Palladium-Catalyzed Oxidative Acyloxylation/Carbocyclization of Allenynes**

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Palladium(II)-catalyzed oxidative carbocyclizations represent an important class of reactions, which have provided powerful and atom-economical approaches to carboc- and heterocycles.[1–5] In particular, oxidative carbocyclization strategies have been efficiently applied to total synthesis.[3] As a continuation of our research on the palladium-catalyzed oxidative carbocyclizations of dienallenes[4] and enallenes,[5] we recently developed palladium-catalyzed arylating or borylating oxidative carbocyclizations of allenynes[6] by using the corresponding arylboronic acid or B₂pin₂.[7]

In connection with our previous studies on acetoxylation(hydroxylation)/carbocyclizations of dienallenes (Scheme 1a),[4] we envisioned an oxidative acetoxylation of allenynes 1 in the presence of HOAc/LiOAc (Scheme 1b).

**Scheme 1. Palladium-catalyzed oxidative acetoxylation/carbocyclization of allenynes (E = CO₂Me).

Table 1: Screening of reaction conditions in the palladium-catalyzed oxidative carbocyclization of allenyne 1a with acetic acid.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd**</th>
<th>Solvent</th>
<th>T [°C]</th>
<th>Yield of 3a [%]**</th>
<th>Yield of 4a [%]**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)₂</td>
<td>HOAc</td>
<td>60</td>
<td>61</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)₂</td>
<td>HOAc</td>
<td>60</td>
<td>63 [63 [%]]</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)₂</td>
<td>acetone</td>
<td>60</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)₂</td>
<td>acetone</td>
<td>60</td>
<td>62 [60 [%]]</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)₂</td>
<td>HOAc</td>
<td>25</td>
<td>&lt;4</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Pd(OAc)₂</td>
<td>HOAc</td>
<td>80</td>
<td>42</td>
<td>10</td>
</tr>
<tr>
<td>7</td>
<td>Pd(OOCCF₃)₂</td>
<td>HOAc</td>
<td>60</td>
<td>52</td>
<td>14</td>
</tr>
<tr>
<td>8</td>
<td>[Pd(acac)₃]</td>
<td>HOAc</td>
<td>60</td>
<td>46</td>
<td>8</td>
</tr>
<tr>
<td>9</td>
<td>PdCl₂</td>
<td>HOAc</td>
<td>60</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>[PdCl₂(MeCN)₂]</td>
<td>HOAc</td>
<td>60</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>11**</td>
<td>Pd(OAc)₂</td>
<td>HOAc</td>
<td>60</td>
<td>50</td>
<td>9</td>
</tr>
<tr>
<td>12**</td>
<td>Pd(OAc)₂</td>
<td>HOAc</td>
<td>60</td>
<td>38</td>
<td>10</td>
</tr>
</tbody>
</table>

[a] Yield determined by NMR spectroscopy with anisole as the internal standard. [b] LiOAc·2H₂O (2 equiv) was added. [c] Yield of isolated product. [d] HOAc (5 equiv) was added. [e] 2 mol % Pd(OAc)₂ was used. [f] 14% of 1a was recovered. [g] 10 mol % Pd(OAc)₂ was used.
ature (e.g. 80 °C) were found to give inferior yields of 3aa (compare entries 2, 5 and 6 in Table 1). When Pd(OAc)₂ was replaced with Pd(OOCCF₃)₂ or [Pd(acac)₃], the yield of carbocyclized product 3aa decreased (Table 1, entries 7 and 8). No conversion was observed with PdCl₂ or [PdCl₂(MeCN)₂] as the catalyst, and all the starting material 1a was recovered in these cases (Table 1, entries 9 and 10). A control experiment without palladium under otherwise the same reaction conditions showed no conversion of 1a according to ¹H NMR spectroscopy. The effect of palladium catalyst loading was also investigated. A lower loading (2 mol%) of Pd(OAc)₂ gave only 86% conversion of 1a with a yield of 3aa of only 50% (Table 1, entry 11). A higher catalyst loading (10 mol%) also resulted in a lower yield of 3aa (Table 1, entry 12).

With the optimized conditions in hand, we investigated the scope of allenynes in the presence of acetic acid (Table 2). When both methyl groups on the terminal carbon atom of the allene moiety of 1a were replaced by pentamethylene (forming the cyclohexylidene group) (1b), the reaction with acetic acid gave the cyclized vinylallene product 3ba in 66% yield with method A. By altering one methyl group on the allene to an ethyl group, the unsymmetrical allenyne 1c displayed a similar reactivity. The reaction of allenyne having an ethyl group (1d) on the triple bond also reacted smoothly to afford product 3da in 52% yield by employing method B. Methyl-substituted allenyne 1e gave terminal allene product 3ea in 39% yield. Moreover, the reactions of allenyynes bearing two hydroxy or ether groups (1g and 1h) instead of the carbomethoxy groups provided the corresponding products 3ga and 3ha in good yields. Even the allenynes (1i and 1j) with the ether as the tether group also worked well and afforded six-membered ring products 3ia and 3ja in moderate yields, respectively.

