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Nitrate as a Redox Co-Catalyst for the Aerobic Pd-Catalyzed Oxidation of Unactivated sp³-C–H Bonds

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Abstract

This paper describes a new method for the catalytic aerobic oxygenation of unactivated sp^3-C–H bonds. This transformation utilizes Pd(OAc)$_2$ as a catalyst in conjunction with NaNO$_3$ as a redox co-catalyst. Both oxime ether and pyridine derivatives are effective directing groups for these reactions. The oxygen incorporated into the product derives from the solvent (acetic acid). Preliminary results show that the addition of simple NaCl to the reaction mixture results in aerobic chlorination under analogous conditions.

Introduction

The development of metal-catalyzed methods for converting sp^3-C–H bonds into C–O bonds using dioxygen as a terminal oxidant remains a grand challenge in organometallic chemistry.[1,2] Methods for the selective aerobic oxygenation of unactivated 1° C–H bonds in the presence of weaker benzylic, allylic, 2°, or 3° C–H bonds remain particularly elusive.[1,2] Over the past decade Pd-catalyzed ligand-directed C–H oxidation has emerged as a powerful approach to achieve sp^3-C–H acetoxylation, alkoxylation, and hydroxylation.[3] However, the oxidants used in these transformations are most typically reagents such as PhI(OAc)$_2$, IOAc, or K$_2$S$_2$O$_8$, which have the significant disadvantages of high cost, poor atom economy, the formation of stoichiometric byproducts, and/or moderate functional group tolerance.

Mechanistic studies suggest that these reactions proceed via three key steps: (a) ligand-directed C–H activation to form cyclometalated Pd^{II} complexes of general structure **I**, (b) 2e^- oxidation of **I** to form high valent Pd complex **II**, and (c) C–O bond-forming reductive elimination from **II** to release the oxygenated product (Figure 1).[4] Importantly, at pH = 1, O$_2$ has a comparable oxidation potential to PhI(OAc)$_2$,[5,6] suggesting that it should be thermodynamically capable of effecting the 2e^- oxidation of palladacycle **I** to high valent Pd intermediate **II**. However, efforts to utilize dioxygen as a terminal oxidant in these transformations have generally been hampered by the slow kinetics of the aerobic oxidation of palladacycles.[7,8] Recent elegant studies by Vedernikov[2a,b] and by Yu[2c] have shown that it is possible to address this challenge through careful selection of the supporting ligand and/or the substrate. However, these successful examples of aerobic Pd-catalyzed ligand-directed C–H oxygenation are far from a general solution, because they exhibit a narrow substrate scope. Most notably, neither is effective for promoting the C–H oxygenation of

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unactivated sp^3-C–H bonds, which are arguably the most challenging substrates for these transformations.[3]

We reasoned that more general aerobic C–H oxidation reactions might be possible by using a redox co-catalyst[9] that has high kinetic reactivity towards both O_2 and palladacycles like **I** (Figure 2). This concept is inspired by the $Pd^{II/0}$-catalyzed Wacker oxidation, in which Cu(II)[10] or polyoxometalates (POM's)[11] are utilized as co-catalysts in conjunction with O_2 as the terminal oxidant. A similar strategy has also been employed in some Pd-catalyzed benzene and methane oxidation reactions, most typically using POM or POM/NO_2 as redox co-catalysts.[12] The current manuscript uses this approach to achieve the Pd-catalyzed aerobic oxidation of unactivated sp^3-C–H bonds in pyridine and oxime ether substrates using nitrate salts as redox co-catalysts. Both the scope and mechanism of these reactions are described, and their implications for expanding this method to diverse sp^3-C–H functionalization reactions are discussed.

