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Synthesis of Cyclopropanes via Pd(II/IV)-Catalyzed Reactions of Enynes

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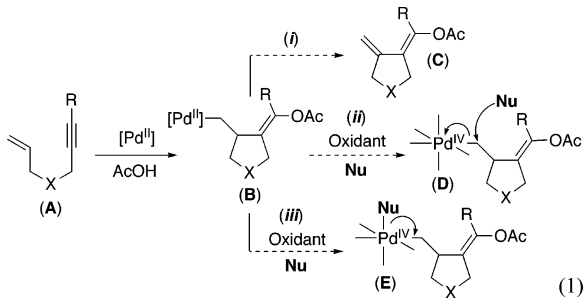
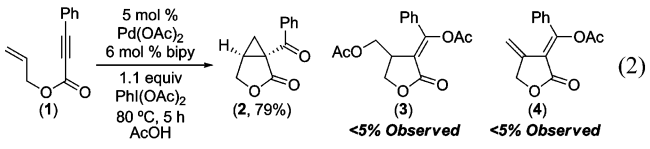
Our group[1] and others[2−6] have recently reported a number of catalytic reactions that involve Pd^{IV} complexes as key intermediates. These transformations are attractive because they can provide access to novel organic products that are highly complementary to those obtained in conventional $Pd^{II/0}$-catalyzed processes. For example, Pd^{IV} complexes readily undergo reductive elimination reactions to form C−F, C−I, C−OAc, and C−OCH_2CF_3 bonds,[1,2,4,5] which have proven challenging to access within $Pd^{II/0}$ reaction manifolds. In addition, Pd^{IV} complexes are often resistant to β-hydride elimination processes (which are facile at Pd^{II} centers), allowing diverse functionalization of Pd^{IV} σ-alkyl intermediates.[1−6]



(1)

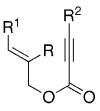
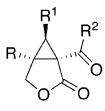
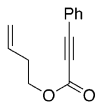
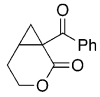
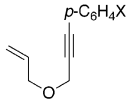
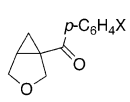
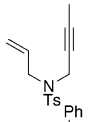
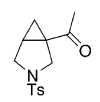
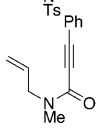
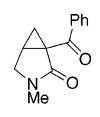
Due to the significant advantages of $Pd^{II/IV}$ catalysis, we have initiated a program to explore the utility of such processes in new organic transformations. As part of this effort, we became interested in the cascade cyclization of enyne derivatives of general structure **A** (eq 1). These substrates have been shown by Lu and co-workers to undergo Pd^{II}-mediated alkyne *trans* acetoxypalladation followed by cyclization to afford Pd^{II} intermediate **B**.[7] Under traditional $Pd^{II/0}$ catalysis, **B** would undergo β-hydride elimination to afford alkene **C** (path *i*). However, we reasoned that, if **B** were intercepted with a strong oxidant,[1−6] the resulting Pd^{IV} intermediate (**D**/**E**) might react with diverse nucleophiles (Nu) to afford novel functionalized compounds (paths *ii* or *iii*).[8] In the course of these studies, we discovered that the Pd-catalyzed cyclization of enyne **A** under such oxidative conditions affords cyclopropyl ketone products, and this communication describes the scope and mechanism of this new transformation. We present evidence in support of a $Pd^{II/IV}$ catalytic cycle, in which a tethered olefin acts as the nucleophile for functionalization of the key Pd^{IV} intermediate **D**.



(2)

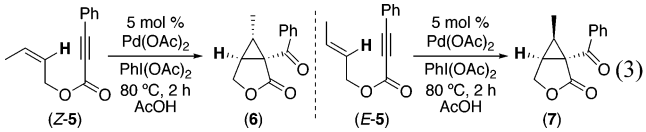
Our initial studies focused on Pd-catalyzed reactions of enyne **1**. Gratifyingly, treatment of **1** with 5 mol % of $Pd(OAc)_2$, 6 mol % of 2,2′-bipyridine (bipy),[10] and 1.1 equiv of the strong oxidant $PhI(OAc)_2$ in AcOH afforded a single major organic product. However, we were surprised to discover that this was not the OAc reductive elimination product **3**, which was anticipated based on previously reported $Pd^{II/IV}$ reactions with this oxidant.[1,4] Instead, a variety of analytical techniques definitively established that this product was β-ketolactone **2** (eq 2).

