Palladium(II)-Catalyzed Asymmetric Oxidative Cyclization of 2-Allylphenols in the Presence of Copper(II) Acetate and Molecular Oxygen. Study of the Catalysis of the Wacker-Type Oxidation

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Abstract: The intramolecular oxidative cyclization of *trans*-2-(2-butenyl)phenol (**2**) using (+)-(3,2,10-η-pinene)palladium(II) acetate (**1**) in the pressure of $Cu(OAc)_2$ and O_2 has been studied in order to gain insight into the catalysis of the Wacker-type oxidation. The main results obtained are as follows: (1) the catalytically active Pd(II) species which is different from complex **1** is formed during the reaction, (2) the chiral pinanyl ligand is retained by the catalyst throughout the reaction, and (3) the catalyst consists of copper and palladium linked with an acetate bridge. These results cannot be accounted for by the conventional Wacker-type catalysis involving the reoxidation of palladium(0). A hydroperoxopalladium(II) species coupled with copper(II) acetate is most likely the active catalyst in the present reaction. A mechanism for the enantioselection is also described in comparison with the results obtained by the oxidative cyclization of *cis*-2-(2-butenyl)phenol.

Since the oxidation of ethylene to acetaldehyde by $PdCl_2$ has been exploited industrially as the Wacker process,[1] a wide variety of organic reactions using palladium has been developed.[2] Of these, much attention has been devoted to the reaction of olefins with nucleophiles such as water,[3] acetate,[4] methanol,[5] and amine[6] in the presence of Pd(II),[7] and the mechansim has been extensively studied by kinetics[8] as well as product analyses.[4,9,10] In such Wacker-type reactions, the Pd(II) is reduced to Pd(0) and hence the reactions are not catalytic. In catalytic reactions where Cu(II) and O_2 are used, the catalysis of these reactions has been frequently described (eq 1 and 2) as the reoxidation of Pd(0) by Cu(II).

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

$$2CuX + 2HX + {}^1/_2O_2 \rightarrow 2CuX_2 + H_2O \quad (2)$$

Thus, it has been widely believed that the oxidation state of palladium in the Wacker-type catalysis changes from Pd(II) → Pd(0) → Pd(II).

Intramolecular versions of the Wacker-type reaction provide useful methods for preparing various heterocyclic compounds.[11,12] During the course of our investigation, we have found that the asymmetric cyclization of 2-allylphenols leading to optically active 2,3-dihydrobenzofurans is catalyzed by chiral Pd(II) complexes in the presence of Cu(II) and O_2.[13] This reaction has the advantage that the optical rotation of products can serve as a probe to disclose the nature of reactive Pd(II) species. Using this technique, we have shown that the Wacker-type catalysis (eq 1 and 2) involving the reoxidation of Pd(0) is not operative in the Pd(II)-catalyzed cyclization of 2-(2-butenyl)phenol, but the formal oxidation state of Pd(II) remains constant throughout the reaction. We now describe a detailed study of this subject and a new aspect of the Wacker-type catalysis. The present reaction is the first example of the asymmetric Wacker-type oxidation and the rarely used metal-catalyzed asymmetric oxidation of olefins.[14] In view of its significance, a mechanistic picture for this enantioselectivity is also reported.

Table I. Solvent Effect on Asymmetric Cyclization of *trans*-2

solvent	time,[a] h	cyclized products: yield,[b] %	cyclized products: product ratio 3/4	$[\alpha]_D$ of 3 (CCl_4), deg
benzene	312	62	63/37	+3.94
THF	30	77	56/44	+3.35
chloroform	142[c]	43	63/37	+3.18
acetic acid	94	59	72/28	+4.90
methanol	4.5	77	83/17	+4.53
methanol/water (95/5 v/v)	4.0	72	89/11	+3.78

[a] Reaction time required for >98% completion, unless otherwise noted. [b] Isolated yield. [c] 72% completion.

Results

Catalytic Reaction of *trans*-2-(2-Butenyl)phenol. The chiral catalyst, (+)-(η^3-pinene)palladium(II) acetate (**1**), employed for the present study was prepared by treatment of the corresponding chloride complex with AgOAc. The chloride complex was synthesized by the reaction of (−)-β-pinene and $Pd(OAc)_2$ followed by addition of NaCl.[15]

The cyclization of *trans*-2-(2-butenyl)phenol (**2**, trans/cis = 95/5) was performed in methanol solution containing complex

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(7) For comprehensive reviews, see: Henry, P. M. "Palladium Catalyzed Oxidation of Hydrocarbon", D. Reidel: Holland, 1980; pp 44-223.

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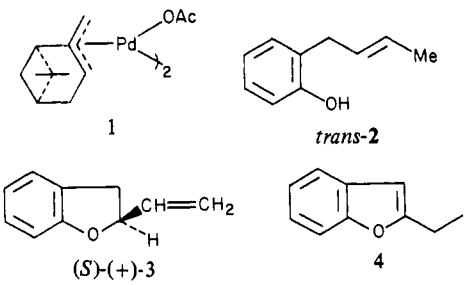

1 *trans*-**2** (*S*)-(+)-**3** **4**

1 (2.5×10^{-2} M as a dimer) and $Cu(OAc)_2$ in a ratio of Pd/Cu/**2** = 1/1/10 at 35 °C under O_2 (1 atm). No precipitation of metallic palladium appeared until the reaction was complete (4.5 h). A mixture of the cyclized products **3** and **4** (83/17) was obtained in 77–81% yield by the usual workup. The optical rotation of **3** isolated was $[\alpha]^{25}_D$ +4.53° (*c* 5.19, CCl_4) which corresponds to 18% optical purity of the *S* enantiomer. The optical yield and absolute configuration of **3** were determined by comparison with the known data of ethyl 2,3-dihydrobenzofuran-2-carboxylate (**5**),[16] after oxidation of **3** with potassium permanganate followed by esterification.

