

Palladium-Catalyzed Oxidation of Phenyl-Substituted Alkenes using Molecular Oxygen as the Sole Oxidant

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Abstract: The palladium-catalyzed aerobic oxidation of styrene and 2-vinylnaphthalene in dimethylacetamide/water or dimethylformamide/water solutions under mild conditions has been developed, in which palladium(II) chloride is used in the absence of co-catalysts or special stabilizing ligands as the sole and recyclable catalyst. The corresponding methyl ketones have been obtained in good to excellent yields with low catalyst loadings (0.2–5 mol%) and high

turnover numbers (up to *ca.* 1000 to palladium). This simple and efficient catalytic method represents an ecologically benign and economically attractive synthetic pathway to industrially important compounds used in the manufacture of various polymers and drugs.

Keywords: oxidation; oxygen; palladium; styrenes; 2-vinylnaphthalenes

Introduction

Palladium complexes are remarkably versatile reagents for the selective oxidation of organic molecules. The important advantage of these reactions is the possibility to involve molecular oxygen as a final oxidant, which is usually achieved by the re-oxidation of reduced palladium species with reversible co-oxidants, CuCl₂ being the most convenient one (Wacker catalyst).^[1] However, the Wacker process requires large amounts of CuCl₂, chloride ions, and acid to maintain the catalytic cycle; therefore, the system is highly corrosive and often causes the formation of chlorinated side products. To overcome these problems, much effort has been devoted to the development of alternative halide-free co-catalysts, such as Cu(OAc)₂, heteropoly acids, nitrates, and benzoquinone;^[2–8] as well as, more recently, palladium catalysts modulated by special ligands.^[8–14] In the latter systems, oxidatively robust (usually, nitrogen-containing) ligands are used to stabilize reduced palladium and promote its regeneration directly by molecular oxygen avoiding the use of corrosive additives. A few examples of the ligand-modulated palladium-catalyzed oxidations of terminal alkenes into methyl ketones using molecular oxygen as the sole oxidant have been published.^[9–11,14]

Recently, Kaneda and co-workers have discovered that dimethylacetamide (DMA) as a solvent serves to stabilize a palladium catalyst preventing its precipitation into inactive metal and to promote a direct di-

oxygen-coupled Wacker oxidation of a number of terminal alkenes.^[15] The system allows for an efficient catalytic turnover without the need for additional co-catalysts or special ligands under relatively mild conditions (80 °C, 6 atm of oxygen). Sigman and co-workers have achieved a further improvement in the practicality of this reaction showing that the use of (–)-sparteine as a ligand on palladium allows one to perform the reaction in a DMA/H₂O solvent system under balloon pressure of oxygen.^[14]

Inspired by these disclosures, we have decided to extend their applications to phenyl-substituted alkenes, i.e., styrene and 2-vinylnaphthalene. These alkenes are usually problematic substrates for oxidation due to a tendency toward oxidative cleavage to the corresponding aldehydes and polymerization.

The palladium-catalyzed oxidation of styrene to acetophenone has been investigated by various research groups due to, in particular, the practical importance of this compound. Acetophenone is a valuable intermediate for the manufacture of a variety of resins, pharmaceuticals, pesticides, and perfumery products and is industrially produced by the Friedel–Crafts acetylation of benzene with acetic aldehyde/acetyl chloride.^[16] Most of reported examples of the palladium-catalyzed oxidation of styrene involve hydrogen peroxide or peroxy compounds as oxidants^[17–24] and only few works use the most attractive oxidant – molecular oxygen.^[25–30] To the best of our knowledge, all reported aerobic palladium-catalyzed oxidations of styrene utilize the conventional Wacker

co-catalyst – CuCl_2 – to mediate the re-oxidation of $\text{Pd}(0)$.^[25–28] One exception is a recently published attempt to oxidize styrene with PdCl_2 as the sole catalyst in an $\text{scCO}_2/\text{MeOH}$ solvent system, which gave only a 12.4% yield of acetophenone.^[30] Sigman and co-workers observed that an N-heterocyclic carbene/ $\text{Pd}(\text{II})$ complex converted styrene to acetophenone under aerobic conditions; however, it was found that the reaction proceeded due to the *in situ* production of a peroxide *via* co-oxidation of THF – the only competent reaction solvent.^[22]

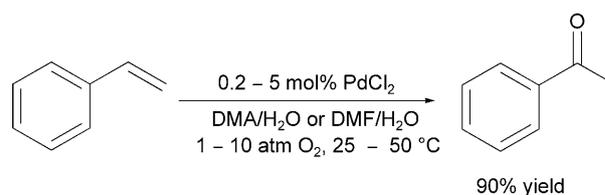
Although 2-acetonaphthones are also industrially important drug and polymer intermediates, the data on the palladium-catalyzed oxidation of 2-vinylnaphthalenes are really scarce.^[31]

In the present paper, we report a simple and efficient palladium-catalyzed direct dioxygen-coupled oxidation of styrene and 2-vinylnaphthalene into corresponding methyl ketones. The reactions do not need additional co-oxidants or special ligands and proceed under mild aerobic conditions. The use of PdCl_2 as the sole and recyclable catalyst and inexpensive high boiling amidic solvents as well as molecular oxygen as the final oxidant is a significant practical advantage of the process.

