

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

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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 (O₂) 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 O₂-coupled Cu-free Wacker-type oxidation system that consists of PdCl₂ 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 HBF₄ in a mixed solvent (DMA/MeCN/H₂O) by adding stoichiometric amounts of benzoquinone (BQ) or catalytic amounts of BQ and Fe(pc) (pc = phthalocyanine) under 1 atm of O₂.^[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 O₂ 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 PdCl₂-DMA catalyst system, which consists of PdCl₂ in DMA as solvent with H₂O under O₂ 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 CuCl₂ as a co-catalyst also failed to promote the oxidation of **1** (Table 1, entry 2). Interestingly, when MeOH was added to the PdCl₂-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 (PdCl₂-CuCl₂-DMF) and Pd(OAc)₂-HBF₄-BQ catalyst systems did not promote the oxidation in the presence or absence of

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

$\text{C}_5\text{H}_{11}\text{CH}=\text{CHCOOMe} \xrightarrow[\text{solvent, O}_2]{\text{H}_2\text{O, catalyst}} \text{C}_5\text{H}_{11}\text{CH}(\text{OMe})\text{CH}=\text{CHCOOMe} + \text{C}_5\text{H}_{11}\text{CH}_2\text{CH}_2\text{C(=O)COOMe}$							
Ent.	Catalyst	Solvent	Alcohol ^[b]	Acid ^[c]	Conv. 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), H₂O (0.5 mL), O₂ (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 CuCl₂ added as co-catalyst. [f] Substrate (1 mmol), DMA (2.2 mL), MeCN (2.2 mL), H₂O (0.63 mL), aq HBF₄ (48%, 0.18 mL), benzoquinone (1 mmol), RT, 16 h. [g] Without H₂O. TFA = trifluoroacetic acid, MsOH = methanesulfonic acid.

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MeOH (Table 1, entries 4–7). Notably, the absence of H₂O in the PdCl₂-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 PdCl₂-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 PdCl₂-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 PdCl₂-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 PdCl₂, 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 PdCl₂-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 O₂, trace amounts of **2** and **3** together with precipitates of Pd black were formed, confirming the necessity of O₂ for this oxidation. The use of ¹⁸O-labeled water in the PdCl₂-DMA-MeOH-TsOH system gave exclusively the ¹⁸O-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 ¹⁸O-labeled **3** was also confirmed when **2** was employed as the starting material under the above-mentioned conditions in the absence of PdCl₂. These results showed that the use of PdCl₂, DMA, H₂O, MeOH, and TsOH under O₂ atmosphere is essential to achieve the highly efficient oxidation of electron-deficient internal olefins. Interestingly, the addition of small amounts of CuCl₂ to this catalyst system significantly suppressed the oxidation of **1**, whereas the Cu salt was vital as co-catalyst in the conventional Wacker–Tsuiji 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 O₂-coupled Cu-free

Table 2: Oxidation of various electron-deficient internal olefins using PdCl₂-DMA-MeOH-TsOH system.^[a]

R-CH=CH-EWG + H ₂ O		PdCl ₂ , MeOH, TsOH DMA, O ₂		R-C(=O)-CH ₂ -EWG	
Entry	Substrate	Product	t [h]	Yield [%] ^[b]	
1	C ₅ H ₁₁ -CH=CH-COOMe	C ₅ H ₁₁ -C(=O)-CH ₂ -COOMe	3	82 (79)	
2 ^[c]			12	81 (78)	
3	CH ₃ -CH=CH-COOMe	CH ₃ -C(=O)-CH ₂ -COOMe	3	78 (73)	
4	C ₃ H ₇ -CH=CH-COOMe	C ₃ H ₇ -C(=O)-CH ₂ -COOMe	3	72	
5	CH ₃ -CH=CH-COOMe	CH ₃ -C(=O)-CH ₂ -COOMe	10	68	
6	CH ₃ -CH=CH-COOMe	CH ₃ -C(=O)-CH ₂ -COOMe	3	73	
7	Ph-CH=CH-COOMe	Ph-C(=O)-CH ₂ -COOMe	40	68 (64)	
8	MeO-C ₆ H ₄ -CH=CH-COOMe	MeO-C ₆ H ₄ -C(=O)-CH ₂ -COOMe	40	70	
9	Cl-C ₆ H ₄ -CH=CH-COOMe	Cl-C ₆ H ₄ -C(=O)-CH ₂ -COOMe	40	65	
10	C ₄ H ₉ -CH=CH-COMe	C ₄ H ₉ -C(=O)-CH ₂ -COMe	10	81 (77)	
11	Ph-CH=CH-COMe	Ph-C(=O)-CH ₂ -COMe	40	64	
12	Ph-C(=O)-CH=CH-Ph	Ph-C(=O)-CH ₂ -C(=O)-Ph	10	81	
13	Ph-C(=O)-CH=CH-OMe	Ph-C(=O)-CH ₂ -C(=O)-OMe	10	78	
14	Ph-C(=O)-CH=CH-Cl	Ph-C(=O)-CH ₂ -C(=O)-Cl	10	74	
15	C ₂ H ₅ -CH=CH-CN	C ₂ H ₅ -C(=O)-CH ₂ -CN	40	63	

