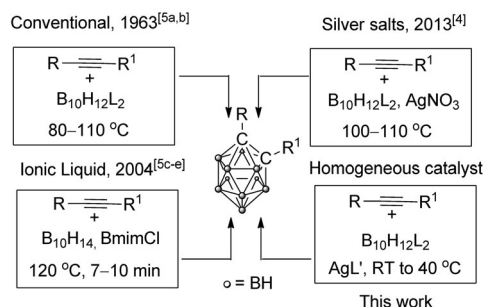


# High Yielding Synthesis of Carboranes Under Mild Reaction Conditions Using a Homogeneous Silver(I) Catalyst: Direct Evidence of a Bimetallic Intermediate\*\*

Mohamed E. El-Zaria, Kunal Keskar, Afaf R. Genady, Joseph A. Ioppolo, James McNulty, and John F. Valliant\*

**Abstract:** Methods used to prepare functionalized carboranes generally require heating to high temperatures, and thus limits the range of derivatives which can be prepared directly from alkynes. We show here that by using a homogeneous silver(I) catalyst it is now possible to prepare carboranes in good to excellent yield at temperatures below 40 °C, including at room temperature. The process is general and provides an important new synthetic strategy for the preparation of functionalized boron clusters.

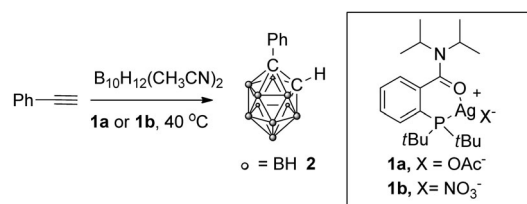
Carboranes are undergoing a renaissance because of their unique structural and electronic properties,<sup>[1]</sup> and potential use in creating new diagnostics, therapeutics, and electronically tunable materials.<sup>[2,3]</sup> A longstanding issue when preparing carboranes is that reactions generally require heating between 80–120 °C to achieve adequate yields and thus limits the range of functionalized derivatives which can be prepared directly from the corresponding alkynes (Figure 1).<sup>[5]</sup>



**Figure 1.** Summary of the main methods used to prepare 1,2-dicarba-closo-dodecaboranes from substituted alkynes. L = CH<sub>3</sub>CN, L' = N,N-diisopropyl-(2-di-*tert*-butylphosphanyl)benzamide.

Recently our group reported that the addition of catalytic silver nitrate to reactions involving alkynes and B<sub>10</sub>H<sub>12</sub>-(CH<sub>3</sub>CN)<sub>2</sub> significantly enhances the yield of carborane formation.<sup>[4]</sup> In the presence of silver(I) salts there is evidence of carborane formation at room temperature, however, to achieve high yields and to solubilize the catalyst, reactions had to be performed at temperatures of greater than 100 °C. We hypothesized that an appropriate homogeneous silver(I) catalyst would similarly increase the yield of cluster formation while reducing the temperature required to promote carborane formation, thus creating a milder alternative to existing synthetic methods.

McNulty and co-workers recently reported the preparation of *N,N*-dialkyl(2-dialkylphosphanyl)benzamide ligands which form crystalline complexes with silver(I). The silver complexes have been shown to act as mild  $\pi$  acids, thus effectively promoting the cycloaddition of azides onto terminal alkynes and intramolecular hydroamination reactions.<sup>[6]</sup> The catalysts are stable, well-defined nonsolvated materials, and soluble in most organic solvents, thus making them attractive homogeneous alternatives to AgNO<sub>3</sub> for potentially promoting the formation of carboranes. A preliminary screening study using phenyl acetylene, B<sub>10</sub>H<sub>12</sub>-(CH<sub>3</sub>CN)<sub>2</sub>, and the catalysts **1a** and **1b**, which differ in the nature of the counter anion, was undertaken (Scheme 1). For



**Scheme 1.** Preliminary screening reaction for catalysts **1a** and **1b**.

the initial studies, reactions were performed in toluene and the temperature was held constant at 40 °C to minimize the overall reaction times prior to attempting reactions at room temperature. Of the factors investigated, the ratio of reactants had the largest impact on yield where the optimal condition was a twofold excess of the alkyne to B<sub>10</sub>H<sub>12</sub>-(CH<sub>3</sub>CN)<sub>2</sub>. With respect to the amount of catalyst, a small increase in yield was observed when 10 mol % of catalyst was employed instead of 5 mol % (70 versus 65 % yield, respectively), whereas the yield decreased to 55 % when 20 mol % catalyst was

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employed. Varying the nature of the catalyst between the acetate in **1a** and nitrate in **1b** had little impact on the yield.

