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Palladium-Catalyzed Oxidative Arylating Carbocyclization of Allenynes: Control of Selectivity and Role of H₂O**

Teresa Bartholomeyzik, Javier Mazuela, Robert Pendrill, Youqian Deng,* and Jan-E. Bäckvall*

Abstract: Highly selective protocols for the carbocyclization/arylation of allenynes using arylboronic acids are reported. Arylated vinylallenes are obtained with the use of BF₃·Et₂O as an additive, whereas addition of water leads to arylated trienes. These conditions provide the respective products with excellent selectivities (generally >97/3) for a range of boronic acids and different allenynes. It has been revealed that water plays a crucial role for the product distribution.

Palladium-catalyzed carbocyclization reactions are powerful tools for the formation of cyclic systems in an atom-economical fashion.^[1–3] In particular, in natural product synthesis considerable attention has been directed toward stereo- and regioselectivity of carbocyclizations,^[2] and there is a continuous demand for new highly selective methods. During the past decade our group has been studying palladium-catalyzed carbocyclization reactions under oxidative conditions.^[4–7] In many of these examples the construction of the ring proceeds with high stereoselectivity and is followed by a regioselective functionalization.^[5] However, more recently we discovered the oxidative carbocyclization of allenynes under arylating conditions that led to a mixture of constitutional isomers.^[6] Depending on the specific structure of the allenyne substrate **1** a mixture of phenylated vinylallene **2** or phenylated triene **3** was obtained with Pd(OAc)₂ as catalyst and PhB(OH)₂ as the arylating agent (Scheme 1).^[6] Under these reaction conditions allenyne **1a** afforded an inseparable mixture of vinylallene **2a** and triene **3a** in a ratio of 1:3, whereas **1b** reacted under the same conditions to yield **2b** and **3b** in a ratio of 7.4:1 (Scheme 1). In this report we present protocols that allow the selective formation of either of the arylated carbocycles **2** or **3**.

In the related Pd-catalyzed borylating carbocyclization, which we previously studied, we were able to obtain full control of selectivity to give either borylated triene or borylated vinylallene

Scheme 1. Palladium-catalyzed oxidative arylating carbocyclization of allenynes **1**.^[6] E = CO₂Me, BQ = 1,4-benzoquinone.

products by the use of additives.^[7] Keeping these results in mind we started modifying the original conditions for the arylating carbocyclization (Scheme 1) in a similar fashion.

Initially we focused on developing a method for the exclusive formation of vinylallene **2a** from **1a**, thus reversing the inherent selectivity for triene **3a**. We found that the use of different acidic additives increased the ratio **2a**:**3a** (Table S1), and in analogy with the carbocyclization/borylation reaction the best result was obtained with Lewis acid BF₃·Et₂O (10 mol%). The latter conditions afforded **2a** as the sole product in 55% isolated yield (Table 1, entry 1).

The study of the substrate scope under optimized reaction conditions (Table 1) illustrates the previous observation that allenyne substrates with a longer alkyl chain on the alkyne more easily form vinylallene product **2**. When the substituent on the alkyne was an ethyl or pentyl group the reaction gave up to 87% yield (Table 1, entries 1–3 vs. 4–7).^[8] On the other hand, the substitution on the allene moiety (dimethyl, pentamethylene, or methyl ethyl substitution) showed little influence on the carbocyclization of **1** to **2** (Table 1).

We also studied the influence of the structure of the boronic acid in the formation of vinylallenes **2** starting from allenyne **1a** (Table 2). In all cases the reaction proceeded in a highly selective manner independently of the steric and electronic properties of the arylboronic acid to give products in isolated yields of up to 72%. Electron-donating alkyl groups in different positions on the phenyl ring (Table 2, entries 2–5) were tolerated as well as different electron-withdrawing functionalities (Table 2, entries 8–10). A synthetically useful bromo substituent in the *para*- or *meta*-position was found to be compatible with the reaction conditions (Table 2, entries 11 and 12).^[9]

To reverse the selectivity to give trienes **3** in the oxidative carbocyclization of allenynes **1**, we studied the effect of various additives and found that H₂O most efficiently promoted the formation of triene products **3** (see SI). Commercially available arylboronic acids consist of variable mixtures of the boronic acid and the boroxine. In order to ensure reproducibility we therefore decided to use phenyl boroxine.^[10]

