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Nitrate-promoted Selective C−H Fluorination of Benzamides and Benzeneacetamides

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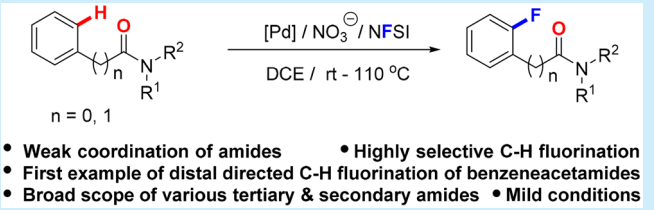
Supporting Information

ABSTRACT: A versatile and site-selective nitrate-promoted C−H bond fluorination using various weak coordinating amides as intrinsic directing groups was developed. Diverse tertiary and secondary amides underwent selective aromatic C−H bond fluorination, which features broad substrate scope, good regioselectivity, and mild conditions. Moreover, the late-stage C−H bond fluorination of the challenging benzeneacetamides via distal directing was reported for the first time.



Amides such as benzamides and benzeneacetamides are considered one of the most ubiquitous moieties among various pharmaceuticals, agrochemicals, and natural products. Moreover, organofluorides have received increasing attention in modern chemical society due to their unique properties in lipophilicity, bioavailability, and metabolic stability.[1] For instance, several *ortho*-fluorinated benzamides such as Olaparib and Xtandi serve as important antitumor drugs (Figure 1).[2]

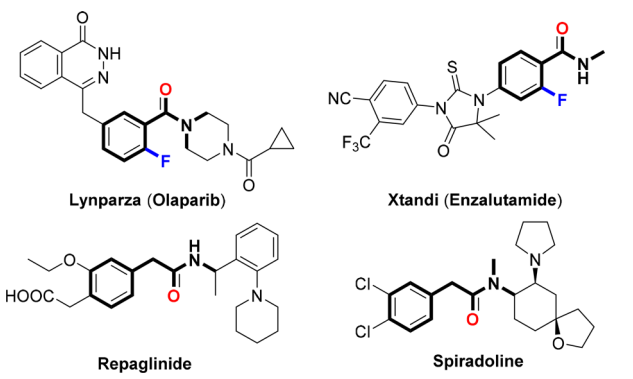


Figure 1. Representative examples of bioactive amides.

Thus, a general fluorination of various benzamides or benzeneacetamides is in growing demand for the preparation of fluorine-containing amide drugs or structure modification of their nonfluorinated analogues, especially for the fluorination of inert C−H bonds in amides.[3] Given the successful application of amides as powerful directing groups in C−H bond functionalization,[4] we envisioned that a selective C−H fluorination would be feasible via a weak coordinating mode of a palladium catalyst and the O-donor ligand of amide groups.

In several recent years, transition-metal catalyzed C−H bond fluorination assisted by different directing groups has been developed as a powerful method for the site-selective fluorination of diverse substrates.[5,6] Among which, amide groups are usually used as auxiliaries for the C−H fluorination of carboxylic acids, and the selective C−H fluorination of more general amides still remains elusive (Figure 2). For instance, Yu's group reported a

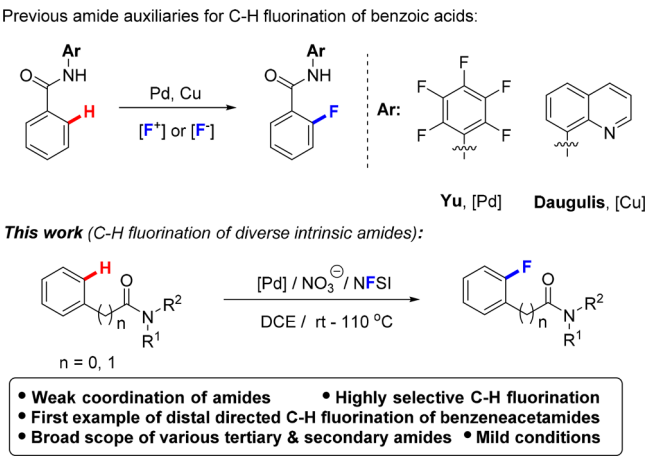


Figure 2. Selective C−H fluorination of benzamides or benzeneacetamides.

