Pd-catalyzed fluoro-carbonylation of aryl, vinyl, and heteroaryl iodides using 2-(difluoromethoxy)-5-nitropyridine

Yumeng Liang1, Zhengyu Zhao1 & Norio Shibata1,2✉

Acyl fluorides have recently gained a lot of attention as robust and versatile synthetic tools in synthetic chemistry. While several synthetic routes to acyl fluorides have been reported, a procedure involving direct insertion of the “fluoro-carbonyl” moiety using a single reagent has not yet been realized. Here we report the preparation of acyl fluorides by palladium-catalyzed fluoro-carbonylation of aryl, vinyl, and heteroaryl iodides using 2-(difluoromethoxy)-5-nitropyridine under CO-free conditions. 2-(difluoromethoxy)-5-nitropyridine is a stable, colorless solid that can be used as an alternative to the toxic gaseous formyl fluoride, which is commonly used under fluoride catalysis conditions. A wide variety of acyl fluorides are efficiently and safely obtained in high yield (up to 99%). A broad range of functional groups is tolerated under the optimized reaction conditions and the method can be applied to the late-stage fluoro-carbonylation of structurally complex Csp2-iodides, including bioactive derivatives, such as Fenofibrate, Isoxepac, and Tocopherol. Furthermore, the one-pot transformation of aryl-iodides, including drug-like molecules, into the corresponding amides by successive fluoro-carbonylation/amidation reactions, demonstrates the potential synthetic utility of this strategy.
During the last few decades, fluorinated molecules have found widespread applications in pharmaceuticals, agrochemicals, and functional materials. Fluorinated organic compounds have also been in high demand as substrates, reagents, and solvents for general organic chemistry. Among the plethora of fluorinated compounds, we have been particularly interested in acyl fluorides (R-COFs), especially aroyl fluorides (Ar-COFs). Due to the inertness of the C-F bond, the properties and reactivity of R-COFs are very different from those of other acyl halides and their equivalents. R-COFs are robust and can avoid the use of toxic and or unstable reagents. However, methods for the direct insertion of the “fluoro-carbonyl” moiety, i.e., “F-C=O”, using a single reagent has not yet been realized. Although gaseous formyl fluoride (F-C(O)H), a potential precursor for an “F-C=O” moiety, has been reported, formyl fluoride is fundamentally impractical due to its instability, potential toxicity, and the difficulties associated with its handling. In fact, formyl fluoride has not yet been used for fluorocarbonylation reactions, while formylation reactions with formyl fluoride represent an established area of research.

The first group, which involves the fluorination of carboxylic acids or their derivatives, including aldehydes via deoxyfluorinations, halogen-exchange reactions, or C-H activation reactions, is the central area of the traditional research (type I, cleavage 1 in Fig. 1b). The other group includes step-wise fluorocarbonylation reactions of organic halides using a combination of toxic gaseous carbon monoxide (CO) or more stable alternative sources of CO, and fluorinating reagents. Currently, the synthetic routes to R-COFs are categorized into two groups.

Fig. 1 Acyl fluorides. a) Synthetic utility, b) retrosynthetic, c) conceptual illustration of fluoro-carbonylation reactions, and d) this work.
research. We thus designed a type III strategy that is based on the fluoride-catalyzed in-situ generation of formyl fluoride, followed by a cross-coupling reaction with aryl halides in the presence of a Pd-catalyst. Initially, the difluoromethoxy anion (–OCF₂H), should be generated from difluoromethoxy ether under fluoride catalysis, and the resulting difluoromethoxy anion can be expected, given its instability, to spontaneously decompose into formyl fluoride by releasing a fluoride anion (F⁻), which is responsible for the negative fluoride effect. Subsequently, the generated formyl fluoride can be used in cross-coupling reactions with aryl halides under Pd-catalysis.

