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Transition-Metal and Solvent-Free Oxidative C−H Fluoroalkoxylation of Quinoxalinones with Fluoroalkyl Alcohols

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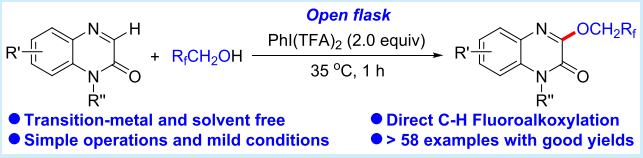
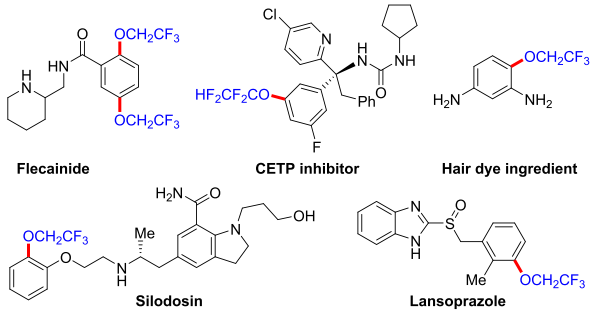
Supporting Information

ABSTRACT: The first example of oxidative C−H fluoroalkoxylation of quinoxalinones with fluoroalkyl alcohols under transition-metal and solvent-free conditions is described. This approach provides the synthesis of fluoroalkoxylated quinoxaline derivatives with good to excellent yields under mild reactions conditions. This method can also be extended to the facile and efficient synthesis of histamine-4 receptor.



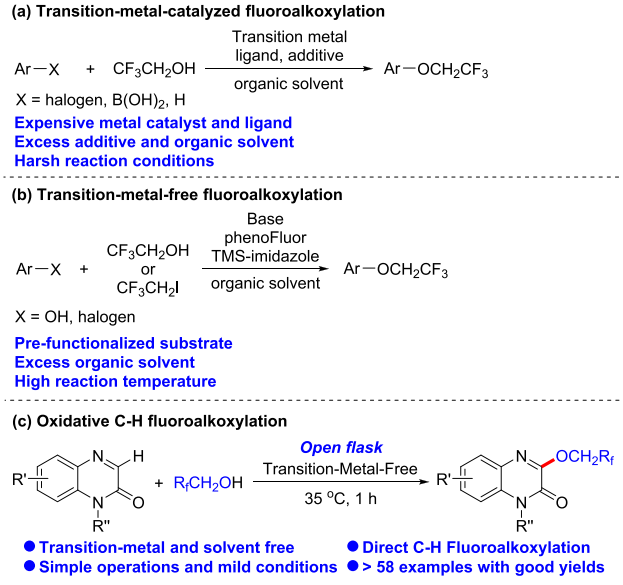
Fluorine-containing molecules have found important applications in drug discovery, agricultural chemicals, and materials science.[1] Fluoroalkoxyl aryl ethers are among those that have received much attention, because of the unique properties such as good electron-withdrawing effect and the significant lipophilicity of the fluoroalkoxyl group (Scheme 1).[2]

Scheme 1. Representative Fluoroalkoxylated Compounds



The transition-metal-catalyzed coupling reactions typically give access to such compounds as shown in Scheme 2a.[3] In 2014, Singh and co-workers reported a palladium/brettphos-catalyzed fluoroalkoxylation of activated aryl halides with fluoroalkyl alcohols.[3a] Subsequently, Weng et al. synthesized fluoroalkoxylation of aryl and heteroaryl bromides by using a well-defined copper(I) fluoroalkoxide complex.[3b] The copper-catalyzed oxidative trifluoroethoxylation of aryl boronic acids with CF_3CH_2OH has also been reported.[3c] Moreover, palladium-catalyzed C−H trifluoroethoxylation of arenes can be facilitated by the N atom of amide.[3d] Despite the tremendous advances that have been made, the generation of fluoroalkoxyl aryl ethers through transition-metal catalysis still suffers from some instinctive drawbacks. For example, it is a costly and challenging task to remove the trace amounts of transition metals remaining in the final products. This is particularly true in the pharmaceuticals industry.[4] Another interesting alternative is based on nucleophilic displacement reactions at high temperature (Scheme 2b).[5] In this way, the use of transition-metal catalysts is avoided.[6] Nevertheless, there is still a substantial interest in developing simple and practical approaches to introduce fluoroalkoxyl groups into organic molecules.

