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COMMUNICATION

Visible-light-induced installation of oxyfluoroalkyl groups

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(Hetero)aryloxytetrafluoroethylation of heteroaromatics and alkenes, have been achieved by visible-light photocatalysis utilizing readily synthesized oxyfluoroalkyl reagents. The mild reaction conditions and the high diversity on both substrates and oxyfluoroalkyl reagents make this a useful method for late-stage modifications in the development of various functional molecules.

Fluorine has the unique ability to alter the biological, physical, and chemical properties of organic molecules, mainly due to its high electronegativity, small size, and high C–F bond dissociation energy. In particular, fluoroalkylated compounds are characterized by superior lipophilicity, binding selectivity, bioavailability, and metabolic stability as compared to their nonfluoroalkylated analogues.[1] Thus, extensive research efforts have been devoted for the preparation of pharmaceutical and agrochemical agents bearing fluoroalkyl moieties.[2]

Oxygen is also an important element in drug development. In particular, when connected to fluoroalkyl groups, oxygen can significantly affect the biological and physical properties of organic molecules, for example, by inducing higher lipophilicity.[3] Accordingly, molecules containing a fluoroalkyl group connected to oxygen have been of great interest, especially in medicinal chemistry, and many biologically active molecules such as roflumilast, pantoprazole, and hexaflumuron contain aryloxyfluoroalkyl groups (Figure 1).[4] Because of the importance of both fluoroalkyl and oxygen moieties, various methods have been developed for their installation, and the most common approach involves the fluoroalkylation of alcohols [Figure 2(a)].[5] Considering the use of both moieties in drug development, a direct oxyfluoroalkylation reaction could offer an efficient strategy for late-stage modifications.

However, only a few direct oxyfluoroalkylation methods have been developed,[4(a),6] and their application is limited because of the harsh reaction conditions. Recently, visible-light photocatalysis has emerged as a powerful preparative tool owing to its environmental benignity and mechanistic versatility in promoting a large number of synthetically important reactions with high levels of selectivity.[7]

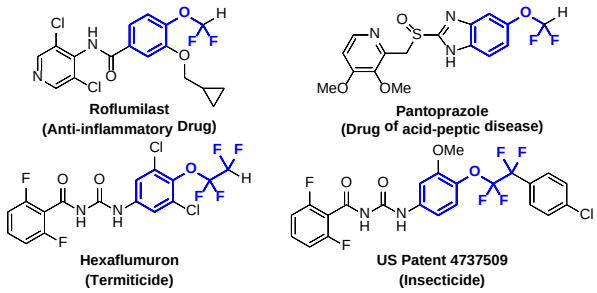

Fig. 1 Aryloxyfluoroalkyl structural motifs in pharmacological compounds.

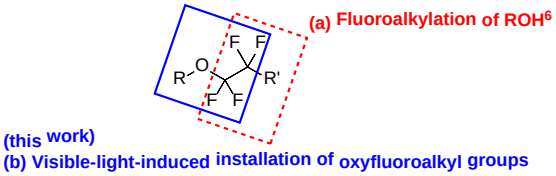

Fig. 2 Strategies for oxyfluoroalkylation

Our group has developed various visible-light-induced fluoroalkylation methods under mild conditions[8] including direct arylthiofluoroalkylation[9] which enabled simultaneous installation of sulfur and fluoroalkyl moieties. As a continuation of our interest and inspired by our success on photocatalytic fluoroalkylations, we envisioned the visible light-induced simultaneous introduction of alkoxy group and fluoroalkyl groups into organic molecules such as heteroaromatics and alkenes by utilizing readily available oxyfluoroalkyl reagents. We expected their incorporation into organic molecules to be easier than the fluoroalkylation of alcohols via the corresponding fluoroalkyl radical, which would be generated regardless of the presence of the alkoxy moiety under mild reaction conditions [Figure 2(b)].

