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Palladium(II)-Catalyzed Oxidative Transformation of Allylic Alcohols and Vinyl Ethers into 2-Alkoxytetrahydrofurans: Catechol as an Activator of Catalyst

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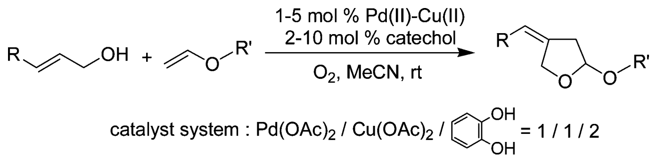
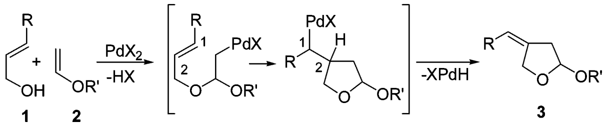
ABSTRACT



A highly effective synthesis of 2-alkoxytetrahydrofurans from allylic alcohols and vinyl ethers was achieved by using catalytic amounts of $Pd(OAc)_2$, $Cu(OAc)_2$, and catechol (1:1:2) under O_2. The use of catechol as an activator of Pd(II)–Cu(II) catalyst has been unprecedented. The 2-alkoxytetrahydrofurans are formed via oxypalladation of allylic alcohols toward vinyl ethers followed by 5-*exo* cyclization of the resulting oxypalladation intermediate and subsequent β-Pd–H elimination. No 6-*endo* cyclization of the oxypalladation intermediate occurs.

Among a variety of Pd(II)-catalyzed oxidative transformations of alkenes with oxygen nucleophiles,[1] the use of allylic alcohols as the nucleophile has not received much attention in synthetic chemistry.[2−4] A paper in 1987 reported the use of allylic alcohols as the nucleophile to attack vinyl ethers.[2a] The oxypalladation intermediates thus formed undergo intramolecular 5-*exo* cyclization to give 2-alkoxytetrahydrofurans via Pd−H elimination (Scheme 1). This reaction appeared to have a high synthetic utility, but it was not catalytic in Pd(II) except for one example with a large amount of Cu(II) as the promoter of catalyst. Very recently, an extension of this reaction to stereoselective synthesis of 4-vinyl-2-alkoxytetrahydrofurans with $Pd(OAc)_2$ catalyst has been reported, but in this case, a large amount of $Cu(OAc)_2$ (2.5 equiv) was also employed as a stoichiometric oxidant.[4] We report herein that the use of catalytic amounts of catechol and $Cu(OAc)_2$ under O_2 remarkably enhances Pd(II) catalysis of this reaction. This finding is not only of significance in

Scheme 1



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(1) (a) Tsuji, J. *Palladium Reagents and Catalysts, Innovation in Organic Synthesis*; John Wiley & Sons: New York, 1995; pp 19−124. (b) Hosokawa, T.; Murahashi, S.-I. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., Ed.; John Wiley & Sons: New York, 2002; Vol. II, pp 2141−2192. (c) Henry, P. M. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., Ed.; John Wiley & Sons: New York, 2002; Vol. II, pp 2119−2139. (d) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285−2309. (e) For related studies, see: Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400−3420. Nishimura, T.; Uemura, S. *Synlett* **2004**, 201−216.

(2) (a) Fugami, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1987**, *28*, 809−812. Also see: Fugami, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2050−2054. (b) Kraus, G. A.; Thurston, J. *J. Am. Chem. Soc.* **1989**, *111*, 9203−9205. (c) Larock, R. C.; Lee, N. H. *J. Am. Chem. Soc.* **1991**, *113*, 7815−7816. (d) Ohshima, M.; Murakami, M.; Mukaiyama, T. *Chem. Lett.* **1984**, 1535−1536.

(3) For the use of allylic alcohols as allylation reagents via π-allylpalladium(II) precursors, see: Kinoshita, H.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2004**, *6*, 4085−4088 and references therein.

