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Pd(II)-Catalyzed Hydroxylation of Arenes with 1 atm of O_2 or Air

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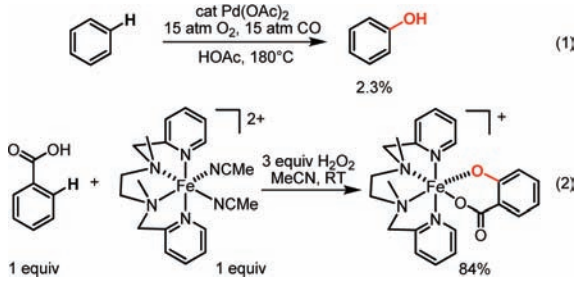
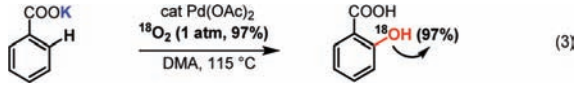
Catalytic hydroxylation of inert C−H bonds using environmentally benign hydrogen peroxide or molecular oxygen remains a significant task in both chemical industry and organic synthesis.[1] Among various metal[2] and nonmetal[3,4] catalytic systems, an early discovery by Fujiwara using $Pd(OAc)_2$ to convert benzene into phenol with molecular oxygen is especially intriguing[5] but required harsh conditions and provided low yields (eq 1). In another pioneering study by Rybak-Akimova and Que,[6] the carboxylic group of benzoic acid was used to direct *ortho*-hydroxylation with H_2O_2 in the presence of a stoichiometric amount of a reactive nonheme iron complex $[Fe(II)(BPMEN)(CH_3CN)_2](ClO_4)_2$ (eq 2).



Our group and others have also reported Pd-catalyzed C−H oxidation with various peroxides[7a] and oxone[7b,8] using Ac_2O as a crucial promoter. Recently, an important study by Vedernikov described a Pd(II)-catalyzed oxidation reaction of benzylic C−H bonds of 8-methylquinoline with molecular O_2 in the presence of $HOAc/Ac_2O$ in which both hydroxylation and acetoxylation were observed.[9a] However, this catalytic system is not compatible with aryl C−H bonds.[9b] Herein we report highly selective Pd-catalyzed *ortho*-hydroxylation of potassium benzoates with 1 atm of O_2 or air giving synthetically useful yields under nonacidic conditions (eq 3). The use of 0.2−1 equiv of benzoquinone is found to significantly accelerate the reaction; however, it is not essential. Labeling studies using both $^{18}O_2$ and $H_2{}^{18}O$ support a direct oxygenation of the arylpalladium intermediates instead of an acetoxylation/hydrolysis sequence.[10]



The fundamental importance of hydroxylation with O_2 and its applications related to drug discovery and natural product synthesis based on salicylic acids prompted us to develop a Pd-catalyzed *ortho*-hydroxylation of benzoic acids with molecular O_2 (Figure 1). Guided by an early observation that alkali metal and other cations promote palladation of proximate C−H bonds,[11] we discovered through extensive screening that potassium salts such as KOAc or K_2HPO_4 promote Pd(II)-catalyzed *ortho*-hydroxylation of benzoic acids under 1 atm of O_2 in DMF, DMA, and DMP. Although only two turnovers were observed (entries 3−5), the yield

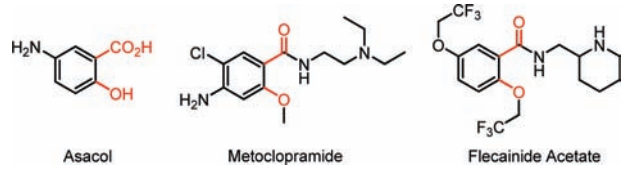
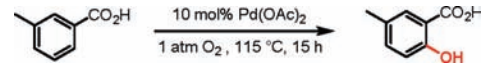


Figure 1. Examples of the top 200 drugs by retail dollars.

Table 1. Screening of Reaction Conditions



entry	solvent	base	BQ (equiv)	% yield[a]	% SM[a]
1	*t*-BuOH	KOAc (2 equiv)	0	0	100
2	THF	KOAc (2 equiv)	0	0	100
3	DMF	KOAc (2 equiv)	0	16	52
4	DMP	KOAc (2 equiv)	0	12	60
5	DMA	KOAc (2 equiv)	0	20	50
6	DMA	KOAc (2 equiv)	0	55[b]	0
7	DMA	K_2HPO_4 (3 equiv)	0	60[b]	0
8	DMA	KOAc (2 equiv)	0.2	40	60
9	DMA	KOAc (2 equiv)	1	82	12
10	DMA	NaOAc (2 equiv)	1	25	70
11	DMA	CsOAc (2 equiv)	1	80	16
12	DMA	K_2HPO_4 (3 equiv)	1	45	45
13	DMA	K_2CO_3 (3 equiv)	1	33	65
14	DMA	KOAc (2 equiv)	1	62[c]	30
15	DMA	KOAc (2 equiv)	1	0[d]	100

[a] The yields were determined by ^1H NMR analysis of crude products using CH_2Br_2 as the internal standard; DMA, *N*,*N*-dimethylacetamide; DMP, *N*,*N*-dimethylpropionamide. [b] 5 atm of O_2. [c] Air instead of O_2. [d] Ar instead of O_2.

was increased to 55−60% by performing this hydroxylation reaction under 5 atm of O_2 (entries 6, 7). We also found that addition of 0.2 and 1 equiv of benzoquinone increases the yield to 40% and 82% respectively under 1 atm of O_2 (entries 8, 9). Among the bases screened, KOAc and CsOAc (entries 9, 11) are superior to NaOAc (entry 10); however, K_2HPO_4 is also compatible (entry 12). These combined data indicate that the acetate anion is not required. Monitoring the reaction by ^1H NMR shows that benzoquinone significantly increases the rate of the hydroxylation (see Supporting Information).[12] We were pleased to find that hydroxylation proceeds using 1 atm of air as the sole oxidant (entry 14). Notably, no reaction was observed using stoichiometric $Pd(OAc)_2$ under 1 atm of argon, suggesting that O_2 is likely to be involved in the product forming step rather than reoxidation of Pd(0) (entry 15).