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† Electronic Supplementary Information (ESI) available: Experimental procedures, additional experimental data, analytical data, and ^{1}H and ^{13}C NMR spectra of aryloxytetraethylated compounds. See DOI: 10.1039/x0xx00000x

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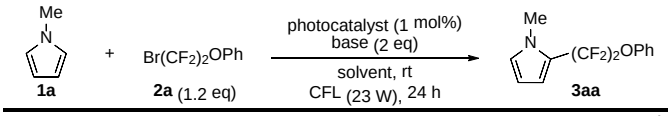
Table 1 Optimization table of heteroaromatics[a]



1a 2a (1.2 eq) 3aa

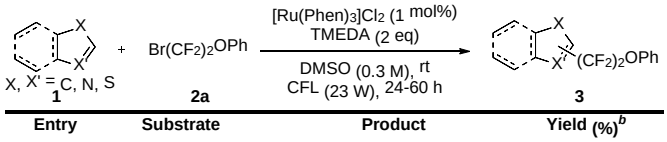
Entry	Photocatalyst	Base	Solvent (Conc.)	Variations	Yield (%)[b]
1	$[Ru(Phen)_3]Cl_2$	TMEDA	MeCN (0.2 M)		46
2	$[Ru(bpy)_3]Cl_2$	TMEDA	MeCN (0.2 M)		43
3	*fac*-Ir(ppy)$_3$	TMEDA	MeCN (0.2 M)		31
4	*fac*-Ir(dFppy)$_3$	TMEDA	MeCN (0.2 M)		28
5	Nile red	TMEDA	MeCN (0.2 M)		-
6	$[Ru(Phen)_3]Cl_2$	TMEDA	DMF (0.2 M)		67
7	$[Ru(Phen)_3]Cl_2$	TMEDA	DMSO (0.2 M)		71
8	$[Ru(Phen)_3]Cl_2$	TMEDA	DMSO (0.2 M)	no hv	trace
9	-	TMEDA	DMSO (0.2 M)		trace
10	$[Ru(Phen)_3]Cl_2$	TMEDA	DMSO (0.3 M)		76
11	$[Ru(Phen)_3]Cl_2$	TMEDA	DMSO (0.3 M)	2 equiv **2a**	82
12	**$[Ru(Phen)_3]Cl_2$**	**TMEDA**	**DMSO (0.3 M)**	**3 equiv 2a**	**87**

[a]Reaction scale: **1a** (0.1 mmol); [b]yield (%) was determined by GC spectroscopy using dodecane as internal standard.

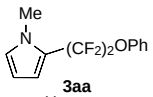
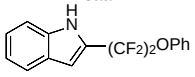
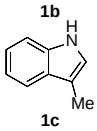
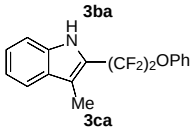
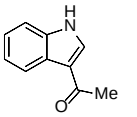
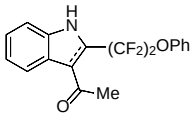
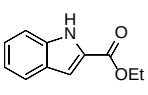
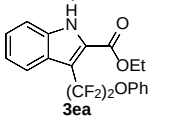
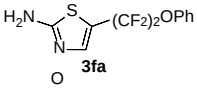
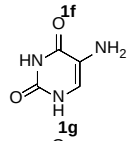
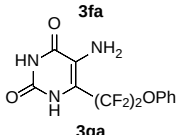
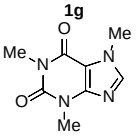
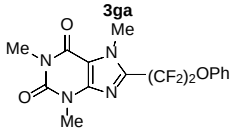
We began our study by using *N*-methylpyrrole **1a** and 2-bromo-1,1,2,2-tetrafluoroethoxybenzene, $Br(CF_2)_2OPh$ **2a**, as model substrates (Table 1, and the full optimization details can be found in Table S1 in the electronic supplementary information). $Br(CF_2)_2OPh$ could be easily synthesized from phenol and dibromotetra-fluoroethane, $Br(CF_2)_2Br$.[10] The reaction of **1a** with 1.2 equiv of **2a** proceeded in the presence of 1 mol% of the photocatalyst and 2 equiv of TMEDA in MeCN (0.2 M) under the irradiation from a 23 W compact fluorescent lamp (CFL) (entries 1-5) to give the phenyloxytetrafluoroethylated product **3aa**. $[Ru(Phen)_3]Cl_2$ was the best photosensitizer among those tested and was chosen for subsequent studies. Solvent screening showed that DMF and DMSO provided higher efficiencies, whereas MeOH, THF, and 1,4-dioxane did not work at all for the reaction (entries 1, 6, and 7). Changing the base from TMEDA to other amine bases or inorganic bases, including TEA, DBU, DIPEA, 2,6-lutidine, K_2CO_3, and Cs_2CO_3 resulted in lower efficiencies. Control experiments indicated that the transformation required both visible light and the photocatalyst (entries 8 and 9). Thorough further screening of the reaction concentration and stoichiometry of the reagents (entries 10-12) revealed the best reaction conditions that provided **3aa** in 87% yield as follows: **1a**, 1 mol% of $[Ru(Phen)_3]Cl_2$, 3 equiv of **2a**, and 2 equiv of TMEDA in DMSO (0.3 M) (entry 12).