The general utility of the catalyst under the most promising conditions was evaluated subsequently by using **1b** and a series of different alkynes for direct comparison to reactions performed in the absence of catalyst (Table 1). In all cases yields of the isolated products are reported. For phenylacetylene the desired carborane formed in 85 % yield after 48 hours at 40 °C. The yield under identical reaction

within eight hours whereas the catalyst-free reaction was only 15 % after 24 hours.

When repeated at room temperature, the yields of the catalyzed reactions were below 50 % after six hours for all compounds tested. However after 48 hours (Table 1) five of the alkynes tested generated carboranes in greater than 70 % yield, with the exception of phenylcarborane, diphenylcarborane, and the phthalimide-protected carborane which were isolated in 58, 37, and 61 % yield respectively. When the control reactions were run in the absence of the catalyst, yields of the products at room temperature were negligible (<2 %). In general, at room temperature the catalyzed reactions showed the largest increase in yield during the first 48 hours. Further extension the reaction times lead to smaller increases in the amount of product produced.

When AgNO<sub>3</sub> is added quickly to large quantities of alkynes the reactions can, in some instances, ignite. Caution should therefore be taken when combining alkynes with silver salts and particular attention paid to the order of addition of reagents. A key advantage of using **1b** is that there was no evidence that the catalyst and alkyne reacted vigorously, including when reactions are done at a larger scale. For instance, when a 10-fold increase in reaction scale was run using 5-chloropentyne and **1b** the desired carborane was readily isolated in 75 % yield after 48 hours at room temperature without issue. One additional advantage of using the homogeneous catalyst as opposed to AgNO<sub>3</sub> is that at the completion of a reaction there was no evidence of silver metal deposition, owing to the robust nature of the metal complex.<sup>[6]</sup> In certain instances reactions did become heterogeneous, however the desired products could be readily isolated by filtration through Celite and simple silica gel chromatography. To test the residual activity of the catalyst, after an initial reaction period an additional aliquot of the borane and propargyl bromide was added and the yield was 80 %. A third cycle produced the carborane in 82 % yield, thus demonstrating that the catalyst remains active.

The ability to perform reactions at significantly reduced temperatures creates opportunities to prepare carboranes from thermally sensitive alkynes which would degrade or undergo unwanted side reactions if subjected to the conventional synthetic methods shown in Figure 1. For example, the *tert*-butyl ester of propiolic acid (**3**, Scheme 2) cannot be converted into a carborane directly because at elevated temperatures the product undergoes thermolysis with rapid loss of CO<sub>2</sub> and isobutene to generate *ortho*-carborane.<sup>[8]</sup> With the homogeneous catalyst, the compound **4** was produced in high yield (86 %) at 40 °C where a crystal structure of the *closo*-carborane was obtained by recrystallization from hexanes (Scheme 2).

2-Ethynylpyridine (**5**) is a similarly difficult starting material from which to prepare carboranes. Several attempts have been made to optimize the yield, which is typically 30 %, of 1-(2'-pyridyl)-1,2-dicarba-*closo*-dodecaborane.<sup>[9]</sup> One method produced the product in 45 % yield but required the use of a solvent-free thermolysis procedure at 100 °C in a sealed tube.<sup>[10]</sup> At 40 °C and room temperature in the presence of **1b** the desired product **6** was isolated in 88 and 63 % yield, respectively (Scheme 3). By using a lower reaction

**Table 1:** Compounds, reaction conditions, and yields for catalyzed and uncatalyzed reactions.

$$\text{R}-\text{C}\equiv\text{C}-\text{R}' \xrightarrow[\text{1b, toluene}]{\text{B}_{10}\text{H}_{12}(\text{CH}_3\text{CN})_2} \text{Carborane}$$

