Palladium Catalysis Hot Paper

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Aerobic Palladium-Catalyzed Dioxygenation of Alkenes Enabled by Catalytic Nitrite**

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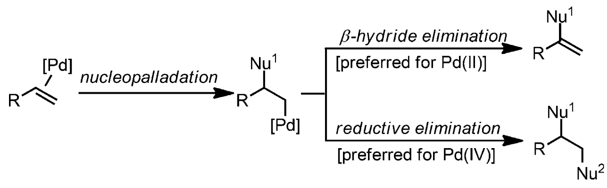
Abstract: *Catalytic nitrite was found to enable carbon–oxygen bond-forming reductive elimination from unstable alkyl palladium intermediates, providing dioxygenated products from alkenes. A variety of functional groups were tolerated, and high yields (up to 94%) were observed with many substrates, also for a multigram-scale reaction. Nitrogen dioxide, which could form from nitrite under the reaction conditions, was demonstrated to be a potential intermediate in the catalytic cycle. Furthermore, the reductive elimination event was probed with* ^{18}*O-labeling experiments, which demonstrated that both oxygen atoms in the difunctionalized products were derived from one molecule of acetic acid.*

The development of selective catalytic oxidations of hydrocarbons has enabled the preparation of functionalized molecules from simple and readily accessible starting materials. Palladium catalysis has enabled a wide variety of practical and broadly adopted oxidative transformations of hydrocarbons.[1] In the past decade, researchers have taken advantage of the facile reductive elimination from high-valent palladium centers (Pd^{IV} and Pd^{III}) to enable reactivity that is complementary to Pd^{II}/Pd^{0} oxidative transformations.[2] This high-valent mechanistic manifold has enabled attractive complexity-building transformations, such as C–H oxidations[2c,e] and alkene difunctionalizations.[3–5] Unfortunately, stoichiometric amounts of wasteful high-energy oxidants, such as $PhI(OAc)_2$, are typically required to access high-valent palladium centers. Despite the apparent advantages of replacing these stoichiometric oxidants with abundant and environmentally benign O_2, the use of O_2 to access high-valent palladium intermediates remains a tremendous challenge owing to the high kinetic barriers of the aerobic oxidation of organopalladium(II) intermediates.[3c,6] Thus, there is a pressing need to develop strategies to facilitate reductive elimination using oxygen as the terminal oxidant.

In contrast to the oxidation of Pd^{II} to Pd^{IV}, strategies to oxidize Pd^{0} to Pd^{II} using molecular oxygen as the terminal oxidant are well established. Pd^{II}/Pd^{0} transformations were rendered aerobic over half a century ago by employing copper salts as electron transfer mediators (ETMs) to circumvent the kinetic barriers that limited direct aerobic oxidation of palladium catalysts.[7,8] This development precipitated the widespread industrial adoption of the Wacker process for the bulk preparation of acetaldehyde from ethylene using O_2 as the terminal oxidant.[9] If a suitably oxidizing and kinetically reactive ETM could be identified, this strategy would enable the use of molecular oxygen as a terminal oxidant in high-valent palladium catalysis. Recently, NO_x species have been shown to be capable of mediating the aerobic oxidation of stable alkyl–Pd^{II} palladacycles to their high-valent congeners.[10–12] However, many Pd^{IV}/Pd^{II} processes require rapid oxidation of a kinetically unstable organopalladium species to circumvent intramolecular decomposition pathways.[13] For example, palladium-catalyzed alkene difunctionalization reactions rely upon immediate oxidation of alkyl–Pd^{II} intermediates to avoid the facile β-hydride elimination that produces Wacker-type side products (Scheme 1). An ETM strategy capable of providing aerobic access to these products would not only be a valuable alternative to conventional synthetic methods but would also demonstrate the potential of an ETM strategy to enable facile reductive elimination in a kinetically challenging context.



Scheme 1. Mechanistic manifolds for alkene oxidation proceeding through nucleopalladation and β-hydride elimination (top) or reductive elimination (bottom).

We have recently developed an unusual nitrite-modified Wacker-type oxidation system. Nitrogen dioxide was suspected to be formed as a reactive intermediate.[14,15] Under acidic conditions, molecular oxygen possesses an oxidation potential comparable to that of $PhI(OAc)_2$.[16] Thus, acidification of our catalytic system could enable catalytic amounts of NO_x to oxidize an alkyl–Pd^{II} intermediate and facilitate C–O bond-forming reductive elimination to provide difunctionalized products. The efficient aerobic oxidation of NO makes these species ideal electron transfer mediators.[15a,17] As a preliminary arena in which to evaluate this strategy, we investigated the dioxygenation of alkenes. An aerobic palladium-catalyzed dioxygenation would provide an attractive

