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Radical Chlorodifluoromethylation: Providing a Motif for (Hetero)arene Diversification

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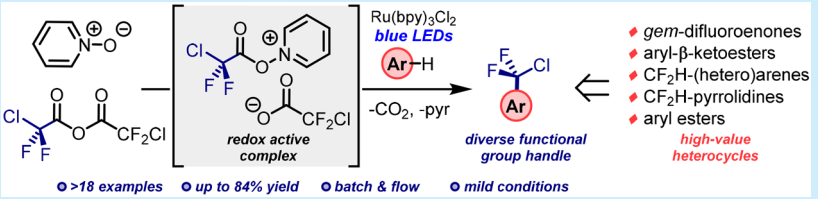
Supporting Information



ABSTRACT: A method for the radical chlorodifluoromethylation of (hetero)arenes using chlorodifluoroacetic anhydride is reported. This operationally simple protocol proceeds under mild photochemical conditions with high functional group compatibility and complements the large body of literature for the trifluoromethylation of (hetero)arenes. Introduction of the chlorodifluoromethyl motif enables rapid diversification to a wide array of aromatic scaffolds. This work showcases the chlorodifluoromethyl group as an attractive entryway to otherwise synthetically challenging electron-rich difluoromethyl-(hetero)arenes. Furthermore, facile conversion of the CF_2Cl moiety into the corresponding aryl esters, *gem*-difluoroenones, and *β*-keto-esters is demonstrated.

Fluorine has the unique ability to alter the physiochemical properties of small molecules,[1] meaning that the introduction of fluorine into molecular scaffolds can dramatically affect their behavior in biological systems, often increasing metabolic stability.[2] Consequently, the fluorine atom is widely acknowledged to be a valuable heteroatomic surrogate.[3] Moreover, organofluorine chemistry has recently found many diverse applications in the development of new pharmaceuticals, agrochemicals, and materials.[1,4]

While a great deal of effort has been directed toward developing new methodologies for introducing the trifluoromethyl (CF_3) moiety into organic molecules,[5] procedures for incorporating the corresponding, yet chemically distinct,[6] difluoromethylene functionality (CF_2X) are less established. In particular, the difluoromethyl group (CF_2H) has garnered recent interest in medicinal chemistry as a lipophilic hydrogen-bond donor and is considered a competent bioisostere for thiols and alcohols (Figure 1A, left).[3,7−9] As a consequence, there is a growing demand to develop efficient and practical methods for the introduction of the difluoromethylene motif, in particular, the difluoromethyl group,[6,10,11] into organic and medicinally relevant compounds. Within the past decade, numerous radical based difluoromethylation reaction platforms have been reported.[12] Many of these methods demonstrate excellent functional group tolerance and have potential to be adopted for applications beyond discovery scale. A notable limitation though of direct radical difluoromethylation may be partly attributed to the limited substrate scope, arising from the difluoromethyl radical preferentially functionalizing electron-deficient *π*-systems. Therefore, the development of a simple and complementary protocol capable of overcoming the inherent electronic paradigm of existing radical difluoromethylation methods would be a valuable addition to the organic practitioner's repertoire.

While the difluoromethyl radical exhibits nucleophilic behavior,[12a] the chlorodifluoromethyl radical may be characterized as an electrophilic radical (Figure 1A right). We targeted the chlorodifluoromethyl radical as an attractive surrogate to the difluoromethyl radical as a means to efficiently prepare electron-rich difluoromethyated (hetero)-arenes and other high-value, fluorinated heterocycles. However, only a few precursors to the chlorodifluoromethyl radical have been reported (Figure 1B), including bromochlorodifluoromethane,[13] bis(chlorodifluoroacetyl)peroxide in the presence of Freon-113,[14] and *O*-octadecyl-*S*-chlorodifluoromethyl xanthate, which requires an AIBN/$(Me_3Si)_3SiH$ combination to reductively remove the xanthate group.[15] Herein, we report the direct chlorodifluoromethylation of (hetero)arenes with commercially available chlorodifluoroacetic anhydride (Figure 1C). The chlorodifluoromethyl group acts as a difluorinated linchpin, which readily participates in postfunctionalization reactions, enabling the rapid generation of aryl esters, *gem*-difluoroenones, and *β*-keto-esters. Notably, the chlorodifluoromethyl group is shown to be a critical entryway to electron-rich difluoromethylated (hetero)arenes,

