

Palladium Catalysts Containing Pyridinium-Substituted Pyridine Ligands for the C–H Oxygenation of Benzene with $K_2S_2O_8$

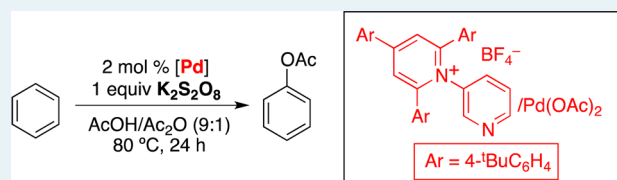
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Supporting Information

ABSTRACT: This manuscript describes the development of Pd catalysts with pyridinium-substituted pyridine ligands for the C–H oxygenation of benzene with potassium persulfate. These new catalysts provide dramatically improved activity compared to simple $Pd(OAc)_2$ in this transformation. Furthermore, the reaction proceeds with high selectivity for phenyl acetate over biphenyl. Preliminary investigations suggest that a key role for the cationic pyridinium ligand is to serve as a phase transfer catalyst for the $K_2S_2O_8$ oxidant.

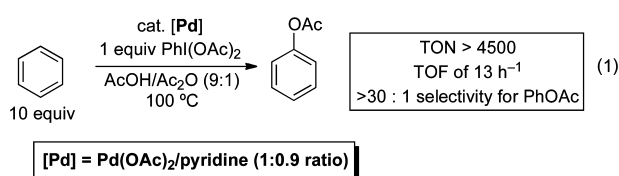
KEYWORDS: oxidation, palladium, catalysis, benzene, ligand, cationic, phase-transfer



INTRODUCTION

The development of catalysts for the efficient and selective C–H oxygenation of benzene and other arenes remains an important challenge in catalysis.^{1–5} Such transformations provide a potentially attractive direct route from simple arene derivatives to phenols.³ In addition, these methods could also find application in the direct C–H functionalization of more complex aromatic substrates including pharmaceuticals, agrochemicals, and natural products.^{4,6,7}

A number of reports have shown that $Pd(OAc)_2$ catalyzes the C–H oxygenation of benzene.^{1,2,8–14} However, with this catalyst, the reaction suffers from (i) slow rates (generally <2 turnovers h^{-1}), (ii) low turnover numbers (often <10), and (iii) modest selectivity for PhOAc, with competitive formation of biphenyl.^{9–15} Our group has sought to identify alternative Pd-based catalysts that address many of these limitations. Most recently, we showed that the use of pyridine as a supporting ligand for $Pd(OAc)_2$ results in dramatically improved catalyst performance in the Pd-catalyzed C–H acetoxylation of benzene with $PhI(OAc)_2$ (eq 1).^{16,17} The



pyridine-ligated Pd catalyst provides turnover numbers of >4500 and increases the reaction rate by more than an order of magnitude compared to $Pd(OAc)_2$ alone.¹⁶ Additionally, the Pd-pyridine catalyst affords high ($>30:1$) selectivity for PhOAc over biphenyl. Notably, this catalyst system is generated in situ, and optimal activity is observed using an approximately 1:1 molar ratio of pyridine: $Pd(OAc)_2$.

While this method represents a significant advance, the use of $PhI(OAc)_2$ as the terminal oxidant is a major limitation. This

reagent is expensive (approximately \$425/mol);¹⁸ furthermore, iodobenzene and AcOH are formed as stoichiometric by-products. In addition, $PhI(OAc)_2$ and PhI both contain aromatic C–H bonds that undergo competing C–H oxygenation under the reaction conditions. This side reaction significantly reduces the yield of phenyl acetate.¹⁶

