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Review

Oxidative reactions by a palladium–alkyl nitrite system[☆]

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Abstract

The typical oxidative reactions ((1) dialkyl oxalate synthesis from carbon monoxide, (2) dialkyl carbonate synthesis from carbon monoxide, (3) acetals and ketals synthesis from olefins, and (4) oxidative carbonylation of olefins) catalyzed by palladium in the presence of alkyl nitrites, are described. The mechanistic studies are conducted based on reaction kinetics. In addition, derivation of acetals obtained by olefin oxidation to various useful fine chemicals is also described. © 1999 Elsevier Science S.A. All rights reserved.

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1. Introduction

Palladium metal and palladium salts are known to catalyze many important organic reactions and have been utilized in various important industrial processes [1–5]. One of the most significant applications of palladium catalysts is the oxidation of ethylene to produce acetaldehyde, known as the Wacker process [6,7]. Since their development in 1958, the catalyst systems based on palladium have emerged as the mainstream oxidative catalyst used in industry. For example, vinyl acetate and allyl acetate are produced by the oxidation of ethylene, and propylene, respectively. Several reviews concerning these industrial processes are found in the literature [2,4,8].

A crucial step in the industrial oxidative reactions catalyzed by palladium is the effective regeneration of Pd(II) from Pd(0) which is reduced in the reaction.

Generally it is quite difficult to directly reoxidize Pd(0) to Pd(II) by molecular oxygen except in the case of Wacker and related processes mentioned above, where reoxidation of Pd(0) is performed by an excess amount of $CuCl_2$ and investigations to improve this process are still an active research field. Major drawbacks for the Wacker type reoxidation process are (1) the use of excess $CuCl_2$ which causes corrosive damage to normal industrial reactors, and requires special anticorrosion materials for the reactors which will result in higher cost for the product and (2) the separation of the reaction product from the catalyst is quite difficult in some cases. In addition to overcoming these drawbacks, high catalyst efficiency, high yield and selectivity for the product, easy recovery of the catalyst, negligible loss of the catalyst (especially palladium), and development of efficient, facile reoxidation process must be achieved to develop an industrial process utilizing expensive palladium as a catalyst. A solution to those subjects is to develop a gas phase reaction process instead of a liquid phase, and only a few palladium catalyzed oxidative reactions which could be operated in gas phase have been successfully developed into industrial processes.

In 1977, we discovered that alkyl nitrites (RONO **1**) act as efficient reoxidizing agents for Pd(0) during the research on the industrial production of dialkyl oxalate

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[☆] Dedicated to Professors Richard F. Heck and Jiro Tsuji.

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Table 1
Physical properties of alkyl nitrites **1**

R	B.p. (°C)	M.p. (°C)	D.p.[a] (°C)	Dissociation energy (kcal mol^{-1})	
				Experiment	Calculated
Methyl (MN **1a**)	−12	−17	141	41.8[b]	45.1[c]
Ethyl (EN **1b**)	17	−35	116	42.0[b]	
n-Butyl (BN **1c**)	103	No data	96	42.5[b]	

[a] Decomposition point.
[b] Refs. [13,14].
[c] Ref. [10].

2 by oxidative coupling of CO and alcohol in the presence of a palladium catalyst [9]. Since then, alkyl nitrite **1** has been found to be also quite effective in the oxidative reactions by palladium catalysts such as oxidative carbonylation of olefins, ketene and diketene, direct synthesis of acetals or ketals from olefins, and the synthesis of dialkyl carbonate from CO and alcohols [10]. UBE has developed these processes into commercial production and the products are further converted to highly valuable fine chemicals [11].

In this review, we refer to these oxidative reactions catalyzed by palladium in the presence of **1** as 'Oxidative reactions by a palladium–alkyl nitrite system' and describe the properties of the reaction, advantages for the industrial production, and derivation of the products.

Since our research interests have been focused on the development of industrial processes, not much research effort has been conducted for the elucidation of the detailed reaction mechanism. Accordingly, it should be acknowledged that the discussed reaction mechanisms are mostly based on kinetic studies by UBE Industries and the past research results.

2. Preparation and properties of alkyl nitrites

Alkyl nitrites have been used for the synthesis of oximes, the Barton reaction, and azide peptide synthesis. They can be synthesized from alcohols, sodium nitrite and sulfuric acid in lab scale [12]. The industrial synthetic method is shown below.

$$2ROH + 2NO + 0.5O_2 \rightarrow 2RONO\ \mathbf{1} + H_2O \qquad (1)$$

Because this reaction involves complicated elementary reactions, a precise reaction control is required to increase the selectivity of alkyl nitrite **1** and suppress the formation of HNO_3, which interrupts the desired reaction. Table 1 shows the physical properties of **1** obtained in this manner.

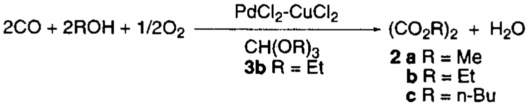
Several examinations of the thermostability revealed that methyl nitrite **1a** could be an explosive, but there is no sign of an explosion under diluted condition. The treatment of **1a** in a commercial plant is therefore, quite feasible under a lower concentration than the explosive limit. Alkyl nitrites are toxic and should be handled carefully though some of them are also employed as medicines.