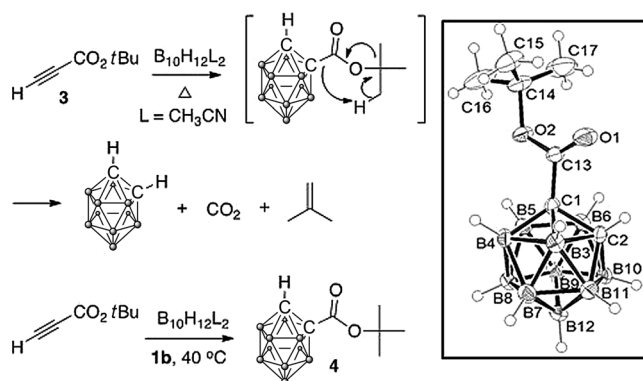
Entry	R	R'	no catalyst <sup>[a]</sup> 40 °C	Yield [%] catalyst <sup>[b]</sup> 40 °C (t [h])	catalyst <sup>[c]</sup> RT
1	Ph	H	34 ± 2.1	85 ± 2.0 (48)	58 ± 1.5
2	CH <sub>2</sub> Br	H	22 ± 2.0	87 ± 2.0 (2)	71 ± 1.5
3	CH <sub>2</sub> OH	H	22 ± 0.6	86 ± 3.0 (2)	72 ± 1.5
4	C <sub>3</sub> H <sub>6</sub> CN	H	19 ± 1.5	87 ± 2.1 (2)	73 ± 2.1
5	C <sub>3</sub> H <sub>6</sub> Cl	H	20 ± 0.6	86 ± 2.5 (2)	70 ± 2.1
6	R <sup>2</sup> CO <sub>2</sub> Me <sup>[d]</sup>	H	17 ± 1.5	93 ± 2.1 (8)	74 ± 1.0
7	PhtNCH <sub>2</sub>	H	15 ± 0.6	86 ± 2.5 (2)	61 ± 1.2
8	Ph	Ph	15 ± 2.0	73 ± 1.5 (8)	37 ± 2.1

[a] Uncatalyzed reaction (*n* = 3); reaction time = 48 h for entry 1 and 24 h for all other entries. [b] Catalyzed reaction (*n* = 3) at 40 °C. [c] Catalyzed reaction (*n* = 3) at room temperature for 48 h (all entries). Yields of uncatalyzed reactions at room temperature were <2 %.

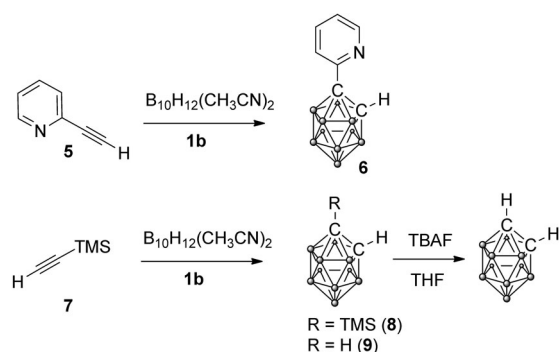
[d] R<sup>2</sup>CO<sub>2</sub>Me = methyl 4,7,10,13,16,19,22,25,28-nonaaxahentriacont-30-yn-1-oate. Pht = phthalimide. Additional details and results can be found in the Supporting Information. *n* = number of repeats.

conditions for the noncatalyzed reaction was 34 %. Propargyl bromide and alcohol (entries 2 and 3) were converted into the corresponding carboranes in 87 and 86 % yield, respectively, after only two hours at 40 °C. The yields in the absence of catalyst after 24 hours were 22 % in both cases. The catalyst worked equally well for 5-hexynenitrile and 5-chloropentyne, thus producing the functionalized carboranes (entries 4 and 5) in 87 and 86 % yields, respectively, which was over four times the yield observed in the absence of the catalyst. The catalyst also increased the yield of carboranes bearing a bifunctional PEG linker (entry 6), which is often used in bioconjugate chemistry as a spacer between targeting vectors and lipophilic prosthetic groups like carboranes.<sup>[7]</sup> The desired PEG-carborane was isolated in over 90 % yield after eight hours.

