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The medicinal chemistry of carboranes

John F. Valliant *, Katharina J. Guenther, Arienne S. King, Pierre Morel, Paul Schaffer, Oyebola O. Sogbein, Karin A. Stephenson

Department of Chemistry, McMaster University, 1280 Main Street West, Hamilton, Ont., Canada L8S 4M1

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* Corresponding author. Tel.: +1-905-525-9140x23303; fax: +1-905-522-2509
E-mail address: valliant@mcmaster.ca (J.F. Valliant).

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Abstract

The medicinal chemistry of dicarba-*closo*-dodecaboranes (otherwise referred to as carboranes) has traditionally centered on their use in boron neutron capture therapy (BNCT). More recently, work has begun to exploit the unique chemical and physical properties of carboranes for the preparation of novel inorganic pharmaceuticals and biological probes. This review is designed to highlight some of the recent work concerning medicinal carborane chemistry including the synthesis and testing of new BNCT agents. Following this review, as an appendix, is an illustrated summary of reactions involving carboranes reported in literature since 1992.

Keywords: Carboranes; Medicinal; BNCT; BNCS; Imaging; Pharmaceuticals

1. Introduction

Polyhedral heteroboranes have been the subject of intense research for over 40 years. A subset of this extensive class of compounds are dicarba-*closo*-dodecaboranes, commonly referred to as carboranes (an abbreviation of the IPUAC name carbaboranes) having the general formula $C_2B_{10}H_{12}$. Because of their unique physical and chemical properties, carboranes have been used to prepare catalysts [1–10], radiopharmaceuticals [11], polymers [12–16], and a assortment of unique coordination compounds [17–28]. The medicinal chemistry of carboranes has traditionally centered on their use in boron neutron capture therapy (BNCT), which is a binary therapy modality for treating cancer (vide infra). More recently, researchers, including our group, have begun to recognize the benefits of using carboranes for the preparation of pharmaceuticals and biological probes. This review is designed to highlight some of the recent work regarding medicinal carborane chemistry including reports of new BNCT agents. It does not extensively cover the medicinal chemistry of polyhedral boranes, nor is it intended to be a comprehensive review of the literature.

1.1. Dicarba-closo-dodecaboranes

Dicarba-*closo*-dodecaboranes exist as *ortho* (**1**), *meta* (**2**) and *para* (**3**) isomers, which differ in the relative positions of the carbon atoms in the cluster. The structures of the three isomers and the IUPAC numbering scheme for *ortho*-carborane are shown in Fig. 1. The clusters have nearly icosahedral geometry in which each of the carbon and boron atoms are hexacoordinate. The average inter-atomic distances are shown in Table 1 [29].

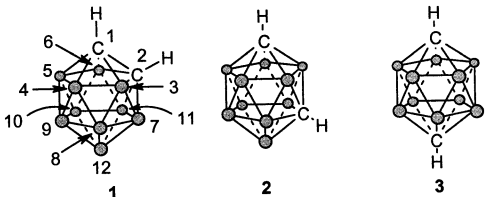


Fig. 1. *Ortho* (**1**), *m*eta (**2**) and *para*-Carborane(**3**).

The synthesis of *ortho*-carborane was first reported in 1963 by two groups [30,31]. *Ortho*-carboranes are prepared by the reaction of acetylenes, including both mono and disubstituted alkynes, with $B_{10}H_{12}L_2$, which is generated, often in situ, from decaborane ($B_{10}H_{14}$) and a weak Lewis base ($L = CH_3CN$, RSR, R_3N) [32,33]. Reactions are typically performed in acetonitrile or in toluene heated to reflux for several hours (6–24 h). The reaction of $B_{10}H_{12}L_2$ with acetylenes can be performed in the presence of a wide range of functional groups including esters, halides, carbamates, ethers, nitro groups, to mention only a few examples. Reactions cannot, however, be performed in the presence of nucleophilic species such as alcohols, acids or amines [34]. These functionalities must be protected prior to conversion of an alkyne to a carborane because the polar groups degrade the $B_{10}H_{12}L_2$ complex leading to poor (or negligible) yields of the desired product. Yields of carboranes are typically modest ranging on average between 40 and 60%.

The *meta* and *para*-carborane isomers are prepared by thermal isomerization of *ortho*-carborane under an inert atmosphere. At 400–500 °C *ortho*-carborane converts to the *meta*-isomer, which in turn rearranges to the *para*-isomer between 600–700 °C. The mechanism of isomerization has been the subject of considerable interest [35–39]. Lipscomb et al. were the first to propose a mechanism for the isomerization of *ortho* to *meta*-carborane [40], unfortunately the reported mechanism, which involves a cubeoctahedral complementary geometry and a diamond-square-diamond rearrangement, could not rationalize the isomerization of *meta*-carborane to the *para*-isomer. Most recently, Johnson et al. proposed a mechanism for the interconversion of the carboranes through anticubeoctahedral complementary geometries [41]. All three carborane

Table 1
Bond distances found in *ortho*-carborane

Bond	Distance (Å)
C–C	1.62–1.70
B–C	1.70–1.75
B–B	1.70–1.79

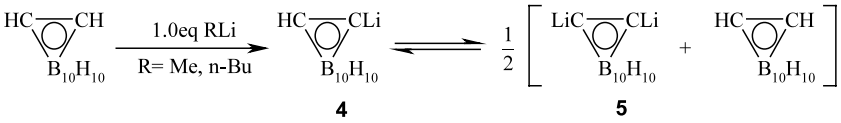


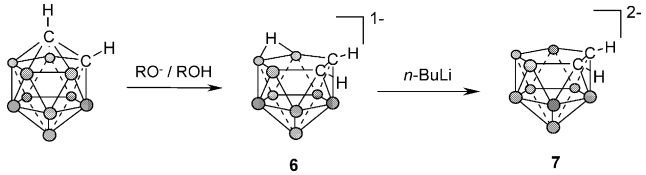
Fig. 2.

isomers and decaborane are widely available from a number of commercial sources at a modest expense.

A unique aspect of carborane chemistry is that the carbon and boron vertices have orthogonal reactivities. The CH groups in the carboranes are weakly acidic (pK_a (*ortho*) = 22.0, pK_a (*meta*) = 25.6, pK_a (*para* = 26.8)) [42,43], and can be readily deprotonated generating nucleophiles. In contrast, the boron vertices are derivatized by reactive electrophiles. It is therefore possible to prepare a wide range of C and/or B derived carboranes regioselectively without the need for complex protecting group strategies.

The CH group in *ortho*-carborane is more acidic than in *meta* and *para*-carborane as a consequence of the greater electronegativity of the proximate carbon atom compared with the adjacent boron vertices found in the other isomers. The preparation of mono-lithiocarboranes of all three isomers is readily achievable using a strong base (MeLi, PhLi, *n*-BuLi etc.). The resulting carboranyl anions are sufficiently nucleophilic to react with a wide range of electrophiles including halogens (I_2, Br_2, Cl_2), alkyl halides, aldehydes, CO_2, acid chlorides, chlorosilanes to mention only a few examples (see appendix). The steric bulk of the carboranes, however, requires that the electrophile be reasonably reactive and unhindered in order to achieve decent yields of the desired products.

The synthesis of mono C-substituted *ortho*-carborane derivatives deserves special mention because it is complicated by the tendency of monolithio *ortho*-carborane **4** to disproportionate to *ortho*-carborane and the dianion **5** (Fig. 2) [44]. This problem can be ameliorated by synthesizing TBDMS protected *ortho*-carborane [45], which can be isolated in >98% yield, or by running the deprotonation–substitution reaction in the presence of dimethoxyethane [46]. The latter approach is not suitable for electrophiles that can react with the second carborane carbon to form thermodynamically favorable ring systems. Another approach to achieving mono substitution, which we have found particularly effective, is to run reactions under high-dilution conditions (i.e. below 0.1 M).



Scheme 1.

Despite the use of strong bases to afford the mono-lithiocarboranes, alkoxide bases react with the B3/B6 and B2/B3 atoms of *ortho*- and *meta*-carboranes, respectively, yielding the more hydrophilic dicarbaundecaborate(1-) ions. The 7,8-(**6**) and 7,9-*nido*-carboranes (Scheme 1) [47,48] can also be generated using amines [49], such as pyrrolidine [50], and fluoride ion [51]. These conditions are particularly useful for converting *closo*-carboranes to the more water-soluble *nido* clusters in the presence of alkoxide sensitive functional groups. It should be also noted that *ortho*-carborane derivatives bearing electron-withdrawing substituents, such as esters or aldehydes, α-to the cage, can degrade to the corresponding *nido*-carborane under neutral conditions [52]. The rate of degradation is solvent dependent and it does not occur for all electron-withdrawing substitutents (ex. carbamates). Degradation under neutral conditions has not been reported for *meta*-carborane derivatives.

The similarity in reactivity between the B3/B6 and B2/B3 atoms in *ortho* and *meta*-carborane has important implications in medicinal chemistry. When substituted carboranes are converted to the corresponding *nido*-species, a 1:1 mixture of enantiomers is produced. The enantiomers can be separated by recrystallization, using a chiral counter ion, or by HPLC [53,54].

Derivatization of the boron vertices can be achieved using a number of different strategies. Treatment of *ortho*-carborane in liquid ammonia with alkali metals (Na, K), followed by oxidation using $KMnO_4$ or CuCl, results in the selective formation of 3-amino-*ortho*-carborane [55,56]. The amino group can be subsequently converted to a variety of other functional groups via the diazonium ion. B-Halo and alkyl derivatives can prepared under Friedel–Crafts type reaction conditions [34]. This includes a recently published method for the conversion of the vertices in *para*-carborane to deca-B-methyl-*p*-carborane, undecamethyl-*p*-carborane and dodecamethyl-*p*-carborane derivatives [57]. The latter compound can be considered a stereochemical surrogate of C_{60} [21].

B-iodo derivatives undergo Pd cross-coupling reactions to afford a wide range of unique B-alkylated derivatives [58–60]. As an alternative to the cross-coupling type reactions, B-derivatives can be prepared by reacting the 7,8 and 7,9 *nido*-carboranes with alkyl or arylboron dihalides ($RBCl_2$) [61].

The *nido*-7,8 and 7,9-$[C_2B_9H_{12}]^-$ ions, which are commonly used to increase the solubility of carborane derivatives in aqueous media, each contain a bridging

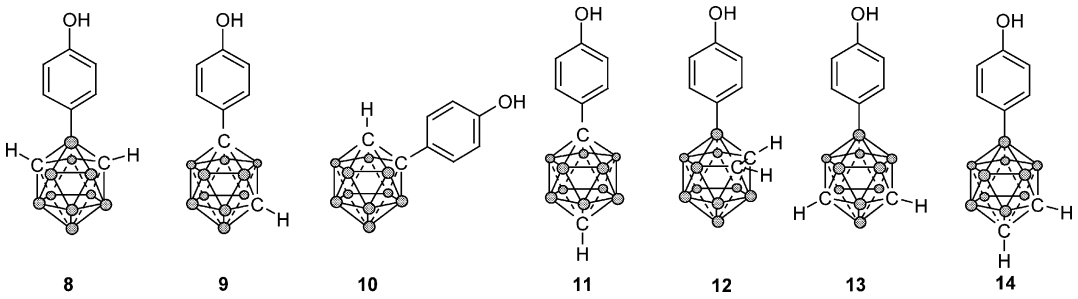


Fig. 3.

hydrogen atom which can be readily removed with base to yield the dicarbollide dianions (**7**), *nido*-7,8-or 7,9-$[C_2B_9H_{11}]^{2-}$. The dicarbollide dianion is formally isolobal to cyclopentadienide and has therefore been used to prepare a wide range of organometallic complexes, including a carborane analogue of ferrocene, first reported by Hawthorne and coworkers [62]. *nido*-carboranes and the dicarbollide dianion can be labeled with a range of radionuclides, which creates the opportunity to prepare radiopharmaceuticals and facilitates the process of screening new compounds both in vitro and in vivo (vide infra).

1.2. Characterization

Carboranes are readily characterized by traditional methods including X-ray crystallography [63]. Several highly specialized reviews have covered the specifics of carborane characterization in detail [43,64,65] consequently, only the most basic features are described herein.

Monitoring the progress of carborane reactions can be readily accomplished by thin layer chromatography (TLC). Carboranes and their derivatives can be visualized on TLC plates using a $PdCl_2$ in HCl spray [66]. Carboranes reduce the Pd(II) to palladium metal leaving behind a dark spot. We have also found in situ IR as another convenient means of following the progress of reactions. The BH stretching frequency is particularly diagnostic, appearing around 2600 cm^{-1} for *closo*-carboranes and shifted slightly for the *nido*-carboranes at 2520 cm^{-1}. The CH stretching frequencies can be found at 3065 (*para*), 3070 (*meta*), and 3079 cm^{-1} (*ortho*).

The ^{1}H-NMR of carboranes typically exhibits a broad signal between 3.00 and −0.75 ppm arising from the protons attached to the boron atoms of the cage. The CH protons are often slightly broadened and typically appear between 2 and 3.5 ppm. *nido*-Carboranes exhibit a characteristic doublet between −2.5 and −3.0 ppm arising from the bridging hydride.

While both ^{10}B and ^{11}B are NMR active nuclei, the latter isotope, which comprises 80.3% of natural boron, is more often used in NMR experiments owing to its high abundance, relatively high receptivity (10% of ^{1}H), reasonable peak width at half-height, and short average relaxation times [64]. The boron resonances are split into doublets as a consequence of coupling with the terminal hydrogen atoms having coupling constants in the range of 125–205 Hz. Because of the boron content in typical borosilicate NMR tubes, it is prudent to use boron-free NMR tubes or alternatively, a more inexpensive solution, is to use a spin-echo pulse sequence with a short delay for removing the background signal from the spectrum [67].

HPLC can be used to characterize the purity of carborane derivatives and to measure log *P* values. Endo and colleagues recently determined the log *P* values for a series of carboranyl phenols (Fig. 3) using a straightforward HPLC protocol [68]. For example, C-substitution of the *ortho*, *meta* and *para* carboranes resulted in compounds (**8**, **9**, **10**, **11**) that are more hydrophobic than the adamantly group while compound **14** was found to be less hydrophobic than 4-cylcohexylphenol. The hydrophobicity of the B-linked phenols decreased in the order **12** > **13** > **14**.

2. Carboranes in medicinal chemistry

The initial attraction to carboranes for medicinal chemistry research was a result of their high boron content and stability to catabolism, which are important criteria for BNCT agents. More recently, it has been demonstrated that carboranes can be used to enhance hydrophobic interactions between pharmaceuticals and

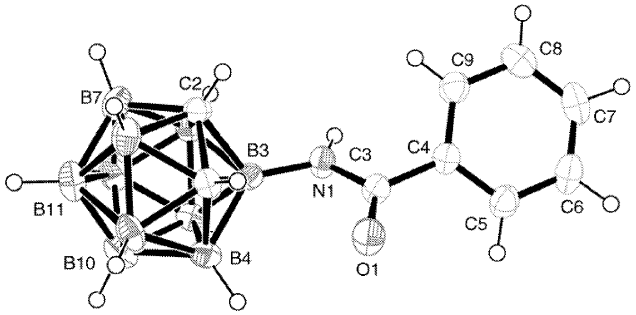


Fig. 4. X-Ray structure of **15**.

their receptors and to increase the in vivo stability, and hence bioavailability, of compounds that are normally rapidly metabolized. These properties, coupled with their diverse chemistry, which includes the opportunity to 'tag' the clusters with diagnostic radionuclides, make carboranes attractive synthons from which to construct novel pharmaceuticals, radiopharmaceuticals and biological probes. When considering preparing a series of derivatives of a specific pharmacophore, it is prudent to consider incorporating dicarba-*closo*-dodecaboranes as a substituent or as part of the basic molecular framework, especially if hydrophobic interactions are an important component of receptor binding.

Carboranes can be incorporated into specific biomolecules using a number of different strategies [69]. In addition to direct conjugation to a pendent functionality, carboranes can be introduced in place of specific aryl groups. The volume occupied by a carborane is similar to the 3-dimensional sweep of a phenyl group [70]. To illustrate this point, the X-ray structure of the benzamide derivative of 3-amino-*ortho*-carborane (**15**), which was solved in our laboratory, is shown in Fig. 4. The diameter of the cluster (without standard deviations from atomic centroids) is 5.25 Å while that of the phenyl ring is 4.72 Å.

At the end of the review, as an appendix, is an illustrated synopsis of reactions involving carboranes, including functional group transformations and cage modifications, which have appeared in the literature since 1992. We hope this summary will be useful when devising synthetic routes to novel carborane derivatives. The development of new methods for preparing functionalized carboranes is an essential component of medicinal carborane chemistry and remarkably, it is still a hot-topic of research nearly 40 years after *ortho*-carborane was first synthesized.

3. Boron neutron capture therapy

Boron neutron capture therapy (BNCT) is a binary approach to cancer treatment originally proposed by Locher in 1936 [71]. It is based on the $^{10}B(n, \alpha)^{7}Li$ reaction, which occurs when boron-10, which has a large capture cross section relative to the more abundant endogenous nuclei (^{1}H, ^{12}C, ^{31}P, ^{14}N), is exposed to thermal neutrons. BNCT is referred to as a binary therapy because the individual components (i.e. the boron atoms and the neutrons) unto themselves are not efficacious. In combination, however, they have the potential to create a highly selective therapy because the daughters of the boron neutron capture reaction, the alpha particle and lithium ion, traverse a distance which is only slightly less than the diameter of a typical cell [72–76], thereby depositing their substantive energies within a confined area.

In order to achieve successful cell killing, BNCT agents must be able to deliver considerable quantities of boron to the tumor cells selectively. It is generally accepted that between 10 and 30 μg $^{10}B\ g^{-1}$ tumor is required for successful therapy [77–79], however, this amount is reduced substantially if the boron is concentrated in or near the cell nucleus [80–82]. The appreciable amount of boron is required to minimize the contribution of radiation dose derived from the capture of neutrons by endogenous nuclei [75,83]. BNCT agents must also clear the blood rapidly to avoid inducing necrosis in the vasculature. The optimal tumor:blood ratio is around 5:1. Another obvious, but not necessarily easily addressable requirement, is that the boron delivery vehicle be non-toxic. This is a challenging issue when one considers the amount of agent that must be administered to achieve the requisite levels of boron in the tumor. Despite these requirements, there are a number of promising BNCT agents that are currently undergoing clinical trials.

Improved targeting and pharmacokinetics, as well as the desire to use of BNCT to treat different types of cancers, such as peripheral melanoma, is continuing to spur- on the development of new BNCT agents [84,85]. Herein we highlight a select number of recent reports on the preparation and evaluation of new carborane-based BNCT agents.

3.1. Carbohydrates

Carbohydrate research has undergone a renaissance over the last decade as a consequence of advances in oligosaccharide synthesis [86–88] and carbohydrate biology [89,90]. One of the advantages of using carbohydrates as targeting agents for BNCT, beyond their ability to target specific receptors found on the surface of tumors, is that simple oligosaccharides typically exhibit low toxicities. A further benefit of this particular class of targeting agent is their ability to compensate for the hydrophobicity of the carborane cores, which could help limit non-specific protein binding and/or high liver uptake.

There have been numerous reports on the synthesis of carborane–carbohydrate conjugates [50,91–96]. More recently, Tietze et al. [97,98] prepared and screened a series of carboranyl glycosides, which included glucoside, lactoside and maltoside conjugates (Fig. 5). The carborane containing carbohydrates were prepared from the corresponding alkynyl–glycosides which were in turn synthesized by glycosylation of propargyl alcohol or 3-butyn-1-ol with trichloroacetimidates of glucose, maltose and lactose (having the remaining free OH groups acetylated). Reaction of the alkynes with decaborane, in the presence of acetonitrile, resulted in the desired products in 40–60% yields.

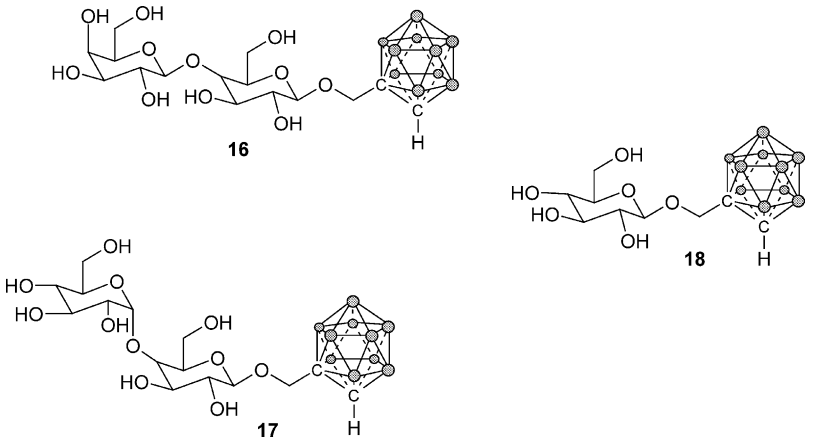


Fig. 5.

The incubation of the glycosides with B-16 melanoma cells showed that the maltoside **17** exhibited the highest uptake. Compound **17** also demonstrated a substantial uptake in C6 rat glioma cells (65.7 ppm at 12 h). When these cells were irradiated with thermal neutrons, a significant killing effect was observed. After 3 h, the boron concentration in the cells was 6.1 ppm, which rose to 20 ppm after 24 h. The lactoside **16** and the glucoside **18** reached a max level of boron of 13.2 ppm (12 h) and 11.2 ppm (3 h), respectively. In vivo uptake studies of **17** in rats bearing brain tumors had mixed results. At a dose of 25 mg B kg^{-1} body weight, the concentration of boron in the tumor was ca. 3.0 ppm at 4 h. Unfortunately the concentration in the blood at that time was about the same and furthermore, the majority of the mice suffered from haematuria 1 h after administration.

In an attempt to increase the ability of carboranyl–lactosides and glucosides to be incorporated into the cell membrane, Tietze and co-workers prepared carbohydrate- carborane derivatives having lipophilic side chains linked through the remaining carborane CH group (Fig. 6) [99]. Furthermore, to facilitate detection of the compound by NMR, a fluorine atom was incorporated as part of the aliphatic chain. The ^{19}F nucleus has a high receptivity and a wide chemical shift dispersion and is absent in most living tissue making it an ideal marker for magnetic resonance imaging (MRI).

The toxicities of various derivatives were evaluated in vitro using cloning efficiency tests on human bronchial carcinoma cells of line A549. The authors demonstrated that the fluorine containing lactosides **21** and **22** displayed almost no cytotoxicity in concentrations up to 300 μM whereas the corresponding carboranyl alcohols were considerably toxic. The in vivo distributions of the carboranes containing the hydrophobic side chains along with the ^{19}F MR experiments have not yet been reported.

In an attempt to develop new glycoside BNCT agents targeted at cellular lectins particularly those found on melanoma cells, Giovenzana et al. [92] reported an alternative approach for the synthesis of carborane–carbohydrate derivatives (Scheme 2). Pentaacetyl-D-glucose **23**, and the equivalent lactose derivative were reacted with 2-propyn-1-ol in the presence of TMSOTf affording compounds **24a** and **b**, which in turn were used to prepare the corresponding carboranes **25a** and **b**.

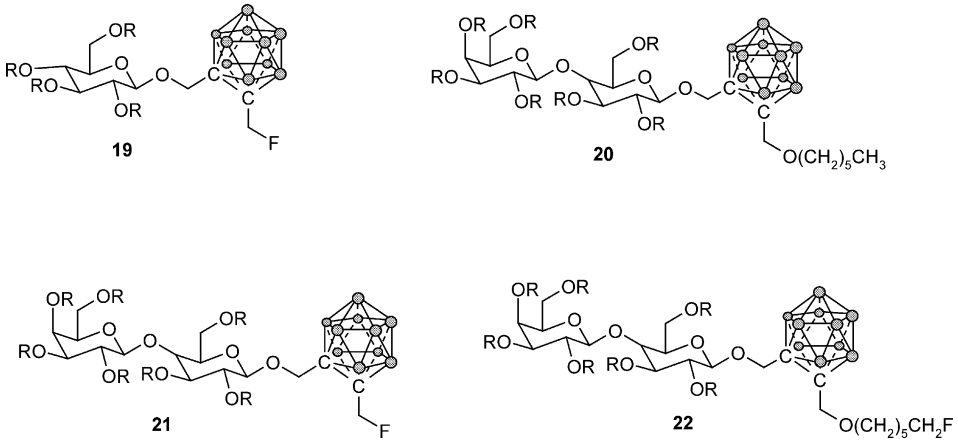
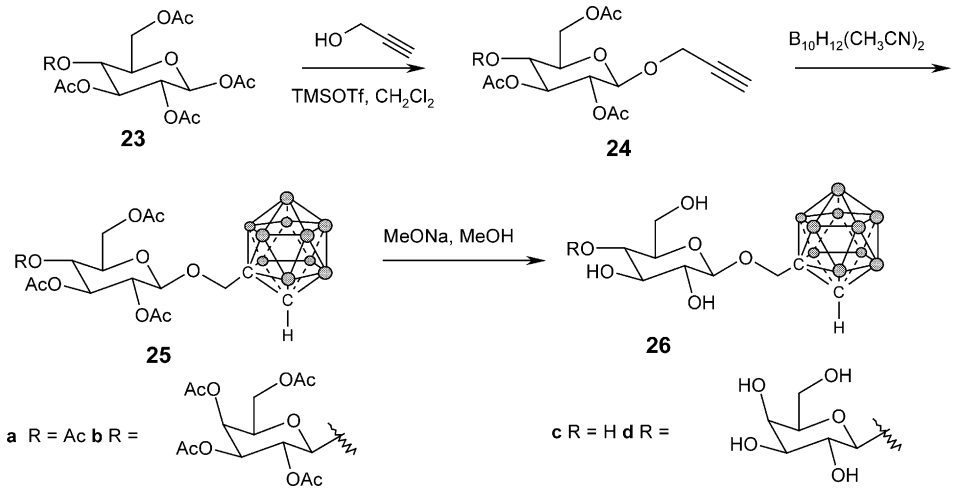


Fig. 6.