Results and Discussion

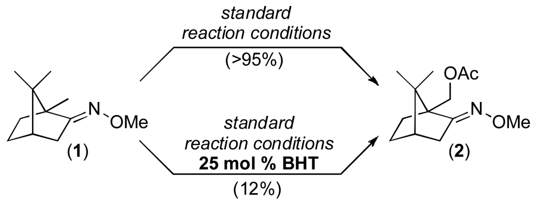
The $Pd(OAc)_2$-catalyzed C–H acetoxylation of substrate **1** was selected as a test reaction, since it has been reported to proceed efficiently with oxidants like $PhI(OAc)_2$ and $K_2S_2O_8$.[13] With air as the oxidant, this transformation provided only traces of product **2** (1% yield, Table 1, entry 1). Redox co-catalysts that are commonly used in $Pd^{II/0}$ catalysis (*e.g.,* $H_5PMo_{10}V_2O_{40}$ (POM-V_2) and $Cu(OAc)_2$) proved ineffective (entries 2 and 3). Thus, we next explored nitrate and nitrite salts as precursors to more kinetically reactive NO_2.[14] Importantly, Campora has shown that NO_2 can oxidize Pd^{II} to Pd^{IV} under mild conditions.[15] Additionally, NO_2 has been used as a redox co-catalyst in a wide variety of different transformations.[9,10b,16] Gratifyingly, the use of $NaNO_2$ or $NaNO_3$ as the co-catalyst resulted in moderate yield (48 and 53%, respectively) of **2** (entries 4 and 5). Interestingly, while these reagents have previously been used for the Pd-catalyzed nitration of aromatics,[17] the corresponding nitrated products were not observed in the current transformations.[18,19] Under an N_2 atmosphere, the $NaNO_3$-mediated reaction proceeded in significantly lower yield (14%), corresponding to approximately 1 turnover of the redox co-catalyst (entry 6).

Further optimization showed that moving from 1 atm of air to 1 atm of O_2 in the $Pd(OAc)_2$/$NaNO_3$-catalyzed reaction resulted in a significant boost in yield to 70% of **2** (entry 7). Increasing the loading of $NaNO_3$ to 25 mol % and the temperature to 110 °C led to further increases in yield. Under the final conditions (5 mol % of $Pd(OAc)_2$, 25 mol % of $NaNO_3$, and 1 atm O_2 in AcOH/Ac_2O at 110 °C for 18 h), **2** was formed in quantitative yield (entry 9).

We next evaluated the substrate scope of this transformation. As shown in Table 2, a variety of substrates containing both oxime ether and pyridine directing groups underwent aerobic $Pd(OAc)_2$/$NaNO_3$-catalyzed sp^3-C–H acetoxylation.[20] Substrates containing 1° sp^3-C–H sites β to the directing group generally underwent smooth and high yielding C–H oxygenation. In contrast, the functionalization of a 2° C–H bond to form **6** proceeded in only modest 41% isolated yield, even with 1 equiv of $NaNO_3$.[21] In substrates containing *tert*-butyl substituents proximal to the directing group, triacetoxylated products predominated (for example, entries 2 and 6-9). Importantly, ligand-directed aerobic oxidation at unactivated 1° sp^3-C–H sites β to the directing group proceeded selectively, even in the presence of much weaker (but not proximal) benzylic C–H bonds (entry 9). In some instances, increased loading of $NaNO_3$ (up to 1 equiv per C–H bond being functionalized) was necessary to achieve high yields (*e.g.,* entries 5 and 10); however, the low cost of this oxidant relative to something like $PhI(OAc)_2$ still makes this a synthetically useful procedure.[22]

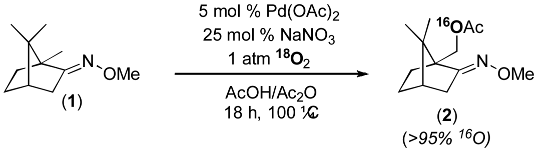
We hypothesize that these transformations proceed via the series of catalytic cycles shown in Figure 3. Step *i* involves the decomposition of nitrate to NO_2. This process is well-precedented,[14] and has been exploited to access NO_X redox co-catalysts in a number of other aerobic oxidation reactions.[16] Next the NO_2 and 2 equiv of AcOH react with cyclopalladated intermediate **I** to generate high oxidation state Pd compound **II** along with NO and H_2O (step *ii*).[15] Carbon-oxygen bond-forming reductive elimination (step *iii*) then releases the C–H oxidation product, while the NO is oxidized by O_2 to regenerate NO_2 (step *iv*).[16]

To directly probe for the intermediacy of NO, we conducted the catalytic reactions in the presence of 2,6-di-*tert*-butyl-4-methylphenol (BHT). NO is known to react rapidly with BHT to afford 2,6-di-*tert*-butyl-4-methyl-4-nitrosocyclohexa-2,5-dienone (TBMND),[23] and the consumption of NO in this manner would be expected to have a detrimental effect on the C–H acetoxylation reaction. As anticipated, the addition of 25 mol % of BHT to the catalytic oxidation of **1** resulted in a significant reduction in the yield of **2**, from >95% to 12% under otherwise analogous conditions (eq. 1).[24] When the $NaNO_3/O_2$ oxidation reaction of **1** was assayed after 30 min, ^1H NMR spectroscopic analysis showed resonances consistent with the formation of TBMND (in 26% yield based on BHT).[25] Together, these two experiments provide preliminary support for the generation of NO as a key intermediate in this transformation.



