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Pd-Catalyzed *Ortho* C−H Hydroxylation of Benzaldehydes Using a Transient Directing Group

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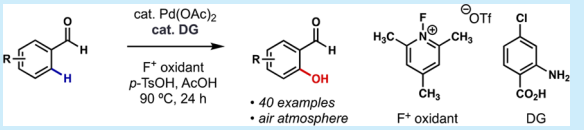
Supporting Information

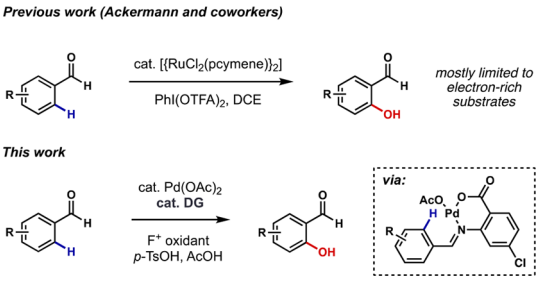
ABSTRACT: The direct Pd-catalyzed *ortho* C−H hydroxylation of benzaldehydes was achieved using 4-chloroanthranilic acid as the transient directing group, 1-fluoro-2,4,6-trimethylpyridnium triflate as the bystanding oxidant, and *p*-toluenesulfonic acid as the putative oxygen nucleophile. The unusual C−H chlorination and polyfluoroalkoxylation reactions signaled the importance of external nucleophiles to the outcome of Pd(IV) reductive eliminations.



Catalytic C−H functionalization of arenes is a topic of increasing importance with a wide range of applications in organic synthesis.[1] In particular, Pd-,[2] Ru-,[3] Cu-,[4] or Rh-catalyzed[5] C(sp^2)−H oxygenation reactions provide direct access to various substituted phenols from relatively simple starting materials.[6] Most of these reactions rely on the use of strongly coordinating structural elements, such as pyridines, oximes, or amides, to facilitate the C−H metalation process. However, directed C(sp^2)−H oxygenations mediated by the moderate-to-weak coordinating power of the carbonyl of ketones and aldehydes pose a steeper challenge.[7] While site-selective C(sp^2)−H oxygenations can be achieved with aromatic ketones,[8] directed oxidations of C(sp^2)−H bonds with benzaldehyde substrates are still largely undeveloped. The seminal examples of these rare reactions, which were reported by Ackermann and co-workers, featured the action of a ruthenium catalyst on benzaldehydes with electron-rich arenes; electron-deficient benzaldehydes displayed low reactivity in this method (Scheme 1).[9] Aldehyde-directed *ortho*-hydroxylations of structurally diverse benzaldehydes are attractive reactions, and yet their continued development is hampered by the weak coordinating ability of the CHO functional group and the tendency of this group to undergo undesired oxidation, as well as competitive metal insertions into formyl C−H bonds.

Our group recently described an efficient method to synthesize fluorenones from benzaldehydes and aryl iodides.[10]

Scheme 1. Direct *Ortho* C−H Hydroxylation of Benzaldehydes



Central to this transformation was the use of anthranilic acid as a transient directing group (TDG), which orchestrates two Pd-catalyzed C−H functionalization events by reversibly binding to the substrates. The TDG strategy is free from the stoichiometric introduction and subsequent removal of directing elements and becoming increasingly utilized to achieve site-selective functionalizations of a wide range of aldehydes, ketones, and amines.[11] Nevertheless, most of these methods have been limited to C−H arylation only, and to date, no C−H oxygenation protocol has been developed with any substrate using the TDG strategy. Our continued focus on C−H functionalizations mediated by TDGs prompted us to develop a new catalytic method for achieving direct *ortho* C−H hydroxylations of benzaldehydes via Pd catalysis (Scheme 1).