Scheme 2.

The compounds were then selectively deacetylatyed giving the desired products **26c** and **d** using sodium methoxide.

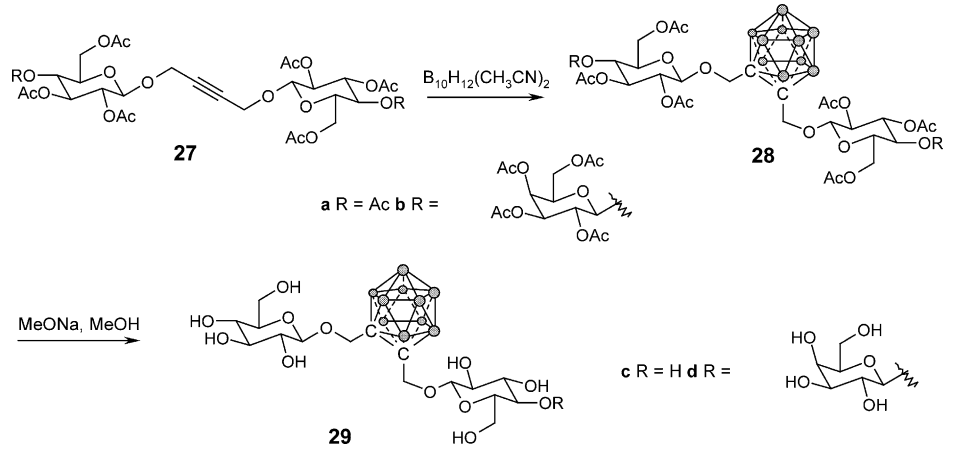
This group also reported a particularly novel carbohydrate derivative in which the carborane was 'hidden' between two sugar units (**29c**, **d**, Scheme 3). The carborane was prepared from the glycoside derivatives of 2-butyne-1,4-diol. Compounds **29c** and **d** were also converted, using pyrrolidine, to the corresponding *nido* derivative affording a more hydrophilic analogue. Alternatively, the authors demonstrated that it is possible to remove the acetate groups without converting the cage to the corresponding *nido*-carborane derivative.

Tietze and colleagues also reported the synthesis of mixed bis-glycosides (**30**, **31**, Fig. 7) [100]. The carborane derivative of the bis-glycosides of mannose and glucose displayed almost no toxicity up to a concentration of 0.50 mM, however, their uptake into B-16 melanoma and C6 cells was very low. This was not of great concern to the authors because they plan to utilize these compounds as prodrugs. The proposed approach entails administering an antibody–glucohydrolase conjugate, specific for malignant cells, along with carbohydrate–carborane derivatives. The enzyme is designed to cleave one or both of the sugar residues in close proximity to the tumor thereby facilitating selective uptake of the more lipophilic catabolite. Results of these studies have not yet been published.

3.2. Porphyrins (and related compounds)

Porphyrins, containing carboranes as substituent groups, have been highly scrutinized as BNCT agents and reviews covering their synthesis and biological properties have been reported elsewhere [85]. As a consequence, only select examples taken from the very recent literature will be covered.

Hogenkamp et al. [101] prepared a series of cyanocobalamine (vitamin B12) conjugates containing *nido*-carboranes linked to specific sites on the porphyrin backbone via amide bonds (Fig. 8). The in vitro binding of the conjugates demonstrated that the analogues were able to competitively block ^{57}Co cyanocobalamin from



Scheme 3.

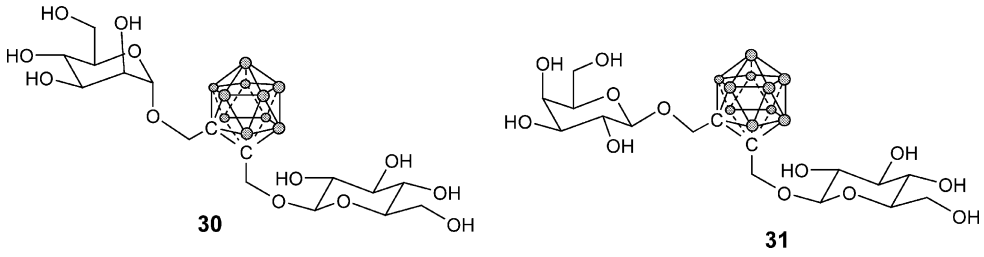


Fig. 7.

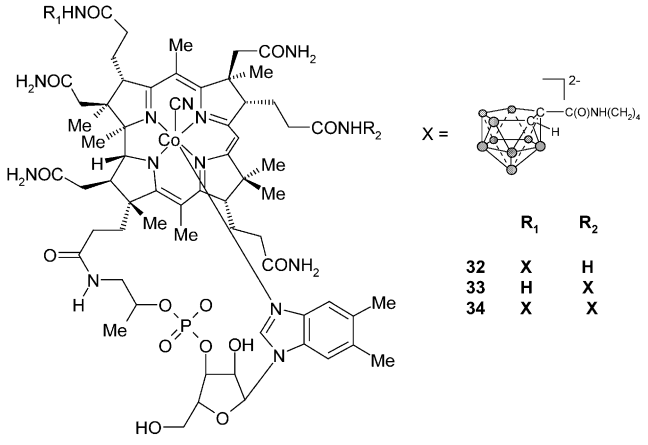
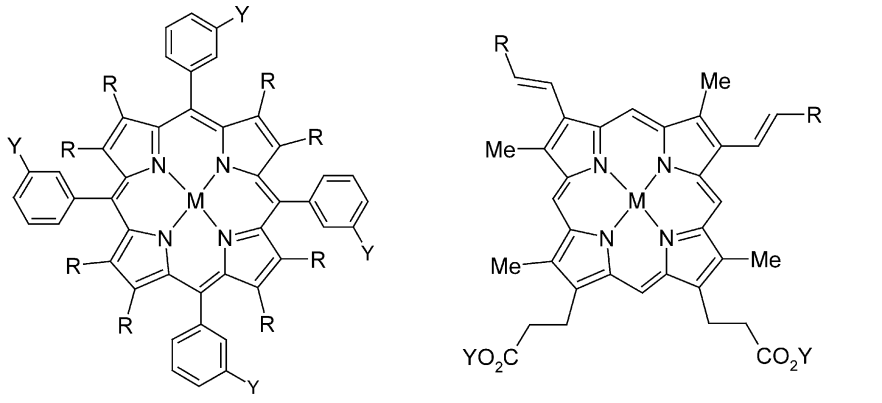


Fig. 8.

binding to the transcobalamin proteins. The percent binding for derivatives **32**, **33**, and **34** was 92.93, 37.5, and 37.02%, respectively. These values are lower than the corresponding DTPA derivatives, whose Gd complexes are being investigated as MR contrast and NCT agents. Studies in vivo have not yet been reported.

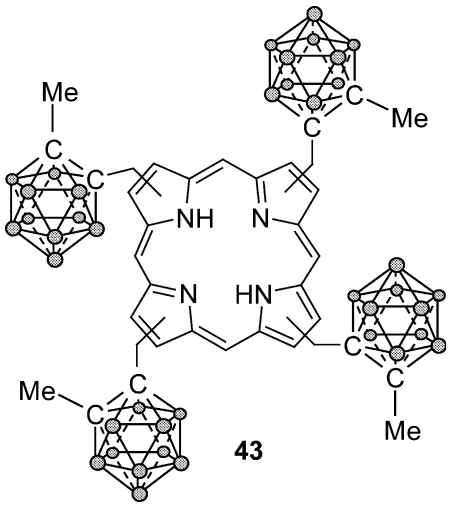
A number of carborane-containing metalloporphyrins, derived from both tetraphenylporphyrins and heme analogues were screened by Miura et al. (Fig. 9) [102]. The inclusion of metal atoms in the porphyrins, aside from influencing biological activity, offers the opportunity to include radionuclides, like ^{67}Cu, to facilitate evaluating new compounds in animals and for treatment planning (vide infra). Multiple doses of the porphyrins were administrated to mice bearing subcutaneously transplanted mammary carcinomas and the toxicity and biodistribution of each compound determined.

The water insoluble tetraphenylporphyrins were less toxic and delivered more boron to the tumors than did the more water soluble compounds. The highest absolute tumor boron concentration and the greatest tumor:blood and tumor:brain boron ratios were obtained using NiTCP–H, NiTCP and CuTCP. The NiTCPH was able to deliver 100 μg B g^{-1} of tumor tissue, respectively, with a tumor:blood boron concentration ratio greater than 500:1 and a tumor:brain boron concentration ratio of greater than 50:1, 4 days after the last of six intra-peritoneal injections (given over 2 days). The NiDPE and NiNTCPH did not deliver therapeutic amounts of boron to the tumor. In a later study, CuTCPH showed similar tumor uptake to the nickel analogue (60–70 μg B g^{-1} tumor) and a 300:1



35, NiTCP, R = $CH_2CO_2CH_3$, Y = $OCH_2C_2HB_{10}H_{10}$, M = Ni
36, NiTCP-H, R = H , Y = Y = $OCH_2C_2HB_{10}H_{10}$, M = Ni
37, NiNTCP-H, R = H, Y = $OCH_2C_2HB_9H_{10}^-K^+$, M = Ni
38, CuTCP, R = $CH_2CO_2CH_3$, Y = $OCH_2C_2HB_{10}H_{10}$, M = Cu
39, NiDPE, R = $C_2HB_{10}H_{10}$, Y= CH_3, M = Ni
40, ZnDPE, $C_2HB_{10}H_{10}$, Y = CH_3, M = Zn
41, VCDP, R = $C_2HB_9H_{10}^-K^+$, Y= H, M = 2H
42, CuTCPH, R = H, Y = $OCH_2CH_2B_{10}H_{10}$, M = Cu

Fig. 9.



43

Fig. 10.

tumor:blood ratio in BALB/c mouse mammary carcinoma model [103].

Allen and co-workers performed biodistribution studies with Gd–TCP in nude mice with human melanoma (MM-138) xenografts [104]. The Gd–TCP showed a 16% decrease in the T_1 value for the tumor relative to that in untreated mice. The amount of Gd in the tumor was ca. 21% of the injected dose as determined by ICP–AES analysis of tissue samples. The report indicated that 24 μg of boron was delivered to the tumor but it appears as though that number was determined from the Gd measurements, which is based on the assumption that the Gd complex remains intact.

Lauceri et al. [105] recently demonstrated that *meso*-tetrakis[4-(*nido*-carboranyl)phenyl]porphyrin [(*p*-H_2TCP)$^{4-}$] and the more acidic *meso*-tetrakis[3-(*nido*-carboranyl)phenyl]porphyrin [(*m*-H_2TCP)$^{4-}$] interact with DNA under physiological conditions. The addition of DNA to (*p*-H_2TCP)$^{4-}$ caused a red shift, hypochromicity and broadening of the Soret band in the absorption spectra. This indicates that the diprotonated form of the porphyrin interacts with DNA. This was further confirmed by resonance light scattering experiments. Similar experiments demonstrated that the *meta*-substituted porphyrin (*m*-H_2TCP)$^{4-}$ self-aggregated onto a DNA matrix.

New synthetic methods are needed to expand the range of different porphyrin structures that can be evaluated as BNCT agents. Chayer et al. recently reported the syntheses of three carboranylpyrroles bearing carborane cages in 3-and/or 4-positions of the pyrrole ring, either directly linked or through a spacer [106]. Tetramerization of two carboranylpyrroles afforded the corresponding β-carboranylporphyrins **43** as a mixture of isomers (Fig. 10).

3.3. Intercalators

BNCT agents that target DNA are attractive because, as mentioned previously, the amount of boron required for successful therapy is reduced if the ^{10}B is deposited proximate to the DNA [107]. To this end, a series of carborane containing analogues of DNA intercalating compounds, phenanthridine and acridine, were prepared by Gedda et al. and analyzed in cultured human malignant glioma spheroids (Fig. 11) [108]. The most lipophilic compounds were cytotoxic and bound primarily to the outermost region of the spheroid with poor penetration into the inner regions. The most hydrophilic compounds, specifically **48**, showed lower cytotoxicity and lower accumulation in monolayer cells with rapid binding in the innermost regions of the spheroid. These compounds are not specific to cancer cells, thus to gain tumor specificity, the proposed strategy is to prepare conjugates with tumor targeting agents (vide infra).

3.4. Polyamines

Polyamines bearing tethered carboranes have been shown to target DNA in vitro [109]. These derivatives, unfortunately, typically exhibit substantial toxicity. In an effort to ameliorate the toxicity issue, carborane–derived polyamines (**49**, **50**, Fig. 12) bearing water-solubilizing substituents were prepared and screened by Zhuo et al. [110] The compounds demonstrated the ability to displace ethidium bromide from calf thymus DNA and were rapidly taken up by F98 glioma cells in vitro at levels which match that of clinically used agents but at media concentrations that were 10–100 fold less. The introduction of the water-solubilizing groups was successful at reducing the toxicity issue. Unfortunately, the results of the in vivo biodistribution studies showed that the compounds were unable to deliver adequate quantities of boron to tumors in C57B1/6 mice bearing intracerebrally implanted Gl261 glioma and subcutaneously implanted B16 melanoma tumors.

3.5. Nucleosides

Because the synthesis of boronated nucleosides was recently reviewed elsewhere [111–113] only the most recent advancements in this area will be discussed.

Of the carboranylnucleosides that have been synthesized, β-5-*ortho*-carboranyl-2′-deoxyuridine, CDU, has received the most attention, due largely to its selective uptake in various cancer cell lines and its low cytotoxicity [114]. Recent work in 9L-glioma-bearing rats indicates that CDU is non-toxic up to 150 mg kg^{-1}, and that if administered in conjunction with a thermal neutron beam, the life of tumor bearing rats is extended. The median survival time of 9L-tumor bearing rats was

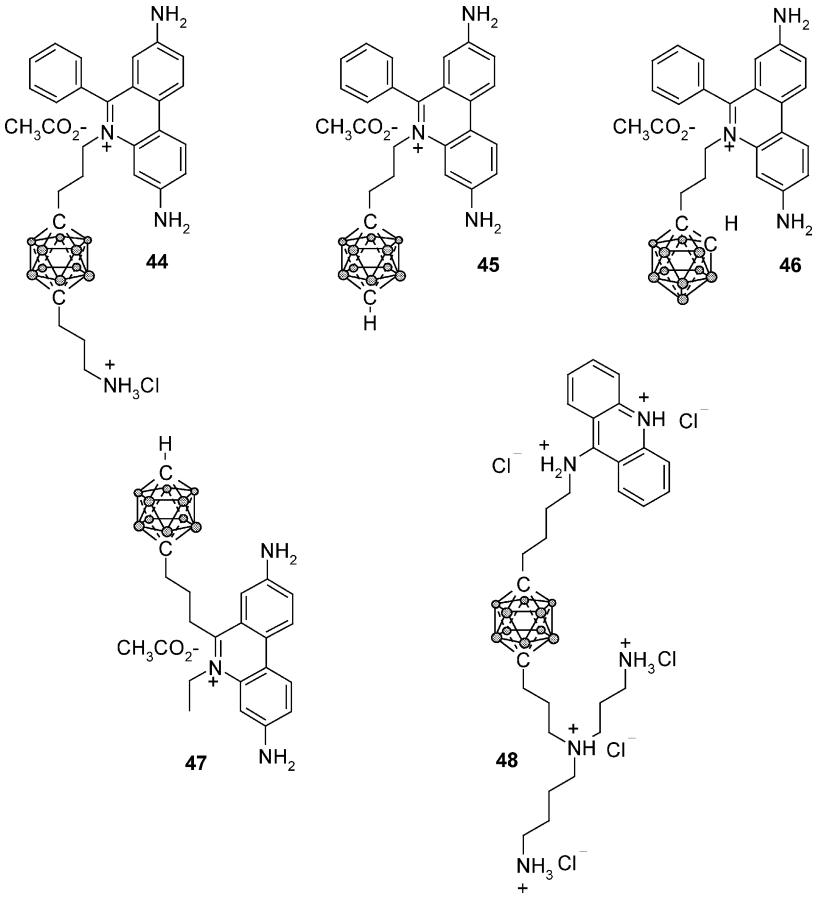
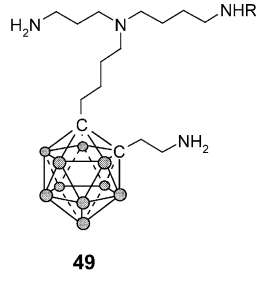


Fig. 11.



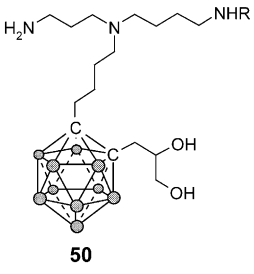


Fig. 12.

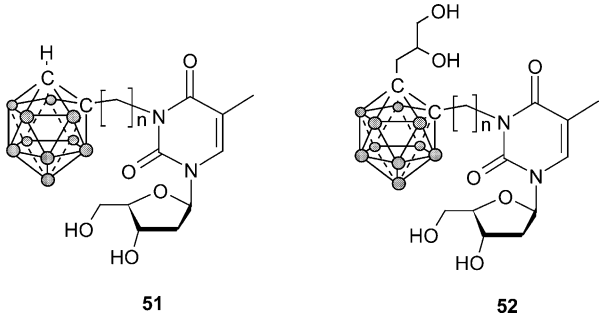


Fig. 13.

lengthened to 55 days, as compared with 20 days for control rats [115].

The uptake of D and L-CDU [116] in human U251 glioblastoma and CEM lymphoblast cells was studied and it was found that there was no discrimination between the isomers in these cell lines [117]. The uptake and cellular retention of both compounds, from a medium containing pharmacologically relevant levels of CDU, was above the threshold to be considered as a BNCT agent. Cellular accumulation of CDU is believed to be due to phosphorylation of the nucleoside by thymidine kinase, which effectively traps the nucleoside inside the cell [118].

Tjarks et al. evaluated a series of thymidine analogues bearing *ortho*-carborane substituents at the N3 position in phosphoryl transfer assays (Fig. 13) [118]. The derivatives contained various spacer chain lengths between the carborane and the thymidine base (**51**, $n = 2–7$) and a select number of derivatives also contained pendent alcohol groups (**52**, $n = 2–7$) in order to enhance solubility in aqueous media. Initial work found that the thymidine kinase 1 activity was greatest for the carborane derivatives bearing the pendant alcohol groups (**52**, $n = 2$, $n = 9$). There was essentially no

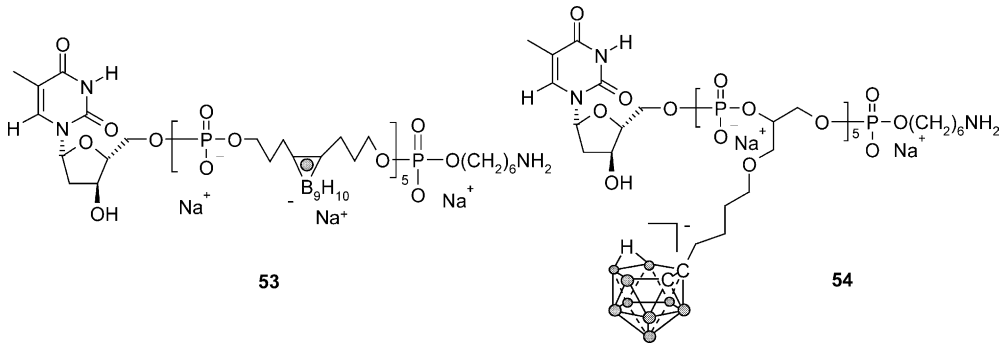


Fig. 14.

thymidine kinase 2 activity observed for any of the compounds tested.

3.6. Immunoconjugates

Guan et al. [119] recently reported the conjugation of boron-rich oligophosphates (Fig. 14) to a genetically-engineered anti-dansyl (DNS) IgG immunoprotein carrying an additional, unnatural, cysteine-residue as a second site of derivatization. The oligophosphates, which were prepared on an automated DNA-synthesis instrument [120,121] contain *nido*-carboranes and a thymidine residue at the psuedo-3′ terminus, which simplifies the synthesis and acts as a UV-active 'tag'. The primary amine at the pseudo-5′ end can be derivatized with a variety of reagents, including maleimidobenzoic acid *N*-hydroxysuccinimide ester (MBS), which in this case was used to link the oligophosphates to two specific cysteine residues found on the immunoprotein.

The activities of the boron-rich immunoconjugates were characterized both in vitro and in vivo. Compound **54** showed similar reactivity with antigen to IgG3, whereas compound **53** showed reduced interactions. The antibody conjugates retained reactivity with the high-affinity Fc receptor, FcγRI (CD 64), however, they both demonstrated a reduction in their ability to bind. Using ^{125}I-labelled conjugates, the biodistribution of the conjugates, which were determined in mice, demonstrated that the compounds exhibit similar rates of clearance. Both immunoconjugates, 24 and 72 h post-injection, were present in the liver and kidney at higher concentrations than the wild-type antibody. There was, however, a substantial amount of conjugate that remained in circulation for a prolonged period of time, which may be still available for targeting tumors.

Analogues of compounds **53** and **54**, bearing a fluorescein derivative in place of the thymidine groups, were shown to selectively accumulate in the nucleus of TC7 cells after microinjection [122]. When the *nido*-carboranyl oligomeric phosphate diesters (*nido*-OPDs) were injected into the cytoplasm, along with rhodamine-labeled BSA, the oligomeric phosphates specifically localized in the nucleus while the BSA derivative remained in the cytoplasm. The *nido*-OPD containing the carborane as part of the phosphate backbone was observed in the nucleus within 10 min of injection where it remained for 24 h. The *nido*-OPD containing the carborane cage on a side chain behaved similarly to the fluorescein-labeled analogue of **53** for up to 2 h but redistributed into the cytoplasm and nucleus 24 h after incubation. Interestingly, the *closo* analogues were not as selective, as they distributed within both the cytoplasm and the nucleus. These studies suggest that if an appropriate targeting vehicle can be developed, the *nido*-OPDs, which did not appear to have an influence on cell growth in vitro, can act as an efficient means of selectively delivering therapeutic quantities of boron to the cell nucleus.

3.7. Liposomes

Liposomes have been extensively investigated as a means of delivering boron to tumor cells [85]. So long as the liposomes are of the appropriate size and of adequate stability, they are able to deliver their payloads to cancer cells via the immature and leaky vasculature typically found in the region surrounding proliferating tumors. To attain effective and prolonged accumulation of boron in the tumor, however, it is also important that the BNCT agent itself have the ability to be retained in the cancer cells through, for example, interactions with intracellular biomolecules (proteins, DNA etc.).

Hawthorne and co-workers have demonstrated the ability of small, unilamellar liposomes containing a series of different polyhedral borane anions in the aqueous core to deliver substantive quantities of boron to tumors in animal models with impressive selectivity [123]. For example, liposomes containing isomers of $[B_{20}H_{17}NH_3]^{3-}$, demonstrated excellent tumor uptake having a peak value of ca. 30–40 μg of B g^{-1} of tissue in BALB/c mice bearing EMT6 tumors at low injected doses [124]. The tumor to blood ratios, which reached a

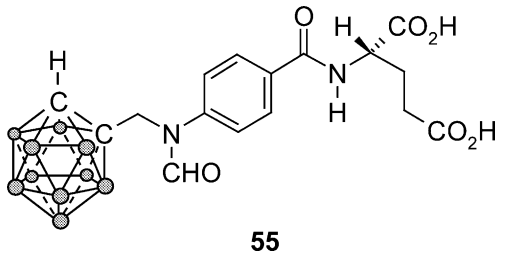
value greater than 5, are among the most impressive reported to date.

Hawthorne and coworkers also reported the preparation of liposomes for BNCT comprised of distearoylphosphatidylcholine (DSPC), cholesterol and the *nido*-carborane [*nido*-7-$CH_3(CH_2)_{15}$-7,8-$C_2B_9H_{11}$]$^-$ [125]. The presence of the latter compound in the lipid bilayer further increased the maximum achievable boron loadings, compared with liposomes having only borane salts in the aqueous core, without compromising vesicle stability. These liposomes were able to deliver up to 34 μg of B g^{-1} of tissue at 16 h in murine tumor models, despite a low injected dose (114 μg of boron), while the tumor to blood ratio reached a value of 8 at 48 h. When $[B_{20}H_{17}NH_3]^{3-}$ was also incorporated into the liposome, tumor boron concentrations of ca. 50 μg of boron per g of tumor were achieved along with a tumor to blood ratio of 6.