In addition, the reaction of allenyne (1f) with a phenyl substitution on the alkyne gave no acetoxylation product, but afforded cycloisomerization product 5f (8%), [6] dimerization products 6f (4%) and 7f (29%); the reaction may be initiated by an allylic C–H bond cleavage on the allene side (Scheme 2).

Furthermore, the scope of the reaction with respect to the carboxylic acid coupling partner was also studied by using allenyne 1b (Scheme 3). In addition to acetic acid, aliphatic carboxylic acids such as propionic acid or butyric acid reacted smoothly by employing method A to give the cyclized vinylallene products 3bb (65%) and 3bc (74%), respectively. Moreover, benzoic acid and other functionalized aromatic carboxylic acids bearing methoxy, fluorine, or chlorine groups were also tolerated under the oxidative procedure giving the corresponding carbocyclization products in good yields (64–84%). Interestingly, only trace amounts (< 1%) of dimerization product 4b (formed by dimerization of 1b through the mechanism shown in Scheme 6) were observed in the reactions in Scheme 3.

![Scheme 2.](image)

![Table 2.](image)
Oxidation processes utilizing molecular oxygen have attracted considerable attention in recent years, and therefore the oxidative carbocyclization in Table 2 and Scheme 3 was studied under various aerobic conditions. It was found that the combination of cocatalyst [Co(salophen)] with molecular oxygen (balloon) in the presence of catalytic amounts of BQ (20 mol%) permits the efficient reoxidation of Pd⁰ to Pd²⁺ and makes it possible to use O₂ as the oxidant in the acetoxylation/carbocyclization of allenynes (Table 2, entries 1–3 with method C. For details, please see Scheme S1 in the Supporting Information).

The synthetic potential of the acyloxylated allene products was demonstrated by a few transformations of the representative product 3aa. Acetoxyallene 3aa was first converted to 3,4-allenol 8 through hydrolysis (Scheme 4). Under different cyclization conditions, the prepared 3,4-allenol 8 was subsequently cyclized to various dihydropyran-fused bicyclic skeletons such as 9 (81%), 10 (82%), and 11 (85%), respectively.

To gain some insight into the reaction mechanism, the deuterium kinetic isotope effect (KIE) was determined from the experiment where a 1:1 mixture of 1a and [D₂]-1a was allowed to react in acetic acid under the reaction conditions used in Table 2 [Eq. (1)]. The product ratio 3aa/[D₃]-3aa at 13% yield (ca. 35% conv.) was 4.8:1, and from this ratio the KIE was determined to \( k_H/k_D = 5.5 \). Furthermore, the intrinsic KIE from intramolecular competition was determined by the use of [D₂]-1a as the allene substrate. In this case \( k_H/k_D = 6.1 \). Parallel kinetic experiments using 1a and [D₂]-1a provided an intermolecular KIE \( (k_H/k_D, \text{from initial rate}) \) value of 5.1 [Eqs. (3) and (4)]. These results indicate that the propargylic C–H bond cleavage is the rate-determining step in the reaction.

Two control experiments with the deuterium-labeled allenynes [D₂]-1a and [D₃]-1a were carried out under the standard conditions. Allene [D₂]-1a gave an increased yield (80%) of acetoxyalted vinylallene ([D₂]-3aa) compared to the undeuterated allene, whereas the yield of the corresponding dimer products decreased to 2% (Scheme 5a). In contrast, the allene [D₃]-1a gave only 20% yield of acetoxyalted vinylallene along with an increased yield (16%) of the corresponding dimers (Scheme 5b).

