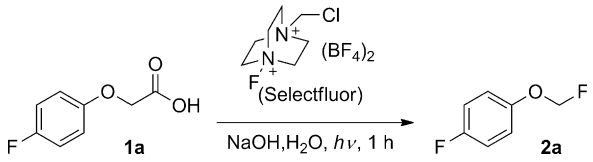
Synthetic Methods

DOI: 10.1002/anie.201206352

Photo-fluorodecarboxylation of 2-Aryloxy and 2-Aryl Carboxylic Acids**

*Joe C. T. Leung, Claire Chatalova-Sazepin, Julian G. West, Montserrat Rueda-Becerril, Jean-François Paquin, and Glenn M. Sammis**

The escalating importance of fluorinated compounds in the pharmaceutical and agrochemical sectors has placed a premium on the development of novel synthetic methods for fluorine incorporation.[1] In that respect, we have recently demonstrated that the electrophilic fluorine sources *N*-fluorobenzenesulfonimide (NFSI)[2] and Selectfluor[3] can effectively fluorinate alkyl radicals.[4] Continuing research in this direction motivated us to examine Hunsdiecker-type[5] fluorodecarboxylation reactions. There are few methods for the direct fluorodecarboxylation of carboxylic acids, including xenon difluoride mediated fluorodecarboxylations,[6] and a very recent method developed by Li and co-workers detailing a silver-catalyzed fluorodecarboxylation using Selectfluor.[7] Studies centering on 2-aryloxyacetic acids, such as **1a**, led to the surprising observation that the fluorodecarboxylated product **2a** forms in the absence of transition metals when an alkaline solution of **1a** and Selectfluor is irradiated (Scheme 1). A control experiment revealed that no reaction occurs in the absence of light. Preparative and mechanistic aspects of this unusual process are detailed herein.



Scheme 1. Photo-fluorodecarboxylation of the α-aryloxy derivative **1a**.

It was rapidly established that optimal results were obtained by irradiating the system with 300 nm[8] light (Table 1, entry 2).[9] Minimal conversion into the fluorinated product **2a** was observed when a visible-light source was utilized (entry 4). The wide range of wavelengths which can effectively promote this fluorodecarboxylation allows this reaction to be run with direct sunlight (entry 5). As seen in Table 2, replacement of Selectfluor with either the triflate or the tetrafluoroborate *N*-fluoropyridinium (NFPY) salts (entries 2 and 3) did not lead to the formation of **2a**. When water was utilized as the solvent, NFSI did not lead to the formation of **2a**, and is most likely a result of the poor aqueous solubility of the fluorinating agent. Adding acetonitrile as a cosolvent afforded trace amounts of the fluorinated product (entry 4). A 28% yield of **2a**, as determined by NMR spectroscopy, was observed with NFSI as the fluorine source in a solution of acetonitrile using 2,6-di-*tert*-butylpyridine as a base (entry 5). The product **2a** was also observed when acetonitrile was utilized with Selectfluor and 2,6-di-*tert*-butylpyridine (entry 6), albeit in lower yield than under the aqueous sodium hydroxide conditions (entry 1). Clearly, Selectfluor is the best reagent for this new photo-decarboxylation.

Table 1: Wavelength optimization for the fluorodecarboxylation of **1a** to give product **2a**.

Entry[a]	λ [nm][8]	Yield [%][b]
1	254	25
2	300	94[c]
3	350	47
4	tungsten lamp	4
5	sunlight	42

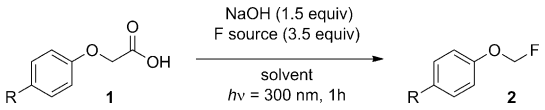
[a] Reaction conditions: NaOH (1.5 equiv) and Selectfluor (3.5 equiv) in H_2O (0.1 M) irradiated for 1 h at the indicated wavelength on a 0.1 mmol scale. [b] The yields were obtained by NMR spectroscopy using trimethoxybenzene as an internal standard. [c] The reported yield is an average of 3 runs.

