Dual Oxidation State Tandem Catalysis in the Palladium-Catalyzed Isomerization of Alkynyl Epoxides to Furans
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Supporting Information

ABSTRACT: A two-catalyst system consisting of different oxidation states of palladium is described, which mediates the isomerization of alkynyl epoxides to furans. In a process termed “dual oxidation state tandem catalysis”, a multistep isomerization pathway is delineated in which the different metal oxidation states and ligands play independent mechanistic roles, but which, in combination, enable the use of milder reaction conditions and lower catalyst loadings than a single catalyst in isolation. In the present context, this rare example of a homobimetallic catalytic transformation provides a mild, scalable, and atom-efficient route for furan synthesis.

KEYWORDS: Tandem catalysis, oxidation state, palladium, cyclization, oxygen heterocycles

The integration of multiple catalysts in a single reaction to mediate sequential chemical transformations, which is known as orthogonal tandem catalysis, has become widely recognized as a powerful synthetic tool.1 In the field of transition-metal catalysis, such processes typically use two different metals and, therefore, require careful control of reaction conditions to ensure compatibility of the two catalyst systems.2 Here, we describe a rare example of an orthogonal tandem catalytic process in which two different oxidation states of the same metal are employed, where a single catalyst is markedly less effective (Figure 1a).3 While distinct metal oxidation states are commonly invoked as part of a single catalytic cycle (e.g., Pd(0)/Pd(II) species), we show that coexisting Pd(0) and Pd(II) catalysts work synergistically by displaying divergent affinity for consecutive substrates in a sequential reaction pathway.4 In the context of this work, this “dual oxidation state tandem catalysis” enables a mild isomerization of readily available alkynyl epoxides to furans,5 heterocycles that are important building blocks in organic chemistry and present in many natural products and pharmaceutical agents (Figure 1b).6

Our interest in alkynyl epoxides arose from earlier work on palladium-catalyzed cyclizations of propargylic carbonates to alkynylated heterocycles, via allenylpalladium intermediates.7 Upon extending this chemistry to epoxide electrophiles, reaction of 1a (Table 1, entry 1) afforded furan 2a, rather than the anticipated tetrahydrofuran 3. With palladium catalysis of this method for furan synthesis being almost unknown,8 epoxide 1b was selected for optimization of the reaction conditions. Interestingly, both Pd(0) and Pd(II) catalysts were able to promote moderate yielding isomerizations of 1b to 2b, albeit high temperatures were required (Table 1, entries 2 and 3). Mindful of ligand effects in allenylpalladium chemistry,7,9 screening of several bidentate phosphine ligands (Table 1, entries 4–6) and acidic additives (Table 1, entries 7–9) resulted in improved reactivity, with the combination of Pd(dba)2, Xantphos, and 2-(trifluoromethyl)-benzoic acid affording 2b in good yield at 70 °C (Table 1, entry 10). However, when this Pd(0)-catalyzed reaction was

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performed under an inert atmosphere, no furan was formed (Table 1, entry 11), with allenyl ketone 4b instead observed by 1H NMR spectroscopy, which then converted to furan 2b upon exposure of the reaction mixture to air. This suggested an oxidation of Pd(0) to Pd(II), with only the latter being capable of effecting the conversion of 4b to 2b. To test this, the reaction was again run under an inert atmosphere, but now with both a Pd(0) and Pd(II) source present from the outset (Pd(dba)2 and Pd(OAc)2; see Table 1, entry 12). To our delight, smooth conversion to the furan was observed, indicating a beneficial effect of this dual oxidation state catalyst combination. Further optimization enabled reduction of the reaction temperature (to 40 °C) and the loadings of both catalysts (to 1.25 mol %), since the consumption of Pd(0) to produce Pd(II) was no longer required; under these optimized conditions (Table 1, entry 13), 2b was isolated in 93% yield.

