

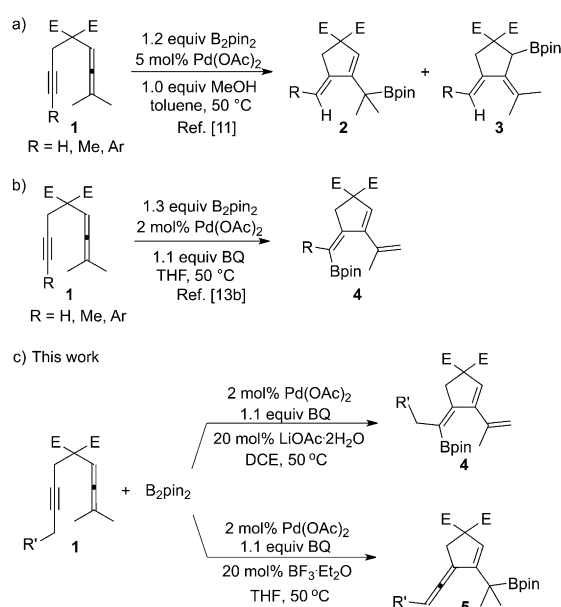
# Control of Selectivity in Palladium-Catalyzed Oxidative Carbocyclization/Borylation of Allenynes\*\*

Youqian Deng, Teresa Bartholomeyzik, and Jan-E. Bäckvall\*

Organoboronates are convenient and versatile reagents owing to their comparatively low toxicity, high functional group compatibility, and good stability.<sup>[1]</sup> Moreover, these compounds can easily be oxidized to alcohols<sup>[2]</sup> or used to construct new C–C bonds by Suzuki–Miyaura cross-couplings.<sup>[3]</sup> Because of the broad applications of these boronates, many borylation methods have been developed.<sup>[4–7]</sup> Amongst the routes reported for C–B bond formation the most common are Miyaura borylation,<sup>[4]</sup> hydroboration,<sup>[5]</sup> and the reaction of lithium or magnesium organometallic compounds with borate esters.<sup>[1]</sup> In addition, recent developments in transition-metal-catalyzed C–H borylation reactions have also provided efficient access to boronates.<sup>[6]</sup>

Furthermore, by combining the borylation with a C–C bond-forming cyclization, complex molecules suitable for various further functionalizations could be obtained in one step.<sup>[8–11,13b,d]</sup> Such borylating carbocyclizations have been successfully developed by the group of Cárdenas.<sup>[9–11]</sup> Starting from unsaturated compounds, such as enynes,<sup>[9]</sup> enediynes,<sup>[10]</sup> enallenes,<sup>[11]</sup> and allenynes,<sup>[11]</sup> homoallylic or allylic boronates were prepared under palladium(0) catalysis. For instance, the non-oxidative borylating carbocyclization of allenynes **1** in the presence of bis(pinacolato)diboron ( $B_2pin_2$ ) yielded two isomers (**2** and **3**), where borylation occurred at the allene (Scheme 1 a).<sup>[11]</sup>

In ongoing investigations our research group has been studying oxidative  $Pd^{II}$ -catalyzed carbocyclizations of various unsaturated molecules.<sup>[12–15]</sup> Recently we accomplished the carbocyclization/arylation of allenynes with arylboronic acids.<sup>[13b]</sup> Also, some preliminary results regarding carbocyclization/borylation were obtained with differently substituted 1,5-allenynes (**1**; R = H, Me, Ar), which only gave borylated triene products **4** (Scheme 1 b).<sup>[13b]</sup> However, under carbocyclization/arylation conditions alkyl-substituted allenynes



**Scheme 1.** Palladium-catalyzed borylating carbocyclizations of allenynes: a) under non-oxidative conditions;<sup>[11]</sup> b) under oxidative conditions;<sup>[13b]</sup> c) under selective oxidative conditions. E =  $CO_2Me$ .

