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Kinetics and Mechanism of the Palladium-Catalyzed Oxidative Arylating Carbocyclization of Allenynes

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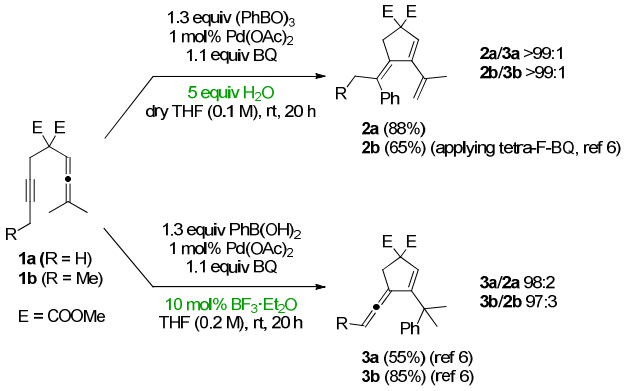
ABSTRACT: Pd-catalyzed C–C bond-forming reactions under oxidative conditions constitute a class of important and widely used synthetic protocols. This article describes a mechanistic investigation of the arylating carbocyclization of allenynes using boronic acids and focuses on the correlation between reaction conditions and product selectivity. Isotope effects confirm that either allenic or propargylic C–H activation, respectively, occurs directly after substrate binding. With an excess of H_2O, a triene product is selectively formed via allenic C–H activation. The latter C–H activation was found to be turnover-limiting and the reaction is zeroth order in reactants as well as the oxidant. A dominant feature is continuous catalyst activation which was shown to occur even in the absence of substrate. Smaller amounts of H_2O lead to mixtures of triene and vinylallene products, where the latter is formed via propargylic C–H activation. The formation of triene occurs only in the presence of $ArB(OH)_2$. Vinylallene, on the other hand, was shown to be formed by consumption of $(ArBO)_3$ as a first order reactant. Conditions with sub-stoichiometric $BF_3{\cdot}OEt_2$ gave selectively the vinylallene product, and the reaction is first order in $PhB(OH)_2$. Both C–H activation and transmetalation influence the reaction rate. However, with electron-deficient $ArB(OH)_2$, C–H activation is turnover-limiting. It was difficult to establish the order of transmetalation vs. C–H activation with certainty, but the results suggest that $BF_3{\cdot}OEt_2$ promotes an early transmetalation. The catalytic active species were found to be dependent on the reaction conditions and H_2O is a crucial parameter in the control of selectivity.

INTRODUCTION

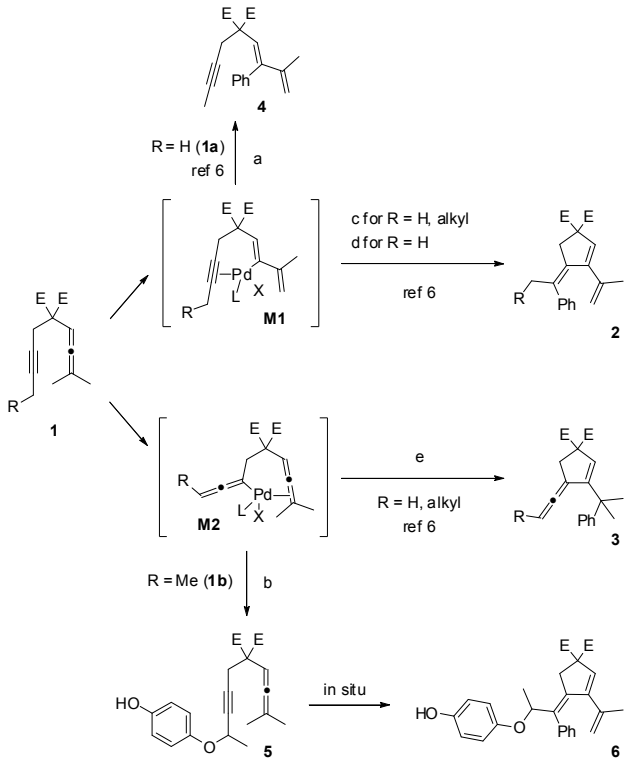
One common characteristic of many Pd-catalyzed oxidative reactions is the occurrence of a C–H bond cleavage step which can mechanistically be classified either as a β-hydride elimination or as a C–H activation. This step is of central importance and has attracted considerable attention recently.[1,2] Currently, an increasing number of selective Pd-catalyzed oxidative transformations are available and accompanying mechanistic studies have provided information concerning the underlying processes.[3,4] This paper presents results that provide mechanistic insight into an arylating carbocyclization reaction, and discusses its different possible pathways and the factors determining the product selectivity.

We have previously described the Pd^{II}-catalyzed arylating oxidative carbocyclization of 1,5-allenynes.[5,6] The reaction can give either an arylated triene product **2** or an arylated vinylallene product **3** (Scheme 1). It was found that conditions employing $BF_3{\cdot}OEt_2$ as additive provided selectively vinylallene products **3** for a broad range of allenynes and arylboronic acids.[6] The selective formation of trienes **2** was accomplished using an excess of H_2O. The optimization of the latter protocol (upper reaction in Scheme 1) showed that for substrates with a longer propargylic alkyl substituent (R = alkyl vs. R = H in Scheme 2) it was necessary to replace the standard oxidant 1,4-benzoquinone (BQ) with tetra-F-BQ in order to obtain satisfying yields. We have furthermore identified the formation of 4-hydroxyphenoxy-substituted side products (**5**, **6**) which explains the low yields of **3** in some cases (Scheme 2).

Scheme 1. Phenylating oxidative carbocyclization of allenyne 1a under selective conditions



Scheme 2. Proposed intermediates M1 and M2 in the formation of arylated carbocycles 2 and 3 and side products 4–6



Possible pathways that account for the formation of all the observed products are shown in Scheme 2. A dienyl-palladium intermediate **M1** was suggested previously for Pd^{II}-catalyzed cyclizations of allene substrates.[7–9] Based on kinetic isotope effects (KIEs) we recently proposed the unusual allenyl-palladium intermediate **M2** in two related transformations.[7,10] This intermediate also rationalizes the generation of **5**, which is the product of a formal oxidative Pd^{II}-catalyzed propargylic C–H functionalization. In this article, we report on a mechanistic study of the arylating carbocyclization based on kinetic analyses. The experimental data presented support the previously proposed pathways involving allenic or propargylic C–H activation, respectively.[6]

RESULTS AND DISCUSSION

The arylating carbocyclization reactions of allenyne **1a** were monitored in situ by ^{1}H NMR spectroscopy.[11] During the study we encountered an inconsistent overall reaction rate related to the quality of the THF-d_8 used. The reaction reached a higher rate when the solvent was freshly distilled compared to when it had been kept over 3Å molecular sieves. Additionally, the reaction was significantly slower when peroxyacetic acid was added to the reaction mixture in order to mimic varying contents of peroxides.[12] To ensure reproducibility, the same THF-d_8 was generally used to perform one set of experiments. $Pd(OAc)_2$ was used as Pd^{II} catalyst precursor throughout this work.[13]

The reaction profile for the selective transformation of **1a** to **2a** under the optimized reaction conditions with 5 equiv of H_2O is given in Figure 1a. Since an excess of H_2O is employed, $(PhBO)_3$ is immediately hydrolyzed to $PhB(OH)_2$. Besides the formation of arylated triene **2a** in 94% yield, we observed the formation of hydroquinone (HQ) and boric acid as by-products and a corresponding decrease in the concentration of H_2O. The formation of benzene by protodeboronation of $PhB(OH)_2$ only occurred at a very low concentration of BQ.[14]

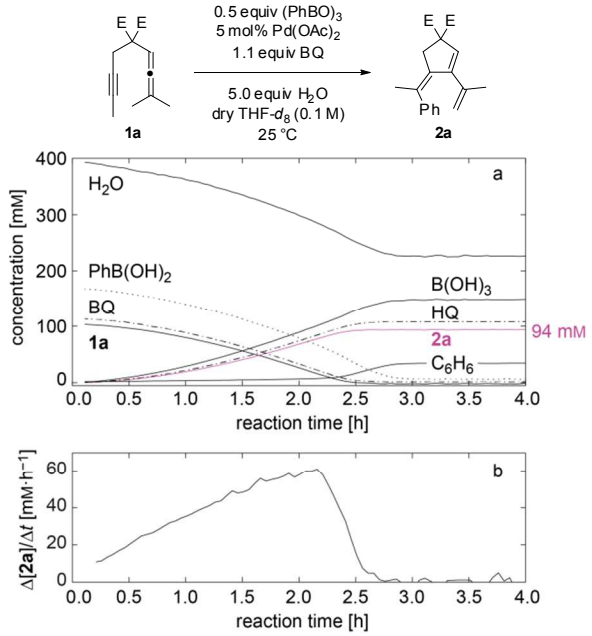


Figure 1. Selective reaction to give **2a**. a) Reaction profile. b) Rate profile of product formation. Scale: 0.1 mmol **1a**.

Investigation of induction in the formation of triene 2a. The reaction is associated with an unusually long induction period extending over the entire reaction time. Initially, the rate of product formation is zero, and it increases linearly with time (Figure 1b).

