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Cyclic oxonium derivatives of cobalt and iron bis(dicarbollides) and their use in organic synthesis

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The rapid progress in the chemistry of carboranes and other polyhedral boron compounds makes the development of methods for the synthesis of their various functional derivatives a high priority. The formation of cyclic oxonium derivatives followed by the ring opening is one of the most efficient methods for the preparation of these compounds. This review addresses the data on the use of the nucleophilic ring opening of cyclic oxonium derivatives based on cobalt and iron bis(dicarbollides), which have been extensively studied in recent years. Reactions involving O-, N-, S-, P- and C-nucleophiles are considered as a route to the targeted synthesis of a wide range of organic boron derivatives, in particular various boron-containing biologically active compounds. Possible applications of the reaction products are discussed.
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1. Introduction

The chemistry of polyhedral boron hydrides emerged as a new field of chemical science in the early 1960s and made a considerable contribution to the development of the structural theory of chemical compounds.[1] Studies of the properties of polyhedral boron hydrides significantly extended the knowledge of two-electron three-centre and multicentre bonds and led to the concept of three dimensional aromaticity, which is currently used to describe the structures of not only polyhedral boron hydrides [2–5] but also fullerenes,[3] π complexes [6–8] and clusters of transition metals [9, 10] and their derivatives (see p. 283 in the monograph [11] and the publication [12]). The formal replacement of two boron atoms in the icosahedral dodecaborate anion $[B_{12}H_{12}]^{2-}$, which is a purely inorganic system,[13] by two carbon atoms affords neutral carboranes $C_2B_{10}H_{12}$ existing as *ortho*, *meta* and *para* isomers. Due to the acidic character of CH groups in carboranes, a great diversity of methods of organic chemistry can be employed to modify these compounds.[11] In the reaction with strong nucleophilic reagents, one boron atom directly bonded to both carbon atoms of *ortho*-carborane can be removed to form the anionic *nido*-carborane $[7,8\text{-}C_2B_9H_{12}]^-$, which has a pentagonal open face with one bridging proton (Fig. 1). The treatment with strong bases leads to the removal of this proton to give the dicarbollide anion $[7,8\text{-}C_2B_9H_{11}]^{2-}$, as an isolobal analogue of the cyclopentadienyl anion (Cp^-). This anion forms sandwich and half-sandwich π complexes with transition metals (see the monograph,[11] p. 711). The cobalt bis(dicarbollide) $[3,3'\text{-}Co(1,2\text{-}C_2B_9H_{11})_2]^-$ (see Fig. 1) is the most well-studied representative of these complexes.[14, 15]

Derivatives of polyhedral boron hydrides are not only of theoretical interest but also of practical importance due to a number of unique properties.[12, 16] In particular, cobalt bis(dicarbollide) derivatives are used in various fields, from nuclear waste reprocessing [17–21] and design of new materials [22–30] to medical technologies.[31–35] The employment of cobalt bis(dicarbollide) derivatives in medicine is

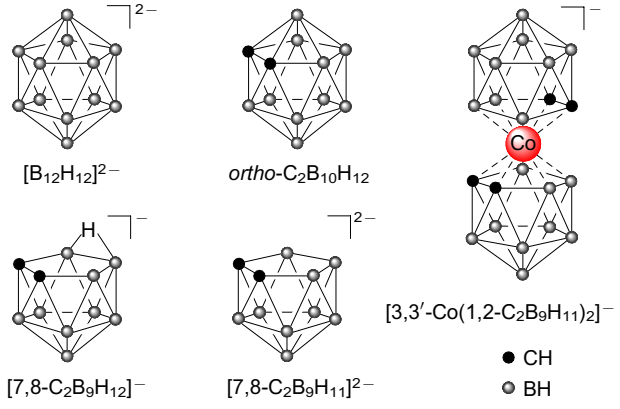


Figure 1. Polyhedral boron hydrides. The Figure was prepared by the authors using the data of Refs 13–15.

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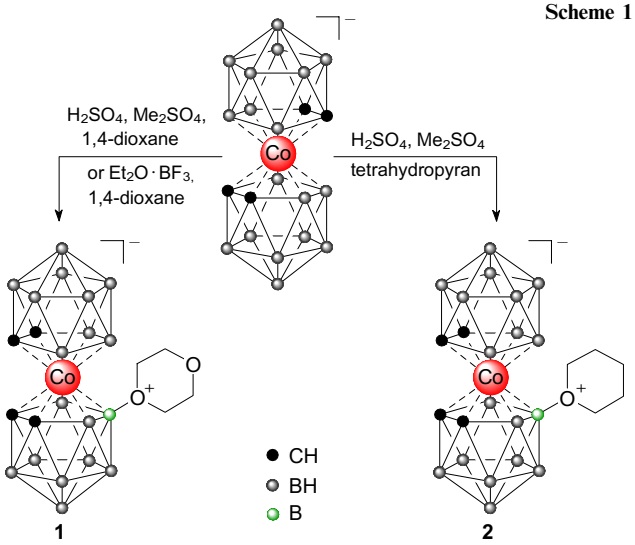
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largely due to good solubility of their sodium salts, low toxicity [36] and the ability to penetrate biological membranes.[37, 38] An important area of potential application of cobalt bis(dicarbollide) derivatives in medicine is boron neutron capture therapy (BNCT) of cancer. This is a binary treatment modality for cancer based on the selective accumulation of boron compounds in a tumour followed by its irradiation by a thermal (slow) neutron flux, resulting in the selective destruction of tumour cells with the preservation of the surrounding normal tissues during an intracellular nuclear reaction [39]

$$^{10}B + n_{th} \longrightarrow [^{11}B]^* \longrightarrow \alpha + {}^{7}Li + 2.31\ MeV \qquad (1)$$

Apart from the selective accumulation of boron compounds in a tumour, an important requirement for BNCT is the achievement of their clinically relevant therapeutic concentration ($\geqslant$20 μg of ^{10}B per gram of tumour).[40] Therefore, cobalt bis(dicarbollide) containing 18 boron atoms per molecule can be considered as a promising compound for the design of BNCT agents. One approach to the selective delivery of a boron component to the tumour site is based on the attachment of this component to molecules that are able to accumulate in tumour cells.[41 – 45] Therefore, there is a need to develop methods for the synthesis of various functional cobalt bis(dicarbollide) derivatives. A characteristic feature of the chemistry of polyhedral boron hydrides is the formation of cyclic oxonium derivatives *via* the electrophile-induced nucleophilic substitution (EINS) mechanism.[46, 47] Thus, the reaction of cobalt bis(dicarbollide) with dimethyl sulfate in the presence of sulfuric acid in 1,4-dioxane or tetrahydropyran affords the dioxane derivative *closo*-[8-$O(CH_2CH_2)_2O$-3,3′-Co(1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{11}$)], **1**) and the tetrahydropyran derivative *closo*-[8-$(CH_2)_5O$-3,3′-Co(1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{11}$)], **2**), respectively (Scheme 1).[48, 49] Compound **1** can also be synthesized using $Et_2O \cdot BF_3$ as Lewis acid (see Scheme 1).[50] The presence of a charge on the onium substituent causes a significant electron density redistribution in the metallacarborane cage accompanied by the deactivation of the second dicarbollide ligand, which, as opposed to many other substitution reactions,[14, 15] results in the formation of exclusively monosubstituted products.

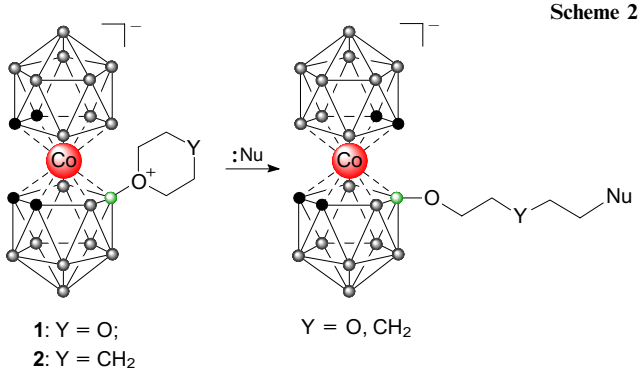
Scheme 1



One of the general approaches commonly used for the functionalization of polyhedral boron hydrides and their binding to different biomolecules is based on the nucleophilic ring opening of cyclic oxonium derivatives. These compounds are characterized by rather high stability compared to organic oxonium salts due to the stabilizing electron-donating effect of the boron cage and can act as alkylating agents.[46, 47] This approach was successfully applied to cyclic oxonium derivatives of cobalt bis(dicarbollides) **1** and **2**. The C – O bond cleavage by a nucleophilic (Nu) pharmacophore gives products, in which a boron cage is attached to the functional group through a chain of atoms that are formed *via* the ring opening of cyclic ester. The presence of a functional group allows these compounds to react with different molecules, and the presence of a long spacer reduces the steric and electronic effects of the boron cluster on the biologically active part of molecule. It is also worth noting that the use of different cyclic esters gives rise to spacers with a different degree of hydrophilicity or lipophilicity (Scheme 2).

Apart from cobalt bis(dicarbollide), this approach can also be employed to synthesize functional derivatives of iron bis(dicarbollide).[51] The chemistry of this compound was much less studied because of its paramagnetic character, which is an obstacle to the use of NMR spectroscopy. As opposed to cobalt bis(dicarbollide), not only dioxane (**3**) and tetrahydropyran (**4**) derivatives but also the tetrahy-

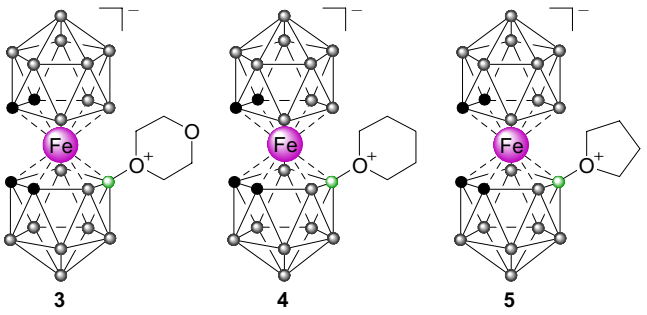
Scheme 2



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Current research interests: organoelement compounds, coordination compounds, boron chemistry, main group metals, carboranes, neutron capture therapy of cancer.

Translation: T.N.Safonova

Structures 3 – 5



drofuran derivative (**5**) are known for iron bis(dicarbollide) (see †).[52, 53]

It should be noted that recent years have witnessed a rapidly growing number of publications on the use of the nucleophilic ring opening of cyclic oxonium derivatives of cobalt and iron bis(dicarbollides) in the synthesis of boron-containing biologically active molecules. The application of this approach went far research dealing with the chemistry of polyhedral boron hydrides and extended the range of synthetic tools used by many researchers working in the fields of bioorganic and pharmaceutical chemistry. This resulted in the accumulation of a great deal of experimental data on this issue, which were not addressed in a systematic fashion. Hence, the comprehensive review and critical analysis of the results of studies from different researchers are of great interest. This prompted us to write the review, which may be helpful for researchers in the field of boron chemistry and related areas, including organic, bioorganic and heteroorganic chemistry.

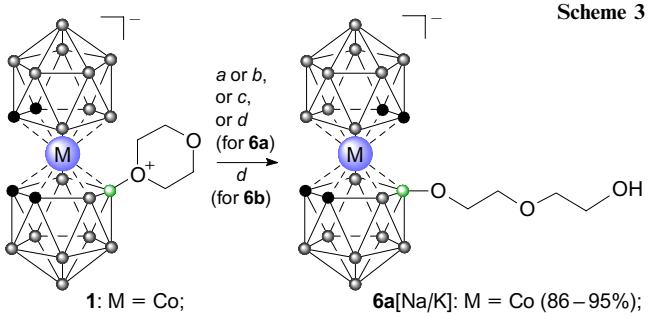
This review summarizes the published data on the application of ring opening reactions of cyclic oxonium derivatives of cobalt and iron bis(dicarbollides) with different types of nucleophiles (O-, N-, S-, P-, C-, Hal-nucleophiles) in the targeted synthesis of a wide range of functional derivatives and considers methods for the synthesis of various bis(dicarbollide)-containing biologically active molecules, including amino acids and peptides, phthalocyanines and porphyrins, nucleosides and nucleotides, lipids and liposomes. The review covers the studies published mainly between 2005 and 2020, with relevant earlier publications being included.

2. Oxonium ring opening with nucleophilic reagents

2.1. Oxygen nucleophiles

The reactions of cyclic oxonium derivatives of cobalt bis(dicarbollide) [8-O(CH_2CH_2)$_2$O-3,3′-Co(1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{11}$)] (**1**) and iron bis(dicarbollide) [8-O(CH_2CH_2)$_2$O-3,3′-Fe(1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{11}$)] (**3**) with oxygen nucleophiles were studied in most detail. The simplest example is the nucleophilic ring opening of the 1,4-dioxane moiety of compounds **1** and **3** with a hydroxide ion (Scheme 3). The reaction of derivative **1** with KOH in a water – benzene mixture in the presence of dibenzo-18-crown-6 (DB18-crown-6) [55] or with NaOH in water – diethyl ether,[55] water – 1,2-dimethoxyethane (DME) [56] or water – 1,4-dioxane mixtures [57] affords the corresponding alcohol [8-OH(CH_2CH_2O)$_2$-3,3′-Co(1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{11}$)] (**6a**) in nearly quantitative yields. The reaction of compound **3** with NaOH in a water – 1,4-dioxane mixture gives [8-OH(CH_2CH_2O)$_2$-3,3′-Fe(1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{11}$)] (**6b**) in moderate yield.[52]

Scheme 3



1: M = Co;
3: M = Fe

6a[Na/K]: M = Co (86 – 95%);
6b[Na]: Me = Fe (68%)

(*a*) KOH, DB18-crown-6, PhH, H_2O, Δ, 4 h; (*b*) NaOH, Et_2O,H_2O, rt, 12 h; (*c*) NaOH, DME, H_2O, 75 °C, 45 min; (*d*) NaOH, 1,4-dioxane, H_2O, Δ, 2 h; rt is room temperature

Alcohol **6a** was used to prepare extractants **7a**,**b** containing three carbamoylphosphine oxide (CMPO) moieties,[58] capable of the selective extraction of Eu^{3+} and Am^{3+} cations from nitric acid solutions (Scheme 4).[59]

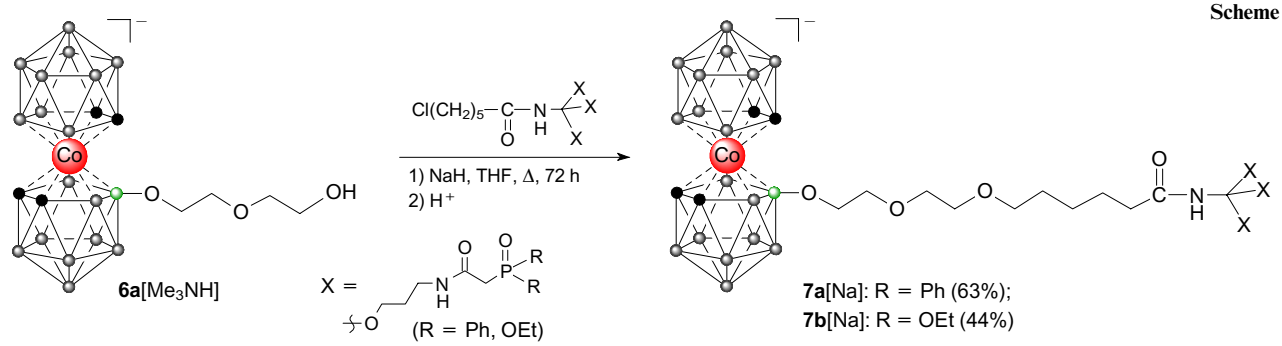
Apart from hydroxide, dioxane derivative **1** easily reacts with alkoxide and phenoxide ions. Thus, the reactions of **1** with methanol, ethanol, methyl or ethyl cellosolve at room temperature in the presence of NaOH as a base affords ethers **8a** – **d** (Scheme 5).[50] The reaction of compound **1** with ethylene glycol and oligo(ethylene glycols) in tetrahydrofuran in the presence of NaH as a base gives the corresponding products containing one (**8e** – **i**) or two (**9a** – **c**) boron clusters depending on the initial ratio of reagents (see Scheme 5).[56, 60 – 62]

Derivatives bearing oligo(ethylene glycol) units can coordinate alkali or alkaline metal ions, cobalt bis(dicarbollide) being involved in the coordination through B – H bonds, resulting in stabilization of its cisoid conformation (Fig. 2). It was expected that such compounds can be used as extractants for radioactive waste produced during operation of nuclear power plants. However, in strongly acidic media, the oxygen atom bonded to boron was found to be protonated, as in the case of related derivatives of the *closo*-decaborate anion,[63] resulting in the release of the coordinated metal atom. More recently, cobalt bis(dicarbollide) derivatives with oligo(ethylene glycol) substituents were proposed as anionic components of molecular liquids.[56, 64]

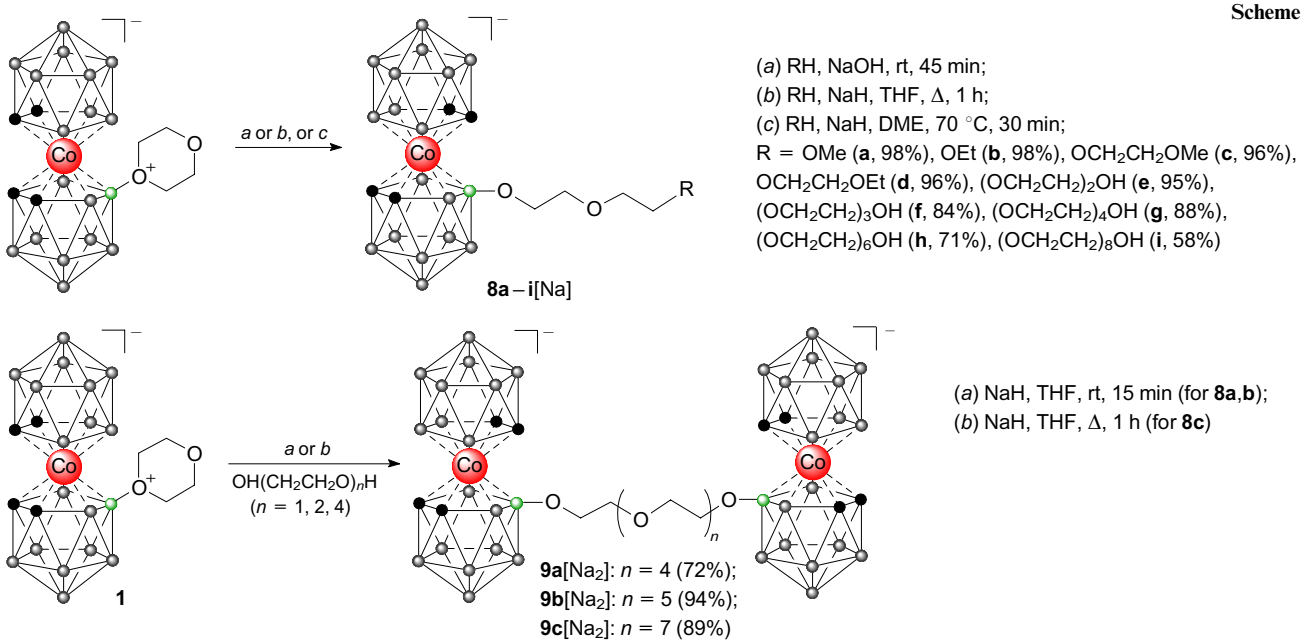
The adverse effect of the protonation of the boron-bound oxygen atom can be avoided by conjugating crown ethers with cobalt bis(dicarbollide). A series of such compounds **10a** – **c** were synthesized by the reaction of complex **1** with crown ethers containing the hydroxymethyl side group in the presence of NaH as a base (Scheme 6).[65] The investigation of the extraction properties of these products for Na^+, Cs^+ and Sr^{2+} ions in a nitrophenyl hexyl ether – water mixture in the presence of HNO_3 showed that the separation coefficients of crown ethers **10a** – **c** for Cs^+ and Sr^{2+} are comparable with those of the corresponding initial crown ethers in a mixture with a hexachloro derivative of cobalt bis(dicarbollide).

† The reaction of cobalt bis(dicarbollide) with tetrahydrofuran in the presence of Lewis or Brønsted acids is accompanied by the ester polymerization even at room temperature.[54]

Scheme 4



Scheme 5



A series of interesting products were synthesized by the reaction of the dioxane derivative [8-O(CH_2CH_2)$_2$O-3,3′-Co(1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{11}$)] (**1**) with alcohol derivatives of *ortho*-carborane in the presence of *n*-butyllithium as a base [Schemes 7 and 8; hereinafter, the abbreviation 2EG-COSAN stands for cobalt bis(dicarbollide) containing two ethylene glycol untis, (CH_2CH_2O)$_2$-3,3′-Co(1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{11}$)].[66, 67] The synthesized dendrimers **11** – **13** contain 46 to 118 boron atoms and can be considered as potential candidates for the use in BNCT of cancer.

Alcohols containing non-nucleophilic functional groups can also be employed as nucleophilic reagents for the oxonium ring opening. Thus, a series of functional derivatives **14** containing the terminal acetylene group were

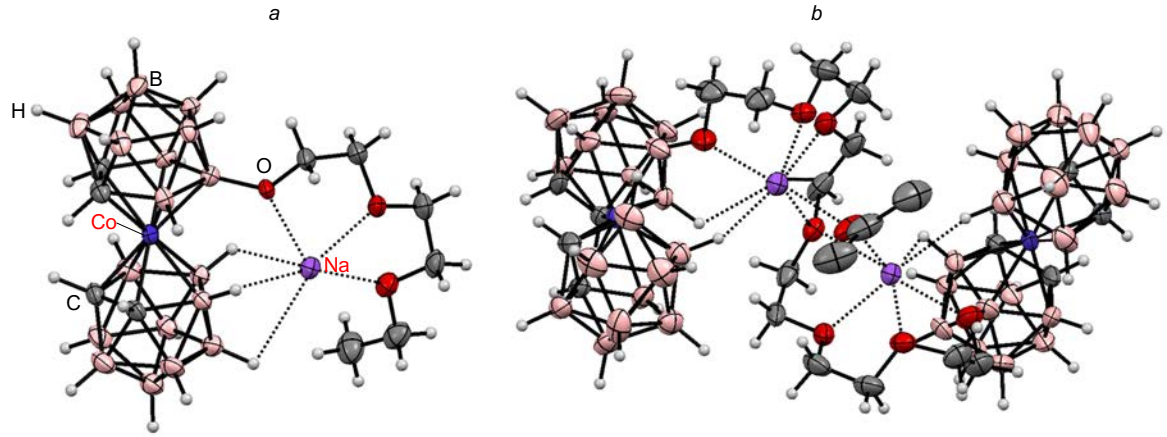
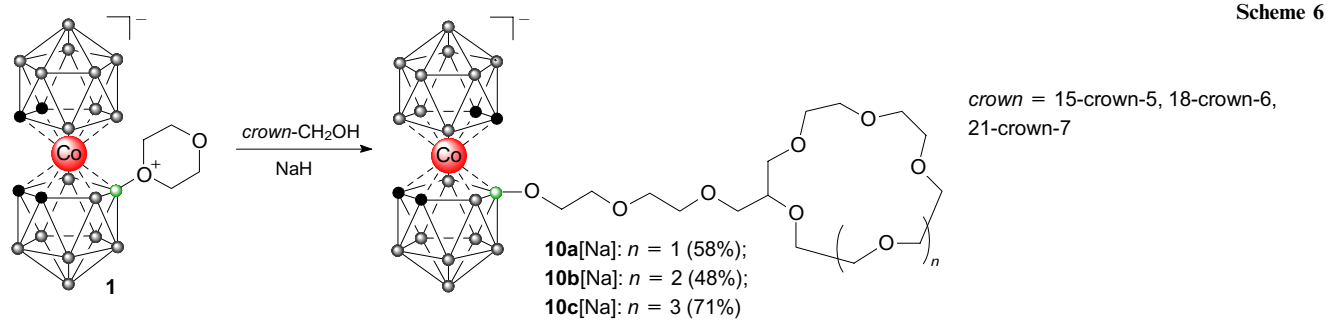


Figure 2. Crystal structures of **8b**[Na] (*a*) and **9b**[Na_2]·Me_2CO (*b*). The Figure was prepared by the authors using the data of Refs 50 and 62, respectively.

Scheme 6



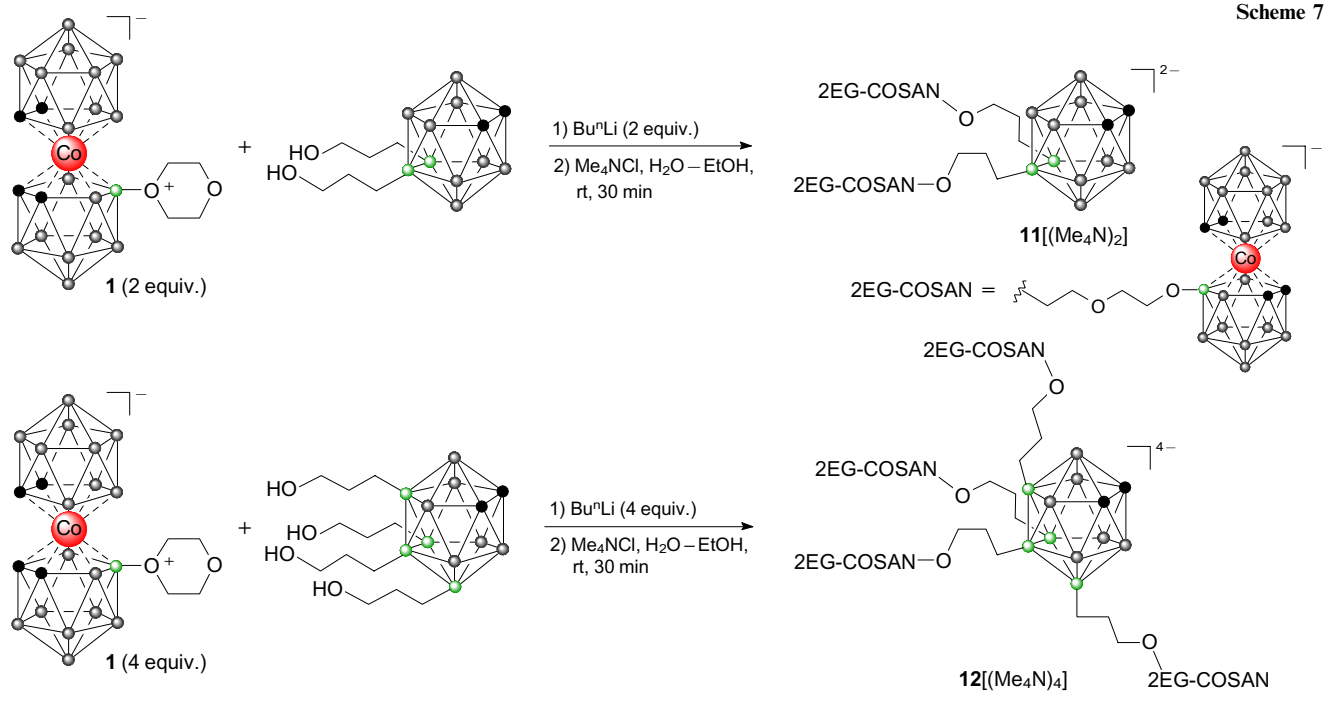
synthesized by the reaction of oxonium derivatives of cobalt bis(dicarbollide) **1** and **2** with alkoxides of acetylenic alcohols (prop-2-yn-1-ol, but-1-yn-3-ol, pent-4-yn-1-ol) (Scheme 9).[68–70] It was shown that these compounds can be subjected to the CuI-catalyzed [3 + 2]-dipolar cycloaddition with organic azides (click reaction) giving 1,4-substituted triazoles **15** (see Scheme 9).[70]

The ring opening of derivative **1** with benzyl alcohol-based alkoxides proceeds in a similar way to give products **16**–**18** (Scheme 10).[57, 62, 71]

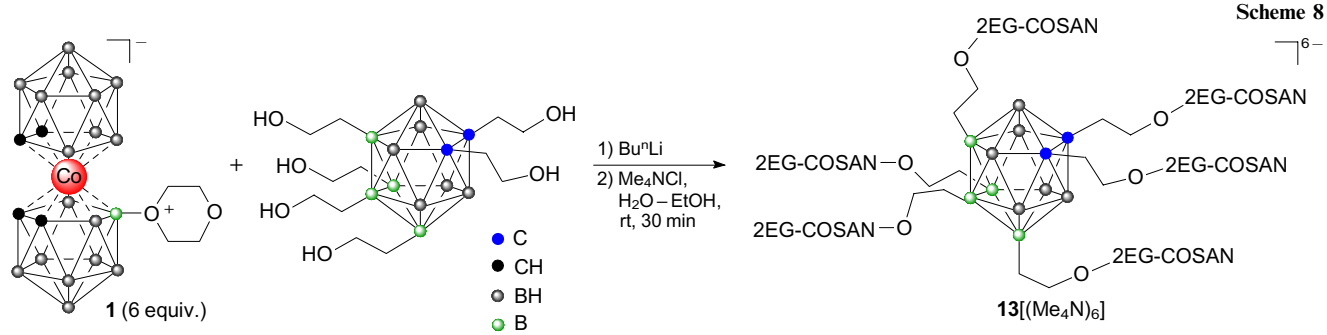
A series of boron-containing dendrimers **19a**–**d** were prepared by the reaction of complex **1** with α,α′-bis[3,5-bis(hydroxymethyl)phenoxy]-*m*-xylene, α,α′-bis[3,5-bis(hydroxymethyl)phenoxy]-*p*-xylene, α,α′-bis{3,5-bis[3,5-bis(hydroxymethyl)phenoxymethyl]phenoxy}-*m*-xylene and α,α′-α,α′-bis{3,5-bis[3,5-bis(hydroxymethyl)phenoxymethyl]phenoxy}-*p*-xylene in the presence of Bu^{t}OK in DMSO.[72]

The reactions of oxonium derivatives of cobalt and iron bis(dicarbollides) with phenoxide ions are among the most commonly employed ring opening reactions. Initially, it was proposed to use phenoxides to synthesize cobalt bis(dicarbollide) derivatives soluble in low-polarity solvents (toluene, xylene, cumene), which can be applied as extractants for radioactive waste disposal. The reactions of dioxane derivatives **1** and **3** with 2-methoxyphenol (guaiacol), 2-benzylphenol and 4-*tert*-octylphenol in a mixture of toluene

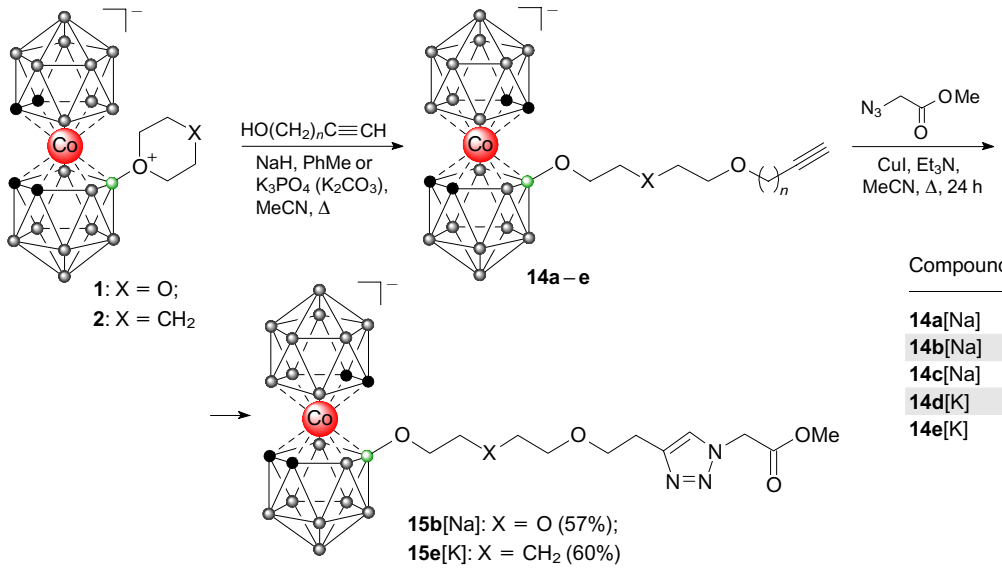
Scheme 7



Scheme 8

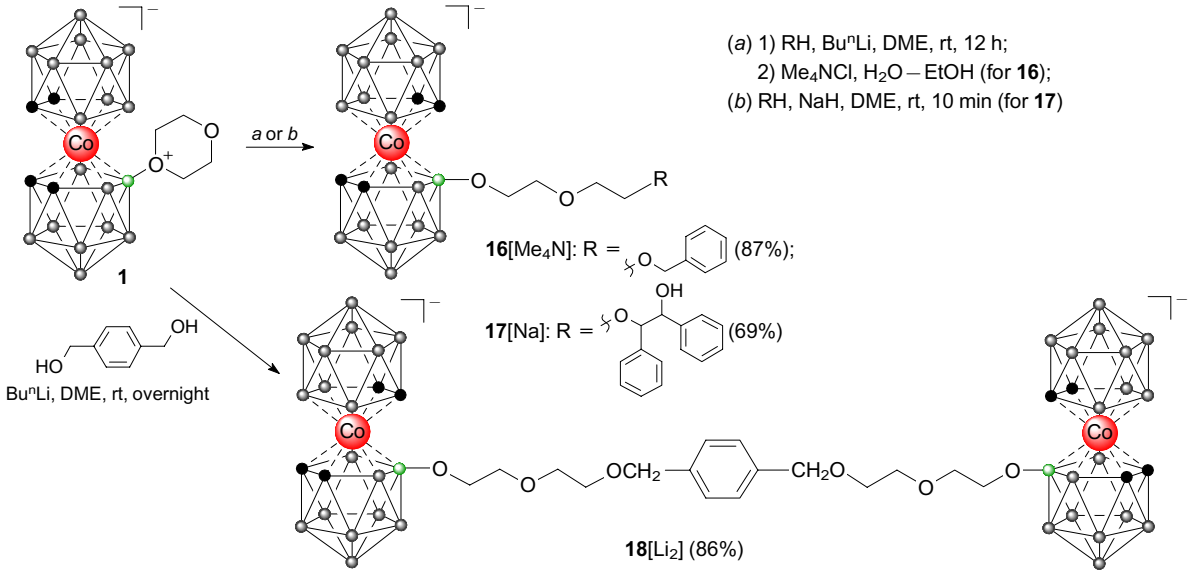


Scheme 9



Compound	X	*n*	Yield (%)
14a[Na]	O	1	85
14b[Na]	O	2	85
14c[Na]	O	3	73
14d[K]	CH_2	1	94
14e[K]	CH_2	2	31

Scheme 10



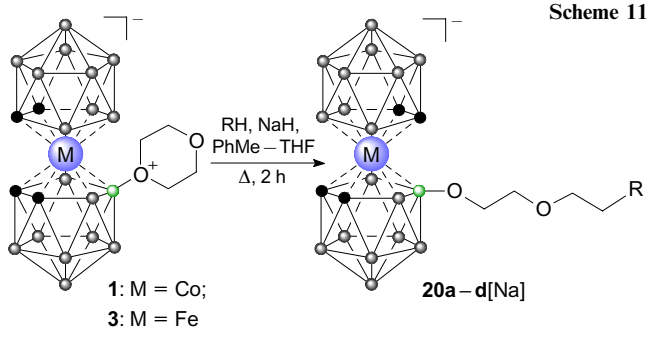
and tetrahydrofuran in the presence of NaH as a base afforded ethers **20a**–**d** in high yields (Scheme 11).[52, 73]

Like other derivative with oligo(ethylene glycol) substituents, compounds **20a**,**d** can coordinate alkali metal ions (Fig. 3).

Phenols containing various functional groups are readily available reagents commonly used in the synthesis of a wide range of functional cobalt and iron bis(dicarbollide) derivatives, which can be conjugated with different biologically active molecules. The reactions of compound **1** with hydroquinone,[61] *p*-hydroxybenzaldehyde,[74] *p*-hydroxybenzoic acid,[75] methyl *p*-hydroxybenzoate[60] and *p*-vinylphenol[76] in the presence of K_2CO_3 as a base in acetonitrile or acetone give products containing the hydroxy (**21a**), aldehyde (**21b**), carboxy (**21c**), ester (**21d**) or vinyl groups (**21e**), respectively. Iron bis(dicarbollide) derivative **21f** bearing the terminal vinyl group is produced under the same conditions as compound **21e** (Scheme 12).

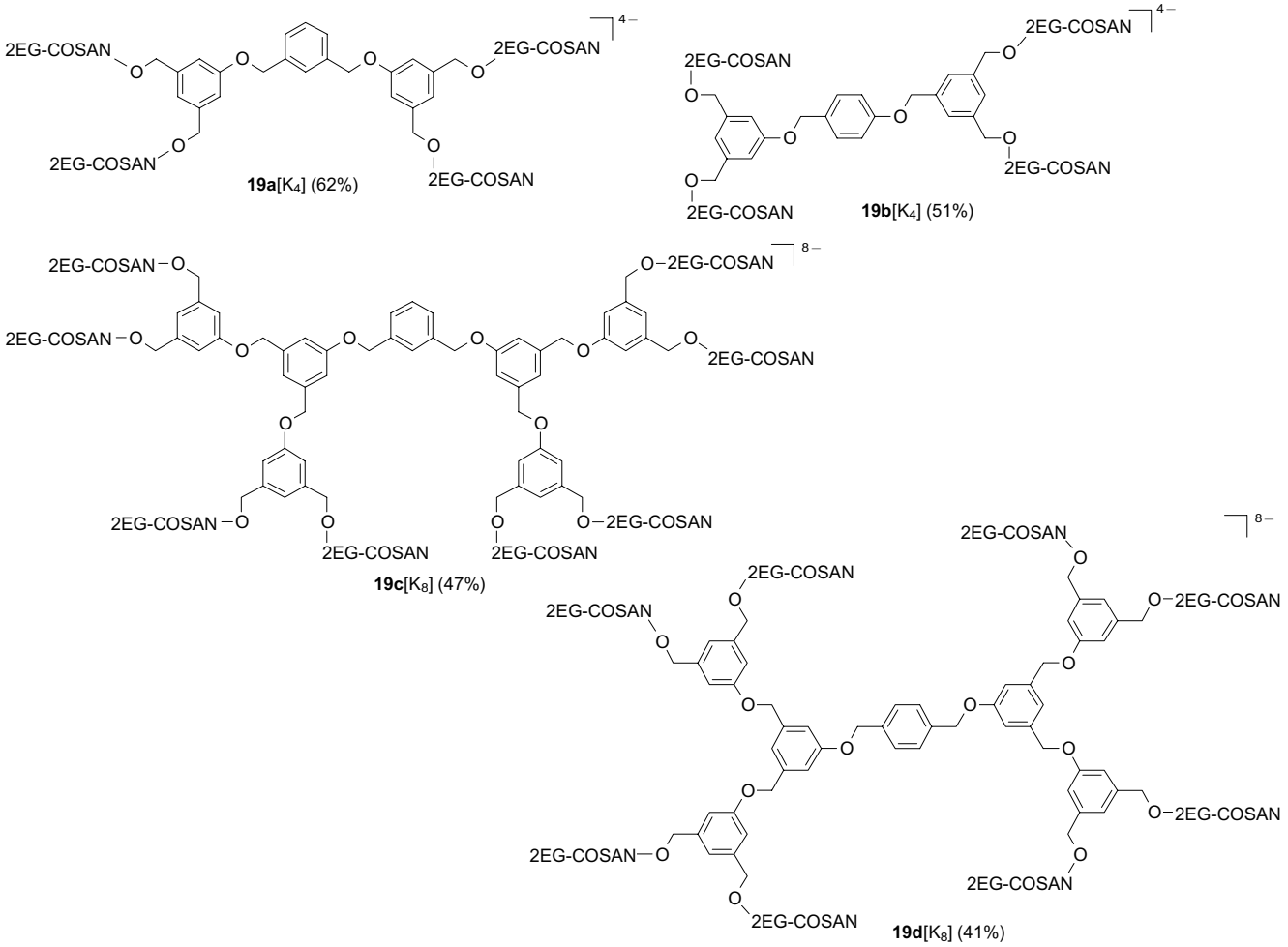
The Ru-catalyzed cross-metathesis of derivatives **21e**,**f** with octavinylsilsesquioxane afforded dendrimers **22** bearing eight metallacarborane units (Scheme 13).[76]

Scheme 11



Compound	M	R	Yield (%)
20a[Na]	Co	2-$MeOC_6H_4O$	82
20b[Na]	Co	2-$BnOC_6H_4O$	84
20c[Na]	Co	4-($Bu^tCH_2CMe_2$)C_6H_4O	79
20d[Na]	Fe	2-$MeOC_6H_4O$	82

Structures 19



The ring opening of the dioxane derivative ([8-O(CH_2CH_2)$_2$O-3,3′-Co(1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{11}$)], **1**) and the tetrahydropyran derivative ([8-(CH_2)$_5$O-3,3′-Co(1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{11}$)], **2**) of cobalt bis(dicarbollide) with hydroquinone monopropargyl ether in the presence of K_2CO_3 or K_3PO_4 as a base gave terminal acetylenes **23a**,**b** in good yields (Scheme 14).[69,77] It was shown that these products can be used in the Cu^I-catalyzed [3 + 2]-dipolar cycloaddition with organic azides to form 1,4-substituted 1,2,3-tirazoles **24a**,**b**.

