ORGANIC LETTERS

2011
Vol. 13, No. 5
992–994

Facile Synthesis of (*E*)-Alkenyl Aldehydes from Allyl Arenes or Alkenes via Pd(II)-Catalyzed Direct Oxygenation of Allylic C−H Bond

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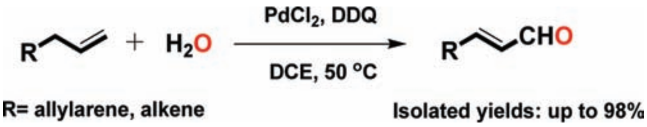
Received December 14, 2010

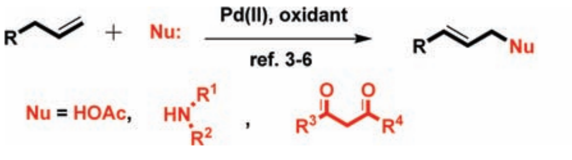
ABSTRACT



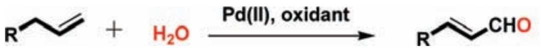
Palladium-catalyzed oxygenation of allyl arenes or alkenes has been developed to produce (*E*)-alkenyl aldehydes with high yields. Allylic C−H bond cleavages occur under the mild conditions during this process. Mechanistic studies show that oxygen source is water.

Transition-metal-catalyzed sequential oxidative cleavage and functionalization of an allylic C−H bond has been an important methodology for the direct installation of functionality into hydrocarbon frameworks.[1] The practical utility of such processes for complex molecule synthesis is governed by their ability to operate with predictable and high levels of chemo-, stereo-, and regioselectivity as well as site selectivity. The strategic application of selective C−H oxidation and functionalization reactions at late stages of syntheses has been demonstrated to increase product diversity.[2]

Recently, White,[3] Shi,[4] Ishii,[5] and Liu[6] made significant progress in the allylic C−O/C−N/C−C formation via Pd(II)-catalyzed C−H activation (eq 1). An allyl-palladium species was proposed as the key intermediate in these processes. To the best of our knowledge, direct oxygenation of an allylic C−H bond via Pd-catalysis using H_2O as a nucleophilic reagent has not been disclosed to date.



(1)



(2)

On the other hand, few examples reported the synthesis of alkenyl aldehydes from allyl arenes or alkenes.[7] And

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(1) (a) Hansson, S.; Heumann, A.; Rein, T.; Åkermark, B. *J. Org. Chem.* **1990**, *55*, 975. (b) Heumann, A.; Reglier, M.; Waegell, B. *Angew. Chem., Int. Ed.* **1982**, *21*, 366. (c) Heumann, A.; Åkermark, B. *Angew. Chem., Int. Ed.* **1984**, *23*, 453. (d) McMurry, J. E.; Kocovsky, P. *Tetrahedron Lett.* **1984**, *25*, 4187. (e) Åkermark, B.; Larsson, E. M.; Oslob, J. D. *J. Org. Chem.* **1994**, *59*, 5729. (f) Macsari, I.; Szabo, K. J. *Tetrahedron Lett.* **1998**, *39*, 6345. (g) Yu, J.-Q.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 3232. (h) Mitsudome, T.; Umetani, T.; Nosaka, N.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Angew Chem., Int. Ed.* **2006**, *45*, 481. *Angew. Chem.* **2006**, *118*, 495. (i) Chen, M. S.; White, M. C. *J. Am. Chem. Soc.* **2004**, *126*, 1346. (j) Chen, M. S.; Prabagaran, N.; Labenz, N. A.; White, M. C. *J. Am. Chem. Soc.* **2005**, *127*, 6970. (k) Fraunhoffer, K. J.; Bachovchin, D. A.; White, M. C. *Org. Lett.* **2005**, *7*, 223.

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(4) Lin, S.; Song, C. X.; Cai, G. X.; Wang, W. H.; Shi, Z. J. *J. Am. Chem. Soc.* **2006**, *130*, 12901.

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(6) (a) Liu, G.; Yin, G.; Wu, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 4733. (b) Yin, G.; Wu, Y.; Liu, G. *J. Am. Chem. Soc.* **2010**, *132*, 11978.

