Angewandte Chemie International Edition

DOI: 10.1002/anie.201301611

Synthetic Methods

# Highly Atom-Efficient Oxidation of Electron-Deficient Internal Olefins to Ketones Using a Palladium Catalyst**

*Takato Mitsudome, Syuhei Yoshida, Tomoo Mizugaki, Koichiro Jitsukawa, and Kiyotomi Kaneda**

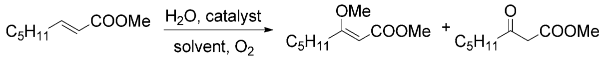
Ketones are ubiquitous in nature and important as diverse synthetic intermediates in organic synthesis and industrial chemistry.[1] Selective oxidation of olefins using molecular oxygen ($O_2$) as a "green" oxidant is a simple and attractive method for the synthesis of ketone compounds.[2] There has long been a special interest in the Wacker–Tsuji reaction as a straightforward and 100% atom-efficient synthesis of methyl ketones from terminal olefins using Pd catalysts combined with Cu salts.[3] This classical reaction, however, inevitably requires large amounts of Cu salts and the substrate scope is limited to terminal olefins.[4] Thus, conventional synthesis of ketones from internal olefins has been conducted employing a strategy with a low atom efficiency, such as the use of peroxide as an oxidant[5] or a multiple-step synthesis through hydroboration followed by oxidation.[6]

To overcome this low atom efficiency, recent advancements in the catalytic oxidation of internal olefins have been achieved. We previously disclosed an $O_2$-coupled Cu-free Wacker-type oxidation system that consists of $PdCl_2$ and *N,N*-dimethylacetamide (DMA) solvent. This simple catalytic system was successfully applied to the oxidation of not only various terminal olefins,[7] but also internal ones to afford the corresponding ketones.[8] Grubbs and co-workers improved the substrate scope for the Pd-catalyzed oxidation of internal olefins under ambient temperature in the presence of strong acid $HBF_4$ in a mixed solvent (DMA/MeCN/$H_2O$) by adding stoichiometric amounts of benzoquinone (BQ) or catalytic amounts of BQ and Fe(pc) (pc = phthalocyanine) under 1 atm of $O_2$.[9] Thus, the highly atom-efficient synthesis of various ketones from olefins is still the subject of considerable interest.

Herein, we report a novel oxidation method of electron-deficient internal olefins to the corresponding ketones. Electron-deficient internal olefins are extremely unreactive toward oxidation, and the development of highly efficient catalytic oxidations of electron-deficient internal olefins has not yet been achieved.[10] The present catalytic method represents a simple and 100% atom-efficient synthesis of ketones from electron-deficient internal olefins using $O_2$ as the sole oxidant. The selectivities for the corresponding ketone products were higher than 99% without any formation of olefin isomers or other oxidized products.

Initially, we carried out the oxidation of methyl *trans*-2-octenoate (**1**) as an electron-deficient internal olefin using our previously reported $PdCl_2$-DMA catalyst system, which consists of $PdCl_2$ in DMA as solvent with $H_2O$ under $O_2$ atmosphere (Table 1, entry 1). Unfortunately, the oxidation hardly proceeded and a trace amount of the oxygenated product methyl 3-oxooctanoate (**3**) was formed. The addition of $CuCl_2$ as a co-catalyst also failed to promote the oxidation of **1** (Table 1, entry 2). Interestingly, when MeOH was added to the $PdCl_2$-DMA system, the oxidation occurred to afford **3** in low yield accompanied by the formation of methyl 3-methoxy-2-octenoate (**2**) in high quantity (Table 1, entry 3). In contrast, the conventional Wacker–Tsuji oxidation ($PdCl_2$-$CuCl_2$-DMF) and $Pd(OAc)_2$-$HBF_4$-BQ catalyst systems did not promote the oxidation in the presence or absence of