From the outset, we realized that a carefully chosen oxidant is needed to (1) avoid the overoxidation of benzaldehydes; (2) ensure its compatibility with the TDG; and (3) suppress other undesired oxygenation reactions. With these considerations in mind, a Pd-catalyzed *ortho* C−H hydroxylation reaction was envisioned by combining electrophilic F^+ reagents as the bystanding oxidant for Pd with *p*-toluenesulfonic acid (*p*-TsOH) as the oxygen nucleophile. Pioneered by the Sanford and the Yu groups,[12] this strategy was recently adopted by Dong and co-workers in an oxime-derived alcohol *β*-C(sp^3)−H tosylation reaction.[13] In our study, we reasoned that in situ hydrolysis of the intermediate *p*-toluenesulfonate ester under acidic conditions would reveal the phenolic hydroxyl of the desired products.

Our study began by subjecting 3,4-dichlorobenzaldehyde to an excess of F^+ oxidants, *p*-TsOH in the presence of various Pd catalysts, and a TDG in AcOH under an air atmosphere at 90 °C. To our delight, the desired hydroxylation product was formed in 56% yield after a 24 h reaction that employed 10 mol % of $Pd(OAc)_2$ as the catalyst, 50 mol % of 2-amino-4-(trifluoromethyl)benzoic acid (**DG1**) as the TDG, 1.5 equiv of 1-fluoro-2,4,6-trimethylpyridnium triflate as the bystanding F^+

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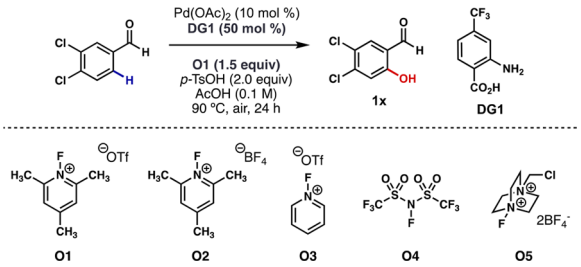
Table 1. Control Experiments[a]

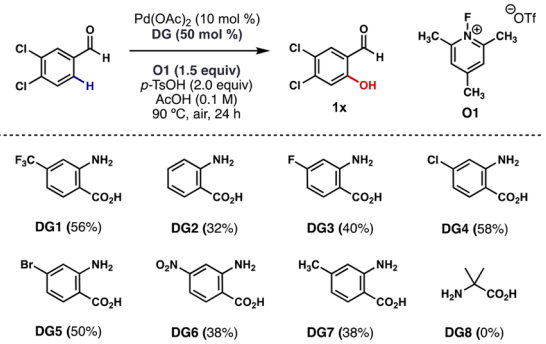


entry	variation from the standard condition	yield of **1x**[b] (%)
1	none	56
2	no $Pd(OAc)_2$	0
3	no DG1	0
4	30 mol % DG1	50
5	70 mol % DG1	44
6	no *p*-TsOH	12
7	1.0 equiv *p*-TsOH	34
8	TFA instead of *p*-TsOH	12
9	TfOH instead of *p*-TsOH	48
10	$Pd(TFA)_2$ instead of $Pd(OAc)_2$	46
11	$PdCl_2$ instead of $Pd(OAc)_2$	44
12	**O2** instead of **O1**	28
13	**O3** instead of **O1**	46
14	**O4** instead of **O1**	24
15	**O5** instead of **O1**	trace
16	in AcOH/HFIP (9:1)	40
17	0.15 M instead of 0.1 M	40
18	0.067 M instead of 0.1 M	34
19	with 5.0 equiv H_2O	42
20	at 70 °C	26
21	at 110 °C	44

[a]The reaction was performed with 3,4-dichlorobenzaldehyde (0.1 mmol), $Pd(OAc)_2$ (0.01 mmol), DG1 (0.05 mmol), **O1** (0.15 mmol), and *p*-TsOH (0.2 mmol) in AcOH (1.0 mL) under air at 90 °C for 24 h. [b]Determined by ^{1}H NMR using CH_2Br_2 as the internal standard.

