Homogeneous Catalysis

DOI: 10.1002/anie.201404264

Palladium-Catalyzed Oxidative Arylating Carbocyclization of Allenynes: Control of Selectivity and Role of H_2O**

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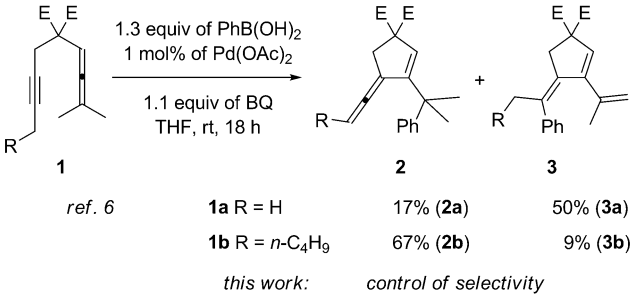
Dedicated to the MPI für Kohlenforschung on the occasion of its centenary

Abstract: *Highly selective protocols for the carbocyclization/arylation of allenynes using arylboronic acids are reported. Arylated vinylallenes are obtained with the use of $BF_3{\cdot}Et_2O$ 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** and 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). Here we present protocols that allow the selective formation of either of the arylated carbocycles **2** or **3**.



Scheme 1. Palladium-catalyzed oxidative arylating carbocyclization of allenynes **1**.[6] E = CO_2Me, BQ = 1,4-benzoquinone.

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 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 in the Supporting Information (SI)), and in analogy with the carbocyclization/borylation reaction the best result was obtained with Lewis acid $BF_3{\cdot}Et_2O$ (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-

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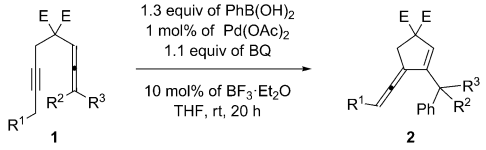
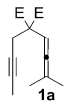
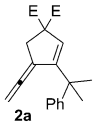
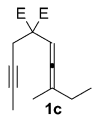
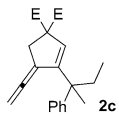
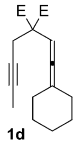
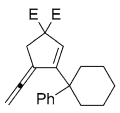
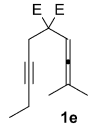
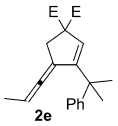
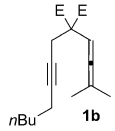
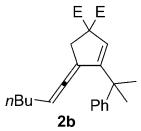
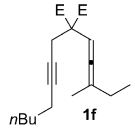
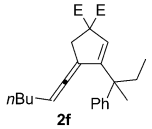
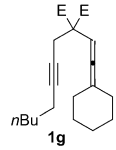
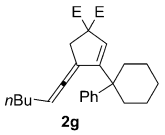
[**] Financial support from the European Research Council (ERC AdG 247014), the Swedish Research Council, the Berzelii Centre EXSELENT, the Knut and Alice Wallenberg Foundation, and the Wenner-Gren Foundation (Y.D.) is gratefully acknowledged. We also thank Tuo Jiang and Abraham Mendoza for valuable discussions.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201404264.

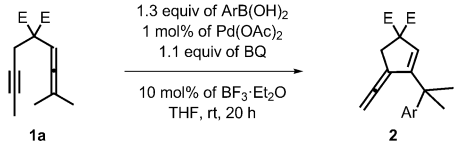
Table 1: Scope of allenynes **1a–g** in the formation of vinylallenes **2a–g**.[a]



Entry	Substrate	Product	Yield [%][b]	**2**/**3**[c]
1	 **1a**	 **2a**	55	98:2
2	 **1c**	 **2c**	66	>99:1
3	 **1d**	 **2d**	63	>99:1
4[d]	 **1e**	 **2e**	85	97:3
5	 **1b**	 **2b**	87	98:2
6[e]	 **1f**	 **2f**	77	94:6
7	 **1g**	 **2g**	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] Yield of isolated products. [c] Determined from the crude ^{1}H NMR spectrum. [d] 0.1 mmol in 0.5 mL of THF. [e] d.r. = 1:1. E = CO_2Me.