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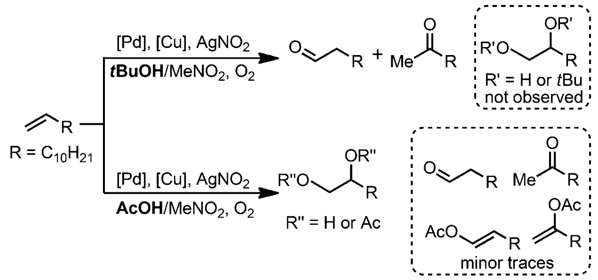


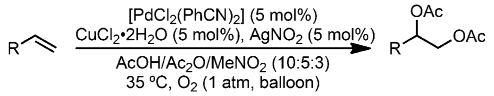
Scheme 2. Divergent reactivity as a function of solvent. [Pd] = [PdCl$_2$(PhCN)$_2$] and [Cu] = CuCl$_2$·2 H$_2$O.

alternative to toxic OsO$_4$, which is classically employed in alkene dihydroxylation.[18]

Replacement of the alcohol solvent in our previously reported nitrite-modified Wacker oxidation conditions with acetic acid suppressed Wacker-type oxidation (characteristic of Pd^{II}) and promoted alkene difunctionalization (characteristic of Pd^{IV} or Pd^{III}; Scheme 2). Initial optimization revealed that increasing the amount of the nitromethane co-solvent and raising the temperature slightly to 35 °C improved the kinetics and reproducibility of the reaction.[19]

Intriguingly, each catalytic component of the original nitrite-modified Wacker oxidation system was necessary to facilitate mild alkene difunctionalization (Table 1, entries 2–4). No oxidation products were observed in the absence of either palladium (entry 2)[20] or nitrite (entry 3). Omission of the copper salt resulted in poor selectivity for the dioxygenated reductive-elimination products relative to the β-hydride-elimination products. Furthermore, copper was found to be necessary to achieve efficient catalytic turnover (entry 4). However, although copper is commonly employed as an oxidant for Pd^0, another classical oxidant to mediate Pd^{II}/Pd^0 catalytic cycles, benzoquinone, proved to be an unsuitable substitute providing poor yield and selectivity (entry 5). Unfortunately, beyond these empirical observations, the role of the copper salt remains unclear.[21] Replacement of AgNO$_2$ with NaNO$_2$ resulted in the dioxygenated products in low yield, demonstrating that nitrite alone is sufficient to facilitate the key product-forming reductive elimination, and that the Ag^I counterion is critical for efficient oxidation (entry 6).[22] Silver nitrate similarly catalyzed product formation, albeit with reduced yield (entry 7). In the presence of nitrite and nitrate salts, no significant Wacker-type side products were observed by ^{1}H NMR spectroscopy. Despite the significant excess of acetic acid, palladium and copper acetate salts were not competent catalysts under these conditions (entry 8).

Table 1: Effect of divergence from the optimized conditions.

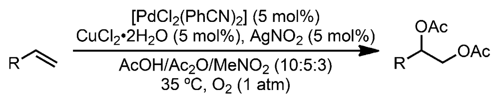


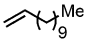
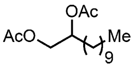
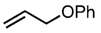
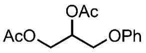
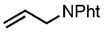
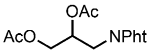
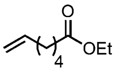
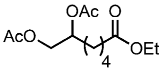
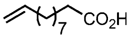
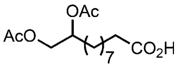
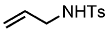
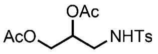
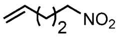
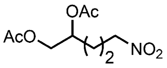
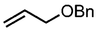
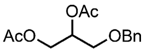
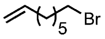
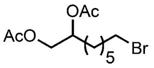
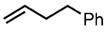
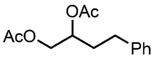
Entry	Variation	Yield [%][a]	Selectivity[b]
1	–	≥ 95	≥ 20:1
2	no [PdCl$_2$(PhCN)$_2$]	0	–
3	no AgNO$_2$	0	–
4	no CuCl$_2$·2 H$_2$O	6	3:2
5	BQ replaces CuCl$_2$·2 H$_2$O	8	1:1.3
6	NaNO$_2$ replaces AgNO$_2$	7	≥ 20:1
7	AgNO$_3$ replaces AgNO$_2$	44	≥ 20:1
8	no Ac$_2$O	≥ 95[c]	≥ 20:1
9	Pd(OAc)$_2$ and Cu(OAc)$_2$	0	–

[a] Determined by ^{1}H NMR analysis of the unpurified reaction mixture. [b] The ratio of dioxygenated products to Wacker-type ketone and vinyl acetate products was determined by ^{1}H NMR analysis of the unpurified reaction mixture. [c] Observed as a 1:1.5 mixture of monoacetates (see the Supporting Information for details). BQ = benzoquinone.

