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COMMUNICATIONS

Published on Web 01/09/2002

Pd(II) Acts Simultaneously as a Lewis Acid and as a Transition-Metal Catalyst: Synthesis of Cyclic Alkenyl Ethers from Acetylenic Aldehydes

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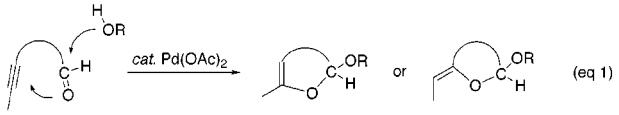
Received October 23, 2001; Revised Manuscript Received December 4, 2001

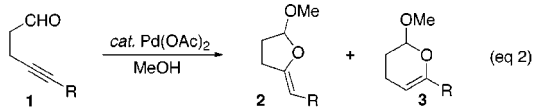
Two different types of molecular catalysts, Lewis acids[1] and transition metals,[2] are becoming increasingly important in modern organic reactions. A typical role of Lewis acid MX_n to enhance the reactivity of a substrate is the formation of a complex with lone pairs of C═Y (Y = O, N, ...) multiple bonds, facilitating the nucleophilic attack of Nu^- to the carbon bearing a positive charge (Scheme 1). One of the representative roles of transition-metal catalysts $M'X_n$, such as $Pd(II)X_2$, is the formation of a complex with π-electrons of alkene or alkyne multiple bonds, which makes feasible the attack of Nu^- to an electron-deficient carbon to give an organopalladium intermediate having a C−Nu bond. To the best of our knowledge, there is no precedent in which a single-metal complex ($MX_n = M'X_n$) exhibits dual roles in a single transformation although it is known that a combination of a Lewis acid (MX_n) and a transition-metal catalyst ($M'X_n$) is useful for enhancing certain organic transformations.[3] We report that a Pd(II) catalyst really exhibits dual roles; $Pd(OAc)_2$ catalyzed the reaction of alkynylaldehydes with ROH to give the alkenyl cyclic ethers in good-to-high yields (eq 1). Here, the attack of ROH to aldehyde is catalyzed



(eq 1)

by Lewis acidic $Pd(OAc)_2$, and the nucleophilic oxygen of the resulting hemiacetal reacts with alkyne complexed by Pd(II), giving the alkenyl ethers (vide post, Scheme 2).[4]

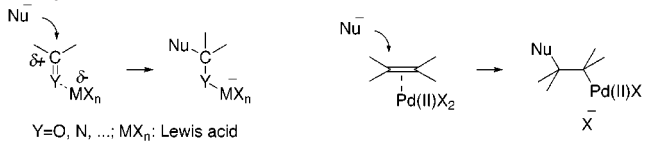
The reaction of the carbon-tethered acetylenic aldehydes **1** with methyl alcohol in the presence of a catalytic amount of palladium was examined (eq 2, Table 1). The reaction of **1a** (R = Ph) with



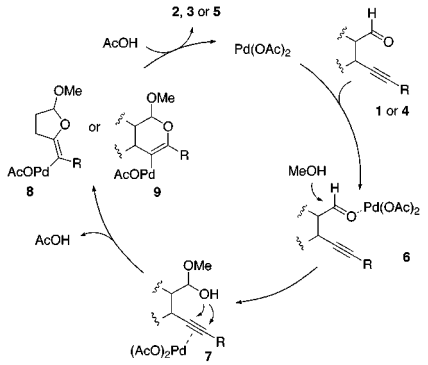
(eq 2)

MeOH in the presence of 10 mol % of $Pd(OAc)_2$ and 1 equiv of benzoquinone in 1,4-dioxane at room temperature gave the five-membered acetal product **2a** in 66% yield together with a small amount of the six-membered product **3a**. On the other hand, only a trace amount of **2a** was obtained in the presence of $PdCl_2$- or $PtCl_2$-catalyst, and a large amount of **1a** was recovered in both cases. Pd(0) catalysts such as $Pd(PPh_3)_4$ and $Pd_2(dba)_3{\cdot}CHCl_3$ were totally ineffective. Benzoquinone was recovered in 83% yield under the conditions of entry 1. However, the total yield of **2a** and **3a** was dramatically decreased when the reaction was carried out in the absence of benzoquinone (entry 2). These results suggest that benzoquinone did not work as an oxidizing agent but as a ligand for the palladium catalyst. Indeed, the reaction of **1a** proceeded smoothly even in the presence of maleic anhydride, which is known as a π-acidic ligand (entry 3).[5] Interestingly, it was found that the