Herein, we report this strategy for the straightforward fluoro-carbonylation of aryl iodides (Ar-I, 1) by using 2-(difluoromethoxy)-5-nitropyridine (2) as both a CO and F source under Pd-catalyzed cross-coupling conditions.

The treatment of 1 with 2 in the presence of CsF furnishes the corresponding aryl fluoride (Ar-CF₂O, 3) in good to high yield. The reactions also proceed well using only a catalytic amount of CsF, provided a stoichiometric amount of a base is added. This cross-coupling reaction using 2 works not only for aryl iodides but can also be extended to aryl halides and heteroaryl iodides available. This cross-coupling reaction using 2 afforded the desired products (3j–3n) in generally good to excellent yield. Meta-substituted aryl iodides (1j–1k) afforded the desired products (3j–3k) in high yield. Sterically hindered ortho-substituted 1l provided 3l in good yield without hampering the reactivity. It should be noted here that the procedure was also efficient for alkyl iodides (1o, 1p), which provided 3o and 3p in excellent yield. Heterocyclic aryl iodides (1q–1t) can also be used and generate the desired products (3q–3t) in good to excellent yield; the results of other heterocyclic aryl substituents are discussed later.

Reactions of α-iodostyrene (1u) and the aliphatic olefin substrate 1v also proceeded smoothly and afforded the desired products (3u, 3v) in acceptable yield. Due to the hydrolysis of the products during purification and the volatility of some products, the isolated product yields are usually lower than the 19F NMR yields, albeit isolation is possible via column chromatography on silica gel. Interestingly, the reaction can also be scaled up; when the reaction was carried out on a 4.5-mmol scale, 3a was isolated in 90% yield.

To highlight the synthetic utility of this procedure, we used 2 for the late-stage fluoro-carbonylation of natural products and bioactive molecules derivatives. As shown in Fig. 2c, menthol was functionalized to afford 3w in 35% yield (84% 19F NMR yield). Fenoibrate, a synthetic phenoxy-isobutyric acid derivate and produg with antihyperlipidemic activity, the fluoro-carbonylation of a fenofibrate derivative 1x furnished 3x in 40% yield (88% 19F NMR yield). Estrone, arguably one of the most important mammalian estrogens, was transformed into 3y and 3z in good yield. Isoxepac, an anti-inflammatory with analgesic and antipyretic activity, afforded 3za in 63% (87% 19F NMR yield). Tocopherol, which exhibits antioxidant activity, could also be fluoro-carbonylated to generate 3zb in 75% (93% 19F NMR yield).

The fluoro-carbonylation of a testosterone derivative furnished the desired fluoroacetylated product (3zc) in 15% (61% 19F NMR yield).
Synthetic application I. As mentioned in “Introduction”, acyl fluorides represent a potent platform for a variety of chemical transformations. To demonstrate the broad synthetic utility of 3, we carried out eight chemical transformations using 3a (Fig. 4). Specifically, 3a was successfully transformed into amide 7a (95%), ester 8a (85%), and thioester 9a (76%) by reaction with the heteroatom nucleophiles aniline, phenol, and p-tolyl-thiol, respectively, in the presence of triethylamine in DMF at rt. A Pd-catalyzed cross-coupling reaction of respectively, in the presence of triethylamine in DMF at rt. A Pd-catalyzed cross-coupling reaction of 3a with PhB(OH)2 using Pd(OAc)2 (2.5 mol%) and PCy3 (10.0 mol%) in the presence of KF under the optimized conditions: 1a (0.1 mmol), 2 (0.2 mmol, 2.0 equiv), CsF (0.2 mmol, 2.0 equiv), Pd, and ligand were stirred for 15 h at 70 °C in anhydrous DMF (1.5 mL).

