Substituent Effects on Palladium(II)-Catalyzed Enantioselective Cyclization of a Series of 2-(2-Butenyl)phenols

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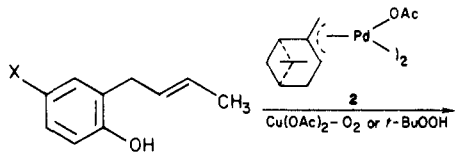
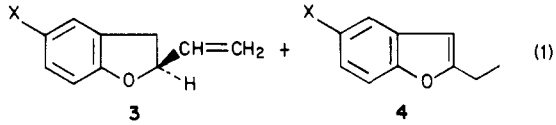
Received September 7, 1984

With either *tert*-butyl hydroperoxide or a combination of molecular oxygen and copper(II) acetate as the oxidizing agent, the enantioselective cyclization of 4-substituted *trans*-2-(2-butenyl)phenols **1** with $[(\eta^3\text{-pinene})PdOAc]_2$ (**2**) has been investigated. The observed enantioselectivity (26–0.1% ee) showed a decrease in accordance with the electronic property of substituent X ($OCH_3 > CH_3 > Cl > COCH_3$), whereas no clear trend was observed for the reactivity. Similarities of such phenomena between the two systems suggest that the same type of catalyst is involved in these reactions. The observed trend in enantioselectivity is discussed in terms of the stereochemical mode of nucleophilic addition of the phenoxyl group.

Enantioselective reactions catalyzed by chiral transition-metal complexes have attracted considerable attention[1] in the development of new asymmetric syntheses. In some of these reactions, even if a high enantiomeric excess is not attained, there is the advantage that the optical rotation of the product serves as a mechanistic probe to elucidate the nature of catalysis.[2] We have recently reported the enantioselective cyclization of 2-(2-butenyl)-phenols **1** catalyzed by chiral (η^3-pinene)palladium(II) complex **2** in the presence of molecular oxygen and copper(II) acetate (eq 1).[3] The percent of enantiomeric excess



1a; X = OCH_3
b; X = CH_3
c; X = H
d; X = Cl
e; X = $COCH_3$



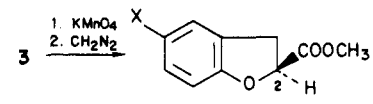
3 **4** (1)

of 2-vinyl-2,3-dihydrobenzofuran (**3c**, X = H) formed in this reaction is not so high, but using the above technique the formal oxidation state of Pd(II) catalyst has been shown to retain constant throughout the reaction. During the course of the study, it has been found that *tert*-butyl hydroperoxide can be utilized as an alternative to the agent of O_2 and $Cu(OAc)_2$. We then intended to get more information on the catalysis through the comparison of the results between the two reaction systems. We describe here the substituent effect of this reaction on the enantioselectivity and reactivity.

Results

Enantioselectivity. In the presence of either *t*-BuOOH (1.2 equiv) or O_2 (1 atm) and $Cu(OAc)_2$ (0.1 equiv), a series of *trans*-2-(2-butenyl)phenols (**1a–e**) were cyclized by using (+)-$[(3,2,10\text{-}\eta^3\text{-pinene})PdOAc]_2$ (**2**) as the catalyst (1/Pd = 10/1) in methanol at 35 °C. As shown in Table I, all the reactions give the dextrotatory 2-vinyl-2,3-dihydrobenzofurans **3a–e** along with small amounts of benzofurans **4a–e**, and there is no significant difference in % ee of the product **3** for each of the parallel series. In either system the enantioselectivity decreases in the order X = $OCH_3 > CH_3 > H > Cl > COCH_3$; the electron-withdrawing substitutents such as Cl and $COCH_3$ gives rise to much lower enantioselectivity (6–0.1% ee).

The enantiomer excesses of **3** were determined by the following methods. Dextrotatory **3a–d** were transformed into 2-carbomethoxy-2,3-dihydrobenzofurans **5** by $KMnO_4$ oxidation followed by esterification with CH_2N_2. Use of



5

the chiral shift reagent tris[3-[(trifluoromethyl)hydroxymethylene]-*d*-camphorato]europium(III) on the methyl ester **5** results in the separation of the enantiomeric C-2 proton as two set of signals. The % ee of **5** and the maximum rotation of **3a–d** have been determined from the relative ratio of these signals. However, estimation of the maximum rotation of **3e** (X = $COCH_3$) with this method is unreliable owing to its extremely low % ee. Hence, the value has been determined by the transformation of a 9.8% ee of (+)-**3c** (X = H) into (+)-**3e** $[[\alpha]_D$ +8.59° (*c* 2.27, CCl_4)] with $SnCl_4$–Ac_2O (see Experimental Section).

Since (+)-**3c** (X = H) has the *S* configuration,[3] the major peak of the two sets of signals separated on addition of $Eu(tfc)_3$ corresponds to the *S* enantiomer. The splitting pattern is common to every compound, thereby allowing us to assign the *S* configuration of dextrotatory **3**.

Reactivity. In the *t*-BuOOH system, the progress of the cyclization was monitored by GLC analyses of the reaction mixture in three representative cases (X = CH_3, H, and Cl). The S-shaped time vs. conversion curve was obtained (Figure 1) in each case. Although the apparent rate of cyclization deduced from the tangent at the inflection point of the curve is nearly the same in all cases, a longer induction perod is observed in the order X = H > CH_3 > Cl.

In the O_2–$Cu(OAc)_2$ system, the rates of the cyclization were followed by measuring the consumption of O_2. Here again, the rate of O_2 uptake is greatly enhanced after an induction period (Figure 2), and the apparent rate of the cyclization also decreases in the order X = H > CH_3 > Cl.

(1) For reviews, see: (a) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1978**, *10*, 175–285. (b) Valentine, D., Jr.; Scott, J. W. *Synthesis* **1978**, 329. (c) Caplar, V.; Comissio, G.; Sunjic, V. *Ibid.* **1981**, 85. (d) Bosnich, B.; Fryzuk, M. D. *Top. Stereochem.* **1981**, *12*, 119–154. (e) Hayashi, T.; Kumada, M. *Acc. Chem. Res.* **1982**, *15*, 395. (f) Pino, P.; Consiglio, G. *Pure Appl. Chem.* **1983**, *55*, 1781.

