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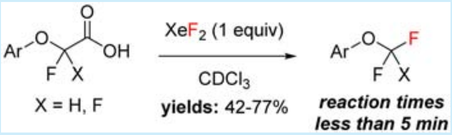
Xenon Difluoride Mediated Fluorodecarboxylations for the Syntheses of Di- and Trifluoromethoxyarenes

Claire Chatalova-Sazepin, Meruyert Binayeva, Maxim Epifanov, Wei Zhang, Paul Foth, Carolyn Amador, Manu Jagdeo, Benjamin R. Boswell, and Glenn M. Sammis*

Chemistry Department, University of British Columbia, 2036 Main Mall, Vancouver, British Columbia V6T 1Z1, Canada

Supporting Information

ABSTRACT: XeF_2 is demonstrated to be a more proficient fluorine-transfer reagent than either NFSI or Selectfluor in fluorodecarboxylations of both mono- and difluoroaryloxy acetic acid derivatives. This method efficiently converts a wide range of neutral and electron-poor substrates to afford the desired di- and trifluoromethyl aryl ethers in good to excellent yields. The purifications are facile, and the reaction times are less than 5 min, which makes these fluorodecarboxylations promising for future PET-imaging applications.



The development of new fluorination methods is largely driven by the widespread application of fluorinated compounds in both the agrochemical and pharmaceutical industries.[1,2] Of these methods, selective radical fluorination[3] has emerged as an intriguing and complementary alternative to the more extensively explored ionic approaches.[4] Since 2012, when both *N*-fluorobenzenesulfonimide (NFSI)[5] and Selectfluor[5,6] were demonstrated to serve as fluorine-transfer agents, there has been a dramatic increase in the number of radical-based methodologies that utilize these two reagents as sources of atomic fluorine.[3] Despite renewed interest in selective radical fluorination, there are no reports comparing the reactivity of these reagents to a previously known radical fluorine transfer reagent, XeF_2.[7,8] Qualitatively, it has been observed in electrophilic fluorinations that reagents with higher electrochemical standard potentials are kinetically more reactive.[9] By analogy, this trend should also hold true for radical fluorine-transfer reactions and XeF_2, with a potential of 2.64 V vs standard hydrogen electrode (SHE) (Figure 1),[10] and may be a more efficient fluorine transfer agent than either NFSI (−1.00 V vs SHE)[11] or Selectfluor (0.57 V vs SHE).[11] Herein, we confirm this trend and exploit the high reactivity of XeF_2 in the context of several synthetically challenging and pharmaceutically important fluorinated moieties.

Previous XeF_2-mediated fluorodecarboxylations were performed on substrates[7] that can readily be fluorinated by NFSI- or Selectfluor-based methods,[3] making direct comparisons from literature precedent difficult. We, therefore, wanted to examine challenging substrates that can clearly differentiate the relative reactivity of the three reagents. Our previous studies indicated that monofluoro acid derivatives (Scheme 1, **3**) were more difficult to fluorodecarboxylate than analogous des-fluoro acids (**1**).[12,13] Following this trend, we envisioned that the difluoro acids (**5**)[14] should be even more difficult to fluorodecarboxylate and, thus, serve as appropriate initial substrates to challenge the relative fluorine transfer abilities of XeF_2, NFSI, and Selectfluor. These substrates are intriguing because the electrochemical standard potential of **5** ($E° = 2.13$ V vs SHE)[15] is significantly higher than that for **1** ($E° = 1.71$ V vs SHE),[13a,15] and thus, it is more difficult to effect the desired fluorodecarboxylation. Furthermore, this route enables rapid access to trifluoromethoxyarenes (**6**), a motif that has industrial potential[16,17] but is difficult to synthesize,[17−20] particularly in late stage synthesis.[21]

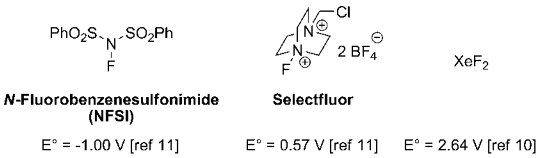
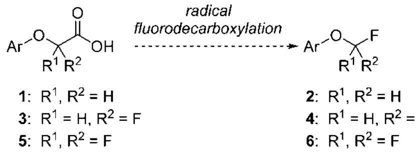


Figure 1. SHE reduction potentials of fluorine-transfer regents.

