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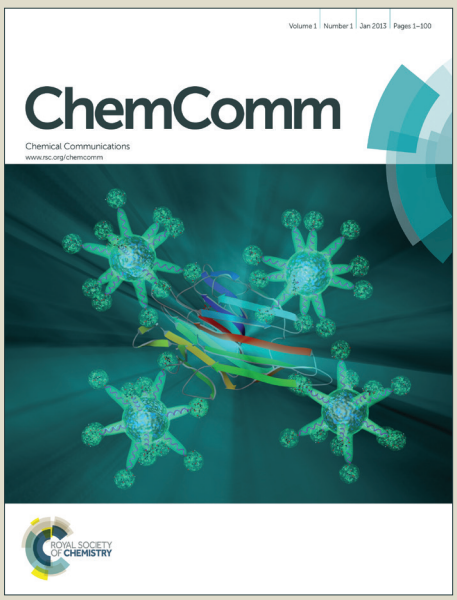

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Palladium Catalyzed C_{sp2}-H Activation for Direct Aryl Hydroxylation: Unprecedented Role of 1,4-Dioxane as Source of Hydroxyl Radical

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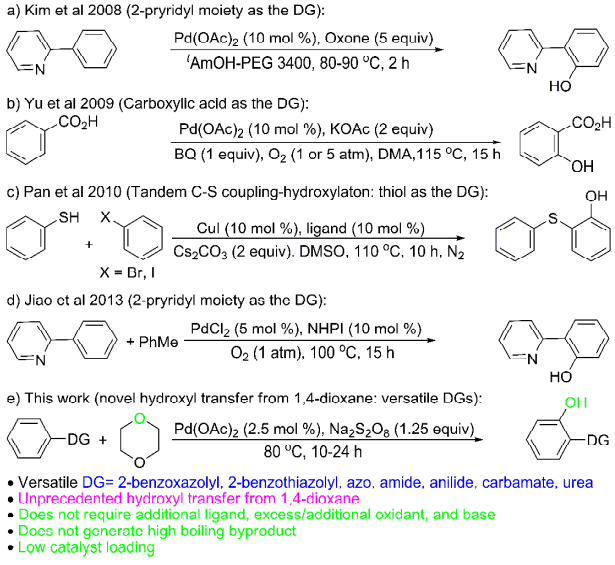
A novel strategy for direct aryl hydroxylation by Pd-catalysed C_{sp2}-H activation through an unprecedented hydroxyl radical transfer from 1,4-dioxane, used as solvent, is reported with bio relevant and sterically hindered heterocycles and various acyclic functionalities as versatile directing groups.

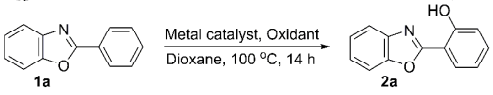
The wide occurrence of hydroxylated aromatics (phenols) in bioactive compounds[1] makes them highly sought for synthetic targets. Aryl hydroxylation through C-H activation has emerged as new synthetic route to phenols.[2] However, these represent indirect hydroxylation as the reaction proceeds via the intermediate formation of the acyloxy arenes that are converted to the hydroxyaromatics during the workup or on further hydrolytic transformation.[3] The issue on direct aryl hydroxylation remains inadequately addressed (Scheme 1).[4]



Scheme 1. Different strategies for direct aryl hydroxylation.

Fujiwara *et al*[4a] revealed the feasibility of direct aryl hydroxylation but the low yield (~5%) and turnover ratio (10-15 to Pd), poor selectivity, and harsh reaction conditions (15 atm O_2, 15 atm CO, 180 °C, AcOH) do not make it attractive. The strategy of Kim *et al*[4b] on the use of 2-pyridyl moiety as the directing group (DG) for C_{sp2}-H activation though affords good yields requires excess oxidant (5 equiv), is applicable to highly substituted DG (2-pyridyl), and does not work with aryl moiety bearing *o*-substitution. The use of carboxylic acid as DG by Yu *et al*[4c] requires excess of base, benzoquinone as additional oxidant (in addition to O_2 at 1-5 atm), and leads to decarboxylation (e.g. 1-naphthoic acid). The tandem C-S coupling-hydroxylation strategy of Pan *et al*[4d] requires special ligand, excess of base, and aryl bromide/iodide as the reaction partner (additional reagent). The recent report on 2-pyridyl directed C_{sp2}-H activation by Jiao *et al*,[4e] though circumvents the limitations of the protocol of Kim *et al*,[4b] requires *N*-hydroxyphthalimide (NHPI) and toluene as additional reagent system (in addition to O_2 at 1 atm) to form benzyl radical that acts as the effective agent/species for hydroxyl radical generation and leads to the formation of high boiling by-products (benzaldehyde/benzoic acid).