afforded two different constitutional isomers (arylated trienes and arylated vinylallenes) in a ratio determined by the substitution on the starting allenyne.<sup>[13b]</sup> The aim of the present study was to develop a carbocyclization/borylation that can be directed towards either a borylated triene or a borylated vinylallene by control of the reaction conditions (Scheme 1 c). We now report a highly selective oxidative carbocyclization/borylation of allenynes **1** with  $B_2pin_2$  under  $Pd^{II}$  catalysis with *p*-benzoquinone (BQ) as the oxidant. The use of  $LiOAc \cdot 2H_2O$  in 1,2-dichloroethane (DCE) or  $BF_3 \cdot Et_2O$  in THF addressed the issue of selectivity, to give either borylated trienes **4** or borylated vinylallenes **5**, respectively.

We first studied the reaction of ethyl-substituted allenyne **1a** with  $B_2pin_2$  under the original carbocyclization/borylation conditions (Scheme 1 b).<sup>[13b]</sup> The use of a catalytic amount of palladium acetate (2 mol%) and stoichiometric amounts of BQ (1.1 equiv) in THF at 50 °C led to an isomeric mixture of borylated triene **4a** and borylated vinylallene **5a** in 28% and 14% yield, respectively (Table 1, entry 1). Analyzing the effect of different solvents showed that a higher selectivity for **4a** was obtained when DCE was used as the solvent (in Table 1, entry 4 vs. entries 1–3). Furthermore, upon the addition of catalytic amounts (20 mol%) of a basic salt,

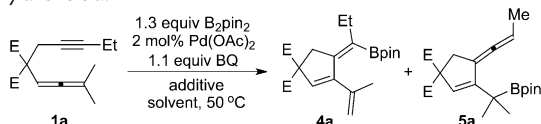
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**Table 1:** Solvent and additive effect in the selective formation of triene **4a** or vinylallene **5a**.<sup>[a]</sup>



Entry	Solvent	Additive (20 mol %)	Time [h]	Yield of <b>4a/5a</b> [%] <sup>[b]</sup>	<b>4a/5a</b>
1	THF	–	15	28:14	2:1
2	cyclohexane	–	15	33:34	1:1
3	CH <sub>2</sub> Cl <sub>2</sub>	–	15	39:35	1:1
4	DCE	–	15	61:13	5:1
5	DCE	Na <sub>2</sub> CO <sub>3</sub>	15	70:7	10:1
6	DCE	NaOAc	15	67:6	11:1
7	DCE	LiOAc·2H <sub>2</sub> O	15	73:7	10:1
8 <sup>[c]</sup>	DCE	LiOAc·2H <sub>2</sub> O	15	71:10	7:1
9	THF	HOAc	20	19:16	ca. 1:1
10	THF	<i>p</i> -TSA	20	0	–
11	THF	BF <sub>3</sub> ·Et <sub>2</sub> O	20	3:78	1:26
12 <sup>[d]</sup>	THF	–	20	5:60	1:12
13	THF	Et <sub>3</sub> B	20	8:24	1:3

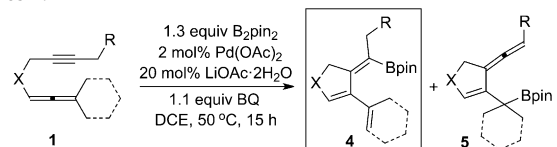
[a] Unless otherwise noted, **1a**, B<sub>2</sub>pin<sub>2</sub> (1.3 equiv), Pd(OAc)<sub>2</sub> (2 mol%), BQ (1.1 equiv), and indicated additive (20 mol%) were dissolved in the indicated solvent (5 mL mmol<sup>-1</sup>) and stirred at 50 °C in a sealed tube. [b] Yield was determined by <sup>1</sup>H NMR spectroscopy using anisole as internal standard. [c] 50 mol% of LiOAc·2H<sub>2</sub>O was added. [d] 2 mol% of [Pd(CH<sub>3</sub>CN)<sub>4</sub>][(BF<sub>4</sub>)<sub>2</sub>] was used in place of Pd(OAc)<sub>2</sub>. E = CO<sub>2</sub>Me.

