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Synthesis of α-Fluorinated Areneacetates through Photoredox/Copper Dual Catalysis

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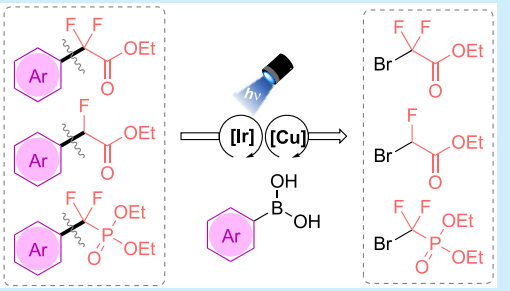
ABSTRACT: The development of mild and practical conditions for the fluoroalkylation of arenes is an ongoing challenge in chemical organic synthesis. Herein, we report a metallaphotoredox method for the preparation of fluoroalkyl arenes based on the synergistic combination of Ir/Cu dual catalysis from boronic acids. The mild conditions allow broad functional group tolerance, including substrates containing aldehydes, free phenols, and *N*-Boc-protected amines. Mechanistic investigations support a process proceeding via photoredox/copper dual catalysis.



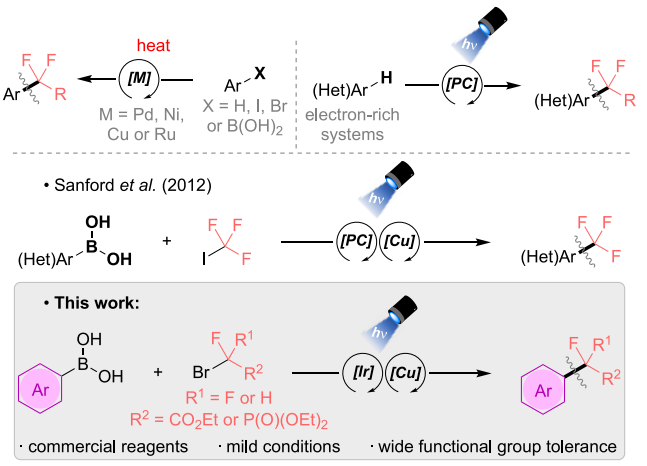
Taking advantage of the unique characteristics of the fluorine atom and fluorinated groups, the introduction of fluoroalkyl substituents onto aromatic rings is a powerful and widely employed tactic used for the construction of molecules of interest in the pharmaceutical industry to enhance binding selectivity, improve lipophilicity, and/or circumvent metabolism issues arising from *in vivo* C−H bond oxidation.[1,2]

Despite great achievements in fluorination and trifluoromethylation of organic substrates over the past decade,[3] strategies for selective introduction of a difluoromethylene (CF_2) group into organic molecules,[4] and, in particular, at the benzylic position, have been less explored. Therefore, the development of such methods would represent an important addition to the synthetic toolbox available to practitioners. Indeed, in addition to offering dramatically improved metabolic stability and oral bioavailability of biologically active molecules, these motifs offer several potential downstream transformations, allowing the construction of highly decorated, fluorine-containing molecular scaffolds.

Although significant progress has been made in recent years,[5] the development of direct (di)fluoroalkylation reactions of arenes is still underexploited.[6] Among examples reported recently, many include the use of thermal reactions[7] catalyzed by transition metals[8] (palladium, nickel, copper, or even ruthenium) and visible-light-induced C−H activation of electron-rich arenes[9] (Scheme 1).

Despite these efficient strategies and promising contributions, many of these examples require expensive transition metal catalysts or fluorination reagents, or sometimes, the protocols remain limited in terms of regioselectivity or scope. Thus, it is particularly important to develop an economical, sustainable, and selective method for introducing CF_2 groups into arenes.

Scheme 1. Fluoroalkylation of Aromatic Compounds



To overcome these obstacles, several recent studies have proposed the use of boronic acids as a very accessible and suitable substrate for a copper-mediated arylfluoromethylation of arene derivatives.[10] Specifically, we were interested in the trifluoromethylation protocol of (hetero)arylboronic acids developed by Sanford et al., which merged visible-light photocatalysis and transition metal catalysis (Scheme 1).[11] Although this method is effective, it is limited to the use of

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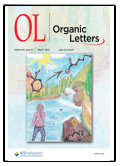

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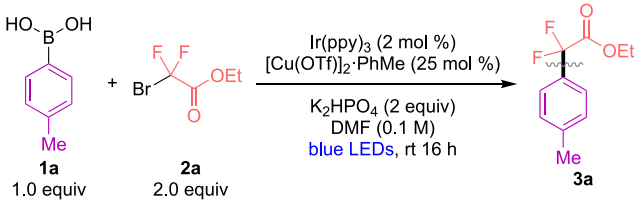
perfluoroalkyl iodides and *para*- or *meta*-substituted arylboronic acids.

Herein, we describe a mild, rapid, and efficient synthesis of aryl(di)fluoroalkylated compounds via photoredox/copper dual catalysis, with broad functional group tolerance. The synthetic utility of this method is demonstrated by providing access to highly attractive and important molecules from commercially available substrates: arylboronic acids as nucleophilic partners and bromo(di)fluoromethyl derivatives as radical precursors.

Initial efforts to explore this transformation were focused on using copper(II) triflate as a metal source (Table 1).

