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Palladium-Catalyzed Oxidative Diarylating Carbocyclization of Enynes

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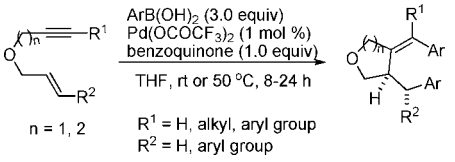
ABSTRACT



A mild and efficient palladium-catalyzed oxidative diarylating carbocyclization of enynes is described. The reaction tolerates a range of functionalized arylboronic acids to give diarylated products in good yields. Control experiments suggest that the reaction starts with an arylpalladation of the alkyne, followed by carbocyclization, transmetalation, and reductive elimination to afford the diarylated product.

Cyclic structures constitute the backbone of a large number of natural products, and therefore, efficient methods for the construction of cyclic structures from simple acyclic building blocks are of current interest. In the past several decades, transition-metal-catalyzed cyclization reactions of enynes[1] have emerged as highly useful tools for the synthesis of functionalized cyclic and heterocyclic compounds.[2,3] Various transition-metal catalysts, such as Pd,[4] Pt,[5] and Au,[6] have been studied extensively. Generally, complexation of the π-electrons of the enyne with a transition-metal catalyst allows the activation of either alkene or alkyne or both simultaneously. Regarding the relative reactivity of the unsaturated subunits, three different mechanisms involving a cyclometalation intermediate,[7] a π-allyl complex,[8] or a vinyl–metal complex[9] have been proposed. Recently, the synthesis of cyclopropanes via metal-catalyzed reactions of enynes has also been reported.[10]

So far, palladium has played a pivotal role in the development of metal-catalyzed cycloisomerization reactions of 1,n-enynes.[4,7a−c,8a,b,9a,b] However, there are only a few reports describing the arylation of alkynes with Pd(II)

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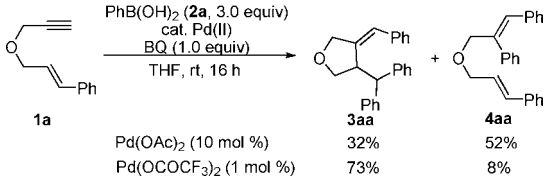
as catalyst, which still is a challenge.[11] Cárdenas and coworkers reported a Pd(0)-catalyzed borylative cyclization of 1,6-enynes and enallenes using B_2pin_2 [bis(pinacolato)diboron] as the boron-transfer reagent.[12] The reaction was proposed to proceed via hydropalladation of the alkyne moiety followed by cyclization via carbopalladation of the alkene and subsequent borylation to afford homoallylic alkylboronates in moderate to high yields. The Pd(0)-catalyzed cyclization of enynes with bimetallic reagents has been found to afford cyclized products including two functional groups.[13]

Our research group has been involved in the development of various palladium-catalyzed carbocyclizations under oxidative conditions.[14,15] Recently, we reported the palladium-catalyzed oxidative carbocyclization−borylation and −arylation of enallenes[14f,g] and allenynes.[14h] In the oxidative carbocyclization/arylation reactions, arylboronic acids were used to readily generate an arylpalladium species from a Pd(II) catalyst. As an extension of our oxidative palladium chemistry, we envisioned that the arylpalladium species formed may undergo arylpalladation of either alkene or alkyne in enynes to generate an alkyl- or vinylpalladium intermediate. These intermediates may trigger cyclization reactions leading to an overall diarylation with novel complexity. Herein, we report a mild and efficient stereoselective diarylating carbocyclization of enynes catalyzed by Pd(II) under oxidative conditions to give the corresponding diarylated carbocycles in good yields.

In our preliminary experiments, O-tethered 1,6-enyne **1a** was treated with 10 mol % of $Pd(OAc)_2$, 3.0 equiv of phenylboronic acid (**2a**), and 1.0 equiv of *p*-benzoquinone (BQ) in tetrahydrofuran (THF) at room temperature. Full conversion of **1a** was achieved in 16 h, and gratifyingly, the desired cyclic diarylated product **3aa** was isolated in 32%. The major byproduct was identified as the diarylated alkyne product **4aa** in 52% yield (Scheme 1). The stereochemistry of the newly formed double bond in both **3aa** and **4aa** was established as *Z* by NOE experiments.

