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Palladium(II)-Catalyzed Regio- and Stereoselective Hydroarylation of Diphenylphosphorylallenes with Arylboronic Acids in the Presence of Sodium Hydroxide and Oxygen

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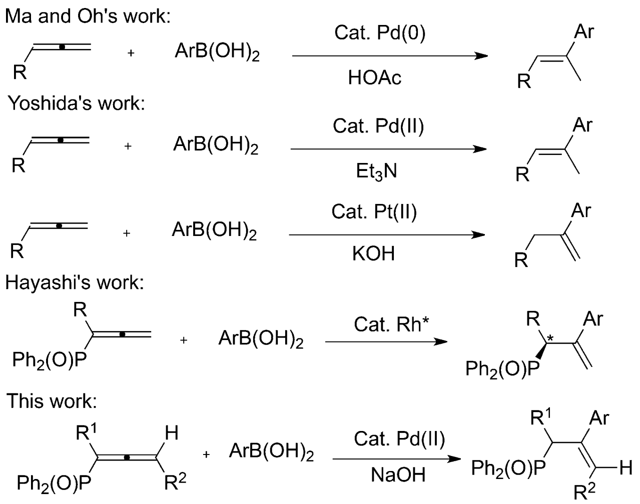
Abstract: The palladium(II)-catalyzed hydroarylation of diphenylphosphorylallenes (*via* 1,2-addition of the allenic double bond) with arylboronic acids in the presence of sodium hydroxide and oxygen is developed. The regioselectivities turn out to be well controlled, affording 2-aryl-3-(diphenylphosphinyl)alkenes as the only product. Moreover, the stereoselectivities for reactions of γ-substituted allenes can also be nicely controlled, resulting in the formation of *Z*-alkenes. The reaction shows high substituent loading capability and tolerance of various substituents. A mechanism, including transmetalation of arylboronic acid with palladium halides, insertion of the 1,2-allenic double bond to the Pd−Ar bond, and protonation to afford the final hydroarylation product is proposed.

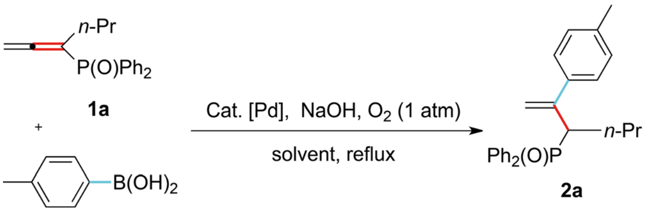
Keywords: allenes; arylboronic acids; hydroarylation; palladium

Allenes are a class of unique and interesting unsaturated compounds with two π-orbitals perpendicular to each other and they are important intermediates in organic synthesis.[1] Despite the fact that control of the chemo-, regio-, and stereoselectivities is challenging, some notable progresses have been made by Ma, Zimmer, Yamamoto and other groups, such as hydro-, carbo-, or heteroatom metalations and cyclizations of allenes.[2] On the other hand, the transition metal-catalyzed addition of organoboronic acids to unsaturated C=C double and C≡C triple bonds as well as C=O, and C=N bonds provides an efficient way for the construction of C−C bonds.[3] In particular, the transition metal-catalyzed hydroarylation or hydroalkenylation of allenes with organoboronic acids is a good strategy for obtaining various functionalized alkenes.[4–8] Ma et al. firstly reported a palladium(0)-catalyzed addition of arylboronic acids with 2,3-allenoates in the presence of acetic acid, in which the regio- and stereoselectivities were well controlled, yielding tri- and tetra-substituted alkenes as 2,3-addition products of allenes.[4] Almost at the same time, Oh et al. reported a similar reaction, and good to excellent yields were also obtained for different allenes including allenic nitriles, allenoates, allenols, allenic ethyl esters and allenals.[5] Subsequently, Ma et al. further extended this reaction to other allenes including allenylphosphonates, allenic sulfones, allenic sulfoxides, and alkyl or aryl-substituted allenes.[6] Yoshida et al. developed an ionic Pd(II) catalyst-promoted hydroarylation of allenes with arylboronic acids, wherein similar regioselective 2,3-addition products were obtained as described above under basic condition (Et_3N).[7] Moreover, the reaction has also been successfully applied in the synthesis of several natural products.[8] Interestingly, Yoshida et al. found that the reaction resulted in completely regioselective 1,2-addition products when catalyzed by an ionic Pt(II) catalyst in the presence of KOH.[7] Hayashi et al. also described a rhodium-catalyzed asymmetric hydroarylation of diphenylphosphorylallenes with arylboronic acids. Similarly, the addition of arylboronic acids to allenes occurs at the 1,2-allenic double bond, affording (*S*)-2-aryl-3-(diphenylphosphinyl)alkenes in high yields and enantioselectivity (Scheme 1).[9] However, to the best of our



