May, 1993] © 1993 The Chemical Society of Japan Bull. Chem. Soc. Jpn., 66, 1511—1515(1993) 1511

A Practical O_2-Oxidation of Functionalized Alcohols Producing Carboxylic Acids Catalyzed by the Pd–C/Pb(OAc)$_2$ System

Mitsuo Akada,* Shinji Nakano, Toshiyuki Sugiyama,† Kazumoto Ichitoh,† Hiroki Nakao,†
Munetaka Akita,† and Yoshihiko Moro-oka*,†
Tokushima Research Laboratories, Otsuka Chemical Co., Ltd., Kagasuno, Kawauchi-cho, Tokushima 771-01
†Research Laboratory of Resources Utilization, Tokyo Institute of Technology,
4259 Nagatsuta, Midori-ku, Yokohama 227

(Received December 18, 1992)

The Pd–C/Pb(OAc)$_2$ system catalyzes selective O_2-oxidation of ArCH(R)CH$_2$OH to ArCH(R)COOH (useful intermediates for drug synthesis) in high yields without contamination of ArCOOH. The turnover number (substrate/Pd) is improved to 85 and >1800 by recycling the catalyst and using a special reactor, respectively. Alkanols are also efficiently oxidized to alkanoic acids by the title catalyst system.

Catalytic oxidation with molecular oxygen, compared to stoichiometric oxidation which uses oxidants much more expensive than dioxygen, has been recognized as an attractive method for oxygenation of organic compounds.[1,2] Although a variety of effective stoichiometric oxidations have been developed so far,[1] improvement of yield and selectivity has remained to be solved for practical O_2-oxidation.

We have been seeking for an efficient large-scale preparative method for derivatives of arylacetic acid (ArCH$_2$COOH), which are widely found in the structures of drugs such as anti-inflammatory drugs (e.g. ibuprofen), β-blockers (e.g. atenolol), antibiotics (e.g. latamoxef), and so on (Fig. 1. The arylacetyl moieties are boldfaced). One of promising preparative routes is oxidation of 2-arylethanols (ArCH$_2$CH$_2$OH), which are readily accessible via the ring-opening reaction of epoxides with aryl Grignard reagents.[3,4] (Eq. 1)

(1)

However, unless reaction conditions are well tuned, formation of benzoic acid (ArCOOH) via a benzylic oxidation becomes a serious side reaction. Herein we report a practical O_2-oxidation of alcohols (in particular, 2-arylethanols) producing carboxylic acids catalyzed by the Pd–C/Pb(OAc)$_2$ system.

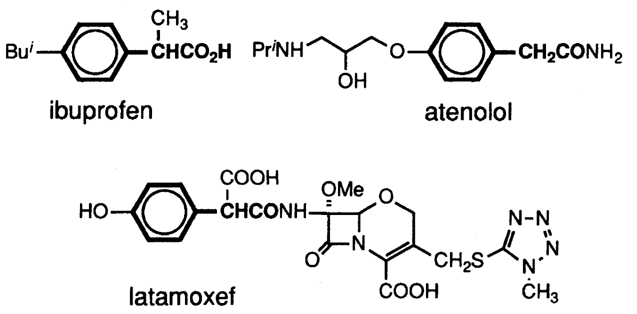
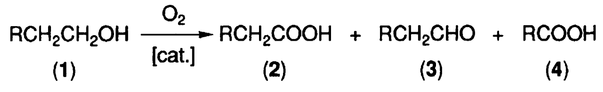


Fig. 1. Structures of representative drugs containing an arylacetyl functional group.

