

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

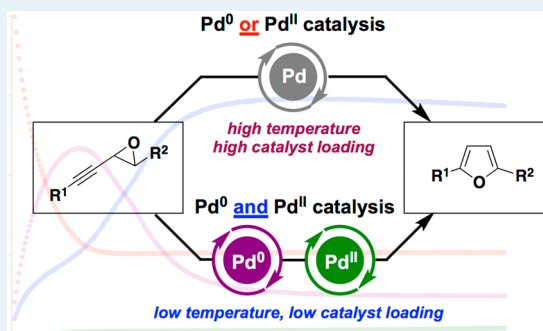
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Supporting Information

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

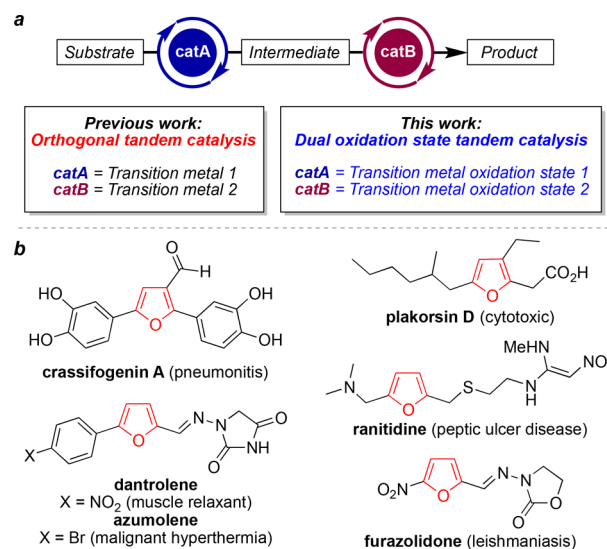


Figure 1. (a) Orthogonal tandem catalysis, and “dual oxidation state” tandem catalysis. (b) Furan-containing pharmaceuticals and bioactive natural products.

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)₃, 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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Table 1. Optimization of the Dual Catalytic Isomerization^a

1a: R = CH₂CH₂OH
1b: R = Et

2a: R = CH₂CH₂OH
2b: R = Et

3

4b

entry	Pd cat. (mol %)	additives (mol %)	temperature (°C)	time (h)	yield ^b (2, %)
1 ^c	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)	dppp (5)	105	2	32
6	Pd(dba) ₂ (5)	dppe (5)	105	2	47
7	Pd(dba) ₂ (5)	dppe (5) <i>o</i> -ClBzOH (5)	105	2	61
8	Pd(dba) ₂ (5)	dppe (5) <i>o</i> -CF ₃ BzOH (5)	105	2	63
9	Pd(dba) ₂ (5)	Xantphos (5) <i>o</i> -CF ₃ BzOH (5)	105	2	67
10	Pd(dba) ₂ (5)	Xantphos (5) <i>o</i> -CF ₃ BzOH (5)	70	2	76
11 ^d	Pd(dba) ₂ (6)	Xantphos (6) <i>o</i> -CF ₃ BzOH (6)	70	2	— ^e
12 ^d	Pd(dba) ₂ (6) Pd(OAc) ₂ (1)	Xantphos (6) <i>o</i> -CF ₃ BzOH (6)	50	6	76
13 ^f	Pd(dba) ₂ (1.25) Pd(OAc) ₂ (1.25)	Xantphos (1.25) <i>o</i> -CF ₃ BzOH (5)	40	16	93

^aReaction conditions: 0.2 mmol of **1b** in toluene (0.2 M). ^bIsolated yields. ^cReaction of **1a** (0.2 mmol) to form **2a** in 1,4-dioxane (0.1 M). ^dUnder Ar atmosphere. ^e**4b** detected by ¹H NMR spectroscopy, see text. ^fUnder Ar in degassed toluene (0.4 M).

