CHEMICAL REVIEWS

REVIEW

pubs.acs.org/CR

Carbaboranes as Pharmacophores: Properties, Synthesis, and Application Strategies

Matthias Scholz and Evamarie Hey-Hawkins*

Institut für Anorganische Chemie der Universität Leipzig, Leipzig, Germany

CONTENTS

1. INTRODUCTION

Medicinal chemistry is still clearly dominated by organic chemistry. Most of the marketed drugs are purely organic molecules. The right-hand neighbors of carbon in the periodic table, such as nitrogen, oxygen, and halogens, have already made it into a variety of pharmaceuticals. The left-hand neighbor, boron, however, is nearly unknown as an element in commercial drugs.[1] Boron, similar to carbon, readily forms compounds with covalent boron−hydrogen bonds and also boron−boron interactions. In contrast to hydrocarbons, boranes avoid the formation of chain structures and clearly prefer the formation of polyhedral clusters (to overcome the electron deficiency) with fascinating globular architectures.[2,3] Most boranes are unstable species in aqueous environments and therefore are not applicable in medicinal chemistry. In contrast, carbaboranes, in which two BH^- units of *closo*-$B_{12}H_{12}^{2-}$ are replaced by two CH vertices, have remarkable biological stability and two carbon atoms as starting points for various organic modifications. Carbaboranes for medicinal applications are preferably used to design boron neutron capture therapy (BNCT) agents. BNCT is a cancer-treating method based on the cytotoxic $^{10}B(n,\alpha)^{7}Li$ reaction. The breakthrough in BNCT has not been achieved yet, and only a very few noncarbaborane compounds, such as L-4-(dihydroxyboryl)phenylalanine (BPA) and the sodium mercapto-undecahydro-*closo*-dodecaborate (BSH) are used in clinical treatments.[4−6] The rationale behind the BNCT approach is the use of carbaboranes as multiple boron carriers. Connection of the cluster to a tumor-targeting vector is a common principle in the design of BNCT agents and is aimed to improve the tumor-to-blood ratio (5:1), a prerequisite for therapeutic application.[7,8] Parallel to utilization as boron carriers, carbaboranes were found to be very good scaffolds for diagnostic and therapeutic labeling.[9] BNCT and imaging research have widely explored carbaborane chemistry and provided detailed information on cluster properties and possible reactions.

Several experts have already summarized the reactivity and characterization methodologies for carbaboranes.[10−16] BNCT has been comprehensively summarized and the medicinal potential of carbaboranes has also been reviewed.[7−9,17−20] However, the expanding field of carbaborane chemistry constantly produces new reaction types and application areas, such as the perception of carbaboranes as pharmacophores.[21]

Received: January 31, 2011
Published: July 25, 2011

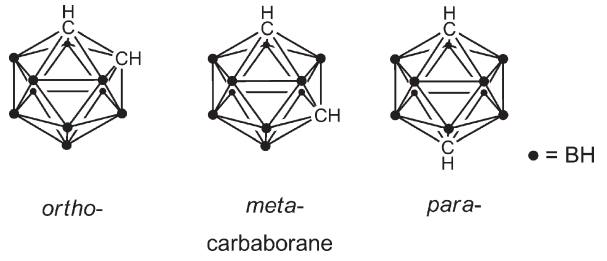


Figure 1. Graphical presentation of the carbaborane isomers in idealized geometry. Solid lines visualize the polyhedron and are not to be regarded as classical two-center, two-electron single bonds.

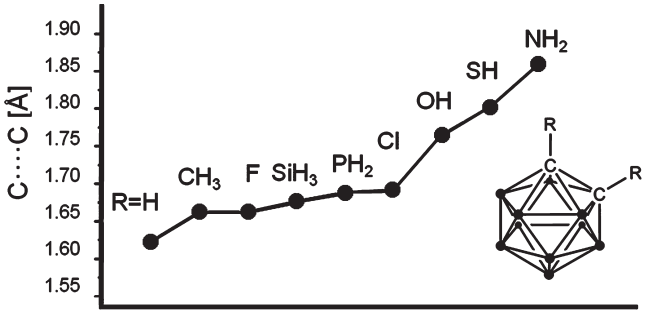


Figure 2. Computed C−C distances of symmetrically disubstituted *ortho*-carbaboranes.[26]

Hence, regular updates of existing reviews and new reviews addressing emerging fields of application are essential. This review is aimed at introducing carbaboranes as potential pharmacophores in drug design, including theory and practice. First, the geometric and electronic features of carbaboranes and resulting properties are summarized. This is of major importance for the interaction with biomolecules according to the perception as pharmacophores. Second, general aspects of the handling of carbaboranes, the current state of synthetic approaches for attaching desired residues, and a guideline for routine analysis are presented with the particular purpose of familiarizing the nonexpert with the field of carbaborane-based drug design. A final section summarizes current achievements in this emerging area, not only with a focus on biological targets but furthermore with the goal to inspire future research by employing general strategies.

2. PROPERTIES OF CARBABORANES

The geometry and electron-deficient nature of the boron atoms determine the cluster properties. The hydrophobicity of the BH shell and the rather acidic CH vertices determine the intermolecular interactions.

2.1. Geometry

Polyhedral boranes are known for their extraordinary molecular architectures containing *closo*, *nido*, *arachno*, and *hypho* structures.[3]

Among those, dicarba-*closo*-dodecaboranes(12) ($C_2B_{10}H_{12}$) are rigid clusters with slightly distorted icosahedral shape, derived from the $B_{12}H_{12}^{2-}$ dianion. Ten BH and two CH vertices are organized in *ortho*, *meta*, or *para* fashion, giving rise to three different isomers (Figure 1). The first two have C_{2v} symmetry; *para*-carbaborane has D_{5d} symmetry.[22]

Table 1. Summary of Geometric Parameters of the Carbaborane Isomers.[a]

	carbaborane		
parameters	*ortho*	*meta*	*para*
symmetry	C_{2v}	C_{2v}	D_{5d}
C−C distance [Å]	1.62	2.61	3.06
H−C−C−H angle[b] [deg]	∼52	∼115	180
S_{IC}	0.10	0.10	0.13
V_{vdW} [Å^3]	148	143	141

[a] The values were either calculated or taken from crystal data.[28,30] Icosahedricity is determined by the S_{IC} value and is zero for ideal icosahedra. [b] The angle of carbon substituents relative to each other was obtained from the crystal structure of the unsubstituted clusters without regarding slight distortions.

The carbon and boron atoms of the C_2B_{10} core are hexacoordinate to compensate for the low electron density, forming 20 triangular faces. The $B_{12}H_{12}^{2-}$ icosahedron has a computed B−B distance of 1.787 Å.[23] The presence of the carbon atoms influences the B−B distances, which vary from approximately 1.76 to 1.81 Å, depending on corresponding isomer and method of determination.[22−25] The computed C−H distances (1.07 Å) are a little shorter than the B−H distances (1.17 Å).[24] The experimental values, determined by gas-phase diffraction studies, are slightly larger (ca. 1.09 Å for C−H, 1.19 Å for B−H).[25] The C−C distance depends, of course, on the isomer, and also on the substituents at the carbon atoms.

The C−C distance of the *ortho* isomer has been intensively studied. It is shortest for the unsubstituted cluster (1.62 Å) and increases when substituents are attached as a result of steric and electronic effects. Bulky groups and electron donors, such as anionic substituents and π donors, increase the C−C distance (Figure 2).[27,28]

The so far largest C−C distance of 2.16 Å was observed in a sterically crowded bis(alkylferrocenyl)-substituted carbaborane.[29] Changes in the C−C distance also influence the orientation of the substituents R, which is of importance when carbaboranes are used as scaffolds to position additional functional groups. *ortho*-Carbaborane allows the attachment of two substituents at the carbon atoms at an angle of approximately 60° (unsubstituted *ortho*-carbaborane shows ca. 52°, calculated from crystal structure data[28]), *meta*-carbaborane at approximately 120° (unsubstituted *meta*-carbaborane shows ca. 115°, obtained from crystal structure data, neglecting a slight distortion[28]), and *para*-carbaborane at an angle of 180°. Introduction of additional substituents at the boron atoms makes a three-dimensional attachment of substituents possible. This synthetic versatility makes carbaboranes very useful scaffolds in designing drugs and superior to benzene systems, which are limited to two dimensions.

The calculated volume of the boron−carbon core is 11.79, 11.72, and 11.71 Å^3 for *ortho*-, *meta*-, and *para*-carbaborane, respectively, and therefore on average 5.6% smaller than the B_{12} core of the $B_{12}H_{12}^{2-}$ dianion.[30] The *para* isomer has the smallest volume, attributable to a contraction along the C···C axis, which consequently shows the greatest deviation from an ideal icosahedral shape (see icosahedral shape measure (S_{IC}) values, Table 1; the higher the value, the greater the deviation from an ideal icosahedron). In drug design, however, the van der Waals volume (V_{vdW}) of the cluster is much more important than the

dx.doi.org/10.1021/cr200038x |*Chem. Rev.* 2011, 111, 7035–7062

better-studied volume of the core. The precise determination and comparison of V_{vdW} is difficult, because it strongly depends on the method applied.[31] Thus, the V_{vdW} of *ortho*-carbaborane was determined as 255 Å^3 by density measurements, 185 Å^3 by small-angle X-ray scattering (SAXS) measurements, and 148 Å^3 by theoretical simulations based on the Connolly method.[32,33] The carbon analogues adamantane and benzene have calculated V_{vdW} of 147 and 80 Å^3 (both according to Bondi), respectively.[31,34,35] The different values illustrate that comparison of V_{vdW} values is difficult and only gives reliable trends when all volumes are obtained by the same method. Determination of the V_{vdW} based on crystal structures gave 148, 143, and 141 Å^3 for *ortho*-, *meta*-, and *para*-carbaborane, 136 Å^3 for adamantane, and 79 Å^3 for benzene (Figure 3).[36] The V_{vdW} of a rotating phenyl ring is ca. 102 Å^3. The size of the carbaborane slightly decreases in the order *ortho*-, *meta*-, *para*-carbaborane, as does the core volume. The differences are generally very small, so that the cluster volume is virtually the same for all isomers. The average size of all carbaboranes is comparable to that of adamantane and almost twice the volume of benzene. Even when the rotation of benzene is taken into consideration, the volume occupied by carbaboranes is still approximately 40% larger. This relation should be considered when using carbaboranes as surrogates for a benzene or adamantane moiety.

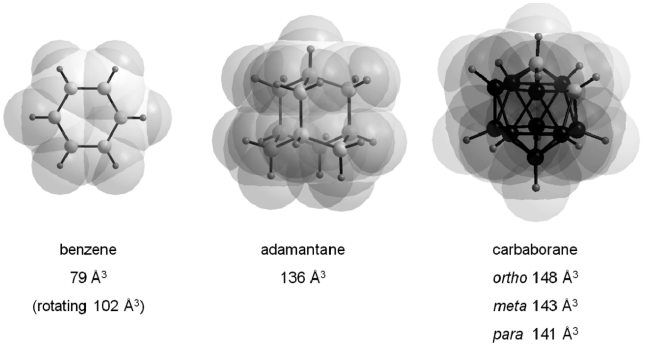


Figure 3. Graphical visualization of the van der Waals volumes of benzene, adamantane, and *ortho*-carbaborane based on the program DIAMOND (C and H = gray, B = black). Calculations are based on the program PLATON with the use of deposited crystal structure data.[36]

2.2. Electronic Structure

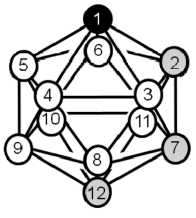
Carbaboranes are *closo* clusters and feature $2n + 2$ skeletal electrons (e^-), that is, 26 e^- for 12 vertices. The clusters characteristically reveal nonclassical bonding interactions giving a very complex overall electronic structure. Since the cluster electrons are delocalized three-dimensionally, carbaboranes can be described as three-dimensional aromatic compounds. In the literature, the designation "benzene analogues" has spread, because a rotating phenyl ring resembles the spherical icosahedra, as seen above. To describe the electronic structure, both the Mulliken and the natural population analysis (NPA) charges were determined.[30] Both calculations give similar trends, but the NPA charges reveal the more proper chemical description (Table 2).

The carbon atoms are slightly more electronegative. The B−C bonds are stronger than the C−C bonds; therefore, the two carbon atoms prefer nonadjacent positions, which makes the *para* isomer the most stable.[37] The NPA additionally shows that the hydrogen atoms at the carbon atoms are far more acidic than those at the boron vertices. All three isomers reveal a HOMO −LUMO gap of about 8 eV.[30] The dipole moments for *ortho*-, *meta*- and *para*-carbaborane are 4.53(5) D, 2.85(5) D, and zero, respectively.[38,39]

The differences in the electron density of the various vertex positions give rise to different inductive and resonance effects, as has been previously summarized by Bregadze and Kalinin.[10,11] The inductive effect (σ_i) is, however, more pronounced than the resonance effect (Figure 4).[40] Studies on several compounds revealed that the σ_i values of *ortho*-carbaborane cover the largest

Table 2. NPA Charges for the Unsubstituted Carbaborane Isomers in Units of |e|[30a]

o-$C_2B_{10}H_{12}$		*m*-$C_2B_{10}H_{12}$		*p*-$C_2B_{10}H_{12}$	
$C_{1/2}$	−0.496	$C_{1/7}$	−0.639	C	−0.664
$H_{1/2}$	0.300	$H_{1/7}$	0.299	H_C	0.299
$B_{3/6}$	0.158	$B_{3/2}$	0.149	B	0.005
$H_{3/6}$	0.054	$H_{3/2}$	0.066	H_B	0.068
$B_{4/5/7/11}$	0.000	$B_{4/6/8/11}$	−0.021		
$H_{4/5/7/11}$	0.069	$H_{4/6/8/11}$	0.073		
$B_{8/10}$	−0.165	$B_{5/12}$	0.058		
$H_{8/10}$	0.078	$H_{5/12}$	0.056		
$B_{9/12}$	−0.139	$B_{9/10}$	−0.176		
$H_{9/12}$	0.073	$H_{9/10}$	0.080		



[a] The general numbering scheme of vertex positions is given as subscripts. Positions 1 and 2, 7, or 12 are carbon atoms. The connecting lines are topological lines and not classical covalent single bonds.

dx.doi.org/10.1021/cr200038x |*Chem. Rev.* 2011, 111, 7035–7062

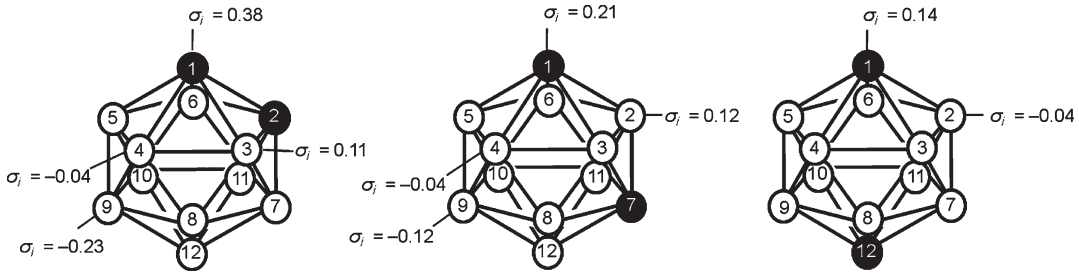


Figure 4. Inductive effect (σ_i) of the carbaborane isomers.[11]

Table 3. pK_a Values of the CH Groups in Unsubstituted Carbaboranes[44]

	carbaborane		
pK_a	*ortho*	*meta*	*para*
Streitwieser's scale	23	28	30
polarographic scale	19	24	26

range from −0.23 to +0.38, *meta*-carbaborane from −0.12 to +0.21, and *para*-carbaborane from −0.04 to +0.14.[10,11] The data show that all cluster carbon atoms exert an electron-withdrawing effect on attached substituents, which decreases in the order *ortho*- to *meta*- to *para*-carbaborane. The effect transmitted to the substituent at a boron atom depends on the isomer and the position of the boron atom within the icosahedron. Boron atoms with only one adjacent carbon atom exert almost no inductive effect, boron atoms with two adjacent carbon atoms are again slightly electron withdrawing, whereas the boron atoms that are antipodal to carbon atoms can be electron-donating.

2.3. Hydrophobicity

The icosahedral carbaborane structure results in a spherical presentation of only slightly polarized hydrogen atoms. The presence of the 10 rather hydride-like hydrogens at the boron atoms makes the clusters extremely hydrophobic.[20] The first experimental investigation of the hydrophobic character was based on the comparison of phenylalanine analogues in *n*-octanol/water. The phenyl ring of phenylalanine was replaced, among others, by *ortho*-carbaborane, adamantane, and a *tert*-butyl group giving hydrophobic parameters (π) of 4.20, 3.64, and 1.79, respectively.[41] The artificial amino acid bearing *ortho*-carbaborane was by far the most hydrophobic compound and was particularly useful for integration into peptides for stabilization against proteolytic degradation and for increasing receptor binding.[41,42] Later, hydrophobic parameters of different phenol-modified carbaborane compounds were studied and revealed π values from 2.69 to 4.44, depending on the cluster isomer and connection pattern. C-substituted compounds were most hydrophobic and again more hydrophobic than adamantane. The presence of free CH groups, which are relatively acidic, seems to lower the hydrophobicity. Attachment of substituents to one of the boron atoms resulted in lower hydrophobicity than adamantane.[43] This is an interesting observation, because the final hydrophobicity of a drug can be tuned not only by the choice of carbaborane isomer but also by choice of the vertex position for substitution.

Table 4. pK_a Values of Carboxylic Acids Determined in 50% Ethanol from Different Sources[10,11,48−51]

R	pK_a values				
	Position of R-COOH				
	1	3	4	8	9
o-$C_2B_{10}H_{11}$	2.61	5.38	5.80	7.01	7.83
m-$C_2B_{10}H_{11}$	3.34				
p-$C_2B_{10}H_{11}$	3.64				
C_6H_5	5.76				

2.4. Acidity

The protons at the cluster carbon atoms are relatively acidic depending on the cluster isomer. Different methods have been applied to determine the pK_a values of the clusters, which are insoluble in water. Two sets of pK_a values for the unsubstituted clusters were obtained and reveal similar trends (Table 3).[44]

The acidity of the protons decreases in the order *ortho*-, *meta*-, *para*-carbaborane.[44] Organometallic bases, normally *n*-BuLi, easily remove one proton from the carbon atoms creating a carbaboranyl nucleophile, which is required in all reactions to modify the carbon atoms, as described below. Substituents at either the boron or the carbon atoms influence the acidity of the cluster protons, and the cluster influences the acidity of the corresponding substituents. In clusters with halogen-substituted boron atoms, for example, the acidity of the CH vertices increases drastically.[45,46] The impact of the choice of the cluster isomer and of the substituent position was demonstrated by Zakharkin, Bregadze, and Kalinin and is nicely illustrated by comparing different carboxylic acids (Table 4).[10,11,47]

The pK_a values correlate with the inductive effects, as pointed out earlier. The strongest acids are obtained when the carboxyl group is attached to the cluster carbon atom, and acidity decreases in the order *ortho*-, *meta*-, *para*-carbaborane (pK_a = 2.61, 3.34, and 3.64). These acids are stronger than benzoic acid (pK_a = 5.76).[50] If the carboxyl group is attached to the electron-deficient boron atom B3 of the *ortho* isomer, the pK_a (5.38) is still lower than that of benzoic acid. A carboxyl group at an electron-donating boron atom (B8,9) shows remarkably decreased acidity. Analogous trends are obtained for the *meta* and *para* isomers. The *ortho*-carbaborane carboxylic acids illustrate clearly that the reactivity of functional substituents can be tuned by the choice of the vertex position, similar to the hydrophobicity, as shown above.

dx.doi.org/10.1021/cr200038x |*Chem. Rev.* 2011, 111, 7035–7062

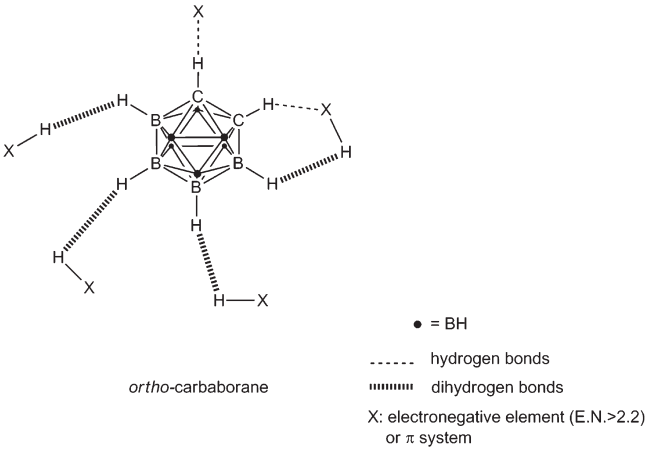


Figure 5. Two-dimensional illustration of intermolecular interactions of *ortho*-carbaborane, representatively for all carbaboranes. BH vertices (●) are also capable of forming dihydrogen bonds.

2.5. Intermolecular Interactions

The prerequisite for being a pharmacophore is the capability to interact with biological targets. Because the outer sphere of carbaboranes consists of hydrogen atoms, intermolecular interactions of unsubstituted clusters are mediated only via hydrogen atoms. Carbaboranes have generally two different sets of hydrogen atoms: acidic CH groups and hydridic BH groups. Crystal engineering and supramolecular chemistry have uncovered the following rather unusual binding behavior (Figure 5).

The acidic CH moiety forms C−H···X (X = O, N, S, F, π system) hydrogen bonds (ca. 8−96 kJ/mol). This feature was already used to obtain crystals of the unsubstituted clusters suitable for X-ray structure determination, which are otherwise highly disordered. Hexamethylphosphoramide as comolecule fixed the orientation of the carbaboranes by forming a supramolecular network via C−H···O hydrogen bonds.[28] Crystal structures of 9,12-bis(4-fluorophenyl)-substituted *ortho*-carbaboranes exhibited C−H···F and C−H···π system interactions.[52,53]

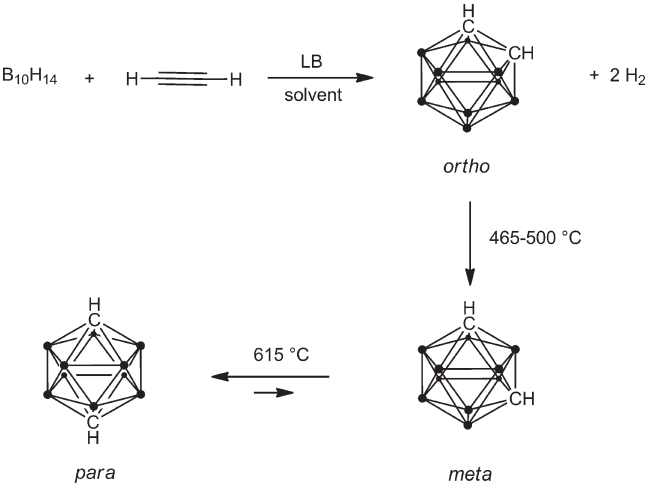
The hydridic character of the BH units allows so-called dihydrogen bonds (4−28 kJ/mol) to be formed, which are hydridic-to-protic B−H···H−X interactions (electronegativity X > H > B).[54−56] The hydridic character depends on the position of the BH vertex of the selected isomer. Dihydrogen bonds have experimentally been observed in crystal structures of small carbaborane-containing molecules.[56] These interactions should also occur for carbaboranes in the active site of enzymes, which needs, however, still to be investigated.