(2) (a) Consiglio, G.; Pino, P. *Adv. Chem. Ser.* **1982**, *196*, 371. (b) Fiaud, J. C.; Hibon de Gournay, A.; Larcheveque, M.; Kagan, H. B. *J. Organomet. Chem.* **1978**, *154*, 175. (c) Groves, J. T.; Meyers, R. S. *J. Am. Chem. Soc.* **1983**, *105*, 5791.

(3) Hosokawa, T.; Uno, T.; Inui, S.; Murahashi, S.-I. *J. Am. Chem. Soc.* **1981**, *103*, 2318.

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Table I. Asymmetric Oxidative Cyclization of 1 Catalyzed by Complex 2 in the Presence of O_2 and $Cu(OAc)_2$ or with *t*-BuOOH in Methanol

substrate, X	oxidizing agent	time,[b] h	cyclized product			
			yield[c] %	product ratio 3/4	$[\alpha]_D$ of 3,[d] deg (c, CCl_4)	ee, %
1a, 4-MeO	*t*-BuOOH	41	19	86/14	+4.61 (2.21)	22
	$Cu(OAc)_2$–O_2	12	44	83/17	+5.41 (6.30)	26
1b, 4-Me	*t*-BuOOH	22	34	82/18	+5.86 (3.14)	18
	$Cu(OAc)_2$–O_2	11	76	83/17	+6.84 (3.86)	21
1c, 4-H	*t*-BuOOH	20	52	82/18	+4.41 (4.18)	17
	$Cu(OAc)_2$–O_2	4.5	77	83/17	+4.53 (5.19)	18
1c, 4-Cl	*t*-BuOOH	39	54	87/13	+3.39 (6.61)	4.5
	$Cu(OAc)_2$–O_2	29	72	90/10	+4.53 (7.13)	6.0
1e, 4-COMe	*t*-BuOOH	48	43	88/12	+0.09 (3.50)	0.1
	$Cu(OAc)_2$–O_2	11	74	96/4	+0.89 (2.71)	1.1

[a] The reaction conditions are shown in the text. [b] Reaction time required for >98% completion. [c] Isolated yield by Kugelrohr distillation. [d] Measured at 25–29 °C.

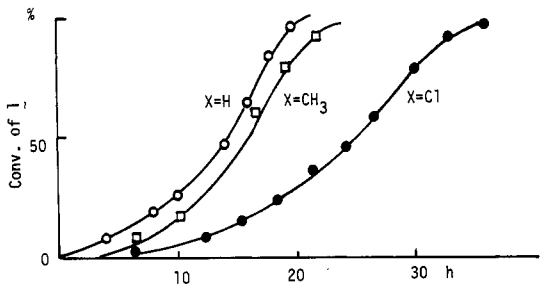


Figure 1. Progress of the catalytic reaction of 1 (X = H, CH_3, and Cl) performed by using *t*-BuOOH as the oxidizing agent. Reaction conditions: 2.5 mmol of 1, 0.125 mmol of the complex 1, and 3.18 mmol of *t*-BuOOH at 35 °C in MeOH (5 mL).

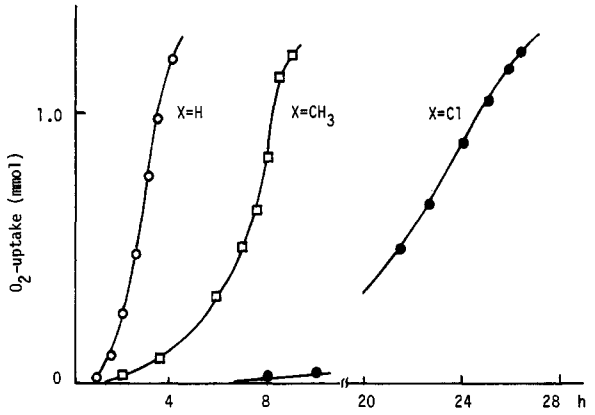


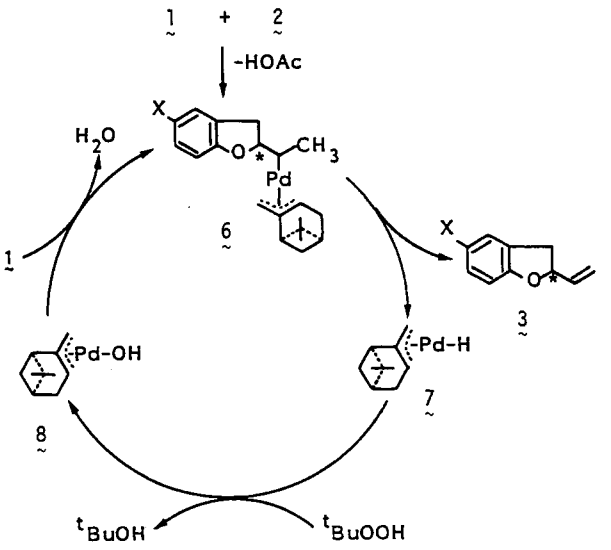
Figure 2. Plots of the O_2 uptake vs. time in the catalytic reaction of 1 (X = H, CH_3, and Cl) in the presence of complex 1 (0.125 mmol) and $Cu(OAc)_2$ (0.25 mmol) at 35 °C in MeOH (5 mL) under O_2 (1 atm).

The similarlities observed in the enantioselectivity and reactivity in the two systems strongly suggest that the function of *t*-BuOOH is virtually the same as that of O_2 and $Cu(OAc)_2$. Thus, the same type of catalyst is likely involved in the two reaction systems.

