Selective C–O bond formation via a photocatalytic radical coupling strategy: access to perfluoroalkoxylated (OR$_F$) arenes and heteroarenes

Johnny W. Lee, Dominique N. Spiegowski and Ming-Yu Ngai

Introduction

Molecules containing a perfluoroalkoxy group (OR$_F$) have emerged as an important class of compounds in the fields of pharmaceutical, agrochemical, and materials science because incorporation of an OR$_F$ group into organic compounds often improves thermal, chemical and metabolic stability, lipophilicity, and bioavailability of parent molecules.$^{1-9}$ While much progress has been made for late stage fluorination,$^{10,11}$ perfluoroalkylation,$^{12,13}$ and perfluoroalkylthiolation$^{14-16}$ of (hetero)arenes, the facile synthesis of perfluoroalkoxylated (hetero)aromatic compounds remains an unmet challenge in synthetic organic chemistry.$^{17-25}$ Unlike their analogous alkoxy groups, formation of an O–RF bond (e.g. RF = CF$_3$) via direct $S_N$2 type displacement is unfavorable due to (i) strong electron repulsion between fluorine atoms and incoming nucleophiles and (ii) the formation of an energetically adverse CF$_3$ carbocation transition state (TS) structure (Fig. 1a).$^{2,26}$ Umemoto et al. addressed this issue with an elegant electrophilic O–RF bond formation strategy via radical intermediates,$^{27}$ yet the non-selective formation of O- and C-perfluoroalkylated products limited its synthetic utility. Although new strategies for the synthesis of perfluoroalkoxylated (hetero)arenes have emerged over the past few years,$^{23,27-29}$ a general and mild catalytic process has yet to be developed. As a result, the full potential of perfluoroalkoxylated (hetero)aromatic compounds has not been fully exploited across a broad spectrum of technological applications.

To address this challenge, we recently developed trifluoromethoxylations reactions of aromatic compounds using N-(hetero)aryl-N-hydroxylamides and Togni reagents under mild reaction conditions.$^{30,31}$ Our operationally simple and scalable protocols provide access to a diverse array of trifluoromethoxylated (hetero)aromatics with complex molecular architectures. Nevertheless, the high cost and multi-step synthesis of Togni reagents (e.g. Togni reagent I costs $55 980 mol$^{-1}$) might hinder their synthetic application. Furthermore, preparation of other O-perfluoroalkoxylated analogues requires the use of unique hypervalent iodine(III) perfluorinating reagents.

![Fig. 1](image-url) Photocatalytic radical coupling for the synthesis of perfluoroalkoxylated (hetero)arenes.
reagents, which are commercially unavailable, synthetically inaccessible, and thermally unstable. In order to develop a general method to access perfluoroalkoxylated (hetero)arenes, we turned our attention to $R_F=\text{I}$ reagents ($R_F=\text{fluoroalkyl}$) that are commercially available and cost efficient (e.g. CF$_3$I costs $\$83 \text{ mol}^{-1}$). Based on our prior mechanistic studies, selective O$^\ominus$-$R_F$ bond formation is feasible if $N$-hydroxyl and $R_F$ radicals are generated simultaneously. Although direct single electron transfer (SET) from $N$-(hetero)aryl-$N$-hydroxylamides to $R_F=\text{I}$ is kinetically and thermodynamically unfavorable, we hypothesized that such a SET process could be facilitated by using an appropriate photoredox catalyst. Herein, we describe our efforts to develop the first photocatalytic radical coupling reaction of $N$-(hetero)aryl-$N$-hydroxylamides with $R_F=\text{I}$ to form $N$-$\text{OR}_F$ compounds, which then undergo $\text{OR}_F$-migration to afford a wide variety of perfluoroalkoxylated (hetero)arenes (Fig. 1b).