3. CARBABORANE CHEMISTRY

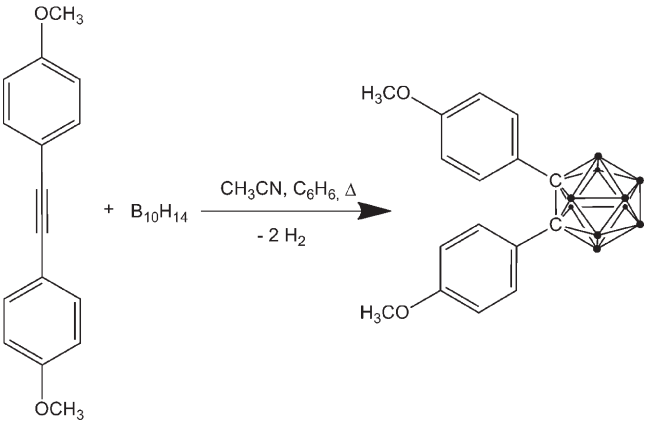
3.1. Synthesis of (Unsubstituted) Carbaboranes

The origin of carbaborane ($C_2B_{10}H_{12}$) chemistry dates back to 1963, when the first syntheses were reported.[57−60] $B_{10}H_{14}$ reacted with acetylenes in the presence of a Lewis base (LB) to give the corresponding *ortho*-carbaborane (Scheme 1). Thermal isomerization of the *ortho* isomer in an autoclave under inert conditions yielded first and irreversibly the *meta* isomer (465−500 °C) and finally the *para* isomer (615−700 °C).[61,62] The latter isomerization is reversible; higher temperatures, however, lead to decomposition. Today, unsubstituted carbaboranes

Scheme 1. Synthesis of the Carbaborane Isomers



Scheme 2. Synthesis of 1,2-Disubstituted *ortho*-Carbaboranes via Reaction with Acetylene Derivatives



are commercially available with increasing costs in the order *ortho*- < *meta*- < *para*-carbaborane.

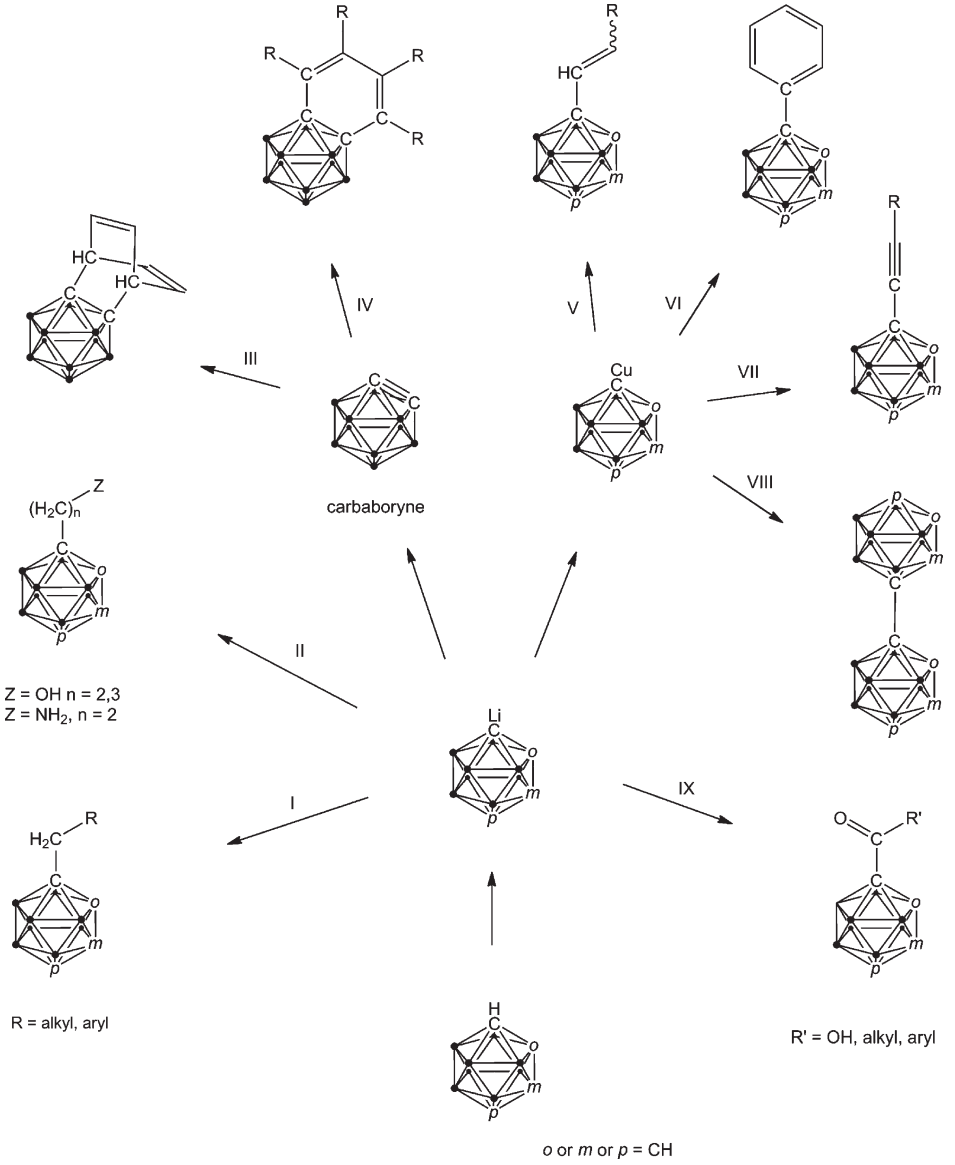
3.2. Synthesis of Substituted Carbaboranes

3.2.1. Synthesis of Carbaboranes Substituted at the Cluster Carbon Atoms. *3.2.1.1. Reaction of Substituted Acetylenes with $B_{10}H_{14}$.* Carbon-substituted carbaboranes can be prepared by reaction of substituted acetylenes with decaborane.[63] This methodology yields primarily *ortho*-substituted isomers and is limited to unreactive acetylene substituents (mostly alkyl, aryl, alkynyl). Due to low yields, toxicity, and explosive reactivity of $B_{10}H_{14}$, however, the use of commercial $C_2B_{10}H_{12}$ as starting material is often favored.[64]

The reaction of acetylene derivatives with $B_{10}H_{14}$ can be of advantage to obtain monosubstituted or sterically crowded diphenyl-substituted *ortho*-carbaboranes, which are a key structural element particularly for estrogen receptor (ER) targeting drug candidates (Scheme 2).[65] Also boroxifen, the carbaboranyl analogue of tamoxifen, and phenylalanine mimetics were prepared by this way.[66,67] In this decade, the use of ionic liquids rendered the presence of a Lewis base redundant and was reported to accelerate

dx.doi.org/10.1021/cr200038x |*Chem. Rev.* 2011, 111, 7035–7062

Scheme 3. Overview of Substitution Reactions at the Cluster Carbon Atoms with Organic, Carbon-Based Residues[a]



[a] The classification is based on the hybridization state of the first carbon atom of the substituent and the reaction type. Reactions I—III: sp^3-hybridized carbon atom (I, salt elimination; II, ring-opening reaction; III, cycloaddition). Reactions IV—VI: sp^2-hybridized carbon atom (IV, cycloaddition; V and VI, salt elimination via Cu). Reactions VII and VIII: sp-hybridized carbon atom (salt elimination via Cu). Reaction IX: sp^2-hybridized carbon atom with carbonyl carbon (CO_2 insertion or salt elimination).

the reaction remarkably and increased the yields.[68,69] The new ionic liquid assisted synthesis of substituted carbaboranes in higher yields will probably be used more frequently in future.

3.2.1.2. Functionalization of the Carbaborane Carbon Atoms. 3.2.1.2.1. General. C-Functionalization of carbaboranes via nucleophilic substitution reactions is generally the favorite method to furnish carbaborane clusters with substituents. The major advantage of this reaction is that it can be applied for all cluster isomers. The following paragraphs describe general aspects of carbaborane chemistry that are worth mentioning from our own experience.

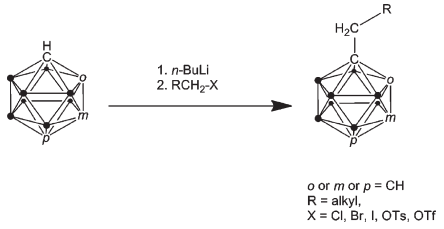
Reactions involving carbaboranes are usually carried out in organic solvents like *n*-pentane, *n*-hexane, toluene, and ethers (diethyl ether, dimethoxyethane, THF). The acidic CH protons can easily be removed with a base creating a carbaboranyl nucleophile. This nucleophile reacts with various electrophiles to form substituted clusters. *ortho*-Carbaborane can be activated with tetrabutylammonium fluoride (TBAF).[70] Because fluoride anions can induce cluster deboronation reactions, lithium bases such as *n*-butyllithium and methyllithium emerged as standard bases for reactions with *ortho*-carbaborane.[71] The application of moisture-sensitive bases requires inert reaction conditions. Because the carbaboranes readily sublime, increasing in the order *ortho* < *meta* < *para*, caution should be taken when applying vacuum. Salt formation or salt elimination is a common principle in carbaborane chemistry. First, the lithiated carbaborane precipitates from the reaction solution depending on the solvent (not necessarily in ether as solvent). Second, most electrophiles used are halides, which result in formation of the corresponding lithium salt. Resulting products are usually air-stable compounds and allow

purification and storage in air. Hence, purification is mostly based on column chromatography. Carbaborane-containing fractions on a TLC control can easily be visualized with a noble metal solution like $PdCl_2$ in methanol or $AgNO_3$ in methanol/water giving dark spots due to formation of metal(0) on heating. Lithiation of carbaboranes is essentially quantitative, and this suggests that the general yield of the reaction strongly depends on the electrophile. Solvents, reaction times, and temperature additionally contribute to the course of the reaction.

Symmetrical difunctionalized carbaboranes are formed after dilithiation of the cluster and reaction with an excess of electrophile. Steric constraints of the electrophilic substituent, however, can hinder one-pot disubstitution in the case of *ortho*-carbaborane.

In contrast, monosubstitution of the carbaborane carbon atoms can be accompanied by the formation of the disubstituted product as result of conversion of the monolithiated carbaborane to the dilithiated carbaborane and the neutral cluster,[72] the extent of which depends on the reaction conditions. Thus, protecting groups such as bulky silyl groups (e.g., Si^tBuMe_2) may be required for the synthesis of monosubstituted products.[73] A less applied alternative is the use of dimethoxyethane as solvent, which is expected to stabilize the monolithiated carbaborane and suppress dilithiation.[74] This method could not, however, completely prevent the formation of the disubstituted product. A high-dilution approach could also favor the monosubstitution. Once optimized reaction conditions are found for one isomer, they can mostly be applied without great variation also to the other isomers (*ortho*-carbaborane shows some exceptions, for example, activation with TBAF[70]).

Scheme 4. Synthesis of C-Alkyl-Substituted Carbaboranes



3.2.1.2.2. C-Functionalized Carbaboranes with Carbon-Based Groups.

3.2.1.2.2.1. sp^3-Hybridized Carbon Atoms (Reactions I–II). 3.2.1.2.2.1.1. Reaction I: Reactions with Alkyl Halides, Tosylates, and Triflates. A very common method to attach alkyl residues to the carbaborane carbon atoms is the reaction of lithiated carbaboranes with alkyl halides driven by salt elimination (Scheme 4).[75−79] The use of alkyl halides like bromides or iodides is more common than tosylates or triflates, but both can also be applied depending on the availability and suitability of the alkyl reagent.[73,76] Long-chain alkyl-substituted carbaboranes have been applied to synthesize ER antagonist and cholesterol mimetics.[80,81]

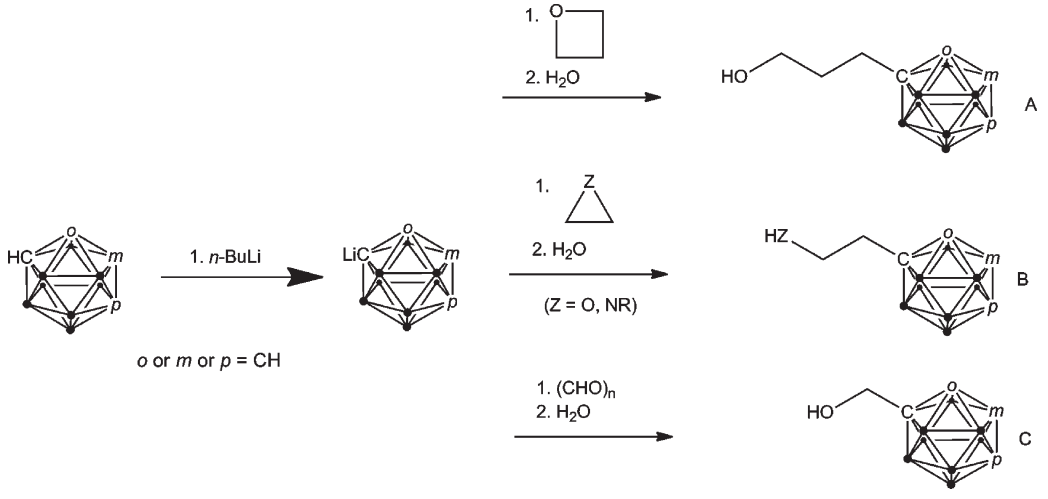
3.2.1.2.2.1.2. Reaction II: Ring-Opening Reactions. 3.2.1.2.2.1.2.1. Reaction IIA: Reaction with Oxetane. The ring-opening reaction of oxetane with lithiated carbaboranes is very popular and yields the corresponding carbaboranyl propanols, which were earlier used to synthesize BNCT agents (Scheme 5).[82,83] Oxidation of the alcohol to the carboxylic acid and integration of an amino group gives carbaboranyl alanine, the analogue of phenylalanine.[84] To selectively obtain the monosubstituted compounds, silyl protection of the other carbaborane carbon atom is recommended.[82,84−86]

3.2.1.2.2.1.2.2. Reaction IIB: Reaction with Oxiranes and Aziridines. The ring-opening reaction of three-membered rings is less popular. The reaction of lithiated carbaborane with ethylene oxide gives the corresponding carbaboranyl ethanol (Scheme 5).[75,87,88] If the length of the spacer is irrelevant, the use of oxetane is mostly preferred.

Almost uninvestigated is the ring-opening reaction of aziridines to obtain ethylamine-modified carbaboranes as an alternative to classical lithium halide elimination.[89] One literature source described the reaction of lithiated 1-phenyl-*ortho*-carbaborane with bicyclic 7-azabicyclo[4.1.0]heptane to give 1-phenyl-2-(2′-aminocyclohexyl)-1,2-$C_2B_{10}H_{10}$.[90]

3.2.1.2.2.1.2.3. Reaction IIC: Reaction with Paraformaldehyde. Carbaboranyl methanol is a frequently observed fragment of steroid-derived drug candidates.[91] It is easily obtained by treating activated carbaborane with paraformaldehyde (Scheme 5) in a "chain-opening" reaction. The carbaborane can be activated either by the well-known lithiation method or, in the case of the *ortho* isomer, also with tetrabutylammonium fluoride.[70,91]

Scheme 5. Ring-Opening Reactions of Lithiated Carbaborane with (A) Oxetane and (B) Ethylene Oxide or Aziridines and (C) Reaction with Paraformaldehyde



dx.doi.org/10.1021/cr200038x |*Chem. Rev.* 2011, 111, 7035–7062

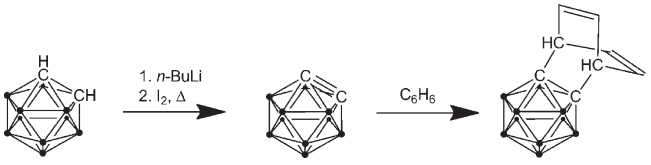
ortho-Carbaboranyl methanol derivatives with additional organic substituents at the methanol carbon atom have readily been obtained via palladium-catalyzed addition of 1-*ortho*-carbaboranyltributyltin to the corresponding aldehydes (not shown).[92] This transition metal mediated reaction was applied to furnish azulene frameworks with carbaboranes for BNCT.[93]

3.2.1.2.2.2. sp^3- and sp^2-Hybridized Carbon Atoms (Reactions III and IV): Cycloaddition Reactions. Different cycloaddition reactions give very versatile disubstituted carbaborane compounds. The possibility to undergo cycloaddition reactions is again limited to *ortho*-carbaborane exclusively, because this is the only isomer having an alkyne-like CC fragment. To prepare the carbaborane for the reaction with π systems, the hydrogen atoms at the cluster carbon atoms must be removed to generate 1,2-dehydro-*ortho*-carbaborane (carbaboryne). This reaction requires dilithiation and the addition of bromine and is based on salt elimination. Latest reports found that the use of iodine is better than bromine.[94,95] Phenyl[*ortho*-(trimethylsilyl)carboranyl]iodonium acetate was also reported as a suitable carbaboryne precursor.[94]

Drawbacks of the reactions are often low yields and the formation of product mixtures. The benzyne−carbaboryne analogy inspired the design of corresponding transition metal complexes for catalysis. Zirconium-, nickel-, and palladium-mediated reactions have been studied and gave various substituted carbaborane products.[94,96,97] These cycloaddition reactions have, to the best of our knowledge, not been used to synthesize drug candidates but will probably be applied in future. The following paragraphs give a short overview of selected reactions.

3.2.1.2.2.2.1. Reaction III: [4 + 2] and [2 + 2] Cycloaddition. The reaction of carbaboryne with a diene system gives a cyclic product with the carbaborane attached to an sp^3-hybridized carbon atom. The [2 + 2] reaction generates a cyclobutane fragment including the cluster carbon atoms in a nonstereospecific reaction (not shown). The [4 + 2] cycloadditions likely proceed with retention of stereochemistry creating a six-membered ring (Scheme 6). Both cycloaddition reactions compete with the ene reaction creating acyclic monosubstituted carbaboranes (not shown).[95,98,99]

Scheme 6. Cycloaddition of Carbaboryne with Benzene



3.2.1.2.2.2.2. Reaction IV: [2 + 2 + 2] Cycloaddition. The reported [2 + 2 + 2] three-component reactions involving the carbaboryne and two acetylenes is nickel-mediated.[96,100] The reaction of the carbaboryne with an ethylene derivative affords an sp^3-hybridized carbon atom in α position to the cluster, whereas the reaction with acetylene derivatives gives an alkenyl residue in α position (Scheme 7). The application of both acetylene and ethylene derivatives gives mixed products.

3.2.1.2.2.3. sp^2- and sp-Hybridized Carbon Atoms (Reactions V−VIII): Copper-Mediated Reactions. The attachment of unsaturated carbon-based substituents (alkenyl, alkynyl, carbaboranyl) to the cluster carbon atom is not possible with lithiated carbaboranes and requires transmetalation, preferably using copper derivatives.

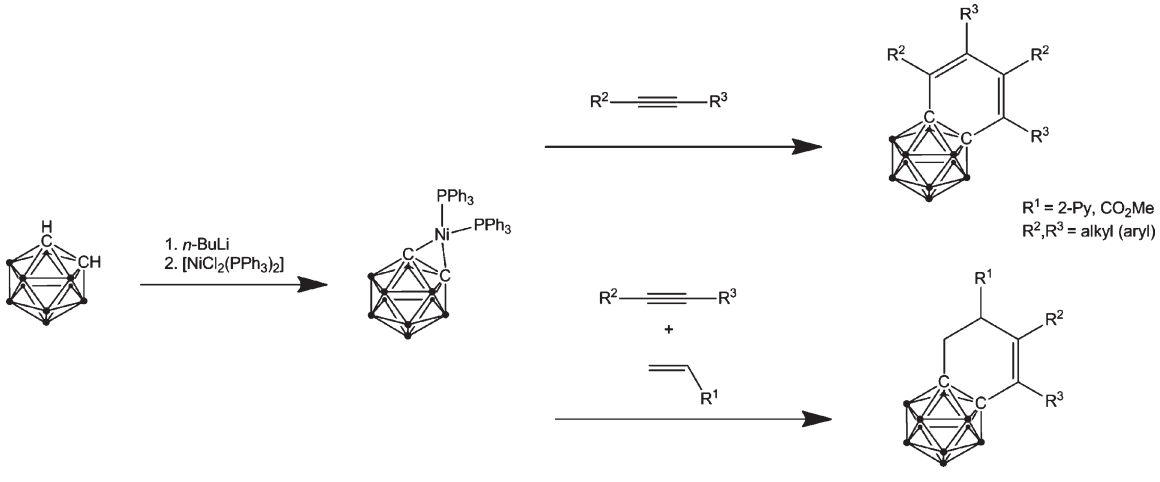
3.2.1.2.2.3.1. Reaction V: Alkenyl Substituents. Vinyl moieties directly attached to the carbaborane carbon atoms can be obtained by using acetylene reagents in cycloaddition reactions with carbaboryne or by reaction of vinyl acetylenes with $B_{10}H_{12}(LB)_2$.[57] These reactions are again limited to *ortho*-carbaborane, and the vinyl fragment is mostly integrated into a ring system including both carbaborane carbon atoms.

