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"Chemical Ligation": A Versatile Method for Nucleoside Modification with Boron Clusters

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Abstract: A general approach to the synthesis of nucleoside conjugates containing carborane and metallocarborane complexes, based on Huisgen 1,3-dipolar cycloaddition ("chemical ligation"), is described. Boron-cluster-donors bearing terminal azide or ethynyl groups were prepared in the ring-opening reaction of dioxane-boron-cluster adducts and an azide anion or suitable alkynol-derived alcoholate nucleophile. Analogous derivatives bearing terminal sulfhydryl groups were also prepared. Nucleosides with various spacers containing terminal azide or ethynyl groups, located within nucleobases or sugar residues, were used as boron-cluster acceptors. The proposed methodology provides a convenient way to synthesize libraries of boron-cluster-modified nucleosides for various applications.

Keywords: alkynes · azides · chemical ligation · nucleosides · thiols

Introduction

Contemporary technologies take advantage of the knowledge of different fields of science. The crossroads of biological and inorganic chemistry, and further, biology and materials engineering is a fruitful field yielding new technologies such as nanobiotechnology, bioelectronics, biocomputing, and biosensing. Progress in these fields depends heavily upon the accessibility of new materials, not yet available, possessing novel physical, chemical, or biological properties that differ significantly from those accessible in solely bioorganic- or inorganic-based compounds. New properties can be often achieved through new compositions or new molecular structures.

Most traditional molecules deal with fewer than ten elements (mainly C, H, N, O, S, P, Cl, Fe), whereas metal and semimetal-containing compounds have properties that are gained through the inclusion of nearly 100 additional elements. Macromolecules containing metal and metal-like elements are widespread in nature; metalloenzymes supplying a number of essential physiological functions are one the best known examples. The variety of molecules containing metal and metal-like components is extremely large, not only because of the larger number of metallic and metalloid elements, but also because of the diversity of available oxidation states, the use of combinations of different metals, and the ability to include a plethora of organic moieties organized in the form of low-molecular compounds or macromolecular structures.[1] One of the most useful platforms for such new materials is nucleic acids. Nucleic acid constructs used for technological applications consist usually of two clearly different domains; the nucleic acid itself in the role of an information-bearing platform, and a second, function-providing modification, in this case a metal or metal-carrying complex.[2] Modified nucleosides are indispensable building blocks needed for the synthesis of modified nucleic acids. This paper describes the modification, metalloid units, in the form of boron clusters or its complex with metal.

Recently, we described several methods for the incorporation of boron clusters and their metal complexes (metallocarboranes) into nucleosides and nucleotides—nucleoside conjugates with a broad range of potential applications and modified building blocks for the synthesis of boron and metal-bearing nucleic acids.[2–4]

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Practical applications of boron clusters/nucleoside conjugates range beyond use for the modification of DNA. Due to the crucial role of nucleosides in many metabolic pathways and interactions with other biomolecules, the nucleosides, their derivatives, and analogues are widely used as chemotherapeutics, mainly as antiviral or anticancer agents. Boron clusters are used as lipophilic pharmacophors and modulators of the nucleosides' physicochemical, biological, and pharmacological properties. They are also extensively studied as boron carriers for boron neutron capture therapy (BNCT) of tumors.

Herein, we propose a new and versatile approach based on Huisgen 1,3-dipolar cycloaddition of azides and terminal alkynes for the modification of pyrimidine as well as purine nucleosides.

The Cu^{I}-catalyzed 1,3-dipolar cycloaddition of azide and alkyne to form a triazole, termed "click chemistry" or "chemical ligation" reaction, was established recently as an important tool for the chemical and biological modification of biomolecules.[5,6] The reactants, azide and alkyne, are convenient to introduce independently, are stable, and do not react with common organic reagents or functional groups in biomolecules (are orthogonal). The triazole formation is irreversible and usually proceeds with high yield. In addition, this reaction benefits from an extremely mild and regioselective copper(I) catalyst system that is surprisingly indifferent to solvent and pH. All these factors allow the application of "click chemistry" approaches to be envisaged not only in general organic synthesis or its offshoots, such as synthesis on solid supports or combinatorial chemistry, but also in the emerging field of "organic chemistry in vivo".[7]

Results and Discussion

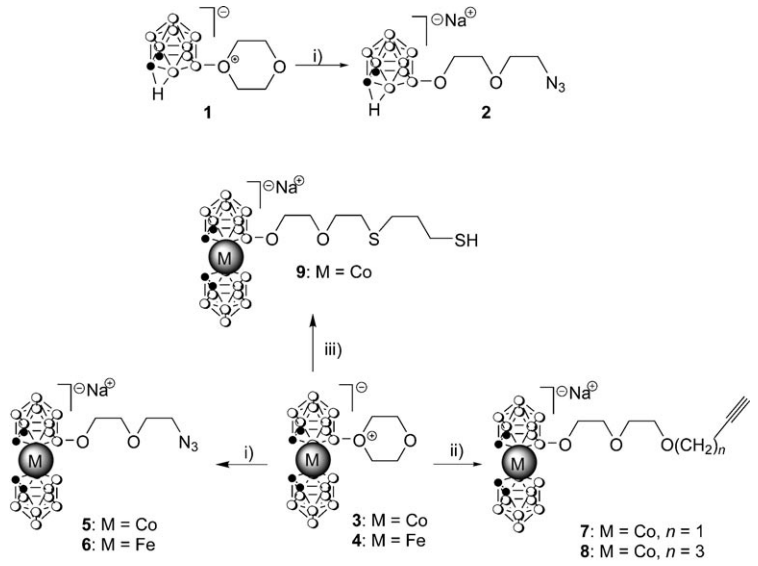
In the "chemical ligation" strategy based on the "click chemistry" approach, reactive molecular building blocks are designed to "click" together selectively and covalently. Although there are several reactions that fulfill in general the requirements of the "click" process,[5,7] the Huisgen dipolar cycloaddition of azides and alkynes[8,9] to give triazoles is the most useful, reliable, and broadly applied member of this family.

In addition to the advantages of the Huisgen-type cycloaddition mentioned above, further interest in this reaction stems from the attractive properties of the 1,2,3-triazole linker formed as a result of azide and alkyne fusion. The 1,2,3-triazole functions as a rigid linking unit that can mimic the atom placement and electronic properties of a peptide bond without the same susceptibility to hydrolytic cleavage, even enough the extra atom in the triazole backbone leads to an increase in distance between N1–C4 substituents relative to the typical amide bond. Due to the high dipole moment (actually higher than an amide bond), the 1,2,3-triazole linker can participate in hydrogen-bond formation as both a hydrogen-bond donor and acceptor, which helps the 1,2,3-triazole unit to fit well into the diverse environments of biological molecules.

The advantageous properties of Huisgen cycloaddition, together with the most useful modular nature of the click chemistry approach, make it well suited for use in the synthesis of new molecules, especially conjugates composed of two quite different subunits. Examples are bioorganic/inorganic conjugates such as the nucleosides and boron clusters presented here.

In our approach, two types of building blocks were constructed: one is the boron-cluster donor equipped with a terminal azido or ethynyl function, the second is the nucleoside–boron-cluster acceptor, similarly furnished with a terminal alkyne or azido group. The combination of all four possibilities, two types of boron-cluster donors and two types of boron-cluster acceptors, provides high versatility for the proposed methodology.

Syntheses of the boron-cluster donors are shown in Scheme 1. These were prepared in two variants: one contained a 7,8-dicarba-*nido*-undecaborate anion $(C_2B_9H_{12})^-$ and the second, a [3-metal bis(1,2-dicarbollide) (-1)]ate



Scheme 1. Synthesis of boron-cluster donors: 10-(5-azido-3-oxa-pentoxy)-7,8-dicarba-*nido*-undecaborane (**2**), 8-(5-azido-3-oxa-pentoxy)-3-cobalt bis(1,2-dicarbollide) (**5**), 8-(5-azido-3-oxa-pentoxy)-3-iron bis(1,2-dicarbollide) (**6**), 8-(5-propargyl-3-oxa-pentoxy)-3-cobalt bis(1,2-dicarbollide) (**7**), 8-[5-(4-pentyn-1-yl)-3-oxa-pentoxy]-3-cobalt bis(1,2-dicarbollide) (**8**), 8-[(5-thia-(3-thiolo-propan-1-yl)-3-oxa-pentoxy)-3-cobalt bis(1,2-dicarbollide) (**9**). i) NaN_3, DMF, RT; ii) $HOCH_2CCH$ or $HO(CH_2)_3CCH$, NaH, toluene, RT; iii) $HS(CH_2)_3SH$, NaH, toluene/DMF, RT.

modification, derivatives **2** and **3–9**, respectively. As a metal component of the metallocarborane complex, cobalt or iron was used. All compounds **2–9** were synthesized through dioxane ring-opening in cyclic oxonium derivatives of the 7,8-dicarba-*nido*-undecaborate or [3-metal bis(1,2-dicarbollide)(-1)]ate ion by azide anion or 2-propyn-1-ol, 4-pentyn-1-ol, 1,3-propanedithiol derived alcoholate or thiolate nucleophiles.

Table 1. Characteristics of boron-cluster azides **2**, **5**, **6** and alkynes **7**, **8**.

