

Wacker-Type Oxidation of Internal Olefins Using a PdCl₂/*N,N*-Dimethylacetamide Catalyst System under Copper-Free Reaction Conditions**

Takato Mitsudome, Keiichi Mizumoto, Tomoo Mizugaki, Koichiro Jitsukawa, and Kiyotomi Kaneda*

Carbonyl groups are key moieties for the construction of carbon skeletons and synthetic intermediates.^[1] Oxygenation of olefins is one of the most straightforward routes for the synthesis of carbonyl compounds. The industrially important oxidation of ethylene to acetaldehyde, using a catalyst system consisting of palladium with copper, is commonly known as the Wacker oxidation process.^[2–5] Since the discovery of this process, this Pd/Cu catalyst system has been extended to the oxidation of diverse terminal olefins using water under liquid-phase conditions (Wacker–Tsuiji oxidation), which offers a powerful method for the synthesis of methyl ketones.^[6–8] However, this catalyst system has been inevitably limited to the oxidation of terminal olefins. This limitation arises because internal olefins show extremely low reactivity and selectivity; that is, non-regioselective oxidations occur to yield various undesired oxygenated products through isomerization of the olefinic bonds.^[9–11] Therefore, the selective synthesis of carbonyl compounds from internal olefins using water remains a major challenge.

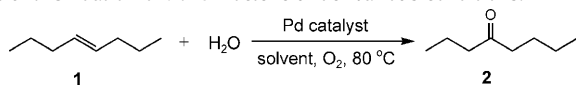
Recently, some advancements of the Wacker–Tsuiji oxidation method have successfully eliminated the requirement for copper additives.^[12–15] We also found that the combination of a PdCl₂ catalyst system with *N,N*-dimethylacetamide (DMA) allows direct O₂-coupled Wacker-type oxidation of various terminal olefins into the corresponding methyl ketones under copper-free reaction conditions.^[14] From the study of cyclic voltammetry, kinetics, and X-ray absorption fine structure (XAFS) data, DMA was found to act as the most efficient solvent for promoting the reoxidation of the

Pd⁰ species by O₂. This discovery opens a new route for the selective and direct synthesis of carbonyl compounds from internal olefins.

We herein present a method by which a PdCl₂/DMA catalyst system can be successfully applied to the oxidation of various internal olefins to carbonyl compounds. This methodology is extremely simple, and the oxidation proceeds efficiently without isomerization of the olefins. Interestingly, the addition of copper compounds decreases the catalytic activity of the palladium for internal olefins. It is revealed that the lack of a requirement for copper is fundamental to overcome the problem of low activity for internal olefins, which the traditional Wacker–Tsuiji oxidation reactions have suffered from.

Initially, *trans*-4-octene (**1**) was treated with 5 mol% PdCl₂ in a mixture of an organic solvent and water with 3 atm of O₂ under copper-free reactions conditions. In a DMA solution, oxidation of **1** proceeded to give 4-octanone (**2**) as the sole product in 91% yield without isomerization or chlorination of **1** (Table 1, entry 1). The use of *N*-methylpyrrolidone (NMP) also gave **2** in good yield (Table 1, entry 4). Other solvents, such as *N,N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), acetonitrile, and toluene resulted in low yields of **2**, which was accompanied by the formation of isomers of **1** or **2** (Table 1, entries 5–8). Among the palladium compounds tested, PdCl₂ and [PdCl₂(PhCN)₂]

Table 1: Oxidation of *trans*-4-octene under various conditions.^[a]

				
Entry	Catalyst	Solvent	Conv. of 1 [%] ^[b]	Yield of 2 [%] ^[b]
1	PdCl ₂	DMA	91	91
2 ^[c]	PdCl ₂	DMA	trace	–
3 ^[d]	PdCl ₂	DMA	trace	–
4	PdCl ₂	NMP	79	76
5	PdCl ₂	DMF	13	12
6	PdCl ₂	DMSO	6	6
7	PdCl ₂	acetonitrile	13	8
8	PdCl ₂	toluene	trace	–
9	[PdCl ₂ (PhCN) ₂]	DMA	87	87
10	Pd(OAc) ₂	DMA	trace	–
11	[PdCl ₂ (NH ₃) ₄]	DMA	trace	–

[a] Reaction conditions: *trans*-4-octene (1 mmol), Pd catalyst (0.05 mmol), solvent (5 mL), H₂O (0.5 mL), 3 atm of O₂, 80 °C, 10 h.

[b] Determined by GC methods using an internal standard. [c] Without H₂O. [d] Ar was used instead of O₂.