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	*p*-MeC_6H_4	**2ab**	65	97:3
3	*m*-MeC_6H_4	**2ac**	64	99:2
4	*o*-MeC_6H_4	**2ad**	67	99:1
5	*p*-*t*BuC_6H_4	**2ae**	72	98:2
6	*p*-vinylC_6H_4	**2af**	46	98:2
7	2-naphthyl	**2ag**	64	98:2
8	*p*-$CHOC_6H_4$	**2ah**	61	98:2
9	*p*-$CF_3C_6H_4$	**2ai**	69	98:2
10	*m*-$NO_2C_6H_4$	**2aj**	63	98:2
11	*p*-BrC_6H_4	**2ak**	69	99:1
12	*m*-BrC_6H_4	**2al**	66	98:2
13	*m*-$MeOC_6H_4$	**2am**	64	98:2
14[d]	*p*-$MeOC_6H_4$	**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] Yield of isolated product. [c] Determined from the crude ^{1}H NMR spectrum. [d] Ca. 5% of remaining **1a** was detected in the crude ^{1}H NMR spectrum with anisole as internal standard. E = CO_2Me.

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 H_2O 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]

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.

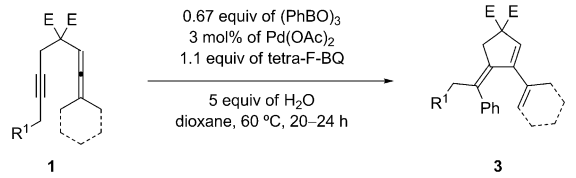
Employing the stronger oxidant tetrafluoro-1,4-benzoquinone (tetra-F-BQ) led to further increase in yield of triene products **3** (see Table S4). Under the optimized conditions in Table 3 the scope of allenyne substrates in triene formation was studied.

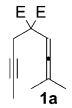
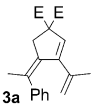
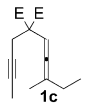
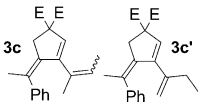
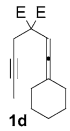
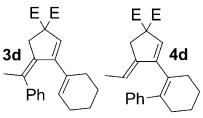
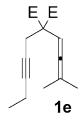
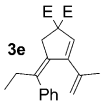
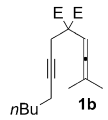
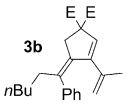
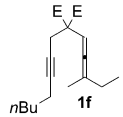
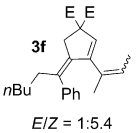
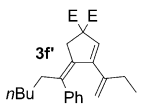
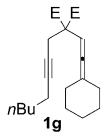
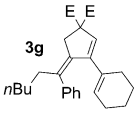
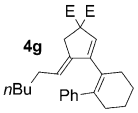
For all substrates with a methyl group on the alkyne, excellent selectivities for triene products **3** over vinylallene products **2** were obtained (Table 3, entries 1–3). More importantly, also allenynes **1e** and **1b** gave triene products **3e** and **3b**, respectively, with high selectivity 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 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 H_2O (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

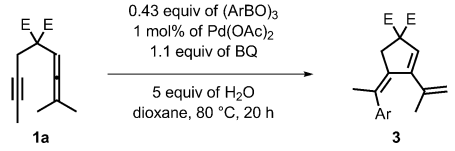
Table 3: Scope of allenynes **1a–g** in the formation of trienes **3a–g**.[a]



Entry	Substrate	Product	Yield [%][b]	Selectivity **3**/**2**[c]
1[d]	 **1a**	 **3a**	72	>99:1
2[e]	 **1c**	 **3c** / **3c'** = 2.4:1, *E*/*Z* = 1:2.4	68	>99:1
3	 **1d**	 **3d**/**4d** = 2:1	73	>99:1
4	 **1e**	 **3e**	65	>99:1
5[d]	 **1b**	 **3b**	66	94:6
6	 **1f**	 **3f**, *E*/*Z* = 1:5.4;  **3f'**, **3f**/**3f'** = 2.5:1	74	>98:2
7	 **1g**	 **3g**;  **4g**	40; 33[f]	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] Yield of isolated product. [c] Determined from the crude ^{1}H NMR. [d] Ca. 5% of remaining **1** was detected in the crude ^{1}H 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 ^{1}H NMR spectrum with anisole as internal standard. E = CO_2Me.