[*] Dipl.-Chem. T. Bartholomeyzik, Dr. J. Mazuela, Dr. R. Pendrill, Dr. Y. Deng, Prof. Dr. J.-E. Bäckvall
Department of Organic Chemistry, Arrhenius Laboratory
Stockholm University, SE-106 91 Stockholm, Sweden
Fax: (+46)8-154-908
E-mail: jeb@organ.su.se; dengyouqian@gmail.com
Homepage: <http://www.organ.su.se/jeb/index.html>

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Table 1. Scope of allenynes **1a-g** in the formation of vinylallenes **2a-g**.^[a]

Entry	Substrate	Product	Yield [%] ^[b]	2/3 ^[c]
1			55	98/2
2			66	>99/1
3			63	>99/1
4 ^[d]			85	97/3
5			87	98/2
6 ^[e]			77	94/6
7			82	>99/1

[a] Unless otherwise stated, all reactions were carried out on a 0.2 mmol scale in 1.0 mL of THF at 25 °C. [b] Isolated yield. [c] Determined from the crude ¹H NMR spectrum. [d] 0.1 mmol in 0.5 mL of THF. [e] *dr* = 1/1. E = CO₂Me.

In our optimization study the use of dioxane instead of THF as solvent increased the relative amount of products **3**. However a higher catalyst loading and an increased temperature were required.

Employing the stronger oxidant tetrafluoro-1,4-benzoquinone (tetra-F-BQ) led to further increase in yield of triene products **3** (see Table S4). Under the optimized conditions in Table 3 the scope of allenyne substrates in triene formation was studied.

For all substrates with a methyl group on the alkyne, excellent selectivities for triene products **3** over vinylallene products **2** were obtained (Table 3, entries 1–3). More importantly, also allenynes **1e** and **1b** gave triene products **3e** and **3b**, respectively, with high selectivity under these reaction conditions (Table 3, entries 4 and 5).

Entries 2 and 6 demonstrate that the reaction proceeds with a high selectivity for **3** over **2** also for unsymmetrically substituted allenes and in these cases an inseparable mixture of isomers is obtained. Owing to the fact that triene formation is disfavored for a pentamethylene-substituted allene moiety and that the long alkyl

Table 2. Scope of arylboronic acids in the formation of vinylallenes **2**.^[a]

Entry	Ar	Product	Yield [%] ^[b]	2/3 ^[c]
1	Ph	2a	55	98/2
2	<i>p</i> -MeC ₆ H ₄	2ab	65	97/3
3	<i>m</i> -MeC ₆ H ₄	2ac	64	99/2
4	<i>o</i> -MeC ₆ H ₄	2ad	67	99/1
5	<i>p</i> - ^t BuC ₆ H ₄	2ae	72	98/2
6	<i>p</i> -vinylC ₆ H ₄	2af	46	98/2
7	2-naphthyl	2ag	64	98/2
8	<i>p</i> -CHOC ₆ H ₄	2ah	61	98/2
9	<i>p</i> -CF ₃ C ₆ H ₄	2ai	69	98/2
10	<i>m</i> -NO ₂ C ₆ H ₄	2aj	63	98/2
11	<i>p</i> -BrC ₆ H ₄	2ak	69	99/1
12	<i>m</i> -BrC ₆ H ₄	2al	66	98/2
13	<i>m</i> -MeOC ₆ H ₄	2am	64	98/2
14 ^[d]	<i>p</i> -MeOC ₆ H ₄	2an	43	>99/1

[a] The reactions were carried out on a 0.2 mmol scale in 1.0 mL of THF at 25 °C. [b] Isolated yield. [c] Determined from the crude ¹H NMR spectrum. [d] Ca. 5% of remaining **1a** was detected in the crude ¹H NMR spectrum with anisole as internal standard. E = CO₂Me.

chain favors the vinylallene product,^[6] the selectivity **3g/2g** drops to 80:20 for entry 7 (cf. entry 5). The yield of pure triene product **3g** isolated from the crude reaction mixture was only 40%, because side product **4g** was formed in significant amounts (see Scheme S1). Similarly, a corresponding side product **4d** was formed in the reaction of cyclohexylidene-substituted **1d**, although in smaller amounts.

