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Catalytic *Ortho*-Acetoxylation of Masked Benzyl Alcohols via an *Exo*-Directing Mode

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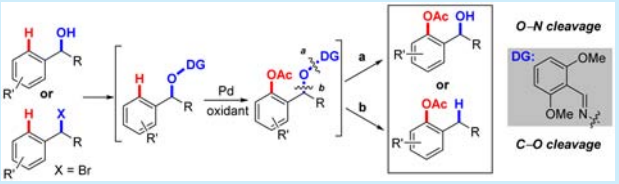
Supporting Information

ABSTRACT: A Pd-catalyzed *ortho*-acetoxylation of masked benzyl alcohols to synthesize various 2-hydroxyalkylphenol derivatives is reported. The 2,6-dimethoxyl benzaldoxime proved to be an efficient *exo*-type directing group for arene (sp^2) C−H functionalization. Two strategies were demonstrated to remove the directing group through N−O and C−O bond cleavages. A high catalyst turnover (>1000) was obtained to illustrate the practicality of this method.

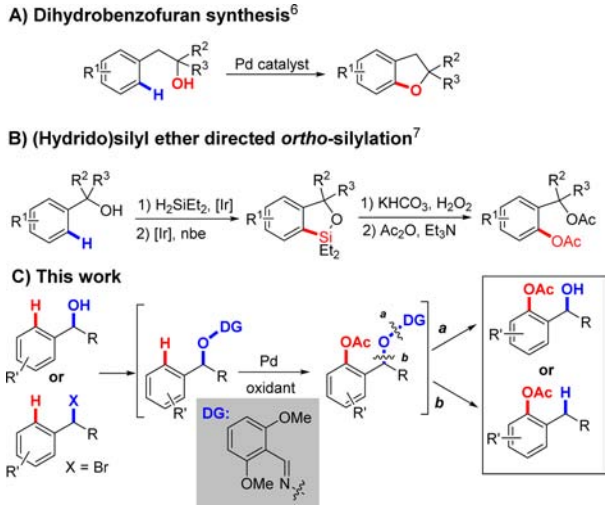


The directing group (DG)-based strategies have been serving as a reliable approach for controlling site selectivity for carbon−hydrogen bond (C−H) functionalization.[1] From a practical viewpoint, an attractive direction is the use of a removable[2] (or temporary[3]) functional group (FG) as DGs, or developing reactions with DGs incorporated as a part of the target molecules. Given the prevalence of hydroxyl group in organic molecules, the use of alcohols or masked alcohols as DGs constitutes a significant interest in transition metal (TM)-catalyzed C−H functionalization.[4] While substantial progress has been made in this area, it is still challenging to develop alcohol or masked alcohol-directed *C−H oxidation* reactions, e.g. C−X (X ≠ C) formation, due to the lability of free alcohols under oxidative conditions and the difficulty of discovering suitable alcohol-based DGs.

In particular, while *ortho*-oxidation of arenes can be achieved using various DGs,[5] only a few examples use free or masked alcohols. In 2008, Yu reported a free alcohol-directed intramolecular C−H cyclization to synthesize dihydrobenzofurans (Scheme 1A).[6] While tertiary alcohol substrates proved to be highly efficient, use of a secondary alcohol leads to a much lower yield. Later, Hartwig and co-workers employed an Ir-catalyzed tandem process, namely O−H/C−H silylation, and developed an elegant *ortho*-silylation protocol (Scheme 1B).[7] A separate Tamao−Fleming oxidation was subsequently conducted to oxidize the C−Si bond into a C−O bond. Herein, we describe a Pd-catalyzed masked benzyl alcohol directed arene *ortho*-acetoxylation method, in which oxime can be used as a removable or traceless DG (Scheme 1C).[8] This method provides a rapid access to various 2-hydroxyalkyl phenol derivatives, a moiety widely found in many bioactive compounds, e.g. salbutamol (for treating asthma) and simocyclinone D8 (antibiotic).[9]

While oxime has been known to be a good ligand for TMs since 1970,[10] Sanford and co-workers developed the first oxime-directed catalytic sp^3 and sp^2 C−H activation reactions.[11]

Scheme 1. Alcohol or Masked Alcohol-Directed Arene C−H Oxidation



In particular, when comparing the directing ability among various FGs, they disclosed a single but seminal example of 2-heptanone oxime-directed *ortho*-arene oxidation, albeit with a moderate yield.[12] Recently, we developed an efficient alcohol *β*-oxidation method through catalytic activation of an sp^3 C−H bond, whereas the use of a 2,6-dimethoxylbenzaldoxime as the DG was found crucial.[13] We hypothesized that use of this special aldoxime DG should also be advantageous for the arene C−H oxidation, because (1) it would prevent undesired oxidation on the DG, for the ketoximes would have acidic *α*-hydrogens that are susceptible to be oxidized under strong oxidative conditions,[14] and (2) the methoxy groups on the DG

