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Ligand Promoted Pd-catalyzed Oxime Ether Directed C-H hydroxylation of Arenes

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ABSTRACT. An efficient Pd-catalyzed oxime ether directed *ortho* C-H hydroxylation of arenes under neutral conditions has been developed. The efficiency of this hydroxylation is significantly improved by ligand. Oxone, an inexpensive, readily available, and safe reagent, was employed as terminal oxidant and oxygen source. The challenging electron-deficient substrates could also be monohydroxylated in high efficiency. Drug modification with this protocol was also successfully demonstrated.

KEYWORDS. *hydroxylation, C-H functionalization, palladium, oxygenation, chemoselectivity*

The hydroxylation of aromatic compounds is a process of considerable industrial and academic importance.[1] Direct oxidative hydroxylation of C-H bonds by transition metals has emerged as a powerful strategy for generating phenols in the past decade.[2,3] *Ortho*-

acylphenols are useful synthetic intermediates and important subunits in bioactive molecules and natural products (Fig. 1).[4] The direct C-H hydroxylation of ketones or ketoxime ethers which could be very easily converted into ketones,[5,6] has been an extremely straight-forward and attractive strategy for the synthesis of *ortho*-acylphenols.[7-13] By using ketoxime ether substrates, Sanford and coworkers pioneeringly disclosed the directed C-H acetoxylation with PIDA[7a] or Oxone/AcOH[7b] oxidative system for the synthesis of corresponding esters, which can be converted to the hydroxyl products by an additional hydrolysis step (a, Scheme 1).[7] The groups of Ackermann,[8,9] Rao,[10,11] Dong,[12] and Kwong[13] groundbreakingly developed the efficient and selective synthesis of *ortho*-acylphenols from acyl arenes *via* in situ hydrolysis of the trifluoroacetoxylated intermediates with PIFA,[8a,12,13] PIDA/TFA[8b] or $K_2S_2O_8$/TFA[10,12] reagents (b, Scheme 1). Despite the significance, there still are some left challenging issues of this direct hydroxylation chemistry: 1) The hydroxylation of strong electron-deficient substrates were less efficient,[8,10,12,13] which restricts the application of these protocols in the synthesis of electron-deficient *ortho*-acylphenol derivatives especially for the important bioactive molecules (Fig. 1);[14] 2) The use of acid TFA or AcOH as solvent limited the functional group compatibility of these transformations; 3) The selectivity for mono- and di-functionalization still has room to improve. Therefore, a practical and efficient direct C-H hydroxylation under mild and especially neutral conditions is still highly desired.

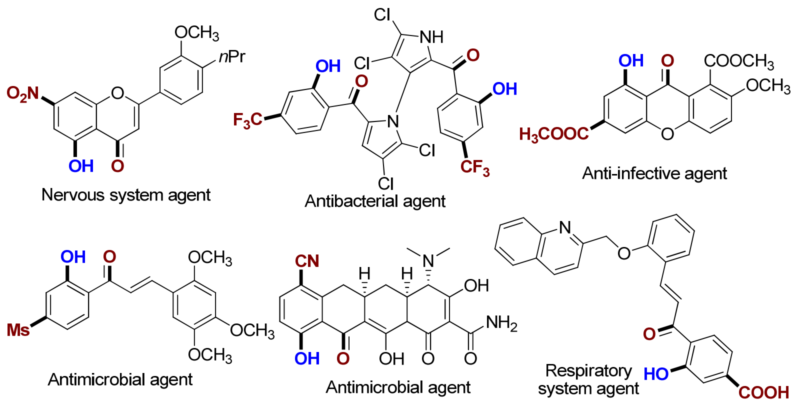
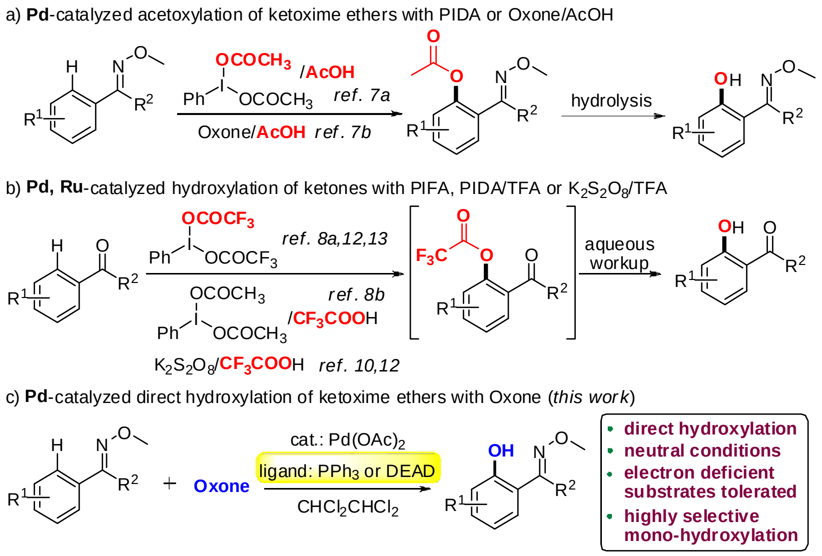


