Intramolecular Oxypalladation. Cyclization Reaction of 2-Allylphenols with Palladium Salts

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The stoichiometric reaction of sodium salts of 2-allylphenols **1** with dichlorobis(benzonitrile)palladium(II) gives generally 2-substituted benzofurans **2** in moderate yields. The formation of cyclized products is explained by intramolecular oxypalladation followed by elimination of a palladium hydride species. The cyclization can be made catalytic by using palladium(II) acetate, cupric acetate, and oxygen.

Recently we found the intramolecular cyclization of 2-allylphenols into 2-substituted benzofurans by means of dichlorobis(benzonitrile)palladium(II).[1] The synthetic usefulness of the reaction is, however, limited by the expence of palladium salt since a stoichiometric amount of palladium salt is utilized. Accordingly, we have investigated to make the cyclization catalytic with respect to the metal salt.

The present paper describes a study of the stoichiometric and catalytic reactions of 2-allylphenols induced by palladium salts. It is also indicated that intramolecular oxypalladation intermediate plays an important role in the reaction.

Results and Discussion

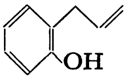
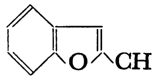
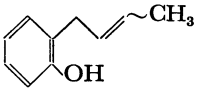
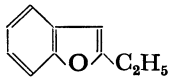
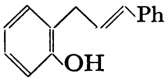
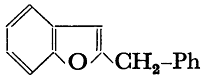
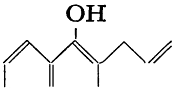
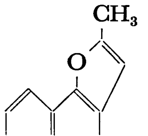
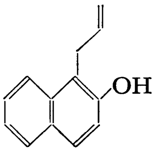
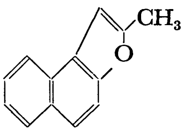
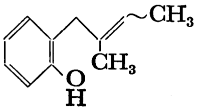
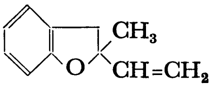
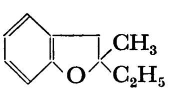
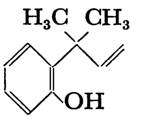
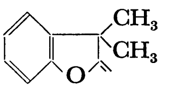
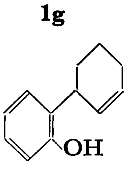
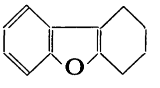
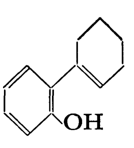
Stoichiometric Cyclization Using Palladium Salts. (a) Dichlorobis(benzonitrile)palladium(II): Sodium salts of 2-allylphenols **1** were employed in the stoichiometric reaction in order to form a Pd–O bond easily *in situ*. An equimolecular amount of dichlorobis(benzonitrile)-palladium(II) was allowed to react with the sodium salts as reported previously.[1]

In general, the reaction gave 2-subsituted benzofurans **2** in moderate yields as shown in Table 1. 2,3-Dihydro-2-methyl-2-ethylbenzofuran (**3**), hydrogenated product of 2,3-dihydro-2-methyl-2-vinylbenzofuran (**2f**), was formed as a by-product in the reaction of 2-(β,γ-dimethylallyl)phenol (**1f**). The structures of products were deduced from elemental analyses and spectral data which are summarized in Tables 2. and 3. In these reactions no starting material was recovered, but polymeric residue was formed.

It was reported that the treatment of 2-allylphenol (**1a**) with palladium on charcol at 500—800 °C gave 2-methylbenzofuran (**2a**).[2] Compared with this, the present method provides a very convenient synthetic method of 2-substituted benzofurans.

