Allene Arylation

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Olefin-Directed Palladium-Catalyzed Regio- and Stereoselective Oxidative Arylation of Allenes**

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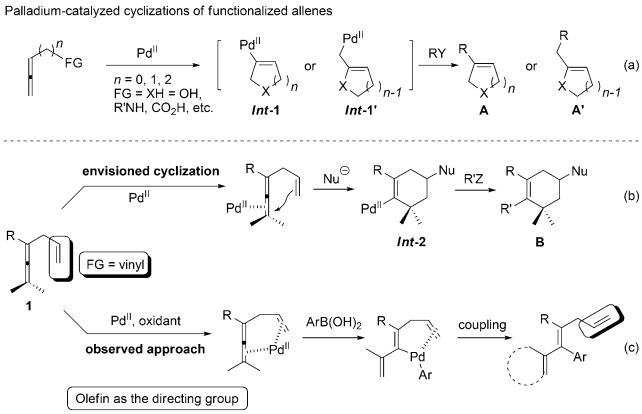
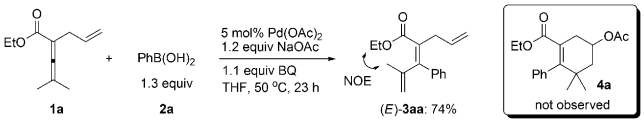
Abstract: *An olefin-directed palladium-catalyzed oxidative regio- and stereoselective arylation of allenes to afford 1,3,6-trienes has been established. A number of functionalized allenes, including 2,3- and 3,4-dienoates and 3,4-dienol derivatives, have been investigated and found to undergo the olefin-directed allene arylation. The olefin moiety has been proven to be a crucial element for the arylating transformation.*

Allenes, a class of compounds with the interesting and special substructure of two cumulative carbon–carbon double bonds,[1] have been demonstrated as powerful building blocks for the construction of complicated natural products, as well as pharmacologically active compounds.[2,3] Therefore, much attention has been focused on transition-metal-catalyzed cyclizations of functionalized allenes, especially those catalyzed by palladium.[4] The Pd^{II}-promoted reactions of allenes with a nucleophilic functionality, mostly an N- or O-containing functional group, would produce cyclic intermediates ***Int*-1** or ***Int*-1′** (Scheme 1 a). A subsequent cross-coupling reaction would lead to product **A** or **A′** respectively. However, the utilization of a π-bond-containing group as a nucleophile for such cyclizations is highly limited.[5] On this basis, we envisioned that enallene (**1**, FG = vinyl) may undergo annulation under the catalysis of Pd^{II} to provide cyclized product **B** by reaction with an external nucleophile via ***Int*-2** (Scheme 1 b).

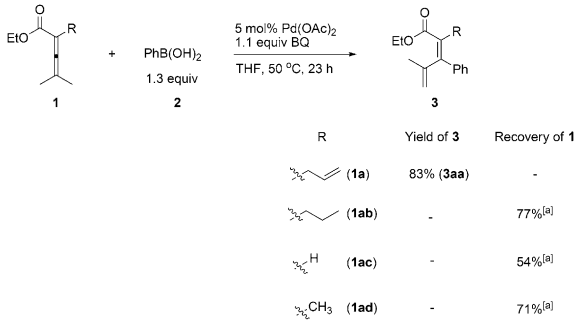
Based on this concept, we initially chose a readily accessible 2,3-dienoate as the standard substrate.[6] When allyl-substituted 2,3-dienoate **1a** was treated with $Pd(OAc)_2$ (5 mol%), $PhB(OH)_2$ (1.3 equiv), and BQ (1.1 equiv) in the presence of NaOAc (1.2 equiv) in THF at 50 °C for 23 h, the envisioned product **4a** was not observed (Scheme 2). Surprisingly, instead the phenylated triene product (*E*)-**3aa** was obtained in 74% yield as a single stereoisomer (Scheme 2, cf. Scheme 1 c). The stereochemistry was determined by NOE measurements. It should be noted that the reaction worked even better without NaOAc, producing (*E*)-**3aa** in 83% yield as shown in Scheme 3. The exclusive stereoselectivity for the



Scheme 1. a) Traditional Pd-catalyzed cyclization of functionalized allenes. b) Envisioned Pd-catalyzed cyclization of enallenes with an external nucleophile. c) Observed approach of olefin-directed Pd-catalyzed oxidative arylation of allenes. FG = functional group. Nu = nucleophilic unit.



Scheme 2. Pd-catalyzed oxidative phenylation of allene **1a**. BQ = 1,4-benzoquinone.