The reaction of carboxylate salts that are not highly soluble in water are more conveniently carried out in a mixed aqueous/organic system. To illustrate, the carboxylate salt of **1b** (Table 2, R = *t*Bu) precipitated out of solution upon the addition of Selectfluor. However, the system remained homogeneous when a 2:1 H_2O/acetonitrile solvent mixture was used, thus resulting in the smooth formation of **2b** (entry 7).[10] A slight decrease in conversion was observed when acetone was used as a cosolvent, at least in the case of substrate **1a** (entries 8 and 9). The nature of the carboxylate

[*] J. C. T. Leung,[+] C. Chatalova-Sazepin,[+] J. G. West, M. Rueda-Becerril, Prof. G. M. Sammis
Department of Chemistry, University of British Columbia
2036 Main Mall, Vancouver, BC V6T 1Z1 (Canada)
E-mail: gsammis@chem.ubc.ca
Prof. J.-F. Paquin
Canada Research Chair in Organic and Medicinal Chemistry
Département de chimie, Université Laval
1045 avenue de la Médecine, Québec, QC G1V0A6 (Canada)
[+] These authors contributed equally to this work.

[**] This work was supported by the University of British Columbia (UBC), the Université Laval, NSERC, the Canadian Research Chair program, a doctoral fellowship from the Consejo Nacional de Ciencia y Tecnología (CONACyT) to M.R.-B., a doctoral fellowship from UBC to C.C.S., and a doctoral fellowship NSERC to J.C.T.L.
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201206352.

Table 2: Screen of fluorine sources for substrates **1a** and **1b**.

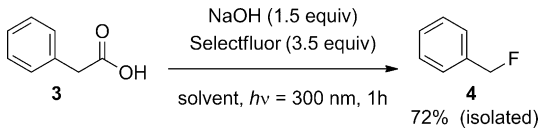


Entry	Fluorine source[a]	**1** (R)	Solvent	Yield [%]
1[a,b]	Selectfluor	**1a** (F)	H_2O	94[e]
2[a,b]	NFPY (OTf)	**1a** (F)	H_2O	0[e]
3[a,b]	NFPY (BF_4)	**1a** (F)	H_2O	0[e]
4[a,b]	NFSI	**1a** (F)	CH_3CN/H_2O (1:2)	< 5[e]
5[b,c]	NFSI	**1a** (F)	CH_3CN	28[f]
6[b,c]	Selectfluor	**1a** (F)	CH_3CN	53[f]
7[a,d]	Selectfluor	**1b** (*t*Bu)	CH_3CN/H_2O (1:2)	66[e]
8[a,c]	Selectfluor	**1a** (F)	CH_3CN/H_2O (1:2)	96[e]
9[a,c]	Selectfluor	**1a** (F)	acetone/H_2O (1:2)	82[e]

[a] Reaction conditions: NaOH (1.5 equiv), fluorine source (3.5 equiv), **1** (1.0 equiv) at 0.1 M in the solvent, irradiated at 300 nm for 1 h. [b] The reaction was run on a 0.1 mmol scale. [c] Reaction conditions: 2,6-di-*tert*-butylpyridine (1 equiv), fluorine source (3.5 equiv), **1** (1.0 equiv)at 0.1 M in the solvent, irradiated at 300 nm for 1 h. [d] The reaction was run on a 0.05 mmol scale. [e] The yields were obtained by NMR spectroscopy using trimethoxybenzene as an internal standard. [f] The yields were obtained by NMR spectroscopy using ethyl trifluoracetate as an internal standard. See the Supporting Information for details. Tf = trifluoromethanesulfonyl.

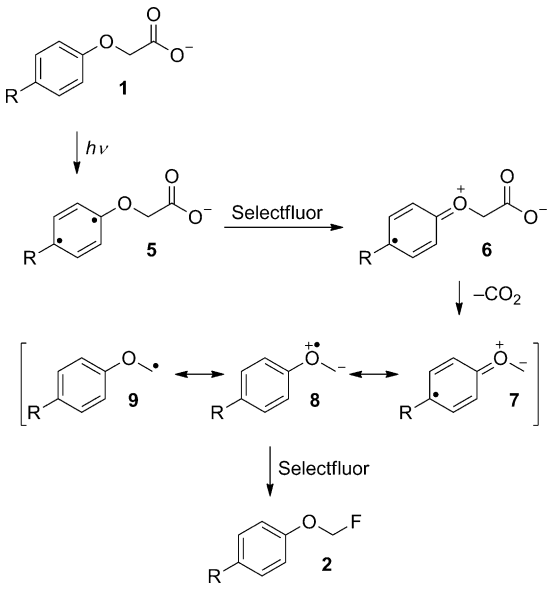
counterion seemed to have no effect on the overall efficiency.[11]

In addition to the α-aryloxy substrates **1a** and **1b**, phenylacetic acid (**3**) was successfully fluorinated in quantitative yield as determined by NMR spectroscopy, and was isolated in 72% yield (Scheme 2). Notably, all substrates



Scheme 2. Photo-fluorodecarboxylation of phenylacetic acid (**3**).