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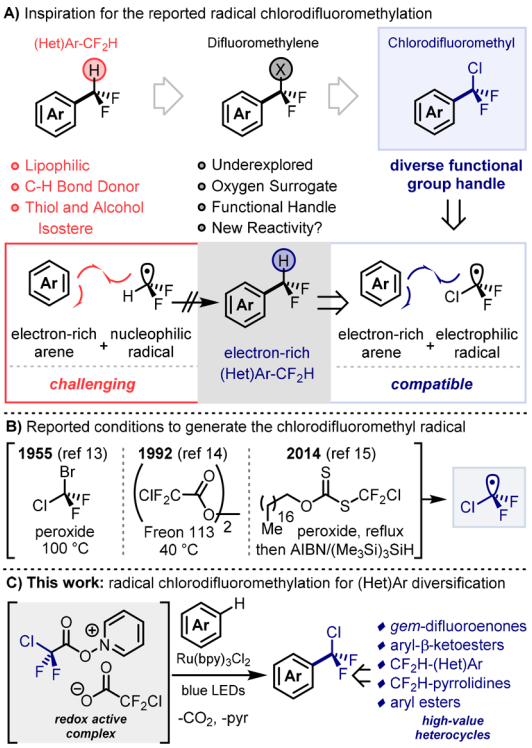
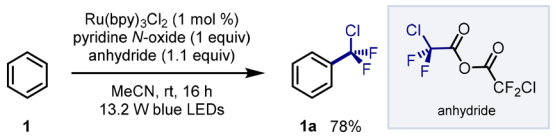


Figure 1. (A) Inspiration for the reported radical chlorodifluoromethylation of (hetero)arenes. (B) Summary of previous efforts toward alkene and arene radical chlorodifluoromethylation. (C) General representation of this work: decarboxylative radical chlorodifluoromethylation of (hetero)arenes to access high-value heterocycles.

which previous methods have been found challenging to prepare.

Recently, our group identified pyridine *N*-oxide as a suitable redox trigger for the reductive decarboxylation of trifluoroacetic anhydride for the intermolecular coupling of a range of vinyl, aryl, and heteroaryl substrates.[16] This inexpensive reagent combination enables the direct generation of the CF_3 radical. In the succeeding manuscript, our group reports a complementary mode of reactivity by altering the electronics of this redox-active system for the direct coupling of electron-deficient heterocyclic *N*-oxides with electron-rich alkyl radicals. This fragment coupling paradigm uses the heterocyclic *N*-oxide reagent as both a transient redox auxiliary as well as the (hetero)aryl coupling partner. Inspired by our success with trifluoromethylation, we envisioned the development of a mild reagent combination (chlorodifluoroacetic anhydride/pyridine *N*-oxide adduct $E_{p/2}^{red}$ −1.57 V vs SCE)[17] for the generation of the chlorodifluoromethyl radical ($^{\bullet}CF_2Cl$). Benzene (**1**) was the substrate of choice for our initial exploration of reaction conditions (eq 1). We were



(1)

pleased to find that the combination of chlorodifluoroacetic anhydride, pyridine *N*-oxide, and 1 mol % $Ru(bpy)_3Cl_2$ furnished the desired chlorodifluoromethylated benzene (**1a**) in 78% ^{19}F NMR yield.[17]

