New Aspects of Oxypalladation of Alkenes

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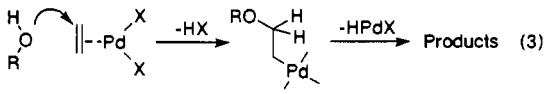
The discovery of the Wacker process, which produces acetaldehyde from ethylene in water by the use of $PdCl_2$ catalyst with $CuCl_2$ and O_2,[1,2] has led to the development of various Pd(II)-catalyzed oxidative functionalizations of alkenes.[3] Among these, the preparation of vinyl acetate from ethylene in acetic acid[4] and that of 1,4-diacetoxy-2-butene from butadiene[5] 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).

$$Pd^0 + 2CuX_2 \longrightarrow PdX_2 + 2CuX \quad (1)$$

$$2CuX + 2HX + \tfrac{1}{2}O_2 \longrightarrow 2CuX_2 + H_2O \quad (2)$$

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



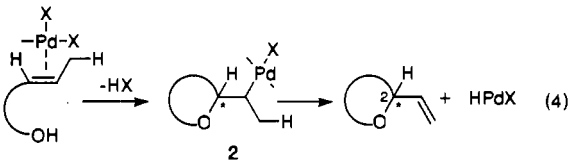
(3)

R: H, Ac 1

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 phenols[12–14] and unsaturated alcohols[15,16] by Pd(II) salts proceeds via oxypalladation adduct 2 as shown in eq 4. When the



(4)

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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 $PdCl_2$ 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 C_2 carbon are formed.[14a,16] If a chiral ligand is incorporated into the catalyst, asymmetry at the C_2 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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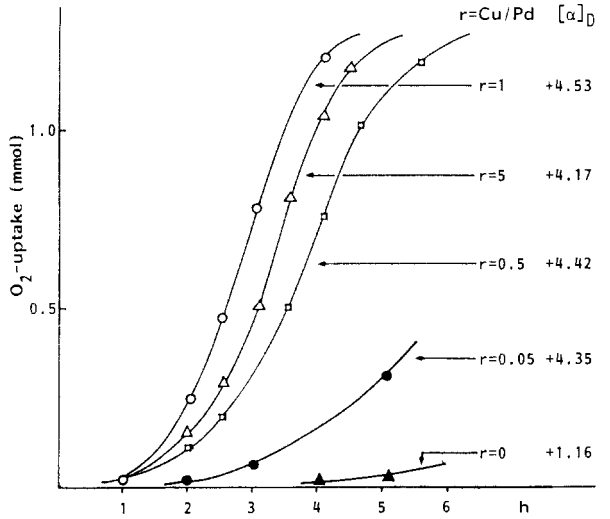
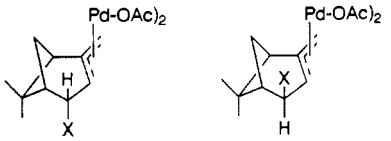


Figure 1. Progress of the catalytic reaction of *trans*-**5** (R = H) performed by using various ratios of Cu/Pd and the $[\alpha]_D$ values of the products **6** (R = H) measured after completion of the reaction. Reaction conditions: 2.5 mmol of *trans*-**5** (R = H), 0.125 mmol of complex **3a**, and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

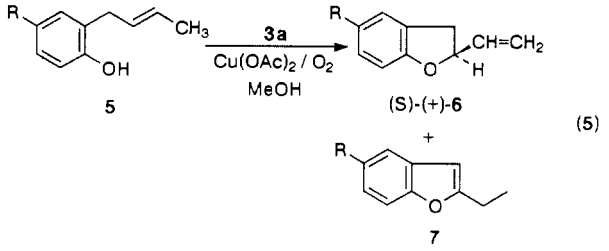
complexes such as **3** leads to an asymmetric version of the cyclization as mentioned below.



