

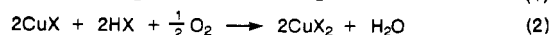
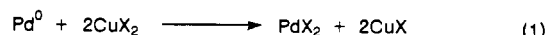
New Aspects of Oxypalladation of Alkenes

TAKAHIRO HOSOKAWA* and SHUN-ICHI MURAHASHI*

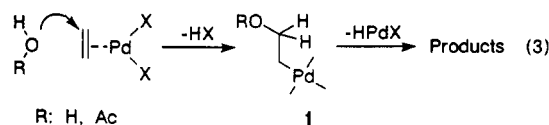
Department of Chemistry, Faculty of Engineering Science, Osaka University, Machikaneyama, Toyonaka, Osaka, Japan 560

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The discovery of the Wacker process, which produces acetaldehyde from ethylene in water by the use of PdCl₂ catalyst with CuCl₂ and O₂,^{1,2} has led to the development of various Pd(II)-catalyzed oxidative functionalizations of alkenes.³ Among these, the preparation of vinyl acetate from ethylene in acetic acid⁴ and that of 1,4-diacetoxy-2-butene from butadiene⁵ have been exploited for industrial processes.⁶ These exploitations are undoubtedly ascribed to the extensive studies based on the conception of the Wacker catalysis (eqs 1 and 2).



In the oxidative functionalization of alkenes by Pd(II) complexes, nucleophiles such as OH⁻ and OAc⁻ attack olefins coordinated to the metal, to give oxypalladation intermediate 1 (eq 3).² Subsequent β-elimination of



Pd-H species leads to products such as acetaldehyde and vinyl acetate, and the resulting PdHX species decomposes to give Pd(0) and HX. In 1973 we found that the intramolecular version of oxypalladation provides a useful entry to oxygen-containing heterocycles.⁷ Thereafter, the use of a chiral Pd(II) catalyst in the cyclization allowed us to develop the first asymmetric Wacker-type oxidation.^{8,9} Our endeavor to expand the scope of oxypalladation succeeded in the development of Pd(II)-catalyzed regioselective acetalization of terminal alkenes with diols.^{10,11} In these studies, we have shown that the redox catalysis of eqs 1 and 2 is not operative, but the formal oxidation state of Pd(II) remains constant throughout the reaction. Focusing on this point, we describe here new aspects of the oxypalladation of alkenes.

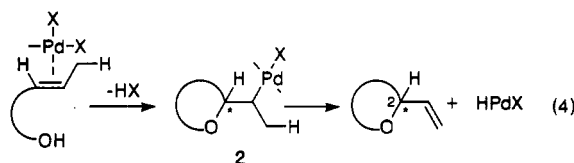
Intramolecular Version of Oxypalladation

Intramolecular cyclization of alkenyl phenols¹²⁻¹⁴ and unsaturated alcohols^{15,16} by Pd(II) salts proceeds via

Takahiro Hosokawa is an Associate Professor in the Department of Chemistry, Faculty of Engineering Science, Osaka University. He received his B.S. degree in 1965, M.S. in 1967, and Ph.D. in 1970 from Osaka University and joined the faculty as Assistant Professor. From 1970 to 1972, he did postdoctoral work with Professor Peter M. Maitlis at McMaster University in Canada. His research interests are in the area of synthetic chemistry using organometallic reagents and catalysts.

Shun-Ichi Murahashi was born in Osaka in 1937 and received his B.S. and Ph.D. from Osaka University. In 1963 he was appointed as Assistant Professor on the Faculty of Engineering Science, Osaka University. He served as a research associate at Columbia University from 1968 to 1970 under the direction of Professor Ronald Breslow. In 1972 he became Associate Professor, and since 1979 he has been a Professor of Organic Chemistry. His research interests include development of new methods using organometallic reagents and transition-metal catalysts, reactive intermediates, and carbene chemistry.

oxypalladation adduct 2 as shown in eq 4. When the



cyclization provides either five- or six-membered-ring products, the regioselectivity is largely dependent on the anionic ligand of Pd(II) salts. In general, the use of PdCl₂ appears to afford six-membered products predominantly, whereas five-membered heterocycles are preferred products with Pd(OAc)₂.¹³ Dependence of the regioselectivity on anionic ligands is also observed in Hg(II)-promoted cyclization of alkenyl phenols.¹⁷