Induction periods in catalytic reactions can be the result of an ongoing pre-catalyst activation. The resulting continuous change in catalyst concentration complicates the interpretation of kinetic data.[15] To obtain insight into the induction of the reaction, we designed so-called pre-stirring experiments. It was found that mixing all reaction components except allenyne **1a** and stirring them for 3 h at 25 °C prior to the addition of **1a** leads to an initial reaction rate larger than zero (experiment A in Figure 2a).[16] This observation shows that the catalytic system undergoes changes which are independent of the substrate.[17]

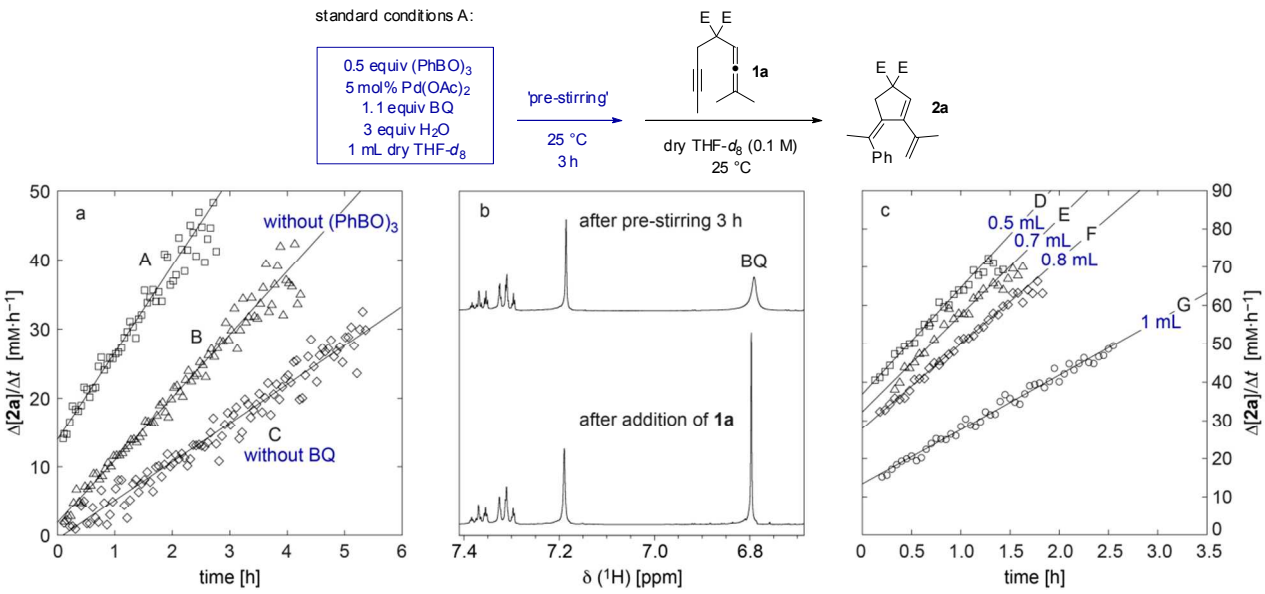


Figure 2. Investigation of catalyst activation with the aid of pre-stirring experiments. Scale: 0.1 mmol **1a**. a) Under standard conditions A, the shown mixture is pre-stirred before substrate **1a** (0.1 mmol) is added. In experiments B and C, $(PhBO)_3$ or BQ, respectively, were added together with **1a** after the pre-stirring period. b) Selected region of the ^{1}H NMR spectrum before and after the addition of **1a** according to conditions A. c) The total volume after addition of **1a** was 1 mL in all experiments, and the values refer to the different volumes during the pre-stirring period in experiments D–G.

Catalyst activation during pre-stirring was found to require the presence of both $PhB(OH)_2$ and BQ, as shown in Figure 2a. When pre-stirring was performed without added H_2O, the initial rate was lower compared to the reference.[12] As there were small amounts of H_2O in the solvent, we speculate that H_2O plays a part in the activation as well.

The slower overall reaction rate in experiment C (without BQ) is likely due to partial decomposition of $Pd(OAc)_2$ as supported by the formation of Pd black. Furthermore, BQ was found to be an indicator for the process occurring during pre-stirring, since its NMR peak broadens significantly before it takes its original shape upon addition of **1a** (Figure 2b). This is suggestive of BQ having a role as ligand to palladium in addition to its function as reoxidant. The overall reaction rates were higher when the pre-stirring was performed in smaller volumes, thus showing that catalyst activation during pre-stirring is concentration dependent (Figure 2c). Additional experiments showed that the activation process during pre-stirring was not influenced by the concentrations of either $PhB(OH)_2$ or BQ.[12] Therefore, the concentration dependence of the catalyst activation shown in Figure 2c is the result of the different $Pd(OAc)_2$ concentration in these experiments.[18] Even though the pre-stirring strategy has provided a tool to modulate the initial reaction rates, it did not lead to full catalyst activation before starting material **1a** was consumed.

One initial experiment (*vide infra*) suggests that this state can be reached by performing multiple consecutive additions of reactants. However, this strategy would be susceptible to reproducibility issues and is therefore not a suitable method for accurate kinetic analysis.

Effect of H_2O. Under H_2O concentrations below 200 mM (2 equiv), the anhydride forms of $PhB(OH)_2$ are present (Figure 3). We speculated that this equilibrium may be related to the previously observed effect of H_2O on the product distribution.[6]

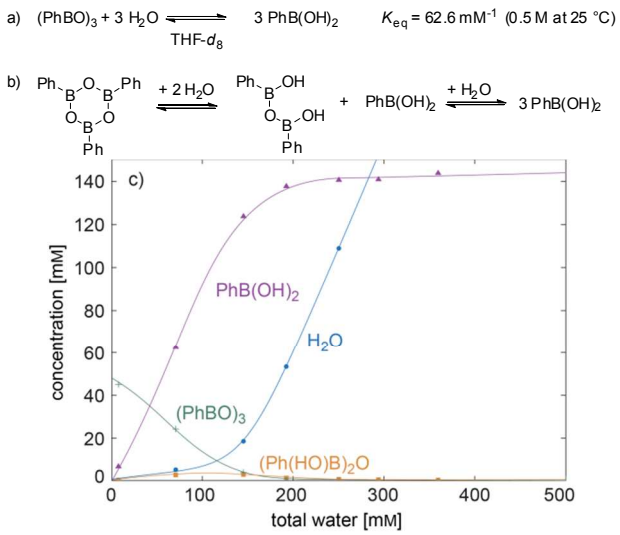


Figure 3. Hydrolysis of $(PhBO)_3$ in THF-d_8: (a) equilibrium between phenyl boroxine and phenylboronic acid; (b) two-step hydrolysis via $(PhBOH)_2O$; (c) change of concentrations of boronic species at increasing amounts of added water.

The yields of reaction products **2a**, **3a** and **4** as a function of the concentration of H_2O are given in Figure 4, and – in support of our hypothesis – the obtained graph resembles Figure 3. For small amounts of H_2O, which corresponds to high $[(PhBO)_3]$, allene **3a** is the major product. With increasing concentration of H_2O (and therefore at higher $[PhB(OH)_2]$), the yield of allene **3a** decreases in favor of formation of triene **2a**. The latter is formed selectively and in

yields of 90–95% for conditions applying >4.5 equivalents of H_2O.

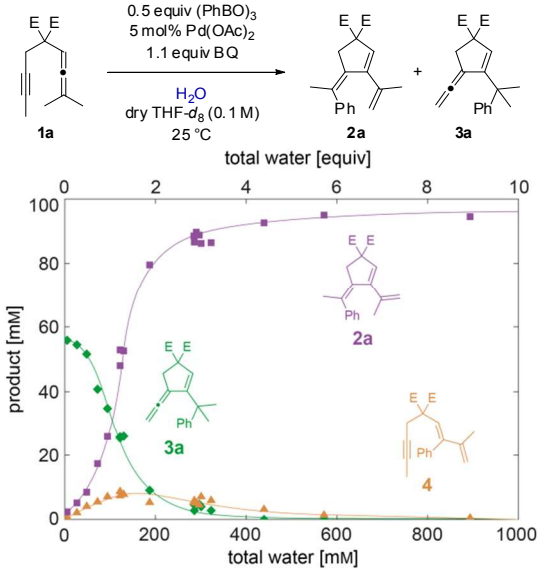


Figure 4. The effect of H_2O on the product distribution; final concentrations of products **2a**, **3a**, and **4** vs. initial $[H_2O]_{total}$ (free $[H_2O]$ plus amount consumed in the hydrolysis of $(PhBO)_3$, determined at <1% conversion). Conditions: 0.1 mmol of **1a**, 0–9 equiv added H_2O. Full conversion was obtained within 10 h for >0.5 equiv H_2O.[19]

The yield of phenylated side product **4** increases at first and reaches ca. 9% at $[H_2O]_{total} \approx 120$ mM, but is suppressed at higher $[H_2O]$. Curiously, the maximum yield of **4** coincides with the maximal concentration of $(Ph(OH)B)_2O$. From the same set of experiments it was also found that the rate of formation of triene **2a** (measured as the highest observed rate) increases with the amount of added H_2O until a maximum is reached at $[H_2O]_{total} \approx 300$ mM. At higher concentrations of H_2O however, the reaction is gradually slowed down.[12]

When the phenylating carbocyclization is performed with $[H_2O]_{total} \leq 100$ mM, the liberated $PhB(OH)_2$ is consumed prior to complete conversion of allenyne **1a**, leaving $(PhBO)_3$ as the only identified boron-reactant ("limiting conditions"). At this point, the generation of triene **2a** stops abruptly while the formation of vinylallene **3a** continues, although at a slower rate (illustrated in Figure 5 for 0.5 equiv of added H_2O). Therefore, our results suggest a relationship between the concentrations of $(PhBO)_3$, $(Ph(OH)B)_2O$ and $PhB(OH)_2$ and the formation of **3a**, **4** and **2a**, respectively. An alternative explanation is that the different products are formed in the presence of different active catalytic species, and that these species are influenced by the concentration of water. We have identified both $Pd_3(\mu^2\text{-}OAc)_6$ and $Pd_3(\mu^2\text{-}OH)(OAc)_5$ in the reaction mixtures.[13,20] With large amounts of added water (3 equiv), $Pd_3(\mu^2\text{-}OAc)_6$ is converted to $Pd_3(\mu^2\text{-}OH)(OAc)_5$ within 10 minutes. In contrast, with small amounts of added water, $Pd_3(\mu^2\text{-}OAc)_6$ is present in large quantities throughout the entire reaction, and only small amounts of $Pd_3(\mu^2\text{-}OH)(OAc)_5$ are formed. These two species are believed to be precursors to the active catalytic species in the formation of the different reaction products.[12] A possible explanation for the lower reaction rates at $[H_2O]_{total} > 300$ mM could be the formation of unreactive Pd^{II} hydroxy complexes.[20b]

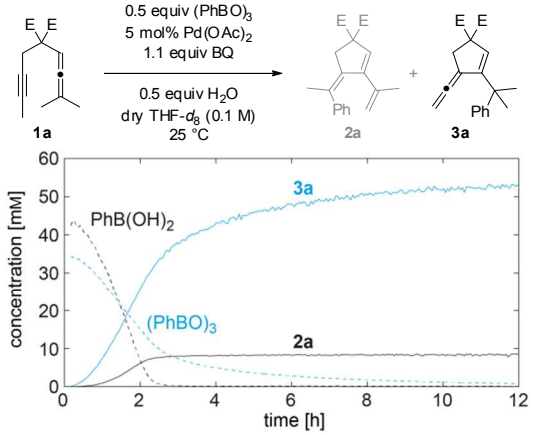


Figure 5. Reaction profile for a reaction with limiting $[H_2O]$. Scale: 0.1 mmol **1a**.