Results and Discussion

Optimization of Catalyst System and Reaction Conditions. Since our final goal is preparation of arylacetic acids in an industrial scale, we choose noble metal–charcoals (M–C) as a catalyst taking account of their facile separation and recovery from a reaction mixture. It has been well-established that M–C's catalyze hydrogen-transfer reactions including reduction and oxidation of organic compounds.[1,2,5]

The results of oxidation of 2-(4-methoxyphenyl)ethanol **1a** (a standard substrate) catalyzed by various M–C's (Eq. 2) are summarized in Table 1. (No other volatile product could be detected by GLC analysis of the reaction mixture.) Reactions were carried out in a basic aqueous solution under pressure of O_2 for 3 h at 90 °C. Of the employed catalysts Pd–C showed the highest activity, but a considerable amount of 4-methoxybenzoic acid (**4a**) was formed. Although Pt–C was reported to be effective for oxidation of 2-phenylethanol (**1e**),[6] the oxidation of **1a** (with air-bubbling in boiling water) afforded only a small amount of **2a** (11%) together with unidentified tarry products (conversion of **1a**: 98%).



$$\underset{(1)}{RCH_2CH_2OH} \xrightarrow[\text{[cat.]}]{O_2} \underset{(2)}{RCH_2COOH} + \underset{(3)}{RCH_2CHO} + \underset{(4)}{RCOOH} \tag{2}$$

Table 1. O_2-Oxidation of 4-Methoxyphenylethanol (**1a**) Catalyzed by Noble Metal Charcoals[a)]

Catalyst (M–C)	O_2 pressure (atm)	**1a** (recovered)	**2a**	**3a**	**4a**
Pd–C	3	0	36.2	0.7	24.6
Pt–C	5	2.8	11.0	9.8	6.0
Rh–C	5	61.0	11.9	7.9	4.5
Ru–C	5	63.7	18.1	3.7	4.7

a) Reaction conditions: **1a** (770 mg, 5.06 mmol), M–C (330 mg; all the catalysts contained 5 wt% M), NaOH (380 mg, 9.50 mmol), water (5 mL), at 90 °C for 3 h. The yields of the products were determined by GLC after acidification.

In order to suppress the side reaction giving **4a**, the Pd–C catalyst was modified by additives, the effect of which is summarized in Table 2. Of the additives examined lead(II) acetate proved to be most effective. Although the Pd–C catalyst deactivated with Pb(II), so-called Lindlar catalyst, has been widely used for partial reduction of alkynes to *cis*-alkenes,[5,7] its application to oxidative transformations has been studied less extensively. Copper(II) acetate which was used as a cocatalyst in Wacker-type alkene oxidation processes[8] also improved the selectivity, but the other additives showed little apparent effect or considerably reduced the catalytic activity itself.

Then the reaction conditions were optimized as the functions of the amounts of Pd–C, $Pb(OAc)_2$, and NaOH, reaction temperature, reaction time, and O_2 pressure. (Fig. 2a—f) As a result, **1a** (770 mg, 5.06 mmol) was converted to **2a** in more than 90% yield (up to 93.8%) with good reproducibility under the catalysis of the 5% Pd–C (330 mg, 0.16 mmol Pd; 3.1 mol % on the basis of **1a**)/$Pb(OAc)_2{\cdot}3H_2O$ (50 mg, 0.13 mmol)/NaOH (380 mg, 9.5 mmol) system (in 5 mL water under 5 $kg\,cm^{-2}$-O_2 pressure for 3 h at 90 °C). While the amount of Pd–C can be reduced to 2.4 mol%, it is recommended to use a 3.1 mol %-amount to get reproducible results.

Recovery and Recycling of the Catalyst. Taking advantage of the heterogeneity of the present system, we attempted recovery and recycling of the rather expensive catalyst. Thus after catalytic oxidation the catalyst was recovered by simple filtration. The product **2a** was isolated from the filtrate after acidification, and the collected solid was used again as the catalyst without further addition of $Pb(OAc)_2{\cdot}3H_2O$. By repeating this procedure the catalyst could be reused twice without any notable deterioration of the selectivity and activity, and the estimated total turnover number was much improved from 32 (batch reaction) to 85 (3 oxidation cycles).[9] (Table 3)

To be noted is that heating the reaction mixture in the absence of **1a** (or after consumption of **1a**) appeared to induce deactivation of the catalyst. XRD analysis of the deactivated catalyst showed formation of PdO (See below). Therefore, when the reaction is continued after consumption of a substrate, the Pd component in the catalyst is irreversibly oxidized to PdO. Although the resulting PdO can be reactivated by treatment with hydrogen, it can not be reduced by the substrate.