Scheme 1. Synthetic Route for the Syntheses of Fluoromethoxy Arenes (2, 4, and 6)



We began our investigations by examining the two reagents with the lower electrochemical standard potentials, NFSI and Selectfluor, in the fluorodecarboxylation of difluoroaryloxy acid derivatives (**5**). Even after significant optimization of previously developed NFSI[12] or Selectfluor-based[13] radical fluorodecarboxylation methodologies, we were unable to achieve a general and high-yielding method to access the corresponding trifluoromethoxyarenes (**6**). It is important to note that, under photochemical conditions with NFSI,[22] we could promote decarboxylation, but no fluorination was observed. We were able to achieve both decarboxylation and fluorination using Selectfluor

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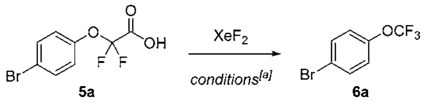
Table 1. Investigations into the Fluorodecarboxylation of Difluoroaryloxyacetic Acid 5a



entry	XeF_2 (equiv)	solvent	concn (M)	NMR/GC yield[b] (%)
1	2	C_6D_6	0.5	17
2	2	$CDCl_3$	0.5	51
3[c]	2	$CDCl_3$	0.5	51
4[d]	2	$CDCl_3$	0.5	5
5	2	$CDCl_3$	0.1	26
6	2	$CDCl_3$	0.2	35
7	2	$CDCl_3$	1.0	54
8	2	$CDCl_3$	2.0	57
9[e]	2	$CDCl_3$	2.0	38
10	1	$CDCl_3$	2.0	42
11[f]	1	$CDCl_3$	2.0	72

[a]Reactions were carried out on a 0.1 mmol scale at 23 °C for 5 min. [b]Yields were measured by ^{19}F NMR spectroscopy using ethyl trifluoroacetate as an internal standard and/or GC−FID using a calibration curve and bromobenzene as an internal standard. [c]The reaction was run at 50 °C. [d]The reaction was run at 0 °C. [e]The reaction was run for 1 h. [f]The reaction was run in a 15 mL plastic polypropylene vial.

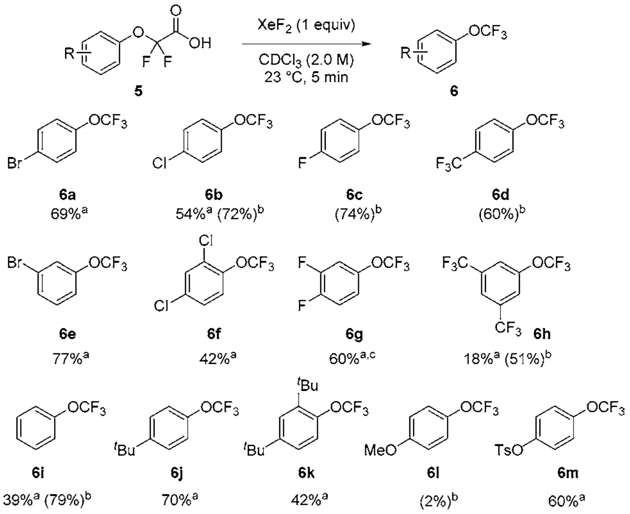
and UV light,[23] but even when large amounts of the fluorination reagent were employed, the yields were very low (<40%) even when the conversion was high. Qualitatively, the faster fluorine transfer with Selectfluor[24] is consistent with the hypothesis that radical fluorination reactivity correlates with electrochemical standard potentials (Figure 1).[25]

Following this reactivity trend, we wanted to explore whether XeF_2 is a superior fluorine-transfer reagent in the fluorodecarboxylation of difluoroacetic acid derivatives (**5**).[26] We note that although XeF_2 is known to effect the fluorodecarboxylation of aryloxyacetic acids (**1**),[27] *it has never been investigated with more oxidatively challenging mono- (**3**) or difluoroaryloxyacetic acid derivatives (**5**).* Preliminary investigations into the fluorodecarboxylation of **5a** (Table 1, entry 1) revealed that XeF_2 is a sufficiently strong oxidant to effectively promote the decarboxylation in the absence of light irradiation or an external oxidant, and fluorine transfer proceeds to afford trifluormethoxy arene **6a** in 17% NMR yield.