Scheme 2. Present Approaches for Fluoroalkoxylation



In recent years, the transition-metal-free oxidative C−H functionalization has received considerable attention.[7] Especially, the hypervalent iodine(III) reagents are a highly effective class of oxidants that have been widely used in oxidative C−H functionalization reactions.[8] Such reagents have high stability, low toxicity, and ready commercial availability, making them practically interesting for synthetic chemistry.[7c,9]

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For a long period of time, we have been focusing on the C−H functionalization of *N*-containing heterocycles[10] and the fluorine chemistry.[11] In a continuation of our efforts, we herein reported a direct C−H fluoroalkoxylation of quinoxalinones with fluoroalkyl alcohols using hypervalent iodine(III) reagent as an oxidant under transition-metal and solvent-free conditions[12] (Scheme 2c). We chose quinoxaline derivatives as substrates for two reasons. First, substituted quinoxalines and their analogues are important organic compounds in pharmaceuticals,[13] natural products,[14] and materials chemistry.[15] Second, although many C−H functionalization reactions have been reported for the construction of C−C,[16] C−N,[17] and C−P[18] bonds of quinoxalines, the development of C−O bond formation reaction remains scarce.

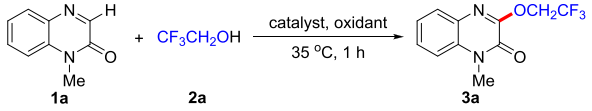
To the best of our knowledge, this is the first sample on the oxidative C−H fluoroalkoxylation of quinoxalinones with fluoroalkyl alcohols under transition-metal and solvent-free conditions.

In a first set of experiments, we investigated the C−H fluoroalkoxylation of quinoxalinone (**1a**) with trifluoroethanol (**2a**) as the fluoroalkoxylating reagent. The reaction to form product (**3a**) gave 65% yield within 1 h by using 1 mol % of Eosin Y as the photocatalyst, 1.5 equiv of $PhI(TFA)_2$ as the external oxidant, and 0.2 mL of MeCN as the solvent under the illumination of blue light-emitting diode (LED) (see Table S1, entry 1, in the Supporting Information). Other photocatalysts such as $Ir(ppy)_3$ and Rhodamine B could also promote this transformation and give the target product in similar yield (Table S1, entries 2 and 3). These results prompted us to further explore if the photocatalyst was indispensable. To our surprise, 64% yield of product **3a** was still isolated even without any photocatalyst (Table S1, entry 4). Instead, it was found that the reactivity of the reaction was the result of thermal activation, because of the actual fact that the C−H fluoroalkoxylation reaction also occurred without light at 35 °C, giving the product **3a** in 63% yield (see Table 1, entry 1). In this case, we could confirm that the heat generated from the blue LEDs utilized in our experiment (at a temperature of ∼35 °C) was sufficient to initiate the reaction. This hypothesis was further proved when the reaction was performed at room temperature (∼15 °C) without light (19% yield; see Table 1, entry 2). Changing the oxidants or solvents did not enhance the product yield (Table S1, entries 5−21). However, a higher yield of 89% was obtained when 2.0 equiv of $PhI(TFA)_2$ was used (Table 1, entry 3). No significant change was observed when the dosage was further increased to 2.5 equiv (Table 1, entry 4). After further screening of the reaction conditions, we were surprised that the transformation could also occur under solvent-free conditions (Table 1, entries 5−8). In this approach, the target product **3a** was isolated in 88% yield when the dosage of **2a** was enhanced to 3.0 equiv (Table 1, entry 7).