When palladium(II) acetate is used for the cyclization shown in eq 4, cyclized products bearing alkenyl substituents at C₂ carbon are formed.^{14a,16} If a chiral ligand is incorporated into the catalyst, asymmetry at the C₂ position can be induced. Usual chiral phosphines are not applicable, since phosphine ligands are oxidized under the reaction conditions. Palladium(II) complexes bearing chiral hydrocarbon ligands could serve as catalysts. Indeed, we found that the use of chiral π-allyl

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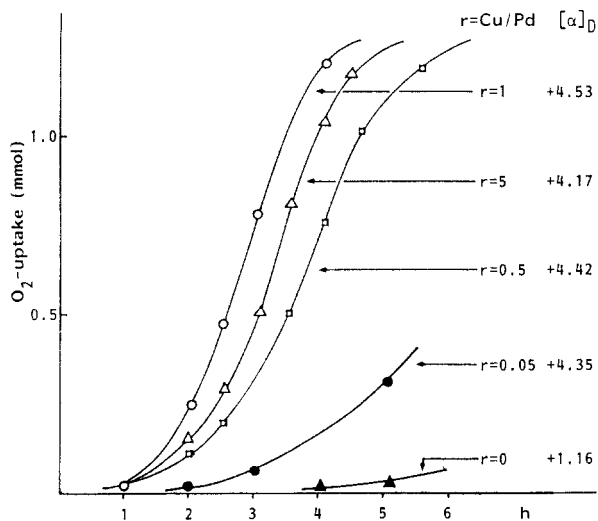
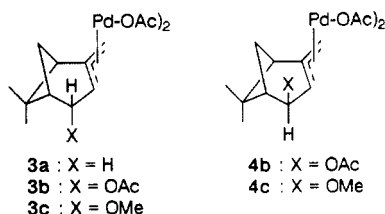
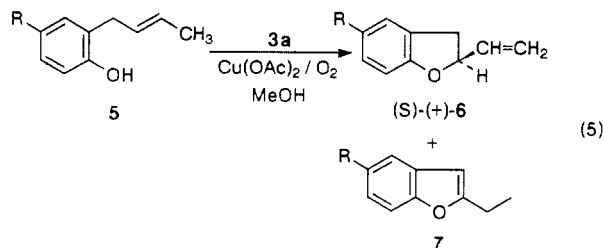


Figure 1. Progress of the catalytic reaction of *trans*-5 ($R = H$) performed by using various ratios of Cu/Pd and the $[\alpha]_D$ values of the products **6** ($R = H$) measured after completion of the reaction. Reaction conditions: 2.5 mmol of *trans*-5 ($R = H$), 0.125 mmol of complex **3a**, and an appropriate amount of $\text{Cu}(\text{OAc})_2$ at 35 °C in MeOH (5 mL) under O_2 (1 atm).

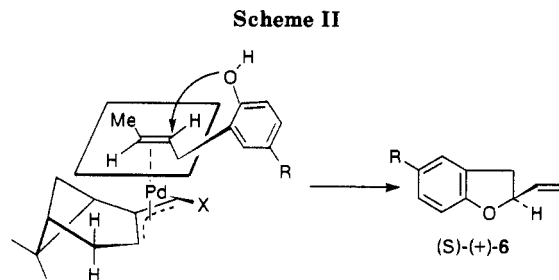
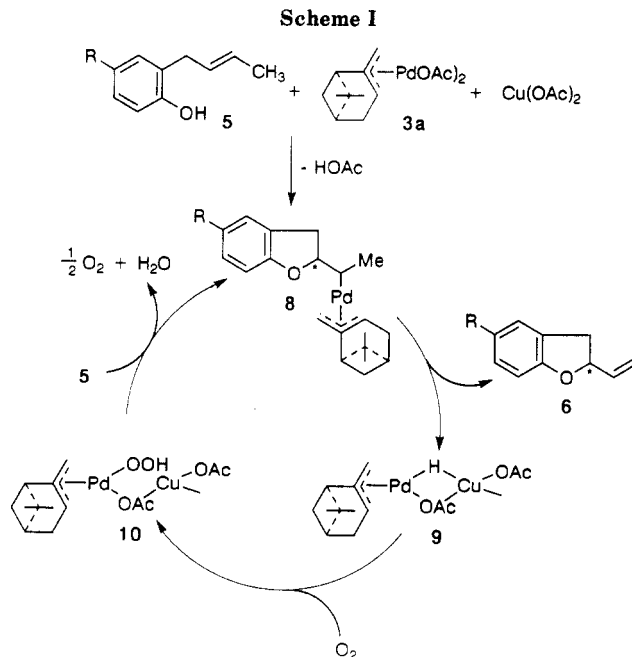
complexes such as **3** leads to an asymmetric version of the cyclization as mentioned below.



