ORGANOMETALLICS

Article

pubs.acs.org/Organometallics

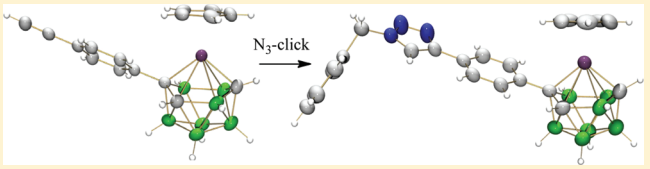
Efficient and Systematic Click-Based Synthetic Routes to Amino Acid Functionalized Metallatricarbadecaboranes

Ariane Perez-Gavilan, Patrick J. Carroll, and Larry G. Sneddon*

Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6323, United States

Supporting Information

ABSTRACT: A general method for the systematic syntheses of amino acid functionalized metallatricarbadecaboranyl complexes has been developed that employs the copper-catalyzed click addition reactions of *N*-azidoacetyl amino acid methyl esters to a *p*-ethynylphenyl substituent at a cage carbon of the metallatricarbadecaboranyl cage. The trimethylsilyl-protected *p*-ethynylphenyl $Li^+[6\text{-}(p\text{-}((CH_3)_3SiC{\equiv}C)C_6H_4)\text{-}nido\text{-}5,6,9\text{-}C_3B_7H_9^-]$ (**1**) tricarbadecaboranyl anion was synthesized via the reaction of *arachno*-4,6-$C_2B_7H_{12}^-$ with *p*-$((CH_3)_3SiC{\equiv}C)C_6H_5CN$. Reaction of **1** with $(\eta^5\text{-}C_5H_5)Fe(CO)_2I$ and $(\eta^5\text{-}C_5H_5)Ru(CH_3CN)_3PF_6$ produced 1-$(\eta^5\text{-}C_5H_5)$-2-(*p*-$((CH_3)_3SiC{\equiv}C)C_6H_4)$-*closo*-1,2,3,4-$MC_3B_7H_9$ (M = Fe (**2**), Ru (**3**)). Deprotection of **2** and **3** with K_2CO_3 in MeOH/THF afforded the ethynyl derivatives 1-$(\eta^5\text{-}C_5H_5)$-2-(*p*-$(HC{\equiv}C)C_6H_4)$-*closo*-1,2,3,4-$MC_3B_7H_9$ (M = Fe (**4**), Ru (**5**)). Click addition of the model compound benzyl azide to **4** and **5** to form the triazole complexes, 1-$(\eta^5\text{-}C_5H_5)$-2-(*p*-(1-$(C_6H_5CH_2)$-1*H*-1,2,3-N_3C_2-4-)$C_6H_4)$-*closo*-1,2,3,4-$MC_3B_7H_9$ (M = Fe (**6**), Ru (**7**)) confirmed the reactivity of the *p*-ethynyl group toward copper-catalyzed click azide addition, with the triazole-linked structure of **7** crystallographically established. Subsequent click addition reactions of the *N*-azidoacetyl amino acid methyl esters to **4** yielded a wide range of amino acid functionalized ferratricarbadecaboranyl complexes: 1-$(\eta^5\text{-}C_5H_5)$-2-(*p*-(1-(Xaa-$C(O)CH_2$)-1*H*-1,2,3-N_3C_2-4-)$C_6H_4)$-*closo*-1,2,3,4-$FeC_3B_7H_9$ (Xaa = PheOMe (**8**), LeuOMe (**9**), ValOMe (**10**), MetOMe (**11**), AlaOMe (**12**), TryOMe (**13**)).



INTRODUCTION

Amino acid substituted metallocenes have recently attracted great interest because of their potential bioapplications.[1] Owing to their stability under aqueous and aerobic conditions, easy chemical modification, and unique electrochemical properties, the amino acid derivatives of ferrocene have been the most extensively studied.[2−5] Examples of bioapplications for which amino acid derivatized ferrocenes are currently being explored include uses as electrochemical probes,[3] organometallic labels in DNA biosensors,[4] and cytotoxic anticancer agents.[5]

We have previously shown[6] that, owing to their similar charge and electron-donating abilities, the tricarbadecaboranide anions 6-R-5,6,9-*nido*-$C_3B_7H_9^-$ (R = Me, Ph) have coordination properties that are in many ways similar to those of the cyclopentadienide $C_5H_5^-$ anion and can be used to make a wide range of metallocene-like sandwich complexes (Figure 1). However, the metallatricarbadecaboranyl complexes have properties, including enhanced oxidative and hydrolytic stabilities and substantially different electrochemical and chemical activities, that are quite distinct from those of their metallocene analogues. These differences could have important advantages in many biomedical applications. For example, we have shown that cationic cyclopentadienyl iron tricarbadecaboranyl complexes[6g] and vanada- and niobatricarbadecaboranyl halide complexes[6j] are not only air and moisture stable but also exhibit potent cytotoxic activities against suspended tumor cells that compliment those of the corresponding metallocenes.

The ultimate utilization of metallatricarbadecaboranyl complexes for many biomedical applications will require the design and synthesis of more complex derivatives with, for example, the chemically reactive groups needed for selective binding properties. With this aim in mind, we report here a new, general route for the syntheses of amino acid modified metallatricarbadecaboranyl complexes, a family of compounds with a range of potential biological applications, including uses as anticancer agents and/or boron carriers for boron neutron capture therapy.[7]

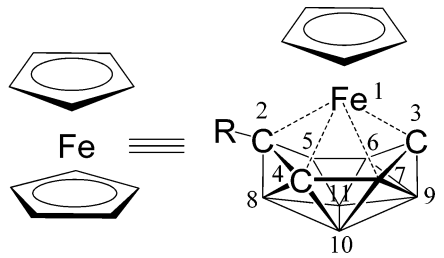


Figure 1. Comparison of the sandwich structures of ferrocene and 1-$(\eta^5\text{-}C_5H_5)$-2-R-*closo*-1,2,3,4-$FeC_3B_7H_9$.

EXPERIMENTAL SECTION

General Synthetic Procedures and Materials. Unless otherwise noted, all reactions and manipulations were performed in dry

Special Issue: F. Gordon A. Stone Commemorative Issue

Received: October 27, 2011
Published: December 23, 2011

   dx.doi.org/10.1021/om201044r | *Organometallics* 2012, 31, 2741−2748

glassware under a nitrogen atmosphere using the high-vacuum or inert-atmosphere techniques described by Shriver.[8]

All azide modified amino acid esters were prepared according to the reported procedures.[9] *p*-[(Trimethylsilyl)ethynyl]benzonitrile, L-methionine methyl ester hydrochloride, L-alanine methyl ester hydrochloride, L-valine methyl ester hydrochloride, L-phenylalanine methyl ester hydrochloride, L-leucine methyl ester hydrochloride, L-tryptophan methyl ester hydrochloride, copper sulfate pentahydrate, sodium ascorbate, dicarbonylcyclopentadienyliodoiron, and sodium azide (Aldrich), tris(acetonitrile)cyclopentadienylruthenium(II) hexafluorophosphate (Strem), and benzyl azide (Pfaltz and Bauer) were used as received. *arachno*-4,6-$C_2B_7H_{13}$ was prepared as described previously.[10] Glyme (Fisher) was freshly distilled from sodium-benzophenone ketyl. All other solvents were used as received unless noted otherwise.

Physical Methods. ^{11}B NMR spectra at 128.4 MHz and ^{1}H NMR spectra at 400.1 MHz were obtained on a Bruker DMX-400 spectrometer equipped with appropriate decoupling accessories. All ^{11}B chemical shifts are referenced to external $BF_3{\cdot}O(C_2H_5)_2$ (0.0 ppm), with a negative sign indicating an upfield shift. All ^{1}H chemical shifts were measured relative to internal residual protons in the lock solvents and are referenced to Me_4Si (0.0 ppm). ^{13}C NMR spectra at 125 MHz were obtained on a Bruker AM-500 spectrometer. High- and low-resolution mass spectra employing chemical ionization with negative ion detection were obtained on a Micromass AutoSpec high-resolution mass spectrometer, while those employing electrospray ionization with positive/negative ion detection were obtained on a Micromass LCT Premier XE high-resolution mass spectrometer. IR spectra were obtained on a Perkin-Elmer Spectrum 100 FT-IR spectrometer. Elemental analyses for **2** and **7**−**9** were carried out at Robertson Microlit Laboratories in Madison, NJ. Elemental analyses for **3**−**6** and **10**−**13** were carried out at the MicroAnalytical Facility at UC Berkeley, Berkeley, CA. Melting points were determined using a standard melting point apparatus and are uncorrected.

Li^+[6-(*p*-$((CH_3)_3SiC{\equiv}C)C_6H_4$)-*nido*-5,6,9-$C_3B_7H_9^-$] (1). LiH (77 mg, 9 mmol) was added to a stirring glyme (20 mL) solution of *arachno*-4,6-$C_2B_7H_{13}$ (1.13 g, 9 mmol) under N_2 at room temperature. The solution was monitored by NMR until ∼97% completion was achieved. At this point, a glyme solution of *p*-[(trimethylsilyl)ethynyl]benzonitrile (8 g, 40.7 mmol in 20 mL glyme) was added by syringe. The reaction mixture was stirred at reflux for 12 h and then cooled and filtered in a glovebag under N_2. The product was stored as a stock solution in the refrigerator. The exact concentration of the stock solution and the yield (87%, 0.15 M) were determined by integrating the resonances in the ^{11}B NMR spectrum of a $B_{10}H_{14}$ sample of known concentration and comparing that value with the integrated value of the resonances of the stock solution. ^{11}B NMR (128.4 MHz, CD_2Cl_2, ppm, *J* in Hz): 5.1 (br, 1B), 0.3 (br, 1B), −5.1 (br, 1B), −10.5 (d, 118, 1B), −13.8 (br, 1B), −23.3 (d, 121, 1B), −28.7 (br, 1B).

