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To be cited as: *ChemCatChem* 10.1002/cctc.201800064

Link to VoR: http://dx.doi.org/10.1002/cctc.201800064

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Direct C(sp2)-H Hydroxylation of Arene with Pd(II)/O_2 Using Sulfoximine as Recyclable Directing Group

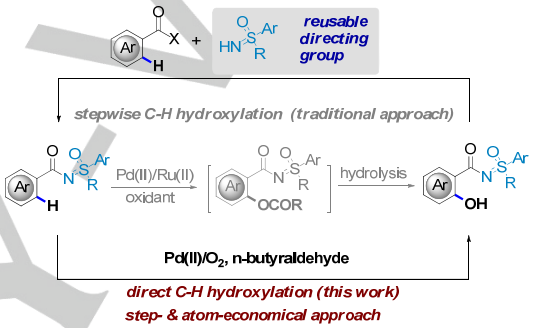
Prasenjit Das and Joyram Guin*[a]

Abstract: The aerobic palladium(II) catalysis presented herein offers facile entry to various substituted phenols through site selective C-H hydroxylation of arenes using sulfoximine as reusable directing group. Notable aspects of our method include: a) the use of molecular oxygen (O_2) as a sole oxidant, b) the activation of molecular oxygen via aldehyde auto-oxidation, c) operational simplicity and d) the mechanistic studies into the catalytic C-H hydroxylation process.

The catalytic methods that allow selective conversion of unactivated arene C-H bond to C-O bond are deemed as the most straightforward approach to substituted phenols.[1] As a result, numerous elegant transition metal catalytic processes for the direct C-H hydroxylation of arenes have been developed.[1c, 2] Among them, the oxidative palladium catalysis involving Pd^{II}/Pd^{IV} catalytic cycle receives significant attraction recently.[3] However, this catalytic C-H hydroxylation strategy requires the use of an excess amount of chemical oxidant like oxone, $K_2S_2O_8$, peroxide, BQ, DDQ, PIDA and others.[3] In view of the increasing demand toward green and sustainable chemical process, the use of molecular oxygen (O_2) as an oxidant is becoming increasily important for organic synthesis.[4] As a result, the development of an efficient palladium catalysis toward direct C-H hydroxylation of arenes employing O_2 as the sole oxidant would be highly attractive.

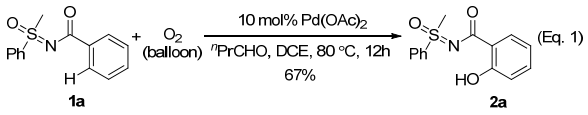
Although the production of substituted phenol using Pd(II)/O_2 catalytic system has been reported, the existing methods require harsh reaction conditions,[5] additional oxidant and base[6] or pyridine based directing group along with co-catalyst.[7] Recently, our group has introduced a novel C-H hydroxylation of 2-arylpyridines with O_2 by simultaneous co-operation of aldehyde auto-oxidation with palladium catalysis.[8] However, the use of non-removable and non-modifiable pyridine moiety as directing group has limited its application. We thus became interested in expanding scope of the novel aerobic C-H hydroxylation method with easily removable and reusable directing group.[9] Along this line, we have examined different directing groups like benzamide, 2-amino pyridine, 8-amino quinoline, oxime, 2-amino pyrimidine, azo compound and sulfoximine amide in the catalytic aerobic C-H hydroxylation process. Among the different directing groups tested, the *N*-sulfoximine benzamide found to be the most promising candidate (See Supporting Information).

Recently, sulfoximine has been introduced as an effective and reusable directing group for the catalytic functionalization of unactivated C-H bonds.[10] Despite these advancements, the installation of free hydroxyl group at arene C-H bond of sulfoximine amide has been realized *via* a two-step reaction procedure involving catalytic C-H acetoxy/benzoyloxylation followed by hydrolysis of the ester functional group.[11] As a result, the direct C-H hydroxylation of sulfoximine amides, which would improve step- and atom-economy of the process, remains challenging. Herein, we present Pd(II)-catalyzed direct C-H hydroxylation of various *N*-sulfoximine amides using O_2. In this protocol, O_2 plays a dual role as a green oxidant for Pd-catalysis and as oxygen source for the hydroxyl group (Scheme 1).



Scheme 1. Different strategies for the synthesis of hydroxylated *N*-sulfoximine amides.