Scheme 1. Principal Role of a Lewis Acid and Transition-Metal Catalyst

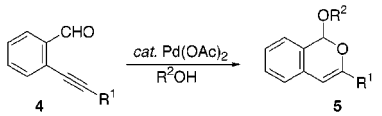


Scheme 2



substituent at the terminal position of alkyne exerts a significant influence on the product ratio. While the **2**:**3** ratio decreased in the reaction of **1b** bearing *p*-tolyl group (entry 4) in comparison with that of **1a** (entry 1), the product **2c** was obtained exclusively in the reaction of **1c** having *p*-trifluorophenyl group (entry 5). These results clearly indicate that an electron-withdrawing group at the terminal position is favorable for the formation of the five-membered cyclic ethers **2**. The reaction of **1d**, having an alkyl group at the terminal position, gave the five-membered acetal product **2d** in a very low yield (entry 6). When the reaction of **1a** was performed *in the absence of Pd(OAc)*$_2$ or in the presence of catalytic amounts of AcOH *instead of Pd(OAc)*$_2$, any cyclization products were not obtained at all. These blank tests clearly indicate that $Pd(OAc)_2$ is an essential catalyst for the present reaction.

Next, we examined the reaction of aryl acetylenic aldehydes **4** in which the carbon-tether is a part of the aromatic ring (eq 3, Table 2). The reaction of **4a** proceeded smoothly in the presence of 5



(eq 3)

mol % of $Pd(OAc)_2$ at 10 °C, and the six-membered acetal **5a** was obtained in 90% yield as a sole product.[6] In contrast to the reaction of **1**, no five-membered product was obtained (entry 1). Even in the presence of 1 mol % of $Pd(OAc)_2$, the reaction proceeded well to afford **5a** in 87% yield. It is worth mentioning that **5a** was obtained in a high yield (85%) even in the absence of benzoquinone. Besides methyl alcohol, ethyl alcohol and isopropyl alcohol worked well as nucleophiles, and the corresponding products **5b** and **5c**

10.1021/ja017366b CCC: $22.00

Table 1. Palladium-Catalyzed Cyclization Reaction of Acetylenic Aldehydes **1**[a]

entry	substrate **1** R		condition	yield of **2** (%)[b]		yield of **3** (%)[b]	
1	Ph	**1a**	rt, 2.5 h	**2a**	66	**3a**	9
2[c]	Ph	**1a**	rt, 1 d	**2a**	13[d]	**3a**	trace
3[e]	Ph	**1a**	rt, 2 h	**2a**	55	**3a**	7
4	*p*-MePh	**1b**	rt, 3.5 h	**2b**	46	**3b**	17
5	*p*-CF_3Ph	**1c**	rt, 2 h	**2c**	64	**3c**	0
6	C_8H_{17}	**1d**	rt, 3 h	**2d**	28	**3d**	0

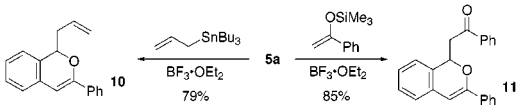
[a] Reaction was performed with MeOH (2 equiv) in the presence of Pd catalyst (10 mol %) and benzoquinone (1 equiv) in 1,4-dioxane at room temperature unless otherwise noted. [b] Isolated yield. [c] Reaction was carried out in the absence of benzoquinone. [d] **1a** was recovered in 40% yield. [e] Reaction was carried out in the presence of maleic anhydride (1 equiv) instead of benzoquinone.