In benzene, THF, chloroform, and acetic acid, the reaction proceeds very slowly, although the $[\alpha]_D$ values of formed **3** are almost comparable (Table I). In coordinating solvents such as pyridine and DMF, no cyclization takes place. Accordingly, methanol appears to be the best solvent for both the reactivity and enantioselectivity observed. The presence of 5% water in methanol lowers the $[\alpha]_D$ value of **3** by 16%.

Among palladium(II) acetate complexes bearing optically active ligands such as (-)-carvone, (+)-calciferol, and *N*,*N*-dimethyl-(−)-α-phenylethylamine, **1** gives the best result (Experimental Section). Cupric acetate seems to be the best cocatalyst. Other cocatalysts such as cupric monochloroacetate, trifluoroacetate, and pivalate decrease the $[\alpha]_D$ value of **3** (vide infra).

Studies on Catalytically Active Species. We have first examined whether or not the pinanyl ligands of **1** remains intact during the reaction. As shown in Table II, the $[\alpha]_D$ value of **3** does not change with time,[17] except for the early stage of the reaction. Consequently, it is clear that the optically active pinanyl moiety is retained as a ligand on the catalyst throughout the reaction.

The apparent rate of the cyclization can be followed by measuring the consumption of O_2, since the uptake correlates well with the amount of cyclized products **3** and **4**. Half a mole of O_2 is consumed for the production of 1 mol of cyclized products (**3** + **4**). Under our standard conditions, the rate of the O_2 absorption is enhanced considerably after an induction period, and the cyclization reaches ~95% completion after 4 h. As shown in Figure 1, when the substrate (10 equiv) is newly added to the reaction mixture of 72% completion, the O_2 absorption immediately starts again, and the cyclization is complete within 2.5 h. These results clearly indicate that a highly active catalyst, which is different from the complex **1**, is formed during the reaction. The addition of the product **3** to intermediate reaction mixture at ~50% completion has no effect on the rate of O_2 uptake, indicating that the active catalyst is not derived from the product. It is to be noted that neither isomerization of **3** into the more stable isomer **4** nor racemization of optically active **3** takes place under the reaction conditions.

The O_2 uptake curves (Figure 2) show that as the relative ratio of added $Cu(OAc)_2$ to complex **1** increases, the rate of O_2 absorption becomes faster and reaches a maximum when Cu/Pd = ~1. A slower rate is observed in the presence of excess amounts of Cu(II) (Cu/Pd = 5).[18] In contrast, the $[\alpha]_D$ values of **3** are approximately constant if the ratio of Cu/Pd is larger than 0.05. Therefore, the active catalyst controlling this reaction must be a Pd–Cu coupled species with the chiral ligand.

The stoichiometric reaction of *trans*-**2** with complex **1** was next examined to gain further insight into the reactive species. Although the detailed data are given in the experimental section, the following remarks are noteworthy. (1) In the absence of both $Cu(OAc)_2$ and O_2, the rate of cyclization is very slow (71 h for >97% completion) and precipitation of metallic palladium

Table II. Analysis of Products with Time in the Catalytic Reaction of *trans*-**2** with Complex **1** and $Cu(OAc)_2$[a]

reaction time, h	cyclized products: yield,[b] %	cyclized products: product ratio[c] 3/4	$[\alpha]_D$ of 3 (CCl_4), deg
2.2	10	82/18	+2.50
3.0	22	82/18	+2.83
3.5	36	83/17	+4.28
4.0	52	81/19	+4.43
4.5	76	82/18	+4.32
5.7	81[d]	83/17	+4.39

[a] The reaction conditions shown in the text. [b] Yields were determined by GLC using biphenyl as an internal standard. It is to be noted that the presence of biphenyl somewhat lowers the rate of cyclization. [c] The ratio was determined from the reaction mixture by GLC. [d] Isolated yield.

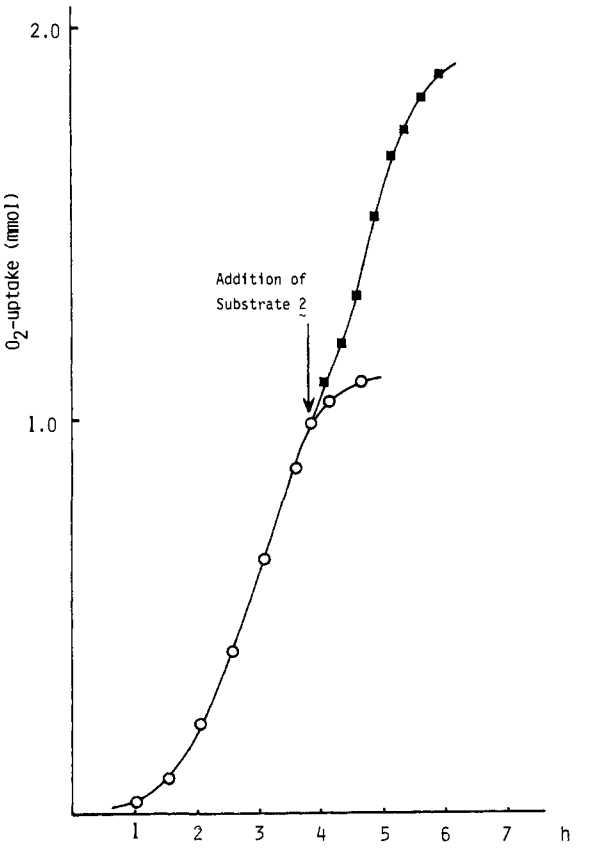

Figure 1. Plots of the O_2 uptake vs. time in the catalytic cyclization of *trans*-**2** (2.5 mmol) in the presence of complex **1** (0.125 mmol) and $Cu(OAc)_2$ (0.25 mmol) in MeOH (5 mL) at 35 °C under O_2 (1 atm). The curve of (■) was obtained by addition of the substrate (2.5 mmol) into the reaction mixture when the first reaction was 72% complete in 3.5 h.