Figure 1. Electron-deficient *Ortho*-acylphenols with Biological Activity.

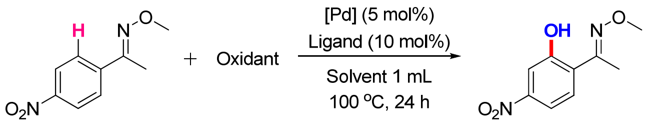


Scheme 1. Strategies for C-H Hydroxylation.

Herein, we report a Pd-catalyzed direct *ortho* C-H hydroxylation ketoxime ether (c, Scheme 1). The following significances exist in this chemistry: 1) The substrate scope is broad including the challenging electron-deficient substrates with highly selectively monohydroxylated products formation; 2) The inexpensive, readily available, easily handled, and safe solid oxidant Oxone (potassium peroxymonosulphate),[15] was employed as oxidant and oxygen source; 3) The reaction proceeded cleanly under neutral condition without addition of acid and could be easily scalable;

4) The modification of drug derivative, which contains a thioether moiety, was demonstrated by this protocol.

Table 1. Optimization of the Reaction Conditions[a]



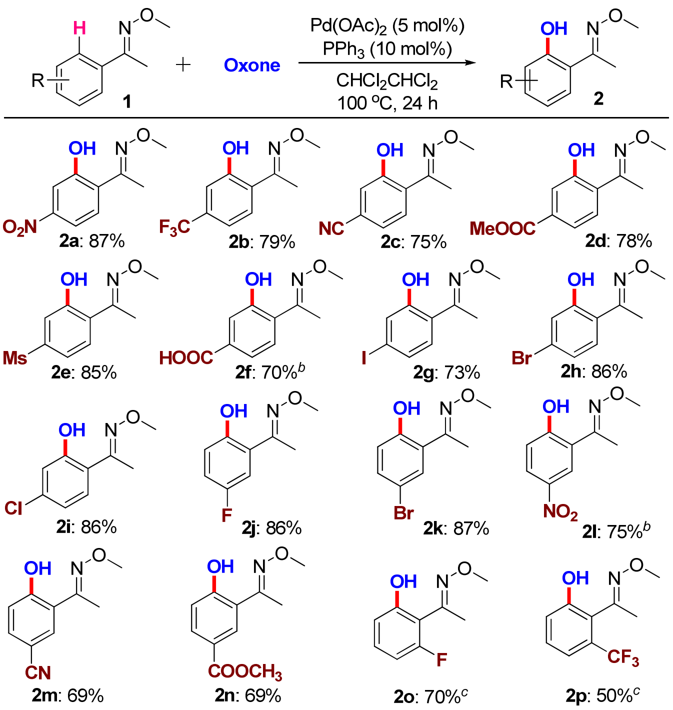
1a **2a**

entry	[Pd]	ligand	oxidant	solvent	yield (%)[b]
1	$Pd(OAc)_2$	–	Oxone	DMF	4
2	$Pd(OAc)_2$	–	Oxone	DCE	14
3	$Pd(OAc)_2$	–	Oxone	TCE	19
4	$Pd(OAc)_2$	PPh_3	Oxone	TCE	87
5	$Pd(OAc)_2$	$POPh_3$	Oxone	TCE	21
6	$Pd(OAc)_2$	DEAD	Oxone	TCE	62
7	$Pd(OAc)_2$	PPh_3	$K_2S_2O_8$	TCE	trace
8	$Pd(OAc)_2$	PPh_3	H_2O_2	TCE	trace
9	$PdCl_2$	PPh_3	Oxone	TCE	32
10	$PdTFA_2$	PPh_3	Oxone	TCE	48
11	Pd_2dba_3	PPh_3	Oxone	TCE	50
12	--	PPh_3	Oxone	TCE	0
13	$Pd(OAc)_2$	PPh_3	--	TCE	0

[a]Standard conditions: **1a** (0.3 mmol), [Pd] (5 mol%), ligand (10 mol%), oxidant (1.2 equiv), solvent (1 mL) was stirred at 100 °C for 24 h under air. [b]Isolated yields. TCE = $CHCl_2CHCl_2$.