oxidant, 2.0 equiv of *p*-TsOH as the oxygen nucleophile, and AcOH (0.1 M) as the solvent (Table 1, entry 1). Several control experiments were subsequently conducted to shed light on the role of each additive. Not surprisingly, the reaction did not occur in the absence of either $Pd(OAc)_2$ or **DG1** (Table 1, entries 2 and 3). Reaction efficiency was slightly affected upon reducing or increasing the loading of **DG1** (Table 1, entries 4 and 5), but removing *p*-TsOH from the reaction resulted in a loss of catalyst turnover (Table 1, entry 6). This suggested that *p*-TsOH might be playing a pivotal role in the catalytic cycle as an oxygen nucleophile. As depicted in entry 7 in Table 1, reaction performance was reduced by using only 1 equiv of *p*-TsOH. Attempts to replace *p*-TsOH with other strong acids, such as trifluoroacetic or triflic acids, led to either no catalyst turnover or a much lower yield (Table 1, entries 8 and 9). Inferior reaction performance was also observed when other Pd catalysts such as $PdCl_2$ or $Pd(TFA)_2$ or other F^+ oxidants such as 1-fluoro-2,4,6-trimethylpyridnium tetrafluoroborate (**O2**), 1-fluoropyridinium triflate (**O3**), NFSI (**O4**), or Selectfluor (**O5**) were used (Table 1, entries 10−15). Reactions run in AcOH/hexafluoroisopropanol (HFIP) (9:1), in other concentrations of AcOH or with an additional 5 equiv of water (Table 1, entries 16−19) gave lower yields. Lowering or raising the reaction temperature also reduced the reaction efficiency (Table 1, entries 20 and 21).

Scheme 2. Screening of Transient Directing Groups[a]



[a]Yields are determined by ^{1}H NMR using CH_2Br_2 as the internal standard.

Using the standard conditions described in Table 1, we next investigated the substituent effect on the TDG (Scheme 2). Although simple anthranilic acid (**DG2**) only gave a moderate performance, electron-poor anthranilic acids delivered superior results. Among the TDGs tested, 2-amino-4-chlorobenzoic acid (**DG4**) was the most efficient TDG, affording the hydroxylated product in 58% yield. In contrast, the electron-rich 2-amino-4-methylbenzoic acid (**DG7**) was less effective. Interestingly, 2-aminoisobutyric acid (**DG8**), which had been previously used for the *ortho* C−H arylation of benzaldehydes,[11h] did not generate any desired product in this process.

With an improved procedure in hand, we proceeded to probe the scope of the method by varying the structure of benzaldehyde reactant. To our delight, various electron-withdrawing groups (EWG) and electron-donating groups (EDG) were all well accommodated at the *ortho* position, affording the desired products in good yields (Scheme 3, **1a−e**). Comparable yields were obtained when we changed the substituents' location from the *ortho* to the *meta* positions (Scheme 3, **1f−j**), and even more EWG became compatible, such as trifluoromethyl and methyl ester groups (Scheme 3, **1h** and **1i**). This robust reactivity with electron-deficient benzaldehydes complements Ackermann's Ru(II)-catalyzed benzaldehyde *ortho* hydroxylation method,[9] which performs best with arenes bearing EDGs. Encouraged by these results, we next evaluated the reactivities of disubstituted benzaldehydes in this reaction. Gratifyingly, the reaction was tolerant of various EWGs at the *ortho* and *para* positions, and it was also possible to introduce both an EWG and an EDG to a single substrate while still maintaining a high efficiency of the reaction (Scheme 3, **1k−v**). *Importantly, the presence of an ortho methoxy group in the substrates did not impede the reaction, and the dioxygenated products were produced in decent yields* (Scheme 3, **1u**, **1v**). We were also pleased to find that switching the substituents' location to the *meta* and *para* positions did not cause a significant erosion in performance. Yields were generally good for substrates containing two EWGs (Scheme 3, **1w−z**) but were very moderate for those bearing two EDGs (Scheme 3, **1aa−1cc**). However, when both EWG and EDG were present on a single substrate, the efficacy of the reaction was restored (Scheme 3, **1dd−jj**). This method was also amenable to a number of *ortho*, *meta*-substituted benzaldehydes, as well as a coumarin-containing aldehyde, in which case consistently good yields were obtained (Scheme 3, **1kk−nn**).

