Inorganic Chemistry Communications 43 (2014) 142–145

Contents lists available at ScienceDirect

Inorganic Chemistry Communications

journal homepage: www.elsevier.com/locate/inoche

C-carboranylation of a quasi-aromatic iron(II) cage complex and its organic aromatic analog by the metal-catalyzed (promoted) cross-coupling reactions[☆]

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ARTICLE INFO

Article history:
Received 10 December 2013
Accepted 18 February 2014
Available online 26 February 2014

Keywords:
Macrocyclic compounds
Clathrochelates
Ligand reactivity
Carboranylation
Cross-coupling reaction

ABSTRACT

One-pot reaction a quasi-aromatic diiodoclathrochelate precursor with the carboranylating agent, generated *in situ* from equimolar amounts of lithium 1-*ortho*-carboranyl and trimethoxyborate, in the presence of a palladium catalyst afforded a ribbed-functionalized iron(II) mono-*ortho*-carboranoclathrochelate. Such a formation of C(carborane)–C(clathrochelate) bond is accompanied by hydrodeiodination in a vicinal position and a monomethinemonocarborane macrobicyclic complex was isolated and characterized by the single crystal X-ray diffraction. The geometry of its FeN_6-coordination polyhedron is intermediate between a trigonal prism and a trigonal antiprism with the distortion angle φ of 24.9° and the height h of this polyhedron is equal to 2.32 Å; Fe–N distances vary from 1.889(2) to 1.921(2) Å and the average bite angle α is approximately 39.1°. The model reaction of this carboranylating agent with 4-iodobiphenyl, giving the corresponding aryl carborane, proceeds only in vigorous reaction conditions with a palladium catalyst and copper(I) iodide as a promotor. The compounds obtained were characterized using elemental analysis, ESI and EI mass spectrometry, IR, Raman, UV–vis, ^{1}H, ^{11}B, ^{19}F and $^{13}C\{^{1}H\}$ NMR spectroscopy. Thus, palladium-catalyzed Suzuki–Miyaura (copper-promoted in the case of an aryl iodide) cross-coupling reactions of a generated *in situ* derivative of carboranylboronic ester have been successfully used, for the first time, for *one-pot* synthesis of a quasi-aromatic hybrid carboranoclathrochelate with an inherent polyhedral ribbed substituent and its aromatic analog 4-(1-*ortho*-carboranyl)biphenyl. The developed strategy has been then found useful in the organic chemistry as a versatile approach towards carborane-based organic compounds.

Polyazomethine iron(II) clathrochelates have highly conjugated three-dimensional macrobicyclic 18 electron framework [1] and this corresponds to Hückel's rule (4n + 2). Therefore, these cage complexes can be regarded as quasi-aromatic compounds with a reactivity similar to those of their organic aromatic analogs. Such clathrochelates have been shown to effectively inhibit the action of T7 RNA polymerase (T7 RNAP) *in vitro*, with the inhibition constant depending on the shape of the inhibitor's molecule [2]. Their bis-clathrochelates analogs, which contain two C–C conjugated macrobicyclic fragments, showed even higher inhibitory activity; being in submicromolecular range [3], it places them among the best metal-based transcription inhibitors.

Bis-polyhedral cobalt bis-carbollides [4] and their dimeric forms [5] have been tested as efficient HIV protease inhibitors; so hybrid ditopic carboranoclathrochelate with inherent carboranyl substituents seems to be very prospective for the design of such type of antiviral and antitumor drug candidates (so-called “topological drugs” [6]).

A series of carborane-containing iron(II) clathrochelates has been earlier obtained in our group using Lewis acidity of *ortho*-carboranylboronic acids and their derivatives [7,8]. As apical groups, the corresponding *ortho*-carboranyl substituents, however, affected the electronic and spatial structures of the clathrochelate framework only slightly.

On the other hand, carboranylated aromatic compounds are known to have a wide range of properties useful for practical purposes, including an intensive phosphorescence [9,10], catalytic [11] and antiandrogenic [12] activities. However, only a limited number of approaches to their synthesis have been described up to date; those include the reaction of lithium [9] and copper [13] carboranes with suitable aromatic precursors as well as “building” of a carborane core by a reaction of decaborane with aryl acetylenes [14]. To the best of our knowledge, there were no examples of the creation of a C(carborane)–C(aryl) bond using the carboranylboronic acids and their derivatives by the metal-promoted (catalyzed) cross-coupling

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[☆] A preliminary account of this work was presented at the 6th European Conferences on Boron Chemistry, Radziejowice, Poland, 8–13th September 2013.