Functionalised 2-(benzoxazol-2-yl)phenols have diverse biological activities.[5] Thus, it would be attractive to use the 2-benzoxazolyl scaffold as the DG for C_{sp2}-H activation for direct aryl hydroxylation to further potentiate their biological activity[6] and as there is no report on direct aryl hydroxylation with 2-benzoxazolyl moiety as the DG. 2-Phenylbenzoxazole (**1a**)[7] was considered as model substrate for oxidative hydroxylation via aryl C_{sp2}-H activation under various conditions (Scheme 2).



Scheme 2. Direct hydroxylation of **1a** to form **2a**.

It appears that the limited reports on direct hydroxylation involve the generation of oxygen/hydroxyl radical[4b-d] that adds on to the metal centre at its higher oxidation state in the

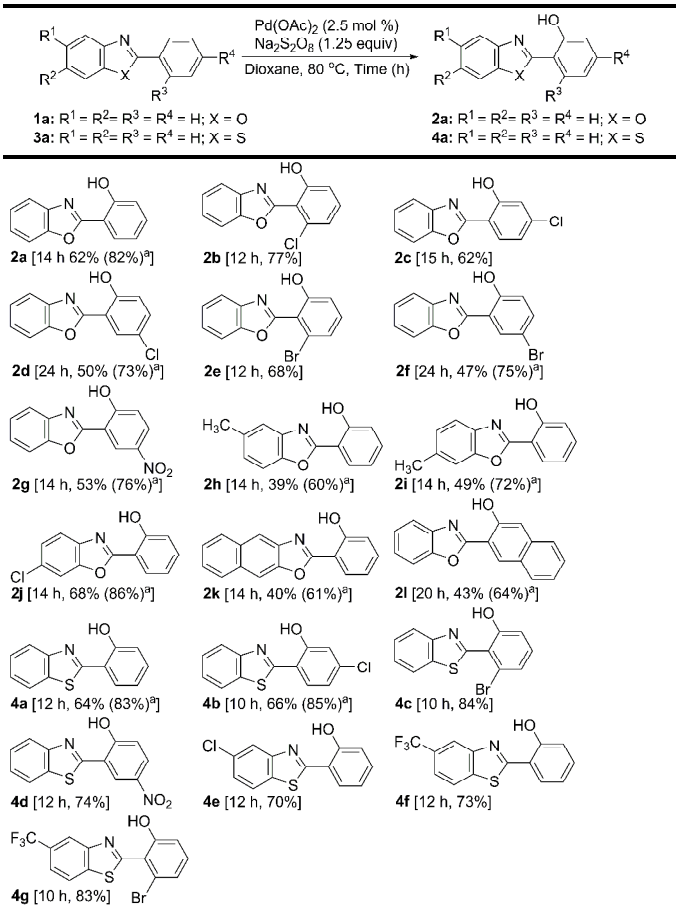
cyclometallated intermediate and acts as the effective species for C-O bond formation. 1,4-Dioxane is reported to generate hydroxyl radical on pyrolysis.[8] However, high temperature (1550-2100 K) is required to generate the hydroxyl radical by ring opening (homolytic C-O cleavage), isomerisation, and dissociation of the resulting linear species. We reasoned that the hydroxyl radical generation from 1,4-dioxane may be achieved under milder condition in the presence of an oxidant that would abstract H from 1,4-dioxane and facilitate its dissociation via ring opening C-O cleavage involving free radical mechanism. Thus, it was hypothesised that the use of 1,4-dioxane in combination with persulfate would serve the dual purpose of the reaction medium and the oxo/hydroxyl transfer agent without the requirement of any additional oxidant/reactant and base.

Treatment of **1a** with different variation of the reaction parameters (ESI: Tables 1A-1E)† revealed the use of $Pd(OAc)_2$ (2.5 mol%) and $Na_2S_2O_8$ (1.25 equiv) in 1,4-dioxane at 80 °C for 14 h to be the best operative reaction condition affording **2a** in 62% yield which could be further improved to 82% after reusing the unreacted **1a** recovered after the first use. The lack of formation of **2a** in any other solvent (ESI: Tables 1D and 1E)† suggested 1,4-dioxane to be the hydroxyl transfer agent as the comparable results with commercial grade as well as dry and degassed 1,4-dioxane under N_2 or O_2 eliminated the possibility of hydroxyl transfer from any dissolved oxygen/moisture. That the reaction forms the hydroxyarene directly was demonstrated by the fact that **2a** was obtained in comparable yield (64%) avoiding aqueous work up. However, the $Pd(OAc)_2$-catalysed reaction of **1a** with $Na_2S_2O_8$ (1.25 equiv) in HOAc-Ac_2O (1:1) or Ac_2O instead of 1,4-dioxane afforded the *O*-acetylated **2a** following non-aqueous workup in 53 and 55% yields, respectively (ESI: Table 2A).† Thus, the persulfate-dioxane combination constitutes a novel reagent system for Pd-catalysed direct aryl hydroxylation.

