C–H Fluorination

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Palladium(II)-Catalyzed Selective Monofluorination of Benzoic Acids Using a Practical Auxiliary: A Weak-Coordination Approach**

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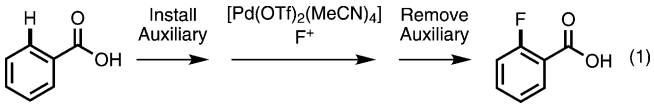
Transition-metal-catalyzed carbon–fluorine bond-forming reactions have been extensively studied because of the significant demand for versatile, mild, and regioselective methods to prepare fluorinated organic compounds, especially fluorinated arenes, which are valuable in pharmaceutical and agrochemical industries.[1,2] In addition to conventional electrophilic aromatic substitution reactions, fluorination reactions of aryl silicon, aryl boron, and aryl tin reagents using electrophilic fluorine sources mediated or catalyzed by transition metals have emerged as useful methods to prepare fluorinated arenes.[3–10] Notably, the Pd^0-catalyzed displacement of the leaving groups in aryl bromides and aryl triflates by the nucleophilic fluoride anion has also been demonstrated recently.[11] However, the development of methods to directly fluorinate unactivated aryl C–H bonds has met with limited success; only two examples of directed *ortho* C–H fluorination have been reported to date.[12,13] In both of these cases, the formation of a mixture of inseparable mono- and difluorinated arenes is often problematic for practical applications. Herein, we report the *ortho* fluorination of an important class of broadly useful benzoic acid substrates using a readily removable acidic amide as the auxiliary [Eq. (1); OTf = trifluoromethanesulfonyl]. Either mono- or



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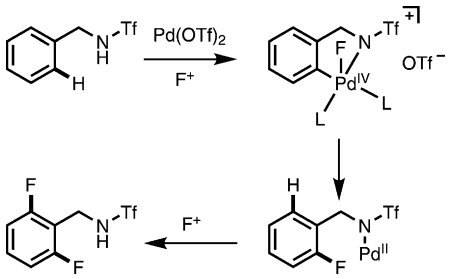
difluorinated arenes can be obtained in a highly selective manner by tuning the reaction conditions.

While a number of Pd-catalyzed electrophilic C–H halogenation reactions of synthetically useful substrates have been developed,[14] a practical protocol for catalytic C–H fluorination using electrophilic fluorine remains elusive. There are two major obstacles for developing reactions of this type. First, directed palladation of C–H bonds is significantly inhibited by the fluorinating reagents. It has been proposed that the supporting pyridine ligand of the fluorinating reagents either competes with the directing group for the binding site at the Pd^{II} center, or the electrophilic fluorine atom could complex with the Lewis basic directing group and weaken its ability to bind to the Pd^{II} center. Second, the use of $Pd(OAc)_2$, which is a broadly useful catalyst for C–H functionalization, would lead to the formation of a Pd^{IV} species following C–H activation and oxidation with F^+; C–OAc reductive elimination of this $\{Pd^{IV}(OAc)(F)\}$ species outcompetes the relatively slow C–F reductive elimination.[15–18] To address the first problem, Sanford and coworkers employed a strongly coordinating pyridine directing group to ensure cyclometalation with 2-phenylpyridines.[12] We had previously devised an X-type (Scheme 1) anionic



Scheme 1. Proposed mechanism for difluorination using an X-type directing group.

triflamide directing group to avoid direct competition with the pyridine moieties of the fluorinating reagents.[13] In addition, we used $Pd(OTf)_2$ as the catalyst to ensure selective C–F reductive elimination instead of C–OAc reductive elimination. It should also be noted that a redox-neutral Pd^{II}/Pd^{II} electrophilic cleavage pathway instead of a Pd^{II}/Pd^{IV} catalytic pathway could be operating with these weakly coordinating substrates.

Although triflamides can be converted into other functional groups to meet synthetic needs, the necessity for the presence of *ortho* or *meta* substitution to prevent difluorination is a significant limitation of the approach. The formation of the difluorination product is probably due to the slow displacement of the X-type monofluorinated product attached to the Pd^{II} center by the substrate. The use of a strongly coordinating L-type directing group such as pyridine caused similar problems.[12] We envisioned that the use of our recently developed weakly coordinating L-type acidic