Results and Discussion

We have studied the oxidation of styrene and 2-vinylnaphthalene by molecular oxygen using PdCl_2 as the sole catalyst in dimethylacetamide (DMA) or dimethylformamide (DMF) solutions containing 10–20 vol% of water. In most of the runs, elevated pressures of oxygen are used in order to ensure efficient capture of reduce palladium and prevent metal precipitation. Some experiments were performed at atmospheric pressure. The reactions with each substrate resulted in corresponding methyl ketone as a major product in 85–95% yields in most of the runs. The GC mass balance was based on the substrate charged using bornyl acetate as the internal standard. The difference in mass balance in the Tables is usually less than 5% and corresponds to unidentified high boiling products. Thus, a high stability of these delicate substrates toward polymerization under the conditions used for oxidation is especially noteworthy.

The main minor products were benzaldehyde and 2-naphthalenecarboxaldehyde formed due to the oxidative cleavage of carbon-carbon double bonds in styrene and 2-vinylnaphthalene, respectively. The cleavage reaction seems to occur through a radical auto-oxidation mechanism, as it can be suppressed, at least in the case of the conventional Wacker ($\text{PdCl}_2/\text{CuCl}_2$ -catalyzed) oxidation of styrene, by adding radical inhibitors to the system.^[20]



Scheme 1. Oxidation of styrene into acetophenone.

Styrene readily reacts with PdCl_2 in DMA solutions in the presence of water. A virtually complete conversion has been attained for 5 h at 50 °C and 10 atm resulting in *ca.* 90% yield of acetophenone (Scheme 1, Table 1, run 1). The reaction is catalytic in palladium and shows a dioxygen-coupled turnover number (TON) of 20, with no palladium mirror being observed on the walls of the reaction vessel after the reaction. Thus, DMA as a coordinating solvent successfully prevents zerovalent palladium species, $\text{Pd}(0)\text{L}_n$, from clustering into inactive bulk metal; so that their oxidation by molecular oxygen occurs faster than aggregation.

The increase in water content from 15 to 20 vol% significantly accelerates the reaction, which can be completed under these conditions for less than 2 h showing the average turnover frequency (TOF) of 12.7 h^{-1} (Table 1, run 2). This value is considerably greater than those usually reported for conventional Wacker oxidations using co-catalysts.^[15] The enhancing effect of water has also been observed in the $\text{Pd}[(+)\text{-sparteine}]\text{Cl}_2/\text{DMA}$ system for the oxidation of other terminal alkenes.^[14] However, it should be mentioned that increasing the water concentration must be equilibrated with the miscibility of the substrates.

The reaction with styrene (and with 2-vinylnaphthalene, as it will be shown below) also occurs smoothly in another amidic solvent, DMF, although at a slightly lower rate (Table 1, run 3 *vs.* run 1). This result is remarkable in light of a previously reported observation that 1-decene gives only a trace yield of the corresponding methyl ketone in DMF under similar conditions.^[15] Thus, DMF also acts as an efficient solvent to promote the regeneration of the palladium species at the oxidation of styrene without the need of co-catalysts or special ligands, making more flexible the choice of solvent for practical purposes. Selectivity for acetophenone in DMF is slightly lower than in DMA (83 *vs.* 92%), but the reaction variables have not been optimized yet.

It is also important that the catalytic system efficiently operates at room temperature (Table 1, runs 4–7). The reaction rate decreases, as expected; however, the effect seems to be partly compensated by the increased solubility of molecular oxygen at lower temperature. Really, the initial reaction rate depends

Table 1. Palladium-catalyzed oxidation of styrene by molecular oxygen in dimethylacetamide.^[a]