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(17) The data are somewhat different from those in our initial report,[13b] although the outcome is essentially invariant. This is largely due to the difference in the trans/cis composition of the substrate used. Previous data were deduced from the substrate of its composition being 89/11, which also contained 1% of phenol as well as 0.5% of 2-(2-methylallyl)phenol. The substrate employed for the present experiment consisted of 95% trans and 5% cis isomer. The overall rate of cyclization has been also found to become slower by ~1.2 times if the contamination of phenol is ~1%.

(18) Since the apparent rate of O_2 uptake is not lowered by decreasing the velocity of stirring (~90 rpm), the O_2 absorption is not controlled by the rate of diffusion of O_2 into the solution.

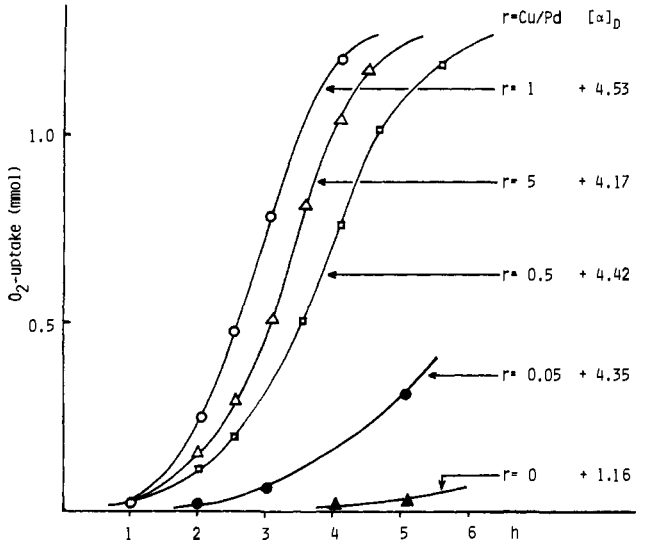


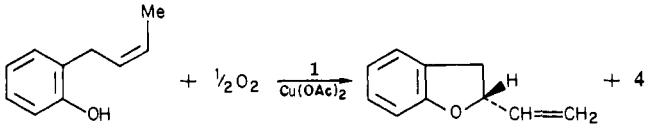
Figure 2. Progress of the catalytic reaction of *trans*-**2** performed by using various ratios of Cu/Pd and the $[\alpha]_D$ values of the product **3** measured after the completion of reaction. Reaction conditions: 2.5 mmol of *trans*-**2**, 0.125 mmol of complex **1**, and an appropriate amount of $Cu(OAc)_2$ at 35 °C in MeOH (5 mL) under O_2 (1 atm).

gradually occurs. The pinanyl ligand of **1** is converted into (−)-α-pinene (**6**) and (+)-dehydro-β-pinene (**7**) (45/55) along with

6 **7**

a trace amount of β-pinene. (2) In the presence of either $Cu(OAc)_2$ or O_2, no significant increase in the rate is observed. However, the use of both $Cu(OAc)_2$ and O_2 accelerates the reaction remarkably, and the cyclization is complete within 2 h. Under the conditions, more than 50% of unchanged starting complex **1** is recovered after completion of the cyclization. These results indicate that a combination of $Cu(OAc)_2$ and O_2 is responsible for the generation of a highly active species.

Catalytic Reaction of *cis*-2-(2-Butenyl)phenol. The enantioselective reaction of *cis*-**2** was investigated in comparison with that



cis-**2** (R)-(−)-**3**

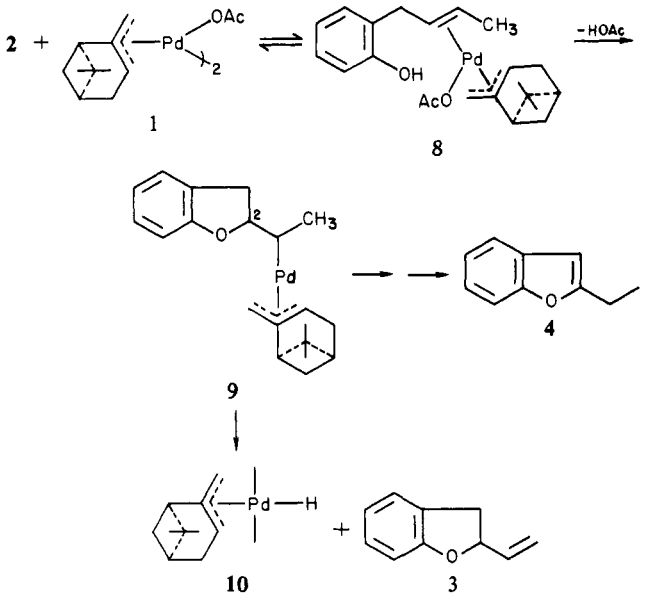
of the trans isomer. The cyclization of *cis*-**2** gave **3** with $[\alpha]_D$ = −0.16° along with **4** (**3**/**4** = 89/11) in 62% isolated yield. The *R* configuration of the major enantiomer **3** was opposite to that of *trans*-**2**, although the optical yield was only 0.7%. The difference in optical yields between *trans*- and *cis*-**2** is ascribed to the geometrical difference in the substrate. Namely, no cis-trans isomerization of the substrate occurs during the reaction, and the chiral pinanyl ligand remains intact also in the case for *cis*-**2**. The $[\alpha]_D$ value of −0.20° at the stage of ~50% completion of the reaction is nearly identical with that observed at the end of the reaction.