lacking either the 2-aryloxy or the 2-aryl substitutent were not successfully fluorinated under the optimized photofluorodecarboxylation conditions, and all that was observed after one hour was minor amounts of nonselective fluorination products. Benzoic acid was also not a viable substrate under the reaction conditions as no formation of fluorobenzene was observed. These noteworthy observations suggest that the reaction may proceed through the mechanism depicted in Scheme 3. Excitation of the B band transition ($\pi \rightarrow \pi^*$) of the benzenoid nucleus of **1** creates an excited state (**5**),[12] which in all likelihood is a better electron donor than the ground-state molecule. A single-electron transfer (SET) event involving **5** and Selectfluor[13] results in the oxidized species **6**,[14] which then undergoes a decarboxylation analogous to a Strecker degradation.[15,16] Regardless of which species, **7**–**9**, is the main resonance contributor, fluorination with Selectfluor can either proceed through a radical[4] or an anion[3b] to afford **2**. Alternative mechanisms, such as the decarboxylation pro-



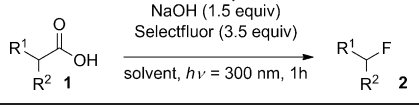
Scheme 3. Current working mechanistic model.[14]

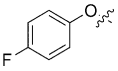
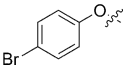
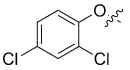
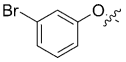
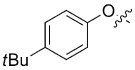
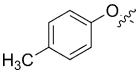
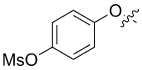
ceeding through hypofluorite intermediates,[17] are not consistent with both the lack of ^{19}F NMR evidence for the formation of hypofluorites[18] and the low amounts of product observed under thermal conditions.[19,20]

Mechanistic investigations are all consistent with the arene excitation/oxidation mechanism detailed in Scheme 3. The UV/Vis spectra of each substrate[21] is within the range of the light source utilized to promote the photofluorodecarboxylation. The wavelength optimization (Table 1) additionally supports the fact that the substrate itself is being excited as the absorption overlap between substrate **1a** and the 350 nm light source (entry 3) is significantly less than the overlap with the 300 nm light source (entry 2). The decrease in yield at 350 nm suggests that the substrate is excited, rather than one of the reagents or a reactive intermediate. Furthermore, this mechanism is consistent with the lack of reactivity of alkyl carboxylic acids and the failure to achieve fluorodecarboxylation under thermal conditions. Additional support for this proposal is provided by the work of Chang et al., who recently described the amination of benzylic positions using hypervalent iodide and dibenzenesulfonamide.[22] Thus, it is apparent that the photo-fluorodecarboxylation mechanism constitutes a variation on the theme of SOMO catalysis,[23] and that sagacious exploitation of this new form of reactivity may lead to novel transformations in the aromatic series.

A practical application of the chemistry is the preparation of aromatic fluoroethers, in particular, difluoroethers, which are of current interest in medicinal and agricultural chemistry.[24] The unsubstituted aryloxy substrate **1c** was cleanly fluorinated in high yield as detrmined by NMR methods (Table 3, entry 1). Halide-substituted aryl derivatives were all fluorodecarboxylated in good to excellent yields (entries 2–5), although the dichloro substrate **1e** required the use of acetonitrile as a cosolvent for enhanced solubility. The substrate **1b**, having a *tert*-butyl group, also underwent fluorodecarboxylation in excellent yield using acetonitrile as a cosolvent (entry 6). The 2-aryloxy substrate **1g** afforded low

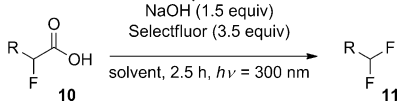
Table 3: Synthesis of monofluoromethyl ethers.

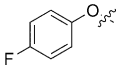
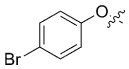
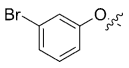
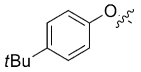


Entry[a]	1	R^1	R^2	Solvent	Yield [%][b]
1	**1c**		H	H_2O	46 (84)
2	**1a**		H	H_2O	60 (94)
3	**1d**		H	H_2O	60 (61)
4	**1e**		H	CH_3CN/H_2O (1:2)	76
5	**1f**		H	H_2O	57 (72)
6	**1b**		H	CH_3CN/H_2O (1:2)	83
7	**1g**		H	H_2O	– (34)[c]
8	**1h**		H	H_2O	78
9[d]	**1i**		OAc	CH_3CN/H_2O (1:2)	68 (78)
10	**3**		H	H_2O	72 (>95%)