1-(η^5-C_5H_5)-2-(*p*-$((CH_3)_3SiC{\equiv}C)C_6H_4$)-*closo*-1,2,3,4-$FeC_3B_7H_9$ (2). A glyme solution of Li^+[6-(*p*-$((CH_3)_3SiC{\equiv}C)C_6H_4$)-*nido*-5,6,9-$C_3B_7H_9^-$] (22 mL of a 0.15 M solution, 3.3 mmol) was added dropwise to a stirring glyme (20 mL) solution of (η^5-C_5H_5)Fe(CO)$_2$I (1 g, 3.3 mmol) under N_2. After it was stirred for 2 h at reflux, the reaction mixture was exposed to air and filtered through a short silica gel plug using CH_2Cl_2 and ether as eluents. The solvent was vacuum-evaporated, and the oily blue residue was redissolved in 5 mL of CH_2Cl_2 and eluted through a silica gel column using 2/1 hexanes/CH_2Cl_2 as the eluent to give **2** in 42% yield (571 mg, 1.3 mmol): blue; mp 177−179 °C. Anal. Calcd: C, 54.98; H, 6.56. Found: C, 54.30; H, 6.42. NCI HRMS *m*/*z* for $C_{19}H_{27}B_7FeSi^-$: calcd 416.1908, found 416.1960. ^{11}B NMR (128.4 MHz, CD_2Cl_2, ppm, *J* in Hz): 3.0 (d, 156, 1B), 0.0 (d, 121, 1B), −10.9 (d, 138, 1B), −11.8 (d, 121, 1B), −25.9 (d, 156, 1B), −28.9 (d, 173, 1B), −33.9 (d, 156, 1B). ^{1}H NMR (400.1 MHz, CD_2Cl_2, ppm, *J* in Hz): 8.52−7.43 (Ph), 6.96 (d, 3, C3*H*), 4.45 (s, Cp), 1.79 (s, C4*H*), 0.29 (s, CH_3Si). ^{13}C NMR (125 MHz, CD_2Cl_2, ppm): 147.4 (Ph), 133.1 (Ph), 132.3 (Ph), 129.5 (Ph), 124.1 (Ph), 122.5 (Ph), 104.4 (C≡*C*H), 95.4 (Ph*C*≡C), 73.1 (*C*3H), 27.1 (*C*4H), −0.5 ((*C*H$_3$)$_3$Si).[11]

1-(η^5-C_5H_5)-2-(*p*-$((CH_3)_3SiC{\equiv}C)C_6H_4$)-*closo*-1,2,3,4-$RuC_3B_7H_9$ (3). A glyme solution of Li^+[6-(*p*-$((CH_3)_3SiC{\equiv}C)C_6H_4$)-*nido*-5,6,9-$C_3B_7H_9^-$] (15 mL of a 0.15 M solution, 2.3 mmol) was added dropwise to a stirred glyme (20 mL) solution of (η^5-C_5H_5)Ru-$(CH_3CN)_3PF_6$ (250 mg, 0.57 mmol) under N_2. After it was stirred at reflux for 12 h, the reaction mixture was exposed to air and filtered through a short silica gel plug using CH_2Cl_2 and ether as eluents. The solvent was vacuum-evaporated and the oily orange residue was redissolved in 5 mL of CH_2Cl_2 and eluted through a silica gel column using 2/1 hexanes/CH_2Cl_2 as the eluent to give **3** in 53% yield (580 mg, 1.22 mmol): orange; mp 174−176 °C. Anal. Calcd: C, 49.58; H, 5.92. Found: C, 49.31; H, 5.75. NCI HRMS *m*/*z* for $C_{19}H_{27}B_7RuSi^-$: calcd 462.1577, found 462.1585. ^{11}B NMR (128.4 MHz, CD_2Cl_2, ppm, *J* in Hz): 4.5 (d, 155, 1B), 2.4 (d, 172, 1B), −10.5 (d, 138, 1B), −11.6 (d, 155, 1B), −29.4 (d, 138, 1B), −30.2 (d, 103, 1B), −30.9 (d, 103, 1B). ^{1}H NMR (400.1 MHz, CD_2Cl_2, ppm, *J* in Hz): 7.63−7.34 (Ph), 5.91 (s, C3*H*), 4.75 (Cp), 2.51 (s, C4*H*), 0.28 (s, $(CH_3)_3$Si). ^{13}C NMR (125 MHz, CD_2Cl_2, ppm): 145.9 (Ph), 132.4 (Ph), 126.7 (Ph), 122.1 (Ph), 104.3 (C≡*C*H), 95.2 (Ph*C*≡C), 83.9 (Cp), 64.9 (*C*3H), 33.1 (*C*4H), −0.5 ((*C*H$_3$)$_3$Si).[11]

1-(η^5-C_5H_5)-2-(*p*-$(HC{\equiv}C)C_6H_4$)-*closo*-1,2,3,4-$FeC_3B_7H_9$ (4). A solution of **2** open to the air (110 mg, 0.27 mmol) and K_2CO_3 (366 mg, 2.7 mmol) in 1/1 MeOH/THF was placed in a sonication bath. After 12 h at ∼43 °C, the solution was filtered through a short silica gel plug using CH_2Cl_2 as eluent. The solvent was vacuum-evaporated, and the oily blue residue was redissolved in 5 mL of CH_2Cl_2 and eluted through a silica gel column using 2/1 hexanes/CH_2Cl_2 as the eluent to give **4** in 83% yield (77 mg, 0.40 mmol): blue; mp 197−200 °C. Anal. Calcd: C, 56.05; H, 5.58. Found: C, 55.76; H, 5.68. NCI HRMS *m*/*z* for $C_{16}H_{19}B_7Fe^-$: calcd 345.1528, found 345.1523. ^{11}B NMR (128.4 MHz, CD_2Cl_2, ppm, *J* in Hz): 3.8 (d, 155, 1B), 0.5 (d, 185, 1B), −10.3 (d, 138, 1B), −11.1 (d, 121, 1B), −25.3 (d, 138, 1B), −28.2 (d, 155, 1B), −33.2 (d, 138, 1B). ^{1}H NMR (400.1 MHz, CD_2Cl_2, ppm, *J* in Hz): 8.52−7.45 (Ph), 6.97 (s, C3*H*), 4.46 (Cp), 3.27 (s, C≡C*H*), 1.80 (s, C4*H*). ^{13}C NMR (125 MHz, CD_2Cl_2, ppm): 147.7 (Ph), 133.2 (Ph), 132.7 (Ph), 129.5 (Ph), 124.0 (Ph), 121.1 (Ph), 82.9 (C≡*C*H), 81.1 (Cp), 78.1 (Ph*C*≡C), 73.3 (*C*3H), 27.1 (*C*4H).[11]

1-(η^5-C_5H_5)-2-(*p*-$(HC{\equiv}C)C_6H_4$)-*closo*-1,2,3,4-$RuC_3B_7H_9$ (5). A solution of **3** open to the air (256 mg, 0.56 mmol) and K_2CO_3 (773 mg, 5.6 mmol) in 1/1 MeOH/THF was placed in a sonication bath. After 12 h at ∼43 °C, the solution was filtered through a short silica gel plug using CH_2Cl_2 as eluent. The solvent was vacuum-evaporated, and the oily orange residue was redissolved in 5 mL of CH_2Cl_2 and eluted through a silica gel column using 2/1 hexanes/CH_2Cl_2 as the eluent to give **5** in 72% yield (154 mg, 0.40 mmol): orange; mp 177−179 °C. Anal. Calcd: C, 49.52; H, 4.93. Found: C, 49.26; H, 4.82. NCI HRMS *m*/*z* for $C_{16}H_{19}B_7Ru^-$: calcd 390.1181, found 390.1142. ^{11}B NMR (128.4 MHz, CD_2Cl_2, ppm, *J* in Hz): 5.0 (d, 153, 1B), 2.3 (d, 170, 1B), −10.3 (d, 153, 1B), −11.4 (d, 136, 1B), −29.2 (d, 129, 1B), −29.9 (br, 1B), −30.8 (d, 114, 1B). ^{1}H NMR (400.1 MHz, CD_2Cl_2, ppm, *J* in Hz): 7.64−7.35 (Ph), 5.92 (s, C3*H*), 4.76 (s, Cp), 3.22 (s, C≡C*H*), 2.51 (s, C4*H*). ^{13}C NMR (125 MHz, CD_2Cl_2, ppm): 146.3 (Ph), 132.6 (Ph), 126.6 (Ph), 120.9 (Ph), 83.9 (Cp), 82.9 (C≡CH), 77.9 (PhC≡C), 65.1 (*C*3H), 59.3 (*C*2H), 33.1 (*C*4H).[11]