With the optimal reaction conditions in hand, the substrate scope of the C−H fluoroalkoxylation was subsequently explored by employing various quinoxalinones (**1**) with trifluoroethanol (**2a**) (Scheme 3). First, the compatibility of different *N*-substituted quinoxalinones in the present transformation was examined. To our delight, a wide range of *N*-protecting groups including methyl, ethyl, butyl, cyclohexylmethyl, esteryl, keto, and allyl groups were well compatible in this transformation, giving access to the desired products in good to excellent yields (**3a**−**3g**). It should be mentioned that the *N*-free protecting quinoxalinone was also suitable for the transformation, the product (**3h**) was obtained in 80% yield. Interestingly, when using Boc as the *N*-protecting group, the deprotection step also happened to provide product **3h** in 75% yield (see the Experimental Section in the Supporting Information, subsection 1.3). Substrates with various *N*-benzyl groups were also tolerated in this reaction, as demonstrated with **3i**−**3u**. The molecular structure of product **3l** was further confirmed by X-ray crystallographic analysis (CCDC No. 1911863). In addition, quinoxalinones bearing the methyl, methoxyl, chloro, and bromo groups on the benzene ring were also investigated under the optimal reaction conditions, and the corresponding products (**3v**−**3aa**) were isolated in good yields.

After the successful implementation of C−H fluoroalkoxylation of quinoxalinones with trifluoroethanol, the transformation was further studied using other fluoroalkyl alcohols

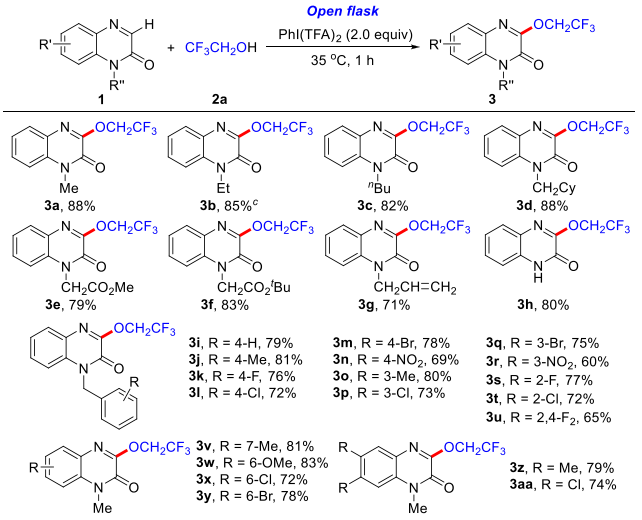
Table 1. Optimization of Reaction Conditions[a,b]



entry	catalyst	oxidant	solvent	yield[b] (%)
1	–	$PhI(TFA)_2$	MeCN	63
2[c]	–	$PhI(TFA)_2$	MeCN	19
3[d]	–	$PhI(TFA)_2$	MeCN	89
4[e]	–	$PhI(TFA)_2$	MeCN	87
5[d]	–	$PhI(TFA)_2$	–	42
6[d,f]	–	$PhI(TFA)_2$	–	52
7[d,g]	–	$PhI(TFA)_2$	–	88
8[d,h]	–	$PhI(TFA)_2$	–	86

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (1.5 equiv), oxidant (1.5 equiv), solvent (0.2 mL), open flask, 35 °C, 1 h. [b]Isolated yields. [c]Stirred at room temperature. [d]$PhI(TFA)_2$ (2.0 equiv). [e]$PhI(TFA)_2$ (2.5 equiv). [f]**2a** (2.0 equiv). [g]**2a** (3.0 equiv). [h]**2a** (4.0 equiv).

Scheme 3. Substrate Scope of Quinoxalinones with Trifluoroethanol[a,b]



[a]Reaction conditions: **1** (0.2 mmol), **2a** (3.0 equiv), $PhI(TFA)_2$ (2.0 equiv), open flask, 35 °C, 1 h. [b]Isolated yields. [c]Reaction was performed on a 1 mmol scale.