The scope of chlorodifluoromethylation was evaluated for a wide array of electron-rich and pharmaceutically relevant (hetero)aromatics (Scheme 1). Several substrates exhibited good reactivity toward the radical fluoroalkylation protocol under the optimized reaction conditions, while modest conversions for select substrates could be overcome by simply increasing the equivalents of pyridine *N*-oxide and anhydride, or changing the redox trigger to 4-phenylpyridine *N*-oxide.[17] The increase in yield can be rationalized by the *in situ* formation of an electron donor−acceptor complex, providing an additional productive mechanistic pathway.[18] Mesitylene (**1b**), pyrroles (**1i**, **1l**, **1m**, **1o**), pyridones (**1f**, **1g**, **1h**, **1n**), benzofuran (**1d**), furan (**1k**), xanthines (**1p**, **1q**), aza-indoles (**1e**), anisole (**1c**), thiophene (**1j**), and quinoline (**1s**) all proved to be competent substrates. Subjection of 4-methylstyrene to the established conditions afforded the *bis*-substituted product (**1r**). This method was further shown to be tolerant of several sensitive functional groups, including esters, aryl halides, Boc-protected heterocycles, aryl methyl ethers, and MIDA boronates. In particular, the MIDA boronate products are appealing as potential fluorinated cross-coupling reagents and are frequently encountered in drug discovery efforts.[19] Moreover, in all reported examples, we observed a high preferential functionalization of the substrate over the concomitantly generated pyridine. The majority of products shown in Scheme 1 are compounds with unreported synthetic preparations. While the title reaction is amenable to gram scale-up in batch (**1p**), successful implementation of a flow reactor manifold (1 mL internal reactor volume, 0.04 in. internal diameter PFA tubing, 0.2 mL/min flow rate, and residence time of 10 min) suggests that this chemistry can translate beyond discovery scale (**1i**).[17]

With several classes of chlorodifluoromethylated (hetero)aromatic products prepared, we turned our attention toward exploring the reactivity of the chlorodifluoromethyl group and in particular to accessing the difluoromethyl group (CF_2H). Notably, subjecting electron-rich 4-^{t}Bu-anisole to the standard conditions with difluoroacetic anhydride or the known difluoromethylation reagent, zinc difluoromethanesulfinate (DFMS),[12a] failed to give radical CF_2H addition (Scheme 2). Satisfyingly, under basic hydrogenolysis conditions, the electron-rich difluoromethylanisole product (**2c**) was generated in excellent yield. These observations align with a literature precedent[12a,20] detailing the preferential addition of electron-rich difluoromethyl radicals to electron-deficient (hetero)aromatics. Sodium carbonate proved crucial for the success of this transformation and only trace amount of product was isolated in its absence, presumably due to deactivation of the palladium catalyst by *in situ* generated HCl. A diverse set of (hetero)arene−CF_2H products could be garnered in high yields (Figure 2A, **2a**−**e**) and, in the case of **2e**, excellent diastereoselectivity. Our two-step protocol stands as a robust synthetic equivalent to direct radical difluoromethylation and is an efficient solution to overcome the radical's electronic limitations (Figure 2B). Chlorodifluoromethylation followed by hydrogenolysis of **2f** provides the electronically mis-matched 5-difluomethylquinoline (**2g**). Notably, direct radical difluoromethylation of dihydroquinine is selective for the electrophilic 2-position of the quinoline core,[12a] further supporting the synthetic value and the complementary nature of the CF_2Cl motif. Additionally, exposing pyridone-CF_2Cl products to methanolysis conditions in either a one or two-pot sequence readily afforded the

