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Selective C−H Bond Fluorination of Phenols with a Removable Directing Group: Late-Stage Fluorination of 2-Phenoxyl Nicotinate Derivatives

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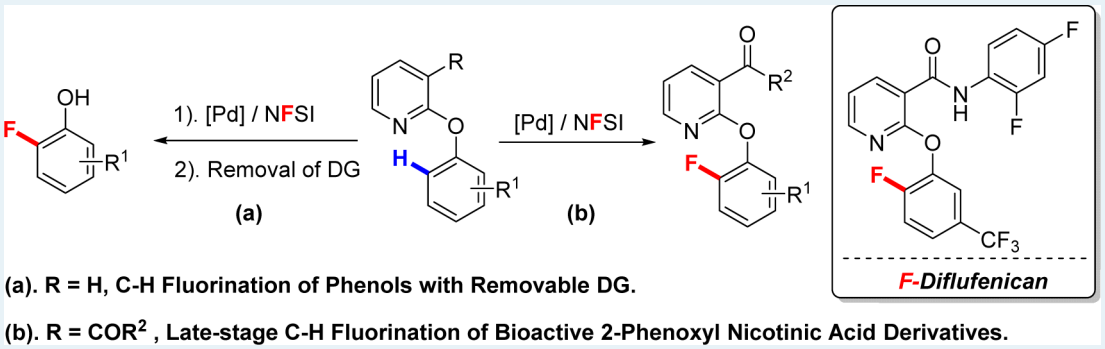
Supporting Information



(a). R = H, C-H Fluorination of Phenols with Removable DG.

(b). R = COR^2 , Late-stage C-H Fluorination of Bioactive 2-Phenoxyl Nicotinic Acid Derivatives.

ABSTRACT: A facile and site-selective C−H bond fluorination of phenols using removable 2-pyridyloxy group as an auxiliary was developed. Alternatively, late-stage C−H bond fluorination of bioactive 2-phenoxyl nicotinate derivatives and diflufenican were also feasible under the present strategy.

KEYWORDS: *C−H bond fluorination, phenols, catalysis, nicotinates, late-stage fluorination*

C−H bond fluorination has emerged as the most powerful protocol to access C−F bond formation because it obviates the use of prefunctionalized substrates.[1] Nevertheless, despite the recent advances, only a handful of directing groups, for example, amides,[2a−c] aryl-*N*-heterocycles,[2d,3b] and oximes-assisted[3a] *ortho*-fluorination of aromatic C−H bonds, have been developed, and the substrate scope is still limited to 2-aryl *N*-heterocycles, aromatic carboxylic acids, benzylic amines, and aryl ketones so far. More directing groups, especially removable directing groups, are highly desirable to be developed for the directed selective C−H bond fluorination of various synthetically relevant substrates.

Phenols are ubiquitous substructures found in various bioactive nature products and materials.[4] Moreover, as fundamental raw materials, phenols are widely occurred in organic synthesis as well. As a commonly used cross-coupling partner, phenols and their derivatives (e.g., aryl-triflates, -pivalates, and -carbamates) are widely involved in classic Ullman reactions, Suzuki reactions, and other recently developed coupling reactions.[5] Moreover, phenols and their derivatives could also undergo *ipso*-deoxylation functionalization to furnish corresponding arenes[6] and aryl fluorides.[7] Given the synthetic and economic potential of phenol derivatives, fluorination of phenols is of great important in construction of fluorine-containing building blocks for further formation of various pharmaceuticals, agrochemicals, and materials.

Up to date, phenols and several phenol derivatives, such as phenol esters and phenol carbamates, among others, have successfully been used as substrates for versatile C−H functionalizations.[8] Among them, 2-phenoxypyridines were employed as efficient phenols surrogates to undergo *ortho*-silylation, -arylation, -borylation, -alkenylation, and -acylation.[9] However, C−H bond fluorination of 2-phenoxypyridines has not been reported yet. Despite the C−H bond fluorination of 2-phenylpyridines, which has been presented by the Sanford group, less mono/difluorination selectivity occurred with respect to the strong coordinating ability of the pyridinyl directing group.[2d] We envisioned that the oxy-bridge in 2-phenoxypyridines might alter the electronic nature of the N-donor ligand and pave the way for selective *ortho*-C−H bond monofluorination. Thus, in continuation of our previous C−H fluorination studies,[3] we developed herein a palladium-catalyzed C−H fluorination via a six-membered cyclopalladation mode using a removable directing group (Figure 1a).[10] Notably, the present protocol could be applied further in the

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late-stage fluorination of bioactive 2-phenoxyl nicotinate derivatives (Figure 1b).