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http://dx.doi.org/10.1016/j.inoche.2014.02.020
1387-7003/

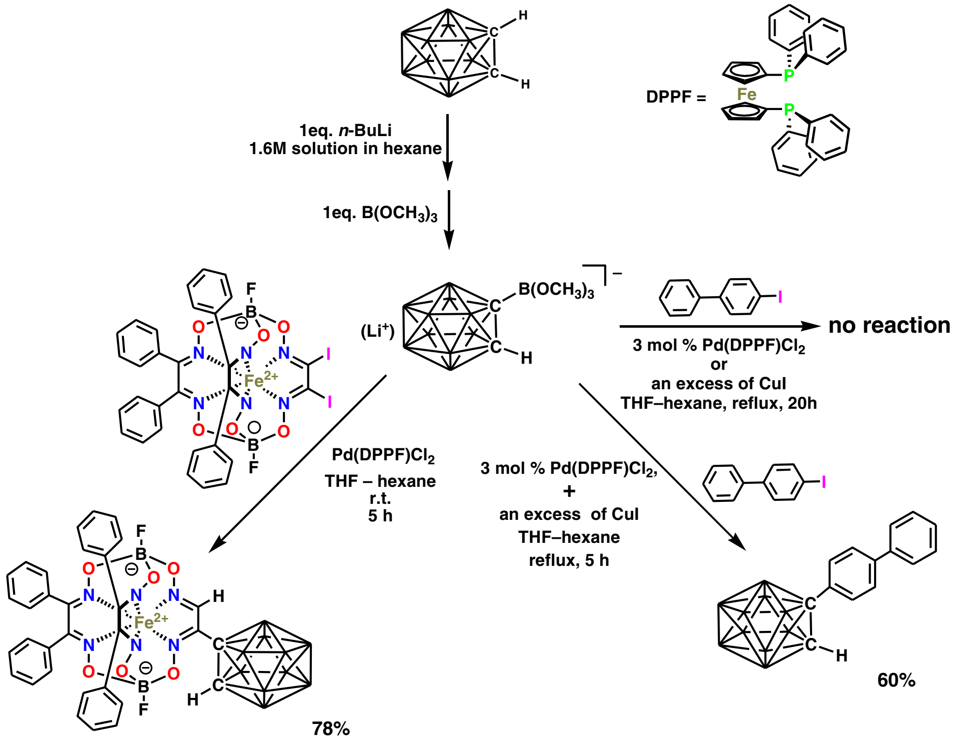
reaction, although the latter is among the most powerful and frequently used approaches in the modern organic chemistry [15]. In the present paper, we describe this new synthetic pathway for the creation of such bond, based on the metal-promoted (catalyzed) cross-coupling reactions of lithium (1-*ortho*-carboranyl)trimethoxyborate with the iodine-containing *quasi*-aromatic clathrochelate and aromatic organic precursors. We also report the synthesis and structure of the first ribbed-functionalized *quasi*-aromatic cage complex with a C–C conjugated carboranyl substituent (a carboranoclathrochelate) and its organic analog 4-(1-*ortho*-carboranyl)biphenyl, trying to compare the reactivity of their precursors under such reaction conditions.

This carboranylating agent was generated *in situ* from equimolar amounts of lithium 1-*ortho*-carboranyl and trimethoxyborate, and its *one-pot* reaction with a *quasi*-aromatic diiodoclathrochelate precursor FeBd$_2$(I$_2$Gm)(BF)$_2$ in the presence of catalytic amounts of Pd(DPPF)Cl$_2$ by Scheme 1 gave a ribbed-functionalized mono-*ortho*-carboranoclathrochelate FeBd$_2$(HGm(C$_2$B$_{10}$H$_{11}$))(BF)$_2$ [16]; no formation of a dicarboranylated clathrochelate product was observed even in the presence of an excess of this carboranylating agent (probably due to some steric restrictions). The formation of a C(carborane)–C(clathrochelate) bond is accompanied by hydrodeiodination in a vicinal position, giving a monomethinemonocarborane clathrochelate product. The plausible mechanism of this reaction, which resulted in the substitution of one of the two iodine atoms by a carboranyl group and the other by a hydrogen atom, includes either the anion radical hydrodeiodination of a diiodoclathrochelate with a solvent followed by substitution of the resulting product with a carboranyl group or the substitution of one of the two iodine atoms by a carboranyl group followed by hydrodehalogenation of the resulted monoiodomonocarborane clathrochelate (see SM, Scheme S1). The same reaction of this clathrochelate precursor has been earlier observed for its modification with copper(I) cyanide [17]; such precursor also undergoes a copper-promoted reductive homocoupling under these reaction conditions.