(4) Evans, M. A.; Morken, J. P. *Org. Lett.* **2005**, *7*, 3367−3370 and 3371−3373. See also ref 2b.

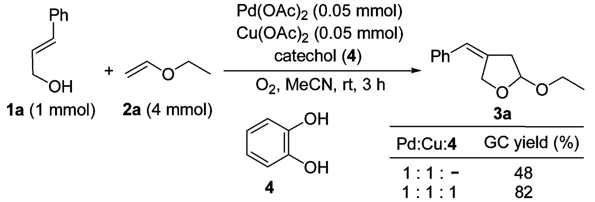
10.1021/ol052377l CCC: $30.25

synthetic chemistry,[5] but it is also unique since such an effect of catechol is unprecedented in the chemistry of palladium.

Previously we reported that a catalyst system of $PdCl_2$, CuCl, and hexamethylphosphoramide (HMPA) activates O_2, resulting in the ketonization of 1-alkenes.[6] The activation of O_2 in this system was thought to occur at the copper site bearing HMPA as the ligand,[7] thereby effecting Pd(II) catalysis. Copper salts have been known to combine with catechol,[8] and catechols activate O_2.[9] These led us to assume that Pd(II) catalysis must be enhanced by an array of Pd(II), Cu(II), and catechol under O_2.

From such a viewpoint, we examined the reaction of (*E*)-3-phenyl-2-propen-1-ol (**1a**) and ethyl vinyl ether (**2a**) with $Pd(OAc)_2$−$Cu(OAc)_2$ catalyst under O_2 (balloon) in MeCN. Indeed, as shown in Scheme 2, the presence of catechol (**4**) (Pd/Cu/**4** = 1/1/1−2) increased the yield of **3a** up to 82−84% (based on **1a**) from 48%.[10] An excess use of **4** (4 equiv) rather decreased the yield (79%). The OAc ligand of catalysts is essential, since with the use of either a combination of $PdCl_2$−$Cu(OAc)_2$−**4** or $Pd(OAc)_2$−CuCl−**4** (Pd/Cu/**4** = 1/1/2) under the conditions shown in Scheme 2 the yield of **3a** was only 4% or 24% along with not yet identified products. Note that the product **3a** in these reactions was obtained solely as the (*Z*)-form.

Scheme 2

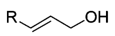
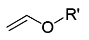
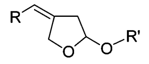
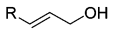
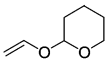
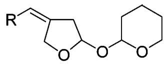
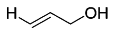
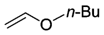
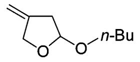
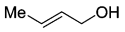
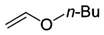
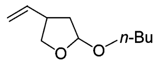


Pd:Cu:4	GC yield (%)
1 : 1 : -	48
1 : 1 : 1	82
1 : 1 : 2	84 (82)[a]
1 : 1 : 4	79

[a]Isolated yield

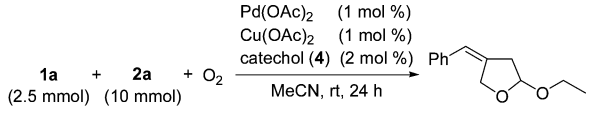
With these results in hand, we examined the reaction of various substrates **1** and **2**. In all cases shown in Table 1, good yields of **3** (73−96%) resulted in the presence of **4**. In the absence of **4**, the precipitation of metallic palladium occurred during the reaction, and the yields became lower as shown in parentheses. In these experiments, 5 mol % of $Pd(OAc)_2$ catalyst per **1** was usually employed, but it could be reduced to 1 mol %. Thus, the reaction of **1a** (2.5 mmol) and **2a** (10 mmol) with $Pd(OAc)_2$−$Cu(OAc)_2$ (0.025 mmol each) and **4** (0.05 mmol) (Scheme 3) gave a 86% yield of **3a** (2.15 mmol), although it took a longer reaction time for completion (24 h). The turnover number of Pd catalyst corresponds to 86. The O_2 absorption measured in this reaction showed a monotonic increase, and the O_2 uptake after 24 h reached 1.08 mmol, which correlated with the amount of **3a** (2.15 mmol) formed. Namely, the production of 1 mol of **3a** requires only half a mole of O_2 as the stoichiometric oxidant. In this case, the absence of **4** again remarkably decreased the yield of **3a** (20%, 24 h).