The relative reactivity of *cis*- and *trans*-**2** was briefly examined and found that the catalytic cyclization of *cis*-**2** was complete in 3.5 h, while the *trans*-**2** was only 72% complete during the same period. The relative reactivity of *cis*-**2**/*trans*-**2** was estimated to be ~1.2 when a large excess of **1** (Pd/substrate = 10/1) was used in the absence of O_2.

Discussion

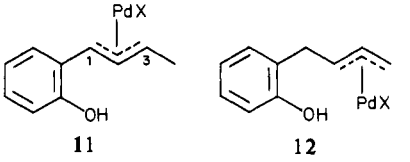
The results described in this paper constitute firm evidence that a catalytically active species which is different from the original

Scheme I



complex **1** is formed during the reaction and that the catalyst retains the chiral pinanyl ligand throughout the reaction. Before discussing the structure of this catalyst, the basic reaction sequences in the Wacker-type reaction will be considered.

As depicted in Scheme I, reversible coordination of the substrate to the dimeric complex **1** affords the monomeric palladium(II) acetate **8**. Intramolecular nucleophilic attack of the phenoxy group on the Pd(II)-complexed olefin in **8** leads to the oxypalladation intermediate **9**.[19] The acetate ligand of palladium is removed as acetic acid in this step. Elimination of the hydrogen from the methyl group of **9** by Pd(II) gives the product **3** and the Pd–H species **10**. The palladium hydride elimination from the C-2 carbon of **9** followed by rearrangement leads to the product **4**. In these steps, the role of $Cu(OAc)_2$ is not clear; however, the OAc must interacts with Pd(II) because of its readily ability to form a variety of bridging ligands between metal atoms.[20] The intervention of possible alternate π-allylpalladium intermediates[21] such as **11** and **12** is excluded because of the following reasons.



11 **12**

Intramolecular nucleophilic attack of the phenoxy group on the π-allyl moiety of **11** (C_1 or C_3) cannot lead to products **3** and **4**. The latter intermediate **12** may explain the formation of **3** and **4** if **3** isomerizes to **4** under the reaction conditions; however, no such isomerization was observed.

The generation of a catalytically active species containing the chiral pinanyl ligand is now rationalized by the sequences outlined in Scheme II where the crucial step is the oxygenation of the Pd–H bond in **10**. The (η^3-pinene)palladium(II) hydroperoxide **13** thus formed is most likely a Pd–Cu bimetallic complex linked with μ-acetate and -peroxo ligands, since the generation of active catalyst requires $Cu(OAc)_2$ as well as O_2. The presence of acetate bridge in **13** is supported by the observation that the reactivity

(19) A very closely related oxypalladation intermediate is trapped by the carbonylation of 2-allylphenol using a catalytic system of $PdCl_2$–$CuCl_2$–NaOAc: Chiba, K.; Inotsume, N.; Mori, M.; Ban, Y. Abstracts, 25th Symposium on Organometallic Chemistry, Osaka, Japan, 1978, p 133.

(20) (a) Butcher, R. J.; Overman, J. W.; Sinn, E. *J. Am. Chem. Soc.* **1980**, *102*, 3276 and references cited therein. (b) Connor, J. A.; Jones, A. C. *J. Chem. Soc., Chem. Commun.* **1980**, 137.

(21) (a) Trost, B. M.; Metzner, P. J. *J. Am. Chem. Soc.* **1980**, *102*, 3572. (b) Frankel, E. N.; Rohwedder, W. K.; Neff, W. E.; Weisleder, D. *J. Org. Chem.* **1975**, *40*, 3247.

Scheme II

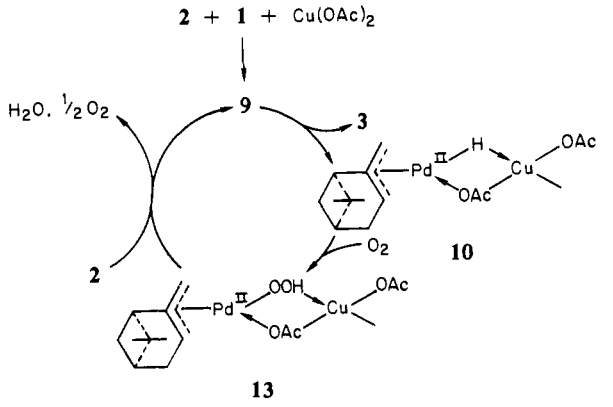


Table III. Effect of Copper(II) Carboxylate on Catalytic Reaction of *trans*-**2**[a]

Copper carboxylate	time,[b] h	cyclized products: yield,[c] %	cyclized products: product ratio 3/4	$[\alpha]_D$ of **3** (CCl_4), deg
$[(CH_3)_3CCOO]_2Cu$	13.5	67	80/20	+2.72
$(CH_3COO)_2Cu$	4.5	77	83/17	+4.53
$(CH_2ClCOO)_2Cu$	6.0	71	84/16	+3.82
$(CF_3COO)_2Cu$	6.5	72	80/20	+2.15
	(5.0)[d]	(40)	(78/22)	(+2.00)

[a] The reaction conditions shown in the text. [b] Reaction time required for >98% completion. [c] Isolated yield. [d] 41% completion.