Compound	Molecular formula	MS[a]	UV[b] [nm]		IR [cm^{-1}]		TLC[e]
			λ_{min}	λ_{max}	ν_{B-H}	ν_{N3}	R_f
2	$C_6H_{19}B_9N_3O_2$	263.3[h]	–	–	2513.4[c]	2119.1[c]	0.42
5	$C_8H_{29}B_{18}CoN_3O_2$	453.2[i]	236.31	313.31	2553.2	2122.2	0.22
			351.56	375.39			
6	$C_8H_{29}B_{18}FeN_3O_2$	450.5[h]	350.30	372.16	2564.8	2123.9	0.22
			293.30	311.82	2554.8		
			237.56	282.44			
7	$C_{11}H_{32}B_{18}CoO_3$	467.0[h]	232.55	312.57	2565.0		0.50
8	$C_{13}H_{36}B_{18}CoO_3$	494.5[h]	232.55	312.29	2565.0		0.53

[a] MS (FAB, -ve), glycerine was used as a matrix. Typically, the most intense signal in the plot corresponds to the relative abundance 100% in the spectrum. Mass of this peak corresponds to the average isotopic mass distribution and is usually close to the M_W. [b] In 95% C_2H_5OH. [c] In Nujol. [d] In KBr. [e] TLC precoated silica gel 60 F254 plates. [f] Eluting solvent system: CH_2Cl_2/CH_3OH 9:1. [g] $[M+H]^-$. [h] $[M]^-$.

The derivative **2**, with a terminal azido group, was prepared from adduct **1** in the reaction with sodium azide in dimethylformamide. The reaction was completed after 1 h and provided **2** in high yield. The alkoxide and thiolate anions were generated in situ by addition of sodium hydride to a solution of adduct **3** or **4** and the corresponding alcohol or thiol in anhydrous toluene, followed by stirring at room temperature for 5–18 h. The reaction progress was monitored by TLC. In some cases, a mixture of toluene and dimethyl formamide was used as the reaction medium.

Following Hawthorne's seminal works on ligand derivatives of the 7,8-dicarba-*nido*-undecaborate anion,[10] Plesek's original concept of the ring-opening reaction in cyclic ethers and polyhedral boron hydride adducts with various nucleophiles[11–13] has been established over last two decades as a very useful methodology for the attachment of functional groups to boron-cluster derivatives.[14–18] In 2006 we demonstrated that the azide anion can serve as a nucleophile in the ring-opening reaction of the 10-dioxane-7,8-dicarba-*nido*-undecaborane (**1**) adduct.[19] An analogous approach, but using ethyl alcohol instead of dimethylformamide as a reaction medium, was published recently by other authors.[20] Table 1 summarizes the characteristics of compounds **2–6**, **7**, and **8**.

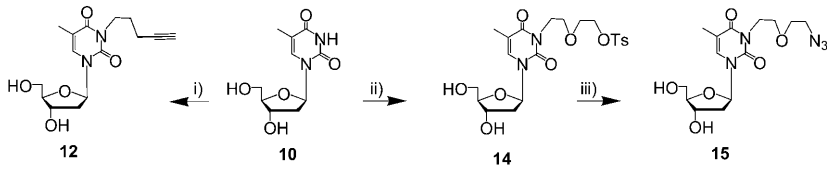
Herein, we demonstrate that this original approach may be successfully extended for [8-dioxane-3-cobalt bis(dicarbollide)]^0 and [8-dioxane-3-iron bis(dicarbollide)]^0 zwitterions with no interference from the quite reactive metalloborane B(8′) site, as no acid catalysis is required to attach the functional group to the cage boron atom. We show also that alcoholate or thiolate nucleophiles derived from alkyne alcohols or thiols, such as 2-propyn-1-ol, 4-pentyn-1-ol, or 1,3-propanedithiol, can cleanly cleave the onium rings of **3** and **4** with no side reaction. Considering utilization of the azide and alkynoxy nucleophiles for oxonium ring-opening, an additional known example is cleavage of the $[B_{12}H_{12}]^{2-}$ tetrahydrofurane adduct.[21–23]

It may be expected that the greater accessibility to two kinds of metalloborane building blocks bearing either terminal azide groups or terminal triple bonds will further enhance the usability of the "click chemistry" approach in the design of molecular constructions based on various boron clusters. A broad range of applications can be expected in the emerging field of the bioorganic chemistry of boron compounds as pharmacophors.

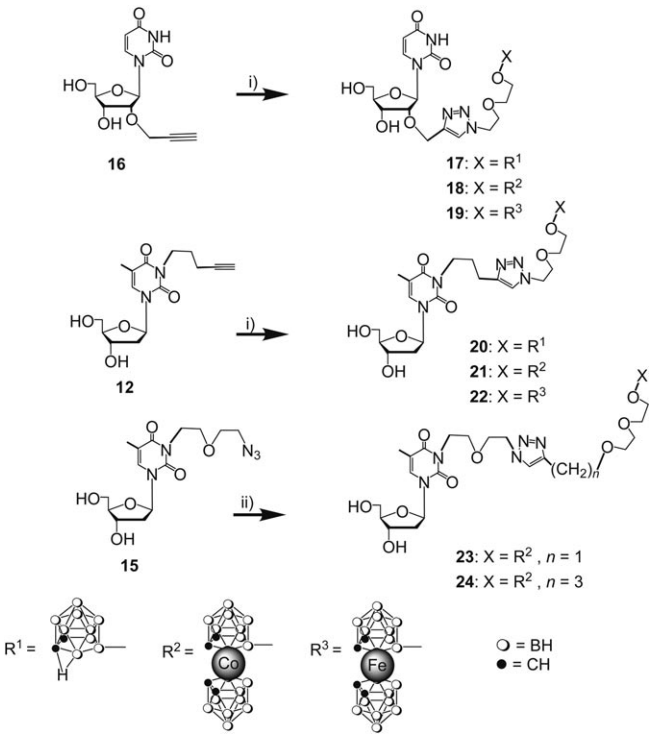
The application of a 1,3-propanedithiol derived thiolate nucleophile for the synthesis of **9** is also noteworthy. The ring-opening reactions of cyclic oxonium derivatives of polyhedral boron hydrides with a sulfur donor atom are quite rare. A single example, published in the simple borane series, is represented by cleavage of the tetrahydrofurane ring attached to the *closo*-dodecaborate or *closo*-decaborate cluster by the hydrosulfide ion.[18]

The synthesis of boron-cluster acceptors, the nucleosides equipped with terminal azido or ethynyl functions, is shown in Scheme 2. Synthesis of 3*N*-(4-pentyn-1-yl)thymidine (**12**) was performed similarly to that described for 3-(2-propyn-1-yl)thymidine, with the exception that in the present synthesis suitable tosylate was applied,[25] instead of alkyne bromide as used previously.[24]

Substitution of the good leaving tosyl group in (**14**), the already described compound,[25] by sodium azide in dry dimethylformamide provided **15** in high yield. The target nucleoside–boron-cluster conjugates were obtained in a simple, one-step procedure shown in Scheme 3. The reaction was performed under the standard "click chemistry" version of Huisgen azide–alkyne cycloaddition.[26] A suitable nucleoside acceptor with a spacer of different type (alkyl, ether)



Scheme 2. Synthesis of nucleoside boron-cluster acceptors 3*N*-[(5-azido-3-oxa-pentoxy)]thymidine (**15**) and 3*N*-(4-pentyn-1-yl)thymidine (**12**): i) $TsO(CH_2)_3CCH$ (**11**), K_2CO_3, DMF; ii) $TsO(CH_2)_2O(CH_2)_2OTs$ (**13**), K_2CO_3, DMF; iii) NaN_3, DMF.



Scheme 3. Synthesis of nucleoside boron-cluster conjugates through "chemical ligation" using nucleoside boron-cluster acceptors and boron-cluster donors: **17**–**24**. i) **2**, **5**, or **6**, $CuSO_4 \cdot 5H_2O$/potassium ascorbate, *tert*-butanol/water 1:1; ii) **7** or **8**, $CuSO_4 \cdot 5H_2O$/potassium ascorbate, *tert*-butanol/water 1:1.

and length (1–4 carbon atoms) was dissolved in a mixture of *tert*-butanol and water, together with an equimolar amount of a boron-cluster donor equipped with a 3-oxa-pentoxy spacer terminated with an azido, a 2-propyn-1-oxy, or 4-pentyn-1-oxy substituent.

Catalytic amounts of $CuSO_4$ and potassium ascorbate solutions were added to the solution obtained. Reactions were performed at room temperature over 8–50 h (usually 24 h) with TLC control. After reaction completion, the solvents were evaporated and the crude products were purified by column chromatography on silica gel. The yields of purified products usually ranged from 30 to 65%.

Several boron-cluster-donor/-acceptor combinations were tested. First, 2′-*O*-propargiluridine (**16**) was used as a boron-cluster acceptor. This allowed attachment of the modification to the sugar residue of the nucleoside. Two other nucleosides, 3*N*-(4-pentyn-1-yl)thymidine (**12**) and 3*N*-[5-azido-3-oxa-pentoxy)]thymidine (**15**), contained a spacer attached to the N3 of thymine base, terminated with an ethynyl or azido group, respectively. These substrates allowed attachment of the modification to the nucleobase part of the nucleoside. Boron clusters used as modifying units represent two important classes of the boron-cage derivatives carborane and metallocarborane. Table 2 compiles some pertinent characteristics of the obtained metallocarborane/nucleoside conjugates.