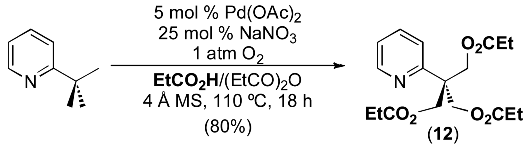
(1)

Another important feature of the mechanism proposed in Figure 3 is that the oxygen atom in the product derives from acetic acid and *not* from O_2. To test this, we performed the reaction of substrate **1** in the presence of 1 atm of $^{18}O_2$. Consistent with the proposed mechanism, HRMS analysis of the isolated product showed that <5% of the ^{18}O label was incorporated into **2** under these conditions (eq. 2).[26]



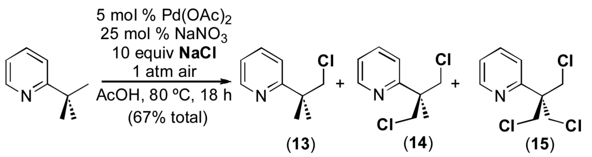
(2)

This observation suggests that the use of different nucleophilic solvents and/or additives should enable the incorporation of other functional groups under aerobic oxidation conditions. To test this possibility, we examined the $Pd(OAc)_2/NaNO_3$-catalyzed aerobic oxidation of 2-*tert*-butylpyridine in propionic acid. Gratifyingly, this transformation provided 80% yield of the corresponding oxygenated product **12** (eq. 3).



(3)

A second preliminary experiment showed that the addition of 10 equiv of NaCl to the $Pd(OAc)_2/NaNO_3$-catalyzed aerobic oxidation of 2-*tert*-butylpyridine produces a mixture of chlorinated products **13**, **14**, and **15** (eq. 4). While the latter reaction has thus far proven challenging to optimize further, this result provides extremely promising precedent that redox cocatalysis can be utilized to achieve diverse aerobic C–H functionalization reactions.



(4)

Conclusions

In summary, this paper demonstrates the use of a combination of $Pd(OAc)_2$ and $NaNO_3$ or $NaNO_2$ to catalyze the aerobic C–H oxygenation of unactivated sp^3-C–H bonds. Preliminary mechanistic and synthetic studies suggest that this approach could enable more general C–H functionalization reactions with dioxygen as the terminal oxidant. Investigations aimed at understanding the mechanism, decreasing catalyst loadings, and further increasing the scope of these reactions are currently underway in our laboratory. More generally, since commercial $Pd(OAc)_2$ is frequently contaminated with nitrite salts,[19] we suggest that redox co-catalysis by NO_x may play a previously unappreciated role in a variety of other '$Pd(OAc)_2$'-catalyzed aerobic oxidation reactions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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18. Nitrated compounds were not observed based on ^1H NMR spectroscopic analysis of the crude reaction mixtures.
19. This lack of nitrated products may be due to a preference for the O-versus N-linkage isomer of Pd-bound NO_X under the reaction conditions. For a recent discussion of cyclometalated $Pd(NO_2)$ complexes, see: Bajwa SE, Storr TE, Hatcher LE, Williams TJ, Baumann CG, Whitwood AC, Allan DR, Teat SJ, Raithby PR, Fairlamb IJS. Chem. Sci. 2012; 3:1656.
20. Several other sp^3-C–H substrates were examined (*e.g.* butan-2-one-O-methyl oxime, butan-2-one-O-acetyl oxime, and 2-*t*-butyl-4,4-dimethyl-4,5-dihydrooxazole) that did not undergo high yielding C–H acetoxylation under the current optimal conditions.
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22. A limitation of these reaction conditions is that they are poorly effective for functionalization of sp^2-C–H substrates (which have previously been viewed as less 'challenging' substrates for Pd C–H oxidation reactions).[21] For example, subjecting 2-phenylpyridine to the reaction conditions resulted in no reaction (>95% recovered starting material). Likewise, acetophenone *O*-methyl oxime showed limited reactivity under the optimized reaction conditions, providing 29% of the monoacetoxylated product (with 58% recovered starting material).