Discussion

In a previous paper,[3] we have shown that the active catalyst involved in the O_2–$Cu(OAc)_2$ system retains the chiral η^3-pinanyl ligand throughout the reaction.[4] This is also the case for the *t*-BuOOH system, since the $[\alpha]_D$ value (+4.38°) of **3c** (X = H) at 55% completion of the cyclization is nearly identical with that (+4.41°) at the end of the reaction. A catalytic cycle for *t*-BuOOH system

Scheme I



accommodating this result is shown in Scheme I. The pathways of intramolecular oxypalladation leading to the Pd–H species 7 is the same as that described previously. Our proposal here is that the catalytically active species containing the chiral pinanyl ligand must be generated from the Pd–H species 7 by the action of oxidizing agents such as *t*-BuOOH or O_2.[5] In the O_2–$Cu(OAc)_2$ system, oxygenation of the Pd–H species 7 by O_2 has been shown to give Pd–OOH species.[3,6]

Unfortunately, reactions of transition-metal hydride complexes with *t*-BuOOH has not been well studied. Strukul et al. have recently reported that $L_2Pt(CF_3)H$ (L = diphos, PPh_2Me, etc) reacts with HOOH to give $L_2Pt(CF_3)OOH$ with evolution of H_2.[7] If the species 7 similarly reacts with *t*-BuOOH, the active catalyst could be (η^3-pinene)Pd–OO-*t*-Bu. However, this seems to be unlikely, since no H_2 evolution was observed in the present reaction, and since no absorption of O_2 was detected in the cyclization 1c (X = H) using *t*-BuOOH in the presence of O_2 (1 atm). Thus, cleavage of the O–O bond of *t*-BuOOH is

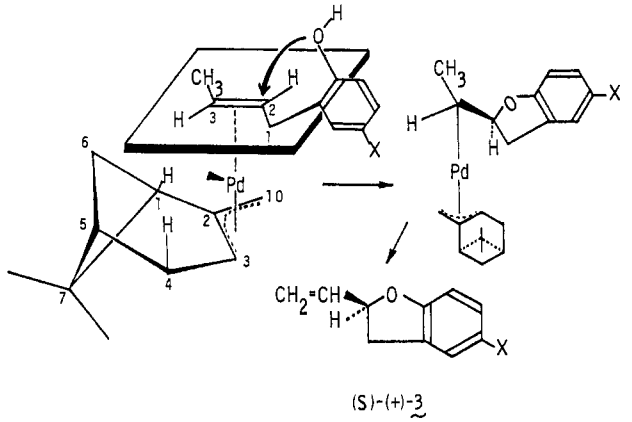
(4) It has been recently observed that a π-allyl moiety of palladium(II) is retained during the course of catalytic reactions, see: (a) Sen, A.; Ta-Wang, L. *Organometallics* **1983**, *2*, 1059. (b) Kurosawa, H.; Asada, N. *Ibid.* **1983**, *2*, 251.

(5) Palladium(II)-catalyzed oxidation of olefins to ketones has been shown to be effected by the aid of hydroperoxide or alkyl hydroperoxides in place of O_2 and Cu(II) salts. These oxidizing agents have been considered to be responsible for either (i) reoxidation of Pd(0) formed during the course of reaction or (ii) generation of Pd–OOR (R = H or alkyl) from Pd(II) species such as Pd–OH, see: (a) Tsuji, J.; Nagashima, H.; Hori, K. *Chem. Lett.* **1980**, 257. (b) Mimoun, H.; Carpeniter, R.; Mitschler, A.; Fischer, J.; Weiss, R. *J. Am. Chem. Soc.* **1980**, *102*, 1047.

(6) Involvement of PdH species in related reactions has been recently noted, see: Muzart, J.; Pete, J. P. *J. Mol. Catal.* **1982**, *15*, 373.

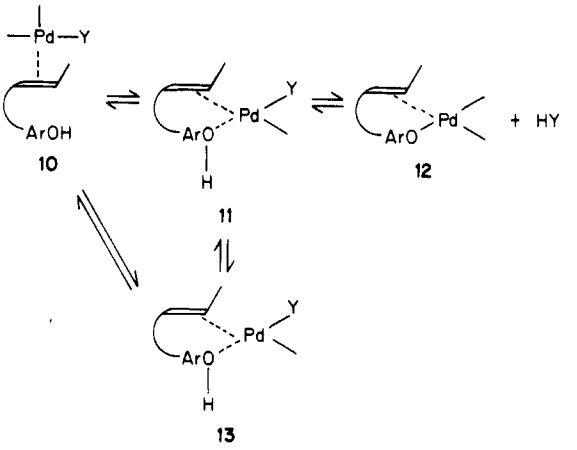
(7) (a) Strukul, G.; Ros, R.; Michelin, R. A. *Inorg. Chem.* **1982**, *21*, 459. (b) Michelin, R. A.; Ros, R.; Strukul, G. *Inorg. Chim. Acta.* **1979**, *37*, L491.

Scheme II



(S)-(+)-3

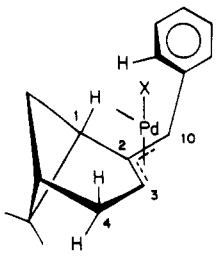
Scheme III



thought to be induced by Pd–H species, giving the Pd–OH species **8** and *t*-BuOOH (Scheme I). The generated (η^3-pinene)Pd–OH species **8** undergoes the intramolecular oxypalladation with elimination of H_2O to afford **6**, thereby completing the catalytic cycle.

Enantioselectivity. The enantioselectivity in the present reaction is determined at least by the following two factors:[8] (i) the differenciation of the prochiral olefin (*re* or *si* face) by palladium and (ii) the attacking mode of phenoxyl nucleophile on the double bond with respect to palladium (trans or cis addition). As proposed previously,[3] the least steric hindrance between the substrate and the pinanyl ligand is established, if the C_3-*re*-face of the olefin approaches the palladium in such a way that the methyl group on the olefin faces the C_1-bridgehead hydrogen of the pinanyl ligand (Scheme II).[9] Attack of the phenoxyl group at the C_2-carbon of the olefin from the opposite side of palladium (trans-oxypalladation) affords the *S* enantiomer of **3**, whereas the cis-oxypalladation leads to its *R* enantiomer.

Inspection of the stereochemical model of the pinanyl ligand reveals that there exists a space over the C_1-bridgehead hydrogen, where the methyl substituent of substrate olefin **1** is situated by virture of its medium size. This space is blocked if the hydrogen on the C_{10} carbon of the π-allyl moiety is replaced by a phenyl substituent as shown below. In fact, use of a complex such as **9** results



9, X = OAc

in poor enantioselectivity (2.5% ee of **3c** with the O_2–Cu(OAc)$_2$ system, see Experimental Section), indicating that the mode of enantio face selection metnioned above is likely. This mode would not be changed even if a series of substituents are introduced into the C_5-position of the phenoxyl group of **1**. Thus, the substituent effect observed on enantioselectivity appears to be associated with the second factor (i.e., the mode of addition of the phenoxy nucleophile).