The general "click chemistry" methodology for the synthesis of boron cluster/nucleoside conjugate presented herein is an extension of our original approach used for the synthesis of 8-{[5-(7,8-dicarba-*nido*-undecaborane-10-yl)-3-oxa-pentoxy]-1*N*-1,2,3-triazole-4-yl}-2′-*O*-deoxyadenosine from 8-ethynyl-2′-deoxyadenosine and boron-cluster donor **2**,[19] and shows its applicability for the synthesis of both purine and pyrimidine nucleosides modified with boron clusters.

The recently published "click chemistry"-based synthesis of *closo*-dodecaborate $[B_{12}H_{12}]^{2-}$ anion derivatives utilizing reactions of compounds with terminal ethynyl or azido groups attached to the cluster through ether spacers with various organic azides and terminal alkynes[22,23] shows the further potential of Huisgen 1,3-dipolar cycloaddition in the synthesis of nucleoside/boron-cluster conjugates.

Compounds **17**–**24**, together with other nucleoside/boron-cluster conjugates synthesized in our laboratory are currently the subject of biological evaluation. Their cytotoxicity and susceptibility to phosphorylation by nucleoside kinases and immunomodulatory properties are being studied. Selected conjugates are transformed into 5′-*O*-dimethoxytrityldeoxynucleoside 3′-*O*-(*N*,*N*-diisopropyl-β-cyanoethyl)phosphor-

Table 2. Characteristics of carborane- and metallocarborane/nucleoside conjugates **17**–**24**.

Compound	Molecular formula	MS	UV[c] [nm]		IR [cm^{-1}]	TLC
			λ_{min}	λ_{max}	ν_{B-H}	R_f
17	$C_{18}H_{31}B_9N_5O_8$	545.4[a,h]	236.31	262.45	2521.5[d]	0.30[f]
18	$C_{20}H_{43}B_{18}CoN_5O_8$	735.5[a,i]	235.68	267.36	2562.0[e]	0.47[f]
			288.92	313.41		
			348.43	373.74		
19	$C_{20}H_{43}B_{18}FeN_5O_8$	732.6[a,i]	235.68	270.54	2542.7[d]	0.36[f]
			294.56	312.61		
20	$C_{21}H_{38}B_9N_5O_7$	572.0[b,j]	243.20	267.91	2530.0[d]	0.29[f]
21	$C_{23}H_{49}B_{18}CoN_5O_7$	762.0[b,k]	240.06	271.31	2562.0[d]	0.35[f]
			291.42	313.10		
22	$C_{23}H_{49}B_{18}FeN_5O_7$	759.0[b,k]	240.06	274.04	2560.0[d]	0.35[f]
			295.19	310.10		
23	$C_{25}H_{53}B_{18}CoN_5O_9$	822.0[b,k]	238.19	271.45	2561.0[d]	0.21[g]
			290.80	312.57		
24	$C_{27}H_{57}B_{18}CoN_5O_9$	850.0[b,k]	240.06	271.20	2561.0[d]	0.18[g]
			291.42	312.57		

[a] MS (FAB, Gly, -ve). [b] MS (ESI, 80 eV). [c] Typically, the most intense signal in the plot corresponds to the relative abundance 100% in the spectrum. Mass of this peak corresponds to the average isotopic mass distribution and is usually close to the M_w. [d] In 95% C_2H_5OH. [e] In KBr. [f] In Nujol. [g] Eluting solvent system: CH_2Cl_2/CH_3OH 8:2. [h] Eluting solvent system: CH_2Cl_2/CH_3OH 9:1. [i] $[M+3H]^-$. [j] $[M]^-$. [k] $[M+2H]^-$. [l] $[M+H]^-$.

amidites or H-phosphonates, the monomers suitable for automated DNA synthesis. Results will be published elsewhere.

Experimental Section

Materials: Most chemicals were obtained from Aldrich and used without further purification, unless stated. Thymidine and uridine were purchased from Pharma–Waldhof GmbH (Düsseldorf, Germany). Sodium hydride (60% suspension in mineral oil) was purchased from Lancaster (Morecambe, England). Flash chromatography was performed using silica gel 60 (230–400 mesh, ASTM, Aldrich). R_f values refer to analytical TLC performed using precoated silica gel 60 F254 plates purchased from Sigma–Aldrich (Steinheim, Germany) and developed in the solvent system indicated. Compounds were visualized by use of UV light (254 nm) or 0.5% acidic solution of $[PdCl_2]$ in HCl/methanol for boron-containing derivatives. The yields are not optimized.

NMR spectroscopy: ^1H, ^{13}C, and ^{11}B NMR spectra were recorded by using a Bruker Avance DPX 250-MHz spectrometer equipped with BB inverse probe-head, the spectra for ^1H, ^{13}C and ^{11}B nuclei were recorded at 250.13, 62.90, and 80.25 MHz, respectively. Tetramethylsilane and $BF_3/(C_2H_5)_2O$ were used as standards for ^1H-, ^{13}C-, and ^{11}B NMR, respectively. All chemical shifts are reported in ppm (δ) relative to external standards. The following abbreviations explain the multiplicities: s = singlet, d = doublet, dd = double doublet, t = triplet, dt = double triplet, q = quartet, quin = quintet, bs = broad singlet, m = multiplet. Coupling constants are reported in Hertz.

Mass spectrometry: Fast atom bombardment (FAB, Gly) mass spectra were recorded by using a Finnigan MAT (Bremen, Germany). Electrospray ionization (ESI trihydroxyacetophenone/ammonium citrate) spectra in negative mode were recorded by using an AMD Intectra mass AMD 402 spectrometer. The m/z values were measured in negative mode. Calculation of the theoretical molecular mass was performed using the "Show Analysis Window" option in the ChemDraw 8.0 program. Typically, the most intense signal in the plot corresponds to 100% relative abundance in the spectrum is provided. The mass of this peak corresponds to the average isotopic mass (average mass) and is usually close to the M_W. The Supporting Information shows data regarding the molecular ions and compares this with calculated values based on the isotopic distribution (exact mass).

UV spectroscopy: UV measurements were performed by using a GBC Cintra10e UV/Vis spectrometer (Dandenong, Australia). Samples for UV experiments, approximately 0.5 A_{260} ODU of each compound, were dissolved in 95% C_2H_5OH. Measurements were performed at ambient temperature.

IR spectroscopy: Infrared absorption spectra were recorded by using a Fourier-transform, infrared spectrophotometer Nexus (Thermo-Nicolet) or an ATI Mattson Infinity series MI-60, equipped with a silicon carbide (SiC) air-cooled source for the IR range, cesium iodide beam splitter, and DTGS (deuterated triglycine sulfate) detectors. Samples were prepared by diluting compounds with potassium bromide (70–140 mg of KBr per sample) and then pressing in the stainless-steel die to form discs of 0.8 cm diameter. Alternatively, the spectra were taken in Nujol mulls.

Methods: Synthesis of pentynyl tosylate (**11**),[27] (diethylene glycol)di-*para*-tosylate (**13**),[28] and 2′-*O*-propargiluridine (**16**)[29] was performed according to literature procedures. 10-Dioxane-7,8-dicarba-*nido*-undecaborane (**1**),[30] [8-dioxane-3-cobalt bis(dicarbollide)]^0 (**3**),[31] and [8-dioxane-3-iron bis(dicarbollide)]^0 (**4**)[32] were obtained as described.

10-(5-Azido-3-oxa-pentoxy)-7,8-dicarba-*nido*-undecaborane [(10-N_3-$(CH_2CH_2O)_2$-7,8-$C_2B_9H_{11}$)]Na (2): The 10-dioxane-7,8-dicarba-*nido*-undecaborane (**1**; 120 mg, 0.54 mmol) and sodium azide (39 mg, 0.59 mmol) were dissolved in dry dimethylformamide (3 mL). The mixture was stirred at RT until TLC monitoring (CH_2Cl_2/CH_3OH 9:1) showed complete conversion of the starting material (ca. 1 h). Then, the solvent was evaporated to dryness under vacuum yielding crude product **2** (250 mg), which was purified by silica gel column chromatography (230–400 mesh) using a linear gradient of methanol in methylene chloride as an eluting solvent system.

Yield **2**: 113 mg, 80%; TLC (CH_2Cl_2/CH_3OH 9:1): $R_f = 0.42$; UV/Vis (96% EtOH): no absorption in the range 220–320 nm was detected; FTIR (Nujol): $\nu_{max} = 2513.4$ (BH), 2119.1 (N_3), 2870.7, 2923.6, 2945.8 cm^{-1} (CH_2); ^1H {^{11}B BB} NMR (250.131 MHz, CD_3COCD_3, 25°C, TMS): $\delta = -0.49$ (s, BH bridge), 0.45 (s, 1H; H3), 1.16 (s, 2H; H5,6), 1.37 (s, 2H; H2,4), 2.15 (s, 2H; H9,11), 3.46–3.71 ppm (m, 8H; CH_2); ^{11}B NMR (80.25 MHz, CD_3COCD_3, 25°C, $BF_3/(C_2H_5)_2O$): $\delta = -9.66$ (s, B10), −12.22 (d, B11,9, $^2J_{BH} = 136.8$ Hz), −17.24 (d, B2,4, $^2J_{BH} = 130.32$ Hz), −23.80 (d, B5,6, $^2J_{BH} = 143.16$ Hz), −25.38 (d, B3, $^2J_{BH} = 110.10$ Hz), −40.40 ppm (d, B1, $^2J_{BH} = 142.52$ Hz); MS (Gly, FAB, -ve): m/z (%): calcd for $C_6H_{19}B_9N_3O_2$: 262.53 $[M+H]^-$; found: 263.3 (100).

