Three-Component [2+2+2] Cycloaddition of Carboryne, Unactivated Alkene, and Alkyne via Zirconacyclopentane Mediated by Nickel: One-Pot Synthesis of Dihydrobenzocarboranes**

Shikuo Ren, Zaozao Qiu, and Zuowei Xie*

Transition-metal-mediated cycloaddition of alkynes and/or alkenes serves as a powerful strategy to construct a wide range of compounds, since complexation of the metal center to an olefin or alkyne significantly modifies the reactivity of this moiety.[1] A variety of transition-metal complexes can catalyze this type of reactions.[2] This catalysis is an attractive approach, but it remains a major challenge to achieve selectivity among different alkenes or alkynes. Therefore, the development of new systems that display both high reactivity and predictable selectivity is essential to increase the efficiency with which complex molecular architectures can be assembled. Carboryne (1,2-dehydro-*o*-carborane) can be viewed as a three-dimensional relative of benzyne.[3] In the presence of a nickel complex, carboryne can undergo, in a controlled manner, coupling reaction with alkenes to generate alkenyl carboranes,[4] two-component [2+2+2] cycloaddition with two equivalents of alkynes to afford benzocarboranes,[5] and three-component [2+2+2] cyclotrimerization with activated alkene and alkyne to give dihydrobenzocarboranes.[6] In the latter case, activated alkenes such as methyl acrylate and 2-vinylpyridine must be employed, because they are more reactive than alkynes in the system and the donor atom of the olefin can stabilize the intermediate by intramolecular coordination, thereby preventing the β-H elimination and making the subsequent alkyne insertion possible to realize the three-component cycloaddition. However, attempts to achieve nickel-mediated selective cycloaddition of carboryne with unactivated alkene and alkyne have not been successful to date but gave a mixture of alkenyl carboranes and benzocarboranes.

Our previous work shows that the nature of transition metals dominates the reactivity pattern of the corresponding metallacycles.[7] For example, nickelacyclopentene incorporating a carboranyl moiety is a reactive intermediate toward alkynes,[5,8] whereas the zirconacyclopentene analogue is inert.[9] We have recently found that the zirconacyclopentane

[*] Dr. S. Ren, Dr. Z. Qiu, Prof. Dr. Z. Xie
Department of Chemistry and State Key Laboratory on Synthetic Chemistry
The Chinese University of Hong Kong
Shatin, N.T., Hong Kong (China)
E-mail: zxie@cuhk.edu.hk

incorporating a carboranyl unit is also very thermally stable and inert toward alkenes and alkynes, which is significantly different from those zirconacyclopentanes without carboranyl groups.[10] In view of literature work on transmetalation from zirconacycles to nickel,[11] we wondered whether the resultant nickelacyclopentane generated through transmetalation from the corresponding zirconacyclopentane would be active toward alkyne insertion. Such an approach may lead to one-pot synthesis of dihydrobenzocarboranes through an equivalent of a three-component [2+2+2] cycloaddition of carboryne, unactivated alkene, and alkyne. The results are reported herein.

Zirconacyclopentanes [1,2-{Cp$_2$ZrCH$_2$CH(nBu)}-1,2-C$_2$B$_{10}$H$_{10}$] (**1a**; Cp = C$_5$H$_5$) and [1,2-{Cp$_2$ZrCH(Ph)CH$_2$}-1,2-C$_2$B$_{10}$H$_{10}$] (**1b**) were prepared by treatment of [Cp$_2$Zr(μ-Cl)(μ-C$_2$B$_{10}$H$_{10}$)Li(OEt$_2$)$_2$][12] with one equivalent of 1-hexene or styrene in toluene heated to reflux and isolated in more than 87% yield (Scheme 1). The reversed insertion regioselectivity can be rationalized by electronic effects of the substituents on the alkenes.[13] They are very thermally stable
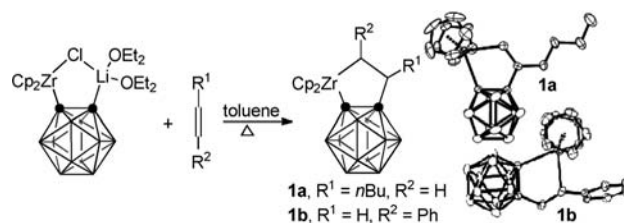
Scheme 1. Preparation of zirconacyclopentanes (left). Crystal structures of **1a** and **1b** (right).

