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Reevaluation of the *ortho*-Carborane Synthesis: Success with Mono-Substituted Acetylenes in the Presence of Silver Salts

Abstract

The study shows that traditional methods for synthesizing ortho-carboranes from *nido*-$B_{10}H_{14}$ and its complexes ($B_{10}H_{12}L_2$) using donor- and acceptor-disubstituted acetylenes yielding low efficiencies (yields 0–12 %). Attempts to improve yields with ionic liquids and silver salts as catalysts were unsuccessful with disubstituted acetylenes. However, it has been found that the use of mono-substituted acetylenes (phenylacetylene, ethyl propiolate) in the presence of silver salts in the reaction with $B_{10}H_{12}L_2$ substrates produces *ortho*-carboranes in high yields (~90 %). This suggests that the key step is the formation and subsequent addition of silver acetylenides, and not the donor-acceptor π-complexes previously assumed. This finding allows us to better understand the mechanisms of the *ortho*-carboranes formation and offers an efficient pathway for their synthesis.

Keywords: *ortho*-carborane; decaborane; acetylenes; silver; synthesis

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Перегляд синтезу *орто*-карборанів: успіх для монозаміщених ацетиленів у присутності солей срібла

Анотація

Дослідження засвідчує, що традиційні методи синтезу *орто*-карборанів з *нідо*-$B_{10}H_{14}$ та його комплексів ($B_{10}H_{12}L_2$) з використанням дизаміщених ацетиленів з донорними та акцепторними замісниками мають низьку ефективність (виходи 0–12 %). Спроби підвищити вихід продуктів за допомогою йонних рідин і солей срібла як каталізаторів були невдалими за використання дизаміщених ацетиленів. Проте було виявлено, що використання монозаміщених ацетиленів (фенілацетилен, етилпропіолат) у присутності солей срібла в реакції із субстратами $B_{10}H_{12}L_2$ призводить до утворення *орто*-карборанів з високим виходом (~90 %). Це свідчить про те, що ключовим етапом взаємодії є утворення та подальше приєднання ацетиленідів срібла, а не донорно-акцепторних π-комплексів, як передбачали раніше. Це відкриття дозволяє краще зрозуміти механізми утворення *орто*-карборанів і надає можливості для їх ефективного синтезу.

Ключові слова: *орто*-карборани; декаборан; ацетилени; срібло; синтез

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Supporting information: Experimental details; spectral and analytical data for the synthetized compounds; copies of ^{1}H, ^{11}B and ^{13}C NMR spectra.
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■ Introduction

The transition from academic discovery to industrial application remains lengthy and complex, often necessitating the development of new or modification of existing production cycles. One illustrative example is the principle of isosterism proposed by Langmuir in 1919 [1], which has been successfully employed in medicinal chemistry over the years [2]. Recently, this concept has been expanded to include the replacement of benzene rings in molecules with more complex frameworks [3], including carboranes.

Carboranes are polyhedral clusters composed of boron, carbon, and hydrogen atoms, known for their unique chemical and physical properties. Initially investigated for the boron neutron capture therapy (BNCT), carboranes have emerged as valuable scaffolds in the development of new pharmaceuticals and chemical probes [4, 5]. Numerous successful applications of carboranes, specifically *ortho*-substituted ones, in medicinal chemistry have been reported, underscoring their great potential in pharmaceutical research [6, 7] (**Figure, B**). Beyond medicinal applications, carborane-based compounds exhibit exceptional properties that make them promising candidates in materials science [8, 9], particularly in the creation of heat-resistant polymers, ceramic precursors [10] (**Figure, A**), and extraction agents [11].

Existing methods for the *ortho*-carborane synthesis typically involve the reaction of decaborane or its complexes with acetylenes under specific conditions. These methods are limited to cycloadditions of precursors like $B_{10}H_{14}$ and its complexes $B_{10}H_{12}L_2$ with acetylenes in various conditions. Essentially, these reactions can be separated into three groups: a direct reaction between *nido*-$B_{10}H_{14}$ [12, 13] or $B_{10}H_{12}L_2$-complexes [14, 15] and acetylene precursors, and several modifications of reactions of $B_{10}H_{12}L_2$-complexes, which employ the metal catalysis [16, 17] or ionic liquids [18, 19]. For all these groups of reactions, very similar conditions are suggested, namely heating in toluene under an inert atmosphere. Although it looks solid on paper, we have found that all these approaches lack reproducibility and are hardly suitable for the up-scale optimization. Addressing these challenges is crucial for opening the opportunity for wider use of carborane derivatives in both medicinal chemistry and materials science. Only increasing the availability of *ortho*-carboranes and a systematic study of their chemical behavior can transform them from "exotic" to "widely used" agents for widespread use. Considering that synthetic routes to *ortho*-carboranes are deeply constrained, there is a pressing need to develop effective, scalable methods for their preparation.