**Results and discussion**

To examine the feasibility of our hypothesis, we started our investigation using $N$-(p-tert-butylphenyl)-$N$-hydroxylamide (1a) and perfluorosopropyl iodide (2a) as model substrates. Pleasingly, after exposure of 1a (1.00 equiv.) and 2a (8.00 equiv.) to visible light irradiation [3 W blue light-emitting diodes (LEDs)] in the presence of a ruthenium photoredox catalyst [Ru(bpy)$_3$ (PF$_6$)$_2$ (0.500 mol%) and potassium carbonate (3.00 equiv.) in acetonitrile (0.100 M) at 23 °C for 12 hours, we obtained the desired product 3a in 38% yield (Table 1, entry 1). Exploration of photoredox catalysts, solvents, bases, concentrations, reactant stoichiometry and catalyst loading did not improve the product yield (entries 2–5). A breakthrough in optimization came when we lowered the reaction temperature to 0 °C, at which an 80% yield of the desired product 3a was obtained (entry 6). It is noteworthy that we did not observe addition of $R_F$ radicals directly to arenes even though such a reaction has been developed under photoredox-catalyzed reaction conditions. Apparently, this is due to the persistent radical effect that coupling of O$^\ominus$- and $R_F$-radicals is more favorable than the addition of $R_F$ radicals to arenes. Finally, control experiments showed that a photoredox catalyst, a base, light, and an oxygen-free atmosphere are critical for the success of the perfluoroalkylation reaction (entries 7–10).

With the optimized reaction conditions in hand, we explored the scope of the perfluoroisopropylation reaction with respect to $N$-(hetero)aryl-$N$-hydroxylamides (1a–1t) (Table 2). The optimized reaction conditions were compatible with both aromatic and heteroaromatic hydroxylamides bearing a wide variety of functional groups and molecular scaffolds. For example, substrates with benzylic hydrogens, which are often prone to hydrogen atom abstraction in the presence of radical species, are tolerated (3b–3e and 3q–3s). Presumably, the rate of O$^\ominus$- and $R_F$-radical coupling is faster than that of benzylic hydrogen atom abstraction. These results further demonstrate the chemoselectivity of our protocol. In addition, halogen functionalities (3f–3i, 3n, 3o and 3q) remained intact after the reaction, providing easy handles for further synthetic elaborations. Substrates containing polyfluoromethyl ethers were also viable and afforded good yields of the desired products (3j and 3k). Moreover, products derived from the heterocyclic $N$-hydroxylamides such as benzofuran (3l) and benzothiophene (3m) were formed smoothly with high levels of regioselectivity. Other functional groups such as esters (3e and 3m), ethers (3q–3t), carbamates (3e), 1,2,4-oxadiazoles (3n), oxindoles (3o), pyrazoles (3p), pyridines (3p–3t) and ketals (3t) were susceptible to $\text{OR}_F$ addition as well. Importantly, more complex $N$-pyridinyl-$N$-hydroxylamides derived from estrone and diacetone-$\alpha$-glucose could be effectively converted to their perfluoroisopropylation analogs (3s and 3t), demonstrating that this method can be used in the preparation of pharmaceutically relevant compounds. Notably, none of the perfluoroisopropylation arenes and pyridines reported herein have been prepared prior to this study.

Trifluoromethoxy aryl ethers ($\text{Ar}$-$\text{OCF}_3$) are constituents of several pharmaceutically active compounds, agrochemicals, and functional materials. As a result, significant effort has recently been directed towards uncovering general and practical protocols for their preparation, yet methods that use commercially available CF$_3$I for their preparation have not been developed. We were pleased to see that our photocatalytic protocol can also be used for the synthesis of trifluoromethoxylated arenes (4a–4d) from CF$_3$I (Table 3). In general, $\alpha$-trifluoromethylation required a longer reaction time (48 h vs. 12–24 h for heptafluoroalkoxylation), possibly due to the lower reduction potential of CF$_3$I ($E_{1/2}^{\text{red}}=−1.52 \text{ V vs. SCE}$) in comparison with (CF$_3$)$_2$CFI ($E_{1/2}^{\text{red}}=−0.66 \text{ V vs. SCE}$), which required an over-potential of 0.19 V for the reduction of CF$_3$I to generate the CF$_3$ radical using Ru(bpy)$_3$ ($E_{1/2}^{\text{red}}=−1.33 \text{ V vs. SCE}$). In addition, other perfluoroalkyl iodides such as $\text{CF}_2=\text{CF}_2$, $\text{CF}_2=\text{CF}_2$, $\text{CF}_2=\text{CF}_2$, and $\text{CF}_2=\text{CF}_2$...
perfluorohexyliodide coupled smoothly to afford the desired products (4e and 4f) in synthetically useful yields. Importantly, our reaction is applicable to polyfluoroalkyl iodides such as 1-chloro-2-iodotetrafluoroethane and 1-bromo-2-iodotetrafluoroethane, albeit that 4h was obtained in a lower yield. This may be due to the instability of the 1-bromotetrafluoroethoxide species generated during the OR-F-migration process. It is worth noting that the anilide moiety of the products could serve as a versatile handle for further synthetic functionalizations.14

