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Palladium-Catalyzed Site-Selective Fluorination of Unactivated C(sp^3)–H Bonds

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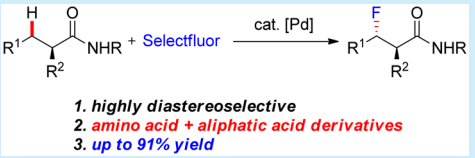
Supporting Information

ABSTRACT: The transition-metal-catalyzed direct C–H bond fluorination is an attractive synthetic tool toward the preparation of organofluorines. While many methods exist for the direct sp^3 C–H functionalization, site-selective fluorination of unactivated sp^3 carbons remains a challenge. Direct, highly site-selective and diastereoselective fluorination of aliphatic amides via a palladium-catalyzed bidentate ligand-directed C–H bond functionalization process on unactivated sp^3 carbons is reported. With this approach, a wide variety of β-fluorinated amino acid derivatives and aliphatic amides, important motifs in medicinal and agricultural chemistry, were prepared with palladium acetate as the catalyst and Selectfluor as the fluorine source.



Fluorine substitution is of great interest in the fields of medicinal chemistry, agricultural chemistry, and material science.[1] Fluorinated compounds affect nearly all physical and chemical properties including stability, solubility, lipophilicity, conformation, and bioavailability compared to the parent molecules.[2] It has been estimated that fluorine-containing molecules account for about 25% of all pharmaceuticals and 30–40% of agrochemicals, including three of the top five best-selling drugs in 2013.[3] Furthermore, the importance of fluorine in medical imaging technologies has also been demonstrated.[4] Therefore, the selective incorporation of a fluorine atom into biologically relevant organic molecules has continuously been an active research area in organic chemistry over the past 40 years.[5]

Transition-metal-catalyzed C–H functionalization has been extensively studied in past decades due to the avoidance of the prefunctionalization step in this process compared to the classical approaches.[6] Within this reaction class, site-selective direct fluorination of aromatic C–H bonds has been documented recently via a palladium or copper catalysis.[7] Despite a challenging process, transition-metal-catalyzed direct fluorination of sp^3 carbons has also been established.[8] Copper,[9] iron,[10] manganese,[11] palladium,[12] silver,[13] and vanadium[14] have all been demonstrated as effective catalysts in this process. However, current studies on unactivated sp^3 C–H bonds suffer from low to moderate site selectivity. In addition, fluorination on C–H bonds of the relatively reactive benzylic or allylic sp^3 carbons is typically favored over that on unactivated sp^3 bonds, which limits the potential applications of this approach. Inspired by the Pd-catalyzed ligand-directed C–H functionalization of unactivated β-sp^3 carbons of amides,[15] we have investigated and report here the direct site-selective fluorination of α-amino acid derivatives and aliphatic amides via palladium catalysis with the assistance of a bidentate directing group. Interestingly, closely related reports were published after original submission of this work.[16]

Fluorine-containing amino acids have attracted considerable attention in past decades due to the importance of these compounds in medicinal chemistry research.[17] Current synthetic methods of these molecules primarily relied on the nucleophilic substitution reaction, which requires preinstallation of a functional group to the C–H bonds.[18] In order to provide a direct synthetic approach for fluorinating unactivated sp^3 carbons, we began our investigation on palladium-catalyzed fluorination of amino acid derivatives with the assistance of a bidentate ligand. Although 8-aminoquinoline has been widely used as a directing group for transition-metal-catalyzed C–H functionalization, electrophilic aromatic substitution on this moiety could be a potential problem with an electrophilic fluorine reagent. Therefore, 2-(pyridin-2-yl)isopropyl amine[19] was chosen as the directing group for fluorination of the 2-aminobutyric acid derivative **1a** (Scheme 1). Initial studies showed that a trace amount of desired β-fluorinated product **2a** could be observed with 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor) as the fluorinating reagent in dichloroethane (entry 1). To our delight, the reaction yield was significantly improved with the addition of stoichiometric amounts of AgOAc or Ag_2CO_3 (entries 3 and 4). Next, an extensive solvent screening was carried out, and the mixture of dichloroethane and isobutyronitrile proved to be optimal, providing **2a** in 38% yield (entry 11). It was then found that replacement of Selectfluor with another fluorinating reagent gave no or only a trace amount of product (entries 13–15). Further screening of the palladium catalysts showed that $Pd(OAc)_2$ is optimal although several other catalysts could also