In this work, we address the challenges in the *ortho*-carborane synthesis by optimizing existing methods. We conducted a comprehensive screening by reacting *nido*-$B_{10}H_{14}$ or $B_{10}H_{12}L_2$ complexes with various acetylenes under different conditions. The use of disubstituted acetylenes consistently yielded poor results (chromatographic

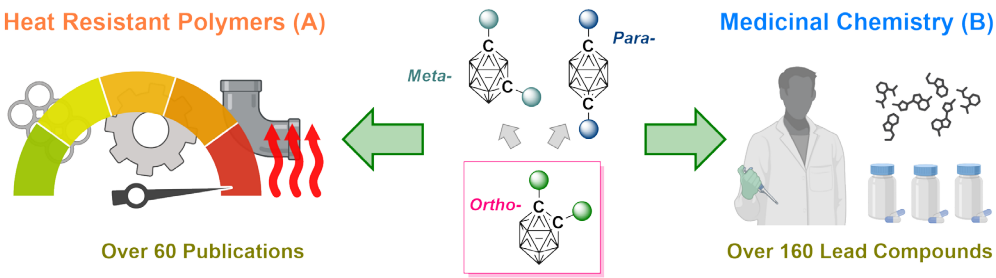


Figure. Carboranes: main fields of application

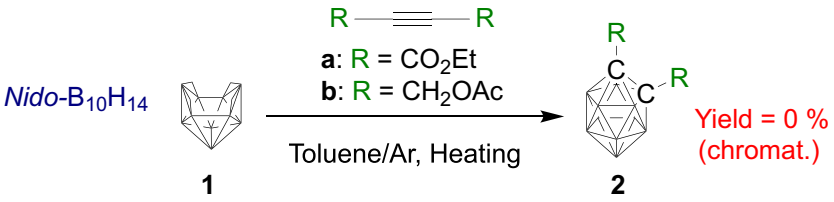
yields ≤12%), and we could not isolate the products. In contrast, employing mono-substituted acetylenes in the presence of silver salts led to significant improvements, achieving yields of approximately 90% with both donor (phenylacetylene) and acceptor (ethyl propiolate) reagents. This suggests that the key step in the silver-catalyzed reactions is the formation and addition of silver acetylenides, not the previously assumed donor-acceptor π-complexes alone [16]. Our study provides an efficient pathway for the *ortho*-carborane synthesis, facilitating their broader application in various fields.

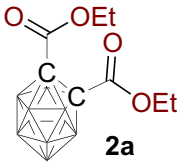
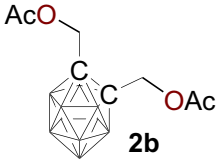
■ Results and discussion

The rigorous analysis of the literature sources showed that the direct addition of symmetrical acetylenes (starting from a bare acetylene molecule and expanding to variously substituted derivatives) to *nido*-decaborane $B_{10}H_{14}$ (**1, Table 1**) was described in the seminal [20] and several other early works [14] in good details, and offered seemingly straightforward protocols and reasonable yields. Considering that our long-term plans involved synthesizing all possible carborane isomers – the "parent" *ortho*-carborane and its thermocatalytic isomerization products [21], specifically *meta*- and *para*-carboranes – we opted for diethyl ester of acetylene dicarboxylic acid as the first-choice cycloaddition partner. *Ortho*-carborane dicarboxylic acid is not only a very convenient starting material for further derivatization (see cubane [22], cuneane [23], and stellane examples [24, 25]). It is also known to undergo isomerization to *meta*- and *para*-carborane dicarboxylic acids with good preparative yields [21]. However, our attempts to cyclize **1** with diethyl ester of acetylene dicarboxylic acid failed, resulting in only starting materials and some unidentified degradation products according to ^{1}H, ^{11}B, and ^{13}C NMR and LC/MS analysis (**Table 1**, entry 1). Repeating the experiment several times yielded similar results. This led us to assume that the strong electron-withdrawing character of diethyl ester of acetylene dicarboxylic acid was the key factor determining the outcome, despite the opposite being reported in the literature. We returned to the work where comprehensive screening of acetylene substrates was performed [15], and selected acetylene dimethoxy acetate as a new test reagent since it showed the best results (89% yield of the desired carborane **2b**) according to the paper. However, reacting this new acetylene with **1** under similar conditions led to the same outcome: no product was detected, and only starting materials with signs of degradation were found (**Table 1**, entry 2).