Table 1. Reaction of Allylic Alcohols **1** and Vinyl Ethers **2**[a]

entry	allylic alcohol 1	vinyl ether 2	time h	product 3	yield of 3 %[b]
					
1	**1a** R=Ph	**2a** R' = Et	3	**3a** R=Ph, R'=Et	82 (48)
2	**1a** R=Ph	**2b** R' = *n*-Bu	3	**3b** R=Ph, R'=*n*-Bu	74 (31)
3	**1b** R=4-NO_2Ph	**2a** R' = Et	12	**3c** R=4-NO_2Ph R'=Et	96 (15)
					
4[c]	**1a** R=Ph	**2c**	6	**3d** R=Ph[d]	72 (23)
5	**1b** R=4-NO_2Ph	**2c**	24	**3e** R=4-NO_2Ph[d]	78 (51)
					
6	**1c**	**2b**	3	**3f**	73 (17)
					
7[e]	**1d**	**2b**	3	**3g**[f]	74 (25)

[a] $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), $Cu(OAc)_2$ (9.1 mg, 0.05 mmol), and catechol (**4**) (11.0 mg, 0.1 mmol) were dissolved in MeCN (0.5 mL) in a 25 mL side-armed round-bottomed flask under O_2 (balloon), and the mixture was stirred for 30 min at room temperature. Vinyl ether **2** (4.0 mmol) was added to the flask, and a solution of allylic alcohol **1** (1.0 mmol) in MeCN (0.5.mL) was then added. The mixture was stirred at room temperature until allylic alcohol **1** was nearly completely consumed. [b] Isolated yields based on **1**. Parentheses contain yields in the case of not using **4**. [c] Using 0.1 mmol of $Pd(OAc)_2$, $Cu(OAc)_2$, and **4** in each with all other conditions the same. [d] The ratio of *R***R**/*R***S** was 87/13 in **3d** and 86/14 in **3e**. In the case of not using **4**, the value was 87/13 and 93/7, respectively. [e] In this entry, GC yields of **3** based on **1** with anisole as an internal standard are shown. [f] The cis/trans ratio was 71/29, and in the case of not using **4**, it was 65/35.

Scheme 3



3a 86%

The previous paper[2a] reported that the reaction of **1a** and **2a** under similar conditions did not give **3a**, but that

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(5) For example, we have recently found that 4-benzylidene-2-butoxytetrahydrofuran serves as the apoptosis inducer of U937 human lymphoma cell: Sazuka, M.; Hosokawa, T. Unpublished results.

(6) (a) Hosokawa, T.; Nakahira, T.; Takano, M.; Murahashi, S.-I. *J. Mol. Catal.* **1992**, *74*, 489−498. (b) Hosokawa, T.; Aoki, S.; Takano, M.; Nakahira, T.; Yoshida, Y.; Murahashi, S.-I. *J. Chem. Soc., Chem. Commun.* **1991**, 1559−1560.

(7) For a related study, see: Hosokawa, T.; Takano, M.; Murahashi, S.-I. *J. Am. Chem. Soc.* **1996**, *118*, 3990−3991.