In order to get an insight into the mechanism of the photocatalytic reaction, we performed a series of Stern-Volmer quenching experiments (Fig. 2a). While deprotonated N-phenyl-N-hydroxylamidide (1a, \( E_{1/2}^{\text{red}} = 0.62 \) V vs. SCE) efficiently quenched \(^{*}\text{Ru(bpy)}_{3}^{2+}\) in MeCN with a quenching constant of \( k_{q} = 7.84 \times 10^{9} \text{ M}^{-1} \text{ s}^{-1} \), N-phenyl-N-hydroxylamidide (1a) and perfluoroisopropyl iodide (2a) quenched the photoexcited photocatalyst \(^{*}\text{Ru(bpy)}_{3}^{2+}\) only to a minor extent. We also observed that the ORF migration is slower with more electron deficient aromatics, which is consistent with our previous observations and suggests an ionic ORF-migration pathway.36

Based on these results, a detailed description of our proposed photocatalytic cycle for selective O–RF bond formation and the consequent ORF-migration is outlined in Fig. 2b. Irradiation of \(^{*}\text{Ru(bpy)}_{3}^{2+}\) with visible light produces a long-lived (1.10 \( \mu \)s) photoexcited state, \(^{*}\text{Ru(bpy)}_{3}^{1+}\), which engages in a SET with 1a to give N-hydroxyl radical (1b) and a strong reductant \(^{*}\text{Ru(bpy)}_{3}^{+}\) (\( E_{1/2}^{\text{red}} = -1.33 \) V vs. SCE).45 A single electron reduction of perfluoroalkyl iodide (2d) with \(^{*}\text{Ru(bpy)}_{3}^{+}\) forms a perfluoroalkyl radical (1f) and regenerates \(^{*}\text{Ru(bpy)}_{3}^{2+}\). Subsequent radical–radical coupling between 1b and 1f affords O-perfluoroalkylated N-phenyl-N-hydroxylamide 1c, which undergoes heterolytic N–ORF bond cleavage47,48 followed by recombination of the resulting short-lived ion pair (1d) and then tautomerization to yield the final perfluoroalkoxylated arene product.36

### Table 2

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<th>Arenes</th>
<th>Pyridines</th>
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| Reaction conditions: 1 (1.00 equiv.), 2a (8.00 equiv.), Ru(bpy)(PF6)_3 (0.500 mol%), K_2CO_3 (3.00 equiv.) in MeCN (0.100 M) at 0 °C. Cited yields are for isolated material. b > 40 °C. c Following perfluoroalkylation, the reaction was heated to 40 °C. d Following O-perfluoroalkylation, the reaction was filtered, concentrated and the residue was dissolved in MeCN and heated to 80 °C. e Following O-perfluoroalkylation, the reaction was filtered, concentrated and the residue was dissolved in MeCN and heated to 120 °C. See ESI for further experimental details.† |

### Table 3

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<th>Selected examples of the polyfluoroalkoxylation of arenes</th>
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Notes and references


Conclusions

In conclusion, we have developed the first photocatalytic protocol for the synthesis of structurally diverse perfluoroalkoxylated (hetero)arenes. The key to the success of our approach is the ability to concomitantly generate persistent and transient radicals under photoredox-catalyzed reaction conditions, which provide direct access to the challenging O–RF bond formation. Our approach is one of the mildest and most general perfluoroalkoxylation of (hetero)arenes reported to date.\(^{9,20–25}\) It features a broad substrate scope and high functional group compatibility. In addition, the use of commercially available R$_2$I reagents and the excellent chemoselectivity of this reaction represents a considerable advance in the construction of the O–RF bond and should have a significant impact on the approach towards the synthesis of perfluoroalkoxylated aromatic building blocks. The success of this method not only provides access to unexplored chemical spaces to aid the discovery and development of novel drugs, agrochemicals, and functional materials, but also establishes a solid framework for further development of the photocatalytic radical coupling strategy using N-(hetero)aryl-N-hydroxylamides.
43 For some substrates, reaction was run at −40 °C, and filtration and/or heating were required for the ORF-migration step. See the ESI† for detailed reaction conditions.