With our continuous interest the oxidative hydroxylation of C-H bonds,[16] we initially tried to investigate the direct hydroxylation of the corresponding *O*-methyl oxime derivative of 4-nitroacetophenone (Table 1), which could not be hydroxylated in previous methods.[8,10,12,13] To our delight, when **1a** was stirred in DMF in the presence of $Pd(OAc)_2$, the hydroxylated product **2a** was obtained although in low yield (entry 1). Solvent screening showed that $CHCl_2CHCl_2$ was superior to CH_3CN, DCE, and PhCl (entries 2-3, also see SI). It is noteworthy that significant improvement was achieved when PPh_3 was employed as ligand (87% yield, entry 4).[17] Since the phosphine compound could be oxidized to phosphine oxide in oxidative conditions, in contrast, the reaction proceeded sluggishly when $POPh_3$ was used as ligand, which indicated the active ligand was PPh_3 itself not its oxide $POPh_3$ (entry 5). But it should be mentioned that there were lots of PPh_3 was oxidized to $POPh_3$ after the reaction (see SI). However, the use of 2,2'-bipyridine or 1,10-phenanthroline did not work (see SI). Interestingly, diethyl azodicarboxylate (DEAD) could also be an efficient ligand with a slightly low efficiency (entry 6). On the contrary, other oxidants such as $K_2S_2O_8$, TBHP, H_2O_2, as well as O_2 were found to be ineffective (entries 7-8, also see SI). Some other Pd catalysts were tested in the reaction as well, such as $PdCl_2$, $PdTFA_2$, and Pd_2dba_3, but were less efficient than $Pd(OAc)_2$ (entries 9-11). Clearly, product **2a** was not generated in the absence of a palladium catalyst or an oxidant (entries 12-13).

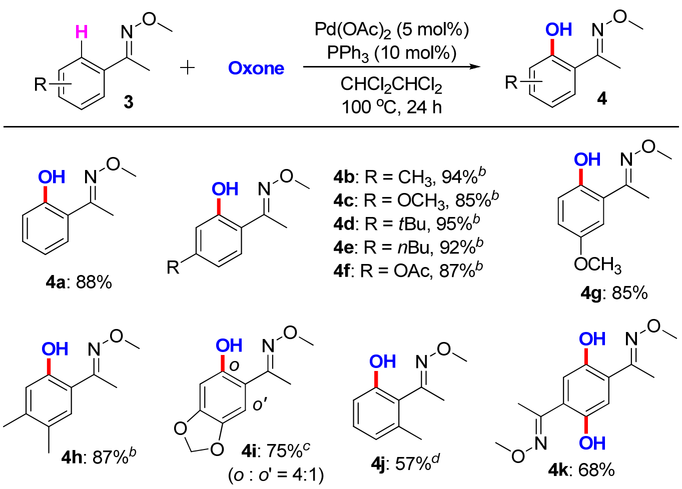
Table 2. C-H Hydroxylation of Electron-deficient Acetophenone Oxime Ethers[a]