Unlike allenynes with a longer alkyl chain on the alkyne (**1b**, **1e–1g**) substrate **1a** does not require the use of tetrafluoro-1,4-benzoquinone. When instead BQ (1.1 equiv), phenyl boroxine (0.43 equiv), Pd(OAc)₂ (1 mol%) and H₂O (5.0 equiv) were used in dioxane at 80 °C, triene **3a** was obtained in 78% yield with excellent selectivity **3a/2a** (Table 4, entry 1). The reaction was run with a range of substituted boroxines^[10] to give triene **3** in good yield with high selectivity (Table 4, entries 2–11). Boroxines with an electron-withdrawing substituent (Table 4, entries 6–9) provided slightly better results (80–85% yield) than electron-rich boroxines.^[11,12] The *cis*- configuration of the tetrasubstituted C–C double bond in these triene products was also confirmed by X-ray diffraction studies of **3ak**.^[13]

The ability of added H₂O to selectively promote the formation of triene **3** suggests an interesting influence of the water content on the reaction mechanism. To the best of our knowledge there is no reported case of a palladium-catalyzed reaction involving boronic acids, in which H₂O as an additive influences the selectivity between reaction products.^[14] We investigated the reaction of allenyne **1a** in dioxane with different amounts of added H₂O (Table 5). With no added H₂O the selectivity between products **2a** and **3a** was poor (Table 5, entry 1), but with addition of ≥0.5 equiv of H₂O, triene **3a** was the only cyclization product. However, significant amounts of uncyclized arylated compound **5** was formed as a side product with 0.5–3.0 equiv (Table 5, entries 2–4). Both **3a** and **5** are likely to arise from a common pathway through allene attack on Pd^{II} via allylic C–H cleavage (see Scheme S2). An increase of H₂O to 5.0 equiv resulted in inhibition of side product **5** in favor of an elevated yield of **3a**, which reached 78% with 5.0 equiv of H₂O as the best conditions (Table 5, entry 5).

Table 3. Scope of allenynes **1a–g** in the formation of trienes **3a–g**.^[a]

Entry	Substrate	Product	Yield [%] ^[b]	Selectivity 3/2 ^[c]
1			72 ^[d]	>99/1
2 ^[e]		 E/Z = 1:2.4 3c / 3c' = 2.4:1	68	>99/1
3		 3d/4d = 2:1	73	>99/1
4			65	>99/1
5 ^[d]			66	94/6
6		 E/Z = 1:5.4 3f/3f' = 2.5:1	74	>98/2
7		 33 ^[f]	40	80/20

[a] Unless otherwise stated, the reactions were carried out on a 0.2 mmol scale in 2.0 mL of dioxane at 60 °C for 20 h (entries 1, 3–4) or 24 h (entries 2, 5–7). [b] Isolated yield of products shown. [c] Determined from the crude ¹H NMR. [d] Ca. 5% of remaining **1** was detected in the crude ¹H NMR spectrum with anisole as internal standard. [e] Reaction was performed using 0.15 mmol **1c** in 1.5 mL of dioxane. [f] Yield determined from crude ¹H NMR spectrum with anisole as internal standard. E = CO₂Me.

Table 4. Scope of aryl boroxines in the formation of trienes **3**.^[a]

Entry	Ar	Product	Yield [%] ^[b]	3/2 ^[c]
1	Ph	3a	78	>99/1
2	<i>p</i> -MeC ₆ H ₄	3ab	77	>99/1
3	<i>m</i> -MeC ₆ H ₄	3ac	76	>99/1
4	<i>p</i> - ^t BuC ₆ H ₄	3ad	75	>99/1
5	2-naphthyl	3ae	65	>99/1
6	<i>p</i> -CHOC ₆ H ₄	3af	80	>99/1
7	<i>p</i> -CF ₃ C ₆ H ₄	3ag	83	>99/1
8	<i>m</i> -NO ₂ C ₆ H ₄	3ah	84	>99/1
9	<i>p</i> -BrC ₆ H ₄	3ai	85	>99/1
10	<i>m</i> -MeOC ₆ H ₄	3aj	61	>99/1
11	<i>p</i> -MeOC ₆ H ₄	3ak	76	>99/1

[a] The reactions were carried out on a 0.2 mmol scale in 2 mL of dioxane. [b] Isolated yield. [c] Determined from the crude ¹H NMR spectrum. E = CO₂Me.

We also studied how the equilibrium between phenyl boroxine and phenylboronic varied with the H₂O concentration in deuterated dioxane. We found that hydrolysis of boroxine is complete at a H₂O concentration corresponding to ca. 3.0 equiv of H₂O in Table 5. This indicates that H₂O not only plays the role of hydrolyzing the boroxine, but it also suppresses the formation of **5**.