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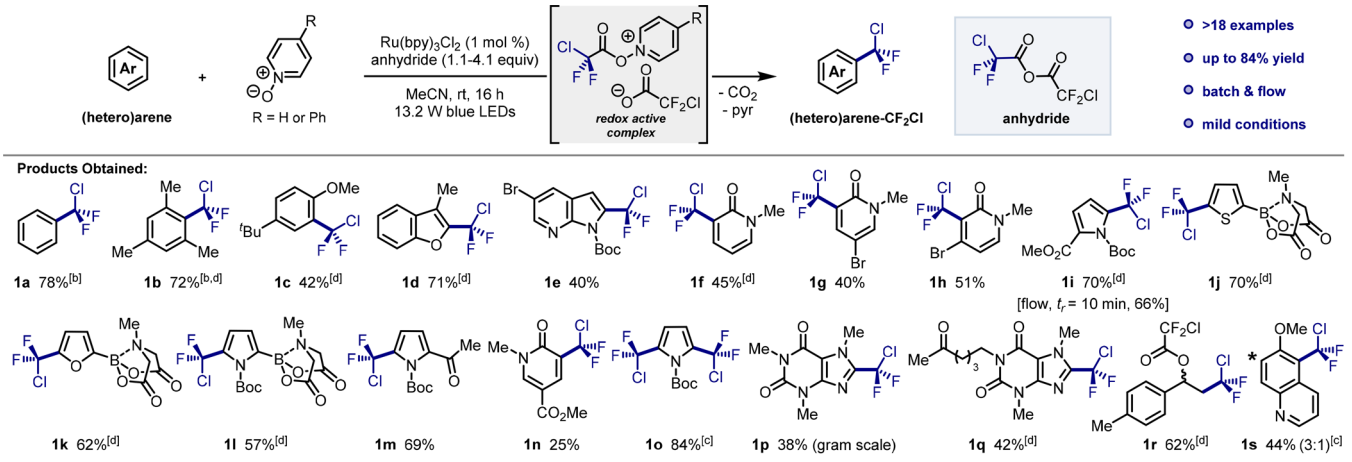
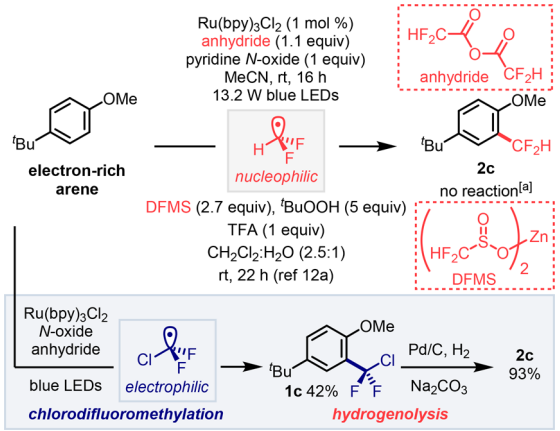
Scheme 1. Chlorodifluoromethylation of (Hetero)arenes[a]



[a]Isolated yields of reactions run on a 0.8 mmol scale with 2 mL of acetonitrile (0.4 M); [b]betermined by ^{19}F NMR spectroscopy using trifluorotoluene as the internal standard; [c]3 equiv of pyridine *N*-oxide and 3.1 equiv of anhydride used; [d]4-phenylpyridine *N*-oxide used.

Scheme 2. Electronic Effects of Fluoroalkyl Radicals



[a]No reaction as determined by TLC, GCMS, ^{1}H NMR, and ^{19}F NMR; DFMS = zinc difluoromethanesulfinate.

corresponding methyl esters in moderate to good yields (Figure 2C, **2h–j**).

Subjection of internal aryl acetylenes to our standard conditions provided exclusive formation of *gem*-difluoroenones in excellent yields (Figure 3A, **3a**,**b**). These difluorinated products are especially attractive synthetic building blocks.[21] A plausible mechanism for this transformation (Figure 3B) may involve vinylic radical oxidation and subsequent chloride elimination, which may lead to the observed *gem*-difluoroenone upon hydrolysis.[22] Terminal and alkyl-substituted alkynes decomposed or failed to react under the same conditions. In an analogous reaction setup, as shown in Figure 3C, quenching the reaction with triethylamine and a primary alcohol furnished the corresponding *β*-keto esters in one reaction pot starting from simple aryl alkyne building blocks (**3c–e**).

