

Borylation

Copper-Catalyzed Borylation Reactions of Alkynes and Arynes**

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Much attention has recently been given to the formation of C–B bonds by borylation reactions of unsaturated carbon linkages under copper catalysis. In this method, nucleophilic borylcopper species, which are formed by σ -bond metathesis between copper(I) complexes and diboron compounds, serve as key intermediates.^[1,2] While various organoboron compounds that are of great synthetic value are readily accessible by the above-mentioned method, efforts have been devoted largely to the development of monoborylation reactions, in which one boryl moiety of a diboron compound is incorporated into the final product. On the other hand, installation of both boryl moieties of a diboron compound into the product, that is, diborylation,^[3,4] is also of high synthetic significance, since the resulting two C–B bonds can both be utilized for the synthesis of complex molecules by Suzuki–Miyaura coupling and other methods.^[5] However, potential copper catalysis for diborylation reactions remains to be exploited.^[6] Herein, we report the first diborylation of unsaturated carbon linkages by copper catalysis; the broad substrate scope makes this a universal method for the synthesis of *vic*-diborylalkenes (from alkynes) and *vic*-diborylarenes (from arynes), furthermore, this method is more practical and economical than that with the well-known catalytic system based on platinum.^[4]

We first carried out the reaction of 4-octyne (**1a**) with bis(pinacolato)diboron ((pin)B–B(pin)) in the presence of PCy₃ and Cu(OAc)₂,^[7,8] and observed that the B–B bond was smoothly added to the C≡C bond in a *cis* fashion to afford diborylated product **2a** in 82% yield (Table 1, entry 1). Trialkylphosphine ligands P(*t*Bu)₃ and P(*n*Oc)₃ also promoted the diborylation, but a prolonged reaction time was required in the latter case (Table 1, entries 2 and 3, respectively); the reaction with PPh₃ resulted in a moderate yield (entry 4). With PCy₃ as the optimum ligand, other aliphatic alkynes, including 2-octyne (**1b**), 5-decyne (**1c**), and 4-methyl-2-

Table 1: Cu-catalyzed diborylation of alkynes.^[a]

$\text{R}-\text{C}\equiv\text{C}-\text{R}' + (\text{pin})\text{B}-\text{B}(\text{pin}) \xrightarrow[\text{toluene, 80}^\circ\text{C}]{\begin{matrix} 2 \text{ mol\% Cu}(\text{OAc})_2 \\ 7 \text{ mol\% ligand} \end{matrix}}$		$\begin{matrix} (\text{pin})\text{B} & & \text{B}(\text{pin}) \\ & \diagdown & / \\ & \text{C}=\text{C} \\ & / & \diagdown \\ \text{R} & & \text{R}' \end{matrix}$		2		$\text{Yield [\%]}^{[b]}$	
Entry	1	R	R'	Ligand	t [h]	2	
1	1a	<i>n</i> Pr	<i>n</i> Pr	PCy ₃	3	2a	82
2 ^[c]	1a	<i>n</i> Pr	<i>n</i> Pr	P(<i>t</i> Bu) ₃	4	2a	83
3 ^[c]	1a	<i>n</i> Pr	<i>n</i> Pr	P(<i>n</i> Oc) ₃	42	2a	81
4 ^[c]	1a	<i>n</i> Pr	<i>n</i> Pr	PPh ₃	16	2a	58
5	1b	Me	<i>n</i> Pen	PCy ₃	3	2b	76
6	1c	<i>n</i> Bu	<i>n</i> Bu	PCy ₃	6	2c	72
7	1d	Me	<i>i</i> Pr	PCy ₃	4.5	2d	78
8	1e	<i>n</i> Hex	(CH ₂) ₂ OMe	PCy ₃	6	2e	73
9	1f	Ph	Ph	PCy ₃	11.5	2f	78
10	1g	Ph	4-MeOC ₆ H ₄	PCy ₃	13.5	2g	82
11	1h	4-MeOC ₆ H ₄	4-MeOC ₆ H ₄	PCy ₃	16	2h	76
12 ^[d]	1i	Ph	4-BrC ₆ H ₄	PCy ₃	77	2i	48
13 ^[e]	1j	Ph	4-NCC ₆ H ₄	PCy ₃	43.5	2j	43
14	1k	Ph	Me	PCy ₃	8.5	2k	78
15	1l	Ph	Et	PCy ₃	24	2l	78
16	1m	Ph	<i>t</i> Bu	PCy ₃	46	2m	64