Further a logical step was to test the reactivity of decaborane complexes **3** ($B_{10}H_{12}L_2$) with various ligands according to the described procedures. Literature sources suggested that such complexes can be obtained *in situ* from $B_{10}H_{14}$ [15] or pre-made [26] and directly subjected to cyclization reactions. To avoid multi-parameter optimization within a single set of experiments, and lacking obviously superior options for acetylene counterparts, we used the same reagents (acetylenes with **R** = **a** and **b**) as in the previous set.

Table 1. Probing *nido*-decaborane $B_{10}H_{14}$ (**1**) in reactions with symmetrically disubstituted acetylenes



#	Reagents/Reaction Conditions	t, °C	Reaction Time, hours	Yield, LCMS, %	Expected Product
1	Substrate: **1**; Acetylene: **R = a**	110	12 h	0	 **2a**
2	Substrate: **1**; Acetylene: **R = b**	110	12 h	0	 **2b**

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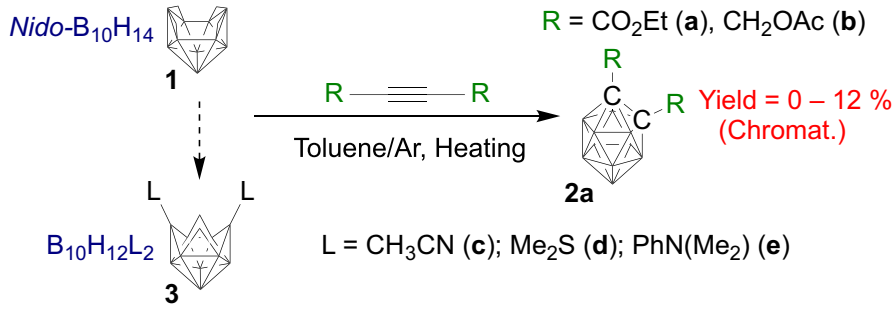
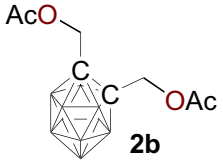
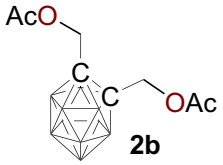
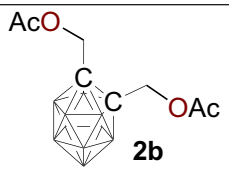
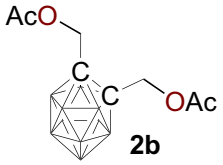
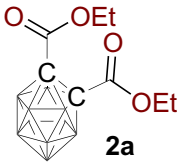
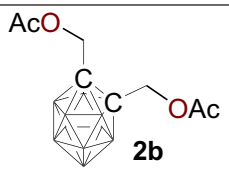
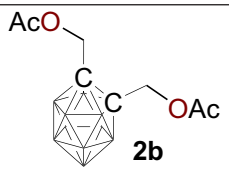
First, we investigated the methods *in situ* (**Table 2**, entries 1–4). To the toluene solution of substrate **1**, we added the ligand and acetylene **b**, then heated the mixture under vigorous reflux in an inert atmosphere for approximately 12 h. Heating acetonitrile (**c**) together with **1** and acetylene **b** [15] yielded the same results as before: the recovery of starting materials and the formation of unidentified degradation products (**Table 2**, entry 1). We then switched to a more basic ligand, dimethylaniline (**e**) [15], under similar conditions, which allowed us to detect the

Table 2. Probing the decaborane complexes $B_{10}H_{12}L_2$ (**3**) in reactions with symmetrically disubstituted acetylenes



#	Reagents/Reaction Conditions	t, °C	Reaction Time, hours	Yield, LCMS, %	Expected Product
1	Substrate: **1**; L = CH_3CN (**c**, 10 equiv., *in situ*); Acetylene: **R = b**	110	12 h	0%	 **2b**
2	Substrate: **1**; L = $PhN(CH_3)_2$ (**e**, 10 equiv., *in situ*); Acetylene: **R = b**	110	12 h	11%	 **2b**
3	1) Substrate: **1** + $PhN(CH_3)_2$ (**e**, 10 equiv., *in situ*); 2) Acetylene: **R = b**	1) 80; 2) 120	1) 2 h 2) 12 h	7%	 **2b**
4	1) Substrate*: **1** + $PhN(CH_3)_2$ (**e**, 10 equiv., *in situ*); 2) Acetylene: **R = b**	1) 80; 2) 120	1) 2 h 2) 48 h	8%	 **2b**
5	Substrate: **3c**; Acetylene: **R = a**	110	12 h	0	 **2a**
6	Substrate: **3d**; Acetylene: **R = b**	110	12 h	12%	 **2b**
7	Substrate: **3c**; Acetylene: **R = b**	110	12 h	10%	 **2b**

Note: *The Schlenk technique was used and additional all reagents and gases were subjected to additional drying according to standard protocols

target carborane **2b** using the LC/MS analysis with an 11% chromatographic yield (**Table 2**, entry 2).