The formation of 2-substituted benzofurans **2** is elucidated by the following Scheme 1** involving intramolecular oxypalladation to give the intermediate **6** followed by β-elimination of PdHCl species.[3]

Table 1. Stoichiometric cyclization of sodium salts of allylphenol **1** with $PdCl_2(PhCN)_2$

Allylphenol 1	Product (Yield, %)	
 **1a**	 **2a** (31%)	
 **1b**	 **2b** (26%)	
 **1c**	 **2c** (53%)	
 **1d**	 **2d** (22%)	
 **1e**	 **2e** (42%)	
 **1f**	 **2f** (41%)	 **3** (13%)
 **1g**	 **2g** (40%)	
 **1h**	 **2h** (19%)	 **4** (43%)

In the oxypalladation intermediate **6**, where R=H or Ph, the hydrogen on the C-2 carbon is an only β-hydrogen to be eliminated with palladium. The elimination gives *exo*-methylenebenzofuran which even-

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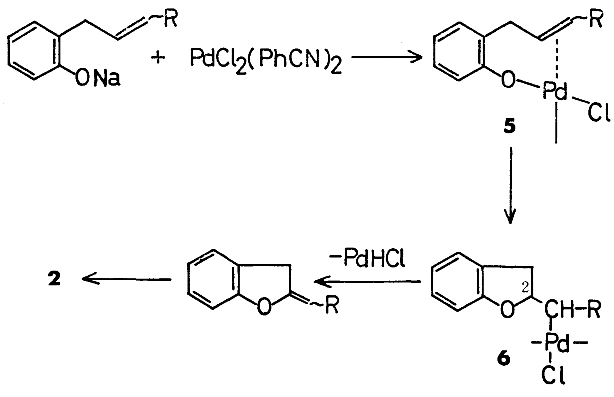
** Although the complex **5** was not isolated, similar complexes are known to be formed by the treatment of 2-allylphenyldimethylarsine or 2-allylphenyldiphenylphosphine with dichlorobis(benzonitrile) palladium(II) (M. A. Bennet, W. R. Keen, and R. S. Nyholm, *Inorg. Chem.*, **7**, 556 (1968).).



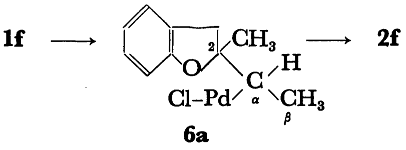
Scheme 1.

Table 2. ELEMENTAL ANALYSES AND MASS SPECTRA OF PRODUCTS

Compd No.	Formula	Calcd (%)		Found (%)		m/e (M^+)
		C	H	C	H	
2a	C_9H_8O	81.79	6.10	81.79	5.95	132
2b	$C_{10}H_{10}O$	81.26	6.90	82.13	6.84	146
2c	$C_{15}H_{12}O$	86.51	5.81	86.63	5.91	208
2d	$C_{13}H_{10}O$	85.69	5.53	86.26	5.41	182
2e	$C_{13}H_{10}O$	85.69	5.53	85.47	5.48	182
2f	$C_{11}H_{12}O$	82.64	7.55	82.59	7.69	160
3	$C_{11}H_{14}O$	81.44	8.70	81.28	8.59	162
2g	$C_{11}H_{12}O$	82.46	7.55	81.98	7.54	160
2h	$C_{12}H_{12}O$	83.69	7.02	83.45	7.05	172
4	$C_{12}H_{14}O$	82.72	8.10	82.26	7.92	174

tually isomerizes to the thermodynamically stable 2-substituted benzofuran (**2a**—**2e**). However, exo-methylenebenzofuran **2g** is isolated in the reaction of **1g**.

In the case of **1f**, β-hydrogen elimination is only possible from the methyl group attached to α-carbon. The elimination gives **2f** as shown below.



The product **3** can be considered to arise from hydrogenolysis of the Pd-C bond in **6a**.