In the course of our study, palladacycle **2** was isolated from the reaction of 2,4-dichlorobenzaldehyde with stoichiometric amounts of $Pd(OAc)_2$, **DG4**, and 4-*tert*-butylpyridine.[14] Upon

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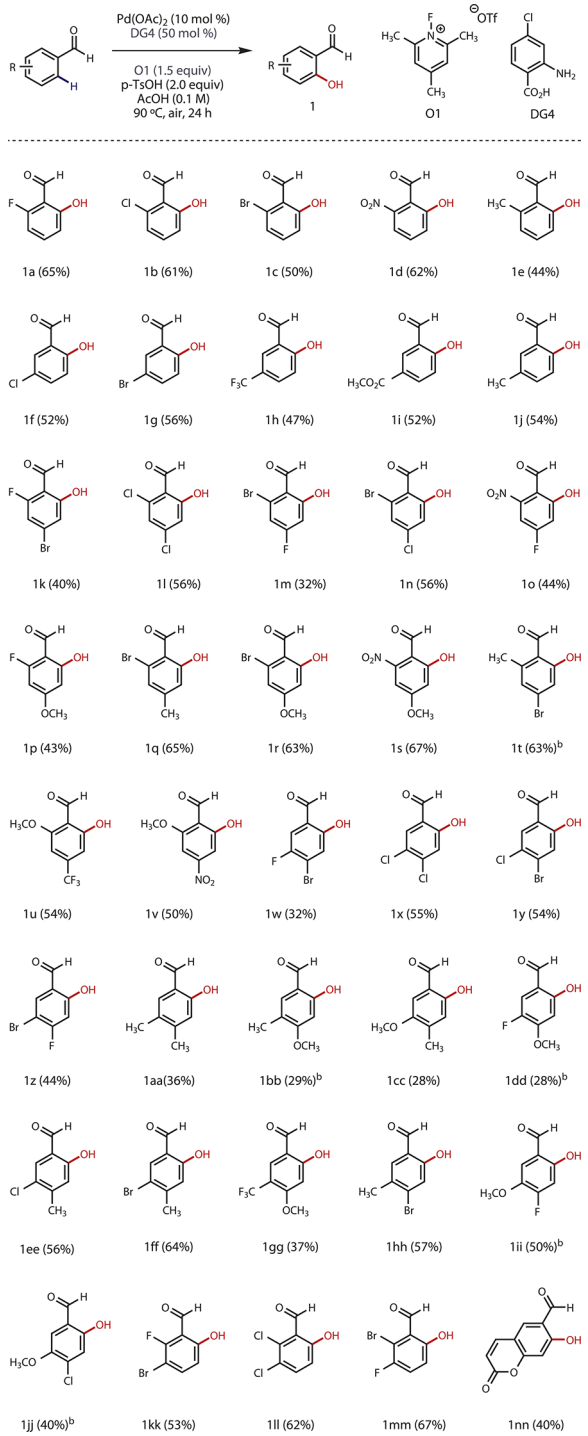
Scheme 3. Scope of the Benzaldehydes[a]

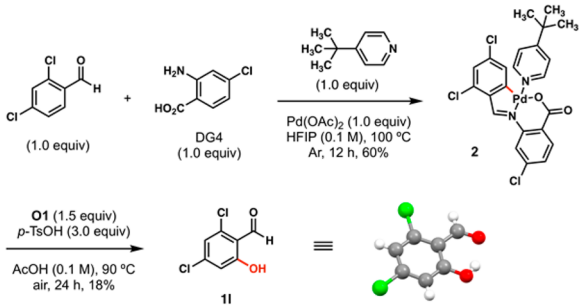


[a]All yields are reported as isolated yields. [b]**DG1** was used as the TDG.

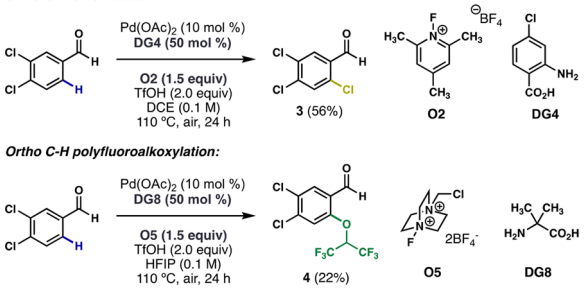
treatment with O1 and *p*-TsOH, this intermediate was transformed into salicylaldehyde **1l**; the structure of **1l** was unambiguously confirmed by X-ray crystallography (Scheme 4).