A control experiment replacing the allene by an enyne, dimethyl-2-(3'-methylbut-2'-enyl)-2-(pent-2'-ynyl)malonate, was also carried out under the standard conditions of Table 2 using method A. No formation of the corresponding cyclized allene products was observed, which shows that the allene moiety in the substrate is crucial for the oxidative transformation (Scheme S2 in the Supporting Information).
On the basis of these experimental findings, we propose the mechanism shown in Scheme 6. π-Complex formation of 1 with Pd(OAc)$_2$ to give chelate A and subsequent rearrangement involving a propargylic C–H bond cleavage would produce vinylpalladium intermediate B. Intramolecular vinylpalladation of the allene moiety would generate (π-allyl)palladium intermediate D, which is attacked by an acetate nucleophile (coordinated or external) to give 3. Competing allenyl attack in A through allylic C–H bond cleavage and subsequent alkyn insertion would generate intermediate E. Reaction of E with another molecule of allene 1 through insertion of the vinyl–Pd bond of E into the allene moiety of 1 would give the π-allyl species F, which would yield dimers (4, 6, and 7; for details, see the Supporting Information). Also, a mechanism involving a pallada(IV)cyclopentene intermediate C could be possible, which would generate intermediates D and E through β-H elimination and subsequent loss of HOAc leading to product 3 and dimeric by-products, respectively. Although β-H elimination in electron-deficient Pd$^{IV}$ intermediates is considered to be less likely, β-H elimination from less electron-deficient Pd$^{II}$ intermediate C may occur.

One could also consider a mechanism through acetoxyallene (for a detailed mechanism, see the Supporting Information). However, with this mechanism one would not obtain any significant change of the ratio between vinylallene 3 and dimers with dideuterated species [D$_2$]-1a compared to nondeuterated 1a, since with this mechanism the ratio between the competing pathways leading to 3 and dimers would be determined in the first step without any possible isotope effect (see the Supporting Information). The low ratio of 1.3:1 between [D$_2$]-3aa and dimers from [D$_2$]-1a (Scheme 5b) therefore rules out this mechanism. In contrast, the two mechanisms proposed in Scheme 6 (via intermediates B and C, respectively) are in agreement with the results observed in Equations (1)–(4) and Scheme 5.

In summary, we have developed a novel palladium-catalyzed oxidative carbocyclization of allenynes in the presence of various carboxylic acids, providing access to potentially synthetically useful acyloxylated vinylallenes. During this carbocyclization a new C–C bond, a new C–O bond, and a new allene structure are formed. Furthermore, an aerobic version of this transformation using a catalytic amount of BQ was developed to enhance the utility of this method. According to the results of deuterium labeling experiments, we propose that the reaction of the allenynes proceeds through competing propargylic and allylic C–H bond cleavage pathways or via a pallada(IV)cyclopentene intermediate with competing β-eliminations. Further studies on the mechanism and synthetic application of this reaction are ongoing.

**Experimental Section**

Typical experimental procedure for palladium-catalyzed oxidative acyloxylation/carbocyclization of allene 1: To a mixture of BQ (26.2 mg, 0.24 mmol) and Pd(OAc)$_2$ (2.4 mg, 0.01 mmol) were added 1b (69.5 mg, 0.20 mmol) and HOAc (0.4 mL) at room temperature. The reaction was stirred at 60°C for 17 h. After full consumption of starting material 1b, as monitored by TLC, the reaction was cooled to room temperature, diluted with Et$_2$O (20 mL), and quenched with H$_2$O (5 mL). The organic phase was separated and the aqueous phase was extracted with Et$_2$O (2 x 20 mL). The combined organic layers were washed with H$_2$O and dried over anhydrous Na$_2$SO$_4$. Evaporation and column chromatography on silica gel (pentane/ethyl acetate = 10:1) afforded 3ba (53.3 mg, 66%) as a liquid; $^1$H NMR (400 MHz, CDCl$_3$); δ = 5.74 (d, J = 1.2 Hz, 1H), 5.34–5.24 (m, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 3.18 (d, J = 3.6 Hz, 2H), 2.46–2.38 (m, 1H), 2.36–2.24 (m, 1H), 2.08–1.98 (m, 2H), 1.97 (s, 3H), 1.66–1.46 (m, 7H), 1.45–1.48 (m, 5H), 0.89 ppm (t, J = 7.2 Hz, 3H); $^1$C NMR (100 MHz, CDCl$_3$); δ = 198.1, 170.8, 170.7, 169.1, 149.4, 125.3, 104.2, 95.0, 79.7, 63.5, 52.9, 52.8, 36.6, 34.8, 33.6, 31.2, 29.2, 25.4, 22.1, 21.6, 21.52, 21.50, 13.9 ppm; HRMS (ESI): calc. for C$_{23}$H$_{32}$NaO$_6$ [M+Na]$^+$: 427.2091; found: 427.2091.

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[12] In the end of the reaction, the product ratio was 4.8:1, and the presence of strong oxidants with little to no formation of elimination products, see: a) L. V. Desai, K. L. Hull, M. S. Sanford, J. Am. Chem. Soc. 2004, 126, 9542; b) see Ref. [5b]; c) see Ref. [5c].