Further attempts to improve this result involved implementing a two-step protocol. In the first step, decaborane **1** was heated with the ligand in toluene at 80 °C for 2 h. Then, acetylene **b** was added to the mixture, and heating was continued for an additional 12 h at 120 °C, leading to a 7% chromatographic yield of carborane **2b** (**Table 2**, entry 4). Using the Schlenk techniques and additional drying protocols for reagents, glassware, and gases did not improve the outcome, yielding 8% of **2b**.

We assumed that the low yields were due to insufficient time for forming $B_{10}H_{12}L_2$ under the given conditions and that the addition of acetylene hindered this reaction. To address this issue, we prepared samples of **3** ($B_{10}H_{12}L_2$) with the most common and reactive ligands reported in the literature (acetonitrile (**c**) and dimethylsulfide (**d**)) using standard protocols [26]. Applying this approach to both acetylenes previously tested resulted in no desired product with acetylene **a**, and similar low (chromatographic) yields of carborane **2b** with acetylene **b** when **3c** and **3d** were used as substrates (**Table 2**, entries 5–7).

These experiments demonstrate that while we could detect the formation of carborane **2b** analytically, we could not reproduce the classical methodologies of the carborane synthesis at the preparative level.

Since approaches involving the use of ionic liquids [18, 19] are impractical for scalability, we opted for metal-catalyzed cycloadditions of acetylenes to decaborane complexes $B_{10}H_{12}L_2$ (**3**), in particular reactions catalyzed by silver salts [16, 17]. The work by *Toppino et al.* [16] in 2013 suggested that π-complexes of acetylenes with silver ions were the reactive species that interacted directly with decaborane complexes to yield the desired carboranes. The following year, *El-Zaria et al.* [17] published a manuscript postulating that it was not the π-complexes, but bimetallic complexes that were the actual active species in these transformations. However, their reaction system proposed, while offering mild conditions, utilized an expensive organophosphorus silver complex as the source of soluble silver ions [17].

In this context, we decided to optimize the reaction conditions using readily available silver nitrate. As the first step in this series of tests, we reacted substrate **3c** with acetylene **b** in the presence of a catalytic amount of $AgNO_3$. Not surprisingly, this attempt (**Table 3**, entry 1) yielded results similar to the previous experiments, namely an 8% chromatographic yield of carborane **2b**. However, when we switched to monosubstituted acetylenes (entries 2 and 3, **Table 3**), we obtained the corresponding carboranes **2f** and **2g** with preparative yields of 69% and 90%, respectively. This result clearly indicates that the formation of silver acetylenides is the determining step in this reaction. These findings provide an opportunity for further optimization of reaction conditions and offer a potentially preparative approach to the synthesis of key carborane precursors suitable for further derivatization.

■ Conclusions

Our systematic study of the synthesis of *ortho*-carboranes has shown that traditional methods using disubstituted acetylenes with *nido*-$B_{10}H_{14}$ or its complexes $B_{10}H_{12}L_2$ consistently yield low amounts of the desired products (≤ 12%), which cannot be isolated. Attempts to enhance these yields through the silver salt catalysis were unsuccessful with disubstituted acetylenes.

On the contrary, the use of mono-substituted acetylenes in the presence of silver salts with $B_{10}H_{12}L_2$ where L = CH_3CN resulted in significantly higher production of *ortho*-carboranes, reaching a yield of up to 90%. This substantial improvement indicates that the formation and addition of silver acetylenides are crucial steps in the reaction mechanism, rather than the formation of donor-acceptor π-complexes as previously assumed.

This efficient and scalable method provides a practical pathway for the synthesis of *ortho*-carboranes, facilitating their potential broader application in medicinal chemistry and materials science. Our findings also offer new insights into the mechanistic aspects of the carborane formation, which could inform future research and optimization of related synthetic processes.