The cyclization of *trans*-2-(2-butenyl)phenols **5** with $[(\eta^3\text{-pinene})\text{PdOAc}]_2$ (**3a**, $X = H$) (10 mol %) in the presence of $\text{Cu}(\text{OAc})_2$ and O_2 (1 atm) gives (*S*)-(+)-2,3-dihydro-2-vinylbenzofuran (**6**) as the prevailing enantiomer (18% ee; $R = H$) along with **7** (eq 5).⁹ Al-

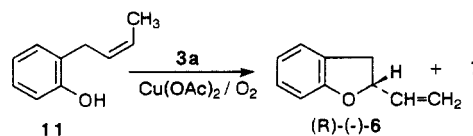


though the enantioselection is not high, the information on the asymmetric induction offers a useful probe to clarify the nature of Pd(II) species in this type of oxidation. The $[\alpha]_D$ values of (+)-**6** ($R = H$) in eq 5 do not change with time, indicating that the chiral pinanyl moiety of **3a** retains intact throughout the reaction. The rate of reaction, which can be deduced by the O_2 uptake curve with time, is enhanced considerably after an induction period. This indicates that a highly active catalyst, different from the complex **3a**, is formed during the reaction. The rate of O_2 absorption becomes faster as the relative ratio of added $\text{Cu}(\text{OAc})_2$ to **3a** increases and reaches a maximum when Cu/Pd = 1 (Figure 1). A slower rate is observed in the presence of excess amounts of Cu(II). In contrast, the $[\alpha]_D$ values of **6** ($R = H$) are approximately constant, if the ratio of Cu/Pd is larger than 0.05. These observations cannot be explained by the simple redox couple of Pd and Cu



shown in eqs 1 and 2. The reaction pathway depicted in Scheme I can, however, accommodate all these results. Coordination of the olefin of **5** to complex **3a** followed by oxypalladation with the loss of HOAc leads to **8**. Elimination of the hydrogen from the methyl group of **8** gives the product **6**, and the resulting Pd-H species **9** reacts with O_2 to give PdOOH species **10** as the active catalyst in which the η^3 -pinanyl ligand is retained. The catalyst is most likely a Pd-Cu bimetallic complex linked with μ -acetate and peroxy ligands.

Other π -allyl complexes **3** and **4** bearing substituents (X) on the pinanyl ligand also induce the asymmetric cyclization of **5**. While *trans* complexes **3b** and **3c** give no influence on the cyclization, the use of *cis* complex **4a** ($X = \text{OAc}$) gives (*R*)-(-)-**6** (18% ee; $R = H$), the configuration of which is opposite to that with the parent complex **3a**.¹⁸ The cyclization of *cis*-2-(2-butenyl)phenol (**11**) with **3a** results in the formation of the *R* enantiomer of **6** (0.7% ee). These results suggest



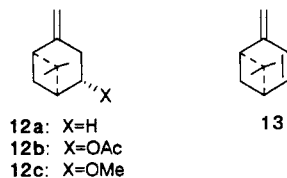
that the enantioselection is largely governed by two factors: *trans* addition of the phenoxy nucleophile to the olefin and the steric environment around the π -allyl ligand as shown in Scheme II.