The catalyst was also effective for alkynes which in our hands gave low and/or variable yields of carboranes when using conventional methods. The phthalimide (Table 1, entry 7) for instance was isolated in 86 % yield where the yield of the catalyst-free control experiment was only 15 %. Internal alkynes are also known to undergo low-yielding reactions with B<sub>10</sub>H<sub>12</sub>(CH<sub>3</sub>CN)<sub>2</sub>. The silver(I) catalyst was successful in producing 1,2-diphenylcarborane in 73 % yield



**Scheme 2.** Reaction of *tert*-butyl propiolate with  $B_{10}H_{12}(CH_3CN)_2$  under thermal and catalyzed reaction conditions and the single-crystal X-ray structure of **4**. Thermal ellipsoids are shown at 50% probability.<sup>[16]</sup>



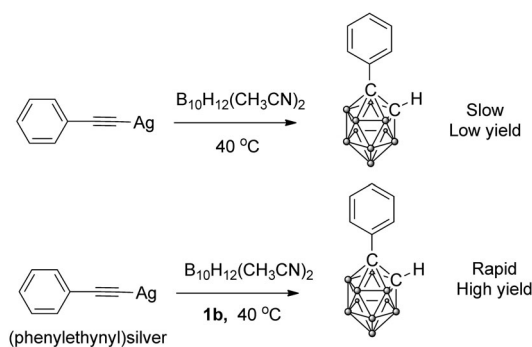
**Scheme 3.** Synthesis of carboranes **6** and **9**. TBAF = tetra-*n*-butylammonium fluoride, THF = tetrahydrofuran.

temperature there was significant reduction in the number of observed side products compared to the uncatalyzed reaction, and it greatly facilitated isolation of **6**.

The preparation of *ortho*-carborane is nontrivial and is typically done using a hazardous procedure involving gaseous acetylene heated to 90 °C over 24 hours.<sup>[5b]</sup> Other methods have been reported and involve heating functionalized carboranes with permanganate or decarboxylation of esters.<sup>[8,11]</sup> One alternative and potentially safer route is one using trimethylsilylacetylene (**7**; bp = 53 °C), which is readily available and easy to handle. Unfortunately conventional reaction conditions do not generate the corresponding carborane from this particular alkyne. When the reaction was performed in the presence of **1b**, trimethylsilyl-*ortho*-carborane (**8**; 47%) and *ortho*-carborane (**9**; 45%) were isolated at 40 °C. Treatment of **8** with TBAF<sup>[12]</sup> at low temperature generated the desired product in high yield, thus providing a convenient and safe method for producing *ortho*-carborane (Scheme 3). The compound **8** is also a useful starting material for preparing monofunctionalized boron cluster compounds.<sup>[13]</sup>

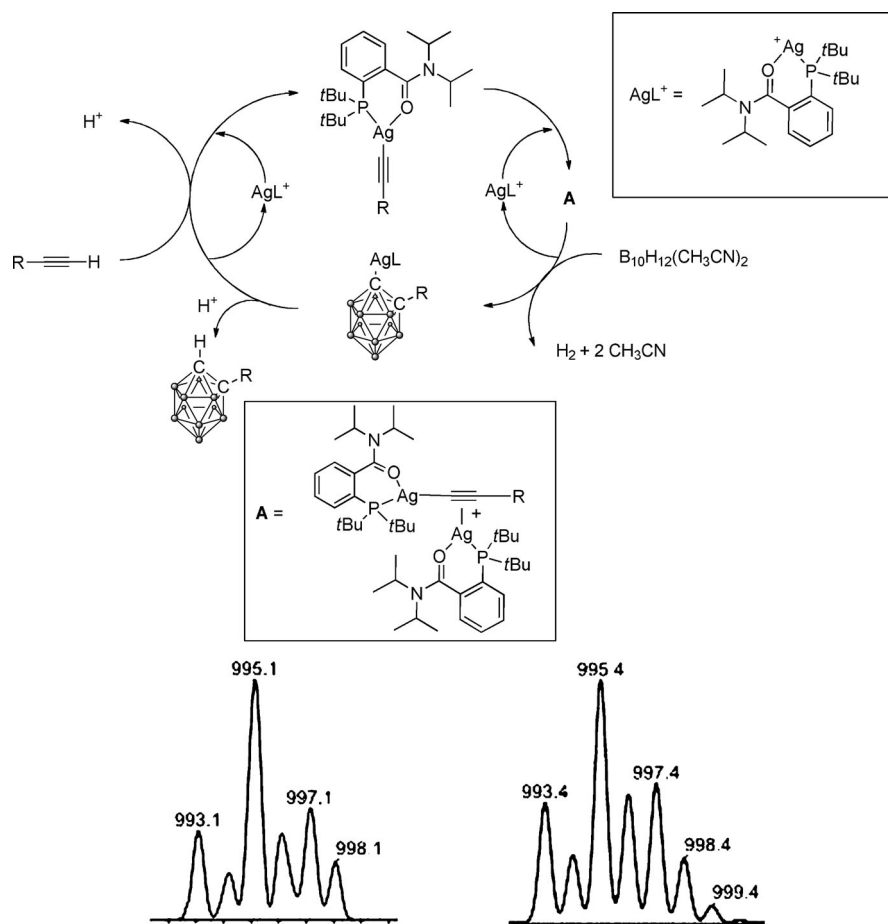
In terms of the mechanism, for terminal alkynes the current hypothesis is that the labile amide group in **1b** is replaced by the alkyne, thus forming an intermediate  $\pi$  complex which ultimately forms the  $\sigma$ -bonded silver acetylide.<sup>[14]</sup> For catalysis by  $AgNO_3$ , which we reported