It is known that an RO–NO bond of alkyl nitrite is easily cleaved homolitically. The bond dissociation energy of **1a** into methoxy radical and NO is estimated to be about 42 kcal mol^{-1}, which is considerably low (45 kcal mol^{-1} was obtained by our theoretical calculation with Gaussian 92 [10]). The decomposition of **1** is accelerated in the presence of acidic catalysts such as zeolites, and affords a fair amount of the corresponding ester (methyl formate from methyl nitrite **1a**, and butyl butylate from butyl nitrite **1c**). In such cases, the activation energy has been estimated to be 12.6 kcal mol^{-1}. It would be also indicated that the decomposition proceeds due to the interaction between the nitrogen atom and the acid point of the zeolites. In addition, the ab initio MO calculation (Gaussian 92) of methyl nitrite **1a**, reveals the large contribution of the atomic orbitals of ONO atoms to HOMO and NO atoms to LUMO [10].

3. Oxidative carbonylation of alcohols utilizing alkyl nitrites

The synthesis of diethyl oxalate **2b** by oxidative carbonylation of ethanol with O_2 in the presence of a $PdCl_2$–$CuCl_2$ catalyst was originally discovered by D.M. Fenton et al. [15] Scheme 1.

Diethyl oxalate **2b** is not formed in the presence of water, so this reaction was carried out with a considerable excess of ethyl orthoformate **3b** as the dehydrating agent, in order to maintain anhydrous conditions in the system. Our research for the development of a new industrial process without using expensive orthoformate



Scheme 1.

Table 2
Catalyst systems for dialkyl oxalate synthesis (liquid phase)

(1) $PdCl_2$–$CUCl_2$–K_2CO_3
(2) $PdCl_2$–$CuCl_2$–R_3N
(3) $Pd(NO_3)_2$–HNO_3
(4) $PdCl_2$–NO
(5) Pd(0)/activated carbon-HNO_3
(6) Pd(0)/activated carbon-NO

as the dehydrating agent revealed that the following catalytic systems afforded oxalate **2** even in the presence of water [16].

Among these Wacker type catalytic systems, (1) and (2) in Table 2 had several drawbacks such as low reactivity, poor selectivity, the deactivation of catalysts due to the precipitation of insoluble cupric oxalate, and so on. The catalytic systems such as (5) and (6) in Table 2 showed a high reactivity, a long catalyst life, and a good selectivity, which were the most favorable properties towards industrialization. Further investigation of the fate of the nitrogen compounds in the system showed that nitric oxide and nitric acid were converted to alkyl nitrite **1** (butyl nitrite **1c** in butanol). A dramatic improvement of the reaction efficiency was observed when **1c** was used instead of HNO_3 or NO. Not only the acceleration of the formation rate of dibutyl oxalate **2c**, but also the selectivity was greatly enhanced. The lifetime of the catalyst also became much longer. Furthermore, **2c** was obtained even under low CO pressure and at lower temperature [9]. In addition we discovered this reaction can be conducted in gas phase as well.

3.1. *Oxidative carbonylation in the liquid phase*

The elementary reactions of dibutyl oxalate **2c** formation in the liquid phase are shown below [9].

$$2CO + 2BuONO\ \mathbf{1c} \xrightarrow{\text{Pd cat.}} (COOBu)_2\ \mathbf{2c} + 2NO \qquad (2)$$

$$\underline{2NO + 2BuOH + 0.5O_2 \rightarrow 2BuONO\ \mathbf{1c} + H_2O} \qquad (3)$$

$$2CO + 2BuOH + 0.5O_2 \rightarrow (COOBu)_2 + H_2O \qquad (4)$$

Besides **2c**, a small amount of dibutyl carbonate **4c** and carbon dioxide are obtained as by-products. In the absence of O_2, two equivalents of the butyl nitrite **1c** (based on the combined amount of **2c** and **4c** produced in the reaction) are consumed. Butanol is indispensable for the formation of **2c**.

In the presence of O_2, the generated NO is transformed into alkyl nitrite **1**, while water is generated at the same time (Eq. (3)). The reaction system should be designed to remove water azeotropically with **1** in a continuous manner to avoid the accumulation of water. For this purpose, butyl nitrite **1c**, was selected as the most favorable alkyl nitrite for the industrial process. Dibutyl oxalate **2c**, was used as the solvent to reduce the formation of **4c** and to facilitate the recycling of palladium.

The ratio of the products **2c** and **4c** is largely influenced by the reaction temperature, the concentration of butanol and CO pressure. The selectivity for oxalate **2c** increases (1) at the lower reaction temperature; (2) lower concentration of butanol; and (3) under the higher CO pressure. For example, at CO pressure lower than 3 kg cm^{-2}, the reaction affords more carbonate **4c** than oxalate **2c** [17].

The effective catalysts towards the liquid phase reaction were found to be palladium metal, palladium salts or those on solid support. In the industrial production, palladium metal supported on activated carbon was the catalyst of choice to prevent loss of palladium and to maintain adequate suspended state.

UBE's first plant for the production of dibutyl oxalate **2c** became operational in 1978. The outline of production process for **2c** is shown in Fig. 1.

A loss of palladium due to the dissolution is extremely small, and the catalytic life is fairly long, however the activity is gradually decreased. This deactivation is caused by a slight amount of CN^- generated in the reaction system and the precipitation of palladium metal is negligible. The catalytic activity is extremely high and TOF (mol/mol-Pd h) exceeds more than 10 000.

Recently polyoxalates have been synthesized from dinitrite [18]. This is the first report that a complex having phosphine ligands is also catalytically active, TOF is, however, 2–3 mol/mol-Pd h, showing quite lower activity.

$$\begin{aligned} &ONO - R - ONO \\ &\quad + 2CO \xrightarrow{\text{Pd(II)}} (-O - R - O - CO - CO -)_n + 2NO \end{aligned} \qquad (5)$$

The selective production of dialkyl carbonate **4**, is also studied both in the gas phase [10] and the liquid phase [17]. Kinetic studies on these reactions are described in Section 7.