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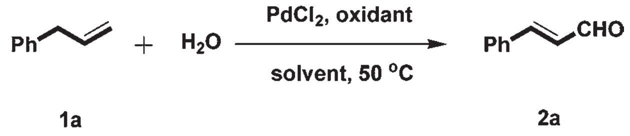
10.1021/ol1030316

they were also limited to reactions with inferior results (low chemo-, stereo-, and regioselectivity and low yields). Therefore, the synthesis of alkenyl aldehydes from allyl arenes or alkenes under mild conditions is desired. Herein, we would like to disclose our preliminary results (eq 2).

We initially employed dioxygen (1 atm) as an oxidant to investigate the transformation of allylbenzene (**1a**) in the presence of $PdCl_2$ (10 mol %) in 1,2-dichloroethane (DCE, 2.5 mL) at 50 °C, and none of the expected product (*E*)-3-phenyl-2-propenealdehyde (**2a**) was detected (Table 1, entry 1). We found that a small amount of product **2a** was obatained when using benzoquinone (BQ) or *tert*-butyl hydroperoxide (TBHP) as an oxidant (Table 1, entries 2, 3). To our delight, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as the oxidant can greatly promote the $PdCl_2$-catalyzed transformation of **1a**, leading to the corresponding product in 100% GC yield with high stereoselectivity (Table 1, entry 4). The investigation on reaction media showed that other solvents let to the inferior results, and the isomers of **1a** were detected (Table 1, entries 6−9). Moreover, both $PdCl_2$ and DDQ are essential for this transformation (Table 1, entries 5, 10).

Under the optimized conditions, various substrates were examined, and the results are summarized in Table 2. In addition to allylbenzene (**1a**), both (*E*)- and (*Z*)-propenylbenzene performed this transformation very well, converting to **2a** with high stereoselectivity in 92 and 88% yields, respectively (Table 2, entries 2 and 3). These results indicated that π-allyl species are involved in this transformation. The substrate scope was tested by using a variety of allyl arenes; the oxygenation afforded (*E*)-alkenyl aldehydes products in high yields, regardless of whether an electron-withdrawing or electron-donating group was introduced on the phenyl ring (Table 2, entries 4−10). Substituents at the para, meta, and ortho positions of the arene ring did not affect the efficiencies (Table 2, entries 4, 9, and 10). Notably, a heteroaryl-substituted propene, 1-allyl-2-thiophene (**1k**), provided **2k** in 94% yield (Table 2, entry 11). 3-Naphthylpropene gave the corresponding product in moderate yield (Table 2, entry 12). It is noteworthy that 2,3-disubstituted propene was tolerated in this transformation, leading to the corresponding trisubstituted (*E*)-alkenyl aldehyde **2m** in high yield (Table 2, entry 13). Additionally, the alkenyl-substituted propene **1o** survived well, generating **2n** (Table 2, entry 14). However, simple alkyl olefins such as 1-octene did not react in the process (Table 2, entry 15).

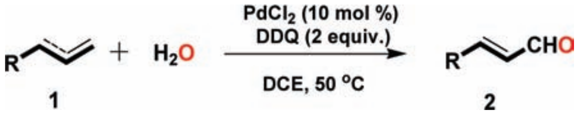
Table 1. Optimization of Reaction Conditions for Direct Transformation of Allylbenzene (**1a**) to Cinnamoaldehyde (**2a**)[a]

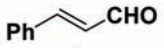
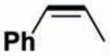
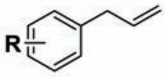
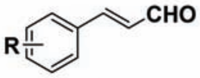
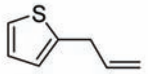
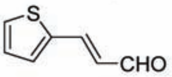
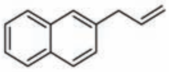
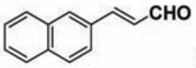
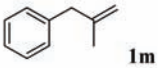
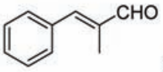
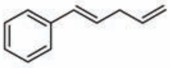
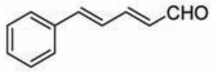


entry	solvent	oxidant	yield of **2a**/%[b]
1	DCE	O_2	0
2	DCE	BQ	<10
3	DCE	TBHP	<10
4	DCE	DDQ	100 (96)
5	DCE	–	0
6	Toluene	DDQ	92
7	DMF	DDQ	13
8	THF	DDQ	30
9	H_2O	DDQ	19
10[c]	DCE	DDQ	18