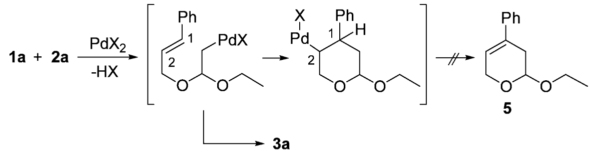
(8) (a) Berreau, L. M.; Mahapatra, S.; Halfen, J. A.; Houser, R. P.; Young, V. G., Jr.; Tolman, W. B. *Angew. Chem., Int. Ed.* **1999**, *38*, 207−210 and references cited therein. (b) Kodera, M.; Kawata, T.; Kano, K.; Tachi, Y.; Ito, S.; Kojo, S. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1957−1964 and references cited therein.

(9) Inui, T.; Nakahara, K.; Uchida, M.; Miki, W.; Unoura, K.; Kokeguchi, U.; Hosokawa, T. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1201−1207.

(10) The use of other solvents such as 1,2-dichloromethane or ethyl acetate under the conditions shown in Scheme 2 (Pd/Cu/**4** = 1/1/2) resulted in poor yields (∼30%) of **3a**. When ethyl orthoformate, which acts as a scavenger of water, was employed, the yield of **3a** was only 42%. Note that in all these cases, the absence of **4** further decreased the yields of **3a**.

2-ethoxy-4-phenyl-3,6-dihydropyran (**5**) arising from 6-*endo* cyclization of the oxypalladation adduct (Scheme 4) was formed. However, the structural assignment of **5** was not made in detail. In addition, we could not determine why only this reaction, among several examples, produces the dihydropyran **5** instead of **3a**. Then, we decided to determine its structure by X-ray analysis. No single crystal was obtained with **3a** itself, but **3c** (R = 4-NO_2Ph) (Table 1, entry 3) gave a crystal suitable for X-ray analysis. The ORTEP drawing shown in Figure 1 proved **3c** to possess the furan structure bearing the (*Z*)-configuration in *exo*-methylene moiety. Thus, the previous structural assignment of **5** was incorrect.

Scheme 4



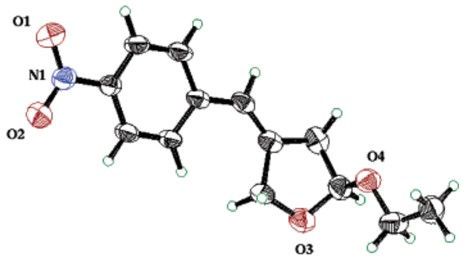


Figure 1. ORTEP drawing of compound **3c**.

The structure assignment of **3e** bearing pyranyl moiety (Table 1, entries 4 and 5) was also made by X-ray analysis. The product **3e** (or **3d**) was obtained as a mixture of two diastereomers, and each isomer was able to be separated by TLC. One of the diastereomers in **3e** (R = 4-NO_2Ph) produced a single crystal suitable for X-ray analysis. The ORTEP drawing in Figure 2 shows the tetrahydrofuran structure of **3e** bearing the *R***R** configuration with respect to the two chiral centers.

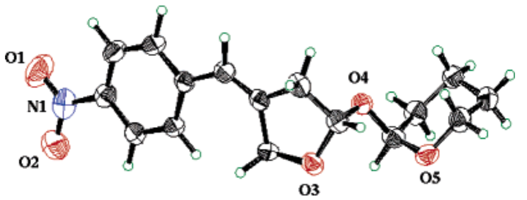


Figure 2. ORTEP drawing of compound **3e**.

Allyl alcohol (**1c**) itself reacts with **2b** to afford a 73% yield of 2-butoxy-4-methylenetetrahydrofuran (**3f**) (Table 1, entry 6), which represents the basic structure of this class of compounds. This is the first preparation of **3f**, as well as for **3d** and **3e**. 2-Buten-1-ol (**1d**) reacts with **2b** to give a 73% yield of 4-vinyltetrahydrofuran **3g** (cis/trans = 71/29, entry 7), the cis/trans configuration of which was assigned by 2D-NOESY experiment in NMR.[11] The product **3g** is formed by oxypalladation and cyclization (Scheme 1) followed by β-hydride elimination from the methyl group (R = Me) in the side chain.

