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Efficient Palladium-Catalyzed C−H Fluorination of C(sp3)−H Bonds: Synthesis of β-Fluorinated Carboxylic Acids

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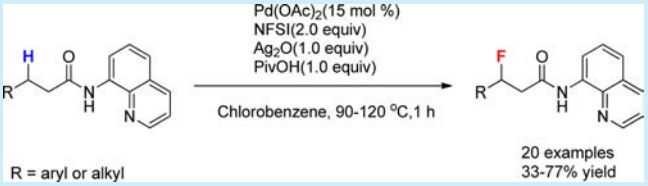
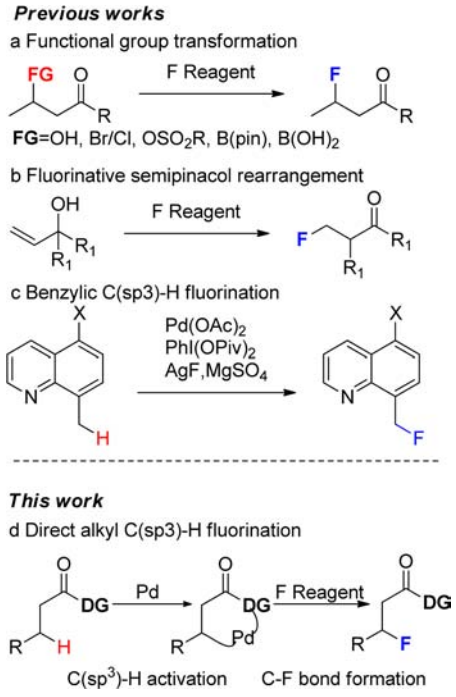
Supporting Information

ABSTRACT: A novel and facile process for direct fluorination of unactivated C(sp3)−H bonds at the β position of carboxylic acids was accomplished by a palladium(II)-catalyzed C−H activation. The addition of Ag_2O and pivalic acid was found to be crucial for the success of this transformation. This reaction provides a versatile strategy for the synthesis of β-fluorinated carboxylic acids.



It has been well recognized that fluorine's size, electronegativity, lipophilicity, and electrostatic interactions have remarkable influence on the chemical and biological activity of organic molecules. The unique properties of the fluorine atom led to its significant application in pharmaceuticals,[1] agrochemicals,[2] materials,[3] and radiotracers for positron emission tomography (PET).[4] In particular, the idea of introducing fluorine into molecules of natural products was widely used since the discovery of fludrocortisone (the first fluorine-containing pharmaceutical product).[1i] Despite the prevalence and importance of fluorinated compound utility, carbon−fluorine bond formation remains a challenge, especially the selective introduction of C−F bonds into organic molecules. It is necessary to develop a practical, selective, and efficient method for the introduction of C−F bonds into organic molecules. Despite the tremendous efforts in the development of the C−F bond next to an electron-withdrawing group using various substrates to form α-fluorinated carbonyl compounds,[5] only a few examples of incorporating fluorine into carbonyl compounds at the β-position have been reported.[6] Several efficient procedures could be used to transform alcohols,[6a] alkyl halides,[6b] alkyl sulfonates,[6c] and alkylboronates[6d] into the corresponding β-fluorinated carbonyl compounds using nucleophilic or electrophilic fluorinating agents (Scheme 1 a). Another useful strategy of building β-fluorinated carbonyl moiety is fluorinative semipinacol rearrangement[6e−g] (Scheme 1 b). However, prior installation of a functional group at the reaction site still limits the application of these procedures. Therefore, it is necessary to develop a method of direct C−H fluorination at the β-position of carbonyl. Fortunately, transition-metal-catalyzed direct functionalization of C−H bonds has developed rapidly and has emerged as a useful tool for organic synthesis over the last two decades.[7] Some examples of C−H bond activations using a directing group have been reported so far.[8] Among these discoveries of C(sp3)−H bond activation, the majority of studies were focused on C−H arylation,[8a−c] alkylation,[8d] alkoxylation,[8e,f] ethynylation,[8g] or amination.[8h] However, to the best of our knowledge, transition-metal-catalyzed C−H fluorinations are particularly rare, especially the selective introduction of fluorine to carboxylic acid β-position. Recently, some groups have reported the Pd-catalyzed conversion of C(sp2)−H bonds to C−F bonds using electrophilic fluorinating reagents (*N*-fluorobenzenesulfonimide, Selectfluor, and *N*-fluoropyridinium salts, etc.).[9] In these reactions, the C−F bond-forming reductive elimination