Scheme 3. Investigation of different substituents on allenes for the Pd-catalyzed oxidative allene-arylation. [a] Yield determined by ^1H NMR analysis using anisole as the internal standard.

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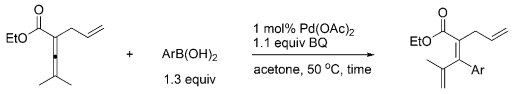
E isomer in this allene arylation indicates coordination of the olefin group during the reaction.

We next investigated how the olefin group in the substrate influenced the outcome of the reaction (Scheme 3). To demonstrate the necessity of the allyl group, we examined the reactivity of allenes with different substituents: 2,3-dienoates with a propyl substituent (**1ab**), hydrogen (**1ac**), or methyl group (**1ad**) all failed to undergo the arylating transformation, indicating that the olefin group of **1a** is an indispensable assisting/directing group[7,8] for the allene arylation. Coordination of the C=C bond during the reaction would account for the high stereoselectivity for the *E* isomer (Scheme 1c).

With these inspiring results in hand, we set out to optimize the reaction conditions (for details, see the Supporting Information). Solvent screening showed that acetone was the best solvent for this transformation, improving the yield further to 91% (yield determined by ^{1}H NMR analysis using anisole as the internal standard). Other solvents such as 1,4-dioxane, 1,2-dichloroethane, and toluene also gave good yields. Catalyst screening showed that $Pd(TFA)_2$ (TFA = trifluoroacetate) produced the corresponding triene in only 40% yield, while $[Pd(PPh_3)_2Cl_2]$ and $[Pd(CH_3CN)_2Cl_2]$ failed to promote the transformation. We were pleased to obtain (*E*)-**3aa** in 90% yield (87% yield of isolated product) with a catalyst loading of 1 mol%. Both $Pd(OAc)_2$ and BQ are required for the reaction to occur. Finally, 50°C was found to be the best temperature for this reaction.

Under the optimal conditions, we next examined the scope of arylboronic acids in the reaction with 2,3-dienoate **1a**. Arylboronic acids bearing electron-donating substituents such as 3-Me, 2-MeO, 3-MeO, and 4-MeO all reacted well and produced the corresponding trienes in good yields (Table 1, entries 2 and 4–6), while the *para*-*t*Bu-substituted arylboronic acid led to a notable decrease in yield probably due to steric effects (Table 1, entry 3). For a series of electron-deficient arylboronic acids, $LiOAc\cdot 2H_2O$ (50 mol%) was required as an additive to ensure an efficient transformation: halogenated arenes proved to be compatible with the reaction conditions (Table 1, entries 7 and 8). Other electron-withdrawing substituents, such as 3-NO_2, 4-NO_2, 4-formyl, and 4-acetyl could be present in the aryl unit, leading to the corresponding trienes in good yields (Table 1, entries 9–12). Finally, it is worth noting that 2-naphthylboronic acid also works well, affording **3am** in 71% yield (Table 1, entry 13).

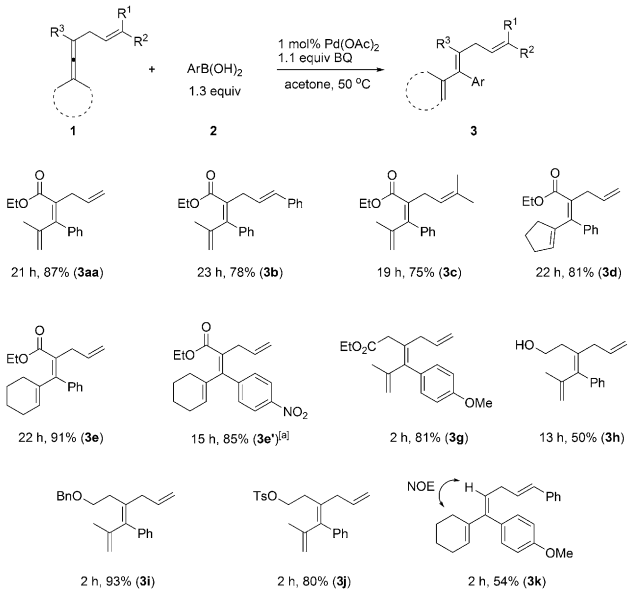
Table 1: Scope of functionalized arylboronic acids.[a]