Persulfate-based oxidants are potentially attractive alternatives for these transformations. $K_2S_2O_8$ is more than an order of magnitude less expensive than $PhI(OAc)_2$,¹⁸ and the byproducts of this oxidant are easily separable, water-soluble salts. Our group has previously shown that $K_2S_2O_8$ serves as an effective oxidant for $Pd(OAc)_2$ -catalyzed ligand-directed C–H oxidation reactions of pyridine and oxime ether derivatives.¹⁹ This confirms that $K_2S_2O_8$ is sufficiently reactive to promote C–O bond formation at Pd. However, despite this promising precedent, the use of $K_2S_2O_8$ in nondirected Pd-catalyzed arene oxidations has historically proven challenging. The most successful example was reported more than 30 years ago, and involved the $Pd(OAc)_2$ -catalyzed conversion of benzene to phenyl acetate with $K_2S_2O_8$ with extremely low turnover numbers (<10) and reaction yields ($<30\%$).¹³

The current manuscript describes our development of Pd-pyridine catalysts for the oxidation of benzene with $K_2S_2O_8$. We demonstrate that the combination of $Pd(OAc)_2$ and a monodentate pyridinium-substituted pyridine ligand provides a particularly active catalyst for this transformation. The mechanistic origins of this high activity are discussed.

RESULTS AND DISCUSSION

The C–H oxygenation of benzene (10 equiv) with $K_2S_2O_8$ (1 equiv) as the terminal oxidant and limiting reagent was evaluated at 80 °C in AcOH/Ac₂O (9:1). As shown in Table 1, entry 1, $Pd(OAc)_2$ is a poor catalyst for this reaction under these

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conditions. The use of 2 mol % of Pd(OAc)₂ resulted in only 0.8% yield of phenyl acetate (approximately 0.5 turnovers) after 24 h.

Pyridine-ligated catalysts were next examined for this transformation. As discussed above, we have previously

Table 1. Initial Evaluation of Pd Catalyst Activity for Benzene C–H Acetoxylation as a Function of Pyridine Ligand

entry	ligand	yield PhOAc (%) ^a	yield PhPh (%) ^a
1	none	0.8	0.6
2	pyridine	37	2.0
3	L2	71	1.9
4	L3	65	1.1

^aReaction conditions: benzene (1.00 mL, 874 mg, 11.2 mmol, 10.0 equiv), K₂S₂O₈ (303 mg, 1.12 mmol, 1.00 equiv), AcOH (0.90 mL), Ac₂O (0.10 mL), Pd(OAc)₂ (5.0 mg, 22.4 μmol, 0.020 equiv), and pyridine (1.81 μL, 1.77 mg, 22.4 μmol, 0.020 equiv), **L2** (14.3 mg, 22.4 μmol, 0.020 equiv) or **L3** (14.3 mg, 22.4 μmol, 0.020 equiv) were combined and sealed in a 1-dram vial and reacted at 80 °C for 24 h. Yields determined by GC.

shown that the combination of Pd(OAc)₂ and pyridine (in an approximately 1:1 ratio) generates a highly active catalyst for benzene C–H acetoxylation with PhI(OAc)₂ as the oxidant.¹⁶ Similarly, the addition of 2 mol % of pyridine to the K₂S₂O₈ reaction under otherwise identical conditions led to an enhancement in both yield and catalyst turnovers (Table 1, entry 2). However, the rate of this reaction remained slow, and only 37% yield of phenyl acetate was obtained after 24 h. Furthermore, a significant quantity of biphenyl (2% yield, PhOAc:PhPh ratio = 14:1) was formed in this transformation.

In an effort to identify more reactive catalysts, we next examined cationic pyridinium-substituted pyridine ligands **L2** and **L3** (Figure 1). We hypothesized that these ligands might enhance

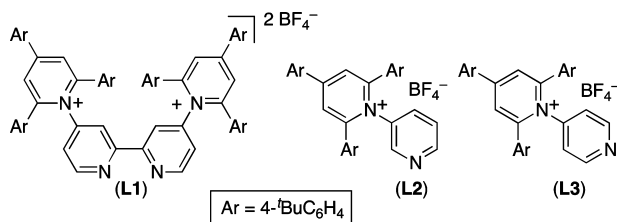


Figure 1. Cationic pyridine derivatives.