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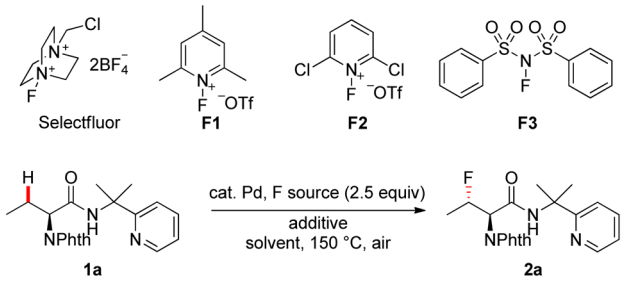
Scheme 1. Optimization of Reaction Conditions[a]



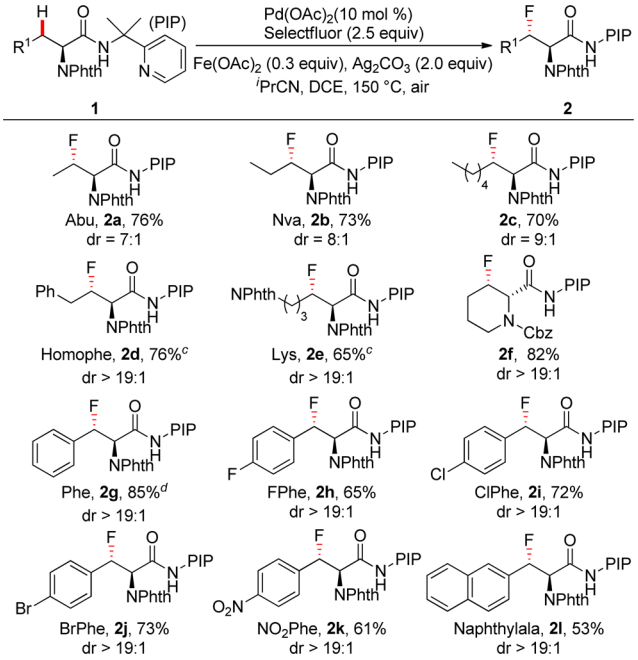
entry	Pd source (10 mol %)	additive (equiv)	solvent (mL)	yield (%)[b]
1	$Pd(OAc)_2$	-	DCE (3.0)	trace
2	$Pd(OAc)_2$	$AgNO_3$ (2.0)	DCE (3.0)	trace
3	$Pd(OAc)_2$	AgOAc (2.0)	DCE (3.0)	21
4	$Pd(OAc)_2$	Ag_2CO_3 (2.0)	DCE (3.0)	25
5	$Pd(OAc)_2$	Na_2CO_3 (2.0)	DCE (3.0)	-
6	$Pd(OAc)_2$	K_2CO_3 (2.0)	DCE (3.0)	-
7	$Pd(OAc)_2$	Ag_2CO_3 (2.0)	MeCN (3.0)	-
8	$Pd(OAc)_2$	Ag_2CO_3 (2.0)	DME (3.0)	18
9	$Pd(OAc)_2$	Ag_2CO_3 (2.0)	chloroform (3.0)	5
10	$Pd(OAc)_2$	Ag_2CO_3 (2.0)	DCE (3.0)/MeCN (0.3)	31
11	$Pd(OAc)_2$	Ag_2CO_3 (2.0)	DCE (3.0)/^{i}PrCN (0.3)	38
12	$Pd(OAc)_2$	Ag_2CO_3 (2.0)	DCE (3.0)/^{t}BuCN (0.3)	33
13[c]	$Pd(OAc)_2$	Ag_2CO_3 (2.0)	DCE (3.0)/^{i}PrCN (0.3)	-
14[d]	$Pd(OAc)_2$	Ag_2CO_3 (2.0)	DCE (3.0)/^{i}PrCN (0.3)	-
15[e]	$Pd(OAc)_2$	Ag_2CO_3 (2.0)	DCE (3.0)/^{i}PrCN (0.3)	trace
16	$Pd(TFA)_2$	Ag_2CO_3 (2.0)	DCE (3.0)/^{i}PrCN (0.3)	29
17	Pd(acac)$_2$	Ag_2CO_3 (2.0)	DCE (3.0)/^{i}PrCN (0.3)	12
18	$PdCl_2$	Ag_2CO_3 (2.0)	DCE (3.0)/^{i}PrCN (0.3)	6
19	$Pd(OAc)_2$	Ag_2CO_3 (2.0)/$Mn(OAc)_2$ (1.0)	DCE (3.0)/^{i}PrCN (0.3)	44
20	$Pd(OAc)_2$	Ag_2CO_3 (2.0)/$Fe(OAc)_2$ (1.0)	DCE (3.0)/^{i}PrCN (0.3)	56
21	$Pd(OAc)_2$	Ag_2CO_3 (2.0)/$Fe(OAc)_2$ (0.3)	DCE (3.0)/^{i}PrCN (0.3)	80(76[f])
22	-	Ag_2CO_3 (2.0)/$Fe(OAc)_2$ (0.3)	DCE (3.0)/^{i}PrCN (0.3)	-
23	$Pd(OAc)_2$	$Fe(OAc)_2$ (0.3)	DCE (3.0)/^{i}PrCN (0.3)	27