An alternative way is the reaction of vinyl halides with lithiated carbaboranes in the presence of a copper(I) salt (Scheme 8). This route gives also access to vinylated *meta*- and *para*-carbaboranes.[101]

3.2.1.2.2.3.2. Reaction VI: Aryl Substituents. *C*-Aryl carbaboranes can be prepared by reaction of aryl acetylenes with decaborane. This reaction is again limited to unreactive aryl groups, and thermal isomerization to the other isomers is not always possible.[40,57] Chromium tricarbonyl haloarene complexes react with lithiated carbaboranes with salt elimination and formation of an aryl carbaborane.[102] The use of copper(I) was again found most practical to perform *C*-arylation and C-heteroarylation of one or, in the case of the *meta* and *para* isomers, also two carbon atoms (Scheme 9).[103] This reaction is of particular interest because the 1-phenyl carbaborane entity is a very potent core in carbaborane-based drug design, as will be pointed out later.[104,105]

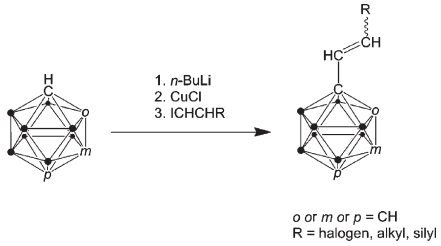
3.2.1.2.2.3.3. Reaction VII: Alkynyl Substituents. The preparation of alkynyl-substituted cluster carbon atoms is achieved analogously to the synthesis of *C*-vinyl-substituted clusters via copper(I) and the corresponding alkynyl halide (Scheme 10).[101,106,107] The corresponding ethynyl carbaboranes are more interesting for applications in nanotechnology rather than for medicinal uses.[108]

Scheme 7. Nickel-Mediated Cycloaddition Reactions

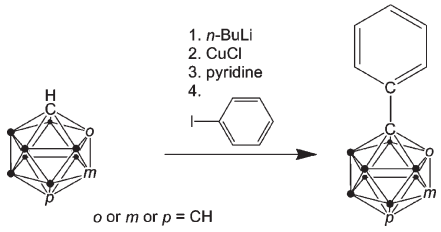


dx.doi.org/10.1021/cr200038x |*Chem. Rev.* 2011, 111, 7035–7062

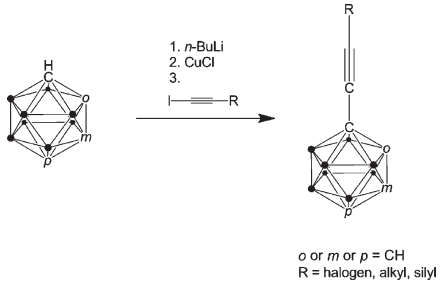
Scheme 8. Synthesis of *C*-Vinylcarbaboranes



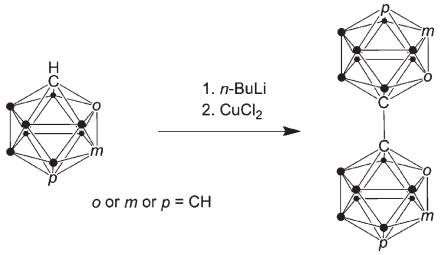
Scheme 9. *C*-Arylation of Carbaboranes



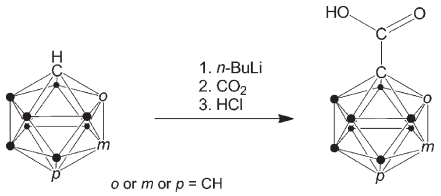
Scheme 10. Synthesis of *C*-Alkynylcarbaboranes



Scheme 11. Synthesis of Dicarbaboranes



Scheme 12. Synthesis of Carbaboranyl Carboxylic Acids



3.2.1.2.2.3.4. Reaction VIII: Carbaboranyl Substituent. Direct C−C bond formation of one or more carbaboranes has attracted interest in material design and for BNCT agents with a high boron content. Beside the reaction of decaborane with diacetylene, a convenient method is again the addition of copper(I) or copper(II) to a solution of lithiated carbaborane (Scheme 11).[63,109−113]

3.2.1.2.2.4. sp^2-Hybridized Carbon (Reaction IX): Carboxy Substituent. Carbaboranes with adjacent carbonyl groups are treated separately, because especially carbaboranyl carboxylic acids are frequently used in medicinal chemistry.

A carboxyl group can easily be attached to the cluster carbon atoms by treating the corresponding lithiated carbaborane with gaseous or solid carbon dioxide. Acidic workup gives the corresponding acids in excellent yields (Scheme 12).[75,114,115] In BNCT agents, the acid group is used as a linker to attach carbaboranes to tumor-seeking moieties like porphyrins or various alcohols.[116,117] Carbaboranyl carboxylic acids are also important pharmacophoric entities of carbaborane-based mimetics of drugs such as diflunisal, flufenamic acid, and aspirin.[118,119] Carbaboranyl ketones and aldehydes are less applied in medicinal chemistry.[120]

3.2.1.2.3. Main-Group Element Substituents. To attach main group substituents to the carbaborane carbon atoms, lithiation is again the first step to obtain the carbaborane as nucleophile. In most cases, lithium halide elimination is the driving force to obtain the modified clusters in relatively high yields. The following paragraphs describe the most important reactions to attach relevant non-carbon main group elements (Scheme 13). Phosphorus- and chalcogen-modified carbaboranes are particularly used as ligands for transition metals, whereas oxygen- and nitrogen-modified clusters are found in biological and medicinal applications.

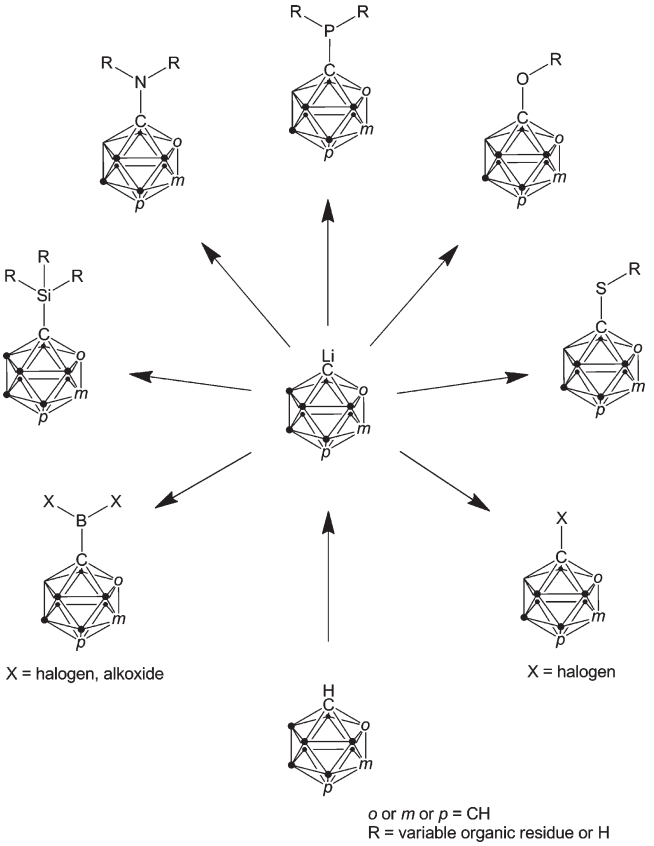
3.2.1.2.3.1. Boron Substituents. Compounds with group 13 elements directly attached to the cluster carbon atoms are limited to only a few examples in the literature. For medicinal applications, only boron is relevant. Boron-substituted carbaboranes can readily be prepared by treating boron(III) halides or boronic acid esters with lithiated carbaborane (Scheme 14).[120−123] Boron-substituted carbaboranes are not used as target compounds in medicinal chemistry but turned out to be very useful intermediates for the preparation of hydroxy carbaboranes, which are used in drugs, as discussed in section 5.[119,124,125]

3.2.1.2.3.2. Silicon Substituents. Silicon is attached to the cluster carbon atoms via the reaction of silyl halides, preferably silyl chlorides, with lithiated carbaborane (Scheme 15). Various organic substituents are tolerated at the silicon atom.[126] Silylation of carbaboranes also increases the solubility of polycarbaborane chains in organic solvents.[110] In most cases, however, the silyl group is used as a protecting group of one cage carbon atom.[73] It can selectively be introduced at only one carbon atom in very high yields for all isomers. Removal is performed with a fluoride source (e.g., TBAF), which should not be applied for longer times to reduce the risk of deboronation.[73,110,127−130] This strategy was used for synthesis of the carbaboranyl analogues of phenylalanine, for example.[84]

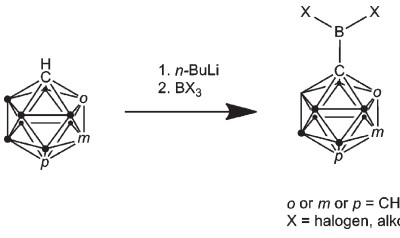
3.2.1.2.3.3. Nitrogen Substituents. Group 15 elements attached to the carbaborane carbon atoms are covered by several examples in the literature.[131,132] However, the more electronegative the element, the less straightforward is the reaction with lithiated carbaboranes, which complicates the formation of C−N bonds. Therefore, the reagent applied has to have a positively polarized nitrogen center. The use of NOCl has recently been reported in the reaction with lithiated 1-methyl- or

dx.doi.org/10.1021/cr200038x |*Chem. Rev.* 2011, 111, 7035–7062

Scheme 13. Reaction Scheme of Modifications at the Cluster Carbon Atoms with Non-Carbon-Based Substituents



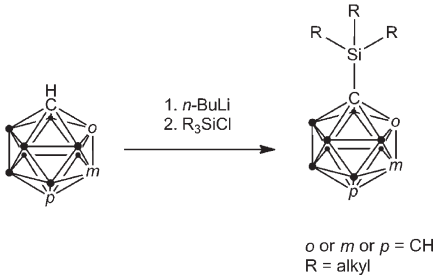
Scheme 14. Carbaboranes Boron-Substituted at Carbon Atoms



1-phenyl-*ortho*-carbaborane to yield the corresponding C−N products, either the expected nitroso carbaborane or dicarbaboranyl amine, strongly depending on the reaction conditions (Scheme 16).[133] The reaction in dimethoxyethane/diethyl ether gives the dicarbaboranyl amine, and the reaction in pentane/diethyl ether yields the nitroso-carbaborane. The latter can be reduced with hydrogen and a palladium/carbon catalyst to the corresponding hydroxylamine. The reduction of nitroso-carbaborane with tin powder and hydrochloric acid yields the primary amine. The use of diazonium salts as nitrogen source in the reaction with carbaboranyl nucleophiles gives azocarbaboranes, which can be reduced to the corresponding hydrazines.[133,134]

An alternative and longer known route to obtain carbaboranyl amines is via the formation of carbaboranyl carbonyl chlorides, which proceeds almost quantitatively for all isomers (Scheme 16).

Scheme 15. Carbaboranes Silicon-Substituted at Carbon Atoms



Treatment of the acid chloride with trimethylsilylazide in refluxing toluene induces a Curtius rearrangement to the isocyanato carbaborane.[135] Hydrolysis of the isocyanato carbaborane yields the amine, and addition of alcohols yields the carbamate, which can be regarded as an amine protecting group.[114,131] The rearrangement reaction was applied to obtain the carbaboranyl amino acids and thalidomide analogues.[114,136]

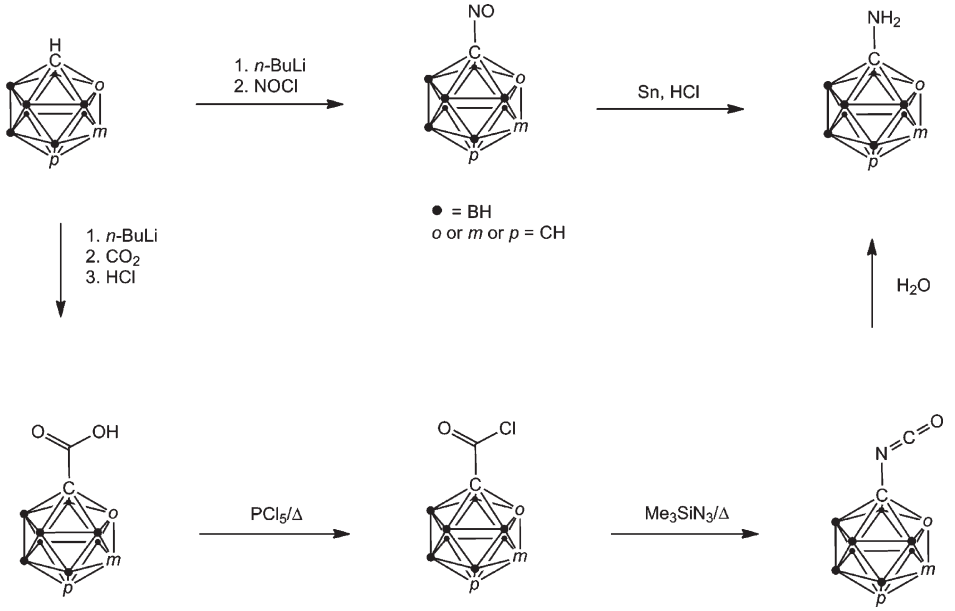
3.2.1.2.3.4. Phosphorus Substituent. The group 15 element phosphorus is also easily attached to the cluster carbon atoms using phosphorus(III) halides, mostly chlorides (Scheme 17). The halides are exchangeable with other amine or alkoxy substituents, either after reaction with the lithiated carbaborane or using R_2PCl (R = amido or alkoxy substituent) as electrophile in the reaction with the lithiated carbaborane.[137−143] The use of two different residues at the phosphorus atom gives P-chiral molecules. The corresponding phosphorus(V) derivatives are obtained by oxidation of the phosphorus(III) compound with, for example, *tert*-butyl hydroperoxide or with the Beaucage reagent to yield the sulfur analogue.[109] Phosphorus(III) derivatives are often used as ligand for transition metals, whereas carbaboranyl phosphonates are potential BNCT agents.[15,109,139]

3.2.1.2.3.5. Oxygen Substituent. The attachment of group 16 elements to the cluster carbon atoms is interesting both for catalytic and for medicinal applications. The high electronegativity of oxygen makes the syntheses difficult. Hence, the reaction of lithio-carbaborane with molecular oxygen suffered from low yields.[144] The use of benzoyl peroxide provides 1-hydroxy-1,2-dicarba-*closo*-dodecaborane but wastes half of the carbaborane due to formation of 1-benzoyl-1,2-dicarba-*closo*-dodecaborane as a byproduct.[145] The reaction of lithiated carbaborane with bis(trimethylsilyl)peroxide successfully resulted in 1-(trimethylsiloxy)-1,2-dicarba-*closo*-dodecaborane in high yield (not shown). The reaction is advantageous in order to obtain directly the protected carbaboranyl alcohol if the relatively high price of the silyl peroxide reagent is acceptable. Liberation of the free alcohol was achieved with HCl/CH_3OH.[144]

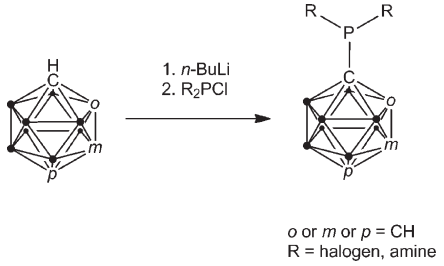
A cheaper alternative to obtain the carbaboranyl alcohol is a detour via dimethyl(carbaboranyl) boronic acid ester (Scheme 18). The C−B bond can easily be oxidized using peracetic acid to give the mono- or dialcohol in very high yield.[124,125] Other alkyl esters, such as the butyl ester, can also be employed.[146]

3.2.1.2.3.6. Sulfur Substituents. Elemental chalcogens readily insert into lithiated carbaboranes. The resulting products, mostly disubstituted *ortho*-carbaboranes, are frequently used as ligands for transition metals. Reaction of lithiated carbaborane with sulfur powder yields the corresponding thiol after acidic workup

Scheme 16. Synthesis of *C*-Amino Carbaboranes



Scheme 17. Carbaboranes Phosphorus-Substituted at Carbon Atoms



in very good yield (Scheme 19). To obtain the monosubstituted thiol of *ortho*-carbaborane methoxyethane was suggested as solvent.[74] However, THF was recommended as solvent later on.[142,147] Carbaboranyl thioethers are directly obtained by using the corresponding disulfide or by alkylation of the carbaboranyl thiol.[129,148−150] Selenium- and tellurium-substituted carbaboranes are analogously prepared but are less common than the sulfur compounds.[151−153] Ferrocenyl-substituted dithio-*ortho*-carbaboranes were recently found to bind to myoglobin and influenced the native conformation of the protein.[154]

3.2.1.2.3.7. Halogen Substituents. *C*-Halogenated carbaboranes are intermediate products rather than target compounds. Lithiation of the carbaboranes yields anions, which also react with elemental halogens and form carbaboranyl chlorides, bromides, and iodides in good yields (Scheme 20).[26,155−158]

Carbaboranyl bromides and iodides have already been mentioned as intermediates for carbaboryne in cycloaddition reactions (sections 3.2.1.2.2.2.1 and 3.2.1.2.2.2.2).[99]

The formation of carbaboranyl fluorides is more tedious and a matter of theoretical investigations rather than experimental approaches. The use of the highly active fluorinating agent perchloryl fluoride $FClO_3$, however, resulted in formation of difluorinated *meta*-carbaborane.[159] The use of *N*-fluorobenzenesulfonamide was far milder, but only low yields were obtained in the reaction with lithiated *ortho*-carbaborane.[160]

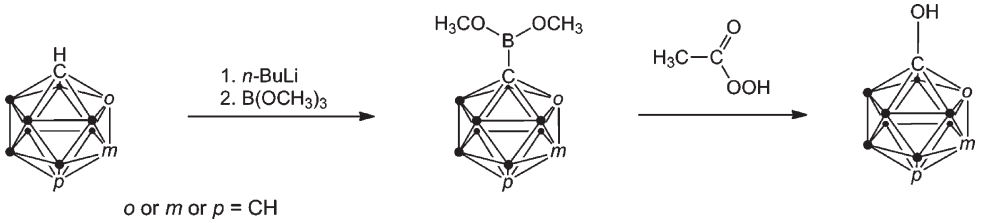
Reports of *C*-halocarbaboranes are limited compared with those of *B*-halocarbaboranes, which are easily obtained via electrophilic substitution reactions as described in the following section.[158]

3.2.2. Synthesis of Carbaboranes Substituted at the Cluster Boron Atoms. Integration of carbaboranes as pharmacophores in potential drugs is almost exclusively carried out through the cluster carbon atoms. Boron modifications, in contrast, have only rarely been applied in this field, and a comprehensive summary would exceed the capacity of this review. Therefore, we will only present selected aspects that are important for the application of carbaboranes as pharmacophores. For more detailed information about reactions at the boron atoms, a review by Kalinin et al. is recommended.[11] Reactions at the boron atoms are generally orthogonal to reactions at the cluster carbon atoms: nucleophilic substitution reactions occur at the C−H vertices, and electrophilic substitution reactions at the B−H vertices. The selective modification of just one of the two C−H vertices requires the use of protecting groups in some cases (section 3.2.1.2.). The selective modification of one out of ten B−H vertices is, not surprisingly, more difficult. The option to furnish selected cluster positions with substituents additionally strongly depends on both the carbaborane isomer and the residue to be attached. The *para* isomer, with ten equal B−H vertices, understandably differs from the *ortho* and *meta* isomers.[161] The following sections describe only important regioselective monosubstitution reactions and selected multisubstitution reactions.

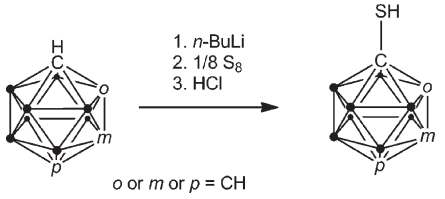
3.2.2.1. Selected Monosubstitutions at the Boron Atoms. 3.2.2.1.1. B9-Substituted Carbaboranes. Halides are common substituents that can directly be attached to the boron vertices. Mild electrophilic aromatic substitution reactions using the halides and AlX_3 replace only a few hydrogen atoms at selected boron positions (Scheme 21).[162] *ortho*-Carbaborane

dx.doi.org/10.1021/cr200038x |*Chem. Rev.* 2011, 111, 7035–7062

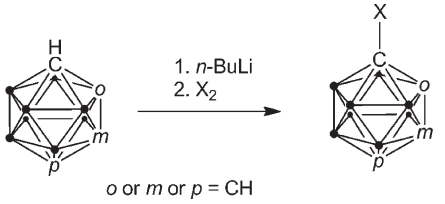
Scheme 18. Synthesis of Carbaboranyl Alcohol



Scheme 19. Synthesis of *C*-Thiocarbaboranes



Scheme 20. Halogenation of Carbaborane Carbon Atoms



and *meta*-carbaborane allow for rather selective modification of the B9 atom.[163,164] The boron halides can then be further substituted by other residues. The use of organomagnesium or organozinc compounds, for example, in the presence of a palladium catalyst replaces the halide by organic residues.[164−167] The application of palladium-catalyzed Buchwald−Hartwig amination and amidation gives the corresponding nitrogen-substituted carbaborane.[168−170]

3.2.2.1.2. B3-Substituted Carbaboranes. The B−H units adjacent to both C−H vertices (B3,B6 for *ortho*-carbaborane, B2,B3 for *meta*-carbaborane) are rather inert toward direct substitution reactions to give the corresponding halide.[161] However, a two-step reaction yields selectively the B3-substituted cluster (Scheme 22). First, the *closo* cluster is deboronated forming a *nido* C_2B_9 cluster. This *nido* cluster reacts with boron(III) halides or alkyl-substituted boron halides to yield the corresponding C_2B_{10} icosahedron carrying substituents at the B3 position.[171,172] Recently, B3-halogenated *ortho*-carbaboranes were employed in palladium/nickel-cocatalyzed cycloadditions resulting in a C−B heterocycle.[173] Amidation, alkylation, and arylation reactions with the halide are also possible, as described for B9 modifications.

The arylation was used to prepare B3/B6 diphenol-substituted compounds acting as selective estrogen receptor modulators (SERM). The candidates with substituents at the boron atoms were less active than the corresponding cluster carbon-substituted analogues.[174]

3.2.2.2. Multisubstitution at the Boron Atoms. The replacement of most or all hydrogen atoms at the boron vertices is a very powerful option to increase the size of the pharmacophore on the one hand and to tune possible interaction sites on the other. Depending on the reaction conditions and on the carbaborane isomer, different numbers of B−H vertices can be substituted. To replace all B−H hydrogen atoms, usually harsh conditions are required. Multihalogenations and -methylations have been reported for the carbaborane isomers.[176]

The introduction of 10 fluorine atoms is achieved with elemental fluorine in liquid HF. The application of FCl exclusively yields the decachlorinated product.[159] Decachlorocarbaborane can also be prepared by passing gaseous Cl_2 into a CCl_4 solution with UV irradiation. The degree of chlorination can be controlled by the time of applying the Cl_2 stream.[45,177] Periodo-*B*-*ortho*-carbaborane was prepared in a multiple-reaction procedure.[46]

Reaction of carbaboranes with methyl iodide and $AlCl_3$ results in *B*-methylated clusters. In the case of the *para* isomer, all B−H units could be replaced (Figure 6), while in *ortho*- and *meta*-carbaborane the less reactive positions (B3/B6) were left unmodified.[161] Boron-polymethylated carbaboranes have the size of a fullerene and have also been investigated as pharmacophoric units for retinoid receptor antagonists.[178]

3.3. Deboronation Reaction

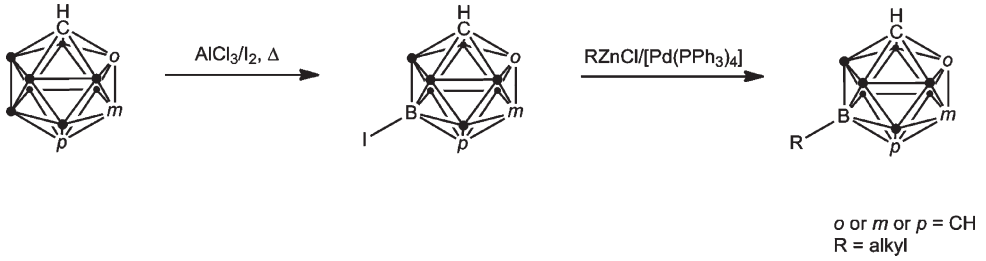
A very important reaction at the boron atoms of carbaboranes besides the introduction of a new substituents for the hydrogen atom is the removal of an entire vertex. Such deboronation reactions were already recognized shortly after carbaboranes had first been synthesized.[62,179,180] Strong Lewis bases such as alkoxides,[179] amines,[181] fluorides,[182,183] and recently *N*-heterocyclic carbenes[184] were found to deboronate *closo*-carbaboranes forming the corresponding anionic C_2B_9 *nido* clusters (Figure 7).

