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A Palladium-Catalyzed Cyclization−Oxidation Sequence: Synthesis of Bicyclo[3.1.0]hexanes and Evidence for S_N2 C−O Bond Formation

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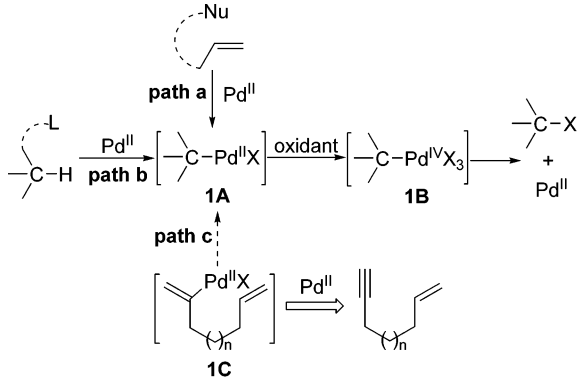
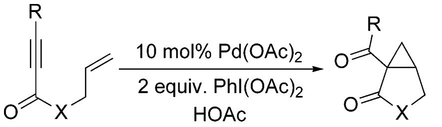
Palladium is probably one of the most widely used metals for organic synthesis, and palladium complexes are known to be efficient catalysts for numerous organic transformations,[1] which are used in the chemical and pharmaceutical industry.[2] Palladium-catalyzed reactions generally proceed via Pd(0)/Pd(II) catalytic cycles, for example Heck, Suzuki, Kumada, Negishi, and Sonogashira reactions, as well as Buchwald−Hartwig aminations,[3] and other reactions.[1] From a mechanistic point of view it is interesting to note that Pd(IV) organometallic compounds have also been proposed as intermediates in some palladium-catalyzed reactions,[4] such as C−N,[5] C−O,[6] and C-halogen[7] bond formation. However, in general there are only some convincing evidence for such intermediates.[8] For example, a recent work by Sanford and coworkers provided direct evidence that square-planar organometallic Pd(II) complexes can be oxidized to the corresponding octahedral Pd(IV) complexes.[9]

Scheme 1 . Generation of Alkyl−Pd(II) Intermediates and Subsequent Oxidation



On the basis of our recent work on the development of novel oxidation reactions,[10] we became interested in the exploitation of domino sequences involving Pd(IV) intermediates. Until to date two different strategies have been employed to form Pd(II) intermediates **1A**, which are further oxidized to Pd(IV) intermediate **1B** followed by C−X (X = OAc, nitrogen, halogen) bond formation (Scheme 1): (i) inter- or intramolecular nucleophilic attack of a nitrogen nucleophile on a Pd(II)-activated alkene to form an alkyl−Pd(II) intermediate **1A** (path a),[5] and (ii) intramolecular chelation-directed activation of a C−H bond to give **1A** (path b).[6,7] Our strategy to generate **1A** is based on the intramolecular insertion of a double bond to a vinyl−Pd(II) species **1C** (path c). Obviously, 1,6-enynes constitute suitable substrates for such reactions. Noteworthy, the cyclization of 1,6-enynes catalyzed by different transition-metal catalysts has been one of the most general and efficient methods for the synthesis of various carbo- and heterocycles.[11] Herein, we report the first $Pd(OAc)_2$-catalyzed cyclization of 1,6-enyne in the presence of oxidant [$PhI(OAc)_2$], which provides a convenient access to bicyclo[3.1.0]hexane derivatives.[12]

Table 1. $Pd(OAc)_2$-Catalyzed Cyclization-Oxidation of **1** in the Presence of $PhI(OAc)_2$[a]



1a-f **2a-f**

entry	R	X	temp (°C)	time (h)	yield (%)[b]
1	Ph (**1a**)	O	room temp	60	79
2	Me (**1b**)	O	room temp	54	83
3	Ph (**1a**)	O	80	2	0[c]
4	Ph (**1a**)	O	80	2	63
5	Me (**1b**)	O	80	2	51
6	*n*-Bu (**1c**)	O	80	3	75
7	$2\text{-}MeOC_6H_4$ (**1d**)	O	80	2	80
8	*n*-Bu (**1e**)	NTs	80	2	83
9	Ph (**1f**)	NTs	80	3	77

[a] Reaction conditions: **1** (0.3 mmol), $Pd(OAc)_2$ (0.03 mmol), $PhI(OAc)_2$ (0.6 mmol), and HOAc (3 mL). [b] Isolated yield. [c] Without $PhI(OAc)_2$.