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(Pt-Bu₃)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

Table 2. Control Experiments^a

1b

2b

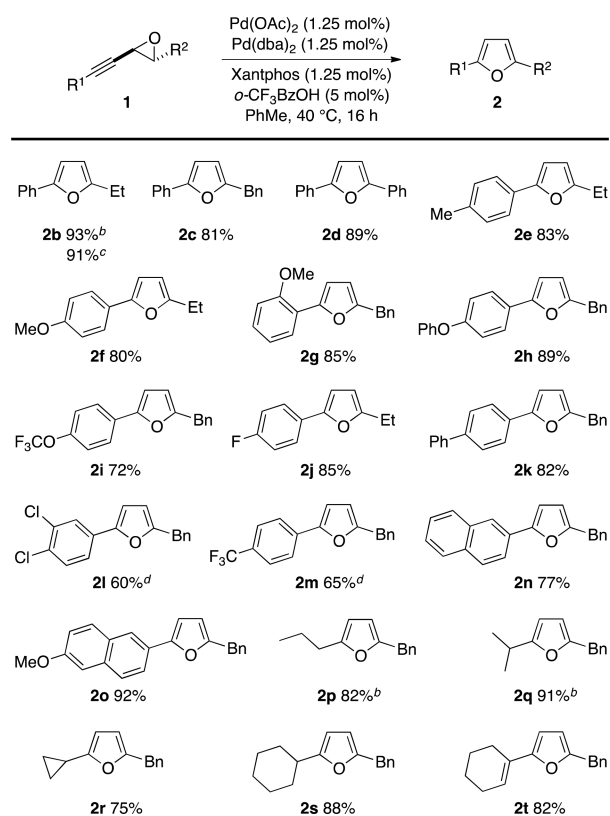
4b

entry	Pd cat. (mol %)	additives (mol %)	temperature (°C)	time (h)	yield ^b (2, %)
1	Pd(dba) ₂ (1.25)	Xantphos (1.25) <i>o</i> -CF ₃ BzOH (5)	40	16	0 ^c
2	Pd(dba) ₂ (2.5)	Xantphos (1.25) <i>o</i> -CF ₃ BzOH (5)	40	16	30
3	Pd(OAc) ₂ (1.25)	Xantphos (1.25) <i>o</i> -CF ₃ BzOH (5)	40	16	15
4	Pd(OAc) ₂ (2.5)	Xantphos (1.25) <i>o</i> -CF ₃ BzOH (5)	40	16	41
5	Pd(OAc) ₂ (2.5)	<i>o</i> -CF ₃ BzOH (5)	40	16	n.r.
6	Pd(dba) ₂ (6) Pd(OAc) ₂ (5)	Xantphos (6) <i>o</i> -CF ₃ BzOH (6)	25	9	80
7	Pd(OAc) ₂ (10)		25	62	n.r.
8	Pd(dba) ₂ (10)	Xantphos (10) <i>o</i> -CF ₃ BzOH (10)	25	62	n.r.
9	Pd(Pt-Bu ₃) ₂ (1.25)	Xantphos (1.25) <i>o</i> -CF ₃ BzOH (5)	40	16	0 ^d
10		Xantphos (1.25)	40	16	n.r.
11		<i>o</i> -CF ₃ BzOH (5)	40	16	n.r.
12		Xantphos (1.25) <i>o</i> -CF ₃ BzOH (5)	40	16	n.r.

^aReaction conditions: 0.2 mmol of **1b** under Ar in degassed toluene (0.4 M). ^bDetermined by integration of ¹H NMR spectra of the crude reaction mixture with mesitylene as internal standard. ^c25% yield of **4b**. ^d4% yield of **4b**. n.r. = no reaction.

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/aliphatic 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

Scheme 1. Reaction Scope^a

^aReaction conditions: 0.2 mmol of **1** in degassed toluene (0.4 M) under an Ar atmosphere. Yields are isolated yields. ^bReaction run neat. ^cReaction run neat using 1 g (5.8 mmol) of **1b**, with 0.5 mol % of each Pd catalyst. ^dReaction 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.