Depending on the carbaborane isomer, different deboronation products are obtained: on deboronation, *ortho*-carbaborane gives *nido*-7,8-$C_2B_9H_{11}^-$, *meta*-carbaborane *nido*-7,9-$C_2B_9H_{11}^-$, and *para*-carbaborane *nido*-2,9-$C_2B_9H_{11}^-$.[185,186] The *nido* carbaboranes arise from the removal of one of the most positive boron vertices. Consideration of the NPA charges is consistent with experimental observations that the deboronation rate decreases from *ortho*- to *para*-carbaborane. The latter requires very harsh conditions to enforce the formation of *nido*-2,9-$C_2B_9H_{11}^-$.[187] The *ortho* isomer, in contrast, is rather vulnerable to nucleophiles and the best investigated (Scheme 23).

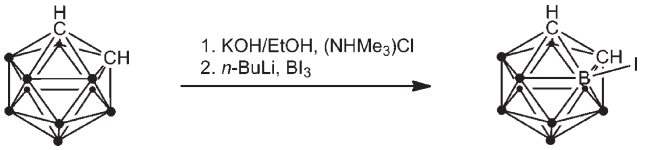
Deboronation is initialized by attack of a nucleophile at one of the most electrophilic boron vertices followed by attack of a second nucleophile at the same boron atom. Protonation of the negatively charged *nido* cluster results in a formal elimination of borane ($BH(Nu)_2$), which is prone to addional reactions with nucleophiles to give the final monoborane byproduct.[156,184,188]

dx.doi.org/10.1021/cr200038x |*Chem. Rev.* 2011, 111, 7035–7062

Scheme 21. B9-Substituted Carbaboranes



Scheme 22. B3-Substituted *ortho*-Carbaborane



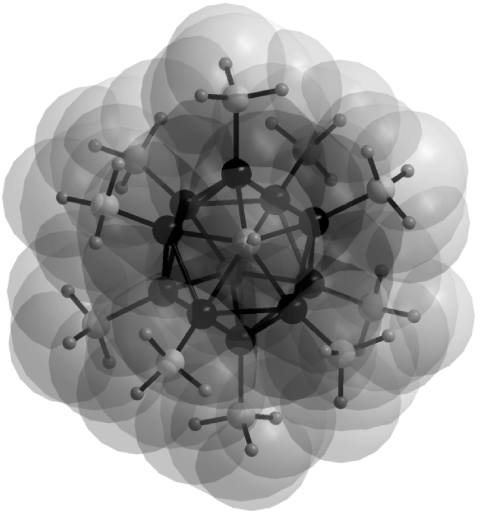


Figure 6. Space-filling model of *B*-decamethyl-1,12-dicarba-*closo*-dodecaborane(12) (C and H = gray, B = black).[175]

This proton bridges two adjacent boron vertices of the pentagonal face and gives a characteristic signal in the ^{1}H NMR spectrum.[189]

Asymmetrically substituted *ortho*- and *meta*-carbaboranes give planar-chiral *nido* products.[119,190] Substituents at the C1 atoms of *ortho*- and *meta*-carbaborane influence the tendency to deboronate intrinsically.[187,191] This is of great importance for carbaborane-based pharmacophores, where the clusters are mostly integrated via C-substitution into the organic drugs. Wet DMSO was found to induce deboronation under mild conditions, and carbaboranes substituted with strongly electron-withdrawing elements, such as oxygen, are deboronated even in water and methanol at ambient temperature.[119,191,192] The deboronation rate generally depends on various parameters such as parent isomer, substituents, temperature, solvent, and presence, ratio, and kind of nucleophiles.[186,189,191]

The monoanionic *nido*-carbaboranes can be deprotonated to the dicarbollide dianion with strong bases. The addition of

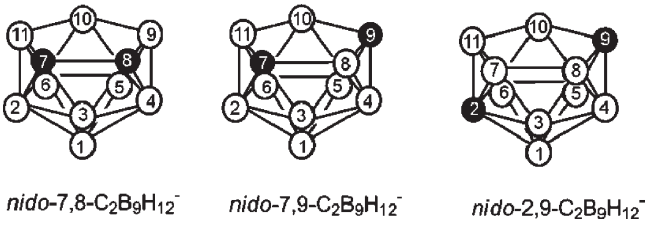
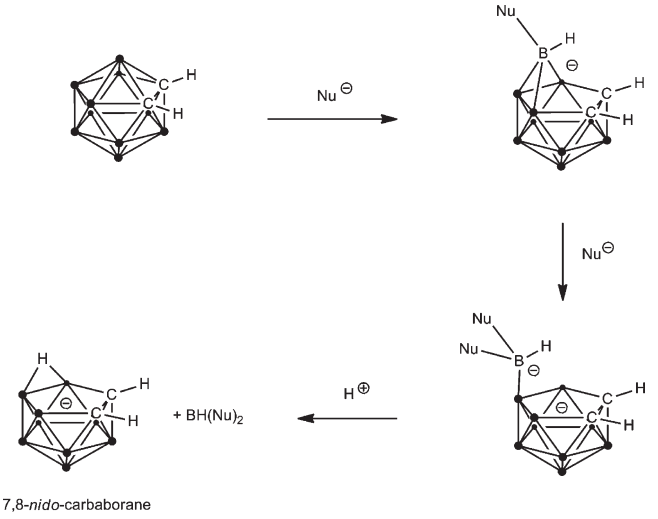


Figure 7. C_2B_9 *nido* isomers.[185]

Scheme 23. Possible Mechanism of Deboronation of *ortho*-Carbaborane with Anionic Nucleophiles[156]



appropriate cations allows solubility to be tuned and the *nido*-carbaboranes to be isolated as neutral salts. The alkali metals sodium and potassium give mostly water-soluble salts, whereas rubidium, cesium, and tetraalkylammonium salts are rather poorly water soluble.[180]

4. CHARACTERIZATION OF CARBABORANYL COMPOUNDS

The availability of appropriate methods to determine the identity and purity of reaction products after or during the reaction is crucial for the use of chemical components. NMR and IR spectroscopy and mass spectrometry are routine methods in carbaborane chemistry. The following chapters describe the most important aspects observed while working with these

dx.doi.org/10.1021/cr200038x |*Chem. Rev.* 2011, 111, 7035–7062

clusters. NMR spectroscopy is most significant because all cluster elements have NMR-active nuclei.

4.1. NMR Spectroscopy

4.1.1. ^{1}H NMR Spectroscopy. Compared with organic compounds, the ^{1}H NMR signals of the hydrogen atoms at the boron and carbon atoms are very broad and overlapping. Therefore, coupling patterns and constants cannot be used for interpretation in standard 1D NMR measurements.

The ten hydrogen atoms connected to the boron quadrupole nuclei cover the broad range from approximately 3.0 to 1.4 ppm and are less significant than the protons at the cluster carbon atoms (Figure 8). The latter are most deshielded for *ortho*-carbaborane (3.55 ppm) and less for *meta*- (2.91 ppm) and *para*-carbaborane (2.75 ppm), which differentiates the *ortho* isomer from the other two. Additional substituents at the boron atoms usually destroy the equivalency of the two C−H protons resulting in two separate C−H signals. Carbon-monosubstituted carbaboranes only feature one remaining C−H group, which is generally more deshielded (up to more than 5 ppm[193]), depending on the NMR solvent and substituent.

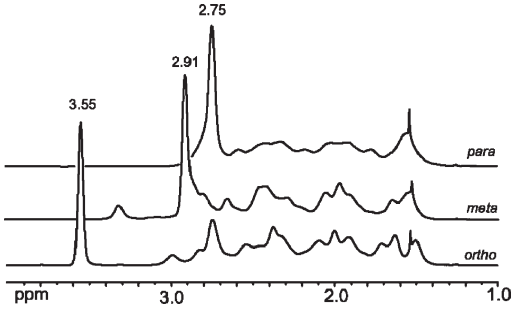


Figure 8. ^{1}H NMR spectra of commercially available unsubstituted carbaboranes in $CDCl_3$ at 400.13 MHz. The highest signals can be assigned to the two C−H protons of *ortho*- (3.55 ppm), *meta*- (2.91 ppm), and *para*-carbaborane (2.75 ppm).

The carbaborane signals are well visible for small molecules, but when larger organic substituents are attached, the spectra have to be magnified to see the signals of the cluster protons. The transformation of the *closo* into a *nido* cluster induces a characteristic signal of the bridging hydrogen atom (μ-H) in the shielded region of −2 to −3 ppm.

4.1.2. ^{11}B NMR Spectroscopy. The ^{11}B nucleus can also be used for NMR spectroscopy (^{11}B, I = 3/2, 80% isotope abundance). *para*-Carbaborane has 10 equal boron atoms with a chemical shift of −14.8 ppm (Figure 9). *ortho*-Carbaborane and *meta*-carbaborane have four different sets of boron atoms in the ratio 2:2:4:2 (*ortho* −2.5, −9.3, −13.6, and −14.7 ppm; *meta* −6.7, −10.5, −13.3, and −17.0 ppm). The boron atoms closest to the carbon atoms are most shielded and exert an *antipodal effect* on the opposite vertices, which are most deshielded.[194] Addition of substituents at different cluster positions usually changes the symmetry and the electron density, which does not necessarily result in more signals, because overlap of the broad signals is possible. 1-Hydroxy-1,2-dicarba-*closo*-dodecaborane, for instance, shows only three signals at −3.8, −12.1, and −14.5 ppm in the ratio 1:7:2 in $CDCl_3$.[125] Substituted *closo* isomers have chemical shifts still in the range of approximately 0 to −20 ppm. Deboronation creates a cluster anion and resonances in the range of −5 to −40 ppm, which can easily be recognized.[194]

The $^{1}J_{BH}$ coupling constants are in the range of 150 to 180 Hz for the unsubstituted isomers and ca. 120−210 Hz for substituted isomers, depending on the substituents.[194] Substituted boron atoms can be identified by the lack of the corresponding coupling. Often, the precise number of boron atoms responsible for one signal and the corresponding $^{1}J_{BH}$ cannot be determined unambiguously, due to overlap.

4.1.3. ^{13}C NMR Spectroscopy. The magnetic properties of the ^{13}C isotope and the low number of protons attached (one or

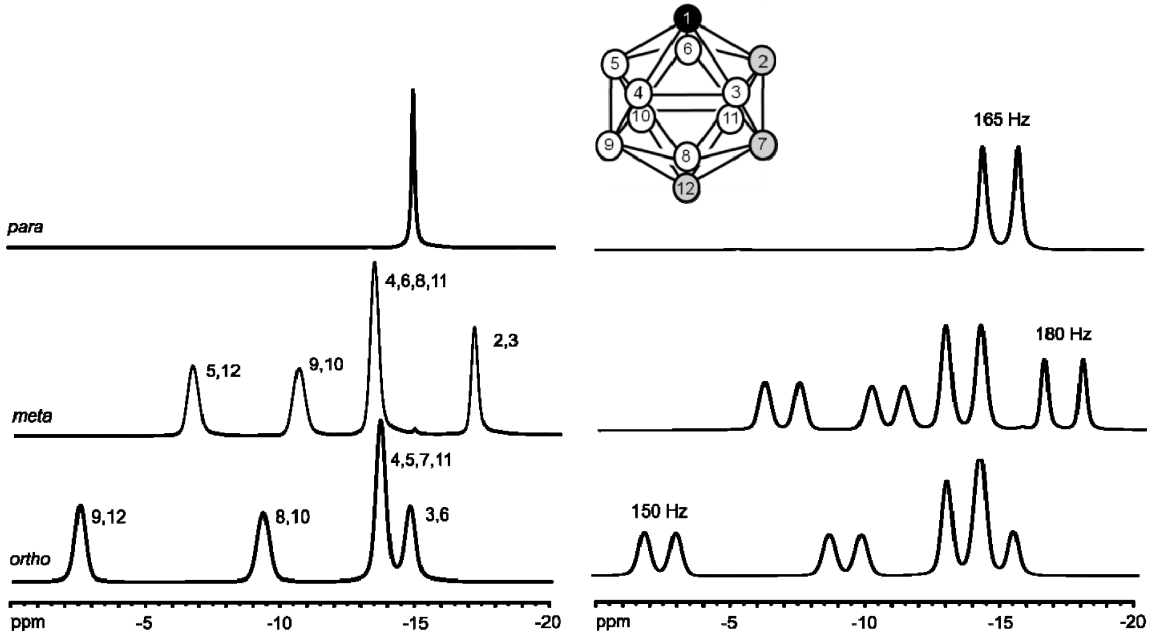


Figure 9. Proton-decoupled (left) and proton-coupled (right) ^{11}B NMR spectra of commercially available unsubstituted carbaboranes in $CDCl_3$ measured at 128.38 MHz with the corresponding positions of the boron atoms labeled. *ortho*-Carbaborane shows four signals (−2.5, −9.3, −13.6, and −14.7 ppm in the ratio 2:2:4:2), *meta*-carbaborane also four signals (−6.7, −10.5, −13.3, and −17.0 ppm in the ratio 2:2:4:2), and *para*-carbaborane only one signal (−14.8 ppm) for all 10 boron atoms. Additionally, selected $^{1}J_{BH}$ coupling constants are given.[194]

dx.doi.org/10.1021/cr200038x |*Chem. Rev.* 2011, 111, 7035–7062

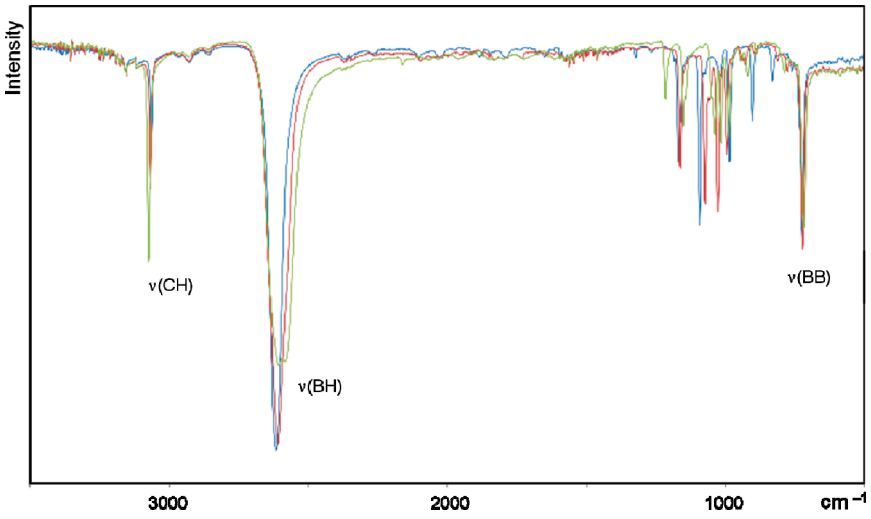


Figure 10. IR spectra of *ortho*- (green), *meta*- (violet), and *para*-carbaborane (blue), with the corresponding ν(CH), ν(BH), and ν(BB) vibrations labeled.

zero) make the recording of ^{13}C NMR spectra very time-consuming. In $CDCl_3$ *ortho*-carbaborane gives one signal at 54.5 ppm ($^1J_{CH}$ = 193 Hz), *meta*-carbaborane gives a resonance at 55.2 ppm ($^1J_{CH}$ = 179 Hz), and *para*-carbaborane is most deshielded at 63.5 ppm ($^1J_{CH}$ = 180 Hz); these singlets split into doublets in the proton-coupled spectra (measured in $CDCl_3$ at 100.63 MHz). The signals are solvent-dependent and slightly broadened. Attachment of an organic substituent at a cluster carbon atom results in deshielding of the corresponding cluster carbon atom and also of the adjacent polyhedral carbon atom.[195,196] This effect is most pronounced for *ortho*-carbaborane (*ortho* effect) and depends on the kind of substituent.[196] Deboronation to the anionic *nido* carbaboranes shields the cluster carbon atoms and results in broad signals.[197] The measurement of 2D NMR spectra gives more detailed information but is usually not in the repertoire of routine analysis.

4.2. IR Spectroscopy

The broad B−H stretching band at 2603 for the *ortho*, 2605 for the *meta*, and 2612 cm^{-1} for the *para* isomer is very characteristic for carbaboranes and does not overlay with other common organic vibrational bands (Figure 10). Compounds with bulky substituents or crystalline samples can show split ν(BH) bands. *nido*-Carbaboranes show this band at lower wavenumbers than 2600 cm^{-1}. The stretching vibrations ν(CH) decrease in the order *ortho*- > *meta*- > *para*-carbaborane (3070, 3064, 3060 cm^{-1}). "Pulsation" of the cage is represented by the ν(BB) vibration at approximately 720 cm^{-1} for all isomers. Each isomer shows an additional individual fingerprint in the region 1200−800 cm^{-1}.[12] These signals are, however, normally overlaid by other vibrations of substituted carbaboranes and difficult to analyze.

4.3. Mass Spectrometry

Due to the isotopic distribution (^{10}B/^{11}B = 2/8), carbaboranes give a very characteristic pattern in the mass spectra (Figure 11). The individual ratio depends on the composition of the cluster, and thus the B_{10} *closo* isomer is easily distinguished from the B_9 *nido* isomer. The ionization method should be selected with respect to the substituent. Favorable is electrospray ionization (ESI) in the negative or positive mode or low-energy electron impact (EI). However, even with the mild ESI, fragmentation or aggregation is often observed. Testing of different solvents or the addition of ions (e.g., Na^+) can facilitate interpretation. Unsubstituted clusters could not be analyzed by ESI-MS.

5. APPLICATION STRATEGIES

The use of carbaboranes as pharmacophores was made popular by the pioneering work of Endo and colleagues.[65,105] However, prior to the introduction of this terminology, the hydrophobicity of carbaboranes was already used to trigger desired biological actions.[42] The following sections present examples in this field not only with respect to the biological targets, but also according to the design strategies. This is aimed to validate carbaboranes as pharmacophores and to inspire further research.

The term pharmacophore was first used by Lemont B. Kier.[198] The IUPAC defines a pharmacophore to be "an ensemble of steric and electronic features that is necessary to ensure the optimal supramolecular interactions with a specific biological target structure and to trigger (or to block) its biological response."[21] Pharmacophores are used in computational chemistry to define the essential features of molecules necessary for molecular recognition and thus the same biological activity. A well-defined pharmacophore model includes both hydrophobic volumes and hydrogen bond vectors.

Due to their spherical shape, in most cases carbaboranes are integrated as substitutes for organic ring systems. The literature comprises different examples in which carbaboranes are used as surrogates for heterocycles, annulated carbon rings, or most popularly, due to the benzene analogy, for substituted or unsubstituted phenyl rings.

5.1. Carbaboranes as Substitutes for Heterocycles

The use of carbaboranes as substitutes for heterocycles was already investigated with the aim of generating BNCT agents. One early example is the carbaboranyl analogue of the DNA alkylator RSU1131 (1-(2-methylaziridin-1-yl)-3-(2-nitroimidazol-1-yl)propan-2-ol) with the nitroimidazole ring replaced by *ortho*-carbaborane (Figure 12).[199] The biological investigation of the boron carrier molecule showed promising selectivity in killing cancer cells compared with normal healthy cells. The compound showed a better boron uptake than BSH, and due to the cell selectivity, the authors declared the

dx.doi.org/10.1021/cr200038x |*Chem. Rev.* 2011, 111, 7035–7062

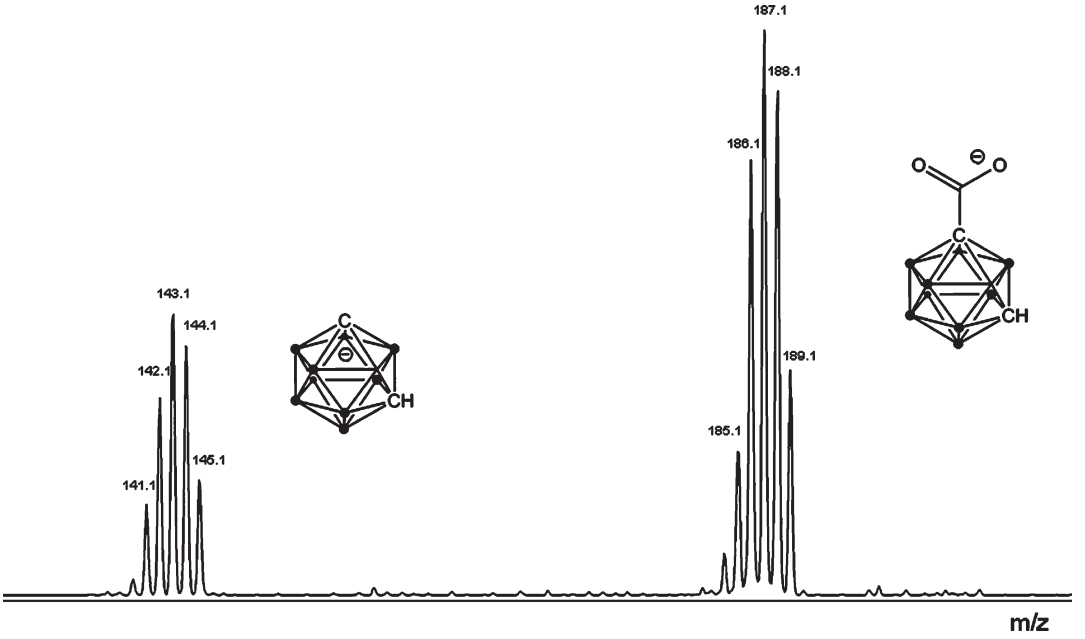


Figure 11. ESI(−) mass spectrum of 1,7-dicarba-*closo*-dodecaborane(12)-1-carboxylic acid measured in acetone with the $[M - H]^-$ and $[M - COOH]^-$ peak and corresponding isotopic pattern.

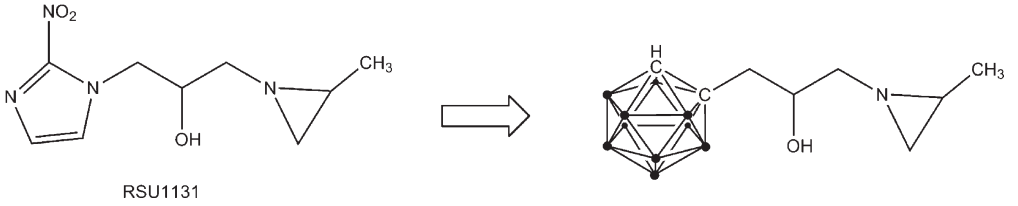


Figure 12. *ortho*-Carbaboranyl-modified DNA alkylator RSU1131.

carbaboranyl analogue also as possible non-BNCT anticancer agent.[199]

Another example is a folic acid-inspired analogue with the pteridine core replaced by *ortho*-carbaborane (Figure 13). The highly amphiphilic disodium analogue revealed low cytotoxicity and accumulated well in B16 melanoma cells.[200]

5.2. Carbaboranes as Substitutes for Annulated Carbon Rings

Saturated annulated carbon rings are highly hydrophobic entities and represent a very promising core for the substitution by carbaboranes. The most common hydrophobic natural biomolecules are steroids with planar annulated ring system and the globular adamantane derivatives.