Entry	Ar	*t* [h]	Yield of **3** [%][b]
1	Ph	21	87 (**3aa**)
2	3-Me-C_6H_4	18	94 (**3ab**)
3	4-*t*Bu-C_6H_4	16	64 (**3ac**)
4	2-MeO-C_6H_4	21	76 (**3ad**)
5	3-MeO-C_6H_4	20	77 (**3ae**)
6	4-MeO-C_6H_4	16	80 (**3af**)
7[c]	3-Br-C_6H_4	14	82 (**3ag**)
8[c]	4-F-C_6H_4	17	90 (**3ah**)
9[c,d]	3-O_2N-C_6H_4	21	91 (**3ai**)
10[c]	4-O_2N-C_6H_4	17	80 (**3aj**)
11[c]	4-formyl-C_6H_4	15	70 (**3ak**)
12[c]	4-acetyl-C_6H_4	16	85 (**3al**)
13[c]	2-naphthyl	17	71 (**3am**)

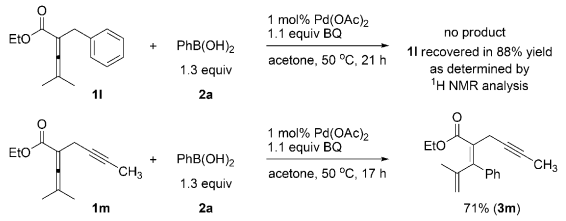
[a] The reaction was conducted at 50°C in acetone (1 mL) with **1a** (0.2 mmol), arylboronic acid **2** (1.3 equiv), and BQ (1.1 equiv) in the presence of $Pd(OAc)_2$ (1 mol%). [b] Yield of isolated product after column chromatography. [c] $LiOAc\cdot 2H_2O$ (50 mol%) was added to the reaction mixture. [d] Product **3ai** was obtained in only 41% yield in the absence of $LiOAc\cdot 2H_2O$.

We further investigated the oxidative allene arylation using different allenes (Scheme 4). The reaction of substrates



Scheme 4. Scope of allenes for the olefin-directed Pd-catalyzed oxidative arylation. [a] $LiOAc\cdot 2H_2O$ (50 mol%) was added to the reaction.

with phenyl or two methyl substituents on the olefin moiety worked well, producing **3b** and **3c** in 78 and 75% yield, respectively. Furthermore, cycloalkylidene allenes could also be employed, affording products **3d**, **3e**, and **3e′** in excellent yields. To demonstrate the broad scope of allenes in our olefin-directed arylation reaction, we chose more general allene-containing structures: 3,4-dienoate **1g** ($R^3 = CH_2CO_2Et$)[9] also showed excellent reactivity. It is worth noting that the reaction of 3,4-dienol **1h** ($R^3 = CH_2CH_2OH$), an allene containing a free OH group, produced triene **3h** instead of proceeding via oxypalladation as shown in Scheme 1a. The corresponding yield is lower probably due to the instability of the starting material and possible reaction with the OH group.[10] Surprisingly, benzyl and tosyl groups could be introduced to improve the corresponding yield significantly as shown by the formation of **3i** and **3j** in 93 and 80% yield, respectively. Finally, it is interesting to note that 54% yield of **3k** could be still obtained using a trisubstituted allene ($R^3 = H$),[11] and the stereochemistry was further confirmed by NOE measurements (for details, see the Supporting Information).

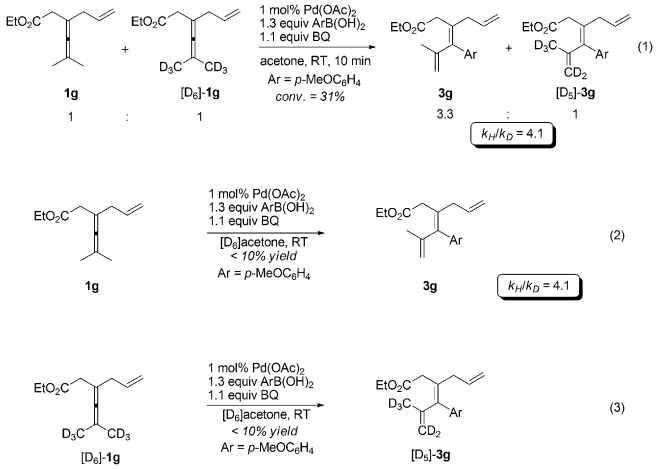


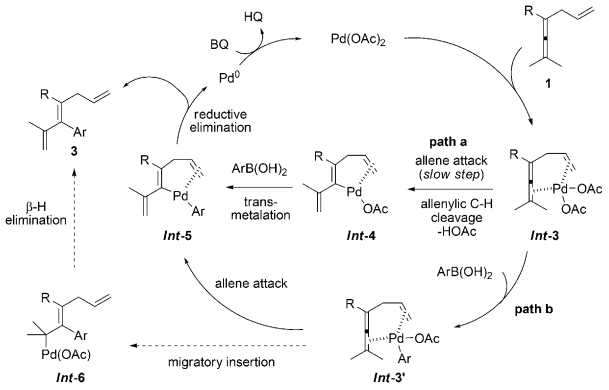
Scheme 5. Directing-group investigation for the allene arylation.