Scheme 1. The transition metal-catalyzed addition reactions of allenes with arylboronic acids.

Table 1. Optimization of the reaction conditions.[a]



Entry	Solvent	Catalyst (mol%)	NaOH (equiv.)	Yield [%]
1	$THF:H_2O=5:1$	$PdCl_2$ (20)	2.0	trace
2	$EtOH:H_2O=5:1$	$PdCl_2$ (20)	2.0	trace
3	$CH_2Cl_2:H_2O=5:1$	$PdCl_2$ (20)	2.0	59
4	toluene:$H_2O=5:1$	$PdCl_2$ (20)	2.0	40
5	$EtOAc:H_2O=5:1$	$PdCl_2$ (20)	2.0	32
6	$CH_3CN:H_2O=5:1$	$PdCl_2$ (20)	2.0	70
7	$CH_3CN:H_2O=5:1$	$PdCl_2$ (10)	2.0	69
8[b]	$CH_3CN:H_2O=5:1$	$PdCl_2$ (5)	2.0	69
9	$CH_3CN:H_2O=5:1$	$PdCl_2$ (3)	2.0	54
10	$CH_3CN:H_2O=5:1$	$Pd(OAc)_2$ (5)	2.0	58
11	$CH_3CN:H_2O=5:1$	$Pd(PPh_3)_4$ (5)	2.0	21
12	$CH_3CN:H_2O=5:1$	$Pd_2(dba)_3$ (5)	2.0	25
13	$CH_3CN:H_2O=5:1$	$PdCl_2$ (5)	0	trace
14	$CH_3CN:H_2O=5:1$	$PdCl_2$ (5)	0.5	50
15	$CH_3CN:H_2O=5:1$	$PdCl_2$ (5)	1.5	61
16	$CH_3CN:H_2O=5:1$	$PdCl_2$ (5)	5.0	56
17	CH_3CN	$PdCl_2$ (5)	2.0	39
18	$CH_3CN:H_2O=10:1$	$PdCl_2$ (5)	2.0	59
19	$CH_3CN:H_2O=5:2$	$PdCl_2$ (5)	2.0	56
20	$CH_3CN:H_2O=1:5$	$PdCl_2$ (5)	2.0	0
21	H_2O	$PdCl_2$ (5)	2.0	0
22[c]	$CH_3CN:H_2O=5:1$	$PdCl_2$ (5)	2.0	trace
23[d]	$CH_3CN:H_2O=5:1$	$PdCl_2$ (5)	2.0	trace
24[e]	$CH_3CN:H_2O=5:1$	$PdCl_2$ (5)	2.0	53

[a] The reaction was carried out using **1a** (0.2 mmol), 4-$CH_3C_6H_4B(OH)_2$ (2.0 equiv.), catalyst (5 mol%), and NaOH in solvent (5:1 mL) under an O_2 atmosphere (1 atm.) at reflux for 16 h.

[b] 21% of 4,4′-dimethyl-1,1′-biphenyl was isolated.

