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Palladium-Catalyzed Oxidative Carbocyclization-Carbonylation of Allenynes and Enallenes **

Chandra M. R. Volla, Javier Mazuela, and Jan-E. Bäckvall*

Abstract: A highly efficient oxidative carbocyclization-carbonylation reaction cascade of allenynes and enallenes has been developed using Pd(II) in low catalytic amounts under ambient temperature and pressure (1 atm of carbon monoxide). The use of DMSO as an additive was found to be important for an efficient reaction. A wide range of alcohols as trapping reagents were used to give the corresponding esters in good yields.

The development of methodologies for the synthesis of polyunsaturated carbo- and heterocycles is an important challenge in modern organic chemistry.¹ In this context, palladium(II)-catalyzed oxidative carbocyclizations have proven to be efficient and useful for the preparation of these compounds.^{2–3} Palladium(II)-catalyzed oxidative carbocyclizations have also been used successfully as key-steps in the total synthesis of several natural products.⁴ Our research group has been previously involved in the development of various palladium-catalyzed oxidative carbocyclization reactions.^{5–7} We have extended the synthetic potential of these carbocyclization reactions by quenching the intermediates with appropriate coupling partners. Reaction of enallenes⁸ or allenynes⁹ **1** with a Pd(II)-catalyst leads to allylic C-H activation to give intermediate **2**, which can be trapped by either an arylboronic acid or bis-(pinacolato)diboron (B_2pin_2) to afford **3** (Scheme 1a). More recently, intermediate **2** resulting from allenynes **1** was also quenched by terminal alkynes to realize a domino carbocyclization-alkynylation reaction.¹⁰ In contrast, alkyl-substituted allenynes **4** follow a different activation pathway, in which the propargylic C-H bond was cleaved to give intermediate **5**. By careful choice of reaction conditions, this intermediate was selectively formed, and subsequent reaction with either an arylboronic acid, B_2pin_2 ,¹¹ or acetic acid¹² provided the corresponding vinylallene products **6** (Scheme 1b).

In the present study, we envisioned that intermediates **2** or **5** can be carbonylated by carbon monoxide insertion to form reactive acylpalladium(II) species, which can further react with alcohol nucleophiles to provide cyclic α,β -unsaturated esters **7** or vinylallene esters **8** (Scheme 1c). To the best of our knowledge, there is no report in the literature combining Pd-catalyzed oxidative carbocycli-

zation and carbonylation reactions of unsaturated substrates.

Scheme 1. E = CO₂Me (a) Palladium-catalyzed oxidative carbocyclizations of enallenes or allenynes. (b) Palladium-catalyzed carbocyclization-borylation or acyloxylation of allenynes. (c) Oxidative palladium-catalyzed carbocyclization – carbonylation of allenynes and enallenes.

Transition metal-catalyzed carbonylation has emerged as a powerful tool for the preparation of carbonyl compounds.¹³ In this respect, palladium-catalyzed carbonylation with carbon monoxide has been extensively studied.¹⁴ In particular, palladium-catalyzed oxidative carbonylations have been widely employed for the introduction of carbonyl functionality in unsaturated substrates.¹⁵

For the initial studies, we chose allenyne **9a** with a terminal alkyne as a model substrate in the presence of 1 atm. of CO (Table 1). Treatment of **9a** with Pd(OAc)₂ (5 mol%) and 1,4-benzoquinone (BQ; 2 equiv) in CD₃OD at room temperature with a CO balloon afforded product [D₄]-**10aa** in 48% NMR yield. An unexpected incorporation of deuterium was observed in the product. The explanation of this observation is that the acidic alkyne C-H of **9a** is exchanged with the deuterium of CD₃OD in the presence of the Pd(II) catalyst as shown by control experiments (See Supporting Information). Among many Pd(II)-catalysts screened, only Pd(OAc)₂ and 1,2-bis(phenylsulfinyl)ethanepalladium(II) diacetate (**11**) gave reasonable yields of the ester [D₄]-**10aa**. When Pd(TFA)₂ (TFA = trifluoroacetate) was used in place of Pd(OAc)₂, lower yields of the product were observed. Other palladium salts such as PdCl₂, Pd(acac)₂ or Pd(DMSO)₂Cl₂ gave no reaction (Entry 3). Interestingly, lowering the catalyst loading to 1 mol% increased the yield of [D₄]-**10aa** to 63% (Entry 4).

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Supporting information for this article is available on the WWW under.