The dioxane ring opening of derivative **1** with 4-acetamidophenoxide affords amide **25**, its acid hydrolysis gives amine **26** and the subsequent treatment with diphosgene produces isocyanate **27** (Scheme 15).[78]

The reaction of carbollide [8-O(CH_2CH_2)$_2$O-3,3′-Co(1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{11}$)] with polyatomic phenols

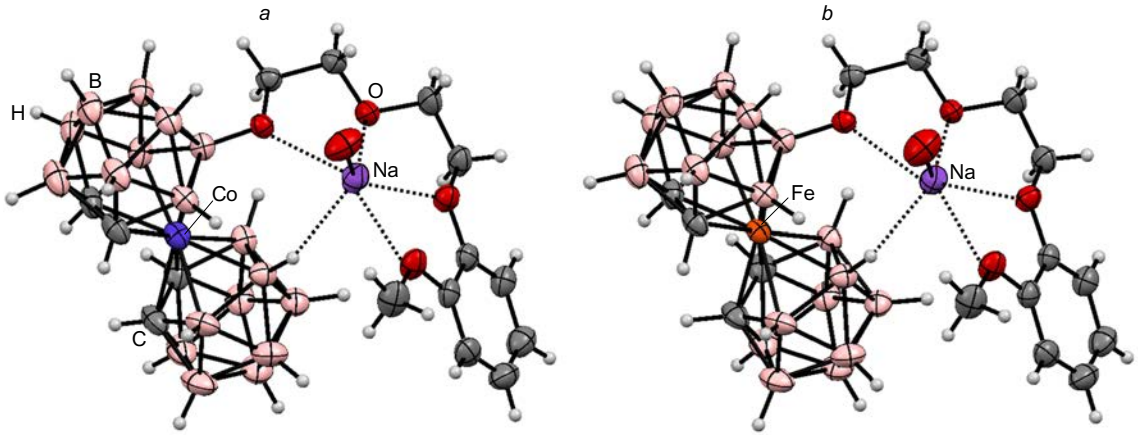
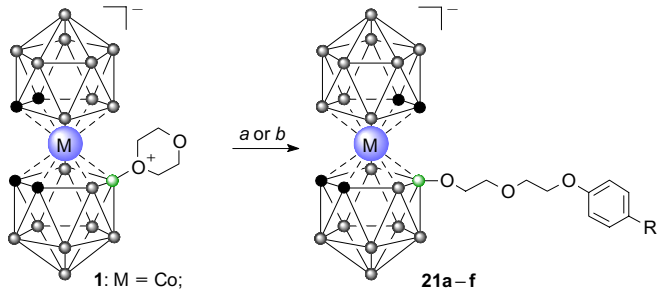


Figure 3. Crystal structures of **20a**[Na]·H_2O (*a*) and **20d**[Na]·H_2O (*b*). The Figure was prepared by the authors using the data of Refs 52 and 73, respectively.

Scheme 12



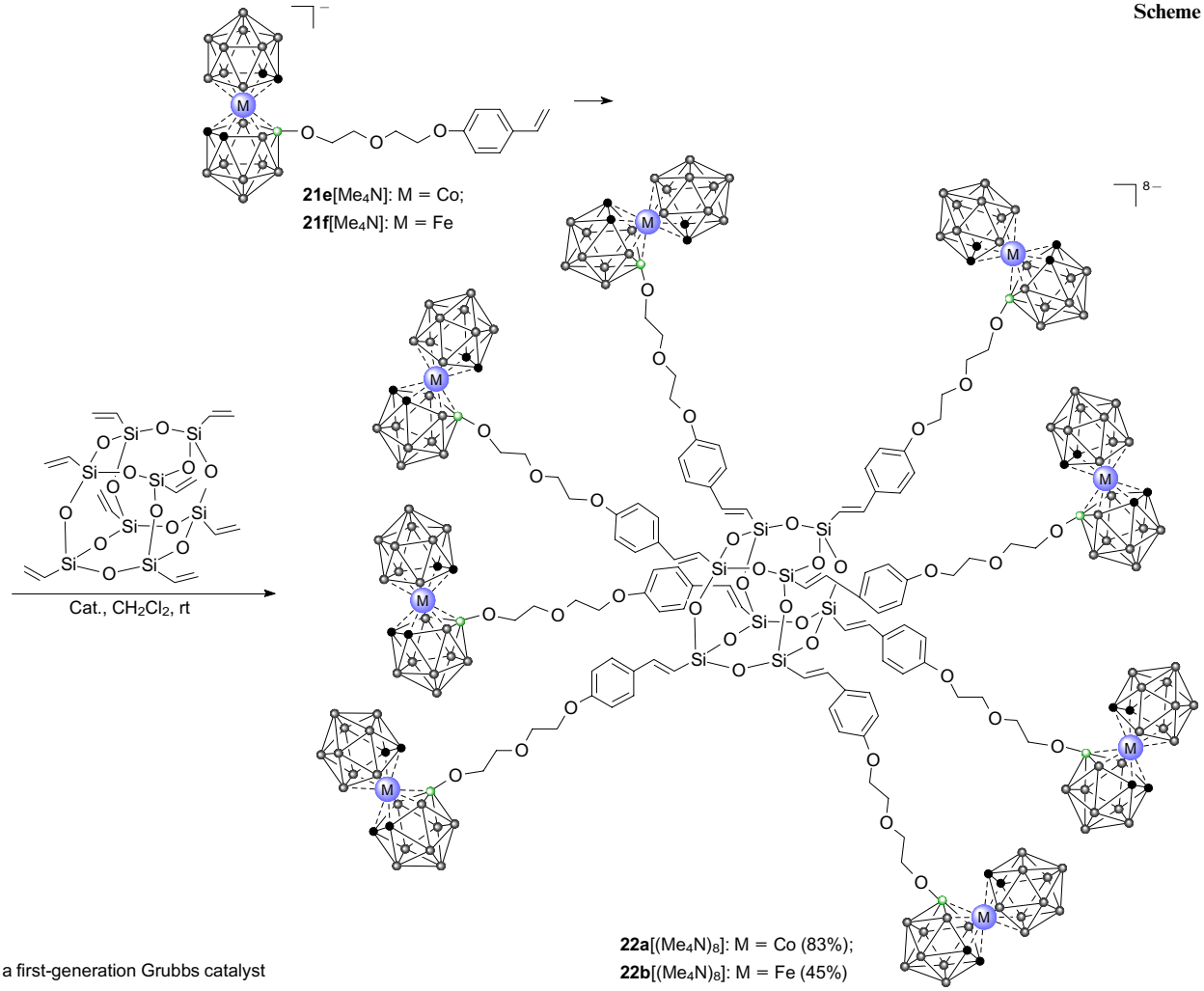
1: M = Co;
3: M = Fe

21a – f

(*a*) RH, K_2CO_3, Me_2CO or MeCN, Δ (for **21a – d**);
(*b*) 1) K_2CO_3, MeCN, Δ; 2) Me_4NCl,
EtOH – H_2O (for **21e**,**f**)

Compound	M	R	Yield (%)
21a[K]	Co	OH	79
21b[K]	Co	CHO	90
21c[K]	Co	CO_2H	96
21d[K]	Co	CO_2Me	99
21e[Me_4N]	Co	$CH{=}CH_2$	99
21f[Me_4N]	Fe	$CH{=}CH_2$	32

Scheme 13

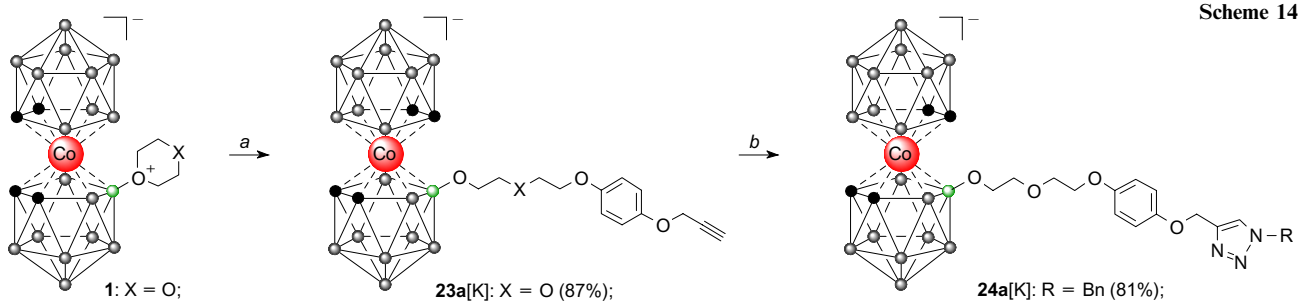


21e[Me_4N]: M = Co;
21f[Me_4N]: M = Fe

22a[$(Me_4N)_8$]: M = Co (83%);
22b[$(Me_4N)_8$]: M = Fe (45%)

Cat is a first-generation Grubbs catalyst

Scheme 14



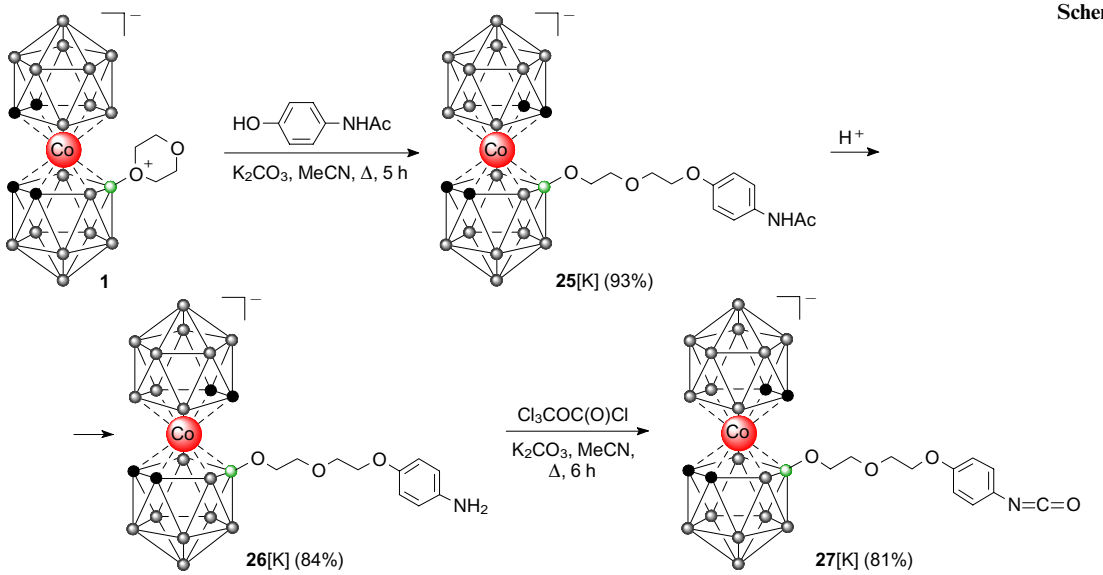
1: X = O;
2: X = CH_2

23a[K]: X = O (87%);
23b[K]: X = CH_2 (98%)

24a[K]: R = Bn (81%);
24b[K]: R = CH_2CO_2Me (79%)

(*a*) 4-$HOC_6H_4OCH_2C{\equiv}CH$, K_2CO_3 or K_3PO_4, MeCN, Δ, 5 h; (*b*) RN_3, CuI, Et_3N, MeCN, Δ

Scheme 15

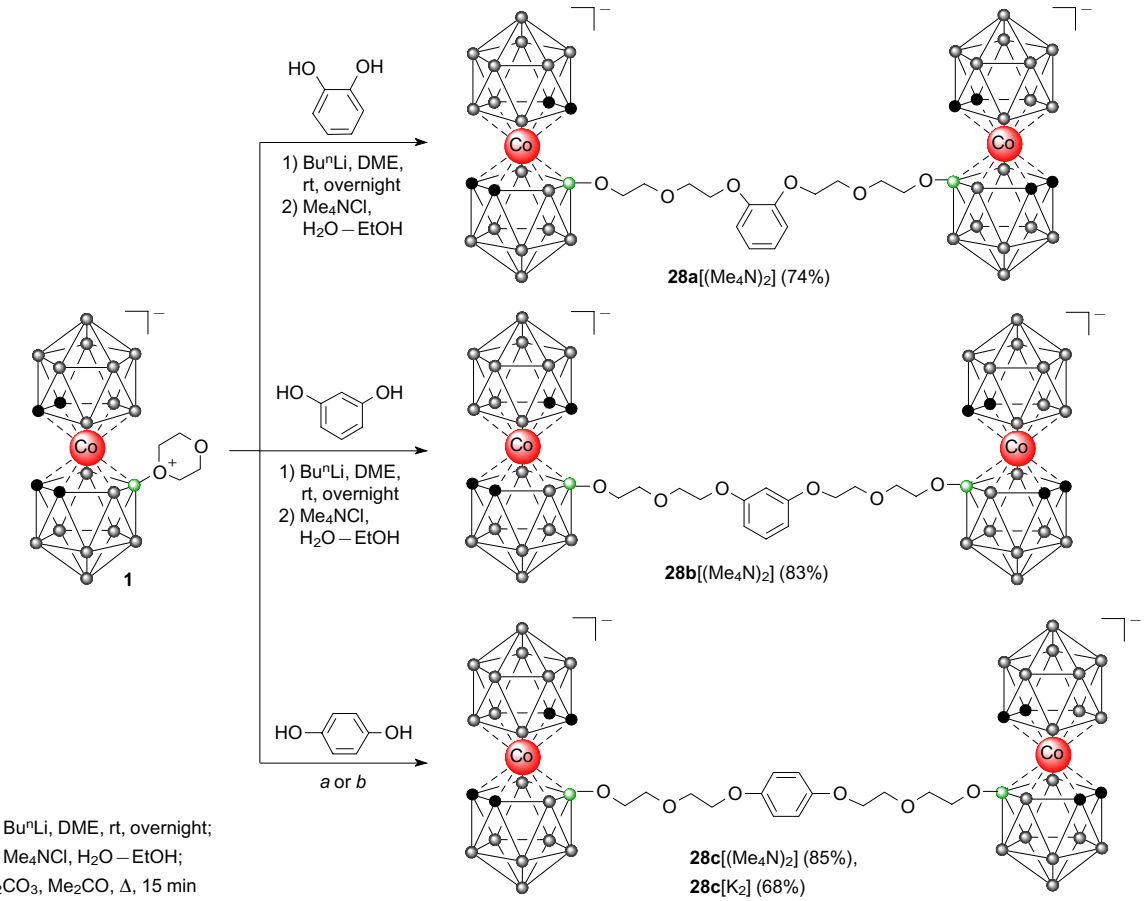


gave derivatives bearing several metallacarborane units. For example, aryl ethers **28a**–**c** were synthesized by the reactions of compound **1** with catechol, resorcinol and hydroquinone in 1,2-dimethoxyethane in the presence of n-butyllithium as a base (Scheme 16). Ether **28c** is also produced in the presence of K_2CO_3 as a base in acetone (see Scheme 16).[61, 62, 71]

Dendrimers **29** bearing three metallacarborane units were synthesized by a similar reaction of $[8\text{-}O(CH_2CH_2)_2O\text{-}3,3'\text{-}Co(1,2\text{-}C_2B_9H_{10})(1',2'\text{-}C_2B_9H_{11})]$ with 1,3,5-trihydroxybenzene (phloroglucinol) under different conditions (Scheme 17).[71]

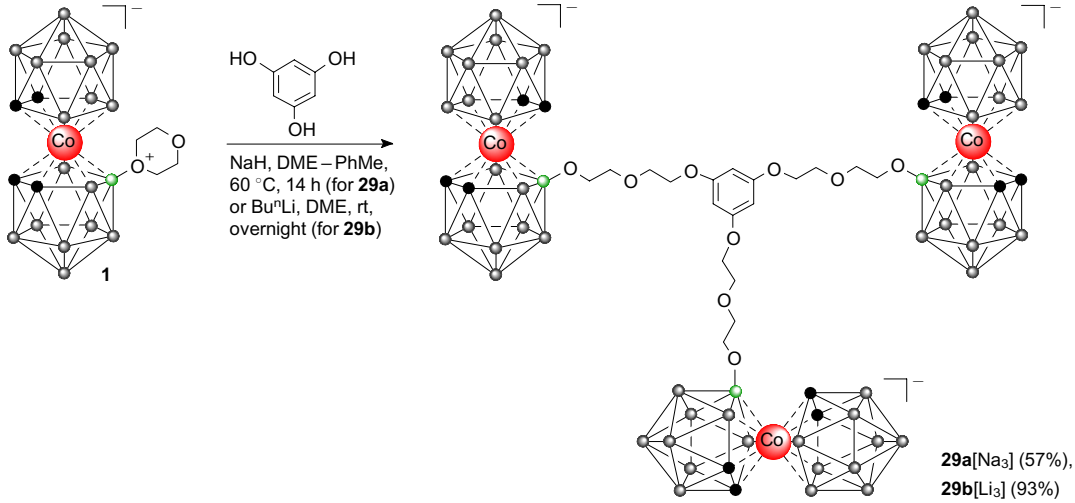
Dendrimer **30** bearing three metallacarborane units based on 1,3,5-tris(4-hydroxyphenyl)benzene was prepared using two synthetic approaches. One approach is based on the divergent synthesis involving compound **1** and 1,3,5-tris(4-hydroxyphenyl)benzene in refluxing acetonitrile in the presence of K_2CO_3 or in refluxing tetrahydrofuran in the presence of NaH (Scheme 18).[79, 80] The convergent synthesis (another approach) of dendrimer **30** occurs in two

Scheme 16

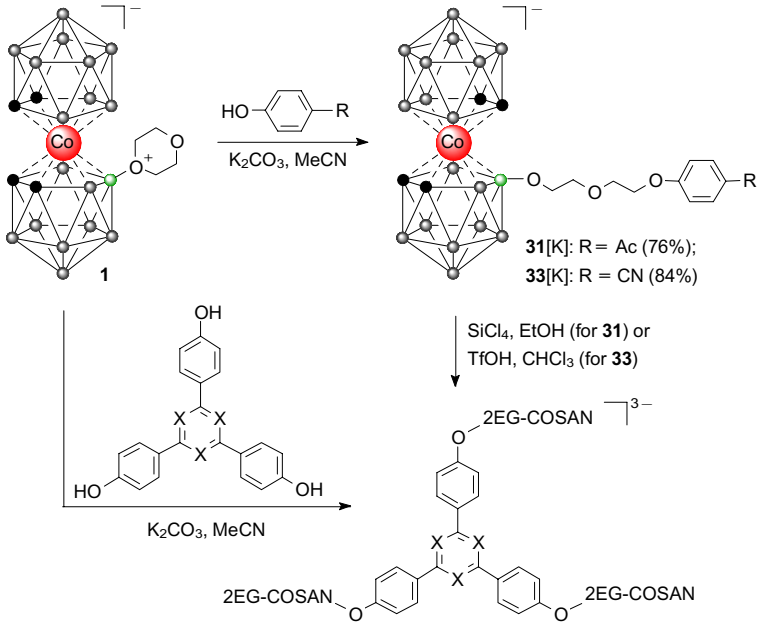


(*a*) 1) Bu^nLi, DME, rt, overnight;
2) Me_4NCl, H_2O–EtOH;
(*b*) K_2CO_3, Me_2CO, Δ, 15 min

Scheme 17



Scheme 18



Tf is trifluoromethanesulfonyl (triflyl)

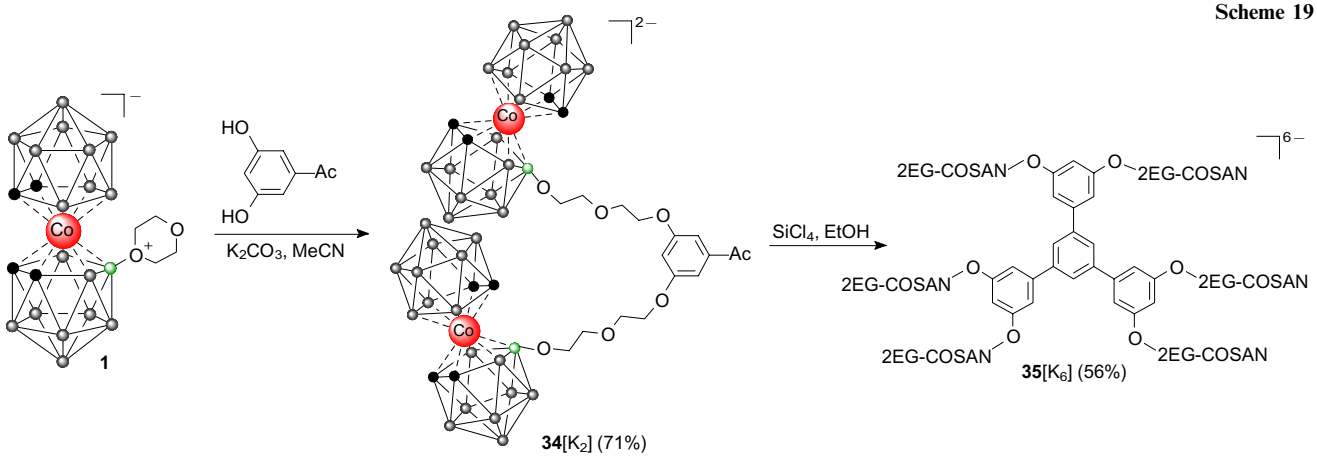
steps, involving the reaction of complex **1** with 4-hydroxyacetophenone in the presence of K_2CO_3 to form ketone **31** and its subsequent cyclotrimerization in the presence of $SiCl_4$ in ethanol to form the target dendrimer **30**.[80] Related dendrimer **32** based on 2,4,6-tris(4-hydroxyphenyl)triazine was also synthesized using two different approaches. The divergent synthesis was accomplished starting from the appropriate triazine and dioxane derivative **1**. The convergent synthesis involved the dioxane ring opening of compound **1** with 4-hydroxybenzonitrile in the presence of K_2CO_3 followed by cyclotrimerization of the resulting nitrile **33** in the presence of trifluoromethanesulfonic acid in chloroform (see Scheme 18).[79] It is worth noting that the divergent approach is preferable because it affords the target dendrimers in almost quantitative yields.

The convergent approach is based on the reaction of derivative **1** with 3,5-dihydroxyacetophenone in the presence of K_2CO_3 in acetonitrile followed by the cyclization of the resulting ketone **34** with $SiCl_4$ in ethanol afforded dendrimer **35** bearing six metallacarborane units (Scheme 19).[79]

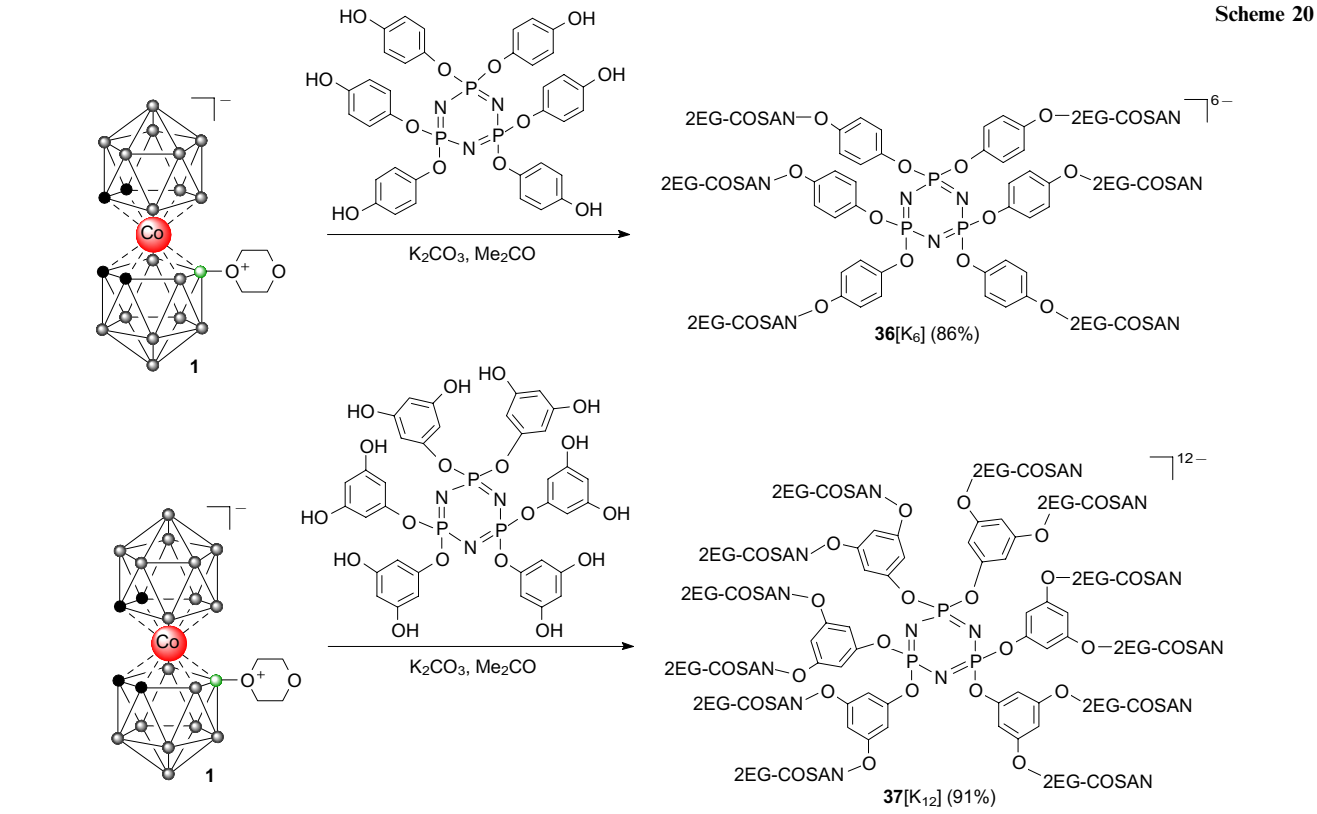
The divergent approach was also applied to synthesize cyclotriphosphazene core-based dendrimers. Dendrimers **36** and **37** bearing six and twelve metallacarborane units, respectively, were produced by the reaction of dioxane derivative **1** with cyclotriphosphazenes decorated with hydroquinone and phloroglucinol, respectively, in the presence of K_2CO_3 (Scheme 20).[81]

Boron-containing calixarenes provide another example of boron-containing compounds, which were prepared by the nucleophilic ring opening of dioxane derivative **1** with phenoxide ions. These compounds were shown to be good ligands for the solvent extraction of metals during the nuclear fuel reprocessing. The possibility of varying the nature of substituents in calixarenes over a wide range allows the control of their extraction properties. Compounds **38a–f** containing up to four metallacarborane units were synthesized by the oxonium ring opening of

Scheme 19



Scheme 20



derivative **1** with phenoxide sites of calixarenes (Scheme 21).[82–84] Compounds **38** can coordinate metal ions both through diethylene glycol bridges and the calixarene basket (Fig. 4).

The similar ring opening of compound **1** by phenoxide and alkoxide sites gave a series of resorcinarenes bearing metallacarborane units in the upper (**39a–d**) or lower (**39e**,**f**) rim of the ligand (Scheme 22).

Carboxylate ions are another type of *O*-nucleophiles employed for the oxonium ring opening of derivative **1**. The reactions of [8-O(CH_2CH_2)$_2$O-3,3′-Co(1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{11}$)] with sodium acetate, benzoate and salicylate in 1,2-dimethoxyethane or with methacrylic acid in the presence of K_2CO_3 in acetonitrile at room temperature afford esters **40a–d** in nearly quantitative yields (Scheme 23).[30,71] Derivative **41** bearing two bis(dicarbollide) units were prepared by the heating of complex **1** (2 equiv.) with terephthalic acid and K_2CO_3 under reflux in 1,2-dimethoxyethane (see Scheme 23).[85]

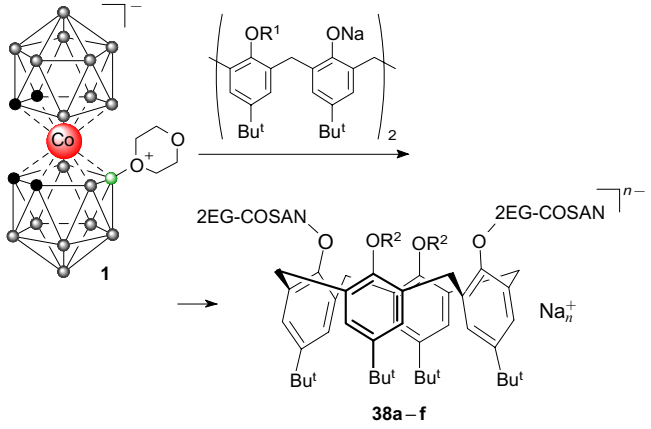
The reaction of derivative **1** with sodium 1,3,5-benzenetricarboxylate in diethyl ether at room temperature in the presence of 18-crown-6 gave dendrimer **42** based on trimesic acid (Scheme 24).[71]

The dioxane ring opening of complex **1** with *para*-carborane-based carboxylate or dicarboxylate yields the products containing one (**43**) or two (**44**) cobalt bis(dicarbollide) units (Scheme 25).[85]

Compound **40c** proved to be an efficient antibacterial agent against methicillin-resistant *Staphylococcus aureus*, and complexes **41** and **44** are efficient antifungal agents against the diploid fungi *Candida albicans*.[85]

The free-radical copolymerization of derivative **40b** with polyethylene glycol monomethyl ether (PEGM) followed by the ion exchange afforded lithium ion conducting polyelec-

Scheme 21



R^1 = Na, R^2 = 2EG-COSAN, n = 4 (**a**, 68%); R^1 = R^2 = H, n = 2 (**b**, 64%), Pr^n (**c**, 33%), $(CH_2)_mCN$ (m = 2–7) (**d**, 30–76%), $(CH_2)_4NHC(O)CH_2P(O)Ph_2$ (**e**, 33%), $(CH_2)_3NHCO_2Bu^t$ (**f**, 65%)

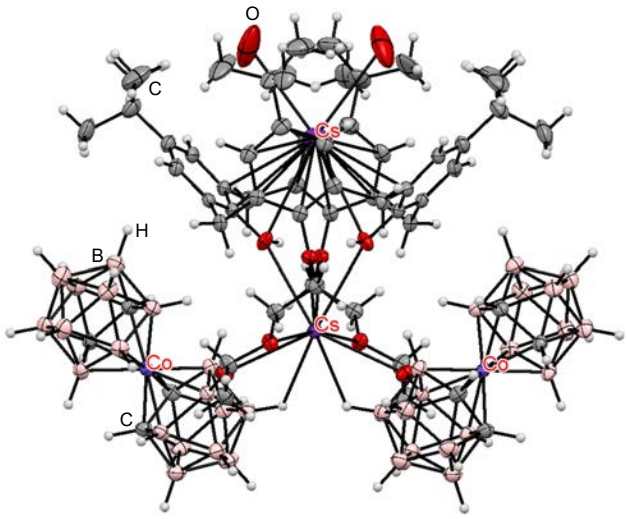


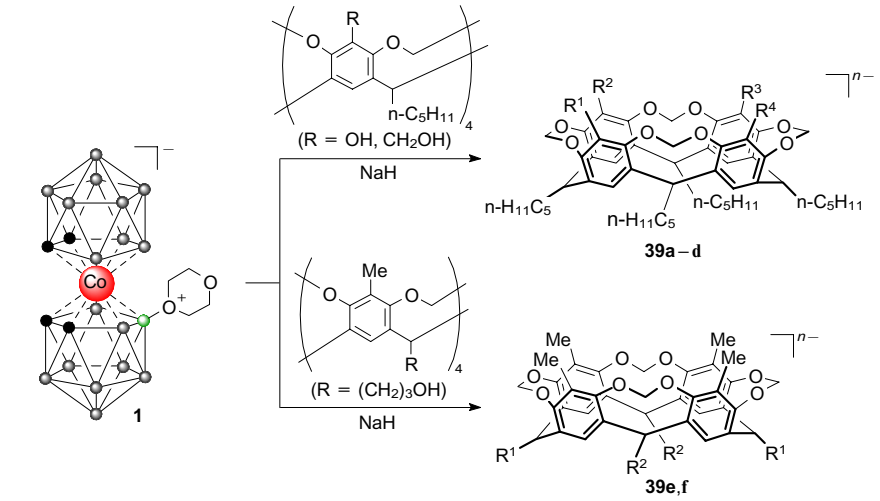
Figure 4. Crystal structure of compound **38b**[Cs_2]. The Figure was prepared by the authors using the data of Ref. 84.

trolyte **45**. The latter is characterized by a low glass-transition temperature (from −53 to −49 °C) and has high electrochemical stability, thereby making it possible to use this compound in rechargeable batteries (Scheme 26).[30]

2.2. Nitrogen nucleophiles

Along with *O*-nucleophiles, nitrogen nucleophiles are also often used for the ring opening of oxonium derivatives of cobalt and iron bis(dicarbollides). For instance, the reaction

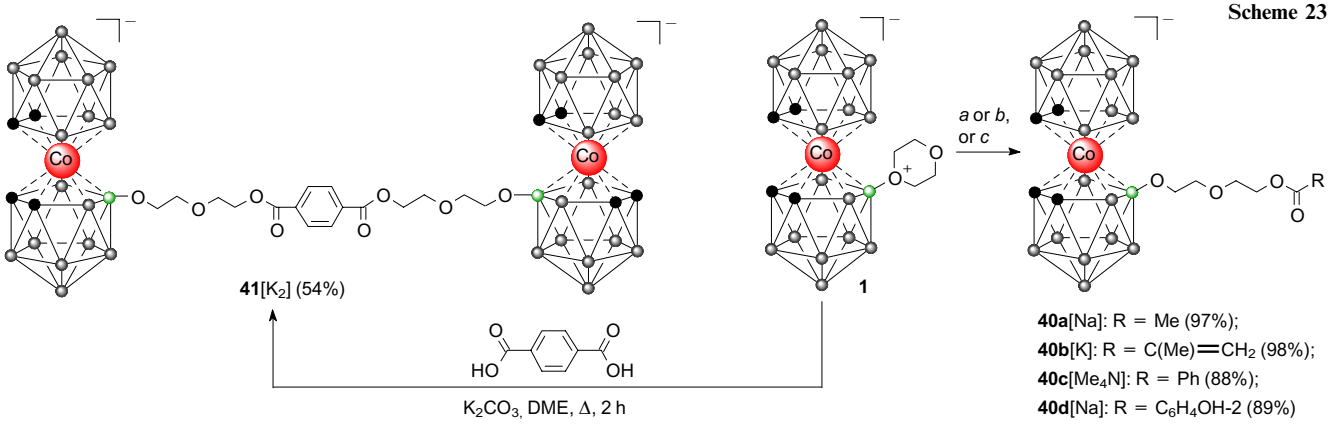
Scheme 22



39a[Na_2]: R^1 = R^3 = O–2EG-COSAN, R^2 = R^4 = OH, n = 2 (42%);
39b[Na_2]: R^1 = R^2 = O–2EG-COSAN, R^3 = R^4 = OH, n = 2 (42%);
39c[Na_2]: R^1 = R^3 = O–2EG-COSAN, R^2 = R^4 = CH_2OH, n = 2 (27%);
39d[Na_4]: R^1 = R^3 = O–2EG-COSAN, R^2 = R^4 = CH_2O–2E-COSAN, n = 4 (5%)

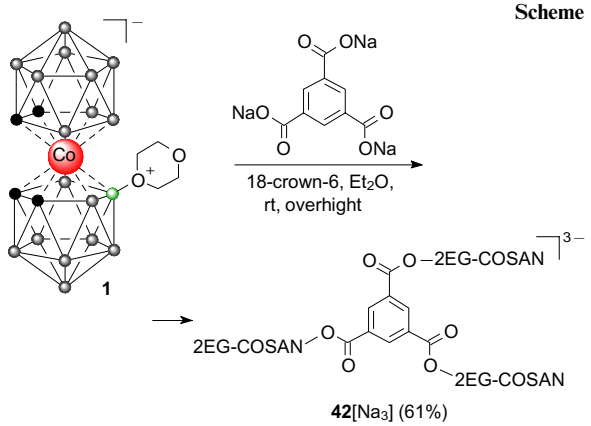
39e[Na_2]: R^1 = $(CH_2)_3O$–2EG-COSAN, R^2 = $(CH_2)_3OH$, n = 2 (31%),
39f[Na_4]: R^1 = R^2 = $(CH_2)_3O$–2EG-COSAN, n = 4 (32%)

Scheme 23

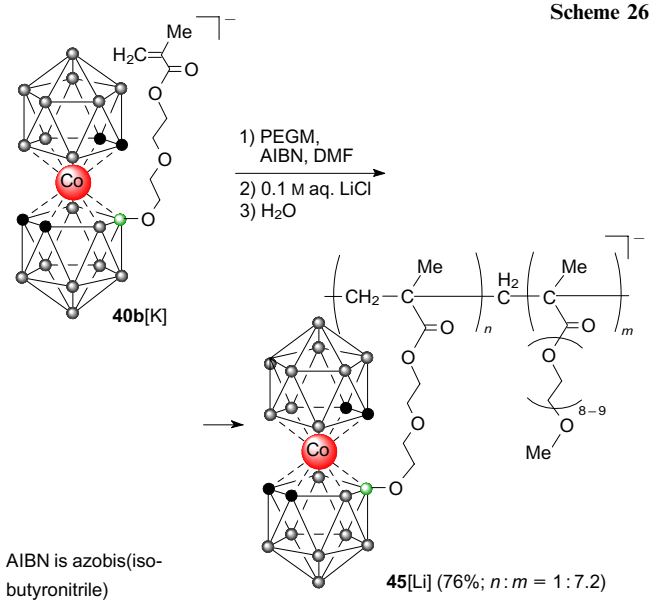


(*a*) RCO_2Na, DME, rt (for **40a**,**d**); (*b*) RCO_2H, K_2CO_3, MeCN, rt (for **40b**); (*c*) 1) RCO_2Na, DME, rt; 2) Me_4NCl, EtOH–H_2O (for **40c**)

Scheme 24



Scheme 26



of complex **1** with potassium phthalimide in DMF at room temperature followed by the phthalimide deprotection of compound **46** with hydrazine gave cobalt bis(dicarbollide) **47** with the terminal amino group as an intramolecular ammonium salt (Scheme 27).[55] Compound **47** proved to be an efficient antibacterial agent against the microorganisms *S. aureus*.[86]

Related iron bis(dicarbollide) derivative **48** was synthesized by the reaction of [8-O(CH_2CH_2)$_2$O-3,3′-Fe(1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{11}$)] (**3**) with an aqueous solution of ammonia in THF at room temperature (Scheme 28).[87]

The reaction of amino derivative **47** with 3-nitronaphthalene-1,8-diracboxylic anhydride in the presence of triethylamine gave naphthalimide **49** exhibiting cytotoxic properties against the human hepatocellular carcinoma cell line (HepG2) and the non-invasive cell line (RPMI 2650) (Scheme 29).[88]

The similar reaction of amine **47** with perylene-3,4,9,10-tetracarboxylic acid derivatives in imidazole gave redox-controlled fluorescent molecular switches **50** and **51** (Scheme 30).[89]

The dioxane ring of derivative **1** is easily cleaved with different primary amines and diamines to form the corresponding protonated ammonium derivatives **52a**–**j** and **53a**–**c** (Scheme 31).[60,61,86,90–93]