The benefit of using the dual oxidation state system was confirmed through control experiments (Table 2). Conducting the reaction without Pd(II) (Table 2, entries 1 and 2) led only to formation of small amounts of allene 4b at 1.25 mol % loading of Pd(dba)2, and poor conversion to furan with 2.5 mol %, which may suggest oxidation of nonligated Pd(0) to generate sufficient Pd(II) to mediate allene-to-furan isomerization in the latter case. Similarly, reactions run in the absence of Pd(0) (Table 2, entries 3 and 4) also showed poor conversion to the furan, albeit Pd(0) could, in these cases, be generated through Xantphos-mediated reduction.10 This is supported by the equivalent reaction in the absence of the phosphine ligand, which showed no reactivity (Table 2, entry 5). These observations were reinforced by further experiments at room temperature (with higher catalyst loadings, Table 2, entries 6–8), where only the binary system resulted in any successful transformation (Table 2, entry 6); no reaction was observed at room temperature with either Pd(0) or Pd(II) catalysis alone. The potential for inhibition of isomerization by the dibenzylidene acetone ligand under solely Pd(0) catalysis was also tested using Pd(Pr-Bu)2 as an alternative Pd(0) source (Table 2, entry 9). However, no conversion was observed, other than a trace quantity of allene 4b. Finally, the need for palladium catalyst (in either oxidation state) was unequivocally demonstrated by attempted metal-free reactions in the presence of Xantphos, benzoic acid additive, or both (Table 2, entries 10–12). No reaction was observed in any of these cases.

The scope of the reaction was studied through the synthesis of 2,5-disubstituted furans featuring a variety of substituents (see Scheme 1). The formation of aryl/alkyl and aryl/aryl disubstituted furans proceeded in good to excellent yields in all cases, with the arenes tolerating both electron-donating (2e–2i) and electron-withdrawing (2j–2m) groups. Naphthyl

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**Table 1. Optimization of the Dual Catalytic Isomerization**

| entry | Pd cat. (mol %) | additives (mol %) | temperature (°C) | time (h) | yield (% | (2, %) |
|-------|----------------|------------------|-----------------|--------|--------|--------|
| 1     | Pd(dba)2 (5)   | dppf (10)        | 100             | 16     | 24     |        |
| 2     | Pd(dba)2 (5)   | dppf (5)         | 100             | 16     | 40     |        |
| 3     | Pd(OAc)2 (10)  |                  | 110             | 16     | 39     |        |
| 4     | Pd(dba)2 (5)   | dppm (5)         | 105             | 2      | 38     |        |
| 5     | Pd(dba)2 (5)   | dpp (5)          | 105             | 2      | 32     |        |
| 6     | Pd(dba)2 (5)   | dppe (5)         | 105             | 2      | 47     |        |
| 7     | Pd(dba)2 (5)   | dppe (5) o-ClBrOH (5) | 105       | 2      | 61     |        |
| 8     | Pd(dba)2 (5)   | dppe (5) o-CF3BrOH (5) | 105     | 2      | 63     |        |
| 9     | Pd(dba)2 (5)   | Xantphos (5) o-CF3BrOH (5) | 105   | 2      | 67     |        |
| 10    | Pd(dba)2 (5)   | Xantphos (5) o-CF3BrOH (5) | 70      | 2      | 76     |        |
| 11    | Pd(dba)2 (6)   | Xantphos (6) o-CF3BrOH (6) | 70      | 2      | –      |        |
| 12    | Pd(dba)2 (6) Pd(OAc)2 (1) | Xantphos (6) o-CF3BrOH (6) | 50      | 6      | 76     |        |
| 13    | Pd(dba)2 (1.25) Pd(OAc)2 (1.25) | Xantphos (1.25) o-CF3BrOH (5) | 40      | 16     | 93     |        |

“Reaction conditions: 0.2 mmol of 1b in toluene (0.2 M). Isolated yields. Reaction of 1a (0.2 mmol) to form 2a in 1,4-dioxane (0.1 M). Under Ar atmosphere. 4b detected by 1H NMR spectroscopy, see text. Under Ar in degassed toluene (0.4 M).