As for the stereochemistry of nucleophilic addition to olefins coordinated to palladium(II), it appears to be one of general agreements that oxygen nucleophiles such as water,[10] methanol,[11] and acetate[12] attack (π-olefin)palladium(II) complexes in a trans fashion. Although no definite information is avaiable on its mode with phenol, the prevailing formation of the *S* enantiomer in the present reaction indicates that the trans addition is preferable. However, this mode of addition could be altered if the phenoxyl oxygen coordinates to palladium(II). Indeed, there have been recent observations that a trans attack by acetate is evidently changed to the cis if the anion coordinates to palladium(II).[13] Conceptual coordination of the phenoxy olefin **1** to palladium(II) is depicted in Scheme III. The equibilation shown will be affected by electronic property of the phenoxy group, and the basic ligand Y on Pd(II) is possibly replaced by relatively more acidic phenols such as **1d** (X = Cl) or **1e** (X = $COCH_3$) to form **12** to some extent. This allows the phenoxy anion to attack the olefin from the same side of palladium (cis attack), lowering the enantioselectivity in the present reaction. Thus, the trend in enantioselectivity observed is accounted for by the involvement of the cis-oxypalladation step.

It is to be noted here that no participation of solvent molecules takes place in a stage controlling the enantioselectivity, because when the cyclization using *t*-BuOOH was performed in benzene instead of methanol, no significant difference in % ee of **3** was observed (see Experimental Section).

Reactivity. The observed substituent effect on the reactivity is not strightforward. Obviously, the nucleo-

(8) To understand the mechanism of enantioselection in metal-catalyzed enantioselective reaction, it is a prerequisite that the nature of catalyst does not change with the nature of substrate. If the substrate is responsible for the liberation of a chiral ligand from a metal atom, or acts as an auxiliary ligand of the catalyst, the nature of the catalyst will be altered. However, we have demonstrated that the observed enantioselectivity and reactivity in the present reaction is not dependent on such an alteration but inherent in the nature of substrate (Hosokawa, T.; Okuda, C.; Murahashi, S.-I., unpublished results).

(9) A similar type of enantio face selection has been proposed by Midland in the asymmetric reduction of carbonyl compounds with *B*-3-pinanyl-9-borabicyclo[3.3.1]nonane: Midland, M. M.; Greer, S.; Tramontano, A.; Zderic, S. A. *J. Am. Chem. Soc.* **1979**, *101*, 2352.

(10) (a) Stille, J. K.; Divakaruni, R. *J. Organomet. Chem.* **1979**, *169*, 239. (b) Stille, J. K.; James, D. E. *Ibid.* **1976**, *108*, 401. (c) Bäckvall, J. E.; Åkermark, B.; Ljunggren, S. O. *J. Am. Chem. Soc.* **1979**, *101*, 2411.

(11) (a) James, D. E.; Hines, L. F.; Stille, J. K. *J. Am. Chem. Soc.* **1976**, *98*, 1806. (b) Majima, T.; Kurosawa, H. *J. Chem. Soc., Chem. Commun.* **1977**, 610. (c) Kurosawa, H.; Majima, T.; Asada, N. *J. Am. Chem. Soc.* **1980**, *102*, 6996.

(12) (a) Henry, P. M.; Ward, G. A. *J. Am. Chem. Soc.* **1972**, *94*, 7305. (b) Andell, O. S.; Bäckvall, J. E. *J. Organomet. Chem.* **1983**, *244*, 401.

(13) (a) Bäckvall, J. E.; Norderg, R. E.; Björkman, E. E.; Moberg, C. *J. Chem. Soc., Chem. Commun.* **1980**, 943. (b) Bäckvall, J. E.; Nordberg, R. E. *J. Am. Chem. Soc.* **1981**, *103*, 4945. (c) Bäckvall, J. E. *Acc. Chem. Res.* **1983**, *16*, 335 and references cited therein. (d) Gragor, N.; Henry, P. M. *J. Am. Chem. Soc.* **1981**, *103*, 681.

philicity of the phenoxy group must be one of the predominate factors governing the reactivity. However, it is anomalous that the electron-donating CH_3 substituent retards the initiation of reaction (X = H > CH_3 > Cl). The lone pair electron of phenoxy group is able to coordinate to palladium(II) of a Lewis acid. Thus, if the type of coordination such as **11** or **13** (Scheme III) which is facilitated by the electron-donating substituent retards the reaction, it explains the observed phenomenon.

In summary, we should like to emphasize the following points again. (1) In the *t*-BuOOH system, the formal oxidation state of Pd(II) remains constant throughout the reaction as in the case of the O_2–$Cu(OAc)_2$ system. (2) The enantioselectivity in the present reaction is correlated well with the electronic property of substituent X. On the basis of this result, we have suggested that the present intramolecular phenoxypalladation most likely proceeds via a trans attack, but the cis attack could take place concurrently, depending on the acidity of the phenoxy group.

Experimental Section

Optical rotations were measured with JASCO DIP-4 polarimeter with 1-dm-long cell at room temperature. ^1H NMM spectra were recorded on JMN-MH-60 (JEOL) and JMN FX-100 (JEOL) spectrometers. GLC analysis was performed on a JEOL Model JGC-20KFP flame ionization chromatograph using a 1 m × 4 mm, 10% PEG 20M Celite column under the conditions of injection temperature (200 °C) and column temperature (100-230 °C).

Preparation of bis[acetoxy(3,2,10-η^3-pinene)palladium(II)] (**2**) was described previously.[3] Cupric acetate (anhydrous) was purchased from Wako Pure Chemical Ind., Ltd., and dried at 80 °C (6 mmHg) before use. *tert*-Butyl hydroperoxide (80%) is commercially avaiable [Maruwaka Chemical Ind., Ltd. (Osaka)].

