Letter

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

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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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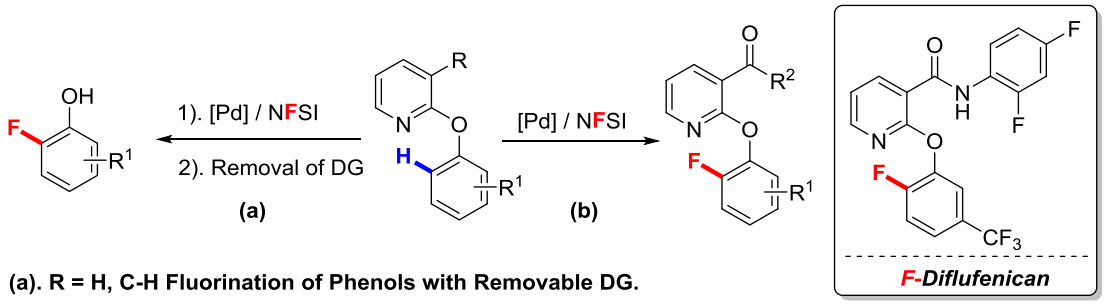


(a). R = H, C-H Fluorination of Phenols with Removable DG.

(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 even more complicated 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 since it obviates the use of pre-functionalized substrates.[1] Nevertheless, despite the recent advances, only handful of directing groups, e.g. amides[2a, 2b, 2c], aryl-N-heterocycles[2d, 3b] and oximes[3a] assisted *ortho*-fluorination of aromatic C-H bonds have been developed and the substrates scope is still limited to 2-aryl *N*-heterocycls, 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, etc. and other latest-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 fluorine-containing building blocks construction for further formation of various pharmaceuticals, agrochemicals and materials.

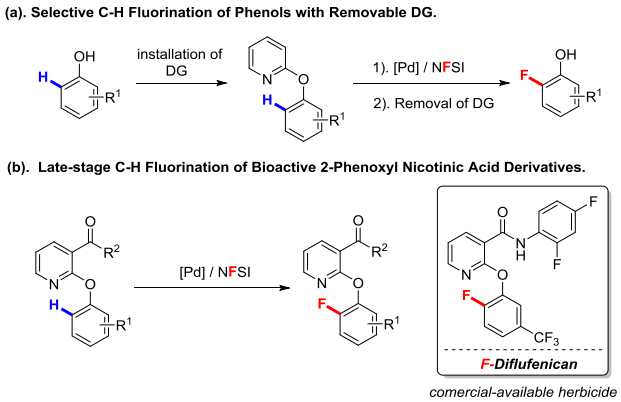
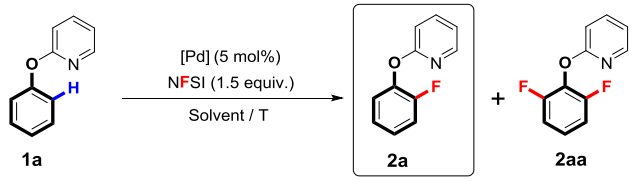


Figure 1. C-H bond fluorination of phenols and bioactive 2-phenoxyl nicotinates.

Up to date, phenols and several phenol derivatives, such as phenol esters and phenol carbamates, *etc.* have successfully been used as substrates for versatile C-H functionalizations.[8] Among them, 2-phenoxypyridines were employed as efficient

