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Palladium-Catalyzed Oxidative Carbocyclization/Arylation of Enallenes

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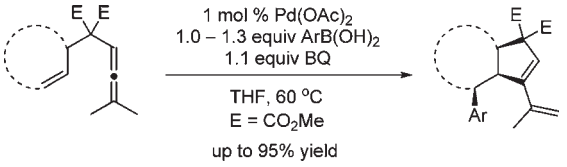
ABSTRACT



A stereoselective palladium-catalyzed oxidative carbocyclization/arylation of enallenes is described. The reaction shows wide tolerance toward highly functionalized arylboronic acids and results in a *cis* addition of two carbon moieties to an olefin in good to excellent yields.

Carbocyclization reactions are considered as some of the most important chemical transformations since tremendous amounts of naturally occurring products bear such a carbocyclic backbone.[1] Despite the rich development of transition-metal-catalyzed carbocyclizations,[2,3] there is still a demand for novel methods with high regio- and stereoselectivity. Our research group has previously reported on the utilization of allenes as carbon nucleophiles in palladium-catalyzed carbocyclizations under oxidative conditions.[4−6] For both enallenes[4] and diene-allenes,[5] new carbon−carbon bonds were formed selectively and efficiently using stoichiometric amounts of BQ (*p*-benzoquinone) as the terminal oxidant. In a few cases, BQ could be successfully replaced by an aerobic biomimetic reoxidation system making the chemical process more environmentally benign.[4e,6]

Organoboron reagents have been widely used by the chemical community to seletively facilitate the formation of new carbon−carbon bonds. Among those elegant

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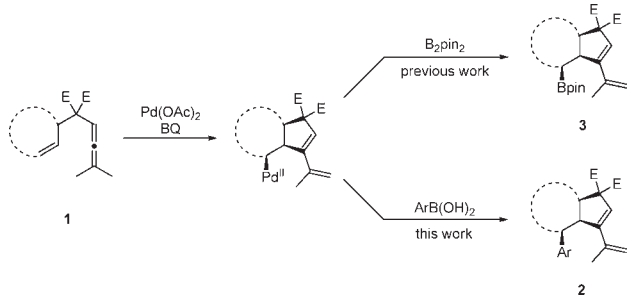
methods, asymmetric allylation[7] and Suzuki–Miyaura cross-coupling[8] are distinguished representatives. In particular the latter is a major method for carbon–carbon bond formation. Recently, also arylation of olefins via oxidative Heck procedures has been successfully accomplished by using arylboronic compounds.[9] The advantages of using organoboron compounds as transmetalation reagents include their low toxicity,[10] the mild reaction conditions involved, and their commercial accessibility. Arylboronic acids, for instance, is a family of commercialized boron compounds with a range of diverse functionalities. These properties have notably contributed to their extensive use in palladium-catalyzed arylation via trapping of aryl-,[8] alkyl-,[11] and allylpalladium[12] species. Such procedures allow for simple and efficient introduction of aryl groups in a range of substrates.

Scheme 1. Palladium-Catalyzed Oxidative Functionalization of Enallenes[a]



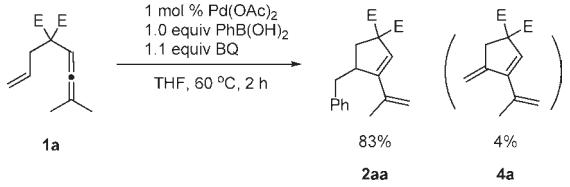
[a] E = CO_2Me, BQ = *p*-benzoquinone, B_2pin_2 = bis(pinacolato)diboron.

Recently, we reported a palladium-catalyzed oxidative borylative carbocyclization of enallenes, in which B_2pin_2 [bis(pinacolato)diboron] served as the borylating reagent (Scheme 1, upper pathway).[13] The proposed mechanism involves formation of an alkylpalladium intermediate, followed by transmetalation with B_2pin_2 and subsequent reductive elimination to furnish the cyclized alkylborates **3** in high yield. The introduction of a pinacol borane allows for further chemical transformations, e.g. oxidation and cross-coupling reactions. As a novel extension of our enallene chemistry, we attempted to actualize the direct functionalization of alkylpalladium species using organoboron reagents such as arylboronic acids. Herein, we report a palladium-catalyzed oxidative carbocyclization/arylation of enallenes.