[a]Reaction conditions: **1** (0.3 mmol), $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%), Oxone (1.2 equiv), $CHCl_2CHCl_2$ (1 mL) was stirred at 100 °C for 24 h under air. Isolated yield. [b]With 10 mol% of $Pd(OAc)_2$ and 20 mol% of PPh_3. [c]With 10 mol% of $Pd(OAc)_2$ and 20 mol% of DEAD.

With these optimized conditions in hand, we were extremely interested in the present transformation with electron-deficient substrates (Table 2). Significantly, the hydroxylation of substrates with electron-withdrawing substituents, such as NO_2, CF_3, CN, $COOCH_3$, Ms, and COOH, was very efficient and produced high yields of corresponding products (**2a**-**2f**), which demonstrates a good complementary to previous hydroxylation methods.[8,10,12,13] Moreover, the halogen substituents were well tolerated under the oxidizing reaction conditions (**2g**-**2k**). The *meta*-substituted substrates afforded the less sterically crowded isomers (**2l**-**2n**). The *ortho*-substituted acetophenone oxime ethers resulted in trace amount of products by using PPh_3 as ligand, which was likely due to steric congestion between the directing group and the *ortho* substituent. To our delight, the efficiency could be significant improved by the use of DEAD as additive (**2o** and **2p**).[18,19]

Table 3. C-H Hydroxylation of Electron-neutral and Electron-rich Acetophenone Oxime Ethers[a]

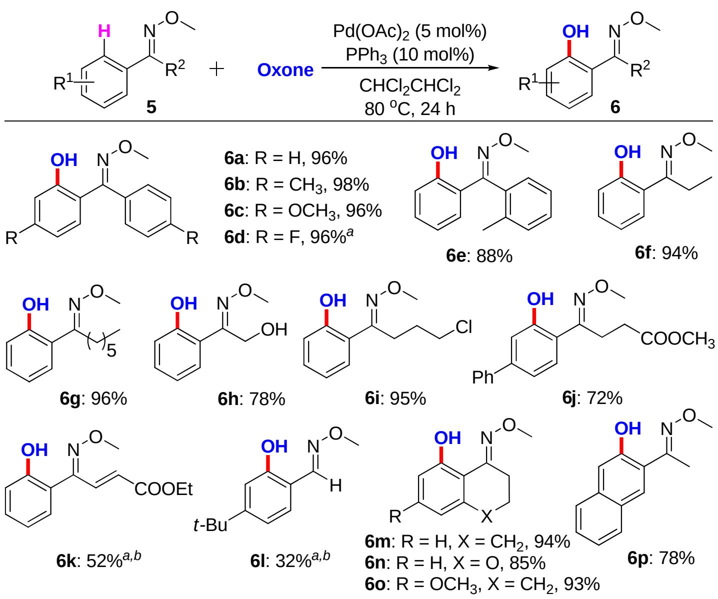


[a]Reaction conditions: **3** (0.3 mmol), $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%), Oxone (1.2 equiv), $CHCl_2CHCl_2$ (1 mL) was stirred at 100 °C for 24 h under air. Isolated yield. [b]At 80 °C. [c]With 10 mol% of $Pd(OAc)_2$ and 20 mol% of PPh_3. [d]With 10 mol% of $Pd(OAc)_2$ and 20 mol% of DEAD.