1-(η^5-C_5H_5)-2-(*p*-(1-$(C_6H_5CH_2)$-1*H*-1,2,3-N_3C_2-4-)C_6H_4)-*closo*-1,2,3,4-$FeC_3B_7H_9$ (6). Benzyl azide (0.1 mL, 0.06 mmol) and **4** (21 mg, 0.06 mmol) were suspended in a 1/1 mixture of H_2O and ^{t}BuOH (4 mL) under N_2. Solutions of sodium ascorbate (0.01 mL, 1 M) and $CuSO_4$ (0.01 mL, 1 M) were added by syringe. A blue oil was observed to separate from the reaction mixture within 5 min. The reaction was then opened to air and the blue oil decanted, redissolved in CH_2Cl_2, and then dried over $MgSO_4$. After filtration, the solvent was vacuum-evaporated and the blue oil was chromatographed on silica gel plates using 2/1 Hex/EtOAc as eluent to give **6** in 82% yield (23.3 mg, 0.05 mmol): R_f = 0.22; blue; mp 173−175 °C. Anal. Calcd: C, 58.04; H, 5.50. Found: C, 59.74 H 5.81. ESI HRMS *m*/*z* for $C_{23}H_{28}N_3B_7Fe^+$: calcd 478.2223; found 478.2233. ^{11}B NMR (128.4 MHz, CD_2Cl_2, ppm, *J* in Hz): 3.1 (d, 155, 1B), 0.4 (br, 1B), −10.8

(d, 138, 1B), −11.4 (br, 1B), −25.8 (d, 138, 1B), −28.7 (d, 148, 1B), −33.5 (d, 103, 1B). ^{1}H NMR (400.1 MHz, CD_2Cl_2, ppm, *J* in Hz): 8.60−7.39 (Ph), 6.93 (s, C3*H*), 5.63 (s, CH_2), 4.48 (s, Cp), 1.85 (s, C4*H*). ^{13}C NMR (125 MHz, CD_2Cl_2, ppm): 147.3 (Ph), 146.8 (Ph), 134.9 (Ph), 130.0 (Ph), 129.9 (PhCN_3), 128.9 (Ph), 128.6 (Ph), 127.9 (Ph), 126.6 (Ph), 125.9 (Ph), 124.4 (Ph), 119.8 (HCN_3), 81.2 (Cp), 72.8 (*C*3H), 34.0 (CH_2), 27.1 (*C*4H).[11]

1-(η^5-C_5H_5)-2-(*p*-(1-($C_6H_5CH_2$)-1*H*-1,2,3-N_3C_2-4-)C_6H_4)-*closo*-1,2,3,4-$RuC_3B_7H_9$ (7). Benzyl azide (0.1 mL, 0.06 mmol) and **5** (25 mg, 0.06 mmol) were suspended in a 1/1 mixture of H_2O and ^{t}BuOH (4 mL) under N_2. Solutions of sodium ascorbate (0.02 mL, 3.48 M) and $CuSO_4$ (0.06 mL, 1 M) were added by syringe. The reaction mixture was stirred for 12 h at room temperature, after which it was opened to air and diluted with H_2O (30 mL) and then cooled to 0 °C. The resulting orange precipitate was filtered and washed with cold H_2O to give **7** in 66% yield (20.5 mg, 0.04 mmol): orange; mp 169−171 °C. Anal. Calcd: C, 53.00; H, 5.03. Found: C, 51.73; H, 4.73. HRMS *m*/*z* for $C_{23}H_{28}N_3B_7Ru^+$: calcd 524.1879; found 524.2108. ^{11}B NMR (128.4 MHz, CD_2Cl_2, ppm, *J* in Hz): 5.1 (br, 1B), 3.1 (br, 1B), −10.0 (d, 136, 1B), −10.9 (d, 153, 1B), −29.0 (d, 133, 1B), −29.7 (d, 138, 2B). ^{1}H NMR (400.1 MHz, CD_2Cl_2, ppm, *J* in Hz): 7.84−7.34 (Ph), 5.89 (s, C3*H*), 5.59 (N3C=C*H*), 4.76 (s, Cp), 3.76 (s, CH_2), 2.55 (s, C4*H*). ^{13}C NMR (125 MHz, CD_2Cl_2, ppm): 147.4 (Ph), 143.3 (Ph), 134.9 (Ph), 129.8 (PhCN_3), 129.2 (Ph), 128.9 (Ph), 128.6 (Ph), 127.9 (Ph), 126.2 (Ph), 125.7 (Ph), 124.2 (Ph), 119.6 (HCN_3), 95.5 (Cp), 68.4 (*C*3H), 31.7 (CH_2), 30.5 (*C*4H).[11]

Syntheses of Amino Acid Derivatives. A sample procedure is given below, followed by specific experimental and characterization data for each individual experiment.

1-(η^5-C_5H_5)-2-(*p*-(1-(*N*-PheC(O)CH_2)-1*H*-1,2,3-N_3C_2-4-)C_6H_4)-*closo*-1,2,3,4-$FeC_3B_7H_9$ (8). *N*-Azidoacetyl-L-phenylalaninate methyl ester (100 mg, 0.3 mmol) and **4** (25 mg, 0.3 mmol) were suspended in a 1/1 mixture of H_2O and ^{t}BuOH (4 mL) in air. Solutions of sodium ascorbate (0.03 mL, 1 M) and $CuSO_4$ (0.03 mL, 1 M) were added by syringe. The reaction mixture was placed in a sonication bath for 30 min at ∼43 °C, after which it was diluted with ethyl acetate (30 mL) and washed with brine (15 mL). The solution was filtered through anhydrous $MgSO_4$, which was then washed with ethyl acetate until all colored material was eluted. The solvent was vacuum-evaporated, and the oily blue residue was redissolved in ethyl acetate and chromatographed on silica gel plates using 1/1 EtOAc/hexanes as eluent to give **8** in 65% yield (115 mg, 0.19 mmol): R_f = 0.63; blue; mp 178−180 °C. Anal. Calcd: C, 55.48; H, 5.65; N, 9.24. Found: C, 54.77; H, 5.10; N, 9.05. ESI HRMS *m*/*z* for $C_{28}H_{35}N_4O_3B_7Fe^+$: calcd 608.2741, found 608.2625. ^{11}B NMR (128.4 MHz, CD_2Cl_2, ppm, *J* in Hz): 1.8 (br, 1B), −0.8 (br, 1B), −11.9 (d, 164, 2B), −26.9 (d, 156, 1B), −29.8 (d, 121, 1B), −34.6 (br, 1B). ^{1}H NMR (400.1 MHz, CD_2Cl_2, ppm, *J* in Hz): 8.65−7.20 (Ph), 8.04 (s, C=C*H*), 6.95 (s, C3*H*), 6.73 (d, 8, N*H*), 5.14 (d, 5, CH_2C(O)), 4.87 (quart, 6, C*H*C(O)), 4.50 (s, Cp), 3.74 (s, OCH_3), 3.17 (dd, 5, 14, CH_2Ph), 3.05 (dd, 7, 14, CH_2Ph), 1.87 (s, C4*H*). ^{13}C NMR (125 MHz, CD_2Cl_2, ppm): 171.2 (*C*(O)=O), 164.6 (*C*=O), 147.4 (Ph), 147.1 (Ph), 135.5 (Ph), 130.0 (Ph), 129.6 (PhCN_3), 129.1 (Ph), 128.5 (Ph), 127.1 (Ph), 126.8 (Ph), 126.2 (Ph), 124.5 (Ph), 121.4 (HCN_3), 81.2 (Cp), 72.8 (*C*3H), 63.0 (*C*2H), 52.9 (NCHC(O)O), 52.7 (*C*H_2C(O)), 52.4 (OCH_3), 37.4 (*C*H_2Ph), 27.1 (*C*4H).[11]

1-(η^5-C_5H_5)-2-(*p*-(1-(*N*-LeuC(O)CH_2)-1*H*-1,2,3-N_3C_2-4-)C_6H_4)-*closo*-1,2,3,4-$FeC_3B_7H_9$ (9): *N*-azidoacetyl-L-leucinate methyl ester (93 mg, 0.41 mmol); **4** (127 mg, 0.41 mmol); sodium ascorbate (0.04 mL, 1 M); $CuSO_4$ (0.04 mL, 1 M); time 19 h; yield: 27% (56.3 mg, 0.10 mmol); R_f = 0.65; blue; mp 118−120 °C. Anal. Calcd: C, 52.58; H, 6.17; N, 9.81. Found: C, 52.51; H, 6.53; N, 9.47. ESI HRMS *m*/*z* for $C_{25}H_{36}N_4O_3B_7Fe^+$: calcd 573.2817, found 573.2805. ^{11}B NMR (128.4 MHz, CD_2Cl_2, ppm, *J* in Hz) 3.4 (br, 1B), 0.7 (br, 1B), −10.6 (br, 2B), −25.5 (d, 156, 1B), −28.4 (d, 138, 1B), −33.1 (br, 1B). ^{1}H NMR (400.1 MHz, CD_2Cl_2, ppm, *J* in Hz): 8.65−7.58 (Ph), 8.14 (s, C=C*H*), 6.95 (s, C3*H*), 6.56 (d, 7, N*H*), 5.20 (s, CH_2C(O)), 4.64 (m, NC*H*C(O)), 4.49 (s, Cp), 3.73 (s, OCH_3), 1.87 (s, C4*H*), 1.67 (m, CH_2), 1.61 (m, C*H*), 0.93 (d, 6, 2CH_3). ^{13}C NMR (125 MHz, CD_2Cl_2, ppm) 172.6 (C(O)=O), 164.7 (*C*=O), 147.4 (Ph), 147.0 (Ph), 130.0 (Ph), 129.9 (Ph), 129.6 (PhCN_3), 126.8 (Ph), 126.1 (Ph), 124.5 (Ph), 121.6 (HCN_3), 81.2 (Cp), 72.9 (*C*3H), 52.7 (NCH_2), 52.3 (OCH_3), 51.0 (NC(H)C(O)), 41.1 (CH_2CH), 27.0 (*C*4H), 24.8 (CHCH_3), 22.3 (CH_3), 21.5 (CH_3).[11]