All the products **3** formed have thus the five-membered furan structure arising from 5-*exo* cyclization of the oxypalladation intermediate (Scheme 1). The preference of this pathway, rather than the 6-*endo* one (Scheme 4), must be due to conformational compatibility of the oxypalladation adduct for undergoing the cyclization toward internal alkene, which must coordinate to Pd(II). The rate of this cyclization is likely influenced by the R group of the allylic moiety, and thereby the NO_2 substituent on the Ph group retards the reaction (Table 1, entries 3 and 5).

Finally, for the role of catechol (**4**) on catalysis, we would like to mention the following. In palladium(II)-catalyzed oxidations, *p*-benzoquinones have been known to act as oxidants.[12] In addition, the catalysis of Pd(II) can be induced by a redox couple of *p*-benzoquinone and hydroquinone under O_2 with metal complexes such as $Cu(OAc)_2$[13] or Co(salen).[12a] However, the use of either hydroquinone (10 mol %) or *p*-benzoquinone (10 mol %), in place of **4**, under the conditions given in Table 1 (entry 1) gave **3a** only in 7% or 17% yield, respectively. This suggests that a redox couple between catechol and *o*-quinone is not operative in the present system. Thus, the role of **4** would be in (i) enhancement of catalyst stability by constructing a Pd−Cu heterometallic species bearing **4** as the ligand of Cu[14] and (ii) effective capture of O_2 and its activation by the Cu−catechol moiety. The catalytic turnover process must involve Pd−H species formed and O_2, the details of which are also the subject of further study.[15]

In conclusion, the present study demonstrated the effectiveness of catechol as the activator of $Pd(OAc)_2$−$Cu(OAc)_2$ catalyst under O_2. The present reaction produces five-membered furan derivatives, irrespective of substituents in substrates. The reaction is environmentally benign, since only

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(11) The details are given in the Supporting Information.

(12) (a) Bäckvall, J.-E.; Hopkins, R. B.; Grennberg, H.; Mader, M. M.; Awasthi, A. K. *J. Am. Chem. Soc.* **1990**, *112*, 5160−5166 and references therein. (b) Bäckvall, J.-E.; Hopkins, R. B. *Tetrahedron Lett.* **1988**, *29*, 2885−2888.

(13) Byström, S. E.; Larsson, E. M.; Åkermark, B. *J. Org. Chem.* **1990**, *55*, 5674−5675.

(14) This view could be supported by the following facts. When either $Pd(OAc)_2$ alone or a combination of $Pd(OAc)_2$ and **4** was employed as the catalyst under otherwise the same conditions described in Table 1 (entry 1), the yield of **3a** was low (15%) and comparable. Thus, a combination of $Cu(OAc)_2$ and **4** together with $Pd(OAc)_2$ was evidently required for a higher production of **3a** (Table 1, entry 1). It is possible that *o*-quinone derived from **4** could be a candidate as the ligand of Cu in catalytically active species.

(15) For the related catalysis, see: (a) Steinhoff, B. A.; Guzei, I. A.; Stahl, S. S. *J. Am. Chem. Soc.* **2004**, *126*, 11268−11278. (b) Mueller, J. A.; Goller, C. P.; Sigman, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9724−9734.

molecular oxygen is the stoichiometric oxidant. A higher turnover of the catalyst and simple manipulations make the reaction synthetically useful. In addition, since a variety of vinyl ethers are readily available by procedures recently reported,[16] the synthetic utility of this reaction will undoubtedly be expanded.

Acknowledgment. We acknowledge Professor K. Oshima of Kyoto University for helpful discussions.

Supporting Information Available: Experimental details, characterization data, and X-ray analysis of compounds **3c** and **3e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[16] (a) Okimoto, Y.; Sakaguchi, S.; Ishii, Y. *J. Am. Chem. Soc.* **2002**, *124*, 1590−159l. (b) Bosch, M.; Schlaf, M. *J. Org. Chem.* **2003**, *68*, 5225−5227.