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Table I
Asymmetric Cyclization of 5

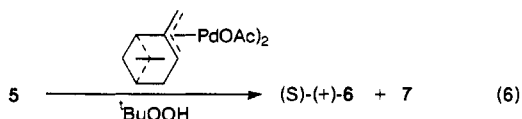
substrate 5, R	oxidizing agent	cyclized product		
		yield, %	product ratio, 6:7	% ee
4-OMe	<i>t</i> -BuOOH	19	86:14	22
	Cu(OAc) ₂ -O ₂	44	83:17	26
4-Me	<i>t</i> -BuOOH	34	82:18	18
	Cu(OAc) ₂ -O ₂	76	83:17	21
4-H	<i>t</i> -BuOOH	52	82:18	17
	Cu(OAc) ₂ -O ₂	77	83:17	18
4-Cl	<i>t</i> -BuOOH	54	87:13	4.5
	Cu(OAc) ₂ -O ₂	72	90:10	6.0
4-COMe	<i>t</i> -BuOOH	43	88:12	0.1
	Cu(OAc) ₂ -O ₂	74	96:4	1.1

The trans complexes 3 are readily prepared by the reaction of the corresponding β -pinenes 12 with Pd(OAc)₂. The cis complexes 4a and 4b are obtained upon treatment of (+)-3,4-dihydro- β -pinene (13) with either



Pd(OAc)₂ and NaCl in AcOH or Na₂PdCl₄ in MeOH, followed by metathesis with AgOAc.¹⁸ This represents a rare example of cis oxypalladation, since oxygen nucleophiles generally attack olefins in a trans fashion.¹⁹

tert-Butyl hydroperoxide serves as an oxidizing agent in place of the combination of O₂ and Cu(OAc)₂ (eq 6).^{20,21} The two catalytic systems (eqs 5 and 6) show



remarkably similar results, as shown in Table I. The enantioselectivity decreases in accordance with the electronic properties of substituents R on the phenoxy group (OCH₃ > CH₃ > Cl > COCH₃), whereas no clear trend is observed for the reactivity. The observed similarity in both reactivity and selectivity in the two catalytic systems suggests that a similar type of catalyst participates in these reactions. In the latter system, the resulting Pd-H species is oxidized by *t*-BuOOH, to give Pd-OH species, which promotes the oxypalladation of 5, to complete a catalytic cycle.²⁰

Synthetic Aspects. Pd(II)-induced intramolecular oxypalladations of alkenes bearing hydroxy groups, such as alkenyl phenols,^{9,12-14,22,23} alcohols,^{15,16} oximes,^{7b,24} and carboxylic acids,²⁵⁻²⁷ give a variety of oxygen-containing

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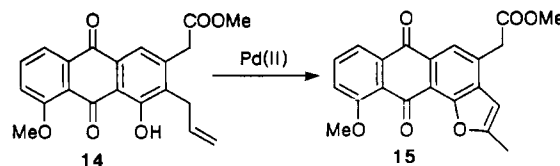
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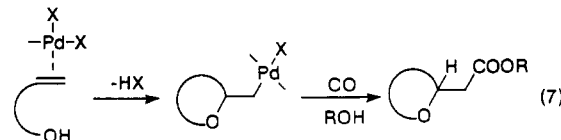
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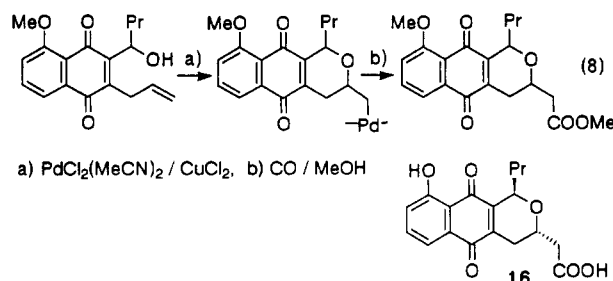
heterocycles. The synthesis of benzofuran 15 of the aklavinone system from 2-allylphenol 14 is a fascinating



example.²⁸ Trapping of the oxypalladation intermediate with CO also creates a unique approach to oxygen-containing heterocycles (eq 7).²⁹ The oxy-



palladation-carbonylation sequence shown in eq 8 serves as a useful strategy for the synthesis of deoxyfrenolicin (16) and related compounds.^{29a,b} Cyclizations



of alkenyl amines³⁰⁻³² give various nitrogen-containing heterocycles such as indoles^{30a} and indoloquinone 17.^{30c} Insertion of CO into intermediate aminopalladation adducts also provides an intriguing entry to functionalized nitrogen heterocycles such as 18 (eq 9).³³ The scope of these reactions has been reviewed by Hegedus.³⁴