**Table 2. Control Experiments**

| entry | Pd cat. (mol %) | additives (mol %) | temperature (°C) | time (h) | yield (%) | (2, %) |
|-------|----------------|------------------|-----------------|--------|----------|--------|
| 1     | Pd(dba)2 (1.25) Xantphos (1.25) o-CF3BrOH (5) | 40     | 16     | 0%     |          |
| 2     | Pd(dba)2 (2.5) Xantphos (1.25) o-CF3BrOH (5) | 40     | 16     | 30%    |          |
| 3     | Pd(OAc)2 (2.5) Xantphos (1.25) o-CF3BrOH (5) | 40     | 16     | 15%    |          |
| 4     | Pd(OAc)2 (2.5) Xantphos (1.25) o-CF3BrOH (5) | 40     | 16     | 41%    |          |
| 5     | Pd(OAc)2 (6) Xantphos (6) o-CF3BrOH (6) | 25     | 9      | 80%    |          |
| 6     | Pd(OAc)2 (10) Xantphos (10) o-CF3BrOH (6) | 25     | 62     | n.r.   |          |
| 7     | Pd(OAc)2 (10) Xantphos (10) o-CF3BrOH (6) | 25     | 62     | n.r.   |          |
| 8     | Pd(dba)2 (10) Xantphos (10) o-CF3BrOH (10) | 25     | 62     | n.r.   |          |
| 9     | Pd(dba)2 (1.25) Xantphos (1.25) o-CF3BrOH (5) | 40     | 16     | 0%     |          |
| 10    | Pd(Pr-Bu)2 (1.25) Xantphos (1.25) o-CF3BrOH (5) | 40     | 16     | 9%     |          |
| 11    | Pd(Pr-Bu)2 (1.25) Xantphos (1.25) o-CF3BrOH (5) | 40     | 16     | n.r.   |          |
| 12    | Pd(Pr-Bu)2 (1.25) Xantphos (1.25) o-CF3BrOH (5) | 40     | 16     | n.r.   |          |

“Reaction conditions: 0.2 mmol of 1b under Ar in degassed toluene (0.4 M). Determined by integration of 1H NMR spectra of the crude reaction mixture with mesitylene as internal standard. 25% yield of 4b, 4% yield of 4b. n.r. = no reaction.
under solely Pd(0) or Pd(II) catalysis. Using Pd(dba)$_2$ (1.25 mol %, 1 g (5.8 mmol) of each precatalyst; see Figure 2a), only a trace of furan $2p$ was observed. The profile of the reaction catalyzed by Pd(OAc)$_2$ (1.25 mol %, Figure 2c) also showed accumulation of alkyne $3p$, but markedly less allene $4p$; in this instance, $4p$ appears to be converted to product $2p$ as the reaction proceeds. Compared to the Pd(0)-catalyzed reaction profile (Figure 2b), a lag in the formation of allene and allene was observed (~10 min; see insets in Figure 2), and also in the consequent production of furan (~40 min). This supports the notion that a Pd(0) species is required to promote epoxide ring-opening, and that Pd(OAc)$_2$ in isolation is first reduced to a Pd(0) complex to initiate the reaction.10

To investigate cyclization of the two acyclic intermediates to the furan, allenyl ketone $4p$, and alkyne $5p$ were isolated,11 and submitted to timecourse experiments in a 1:1 ratio under solely Pd(0) or Pd(II) catalysis (see Figures 3a and 3b respectively). In both cases, a direct correlation was observed between the consumption of allene $4p$ and the formation of furan $2p$, while alkyne $5p$ was barely consumed. Interestingly, while Pd(OAc)$_2$ proved an active catalyst from the outset of the experiment, Pd(dba)$_2$ was inactive for the reaction.

The unusual use of two different oxidation states of a single metal in a tandem catalytic process is intriguing from a mechanistic perspective. In our optimization studies, we had observed the formation, and subsequent consumption, of allenyl ketone $4b$, suggesting that the reaction passes through this intermediate. To prove this, the cycloisomerization of $1p$ under the optimized conditions was monitored by $^1$H NMR spectroscopy (1.25 mol % of each precatalyst; see Figure 2a). To our surprise, allenyl ketone $4p$ was observed only briefly at the beginning of this reaction, with $\beta,\gamma$-alkynyl ketone $5p$ instead being rapidly formed over the first hour of the reaction, and then consumed at a rate equivalent to the production of $2p$. The detection of this additional compound thus revealed the involvement of two distinct intermediates ($4p$ and $5p$) in the isomerization of $1p$ to $2p$.

To provide insight on the specific contribution of each catalyst and intermediate, the reaction was next monitored under solely Pd(0) or Pd(II) catalysis. Using Pd(dba)$_2$ (1.25 mol %; see Figure 2b), both allene $4p$ and alkyne $5p$ were formed rapidly at the onset of the reaction; when the consumption of epoxide ceased (~2 h), the concentration of $5p$ began to decrease while $4p$ continued to increase, implying that the alkyne is formed directly from the epoxide, but then consumed/converted to allene $4p$. In sharp contrast to the two-catalyst system (Figure 2a), only a trace of furan $2p$ was observed. The profile of the reaction catalyzed by Pd(OAc)$_2$ (1.25 mol %, Figure 2c) also showed accumulation of alkyne $3p$, but markedly less allene $4p$; in this instance, $4p$ appears to be converted to product $2p$ as the reaction proceeds. Compared to the Pd(0)-catalyzed reaction profile (Figure 2b), a lag in the formation of allene and allene was observed (~10 min; see insets in Figure 2), and also in the consequent production of furan (~40 min). This supports the notion that a Pd(0) species is required to promote epoxide ring-opening, and that Pd(OAc)$_2$ in isolation is first reduced to a Pd(0) complex to initiate the reaction.10

