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Ligand-Promoted Palladium-Catalyzed C–H Acetoxylation of Simple Arenes

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The palladium-catalyzed C–H oxidation of simple arenes is an attractive strategy to obtain phenols, which have many applications in the fine chemicals industry. Although some advances have been made in this research area, low reactivity and selectivity are, in general, observed. This report describes a new catalytic system for the efficient C–H acetoxylation of simple arenes based on $Pd(OAc)_2$ and a pyridinecarboxylic acid ligand.

Metal-catalyzed C–H functionalization has emerged as a powerful tool to construct complex molecules with the potential to revolutionize chemical synthesis.[1] However, this approach is still in its infancy and many challenges need to be overcome before this strategy can become a routine synthetic tool for organic chemists. The main limitations of this approach are the low reactivity of the C–H bond and the low selectivity obtained in substrates that contain diverse C–H bonds. In general, these limitations can be circumvented by using directing groups that are able to increase the reactivity and selectivity of the C–H functionalization process.[2–4] Nevertheless, the use of directing groups generally implies the addition of two extra steps in the synthetic sequence, the introduction and removal of the directing group, which frustrates the real goal of this strategy. An ideal approach to increase the reactivity and selectivity of these processes is the use of suitable ligands. However, to date only a limited number of ligands are able to promote the direct functionalization of C–H bonds,[5] and in the majority of these examples, the presence of a directing group is still required. Therefore, to unlock the full potential of metal-catalyzed C–H functionalization, the discovery of new ligands capable of increasing the reactivity and selectivity of these processes is of central importance.

The direct oxidation of simple arenes is an attractive process to obtain phenols, which have many applications in organic synthesis.[6,7] The palladium-catalyzed C–H acetoxylation of benzene has been described in the presence of strong oxidants (e.g., $K_2Cr_2O_7$, $K_2S_2O_8$),[8] albeit with low catalytic turnover and significant formation of the biphenyl byproduct. In 1996, Crabtree reported the use of $PhI(OAc)_2$ as an oxidant, and it showed higher activity and precluded the formation of biphenyl.[9] More recently, Sanford described that the addition of pyridine accelerates the $Pd(OAc)_2$-catalyzed C–H acetoxylation of simple arenes by using $PhI(OAc)_2$ as the oxidant and partially controls the site selectivity of the reaction.[10] Less-active catalytic systems for the C–H acetoxylation of arenes by using different types of ligands and oxidants have been described.[11] Herein, we report a new catalytic system based on a bidentate picolinic acid ligand for the $Pd(OAc)_2$-catalyzed C–H acetoxylation of simple arenes by using $PhI(OAc)_2$ as the oxidant. The presence of the picolinic acid ligand enhanced the reactivity and provided the highest turnover number (TON = 7800) reported for the $Pd(OAc)_2$-catalyzed C–H acetoxylation of benzene and, furthermore, increased the site selectivity of the reaction with substituted arenes.

Our ligand design was inspired by the recent success of pyridine ligands in Pd-catalyzed C–H functionalization reactions[5b,10,12] as well as by the fact that carboxylic acids are capable to assist C–H bond cleavage[13] in a wide number of metal-catalyzed C–H functionalization reactions, including C–H acetoxylation.[14] We envisioned that the combination of both functionalities would enhance the reactivity and site selectivity of the Pd-catalyzed C–H acetoxylation of simple arenes as well as the stability of the catalyst.

In our model reaction involving the use of benzene, $Pd(OAc)_2$ (2 mol%), and $PhI(OAc)_2$ (1 equiv.) in $AcOH/Ac_2O$, we tested different pyridinecarboxylic acid derivatives (Scheme 1). The reactions were performed by using $Pd(OAc)_2$ (2 mol%) and a 1:1 ratio of Pd/ligand, and the mixtures were stirred at 100 °C for 3 h, the moment at which the formation of Pd black was detected in the majority of the reactions.