With these optimized conditions in hand, we proceeded to establish the substrate scope. Electron-rich arenes are readily hydroxylated to give the anticipated products **1**−**9** in 60−82% yields. The hydroxylation product from 1-naphthoic acid was decarboxylated spontaneously to give **6**. Surprisingly, the well-known directing group acetamide in **9** did not scramble the regioselectivity. Halides (**10**−**13**), as well as other stronger electron-withdrawing groups such as trifluoromethyl, acetyl, cyanide, and nitro (**14**−**20**), are reasonably well tolerated, giving

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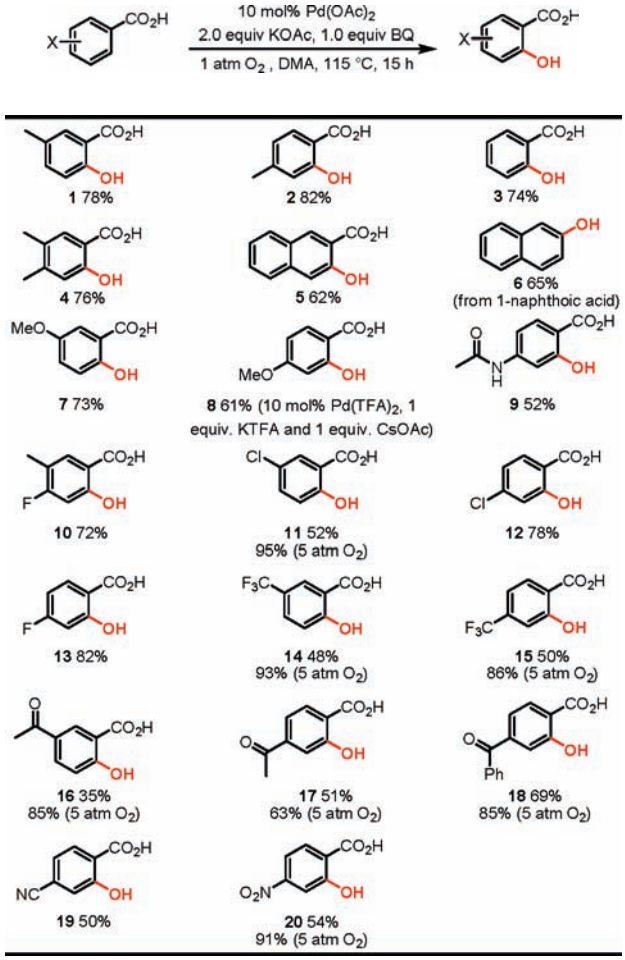
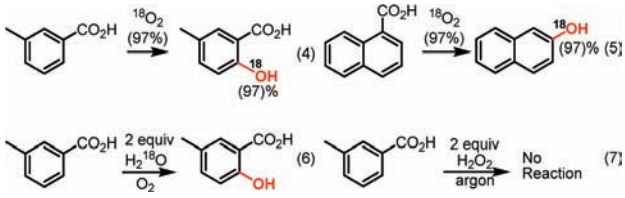
Table 2. Pd-Catalyzed *ortho*-Hydroxylation with O_2[a]



[a] Isolated yield.

moderate yields. In these cases, 85−95% yields can be obtained by using 5 atm of O_2.

Preliminary mechanistic investigations were carried out to shed light onto this hydroxylation pathway. Our earlier studies on Pd-catalyzed C−H oxidation using peroxides[7a] and O_2 as the oxygen source were initially inspired by seminal works regarding organometallic reactions of C−Pd bonds with peroxides[13] and C−Pt bonds with O_2.[14,15] These oxidants are shown to oxidize C−Pt (Pd) bonds to form Pt(IV) and Pd(IV) species **I** and **II** or directly insert oxygen atoms into C−Pt(Pd) bonds to form **III** and **IV**.[7a]



While no data are currently available to distinguish among these reaction pathways, labeling experiments were performed to rule out the involvement of carboxylation or lactonization intermediates **V** and **VI** (Figure 2). First, $^{18}O_2$ was incorporated into the products with high

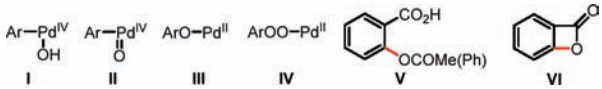


Figure 2. Possible reaction intermediates.

fidelity (eq 4). Second, the decarboxylated product showed that $^{18}O_2$ is incorporated into the hydroxyl rather than the carboxyl group (eq 5). These observations are inconsistent with the carboxylation/hydrolysis pathway from the catalytic amount of OAc^- or the benzoic acids. Finally, experiments using 2 equiv of $H_2{}^{18}O$ (eq 6) or H_2O_2 (30% in H_2O) (eq 7) also rule out oxygen incorporation from H_2O or H_2O_2 formed through a Pd(II)/Pd(0) catalysis.[16]

In summary, we have developed a versatile Pd-catalyzed *ortho*-hydroxylation of benzoic acids with 1 atm of O_2 or air under nonacidic conditions. Mechanistic investigations point to a direct oxygenation of the aryl-Pd species by molecular O_2.

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Supporting Information Available: Experimental procedure and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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