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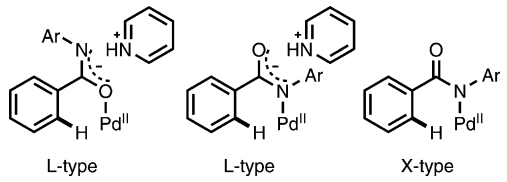
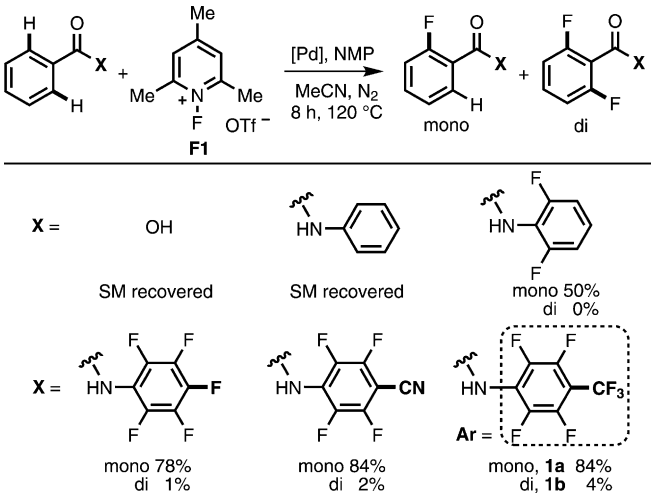
amide[19] could allow for the rapid displacement of the monofluorinated product by the substrate, thereby affording monoselectivity (Scheme 2). At this stage, the X-type coordination mode of these acidic amides cannot be ruled out and extensive investigations are being carried out in our laboratory.



Scheme 2. Three possible coordination modes.

With these considerations in mind, we initiated our study on the *ortho* fluorination of benzoic acid derivatives by carrying out a systematic tuning of the directing group (Scheme 3). Starting materials were fully recovered when

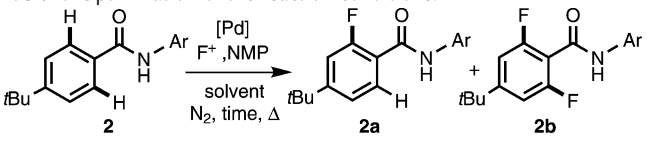


Scheme 3. Systematic tuning of the directing group. The reaction conditions used were: 0.1 mmol of substrate, 10 mol% of $[Pd(OTf)_2(MeCN)_4]$, 20 mol% of NMP, 1.5 equiv of *N*-fluoro-2,4,6-trimethylpyridinium triflate (**F1**), 2 mL of MeCN, 120°C, N_2, 8 h. The yield was determined by ^{1}H NMR analysis of the crude reaction mixture in $CDCl_3$ using CH_2Br_2 as the internal standard. NMP = *N*-methyl-2-pyrrolidinone, SM = starting material.

simple benzoic acid or *N*-phenylbenzamide were used as substrates. However, it was found that when the acidic amide *N*-2,6-difluorophenylbenzamide was treated with *N*-fluoro-2,4,6-trimethylpyridinium triflate (**F1**) and $[Pd(OTf)_2(MeCN)_4]$ (10 mol%) in MeCN at 120°C the desired monofluorinated product was obtained in 50% yield. No fluorination took place in the absence of the Pd catalyst. The yields were further improved to 84% when the acidity of the amides was increased (Scheme 3). Most importantly, only less than 5% of the difluorinated product was formed, thus providing a useful method for selectively introducing the fluorine atom at the *ortho* position.

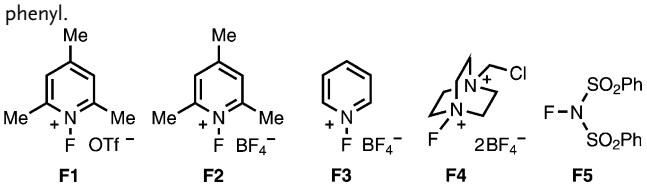
Having optimized the directing group, we subsequently carried out an extensive survey of reaction conditions using substrate **2** (Table 1). Among the solvents examined, only

Table 1: Optimization of the reaction conditions.[a]



Entry	Solvent	*T* [°C]	*t* [h]	F^+	Yield [%][b] 2a	2b	2 [%][c]
1	$PhCF_3$	120	2	**F1**	16	53	18
2	EtOAc	120	2	**F1**	15	42	8
3	MeCN	120	2	**F1**	82	5	11
4[d]	MeCN	120	2	**F1**	50	0	16
5[e]	MeCN	120	2	**F1**	76	8	9
6	MeCN	80	2	**F1**	60	0	39
7	MeCN	100	2	**F1**	73	1	25
8	MeCN	120	0.5	**F1**	50	1	49
9	MeCN	120	1	**F1**	66	1	33
10[f]	MeCN	120	2	**F1**	79	13	8
11	MeCN	120	2	**F2**	63	2	27
12	MeCN	120	2	**F3**	34	0	66
13	MeCN	120	2	**F4**	70	0	30
14	MeCN	120	2	**F5**	60	0	40