Preparation of Substituted *trans*-2-(2-Butenyl)phenols 1. 4-Methoxy- and 4-methyl-*trans*-2-(2-butenyl)phenol (**1a** and **1b**) were prepared by C-alkylation of *p*-methoxy- and *p*-methylphenol, respectively, with *trans*-1-chloro-2-butene (Tokyo Ksaei). The preparation of **1c** (X = H) by the same method has been reported previously.[3] 4-Chloro and 4-acetyl derivatives (**1d** and **1e**) were synthesized by O-alkylation of the corresponding phenols with 3-chloro-2-butene (Tokyo Kasei) followed by the Claisen rearrangement (290 °C, *N,N*-diethylaniline).[14] The preparation of these compounds is accompanied by contamination of the cis isomer and the corresponding 2-(2-methylallyl)phenol. Separation of the latter compound was achieved by a simple fractional distillation, but the pure trans isomer could not be obtained because of small difference in boiling points[15] between the cis and trans isomers. The ratios of trans/cis isomers used in the present study are as follows: **1a** (90:10); **1b** (85:15); **1c** (95:5); **1d** (86:14). Purification of **3e** was performed by recrystallization from ether–*n*-pentane. In this case, the contamination of cis isomer was 5%. All these compounds show characteristic IR absorption at ca. 3450 (ν_{OH}) and 970 cm^{-1} ($\nu_{C=C}$).

General Procedure for the Catalytic Cyclization of 1 Using Complex 2 in the Presence of O_2 and $Cu(OAc)_2$. The cyclization was performed in a 25-mL round-bottomed flask equipped with a magnetic stirrer bar and a three-way stopcock connected to a gas burette filled with O_2. Into the flask immersed in a constant temperature bath (35 ° ± 0.2 °C) was placed the acetate complex **2** (75.19 mg, 0.125 mmol as a dimer) and $Cu(OAc)_2$ (45.40 mg, 0.25 mmol). After the flask was flashed with O_2, a solution of **1** (2.5 mmol) in anhydrous methanol (5 mL) was introduced into the flask with stirring. Progress of the reaction was followed by GLC analyses of aliquot samples and O_2-uptake measurement. After the cyclization was ~95% complete, the reaction mixture was extracted with ether (3 × 50 mL), washed with water and brine, and dried over Na_2SO_4. The solvent was removed by rotary evaporator, and the residue was passed through a short column of Al_2O_3 by using *n*-hexane as the eluent. Kugelrohr distillation gave a mixture of **3** and **4** in the yields and ratios listed in Table I. These products were collected together by preparative GLC (20% PEG 20 M, 2 m, 160 °C) owing to their poor separation. The optical rotation of **3** was measured as a mixture of **3** and **4** as described previously.[3]

General Procedure for Catalytic Cyclization of 1 Using *t*-BuOOH in Methanol. Into a 25-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar, a reflux condenser, and a $CaCl_2$ drying tube was charged the complex **2** (75.15 mg, 0.125 mmol as a dimer), substrate **1** (2.5 mmol), *t*-BuOOH (80%, d = 0.94, 0.38 mL, 3.18 mmol), and anhydrous methanol (5 mL). The mixture was stirred at 35 °C in a constant temperature bath. The progress of reaction was followed by GLC analyses of aliquot samples. Since no appropriate compound soluble in methanol was available as an internal standard for GLC analysis, the time vs. conversion curves (Figure 1) were deduced by measuring the relative peak areas of the substrate **1** and products **3** and **4**. After the substrate was ~98% consumed, the mixture was extracted with ether, washed with a 10% aqueous solution of Na_2SO_3 and brine, and dried over Na_2SO_4. After removal of ether, the residue was passed through a short column of Al_2O_3 by using *n*-pentane as the eluent. Kugelrohr distillation gave a mixture of products **3** and **4** in the yields and ratios shown in Table I. Isolation of **3** and **4** was performed by preparative TLC (SiO_2, 1:1 $CHCl_3$/benzene for **3a**, 4:1 *n*-pentane/$CHCl_3$ for **3b–d**, and 1:2 EtOAc/cyclohexane for **3e**). Isolated product **3** was further Kugelrohr distilled and subjected into the measurement of optical rotation. The spectral and analytical data are listed below.

5-Methoxy-2-vinyl-2,3-dihydrobenzofuran (3a): Kugelrohr distillation 125–131 °C (6 mmHg); TLC R_f 0.61 (1:1 $CHCl_3$/benzene); ^1H NMR (CCl_4) δ 2.67 (dd, J = 15 and 8 Hz, 1 H, Ar CH), 3.10 (dd, J = 15 and 10 Hz, 1 H, Ar CH), 3.57 (s, 3 H, OCH_3), 4.75–5.34 (m, 3 H —CHO and CH_2=C), 5.62–6.16 (m, 1 H, —CH=), 6.4–6.6 (m, 3 H, Ar H); IR (neat) 1490, 1200, 1140, 1030, 805 cm^{-1}. Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.16; H, 8.87.

5-Methyl-2-vinyl-2,3-dihydrobenzofuran (3b): Kugelrohr distillation ~110 °C (6 mmHg); ^1H NMR (CCl_4) δ 2.16 (s, 3 H, CH_3), 2.72 (dd, J = 16 and 8–9 Hz, 1 H, Ar CH), 3.15 (dd, J = 16 and 9 Hz, 1 H, Ar CH). 4.70–5.30 (m, 3 H, —CHO and CH_2=C), 5.58–6.13 (m, 1 H, —CH=), 6.35–6.70 (m, 3 H, Ar H); IR (neat) 1500, 1255, 930, 810 cm^{-1}. Anal. Calcd for $C_{11}H_{12}O$: C, 82.46, H, 7.55. Found: C, 82.74; H, 7.58.

2-Vinyl-2,3-dihydrobenzofuran (3c): Kugelrohr distillation 99–101 °C (6 mmHg); ^1H NMR (CCl_4) δ 2.78 (dd, J = 16 and 9 Hz, 1 H, ArCH), 3.22 (dd, J = 16 and 10 Hz, 1 H, ArCH), 4.90–5.48 (m, 3 H, —CHO and CH_2=C), 5.76–6.32 (m, 1 H, —CH=), 6.61–7.17 (m, 4 H, Ar H); IR (neat) 1600, 1490, 1240, 930, 750 cm^{-1}. Anal. Calcd for $C_{10}H_{10}O$: C, 82.16; H, 6.90. Found: C, 82.24; H, 6.89.