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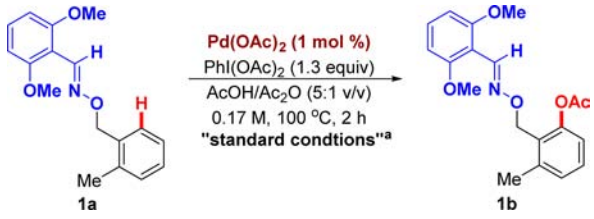
could enhance the catalyst stability during the catalytic cycle through a weak chelation effect (*vide infra*, X-ray obtained, Scheme 5), leading to a high catalyst turnover (TON> 1000).

To test our hypothesis, substrate **1a** was used as the initial substrate. After a careful optimization, the desired *ortho*-acetoxylated product (**1b**) was isolated within 2 h in 87% yield, when using 1 mol % $Pd(OAc)_2$ as the catalyst and 1.3 equiv of $PhI(OAc)_2$ as the oxidant in $AcOH/Ac_2O$ (5:1) at 100 °C (Table 1). A number of control experiments were conducted to

Table 1. Selected Optimization of Reaction Conditions[a]



entry	variation from the "standard conditions"	yield[b,c]
1	none	87%[d]
2	no $Pd(OAc)_2$	0%
3	no $PhI(OAc)_2$	0%
4	$Pd(OAc)_2$ (10 mol %)	68%
5	no Ac_2O	61%
6	$Co(OAc)_2$ (10 mol %) instead of $Pd(OAc)_2$	0%
7	AgOAc (10 mol %) instead of $Pd(OAc)_2$	0%
8	$K_2S_2O_8$ instead of $PhI(OAc)_2$	30%
9	$K_2S_2O_8$ (2 equiv) and $PhI(OAc)_2$ (10 mol %)	79%
10	$K_2S_2O_8$ (2 equiv) and PhI (10 mol %)	72%
11	$K_2S_2O_8$ (2.5 equiv) and $PhI(OAc)_2$ (10 mol %)	85%[d]

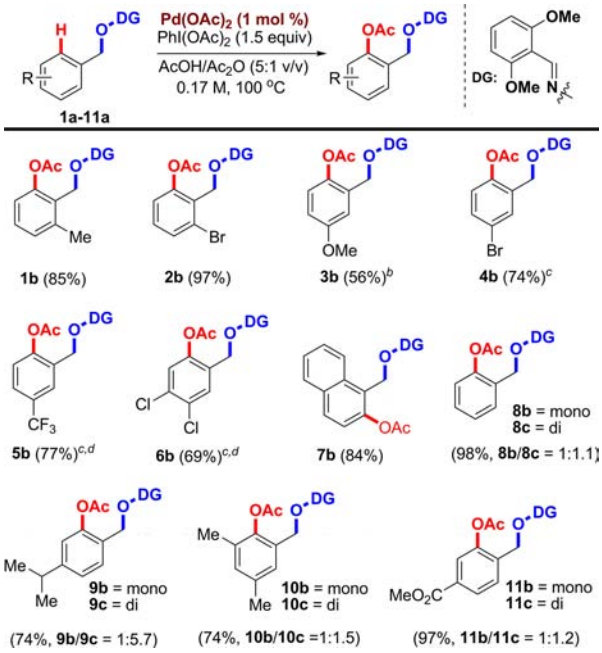
[a]Reaction conditions: all the reactions were run on a 0.1 mmol scale with 0.6 mL of solvents. [b]NMR yields with 1,1,2,2-tetrachloroethane as the internal standard. [c]Product **1b** consisted of a mixture of oxime *E*/*Z* stereoisomers; see Supporting Information. [d]Isolated yield.

gain further insights into this reaction. In the absence of the Pd catalyst or the oxidant, no desired product was observed (Table 1, entries 2 and 3). A higher catalyst loading (e.g., 10 mol %, Table 1, entry 4) gave a faster reaction but a lower yield, which is likely attributed to the Pd-mediated decomposition. Without acetic anhydride, the yield was decreased to 61%, which suggests that water may hamper the reaction (Table 1, entry 5).[15] Other metal salts, such as Co(II) or Ag(I) acetate, did not catalyze this reaction (Table 1, entries 6 and 7). When $K_2S_2O_8$ was used as the oxidant, the yield dramatically decreased to 30% (Table 1, entry 8). However, the addition of a catalytic amount of $PhI(OAc)_2$ or PhI (10 mol %) along with $K_2S_2O_8$ increased the yield to 79% and 72% respectively (Table 1, entries 9 and 10). It is likely that under these conditions the more reactive oxidant, $PhI(OAc)_2$, was generated *in situ* from a less expensive oxidant.[16] Moreover, by using 2.5 equiv of $K_2S_2O_8$, the isolated yield can reach 85% (Table 1, entry 11).