With the optimized conditions in hand, we next investigated the scope of various hetero-aromatic substrates with $Br(CF_2)_2OPh$ **2a** (Table 2). *N*-heteroaromatics including pyrrole, indole, and thiazole derivatives worked well under the optimized conditions to give the corresponding phenyloxytetra-fluoroethylated products (entries 1-6). Despite the moderate yield and the formation of some side products, including small amounts of 2-bromo-3-phenyloxytetrafluroethylindole, 3-bromo-2-phenyloxytetrafluoroethylindole, and 2-bromoindole, the reaction of indole **1b** showed high regioselectivity, providing 33% of the 2-substituted product **3ba** without the formation of the 3-substituted product (entry 2).[11] Interestingly, the reaction of **1d** having an acetyl substituent provided indoline **3da'** as the major product under the standard conditions (entry 4). Instead, the desired phenyloxytetrafluoroethylatedindole (**3da**) could be obtained by using $(NH_4)_2S_2O_8$ as the oxidant additive.[12] In addition, bioactive compounds such as 5-aminouracil **1g** and caffeine **1h** were suitable substrates for the oxyfluoroalkylation, proving the utility and practicality of our method. The reaction conditions were amenable to a large-scale reaction such that **3aa** could be prepared on a 5 mmol scale with yield similar to that of a 0.3 mmol scale reaction. Reactions of other heterocycles such as thiophenes, benzothiophenes, benzofurans, and benzoxazoles were also tried, but did not show good reactivity, giving low yields of products with several side products. In addition, aromatic compounds were not reactive under the standard conditions.

Table 2 Substrate scope of heteroaromatics[a]

