Pd-catalyzed, *ortho* C-H Methylation and Fluorination of Benzaldehydes Using Orthanilic Acids as Transient Directing Groups

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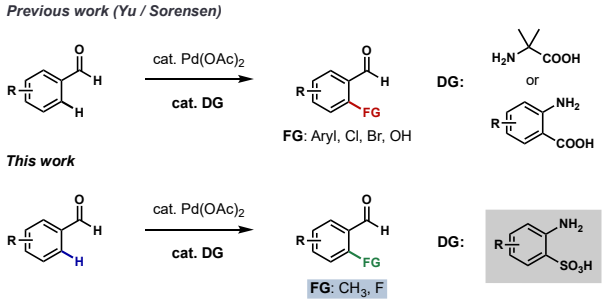
Supporting Information Placeholder

ABSTRACT: The direct, Pd-catalyzed *ortho* C-H methylation and fluorination of benzaldehydes have been accomplished using commercially available orthanilic acids as efficient transient directing groups. The 1-fluoro-2,4,6-trimethylpyridinium salts in these transformations can be either a bystanding F^+ oxidant or an electrophilic fluorinating reagent. An X-ray crystal structure of a benzaldehyde *ortho* C-H palladation intermediate was successfully obtained using triphenylphosphine as the stabilizing ligand.

Pre-complexation of a transition metal with chelating functional groups in substrates has been extensively utilized to promote reactivity and selectivity in C-H functionalization reactions.[1] While significant progress has been made in the development of versatile and efficient directing groups, the additional two steps for their stoichiometric installation and removal limit their applications. Transient directing groups (TDGs), which form reversible linkages with the substrates *in situ* to effect C-H metalation, constitute a promising approach to direct Pd-catalyzed C-H functionalization reactions using native functionalities.[2] Pioneered by the Yu group, this strategy has been exploited to achieve functionalizations of a wide variety of ketones, aldehydes and amines.[3] Nevertheless, most substrates can only undergo C-H arylation, thus the considerable potential of directed *ortho* C-H functionalizations in benzaldehydes is currently underdeveloped (Scheme 1).[3g,3i] Furthermore, the vast majority of the L, X-type TDGs are amino acid derivatives, with only one report using an acid amide as the X-type ligand to promote proximity-driven C-H palladation.[3k]

Herein, we wish to disclose an efficient protocol for benzaldehyde *ortho* C-H methylation and fluorination via Pd catalysis. These transformations feature orthanilic acids as new, inexpensive TDGs, consisting of a sulfonic acid as the X-type ligand. In contrast to the traditional carboxylic acid-type TDGs, these more electron-deficient TDGs can permit reactivity that would otherwise be difficult to achieve (Scheme 1). To the best of our knowledge, amino sulfonic acid derivatives have never been described as TDGs in any type of C-H functionalization reaction.

Scheme 1. *ortho*-Selective C-H methylation and fluorination of benzaldehydes using orthanilic acids as TDGs

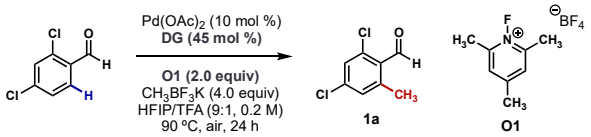


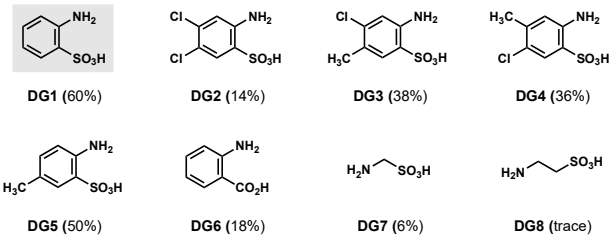
The performance of orthanilic acid as a TDG in *ortho* functionalizations of benzaldehydes was first evaluated in C-H methylations. Though generally considered to be chemically inert, methyl groups can substantially influence the pharmacological properties of biologically active compounds.[4] Various directing groups have been used to methylate proximal C-H bonds via Pd catalysis;[5] however, to the best of our knowledge, transition-metal-catalyzed, direct *ortho* C-H methylation of benzaldehydes has not been reported. We realized that for such chemistry to occur, the coupling reagent and the oxidative conditions need to be compatible with acidic solvents, which are required for the effective turnover of the TDGs. On the foundation of our prior uses of electrophilic F^+ reagents as bystanding oxidants for Pd in *ortho* C-H hydroxylations of benzaldehydes,[3g] we reasoned that after an initial C-H palladation and transmetalation with a methyl boron reagent, the putative Pd(II) species could be readily oxidized by an appropriate F^+ oxidant under acidic conditions. Such a process is well documented in Sanford's elegant C-H alkylation method.[5i] The resulting Pd(IV) complex could then undergo a selective C-C bond-forming reductive elimination in preference to a more sluggish C-F bond formation.[6] To

achieve efficient transmetalation, potassium methyl trifluoroborate was chosen as an acid-compatible nucleophilic coupling partner.[7]