[a] General procedure: alkyne (0.30 mmol), (pin)B–B(pin) (0.39 mmol), Cu(OAc)₂ (6.0 μ mol), ligand (0.021 mmol), toluene (0.1 mL). [b] Yields of isolated products. [c] Alkyne (1 equiv), (pin)B–B(pin) (2 equiv), Cu(OAc)₂ (10 mol%), ligand (35 mol%), no solvent. [d] Toluene (0.2 mL). [e] Toluene (0.3 mL). Cy = cyclohexyl, *n*Hex = *n*-hexyl, *n*Pen = *n*-pentyl, *n*Oc = *n*-octyl.

pentynyl (**1d**), could be diborylated and afforded the respective *vic*-diborylalkenes in high yields (**2b–2d**; Table 1, entries 5–7). The reaction of homopropargyl ether **1e** resulted in the formation of **2e**, the C–OMe bond of which remained intact throughout the reaction (Table 1, entry 8). The broad substrate scope of alkynes was further demonstrated by the successful reaction of diarylalkynes (**1f–1j**) and aryl-(alkyl)alkynes (**1k** and **1l**) to products **2f–2l** (Table 1, entries 9–15), and also by the reaction of (*tert*-butyl)phenylacetylene (**1m**), which is sterically hindered around the triple bond (entry 16).

The copper-catalyzed diborylation was also applicable to transient arynes.^[9] The *vic*-diborylbenzene **4a** was produced in 68% yield by treatment of an in situ generated benzyne (obtained from **3a**^[10] and K⁺[18]crown-6) with (pin)B–B(pin) in the presence of [(PPh₃)₃CuOAc] (Table 2, entry 1). In addition, a variety of monosubstituted (from **3b–3d**) and disubstituted (from **3e–3h**) arynes reacted smoothly with the diboron reagent to afford the respective *vic*-diborylarenes **4b–4h** in good yields (Table 2, entries 2–8).

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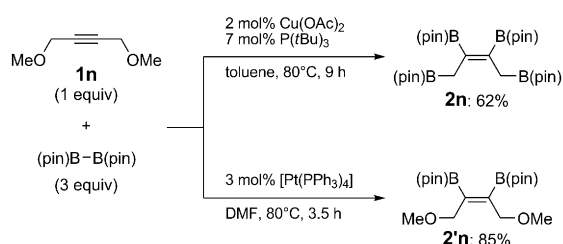
Table 2: Cu-catalyzed diborylation of arynes.^[a]

$ \begin{array}{c} \text{R} \\ \\ \text{C}_6\text{H}_3(\text{TMS})(\text{OTf}) \\ \text{3} \quad (1.5 \text{ equiv}) \end{array} + (\text{pin})\text{B}-\text{B}(\text{pin}) \quad (1 \text{ equiv}) \xrightarrow[\text{1,2-diethoxyethane, } 100^\circ\text{C}]{\begin{array}{l} 2 \text{ mol\% } [(\text{PPh}_3)_3\text{CuOAc}] \\ \text{KF (3 equiv)} \\ [18]\text{crown-6 (1.5 equiv)} \end{array}} \begin{array}{c} \text{R} \\ \\ \text{C}_6\text{H}_3(\text{B}(\text{pin}))_2 \\ \text{4} \end{array} $					
Entry	3	R	t [h]	4	Yield [%] ^[b]
1	3a	H	7	4a	68
2	3b	4-Me	14	4b	79
3	3c	4- <i>t</i> Bu	20	4c	61
4	3d	4-Ph	20	4d	55
5	3e	4,5- $-(\text{CH}_2)_3-$	24	4e	73
6	3f	4,5- $-(\text{CH}_2)_4-$	18	4f	73
7	3g	4,5-Me ₂	12	4g	69
8	3h	4,5-(<i>n</i> Hex) ₂	60	4h	62
9 ^[c]	3i	4-TMS	22	4i	69

[a] General procedure: aryne precursor (0.45 mmol), (pin)B–B(pin) (0.30 mmol), KF (0.90 mmol), [18]crown-6 (0.45 mmol), [(PPh₃)₃CuOAc] (6.0 μmol), 1,2-diethoxyethane (1 mL). [b] Yields of isolated products. [c] [(PPh₃)₃CuOAc] (5 mol %). TMS = trimethylsilyl.