[c] The reaction was carried out in the air.

[d] Under argon atmosphere (1 atm.).

[e] The reaction was carried out at 40 °C.

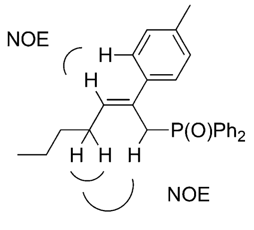
knowledge, the selective 1,2-addition of functionalized allenes with organoboronic acids to afford multi-substituted alkenes using palladium as catalyst has not yet been reported.[10–12] In continuation of our study on transition metal-catalyzed reactions of allenes, we have recently studied the $PdCl_2$-catalyzed regio- and stereoselective addition of arylboronic acids with diphenylphosphorylallenes in the presence of NaOH and O_2, and we wish to report our preliminary results here.

To explore the reactivity, the reaction using diphenylphosphorylallene **1a** as model substrate was fully studied for reaction optimization (Table 1). The reactions were initially carried out in various solvent systems with volume ratio of solvent:water = 5:1 using 20 mol% of $PdCl_2$ as catalyst in the presence of NaOH and O_2. Disappointingly, no products could be isolated when using THF or EtOH (entries 1 and 2). Further efforts showed that 32–59% yields of 2-aryl-3-(diphenylphosphinyl)alkene **2a** could be achieved when carrying out the reactions in CH_2Cl_2/H_2O, toluene/H_2O or $EtOAc/H_2O$ system, but the yields were still not satisfactory (entries 3–5). To our delight, up to 70% of **2a** could be isolated when the reaction was run in CH_3CN/H_2O (entry 6). Subsequently, the reaction was carried out with different catalyst loadings in CH_3CN/H_2O. The results showed that the high yield could be maintained even when decreasing the $PdCl_2$ amount to 5 mol% (entry 8). Under the conditions of 5 mol% catalyst, $Pd(OAc)_2$, $Pd(PPh_3)_4$ and $Pd_2(dba)_3$ were also found to be effective to catalyze the examined reaction, but afforded relatively lower product yields as compared to $PdCl_2$ (entries 10–12). Further studies indicated that the amount of NaOH affected the reaction efficiency. On decreasing the NaOH amount, the yields were also significantly decreased, and 2 equiv. of NaOH proved to be most efficient (entries 13–16). Moreover, the involvement of water as co-solvent proved to be very important. When carrying out the reaction in CH_3CN (entry 17), only 39% of **2a** could be obtained.

On varying the volume ratio between CH_3CN and H_2O, the product yield also varied, and the favorable ratio was 5:1. However, owing to the low solubility of organic substrates in water, the reaction could not proceed when $CH_3CN:H_2O=1:5$ or in pure water (entries 21 and 22). Under an argon atmosphere or in air, the reactions resulted in only trace amounts of product **2a**, revealing that the involvement of a sufficient amount of O_2 is necessary to promote the reaction (entries 22 and 23). Lower reaction temperature

(40 °C) led to lower **2a** yield (entry 24). Based on the above studies, standard reaction conditions **A** [5 mol% of $PdCl_2$, 2 equiv. of NaOH, $CH_3CN{:}H_2O = 5{:}1$, O_2 atmosphere (1 atm), reflux] were obtained. Under these optimal conditions, the regioselectivity of this reaction was nicely controlled, in which the addition of allene occurred at the 1,2-allenic double bond with the aryl group of arylboronic acid adding to the central carbon of the allene moiety. The reaction afforded 2-aryl-3-(diphenylphosphinyl)alkene **2a** as the only product. It should be noted that *ca.* 21% of 4,4′-dimethyl-1,1′-biphenyl could be isolated in the examined system under the optimal reaction conditions (entry 8). Moreover, the blackening of the reaction solution – which may be due to the decomposition of $PdCl_2$ to palladium nanoparticles – could also be observed. These phenomena provide key information for the mechanism (*vide infra*).