weak coordinating anionic auxiliary to access high mono/difluorination selectivity.[5e] A copper-catalyzed C−H fluorination of benzoic acids was developed by Daugulis' group using 8-aminoquinoline as a bidentate directing group.[5d] Despite the advances of using these special amides as removable auxiliaries in C−H fluorination, it would be highly desirable to develop a selective C−H fluorination protocol using diverse amides as intrinsic directing groups due to the wide application of amides in organic chemistry. Nevertheless, there are two major obstacles

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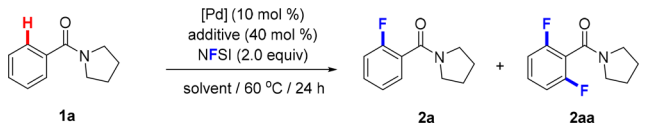
for developing C−H fluorination of amide substrates. First, amides are usually considered a weak coordinating O-donor ligand,[4a,d] which might be less efficient in the palladium catalysis, especially for the C−H fluorination of distal weak coordinating benzeneacetamides, which has not yet been achieved.[7] Second, benzamides are strong electron-withdrawing functional groups, which significantly suppress the reactivity of the aromatic rings. To address the above-mentioned issues, some in situ generated cationic palladium catalysts with enhanced electrophilicity were often used to accelerate the coordination and facilitate C−H bond activation.[8] Our group has developed a Pd−nitrate catalytic system for the mild C−H fluorination of oximes,[6b] in which a cationic palladium nitrate was proposed to promote the transformation. We proposed that a similar strategy might also promote the challenging C−H fluorination of general amides. Herein, as part of our continuous interest in the C−H fluorination of diverse general substrates,[6] we reported a nitrate-promoted selective and mild C−H bond fluorination of diverse benzamides and benzeneacetamides.

Benzamide **1a** was selected as the pilot substrate for the initial exploration (Table 1). Monofluorinated product **2a** and

Table 1. Condition Screening for C−H Bond Fluorination of Benzamides[a]



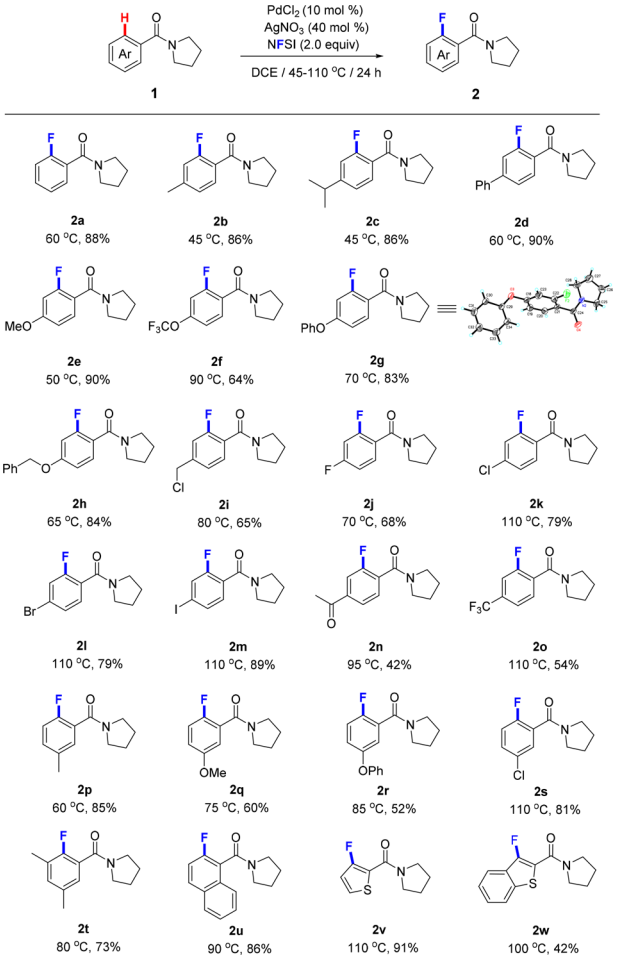
entry	[Pd]	solvent	additive (40 mol %)	yield of **2a** (%)	yield of **2aa** (%)
1	$Pd(OAc)_2$	DCE	$AgNO_3$	65	24
2	$Pd(dba)_2$	DCE	$AgNO_3$	74	2
3	$Pd(PPh_3)_4$	DCE	$AgNO_3$	76	2
4	$Pd(TFA)_2$	DCE	$AgNO_3$	64	0
5	$PdCl_2$	DCE	$AgNO_3$	91	5
6	$PdCl_2$	$CHCl_3$	$AgNO_3$	49	0
7	$PdCl_2$	PhMe	$AgNO_3$	37	0
8	$PdCl_2$	hexane	$AgNO_3$	28	0
9	$PdCl_2$	EtOAc	$AgNO_3$	25	0
10	$PdCl_2$	$MeNO_2$	$AgNO_3$	53	0
11[b]	$PdCl_2$	DCE	$AgNO_3$	45	0
12	–	DCE	$AgNO_3$	0	0
13	$PdCl_2$	DCE	–	34	0
14	$PdCl_2$	DCE	$AgNO_2$	84	2
15	$PdCl_2$	DCE	KNO_3	43	0
16	$PdCl_2$	DCE	$Ba(NO_3)_2$	48	0