Some unusual reactivity was also revealed when the reaction conditions were changed. As shown in Scheme 5, *ortho* C−H chlorination of 3,4-dichlorobenzaldehyde was achieved by using **DG4** as the TDG, **O2** as the F^+ oxidant, triflic acid as the acid additive, and dichloroethane (DCE) as the solvent. We postulate that the thermal decomposition of DCE into vinyl chloride and HCl may be responsible for the generation of chloride anion in

Scheme 4. Isolation and Subsequent Oxidation of Palladacycle 2



Scheme 5. *Ortho* C−H Chlorination and Polyfluoroalkoxylation



the reaction,[15] which subsequently participates in the C−Cl reductive elimination through a ligand-exchange reaction of the putative Pd(IV) center.[16] A similar C−H polyfluoroalkoxylation, which presumably follows the same mechanistic process, was also accomplished by employing **DG8** as the TDG, **O5** as the F^+ oxidant, triflic acid as the acid additive, and HFIP as both the solvent and the external nucleophile (Scheme 5). While it has thus far proven difficult to intercept the Pd(IV) intermediate with other anions, our results corroborate the importance of external nucleophiles in promoting otherwise challenging reductive eliminations from Pd(IV) intermediates generated through bystanding F^+ oxidants.[12]

On the basis of this study, a putative mechanism is outlined in Scheme 6. We propose that the first step is the transient formation of **I-1** from benzaldehyde and **DG4**. Following deprotonation and metal complexation, cyclopalladation of **I-2** would give rise to the six-membered palladacycle **I-3**. Oxidative addition with **O1** would generate the putative Pd(IV) intermediate **I-4**, with the fluoride and triflate anions of **O1** being the X-type ligands on this Pd(IV) complex. Nucleophilic displacement of the fluoride anion with a tosylate anion would produce the tosylate-bound Pd(IV) intermediate **I-5**, which could subsequently undergo C−O reductive elimination to forge the *p*-toluenesulfonate-bearing **I-6**. Dissociation of the Pd complex, followed by imine hydrolysis, would restore both the free **DG4** and the Pd catalyst with concomitant formation of the *ortho*-tosylated benzaldehyde **I-8**. Finally, in situ hydrolysis of the *p*-toluenesulfonate ester would furnish the desired salicylaldehyde.

In summary, an efficient method was developed for the direct *ortho* C−H hydroxylation of benzaldehydes under an air atmosphere. By merging **O1** as a bystanding F^+ oxidant with *p*-TsOH as the putative oxygen nucleophile, the desired transformation was achieved using a readily available TDG. The combination of dynamic chemical processes with catalyst-

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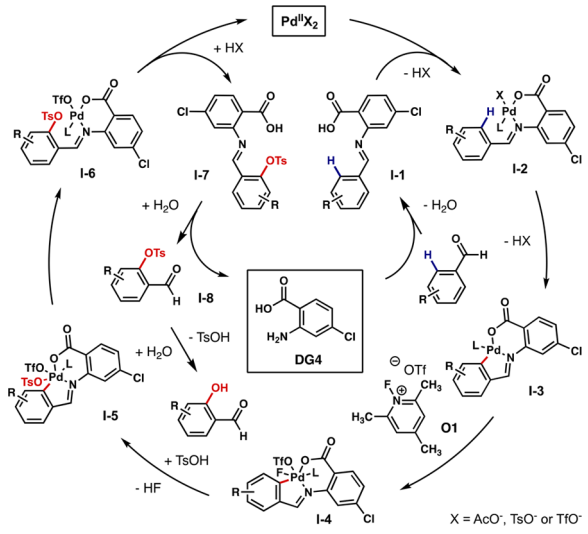
Scheme 6. Possible Reaction Mechanism



controlled, direct C−H functionalizations is a fruitful area for continued development.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02906.

Experimental procedures, spectral data, and crystallographic data (PDF)

X-ray data for compound **1l** (CIF)

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Notes

The authors declare no competing financial interest.

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