such as Na<sub>2</sub>CO<sub>3</sub>, NaOAc, or LiOAc·2H<sub>2</sub>O, formation of triene **4a** was favored (Table 1, entries 5–7). Boronate **4a** was obtained in high selectivity in 73% yield with LiOAc·2H<sub>2</sub>O as the base additive and with DCE as the solvent (Table 1, entry 7; defined as Method A). An increase of the amount of LiOAc·2H<sub>2</sub>O to 50 mol% gave no additional improvement in selectivity or yield (Table 1, entry 8).

The finding that the addition of a basic salt substantially enhanced the selective formation of alkenyl boronate **4** encouraged us to study the effect of acidic reaction conditions. To our surprise, the addition of a Brønsted acid, such as HOAc, generated an approximately 1:1 mixture of **4a** and **5a** in moderate yields (Table 1, entry 9) and the use of *p*-toluenesulfonic acid (*p*-TSA) even did not afford any borylation products (Table 1, entry 10). However, the use of a Lewis acid, BF<sub>3</sub>·Et<sub>2</sub>O, resulted in a high selectivity for **5** and afforded products **4a** and **5a** in 3% and 78% yield, respectively (Table 1, entry 11; defined as Method B). Notably when the cationic palladium catalyst [Pd(CH<sub>3</sub>CN)<sub>4</sub>][(BF<sub>4</sub>)<sub>2</sub>] was used the same trend in selectivity was seen but a lower yield was obtained (Table 1, entry 12 vs. entry 11).<sup>[16]</sup> The structurally similar Lewis acid BEt<sub>3</sub> was also tried and moderate selectivity for **5a** over **4a** was seen with low yields of products (Table 1, entry 13).

With the optimized conditions for the selective formation of borylated triene **4a** established, we applied them to differently substituted allenynes (Table 2). The allenynes bearing a methyl group on the alkyne moiety (**1b** and **1c**) afforded the borylated trienes as the sole products (Table 2, entries 2 and 3). For substrates with a longer alkyl group (**1d** and **1f**) on the alkyne moiety, the competing allene formation took place to a notable extent (Table 2, entries 4 and 6), but

**Table 2:** Selective carbocyclization of allenynes **1** yielding borylated trienes **4**.<sup>[a]</sup>



Entry	Allenyne	Product	<b>4/5</b> <sup>[b]</sup>	Yield of <b>4</b> [%], <sup>[c]</sup> ratio <sup>[b]</sup>
1	<b>1a</b>	<b>4a</b>	10:1	73
2	<b>1b</b>	<b>4b</b>	99:1	92
3	<b>1c</b>	<b>4c</b> Z/E = 3.3 + <b>4c'</b>	99:1	55 <b>4c/4c'</b> = 2.4:1
4	<b>1d</b>	<b>4d</b>	9:1 > 11:1	81 92 <sup>[d]</sup>
5	<b>1e</b>	<b>4e</b> Z/E = 3.5 + <b>4e'</b>	18:1	65 <b>4e/4e'</b> = 2.3:1
6	<b>1f</b>	<b>4f</b> + <b>4f'</b>	5:1	48 <b>4f/4f'</b> = 1.4:1
7	<b>1g</b>	<b>4g</b>	> 20:1	57