1-(η^5-C_5H_5)-2-(*p*-(1-(*N*-ValC(O)CH_2)-1*H*-1,2,3-N_3C_2-4-)C_6H_4)-*closo*-1,2,3,4-$FeC_3B_7H_9$ (10): *N*-azidoacetyl-L-valinate methyl ester (74.5 mg, 0.4 mmol); **4** (100 mg, 0.3 mmol); sodium ascorbate (0.03 mL, 1 M); $CuSO_4$ (0.03 mL, 1 M); time 12 h; yield 45% (65 mg, 0.13 mmol); R_f = 0.67; blue; mp 118−120 °C. Anal. Calcd: C, 51.75; H, 5.97; N, 10.06. Found: C, 51.70; H, 6.15; N, 9.86. ESI HRMS *m*/*z* for $C_{24}H_{33}N_4O_3B_7FeCl^-$: calcd 593.2275, found 593.2261. ^{11}B NMR (128.4 MHz, CD_2Cl_2, ppm, *J* in Hz): 3.1 (br, 1B), 0.5 (br, 1B), −10.7 (br, 2B), −25.6 (d, 138, 1B), −28.4 (d, 121, 1B), −33.1 (br, 1B). ^{1}H NMR (400.1 MHz, CD_2Cl_2, ppm, *J* in Hz): 8.19−7.67 (Ph), 8.64 (s, C=C*H*), 6.96 (s, C3*H*), 6.94 (d, 8, N*H*), 5.26 (d, 1, CH_2), 4.57 (quart, 5, NC*H*C(O)), 4.47 (s, Cp), 3.74 (s, OCH_3), 2.21 (m, C*H*), 1.86 (s, C4*H*), 0.95 (dd, 7, 15, 2CH_3). ^{13}C NMR (125 MHz, CD_2Cl_2, ppm): 171.9 (*C*(O)=O), 165.2 (*C*=O), 147.3 (Ph), 147.0 (Ph), 129.9 (Ph), 129.6 (PhCN_3), 126.8 (Ph), 126.2 (Ph), 124.5 (Ph), 121.8 (HCN_3), 81.4 (Cp), 72.6 (*C*3H), 63.0 (*C*2H), 57.6 (NCHC(O)), 52.6 (NCH_2), 52.2 (OCH_3), 31.1 (CH(CH_3)$_2$), 27.1 (*C*4H), 18.6 (CH_3), 17.5 (CH_3).[11]

1-(η^5-C_5H_5)-2-(*p*-(1-(*N*-MetC(O)CH_2)-1*H*-1,2,3-N_3C_2-4-)C_6H_4)-*closo*-1,2,3,4-$FeC_3B_7H_9$ (11): *N*-azidoacetyl-L-methioninate methyl ester (70 mg, 0.3 mmol); **4** (100 mg, 0.3 mmol); sodium ascorbate (0.03 mL, 1 M); $CuSO_4$ (0.03 mL, 1 M); time 12 h; yield 29% (66 mg, 0.11 mmol); R_f = 0.53; blue; mp 93−95 °C. Anal. Calcd: C, 48.93; H, 5.65; N, 9.51; S, 5.39. Found: C, 48.73; H, 5.78; N, 9.33; S, 5.49. ESI HRMS *m*/*z* for $C_{24}H_{34}N_4O_3B_7FeS^+$: calcd 591.2381, found 591.2384. ^{11}B NMR (128.4 MHz, CD_2Cl_2, ppm, *J* in Hz): 3.9 (br, 1B), 1.2 (br, 1B), −9.8 (br, 2B), −24.8 (d, 156, 1B), −27.8 (d, 121, 1B), −32.7 (br, 1B). ^{1}H NMR (400.1 MHz, CD_2Cl_2, ppm, *J* in Hz): 8.64−7.57 (Ph), 8.11 (s, C=C*H*), 6.94 (C3*H*), 6.75 (d, 8, N*H*), 5.19 (s, CH_2C(O)), 4.49 (s, Cp), 4.08 (quart, 7, NC*H*C(O)), 3.75 (s, OCH_3), 2.51 (t, 7, CHCH_2), 2.06 (s, SCH_3), 1.87 (s, C4*H*), 1.23 (t, 7.1, CH_2S). ^{13}C NMR (125 MHz, CD_2Cl_2, ppm): 171.6 (*C*(O)=O), 164.9 (*C*=O), 147.8 (Ph), 147.4 (Ph), 130.1 (Ph), 130.0 (Ph), 129.3 (PhCN_3), 127.0 (Ph), 126.3 (Ph), 124.5 (Ph), 121.3 (HCN_3), 81.0 (Cp), 72.7 (*C*3H), 63.3 (*C*2H), 52.9 (NC(H)C(O)), 52.7 (NCH_2), 51.9 (OCH_3), 30.7 (CHCH_2), 29.9 (CH_2S), 27.2 (*C*4H), 15.4 (SCH_3).[11]

1-(η^5-C_5H_5)-2-(*p*-(1-(*N*-AlaC(O)CH_2)-1*H*-1,2,3-N_3C_2-4-)C_6H_4)-*closo*-1,2,3,4-$FeC_3B_7H_9$ (12): *N*-azidoacetyl-L-alaninate methyl ester (48.5 mg, 0.2 mmol); **4** (68 mg, 0.2 mmol); sodium ascorbate (0.03 mL, 1 M); $CuSO_4$ (0.03 mL, 1 M); time 10 h; yield 47% (46 mg, 0.09 mmol); R_f = 0.44; blue; mp 120−123 °C. Anal. Calcd: C, 49.94; H, 5.53; N, 10.59. Found: C, 49.64; H, 5.54; N, 10.31. ESI HRMS *m*/*z* for $C_{22}H_{29}N_4O_3B_7Fe^-$: calcd 531.2345, found 530.2424. ^{11}B NMR (128.4 MHz, CD_2Cl_2, ppm, *J* in Hz): 3.5 (br, 1B), 0.8 (br, 1B), −10.3 (br, 2B), −25.3 (d, 138, 1B), −28.1 (d, 155, 1B), −33.1 (d, 121, 1B). ^{1}H NMR (400.1 MHz, CD_2Cl_2, ppm, *J* in Hz): 8.66−7.57 (Ph), 8.13 (s, C=C*H*), 6.96 (s, C3*H*), 6.66 (d, 6, N*H*), 5.21 (s, CH_2C(O)), 4.61 (quint, 7, NC*H*C(O)), 4.47 (s, Cp), 3.75 (s, OCH_3), 1.88 (C4*H*), 1.44 (d, 7, NCH_3). ^{13}C NMR (125 MHz, CD_2Cl_2, ppm): 172.6 (*C*(O)=O), 164.7 (*C*=O), 147.4 (Ph), 147.1 (Ph), 130.0 (Ph), 129.5 (PhCN_3), 126.8 (Ph), 126.2 (Ph), 121.5 (HCN_3), 81.2 (Cp), 72.7 (*C*3H), 52.7 (NCH_2), 52.5 (OCH_3), 48.4 (NC(H)CH_3), 27.2 (*C*4H), 17.7 (CH_3).[11]

1-(η^5-C_5H_5)-2-(*p*-(1-(*N*-TrypC(O)CH_2)-1*H*-1,2,3-N_3C_2-4-)C_6H_4)-*closo*-1,2,3,4-$FeC_3B_7H_9$ (13): *N*-azidoacetyl-L-tryptophanate methyl ester (171 mg, 0.5 mmol); **4** (157 mg, 0.46 mmol); sodium ascorbate (0.03 mL, 1 M); $CuSO_4$ (0.03 mL, 1 M); time 84 h; yield 11% (30 mg, 0.05 mmol); R_f = 0.50; blue; mp 141−145 °C. Anal. Calcd: C, 55.94; H, 5.32; N, 10.87. Found: C, 54.83; H, 5.58; N, 10.44. ESI HRMS *m*/*z* for $C_{30}H_{34}N_5O_3B_7Fe^-$: calcd 645.2662, found 645.2729. ^{11}B NMR (128.4 MHz, CD_2Cl_2, ppm, *J* in Hz): 3.6 (br, 1B), 0.8 (br, 1B), −10.3 (br, 2B), −25.3 (d, 138, 1B), −28.2 (d, 138, 1B), −32.9 (br, 1B). ^{1}H NMR (400.1 MHz, CD_2Cl_2, ppm, *J* in Hz): 7.98−7.09 (Ph), 7.84 (s, N=NC=C*H*), 6.97 (s, C=C*H*), 6.96 (s, C3*H*), 6.55 (d, 8, N*H*), 5.07 (m, NCH_2C(O)), 4.91 (m, NC*H*C(O)), 4.49 (Cp), 3.72 (OCH_3), 3.37 (dd, 5, 15, CHCH_2C=C), 3.29 (dd, 6, 15, CHCH_2C=C), 1.87 (s, C4*H*). ^{13}C NMR (125 MHz, CD_2Cl_2, ppm): 171.7