3.2. *Oxidative carbonylation in the gas phase*

Our continuous research revealed that oxalate **2** are formed even in the gas phase at atmospheric pressure. Here we selected methyl nitrite **1a** as the suitable alkyl nitrite for the gas phase process for the following reasons, (1) low boiling point of **1a**; (2) facile separation of **1a** from water; and (3) low boiling points of the reaction products, dimethyl oxalate **2a** and dimethyl carbonate **4a**.

By changing the catalyst system, selective formation of **2a** or **4a** can be achieved. Thus, Pd(0) on solid support is used as a catalyst for the **2a** production and $PdCl_2$ on solid support is used for the production of **4a** [19,10].

$$2CO + 2MeONO\ \mathbf{1a} \xrightarrow{\text{Pd/support}} (COOMe)_2\ \mathbf{2a} + 2NO \qquad (6)$$

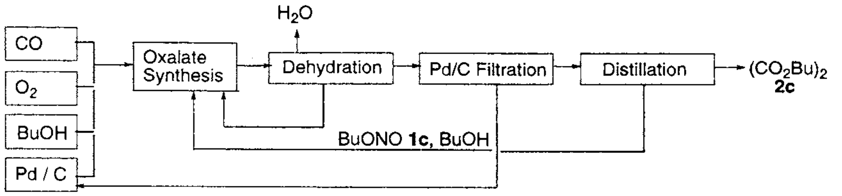


Fig. 1. Flow diagram of UBE liquid phase process of $(CO_2Bu)_2$ **2c**.

$$CO + 2MeONO\ \mathbf{1a} \xrightarrow{PdCl_2-CuCl_2/support} (MeO)_2CO\ \mathbf{4a} + 2NO \quad (7)$$

$$2NO + 2MeOH + 0.5O_2 \rightarrow 2MeONO\ \mathbf{1a} + H_2O \quad (8)$$

Tables 3 and 4 show the product ratio based on the catalyst systems including various solid supports [10,20].

Palladium metal catalyst supported on activated carbon affords dimethyl oxalate **2a** selectively. On the other hand, dimethyl carbonate **4a** is selectively formed when the same catalyst is treated with methyl nitrite **1a** and HCl. This may be due to the oxidation of the Pd(0) to Pd(II) by **1a** and HCl (Table 5).

To keep the oxidation state of palladium at 2+, the presence of a halogen ion like Cl^- and Br^- is important for the formation of **4a** in the gas phase reaction. Surprisingly, NaY zeolite produces **4a** selectively even without halogens.

As it happens in the liquid phase, water becomes a cause of CO_2 formation in the gas phase. Therefore, **1a** is regenerated in a separate reactor to maintain anhydrous conditions for the formation of desired products.

Though the deactivation of the catalyst is caused by aggregation of palladium metal (different from the liquid phase reaction, see Section 3.1), the catalytic lifetime can be as long as 1 year.

UBE Industries constructed a plant for dimethyl carbonate **4a** production with a capacity of 3000 t/year in 1993, the current capacity is twice that. The production process of **4a** is shown in Fig. 2. A pilot plant test in dimethyl oxalate **2a** production was also completed and the technology for the commercial production has been established.

Table 3
Effect of solid supports on $(CO_2Me)_2$ **2a** synthesis[a]

Support[b]	Space time yield (g/l-cat. h)		
	2a	**4a**	MF[c]
Activated carbon	286	12	2
Silica	255	13	4
Activated alumina	114	7	3
α-Alumina	489	11	1
NaY zeolite	58	3	4
Si–Al–O (silica alumina)	112	11	5

[a] Reaction conditions: 110°C, atmospheric pressure, GHSV 2000 h^{-1}; inlet gas composition: CO 10%; **1a** 10%; N_2 base.

[b] Catalyst component: 0.5 wt.% Pd/support.

[c] Methyl formate.

4. Oxidation of olefins

After the development of the oxalate process, we started research on the application of palladium–alkyl nitrite systems toward the Wacker type reaction. It had been well known since 1960 that olefins are oxidized in the presence of alcohol and $PdCl_2$ to give acetals or ketals [22]. However, these products are hydrolyzed with water generated in situ to form aldehydes and ketones which inhibit the reaction. Thus, successful application of these reactions to industrial processes has not been achieved.

Our palladium–alkyl nitrite system, which is free from water, was successfully applied to the oxidation of acrylonitrile **5a**, methyl acrylate **5b**, propylene **7a**, and eugenol derivative **7b** in alcohol to give corresponding acetals and ketals in satisfactory yields, selectivities and catalyst efficiency [23–25] Scheme 2.

This olefin oxidation proceeds only when Pd(II) halides are used as catalysts. Pd(II) halides having weakly coordinating ligands, like RCN, are also active. But the complexes possess strongly coordinating ligands such as phosphines, which do not act as catalysts. The presence of chloride ions accelerates the reaction, especially added to the system as copper (II) chloride. The addition of organic amines does not inhibit the

Table 4
Effect of solid supports on $(MeO)_2CO$ **4a** synthesis[a]

Support[b]	Space time yield (g/l-cat. h)		
	2a	**4a**	MF[c]
Activated carbon	29	553	3
Silica	Trace	58	2
Activated alumina	7	246	2
NaY zeolite[d]	0	210	56
Li–Al–O (spinel)	9	670	Trace

[a] Reaction conditions: 120°C, 0.4 MPa, GHSV 4000 h^{-1}; inlet gas composition: CO 20%; **1a** 10%; HCl 100 ppm; N_2 base.

[b] Catalyst component: Pd 1 wt.%–Cu 1.2 wt.%–Cl 2.0 wt.%/support.

[c] Methyl formate.

[d] Contains no chloride ion. See [21].