3a : X = H
3b : X = OAc
3c : X = OMe

4b : X = OAc
4c : X = OMe

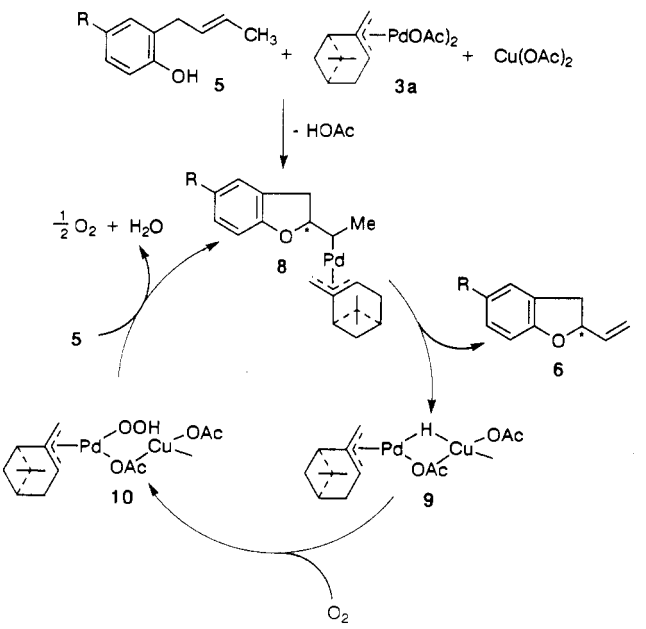
The cyclization of *trans*-2-(2-butenyl)phenols **5** with $[(\eta^3\text{-pinene})PdOAc]_2$ (**3a**, X = H) (10 mol %) in the presence of $Cu(OAc)_2$ and O_2 (1 atm) gives (*S*)-(+)-2,3-dihydro-2-vinylbenzofuran (**6**) as the prevailing enantiomer (18% ee; R = H) along with **7** (eq 5).[9] Al-



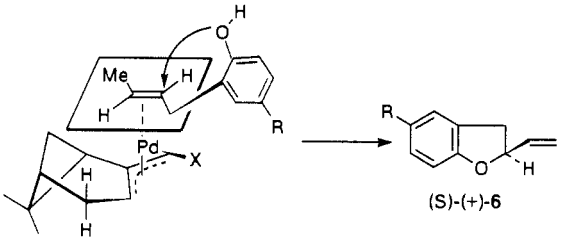
(5)

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 $Cu(OAc)_2$ 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

Scheme I

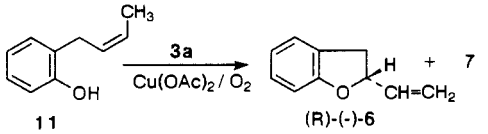


Scheme II



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 peroxo 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 = 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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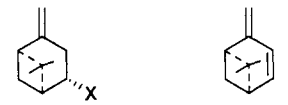
Table I
Asymmetric Cyclization of 5

substrate 5, R	oxidizing agent	cyclized product: yield, %	product ratio, 6:7	% ee
4-OMe	*t*-BuOOH	19	86:14	22
	$Cu(OAc)_2$–O_2	44	83:17	26
4-Me	*t*-BuOOH	34	82:18	18
	$Cu(OAc)_2$–O_2	76	83:17	21
4-H	*t*-BuOOH	52	82:18	17
	$Cu(OAc)_2$–O_2	77	83:17	18
4-Cl	*t*-BuOOH	54	87:13	4.5
	$Cu(OAc)_2$–O_2	72	90:10	6.0
4-COMe	*t*-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

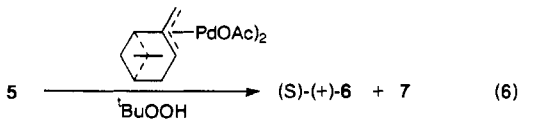


12a: X=H
12b: X=OAc
12c: X=OMe

13

$Pd(OAc)_2$ and NaCl in AcOH or Na_2PdCl_4 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]

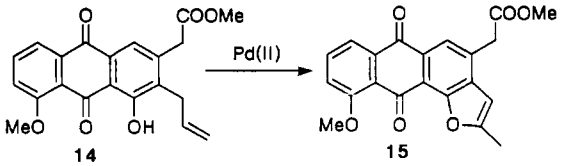
tert-Butyl hydroperoxide serves as an oxidizing agent in place of the combination of O_2 and $Cu(OAc)_2$ (eq 6).[20,21] The two catalytic systems (eqs 5 and 6) show