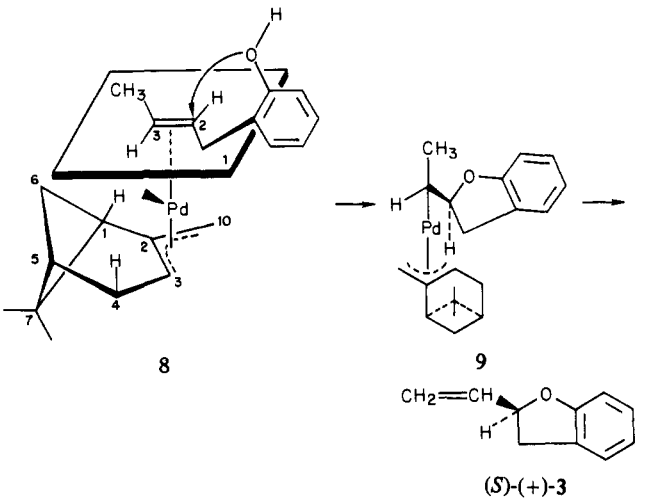
and enantioselectivity are influenced by both steric and electronic factors of carboxylate ligands of Cu(II) as shown in Table III The formulation of **13** as depicted in Scheme II is compatible with that of μ-peroxo-copper(II) acetate[22] derived from $Cu(OAc)_2$ and H_2O_2. The oxygenation of Pd–H bond is feasible since rhodium hydride complexes have been shown to react with O_2 to give hydroperoxorhodium complexes,[23] and such a process has been already invoked by us[11a] and other workers[24-26] in related reactions.

Coordination of the substrate to Pd(II) in **13** by cleaving the acetate bridge, followed by oxypalladation with the loss of HOOH again leads to the intermediate **9**, completing the catalytic cycle. The stoichiometry for the O_2 uptake observed is satisfied if HOOH decomposes to 0.5 O_2 an H_2O.

On the basis of Scheme II, other experimental facts are explained as follows. (1) The induction period shown in Figure 1 corresponds to the time required for generating the bimetallic species **13**. (2) Since the extent of its generation depends on the amount of added $Cu(OAc)_2$, the rate of the O_2 uptake changes as can be seen in Figure 2. (3) The presence of excess $Cu(OAc)_2$ would suppress the coordination of the substrate to Pd(II) in **13** or induce the collapse of μ-peroxo ligand of **13**,[27] resulting in rate retardation. (4) Finally, if Cu(II) serves as a transient oxygen carrier,[28] the oxygenation of the Pd–H bond would occur with greater efficiency in the bimetallic form of palladium and copper. This could account for the high catalytic activity in the presence of both $Cu(OAc)_2$ and O_2.

It should be noted from Scheme II that the formal oxidation state of Pd(II) remains constant which is different from the conventional Wacker process. However, considering that in the

Scheme III



stoichiometric reaction the pinanyl ligand of **1** is converted into (−)-α-pinene (**6**) and (+)-dehydro-β-pinene (**7**), one may argue that $Pd(OAc)_2$ regenerated from Pd(0) (eq 3 and 4) reacts with

$$Pd(0) + 2Cu(OAc)_2 \rightarrow Pd(OAc)_2 + 2CuOAc \quad (3)$$

$$2CuOAc + 2HOAc + {}^1/_2O_2 \rightarrow 2Cu(OAc)_2 + H_2O \quad (4)$$

either **6** or **7**, giving rise to a catalyst in the present reaction, because $Pd(OAc)_2$ readily reacts with (−)-β-pinene to give the chiral complex **1**. However, this possibility is rigorously ruled out by the following results. The catalytic reaction of *trans*-**2** with $Pd(OAc)_2$ in the presence of **6** does not induce chirality in **3**, while the use of **7** gives rise to (*R*)-(−)-**3** ($[\alpha]_D = -2.62°$), the configuration of which is opposite to that of the product of the parent reaction.

Enantioselectivity. The enantioselection observed in this reaction is readily accounted for by a stereochemical model involving π complexation. Inspection of molecular models[29] reveals that the arrangement illustrated in Scheme III gives the least steric hindrance between the substrate (*trans*-**2**) and the pinanyl ligand of **1**, wherein the substrate approaches palladium in such a way that the C-3 hydrogen of the *trans*-olefin faces the C-5 bridgehead carbon of the pinanyl ligand. Trans oxypalladation[9,10,11a] followed by Pd–H elimination affords the *S* enantiomer of **3**. In the case of *cis*-**2**, using the same model of opposite geometry (C-2 carbon of olefin) leads to the *R* enantiomer. The formation of the predominant enantiomer **3** obtained from *cis*- or *trans*-**2** is compatible with this scheme.

The enhanced reactivity observed with *cis*-**2**[30] reflects the fact that *cis*-olefins give more stable π complexes with Pd(II) in comparison with the trans isomers.[8a,31,32] Accordingly, the greater ability of *cis*-**2** to coordinate to Pd(II) may compensate for the steric repulsion between the substrate and the pinanyl ligand, resulting in a lower enantioselectivity in the cyclization of *cis*-**2**.