Moraes and co-workers [126] recently investigated the entrapment of *o*-carboranylpropylamine (CPA) into conventional and polyethyleneglycol (PEG)-modified, or stealth, liposomes. In addition to studying the optimal conditions for entrapment of the carborane derivative and the stability of different liposomes in the presence of non-ionic surfactants, the authors demonstrated that liposome entrapment could ameliorate the toxicity of the carborane derivative in vitro. It should also be noted that one of the reported liposomes was comprised of DSPC, cholesterol and dimyristoylphosphatidylethanolamine (DMPE), the latter of which can be used to prepare iummunoliposomes by covalent attachment of antibodies to the amino group of the phospholipid. This approach, which has been reviewed elsewhere [127], has been used to target boron-containing liposomes to specific receptors expressed on tumor cells.

Along similar lines, Sjöberg and coworkers reported the encapsulation of DNA intercalating compounds **44**, **48** (Fig. 11) mentioned previously, and a naphtalimide derivative similar to the structure of **48**, into sterically stabilized liposomes comprised of DSPC, cholesterol and 1,2-distearoyl-sn-glycero-3-phosphatidylethanolamine-*N*-[poly(ethyleneglycol)-2000] (DSPE-PEG) [128]. The boronated compounds were entrapped efficiently (greater than 90% trapping efficiency) and the liposomes demonstrated good stability in vitro. The ability of these compounds to deliver boron to tumors has not yet been reported.

Feakes and coworkers recently prepared a series of cholesterol–carborane conjugates, as a means of increasing the boron loading in liposomes, without dramatically altering the composition of the lipid layer, which is typically a 1:1 (mole) mixture of DSPC and cholesterol [129]. The steroid–carborane conjugates were prepare through the formation of ester and ether linkages between cholesterol and 6-(1,2-dicarba-*closo*-dodecaboran(12)-1-yl)hexanoic acid and 6-(1,2-dicarba-*closo*-dodecaboran(12)-1-yl)hexan-1-ol, respectively. The *closo* carboranes were subsequently converted to the anionic *nido*-carboranes, as a consequence of the fact that carboranes bearing a charged or polar head group and a hydrophobic tail, like [*nido*-7-$CH_3(CH_2)_{15}$-7,8-$C_2B_9H_{11}$]$^-$, have been shown to improve tumor specificity. Incorporation of the steroid–carborane conjugates into liposome has not, to the best of our knowledge, been reported.



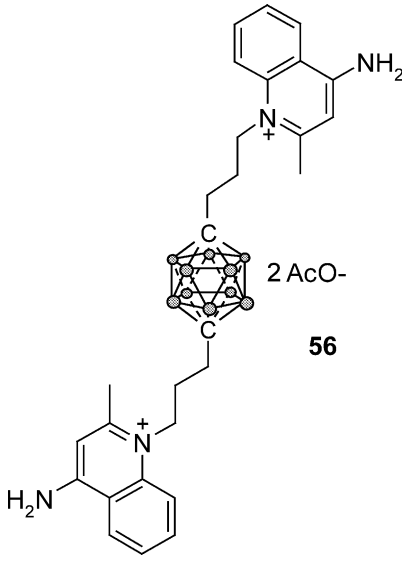
55

Fig. 15.

3.8. Miscellaneous agents

3.8.1. Closomers

A new and innovative BNCT delivery vehicle based on closomers was reported by Hawthorne and coworkers [130]. Closomers are polyhedra whose surfaces support poly-atomic substituents [131]. The closomer in the reported work, which contains 12 pendent carboranes, was prepared by reacting an excess of a carboranyl acid chloride with *closo*-$[B_{12}(OH)_{12}]^{2-}$ [132]. The product, which contains nearly 40% boron by weight, was also converted to the highly charged (14^-) *nido* analogue using CsF. The closomers are particularly attractive BNCT agents because of their high boron



56

Fig. 16.

content and the fact that they can be used to prepare nanoparticles in sizes ranging from micelles to that of liposomes [124,125].

3.8.2. Folic acid derivatives

Rho et al. [133] reported the synthesis of a carborane analogue of tetrahydrofolic acid (Fig. 15). The target compound **55**, which was tested as its disodium salt to confer water solubility, demonstrated low toxicity towards melanoma cells (IC_{50} 6.9×10^{-4} M). The authors reported a boron incorporation of 0.37 μg B 10^{-6} cells 24 h after the cells were administered compound **55** at a concentration of 6.9×10^{-4} M. The method of boron analysis and the exact details of the in vitro studies were not described.

3.8.3. Targeting mitochondria

A carborane derivative of dequalinium (Fig. 16), a delocalized lipophilic cation, was synthesized in the effort to selectively target the mitochondria, instead of the cell nucleus, of malignant cancer cells [134]. The boronated compound **56**, designated dequalinium-B, was taken up and retained in vitro in KB, F98, and C6 tumor cell lines but not in normal CV1 epithelial cell lines. It also had comparable toxicity profiles to that of other dequalinium compounds and further biological evaluation is warranted.

4. Boron neutron capture synovectomy

Radiation synovectomy has been used as a method to relieve symptoms in severe cases of rheumatoid arthritis [135]. Unfortunately, concerns about leakage of the isotope from the treatment zone and the exposure of staff to appreciable quantities of radioactive material have limited its widespread application. These issues, along with the limited effectiveness of pharmaceutical and surgical treatment methods, led to the evaluation of boron neutron capture therapy as an alternative treatment technique for rheumatoid arthritis. This approach, which is referred to as boron neutron capture synovectomy (BNCS) [136], involves using the daughters of the boron neutron capture reaction to ablate arthritic tissue thereby preventing further damage to surrounding structures (cartilage, bone etc.). The advantages of this approach over radiation synovectomy is that the ionizing events can be made to be highly localized (through the use of a highly selective targeting agent) and, because the boron-10 delivery vehicles are stable (i.e. not radioactive) both before and after irradiation, they will minimize damage to healthy tissue if they leak from the treatment zone. Furthermore, the non-radioactive boron compounds pose no contamination hazard, thereby simplifying administration of the treatment.

Yanch and colleagues investigated the experimental parameters required for the successful implementation of BNCS as a treatment modality for RA [136,137]. The results of their work clearly demonstrated that the boron neutron capture reaction could be used to selectively ablate arthritic tissue, without causing damage to other tissue–organs so long as highly selective and efficient boron delivery vehicles could be developed.

Hawthorne and coworkers investigated the potential for small unilamellar liposomes for delivering boron to synovial tissue in rats with collagen-induced arthritis [138]. Liposomes were prepared in a 3:3:1 ratio of distearoylphosphatidylcholine (DSPC): cholesterol: K[*nido*-7-$CH_3(CH_2)_{15}$-7,8-$C_2B_9H_{11}$], **57**, containing Na_3[a^2-1-(1′-$B_{10}H_9$)-2-$NH_2CH_2CH_2NH_2B_{10}H_8$], **58**, in the aqueous layer. Peak boron concentration in the synovium of rats with collagen induced arthritis, was found to be 29 μg of boron per g of tissue at 30 h after injection. The highest synovium to blood ratio was 3.0 at 96 h when the synovial boron concentration was 22 μg of boron per gram of tissue. When a 3:3:2 DSPC: cholesterol: **57** liposome formulation was used, still having **58** encapsulated in the aqueous core, the maximum amount of boron found in the synovial tissue was 26 μg at 48 h with a synovium to blood ratio of 2. At 96 h, the boron content in the synovium dropped to 14 μg of boron per g of tissue, which is slightly lower than the desired therapeutic level, however, the synovium to blood ratio was an impressive 7.5.

Our work in this area led us to develop a method to prepare carborane derivatives of cortisone and α-methylprednisolone (Fig. 17) [139]. Corticosteroid esters have been shown to be selectively taken-up by inflamed synovial tissues when administered intraarticularly. Using a novel coupling strategy, we were able to prepare the carboranyl esters **59** and **60** in good overall yield. Testing of these compounds in animal models remains work in progress.

5. Carboranes and medical imaging

Because BNCT and BNCS are binary therapies, treatment planning requires accurate knowledge of the ideal time (and duration) post-injection, to expose patients to neutrons. The traditional approach is to use data obtained from ex vivo boron analysis from animals or human subjects involved in phase I clinical trials [140]. The inaccuracy and invasiveness of this approach led several group to investigate the potential for using clinical imaging techniques to evaluate the biodistribution of BNCT agents.

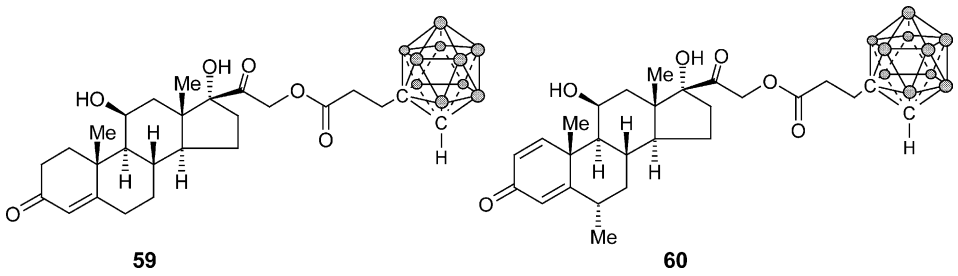


Fig. 17.

5.1. Radioimaging and radiopharmaceuticals

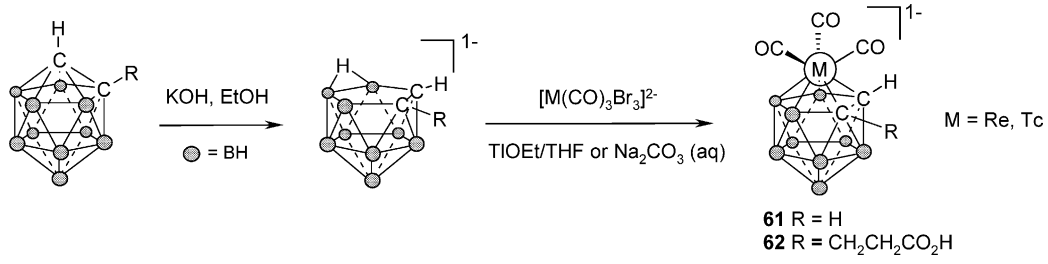
Positron emission tomography (PET) has been shown to be particularly useful as a tool for evaluating the biodistribution and pharmacokinetics of BNCT agents in vivo [141–143]. Studies in vivo can be carried out in animals as a way to screen new compounds or in humans for treatment planning purposes. Experiments can be performed using a standard clinical tomograph or through the use of a small animal scanner (micro-PET) [144]. The latter technique is being increasingly employed to evaluate new pharmaceuticals in vivo [145].

Radiolabeled carboranes, which were reviewed recently by Hawthorne and Maderna [11], have been used both as a means to measure the distribution of BNCT agents and as the cores from which to construct radiopharmaceuticals. For example, Hawthorne and co-workers prepared a ^{57}Co complex of the Venus flytrap ligand [146], which in turn was conjugated to the *anti*-CEA monoclonal antibody, T84.66. The carborane–radionuclide–antibody conjugate demonstrated excellent localization in tumor xenografts in nude mice [147].

Our group recently developed a robust approach for using carboranes, derivatives of the dicarbollide dianion in particular, in place of cyclopentadienide, as ligands for the preparation of Tc and Re organometallic radiopharmaceuticals [148]. We showed that $[M(CO)_3]^+$ (M = Re, ^{99}Tc) complexes of carboranes, including bifunctional derivatives **62** (Scheme 4), could be readily prepared in organic and aqueous solutions under conditions suitable for labeling at the tracer level. Because of the synthetic diversity of the carborane core, the mild labeling conditions, and stability of the resulting complex, a significant number of different strategies can be used to incorporate the carborane–$M(CO)_3$ synthons into biomolecules as a means of creating novel, receptor targeted, diagnostic and therapeutic radiopharmaceuticals.

The use of radioimaging for evaluating new BNCT agents and for treatment planning, requires the development of new methods for incorporating diagnostic radionuclides into BNCT agents in such a manner that addition of the isotope does not influence the biodistribution of the labeled substrate compared with that of the unlabelled parent compound.

Hansen and co-workers recently reported the synthesis of a carborane analogue of compound **63** (known as Hoechst 33258), which has been shown to bind to the minor grooves of DNA, as a novel BNCT agent (Fig. 18) [149]. Subsequent to this work, the same group reported a method, which in principle can be used to incorporate ^{73}Se ($t_{1/2} = 7.1$ h) into the core of the 2′-carboranyl-2-5′-bi-1*H*-benzimidazole so that the distribution of the compound can be determined using PET [150]. Their strategy looked toward replacing the 4-methylpiperazin-1-yl group in **64** with a tetrahydro-2*H*-1,4-selenazin-4-yl group (**65**). The synthetic approach was modified from that used to prepare **64** so that the isotope could be introduced in the final step of the synthesis. The reported methodology, which involved the reaction of cold Li_2Se with the appropriate ditosylate, led to the formation of compound **65**, along with a mixture of *N*-tosyl derivatives, in modest yield. Labeling with ^{73}Se and the subsequent biodistribution studies in animal models using PET have not yet been reported.



Scheme 4.

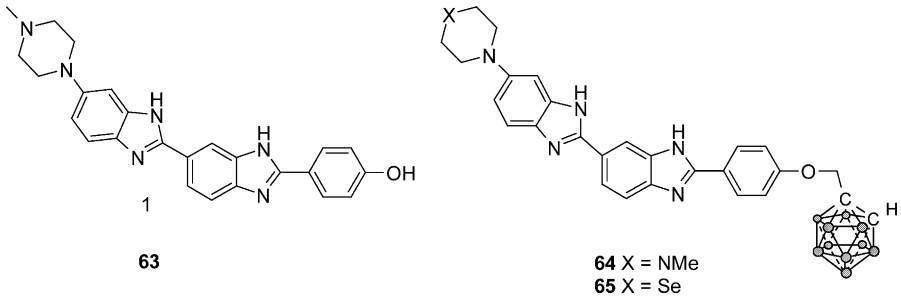


Fig. 18.

5.2. Magnetic resonance imaging (MRI)

As mentioned previously, boron-10 and boron-11 are NMR active nuclei. Unfortunately their short relaxation times cause signals to broaden and decay rapidly. This makes it nearly impossible to use standard clinical magnetic resonance (MR) scanners and pulse sequences to image the distribution of boron compounds in vivo [140]. Several groups have, however, developed techniques that address the short relaxation time issue, and used MR to determine not only bulk biodistribution of BNCT agents but pharmacokinetics as well. One technique, referred to as Single Point Imaging (SPI) was used to map the boron distribution of a polyhedral borane μ-disulfido-bis(undecahydro-*closo*-dodecaborate) (BSSB) in intact rats [151]. In this technique, only one data point is acquired so that issues arising as a consequence of the short relaxation time of ^{11}B are minimized. The limitation of this technique, however, is the modest signal to noise ratio, which arises because only one data point is acquired for each excitation. Alternatively Glover et al. [152,153] developed a 3D projection method, which was used to image the distribution of sodium mercaptoendecahydro-*closo*-dodecaborate (BSH) in dogs. The detection limit for boron-11 in MR is in the range of 25 ppm with a spatial resolution of 7.5 mm^3. The corresponding boron images superimposed over the filtered proton images allows one to select regions of interest (ROI) and utilize the changes in signal intensities over time as an indicator of pharmacokinetic behavior [140]. Localized spectra can therefore be used to monitor the influx and/or efflux of the BNCT agent from various organs.

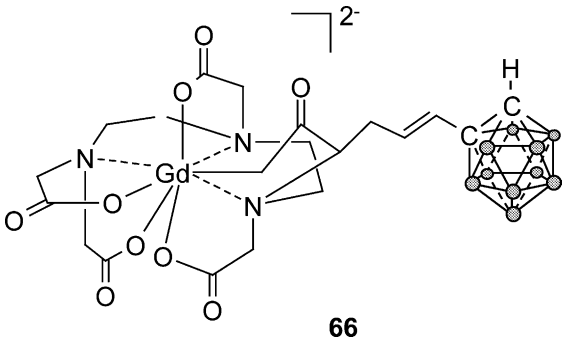


Fig. 19.

There are a number of significant disadvantages to using MRI for imaging the distribution of BNCT–BNCS agents. Clinical MRI scanners would need to be upgraded to perform the ^{11}B experiments. Secondly, since ^{10}B is the isotope used for BNCT, imaging studies would have to be run using ^{11}B in order to acquire the requisite pharmacokinetic data, prior to administration of the complex enriched in ^{10}B. Finally, because the signal intensities, which are used to determine the concentration of boron, depend upon the physical state of the boron, behavior of each boron carrier in different biological environments is needed prior to interpreting data from imaging experiments [140].

In place of looking at the boron nuclei, it may be more feasible to use MRI to study agents labeled with nuclei with better imaging characteristics, such as ^{19}F, or agents containing paramagnetic metals. Tatham et al. [154] investigated the potential for using MRI to measure the concentration of boron in a complex containing both Gd and a carborane. The idea is founded on the fact that the amount of Gd in a sample, which can be calculated-based on changes in T_1, is directly related to the amount of boron in the sample, so long as the complex remains intact.

It was recently demonstrated that for Gd(III)–diethylenetriaminepentaacetate–carborane [Gd(III)–DTPA–carborane, **66**] (Fig. 19), the archetype Gd–BNCT complex, the longitudinal relaxation rate is linear with respect to the Gd concentration (based on three calibration points). The relaxivity of the agent was 3.92 ± 0.01 (mMs)$^{-1}$ measured at 30 MHz and 35 °C which is similar to the reported value for the underivatized Gd–DTPA complex (3.0 ± 0.5 (mMs)$^{-1}$ at 37 °C) [155].

In the presence of 1% bovine serum albumin, the carborane–Gd complex demonstrated an enhanced relaxivity relative to that of the complex in the absence of the protein. The authors showed that this was a result of slower molecular tumbling of the protein–Gd–carborane complex. Interestingly, but not unexpectedly, this effect was not observed for the Gd–DTPA complex suggesting that the carborane substituent promotes protein binding.

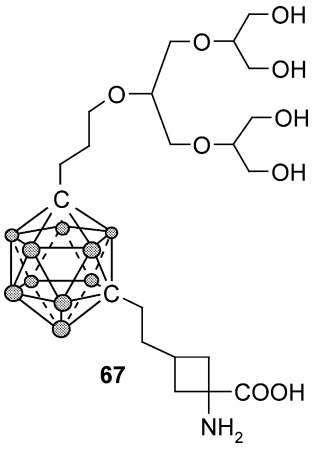


Fig. 20.

After compound **66** was administered to tumor bearing rats, the signal intensity in the tumor tissue increased rapidly but then decreased slowly over time. The intensity in the kidney and the bladder increased rapidly post-injection then remained at a high level. The Gd concentration in the blood was 9.1 ppm, 5 min after injection, and then decreased rapidly. The concentration of Gd in the tumor and the brain was very low, as was the tumor to blood ratio (0.075 at 20 min after injection), demonstrating that **66** is not a suitable BNCT agent.

6. Carboranyl amino acids and peptides

Since they were last reviewed [85], there have been a number of new reports regarding the synthesis of carborane containing amino acids, including some that are based on unnatural amino acids, and bioactive peptides.

6.1. Amino acid analogues

Carboranylalanine, a highly boronated analogue of phenylalanine, is the quintessential carborane amino acid analogue [156–163]. In addition to acting as a BNCT agent, carboranylalanine has recently been shown to exhibit biological activity as a fungicide. It demonstrated over a thousand-fold increase in activity compared with a zoospore inhibitor fungicide used against the asexual spores of *P. halstedii* [164].

The preparation of carborane analogues of unnatural amino acids is currently being explored as a means to deliver boron to tumor cells. The unnatural amino acid 1-aminocyclobutanecarboxylic acid (ACBC), for example, is non-toxic and is preferentially retained in intracerebral tumors. The *meta*-carborane analogue of ACBC and the more polar *nido* derivative have been reported [165,166] but are of limited utility as BNCT agents. This is a result of the hydrophobicity of the *closo* derivative and the non-specific protein binding observed for the more hydrophilic *nido*-species. To address these issues, Das et al. [167] prepared a *meta*-carborane analogue of ACBC bearing a polyol substituent (Fig. 20). The product, which is currently being evaluated as a BNCT agent, demonstrated appreciable solubility in water (>60 g l^{-1}) without needing to generate the charged *nido* ion.

Kahl and coworkers reported a convenient methodology for the preparation of 3-amino-1-carboxy-*ortho*-carborane and protected forms of all three C-amino-C-carboxycarboranes (Fig. 21) [56]. The reported synthetic methodology involved generating carboranyl acids by deprotonation and carboxylation, followed by conversion of the resulting acid to the corresponding Boc-protected amine via the Curtius rearrangement in the presence of *tert*-butanol. Subsequent deprotonation of the remaining carborane CH group, followed by treatment with CO_2 resulted in the formation of protected C-amino-C-carboxy-carboranes in excellent overall yields. In addition to the C-amino derivatives, Kahl and coworkers were also able to prepare a B-amino-C-carboxy carborane **71** in which the amino group was located at B3. These unnatural amino acid analogues can be used for a variety of different applications including peptidomimetic research.

There are few boronated analogues of tyrosine other than (4-boronophenyl)alanine, in which the phenolic group is replaced by a boronic acid moiety. Ujváry and Nachman reported the synthesis of 3-(12-hydroxy-*para*-carboranyl)propionic acid, as a hydrophobic *N*-terminal tyrosine mimetic (Scheme 5) [168]. It was synthesized from 1-hydroxy-*para*-carborane **72**, which was prepared in 35% yield by introducing dry air into mono-lithiated *para*-carborane. The carboxylate functionality was in-

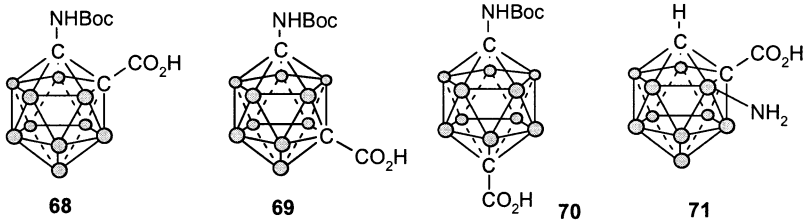
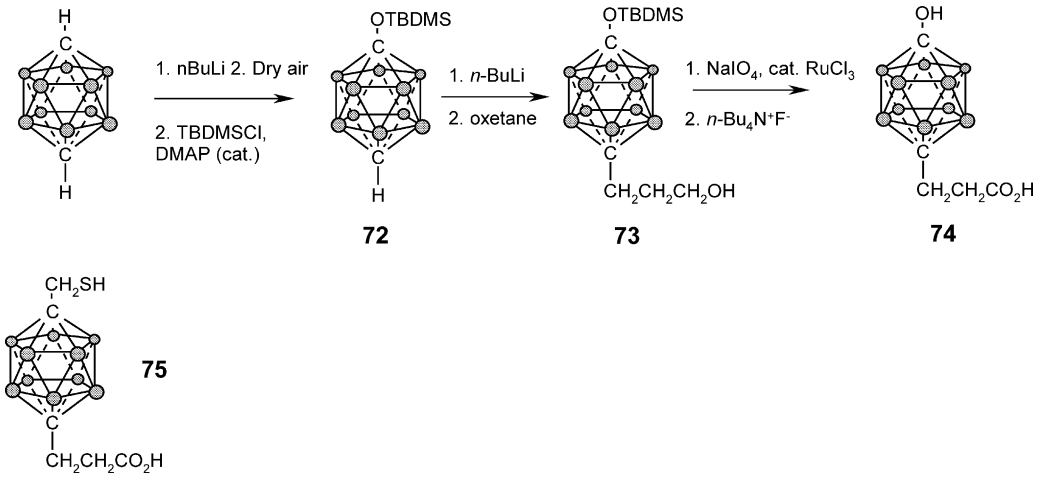


Fig. 21.



Scheme 5.

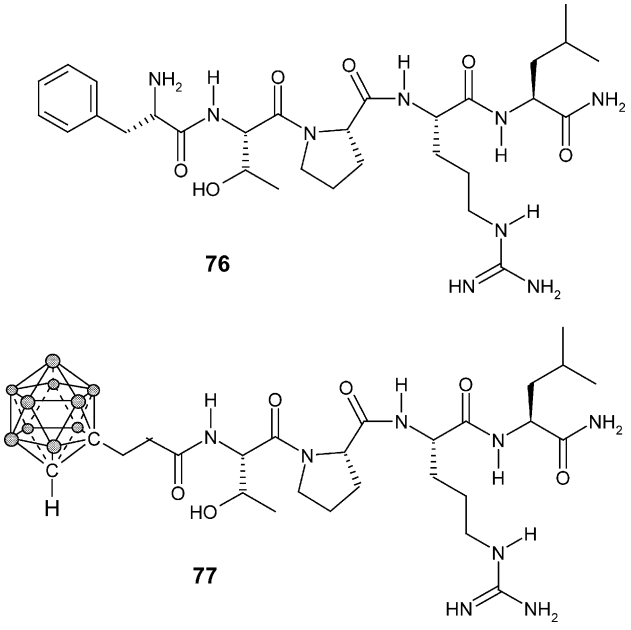


Fig. 22.

troduced after protection of the hydroxyl group, by reacting the corresponding deprotonated carborane with oxetane, followed by oxidation of the resultant alcohol **73** using $NaIO_4$ and catalytic amounts of $RuCl_3$. Removal of the TBDMS protecting group with TBAF led to the isolation of the desired product **74**.

The same group [169] also prepared 3-[12-(mercaptomethyl)-1,12-dicarba-*closo*-dodecaboran(12)-1-yl]propionic acid **75** as a substitute, after oxidation, for Tyr(SO3H) residues which are found in several bioactive peptides. The compound was prepared in good overall yield in six steps. To broaden the potential applications of **74** and **75**, it may be necessary to prepare analogues that also contain α-amino groups. This would create the opportunity to incorporate the carboranes into growing peptide chains as opposed to their current potential for acting solely as capping units.

