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

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

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.[8–11,13b,d] Such borylating carbocyclizations have been successfully developed by the group of Cárdenas.[9–11] Starting from unsaturated compounds, such as enynes,[9] enediynes,[10] enallenes,[11] and allenynes,[11] 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\textsubscript{2}pin\textsubscript{2}) yielded two isomers (2 and 3), where borylation occurred at the allene (Scheme 1a).[11]

In ongoing investigations our research group has been studying oxidative Pd\textsuperscript{II}-catalyzed carbocyclizations of various unsaturated molecules.[8–11,13b,d] Recently we accomplished the carbocyclization/arylation of allenynes with arylboronic acids.[13b] Also, some preliminary results regarding carbocyclization/borylation were obtained with differently substituted 1,5-allenyne (1: R = H, Me, Ar), which only gave borylated triene products 4 (Scheme 1b).[13b] However, under carbocyclization/arylation conditions alkyl-substituted allenynes afforded two different constitutional isomers (arylated trienes and arylated vinylallenynes) in a ratio determined by the substitution on the starting allenynes.[13b] 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 1c). We now report a highly selective oxidative carbocyclization/borylation of allenynes 1 with B\textsubscript{2}pin, under Pd\textsuperscript{II} catalysis with p-benzoquinone (BQ) as the oxidant. The use of LiOAc:H\textsubscript{2}O in 1,2-dichloroethane (DCE) or BF\textsubscript{3}:Et\textsubscript{2}O in THF addressed the issue of selectivity, to give either borylated trienes 4 or borylated vinylallenynes 5, respectively.

We first studied the reaction of ethyl-substituted allene 1a with B\textsubscript{2}pin\textsubscript{2} under the original carbocyclization/borylation conditions (Scheme 1b).[13b] 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,
Selective carbocyclization of allenynes 1 yielding borylated trienes 4.[5]

Table 2: Selective carbocyclization of allenynes 1 yielding borylated trienes 4.[5]

| Entry | Allenyne Product | 4/5[6] | Yield of 4 [%][6] |
|-------|------------------|--------|------------------|
| 1     |                  |        |                  |
| 2     |                  |        |                  |
| 3     |                  |        |                  |
| 4     |                  |        |                  |
| 5     |                  |        |                  |
| 6     |                  |        |                  |
| 7     |                  |        |                  |

[a] Unless otherwise noted, 1 (0.1–0.2 mmol), B(pin) (1.3 equiv), Pd(OAc)_2 (2 mol%), BQ (1.1 equiv), and LiOAc·2H_2O (20 mol%) were dissolved in DCE (5 mL mmol⁻¹) and stirred at 50°C for 15 h. [b] The ratio was determined by ¹H NMR analysis of the reaction mixture. [c] Yield of the isolated product. [d] 1 mmol of 1d was used. E = CO_2Me.

Table 1: Solvent and additive effect in the selective formation of triene 4a or vinyllene 5a.[6]

| Entry | Solvent | Additive | Time | Yield of 4a/5a [%][6] |
|-------|---------|----------|------|-----------------------|
| 1     | THF     | –        | 15   | 28:14 2:1            |
| 2     | cyclohexane | –      | 15   | 33:34 1:1            |
| 3     | CHCl_3  | –        | 15   | 39:35 1:1            |
| 4     | DCE     | –        | 15   | 61:13 5:1            |
| 5     | DCE     | Na_2CO_3 | 15   | 70:7 10:1           |
| 6     | DCE     | NaOAc    | 15   | 67:6 11:1           |
| 7     | DCE     | LiOAc·2H_2O | 15 | 73:7 10:1          |
| 8     | DCE     | LiOAc·2H_2O | 15 | 71:10 7:1         |
| 9     | THF     | HOAc     | 20   | 19:16 ca. 1:1      |
| 10    | THF     | p-TSA    | 20   | 0                 |
| 11    | THF     | BF_3·Et_2O | 20 | 3:78 1:26         |
| 12[6] | THF     | Et_3B    | 20   | 5:60 1:12          |
| 13    | THF     | –        | 20   | 8:24 1:3          |

[a] Unless otherwise noted, 1, B(pin) (1.3 equiv), Pd(OAc)_2 (2 mol%), BQ (1.1 equiv), and indicated additive (20 mol%) were dissolved in the indicated solvent (5 mL mmol⁻¹) and stirred at 50°C in a sealed tube. [b] Yield was determined by ¹H NMR spectroscopy using anisole as internal standard. [c] 50 mol % of LiOAc·2H_2O was added. [d] 2 mol % of [Pd(CH_3CN)_4][(BF_4)_2] was used in place of Pd(OAc)_2. E = CO_2Me.