Experimental Section

The specific optical rotation was measured by using JASCO DIP-4 polarimeter with 1-dm long cell at room temperature. The GLC analysis was performed on a JEOL Model JGC-20KFP flame ionization chromatography by using a 1 m × 4 mm, 10% PEG 20M Celite column

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(30) A comparison of relative reactivities between *cis*- and *trans*-olefins leads to an implication on the picture of transition state.[31] A higher reactivity with *cis*-olefin in our reaction suggests a "reactant-like" transition state such as **8**. It is to be noted that our reaction resembles methoxypalladation (James, D. E.; Hine, L. F.; Stille, J. K. *J. Am. Chem. Soc.* **1976**, *98*, 1806) rather than hydroxypalladation[8b] or aminopalladation[31] where *trans*-olefins react faster than *cis*-olefins.
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under the conditions of injection temperature (200 °C) and column temperature (100–230 °C).

Palladium(II) acetate was prepared as reported previously.[11a] Cupric acetate (anhydrous) was purchased from Wako Pure Chemical Ind., Ltd., and dried at 80 °C (6mmHg) before use. Other copper(II) compounds were synthesized by the reported procedure.[33] β-Pinene was commercial reagent (Tokyo Kasei Kogyo Co., Ltd., 95% purity, $[\alpha]^{20}_D = -21°$ (neat)). *trans*-2-(2-Butenyl)phenol (**2**) was prepared by C-alkylation of phenol[34] with *trans*-1-chloro-2-butene (Tokyo Kasei). Since the commerically available "*trans*-1-chloro-2-butene" contains small amounts of its cis isomer and 3-chloro-1-butene, it has been difficult to obtain pure *trans*-2-(2-butenyl)phenol (**2**).[35] A fractional distillation (90–91 °C (6mmHg)) of the products which was obtained by the above reaction leads to a 95/5 mixture of *trans*- and *cis*-2-butenylphenol with reproducibility. The contamination of 2-(2-methylallyl)phenol was less than 0.5%. *cis*-2-(2-Butenyl)phenol was prepared with the same method by using *cis*-2-butenyl chloride.[36] In this case, a 97/3 mixture of *cis*- and *trans*-2-butenylphenol was obtained by a simple distillation (bath temperature 115–120 °C (6mmHg)), and the contamination of 2-(2-methylallyl)phenol was also less than 0.5%.

Preparation of Bis[acetoxy(3,2,10-η-pinene)palladium(II)] (1). Into a suspended solution of $Pd(OAc)_2$ (4.49 g, 20 mmol) in anhydrous methanol (100 mL) was added (−)-β-pinene (2.72 g, 20 mmol). After the resulted brown solution was stirred at room temperature for 10 min, sodium chloride (92.3 g, 39.4 mmol) was added into this solution. The mixture was further stirred for 30 min, and methanol was removed under reduced pressure. The residue was extracted with chloroform (2 × 50 mL), washed with saturated aqueous sodium chloride solution, and dried over $MgSO_4$. Removal of the solvent in vacuo afforded a yellow oil which was purified by Al_2O_3 column chromatography and then crystallized by addition of hexane to give bis[chloro(3,2,10-η-pinene)palladium(II)] (5.05 g, 91%). The spectroscopic properties of this compound were identical with those of the authentic sample prepared by the reported procedures.[37,38] The chloride complex was converted into the acetate complex **1** by treatment with AgOAc. Thus, a mixture of the chloride complex (2.806 g, 10.09 mmol) and AgOAc (1.837 g, 11.00 mmol) in chloroform (50 mL) was stirred for 30 min in the dark. After the resulting AgCl was filtered off, the solution was passed through a column of SiO_2 (12 g, 1.5 × 5 cm). A yellow solution eluted with chloroform was concentrated in vacuo to afford a yellow oil. Addition of hexane to this oil induced crystallization to give the acetate complex **1** (2.130 g, 70.2%) as yellow crystals: mp 125–127 °C dec; $[\alpha]^{25}_D = +48.35°$ (*c* 3.04, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.90 (m, H-3), 3.57 (s, anti H-10), 2.72 (s, syn H-10), 2.6–1.4 (m, other H), 2.02, 1.37, 0.98 (3 s, 3 Me). Anal. Calcd for $C_{24}H_{36}O_4Pd_2$: C, 47.93; H, 6.03. Found: C, 47.59; H, 6.11.

Typical Procedure for Catalytic Cyclization of *trans*-2-(2-Butenyl)-phenol (2) Using Complex 1 and Product Analysis. The acetate complex **1** (0.075 19 g, 0.125 mmol as a dimer) and $Cu(OAc)_2$ (0.045 40 g, 0.25 mmol) was placed in a 50-mL round-bottomed flask equipped with a three-way stopcock and a magnetic stirring bar and the flask immersed in a constant temperature bath (35 °C ± 0.2) was connected to a gas burette filled with O_2. After the flask was flashed with O_2, a solution of *trans*-**2** (trans/cis = 95/5, 0.370 g, 2.5 mmol) in anhydrous methanol (5 mL) was introduced into the reaction flask with stirring. The progress of reaction was followed by GLC analysis of aliquot samples and O_2-uptake measurement. After 4.5 h, GLC analysis of the reaction mixture showed that the substrate was >99% consumed and the products **3** and **4** were formed in the GLC ratio of 84/16 along with less than 2% of unidentified products. The O_2 uptake was 28 mL at this time. The reaction mixture was extracted with ether (3 × 50 mL), washed with water and aqueous sodium chloride solution, and dried over Na_2SO_4. After the solvent was removed in vacuo, the residue was allowed to pass through a short column of Al_2O_3 (3 g, 1.5 × 3 cm) by using hexane as the eluant. A mixture of products **3** and **4** (0.281 g, 77%) in the GLC ratio of 83/17 was obtained by Kugelrohr distillation (99–101 °C (7mmHg)). These products were collected together by preparative GLC (PEG-20M 10% 2 m, 160 °C) owing to their poor separation. The optical rotation of this mixture (82/18) was $[\alpha]_D = +4.49°$ (*c* 5.90,[39] CCl_4). The optically active **3** separated from **4** by preparative TLC (SiO_2, hexane/toluene = 4/1) was $[\alpha]_D = +4.53°$ (*c* 5.19, CCl_4) which corresponds to 18% optical yield (vide infra). The spectral data of **3** and **4** has been already reported.[40]