Table 2. Effect of the Additives on the Oxidation of **1a**[a)]

Additive (mg)	1a	2a	3a	4a
None	0	36.2	0.7	24.6
$Pb(OAc)_2{\cdot}H_2O$ (50)	0.6	93.8	0.2	0.6
$Cu(OAc)_2$ (50)	0	72.4	0.5	11.9
$ZnCl_2$ (25)	0	33.7	1.3	27.6
Pyridine (50)	0	33.7	0.4	17.1
PPh_3 (50)	0	31.8	1.0	26.6
Thiourea (25)	82.3	0.5	6.1	1.9
Pd–S–C[b)]	0	34.2	1.0	19.5

a) Reaction conditions: **1a** (770 mg, 5.06 mmol), 5% Pd–C (330 mg), NaOH (380 mg, 9.50 mmol), O_2 (5 $kg\,cm^{-2}$), water (5 mL), for 3 h at 90 °C. b) Commertially available deactivated Pd–C.

Table 3. Recycling Use of the Recovered Catalyst

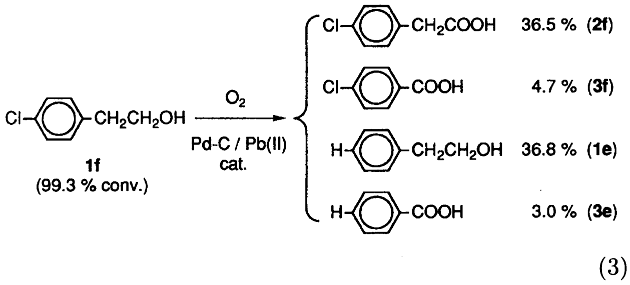
Cycles	1a	2a	3a	4a
Fresh[a)]	0.8	91.5	0.7	4.8
1[b)]	5.8	90.0	0.3	2.3
2[b)]	10.1	87.5	0	2.0
3[b)]	73.6	14.2	1.0	5.4
4[b)]	70.0	15.8	1.5	6.7

a) Reaction conditions: **1a** (770 mg, 5.06 mmol), 5% Pd–C (330 mg), NaOH (380 mg, 9.50 mmol), O_2 (5 $kg\,cm^{-2}$), water (5 mL), for 3 h at 90 °C. b) The same amounts of **1a**, NaOH, and water were added, and reactions were carried out under the same conditions.

This problem could be overcome by using a special reactor, which was designed so as to, under pressure of O_2, add reactants and remove contents through a filter (Fig. 3). For example, in this special autoclave (1L) charged with **1a** (15.4 g, 101 mmol), 5% Pd–C (6.6 g, 2.8 mmol Pd), $Pb(OAc)_2{\cdot}3H_2O$ (0.5 g), NaOH (8.2 g), and water (200 mL) the oxidation was carried out under 3 $kg\,cm^{-2}$-O_2 pressure at 90 °C with continuous, simultaneous addition of the reactants (**1a**/NaOH/water=15.4 g/8.2 g/200 mL) and removal of the aqueous phase. In order to avoid deactivation of the catalyst it was essential to control the conversion of **1a** between 80 and 90% by adjusting the rates of the addition and removal (2.9 $mL\,min^{-1}$). After addition of 66 batches of the reactants the total turnover number exceeded 1800 (2.8 kg **2a**/1 g Pd) when the formation of **4a** was negligible (<2%).

Catalytic Oxidation of Other Alcohols. The present oxidation method was applied to other substrates to define its limitation (Table 4).