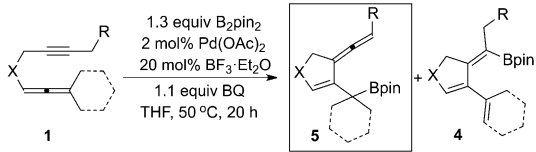
[a] Unless otherwise noted, **1** (0.1–0.2 mmol), B<sub>2</sub>pin<sub>2</sub> (1.3 equiv), Pd(OAc)<sub>2</sub> (2 mol%), BQ (1.1 equiv), and LiOAc·2H<sub>2</sub>O (20 mol%) were dissolved in DCE (5 mL mmol<sup>-1</sup>) and stirred at 50 °C for 15 h. [b] The ratio was determined by <sup>1</sup>H NMR analysis of the reaction mixture. [c] Yield of the isolated product. [d] 1 mmol of **1d** was used. E = CO<sub>2</sub>Me.

the corresponding triene products **4d** and **4f/4f'** could be isolated in good to moderate yields. In those cases where the substrates were unsymmetrically substituted at the allene

moiety (**1c** and **1e**) a comparatively high selectivity for the triene products was observed (Table 2, entries 3 and 5). However, a mixture of borylated triene products was obtained, with a preference for formation of the products with the more substituted double bond. Products **4c** and **4e** were obtained as a mixture of *Z/E* isomers in a ratio of 3.3:1 and 3.5:1, respectively. The allenyne **1f** with a cyclohexylidene group on the allene cyclized to give a mixture of isomers **4f** and **4f'**, where the formation of **4f** could be explained by a Pd-catalyzed isomerization of **4f'** (Table 2, entry 6; for the detailed mechanism, please see the Supporting Information). Moreover, the reaction of allenyne **1g**, having two benzyl ether groups on the linker part X, also gave borylated triene product **4g** selectively in 57% yield (Table 2, entry 7), thus proving that the malonate group of linker X is not necessary for a successful transformation.

The optimized reaction conditions for the selective formation of borylated vinylallene **5** (20 mol % of  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ ,

**Table 3:** Selective carbocyclization of allenyne **1** yielding borylated vinylallenes **5**.<sup>[a]</sup>

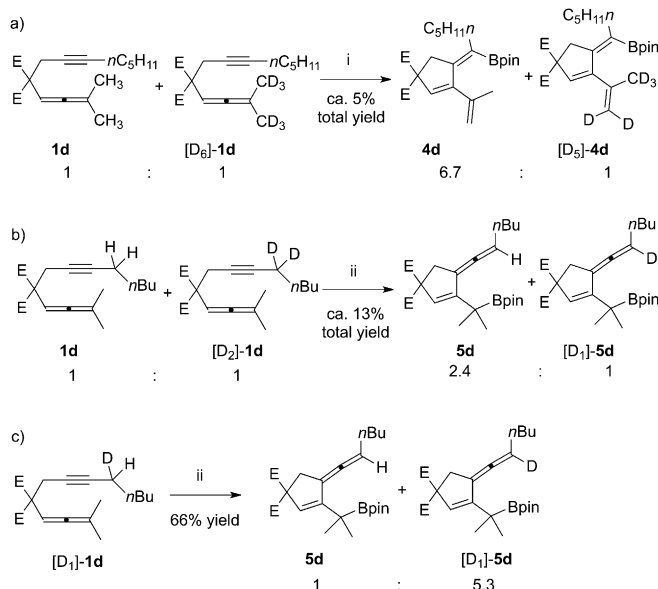


Entry	Allenyne	Product	5/4 <sup>[b]</sup>	Yield of <b>5</b> [%] <sup>[c]</sup>
1			> 20:1	77
2			> 20:1	73
3			> 20:1	56
4			> 20:1	79 87 <sup>[d]</sup>
5			20:1	77
6			> 20:1	70
7 <sup>[e]</sup>			> 20:1	37

[a] Unless otherwise noted, **1** (0.1–0.2 mmol),  $\text{B}_2\text{pin}_2$  (1.3 equiv),  $\text{Pd}(\text{OAc})_2$  (2 mol%), BQ (1.1 equiv), and  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  (20 mol%) were dissolved in THF (5 mL mmol<sup>-1</sup>) and stirred at 50 °C for 20 h. [b] Ratio determined by <sup>1</sup>H NMR analysis of the crude reaction mixture. [c] Yield of the isolated product. [d] 1 mmol of **1d** was used. [e] 2 mol % of  $[\text{Pd}(\text{CH}_3\text{CN})_4][(\text{BF}_4)_2]$  was used in place of  $\text{Pd}(\text{OAc})_2$  and  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ . E =  $\text{CO}_2\text{Me}$ .