6.2. Carborane-containing peptides

Nachman et al. [170] incorporated a hydrophobic carborane moiety in place of a terminal Phe amino acid in one of the pyrokinin family of insect neuropeptides in hopes of increasing the ability of the peptide to penetrate the insect cuticle and to increase the compounds resistance to catabolism (Fig. 22). The carboranyl unit, 2-*ortho*-carboranylethanoic acid (Cbe), was incorporated into the target peptide using DIC–HOBt coupling in DMSO and the product, Cbe–Thr–Pro–Arg–Leu–NH_2, cleaved from the Rink amide resin using a solution of TFA (95%), anisole (5%), thioanisole (4%) and EDT (1%).

The carborane analogue demonstrated potent activity in a cockroach hindgut bioassay at a threshold concentration of 70 pM which is over 30 times more potent than the parent pentapeptide **76**. Compound **77** also elicited pheromone production following injection into female tobacco budworm moth *Heliothis virescens*. Dose–response data showed that the carboranyl analogue had an ED_{50} of 0.1 pmol per female and elicited a 100% response at 2.5 pmol per female which is more potent that the molecule endogenous to Helicoverpa. The hydrophobic nature of the cage, not the blocking of the N-terminus, was shown to be responsible for the observed activity in the isolated cockroach hindgut. The carborane peptide is 10 times more potent than the N-terminally blocked analogue of **76**, consequently, the observed activity must be associated with enhanced receptor binding mediated by the carborane. The observed receptor binding characteristics make **77** unique amongst the prokinin peptide family.

Qualmann et al. reported the preparation of dendritic peptides containing L-5-(2-methyl-1,2-dicarba-*closo*-dodecaborane(12)-1-yl-)-2-amino-pentanoic acid, as labels for electron spectroscopic imaging (ESI)-based immunocytochemistry studies [171]. The target compounds, which contained eight carboranyl amino acids attached

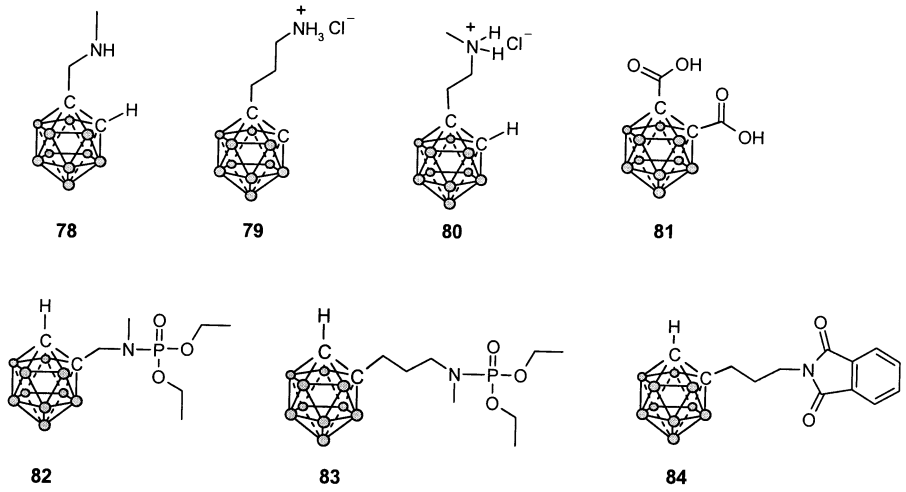


Fig. 23.

to a branched core, were prepared by FMOC solid phase synthesis using tentacle resins. The peptides, which contained a cys residue for conjugation to an antibody fragment, were also linked to a fluorescent label for monitoring coupling efficiency. The suitability of the boronated compounds for the proposed application was tested in a study of the mechanism of the transcellular transport of bovine serum albumin (BSA) through ileal enterocytes of newborn piglets in comparison with conventional immunogold reagents. The carboranyl peptides, coupled to antibody fragments raised against BSA, gave considerably higher tagging frequencies than was seen with conventional labels. Interestingly, the stability of the carborane conjugate in the electron beam was shown to be much greater than that of borate-coated polystyrene beads. This property may be a consequence of the unique stabilities of the carborane substituents.

7. Carboranes as pharmacophores

7.1. Anti-neoplastic–cytotoxic agents

A series of carboranes (Fig. 23) and polyhedral hydroborate salts were tested for their *anti*-neoplastic–cytotoxic activity [172]. Hall et al. observed that a number of compounds exhibited cytotoxicity in single cell suspended tumors (leukemia and HeLa–S^3) and not surprisingly, the substituents off the carboranes dramatically influenced the observed ED_{50} values in a given screen. The most active compound was the amino-*ortho*-carborane hydrochloride **79**, which reduced DNA synthesis primarily via inhibition of the regulatory enzymes in the purine pathway. Compound **79** also inhibited nucleoside kinase activities leading to reductions in deoxyribonucleotide pools. Compound **79** did not, however, specifically target DNA.

7.2. Estrogen agonists and antagonists

Endo et al. [173,174] used carboranes as the cores from which to construct a series of potent estrogen receptor (ER) agonists. The rationale behind the design of the agonists was that hydrophobic carboranes could be used in place of the C and D rings of 17β-estradiol, which play an important role in the binding of the steroid to the ER through hydrophobic interactions. Good ER binding and estrogenic activity requires the appropriate hydrophobic group be located adjacent to a phenolic ring, in addition to the having an appropriately positioned H-bonding substituent. To this end, the authors prepared a series of carborane derivatives containing phenolic substituents. The position of the phenolic OH group, the nature of the substituents off the remaining carborane CH group, and the choice of carborane isomer were all varied to obtain structure-activity relationships (SAR).

The estrogenic activities of the carborane derivatives were determined by a luciferase reporter gene assay [175]. Compounds **86** and **87** (Fig. 24) were more active than 17β-estradiol, with the latter compound, which contained a methylene spacer between the carborane and the alcohol group, being ten times more potent than 17β-estradiol. Interestingly the amino carborane **89** was slightly more active than 17β-estradiol, while the acid derivative **88** exhibited only moderate activity. The inclusion of additional methylene groups beyond $n = 1$, between the carborane and the hydroxyl substituents, dramatically reduced the compounds activity. Switching the 1,4 substituted phenol to a 1,3 derivative, resulted in a slight decrease in the activity, however, **91c** was still more potent than 17β-estradiol. The use of *meta*-carborane led to a decrease in potency compared with the analogous *para*-carborane derivatives.

ER_α binding assays for the most potent derivatives correlated with the luciferase reporter gene experiments.

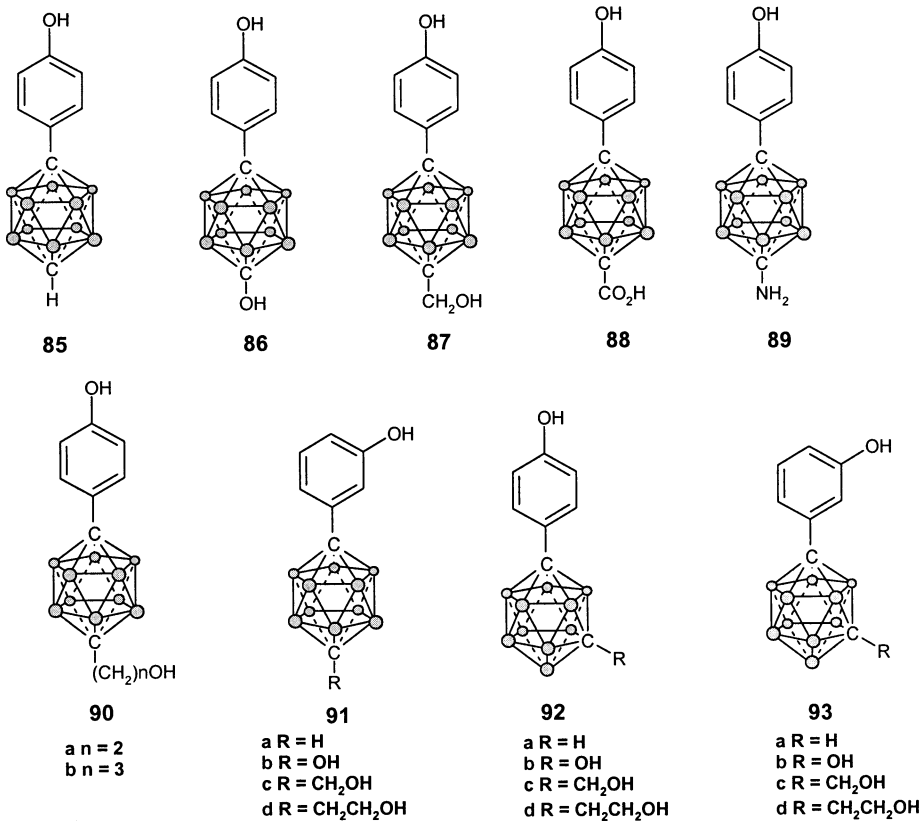


Fig. 24.

The K_i values, which were determined by measuring the inhibition of [6,7-^{3}H]17β-estradiol ($K_d = 0.4$ nM) to human recombinant ER_α, for **85**, **87**, and **89** were 0.4, 0.10 and 0.65 nM, respectively. Compound **87** was further tested in ovariectomized mice and shown to restore uterine weight and prevent bone loss at a dose of 100 ng per day.

In an attempt to enhance the agonist activities, a series of a series of *ortho*- and *meta*-carborane derivatives containing alkyl substitutents were also prepared (Fig. 25) [176,177]. Compounds **94a** and **94b** inhibited the activity of 17β-estradiol in the concentration range of 1×10^{-8} M–1×10^{-7} M, unfortunately, the *meta* compounds (**95a**, **b**) exhibited no antagonistic activity.

The fact that the carborane derivatives, like **85**, have a greater potency than 4-alkylphenols, strongly suggests that the hydrophobic carborane core plays an important role in mediating high receptor binding affinity. Furthermore, the results of this work highlights another advantage of using carboranes in drug development, in that the incorporation of different carborane isomers is a facile means of probing for different interactions within the drug binding site.

Estrogen receptor antagonists are widely used in the treatment of hormone dependent breast cancer. Building upon their prior results, described above, Endo and colleagues prepared a series of carborane analogues of steroidal antiestrogens (Fig. 26) [178]. The estrogenic

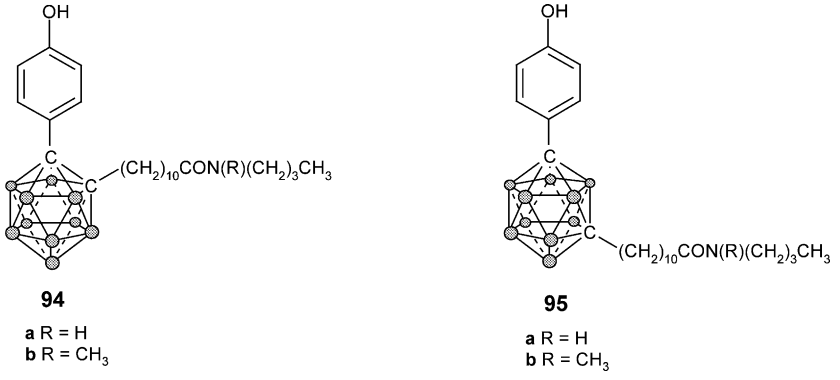


Fig. 25.

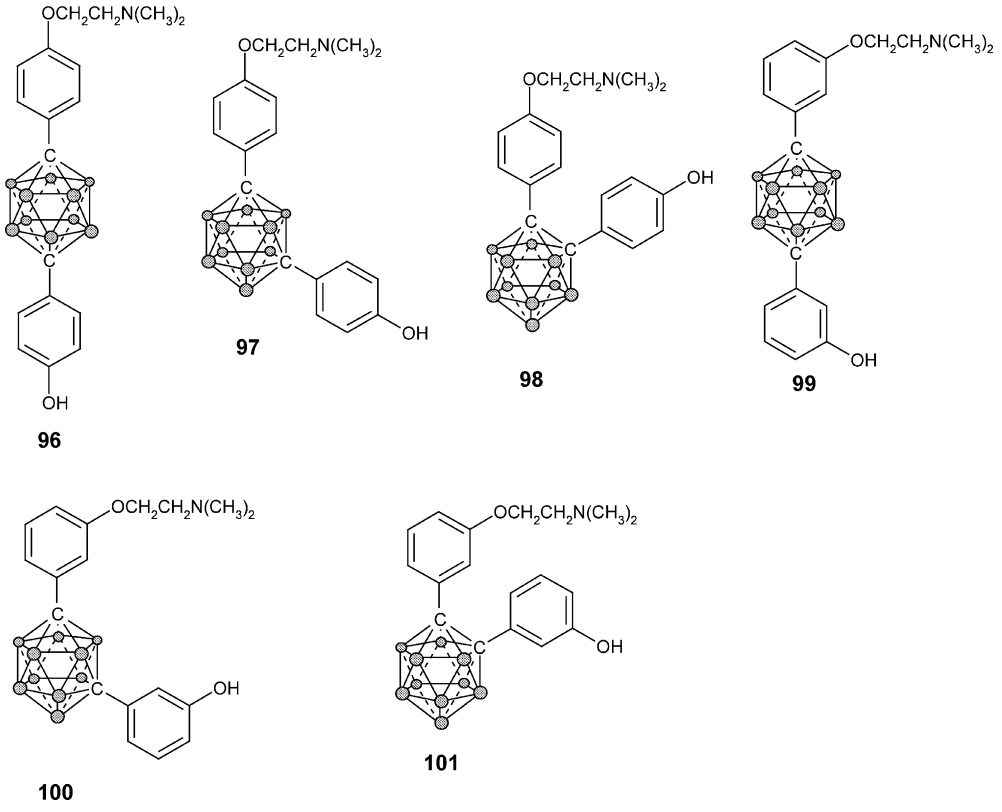
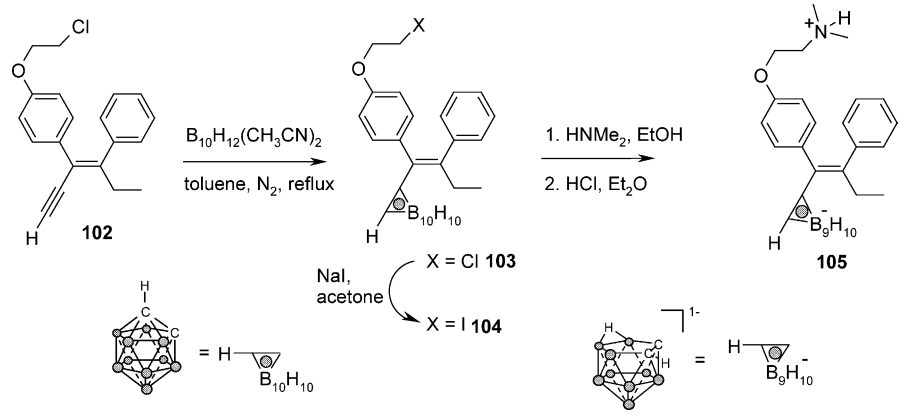


Fig. 26.

activities of the compounds were again examined by luciferase reporter gene assay in which the compounds were evaluated for their ability to inhibit the transcriptional activity of 17β-estradiol at a concentration of 10^{-9} M. Compound **96** exhibited *anti*-estrogenic activity towards 17β-estradiol at a concentration of 1×10^{-8} M but it did not, however, inhibit the activity to the control level even at a concentration of 1×10^{-6} M. The *meta*-carborane analogue **97** inhibited the activity of 17β-estradiol in the concentration range 1×10^{-7}–10^{-6} M in a dose dependent manner. The antagonistic activity was increased in the case of *ortho*-carborane derivative **98**, which inhibited 70% of the transcriptional response to 17β-estradiol at a concentration of 1×10^{-7} M and almost completely inhibited it at 1×10^{-6} M. The antagonistic activity of the compounds bearing a *meta* hydroxy group (**100**, **101**) were somewhat weaker than in the *para* compounds, however, **101** almost completely inhibited the transcriptional response to 17β-estradiol at a concentration of 1×10^{-6} M.

We recently reported a general, stereoselective method for the synthesis of a *nido*-carborane analogue of the *anti*-estrogen tamoxifen, nicknamed Boroxifen **105** (Scheme 6) [179]. The product, which contained a carborane in place of the ring-A phenyl group in tamoxifen, was not only prepared as a novel BNCT agent, but it was also designed to act as a new tamoxifen



Scheme 6.

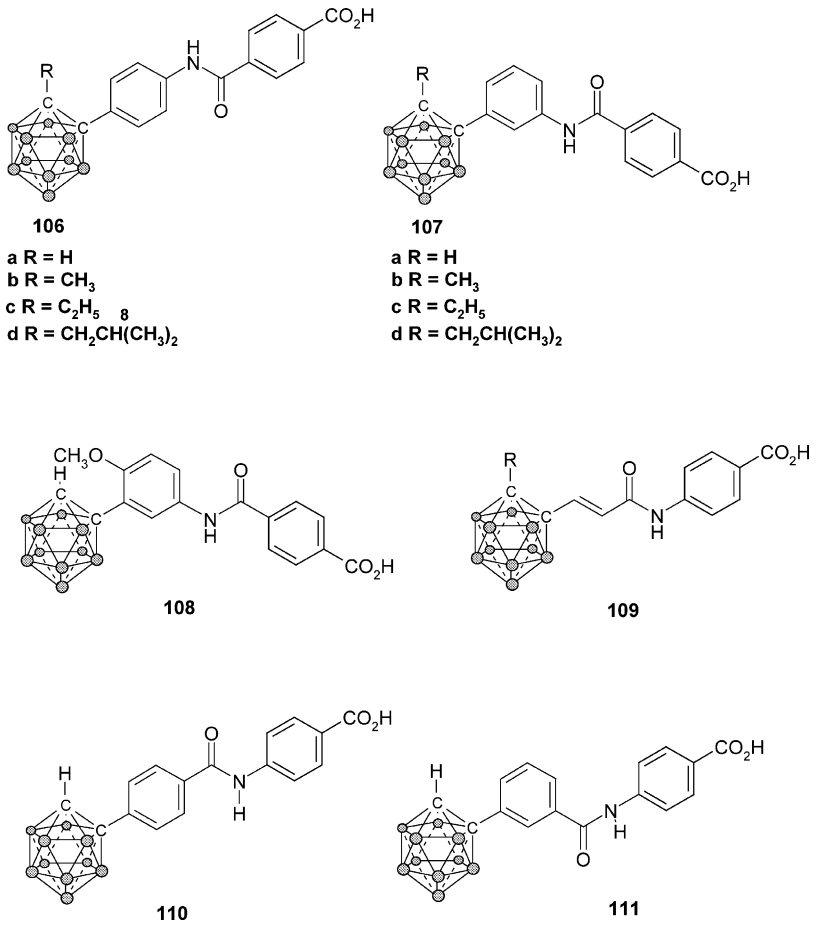


Fig. 27.

analogue having enhanced resistance to catabolism. Metabolism resistant tamoxifen analogues such as idoxifene, prevent catabolism of the amino side chain and hydroxylation at the four-position of ring A [180,181]. Hydroxylation at this position, which would not be possible in Boroxifen, is problematic because it leads to facile *E*/*Z* isomerization, resulting in compounds having differing types (estrogenic versus antiestrogenic) and levels of biological activities [182]. Idoxifene has been shown to have-reduced agonist activity on breast and uterine cells and it acquires antiestrogen resistance much more slowly than tamoxifen [183].

The initial phase of the synthetic work involved preparation of the ene-yne **102**, which was subsequently converted to the corresponding *closo*-carborane **103**. A crystal structure of **103**, clearly demonstrated the structural similarities, in the solid-state, between the carborane derivative and the corresponding aryl analogue. Conversion of **104** to the amine **105** resulted in

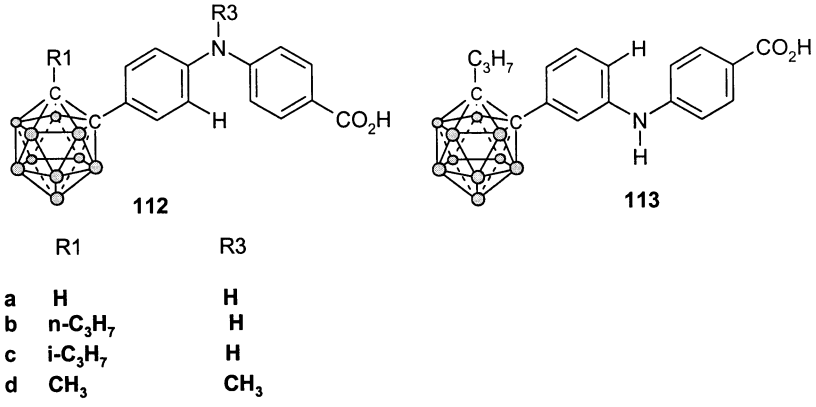


Fig. 28.

concomitant formation of the *nido*-carborane. A modification of this approach is currently being developed in order to prepare other structural variants, including the corresponding *para*-carborane-hydroxy tamoxifen analogue, in order to identify compounds having selective affinity for the ER receptors.

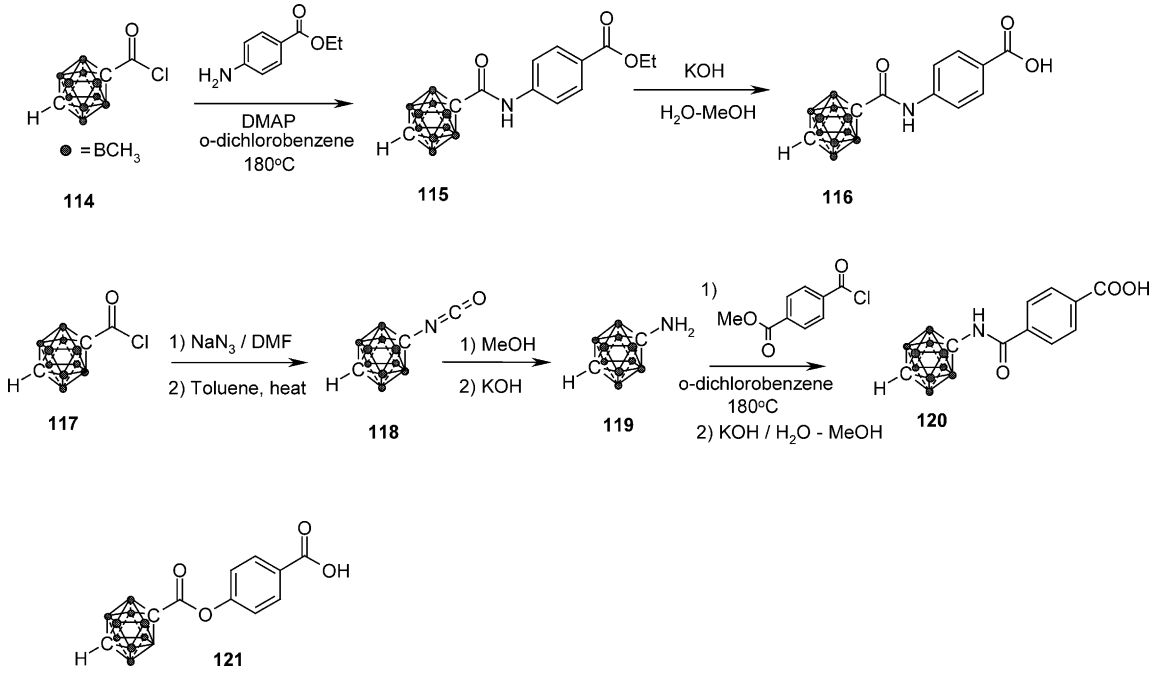
7.3. Retinoids

Analogues of retinoic acid are of interest as chemopreventive and therapeutic agents in the field of dermatology and oncology [184]. It is known that the introduction of bulky hydrophobic groups into retinobenzoic acids can lead to antagonistic activity [185]. Consequently, Endo and coworkers [186] prepared and screened a series of retinobenzoic derivatives, having both amide (Fig. 27) and amine (Fig. 28) cores, containing *ortho*-carborane substituents at the 3 and 4 positions of the central aryl group [187].

The 4-carboranyl substituted amides showed antagonistic activity but no agonist activity even in the presence of a potent synergist. The 3-carboranyl substituted compounds showed potential agonist activity in the presence of a synergist but no antagonistic activity. Compounds bearing an *ortho*-carborane at the 4-position of the benzene nucleus were completely inactive as differentiation inducers towards human promyelocytic leukemia HL-60 cells at a concentration below 10^{-6} M. These compounds were able, however, to inhibit the activity of Am80, a potent retinoid, at a concentration of 1×10^{-6} M. Compounds bearing an alkyl group at the 2-position of the carboranyl cage also exhibited potent activity. The most potent **106b**, dose dependently decreased the percentage of differentiated cells induced by Am80. Compound **110**, exhibited a similar antagonistic activity to that of **106a**. Derivatives bearing the carborane at the 3-position of the aryl group (**107**, **111**) were almost inactive as differentiation inducers at concentrations below 10^{-6} M, however, the extent of differentiation was increased at 10^{-6} M by the addition of a potent retinoidal synergist.