[a] Reaction conditions: NaOH (1.5 equiv), Selectfluor (3.5 equiv), **1** or **3** (1.0 equiv) at 0.1 M in the solvent, and irradiated at 300 nm for 1 h. [b] Yield of product isolated after extraction and filtration through a silica gel plug. All yields were determined for reactions run on a 0.5 mmol scale. The number in parentheses refers in to the yield, determined by NMR methods, for the reaction run on 0.1 mmol scale. The yields were obtained using trimethoxybenzene as an internal standard. [c] The yield of the isolated product was not determined. [d] 1.5 equiv of K_2CO_3 was used instead of NaOH. Ms = methanesulfonyl.

Table 4: Synthesis of difluoromethyl ethers.



Entry[a]	10	R	Solvent	Yield [%][b]
1	**10a**		H_2O	25 (59)
2	**10b**		H_2O	44 (79)
3	**10c**		H_2O	64 (66)
4	**10d**		H_2O	44
5	**10e**		CH_3CN/H_2O (1:2)	77 (77)

[a] Reaction conditions: NaOH (1.5 equiv), Selectfluor (3.5 equiv), **10** (1.0 equiv) at 0.1 M in the solvent, and irradiated at 300 nm for 2.5 h. [b] Yield of product isolated after extraction and filtration through a silica gel plug. All yields for isolated products were determined for reactions run on a 0.5 mmol scale. The number in parentheses refers to the yield, as determined by NMR methods, of the reaction run on a 0.1 mmol scale. Trimethoxybenzene was used as an internal standard. See the Supporting Information for details.

yields of the desired fluorinated product **2g** (entry 7).[25] Substrates with strongly electron-rich aromatic rings, such as the *para*-methoxyphenyl analogue of **1** (R^1 = *para*-OMeAr), also were not fluorinated effectively under the photoreaction conditions, and is likely a result of a competing nonselective aryl fluorination reaction (entry 8). Similar oxygenation patterns can be accessed when the electron density is diminished, such as with the *para*-mesyloxy substrate **1h** which was fluorinated in 78% yield. 2-Aryl acids, such as acetylmandelic acid (**1i**) and phenyl acetic acid (**3**) were also fluorinated in good to excellent yields (entries 9 and 10). These facile reaction conditions also allow the reaction to be readily scalable to millimole scale. To wit, when the photofluorodecarboxylation of **1e** was run on a 2 mmol scale, the fluorinated product was afforded in 86% yield upon isolation.[26]

With the successful application of this new fluorodecarboxylation to monofluoroethers, studies next focused on the application of the method to the synthesis of difluoroethers (**11**; Table 4). Gratifyingly, the unsubstituted α-fluoro acid derivative **10a** underwent fluorodecarboxylation in high yield, as determined by NMR spectroscopy, and a lower yield was determined upon isolation because of product volatility (entry 1). While halogen-substituted aryl derivatives were successfully fluorinated (entries 2–4), the yields were lower than for the synthesis of the analogously substituted monofluorinated products (Table 3, entries 2, 3, and 5). The *para-tert*-butyl substrate **10e** was successfully fluorinated in 77% yield (Table 4, entry 5). As with the analogous analogous acid, an electron-rich *para*-methoxy derivative (R = *para*-MeOAr) also did not undergo the desired fluorination reaction.

This new fluorodecarboxyation has numerous procedural advantages. The carboxylic acid substrates can readily be synthesized from the corresponding phenol[27,28] and all of the reagents required for the fluorodecarboxylation, including Selectfluor, are inexpensive on bulk scale. One particular benefit of this new methodology is the ease of product purification. Under the optimized NaOH conditions, all of the starting materials and reagents are readily soluble in the reaction mixture. After irradiation, the fluorinated product is insoluble, thus slowing the rate of hydrolysis and product decomposition. The product can then be recovered by extraction with an organic solvent, thereby leaving the majority of the by-products in the aqueous layer.

In conclusion, this transition-metal-free photo-fluorodecarboxylation marks the first example of a direct and selective photochemical formation of C–F bonds, and it is most likely proceeds through initial excitation of the initial aryl group with subsequent SET. This approach works well for a broad range of α-aryloxy substrates using very mild and inexpensive reaction conditions. Current efforts are directed towards further examination of the reaction mechanism for

this photo-fluorodecarboxylation, as well as investigating other reactions that exploit this new form of reactivity.

