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Nickel-Catalyzed Regioselective [2+2+2] Cycloaddition of Carboryne with Alkynes**

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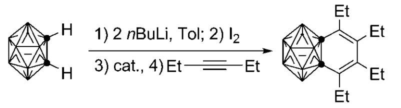
Carboryne (1,2-dehydro-*ortho*-carborane), a three-dimensional relative of benzyne, was first reported in 1990 as a highly reactive intermediate.[1] Subsequent studies of its reactivity showed that it can react with alkenes, dienes, and alkynes in [2+2] and [2+4] cycloaddition, and ene-reaction patterns,[2] similar to that of benzyne. The carboryne reactions are usually complicated and do not proceed in a controlled manner. On the other hand, nickel–carboryne complex [(η^2-$C_2B_{10}H_{10}$)Ni(PPh_3)$_2$][3] can undergo regioselective [2+2+2] cycloaddition reactions with 2 equivalents of alkyne to afford benzocarboranes,[4] can react with 1 equivalent of alkenes to generate alkenylcarborane coupling products,[5] and can undergo a three-component [2+2+2] cyclotrimerization reaction with 1 equivalent of activated alkene and 1 equivalent of alkyne to give dihydrobenzocarboranes.[6] However, these reactions require a stoichiometric amount of nickel reagent. In view of the analogy between metal–benzyne and metal–carboryne complexes[7,8] and the metal-catalyzed reactions of benzyne with alkenes and alkynes,[9] we wondered if a catalytic version of these nickel-mediated carboryne reactions could be developed.

We learnt from the previous stoichiometric reactions that high temperatures were necessary for the insertion of alkynes into the Ni–C_{cage} bonds in nickel–carborynes, and that the final metal complex was a Ni^0 species.[4–6] Also, 1-bromo-2-lithiocarborane is a known precursor of carboryne.[2a–e] Therefore, it is rational to assume that 1-bromo-2-lithiocarborane can undergo oxidative addition with Ni^0 to give the desired nickel–carboryne complex after elimination of LiBr. Unfortunately, such an oxidative addition reaction does not proceed at temperatures less than 0 °C and 1-bromo-2-lithiocarborane is not stable at temperatures greater than 0 °C.[1,2a] Therefore, a new precursor to carboryne is required. After many attempts, we discovered that 1-iodo-2-lithiocarborane is a good precursor for this catalytic cycle. Herein, we report the nickel-catalyzed [2+2+2] cycloaddition of carboryne with 2 equivalents of an alkyne to afford benzocarborane compounds.

1-Iodo-2-lithiocarborane was conveniently prepared in situ from the reaction of dilithiocarborane with 1 equivalent of iodine in toluene at room temperature; importantly, 1-iodo-2-lithiocarborane was much more thermally stable than 1-bromo-2-lithiocarborane. Heating a solution of 1-iodo-2-lithiocarborane in benzene overnight afforded the [4+2] cycloaddition product 1,2-(2,5-cyclohexadiene-1,4-diyl)-*ortho*-carborane in 25 % yield, much higher than the 8 % yield that is afforded from the 1-bromo-2-lithiocarborane precursor.[10] This result suggests that 1-iodo-2-lithiocarborane is a more efficient precursor than the bromo one. We then examined the catalytic activity of various metal complexes in the reaction of 1-iodo-2-lithiocarborane with an excess amount of 3-hexyne in toluene at 110 °C for 2 hours and the results are summarized in Table 1. The Ni^0 complexes were all catalytically active with [Ni(cod)$_2$] (cod = 1,5-cyclooctadiene) being the most active, giving the desired [2+2+2] cycloaddition product **2a** in 33–49 % yield (Table 1, entries 1–3). Addition of PPh_3 led to a big drop in the yield of **2a** from 49 % to 33 %, presumably because free PPh_3 molecules compete with the alkyne for the coordination site on the nickel atom.