catalyst reactivity based on our prior studies of the bidentate analogue **L1**.²⁰ Our previous work showed that Pd and Pt complexes of **L1** catalyze benzene C–H activation (as measured by H/D exchange) with 10–100-fold faster rates than those containing neutral bipyridine derivatives.²⁰ By analogy, we anticipated that **L2** and **L3** might outperform pyridine as ligands in Pd-catalyzed benzene C–H activation/acetoxylation. Pyridines **L2** and **L3** were synthesized by condensation of 2,4,6-tris(4-(*t*-butyl)phenyl)pyrylium tetrafluoroborate with the corresponding aminopyridine (see Supporting Information for details).²¹ The

ligands were fully characterized by ¹H and ¹³C NMR spectroscopy as well as elemental analysis.

Ligands **L2** and **L3** provided significant improvements in the rate and chemoselectivity of Pd-catalyzed benzene acetoxylation with K₂S₂O₈. The use of **L2** or **L3** (2 mol %) in conjunction with Pd(OAc)₂ (2 mol %) afforded PhOAc in 71 and 65% yield, respectively, after 24 h (Table 1, entries 3 and 4). Additionally, the selectivity for PhOAc versus PhPh was high in both cases (approximately 36:1 for **L2** and 65:1 for **L3**).

A more detailed comparison of the reactivity of Pd(OAc)₂, Pd(OAc)₂/pyridine, and Pd(OAc)₂/**L2** is shown in Figure 2.

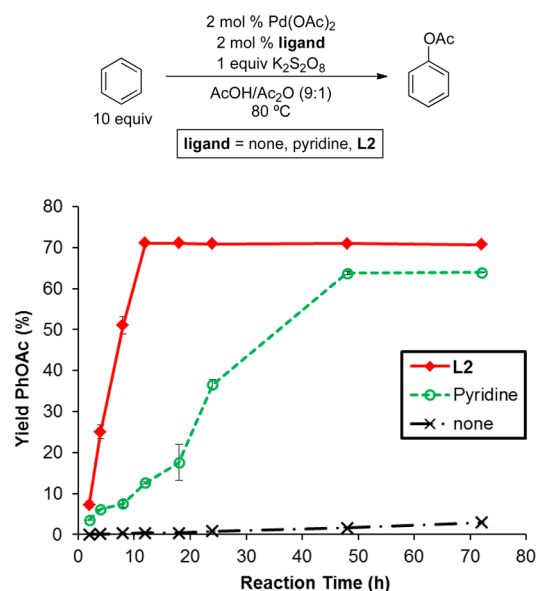


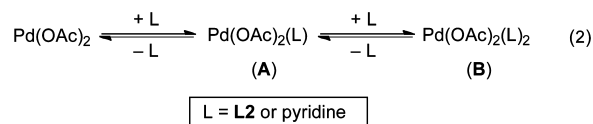
Figure 2. Time study of benzene C–H acetoxylation with K₂S₂O₈ catalyzed by Pd(OAc)₂, Pd(OAc)₂/pyridine, and Pd(OAc)₂/**L2**. Reaction conditions: benzene (1.00 mL, 874 mg, 11.2 mmol, 10.0 equiv), K₂S₂O₈ (303 mg, 1.12 mmol, 1.00 equiv), AcOH (0.90 mL), Ac₂O (0.10 mL), Pd(OAc)₂ (5.0 mg, 22.4 μmol, 0.020 equiv), and pyridine (1.81 μL, 1.77 mg, 22.4 μmol, 0.020 equiv), or **L2** (14.3 mg, 22.4 μmol, 0.020 equiv) were combined and sealed in a 1-dram vial and reacted at 80 °C. Yields determined by GC.

The initial rate with Pd(OAc)₂/**L2** is approximately 5 times faster than that with Pd(OAc)₂/pyridine and at least 2 orders of magnitude faster than that with Pd(OAc)₂ alone. Furthermore, the Pd(OAc)₂/**L2**-catalyzed reaction proceeds to higher overall yield at completion than the analogous Pd(OAc)₂/pyridine system (71% versus 64%, respectively).