Table 1. Substrate Scope of Oxidative Cyclopropane Formation[a]

entry	substrate	product	substituents R, R^1, R^2	yield[b]
1			H, H, Ph	79%[c]
2			H, H, Me	55%[c]
3			Me, H, Ph	78%[c]
4			Me, H, Me	66%[c]
5			H, CO_2Et, Ph	79%
6				55%
7			X: H	48%[c]
8			CF_3	44%
9			OMe	44%[c]
10				71%[c]
11				47%[c]

[a] Conditions: 5 mol % of $Pd(OAc)_2$, 1.1−4 equiv of $PhI(OAc)_2$, 60−80 °C, 1−16 h. [b] Isolated yields (average of two runs). [c] 6 mol % of bipy added.

The scope of this transformation was next examined with a variety of different enyne substrates.[10] As summarized in Table 1, diverse bicyclo[3.1.0] and [4.1.0] ring systems containing lactones (entries 1−6), tetrahydrofurans (entries 7−9), pyrrolidines (entry 10), and lactams (entry 11) could be constructed using this method. Importantly, the reactions proceeded efficiently in the presence of ambient air and under relatively mild conditions (AcOH, 60−80 °C, 1−16 h). Aryl and alkyl substitution was well tolerated on the alkyne component. Furthermore, both 1,1- and 1,2-disubstituted olefins were effective substrates and led to the stereospecific assembly of highly substituted cyclopropane products (entries 3−5).



(3)

In order to probe the mechanism of these transformations, the stereochemically pure olefins (*Z*)-**5** and (*E*)-**5** were subjected to the reaction conditions (eq 3). In each case, cyclopropane formation proceeded *with clean inversion of the starting olefin geometry* (i.e., the *cis* substituents on the alkene ended up *trans* to one another in the cyclopropane product). Notably, this result is opposite to that observed in the $Pd^{II/0}$-catalyzed formation of bicyclo[3.1.0] ring systems, which proceeds via syn olefin insertion into Pd−C bonds (leading to retention of the olefin stereochemical information in

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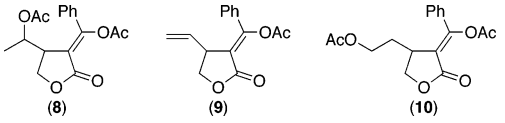
the cyclopropane products).[9] Our observations are also in contrast to the results of Pt/Au-catalyzed enyne cycloisomerizations, which form bicyclo[3.1.0]hexenes via metallocarbene intermediates. In these Pt/Au-catalyzed reactions, the initial olefin geometry is maintained in the resulting cyclopropane.[11]

While cyclopropanes **6** and **7** were the major products in reactions of (*Z*)-**5** and (*E*)-**5**, a variety of lactone side products were also formed (Table 2). Separation and characterization of this mixture revealed the presence of two isomeric acetoxylated species (**8** and **10**) as well as alkene product **9**. As discussed below, we believe that these side products may offer insights into Pd intermediates on the cyclopropane-forming reaction pathway.

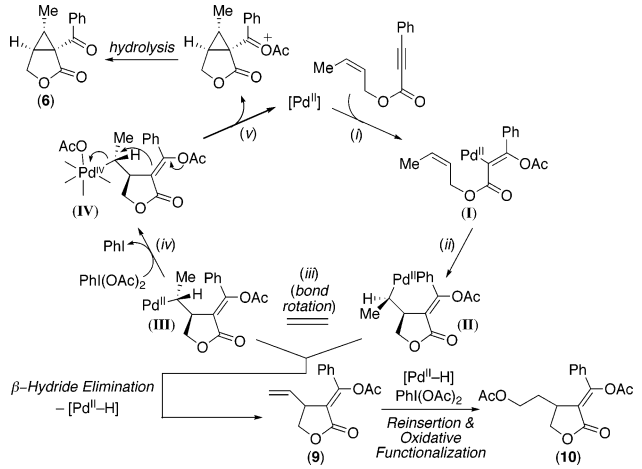
Table 2. Distribution of Products from Reactions of (*E*)-**5** and (*Z*)-**5**[a]