and inert toward alkynes even at reflux in toluene for several days, whereas the corresponding nickelacyclopentanes are thermally unstable, leading to the formation of alkenyl carboranes through β-H elimination upon heating in the absence of other substrates.[4] Addition of nickel(II) to the zirconacyclopentanes **1** can effectively promote the further insertion of alkynes to form dihydrobenzocarboranes. Only trace amount of β-H elimination product was observed in the reaction of **1a**. The optimization of reaction conditions for the reaction of **1a** with PhC≡CnBu (**2g**) is summarized in Table 1. A variety of Ni^{II} species were examined for this reaction. No detectable product was observed in the presence of one equivalent NiCl$_2$ at 90°C in toluene owing to the poor solubility of NiCl$_2$ (Table 1, entry 1). An increase of the reaction temperature to 110°C resulted in a low yield of

Table 1: Optimization of reaction conditions.[a]

Entry	[Ni][b]	T [°C]	Solvent	3g:3g'	Yield [%][c]
1	NiCl$_2$	90	toluene	–	0
2	NiCl$_2$	110	toluene	78:22	22
3	NiCl$_2$	90	THF	90:10	95
4	NiCl$_2$	110	THF	90:10	95
5	NiCl$_2$	90	DME	84:16	90
6	[NiCl$_2$(PMe$_3$)$_2$]	110	toluene	64:34	91
7	[NiCl$_2$(PMe$_3$)$_2$]	110	THF	60:40	93
8	[NiCl$_2$(PMe$_3$)$_2$]	110	DME	62:38	93
9	[NiCl$_2$(PPh$_3$)$_2$]	110	toluene	39:61	96
10	[NiCl$_2$(dppe)]	110	toluene	51:49	94
11	[NiCl$_2$(dppp)]	110	toluene	60:40	91

[a] Conditions: **1a** (0.02 mmol), **2g** (0.07 mmol), and [Ni] (0.02 mmol) in the solvent (0.6 mL). [b] dppe = 1,2-bis(diphenylphosphino)ethane; dppp = 1,3-bis(diphenylphosphino)propane. [c] Yields determined by GC–MS. DME = 1,2-dimethoxyethane.

Table 2: Preparation of dihydrobenzocarboranes.[a]

Entry	1	2, R^3/R^4	Product 3/3'	3:3'[b]	Yield of 3:3' [%][g]
1	1a	2a, Et/Et	3a	–	83
2	1a	2b, nPr/nPr	3b	–	85
3	1a	2c, nBu/nBu	3c	–	86
4	1a	2d, Ph/Ph	3d	–	88
5	1a	2e, Me/Ph	3e/3e'	90:10	71:8
6	1a	2f, Et/Ph	3f/3f'	89:11	71:9
7	1a	2g, nBu/Ph	3g/3g'	85:15	72:7
8	1a	2h, Ph/TMS	3h	–	81
9	1a	2i, nBu/TMS	3i	–	86
10	1a	2j, nBu/tBu	3j/3j'	70:30	51:–
11[c]	1a	2k, Me/tBu	3k/3k'	73:27	45:–
12	1a	2l, Me/iPr	3l/3l'	70:30	79[d]
13	1a	2m, Me/Et	3m/3m'	53:47	79[d]
14	1a	2n, Ph/C≡CPh	3n	–	37
15	1a	2o, CH$_2$CH=CH$_2$/Ph	3o	–	23
16	1a	2p, (CH$_2$)$_3$Cl/Ph	3p/3p'	86:14	42:6
17[e]	1a	2q, CH$_2$OMe/Ph	3q/3q'	71:29	33:13
18	1a	2r, (CH$_2$)$_3$O(C$_5$H$_9$O)/Ph	3r	–	21
19	1a	2s, CH$_2$NMe$_2$/Ph	3s/3s'	81:19	23:6
20[f]	1b	2a, Et/Et	3t	–	39
21[f]	1b	2c, nBu/nBu	3u	–	41
22[f]	1b	2e, Me/Ph	3v	–	27
23[f]	1b	2f, Et/Ph	3w	–	30
24[f]	1b	2g, nBu/Ph	3x	–	32