We clearly observed that the addition of the picolinic acid ligand enhanced the reactivity of the C–H acetoxylation of benzene (50% yield, see kinetic profile in the Supporting Information). The reaction proceeded without the formation of byproducts; neither overoxidation of phenyl acetate nor biphenyl were observed in the reaction. The screening of other commercially available pyridinecarboxylic acid derivatives as ligands did not provide a significant difference in the outcome of the reaction; nevertheless, some trends were identified. If electron-donating groups were attached to the C6 position of the picolinic acid ligand (e.g., 6-methylpicolinic acid and 6-methoxypicolinic acid), phenyl acetate (**1**) was obtained in lower yields (38–43%). If electron-withdrawing groups were attached to the C6 position of the picolinic acid ligand [e.g., 6-fluoropicolinic acid and 6-(trifluoromethyl)picolinic acid], phenyl acetate (**1**) was delivered in comparable yields (52–55%) with the exception of 6-nitropicolinic acid, which provided phenyl acetate (**1**) in only 17% yield. Moreover, similar results were obtained if the reaction was performed in the presence of 5-fluoropicolinic acid, 2-quinolinecarboxylic acid, 8-quinolinecarboxylic acid, or 2-pyridinesulfonic acid ligands.

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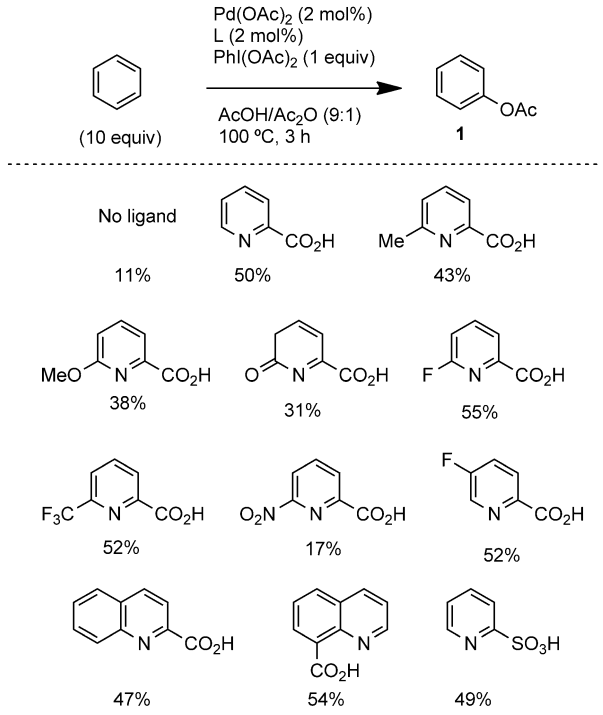


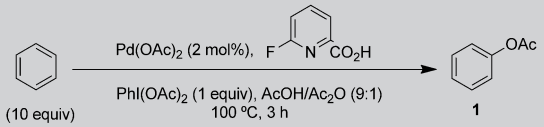
[a]Yields were determined by GC analysis using PhCl as internal standard.

Scheme 1. Screening of bidentate ligands in the Pd-catalyzed C–H acetoxylation of benzene.[a]

Different palladium salts and solvents were evaluated in the model reaction by using picolinic acid as the ligand without any significant improvement in the yield of phenyl acetate (**1**) (see Supporting Information). We next optimized the ligand/Pd ratio in the C–H acetoxylation of benzene at 100 °C by using 2 mol% of $Pd(OAc)_2$ and 6-fluoropicolinic acid as the ligand (Table 1).