[a]Conditions: **1a** (0.1 mmol), [Pd] (10 mol %), NFSI (2.0 equiv), additive (40 mol %), solvent (1.0 mL), 60 °C, under air, 24 h, GC−MS yields DCE = 1,2-dichloroethane. [b]$PdCl_2$ (5 mol %) was used.

difluorinated product **2aa** were both detected when using $Pd(OAc)_2$ as catalyst in the presence of additive $AgNO_3$, albeit in poor selectivity (**2a**/**2aa** = 65/24, entry 1). Gratefully, $PdCl_2$ exhibited superior performance among the Pd catalysts screened, which gave 91% yield of **2a** with good mono/difluorination selectivity (**2a**/**2aa** = 91/5, entry 5). Fluorinations in several other solvents were also investigated, and only moderate results were obtained (entries 6−10). Reducing the loading of catalyst to 5 mol % could also afford the desired product **2a** in moderate yield; however, omission of Pd catalyst led to a negative result (entries 11−12). As anticipated, nitrate additives played an indispensable role in this transformation, and only 34% yield of **2a** was detected in the absence of $AgNO_3$ (entry 13).[9] A comparable result was obtained with $AgNO_2$ in lieu of $AgNO_3$ (entry 14). However, other nitrate additives only gave moderate yields, probably due to the slow interaction between nitrates with palladium chloride, which indicated that the in situ generated electrophilic palladium nitrate species might initiate the catalytic cycle (entries 15−16).

With the optimized conditions in hand, we sought to explore the scope and generality of this C−H fluorination protocol. Various benzamides bearing diverse functional groups were evaluated. In general, both electron-donating and electron-withdrawing functional groups proved well tolerated (Scheme 1). Different functional groups such as alkyl, aryl, alkyoxyl,

Scheme 1. Scope of Substituted Benzamides[a]



[a]Conditions: **1** (0.2 mmol), $PdCl_2$ (10 mol %), NFSI (2.0 equiv), $AgNO_3$ (40 mol %), DCE (2.0 mL), indicated temperatures, under air, 24 h, isolated yields.

trifluoromethoxyl, and aryloxyl were compatible in the present fluorination condition (**2a**−**2g**). Moreover, substrates bearing sensitive functional groups, e.g., benzyloxyl or chloromethyl, also underwent fluorination smoothly (**2h**, **2i**). Halo groups remained intact during the Pd-catalyzed C−H fluorination (**2j**−**2m**). Relatively lower yields were obtained when strong trifluoromethyl or acetyl electron-withdrawing groups were tethered to the substrates (**2n**, **2o**). C−H fluorination of *meta*-functionalized benzamides showed remarkable steric effects, the less congested C−H sites at the *para*-position of the

