C–H Activation

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Remarkably High Reactivity of $Pd(OAc)_2$/Pyridine Catalysts: Nondirected C–H Oxygenation of Arenes**

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Over the past eight years there has been tremendous progress in the development of $Pd^{II/IV}$-catalyzed ligand-directed C–H oxidation reactions to form C–O, C–N, C–S, C–halogen, and C–C bonds.[1] In marked contrast, analogous C–H oxidation reactions of substrates that do not contain directing groups remain challenging.[2–7] The lack of a directing group typically renders these transformations (as exemplified by C–H oxygenation) kinetically slow, particularly with electron-deficient arene substrates.[3d,6,7c] The palladium-catalyzed C–H oxygenation of simple arenes is also plagued by low turnover numbers[3–6] and competing biaryl formation, which often leads to catalyst decomposition through precipitation of palladium black.[5] Furthermore, with substituted aromatic substrates, the site selectivity is typically low and difficult to control. As part of a program aimed at developing efficient, selective, and robust catalysts for nondirected C–H functionalization reactions,[7] we sought to identify supporting ligands that would address these limitations and promote the $Pd^{II/IV}$-catalyzed C–H acetoxylation of arenes.

The vast majority of palladium-catalyzed arene C–H oxygenations utilize simple palladium salts (e.g., $Pd(OAc)_2$ or $PdCl_2$),[3–5] and literature studies have provided conflicting data about the influence of added ligands on these reactions. Several reports have shown that most common ligands (e.g., 2,2′-bipyridine, 1,10-phenanthroline, pyridine, triphenylphosphine oxide, etc.) inhibit the palladium-catalyzed C–H acetoxylation of arenes.[3b,d] In contrast, in a few related systems bidentate sp^2 N-donor ligands (e.g., 2,2′-bipyridine and/or 1,10-phenanthroline) were shown to provide modest enhancement of catalytic activity.[4c,d,6] However, these latter reactions exhibited low turnover numbers (typically <10); furthermore, the origin of the observed effects was not explored in detail. Herein we describe the use of careful mechanistic analysis to identify new, efficient, and general palladium catalysts for the C–H acetoxylation of benzene derivatives. Remarkably, these catalysts can be formed in situ from $Pd(OAc)_2$ and the simple ligand pyridine (pyr). Furthermore, their catalytic activities and site selectivities can be dramatically modulated through variation of the palladium/pyridine ratio.

Inspired by recent reports of $Pd^{0/II}$-catalyzed C–H functionalizations,[8–10] our initial explorations focused on pyridine as a ligand for the $Pd^{II/IV}$-catalyzed C–H acetoxylation of benzene with $[PhI(OAc)_2]$. As shown in Figure 1, the $Pd(OAc)_2$-catalyzed transformation proceeded to completion after 24 hours at 100 °C. However, in marked contrast, $[(pyr)_2Pd(OAc)_2]$ (generated in situ from 1 equiv of $Pd(OAc)_2$ and 2 equiv of pyr) performed very poorly, providing less than 20 % yield under the same reaction conditions (Figure 1).

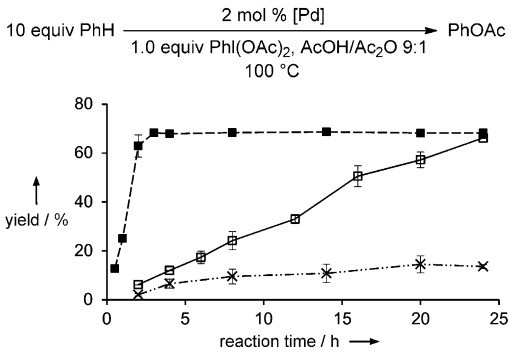

Figure 1. Influence of pyridine on the $Pd(OAc)_2$-catalyzed acetoxylation of benzene. $Pd(OAc)_2$/pyr 1:1 (■); $Pd(OAc)_2$ (□); $Pd(OAc)_2$/pyr 1:2 (x).

