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Communications

Complete Reverse Regioselection in Wacker Oxidation of Acetonides and Cyclic Carbonates of Allylic Diols

Suk-Ku Kang,* Kyung-Yun Jung, Jea-Uk Chung, Eun-Young Namkoong, and Tae-Hyun Kim

Department of Chemistry, Sung Kyun Kwan University, Natural Science Campus, Suwon 440-746, Korea

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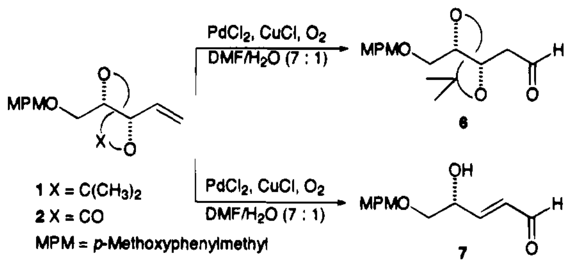
The palladium(II)-catalyzed oxidation of terminal olefins to methyl ketones (Wacker process) is well established both as an industrial process and an organic synthetic reaction.[1] This reaction appears to involve Markovnikov hydration of the complexed double bond followed by oxidation in a one-step conversion to a methyl ketone.[2] Thus, terminal olefins can be regarded as masked methyl ketones. Although this process is well-known for the conversion of higher olefins to methyl ketones, few reports have involved preferential aldehyde formation.[3] Furthermore, it is reported[4] that anti-Markovnikov addition occurs in the presence of a heteroatom (i.e., N atom or electron-withdrawing group), whereas terminal olefins bearing neighboring γ-alkoxy or γ-acetoxy functions were oxidized[1b] to the corresponding methyl ketones.

Because the direct formation of an aldehyde *via* attack at the terminal carbon of a terminal double bond would be valuable synthetic process, we report here the completely regioselective oxygen-oriented Wacker-type reaction of the acetonides and cyclic carbonates of allylic diols, as shown in Scheme 1.

Scheme 1



The results are summarized in Table 1.[5] The terminal allylic diol **1** was treated with a catalytic amount of $PdCl_2$ and CuCl under an atmospheric pressure of O_2, in DMF and H_2O, at room temperature for 12 h to afford the expected methyl ketone **5** in 90% yield (entry 1). However, treatment of the acetonide of the allylic diol **2**, under the same conditions at 60 °C for 6 h, afforded the terminal aldehyde **6** as the sole product (presumably due to the anti-Markovnikov hydration) in 93% yield with no formation of the methyl ketone (entry 2). This result is in contrast to the published result[1b] that Wacker oxidation of an α-methoxy terminal olefin gives only a methyl ketone. It is presumed that simultaneous chelation of palladium with two adjacent oxygen atoms might induce water to attack in an anti-Markovnikov fashion. As supporting evidence that diol functionality is essential, Wacker oxidation of α- or β-alkoxy olefin did not afford β- or γ-substituted aldehyde as the only product.[6]

Alternatively, when the diastereoisomer (2*R*,3*S*)-**2** was subjected to the same Wacker conditions, the aldehyde (3*S*,4*R*)-**6** was obtained as the sole product after being stirred at 60 °C for 24 h (entry 3). For the allylic cyclic carbonate **3**,[7] under the same conditions, γ-hydroxy-α,β-unsaturated aldehyde **7** was obtained in 95% yield (entry 4). By the same methodology, the allylic cyclic carbonate **4** provided the aldehyde **8**,[8] $[\alpha]^{25}_{D}$ +48 (*c* 0.7, $CHCl_3$) [lit.[8b] $[\alpha]^{25}_{D}$ +46 (*c* 0.1, $CHCl_3$)], which is a cytotoxic lipid peroxidation product,[9] and also an important chiral synthon for the synthesis of (+)-coriolic acid,[8e,10] a self-defensive substance for the rice blast disease (entry 5).

Alternatively, we have investigated regioselective palladium(II)-catalyzed oxidation of internal olefins. For the

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(1) (a) Smidt, J.; Hafner, W.; Jira, R.; Sieber, R.; Sedlmeier, J.; Sabel, A. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 80. (b) Tsuji, J. *Synthesis* **1984**, 369. (c) Tsuji, J.; Nagashima, H.; Nemoto, H. *Org. Synth.* **1984**, *62*, 9. (d) Heck, R. F. In *Palladium Reagents in Organic Syntheses*; Academic Press: London, 1985.