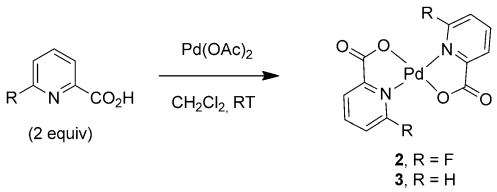
The reaction proceeded with similar yields by using 2 or 1.5 mol% of the ligand (Table 1, entries 3 and 4) and with a minimal deleterious effect in the yield by using 0.5 mol% of the ligand (Table 1, entry 1; 50% yield). On the other hand, if the reaction was performed with 3 mol% of ligand, the product was obtained in only 27% yield (Table 1, entry 5), and no product formation was observed upon using 4 mol% of ligand (Table 1, entry 6). In all these reactions using 2 mol% of $Pd(OAc)_2$ and different amounts of 6-fluoropicolinic acid, an insoluble palladium complex precipitated, which was isolated by filtration from the mixture and identified by IR spectroscopy and mass spectrometry as complex **2** (Scheme 2).

Table 1. Optimization of the ligand ratio in the Pd-catalyzed C–H acetoxylation of benzene.



Entry	6-Fluoropicolinic acid [mol%]	Yield[a] [%]
1	0.5	50
2	1	52
3	1.5	56
4	2	55
5	3	27
6	4	0

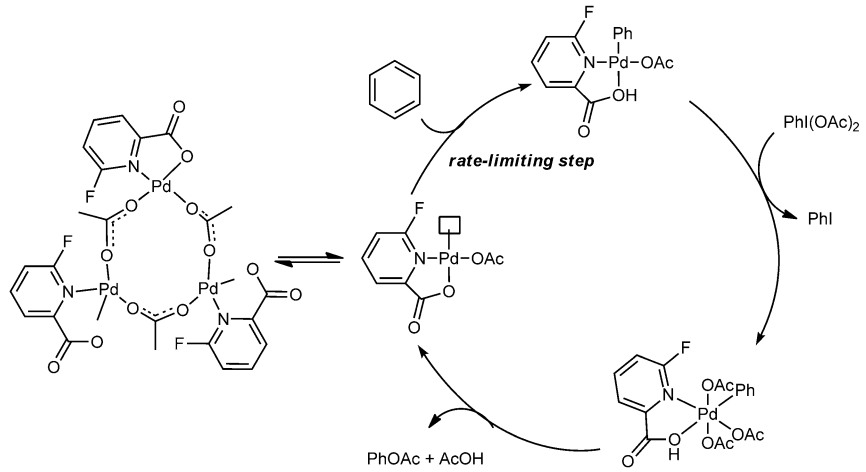
[a] Yields were determined by GC analysis by using PhCl as an internal standard.



Scheme 2. Synthesis of palladium complexes **2** and **3**.

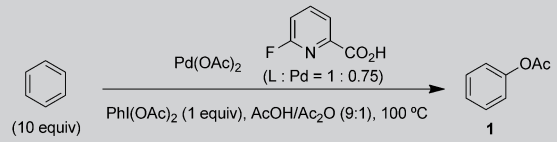
Palladium complex **2** possess two molecules of the ligand and was independently prepared by the reaction of $Pd(OAc)_2$ with 2 equivalents of 6-fluoropicolinic acid in CH_2Cl_2 at room temperature to confirm its identity. In addition, similar results were observed if the C–H acetoxylation of benzene was performed by using picolinic acid as the ligand. In this case, the solid that precipitated from the reaction was identified as palladium complex **3**.[15] Both palladium complexes were found to be insoluble at room temperature in all solvents tested and nearly inactive in the C–H acetoxylation of benzene. Indeed, the C–H acetoxylation of benzene in the presence of complex **2** (2 mol%) at 100 °C after 14 h provided phenyl acetate (**1**) in only 15% yield. Under the same reaction conditions upon using complex **3** (2 mol%), no conversion into phenyl acetate (**1**) was observed. These results explain why low conversions were observed upon increasing the amount of ligand (Table 1, entries 5 and 6). Notably, during the reaction and independent of the amount of ligand added, these inactive complexes were formed, which lowered the real catalyst loading. The high catalytic activity observed for this system can be attributed to the formation of the active catalyst, which we speculate is a monomeric complex with one ligand (see Scheme 3).