Our initial investigations focused on 1,6-enyne **1a**, on the basis of its ready availability from phenylpropiolic acid and allyl bromide. After some optimization, **2a** was obtained in 63% isolated yield in the presence of 10 mol % $Pd(OAc)_2$, 2 equiv $PhI(OAc)_2$ in HOAc at 80 °C from a vinyl−Pd(II) species **1C** (Table 1, entry 4). Apparently, the keto carbonyl group results from the oxidation reaction. In the absence of the oxidizing agent, **2a** was not observed at all, and a complex reaction mixture was obtained with Pd-black precipitation (Table 1, entry 3).[13] Applying similar reaction conditions, a variety of substrates **1** were tested for this cyclization−oxidation with $Pd(OAc)_2$ as the catalyst (Table 1). The product yield increases at room temperature with longer reaction time (Table 1, entries 1−2). Both alkyl- and aryl-substituted enynes furnished the corresponding 3-oxabicyclo[3.1.0]hexan-2-ones in good yield (Table 1, entries 4−7). Notably, nitrogen linked 1,6-enynes were also reactive under the reaction conditions and resulted in 3-azabicyclo-[3.1.0]hexan-2-ones (Table 1, entries 8−9). Moreover, the novel cyclization−oxidation sequence can be performed with 1,6-enynes with electronic-rich triple bonds in good yield (Scheme 2). Hence, the 3-oxa- and 3-azabicyclo[3.1.0]hexanes **4a−b** are provided in 61% and 79% yield, respectively.

With the catalytic results in hand, we focused on the reaction mechanism (Scheme 3). After acetoxypalladation of the triple bond,[14] the produced vinyl−Pd(II) intermediate **3A** is expected to undergo an intramolecular insertion of the double bond to give **3B**.

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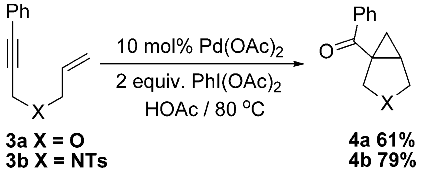
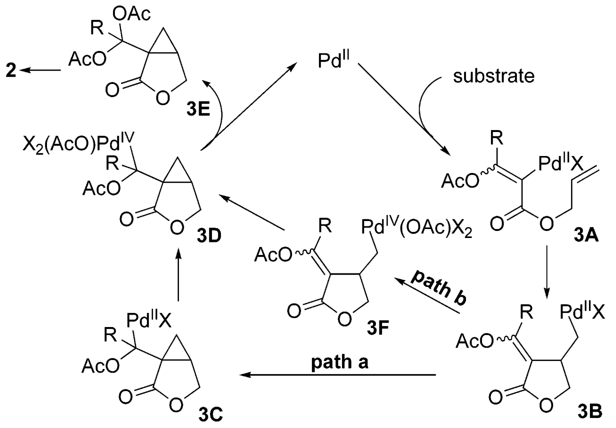
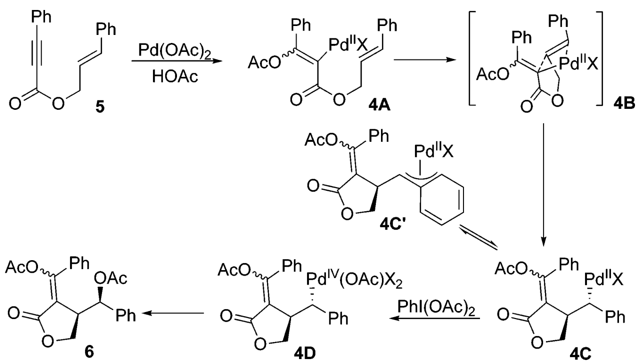
Scheme 2 . Cyclization−Oxidation of 1,6-Enynes with Electron-Rich Triple Bonds



Scheme 3 . Proposed Mechanism for the Formation of **2**



Scheme 4 . Proposed Mechanism for the Formation **6**



Under the reaction conditions, we have not detected any product that might be generated via β-hydride elimination from **3B**.[15] Thus, we believe that the insertion of double bond is fast and **3C** forms preferentially (path a).[16] **3C** is then oxidized by $PhI(OAc)_2$ to produce the corresponding Pd(IV) intermediate **3D**.[17] Nevertheless, another possibility for the formation of **3D** should be considered (path b). Finally, C−O bond formation from **3D** produces **3E** and regenerates the Pd(II) catalyst. **3E** is hydrolyzed to yield **2**.

To further investigate the mechanistic pathway, **5** was tested under the same conditions. The introduction of a phenyl group at the α-position of Pd(II) in **3B** might inhibit the formation of the cyclopropane ring. Indeed, only compound **6** was observed and isolated in 84% yield. This result is explained by the proposal outlined in Scheme 4. The insertion of the olefin in **4A** proceeds stereospecifically via **4B** to generate alkyl−Pd(II) intermediate **4C**, which is possibly stabilized by the η^3-benzylic complex **4C′**. The cyclopropane ring does not form at least partially because of steric hindrance of the phenyl group. Alternatively, **4C** is oxidized selectively to produce **4D**. Finally, reductive elimination takes place with inversion of the stereochemistry. This result also provides strong evidence that the C−O reductive elimination from the alkyl−Pd(IV) species proceeds by an S_N2 mechanism.[5a,18]

In summary, we realized a new domino cyclization−oxidation sequence of 1,6-enynes. This attractive cascade reaction allows for the synthesis of various bicyclo[3.1.0]hexane derivatives. Regarding the mechanism, a Pd(II)−Pd(IV) catalytic cycle is proposed, and evidence for an S_N2 C−O bond formation from alkyl−Pd(IV) species has been established. Further studies on the application of products and reaction mechanism are ongoing in our laboratories and will be reported in due course.

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

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