We next explored the reaction parameters to facilitate the fluorine-transfer step. A solvent screen found that $CDCl_3$ is optimal for this reaction, providing **6a** in 51% yield (entry 2).[28] Examining the reaction temperature revealed that heating the reaction to 50 °C had no impact on the yield (entry 3), and only 5% of **6a** was detected when the reaction was run at 0 °C (entry 4). We then explored concentration effects on reaction yield (entries 5−9). Concentrations less than 0.5 M (entries 5 and 6) afforded lower yields, while concentrations greater than 0.5 M provided the desired trifluoromethoxy arene (**6a**) in comparable yields (entries 7 and 8).[29]

An investigation of product stability in the presence of excess XeF_2 revealed that the NMR yield of **6a** decreases significantly if the reaction time is extended to 1 h (Table 1, entry 9). While fluorodecarboxylation with 1 equiv of XeF_2 led to a slight erosion in the yield of **6a** (entry 10),[30] we continued our optimization with the lower amount as it is both synthetically more practical and minimizes the possibility of over-oxidation. Basic additives either led to no change in the observed yield of **6a** or more typically suppressed the reaction. XeF_2 reactions are known to be affected by the reaction vessel material due to the ability of the reagent to interact with the borosilicate surface.[31] Thus, the use of a plastic vessel led to a significant improvement in reaction yield (72%, entry 11).[32] This yield is significantly higher than the analogous reaction with Selectfluor.[33] This supports the conjecture that the reagent with the highest electrochemical standard potential, XeF_2, is the most effective radical fluorine transfer reagent.

Scheme 2. Investigations into the Scope of the XeF_2-Promoted Fluorodecarboxylation of α,α-Difluoroaryloxyacetic Acid Derivatives (5)



[a]Isolated yield on 0.5 mmol scale of difluoro acid **5**. [b]Yields were measured by ^{19}F NMR spectroscopy using ethyl trifluoroacetate as an internal standard. [c]The substrate is volatile and was isolated with some remaining solvent residue. See the Supporting Information for details.

There are many aspects about the optimized reaction conditions (Table 1, entry 11) that suggest this may serve as a practical and synthetically powerful method for the synthesis of trifluoromethoxyarenes. Under the optimized conditions, the reaction proceeds very rapidly; at room temperature, xenon gas and CO_2 vigorously evolve, and within minutes the reaction is complete. Furthermore, purification is facile as any residual xenon species can be removed readily with a silica plug. It should also be stressed that while XeF_2 is known to induce aryl ring fluorination,[34] no fluorinated side products were detected in crude reaction mixtures.

Encouraged by the synthetic potential of this transformation, we next explored the substrate scope (Scheme 2). Substrate **5a** successfully underwent the fluorodecarboxylation to afford trifluoromethoxyarene **6a** in 69% isolated yield. Other chloro-, bromo-, fluoro-, and trifluoromethyl substrates underwent successful fluorodecarboxylation (products **6b**−**e**). The high volatility of **6c** and **6d** made isolation difficult; thus, only NMR yields are reported. Disubstituted trifluoromethoxyarenes (**6f**−**h**) were obtained in good, albeit lower, yield than their monosubstituted counterparts. Unsubstituted substrate **5i** afforded lower isolated yields of trifluoromethoxybenzene (**6i**), partially due to the volatility of the product. The reaction tolerated alkyl substitution (**5j**), but a more highly substituted substrate (**5k**) afforded **6k** in lower yield. Electron-rich substrate **5l** was not successful, and significant amounts of ring fluorination were observed. Substrates bearing oxygen-containing electron-withdrawing groups, such as tosyl substrate **5m**, proceeded in

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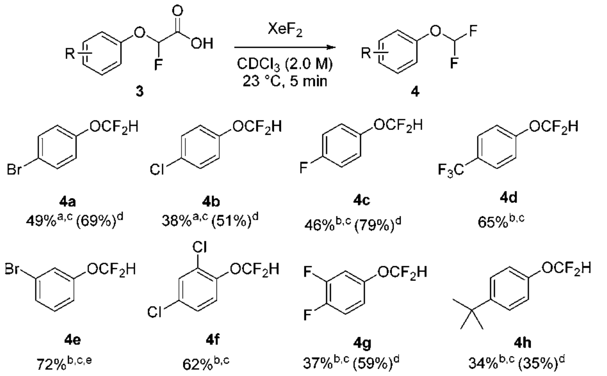
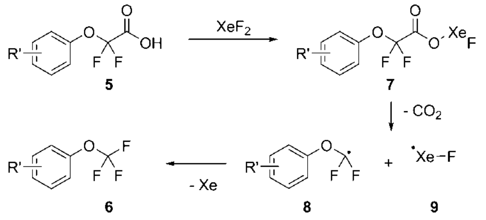
Scheme 3. Investigations into the Scope of the XeF_2-Promoted Fluorodecarboxylation of α-Fluoroaryloxyacetic Acid Derivatives 3



[a] 1.5 equiv of XeF_2 were utilized. [b] 1 equiv of XeF_2 was utilized. [c] Isolated yield on 0.5 mmol scale of difluoroacid 3. In all cases, the isolated yield includes 1−3% pentane. See the Supporting Information for details. [d] Yields were measured by ^{19}F NMR spectroscopy using ethyl trifluoroacetate as an internal standard. [e] The reaction time was 20 min.