In contrast to the observed kinetics for the formation of triene **2a**, the induction is less pronounced under conditions for selective formation of vinylallene **3a** using low concentrations of H_2O (Figure 5). Considering only the phase of the reaction for which $[PhB(OH)_2] = 0$ and $[\mathbf{2a}] = \text{const}$, the rate of vinylallene formation has a first order dependence on $(PhBO)_3$ (Figure 6).

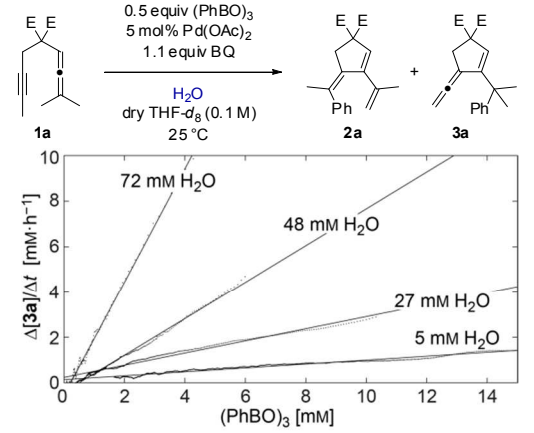


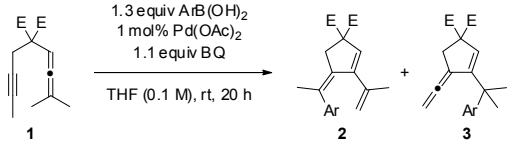
Figure 6. Rate of formation of **3a** vs. $[(PhBO)_3]$ for different $[H_2O]_{total}$ (0–0.75 equiv added H_2O) illustrating a first order dependence on $(PhBO_3)$. Plotted is the region of the reactions in which $[\mathbf{2a}] = \text{const}$ due to the complete consumption of $PhB(OH)_2$ and water (e.g., t = 2.5–12 h in Figure 5). Scale: 0.1 mmol **1a**.

Furthermore, the rate of the reaction to give vinylallene **3a** is comparatively higher with higher initial concentration of H_2O. The observed faster rate of formation of **3a** could be explained by a higher degree of catalyst activation in the presence of more water.[21]

Effect of boronic acid substituent. Our original report demonstrated the dependence of the ratio **2**/**3** on the structure of the substrate.[5] Table 1 provides the corresponding results regarding the influence of the arylboronic acid. Clearly, electron-deficient arylboronic acids favor the formation of the corresponding vinylallenes **3**, whereas electron-rich arylboronic acids favor triene **2**. Commercially available

boronic acids generally consist of a mixture of $ArB(OH)_2$ and $(ArBO)_3$. For more electron-deficient arylboronic acids the relative amount of $ArB(OH)_2$ is expected to be higher due to the facilitated hydrolysis of $(ArBO)_3$.[22] The results described above (cf. Figure 4) suggest that $(PhBO)_3$ reacts to give vinylallene **3a**, whereas $PhB(OH)_2$ is responsible for the formation of triene **2a**. If the product distribution were solely controlled by the ratio of the boronic acid derivatives present, we would have expected the opposite trend regarding the substituent effect in Table 1.

Table 1. Selectivities for various $ArB(OH)_2$.[a,b]



Entry	Ar	2 (%)	3 (%)	2/3
1[c]	C_6H_5	50	17	75:25
2[d]	2-naphthyl	68	6	92:8
3[e]	4-Br-C_6H_4	3	45	6:94
4	4-CHO-C_6H_4	30	39	43:5
5	4-MeO-C_6H_4	53	5	91:9
6	3-NO_2-C_6H_4	<3	55	5:95

(a) Scale: 0.1 mmol **1a**. (b) Yields and selectivities were determined by ^{1}H NMR analysis of crude reaction mixtures using anisole as an internal standard. (c) Isolated yields, see ref 5. (d) 0.1 mmol in 0.5 mL. (e) 9% of **1a** remained.

Consequently, we chose 4-NO_2- and 4-MeO-phenyl boroxines and investigated their kinetic behavior under strict control of the water concentration present (0.5 equiv added H_2O, Figure 7). As for phenyl boroxine, the generation of the corresponding trienes **2** relied on the presence of $ArB(OH)_2$. Furthermore, it was confirmed that the electronic properties of the aryl boroxine play a dominant role with respect to the product distribution. The use of (4-NO_2-C_6H_4-BO)$_3$ provided vinylallene **3ab** with high selectivity. Changing from $PhB(OH)_2$ to the 4-NO_2-substituted derivative substantially increased the fraction of $ArB(OH)_2$ that is consumed in the pathway towards vinylallene **3**. In contrast, the preference of $ArB(OH)_2$ to react towards the corresponding triene **2** is significantly enhanced for the electron-rich 4-MeO-C_6H_4-$B(OH)_2$. Once the latter is consumed, the reaction towards the corresponding vinylallene **3ac** (thereby consuming (4-MeO-C_6H_4-BO)$_3$) accelerates. In accordance with the results for $(PhBO)_3$ (cf. Figure 6), it was verified for an electron-rich boroxine (4-MeO) and an electron-deficient derivative (4-CF_3) that the rate of formation of **3** is consistent with a first order dependence on [$(ArBO)_3$] after the consumption of $ArB(OH)_2$.[12,23,24]

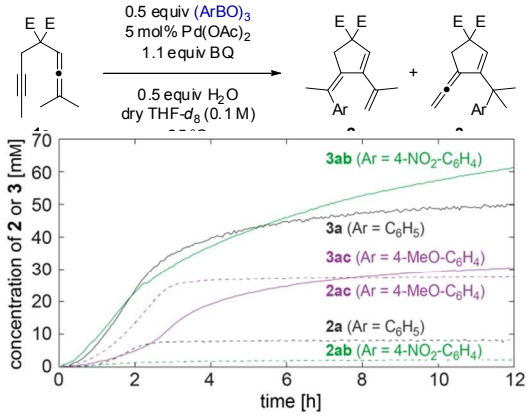


Figure 7. Formation of triene **2** and vinylallene **3** for different $(ArBO)_3$. Scale: 0.1 mmol **1a**.

Influence of other reaction components in the selective formation of triene 2a. When studying the reaction at different pre-catalyst loadings saturation behavior was observed (Figure 8). A possible explanation is that formation of the active catalyst from oligomeric species is slow and not proportional to the amount of added pre-catalyst (*vide supra*).[12,25,26]

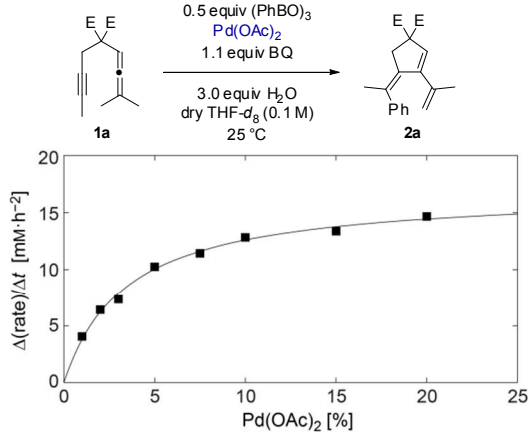


Figure 8. Saturation behavior in $Pd(OAc)_2$; Δ(rate)/Δt vs. added $Pd(OAc)_2$, with rate being Δ[**2a**]/Δt. Conditions: **1a** (0.1 mmol), 1–20 mol% $Pd(OAc)_2$.

Further, the dependence on the concentration of the various reactants was studied by pre-stirring identical mixtures, but varying concentrations of either substrate **1a**, $(PhBO)_3/H_2O$ or BQ, respectively, after the pre-stirring period (cf. Figure 2). All of these experiments provided an initial reaction rate similar to that obtained under standard conditions (experiment A in Figure 2a) suggesting that the reaction is of zeroth order in these reactants. This interpretation was confirmed by an experiment based on multiple additions of all the reactants (Figure 9). After the third addition it appears that the reaction rate had reached its maximum value. The conversion of **1a** to give **2a** proceeded with a nearly constant rate and essentially the same rate just before and after additions B and C – independent of the change in [**1a**], $[(PhBO)_3]$, and [BQ].

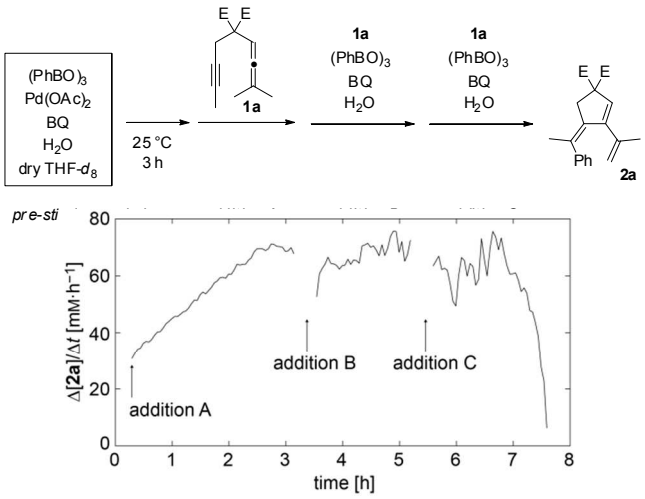


Figure 9. Multiple addition experiment; Δ[**2a**]/Δt vs. time. Conditions: pre-stirring period: $(PhBO)_3$ (100 µmol), $Pd(OAc)_2$ (5 µmol), BQ (220 µmol), H_2O (650 µmol) in 1 mL THF-d_8, 25 °C; addition A: **1a** (200 µmol); addition B and C: **1a** (200 µmol), $(PhBO)_3/H_2O$ (to give 300 µmol $PhB(OH)_2$ and 350 µmol free H_2O), BQ (to give 220 µmol); additions B and C were performed before complete consumption of **1a** (<15 µmol) to avoid potential catalyst decomposition.