It should be noted that the silyl moiety of 4-(trimethylsilyl)-benzyne (from **3i**) was stable in the presence of the fluoride ion, and diborylated product **4i** was formed selectively (Table 2, entry 9).

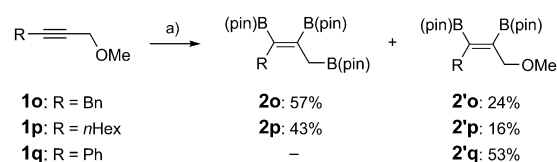
The most striking feature of the copper catalysis was observed in the reactions of propargyl ethers (Scheme 1). With the aid of the copper catalyst, 1,4-dimethoxy-2-butyne (**1n**) was converted exclusively into a tetraborylated product, 1,2,3,4-tetraboryl-2-butene (**2n**),^[11] in which the MeO groups



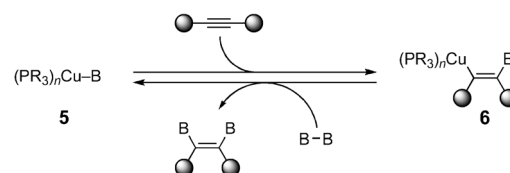
Scheme 1. Cu- or Pt-catalyzed reaction of **1n** with (pin)B–B(pin). DMF = *N,N*-dimethylformamide.

are replaced by boryl groups, and all four C–B bonds were formed in one pot. This result was completely different from that obtained by using the established platinum catalyst [Pt(PPh₃)₄], which furnished the expected diborylation product **2'n**. In addition, propargyl ethers **1o** and **1p** likewise underwent triborylation under the copper catalysis to give **2o** and **2p** as major products (Scheme 2), thus demonstrating that the borylation of propargyl ethers offers direct and unique access to multifunctionalized organoboron compounds that bear two alkenyl boryl and two (or one) allyl boryl moieties. In contrast, phenyl-substituted propargyl ether **1q** provided exclusively diborylation product **2'q**.

A key intermediate of the diborylation might be boryl-copper species **5**, which is generated from copper acetate and a diboron reagent (Scheme 3). Insertion of the C≡C triple

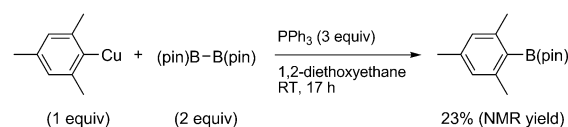


Scheme 2. Cu-catalyzed reaction of methyl propargyl ether with (pin)B–B(pin). a) Methyl propargyl ether (1 equiv), (pin)B–B(pin) (2.5 equiv), Cu(OAc)₂ (2 mol %), PCy₃ (7 mol %), toluene, 80°C, **1o** (21 h), **1p** (22 h), **1q** (29 h).



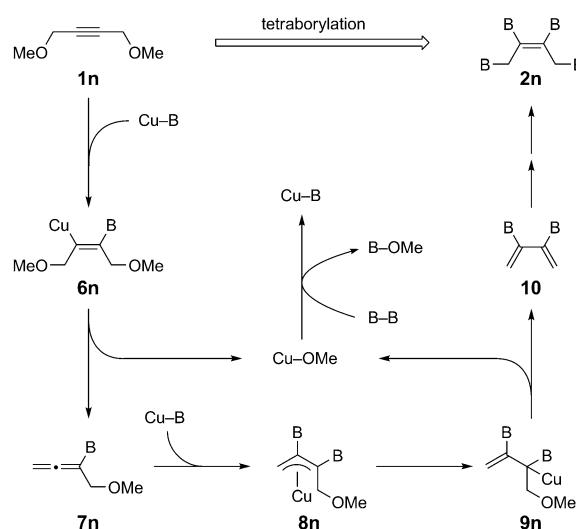
Scheme 3. Proposed catalytic cycle for the diborylation.

bond of an alkyne or an aryne into the Cu–B bond gives organocopper species **6**, subsequent σ-bond metathesis with a diboron compound provides a diborylation product and regenerates **5**.^[12] The validity of the proposed second step of the catalytic cycle was confirmed by the stoichiometric reaction of mesityl copper(I) with (pin)B–B(pin) that led to the transformation of the C(sp²)–Cu bond into the C(sp²)–B bond (Scheme 4).