Table 1 Optimization of the reaction conditions for the fluoro-carbonylation of 1 and 2.

| Entry | Pd (mol%) | Ligand (mol%) | CsF (equiv) | Yield* |
|-------|-----------|---------------|-------------|--------|
| 1     | Pd(OAc)2 (10) | PPh3 (10)    | 2.0         | 73     |
| 2     | –         | PPh3 (10)    | 2.0         | 0      |
| 3     | Pd(OAc)2 (10) | –             | 2.0         | 18     |
| 4     | Pd(OAc)2 (10) | PPh3 (20)    | 2.0         | 77     |
| 5     | Pd(OAc)2 (10) | PPh3 (30)    | 2.0         | 84     |
| 6     | Pd(OAc)2 (10) | PPh3 (40)    | 2.0         | 77     |
| 7     | Pd(TFA)2 (10) | PPh3 (30)    | 2.0         | 95     |
| 8     | Pd(TFA)2 (10) | TFP (30)     | 2.0         | 83     |
| 9     | Pd(TFA)2 (10) | PCy3 (30)    | 2.0         | 43     |
| 10    | Pd(TFA)2 (10) | PCy3 (30)    | 2.0         | 40     |
| 11    | Pd(TFA)2 (10) | Xphos (30)   | 2.0         | 49     |
| 12    | Pd(TFA)2 (10) | P(o-Tol)3 (30) | 2.0 | 40     |
| 13    | Pd(TFA)2 (10) | DPPE (15)    | 2.0         | 74     |
| 14    | Pd(TFA)2 (10) | BINAP (15)   | 2.0         | 84     |
| 15    | Pd(TFA)2 (10) | DPEphos (15) | 2.0         | 86     |
| 16b   | Pd(TFA)2 (10) | Xanthos (15) | 2.0         | >99 (92) |
| 16c   | Pd(TFA)2 (10) | Xanthos (1.5) | 1.5 | >99 (92) |

Conditions: **a** Determined by 19F NMR spectroscopy. The numbers in parentheses refer to the isolated yield.

Synthetic application II. Since the reaction conditions for these fluoro-carbonylation reactions are relatively mild, we examined a one-pot synthesis of amides 7 from aryl iodides 1 via a fluoro-carbonylation/amidation reaction mechanism. To shed light on the underlying reaction mechanism, we examined a series of experiments under reaction conditions that are slightly different from the optimal conditions (entry 1, Table 2). Initially, we carried out the reaction under the optimized conditions: 2 (1.2 equiv), CsF (1.5 equiv), Pd(TFA)2 (1.0 mol%), and Xanthos (1.5 mol%) in DMF, but using a catalytic amount of CsF (10 mol%). This dramatically decreased the yield of 3a to 10% (entries 1 and 2), albeit that the yield was recovered to 70% (entry 3) in the presence of a stoichiometric amount of Cs2CO3. Stoichiometric amounts of organic bases such as Et3N or N,N-dimethyl-4-aminopyridine (DMAP) are also effective for this transformation in the presence of a catalytic amount of CsF to furnish 3a in 51 and 79% yield, respectively (entries 4 and 5). These results suggest that the fluoride in 3a stems from 2, not from CsF. Subsequently, we changed the order...
of the reagents (entries 6 and 7). When 1a was first treated with Pd(TFA)₂ (1.0 mol%) and Xantphos (1.5 mol%) at 70 °C for 5 h in DMF, and then with 2 (1.2 equiv) and CsF (1.5 equiv) at 70 °C for another 5 h in DMF, 3a was obtained in 97% yield (entry 6). However, only 6% of 3a was detected when the order of addition was reversed, i.e., when 2 was treated with CsF, Pd(TFA)₂, and Xantphos in DMF at 70 °C for 5 h, followed by the addition of 1a (entry 7). Since the optimized reaction conditions (entry 1, Table 2) refer to a reaction where all reagents are mixed from the beginning, it can be concluded that the reaction of 1a with the Pd-catalyst is much faster than the reaction of formyl fluoride with the Pd-catalyst.