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Figure 2. $^1$H NMR spectroscopic profiles of reaction of epoxide $1p$ under (a) Pd(0)/Pd(II) catalysis, (b) Pd(0) catalysis, and (c) Pd(II) catalysis. All reactions run using Xantphos (1.25 mol %) and o-CF$_3$BzOH (5 mol %) in degassed $d_2$-toluene (0.4 M) at 40 °C.

Scheme 1. Reaction Scope

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"Reaction conditions: 0.2 mmol of 1 in degassed toluene (0.4 M) under an Ar atmosphere. Yields are isolated yields.2 Reaction run neat. Reaction run using 1 g (5.8 mmol) of 1b, with 0.5 mol % of each Pd catalyst.4 Reaction run for 24 h using double the amount of catalysts/additives.

derivatives also underwent high-yielding cyclizations to give furans $2n$ and $2o$. Aliphatic side chains containing linear, branched, or cyclic substituents were similarly accommodated, leading to furans $2p$–$2t$ in excellent yields. On larger scales, the reaction could be run under solvent-free conditions and the catalyst loading further reduced, with 1 g (5.8 mmol) of 1b affording $2b$ in 91% yield using just 0.5 mol % of each precatalyst.

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isomerization steps, presumably by sequestering Pd(II), or by mediating reduction of Pd(II) to Pd(0).\textsuperscript{10}

These experiments seemed to suggest a reaction sequence involving initial Pd(0)-catalyzed epoxide ring opening, followed by Pd(II)-catalyzed cyclization of an allene intermediate.\textsuperscript{13} To further probe the relative rates of the different isomerization processes, a 1:1:1 mixture of 1p, 4p, and 5p was subjected to the optimal dual catalysis conditions (Figure 4). Allene 4p was consumed rapidly to produce 2p (<10 min; see Figure 4b), indicating that the cyclization of the allene to the furan is a fast reaction step. Over a longer period (~45 min), epoxide 1p was converted equally to furan 2p and alkyne 5p, the latter accumulating until 1p is consumed.

Finally, 5p is transformed to furan 2p, presumably via (relatively slow) conversion to the allene.

These experiments lead to a mechanistic proposal (Scheme 2) in which oxidative addition of Pd(0) into the alkyne epoxide generates allenylpalladium(II) species 6. Formal reductive elimination via (intramolecular or intermolecular) deprotonation leads to enol 7, which can tautomerize to alkyne ketone 5p—a temporary resting state in the transformation.\textsuperscript{14} Further tautomerization to the allenyl ketone 4p precedes Pd(II)-activated cyclization, giving furanylpalladium complex 8; protodepalladation under the mildly acidic reaction conditions would then afford furan 2p. The fact that the furan appears to be formed more rapidly while epoxide 1p is still being consumed, compared to its absence, may suggest an alternative pathway exists for immediate conversion of the alkyne to the furan, for example via a palladium complex of alkyne 5p formed by enol-keto tautomerization of 9 before decomplexation of the metal.\textsuperscript{15}

In conclusion, we have demonstrated an unusual tandem orthogonal catalysis process that benefits from the use of two oxidation states of a single metal, in the context of the conversion of alkyne epoxides to furans. Such “dual oxidation state” catalysis is relatively unexplored and offers new possibilities in the arena of tandem catalytic reactions; it avoids problems of catalyst incompatibility, and offers opportunities for the invention of sequenced catalytic cascades.

**Figure 3.** $^1$H NMR spectroscopic profiles of reaction of a 1:1 mixture of allenyl ketone 4p and alkyne ketone 5p under (a) Pd(0)/Xantphos catalysis, (b) Pd(II)/Xantphos catalysis, and (c) Pd(II) catalysis (no Xantphos).

**Figure 4.** $^1$H NMR spectroscopic profiles of reaction of a 1:1:1 mixture of alkyne epoxide 1p, allenyl ketone 4p, and alkyne ketone 5p under dual Pd(0)/Pd(II) catalysis. Graph (a) shows the reaction profile for 9 h. Graph (b) shows the reaction profile for the first 45 min.

**Scheme 2.** Possible Mechanistic Pathway
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