dx.doi.org/10.1021/om201044r | *Organometallics* 2012, 31, 2741−2748

Table 1. Crystallographic Data Collection and Structure Refinement Information

	2	4	5	7
empirical formula	$C_{19}B_7H_{27}SiFe$	$C_{16}B_7H_{19}Fe$	$C_{16}B_7H_{19}Ru$	$C_{23}B_7H_{26}N_3Ru$
formula wt	415.02	342.83	388.05	521.21
cryst class	orthorhombic	monoclinic	monoclinic	monoclinic
space group (No.)	*Pbca* (61)	$P2_1/c$ (14)	$P2_1/c$ (14)	$C2/c$ (15)
Z	8	4	4	8
a, Å	19.3158(4)	9.5587(14)	9.6436(8)	16.615(4)
b, Å	8.8170(2)	13.199(2)	13.2356(10)	9.876(2)
c, Å	25.1475(5)	13.245(2)	13.4660(10)	31.354(8)
β, deg		94.486(3)	95.869(2)	91.289(3)
V, Å^3	4282.81(16)	1666.0(5)	1709.8(2)	5144(2)
D_{calcd}, Mg/m^3	1.287	1.367	1.508	1.346
μ, mm^{-1}	0.762	0.896	0.908	0.626
λ, Å (Mo Kα)	0.710 73	0.710 73	0.710 73	0.710 73
cryst size, mm	0.32 × 0.08 × 0.03	0.32 × 0.24 × 0.06	0.27 × 0.25 × 0.07	0.25 × 0.18 × 0.10
F(000)	1728	704	776	2112
2θ angle, deg	3.24−55.02	5.28−48.20	5.24−55.12	5.44−55.04
temp, K	143	143	170	140
hkl collected	$-25 \le h \le 24$	$-10 \le h \le 10$	$-12 \le h \le 7$	$-21 \le h \le 21$
	$-11 \le k \le 11$	$-15 \le k \le 11$	$-16 \le k \le 15$	$0 \le k \le 12$
	$-32 \le l \le 32$	$-15 \le l \le 15$	$-17 \le l \le 17$	$0 \le l \le 40$
no. of rflns measd	83 077	12 630	13 049	21 114
no. of unique rflns	4921 (R_{int} = 0.0412)	2637 (R_{int} = 0.0468)	12 266 (R_{int} = 0.0210)	5884 (R_{int} = 0.0556)
no. of obsd rflns ($F > 4\sigma$)	4146	2332	10360	4961
no. of rflns used in refinement	83 077	12 630	12 266	5884
no. of params	362	274	255	308
R^a indices ($F > 4\sigma$)	R1 = 0.0286	R1 = 0.0410	R1 = 0.0419	R1 = 0.0504
	wR2 = 0.0663	wR2 = 0.0977	wR2 = 0.1101	wR2 = 0.1453
R^a indices (all data)	R1 = 0.0390	R1 = 0.0471	R1 = 0.0535	R1 = 0.0577
	wR2 = 0.0714	wR2 = 0.1032	wR2 = 0.1213	wR2 = 0.1525
GOF^b	0.993	1.084	1.071	1.081
final diff peaks, e/Å^3	+0.330, −0.218	+0.339, −0.392	+0.497, −0.793	+0.986, −0.915

^{a}R1 = $\sum||F_o| - |F_c||/\sum|F_o|$; wR2 = $\{\sum w(F_o^2 - F_c^2)^2/\sum w(F_o^2)^2\}^{1/2}$. ^{b}GOF = $\{\sum w(F_o^2 - F_c^2)^2/(n-p)\}^{1/2}$, where n = no. of reflections and p = no. of parameters refined.

(C(O)═O), 164.7 (*C*═O), 147.3 (Ph), 147.1 (Ph), 136.1 (Ph), 130.0 (Ph), 129.5 (PhCN$_3$), 127.4 (Ph), 126.8 (Ph), 126.1 (Ph), 124.5 (C═CHNH), 123.2 (Ph), 122.1 (Ph), 121.4 (HCN$_3$), 119.6 (Ph), 118.2 (Ph), 111.4 (Ph), 109.22 (CH$_2$C═CH), 81.2 (Cp), 72.7 (*C*3H), 63.0 (*C*2H), 52.7 (NCHC(O)), 52.5 (NCH$_2$), 52.4 (OCH$_3$), 27.2 (C(H)*C*H$_2$), 27.0 (*C*4H).[11]

Crystallographic Data. Single crystals of **2**, **4**, **5**, and **7** were grown through slow solvent evaporation from dichloromethane solutions in air or through vapor-liquid diffusion of pentane into a dichloromethane solution.

Collection and Reduction of the Data. X-ray intensity data for **2** (Penn3402) were collected on a Bruker APEXII CCD area detector, while those for **4** (Penn3356), **5** (Penn3337), and **7** (Penn3344) were collected on a Rigaku Mercury CCD area detector; both detectors employed graphite-monochromated Mo Kα radiation (λ = 0.710 73 Å) at temperatures ranging from 140(1) K to 170(1) K. Rotation frames were integrated using SAINT,[12] producing a list of unaveraged F^2 and $\sigma(F^2)$ values that were then passed to the SHELXTL[13] program package for further processing and structure solution on a Dell Pentium 4 computer. The intensity data were corrected for Lorentz and polarization effects and for absorption using SADABS.[14]

Solution and Refinement of the Structures. The structures were solved by direct methods (SIR97[15]). Refinement was by full-matrix least squares based on F^2 using SHELXL-97.[16] All reflections were used during refinement (values of F^2 that were experimentally negative were replaced with F^2 = 0). All non-hydrogen atoms were refined anisotropically, and hydrogen atoms were refined isotropically.

Crystal and refinement data are given in Table 1. Selected bond distances and angles are given in the corresponding figure captions.

RESULTS AND DISCUSSION

We have previously reported[6n] the development of efficient synthetic methods for the formation of boron-functionalized metallatricarbadecaborane complexes based on a strategy of selective cage-boron halogenation followed by palladium-catalyzed coupling reactions. While these methods provide general routes to many important derivatives, they have not as of yet proven useful for the attachment of amino acid groups. This stimulated our development of an alternative strategy targeted at achieving general methods for metallatricarbadecaborane cage-carbon functionalization.

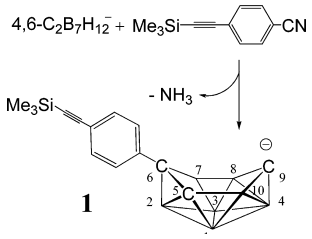
Copper-catalyzed Huisgen 1,3-dipolar cycloaddition (click reaction) is a versatile synthetic tool used to promote the addition of 1,3-dipoles to alkenes and alkynes.[17] Both Metzler-Nolte[18] and Chandrasekaran[19] have used the click reactions of azide-modified amino acids to ethynylferrocenes to produce amino acid functionalized ferrocenes that are joined with a triazole linker. We pursued a similar click-addition strategy to achieve the range of amino acid functionalized metallatricarbadecaboranyl complexes reported herein.

As shown in Scheme 1, the Kang method[20] was utilized for the synthesis of Li$^+$[6-(*p*-((CH$_3$)$_3$SiC≡C)C$_6$H$_4$)-*nido*-5,6,

dx.doi.org/10.1021/om201044r | *Organometallics* 2012, 31, 2741−2748

9-$C_3B_7H_9^-$] (**1**) in ~87% yield via the reaction of *arachno*-4,6-$C_2B_7H_{12}^-$ with TMS-protected *p*-ethynylbenzonitrile (Scheme 1).

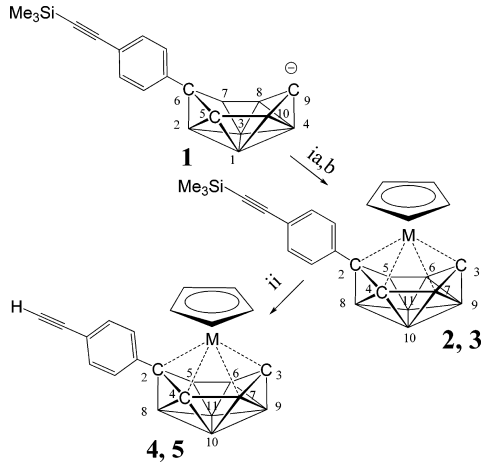
Scheme 1. Synthesis of the Tricarbadecaboranyl Ligand [6-(*p*-((CH$_3$)$_3$SiC≡C)C$_6$H$_4$)-*nido*-5,6,9-$C_3B_7H_9^-$] (1) via the Reaction of [*arachno*-4,6-$C_2B_7H_{12}^-$] with Trimethylsilyl-Protected *p*-Ethynylbenzonitrile



Analysis by ^{11}B NMR of this reaction mixture after 12 h of reflux showed the formation of the characteristic seven-boron pattern previously observed for 6-R-*nido*-5,6,9-$C_3B_7H_9^-$ salts.[20] **1** was not isolated but stored as a stock solution under N_2 until use.

As shown in Scheme 2, reactions of **1** with (η^5-C_5H_5)Fe(CO)$_2$I and (η^5-C_5H_5)Ru(CH$_3$CN)$_3$PF$_6$ produced

Scheme 2. Complexation and Deprotection Reactions of Li$^+$[6-(*p*-((CH$_3$)$_3$SiC≡C)C$_6$H$_4$)-*nido*-5,6,9-$C_3B_7H_9^-$] (1) with Ru and Fe[a]

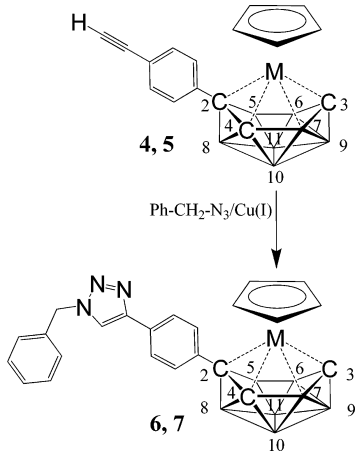


[a]Legend: (i) (a) (η^5-C_5H_5)Ru(CH$_3$CN)$_3$PF$_6$/glyme; (b) (η^5-C_5H_5)Fe(CO)$_2$I/glyme; (ii) K_2CO_3/MeOH/THF.