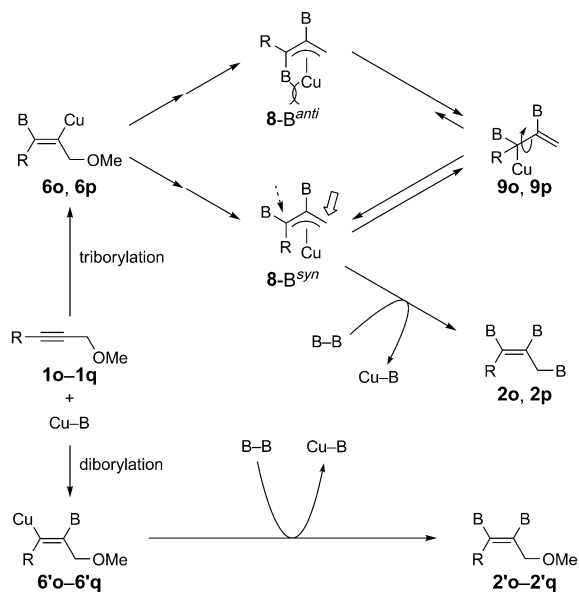
Scheme 4. Reaction of mesityl copper(I) with (pin)B–B(pin).

Formation of boryllallene **7n** by β-oxygen elimination from alkenyl copper species **6n** should trigger the tetraborylation of **1n** (Scheme 5).^[13,14] The resulting boryllallene is then inserted into the Cu–B bond of **5** to furnish π-allyl



Scheme 5. Proposed catalytic cycle for the tetraborylation.

copper species **8n**, which is transformed into 2,3-diborylbutadiene (**10**) by a second β -oxygen elimination from σ -allyl copper species **9n**. Finally, 1,4-diborylation of **10** occurs in a similar manner as mentioned above (Scheme 3) to provide **2n**.^[15,16] In the reaction of **1o** or **1p**, the triborylation product (**2o** or **2p**) would arise from the σ -bond metathesis of the π -allyl copper species (**8o-B^{syn}** or **8p-B^{syn}**), generated via the alkenyl copper species (**6o** or **6p**), with the diboron compound attacking at the sterically less-hindered carbon center; the regioisomeric alkenyl copper species (**6'o** or **6'p**) gives the diborylation product (**2'o** or **2'p**) according to the simple diborylation process (Scheme 6). Although π -allyl species **8-**

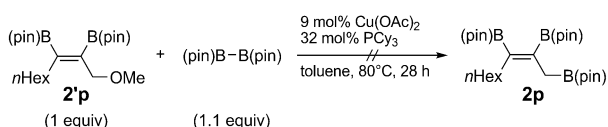


Scheme 6. Proposed catalytic cycle for the triborylation.

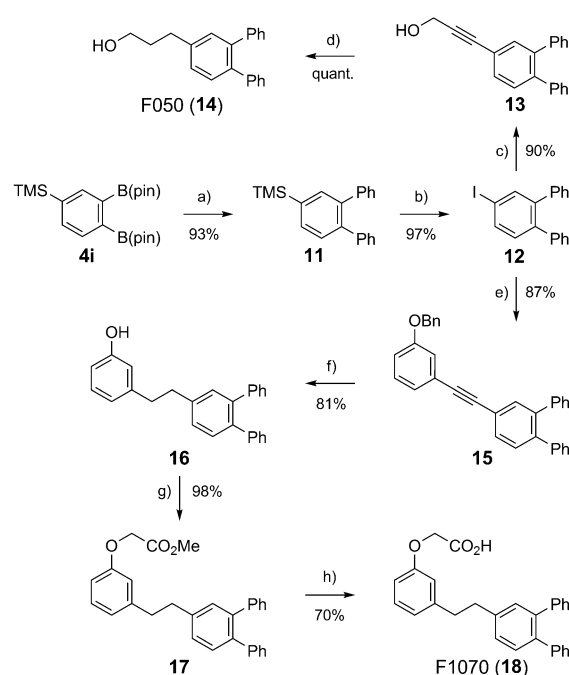
B^{anti} would also be produced in the borylcupration of boryllallene **7**, owing to sterically disfavored **B^{anti}** configuration, isomerization to **8-B^{syn}** proceeds readily through π - σ - π rearrangement, which leads to the exclusive formation of *Z* triborylation products. In addition, the selective diborylation of **1q** can be ascribed to the regioselective generation of intermediate **6'q**, which is induced by the directing electronic effect of the phenyl moiety.^[11,17]