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24. The addition of BHT had a much smaller effect on the C–H acetoxylation of 1 with $PhI(OAc)_2$ (87% yield without BHT and 58% yield with 25 mol % of BHT). This suggests that the results in eq 1 are not solely due to detrimental interactions between BHT and Pd intermediates during catalysis.

25. TBMND is unstable under the reaction conditions, which likely accounts for the less-than-quantitative yield.

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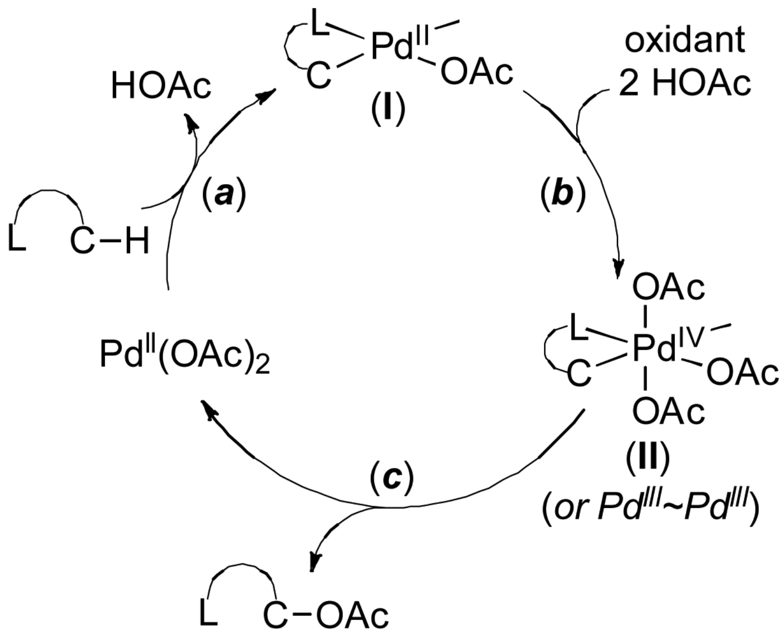


Figure 1.

Proposed mechanism for Pd-catalyzed ligand-directed C–H oxidation.

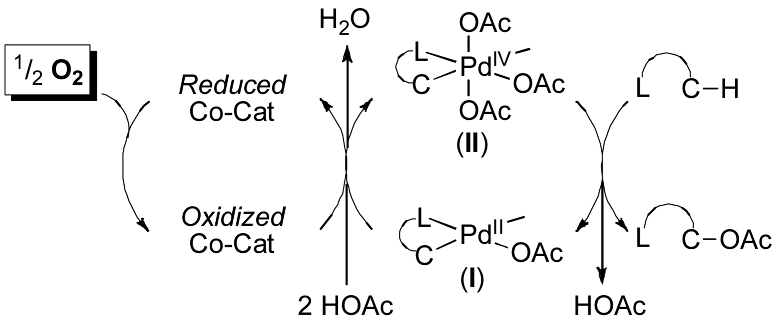


Figure 2.

Concept of redox co-catalysis for aerobic C–H oxidation

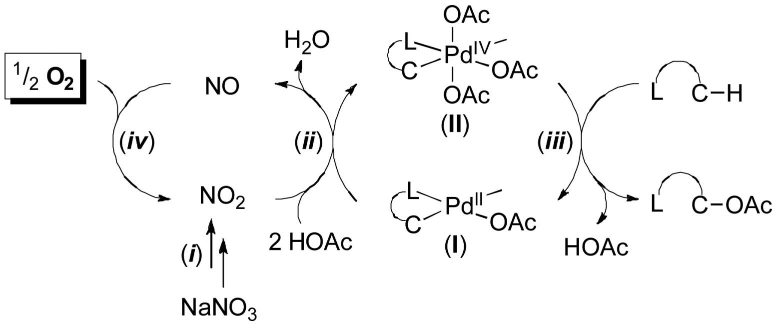
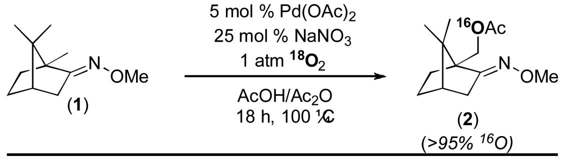


Figure 3.

Proposed catalytic cycle. The complete supporting ligand set on Pd is unclear at this time, and nitrate and/or nitrite may serve as ligands during catalysis.