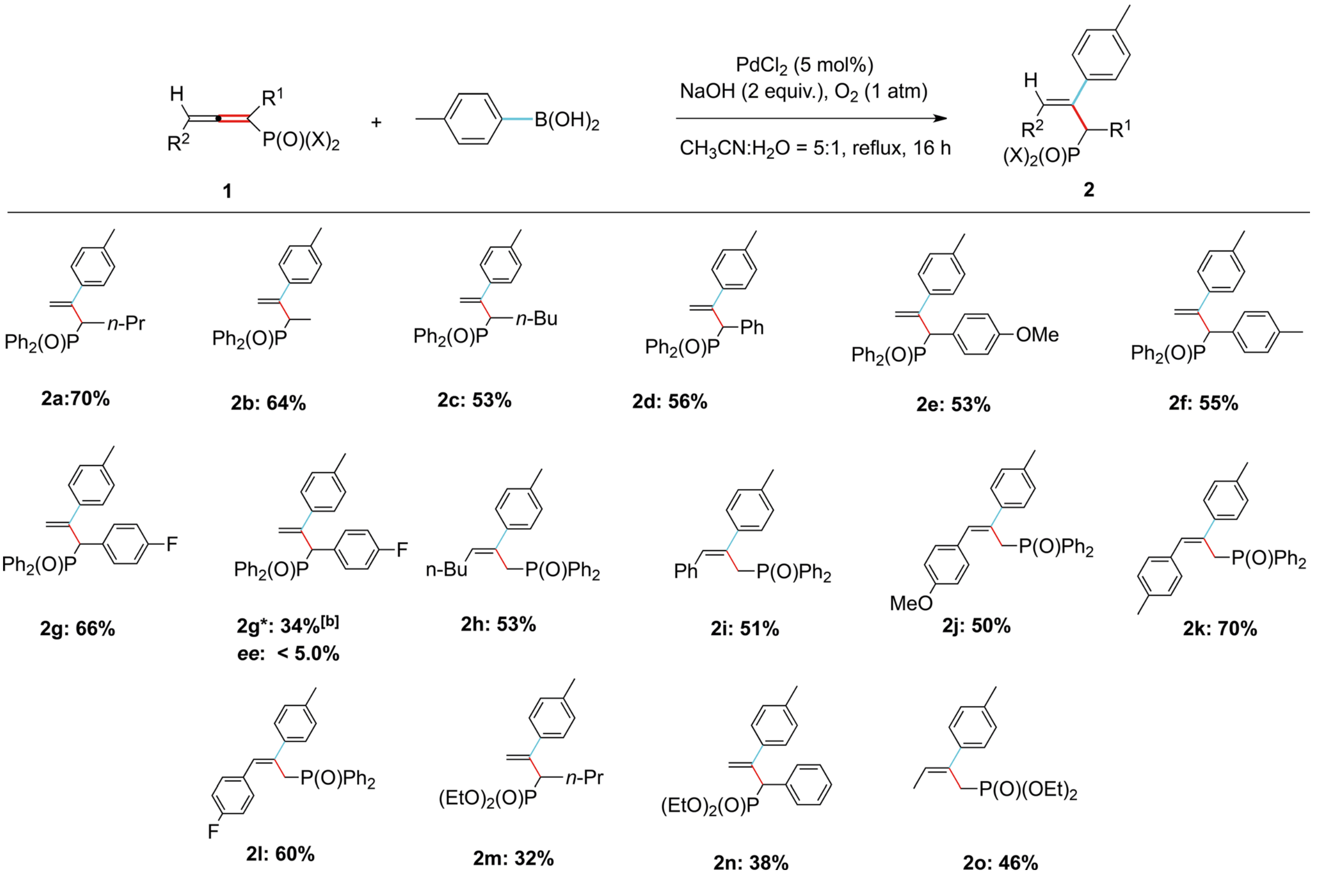
The scope of this reaction was then carefully studied by using various allenes and arylboronic acids as substrates under conditions **A**. Products **2a–2l** were obtained by using diphenylphosphorylallenes as substrates. The reaction proved to be applicable for allenes bearing alkyl groups at the α-position (R^1) (Table 2, **2a–2c**). The reaction was also applicable for various aryl (R^1) substituted allenes (**2d–2g**), indicating that the electron density of the aryl group has no obvious influence on the reaction. Notably, good yields could also be obtained when introducing alkyl or aryl groups to the γ-position (R^2) of the allene moiety, and the reactions afforded only *Z*-alkenes as the addition products (**2h–2l**), revealing a high stereoselectivity of the reaction. The configuration of the C=C bond in **2h** was determined by the ^{1}H-^{1}H NOESY spectrum (Scheme 2). In all tested reactions,