Treatment of **1a** under the reported conditions for acetoxylation/hydroxylation and minor variation (using 1,4-dioxane as solvent) did not produce significant amount of **2a** (ESI: Tables 3A and 3B)† and established the distinctiveness of the present work.

The direct hydroxylation protocol is applicable to benzoxazoles bearing substituent in the 2-aryl moiety as well as in the benzenoid ring of the benzoxazole scaffold (Table 1). The applicability of the direct hydroxylation towards various substituted 2-arylbenzothiazoles (Table 1),[9] another bio relevant and sterically hindered DG, demonstrated the versatility with respect to the DG.[10] The presence of Cl, Br, CF_3, and NO_2 in the 2-aryl moiety appears to be beneficial as such substrates afforded the corresponding hydroxyarenes in better yields compared to that of the unsubstituted analogue **1a**/**3a**. The effect of these substituents was more pronounced with 2-benzothiazolyl moiety as the DG. The presence of electron donating substituent such as the Me group decreased the yield.

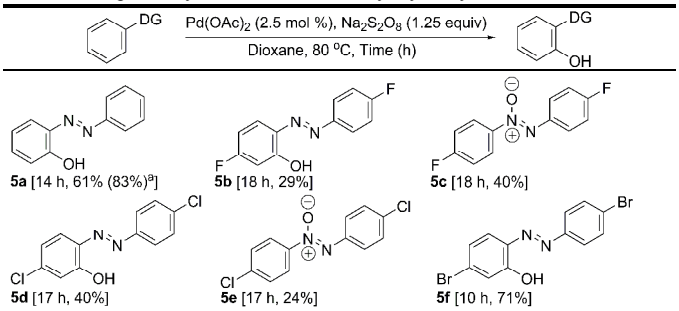
Table 1. Substrate scope for direct aryl hydroxylation via C-H activation with bio relevant and sterically hindered DGs.

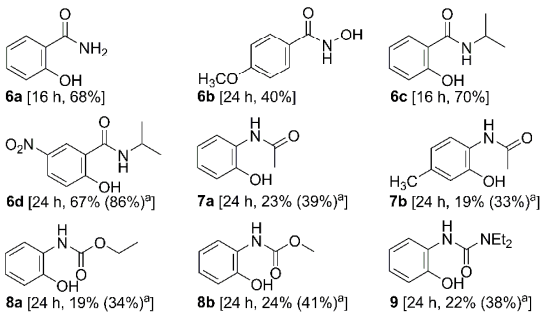


[a]The figure in the parenthesis is the total yield based on recovery and reuse of the unreacted starting material after the first attempt.

The results of Table 2 demonstrate further scope with acyclic DGs such as azo, amide, anilide, carbamate, and unsymmetrical urea. The F and Cl substituted azo benzenes produced the corresponding azoxy-benzene in 40 and 24% yields, respectively, along with the desired hydroxylated products. The chemoselective hydroxylation with substrates bearing halogen provide scope of structural modification through Suzuki coupling[11] to broaden the chemical space. The catalyst [$Pd(OAc)_2$] was recovered and reused for five consecutive reactions affording comparable yields.†

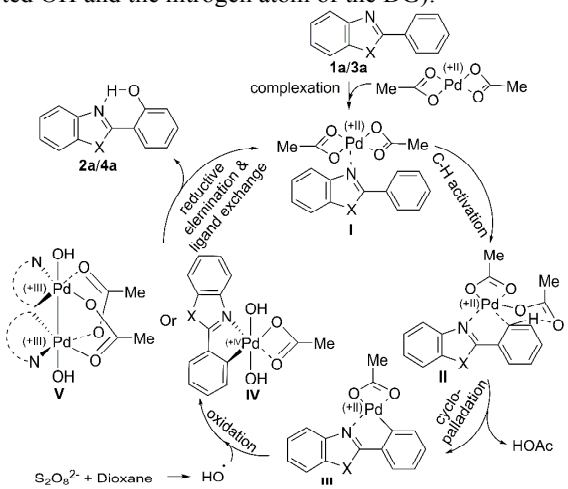
Table 2. Scope of acyclic DGs for direct aryl hydroxylation.





