

Deoxyfluorination of Carboxylic Acids with CpFluor: Access to Acyl Fluorides and Amides

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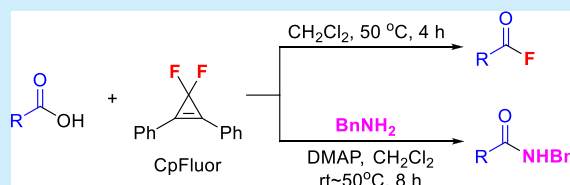


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Supporting Information

ABSTRACT: 3,3-Difluoro-1,2-diphenylcyclopropene (CpFluor), a bench-stable fluorination reagent, has been developed in the deoxyfluorination of carboxylic acids to afford various acyl fluorides. This all-carbon-based fluorination reagent enabled the efficient transformation of (hetero)aryl, alkyl, alkenyl, and alkynyl carboxylic acids to the corresponding acyl fluorides under the neutral conditions. This deoxyfluorination method was featured by the synthesis of acyl fluorides with *in-situ* formed CpFluor, as well as the one-pot amidation reaction of carboxylic acids via *in-situ* formed acyl fluorides.

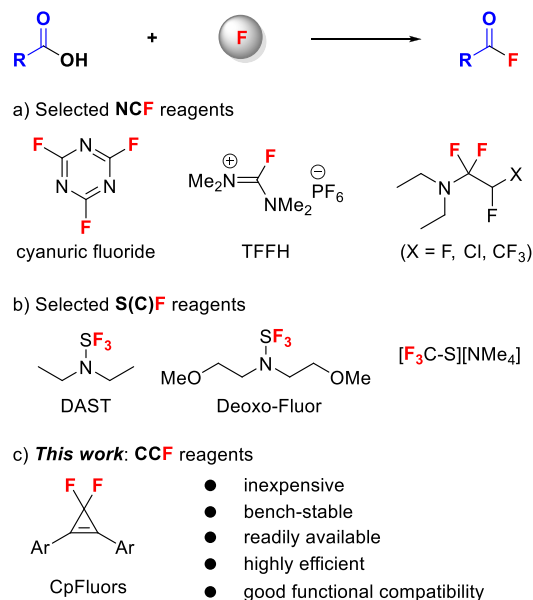


Recently, acyl fluorides have attracted much attention in organic synthesis, owing to their unique balance of stability and reactivity.¹ They are widely used as acyl,² aryl,³ and fluoride sources.⁴ Acyl fluorides are superior synthons compared to their corresponding carboxylic acid derivatives in terms of stability, reactivity, and transmetalation ability.^{1,3} Therefore, the development of a reliable and general method to prepare acyl fluorides is highly appealing, among which the deoxyfluorination of carboxylic acids with a fluorination reagent has become a routine method.^{1b–d} In this context, a bench-stable, readily available and efficient fluorination reagent is highly desirable.

Until now, two types of conventional fluorination reagents have been established in the synthesis of acyl fluorides. One is nitrogen-containing fluorination reagents (NCF reagents) (Scheme 1a),^{5–8} such as cyanuric fluoride,⁶ TFFH,⁷ and perfluoroalkylamines.⁸ The other is sulfur-containing fluorination reagents (S(C)F reagents) (Scheme 1b),^{9–12} such as DAST,¹⁰ Deoxo-Fluor,¹¹ and (Me₄N)SCF₃.¹² The introduction of a heteroatom is of great importance to stabilize and improve the reactivity of fluorination reagents for carbonyl compounds. However, these fluorination reagents have some drawbacks, such as sensitivity to air and moisture, tediousness, and costly synthetic routes, as well as the requirement of an additional base, which limit their applications in the synthesis of acyl fluorides.

3,3-Difluoro-1,2-diarylcyclopropenes, a class of carbon-based fluorinating reagents (also called CpFluors), could be synthesized by stable and inexpensive 1,2-diarylcyclopropenes with difluorocarbene reagents via [2 + 2] cycloaddition.¹³ With our continuous efforts in organofluorine chemistry, we found that CpFluors could not only convert a variety of alcohols to alkyl fluorides¹⁴ but also efficiently convert a diversity of carboxylic acids to acyl fluorides. Herein, we describe a practicable and straightforward approach to acyl fluorides via deoxyfluorination of carboxylic acids with CpFluor (Scheme 1c).