Since only the change in concentration of added $Pd(OAc)_2$ leads to a clear effect on the reaction rate (Figure 8), we suggest that the turnover-limiting step follows an equilibrium that is controlled by the concentration of Pd catalyst.

The reaction of **1a** to give **2a** is accompanied by the release of HOAc originating from $Pd(OAc)_2$. The concentration of liberated HOAc is linearly correlated to the reaction rate (Figure 10). However, the addition of HOAc (20 mol%) to the reaction mixture did not cause an increase in the rate of the reaction suggesting that more HOAc is released when the reaction is faster, rather than the released HOAc causing a faster reaction. Addition of HOAc-d_4 (20 mol%) to the reaction mixture resulted in more HOAc being released in relation to the reaction rate. This observation can be attributed to catalyst-bound AcO^- being replaced by AcO^--d_3 and provides experimental evidence for a reversible release of acetate during the catalytic cycle.

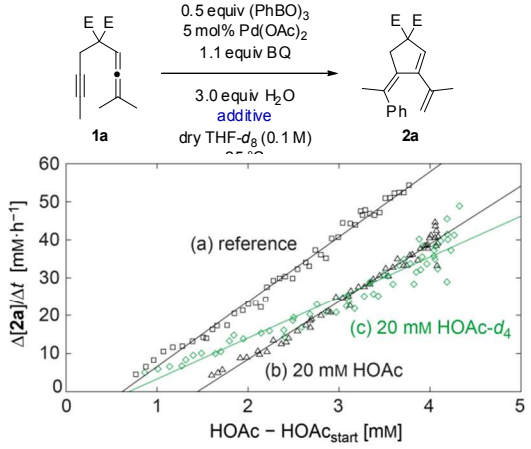
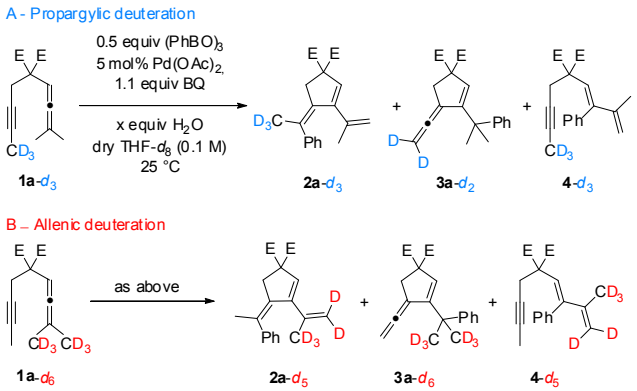


Figure 10. Rate of formation of **2a** vs. released [HOAc]. Conditions: 0.1 mmol **1a**; a) no additive; b) 20 mol% HOAc; c) 20 mol% HOAc-d_4.

Kinetic Isotope Effects for reactions with water-controlled selectivity. To obtain the phenylated products **2** (triene) or **3** (vinylallene), either an allenic or a propargylic C–H bond must be broken, respectively.[27] Under non-selective conditions ($[H_2O]_{total}$ <300 mM) methyl group deuteration at either the propargylic (A) or the allenic position (B) resulted in a significant change of the ratio **2a**/**3a** (Scheme 3).

Scheme 3. Effect of deuteration on the product ratio



		2a	3a	4	2a/3a
for 1.0 equiv H_2O:					
1a-d_3 (A)	a)	49%	10%	8%	83:16
reference (**1a**)		(33%)	(34%)	(7%)	(49:51)
for 1.2 equiv H_2O:					
1a-d_3 (A)	b)	63%	8%	7%	89:11
1a-d_6 (B)	c)	7%	50%	1%	12:88
reference (**1a**)		(48%)	(27%)	(8%)	(64:36)
for 1.6 equiv H_2O:					
1a-d_6 (B)	d)	21%	40%	<1%	34:66
reference (**1a**)		(73%)	(15%)	(7%)	(83:17)

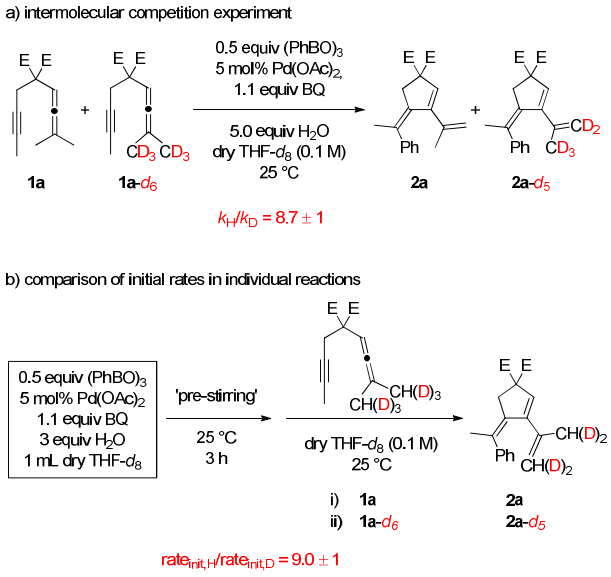
Scale: 0.1 mmol **1a**-d_3 (A) or **1a**-d_6 (B). Yields in red and blue refer to products from reactions starting from **1a**-d_3 and **1a**-d_6, respectively. Yields in black serve as reference and were interpolated from the data in Figure 4. Yields and the amount of added H_2O were determined from the ^{1}H NMR spectra of the crude reaction mixture. Full conversion was reached for a) and b) at 4.5 h and 4 h, respectively, and 27 mM and 36 mM of C_6H_6

were formed, respectively. For c) 15% of **1a**-d_6 remained after full consumption of the phenyl source at 5 h; 51 mM of C_6H_6 was formed. For d) 15% of **1**-d_6 remained after full consumption of the phenyl source at 6 h; 33 mM of C_6H_6 was formed.

This means that the selectivity is determined by the C–H bond cleavage as an early step in the reaction and that pathways starting with arylpalladation are ruled out.[28]

For the selective reaction to give triene **2a** (i.e. with 5 equiv of H_2O) we determined the KIE in a competitive reaction setup which gave a large value of k_H/k_D = 8.7 ± 1 (Scheme 4a).[29] Due to the underlying induction process and the continuous change in rate, it was not possible to conclusively determine KIE (k_H/k_D) from individual runs with a conventional reaction set-up. Instead, we applied the pre-stirring strategy (cf. Figure 2) to obtain information about the KIE (Scheme 4b). Since the catalyst activation during pre-stirring and therefore the amount of active catalyst in the very beginning is identical, the ratio of the initial reaction rates for the protonated or deuterated substrate, respectively, is considered comparable to a conventional KIE. And indeed, with $rate_{init,H}/rate_{init,D}$ = 9.0 ± 1, a value similar to the competitive KIE (Scheme 4) was obtained.[29]

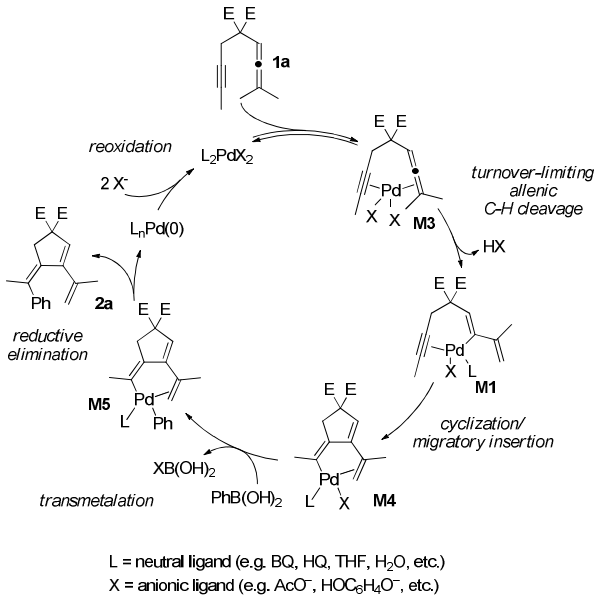
Scheme 4. KIEs in the formation of triene 2a



Scale: 0.1 mmol **1a** + **1a**-d_6 (1:1) (a), **1a** or **1a**-d_6 (b). k_H/k_D = $[(rate_H/rate_D)] / ([\mathbf{1a}]/[\mathbf{1a}\text{-}d_6])$; $rate_{init,H(D)}$ is the initial rate after addition of **1a** (**1a**-d_6).[12]

Proposed mechanism for the formation of triene 2a. We suggest that the formation of triene **2a** follows a mechanism involving allene attack on Pd^{II} with concomitant allylic C–H bond cleavage to give intermediate **M1** (Scheme 5). Subsequent cyclization to **M4** and transmetalation with phenylboronic acid would give **M5**. A reductive elimination from the latter releases the product (**2a**). After reoxidation of Pd^0 to Pd^{II} by BQ, the catalyst is available for the next catalytic cycle. We consider it likely that transmetalation can occur either in **M1** or **M4** (the latter option is shown in Scheme 5). The formation of side product **4** (cf. Scheme 2), which is formed in small amounts, shows that at least some early transmetalation occurs.[30,31] The observed zeroth order in the reactants is rationalized by the equilibrium between **1a** and **M3** lying far towards intermediate **M3**. The large isotope effect measured in individual experiments (cf. Scheme 4b) identifies the C–H cleavage as the turnover-limiting step, and is thus in full agreement with the zero order dependence on the reactants.