Being inspired by our earlier work on the aerobic functionalization of unactivated C-H bonds,[12] we commenced our studies by investigating the direct C-H hydroxylation of *N*-sulfoximine benzamide **1a** using Pd(II)-catalyst in the presence of an aldehyde under O_2 atmosphere. By performing the reaction with **1a** using 10 equiv. of *n*-butyraldehyde and 10 mol% of $Pd(OAc)_2$ in DCE at 80 °C under O_2 atmosphere, the desired phenol **2a** was isolated in 67% yield (Eq. 1) (See Supporting Information).



After identifying the optimal reaction conditions for the aerobic C-H hydroxylation process, we decided to explore the scope of the reaction with diversely decorated sulfoximine amides (Table 1). Accordingly, we first tested different substrates with varying substituent on the aromatic ring of the benzamide unit. Substrates having benzamide as well as its *ortho*, *meta*, and *para* alkyl derivatives were converted to the corresponding *ortho*-hydroxylated products **2a-e** in good yields (53-73%). Likewise, the reaction proceeded well with sulfoximine amides bearing methoxy (**2f** and **2g**), benzyloxy (**2h**), *O*-phenyl (**2i**), *NH*-acetyl (**2j**) and *O*-acetyl (**2k**) functional groups at 3- or 4-position of the benzamide unit. Substrates containing electron

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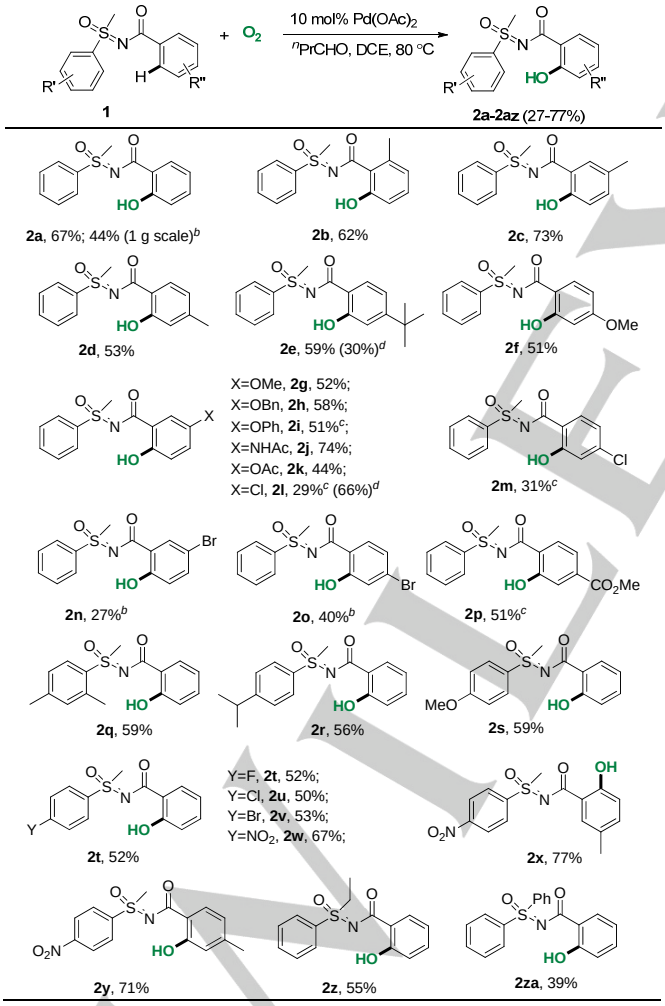
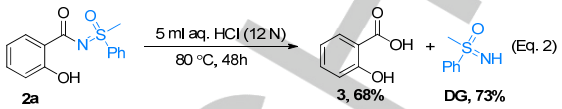
deficient chloro, bromo, and ester groups at benzoyl moiety were transformed to the corresponding products **2l-p** with this simple hydroxylation protocol, albeit with slightly low yield of the desired products. Further substrate scope studies were carried out with varying substituent in both the aromatic rings of sulfoximine amide (Table 1). Amides bearing di-methyl and *iso*-propyl substituents on the sulfoximine aromatic ring exhibited good reactivity (products **2q** and **2r**). The reaction showed no considerable electronic effect on yields of the hydroxylated products **2s-y** when electronic property of the aromatic rings of sulfoximine units were altered by changing substituent from electron rich (OMe) to electron deficient (F, Cl, Br, NO_2) functional groups. The reaction furnished good yield with ethyl substituted sulfoximine benzamide (product **2z**). However, slightly low yield of the hydroxylated product **2za** was obtained with diphenyl sulfoximine benzamide presumably due to steric reason. Notably, the reaction neither furnished C-H hydroxylation of sulfoximine benzene ring nor bis-hydroxylated product under the optimized reaction conditions.