In the case of **1b** (or **1h**), there are two possibilities for β-elimination of a palladium hydride in the intermediate **6** ($R=CH_3$). One is from the C-2 carbon leading to 2-ethylbenzofuran (**2b**), and the other from the methyl group to give 2,3-dihydro-2-vinylbenzofuran (**8a**) (*vide infra*). Similarly, dihydrobenzofuran **8b** is expected from **1h**. However, **8a** (or **8b**) would be isomerized to the thermodynamically more stable isomer **2b** (or **2h**) by the generated PdHCl species.[4] The species is known to prompt double bond isomerization.[5]

It was also found that 2-(1'propenyl)phenol (**7a**) and 2-hydroxystilbene (**7b**) gave 2-substituted benzofurans

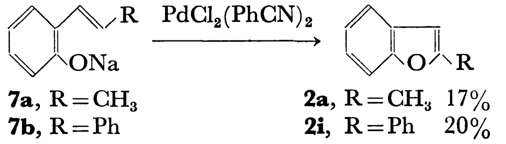


Table 3. SPECTRAL DATA OF PRODUCTS

Compd No	NMR (δ, in CCl_4)[a] C-3-H	Side chain-H	Phenyl-H	IR (ν_{max}, cm^{-1})
2a	6.02(m, 1H)	2.36(d, 1H, $J=1$)	7.07(m, 4H)	1610, 1590, 1450, 1252, 1180, 1010
2b	6.17—6.30 (m, 1H)	1.34(t, 3H, $J=8$) 2.78(q, 2H, $J=8$)	6.8—7.4(m, 4H)	1604, 1590, 1250, 1050
2c	6.10(m, 1H)	3.91(broad s, 2H)	7.08(m, 6H)	1640, 1584, 1453, 1257, 940
2d	6.41(m, 1H)	2.48(d, 3H, $J=1$)	7.1—8.3(m, 6H)	1602, 1580, 1386, 1318, 1175, 1084
2e	6.55(m, 1H)	2.40(d, 3H, $J=1$)	7.2—7.9(m, 6H)	1601, 1580, 1464, 1443, 1386, 1269, 1184, 940
2f	3.04(broad s, 2H)	1.49(s, 3H) 4.98(dd, 1H, $J=11$, 2) 5.21(dd, 1H, $J=16$, 2) 6.00(dd, 1H, $J=11$, 16)	6.48—7.14(m, 4H)	1640, 1608, 1598, 1250, 1070
3	2.85—3.05 (m, 2H)	0.98(t, 3H, $J=8$) 1.42(s, 3H) 1.74(q, 2H, $J=8$)	6.46—7.15(m, 4H)	1602, 1250, 1020
2g		1.45(s, 6H) 4.76(s, 1H) 5.29(s, 1H)	6.81(dd, 2H, $J=2$) 7.24(dd, 2H, $J=2$)	1640, 1608, 1598, 1275, 1080, 1010, 880,
2h		1.68—2.2(m, 4H) 2.4—3.0(m, 4H)	6.85—7.55(m, 4H)	1640, 1615, 1585, 1280 1260, 1225, 1010
4		1.56—2.40(m, 6H) 5.22—5.50(m, 1H) 5.80—5.94(m, 1H)	6.65—7.16(m, 4H)	3500, 1640

a) Coupling constants, J, have the unite of Hz.

2a and **2i**, respectively, but in low yields.[6]

(b) Palladium(II) Acetate: Palladium(II) acetate was found to cause the cyclization of 2-allyl phenols **1** themselves. The treatment of **1b** with an equimolecular amount of palladium(II)acetate gave **2b**(20%) and **8a** (21%). In this case, however, these two isomers were primary products because the isomerization of **8a** to the stable isomer **2b** was eliminated by the following results. 1) The amounts of both products **2b** and **8a** increased with reaction time, and the product ratio of **2b** and **8a** did not change with time. 2) The treatment of **8a** under the same conditions resulted in the recovery of **8a**. 3) Even when **8a** was added to the starting substrate in advance, the amount of **2b** did not increase under the corresponding conditions. The difference of product composition between two stoichiometric cyclizations of **1b** would be due to the difference of palladium salts used.

Moreover, the composition of products **2b** and **8a** was found to vary with the relative amount of **1b** to palladium(II) acetate. As indicated in Table 4, the ratio of **8a** to **2b** increased with increase in the relative amount of **1b** to palladium(II) acetate. Further study is required to understand the result.

