis of Re(I) metallocarborane complexes in water under mildly basic reaction conditions was developed. The synthetic strategy was used to prepare metal complexes of a wide variety of both ortho and meta carborane derivatives. The fluoride-based approach is mild compared to traditional synthetic methods and should be adaptable for the preparation of the corresponding ^{99m}Tc-carborane complexes. Experiments of this nature are described in the accompanying manuscript.

Acknowledgment. We would like to acknowledge The National Sciences and Engineering Research Council (NSERC) of Canada for funding.

Supporting Information Available: MS, ^{1}H, ^{11}B, and ^{13}C NMR and FT-IR. This material is available free of charge via the Internet at http://pubs.acs.org.

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