Synthetic potential to optically active natural products is addressed by the Pd(II)-catalyzed asymmetric cyclization of alkenyl phenols. Naturally occurring

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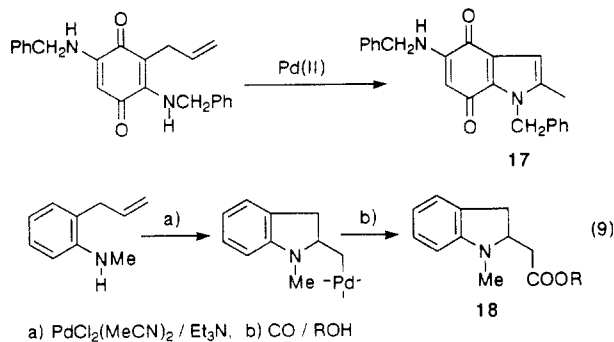
(30) (a) Hegedus, L. S.; Allen, G. F.; Waterman, E. L. *J. Am. Chem. Soc.* 1976, 98, 2674. (b) Hegedus, L. S.; Allen, G. F.; Bozell, J. J.; Waterman, E. L. *J. Am. Chem. Soc.* 1978, 100, 5800. (c) Hegedus, L. S.; Winton, P. M.; Varaprath, S. *J. Org. Chem.* 1981, 46, 2215. (d) Hegedus, L. S.; McKearin, J. M. *J. Am. Chem. Soc.* 1982, 104, 2444. (e) Weider, P. R.; Hegedus, L. S.; Asada, H.; D'Andrea, S. V. *J. Org. Chem.* 1985, 50, 4276. (f) Hegedus, L. S.; Holden, M. S.; McKearin, J. M. *Org. Synth.* 1984, 62, 48.

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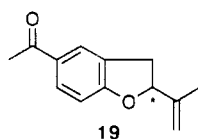
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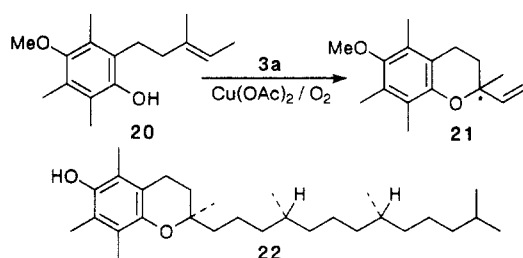
(34) (a) Hegedus, L. S. *Tetrahedron* 1984, 40, 2415. (b) Hegedus, L. S. *Angew. Chem., Int. Ed. Engl.* 1988, 27, 1113.



(*R*)-tremetone (19), which induces "tremble" in cattle

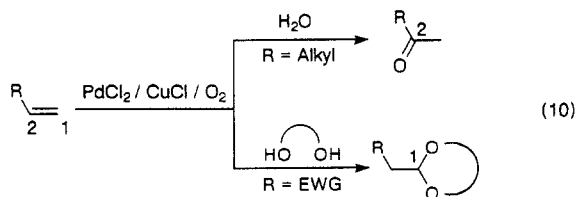


and "milk sickness" in higher animals and humans, can thus be derived from optically active 2-vinyl-2,3-dihydrobenzofuran (6) (*R* = H).^{18a} Asymmetric cyclization of pentenylphenol 20 gives an 80% yield of chroman 21 (10% ee), which corresponds to the chroman moiety of α -tocopherol (22) (vitamin E).³⁵



Acetalization of Alkenes

The Pd(II)-catalyzed oxidation of terminal alkenes bearing alkyl groups with water^{2,36} and alcohols³⁷ produces methyl ketones via the attack of oxygen nucleophiles at the nonterminal olefinic carbon (C₂). Formation of aldehydes and their derivatives via the attack at the terminal carbon (C₁) is one of the important processes currently attracting attention in synthetic organic chemistry.^{38,39} With alkenes bearing electron-withdrawing groups, oxygen nucleophiles such as diols or alcohols attack at the C₁ carbon, to give acetals of aldehyde precursors (eq 10).³⁷ However, the reaction



has so far not been evaluated as a synthetic tool.⁴⁰ We

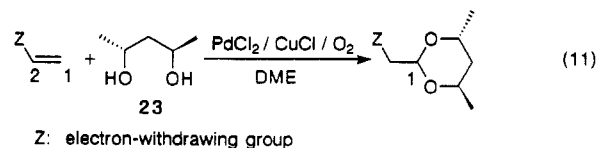
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Table II
Acetalization of Alkenes^a