[a] Conditions: **1** (0.2 mmol), **2** (0.6 mmol), and [Ni] (0.2 mmol) in THF (6 mL). [b] The molar ratio of **3/3'** was determined by GC–MS. [c] [NiCl$_2$(PMe$_3$)$_2$] was used. [d] Yield for inseparable mixture of **3/3'**. [e] [NiCl$_2$(PPh$_3$)$_2$] was used. [f] For all reactions with **1b**, [1-(PhCH=CH)-1,2-C$_2$B$_{10}$H$_{11}$] was isolated in about 30% yield in addition to **3**. [g] Yield of isolated product.

dihydrobenzocarboranes **3g/3g'** with poor selectivity (Table 1, entry 2). However, the reaction in THF afforded **3g/3g'** in excellent yield with very good selectivity even at 90°C (Table 1, entries 3 and 4). In DME, both selectivity and yield decreased a little (Table 1, entry 5). Phosphine-coordinated nickel complexes all gave the product in yields higher than 91% but with poor selectivity (Table 1, entries 6–11).

Under the optimal reaction conditions (Table 1, entry 4), a variety of alkynes was examined (Table 2). Symmetrical alkynes gave the single products **3a–d**, which could be isolated in very good yields (Table 2, entries 1–4). For unsymmetrical alkynes, the regioselectivity was dependent on both the polarity of alkynes and relative bulkiness of two substituents. Phenyl- and trimethylsilyl-substituted alkynes **2e–i** afforded very good regioselectivity owing to electronic effects (Table 2, entries 5–9),[13,14] but substituted alkyl alkynes **2j,k** gave **3j,k** as the major regioisomers because of steric effects (Table 2, entries 10 and 11). For alkynes bearing functional groups **2n–s**, the cycloaddition products were formed in low yields, which might be ascribed to the functional group competing with the C≡C unit for the vacant site at nickel (Table 2, entries 14–19). For zirconacyclopentane **1b**, the alkyne annulation products **3t–x** were obtained in low yields together with the isolation of alkenyl carborane [1-(PhCH=CH)-1,2-C$_2$B$_{10}$H$_{11}$] in about 30% yield. The latter resulted from β-H elimination of the nickelacycle intermediate, in which the phenyl group may facilitate such an elimination process.[4]

It was noted that these dihydrobenzocarboranes were also prepared in similar yields from the one-pot reaction of [Cp$_2$Zr(μ-Cl)(μ-C$_2$B$_{10}$H$_{10}$)Li(OEt$_2$)$_2$] with alkene and subsequent treatment with alkyne in the presence of NiCl$_2$. This reaction represents an equivalent of a three-component [2+2+2] cycloaddition of carboryne with one alkene and one alkyne.

Compounds **3** were fully characterized by ^{1}H, ^{13}C, and ^{11}B NMR spectroscopy as well as high-resolution mass spectrometry.[15] The molecular structures of **3h**, **3n**, **3o**, and **3w** were further confirmed by single-crystal X-ray analyses.[16]

We attempted to isolate the nickelacycle to understand the reaction mechanism. Reaction of **1a** with NiCl$_2$ in the absence of alkynes resulted in a complicated mixture containing alkenyl carboranes as β-H elimination products. After many attempts, the transmetalation intermediate, nickelacyclopentane [1,2-[Ni(dppe)CH$_2$CH(nBu)]-1,2-C$_2$B$_{10}$H$_{10}$] (**4**) was isolated in 48% yield after the reaction of **1a** with [NiCl$_2$(dppe)] in refluxing toluene (Scheme 2). Complex **4** was fully characterized by various NMR spectroscopic techniques and elemental analyses. A single-crystal X-ray diffraction study revealed that the nickel atom in **4** adopts a square-planar geometry (Figure 1).[17] It is obvious that the coordination of the dppe ligand to the nickel atom can
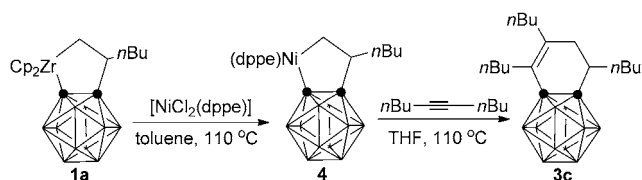
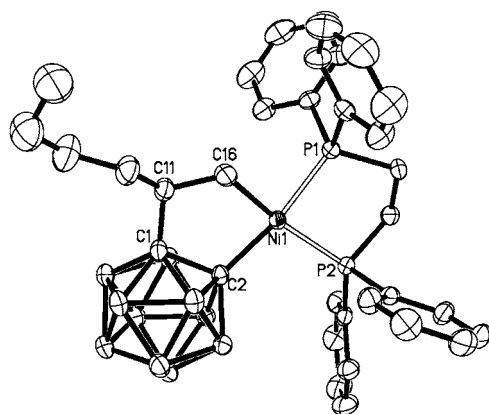**Scheme 2.** Synthesis of intermediate **4** and its reaction with alkyne **2c**.