1-(η^5-C_5H_5)-2-(*p*-((CH$_3$)$_3$SiC≡C)C$_6$H$_4$)-*closo*-1,2,3,4-$MC_3B_7H_9$ (M = Fe, **2**, 42%; M = Ru, **3**, 53%). The commonly utilized Bu$_4$NF deprotecting agent proved ineffectual in desilylating **2** and **3**, owing to fluoride-induced cage deboronation.[21] However, the use of milder conditions (K_2CO_3/MeOH) allowed for the effective removal of the trimethylsilyl protecting group to produce the ethynyl derivatives 1-(η^5-C_5H_5)-2-(*p*-(HC≡C)C$_6$H$_4$)-*closo*-1,2,3,4-$MC_3B_7H_9$ (M = Fe, **4**, 83%; M = Ru, **5**, 72%). **2**–**5** were easily purified by column chromatography and isolated as moisture-stable solids that are soluble in a wide variety of polar and nonpolar solvents.

The room-temperature click addition of the model compound benzyl azide to **4** and **5** to form the triazole complexes 1-(η^5-C_5H_5)-2-(*p*-(1-(C$_6$H$_5$CH$_2$)-1*H*-1,2,3-N$_3$C$_2$-4-)C$_6$H$_4$)-*closo*-1,2,3,4-$MC_3B_7H_9$ (M = Fe, **6**, 82%; Ru, **7**, 66%) confirmed the reactivity of the *p*-ethynyl group toward copper-catalyzed click azide addition (Scheme 3). **6** was purified by plate

Scheme 3. Copper-Catalyzed Click Addition of Benzyl Azide to 1-(η^5-C_5H_5)-2-(*p*-(HC≡C)C$_6$H$_4$)-*closo*-1,2,3,4-$MC_3B_7H_9$ (M = Fe (4), Ru (5)) to Yield 1-(η^5-C_5H_5)-2-(*p*-(1-(C$_6$H$_5$CH$_2$)-1*H*-1,2,3-N$_3$C$_2$-4-)C$_6$H$_4$)-*closo*-1,2,3,4-$MC_3B_7H_9$ (M = Fe (6), Ru (7))



chromatography, and **7** was isolated in pure form by precipitation from H_2O and ^{t}BuOH as air- and moisture-stable blue and orange solids, respectively.

The ^{11}B NMR spectra of **2**–**7** each showed seven doublet resonances at chemical shifts similar to those observed for other 2-R-*closo*-1,2,3,4-$MC_3B_7H_9$ cluster systems.[6] Their ^{1}H NMR spectra each exhibited two cage C–H resonances: one occurring at a higher field shift (1.79–2.55 ppm) characteristic of a proton attached to a high-coordinate carbon adjacent to the metal (C4H cage atom) and one at a lower field shift (5.9–7.0 ppm) characteristic of a low-coordinate carbon adjacent to the metal (C3H cage atom).[6a–c] The trimethylsilyl intensity 9 singlet observed at high field (0.29 and 0.28 ppm) in **2** and **3** was replaced in **4** and **5** by an intensity 1 singlet at midfield (3.27 and 3.22 ppm) arising from their acetylenic protons. The disappearance of this midfield acetylenic resonance in the spectra of **6** and **7** coupled with the appearance of new signals in the benzyl region supports their formulations as triazole compounds resulting from click addition of the azide.

As shown in Figures 2–4, crystallographic determinations confirmed the proposed hybrid structures of **2**, **4**, **5**, and **7**, where the Ru and Fe atoms are sandwiched between the cyclopentadienyl and tricarbadecaboranyl ligands. In agreement with the spectroscopic data and the predicted closo electron count of their MC_3B_7 fragments (24 skeletal electrons), the metallatricarbadecaboranyl cages adopt octadecahedral geometries with the metal coordinated to, and approximately centered over, the puckered six-membered C2–B5–B6–C3–B7–C4 face of the tricarbadecaboranyl cage. The Ru–Cp$_{centroid}$ (1.824(2) and 1.826(2) Å) distances for **5** and **7** and the Fe–Cp$_{centroid}$ (1.683(2) and 1.685(4) Å) distances for **2** and **4** are consistent with those of previously reported cyclopentadienyl ruthenium and iron complexes.[22]

In all complexes, the metals are bonded to the six atoms on the open face with the shortest distances being between M and C2 (average: Ru1–C2, 2.083 Å; Fe1–C2, 1.982 Å) and M and C3 (average: Ru1–C3, 2.079 Å; Fe1–C3, 1.958 Å). However, again in all complexes, the metals are slightly shifted toward the

dx.doi.org/10.1021/om201044r | *Organometallics* 2012, 31, 2741–2748

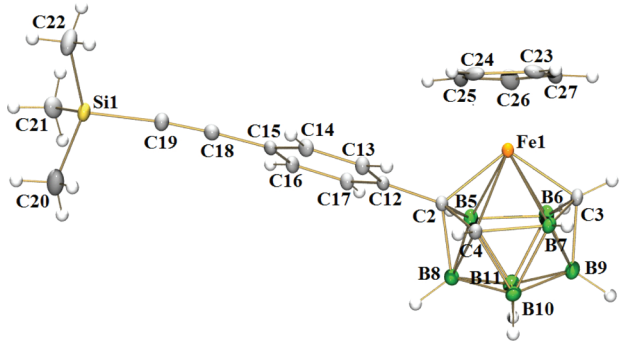


Figure 2. Crystallographically determined structure of 1-(η^5-C_5H_5)-2-(*p*-((CH$_3$)$_3$SiC≡C)C$_6$H$_4$)-*closo*-1,2,3,4-FeC$_3$B$_7$H$_9$ (**2**). Selected distances (Å) and angles (deg): Fe1−C2, 1.9828(14); Fe1−C3, 1.9570(15); Fe1−C4, 2.2976(15); Fe1−B5, 2.2157(18); Fe1−B6, 2.2240(19); Fe1−B7, 2.3009(18); Fe1−Cp$_{Centroid}$, 1.683(2); C2−B5, 1.588(2); B5−B6, 1.850(3); C3−B6, 1.576(2); C3−B7, 1.564(2); C4−B7, 1.740(2); C2−C4, 1.501(2); C2−C12, 1.494(2); C18−C19, 1.207(2); C19−Si1, 1.8419(16); C3−Fe1−C2, 110.25(6); C12−C2−Fe1, 124.77(10); C15−C18−C19, 177.14(17).

B5−B6 edge. For example, in **2** the Fe1−B5 (2.2157(18) Å) and Fe1−B6 (2.2240(19) Å) distances are significantly shorter than those to the opposite edge Fe1−B7 (2.3009(18) Å) and Fe1−C4 (2.2976(15) Å).

The acetylenic C−C distances in the ethynyl derivatives **4** (1.172(5) Å) and **5** (1.179(3) Å) are consistent with those observed in the analogous acetylene-substituted ferrocenes,[23] with the observed distance in the silyl-protected derivative **2** (1.207(2) Å) being, as expected, slightly longer.[24] The crystallographic determination of **7** in Figure 4 confirmed click addition of the benzyl azide to **5** to form the triazole five-membered ring attached to the pendant phenyl group, with the observed triazole ring distances consistent with those in previously reported structures.[25]

Syntheses of Amino Acid Derivatives. The sonicated reactions at ∼43 °C of **2** with the corresponding azido-modified *N*-azidoacetyl-L-amino acid methyl esters in the presence of copper sulfate and sodium ascorbate afforded the amino acid substituted derivatives 1-(η^5-C_5H_5)-2-(*p*-(1-(Xaa-C(O)CH$_2$)-1*H*-1,2,3-N$_3$C$_2$-4-)-C$_6$H$_4$)-*closo*-1,2,3,4-FeC$_3$B$_7$H$_9$ (**8**−**13**) shown in Scheme 4, containing phenylalanine methyl ester (**8**), leucine methyl ester (**9**), valine methyl ester (**10**), methionine methyl ester (**11**), alanine methyl ester (**12**), and tryptophan methyl ester (**13**), respectively. Only one product was observed in each reaction, and **8**−**13** were easily isolated using thin-layer plate chromatography and obtained as air- and moisture-stable blue solids that were soluble in several polar and nonpolar organic solvents.