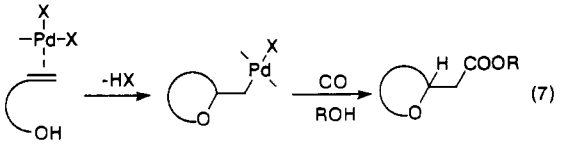
(6)

remarkably similar results, as shown in Table I. The enantioselectivity decreases in accordance with the electronic properties of substituents R on the phenoxy group ($OCH_3 > CH_3 > Cl > COCH_3$), 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 heterocycles. The synthesis of benzofuran **15** of the aklavinone system from 2-allyphenol **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-



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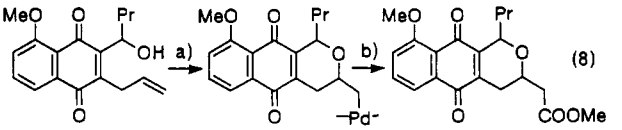
palladation–carbonylation sequence shown in eq 8 serves as a useful strategy for the synthesis of deoxyfrenolicin (**16**) and related compounds.[29a,b] Cyclizations



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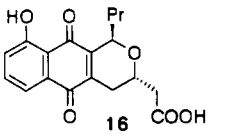
a) $PdCl_2(MeCN)_2$ / $CuCl_2$, b) CO / MeOH



of alkenyl amines[30-32] give various nitrogen-containing heterocycles such as indoles[30a] and indoloquinone **17**.[30e] 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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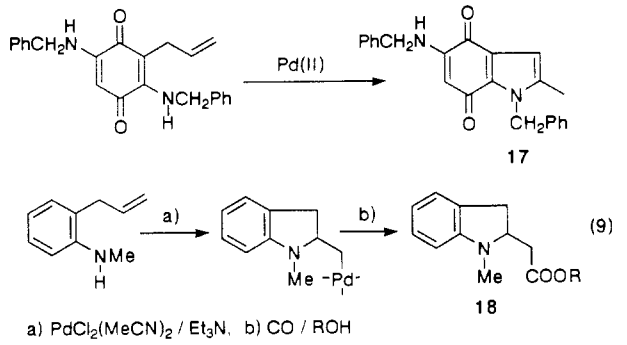
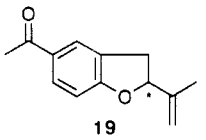
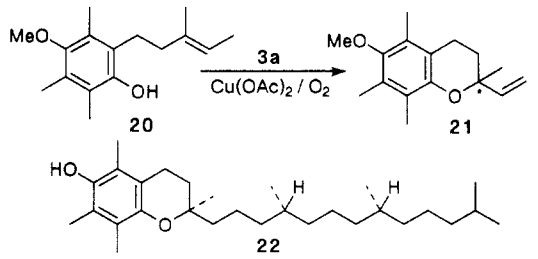


(*R*)-tremetone (**19**), which induces "tremble" in cattle

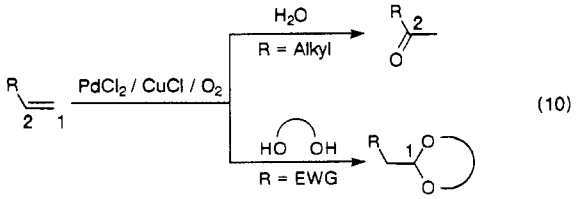


and "milk sickness" in higher animals and humans, can thus be derived from optically active 2-vinyl-2,3-dihydrobenzofuran (**6**) (R = H).[18a] Asymmetric cyclization of pentenylphenol **20** gives an 80% yield of chroman **21** (10% ee), which corresponds to the chroman moiety of α-tocopherol (**22**)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



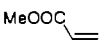
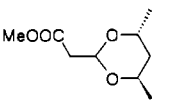
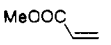
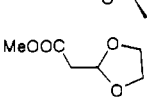
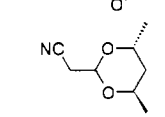
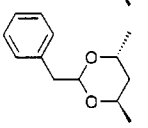
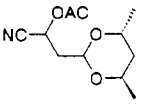
Acetalization of Alkenes

The Pd(II)-catalyzed oxidation of terminal alkenes bearing alkyl groups with water[2,36] and alcohols[37] produces methyl ketones via the attack of oxygen nucleophiles at the nonterminal olefinic carbon (C_2). Formation of aldehydes and their derivatives via the attack at the terminal carbon (C_1) 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 C_1 carbon, to give acetals of aldehyde precursors (eq 10).[37] However, the reaction