5.2.1. Steroid Analogues. Steranes are annulated hydrocarbon rings of three six-membered rings and one five-membered ring (Figure 14). The addition of substituents to the sterane allows different receptors to be triggered and gives rise to a plethora of medicinally relevant lipid components and hormones, such as cholesterol, 17β-estradiol, and testosterone.

Endo and colleagues found that 1-phenyl-substituted carbaboranes resemble very well the sterane scaffold. The carbaborane formally replaces the C and D rings. By introduction of different residues either at the carbaborane or at selected positions of the aryl ring different steroids could be imitated.

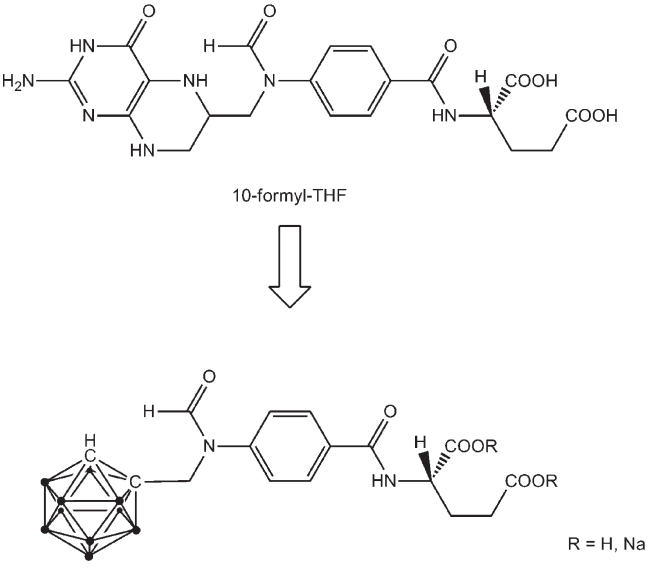


Figure 13. Folic acid-inspired analogue with *ortho*-carbaborane.

5.2.1.1. Estradiol Analogues. 17β-Estradiol (or estradiol) became attractive early in carbaborane chemistry both as boron carrier for BNCT agents and as a non-BNCT drug. It binds to the

dx.doi.org/10.1021/cr200038x |*Chem. Rev.* 2011, 111, 7035–7062

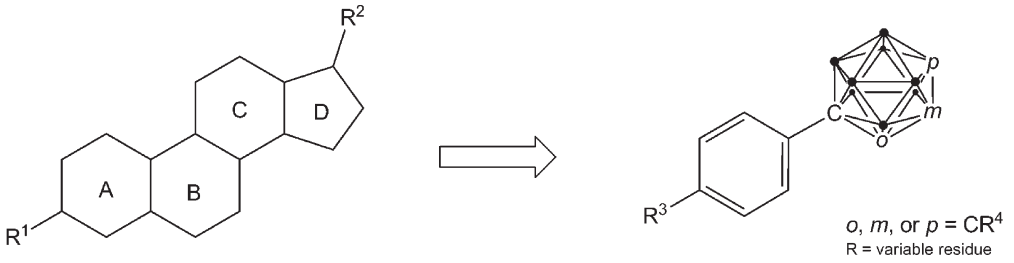


Figure 14. *C*-Phenyl carbaborane as sterane mimetics.

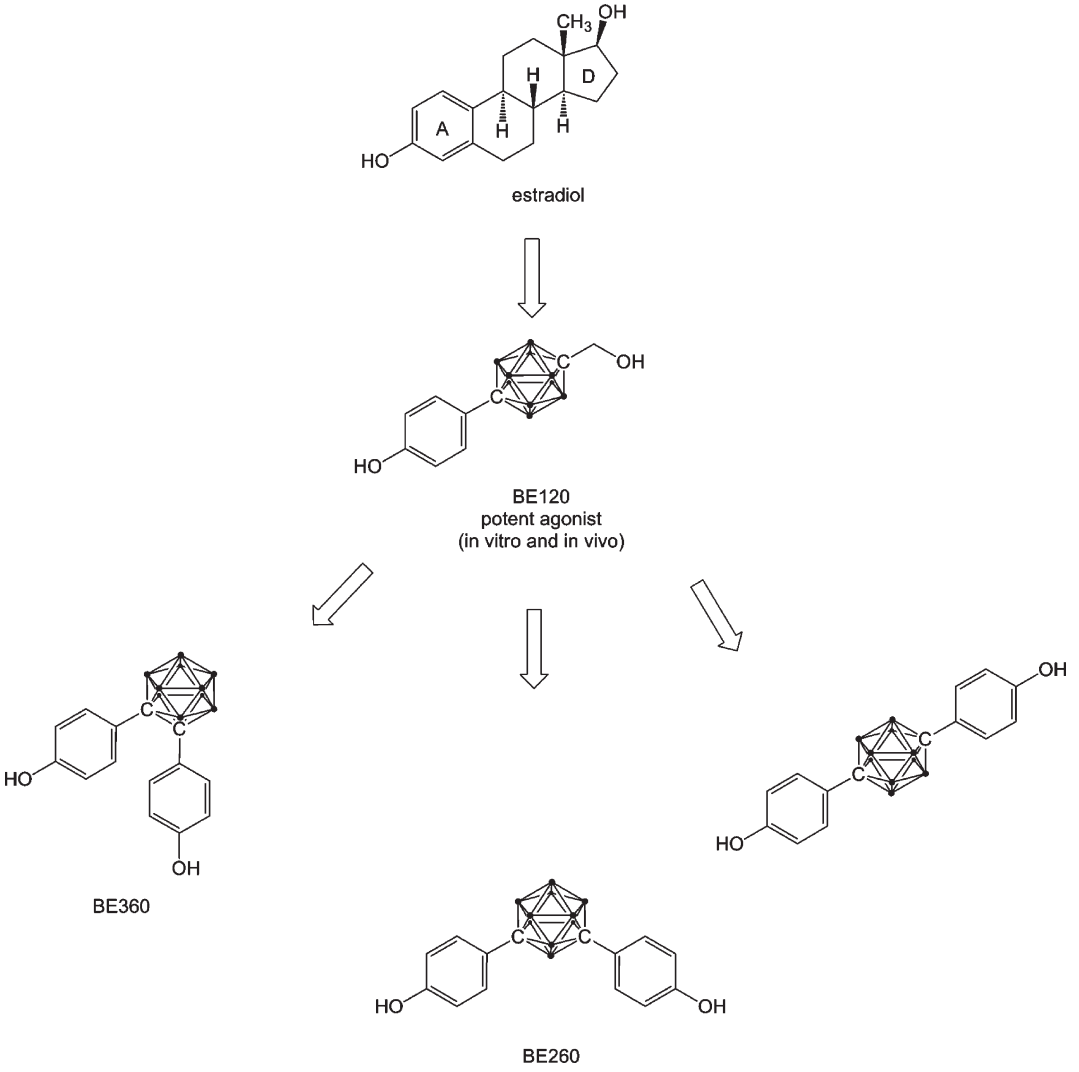


Figure 15. *C*-Phenol-substituted carbaboranes as estrogen receptor agonists.

estrogen receptor, which is a popular drug target due to its relevance for the reproductive, cardiovascular, and central nervous systems.[201−203]

The first attempts using estradiol aimed to yield BNCT agents. The carbaboranyl entity was attached to the hydroxyl group of ring A leaving the estradiol and estrogen core unmodified (not illustrated).[204] About 20 years later, Endo and colleagues introduced the 1-(4-hydroxyphenyl)carbaborane core as sterane analogue and created a small, first-generation library of estradiol mimetics (Figure 15).[105] The 17β-estradiol imitation required the presence of the hydroxyl group in *para* position of the phenyl ring to interact via hydrogen bonds with Glu353 and Arg394 of the receptor binding domain.[205] BE120, with a hydroxymethyl substituent at the second *para*-carbaborane carbon atom, gave an analogue at least ten times more potent than the natural 17β-estradiol.[206,207] The activity decreased when *meta*-carbaborane or adamantane were used.[105,206] Addition of a second phenol group, either directly or via a spacer, to 1-(4-hydroxyphenyl)-*ortho*-carbaborane could tune the agonistic/antagonistic profile.[208] BE360 with two 4-hydroxyphenyl groups directly attached to *ortho*-carbaborane proved to act as a selective

dx.doi.org/10.1021/cr200038x |*Chem. Rev.* 2011, 111, 7035–7062

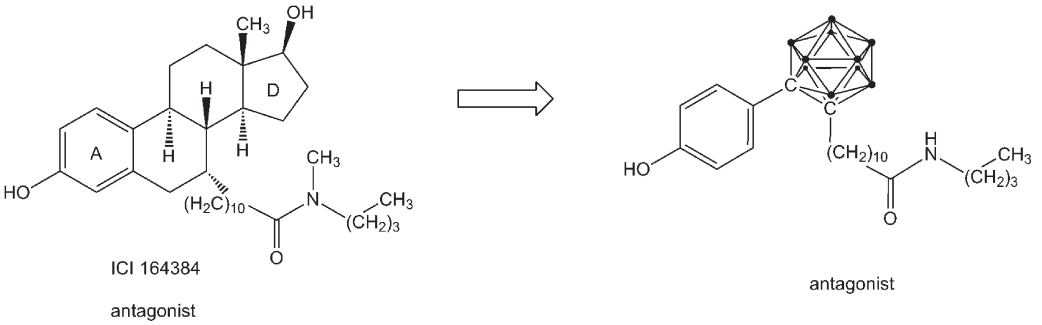


Figure 16. *ortho*-Carbaboranyl-modified ER antagonist.

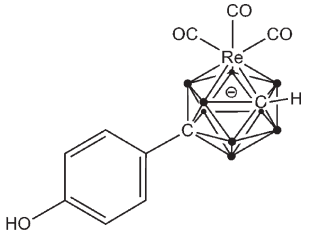


Figure 17. Metallacarbaborane-modified ER ligand.

estrogen receptor modulator (SERM) in bone tissue with potential application to treat osteoporosis.[209] Replacement of *ortho*-carbaborane by other 3D hydrocarbons like bicyclo[2.2.2]octene increased the agonist activity again.[208] Diphenol derivatives of *para*- and *meta*-carbaborane, such as BE260, were promising agonists.[205] A comparison between C-substituted and B-substituted isomers gave interesting insight into selection of the carbaborane isomer and the mode of substitution. C-Substituted *meta*-carbaboranyl diphenol was more active than the *ortho*-carbaborane carrying the phenol groups in *meta* orientation but attached to boron atoms B3 and B6. The authors consider the lower hydrophobicity of the *ortho* isomer, due to the acidic CH units, responsible for the differences in activity.[174,210]

In fact, the 1-(4-hydroxyphenyl)carbaborane core could be used not only to design ER agonists, which trigger receptor signaling but also to design ER antagonists to block or decrease the receptor response (Figure 16). 7α-Substituted estradiol derivatives with long-chain amides, such as ICI 164384, were found to act highly antagonistically and inspired the use of *ortho*- and *meta*-carbaborane to attach a second substituent at the second cluster carbon atom. The application of the *meta* isomer gave inactive analogues; the use of the *ortho* isomer, however, revealed moderate antagonistic activity.[80]

Valliant and co-workers have modified 1-(4-hydroxylphenyl)-carbaborane not only by variation of the substituents at the carbon atom but also by replacing a B−H vertex with a metal (Re or Tc) carbonyl fragment (Figure 17). The resulting anionic metal analogues showed lower activity compared with the neutral *closo* carbaboranes. However, activity could be increased by replacing one CO ligand by NO^+, giving a neutral complex. The successful integration of ^{99m}Tc in good yields into selected compounds opens the door for new labeling approaches.[211]

In summary, the 1-(4-hydroxyphenyl)-carbaborane core is an excellent substitute for the sterane skeleton. The hydrophobicity matches the receptor requirement. The choice of the carbaborane isomer allows orientation of further pharmacophoric entities.

5.2.1.2. Cholesterol Analogues. Cholesterol is, besides estradiol, one of the most prominent and relevant steroids. Cholesterol was already studied as a boron carrier molecule to target tumor cells in BNCT.[212] Early attempts focused on cholesterol-ester conjugates for BNCT applications, with the carbaborane outside the sterane core (Figure 18).[213−215] In this application, not only did the carbaboranes represent the boron carrier entity, but the hydrophobic nature of the carbaborane also supported the formation of low-density lipoprotein (LDL). LDLs contain cholesterol esters as the most abundant lipid and are particularly interesting because they target tumor cells via the LDL pathway.[64,215] The high cell uptake of carbaboranyl−cholesterol conjugates (BCH), mediated through the LDL receptor, gave promising results for further studies.[216−218]

More promising than the modification of the cholesterol periphery was the use of 1-(4- hydroxyphenyl)-carbaborane as sterane mimetic core (Figure 18). In order to facilitate synthesis, 6-methylheptyl was selected as second carbaborane carbon residue instead of 2,6-dimethylheptyl. The analogue revealed a good computed structural overlap with cholesterol and represented an excellent lipid bilayer component for both nontargeted and receptor-targeted liposomes, potentially useful in BNCT.[81]

5.2.1.3. Testosterone Analogues. The natural hormone testosterone binds to the androgen receptor (AR) as an agonist, whereas AR antagonists are used to treat cancer.[219] Testosterone differs from cholesterol and estradiol in that the alcohol group of the A ring is oxidized to a keto group. Therefore, replacement of the 4-hydroxyphenyl ring by 4-keto-*cyclo*-2-hexenyl gave access to various first-generation ligands for the AR, which were moderate antagonists (Figure 19).[220]

The return to the 1-phenylcarbaborane skeleton, however, gave far more active analogues acting antagonistically. The best androgen antagonists revealed the same core structure as ER agonist BE120, but with a nitro or cyano group (BA341) at the 3-position instead of the 4-hydroxy group.[104] Introduction of a CH_2 spacer as well as pyridine or other heterocycles (e.g., 1,2,4-oxadiazole-5-thione) as substituents in *para*-carbaboranyl methanol also yielded active analogues.[91,221,222] Based on the lead structure BA341, different substituents were introduced at the CH_2 group with similar results.[223]

5.2.2. Adamantane Analogues. Carbaboranes resemble adamantane, which is already employed in pharmaceuticals as an organic entity, in shape and hydrophobicity very well. Therefore, integration of carbaboranes in place of adamantane is a promising strategy for modifying the hydrophobic profile of drugs.

5.2.2.1. Retinoic Acid Receptor (RAR) Agonists and Antagonists. A demonstrative example of adamantane-inspired

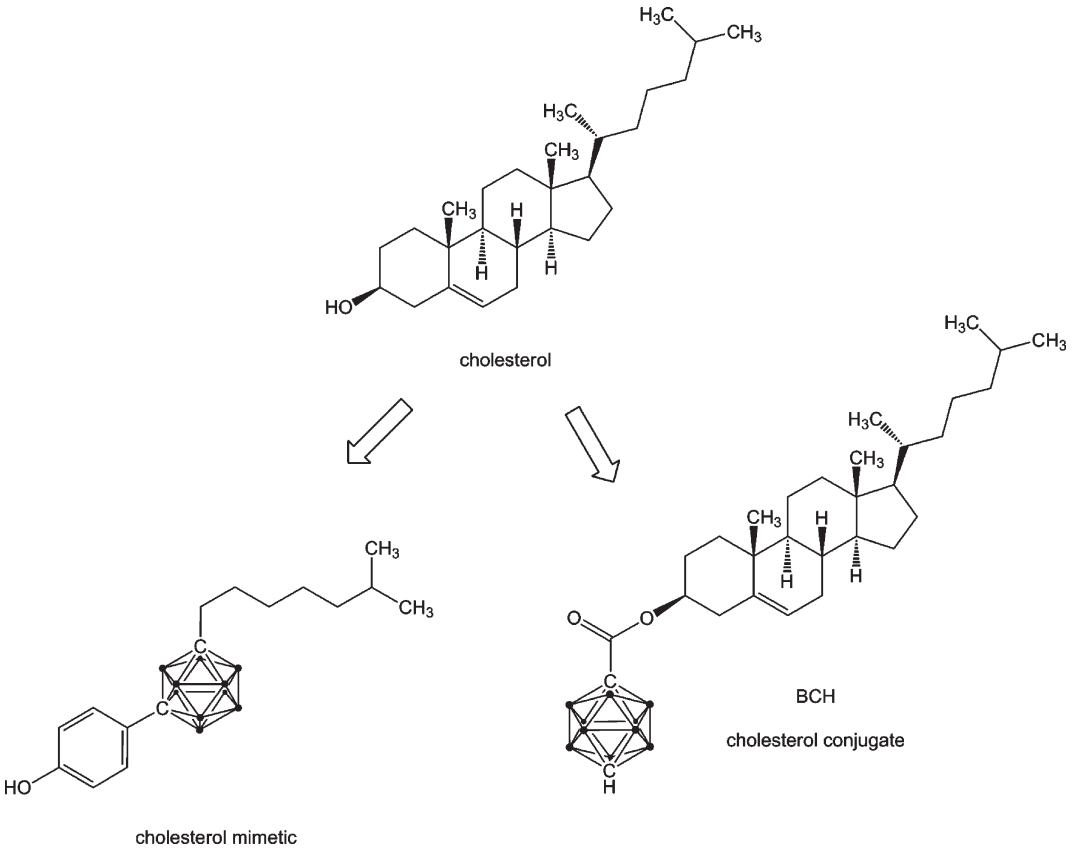


Figure 18. Carbaborane-based cholesterol mimetics.

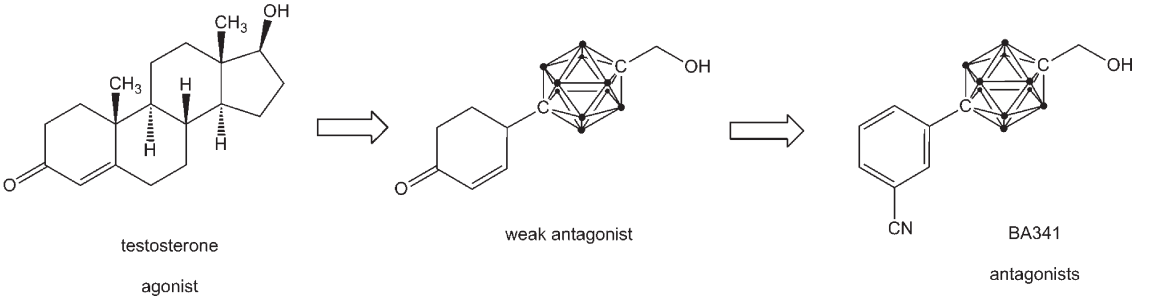


Figure 19. Carbaborane-based testosterone derivatives.

carbaborane drug discovery is the series of retinoic acid receptor (RAR) agonists and antagonists. These compounds contribute to cell differentiation and proliferation and are of medicinal relevance in dermatology and oncology.[224] According to the retinoic acid structure, it was early recognized that ligands for the receptor should contain a polar (carboxylic acid) headgroup and a hydrophobic, globular tail (Figure 20). From earlier series of artificial ligands, the partial agonist CD-394 emerged with an adamantyl residue, which was substituted for a more bulky and hydrophobic diamantyl-group in TD550. The latter showed promising antagonistic activity. The requirement of highly hydrophobic substituents motivated the study of carbaboranes, which are more hydrophobic than adamantane. The *ortho*-carbaborane substitute of CD-394 revealed the same antagonistic activity as TD550, if the influence of the inverted amide group linking the two aryl groups is neglected. This result illustrated that the increased hydrophobic nature of *ortho*-carbaborane analogues is advantageous in this particular case. Further variation of the lead structure with carbaboranes showed that agonist or antagonist activity can be controlled by the position of the carbaborane moiety at the 3- or 4-position of the aryl ring.[225]

Replacement of the amide linkage by an amine linker and furnishing the carbaborane with an *n*-propyl residue at the second cluster carbon atom produced a drug candidate, with an agonistic activity comparable to the natural ligand *trans*-retinoic acid.[226,227] Later on, similar carbaboranyldiphenylamine derivatives proved to be interesting retinoid X receptor (RXR)-selective antagonists.[228]

In a second approach the adamantyl group and the connected aryl ring were replaced with the carbaborane moiety as hydrophobic tail. The use of carbaboranes with unsubstituted B−H vertices gave inactive analogues. Employing carbaboranes with 10 methylated vertices, however, increased the volume of the carbaborane pharmacophore to the size of a C_{60} fullerene, which

dx.doi.org/10.1021/cr200038x |*Chem. Rev.* 2011, 111, 7035–7062

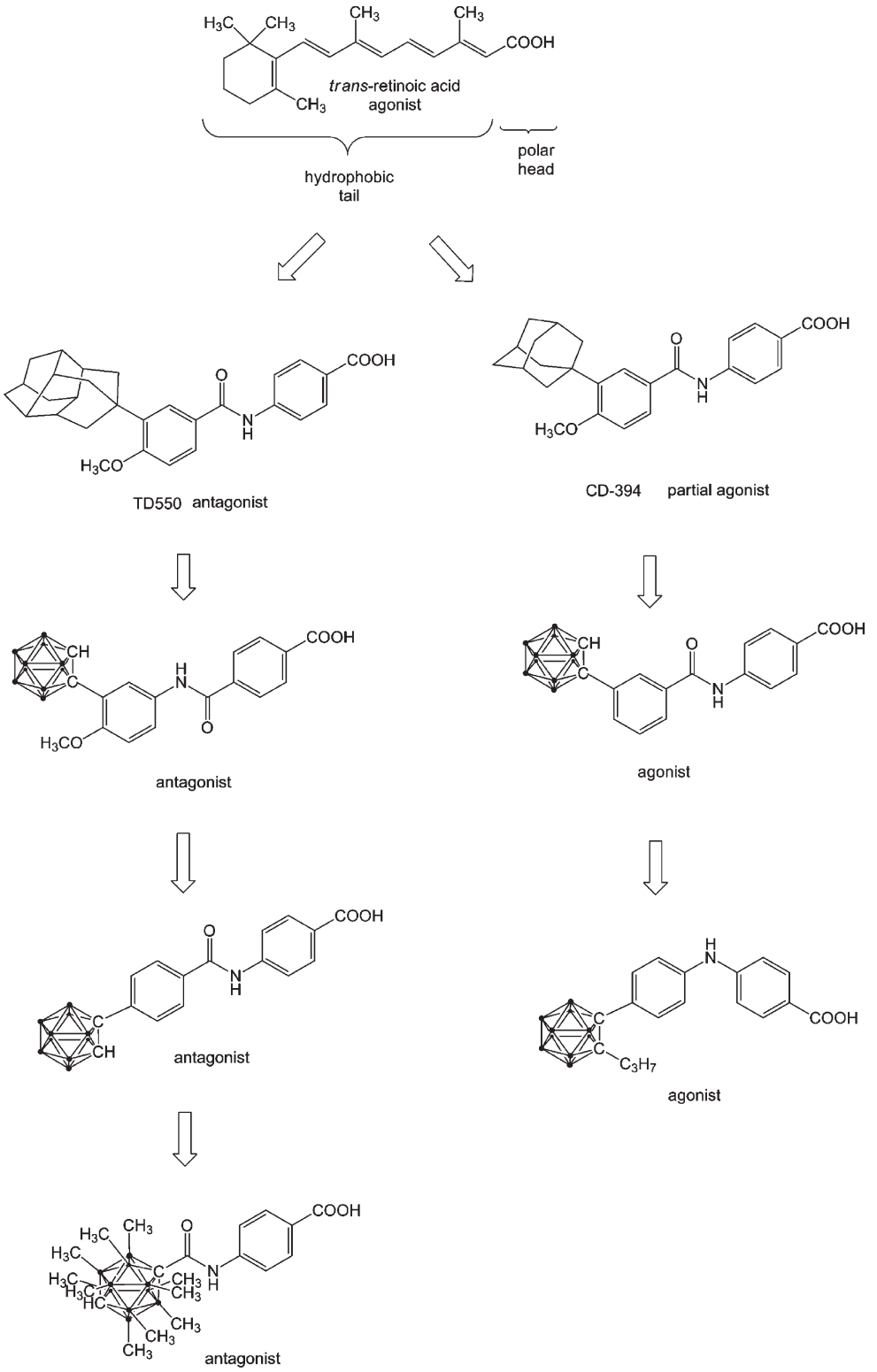


Figure 20. Carbaborane-modified retinoic acid receptor ligands.

was large and hydrophobic enough to yield highly active antagonists. Inversion of the amide bond did not influence the activity, while the use of the smaller octamethyl-substituted carbaborane (*ortho*- or *meta*-carbaborane, with two B−H groups adjacent to carbon) instead of the *B*-permethylated *para*-carbaborane led to diminished activity.[178]

5.2.2.2. Thalidomide Analogues. Phthalimide in which the N−H proton is replaced with an *ortho*-carbaborane proved to modulate production of tumor necrosis factor α (TNF-α).[136] The compound is originally derived from thalidomide, a drug with controversial history. In this case, the carbaborane could be regarded as surrogate for the glutarimide heterocycle (Figure 21). Because the TNF-α

dx.doi.org/10.1021/cr200038x |*Chem. Rev.* 2011, 111, 7035–7062

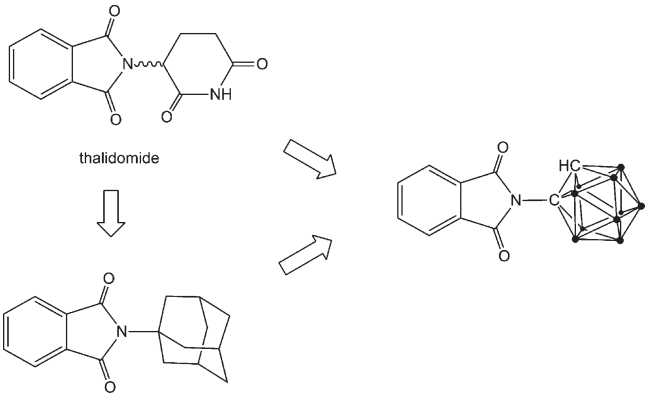


Figure 21. Thalidomide analogues.