Based on these experiments, additional ¹⁹F NMR experiments, and mass spectroscopy analyses (for details, see Supplementary Figs. 26–28) as well as information from the literature, we would like to propose a plausible reaction mechanism (Fig. 6). Reaction mechanism starts with the generation of a phosphine-ligated Pd(0) species (LnPd⁰), which undergoes an oxidative addition into the C–I bond of Ar–I (1a), resulting in the formation of aryl Pd(II) species. Related pathways, involving related complexes, would directly afford 3a under regeneration of the Pd(0) catalyst. Related pathways, involving β-hydride elimination, steps for cross-coupling reactions, have been reported by Martin (Pd-catalysis)⁶², Newman (Ni-catalysis),⁶³, and Lee.

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**Table 2.**

| R–I | R–F |
|-----|-----|
| 1a  | 3a  |
| 1b  | 3b  |
| 1c  | 3c  |
| 1d  | 3d  |
| 1e  | 3e  |
| 1f  | 3f  |
| 1g  | 3g  |
| 1h  | 3h  |
| 1i  | 3i  |
| 1j  | 3j  |
| 1k  | 3k  |
| 1l  | 3l  |
| 1m  | 3m  |
| 1n  | 3n  |
| 1o  | 3o  |
| 1p  | 3p  |
| 1q  | 3q  |
| 1r  | 3r  |
| 1s  | 3s  |
| 1t  | 3t  |
| 1u  | 3u  |
| 1v  | 3v  |
| 1w  | 3w  |
| 1x  | 3x  |
| 1y  | 3y  |
| 1z  | 3z  |

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**Fig. 3.** Substrate scope and gram-scale reaction of 3a. Yield values refer to products isolated on a 0.3 mmol scale; yield values in parentheses were determined by ¹⁹F NMR spectroscopy. ²2 (0.45 mmol, 1.2 equiv) and CsF (0.6 mmol, 2.0 equiv) was used.
However, the details of the reaction mechanism remain to be determined.

In summary, we have developed an efficient strategy for the Pd-catalyzed fluoro-carbonylation of aryl, vinyl, and heteroaryl iodides using formyl fluoride that is generated spontaneously from 2-(difluoromethoxy)-5-nitropyridine (2). The high reactivity and broad applicability of this synthetic methodology suggest that this protocol may become a compelling alternative synthetic route to acyl fluorides, which represent essential intermediates in the process of pharmaceutical integration. So far, four methods for the Pd-catalyzed (or mediated) fluoro-carbonylation have been reported using toxic CO (Tanaka50, Kiji51, Hiyama52) or a stable CO-equivalent (Manabe53) with different combinations of fluoride sources; in comparison, our method exhibits a substantially broader substrate scope and uses 2 as a combined source of CO and fluoride. Further investigations into the extension of this fluoro-carbonylation strategy to generate more complex substrates, as well as establishing the details of the reaction mechanism, are currently in progress in our laboratory.

Fig. 4 Chemical diversification of 3a. Reaction conditions: a PhNH2 (2.0 equiv), NEt3 (3.0 equiv), DMF, rt. b PhOH (1.2 equiv), NEt3 (2.0 equiv), DMF, rt. c 4-Me-PhSH (1.2 equiv), NEt3 (2.0 equiv), DMF, rt. d PhB(OH)2 (1.5 equiv), Pd(OAc)2 (2.5 mol%), PCy3 (10.0 mol%), KF (1.5 equiv), toluene, 120 °C. e NaBH4 (1.0 equiv), iPrOH, rt. f H2O, reflux. g HSiEt3 (1.4 equiv), Pd(OAc)2 (2.5 mol%), PCy3 (7.5 mol%), toluene, 100 °C. h HSiEt3 (1.4 equiv), Pd(OAc)2 (2.5 mol%), DCPE (3.8 mol%), toluene, 100 °C. For full experimental details, see Supplementary Figs. 10-17.