***Table 1:*** Oxidation of **1** under various conditions.[a]



**1** **2** **3**

| Ent. | Catalyst | Solvent | Alcohol[b] | Acid[c] | Conv. of | Yield of | |
|---|---|---|---|---|---|---|---|
| | | | | | **1** [%][d] | **2** [%][d] | **3** [%][d] |
| 1 | $PdCl_2$ | DMA | – | – | < 1 | 0 | < 1 |
| 2[e] | $PdCl_2$ | DMA | – | – | < 1 | 0 | < 1 |
| 3 | $PdCl_2$ | DMA | MeOH | – | 80 | 52 | 28 |
| 4[e] | $PdCl_2$ | DMF | – | – | 0 | 0 | 0 |
| 5[e] | $PdCl_2$ | DMF | MeOH | – | < 1 | < 1 | < 1 |
| 6[f] | $Pd(OAc)_2$ | DMA/ MeCN | – | $HBF_4$ | 0 | 0 | 0 |
| 7[f] | $Pd(OAc)_2$ | DMA/ MeCN | MeOH | $HBF_4$ | < 1 | < 1 | < 1 |
| 8[g] | $PdCl_2$ | DMA | MeOH | – | 66 | 65 | < 1 |
| 9 | $PdCl_2$ | DMA | MeOH | TsOH | 82 | 0 | 82 |
| 10 | $PdCl_2$ | DMA | MeOH | AcOH | 69 | 2 | 67 |
| 11 | $PdCl_2$ | DMA | MeOH | TFA | 64 | 3 | 61 |
| 12 | $PdCl_2$ | DMA | MeOH | MsOH | 66 | 3 | 63 |

[a] Reaction conditions: substrate (0.5 mmol), Pd catalyst (0.05 mmol), solvent (4 mL), $H_2O$ (0.5 mL), $O_2$ (6 atm), 80 °C, 3 h. [b] 1.5 mL. [c] 0.2 mmol. [d] Determined by GC analysis using an internal standard. [e] 0.5 mmol $CuCl_2$ added as co-catalyst. [f] Substrate (1 mmol), DMA (2.2 mL), MeCN (2.2 mL), $H_2O$ (0.63 mL), aq $HBF_4$ (48%, 0.18 mL), benzoquinone (1 mmol), RT, 16 h. [g] Without $H_2O$. TFA = trifluoroacetic acid, MsOH = methanesulfonic acid.

---

[*] Dr. T. Mitsudome, S. Yoshida, 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)
E-mail: kaneda@cheng.es.osaka-u.ac.jp

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

[**] This work was supported by JSPS KAKENHI (grant numbers 23686116, 23360357, 24246129, and 22360339).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201301611.

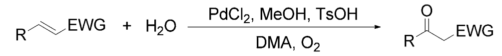
MeOH (Table 1, entries 4–7). Notably, the absence of $H_2O$ in the $PdCl_2$-DMA-MeOH catalyst system resulted in the selective formation of **2** in 65% yield as the sole product (Table 1, entry 8). This suggested that the desired product **3** was formed through the hydrolysis of **2** in the $PdCl_2$-DMA-MeOH system. The oxidation of **1** occurred regioselectively at the olefinic carbon atom in β-position to the ester group, which was consistent with previous reports on the oxidation of functionalized internal olefins.[5,8b]

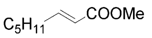
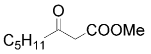
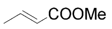
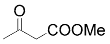
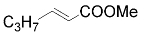
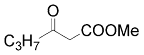
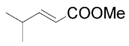
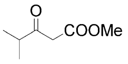
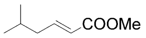
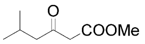
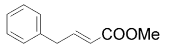
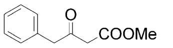
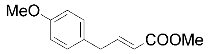
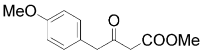
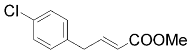
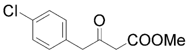
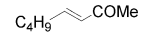
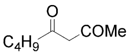
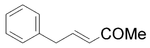
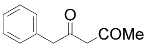
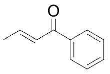
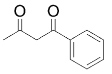
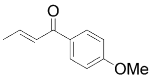
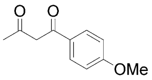
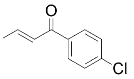
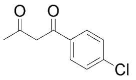
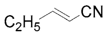
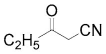
In order to increase the selectivity toward **3**, the addition of various acid catalysts to the $PdCl_2$-DMA-MeOH catalyst system was investigated next (Table 1, entries 9–12). As expected, all the tested acid catalysts successfully promoted the selective production of **3**. *p*-Toluenesulfonic acid (TsOH) was particularly effective, affording **3** in 82% yield with over 99% selectivity without the formation of either olefin isomers or other oxidized products (Table 1, entry 9). Thus, the addition of MeOH and TsOH to our $PdCl_2$-DMA system enables the synthesis of ketones from electron-deficient internal olefins, which has not been accomplished by the recently reported Wacker-type oxidation systems.