Scheme 5. Proposed mechanism for the formation of triene 2a

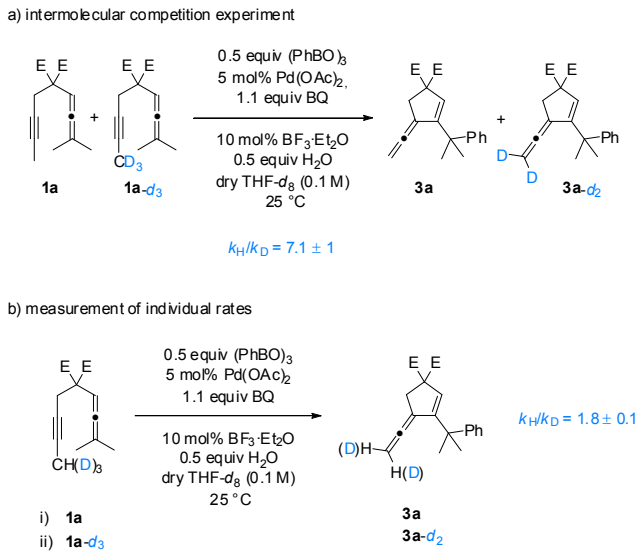


Only the equilibrium that is crucial to match the experimental results is indicated.

Kinetic Isotope Effects in the formation of vinylallene 3a. To investigate the KIE in the selective formation of vinylallene **3a**, we used the reaction conditions employing $BF_3{\cdot}OEt_2$ as an additive (cf. Scheme 1).[32] In a competitive experiment, we obtained a value of k_H/k_D = 7.1 ± 1 (Scheme 6a).[29] This large competitive isotope effect is in agreement with a mechanism in which the first irreversible step involving **1a** is propargylic C–H bond cleavage.

Interestingly, under conditions using $BF_3{\cdot}OEt_2$, we observed a reasonably short induction period (*vide infra*) allowing for the determination of $k_{obs,H}$ and $k_{obs,D}$. From these rate constants, a KIE of $k_{obs,H}/k_{obs,D}$ = 1.8 ± 0.1 was obtained (Scheme 6b).[33] The rate constant $k_{obs,H(D)}$ is determined by the overall rate of the catalytic cycle, whereas the measured value for the competitive KIE reports on the relative reactivity of **1a** or **1a**-d_3 in the step where the C–H(D) bond is broken.[34] Therefore, the deviation between the KIEs from the parallel and competitive experiments suggests that the C–H bond cleavage is only to a minor extent turnover-limiting and that a second step in the catalytic cycle has a slightly higher activation barrier.[35,36] An alternative explanation would be that monomeric catalyst is delivered into the cycle via an off-cycle equilibrium, which is influenced by the different C–H(D) cleavage rates, resulting in a lower "on-cycle catalyst" concentration for the reaction of **1a**-d_3. In this case, $k_{obs,H}$ would be larger than $k_{obs,D}$ even though C–H(D) cleavage is not turnover-limiting.[37] This is considered less likely based on KIE experiments under different conditions which indicate that the KIE is independent of the "on-cycle catalyst" concentration.[12]

Scheme 6. KIEs in the formation of vinylallene 3a



Scale: 0.1 mmol **1a** + **1a**-d_3 (1:1) (a), **1a** or **1a**-d_3 (b). k_H/k_D = [(rate$_H$/rate$_D$)] / ([**1a**]/[**1a**-d_3]) for (a) and $k_H/k_D = k_{obs,H}/k_{obs,D}$ for (b).[12]

Kinetics in the formation of vinylallene 3a. Under selective conditions for formation of **3a** as given in Scheme 6b, the phenylating carbocyclization reaction of **1a** provided a 63% NMR yield of **3a** and ≤5% of **2a**. There was 15–20% of material that the observed side products could not account for.

At first, we studied the relationships between the reaction rate and BQ, **1a**, $(PhBO)_3$, and $PhB(OH)_2$ by varying their initial concentrations (cf. reactions A–D in Figure 11).[38] An overall reaction order of one was established as the concentration of each of these reactants was linearly related to the rate througout the reaction.[12] Only when plotting the rate vs. $[PhB(OH)_2]$ was the intercept zero, revealing that the reaction is first order in $[PhB(OH)_2]$ (Figure 11).[39]

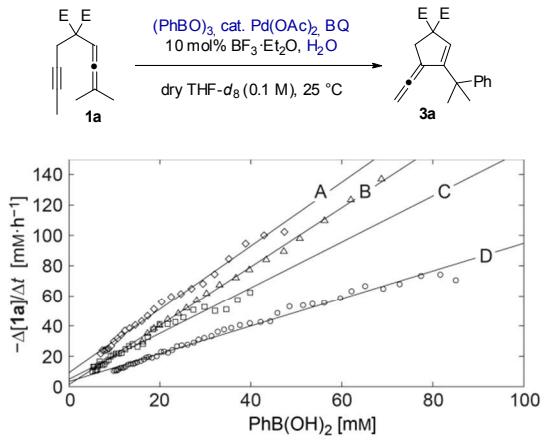


Figure 11. Rate of **1a** consumption vs. $[PhB(OH)_2]$ illustrating the first order relation. The experiments are shown for the region between 10–95% conversion or until the reaction had stopped (see note 40). Conditions for experiments A–D: 0.1 mmol **1a**; A: 2.5 mol% $Pd(OAc)_2$, 1 equiv $(PhBO)_3$, 1.1 equiv BQ, 0.75 equiv H_2O; B: 5 mol% $Pd(OAc)_2$, 1 equiv $(PhBO)_3$, 1.1 equiv BQ, 1.0 equiv H_2O; C: 5 mol% $Pd(OAc)_2$, 0.5 equiv $(PhBO)_3$, 1.1 equiv BQ, 0.5 equiv H_2O; D: 5 mol% $Pd(OAc)_2$, 0.5 equiv $(PhBO)_3$, 2.0 equiv BQ, 1.0 equiv H_2O.

Furthermore, experiments using different amounts of $BF_3{\cdot}Et_2O$ suggested that there is a slight inhibitory effect of this additive (Figure 12a). This may be related to an involvement of $BF_3{\cdot}Et_2O$ in an off-cycle reaction. The fastest reaction was achieved with ca. 2 mol% of $BF_3{\cdot}Et_2O$.[41] The ratio **2a**/**3a** and also the yield of vinylallene product **3a** were unaffected proving the potency of this additive. The dependence of the reaction rate on the added $Pd(OAc)_2$ was studied for 10 mol% added $BF_3{\cdot}OEt_2$, and a saturation behavior was observed (Figure 12b). This saturation occurred at even lower catalyst loading than that in the absence of $BF_3{\cdot}OEt_2$ (cf. Figure 8). This could possibly be the result of the optimal ratio $[Pd]/[BF_3{\cdot}Et_2O]$ being exceeded.[42] Since the fraction of active Pd-species is not known, it is difficult to make assumptions about the required stoichiometry between the Pd-catalyst and the $BF_3{\cdot}OEt_2$ co-catalyst.[43]

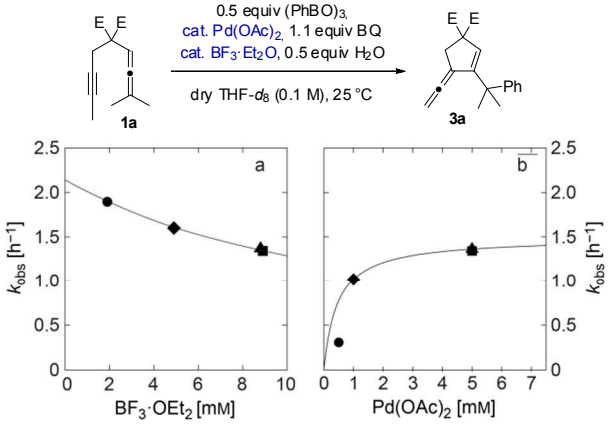


Figure 12. Influence of $[BF_3{\cdot}Et_2O]$ (a) and added $[Pd(OAc)_2]$ (b) on k_{obs}. With rate = k_{obs} $[PhB(OH)_2]$. Conditions: 0.1 mmol **1a**; a) 5 mol% $Pd(OAc)_2$, 1–10 mol% $BF_3{\cdot}Et_2O$;[41] b) 0.5–5 mol% $Pd(OAc)_2$, 10 mol% $BF_3{\cdot}Et_2O$.

The analysis of the reaction progress with regard to the concentration of H_2O is complicated by the interplay of different equilibria (e.g. the hydrolysis of $(PhBO)_3$) and its consumption throughout the reaction. If a sufficient amount of protons are available in the form of H_2O, then HQ and $B(OH)_3$ are formed as by-products of the reaction.[44] For less than ca. 1 equivalent of H_2O the formation of boron-adducts of deprotonated HQ is expected.[45] Figure 13 depicts experiments with different amounts of $(PhBO)_3$ and H_2O. The fastest reactions are observed for $(PhBO)_3/H_2O$ = 1:1 (A and B), thus when only minimal amounts of free H_2O are expected. This result may therefore be indicative of an inhibitory effect of H_2O, possibly due to formation of non-reactive $Pd_3(\mu^2\text{-}OH)(OAc)_5$.[12] It is worth noting that for vinylallene formation, the effect of H_2O on k_{obs} (reaction rate/[1st order reactant]) under conditions with $BF_3{\cdot}Et_2O$ is the opposite of that with limiting H_2O (Figure 13 vs. Figure 6).

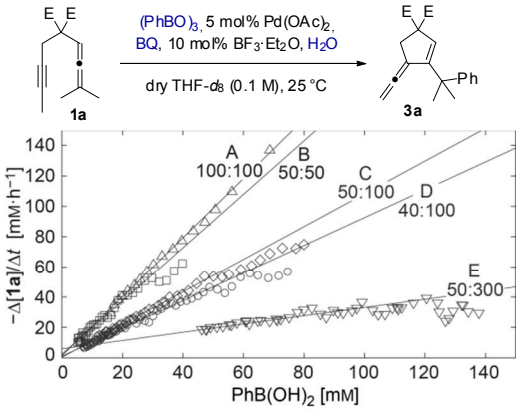


Figure 13. Rate of **1a** consumption vs. $[PhB(OH)_2]$ illustrating the effect of $(PhBO)_3/H_2O$. Variation in [BQ] is expected to be irrelevant. The experiments are shown for the region between 10–95% conversion or until the reaction had stopped, see note 40. Conditions: 0.1 mmol **1a**, $(PhBO)_3$ (A: 1 equiv, B, C, E: 0.5 equiv, D: 0.4 equiv), H_2O (A, C, D: 1 equiv, B: 0.5 equiv, E: 3 equiv), BQ (A, B, E: 1.1 equiv, C: 1.5 equiv, D: 2 equiv).