Table 1: Optimization of reaction conditions.[a]



2a

Entry	Catalyst[b]	Loading [mol %]	*t* [h]	*T* [°C]	Yield [%][c]
1	[Ni(cod)$_2$]	20	2	110	49
2	[Ni(cod)$_2$]/4PPh_3	20	2	110	33
3	[Ni(PPh_3)$_4$]	20	2	110	37
4	[$NiCl_2$(PMe_3)$_2$]	20	2	110	17
5	[$NiCl_2$(PnBu$_3$)]	20	2	110	57
6	[$NiCl_2$(PPh_3)$_2$]	20	2	110	65
7	[$NiCl_2$(PPh_3)$_2$]	10	2	110	31
8	[$NiCl_2$(PPh_3)$_2$]	20	4	110	63
9	[$NiCl_2$(PPh_3)$_2$]	20	4	90	60
10	[$NiCl_2$(dppe)]	20	2	110	29
11	[$NiCl_2$(dppp)]	20	2	110	22
12	[NiI_2(Me_2Im)$_2$]	20	2	110	16
13	[Pd(PPh_3)$_4$]	20	2	110	1
14	[$PdCl_2$(PPh_3)$_2$]	20	2	110	1
15	[$FeCl_2$]/2PPh_3	20	2	110	–
16	[$CoCl_2$(PPh_3)$_2$]	20	2	110	–

[a] Conditions: 1) carborane (0.5 mmol), nBuLi (1.0 mmol), in toluene at room temperature for 1 h. 2) I_2 (0.5 mmol), at room temperature for 0.5 h; 3) catalyst, 3-hexyne (2 mmol). [b] cod = cyclooctadiene; dppe = 1,2-bis(diphenylphosphino)ethane. dppp = 1,3-bis(diphenylphosphino)-propane; Me_2Im = 1,3-dimethylimidazol-2-ylidene. [c] Yield of isolated product.

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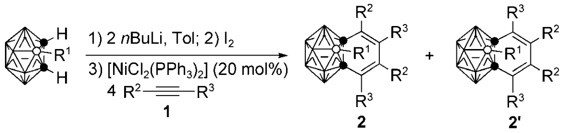
The Ni^{II} salts were also active, and their activities depended largely on the ligands around the nickel center (Table 1, entries 4–12). [NiCl$_2$(PPh$_3$)$_2$] was found to be the best catalyst, producing **2a** in 65% yield, thus suggesting that the Ni^0 species that was generated in situ is more active than [Ni(cod)$_2$] (see below; Table 1, entry 6). Lower catalyst loading (10 mol%) resulted in a significant decrease in the yield of **2a** from 65% to 31% (Table 1, entry 7). Prolonging the reaction time from 2 to 4 hours did not affect the yield of **2a** (Table 1, entry 8). Temperature was crucial to the reaction: compound **2a** was not observed at all if the reaction temperature was below 60°C. The reaction proceeded well at 90°C, but needed a longer time to proceed to completion (Table 1, entry 9). In sharp contrast, palladium complexes, such as [PdCl$_2$(PPh$_3$)$_2$] and [Pd(PPh$_3$)$_4$], showed almost no activity (Table 1, entries 13 and 14). [FeCl$_2$]/PPh$_3$ and [CoCl$_2$(PPh$_3$)$_2$] were inactive (Table 1, entries 15 and 16).

We then expanded the substrate scope to include various carboranes and alkynes using the above optimum reaction conditions (Table 1, entry 6), and the results are shown in Table 2. The yields of **2** were comparable with those obtained from the stoichiometric reactions of nickel–carboryne with alkynes (Table 2, entries 1, 4–6, and 9).[4] Steric factors played an important role in these reactions. Sterically less-demanding 3-hexyne afforded the highest yield (Table 2, entry 1). Carboranes with 3-chloro and 3-phenyl substituents showed a big decrease in the yields of **2b**,**c** from 65% to 31 and 38%, respectively (Table 2, entries 2 and 3). 4-Methyl-2-pentyne **1f** gave two inseparable regioisomers **2h**/**2′h** in a molar ratio of 7:3 (Table 2, entry 8). However, excellent regioselectivity was observed for unsymmetrical arylalkynes **1g**–**l**, presumably owing to electronic effects as the phenyl group can be considered as electron-withdrawing (Table 2, entries 9–14).[11] When alkynes containing ether groups were employed in the reaction (**1e** and **1m**), the products were formed in low yields, probably owing to the coordination of oxygen atoms occupying the vacant site on the nickel centre (Table 2, entries 7 and 15). Such interactions may also influence the regioselectivity of the alkyne insertion and stabilize the inserted product, which leads to the formation of **2′o** and a small amount of mono-alkyne insertion products after hydrolysis (Table 2, entry 15).[12] Alkynes bearing an amido or carbonyl group, such as **1n** and **1o**, were incompatible with this reaction because they could react with the carboryne precursor 1-iodo-2-lithiocarborane (Table 2, entries 16 and 17). For methyl 2-butynoate, the homocyclotrimerization product was observed.[12a,b]

