Synthetic Methods

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Convenient and Efficient Pd-Catalyzed Regioselective Oxyfunctionalization of Terminal Olefins by Using Molecular Oxygen as Sole Reoxidant**

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The evolution of selective oxidation routes that use molecular oxygen (O_2) is one of the ultimate goals of present-day chemical research.[1] In particular, the Pd-catalyzed Wacker oxidation and acetoxylation of terminal olefins have received

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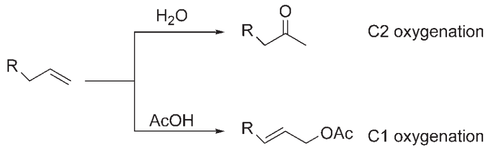
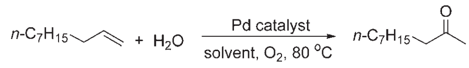
much attention because of useful protocols for direct oxy-functionalization at the C1 and C2 positions.[2] These processes, however, require cocatalysts, such as copper,[3] heteropolyacids,[4] or benzoquinone,[5] or reducing agents[6] to facilitate the reoxidation of the Pd^0 species by O_2 and prevent its precipitation into inactive metals. Current research has focused on the development of promising methodologies that do not rely on these cocatalysts because of practical and environmental concerns.[7] However, few examples of oxy-functionalization systems using O_2 as the sole reoxidant have appeared, and these Pd-catalyzed oxidation reactions often suffer from low activities and a limited substrate scope.[8,9] We disclose that $PdCl_2$ in combination with DMA as the solvent is an extremely simple and highly efficient catalytic system for the Wacker oxidation of terminal olefins. This catalytic system allows for an efficient dioxygen-coupled turnover without the need for additional cocatalysts or reducing reagents; it is tolerant toward long-chain and functionalized olefins and is also applicable to Wacker-type intramolecular cyclization. Furthermore, it facilitates acetoxylation of the terminal olefins, thus affording selectively linear allylic acetates. An oxygen atom can be selectively incorporated at the C1 or C2 position of terminal olefins by using an appropriate nucleophile, namely, H_2O or AcOH (Scheme 1). The work-up procedure is also straightforward, and the solution containing the catalyst can be recycled without any loss of activity and selectivity.



Scheme 1. Selectively incorporation of an oxygen atom at the C1 or C2 position of terminal olefins.

The reaction conditions were optimized for the Wacker oxidation of 1-decene (**1a**) using various Pd complexes and solvents under an atmospheric pressure of O_2 (Table 1). The combination of $PdCl_2$ and DMA exhibited the highest catalytic activity, thus affording 2-decanone (**2a**) in 84% yield after 6 h without formation of olefinic isomers (Table 1, entry 1).[10] No Pd precipitation was observed during the above reaction, and the retention of monomeric Pd^{II} species was confirmed after the reaction by Pd K-edge X-ray absorption fine-structure (XAFS) spectroscopic analysis.[11] The use of NMP and DMPA in place of DMA gave moderate yields (Table 1, entries 2 and 3), whereas dimethylformamide (DMF), ethanol, and acetonitrile were significantly less effective (Table 1, entries 4–6). The choice of Pd source was found to influence catalytic efficiency: only $PdCl_2$ could function as a catalyst (Table 1, entry 1 vs. entries 7 and 8). Compound **1a** (20 mmol, 2.8 g) was successfully converted into **2a** (83% yield of isolated product, 2.6 g) with a turnover frequency (TOF) of 17 h^{-1} and a turnover number (TON) of up to 170 (Table 1, entry 9). These values are considerably greater than those reported for other catalytic systems of Pd

Table 1: Wacker oxidation of 1-decene under various conditions,[a] and the peak potentials for reduction (E_{red}) and oxidation (E_{ox}) obtained by cyclic voltammetry.