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 probe this, the cycloisomerization of **1p** under the optimized conditions was monitored by ¹H 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 β,γ -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

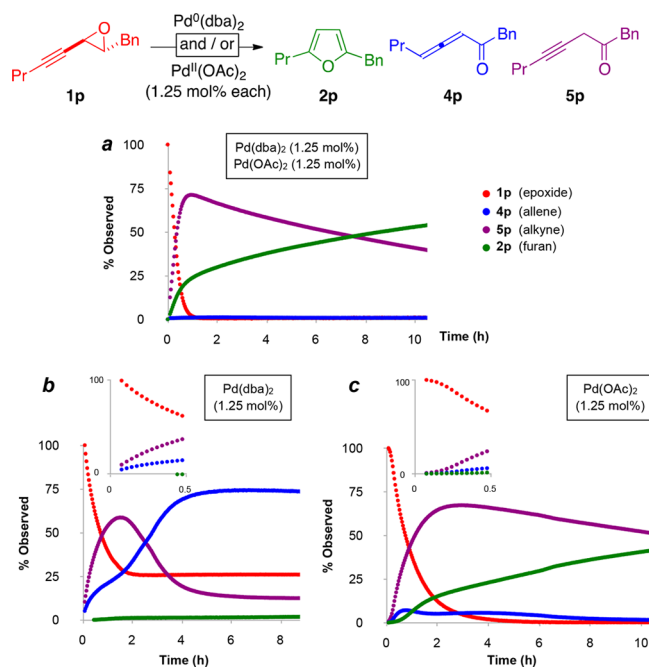


Figure 2. ¹H NMR spectroscopic profiles of reaction of epoxide **1p** under (a) Pd(0)/Pd(II) catalysis, (b) Pd(0) catalysis, and (c) Pd(II) catalysis. All reactions run using Xantphos (1.25 mol %) and *o*-CF₃BzOH (5 mol %) in degassed *d*₈-toluene (0.4 M) at 40 °C.

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 **5p**, 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 alkyne 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 alkynyl ketone **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 first hour, suggesting that Pd(dba)₂ must be oxidized to a Pd(II) species¹² to trigger allene cyclization. We further questioned whether Xantphos was beneficial for the Pd(II)-catalyzed conversion of the alkyne or allene to the ketone. In fact, the opposite was found to be the case: the reaction profile in the absence of this ligand (Figure 3c) showed rapid consumption of both intermediates, with this reaction reaching completion in <2 h, which contrasts markedly with the reaction profile in Figure 3b. Paradoxically, Xantphos seems to be required for the initial ring-opening of the epoxide, but inhibits the later

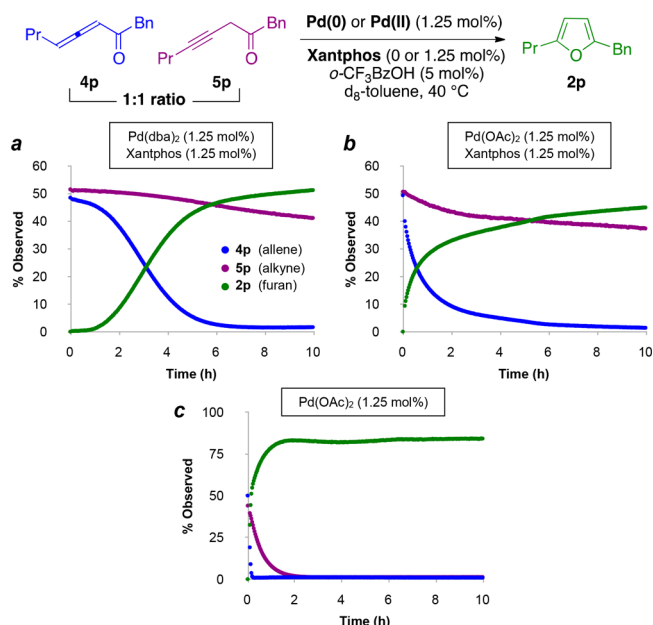


Figure 3. ^1H NMR spectroscopic profiles of reaction of a 1:1 mixture of allenyl ketone **4p** and alkynyl ketone **5p** under (a) $\text{Pd}(0)$ /Xantphos catalysis, (b) $\text{Pd}(\text{II})$ /Xantphos catalysis, and (c) $\text{Pd}(\text{II})$ catalysis (no Xantphos).