[a]Reaction conditions: **1a** (0.30 mmol), Pd source (10 mol %), F source (2.5 equiv), Ag_2CO_3 (2.0 equiv), additive, solvent, 150 °C, air, 14 h. [b]Yields are based on **1a**, determined by ^{1}H NMR using dibromomethane as internal standard. [c]2.5 equiv of **F1** were used instead of Selectfluor. [d]2.5 equiv of **F2** were used instead of Selectfluor. [e]2.5 equiv of **F3** were used instead of Selectfluor. [f]Isolated yield, dr = 7:1. Selectfluor = 1-chloromethyl-4fluoro-1,4-diasoniabicyclo[2.2.2]octanebis(tetrafluoroborate). **F1** = 1-Fluoro-2,4,6-trimethylpyridinium triflate. **F2** = 2,6-Dichloro-1-fluoropyridinium triflate. **F3** = *N*-Fluorobenzenesulfonimide.

provide the desired product (entries 16−18). Interestingly, the addition of $Mn(OAc)_2$ or $Fe(OAc)_2$ significantly improved the reaction yield, with 0.3 equiv of $Fe(OAc)_2$ giving the best result (entries 19−21). As we expected, this reaction showed high site selectivity by favoring β-C−H bonds due to the preference of the formation of a five-membered ring intermediate in the cyclopalladation step. Delightfully, high diastereoselectivity was also observed by favoring the *anti* diastereoisomer. It is noteworthy that only low to moderate diastereoselectivities have been reported in previous Pd-catalyzed sp^3 C−H functionalizations of linear aliphatic α-amino acids with relatively small functional groups, such as Me,[15g] OMe,[18a] and OAc.[20] It should be mentioned that, under the optimized conditions, 2-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)-butanamide with 8-aminoquinoline as the bidentate directing group failed to provide the corresponding β-fluorinated product.

With optimized conditions in hand, the scope of amino acids was studied (Scheme 2). As expected, good yields were obtained with linear aliphatic amino acid derivatives with high

Scheme 2. Scope of Amino Acid Derivatives[a,b]



[a]Reaction conditions: **1** (0.30 mmol), $Pd(OAc)_2$ (10 mol %), Selectfluor (2.5 equiv), Ag_2CO_3 (2.0 equiv), $Fe(OAc)_2$ (0.3 equiv), ^{i}PrCN (300 μL), 3.0 mL of DCE, 150 °C, air, 14 h. [b]Isolated yields. [c]0.25 equiv of $Fe(OAc)_2$. [d]Without $Fe(OAc)_2$. PIP = 2-(pyridin-2-yl)isopropyl.