Table 5
Change of the catalytic activity by reoxidation treatment[a]

Starting catalyst	Treatment	Valence (XPS)	Catalyst activities[b]	
			2a	**4a**
Pd–Cl/AC[c]	↓	Pd^{2+}	0.05	2.21
	H_2 (200°C, 1 h) ↓	Pd^0	2.14	0.60
	1a+HCl (200°C)	Pd^{2+}	0.13	2.17

[a] Reaction conditions: 120°C, 0.1 MPa, GHSV 8000 h^{-1}; inlet gas composition: CO 8%; **1a** 8%; N_2 base.

[b] Mol/l-cat. h.

[c] Catalyst component: Pd 1 wt.%.

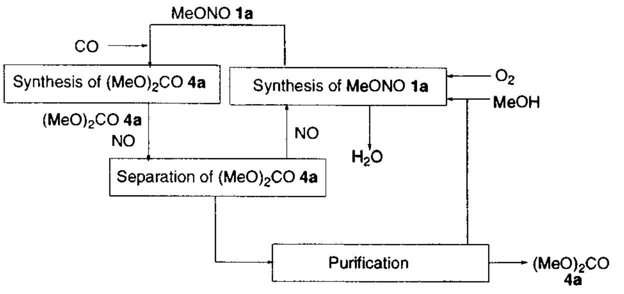
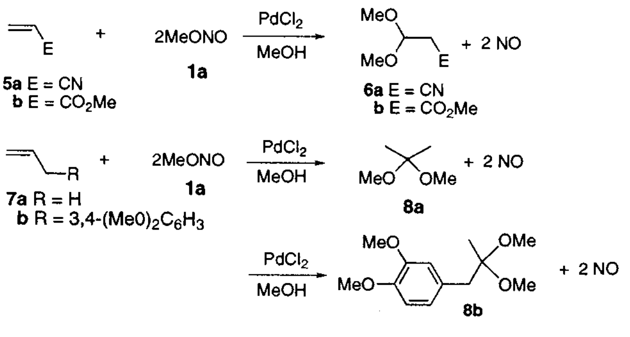


Fig. 2. Flow diagram of UBE gas phase process of $(MeO)_2CO$ **4a**.



Scheme 2. Synthesis of acetals and ketals by the palladium–alkyl nitrite system.

reaction if their amount is less than 0.5 equivalent to the palladium catalyst. Therefore at least one chloride ion per palladium is required for the reaction to be successful.

The migration of a double bond has been reported in the Wacker reaction especially in alcoholic solvents [22]. But no olefin isomerization is observed with our system even in alcohol. Ketal **8b** is isolated without any sign of double bond isomers[1] [26,27].

Only a small amount of vinyl ether is observed which is consistent with the reaction mechanism in which vinyl ethers are converted to acetals without leaving the coordination sphere of palladium [28].

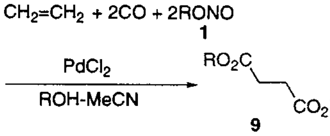
The reactivity of a palladium–alkyl nitrite system toward the olefin oxidation is the same as those reported for Wacker type reactions. Thus, terminal olefins are selectively oxidized while the oxidation of internal olefins proceeds very slowly. In addition, significant substituent effect is observed on the reactivity of olefins. The olefins with an electron withdrawing group are oxidized at the terminal carbon to afford acetals, while only katals are formed from the olefins with an electron donating group due to the oxidation at the α-carbon.

Deactivation of the catalytic system is due to the formation of palladium cyanide. Cyanide ion is formed by decomposition of oximes, which are formed by the reaction of methylene protons of acetals and alkyl nitrite **1**. This can also be explained by the fact that the use of acrylonitrile **5a** as a substrate leads to a shorter catalytic lifetime than that of methyl acrylate **5b**.

5. Oxidative carbonylation of olefins

In the oxidative carbonylation of olefins, alkyl nitrites **1** also act as reoxidizing agents of palladium, and the reaction proceeds both in the gas and liquid phases [29]. As the appropriate catalytic system, $PdCl_2$–$CuCl_2$ for the gas phase reaction and $PdCl_2$ for the liquid phase reaction are selected. Pd/C catalyst gives no carbonylation product, but affords oxalate slowly in the liquid phase.

In the presence of $PdCl_2$, dialkyl succinate **9** is obtained selectively in mixed solvents of acetonitrile and alcohol [30].



(9)

Ethylene is carbonylated preferentially into succinate **9**, rather than an acetal, while acrylonitrile **5a** and methyl acrylate **5b** are selectively converted into the corresponding acetals[2]. This reactivity difference is considered to be due to the preference between nucleophilicity and electrophilicity of the substrate olefins. In addition, the carbonylation of ethylene in the palladium–alkyl nitrite system gives neither alkoxypropionate nor unsaturated carboxylate which are known to be formed with usual Wacker type reactions [31]. The oxidative carbonylation of propylene in the gas phase

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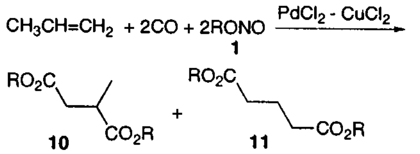
[1] Reactions of cyclic olefins are considerably complicated due to the isomerization.

[2] No ester formation was observed.

affords succinate derivative **10** and glutarate **11** as the Wacker type reaction. No improvement in the product selectivity was observed by changing of the catalysts.



(10)

The byproducts from oxidative carbonylation of olefins are oxalate **2**, carbonate **4** and ketals or acetals.