Table 1

Optimization of redox co-catalyst



entry	co-cat	mol % co-cat	oxidant	yield[a]
1	none	0	Air	1%
2	POM-V_2[b]	10	Air	0%
3	$Cu(OAc)_2$	10	air	1%
4	$NaNO_2$	10	air	48%
5	$NaNO_3$	10	air	53%
6	$NaNO_3$	10	none[c]	14%
7	$NaNO_3$	10	O_2	70%
8	$NaNO_3$	25	O_2	91%
9[d]	$NaNO_3$	25	O_2	>95%

[a] Yields determined by ^1H NMR spectroscopic analysis and represent an average of 2 runs.

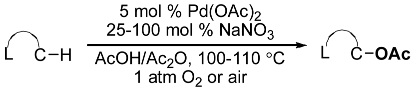
[b] POM-V_2 = $H_5PMo_{10}V_2O_{40}$.

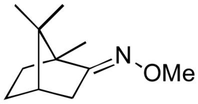
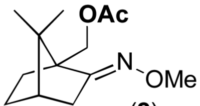
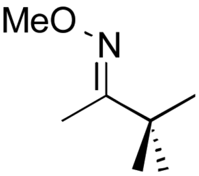
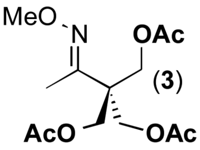
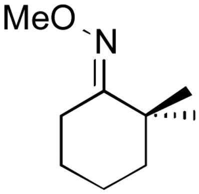
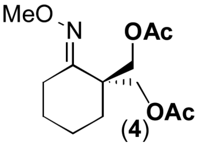
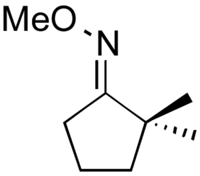
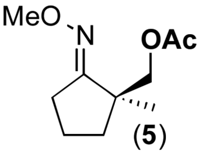
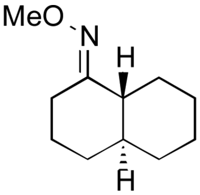
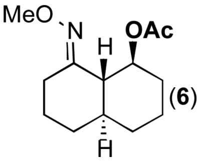
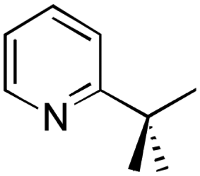
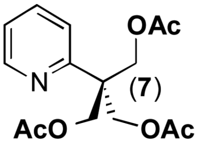
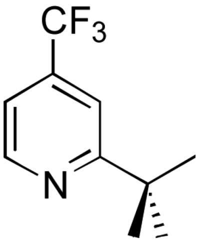
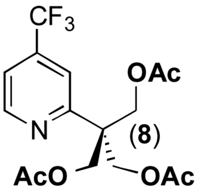
[c] N_2 atmosphere.

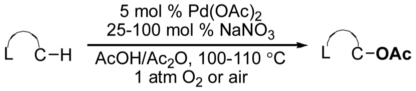
[d] 110 °C.

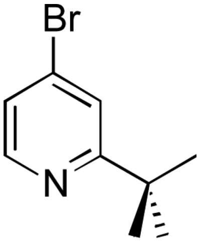
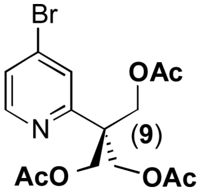
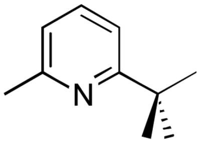
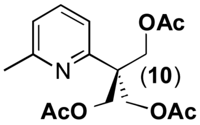
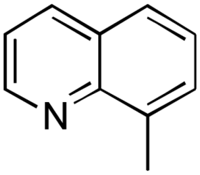
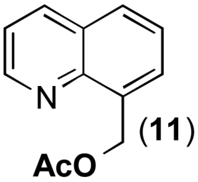
Table 2

Substrate scope for C–H oxygenation



entry	substrate	product	isolated yield
1		 (**2**)	80%
2		 (**3**)	83%
3		 (**4**)	60%
4		 (**5**)	51%
5		 (**6**)	41%
6[a]		 (**7**)	79%
7[a]		 (**8**)	78%



entry	substrate	product	isolated yield
8[a]		 (**9**)	77%
9		 (**10**)	68%
10		 (**11**)	80%

[a] 4 Å molecular sieves added.