Given the potential synthetic utility of this aerobic palladium-catalyzed dioxygenation reaction, the functional-group tolerance of the transformation was next examined by subjecting alkenes bearing a variety of functional groups to the reaction conditions (Table 2). Primary alkyl bromides, esters, alkyl and aryl ethers, phthalimides, sulfonamides, carboxylic acids, and nitro groups were all well tolerated under the reaction conditions. This broad functional-group compatibility bodes well not only for the adoption of this aerobic dioxygenation reaction in synthesis but also for the potential application of a nitrite-based ETM strategy for other aerobic palladium-catalyzed alkene difunctionalization reactions, such as aminooxygenation and diamination.

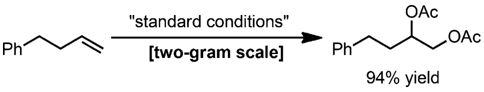
Table 2: Evaluation of the functional-group tolerance.[a]



Entry	Starting material	Product	Yield [%][b]
1			83
2			81
3			73
4			91
5[c]			74
6			53
7			83
8[d]			63
9			84
10			90

[a] Alkene (0.5 mmol) treated with [PdCl$_2$(MeCN)$_2$] (5 mol %), CuCl$_2$·2 H$_2$O (5 mol %), and AgNO$_2$ (5 mol %) in AcOH/Ac$_2$O/MeNO$_2$ (10:5:3, 8 mL) under an O$_2$ atmosphere (1 atm) at 35 °C. Each reaction was shielded from light with aluminum foil. [b] Yield of isolated product. [c] Yield determined by ^{1}H NMR analysis of the unpurified reaction mixture. [d] The crude reaction mixture was treated with 4-dimethylaminopyridine and Ac$_2$O to complete the conversion from the monoacetate into the diacetate prior to isolation. Bn = benzyl, Pht = phthalimido, Ts = *para*-toluenesulfonyl.

To fully realize the environmental and economic benefits offered by employing molecular oxygen as the stoichiometric oxidant, the process must be scalable. To evaluate the reaction efficacy on preparative scale, a two-gram scale reaction was performed [Eq. (1)]. The high efficiency that was observed on the small scale was mirrored upon scale-up.



(1)

Having demonstrated the synthetic utility of the process, we sought to elucidate the role of the key nitrite co-catalyst in the reaction. We suspected that the $AgNO_2$ salt produces an NO_x species, such as nitrogen dioxide, in situ, which would be sufficiently oxidizing and kinetically reactive to oxidize unstable palladium(II)–alkyl intermediates to Pd^{III} or Pd^{IV} analogues in a process that is faster than β-hydride elimination. To probe this hypothesis, reaction profiles of the stoichiometric oxidation of 1-dodecene employing nitrite and nitrogen dioxide were compared (Figure 1). Both nitrite and nitrogen dioxide mediated the conversion of the alkene into the diacetate product, conclusively demonstrating that nitrogen dioxide is a kinetically competent reactive intermediate.[23] Importantly, if neither oxidant was added, stoichiometric amounts of palladium and copper were insufficient to provide the dioxygenated products, illustrating that the NO_x catalyst is necessary to reach the product-forming step of the transformation. These experiments are consistent with a mechanistic picture in which the NO_x species mediates the C–O bond-forming reductive-elimination step. Given the high oxidation potential of NO_x species such as NO_2, an NO_x species derived from nitrite may oxidize the Pd^{II}–alkyl species to a high-valent palladium–alkyl intermediate to circumvent β-hydride elimination and accelerate reductive elimination. However, the intriguing possibility of a rapid ligand-mediated C–O bond-forming reductive elimination from Pd^{II} cannot be ruled out.

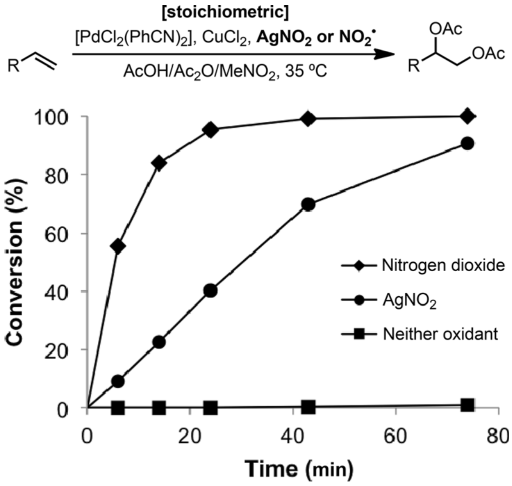
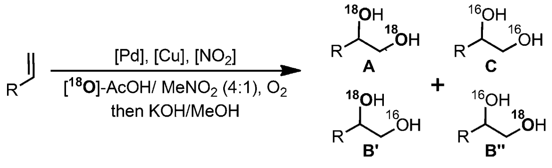
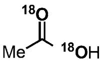
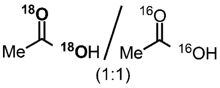


Figure 1. Stoichiometric reaction profiles to explore the role of the nitrite additive.