TABLE 4. PRODUCT COMPOSITION IN THE REACTION OF **1b** WITH PALLADIUM(II) ACERTATE[a)]

Mole ratio **1b**/Pd(OAc)$_2$	Yield on Pd(OAc)$_2$ **2b**, %	Yield on Pd(OAc)$_2$ **8a**, %	Product ratio **8a**/**2b**
1	19.5	20.8	1.1
2	19.0	46.4	2.4
5	17.4	85.6	4.9
10	13.6	92.5	6.8

a) The reaction was carried out at 55°C for 30 min in methanol–water. Yields were determined by glc with biphenyl as an internal standard.

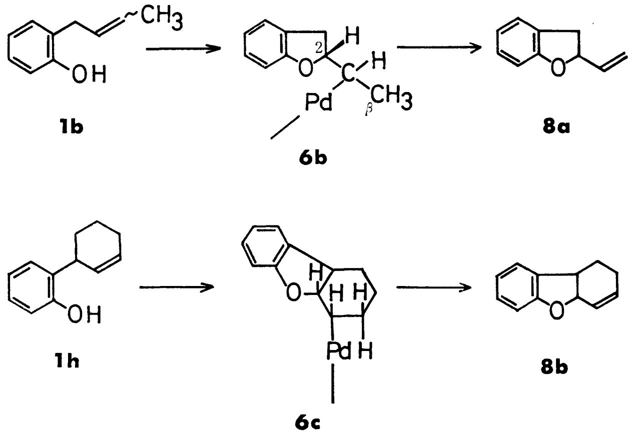
Catalytic Cyclization Using Palladium(II) Acetate. Palladium(II) acetate was found to be a convenient reagent for the reaction because it caused the cyclization of 2-allylphenols directly without using the sodium salts. Hence, the catalytic reaction was performed by use of the reagent.

TABLE 5. CATALYTIC CYCLIZATION OF ALLYLPHENOLS WITH PALLADIUM(II) ACETATE IN THE PRESENCE OF CUPRIC ACETATE[a)]

Allylphenol **1**	Product	Yield on Pd(OAc)$_2$, % (Yield on **1** used, %)	Conversion of **1**, %
1a	**2a**	1960(34)	99
1b	**8a**	2720(54)	99
	2b	trace	
1c	**2c**	1170(23)	63
1d	—	—	—
1e	**2e**	786(16)	53.5
1h	**8b**	1000(20)	46

a) All reactions were carried out at ~55 °C for 24 hr in methanol (25 ml)–water (2 ml). Allylphenol **1** (10 mmol), Pd(OAc)$_2$ (0.2 mmol), and Cu(OAc)$_2$·H$_2$O (5 mmol) were used. Yields and conversions were determined by glc and/or NMR analyses.

By considering the fact that reduced palladium metal is readily reoxidized with cupric salt and molecular oxygen as is well known in the Wacker process,[7] the reaction of 2-allylphenols **1** (10 mmol) was carried out in methanol–water solvent in the presence of a catalytic amount of palladium(II) acetate (0.2 mmol) and cupric acetate (5 mmol) under oxygen atomosphere. As indicated in Table 5, the reaction gave 2-substituted benzofurans catalytically with palladium(II) acetate, but 2-allyl-1-naphthol (**1d**) afforded polymeric material probably because of its oxidation with oxygen. In the catalytic reaction it should be noted that 2-(2′-butenyl) phenol (**1b**) gave 2,3-dihydro-2-vinylbenzofuran (**8a**) exclusively with a trace amount of 2-ethylbenzofuran (**2b**). Furthermore, 2-(2′-cyclohexenyl)phenol (**1h**) gave **8b** exclusively. (Scheme 2).



Scheme 2.