A C=C bond in the chain has been demonstrated as an indispensable directing group for the allene arylation reaction developed, while 2,3-dienoates lacking this double bond failed to undergo the arylation (see Scheme 3). We subsequently examined two other substrates (**1l** and **1m**) with π-bond-containing groups. Treatment of benzyl-substitued 2,3-dienoate **1l** under the standard conditions of Table 1 failed to give the desired product, and **1l** was recovered in 88% yield (Scheme 5). Interestingly, an alkynyl-substituent was found to work as a directing group for the allene arylation. Thus, reaction of the alkynyl-substituted 2,3-dienoate **1m** afforded the corresponding dienyne product **3m** in 71% yield.

To gain a deeper insight into the reaction mechanism, the deuterium kinetic isotope effect (KIE) was determined from the reaction of a 1:1 mixture of **1g** and [D_6]-**1g** at room temperature for 10 min [Eq. (1)]. The product ratio **3g**/[D_5]-**3g** (ca. 31% conv.) measured was 3.3:1, while the ratio of the recovered **1g** and [D_6]-**1g** was 1:1.6. From these ratios the KIE was determined to be $k_H/k_D = 4.1$. Furthermore, parallel kinetic experiments using **1g** and [D_6]-**1g** provided an intermolecular KIE (k_H/k_D, from initial rate) value of 4.1 [Eqs. (2) and (3)].[12] These results indicate that the allenylic C–H bond cleavage is the rate-determining step in the olefin-directed allene arylation reaction and that the cleavage of the C–H bond has to occur before any irreversible steps.[13]

Based on the observed kinetic isotope effects, the stereochemical outcome, and the experiments in Scheme 3, a possible mechanism for the reaction is proposed in Scheme 6. Simultaneous coordination of the allyl C=C bond and the allenic C=C bond of substrate **1** to the Pd^{II} center[14] would generate chelate ***Int*-3**, followed by allene attack to afford vinylpalladium intermediate ***Int*-4** involving allenylic





Scheme 6. Proposed mechanism for the olefin-directed Pd-catalyzed oxidative arylation of allenes. HQ = hydroquinone.

C–H bond cleavage. Further, transmetalation of ***Int*-4** with $ArB(OH)_2$ would produce ***Int*-5**, which on subsequent reductive elimination would lead to 1,3,6-triene **3** (path a). However, transmetalation of the Pd^{II} species with $ArB(OH)_2$ via ***Int*-3′** could also occur before allene attack (path b).[15] The pathway via ***Int*-4** (path a) seems more likely than that via ***Int*-3′** (path b) considering the fact that the Pd^{II} center is more electrophilic in ***Int*-3** than in ***Int*-3′**. Furthermore, a pathway via ***Int*-3′** would not give a large competitive isotope effect [Eqs. (2) and (3)] unless the transmetalation (***Int*-3**→***Int*-3′**) is reversible, which seems unlikely.[16]

In conclusion, we have developed an efficient olefin-directed palladium-catalyzed oxidative regio- and stereoselective[17] arylation of allenes to afford 1,3,6-trienes. The reaction showed a broad substrate scope for the arylboronic acids and allene substrates. The catalyst loading could be decreased to as low as 1 mol%, giving products in good to excellent yields. Mechanistic studies indicate that the allenylic C–H bond cleavage is the rate-limiting step. The olefin unit was proven to be essential to realize the transformation, and this observation has important mechanistic implications for our previously developed oxidative carbocyclizations involving allenes.[18] In these Pd^{II}-catalyzed reactions, it has now been confirmed that the allene attack on Pd^{II} requires an additional coordination of an olefin or acetylene. Finally, because of the regio- and stereoselective formation of multi-substituted trienes, this method will be useful in synthetic and materials chemistry. Further studies on the scope, mechanism, and synthetic application of this reaction are currently under way in our laboratory.

Keywords: allenes · arylation · directing groups · oxidation · palladium

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