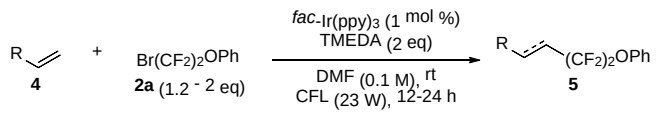


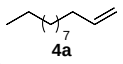
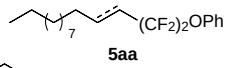
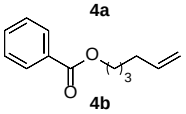
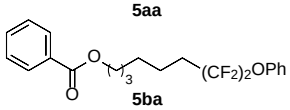
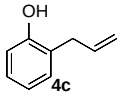
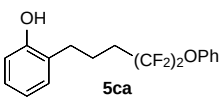
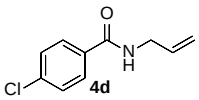
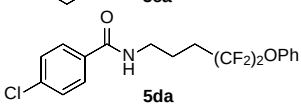
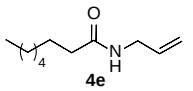
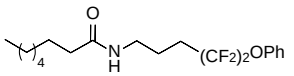
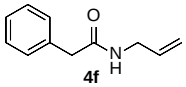
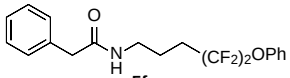
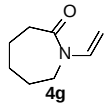
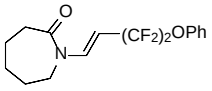
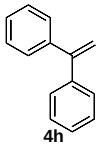
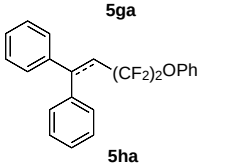
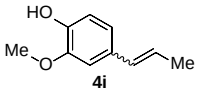
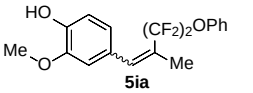
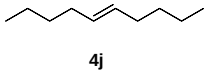
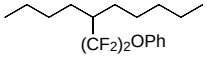
1 2a 3

Entry	Substrate	Product	Yield (%)[b]
1	 **1a**	 **3aa**	82
2	 **1b**	 **3ba**	33
3	 **1c**	 **3ca**	72
4	 **1d**	 **3da, 3da'**	40 (Indoline, **3da'**) 37 (Indole, **3da**)[c]
5	 **1e**	 **3ea**	60
6	 **1f**	 **3fa**	88
7	 **1g**	 **3ga**	44
8	 **1h**	 **3ha**	21

[a]Reaction scale: **1** (0.3 mmol), **2a** (0.9 mmol); [b]isolated yield; [c]$(NH_4)_2S_2O_8$ (4 equiv) was added as oxidizing additive.

Table 3 Substrate scope of aliphatic and aromatic alkenes[a]

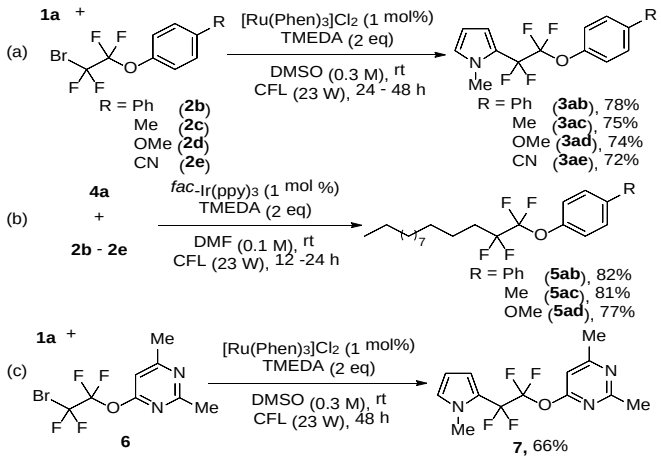


Entry	Substrate	Product	Yield (%)[b]
1	 **4a**	 **5aa**	84 (18:1)[c]
2	 **4b**	 **5ba**	52
3	 **4c**	 **5ca**	65
4	 **4d**	 **5da**	60
5	 **4e**	 **5ea**	75
6	 **4f**	 **5fa**	64
7[d]	 **4g**	 **5ga**	80
8[d]	 **4h**	 **5ha**	60 (1:5)[c]
9[d]	 **4i**	 **5ia**	74 (2.5:1)[e]
10	 **4j**	 **5ja**	30

[a]Reaction scale: **4** (0.3 mmol); [b]isolated yield; [c]ratio between the alkane and alkene form of the product. [d]$(NH_4)_2S_2O_8$ (4 equiv) was added as oxidizing additive; [e]E/Z ratio of **5ia**.