We next explored the catalyst loading for the C–H acetoxylation of benzene by using a $Pd(OAc)_2$/6-fluoropicolinic acid ratio of 1:0.75. As shown in Table 2, the addition of 4 mol% $Pd(OAc)_2$ led to the formation of phenyl acetate (**1**) in 69% yield (Table 2, entry 1). Upon performing the reactions with Pd loadings between 3 and 1.5 mol%, the yields of the product were approximately 54–56% (Table 2, entries 2–4). Slightly lower yields were observed upon employing a catalyst loading of 1 or 0.5 mol% (Table 2, entries 5 and 6). In a previous report for the C–H acetoxylation of benzene it was observed that the reaction stopped after the formation of Pd black.[10a] In all these reactions, the formation of Pd black was observed after 3 h with the exception of the reaction performed in the presence of 0.5 mol% $Pd(OAc)_2$. Therefore, we repeated the C–H acetoxylation of benzene with 0.5 mol% $Pd(OAc)_2$, and the mixture was stirred until the formation of Pd black was ob-



Scheme 3. Proposed mechanism with $Pd(OAc)_2$/6-fluoropicolinic acid.

Table 2. Catalyst loading study for the C–H acetoxylation of benzene.



Entry	$Pd(OAc)_2$ [mol%]	Reaction time [h]	Yield[a] [%]	TON
1	4	3	69	17
2	3	3	56	19
3	2	3	55	–
4	1.5	3	54	36
5	1	3	47	47
6	0.5	3	35	–
7	0.5	7.5	59	118
8	0.1	24	75	750
9	0.01	309	78	7800
10	2	14	76	38
11[b]	2	3	67	–

[a] Yields were determined by GC analysis by using PhCl as an internal standard. [b] 0.37 M concentration.

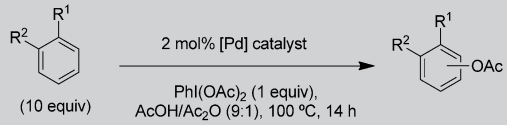
served (7.5 h), and in this case, phenyl acetate (**1**) was delivered in 59% yield (Table 2, entry 7). Importantly, the reaction provided 78% yield of phenyl acetate (**1**) in the presence of 0.01 mol% catalyst, which led to the highest TON (7800) reported for the $Pd(OAc)_2$-catalyzed C–H acetoxylation of benzene (Table 2, entry 9). Although this result was extremely positive, we were concerned about the high yield obtained relative to previous experiments. We hypothesized that lower concentrations as well as longer reaction times led to higher yields, even if Pd black was formed. Indeed, the reaction performed with the use of 2 mol% Pd furnished phenyl acetate (**1**) in 55% yield after 3 h (Table 2, entry 3) and in 76% yield after 14 h (Table 2, entry 10) even if the formation of Pd black was observed after 2 h. In addition, a higher yield (67%) was observed if the reaction was performed at higher dilution (0.37 M vs. 1.12 M; Table 2, entry 11).

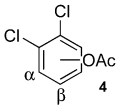
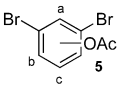
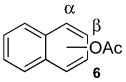
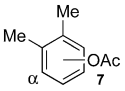
After proving the high activity of the new catalytic system in the C–H acetoxylation of benzene, we evaluated different substituted arenes (Table 3).[16] $PhI(OAc)_2$ was used as the oxidant for all substrates and we compared the conditions without (conditions A) or with 6-fluoropicolinic acid (conditions B) for each substrate.

The reaction of 1,2-dichlorobenzene under conditions A provided almost an equimolecular mixture of acetoxylated products in 9% yield. In contrast, the reaction in the presence of 6-fluoropicolinic acid provided the regioisomeric products in 74% yield with a clear preference to activate the least sterically hindered C–H bond (**4**α/**4**β = 11:89). In a similar manner, the reaction with 1,3-dibromobenzene as the starting material furnished the corresponding products in low yield (36%) under conditions A and in 86% yield under conditions B. Regarding the site selectivity, regioisomer **5b**, derived from acetoxylation at the electronically more activated and least hindered position, was obtained in higher ratio than that observed under conditions A (Table 3, entry 2). The reaction of naphthalene provided the acetoxylated product in good yield under both conditions, and the site selectivity was enhanced towards the functionalization of the least sterically hindered C–H bond under conditions B (**6**α/**6**β = 29:71; Table 3, entry 3). Similar behavior was observed in the reaction with *o*-xylene, which showed an increase in site selectivity in the presence of the ligand (**7**α/**7**β = 23:77; Table 3, entry 4).