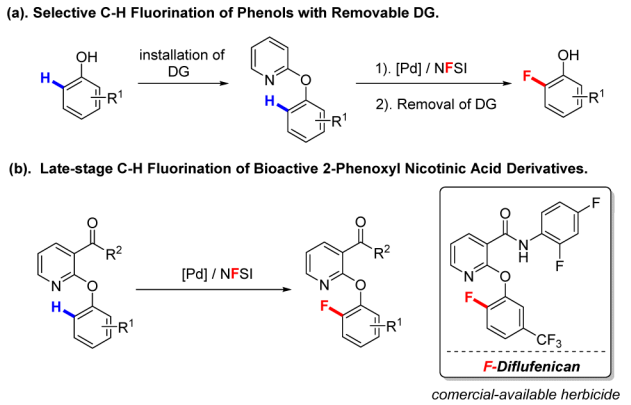
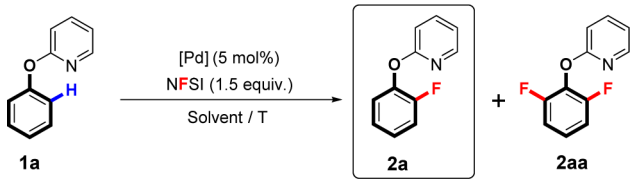


Figure 1. C−H bond fluorination of phenols and bioactive 2-phenoxyl nicotinates.

The initial step of our research was the treatment of the pilot substrate 2-phenoxypyridine (**1a**) with 5 mol % $Pd_2(dba)_3$ and *N*- fluorobenzenesulfonimide (NFSI) in various solvents at different temperatures (Table 1, entries 1−8).[11] Gratefully, with

Table 1. Condition Screening for the C−H Bond Fluorination of 2-Phenoxyl Pyridine[a]



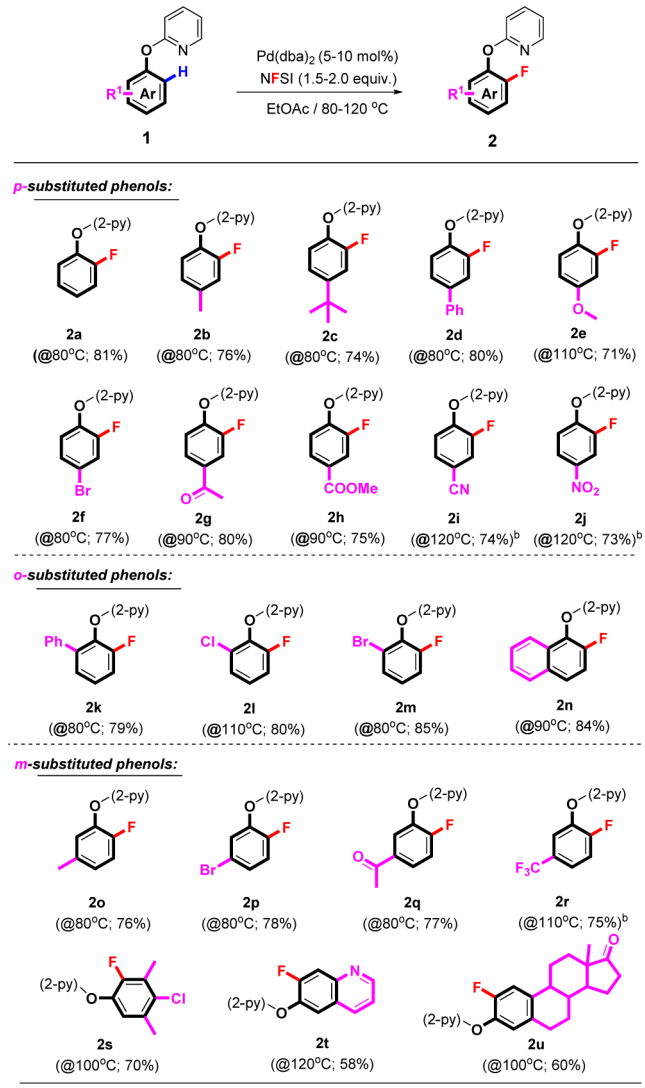
entry	[Pd]	solvent	*T* (°C)	yield of **2a** (%)	yield of **2aa** (%)
1[b]	$Pd_2(dba)_3$	CH_3NO_2	80	19	3
2[b]	$Pd_2(dba)_3$	EtOAc	80	84	6
3[b]	$Pd_2(dba)_3$	EtOAc	60	49	2
4	$Pd_2(dba)_3$	EtOAc	80	84	5
5	$Pd_2(dba)_3$	CH_3CN	80	10	2
6	$Pd_2(dba)_3$	toulene	80	72	3
7	$Pd_2(dba)_3$	DCE	80	13	1
8	$Pd_2(dba)_3$	*n*-hexane	80	12	0
9	$Pd(OAc)_2$	EtOAc	80	80	3
10	$Pd(TFA)_2$	EtOAc	80	47	1
11	$PdCl_2$	EtOAc	80	47	trace
12	$Pd(PPh_3)_4$	EtOAc	80	40	5
13	***Pd(dba)*$_2$**	***EtOAc***	***80***	***86***	***3***
14[c]	$Pd(dba)_2$	EtOAc	80	44	1
15	--	EtOAc	80	0	0