5-Chloro-2-vinyl-2,3-dihydrobenzofuran (3d): Kugelrohr distillation 115–120 °C (6 mmHg); ^1H NMR (CCl_4) δ 2.77 (dd, J = 16 and 8 Hz, 1 H, ArCH), 3.22 (dd, J = 16 and 10 Hz, 1 H, ArCH), 4.92–5.46 (m, 3 H, —CHO and CH_2=C), 5.72–6.26 (m, 1 H, —CH=), 6.5–6.7 (m, 1 H, Ar H), 6.9–7.1 (m, 1 H, Ar H); IR (neat) 1470, 1230, 1170, 925, 800 cm^{-1}. Anal. Calcd for $C_{10}H_9OCl$: C, 66.49; H, 5.02. Found: C, 66.09; H, 5.00.

5-Acetyl-2-vinyl-2,3-dihydrobenzofuran (3e): Kugelrohr distillation 125–130 °C (0.1 mmHg); TLC R_f 0.71 (4:1 benzene/EtOAc); ^1H NMR (CCl_4) δ 2.35 (s, 3 H, $COCH_3$), 2.83 (dd, J = 15 and 8 Hz, 1 H, ArCH), 3.28 (dd, J = 15 and 8 Hz, 1 H, ArCH), 4.93–5.40 (m, 3 H, —CHO and CH_2=C), 5.60–6.35 (m, 1 H, —CH=), 6.45–6.70 (m, 1 H, Ar H), 7.25–7.70 (m, 2 H, Ar H); IR (neat) 1680, 1610, 1490, 1270, 940 cm^{-1}. Anal. Calcd for $C_{12}H_{12}O$: C, 76.57; H, 6.43. Found: C, 76.33; H, 6.26.

5-Methoxy-2-ethylbenzofuran (4a): Kugelrohr distillation ~130 °C (6 mmHg); TLC R_f 0.73 (1:1 $CHCl_3$/benzene); ^1H NMR (CCl_4) δ 1.28 (t, J = 8 Hz, 3 H, CH_3) 2.70 (q, J = 8 Hz, 2 H, -CH_2-), 3.58 (s, 3 H, OCH_3), 6.12 (br s, 1 H, ArCH); 6.48–7.20 (m, 3 H, Ar H); IR (neat) 2970, 1475, 1200, 1030, 920 cm^{-1}. Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.63; H, 6.77.

6-Methyl-2-ethylbenzofuran (4b): Kugelrohr distillation ~110 °C (6 mmHg); ^1H NMR (CCl_4) δ 1.34 (t, J = 8 Hz, 3 H, CH_3), 2.41 (s, 3 H, Ar CH_3), 2.75 (q, J = 8 Hz, 2 H, -CH_2-), 6.19 (br s, 1 H, Ar CH), 6.80–7.27 (m, 3 H, Ar H); IR (neat) 2970, 1480,

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Table II. Experimental Details for the Conversion of 3 into 5

vinylbenzofuran 3			$KMnO_4$		solvent		ester 5	
X	mg	mmol	mg	mmol		mL	mg	yield, %
3a, 5-MeO	500	2.84	1496	9.47	glyme	5	258	44
					CH_3CN	15		
3b, 5-Me	390	2.40	1014	6.42	acetone	7	111	23
					H_2O	16		
3c, 5-H	350	2.40	1014	6.42	acetone	7	116	27
					H_2O	16		
3d, 5-Cl	500	2.77	1459	9.23	acetone	10	157	27
					H_2O	20		

Table III. Estimated Maximum Rotation of 3 as Determined through Ester 5 Using $Eu(tfc)_3$

vinylbenzofuran 3				
X	$[\alpha]_D$ of 3,[a] deg (c, CCl_4)	5/$Eu(tfc)_3$,[b] mg ester/mg	ee of 5, %	estimated $[\alpha]_{D,max}$ of 3, deg
3a, 5-MeO	+4.94 (3.08)	23.4/29.8	24 ± 4	20.6
3b, 5-Me	+5.18 (0.75)	17.9/17.4	16 ± 3	32.4
3c, 5-H	+3.14 (6.44)	22.7/37.4	13 ± 1	24.1 (25.5)[c]
3d, 5-Cl	+4.49 (2.45)	30.2/76.1	6 ± 1	74.8
3e, 5-COMe				(87.6)[d]

[a] $[\alpha]_D$ value used for this experiment. [b] Purchased from Alfa, Ventron Division. [c] The value was estimated by transforming (+)-**3c** into (+)-ethyl 2,3-dihydrobenzofuran-2-carboxylate; see ref 3. [d] The value was estimated by converting (+)-**3c** into (+)-**3e**; see Experimental Section.

1270, 930, 800 cm^{-1}. Anal. Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 81.83; H, 7.46.

2-Ethylbenzofuran (4c): Kugelrohr distillation 85–90 °C (6 mmHg); ^1H NMR (CCl_4) δ 1.34 (t, J = 8 Hz, 3 H, CH_3), 2.78 (q, J = 8 Hz, 2 H, -CH_2-), 6.32 (br s, 1 H, Ar CH), 7.03–7.49 (m, 4 H, Ar H); IR (neat) 2970, 1460, 1260, 935, 750 cm^{-1}. Anal. Calcd for $C_{10}H_{10}O$: C, 82.16; H, 6.90. Found: C, 81.56; H, 6.87.

5-Chloro-2-ethylbenzofuran (4d): Kugelrohr distillation 115–120 °C (6 mmHg); ^1H NMR (CCl_4) δ 1.32 (t, J = 8 Hz, 3 H, CH_3), 2.74 (q, J = 8 Hz, 2 H, -CH_2-), 6.17 (br s, 1 H, Ar CH), 7.03–7.20 (m, 3 H, Ar H). Anal. Calcd for $C_{10}H_9OCl$: C, 66.49; H, 5.02. Found: C, 66.44; H, 4.94.

5-Acetyl-2-ethylbenzofuran (4e): TLC R_f 0.77 (4:1 benzene/EtOAc); ^1H NMR (CCl_4) δ 1.35 (t, J = 8 Hz, 3 H, CH_3), 2.51 (s, 3 H, $COCH_3$), 2.80 (q, J = 8 Hz, 2 H, -CH_2-), 6.18 (br s, 1 H, Ar H), 6.50–7.90 (m, 2 H, Ar H).