In the carboranyl–amine series (Fig. 28) compound **112a** exhibited a potent differentiation-inducing activity towards the HL-60 cells with an EC_{50} value of 3.7×10^{-8} M. This particular compound demonstrated no synergistic effect with Am80 [188]. The agonist activity was increased by introduction of an *n*-propyl or isopropyl groups on the carborane cage. The EC_{50} values for **112b** and **112c** were 1.5×10^{-9} and 2.9×10^{-9} M, respectively. Introduction of longer alkyl groups diminished the reactivity. Compounds having *ortho*-carborane at the 3-position of the benzene nucleus also exhibited potent retinoid agonist activity. The EC_{50} of the most potent, **113**, was 3.4×10^{-9} M. The differentiating-inducing activity disappeared for compounds bearing a methyl group on the central nitrogen atom.

To further enhance the hydrophobic nature of the core, retinobenzoic acid analogues were prepared using poly-B-methylated carboranes [189]. The target compounds were synthesized from the acid chloride of polymethylated *para*-carboranyl acids, through the addition of ethyl aminobenzoates (Scheme 7). Forcing conditions were needed to convert the acid chloride, which could be isolated as a crystalline solid, to the corresponding amide. To prepare amino polymethylated carborane, the acid chloride was converted to the



114 115 116 117 118 119 120 121

Scheme 7.

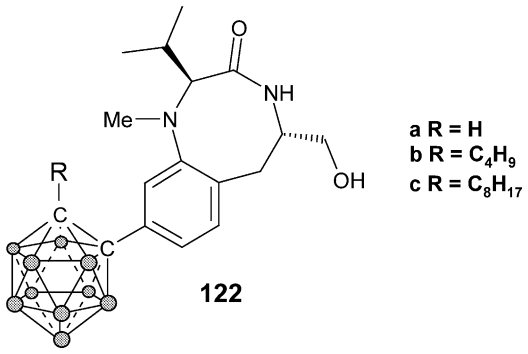


Fig. 29.

corresponding isocyanate, which in turn was trapped as the methyl carbamate, which was then hydrolysed to give the free amine. Conversion to the reversed amide was accomplished by reacting the amine with the acid chloride of terephthalic acid mono methyl ester. Analogues using 4,5,7,8,9,10,11,12-octamethyl-1,2-dicarba-*closo*-dodecaborane and 4,5,6,8,9,10,11,12-octamethyl-1,7-dicarba-*closo*-dodecaborane were also prepared. Their synthesis required less forcing conditions due to reduced steric encumbrance.

All compounds were inactive as differentiation inhibitors below 1×10^{-6} M. The B-methylated carboranes, unlike the non-methylated analogues, however, exhibited potent antagonist activities at concentrations of 10^{-7}–10^{-8} M towards the differentiating-inducing power of Am80. Compounds **116**, **120**, **121** showed the same activity as a synthetic antagonist, LE540; a compound which is known to antagonize Am80 with an IC_{50} value of 1.7×10^{-8} M [190]. Reversing the amide group did not appear to influence the observed activity and the introduction of the smaller octamethyl cages only slight decreased the activity.

7.4. Protein kinase C modulators

Endo et al. reported the synthesis of carborane derivatives targeted at protein kinase C (PKC) [191].

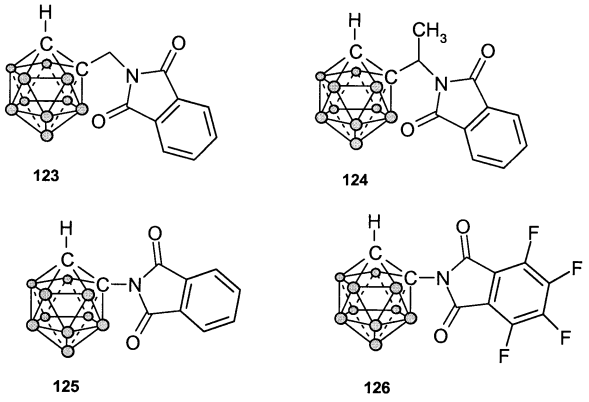


Fig. 30.

ortho-Carborane was placed at the 9-position off the benzene ring of a benzolactam core, which is found in a number of compounds that are known to activate PKC (Fig. 29). The remaining carborane CH group was substituted with linear hydrocarbon chains in an attempt to further influence the compounds biological activity and receptor binding affinity. Compound **122a** showed tumor growth inhibitory activity with an ED_{50} value of 3×10^{-8} M while **122b** and **122c** showed ED_{50} values of 7×10^{-9} M which is comparable with BL-V8-210 (ED_{50} 5×10^{-9} M), one of the most potent benzolactams known. Binding assays to human recombinant PKCδ for compounds **122a**–**c** showed K_i values of 2.0, 1.4 and 1.8 nM, respectively, which is similar to the value for BL-V8-310 itself (K_i = 1.8 nM).

7.5. TNF-α modulators

Carborane analogues of the controversial drug Thalidomide were prepared and their ability to regulate the TNFα producing ability of HL-60 cells was determined (Fig. 30) [192]. HL-60 cells were incubated with 12-*o*-tetradecanoylphorbol-13-acetate TPA (10 nm), which causes the production of TNFα. Compounds **123**–**126** showed a dose-dependent TNFα production-enhancing activity with compounds **123**–**125** showing activities comparable with *N*-phenylphthalimide. Compound **126**, the tetrafluorinated analogue, caused the appearance of cytotoxicity. The efficacy seemed to decrease in the order **125** > **124** > **123**, however, the differences were quite small. With okadaic acid (OA) stimulated HL60 cells, all compounds showed TNFα production-inhibiting activities.

8. Bio-active metallocarboranes

In addition to the metalloporphyrin work described above, there are a number of patents and meeting-abstracts that describe the synthesis and biological evaluation of metallocarboranes. Furthermore, biological testing of metallocarboranes other than those based on dicarba-*closo*-dodecaboranes have been described elsewhere [193,194]. As a consequence of the particular focus of this paper, and owing to time and space considerations, these publications will not be covered here.

Recently, Gielen et al. reported the synthesis, spectral characterization, X-ray structure and in vitro anti-tumor activity of a tin-*meta*-carborane derivative $\{[(1,7\text{-}C_2B_{10}H_{11}\text{-}1\text{-}COO)Bu_2Sn]_2\}O_2$ [195]. This compound was screened in vitro against six tumor cell lines of human origin and it was shown to be somewhat less active than methotrexate and doxorubicin. The com-

pound was, however, more active than 5-fluorouracil, cisplatin, and carboplatin suggesting that the carborane derivative has intermediate anti-cancer activity. Clearly, these results, along with work described in the patent literature, suggest that there is a tremendous opportunity to expand the field of metallocarborane-based therapeutic agents.

9. Future directions

The work covered in this review elegantly demonstrates the many benefits of using carboranes and metallocarboranes as components of diagnostic and therapeutic agents and biological probes. Consequently, it seems that the time has come to develop the ability to

Appendix to The Medicinal Chemistry of Carboranes

Reaction	Reference
1. Reactions at Pendent Groups	
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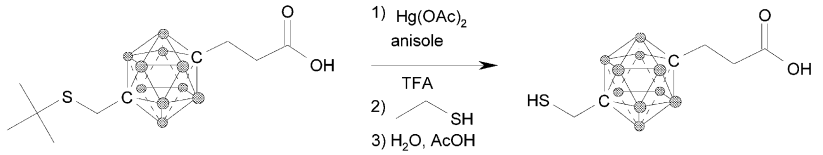
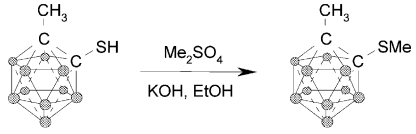
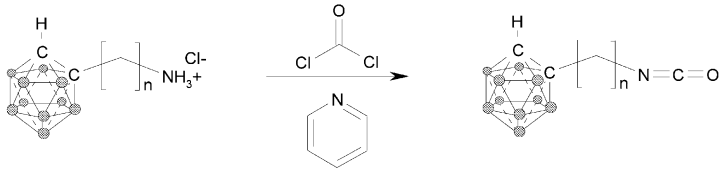
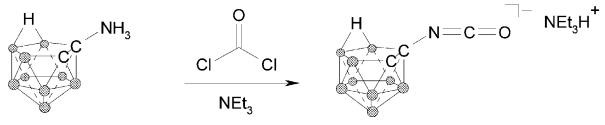
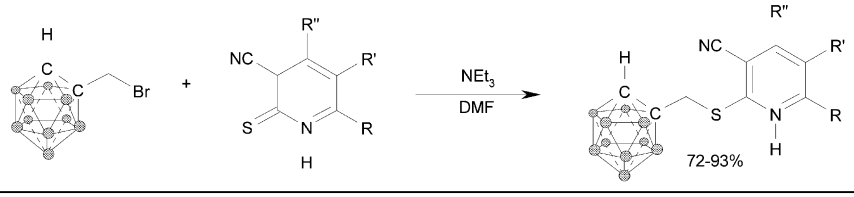
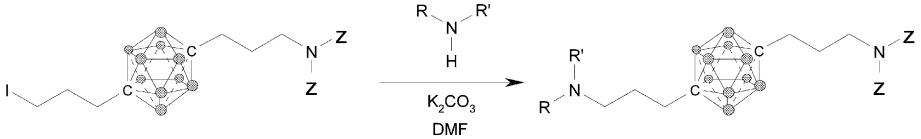
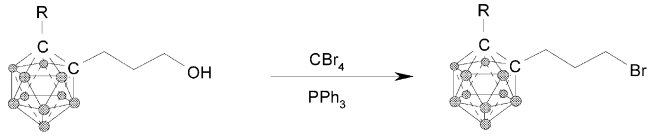
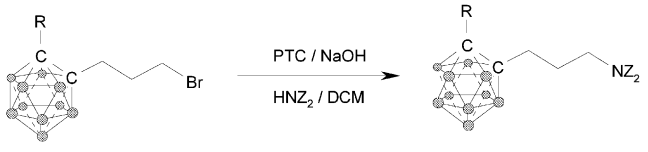
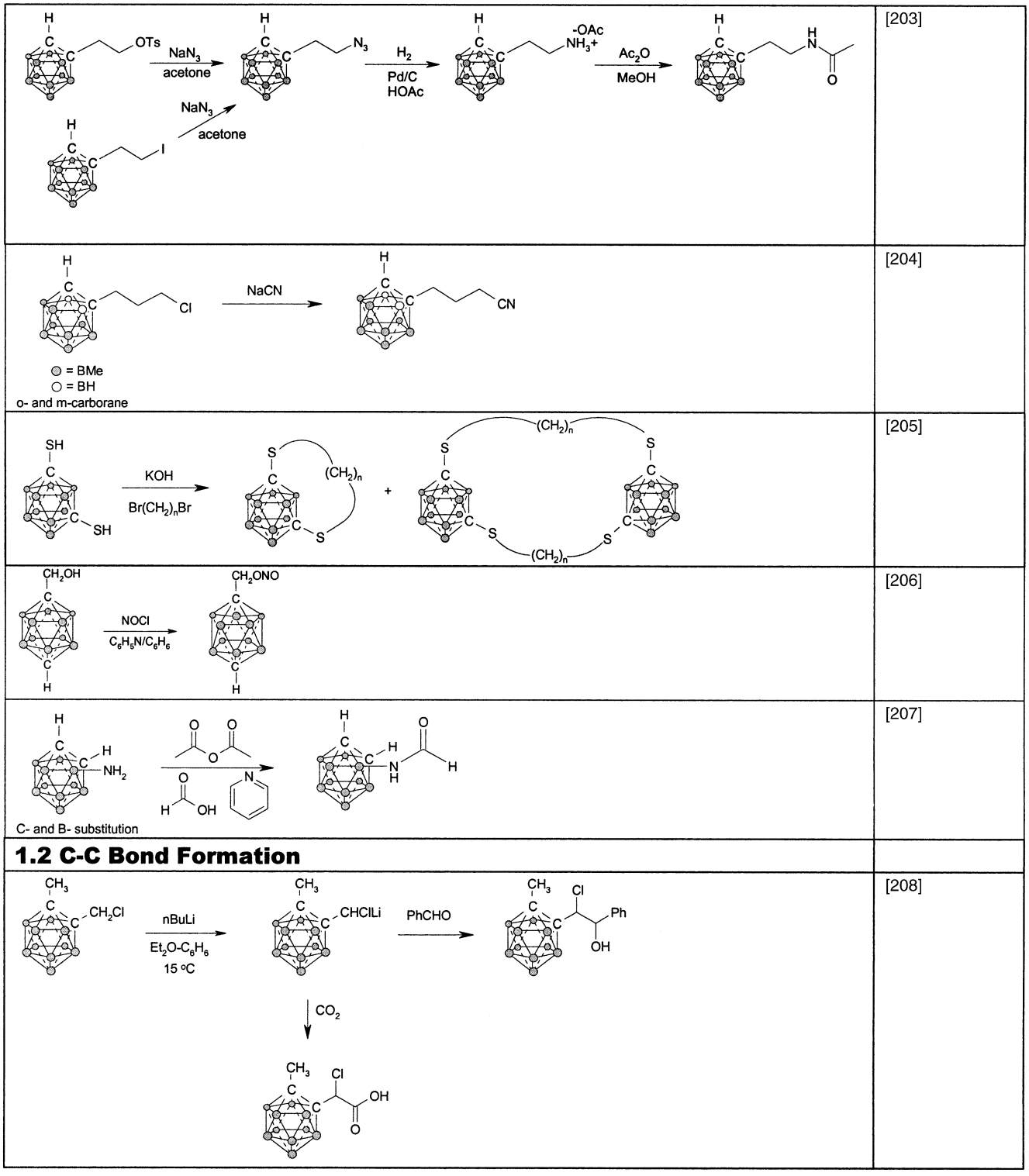
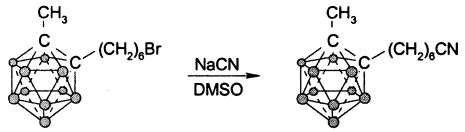
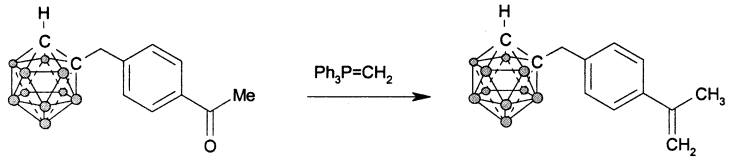
	[196]
	[197]
	[198]
	[199]
	[200]
	[201]
	[202]
	[202]

employ modern drug discovery techniques, including combinatorial chemistry, high-throughput screening and small animal imaging techniques, to more rapidly prepare and identify potent carborane derivatives. Achieving these goals will rely upon chemists to continue exploring and expanding the unique chemistry of carboranes.

Acknowledgements

We gratefully acknowledge The National Sciences and Engineering Research Council (NSERC) of Canada, The Canadian Institutes of Health Research (CIHR), The Thode Family and McMaster University, for their financial support.



	[209]
1.3 C=C Bond Formation	
	[210]
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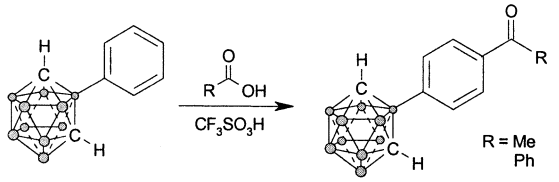
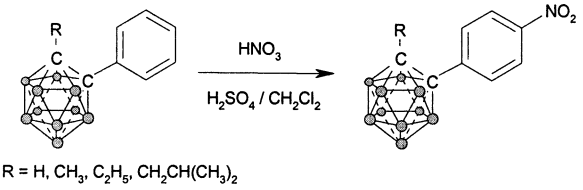
	[211,212]
	[213]
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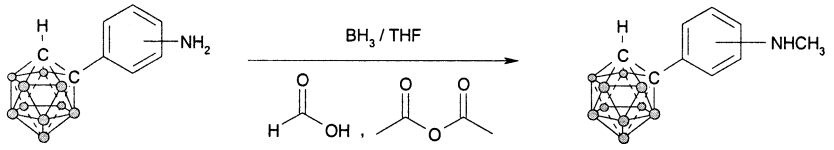
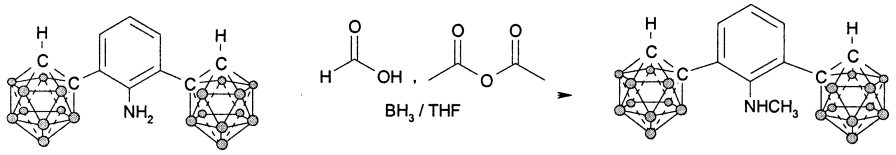
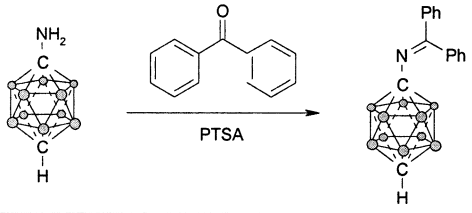
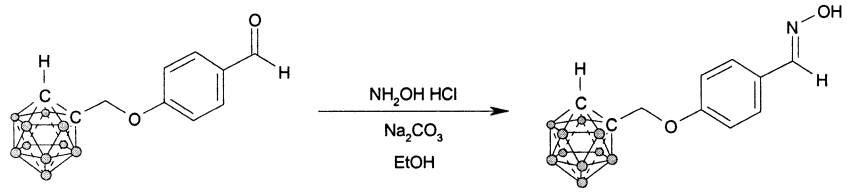
	[214]
	[214]
	[215]



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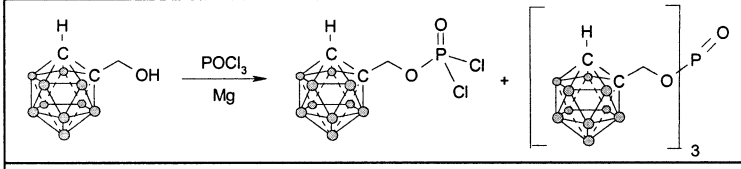
1.6 Miscellaneous



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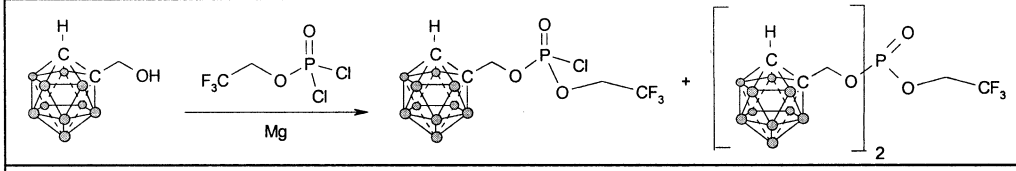

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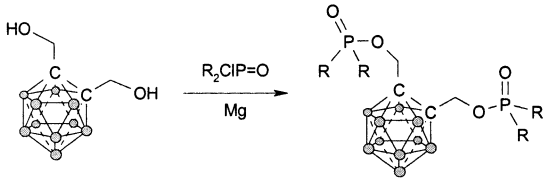

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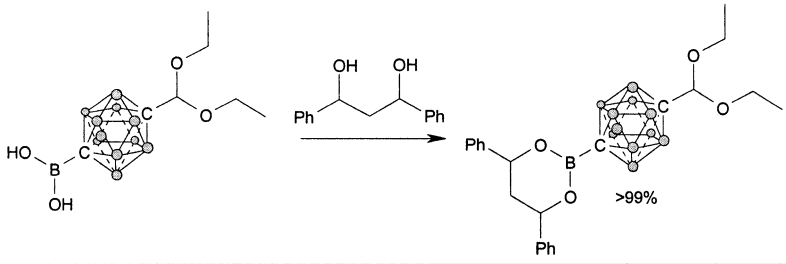

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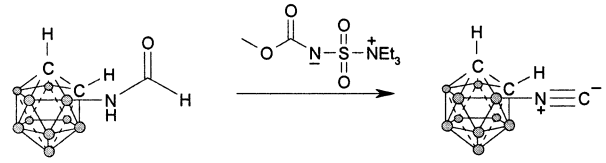

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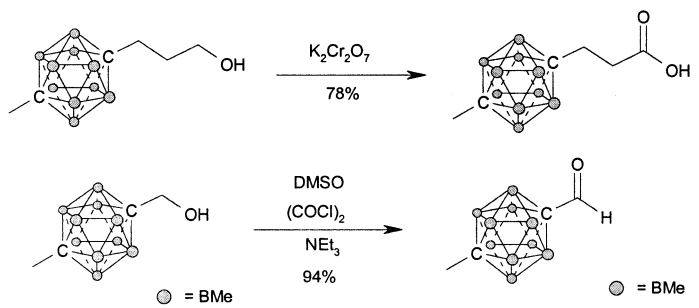
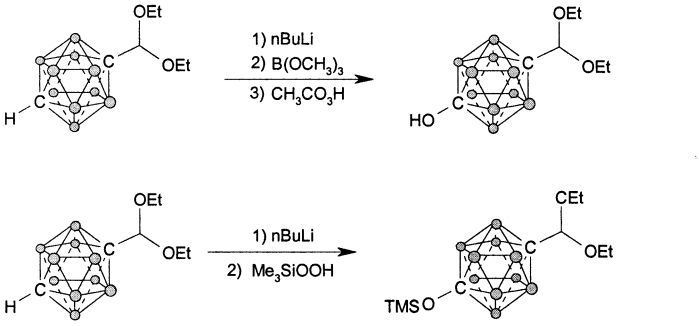
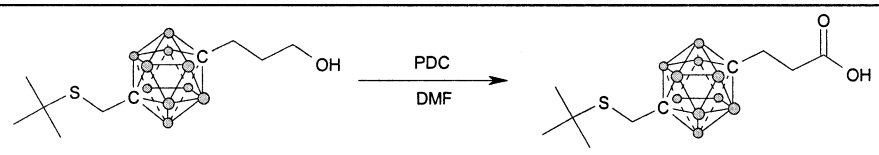
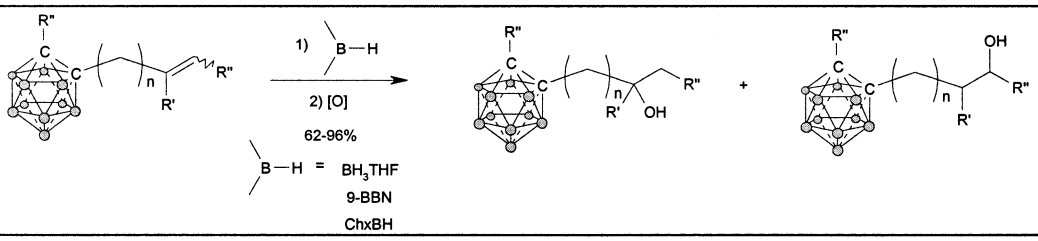
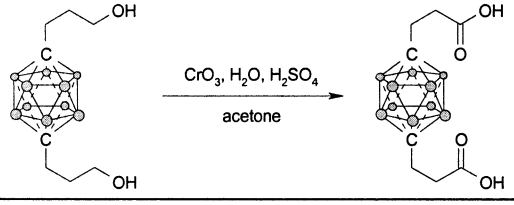
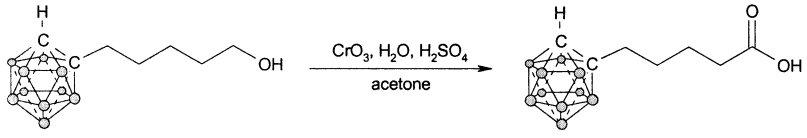
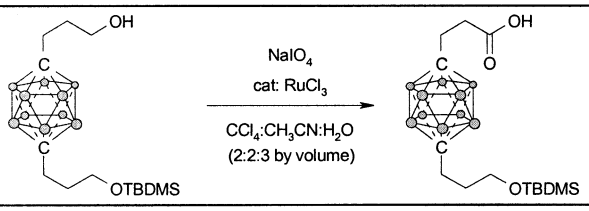
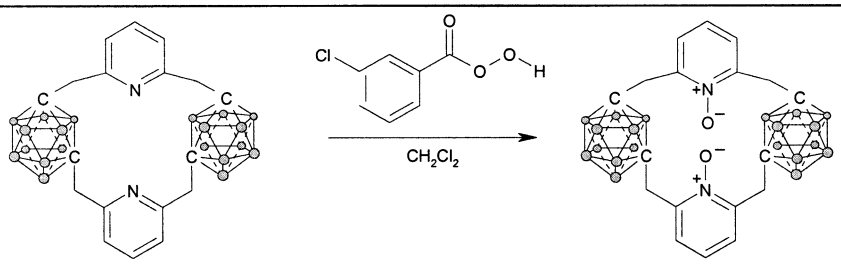
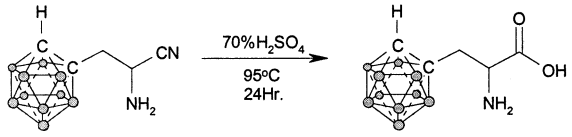
	[219]
	[218]
	[196]
	[220]
	[201]
	[221]