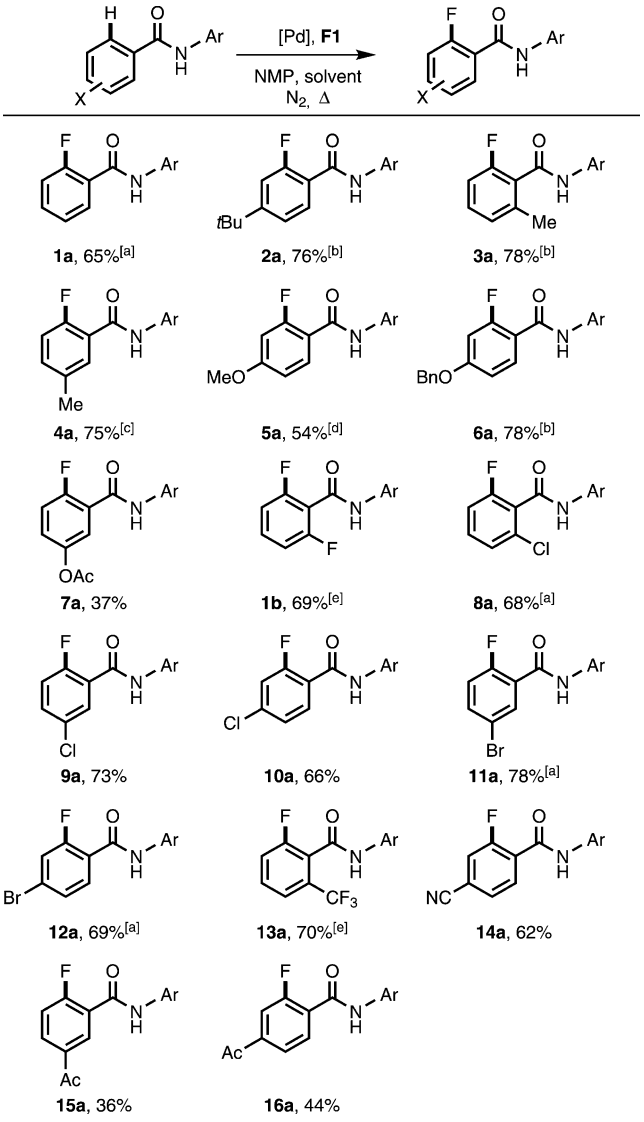
[a] Reaction conditions: 0.1 mmol of substrate, 10 mol% of $[Pd(OTf)_2(MeCN)_4]$, 20 mol% of NMP, 1.5 equiv of F^+ reagent, 2 mL of solvent, N_2. [b] Yield was determined by ^{1}H NMR analysis of the crude reaction mixture in $CDCl_3$ using CH_2Br_2 as the internal standard. [c] Recovered starting material **2**. [d] $Pd(OAc)_2$ was used. [e] No NMP was added. [f] 3.0 equiv of **F1** was used. Ar = 2,3,5,6-tetrafluoro-4-(trifluoromethyl)-phenyl.



$PhCF_3$, EtOAc, and MeCN gave the fluorinated products **2a** and **2b** in respectable yields (entries 1–3). We found that the use of MeCN as the solvent was essential for obtaining high monoselectivity (entry 3). This observation is consistent with the hypothesis that the acidic amide acts as an L-type directing group, and MeCN serves as a spectator ligand that can displace the relatively weakly coordinated L-type product from the Pd^{II} center to avoid a second fluorination (Schemes 1 and 2). When $Pd(OAc)_2$ was used as the catalyst, undesired *ortho*-acetoxylated products were consistently observed in 10–15% yields by ^{1}H NMR spectroscopy (entry 4), however, this could be prevented by using $[Pd(OTf)_2(MeCN)_4]$ (entry 3). The presence of a catalytic amount of *N*-methyl-2-pyrrolidinone (NMP) slightly improved the yield from 76 to 82% of the monofluorinated product **2a** (entries 5 and 3). The reaction temperature could be lowered from 120°C (entry 3) to 80 and 100°C (entries 6 and 7) to afford **2a** exclusively, albeit in lower yields. A gradual increase in the conversion was observed with an increase in reaction time (entries 8 and 9). Attempts to further improve the conversion by prolonging the reaction time resulted in the formation of

more difluorinated product **2b** and poorer mass balance (see the Supporting Information). Increasing the amount of the F^+ source (**F1**) from 1.5 to 3 equivalents resulted in higher conversion but inferior monoselectivity (entry 10). We also screened for other F^+ sources (entries 11–14), and found that **F1** provided the best result; notably the less-expensive fluorinating reagent Selectfluor **F4** gave a respectable 70% yield of **2a** (entry 13).