Run	H ₂ O [vol%]	Temp. [°C]	Pressure [atm]	Time [h]	Conversion [%]	Rate ^[b] [10 ⁻² Mh ⁻¹]	TON ^[c]	Selectivity (isolated yield) [%]	
								acetophenone	benzaldehyde
1	15	50	10	5	99	7.0	20	92	6
2	20	50	10	1.5	95	12.6	19	91 (76)	7
3 ^[d]	15	50	10	8	96	4.6	19	83	11
4	15	25	10	8	95	3.0	19	90	5
5	15	25	5	9	97	2.2	19	90	7
6	20	25	10	7	96	4.0	19	93	5
7 ^[e]	15	25	10	32	95	1.7	95	94	4
8 ^[e]	20	50	10	5	97	20.0	97	91 (74)	5
9 ^[f]	15	60	10	24	98	12.0	490	80	16
10 ^[g]	15	50	1	6	33	–	–	–	–
				16	40	1.3	8	96	4
11	15	50	1	16	95	4.0	19	82 (65)	18
12 ^[h]	15	60	10	28	98	10.0	490	80	12

^[a] Conditions: [styrene]=0.20 M; [PdCl₂]=0.01 M; gas phase – O₂; conversion and selectivity were determined by GC and based on the consumed styrene.

^[b] Initial rate of the substrate conversion.

^[c] TON – moles of the substrate converted/moles of Pd.

^[d] DMF was used as the solvent.

^[e] [PdCl₂]=0.0025 M; [styrene]=0.25 M.

^[f] [PdCl₂]=0.0020 M; [styrene]=1.0 M.

^[g] [(–)-sparteine]=0.01 M.

^[h] After run 9, the products were separated by extraction with *n*-heptane, the reactor was recharged with fresh styrene (1.0 M) and the reaction was allowed to proceed further. TON is given for the second reaction cycle.

on the oxygen pressure showing a positive order (Table 1, runs 4 and 5), but even at 5 atm no palladium precipitation has been observed and the reaction has been completed for 9 h. These observations suggest that the step which determines the rate of the whole process is the re-oxidation of the reduced palladium species by molecular oxygen. The accelerating effect of water is also pronounced at room temperature and the catalyst is still stable at 20 vol% of water in DMA (Table 1, run 4 vs. run 6).

To improve the catalyst efficiency in terms of TONs, the substrate/catalyst ratio was raised to 100 by decreasing the PdCl₂ concentration (Table 1, run 7). We were cautious in increasing the concentration of the substrate in order to avoid its polymerization. The reaction was virtually completed even at room temperature, albeit at a rather low rate, and showed an excellent selectivity of 94% for acetophenone. Thus, a dioxygen-coupled TON in this run reached the value of 95 with no precipitation of the palladium metal being observed. A TON of *ca.* 100 can be attained much faster at higher temperature and higher water content without a significant polymerization of the substrate (Table 1, run 8). Moreover, a further increase in the substrate concentration allowed attaining TON of near 500 (Table 1, run 9). Although large amounts of styrene (1.0 M) were charged in one portion at the beginning of this reaction, no significant amounts of high boiling products were observed as

acetophenone and benzaldehyde accounted for near 95% of the mass balance. Thus, the substrate is quite tolerant to polymerization under the conditions used. The average TOF of 16.6 h⁻¹ was obtained in this reaction without the precipitation of palladium metal, although the selectivity for acetophenone decreased to 80% at the expense of benzaldehyde (16%).

The reaction also operates at ambient pressure of oxygen in the presence of (–)-sparteine (1 equiv. to Pd) used to stabilize reduced palladium species^[14] (Table 1, run 10). No precipitation of palladium metal occurs, but the reaction is slow and becomes stagnated at near 40% conversion (TON=8). Finally, the reaction was performed at 1 atm of oxygen in the absence of the auxiliary ligand to verify if the coordinating ability of DMA is sufficient to keep palladium in the solution. To our surprise, the reaction was even much faster than that in the presence of (–)-sparteine and reached a near complete conversion (TON=19) without the precipitation of palladium (Table 1, run 11). Thus, the catalytic system in DMA is quite stable and efficient for the oxidation of styrene even at ambient pressure of oxygen without the use of any auxiliary stabilizing ligand on palladium.

In a further attempt to improve the practicality of this reaction, the catalyst after run 9 was re-used. The products were separated from the catalytic system by extraction with *n*-heptane upon the completion of the reaction. The residual DMA/H₂O solution of PdCl₂

Table 2. Palladium catalyzed oxidation of 2-vinylnaphthalene by molecular oxygen.^[a]

Run	Solvent [vol%]	Temp. [°C]	Pressure [atm]	Time [h]	Conversion [%]	Rate ^[b] [10 ⁻² M h ⁻¹]	TON ^[c]	Selectivity (isolated yield) [%]	
								acetone	aldehyde
1	DMA/H ₂ O (15)	80	10	1	98	17.2	20	87 (75)	13
2 ^[d]	DMA/H ₂ O (10)	60	10	12	98	5.0	78	87	10
3	DMF/H ₂ O (15)	80	10	2	50	4.0	10	85	15
4	DMF/H ₂ O (20)	80	10	5	80	9.0	16	80	10

^[a] Conditions: [2-vinylnaphthalene]=0.10 M; [PdCl₂]=0.005 M; gas phase – O₂; conversion and selectivity were determined by GC and based on the consumed styrene; aldehyde – 2-naphthalenecarboxaldehyde.