Methyl Esters 5 Prepared for Percent Enantiomeric Excess Determination. To a ~0.3 M solution of **3** (except **3a**) in acetone was added an aqueous solution of $KMnO_4$ (~0.4 M) with stirring at room temperature. After the mixture was stirred for 1 h, the resulting manganese dioxide was filtered off, and the filtrate was acidified with 10% aqueous solution of H_2SO_4. The products were extracted with ether, washed with water and brine, and dried over Na_2SO_4. After removal of ether, the resulting material was treated with an ethereal solution of diazomethane until the yellow color persisted. Removal of ether followed by Kugelrohr distillation gave the ester **5** which was purified by preparative GLC (20% PEG 20M, 1 m, 190 °C) or TLC (SiO_2, 4:1 cyclohexane/EtOAc).

In the case of **3a**, the $KMnO_4$ oxidation was performed in glyme–acetonitrile solvent.[16] Thus, $KMnO_4$ was dissolved in glyme[17] –acetonitrile (1:3 v/v) into which was added an acetonitrile solution of **3a** in a few minitues with vigorous stirring at room temperature. After being stirred for 45 min, the mixture was filtered with suction. The resulting solid material was dissolved in 10% aqueous solution of NaOH to remove manganese dioxide. The aqueous solution was then acidified with a 10% aqueous solution of H_2SO_4 and extracted with ether. Removal of ether gave crude carboxylic acid which was treated with diazomethane. Details in these experiments are given in Table II. Spectral and analytical data of **5** are listed below.

5-Methoxy-2-carbomethoxy-2,3-dihydrobenzofuran (5a): Kugelrohr distillation 110–118 °C (0.1 mmHg); ^1H NMR ($CDCl_3$) δ 3.38 (d, J = 7.6 Hz, 1 H, C_3-H), 3.43 (d, J = 9.1 Hz, 1 H, C_3-H), 3.69 (s, 3 H, OCH_3), 3.75 (s, 3 H, $COOCH_3$), 5.14 (dd, J = 9.1 and 7.6 Hz, 1 H, C_2-H), 6.70–6.65 (m, 3 H, Ar H).

5-Methyl-2-carbomethoxy-2,3-dihydrobenzofuran (5b): Kugelrohr distillation ~108 °C (0.03 mmHg); ^1H NMR ($CDCl_3$) δ 2.24 (s, 3 H, CH_3), 3.38 (d, J = 9.2 Hz, 1 H, C_3-H). 3.42 (d, J = 7.8 Hz, 1 H, C_3-H), 3.76 (s, 3 H, $COOCH_3$), 5.15 (dd, J = 9.2 and 7.8 Hz, 1 H, C_2H), 7.05–6.64 (m, 3 H, Ar H); IR (neat) 1763, 1745, 1500, 1210, 1050, 810 cm^{-1}. Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.75; H, 6.14.

2-Carbomethoxy-2,3-dihydrobenzofuran (5c): Kugelrohr distillation ~180 °C (2 mmHg); ^1H NMR ($CDCl_3$) δ 3.43 (d, J = 7.6 Hz, 1 H, C_3-H), 3.48 (d, 1 H, J = 9.6 Hz), 3.78 (s, 3 H, $COOCH_3$), 5.19 (dd, 1 H, J = 9.6 and 7.6 Hz), 7.21–6.71 (m, 4 H, Ar H).

5-Chloro-2-carbomethoxy-2,3-dihydrobenzofuran (5d): Kugelrohr distillation ~140 °C (1 mmHg); TLC R_f 0.41 (4:1 cyclohexane/EtOAc); ^1H NMR ($CDCl_3$) δ 3.39 (d, J = 7.6, 1 H, C_3-H), 3.44 (d, J = 9.1 Hz, 1 H, C_3-H), 3.79 (s, 3 H, $COOCH_3$), 5.13 (dd, J = 9.1 and 7.6 Hz, 1 H, C_2-H), 7.20–6.73 (m, 3 H, Ar H); IR (neat) 1750, 1470, 1210, 1030, 810 cm^{-1}. Anal. Calcd for $C_{10}H_3Cl$: C, 56.48; H, 4.27. Found: C, 56.25; H, 4.44.

Determination of Enantiomeric Excess of 3 through Esters 5. The ^1H NMR spectra of esters **5** showed a doublet signal due to the C_2 proton near δ 5.13 (J = ~7 and ~9 Hz). The proton was separated into two sets of triplets (J = 8–9 Hz) by addition of $Eu(tfc)_3$. Amoung three sets of the splitting peaks, the relative areas of two sets of signals at the right- and left-hand sides were determined by "cut and weight" procedures, since the central signals were relatively not well separated. Listed in Table III are the specific rotations of **3** used for the NMR measurement, the percent enantiomeric excess (% ee) as the average of at least two measurements, and the maximum rotation of **3** estimated from these experiments.

Determination of Enantiomeric Excess of 3e (X = COMe). Optically active **3c** (X = H) (0.635 g, 4.35 mmol) of $[\alpha]_D^{19}$ +2.50° (c 3.89, CCl_4) (9.8% ee) was stirred in benzene (5 mL) containing acetic anhydride (0.75 g) in an ice bath, while a solution of stannic chloride (3.86 g, 14.82 mmol) in benzene (2.5 mL) was added dropwise over a period of 15 min. After the solution was stirred for an additional 15 min, it was poured into ice. The product was extracted with ether, washed with water until neutral, and dried ovr Na_2SO_4. Removal of ether followed by Kugelrohr distillation at 125–130 °C (0.1 mmHg) gave **3e** (0.371 g, 45%). The $[\alpha]_D$ of **5e** purified by preparative GLC (10% PEG 20M, 1 m, 180 °C) was +8.59° (c 2.27, CCl_4). Since this value corresponds to 9.8% ee (±1), the maximum rotation of (*S*)-2-vinyl-4-acetyl-2,3-dihydrobenzofuran (**3e**) is estimated to be +87.6 ±0.8° (CCl_4).