Z-2h

Scheme 2. ^{1}H-^{1}H NOESY of *Z*-**2h**.

Table 2. The reactions of various allenes with *p*-tolylboronic acid.[a]



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[a] The reaction was carried out using allene (0.2 mmol), $4\text{-}CH_3C_6H_4B(OH)_2$ (2.0 equiv.), $PdCl_2$ (5 mol%), and NaOH (2.0 equiv.) in $CH_3CN{:}H_2O$ (5:1 mL) under an O_2 atmosphere (1 atm.) at reflux for 16 h.

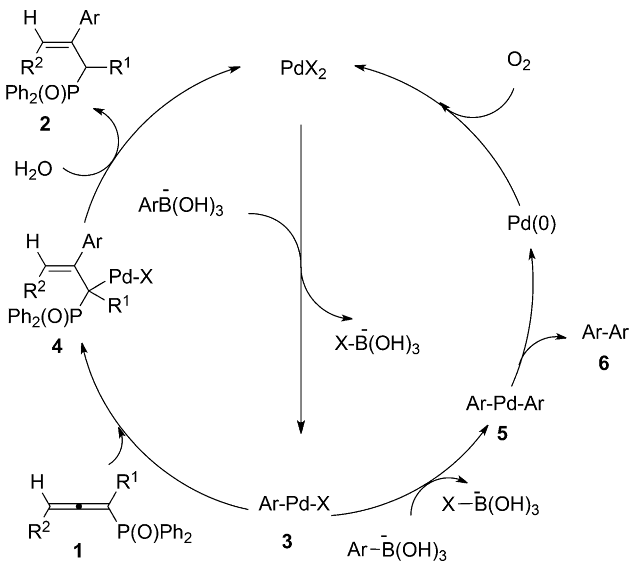
[b] 20 mol% of the chiral ligand (*R*)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl was applied.

small amounts of oligomers could also be detected. Nevertheless, only 2-aryl-3-(diphenylphosphinyl)alkene **2a–2l** products were able to be isolated. Similar results can be also achieved when using diethoxyphosphorylallenes as substrates, affording **2m–2o** in 32–46% isolated yields. Moreover, the reaction was also carried out with the introduction of 20 mol% chiral ligand (*R*)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl using **1g** as substrate. Unfortunately, the reaction exhibited negligible enantioselectivity for **2g***.

The data for the $PdCl_2$-catalyzed addition of **1g** with various organoboronic acids under conditions **A** are shown in Table 3. Among various arylboronic acids, the addition of non-substituted phenylboronic acid with **1g** resulted in the highest product yield (Table 3, **2q**). It can be seen that good yields could be obtained for both electron-rich and electron-poor arylboronic acids.