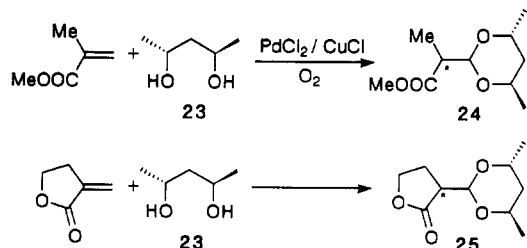
alkene	acetal	yield, ^b %
		79
		72
		45
		79
		81 ^c

^a Reaction conditions: alkene (2 mmol), diol (2 mmol), PdCl₂ (0.2 mmol), CuCl (2 mmol), DME (2 mL), 50 °C, O₂ (1 atm); see ref 11. ^b Isolated yield. ^c Unpublished results.

have found that the acetalization proceeds efficiently and provides a useful method for preparing chiral acetals from alkenes, if optically active diols such as (*R,R*)-2,4-pentanediol (23) are used as nucleophiles (eq 11).^{10,11} Given in Table II are typical examples of the



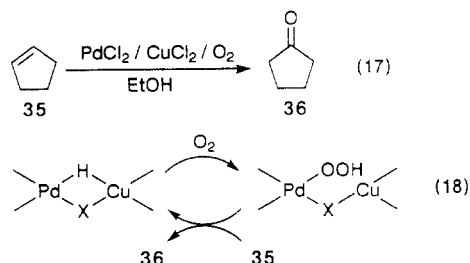
acetalization. Regardless of the structural variance in diols, the reaction proceeds smoothly under the conditions of using PdCl₂ as catalyst in the presence of CuCl and O₂ (1 atm) in dimethoxyethane (DME). Methyl acrylate, acrylonitrile, styrene, and α -cyanoallyl acetate can be converted into the corresponding terminal acetals. The first enantioselective acetalization of alkenes has been performed with prochiral olefins. Thus, the reaction of methyl methacrylate with homo-chiral diol 23 gives acetal 24 (25%) in 20% de. Similarly, α -methylene- γ -butyrolactone affords 25 (61%, 4% de).



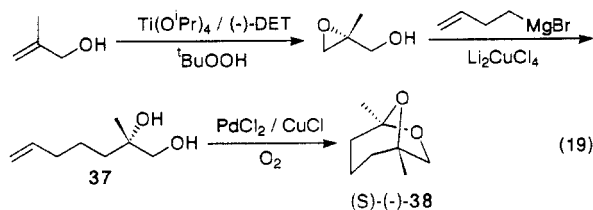
Vinyl ketones are likewise acetalized; however, Michael adducts such as 27 are formed as byproducts (eq 12). Addition of a base such as Na₂HPO₄ suppresses the formation of byproducts completely. In turn, Michael adducts can be obtained exclusively, when

- (40) For related reactions, see: (a) Hunt, D. F.; Rodeheaver, G. T. *Tetrahedron Lett.* 1972, 3595. (b) Lee, H. B.; Henry, P. M. *Can. J. Chem.* 1976, 54, 1726. (c) Alyea, E. C.; Dias, S. A.; Ferguson, G.; McAlees, A. J.; McCrindle, R.; Roberts, P. J. *J. Am. Chem. Soc.* 1977, 99, 4985.

ceeds without CuCl_2 , when $\text{PdCl}_2(\text{N,N-dialkylacetamide})_2$ complex is used as the catalyst.⁴⁶ The O atom transfer to olefin seems to occur by a hydroperoxide species consisting of Pd and Cu (eq 18). The involvement of Pd-OOH species has also been proposed in the ketonization of 1-octene by using $\text{PdCl}_2\text{-BiCl}_3\text{-LiCl}$ in ethanol.⁴⁷



Synthetic Aspects. The homochiral acetals derived from the present reaction serve as chiral auxiliaries in the recently developed methods of asymmetric synthesis.^{48,49} Intramolecular acetalization of alkenyl diols is valuable. Typically, the shortest synthesis of natural (*S*)-(-)-frontalin (38) has been accomplished as shown in eq 19.⁵⁰ Enantioselective epoxidation of β -methallyl



(45) (a) Takehira, K.; Hayakawa, T.; Orita, H.; Shimizu, M. *The Role of Oxygen in Chemistry and Biochemistry*; Ando, W., Moro-oka, Y., Eds.; Elsevier: Amsterdam, 1988; pp 307-310. (b) Takehira, K.; Orita, H.; Oh, I. W.; Leobardo, C. O.; Martinez, G. C.; Shimidzu, M.; Hayakawa, T.; Ishikawa, T. *J. Mol. Catal.* **1987**, *42*, 247.