	[222]
	[223]
	[224]
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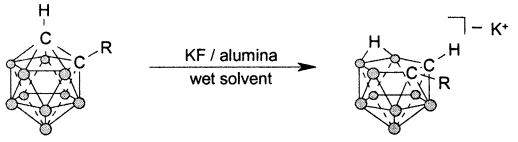	[225]
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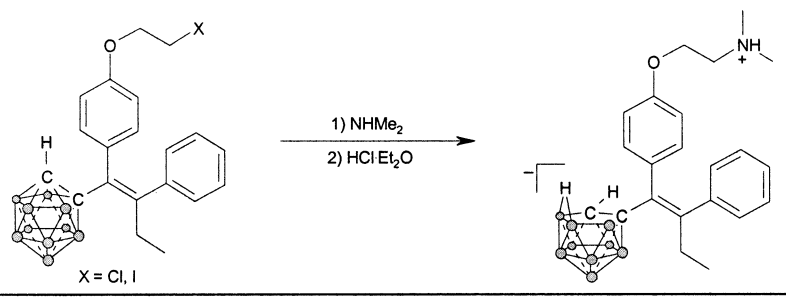
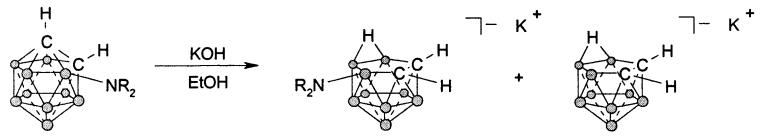
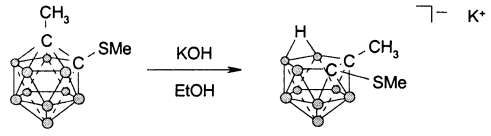
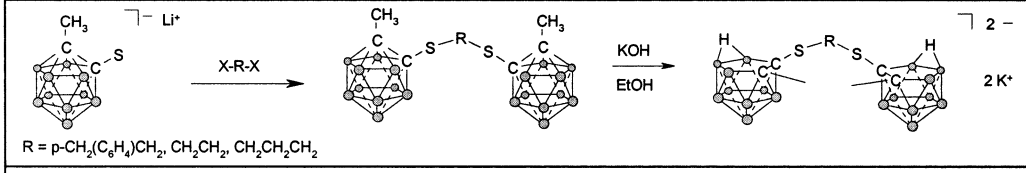
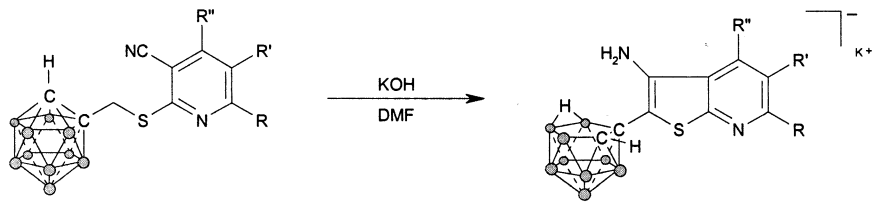
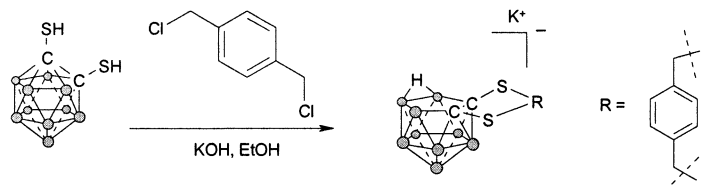
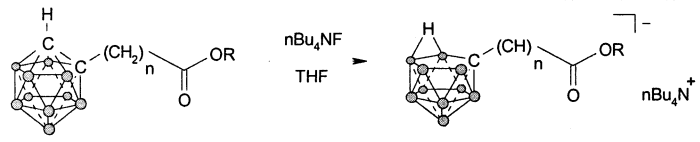
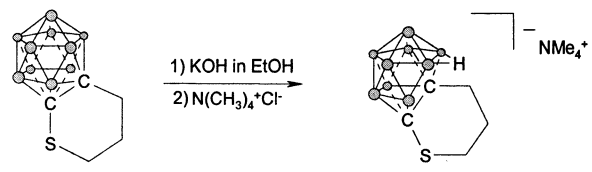
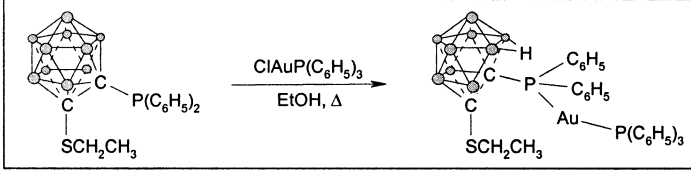
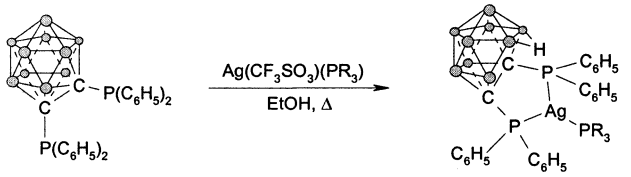
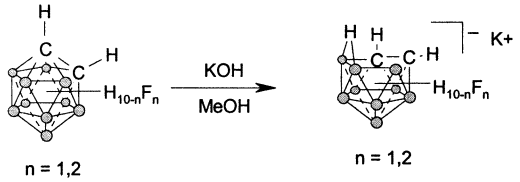
	[228]

	[229]
	[197,230]
	[197]
	[200]
	[197]
	[221]
	[231]
	[232]

	[233]
	[234]
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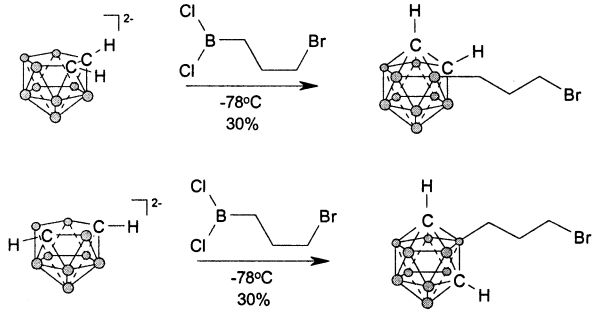
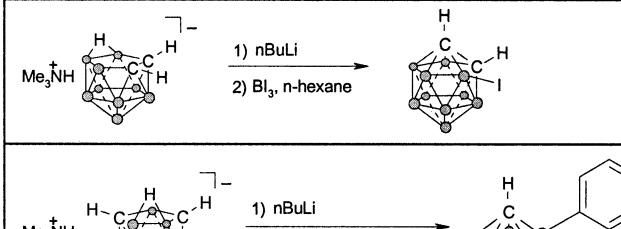
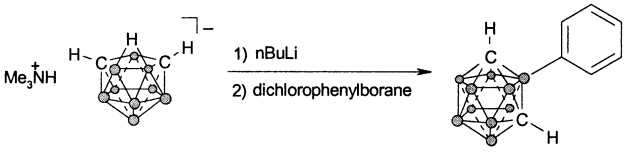
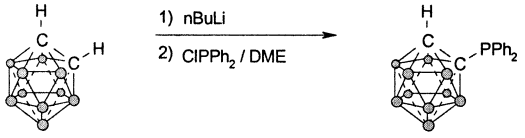
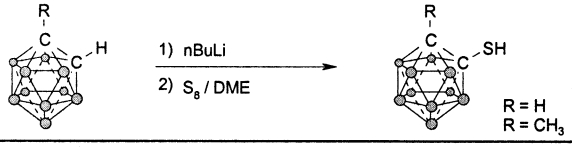
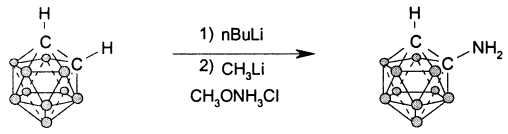
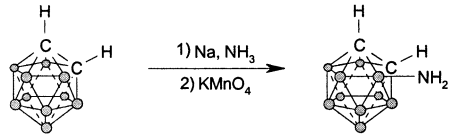
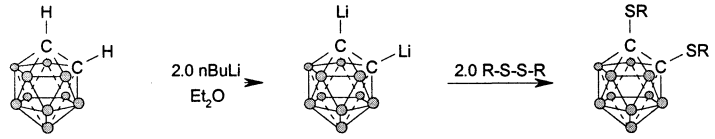
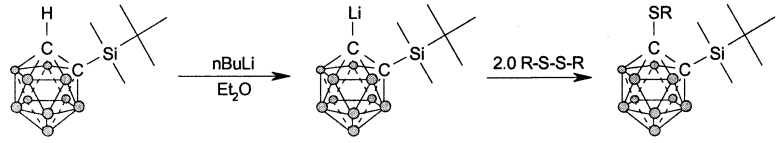
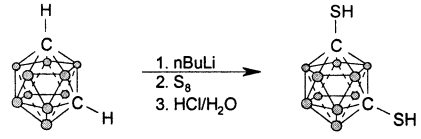
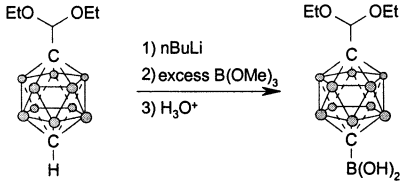
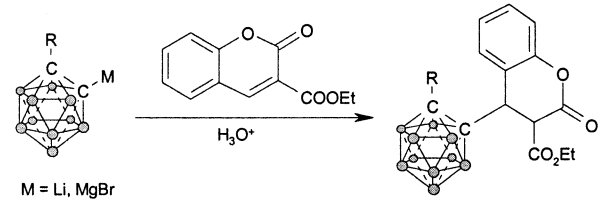
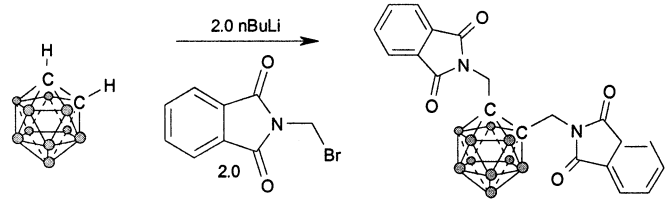
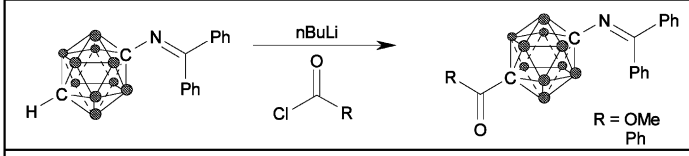
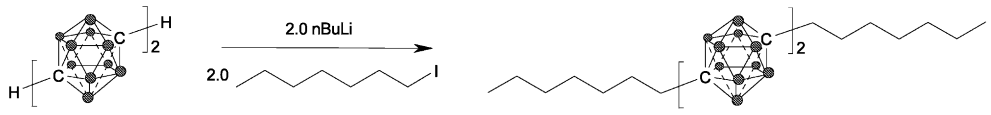
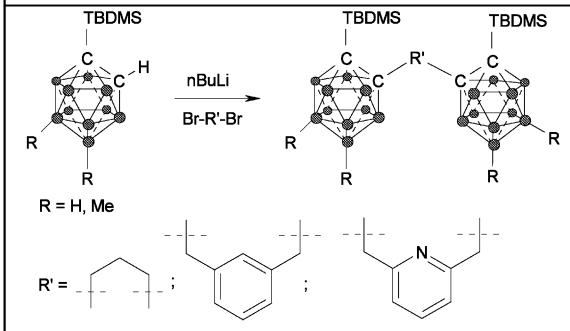
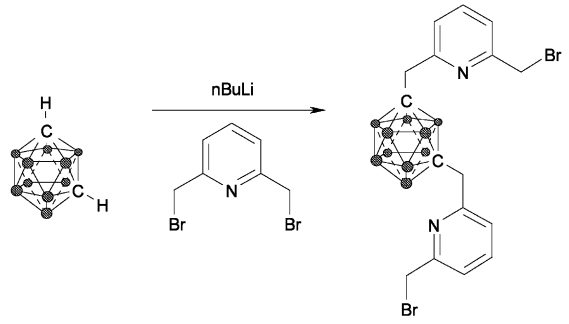
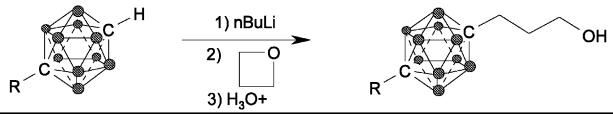
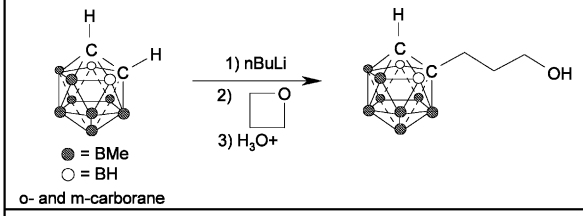
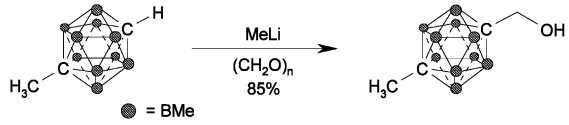
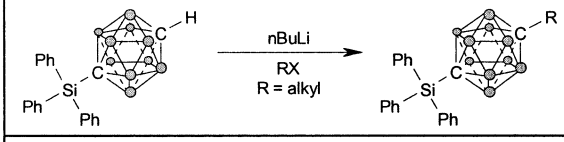
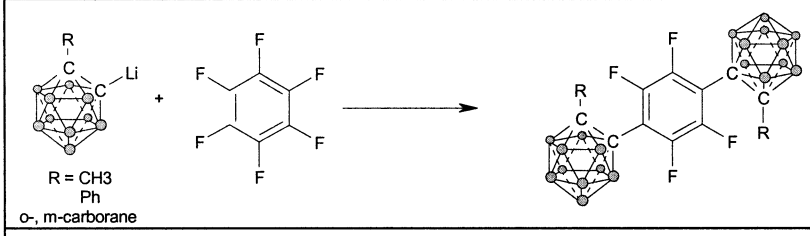
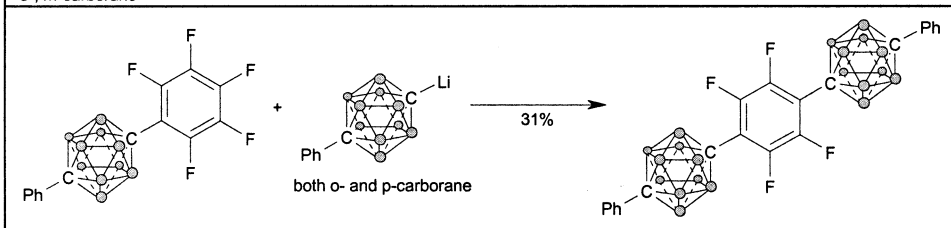
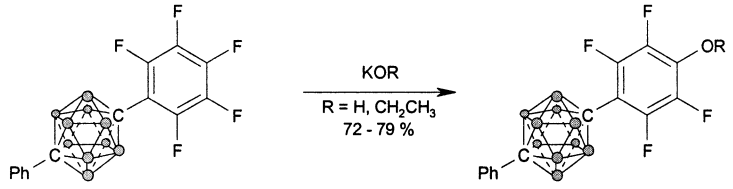
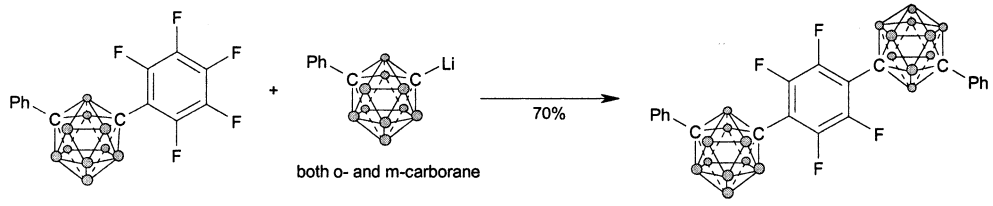
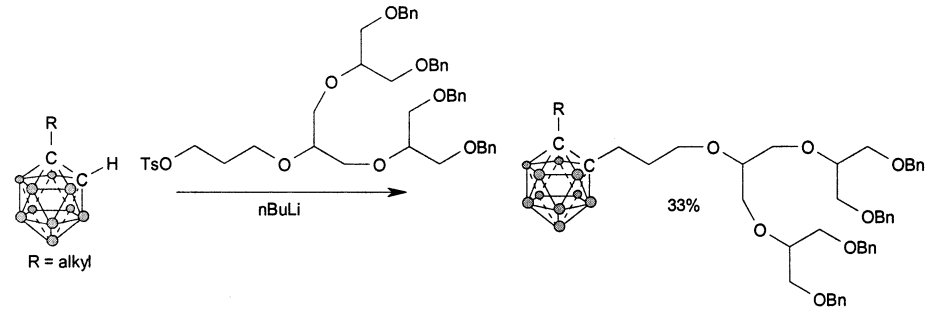
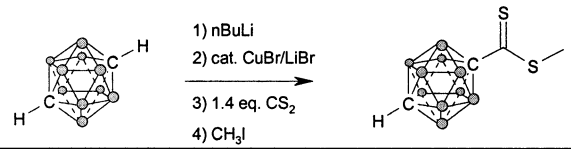
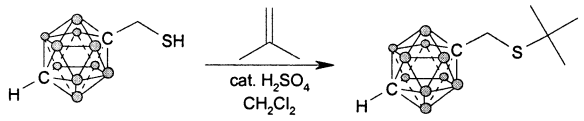
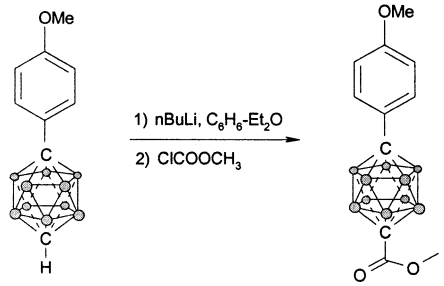
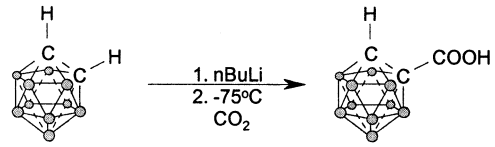
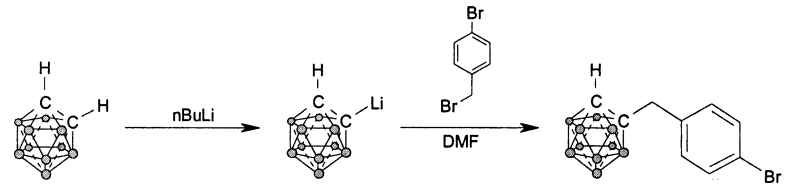
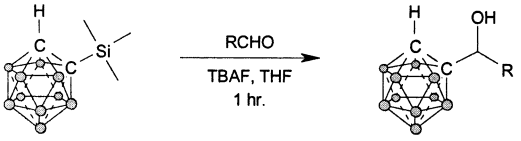
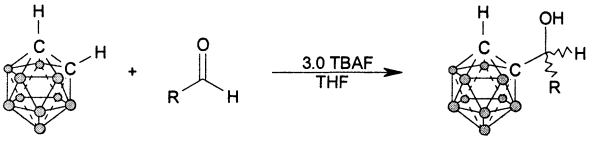
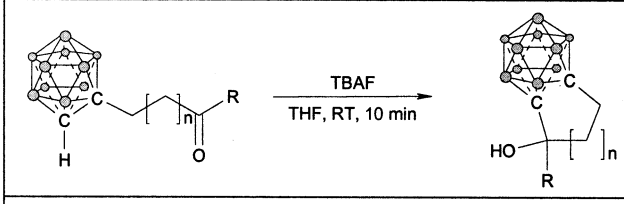
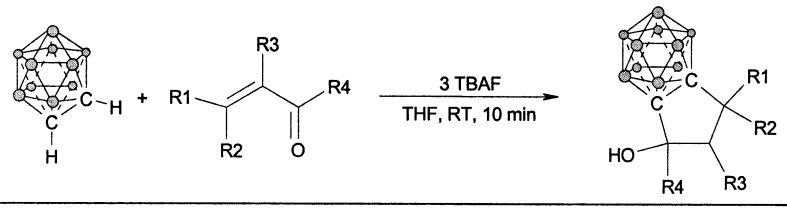
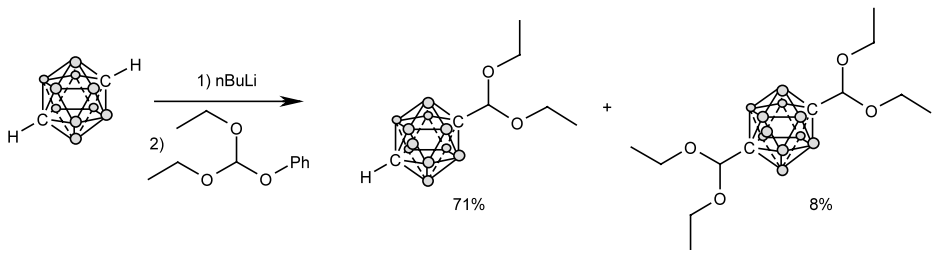
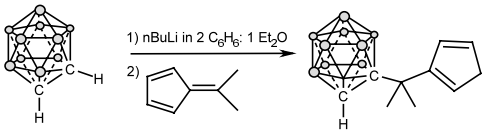
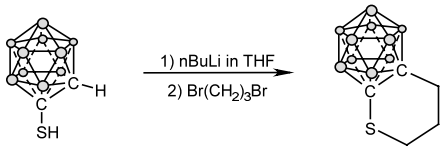
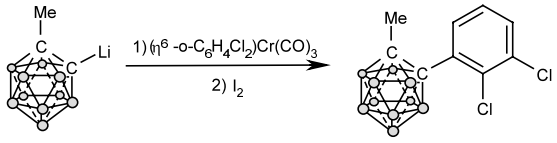
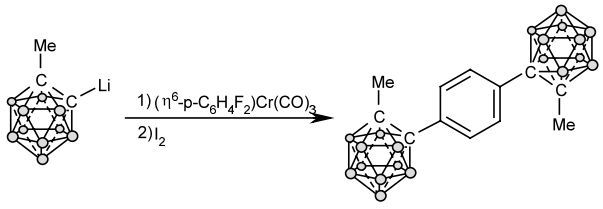
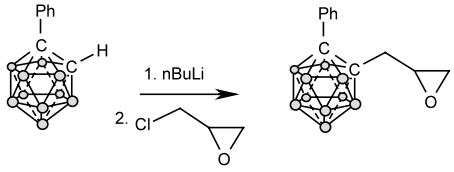
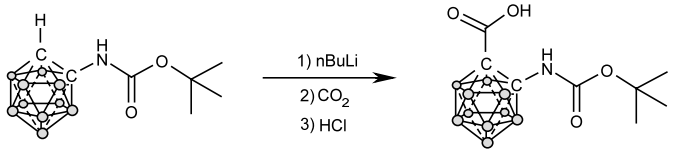
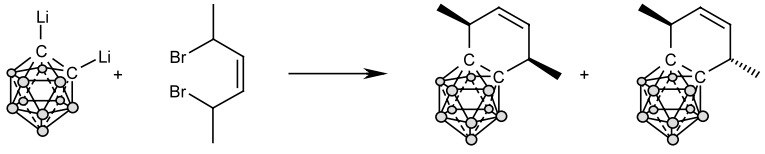
	[235]
	[211]
	[211]
5. Cage Modification	
5.1 C-X bond formation	
	[236]
	[197,236]

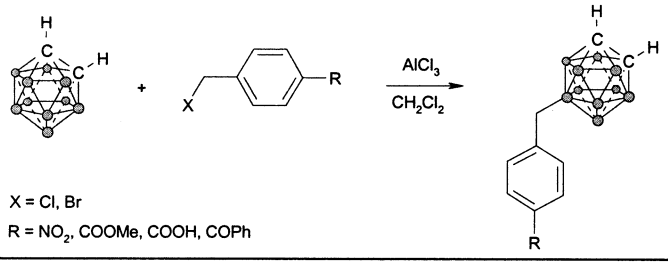
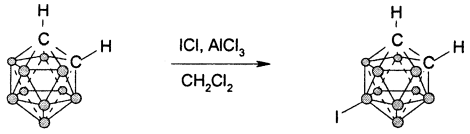
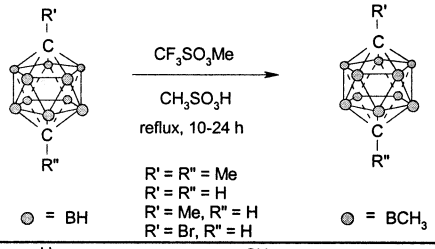
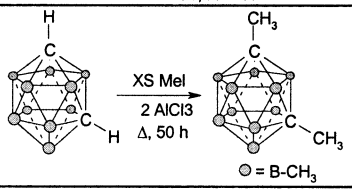
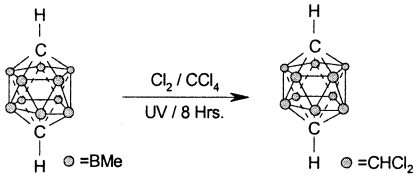
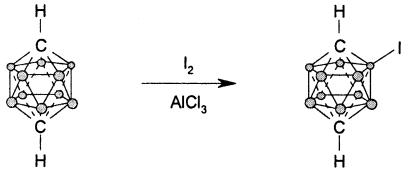
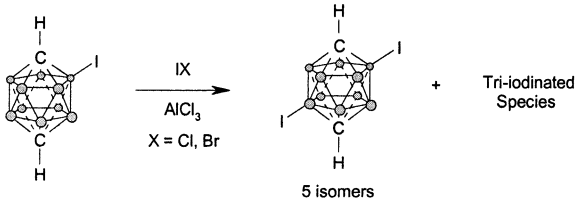
	[215]
	[207]
	[227]
	[227]
	[205]
	[218]
5.2 C-C bond formation	
	[237]
	[238]