Recently, the synthesis of polysuccinate from ethylene, carbon monoxide and α,ω-dinitrite has been reported [32].

$$\mathrm{ONO{-}R{-}ONO} + \mathrm{R'CH{=}CH_2} + \mathrm{CO} \xrightarrow{\mathrm{Pd(II)}} (\mathrm{{-}O{-}R{-}OCO{-}CH(R')CH_2{-}CO{-}})_n + 2\mathrm{NO} \qquad (11)$$

In this reaction system, polyoxalate is the only product under high CO pressure even in the presence of ethylene (Eq. (12)). Polysuccinate can be obtained as the main product only under low CO pressure (Eq. (13)). Polyketone becomes the main product under the low CO pressure combined with high ethylene pressure (Eq. (14)).

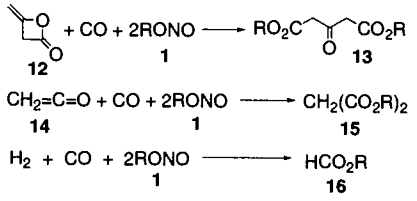
$$\mathrm{ONO\text{-}R\text{-}ONO + CO(900psi) + C_2H_4(100psi)} \longrightarrow \mathrm{\text{-}(O\text{-}CO\text{-}CO\text{-}O\text{-}R)n\text{-}} \qquad (12)$$

$$\mathrm{ONO\text{-}R\text{-}ONO + CO(100psi) + C_2H_4(200psi)} \longrightarrow \mathrm{\text{-}(O\text{-}CO\text{-}CH_2CH_2\text{-}CO\text{-}O\text{-}R)n\text{-}} \qquad (13)$$

$$\mathrm{ONO\text{-}R\text{-}ONO + CO(100psi) + C_2H_4(900psi)} \longrightarrow \mathrm{\text{-}(CH_2CH_2\text{-}CO)n\text{-}} \qquad (14)$$

6. Oxidative carbonylation of ketene and diketene

The oxidative carbonylation was further applied to ketene and diketene and the following reactions have been developed. The liquid phase synthesis of 3-oxoglutarate **13** from diketene **12** [33], and the gas phase synthesis of malonate **15** from ketene **14** [34] and formate **16** from hydrogen [35], were investigated, respectively (Scheme 3).



Scheme 3.

In the oxidative carbonylation of ketene and diketene, it is considerably difficult to increase their reaction rates because the CO pressure has no influence on the rates. This is considered to be due to the formation of Pd(0) under higher CO pressure, which inhibits the oxidation of olefins.

Diagnostic procedures like increasing concentration of alkyl nitrite **1** or the addition of chloride ion to the systems tend to result in undesirable reactions (decomposition of the product by **1** and/or HCl) or deactivation of the reaction by producing inhibiting substances.

As a result, optimized conditions required to produce these products have many limitations and the production of 3-oxoglutarate **13** is the only process operating on an industrial scale.

Even for the preparation of **13**, many technological breakthroughs and modifications have been achieved. And even after optimization, the value of TOF is one order of magnitude lower than that of the oxidation of olefins.

7. The kinetics and reaction mechanisms

7.1. Oxidative carbonylation of alcohols utilizing alkyl nitrites

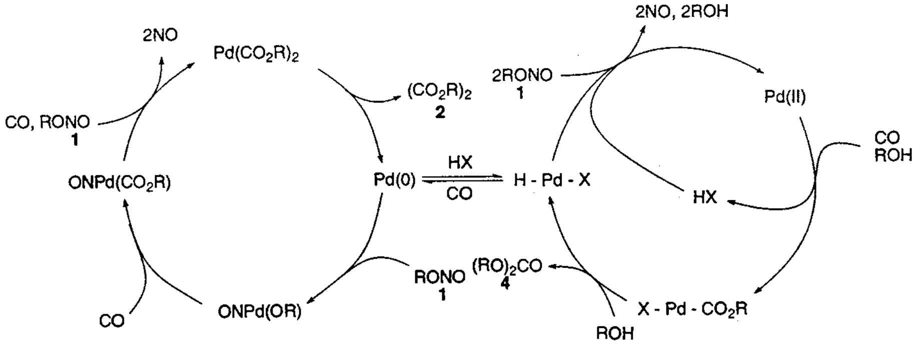
Several reaction mechanisms are proposed for the palladium–alkyl nitrite oxidative reaction. The major discussion has been focused on the valence of palladium of the catalytically active species. Sen and coworkers proposed the mechanism via the same intermediate derived from the oxidative addition of alkyl nitrite **1** to Pd(0) for the formation of both polyoxalate and polycarbonate [32]. But it is obviously based on the experimental results that the active species for the formation of oxalate **2** are Pd(0), and Pd(II) complexes are those for the formation of carbonate **4**.

Waller et al. proposed the mechanism for the formation of oxalate **2** that the oxidative addition of alkyl nitrite **1** to Pd(0) followed by intramolecular coupling reaction [8], and we basically agree with their discussion.

As described in the previous section, the TOF for our reaction system is more than several thousands in the production of both oxalate **2** and carbonate **4** under optimized conditions. The precise study of the reaction kinetics has provided detailed insight into the reaction mechanism. The results are shown below.

7.1.1. Liquid phase reaction

Kinetic studies on the dibutyl oxalate **2c** formation in the liquid phase revealed the following conclusions. (1) The rate of **2c** formation is first order to the concentra-



Scheme 4. Proposed reaction mechanism for oxidative carbonylation of alcohols utilizing alkyl nitrites [8].

tion of palladium, the concentration of butyl nitrite **1c**, and CO pressure. (2) The concentration of palladium in the solution is considerably low (< 20 ppm), and intermolecular reaction path is unlikely due to the high TOF. (3) Alcohols accelerate the reaction, however no further acceleration is observed if their concentration exceeds 10%. (4) Pd(0) species are desirable for the selective formation of **2c** and Pd(II) species (i.e. $PdCl_2$, $Pd(NO_3)_2$) selectively catalyze the formation of dibutyl carbonate **4c**.