2-Arylethanols (**1b**—**e**) including the **1a**'s isomers (**1b,c**) were successfully oxidized to the corresponding arylacetic acids (**2b**—**e**) in high yields. However, in the case of the 4-Cl derivative (**1f**) another side reaction affording the reduced products (**1e** and so on) became evident. (Eq. 3)



(3)

2-Arylethanol bearing a substituent at the benzylic

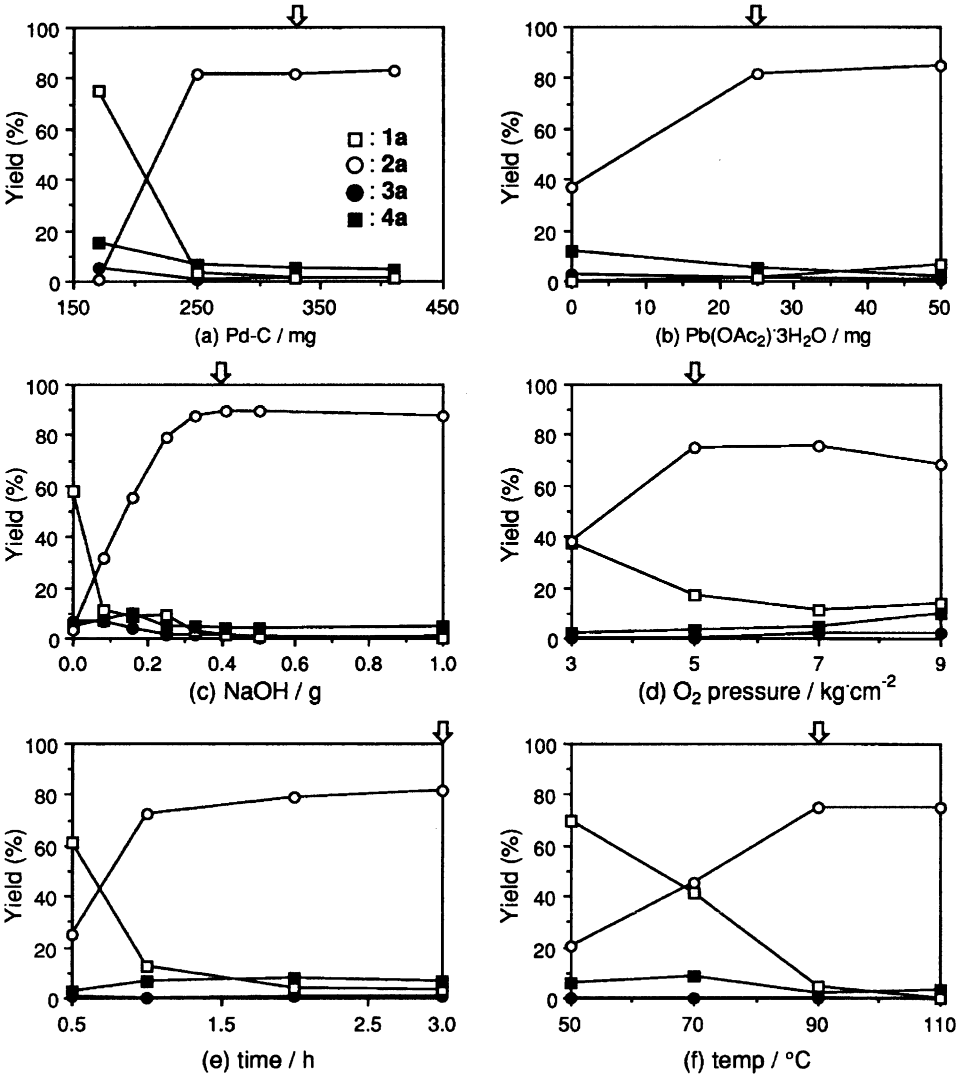


Fig. 2. Optimization of the catalyst system and the reaction conditions. The optimized conditions are indicated by arrows. Fixed conditions are as follows. [A/mg (5% Pd–C), B/mg ($Pb(OAc)_2\cdot 3H_2O$), C/g (NaOH), D/mL (H_2O), E/kg cm^{-2} (O_2 pressure), F/°C (temperature), G/h (time).] (a) 5% Pd–C: B 25, C 0.25, D 5, E 5, F 90, G 3. (b) $Pb(OAc)_2\cdot 3H_2O$: A 330, C 0.25, D 5, E 5, F 90, G 3. (c) NaOH: A 330, B 50, D 5, E 5, F 90, G 3. (d) O_2 pressure: A 330, B 50, C 0.25, D 15, F 90, G 3. (e) reaction time: A 330, B 25, C 0.25, D 5, E 5, F 90. (f) reaction temperature: A 250, B 25, C 0.25, D 15, E 5, G 3.