Scheme 1. Palladium-Catalyzed Oxidative Diarylating Carbocyclization of Enyne



Optimization of the reaction conditions initially focused on the variation of the palladium catalyst. The catalytic activity of various palladium(II) species differed, and $PdCl_2$, $PdCl_2(PPh_3)_2$, and $Pd(acac)_2$ failed to promote any arylation resulting in full recovery of the starting material. $Pd(OAc)_2$ afforded the cyclic diarylated compound **3aa** but only as a minor product. Electron-deficient $Pd(OCOCF_3)_2$ proved to be superior to $Pd(OAc)_2$ providing the diarylated product **3aa** in 73% yield together with 8% of **4aa** (Scheme 1). The catalyst loading could be lowered to 1 mol % without any erosion in yield and stereoselectivity. Other stoichiometric oxidants such as $Cu(OAc)_2 \cdot 2H_2O$ and DDQ were also evaluated, but none of them was successful in forming **3aa**. Further examination of solvent effects revealed that acetone, diethyl ether, 1,2-dichloroethane (DCE), and DMF gave significantly lower yields, and no reaction was observed with acetonitrile or toluene as solvents. An increase of the temperature to 50 °C had a negative effect on the reaction leading to a decreased yield of **3aa** to 42%. Therefore, the optimal conditions were set to 1 mol % of $Pd(OCOCF_3)_2$, 3 equiv of phenylboronic acid, and 1 equiv of BQ in THF at room temperature.

Attempts to use malonate- or N-tethered enynes gave no reaction, and ester-tethered enyne produced a diene side product (Figure SI-1 in the Supporting Information), suggesting that the oxygen tether is crucial for the diarylating carbocyclization.

Using the optimized conditions, we further examined the scope of arylboronic acids **2**. A variety of both electron-deficient and electron-rich arylboronic acids were evaluated, and the results are summarized in Table 1. The diarylating carbocyclization procedure tolerated a broad range of functional groups, and the electronic nature of the arylboronic acids **2** had little influence on the yield of the reaction. Halide-substituted arylboronic acids reacted well with enyne **1a** to give the corresponding diarylated product **3** in good yields (Table 1, entries 2−6). A bromoaryl functionality, which is a labile moiety in Pd(0)-catalyzed cross-coupling reactions, showed good compatibility with the oxidative palladium conditions (entries 5 and 6). The use of a bromo substitution allows modification of the diarylated carbocycles. Electron-rich arylboronic acids bearing alkyl (entries 7−9), alkoxy (entry 10), or silyl substitution (entry 11) proceeded well under the optimal reaction conditions, while a slightly prolonged reaction time was required to reach full conversion. Additional olefin functionality was tolerated, and no cross-insertion

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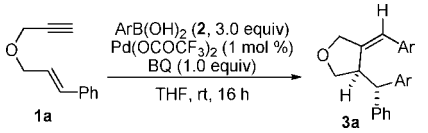
was observed (entry 12). Heteroarylboronic acids (entries 13 and 14) and (*E*)-styrylboronic acid (entry 15) worked well and afforded the corresponding diarylated products in good yields. Each product was obtained as a single diastereomer.

Table 1. Scope of Functionalized Arylboronic Acids

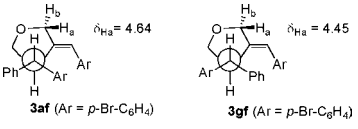


entry[a]	$ArB(OH)_2$, Ar	product	yield[b] (%)
1	**2a**, C_6H_5	**3aa**	73
2	**2b**, 4-FC_6H_4	**3ab**	70
3	**2c**, 4-ClC_6H_4	**3ac**	71
4	**2d**, 3,4−$2ClC_6H_3$	**3ad**	65
5	**2e**, 2-BrC_6H_4	**3ae**	64
6	**2f**, 4-BrC_6H_4	**3af**	66
7[c]	**2g**, 4-MeC_6H_4	**3ag**	75
8[c]	**2h**, 3-MeC_6H_4	**3ah**	72
9[c]	**2i**, 4-$^tBuC_6H_4$	**3ai**	77
10[c]	**2j**, 3-$MeOC_6H_4$	**3aj**	81
11	**2k**, 4-$TMSC_6H_4$	**3ak**	65
12	**2l**, 4-vinylC_6H_4	**3al**	76
13	**2m**, 2-furyl	**3am**	81
14	**2n**, 3-furyl	**3an**	77
15	**2o**, *E*-styryl	**3ao**	71

[a] Reaction conditions: **1a** (0.2 mmol), $Pd(OCOCF_3)_2$ (0.002 mmol), BQ (0.2 mmol), and arylboronic acid **2** (0.6 mmol) in THF (2.0 mL) at room temperature for 16 h. [b] Isolated yields. [c] The reaction time was 24 h.