[a] Reaction conditions: All reactions were performed with **1a** (0.5 mmol), H_2O (1.5 equiv), Pd catalyst (10 mol %), and oxidant (2.0 equiv) in 2.5 mL of DCE for 2 h. [b] Determined by GC. Number in parentheses is isolated yield. [c] In the absence of $PdCl_2$.

Table 2. $PdCl_2$−Catalyzed Direct Oxygenation of **1** to **2**[a]

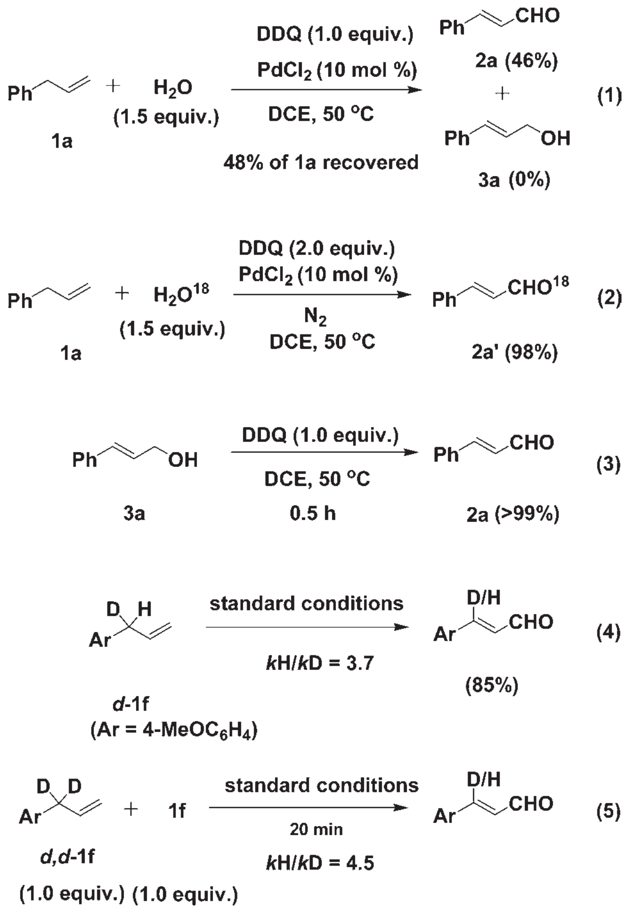


entry	1		2		yield of **2**/%[b]
1		**1a**		**2a**	96
2		**1b**			92
3		**1c**			88
					
4	R = *p*-Me	**1d**		**2d**	90
5	R = *p*-Et	**1e**		**2e**	98
6	R = *p*-OMe	**1f**		**2f**	93
7	R = *p*-(*t*-Bu)	**1g**		**2g**	85
8	R = *p*-F	**1h**		**2h**	79
9	R = 3,5-Dimelthyl	**1i**		**2i**	85
10	R = *o*-Me	**1j**		**2j**	96
11		**1k**		**2k**	94
12[c]		**1l**		**2l**	78
13		**1m**		**2m**	98
14		**1n**		**2n**	61
15[b]		**1o**		**2o**	0