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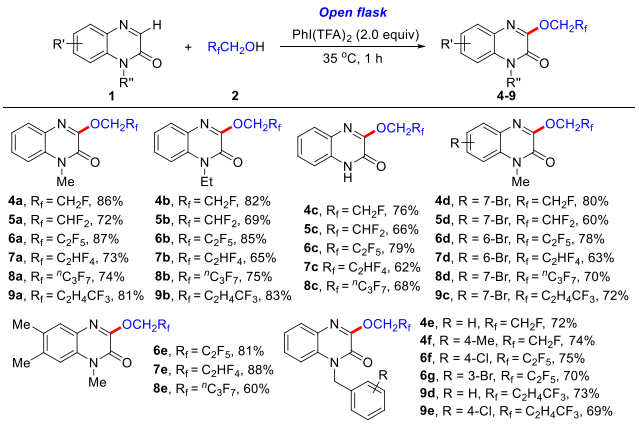
as fluoroalkoxylating reagents (Scheme 4). The present method was also suitable for C−H fluoroalkoxylation of

Scheme 4. Substrate Scope of Quinoxalinones with Fluoroalkyl Alcohol[a,b]

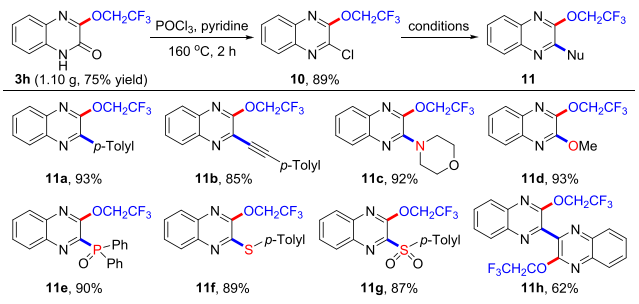


[a]Reaction conditions: **1** (0.2 mmol), **2** (3.0 equiv), PhI(TFA)$_2$ (2.0 equiv), open flask, 35 °C, 1 h. [b]Isolated yields.

quinoxalinones with a variety of fluoroalkyl alcohols, such as fluoroethanol (**4a**−**4f**), difluoroethanol (**5a**−**5d**), pentafluoropropanol (**6a**−**6g**), tetrafluoropropanol (**7a**−**7e**), heptafluorobutanol (**8a**−**8e**), and trifluorobutanol (**9a**−**9e**), which provided the corresponding products in good to excellent yields. Furthermore, the molecular structure of product **7d** was confirmed by X-ray crystallographic analysis (CCDC No. 1913960). An exception is that the hexafluoroisopropanol could not be transformed to the corresponding product. We suspected that the effect of steric hindrance prevented the transformation.

To further display the scalability and synthetic utility of the transformation, we performed the C−H fluoroalkoxylation of trifluoroethanol with quinoxalinones on a 6.0 mmol scale, and the desired product **3h** was obtained in 75% yield (Scheme 5).

Scheme 5. Gram-Scale Synthesis and Product Transformations[a]

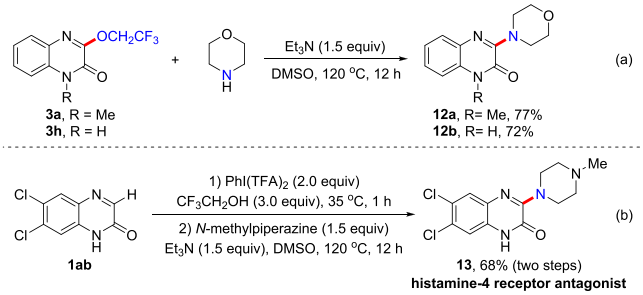


[a]For the detailed reaction conditions, see the Supporting Information.

In addition, the fluoroalkoxylated quinoxalinone could be transformed to various quinoxaline derivatives, which are challenging reactions using traditional methods (Scheme 5). For instance, the above product **3h** could be first converted to the chlorinated quinoxaline **10** in the presence of $POCl_3$. Further transformations of chlorinated quinoxaline **11** with various reactants under different conditions gave the corresponding products in excellent yields.