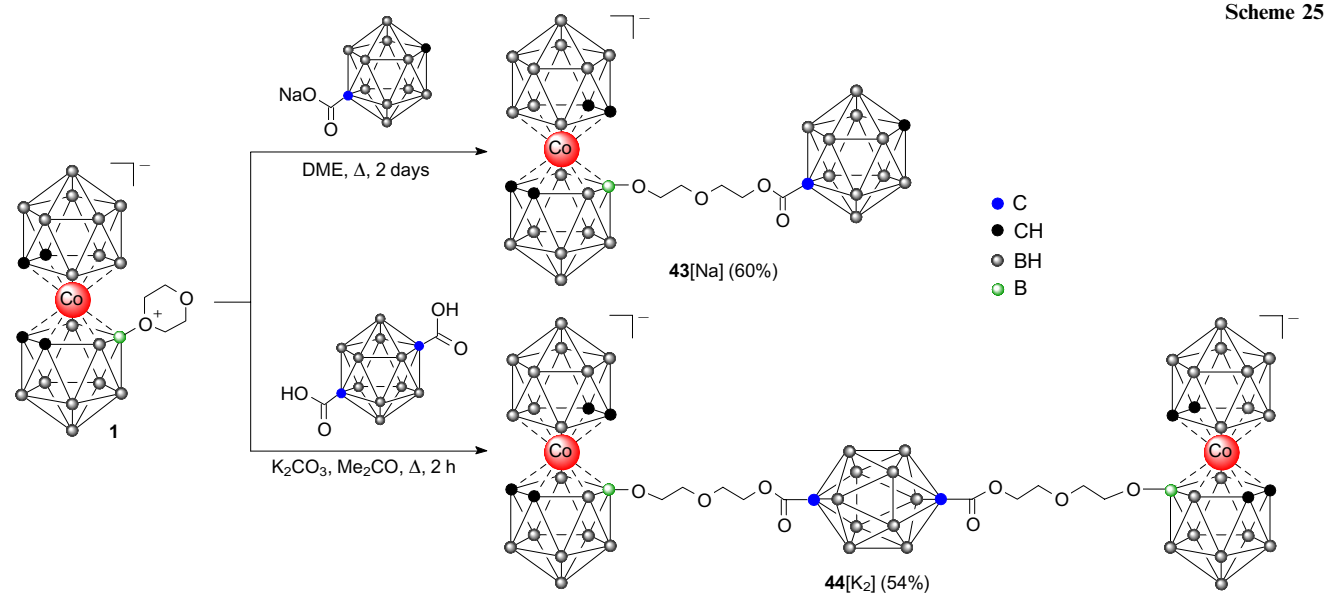
The oxonium ring opening can be induced even by sterically hindered amines. However, such reactions are very slow. An example is the synthesis pf extractants **54a**,**b** by the reaction of oxonium derivative **1** with amine containing the tertiary alkyl group with three carbamoyl methylene phosphine oxide moieties. These compounds can be used to extract Eu^{3+} and Am^{3+} from nitric acid solutions (Scheme 32).[59]

The reactions of compound **1** with secondary and tertiary amines proceed in a similar way and give intramolecular tri- and tetraalkylammonium salts **55a**–**e**, respectively (Scheme 33).[55,60,86]

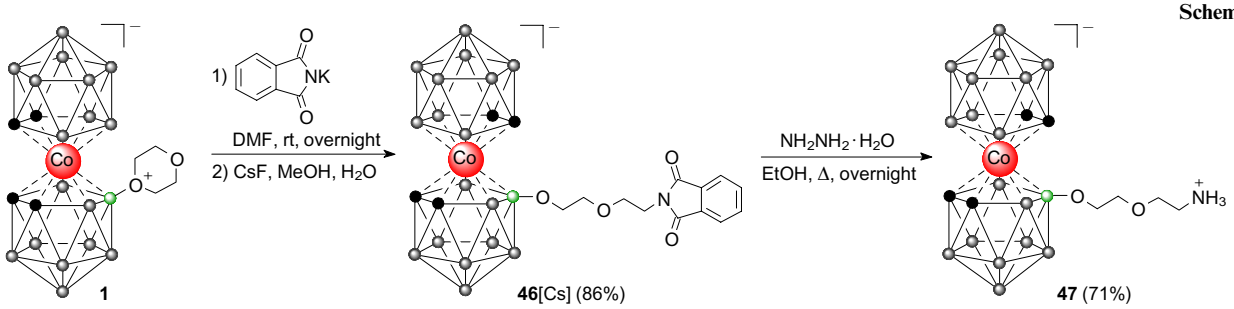
Cyclic oxonium derivatives of iron bis(dicarbollide) also react with amines to form the corresponding ammonium salts. For example, the reactions of compounds **3**–**5** with morpholine on heating in mesitylene afford *N*-alkylmorpholinium salts **56a**–**c** (Scheme 34).[53]

Since the oxonium ring opening in the reactions of bis(dicarbollides) with primary and secondary amines results in the formation of intramolecular protonated

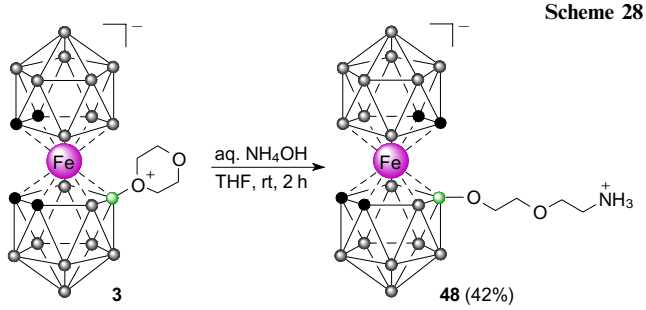
Scheme 25



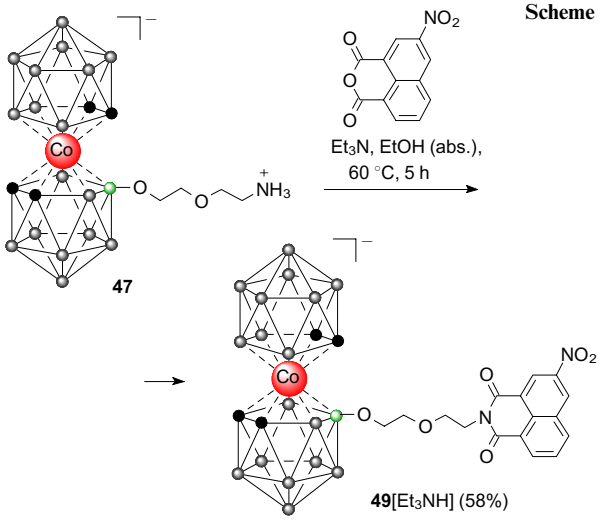
Scheme 27



Scheme 28



Scheme 29

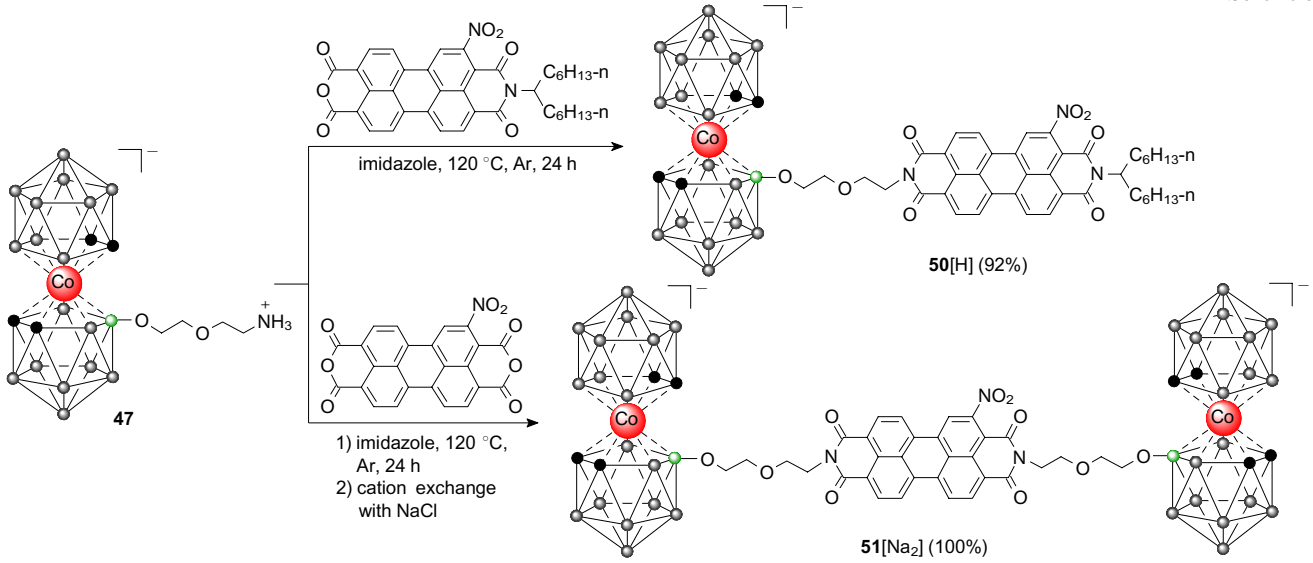


ammonium salts, compounds containing several boron cages can be prepared in the presence of a non-nucleophilic base and an excess of an alkylating agent. This process can also be performed in a sequential manner through the deprotonation of the intramolecular ammonium salt, which is produced in the reaction of amine with one equivalent of the cyclic oxonium derivative, followed by the addition of the second equivalent of the oxonium derivative to the resulting free amine. This method was applied to prepare ammonium salts **57a–i** bearing two bis(dicarbollide) units. It was shown that these compounds can act as HIV protease inhibitors (HIV is human immunodeficiency virus).[31,94]

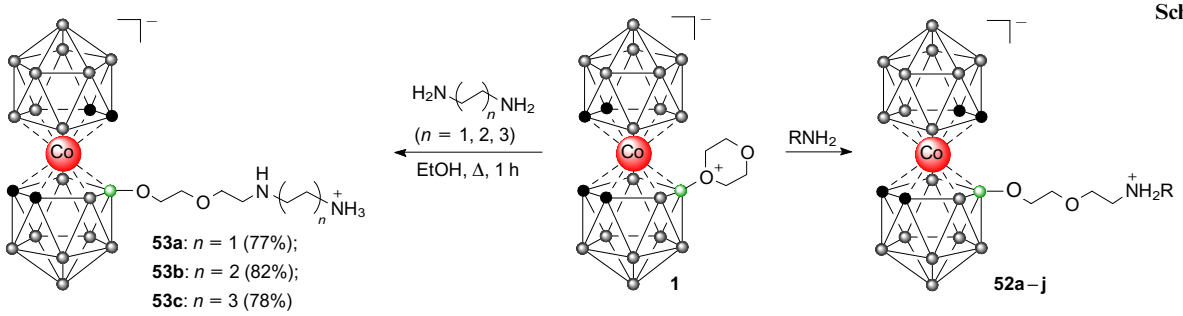
Derivatives **58–61** with a high boron content were synthesized by the reaction of dioxane derivatives of cobalt and iron bis(dicarbollides) with amino derivatives of different polyhedral borane anions in the presence of NaH as a non-nucleophilic base.[94,95] Compounds **58** and **59** are efficient HIV protease inhibitors.[94]

The ring opening of cyclic oxonium derivatives of iron and cobalt bis(dicarbollides) with dimethylalkylamines containing different functional groups can be considered as a convenient route to the synthesis of functional derivatives, in which the negative charge of the bis(dicarbollide) unit is compensated by the positive charge of the intramolecular ammonium cation. Products **62a–i** containing the terminal amino, hydroxy or acetylene groups were synthesized by the

Scheme 30

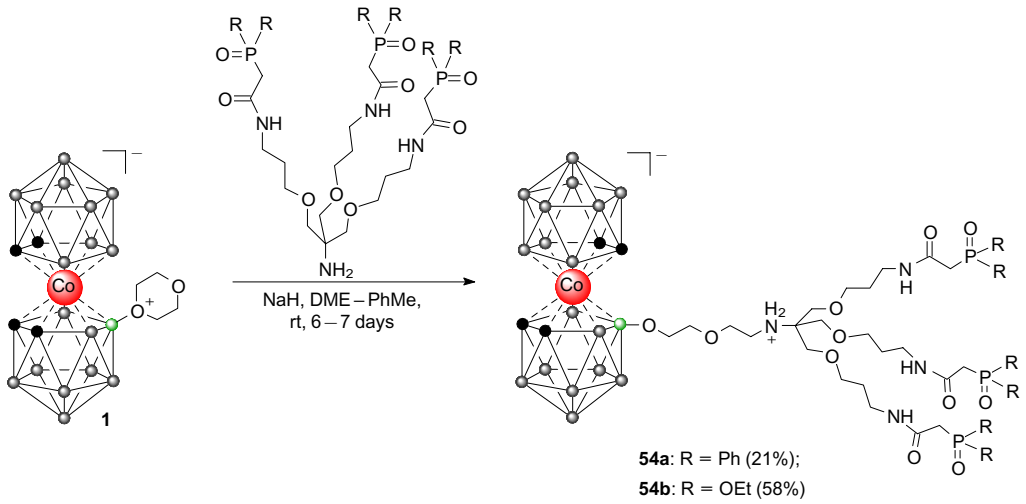


Scheme 31

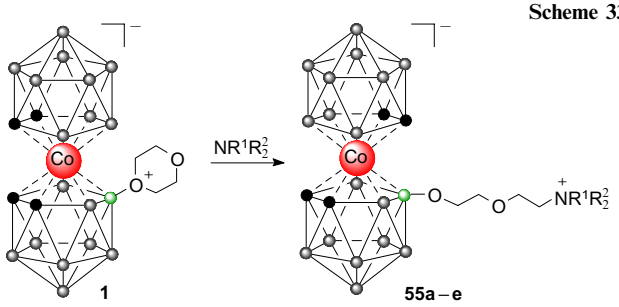


52: R = Me (**a**, 99%), Et (**b**, 98%), Bu^n (**c**, 97%), n-$C_{12}H_{25}$ (**d**, 89%), *tert*-C_8H_{17} (**e**, 84%), $(CH_2)_2O(CH_2)_2OH$ (**f**, 93%), CH_2CO_2Me (**g**, 68%), $(CH_2)_2$-2-(1,3-$N_2C_3H_3$) (**h**, 85%), Bn (**i**, 80%), Ph (**j**, 93%)

Scheme 32

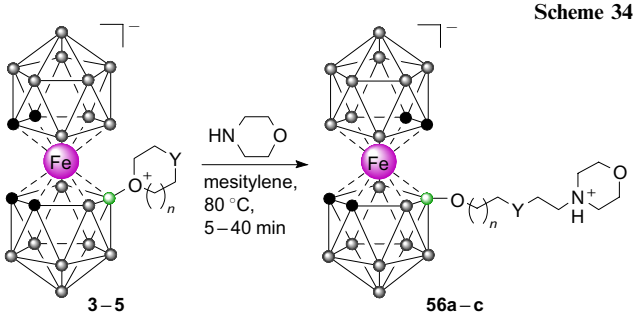


Scheme 33



R^1 = H: R^2 = Me (**a**, 99%), Et (**b**, 98%);
R^1 = R^2 = Me (**c**, 99%), Et (**d**, 99%), $(CH_2)_2OH$ (**e**, 96%)

Scheme 34



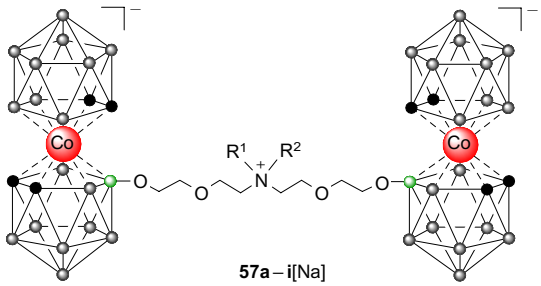
n = 1: Y = O (**3**: **56a**, 83%), CH_2 (**4**; **56b**, 82%); *n* = 0, Y = CH_2 (**5**; **56c**, 55%)

reaction of cyclic oxonium derivatives of bis(dicarbollides) **1**–**5** with protected *N*,*N*-dimethylethylenediamine, *N*,*N*-dimethylethanolamine and *N*,*N*-dimethylpropargylamine (Scheme 35).[53, 61, 96]

The reaction of compound **1** with the cage-like tricyclic tetraamine — [6^4]-adamanzane — affords zwitterionic derivative **63** with four quaternized nitrogen atoms, which can form inclusion compounds with I^-, HCO_3^-, SCN^-, BF_4^-, *etc*. anions (Scheme 36).[97]

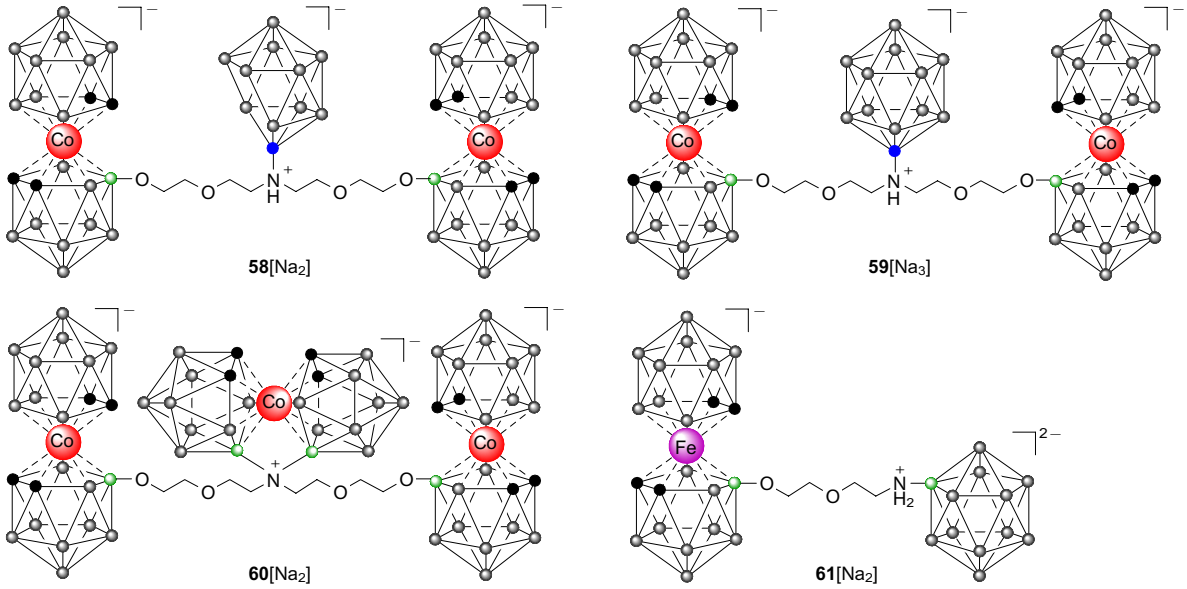
The dioxane ring in cobalt and iron bis(dicarbollide) derivatives is also easily cleaved with different nitrogen-containing aromatic heterocycles, such as pyridine, acridine, phenazine, 1,10-phenanthroline and benzothiazole, to form the corresponding *N*-alkylated products **64a**–**g**

Structures 57

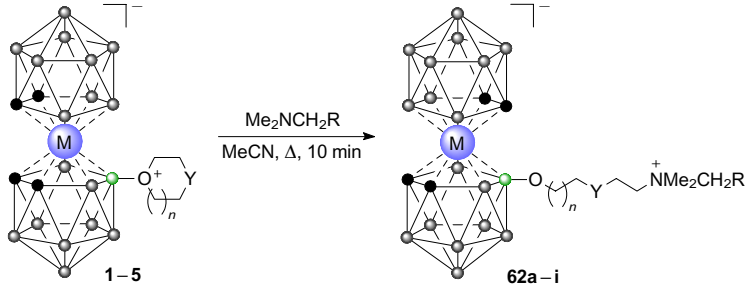


R^1 = R^2 = H (**a**), Et (**b**); R^2 = H: R^1 = Bu^n (**c**), $(CH_2)_2OH$ (**d**), Bu^t (**e**), $C(CH_2OH)_3$ (**f**), $(CH_2)_3CO_2H$ (**g**), $(CH_2)_2SO_3H$ (**h**), Bn (**i**)

Structures 58–61



Scheme 35



Compound	M	Y	*n*	R	Yield (%)
62a	Co	O	1	$CH_2NHC(O)CF_3$	92
62b	Co	O	1	C≡CH	72
62c	Co	CH_2	1	C≡CH	74
62d	Fe	O	1	C≡CH	92
62e	Fe	CH_2	1	C≡CH	75
62f	Fe	CH_2	0	C≡CH	83
62g	Fe	O	1	CH_2OH	92
62h	Fe	CH_2	1	CH_2OH	83
62i	Fe	CH_2	0	CH_2OH	98

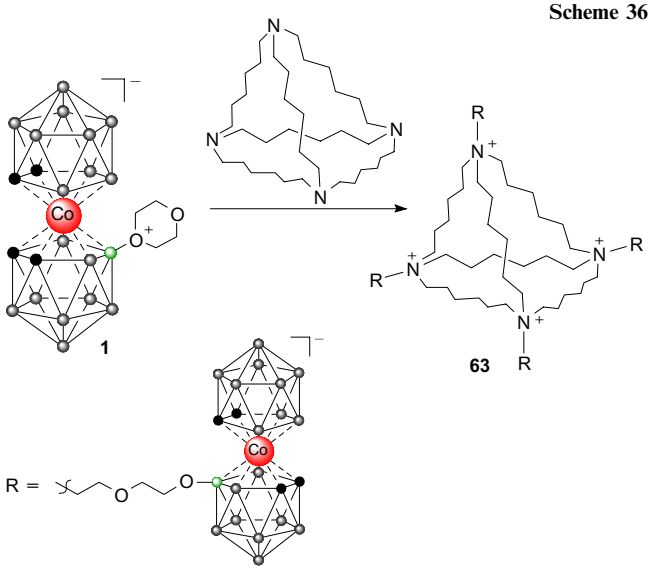
(Scheme 37).[55,60,61,87] Pyrrole (**65a**,**b**), indole (**65c**,**d**) and carbazole (**65e**,**f**) derivatives were prepared by the oxonium ring opening of complexes **1** and **2** with potassium salts of the corresponding heterocycles (see Scheme 37).[49]

The reactions of cyclic oxonium derivatives were also performed with other amino-containing *N*-nucleophiles. For instance, the dioxane ring of derivative **1** is cleaved with anions of urea, acetamidine, guanidine, aninoguanidine, *N*,*N*′-diaminoguanidine, trimethylaminoacetohydrazide (Girard reagent T), 2-aminoimidazole and 2-ethylaminoimidazole (Scheme 38).[60,61,90,91] Guanidine-containing derivatives **66c**,**d**,**f** efficiently regulate NO synthase, which is involved in many physiological processes and performs different regulatory and immune functions.[91]

Deprotonated amides can act as *N*-nucleophiles in the ring opening of oxonium cyclic derivatives. For example, the reaction of two equivalents of complex **1** with *N*,*N*′-di(isooctyl)diamide of fumaric acid in the presence of NaH gave amide **67** (Scheme 39). This compound was used as a negative charge-bearing linear component of rotaxanes, resulting in the hindered rotation of the positively charged cyclic component.[98]

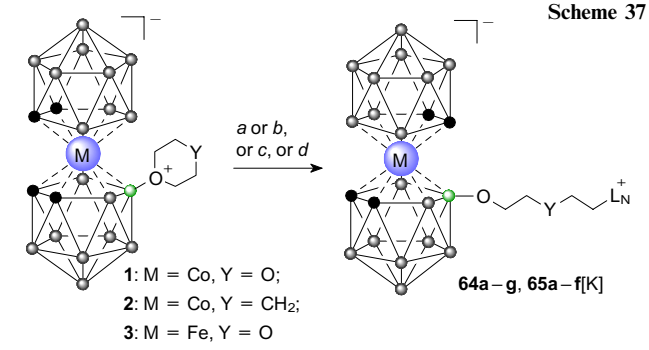
Amides containing cobalt bis(dicarbollide) units can be synthesized by the acylation of secondary amines, which are generated through the ring opening of oxonium derivative **1** with primary amines. For example, the acylation of boron-containing secondary amines **47** and **52** with

Scheme 36

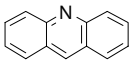
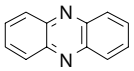


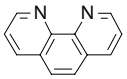
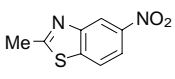
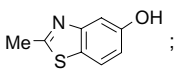
p-nitrophenyl esters of alkyl phenyl phosphoryl acetic acid in the presence of NaH afforded CMPO-containing compounds **68a**–**h** (Scheme 40) acting as highly efficient extractants for lanthanides and actinides from nitric acid solutions.[91,92]

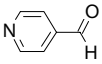
Scheme 37

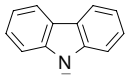


(*a*) L_N, $MeNO_2$, rt, 1 h (for **64a**); (*b*) L_N, THF–PhMe, 70 °C, 0.5–8 h (for **64b**–**f**); (*c*) L_N, CH_2Cl_2, rt, 24 h (for **64g**); (*d*) KL_N, THF, rt, 1 h (for **65a**–**f**);

M = Co, Y = O: L_N^+ =  (**64a**, 99%)  (**64b**, 90%)  (**64c**, 70%)

 (**64d**, 93%)  (**64e**, 87%)  (**64f**, 90%);

M = Fe, Y = O, L_N^+ =  (**64g**, 59%);

M = Co: L_N =   

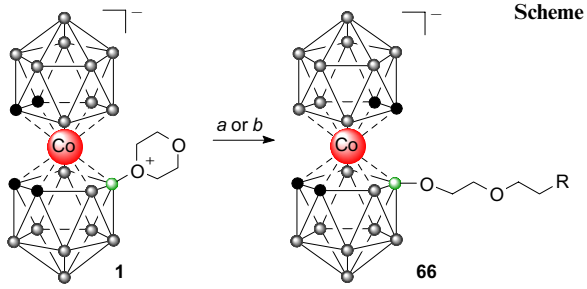
Y = O (**65a**[K], 84%), CH_2 (**65b**[K], 80%); Y = O (**65c**[K], 87%), CH_2 (**65d**[K], 89%); Y = O (**65e**[K], 83%), CH_2 (**65f**[K], 80%)

Other promising cobalt bis(dicarbollide)-based extractants are derivatives **69a**–**h** bearing two metallacarborane units linked together by a diglycol diamide chain. These compounds can be synthesized from secondary amines, which are generated through the ring opening of cyclic oxonium derivative **1** with primary amines and then acylated with diethylene glycol dichloride (Scheme 41).[99] It was found that the efficiency of the extraction of Eu^{3+} and Am^{3+} by extractants **69** from nitric acid solutions is two-three orders of magnitude higher compared to mixtures of hexachlorinated cobalt bis(dicarbollide) and *N*,*N*′-tetra-n-octyl diglycol diamide (TODGA).

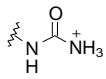
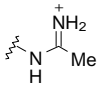
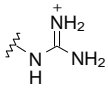
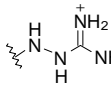
Amino derivatives of cobalt and iron bis(dicarbollides) **47** and **48** were used to modify multilayer carbon nanotubes,[87] graphite oxide [100] silicon dioxide.[101]

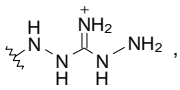
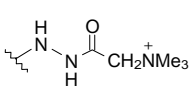
The azide ion is another *N*-nucleophile widely used for the ring opening of cyclic oxonium derivatives of cobalt and iron bis(dicarbollides). The reaction of derivatives **1**–**3** with NaN_3 affords azide-containing oxonium ring opening products **70a**–**c** (Scheme 42).[68, 70] In the presence of CuI and triethylamine in acetonitrile, the 1,3-dipolar [3 + 2]-cycloaddition reactions of azides **70a**,**b** with propargyl alcohol, but-3-yn-1-ol, phenylacetylene and octyne produce 1,2,3-triazoles **71a**–**g** (see Scheme 42).[68] Under the click reaction conditions, a similar reaction of azides **70a**,**b** with alkynes **14b**,**e** gives 1,2,3-triazoles **72a**–**d** bearing two metallacarborane units (see Scheme 42).[70, 102]

Scheme 38



(*a*) NaH, THF or THF–PhMe rt, 30–60 min (for **66a**–**f**);
(*b*) THF–PhMe, rt, 30–60 min (for **66g**);

R =  (**66a**, 89%)  (**66b**, 88%)  (**66c**, 95%)  (**66d**, 98%)

 (**66e**, 93%)  (**66f**, 87%)  (**66g**, 93%)

2.3. Sulfur nucleophiles

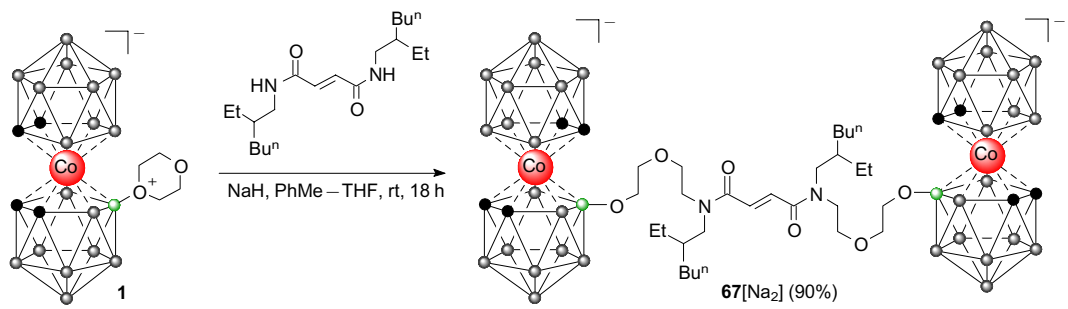
As opposed to *O*- and *N*-nucleophiles, examples of the use of *S*-nucleophiles for the 1,4-dioxane ring opening of the cobalt bis(dicarbollide) derivative *closo*-[8-$(CH_2CH_2O)_2$-3,3′-Co(1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{11}$)] (**1**) are much less frequent. For instance, the reaction of compound **1** with NaSH in refluxing THF affords thiol **73** (Scheme 43).[103]

The dioxane ring of derivative **1** is cleaved in the presence of non-nucleophilic bases (*e.g.*, NaH) with other *S*-nucleophiles, such as propane-1,3-dithiol, 2-(dimethylamino)ethanethiol, thiourea and thiosemicarbazide, to form the corresponding derivatives **74a**–**d** (Scheme 44).[68, 90] Derivative **74c** was found to efficiently regulate NO synthase.[91]

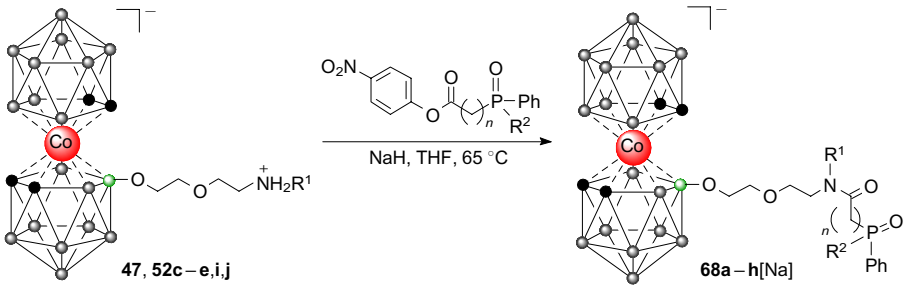
Lithium salts of sulfanylcarboranes were also employed as *S*-nucleophiles in reactions with complex **1**, resulting in the formation of compounds **75** and **76** bearing one or two metallacarborane clusters, respectively (Scheme 45).[71]

Apart from different thiolates, such weak nucleophiles as dialkyl sulfides can be used for the dioxane ring opening. For example, the reaction of compound **1** with dimethyl

Scheme 39



Scheme 40

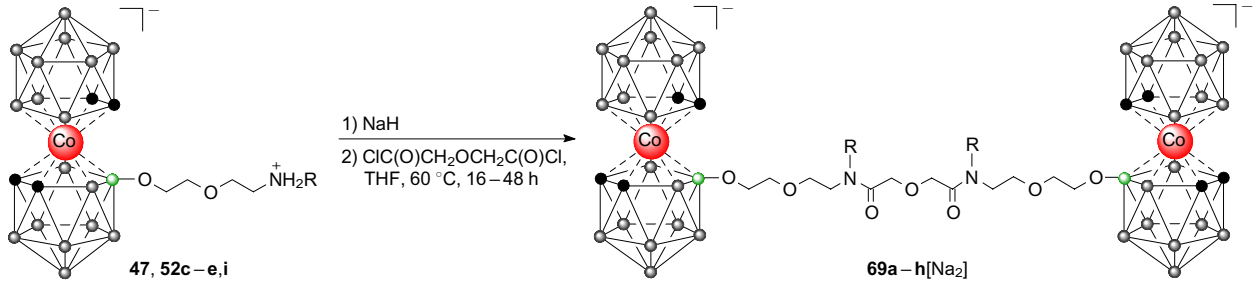


47, **52c** – **e**,**i**,**j**

68a – **h**[Na]

68: n = 1, R^2 = Ph: R^1 = Bu^n (**a**, 95%), n-$C_{12}H_{25}$ (**b**, 91%), Bn (**c**, 82%), *tert*-C_8H_{17} (**d**, 84%), H (**e**, 82%), Ph (**f**, 82%); R^1 = *tert*-C_8H_{17}: n = 1, R^2 = n-C_8H_{17} (**g**, 42%); n = 2, R^2 = Ph (**h**, 44%)

Scheme 41

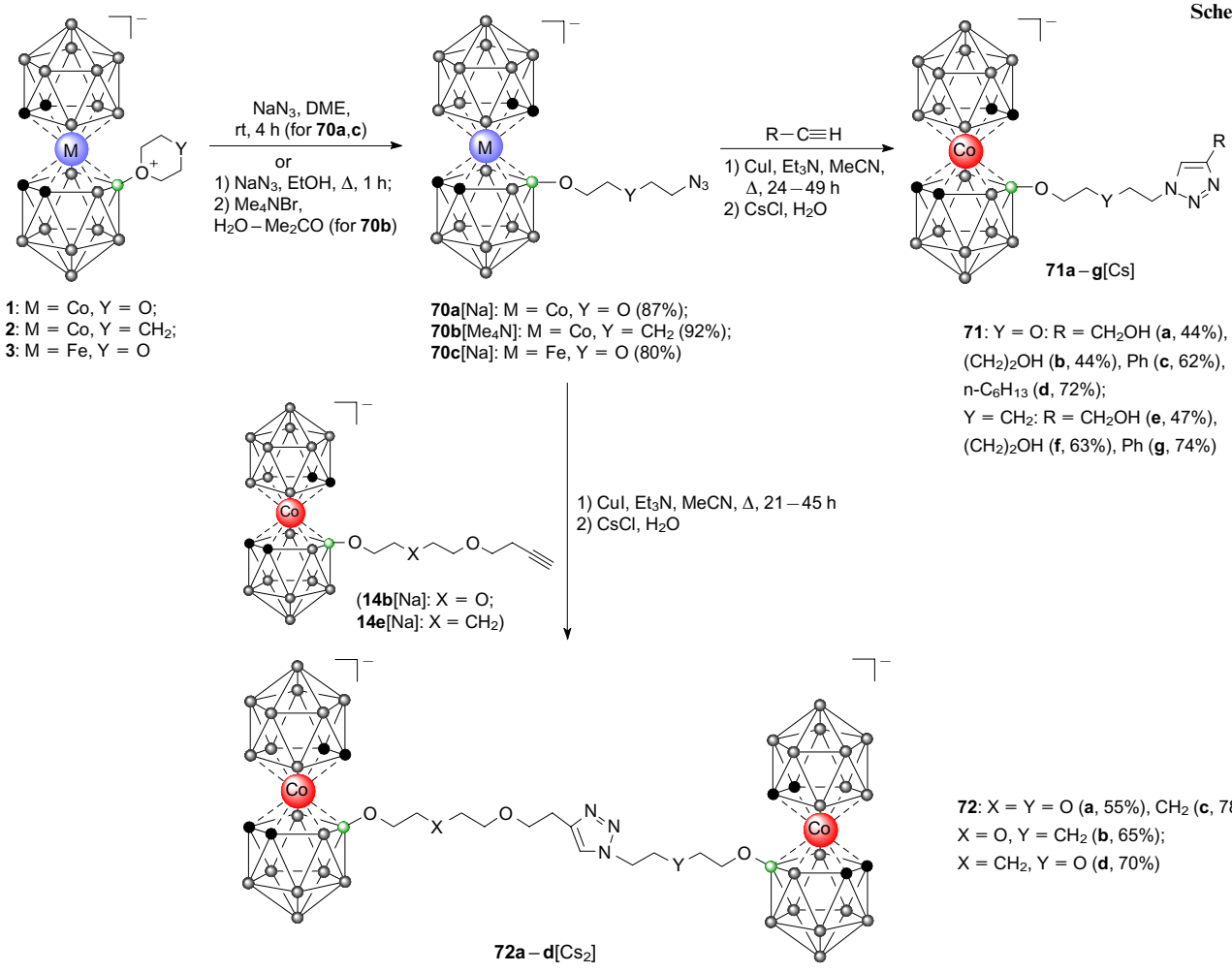


47, **52c** – **e**,**i**

69a – **h**[Na_2]

69: R = H (**a**, 23%), Bu^n (**b**, 57%), n-C_6H_{13} (**c**, 53%), n-C_8H_{17} (**d**, 88%), n-$C_{12}H_{25}$ (**e**, 70%), *tert*-C_8H_{17} (**f**, 5%), 4-MeC_6H_4 (**g**, 48%), Bn (**h**, 62%)

Scheme 42



1: M = Co, Y = O;
2: M = Co, Y = CH_2;
3: M = Fe, Y = O

70a[Na]: M = Co, Y = O (87%);
70b[Me_4N]: M = Co, Y = CH_2 (92%);
70c[Na]: M = Fe, Y = O (80%)

71a – **g**[Cs]

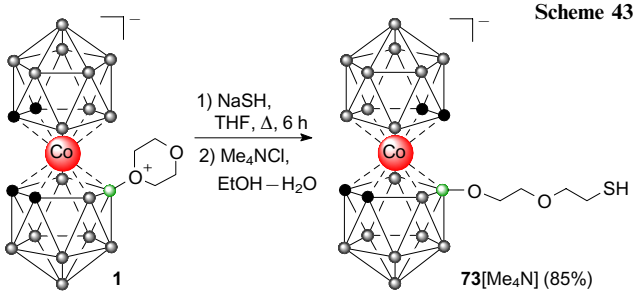
71: Y = O: R = CH_2OH (**a**, 44%), $(CH_2)_2OH$ (**b**, 44%), Ph (**c**, 62%), n-C_6H_{13} (**d**, 72%); Y = CH_2: R = CH_2OH (**e**, 47%), $(CH_2)_2OH$ (**f**, 63%), Ph (**g**, 74%)

(**14b**[Na]: X = O;
14e[Na]: X = CH_2)

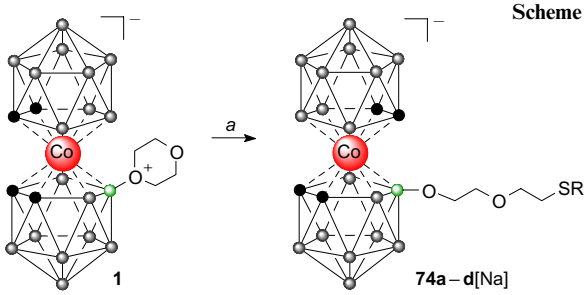
72a – **d**[Cs_2]

72: X = Y = O (**a**, 55%), CH_2 (**c**, 78%); X = O, Y = CH_2 (**b**, 65%); X = CH_2, Y = O (**d**, 70%)