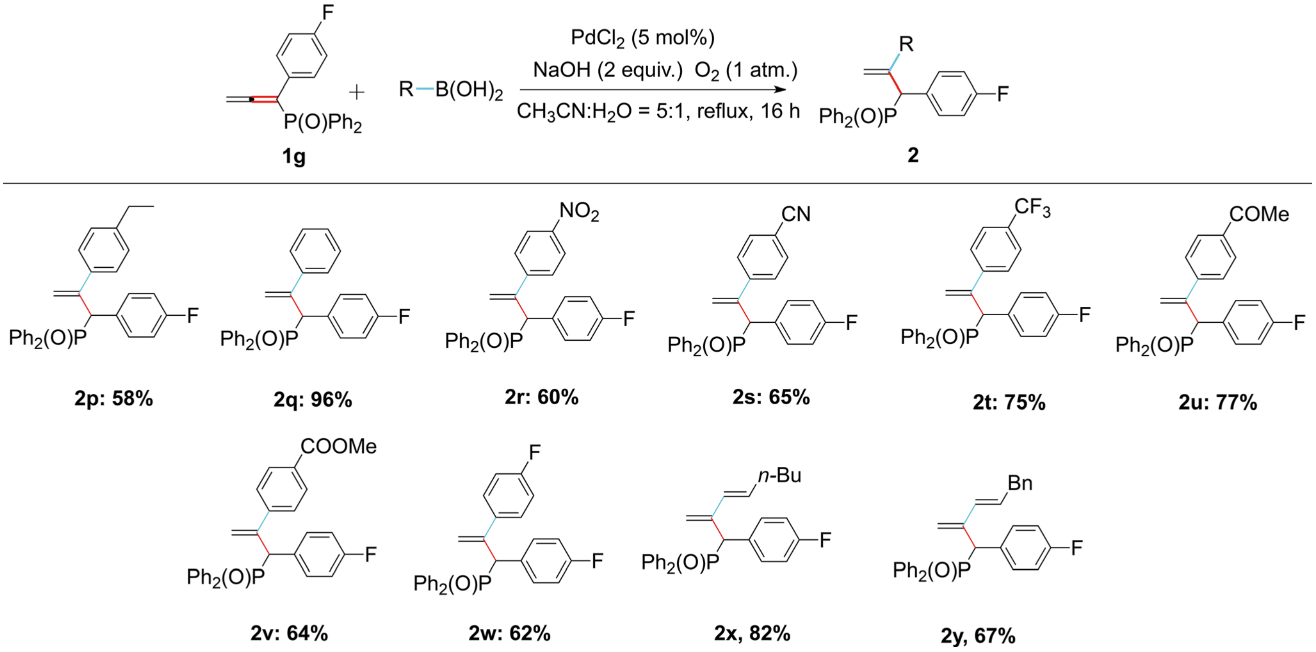
The electron-poor arylboronic acids bearing NO_2, CN, CF_3, COMe, COOMe or F substituents afforded 60–77% product yields, while a good yield could also be achieved for the electron-rich C_2H_5 substituted arylboronic acid (58%). To our delight, the reaction was found to be also applicable for vinylboronic acids. As is shown in Table 3, the addition of (*E*)-hex-1-en-1-ylboronic acid or (*E*)-(3-phenylprop-1-en-1-yl)boronic acid with **1g** afforded 82% of **2x** and 67% of **2y**, respectively. In all examined reactions, **2p–2y** were isolated as the only products. Thus, the reaction showed high selectivity with good substituent-loading capability and tolerance of various substituents.

Based on literature precedents[13] and experimental observations, a plausible mechanism is proposed (Scheme 3). Firstly, the transmetalation of the arylboronic acid with PdX_2 leads to the formation of intermediate **3**. Similar to that reported for Suzuki coupling reactions,[14] the presence of the strong base NaOH should be helpful for this transmetalation process. The involvement of NaOH may enhance the nu-



Scheme 3. Proposed mechanism for palladium(II)-catalyzed hydroarylation of diphenylphosphorylallenes with arylboronic acids.