Table 1. Pd-catalyzed carbocyclization-carbonylation

Entry	Pd Cat.	mol%	NMR Yield ^[a]
1	Pd(OAc) ₂	5	48%
2	 11 Pd(OAc) ₂	5	59%
3	Pd(TFA) ₂ , Pd(acac) ₂ , PdCl ₂ , Pd(DMSO) ₂ Cl ₂	5	<10%
4	Pd(OAc) ₂	1	63%

[a] Mesitylene was used as internal standard

After several unsuccessful attempts to increase the yield by screening different parameters such as temperature, catalyst loading, oxidant and concentration, we assumed that the decomposition of Pd(II) to Pd(0) under the reducing CO atmosphere might be the main reason for the low yields (See Supporting Information). To circumvent this problem, we studied the effect of various stabilizing ligands in the carbonylation reaction. As can be seen from Scheme 2, addition of 10 mol% of DMSO (**L1**) has a beneficial effect on the reaction and under these conditions the yield increased to 78% (74% isolated yield). Other sulfoxide (**L2** – **L4**) and sulfone ligands (**L5** – **L7**) were also screened but in all these cases, lower yields were obtained. We investigated the effect of the amount of DMSO on the reaction and it was found that the DMSO concentration plays a crucial role for the carbonylation reaction. While catalytic amounts of DMSO (10–20 mol%) were found to be profitable, increasing the amount of DMSO further led to a lower yield. For example, a 1:1 mixture of CD₃OD and DMSO (50 equiv) gave only 32% of [D₄]-**10aa** along with 60% of unreacted **9a** after reaction overnight (See Supporting Information).

Scheme 2. Effect of additives in the Pd-catalyzed carbocyclization-carbonylation.

The optimized conditions established for the formation of α,β -unsaturated ester **10aa** were applied to differently substituted

allenynes (Table 2). When both methyl groups of the allene unit were replaced by a pentamethylene group (**9b**), the reaction with CO in MeOH gave the α,β -unsaturated ester **10ba** in a 56% yield, but the catalyst loading had to be increased to 5 mol% (Table 2, entry 2). Unsymmetrical allene **9c** also showed a similar reactivity and gave a mixture of isomers **10ca** and **10ca'** in a 3:1 ratio (Table 2, entry 3).

Table 2. Scope of the Pd-catalyzed carbocyclization-carbonylation of allenynes and enallenes.

Entry	Allenyn	Product	Yield [%] ^[a]
1	9a	10aa	74 ^[b]
2	9b	10ba	56 ^[c]
3	9c	10ca and 10ca' (Z/E) = 2:1, 10ca:10ca' = 3:1	66 ^[c]
4	9d	10da	59 ^[d,e]
5	9e	10ea	58 ^[d]
6	9f	10fa	47 ^[d]
7	12a	13aa	85 ^[b]
8	12b	13ba	63 ^[c]
9	12c	13ca	71 ^[d]

[a] Isolated yield of the product after column chromatography. [b] 1 mol% of Pd(OAc)₂ was used. [c] 5 mol% of Pd(OAc)₂ was used. [d] Reaction was done at 55 °C using 5 mol% of Pd(OAc)₂. [e] Reaction with EtOH gave the corresponding ethyl ester (**10db**) in 60% yield.

Allenyne with internal alkynes were used for the formation of tetra-substituted α,β -unsaturated esters. As expected, aromatic substituted allenynes **9d–9f** required a slightly elevated temperature (55 °C) for the carbonylation reaction to occur and afforded the corresponding products **10da–10fa** in good yields (Table 2, entries 4–6). We then turned our attention to the use of enallenes **12a–12c** in the domino carbocyclization-carbonylation reaction. In contrast to the allenyne substrates, enallenes have a propensity for β -elimination after the carbocyclization because of the presence of β -hydrogen(s). However we were pleased to find that under the optimized reaction conditions enallenes, **12a** and **12b** gave selectively the corresponding esters **13aa** and **13ba** in 85% and 63% yields, respectively, without giving the β -elimination product (Entries 7–8). Enallene **12c** gave the ester **13ca** center in 71% yield (Entry 9).

Table 3. Scope of the alcohol partners in Pd-catalyzed carbocyclization-carbonylation of allenynes and enallenes.

[a] The alcohol was used as solvent. [b] DCE was used as solvent together with 5.0 equiv of alcohol. [c] The yield corresponds to NMR yield using mesitylene as the internal standard. [d] 1.0 equiv of hydroquinone (HQ) was used as alcohol partner in DCE. [e] 3:1 mixture of **10al** and **15al**. (For **15al** see Scheme 4)