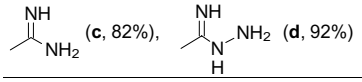
Scheme 43



Scheme 44

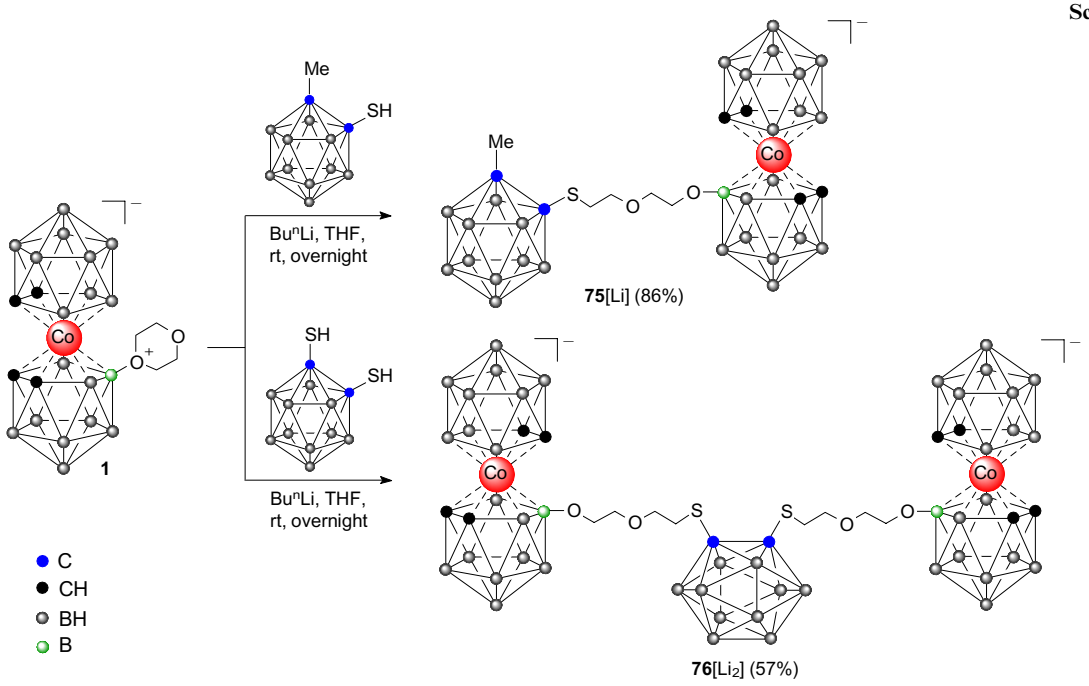


(*a*) RSH, NaH,PhMe-DMF, rt, 5 h (for **74a**) or NaH, THF – PhMe, 60 °C, 1 h (for **74b–d**); **74**: R = $(CH_2)_3SH$ (**a**, 31%), $(CH_2)_2NMe_2$ (**b**, 95%),

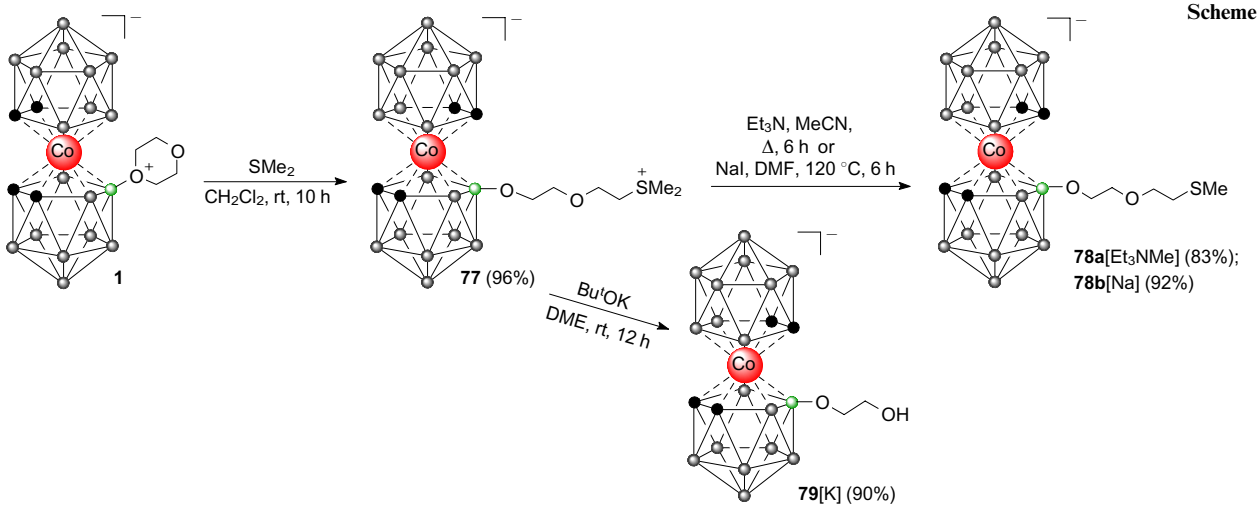


sulfide in dichloromethane at room temperature affords dimethylsulfonium derivative **77** (Scheme 46).[104] Although trialkylsulfonium salts are less reactive than trialkyloxonium salts, they are widely used in organic synthesis as alkylating agents. Since the sulfonium centre of compound **77** bears substituents of two different types, its reactions with nucleophiles would be expected to form a mixture of two products generated through the abstraction of the methyl group and the replacement of the dimethyl sulfide group. However, this process proved to be selective, the type of the reaction product being dependent on the nature of the nucleophile. Thus, the reaction of compound **77** with triethylamine (a strong nucleophile and a strong base) in

Scheme 45



Scheme 46

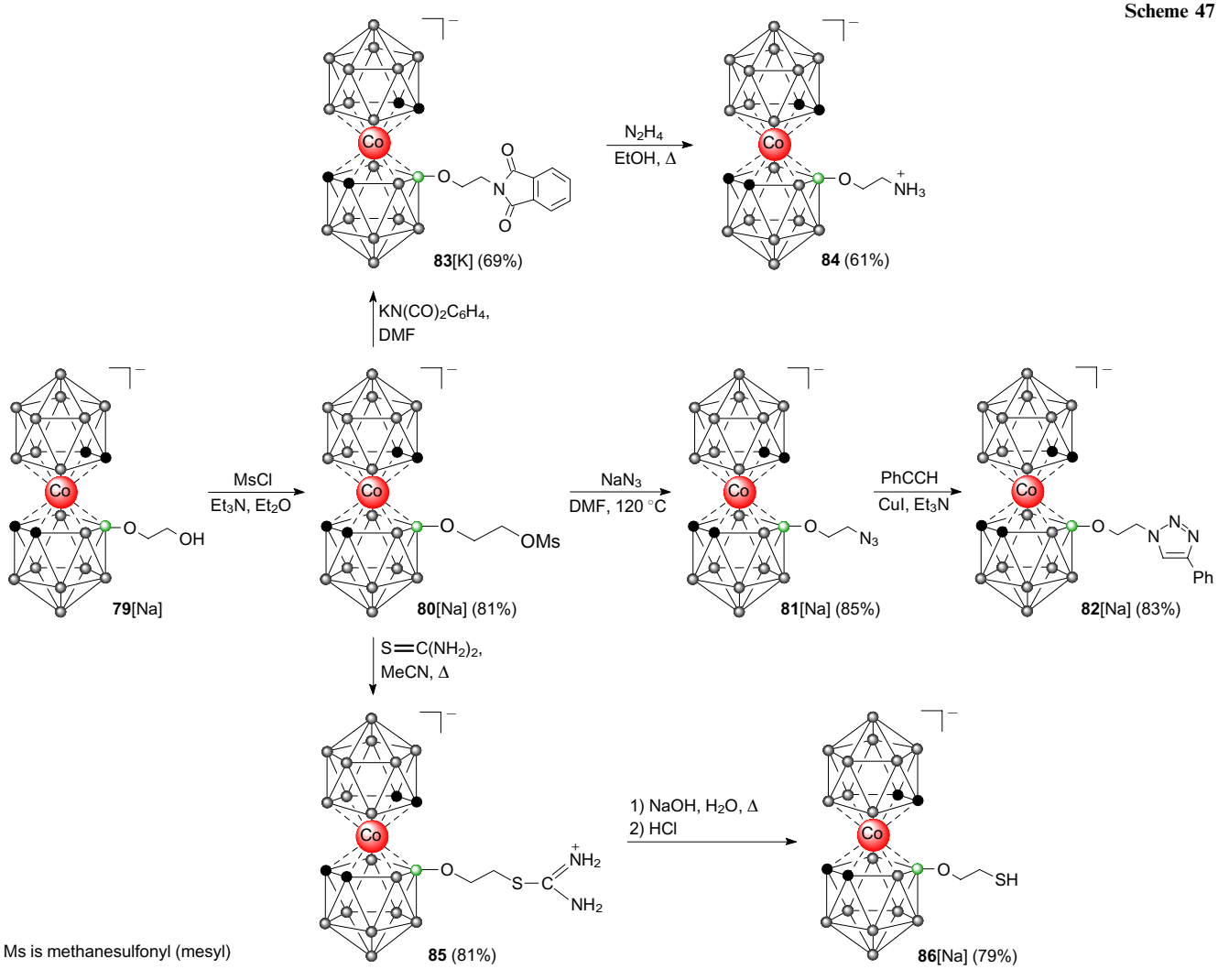


refluxing acetonitrile leads to the selective demethylation of the sulfur atom and the methylation of the nitrogen atom to form (Et_3NMe)[8-MeS$(CH_2CH_2O)_2$-3,3′-Co(1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{11}$)] (**78a**). The similar reaction with the iodide ion (a nucleophile, which does not have basic properties) in DMF at 120 °C affords Na[8-MeS$(CH_2CH_2O)_2$-3,3′-Co(1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{11}$)] (**78b**). On the other hand, the reaction of compound **77** with a weakly nucleophilic base (potassium *tert*-butoxide) in dimethoxyethane at room temperature is not accompanied by the replacement of the Me_2S group, but leads to the side-chain shortening to form the hydroxy derivative K[8-$HOCH_2CH_2O$-3,3′-Co(1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{11}$)] (**79**) (see Scheme 46).[104] It is worth noting that the behaviour of the dioxane derivative of cobalt bis(dicarbollide) **1** is significantly different from that of the corresponding derivatives of the *closo*-decarborate ($[2\text{-}B_{10}H_9O(CH_2CH_2)_2O]^-$) and *closo*-dodecarborate ($[B_{12}H_{11}O(CH_2CH_2)_2O]^-$) anions, which do not react with dimethyl sulfide even on heating. This difference is attributed to the stronger electron-donating effect of the *closo*-decarboranyl and *closo*-dodecarboranyl groups, resulting in higher stability and lower reactivity of their cyclic oxonium derivatives.[105]

The length of the spacer between the boron cluster and the biologically active part of the molecule can exert a significant effect on the biological properties of the compound. Generally, the length of the spacer generated through the ring opening of cyclic oxonium derivatives can be increased by the rational choice of an appropriate nucleophile. Some examples are given above (see Scheme 5). Meanwhile, the reaction of dioxane derivative **1** with dimethyl sulfide followed by the treatment of sulfonium derivative **77** with a strong base provides a convenient route to the shortening of the diethylene glycol chain generated through the 1,4-dioxane ring opening. This approach was used to prepare a series of functional cobalt bis(dicarbollide) derivatives containing different terminal groups, such as hydroxy, amino, thiol and azide, separated from the boron cluster by a three-atom chain, of the general formula $[8\text{-}XCH_2CH_2O\text{-}3,3'\text{-}Co(1,2\text{-}_2B_9H_{10})(1',2'\text{-}C_2B_9H_{11})]^-$ (X = OH, NH_2, SH, N_3). Thus, the reaction of mesylate **80**, generated from alcohol **79**, with sodium azide in dimethylformamide at 120 °C affords azide **81**, and the reaction of the latter with phenylacetylene in the presence of CuI and Et_3N in acetonitrile gives triazole **82**. The reaction of mesylate **80** with potassium phthalimide in DMF at 120 °C produces phthalimide derivative **83**, and its treatment with hydrazine hydrate in ethanol gives amine **84**. The reaction of mesylate **80** with thiourea in refluxing acetonitrile affords the corresponding derivative **85**, which is transformed by alkaline hydrolysis into thiol **86** (Scheme 47).[104]

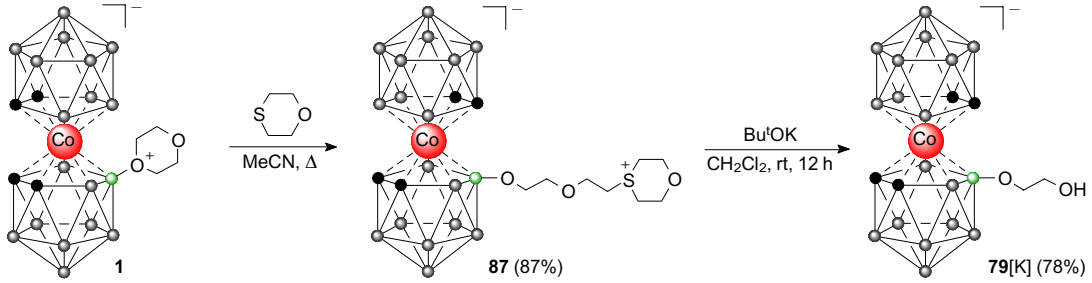
The reactions of derivative **1** with other alky sulfides are also accompanied by the dioxane ring opening. For instance, the heating of derivative **1** with thioxane under

Scheme 47

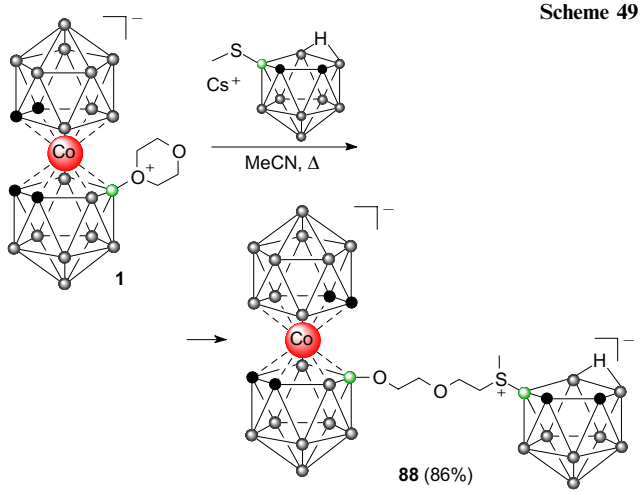


Ms is methanesulfonyl (mesyl)

Scheme 48



Scheme 49



reflux in acetonitrile affords sulfonium derivative **87**, which is inert towards triethylamine and pyridine, but reacts with potassium *tert*-butoxide in dichloromethane to form compound **79** as the side-chain shortening product (Scheme 48).[104]

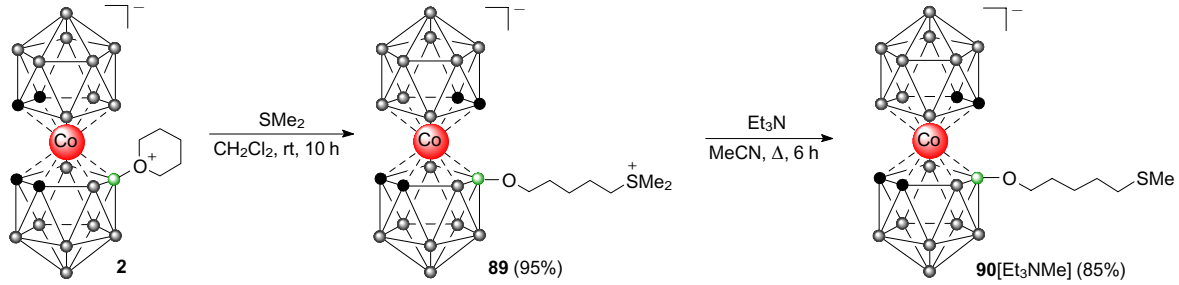
9-Methylthio-*nido*-carborane $[9\text{-MeS-}7,8\text{-}C_2B_9H_{11}]^-$ can be used as the *S*-nucleophile for the 1,4-dioxane ring opening of complex **1**. The reaction of this *S*-nucleophile in refluxing acetonitrile yields sulfonium derivative **88** with three different substituents (Scheme 49). The sulfonium centre in compound **88** is additionally stabilized due to the strong electron-donating effect of the *nido*-carboranyl group and, consequently, it remains inert towards triethylamine in refluxing acetonitrile. Meanwhile, under similar conditions, the reactions of compound **77** and the dimethylsulfonium derivative of *nido*-carborane $[9\text{-Me}_2\text{S-}7,8\text{-}C_2B_9H_{11}]$ give the demethylation products.[104]

A similar reaction of the tetrahydropyran-containing cobalt bis(dicarbollide) **2** with dimethyl sulfide in dichloromethane at room temperature gives dimethylsulfonium derivative **89**, and the treatment of the latter with triethylamine in refluxing acetonitrile leads to the demethylation to form methyl sulfide derivative **90** (Scheme 50).[78]

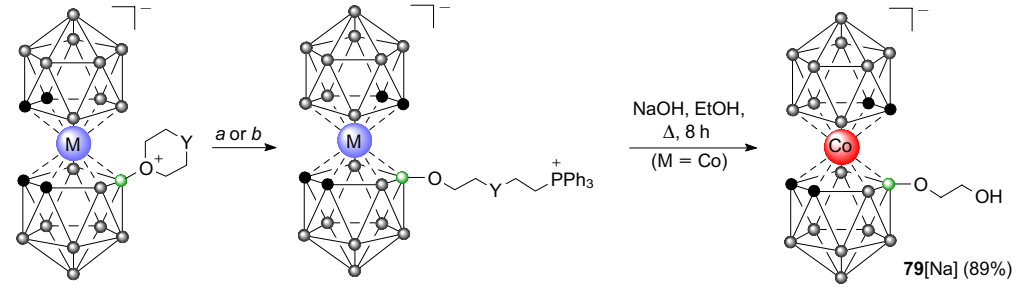
2.4. Phosphorus nucleophiles

There are only a few examples, in which *P*-nucleophiles were used in the ring opening reactions of cyclic oxonium derivatives of cobalt and iron bis(dicarbollides). The reactions of compounds **1** and **2** with triphenylphosphine in acetonitrile at room temperature produce the corresponding triphenylphosphonium derivatives **91a**,**b** (Scheme 51).[76, 102] Product **91c** was synthesized by the reaction of the dioxane derivative of iron bis(dicarbollide) **3** with triphenyl-

Scheme 50



Scheme 51

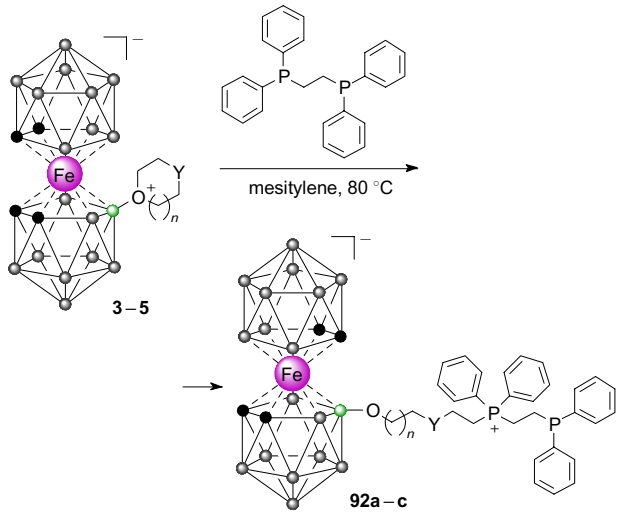


1: Y = O, M = Co;
2: Y = CH_2, M = Co;
3: Y = O, M = Fe

91a: Y = O, M = Co (87%);
91b: Y = CH_2, M = Co (91%);
91c: Y = O, M = Fe (93%)

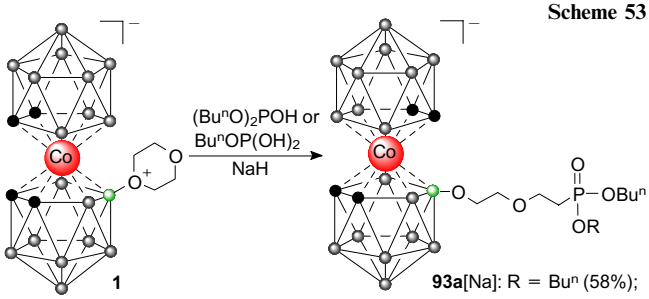
(*a*) PPh_3, MeCN, rt, 12 h (for **91a**,**b**);
(*b*) PPh_3, PhMe–DME, 80 °C (for **91c**)

Scheme 52



n = 1: Y = O (**3**; **92a**, 30%), CH_2 (**4**; **92b**, 92%); *n* = 0, Y = CH_2 (**5**; **92c**, 50%)

Scheme 53



phosphine in a refluxing mixture of toluene and 1,2-dimethoxyethane (see Scheme 51).[52] The heating of triphenylphosphonium derivative **91a** with NaOH under reflux in ethanol leads to the side-chain shortening and the formation of compound **79** (see Scheme 51).[104]

A similar reaction of cyclic oxonium derivatives of iron bis(dicarbollide) **3**–**5** with 1,2-bis(diphenylphosphino)-ethane in mesitylene affords phosphonium derivatives **92a**–**c** (Scheme 52).[53]

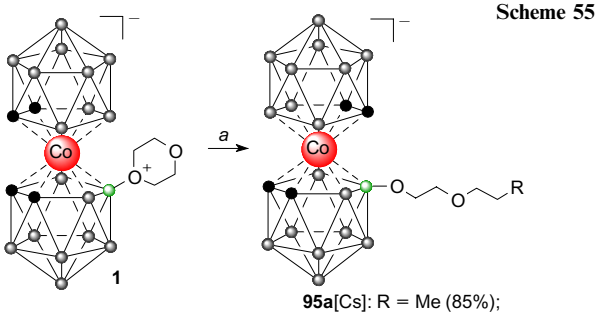
Boron-containing phosphonic acid esters **93** were synthesized by the Michaelis–Becker reaction of compound **1** with mono- and dibutylphosphites (Scheme 53).[73]

2.5. Carbon nucleophiles

Examples of the ring opening of cyclic oxonium derivatives with *C*-nucleophiles are also scarce. The first example is the reaction of compound **1** with cyanide in dichloromethane giving nitrile **94**. The treatment of the latter with sodium hydroxide in ethanol causes the elimination of acrylonitrile to form side-chain shortening product **79** (Scheme 54).[55]

The dioxane ring of cobalt bis(dicarbollide) **1** can also be cleaved with Grignard reagents. Thus, the reactions of compound **1** with methylmagnesium bromide and allylmagnesium chloride afford the corresponding ethers **95a**,**b** (Scheme 55).[71]

Scheme 55



(*a*) 1) RMgHal, DME, rt, overnight; 2) CsCl, EtOH–H_2O

Lithium derivatives of carboranes can also act as *C*-nucleophiles. The reactions of complex **1** with lithiated *ortho*-, *meta*- and *para*-carboranes in a molar ratio of 1 : 1 or 2 : 1 in THF give products **96**–**99** (Scheme 56).[106]

2.6. Halogens as nucleophiles

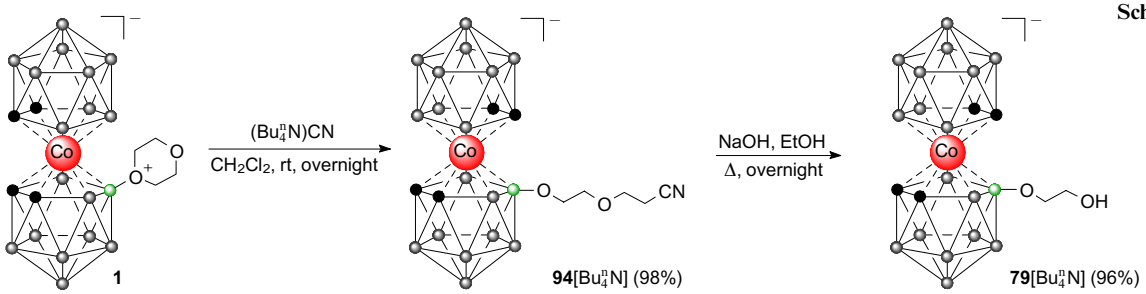
The oxonium ring of derivative **1** can also be cleaved with hydrogen halides in THF at room temperature to form halogen-containing complexes **100a**–**d**. Alcohol **79** can be synthesized by the treatment of compound **100c** with magnesium in the presence of 1,2-dibromoethane in THF followed by hydrolysis of the intermediates (Scheme 57).[103]

3. Cobalt and iron bis(dicarbollide) conjugates with biologically active molecules

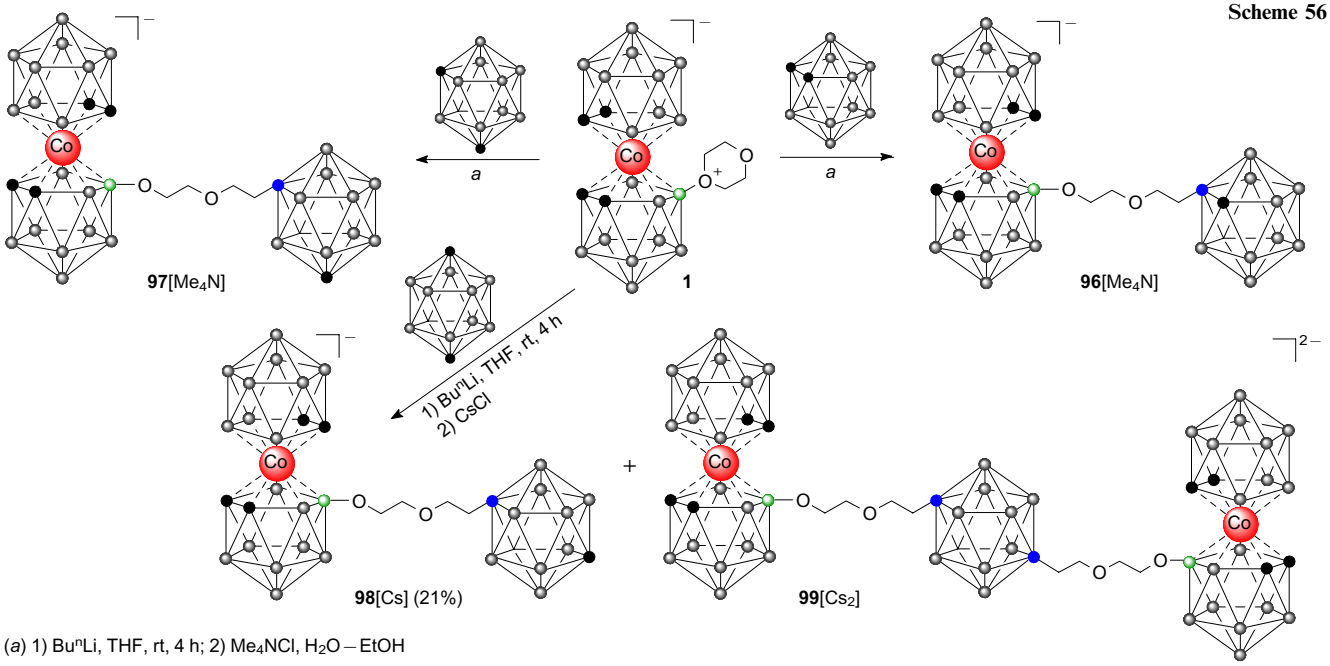
3.1. Amino acids and peptides

One intrinsic difference between normal and tumour cells is their altered metabolism. Oncocytes are characterized by elevated consumption of amino acids compared to normal cells. Therefore, amino acid derivatives can be considered as a unique platform for targeted drug delivery to tumour sites.[107] The blood-brain barrier (BBB) is a significant obstacle to boron neutron capture therapy of malignant brain tumours. This barrier is a selectively permeable membrane, which controls the transport of numerous molecules towards and from the neuronal micromedium. Gases and small lipophilic molecules are transported *via* simple diffusion, whereas large molecules are transferred by special

Scheme 54

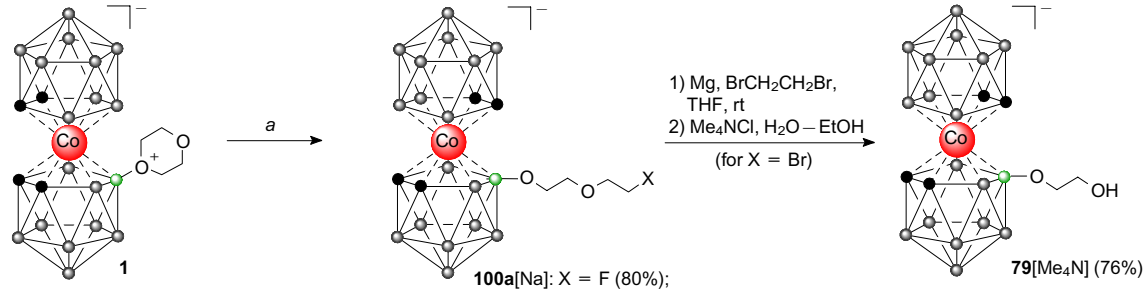


Scheme 56



(*a*) 1) Bu^{n}Li, THF, rt, 4 h; 2) Me_4NCl, H_2O–EtOH

Scheme 57



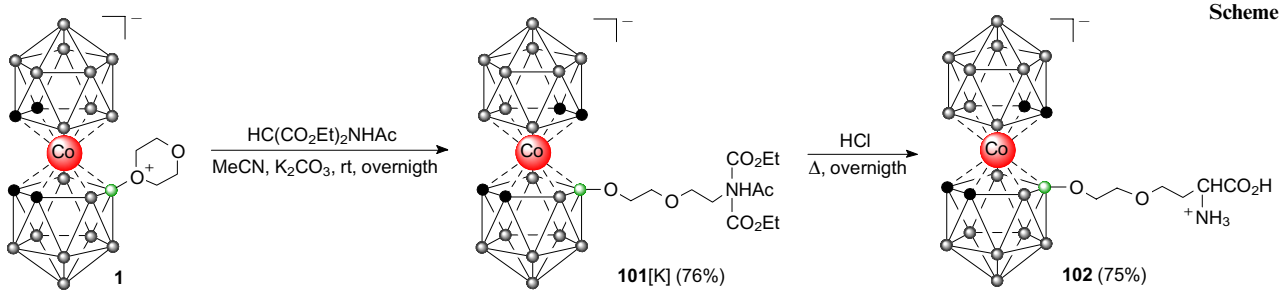
(*a*) 1) HX, THF, 0–25 °C, overnight (for X = F, Cl, Br, I); 2) $NaHCO_3$, H_2O–Et_2O (for X = F); CsCl, H_2O–acetone (for X = Cl); Me_4NCl, H_2O–EtOH (for X = Br, I)

transport systems, *e.g.*, large neutral amino acid transporter 1 (LAT-1). This transporter efficiently transfers different L-amino acids (tyrosine, phenylalanine, tryptophan, histidine, valine, leucine, isoleucine) across the BBB. It was found that LAT-1 is also overexpressed on the cytoplasmic membrane of many types of tumour cells.[108–110] Therefore, the synthesis of different boron-containing amino acids as potential BNCT agents has attracted great interest.[111–119]

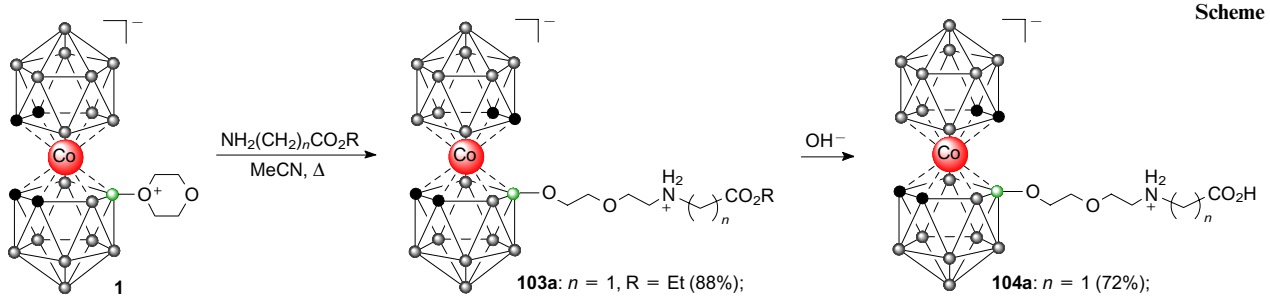
Several examples of the synthesis of amino acids containing the cobalt bis(dicarbollide) cluster were described in the literature. First boron-containing amino acid **102** was synthesized by the dioxane ring opening of compound **1** with diethyl acetamidomalonate proposed by Sørensen followed by the acid hydrolysis of product **101**. This acid was isolated as intramolecular salt, in which the charge of the metallacarborane anion is compensated by the protonated amino group (Scheme 58).[55]

Besides, a number of oxonium ring opening reactions of complex **1** with natural amino acid derivatives were described. Amino acids contain at least two nucleophilic centres — the amino group and the carboxy group; some acids include also other functional groups, which can serve as nucleophilic centres. Therefore, the synthesis of amino acids based on cobalt bis(dicarbollide) generally requires

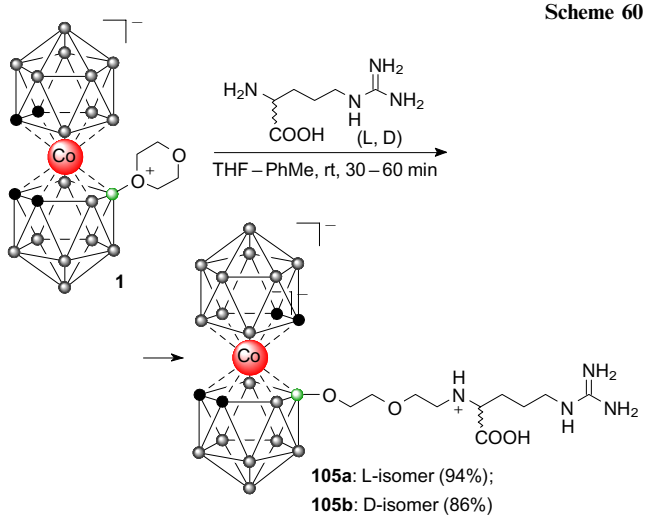
Scheme 58



Scheme 59



Scheme 60



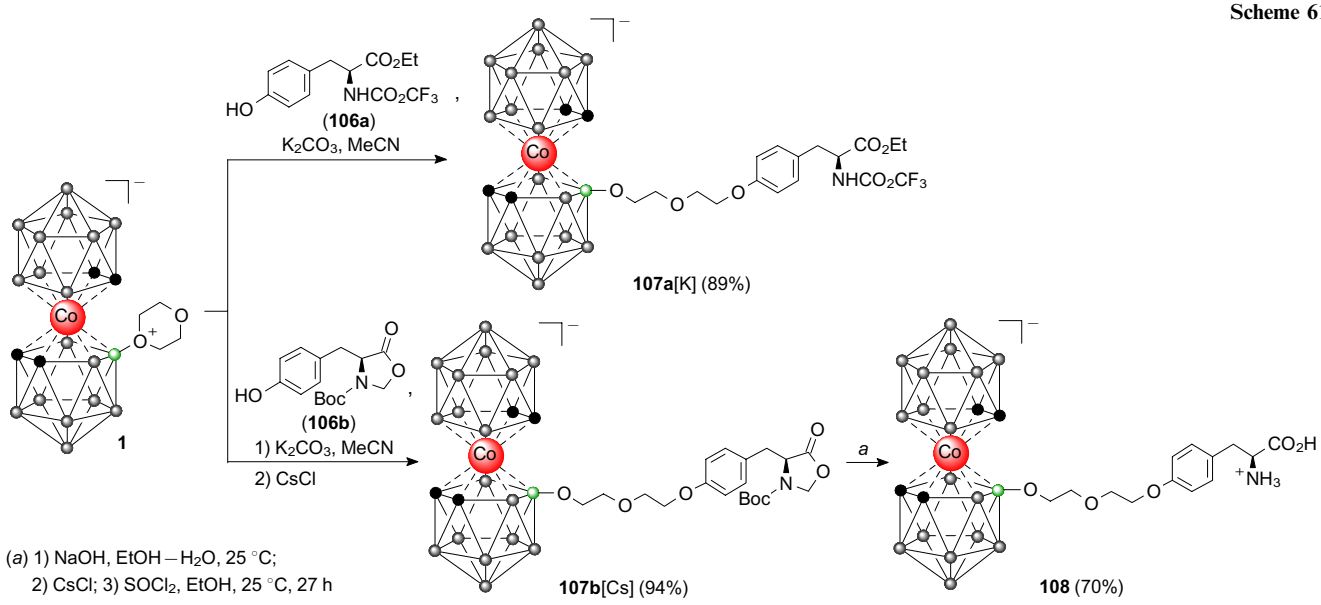
the protection of one or several reactive nucleophilic centres. For instance, the oxonium ring opening of compound **1** with amino groups of ω-amino acids, such as glycine and γ-aminobutyric acid, was accomplished using their esters, and the resulting derivatives **103** were subjected to alkaline hydrolysis to the corresponding *N*-alkylated amino acids **104** (Scheme 59).[120]

In some cases, the reactions proceed in a selective manner even without involving protecting groups. For example, the reaction of complex **1** with arginine results in the selective alkylation of the α-amino group to form product **105** (Scheme 60).[95]

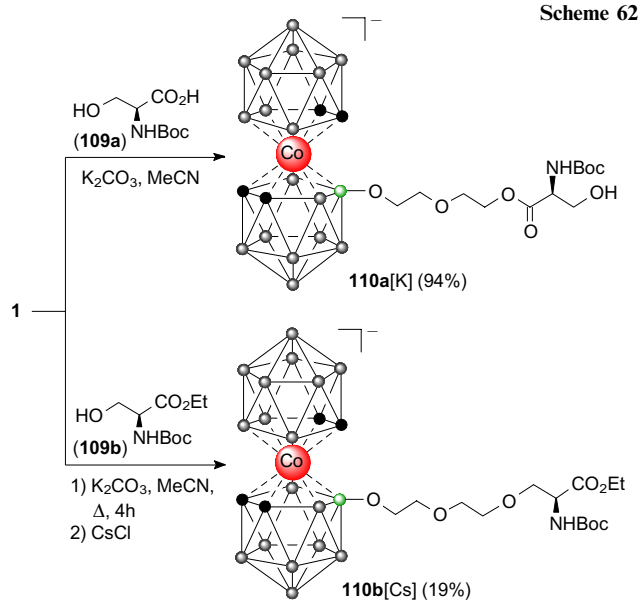
An importance of the proper choice of protecting groups was demonstrated using L-tyrosine as an example. The reaction of *N*-Boc-L-tyrosine (Boc is *tert*-butoxycarbonyl) with compound **1** in acetonitrile in the presence of K_2CO_3 leads exclusively to the oxonium ring opening with the carboxylate ion. Under the same conditions, the reaction of *N*-(trifluoroacetyl)-L-tyrosine ethyl ester (**106a**) gave the corresponding tyrosine ethyl ester based on cobalt bis(dicarbollide) — compound **107a**. However, an attempt to remove protecting groups in this compound failed. The success was achieved only in the case of (4*S*)-3-*tert*-butoxycarbonyl-4-(4-hydroxybenzyl)-5-oxazolidinone (**106b**), the reaction of which with complex **1** gave protected amino acid **107b**. The treatment of the latter with a solution of NaOH in aqueous ethanol at room temperature led to the hydrolysis of the aminal acetal moiety, and the subsequent treatment with $SOCl_2$ in ethanol resulted in the removal of Boc protection to form boron-containing tyrosine **108** isolated in the *N*-protonated form (Scheme 61).[121]

A similar reaction of complex **1** with *N*-Boc-L-serine (**109a**) in acetonitrile in the presence of K_2CO_3 involves the oxonium ring opening with carboxylate to form ester **110a**; in the case of alkoxide ions, *N*-Boc-L-serine ethyl ester (**109b**) is required, and the reaction affords the corresponding protected amino acid **110b** (Scheme 62).[121]

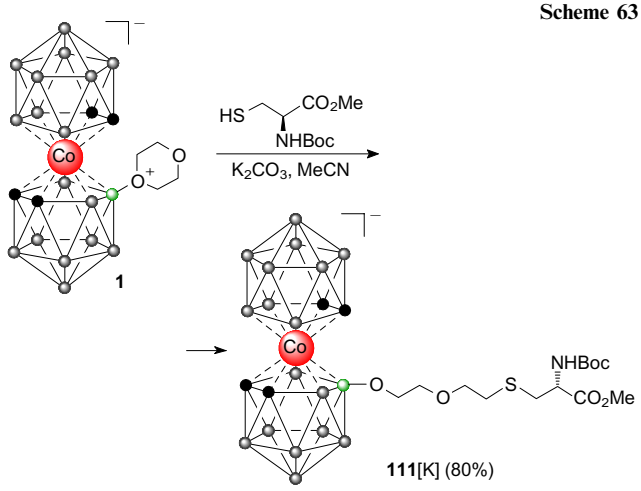
Scheme 61



Scheme 62



Scheme 63



The reaction of compound **1** with *N*-Boc-cysteine methyl ester in acetonitrile in the presence of K_2CO_3 produced boron-containing protected amino acid **111** (Scheme 63).[78]