[a] Reaction conditions: substrate (0.5 mmol), PdCl₂ (0.05 mmol), DMA (4 mL), MeOH (1.5 mL), H₂O (0.5 mL), TsOH (0.2 mmol), O₂ (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), PdCl₂ (1.2 mmol), DMA (60 mL), MeOH (10 mL), H₂O (10 mL), TsOH (4 mmol), O₂ (9 atm), 12 h. The selectivities of all reactions were higher than 99%.

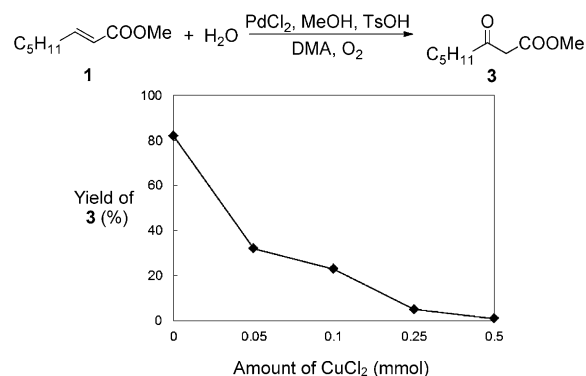
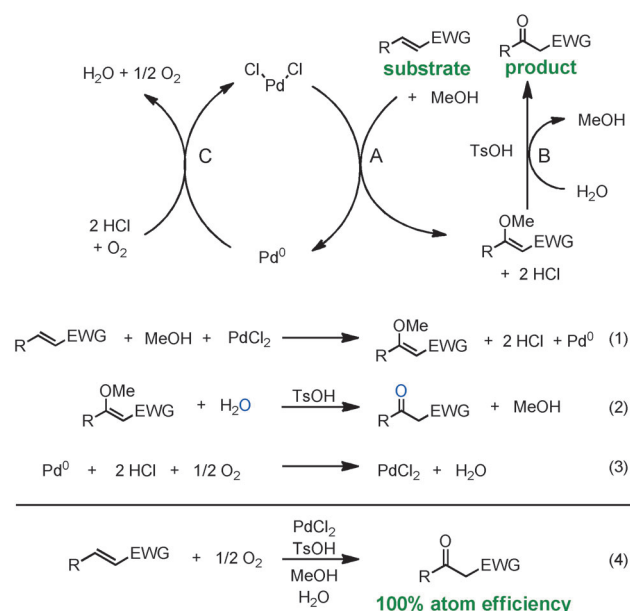


Figure 1. Effect of the amount of CuCl₂ on the oxidation of **1**. Reaction conditions: substrate (0.5 mmol), PdCl₂ (0.05 mmol), DMA (4 mL), MeOH (1.5 mL), H₂O (0.5 mL), TsOH (0.2 mmol), O₂ (6 atm), 80 °C, 3 h.

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



Scheme 1. Proposed reaction pathway and reaction equations of the PdCl₂-DMA-MeOH-TsOH catalyst system.

olefin and MeOH to afford a methyl vinyl ether intermediate and a Pd⁰ species (step A). Next, the methyl vinyl ether is hydrolyzed by TsOH, giving the corresponding ketone accompanied by the regeneration of MeOH (step B). The Pd⁰ 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 O₂, thus showing that the rate-determining step is the reoxidation of the Pd⁰ species (step C).^[11] DMA may coordinate to the transient Pd⁰ species, suppressing the irreversible aggregation of the Pd⁰ species and promoting the facile reoxidation of the Pd⁰ species by O₂^[7] (these reaction steps are represented in Equations (1)–(3), respectively). The summation formula Eq. (4) shows that PdCl₂, TsOH, MeOH, and H₂O act catalytically, and an oxygen atom of O₂ is formally incorporated into the olefin to afford the oxidized product without any co-products. Namely, this oxidation method provides 100% atom efficiency using O₂ as a terminal oxidant.

In conclusion, we have developed a highly efficient catalytic system consisting of PdCl₂, 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 O₂

as a terminal oxidant. Furthermore, this O₂-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: PdCl₂ (0.05 mmol), DMA (4 mL), MeOH (1.5 mL), H₂O (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 O₂, and the mixture was vigorously stirred at 80°C for 3 h. After the reaction, the reactor was cooled to room temperature and O₂ 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 $\times$ 30 mL). The diethylether layer, which contained the products, was dried over MgSO₄, 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.

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