(46) Takehira, K.; Hayakawa, T.; Orita, H. *Chem. Lett.* **1985**, 1835.

(47) Brégeault, J. M.; Faraj, M.; Martin, J.; Martin, C. *Nouv. J. Chim.* **1987**, *11*, 337.

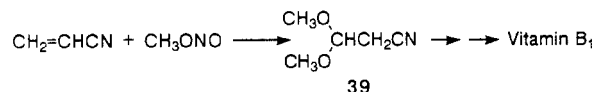
(48) (a) Bartlett, P. A.; Johnson, W. S.; Elliott, J. D. *J. Am. Chem. Soc.* **1983**, *105*, 2088. (b) Mori, A.; Fujiwara, J.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1983**, *24*, 4581.

(49) For a review, see: Alexakis, A.; Mangeney, P.; Ghribi, A.; Marek, I.; Sedrani, R.; Guir, C.; Normant, J. *Pure Appl. Chem.* **1988**, *60*, 49.

(50) (a) Hosokawa, T.; Makabe, Y.; Shinohara, T.; Murahashi, S.-I. *Chem. Lett.* **1985**, 1529. (b) For related reactions, see: Byrom, N. T.; Grigg, R.; Kongkathip, B.; Reimer, G.; Wade, A. R. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1643. Kongkathip, B.; Sookkho, R.; Kongkathip, N. *Chem. Lett.* **1985**, 1849.

alcohol (44%) followed by copper-catalyzed stereoselective ring opening gave dihydroxyalkene 37 (85%). Intramolecular acetalization of 37 with PdCl_2 catalyst (CuCl-O_2 , triglyme, 50 °C) gave a 76% yield of (*S*)-(-)-38 in 92% ee.

Recently, acetalization of acrylonitrile with methyl nitrite in the presence of PdCl_2 catalyst⁵¹ has been exploited for an industrial process, and 2-(methoxymethylene)-3,3-dimethoxypropanenitrile⁵² derived from acetal 39 has been utilized as a starting material for the synthesis of vitamin B₁.



Concluding Remarks

In this Account, we have shown that, in the Wacker-type oxidation, the formal oxidation state of palladium(II) remains constant throughout the reaction and that the Pd-OOH species derived from the oxygenation of the Pd-H species by O₂ is the active catalyst. Although a few metal hydroperoxide complexes have been characterized,⁵³ understanding of their role in catalysis is of importance in view of the activation of molecular oxygen⁵⁴ and will certainly be the subject of a further study. The intramolecular version of the Wacker reaction provides a unique approach to preparation of various heterocycles. The Pd(II)-catalyzed acetalization of alkenes with diols is also a promising process for the synthesis of optically active acetals and aldehyde derivatives.

(51) (a) Matsutame, S.; Uchiumi, S.; Iwai, H. *Japan Kokai* **1983**, 58-21636. (b) Uchiumi, S.; Iwai, H.; Abe, K.; Matsunaga, H. *Japan Kokai* **1981**, 56-5429.

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(53) (a) Strukul, G.; Ros, R.; Michelin, R. A. *Inorg. Chem.* **1982**, *21*, 495. (b) Morivillo, A.; Bressan, M. *J. Organomet. Chem.* **1987**, *332*, 337 and references cited therein.

(54) (a) Groves, J. T.; Watanabe, Y. *J. Am. Chem. Soc.* **1988**, *110*, 8443 and references cited therein. (b) Also, see: Valentine, J. S.; Burstyn, J. N.; Margerum, L. D. *Oxygen Complexes and Oxygen Activation by Transition Metals*; Martell, A. E., Sawyer, D. T., Eds.; Plenum Press: New York, 1988; pp 175-187.