1a **2a**

Entry	Catalyst	Solvent	Yield [%][b]	E_{red} [V vs. SCE]	E_{ox} [V vs. SCE]
1	$PdCl_2$	DMA	84	−0.70	−0.26
2	$PdCl_2$	NMP	74	−0.69	−0.20
3	$PdCl_2$	DMPA	33	−0.57	−0.13
4	$PdCl_2$	DMF	trace	−0.50	−0.12
5	$PdCl_2$	EtOH	trace	−0.10	0.19
6	$PdCl_2$	MeCN	trace	−0.40	0.10
7	$Pd(OAc)_2$	DMA	trace	–	–
8	$[PdCl_2(NH_3)_4]$	DMA	trace	–	–
9[c]	$PdCl_2$	DMA	85 (83)	–	–

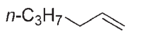
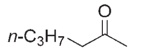
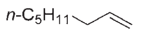
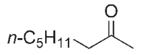
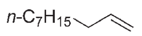
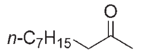
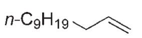
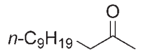
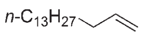
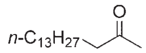
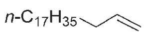
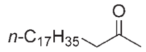
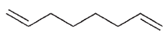
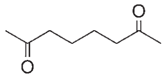
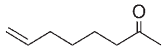
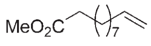
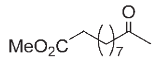
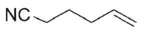
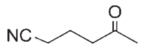
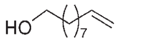
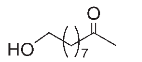
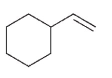
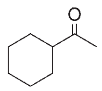
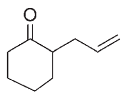
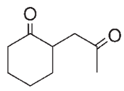
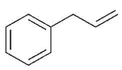
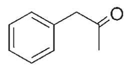
[a] Reaction conditions: 1-decene (0.5 mmol), Pd catalyst (0.005 mmol), solvent (5 mL), H_2O (0.3 mL), 1 atm of O_2, 6 h, 80°C. [b] Values in parenthesis are yields of the isolated product. [c] 1-Decene (20 mmol), $PdCl_2$ (0.1 mmol), DMA (60 mL), H_2O (10 mL), 10 atm of O_2, 10 h. SCE = saturated calomel electrode, NMP = *N*-methylpyrrolidone, DMA = *N*,*N*-diemthylacetamide, DMPA = *N*,*N*-dimethylpropionamide.

with cocatalysts, such as $PdSO_4$/per(2,6-di-*o*-methyl)-β-cyclodextrin/$H_9PV_6Mo_6O_{40}$/$CuSO_4$ (TOF and TON: 7.7 h^{-1} and 46),[4a] $Pd(OAc)_2$/carbon/molybdovanadophosphate/NH_4Cl/$MeSO_4$ (TOF and TON: 3.3 h^{-1} and 16),[4b] $PdCl_2$/α-cyclodextrin/$CuCl_2$ (1.9 h^{-1} and 19),[3e] and $PdCl_2$/β-cyclodextrin/$CuCl_2$ (0.3 h^{-1} and 15).[3d]

A wide range of terminal olefins were oxidized to form the corresponding methyl ketones in high yields (Table 2).[11] For example, the oxidation of long-chain olefins 1-hexadecene and 1-eicosene occurred efficiently to give the ketones in 85 and 81% yields, respectively (Table 2, entries 5 and 6). In contrast, oxidation of 1-eicosene with $PdCl_2$/$CuCl_2$ in polyethyleneglycol[3c] and $Pd(OAc)_2$/hydroquinone/Fe(phthalocyanine) in DMF[5] resulted in less than 10% yields of 2-eicosenone. In the case of 1,7-octadiene, the use of the $PdCl_2$–DMA catalytic system afforded the corresponding diketone in 81% yield (Table 2, entry 7). The system was also found to be applicable to the oxidation of functionalized terminal olefins possessing cyano and hydroxyl groups. 5-Hexenenitrile and 9-octene-1-ol afforded the corresponding ketones selectively, with suppression of hydration and alcohol oxidation (Table 2, entries 9 and 10).

A further advantage of this catalytic system is the facile separation of the oxidized products from the reaction mixture. Addition of *n*-heptane to the reaction mixture upon completion of the reaction followed by decantation of the *n*-heptane phase containing the oxidized products allows the active Pd species in the residual DMA solution to be recycled. We conducted further oxidations by the addition of successive portions of the olefin to the Pd–DMA phase followed by stirring under identical reaction conditions. The second and third oxidation cycles of **1a** proceeded at rates similar to that of the original reaction, thus affording **2a** in yields of more than 80% with 99% selectivity. The total TON reached 250 after the third recycling process. This separation

Table 2: Wacker oxidation of various olefins catalyzed by the $PdCl_2$–DMA system.[a]