8-(5-Azido-3-oxa-pentoxy)-3-cobalt bis(1,2-dicarbollide) [(8-N_3-$(CH_2CH_2O)_2$-1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{11}$-3,3′-Co)]Na (5) and 8-(5-azido-3-oxa-pentoxy)-3-iron bis(1,2-dicarbollide) [(8-N_3-$(CH_2CH_2O)_2$-1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{11}$-3,3′-Fe)]Na (6): The 8-dioxane-3-cobalt bis(dicarbollide) (**3**; 150 mg, 0.362 mmol) or 8-dioxane-3-iron bis(dicarbollide) (**4**, 150 mg, 0.364 mmol) and sodium azide (28 mg, 0.43 mmol) were dissolved in dry dimethylformamide (3 mL). The mixture was stirred at RT until TLC monitoring (CH_2Cl_2/CH_3OH 9:1) showed complete conversion of the starting material (ca. 4 h). Then, the solvent was evaporated to dryness under vacuum yielding crude product **5** (280 mg) or **6** (300 mg), which was purified by silica gel column chromatography (230–400 mesh) using a linear gradient of methanol in methylene chloride as an eluting solvent system.

Yield **5**: 144 mg, 87%; TLC (CH_2Cl_2/CH_3OH 9:1): $R_f = 0.22$; UV/Vis (96% EtOH): $\lambda_{min} = 351.56$, 236.31, $\lambda_{max} = 375.39$, 313.31 nm; FTIR (Nujol): $\nu_{max} = 2553.2$ (BH), 2122.2 (N_3), 2874.4, 2929.3, 3038.3 cm^{-1} (CH_2); ^1H {^{11}B BB} NMR (250.131 MHz, CD_3COCD_3, 25°C, TMS): $\delta = 1.42$ (s, 1H; H6), 1.56 (s, 2H; H5,11), 1.66 (s, 2H; H5′,11′), 1.78 (s, 1H; H6′), 1.99 (s, 2H; H9,12), 2.45 (s, 2H; H9′,12′), 2.70 (s, 1H; H10′), 2.91 (s, 2H; H4,7), 3.13 (s, 1H; H8′), 3.54–3.69 (m, 8H; CH_2), 4.26 ppm (s, 4H; $CH^{carborane}$); ^{11}B {^1H BB} NMR (80.25 MHz, CD_3COCD_3, 25°C, $BF_3/(C_2H_5)_2O$): $\delta = 22.933$ (s, B8), 4.02 (s, B8′), 0.41 (s, B10′), −2.45 (s, B10), −4.16 (s, B4′,7′), −7.40 (s, B9′,12′), −8.20 (s, B9,12), −17.22 (s, B5′,11′), −20.35 (s, B5,11), −28.47 ppm (s, B6); ^{11}B NMR (80.25 MHz, CD_3COCD_3, 25°C, $BF_3/(C_2H_5)_2O$): $\delta = 22.93$ (s, B8), 4.02 (d, B8′, $J = 128.48$ Hz), 0.41 (d, B10′, $^2J_{BH} = 148.38$ Hz), −2.45 (d, B10, $^2J_{BH} = 139.8$ Hz), −4.16 (d, B4′,7′, $^2J_{BH} = 139.8$ Hz), −7.40 (d, B9′,12′, $^2J_{BH} = 155.28$ Hz), −8.20 (d B9,12, $^2J_{BH} = 135.14$ Hz), −17.22 (d, B5′,11′, $^2J_{BH} = 159.45$ Hz), −20.35 (d, B5,11, $^2J_{BH} = 156.00$ Hz), −28.47 ppm (d, B6, $^2J_{BH} = 153.84$ Hz); MS (Gly, FAB, -ve): m/z (%): calcd for $C_8H_{29}B_{18}CoN_3O_2$: 452.87 $[M]^-$; found: 453.2 (100) $[M]^-$.

Yield **6**: 132 mg, 80%; TLC (CH_2Cl_2/CH_3OH 9:1): $R_f = 0.22$; UV/Vis (96% EtOH): $\lambda_{min} = 350.30$, 293.30, 237.56, $\lambda_{max} = 372.16$, 311.82, 282.44 nm; FTIR (KBr): $\nu_{max} = 2564.8$, 2554.8 (BH), 2123.9 (N_3), 2872.8, 2925.4, 3029.7 cm^{-1} (CH_2); ^{11}B {^1H BB} NMR (80.25 MHz, CD_3COCD_3, 25°C, $BF_3/(C_2H_5)_2O$): $\delta = 117.12$, 100.80 (s, B6,6′), 52.24, 41.14, 30.44, −1.23, −6.05, −40.73 (B5,5′,9,9′,10,10′,11,11′,12,12′), −70.05 ppm (B10, B10′); MS (Gly, FAB, -ve): m/z (%): calcd for $C_8H_{29}B_{18}FeN_3O_2$: 449.78 $[M+H]^-$; found: 450.5 (100).

8-(5-Propargyl-3-oxa-pentoxy)-3-cobalt bis(1,2-dicarbollide) [(8-C_3H_3O-$(CH_2CH_2O)_2$-1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{11}$-3,3′-Co]Na (7): NaH (10 mg, 0.42 mmol) (60% suspension in mineral oil) was added at RT to a stirred solution of [8-dioxane-3-cobalt bis(dicarbollide)]^0 (**3**) (100 mg, 0.24 mmol) and propargyl alcohol (14 mg, 0.24 mmol) in dry toluene (3 mL). The progress of the reaction was monitored by TLC chromatography using CH_2Cl_2/CH_3OH (9:1) as developing solvent system. After 18 h the solvent was evaporated to dryness under vacuum yielding crude product (**7**), which was purified by silica gel column chromatography (230–400 mesh) using a linear gradient of methanol in methylene chloride as an eluting solvent system.

Yield **7**: 100 mg, 85%; TLC (CH_2Cl_2/CH_3OH 9:1): $R_f = 0.50$; UV/Vis (96% EtOH), $\lambda_{min} = 232.55$, $\lambda_{max} = 312.57$ nm; FTIR (KBr): $\nu_{max} = 2565$ (BH), 2871, 2923, 3040 (CH_2), 3290 cm^{-1} (CH); ^1H NMR (250.131 MHz, CD_3OH, 25°C, TMS): $\delta = 2.82$ (t, 1H; C≡CH, $^4J_{HH} = 2.50$ Hz), 3.63–3.70 (m, 8H; 2×CH_2CH_2), 4.14 (br s, 4H; $CH^{carborane}$), 4.19 ppm (2H; CH_2C≡

CH, $^4J_{HH}$=2.50 Hz); ^{1}H {^{11}B BB} NMR (250.131 MHz, CD_3OH, 25°C, TMS): δ=1.44 (s, 1H; H6), 1.51 (s, 2H; H5,11), 1.59 (s, 2H; H5′,11′), 1.70 (s, 2H; H9,12), 1.94 (s, 2H; H9′,12′), 2.49 (s, 1H; H10), 2.65 (s, 1H; H10′), 2.81 (s, 1H; C≡CH), 2.86 (s, 1H; H8′), 3.52–3.57 (m, 4H; CH_2CH_2), 3.62–3.69 (m, 4H; CH_2CH_2), 4.14 (s, 4H; $CH^{carborane}$), 4.19 ppm (d, 2H; CH_2C≡CH, $^4J_{HH}$=0.75 Hz); ^{11}B NMR (80.25 MHz, CD_3COCD_3, 25°C, $BF_3/(C_2H_5)_2O$): δ=22.98 (s, B8), 4.00 (d, B8′, $^2J_{BH}$=140.38 Hz), 0.44 (d, B10′, $^2J_{BH}$=143.43 Hz), −2.42 (d, B10, $^2J_{BH}$=140.38 Hz), −4.29 (d, B4′,7′, $^2J_{BH}$=146.48 Hz), −7.33 (d, B9′, 12′, $^2J_{BH}$=125.13 Hz), −8.16 (d, B9,12,4,7, $^2J_{BH}$=128.17 Hz), −17.27 (d, B5′,11′, $^2J_{BH}$=155.64 Hz), −20.44 (d, B5,11, $^2J_{BH}$=158.69 Hz), −21.98 (B6′, overlap), −28.42 ppm (d, B6, $^2J_{BH}$=167.84 Hz); ^{11}B {^{1}H BB} NMR (80.25 MHz, CH_3OD, 25°C, $BF_3/(C_2H_5)_2O$): δ=22.90 (s, B8), 4.00 (s, B8′), 0.44 (s, B10), −2.44 (s, B10′), −4.25 (s, B4′,7′), −7.39 (s, B9′,12′), −8.16 (s, B9,12,4,7), −17.27 (s, B5′,B11′), −20.44 (s, B5,B11), −21.90 (s, B6′), −28.43 ppm (s, B6); MS (ES$^-$): *m*/*z* (%): calcd for $C_{11}H_{32}B_{18}CoO_3$: 465.90 [*M*+H]$^-$; found: 467.0 (100).