Table 5. Effect of H₂O on the product ratio (**2a/3a**).^[a,b]

Entry	H ₂ O (equiv)	2a [%]	3a [%]	2a/3a ^[c]	5 [%]
1	-	16	39	29/71	3
2	0.5	-	64	<1/99	15
3	1.0	-	65	<1/99	18
4	3.0	-	74	<1/99	14
5	5.0	-	78	<1/99	7
6	10.0	-	74	<1/99	3

[a] The reactions were carried out on a 0.1 mmol scale in 1.0 mL of dioxane at 80 °C. [b] Yields were determined from the ¹H NMR spectrum with anisole as internal standard. [c] Determined from the ¹H NMR spectrum. E = CO₂Me.

The mechanisms for formation of **2** and **3**, respectively, most likely follow the corresponding mechanisms for the analogous borylating carbocyclization reactions of allenynes.^[7,15]

In summary, control of selectivity was achieved in the palladium-catalyzed oxidative arylating carbocyclization of alkyl-substituted allenynes under mild reaction conditions. With BF₃·Et₂O as an additive (10 mol%) arylated vinylallenes were selectively formed. Addition of H₂O (5.0 equiv) resulted in selective formation of arylated trienes. In both of these procedures, a wide range of aryl boronic acids and boroxines with functional groups are tolerated. The detailed mechanism regarding the roles of BF₃·Et₂O and H₂O is not clear at present. Further studies on the mechanism by DFT calculations are underway.