After a substantial screening effort, the desired *ortho* C-H methylation product was formed in 60% yield after a 24 h reaction that used 10 mol % of $Pd(OAc)_2$ as the catalyst, 45 mol % of orthanilic acid (**DG1**) as the TDG, 2.0 equivalents of 1-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate (**O1**) as the bystanding F^+ oxidant, 4.0 equivalents of potassium methyl trifluoroborate as the coupling partner and hexafluoroisopropanol (HFIP)/trifluoroacetic acid (TFA) (9:1, 0.2 M) as the solvent (Scheme 2, **DG1**; See SI for a complete list of control experiments). The substituent effects on the TDG were next investigated. Interestingly, neither electron-withdrawing groups (EWG) nor electron-donating groups (EDG) on the 4' or 5' positions of orthanilic acid were effective in improving this reaction (Scheme 2, **DG2**-**DG5**), leaving **DG1** the most efficient TDG for this transformation. Replacing orthanilic acid with simple anthranilic acid as the TDG resulted in a significantly diminished yield (e.g. 18%), illustrating the importance of the sulfonic acid as the X-type ligand (Scheme 2, **DG6**). Other amino sulfonic acids, such as aminomethanesulfonic acid and taurine, were ineffective TDGs in this transformation (Scheme 2, **DG7** and **DG8**).

Scheme 2. Effects of TDGs on *ortho* C-H methylation[a]

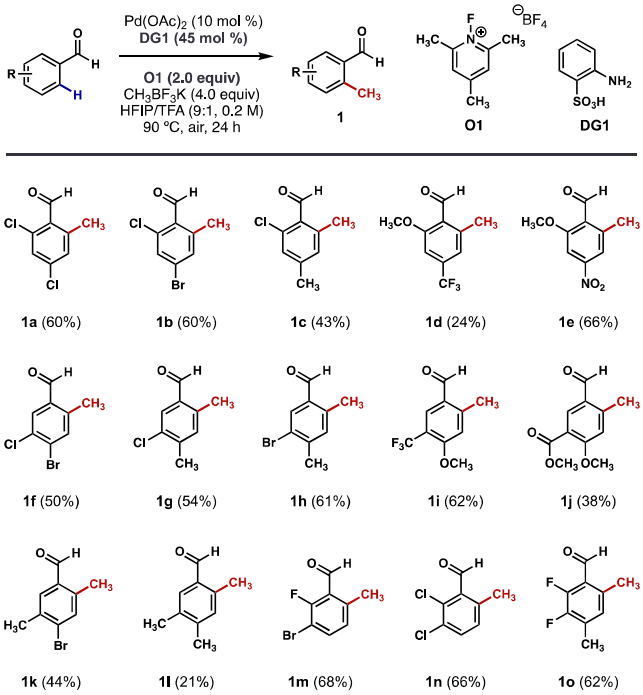




[a]Yields are determined by ^1H NMR using CH_2Br_2 as the internal standard.

With an optimized procedure in hand, the reactions of variously substituted benzaldehydes were investigated to probe the scope of this directed methylation process. To our delight, various EWGs at the *ortho* and *para* positions were well tolerated, and it was possible to introduce both an EWG and an EDG to a single substrate without significant erosion in performance (Scheme 3, **1a**-**1e**). Benzaldehydes with substituents in the *meta* and *para* positions were also compatible substrates in this reaction. Yields were generally good for substrates containing two EWGs, or one EWG and one EDG, but were poor for the one containing two EDGs (Scheme 3, **1f**-**1l**). This method was also amenable to a number of *ortho*, *meta*-substituted benzaldehydes, as well as a trisubstituted benzaldehyde, in which cases consistently good yields were obtained (Scheme 3, **1m**-**1o**). The current limitations of this method are: (1) It does not tolerate a bromine substituent at the *ortho* position of the benzaldehyde substrate; and (2) It displays low reactivity with long-chain alkyl trifluoroborates as the coupling reagent (See SI).