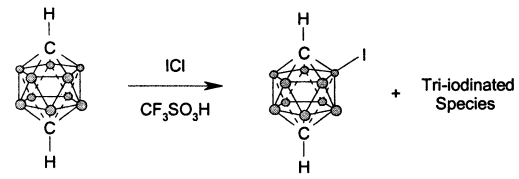
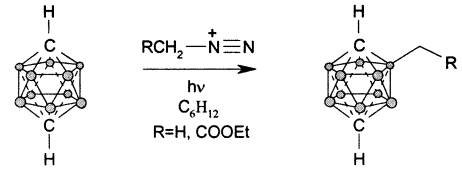
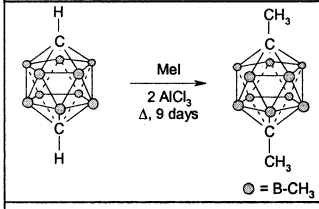
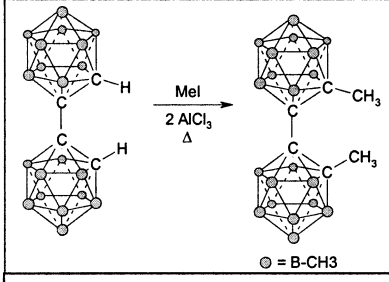
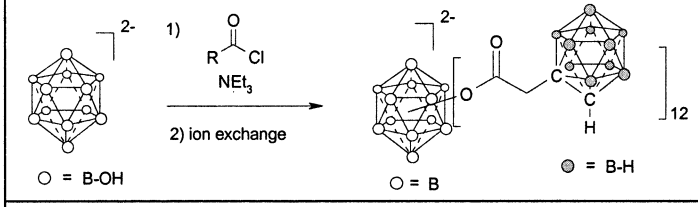
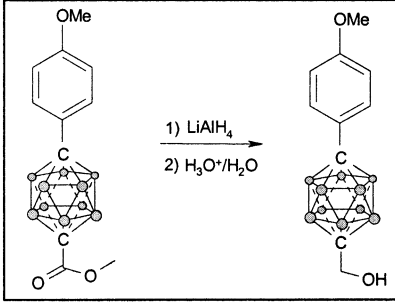
	[215]
	[239]
	[223,240]
	[223,230]
	[196,202,219]
	[204,219]
	[219]

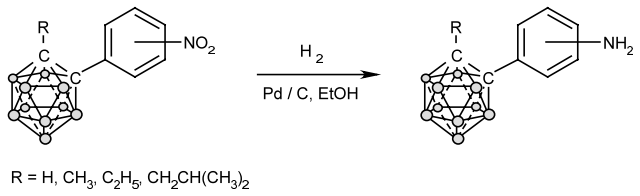
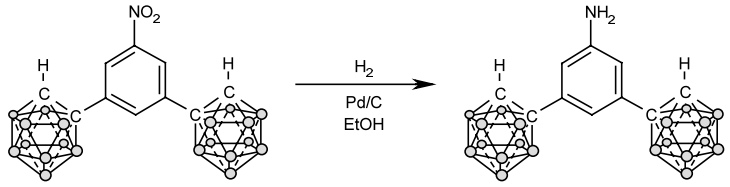
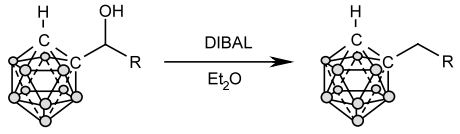
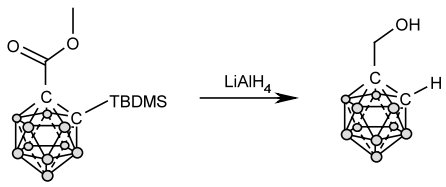
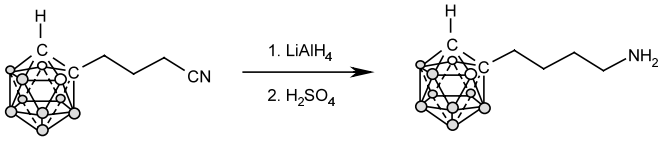
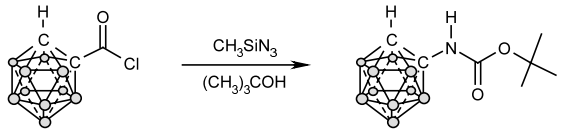
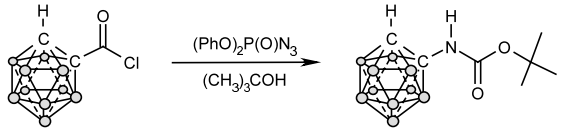
	[241,242]
	[243]
	[243]
	[243]
	[243]
	[202,244]
	[196]

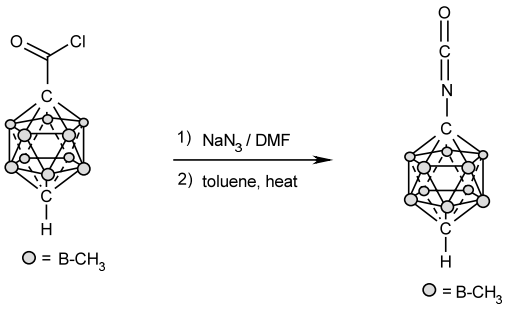
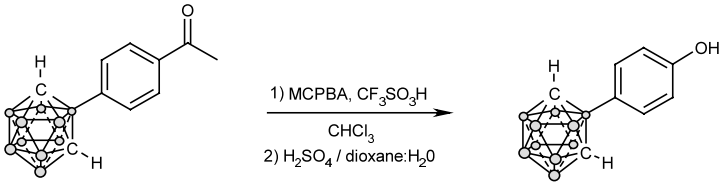
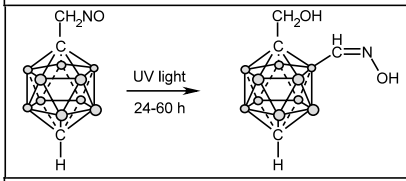
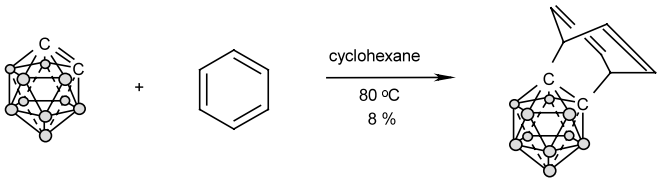
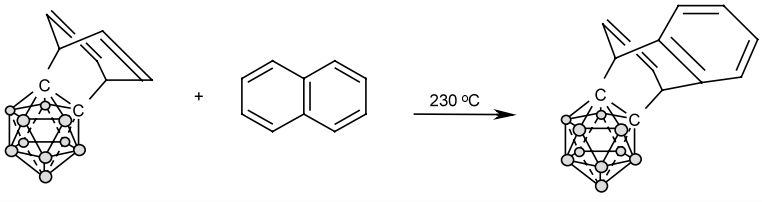
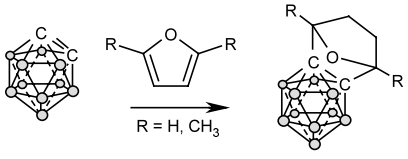
	[196]
	[245]
	[215,246]
	[247]
	[248]
	[249]
	[249]
	[249]

	[218]
	[250]
	[231]
	[251]
	[251]
	[252]
	[215]
	[253]
5.3 Electrophilic Substitution	

	[254]
	[211,255]
	[256]
	[257]
	[258]
	[255]
	[255]

	[255]
	[259]
	[257]
	[257]
5.4 Miscellaneous	
	[209]
6. Reduction	
	[245]

 R = H, CH_3, C_2H_5, $CH_2CH(CH_3)_2$	[213,214]
	[214]
	[196]
	[260]
	[241]
 O = BMe O = BH o- and m-carborane	[204]
7. Rearrangements	
	[215]
	[215]

	[261]
	[211]
	[206]
8. Cycloadditions	
8.1 [4 + 2]	
	[262]
	[253,262]
	[253,263]
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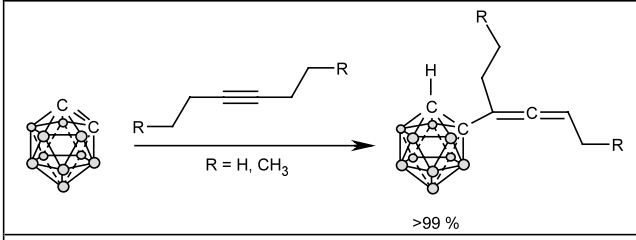
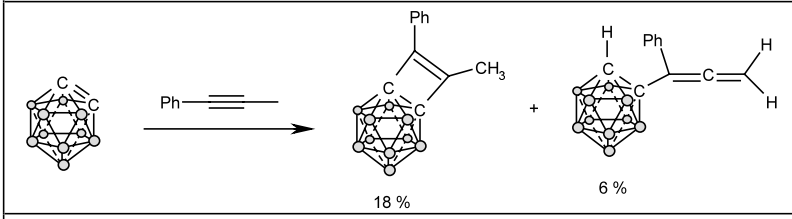
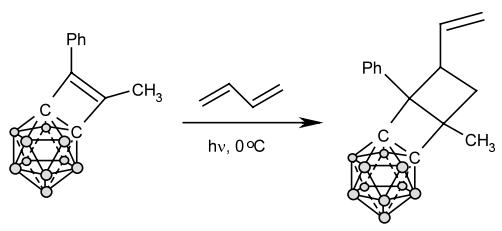
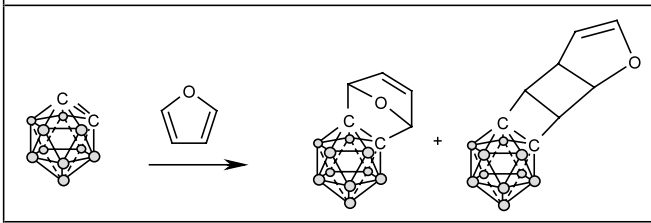
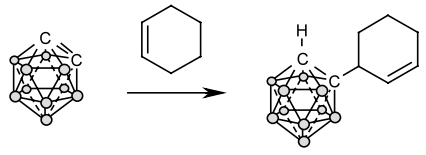
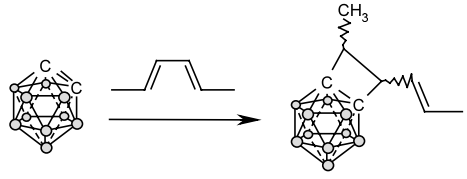
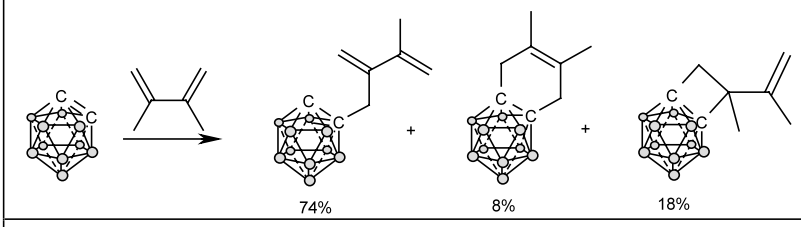
	[264]
	[265]
	[265]
	[263]
	[266]
	[264,266]
	[223,253]
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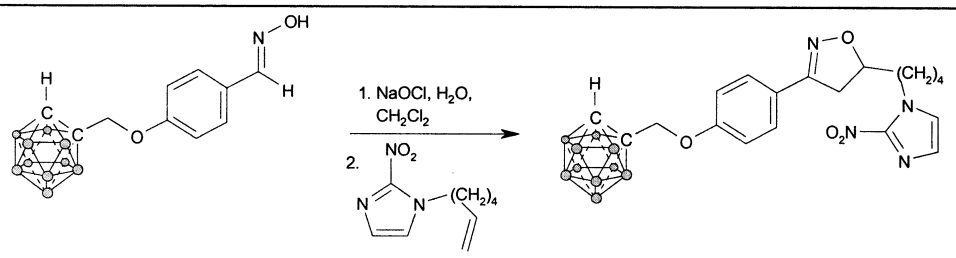

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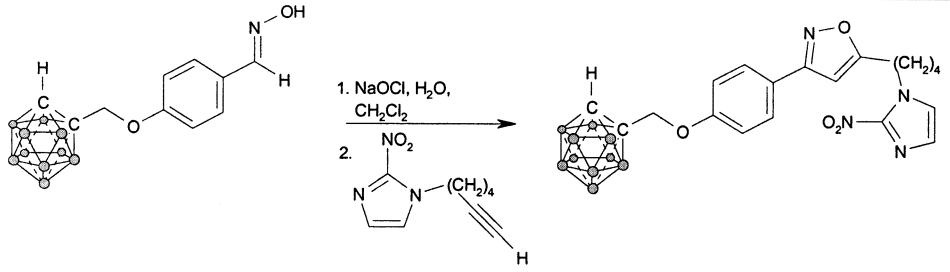
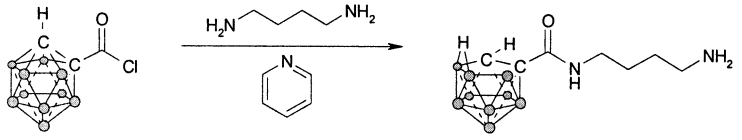


[216,252]

9. General Coupling Reactions



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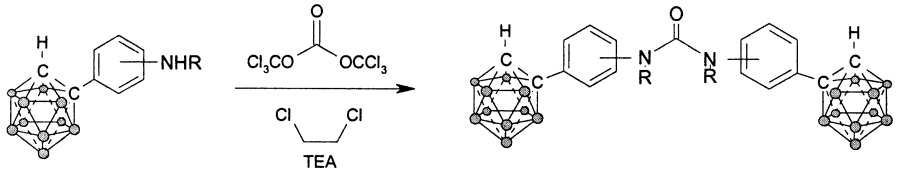

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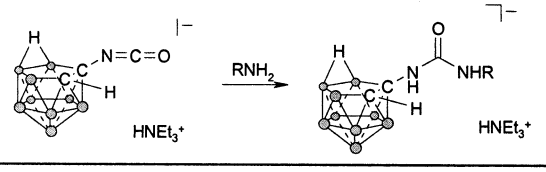

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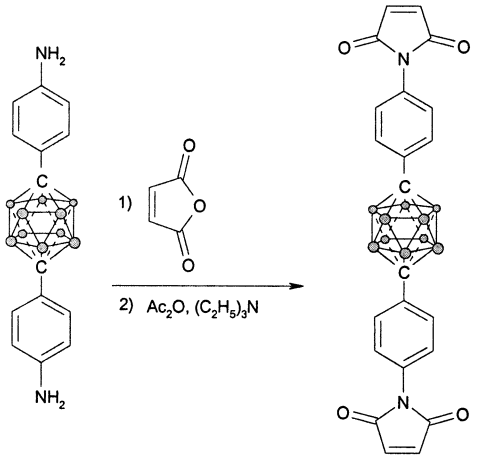

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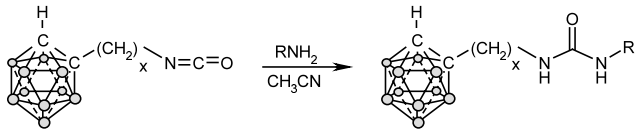
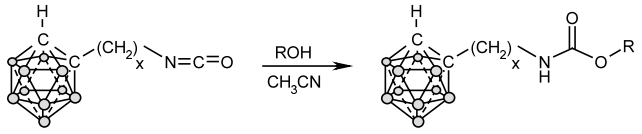
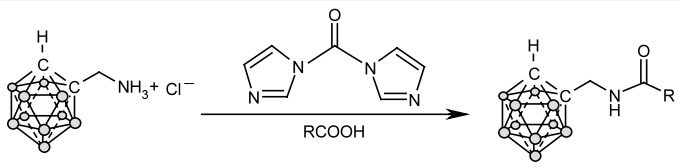
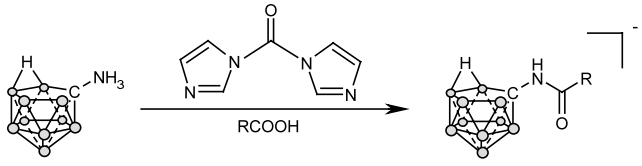
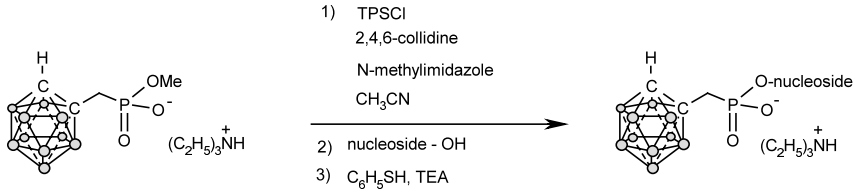
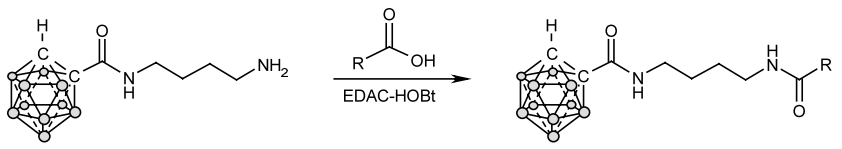
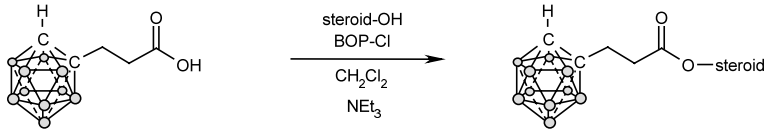
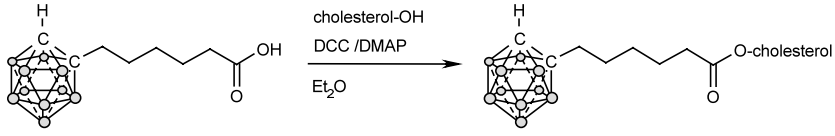
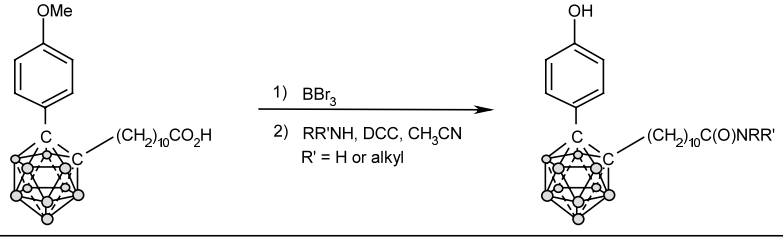
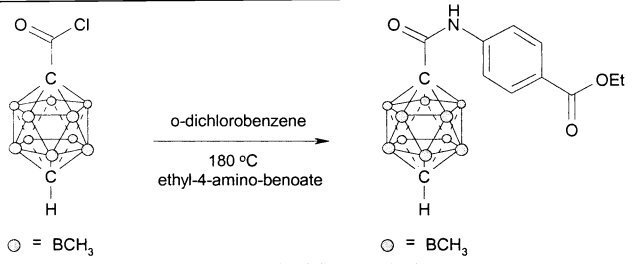
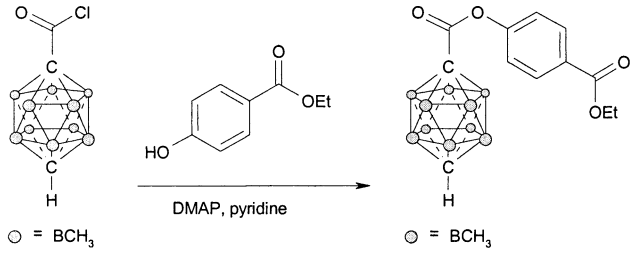
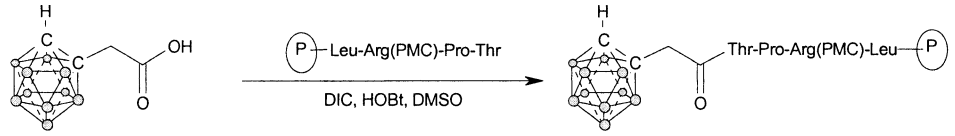
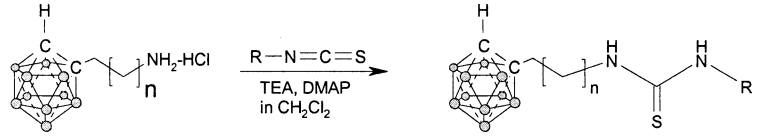
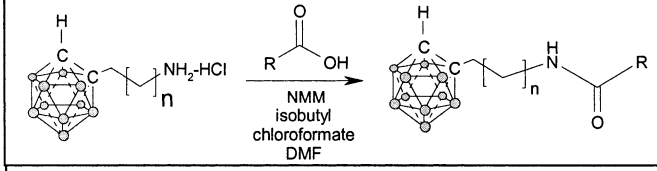
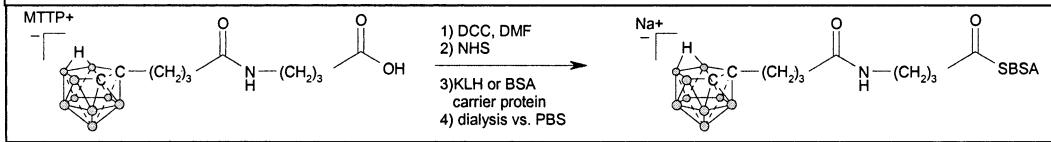
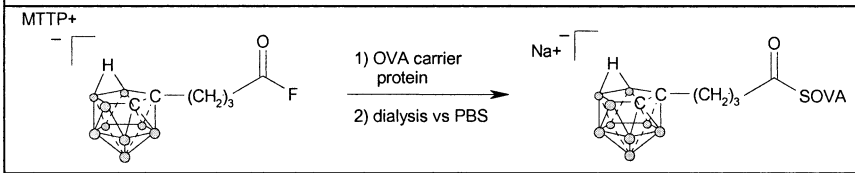
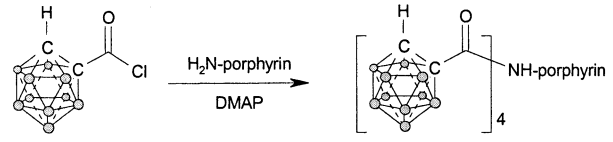
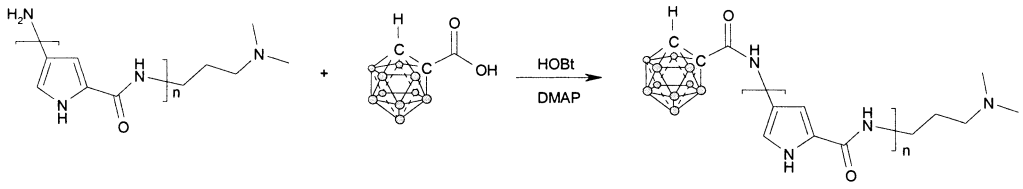
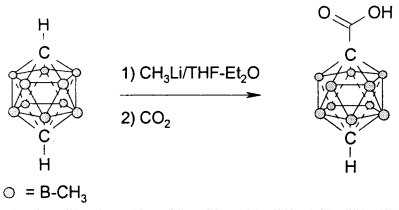
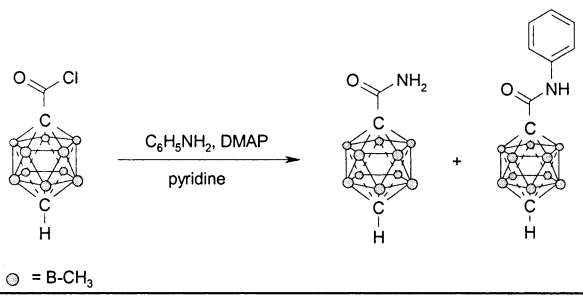
	[198]
	[199]
	[268]
	[199]
	[269]
	[246]
	[270]
	[221]
	[271]

	[261]
	[261]
	[272]
	[203]
	[203]
	[273]
	[273]
	[274]