With the optimized system consisting of $PdCl_2$, DMA, MeOH, and TsOH in hand, the applicability of this catalytic system to the oxidation of various electron-deficient internal olefins was explored (Table 2). Aliphatic and aromatic α,β-unsaturated esters were efficiently converted to the corresponding β-keto esters with over 99% selectivities without isomerization of the starting materials (Table 2, entries 1, 3–9). Other electron-deficient internal olefins with carbonyl and cyano groups at the vinyl position were also oxidized to afford the 1,3-diketones and β-keto nitriles as the sole products, respectively (Table 2, entries 10–15). Furthermore, this catalyst system was applicable to the reaction on a gram-scale; 1.87 g of **1** (12 mmol) gave 1.61 g of isolated product **3** (78% yield; Table 2, entry 2).

To gain more insight into the developed $PdCl_2$-DMA-MeOH-TsOH system, several control experiments were carried out. Among the various solvents and alcohols tested, the combination of DMA and MeOH was outstanding, giving the highest yield of **3**.[11] Under an Ar atmosphere in place of $O_2$, trace amounts of **2** and **3** together with precipitates of Pd black were formed, confirming the necessity of $O_2$ for this oxidation. The use of $^{18}$O-labeled water in the $PdCl_2$-DMA-MeOH-TsOH system gave exclusively the $^{18}$O-labeled **3** with 99% selectivity, proving that the oxygen atom incorporated into **3** was derived not from molecular oxygen but from water. The selective formation of $^{18}$O-labeled **3** was also confirmed when **2** was employed as the starting material under the above-mentioned conditions in the absence of $PdCl_2$. These results showed that the use of $PdCl_2$, DMA, $H_2O$, MeOH, and TsOH under $O_2$ atmosphere is essential to achieve the highly efficient oxidation of electron-deficient internal olefins. Interestingly, the addition of small amounts of $CuCl_2$ to this catalyst system significantly suppressed the oxidation of **1**, whereas the Cu salt was vital as co-catalyst in the conventional Wacker–Tsuji oxidation. The yield of **3** decreased with an increasing amount of Cu salt (Figure 1), thus agreeing with our previous results for the Pd-catalyzed oxidation of internal olefins.[8a] This finding showed that the $O_2$-coupled Cu-free

***Table 2:*** Oxidation of various electron-deficient internal olefins using $PdCl_2$-DMA-MeOH-TsOH system.[a]



| Entry | Substrate | Product | *t* [h] | Yield [%][b] |
|---|---|---|---|---|
| 1 |  |  | 3 | 82 (79) |
| 2[c] | | | 12 | 81 (78) |
| 3 |  |  | 3 | 78 (73) |
| 4 |  |  | 3 | 72 |
| 5 |  |  | 10 | 68 |
| 6 |  |  | 3 | 73 |
| 7 |  |  | 40 | 68 (64) |
| 8 |  |  | 40 | 70 |
| 9 |  |  | 40 | 65 |
| 10 |  |  | 10 | 81 (77) |
| 11 |  |  | 40 | 64 |
| 12 |  |  | 10 | 81 |
| 13 |  |  | 10 | 78 |
| 14 |  |  | 10 | 74 |
| 15 |  |  | 40 | 63 |

[a] Reaction conditions: substrate (0.5 mmol), $PdCl_2$ (0.05 mmol), DMA (4 mL), MeOH (1.5 mL), $H_2O$ (0.5 mL), TsOH (0.2 mmol), $O_2$ (6 atm), 80°C. [b] Determined by GC analysis using an internal standard. The values within parentheses are the yields of the isolated products.
[c] Substrate (12 mmol), $PdCl_2$ (1.2 mmol), DMA (60 mL), MeOH (10 mL), $H_2O$ (10 mL), TsOH (4 mmol), $O_2$ (9 atm),12 h. The selectivities of all reactions were higher than 99%.