The reactions of enynes **1a**−**g** in the diarylating carbocyclization are summarized in Table 2. 1,6-Enyne **1a** afforded diarylated products in good yields (Table 2, entries 1−3). When a terminal substituent of the alkyne was introduced, the reaction was slower and required an increase of the temperature to 50 °C. Under these conditions, the desired diarylated products **3bm** and **3cm** were isolated in 87% and 51% yield, respectively (entries 4 and 5). Additional dimethyl substitution at the propargyl position had minor influence on the reaction outcome and the diarylated products **3dn** and **3do** were obtained in 68 and 53% yield, respectively (entries 6 and 7). The diarylating carbocyclization process of nonsubstituted enyne **1e** also gave the desired product **3el** at 50 °C (entry 8). 1,7-Enyne **1f** showed lower activity under the optimal conditions, which may be attributed to the less favored coordination. By increasing the catalyst loading to 3 mol %, the reaction of enyne **1f** at 50 °C with boronic acids **2a** and **2l** gave the corresponding six-membered ring products **3fa** and **3fl** in 73% and 68% yield, respectively (entries 9 and 10). *E*- and *Z*-enyne isomers **1a** and **1g** afforded diastereoisomers **3af** and **3gf**, respectively (entries 11 and 12). The ^1H NMR spectra of **3af** and **3gf** are in accordance with the stereochemistry assigned.[16] Reaction of 2-cyclohexenyl propargyl ether was unsuccessful and no carbocyclization product was formed (see the Supporting Information).

(16) The stereochemical assignment of **3af** and **3gf** from the mechanism in Scheme 3 is in accord with δ_{Ha} occurring at a lower field (higher shift) in **3af** than in **3gf** due to the closeness to the *p*-bromophenyl group.



3af (Ar = *p*-Br-C_6H_4) **3gf** (Ar = *p*-Br-C_6H_4)

Table 2. Palladium-Catalyzed Oxidative Diarylating Carbocyclization of Enynes

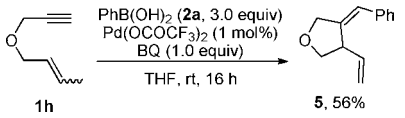
entry[a]	enyne	$ArB(OH)_2$	product	yield (%)[b]
1	**1a**	**2a**	**3aa**	73
2	**1a**	**2j**	**3aj**	81
3	**1a**	**2m**	**3am**	81
4[c]	**1b**	**2m**	**3bm**	87
5[c]	**1c**	**2m**	**3cm**	51
6	**1d**	**2n**	**3dn**	68
7	**1d**	**2o**	**3do**	53
8[c]	**1e**	**2l**	**3el**	41
9[c]	**1f**	**2a**	**3fa**	73
10[c]	**1f**	**2l**	**3fl**	68
11	**1a**	**2f**	**3af**	66
12	**1g**	**2f**	**3gf**	62

[a] Reaction conditions: **1** (0.2 mmol), $Pd(OCOCF_3)_2$ (0.002 mmol), BQ (0.2 mmol), and arylboronic acid **2** (0.6 mmol) in THF (2.0 mL) at room temperature for 16 h. [b] Isolated yields. [c] 3 mol % of $Pd(OCOCF_3)_2$ was used at 50 °C for 8 h.

By altering the terminal substituent on the alkene to an alkyl group, a different product was obtained which arose from a β-elimination in the final step. In the presence of β-hydrogens, β-elimination is apparently favored over transmetalation−reductive elimination and enyne **1h** afforded diene **5** in 56% yield (Scheme 2).