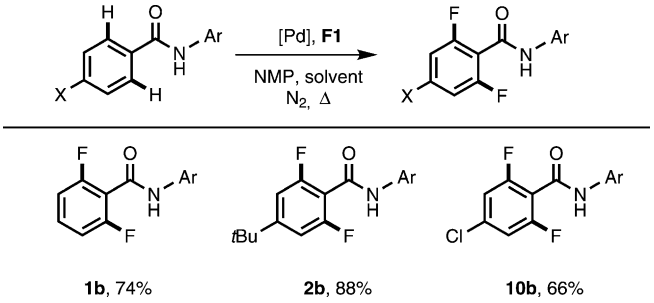
With the optimized reaction conditions established, we converted a wide variety of commercially available benzoic acids into the corresponding *N*-arylbenzamides to examine the scope of the fluorination protocol (Scheme 4). A range of



Scheme 4. Monofluorination of benzamides. Unless otherwise specified the reaction conditions used were: 0.1 mmol of substrate, 10 mol% of $[Pd(OTf)_2(MeCN)_4]$, 20 mol% of NMP, 1.5 equiv of *N*-fluoro-2,4,6-trimethylpyridinium triflate (**F1**), 2 mL of MeCN, 120°C, N_2, 24 h. The yield is of the isolated products. [a] The reaction was carried out for 8–12 h. [b] The reaction was carried out for 2–3 h. [c] The reaction was carried out at 100°C for 2 h. [d] The reaction carried out at 100°C. [e] 1 mL of $PhCF_3$ was used as the solvent, 50 mol% of NMP was used and the reaction was carried out for 2 h. Ar = 2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl.

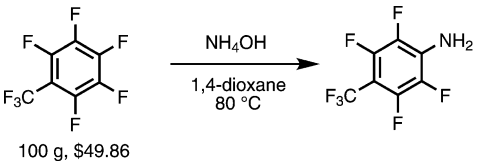
different functional groups on the aromatic ring were tolerated, albeit in various product yields. Generally, a shorter reaction time was required in the presence of electron-donating alkyl and alkoxy substituents (**2a**, **3a**, **4a**, and **6a**) and resulted in improved yields. The presence of a methoxy group led to substantial loss of material; gratifyingly, the monofluorinated product **5a** was obtained in 54% yield by carrying out the reaction at 100°C for 24 h. Substrates containing electron-withdrawing substituents and/or strongly coordinating heteroatoms, such as acetoxy, acetyl, cyano, halo, and trifluoromethyl substituents (**1b**, **7a**–**16a**), required longer reaction times and gave compromised yields. Only a trace amount of the difluorinated products was obtained, if any (see the Supporting Information). The difficulty in the chromatographic separation of the starting material, monofluorinated product, and the trace amount of difluorinated product resulted in reduced yields upon isolation. Chloro and bromo substitution at the *ortho*, *meta*, and *para* positions were tolerated (**8a**–**12a**), and these products could serve as valuable synthons for further elaboration.

To obtain the difluorinated products, we screened reaction conditions to minimize the presence of monofluorinated products, and thus facilitate the purification process. We found that fluorination in $PhCF_3$ with 3 equivalents of **F1** at 120°C for 2 h afforded the desired difluorinated products in good yields, accompanied by less than 5% of the corresponding monofluorinated products, as observed by ^1H NMR spectroscopy (Scheme 5).



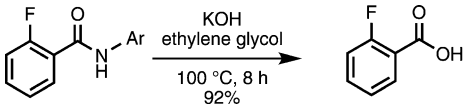
Scheme 5. Difluorination of benzamides. The reaction conditions used were: 0.1 mmol of substrate, 10 mol% of $[Pd(OTf)_2(MeCN)_4]$, 50 mol% of NMP, 3.0 equiv of *N*-fluoro-2,4,6-trimethylpyridinium triflate (**F1**), 1 mL of $PhCF_3$, 120°C, N_2, 2 h. The yield is of the isolated products. Ar = 2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl.

It merits mentioning that 4-aminoheptafluorotoluene, which is used for the preparation of the *N*-arylbenzamide substrates, can be readily prepared by treating inexpensive octafluorotoluene with ammonium hydroxide in 1,4-dioxane, or purchased from commercial sources [Eq. (2)]. After the Pd^{II}-catalyzed selective monofluorination of the *N*-arylbenzamides, base-catalyzed hydrolysis of the amides readily



(2)

furnishes the corresponding fluorinated benzoic acids in excellent yields [Eq. (3)].



(3)

In summary, we have developed a highly selective Pd^{II}-catalyzed *ortho*-monofluorination protocol for benzoic acids using a practical *N*-arylamide auxiliary. This reaction protocol has allowed us to prepare both mono- and difluorinated benzoic acid derivatives, which are of tremendous importance in the pharmaceutical and agrochemical industries. Studies to expand the scope of this reaction to simple carboxylic acid substrates without using auxiliaries are currently ongoing in our laboratory.

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