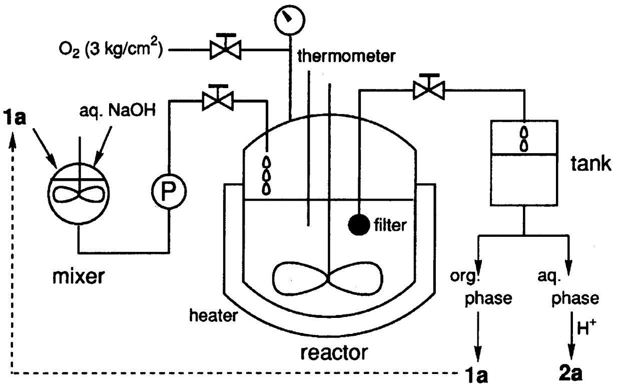


Fig. 3. Schematic representation of a special reactor for the simultaneous, continuous addition-removal experiment.

position was subjected to the oxidation. As a typical example, ibuprofen (**2g**) was prepared from 2-(4-isobutylphenyl)-1-propanol (**1g**). In this case, too, a satisfactory results was obtained, when the oxidation was carried out at higher temperature. This result implicates that the present method serves as a promising route for synthesis of drugs, for example, shown in Fig. 1.

The present system proved to be effective also for oxidation of 1-alkanols (**1h**—**k**). Since the side reaction giving a product with a shorter carbon chain was not observed at all for these substrates, application of more vigorous reaction conditions (150 °C, 10 kg cm^{-2} O_2) completed the oxidation within 1 h. In the case of longer chain alcohols vigorous stirring was essential for high conversion owing to their lower solubility in

Table 4. Catalytic Oxidation of Various Alcohols Giving Carboxylic Acids

Alcohol	Conditions[a]	O_2 kg cm^{-2}	Temp. °C	Reaction time h	**2** %	Recovered alcohol
4-MeO–$C_6H_4CH_2CH_2OH$ (**1a**)	A	5	90	3	93.8	0.6
2-MeO–$C_6H_4CH_2CH_2OH$ (**1b**)	A	5	90	3	82.3	0.8
3-MeO–$C_6H_4CH_2CH_2OH$ (**1c**)	A	5	90	3	82.8	0.5
4-HO–$C_6H_4CH_2CH_2OH$ (**1d**)	A	5	90	3	80.5	1.8
$C_6H_4CH_2CH_2OH$ (**1e**)	A	5	90	3	83.8	1.8
4-$ClC_6H_4CH_2CH_2OH$ (**1f**)[b]	A	5	90	3	36.5	0.7
4-*i*-Bu–$C_6H_4CH(CH_3)CH_2OH$ (**1g**)	A	5	90	3	56.3	29.6
	A	5	110	4.5	77.6	0.8
n-C_3H_7OH (**1h**)	A	10	150	1	90.3	0
n-$C_6H_{13}OH$ (**1i**)	A	10	150	1	79.3	0
n-$C_7H_{15}OH$ (**1j**)	A	10	150	1	73.4	0
n-$C_8H_{17}OH$ (**1k**)	A	10	150	1	76.0	7.5
$HO(CH_2)_3OH$ (**1l**)	A	10	150	1	89.5	0
$HO(CH_2)_4OH$ (**1m**)	A	10	150	1	85.2	0
$CH_3(CH_2)_5CH(OH)CH_3$ (**1n**)[c]	A	10	150	0.5	42.8[d]	0.3
PhCH=$CHCH_2OH$ (**1o**)[e]	B	10	25	5	72.5	2.7
Geraniol (**1p**)	B	10	25	6	38.5	15.5

a) Reaction conditions: A: Alcohol (5 mmol; diol: 2.5 mmol), Pd–C (330 mg), $Pb(OAc)_2{\cdot}3H_2O$ (25 mg), NaOH (380 mg), H_2O (5.0 mL). B: alcohol (5 mmol), Pd–C (330 mg), $Pb(OAc)_2{\cdot}3H_2O$ (50 mg), NaOH (410 mg), H_2O (5.0 mL). b) See text. c) See text. d) 2-Octanone. e) PhCH=CHCHO (3.2%) and PhCOOH (4.6%) were also formed.