The model reaction in the case of organic aromatic compounds of lithium (1-*ortho*-carboranyl)trimethoxyborate with 4-iodobiphenyl gave no target 4-(1-*ortho*-carboranyl)biphenyl even after reflux of the reaction mixture for 20 h with Pd(DPPF)Cl$_2$ as a catalyst. This product was obtained by Scheme 1 only in the presence of an excess of CuI; the plausible reaction scheme includes the formation of coppercarborane species and binding of iodide anion by a copper ion. We also found that this copper-promoted reaction did not proceed without a palladium complex as a probable catalyst for the formation of a coppercarborane derivative.

The compounds obtained were characterized using elemental analysis, ESI and EI mass spectrometry, IR, Raman, UV–vis, ^{1}H, ^{11}B, ^{19}F and ^{13}C{^{1}H} NMR spectroscopy, and by X-ray diffraction (the iron(II) carboranoclathrochelate).

The molecular structure of the carboranoclathrochelate FeBd$_2$(HGm(C$_2$B$_{10}$H$_{11}$))(BF)$_2$ is shown in Fig. 1; its main geometrical parameters are listed in Table S1 (see SM). The geometry of its *FeN$_6$*-coordination polyhedron is intermediate between a trigonal prism (TP, the distortion angle $\varphi = 0°$) and a trigonal antiprism (TAP, $\varphi = 60°$) with the average φ angle of 24.9°. Fe–N distances (from 1.889(2) to 1.921(2) Å), the average bite angle α (39.1°) and the height of this coordination polyhedron h (2.32 Å) are characteristic of the X-rayed fluoroboron-capped monoribbed-functionalized iron(II) clathrochelates [17–19]. The φ values for the monomethinemonofunctionalized iron(II) clathrochelates vary from 23.2 to 24.9° (this work, [17–19]) and are higher than that of their glyoximate analog ($\varphi = 21.6°$ [19]). So the presence of such ribbed functionalized substituents (C$_2$B$_{10}$H$_{11}$, CH$_3$, CN or 2,6-di-tert-butylphenol substituents) causes an additional rotation–contraction distortion of the macrobicyclic frameworks around their three-fold *pseudo*-symmetry axis B…Fe…B in comparison with their dimethinoclathrochelate analog. Moreover, in the case of the bulky *ortho*-carboranyl substituent this distortion is the most pronounced due to the steric hindrances in the rigid cage complex, which may be the reason for the formation of the monocarboranylated clathrochelate product only. Its carboranyl substituent forms six-membered cycle O1.N1.C1.C31.C32.H32A *via* an intramolecular C(carborane)–H…O interaction. Typically, C…O distances for inter-



FeBd$_2$(HGm(C$_2$B$_{10}$H$_{11}$))(BF)$_2$

Scheme 1. The synthesis of lithium (1-*ortho*-carboranyl)trimethoxyborate and its reactions with iron(II) diiodoclathrochelate and 4-iodobiphenyl.