Table 2. Palladium-Catalyzed Cyclization Reaction of Aryl Acetylenic Aldehydes **4**[a]

entry	substrate **4** R^1		R^2OH	conditions	yield of **5** (%)[b]	
1	Ph	**4a**	MeOH	10 °C, 0.5 h	**5a**	90
2	Ph	**4a**	EtOH	10 °C, 0.5 h	**5b**	76
3	Ph	**4a**	*i*PrOH	rt, 1 h	**5c**	81
4[c]	C_4H_9	**4b**	MeOH	rt, 0.5 h	**5d**	74
5[d]	Me_3Si	**4c**	MeOH	50 °C, 2 h	**5e**	72
6[d]	H	**4d**	MeOH	50 °C, 2 h	**5f**	22

[a] Reaction was performed with R^2OH (2 equiv) in the presence of Pd catalyst (5 mol %) and benzoquinone (1 equiv) in 1,4-dioxane at room temperature unless otherwise noted. [b] Isolated yield. [c] Reaction was carried out in the absence of benzoquinone. [d] 20 mol % of $Pd(OAc)_2$ was used.

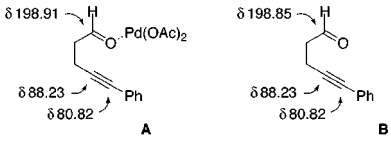
Scheme 3



were formed in high yields (entries 2, 3, respectively). The reaction of **4b**, bearing butyl group as R^1, proceeded smoothly to give **5d** in 74% yield (entry 4). Similarly, the trimethylsilyl-substituted alkyne **4c** also cyclized in a good yield (entry 5). However, the reaction of the nonsubstituted alkyne **4d** gave only a small amount of **5f** along with unidentified byproducts (entry 6).

A conceivable mechanism of the present reaction is shown in Scheme 2. $Pd(OAc)_2$ acts as a Lewis acid, forms a complex with the carbonyl oxygen (**1** or **4**), and makes feasible the attack of MeOH (**6**) to produce the hemiacetal **7**.[7,8] The coordination of an alkyne of **7** to palladium(II) would induce an attack of a hydroxyl moiety to the alkyne from the side opposite to the palladium via the *exo* or *endo* pathway to produce the corresponding vinylpalladium complex **8** or **9**. These intermediates would be protonated by acetic acid, generated in the cyclization step from **7** to **8** or **9**, to give the alkenyl cyclic ethers.[9] As mentioned above, the cyclization of **1c** proceeded only via 5-*exo*-*dig* mode. This experimental result is in good agreement with the intervention of the proposed intermediate **7**. A positive charge would be generated on the internal acetylenic carbon of **7**, rather than the terminal one, since the electron-withdrawing group is present at the R position.

The ^{13}C NMR studies of a 1:1 mixture of **1a** and $Pd(OAc)_2$ in THF-d_8 at room temperature were carried out.[10] *In the absence of* $Pd(OAc)_2$, the aldehyde carbon of **1a** appeared at δ 198.85, and the acetylenic carbons, at δ 88.23 and 80.82 (**B**), while the downfield shift of the aldehyde carbon was observed *in the presence of* $Pd(OAc)_2$ without any shift change of the acetylenic carbons (**A**). On the contrary, the downfield shift of acetylenic carbons of 1-phenyl-1-propyne (δ 85.15, 79.42) was observed (δ 85.18, 79.43) in the presence of $Pd(OAc)_2$.[11] Moreover, a 1:1.5:1 mixture of heptanal, MeOH, and $Pd(OAc)_2$ gave the corresponding acetal (Supporting Information). These results clearly indicate that $Pd(OAc)_2$ can be coordinated potentially both by aldehyde oxygen and by alkyne, but complexes preferentially with aldehyde oxygen in the presence of alkyne.[12]



The acetal functional group of **5** can be used as a key for further manipulation. For instance, **5a** was converted to **10** and **11** in high yields, respectively, upon treatment with allyltributyltin and 1-phenyl-1-(trimethylsilyloxy)ethylene in the presence of $BF_3{\cdot}OEt_2$ (Scheme 3).