We hypothesized that the low reactivity of $[(pyr)_2Pd(OAc)_2]$ might be due to the lack of open coordination sites at the palladium center. Therefore, we next explored the use of a palladium/pyridine ratio of 1:1 to generate a coordinatively unsaturated pyridine-ligated palladium species such as $[(pyr)Pd(OAc)_2]$ in situ.[9–11] The combination of 2 mol % of $Pd(OAc)_2$ and 2 mol % of pyridine (1:1 ratio of [Pd] to [pyr]; catalyst loading relative to oxidant) clearly provided a dramatic rate enhancement, with the reaction proceeding to completion in less than 3 hours (Figure 1).[12,13] A systematic study of the initial reaction rate (approximated by the yield of PhOAc after 2 h) as a function of the palladium/pyridine ratio is shown in Figure 2. A large dependence was observed, with the fastest initial rates at palladium/pyridine ratios between 1:0.5 and 1:1.3. Further experimentation (see the Supporting Information for details) revealed that a palladium/pyridine ratio of 1:0.9 is optimal.[14]

We next sought to probe the longevity of the palladium/pyridine catalysts. Importantly, literature reports suggest that

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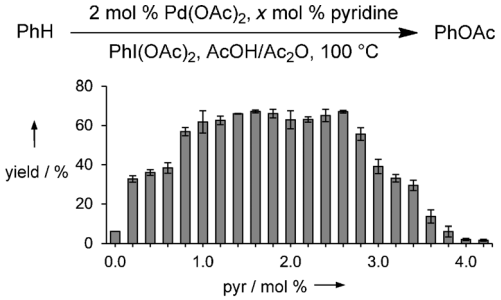


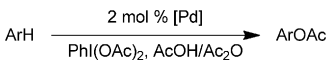
Figure 2. The yield (GC) of PhOAc (after 2 hours) versus mol % of pyridine.

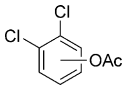
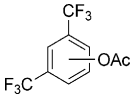
monopyridine/palladium catalysts are short-lived in $Pd^{II/0}$-catalyzed reactions because of fast aggregation of palladium black from coordinatively unsaturated Pd^0 intermediates.[11] We anticipated that such catalyst decomposition pathways should not be accessible in the current transformation because of the $Pd^{II/IV}$ catalytic cycle. Indeed, we found that the palladium/pyridine (1:0.9) catalyst system maintained high activity for C–H acetoxylation over days at 100 °C.[15] For example, under our optimal conditions, the catalyst loading could be lowered to 0.01 mol % $Pd(OAc)_2$/0.009 mol % pyridine, which provided a 48 % yield of PhOAc (TON of 4756) after 306 hours at 100 °C. To our knowledge, this is the highest reported TON for a homogeneous palladium-catalyzed arene C–H oxygenation reaction.

As summarized in Table 1, the increased reactivity of the $Pd(OAc)_2$/pyridine system is general across a wide scope of arene substrates. Our studies particularly focused on electron-deficient arenes such as bromobenzene, chlorobenzene, ethylbenzoate, α,α,α-trifluorotoluene, and 1,3-bis(trifluoromethyl)benzene, since these are typically challenging substrates for palladium-catalyzed C–H functionalization.[3d,6,7c] In all cases, the yield of monoacetoxylated product under our optimal reaction conditions [$Pd(OAc)_2$/pyr 1:0.9] was compared to that obtained with $Pd(OAc)_2$ and with [$(pyr)_2Pd(OAc)_2$] (generated in situ from a 1:2.1 ratio of $Pd(OAc)_2$ to pyr). Gratifyingly, a $Pd(OAc)_2$/pyr ratio of 1:0.9 provided significantly enhanced yields in all cases. With many substrates, the yield could be further improved by substituting $PhI(OAc)_2$ with iodomesitylene diacetate ($MesI(OAc)_2$; Table 1, entries 4, 6, 8, 10, and 12).[16]

The addition of 0.9 equivalents of pyridine also had a significant influence on the site selectivity of C–H functionalization. For example, the α/β selectivity for the C–H acetoxylation of 1,2-dichlorobenzene changed from 41:59 to 29:71 upon moving from $Pd(OAc)_2$ to $Pd(OAc)_2$/pyr (1:0.9) as the catalyst (Table 2, entries 1 and 2). Interestingly, the use of the sterically more hindered oxidant $MesI(OAc)_2$ in place of $PhI(OAc)_2$ also increased the site selectivity. With $Pd(OAc)_2$ as the catalyst, the α/β ratio changed from 41:59 to 37:63 (Table 2, entries 1 and 3). This effect was even more pronounced in the presence of pyridine ($Pd(OAc)_2$/pyr 1:0.9), in which case the α/β selectivity moved from 29:71 to 11:89 (Table 2, entries 2 and 4). Furthermore, analogous trends were observed with other substrates (see the Supporting Information for details). These observations demonstrate the viability of catalyst control of site selectivity in arene C–H acetoxylation through the use of suitable ancillary ligands.[6,8a,c,17] Moreover, the use of sterically differentiated oxidants provides a novel strategy of reagent control for influencing selectivity in palladium catalyzed C–H functionalization.

