Allene Arylation

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,[3] 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 PdII-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 1a). 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 PdII to provide cyclized product B by reaction with an external nucleophile via Int-2 (Scheme 1b).

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 1c). 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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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\cite{7,8} for the allene arylation. Coordination of the \(\text{C} = \text{C}\) 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 acetonitrile 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 \(\text{Pd(TFA)}_2\), \((\text{TFA} = \text{trifluoroacetate})\) produced the corresponding triene in only 40\% yield, while \([\text{Pd(PPh}_3\text{)}\_2]\text{Cl}_2\) and \([\text{Pd(CH}_3\text{CN)}\text{Cl}_2]\) failed to promote the transformation. We were pleased to obtain \((E)-3\text{aa}\) in 90\% yield (87\% yield of isolated product) with a catalyst loading of 1 mol\%. Both \(\text{Pd(OAc)}_2\) and BO are required for the reaction to occur. Finally, 50\(^\circ\)C was found to be the best temperature for this reaction.

Under the optimal conditions, we next examined the scope of aryloboronic acids in the reaction with 2,3-dienoate 1a. Aryloboronic 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-Bu-substituted aryloboronic acid led to a notable decrease in yield probably due to steric effects (Table 1, entry 3). For a series of electron-deficient aryloboronic acids, \(\text{LiOAc H}_2\text{O}\) (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).

We further investigated the oxidative allene arylation using different allenes (Scheme 4). The reaction of substrates 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 3f 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\(^2\) = CH\(_2\text{CO}_{\text{Et}}\)\cite{9}) also showed excellent reactivity. It is worth noting that the reaction of 3,4-dienol 1h (R\(^2\) = CH\(_2\text{CH}_2\text{OH}\)), 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.\cite{10} Surprisingly, benzy1 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\(^2\) = H)\cite{11} and the stereochemistry was further confirmed by NOE measurements (for details, see the Supporting Information).

![Scheme 4](image-url)
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 (11 and 1m) with π-bond-containing groups. Treatment of benzyl-substituted 2,3-dienoate 11 under the standard conditions of Table 1 failed to give the desired product, and 11 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 diene 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 [D₆]-1g at room temperature for 10 min [Eq. (1)]. The product ratio 3g/[D₆]-3g (ca. 31% conv.) measured was 3.3:1, while the ratio of the recovered 1g and [D₆]-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 [D₆]-1g provided an intermediate KIE (k_H/k_D from initial rate) value of 4.1 [Eqs. (2) and (3)]. These results indicate that the allenyl 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.

Based on the observed kinetic isotope effects, the stereocchemical 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 Pd³⁺ center would generate chelate Int-3, followed by allene attack to afford vinylpalladium intermediate Int-4 involving allenyl 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 Pd³⁺ species with ArB(OH)₂ via Int-3 could also occur before allene attack (path b). The pathway via Int-4 (path a) seems more likely than that via Int-3 (path b) considering the fact that the Pd³⁺ 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 unless the transmetalation (Int-3→Int-3) is reversible, which seems unlikely.

In conclusion, we have developed an efficient olefin-directed palladium-catalyzed oxidative regio- and stereoselective 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 allenyl 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. In these Pd³⁺-catalyzed reactions, it has now been confirmed that the allene attack on Pd³⁺ 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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[1] a) H. F. Schuster, G. M. Coppola, *Allenes in Organic Synthesis*, Wiley, New York, 1984; b) S. Patai, *The Chemistry of Ketenes, Allenes, and Related Compounds, Part I*, Wiley, New York, 1980.

[2] a) S. Ma in *Handbook of Organopalladium Chemistry for Organic Synthesis* (Eds.: E. Negishi, A. de Meijere), Wiley, New York, 2002, p. 1491; b) S. Ma in *Topics in Organometallic Communications*
For selected examples of platinum- or gold-catalyzed cyclizations of allenes with a π-bond-containing group as a nucleophilic group, see: a) Z. Liu, A. S. Wasmuth, S. G. Nelson, J. Am. Chem. Soc. 2006, 128, 10352; b) B. Chen, W. Fan, G. Chai, S. Ma, Org. Lett. 2012, 14, 3616; c) W. Kong, C. Fu, S. Ma, Chem. Commun. 2009, 4572; d) Y. Qiu, C. Fu, X. Zhang, S. Ma, Chem. Eur. J. 2014, 20, 10314; e) H. Funami, H. Kusama, I. Wase, Angew. Chem. Int. Ed. 2007, 46, 909; Angew. Chem. 2007, 119, 927; f) J. H. Lee, F. D. Toste, Angew. Chem. Int. Ed. 2007, 46, 912; Angew. Chem. 2007, 119, 930.

[6] R. W. Lang, H.-J. Hansen, Org. Synth. 1984, 62, 202.

[7] For a recent review of transition-metal-catalyzed π-bond-assisted C–H bond functionalization, see: P. Gandeepan, C.-H. Cheng, Chem. Asian J. 2015, 10, 824.

[8] For selected examples of π-bond-directed C–H bond functionalization, see: a) P. Gandeepan, C.-H. Cheng, J. Am. Chem. Soc. 2012, 134, 5738; b) J. Zhao, N. Asao, Y. Yamamoto, T. Jin, J. Am. Chem. Soc. 2014, 136, 9540; c) S.-i. Kiyooka, Y. Takeshita, Tetrahedron Lett. 2005, 46, 4279; d) M. Tobisu, I. Hyodo, M. Onoe, N. Chatani, Chem. Commun. 2008, 6013; e) P. Gandeepan, C.-H. Cheng, Org. Lett. 2013, 15, 2084; f) N. Chernyak, V. Gevorgyan, J. Am. Chem. Soc. 2008, 130, 5636; g) N. Chernyak, V. Gevorgyan, Adv. Synth. Catal. 2009, 351, 1101; h) N. Chernyak, S. I. Gorelsky, V. Gevorgyan, Angew. Chem. Int. Ed. 2011, 50, 2342; Angew. Chem. 2011, 123, 2390; i) Y. Minami, Y. Shiraishi, K. Yamada, T. Hiyama, J. Am. Chem. Soc. 2012, 134, 6124; j) Y. Minami, K. Yamada, T. Hiyama, Angew. Chem. Int. Ed. 2013, 52, 10611; Angew. Chem. 2013, 125, 10805; k) T. Mackawa, Y. Segawa, K. Itami, Chem. Sci. 2013, 4, 2389; l) E. M. Ferreira, B. M. Stoltz, J. Am. Chem. Soc. 2003, 125, 9578.