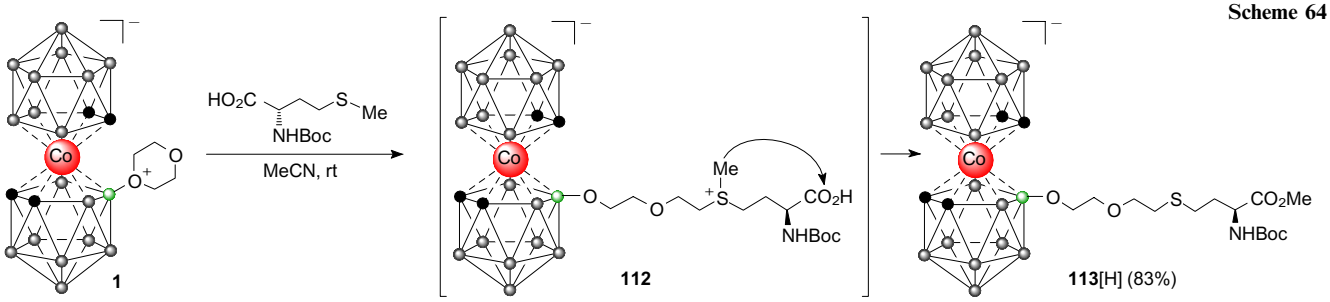
An attempt was made to synthesize an analogue of *S*-methylmethionine [$Me_2S^+CH_2CH_2CH(NH_2)COO^-$], a sulfur-containing compound essential for plant metabolism, which is involved in the methylation and regulation of methionine biosynthesis.[122, 123] However, the reaction of the dioxane derivative of cobalt bis(dicarbollide) **1** with *N*-Boc-methionine in acetonitrile at room temperature gave methyl ester **113** rather than the expected sulfonium derivative of methionine **112**. Apparently, this compound is produced *via* the intramolecular methylation of the carboxyl function of amino acid **112**, generated in the first step, with the sulfonium methyl group (Scheme 64).[104]

Natural peptides exhibit high biological activity and are involved in the regulation of different physiological processes. Cobalt bis(dicarbollide) conjugates with thymosin β4 (Tβ4), a therapeutic peptide with pleiotropic activity, were described. This type of activity is responsible for the enhanced regeneration and healing of injured tissues,[124, 125] for example, cardiac repair after myocardial infarction.[126] It is worth noting that Tβ4 contains 12 free carboxy groups distributed along the amino acid sequence. The solid-phase synthesis by the reaction of derivative **1** with carboxy groups of Tβ4 gave conjugates **114**, in which metallacarborane clusters are bound to thymosin through ester bonds (Scheme 65). It was found that the modification of amino acids at particular sites of thymosin causes a significant increase in its anti-inflammatory activity after cardiac rupture and supports survival of cardiomyocytes (cardiac muscle cells).[127] Besides, this modification enhances their promigratory effect on human fibroblast cells in wound healing.[128]

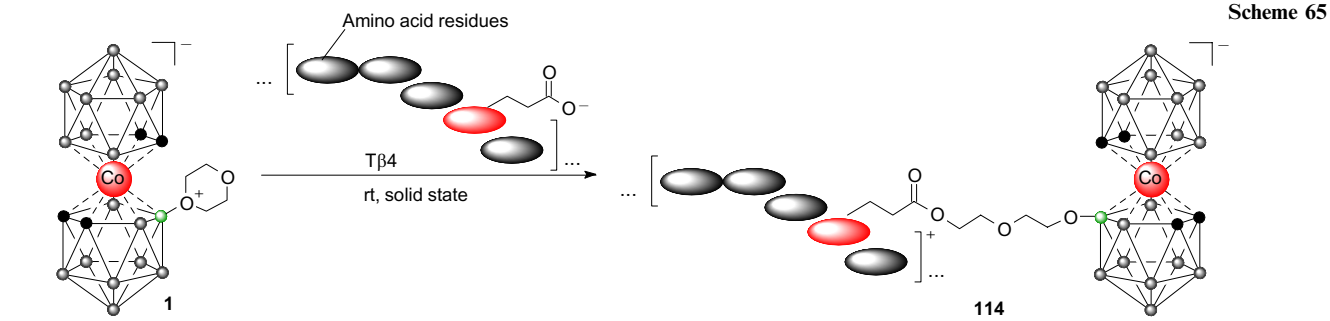
3.2. Phthalocyanines and porphyrins

Due to the unique properties of porphyrins and phthalocyanines, such as their selective accumulation in cancer tissues and the emission of far-red fluorescence, these compounds are good transport systems for the targeted delivery of boron clusters to tumour sites. Hence, these

Scheme 64



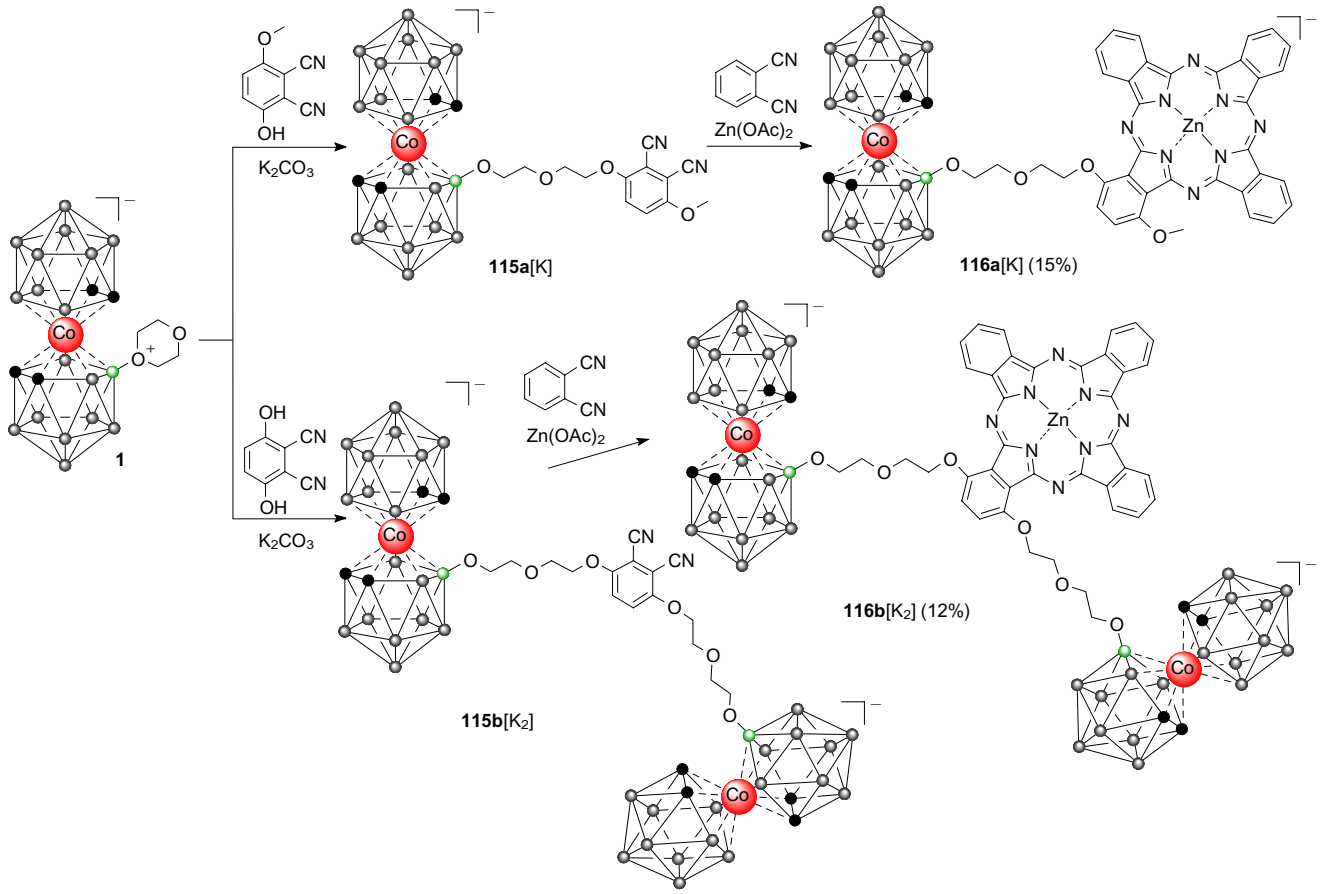
Scheme 65



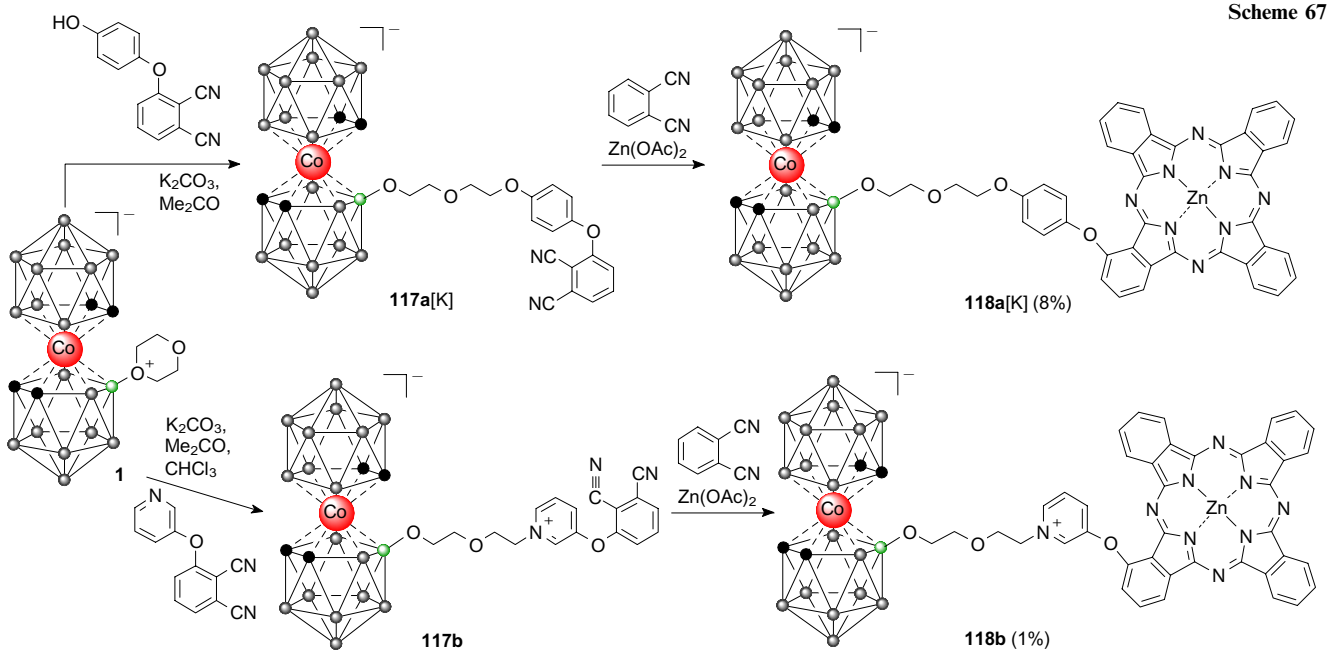
compounds can be used both in BNCT [39,41–45] and photodynamic therapy (PDT) [129–131] of cancer or their combination. Various boron-containing phthalocyanines and also synthetic and natural porphyrins were described.[132–140] This Section addresses boron-containing phthalocyanines and synthetic and natural porphyrins bearing cobalt and iron bis(dicarbollides) $[3,3'\text{-}M(1,2\text{-}C_2B_9H_{11})_2]^-$ (M = Co, Fe) as boron clusters.

Phthalocyanines containing cobalt bis(dicarbollide) as a substituent can be synthesized using the following two approaches:

Scheme 66



Scheme 67



— the synthesis of a boron-containing phthalonitrile derivative followed by its tetramerization (phthalonitrile method);

— the introduction of a boron cluster into pre-functionalized phthalocyanine (phthalocyanine method).

The phthalonitrile method was applied to prepare a series phthalocyanines containing one or two cobalt bis(dicarbollide) units. Boron-containing phthalonitriles **115a**,**b** were synthesized by the nucleophilic dioxane ring opening of compound **1** with 3,6-dihydroxyphthalonitrile or its monomethylated analogue in the presence of K_2CO_3. The reaction of the latter with a 40-fold excess of phthalonitrile and zinc acetate in quinoline at 220 °C affords the corresponding phthalocyanines **116a**,**b** (Scheme 66).[141]

The reactions of compound **1** with 3-(4-hydroxyphenoxy)phthalonitrile and 3-pyridylphthalonitrile give phthalonitriles **117a**,**b**, and the template cyclotetramerization of the latter with a 30-fold excess of phthalodinitrile and zinc acetate produces phthalocyanines **118a**,**b** (Scheme 67).[142]

The introduction of a boron cluster at the peripheral position of the phthalocyanine macrocycle has almost no effect on the degree of singlet oxygen generation. However, the use of this approach is limited because of very low yields of boron-containing phthalocyanines.

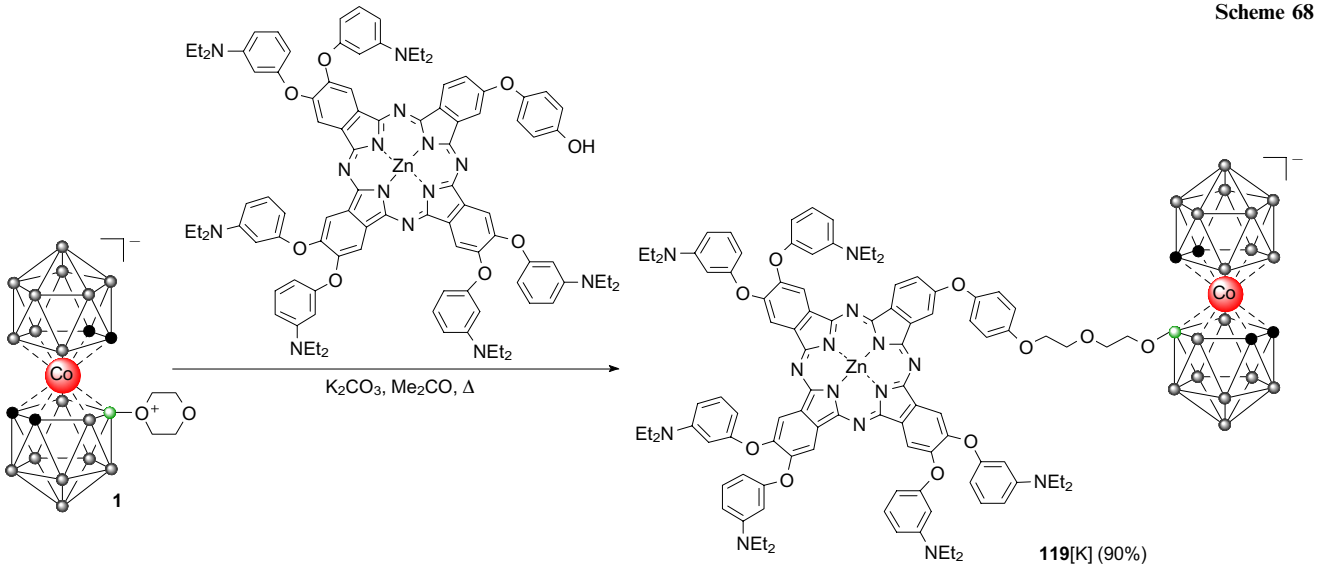
Several boron-containing phthalocyanines were synthesized by the phthalocyanine method. Thus, the reaction of dioxane derivative **1** with phenol-containing phthalocyanine in acetone in the presence of K_2CO_3 produced phthalocyanine **119** (Scheme 68).[143] It is worth noting that under these conditions, *N*,*N*-dimethylaniline groups are not involved in the oxonium ring opening.

The reaction of complex **1** with phthalocyanine containing four phenol groups at the macrocycle periphery in acetone in the presence of K_2CO_3 afforded phthalocyanine **120** bearing four metallacarborane units bound to the macrocycle through diethylene glycol spacers (Scheme 69).[144]

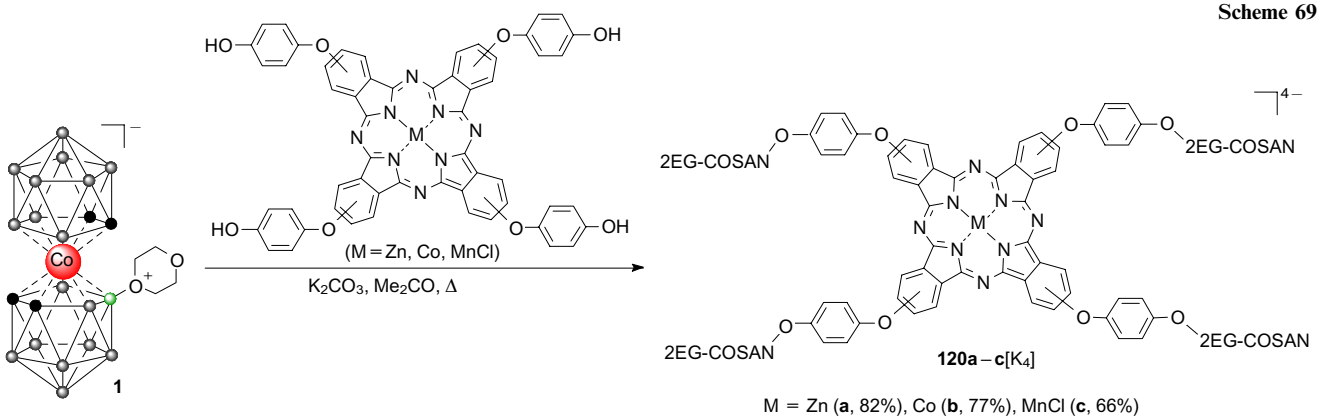
Phthalocyanine **121** decorated by eight metallacarborane units was synthesized from compound **1** and phthalocyanine bearing four resorcinol substituents in acetonitrile in the presence of K_2CO_3 (Scheme 70).[145] It was found that compound **121** can accumulate in human glioblastoma cells (GL-6), but its concentration was insufficient for effective BNCT.

Cobalt bis(dicarbollide) was conjugated with synthetic porphyrins *via* the ring opening reaction of dioxane derivative **1** with *N*- and *O*-nucleophiles. For instance, the reaction with 5,10,15,20-tetraarylporphyrins, in which one to four phenyl groups are replaced by pyridyl rings, afforded zwitterionic conjugates **122a**–**e** (Scheme 71).[74, 146] It was demonstrated that porphyrins **122** can penetrate the HEp2 epithelial cells (human larynx adenocarcinoma) and accumulate mainly in lysosomes. The accumulation depends both on the number of metallacarborane units bound to the

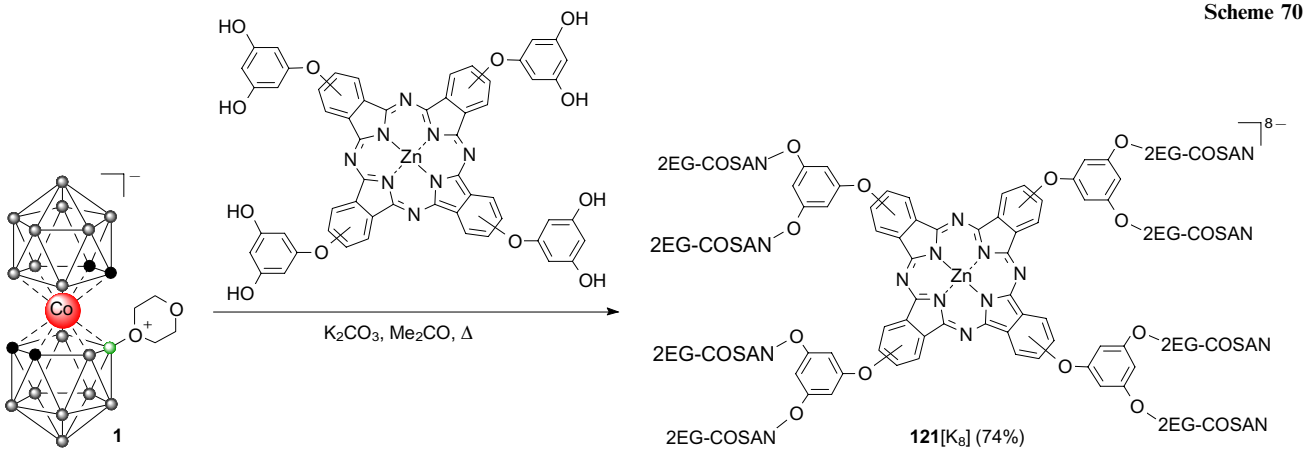
Scheme 68



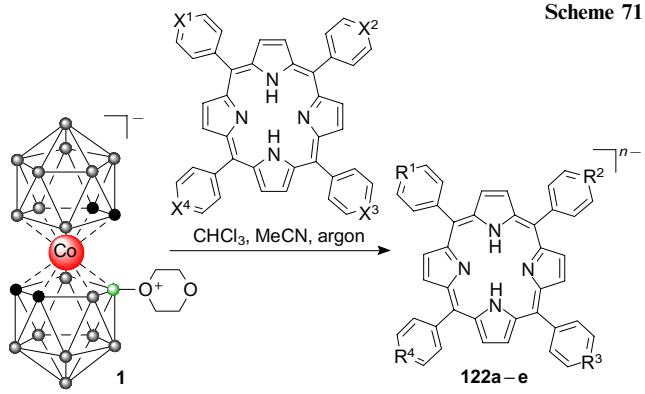
Scheme 69



Scheme 70



Scheme 71



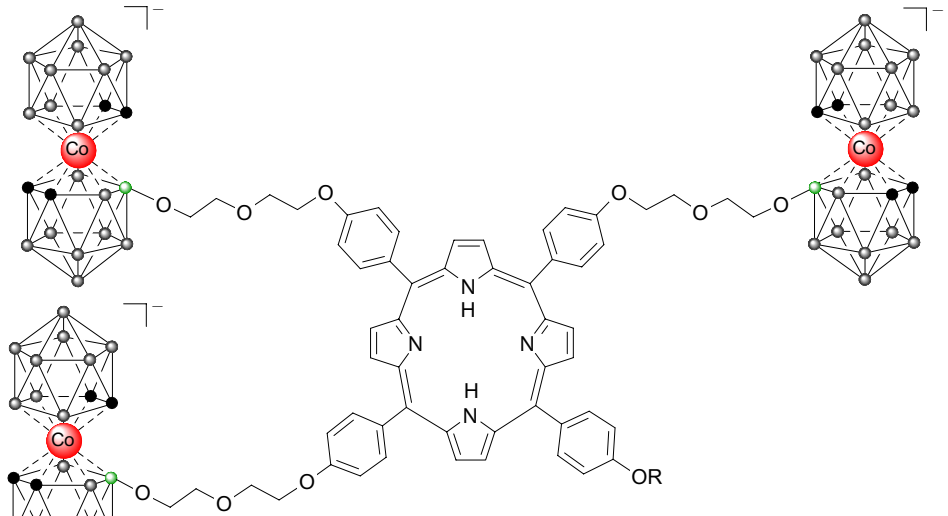
X^1 = N, X^2 = X^3 = X^4 = R^2 = R^3 = R^4 = CH,
R^1 = N^+–2EG-COSAN, *n* = 1 (**a**, 98%);
X^1 = X^2 = N, X^3 = X^4 = R^3 = R^4 = CH,
R^1 = R^2 = N^+–2EG-COSAN, *n* = 2 (**b**, 91%);
X^1 = X^3 = N, X^2 = X^4 = R^2 = R^4 = CH,
R^1 = R^3 = N^+–2EG-COSAN, *n* = 2 (**c**, 91%);
X^1 = X^2 = X^3 = N, X^4 = CH,
R^1 = R^2 = R^3 = N^+–2EG-COSAN, *n* = 3 (**d**, 90%);
X^1 = X^2 = X^3 = X^4 = N,
R^1 = R^2 = R^3 = R^4 = N^+–2EG-COSAN, *n* = 4 (**e**, 88%)

porphyrin macrocycle and their location. Thus, the accumulation of porphyrin **122e** bearing four metallacarborane units is higher than that of porphyrin **122a** with one metallacarborane unit, while porphyrin **122b** containing metallacarborane units in adjacent positions showed higher accumulation than porphyrin **122c** with substituents in the opposite positions of the macrocycle.

The reaction of complex **1** with 5-4-aminophenyl)-10,15,20-triphenylporphyrin giving a mixture of mono- and disubstituted products (**123** and **124**, respectively; see Scheme 72) [147] is another example of the synthesis of boron-containing porphyrins using the ring opening of oxonium derivatives with *N*-nucleophiles.

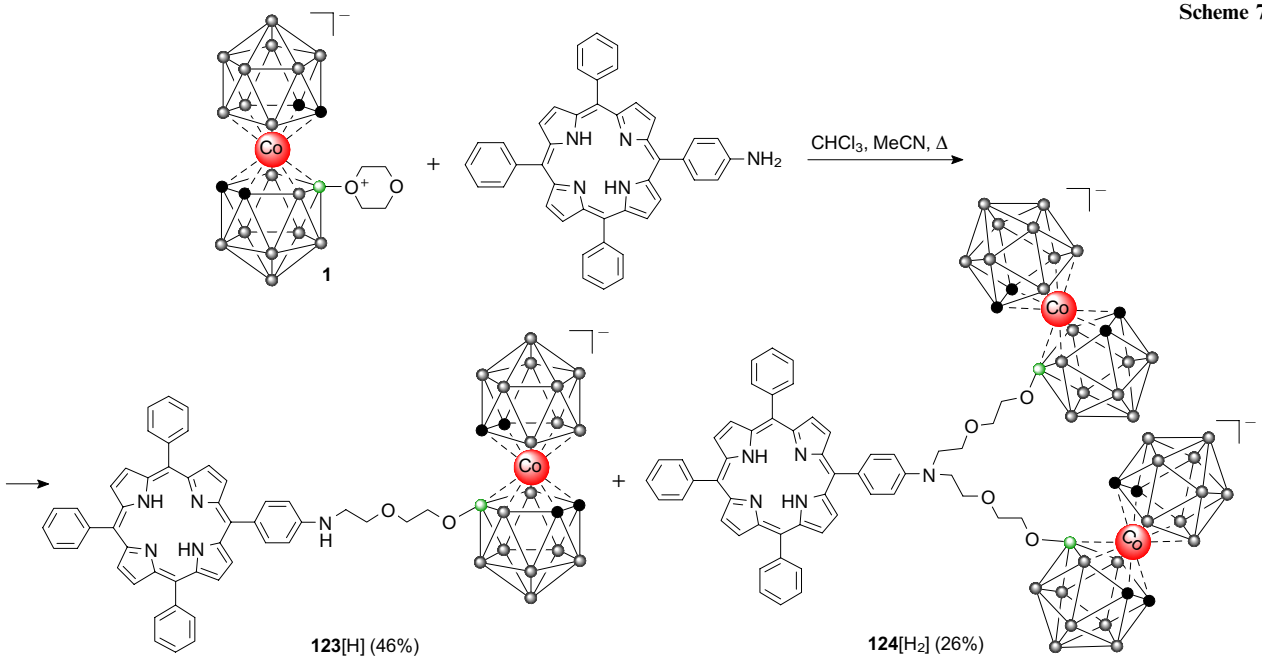
It should be noted that in the absence of peripheral nucleophilic centres in porphyrin, the oxonium ring of derivative **1** can be cleaved with the pyrrole moiety of the macrocycle to form conjugates **125**. In the presence of a base, these conjugates can be transformed into products **126** (Scheme 73).[147] These conjugates show different degrees of distortion of the porphyrin macrocycle, exerting a strong effect on their spectroscopic and electrochemical properties. In particular, the cores of *N*-substituted conjugates exhibit significant fluorescence quenching compared to that of unsubstituted macrocycles.

Scructures 128

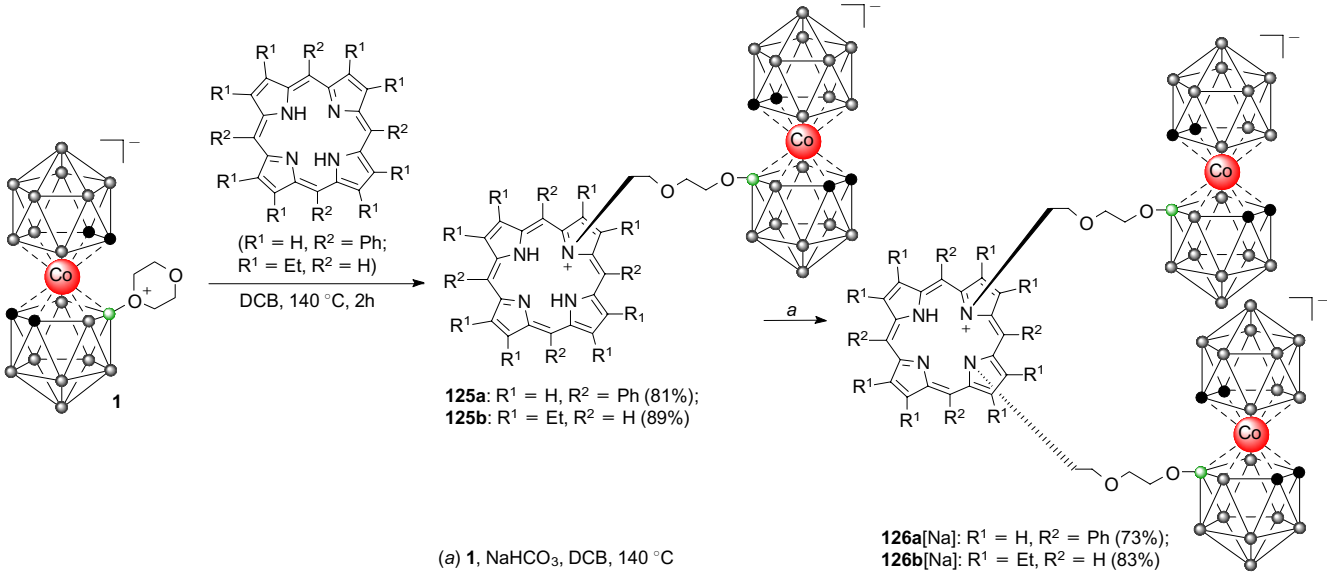


128a[K_3]: R = Me (93%); **128b**[K_3]: R = $CH_2CO_2Bu^t$ (91%);
128c[K_3]: R = $CH_2C(O)NH(CH_2CH_2O)_7CH_2CH_2NHC(O)CH_2OCH_2C(O)NH$-peptide-$NH_2$ (8%)

Scheme 72



Scheme 73

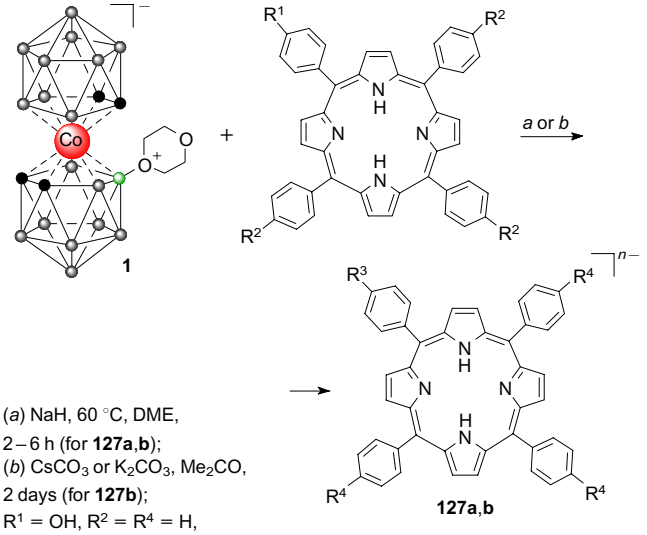


The ring opening reactions of the dioxane derivative of cobalt bis(dicarbollide) **1** with different hydroxy derivatives of 5,10,15,20-tetraphenylporphyrin are more commonly used. Thus, the reactions of compound **1** with 5-(4-hydroxyphenyl)-10,15,20-triphenyl- and 5,10,15,20-tetrakis(4-hydroxyphenyl)porphyrins in the presence of a base afford porphyrins **127a**,**b** bearing one and four metallacarborane units, respectively (Scheme 74).[74, 146, 148] Besides, porphyrin **127b** can be synthesized by the condensation of the appropriate aldehyde with pyrrole under Lindsey conditions ($BF_3 \cdot Et_2O$ as the catalyst and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as the oxidant); however, the yield of the products was at most 20%. Porphyrins **127** are effective HIV-1 protease inhibitors *in vitro*,[148] the presence of boron clusters in the molecule playing a key role. Thus, the activity of derivative **127b** bearing four cobalt bis(dicarbollide) units is four times higher than that of conjugate **127a** with one boron cluster.

A similar reaction using monosubstituted 5,10,15,20-tetrakis(4-hydroxyphenyl)porphyrins, upon activation of hydroxy groups with potassium carbonate, afforded boron-containing porphyrins **128a**–**c** bearing three metallacarborane units. Porphyrin **128c** containing the human immunodeficiency virus HIV-1 Tat 48–60 peptide sequence showed good accumulation in the human carcinoma cells HEp2.[149]

Boron-containing porphyrins **129a**–**e** bearing two to eight metallacarborane units, which are linked to the macrocycle by a flexible diethylene glycol spacer, were synthesized using the same approach and varying the number of oxygen nucleophilic centres in 5,10,15,20-tetraphenylporphyrin (Scheme 75). Figure 5 shows the molecular structure of conjugate **129c**. The accumulation of these

Scheme 74



(*a*) NaH, 60 °C, DME,
2–6 h (for **127a**,**b**);
(*b*) $CsCO_3$ or K_2CO_3, Me_2CO,
2 days (for **127b**);
R^1 = OH, R^2 = R^4 = H,
R^3 = O–2EG-COSAN (**a**[Na], 72%), *n* = 1;
R^1 = R^2 = OH, R^3 = R^4 = O–2EG-COSAN (**b**[Na_4/Cs_4/K_4], 75–85%), *n* = 4

porphyrins in the human epithelial cell line HEp2 depends on the number of metallacarborane units at the porphyrin periphery and their mutual arrangement. Conjugate **129b** bearing four metallacarborane units in adjacent positions and conjugate **129d** bearing six metallacarborane units showed the highest intracellular accumulation. Lysosomes are the major subcellular localization sites of conjugates **129**.[150]

There are the following three main methods for the conjugation of natural chlorins and bacteriochlorins with cobalt bis(dicarbollide):

— the nucleophilic dioxane ring opening of a cobalt bis(dicarbollide) derivative;

— the Cu^I-catalyzed 1,3-dipolar cycloaddition of terminal alkynes to azides;

— the Pd-catalyzed C–C bond formation.

Bacteriochlorophyll *a*–cobalt bis(dicarbollide) conjugates were synthesized using *N*-aminobacteriopurpurinimide. Due to the presence of the exocyclic amino group in the latter compound, target conjugates can be prepared by

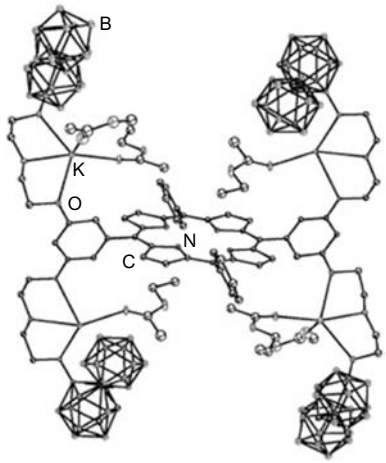


Figure 5. Crystal structure of **129c**[K_4]$(EtOAc)_6$.[150] Published with the permission of Wiley. (Hydrogen atoms are omitted for clarity.)