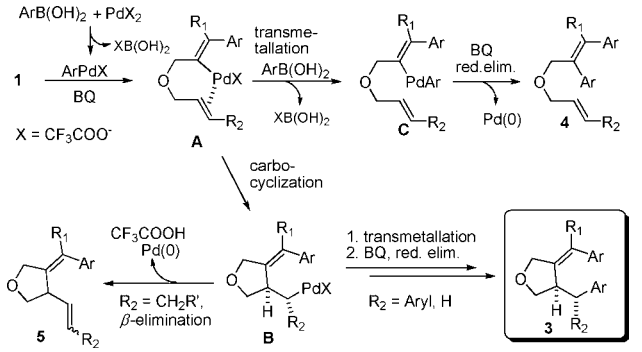
Control experiments showed that the diarylating carbocyclization does not occur with the corresponding 1,6-dienes under the reaction conditions used in Table 2. When

Scheme 2. Reaction of **1h** with Substituted Alkyl Group



the 1,6-diene corresponding to **1a** was employed as the substrate, no reaction was observed (see the Supporting Information). Apparently, the alkynyl group is essential for the palladium-catalyzed oxidative diarylating carbocyclization, which indicates that the reaction is initiated by an arylpalladation of the alkyne. Another control experiment monitored by ^{1}H NMR showed that fast arylpalladation of 1-benzyloxymethyl-1-butyne takes place at 25 °C on reaction with $PhB(OH)_2$/$PdOCOCF_3$ (1:1) (see Supporting Information).

Scheme 3. Proposed Mechanism for Pd-Catalyzed Oxidative Diarylating Carbocyclization of Enynes



On the basis of the above experimental results, a plausible reaction pathway is proposed in Scheme 3. Fast transmetalation between the arylboronic acid and the Pd(II) catalyst generates an ArPdX species,[17] which adds to the alkyne in a *syn*-arylpalladation. The vinylpalladium intermediate **A**[9] formed subsequently undergoes a carbocyclization where the alkene inserts into the vinyl–Pd bond to give intermediate **B**.[4] When R_2 = H or phenyl, transmetalation of cyclic intermediate **B** with a second arylboronic acid occurs. Reductive elimination is accelerated by coordination of BQ[18] and occurs with retention of configuration to give diarylated product **3**. The released Pd(0) is reoxidized to Pd(II) by the coordinated BQ.[18] When R_2 is an alkyl group, rapid β-hydride elimination would be favored to produce alkene **5**. The formation of the undesired acyclic side product **4** is attributed to a slow carbocyclization where competing transmetalation of the vinylpalladium intermediate **A** to give intermediate **C** occurs. Subsequent reductive elimination from intermediate **C** would give the acyclic diarylated product **4**.[19]

In the proposed mechanism, the enyne coordinates to the metal in an ArPdX species. When the tether is a carbon or nitrogen atom, formation of the corresponding intermediate **A** may be less favored in accordance with the above experiments. Comparison of the ^{1}H NMR spectra of 1,6-enynes **1e**, **I**, **II**, and **III** shows that there are differences in chemical shift of the alkynyl proton: 2.42 ppm (**1e**), 2.02 ppm (**I**), 2.02 ppm (**II**) and 2.90 ppm (**III**) (Figure 1). We argue that the induction effect from the propargyl oxygen contributes to the activation of the alkyne moiety while a carbon or a nitrogen atom in the tether does not. Also, ester-tethered enyne **III** gave a fast reaction of the alkyne; however, in this case fast protonolysis of the arylpalladation intermediate corresponding to **A** occurs. Trost has also suggested that the electronic effects of substituents on the tether between both unsaturated moieties would considerably influence the rate and regioselectivity of the cycloisomerizations of enynes.[20]

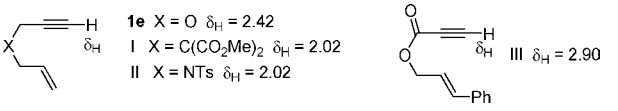


Figure 1. Shift of the alkynyl proton in enynes **1e** and **I**–**III**.

In summary, we have developed a mild and efficient Pd-catalyzed oxidative diarylating carbocyclization of enynes using arylboronic acids with stereoselective formation of tetrahydrofurans and tetrahydropyranes. Formally it occurs with *cis*-addition to the alkyne and olefin with double assembly of various aryl functionalities. Further studies regarding the scope, mechanism, and synthetic application of this reaction are currently underway in our laboratory.

Acknowledgment. Financial support from the European Research Council (ERC AdG247014) and the Swedish Research Council is gratefully acknowledged.

Supporting Information Available. Description of experimental procedures and full characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) The use of **1a** deuterated on the alkyne (**1a**-d_1) showed that the diarylative carbocyclization occurs without loss of deuterium (see the Supporting Information).

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The authors declare no competing financial interest.