The ^{11}B{^{1}H} NMR spectra of **8**−**13** each show patterns similar to that of **4**. As expected, the C4H cage resonances in their ^{1}H NMR spectra occur at higher field (1.86−1.88 ppm), while their C3H resonances are at lower field (6.94−6.96 ppm). Their conversions to triazole structures are again supported by the absence of the midfield acetylenic resonance found for **2**. The observed ^{1}H and ^{13}C NMR resonances are those expected for the substituted functional groups and are similar to those observed in the spectra of the free amino acid methyl esters.[26]

Owing to their unique stability and electrochemical properties, these new amino acid ferratricarbadecaborane complexes should have properties that complement their amino-acid metallocene analogues. The cytotoxic properties of **8**−**13** are

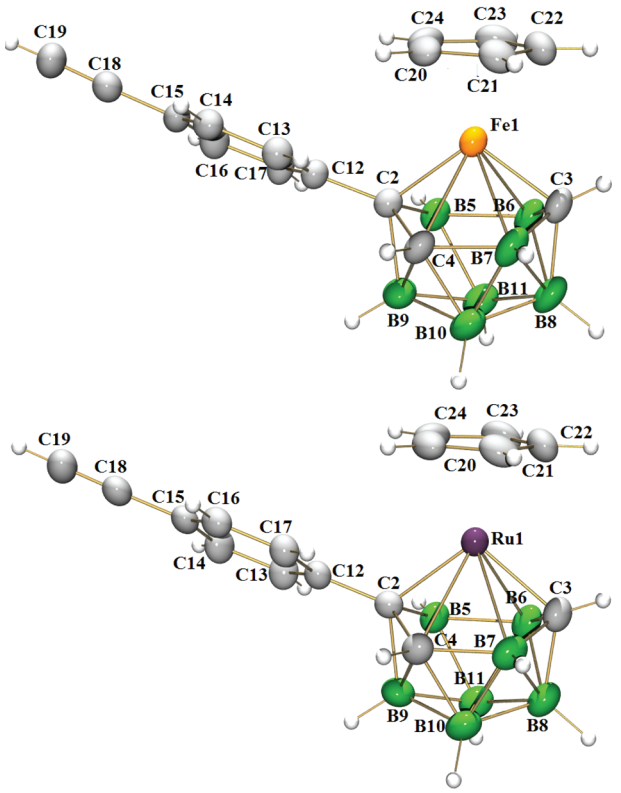


Figure 3. Crystallographically determined structures of (top) 1-(η^5-C_5H_5)-2-(*p*-(HC≡C)C$_6$H$_4$)-*closo*-1,2,3,4-FeC$_3$B$_7$H$_9$ (**4**) and (bottom) 1-(η^5-C_5H_5)-2-(*p*-(HC≡C)C$_6$H$_4$)-*closo*-1,2,3,4-RuC$_3$B$_7$H$_9$ (**5**). Selected distances (Å) and angles (deg) for **4**: Fe1−C2, 1.981(3); Fe1−C3, 1.958(3); Fe1−C4, 2.242(3); Fe1−B5, 2.242(3); Fe1−B6, 2.240(3); Fe1−B7, 2.259(3); Fe1−Cp$_{Centroid}$, 1.685(4); C2−B5, 1.579(4); B5−B6, 1.834(5); C3−B6, 1.575(4); C3−B7, 1.563(4); C4−B7, 1.740(5); C2−C4, 1.500(4); C2−C12, 1.487(4); C18−C19, 1.172(5); C3−Fe1−C2, 110.71(12); C12−C2−Fe1, 124.84(19); C15−C18−C19, 178.1(3). Selected distances (Å) and angles (deg) for **5**: Ru1−C2, 2.079(2); Ru1−C3, 2.081(2); Ru1−C4, 2.348(2); Ru1−B5, 2.345(3); Ru1−B6, 2.341(3); Ru1−B7, 2.368(3); Ru1−Cp$_{Centroid}$, 1.824(2); C2−B5, 1.587(4); B5−B6, 1.863(4); C3−B6, 1.587(4); C3−B7, 1.585(4); C4−B7, 1.792(4); C2−C4, 1.504(3); C2−C12, 1.499(3); C18−C19, 1.179(3); C3−Ru1−C2, 105.83(9); C12−C2−Ru1, 123.20(2); C15−C18−C19, 178.2(3).

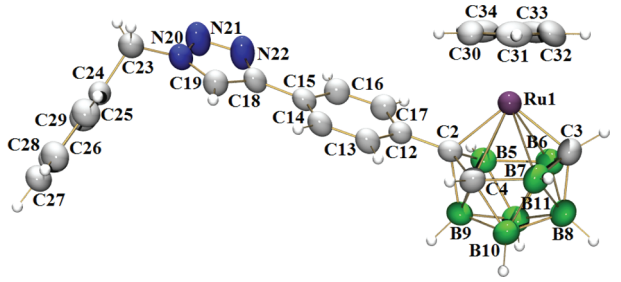
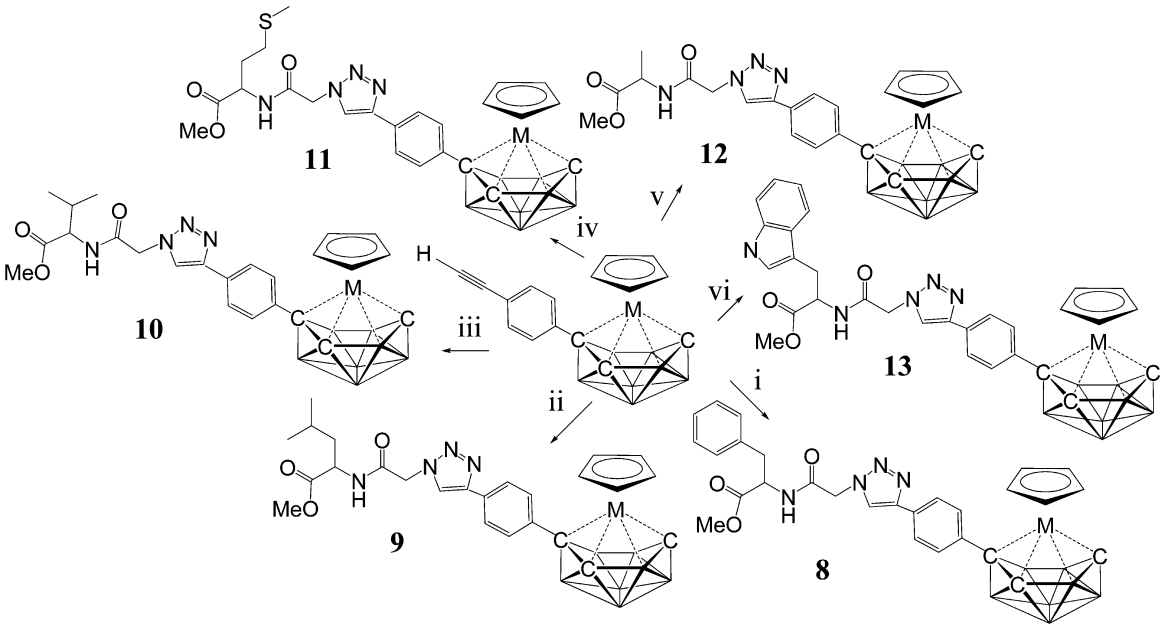


Figure 4. Crystallographically determined structure of 1-(η^5-C_5H_5)-2-(*p*-(1-(C$_6$H$_5$CH$_2$)-1*H*-1,2,3-N$_3$C$_2$-4-)C$_6$H$_4$)-*closo*-1,2,3,4-RuC$_3$B$_7$H$_9$ (**7**). Selected distances (Å) and angles (deg): Ru1−C2, 2.086(3); Ru1−C3, 2.076(3); Ru1−C4, 2.385(3); Ru1−B5, 2.311(4); Ru1−B6, 2.342(4); Ru1−B7, 2.399(4); Ru1−Cp$_{Centroid}$, 1.826(2); C2−B5, 1.613(5); B5−B6, 1.875(6); C3−B6, 1.572(6); C3−B7, 1.596(6); C4−B7, 1.776(6); C2−C4, 1.506(4); C2−C12, 1.469(4); C18−C19, 1.372(5); C19−N20, 1.345(4); C18−N22, 1.360(4); N20−N21, 1.344(4); N21−N22, 1.312(4); N20−C23, 1.465(4); C3−Ru1−C2, 105.74(14); C12−C2−Ru1, 123.5(2); N20−N21−N22, 107.1(3); N20−C23−C24, 112.8(3); C18−C19−N20, 105.4(3); C19−N20−N21, 110.6(3); N21−N22−C18, 109.5(3); N22−C18−C19, 107.4(3).

dx.doi.org/10.1021/om201044r | *Organometallics* 2012, 31, 2741−2748

Scheme 4. Copper-Catalyzed Click Addition of the Azide Modified Amino Acid Methyl Esters (i) $N_3CH_2C(O)$Phe, (ii) $N_3CH_2C(O)$Leu, (iii) $N_3CH_2C(O)$Val, (iv) $N_3CH_2C(O)$Met, (v) $N_3CH_2C(O)$Ala, and (vi) $N_3CH_2C(O)$Try to 1-(η^5-C_5H_5)-2-(*p*-(HC≡C)C_6H_4)-*closo*-1,2,3,4-$FeC_3B_7H_9$ (4) To Yield 1-(η^5-C_5H_5)-2-(*p*-(1-(Xaa-C(O)CH_2)-1*H*-1,2,3-N_3C_2-4-)C_6H_4)-*closo*-1,2,3,4-$FeC_3B_7H_9$ (Xaa = PheOMe (8), LeuOMe (9), ValOMe (10), MetOMe (11), AlaOMe (12), TryOMe (13))



currently being screened in the Development Therapeutics Program of the NCI/NIH in Rockville, MD, and these results will be discussed in future publications. Derivatives exhibiting significant and selective cytotoxicity could find applications as anticancer agents, whereas those with low cytotoxicity are potential agents to deliver high boron concentrations to cells for use in boron neutron capture therapy.[7] It is also important to note that click-addition reactions of *p*-ethynylphenyl-substituted metallatricarbadecaboranes should prove to be a general strategy allowing the syntheses of a great range of other types of bioactive and/or electronically active complexes. We are continuing to explore the scope of these reactions to produce such complexes.

■ ASSOCIATED CONTENT

Supporting Information

CIF files giving X-ray crystallographic data for the structural determinations of **2**, **4**, **5**, and **7** and text giving IR data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Fax: 215-573-6743. E-mail: lsneddon@sas.upenn.edu.

■ ACKNOWLEDGMENTS

The National Science Foundation is gratefully acknowledged both for the support of this research and for an instrumentation grant (No. CHE-0840438) that was used for the purchase of the X-ray diffractometer employed in these studies.

■ DEDICATION

Dedicated to the memory of our friend, Gordon Stone.