Scheme 1. New Approach for Unactivated Alkyl C(sp3)−H Bond Fluorination



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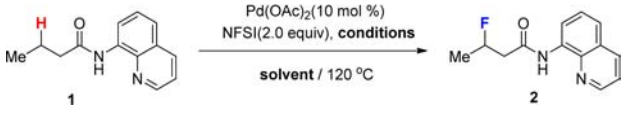
from the Pd^{IV}–F complex is believed as a key step.[10] An active $FPdN(SO_2Ph)_2$ species was suggested to be formed via the oxidative addition of Pd to the N–F bond of NFSI.[11] An early report of Sanford revealed a strategy depending on the use of a directing group (8-methylquinoline) for Pd-catalyzed fluorination of benzylic C(sp3)–H bonds (Scheme 1 c).[12a] Inspired by these successful transformations with a directing group, we hypothesized that direct fluorination of carboxylic acids at β-position could be accomplished via C–H activation with the aid of a directing group (Scheme 1 d). Just as we prepared our paper, Yu and Shi reported their research results of direct fluorination at β-position of amino acids by Pd-catalyzed, respectively.[12b,c] Our method, while similar to these publications in strategy and products, is still relevant for the more general substrate scope and conditions. Herein, we report the Pd-catalyzed fluorination of an unactivated methylene to form β-fluorinated carboxylic acids. This β-C(sp3)–H fluorination of carboxylic acids can provide a new method for the introduction of fluorine atom into a drug candidate which is of great value for SAR studies.[1f,j]

To test this hypothesis, a model study was initiated with butyramide derivative **1**, which contains an 8-aminoquinoline-derived auxiliary (Table 1).[13] This specific auxiliary[8a,g,14] was

Table 1. Optimization of the Reaction Conditions[a]



entry	conditions[b]	solvent	T (°C)	yield[c] (%)
1		xylene	120	0
2	Ag_2O	xylene	120	4
3	Ag_2O + AcOH	xylene	120	13
4	Ag_2O + $NaHCO_3$	xylene	120	0
5	Ag_2O + PivOH	xylene	120	37
6	Ag_2CO_3 + PivOH	xylene	120	7
7	$Cu(OAc)_2$ + PivOH	xylene	120	0
8	Ag_2O + PivOH	1,2-dichlorobenzene	120	41
9	Ag_2O + PivOH	DMF	120	0
10	Ag_2O + PivOH	chlorobenzene	120	70
11	Ag_2O + vOH	toluene	120	40
12	Ag_2O + PivOH	dioxane	120	0
13	Ag_2O + PivOH	MeCN	120	0
14[d]	Ag_2O + PivOH	chlorobenzene	120	83 (58[e])
15[f]	Ag_2O + PivOH	chlorobenzene	120	0
16[g]	Ag_2O + PivOH	chlorobenzene	rt	trace
17[g]	Ag_2O + PivOH	chlorobenzene	50	15
18[g]	Ag_2O + PivOH	chlorobenzene	80	45

[a]Standard reaction conditions: **1** (0.2 mmol), $Pd(OAc)_2$ (0.02 mmol), NFSI (0.4 mmol), solvent (1.5 mL), 1 h. [b]Used 1.0 equiv each additive. [c]Yields were determined by HPLC using area normalization method. [d]$Pd(OAc)_2$ (15 mol %). [e]Yields of isolated product. [f]No $Pd(OAc)_2$. [g]12 h.