Table 1. Substrate scope.

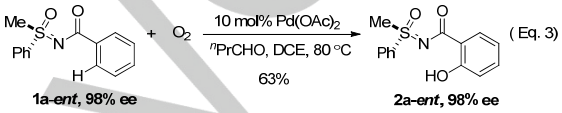


[a] Reaction conditions: sulfoximine amides (1.0 equiv), aldehyde (10-15 equiv), $Pd(OAc)_2$ (10 mol%) and DCE (0.1 M) at 80 °C for 24 h under O_2. [b] Performed using 1g of substrate. [c] Run for 36 h. [d] Recovered starting material.

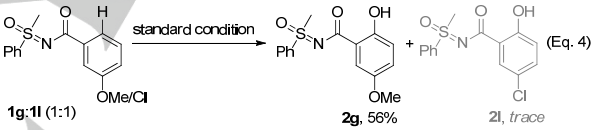
The synthetic usefulness of the method was demonstrated by the preparation of salicylic acid **3** in 68% yield via facile exclusion of the sulfoximine auxiliary from the product **2a** in a traceless manner (Eq. 2). It is important to note that, unlike other *N*-directing group, the sulfoximine can be recycled easily in this hydroxylation process.



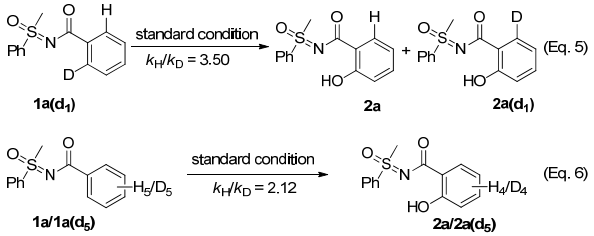
The aerobic direct C-H hydroxylation process was then tested to enantioenriched *N*-sulfoximine amide **1a-*ent*.** As expected, the reaction afforded the hydroxylated product **2a-*ent*** with complete conservation of chirality (Eq. 3).



To get insight into the reaction mechanism of the catalytic C-H hydroxylation process, a series of control experiments were carried out. Intermolecular competition experiment between electronically non-equivalent substrates resulted in preferentially C-H hydroxylation of electron rich substrate over the electron deficient *N*-sulfoximine amide (Eq. 4). Likewise, difference in



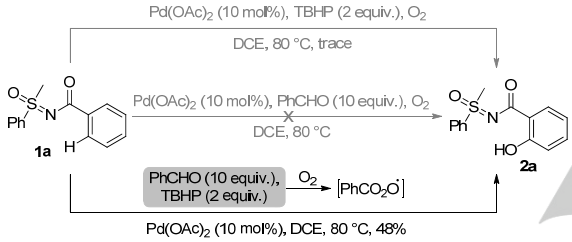
reaction rate of the hydroxylation process was realized by conducting the reaction using *N*-sulfoximine amide **1a** and its deuterated analogue. When the hydroxylation reaction was studied using substrates **1a** and **1a**($\mathbf{d_5}$) separately, otherwise identical reaction conditions, the substrate with perdeuterated benzamide moiety was sluggishly transformed to the corresponding product. In line with this observation, the intra- as well as intermolecular kinetic isotope effect (KIE) experiments revealed k_H/k_D = 3.50 for intramolecular study (Eq. 5) and k_H/k_D = 2.12 for intermolecular study (Eq. 6). These results may indicate that an intramolecular C–H metalation step is involved that could also be the rate-limiting step of the process.[13]



We then performed the reaction using stoichiometric amount of various chemical oxidants such as H_2O_2, *m*-CPBA, oxone and $(NH_4)_2S_2O_8$ that are often used in Pd(II)-catalyzed C-H hydroxylation process under anaerobic condition.[3] To our

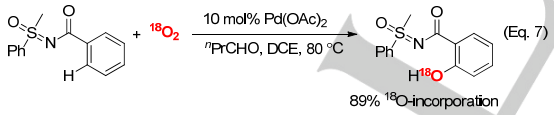
surprise, none of them afforded desired hydroxylated product with *N*-sulfoximine benzamide **1a**. The reaction also did not give any hydroxylated product in the absence of either aldehyde or O_2. Additionally, only trace amount of the product **2a** was obtained with air. These observations suggest that both O_2 and *n*-butyraldehyde are essential for the success of the aerobic C-H hydroxylation process (See Supporting Information).