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- [1] For selected reviews involving palladium-catalyzed carbocyclization reactions, see: a) I. Ojima, M. Tzamarioudaki, Z. Li, R. J. Donovan, *Chem. Rev.* **1996**, *96*, 635; b) E. M. Beccalli, G. Broggini, M. Martinelli, S. Sottocornola, *Chem. Rev.* **2007**, *107*, 5318; c) F. Dénès, A. Pérez-Luna, F. Chemla, *Chem. Rev.* **2010**, *110*, 2366; d) C. Aubert, L. Fensterbank, P. Garcia, M. Malacria, A. Simonneau, *Chem. Rev.* **2011**, *111*, 1954; e) C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215; f) Y. Deng, A. K. Å. Persson, J.-E. Bäckvall, *Chem. Eur. J.* **2012**, *18*, 11498; g) T. Lechel, F. Pfeingel, H.-U. Reissig, R. Zimmer, *ChemCatChem* **2013**, *5*, 2100.
- [2] For selected examples in natural product syntheses, see: a) M. Nakanishi, M. Mori, *Angew. Chem.* **2002**, *114*, 2014; *Angew. Chem. Int. Ed.* **2002**, *41*, 1934; b) P. S. Baran, E. J. Corey, *J. Am. Chem. Soc.* **2002**, *124*, 7904; c) N. K. Garg, D. D. Caspi, B. M. Stoltz, *J. Am. Chem. Soc.* **2004**, *126*, 9552; d) E. M. Beck, R. Hatley, M. J. Gaunt, *Angew. Chem.* **2008**, *120*, 3046; *Angew. Chem. Int. Ed.* **2008**, *47*, 3004; e) M. Li, D. J. Dixon, *Org. Lett.* **2010**, *12*, 3784; f) X. Sui, R. Zhu, G. Li, X. Ma, Z. Gu, *J. Am. Chem. Soc.* **2013**, *135*, 9318.
- [3] For selected recent oxidative carbocyclization reactions by other groups, see: a) K.-T. Yip, D. Yang, *Org. Lett.* **2011**, *13*, 2134; b) B. S. Matsuura, A. G. Condie, R. C. Buff, G. J. Karahalios, C. R. J. Stephenson, *Org. Lett.* **2011**, *13*, 6320; c) T. Wu, X. Mu, G. Liu, *Angew. Chem.* **2011**, *123*, 12786; *Angew. Chem. Int. Ed.* **2011**, *50*, 12578; d) X. Mu, T. Wu, H. Wang, Y. Guo, G. Liu, *J. Am. Chem. Soc.* **2012**, *134*, 878; e) R. Zhu, S. L. Buchwald, *Angew. Chem.* **2012**, *124*, 1962; *Angew. Chem. Int. Ed.* **2012**, *51*, 1926; f) Y. Wei, I. Deb, N. Yoshikai, *J. Am. Chem. Soc.* **2012**, *134*, 9098.
- [4] a) J. Piera, K. Närhi, J.-E. Bäckvall, *Angew. Chem.* **2006**, *118*, 7068; *Angew. Chem. Int. Ed.* **2006**, *45*, 6914; b) J. Franzén, J.-E. Bäckvall, *J. Am. Chem. Soc.* **2003**, *125*, 6056.
- [5] For allene substrates, see: a) Y. Deng, J.-E. Bäckvall, *Angew. Chem.* **2013**, *125*, 3299; *Angew. Chem. Int. Ed.* **2013**, *52*, 3217; b) A. K. Å. Persson, T. Jiang, M. T. Johnson, J.-E. Bäckvall, *Angew. Chem.* **2011**, *123*, 6279; *Angew. Chem. Int. Ed.* **2011**, *50*, 6155; c) T. Jiang, A. K. Å. Persson, J.-E. Bäckvall, *Org. Lett.* **2011**, *13*, 5838; d) A. K. Å. Persson, J.-E. Bäckvall, *Angew. Chem.* **2010**, *122*, 4728; *Angew. Chem. Int. Ed.* **2010**, *49*, 4624; e) J. Piera, A. Persson, X. Caldentey, J.-E. Bäckvall, *J. Am. Chem. Soc.* **2007**, *129*, 14120; f) J. Löfstedt, K. Närhi, I. Dorange, J.-E. Bäckvall, *J. Org. Chem.* **2003**, *68*, 7243; g) C. M. R. Volla, J.-E. Bäckvall, *Angew. Chem.* **2013**, *125*, 14459; *Angew. Chem. Int. Ed.* **2013**, *52*, 14209; for other unsaturated substrates, see: h) M. Jiang, T. Jiang, J.-E. Bäckvall, *Org. Lett.* **2012**, *14*, 3538; i) M. Jiang, J.-E. Bäckvall, *Chem. Eur. J.* **2013**, *19*, 6571.
- [6] Y. Deng, T. Bartholomeyzyk, A. K. Å. Persson, J. Sun, J.-E. Bäckvall, *Angew. Chem.* **2012**, *124*, 2757; *Angew. Chem. Int. Ed.* **2012**, *51*, 2703.
- [7] Y. Deng, T. Bartholomeyzyk, J.-E. Bäckvall, *Angew. Chem.* **2013**, *125*, 6403; *Angew. Chem. Int. Ed.* **2013**, *52*, 6283.
- [8] With an isopropyl-substituent the corresponding vinylallene **2** was also formed. Due to low conversion (~20%) we could not isolate it from the starting allenyne.
- [9] *ortho*-Bromophenylboronic acid did not work, probably due to steric effects. A vinylboronic acid (*trans*-PhCH=CHB(OH)₂) provided not more than 20% (NMR yield) of the corresponding product **2**.
- [10] For the preparation of aryl boroxines, see: S. K. Alamsetti, A. K. Å. Persson, T. Jiang, J.-E. Bäckvall, *Angew. Chem.* **2013**, *125*, 13990; *Angew. Chem. Int. Ed.* **2013**, *52*, 13745.
- [11] Vinylboronic acid (*trans*-PhCH=CHB(OH)₂) gave the corresponding triene **3a** in 47% NMR yield (see SI).
- [12] No conversion was observed when alkylboronic acids were used under conditions to form vinylallenes **2** or trienes **3**.
- [13] See the Supporting Information for the crystal data of **3ak**.
- [14] Boronic Acids: Preparation and Applications in Organic Synthesis and Medicine (Ed.: D. G. Hall), Wiley-VCH, Weinheim, **2005**.
- [15] The formation of **3** is proposed to occur via a pathway through allene attack on Pd^{II} via allylic C-H cleavage (Scheme S2). Formation of **2** would in analogy with the borylating carbocyclization of allenyne **1** occur via alkyne attack on Pd^{II} via propargylic C-H cleavage. Support for the latter mechanism was provided by a preliminary competitive isotope experiment in which a 1:1 mixture of **1b** and [**D**₂]-**1b** (dideuterated at the propargylic position; α in pentyl group) afforded **2b** and [**D**]-**2b** in a ratio of 3.9:1 at ~30% conversion (which gives k_H/k_D ~5).

Homogeneous Catalysis

Teresa Bartholomeyzik, Javier Mazuela,
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Jan-E. Bäckvall* **Page –**
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Palladium-Catalyzed Oxidative Arylating
Carbocyclization of Allenynes: Control
of Selectivity and Role of H₂O

Herein we disclose selective protocols for the carbocyclization/arylation of allenynes using arylboronic acids that allow for the formation of either arylated vinylallenes or arylated trienes. Formation of the former product is promoted by the use of BF₃·Et₂O whereas the latter product is selectively formed when water is used as additive. It has been revealed that water plays a crucial role for the product distribution.