The substrate scope was next explored. Three general ways are available to prepare the benzyl alcohol derived oxime substrates (see Supporting Information). The first is our previously established protocol, using a Mitsunobu reaction between the corresponding alcohol and hydroxyphthalimide followed by a one-pot deprotection/condensation.[13a] The second is through an S_N2 reaction between the corresponding benzyl halides and 2,6-dimethoxybenzaldoxime. Alternatively, by applying Ellman's oxaziridine,[17] the oxime substrates can be prepared in one pot from the corresponding alcohols via *O*-amination followed by aldehyde condensation.

Masked primary alcohol substrates were investigated first (Scheme 2). Arenes with various electronic and steric

Scheme 2. Scope with Primary Alcohol-Derived Substrates[a]



[a]Isolated yields. Product consists of a mixture of oxime *E*/*Z* stereoisomers (for details, see Supporting Information). [b]$K_2S_2O_8$ (2.5 equiv) and $PhI(OAc)_2$ (10 mol %) were used. [c]80 °C. [d]5 mol % $Pd(OAc)_2$ were used.

properties all underwent the desired *ortho*-acetoxylation; with a 1 mol % catalyst loading, the corresponding 2-hydroxymethylphenol derivatives can be isolated in good to excellent yields. A number of FGs can be tolerated, including aryl bromides and chlorides, trifluoromethyl, anisole, naphthalene, and esters. Mono-oxidation can be achieved when there is an *ortho*- or *meta*-substituent. While bis-oxidation was observed for symmetrical substrates, the products are easily separable due to their significant polarity difference. In addition, by controlling the loading of the catalyst and oxidant, the mono-oxidation product can also be obtained with good selectivity (*vide infra*, Scheme 4, eq 2). Moreover, a lower reaction temperature (e.g., 80 °C) can be used. It is encouraging to note that sterically encumbered substrates, such as **10a**, can also be acetoxylated at the *ortho* position.

Secondary alcohol-derived substrates were subsequently examined (Scheme 3). Both acyclic and cyclic substrates provided the desired *ortho*-oxidation products in good to excellent yields. While these substrates contain β-aliphatic C−H bonds that are available for the Pd-catalyzed vicinal oxidation,[13] only substrate **12a** gave a small amount of the sp^3 C−H activation product (7.5% yield) along with an 87% yield on the arene oxidation. Apparently, functionalization of an sp^2 C−H bond is much more favorable. Both the α-tetralol and 1-indanol-derived oximes proved to be excellent substrates **17b** and **18b**. It is exciting to find that the 9-fluorenol-derived substrate gave the desired 1,8-di-*O*-substituted product **19b** in almost a quantitative yield, which is difficult to prepare by other means.[18] In the case of the diphenylmethanol substrate, by

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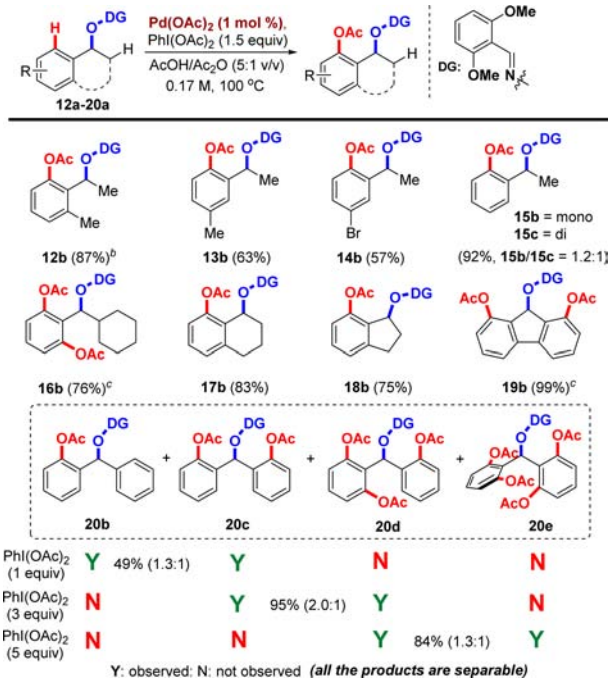
Scheme 3. Scope with Secondary Alcohol-Derived Substrates[a]