previously, the proposed mechanism likely involves formation of a comparable intermediate. The coordination to silver decreases the Lewis basicity of the alkyne, thereby preventing unwanted hydroboration and related alkyne degradation pathways, while also lowering the activation energy barrier to carborane formation.<sup>[4]</sup> To test the proposed mechanism, silver phenylacetylide was combined with  $B_{10}H_{12}(CH_3CN)_2$ , and should, according to the proposed mechanism, generate the desired product in comparable yield and time to that for the silver catalyzed reaction with phenylacetylene. Somewhat surprisingly the reaction (Scheme 4) was sluggish and required 48 hours to generate the desired product, which was isolated in a lower than expected yield both at room temperature (21 %) and 40 °C (55 %).



**Scheme 4.** Reaction of silver phenylacetylide with  $B_{10}H_{12}(CH_3CN)_2$  in the presence and absence of a silver(I) catalyst.

When silver phenylacetylide was combined with  $B_{10}H_{12}(CH_3CN)_2$  and catalyst **1b** the reaction proceeded much more rapidly and there was clear evidence of product formation after two hours at 40 °C. After 48 hours the yield exceeded 80 %. These yields and rates were comparable to head-to-head reactions run using phenylacetylene in the presence of the catalyst. The same trend was observed when **1b** was replaced with  $AgNO_3$ , although the yields were lower since the latter catalyst requires higher temperatures than does **1b**. These results suggest that the reaction mechanism may involve a bimetallic species (Figure 2) comparable to the mechanism recently proposed for copper(I)-catalyzed Huisgen cycloaddition reaction uncovered using elegant crossover experiments with an isotopically enriched copper source.<sup>[15]</sup> In support of the proposed mechanism, we were able to obtain direct evidence for the formation of a bimetallic complex. A mass spectrum of 1-hexyne in the presence of **1b** exhibited peaks corresponding to the bimetallic complex **A** (Figure 2) with the molecular formula  $C_{48}H_{81}N_2P_2O_2Ag_2$ , displaying the expected isotopic distribution pattern ( $m/z$  993 to 998) associated with the natural isotopic abundance of silver ( $^{107}Ag$ ,  $^{109}Ag$ ) and other relevant ( $^{12}C$ / $^{13}C$ ) isotopes (Figure 2). This mechanism also offers an explanation as to why for internal alkynes, which cannot form the  $\sigma$ -Ag-alkyne complex, the observed yield enhancement is not as significant as for terminal alkynes and that significantly longer reaction times are needed.



**Figure 2.** Proposed catalytic cycle involving a bimetallic intermediate (A). Bottom: the actual (left) and calculated (right) MS spectra corresponding to the bimetallic intermediate A. MS spectra with a wider  $m/z$  range are provided in the Supporting Information.

A preliminary kinetic study of the reaction of **1b**, propargyl bromide, and  $B_{10}H_{12}(CH_3CN)_2$  using  $^1H$  NMR spectroscopy showed that there is an initial induction period where product formation is slow (see the Supporting Information). After roughly 60 minutes the rate increases dramatically where the delay may be associated with the time required to form the bimetallic intermediate. MS experiments support this and show that the bimetallic species is the dominant peak in the mass spectrum after 60 minutes.  $^{31}P$  NMR spectroscopy shows no evidence of free ligand and also indicates the formation of a new species after an hour. Additional kinetic, multi-NMR, and theoretical studies are currently underway to study the reaction pathway in greater detail. In the meantime **1b**, which can be synthesized in a minimal number of steps in high yield,<sup>[6]</sup> can be used to prepare carboranes using substantially reduced temperatures, thus offering a new avenue for preparing novel boron-based materials.

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- [16] CCDC 975845 (**4**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).