In preliminary experiments, we applied the same conditions as in the borylation case, treating enallene **1a** with 5 mol % of $Pd(OAc)_2$, 1.2 equiv of BQ, and 1 equiv of $PhB(OH)_2$ in toluene at 40 °C. After 24 h, the reaction afforded the desired phenylated product **2aa** in 53% yield accompanied by unreacted starting material.[14] Trace amounts of the byproduct **4a**, arising from β-hydride elimination of the alkylpalladium intermediate, was also observed.

Encouraged by this result, we screened a range of reaction parameters to find a suitable protocol for selective formation of **2aa**. We found that the role of the solvent was of great importance for a successful reaction: solvents such as THF, acetone, and 1,4-dioxane promoted the formation of the desired product in good yields.[15] Among the solvents tested, THF was by far the most effective, resulting in the best selectivity for arylation over β-elimination. The catalytic activity varied with the palladium salts employed: $Pd(OOCCF_3)_2$ showed good activity comparable to $Pd(OAc)_2$, whereas other palladium salts [e.g., $PdCl_2DMSO_2$ and $Pd(acac)_2$] showed much lower activity. The catalyst loading could be lowered to 1 mol % without a significant decrease in yield. Gratifyingly, only trace amounts (2%) of biphenyl via homocoupling of phenylboronic acids could be detected in the crude reaction mixture. The amount of *p*-benzoquinone (BQ) could be reduced to 1.1 equiv without a significant loss in yield or selectivity. Increasing the temperature accelerated the reaction, and 60 °C was found to be the optimal temperature (Scheme 2). Under these conditions **2aa** was obtained in 83% yield with only 4% of the β-elimination product **4a**.

Scheme 2. Palladium-Catalyzed Oxidative Carbocyclization/Arylation of Enallenes



The conditions in Scheme 2 were used to investigate the scope of the palladium-catalyzed oxidative carbocyclization/arylation of enallenes. Both electron-rich and electron-deficient arylboronic acids were evaluated and the results are summarized in Table 1.[16] Arylboronic acids bearing electron-donating substituents such as alkyl- (entries 2 – 4 and 8), alkoxy- (entries 5 – 7) and

(10) Organosilicon reagents have also been widely used due to its low toxicity, see: (a) Hatanaka, Y.; Hiyama, T. *Synlett* **1991**, 845. (b) Hiyama, T.; Shirakawa, E. *Topp. Curr. Chem.* **2002**, *219*, 61. (c) Denmark, S. E.; Sweis, R. F. *Acc. Chem. Res.* **2002**, *35*, 835. (d) Denmark, S. E.; Sweis, R. F. *Chem. Pharm. Bull.* **2002**, *50*, 1531.

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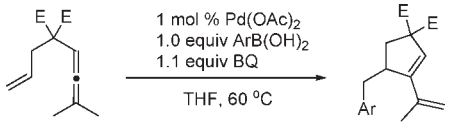
(14) Yields were determined by ^1H NMR analysis of the crude mixture using anisole as the internal standard.

(15) NMR yields for reactions in THF, acetone, and 1,4-dioxane were greater than 85%. Other solvents (ethyl acetate, toluene, DCM, DCE, and CH_3CN) gave incomplete reactions under the same conditions. For more details, see Supporting Information.

(16) The use of $ArBF_3K$ or ArB(pin) does not lead to any trapping product, and only the β-elimination product was observed.

silyl-groups (entry 9) reacted well under the standard conditions and reached full conversion within 4 h. *ortho*-Substituted arylboronic acids showed a notable decrease in yield probably due to the steric effects, resulting in a less facile transmetalation. Also, additional olefin functionality was tolerated without any notable formation of aryl-olefin coupling products (entry 10).