Method B) were applied to various allenyne (Table 3). Allenyne **1a–1f** were transformed into vinylallenic boronates **5a–5f**; for most cases the yield was between 70% and 80% and the formation of the corresponding triene isomers **4a–4f** was efficiently suppressed. Even the methyl-substituted substrate **1b**, which intrinsically favors formation of triene **4b**,<sup>[13b]</sup> displayed opposite selectivity under these reaction conditions, that is, favoring vinylallene formation (Table 3, entry 2). The reaction of allenyne **1g** under the standard conditions of Table 3 was sluggish and did not give the desired product **5g**, probably because of the incompatibility between the benzyl ether group and  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ . However, by switching the palladium catalyst to  $[\text{Pd}(\text{CH}_3\text{CN})_4][(\text{BF}_4)_2]$  and in the absence of  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ , product **5g** was obtained in 37% yield (entry 7).

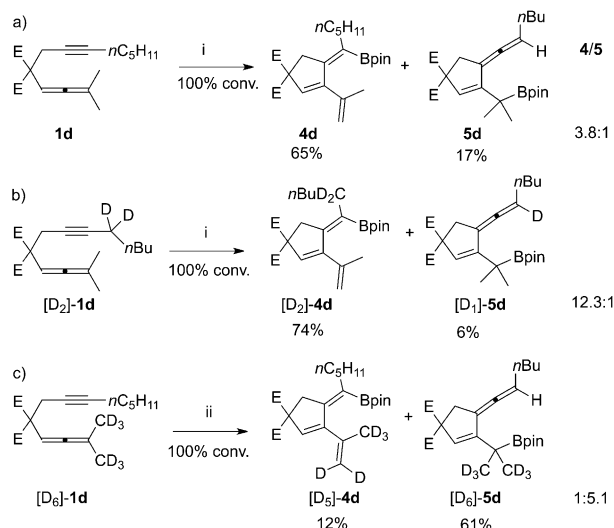
To gain further insights into the mechanism of the oxidative carbocyclization/borylation, kinetic deuterium isotope effects were studied (Scheme 2). An intermolecular competition experiment using **1d** and its hexadeuterated derivative  $[\text{D}_6]\text{-1d}$  under the conditions for selective triene formation for 1 h provided a large intermolecular KIE value of 6.7<sup>[17]</sup> (Scheme 2a). This result indicates that the allylic C–H bond cleavage involved has to occur prior to any irreversible step of the reaction, for example, the carbocyclization step.<sup>[18]</sup> On the other hand, when a 1:1 mixture of **1d** and  $[\text{D}_2]\text{-1d}$  was subjected to the conditions for selective vinylallene formation for 1 h the ratio between **5d** and  $[\text{D}_1]\text{-5d}$  was 2.4, from which the KIE was determined to be 2.7<sup>[19]</sup> (Scheme 2b).<sup>[17]</sup> The intrinsic KIE from intramolecular competition for vinylallene formation was determined to be 5.3<sup>[17]</sup> by the use of  $[\text{D}_1]\text{-1d}$  as the allenyne substrate (Scheme 2c). The results in Scheme 2b and 2c indicate that the propargylic C–H bond cleavage does not fully determine the selectivity