Received: August 8, 2012
Published online: September 28, 2012

Keywords: fluorine · photochemistry · radical reactions · reaction mechanisms · synthetic methods

[1] a) W. K. Hagmann, *J. Med. Chem.* **2008**, *51*, 4359 – 4369; b) K. L. Kirk, *Org. Process Res. Dev.* **2008**, *12*, 305 – 321.
[2] E. Differding, H. Ofner, *Synlett* **1991**, 187 – 189.
[3] a) R. E. Banks, S. N. Mohialdin-Khaffa, G. S. Lal, I. Sharif, R. G. Syvret, *J. Chem. Soc. Chem. Commun.* **1992**, 595 – 596; b) P. T. Nyffeler, S. G. Durón, M. D. Burkart, S. P. Vincent, C. H. Wong, *Angew. Chem.* **2005**, *117*, 196 – 217; *Angew. Chem. Int. Ed.* **2005**, *44*, 192 – 212.
[4] M. Rueda-Becerril, C. Chatalova Sazepin, J. C. T. Leung, T. Okbinoglu, P. Kennepohl, J. F. Paquin, G. M. Sammis, *J. Am. Chem. Soc.* **2012**, *134*, 4026 – 4029.
[5] For a general review on halodecarboxylations, see: R. G. Johnson, R. K. Ingham, *Chem. Rev.* **1956**, *56*, 219 – 269.
[6] For a review on XeF_2: M. A. Tius, *Tetrahedron* **1995**, *51*, 6605 – 6634.
[7] F. Yin, Z. Wang, Z. Li, C. Li, *J. Am. Chem. Soc.* **2012**, *134*, 10401 – 10404.
[8] All of the light sources utilized for these experiments are not strictly monochromatic. The indicated wavelength refers to the maximum light intensity emitted. See the Supporting Information for details about emission profiles.
[9] Increasing the wavelength to 350 nm afforded comparable amounts of decomposition as was observed at 254 nm.
[10] Replacing the tetrafluoroborate salt of Selectfluor with the more organic-soluble PF_6 salt provided **2b** in 38% yield as determined by NMR methods.
[11] Comparable yields were observed when a variety of bases, including K_2CO_3, KOH, and LiOH were used for both substrates **1a** and **1b**.
[12] The nature of the excited-state **5** will differ depending upon the substitution at R. Only one excited state has been shown for clarity.
[13] Selectfluor is known to be an effective single-electron oxidant. For representative examples, see Ref. [3b].
[14] It is also possible that the reaction proceeds through a PET from the carboxylate to Selectfluor.
[15] A. Strecker, *Justus Liebigs Ann. Chem.* **1862**, *123*, 363 – 365.
[16] For a review on the Strecker degradation, see: A. Schönberg, R. Moubasher, *Chem. Rev.* **1952**, *50*, 261 – 277.
[17] For a review on the reactivity of acyl hypofluorite and hypofluorite derivatives, see: S. Rozen, *Chem. Rev.* **1996**, *96*, 1717 – 1736.
[18] ^{19}F NMR analysis of reaction mixtures, both before and after irradiation, shows no evidence of hypofluorite formation.
[19] Heating an aqueous solution of sodium hydroxide, substrate **1a**, and Selectfluor at 100 °C for 1 hour yielded complete conversion of the starting material, but only trace amounts of the fluoromethoxy ether.
[20] See the Supporting Information for a discussion of all of the evidence against the formation of either acyl hypofluorites or other hypofluorite derivatives.
[21] All of the UV/Vis data is provided in the Supporting Information.
[22] H. J. Kim, J. Kim, S. H. Cho, S. Chang, *J. Am. Chem. Soc.* **2011**, *133*, 16382 – 16385.
[23] For initial studies on SOMO catalysis, see: a) T. D. Beeson, A. Mastracchio, J. B. Hong, K. Ashton, D. W. C. MacMillan, *Science* **2007**, *316*, 582 – 585; b) H. Jang, J. B. Hong, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2007**, *129*, 7004 – 7005.
[24] For a recent review, see: B. Manteau, S. Pazenok, J. P. Vors, F. R. Leroux, *J. Fluorine Chem.* **2010**, *131*, 140 – 158.
[25] Background aryl fluorination was observed for this substrate.
[26] The reaction conditions were slightly altered for the 2 mmol scale. See the Supporting Information for details.
[27] For a representative example of the synthesis of an α-aryloxy acid, see: K. Lee, *J. Med. Chem.* **2007**, *50*, 1675 – 1684.
[28] For a representative example of the synthesis of an α-fluoro-α-aryloxy acid, see: C. C. Ciocoiu, *Bioorg. Med. Chem.* **2011**, *19*, 6982 – 6988.