Oxyfluoroalkylation reactions of alkenes proceeded more efficiently than that of heteroaromatics (Table 3). After the optimization process using 1-dodecene **4a** as the model substrate with **2a**, we found that the transformation worked best with 1.2 equiv of **2a**, 2 equiv of TMEDA, and 1 mol% of *fac*- Ir(ppy)$_3$ in DMF (0.1 M) to give hydrophenyloxytetrafluoroethylated product **5aa** as the major compound (entry 1). The full optimization details can be found in Table S2 in the electronic supplementary information. Under the optimal conditions, aliphatic and aromatic alkenes containing various functional groups, including ester (entry 2), alcohol (entry 3), and amide (entries 4-6), underwent oxyfluoroalkylation. The reaction of lactam substrate **4g** produced a mixture of phenyloxytetra-fluoroethylated alkene and alkane products under the standard conditions; the alkene product **5ga** could be selectively obtained by using 4 equiv of $(NH_4)_2S_2O_8$. In general, aromatic alkenes showed low reactivity[13]; thus, reactions of styrene provided low yields of the corresponding products except of disubstituted styrene derivatives. Interestingly, reactions of 1,1-disubstituted styrene derivative **4h** and 1,2-disubstituted styrene derivative **4i** proceeded well to yield oxyfluoroalkylated alkene **5ha** and **5ia** as the major product, respectively (entries 8 and 9), while those of aliphatic alkenes provided the alkane products. Despite the lower reactivity, internal alkene **4j** also underwent the transformation to give hydrophenyloxytetra-fluoroethylated product **5ja** (entry 5).

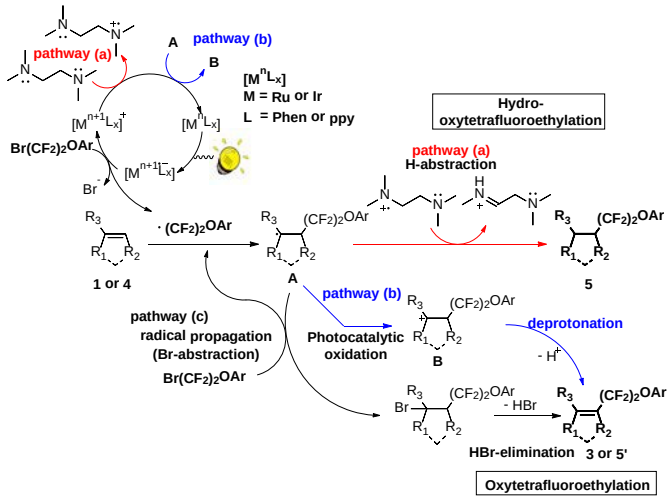
Scheme 1 Diversity of the (hetero)aryloxytetrafluoroethylation[a,b]



[a]Reaction scale: **1a** or **4a** (0.3 mmol), **2b**-**2e** or **6** (0.9 mmol with **1a** and 0.6 mmol with **4a**); [b]isolated yield or GC yield due to the volatility of products.

To prove the diversity and potential application of this transformation, other oxyfluoroalkyl reagents were employed (Scheme 1). Reactions of **1a** and **4a** were conducted with various (hetero)aryloxytetrafluoroethyl reagents containing either electronwithdrawing (EWG) substituents (**2e**) or electrondonating (EDG) substituents (**2b**, **2c**, **2d**). The moderate to good yields of corresponding products **3ab**-**3ae** and **5ab**-**5ad** indicated that the method is applicable to the synthesis of various aryloxyfluoroalkylated products [Scheme 1(a) and 1(b)]. A heterocycle containing a dimethylpyrimidine moiety (**6**) was also synthesized and successfully utilized for the reaction with **1a** to provide **7** in 66% yield [Scheme 1(c)].

Based on the results of our studies, a proposed mechanism is shown in Scheme 2 for the aryloxytetrafluoroethylation of heteroaromatics and alkenes using $[Ru(Phen)_3]Cl_2$ or *fac*-Ir(ppy)$_3$ as the photocatalyst. The catalyst in its normal state, $[M^nL_x]$, is photoexcited under visible-light irradiation using a 23 W compact fluorescent light (CFL) and is converted into $[M^{n+1}L_x^{\bullet-}]$ through a metal-to-ligand charge-transfer (MLCT) transition. Then, $[M^{n+1}L_x^{\bullet-}]$ is oxidatively quenched by a one-electron transfer to $Br(CF_2)_2OAr$, generating $[M^{n+1}L_x]^+$, a bromide ion, and the key intermediate $\cdot(CF_2)_2OAr$.[14] The radical intermediate is then added to substrate **1** or **4** to generate aryloxytetrafluoroethylated radical species **A**. Radical species **A** can then proceed through three possible pathways. Tetrafluoroethylated alkane product **5** would be generated by