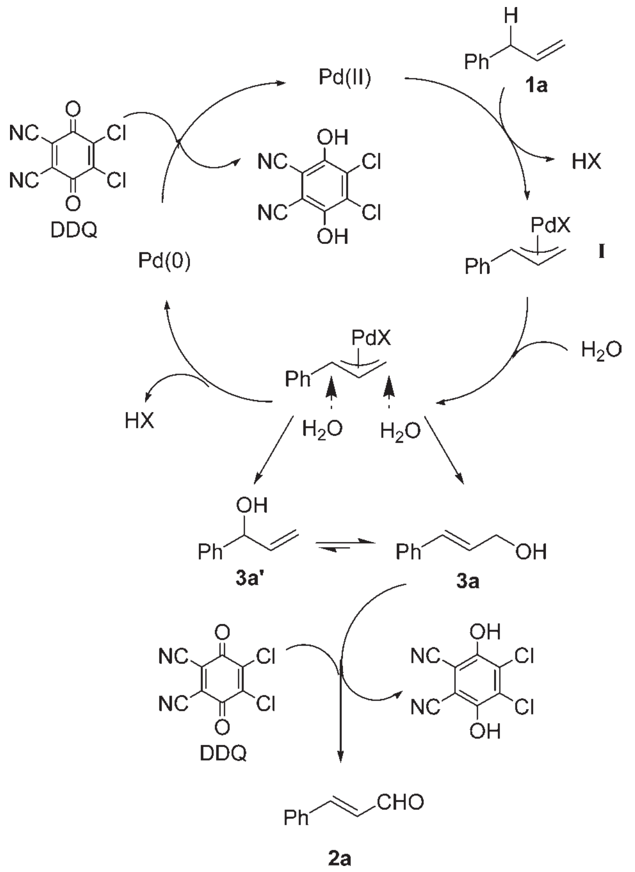
[a] Reaction conditions: Substrate **1** (0.5 mmol), H_2O (1.5 equiv), Pd catalyst (10 mol %), and DDQ (2.0 equiv) in 2.5 mL of DCE for 2 h. [b] Isolated yields. [c] The isomers of **1o** were not detected, indicating that the isomerization did not occur.

Several control experiments were performed to probe a plausible reaction path (Scheme 1): (1) the reaction of **1a** was carried out using 1.0 equiv of DDQ as the oxidant,

Scheme 1. Control Experiments



Scheme 2. Proposed Mechanism



affording **2a** in 46% yield, and 48% of **1a** was recovered. Cinnamyl alcohol **3a** was not detected; (2) the reaction of **1a** with H_2O^{18}, under N_2 atmosphere, afforded O^{18}-labled product **2a′** in 98% yield; (3) the reaction of **3a** with 1.0 equiv of DDQ produces the desired product **2a**. These results suggest that the oxygen source is water, and **3a** might be the intermediate in this process; (4 and 5) both intra- and intermolecular kinetic isotopic effects were evident (kH/kD = 3.7 and 4.5, respectively). It indicated that the cleavage of the allyl C(sp^3)−H bond is involved in the rate-determining step.

On the basis of these results, a plausible mechanism for the palladium-catalyzed oxygenation of allyl arenes or alkenes is shown in Scheme 2. First, Pd(II) reacted with allylbenzene **1a** to produce the corresponding π-allyl-palladium species **I** through the allylic C−H bond activation.[3−6] Next, intermediate **I** is subjected to the nucleophilic attack of H_2O to afford Pd(0) and the oxidative allylic oxygenation product **3a** and/or **3a′**. **3a**/**3a′** would exist as an equilibrating mixture by [3,3]-sigmatropic rearrangement.[8] Product **2a** is subsequently formed through subsequent oxidation of **3a**/**3a′** by DDQ. Finally, Pd(0) is reoxidized to generate active species Pd(II) by DDQ.

In summary, we have successfully developed a facile synthesis of (E)-alkenyl aldehydes from allyl arenes or alkenes via Pd(II)-catalyzed allylic C−H oxygenation. In this process, water was used as a nucleophilic reagent and an oxygen source for direct oxygenation of an allylic C−H bond. This observation will provide a new synthetic tool for constructing alkenyl aldehydes. Further studies to clearly understand the reaction mechanism and the synthetic applications are ongoing in our group.

Acknowledgment. We thank the National Natural Science Foundation of China (20625205, 20772034, and 20932002), National Basic Research Program of China (973 Program) (2011CB808600), Doctoral Fund of Ministry of Education of China (20090172110014), and Guangdong Natural Science Foundation (10351064101-000000) for financial support.

Supporting Information Available. Experimental procedure and characterization of compounds **2a**−**2l**. This material is available free of charge via the Internet at http://pubs.acs.org.

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