Scheme 4. Postulated Mechanism for the Fluorodecarboxylation of Difluoroaryloxyacetic Acids 5



high isolated yield. In all cases, the reaction proceeded very rapidly, and full conversion was achieved within a few minutes. Other than products **6c**, **6d**, and **6l**, all other trifluoromethoxyarenes were readily isolated. Substrates that were not fully soluble under the reaction conditions often afforded lower yields.[15]

A variant of the above chemistry enabling access to difluoromethyl aryl ethers (**4**) would nicely complement existing synthetic technologies,[19i,35] particularly given the fast XeF_2 reaction times coupled with the ease of isolation. Reaction optimization identified that two sets of conditions promoted the decarboxylation of difluoroaryloxy acids **3**; the amount of XeF_2 had to be increased from 1 equiv to 1.5 for substrates that are poorly soluble under the reaction conditions (Scheme 3). Both the *p*-bromo (**3a**) and *p*-fluoro (**3c**) substrates were cleanly converted to the corresponding difluoromethyl ethers, although the isolated yield of **4c** was low due to substrate volatility. The *p*-chloro substrate **3b** was poorly soluble, and thus, only moderate yields were obtained. Other electron-deficient substrates (**3d−g**) afforded the desired difluoromethoxyarenes (**4d−g**) in good yields. Unlike the fluorodecarboxylation of the difluoro acids (**5**), small amounts of ring-fluorinated products (<3%) were detected in select substrates (**4a**, **4f**, and **4h**). Increasing the electron density of the ring (**3h**) resulted in lower yields and greater amounts of ring-fluorinated products (4%). While these substrates illustrate the synthetic potential of this methodology, it is difficult to draw any conclusions regarding the relative fluorine transfer abilities compared to Selectfluor[13a] because the yields of both processes are comparable.

Our current mechanistic hypothesis for the fluorodecarboxylation of mono- and difluoroaryloxyacetic acid derivatives **3** and **5** is based on previous reports by Patrick and co-workers (**5** is depicted in Scheme 4).[26,31,36] Combination of substrate **5** with xenon difluoride results in the formation of a xenon ester (**7**), which rapidly undergoes decarboxylation to form radical **8**.[7,37] The detection of hydrogen-trapped products[28] supports the proposed formation of a radical intermediate (**8**). The large disparity in bond dissociation enthalpies between starting acid **5** and **9**[38] provides a very strong thermodynamic driving force for the formation of fluoromethoxy arene products **6**. Our optimization experiments (Table 1) indicate that the fluorine transfer from **9** to **8** is faster than the analogous processes using either NFSI or Selectfluor as reagent.

The high yields of XeF_2-mediated fluorodecarboxylation of difluoroaryloxyacetic acid derivatives (**5**) compared to analogous NFSI- or Selectfluor-mediated reactions strongly supports the hypothesis that the rate of radical fluorine transfer correlates with the electrochemical standard potential of the reagents. Furthermore, this new XeF_2-mediated decarboxylative fluorination approach affords the desired trifluoromethoxyarenes in *high yields in less than 5 min at room temperature*. This reaction has the additional advantage of not requiring a separate oxidant or source of energy as XeF_2 has a sufficiently high redox potential. Similar reaction conditions can also be used for the syntheses of a range of difluoromethoxyarenes from the corresponding α-fluoroacetic derivatives. The fast reaction times, coupled with the availability of ^{18}F-enriched xenon difluoride from fluoride sources,[39] make these new XeF_2-mediated fluorodecarboxylations particularly promising as a new method for the incorporation of ^{18}F in PET applications.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02208.

> General methods and instrumentation, optimization results, general experimental procedures, cyclic voltammetry experiments, and spectroscopic data for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: gsammis@chem.ubc.ca.

Notes

The authors declare no competing financial interest.

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(29) Higher concentrations than 2.0 M did not fully solubilize the reagents, and thus, lower yields were obtained.

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(33) After optimization, light-mediated fluorodecarboxylation of **5a** with a large excess of Selectfluor afforded **6a** in 6% yield. No reaction was observed with **5j** when either NFSI or Selectfluor was used under conditions analogous to those used in Table 1, entry 11. See the Supporting Information for details.

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