In some of the performed experiments a process was observed which consumed HQ, but not BQ and led to decomposition of product **3a** into undetectable species. This decomposition was suppressed by decreasing the concentration of $(PhBO)_3$ and the product yield was increased with higher BQ concentration. After optimization of the reaction conditions based on the kinetic analysis, the reaction provided an NMR yield of almost 80% with <1% of **2a**. The induction was found to be completed at ca. 20% conversion (Figure 14).

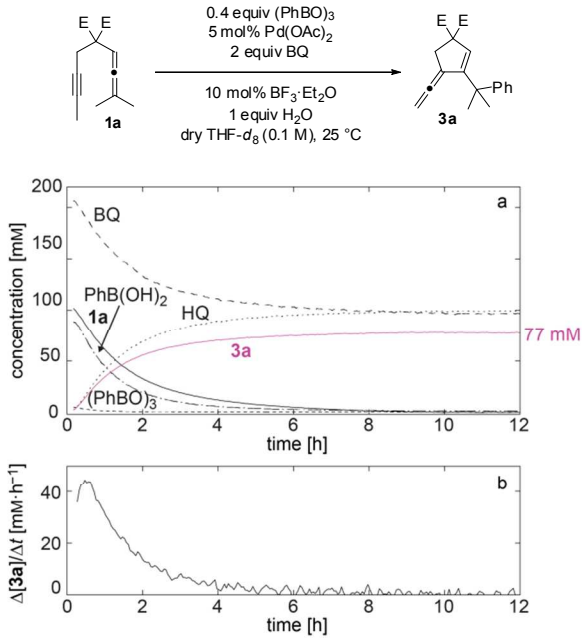


Figure 14. a) Reaction profile of selective phenylating carbocyclization of **1a** giving **3a** under optimized conditions. b) Rate profile of product formation. Scale: 0.1 mmol **1a**.

Effect of boronic acid substituent in the formation of vinylallene. According to the KIE measurements using $(PhBO)_3$, the propargylic C–H bond activation is only to a minor extent turnover-limiting in the formation of **3a** (cf. Scheme 6). Since we observed a first order dependence on $[PhB(OH)_2]$ (Figure 11), the transmetalation is to a major extent turnover-limiting, probably due to a slightly higher activation barrier than that for the C–H bond cleavage.[46] This transmetalation step is expected to be sensitive to electronic changes. We therefore studied the reaction with seven *para*-substituted boroxines under the optimized conditions (Figure 15) and performed additional KIE measurements for the most electron-donating and electron-withdrawing substituents (4-OMe and 4-NO_2, respectively) (Scheme 7).

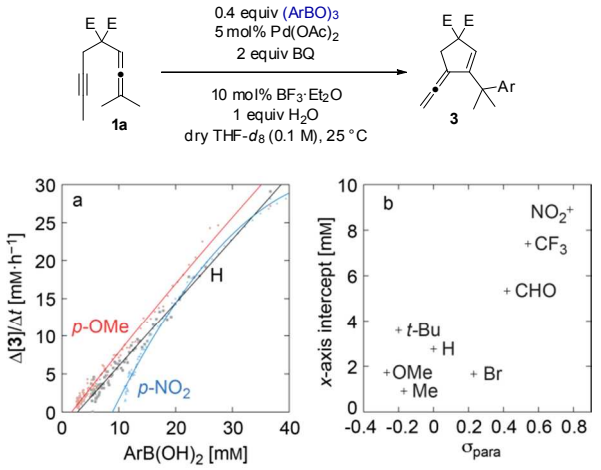
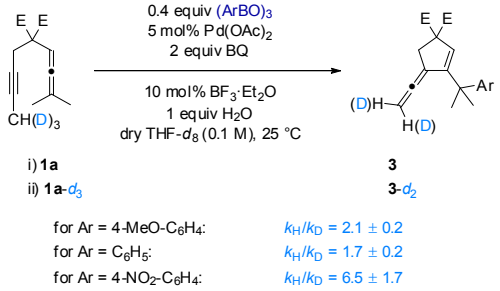


Figure 15. Substitutent effect in the formation of vinylallenes **3**. a) Rate vs. [ArB(OH)$_2$] for selected boronic acids illustrating the change in reaction order for 4-NO$_2$-C$_6$H$_4$-B(OH)$_2$. b) The deviation from linearity in the plot Δ[**3**]/Δt vs. [ArB(OH)$_2$] illustrated as the *x*-axis intercept vs. σ_{para}.[12,47] Scale: 0.1 mmol **1a**. The following yields were obtained (corresponding reaction time and conversion in brackets): OMe: 70% (11 h, 92%); *t*-Bu: 79% (10 h, 99%); Me: 76% (13 h, 100%); H: 73% (5 h, 91%; cf. Figure 14); Br: 81% (6 h, 99%); CHO: 80% (5 h, 98%); CF$_3$: 82% (6 h, 98%); NO$_2$: 77% (5 h, 95%).

Scheme 7. KIEs from individual rates in the formation of vinylallene 3 using different boronic acids

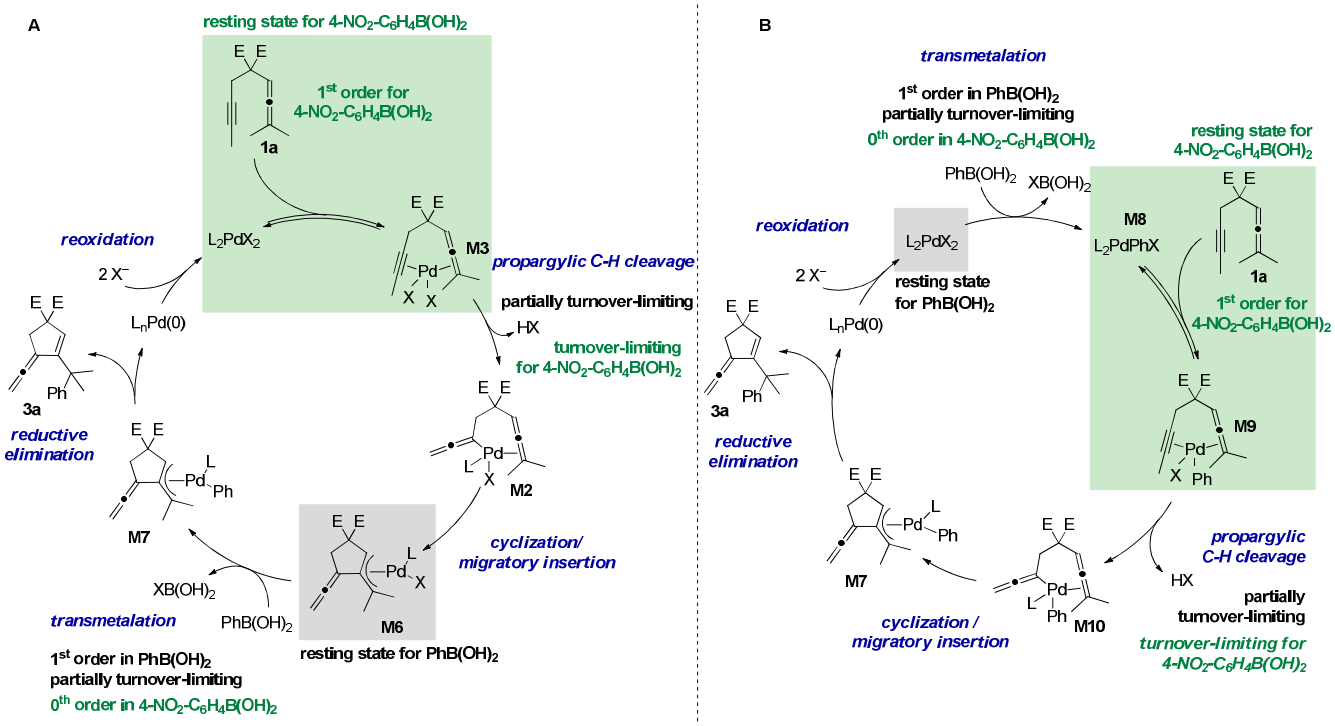


Scale: 0.1 mmol **1a** or **1a**-d_3. $k_{H(D)}$ was obtained as the slope in Δ[**3**]/Δt vs. [ArB(OH)$_2$] for Ar = C$_6$H$_5$, 4-MeO-C$_6$H$_4$ or in Δ[**3ab**]/Δt vs. [**1a**] for Ar = 4-NO$_2$-C$_6$H$_4$; **2**-d_3 was formed in varying amounts; for Ar = 4-MeO-C$_6$H$_4$: 14%, for Ar = C$_6$H$_5$: 11%, for Ar = 4-NO$_2$-C$_6$H$_4$: 8%.[12]

Electron-donating groups (OMe, *t*-Bu, Me) as well as Br as substituents displayed very similar kinetics as the unsubstituted phenyl boroxine – a first order dependence on [ArB(OH)$_2$] and for the methoxy substituent a KIE of k_H/k_D = 2.1 ± 0.2 (vs. 1.7 ± 0.2 for Ar = C$_6$H$_5$). However, for electron-withdrawing substituents (CHO, CF$_3$, NO$_2$), and thus with a facilitated transmetalation, the turnover-limiting step is shifted towards the C–H cleavage. This resulted in a first order dependence on the starting material **1a** and a zero order dependence on the arylboronic acid. For Ar = 4-NO$_2$-C$_6$H$_4$, the KIE was measured and a large value of k_H/k_D = 6.5 ± 1.7 was determined (Scheme 7).[12]