Scheme 2. Proposed mechanism for aryloxytetrafluoroethylation of heteroaromatics and alkenes.

the hydrogen abstraction from ammonium radical cations, which are formed from the corresponding tertiary amines via a one-electron transfer to $[M^{n+1}L_x]^+$ [pathway (a) in the catalytic cycle]. On the other hand, tetrafluoroethylated product **3** or **5'** would be generated from A by pathway (b) or (c). A one-electron transfer from **A** to $[M^{n+1}L_x]^+$ produces the oxidized carbocation intermediate **B**, which is deprotonated by TMEDA to complete the reaction, providing product **3** or **5'** [pathway (b)]. Alternatively, **3** or **5'** can be generated by Br-abstraction and HBr elimination processes, which involve radical propagation to produce the key radical intermediate $\cdot(CF_2)_2OAr$ [pathway (c)].

In summary, we have developed a practical visible-light-induced (hetero)aryloxytetrafluoroethylations of heteroaromatics and alkenes under mild reaction conditions. Two functional groups consisting of oxygen and fluoroalkyl moieties could be simultaneously installed into unactivated heteroaromatics and alkenes, demonstrating the potential use of the method for late-stage modifications in the development of functional molecules. In addition, this method can be utilized for the fine-tuning of properties in drug development by modifying the oxyfluoroalkyl reagent.

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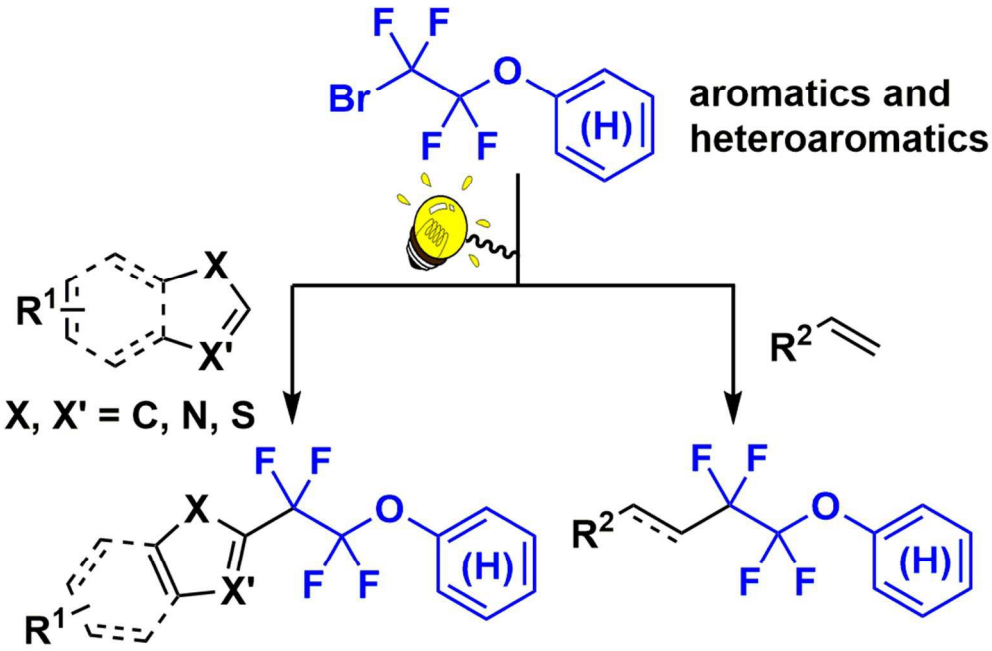

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