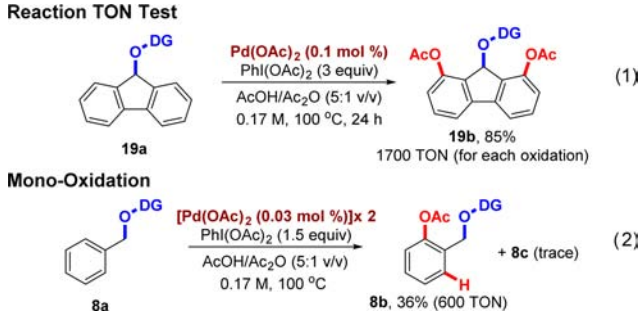


[a]Isolated yields. Product consists of a mixture of oxime *E*/*Z* stereoisomers (for details, see Suppoting Information). [b]Oxidation of the sp^3 C−H bond was observed. [c]3 equiv of $PhI(OAc)_2$ were used.

choosing different amounts of oxidants, mono- to tetra-acetoxylated products **20b−e** can be formed with different selectivity. It is noteworthy that the second oxidation took place on the other phenyl group. The fourth oxidation was much slower which could be the result of a higher rotation barrier. Again, all these products can be easily separated.

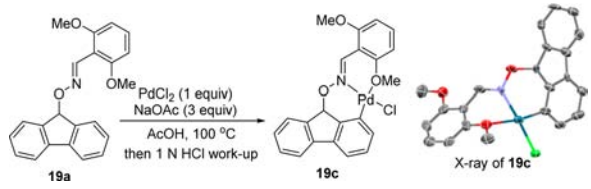
The TON of the catalytic reaction was examined using substrate **19a**. Indeed, with this 2,6-dimethoxyl benzaldoxime DG, the TON can reach 1700 for each acetoxylation with 0.1 mol % of the catalyst (Scheme 4, eq 1). We further discovered

Scheme 4. Reaction TON Test and Mono-oxidation



when using a lower catalyst loading (0.06 mol %) and less oxidant, the mono-oxidation product **8b** can be selectively obtained with 600 TON of the palladium catalyst (only a trace amount of bis-oxidation product was observed) (Scheme 4, eq 2). Furthermore, to explore the coordination mode of the DG during the C−H activation, a C−H metalation intermediate was obtained for substrate **19a** (Scheme 5). Upon workup with HCl (to break the palladium dimer), a mononuclear

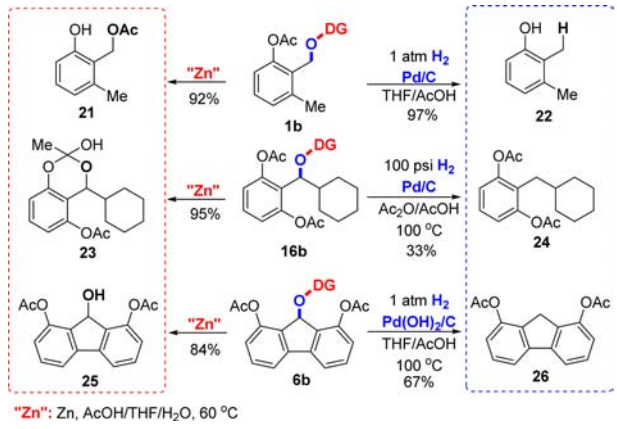
Scheme 5. Isolation of Palladacycle 19c



pseudosquare planar *exo*-palladacycle (**19c**) was isolated and characterized through X-ray crystallography. Indeed, the methoxy group plays a role as a ligand to assist the chelation, which is expected to be responsible for the high catalyst turnover of this reaction.

Finally, we demonstrated that two strategies can be adopted to remove the DG through either N−O bond or C−O bond cleavage (Scheme 6). Using inexpensive zinc metal, the N−O

Scheme 6. Cleavage of the Directing Group



bond of the oximes was selectively cleaved. Interestingly, after the cleavage, the resulting benzyl alcohol from **1b** underwent transesterification to give a free phenol. However, for substrate **16b**, an orthoacetate **23** was obtained. On the other hand, the benzyl C−O bond cleavage can be realized through a Pd-catalyzed hydrogenolysis.[19] Given that the oxime substrates can ultimately come from the corresponding saturated alkyl precursors via benzylic functionalization (e.g., bromination) followed by an S_N2 reaction, this approach offers a net *ortho*-oxidation of alkyl-arenes.

In conclusion, we developed a unique Pd-catalyzed *ortho*-acetoxylation of masked benzyl alcohols and demonstrated that the *exo*-directing strategy can be efficient for aromatic C−H oxidation. Using this method, a variety of 2-hydroxyalkyl phenol derivatives can be synthesized in good to excellent yields. The 2,6-dimethoxybenzaldoxime proved to be a highly efficient DG, which can be removed to offer synthetically versatile benzyl alcohols or act in a traceless fashion to give the corresponding alkylated phenols.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectroscopic data (^{1}H NMR, ^{13}C NMR, IR, HRMS). The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01098.

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Notes

The authors declare no competing financial interest.

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