The exclusive formation of **8a** is probably due to the excess amount of **1b** to palladium(II) acetate as already shown in Table 4, although the influence of cupric salt cannot be neglected.[8] Mechanistic detail is not yet clear at present, but exclusive formation of **8a** in *the catalytic reaction* indicates that the β-hydrogen elimination occurs preferentially from the methyl group in **6b** as shown in Scheme 2. Thus, it is reasonable to suppose that the hydrogen on the C-2 carbon in **6b** is to take *trans*-configuration to palladium, since *cis*-palladium hydride eliminations are generally accepted.[9] In other words, the present catalytic reaction conceivably proceeds *via* a *cis*-oxypalladation step.

Exclusive formation of **8b** in the catalytic reaction of **1h** is also explained by the *cis*-oxypalladation followed by *cis*-elimination of a hydridopalladium species. *cis*-Oxypalladation of **1h** leads to the intermediate **6c** which bears only one *cis*-β-hydrogen to palladium as shown in Scheme 2. The elimination of the hydrogen gives only **8b**.

Experimental

2-Allylphenols 1. 2-Allylphenol (**1a**) and 2-cinnamylphenol (**1c**) were prepared by the method described in the literature.[10] 2-Allyl-1-naphthol (**1d**) and 1-allyl-2-naphthol (**1e**) were prepared by heating the corresponding allyloxynaphthalenes at 210—230 °C for 1 hr according to the method of Claisen.[11,12] 2-(2′-Cyclohexenyl)phenol (**1h**) was prepared by heating cyclohex-2-enyl phenyl ether in *N*,*N*-diethyl aniline at 200—215 °C for 30 min.[13] 2-(α,α-Dimethylallyl)phenol (**1g**) was prepared from 3-methylbut-2-enyl phenyl ether according to the method of Vdovtsova[14] and purified by preparative glc.

2-(2′-Butenyl)phenol (**1b**) and 2-(2′-methyl-2′-butenyl)phenol (**1f**) were synthesized by C-alkylation of sodium phenoxide with crotylbromide and 1-bromo-2-methylbut-2-ene[15], respectively, according to the procedure of Hurd and Hoffman.[16] (2′-Butenyl)phenol (**1b**) was obtained in a mixture of *trans* and *cis*-isomers on a ratio of 1.9:1. 2-(2′-Methyl-2′-butenyl)phenol (**1f**) was obtained in a mixture of *trans* and *cis*-isomers on the ratio of 4.5:1. **1f** *trans-dimethyl*, NMR, δ 1.59 (broad s, 3H), 1.63 (nearly dd, J=7 and 1 Hz, 3H), 3.30 (broad s, 2H), 5.13 (broad s, 1H), 5.15—5.56 (m, 1H), and 6.53—7.20 (m, 4H). (Found: C, 81.04; H, 8.93%. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70%). **1f** *cis-dimethyl*, NMR, δ 1.62 (nearly dd, J=1.5 and 2.0 Hz, 3H), 1.74 (broad d, J=7 Hz, 3H), 3.38 (broad s, 2H), 4.82—5.10 (m, 1H), 5.48 (nearly q, J=7 Hz, 1H), and 6.50—7.18 (m, 4H). (Found: C, 81.00; H, 8.78%. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70%).

General Procedure for Stoichiometric Cyclization. A suspension of allylphenol **1** (5 mmol) and sodium methoxide (5 mmol) in dry benzene (50 ml) was stirred at room temperature under argon atmosphere. Dark green or blue coloration developed after 1—2 day's stirring. Dichlorobis(benzonitrile) palladium (5 mmol) was added into the suspension. The mixture was slowly heated to reflux for 3 hr. Palladium black gradually precipitated. After filtration of palladium black, the filtrate was concentrated *in vacuo* to leave reddish oil which was distilled under reduced pressure. Generally, distillation gave a mixture of benzonitrile and cyclized product, but the following products were separated from benzonitrile by distillation; bp **2c**, 94—95 °C/4 mmHg, **2d**, 70—72 °C/6 mmHg, and **2e**, 90 °C/8 mmHg. Analytically pure samples were obtained by preparative glc using 10% PEG 20 M–Celite or Apiezon L–Celite column. Elemental analyses and spectral data of the products are listed in Tables 2 and 3.