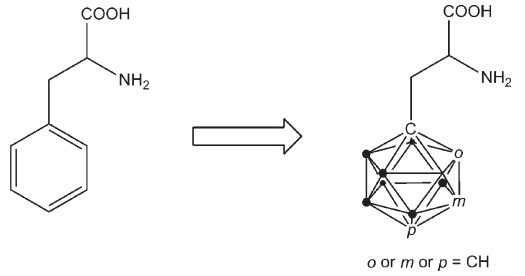


Figure 22. Carboranylalanine the carbaborane analogue of phenylalanine.

modifying activity is attributed to the presence of a highly hydrophobic residue at the nitrogen atom, the synthesis was originally inspired by the adamantyl derivative rather than by thalidomide. Nevertheless, this example illustrates clearly that carbaborane integration strategy can be inspired by replacement of both adamantanes and heterocycles.

5.3. Carbaboranes as Substitutes for Phenyl Rings

Integration of carbaboranes in place of benzene rings is one of the most popular integration strategies. This is due to the three-dimensional aromaticity and the icosahedral shape, which resembles a rotating phenyl ring. As pointed out in section 2.1, the V_{vdW} of the carbaborane cluster (~144 Å^3) is approximately 40% larger than that of a rotating benzene ring (102 Å^3). Thus, the cluster can also be used as a surrogate for phenyl rings carrying small substituents. Examples illustrating this strategy comprise the carbaboranyl analogues of amino acids, tamoxifen, the antifolate drug trimethoprim (TMP), and modified cyclooxygenase inhibitors, such as flufenamic acid, diflunisal, indomethacin, and aspirin, which are discussed in the next sections.

5.3.1. Amino Acid Analogues. The first example based on this integration strategy is *ortho*-carbaboranylalanine, the analogue of the amino acid phenylalanine (Figure 22). This compound was first prepared as a racemic mixture.[229] Later, stereoselective syntheses were performed using chiral propargyl precursors for the reaction with decaborane.[67,230]

The *ortho*-carbaboranylalanine showed fungicidal activity but was also found to form a diastereomeric mixture of *nido* analogues in a pH-dependent self-deboronation process.[192,231] In addition to the *ortho*-carbaborane derivative, *meta*- and *para*-carbaborane analogues have been synthesized from unsubstituted carbaboranes by using Oppolzer's sultam methodology to

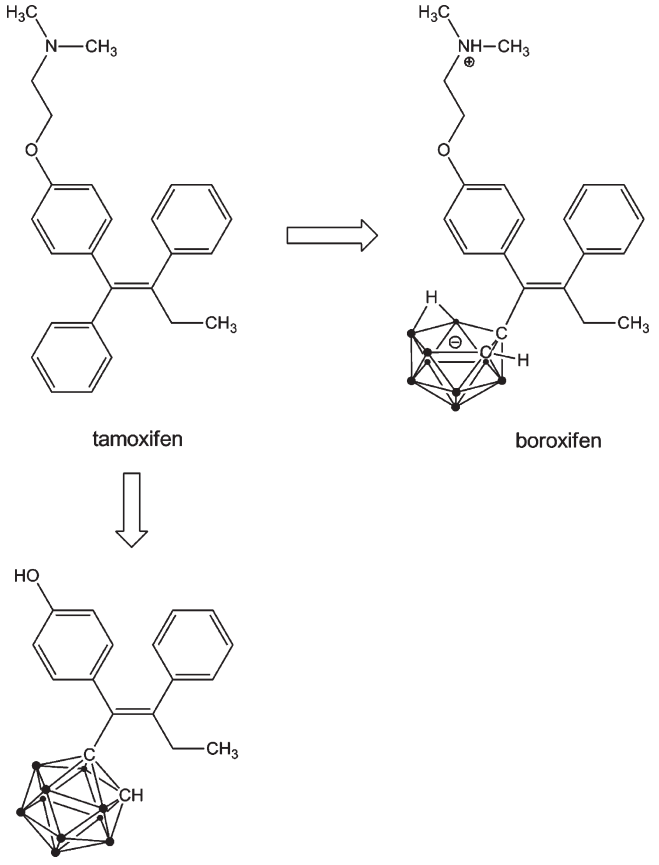


Figure 23. Tamoxifen analogue.

introduce the amino group asymmetrically at the α-carbon atom of the corresponding carboxylic acid.[84,232,233]

Achiral carbaboranyl propionic acids gave already active phenylalanine analogues even without the amino group when integrated in peptides. A successful example hereof is the *C*-terminal integration of 2-(*ortho*-carbaboranyl)propionic acid as phenylalanine substitute into a pseudopentapeptide analogue (Phe-Thr-Pro-Arg-Leu) of pyrokinin neuropeptide.[234] The carbaborane analogue was 30 times more active than the phenylalanine paradigm and resulted in a nearly irreversible myostimulatory response on the isolated cockroach hindgut. The highly hydrophobic nature of the carbaborane moiety is considered responsible for strong receptor binding with enhanced resistance to inactivation by peptidases, and it also allowed the peptide to transmigrate through the cuticular surface of the moth.[234]

Later on, hydroxyl-*para*-carbaborane propionic acid was prepared as tyrosine mimetic, and also other carbaboranes furnished with both carboxyl and amino groups at different positions of different cluster isomers.[85,114,235] A detailed presentation of the amino acid analogues has already been given by Kabalka and colleagues.[236]

5.3.2. Tamoxifen Analogues. A prominent example in this series is the tamoxifen analogue boroxifen, bearing a *nido* carbaborane cluster (Figure 23).[66] The 1,2-dicarba-*closo*-dodecaborane analogue could not be isolated, because *nido* formation proceeded concomitant with introduction of the amino group. The high activity of compounds combining a 4-hydroxyphenyl residue with *closo*-carbaboranes recently inspired the abandonment of the dimethylethylamino substituent and led to a highly active analogue, both as *E* and *Z* isomer, that is more stable toward degradation than tamoxifen itself.[237] Integration of the more stable *para*-carbaborane analogue is also reported to be underway.[7]

dx.doi.org/10.1021/cr200038x |*Chem. Rev.* 2011, 111, 7035–7062

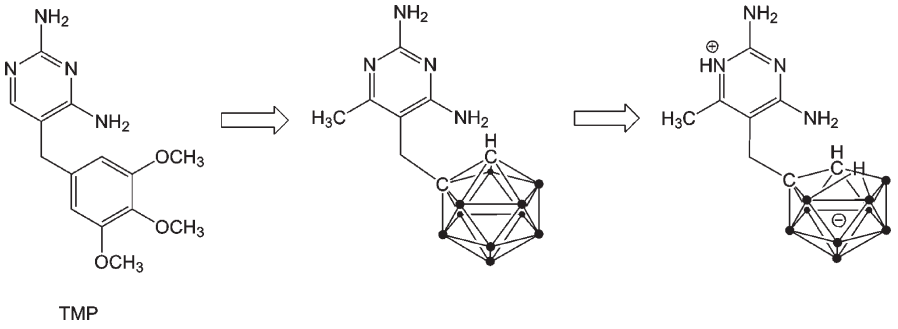


Figure 24. TMP analogues.

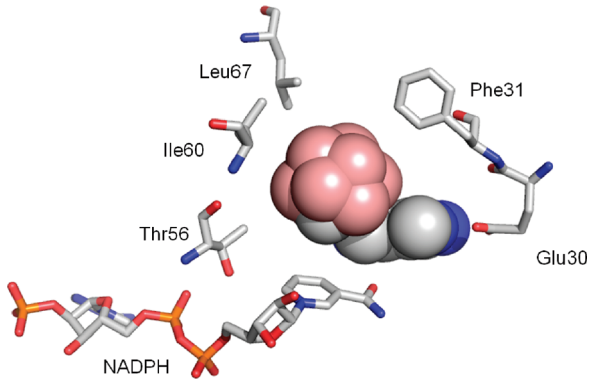


Figure 25. *ortho*-Carbaborane TMP analogue in hDHFR together with NADPH (pink = boron, gray = carbon, blue = nitrogen, red = oxygen, orange = phosphorus). Further hydrophobic interactions with Leu22, Phe34, and Val115 were omitted for clarity. The structural data were taken from PDP entry C2S2 and visualized using PYMOL.[193]

5.3.3. Trimethoprim Analogues. Dihydrofolate reductases (DHFR) are relevant antibacterial and anticancer drug targets, such as the standard antibacterial lipophilic trimethoprim (TMP). TMP was converted to a carbaboranyl analogue with the trimethoxy-substituted phenyl ring being replaced with *ortho-closo*- and the corresponding *nido*-carbaborane (Figure 24).[193,238]

Detailed biological studies gave interesting insights into the behavior of the TMP analogues, which can be summarized as follows. First, compared with the *nido* isomer the *closo* isomer was a better DHFR inhibitor and more toxic. Second, the activity of the *closo* analogue was high against human DHFR and weak against bacterial DHFRs. This profile was rather reverse to TMP, even though the accommodation within the hDHFR active site was essentially identical to that of TMP, as proven by crystal structures. The crystal structure and computational studies investigated the detailed binding mode of the cluster analogue inside the enzyme (Figure 25).[239] Interestingly, the neutral *closo*-carbaborane and TMP occupied the same position as the anionic *nido* derivative. Furthermore, the crystal structure revealed that the carbaborane was not disordered but was present only in a single rotational orientation, which was very surprising in the case of the *closo* isomer.[193] The carbaborane cluster is exclusively surrounded by hydrophobic amino acids.

5.3.4. Nonsteroidal Anti-inflammatory Drug Analogues. Nonsteroidal anti-inflammatory drugs (NSAIDs) are a group of pharmaceuticals targeting cyclooxygenase (COX) enzymes, the key proteins in the prostanoid system.[240] Because prostaglandins are involved in a variety of syndromes, the NSAIDs are commercially highly relevant and have therefore widely been investigated. Classical NSAIDs are nonselective COX inhibitors and often reveal negative side effects, which are mostly attributed to the inhibition of COX-1. Inhibition of COX-2, in contrast, accounts for most of the therapeutic effects, which made this enzyme the favorite drug target.[241−243] Since the active site of COX-2 is larger than that of COX-1, a size-extension of classical NSAIDs successfully yielded COX-2 selective inhibitors.[244−246] Consequently, the use of the three-dimensional and bulky carbaboranes in place of the smaller phenyl ring could be advantageous for obtaining COX-2 selectivity.

5.3.4.1. Flufenamic Acid and Diflunisal Analogues. The first report focused on flufenamic acid and diflunisal in which one of the phenyl rings was substituted for *ortho*- or *meta*-carbaborane. Interestingly, this research was not designed to construct cyclooxygenase inhibitors but transthyretin (TTR) amyloidosis inhibitors instead without COX activity, because the lead structures were found to stabilize TTR and thereby reduce amyloid diseases.[118,247] The inside of the funnel-shaped TTR inspired the design of inhibitors with the bulky carbaborane attached to the essential carboxylic acid group to address the outer enzyme pocket, whereas a smaller phenyl ring was expected to penetrate the inner enzyme chamber. 1-*ortho*-Carbaboranyl-carboxylic acid was slightly active and supported the assumption that the carbaborane fits inside the enzyme. Substitution of the B−H protons with methyl groups or esterification decreased the activity. Among various compounds, the most active TTR amyloidosis inhibitor without activity against COX was the *meta*-carbaborane analogue of diflunisal (Figure 26). The most active TTR amyloidosis inhibitor derived from flufenamic acid, which was also a quite potent COX inhibitor, was modified with an *ortho*-carbaborane pharmacophore.

5.3.4.2. Aspirin Analogue. Asborin is the carbaborane analogue of aspirin (Figure 27).[119] Replacement of the phenyl ring by *ortho*-carbaborane produced a rather weak inhibitor of both COX variants but a highly potent aldo/keto reductase 1A1 (AKR1A1) inhibitor instead.[248] Both effects are attributed to the increased acetylation potential of asborin, which can be attributed to the strongly electron-withdrawing character of the *ortho* isomer transmitted by the cluster carbon atoms. Nonspecific enzyme acetylation diminished COX inhibition but increased AKR1A1 inhibition. Salborin (not shown), the deacetylated version of asborin, was also a competitive AKR1A1 inhibitor.[248] Compared with their phenyl analogues, both carbaborane derivatives were more toxic with almost equal IC_{50} values, whereas detoxification was observed upon deboronation. This reaction occurred under aqueous conditions at ambient temperature.[249]

5.3.4.3. Indomethacin Analogues. Indomethacin is also a very potent NSAID used to treat fever, swelling, and pain.[250] This drug

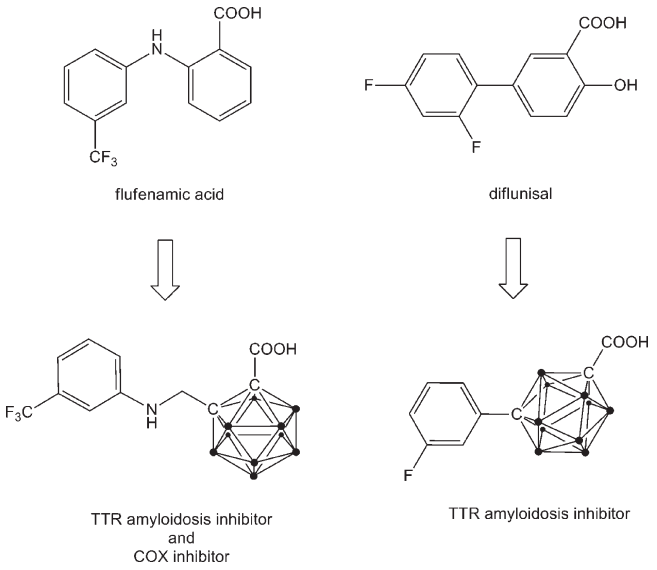


Figure 26. Carbaborane analogues of flufenamic acid and diflunisal.

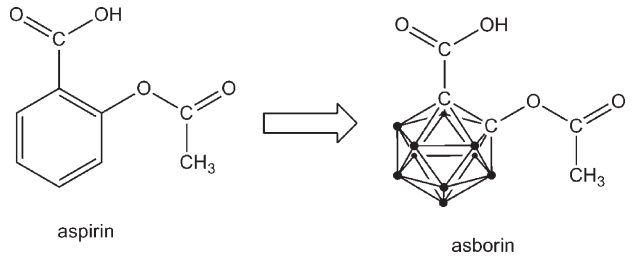


Figure 27. Aspirin analogue.

emerged as a powerful scaffold that allowed for various modifications to influence the selectivity for COX-1 and COX-2. Previous studies showed that addition of substituents either at the carboxylic acid group or at the chlorophenyl ring increased the COX-2 selectivity.[251−254] Hence, these two positions were modified with the carbaborane isomers (Figure 28). Selected *ortho*- and *meta*-carbaboranyl entities were connected either directly or via spacers to the carboxylic acid group of indomethacin. *ortho*-Carbaborane directly attached to the carboxyl group gave the only ester that was active in the micromolar range; the corresponding adamantyl and *meta*-carbaboranyl derivatives were inactive.[255]

Replacement of the chlorophenyl ring with unsubstituted carbaborane isomers revealed the most promising analogues again with the *ortho* isomer.[256]

5.4. Carbaboranes as Hydrophobic Substitutes for Alkyl Chains

Some of the earliest examples describing the application of carbaboranes as hydrophobic pharmacophores are modified protein kinase C modulators. Based on the benzolactam lead structure BL-V8-310, unsubstituted and C-substituted *ortho*-carbaboranes were integrated at the C9 atom in place of the linear alkyl chain, which was expected to be folded upon receptor binding (Figure 29). The carbaboranes were integrated as a hydrophobic component to study substituent effects and the usefulness of carbaboranes as pharmacophores. Computational docking studies of the butyl analogue showed the same hydrogen-bonding pattern as BL-V8-310 and explained the similar activity observed in biological experiments.[257]

5.5. Carbaboranes in the Periphery of Biologically Relevant Molecules

The integration of carbaboranes in place of central ring systems changes the biological profile of the lead structure. The attachment of carbaboranes in the periphery of pharmaceutically relevant compounds can, however, also be utilized to fine-tune drug activity.

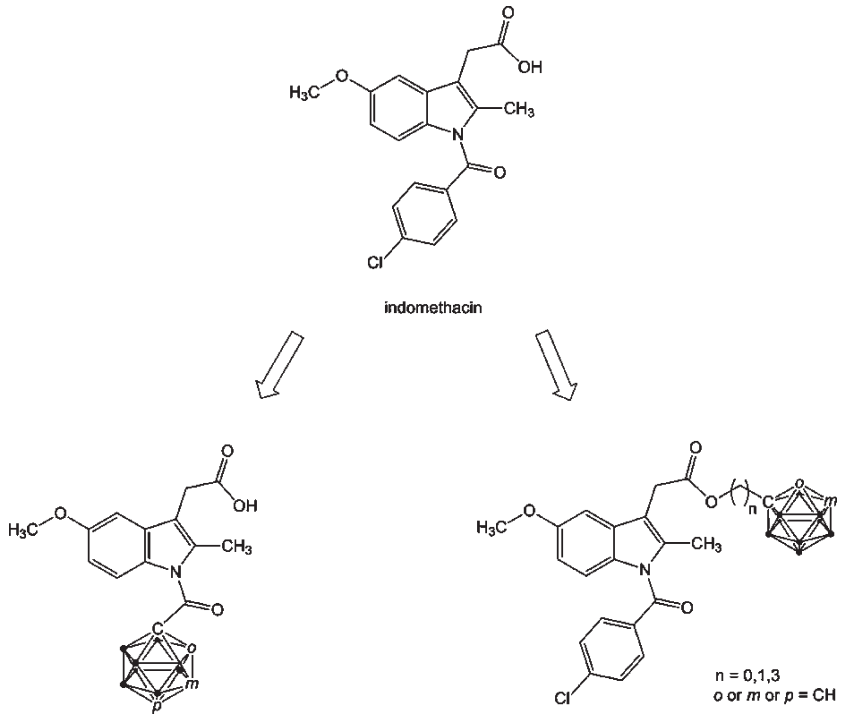


Figure 28. Carbaborane-modified indomethacin analogues.

dx.doi.org/10.1021/cr200038x |*Chem. Rev.* 2011, 111, 7035–7062

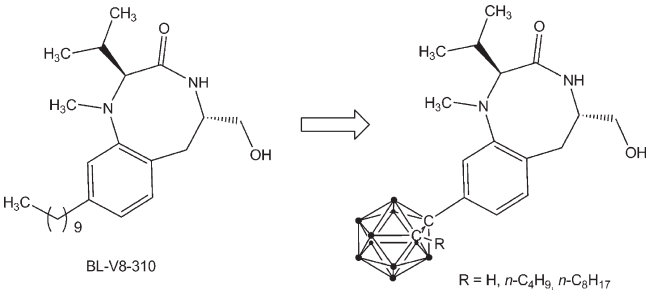


Figure 29. Protein kinase C modulators bearing *ortho*-carbaboranes.

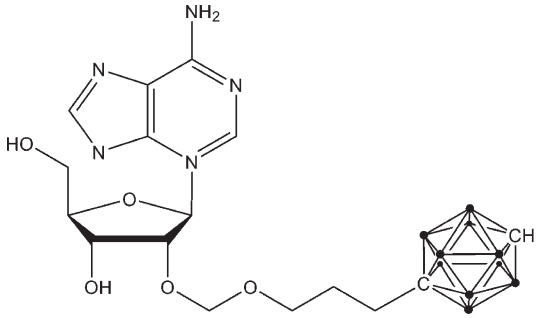


Figure 30. Adenosine with *para*-carbaborane connected via spacer to the 2′-position.