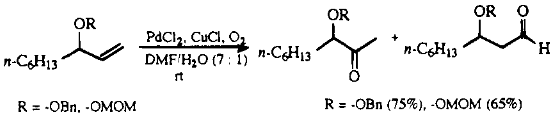
(2) (a) Tsuji, J. In *Organic Synthesis by Means of Transition Metal Complexes*; Springer-Verlag: Berlin, 1975. (b) Zaw, K.; Henry, P. M. *J. Org. Chem.* **1990**, *55*, 1842 and references therein. (c) Backvall, J.-E.; Akermark, B.; Ljunggren, S. O. *J. Am. Chem. Soc.* **1979**, *101*, 2411. (d) Henry, P. M. *Adv. Organomet. Chem.* **1975**, *13*, 363. (e) Stille, J. K.; Divakaruni, R. *J. Am. Chem. Soc.* **1978**, *100*, 1303.

(3) (a) Feringa, B. L. *J. Chem. Soc., Chem. Commun.* **1986**, 909. (b) Ogawa, H.; Miyamoto, S.; Mandai, T.; Wakabayashi, S.; Tsuji, J. *Tetrahedron Lett.* **1988**, *29*, 5181. (c) Hosokawa, T.; Aoki, S.; Takano, M.; Nakahira, T.; Yoshida, Y.; Murahashi, S.-I. *J. Chem. Soc., Chem. Commun.* **1991**, 1559. (d) Pellissier, H.; Michelly, P.-Y.; Santelli, M. *Tetrahedron Lett.* **1994**, *35*, 6481.

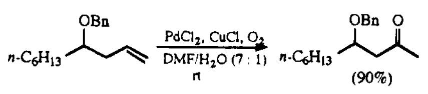
(4) (a) Bose, A. K.; Krishnan, L.; Wagle, D. R.; Manhas, M. S. *Tetrahedron Lett.* **1986**, *27*, 5955. (b) Lai, J.-y.; Shi, X.-x.; Dai, L.-x. *J. Org. Chem.* **1992**, *57*, 3485. (c) Hosokawa, T.; Ohta, T.; Murahashi, S.-I. *J. Chem. Soc., Chem. Commun.* **1983**, 848. Hosokawa, T.; Ohta, T.; Kanayama, S.; Murahashi, S.-I. *J. Org. Chem.* **1987**, *52*, 1758.

(5) The diols, acetonides, and cyclic carbonates **1**, (2*S*,3*S*)-**2**, **3**, and **4** were prepared from diethyl L-tartrate. The compound (2*R*,3*S*)-**2** was prepared from (−)-2, 3-*O*-isopropylidene-D-erythronolactone: (a) DIBAH, toluene, −78 °C, 1 h (90%); (b) $Ph_3P{=}CH_2$, THF, HMPA, −78 °C, 30 min → 0 °C, 1 h (68%); (c) NaH, MPMCl, DMF, −30 °C, 2 h (87%).

(6) In the literature, Wacker oxidation of α-methoxy terminal olefins gave methyl ketones only.[1b] However, in our hands, treatment of α-*O*-(benzyloxy) or α-*O*-MOM olefins afforded α-substituted ketones and aldehydes in ratios of ca. 1:1, respectively.



For β-*O*-(benzyloxy) olefin, only methyl ketone was obtained.



(7) The diols, acetonides, and cyclic carbonates **9–11** were prepared from (2*S*,3*S*)-2,3-*O*-(isopropylidenedioxy)-1,4-butanediol derived from diethyl L-tartrate. See: Kang, S.-K.; Park, D. C.; Park, C.-H.; Hong, R.-K. *Tetrahedron Lett.* **1995**, *36*, 405.

(8) Synthesis of optically active **8**. (a) By asymmetric reduction: Bringmann, G.; Gassen, M.; Lardy, R. *Tetrahedron* **1994**, *50*, 10245. (b) Enzymatic resolution: Allevi, P.; Anastasia, M.; Cajone, F.; Ciuffreda, P.; Sanvito, A. M. *J. Org. Chem.* **1993**, *58*, 5000. (c) Sharpless epoxidation: Yu, L.; Wang, Z. *J. Chem. Soc., Chem. Commun.* **1993**, 232. (d) Enzymatic hydrolysis: Bloch, R.; Perfetti, M.-T. *Tetrahedron Lett.* **1990**, *31*, 2577. (e) $Fe(CO)_3$ complex as resolving agent: Montarby, L. de.; Mosset, P.; Gree, R. *Ibid.* **1988**, *29*, 3937.

(9) (a) Esterbauer, H.; Zollner, H.; Schaur, R. J. In *Membrane Lipid Oxidation*; Vigo-Pelfrey, C., Ed., CRC Press: Boca Raton, FL, 1990; Vol. 1, p 239. (b) Kappus, H. Lipid Peroxidation: Mechanisms, Analysis, Enzymology and Biological Relevance. In *Oxidative Stress*; Sies, H., Ed.; Academic Press, Inc.: London, 1985; p 273.