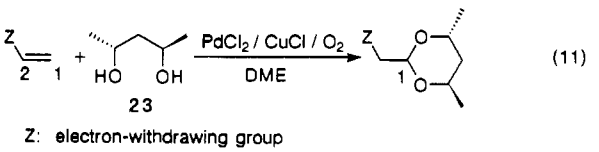


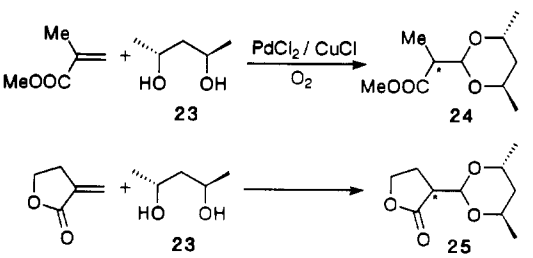
has so far not been evaluated as a synthetic tool.[40] We have found that the acetalization proceeds efficiently and provides a useful method for preparing chiral acetals from alkenes, if optically active diols such as (*R*,*R*)-2,4-pentanediol (**23**) are used as nucleophiles (eq 11).[10,11] Given 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 $PdCl_2$ as catalyst in the presence of CuCl and O_2 (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 homochiral diol **23** gives acetal **24** (25%) in 20% de. Similarly, α-methylene-γ-butyrolactone affords **25** (61%, 4% de).

Table II
Acetalization of Alkenes[a]

alkene	acetal	yield,[b] %
		79
		72
		45
		79
		81[c]

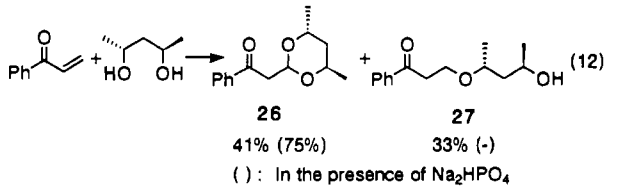
[a] Reaction conditions: alkene (2 mmol), diol (2 mmol), $PdCl_2$ (0.2 mmol), CuCl (2 mmol), DME (2 mL), 50 °C, O_2 (1 atm); see ref 11. [b] Isolated yield. [c] Unpublished results.



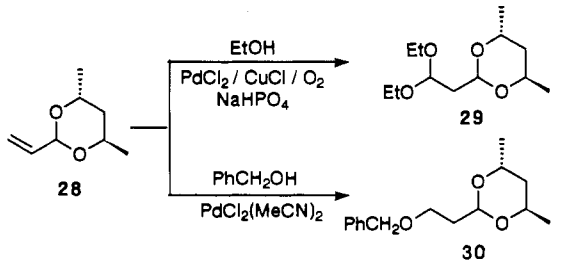


Vinyl ketones are likewise acetalized; however, Michael adducts such as **27** are formed as byproducts (eq 12). Addition of a base such as Na_2HPO_4 suppresses the formation of byproducts completely. In turn, Michael adducts can be obtained exclusively, when

(35) Hosokawa, T.; Kono, T.; Murahashi, S.-I., unpublished results.
(36) (a) Tsuji, J. *Synthesis* **1984**, 369. Tsuji, J.; Nagashima, H.; Nemoto, H. *Org. Synth.* **1984**, *62*, 9. (b) McQuillin, F. J.; Parker, D. G. *J. Chem. Soc., Perkin Trans. 1* **1974**, 809. (c) Clement, W. H.; Selwitz, C. M. *J. Org. Chem.* **1964**, *29*, 241.
(37) Lloyd, W. G.; Luberoff, B. J. *J. Org. Chem.* **1969**, *34*, 3949.
(38) Feringa, B. L. *J. Chem. Soc., Chem. Commun.* **1986**, 909.
(39) (a) Nogami, J.; Ogawa, H.; Miyamoto, S.; Mandai, T.; Wakabayashi, S.; Tsuji, J. *Tetrahedron Lett.* **1988**, *29*, 5181. (b) Bose, A. K.; Krishnan, L.; Wagle, D. R.; Manhas, M. S. *Tetrahedron Lett.* **1986**, *27*, 5955.
(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.