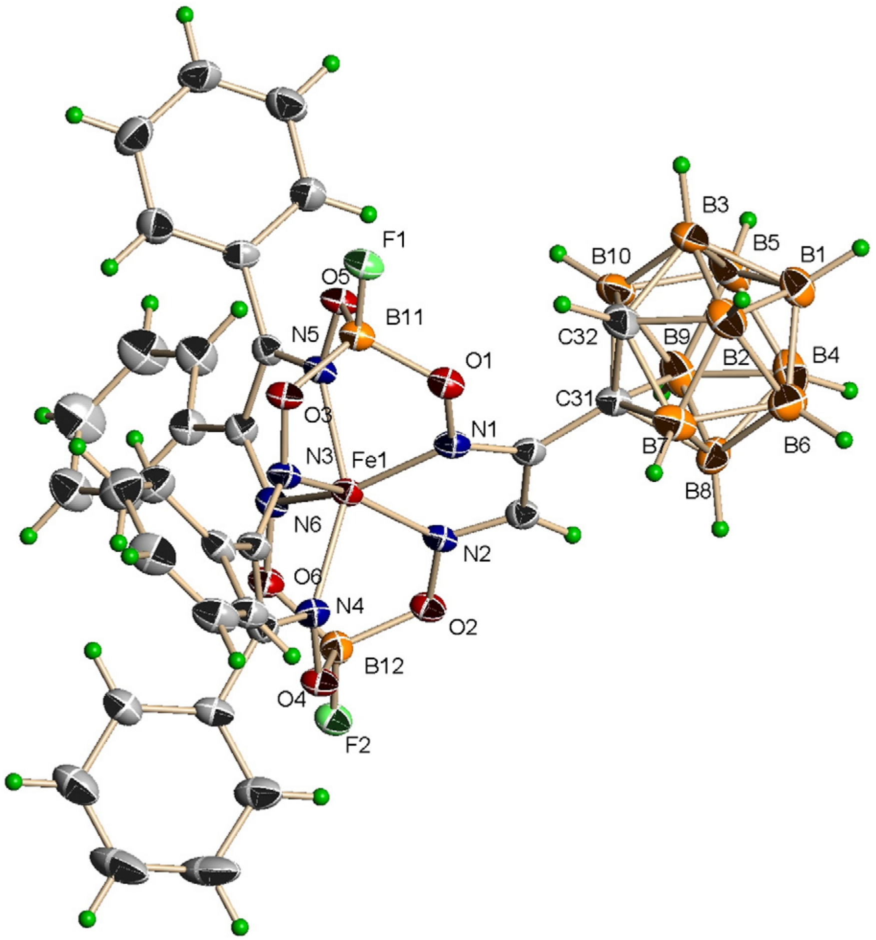


Fig. 1. General view of the carboranoclathrochelate $FeBd_2(HGm(C_2B_{10}H_{11}))(BF)_2$. Hereafter, the non-hydrogen atoms are represented as thermal ellipsoids (p = 50%).

and intramolecular interactions C–H…O in carboranes fall in the range of 2.65–3.55 Å [20]. In the crystal $FeBd_2(HGm(C_2B_{10}H_{11}))(BF)_2\ C_8H_{18}$, the corresponding value of 2.767(4) Å suggests rather strong bonding in accordance with unexpectedly large value of chemical shift for carboranyl C–H proton signal ($\delta^1{}_H = 5.67$ ppm).

IR spectra of the carboranoclathrochelate $FeBd_2(HGm(C_2B_{10}H_{11}))(BF)_2$ show C = N, N–O and B–O stretching vibrations characteristic of the boron-capped tris-dioximate clathrochelates; in the Raman spectrum the cage breathing and stretching vibrations ν(B–H) and ν(C–H) are observed at 770, 2590 and 3074 cm^{-1}, respectively, being characteristic of the *ortho*-carboranyl substituent. The same vibrations of *ortho*-carboranyl fragment in the Raman spectrum of 4-phenyl(1-*ortho*-carboranyl)benzene are observed at approximately 750, 2600 and 3070 cm^{-1}, while its biphenyl fragment shows the intensive Raman lines at 1275, 1584 and 1598 cm^{-1}.

UV–vis spectra of the dichloromethane solutions of the clathrochelate precursor $FeBd_2(I_2Gm)(BF)_2$ and its carboranylated derivative $FeBd_2(HGm(C_2B_{10}H_{11}))(BF)_2$ (see SM, Fig. S1) contain, in the visible range, four intensive absorption bands assigned to the metal-to-ligand charge transfer Fe*d* → Lπ^* (see SM, Table S2). Only one of these bands is substantially (by 30 nm) longwave-shifted and suffers from a dramatical decrease in its relative intensity. The latter may be explained by substantial electronic changes in only one of the three ribbed fragments of a clathrochelate framework, resulting from its hydrodehalogenation and C–C conjugation with a strong electron-withdrawing carboranyl substituent.