Preparation of Bis[chloro(3,2,10-η^3-10-phenylpinene)]-palladium(II) (14). (–)-β-Pinene was at first phenylated according to Heck's procedure.[18] Thus, a mixture of phenylmercuric

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Table IV. Asymmetric Oxidative Cyclization of 1 Catalyzed by Complex 2 with t-BuOOH in Benzene

substrate, X	time,[b] h	cyclized products: yield,[c] %	product ratio 3/4	$[\alpha]_D$ of 3,[d] deg (c, CCl_4)	ee, %
1b, Me	70	67	58/42	+6.87 (7.56)	21
1c, 4-H	59	75	58/42	+4.48 (3.03)	18
1d, 4-Cl	151	81	76/24	+5.53 (7.96)	7.4

[a] The reaction conditions are shown in the text. [b] Reaction time required for >98% completion. [c] Determined by GLC using n-pentadecane as an internal standard. [d] Measured at 25-29 °C.

acetate (4.64 g, 13.8 mmol), palladium acetate (3.10 g, 13.8 mmol), and acetonitrile (35 mL) was stirred at room temperature for 1 h. To this mixture was added (-)-β-pinene (6 mL, 37.8 mmol), and stirring was continued for 1.5 h. After the resulting metallic palladium was filtered off, a small spatulaful of phenylmercuric acetate was added to the filtrate, and the mixture was left overnight at room temperature. Metallic palladium further precipitated was filtered again, and the filtrate was diluted with ether, washed with brine and 10% aqueous solution of $NaHCO_3$, and dried over $MgSO_4$. Removal of ether followed by column chromatography on Al_2O_3 with n-pentane as the eluent gave a yellow solution. From the solution [(3,2,10-η^3-pinene)PdCl]$_2$ (1.22 g, 32%) was precipitated as yellow crystals. After collection of the crystals, the filtrate was distilled at 82-85 °C (1.5 mmHg) to give a 7:8 mixture of 2-benzylidene-6,6-dimethylbicyclo[3.1.1]heptane (15) and 2-benzyl-6,6-dimethylbicyclo[3.1.1]hept-2-ene (16) (0.860 g, 29%). The spectral properties of 15 and 16 are in good agreement with the published data.[19]

The title complex 14 was then prepared from the above mixture according to the method of Trost et al.[20] To glacial acetic acid (80 mL) and acetic anhydride (3 mL) were added sodium acetate (4.80 g, 58 mmol), sodium chloride (3.36 g, 56 mmol), cupric acetate (3.68 g, 20 mmol), and then palladium chloride (0.80 g, 4.5 mmol) in that order. The mixture was heated at 95 °C for 3 h and cooled to 60 °C. The above mixture of 15 and 16 (0.850 g, 4.0 mmol) in glacial acetic acid (5 mL) was then added in one portion, and the solution was stirred at 60 °C for 24 h. The solution was cooled, filtered, poured into water, and extracted with benzene. The organic layer was washed with water, saturated aqueous solution of $NaHCO_3$ and brine and dried over $MgSO_4$. Removal of ether followed by column chromatography on SiO_2 with chloroform as the eluent gave yellow crystals. Recrystallization from chloroform-n-pentane gave the pure compound 14 (0.090 g, 6.3%): mp 181-183 °C dec; $[\alpha]^{27}_D$ +9.96° (c 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.22 (s, Me), 1.40 (s, Me) 2.10 (m, 2 H), 2.52 (br s, 1 H), 3.30 (m, 2 H), 3.78 (br s, 1 H, C_{10}-H), 7.21 (s, 5 H, Ph). Anal. Calcd for $C_{32}H_{38}Cl_2Pd_2$: C, 54.41; H, 5.42. Found: C, 54.15; H, 5.29.

Catalytic Cyclization of 2c (X = H) Using Complex 9 in the O_2-Cu(OAc)$_2$ System. The chloride complex 14 was converted into the acetate complex 9 by treatment with AgOAc. Thus, a mixture of the chloride complex 14 (0.080 g, 0.113 mmol as a dimer) and AgOAc (0.038 g, 0.226 mmol) in chloroform (5 mL) was stirred for 30 min in the dark. After the resulting AgCl was filtered off, the solution was passed through a short column of SiO_2. A yellow solution eluted with chloroform was concentrated in vacuo to leave a yellow oil of 9. According to the general procedure described above, the cyclization of 2c (0.335 g, 2.26 mmol) was performed by using this material as the catalyst and Cu(OAc)$_2$ (0.410 g, 2.26 mmol) in methanol (4.6 mL). After the reaction was complete in 34 h, usual workup followed by Kugelrohr distillation gave an 87:13 mixture of 3c and 4c (0.230 g, 70%). The optical rotation of purified 3c was $[\alpha]^{22}_D$ +0.64° (c 3.88, CCl_4), which corresponds to 2.5% ee.

Catalytic Cyclization of 1 Using t-BuOOH in Benzene. An anhydrous, 5.6 M solution of t-BuOOH in benzene was prepared by azeotropic drying of 80% t-BuOOH. Using this reagent (3.0 mmol), the cyclization of 1 (2.5 mmol) was carried out in benzene (4.8 mL) under otherwise the same conditions as above. In this case, n-pentadecane was used as an internal standard for GLC analyses. Results are summarized in Table IV.

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Competitive Dehydration and Deamination of α,ω-Amino Alcohols and α,ω-Amino Acids in the Gas Phase

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Received September 11, 1984

Acid-catalyzed cyclization of straight chain α,ω-amino acids and α,ω-amino alcohols (chain lengths from C_2 to C_5) has been studied as a function of reaction conditions in the gas phase. Tandem mass spectrometry was used for product analysis. Competitive dehydration and deamination from the protonated amino alcohols and amino acids were found to depend on the reaction region (mass spectrometer ion source vs. mass spectrometer collision region) in two types of mass spectrometers. The ratio of deamination to dehydration for both types of compounds was found to show dramatic variation with varying chain length in the collision region of the mass spectrometer. No such effect was observed for reactions occurring in the ion source. These results can be rationalized with calculated thermochemical data on the assumption of thermodynamic control in the ion source and kinetic control in the collision region of the mass spectrometer.

Acid-catalyzed intramolecular cyclization of straight chain α,ω-amino alcohols can result in either dehydration or deamination.[2-5] When the reaction is examined in the chemical ionization source of a mass spectrometer,[6,7] that is under conditions where numerous collisions occur,[6-8] the

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