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



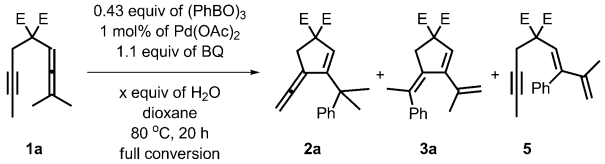
Entry	Ar	Product	Yield [%][b]	**3**/**2**[c]
1	Ph	**3a**	78	>99:1
2	*p*-MeC_6H_4	**3ab**	77	>99:1
3	*m*-MeC_6H_4	**3ac**	76	>99:1
4	*p*-*t*BuC_6H_4	**3ad**	75	>99:1
5	2-naphthyl	**3ae**	65	>99:1
6	*p*-$CHOC_6H_4$	**3af**	80	>99:1
7	*p*-$CF_3C_6H_4$	**3ag**	83	>99:1
8	*m*-$NO_2C_6H_4$	**3ah**	84	>99:1
9	*p*-BrC_6H_4	**3ai**	85	>99:1
10	*m*-$MeOC_6H_4$	**3aj**	61	>99:1
11	*p*-$MeOC_6H_4$	**3ak**	76	>99:1

[a] The reactions were carried out on a 0.2 mmol scale in 2 mL of dioxane. [b] Yield of isolated product. [c] Determined from the crude ^{1}H NMR spectrum. E = CO_2Me.

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 confirmed by X-ray diffraction studies of **3ak**.[13]

The ability of added H_2O 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 H_2O as an additive influences the selectivity between reaction products.[14] We investigated the reaction of allenyne **1a** in dioxane with different amounts of added H_2O (Table 5). With no added H_2O the selectivity between products **2a** and **3a** was poor (Table 5, entry 1), but with addition of $\geq$0.5 equiv of H_2O,

Table 5: Effect of H_2O on the product ratio (**2a**/**3a**).[a,b]



Entry	H_2O (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 ^{1}H NMR spectrum with anisole as internal standard. [c] Determined from the ^{1}H NMR spectrum. E = CO_2Me.

triene **3a** was the only cyclization product. However, significant amounts of uncyclized arylated side product **5** were 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 H_2O 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 H_2O as the best conditions (Table 5, entry 5).

We also studied how the equilibrium between phenyl boroxine and phenylboronic acids varied with the H_2O concentration in deuterated dioxane. We found that hydrolysis of boroxine is complete at a H_2O concentration corresponding to ca. 3.0 equiv of H_2O in Table 5. This indicates that H_2O not only plays the role of hydrolyzing the boroxine, but it also suppresses the formation of **5**.

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 $BF_3{\cdot}Et_2O$ as an additive (10 mol%) arylated vinylallenes were selectively formed. Addition of H_2O (5.0 equiv) resulted in selective formation of arylated trienes. In both of these procedures, a wide range of arylboronic acids and boroxines with functional groups are tolerated. The detailed mechanism regarding the roles of $BF_3{\cdot}Et_2O$ and H_2O is not clear at present. Further studies on the mechanism by DFT calculations are underway.

Received: April 12, 2014
Published online: June 30, 2014

Keywords: allenes · boronic acids · cyclization · oxidation · palladium

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[8] With an isopropyl-substituent the corresponding vinylallene **2** was also formed. Due to low conversion ($\approx$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**.

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[11] Vinylboronic acid (*trans*-PhCH=CHB$(OH)_2$) gave the corresponding triene **3al** 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 through allene attack on Pd^{II} and 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} and 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_1]-2b** in a ratio of 3.9:1 at ca. 30% conversion (which gives $k_H/k_D \approx 5$).