Kinetic studies on the dibutyl carbonate **4c** formation in the liquid phase revealed following conclusions. (1) The rate of **4c** formation is proportional to the concentration of **1c** and alcohol. However it is independent on CO pressure. (2) Pd(0) does not catalyze the reaction while $PdCl_2$, $Pd(NO_3)_2$ and Pd/C–MCl_n ($n = 2 \sim 3$, M = Fe, Sb, Te, Bi, Cu) turned out to be good catalysts. (3) The best results are obtained when $PdCl_2$, Pd/C–HCl, or Pd/C-methyl chloroformate are used as catalysts.

The pressure of CO is zero order in the formation rate of carbonate **4c**. A possible interpretation is that the rate determining step is not the formation of Pd–COOR, but the alcoholysis of Pd–COOR. Another explanation is that CO pressure suppresses the formation of the active catalyst. The former possibility can be denied by the fact that an addition of the chloroformate, which promotes the formation of Pd–COOR, increases the reaction rate.

It seems that the following equilibrium shown in Eq. (15) in the liquid phase reaction would be consistent with many experimental results.

$$\mathrm{Pd(0)} \underset{\mathrm{CO}}{\overset{\mathrm{RONO}\ \mathbf{1},\ \mathrm{X^-}}{\rightleftharpoons}} \mathrm{Pd(II)} \tag{15}$$

It could also be illustrated in the following equation.

$$\mathrm{Pd(0)} \underset{\mathrm{CO}}{\overset{\mathrm{HX}}{\rightleftharpoons}} \mathrm{H\text{-}Pd\text{-}X} \xrightarrow{\mathrm{RONO}\ \mathbf{1},\ \mathrm{HX}} \mathrm{Pd(II)} \tag{16}$$

Carbon monoxide is known to reduce Pd(II) into Pd(0). On the other hand, alkyl nitrite **1** can oxidize Pd(0) into Pd(II) in the presence of an acid.

Palladium(metal) originated from $PdCl_2$ may be in equilibrium between Pd(0) and Pd(II) in the presence of both CO and **1**. It is likely that chloride ion promotes this equilibrium in the same manner as cupric ion does as a reoxidizing agent.

We already observed that the rate of the carbonate formation in the liquid phase is not affected by CO pressure. Higher CO pressure causes Pd(0) formation via equilibrium shown in Eq. (15) or Eq. (16), which is undesirable for the carbonate **4** formation. However the formation rate itself increases, thus the observed formation rate of the carbonate appears to be unaffected by CO pressure.

Proposed mechanisms for the selective formation of oxalate **2** or carbonate **4** are shown in Scheme 4.

7.1.2. Gas phase reaction

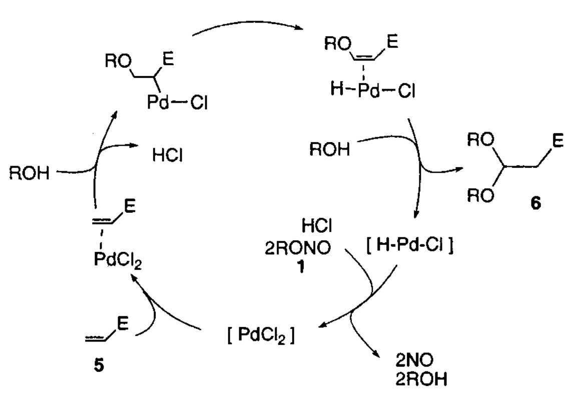
In the gas phase reactions, the results obtained are rather complicated. For dimethyl oxalate **2a** formation, several features were observed. (1) The rate of **2a** formation becomes maximum when the CO partial pressure is around 20%. (2) It depends on the partial pressure of methyl nitrite **1a**. (3) Higher NO partial pressure retards **2a** formation. (4) The partial pressure of alcohol does not affect the reaction rate.

The maximum rate observed around 20% of CO partial pressure is considered to be due to the optimized mass balance of CO and **1a**. The Pd–OR species are mostly generating via decomposition of **1a**, because alcohol concentration has no effect on the rate.

There is a possibility for the existence of an equilibrium between **1a** and ON–PdOMe species due to the fact that NO suppresses the reaction rate.

It is still uncertain that formation of dialkyl oxalate proceeds via coupling of two acyl groups or double carbonylation.

In the dimethyl carbonate **4a** formation in the gas phase, the following features were observed. (1) The rate of **4a** formation is first order to the partial pressure of CO. (2) It is independent on the partial pressure of **1a**. (3) The best results were obtained when $PdCl_2$ or Pd/C–HCl or Pd/C-methyl chloroformate were used as



Scheme 5. Proposed reaction mechanism for oxidation of olefin [36].

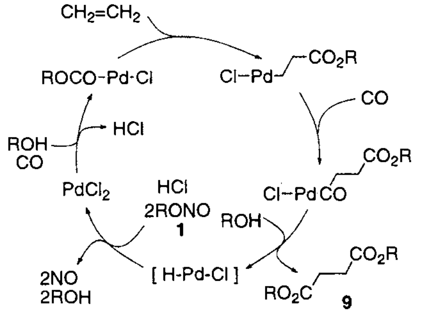
a catalyst. (4) The alcohol partial pressure does not affect the reaction rate.

The Pd(II) supported on activated carbon easily turns into Pd(0), which is the most suitable catalyst for the oxalate synthesis, thus when Pd(II) on activated carbon is used for the carbonate synthesis, more oxalate is formed, compared with the other catalysts under the same conditions (see Table 4).

Moreover, Li–Al–O spinel gives the stable divalent palladium, maybe due to the difficulty in reduction by CO so that the formation of oxalate is much less even after a long period of time.