In conclusion, we report a robust and efficient method for the decarboxylative radical chlorodifluoromethylation of medicinally valuable (hetero)arenes. Chlorodifluoromethylation with the corresponding acetic anhydride under visible light irradiation, in both batch and flow processing, proceeds with broad substrate scope compatibility, high regioselectivity,

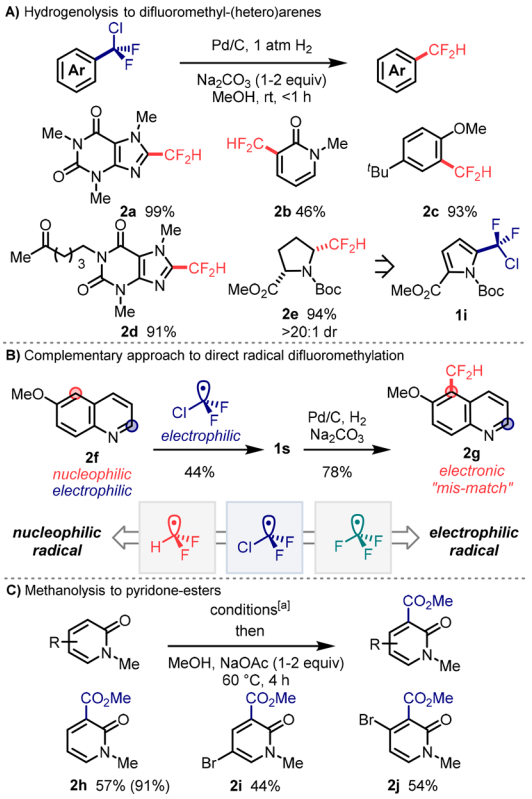


Figure 2. Synthetic utility of the chlorodifluoromethyl group. (a) Reagents and conditions: 4-phenylpyridine *N*-oxide (1 equiv), $Ru(bpy)_3Cl_2$ (1 mol %), and chlorodifluoroacetic anhydride (1.1 equiv) [unless otherwise noted], MeCN, rt, 16 h, blue LEDs; yield in parentheses is of direct methanolysis from the isolated chlorodifluoromethylated product (see the SI for details).

and operational simplicity. The work herein demonstrates that the electrophilic chlorodifluoromethyl radical is a valuable synthetic precursor to prepare electron-rich difluoromethylated (hetero)arenes. Furthermore, the CF_2Cl group is shown to participate in a wide array of postfunctionalization reactions to provide new and rapid avenues to important molecular complexity.

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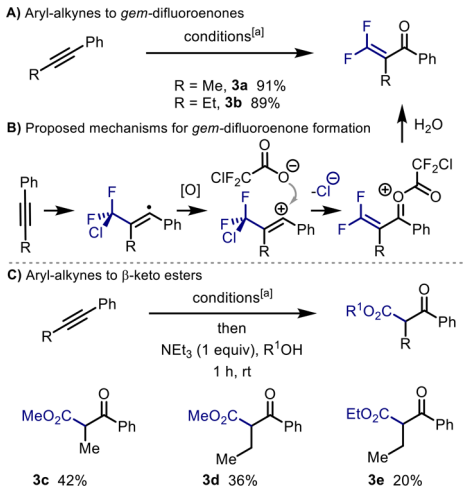

Figure 3. Chlorodifluoromethylation and diversification of internal aryl alkynes. (a) Reagents and conditions: 4-phenylpyridine *N*-oxide (1 equiv), $Ru(bpy)_3Cl_2$ (1 mol %), and chlorodifluoroacetic anhydride (1.1 equiv) (unless otherwise noted), MeCN, rt, 16 h, blue LEDs.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01249.

Description of batch and flow photochemical apparatuses; additional data; procedures and characterization data for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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