^[b] Initial rate of the substrate conversion.

^[c] TON – moles of the substrate converted/moles of Pd.

^[d] [PdCl₂]=0.0025 M; [2-vinylnaphthalene]=0.20 M.

was recharged with fresh styrene and the reaction was allowed to proceed further (Table 1, run 12). The total TON obtained in two reaction cycles reached the value of 980. The reaction rate with the recharged styrene varied only slightly and the selectivity for acetophenone was near 80%.

2-Vinylnaphthalene can also be oxidized smoothly by molecular oxygen in DMA/H₂O solutions containing PdCl₂ (Table 2, runs 1 and 2). An industrially important compound, i.e., acetone, is obtained in *ca.* 85% yield, with 2-naphthalenecarboxaldehyde formed due to the oxidative cleavage of the carbon-carbon double bond being the only minor product (Scheme 2). The reaction is fast and shows the average TOF of 20 h⁻¹ (Table 2, run 1). DMF also can be used as the solvent for the oxidation of 2-vinylnaphthalene; however, not with the same efficiency (Table 2, runs 3 and 4). Although no palladium mirror is formed and selectivity for acetone is high (80–85%), the reaction becomes stagnated at incomplete conversion of the substrate and the best yields of acetone do not exceed 60–65%.

Conclusions

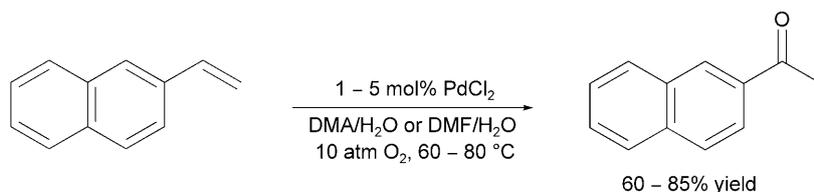
In summary, we have reported a highly selective method for the oxidation of styrene and 2-vinylnaph-

thalene into corresponding methyl ketones, under mild aerobic conditions. The use of PdCl₂ as the sole and recyclable catalyst and inexpensive high boiling solvents as well as molecular oxygen as the final oxidant is a significant practical advantage of the process. It is also important that the reaction does not require co-oxidant, often corrosive, which must be employed in conventional palladium-catalyzed oxidations of alkenes. This simple and efficient catalytic method represents an attractive synthetic pathway to the industrially important compounds used in the manufacture of various polymers and drugs. Further studies are targeted towards the development of solid palladium catalysts resistant to leaching in polar solvents in order to facilitate catalyst separation.

Experimental Section

All reagents were purchased from commercial sources and used as received, unless otherwise indicated. Styrene and 2-vinylnaphthalene were distilled under reduced pressure before use.

The reactions at atmospheric pressure were carried out in a glass reactor under magnetic stirring and equipped with a condenser and followed by measuring dioxygen uptake and by gas chromatography (GC).

**Scheme 2.** Oxidation of 2-vinylnaphthalene into acetone.

The reactions at higher pressures were carried out in a stainless steel magnetically stirred 100-mL reactor (autoclave) and followed by GC.

In a typical run, the solution of the substrate (2.0–20.0 mmol, 0.1–1.0 M), PdCl₂ (0.04–0.2 mmol, 0.002–0.01 M) and bornyl acetate (internal standard, 2 mmol, 0.1 M) in the mixture of amidic solvent with water in indicated proportions (20 mL) was transferred in the reactor. Concentrations of the components are given in the Table 1 and Table 2. The glass reactor was connected to a gas burette containing molecular oxygen to measure the gas uptake. The autoclave was pressurized with dioxygen to the total pressure indicated in the Table 1 and Table 2 (1–10 atm). The reactors were placed in an oil bath; then, the solutions were stirred at a specified temperature (25–80 °C). At appropriate time intervals, aliquots were taken via special sampling systems without depressurization of the reactors and analyzed by GC using a Shimadzu 17B instrument fitted with a Carbowax 20 m capillary column and a flame ionization detector. After carrying out the reaction and cooling to room temperature, the excess of oxygen was slowly vented from the autoclave. Products were identified by GC/MS (Shimadzu QP2010-PLUS, 70 eV).

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