

Transition-Metal-Mediated Three-Component Cascade Cyclization: Selective Cage B–C(sp²) Coupling of Carborane with Aromatics and Synthesis of Carborane-Fused Tricyclics

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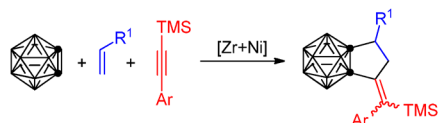
S Supporting Information

ABSTRACT: Zirconium/nickel mediated one-pot three-component cascade cyclization of carborane, alkene, and 2-bromophenyltrimethylsilylacetylene has been achieved, leading to the formation of a series of C,C,B-substituted carborane-fused tricyclics. On the basis of experimental results, a plausible mechanism is proposed including [2 + 2 + 1] cross-cyclotrimerization followed by intramolecular direct selective cage B–C(sp²) coupling. This represents the first example of direct cage B–C(phenyl) coupling via cage B–H activation.

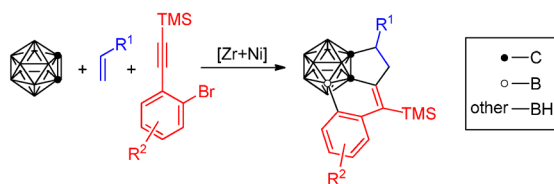
Carboranes are a class of structurally unique molecules with exceptionally thermal and chemical stabilities and the

Scheme 1. Transition-Metal Co-Mediated Three-Component Cyclization

previous work

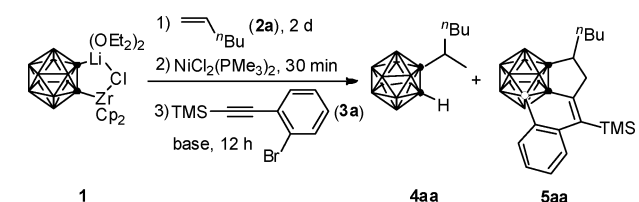


this work



ability to hold various substituents. These properties have made them as useful basic units in boron neutron capture therapy agents,¹ in supramolecular design/materials,² and in coordination/organometallic chemistry.³ Thus, the functionalization of carboranes has received growing interest.⁴ Generally, electrophilic substitution at cage BH vertices⁵ and capitation reaction of nido-C₂B₉H₁₁²⁻ with boron halides⁶ are two common synthetic methods for direct cage boron derivatization. Examples of transition-metal-mediated hydroboration of *o*-carboranes with alkynes via cage B–H activation are also known.⁷ However, how to achieve selective functionalization of

Table 1. Optimization of Reaction Conditions^a



entry	base	solvent	T (°C)	yield (%) ^b (4aa/5aa)
1	–	toluene	rt	15/73
2	–	toluene	60	5/79
3	–	toluene	110	5/79
4	–	THF	rt	13/73
5	Cs ₂ CO ₃	toluene	rt	7/80
6	LiN(TMS) ₂	toluene	rt	5/80
7	NEt ₃	toluene	rt	7/78
8	pyridine	toluene	rt	88/0

^aReaction conditions: **1** (0.05 mmol), **2a** (0.15 mmol), NiCl₂(PMe₃)₂ (0.05 mmol), **3a** (0.15 mmol), and base (0.1 mmol). ^bGC yields.

a BH vertex of carboranes is still a rather challenging subject, and direct coupling of a cage B with phenyl sp²-C via B–H activation has remained elusive.⁸

In view of the spectacular role of transition metals in chemical transformations, we are interested in developing transition-metal-mediated multicomponent reactions to construct complex molecules from readily available simple precursors in a single operation. To this end, we have developed transition-metal-promoted/-catalyzed [2 + 2 + 2] cycloaddition reactions for the preparation of benzocarboranes⁹ and dihydrobenzocarboranes.¹⁰ Very recently, our group has reported a Zr/Ni mediated three-component [2 + 2 + 1] cross-cyclotrimerization of carborane, alkene, and trimethylsilylacetylene for the synthesis of dihydrofulvenocarboranes.¹¹ During the course of this study, an unprecedented C,C,B-substituted carborane-fused tricyclic **5aa** was isolated from the reaction of C_p₂Zr(μ-Cl)(μ-C₂B₁₀H₁₀)Li(OEt₂)₂ (**1**), 1-hexene (**2a**), and 2-bromophenyltrimethylsilylacetylene (**3a**) in the presence of NiCl₂(PMe₃)₂ (Table 1). Compound **5aa** may