Proposed mechanism for formation of vinylallenes. The KIE measurements have clarified that the essential feature for the formation of phenylated **3a** is the propargylic C–H bond cleavage occurring prior to the cyclization and that there is an equilibrium between catalyst-bound and free substrate **1a**. With this in mind we consider the two possible mechanisms for the formation of **3a** shown in Scheme 8. The proposed mechanism A starts with reversible complexation of the active Pd^{II} species by substrate **1a** leading to an adduct which subsequently can undergo C–H bond cleavage to give **M2**. After this step, which was found to be partially turnover-limiting when using PhB(OH)$_2$, the allenylpalladium intermediate **M2** undergoes cyclization, followed by reductive elimination from allylpalladium species **M7** to provide product **3a**. Transmetalation with PhB(OH)$_2$ may occur either in intermediate **M2** or **M6** (the latter option is shown in Scheme 8A). In the second possible mechanism (Scheme 8B), the catalytic cycle starts with the transmetalation between the catalyst and PhB(OH)$_2$ which is followed by reversible complexation of the substrate, C–H bond cleavage, irreversible cyclization, and reductive elimination. Both proposed mechanisms A and B can only account for the observed first order dependence on [PhB(OH)$_2$] if transmetalation is slow and to a major extent turnover-limiting. Furthermore, the observed zeroth order in starting material **1a** is rationalized by **M6** or L$_2$PdX$_2$ being resting states in mechanism A and B, respectively. The high regioselectivity in the last step of both alternative mechanisms (the reductive elimination from a π-allyl Pd intermediate) may be attributed to the formation of the stabilized π-system.[48] Mechanisms A and B can both rationalize the formation of the side products that were observed in the absence of BF$_3$·Et$_2$O for substrates with a propargylic CH$_2$ (cf. Scheme 2) or a propargylic CH group instead of CH$_3$.[12] This suggests that an allenyl-palladium intermediate (such as **M2** or **M10**) is also involved in the pathway towards **3** under unselective conditions and can be intercepted by a reaction with HQ to give 4-hydroxy-phenoxy-substituted compounds **5** and **6**.[49]

Scheme 8. Possible mechanisms for the formation of 3a in the presence of $BF_3 \cdot Et_2O$



L = neutral ligand (e.g. BQ, HQ, THF, H_2O etc.), X = anionic ligand (e.g. AcO^-, $HOC_6H_4O^-$ etc.)

Only those equilibria are indicated that are crucial to match the experimental results.

Most kinetic results for the selective formation of vinylallenes **3** from substrate **1a** are easily rationalized with either mechanism A or B in Scheme 8 as illustrated by the following discussion. When electron-deficient arylboronic acids such as 4-NO_2-C_6H_4-$B(OH)_2$ are used, the rate of the reaction shows a first order dependence on [**1a**], and a zero order dependence on [$ArB(OH)_2$]. This is explained by facilitated transmetalation shifting the turnover-limiting step from transmetalation to C–H bond cleavage (**M3**→**M2** or **M9**→**M10**), and the resting state to the substrate-binding equilibrium (L_2PdX_2+**1a**⇌**M3** or **M8**+**1a**⇌**M9**). These changes are in line with a distinctively larger KIE value for the 4-NO_2-C_6H_4-$B(OH)_2$ than for the more electron-rich derivatives.

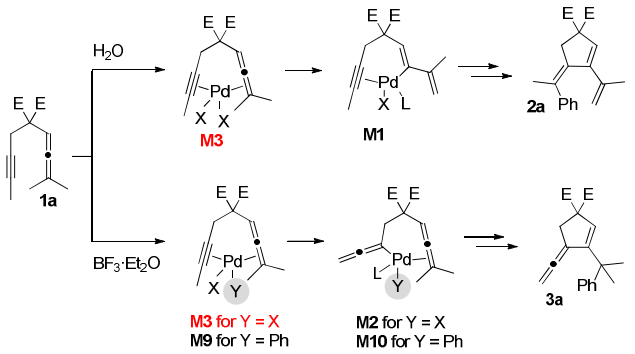
The general influence of $BF_3 \cdot Et_2O$ on the arylating cyclization (Scheme 8) could be the formation of more cationic Pd^{II} complexes containing more weakly coordinating counterions X^- compared to reaction mixtures without $BF_3 \cdot Et_2O$. For example, $BF_3 \cdot Et_2O$ could promote early transmetalation as suggested in mechanism B, i.e. accelerating it compared to the complexation with substrate **1a**.[50,51] On the other hand, $BF_3 \cdot Et_2O$ could be responsible for propargylic C–H abstraction (*vide infra*) in either mechanism A or B.

When the reaction was performed with **1a**-d_3, triene **2**-d_3 was formed as side product. Its amount was found to depend on the arylboronic acid used, with higher yields for more electron-rich arylboronic acids (Scheme 7). In mechanism B, the electronic properties of intermediate **M9** (which undergoes either propargylic or allenic C–H bond cleavage) are influenced by substitution of $ArB(OH)_2$, thus offering an explanation for the differences in the yield of **2**-d_3. In contrast, these are difficult to account for in mechanism A.

However, on the basis of the present data it is difficult to conclusively discern mechanisms A from B, and it could well be that a mixture/cross-over of pathways is involved in the selective formation of vinylallenes **3**.[12]

Discussion of the origin of selectivity. The high control of product selectivity in the arylating carbocyclization (Scheme 1) is of great interest for synthetic applications. Despite the extensive study of this reaction, the obtained experimental data do not provide any conclusive evidence regarding the origin of this selectivity and the question remaining to be answered is why the allene is activated in the presence of water, whereas the alkyne is activated in the presence of $BF_3 \cdot Et_2O$ (Scheme 9).

Scheme 9. Summary of proposed mechanisms for the formation of 2a and 3a



One explanation could be that in the absence of $BF_3{\cdot}Et_2O$ the reaction is frontier orbital-controlled, whereas in the presence of $BF_3{\cdot}Et_2O$ the reaction becomes charge controlled.[52,53] In the frontier orbital-controlled reaction, the interaction between the LUMO on Pd^{II} and the HOMO on the allene and alkyne, respectively, would determine the outcome of the reaction. A simple calculation shows that the HOMO of an allene is higher in energy than the HOMO of an alkyne,[54] which would lead to preferential reaction of the allene in the frontier orbital-controlled reaction. Under charge-controlled reaction conditions, the alkyne is expected to react faster than the allene due to a larger partial negative charge of the triple bond.

Summary. The mechanistic investigation of the oxidative phenylating carbocyclizations using deuterium labeled derivatives of allenyne substrate **1a** provided conclusive evidence for selectivity being determined in the first irreversible step after substrate binding. Allenic C–H abstraction leads to functionalized triene **2a** while propargylic C–H abstraction gives functionalized vinylallenes **3**. The KIE results also demonstrate that the C–H abstraction is turnover-limiting for the formation of **2a**, whereas in the reaction employing $BF_3{\cdot}OEt_2$ to give **3a** it is partially turnover-limiting for electron-rich arylboronic acids and fully turnover-limiting for electron-deficient boronic acids. Kinetic measurements of the phenylating carbocyclization without added $BF_3{\cdot}OEt_2$ revealed that there is a long induction period due to the activation of the Pd pre-catalyst, which requires the presence of both arylboronic acid and BQ. Under these conditions, the kinetics of the two pathways leading to trienes **2** or vinylallenes **3**, respectively, appear quite different from one another. The formation of trienes **2** only occur in the presence of $ArB(OH)_2$, whereas the rate of vinylallene formation exhibits a first order dependence on $(ArBO)_3$ after the consumption of $ArB(OH)_2$. When the reaction using $(PhBO)_3$ is performed with an excess of H_2O to give selectively triene **2a**, the observed zero order in all the reactants agrees with the C–H cleavage being the slowest step in the catalytic cycle (cf. Scheme 5). The reaction order in $Pd(OAc)_2$ appeared to be of complex nature due to a saturation behavior. Although the active catalytic species was not identified, the conversion of $Pd_3(\mu^2\text{-}OAc)_6$ to $Pd_3(\mu^2\text{-}OH)(OAc)_5$ in the presence of water was observed. Under conditions employing $BF_3{\cdot}OEt_2$ only a very short induction period was observed, possibly related to the conversion of $Pd_3(\mu^2\text{-}OAc)_6$ to the active species. This reaction giving phenylated vinylallene **3a** was found to be zeroth order in substrate and BQ, first order in $PhB(OH)_2$ and inverse order in $BF_3{\cdot}OEt_2$. The energy barriers for C–H activation and transmetalation should be similar to one another since the turnover-limiting step can be altered by changing the Ar group in $ArB(OH)_2$ from an electron-rich to an electron-deficient one. Additionally, the observed change in reactivity of differently *para*-substituted $ArB(OH)_2$ indicates that $BF_3{\cdot}OEt_2$ may promote an early transmetalation.

The present investigation has provided a better understanding of the mechanism for oxidative Pd^{II}-catalyzed carbocyclizations involving allenes, where arylboronic acids are used in cascade reactions. These reactions are important in creating novel carbocycles of relevance for natural products and biologically active compounds. A detailed knowledge of the mechanism of these and related reactions, including the relevance of underlying processes is crucial for the further development of applications of cyclization chemistry in selective synthesis.

ASSOCIATED CONTENT

Supporting Information. Experimental and spectral details, detailed experimental procedures, additional data, and discussions of the results of kinetic experiments are available free of charge via the Internet at http://pubs.acs.org.

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(11) The approach to monitor the entire course of the reaction is also referred to as Reaction Progress Analysis: (a) Blackmond, D. G. *Angew. Chem. Int. Ed.* **2005**, *44*, 4302. (b) Mathew, J. S.; Klussmann, M.; Iwamura, H.; Valera, F.; Futran, A.; Emanuelsson, E. A. C.; Blackmond, D. G. *J. Org. Chem.* **2006**, *71*, 4711.

(12) For more information see the SI.

(13) Please note that "$Pd(OAc)_2$" is used as a simplification and the material used consists of the trimeric $[(Pd(OAc)_2]_3$. The existence of the trimeric form of $Pd(OAc)_2$ in THF-d_8 was confirmed through ^{1}H NMR diffusion measurement (DOSY) and has also been reported previously (see ref 20a).

(14) Regarding protodeboronation of $PhB(OH)_2$, see: Kuivila, H. G.; Reuwer, J. F., Jr.; Mangravite, J. A. *J. Am. Chem. Soc.* **1964**, *86*, 2666.

(15) (a) Rosner, T.; Pfaltz, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2001**, *123*, 4621. (b) Singh, U. K.; Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 14104. (c) Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 13978.

(16) In the pre-stirring experiments, yields of **2a** and selectivities were marginally improved.

(17) Conversion of $Pd_3(\mu^2\text{-}OAc)_6$ to $Pd_3(\mu^2\text{-}OAc)_5OH$ was observed during the pre-stirring period. However, we were unable to relate this conversion to the degree of activation (cf. SI section S6.11).