diastereoselectivities (**2a−e**). In addition, the cyclic amino acid derivative, benzyl-2-((2-(pyridin-2-yl)propan-2-yl)carbamoyl)-piperidine-1-carboxylate (**1f**), was an effective substrate, affording the desired product **2f** in 82% yield. Moreover, a predominant preference of functionalizing β-C−H bonds over the relatively reactive benzylic γ-C−H bonds was also observed (**2d**), distinguishing this process from the current direct fluorination methods which favor the benzylic C−H bonds. Furthermore, phenylalanine and naphthylalanine derivatives were also effective substrates, providing the corresponding β-fluorinated amino acid derivatives in good yields with excellent diastereoselectivities (**2g−l**). Additionally, the structure and absolute configuration of the phenylalanine derivative ***L*-2g** (CCDC no. 1052086) were confirmed with X-ray analysis (Figure 1).

Next, a substrate scope study of nonamino acid aliphatic amides was carried out. As shown in Scheme 3, both linear and α-branched aliphatic amides afforded the desired products in

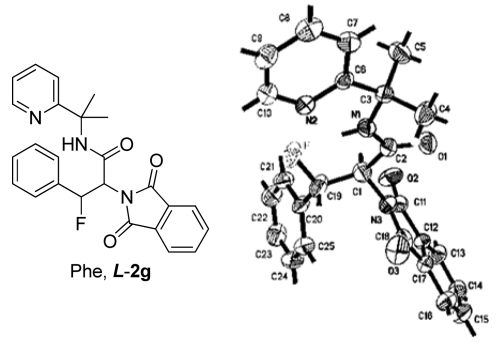


Figure 1. X-ray crystal structure of ***L*-2g**.

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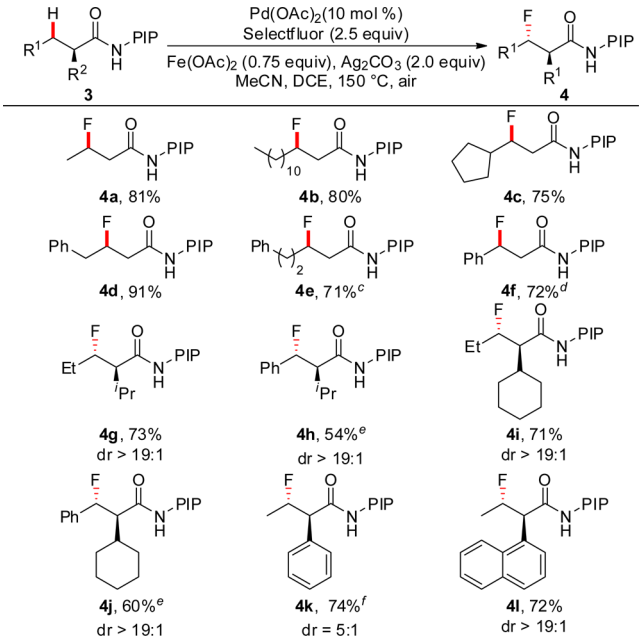
Scheme 3. Scope of Aliphatic Amides[a,b]

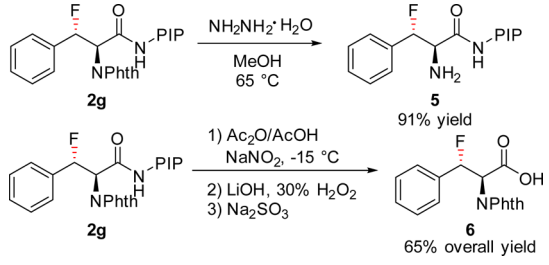


[a]Reaction conditions: **3** (0.30 mmol), $Pd(OAc)_2$ (10 mol %), Selectfluor (2.5 equiv), Ag_2CO_3 (2.0 equiv), $Fe(OAc)_2$ (0.75 equiv), MeCN (400 μL), 3.0 mL of DCE, 150 °C, air, 14 h. [b]Isolated yields. [c]3.0 equiv of Selectfluor. [d]0.2 equiv of $Fe(OAc)_2$. [e]Without $Fe(OAc)_2$. [f]0.5 equiv of $Fe(OAc)_2$. PIP = 2-(pyridin-2-yl)isopropyl.

good yields under modified reaction conditions (**4a–l**). Similarly, functionalization of β-C–H bonds was favored over the relatively reactive benzylic γ- or δ-C–H bonds (**4d** and **4e**). As expected, high diastereoselectivity was also observed with α-branched aliphatic amides (**4g–l**). Furthermore, it was found that the current process favored functionalization of β-C–H bonds of the sp^3 carbons over γ-C–H bonds of the sp^2 carbons, indicating that formation of a five-membered ring intermediate is preferred to the six-membered ring intermediate in the cyclopalladation step (**4k** and **4l**).