first described by Daugulis and co-workers and has been developed as an effective directing group for the activation of C–H bonds. At the beginning of our investigations, it was found that **1** failed to undergo the fluorination reaction upon treatment with $Pd(OAc)_2$ (10 mol %) and NFSI (as F source and oxidant at the same time[11b]) at 120 °C, and butyramide derivative **1** was recovered after 24 h (entry 1). Next, a variety of oxidants, such as $PhI(OAc)_2$, $K_2S_2O_8$, $NaIO_4$, Ag_2O, DMP (Dess–Martin periodinane), BQ (benzoquinone), Cu_2O, and $NaNO_2$, were examined in the presence of $Pd(OAc)_2$ and NFSI in a xylene system. Among them, only a small amount of the desired product **2**[15] (4%) was observed with Ag_2O (entry 2). However, further attempts failed to improve the yields. Considering that NFSI is also a nitrogen source in C–H amination reactions,[16] the active $FPdN(SO_2Ph)_2$ species can potentially undergo competing C–N and C–F bond-forming reductive elimination. Recently, Sanford and co-workers designed a model complex to study competing C(sp3)–F and C(sp3)–NHTs bond-forming reductive elimination from Pd^{IV}.[10e] In their study, acids that can protonate $TsNH^-$ should remove this nucleophile from solution, thereby leading to increased reductive elimination selectivity. Bearing this in mind, we turned our attention to adding acid additives to the catalyst system. To our delight, fluorination product **2** was observed in 13% yield in the presence of AcOH (entry 3), and the basic additive $NaHCO_3$ did not work as expected (entry 4). Inspired by the significant role of AcOH, we then screened various acids including propionic acid, *n*-butyric acid, trifluoroacetic acid (TFA), pivalic acid (PivOH), *p*-toluenesulfonic acid (TsOH), benzoic acid, phenylacetic acid, and formic acid. These investigations revealed that PivOH was superior to AcOH with a notably higher level of yield (entry 5). However, further attempts to exchange oxidants (Ag reagent) failed to improve the yields. All other metal salts[13] were found to be much less effective than Ag_2O, and little or no fluorination product was obtained (entries 6 and 7). Subsequently, a series of solvents, including toluene, MeCN, dioxane, DMF, CH_3NO_2, ethylene glycol dimethyl ether, benzonitrile, THF, 1,2-dichlorobenzene, chlorobenzene, 1,2-dichloroethane, *p*-chlorotoluene, and *o*-xylene, were screened (entries 8–13). The results indicated that chlorobenzene, which gave better results than others, was the most suitable solvent for this protocol, and a higher $Pd(OAc)_2$ loading (15 mol %) afforded product **2** in 83% yields when chlorobenzene was used as the solvent (entry 14). To our surprise, the reaction can take place at much lower temperature, such as 80 °C, though in low yield (entry 18). Finally, a control reaction showed that omission of the $Pd(OAc)_2$ catalyst resulted in complete inactivity of this catalytic system (entry 15).

Having identified the optimized conditions, we set out to explore the scope for this new reaction. As displayed in Scheme 2, the scope of this new C–H fluorination reaction was found to be very broad. Substrates of linear carboxylic acid derivatives **2**–**4** were smoothly β-monofluorinated in modest yields 57–60% under optimized reaction conditions. In contrast, substrates of branched carboxylic acid derivatives **6** and **7** were less reactive. However, fluorination of methyl groups of propanoic acid derivative **9** gave a relatively low yield of 33%. Gratifyingly, this new method was successfully applied in cyclic methylene C–H bonds as well (**10**–**12**). Besides monofluorination products, difluorination can be obtained as the major products (**11** and **12**) with a higher fluorine source loading in a satisfactory yield of 46% and 45%. As shown in Scheme 2, the fluorination of amino acid **5** using N-protected α-amino butyramide also gave the corresponding fluoride under this condition.

To further expand the scope of this new reaction, we examined the efficiency of our protocol in fluorination of benzylic C(sp3)–H bonds. As demonstrated in Scheme 3, the optimized reaction conditions were found to be effective in the

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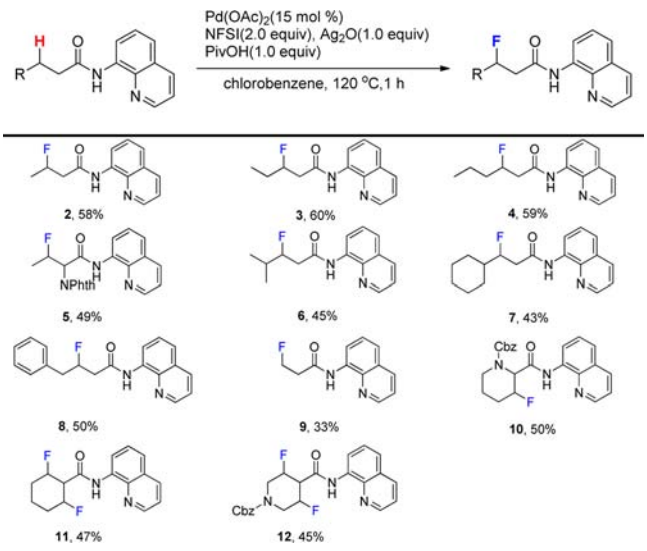
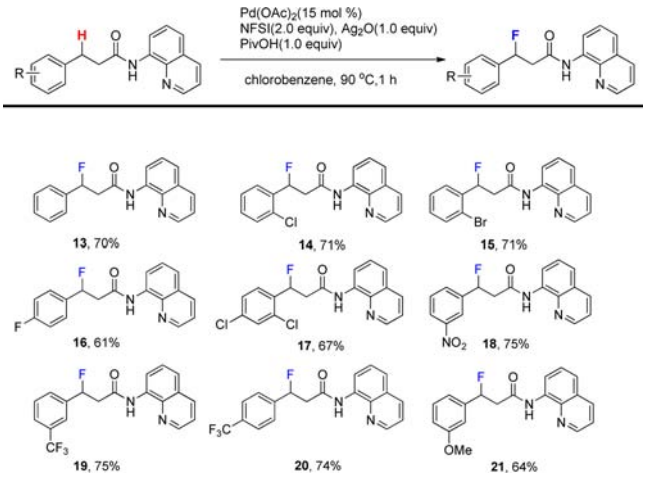
Scheme 2. Unactivated Aliphatic C(sp3)−H Bond Fluorination[a,b]