8-[5-(4-Pentyn-1-yl)-3-oxa-pentoxy]-3-cobalt bis(1,2-dicarbollide) [(8-C_5H_7O-$(CH_2CH_2O)_2$-1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{11}$-3,3′-Co]Na (8): NaH (5 mg, 0.21 mmol, 60% suspension in mineral oil) was added at RT to a stirred solution of [8-dioxane-3-cobalt bis(dicarbollide)]^0 (**3**) (50 mg, 0.12 mmol) and 4-pentyn-1-ol (10 mg, 0.12 mmol) in dry toluene (3 mL). The reaction progress was monitored by TLC chromatography using CH_2Cl_2/CH_3OH (9:1) as eluting solvent system. After 18 h the solvent was evaporated to dryness under vacuum yielding crude product (**8**), which was purified by silica gel column chromatography (230–400 mesh) using a linear gradient of methanol in methylene chloride as an eluting solvent system.

Yield **8**: 44 mg, 73%; TLC (CH_2Cl_2/CH_3OH 9:1): R_f=0.53; UV/Vis (96% EtOH): λ_{min}=232.55, λ_{max}=312.29 nm; FTIR (KBr): ν_{max}=2565 (BH), 2873, 2924, 3037 (CH_2), 3293, 3275 cm^{-1} (CH); ^{1}H NMR (250.131 MHz, CD_3OH, 25°C, TMS): δ=1.75 (quin, 2H; $CH_2CH_2CH_2$, $^3J_{HH}$=7.06 Hz), 2.17 (t, 1H; CCH, $^4J_{HH}$=2.79 Hz), 2.24 (dt, 2H; CH_2CCH, $^3J_{HH}$=7.06 Hz, $^4J_{HH}$=2.68 Hz), 3.50–3.61 (m, 8H; 2×CH_2CH_2), 4.15 ppm (brs, 4H; $CH^{carborane}$); ^{11}B {^{1}H BB} NMR (80.25 MHz, CD_3COCD_3, 25°C, $BF_3/(C_2H_5)_2O$): δ=22.94 (s, B8), 3.91 (s, B8′), 0.44 (s, B10′), −2.41 (s, B10), −4.24 (s, B4′,7′), −7.35 (s, B9′,12′), −8.16 (s, B9,12,4,7), −17.27 (s, B5′,11′), −20.44 (s, B5,11), −21.91 (s, B6′), −28.40 ppm (s, B6); ^{11}B NMR (80.25 MHz, CD_3COCD_3, 25°C, $BF_3/(C_2H_5)_2O$): δ=22.90 (s, B8), 3.91 (d, B8′, $^2J_{BH}$=137.32 Hz), 0.55 (d, B10′, $^2J_{BH}$=143.43 Hz), −2.41 (B10, $^2J_{BH}$=137.33 Hz), −4.23 (B4′,7′, $^2J_{BH}$=146.48 Hz), −7.28 (B9′,12′, $^2J_{BH}$=125.12 Hz), −8.23 (B9,12,4,7, *J*=125.12 Hz), −17.26 (B5′,11′, $^2J_{BH}$=155.64 Hz), −20.45 (B5,11, $^2J_{BH}$=158.69 Hz), −21.80 (B6′, overlap), −28.40 ppm (B6, $^2J_{BH}$=170.89 Hz); MS (Gly, FAB, -ve): *m*/*z* (%): calcd for $C_{13}H_{36}B_{18}CoO_3$: 493.95 [*M*+H]$^-$; found: 494.5 (100).

8-[(5-Thia-(3-thiolo-propan-1-yl)-3-oxa-pentoxy)-3-cobalt bis(1,2-dicarbollide) [(8-HS(CH_2)3S-$(CH_2CH_2O)_2$-1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{11}$-3,3′-Co)]Na (9): [8-Dioxane-3-cobalt bis(dicarbollide)]^0 (**3**, 50 mg, 0.12 mmol) was dissolved in a mixture of dry toluene and DMF (6:1 v/v, 600 μL). The resultant solution was added dropwise over 30 min to the mixture of suspension of sodium hydride (60% suspension in mineral oil) and 1,3-propanedithiol in dry toluene (500 μL). The reaction was monitored by TLC (MeOH/CH_2Cl_2 1:9) After reaction completion (approximately 4–5 h) the solvents were evaporated under vacuum. The crude product was purified by silica gel chromatography using a linear gradient of methanol in CH_2Cl_2.

Yield **9**: 20 mg, 31%; TLC ($CHCl_3/CH_3OH$ 8:2): R_f=0.35; UV/Vis (96% MeOH): λ_{max}=312.32, 363.87 nm, λ_{min}=234.42, 397.37 nm; FTIR (KBr): ν_{max}=2563.0 (BH), overlapped with 2553 (SH), 2870.0, 2924.0, 3039.0 cm^{-1} (CH_2); ^{1}H NMR (250.131 MHz, MeOD, 25°C, TMS): δ=1.87 (quin, 2H; $CH_2CH_2CH_2$, $^3J_{HH}$=7.11 Hz), 2.61 (t, 2H; SCH_2, $^3J_{HH}$=6.93 Hz), 2.68 (t, 2H; CH_2SH, $^3J_{HH}$=6.83 Hz), 2.69 (t, 2H; CH_2S, $^3J_{HH}$=5.84 Hz), 3.25–3.29 (m, 2H; 2×OCH_2), 4.17 (brs, 4H; $CH^{carborane}$), 4.87–4.96 ppm (m, 2H; 2×OCH_2); ^{11}B {^{1}H BB} NMR (80.25 MHz, CD_3COCD_3, 25°C, $BF_3/(C_2H_5)_2O$): δ=22.68 (s, B8), 3.63 (s, B8′), 0.44 (s, B10′), −2.41 (s, B10), −4.17 (s, B4′,7′), −7.45 (s, B9′,12′), −8.31 (s, B9,12,4,17), −17.27 (s, B5′,11′), −20.44 (s, B5,11), −21.88 (s, B6′, overlap), −28.38 ppm (s, B6); ^{11}B NMR (80.25 MHz, CD_3COCD_3, 25°C, $BF_3/(C_2H_5)_2O$): δ=22.67 (s, B8), 3.61 (d, B8′, $^2J_{BH}$=134.28 Hz), 0.54 (d, B10′, $^2J_{BH}$=140.38 Hz), −2.41 (d, B10, $^2J_{BH}$=137.33 Hz), −4.13 (d, B4′,7′, $^2J_{BH}$=143.43 Hz), −7.40 (d, B9′,12′, $^2J_{BH}$=128.18 Hz), −8.35 (d, B9,12,4,17, $^2J_{BH}$=131.22 Hz), −17.25 (d, B5′,11′, $^2J_{BH}$=152.58 Hz), −20.41 (d, B5,11, $^2J_{BH}$=158.69 Hz), −21.74 (B6′, overlap), −28.34 ppm (B6, $^2J_{BH}$=164.79 Hz); MS (Gly, FAB, -ve): *m*/*z* (%): calcd for $C_{11}H_{36}B_{18}CoO_2S_2$: 518.06 [*M*]$^-$; found: 518.1 (100).

3*N*-(4-Pentyn-1-yl)thymidine (12): A solution of pentynyl tosylate (**11**) (0.98 g, 4.12 mmol) in dry dimethylformamide (2 mL) was added at RT to a stirred solution of thymidine (**10**) (1.00 g, 4.12 mmol) and potassium carbonate (1.82 g, 13.18 mmol) in the same solvent (8 mL). The progress of the reaction was monitored by TLC using CH_2Cl_2/CH_3OH (92:8) as a solvent system. After 18 h the solvent was evaporated to dryness under vacuum yielding crude product (**12**) (0.96 g), which was purified by silica gel column chromatography (230–400 mesh) using a linear gradient of methanol in methylene chloride as an eluting solvent system.

Yield **12**: 956 mg, 74%; TLC (CH_2Cl_2/CH_3OH 92:8): R_f=0.39; UV/Vis (96% EtOH): λ_{min}=237.56, λ_{max}=268.03 nm; FTIR (KBr): ν_{max}=3423 (OH), 2929, 3080 (CH_2), 1629 cm^{-1} (C=O); ^{1}H NMR (250.131 MHz, CH_3OD, 25°C, TMS): δ=1.77–1.88 (quin, 2H; CH_2CH_2C≡CH), 1.89 (d, 3H; CH_3, $^4J_{HH}$=1.16 Hz), 2.19–2.27 (m, 5H; CH_2-C≡CH, C≡C*H*, H-2′), 3.73–3.79 (m, 2H; 5′$_\alpha$,5′$_\beta$-H, $^3J_{HH}$=3.07, 12.04, 8.55 Hz), 3.89–3.90 (m, 1H; H-4′), 3.98–4.04 (dt, 2H; CH_2N, $^4J_{HH}$=1.13 Hz, $^3J_{HH}$=7.19 Hz), 4.37–4.39 (m, 1H; H-3′), 6.28 (t, 1H; H-1′, $^3J_{HH}$=6.94 Hz), 7.82 ppm (d, 1H; H-6, $^4J_{HH}$=1.18 Hz); ^{13}C NMR (62.90 MHz, CD_3OH, 25°C, TMS): 13.37 (CH_3), 16.93 (CH_2), 27.43 (CH_2), 41.31 (CH_2N), 41.71 (C-2′), 62.70 (C-5′), 69.78 (C≡*C*H), 72.00 (C-3′), 84.06 (*C*≡CH), 87.12 (C-1′), 88.79 (C-4′), 110.88 (C-5), 136.48 (C-6), 152.36 (C-2), 165.48 ppm (H-4); MS (ES$^-$): *m*/*z* (%): calcd for $C_{15}H_{20}N_2O_5$: 308.33 [*M*+Na]$^-$; found: 331.0 (100).