Scheme 3. Substrate scope in *ortho* C-H methylation[a]



[a]All yields are reported as isolated yields

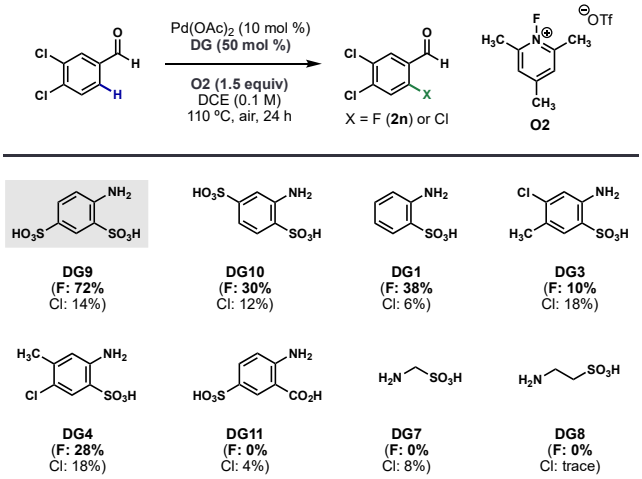
Encouraged by the above success, we next sought to develop an efficient method for benzaldehyde *ortho* C-H fluorination using orthanilic acids as TDGs. While broadly viewed as a privileged pharmacophore due to its improved lipophilicity and inertness to metabolic transformations, the C-F bond can be notoriously difficult to construct.[8] Relatively few approaches are available for forming C-F bond,[9] and examples of Pd-catalyzed, directed C-H fluorination are particularly rare.[10] To the best of our knowledge, no method currently exists for the direct *ortho* C-H fluorination of benzaldehydes.

One fundamental challenge in achieving C-H fluorination via Pd catalysis is to facilitate C-F reductive elimination in a myriad of undesired reductive elimination pathways that could occur at the octahedral Pd(IV) intermediate.[11] Due to the polarization of the Pd(IV)-F bond and the low nucleophicity of fluoride anion, various nucleophilic anions could compete with fluoride ion in their reductive elimination from Pd(IV).[6] Our previous attempts to employ anthranilic acids as the TDGs were all thwarted by the undesired C-H chlorination reaction when dichloroethane (DCE) was used as the solvent.[3g] To induce selective C-F reductive elimination, we reasoned that by replacing a carboxylic acid with a sulfonic acid as the X-type ligand on the TDG, the ligated Pd metal center might become more electrophilic, thereby attenuating the polarization of Pd(IV)-F bond. We

also hypothesized that anchoring another sulfonic acid group onto the orthanilic acid scaffold might be even more beneficial, because it would further increase the electron-withdrawing nature of the TDG and serve as an "internal acid" to facilitate the hydrolytic turnover of the TDG.

We were excited to find that, while C-H chlorination still occurred as a minor side reaction, the desired *ortho* C-H fluorination product was formed in 72% yield following a 24 h reaction employing 10 mol % of $Pd(OAc)_2$ as the catalyst, 50 mol % of aniline-2,4-disulfonic acid (**DG9**) as the TDG, 1.5 equivalents of 1-fluoro-2,4,6-trimethylpyridinium triflate (**O2**) as the fluorinating reagent and DCE (0.1 M) as the solvent (Scheme 4; See SI for a complete list of control experiments). Interestingly, a similar TDG, **DG10**, where the sulfonic acid group is located at the 5' position of orthanilic acid, was far less effective. Inferior reaction performance was also observed when other orthanilic acids were used (Scheme 4, **DG1**, **DG3** and **DG4**). A similar anthranilic acid, **DG11**, which differs from **DG9** only in its X-type ligand, led to only C-H chlorination reaction with minimal reactivity. Other amino sulfonic acids exhibited no reactivity in this transformation (Scheme 4, **DG7** and **DG8**).

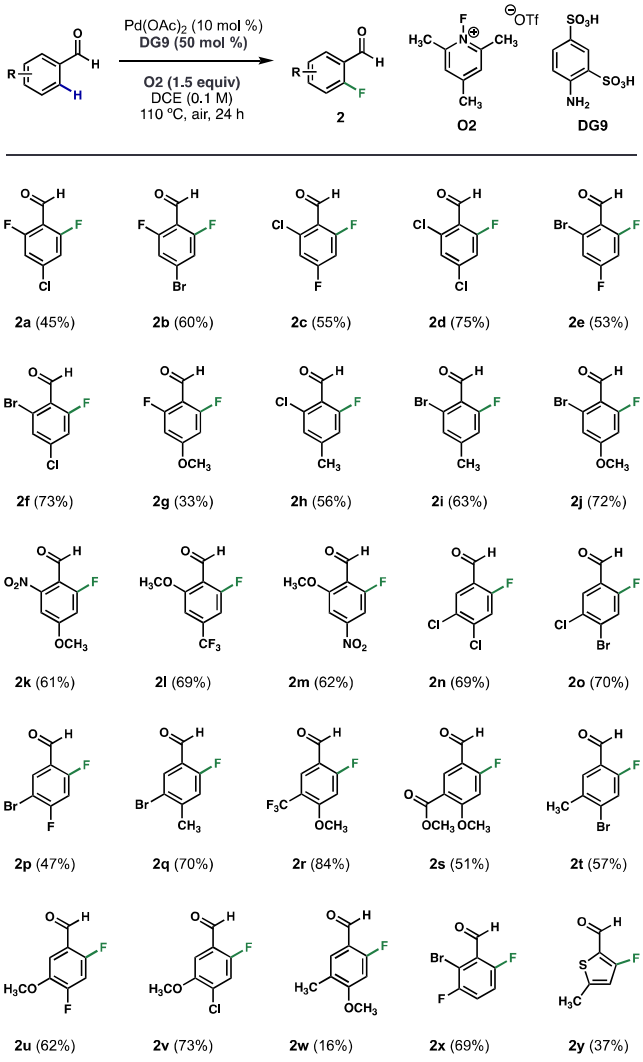
Scheme 4. Effects of TDGs on *ortho* C-H fluorination[a]