	[275]
	[276]
	[276]
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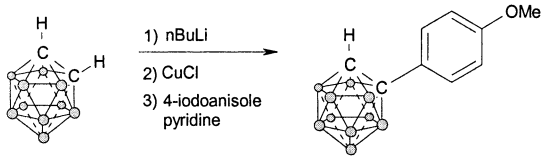
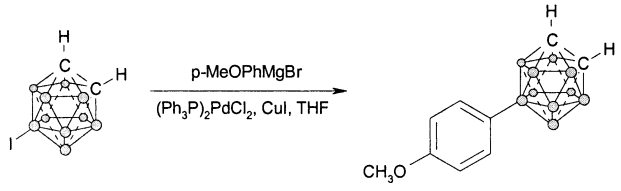
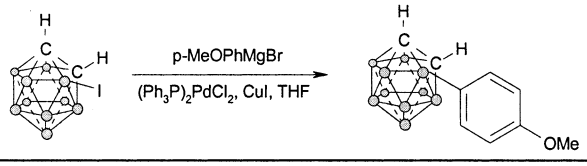
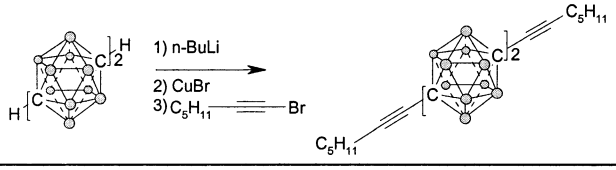
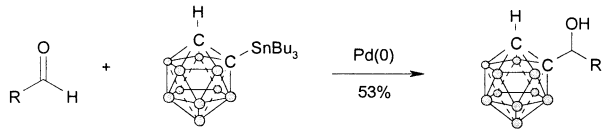
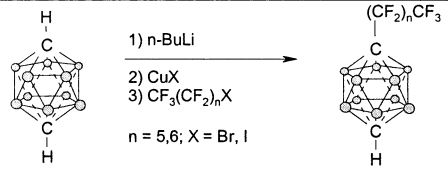
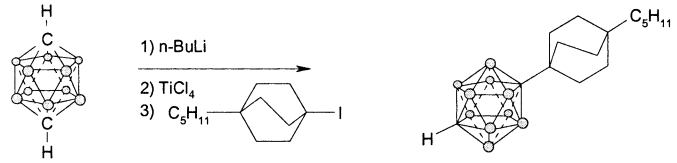
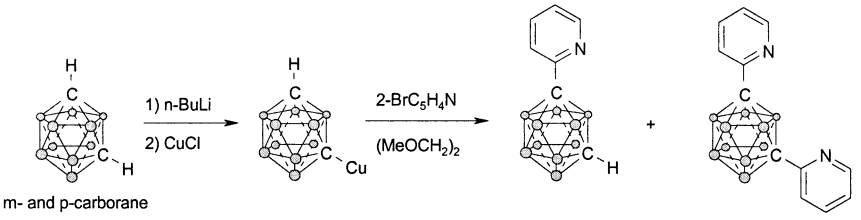
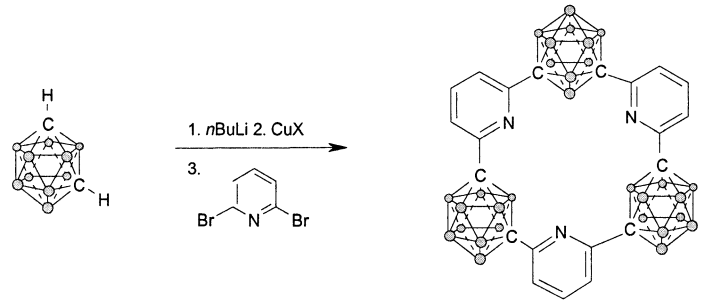
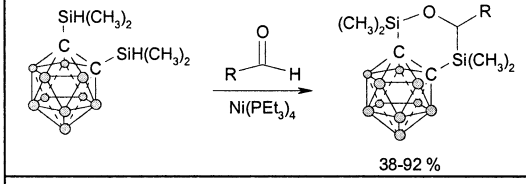
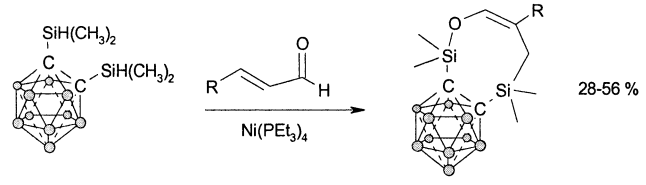
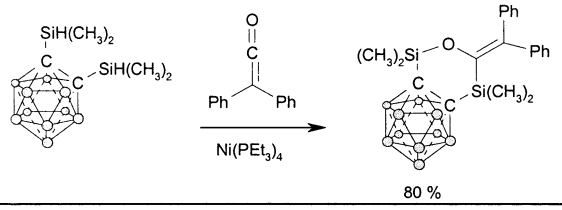
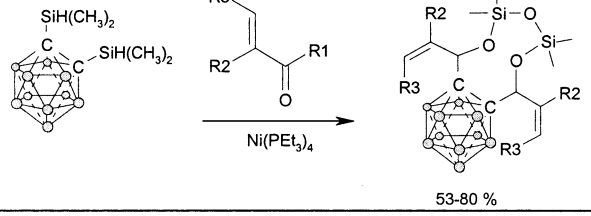
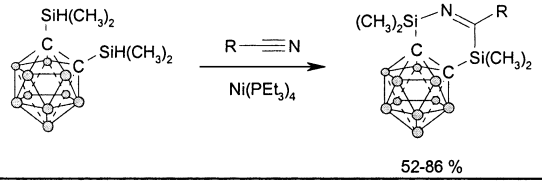
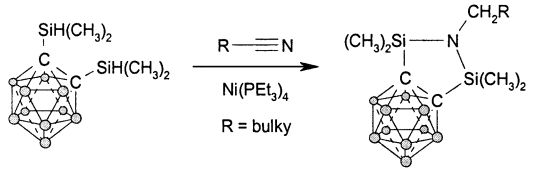
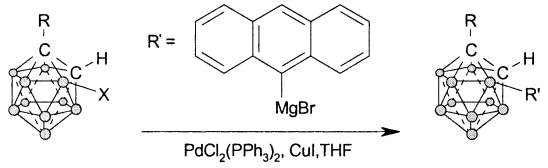
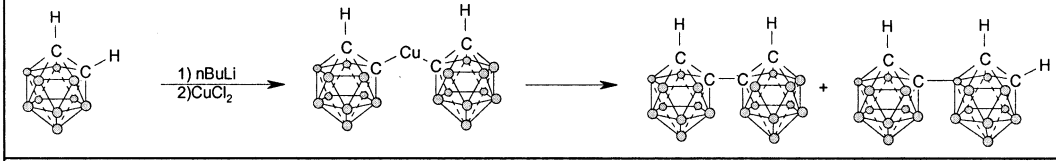
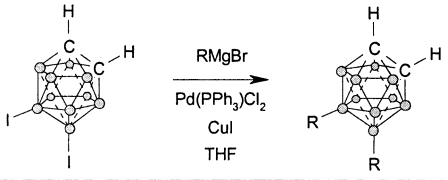
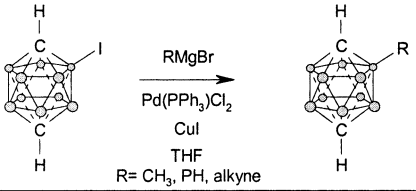
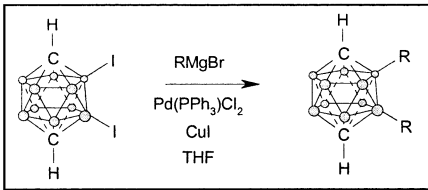
	[211]
	[211]
	[211]
	[239]

	[260,277]
	[242]
	[242]
	[278]
	[278]
	[279]
	[279]

m- and p-carborane

 80 %	[279]
 53-80 %	[279]
 52-86 %	[279]
	[279]
	[201]
	[280]
	[281]
	[239,255]



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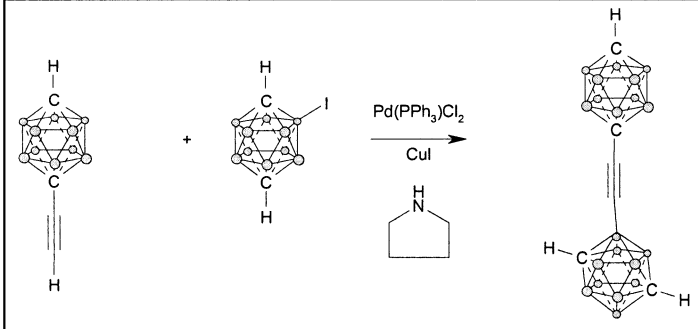

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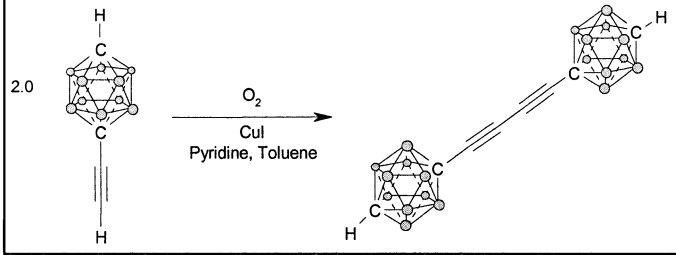

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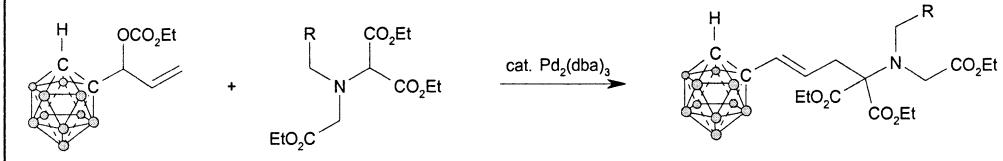

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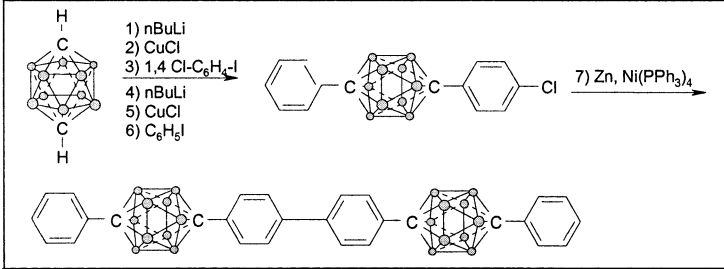

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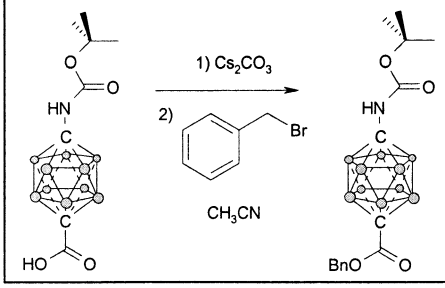
11. Protection



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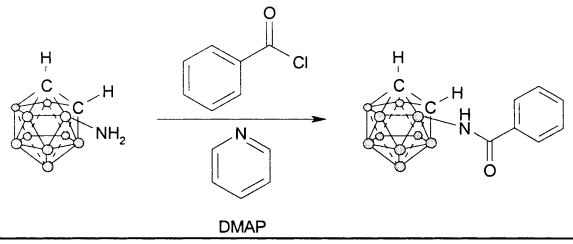
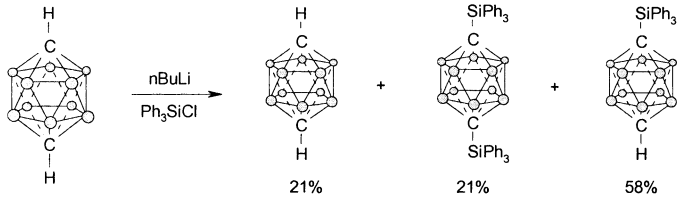
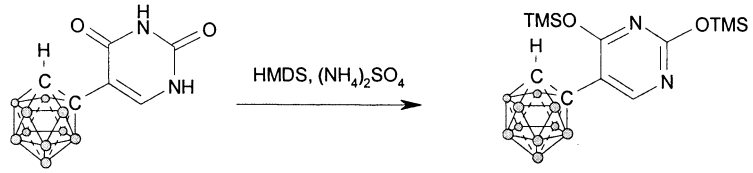
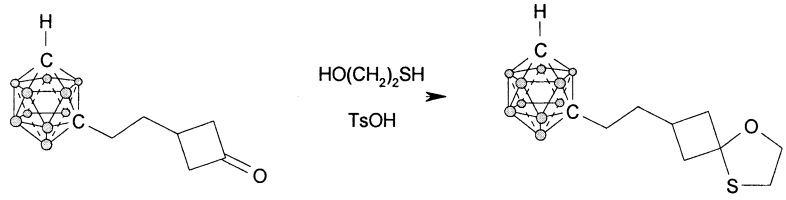
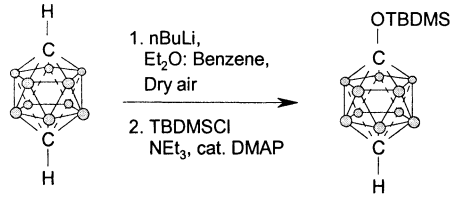
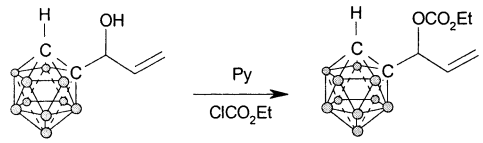
	[285]
	[219]
	[286]
	[244]
	[222]
	[283]
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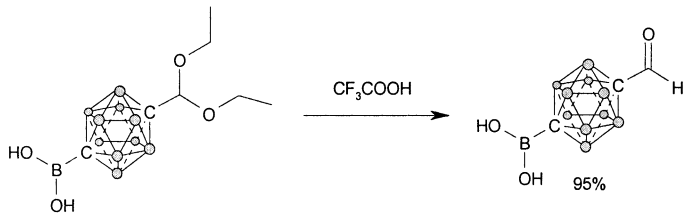
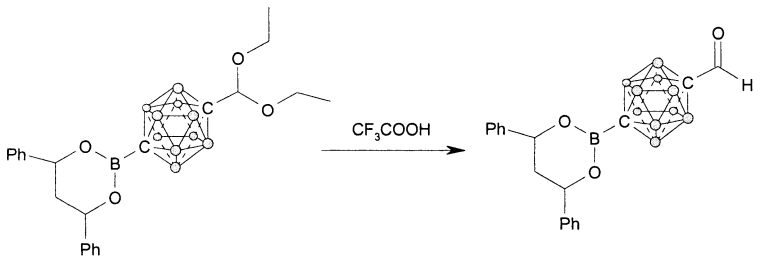
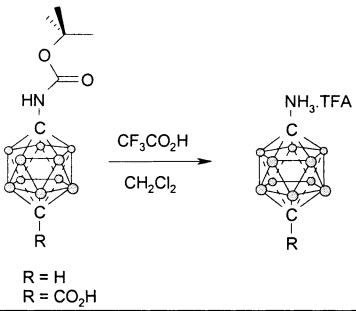
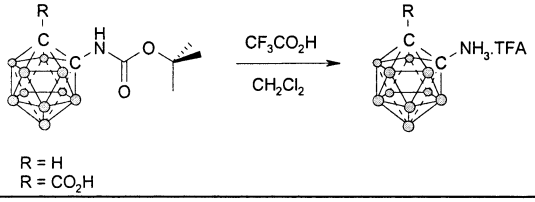
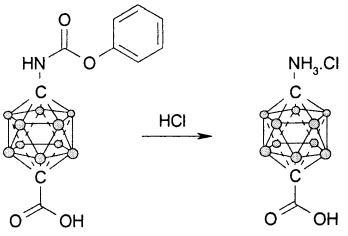
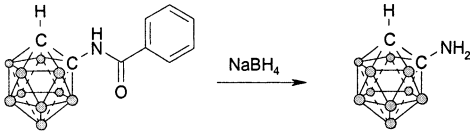
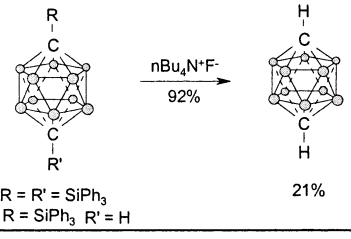
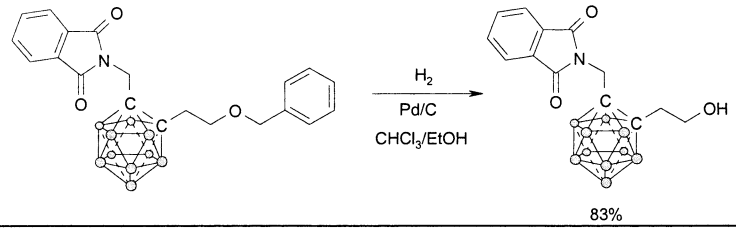
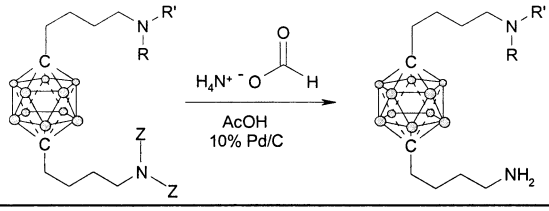
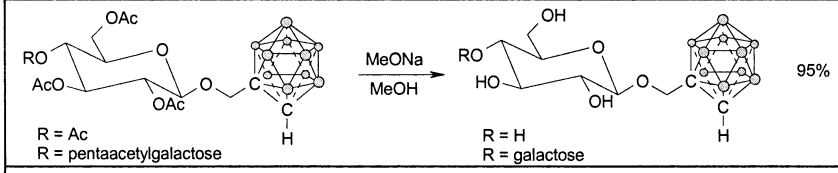
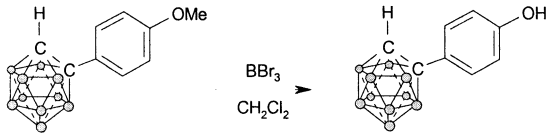
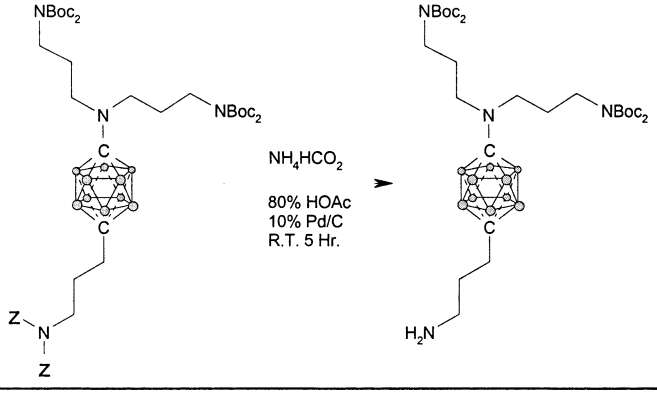
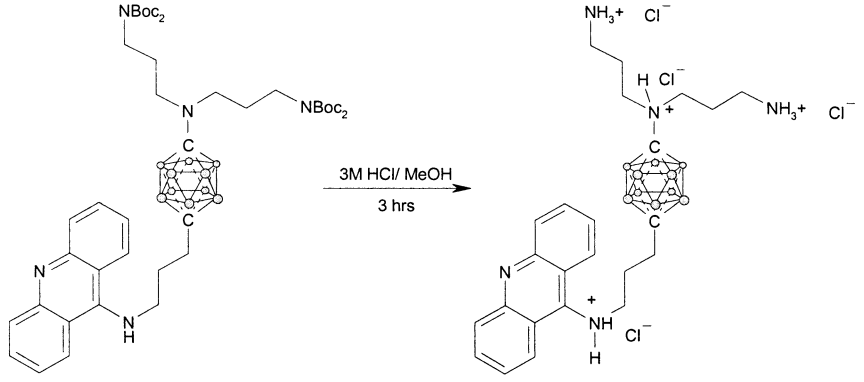
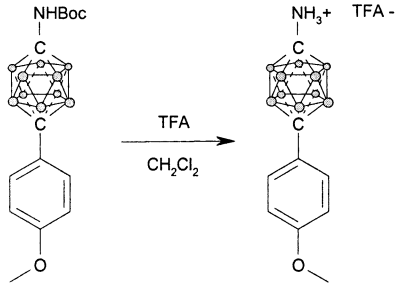
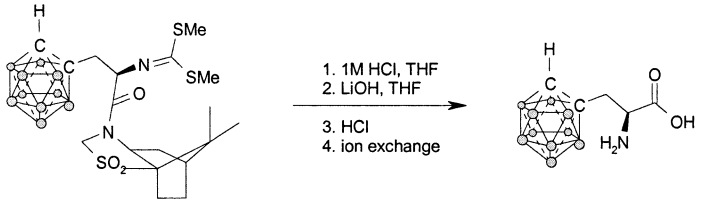
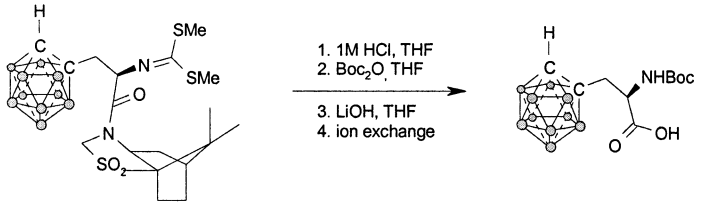
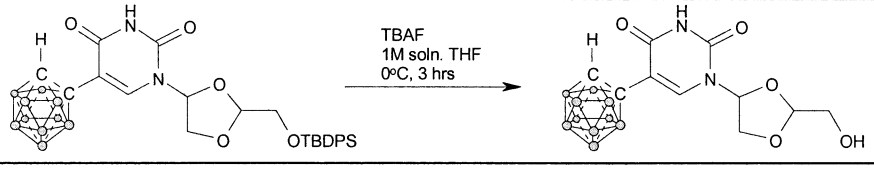
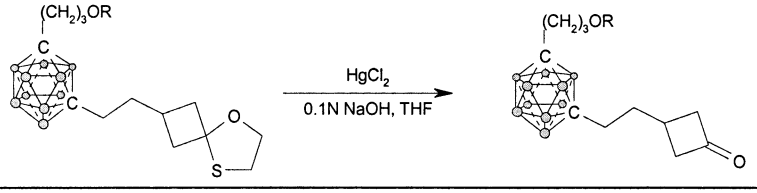
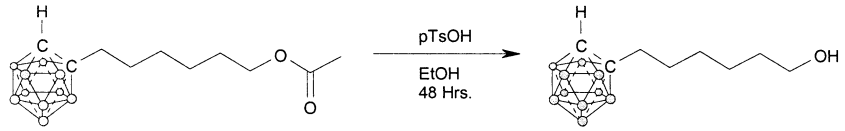
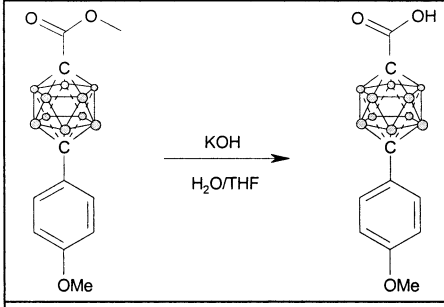
	[218]

	[218]
	[285]
	[285]
	[285]
	[268]
	[219,223,227,241]

	[287]
	[201]
	[288]
	[211]
	[201]

	[201]
	[289]
	[290]
	[290]
	[286]
	[244]

	[221]
	[245]
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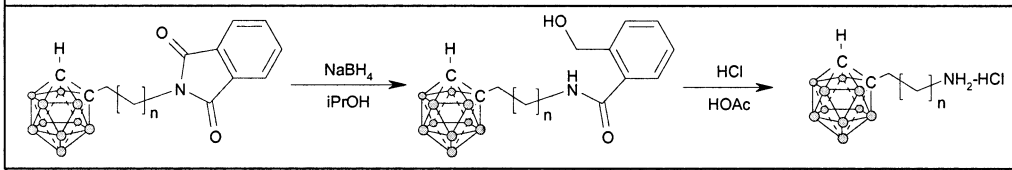
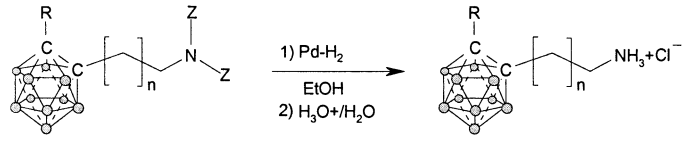
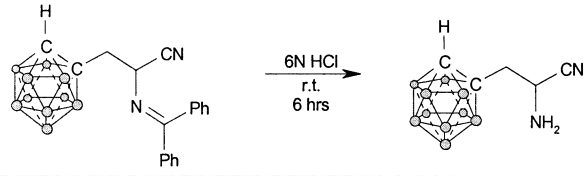
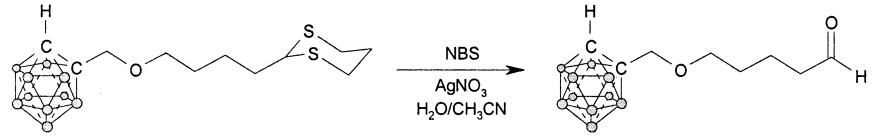
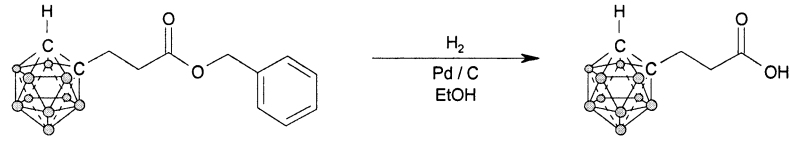
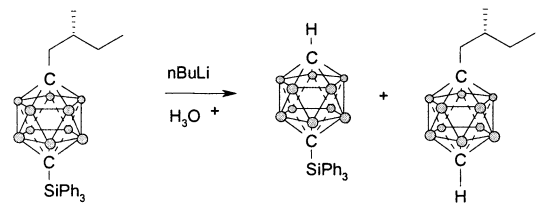
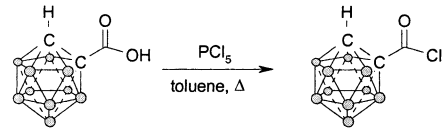
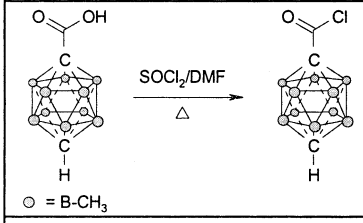
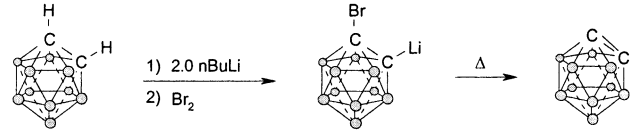
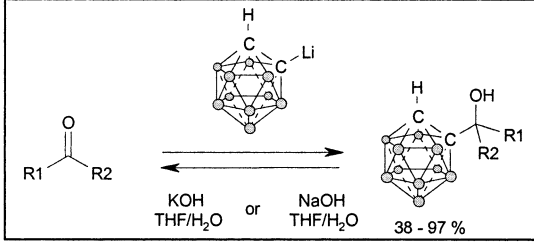
	[203]
	[202,291]
	[224]
	[216]
	[270]
13. Miscellaneous Reactions	

	[241]
	[285]
	[276]
	[262]
	[277,283]

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