We also showed that diborylated products **2'** are not intermediates of the tetra- and triborylation. The reaction of **2'p** with (pin)B-B(pin) under copper catalysis gave no trace of **2p**, thus verifying that S_N2 -type reactions at the allyl carbon do not occur in the process (Scheme 7).^[1b]

Finally, the synthetic utility of diborylation products was demonstrated by the total synthesis of F050^[18] and F1070,^[19] which are new candidates and lead compounds for the



Scheme 7. Reaction of **2'p** with (pin)B-B(pin) under copper catalysis.



Scheme 8. Synthesis of F050 and F1070. a) **4i** (1 equiv), iodobenzene (2.5 equiv), Cs_2CO_3 (2.5 equiv), H_2O (20 equiv), $[\text{Pd}(\text{P}t\text{Bu}_3)_2]$ (5 mol %), DME, 80°C, 40.5 h; b) **11** (1 equiv), ICl (1.5 equiv), 1,2-dichloroethane, 0°C, 5.5 h; c) **12** (1 equiv), propargyl alcohol (2 equiv), CuI (6 mol %), $[(\text{PPh}_3)_2\text{PdCl}_2]$ (6 mol %), THF/ NEt_3 (2.5:1), RT, 21 h; d) **13** (1 equiv), H_2 (4 atm), Pd/C (10 mol %), EtOH, 30°C, 21 h; e) **12** (1 equiv), (3-benzyloxyphenyl)acetylene (2 equiv), CuI (6 mol %), $[(\text{PPh}_3)_2\text{PdCl}_2]$ (6 mol %), THF/ NEt_3 (2.5:1), RT, 18 h; f) **15** (1 equiv), H_2 (4 atm), Pd/C (10 mol %), EtOH, 30°C, 22 h; g) **16** (1 equiv), methyl bromoacetate (1.3 equiv), K_2CO_3 (1.3 equiv), DMF, RT, 24 h; h) **17** (1 equiv), 1 N NaOH (10 equiv), MeOH, RT, 6.5 h. Bn = benzyl, DME = 1,2-dimethoxyethane, THF = tetrahydrofuran.

treatment of thrombotic diseases (Scheme 8). Suzuki–Miyaura coupling of **4i** with iodobenzene afforded *ortho*-terphenyl **11**, which was then converted into **12** by iododesilylation using iodine monochloride. Sonogashira coupling of **12** with propargyl alcohol gave **13**, the alkynyl moiety of which was hydrogenated to give F050 (**14**, 81% overall yield based on **4i**). Similarly, **12** was coupled with 3-(benzyloxy)phenylacetylene to produce diarylacetylene **15**, which was transformed into **16** by hydrogenation and deprotection of the benzyl moiety in one step. Subsequent alkylation of the hydroxy group with methyl bromoacetate afforded **17**, and subsequent hydrolysis gave F1070 (**18**, 44% overall yield based on **4i**).

In conclusion, we have demonstrated that an easily accessible copper–phosphine complex served as a potent catalyst for the direct formation of diverse *cis-vic*-diboryllalkenes (or *vic*-diborylarenes) by diborylation of alkynes (or arynes). With this catalyst, propargyl ethers smoothly underwent tetra- and triborylation by formal C–O bond borylation accompanied by diborylation of the alkyne moieties. Moreover, the resulting diborylation product has been demonstrated to serve as an intermediate in the synthesis of the pharmacologically significant compounds F050 and F1070. Further studies on insertion reactions of unsaturated hydro-

carbons into boron-containing σ bonds under copper catalysis, and on synthetic applications of the borylation products are in progress.

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