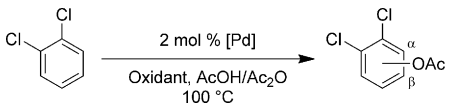
Table 1: Substrate scope of arene C–H acetoxylation with $Pd(OAc)_2$/pyr.[a]



Entry	Product	$Pd[OAc]_2$	Yield [%][b] $Pd(OAc)_2$/pyr (1:0.9)	$Pd(OAc)_2$/pyr (1:2.1)
1		8[c]	70[c]	5[c]
2		–	70[d,e]	–
3		7[c]	62[c]	3[c]
4		–	68[e,f]	–
5		8[g]	59[g]	4[g]
6		–	64[e,h]	–
7		5[g]	68[g]	3[g]
8		–	70[e,i]	–
9		5[j]	47[j]	3[j]
10		–	61[e,k]	–
11		1[l]	24[l]	3[l]
12		–	56[e,m]	–

[a] For reaction conditions see the Supporting Information. [b] Yields are determined by GC analysis using PhCl or $PhCH_2C(CH_3)_3$ as an internal standard. Reaction endpoints for the most active catalyst system ($Pd(OAc)_2$/pyr 1:0.9) are determined by observation of palladium black formation which indicates complete conversion of the oxidant. The less reactive catalysts are compared at the same reaction times. [c] 5 h. [d] 9 h. [e] $MesI(OAc)_2$ was used as oxidant instead of $PhI(OAc)_2$. [f] 10 h. [g] 8 h. [h] 12 h. [i] 21 h. [j] 18 h. [k] 17 h. [l] 22 h. [m] 10 mol % [Pd], 50 h.

Table 2: Site selectivity of C–H acetoxylation as a function of catalyst and oxidant.[a]

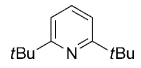


Entry	Catalyst	Yield [%][b]	Oxidant	α/β
1	$Pd(OAc)_2$	8[c,d]	$PhI(OAc)_2$	41:59
2	$Pd(OAc)_2$/pyr (1:0.9)	59[c]	$PhI(OAc)_2$	29:71
3	$Pd(OAc)_2$	8[e,f]	$MesI(OAc)_2$	37:63
4	$Pd(OAc)_2$/pyr (1:0.9)	64[e]	$MesI(OAc)_2$	11:89

[a] For reaction conditions see the Supporting Information. [b] Yields are determined by GC analysis using $PhCH_2C(CH_3)_3$ as an internal standard. [c] 8 h. [d] After longer reaction times (114 h), the acetoxylated products were formed in higher yield (64 %), but with comparable selectivity (α/β 41:59). [e] 12 h. [f] 51 % yield after 68 h (α/β 29:71).

We next initiated studies to gain more detailed insights into the role of pyridine in the catalytic cycle. As discussed above, we originally hypothesized that pyridine was acting as a ligand for the active palladium catalyst; however, this additive could also serve as an external base to accelerate C–H activation. To preliminarily distinguish these roles, we examined the effect of a series of 2- and 2,6-substituted pyridine derivatives on this transformation. As shown in Table 3, the initial rate (as approximated by the yield after 1 and 2 h) tracked extremely well with the steric environment around the pyridine nitrogen atom. For example, moving from unsubstituted pyridine to 2-picoline to 2,6-lutidine significantly slowed the reaction (Table 3, entries 1–3, respectively); furthermore, highly sterically hindered 2,6-di-*tert*-butylpyridine afforded a similar initial rate to that with

Table 3: Yield of C–H acetoxylation of benzene as a function of pyridine structure.[a]

Entry	Additive	Yield [%][b] (after 1 h)	Yield [%][b] (after 2 h)
1		33	66
2		13	26
3		6	14
4		3	8
5	none	2	6

[a] Reaction conditions: benzene (1.00 mL, 875 mg, 11.2 mmol, 10.0 equiv), AcOH (0.90 mL), Ac_2O (0.10 mL), $PhI(OAc)_2$ (361 mg, 1.12 mmol, 1.00 equiv), $Pd(OAc)_2$ (5.0 mg, 22.4 μmol, 2.0 mol%), 0.45 mL stock solution of additive (448 μmol in 10 mL AcOH; 1.8 mol%), 100°C. [b] Yields are determined by GC analysis using PhCl as an internal standard.