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



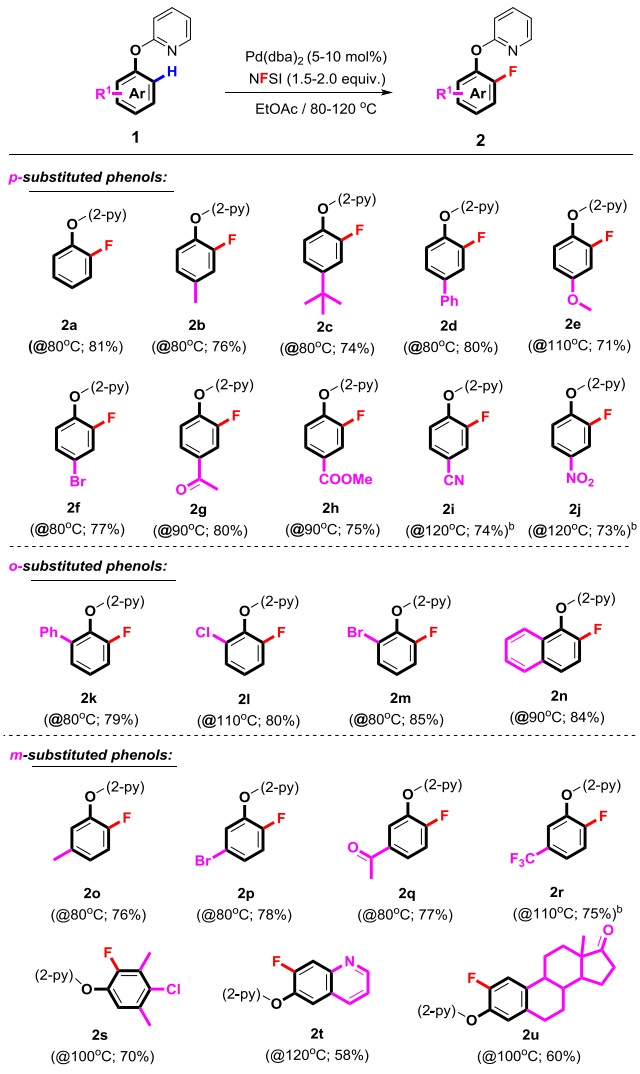
Entry	[Pd]	Solvent	T (°C)	Yield of **2a** (%)	Yield of **2aa** (%)
1[b]	$Pd_2(dba)_3$	CH_3NO_2	80	19	3
2[b]	$Pd_2(dba)_3$	EtOAc	80	84	6
3[b]	$Pd_2(dba)_3$	EtOAc	60	49	2
4	$Pd_2(dba)_3$	EtOAc	80	84	5
5	$Pd_2(dba)_3$	CH_3CN	80	10	2
6	$Pd_2(dba)_3$	Toulene	80	72	3
7	$Pd_2(dba)_3$	DCE	80	13	1
8	$Pd_2(dba)_3$	*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, 2h, GC-MS yields (unless otherwise noted); [b] 12h; [c] $Pd(dba)_2$ (1 mol%), NFSI (1.5 *equiv.*), under air, 6 h.

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 that presented by Sanford group, less mono- / di-fluorination selectivity was 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 mono-fluorination. Thus, in continuation of our previous C-H fluorination studies,[3] we developed herein a palladium-catalyzed C-H fluorination *via* 6-membered cyclopalladation mode using a removable directing group (Figure 1, a).[10] Notably, the present protocol could further be applied in the late-stage fluorination of bioactive 2-phenoxyl nicotinate derivatives (Figure 1, b).

At the outset, we initialed our research by treating 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 slightly modifying of solvents and reaction temperatures, **1a** was selectively converted to **2a** in EtOAc solvent at 80 °C in a short period of 2 hours (entry 4). Additionally, the mono-/di-fluorination selectivity could slightly been enhanced with 5 mol% $Pd(dba)_2$ in lieu of $Pd_2(dba)_3$ (entries 9-13). Reducing

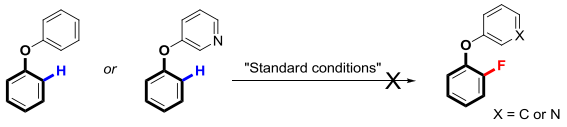
Table 2. C-H Fluorination of 2-aryloxyl pyridine.[a]



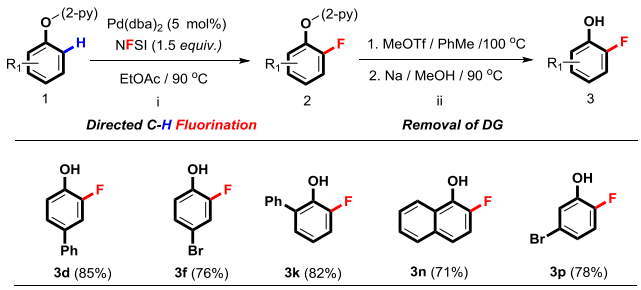
[a] Conditions: **1** (0.3 mmol), $Pd(dba)_2$ (5 mol%), NFSI (1.5 *equiv.*), EtOAc (3.0 mL), indicated temperature, under air, 2-6 h, isolated yields (unless otherwise noted). [b] $Pd(dba)_2$ (10 mol%), NFSI (2.0 equiv.), KNO_3 (30 mol%), 6h.