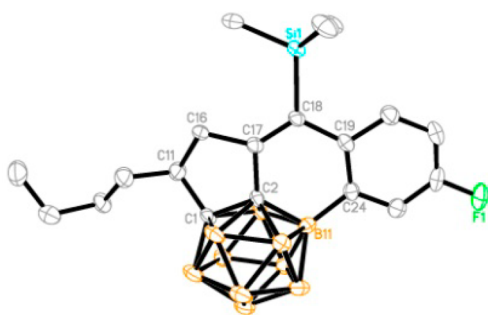
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Table 2. Synthesis of C,C,B-Substituted Carborane-Fused Tricyclics^a

entry	R ¹ (2)	Br (3)	yield % ^b (5)	entry	R ¹ (2)	Br (3)	yield % ^b (5)
1	ⁿ Bu (2a)		68 (5aa)	10	ⁿ Bu (2a)		55 (5aj)
2	ⁿ Bu (2a)		68 (5ab)	11	H (2b)		15 (5ba)
3	ⁿ Bu (2a)		65 (5ac)	12	PhCH ₂ (2c)		70 (5ca)
4	ⁿ Bu (2a)		66 (5ad)	13	CH ₃ SCH ₂ (2d)		55 ^c (5da)
5	ⁿ Bu (2a)		66 (5ae)	14	ⁱ Bu (2e)		62 (5ea)
6	ⁿ Bu (2a)		64 (5af)	15	CH ₃ OCH ₂ (2f)		52 ^c (5fa)
7	ⁿ Bu (2a)		68 (5ag)	16	(CH ₃) ₂ NCH ₂ (2g)		40 ^c (5ga)
8	ⁿ Bu (2a)		58 (5ah)	17	4-FC ₆ H ₄ CH ₂ (2h)		71 (5ha)
9	ⁿ Bu (2a)		62 (5ai)	18	4-CH ₃ C ₆ H ₄ CH ₂ (2i)		72 (5ia)

^aReaction conditions: **1** (0.5 mmol), **2** (1.5 mmol), NiCl₂(PMe₃)₂ (0.5 mmol), **3** (1.5 mmol), and Cs₂CO₃ (1.0 mmol). ^bIsolated yields. ^cReaction was heated at 60 °C.

Figure 1. Molecular structure of **5ab**.

result from a three-component [2 + 2 + 1] cross-cyclotrimerization of carborane, alkene, and alkyne,¹¹ followed by nickel(0) mediated cage B–C(sp²) coupling via direct B–H activation (Scheme 1). This finding intrigues us to investigate such a brand new three-component cascade reaction, and the results are reported here.

On the basis of the optimal reaction condition for the synthesis of dihydrofulvenocarboranes,¹¹ we screened various reaction conditions for the above multicomponent cascade reaction. The results were summarized in Table 1. Reaction temperatures had little effect on the formation of **5aa** (entries 1–3, Table 1). Addition of bases could neutralize the hydrogen bromide generated from the reaction to minimize the formation of **4aa**, resulting in the increased yields of **5aa** (entries 5–7 vs 1,

Scheme 2. Proposed Reaction Mechanism

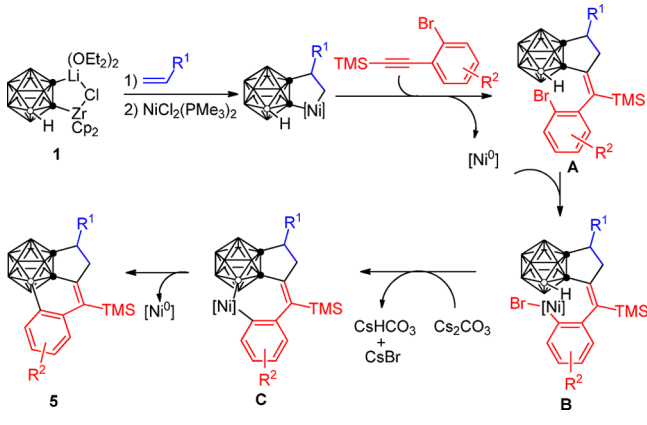


Table 1). On the other hand, no **5aa** was observed if pyridine was used as the base, probably owing to the coordination of pyridine to nickel center prohibiting the further reaction (entry 8, Table 1). In view of the yield of **5aa**, reaction temperature, and easy work-up procedures, entry 5 in Table 1 was chosen as the optimal reaction condition.