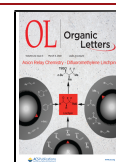
Scheme 1. Representative Fluorination Reagents in Deoxyfluorination of Carboxylic Acids



Encouraged by our previous work on deoxyfluorination of alcohols with CpFluors,¹⁴ the deoxyfluorination of 3-methylbenzoic acid (**1a**) via nucleophilic attack of 3,3-difluoro-1,2-diphenylcyclopropene (CpFluor **2**) was evaluated

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(Table 1). As expected, acyl fluoride 3a was obtained in 13% yield at room temperature (entry 1). Conducting the reaction

Table 1. Optimization of the Reaction Conditions^a

entry	2 (equiv)	temp (°C)	3a (%) ^b
1	1.2	25	13
2	1.2	30	53
3	1.2	50	57
4	1.2	70	53
5	1.6	50	76 (70)
6	2.0	50	65

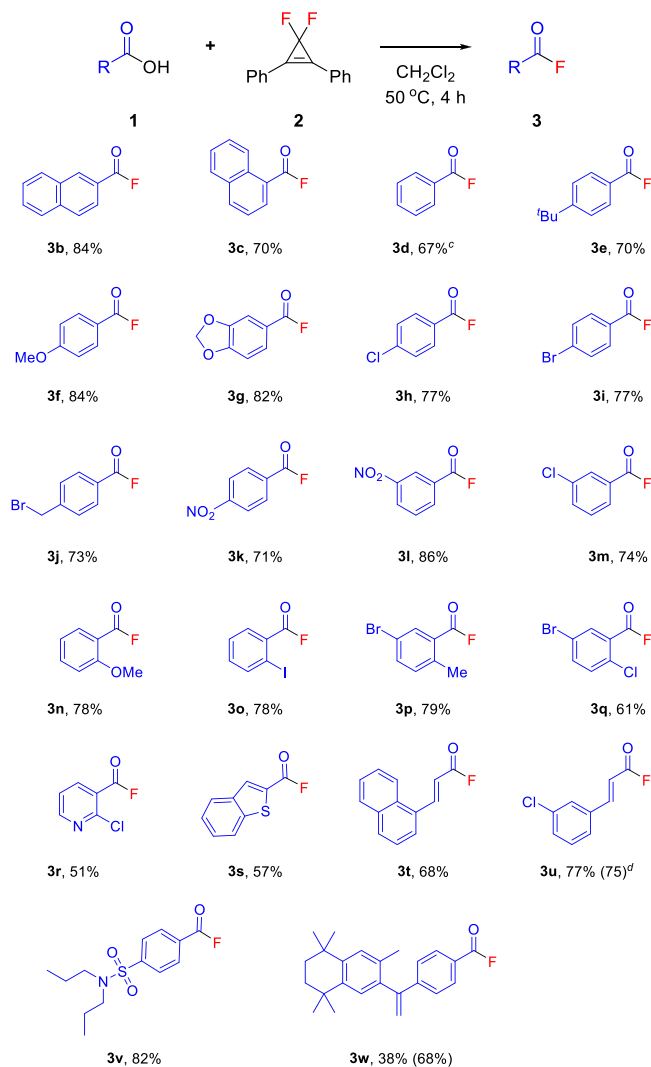
^aReaction conditions: 1a (0.5 mmol), CH₂Cl₂ (2.5 mL), 4 h.

^bDetermined by ¹⁹F NMR analysis of the crude mixture, using benzotrifluoride as an internal standard. An isolated yield is given in parentheses.

at an elevated temperature (50 °C) provided the desired product 3a in 57% yield (entry 3). Furthermore, the use of 1.6 equiv of CpFluor 2 improved the yield of 3a to 76% (entry 5). However, the use of 2 equiv of CpFluor 2 resulted in the formation of more anhydride, as well as a low yield of target product 3a (entry 6), probably arising from the increased concentration of intermediate 1 at the initiation stage (see Scheme 4). Notably, no bases or additives are required in this deoxyfluorination process, and the byproduct 2,3-diphenylcycloprop-2-en-1-one (5) can be easily separated from the target molecule.