**Scheme 2.** Kinetic isotope effect study. Reaction conditions: i)  $\text{B}_2\text{pin}_2$  (1.3 equiv),  $\text{Pd}(\text{OAc})_2$  (2 mol%), BQ (1.1 equiv),  $\text{LiOAc} \cdot 2\text{H}_2\text{O}$  (20 mol%), DCE, 50 °C, 1 h. ii)  $\text{B}_2\text{pin}_2$  (1.3 equiv),  $\text{Pd}(\text{OAc})_2$  (2 mol%), BQ (1.1 equiv),  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  (20 mol%), THF, 50 °C, 1 h for b) and 20 h for c). E =  $\text{CO}_2\text{Me}$ .

between **5d** and  $[D_1]$ -**5d** in the competitive experiment (Scheme 2b).<sup>[18]</sup>

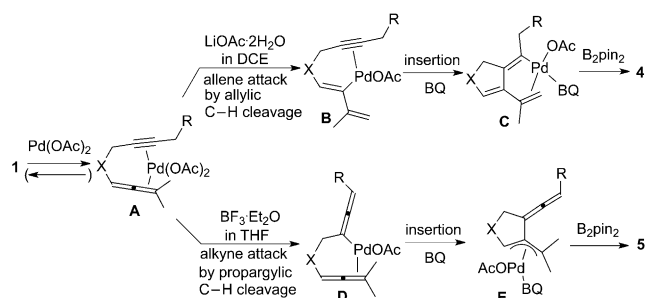
Three control experiments with allenyne **1d** and the corresponding deuterium-labeled allenyne  $[D_2]$ -**1d** and  $[D_6]$ -**1d** were conducted under palladium catalysis in the absence of any additional basic or acidic additive and using DCE as the solvent (Scheme 3). Under these conditions the reaction



**Scheme 3.** Effect of isotope substitution on product distribution. Reaction conditions: i)  $B_2pin_2$  (1.3 equiv),  $Pd(OAc)_2$  (2 mol%), BQ (1.1 equiv), DCE, 50 °C, 15 h. ii)  $B_2pin_2$  (1.3 equiv),  $Pd(OAc)_2$  (5 mol%), BQ (1.1 equiv), DCE, 50 °C, 15 h. E =  $CO_2Me$ .

of **1d** gave a mixture of **4d** and **5d** in a ratio of 3.8:1 (Scheme 3a). When substrate  $[D_2]$ -**1d** was employed (Scheme 3b) under the same reaction conditions, the ratio increased to 12.3:1.<sup>[20]</sup> Allenyne  $[D_6]$ -**1d** showed the opposite selectivity, with  $[D_5]$ -**4d** and  $[D_6]$ -**5d** being formed in a ratio of 1:5.1<sup>[20]</sup> (Scheme 3c).

The results in Scheme 2 and Scheme 3 indicate that competing allylic and propargylic C–H bond cleavage occurs in **1**, and this determines the ratio of boronates **4** and **5** (Scheme 4). The allene attack on  $Pd^{II}$  complex **A** through allylic C–H bond cleavage<sup>[12, 13a–d]</sup> would give **B** and subsequent alkyne insertion would generate intermediate **C**.



**Scheme 4.** Proposed mechanism for palladium-catalyzed oxidative selective carbocyclization/borylation of allenyne **1**.

Transmetalation of **C** with  $B_2pin_2$  and reductive elimination would form product **4**. The competing alkyne attack through propargylic C–H bond cleavage in **A** would produce allenyl-palladium intermediate **D**. Intramolecular vinylpalladation of the allene moiety would generate  $(\pi$ -allyl)palladium intermediate **E**. Transmetalation with  $B_2pin_2$  and subsequent reductive elimination would give **5**. The mechanism in Scheme 4 is supported by the kinetic isotope effects and the experiments with deuterium-labeled compounds (Scheme 2 and Scheme 3). The lower kinetic isotope effect observed for the competitive experiment in Scheme 2b compared to the intramolecular experiment in Scheme 2c may reflect that **1** and **A** are not in full equilibrium under the conditions for formation of **5**. In the path for formation of **5** it is likely that  $BF_3 \cdot Et_2O$  creates a cationic palladium species, which interacts better with the acetylene compared to the allene in **A**.<sup>[21]</sup>