Table 3. The reactions of **1g** with various organoboronic acids.[a]



2p: 58% **2q: 96%** **2r: 60%** **2s: 65%** **2t: 75%** **2u: 77%**

2v: 64% **2w: 62%** **2x, 82%** **2y, 67%**

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[a] The reaction was carried out using **1g** (0.2 mmol), $ArB(OH)_2$ (2.0 equiv.), $PdCl_2$ (5 mol%), and NaOH (2.0 equiv.) in $CH_3CN{:}H_2O$ (5:1 mL) under an O_2 atmosphere (1 atm.) under reflux for 16 h.

cleophilicity of the arylboronic acid, owing to its coordination with OH^- to form $ArB(OH)_3^-$ species. Thus, the further coordination of PdX_2 with $ArB(OH)_3^-$ could be facilitated smoothly, affording the transmetalation intermediate **3**. This speculation is also in agreement with that reported for the Pt/KOH-catalyzed hydroarylation of allenes described by Yoshida et al.[7] Subsequent highly regioselective insertion of the 1,2-allenic double bond of **1** to the Pd–Ar bond of **3** results in the formation of intermediate **4**, in which the aryl group of the arylboronic acid is added to the central carbon of allene moiety. The stereoselectivity of γ-substituted allenes is also determined in this step, affording the less hindered *Z*-alkene derivatives. Further protonation of **4** leads to the formation of final product **2** and regenerates the PdX_2 catalyst. On the other hand, a second transmetalation of the arylboronic acid with **3** may also lead to the formation of **5**. Therefore, the by-product Ar-Ar (**6**) might be obtained through the reductive elimination of **5**, resulting in the formation of a Pd(0) species. The observed blackening of the reaction media may due to the deposition of Pd(0) species to palladium nanoparticles, which also nicely supports our speculation. Such a side reaction might be highly active, thus the main reaction could be strongly hindered since a significant amount of Pd(II) catalyst is consumed in this process. As was observed in our experiments, only trace amounts of product could be isolated when carrying out the reaction under argon or in air. Therefore, the involvement of a sufficient amount of O_2 is very important, which might be helpful for the recovery of Pd(0) species back to Pd(II) species.

In summary, we have developed a highly regio- and stereoselective $PdCl_2$-catalyzed hydroarylation of allenes with arylboronic acids in the presence of NaOH and O_2. The catalyst $PdCl_2$ proves to be efficient for the addition of arylboronic acids with diphenylphosphorylallenes, affording 2-aryl-3-(diphenylphosphinyl)alkenes as the 1,2-addition products. A mechanism, including transmetalation of the arylboronic acid with PdX_2, insertion of the 1,2-allenic double bond to Pd–Ar, and protonation to the final hydroarylation product, is proposed. The study provides a selective and cost-effective method for the synthesis of various substituted alkenes using allenes as substrates.

Experimental Section

Typical Procedure for the Catalytic Reaction

A solution of allene substrate **1** (0.2 mmol), $PdCl_2$ (1.77 mg, 5 mol%), aryboronic acid (0.4 mmol), and NaOH (16 mg, 0.4 mmol) in $CH_3CN{:}H_2O = 5\ mL{:}1\ mL$ under an O_2 atmosphere (1 atm.) was refluxed for 16 h. After the reaction was completed, as monitored by TLC (eluent: petroleum ether/ethyl acetate = 1/1), the resulting reaction mixture was cooled to room temperature, then extracted with dichloromethane and water. The combined organic layer was dried over $MgSO_4$. Filtration, concentration, and purification by flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 5/1→3/1→1/1) afforded **2**.[15]

Acknowledgements

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[15] For spectroscopic data and detailed descriptions of experimental procedures, see the Supporting Information.

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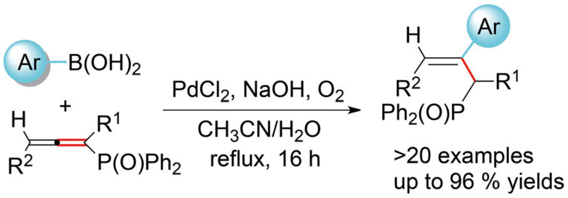

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