Table IV. Catalytic Cyclization of *trans*-**2** with Complex **1** Using Various Ratios of Cu/Pd[a]

ratio of Cu/Pd	time,[b] h	cyclized products: yield,[c] %	cyclized products: product ratio **3**/**4**	$[\alpha]_D$ of **3** (CCl_4), deg
0	72	47	73/27	+1.16
0.01	32	67	82/18	+3.72
0.05	22	74	83/17	+4.35
0.1	6.5	70	83/17	+4.45
0.3	6.5	66	83/17	+4.78
0.5	5.5	73	83/17	+4.42
1.0	4.5	77	83/17	+4.53
5.0	5.0	73	83/16	+4.17
10.0	5.0	53	84/16	+4.14

[a] The reaction conditions shown in the text. [b] Reaction time required for >98% completion. [c] Isolated yield.

The optical rotation of **3** was found not to be affected by the contamination of optically inactive **4**, since the solution of **3** containing **4** in a range of 5–45% in CCl_4 showed the $[\alpha]_D$ values virtually identical with those derived from a single compound. The $[\alpha]_D$ values derived from a mixture of **3** and **4** obtained by preparative GLC were thus reported in this paper.

A large scale experiment was performed by using 17.5 mmol of *trans*-**2** (2.590 g), 1.75 mmol of $Cu(OAc)_2$ (0.317 g), and 0.87 mmol of complex **1** (0.526 g) in 35 mL of anhydrous methanol. Biphenyl[41] (0.350 g) was in advance added into this mixture as internal standard for GLC analysis. At appropriate intervals, 3–9 mL of the reaction mixture were taken out, and the products **3** and **4** were isolated according to the procedure described above. Results are given in Table II.

Determination of Optical Yield. A solution of potassium permanganate (1.440 g, 9.1 mmol) in water (20 mL) was added with stirring into a solution of **3** (0.550 g, 2.4 mmol, $[\alpha]_D = +4.26°$ (*c* 5.99, CCl_4)) in acetone (10 mL) at such a rate that the temperature did not exceed over 30 °C, and the mixture was stirred for 1 h at room temperature. After the whole mixture was warmed at 50 °C for a few minutes, the resulting manganese dioxide was filtered off. The filtrate (pH 8) was acidified to pH 3–4 by 10% H_2SO_4 solution, and the products were extracted with ether, washed with water and saturated sodium chloride solution, and dried over Na_2SO_4. After removal of the ether, the resulting crude material (0.213 g) was dissolved in a mixture of anhydrous ethanol (40 mL) and benzene (40 mL) containing a few drops of concentrated H_2SO_4. The mixture was refluxed for 2 h while water was continuously withdrawn and extracted with ether (200 mL). The ethereal solution was washed with 5% $NaHCO_3$ solution and water and then dried over $MgSO_4$. After removal of the solvent, Kugelrohr distillation (182–184 °C (3mmHg)) gave ethyl 2,3-dihydrobenzofuran-2-carboxylate (**5**) (0.176 g, 26.8%) which was purified by preparative GLC (CW 20M 10% 1 m, 175 °C). The $[\alpha]_D$ value of this compound was +3.07 ± 0.05° (*c* 3.45, hexane), and its optical purity was 16.7% (±0.3) on the basis of the reported maximum rotation of (*R*)-(−)-**5** ($[\alpha]_D = -18.4°$ (*c* 0.935, hexane)).[16] Thus, the maximum rotation of (*S*)-(+)-2-vinyl-2,3-dihydrobenzofuran (**3**) can be estimated to be +25.5 ± 0.4° (CCl_4).

5: ^1H NMR (CCl_4) δ 1.28 (t, *J* = 7 Hz, Me), 3.7–3.1 (m, 2 H, H-3), 4.23 (q, *J* = 7 Hz, CH_2), 5.07 (dd, *J* = 10 and 8 Hz), 6.5–7.3 (m, 4 H, Ph). Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.42; H, 6.23.

Catalytic Cyclization Preformed at Different Ratios of Cu/Pd. The catalytic cyclization of *trans*-**2** was carried out by changing the amount of added $Cu(OAc)_2$ relative to the complex **1** under the conditions described in the typical procedure. Results are given in Table IV and Figure 2.

Stoichiometric Reaction. (1) In the Absence of $Cu(OAc)_2$ and under N_2. A homogeneous solution of *trans*-**2** (0.185 g, 1.25 mmol), complex **1** (0.376 g, 0.625 mmol), and biphenyl (0.025 29 g, internal standard for GLC) in anhydrous methanol (25 mL) was stirred at 35 °C under N_2. The yellow solution gradually changed to brown-black with the precipitation of metallic palladium. The substrate was 97% consumed after 71

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h, and a 58/42 mixture of the products **3** and **4** was formed in 37% yield along with at least three minor amounts of unidentified products. After usual workup, the organic products was isolated by means of a short column of Al_2O_3 using hexane (50 mL) as the eluant. GC–Mass analysis (SF 96 0.28 mm × 40 m, 70–180 °C) of this elution showed that (−)-α-pinene (**6**) and (+)-dehydro-β-pinene (**7**) were formed in a ratio of 45/55 with a negligible amount of β-pinene. Structure **7** was identified by comparison with the spectral data of the authentic sample prepared by the procedure described below.