In summary, we have developed an unprecedented selective  $Pd^{II}$ -catalyzed carbocyclization/borylation of allenyne under oxidative conditions. By controlling the reaction conditions the reaction can be directed to either the triene **4** or the vinylallene **5**. On the basis of the results of deuterium-labeling experiments, we propose that the reactions of allenyne proceed through competing allylic and propargylic C–H bond cleavage pathways to give borylated trienes and borylated vinylallenes, respectively.

## Experimental Section

Typical experimental procedure for palladium-catalyzed oxidative borylating carbocyclization of allenyne **1** to boronate **4**: **1a** (26.0 mg, 0.10 mmol) and 0.5 mL of DCE were added to a mixture of  $B_2pin_2$  (33.1 mg, 0.13 mmol), BQ (12.2 mg, 0.11 mmol),  $Pd(OAc)_2$  (0.5 mg, 0.002 mmol), and  $LiOAc \cdot 2H_2O$  (1.8 mg, 0.02 mmol) at RT. The reaction was stirred at 50 °C for 15 h. After the reaction was complete, as monitored by TLC, evaporation and column chromatography on silica gel (pentane/ethyl acetate = 10:1) afforded **4a** (27.9 mg, 73 %) as a liquid;  $^1H$  NMR (500 MHz,  $CDCl_3$ ):  $\delta$  = 5.93 (s, 1H), 5.02–5.00 (m, 2H), 3.72 (s, 6H), 3.20 (s, 2H), 2.19 (q,  $J$  = 7.5 Hz, 2H), 1.95 (s, 3H), 1.26 (s, 12H), 1.02 ppm (t,  $J$  = 7.5 Hz, 3H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ ):  $\delta$  = 171.1, 151.1, 147.9, 139.8, 129.1, 116.6, 83.3, 63.0, 52.9, 37.5, 27.0, 25.2, 23.8, 13.4 ppm; HRMS (ESI): calc. for  $C_{21}H_{31}BNaO_6$  [ $M + Na$ ] $^+$ : 413.2110; found: 413.2113.

Typical experimental procedure for palladium-catalyzed oxidative borylating carbocyclization of allenyne **1** to boronate **5**: **1a** (52.7 mg, 0.20 mmol) and 1.0 mL of THF were added to a mixture of  $B_2pin_2$  (66.2 mg, 0.26 mmol), BQ (24.0 mg, 0.22 mmol),  $Pd(OAc)_2$  (1.0 mg, 0.004 mmol), and  $BF_3 \cdot Et_2O$  (6  $\mu$ L, 0.04 mmol) at RT. The reaction was stirred at 50 °C for 20 h. After the reaction was complete, as monitored by TLC, evaporation and column chromatography on silica gel (pentane/ethyl acetate = 10/1) afforded **5a** (59.6 mg, 77 %) as a liquid;  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  = 5.55 (d,  $J$  = 1.6 Hz, 1H), 5.34–5.23 (m, 1H), 3.716 (s, 3H), 3.715 (s, 3H), 3.19–3.17 (m, 2H), 1.68 (d,  $J$  = 7.2 Hz, 3H), 1.18 (s, 12H), 1.17 (s, 3H), 1.13 ppm (s, 3H);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ ):  $\delta$  = 199.1, 171.5, 171.3, 153.8, 122.9, 107.1, 91.2, 83.1, 63.5, 52.7, 36.5, 25.0, 24.7, 24.5, 23.9, 23.8, 14.8 ppm; HRMS (ESI): calcd for  $C_{21}H_{31}BNaO_6$  [ $M + Na$ ] $^+$ : 413.2110; found: 413.2103.

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