Figure 1. X-ray crystal structure of [1,2-{(dppe)NiCH$_2$CH(*n*Bu)}-1,2-C$_2$B$_{10}$H$_{10}$] (**4**). Thermal ellipsoids are set at the 35% probability level. Selected bond lengths [Å] and angles [°]: Ni1–C2 1.935(3), Ni1–C16 1.953(2), Ni1–P1 2.154(1), Ni1–P2 2.214(1), C1–C2 1.708(4), C1–C11 1.527(5), C11–C16 1.501(5); C2-Ni1-C16 86.5(1), C16-Ni1-P1 86.5(1), P1-Ni1-P2 86.7(1), P2-Ni1-C2 101.3(1).

stabilize complex **4** and prevent the β-H elimination of the nickelacyclopentane. Further reaction of **4** with alkyne **2c** in THF at 110°C gave **3c** in greater than 90% yield as determined by GC (Scheme 2). Accordingly, the formation of products **3** can be rationalized by the steps of transmetalation of Zr to Ni, insertion of alkyne into the Ni–C(alkyl) bond and reductive elimination reaction (Scheme 3).

In summary, we have developed an efficient transition-metal-mediated three-component [2+2+2] cycloaddition of
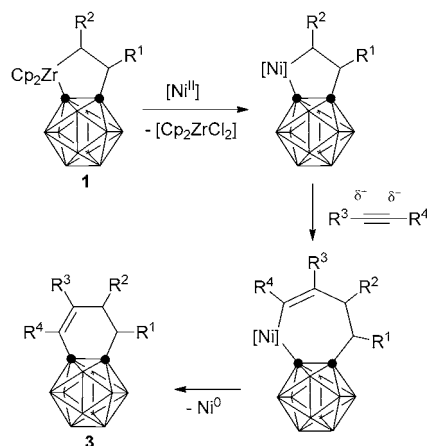
carboryne, unactivated alkene, and alkyne for the preparation of dihydrobenzocarboranes. This offers an example of how to control the selectivity among different alkenes and alkynes to assemble complex molecular architectures.

Experimental Section

1: 1-Hexene (168 mg, 2.0 mmol) was added to [Cp$_2$Zr(μ-Cl)(μ-C$_2$B$_{10}$H$_{10}$)Li(OEt$_2$)$_2$] (554 mg, 1.0 mmol) in toluene (20 mL), and the reaction mixture was heated to reflux for 48 h. After removal of the precipitate (LiCl) by filtration, the clear solution was concentrated to about 5 mL, from which **1a** was isolated as light-yellow crystals after this solution stood at room temperature overnight (394 mg, 88%). Complex **1b** was prepared in the same manner as red crystals in 87% yield.

4: A suspension of **1a** (90 mg, 0.2 mmol) and [NiCl$_2$(dppe)] (110 mg, 0.2 mmol) in toluene (10 mL) was heated to reflux for two hours and stirred. The mixture was filtrated to give a brown solution, from which complex **4** was isolated as light-brown crystals after this solution stood for two days at room temperature (66 mg, 48%).