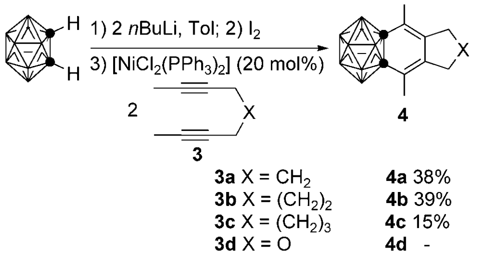
Table 2: Nickel-catalyzed cycloaddition of carborynes with alkynes.



Entry	R^1	R^2	R^3	1	Product	Yield [%][a,b]
1	H	Et	Et	**1a**	**2a**	65 (67)
2	3-Cl	Et	Et	**1a**	**2b**	31
3	3-Ph	Et	Et	**1a**	**2c**	38
4	H	nPr	nPr	**1b**	**2d**	59 (65)
5	H	nBu	nBu	**1c**	**2e**	54 (65)
6	H	Ph	Ph	**1d**	**2f**	28 (33)
7	H	CH$_2$OMe	CH$_2$OMe	**1e**	**2g**	13
8	H	iPr	Me	**1f**	**2h**+**2′h**	44 (**2h**/**2′h** =70:30)[c]
9	H	Me	Ph	**1g**	**2i**	50 (54)
10	H	Me	p-Me-C$_6$H$_4$	**1h**	**2j**	39
11	H	Me	p-CF$_3$-C$_6$H$_4$	**1i**	**2k**	49
12	H	Et	Ph	**1j**	**2l**	49
13	H	nBu	Ph	**1k**	**2m**	43
14	H	C≡CPh	Ph	**1l**	**2n**	51
15	H	CH$_2$OMe	Ph	**1m**	**2o**+**2′o**	24+2
16	H	CH$_2$NMe$_2$	Ph	**1n**	–	–
17	H	CO$_2$Me	Me	**1o**	–	–

[a] Yield of isolated product. [b] Yields in parentheses correspond to those from the stoichiometric reactions of Ni-carboryne with 2 equivalents of alkynes, reported in Ref. [4]. [c] Molar ratio was determined by ^{1}H NMR analysis of the crude product mixture.

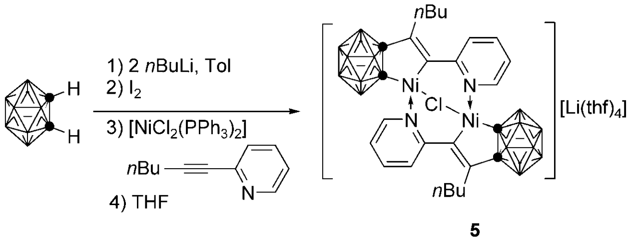
Internal diynes **3a**–**c** were also compatible with these nickel-catalyzed cycloaddition reactions and gave the desired products **4** in 15–39% yields with a good tolerance of the fused-ring size (Scheme 1). The yield was rather low for seven-membered fused-ring species **4c**, and no reaction proceeded for the oxo-bridged diyne **3d**.



Scheme 1. Nickel-catalyzed cycloaddition of carboryne with diynes.