aqueous phase. Even under the optimized conditions a small amount of 1-octanol (**1k**) remained unreacted. Although addition of a crown ether (18-crown-6) improved the yield, instead separation of the product became difficult. Diols (**1l,m**) were similarly converted to the corresponding alkanedioic acids in good yields. However, oxidation of a secondary alcohol (2-octanol: **1n**) gave a mixture of products containing 2-octanone (**2n**: 42.8%) and heptanoic acid (3.3%).

Allylic alcohols were too reactive to be oxidized in a controlled manner. While cinnamyl alcohol (**1o**) was converted to *trans*-cinnamic acid (**2o**) in 72.5% yield even at room temperature, alkylated allyl alcohols except geraniol (**1p**) (e.g. allyl, crotyl, methallyl, and prenyl alcohols) produced the expected carboxylic acids in less than 10% yields. The quite low recovery of volatile organic compounds, in particular in the case of lower molecular weight substrates, might result from polymerization or further oxidation of products.

Comments on the Reaction Mechanism. The Pd–C catalyzed oxidation of 2-arylethanols (**1**) (Table 1) produces mixture of arylacetic acid (**2**) and benzoic acid (**4**). Because exposure of **2a** to the reaction conditions shown in Table 1 (Pd–C) does not produce **4a** at all (recovery of **2a**: 98.4%), the two products are formed via separate reaction pathways, i.e. **2** and **4** arise from oxidation of the CH_2OH functional group and benzylic oxidation of the $ArCH_2$ moiety with C–C bond cleavage, respectively. The latter process is almost completely suppressed upon the addition of Pb(II), and, consequently, the modified Pd–C/$Pb(OAc)_2$ system serves as an efficient catalyst for O_2-oxidation of **1** leading to arylacetic acids (**2**).

With respect to the former process (**1**→**2**), a Wacker-type mechanism[8,10] is apparently supported by the following two observations: (1) the addition of copper(II) acetate (a representative Wacker cocatalyst) improves the selectivity of the oxidation in a manner similar to Pb(II) (Table 2) and (2) the present system catalyzes reduction of the Cl–C (sp^2) bond in **1f** (Eq. 3), a characteristic reactivity of a Pd(0) species. It is notable that, in the experiment using the special reactor, the initial addition of a small amount of Pb(II) is adequate for the high turnover. This means that Pd–C and Pb(II) ion form a composite or an alloy which is sparingly soluble to the reaction media. In order to get insight into the state of the solid phase the active and deactivated catalysts were analyzed by XRD. For the inactive catalyst, covering the Pd surface with Pb and sintering of the catalyst were evident in addition to the formation of PdO (see above). However, no meaningful information could be deduced from the active one. In addition, the role of Pb(II) is not clear until now. (Does it suppress the benzylic oxidation or accelerate the alcohol oxidation ?) Further study is necessary to clarify the reaction mechanism.

Experimental

All the substrates and chemicals were obtained commercially and used as received. 5% Pd–C was obtained from Engelhard and Nikki Chemical Co. Water was passed through an ion-exchange resin. The products were identified by comparison of their spectral data (^{1}H NMR, IR) and GLC retention time with those of the authentic samples.

Catalytic Oxidation of Alcohol. A 50 mL stainless steel autoclave was charged with 5% Pd–C, $Pb(OAc)_2{\cdot}3H_2O$, NaOH, alcohol (**1**), and water. After being pressurized with O_2 the autoclave was heated with vigorous magnetic stirring in a temperature-controled oil bath.