Furthermore, a variety of electron-neutral and electron-rich acetophenone oxime ethers were readily converted to the corresponding products (**4a-4j**) in excellent yields (Table 3). Substrate containing two oxime ether directing groups could afford product (**4k**) with two OH groups.

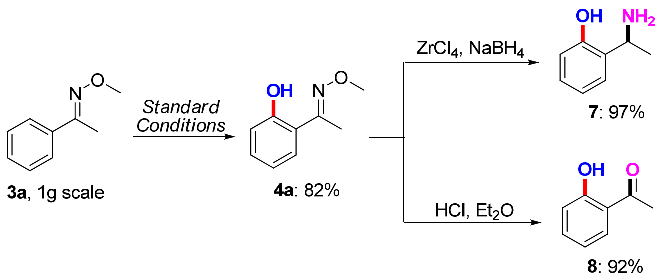
In addition, the different *O*-methyl oximes as substrates were also tested (Table 4). Interestingly, in contrast to previous work which afforded a mixture of products in many examples,[8-13] the reactions highly selectively generated monohydroxylated products (**6a-6g**) without the detection of dihydroxylated products or C(sp^3)-H functionalized products. It is noteworthy that the OH, Cl, COOEt and acrylic ester groups were well compatible (**6h-6k**). Interestingly, the hydroxylation of 4-*tert*-butylbenzaldehyde *O*-methyl oxime could also proceeded although gave the hydroxylated product in relative low yield (**6l**). Moreover, the cyclic *O*-methyl oximes can be tolerated in this transformation to produce desired products in excellent yields (**6m-6o**). The reaction of 2-acetonaphthone *O*-methyl oxime generated the β'-hydroxylated product (**6p**).

Table 4. Substrate Scope of Different *O*-methyl Oximes



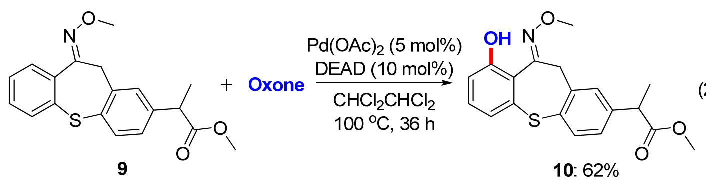
[a] At 100 °C. [b]With 10 mol% of $Pd(OAc)_2$ and 20 mol% of PPh_3.

Notably, this hydroxylation process with Oxone is extremely attractive because it can be easily performed in gram-scale [eq. (1)], which shows great potential for further applications. The oxime group could be easily reduced to amino group by $ZrCl_4$ and $NaBH_4$ to afford *ortho*-aminomethylphenol **7**. And the removal of the directing group to afford *ortho*-acylphenol **8** was also easily achieved by the treatment with HCl in Et_2O [eq. (1)].



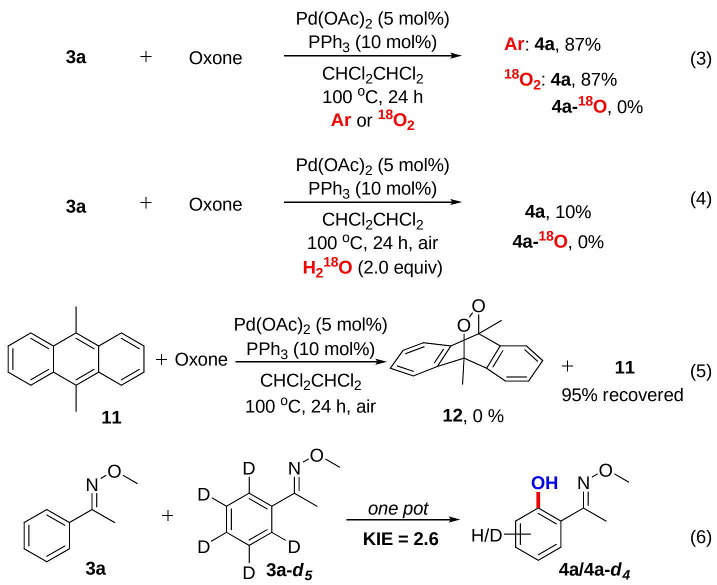
(1)