Perhaps, the concept presented here may be applicable to the reactions of a wide range of nucleophiles other than alcohols and to the reactions involving C−C multiple bonds other than alkyne; therefore, there is a possibility that a variety of heterocycles can be synthesized by similar procedures.

Acknowledgment. This paper is dedicated to Professor Herbert C. Brown on the occasion of his 90th birthday.

Supporting Information Available: Spectroscopic and analytical data for **2a**−**d**, **3a**−**b**, **5a**−**f**, **10**, **11**, and **13**, ^{13}C and ^1H NMR studies in THF-d_8, and the representative procedure for the synthesis of **5a** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(2) For reviews, see: (a) *Transition Metal Catalysed Reactions*; Murahashi, S.-I., Davies, S. G., Eds.; Blackwell Science: Cambridge, MA, 1999. (b) Tsuji, J. *Transition Metal Reagents and Catalysts: Innovations in Organic Synthesis*; Wiley: New York, 2000.

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(4) While the palladium-catalyzed cyclization of 2-alkynylbenzonitriles via the addition of methyl alcohol to a nitrile group has been reported, sodium methoxide was needed for activation of the nitrile moiety, see: Wei, L.-M.; Lin, C.-F.; Wu, M.-J. *Tetrahedron Lett.* **2000**, *41*, 1215−1218.

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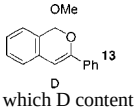
(6) The ^1H NMR spectrum of **5a** was identical to that of the known compound, see: Padwa, A.; Au, A. *J. Am. Chem. Soc.* **1976**, *98*, 5581−5590.

(7) Palladium complexes can be used to effect deacetalization under mild conditions, see: (a) Lipshutz, B. H.; Pollart, D.; Monforte, J.; Kotsuki, H. *Tetrahedron Lett.* **1985**, *26*, 705. (b) Park, M. H.; Takeda, R.; Nakanishi, K. *Tetrahedron Lett.* **1987**, *28*, 3823. (c) Anthony, N. J.; Clarke, T.; Jones, A. B.; Ley, S. V. *Tetrahedron Lett.* **1987**, *28*, 5755. (d) McKillop, A.; Taylor, R. J. K.; Watson, R. J.; Lewis, N. *Synlett* **1992**, 1005. (e) Schmeck, C.; Hegedus, L. S. *J. Am. Chem. Soc.* **1994**, *116*, 9927.

(8) Transition metal-catalyzed acetalization of aldehydes and ketones has been reported, see: (a) Ott, J.; Ramos Tombo, G. M.; Schmid, B.; Venanzi, L. M.; Wang, G.; Ward, T. R. *Tetrahedron Lett.* **1989**, *30*, 6151−6154. (b) Hudson, P.; Parsons, P. J. *Synlett* **1992**, 867−868. (c) Cataldo, M.; Nieddu, E.; Gavagnin, R.; Pinna, F.; Strukul, G. *J. Mol. Catal.* **1999**, *142*, 305−316.

(9) When the reaction of **4a** with MeOD was examined under the same reaction condition, the deuterated product **13**



was obtained in 85% yield in which D content was 95% and no deuterium was found in other carbons of the product.

(10) The $Pd(OAc)_2$-catalyzed reaction of **1a** with MeOH also proceeded in THF and **2a** was obtained in 53% yield together with **3a** in 4% yield.

(11) The downfield shift of aldehyde carbon of heptanal (δ 200.37) was observed (δ 200.41) in the presence of $Pd(OAc)_2$.

(12) It is reported that coordination of the alkyne to Pd(II) induces attack of ester oxygen to alkyne. (a) Kataoka, H.; Watanabe, K.; Goto, K. *Tetrahedron Lett.* **1990**, *31*, 4181−4184. (b) Kataoka, H.; Watanabe, K.; Miyazaki, K.; Tahara, S.; Ogu, K.; Matsuoka, R.; Goto, K. *Chem. Lett.* **1990**, 1705−1708.

JA017366B