This possibility was already investigated for several BNCT agents, for example, the ability to form LDLs as result of the high lipophilicity of carbaboranes.[215] Leśnikowski and colleagues used this concept and created an interesting library of adenosine derivatives with different *closo*-, *nido*-, and metallacarbaboranes. *para*-Carbaborane, attached via a spacer to the 2′-C position, gave a potent candidate for inhibiting platelet aggregation (Figure 30).[258−260]

6. CONCLUSION

Geometry and electronic structure make carbaboranes unique artificial pharmacophores that are inert to catabolism, because corresponding enzymes are not known. Most frequently, carbaboranes are used as hydrophobic pharmacophores to address hydrophobic binding sites of biological targets. The icosahedral cluster with its very versatile chemistry allows attachment of all organic substituents that are necessary in drug design in mostly high yielding syntheses. The orthogonality of the reactions at the carbon atoms to those at the boron atoms renders regioselective substitutions easily possible. The extraordinary electronic structure makes the carbaboranes yet more than just scaffolds. This is expressed by hydrogen and dihydrogen bonds with CH or BH vertices and by the influence on adjacent substituents. The inductive effects at different cluster positions fine-tune adjacent functionalities, which is particularly useful to adjust a pharmacophoric entity to a biological target. The option to increase the size by modifying multiple boron vertices makes the cluster additionally superior to classical organic fragments such as benzene and adamantane. The deboronation reaction allows formation of charged cluster species and thus modification of the solubility. This option is very pronounced for *ortho*-carbaborane, which also clearly differs from the other two isomers in pharmacological behavior and should therefore be regarded as functional group. The carbaboranyl−phenyl arrangement in general turned out to be a very good scaffold to address different targets by addition of particular substituents. All these aspects make carbaboranes unique and yet underrepresented pharmacophores, which will hopefully change in the near future.

AUTHOR INFORMATION

Corresponding Author

*Tel: +49-341-9736151. Fax: +49-341-9739319. E-mail: hey@rz.uni-leipzig.de.

BIOGRAPHIES

Matthias Scholz studied chemistry at the University of Leipzig (Germany) and biochemistry at Uppsala University (Sweden). After his diploma (2006), he worked on transition metal complexes in the group of Prof. A. Otero and Prof. A. Antiñolo at the University of Castilla-La Mancha in Toledo (Spain). He returned to the University of Leipzig to carry out a Ph.D. under the supervision of Prof. E. Hey-Hawkins. As a fellow of the "Studienstiftung des deutschen Volkes" and the Graduate School of Excellence "Building with Molecules and Nano-objects (BuildMoNa)" he worked mainly on the synthesis and biological evaluation of drug candidates containing carbaboranes as pharmacophores. After he received his doctoral degree in 2011, he spent some time at Vanderbilt University School of Medicine (USA) with Prof. T. Lybrand and Prof. L. Marnett to investigate the activity and binding of carbaborane-modified cyclooxygenase inhibitors.

Evamarie Hey-Hawkins has been a Full Professor of Inorganic Chemistry at Universität Leipzig, Germany, since 1993. She received her diploma (1982) and doctoral degree (1983) at the University of Marburg, Germany. After stays at the University of

Sussex, UK (Liebig Grant VCI, 1984/85), the University of Western Australia (Liebig Grant, 1985/86), and the ANU, Canberra, Australia (research grant, DFG, 1986/87), she returned to Germany and completed her habilitation (Marburg, 1988). From 1988 to 1990, she was a Research Associate at the Max Planck Institute for Solid State Research, Stuttgart, Germany. She was awarded a Heisenberg Grant from the DFG (1990-94), Visiting Professorships at Pamukkale University, Turkey (by TÜBITAK), the Université de Rennes 1, France (2007), and Monash University, Melbourne, Australia (2008, 2009), and has received a Visiting Erskine Fellowship, University of Canterbury, New Zealand (2007) and an ANU Fellowship (Canberra, Australia, 2009). Her scientific interests are in the field of biologically active boron compounds, organophosphorus chemistry, heterometallic transition metal complexes, and catalysis. She is the author of more than 310 publications. Since 2008, she has been the Chair of the EU-COST Action CM0802 "European Phosphorus Sciences Network" (PhoSciNet, www.phoscinet.org) and since 2007, she has been the Speaker of the Excellence Graduate School "Building with Molecules and Nano-objects (BuildMoNa)" (www.buildmona.de) funded by the DFG.

ACKNOWLEDGMENT

We thank Prof. Dr. J. Sieler for his support in determining the van der Waals volumes. M.S. thanks the Studienstiftung des Deutschen Volkes for a Ph.D. grant and the Excellence Graduate School "Building with Molecules and Nano-objects (BuildMoNa)" (GSC 185, DFG) for financial support.

REFERENCES

(1) Jones, B.; Adams, S.; Miller, G. T.; Jesson, M. I.; Watanabe, T.; Wallner, B. P. *Blood* **2003**, *102*, 1641.
(2) Lipscomb, W. N. *Angew. Chem.* **1977**, *89*, 685.
(3) Williams, R. E. *Chem. Rev.* **1992**, *92*, 177.
(4) Barth, R. F.; Coderre, J. A.; Vicente, M. G.; Blue, T. E. *Clin. Cancer Res.* **2005**, *11*, 3987.
(5) Yokoyama, K.; Miyatake, S.-I.; Kajimoto, Y.; Kawabata, S.; Doi, A.; Yoshida, T.; Asano, T.; Kirihata, M.; Ono, K.; Kuroiwa, T. *J. Neurooncol.* **2006**, *78*, 227.
(6) Barth, R. F. *Appl. Radiat. Isot.* **2009**, *67*, S3.
(7) Valliant, J. F.; Guenther, K. J.; King, A. S.; Morel, P.; Schaffer, P.; Sogbein, O. O.; Stephenson, K. A. *Coord. Chem. Rev.* **2002**, *232*, 173.
(8) Hawthorne, M. F.; Lee, M. W. *J. Neurooncol.* **2003**, *62*, 33.
(9) Armstrong, A. F.; Valliant, J. F. *Dalton Trans.* **2007**, 4240.
(10) Bregadze, V. I. *Chem. Rev.* **1992**, *92*, 209 and references therein.
(11) Kalinin, V. N.; Ol'shevskaya, V. A *Russ. Chem. Bull* **2008**, *57*, 815 and references therein.
(12) Leites, L. A. *Chem. Rev.* **1992**, *92*, 279.
(13) Heřmánek, S. *Chem. Rev.* **1992**, *92*, 325.
(14) Grimes, R. N., Ed. *Carboranes*, 2nd ed.; Academic Press (Elsevier): London, 2011.
(15) Hosmane, N. S., Ed. *Boron Science: New Technologies and Applications*; CRC Press: Boca Raton, FL, 2011.
(16) Hosmane, N. S.; Maguire, J. A.; Zhu, Y.; Takagaki, M., in *Boron and Gadolinium Neutron Capture Therapy for Cancer Treatment*; World Scientific Publishers, 2011.
(17) Hawthorne, M. F.; Maderna, A. *Chem. Rev.* **1999**, *99*, 3421.
(18) Bregadze, V. I.; Sivaev, I. B.; Glazun, S. A. *Anticancer Agents Med. Chem.* **2006**, *6*, 75.
(19) Sivaev, I. B.; Bregadze, V. I. *Eur. J. Inorg. Chem.* **2009**, 1433.
(20) Leśnikowski, Z. J. *Collect. Czech. Chem. Commun.* **2007**, *72*, 1646.
(21) Wermuth, C. G.; Ganellin, C. R.; Lindberg, P.; Mitscher, L. A. *Pure Appl. Chem.* **1998**, *70*, 1129.
(22) Bohn, R. K.; Bohn, M. D. *Inorg. Chem.* **1971**, *10*, 350.
(23) Kiran, B.; Anoop, A.; Jemmis, E. D. *J. Am. Chem. Soc.* **2002**, *124*, 4402.
(24) Hitchcock, A. P.; Urquhart, S. G.; Wen, A. T.; Kilcoyne, A. L. D.; Tyliszczak, T.; Rühl, E.; Kosugi, N.; Bozek, J. D.; Spencer, J. T.; McIlroy, D. N.; Dowben, P. A. *J. Phys. Chem. B* **1997**, *101*, 3483.
(25) Turner, A. R.; Robertson, H. E.; Borisenko, K. B.; Rankin, D. W. H.; Fox, M. A. *Dalton Trans.* **2005**, 1310.
(26) Oliva, J. M.; Klein, D. J.; Schleyer, P. v. R.; Serrano-Andrés, L. *Pure Appl. Chem.* **2009**, *81*, 719.
(27) Oliva, J. M.; Serrano-Andrés, L.; Klein, D. J.; Schleyer, P. v. R.; Michl, J. *Int. J. Photoenergy* **2009**, *2009*, 1.
(28) Davidson, M. G.; Hibbert, T. G.; Howard, J. A. K.; Mackinnon, A.; Wade, K. *Chem. Commun.* **1996**, 2285.
(29) Hutton, B. W.; MacIntosh, F.; Ellis, D.; Herisse, F.; Macgregor, S. A.; McKay, D.; Petrie-Armstrong, V.; Rosair, G. M.; Perekalin, D. S.; Tricas, H.; Welch, A. J. *Chem. Commun.* **2008**, 5345.
(30) Oliva, J. M.; Schleyer, P. v. R.; Aullón, G.; Burgos, J. I.; Fernández-Barbero, A.; Alkorta, I. *Phys. Chem. Chem. Phys.* **2010**, *12*, 5101.
(31) Zhao, Y. H.; Abraham, M. H.; Zissimos, A. M. *J. Org. Chem.* **2003**, *68*, 7368.
(32) Ristori, S.; Oberdisse, J.; Grillo, I.; Donati, A.; Spalla, O. *Biophys. J.* **2005**, *88*, 535.
(33) Connolly, M. L. *J. Math. Chem.* **1994**, *15*, 339.
(34) Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441.
(35) Lunato, A. J.; Wang, J.; Woollard, J. E.; Anisuzzaman, A. K.; Ji, W.; Rong, F. G.; Ikeda, S.; Soloway, A. H.; Eriksson, S.; Ives, D. H.; Blue, T. E.; Tjarks, W. *J. Med. Chem.* **1999**, *42*, 3378.
(36) Data taken from CCDC entries TOKGIJ, TOKGOP, TOKGUV, ADAMAN08, and ABELUO and determined with the PLATON program.
(37) Schleyer, P. v. R.; Najafian, K. *Inorg. Chem.* **1998**, *37*, 3454.
(38) Laubengayer, A. W.; Rysz, W. R. *Inorg. Chem.* **1965**, *4*, 1513.
(39) Clark, T. E.; Makha, M.; Raston, C. L.; Sobolev, A. N. *Dalton Trans.* **2006**, 5449.
(40) Hawthorne, M. F.; Berry, T. E.; Wegner, P. A. *J. Am. Chem. Soc.* **1965**, *87*, 4746.
(41) Fauchére, J.-L.; Do, K. Q.; Jow, P. Y.; Hansch, C. *Experientia* **1980**, *36*, 1203.
(42) Schwyzer, R.; Do, K. Q.; Eberle, A. N.; Fauchére, J.-L. *Helv. Chim. Acta* **1981**, *64*, 2078.
(43) Yamamoto, K.; Endo, Y. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2389.
(44) Hermansson, K.; Wójcik, M.; Sjöberg, S. *Inorg. Chem.* **1999**, *38*, 6039.
(45) Zakharkin, L. I.; Ogorodnikova, N. A. *J. Organomet. Chem.* **1968**, *12*, 13.
(46) Teixidor, F.; Barberà, G.; Viñas, C.; Sillanpää, R.; Kivekäs, R. *Inorg. Chem.* **2006**, *45*, 3496.
(47) Zakharkin, L. I.; Kalinin, V. N.; Kobel'kova, N. I. *Syn. React. Inorg. Met. Chem.* **1976**, *6*, 91.
(48) Zakharkin, L. I.; Kalinin, V. N. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1968**, 1423.
(49) Zakharkin, L. I.; Kalinin, V. N.; Gedymin, V. V. *Syn. React. Inorg. Met. Chem.* **1971**, *1*, 45.
(50) Grunwald, E.; Berkowitz, B. J. *J. Am. Chem. Soc.* **1951**, *73*, 4939.
(51) Zakharkin, L. I.; Kalinin, V. N.; Podvisotskaya, L. S. *Russ. Chem. Bull* **1970**, *19*, 1227.
(52) Lee, H.; Knobler, C. B.; Hawthorne, M. F. *Chem. Commun.* **2000**, 2485.
(53) Blanch, R. J.; Williams, M.; Fallon, G. D.; Gardiner, M. G.; Kaddour, R.; Raston, C. L. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 504.
(54) Custelcean, R.; Jackson, J. E. *Chem. Rev.* **2001**, *101*, 1963.
(55) Alkorta, I.; Rozas, I.; Elguero, J. *Chem. Soc. Rev.* **1998**, *27*, 163.
(56) Dou, J.; Su, F.; Nie, Y.; Li, D.; Wang, D. *Dalton Trans.* **2008**, 4152.
(57) Heying, T. L.; Ager, J. W.; Clark, S. L.; Mangold, D. J.; Goldstein, H. L.; Hillman, M.; Polak, R. J.; Szymanski, J. W. *Inorg. Chem.* **1963**, *2*, 1089.

(58) Fein, M. M.; Bobinski, J.; Mayes, N.; Schwartz, N.; Cohen, M. S. *Inorg. Chem.* **1963**, *2*, 1111.
(59) Zakharkin, L. I.; Stanko, V. I.; Brattsev, V. A.; Chapovskii, Y. A.; Struchkov, Y. T. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1963**, *12*, 1911.
(60) Zakharkin, L. I.; Stanko, V. I.; Brattsev, V. A.; Chapovskii, Y. A.; Okhlobystin, O. Y. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1963**, *12*, 2074.
(61) Edvenson, G. M.; Gaines, D. F. *Inorg. Chem.* **1990**, *29*, 1210.
(62) Grafstein, D.; Dvorak, J. *Inorg. Chem.* **1963**, *2*, 1128.
(63) Dupont, J. A.; Hawthorne, M. F. *J. Am. Chem. Soc.* **1964**, *86*, 1643.
(64) Feakes, D. A.; Spinler, J. K.; Harris, F. R. *Tetrahedron* **1999**, *55*, 11177.
(65) Endo, Y.; Yoshimi, T.; Iijima, T.; Yamakoshi, Y. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3387.
(66) Valliant, J. F.; Schaffer, P.; Stephenson, K. A.; Britten, J. F. *J. Org. Chem.* **2002**, *67*, 383.
(67) Karnbrock, W.; Musiol, H.-J.; Moroder, L. *Tetrahedron* **1995**, *51*, 1187.
(68) Kusari, U.; Li, Y.; Bradley, M. G.; Sneddon, L. G. *J. Am. Chem. Soc.* **2004**, *126*, 8662.
(69) Li, Y.; Carroll, P. J.; Sneddon, L. G. *Inorg. Chem.* **2008**, *47*, 9193.
(70) Nakamura, H.; Aoyagi, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 1167.
(71) Clegg, W.; Brown, D. A.; Bryan, S. J.; Wade, K. *Polyhedron* **1984**, *3*, 307.
(72) Zakharkin, L. I.; Grebennikov, A. V.; Kazantsev, A. V. *Izv. Akad. Nauk. SSSR. Ser. Khim.* **1967**, *9*, 2077.
(73) Gomez, F. A.; Hawthorne, M. F. *J. Org. Chem.* **1992**, *57*, 1384.
(74) Viñas, C.; Benakki, R.; Teixidor, F.; Casabó, J. *Inorg. Chem.* **1995**, *34*, 3844.
(75) Heying, T. L.; Ager, J. W.; Clark, S. L.; Alexander, R. P.; Papetti, S.; Reid, J. A.; Trotz, S. I. *Inorg. Chem.* **1963**, *2*, 1097.
(76) L'Esperance, R. P.; Li, Z. -H.; Van Engen, D.; Jones, M., Jr. *Inorg. Chem.* **1989**, *28*, 1823.
(77) Thomas, J.; Hawthorne, M. F. *Chem. Commun.* **2001**, 1884.
(78) Jiang, W.; Chizhevsky, I. T.; Mortimer, M. D.; Chen, W.; Knobler, C. B.; Johnson, S. E.; Gomez, F. A.; Hawthorne, M. F. *Inorg. Chem.* **1996**, *35*, 5417.
(79) Kaszynski, P.; Pakhomov, S.; Tesh, K. F.; Young, V. G. *Inorg. Chem.* **2001**, *40*, 6622.
(80) Endo, Y.; Yoshimi, T.; Yamakoshi, Y. *Chem. Pharm. Bull.* **2000**, *48*, 312.
(81) Thirumamagal, B. T.; Zhao, X. B.; Bandyopadhyaya, A. K.; Naranyanasamy, S.; Johnsamuel, J.; Tiwari, R.; Golightly, D. W.; Patel, V.; Jehning, B. T.; Backer, M. V.; Barth, R. F.; Lee, R. J.; Backer, J. M.; Tjarks, W. *Bioconjugate Chem.* **2006**, *17*, 1141.
(82) Drechsel, K.; Lee, C. S.; Leung, E. W.; Kane, R. R.; Hawthorne, M. F. *Tetrahedron Lett.* **1994**, *35*, 6217.
(83) Woodhouse, S. L.; Rendina, L. M. *Chem. Commun.* **2001**, 2464.
(84) Naeslund, C.; Ghirmai, S.; Sjöberg, S. *Tetrahedron* **2005**, *61*, 1181.
(85) Ujváry, I.; Nachman, R. J. *Peptides* **2001**, *22*, 287.
(86) Ujváry, I.; Nachman, R. J. *Tetrahedron Lett.* **1999**, *40*, 5147.
(87) Cheung, M.-S.; Chan, H.-S.; Xie, Z. *Organometallics* **2004**, *23*, 517.
(88) Herzog, A.; Jalisatgi, S. S.; Knobler, C. B.; Wedge, T. J.; Hawthorne, M. F. *Chem.—Eur. J.* **2005**, *11*, 7155.
(89) Lee, J.-D.; Lee, Y.-J.; Jeong, H.-J.; Lee, J. S.; Lee, C.-H.; Ko, J.; Kang, S. O. *Organometallics* **2003**, *22*, 445.
(90) Yinghuai, Z.; Pei Sia, S. L.; Kooli, F.; Carpenter, K.; Kemp, R. A. *J. Organomet. Chem.* **2005**, *690*, 6284.
(91) Goto, T.; Ohta, K.; Suzuki, T.; Ohta, S.; Endo, Y. *Bioorg. Med. Chem.* **2005**, *13*, 6414.
(92) Nakamura, H.; Sadayori, N.; Sekido, M.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1994**, 2581.
(93) Nakamura, H.; Sekido, M.; Yamamoto, Y. *J. Med. Chem.* **1997**, *40*, 2825.
(94) Lee, T.; Jeon, J.; Song, K. H.; Jung, I.; Baik, C.; Park, K.-M.; Lee, S. S.; Kang, S. O.; Ko, J. *Dalton Trans.* **2004**, 933.
(95) Wang, S. R.; Qiu, Z.; Xie, Z. *J. Am. Chem. Soc.* **2010**, *132*, 9988.
(96) Deng, L.; Chan, H.-S.; Xie, Z. *J. Am. Chem. Soc.* **2006**, *128*, 7728.
(97) Ren, S.; Chan, H.-S.; Xie, Z. *J. Am. Chem. Soc.* **2009**, *131*, 3862.
(98) Gingrich, H. L.; Ghosh, T.; Huang, Q.; Jones, M., Jr. *J. Am. Chem. Soc.* **1990**, *112*, 4082.
(99) Ghosh, T.; Gingrich, H. L.; Kam, C. K.; Mobraaten, E. C.; Jones, M., Jr. *J. Am. Chem. Soc.* **1991**, *113*, 1313.
(100) Qiu, Z.; Xie, Z. *J. Am. Chem. Soc.* **2009**, *131*, 2084.
(101) Zakharkin, L. I.; Kovderov, A. I.; Ol'shevskaya, V. A. *Russ. Chem. Bull* **1986**, *35*, 1260.
(102) Henly, T. J.; Knobler, C. B.; Hawthorne, M. F. *Organometallics* **1992**, *11*, 2313.
(103) Coult, R.; Fox, M. A.; Gill, W. R.; Herbertson, P. L.; MacBride, J. A. H.; Wade, K. *J. Organomet. Chem.* **1993**, *462*, 19.
(104) Fujii, S.; Goto, T.; Ohta, K.; Hashimoto, Y.; Suzuki, T.; Ohta, S.; Endo, Y. *J. Med. Chem.* **2005**, *48*, 4654.
(105) Endo, Y.; Iijima, T.; Yamakoshi, Y.; Yamaguchi, M.; Fukasawa, H.; Shudo, K. *J. Med. Chem.* **1999**, *42*, 1501.
(106) Batsanov, A. S.; Fox, M. A.; Howard, J. A. K.; MacBride, J. A. H.; Wade, K. *J. Organomet. Chem.* **2000**, *610*, 20.
(107) Fox, M. A.; Cameron, A. M.; Low, P. J.; Paterson, M. A. J.; Batsanov, A. S.; Goeta, A. E.; Rankin, D. W. H.; Robertson, H. E.; Schirlin, J. T. *Dalton Trans.* **2006**, 3544.
(108) Morin, J.-F.; Sasaki, T.; Shirai, Y.; Guerrero, J. M.; Tour, J. M. *J. Org. Chem.* **2007**, *72*, 9481.
(109) Stadlbauer, S.; Lönnecke, P.; Welzel, P.; Hey-Hawkins, E. *Eur. J. Org. Chem.* **2010**, *2010*, 3129.
(110) Yang, X.; Jiang, W.; Knobler, C. B.; Hawthorne, M. F. *J. Am. Chem. Soc.* **1992**, *114*, 9719.
(111) Yang, X.; Jiang, W.; Knobler, C. B.; Mortimer, M. D.; Hawthorne, M. F. *Inorg. Chim. Acta* **1995**, *240*, 371.
(112) Zakharkin, L. I.; Kalinin, V. N.; Gedymin, V. V. *Russ. Chem. Bull.* **1976**, *25*, 1583.
(113) Ren, S.; Xie, Z. *Organometallics* **2008**, *27*, 5167.
(114) Kasar, R. A.; Knudsen, G. M.; Kahl, S. B. *Inorg. Chem.* **1999**, *38*, 2936.
(115) Venkatasubramanian, U.; Donohoe, D. J.; Ellis, D.; Giles, B. T.; Macgregor, S. A.; Robertson, S.; Rosair, G. M.; Welch, A. J.; Batsanov, A. S.; Boyd, L. A.; Copley, R. C. B.; Fox, M. A.; Howard, J. A. K.; Wade, K. *Polyhedron* **2004**, *23*, 629.
(116) Kahl, S. B.; Koo, M.-S. *J. Chem. Soc., Chem. Commun.* **1990**, 1769.
(117) Kahl, S. B. *Tetrahedron Lett.* **1990**, *31*, 1517.
(118) Julius, R. L.; Farha, O. K.; Chiang, J.; Perry, L. J.; Hawthorne, M. F. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 4808.
(119) Scholz, M.; Bensdorf, K.; Gust, R.; Hey-Hawkins, E. *ChemMedChem* **2009**, *4*, 746.
(120) Brown, D. A.; Colquhoun, H. M.; Daniels, J. A.; MacBride, J. A. H.; Stephenson, I. R.; Wade, K. *J. Mater. Chem.* **1992**, *2*, 793.
(121) Nie, Y.; Pritzkow, H.; Siebert, W. *Eur. J. Inorg. Chem.* **2004**, *2004*, 2425.
(122) Zi, G.; Li, H.-W.; Xie, Z. *Organometallics* **2002**, *21*, 1136.
(123) Zi, G.; Li, H.-W.; Xie, Z. *Organometallics* **2002**, *21*, 3850.
(124) Malan, C.; Morin, C. *Tetrahedron Lett.* **1997**, *38*, 6599.
(125) Ohta, K.; Goto, T.; Yamazaki, H.; Pichierri, F.; Endo, Y. *Inorg. Chem.* **2007**, *46*, 3966.
(126) Gomez, F. A.; Johnson, S. E.; Hawthorne, M. F. *J. Am. Chem. Soc.* **1991**, *113*, 5915.
(127) Müller, J.; Baše, K.; Magnera, T. F.; Michl, J. *J. Am. Chem. Soc.* **1992**, *114*, 9721.
(128) Douglass, A. G.; Pakhomov, S.; Reeves, B.; Janoušek, Z.; Kaszynski, P. *J. Org. Chem.* **2000**, *65*, 1434.
(129) Crespo, O.; Gimeno, M. C.; Laguna, A. *Polyhedron* **1999**, *18*, 1279.
(130) Kang, Y.; Kim, J.; Kong, Y. K.; Lee, J.; Lee, S. W.; Kang, S. O.; Ko, J. *Organometallics* **2000**, *19*, 5026.
(131) Kahl, S. B.; Kasar, R. A. *J. Am. Chem. Soc.* **1996**, *118*, 1223.
(132) Sivaev, I. B.; Solntsev, K. A.; Kuznetsov, N. T. *Russ. J. Coord. Chem.* **1992**, *18*, 227.