Compounds **2** and **4** were fully characterized by ^{1}H, ^{13}C, and ^{11}B NMR spectra, as well as high-resolution mass spectrometry.[13] The molecular structures of **2h, 2n**, and **4b** were further confirmed by single-crystal X-ray analyses (see the Supporting Information).[14]

To gain some insight into the reaction mechanism, a reaction of 1-I-2-Li-1,2-C$_2$B$_{10}$H$_{10}$ with 1 equivalent of [Ni(cod)$_2$]/4PPh$_3$ was performed on an analytical scale in toluene and monitored by ^{11}B and ^{31}P NMR spectroscopy. The results suggested the formation of [(η^2-C$_2$B$_{10}$H$_{10}$)Ni(PPh$_3$)$_2$], even at room temperature, which indicates the oxidative addition of an I–C$_{cage}$ bond on the Ni^0 center. Treatment of the in situ generated 1-I-2-Li-1,2-C$_2$B$_{10}$H$_{10}$ with 1 equivalent of [NiCl$_2$(PPh$_3$)$_2$] in the presence of 2 equivalents of n-butyl-2-pyridinylacetylene in refluxing toluene gave mono-alkyne-insertion product **5** [{[2-C(nBu)=C(o-C$_5$H$_4$N)-1,2-C$_2$B$_{10}$H$_{10}$]Ni}$_2$(μ-Cl)][Li(thf)$_4$] after recrystallization from tetrahydrofuran as red crystals in 25% yield (Scheme 2). This product was fully characterized by various NMR spectroscopic techniques and by elemental analysis.[15] Single-crystal X-ray analysis revealed that **5** is an ionic complex that consists of dimeric complex anions and tetrahedral cations. In the anion, two square-planar nickel moieties share one μ$_2$-Cl atom



Scheme 2. Reaction with n-butyl-2-pyridinylacetylene.

(Figure 1). Coordination of the pyridinyl group to the nickel atom can stabilize complex **5** and prevent the further insertion of the second equivalent of n-butylpyridinylacetylene.

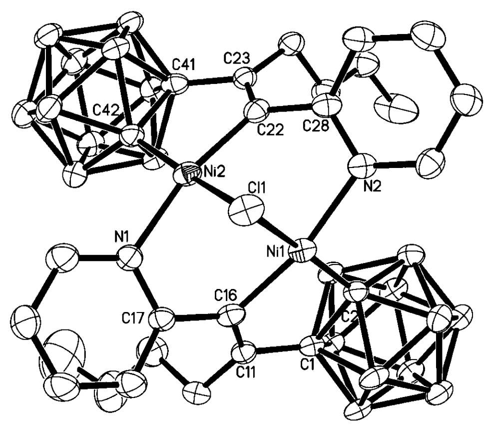
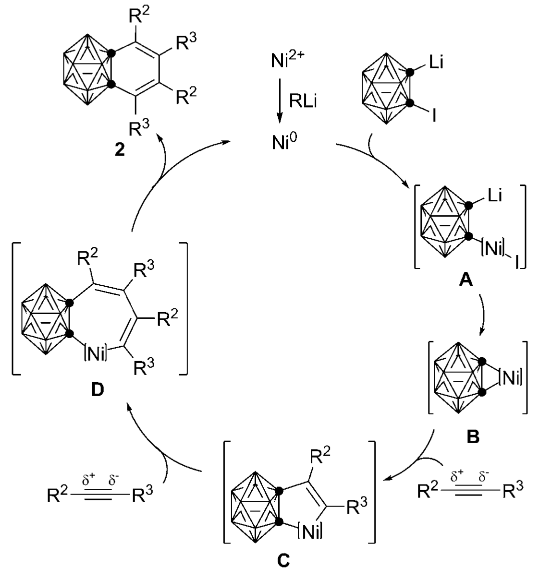