The reaction employing monosubstituted arenes, different behaviors were observed depending of the nature of the substituent. Under both conditions, the reaction of toluene gave good yields and low site selectivity (Table 3, entry 5). In a similar manner, under both conditions, the reaction of anisole provided moderate to low yields and site selectivity (Table 3, entry 6). On the other hand, the reaction of bromobenzene furnished the acetoxylated product in a slightly higher yield and site selectivity under conditions B than under conditions A (Table 3, entry 7). The reaction of trifluoromethylbenzene (Table 3, entry 8) or ethyl benzoate (Table 3, entry 9) under conditions A provided a mixture of acetoxylated products in low yields (18–

Table 3. Pd-catalyzed C–H acetoxylation of mono- and disubstituted arenes.[a]



Entry	Product	Yield [%] (Selectivity)[b] Conditions A	Conditions B
1	 4	9 (α/β = 44:56)	74 (α/β = 11:89)
2	 5	36 (a/b/c = 14:17:69)	86 (a/b/c = 5:50:45)
3	 6	81 (α/β = 57:43)	69 (α/β = 29:71)
4	 7	40 (α/β = 38:62)	54 (α/β = 23:77)
5	 8	70 (*o*/*m*/*p* = 37:32:31)	62 (*o*/*m*/*p* = 29:35:36)
6	 9	46 (*o*/*m*/*p* = 39:4:56)	37 (*o*/*m*/*p* = 21:11:68)
7	 10	71 (*o*/*m*/*p* = 35:39:25)	93 (*o*/*m*/*p* = 16:49:35)
8	 11	18 (*o*/*m*/*p* = 33:55:17)	94 (*o*/*m*/*p* = 5:85:10)
9	 12	19 (*o*/*m*/*p* = 24:47:29)	64 (*o*/*m*/*p* = 9:63:28)

[a] Conditions A: $Pd(OAc)_2$ (2 mol%); conditions B: $Pd(OAc)_2$ (2 mol%) and 6-fluoropicolinic acid (2 mol%). [b] Yields and selectivities were determined by GC analysis by using PhCl as an internal standard.

19%). When the reactions were performed in the presence of the ligand, an increase on reactivity and site selectivity was observed. In both cases, the *meta* isomer was the major product, which was obtained from functionalization at the electronically more activated position. In general, reactions with arenes bearing electron-withdrawing groups led to higher yields of the products in the presence of the 6-fluoropicolinic acid ligand, whereas the reaction with electron-rich arenes under conditions A or B afforded similar yields. The site selectivity in the presence of the 6-fluoropicolinic acid ligand is controlled by both steric and electronic factors, with preferential functionalization at the most electronic-rich and least sterically hindered position in the arene. The effect on the reactivity and site selectivity of the reaction upon using $MesI(OAc)_2$ (Mes = 2,4,6-trimethylphenyl) was evaluated with and without 6-fluoropicolinic acid, but no improvement was observed (see the Supporting Information).