(18) Water can be excluded as an important factor under these conditions (3 equiv H_2O), because increasing the initial water content in a "regular" reaction from 3 to 6 equiv does not lead to an accelerated rate (cf. Figure S11).

(19) For 0.5 equiv H_2O <2% of **1a** remained after 20 h; for 0.3 equiv H_2O <5% of **1a** remained after 23 h; without additional H_2O 9% of **1a** remained after 48 h, and 56% of **3a** was formed.

(20) (a) Bedford, R. B.; Bowen, J. G.; Davidson, R. B.; Haddow, M. F.; Seymour-Julen, A. E.; Sparkes, H. A.; Webster, R. L. *Angew. Chem. Int. Ed.* **2015**, *54*, 6591. (b) Mekareeya, A.; Walker, P. R.; Couce-Rios, A.; Campbell, C. D.; Steven, A.; Paton, R. S; Anderson, E. A. *J. Am. Chem. Soc.* **2017**, *139*, 10104.

(21) $(\Delta[\mathbf{3a}]/\Delta t) / [(PhBO)_3]$ was found to be proportional to the rate of formation of $Pd_3(\mu^2\text{-}OH)(OAc)_5$ (see Figure S27). In a separate experiment, it was excluded that [**2a**] influences the rate of formation of **3a**, see Figure S14.

(22) Tokunaga, Y.; Ueno, H.; Shimomura, Y.; Seo, T. *Heterocycles* **2002**, *57*, 787.

(23) In the case of $(4\text{-}NO_2\text{-}C_6H_4\text{-}BO)_3$ the accurate quantification of $[(ArBO)_3]$ is problematic because of overlaying ^{1}H NMR signals in the aromatic region and therefore $(4\text{-}CF_3\text{-}C_6H_4\text{-}BO)_3$ was chosen as an exemplary electron-deficient aryl boroxine.

(24) Due to similar concentration profiles for **1a** and $[(ArBO)_3]$, it is not possible to unequivocally determine which is the first order reactant. However, for $(4\text{-}NO_2\text{-}C_6H_4\text{-}BO)_3$ as well as for $(C_6H_5\text{-}BO)_3$ a first order dependence on **1a** can be ruled out.

(25) (a) Cunningham, I. D.; Fassihi, K. *J. Mol. Catal. A: Chem.* **2005**, *232*, 187. (b) Driver, T. G.; Woerpel, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 9993.

(26) It is common that pre-catalyst saturation is attributed to an off-cycle equilibrium with oligomeric forms. However, the reaction studied here differs from published examples due to the pronounced induction period indicating that equilibration is slow and that an equilibrium state is not reached within the reaction time. (a) ref 20b (b) Rosner, T.; Le Bars, J.; Pfaltz, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2001**, *123*, 1848.

(27) For a KIE study of the related borylating oxidative carbo-cyclization of allenynes, see ref 7b.

(28) A pathway beginning with an arylpalladation followed by a carbocyclization and ending with a β-elimination is ruled out by the competition experiment. There would be no competitive deuterium isotope effect observed if the cleavage of the C–H bond would occur after any irreversible step involving substrate **1a** (see ref 7b).

(29) This large value refers to a primary KIE, but is also affected by a secondary KIE. A possible contribution of hydrogen tunneling should also be considered. However, a primary KIE may reach ca. 10 (at room temperature) if bending vibrations are taken into consideration, see: Bell, R. P. *Chem. Soc. Rev.* **1974**, *3*, 513.

(30) A pathway towards **2a** involving transmetalation followed by complexation of **1a** cannot be excluded, but is considered less likely due to the absence of a base.

(31) The formation of **4** is proposed to proceed through a dienylpalladium intermediate such as **M1**. Other pathways may also be possible, see: Deagostino, A.; Prandi, C.; Tabasso, S.; Venturello, P. *Molecules* **2010**, *15*, 2667.

(32) To ensure reproducible conditions, it was necessary to use $(PhBO)_3$ and a defined amount of H_2O (0.5 equiv after a quick optimization) in anhydrous solvent.

(33) This value is affected by a secondary KIE.

(34) Simmons, E. M.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2012**, *51*, 3066.

(35) The possibility that the observed KIE results from a C–H(D) cleavage during the reoxidation of Pd^0 (and hence the formation of HQ from BQ) seems not compatible with the observed zeroth order in BQ. The data would also be in agreement with two completely different turnover-limiting steps for the reactions of **1a** or **1a**-d_3, respectively. Considering the relatively small difference in the activation barriers for the C–H(D) cleavage, this explanation seems less likely. See also note 46. The magnitude of KIE = 1.8 itself would also be in agreement with an equilibrium isotope effect (see ref 34). However, this scenario cannot explain the difference between KIE and KIE_{comp}.

(36) For examples where a modest KIE was explained by a partially rate-determining step, i.e. that there is a second step with a similar barrier, see: (a) ref 3f. (b) Bissember, A. C.; Levina, A.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 14232.

(37) An analogous rationalization is described in ref 20b.

(38) $[PhB(OH)_2]$ was varied by regulating the hydrolysis of $(PhBO)_3$ with the amount of added water. We did not see a significant

change in the $(PhBO)_3/PhB(OH)_2$ equilibrium related to the presence of $BF_3{\cdot}Et_2O$, see SI.

(39) In some cases decomposition of product **3a** took place after all starting material was consumed. It is plausible that some decomposition also occurs during the reaction. Therefore, the reaction rate is generally given based on the consumption of **1a**. Nonetheless, some randomly chosen examples showed that using the rate based on formation of **3a** led to the same conclusions.

(40) The region below 10% of the maximal rate where noise becomes dominating was excluded.

(41) Experimentally it was not feasible to test lower $[BF_3{\cdot}Et_2O]$ (1 mol% ≙ 0.12 μL). In the experiment, 0.12 μL $BF_3{\cdot}Et_2O$ were measured. However, according to the integration in the ^{1}H NMR spectrum, 2 mol% were added.

(42) Alternatively, there could be an off-cycle equilibrium involving active catalyst, see ref 26a,b.

(43) Both $Pd_3(\mu^2\text{-}OAc)_6$ and $Pd_3(\mu^2\text{-}OH)(OAc)_5$ have been identified in the reaction mixtures (cf. ref 20). Neither was found to be the active catalytic species which appeared to form from $Pd_3(\mu^2\text{-}OAc)_6$ rather than from $Pd_3(\mu^2\text{-}OH)(OAc)_5$ (see section S7.4 in the SI).

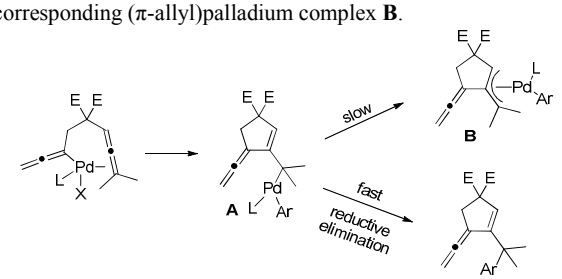
(44) The reduction of BQ to HQ requires two protons. One of them may come from the initial C–H abstraction involving the starting material **1a**.

(45) It was not possible to characterize these compounds as they are of transient nature, and do not have resolved peaks in the ^{1}H NMR spectrum.

(46) We have confirmed a first order dependence on $[PhB(OH)_2]$ also for the reaction of **1a**-d_3. This is important since it serves as evidence that the reactions of **1a** and **1a**-d_3 follow the same mechanisms (elementary steps).

(47) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* 1991, *91*, 165.

(48) Another explanation is that the initially formed (σ-allyl)palladium complex **A** is highly reactive and undergoes reductive elimination to give product faster than it rearranges to the corresponding (π-allyl)palladium complex **B**.



(49) We have not detected a diallene side-product that would result from reductive elimination in intermediate **M10** in mechanism B (this would also apply to the case in mechanism A for transmetalation occurring prior to cyclization).

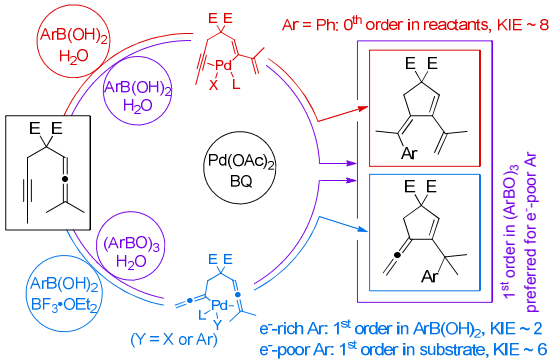
(50) In a control experiment the transmetalation between $Pd(OAc)_2$ and $PhB(OH)_2$ (1:1 mixture) in THF-d_8 was shown to proceed very slowly and only trace amounts of biphenyl were formed. In the presence of 20 mol% $BF_3{\cdot}Et_2O$, full conversion was observed after 4 h.

(51) The formation of biphenyl as a side product was not observed. Possibly, the complexation of substrate is more beneficial compared to a second transmetalation.

(52) Fleming, I. "Frontier Orbitals and Organic Chemical Reactions", Wiley, 1976.

(53) It is likely that the acetate is efficiently removed from palladium upon addition of $BF_3{\cdot}Et_2O$, which would lead to a cationic Pd^{II} complex such as $[\mathbf{1a}(Pd)(\kappa^2\text{-}OAc)]$ with $BF_3(OAc)^-$ as counterions.

(54) A DFT calculation of simple allene ($CH_2{=}C{=}CH_2$) and simple acetylene (CH≡CH) using B3LYP/6-31G(d,p) gave $HOMO_{allene}$ = –7.16 eV and $HOMO_{acetylene}$ = –7.68 eV.


ArB(OH)2
H2O
ArB(OH)2
H2O
E E
Pd
X L
Ar = Ph: 0th order in reactants, KIE ~ 8
E E
Ar
E E
Ar
1st order in (ArBO)3
preferred for e--poor Ar
Pd(OAc)2
BQ
(ArBO)3
H2O
ArB(OH)2
BF3•OEt2
E E
Pd
L
Y
(Y = X or Ar)
e--rich Ar: 1st order in ArB(OH)2, KIE ~ 2
e--poor Ar: 1st order in substrate, KIE ~ 6