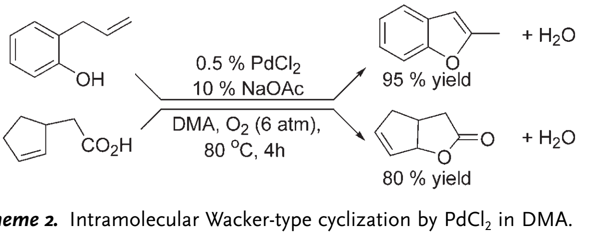
Entry	Substrate	t [h]	Conv. [%]	Product	Yield [%][b]
1		3	85		82 (78)
2		3	82		81 (75)
3		3	86		85 (83)
4[c]		3	88		88 (85)
5[c]		3	88		85 (82)
6[c]		3	82		81 (76)
7[d]		40	100		81 (78)
					19
8[d]		40	97		96 (92)
9[d]		40	84		80 (75)
10[d]		24	89		89 (85)
11[d]		3	86		74 (66)
12[d]		24	96		91 (88)
13[d]		40	94		87 (85)

[a] Reaction conditions: substrate (1 mmol), $PdCl_2$ (0.005 mmol), DMA (3 mL), H_2O (0.5 mL), 6 atm of O_2, 80 °C. [b] Yields were determined by GC analysis; values in parenthesis are the yields of the isolated products. [c] DMA (5 mL). [d] Substrate (0.5 mmol). Conv. = conversion

method is strikingly simple in comparison to the previously reported methods using fluoro solvents[12] and ionic liquids.[13]

This catalytic system was also found to be applicable to Wacker-type intramolecular cyclizations, even in the presence of a catalytic amount of sodium acetate.[9] 2-Allylphenol and 2-cyclopentene-1-acetic acid were smoothly converted into 2-methylbenzofuran and 3,3a,4,6a-tetrahydro-2*H*-cyclopenta[b]furan-2-one, respectively, in high yields (Scheme 2).

When AcOH is used as a nucleophile instead of H_2O, regioselective acetoxylation of terminal olefins to the corresponding linear allylic acetates takes place without the use of a cocatalyst (Table 3). For example, **1a** predominantly underwent acetoxylation to provide 2-decenyl ester in 80% yield with 93% selectivity, accompanied by a 6% yield of branched allylic acetate, without the formation of olefinic isomers or Wacker products (Table 3, entry 1). Both the activity and regioselectivity of the acetoxylation are significantly superior to those reported for a $Pd(OAc)_2$–dimethyl sulfoxide (DMSO) system, which required a large amount of benzoquinone as a redox reagent.[14,15] To the best of our knowledge, this is the first demonstration of a cocatalyst-free regioselective acetoxylation of terminal olefins to linear allylic acetates using O_2 as a terminal oxidant.

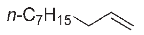
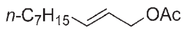
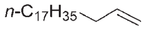
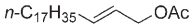
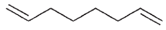
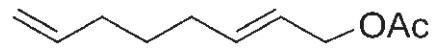
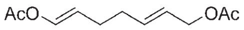
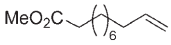
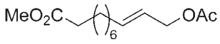
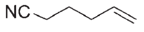
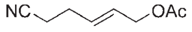
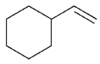
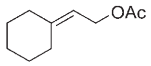
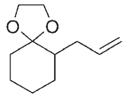
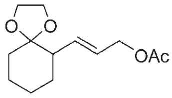
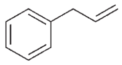
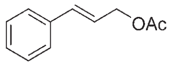


Scheme 2. Intramolecular Wacker-type cyclization by $PdCl_2$ in DMA.

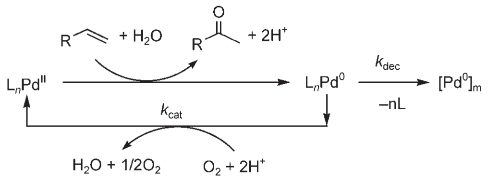
As well as long-chain aliphatic olefins, acetoxylation proceeded efficiently to give the corresponding linear allylic acetates, even for those olefins with sensitive functional groups, such as ester, nitrile, and acetal groups (Table 3, entries 2–8). This method is a powerful candidate for the α-oxyfunctionalization of versatile terminal olefins, such as hydroboration–oxidation[16] and oxidation using chromyl chloride.[17]