Therefore, the oxidation state of palladium would be maintained to a certain extent by catalytic supports in the gas phase reaction. We still do not understand the exact relationship between support properties and the oxidation state of palladium.

The rate of oxalate **2a** formation depends on the concentration of methyl nitrite **1a**, while the carbonate **4a** formation rate is independent. This fact is consistent with the ease of decomposition of **1a** by acidic catalyst as described in Section 2, because Pd(II) catalyst on support for production of **4a** is much more acidic than the Pd(0) catalyst for the production of **2a**.



Scheme 6. Proposed reaction mechanism for oxidative carbonylation of olefin [38].

7.2. Oxidation of olefins

Detailed study on precise reaction mechanism has not been carried out, but we assume a possible reaction mechanism via oxypalladation shown below [36] Scheme 5.

The role of alkyl nitrite **1** in this reaction system seems to be the reoxidation of palladium. The rate of reoxidation in our system is much faster than that observed in the usual Wacker reactions. For example, the turnover rate for the reaction is about once every few seconds (several hundreds mol/mol-Pd/h) in the production of acetals **6a** and **6b**, which is five to six times higher than the reported values for Wacker reaction. The reason for this fast turnover rate is considered to be the difference of the catalyst reoxidation process. In the usual Wacker system, Pd(II) is reduced to Pd(0) and reoxidized to Pd(II), but in the alkyl nitrite system, Pd(II) is not reduced all the way to Pd(0) but to H–Pd(II)–Cl and this intermediate is oxidized to regenerate Pd(II).

7.3. Oxidative carbonylation of olefins

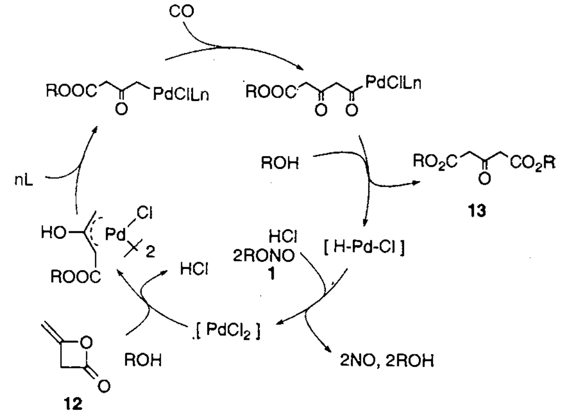
For the polysuccinate synthesis from dinitrite, Sen suggested a reaction mechanism via Pd(0) species. However, observed reactivity difference by changing CO pressure shown in Eqs (12) and (13) is considered to be due to the equilibrium between Pd(0) and Pd(II) shown in Eq. (15) or Eq. (16), and it is unlikely that Pd(0) species are acting as catalytic intermediates.

The equilibrium between Pd(II)NO$^+$ and Pd(IV)NO$^-$ in carbonylation of ethylene was proposed by Chauvin et al. [37]. However, distribution of the products in the Chauvin's system is different from that observed in our system and the TOF observed is shown to be much lower (10 mol/mol-Pd h) compared to our system.

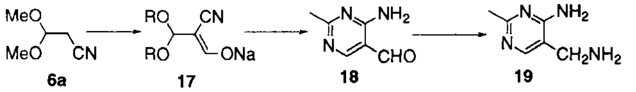
Based on the experimental observations, (1) reaction is catalyzed only by Pd(II) halides, and (2) the rate of carbonylation in the liquid phase is not affected by CO pressure like the cases of carbonate synthesis etc., the oxidative carbonylation of olefins by palladium–alkyl nitrite systems is considered to proceed via the reaction mechanism proposed by Stille as shown in Scheme 6 [38].

7.4. Oxidative carbonylation of diketene

The 3-oxoglutarate **13** formation is believed to proceed via the reaction of diketene **12** with $PdCl_2$ to produce hydroxy η^3-allyl palladium complex [39], followed by the isomerization to σ-alkyl complex [40]. The role of alkyl nitrite **1** in this system is considered to be reoxidizing H–Pd–Cl species in the same manner as the olefin-oxidation (Scheme 7).



Scheme 7. Proposed reaction mechanism for synthesis of 3-oxoglutarate **13**.



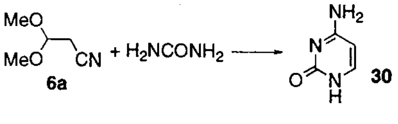
Scheme 8. Preparation of vitamin B1 intermediate **19**.

8. Applications of acetals to fine chemicals

The products from these reactions are useful starting materials or intermediates for a variety of fine chemicals. Though dimethoxy propionitrile **6a** and dimethoxy propionate **6b** can also be synthesized via formylation of acetonitrile, and alkyl acetate, respectively, the palladium–alkyl nitrite system is extremely favorable as an industrial process because only liquid reagents are required.

UBE developed commercial production of vitamin B1 intermediate **19** from acetal **6a** [41–43] Scheme 8.

The compounds **20** and **21**, derived from **6a**, are dimerized easily in the presence of acid. The dimers **22** and **23** are treated with hydrochloric acid to give nicotinonitrile derivative **24** [44–47], which is an important intermediate for the agrochemicals **27** [48], **28** [49] and **29** [50] (Scheme 9).



Scheme 10.

The reaction of acetal **6a** with urea gives cytosine **30** in one step, which is an important intermediate for an anti-cancer drug [51] (Scheme 10).