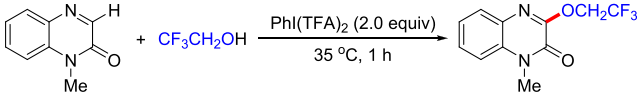
In addition to the special bioactivity, the trifluoroethoxyl group could also be used as an available leaving group in S_NAr reactions.[19] In this case, the reactivity of trifluoroethyl ethers **3** toward nucleophilic substitution with morpholine was investigated and the aminated products **12** were obtained in good yields (Scheme 6a). Subsequently, the two-step synthesis of histamine-4 receptor antagonist **13** was successfully achieved in 68% yield (Scheme 6b).

Scheme 6. Application of Products in S_NAr Reactions and Synthesis of Histamine-4 Receptor Antagonist



As reported previously, most of C−H functionalization reactions that contain hypervalent iodine reagents involve radical mechanisms.[9] To explain the reaction mechanism, we performed a preliminary mechanism investigation (Scheme 7).

Scheme 7. Control Experiments for Preliminary Mechanism Study



	yield of **3a**	recovery of **1a**
No Inhibitor	88%	0%
TEMPO (2.0 equiv)	trace	83%
DPE (2.0 equiv)	23%	65%

adduct A [M+H]$^+$ 256.1519; Found 256.1519

adduct B [M+H]$^+$ 279.0991; Found 279.0981

First, the transformation was suppressed when an amount of 2 equiv of TEMPO (2,2,6,6-tetramethyl-piperidin-1-oxyl) or DPE (diphenylethlene) was added as a radical inhibitor, respectively. Meanwhile, a considerable amount of quinoxalinones (**1a**) was recovered in 83% or 65% yields, respectively. Furthermore, the adducts A and B were also detected by HRMS. These experimental results clearly revealed that a radical pathway was involved in the reaction.

Based on the above-mentioned results and previous reports,[7,9,16−18] a single electron transfer (SET) mechanism was proposed (Scheme 8). Initially, trifluoroethoxyl radical was formed from trifluoroethanol through the oxidation of PhI(TFA)$_2$. The obtained radical then attacked substrate **1a** to produce nitrogen radical intermediate **C** (path A). However, an alternative route for the formation of nitrogen radical intermediate **C** cannot be excluded. In this case, the substrate **1a** first coordinated with PhI(TFA)$_2$ to generate intermediate **A**, and the reactive radical cation **B** was then generated through a single electron transfer (SET) process, which was trapped by

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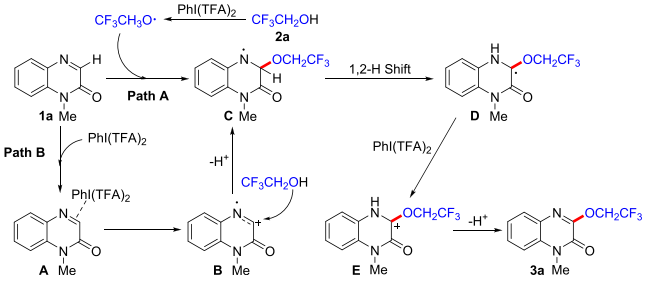
Scheme 8. Plausible Mechanism



the intermolecular nucleophile to form nitrogen radical intermediate **C** (path B).[20] Overall, intermediate **C** underwent the 1,2-hydrogen shift to form carbon radical **D**. Subsequently, carbon radical **D** was oxidized by $PhI(TFA)_2$ to afford carbon cation intermediate **E** via another single electron transfer (SET) process. In a final step, the target product **3a** was obtained through a deprotonation process of carbon cation intermediate **E**.

In conclusion, we have first reported a transition-metal and solvent-free approach for the C−H fluoroalkoxylation of quinoxalinones with fluoroalkyl alcohols. This reaction provides a simple and efficient method for the synthesis of previously unknown fluoroalkoxylated quinoxaline derivatives, and also gives access to amination of the quinoxalinones. Further investigations to introduce the fluoroalkoxyl into other challenging substrates are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01578.

Experimental procedures, characterization data, and ^{1}H, ^{13}C and ^{19}F NMR spectra for the synthesized compounds (PDF)

Accession Codes

CCDC 1911863 and 1913960 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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