Further mechanistic studies revealed that the reaction was ineffective with either benzaldehyde or TBHP alone under O_2 atmosphere(Scheme 2). Interestingly, by repeating the same experiment in the presence of both the reagents afforded the product **2a** in 45% yield. These results indicate that benzoylperoxy radical, which is known to form by the reaction of TBHP and benzaldehyde in the presence of O_2, could promote the reaction.[14] In accordance with this observation, we proposed that the acylperoxy radical generated in situ during auto-oxidation of aldehyde[15] could be a key reactive intermediate for the aerobic hydroxylation process. Furthermore, the reaction was inhibited in the presence of a radical scavenger like TEMPO. This observation may lead to the involvement of radical intermediate in this process.

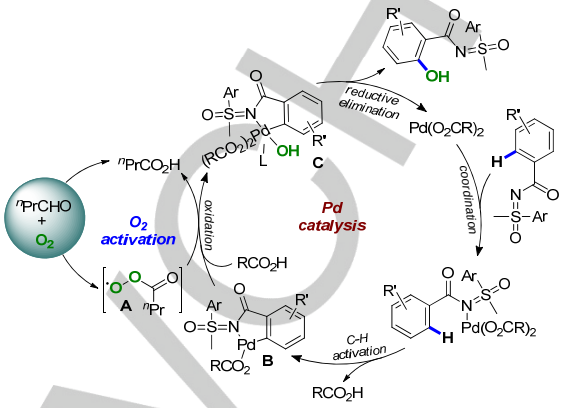


Scheme 2. Control experiments.

Finally, ^{18}O labeling experiment proved that the oxygen atom of the hydroxyl group is indeed originated from molecular oxygen (Eq. 7), as hydroxylated product with 89% ^{18}O incorporation was obtained.



Based on the results obtained in our mechanistic studies and the literature reports,[16] a probable reaction mechanism is presented in Scheme 3. We propose that the catalytic cycle begins with the intramolecular sulfoximine assisted ortho C-H palladation of substrate to form the complex **B**. Meanwhile, the aerobic oxidation of aldehyde produces an active acylperoxy radical intermediate **A**. The association of the radical **A** with the complex **B** followed by single electron oxidation may lead to a most likely pd^{IV}-intermediate **C**. The reductive elimination via putative pd^{IV}-species is expected to provide the desired hydroxylated product and regenerate the Pd(II)-biscarboxylate catalyst. Alternatively, the involvement of a binuclear Pd^{II}/Pd^{III} catalytic cycle for the reaction cannot be excluded at this point.[17] Additional mechanistic investigation would be required to gain better inside of the reaction mechanism. The formation of butyric acid was confirmed by GC/MS analysis. It is important to mention that dioxygen activation via auto-oxidation of aldehyde is an independent process. Furthermore, the in situ generated acylperoxy radical **A** is highly reactive species, which is known to decompose to the corresponding carboxylic acid through alternative reaction pathway.[15] As a result, slight excess of aldehyde was required to achieve good yield of the desired hydroxylated product.



Scheme 3. Proposed reaction mechanism.

In summary, the first aerobic direct C-H hydroxylation of arene using sulfoximine as reusable directing group with Pd-catalysis is described. Abundant, safe and environmentally benign molecular oxygen (O_2) is used as the sole oxidant for the catalytic process to afford various hydroxylated products in good yields and functional group tolerance. Based on our mechanistic studies, a cooperative mechanism between Pd(II)-catalysis and aldehyde auto-oxidation is implicated for the hydroxylation process. Our ongoing research in this area directs to expand the scope and to study further mechanism investigations of this aerobic hydroxylation reaction.

Experimental Section

Experimental details such as synthesis, control experiment and spectroscopy can be found in supporting information.

Acknowledgements

We gratefully acknowledge the generous financial support from Science and Engineering Research Board, India (EMR/2016/006344) and CSIR for fellowship to PD.

Keywords: C-H hydroxylation • Pd-catalysis • sulfoximine • molecular oxygen • aerobic oxidation

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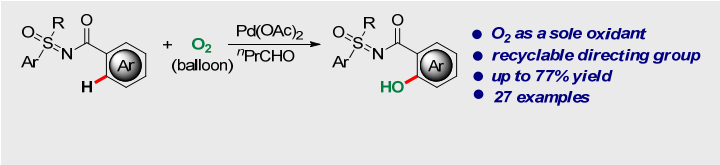

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