Table 1. Scope of Functionalized Arylboronic Acids[a]



1a 2a

entry	aryl group (Ar)	product	time (h)	yield[b] (%)
1	C_6H_5	**2aa**	2	83
2	2-Me-C_6H_4	**2ab**	4	79
3	3-Me-C_6H_4	**2ac**	4	88
4	4-Me-C_6H_4	**2ad**	4	84
5	2-OMe-C_6H_4	**2ae**	4	61
6	3-OMe-C_6H_4	**2af**	4	87
7	4-OMe-C_6H_4	**2ag**	4	75
8	4-^{t}Bu-C_6H_4	**2ah**	5	82
9	4-TMS-C_6H_4	**2ai**	5	88
10	4-vinyl-C_6H_4	**2aj**	5	90
11	4-F-C_6H_4	**2ak**	5	90
12	4-Cl-C_6H_4	**2al**	5	82
13	4-Br-C_6H_4	**2am**	5	92
14	4-CF_3-C_6H_4	**2an**	5	73
15	4-acetyl-C_6H_4	**2ao**	5	86
16	4-formyl-C_6H_4	**2ap**	5	95
17	3-NO_2-C_6H_4	**2aq**	5	86
18[c]	4-OH-C_6H_4	**2ar**	21	68

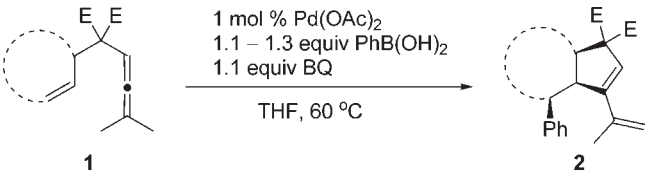
[a] Reaction conditions: 0.2 mmol **1a**, 1 mol % of $Pd(OAc)_2$, 1.1 equiv of BQ, 1.0 equiv of $ArB(OH)_2$, THF (0.1 mmol/mL), 60 °C. [b] Isolated yield after column chromatography. [c] 1.3 equiv of $ArB(OH)_2$ was used.

Electron-deficient arylboronic acids required slightly longer reaction time to reach full conversion. *para*-Halogenated aromatics also proved compatible with the reaction conditions (entries 11 – 13) including the bromo-substituted substrates, which are sensitive coupling partners in Pd(0)-catalyzed cross-coupling reactions. The remaining bromo functionality serves as a valuable handle for further modification of the product. Other electron-withdrawing substituents that are tolerated include trifluoromethyl, acetyl, formyl and nitro groups (entries 14 – 17). Among these, formyl and acetyl groups are of specific importance since carbonyl-related chemistry might be implemented subsequently. Interestingly, *p*-hydroxyphenylboronic acid proved less effective as an excess of the boronic acid and prolonged reaction time were required to afford the arylated product in 68% yield (entry 18). This may be attributed to the change of the overall acidity or factors involving transmetalation.[17]

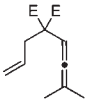
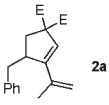
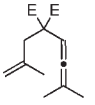
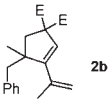
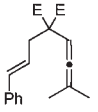
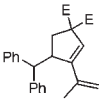
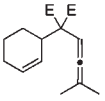
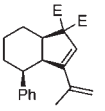
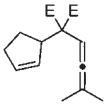
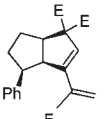
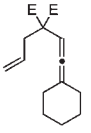
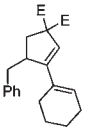
(17) The use of vinylboron compounds CH_2=C(Ph)$B(OH)_2$ and (*E*)-PhCH=CH$B(OH)_2$ gave an incomplete conversion of 47% and 35% respectively. Alkylboron compounds gave no reaction.

The reaction of different acyclic and cyclic enallenes with phenylboronic acid was also investigated (Table 2). Notably, this procedure appeared to be most efficient for enallenes with a terminal alkene, which afforded the corresponding phenylated product in good yield (Table 2, entries 1 and 2). For substrates with a substituent on the terminal position of the alkene we were pleased to find that utilization of a slight excess of phenylboronic acid

Table 2. Scope of Different Enallenes[a]



1 2

entry	substrate	product	time (h)	yield[b] (%)
1	 1a	 2a	2	83
2	 1b	 2b	7	76
3	 1c	 2c	24	55
4	 1d	 2d	2	61
5	 1e	 2e	4	63
6	 1f	 2f	24	N.R.[c]

[a] Reaction conditions: 0.2 mmol of **1**, 1 mol % of $Pd(OAc)_2$, 1.1 equiv of BQ, 1.0 equiv (entries 1–2) or 1.3 equiv (entries 3–6) of $PhB(OH)_2$, THF (0.1 mmol/mL), 60 °C. [b] Isolated yield after column chromatography. [c] No reaction based on ^{1}H NMR analysis of the crude mixture.