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

These experiments seemed to suggest a reaction sequence involving initial $\text{Pd}(0)$ -catalyzed epoxide ring opening, followed by $\text{Pd}(\text{II})$ -catalyzed cyclization of an allene intermediate.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.

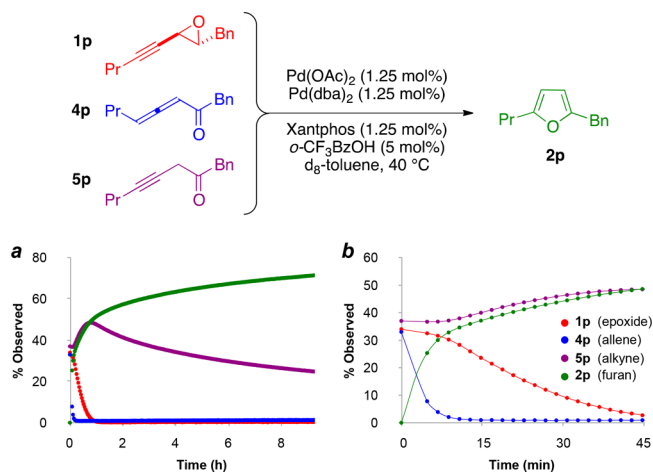
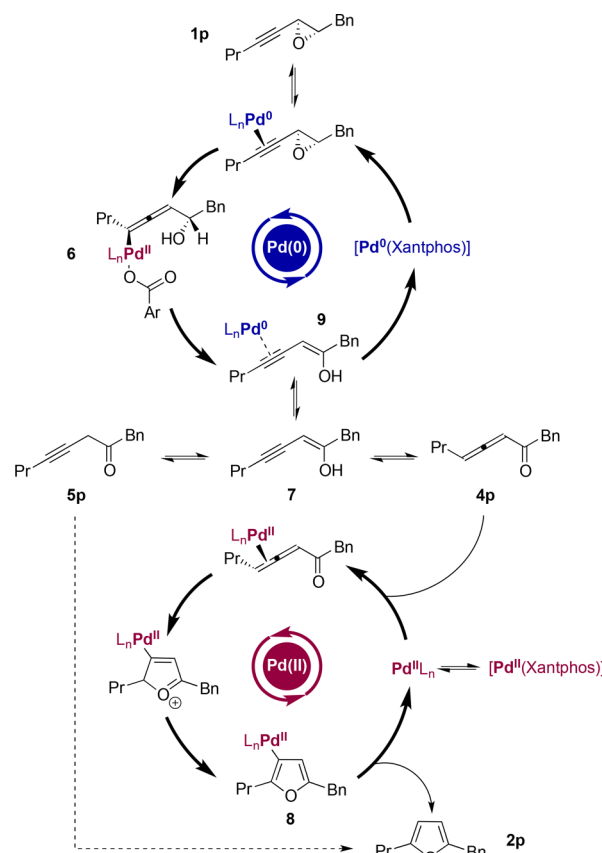


Figure 4. ^1H NMR spectroscopic profiles of reaction of a 1:1:1 mixture of alkynyl epoxide **1p**, allenyl ketone **4p**, and alkynyl ketone **5p** under dual $\text{Pd}(0)$ / $\text{Pd}(\text{II})$ catalysis. Graph (a) shows the reaction profile for 9 h. Graph (b) shows the reaction profile for the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

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 $\text{Pd}(0)$ into the alkynyl

Scheme 2. Possible Mechanistic Pathway



epoxide generates allenylpalladium(II) species **6**. Formal reductive elimination via (intramolecular or intermolecular) deprotonation leads to enol **7**, which can tautomerize to alkynyl ketone **5p**—a temporary resting state in the transformation.¹⁴ Further tautomerization to the allenyl ketone **4p** precedes $\text{Pd}(\text{II})$ -activated cyclization, giving furanyl-palladium 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 in 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.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 alkynyl 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.

■ ASSOCIATED CONTENT

■ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.8b02248.

Experimental procedures, characterization data, and copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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