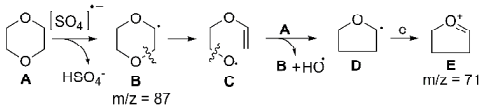
[a]The figure in the parenthesis is the total yield based on recovery and reuse of the unreacted starting material after the first attempt.

A plaussible mechanism is depicted in Scheme 3. The Pd-catalyst forms the complex **I** through coordination with the nitrogen centre of the DG and trigers aryl C_{sp2}-H activation and ligand-assisted intra-molecular aryl proton abstraction in **II** to form the cyclopalladated species **III**. Oxidative addition of the hydroxyl radical, formed by degradation of 1,4-dioxane with the persulfate anion, (Scheme 4) generates the Pd(IV) species **IV**[12] or the Pd^{III}-Pd^{III} species **V**.[13] The aryl C-O bond forming reductive elimination from **IV**/**V** leads to the hydroxyarene (phenol) and brings the Pd(II) compound back to the catalytic cycle to form **I** through ligand exchange (facilitated by intramolecular hydrogen bond formation between the newly inserted OH and the nitrogen atom of the DG).[14]



Scheme 3. Plaussible pathway for the direct aryl hydroxylation.

The generation of hydroxyl radical from $Na_2S_2O_8$ and 1,4-dioxane is visualized in Scheme 4. The sulfate anion radical, generated from persulfate anion,[15] has the ability to abstract C-H hydrogen[15a] and reacts with 1,4-dioxane (**A**) to form the 1,4-dioxan-2yl radical (**B**). Homolytic ring C-O cleavage[8] of **B** produces the radical **C** which on further homolytic C-O cleavage is converted to the tetrahydrofuran-2-yl radical **D**. The liberated oxygen diradical is converted to the hydroxyl radical through H-abstraction from another molecule of 1,4-dioxane generating the radical **B** to propagate the radical chain reaction. The relevant intermediates could be identified in the GC-MS spectra of aliquot samples (withdrawn at an interval of 2 h) of the reaction mixture of 1,4-dioxane and $Na_2S_2O_8$ at 80 °C that showed ion peaks corresponding to **B** (m/z 87) (ESI: 10.2.3) and **D**/**E** (m/z 71) (ESI: 10.2.2) that compared well with the GC-MS and ms^2 (of the ion at m/z 71) spectra of an authentic sample of THF.† Some of the daughter ions observed in the ms^2 of the ion at m/z 71 were also observed in the ms^2 of the ion at m/z 87 (e.g. 70.81 vs. 70.82; 42.93 vs. 42.87) suggesting the ion with m/z 71 to derive from the ion of m/z 87 through loss of active oxygen species. The GC-MS spectra of aliquots of the reaction mixture during the treatment of 2-phenylbenzoxazole (**1a**) with $Na_2S_2O_8$ and 1,4-dioxane at 80 °C revealed the presence of the ion peaks at m/z 87 and 71 corresponding to **B** and **D**/**E**, respectively (ESI:10.5.3 and 10.5.2).†



Scheme 4. Generation of OH radical from 1,4-dioxane and $Na_2S_2O_8$.

The influence of ligand/counter anion on the catalytic potential of the Pd-compounds (ESI: Table 1B)† and the lack of improvement of yield in using NH_4OAc, KOAc and (KOAc + 18-C-6) as external base (ESI: Table 5A)† during the Pd-catalysed reactions implicate that the abstraction of the aryl proton during the C-H activation step occurs via intramolecular process involving **II**. Thus the strong electron withdrawing CF_3 group reduces the HB acceptor property of TFA in $Pd(TFA)_2$[16] making it inferior catalyst compared to $Pd(OAc)_2$. The HB formation ability of the counter anion plays key role in the formation of the reaction intermediate (transition state) in various organic reactions.[17] The importance of the HB has also been realised in forming metal centred transition state.[18]

The involvement of radical species was corroborated by the fact that a drastic decrease in the product (**2a**) yield (17%) was observed in performing the $Pd(OAc)_2$-catalysed reaction of **1a** in the presence of radical scavenger (TEMPO) (ESI: Scheme 5C).† The indispensable role of 1,4-dioxane is reflected in its ability to form radical species in the presence of persulfate[15] or other oxidant.[19]

The present work provides a novel strategy for direct aryl hydroxylation via palladium-catalysed aryl C_{sp2}-H activation with bioactive and sterically hindered heterocylic moieties and other acyclic functionalities (azo, amide, anilide, carbamate, and urea) as versatile directing groups through unprecedented generation of hydroxyl radical, as the effective aryl hydroxylation species, from 1,4-dioxane (used as solvent).

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Notes and references

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† Electronic Supplementary Information (ESI) available: Spectroscopic data of all compounds, scanned spectra of new compounds. See DOI: 10.1039/b000000x/

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