[1] For reviews, see: a) N. E. Schore, *Chem. Rev.* **1988**, *88*, 1081–1119; b) B. M. Trost, *Science* **1991**, *254*, 1471–1477; c) M. Lautens, W. Klute, W. Tam, *Chem. Rev.* **1996**, *96*, 49–92; d) S. Saito, Y. Yamamoto, *Chem. Rev.* **2000**, *100*, 2901–2915.

[2] For reviews on the synthesis of ring systems using [2+2+2] cycloadditions, see: a) S. Kotha, E. Brahmachary, K. Lahiri, *Eur. J. Org. Chem.* **2005**, 4741–4767; b) P. R. Chopade, J. Louie, *Adv. Synth. Catal.* **2006**, *348*, 2307–2327; c) K. Tanaka, *Synlett* **2007**, 1977–1993; d) T. Shibata, K. Tsuchikama, *Org. Biomol. Chem.* **2008**, *6*, 1317–1323; e) Y. Yamamoto, *Curr. Org. Chem.* **2005**, *9*, 503–519; f) B. Heller, M. Hapke, *Chem. Soc. Rev.* **2007**, *36*, 1085–1094; g) J. A. Varela, C. Saá, *Chem. Rev.* **2003**, *103*, 3787–3801; h) G. D. Henry, *Tetrahedron* **2004**, *60*, 6043–6061; i) N. Agenet, O. Busine, F. Slowinski, V. Gandon, C. Aubert, M. Malacria, *Org. React.* **2007**, *68*, 1–302; j) B. R. Galan, T. Rovis, *Angew. Chem.* **2009**, *121*, 2870–2874; *Angew. Chem. Int. Ed.* **2009**, *48*, 2830–2834.

[3] a) H. L. Gingrich, T. Ghosh, Q. Huang, M. Jones, Jr., *J. Am. Chem. Soc.* **1990**, *112*, 4082–4083; b) T. Ghosh, H. L. Gingrich, C. K. Kam, E. C. M. Mobraaten, M. Jones, Jr., *J. Am. Chem. Soc.* **1991**, *113*, 1313–1318; c) Q. Huang, H. L. Gingrich, M. Jones, Jr., *Inorg. Chem.* **1991**, *30*, 3254–3257; d) R. J. Cunningham, N. Bian, M. Jones, Jr., *Inorg. Chem.* **1994**, *33*, 4811–4812; e) D. M. Ho, R. J. Cunningham, J. A. Brewer, N. Bian, M. Jones, Jr., *Inorg. Chem.* **1995**, *34*, 5274–5278; f) L. Barnett-Thamattoor, G. Zheng, D. M. Ho, M. Jones, Jr., J. E. Jackson, *Inorg. Chem.* **1996**, *35*, 7311–7315; g) J. Jeon, T. Kitamura, B.-W. Yoo, S. O. Kang, J. Ko, *Chem. Commun.* **2001**, 2110–2111; h) B. Kiran, A. Anoop, E. D. Jemmis, *J. Am. Chem. Soc.* **2002**, *124*, 4402–4407; i) T. Lee, J. Jeon, K. H. Song, I. Jung, C. Baik, K.-M. Park, S. S. Lee, S. O. Kang, J. Ko, *Dalton Trans.* **2004**, 933–937; j) S. R. Wang, Z. Qiu, Z. Xie, *J. Am. Chem. Soc.* **2010**, *132*, 9988–9989; k) S. R. Wang, Z. Qiu, Z. Xie, *J. Am. Chem. Soc.* **2011**, *133*, 5760–5763.

[4] Z. Qiu, Z. Xie, *Angew. Chem.* **2008**, *120*, 6674–6677; *Angew. Chem. Int. Ed.* **2008**, *47*, 6572–6575.

Scheme 3. Proposed reaction mechanism.

[5] L. Deng, H.-S. Chan, Z. Xie, *J. Am. Chem. Soc.* **2006**, *128*, 7728 – 7729.

[6] Z. Qiu, Z. Xie, *J. Am. Chem. Soc.* **2009**, *131*, 2084 – 2085.

[7] For reviews, see: a) Z. Qiu, S. Ren, Z. Xie, *Acc. Chem. Res.* **2011**, *44*, 299 – 309; b) Z. Qiu, Z. Xie, *Sci. China Ser. B* **2009**, *52*, 1544 – 1558.