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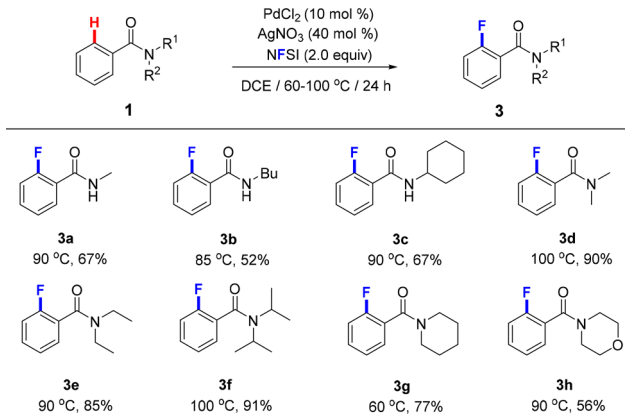
functionalities were highly selectively fluorinated (**2p**−**2s**). However, fluorination of sterically congested C−H bonds of *meta*-dimethyl benzamide also proceeded smoothly in good yield (**2t**). Notably, attempts to expand this chemistry to other aromatics such as naphthalene, thiophene, and benzothiophene were also successful (**2u**−**2w**). In addition, *ortho*-fluorination selectivity was further confirmed by the X-ray crystal structure of product **2g**.[10]

The versatile Pd-catalyzed C−H fluorination was not limited to the pyrrolidine masked benzamides. To our delight, diverse amine masked secondary and tertiary benzamides were also well tolerated, giving the monofluorinated products in moderate to excellent yields (Scheme 2). The remarkable compatibility showed a potential application prospect of the present fluorination protocol using various amides as intrinsic directing groups.

Scheme 2. Scope of Other Benzamides[a]

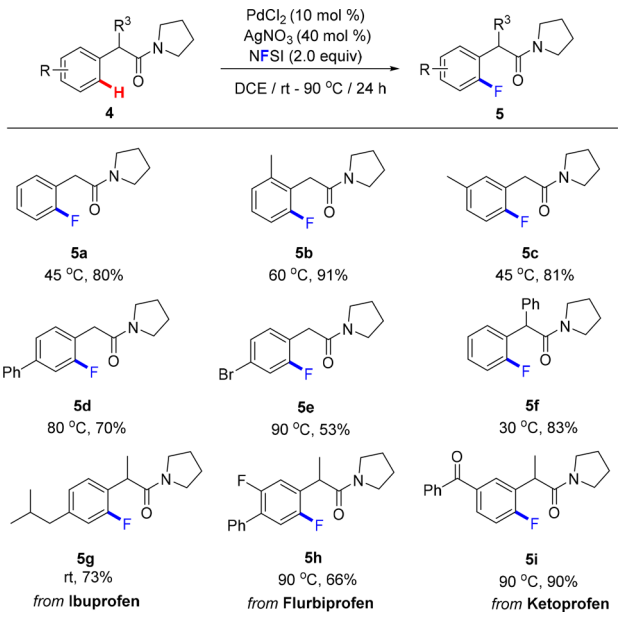


[a]Conditions: **1** (0.2 mmol), $PdCl_2$ (10 mol %), NFSI (2.0 equiv), $AgNO_3$ (40 mol %), DCE (2.0 mL), indicated temperatures, under air, 24 h, isolated yields.

Having the C−H fluorination of benzamides established, we turned our attention to the more challenging distal O-coordinating benzeneacetamides. We were pleased to find that the optimized conditions for fluorination of benzamides were also viable in the case of benzeneacetamides, giving the monofluorinated products in good yields, even at room temperature in some cases (Scheme 3). Notably, benzeneacetamides derived from commercially available phenylacetic acid drugs, e.g., ibuprofen, flurbiprofen, and ketoprofen, were identified as feasible substrates, which might provide great opportunities for the late-stage fluorinating modification of complex amide drugs.[11] To the best of our knowledge, it is the first example of C−H fluorination of various benzeneacetamides.