(2) In the Absence of $Cu(OAc)_2$ and under O_2. The reaction was complete in 30 h, and a 57/43 mixture of **3** and **4** was formed in 50% yield. The $[\alpha]_D$ value of **3** obtained was +2.00°.

(3) In the Presence of $Cu(OAc)_2$ and under N_2. The reaction was complete in 24 h, and a 43/57 mixture of **3** and**4** was formed in 63% yield. The $[\alpha]_D$ value of **3** obtained was +3.86°.

(4) In the Presence of $Cu(OAc)_2$ and O_2. A homogeneous solution of *trans*-**2** (0.222 g, 1.5 mmol), the complex **1** (0.451 g, 0.75 mmol), and $Cu(OAc)_2$ (0.272 g, 1.5 mmol) was stirred at 35 °C under O_2 (1 atm). The substrate was completely consumed within 2 h. After usual workup, a 46/54 mixture of **3** and **4** was isolated in 51% yield, and the unreacted complex **1** was recovered as the corresponding chloride complex (0.226 g, 54%); the acetate ligand of **1** must be replaced by the chloride during the extraction process using saturated aqueous sodium chloride solution. The $[\alpha]_D$ value of **3** obtained was +4.22°.

Catalytic Cyclization of *cis*-2-(2-Butenyl)phenol. The reaction of *cis*-**2** was performed under the same conditions as those with *trans*-**2**. The progress of reaction was followed by the O_2 uptake and GLC. In this case, the cyclization was 99% complete in 3.5 h. After usual workup, a 89/11 mixture of **3** and **4** was isolated in 62% yield. The optical rotation of **3** isolated was $[\alpha]_D = -0.16$ and $[\alpha]^{25}_{365(Hg)} = -2.20°$ (*c* 4.55, CCl_4).

2-Methylene-6,6-dimethylbicyclo[3.1.1]hept-3-ene (7) (Dehydro-β-pinene). This compound was prepared from the acetate complex **1**, according to the recently reported procedure.[42] A mixture of **1** (2.41 g, 4 mmol) and triphenylphosphine (1.31 g, 5 mmol) in dry Me_2SO (40 mL) was stirred at 100 °C under Ar for 4 h. After usual workup, distillation (~40 °C (6mmHg)) gave **7** (0.24 g, 22%) as a single product: $[\alpha]^{21}_D = +106.4°$ (*c* 1.79, MeOH); ^1H NMR ($CDCl_3$) δ 0.87 (s, Me), 1.36 (s, Me), 1.40 (m, 1 H, H-7), 2.31 (m, 1 H, H-5), 2.50 (m, 1 H, H-7), 2.60 (m, 1 H, H-1), 4.66 (s, 2 H, $=CH_2$), 6.02 (d, J = 8 Hz, H-3), 6.31 (t, J = 8 Hz, H-4) (these resonances were in accordance with the reported values[43]) MS *m/e* (relative intensity) 134 (M^+, 12), 119 (43), 105 (12) 92 (82), 91 (100), 78 (17), 65 (5), 55 (14), 43 (17), 41 (15).

Pyrolysis of the complex **1** at 150–170 °C (0.07mmHg) also gave **7** along with with (−)-α-pinene (**6**) ($[\alpha]^{23}_D = -51.7°$ (*c* 1.13, CCl_4)) in a ratio of **6**/**7** = 36/64.

Catalytic Cyclization of *trans*-2 with $Pd(OAc)_2$ in the Presence of Dehydro-β-pinene (7) or α-Pinene (6). (+)-Dehydro-β-pinene (0.033 56 g, 0.25 mmol), $Pd(OAc)_2$ (0.056 13 g, 0.25 mmol), and $Cu(OAc)_2$ (0.045 40 g, 0.25 mmol) in anhydrous methanol (2.5 mL) were stirred at 35 °C for 10 min. To this mixture was added solution of *trans*-**2** (0.370 g, 2.5 mmol) in methanol (2.5 mL) under O_2 (1 atm). Progress of the cyclization was monitored by the O_2 uptake and GLC. After 6 h, the cyclization was complete and a 83/17 mixture of **3** and **4** were isolated in 41% yield. The $[\alpha]_D$ value of **3** obtained was −2.62° (*c* 3.43, CCl_4).

In the experiment performed by using (−)-α-pinene ($[\alpha]^{25}_D = -31.23$ (neat)), the cyclization was complete after 2 h, and a 90/10 mixture of **3** and **4** was isolated in 40% yield. No optical activity was observed in the product **3** obtained.

Catalytic Reaction of *trans*-2 Using Other Chiral Palladium(II) Catalysts. Palladium(II) chloride complexes derived from (−)-carvone,[37] (+)-calciferol,[44] (−)-*N*,*N*-dimethyl-α-phenylethylamine[45] were prepared by the reported procedures. The corresponding acetate complexes obtained by anion methansesis using AgOAc were purified by SiO_2 column chromatography. Results for the catalytic cyclization of *trans*-**2** are listed in an order of (i) chiral source, (ii) reaction time required for >98% completion of reaction, (iii) product ratio of **3**/**4**, and (iv) $[\alpha]_D$ value of **3**: (a) (i) (−)-carvone, (ii) 9 h, (iii) 86/14, (iv) −0.25°; (b) (i) (+)-calciferol, (ii) 7 h, (iii) 97/3, (iv) −0.13°; (c) (i) (−)-*N*,*N*-dimethyl-α-phenylethylamine, (ii) 144 h at 60 °C, but no reaction occurs at 35 °C, (iii) 83/17, (iv) +0.52°.

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