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

With an optimized condition in hand, we next explored the substrate scope of di-substituted benzaldehydes. As depicted in Scheme 5, a number of halogen substituents at the *ortho* and *para* position of benzaldehydes were well accommodated, affording the desired products in good yields (Scheme 5, **2a**-**2f**). The reaction also tolerated other EWGs, such as trifluoromethyl and nitro groups, and EDGs, such as methyl and methoxy groups (Scheme 5, **2g**-**2m**). We were also pleased to find that the reaction performed well with benzaldehydes bearing diverse functional groups at the *meta* and *para* position, such as halogens, trifluoromethyl, ester, methyl and methoxy groups (Scheme 5, **2n**-**2w**). The benzaldehyde with donor methyl and methoxy groups could also undergo a position-selective C-H fluorination, although with low efficiency (Scheme 5, **2w**). Finally, this method was amenable to an *ortho*, *meta*-substituted benzaldehyde, as well as a thiophene-carboxaldehyde, from which the corresponding fluorinated products were produced in satisfactory yields (Scheme 5, **2x**-**2y**).

Scheme 5. Substrate scope in *ortho* C-H fluorination[a]



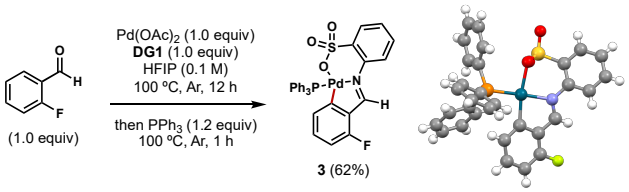
[a]All yields are reported as isolated yields

In our efforts to gain mechanistic insights into this process, 2-fluorobenzaldehyde was subjected to a stoichiometric amount of $Pd(OAc)_2$ and orthanilic acid (**DG1**) in HFIP at 100 °C for 12 hours. In the wake of this reaction, we isolated a stable palladacycle complex in 62% yield by trapping the C-H insertion intermediate with triphenylphosphine (Scheme 6).[12] The structure of this complex was confirmed by X-ray crystallography (Scheme 6). This outcome provides the first direct evidence of a L, X-type TDG acting on Pd in a benzaldehyde *ortho* C-H palladation process.

In summary, a convenient method was developed for achieving direct, *ortho* C-H methylation and fluorination of benzaldehydes via Pd catalysis. Central to these transformations was the use of orthanilic acids as new L,X-

type TDGs, which provide unparalleled reactivity compared to their anthranilic acid counterparts. We envision that prudent modifications of the TDGs might enable direct C-H functionalizations of new classes of aldehydes, and possibly also ketones by analogous, catalytic processes.

Scheme 6. Isolation and structure of palladacycle **3**



ASSOCIATED CONTENT

Supporting Information.
Experimental procedures, spectral data, and crystallographic data (CIF). 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 interests.

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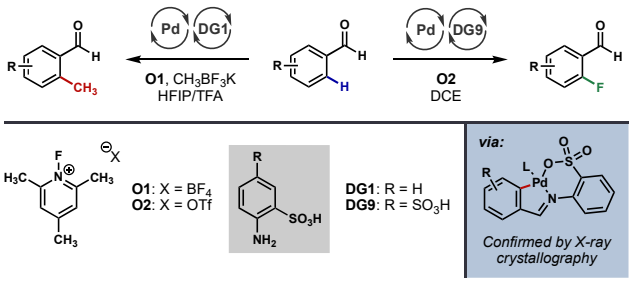
Pd
DG1
O1, CH3BF3K
HFIP/TFA
Pd
DG9
O2
DCE
O1: X = BF4
O2: X = OTf
DG1: R = H
DG9: R = SO3H
via:
Confirmed by X-ray crystallography