[a]Experiments were performed with **1** (0.2 mmol), $Pd(OAc)_2$ (0.03 mmol), NFSI (0.4 mmol), Ag_2O (0.2 mmol), PivOH (0.2 mmol), in chlorobenzene (1.5 mL) for 1 h at 120 °C. [b]The numbers refer to isolated yields.

Scheme 3. Benzylic C(sp3)−H Bond Fluorination of Benzenepropanamide Derivatives[a,b]

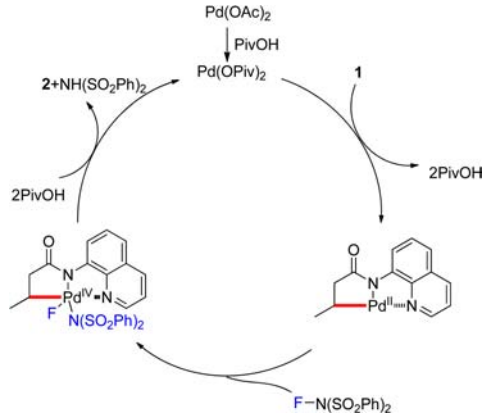


[a]Experiments were performed with **1** (0.2 mmol), $Pd(OAc)_2$ (0.03 mmol), NFSI (0.4 mmol), Ag_2O (0.2 mmol), PivOH (0.2 mmol), in chlorobenzene (1.5 mL) for 1 h at 90 °C. [b]The numbers refer to isolated yields.

fluorination of benzylidene. To our delight, fluorination of benzenepropanamide derivatives with no substituents **13** gives better yield than butyramide derivative, and the reaction could take place at lower temperature (90 °C). Encouraged by this outcome, we examined some halogen substituents such as *o*-Cl, *o*-Br, *p*-F, and 2,4-Cl substrates **14**−**17**. All of them gave similar yields. The electron-withdrawing substituent derivatives including *m*-NO_2, *m*-CF_3, *p*-CF_3, and *m*-OCH_3 (**18**−**21**) also render a good yield under these conditions.

Although a full mechanistic understanding of this reaction still requires further experimentation, based on the related results reported[10] and those obtained in this work, a plausible mechanism is illustrated in Scheme 4. The first step involves

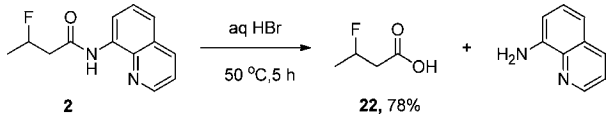
Scheme 4. Proposed Mechanism



the quinolone and the amide N atom chelate-directed C(sp3)−H activation of the substrate to afford the [5,5]-fused bicyclic cyclopalladated intermediate A. Then, Pd^{II} is oxidized into a Pd^{IV} intermediate[7d,17] by NFSI and Ag_2O (the presence of Ag_2O was also crucial for this reaction to proceed). The role of PivOH in this reaction is presumably to help reductive elimination of strong metal−fluorine bond by replacing the $N(SO_2Ph)_2$ ligand on Pd^{IV} complex or to help regenerate the active catalyst by replacing the $N(SO_2Ph)_2$ ligand on Pd^{II}. Finally, reductive elimination of C leads to the fluorination product D with concomitant regeneration of Pd^{II}.

Finally a one-step deprotection procedure can easily remove the 8-aminoquinoline-derived auxiliary with aqueous HBr.[18] Thus, the desired *β*-fluorinated carboxylic acids **22** were obtained in a modest yield of 78%, with the recovery of an appreciable amount of 8-aminoquinoline (Scheme 5).

Scheme 5. Removal of the Directing Group



In summary, we have developed a novel palladium(II)-catalyzed fluorination of unactivated methylene and methyl C(sp3)−H bonds at the *β*-position of carboxylic acids. The reaction reveals excellent reactivity, good functional group tolerance, and moderate-to-high yields. The success of this C−H fluorination reaction suggests a general strategy for late-stage drug diversification. Ongoing efforts in our laboratories will explore the mechanism of the current transformation and expand the scope of this transformation to diverse C(sp3)−H substrates as well as the applicability of the present catalytic system.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectroscopic data for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01774.

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Author Contributions

[§]Q.Z. and D.J. contributed equally.

Notes

The authors declare no competing financial interest.

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