As noted in Figure 2, this C–H acetoxylation reaction proceeded to less than 75% yield in all cases. (Note that the yields are based on K₂S₂O₈ as the limiting reagent.) This is not due to overoxidation of the benzene substrate. Under the standard conditions, <4% yield of diacetoxybenzene was observed. Instead, the observed yields are believed to be due to competing thermal decomposition of K₂S₂O₈ in acetic acid, a well precedented process.^{22–24} Increasing the reaction temperature to 120 °C appears to accelerate competing oxidant decomposition. While the initial rate of C–H acetoxylation was significantly faster at 120 °C than at 80 °C (yield after 2 h was 24% versus 7%), the reaction proceeded to a maximum of only 44% yield at 120 °C. We attribute this to increased background decomposition of K₂S₂O₈.

The combination of 1 equiv of pyridine or **L2** with 1 equiv of Pd(OAc)₂ is expected to generate a number of equilibrating species in solution, including monopyridine complex **A** and

bis-pyridine adduct **B** (eq 2). We have previously hypothesized that **A** (or a related acetate bridged dimer) is the most active catalyst generated under these conditions.^{16,25}



On the basis of this mechanistic framework, there are several possible factors that could contribute to the observed rate enhancement with cationic ligand **L2**. These include: (1) *electronic effects* (i.e., the electron withdrawing pyridinium substituent leads to a more electrophilic Pd catalyst (**A**) that is then more reactive toward benzene C–H activation); (2) *equilibrium effects* (i.e., the large size and cationic charge of ligand **L2** result in an increased equilibrium population of the most active monopyridine catalyst **A**); or (3) *phase transfer effects* (i.e., the cationic pyridine ligand serves as a phase transfer catalyst to bring poorly soluble $\text{S}_2\text{O}_8^{2-}$ into solution and into contact with the Pd catalyst). Experiments designed to preliminarily test each of these possibilities are described in detail below.

Electronic Effects. To test the role of electronic effects, we compared catalyst activity in the presence of **L2** to that with 3-fluoropyridine (3-F-pyr). The Hammett σ -value for a *meta*-fluoro group²⁶ is the same as that for a *meta*-pyridinium substituent²⁶ ($\sigma = 0.34$ in both cases), indicating that these ligands should have comparable electronic properties. As shown in Figure 3, the $\text{Pd}(\text{OAc})_2/3\text{-fluoropyridine}$ catalyst system showed essentially identical reactivity to $\text{Pd}(\text{OAc})_2/\text{pyridine}$. In addition, the chemoselectivity with pyr and 3-F-pyr were both lower than with **L2** (PhOAc:PhPh ratio = 14:1, 20:1, and 36:1 respectively). Collectively, this data suggests against a purely electronic effect.

Equilibrium Effects. If equilibrium effects were the main factor responsible for the enhanced reactivity of $\text{Pd}(\text{OAc})_2/\text{L2}$, this catalyst would be expected to outperform $\text{Pd}(\text{OAc})_2/\text{pyridine}$ in other C–H oxidation reactions as well. To test this possibility, we compared the two catalysts using $\text{PhI}(\text{OAc})_2$ as the oxidant under otherwise identical conditions. As shown in Figure 4, with $\text{PhI}(\text{OAc})_2$, the pyridine and pyridinium-derived catalysts afforded nearly identical reaction rates. This suggests that the favorable effect of ligand **L2** does not transfer to other C–H oxidation reactions.

Phase Transfer Effects. To test the effect of phase transfer catalysts on this system, we added 2 mol % of NEt_4BF_4 (a known phase transfer catalyst) to the $\text{Pd}(\text{OAc})_2/\text{pyridine}$ -catalyzed reaction. As shown in Figure 5, the NEt_4BF_4 led to a significant acceleration of the initial reaction rate, very similar to that observed with **L2**. However, the overall yield was lower with $\text{Pd}(\text{OAc})_2/\text{pyridine}/\text{NEt}_4\text{BF}_4$ versus $\text{Pd}(\text{OAc})_2/\text{L2}$ (52% versus 71%). A variety of other phase transfer catalysts had similar effects on the $\text{Pd}(\text{OAc})_2/\text{pyridine}$ -catalyzed reaction (see Supporting Information for full details).²⁷ The lower yields observed in the presence of tetraalkylammonium salts are likely due to their reported ability to catalyze the conversion of $\text{K}_2\text{S}_2\text{O}_8$ to peracetic acid in AcOH.²⁴ Importantly, peracetic acid is not a viable oxidant for this C–H acetoxylation reaction (see Supporting Information).