Figure 1. Molecular structure of the anion in **5**. Selected bond lengths [Å] and angles [°]: Ni1–C2 1.891(8), Ni1–C16 1.930 (8), Ni1–Cl1 2.267(2), Ni1–N2 1.966(7), C1–C2 1.656(12), C1–C11 1.487(11), C11–C16 1.378(11), Ni2–C42 1.911(6), Ni2–C22 1.926(8), Ni2–Cl1 2.267(2), Ni2–N1 1.946(6), C41–C42 1.641 (11), C41–C23 1.506 (10), C23–C22 1.345 (9); C2-Ni1-C16 86.8(3), C16-Ni1-Cl1 95.8(2), Cl1-Ni1-N2 83.8(2), N2-Ni1-C2 96.7(3), C42-Ni2-C22 85.6(3), C22-Ni2-Cl1 97.1(2), Cl1-Ni2-N1 82.7(2), N1-Ni2-C42 97.6(3), Ni1-Cl1-Ni2 70.8(1).

Given the above experimental evidence, a plausible mechanism for the nickel-catalyzed cycloaddition is shown in Scheme 3. The catalysis is likely to be initiated by a Ni^0 species that is generated from the reduction of Ni^{II} with a lithiocarborane salt.[16] Oxidative addition between the $I{-}C_{cage}$ bond and Ni^0, followed by the subsequent elimination of lithium iodide, produces nickel–carboryne intermediate **B**. An alternative pathway proceeded through the elimination of lithium iodide to form carboryne, and subsequent coordination to the metal center cannot be ruled out. Insertion of the first equivalent of alkyne into the nickel–carboryne $Ni{-}C_{cage}$ bond gives nickelacyclopentene intermediate **C**. The second equivalent of alkyne inserts into the $Ni{-}C_{vinyl}$ bond to afford the seven-membered intermediate **D**.[4,17] Reductive elimination yields the cycloaddition product **2** and releases a Ni^0 species to complete the catalytic cycle. The regioselectivity observed in these reactions can be rationalized by the polarity of alkynes.[11]



Scheme 3. Proposed mechanism for the nickel-catalyzed [2+2+2] cyclization reaction.

In summary, we have developed the first metal-catalyzed reaction of carboryne with unsaturated molecules using 1-iodo-2-lithiocarborane as a precursor and $[NiCl_2(PPh_3)_2]$ as the catalyst. The mechanism was proposed after structural confirmation of the key intermediate, nickelacyclopentene.

Experimental Section

Representative procedure: I_2 (0.5 mmol) was added to a solution of $Li_2C_2B_{10}H_{10}$ (0.5 mmol) in toluene (5 mL), prepared in situ from the reaction of nBuLi (1.0 mmol) with *ortho*-carborane (0.5 mmol), and the reaction mixture was stirred at room temperature for 0.5 h. $[NiCl_2(PPh_3)_2]$ (0.1 mmol), and either the alkyne (2.0 mmol) or diyne (1.0 mmol) were then added and the reaction vessel was closed and heated at 110 °C overnight. After addition of 5 mL of water and extraction with ether (3 × 10 mL), the resulting solution was concentrated in vacuo. The residue was purified by column chromatography on silica gel (230–400 mesh) using n-hexane as eluent to give the cycloaddition product.

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

[14] CCDC 767698 (**2h**), CCDC 767699 (**2n**), CCDC 767700 (**4b**), and CCDC 767701 (**5**) 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.

[15] a) Complete characterization data are provided in the Supporting Information; b) Crystal data for **5**·THF: $C_{46}H_{86}B_{20}ClLiN_3Ni_2O_5$, $M_r = 1123.2$, triclinic, space group $P\bar{1}$, $a = 11.388(3)$, $b = 14.951(3)$, $c = 19.334(4)$ Å, $\alpha = 86.53(1)$, $\beta = 83.80(1)$, $\gamma = 74.03(1)°$, $V = 3145(1)$ Å^3, $T = 296$ K, $Z = 2$, $\rho_{\text{calcd}} = 1.186$ gcm^{-3}, $2\theta_{\text{max}} = 50°$, $\mu(\text{Mo}_{\text{K}\alpha}) = 0.71073$ Å. A total of 17044 reflections were collected and led to 11023 unique reflections, 11023 of which with $I > 2\sigma(I)$ were considered as observed, $R_1 = 0.0800$, wR_2 $(F^2) = 0.2052$. 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.

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