3*N*-[1-(*para*-Toluensulfonyl)-3-oxa-pentoxy)]thymidine (14): A solution of diethylene glycol di(*p*-toluenesulfonate)(**13**) (0.65 g, 1.57 mmol) in dry dimethylformamide (3 mL) was added at RT to a stirred solution of thymidine (**10**) (0.127 g, 0.52 mmol) and potassium carbonate (0.216 g, 1.57 mmol) in the same solvent (4 mL). The progress of the reaction was monitored by TLC using CH_2Cl_2/CH_3OH (8:2) as a solvent system. After 18 h the solvent was evaporated to dryness under vacuum yielding crude product, which was purified by silica gel column chromatography (230–400 mesh) using a linear gradient of methanol in methylene chloride as an eluting solvent system.

Yield **14**: 225 mg, 89%; TLC (CH_2Cl_2/CH_3OH 8:2): R_f=0.42; UV/Vis (96% EtOH): λ_{min}=242.00, λ_{max}=267.76 nm; FTIR (Nujol): ν_{max}=3409 (OH), 2875, 2928, 3067 cm^{-1} (CH_2), 1652, 1705 (C=O); ^{1}H NMR (250.131 MHz, $CDCl_3$), 25°C, TMS): δ=1.92 (s, 3H; CH_3), 2.33–2.49 (m, 2H; H-2′), 3.63–3.68 (m, 4H; OCH_2CH_2O), 3.81–3.95 (part AB of ABX spin system, 2H; $H_{a,b}$-5′, $^3J_{HH}$=3.04, 3.28 Hz, $^2J_{HH}$=11.45 Hz), 3.98–4.01 (part X of ABX spin system, 1H; H-4′, $^3J_{HH}$=3.16, 3.41 Hz), 4.08–4.15 (m, 4H; NCH_2CH_2,), 4.58 (dt, 1H; H-3′, $^3J_{HH}$=3.97, 6.64 Hz), 6.17 (t, 1H; H-1′, $^3J_{HH}$=6.64 Hz), 7.41 (d, 1H; H-6, $^4J_{HH}$=1.13 Hz), 7.56 ppm (4H; dd, Ar, $^3J_{HH}$=8.27, 8.58 Hz); MS (ESI): *m*/*z* (%): calcd for $C_{21}H_{28}N_2O_9S$: 484.52 [*M*+H]$^-$; found: 485.0 (10).

3*N*-[5-Azido-3-oxa-pentoxy)]thymidine (15): Thymidine **14** (430 mg (0.89 mmol) and sodium azide (145 mg, 2.25 mmol) were dissolved in dry dimethylformamide (7 mL). The mixture was stirred at RT until TLC monitoring (CH_2Cl_2/CH_3OH 92:8) showed complete conversion of the starting material (ca. 18 h). Then, the solvent was evaporated to dryness under vacuum yielding crude product **15** (259 mg), which was purified by silica gel column chromatography (230–400 mesh) using a linear gradient of methanol in methylene chloride as an eluting solvent system.

Yield **15**: 259 mg, 82%; TLC (CH_2Cl_2/CH_3OH 92:8): R_f=0.37; UV/Vis (96% EtOH): λ_{min}=236.20, λ_{max}=268.03 nm; FTIR (Nujol): ν_{max}=3431 (OH), 2872, 2927, 3076 (CH_2), 2108 (N_3), 1698 cm^{-1} (C=O); ^{1}H NMR (250.131 MHz, CD_3OH, 25°C, TMS): δ=1.89 (d, 3H; CH_3, $^4J_{HH}$=1.18 Hz), 2.20–2.26 (m, 2H; H-2′), 3.63–3.65 (m, 4H; OCH_2CH_2N), 3.66 (t, 2H; CH_2CH_2O, $^3J_{HH}$=5.93 Hz), 3.63–3.76 (part AB of ABX spin system, 2H; $H_{a,b}$-5′,$^3J_{HH}$=3.16, 8.71, 3.77 Hz), 3.77–3.88 (part X of ABX spin system, 1H; H-4′, $^3J_{HH}$=3.37, 3.41 Hz), 4.14 (t, 2H; CH_2N, $^3J_{HH}$=5.85 Hz), 4.37 (m, 1H; H-3′), 6.28 (t, 1H; H-1′, $^3J_{HH}$=6.76 Hz), 7.82 ppm

(d, 1H; H-6, $^4J_{HH}$=1.06 Hz); MS (ESI): *m/z* (%): calcd for $C_{14}H_{21}N_5O_6$: 355.35 $[M+Na]^-$; found: 378.0 (100).

General procedure for the synthesis of compounds 17–24: The boron-clusters acceptor furnished with terminal alkyne (**16**, **17**) or azido group (**15**) (0.04–0.14 mmol, typically 0.05 mmol) and an equimolar amount or slight excess (ca. 5%) of boron-cluster donor equipped with terminal azido (**5**, **6**) or ethynyl function (**7**, **8**)) (0.04–0.14 mmol, typically 0.05 mmol) were dissolved in 0.6–2.1 mL of a mixture of *tert*-butanol and water (1:1). To the obtained solution, a solution of $CuSO_4{\cdot}5H_2O$ (0.002–0.007 mmol, 5% mol, 20–70 μL of 100-mM solution) was added, followed by addition of a twofold molar excess of potassium ascorbate solution (0.004–0.017 mmol, 40–170 μL of 100-mM solution) generated in situ from solutions of potassium hydroxide and ascorbic acid (an equimolar amount of potassium ascorbate can be used with only slight yield decrease). The mixture was stirred at RT until TLC monitoring (CH_2Cl_2/CH_3OH 8:2 for **17**, **19**, **21**, **22** or CH_2Cl_2/CH_3OH 9:1 for **18**, **20**, **23**, **24**) showed complete conversion of the nucleoside starting material (8–50 h, typically 24 h). Then, the solvent was evaporated to dryness under vacuum and the crude product was purified by silica gel column chromatography (230–400 mesh) using a linear gradient of methanol in dichloromethane as an eluting solvent system. Pure product was lyophilized from a mixture of benzene/methanol (9:1).

2′-*O*-{[5-(7,8-Dicarba-*nido*-undecaborane-10-yl)-3-oxa-pentoxy]-1*N*-1,2,3-triazole-4-yl}methyluridine (17): Yield **17**: 32 mg, 65%; TLC (CH_2Cl_2/CH_3OH 8:2): R_f=0.30; UV/Vis (96% EtOH): λ_{min}=236.31, λ_{max}=262.45 nm; FTIR (Nujol): ν_{max}=2521.5 (BH), 2925.8, 2874.6 (CH_2), 1690.8 cm^{-1} (C=O); ^{1}H NMR (250.131 MHz, CD_3OH, 25°C, TMS): δ= 0.85–3.0 (bm, 11H; $CH^{carborane}$), 3.51–3.65 (m, 6H; $CH_2OCH_2CH_2O$), 3.67–3.90 (m, 4H; H-5′, OCH_2), 4.10–4.15 (m, 1H; H-4′), 4.20–4.25 (m, 1H; H-3′), 4.54–4.58 (m, 3H; NCH_2CH_2), 5.64 (d, 1H; H-5, $^3J_{HH}$= 8.54 Hz), 5.79 (d, 1H; H-1′, $^3J_{HH}$=3.78 Hz), 7.98 (d, 1H; H-6, $^3J_{HH}$= 8.53 Hz), 8.05 ppm (s, 1H; 1-$H^{triazole}$); ^{11}B NMR (80.25 MHz, CD_3COCD_3, 25°C, $BF_3/(C_2H_5)_2O$): δ=−9.50 (s, B10), −11.96 (d, B9,11, $^2J_{BH}$= 152.59 Hz), −16.80 (d, B5,6, $^2J_{BH}$=125.12 Hz), −23.25 (d, B2,4, $^2J_{BH}$= 149.54 Hz, B3 overlap), −40.18 ppm (d, B1, $^2J_{BH}$=140.38 Hz); ^{11}B {^{1}H BB} NMR (80.25 MHz, CD_3COCD_3, 25°C, $BF_3/(C_2H_5)_2O$): δ=−9.51 (s, B10), −11.95 (d, B9,11), −16.81 (s, B5,6), −23.25 (s, B2,4, B3 overlap), −40.19 ppm (s, B1); MS (FAB, Gly, -ve): *m/z* (%): calcd for $C_{18}H_{31}B_9N_5O_8$: 542.77 $[M+3H]^-$; found: 545.4 (100).