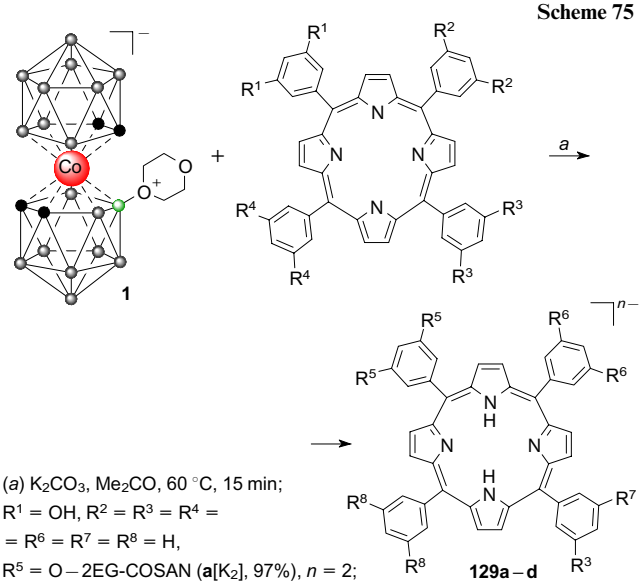
two methods. One approach is based on the modification of metallacarborane with a carboxy group followed by the formation of an amide bond [C(O)–NH] between the boron cluster and the macrocycle. Another approach is based on the formation of a conjugate *via* the direct oxonium ring opening of derivative **1** with the NH_2 group of *N*-aminocycloimide. The condensation of *N*-aminobacteriopurpurinimide with boron-containing acid **21c** using dicyclohexylcarbodiimide (DCC) in the presence of 4-dimethylaminopyridine (DMAP) affords conjugate **130** (Scheme 76).[75] A more efficient approach involves the nucleophilic ring opening of complex **1** with the *exo*-amino group of bacteriopurpurinimide in the presence of diisopropylethylamine (DIPEA) as a non-nucleophilic base to form conjugate **131** bearing two metallacarborane units (see Scheme 76).[93]

The chlorin e_6–cobalt bis(dicarbollide) conjugate was synthesized by the [3 + 2]-dipolar cycloaddition of azides to alkynes. Thus, the reaction of azide **70a** involving the terminal triple bond of the chlorin e_6-based propargyl-containing zinc complex in the presence of CuI and DIPEA followed by the demetallation gave conjugate **132** (Scheme 77). This conjugate can accumulate in human lung adenocarcinoma cells (A549); however, its intracellular concentration is insufficient for BNCT applications.[151]

The cross-coupling of alkynylated cobalt bis(dicarbollide) **14a** with *p*-iodophenyl derivatives of chlorin e_6 and purpurinimide in a mixture of benzene and DIPEA in the presence of $Pd_2(dba)_3$ (dba is dibenzylideneacetone) and PPh_3 gave conjugates **133a**,**b** (Scheme 78). Conjugates **133** are capable of penetrating the A549 cell line and accumulating in the cytoplasm.[152]

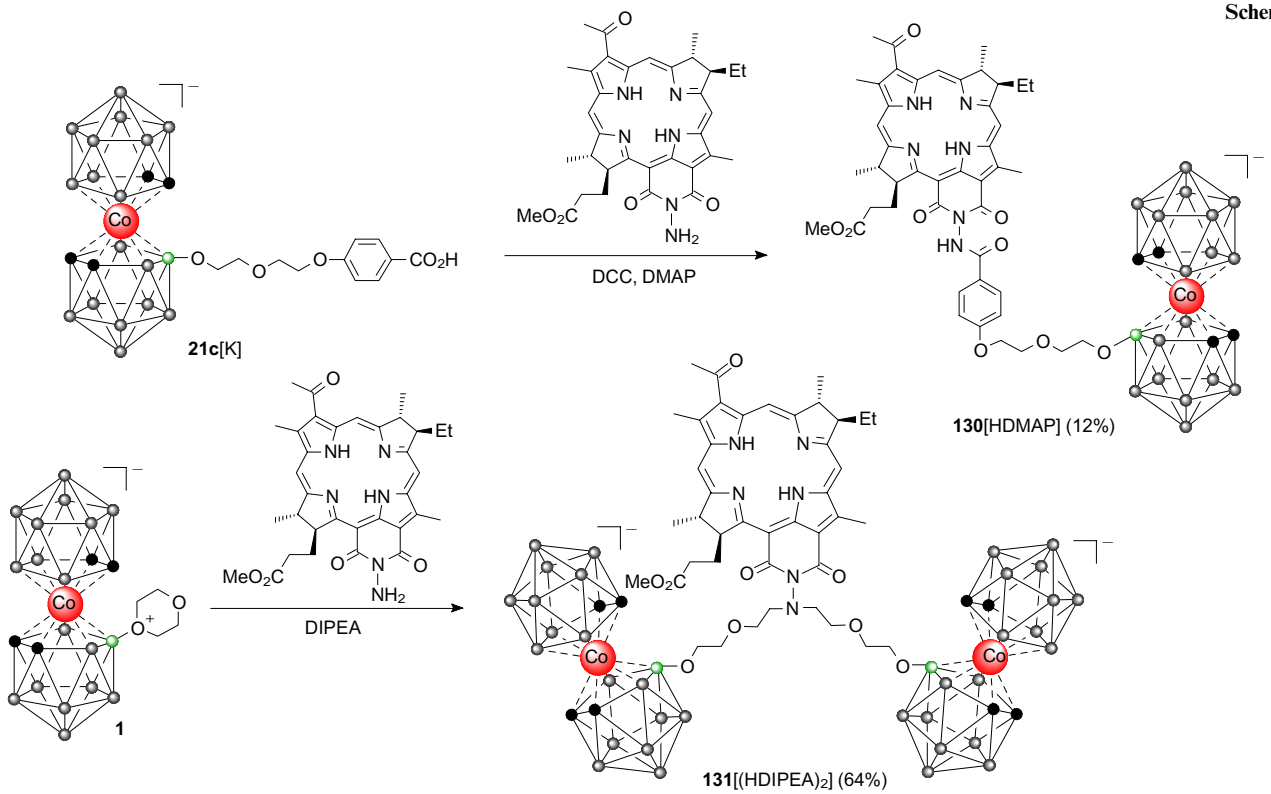
The oxonium ring opening of the dioxane derivative of cobalt bis(dicarbollide) with amino groups of modified

Scheme 75

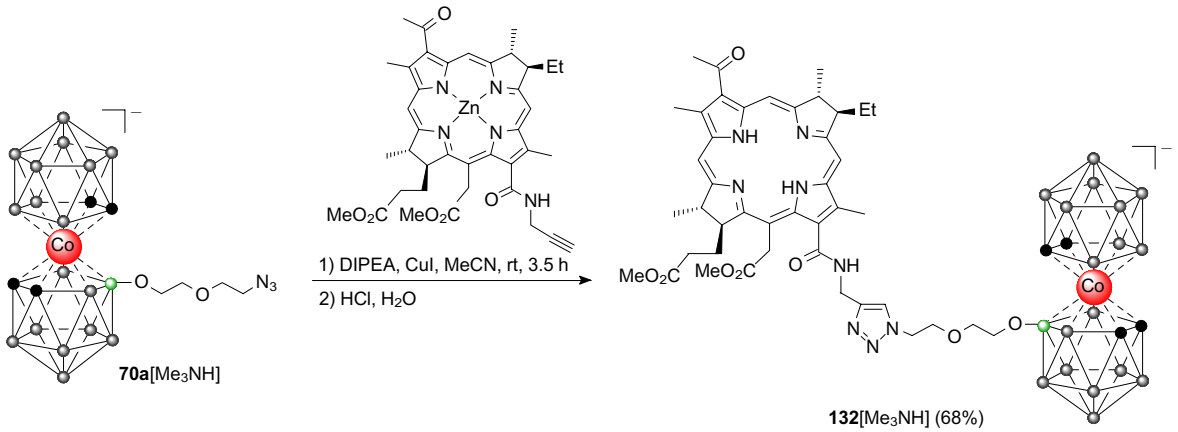


(*a*) K_2CO_3, Me_2CO, 60 °C, 15 min;
R^1 = OH, R^2 = R^3 = R^4 =
= R^6 = R^7 = R^8 = H,
R^5 = O–2EG-COSAN (**a**[K_2], 97%), *n* = 2;
R^1 = R^2 = OH, R^3 = R^4 =
= R^7 = R^8 = H, R^5 = R^6 = O–2EG-COSAN (**b**[K_4], 91%), *n* = 4;
R^1 = R^3 = OH, R^2 = R^4 = R^6 = R^8 = H,
R^5 = R^7 = O–2EG-COSAN (**c**[K_4], 90%), *n* = 4;
R^1 = R^2 = R^3 = OH,
R^4 = R^8 = H, R^5 = R^6 = R^7 = O–2EG-COSAN (**d**[K_6], 93%), *n* = 6;
R^1 = R^2 = R^3 = R^4 = OH, R^5 = R^6 = R^7 =
= R^8 = O–2EG-COSAN (**e**[K_8], 95%), *n* = 8

Scheme 76



Scheme 77

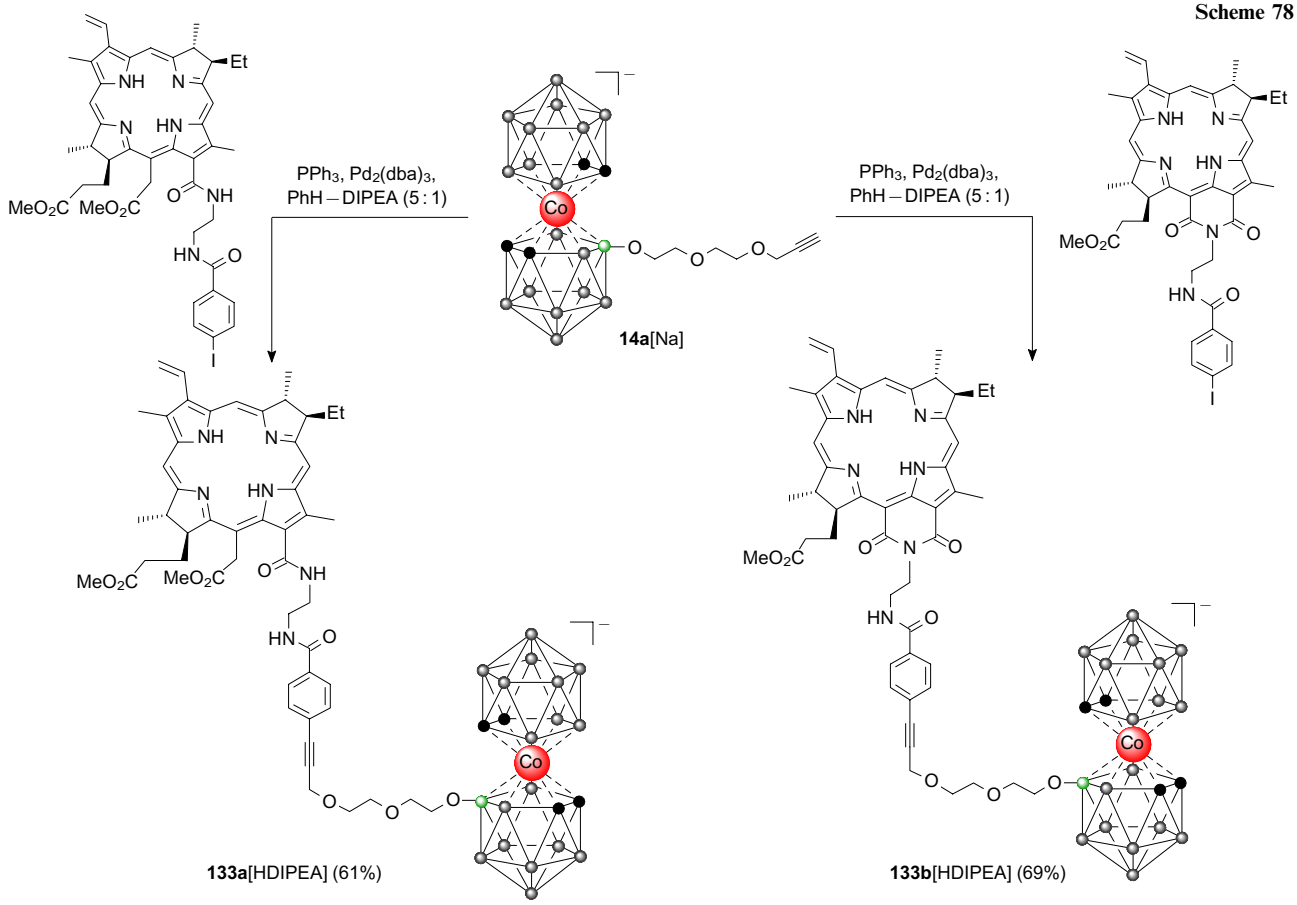


natural chlorins e_6 gave the corresponding boron-containing conjugates **134a–d** and **135a–c** (Scheme 79).[93] The structures of these conjugates depend on the presence of a non-nucleophilic base in the reaction mixture. The reaction performed in the absence of a base allows the synthesis of target conjugates **134** bearing one metallacarborane unit, whereas in the presence of DIPEA, the reaction affords conjugates **135** with two metallacarborane units. The selectivity of the *in vitro* accumulation of these compounds in human lung adenocarcinoma cells (A549) depends on two factors: the number of metallacarborane units in the conjugate molecule and the length of the spacer between chlorin and the metallacarborane unit. Compounds **134** bearing one boron cluster are characterized by significantly higher cellular accumulation ratios‡ compared to those of derivatives **135** with two boron clusters. This is apparently due to a lower total charge of the molecule, which enhances its transport across the cell membrane. For conjugates **134** and **135** bearing the same number of boron clusters, the cellular accumulation ratio increases with increasing spacer lengths. Chlorin e_6 conjugate **134c** with one metallacarborane unit that is linked to the macrocycle by the longest spacer ($n = 3$) proved to be the most promising for accumulation in tumour cells. This conjugate showed the maximum accumulation ratio in the *in vitro* assay in tumour cells (80 : 1).[153,154]

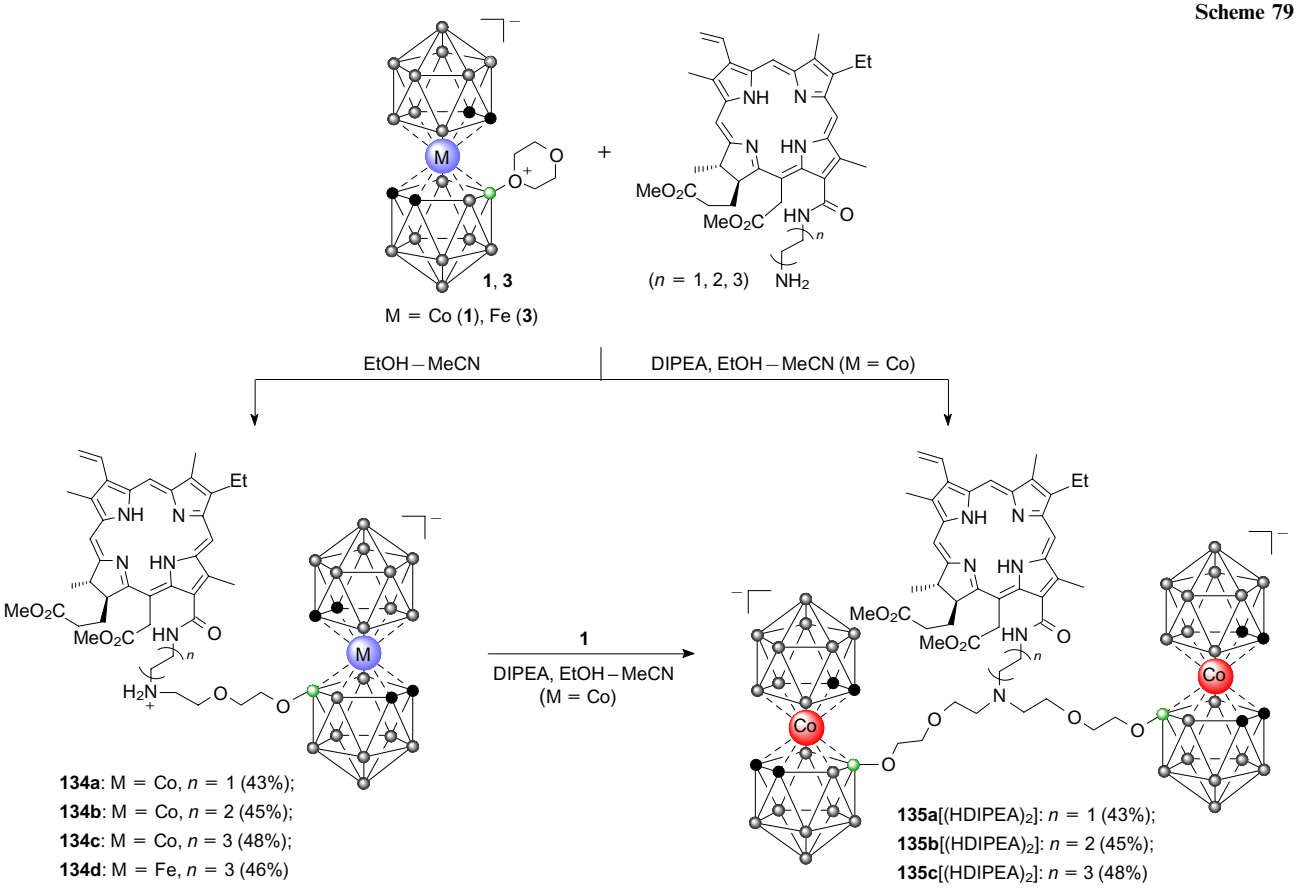
In vivo assays using the transplantable murine colon carcinoma model (CT-26) demonstrated that compound **134c** can selectively accumulate in oncocytes with a tumour to normal tissue ratio of 3 : 1. Compound **134c** showed low accumulation in skin cells, thereby suggesting its low phototoxicity and possible use under light conditions. Good fluorescence of chlorin allows the control of the boron concentration in tissues and organs. The results of bio-

‡ The cellular accumulation ratio is the maximum ratio of the intracellular concentration of the compound to its concentration in the incubation medium.

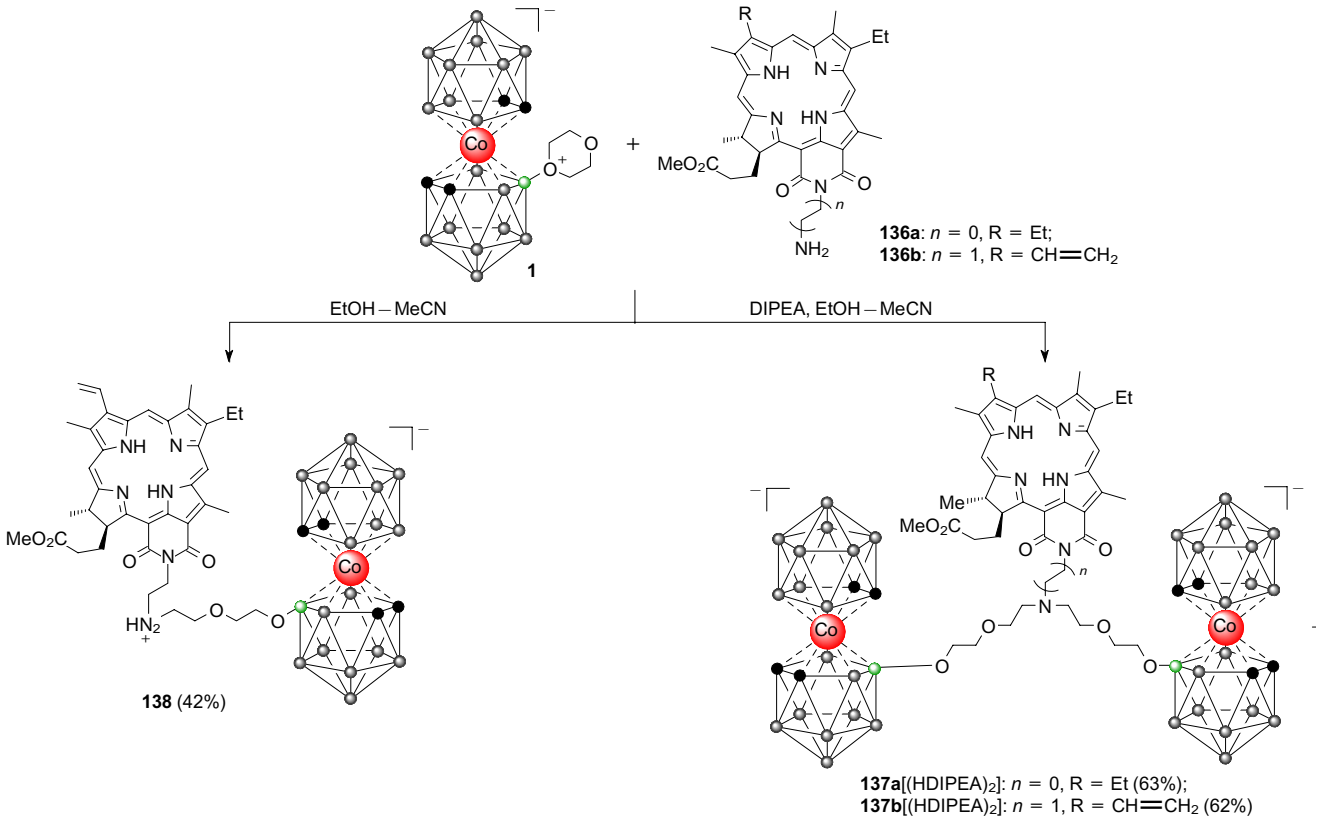
Scheme 78



Scheme 79



Scheme 80



logical assays provide evidence that boron-containing conjugate **134c** is a promising agent for the treatment of malignant tumours by PDT and BNCT.[155, 156] An analogue of compound **134c** based on iron bis(dicarbollide) (**134d**) was synthesized using dioxane derivative **3** as the starting compound (see Scheme 79). Conjugate **134d** efficiently accumulates in rat glioma cells (C6), providing the delivery of $> 10^9$ boron atoms per cell, which meets the requirements for effective BNCT, causes photoinduced death of 80% of the C6 cell line at a concentration of 80 nM and is not toxic to cells in the absence of activating factors.[157]

Another group of conjugates was synthesized using cyclic imides **136** as the chlorin unit. In these imides, the terminal amino group is either directly attached to the nitrogen atom of exocycle 4 (**136a**) or is spaced from this atom (**136b**). The reaction of *N*-aminocycloimide **136a** with complex **1** in the presence of DIPEA affords disubstituted product **137a**, whereas in the absence of the base, the reaction does not take place. A somewhat different reaction pathway was observed for *N*-(aminoethyl)cycloimide **136b**. The reaction of compound **136b** with derivative **1** in the presence of DIPEA is accompanied by the addition of two boron clusters to form conjugate **137b**, whereas this reaction in the absence of the base produces monosubstituted cycloimide **138**. The difference in the reactivity of cycloimides **136a**,**b** can be attributed to low nucleophilicity of the amino group directly attached to the imide nitrogen atom in the former compound (Scheme 80).[93]

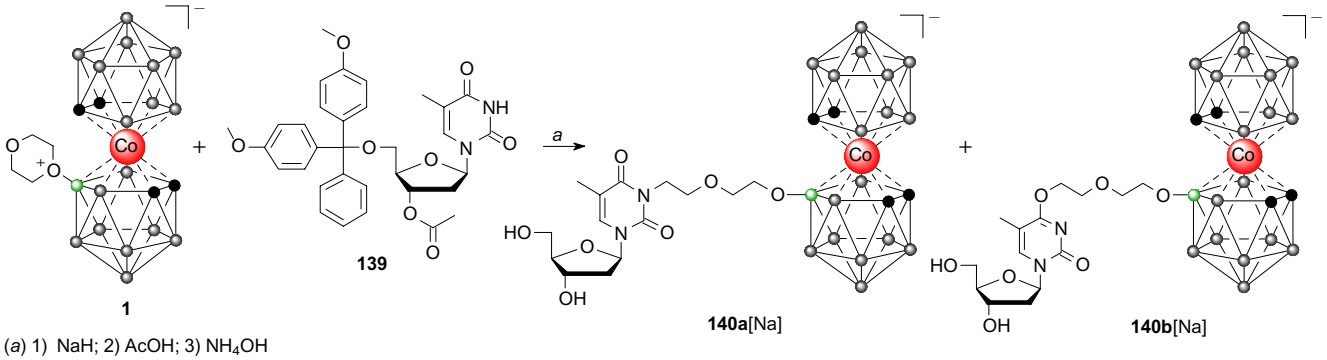
3.3. Nucleosides and nucleotides

Boron-containing nucleosides and nucleotides are commonly used in biology and medicines.[158] They are considered as antiviral agents, antisense RNA agents, molecular probes for diagnosis of genetic diseases, lipophilic pharmacophores, electrochemical and IR probes; the methods for the synthesis of these compounds are described in reviews.[159–162] Boron neutron capture therapy[163] is an important area of potential use of boron-containing nucleosides because nucleosides can selectively accumulate in tumour cells, being converted into DNA and RNA nucleotides in dividing cells.[164–166] The major drawback of carborane-containing nucleosides is their very high lipophilicity, which hinders the study of their interaction with phosphorylating enzymes and interferes with the evaluation of *in vitro* activity at the cellular level. Metallacarborane-containing nucleosides with different hydrophilic substituents were synthesized in order to overcome this drawback. This Section considers examples of the synthesis of nucleosides modified with cobalt and iron bis(dicarbollides), in which the boron cluster is attached to a carbohydrate residue or to a heterocyclic base.

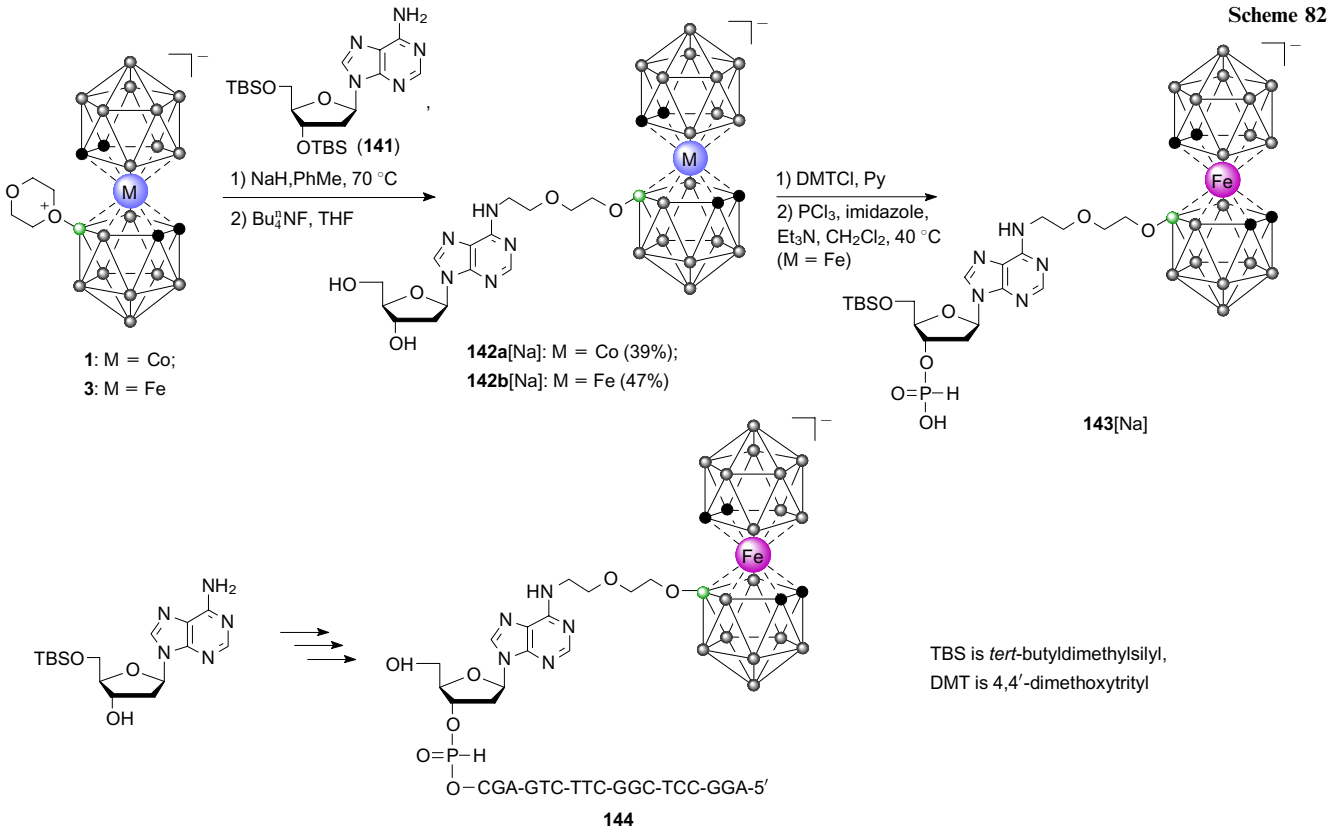
First metallacarborane-containing nucleosides were synthesized in 2003.[167] The reaction of 2′-deoxythymidine **139** bearing a protected carbohydrate residue with complex **1** in the presence of NaH affords two protected alkylation products at the N^3 and O^4 positions of the thymidine ring. The removal of the acetyl and trityl protection from the 3′- and 5′-OH groups gives two isomers, 2′-deoxythymidine–metallacarborane conjugates **140a**,**b** in a molar ratio of 1 : 2 (Scheme 81).

In subsequent studies, this research group[168, 169] reported the two-step synthesis starting from 3′,5′-(*O*,*O*-dimethyl-*tert*-butylsilyl)-2′-deoxyadenosine (**141**) and dioxane complexes **1** and **3** to form 2′-deoxyadenosine–cobalt and iron bis(dicarbollides) conjugates **142a**,**b**, in which the boron cluster is attached to the nucleoside at the N^6-amino group. Derivative **142b** was used to synthesize adenosine 5′-monophosphate (AMP) **143** (Scheme 82).[170] In the cited

Scheme 81



Scheme 82



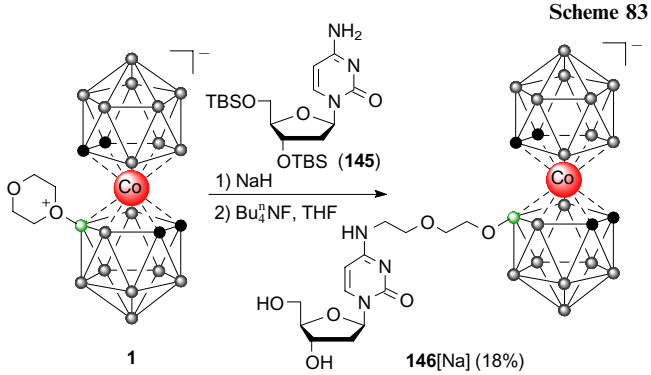
study, the authors developed an efficient method for the synthesis of oligonucleotides, in which iron bis(dicarbollide) complex **144** is immobilized on a solid support *via* the H-phosphonate method (see Scheme 82).

The ring opening of derivative **1** with 3′,5′-(*O*,*O*-dimethyl-*tert*-butylsilyl)-2′-deoxycytidine (**145**) affords 2′-deoxycytidine–cobalt bis(dicarbollide) conjugate **146** as the only N^4-alkylated product (Scheme 83).[168]

However, the reaction of compound **1** with protected 2′-deoxyguanosine **147a** or 2′-deoxythymidine **147b** in the presence of NaH in toluene produces a mixture of three isomeric products due to the alkylation at the N and O positions of both the purine and pyrimidine bases. The deprotection gives products **148a–c** and **149a–c** (Scheme 84).[168]

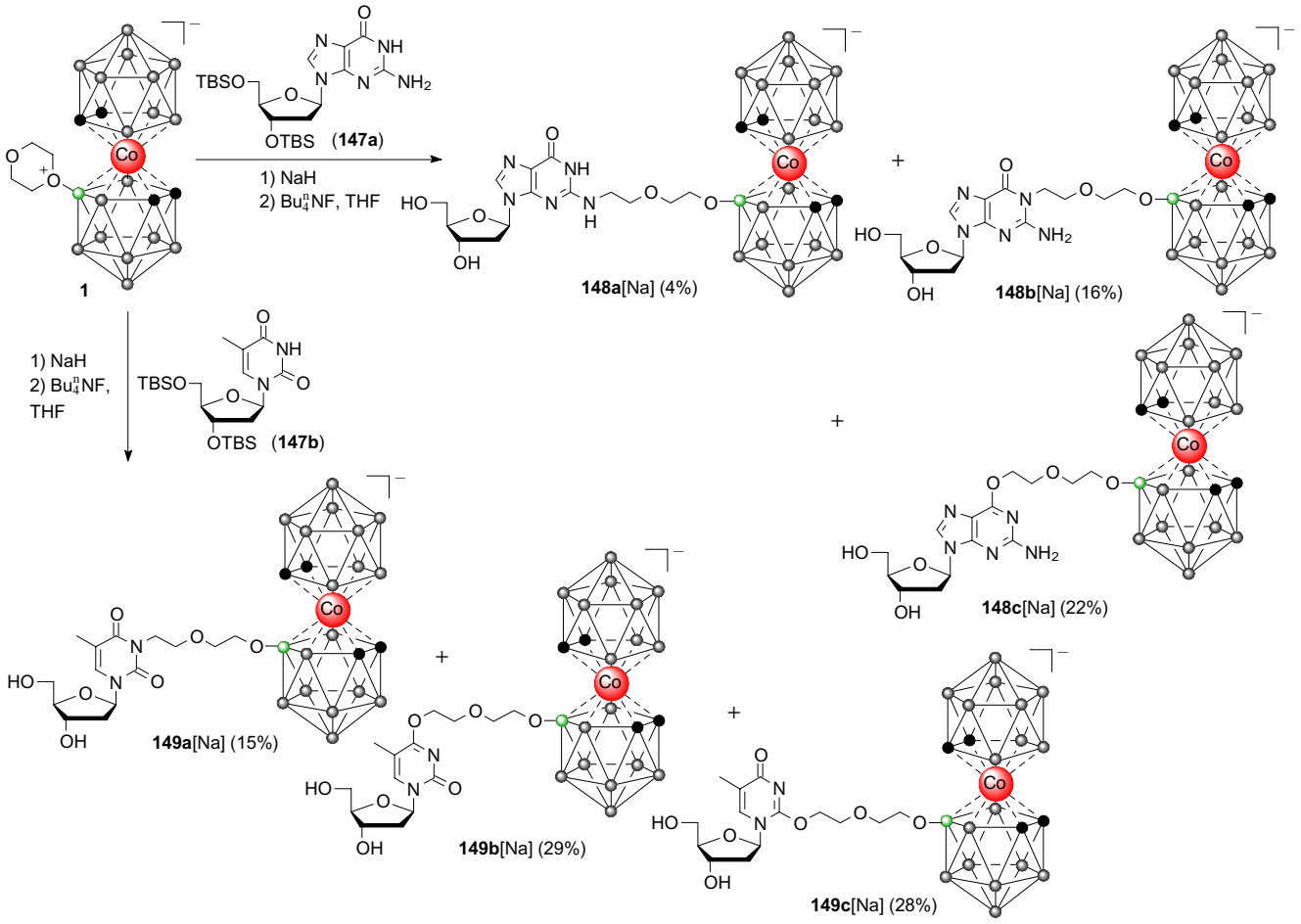
The Cu^I-catalyzed 1,3-dipolar cycloaddition reaction[171] of boron-containing azides **70** with 2′-*O*-propargyluridine (**150a**) and 3-*N*-(pent-4-yn-1-yl)thymidine (**150b**) in the presence of aqueous copper sulfate and sodium ascorbate

Scheme 83

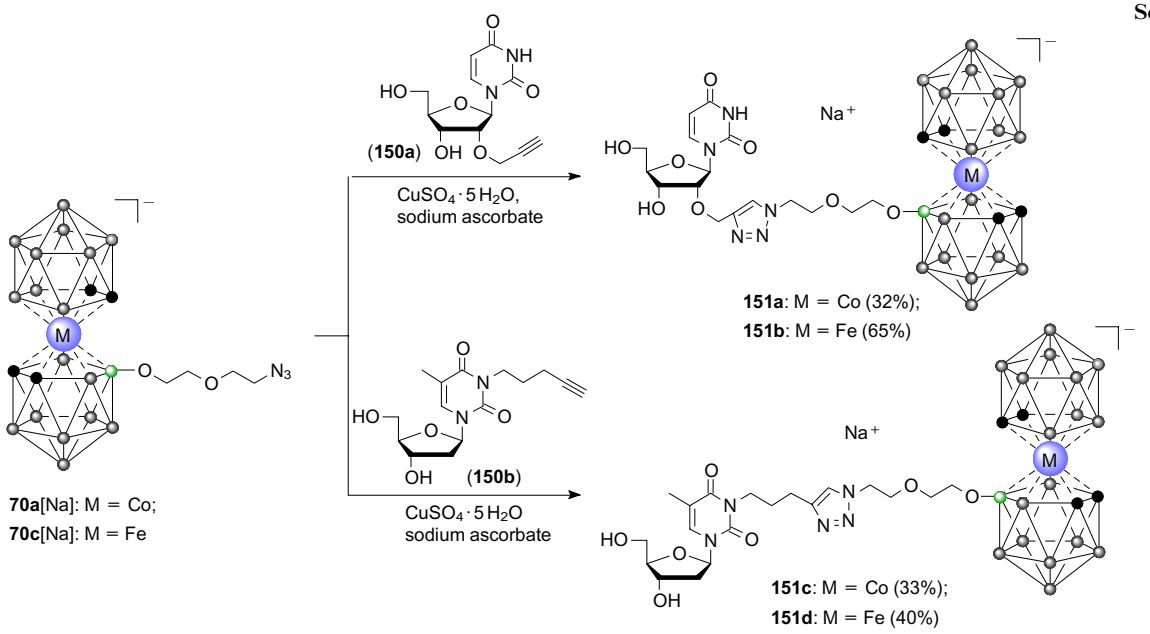


gave 1,4-substituted 1,2,3-triazoles **151a–d**. In these products, the boron cluster is attached to the nucleoside through the triazole ring at the 2′-OH position of deoxyribose and the N^3 position of the pyrimidine base (Scheme 85).[168]

Scheme 84

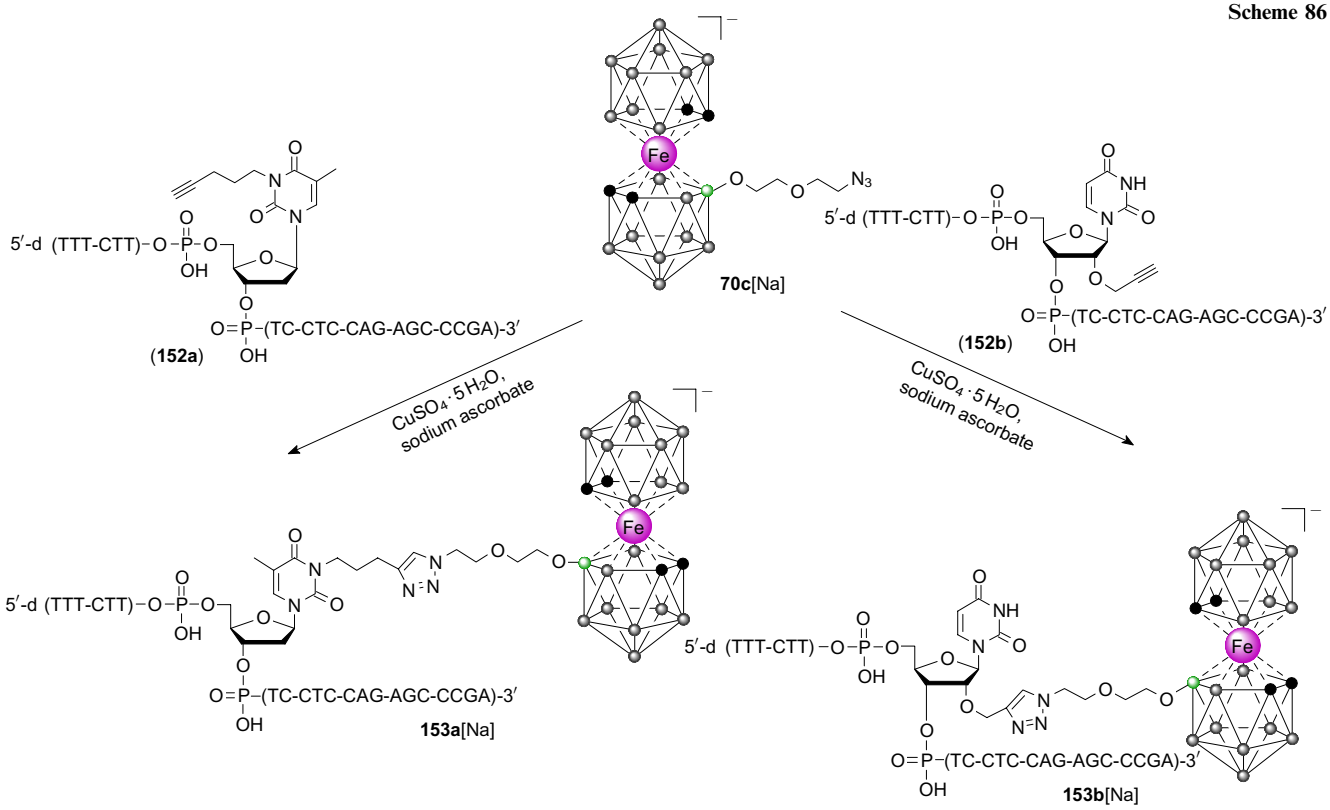


Scheme 85



A convenient method was developed for the incorporation of boron clusters at specific locations of the DNA oligonucleotide chain based on the automated phosphoramidite method for the synthesis of oligonucleotides **152a**,**b** followed by the Cu-catalyzed 1,3-dipolar cycloaddition (Scheme 86).[172] The authors showed that antisense oligonucleotides **153a**,**b** bearing the boron cluster in the middle of the oligonucleotide chain are much more effective inhibitors of gene expression compared to unmodified oligonucleotides.