Cyclic-voltammetric analysis of $PdCl_2$ in various solvents was carried out to elucidate the positive effect of DMA on the Wacker oxidation. These spectra showed single irreversible reduction and oxidation peaks: the oxidation peak of the electrogenerated Pd^0 species appeared at a more negative potential value in DMA ($E_{ox} = -0.26$ V) than in other solvents (Table 1, entries 1–6). Interestingly, yields of **2a** increase with increasing negative E_{ox} values of DMA, NMP, and DMPA (Table 1, entries 1–3), which supports the contention that DMA acts as the most efficient solvent for promoting the reoxidation of the Pd^0 species.[11,18] In a separate experiment, XAFS analysis showed that Pd sponge was readily oxidized to a homogeneous Pd^{II} species in a solution of DMA in the presence of two equivalents of HCl under atmospheric O_2 at 80 °C.[11] Wacker oxidation proceeded to afford **2a** in 76% yield in 8 h upon addition of **1a** to this solution of Pd. Kinetic studies revealed that the initial reaction rate of **1a** (R_0) was dependent on O_2 pressure (pO_2) and the concentration of the catalyst ([Pd]) and independent of the concentration of **1a**, H_2O, and H^+. Taking into account the mechanism proposed by Stahl and coworkers for Pd-catalyzed aerobic oxidation, we propose a possible reaction cycle for the present Wacker oxidation in which the rate-determining reoxidation step of Pd^0 k_{cat} competes with its decomposition into inactive Pd^0 metal k_{dec} (Scheme 3).[19] The R_0 value for the Wacker oxidation of **1a**

Table 3: Acetoxylation of various olefins by $PdCl_2$ using molecular oxygen.[a]

Entry	Substrate	Conv. [%]	Major product	Linear/ branched[b]	E/Z[c]	Yield [%][d]
1		86		13:1	1:1	86 (85)
2		93		10:1	2:1	90 (82)
3[e]		65		10:1	6:1	43 (40)
				7:1		20 (18)[f]
4[e]		95		8:1	9:1	90 (85)
5[e]		85		10:1	8:1	80 (76)
6[e]		56		45:1	–	56 (50)[g]
7[e]		85		20:1	>99:1	79 (75)
8		85		17:1	>99:1	85 (84)

[a] Reaction conditions: substrate (1 mmol), $PdCl_2$ (0.01 mmol), NaOAc (0.2 mmol), 4-Å molecular sieves (0.2 g), DMA (5 mL), AcOH (0.2 mL), 6 atm of O_2, 40 h, 80 °C. [b] Ratio based on GC analysis of crude product. [c] Ratio based on ^1H NMR spectroscopic analysis of the crude product. [d] Yields of linear + branched allylic acetates were determined by GC analysis; values in parenthesis are yields of the isolated products. [e] Substrate (0.5 mmol). [f] $(E,E)/(E,Z)/(Z,Z)$ = 15:4:1. [g] Mixture of 1-cyclohexene ethanol acetate/2-cyclohexylidene ethanol acetate (1:1).



Scheme 3. Proposed catalytic cycle. k_{cat} = rate of the reoxidation step, k_{dec} = rate of the decomposition.

can be expressed as follows: $R_0 = k_{cat}\ pO_2[Pd]_t$, $[Pd]_t = [Pd]_0/(1+[Pd]_0 k_{dec} t)$ (the values of k_{cat} and k_{dec} at 80 °C in DMA were determined to be 0.02 and $1.81\,M^{-1}s^{-1}$, respectively). The value of k_{cat}/k_{dec} was almost 2.3 times greater than that observed in DMF.[11] These observations clearly show that DMA promotes the reoxidation of the Pd^0 species by O_2 and simultaneously suppresses competing Pd^0 aggregation. It can be said that the use of DMA results in a unique catalytic system capable of performing the Wacker oxidation in the absence of a cocatalyst. With respect to the above acetoxylation, DMA might accelerate the reoxidation of Pd^0 species by O_2.

In conclusion, the combination of $PdCl_2$ and DMA allows highly effective oxygenation of terminal olefins under cocatalyst-free conditions. The use of a different nucleophile (H_2O or AcOH) can lead to a complete switch in regioselectivity between the C1 and C2 positions. The versatility demonstrated by this simple catalytic system holds significant promise for achieving new oxidation system using O_2 as a sole reoxidant.

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