2′-*O*-{[5-[3-cobalt bis(1,2-dicarbollide)-8-yl]-3-oxa-pentoxy}-1*N*-1,2,3-triazole-4-yl} methyluridine (18): Yield **18**: 17 mg, 32%; TLC (CH_2Cl_2/CH_3OH 9:1): R_f=0.47; UV/Vis: (96% EtOH): λ_{min}=235.68, 288.92, 348.43, λ_{max}=267.36, 313.41, 373.74 nm; FTIR (Nujol): ν_{max}=2562.0 (BH), 2869.2, 2924.1, 3050.3 (CH_2), 1699.6 cm^{-1} (C=O); ^{1}H NMR (250.131 MHz, CD_3OH, 25°C, TMS): δ=0.5–3.0 (brs, 18H; $BH^{carborane}$), 3.54–3.88 (m, 8H; $3OCH_2$), 3.96–4.25 (m, 7H; H-3′, H-4′, H-5′, $4CH^{carborane}$), 4.52–4.56 (m, 3H; NCH_2, H-2′), 5.63 (d, 1H; H-5, $^3J_{HH}$= 8.04 Hz), 5.95 (d, 1H; H-1′, $^3J_{HH}$=4.2 Hz), 7.94 (d, 1H; H-6, $^3J_{HH}$= 8.0 Hz), 8.10 ppm (s, 1H; $H^{triazole}$); ^{11}B NMR (80.25 MHz, CD_3COCD_3, 25°C, $BF_3/(C_2H_5)_2O$): δ=23.31 (s, B8), 4.63 (d, B8′, $^2J_{BH}$=131.23 Hz), 0.56 (d, B10′, $^2J_{BH}$=143.43 Hz), −2.51 (d, B10 overlap), −4.33 (d, B4′,7′, $^2J_{BH}$=143.44 Hz), −7.16 (d, B9′,12′, $^2J_{BH}$=128.17 Hz), −8.12 (d, B9,12, $^2J_{BH}$=115.97 Hz), −17.26 (d, B5′11′, $^2J_{BH}$=155.64 Hz), −20.33 (d, B5,11, $^2J_{BH}$=137.33 Hz), −22.09 (d, B6′ overlap), −28.61 ppm (d, B6); ^{11}B {^{1}H BB} NMR (80.25 MHz, CD_3COCD_3, 25°C, $BF_3/(C_2H_5)_2O$): δ=23.32 (s, B8), 4.55 (s, B8′), 0.35 (s, B10′), −2.51 (s, B10 overlap), −4.48 (s, B4′,7′), −7.26 (s, B9′,12′), −8.12 (s, B9,12), −17.34 (s, B5′,11′), −20.39 (s, B5,11), −22.10 (s, B6′ overlap), −28.62 ppm (s, B6); MS (FAB, Gly, -ve,): *m/z* (%): calcd for $C_{20}H_{43}B_{18}CoN_5O_8$: 735.11 $[M]^-$; found: 735.5 (36).

2′-*O*-{[5-[3-iron bis(1,2-dicarbollide)-8-yl]-3-oxa-pentoxy}-1*N*-1,2,3-triazole-4-yl}methyluridine (19): Yield **19**: 20 mg, 65%; TLC (CH_2Cl_2/CH_3OH 8:2): R_f=0.36; UV/Vis: (96% EtOH): λ_{min}=235.68, 294.56, λ_{max}=270.54, 312.61 nm; FTIR (KBr): ν_{max}=2542.7 (BH), 2861.4, 2924.5, 2955.6 (CH_2), 1698.6 cm^{-1} (C=O); ^{11}B {^{1}H BB} NMR (80.25 MHz, CD_3COCD_3, 25°C, $BF_3/(C_2H_5)_2O$): δ=−482.54 (s, B8′), −441.68 (s, B8), −377.14, −371.68 (s, B4,7,4′,7′), −40.27, −5.41, −1.03, 30.31, 39.15 (s, B5,5′,11,11′,9,9′,12,12′), 102.98, 120.06 ppm (s, B6,6′); MS (FAB, Gly, -ve,): *m/z* (%): calcd for $C_{20}H_{43}B_{18}FeN_5O_8$: 732.03 $[M]^-$; found: 732.6 (100).

3*N*-{[5-(7,8-dikarba-*nido*-undekaborane-10-yl)-3-oxa-pentoxy]-1*N*-1,2,3-triazole-4-yl}(4-propan-1-yl)thymidine (20): Yield **20**: 23 mg, 40%; TLC (CH_2Cl_2/CH_3OH 8:2): R_f=0.29; UV/Vis: (96% EtOH): λ_{min}=243.20, λ_{max}=267.91 nm; FTIR (KBr): ν_{max}=2530.0 (BH), 2873, 2930, 2972 (CH_2), 1697, 1667, 1632 cm^{-1} (CO); ^{1}H NMR (250.131 MHz, DMSO, 25°C, TMS): δ=2.10 (quin, 2H; $CH_2CH_2CH_2$, $^3J_{HH}$=7.01 Hz), 2.26–2.29 (m, 2H; H-2′), 3.30 (t, 2H; $CH_2CH_2CH_2$, $^3J_{HH}$=7.70 Hz), 3.56–3.90 (m, 10H; $4CH_2O$, H-5′), 4.02 (t, 2H; H-3′, J=6.65 Hz), 4.30–4.40 (m, 1H; H-4′), 4.55 (t, 2H; NCH_2, $^3J_{HH}$=5.13 Hz), 6.29 (t, 1H; H-1, $^3J_{HH}$=7.50 Hz), 7.80 (s, 1H; H-6), 7.94 ppm (s, 1H; $H^{triazole}$); ^{11}B {^{1}H BB} NMR (80.25 MHz, CD_3COCD_3, 25°C, $BF_3/(C_2H_5)_2O$): δ=−40.46 (s, B1), −25.36 (s, B3), 24.00 (s, B2,4), −17.32 (s, B5,6), −12.26 (B9,11), −9.21 ppm (s, B10); ^{11}B NMR (80.25 MHz, CD_3COCD_3, 25°C, $BF_3/(C_2H_5)_2O$): δ=−40.46 (d, B1, $^2J_{BH}$=134.28 Hz), −25.23 (d, B3 overlap), −24.01 (d, B2,4, $^2J_{BH}$=149.53 Hz), −17.31 (d, B5,6, $^2J_{BH}$= 134.27 Hz), −12.34 (d, B9,11, $^2J_{BH}$=134.28 Hz), −9.33 ppm (s, B10); MS (ES^-): *m/z* (%): calcd for $C_{21}H_{38}B_9N_5O_7$: 569.85 $[M+2H]^-$; found: 572.0 (100).

3*N*-{[5-[3-cobalt bis(1,2-dicarbollide)-8-yl]-3-oxa-pentoxy}-1*N*-1,2,3-triazole-4-yl}(4-propan-1-yl)thymidine (21): Yield **21**: 19 mg, 33%; TLC (CH_2Cl_2/CH_3OH 8:2): R_f=0.35; UV/Vis: (96% EtOH): λ_{min}=240.06, 291.42, λ_{max}=271.31, 313.10 nm; FTIR (KBr): ν_{max}=2562 (BH), 2872, 2926 (CH_2), 1695, 1667, 1632 cm^{-1} (CO); ^{1}H NMR (250.131 MHz, CD_3OH, 25°C, TMS): δ=0.5–3.0 (brs, 18H; $BH^{carborane}$), 1.90 (s, 3H; CH_3), 1.99 (t, 2H; $CH_2CH_2CH_2$, $^3J_{HH}$=7.47 Hz), 2.21–2.33 (m, 2H; H-2′), 2.76 (quin, 2H; $CH_2CH_2CH_2$, $^3J_{HH}$=7.68 Hz), 3.52–3.62 (m, 6H; 3× CH_2O), 3.74–3.90 (m, 3H; H-4′,H-5′), 4.00 (t, 2H; NCH_2, $^3J_{HH}$=7.88 Hz), 4.08 (brs, 4H; $CH^{carborane}$), 4.25–4.30 (m, 1H; H-3′), 4.50–4.55 (m, 2H; NCH_2CH_2), 6.29 (t, 1H; H-1, $^3J_{HH}$=7.50 Hz), 7.80 (s, 1H; H-6), 7.88 ppm (s, 1H; $H^{triazole}$); ^{13}C NMR (62.90 MHz, $CDCl_3$, 25°C, TMS): δ=13.30 (CH_3), 23.96 ($CH_2CH_2CH_2$), 28.08 ($CH_2CH_2CH_2$), 41.30 (C-2′), 41.88 ($NCH_2CH_2CH_2$), 47.98 (2×$CH^{carborane}$), 50.62 (2×$CH^{carborane}$) 51.37 (NCH_2), 62.74 (CH_2–5′), 69.84 (CH_2O), 70.31 (CH_2O), 72.00 (CH-3′), 72.96 (CH_2O), 87.12 (CH-1′), 88.70 (CH-4′), 110.74 (C-5), 124.40 ($CH^{triazole}$), 136.38 (CH-6), 152.25 (C-2), 165.39 ppm (C-4); ^{11}B {^{1}H BB} NMR (80.25 MHz, CD_3OD, 25°C, $BF_3/(C_2H_5)_2O$): δ=23.71(s, B8), 5.49 (s, B8′), 1.14 (s, B10′), −1.71 (s, B10), −4.11(s, 4′,7′), −6.82 (s, B9′,12′,9,12,4,7), −16.64 (s, B5′,11′), −19.80 (s, B5,11), −21.87 (s, B6), −27.75 ppm (s, B6); ^{11}B NMR (80.25 MHz, CD_3OD, 25°C, $BF_3/(C_2H_5)_2O$): 23.71 (s, B8), 5.50 (d, B8′, $^2J_{BH}$=143.44 Hz), 1.10 (d, B10′, $^2J_{BH}$=143.43 Hz), −1.73 (d, B10, $^2J_{BH}$=146.48 Hz), −4.01 (d, B4′,7′, $^2J_{BH}$=146.48 Hz), −6.10–(−8.9) (m, B9′, 12′,9,12,4,7), −16.70 (d, B5,11′, $^2J_{BH}$=155.64 Hz), −19. ppm (d, B5,11, $^2J_{BH}$=164.8 Hz); MS (ESI^-): *m/z* (%): calcd for $C_{23}H_{49}B_{18}CoN_5O_7$: 761.20 $[M+H]^-$; found: 762.0 (100).