In order to demonstrate the synthetic utility of this C-H hydroxylation reaction to complex bioactive molecules, zaltoprofen (a nonsteroidal anti-inflammatory drug) *O*-methyl oxime methyl ester derivative **9** was conducted under the hydroxylation conditions with DEAD as ligand.[20] We successfully isolated the hydroxylated product **10** in 62% yield [eq. (2)], which can offer a novel protocol for the synthesis of zaltoprofen analogues. The thioether moiety was well compatible with this C-H hydroxylation process.



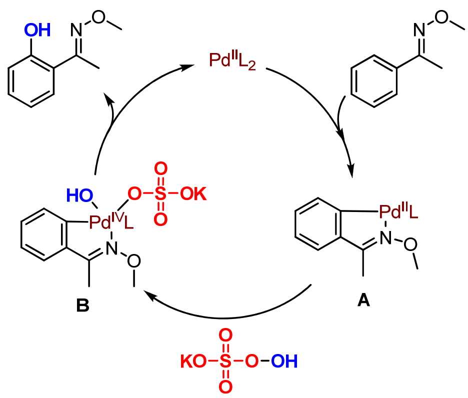
(2)

To further probe the reaction mechanism, some control experiments were investigated. Firstly, the reaction proceeded well under Ar or $^{18}O_2$ atmosphere instead of air and none of ^{18}O-labled product was detected [eq. (3)]. When $H_2{}^{18}O$ (2.0 equiv) was added into the reaction, the yield was significant decreased without the detection of **4a**-^{18}O [eq. (4)], which excludes the possibilities of the oxygen atom in the produced hydroxyl group generated from O_2 in air or water in the solvent. These results suggest that the additional oxygen atom in product originated from Oxone. No superoxide radical or hydroxyl radical signal was observed when this reaction was detected in situ by EPR (electron paramagnetic resonance) (see SI). In addition, it is well recognized that Oxone could generate singlet oxygen,[21] which would be the species responsible for this oxidative hydroxylation. However, the trapping experiment with 9,10-dimethylanthracene **11** under the standard conditions did not afford the endoperoxide product **12** formed through [4+2] cycloaddition involving $^1O_2$ [eq. (5)],[22] which indicated that the $^1O_2$ was not produced in this transformation. Furthermore, the intermolecular k_H/k_D of **3a** was determined to be 2.6 [eq. (6)], which indicated that the C-H activation process should be irreversible.



On the basis of above results, although the mechanism is not completely clear yet, a catalytic cycle of the present Pd^{II}-catalyzed direct C-H hydroxylation is tentatively illustrated in Scheme 2.

Initially, the active $Pd^{II}L_2$ catalyst is generated from the combination of Pd^{II} salt and ligand, followed by coordination of the N atom of oxime ether to Pd^{II} and the subsequent C-H activation produces intermediate **A**. Then the oxidation of the intermediate **A** by potassium peroxymonosulphate ($KOSO_2OOH$), the active ingredient of Oxone, affords a Pd^{IV} intermediate **B**, which finally, undergoes reductive elimination to form the desired hydroxylated product with the regeneration of Pd^{II}-catalyst. The important role of ligand may accelerate the C-O bond reductive elimination step. Alternatively, the Pd^0/Pd^{II} catalytic cycle could not be excluded.



Scheme 2. Proposed Reaction Mechanism

In summary, we have developed an efficient ligand promoted Pd-catalyzed oxime ether directed *ortho* C-H hydroxylation of arenes using Oxone as oxidant. The protocol features an ample substrate scope particularly for the challenging electron-deficient substrates. The highly selective mono-hydroxylated products were obtained in high efficiencies. Deep studies into the detailed reaction mechanism and further application are ongoing in our laboratory.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, analytical data for products, NMR spectra of products. 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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