Cyclization of 2-(1′-Propenyl)phenol (7a) and 2-Styrylphenol (7b). 2-1′-Propenyl)phenol was prepared by isomerization of 2-allylphenol.[10] 2-Hydroxystilbene was synthesized by the procedure of Kauffman.[17]

The cyclization reaction was carried out by the same procedure described above. The yield of the product **2a** (17%) was determined by glc and NMR analyses. Sodium salt of **7b** (0.50 g, 2.5 mmol) was treated by the same procedure. The product was separated by column chromatography on alumina. Elution with benzene gave colorless crystals of **2i** (0.10 g, 20%) which was recrystallized from petroleum ether, mp 120—121 °C (lit,[18] 120 °C). (Found: C, 86.55; H, 5.10%. Calcd. for $C_{14}H_{10}O$: C, 86.57; H, 5.19%). From a fraction eluted by ether and methanol, 2-styrylphenol (0.24 g) was recovered.

General Procedure for Catalytic Cyclization. A suspension of allylphenol **1** (10 mmol) in methanol (25 ml) and water (2 ml) was stirred at ~55 °C for 24 hr in the presence of $Pd(OAc)_2$ (0.2 mmol) and $Cu(OAc)_2 \cdot H_2O$ (5 mmol) under slow stream of oxygen. After filtration, the solution was diluted with water, extracted with ether, and dried over magnesium sulfate and the solvent was removed. The cyclized product was separated by distillation under reduced pressure and was analyzed by glc and NMR analyses. In some cases, the starting phenol was removed by washing the distillate with Claisen's alkali. Analytically pure samples were obtained by preparative glc. The yields of the products and the conversions of the starting materials are given in Table 5. Specific results were described below.

Reaction of 1b. **1b** (*trans*/*cis*=1.9/1) was treated by the general procedure. The product **8a** was separated by distillation (bp 75 °C/4 mmHg). The NMR spectrum of **8a** was identical with the reported data.[19]

Reaction of 1h. **1h** was treated by the general procedure. The distillate was washed four times with Claisen's alkali, extracted with ether, washed with water, and dried over magnesium sulfate. Evaporation of ether gave a colorless oil which was only **8b** by glc analysis. Distillation gave pure **8b**, bp 109—110 °C/3 mmHg. **8b**, NMR, δ 1.4—2.4 (m, 4H), 3.28 (m, 1H), 4.85 (dd, J=8 and 2 Hz, 1H), 5.90 (m J=2 Hz, olefinic H), 6.69 (phenyl, 2H), and 6.98 (phenyl, 2H); IR, 1650 cm^{-1} (C=C); Mass *m*/*e* 172; Found: C, 83.44; H, 7.00%. Calcd for $C_{12}H_{12}O$: C, 83.67; H, 7.02%. The assignment of the structure **8b** was supported by double irradiation experiment in NMR. The signal of the tertiary proton (H_a) adjacent to oxygen atom (δ 4.85) was simplified by double irradiation at the signal of the other tertiary proton (H_b) to show a doublet (J=2 Hz). Also, the irradiation of olefinic proton (δ 5.90) simplified the signal of H_a to show clearly a doublet (J=8 Hz). Double irradiation of H_a proton transformed the signal of H_b from a multiplet to nearly double doublet (J=4 and 8 Hz). The irradiation at δ 1.99 (one of protons on cyclohexene ring) simplified the multiplet of H_b proton to show nearly triplet (J=8 Hz).

Reaction of 2-γ-Methylallylphenol (1b) with Palladium(II) Acetate. Palladium(II) acetate was allowed to react with various amounts of **1b** in methanol–water at 55 °C for 30 min. In each run the crude reaction mixture was analyzed by glc (flame ionization detector, 5% PEG-20M on Gas Chrom Q, lm) with biphenyl as an internal standard.

References

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