[a]Conditions: **1a** (0.1 mmol), [Pd] (5 mol %), NFSI (1.5 equiv), solvent (1.0 mL), indicated temperature, under air, 2 h, GC-MS yields (unless otherwise noted). [b]12 h. [c]$Pd(dba)_2$ (1 mol %), NFSI (1.5 equiv), under air, 6 h.

slight modification of solvents and reaction temperatures, **1a** was selectively converted to **2a** in EtOAc solvent at 80 °C in a short period of 2 h (entry 4). Additionally, the mono/difluorination selectivity could slightly been enhanced with 5 mol % $Pd(dba)_2$ in lieu of $Pd_2(dba)_3$ (entries 9−13). Reducing the loading of catalyst to 1 mol % could also afford a moderate yield along with a longer reaction time (entry 14). However, omission of Pd catalyst led to a negative result (entry 15).

Encouraged by our initial results, we sought to explore the scope and generality of our C−H fluorination protocol. Various decorated phenols masked by 2-pyridyl directing group were evaluated. In generally, both electron-donating and electron-withdrawing functional groups were well tolerated by cautiously adjusting the reaction temperatures (Table 2). A milder

Table 2. C−H Fluorination of 2-Aryloxyl Pyridine[a]



[a]Conditions: **1** (0.3 mmol), $Pd(dba)_2$ (5 mol %), NFSI (1.5 equiv), EtOAc (3.0 mL), indicated temperature, under air, 2−6 h, isolated yields (unless otherwise noted). [b]$Pd(dba)_2$ (10 mol %), NFSI (2.0 equiv), KNO_3 (30 mol %), 6 h.

condition was required with respect to the electron-rich aryl rings in order to obviate the undesired difluorination. However, more forcing conditions were beneficial for the fluorination of electron-deficient aryl rings. Furthermore, in the case that some strong electron-withdrawing groups (e.g., $-CF_3$, $-CN$, or $-NO_2$) were tethered to the substrates (**2i**, **2j**, **2r**), a catalytic amount of a nitrate additive (30 mol %)[3a] was required to drive the transformations. Monofluorination occurred smoothly even when the bulky phenyl or bromo groups were substituted on the *ortho* position (**2k**, **2m**). Intriguingly, fluorination took

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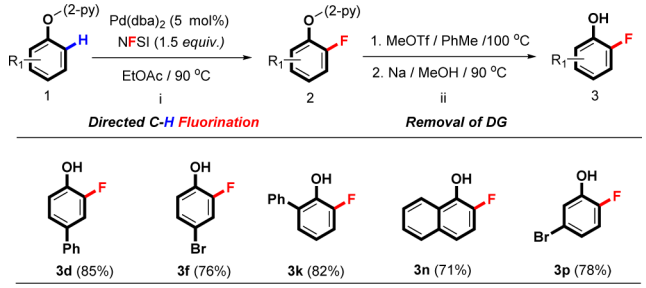
place exclusively on the "inactive" *ortho*-C−H bond with the more "reactive" *ortho*-C−X (Cl, Br) bond remaining intact (**2l**, **2m**).[12] Steric effects adjacent to the reaction center had a remarkable influence on the reaction, as evidenced by the investigation of the *meta*-functionalized substrates. As shown in Table 2, less congested C−H bonds at the *para*-position of the functionalities were highly selectively fluorinated (**2o**−**2u**). Notably, attempts to expand this chemistry to quinoline and a more complex estrone structure were also proved to be viable, albeit with lower yields (**2t**, **2u**).

The 2-pyridyl directing group was essential to the reaction profile as evidenced by the parallel tests of 2-phenoxybenzene and 3-phenoxy pyridine, which did not give the target fluorinated product (Scheme 1). In addition, the 2-pyridyl

Scheme 1. Control Experiments

group can readily be removed to deliver the 2-fluorinated phenols using the previously reported method (Scheme 2).[9] Very recently, a Rh-catalyzed C−O bond cleavage borylation of pyridyl ethers extended the further application of our fluorination strategy.[13]