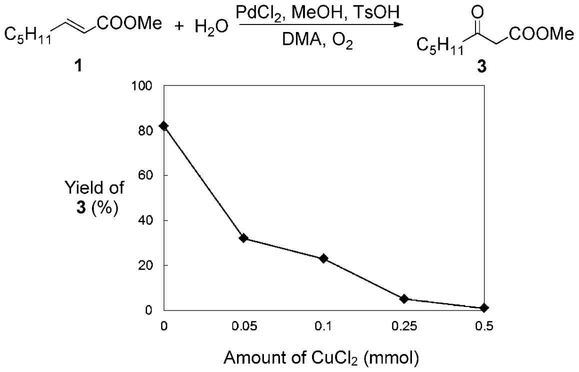
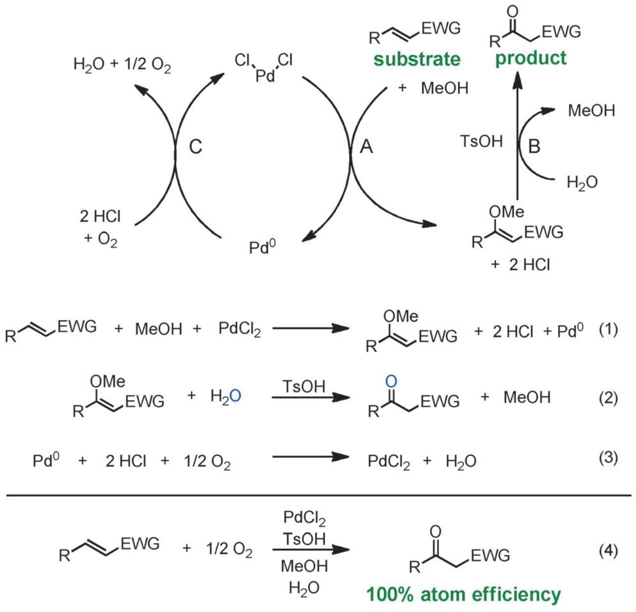


***Figure 1.*** Effect of the amount of $CuCl_2$ on the oxidation of **1**. Reaction conditions: substrate (0.5 mmol), $PdCl_2$ (0.05 mmol), DMA (4 mL), MeOH (1.5 mL), $H_2O$ (0.5 mL), TsOH (0.2 mmol), $O_2$ (6 atm), 80°C, 3 h.

catalyst system allowed the efficient oxidation of electron-deficient internal olefins. Cu may inhibit π-coordination of an olefin to the Pd species through the complexation of Cu with Pd.[12]

From these phenomena, a reaction pathway could be proposed as Scheme 1. First, the $Pd^{II}$ species reacts with an olefin and MeOH to afford a methyl vinylether intermediate and a $Pd^0$ species (step A). Next, the methyl vinylether is hydrolyzed by TsOH, giving the corresponding ketone accompanied by the regeneration of MeOH (step B). The $Pd^0$ species generated in situ is reoxidized to a $Pd^{II}$ species by molecular oxygen, thereby completing the catalytic cycle (step C). A preliminary kinetic study showed that the reaction rate depends on the pressure of $O_2$, thus showing that the rate-determining step is the reoxidation of the $Pd^0$ species (step C).[11] DMA may coordinate to the transient $Pd^0$ species, suppressing the irreversible aggregation of the $Pd^0$ species and promoting the facile reoxidation of the $Pd^0$ species by $O_2$[7] (these reaction steps are represented in Equations (1)–(3), respectively). The summation formula Eq. (4) shows that $PdCl_2$, TsOH, MeOH, and $H_2O$ act catalytically, and an oxygen atom of $O_2$ is formally incorporated into the olefin to afford the oxidized product without any co-products. Namely, this oxidation method provides 100% atom efficiency using $O_2$ as a terminal oxidant.



*Scheme 1.* Proposed reaction pathway and reaction equations of the $PdCl_2$-DMA-MeOH-TsOH catalyst system.

In conclusion, we have developed a highly efficient catalytic system consisting of $PdCl_2$, DMA, MeOH, and TsOH for the aerobic oxidation of electron-deficient olefins to ketones. Various electron-deficient olefins were selectively oxidized to the corresponding ketones, such as β-keto esters, 1,3-diketones, and β-keto nitriles with over 99% selectivities. To the best of our knowledge, this is the first demonstration of the selective oxidation of electron-deficient olefins using $O_2$ as a terminal oxidant. Furthermore, this $O_2$-coupled Cu-free catalytic method provides 100% atom efficiency, thus leading to the efficient synthesis of a wide range of ketones from olefins.

## Experimental Section

Typical example of the oxidation of an electron-deficient olefin: $PdCl_2$ (0.05 mmol), DMA (4 mL), MeOH (1.5 mL), $H_2O$ (0.5 mL), TsOH (0.2 mmol), and methyl *trans*-2-octenoate (0.5 mmol) were placed into a 50 mL stainless steel autoclave (with a Teflon inner cylinder) with a Teflon-coated magnetic stir bar. The vessel was pressurized to 6 atm of $O_2$, and the mixture was vigorously stirred at 80 °C for 3 h. After the reaction, the reactor was cooled to room temperature and $O_2$ pressure was carefully lowered until atmospheric pressure was reached (CAUTION: reaction temperature is beyond the flame point of DMA (77 °C)). GC analysis of the solution using naphthalene as an internal standard indicated methyl 3-oxooctanoate as the sole product in 82% yield. The product was then extracted using a 1:1 mixture of diethyl ether and brine (2 × 30 mL). The diethylether layer, which contained the products, was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resultant crude mixture was purified by column chromatography (silica gel), using a 1:4 mixture of EtOAc and *n*-hexane as the eluent, to obtain the pure methyl 3-oxooctanoate.