To further demonstrate the synthetic utility of this fluorination method, removal of the protecting and the directing group PIP was carried out, and the corresponding products were obtained in good yields (Scheme 4).

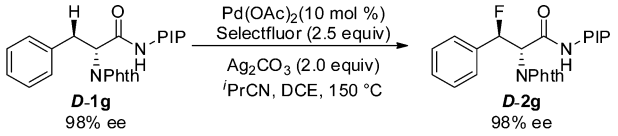
Scheme 4. Removal of Protecting Group and Directing Group



In addition, no apparent racemization of the α-chiral center was observed during the fluorination of the *D*-2-(1,3-dioxoisoindolin-2-yl)-3-phenyl-*N*-(2-(pyridin-2-yl)propan-2-yl)propanamide (***D*-1g**) (Scheme 5).

On the basis of the above obtained results and the previous reports,[7,12b,21] a plausible reaction mechanism is proposed

Scheme 5. Synthesis of *D*-2g



(Figure 2). Coordination of amide **1** or **3** to a palladium species followed by a base-promoted ligand exchange process produces

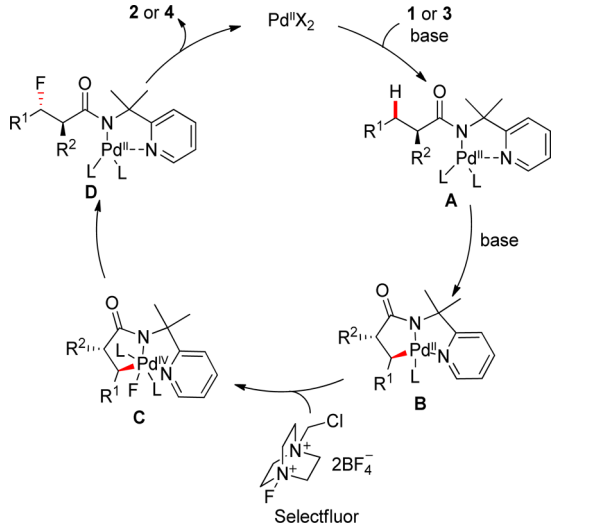


Figure 2. Proposed catalytic cycle of β-fluorination.

the palladium complex **A**. Subsequently, cyclometalation of the palladium complex **A** occurs to generate the intermediate **B** via a C–H bond activation process. Oxidative addition of the intermediate **B** with Selectfluor provides the palladium(IV) species **C**, which then gives rise to the final product **2** or **4** via reductive elimination followed by ligand dissociation.[22] Although the exact role of Ag_2CO_3 in the reaction is not clear, it is believed that this species participates in the ligand exchange and subsequent C–H bond cleavage steps by acting as a base, and also possibly promotes the oxidative addition of Selectfluor to the intermediate **B**. On the other hand, the role of $Fe(OAc)_2$ in the reaction could be the promotion of releasing Pd(II) species from the intermediate **D**.

In summary, the palladium-catalyzed ligand-directed highly site-selective fluorination of amino acid derivatives and aliphatic amides was developed via an sp^3 C–H bond functionalization process. This reaction showed high diastereoselectivity and good functional group compatibility. Additionally, a great preference for functionalizing the C–H bonds of β-sp^3 carbons over those of relatively reactive γ-sp^2 or benzylic sp^3 carbons was observed. As mentioned earlier, current methods for the direct fluorination of unactivated sp^3 carbons suffer from poor site selectivity, incompatibility with benzylic carbons, and low diastereoselectivity in many cases. Therefore, this reported process provides a complementary and advantageous approach to access fluorine-containing organic molecules. The detailed mechanistic study of this transformation is currently underway in our laboratory.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, analytical data for products, NMR spectra of products. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01710.

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Notes

The authors declare no competing financial interest.

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