Overall, these results lead us to conclude that phase transfer catalysis is a key factor in the enhanced reaction rate with ligand **L2**. The differences in yield observed between **L2** and more

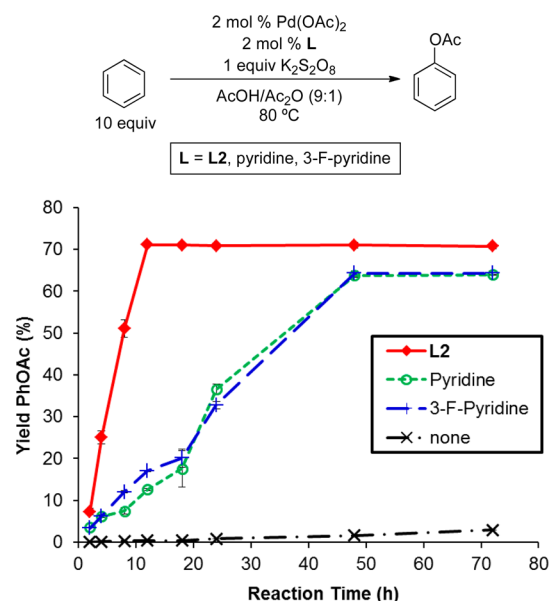


Figure 3. Time study of benzene C–H acetoxylation with $\text{K}_2\text{S}_2\text{O}_8$ catalyzed by $\text{Pd}(\text{OAc})_2/\text{pyridine}$, $\text{Pd}(\text{OAc})_2/3\text{-fluoropyridine}$, and $\text{Pd}(\text{OAc})_2/\text{L2}$. Reaction conditions: benzene (1.00 mL, 874 mg, 11.2 mmol, 10.0 equiv), $\text{K}_2\text{S}_2\text{O}_8$ (303 mg, 1.12 mmol, 1.00 equiv), AcOH (0.90 mL), Ac_2O (0.10 mL), $\text{Pd}(\text{OAc})_2$ (5.0 mg, 22.4 μmol , 0.020 equiv), and pyridine (1.81 μL , 1.77 mg, 22.4 μmol , 0.020 equiv), **L2** (14.3 mg, 22.4 μmol , 0.020 equiv), or 3-fluoropyridine (1.92 μL , 2.17 mg, 22.4 μmol , 0.020 equiv) were combined and sealed in a 1-dram vial and reacted at 80 °C. Yields determined by GC.

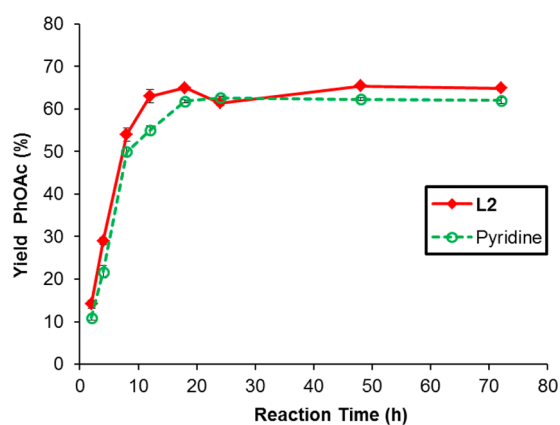


Figure 4. Time study of benzene C–H acetoxylation with $\text{PhI}(\text{OAc})_2$ catalyzed by $\text{Pd}(\text{OAc})_2/\text{pyridine}$ and $\text{Pd}(\text{OAc})_2/\text{L2}$. Yields determined by GC based on PhCl as a standard. Reaction conditions: benzene (1.00 mL, 874 mg, 11.2 mmol, 10.0 equiv), $\text{PhI}(\text{OAc})_2$ (361 mg, 1.12 mmol, 1.00 equiv), AcOH (0.90 mL), Ac_2O (0.10 mL), $\text{Pd}(\text{OAc})_2$ (5.0 mg, 22.4 μmol , 0.020 equiv), and pyridine (1.81 μL , 1.77 mg, 22.4 μmol , 0.020 equiv) or **L2** (14.3 mg, 22.4 μmol , 0.020 equiv) were combined and sealed in a 1-dram vial and reacted at 80 °C. Yields determined by GC.