The scope of the alcohol partners in the carbocyclization-carbonylation reaction was then explored using allenynes **9a** or enallene **12a** (Table 3). In addition to MeOH, other aliphatic alcohols reacted smoothly to provide the desired α,β -unsaturated esters in good yields. It should be noted that the reaction could be carried out in DCE as solvent using 5 equiv of the alcohol to obtain comparable results (see Supporting Information). Similar yields were obtained when increasing the chain length of the alcohol partner (products **10aa** vs. **10ab** vs. **10ac**). On the other hand, yields decreased when bulky secondary and tertiary alcohols were employed, in particular with *t*-butanol (**10ae**). Cyclic alcohols could also be used as alcohol partners with maintained good yields of the α,β -unsaturated ester (**10af** and **10ag**). The product **10ah** is particularly interesting as allylcarboxylates were often used as electrophiles in metal-catalyzed allylation reactions.¹⁶ Good yields were obtained when using either 1- or 2-phenyl ethanol in the carbocyclization-carbonylation of the allenynes **9a** (**10ai–10aj**). Phenols were found to react with allenynes **9a** to give the corresponding phenolic esters **10al–10an** in moderate yields. Enallene

12a also reacted nicely with other aliphatic alcohols to give the products **13aa**, **13ab** and **13ao** in good to excellent yields.

When alkyl-substituted allenynes **9g** and **9h** were used for the carbonylation reaction, the product outcome changed completely and the major product obtained was the vinylallenenic ester **14** (Scheme 3). The formation of these products could be explained by the previously proposed propargylic C–H activation^{11,12} (cf Scheme 1b) affording a vinyl-palladium intermediate, which undergoes vinylpalladation with the allene moiety to give intermediate **5** (Scheme 1b). Subsequent carbonylation and reaction with methanol would give the vinylallenenic esters **14** (Scheme 3).

Scheme 3. Pd(II)-catalyzed carbocyclization-carbonylation of alkyl-substituted allenynes.

Interestingly, a control experiment carried without any alcohol partner resulted in the formation of **15al** as the major product along with **10al** in a combined NMR yield of 57% (Scheme 4). Highly reducing carbon monoxide atmosphere together with palladium catalyst might result in the formation of small amounts of hydroquinone (HQ) from BQ. The HQ may add as the alcohol partner to give ester and Pd(0). The reoxidation of Pd(0) to Pd(II) by BQ will then generate more HQ, necessary for the next cycle.

Scheme 4. Double carbocyclization-carbonylation with *in situ* generated hydroquinone.

To increase the synthetic utility of the carbocyclization-carbonylation, the reaction was also tested under aerobic biomimetic oxidative conditions using catalytic amounts of benzoquinone. We have previously reported such aerobic procedures for a wide range of palladium-catalyzed oxidative reactions where molecular oxygen was used as the terminal oxidant together with electron transfer mediators (ETMs) in catalytic amounts.^{6b–c,17,18} Under the optimized biomimetic conditions consisting of 5 mol% of Co(salophen) and 20 mol% of BQ as ETMs for the reoxidation of Pd(0) to Pd(II), **9a** afforded the α,β -unsaturated carbocyclic ester **10aa** in 72% yield. The aerobic conditions were also applied to two other substrates **9a** and **12a**, which afforded **10af** and **13aa** in 55% and 83% yield respectively (See Supporting Information).

A possible mechanism for the carbonylation reaction based on previous studies in our group is given in Scheme 5. In the first step, the Pd(II) catalyst forms chelated π -complex **17** with **9** or **12**. Nucleophilic attack of the allene moiety on Pd(II) generates dienyl-Pd(II) species **18**, which undergoes carbopalladation with the alkyne/alkene unit to give **19**. Insertion of carbon monoxide leads to acyl-Pd(II) complex **20**, and subsequent reaction with the alcohol provides the product and Pd(0). Reoxidation of Pd(0) to Pd(II) by either benzoquinone or molecular oxygen completes the catalytic cycle.

Scheme 5. Proposed mechanism for the domino carbocyclization-carbonylation of allenynes and enallenes ([O] = BQ or O₂/ETMs, E = CO₂Me).

In summary, we have reported the first Pd-catalyzed oxidative domino carbocyclization-carbonylation reaction of allenynes and enallenes. Moderate to good yields were obtained for various allenynes and enallenes, and a wide range of alcohols could be used as coupling partners in the carbonylation reaction. The use of 1 mol% of Pd catalyst at room temperature under 1 atm. of CO is noteworthy. The aerobic version of this transformation allows for a decrease of benzoquinone to catalytic amounts while using the environmentally friendly O₂ as terminal oxidant.

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Homogeneous Catalysis

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Palladium-catalyzed Oxidative
Carbocyclization-Carbonylation of
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A highly efficient oxidative carbocyclization-carbonylation reaction cascade of allenynes and enallenenes has been developed using a low catalyst loading of Pd(OAc)₂ at room temperature and atmospheric pressure (1 atm of carbon monoxide). The use of DMSO as an additive was found to be important for an efficient reaction. A wide range of alcohols as trapping reagents were used to give the corresponding esters in good yields.