■ REFERENCES

(1) Severin, K.; Bergs, R.; Beck, W. *Angew. Chem., Int. Ed.* **1998**, *37*, 1634−1654.

(2) (a) van Staveren, D. R.; Metzler-Nolte, N. *Chem. Rev.* **2004**, *104*, 5931−5985. (b) Metzler-Nolte, N.; Salmain, M. The Bioorganometallic Chemistry of Ferrocene. In *Ferrocenes: Ligands, Materials and Biomolecules*, 1st ed.; Štěpnička, P., Ed.; Wiley: Chichester, U.K., 2008; pp 499−639.

(3) (a) Gallagher, J. F.; Kenny, P. T. M.; Sheehy, M. J. *Inorg. Chem. Commun.* **1999**, *2*, 200−202. (b) Kraatz, H. B. *J. Inorg. Organomet. Polym. Mater.* **2005**, *15*, 83−106.

(4) (a) Hess, A.; Metzler-Nolte, N. *Chem. Commun.* **1999**, 885−886. (b) Verheijen, J. C.; van der Marel, G. A.; van Boom, J. H.; Metzler-Nolte, N. *Bioconjugate Chem.* **2000**, *11*, 741−743.

(5) Mooney, A.; Corry, A. J.; Ruairc, C. N.; Mahgoub, T.; O'Sullivan, D.; O'Donovan, N.; Crown, J.; Varughese, S.; Draper, S. M.; Rai, D. K.; Kenny, P. T. M. *Dalton Trans.* **2010**, *39*, 8228−8239.

(6) (a) Plumb, C. A.; Carroll, P. J.; Sneddon, L. G. *Organometallics* **1992**, *11*, 1665−1671. (b) Plumb, C. A.; Carroll, P. J.; Sneddon, L. G. *Organometallics* **1992**, *11*, 1672−1680. (c) Plumb, C. A.; Carroll, P. J.; Sneddon, L. G. *Organometallics* **1992**, *11*, 1681−1685. (d) Weinmann, W.; Wolf, A.; Pritzkow, H.; Siebert, W.; Barnum, B. A.; Carroll, P. J.; Sneddon, L. G. *Organometallics* **1995**, *14*, 1911−1919. (e) Barnum, B. A.; Carroll, P. J.; Sneddon, L. G. *Organometallics* **1996**, *15*, 645−654. (f) Barnum, B. A.; Carroll, P. J.; Sneddon, L. G. *Inorg. Chem.* **1997**, *36*, 1327−1337. (g) Wasczak, M. D.; Lee, C. C.; Hall, I. H.; Carroll, P. J.; Sneddon, L. G. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2228−2230. (h) Ramachandran, B. M.; Carroll, P. J.; Sneddon, L. G. *J. Am. Chem. Soc.* **2000**, *122*, 11033−11034. (i) Ramachandran, B. M.; Trupia, S. M.; Geiger, W. E.; Carroll, P. J.; Sneddon, L. G. *Organometallics* **2002**, *21*, 5078−5090. (j) Hall, I. H.; Durham, R.; Tran, M.; Mueller, S.; Ramachandran, B. M.; Sneddon, L. G. *J. Inorg. Biochem.* **2003**, *93*, 125−131. (k) Ramachandran, B. M.; Carroll, P. J.; Sneddon, L. G. *Inorg. Chem.* **2004**, *43*, 3467−3474. (l) Ramachandran, B. M.; Wang, Y.; Kang, S. O.; Carroll, P. J.; Sneddon, L. G. *Organometallics* **2004**, *23*, 2989−2994. (m) Butterick, R. III; Ramachandran, B. M.; Carroll, P. J.; Sneddon, L. G. *J. Am. Chem. Soc.* **2006**, *128*, 8626−8637. (n) Nafady, A.; Butterick, R. III; Calhorda, M. J.; Carroll, P. J.; Chong, D.; Geiger, W. E.; Sneddon, L.

G. *Organometallics* **2007**, *26*, 4471−4482. (o) Butterick, R. III; Carroll, P. J.; Sneddon, L. G. *Organometallics* **2008**, *27*, 4419−4427.
(7) For general reviews on boron neutron capture therapy (BNCT) see: (a) Sivaev, V. B.; Bregadze, V. I. *Eur. J. Inorg. Chem.* **2009**, 1433−1450. (b) Hawthorne, M. F. *Angew. Chem., Int. Ed.* **1993**, *32*, 950−984. (c) Soloway, A. H.; Tjarks, W.; Barnum, B. A.; Rong, F.-G.; Barth, R. F.; Codogni, I. M.; Wilson, J. G. *Chem. Rev.* **1998**, *98*, 1515−1562.
(8) Shriver, D. F.; Drezdzon, M. A. *The Manipulation of Air-Sensitive Compounds*, 2nd ed.; Wiley: New York, 1986.
(9) Aucagne, V.; Leigh, D. A. *Org. Lett.* **2006**, *8*, 4505−4507.
(10) (a) Hawthorne, M. F.; Young, D. C.; Garrett, P. M.; Owen, D. A.; Schwerin, S. G.; Tebbe, F. N.; Wegner, P. A. *J. Am. Chem. Soc.* **1968**, *90*, 862−868. (b) Garrett, P. M.; George, T. A.; Hawthorne, M. F. *Inorg. Chem.* **1969**, *8*, 2008−2009.
(11) As previously noted for other metallatricarbadecaboranes,[6c] the ^{13}C resonances of the substituted C2 cage-carbon expected near 64 ppm could not be observed in most compounds due to the absence of an NOE enhancement.
(12) *SAINT version 7.68A*; Bruker AXS Inc., Madison, WI, USA.
(13) *SHELXTL version 6.14*; Bruker AXS Inc., Madison, WI, USA.
(14) *SADABS version 2008/1*; Bruker AXS Inc., Madison, WI, USA.
(15) SIR-97: Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, M.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A.; Polidori, G. J.; Spagna, R. *J. Appl. Crystallogr.* **1999**, *32*, 115−119.
(16) Sheldrick, G. M. *Acta Crystallogr.* **2008**, *A64*, 112−122.
(17) (a) Gothelf, K. V.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 863−909. (b) Aromí, G.; Barrios, L. A.; Roubeau, O.; Gamez, P. *Coord. Chem. Rev.* **2011**, *255*, 485−546. (c) Schilling, C.; Jung, N.; Bräse, S. Cycloaddition Reactions with Azides: An Overview. In *Organic Azides: Syntheses and Applications*; Bräse, S., Banert, K., Eds.; Wiley: Chichester, U.K., 2010; pp 269−284.
(18) Koster, S. D.; Dittrich, J.; Gasser, G.; Hüsken, N; Henao Castañeda, I. C.; Jios, J. L.; Della Védova, C. O.; Metzler-Nolte, N. *Organometallics* **2008**, *27*, 6326−6332.
(19) (a) Sudhir, V. S.; Venkateswarlu, Ch.; Musthafa, O. T. M.; Sampath, S.; Chandrasekaran, S. *Eur. J. Org. Chem.* **2009**, 2120−2129. (b) Sudhir, V. S.; Kumar, N. Y. P.; Chandrasekaran, S. *Tetrahedron* **2010**, *66*, 1327−1334.
(20) Kang, S. O.; Furst, G. T.; Sneddon, L. G. *Inorg. Chem.* **1989**, *28*, 2339−2347.
(21) Perez-Gavilan, A.; Carroll, P. J.; Sneddon, L. G. *Collect. Czech. Chem. Commun.* **2010**, *75*, 905−917.
(22) (a) Hardgrove, G. L.; Templeton, D. H. *Acta Crystallogr.* **1959**, *12*, 28−32. (b) Dunitz, J. D.; Orgel, L. E.; Rich, A. *Acta Crystallogr.* **1956**, *9*, 373−375.
(23) Ingham, S. L.; Khan, M. S.; Lewis, J.; Long, N. J.; Raithby, P. R. *J. Organomet. Chem.* **1994**, *470*, 153−159.
(24) (a) Butler, I. R.; Callabero, A. G.; Kelly, G. A.; Amey, J. R.; Kraemer, T.; Thomas, D. A.; Light, M. E.; Gelbrich, T.; Coles, S. J. *Tetrahdron Lett.* **2004**, *45*, 467−472. (b) Gessner, V. H.; Tilley, T. D. *Org. Lett.* **2011**, *13*, 1154−1157.
(25) Kálmán, A.; Kálmán, S.; Schawartz, J.; Hovárth, G. *J. Chem. Soc., Perkin Trans. 2* **1974**, 1849−1852.
(26) (a) Croft, A. K.; Foley, M. K. *Org. Biomol. Chem.* **2008**, *6*, 1594−1600. (b) Ando, N.; Yamamoto, Y.; Oda, J.; Inouye, Y. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2369−2371. (c) Alexander, K.; Cook, S.; Gibson, C. L.; Kennedy, A. R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1538−1549. (d) Tauchman, J.; Císařová, I.; Štěpnička, P. *Eur. J. Org. Chem.* **2010**, 4276−4287. (e) Florini, N.; Arnaud, G. F.; Kónya, B.; Zucchi, C.; Pályi, G. *Tetrahedron: Asymmetry* **2009**, *20*, 1036−1039. (f) Kasala, D.; Lin, T.-S.; Chen, C.-Y.; Liu, G.-C.; Kao, C.-L.; Cheng, T.-L.; Wang, Y.-M. *Dalton Trans.* **2011**, *40*, 5018−5025. (g) SDBSWeb: http://riodb01.ibase.aist.go.jp/sdbs/ (National Institute of Advanced Industrial Science and Technology, Date of Access: August 2011).