Received: February 25, 2013
Revised: March 26, 2013

**Keywords:** ketones · molecular oxygen · olefins · oxidation · palladium

---

[1] H. Siegel, M. Eggersdorfer, *Ullmann's Encyclopedia of Industrial Chemistry, Vol. 18*, 6th ed., VCH, Weinheim, **2003**.
[2] For catalytic oxidation using molecular oxygen, see: a) J. E. Bäckvall, *Modern Oxidation Methods*, Wiley-VCH, Weinheim, **2004**; b) S. S. Stahl, *Angew. Chem.* **2004**, *116*, 3480; *Angew. Chem. Int. Ed.* **2004**, *43*, 3400; c) N. Mizuno, *Modern Heterogeneous Oxidation Catalysis*, Wiley-VCH, Weinheim, **2009**; d) Z. Shi, C. Zhang, C. Tang, N. Jiao, *Chem. Soc. Rev.* **2012**, *41*, 3381.
[3] a) J. Smidt, W. Hahner, R. Jira, J. Sedlmeier, R. Sieber, R. Rüttingger, K. Kojer, *Angew. Chem.* **1959**, *71*, 176; b) J. Smidt, W. Hahner, R. Jira, R. Sieber, J. Sedlmeier, A. Sabel, *Angew. Chem.* **1962**, *74*, 93; *Angew. Chem. Int. Ed. Engl.* **1962**, *1*, 80; c) W. H. Clement, C. M. Selwitz, *J. Org. Chem.* **1964**, *29*, 241; d) J. Tsuji, *Synthesis* **1984**, 369; e) J. M. Takacs, X. T. Jiang, *Curr. Org. Chem.* **2003**, *7*, 369; f) J. Tsuji, *Palladium Reagents and Catalysts*, Wiley, Chichester, **2004**; g) R. Jira, *Angew. Chem.* **2009**, *121*, 9196; *Angew. Chem. Int. Ed.* **2009**, *48*, 9034; h) J. A. Keith, P. M. Henry, *Angew. Chem.* **2009**, *121*, 9200; *Angew. Chem. Int. Ed.* **2009**, *48*, 9038; i) R. I. McDonald, G. Liu, S. S. Stahl, *Chem. Rev.* **2011**, *111*, 2981.
[4] For the success of the oxidation of some internal olefins with suitable functional groups, see: a) J. Tsuji, H. Nagashima, K. Hori, *Tetrahedron Lett.* **1982**, *23*, 2679; b) B. Weiner, A. Baeza, T. Jerphagnon, B. L. Feringa, *J. Am. Chem. Soc.* **2009**, *131*, 9473; c) M. S. Majik, S. G. Tilve, *Tetrahedron Lett.* **2010**, *51*, 2900.
[5] J. Tsuji, H. Nagashima, K. Hori, *Chem. Lett.* **1980**, 257.
[6] M. B. Smith, J. March, *March's Advanced Organic Chemistry*, 5th ed., Wiley, New York, **2001**.
[7] T. Mitsudome, T. Umetani, N. Nosaka, K. Mori, T. Mizugaki, K. Ebitani, K. Kaneda, *Angew. Chem.* **2006**, *118*, 495; *Angew. Chem. Int. Ed.* **2006**, *45*, 481.

[8] a) T. Mitsudome, K. Mizumoto, T. Mizugaki, K. Jitsukawa, K. Kaneda, *Angew. Chem.* **2010**, *122*, 1260; *Angew. Chem. Int. Ed.* **2010**, *49*, 1238; b) T. Mitsudome, S. Yoshida, Y. Tsubomoto, T. Mizugaki, K. Jitsukawa, K. Kaneda, *Tetrahedron Lett.* **2013**, *54*, 1596.

[9] B. Morandi, Z. K. Wickens, R. H. Grubbs, *Angew. Chem.* **2013**, *125*, 3016; *Angew. Chem. Int. Ed.* **2013**, *52*, 2944.

[10] For a report on the catalytic oxidation of electron-deficient olefins using *tert*-butyl hydroperoxide, see: Ref. [5].

[11] See the Supporting Information for details.

[12] T. Hosokawa, T. Nomura, S.-I. Murahashi, *J. Organomet. Chem.* **1998**, *551*, 387.