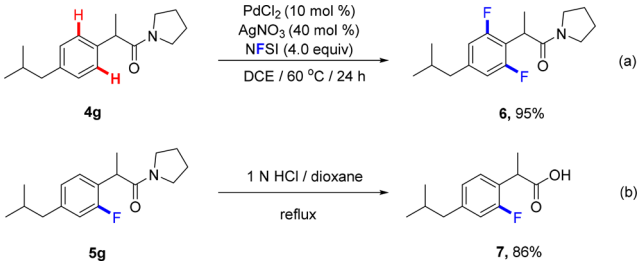
Encouraged by the remarkably mild conditions in monofluorination of ibuprofen amide **4g**, selective C−H difluorination was carried out under an elevated temperature to give the desired product **6** in excellent yield (Scheme 4a). Given the importance of phenylacetic acid drugs, the removal of the amide auxiliary took place smoothly to produce the fluorinated ibuprofen **7** in good yield (Scheme 4b). Deuterated substrate [D_1]-**1a** was prepared in order to gain a better understanding of the nature of the C−H cleavage step. A significant KIE value of 3.2 was obtained, which indicated that the C−H activation might be involved in the rate-determining step of the present fluorination (Scheme 5).[10] Based on the current results and previous reports, a plausible mechanism involving a Pd (II/IV) catalytic cycle was

Scheme 3. Scope of Substituted Benzeneacetamides[a]

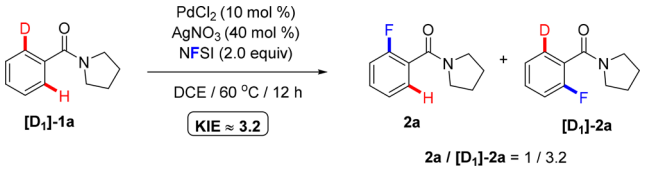


[a]Conditions: **4** (0.2 mmol), $PdCl_2$ (10 mol %), NFSI (2.0 equiv), $AgNO_3$ (40 mol %), DCE (2.0 mL), indicated temperatures, under air, 24 h, isolated yields.

Scheme 4. Transformation of Ibuprofen Derivatives



Scheme 5. Intramolecular KIE Experiment of 1a



depicted in Figure 3.[12] Though the exact role of the nitrate is still not clear so far, we believe that C−H activation should be triggered by the in situ generated palladium nitrate species, which is more electrophilic due to the nitrate anion.[9a] Pd(IV) intermediate **A** was then formed by the oxidative addition of fluorinating reagent NFSI. Notably, the ligand effect of poorly nucleophilic nitrate additive (L = NO_3) in the selective C−F

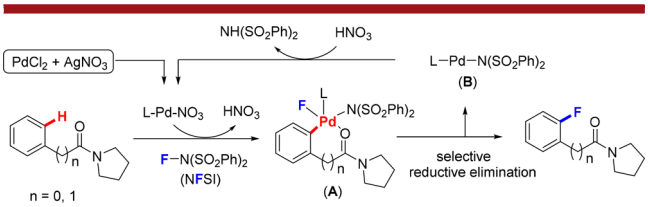


Figure 3. Proposed Mechanism.

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bond reductive elimination could not be excluded in this case.[9b] Final ligand exchange of Pd(II) intermediate **B** regenerated the reactive palladium nitrate species and drove the catalytic cycle.

In conclusion, we have developed a site-selective C−H bond fluorination of various amides via the weak coordination between their intrinsic O-donor ligand and reactive palladium catalyst. Diverse secondary and tertiary benzamides were well tolerated to give the selective monofluorination products in moderate to excellent yields. Notably, C−H fluorination of the more challenging benzeneacetamide substrates was also achieved for the first time. In addition, this reaction protocol was found to be applicable to late-stage C−H bond fluorination of some bioactive phenylacetic acid-derived amides. The present methodology has a broad substrate scope with high functional group tolerance and features mild conditions. Attempts to apply this late-stage fluorination protocol in the preparation of more useful and bioactive fluorine-containing amides are still ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00793.

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

Accession Codes

CCDC 1828843 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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