(1.3 equiv) significantly suppressed the formation of the β-elimination product (entries 3–5, Table 2).[18] Cyclic enallenes underwent the carbocyclization/arylation sequence affording the products with stereospecific *cis* addition of both the allene and the phenyl to the olefin (entries 4 and 5). The stereochemistry of **2d** and **2e** was determined by comparing the coupling constant with analogous compounds from our previous studies.[13] It is also worth mentioning that in these cases we observed side products

(18) β-Elimination products were formed in < 1% yields in the crude mixtures in entries 3–5 when 1.3 equiv of phenylboronic acid was used.

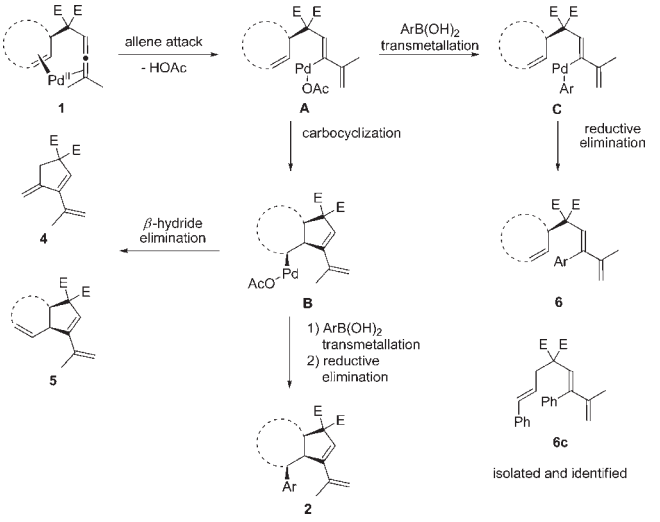
where arylation occurred on the allene moiety. This type of byproduct is of special interest when considering various mechanistic pathways (Scheme 3, **6c**).

The unsuccessful reaction of **1f** shows the limitation of this reaction; steric hindrance of the allene part has a large negative effect on the reaction outcome. Some further modifications were tried to increase the yield of **2c**, **2d**, and **2e**. Addition of a range of additives such as H_2O, NaOAc, Na_2CO_3, and DMSO failed in both diminishing the amount of β-elimination product and improving the yield of the desired carbocycles.

Mechanistically, we postulate a reaction pathway based on our previous results.[4] Initial coordination between enallene **1** and $Pd(OAc)_2$ enables allene attack on Pd(II) generating vinylpalladium intermediate **A**, the key species promoting the carbocyclization to **B** as previously suggested. The undesired β-hydride elimination from alkylpalladium species **B** could be suppressed, and **4** was formed in $<4\%$ and **5** in $<1\%$. Transmetalation of cyclic intermediate **B** with arylboronic acids, followed by reductive elimination with retention of configuration, would give the desired product **2**. The released Pd(0) is reoxidized to Pd(II) by *p*-benzoquinone. Isolation of product **6c** indicates that the carbocyclization/arylation reaction of enallenes proceeds via our proposed pathway. We should point out that formation of the undesired, phenylated product **6** can be rationalized through other palladium-catalyzed pathways.[19] Also we cannot rule out the possibility of intermediate **C** triggering carbocyclization or that a Pd(IV)-type cyclometalation mechanism is in operation.

In summary, we have successfully extended the scope of our carbocyclization chemistry by introducing a variety of functionalized aryl groups with the aid of commercially available arylboronic acids. This extension further increases the chemical complexity by the formation of two carbon−carbon bonds under oxidative conditions. Studies leading to a more detailed insight of the reaction mechanism are underway and will be reported in the near future.

Scheme 3. Mechanistic Proposal



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Supporting Information Available. Detailed experimental procedure and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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