Fig. 5 One-pot amidations of 1 to afford 7. Yield values refer to products 7 isolated on a 0.3 mmol scale. Yield values in parentheses refer to the yield of intermediates 3 as determined by a 19F NMR spectroscopic analysis of the reaction mixture without a work-up procedure. a (0.45 mmol, 1.5 equiv) and CsF (0.6 mmol, 2.0 equiv) was used. For full experimental details, see Supplementary Figs. 18-24.
Methods

General procedure for the generation of acyl fluorides 3a using a stoichiometric amount of CsF. An oven-dried vessel containing a magnetic stirrer bar was charged with Pd(TFA)\textsubscript{2} (1.0 mg, 0.003 mmol, 1.0 mol%), Xantphos (2.6 mg, 0.0045 mmol, 1.5 mol%), CsF (68.4 mg, 0.45 mmol, 1.5 equiv), and anhydrous N,N-dimethylformamide (DMF, 2.0 mL, 0.15 M) in a nitrogen-filled glovebox. After stirring the reaction mixture for 10 min at room temperature, 2 (0.36 mmol, 1.2 equiv) and aryl iodide 1a (0.3 mmol, 1.0 equiv) were added. The vessel was capped with a rubber septum, removed from the glovebox, and stirred for 15 h at 70 °C. Then, the mixture was cooled to room temperature and the yield (>99%) was determined by 19F NMR analysis of the crude reaction mixture using C\textsubscript{6}H\textsubscript{5}F (28.5 μL, 0.3 mmol, 1.0 equiv) as an internal standard. The crude mixture was directly purified by flash chromatography on silica gel (thickness: 10 cm; diameter: 2 cm) to afford 3a (55.3 mg, 92% yield) as a white solid.

Table 2  Mechanistic understanding through catalyst- and base-loading studies and the order of addition of 1a and 2.

| Entry\(^a\) | CsF (equiv) | Base (equiv) | Yield (%\(^b\)) |
|------------|-------------|--------------|------------------|
| 1          | 1.5         | -            | >99              |
| 2          | 0.1         | -            | 10               |
| 3          | 0.1         | Cs\textsubscript{2}CO\textsubscript{3} (1.0) | 70               |
| 4          | 0.1         | Et\textsubscript{3}N (2.0) | 51               |
| 5          | 0.1         | DMAP (2.0)   | 79               |
| 6\(^c\)    | 1.5         | -            | >97              |
| 7\(^d\)    | 1.5         | -            | 6                |

\(\text{a} (0.3 \text{ mmol}), \text{b} (0.36 \text{ mmol, 1.2 equiv}), \text{CsF, base, Pd(TFA)}\textsubscript{2} (1.0 \text{ mol%}), \text{and Xantphos (1.5 mol%) were stirred for 15 h at 70 °C in anhydrous DMF (2.0 mL).} \)

\(\text{19F NMR yield.} \)

\(\text{a} (0.3 \text{ mmol}) \text{ was stirred in the presence of Pd(TFA)}\textsubscript{2} (1.0 \text{ mol%}) \text{ and Xantphos (1.5 mol%) at 70 °C. After 5 h of stirring, 2 (0.36 \text{ mmol, 1.2 equiv}) \text{ and CsF (1.5 equiv) were added to the reaction mixture, before stirring was continued for another 5 h.} \)

\(\text{2 (0.36 \text{ mmol, 1.2 equiv}) \text{ was stirred at 70 °C in the presence of CsF (1.5 equiv), Pd(TFA)}\textsubscript{2} (1.0 \text{ mol%}), \text{and Xantphos (1.5 mol%). After 5 h of stirring, 1a (0.3 \text{ mmol}) \text{ was added to the reaction mixture, before stirring was continued for another 5 h.} \)

Fig. 6  A plausible reaction mechanism. \(\text{a} \) A proposed catalytic cycle for Pd-catalyzed acyl fluoride synthesis. \(\text{b} \) Key reaction intermediates detected by mass spectrometry (MS). \(\text{c} \) A process for the generation of formyl fluoride catalyzed by CsF.