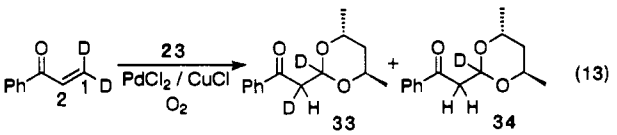


$PdCl_2(MeCN)_2$ is employed as a catalyst under argon.[41] Either acetal **29** (44%) or ether **30** (89%) can be thus obtained from acrolein acetal **28** by changing the reaction conditions.[41,42]



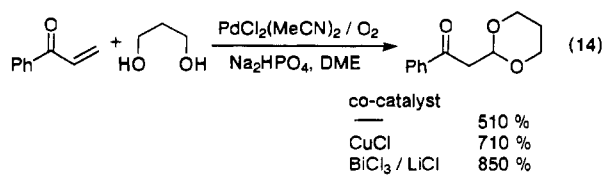
The formation of both acetals and Michael adducts can be envisioned as shown in Scheme III. Coordination of olefin to $PdCl_2$ followed by oxypalladation with the loss of HX (X = Cl) gives the σ-bonded intermediate **31**, where the oxygen nucleophile prefers to attack the more electron deficient carbon of olefin. Elimination of PdHX gives enol ether **32**, which undergoes cyclization to give the acetal. Protonolysis of intermediate **31** with HCl affords the Michael adduct. The resulting PdHX reacts with O_2 to give Pd–OOH species, thereby completing the catalytic cycle. The principal feature of the catalysis is identical with that shown in Scheme I.

Involvement of Pd–H species is verified by d-scrambling in the acetalization of $PhCH{=}CD_2$ and $PhCOCH{=}CD_2$. In particular, the acetalization of $PhCOCH{=}CD_2$ with **23** gives **33** and **34** (1:1) with 1,2-deuterium migration (eq 13), indicating that elimination

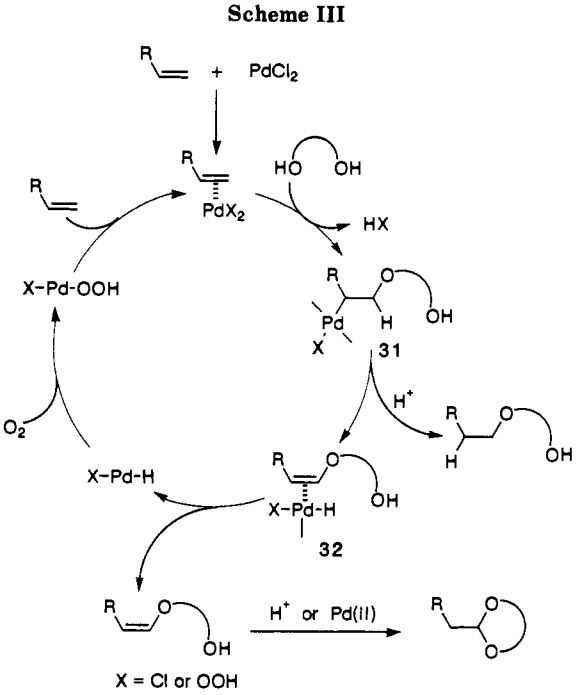


and readdition of Pd–H(D) take place reversibly between intermediates **31** and **32** in Scheme III.

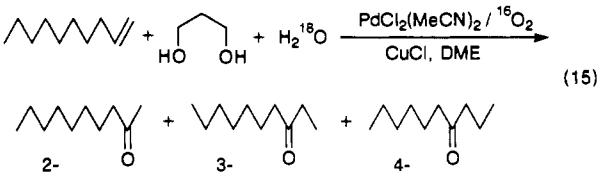
If the PdHX species decomposes into Pd(0) and HX, the catalysis may be described as the conventional redox couple (eqs 1 and 2). However, in the presence of base, the Michael adduct is not formed because of the capture of HX. Since eq 2 requires HX, the redox catalysis (eqs 1 and 2) is unlikely in the present acetalization. The following fact provides firm evidence to support the mechanism presented here. Even in the absence of copper salts, acetalization of vinyl ketones with 1,3-propanediol proceeds catalytically (eq 14). A