A variety of 2-bromophenyltrimethylsilylacetylene was examined under the above optimal reaction condition, and the results were compiled in Table 2. Electron-withdrawing groups on phenyl ring generally offered higher yields of **5** than those of electron-donating substituents (entries 2–7 vs 8–10, Table 2). Effects of R^1 on reaction results were also examined. For substituents containing a heteroatom such as $-\text{CH}_2\text{SMe}$, $-\text{CH}_2\text{OMe}$, and $-\text{CH}_2\text{NMe}_2$, products **5da**, **5fa**, and **5ga** were isolated in relatively lower yields, probably owing to the interactions of the heteroatom with the metal center (entries 13, 15, and 16, Table 2). On the other hand, if $R^1 = \text{benzyl}$ groups, the corresponding products **5ca**, **5ha**, and **5ia** were obtained in higher yields (entries 12, 17, and 18, Table 2). It was noted that one pair of diastereoisomers was observed for **5** except for **5ba**, which was generated by the chiral carbon bonded to R^1 and cage boron substituent at either 7- or 11-position (see Scheme S1). The dr ratios were about 1:1 as determined by ^1H NMR spectra of the crude products. Replacement of R^1 by H resulted in the loss of the chirality, preventing the formation of diastereoisomers and facilitating the characterization of the product (entry 11, Table 2). The low yield of **5ba** might be ascribed to the poor reaction efficiency of **1** with ethylene.¹² When TMS was substituted by ^tBu , only $[2 + 2 + 2]$ cross-cyclotrimerization products dihydrobenzocarboranes were isolated without the observation of B–H activation species, suggesting the importance of TMS group in this reaction.¹¹

Compounds **5** were fully characterized by ^1H , ^{13}C , and ^{11}B NMR spectroscopy as well as high-resolution mass spectrometry. The molecular structures of **5aa**, **5ab**, **5ai**, and **5ba** were further confirmed by single-crystal X-ray analyses, and the representative structure of **5ab** is shown in Figure 1.

We have previously proposed a reaction mechanism for the formation of dihydrofulvenocarboranes (**A** in Scheme 2) via transition-metal-mediated $[2 + 2 + 1]$ cross-cyclotrimerization of *o*-carboryne, alkene, and trimethylsilylalkyne, in which the alkyne acts as a one-carbon component.¹¹ We attempted to isolate **A** by quenching the reaction of entry 1 in Table 2. However, the corresponding **A** was not observed by GC-MS. Instead, a trace amount of debrominated species of **A**, 1,2-

$[\text{CH}(^t\text{Bu})\text{CH}_2\text{C}=\text{C}(\text{TMS})\text{Ph}]$ -1,2- $\text{C}_2\text{B}_{10}\text{H}_{10}$, was identified by GC-MS using an authenticated sample.¹¹ The observed products ratios of the above quenching experiments were **4aa**:**5aa** = 70:30 after 4 h and 32:68 after 8 h. These results implied that the intramolecular cage B–C(sp^2) coupling in this system was very efficient. Since **A** could not be trapped, a model compound 1-(*cis*- $\text{CH}=\text{CH}-\text{C}_6\text{H}_4-\text{o}-\text{Br}$)-1,2- $\text{C}_2\text{B}_{10}\text{H}_{11}$ (**A'**) was used in place of **A** to confirm the Ni(0)-mediated cage B–C(sp^2) coupling. Indeed, in situ generated Ni(0), from the reaction of $\text{NiCl}_2(\text{PMe}_3)_2$ with 2 equiv of $^t\text{BuLi}$ in THF, can promote the cage B–C(sp^2) coupling to give two regioisomers 1,3-($\text{CH}=\text{CH}-\text{o}-\text{C}_6\text{H}_4$)-1,2- $\text{C}_2\text{B}_{10}\text{H}_{10}$ and 1,4-($\text{CH}=\text{CH}-\text{o}-\text{C}_6\text{H}_4$)-1,2- $\text{C}_2\text{B}_{10}\text{H}_{10}$ in 20% and 30% isolated yields, respectively (see SI). On the basis of previous work¹¹ and aforementioned experimental data, a plausible mechanism is suggested in Scheme 2. Zr/Ni comediated $[2 + 2 + 1]$ cross-cyclotrimerization of *o*-carboryne, alkene, and trimethylsilylalkyne generates the key intermediate **A**.¹¹ Oxidative addition of C(sp^2)-Br bond on in situ generated Ni(0)¹³ forms the intermediate **B**. Intramolecular electrophilic substitution on B–H at the 7- or 11-position,^{5,14} followed by removal of HBr by base, produces intermediate **C**.¹⁵ Reductive elimination affords the final product **5**. This could be viewed as a Ni(0) promoted intramolecular direct selective cage B–C(sp^2) coupling via B–H activation.

In summary, we have developed a novel three-component cascade reaction of carboryne, alkene, and 2-bromophenyltrimethylsilylacetylene for the preparation of a series of C,C,B-substituted carborane-fused tricyclics through direct B–H activation. This represents the first example of direct cage B–C(phenyl) coupling, which may shed some light on developing methodologies for direct selective cage B–C(sp^2) coupling for the preparation of carborane functionalized aromatics.

■ ASSOCIATED CONTENT

📄 Supporting Information

Detailed experimental procedures, complete characterization data, and X-ray data in CIF format for **5aa**, **5ab**, **5ai** and **5ba**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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