[*] Dr. T. Mitsudome, K. Mizumoto, Dr. T. Mizugaki, Prof. Dr. K. Jitsukawa, Prof. Dr. K. Kaneda
Department of Materials Engineering Science
Graduate School of Engineering Science, Osaka University
1-3 Machikaneyama, Toyonaka, Osaka 560-8531 (Japan)
Fax: (+81) 6-6850-6260
E-mail: kaneda@cheng.es.osaka-u.ac.jp
Homepage: <http://www.cheng.es.osaka-u.ac.jp/kanedalabo/GSCLabo/index.html>

Prof. Dr. K. Kaneda
Research Center for Solar Energy Chemistry, Osaka University
1-3 Machikaneyama, Toyonaka, Osaka 560-8531 (Japan)

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were effective as catalysts in the DMA solvent (Table 1, entries 1 and 9). The oxidation of **1** did not proceed in the absence of water. Under an argon atmosphere instead of O₂, a trace amount of **2** together with a precipitate of palladium black was observed. The use of ¹⁸O-labeled water provided exclusively the ¹⁸O-labeled ketone with 99% selectivity. No oxygen scrambling between ¹⁶O ketone and ¹⁸O water was observed when 4-octanone (¹⁶O) was treated with ¹⁸O-labeled water under identical conditions for 1 hour. These results indicate that the oxygen atom incorporated into **2** is derived not from molecular oxygen but from water.

The applicability of this catalyst system to other types of olefins is shown in Table 2. The compounds *trans*-2-octene and *trans*-3-octene provided 2- and 3-octanones, and 3- and 4-octanones, respectively, suggesting that the oxygen atoms are incorporated into the original olefinic position of the starting materials (Table 2, entries 1 and 2). *cis*-4-Octene showed a similar reactivity to the *trans*-4-octene, affording **2** as the sole product (Table 2, entry 4). Although the long-chain olefin 7-tetradecene does not undergo the oxidation under the previously reported copper-free Wacker oxidation systems,^[15,16] the present catalyst system effectively converted 7-tetradecene into 7-tetradecanone in excellent yield (Table 2, entry 7). A cyclic olefin, cyclohexene, reacted to

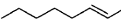
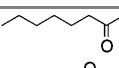
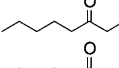
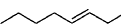
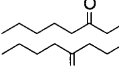
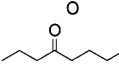
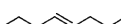
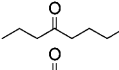
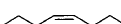
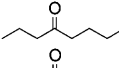
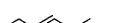
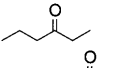

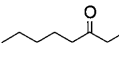

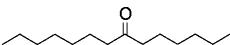


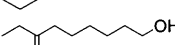

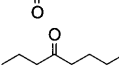
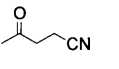
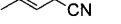
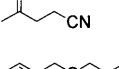
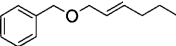
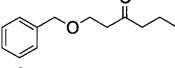

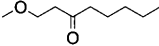
give cyclohexanone in good yield, and was accompanied by a small amount of an allylic oxidation product (2-cyclohexene-1-one; Table 2, entry 8). The oxidation of functionalized internal olefins also proceeded efficiently wherein only the carbon–carbon double bonds were oxidized to ketones, and the functional groups (hydroxy, cyano, and ether groups) remained intact under the present reaction conditions (Table 2, entries 9–12). More interestingly, olefins having functional groups in the allylic position were regioselectively oxidized to give the respective β-functionalized ketones as the sole products with excellent yields (Table 2, entries 10–12). For example, in the oxidation of *trans*-3-pentenitrile, an oxygen atom was selectively incorporated at the γ position relative to the cyano group, affording 4-oxopentanenitrile in 86% isolated yield (Table 2, entry 10).^[17]

All of the internal olefins that we tested were hardly oxidized under the standard reaction conditions of traditional the Wacker–Tsuji oxidation, using 10 mol % PdCl₂ and 100 mol % CuCl in a DMF solvent.^[19] In a control experiment for the oxidation of **1**, the addition of 10 mol % CuCl₂ to the PdCl₂/DMA mixture decreased the yield of **2** to 68% yield after 6 hours. Moreover, increasing the amounts of CuCl₂ to the reaction mixture dramatically decreased the conversion of **1** (Figure 1).^[20] The above phenomenon is in sharp contrast

with the result obtained with 1-octene for which an increase of CuCl₂ resulted in an increased yield of 2-octanone (Figure 2). Presumably, the low activity of the palladium species in the presence of copper is due to the formation of a bulky Pd/Cu bimetallic complex^[22] which cannot easily coordinate to an internal olefin.^[23]

In conclusion, we have demonstrated the direct O₂-coupled Wacker oxidation of internal olefins into carbonyl compounds using a PdCl₂/DMA catalyst system. The presence of copper was shown to have a negative effect on Wacker oxidation of internal olefins. The conventional Wacker–Tsuji oxidation system may suffer from the dilemmatic problem: the copper species, which promotes the reoxidation of Pd⁰ into Pd^{II}, inhibits the oxidation of internal olefins. The discovery of the direct O₂-coupled Wacker oxidation without the need for copper as a co-catalyst will lead to novel Wacker-type oxidations of internal olefins.