The generality of this protocol was explored with a wide range of carboxylic acids as shown in Scheme 2. Naphthyl substrates provided the corresponding acyl fluorides 3b and 3c in good yields. Nonsubstituted benzoyl fluoride 3d was observed with moderate yield. In addition, benzoic acid bearing electron-donating groups such as *p*-*tert*-butyl, *p*-methoxyl, and acetyl substituents were well tolerated, affording aryl fluorides 3e–3g in 70–84% yields. The introduction of electron-withdrawing groups such as halogens, bromomethyl, and nitro groups onto benzoic acid in the *para*-position gave the target products 3h–3k in 71–77% yields. Benzoic acid with electronically diverse functional groups in the *ortho*- and *meta*-positions also successfully converted into the desired aryl fluorides (3l–3o), which illustrated that the present reaction is insensitive to electronic effect and steric hindrance. In addition, disubstituted acyl fluorides 3p and 3q were obtained in 79% and 61% yields, respectively. Other heterocycles including pyridyl (1r) and benzothiophene (1s) were also compatible in this reaction. Particularly, alkenyl acyl fluorides (3t and 3u) were accommodated during the reaction regardless of the electronic nature of the aromatic ring. To prove the utility of our method, carboxylic acid-containing drugs were examined; probenecid coupled with CpFluor yielded 3v in 82% yield, whereas bexarotene only afforded 3w in 38% isolated yield. The reaction could further be extended to the aliphatic and alkynyl carboxylic acids; however, low yields of desired products were observed due to the instability of the formed acyl fluorides during isolation by silica gel flash column chromatography.

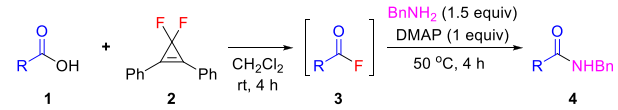
Scheme 2. Deoxyfluorination of Carboxylic Acids^{a,b}



^aReaction conditions: 1 (0.5 mmol), 2 (0.8 mmol), CH₂Cl₂ (2.5 mL), 50 °C, 4 h. ^bIsolated yields. ^c¹⁹F NMR yields using benzotrifluoride as an internal standard. ^dThe isolated yield of the reaction performed on 1 mmol scale is given in parentheses.

One-pot deoxyfluorination/amidation of several selected carboxylic acids were investigated using benzylamine as the substrate. Acyl fluorides were formed by an optimized deoxyfluorination procedure, followed by the addition of 1.5 equiv of benzylamine activated by 1 equiv of 4-dimethylaminopyridine (DMAP), and then direct amidation proceeded smoothly at 50 °C for another 4 h (Table 2). Notably, benzylic (1x and 1y), aliphatic (1z), and alkynyl (1aa) carboxylic acids were well participated in the formation of acyl fluorides at room temperature, affording the corresponding acyl fluorides 3x–3aa in good to excellent yields. Meanwhile, the one-pot amidation process furnished target products 4x–4aa in moderate to good yields. On the other hand, representative aromatic carboxylic acid 1ab and alkenyl carboxylic acid 1ac were also subjected to the one-pot deoxyfluorination/amidation. Besides, carboxylic acid containing bioactive molecules, including bindazac 1ad and sulindac 1ae, were proved to be effective coupling partners at the elevated temperature, providing 4ad–4ae in 78% and 75% yields, respectively. In some cases, in situ formed 2,3-diphenylcyclo-

Table 2. One-Pot Deoxyfluorination/Amidation of Carboxylic Acids via *in Situ* Formed Acyl Fluorides^a



Compound	1	3 (%) ^b	4 (%) ^c
1x		79	55
1y		94	69
1z		85	83
1aa		82	65
1ab ^d		94	73
1ac ^d		78	41
1ad ^d		82	78
1ae ^d		83	75

^aReaction conditions: **1** (0.5 mmol), **2** (0.8 mmol), CH₂Cl₂ (2.5 mL), rt, 4 h. Then BnNH₂ (1.5 equiv), DMAP (1 equiv), 50 °C, 4 h.

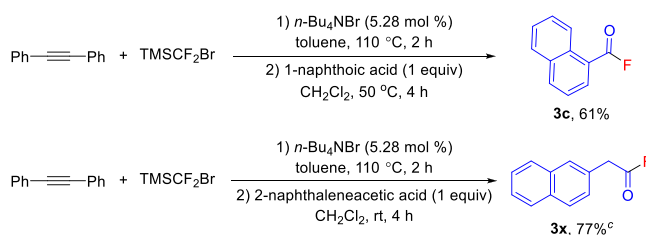
^bDetermined by ¹⁹F NMR analysis of the crude mixture, using benzotrifluoride as an internal standard. ^cIsolated yields. ^dDeoxyfluorination step was performed at 50 °C.

prop-2-en-1-one (**5**) in the deoxyfluorination step could also react with benzylamine, which decreased the amount of benzylamine for the amidation procedure and resulted in the low efficiency of the subsequent amidation.