$Pd(OAc)_2$ alone. These results implicate a primary role for pyridine as a ligand that binds to the palladium center during one or more key steps of the catalytic cycle.

Finally, the method of initial rates was used to compare the C–H acetoxylation of benzene to that of [D_6]benzene with three different catalysts: $Pd(OAc)_2$ (**A**), $Pd(OAc)_2$/pyr 1:0.9 (**B**), and $Pd(OAc)_2$/pyr 1:2 (**C**). The values of k_H/k_D were all relatively large (2.9, 4.8, and 3.8 respectively), implicating C–H activation as the rate-determining step with all three catalysts.[18] Since the reaction is clearly fastest with catalyst **B** (Figure 1), these data suggest a critical role for the pyridine ligand in accelerating the C–H activation step of the catalytic cycle. We hypothesize that this is due to the generation of an open coordination site at the palladium center (by de-aggregation of trimeric/polymeric $Pd(OAc)_2$)[19] in the presence of 1 equivalent of pyridine.

In conclusion, this report describes a catalytic system based on a commercial palladium source [$Pd(OAc)_2$] and ligand (pyridine), that shows the highest reactivity reported for the acetoxylation of unactivated aromatic C–H bonds. In the investigated systems, the ratio of palladium/pyridine proved absolutely critical and the use of 1 equivalent of pyridine per palladium center led to dramatic enhancements in both reactivity and site selectivity. These studies highlight the importance of exploring the ligand to metal ratio, along with the structure of spectator ligands, during the optimization of reaction conditions for catalytic C–H functionalization. Current efforts are focused on gaining a detailed mechanistic understanding of the palladium/pyridine ratio effects reported herein. Such mechanistic insights will be crucial for developing new N-ligated palladium catalysts that display enhanced stability, activity, and site selectivity in C–H oxidation reactions.

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[9] Several literature reports (e.g., see Refs. [8a,c,10,11]) have implicated monopyridine Pd^{II} complexes [(pyr*)PdX_2] as reactive intermediates in $Pd^{II/0}$-catalyzed oxidation reactions.

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[12] The reactivity of the catalyst system $Pd(OAc)_2$/pyr 1:1 surpasses by far the reactivity observed when 2,2′-bipyridine or a pyridinium-substituted bipyridine analogue are used as ligands (see Ref. [7c]).

[13] Yields are based on the oxidant $PhI(OAc)_2$, which has been shown to decompose upon heating through metal-catalyzed (V. V. Zhdankin, P. J. Stang, *Chem. Rev.* **2008**, *108*, 5299) and uncatalyzed pathways (J. E. Leffler, L. J. Story, *J. Am. Chem. Soc.* **1967**, *89*, 2333 – 2338). The by-products detected included $C_6H_4I(OAc)$, $C_6H_4(OAc)_2$, and biphenyl in accordance with Ref. [7c]. Both factors presumably contribute to the moderate yields of acetoxylated products (ca. 70%) upon complete conversion of the oxidant.

[14] The observed exquisite sensitivity of the catalyst activity on the ligand to metal ratio is likely the reason that ancillary ligands were previously reported to inhibit C–H acetoxylation (see Ref. [3b,d]).

[15] The longevity of the catalyst system $Pd(OAc)_2$/pyr 1:0.9 was also evaluated by addition of a second batch of oxidant after 3 h. This "second run" afforded a 54% yield of PhOAc (see the Supporting Information).

[16] This may be due to the greater stability of $MesI(OAc)_2$ under the reaction conditions (as indicated by Ref. [13]) and/or to diminished formation of the by-product ArI(OAc) (formed by C–H acetoxylation of oxidant-derived ArI).

[17] Preliminary studies do not show a conclusive trend in the site selectivity of C–H acetoxylation as a function of the substitution pattern on the pyridine ligand. Data for the acetoxylation of 1,2-dichlorobenzene using 2-picoline, 2,6-lutidine, and 2,6-di-*tert*-butylpyridine as ligands is given in the Supporting Information. Additional studies of ligand effects on site selectivity are ongoing in our laboratory.

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