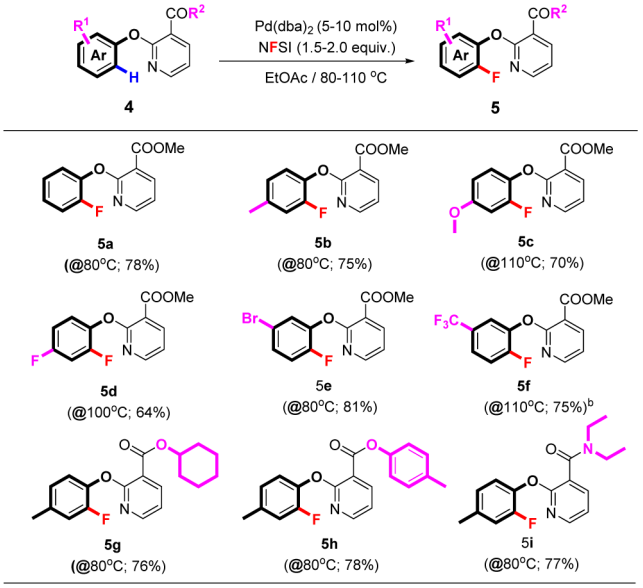
Scheme 2. Removal of the Directing Group



Though the readily removable 2-pyridyloxy directing group could sever as a practical auxiliary for the C−H fluorination of phenols, the 2-phenoxy pyridine substructures are also widely found in various agrochemicals.[14] Among them, 2-phenoxy nicotinate derivatives frequently appear in the pesticide industry, and the selective and late-stage fluorination of these bioactive structures are of great important for the modification of their lipophilicity, bioavailability, and metabolic stability.[15]

Substituted methyl 2-phenoxy nicotinates, which can be prepared facilely via the coupling of 2-chloronicotinate and phenols, were employed to evaluate the application prospect of the present fluorination protocol. To our delight, diverse functionalized methyl 2-phenoxy nicotinates were monofluorinated in good yields under the indicated conditions (Table 3, **5a**−**5f**). Notably, C−H bond fluorination of other nicotinates including cyclohexyl, phenyl nicotinates, and *N*, *N*-diethyl nicotinamide also proceeded smoothly in good yields (**5g**−**5i**). It seemed that the carboxylate tethered at the C-3 position did not hamper the C−H bond activation directed by the pyridine group, which provided an efficient route for the new discovery of pesticides via the late-stage replacement of inert C−H bonds of these bioactive 2-phenoxy nicotinate analogues.[16]

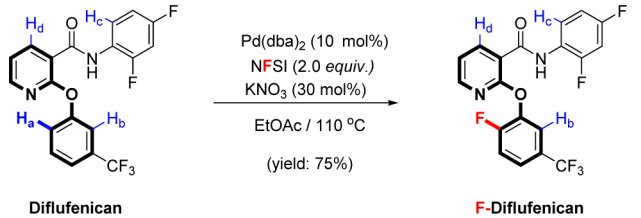
Table 3. C−H Bond Fluorination of 2-Phenoxyl Nicotinic Acid Derivatives[a]



[a]Conditions: **4** (0.3 mmol), $Pd(dba)_2$ (5 mol %), NFSI (1.5 equiv), EtOAc (3.0 mL), indicated temperature, under air, 2 h, isolated yields (unless otherwise noted). [b]$Pd(dba)_2$ (10 mol %), NFSI (2.0 equiv), KNO_3 (30 mol %), 6h.

Encouraged by the remarkable compatibility of nicotinate directing group with the present fluorination protocol, we then turned our attention to the more challenging late-stage fluorination of diflufenican, a widely used commercial-available herbicide in winter wheat and barley.[17] The great problem needed to be overcome in this case is the site-selective C−H_a bond fluorination in the presence of multiple potentially reactive C−H bonds. For instance, the C−H_b bond could be cleaved, as directed by the same nicotinate group in competition with C−H_a bond. C−H_c and C−H_d bonds are also reactive enough to be fluorinated, as assisted by the amide-directing group. Pleasingly, monofluorinated product was yielded exclusively from the 2-pyridyloxy-directed activation at the less sterically hindered C−H_a bond (Scheme 3). Late-

Scheme 3. Regioselective Late-Stage C−H Bond Fluorination of Diflufenican



stage fluorination of C−H bonds without touching the other functional groups is the most efficient way to introduce fluorine into complicated molecules and enrich the strategies of building the highly important fluorine-containing structures.[18]

In conclusion, we have developed a facile and site-selective C−H bond fluorination of phenols using 2-pyridyloxy group as an auxiliary. The methodology has a broad substrate scope with high functional group tolerance. Furthermore, late-stage C−H bond fluorination of bioactive 2-phenoxyl nicotinate derivatives

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such as diflufenican were also implemented successfully under the present conditions. Attempts to apply this late-stage diversification to more useful and bioactive compounds with complex structures are still ongoing in our lab.

■ ASSOCIATED CONTENT

Supporting Information

The following file is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.5b00306.

General experimental procedures, characterization details, and copies of spectra (PDF)

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Notes

The authors declare no competing financial interest.

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