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



Scheme 1. Control experiments.



Scheme 2. Removal of the Directing Group.

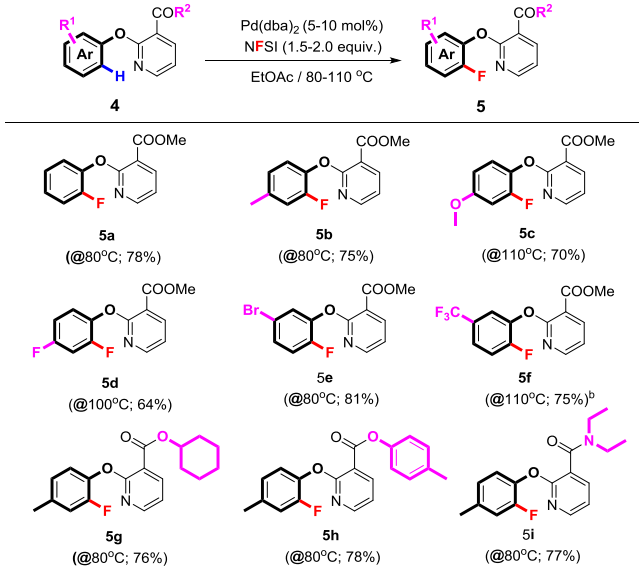
exclusively took place on the "inactive" *ortho*-C-H bond with the more "reactive" *ortho*-C-X (Cl, Br) bond remaining intact (**2l**, **2m**).[12] Steric effects adjacent to the reaction center had a remarkable influence on the reaction as evidenced by the investigation of the *meta*-functionalized 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, attempt to expand this chemistry to quinoline and a more complex estrone structure were also proved 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-phenoxy benzene and 3-phenoxy pyridine, which did not give the target fluorinated product (Scheme 1). In addition, the 2-pyridyl group can readily be removed to deliver the 2-fluorinated phenols using the previous 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]

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 are frequently appeared in pesticide industry, selective and late-stage fluorination of these bioactive structures are of great important for the modification of their lipophilicity, bioavailability and metabolic stability.[15]

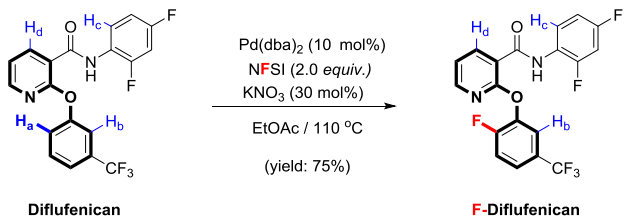
Substituted methyl 2-phenoxy nicotinates, which can facilely be prepared *via* the coupling of 2-chloronicotinate and phenols, were employed to evaluate the application prospect of the present fluorination protocol. To our delight, diverse functionalized methyl 2-phenoxy nicotinates were monofluorinated in good yields under the indicated conditions (Table 3, **5a**-**5g**). Notably, C-H bond fluorination of other nicotinates including cyclohexyl, phenyl nicotinates and *N*, *N*-diethyl nicotinamide also proceeded smoothly in good yields (**5h**-**5j**). It seemed that the carboxylate tethered at the C-3 position did not hamper the C-H bond activation directed by pyridine group, which provided an efficient route for the new pesticides discovery *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 more challenging late-stage fluorination of *diflufenican*, a widely used commercial-available herbicide in winter wheat and bar ley.[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, C-H_b bond could be cleaved 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 assisted by the amide directing group. Pleasingly, mono-fluorinated product was exclusively yielded from the 2-pyridyloxy-directed activation at the less sterically hindered C-H_a bond (Scheme 3). Late-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-contained structures.[18]



Scheme 3. Regio-selective Late-Stage C-H bond Fluorination of Diflufenican.

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 such as *diflufenican* were also implemented successfully under the present conditions. Attempt 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. General experimental procedures, characterization details and spectra copies.

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Notes

The authors declare no competing financial interest.

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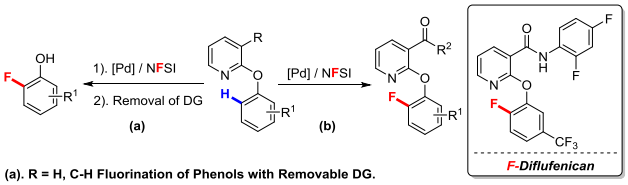

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