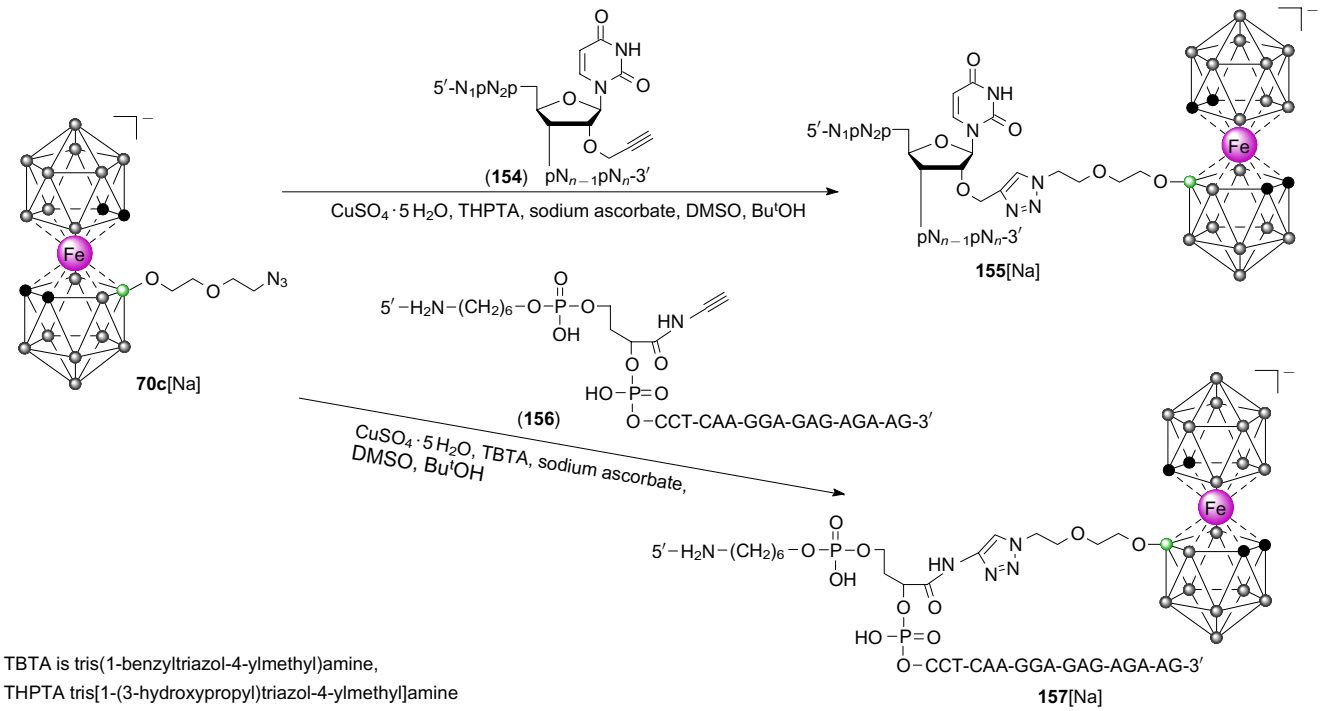
Scheme 86



The click reaction of azide **70c** with alkyne **154** was applied to prepare oligonucleotide–iron bis(dicarbollide) conjugate **155**, which can inhibit gene expression (Scheme 87).[173] A similar reaction with oligonucleotide **156** gave iron bis(dicarbollide) derivative **157**, which was used as a probe for the electrochemical determination of the DNA sequence of avian influenza virus (AIV) serotype H5N1 (see Scheme 87).[174]

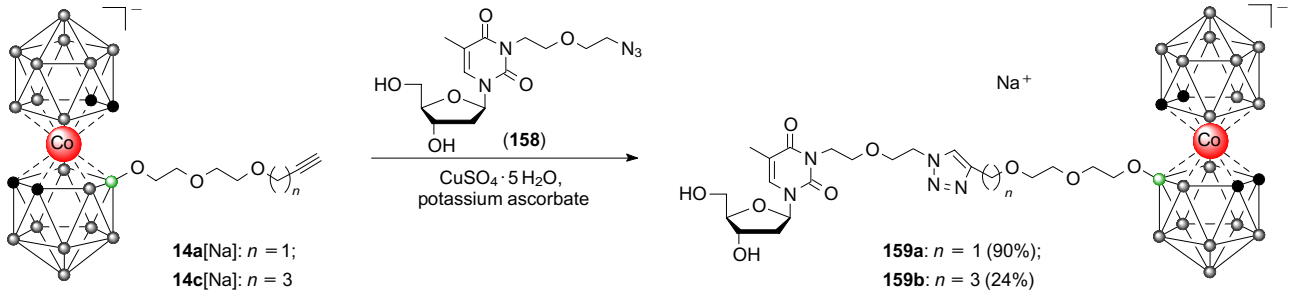
The reaction of azidothymidine **158** (Ref. 68) with terminal alkynes **14** in a mixture of *tert*-butyl alcohol and water at room temperature in the presence of copper(II) sulfate pentahydrate as the catalyst and potassium ascor-

Scheme 87



TBTA is tris(1-benzyltriazol-4-ylmethyl)amine,
THPTA tris[1-(3-hydroxypropyl)triazol-4-ylmethyl]amine

Scheme 88



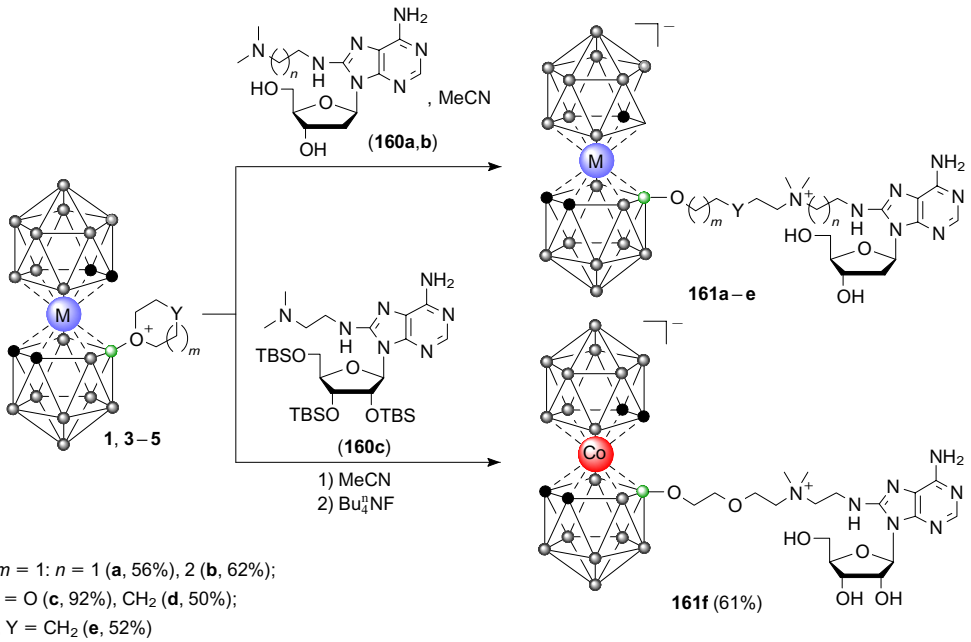
bate gives 1,4-substituted 1,2,3-triazoles **159a**,**b** (Scheme 88).[68]

The reaction of NMe_2-modified 2′-deoxyadenosines **160** with oxonium derivatives of cobalt and iron bis(dicarbollide) **1** and **3**–**5** at room temperature in acetonitrile produces zwitterionic 2′-deoxyadenosine–bis(dicarbollides) conjugates **161a**–**e**, in which the nucleoside is attached to the boron cluster through the 8 position of the purine base.[53, 175, 176] This method requires the protection of the carbohydrate hydroxy group, unlike the method for the synthesis of adenosine–cobalt bis(dicarbollide) conjugate **161f**. The latter method utilizes protected 8-(2-dimethylaminoethyl)amino-2′,3′,5′-tris(*tert*-butyldimethylsilyl)adenosine (**160c**).[177] Protected compound **160c** is soluble in polar organic solvent. Its reaction with complex **1** and the subsequent deprotection give adenosine–cobalt bis(dicarbollide) conjugate **161f** (Scheme 89).[175] The authors noted that the addition of cobalt bis(dicarbollide) derivatives **161a**,**b** dissolved in DMSO to the culture medium at concentrations of 0.1–100 μM led to their precipitation, which made it impossible to evaluate their cytotoxicity.

The oxonium ring opening of dioxane and tetrahydropyran derivatives of cobalt bis(dicarbollide) **1** and **2** with the NMe_2 group of 5-ethynyl-2′-deoxyuridine (**162**) in MeCN at room temperature followed by the treatment with Bu^n_4NF produced boron-containing derivatives **163a**,**b** (Scheme 90).[178] It is worth noting that the intramolecular heterocyclization of 5-alkylated nucleosides is not accompanied by the formation of the furano[2,3-*d*]pyrimidine system as the side product due to the presence of two methyl groups in the α position at the triple bond of alkynamine **162**.

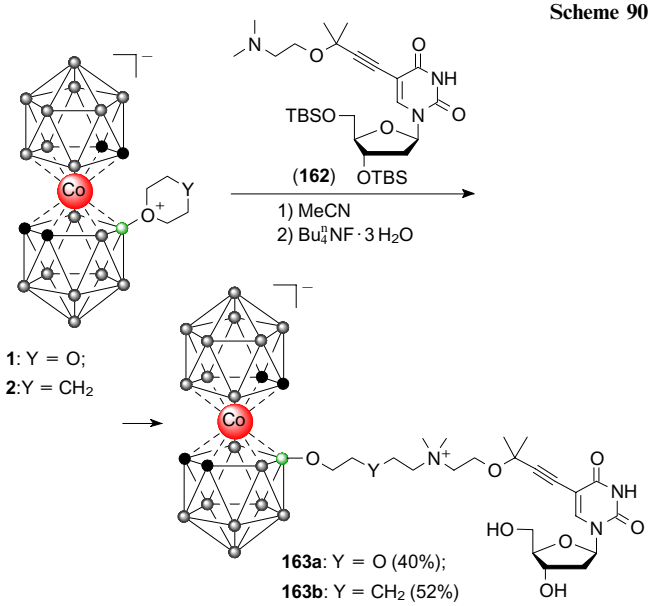
The Sonogashira reaction of alkynylated cobalt bis(dicarbollides) **14** was described.[70] The Cu^I-catalyzed cross-coupling of boron-containing terminal alkynes **14a**–**d** with 5-iodo-2′-deoxyuridine (**164a**) in DMF at room temperature in the presence of $Pd(PPh_3)_4$ and Et_3N followed by the treatment of the reaction mixture with a saturated K_2CO_3 solution gave anionic 5-ethynyl-2′-deoxyuridine–cobalt bis(dicarbollide) conjugates **165a**–**d** as water-soluble potassium salts.[179] This reaction is also not accompanied by the formation of the furano[2,3-*d*]pyrimidine derivative as the side product.[180, 181] Based on this fact, it can be suggested that the successful use of *O*-unprotected nucleosides in the coupling reactions of alkynes is determined by the choice of an appropriate solvent (DMF) rather than by the presence of a palladium catalyst. Cobalt bis(dicarbollide)-based furano[2,3-*d*]pyrimidine nucleosides **166a**–**d** can be synthesized by the direct cyclization of conjugates **165a**–**d** under reflux in acetonitrile for 45 min in the presence of catalytic amounts of Et_3N and CuI. Acylated furano[2,3-*d*]pyrimidin-2(3*H*)-one nucleoside –cobalt bis(dicarbollide) conjugates **167a**–**d** were synthesized by the reaction of alkynes **14a**–**d** with (3′,5′-di-*O*-acetyl)-5-iodo-2′-deoxyuridine

Scheme 89



160: *n* = 1 (**a**), 2 (**b**);
161: M = Co, Y = O, *m* = 1: *n* = 1 (**a**, 56%), 2 (**b**, 62%);
M = Fe, *n* = *m* = 1: Y = O (**c**, 92%), CH_2 (**d**, 50%);
M = Fe, *n* = 1, *m* = 0, Y = CH_2 (**e**, 52%)

Scheme 90



(**164b**) in refluxing acetonitrile in the presence of palladium on carbon (Pd/C), CuI and Et_3N. The subsequent treatment of compounds **167a–d** with 25% aqueous ammonia at room temperature leads to the removal of acyl protecting groups from the carbohydrate residue and the O–N exchange to form (3*H*)-pyrrolo[2,3-*d*]pyrimidin-2(3*H*)-one nucleoside–cobalt bis(dicarbollide) conjugates **168a–d** (Scheme 91).[179]

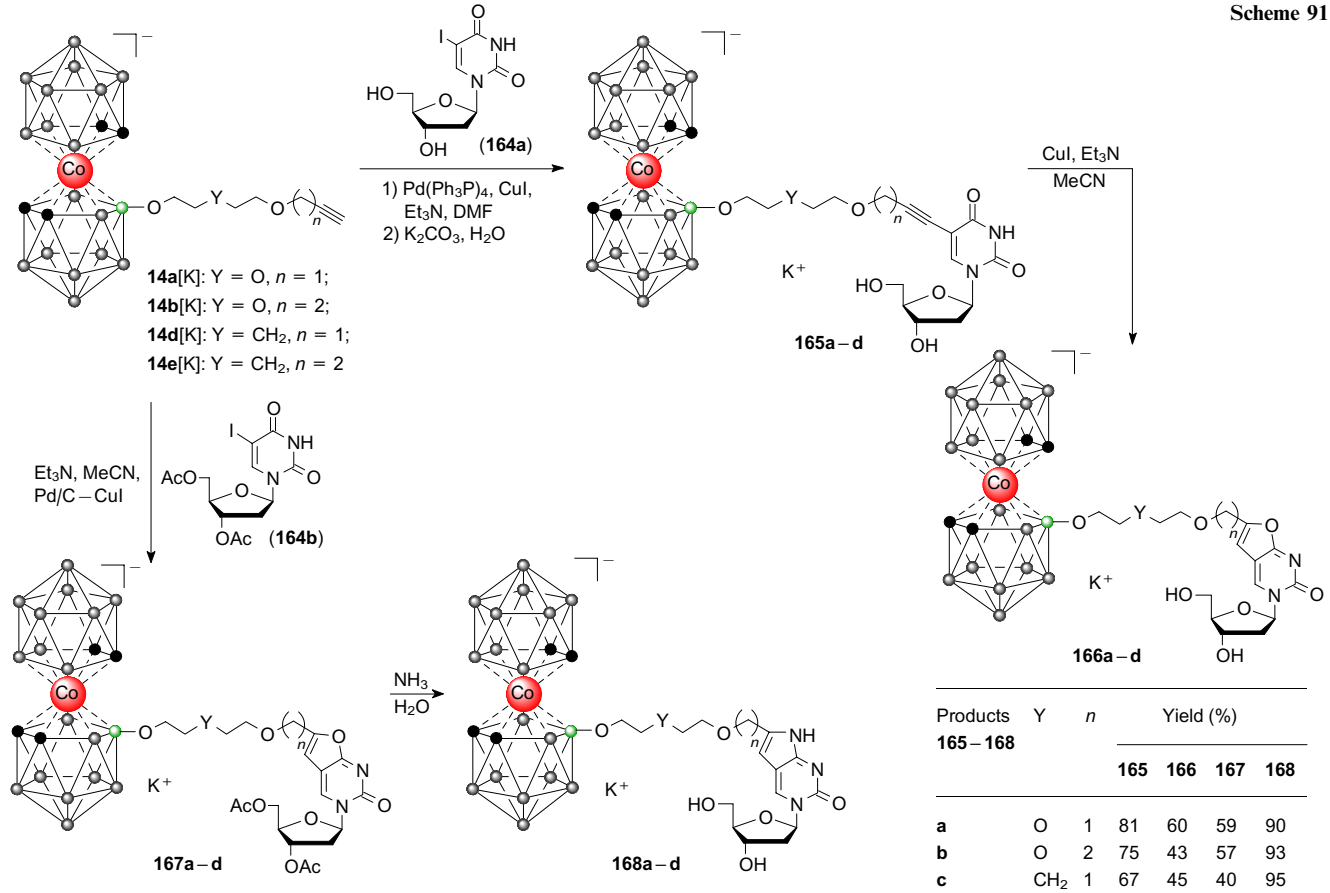
The evaluation of cytotoxicity and antiviral activity of conjugates **163**, **165**, **166** and **168** demonstrated that these compounds, used at a non-toxic concentration, has almost no effect on cytomegalovirus (HCMv), herpes simplex type 1 virus (HSV-1), human parainfluenza virus type 3 (HPIV-3), encephalomyocarditis virus (EMCV) and vesicular stomatitis virus (VSV). Exceptions are compound **166b** exhibiting anti-VSV activity (IC_{50} = 0.9 μmol L^{-1}) and **165c** showing moderate anti-EMCV activity (IC_{50} = 4.0 μmol L^{-1}) with a relatively high selectivity index (SI)§.[179]

3.4. Lipids and liposomes

Boron-containing liposomes mediate the selective delivery of boron to tumour cells. Due to high blood vessel permeability, blood stasis is formed within the tumour as a result of the circulatory failure and lymphatic flow. These changes lead to the enhanced permeability and retention (EPR) effect: macromolecules and nanoparticles, the sizes of which match the pore size of the vascular walls of capillaries (~500 nm), extravasate from the tumour blood vessel into the tumour interstitial space[182] and accumulate mainly in tumour cells. By varying the size of liposomes, one can regulate their accumulation in the tumour site due to the EPR effect.[183] Besides, tumour cells contain a large number

§SI is the selectivity index (the CC_{50} to IC_{50} ratio), where CC_{50} is the concentration of the agent that causes the death of 50% of non-infected cells and IC_{50} is the effective concentration for 50% inhibition of virus replication.

Scheme 91



Products 165–168	Y	*n*	Yield (%)			
			165	**166**	**167**	**168**
a	O	1	81	60	59	90
b	O	2	75	43	57	93
c	CH_2	1	67	45	40	95
d	CH_2	2	65	41	40	96

of low-density lipoprotein receptors capable of binding to liposomes.

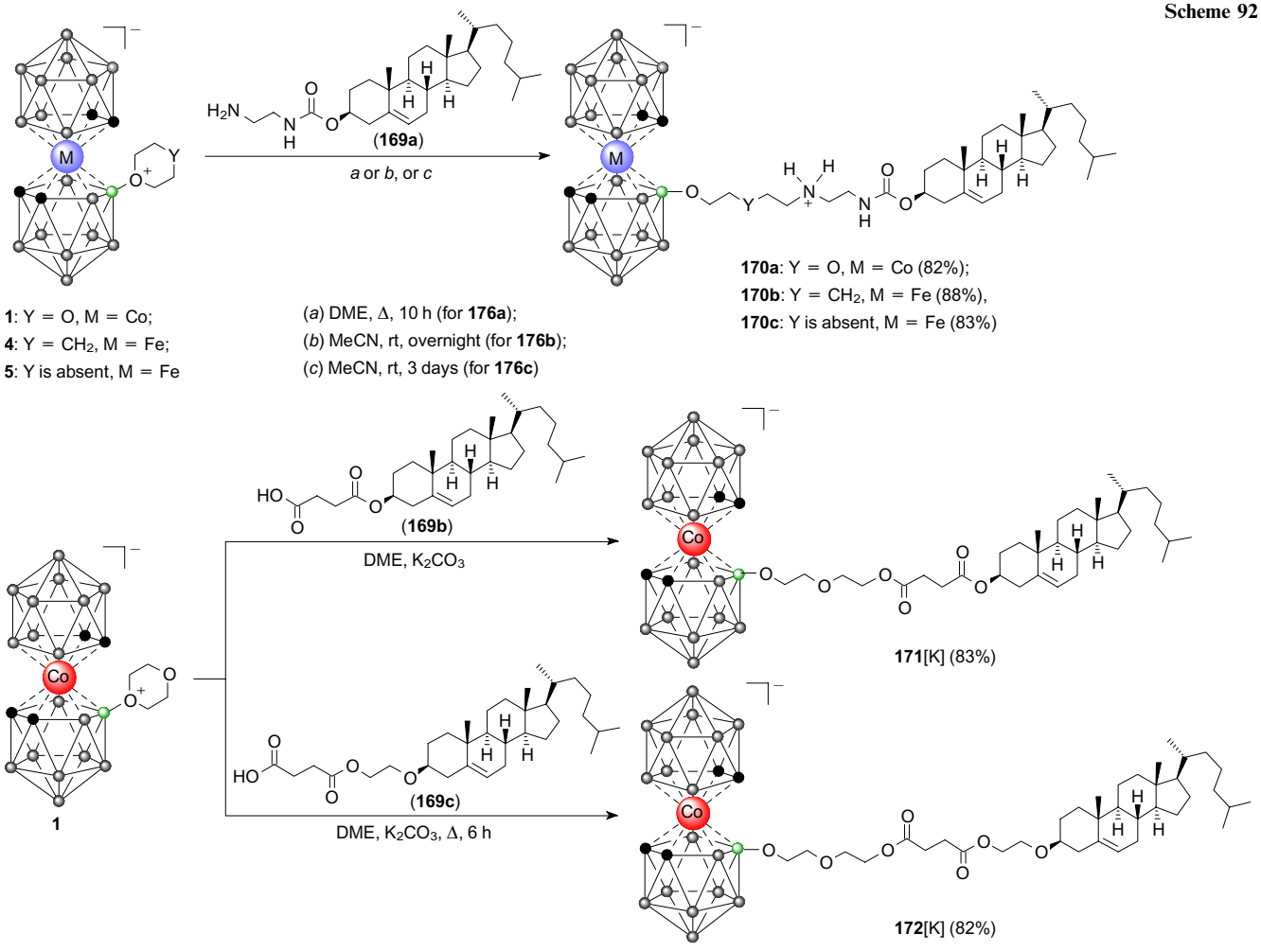
Liposomes can be used for the boron delivery in two ways: by the encapsulation of boron compounds into the interior cavity of liposomes coated by natural phospholipids or by the incorporation of boron-containing synthetic analogues of lipids into the liposomal bilayer. A combined approach is also possible.[184] It was shown that the nature of the spacer affects both the structure and toxicity of liposomes.[185, 186] Several lipid analogues based on polyhedral boron hydrides are known.[187–189] Examples of such cobalt and iron bis(dicarbollide) conjugates are considered in this Section. The hydrophilic portion of these lipids contains the bis(dicarbollide) cluster; the lipophilic portion, cholesterol or diethanolamine dipalmitate.

The oxonium ring opening of the corresponding cobalt and iron bis(dicarbollide) derivatives involving terminal amino and carboxy groups of cholesterols **169a–c** afforded lipids with different spacer lengths between the steroid moiety and the terminal functional group[190] (Scheme 92). The reactions of amine **169a** with cyclic oxonium derivatives of bis(dicarbollide) complexes **1**, **4** and **5** produce charge-compensated ammonium salts **170a–c** in high yields. Cholesterol–cobalt bis(dicarbollide) conjugates **171** and **172** were synthesized by the reaction of carboxylic acids **169b,c** with complex **1** in the presence of K_2CO_3. Lipid derivatives **171** and **172** form stable liposomes of the following composition: boron-containing cholesterol, 15%; 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-*N*-[methoxy(polyethylene glycol)] (DSPE-mPEG), 5%; hydrogenated soybean phosphatidylcholine (lecithin, HSPC), 80%. The average diameter of these liposomes is 170 and 150 nm for lipid derivatives **171** and **172**, respectively. They are characterized by the uniform size distribution. The efficiency of the incorporation of boron-containing cholesterol into the bilayer membrane is equal to 97.0 and 90.3%, respectively. In the absence of thermal neutron irradiation, compounds **171** and **172** have no cytotoxicity against breast cancer cells (MCF-7 cell line) and mammary epithelial cells (MCF-10A cell line).

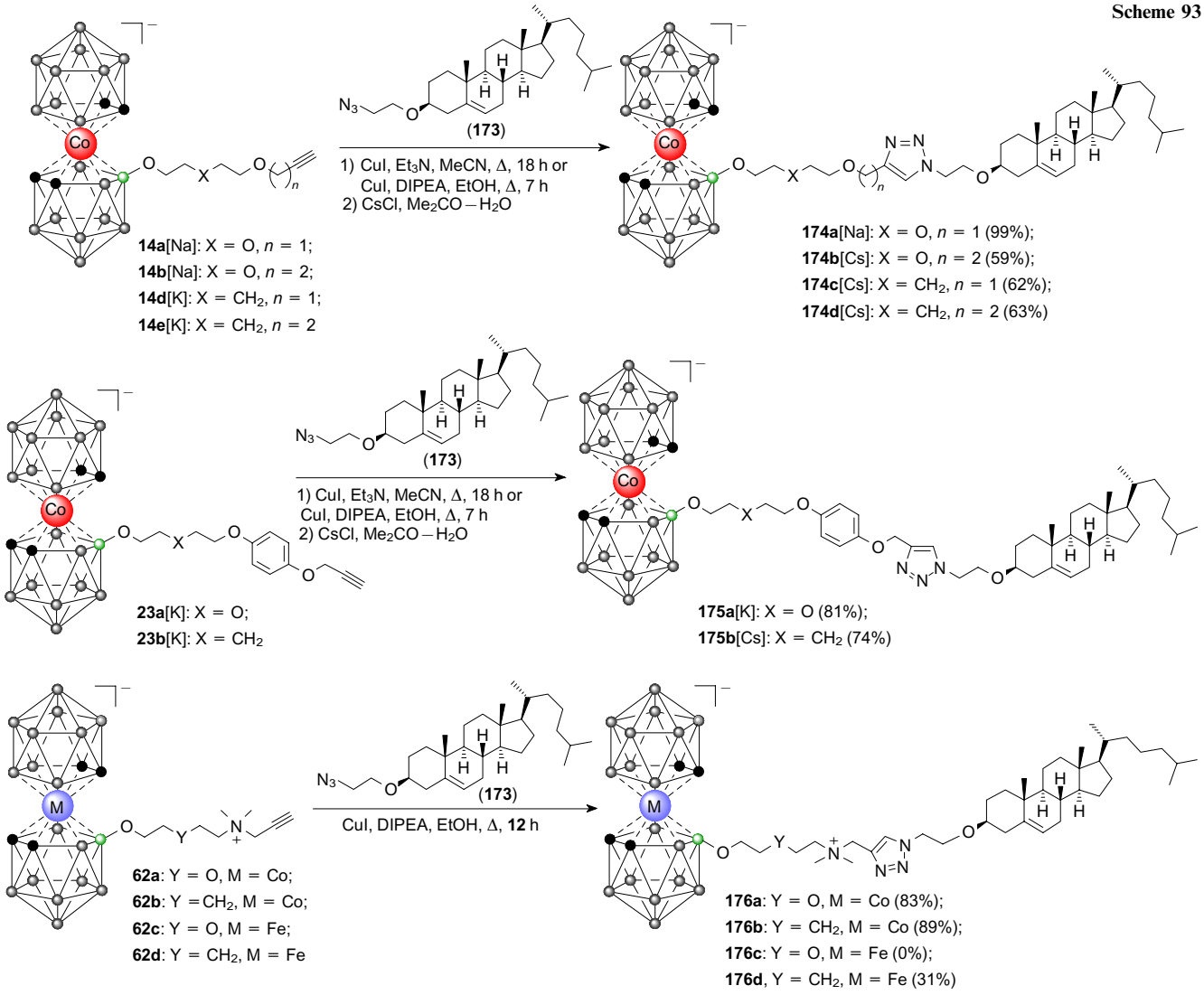
Another group of cholesterol–cobalt and iron bis(dicarbollide) conjugates was prepared by the Cu-catalyzed [3 + 2]-dipolar cycloaddition of alkynes to azides. Modified cholesterol **173** is used as the azide component; different cobalt and iron bis(dicarbollide) derivatives with the terminal triple bond (compounds **14**, **23** and **62**), as the alkyl moiety. The reactions of these acetylenes with cholesterol-based azide in refluxing acetonitrile or ethanol in the presence of CuI and Et_3N or DIPEA produce charged[69] (**174a–d**, **175a,b**) and charge-compensated[96] (**176a–d**) boron-containing cholesterols (Scheme 93).

The click reaction of cobalt bis(dicarbollide)-based azide **70a** with (17β)-17-ethynyl-17-hydroxyestra-1,3,5(10)-trien-3-yl acetate (**177**) in the presence of the catalyst CuI and Et_3N as a base under prolonged reflux in acetonitrile affords conjugate **178** containing cobalt bis(dicarbollide) and the steroid hormone estradiol (Scheme 94).[70]

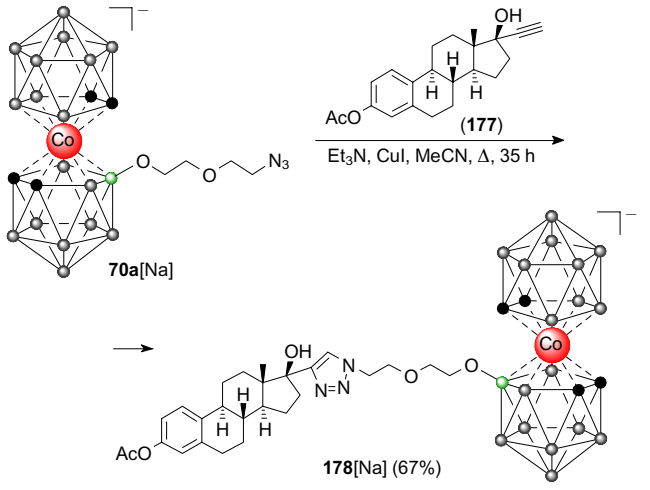
Scheme 92



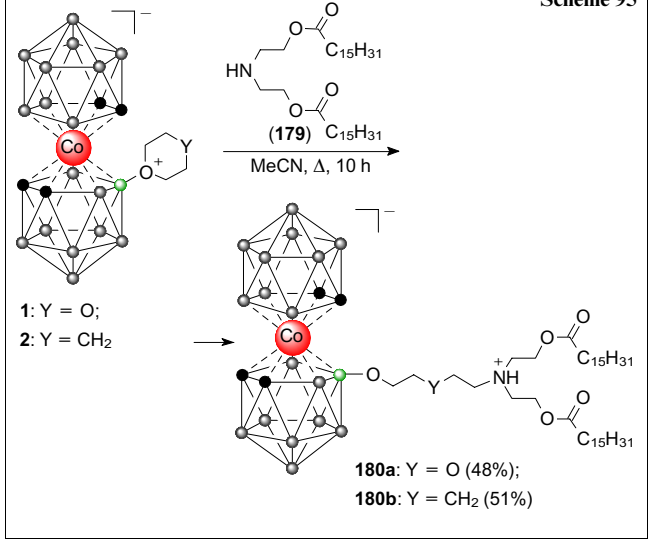
Scheme 93



Scheme 94



Scheme 95



Boron-containing lipids based on cobalt bis(dicarbollide) were prepared by the heating of compounds **1** and **2** with diethanolamine dipalmitate (**179**) under reflux in MeCN for 10 h (Scheme 95). Thus, the dioxane and tetrahydropyran ring opening gave compounds with a hydrophilic (**180a**) and hydrophobic (**180b**) spacer between the boron cluster and the lipid portion.[191]

3.5. Miscellaneous biomolecules

A large number of methods are available for the labeling of boron-containing conjugates and numerous types of probes were developed. Due to the popularity of fluorescence microscopy, considerable attention is given to fluorescent probes, which are characterized by low toxicity and can be used for safe staining of biological samples to monitor the biodistribution of the boron-containing component. Several cobalt and iron bis(dicarbollides) conjugated with fluorescent molecules were synthesized.

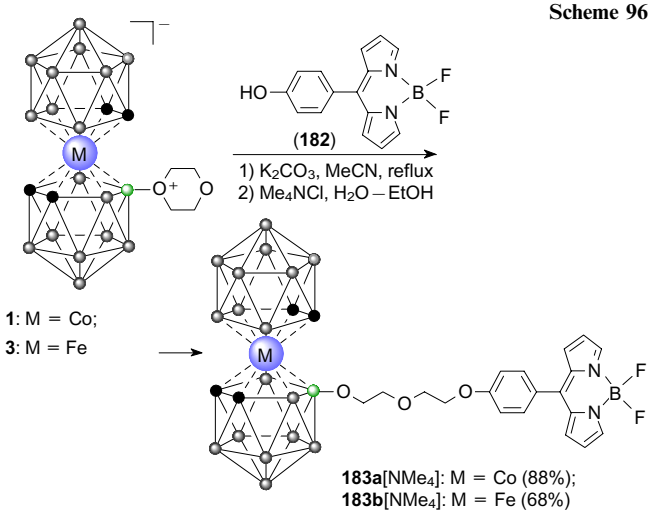
Conjugate **181a** based on fluorescein and two cobalt bis(dicarbollide) units was prepared by the ring opening of complex **1** involving phenoxide groups of fluorescein in a toluene–dimethyl ether mixture at room temperature in the presence of NaH. The 5- and 6-isomers of conjugate **181b** bearing one bis(dicarbollide) unit were synthesized in a molar ratio of 2 : 1 by the reaction of 8-[2-(aminoethoxy)-ethoxy]cobalt bis(dicarbollide) with fluorescein isothiocyanate in MeCN at room temperature.[192] Derivatives **181** are poorly soluble in water and form large aggregates in aqueous solutions. However, the incorporation of the compounds into the cavity of cyclodextrins, which are often employed in drug delivery systems, increases their solubility in water. It was shown that conjugates **181** are easily attached to the phospholipid bilayer, and the presence of fluorescein allows the imaging of conjugates incorporated into the membrane. Therefore, these conjugates can be considered as promising dyes for diagnostic applications.

Fluorescent BODIPY anionic (BODIPY is 4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene) conjugates with cobalt and iron bis(dicarbollides) were synthesized by the dioxane ring opening of compounds **1** and **3** with the OH group of BODIPY derivative **182** in MeCN under reflux in the presence of K_2CO_3 (Scheme 96).[193] Conjugates **183a–c** have no cytotoxicity against the HeLa cells (immortal cervical cancer cell line, the cells of which can divide an unlimited number of times), and the penetration of the starting BODIPY derivative **182** across the cell membrane is improved after its functionalization with a boron cluster. Compounds **182** and **183** have very similar luminescence properties with a quantum yield of 3–6%. Due to a good cellular uptake, the intracellular boron release and luminescence properties, boron-containing derivatives **183a**,**b** are promising candidates as fluorescent probes for *in vitro* assays in biology and medicine.

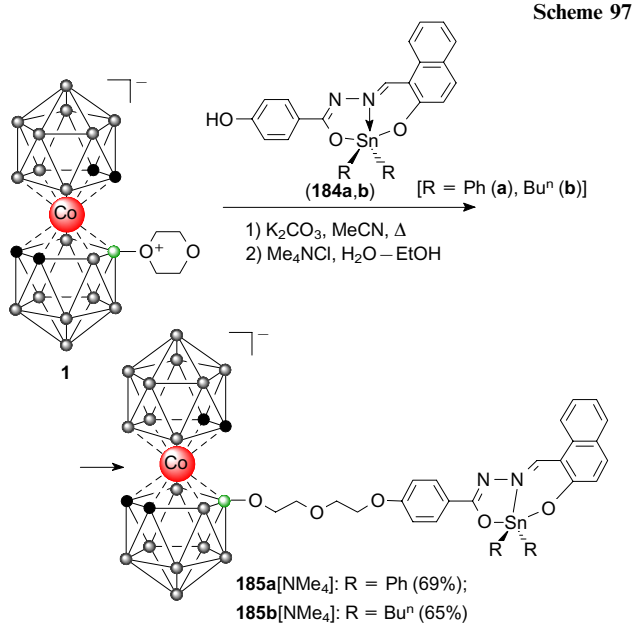
Fluorescent organotin compounds **185a**,**b** were synthesized from tin complexes and 4-hydroxy-*N*′-[(2-hydroxynaphthalen-1-yl)methylidene]benzhydrazides **184a**,**b** and the dioxane derivative of cobalt bis(dicarbollide) **1**.[194] These compounds exhibit good luminescence quantum yields in solution (24–49%) (Scheme 97). Complexes **185** bearing the cobalt bis(dicarbollide) unit show cytoplasmic staining of highly metastatic mouse melanoma cells ($B_{16}F_{10}$). Therefore, these compounds can be considered as promising candidates for the *in vitro* bioluminescence imaging.

The Cu-catalyzed [3 + 2]-dipolar cycloaddition reaction was applied to prepare cobalt bis(dicarbollide) conjugates with tyrosine kinase receptor inhibitors. The reaction of boron-containing azide **70a** with alkynylated erlotinib (**186**),[195] lapatinib (**187**)[196] and sunitinib (**188**)[197] in the

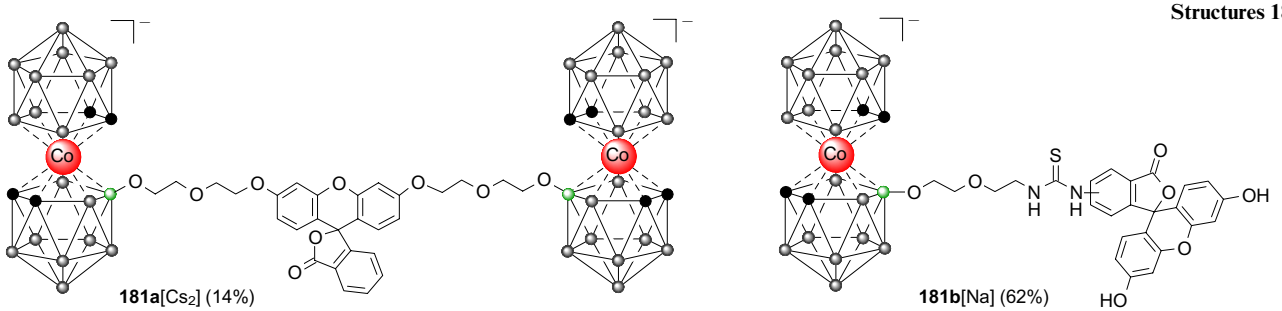
Scheme 96



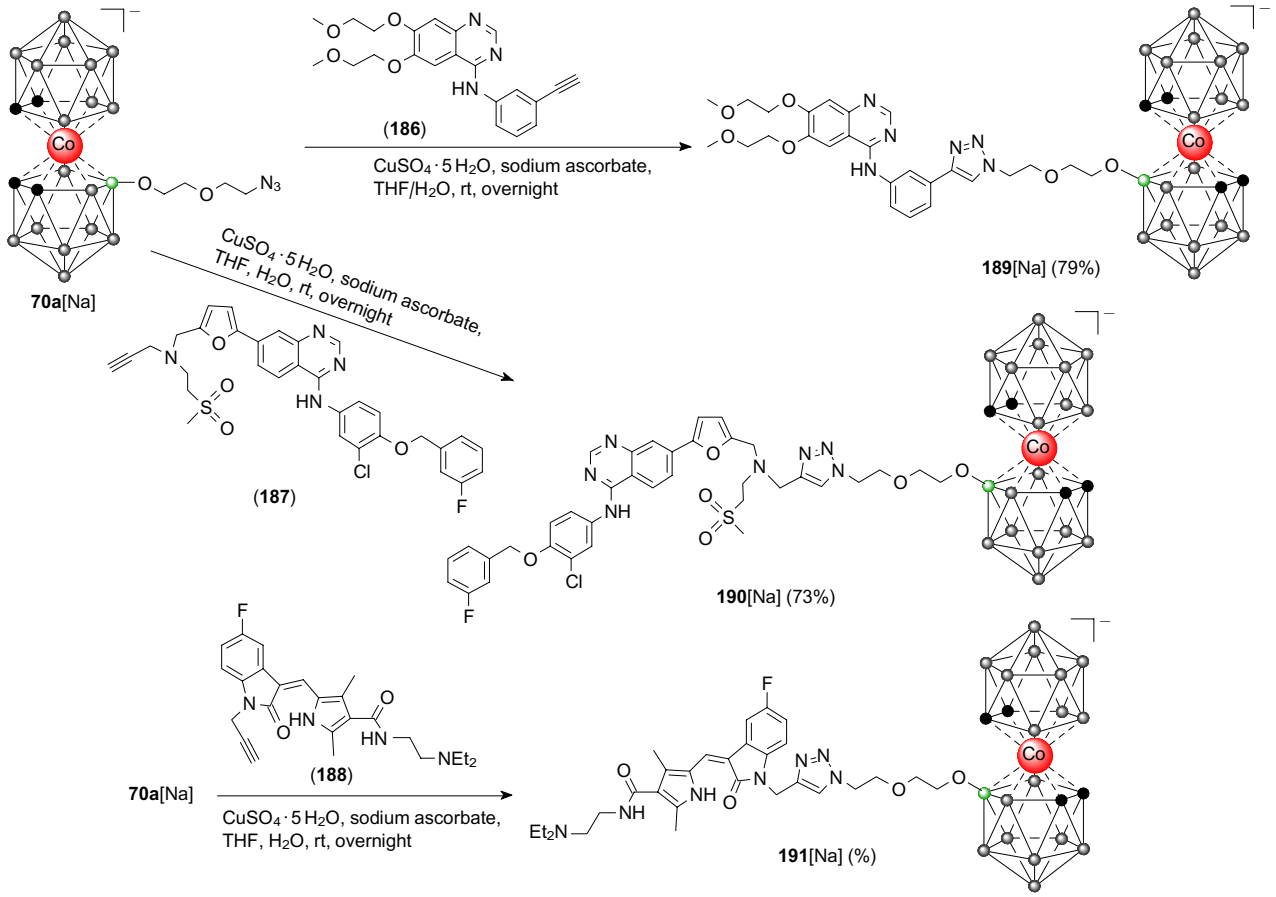
Scheme 97



Structures 181



Scheme 98



presence of aqueous copper sulfate and sodium ascorbate afforded 1,4-triazoles **189** – **191** in good yields (Scheme 98). These conjugates exhibit antitumour activity against glioma cells. Compound **189** shows 3.3 times higher activity compared to the starting erlotinib. Therefore, this compound can be considered as a potential anticancer agent with a dual mechanism of action.

4. Conclusion

Since the 1960s, when the first publications on the synthesis of polyhedral boron compounds appeared, researchers in different countries made a lot of attempts to prepare such compounds for their application in boron neutron capture therapy of cancer, because their molecules contain a large number of boron atoms. The synthesis of cyclic oxonium derivatives of anionic polyhedral boron hydrides [*closo*-deca- and dodecaborates, dicarbaundecaborate, cobalt and iron bis(dicarbollides)] followed by the nucleophilic ring opening is one of the most important ways to pursue the goal. This approach gives exclusively monosubstituted products, thereby facilitating the preparation of BNCT agents. As follows from the analysis of the published data on the synthesis of functional derivatives based on anionic polyhedral boron hydrides, cobalt and iron bis(dicarbollide) complexes containing the largest number of boron atoms (18) have attracted the most attention. The ring opening of these oxonium salts with nucleophilic agents allows one not only to directly incorporate the bis(dicarbollide) unit into biologically active molecules but also to prepare their various functional derivatives, which can be employed for the conjugation with biological molecules using conventional methods of organic synthesis. This approach is highly promising because it provides a convenient route to the synthesis of compounds, in which the boron-containing unit is separated from the biologically active portion of the molecule by a flexible spacer. Hydrophilicity or lipophilicity of the spacer is to a large extent determined by the choice of the initial ethereal solvent and the employed nucleophile. This method was applied to prepare a wide range of boron-containing amino acids, phthalocyanines, synthetic and natural porphyrins, nucleosides and nucleotides, lipids and other biologically active compounds. Despite the rapid development of this area of research and numerous publications, this publication is the first exhaustive review on this issue. We hope that it will be helpful for a broad range of researchers, who are interest in organic, bioorganic and medicinal chemistry.