[8] Z. Qiu, S. R. Wang, Z. Xie, *Angew. Chem.* **2010**, *122*, 4753 – 4756; *Angew. Chem. Int. Ed.* **2010**, *49*, 4649 – 4652.

[9] a) S. Ren, H.-S. Chan, Z. Xie, *J. Am. Chem. Soc.* **2009**, *131*, 3862 – 3863; b) S. Ren, H.-S. Chan, Z. Xie, *Organometallics* **2009**, *28*, 4106 – 4114.

[10] a) *Titanium and Zirconium in Organic Synthesis* (Ed.: I. Marek,), Wiley-VCH, Weinheim, **2002**; b) Z. Xi, R. Fischer, R. Hara, W.-H. Sun, Y. Obora, N. Suzuki, K. Nakajima, T. Takahashi, *J. Am. Chem. Soc.* **1997**, *119*, 12842 – 12848; c) D. Thomas, W. Baumann, A. Spannenberg, R. Kempe, U. Rosenthal, *Organometallics* **1998**, *17*, 2096 – 2102; d) Y. Liu, B. Shen, M. Kotora, T. Takahashi, *Angew. Chem.* **1999**, *111*, 966 – 968; *Angew. Chem. Int. Ed.* **1999**, *38*, 949 – 952; e) H. Sun, V. V. Burlakov, A. Spannenberg, W. Baumann, P. Arndt, U. Rosenthal, *Organometallics* **2001**, *20*, 5472 – 5477.

[11] a) T. Takahashi, F.-Y. Tsai, Y. Li, K. Nakajima, M. Kotora, *J. Am. Chem. Soc.* **1999**, *121*, 11093 – 11100; b) L. Zhou, C. Xi, H. Wang, F. Kong, T. Takahashi, *Bull. Chem. Soc. Jpn.* **2006**, *79*, 950 – 952.

[12] L. Deng, H.-S. Chan, Z. Xie, *J. Am. Chem. Soc.* **2005**, *127*, 13774 – 13775.

[13] M. A. Bennett, S. A. Macgregor, E. Wenger, *Helv. Chim. Acta* **2001**, *84*, 3084 – 3104.

[14] a) J. B. Lambert, G.-T. Wang, R. B. Finzel, D. H. Teramura, *J. Am. Chem. Soc.* **1987**, *109*, 7838 – 7845; b) S. G. Wierschke, J. Chandrasekhar, W. L. Jorgensen, *J. Am. Chem. Soc.* **1985**, *107*, 1496 – 1500; c) A. S. Guram, R. F. Jordan, *Organometallics* **1990**, *9*, 2190 – 2192.

[15] Experimental details and complete characterization data are provided in the Supporting Information.

[16] CCDC 840641 (**1a**), 840642 (**1b**), 840643 (**4**), 840644 (**3h**), 840645 (**3n**), 840646 (**3o**), and 840647 (**3w**) contain 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.

[17] Crystal data for **4**: $C_{34}H_{46}B_{10}NiP_2$, $Mr = 683.5$, triclinic, space group $P\bar{1}$, $a = 11.100(1)$, $b = 11.619(1)$, $c = 15.742(1)$ Å, $\alpha = 74.34(1)°$, $\beta = 73.30(1)°$, $\gamma = 89.08(1)°$, $V = 1868.3(2)$ Å^3, $T = 296$ K, $Z = 2$, $\rho_{calcd} = 1.215$ g cm^{-3}, $2\theta_{max} = 50.5°$, $\mu(Mo_{Ka}) = 0.71073$ Å. A total of 6543 reflections were collected and led to 5441 unique reflections, 5441 of which with $I > 2\sigma(I)$ were considered as observed, $R_1 = 0.040$, w$R_2(F^2) = 0.106$. This structure was solved by direct methods and refined by full-matrix least-squares on F^2 by using the SHELXTL/PC package of crystallographic software.[18] All non-hydrogen atoms were refined anisotropically and all hydrogen atoms were geometrically fixed using the riding model.

[18] G. M. Sheldrick, SHELXTL 5.10 for Windows NT: Structure Determination Software Programs. Bruker Analytical X-ray Systems, Inc., Madison, Wisconsin, USA, **1997**.