■ Experimental part

The solvents were purified according to the standard procedures. All starting materials were obtained from Enamine Ltd. Melting points were measured on an automated melting point system. ^1H, ^{11}B, ^{13}C, and NMR spectra were recorded on a Bruker Avance 500 spectrometer (at 500 MHz for ^1H, 160 MHz for ^{11}B, and 126 MHz for ^{13}C) and Varian Unity Plus 400 spectrometers (at 400 MHz

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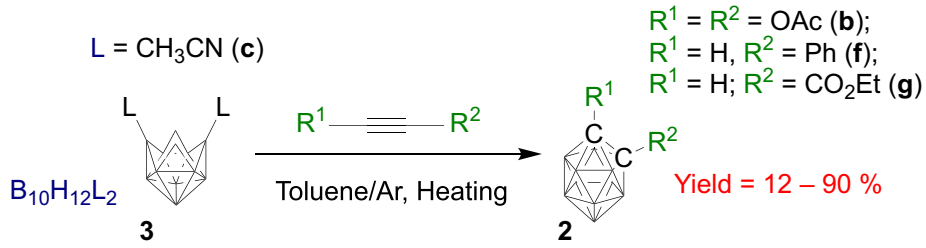
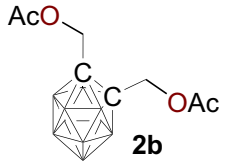
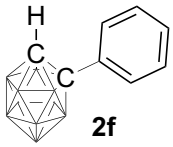
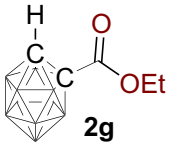
Table 3. Probing the decaborane complex $B_{10}H_{12}L_2$ (**3c**) in reactions with substituted acetylenes in the presence of silver nitrate



#	Reagents/Reaction Conditions	t, °C	Reaction Time, hours	Yield, LCMS, %	Expected Product
1	Substrate: **3c** Acetylene: **R = b** Catalyst: $AgNO_3$	110	8 h	8	 **2b**
2	Substrate: **3c** Acetylene: **R^1 = H; R^2 = Ph** Catalyst: $AgNO_3$	110	7 h	69*	 **2f**
3	Substrate: **3c** Acetylene: **R^1 = H; R^2 = COOEt** Catalyst: $AgNO_3$	110	1 h	90*	 **2g**

Note: *Preparative yields after isolating the title compound as a pure sample from the reaction mixture

for ^{1}H, 128 MHz for ^{11}B and 101 MHz for ^{13}C). Tetramethylsilane (^{1}H, ^{11}B, ^{13}C) was used as a standard. HPLC analyses were done on Agilent 1200. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (APCI)). Column chromatography was performed with silica gel (200–300 mesh).

The general protocol for reacting decaborane $B_{10}H_{14}$ (1) with acetylenes

A mixture of 1.0 equiv. of decaborane **1** ($B_{10}H_{14}$), 2.0 equiv. of acetylene (**a** or **b**), and toluene 5 L per mole of decaborane (**1**) was refluxed for 12 h under Ar atmosphere. Toluene was removed under reduced pressure, and the residue was treated with pentane to extract the product.

The general protocol for reacting decaborane $B_{10}H_{14}$ (1) with acetylenes in the presence of the nucleophilic ligand for *in situ* generating $B_{10}H_{12}L_2$ (3)

A mixture of 1.0 equiv. of decaborane **1** ($B_{10}H_{14}$), 10.0 equiv. of the ligand (L) source (L = CH_3CN (**c**); Me_2S (**d**); $PhN(Me_2)$ (**e**)), 2.0 equiv. of acetylene (**a** or **b**), and toluene 5 L per mole of decaborane (**1**) was refluxed for 12 h under Ar atmosphere. Toluene was removed under reduced pressure, and the residue was treated with pentane to extract the product.

The general protocol for reacting decaborane complexes $B_{10}H_{12}L_2$ (3) with acetylenes

A mixture of 1.0 equiv. of decaborane complex **3** ($B_{10}H_{12}L_2$) with ligands L = CH_3CN (**c**) or Me_2S (**d**), 2.0 equiv. of acetylene (**a** or **b**), and toluene 5 L per mole of the decaborane complex (**3**) was refluxed for 12 h under Ar atmosphere. The toluene was removed under reduced pressure, and the residue was treated with pentane to extract the product.

The general protocol for reacting decaborane complexes $B_{10}H_{12}L_2$ (3) with acetylenes in the presence of silver nitrate

1.0 equiv. of $B_{10}H_{12}(CH_3CN)_2$ (**3c**) and 2.0 equiv. of phenylacetylene were combined in the presence of $AgNO_3$ (7 mol%) in anhydrous toluene (1.2 L per mole of the decaborane complex (**3c**)) and heated at 100 °C for 1–8 h depending on the substrate under Ar atmosphere. After cooling the resulting mixture to room temperature and evaporating the solvent, the residue was purified via flash chromatography on silica gel.

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