Finally, we performed some experiments to gain more insight into the mechanism of this transformation. We first followed the reaction by ^1H NMR spectroscopy, which showed the formation of some palladium complexes. Unfortunately, we were not able to identified these complexes that were different from the ones formed in the stoichiometric reaction of $Pd(OAc)_2$ and the picolinic acid derivatives. Afterwards, we compared the C–H acetoxylation of benzene to that of [D_6]benzene (see the Supporting Information), which gave a large kinetic isotope effect (4). In addition, a zero-order dependence in $PhI(OAc)_2$ was observed in the reaction by using the initial rate method (see the Supporting Information). These results indicate that the C–H activation is the rate-limiting step.[17] We determined the order of the reaction in Pd. The plot of the logarithms of the reaction rate against the concentration provided a straight line with a slope of 0.3, which suggested a trimeric precatalyst. With these data we proposed the mechanism outlined in Scheme 3 in which a trimeric precatalyst enters the catalytic cycle by dissociation to a monomer and the C–H activation is the rate-limiting step.

In conclusion, we developed a new catalytic system for the direct C–H acetoxylation of simple arenes based on $Pd(OAc)_2$ and a 6-fluoropicolinic acid ligand that shows high reactivity and site selectivity. This system proved to be active at low catalyst loadings, which led to the highest turnover number reported to date for the palladium-catalyzed C–H acetoxylation of benzene. The precipitation during the C–H acetoxylation of an inactive palladium complex bearing two molecules of the ligand suggests that this system may be more reactive than it shows. The site selectivity of the acetoxylation of the arenes is dictated by both electronic and steric factors. Overall, this catalytic system shows promising perspectives in terms of reactivity and selectivity in the C–H oxidation field. Current efforts are focused on expanding the application of this catalytic system and on gaining detailed mechanistic insight into this transformation.

Experimental Section

General procedure for the C–H acetoxylation of benzene

$PhI(OAc)_2$ (180 mg, 0.56 mmol, 1.00 equiv.), $Pd(OAc)_2$ (2.5 mg, 11.2 μmol, 0.02 equiv.), and 6-fluoropyridine-2-carboxylic acid (1.6 mg, 11.2 μmol, 0.02 equiv.) were weighed into a pressure vial. Glacial acetic acid and acetic anhydride (1.12 M, in a ratio of 9:1) were added. The resulting suspension was stirred at RT for 15 s and then benzene (0.5 mL, 437 mg, 5.6 mmol, 10.0 equiv.) was added. The vial was sealed with a Teflon-lined cap, and the mixture was heated to 100 °C by using a preheated bath oil. At the end of the reaction, the vial was cooled to RT, and PhCl (20 μL) was added as an internal standard for quantitative GC analysis. The mixture was diluted with EtOAc (1 mL) and filtered through a plug of

Celite. The filtrate was extracted with a saturated aqueous solution of K_2CO_3 (3 M in deionized H_2O, 2×2 mL) to quench and separate the acid. The organic layer was then carefully separated and diluted with additional EtOAc to a total volume of 10 mL. The resulting solution was analyzed by GC.

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Keywords: arenes · C–H activation · N,O ligands · oxidation · palladium

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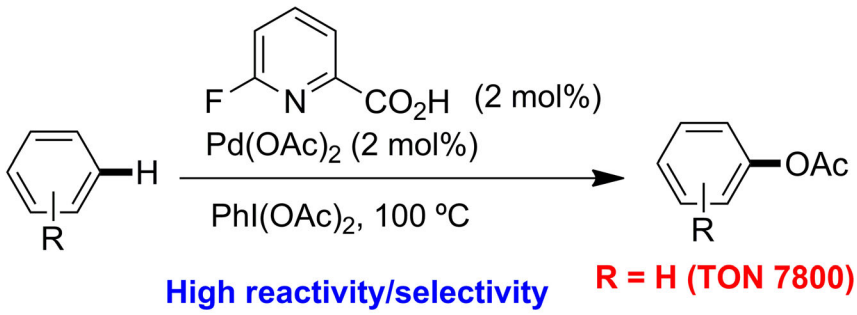
Ligand-Promoted Palladium-Catalyzed C–H Acetoxylation of Simple Arenes



Fast and selective: A catalytic system based on a bidentate picolinic acid ligand and $Pd(OAc)_2$, capable of increasing the reactivity and site selectivity of the C–H acetoxylation of simple arenes, is reported.