After appropriate reaction time the oxidation was stopped by immersing the autoclave in an ice–water bath. Then the O_2 pressure was released, the contents were filtered with suction, and the autoclave and the recovered catalyst were washed with water several times. After the filtrate was washed with ether three times to remove organic impurities, the aqueous phase was acidified to pH 4 by addition of 6 M HCl aqueous solution. Then the product (carboxylic acid) was back-extracted with dichloromethane. Drying the organic phase over sodium sulfate and successive distillation or crystallization afforded the expected carboxylic acid.

In determining yields of the products by GLC (internal standard method), **2a**—**g** were quantified directly after acidification [column: 5% Thermon 3000/Chromosorb W (AW-DMCS). Shimadzu GC-9A (FID)]. The remaining products **2h**—**p** were quantified after methylation. The contents of the autoclave were washed out with methanol.[11] Then the filtrate was acidified with 6 M HCl aq and organics were extracted with dichloromethane. Carboxylic acids were methylated by treatment with a CH_2Cl_2 solution of an excess amount of diazomethane for 10 min at ambient temperature, and the remaining diazomethane was destroyed by addition of acetic acid. Then yields were determined by GLC after drying over sodium sulfate [10% PEG-20M/Uniport HD. Hitachi 163 (FID)].

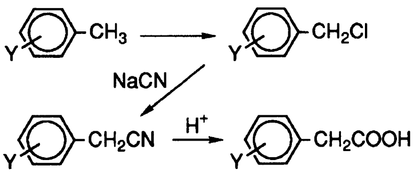
References

1) M. Hudlicky, "Oxidations in Organic Chemistry," in "ACS Monograph 186," American Chemical Society, Washington DC (1990).

2) R. A. Sheldon and J. K. Kochi, "Metal-Catalyzed Oxidations of Organic Compounds," Academic Press, New York (1981).

3) N. G. Gaylord and E. I. Becker, *Chem. Rev.*, **40**, 413 (1951).

4) Another attractive preparative method is shown below (Eq. 4). This method uses a stoichiometric amount of the highly toxic reagent (NaCN), and the initial radical chlorination is not compatible with reducible substituents (Y) such as OH. Furthermore such electron-donating substituents (Y) often induce electrophilic chlorination at the ortho-position. M. Akada, unpublished result.



(4)

5) M. Hudlicky, "Reductions in Organic Chemistry," Ellis Horwood, Chichester, England (1984).

6) K. Heyns and L. Blazewicz, *Tetrahedron*, **9**, 676 (1960).

7) H. Lindlar, *Helv. Chim. Acta*, **35**, 446 (1952).

8) J. P. Collman, L. S. Hegedus, J. R. Norton, and R. G. Finke, "Principles and Applications of Organo-Transition Metal Chemistry," 2nd ed, University Science Book, Mill Valley, CA (1987).

9) The turnover numbers were calculated on the basis of the amount of Pd (mmol) present in Pd–C.

10) Oxidation of alcohol may proceed via β-elimination of an alkoxy-Pd(II) intermediate (R–CH_2O–Pd) with liberation of aldehyde (R–CHO), which is further oxidized to carboxylic acid (R–COOH) via a free radical mechanism. Subsequent deprotonation of the resulting H–Pd(II) species forms Pd(0), oxidation of which is coupled with the Pb(II)→Pb(0) process to give Pd(II). Regeneration of Pb(II) by O_2 oxidation of Pb(0) completes the catalytic cycle. However, since homogeneous $PdCl_2/Pb(OAc)_2$ system did not show any catalytic activity for the oxidation, we may need to consider other mechanisms. Another possibility is a Pb-centered mechanism, where a Pb(IV) species oxidizes alcohol and Pd–C catalyzes reoxidation of Pb(II) and/or oxidation of the resulting aldehyde. Stoichiometric oxidation of alcohol with Pb(IV) is precedented: R. E. Partch, *Tetrahedron lett.*, **1964**, 3071; K. Heusler, *Tetrahedron Lett.*, **1964**, 3975; M. L. Michailovic, J. Bosnjak, Z. Maksimovic, Z. Cekovic, and L. Lorenc, *Tetrahedron*, **21**, 955 (1966).

11) When methanol was used as the washing solvent in the case of isolation experiments, a considerable amount of the methyl ester was formed.