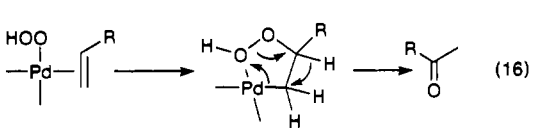
Scheme III



combination of $BiCl_3$ and LiCl in place of CuCl also results in catalytic acetalization.[43] Accordingly, a bimetallic catalyst consisting of Pd and Cu (or Bi), similar to that shown in Scheme I, must participate in the reaction. In the catalysis of Scheme III, O atom transfer from Pd–OOH species to olefins does not occur, and the hydroperoxo anion acts as a leaving ligand. In this regard, the following fact is noteworthy. The reaction of 1-decene with 1,3-propanediol in the presence of $H_2{}^{18}O$ results in the predominant formation of 3- and 4-decanones arising from isomerization of the carbon–carbon double bond followed by oxidation (eq 15).



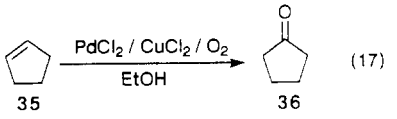
Incorporation of ^{18}O into the decanones is not high (~35% in each of 2-, 3-, and 4-decanones).[43] Neither nucleophilic attack of water ($H_2{}^{18}O$) on the olefin nor hydrolysis of the corresponding acetals accounts for this observation. Therefore, the reaction must involve the O atom transfer to olefin from Pd–OOH species derived from Pd–H species and molecular oxygen (eq 16). The pseudoperoxypalladation process shown in eq 16 has been demonstrated by Mimoun.[44a]



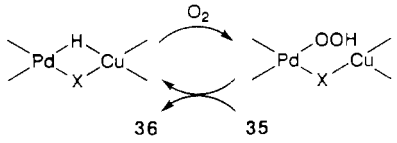
It has been reported that cyclopentene (**35**) is readily oxidized into cyclopentanone (**36**) in ethanol by using a catalyst system of $PdCl_2$–$CuCl_2$–O_2, accompanied by cooxidation of ethanol (eq 17).[45] The oxidation pro-

(41) Hosokawa, T.; Shinohara, T.; Ooka, Y.; Murahashi, S.-I. *Chem. Lett.* **1989**, 2001.
(42) Hosokawa, T.; Yagi, T.; Ataka, Y.; Murahashi, S.-I. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3380.
(43) Hosokawa, T.; Ataka, Y.; Murahashi, S.-I. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 166.
(44) (a) Mimoun, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 734. (b) Also, see: Muzart, J. *Bull. Soc. Chim. Fr.* **1986**, *II*, 65.

ceeds without $CuCl_2$, when $PdCl_2$(*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 $PdCl_2$–$BiCl_3$–LiCl in ethanol.[47]

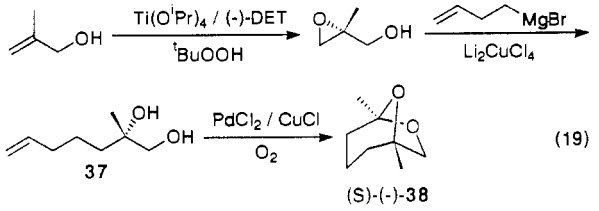


(17)



(18)

Synthetic Aspects. The homochiral acetals derived from the present reaction serve as chiral auxiliaries in the recently developed methods of asymmetric synthesis.[48,49] Intramoleclar 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



(19)

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

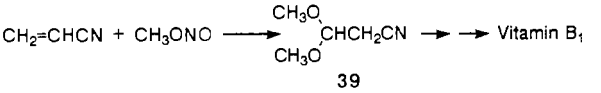
(48) (a) Bartlett, P. A.; Johnson, W. S.; Elliott, J. D. *J. Am. Chem. Soc.* **1983**, *105*, 2088. (b) Mori, A.; Fujiwara, J.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1983**, *24*, 4581.

(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 $PdCl_2$ catalyst[51] has been exploited for an industrial process, and 2-(methoxymethylene)-3,3-dimethoxypropanenitrile[52] derived from acetal **39** has been utilized as a starting material for the synthesis of vitamin B_1.



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 O_2 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 oxygen[54] 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.

(52) Fujii, K.; Nishihira, K.; Sawada, H.; Tanaka, H.; Nakai, M.; Yoshida, H.; Inoue, K. *Japan Kokai* **1984**, 59-46255.

(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.