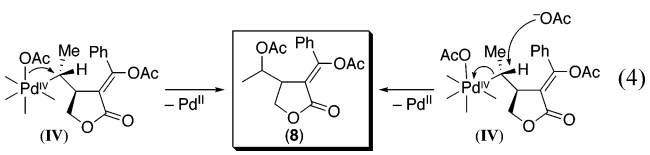
substrate	yield of **6**/**7**	yield of **8**	yield of **9**	yield of **10**
(*Z*)-**5**	25% (**6**)	11%	8%	19%
(*E*)-**5**	59% (**7**)	4%	8%	8%

[a] Conditions: 5 mol % of $Pd(OAc)_2$, 8 equiv of $PhI(OAc)_2$, dry AcOH, 80 °C, 2 h. Calibrated GC yields represent an average of two runs.

Scheme 1. Proposed Mechanism of Formation of Products **6**−**11**



The stereochemical course of these reactions as well as the observation of side products **8**−**10** are both consistent with the mechanism outlined in Scheme 1. In this catalytic cycle, initial *trans* acetoxypalladation of the alkyne (*i*) is followed by intramolecular olefin insertion (*ii*) to afford Pd^{II} intermediate **II**.[7,8] Subsequent σ-bond rotation (*iii*) and oxidation with $PhI(OAc)_2$ would then afford the Pd^{IV} intermediate **IV** (*iv*).[12] From there, the key cyclopropane-forming step could proceed via S_N2-type attack by the electron-rich tethered olefin on the Pd^{IV}-bound carbon (C_α) to afford cyclopropane product **6** *with inversion of configuration at* C_α (*v*). Importantly, the side product **8** is believed to derive from competing C−OAc bond-forming reductive elimination from **IV** (eq 4).[13,14] Such C−OAc coupling reactions are known to occur



(4)

readily at Pd^{IV} but not at Pd^{II} centers;[13] therefore, the formation of **8** provides strong evidence to support the intermediacy of Pd^{IV} complex **IV**.[14] In contrast, the other side products are presumably formed by β-hydride elimination from Pd^{II} intermediates **II** or **III** to provide **9**, which can then undergo olefin insertion/oxidation/Pd^{IV}-mediated C−OAc coupling at the terminal position to afford **10**.

Additional evidence in support of the proposed $Pd^{II/IV}$ mechanism came from an examination of alternative oxidants in the reaction of enyne **1** (Table S2). This study showed that traditional $Pd^{II/0}$ oxidants, such as air, benzoquinone, or $Cu(OAc)_2$, did not provide any of the cyclopropyl ketone product **2** under our standard conditions. In contrast, strong oxidants such as Oxone and $K_2S_2O_8$, which have been shown to mediate $Pd^{II/IV}$-catalyzed processes,[15] afforded **2** in 50 and 27% yield, respectively.

In conclusion, this report describes a new Pd-catalyzed oxidation reaction for the stereospecific conversion of enynes into cyclopropyl ketones. Unlike related $Pd^{II/0}$, Au, and Pt-catalyzed cyclopropane-forming reactions, these transformations proceed with net inversion of geometry with respect to the starting olefin. This result is consistent with a $Pd^{II/IV}$ mechanism in which the key cyclopropane-forming step involves nucleophilic attack of a tethered olefin onto the Pd^{IV}−C bond. This unique reactivity and selectivity further demonstrate the unusual mechanisms and potential applications of $Pd^{II/IV}$ reaction manifolds.

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Supporting Information Available: Experimental details and spectroscopic and analytical data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) For a review that discusses oxidative interception of intermediates such as **B** with $CuX_2/LiX/O_2$, see: Lu, X.; Zhu, G.; Wang, Z. *Synlett* **1998**, 115.

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(10) The presence/absence of bipy had little affect on the yield of **2**; however, 6 mol % of bipy significantly affected the yield of cyclopropane for some other enynes (see Table S1). The specific role of bipy in these transformations is currently under investigation.

(11) For a recent review, see: Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271.

(12) Importantly, *iii* and *iv* in Scheme 1 could also occur in reverse order.

(13) Dick, A. R.; Kampf, J.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 12790.

(14) Compound **8** was isolated from reactions of (*Z*)-**5** as predominantly one diastereomer. (Notably, isolation of the corresponding product from (*E*)-**5** was challenging due to the low yield of this reaction.) The stereochemistry of **8** could not be definitively established using coupling constant analysis. Efforts to obtain a crystalline derivative of **8** are ongoing and will be reported in a full paper.

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