General procedure for the generation of acyl fluorides 3a Using a catalytic amount of CsF. An oven-dried vessel containing a magnetic stirrer bar was charged with Pd(TFA)\textsubscript{2} (1.0 mg, 0.003 mmol, 1.0 mol%), Xantphos (2.6 mg, 0.0045 mmol, 1.5 mol%), CsF (4.6 mg, 0.03 mmol, 10.0 mol%), Cs\textsubscript{2}CO\textsubscript{3} (97.7 mg, 0.3 mmol, 1.0 equiv), and anhydrous DMF (2.0 mL, 0.15 M) in a nitrogen-filled glovebox. After stirring the reaction mixture for 15 h at room temperature, 2 (0.36 mmol, 1.2 equiv) and aryl iodide 1a (0.3 mmol, 1.0 equiv) were added. The vessel was capped with a rubber septum, removed from the glovebox, and stirred for 15 h at 70 °C. Then, the mixture was cooled to room temperature and the yield (>99%) was determined by 19F NMR analysis of the crude reaction mixture using C\textsubscript{6}H\textsubscript{5}F (28.5 μL, 0.3 mmol, 1.0 equiv) as an internal standard. The crude mixture was directly purified by flash chromatography on silica gel (thickness: 10 cm; diameter: 2 cm) to afford 3a (55.3 mg, 92% yield) as a white solid.

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for 15 h at 70 °C. Then, the mixture was cooled to room temperature, and the yield (70%) was determined by $^{19}$F NMR analysis of the crude reaction mixture using $\text{C}_2\text{H}_5\text{F}$ (28.5 μL, 0.3 mmol, 1.0 equiv) as an internal standard.

**General procedure for the one-pot transformation of 1 into amides 7zd**

An oven-dried vessel containing a magnetic stirrer bar was charged with Pd(TFA)$_2$ (1.0 mg, 0.003 mmol, 1.0 mol%), Xanphos (2.6 mg, 0.0045 mmol, 1.5 mol%), C$\text{F}_7$H$_5$ (28.5 μL, 0.3 mmol, 1.0 equiv) and CsF (84.4 mg, 0.5 mmol, 1.5 equiv). The vessel was capped with a rubber septum, removed from the glovebox, and stirred at 150 °C for 10 min. Then, the mixture was cooled to room temperature, 1.0 mL of $\text{H}_2\text{O}$, 3.0 mL of 1.5 mmol of 1, and 1.5 mol% of Ru$_2$Cl$_2$(CO)$_9$ were added. The vessel was capped with a rubber septum, removed from the glovebox, and stirred at 150 °C for 10 min. Then, the mixture was cooled to room temperature. After quenching with $\text{H}_2\text{O}$ (20 mL), the mixture was extracted with $\text{CH}_2\text{Cl}_2$ (3 × 20 mL) and the combined organic layers were dried over anhydrous Na$_2$SO$_4$. After filtration, the filtrate was concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (eluent: n-Hexane:AcOEt = 1:1, v/v) to afford 7zd (45.8 mg, 63% yield) as a pale yellow solid.

The NMR yield of $^{19}$F transformation into acrylates 7zd (76%) was directly determined by $^{19}$F NMR analysis of the crude reaction mixture using $\text{C}_2\text{H}_5\text{F}$ (28.5 μL, 0.3 mmol, 1.0 equiv) as an internal standard.

**Data availability**

The data supporting the findings of this study are available within the paper and its Supplementary Information. All relevant data are also available from the authors.

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Author contributions

N.S. conceived the concept of this study. Y.L. optimized the reaction conditions and surveyed the substrate scope. Y.L. and Z.Z. prepared the starting materials. N.S. directed the project. N.S. and Y.L. prepared the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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Correspondence and requests for materials should be addressed to N.S.

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