This is the first example of the *one-pot* C-carboranylation of a *quasi*-aromatic cage metal complex and its organic aromatic analog by the palladium-catalyzed Suzuki–Miyaura and, in the case of aryl iodide, copper-promoted cross-coupling reaction with a generated *in situ* derivative of carboranylboronic ester as a carboranylating agent. Starting from a cage complex, it gave the first hybrid carboranoclathrochelate with an inherent polyhedral ribbed substituent, while from the aromatic precursor the corresponding aryl carborane was obtained, such C-carboranylation reaction with a derivative of carboranylboronic ester was used for the synthesis of such carborane-containing aromatic compounds for the first time. Therefore, this synthetic approach paves the way towards a wide range of metal complexes as well as organic compounds.

Acknowledgments

The authors gratefully acknowledge the support of RFBR (grants 12-03-00955, 12-03-90431 and 13-03-90452), the Marie Curie International Research Staff Exchange Scheme (IRSES) of the 7th EU Framework Program (grant 295160), RAS (programs 6 and P8) and Russian State Atomic Energy Corporation "ROSATOM" (project D.4 f.43.90.13.1053). We also thank Dr. A. Belov and Dr. V. Novikov for their donation of the diiodoclathrochelate precursor and for NMR measurements. High resolution mass spectra were recorded in the Department of Structural Studies of Zelinsky Institute of Organic Chemistry RAS.

Appendix A. Supplementary material

The details of analytical, spectral and X-ray data collections, the corresponding tables and the description of the initial compounds and reagents are given in Supplementary material.

CCDC 961075 contains the supplementary crystallographic data for $FeBd_2(HGm(C_2B_{10}H_{11}))(BF)_2 \cdot C_8H_{18}$. These data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/conts/retrieving.html. Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.inoche.2014.02.020.

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[16] **Syntheses. Lithium (1-*ortho*-carboranyl)trimethoxyborate.** 1.6 M solution of *n*-BuLi (0.33 ml, 0.54 mmol) in hexane was added to a solution of *ortho*-carborane (0.78 g, 0.54 mmol) in THF (7 ml) at −78 °C and the reaction mixture was stirred for 1 h at this temperature. Then trimethoxyborate (0.60 ml, 0.54 mmol) was added and the reaction mixture was stirred for 1 h at −78 °C and for 1 h at 20 °C. The obtained solution of lithium (1-*ortho*-carboranyl)trimethoxyborate in THF-hexane mixture was used without its further purification.

ortho-carboranoclathrochelate $FeBd_2(HGm(C_2B_{10}H_{11}))(BF)_2$. Complex $FeBd_2(I_2Gm)(BF)_2$ (0.50 g, 0.54 mmol) was dissolved/suspended in THF (5 ml) and a solution of lithium (1-*ortho*-carboranyl)trimethoxyborate (0.54 mmol) in THF-hexane mixture and $Pd(DPPF)Cl_2$ (0.010 g, 3 mol%) were added. The reaction mixture was stirred for 5 h at r.t. and then filtered off. The filtrate was evaporated to dryness *in vacuo* and the solid residue was extracted with dichloromethane (10 ml). The extract was washed with water (30 ml, in three portions) and dried with $MgSO_4$. The target iron(II) *ortho*-carboranoclathrochelate was isolated by column chromatography on silica gel (eluent: dichloromethane–hexane 2:1 mixture) as a major elute. Yield: 0.34 g (78%).

4-(1-_ortho_-carboranyl)biphenyl. 4-iodobiphenyl (0.15 g, 0.54 mmol) and a solution of lithium (1-*ortho*-carboranyl)trimethoxyborate (0.54 mmol) in THF-hexane mixture were mixed, and $Pd(DPPF)Cl_2$ (0.010 g, 3 mol%) and an excess of CuI (0.23 g, 1.18 mmol) were added. The reaction mixture was refluxed for 5 h, then filtered off and evaporated to dryness *in vacuo*. The solid residue was extracted with dichloromethane (10 ml), the extract was washed with water (30 ml, in three portions) and dried with $MgSO_4$. The solution obtained was evaporated to dryness and the solid residue was separated by column chromatography on silica gel (eluent: dichloromethane–hexane 2:1 mixture). A major elute was evaporated to dryness and recrystallized from hexane. Yield: 0.96 g (60%).

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