To evaluate the utility of this approach, deoxyfluorination of carboxylic acids with *in situ* formed CpFluor was tested in Scheme 3. Initially, CpFluor **2** was prepared by [2 + 1] cycloaddition reaction of diphenyl acetylene with commercially available Me₃SiCF₂Br without further purification. Subsequently, 1 equiv of aromatic or benzylic carboxylic acid was directly added under the identical reaction conditions. Fortunately, 1-naphthoyl fluoride **3c** and 2-(naphthalen-2-yl)acetyl fluoride **3x** were obtained without a great loss compared to reaction with isolated CpFluor. This set of studies revealed that the present methodology is complementary to the deoxyfluorination of carboxylic acids without presynthesis of a fluorination reagent.

Based on our experimental results as well as the reported aromatic cation activation mode of *gem*-dihalocyclopropene in nucleophilic halogenation of alcohols and carboxylic acids,^{14,15} the proposed mechanism of deoxyfluorination of carboxylic acids to acyl fluorides was reasoned as shown in Scheme 4. In the initiation stage, CpFluor (**2**) is prone to be in equilibrium with cyclopropenium salt **I** in the presence of carboxylic acids.

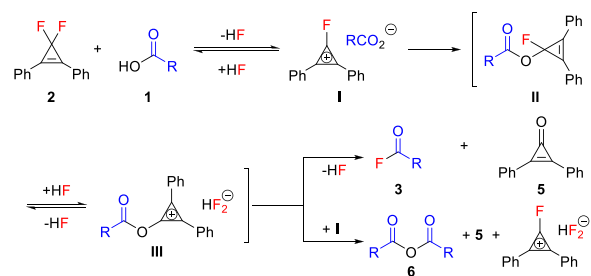
Scheme 3. Two-Step [2 + 1] Cycloaddition/Deoxyfluorination for the Synthesis of Acyl Fluorides^{a,b}



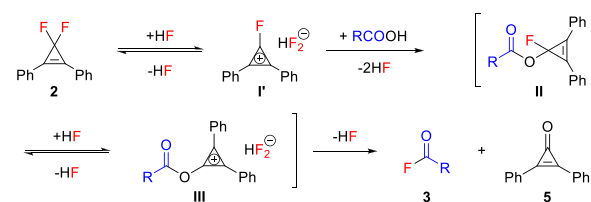
^aReaction conditions: (1) diphenylacetylene (0.88 mmol), TMSCF₂Br (1.32 mmol), ⁿBu₄NBr (0.026 mmol), toluene (2.0 mL), 110 °C, 2 h; (2) Toluene was removed under the vacuum, added acid (0.5 mmol), CH₂Cl₂ (2 mL), rt or 50 °C, 4 h. ^bIsolated yields. ^cDetermined by ¹⁹F NMR analysis of the crude mixture, using benzotrifluoride as an internal standard.

Scheme 4. Proposed Mechanism

Initiation stage (activated by RCO₂H, involving RCO₂[−], anhydride is formed as the side product):



Fluorination stage (activated by HF, no RCO₂[−]):



Intermediate **II** resulting from the combination of a cyclopropenium cation and carboxylate anion of **I** is activated by a proton to afford intermediate **III**, which further undergoes competitive nucleophilic substitution reaction with a carboxylate anion and bifluoride anion to provide anhydride **6** and acyl fluoride **3**, respectively. In the fluorination stage, the formation of a carboxylate anion is inhibited due to the accumulation of HF; thus, HF acts as the activator. In this stage, the formation of intermediate **III** is dominated by the direct attack of carboxylic acid **1** on the cyclopropenium cation and the formation of acyl fluoride **3** is the main pathway.

In summary, we have disclosed the high fluorination ability of *gem*-difluorocyclopropene in deoxyfluorination of carboxylic acids to synthesize a wide range of acyl fluorides. This deoxyfluorination method was featured by the synthesis of acyl fluorides with *in situ* formed CpFluor, as well as the one-pot amidation reaction of carboxylic acids via *in situ* formed acyl fluorides.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.1c00190>.

More detailed results of deoxyfluorination of carboxylic acids and characterization data of the representative starting materials and products (PDF)

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Notes

The authors declare no competing financial interest.

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