3*N*-{[5-[3-iron bis(1,2-dicarbollide)-8-yl]-3-oxa-pentoxy}-1*N*-1,2,3-triazole-4-yl}(4-propan-1-yl)thymidine (22): Yield **22**: 23 mg, 40%; TLC (CH_2Cl_2/CH_3OH 8:2): R_f=0.35; UV/Vis: (96% EtOH): λ_{min}=240.06, 295.19, λ_{max}=274.04, 310.10 nm; FTIR (KBr): ν_{max}=2560 (BH), 2872, 2927, 2967, 3040 (CH_2), 1695, 1667, 1633 cm^{-1} (C=O); ^{11}B {^{1}H BB} NMR (80.25 MHz, CD_3COCD_3, 25°C, $BF_3/(C_2H_5)_2O$): δ=−480.97 (s, B8′), −441.40 (s, B8), −374.76, −370.25 (s, B4,7,4′,7′), −40.60, −5.50, −1.03, 30.83, 40.29 (s, B5,5′,11,11′,9,9′,12,12′), 103.03, 120.15 ppm (s, B6,6′); MS (ESI^-): *m/z* (%): calcd for $C_{23}H_{49}B_{18}FeN_5O_7$: 758.11 $[M+H]^-$; found: 759.0 (100).

3*N*-{[5-[3-cobalt bis(1,2-dicarbollide)-8-yl]-3-oxa-pentoxy}methyl-(4-1,2,3-triazole-1*N*-yl)} (1-ethoxyethan-4-yl)thymidine (23): Yield **23**: 42 mg, 90%; TLC (CH_2Cl_2/CH_3OH 9:1): R_f=0.21; UV/Vis: (96% EtOH): λ_{min}= 238.19, 290.80, λ_{max}=312.57, 271.45 nm; FTIR (KBr): ν_{max}=2561 (BH), 2873, 2926, 3036 (CH_2), 1636, 1664, 1699 cm^{-1} (C=O); ^{1}H NMR (250.131 MHz, CD_3OH, 25°C, TMS): δ=0.5–3.0 (bm, 18H; $BH^{carborane}$), 1.89 (d, 3H; CH_3, $^4J_{HH}$=1.15 Hz), 2.22–2.27 (m, 2H; H-2′), 3.61–3.68 (m, 8H; 4×CH_2O), 3.75–3.83 (m, 5H; H-4′, H-5′, NCH_2), 4.10–4.14 (m, 7H; 2×CH_2O, 4×$CH^{carborane}$), 4.32–4.42 (m, 1H; H-3′), 4.53 (t, 2H; NCH_2, $^3J_{HH}$=5.0 Hz), 4.63 (s, 2H; CH_2), 6.26 (t, 1H; H-1′, $^3J_{HH}$=6.78 Hz), 7.81 (t, 1H; H-1′, $^4J_{HH}$=1.21 Hz), 7.94 ppm (s, 1H; $H^{triazole}$); ^{11}B {^{1}H BB} NMR (80.25 MHz, CD_3COCD_3, 25°C, $BF_3/(C_2H_5)_2O$): δ=22.91 (s,

B8), 4.00 (s, B8′), 0.44 (s, B10′), −2.44 (s, B10), −4.24 (s, B4′,7′), −7.38 (s, B9′,12′), −8.19 (s, B9,12,4,7 overlap), −17.30 (s, B5′,11′), −20.41 (s, B5,11), −21.88 (s, B6′, overlap), −28.38 ppm (s, B6); ^{11}B NMR (80.25 MHz, CD_3COCD_3, 25 °C, $BF_3/(C_2H_5)_2O$): $\delta = 22.80$ (s, B8), 3.91 (d, B8′, $^2J_{BH} = 134.27$ Hz), 0.47 (d, B10′, $^2J_{BH} = 134.27$ Hz), −2.44 (d, B10, $^2J_{BH} = 113.38$ Hz), −4.19 (d, B4′,7′, $^2J_{BH} = 152.58$ Hz), −7.29 (d, B9′,12′, $^2J_{BH} = 128.17$ Hz), −8.25 (d, B9,12,4,7 overlap, $^2J_{BH} = 122.07$ Hz), −17.26 (d, B5′,11′, $^2J_{BH} = 152.58$ Hz), −20.45 (d, B5,11, $^2J_{BH} = 152.59$ Hz), −21.88 (d, B6′, overlap), −28.39 ppm (s, B6, $^2J_{BH} = 119.02$ Hz); MS (ESI$^-$): *m*/*z* (%): calcd for $C_{25}H_{53}B_{18}CoN_5O_9$: 821.25 $[M+H]^-$; found: 822 (90) 429.0 (100) [*M*−(metallocarborane group and linker]).

3*N*-{[5-[3-cobalt bis(1,2-dicarbollide)-8-yl]-3-oxa-pentoxy}propyl-(4–1,2,3-triazole-1*N*-yl)} (1-ethoxyethan-4-yl)thymidine (24): Yield **24**: 23 mg, 24%; TLC (CH_2Cl_2/CH_3OH 9:1): $R_f = 0.18$; UV/Vis: (96% EtOH): $\lambda_{min} =$ 240.06, 291.42, $\lambda_{max} = 312.57$, 271.20 nm; FTIR (KBr): $\nu_{max} = 2561$ (BH), 2872, 2926, 3036 (CH_2), 1636, 1664, 1698 cm^{-1} (C=O); ^{1}H NMR (250.131 MHz, CD_3OH, 25 °C, TMS): $\delta = 0.5$–3.0 (bm, 18H; $BH^{carborane}$), 1.89–1.93 (m, 3H; $CH_2CH_2CH_2O$), 1.92 (d, 3H; CH_3, $^4J_{HH} = 1.11$ Hz), 2.20–2.25 (m, 2H; H-2′), 2.76 (t, 2H; H, $CH_2CH_2CH_2O$, $^3J_{HH} = 7.49$ Hz), 3.51–3.65 (m, 10H; $5 \times CH_2O$), 3.73–3.83 (m, 5H; H-4′, H-5′, NCH_2), 4.12–4.20 (m, 5H; $4 \times CH^{carborane}$, CH_2O), 4.36–4.42 (m, 1H; H-3′), 4.50 (t, 2H; NCH_2, $^3J_{HH} = 5.36$ Hz), 6.27 (t, 1H; H-1′, $^3J_{HH} = 6.61$ Hz), 7.70 (s, 1H; $H^{triazole}$), 7.82 ppm (d, 1H; H-6, $^4J_{HH} = 1.20$ Hz); ^{11}B {^{1}H BB} NMR (80.25 MHz, CD_3COCD_3, 25 °C, $BF_3/(C_2H_5)_2O$): $\delta = 22.82$ (s, B8), 3.77 (s, B8′), 0.44 (s, B10′), −2.39 (s, B10), −4.15 (s, B4′,7′), −7.43 (s, B9′,12′), −8.24 (s, B9,12,4,7), −17.27 (s, B5′,11′), −20.39 (s, B5,11), −21.93 (s, B6′), −28.21 ppm (s, B6); ^{11}B NMR (80.25 MHz, CD_3COCD_3, 25 °C, $BF_3/(C_2H_5)_2O$): $\delta = 22.80$ (s, B8), 3.76 (d, B8′, $^2J_{BH} = 140.38$ Hz), 0.49 (d, B10′, $^2J_{BH} = 140.38$ Hz), −2.39 (d, B10, $^2J_{BH} = 137.33$ Hz), −4.18 (d, B4′,7′, $^2J_{BH} = 140.38$ Hz), −7.36 (d, B9′,12′, $^2J_{BH} = 128.18$ Hz), −8.33 (d, B9,12,4,7, $^2J_{BH} = 125.13$ Hz), −17.31 (d, B5′,11′, $^2J_{BH} = 158.69$ Hz), −20.45 (d, B5,11, $^2J_{BH} = 155.64$ Hz), −21.93 (B6′, overlap), −28.21 ppm (B6); MS (ESI$^-$): *m*/*z* (%): calcd for $C_{27}H_{57}B_{18}CoN_5O_9$: 849.30 $[M+H]^-$; found: 850.0 (100).

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