Table 2: Wacker oxidation of various internal and cyclic olefins catalyzed by the PdCl₂/DMA system.^[a]

Entry	Substrate	t [h]	Conv. [%] ^[b]	Product	Yield [%] ^[b]
1		10	98	 	62 36
2		10	98	 	54 44
3		10	91		91 (88)
4		10	83		83
5		10	98		98
6		10	86		86 (80)
7		20	81		81 (77)
8 ^[c,d,e]		10	85	 	73 ^[f] 47
9 ^[c]		10	92	 	45 45
10 ^[c]		20	94		94 (86)
11 ^[c,d]		20	95		91 ^[g]
12 ^[c]		20	85		80 ^[h]

[a] Reaction conditions: substrate (1 mmol), PdCl₂ (0.05 mmol), DMA (5 mL), H₂O (0.5 mL), 3 atm of O₂, 80 °C. [b] Determined by GC methods using an internal standard. The values within parentheses are the yields of the isolated products. [c] PdCl₂ (0.1 mmol). [d] Substrate (0.5 mmol). [e] 70 °C. [f] 2-Cyclohexene-1-one was formed as a by-product in 12% yield. [g] 1-Benzyloxy-2-hexanone formed as a minor product in 4% yield. [h] 1-Methoxy-2-octanone formed as a minor product in 5% yield.

Experimental Section

A typical procedure for the Wacker oxidation of various olefins: To completely dissolve the PdCl₂ in DMA, the

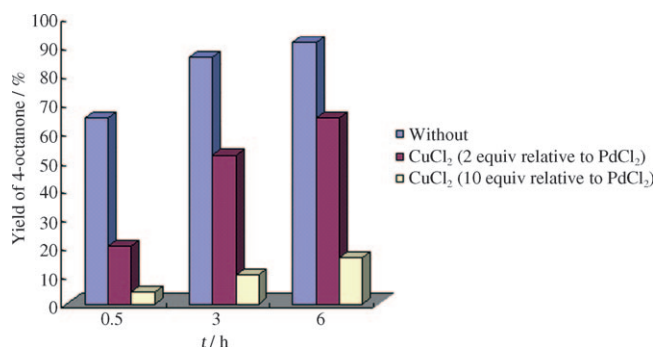


Figure 1. Effect of the amount of CuCl₂ upon the oxidation of **1**. Reaction conditions: *trans*-4-octene (1 mmol), H₂O (0.5 mL), DMA (5 mL), PdCl₂ (0.05 mmol), 3 atm of O₂, 80 °C.

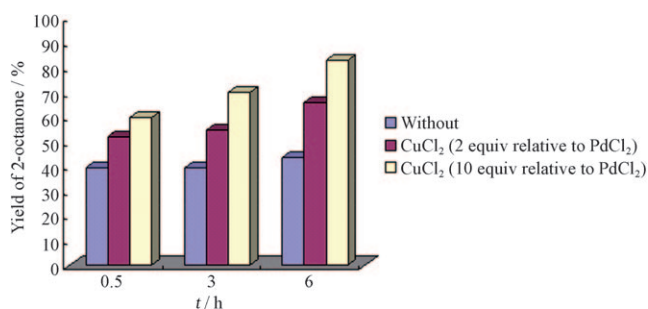


Figure 2. Effect of the amount of CuCl₂ upon the oxidation of 1-octene. Reaction conditions: 1-octene (1 mmol), H₂O (0.5 mL), DMA (5 mL), PdCl₂ (0.002 mmol), 3 atm of O₂, 80 °C.

following pretreatment protocol was conducted:^[24] PdCl₂ (5 × 10⁻² mmol), DMA (5 mL), and H₂O (0.5 mL) were placed in a 50 mL stainless-steel autoclave (with a Teflon inner cylinder) along with a Teflon-coated magnetic stir bar, and the mixture was stirred at room temperature for 1 h under 9 atm of O₂. After the pretreatment, *trans*-4-octene (1 mmol) was added. The vessel was pressurized to 3 atm of O₂, and then the mixture was vigorously stirred at 80 °C for 10 h. After the reaction, the reactor was cooled to room temperature, and then the O₂ pressure was carefully released to the atmospheric pressure [CAUTION: the reaction temperature was beyond the flash point of DMA (77 °C)]. GC analysis of the solution, using naphthalene as an internal standard, indicated 4-octanone as the sole product with 91 % yield. The product was then extracted using a 1:1 diethyl ether/brine mixture (2 × 30 mL). The diethyl ether layer containing the products was dried over MgSO₄, filtered, and then concentrated under reduced pressure. The resultant crude mixture was purified by column chromatography (silica gel) using EtOAc/*n*-hexane (1:4) as the eluent to obtain pure 4-octanone (0.11 g, 88 %).

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