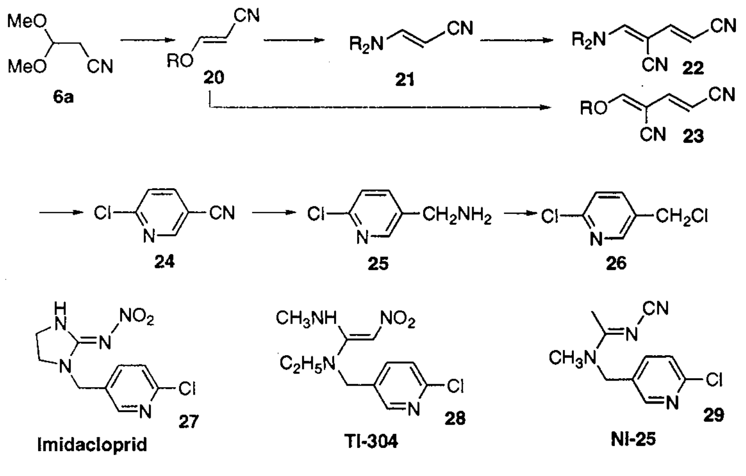
The compound **6b** is also derivatized to a starting material for the anti-bacterial drug quinolone carboxylate **35** [52–55]. Enol ether **31** prepared from **6b** is treated with amines to give enamines **32**. Reaction of benzoyl chlorides **33** with **32a** affords **34a**, which is cyclized to produces **35**. While more stable enamine **32b** is derived to **34b**, which is easily converted to **34a** by treatment with primary amine (Scheme 11).

In addition to the above mentioned examples, **6a**, **6b**, **20** and **31** can be used as important intermediates for the synthesis of a variety of heterocyclic compounds.

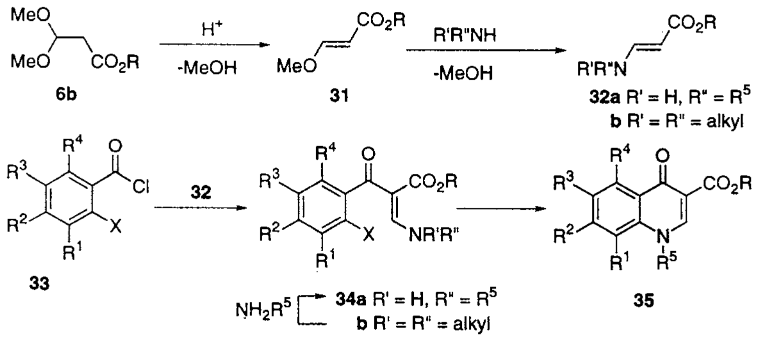
9. Experimental section

Oxidative reactions by the palladium–alkyl nitrite system are quite useful as we have described so far, but they have not been applied to general organic syntheses in research compared with the Wacker reaction. This may be partially because we have not published our research results (as often happens in research in industry) and the treatment of alkyl nitrites is troublesome. The lab-scale preparation of methyl nitrite **1a** is difficult, though it is ideal for oxidative reactions because of a simple separation of the resulting product.

Our practical laboratory procedures will be described below with the hope that this oxidative reaction will be



Scheme 9.



Scheme 11.

widely applied to various organic syntheses. Methyl nitrite **1a** obtained by this method is considerably diluted so the gas itself is not explosive. However, the gas should not be concentrated because it becomes explosive in a concentrated state. Moreover, it is also important to handle **1a** in a well-ventilated hood because of its toxicity.

Two glass gas-washing bottles are connected. *n*-BuONO **1c** [12] is introduced to a bottle (A), and methanol into the other (B). Nitrogen gas is introduced under control with a flow meter from bottle A to bottle B. Vaporized **1c** immediately reacts with methanol to afford **1a**, which is then transferred into a reactor by a stream of nitrogen.

$$\text{n-BuONO } \mathbf{1c} + \text{MeOH} \rightarrow \text{n-BuOH} + \text{MeONO } \mathbf{1a} \tag{17}$$

Methyl nitrite **1a** is easily dissolved into organic solvents such as alcohols. The amount of evolved **1a** can be controlled by the gas flow and by heating **1c**. Oxidation of olefins can be simply carried out by following this procedure. In addition, carbonylation reactions at atmospheric pressure can be performed by using carbon monoxide gas.

10. Conclusions

It has been shown that alkyl nitrite **1** possesses two different functions as a reactant in the palladium catalyzed oxidative reactions. First, its alkoxy functionality acts as a nucleophile to CO as well as other electrophiles. Second, nitrosyl functionality reoxidizes Pd(0) to Pd(II). New synthetic methodologies have been developed and successfully applied to commercial production.

The following are the special features of the oxidative reactions by the palladium–alkyl nitrite system:

1. The reaction is remarkably fast.
2. The oxidative reaction is carried out in the absence of oxygen and water by recycling NO.
3. The compounds which are sensitive to hydrolysis can be prepared without any complicated treatments.
4. Oxidative carbonylations can be performed in atmospheric pressure in the gas phase.
5. Oxidative carbonylations of ketene, diketene and hydrogen are possible.
6. The reaction proceeds without isomerization of double bonds.

The palladium–alkyl nitrite system may be a rare case in which one reaction system has been successfully applied to various types of reactions in the industrial process by overcoming many technical problems.

UBE Industries is now producing dibutyl oxalate **2c**, dimethyl carbonate **4a**, 3,3-dimethoxy propionitrile **6a**, methyl 3,3-dimethoxy propionate **6b** and dimethyl 3-oxoglutarate **13** by the palladium–alkyl nitrite system. Moreover, from these compounds, oxamide (slow acting nitrogen fertilizer), oxalic acid, vitamin B1, pharmaceuticals, and many other products are prepared.

UBE's research on the palladium–alkyl nitrite system is still continuing for the practical production of useful chemicals. We sincerely hope and expect the applications of this powerful methodology to make a significant contribution to synthetic organic chemistry.

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