such as Na_2CO_3, NaOAc, or LiOAc·2H_2O, formation of triene 4a was favored (Table 1, entries 5–7). Boronate 4a was obtained in high selectivity in 73% yield with LiOAc·2H_2O was favored (Table 1, entries 5–7). Boronate 4a was obtained in high selectivity in 73% yield with LiOAc·2H_2O 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_2O 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 alkynyl 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_3·Et_2O, resulted in a high selectivity for borylation products (Table 1, entry 10). However, the use of a Lewis acid, BF_3·Et_2O, resulted in a high selectivity for 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_3CN)_4][BF_4]_2 was used the same trend in selectivity was seen but a lower yield was obtained (Table 1, entry 12 vs. entry 11).[6] The structurally similar Lewis acid BEt_3 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 the corresponding triene products 4d and 4f/4f' could be isolated in good to moderate yields. In those cases where the substrates are unsymmetrically substituted at the allene
Selective carbocyclization of allenynes

Table 3: Selective carbocyclization of allenynes 1 yielding borylated vinylallenes 5.

| Entry | Allenyne | Product | $S/4[^{a}]$ | Yield of 5 [%][^c] |
|-------|----------|---------|-------------|------------------|
| 1     | 1b       | E       | >20:1       | 77               |
| 2     | 1b       | E       | >20:1       | 73               |
| 3     | 1c       | E       | >20:1       | 56               |
| 4     | 1d       | E       | >20:1       | 79               |
| 5     | 1e       | E       | 20:1        | 77               |
| 6     | 1f       | E       | >20:1       | 70               |
| 7[^f] | 1g       | E       | >20:1       | 37               |

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

Method B) were applied to various allenynes (Table 3). Allenynes 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,[13b] displayed opposite selectivity under these reaction conditions. However, by switching the palladium catalyst to [Pd(CH$_3$CN)$_4$]$_2$·(BF$_4$)$_2$ and in the absence of BF$_3$·Et$_2$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 [D$_6$]-1d under the conditions for selective triene formation for 1 h provided a large intermolecular KIE value of 6.7[17] (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.[18] On the other hand, when a 1:1 mixture of 1d and [D$_2$]-1d was subjected to the conditions for selective vinylallene formation for 1 h the ratio between 5d and [D$_2$]-5d was 2.4, from which the KIE was determined to 2.7[10] (Scheme 2b).[17] The intrinsic KIE from intramolecular competition for vinylallene formation was determined to 5.3[17] by the use of [D$_2$]-1d as the allene substrate (Scheme 2c). The results in Scheme 2b and 2c indicate that the propargylic C–H bond cleavage does not fully determine the selectivity.
between [D4]-5d and [D5]-5d in the competitive experiment (Scheme 2b).\[19\]

Three control experiments with allene 1d and the corresponding deuterium-labeled allenynes [D2]-1d and [D3]-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 of 1d gave a mixture of 4d and 5d in a ratio of 3.8:1 (Scheme 3a). When substrate [D2]-1d was employed (Scheme 3b) under the same reaction conditions, the ratio increased to 12.3:1.\[20\] Allenylene [D3]-1d showed the opposite selectivity, with [D2]-4d and [D3]-5d being formed in a ratio of 1:5.1.\[20\] (Scheme 3c).

The results in Scheme 2 and Scheme 3 indicate that competing allylic and propargylic C–H bond cleavage occurs in 1d, and this determines the ratio of boronates 4 and 5 (Scheme 4). The allene attack on PdII complex A through allylic C–H bond cleavage\[12,13a–d\] would give B and subsequent alkyne insertion would generate intermediate C. Transmetalation of C with B2pin2 and reductive elimination would form product 4. The competing alkyne attack through propargylic C–H bond cleavage in A would produce allenylpalladium intermediate D. Intramolecular vinylpalladation of the allene moiety would generate (π-allyl)palladium intermediate E. Transmetalation with B2pin2 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 BF3·Et2O creates a cationic palladium species, which interacts better with the acetylene compared to the allene in A.\[21\]

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

**Experimental Section**

Typical experimental procedure for palladium-catalyzed oxidative borylating carbocyclization of allene 1 to boronate 4: 1a (260.0 mg, 0.10 mmol) and 0.5 mL of DCE were added to a mixture of B2pin2 (33.1 mg, 0.13 mmol), BQ (12.2 mg, 0.11 mmol), Pd(OAc)2 (0.5 mg, 0.002 mmol), and LiOAc·2H2O (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, CDCl3): δ = 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); 13C NMR (125 MHz, CDCl3): δ = 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): calcd for C21H31BNaO6: [M + Na]+: 413.2110; found: 413.2113.

Typical experimental procedure for palladium-catalyzed oxidative borylating carbocyclization of allene 1 to boronate 5: 1a (52.7 mg, 0.20 mmol) and 1.0 mL of THF were added to a mixture of B2pin2 (66.2 mg, 0.26 mmol), BQ (24.0 mg, 0.22 mmol), Pd(OAc)2 (1.0 mg, 0.004 mmol), and BF3·Et2O (6 μL, 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, CDCl3): δ = 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), 1.95 (s, 3H), 1.26 (s, 12H), 1.18 ppm (s, 3H), 1.13 ppm (s, 3H); 13C NMR (100 MHz, CDCl3): δ = 171.5, 171.3, 153.8, 122.9, 107.1, 91.2, 83.1, 63.5, 52.7, 36.5, 25.0, 24.7, 23.9, 23.8, 14.8 ppm; HRMS (ESI): calcd for C22H20BNaO6 [M + Na]+: 413.2110; found: 413.2103.

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