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5. List of acronyms and designations

A549 — human lung adenocarcinoma cells,
AIBN — azobis(isobutyronitrile),
AMP — adenosine 5′-monophosphate,
B16F10 — highly metastatic mouse melanoma cells,
BBB — blood-brain barrier,
BNCT — boron neutron capture therapy,
BODIPY — 4,4-difluoro-4-bira-3a,4a-diaza-*s*-indacene,

Boc — *tert*-butoxycarbonyl,
CC_{50} — concentration of the agent that causes the death of 50% of non-infected cells,
CMPO — carbamoylphosphine oxide,
dba — dibenzylideneacetone,
DB18C6 — dibenzo-18-crown-6,
DBU — 1,8-diazabicyclo [5.4.0]undec-7-ene,
DCB — dichlorobenzene,
DCC — dicyclohexylcarbodiimide,
DDQ — 2,3-dichloro-5,6-dicyano-1,4-benzoquinone,
DIPEA — diisopropylethylamine,
DMAP — 4- dimethylaminopyridine,
DME — 1,2-dimethoxyethane,
2EG-COSAN — cobalt bis(dicarbollide) containing two ethylene glycol units;
EINS — electrophile-induced nucleophilic substitution,
EMCV — encephalomyocarditis virus,
IC_{50} — effective concentration for 50% inhibition of virus replication,
GL-6 — human glioblastoma cells,
HCMv — cytomegalovirus,
HEp2 — human epithelial cells,
HeLa — immortal cell line, the cells of which can divide an unlimited number of times,
HepG2 — human hepatocellular carcinoma cell line,
HIV — human immunodeficiency virus,
HPIV-3 — human parainfluenza virus type 3,
HSV-1 — herpes simplex type 1 virus,
L929 — mouse fibroblast cell line,
LAT-1 — large neutral amino acid transporter 1,
MCF-7 — breast cancer cells,
MCF-10A — mammary epithelial cells,
MRSA — methicillin-resistant *Staphylococcus aureus*,
Nu — nucleophile,
PDT — photodynamic therapy,
RPMI 2650 — non-invasive cell line,
rt — root temperature,
SI — selectivity index (CC_{50} to IC_{50} ratio),
Tβ4 — thymosin β4,
TBS — *tert*-butyldimethylsilyl,
TODGA — *N*,*N*′-tetra-*n*-octyl diglycol diamide,
VSV — vesicular stomatitis virus.

References

1. J.A.McCleverty. *Annu. Rep. Prog. Chem., Sect. A*, **100**, 3 (2004)
2. R.B.King. *Chem. Rev.*, **101**, 1119 (2001)
3. Z.Chen, R.B.King. *Chem. Rev.*, **105**, 3613 (2005)
4. J.Poater, M.Solà, C.Viñas, F.Teixidor. *Chem. – Eur. J.*, **22**, 7437 (2016)
5. J.Poater, C.Viñas, I.Bennour, S.Escayola, M.Solà, F.Teixidor. *J. Am. Chem. Soc.*, **142**, 9396 (2020)
6. E.Urnežius, W.W.Brennessel, C.J.Cramer, J.E.Ellis, P.R.Schleyer. *Science*, **295**, 832 (2002)
7. J.Frunzke, M.Lein, G.Frenking. *Organometallics*, **21**, 3351 (2002)
8. M.Lein, J.Frunzke, G.Frenking. *Inorg. Chem.*, **42**, 2504 (2003)
9. A.I.Boldyrev, L.S.Wang. *Phys. Chem. Chem. Phys.*, **18**, 11589 (2016)
10. *Aromaticity and Metal Clusters*. (Ed. P.K.Chattaraj). (Boca Raton, FL: CRC Press, 2011)
11. R.N.Grimes. *Carboranes*. (3rd Edn.). (London: Academic Press, 2016)
12. V.I.Bregadze. *Russ. Chem. Bull., Int. Ed.*, **63**, 1021 (2014)
13. I.B.Sivaev, V.I.Bregadze, S.Sjöberg. *Collect. Czech. Chem. Commun.*, **67**, 679 (2002)
14. I.B.Sivaev, V.I.Bregadze. *Collect. Czech. Chem. Commun.*, **64**, 783 (1999)
15. B.P.Dash, R.Satapathy, B.R.Swain, C.S.Mahanta, B.B.Jena, N.S.Hosmane. *J. Organomet. Chem.*, **849 – 850**, 170 (2017)
16. I.B.Sivaev, V.I.Bregadze. *Polyhedral Boron Hydrides in Use: Current Status and Perspectives*. (Hauppauge, NY: Nova Science Publ., 2009)
17. V.N.Romanovsky, I.V.Smirnov, V.A.Babain, A.Yu.Shadrin. In *Advanced Separation Techniques for Nuclear Fuel Reprocessing and Radioactive Waste Treatment*. (Eds K.L.Nash, G.J.Lumetta). (Cambridge: Woodhead Publ., 2011). P. 229
18. J.Rais, B.Grüner. In *Ion Exchange and Solvent Extraction*. (Eds Y.Marcus, A.K.Sen Gupta). (New York: CRC Press, 2004). P. 243
19. B.Grüner, J.Rais, P.Selucký, M.Lucaníkova. In *Boron Science: New Technologies and Applications*. (Ed. N.S.Hosmane). (Boca Raton, FL: CRC Press, 2012). P. 463
20. V.I.Bregadze, I.B.Sivaev. In *Boron Science: New Technologies and Applications*. (Ed. N.S.Hosmane). (Boca Raton, FL: CRC Press, 2012). P. 181
21. G.S.Kazakov, M.Yu.Stogniy, I.B.Sivaev, K.Yu.Suponitsky, I.A.Godovikov, A.D.Kirilin, V.I.Bregadze. *J. Organomet. Chem.*, **798**, 196 (2015)
22. R.D.Kennedy, D.J.Clingerman, W.Morris, C.E.Wilmer, A.A.Sarjeant, C.L.Stern, M.O'Keeffe, R.Q.Snurr, J.T.Hupp, O.K.Farha, C.A.Mirkin. *Cryst. Growth Des.*, **14**, 1324 (2014)
23. V.I.Bregadze, O.A.Dyachenko, O.N.Kazheva, A.V.Kravchenko, I.B.Sivaev, V.A.Starodub. *CrystEngComm*, **17**, 4754 (2015)
24. V.I.Bregadze, O.A.Dyachenko, O.N.Kazheva, I.D.Kosenko, A.V.Kravchenko, I.B.Sivaev, V.A.Starodub. *Russ. J. Gen. Chem.*, **89**, 971 (2019)
25. M.Tarres, V.S.Arderiu, A.Zaulet, C.Viñas, F.Fabrizi de Biani, F.Teixidor. *Dalton Trans.*, **44**, 11690 (2015)
26. A.B.Buades, V.S.Arderiu, D.Olid-Britos, C.Viñas, R.Sillanpää, M.Haukka, X.Fontrodona, M.Paradinas, C.Ocal, F.Teixidor. *J. Am. Chem. Soc.*, **140**, 2957 (2018)
27. K.R.Pichaandi, L.Nilakantan, A.V.Safronov, Yu.V.Sevryugina, S.S.Jalisatgi, M.F.Hawthorne. *Eur. J. Inorg. Chem.*, 666 (2018)
28. I.B.Sivaev. *Russ. Chem. Bull., Int. Ed.*, **67**, 1117 (2018)
29. I.Fuentes, A.Andrio, A.García-Bernabe, J.Escorihuela, C.Viñas, F.Teixidor, V.Compañ. *Phys. Chem. Chem. Phys.*, **20**, 10173 (2018)
30. E.I.Lozinskaya, M.Cotessat, A.V.Shmalko, D.O.Ponkratov, L.V.Gumileva, I.B.Sivaev, A.S.Shaplov. *Polym. Int.*, **68**, 1570 (2019)
31. P.Řezačova, P.Cigler, P.Matejiček, M.Lepšik, J.Pokorna, B.Grüner, J.Konvalinka. In *Boron Science: New Technologies and Applications*. (Ed. N.S.Hosmane). (Boca Raton, FL: CRC Press, 2012). P. 41
32. B.Grüner, J.Brynda, V.Das, V.Šicha, J.Stepankova, J.Nekvinda, J.Holub, K.Pospisilova, M.Fabry, P.Pachtl, V.Kral, M.Kugler, V.Masek, M.Medvedikova, S.Matějkova, A.Nova, B.Liškova, S.Gurska, P.Džubak, M.Hajduch, P.Řezačova. *J. Med. Chem.*, **62**, 9560 (2019)
33. Y.Zheng, W.Liu, Y.Chen, H.Jiang, H.Yan, I.Kosenko, L.Chekulaeva, I.Sivaev, V.Bregadze, X.Wang. *Organometalics*, **36**, 3484 (2017)
34. E.Vakova, K.Lokočova, O.Mat'atkova, I.Křižova, J.Masak, B.Grüner, P.Kaule, J.Čermak, V.Šicha. *J. Organomet. Chem.*, **899**, 120891 (2019)
35. A.B.Olejniczak, B.Nawrot, Z.J.Lesnikowski. *Int. J. Mol. Sci.*, **19**, 3501 (2018)
36. I.Fuentes, T.Garcia-Mendiola, S.Sato, M.Pita, H.Nakamura, E.Lorenzo, F.Teixidor, F.Marques, C.Viñas. *Chem. – Eur. J.*, **24**, 17239 (2018)

37. T.I.Rokitskaya, I.D.Kosenko, I.B.Sivaev, Yu.N.Antonenko, V.I.Bregadze. *Phys. Chem. Chem. Phys.*, **19**, 25112 (2017)
38. K.I.Assaf, B.Begaj, A.Frank, M.Nilam, A.S.Mougharbel, U.Kortz, J.Nekvinda, B.Grüner, D.Gabel, W.M.Nau. *J. Org. Chem.*, **84**, 11790 (2019)
39. A.G.Sauerwein. In *Neutron Capture Therapy*. (Eds W.A.G.Sauerwein, A.Wittig, R.Moss, Y.Nakagawa). (Heidelberg: Springer, 2012. P. 553
40. A.R.Tsygankova, V.V.Kanygin, A.I.Kasatova, E.L.Zavyalov, T.Ya.Guselnikova, A.I.Kichigin, R.A.Mukhamadiyarov. *Russ. Chem. Bull., Int. Ed.*, **69**, 601 (2020)
41. M.F.Hawthorne. *Angew. Chem., Int. Ed. Engl.*, **32**, 950 (1993)
42. A.H.Soloway, W.Tjarks, B.A.Barnum, F.-G.Rong, R.F.Barth, I.M.Codogni, J.G.Wilson. *Chem. Rev.*, **98**, 1515 (1998)
43. I.B.Sivaev, V.I.Bregadze. *Ros. Khim. Zh.*, **48** (4), 109 (2004)
44. I.B.Sivaev, V.I.Bregadze. *Eur. J. Inorg. Chem.*, 1433 (2009)
45. K.Hu, Z.Yang, L.Zhang, L.Xie, L.Wang, H.Xu, L.Josephson, S.H.Liang, M.-R.Zhang. *Coord. Chem. Rev.*, **405**, 213139 (2020)
46. A.A.Semioshkin, I.B.Sivaev, V.I.Bregadze. *Dalton Trans.*, 977 (2008)
47. I.B.Sivaev, V.I.Bregadze. In *Boron Science: New Technologies and Applications*. (Ed. N.S.Hosmane). (Boca Raton, FL; CRC Press, 2012). P. 623
48. J.Plešek, S.Heřmánek, A.Franken, I.Cisarova, C.Nachtigal. *Collect. Czech. Chem. Commun.*, **62**, 47 (1997)
49. J.Llop, C.Masalles, C.Viñas, F.Teixidor, R.Sillanpää, R.Kivekäs. *Dalton Trans.*, 556 (2003)
50. F.Teixidor, J.Pedrajas, I.Rojo, C.Viñas, R.Kivekäs, R.Sillanpää, I.Sivaev, V.Bregadze, S.Sjöberg. *Organometallics*, **22**, 3414 (2003)
51. I.B.Sivaev, V.I.Bregadze. *J. Organomet. Chem.*, **614 – 615**, 27 (2000)
52. J.Plešek, B.Grüner, J.Macháček, I.Císařová, J.Čáslavský. *J. Organomet. Chem.*, **692**, 4801 (2007)
53. I.Lobanova, I.Kosenko, J.Laskova, I.Ananyev, A.Druzina, I.Godovikov, V.I.Bregadze, S.Qi, Z.J.Leśnikowski, A.Semioshkin. *Dalton Trans.*, **44**, 1571 (2015)
54. M.Tarrés, C.Viñas, A.M.Cioran, M.M.Hänninen, R.Sillanpää, F.Teixidor. *Chem. – Eur. J.*, **20**, 15808 (2014)
55. I.B.Sivaev, Z.A.Starikova, S.Sjöberg, V.I.Bregadze. *J. Organomet. Chem.*, **649**, 1 (2002)
56. J.Rak, M.Jakubek, R.Kaplánek, V.Král. *Inorg. Chem.*, **51**, 4099 (2012)
57. P.Cígler, M.Kožíšek, P.Řezáčová, J.Brynda, Z.Otwinowski, J.Pokorná, J.Plešek, B.Grüner, L.Dolečková-Marešová, M.Máša, J.Sedláček, J.Bodem, H.-G.Kräusslich, V.Král, J.Konvalinka. *Proc. Natl. Acad. Sci. USA*, **43**, 15394 (2005)
58. E.V.Sharova, O.I.Artyushin, I.L.Odinets. *Russ. Chem. Rev.*, **83**, 95 (2014)
59. M.M.Reinoso-García, D.Janczewski, D.N.Reinhoudt, W.Verboom, E.Malinowska, M.Pietrzak, C.Hill, J.Báča, B.Grüner, P.Selucky, G.Grüttner. *New. J. Chem.*, **30**, 1480 (2006)
60. J.Rak, R.Kaplánek, V.Král. *Bioorg. Med. Chem. Lett.*, **20**, 1045 (2010)
61. J.Rak, B.Dejlová, H.Lampová, R.Kaplánek, P.Matějíček, P.Cígler, V.Král. *Mol. Pharm.*, **10**, 1751 (2013)
62. M.Tarrés, C.Viñas, P.González-Cardoso, M.M.Hänninen, R.Sillanpää, V.Dordovič, M.Uchman, F.Teixidor, P.Matějíček. *Chem. – Eur. J.*, **20**, 6786 (2014)
63. A.V.Prikaznov, A.V.Shmal'ko, I.B.Sivaev, P.V.Petrovskii, V.I.Bragin, A.V.Kisin, V.I.Bregadze. *Polyhedron*, **30**, 1494 (2011)
64. I.B.Sivaev. *Chem. Heterocycl. Compd.*, **53**, 638 (2017)
65. B.Grüner, J.Plešek, J.Bača, J.F.Dozol, V.Lamare, I.Cisařova, M.Belohradsky, J.Časlavsky. *New J. Chem.*, **26**, 867 (2002)
66. F.Teixidor, R.Sillanpää, A.Pepiol, M.Lupu, C.Viñas. *Chem. – Eur. J.*, **21**, 12778 (2015)
67. F.Teixidor, A.Pepiol, C.Viñas. *Chem. – Eur. J.*, **21**, 10650 (2015)
68. B.A.Wojtczak, A.Andrysiak, B.Grüner, Z.J.Lesnikowski. *Chem. – Eur. J.*, **14**, 10675 (2008)
69. A.A.Druzina, A.V.Shmalko, E.P.Andreichuk, O.B.Zhidkova, I.D.Kosenko, A.Semioshkin, I.B.Sivaev, S.Mandal, Z.Shen, V.I.Bregadze. *Mendeleev Commun.*, **29**, 628 (2019)
70. I.D.Kosenko, I.A.Lobanova, L.A.Chekulaeva, I.A.Godovikov, V.I.Bregadze. *Russ. Chem. Bull., Int. Ed.*, **62**, 497 (2013)
71. P.Farrás, F.Teixidor, R.Kivekäs, R.Sillanpää, C.Viñas, B.Grüner, I.Cisarova. *Inorg. Chem.*, **47**, 9497 (2008)
72. R.Núñez, E.J.Juárez-Pérez, F.Teixidor, R.Santillan, N.Farfán, A.Abreu, R.Yépez, C.Viñas. *Inorg. Chem.*, **49**, 9993 (2010)
73. J.Plešek, B.Grüner, S.Heřmánek, J.Bača, V.Mareček, J.Jänchenova, A.Lhotsky, K.Holub, P.Selucky, J.Rais, I.Cisařova, J.Časlavsky. *Polyhedron*, **21**, 975 (2002)
74. E.Hao, M.G.H.Vicente. *Chem. Commun.*, 1306 (2005)
75. M.A.Grin, R.A.Titeev, O.M.Bakieva, D.I.Brittal, I.A.Lobanova, I.B.Sivaev, V.I.Bregadze, A.F.Mironov. *Russ. Chem. Bull., Int. Ed.*, **57**, 2230 (2008)
76. J.Cabrera-Gonzalez, V.Sanchez-Arderiu, C.Viñas, T.Parella, F.Teixidor, R.Nuñez. *Inorg. Chem.*, **55**, 11630 (2016)
77. A.V.Shmal'ko, I.B.Sivaev, V.I.Bregadze, L.V.Kovalenko. *Inorg. Lett.*, **2**, 1 (2015)
78. A.V.Shmal'ko. Candidate Thesis in Chemical Sciences, A.N.Nesmeyanov Institute of Organoelement Compounds of Russian Academy of Sciences, Moscow, 2016
79. B.P.Dash, R.Satapathy, J.A.Maguire, N.S.Hosmane. *Organometallics*, **29**, 5230 (2010)
80. J.Cabrera-Gonzalez, M.Chaari, F.Teixidor, C.Viñas, R.Nuñez. *Molecules*, **25**, 1210 (2020)
81. C.S.Mahanta, R.Bhavsar, B.P.Dash, R.Satapathy. *J. Organomet. Chem.*, **865**, 183 (2018)
82. L.Mikulašek, B.Grüner, C.Danila, V.Böhmer, J.Čáslavský, P.Selucký. *Chem. Commun.*, 4001 (2006)
83. L.Mikulašek, B.Grüner, C.Dordea, V.Rudzevich, V.Böhmer, J.Haddaoui, V.Hubscher-Bruder, F.Arnaud-Neu, J.Čáslavský, P.Selucký. *Eur. J. Org. Chem.*, 4772 (2007)
84. B.Grüner, L.Mikulašek, J.Bača, I.Cisařova, V.Böhmer, C.Danila, M.M.Reinoso-Garcia, W.Verboom, D.N.Reinhoudt, A.Casnati, R.Ungaro. *Eur. J. Org. Chem.*, 2022 (2005)
85. I.Romero, M.Martinez-Medina, C.Camprubí-Font, I.Bennour, D.Moreno, L.Martínez-Martínez, F.Teixidor, M.Fox, C.Viñas. *Organometallics*, **39**, 4253 (2020)
86. E.Kvasničková, J.Masák, J.Čejka, O.Mat'átková, V.Šícha. *J. Organomet. Chem.*, **827**, 23 (2017)
87. P.A.Jelliss, S.S.Graham, A.Josipovic, S.Boyko, S.D.Minteer. *Polyhedron*, **50**, 36 (2013)
88. J.Nekvinda, D.Rózycka, S.Rykowski, E.Wyszko, A.Fedoruk-Wyszomirska, D.Gurda, M.Orlicka-Płocka, M.Giel-Pietraszuk, A.Kiliszek, W.Rypniewski, R.Bachorz, J.Wojcieszak, B.Grüner, A.B.Olejniczak. *Bioorg. Chem.*, **94**, 103432 (2020)
89. L.Parejo, M.Chaari, S.Santiago, G.Guirado, F.Teixidor, R.Núñez, J.Hernando. *Chem. – Eur. J.*, **27**, 270 (2021)
90. R.Kaplánek, P.Martásek, B.Grüner, S.Panda, J.Rak, B.Masters, V.Král, L.Roman. *J. Med. Chem.*, **55**, 9541 (2012)
91. B.Grüner, J.Plešek, J.Báča, I.Císařová, J.F.Dozol, H.Rouquette, C.Vias, P.Selucký, J.Rais. *New J. Chem.*, **26**, 1519 (2002)
92. P.Selucký, J.Rais, M.Lučaníková, B.Grüner, M.Kvíčalová, K.Fejfarová, I.Císařova. *Radiochim. Acta.*, **96**, 273 (2008)

93. M.A.Grin, R.A.Titeev, D.I.Brittal, O.V.Ulybina, A.G.Tsiprovskiy, M.Y.Berzina, I.A.Lobanova, I.B.Sivaev, V.I.Bregadze, A.F.Mironov. *Mendeleev Commun*., **21**, 84 (2011)
94. P.Řezáčová, J.Pokorná, J.Brynda, M.Kožíšek, P.Cígler, M.Lepšík, J.Fanfrlík, J.Řezáč, K.G.Šašková, I.Sieglová, J.Plešek, V.Šícha, B.Grüner, H.Oberwinkler, J.Sedláček, H.G.Kräusslich, P.Hobza, V.Král, J.Konvalinka. *J. Med. Chem*., **52**, 7132 (2009)
95. P.Srb, M.Svoboda, L.Benda, M.Lepšik, J.Tarabek, V.Šicha, B.Grüner, K.Grantz-Šaškova, J.Brynda, P.Řezačova, J.Konvalinka, V.Veverka. *Phys. Chem. Chem. Phys*., **21**, 5661 (2019)
96. A.A.Druzina, I.D.Kosenko, O.B.Zhidkova, I.V.Ananyev, S.V.Timofeev, V.I.Bregadze. *Eur. J. Inorg. Chem*., 2658 (2020)
97. A.Ursu, F.P.Schmidtchen. *Angew. Chem., Int. Ed*., **51**, 242 (2012)
98. P.Farràs, E.C.Escudero-Adán, C.Viñas, F.Teixidor. *Inorg. Chem*., **53**, 8654 (2014)
99. M.Lučaníková, P.Selucký, J.Rais, B.Grüner, M.Kvíčalová. *Proc. Radiochim. Acta*, **1**, 89 (2011)
100. J.Cabrera-Gonzalez, L.Cabana, B.Ballesteros, G.Tobias, R.Nuñez. *Chem. – Eur. J*., **22**, 5096 (2016)
101. E.J.Juarez-Perez, M.Granier, C.Viñas, P.H. Mutin, R.Nuñez. *Chem. – Asian J*., **7**, 277 (2012)
102. I.D.Kosenko, I.A.Lobanova, V.I.Bregadze. *Vestn. Lobachevsk. Univ. Nizhni Novgorod*, **3** (1), 110 (2013)
103. P.Farràs, F.Teixidor, R.Sillanpää, C.Viñas. *Dalton Trans*., **39**, 1716 (2010)
104. A.V.Shmal'ko, M.Yu.Stogniy, G.S.Kazakov, S.A.Anufriev, I.B.Sivaev, L.V.Kovalenko, V.I.Bregadze. *Dalton Trans*., **44**, 9860 (2015)
105. I.B.Sivaev, A.V.Prikaznov, S.A.Anufriev. *J. Organomet. Chem*., **747**, 254 (2013)
106. V.Šícha, P.Farràs, B.Štíbr, F.Teixidor, B.Grüner, C.Viñas. *J. Organomet. Chem*., **694**, 1599 (2009)
107. M.J.Lukey, W.P.Katt, R.A.Cerione. *Drug Discov. Today*, **22**, 796 (2017)
108. O.Yanagida, Y.Kanai, A.Chairoungdua, D.K.Kim, H.Segawa, T.Nii, S.H.Cha, H.Matsuo, J.Fukushima, Y.Fukasawa, Y.Tani, Y.Taketani, H.Uchino, J.Y.Kim, J.Inatomi, I.Okayasu, K.Miyamoto, E.Takeda, T.Goya, H.Endou. *Biochim. Biophys. Acta (BBA); Biomembranes*, **1514**, 291 (2001)
109. Y.Zhao, L.Wang, J.Pan. *Intractable Rare Dis. Res*., **4**, 165 (2015)
110. P.Häfliger, R.-P.Charles. *Int. J. Mol. Sci*., **20**, 2428 (2019)
111. G.W.Kabalka, M.L.Yao. *Anti-Cancer Agents Med. Chem*., **6**, 111 (2006)
112. I.B.Sivaev, V.I.Bregadze. *ARKIVOC*, (iv), 47 (2008)
113. G.W.Kabalka, M.-L.Yao, S.R.Marepally, S.Chandra. *Appl. Radiat. Isot*., **67**, S374 (2009)
114. J.Miyabe, R.Ohgaki, K.Saito, L.Wei, L.Quan, C.Jin, X.Liu, S.Okuda, S.Nagamori, H.Ohki, K.Yoshino, H.Inohara, Y.Kanai. *J. Pharm. Sci*., **139**, 215 (2019)
115. A.V.Prikaznov, Yu.N.Las'kova, A.A.Semioshkin, I.B.Sivaev, A.V.Kisin, V.I.Bregadze. *Russ. Chem. Bull., Int. Ed*., **60**, 2550 (2011)
116. M.Yu.Stogniy, M.V.Zakharova, I.B.Sivaev, I.A. Godovikov, A.O.Chizov, V.I.Bregadze. *Polyhedron*, **55**, 117 (2013)
117. Y.Hattori, S.Kusaka, M.Mukumoto, K.Uehara, T.Asano, M.Suzuki, S.Masunaga, K.Ono, S.Tanimori, M.Kirihata. *J. Med. Chem*., **55**, 6980 (2012)
118. G.Futamura, S.Kawabata, N.Nonoguchi, R.Hiramatsu, T.Toho, H.Tanaka, S.Masunaga, Y.Hattori, M.Kirihata, K.Ono, T.Kuroiwa, S.Miyatake. *Radiat. Oncol*., **12**, 26 (2017)
119. T.He, R.A.Musah. *ACS Omega*, **4**, 3820 (2019)
120. A.V.Shmal'ko, I.B.Sivaev, V.I.Bregadze, L.V.Kovalenko. *Russ. Chem. Bull., Int. Ed*., **63**, 2334 (2014)
121. I.A.Lobanova, M.Ya.Berzina, I.B.Sivaev, P.V.Petrovskii, V.I.Bregadze. *Russ. Chem. Bull., Int. Ed*., **59**, 2302 (2010)
122. A.D.Patel, N.K.Prajapati. *J. Chem. Pharm. Res*., **4** (1), 209 (2012)
123. E.Ludmerszki, K.Paldi, I.Racz, Z.Szigeti, S.Rudnoy. *Appl. Ecol. Enviroment. Res*., **12**, 777 (2014)
124. A.L.Goldstein, H.K.Kleinman. *Expert Opin. Biol. Ther*., **15**, S139 (2015)
125. N.Smart, S.Bollini, K.N.Dubé, J.M.Vieira, B.Zhou, J.Riegler, A.N.Price,M.F.Lythgoe, S.Davidson, D.Yellon,W.T.Pu, P.R.Riley. *Ann. NY Acad. Sci*., **1269**, 92 (2012)
126. A.Rossdeutsch, N.Smart, P.R.Riley. *J. Mol. Med*., **86**, 29 (2008)
127. K.Fink, K.Kobak, M.Kasztura, J.Boratyński, T.M.Goszczyński. *Bioconjug. Chem*., **29**, 3509 (2018)
128. K.Fink, J.Boratyński, M.Paprocka, T.M.Goszczyński. *Ann. N.Y. Acad. Sci*., **1457**, 128 (2019)
129. M.R.Hamblin, P.Mroz. In *Advances in Photodynamic Therapy: Basic, Translational, and Clinical.* (Eds M.R.Hamblin, P.Mroz). (Norwood, MA: Artech House, 2008). P. 1
130. M.Ethirajan, Y.Chen, P.Joshi, R.K.Pandey. *Chem. Soc. Rev*., **40**, 340 (2011)
131. W.Liu, H.Cai. In *Photomedicine: Advances in Clinical Practice*. (Ed. Y.Tanaka). (London: IntechOpen, 2017). P. 547
132. V.I.Bregadze, I.B.Sivaev, D.Gabel, D.Wöhrle. *J. Porphyrins Phthalocyanines*, **5**, 767 (2001)
133. M.W.Renner, M.Miura, M.W.Easson, M.G.H.Vicente. *Anti-Cancer Agents Med. Chem*., **6**, 145 (2006)
134. M.Ratajski, J.Osterloh,D.Gabel. *Anti-Cancer Agents Med. Chem*., **6**, 159 (2006)
135. M.A.Grin, D.I.Brittal, A.G.Tsiprovskiy, V.I.Bregadze, A.F.Mironov. *Macroheterocycles*, **3**, 222 (2010)
136. I.B.Sivaev, V.I.Bregadze, A.Gül, A.F.Mironov. *Macroheterocycles*, **5**, 292 (2012)
137. D.Pietrangeli, A.Rosa, S.Ristori, A.Salvati, S.Altieri, G.Ricciardi. *Coord. Chem. Rev*., **257**, 2213 (2013)
138. S.Özcelik, A.Gül. *Turk. J. Chem*., **38**, 950 (2014)
139. V.A.Ol'shevskaya, A.V.Zaitsev, A.A.Shtil. In *Boron-Based Compounds: Potential and Emerging Applications in Medicine* Wiley, (Eds E.Hey-Hawkins, C.Viñas-Teixidor). (Chichester: Wiley, 2018). P. 343
140. A.A.Semioshkin. Doctoral Thesis in Chemical Sciences, A.N.Nesmeyanov Institute of Organoelement Compounds of Russian Academy of Sciences, Moscow, 2014
141. H.Li, F.R.Fronczek, M.G.H.Vicente. *Tetrahedron Lett*., **49**, 4828 (2008)
142. H.Li, F.R.Fronczek, M.G.H.Vicente. *J. Organomet. Chem*., **694**, 1607 (2009)
143. I.Nar, A.Atsay, S.Gümrükçü, T.Karazehir, E.Hamuryudan. *Eur. J. Inorg. Chem*., 3878 (2018)
144. I.Nar, A.Gül, I.B.Sivaev, E.Hamuryudan. *Synth. Met*., **210**, 376 (2015)
145. A.V.Shmal'ko, A.V.Efremenko, A.A.Ignatova, I.B.Sivaev, A.V.Feofanov, E.Hamuryudan, A.Gül, L.V.Kovalenko, S.Qi, V.I.Bregadze. *J. Porphyrins Phthalocyanines*, **18**, 960 (2014)
146. E.Hao, T.J.Jensen, B.H.Courtney, M.H.Vicente. *Bioconjug. Chem*., **16**, 1495 (2005)
147. E.Hao, M.Zhang, E.Wenbo, K.M.Kadish, F.R.Fronczek, B.H.Courtney, M.G.H.Vicente. *Bioconjug. Chem*., **19**, 2171 (2008)
148. P.Kubát, K.Lang, P.Cígler, M.Kožíšek, P.Matějíček, P.Janda, Z.Zelinger, K.Procházka, V.Král. *J. Phys. Chem. B*, **111**, 4539 (2007)
149. M.Sibrian-Vasquez, E.Hao, T.J.Jensen, M.G.H.Vicente. *Bioconjug. Chem*., **17**, 928 (2006)
150. E.Hao, M.Sibrian-Vazquez, W.Serem, J.C.Garno, F.R.Fronczek, M.G.H.Vicente. *Chem. – Eur. J*., **13**, 9035 (2007)

151. V.I. Bregadze, A.A.Semioshkin, J.N.Las'kova, M.Ya.Berzina, I.A.Lobanova, I.B.Sivaev, M.A.Grin, R.A.Titeev, D.I.Brittal, O.V.Ulybina, A.V.Chestnova, A.A.Ignatova, A.V.Feofanov, A.F.Mironov. *Appl. Organomet. Chem.*, **23**, 370 (2009)
152. M.A.Grin, R.A.Titeev, D.I.Brittal, A.V.Chestnova, A.V.Feofanov, I.A.Lobanova, I.B.Sivaev, V.I.Bregadze, A.F.Mironov. *Russ. Chem. Bull., Int. Ed.*, **59**, 219 (2010)
153. A.V.Efremenko, A.A.Ignatova, A.A.Borsheva, M.A.Grin, V.I.Bregadze, I.B.Sivaev, A.F.Mironov, A.V.Feofanov. *Photochem. Photobiol. Sci.*, **11**, 645 (2012)
154. A.V.Efremenko, A.A.Ignatova, M.A.Grin, I.B.Sivaev, A.F.Mironov, V.I.Bregadze, A.V.Feofanov. *Photochem. Photobiol. Sci.*, **13**, 92 (2014)
155. A.B.Volovetsky, N.Yu.Shilyagina, V.V.Dudenkova, S.O.Pasynkova, M.A.Grin, A.F.Mironov, A.V.Feofanov, I.V.Balalaeva, A.V.Maslennikova. *Modern Technol. Med.,* **8** (1), 34 (2016)
156. A.B.Volovetsky, V.S.Sukhov, I.V.Balalaeva, V.V.Dudenkova, N.Yu.Shilyagina, A.V.Feofanov, A.V.Efremenko, M.A.Grin, A.F.Mironov, I.B.Sivaev, V.I.Bregadze, A.V.Maslennikova. *Int. J. Mol. Sci.*, **18**, 2556 (2017)
157. A.A.Ignatova, Yu.S.Korostey, M.K.Fedotova, I.B.Sivaev, V.I.Bregadze, A.F.Mironov, M.A.Grin, A.V.Feofanov. *Future Med. Chem.*, **12**, 1015 (2020)
158. A.R.Martin, J.-J.Vasseur, M.Smietana. *Chem. Soc. Rev.*, **42**, 5684 (2013)
159. Z.J.Lesnikowski. *Eur. J. Org. Chem.*, 4489 (2003)
160. Z.J.Lesnikowski. *Collect. Czech. Chem. Commun.*, **72**, 1646 (2007)
161. Z.J.Lesnikowski. *J. Organomet. Chem.*, **694**, 1771 (2009)
162. A.A.Druzina, V.I.Bregadze, A.F.Mironov, A.A.Semioshkin. *Russ. Chem. Rev.*, **85**, 1229 (2016)
163. H.Nakamura, M.Kirihata. In *Boron Compounds: New Candidates for Boron Carriers in BNCT*. (Ed. W.A.G.Sauerwein). (Berlin, Heidelberg: Springer-Verlag, 2012). P. 99
164. Y.Byun, S.Narayanasamy, J.Johnsamuel, A.K.Bandyopadhyaya, R.Tiwari, A.S.Al-Madhoun, R.F.Barth; S.Eriksson, W.Tjarks. *Anti-Cancer Agents Med. Chem.*, **6**, 127 (2006)
165. P.Li, Z.A.Sergueeva, M.Dobrikov, R.S.Shaw. *Chem. Rev.*, **107**, 4746 (2007)
166. A.Khalil, K.Ishita, T.Ali, W.Tjarks. *Future Med. Chem.*, **5**, 677 (2013)
167. A.B.Olejniczak, J.Plešek, O.Kříž, Z.J.Lesnikowski. *Angew. Chem., Int. Ed.*, **42**, 5740 (2003)
168. A.B.Olejniczak, Z.J.Lešnikowski, J.Plešek. *Chem. – Eur. J.*, **13**, 311 (2007)
169. A.B.Olejniczak, P.Mucha, B.Grüner, Z.J.Lesnikowski. *Organometallics*, **26**, 3272 (2007)
170. B.A.Olejniczak. *Can. J. Chem.*, **89**, 465 (2011)
171. H.C.Kolb, M.G.Finn, K.B.Sharpless. *Angew. Chem., Int. Ed.*, **40**, 2004 (2001)
172. K.Ebenryter-Olbin'ska, D.Kaniowski, M.Sobczak, B.A.Wojtczak, S.Janczak, E.Wielgus, B.Nawrot, Z.J.Leśnikowski. *Chem. – Eur. J.*, **23**, 16535 (2017)
173. D.Kaniowski, K.Kulik, K.Ebenryter-Olbínska, E.Wielgus, Z.Lesnikowski, B.Nawrot. *Biomolecules*, **10**, 718 (2020)
174. I.Grabowska, A.Stachyra, A.Góra-Sochacka, A.Sirko, A.B.Olejniczak, Z.J.Leśnikowski, J.Radecki, H.Radecka. *Biosens. Bioelectron.*, **52**, 170 (2014)
175. A.Semioshkin, V.Bregadze, I.Godovikov, A.Ilinova, Z.J.Lesnikowski, I.A.Lobanova. *J. Organomet. Chem.*, **696**, 3750 (2011)
176. A.A.Ilinova, V.I.Bregadze, A.N.Bogomazova, I.A.Lobanova, A.F.Mironov, A.A.Semioshkin. *Russ. Chem. Bull., Int. Ed.*, **62**, 1115 (2013)
177. E.Halbfinger, D.T.Major, M.Ritzmann, J.Ubl, G.Reiser, L.Jose, J.L.Boyer, K.T.Harden, B.Fischer. *J. Med. Chem.*, **42**, 5325 (1999)
178. A.Semioshkin, A.Ilinova, I.Lobanova, V.Bregadze, E.Paradowska, M.Studzinska, A.Jablońska, Z.J.Lesnikowski. *Tetrahedron*, **69**, 8034 (2013)
179. A.Ilinova, A.Semioshkin, I.Lobanova, V.Bregadze, A.Mironov, E.Paradowska, M.Studzinska, A.Jablońska, M.Pietras, Z.J.Lesnikowski. *Tetrahedron*, **70**, 5704 (2014)
180. V.A.Korshun, E.V.Manasova, Y.A.Berlin. *Russ. J. Bioorg. Chem.*, **23**, 300 (1997)
181. M.J.Robins, R.S.Vinayak, S.G.Wood. *Tetrahedron Lett.*, **31**, 3731 (1990)
182. H.Maeda, H.Nakamura, J.Fang. *Adv. Drug Deliv. Rev.*, **65**, 71 (2013)
183. A.Jain, S.K.Jain. *Curr. Mol. Med.*, **18**, 44 (2018)
184. H.Nakamura. In *Boron Science: New Technologies and Applications*. (Ed. N.S.Hosmane). (Boca Raton, FL: CRC Press, 2012). P. 165
185. T.Schaffran, F.Lissel, A.Burghardt, R.Peschka-Süss, R.Schuberg, D.Gabel. In *Proceedings of the 13th International Congress on Neutron Capture Theraphy: A New Option Against Cancer*. (Eds A.Zonta, S.Altieri, L.Roveda, R.Barth). (Florence, 2008). P. 144
186. T.Schaffran, F.Lissel, B.Samatanga, G.Karlsson, A.Burghardt, K.Edwards, M.Winterhalter, R.Peschka-Süss, R.Schubert, D.Gabel. *J. Organomet. Chem.*, **694**, 1708 (2009)
187. A.A.Druzina, O.B.Zhidkova, I.D.Kosenko. *Russ. Chem. Bull., Int. Ed.*, **69**, 1080 (2020)
188. D.A.Feakes, J.K.Spinler, F.R.Harris. *Tetrahedron*, **55**, 11177 (1999)
189. H.Nakamura, M.Ueno, J.Lee. *Tetrahedron Lett.*, **48**, 3151 (2007)
190. V.I.Bregadze, I.B.Sivaev, R.D.Dubey, A.Semioshkin, A.V.Shmal'ko, I.D.Kosenko, K.V.Lebedeva, S.Mandal, P.Sreejyothi, A.Sarkar, Z.Shen, A.Wu, N.S.Hosmane. *Chem. – Eur. J.*, **26**, 13832 (2020)
191. A.V.Shmal'ko, I.B.Sivaev, L.V.Kovalenko, V.I.Bregadze, D.Gabel'. *Usp. Khim. Khim. Tekhnol.*, **27** (4), 119 (2013)
192. M.Uchman, P.Jurkiewicz, P.Cígler, B.Grüner, M.Hof, K.Procházka, P.Matějíček. *Langmuir*, **26**, 6268 (2010)
193. M.Chaari, N.Gaztelumendi, J.Cabrera-González, P.Peixoto-Moledo, C.Viñas, E.Xochitiotzi-Flores, N.Farfán, A.B.Salah, C.Nogués, R.Núñez. *Bioconjug. Chem.*, **29**, 1763 (2018)
194. B.M.Muñoz-Flores, J.Cabrera-González, C.Viñas, A.Chávez-Reyes, H.V.R.Dias, V.M.Jiménez-Pérez, R.Núñez. *Chem. – Eur. J.*, **24**, 5601 (2018)
195. M.Couto, I.Mastandrea, M.Cabrera, P.Cabral, F.Teixidor, H.Cerecetto, C.Viñas. *Chem. – Eur. J.*, **23**, 9233 (2017)
196. M.Couto, C.Alamón, M.F.García, M.Kovacs, E.Trias, S.Nievas, E.Pozzi, P.Curotto, S.Thorp, M.A.Dagrosa, F.Teixidor, C.Viñas, H.Cerecetto. *Cells*, **9**, 1408 (2020)
197. M.Couto, C.Alamón, S.Nievas, M.Perona, M.A.Dagrosa, F.Teixidor, P.Cabral, C.Viñas, H.Cerecetto. *Chem. – Eur. J.*, **26**, 14335 (2020)