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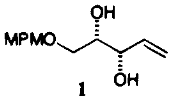
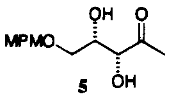
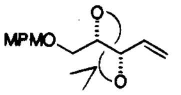
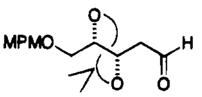
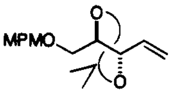
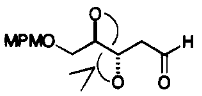
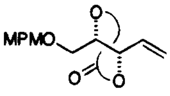
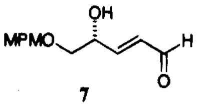
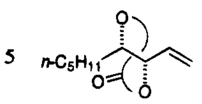
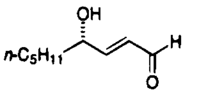
Table 1. Pd(II)-Catalyzed Oxidation of Terminal Olefins of Allylic Diols, Acetonides, and Cyclic Carbonates[a]

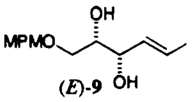
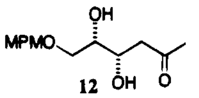
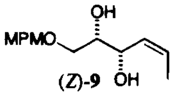
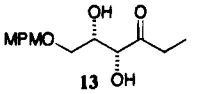
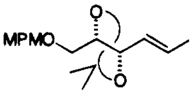
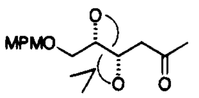
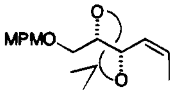
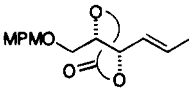
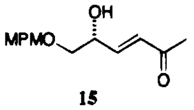
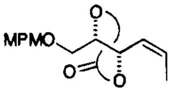
Entry	Substrate	Time(h)	Temp(°C)	Products	Yield(%)[b]
1	 1	12	rt	 5	90
2	 (2*S*, 3*S*)-**2**	6	60	 (3*S*, 4*S*)-**6**	93
3	 (2*R*, 3*S*)-**2**	24	60	 (3*S*, 4*R*)-**6**	83
4	 **3**	12	rt	 **7**	95
5	 **4**	12	rt	 **8**	90

[a] All the reactions were run with $PdCl_2$ (10 mol %), CuCl (1 equiv) in DMF/H_2O (7 : 1) under atmospheric pressure of oxygen.
[b] The yields are isolated yields.

internal olefins, it is known[1b,11] that there is a definite influence by the alkoxy or acetoxy group, which may be explained by coordination of palladium with the oxygen function resulting in control of the regioselection.

The methyl-substituted diol (*E*)-**9** was oxidized under Wacker conditions to β-keto diol **12** in 93% yield (entry 1). However, treatment of (*Z*)-**9** under the same conditions afforded α-keto diol **13** as the only isolated product in 90% yield (entry 2). It is presumed that in this particular case, steric hindrance around the double bonds considerably affects the regiochemistry of the olefin oxidation. From the (*E*)- or (*Z*)-methyl-substituted acetonides **10**, β-keto acetonide **14** was obtained (entries 3 and 4). When the cyclic carbonates of (*E*)- or (*Z*)-**11** were subjected to Wacker oxidation, γ-hydroxy-α,β-unsaturated ketone **15** was afforded (entries 5 and 6). The results are summarized in Table 2.[7]

Table 2. Pd(II)-Catalyzed Oxidation of Internal Olefins[a]

Entry	Substrate	Time(h)	Temp(°C)	Products	Yield(%)[b]
1	 (*E*)-**9**	12	rt	 **12**	93
2	 (*Z*)-**9**	12	rt	 **13**	90
3	 (*E*)-**10**	6	60	 **14**	93
4	 (*Z*)-**10**	6	60	**14**	91
5	 (*E*)-**11**	12	rt	 **15**	90
6	 (*Z*)-**11**	12	rt	**15**	91

[a] All the reactions were run with $PdCl_2$ (10 mol %), CuCl (1 equiv) in DMF/H_2O (7 : 1) under atmospheric pressure of oxygen.
[b] The yields are isolated yields.

A typical procedure is as follows. Preparation of **8**: To a stirred solution of $PdCl_2$ (8 mg, 0.05 mmol) and CuCl (42 mg, 0.54 mmol) in DMF and H_2O (7:1, 5 mL) under oxygen atmosphere was added **4** (100 mg, 0.54 mmol). The resulting dark brown solution was stirred at room temperature for 12 h and then extracted with ether. The organic layer was dried over anhydrous $MgSO_4$ and evaporated *in vacuo*. The crude product was purified by SiO_2 column chromatography (EtOAc:hexanes = 1:2, R_f = 0.30) to afford **8** (75.9 mg, 90%).

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Supporting Information Available: Experimental procedures and spectral and analytical data for the new compounds (3 pages).

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