(133) Fox, M. A.; Peace, R. J.; Clegg, W.; Elsegood, M. R. J.; Wade, K. *Polyhedron* **2009**, *28*, 2359.
(134) Fox, M. A.; MacBride, J. A. H.; Peace, R. J.; Clegg, W.; Elsegood, M. R. J.; Wade, K. *Polyhedron* **2009**, *28*, 789.
(135) Scobie, M.; Threadgill, M. D. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2059.
(136) Tsuji, M.; Koiso, Y.; Takahashi, H.; Hashimoto, Y.; Endo, Y. *Biol. Pharm. Bull.* **2000**, *23*, 513.
(137) Alexander, R. P.; Schroeder, H. *Inorg. Chem.* **1963**, *2*, 1107.
(138) Balema, V. P.; Somoza, F., Jr.; Hey-Hawkins, E. *Eur. J. Inorg. Chem.* **1998**, *1998*, 651.
(139) Rys, E. G.; Lönnecke, P.; Stadlbauer, S.; Kalinin, V. N.; Hey-Hawkins, E. *Polyhedron* **2009**, *28*, 3467.
(140) Maulana, I.; Lönnecke, P.; Hey-Hawkins, E. *Inorg. Chem.* **2009**, *48*, 8638.
(141) Stadlbauer, S.; Frank, R.; Maulana, I.; Lönnecke, P.; Kirchner, B.; Hey-Hawkins, E. *Inorg. Chem.* **2009**, *48*, 6072.
(142) Huo, X.-K.; Su, G.; Jin, G.-X. *Dalton Trans.* **2010**, *39*, 1954.
(143) Crespo, O.; Gimeno, M. C.; Jones, P. G.; Laguna, A. *J. Chem. Soc., Chem. Commun.* **1993**, 1696.
(144) Zharov, I.; Saxena, A.; Michl, J. *Inorg. Chem.* **1997**, *36*, 6033.
(145) Zakharin, L. I.; Zhigareva, G. G. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1970**, *10*, 2290.
(146) Scholz, M.; Hey-Hawkins, E. Unpublished results.
(147) Musteti, A. D.; Popescu, A. R.; Viñas, C.; Teixidor, F.; Nuñez, R. EUROBORON5, 29th August−2nd September Heriot-Watt University, Edinburgh, U.K., Programme, Abstracts, Participants, 2010, p 81.
(148) Smith, H. D., Jr.; Obenland, C. O.; Papetti, S. *Inorg. Chem.* **1966**, *5*, 1013.
(149) Teixidor, F.; Viñas, C.; Benakki, R.; Kivekäs, R.; Sillanpää, R. *Inorg. Chem.* **1997**, *36*, 1719.
(150) Stogniy, M. Y.; Sivaev, I. B.; Petrovskii, P. V.; Bregadze, V. I. *Dalton Trans.* **2010**, *39*, 1817.
(151) Zhang, J.-S.; Lin, Y.-J.; Jin, G.-X. *J. Organomet. Chem.* **2009**, *694*, 2069.
(152) Canales, S.; Crespo, O.; Gimeno, M. C.; Jones, P. G.; Laguna, A.; Romero, P. *Dalton Trans.* **2003**, 4525.
(153) Herberhold, M.; Jin, G.-X.; Yan, H.; Milius, W.; Wrackmeyer, B. *J. Organomet. Chem.* **1999**, *587*, 252.
(154) Wu, C.; Xu, B.; Zhao, J.; Jiang, Q.; Wei, F.; Jiang, H.; Wang, X.; Yan, H. *Chem.—Eur. J.* **2010**, *16*, 8914.
(155) Clegg, W.; Brown, D. A.; Bryan, S. J.; Wade, K. *J. Organomet. Chem.* **1987**, *325*, 39.
(156) Taoda, Y.; Sawabe, T.; Endo, Y.; Yamaguchi, K.; Fujii, S.; Kagechika, H. *Chem. Commun.* **2008**, 2049.
(157) Streubel, R.; Özbolat-Schön, A.; Bode, M.; Daniels, J.; Schnakenburg, G.; Teixidor, F.; Viñas, C.; Vaca, A.; Pepiol, A.; Farràs, P. *Organometallics* **2009**, *28*, 6031.
(158) Barberà, G.; Vaca, A.; Teixidor, F.; Sillanpää, R.; Kivekäs, R.; Viñas, C. *Inorg. Chem.* **2008**, *47*, 7309.
(159) Kongpricha, S.; Schroeder, H. *Inorg. Chem.* **1969**, *8*, 2449.
(160) Boyd, L. A.; Clegg, W.; Copley, R. C. B.; Davidson, M. G.; Fox, M. A.; Hibbert, T. G.; Howard, J. A. K.; Mackinnon, A.; Peace, R. J.; Wade, K. *Dalton Trans.* **2004**, 2786.
(161) Herzog, A.; Maderna, A.; Harakas, G. N.; Knobler, C. B.; Hawthorne, M. F. *Chem.—Eur. J.* **1999**, *5*, 1212.
(162) Sieckhaus, J. F.; Semenuk, N. S.; Knowles, T. A.; Schroeder, H. *Inorg. Chem.* **1969**, *8*, 2452.
(163) Andrews, J. S.; Zayas, J.; Jones, M., Jr. *Inorg. Chem.* **1985**, *24*, 3715.
(164) Zheng, Z.; Jiang, W.; Zinn, A. A.; Knobler, C. B.; Hawthorne, M. F. *Inorg. Chem.* **1995**, *34*, 2095.
(165) Zakharkin, L. I.; Kovredov, A. I.; Ol'shevskaya, V. A.; Shaugumbekova, Z. S. *J. Organomet. Chem.* **1982**, *226*, 217.
(166) Li, J.; Logan, C. F.; Jones, M., Jr. *Inorg. Chem.* **1991**, *30*, 4866.
(167) Beletskaya, I. P.; Bregadze, V. I.; Ivushkin, V. A.; Petrovskii, P. V.; Sivaev, I. B.; Sjöberg, S.; Zhigareva, G. G. *J. Organomet. Chem.* **2004**, *689*, 2920.
(168) Mukhin, S. N.; Kabytaev, K. Z.; Zhigareva, G. G.; Glukhov, I. V.; Starikova, Z. A.; Bregadze, V. I.; Beletskaya, I. P. *Organometallics* **2008**, *27*, 5937.
(169) Beletskaya, I. P.; Bregadze, V. I.; Kabytaev, K. Z.; Zhigareva, G. G.; Petrovskii, P. V.; Glukhov, I. V.; Starikova, Z. A. *Organometallics* **2007**, *26*, 2340.
(170) Sevryugina, Y.; Julius, R. L.; Hawthorne, M. F. *Inorg. Chem.* **2010**, *49*, 10627.
(171) Hawthorne, M. F.; Wegner, P. A. *J. Am. Chem. Soc.* **1968**, *90*, 896.
(172) Ramachandran, B. M.; Knobler, C. B.; Hawthorne, M. F. *Inorg. Chem.* **2006**, *45*, 336.
(173) Qiu, Z.; Xie, Z. *J. Am. Chem. Soc.* **2010**, *132*, 16085.
(174) Ogawa, T.; Ohta, K.; Yoshimi, T.; Yamazaki, H.; Suzuki, T.; Ohta, S.; Endo, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3943.
(175) Jiang, W.; Knobler, C. B.; Mortimer, M. D.; Hawthorne, M. F. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1332.
(176) Rockwell, J. J.; Herzog, A.; Peymann, T.; Knobler, C. B.; Hawthorne, M. F. *Curr. Sci.* **2000**, *78*, 405.
(177) Schroeder, H.; Heying, T. L.; Reiner, J. R. *Inorg. Chem.* **1963**, *2*, 1092.
(178) Endo, Y.; Yaguchi, K.; Kawachi, E.; Kagechika, H. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1733.
(179) Wiesboeck, R. A.; Hawthorne, M. F. *J. Am. Chem. Soc.* **1964**, *86*, 1642.
(180) Hawthorne, M. F.; Young, D. C.; Garrett, P. M.; Owen, D. A.; Schwerin, S. G.; Tebbe, F. N.; Wegner, P. A. *J. Am. Chem. Soc.* **1968**, *90*, 862.
(181) Zakharkin, L. I.; Kalinin, V. N. *Tetrahedron Lett.* **1965**, *6*, 407.
(182) Tomita, H.; Luu, H.; Onak, T. *Inorg. Chem.* **1991**, *30*, 812.
(183) Yoo, J.; Hwang, J. -W.; Do, Y. *Inorg. Chem.* **2001**, *40*, 568.
(184) Willans, C. E.; Kilner, C. A.; Fox, M. A. *Chem.—Eur. J.* **2010**, *16*, 10644.
(185) Fox, M. A.; Goeta, A. E.; Hughes, A. K.; Johnson, A. L. *J. Chem. Soc., Dalton Trans.* **2002**, 2132.
(186) Fox, M. A.; Wade, K. *J. Organomet. Chem.* **1999**, *573*, 279.
(187) Fox, M. A.; Gill, W. R.; Herbertson, P. L.; MacBride, J. A. H.; Wade, K.; Colquhoun, H. M. *Polyhedron* **1996**, *15*, 565.
(188) Batsanov, A. S.; Copley, R. C. B.; Davidson, M. G.; Fox, M. A.; Hibbert, T. G.; Howard, J. A. K.; Wade, K. *J. Cluster Sci.* **2006**, *17*, 119.
(189) Fox, M. A.; MacBride, J. A. H.; Wade, K. *Polyhedron* **1997**, *16*, 2499.
(190) Viñas, C.; Laromaine, A.; Teixidor, F.; Horáková, H.; Langauf, A.; Vespalec, R.; Mata, I.; Molins, E. *Dalton Trans.* **2007**, 3369.
(191) Powell, C. L.; Schulze, M.; Black, S. J.; Thompson, A. S.; Threadgill, M. D. *Tetrahedron Lett.* **2007**, *48*, 1251.
(192) Svantesson, E.; Pettersson, J.; Olin, Å.; Markides, K.; Sjöberg, S. *Acta Chem. Scand.* **1999**, *53*, 731.
(193) Reynolds, R. C.; Campbell, S. R.; Fairchild, R. G.; Kisliuk, R. L.; Micca, P. L.; Queener, S. F.; Riordan, J. M.; Sedwick, W. D.; Waud, W. R.; Leung, A. K. W.; Dixon, R. W.; Suling, W. J.; Borhani, D. W. *J. Med. Chem.* **2007**, *50*, 3283.
(194) Heřmánek, S. *Inorg. Chim. Acta* **1999**, *289*, 20.
(195) Wrackmeyer, B.; García Hernández, Z.; Lang, J.; Tok, O. L. *Z. Anorg. Allg. Chem.* **2009**, *635*, 1087.
(196) Todd, L. J.; Siedle, A. R.; Bodner, G. M.; Kahl, S. B.; Hickey, J. P. *J. Magn. Reson.* **1976**, *23*, 301.
(197) Diaz, M.; Jaballas, J.; Arias, J.; Lee, H.; Onak, T. *J. Am. Chem. Soc.* **1996**, *118*, 4405.
(198) Kier, L. B. *Mol. Pharmacol.* **1967**, *3*, 487.
(199) Yamamoto, Y.; Nakamura, H. *J. Med. Chem.* **1993**, *36*, 2232.
(200) Rho, K. Y.; Cho, Y. J.; Yoon, C. M.; Nakamura, H. *Tetrahedron Lett.* **1999**, *40*, 4821.
(201) Katzenellenbogen, B. S. *Biol. Reprod.* **1996**, *54*, 287.
(202) Katzenellenbogen, B. S.; Choi, I.; Delage-Mourroux, R.; Ediger, T. R.; Martini, P. G.; Montano, M.; Sun, J.; Weis, K.; Katzenellenbogen, J. A. *J. Steroid Biochem. Mol. Biol.* **2000**, *74*, 279.
(203) Rubanyi, G. M.; Kauser, K.; Johns, A. *Vasc. Pharmacol.* **2002**, *38*, 81.

(204) Sweet, F. *Steroids* **1981**, *37*, 223.
(205) Ogawa, T.; Ohta, K.; Iijima, T.; Suzuki, T.; Ohta, S.; Endo, Y. *Bioorg. Med. Chem.* **2009**, *17*, 1109.
(206) Endo, Y.; Iijima, T.; Yamakoshi, Y.; Fukasawa, H.; Miyaura, C.; Inada, M.; Kubo, A.; Itai, A. *Chem. Biol.* **2001**, *8*, 341.
(207) Endo, Y.; Ohta, K.; Yoshimi, T.; Yamaguchi, K. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2004**, *179*, 799.
(208) Endo, Y.; Yoshimi, T.; Ohta, K.; Suzuki, T.; Ohta, S. *J. Med. Chem.* **2005**, *48*, 3941.
(209) Hirata, M.; Inada, M.; Matsumoto, C.; Takita, M.; Ogawa, T.; Endo, Y.; Miyaura, C. *Biochem. Biophys. Res. Commun.* **2009**, *380*, 218.
(210) Ohta, K.; Ogawa, T.; Suzuki, T.; Ohta, S.; Endo, Y. *Bioorg. Med. Chem.* **2009**, *17*, 7958.
(211) Causey, P. W.; Besanger, T. R.; Valliant, J. F. *J. Med. Chem.* **2008**, *51*, 2833.
(212) Firestone, R. A.; Pisano, J. M.; Falck, J. R.; McPhaul, M. M.; Krieger, M. *J. Med. Chem.* **1984**, *27*, 1037.
(213) Laster, B. H.; Kahl, S. B.; Popenoe, E. A.; Pate, D. W.; Fairchild, R. G. *Cancer Res.* **1991**, *51*, 4588.
(214) Soloway, A. H.; Tjarks, W.; Barnum, B. A.; Rong, F.-G.; Barth, R. F.; Codogni, I. M.; Wilson, J. G. *Chem. Rev.* **1998**, *98*, 1515.
(215) Ji, B.; Peacock, G.; Lu, D. R. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2455.
(216) Peacock, G. F.; Ji, B.; Wang, C. K.; Lu, D. R. *Drug Delivery* **2003**, *10*, 29.
(217) Peacock, G.; Sidwell, R.; Pan, G.; ØIe, S.; Lu, D. R. *J. Pharm. Sci.* **2004**, *93*, 13.
(218) Pan, G.; Oie, S.; Lu, D. R. *Pharm. Res.* **2004**, *21*, 1257.
(219) Mooradian, A. D.; Morley, J. E.; Korenman, S. G. *Endocr. Rev.* **1987**, *8*, 1.
(220) Fujii, S.; Hashimoto, Y.; Suzuki, T.; Ohta, S.; Endo, Y. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 227.
(221) Ohta, K.; Goto, T.; Fijii, S.; Suzuki, T.; Ohta, S.; Endo, Y. *Bioorg. Med. Chem.* **2008**, *16*, 8022.
(222) Fujii, S.; Ohta, K.; Goto, T.; Kagechika, H.; Endo, Y. *Bioorg. Med. Chem.* **2009**, *17*, 344.
(223) Goto, T.; Ohta, K.; Fujii, S.; Ohta, S.; Endo, Y. *J. Med. Chem.* **2010**, *53*, 4917.
(224) Njar, V. C.; Gediya, L.; Purushottamachar, P.; Chopra, P.; Vasaitis, T. S.; Khandelwal, A.; Mehta, J.; Huynh, C.; Belosay, A.; Patel, J. *Bioorg. Med. Chem.* **2006**, *14*, 4323.
(225) Iijima, T.; Endo, Y.; Tsuji, M.; Kawachi, E.; Kagechika, H.; Shudo, K. *Chem. Pharm. Bull* **1999**, *47*, 398.
(226) Endo, Y.; Iijima, T.; Kagechika, H.; Ohta, K.; Kawachi, E.; Shudo, K. *Chem Pharm Bull* **1999**, *47*, 585.
(227) Endo, Y.; Iijima, T.; Yaguchi, K.; Kawachi, E.; Inoue, N.; Kagechika, H.; Kubo, A.; Itai, A. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1307.
(228) Ohta, K.; Iijima, T.; Kawachi, E.; Kagechika, H.; Endo, Y. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5913.
(229) Brattsev, V. A.; Stanko, V. I. *J. Gen. Chem. USSR* **1969**, *39*, 1175.
(230) Leukart, O.; Caviezel, M.; Eberle, A.; Escher, E.; Tun-Kyi, A.; Schwyzer, R. *Helv. Chim. Acta* **1976**, *59*, 2184.
(231) Oros, G.; Ujváry, I.; Nachman, R. J. *Amino Acids* **1999**, *17*, 357.
(232) Lindström, P.; Naeslund, C.; Sjöberg, S. *Tetrahedron Lett.* **2000**, *41*, 751.
(233) Malmquist, J.; Sjöberg, S. *Tetrahedron* **1996**, *52*, 9207.
(234) Nachman, R. J.; Teal, P. E. A.; Radel, P. A.; Holman, G. M.; Abernathy, R. L. *Peptides* **1996**, *17*, 747.
(235) Levit, G. L.; Krasnov, V. P.; Gruzdev, D. A.; Demin, A. M.; Bazhov, I. V.; Sadretdinova, L. Sh.; Olshevskaya, V. A.; Kalinin, V. N.; Cheong, C. S.; Chupakhin, O. N.; Charushin, V. N. *Collect. Czech. Chem. Commun.* **2007**, *72*, 1697.
(236) Kabalka, G. W.; Yao, M. L. *Anticancer Agents Med. Chem.* **2006**, *6*, 111.
(237) Beer, M. L.; Lemon, J.; Valliant, J. F. *J. Med. Chem.* **2010**, *53*, 8012.
(238) Reynolds, R. C.; Trask, T. W.; Sedwick, W. D. *J. Org. Chem.* **1991**, *56*, 2391.
(239) Tiwari, R.; Mahasenan, K.; Pavlovicz, R.; Li, C.; Tjarks, W. *J. Chem. Inf. Model* **2009**, *49*, 1581.
(240) Simmons, D. L.; Botting, R. M.; Hla, T. *Pharmacol. Rev.* **2004**, *56*, 387.
(241) Hinz, B.; Brune, K. *J. Pharmacol. Exp. Ther.* **2002**, *300*, 367.
(242) Chandrasekharan, N. V.; Simmons, D. L. *Genome Biol.* **2004**, *5*, 241.
(243) Mitchell, J. A.; Warner, T. D. *Nat. Rev. Drug Discovery* **2006**, *5*, 75.
(244) Pouplana, R.; Lozano, J. J.; Ruiz, J. *J. Mol. Graph. Model.* **2002**, *20*, 329.
(245) Kurumbail, R. G.; Stevens, A. M.; Gierse, J. K.; McDonald, J. J.; Stegeman, R. A.; Pak, J. Y.; Gildehaus, D.; Miyashiro, J. M.; Penning, T. D.; Seibert, K.; Isakson, P. C.; Stallings, W. C. *Nature* **1996**, *384*, 644.
(246) Michaux, C.; Charlier, C. *Mini Rev. Med. Chem.* **2004**, *4*, 603.
(247) Johnson, S. M.; Wiseman, R. L.; Sekijima, Y.; Green, N. S.; Adamski-Werner, S. L.; Kelly, J. W. *Acc. Chem. Res.* **2005**, *38*, 911.
(248) Scholz, M.; Steinhagen, M.; Heiker, J. T.; Beck-Sickinger, A. G.; Hey-Hawkins, E. *ChemMedChem* **2011**, *6*, 89.
(249) Scholz, M.; Kaluđerović, G. N.; Kommera, H.; Paschke, R.; Will, J.; Sheldrick, W. S.; Hey-Hawkins, E. *Eur. J. Med. Chem.* **2011**, *46*, 1131.
(250) Hart, F. D.; Boardman, P. L. *Br. Med. J.* **1963**, *2*, 965.
(251) Kalgutkar, A. S.; Marnett, A. B.; Crews, B. C.; Remmel, R. P.; Marnett, L. J. *J. Med. Chem.* **2000**, *43*, 2860.
(252) Kalgutkar, A. S.; Crews, B. C.; Rowlinson, S. W.; Marnett, A. B.; Kozak, K. R.; Remmel, R. P.; Marnett, L. J. *Proc. Natl. Acad. Sci. U.S. A.* **2000**, *97*, 925.
(253) Loll, P. J.; Picot, D.; Ekabo, O.; Garavito, R. M. *Biochemistry* **1996**, *35*, 7330.
(254) Black, W. C.; Bayly, C.; Belley, M.; Chan, C. C.; Charleson, S.; Denis, D.; Gauthier, J. Y.; Gordon, R.; Guay, D.; Kargman, S.; Lau, C. K.; Leblanc, Y.; Mancini, J.; Ouellet, M.; Percival, D.; Roy, P.; Skorey, K.; Tagari, P.; Vickers, P.; Wong, E.; Xu, L.; Prasit, P. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 725.
(255) Scholz, M.; Blobaum, A. L.; Marnett, L. J.; Hey-Hawkins, E. *Bioorg. Med. Chem.* **2011**, *19*, 3242.
(256) Scholz, M.; Blobaum, A. L.; Marnett, L. J.; Hey-Hawkins, E.; unpublished results.
(257) Endo, Y.; Yoshimi, T.; Kimura, K.; Itai, A. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2561.
(258) Wojtczak, B. A.; Olejniczak, A. B.; Przepiorkiewicz, M.; Andrysiak, A.; Leśnikowski, Z. J. *Collect. Czech. Chem. Commun.* **2008**, *73*, 175.
(259) Bednarska, K.; Olejniczak, A. B.; Wojtczak, B. A.; Sulowska, Z.; Leśnikowski, Z. J. *ChemMedChem* **2010**, *5*, 749.
(260) Olejniczak, A. B.; Wojtczak, B. A.; Leśnikowski, Z. J. *Nucleosides, Nucleotides Nucleic Acids* **2007**, *26*, 1611.