conventional phase transfer catalysts like NEt_4BF_4 may be due to differences in the rate of undesired $\text{K}_2\text{S}_2\text{O}_8$ to AcOOH conversion between these systems and/or anion pairing between the persulfate anion and the cationic Pd-ligated complex. Notably, Neumann has proposed similar accelerative effects of interactions between cationic ligands and anionic oxidants in Pd/polyoxometallate-catalyzed Wacker oxidation reactions²⁸ and in Pt/polyoxometallate-catalyzed CH_4 oxidation.^{29,30}

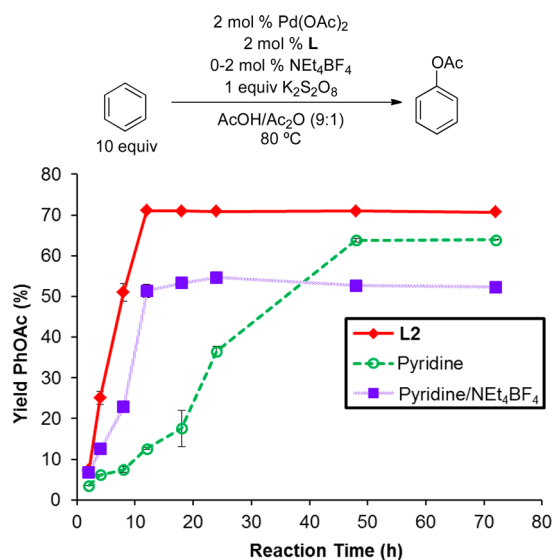


Figure 5. Time study of benzene C–H acetoxylation with $K_2S_2O_8$ catalyzed by $Pd(OAc)_2/L2$, $Pd(OAc)_2/pyridine$, and $Pd(OAc)_2/pyridine/NEt_4BF_4$. Reaction conditions: benzene (1.00 mL, 874 mg, 11.2 mmol, 10.0 equiv), $K_2S_2O_8$ (303 mg, 1.12 mmol, 1.00 equiv), AcOH (0.90 mL), Ac_2O (0.10 mL), $Pd(OAc)_2$ (5.0 mg, 22.4 μ mol, 0.020 equiv), pyridine (1.81 μ L, 1.77 mg, 22.4 μ mol, 0.020 equiv) or L2 (14.3 mg, 22.4 μ mol, 0.020 equiv), and NEt_4BF_4 (4.9 mg, 22.4 μ mol, 2.0 mol %) (or no NEt_4BF_4) were combined and sealed in a 1-dram vial and reacted at 80 °C. Yields determined by GC.

CONCLUSIONS

In conclusion, this manuscript describes the development of Pd catalysts containing pyridinium-substituted pyridine ligands for the C–H oxygenation of benzene with potassium persulfate. These new catalysts provide dramatically improved activity compared to $Pd(OAc)_2$ in this transformation. Furthermore, the reaction proceeds with high selectivity for phenyl acetate over biphenyl. Preliminary mechanistic investigations suggest that a key role for the cationic ligand is to serve as a phase transfer catalyst to bring poorly soluble $S_2O_8^{2-}$ into solution and into contact with the Pd catalyst. This represents one of an expanding number of reports suggesting that ionic association between ligands and oxidants can serve as a valuable design principle in oxidation catalysis.^{28,29,31}

ASSOCIATED CONTENT

Supporting Information

Synthesis and characterization of new ligands and experimental procedures for all catalytic reactions. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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