To gain further insight into the C–O bond-forming reductive-elimination event, the source of the oxygen atoms in the dioxygenated product was elucidated. The oxygen atoms could conceivably be derived from molecular oxygen, nitrite, acetic acid, or adventitious water. To discriminate between these possibilities, the reaction was conducted with ^{18}O-labeled AcOH (Table 3). Upon ester hydrolysis, this experiment provided conclusive evidence that both oxygen atoms in the difunctionalized product were derived from the solvent, AcOH.[24] To determine whether the two oxygen atoms were derived from a single molecule of acetic acid, we devised a modified ^{18}O-labeling experiment in which the reaction was conducted in a 1:1 mixture of $[^{18}O]$-AcOH and $[^{16}O]$-AcOH. Only $^{18}O/^{18}O$- and $^{16}O/^{16}O$-diol products (**A** and **C**, respectively) were observed, illustrating that both oxygen atoms are derived from a single molecule of acetic acid.

Table 3: ^{18}O-labeling experiments.

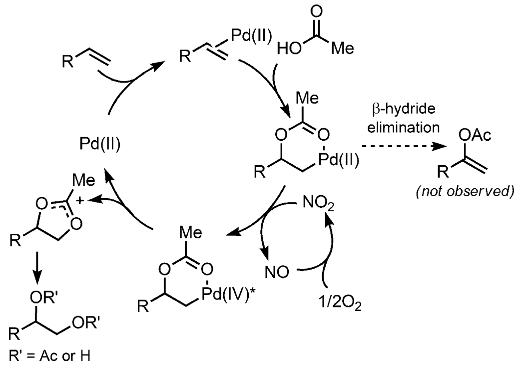


Acetic acid source	$^{18}O/^{18}O$ (**A**)	$^{18}O/^{16}O$ (**B′+B″**)	$^{16}O/^{16}O$ (**C**)
	**91%**	≤5%	≤5%
 (1:1)	**51%**	≤5%	**48%**

[a] 4-Phenylbutene (0.1 mmol) treated with $[PdCl_2(PhCN)_2]$ (10 mol%), $CuCl_2\cdot 2H_2O$ (10 mol%), and $AgNO_2$ (10 mol%) in AcOH/$MeNO_2$ (4:1, 0.5 mL) under an O_2 atmosphere (1 atm) at 35 °C. See the Supporting Information for details.

Taken together, these experiments suggest a reaction manifold in which initial alkene nucleopalladation with acetic acid is followed by oxidation to a high-valent palladium intermediate (Pd^{IV} or Pd^{III}) by an NO_x species (potentially NO_2; Scheme 3). This high-valent palladium intermediate next undergoes intramolecular reductive elimination to liberate an acetoxonium ion, which is subsequently hydrolyzed. This mechanism is analogous to the mechanism suggested by Dong and co-workers for the $PhI(OAc)_2$ mediated dioxygenation of alkenes.[26]

In summary, we have demonstrated that challenging C–O bond-forming reductive eliminations from unstable palladium–alkyl species that are capable of β-hydride elimination can be affected by the addition of a nitrite co-catalyst and molecular oxygen. This ETM strategy was demonstrated in the efficient dioxygenation of alkenes, providing a non-toxic and environmentally benign alternative to traditional alkene dioxygenation conditions. Aside from the synthetic value of this transformation, important mechanistic evidence regarding the role of the nitrite co-catalyst and the reductive-elimination step was provided. We anticipate that this work



Scheme 3. Preliminary mechanistic proposal. Pd$^{\mathrm{IV}}$* indicates a high-valent palladium species (monomeric Pd$^{\mathrm{IV}}$ and Pd$^{\mathrm{III}}$[25] as well as dimeric Pd$^{\mathrm{III}}$ are equally consistent with the current mechanistic evidence).

will stimulate the further exploration of strategies to replace high-energy stoichiometric oxidants with molecular oxygen.

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Keywords: alkenes · high-valent palladium · nitrite · oxidation · oxygen

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[21] It is possible that a heterobimetallic complex is formed with bridging chloride ligands. Alternatively, copper could be necessary to oxidize the Pd^0 species even though benzoquinone is not a competent replacement.

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