Table 1. Optimization of the Reaction Conditions[a]



entry	deviation from standard conditions	yield of **3a** (%)[b]
1	none	55 (54)[c]
2	CuBr	5
3	CuCl	no reaction
4	CuOAc	no reaction
5	CuI	no reaction
6	$Cu(MeCN)_4PF_6$	15
7	$Cu(MeCN)_4OTf$	40
8	$Cu(OTf)_2$	40
9	no light	no reaction
10	no $Ir(ppy)_3$	no reaction
11	no base	no reaction
12	no $(CuOTf)_2{\cdot}C_6H_5CH_3$	no reaction

[a]Reaction conditions: boronic acid **1a** (0.1 mmol), **2a** (0.2 mmol), K_2HPO_4 (0.2 mmol), $Ir(ppy)_3$ (2 mol %), $(CuOTf)_2{\cdot}C_6H_5CH_3$ (25 mol %) in DMF (1.0 mL, 0.1 M), 16 h irradiation with blue LED strips (λ_{max} = 455 nm). [b]Yields were determined by ^{19}F NMR analysis using (trifluoromethyl)benzene as an internal standard. [c]Isolated yield.

Phenylboronic acid **1a** and ethyl bromodifluoroacetate (**2a**) were selected as model substrates. Despite the exploration of different photocatalysts, photocatalyst loading, and solvent screening, in none of the further explored conditions was it possible to exceed a 40% yield of **3a** (see the Supporting Information). The use of diverse copper(I) sources did not improve the reactivity, except when using a 2:1 copper(I) trifluoromethanesulfonate−toluene complex [$(CuOTf)_2{\cdot}PhMe$ (see the Supporting Information for additional details)]. The use of K_2HPO_4 and 25 mol % copper source afforded arene **3a** in 55% yield (entry 1 and the Supporting Information), with biaryl dimer **6** from the boronic acid being the main byproduct. It is noteworthy that scaling up the reaction to 0.5 mmol provided **3a** in 54% yield (entry 1). Next, control experiments were explored to examine the nature of the photoredox/copper dual catalysis of this transformation (entries 9−12).

In general, the reported syntheses of α-aryl-α,α-difluoroethyl ester **3a** require a stoichiometric amount of a copper source[10b] or high temperatures,[8f] while through this photoredox/Cu dual catalysis, **3a** could be prepared at room temperature.

Once the optimal conditions were established, different arylboronic acids were screened using ethyl bromodifluoroacetate as a radical precursor (Scheme 2). In general, various aromatic boronic acids bearing either electron-donating groups [EDGs (alkyl, ether, sulfide, and amide)] or electron-withdrawing groups [EWGs (methyl ester, cyano, aldehyde, and trifluoromethyl)] were efficiently incorporated, with protodeboronation being a competitive side reaction in the process. As expected, EDGs afforded the desired product if they were located at the *para* position (**3a**, **3b**, **3d**−**f**, **3h**, and **3i**), while EWGs must be located at the *meta* position (**3o** and **3p**). Surprisingly, *ortho*-substituted boronic acids displayed different reactivities, being amenable to both an EDG (**3t**) and EWGs (**3u** and **3v**) in moderate yields. Boc-protected amines were successfully introduced (**3g**, **3h**, and **3n**). Various potentially reactive functional groups (free phenol, aldehyde, and ester) were tested, demonstrating the group tolerance and specificity of this metallaphotoredox reaction by exclusively forming the desired difluoro products. Dihalogenated aromatic boronic acids underwent selective difluoroalkylation, with better results being achieved with the *meta* regioisomers. Thus, ethyl difluoro acetates **3j**−**m** and **3q**−**s** were formed in moderate to good yields, leaving a halide handle intact for further diversification of their structures by well-established procedures,[12] and showcasing the complementarity of this method with respect to other difluorination procedures.[8−10] Additionally, sterically hindered dibenzo[*b*,*d*]furan-4-ylboronic acid was successfully incorporated (**3y**), as well as multifunctional boronic acids (**3w** and **3x**). To establish the synthetic utility of this photoredox/copper dual catalysis, ethyl difluoro acetate **3q** was synthesized on a gram scale from (3-chlorophenyl)boronic acid.

Related conditions enabled the use of other commercially available, fluorinated analogues [ethyl 2-bromo-2-fluoroacetate and diethyl (bromodifluoromethyl)phosphonate] as substrates. These building blocks are medicinally relevant scaffolds in drug discovery and development,[13] especially the difluorophosphonate motif, which exhibits biological properties that are better than those of its nonfluorinated analogue.[14] This photoredox/Cu dual catalysis procedure allows the synthesis of various α-fluoro benzylic ethyl esters (**3z**−**ac**) and α,α-difluoro benzylic phosphonates (**3ae**−**ag**) in moderate yields, as a complement to protocols reported previously.[15] To complete this study, we also performed the experiment in the presence of pinacol ester or potassium trifluoroborate derivatives instead of boronic acid. However, none of these new substrates led to the formation of the desired product.

On the basis of previous (di)fluorinated and trifluoromethylated metallaphotoredox transformations,[10d,11] a plausible synergistic dual mechanistic pathway to **3** is displayed in Scheme 3A. Photoexcitation of $Ir(ppy)_3$ under blue-light irradiation generates a potent excited state $*[Ir]^{III}$ complex ($E_{1/2}[Ir^{*III}/Ir^{II}]$ = 0.31 V vs SCE).[16] Single-electron transfer (SET) by the Cu^{I} complex affords a strongly reducing Ir^{II} and Cu^{II} complex. Subsequent single-electron reduction of ethyl bromodifluoroacetate ($E_{1/2}^{red}$ = −1.60 V vs SCE in MeCN)[17] by $[Ir]^{II}$ ($E_{1/2}[Ir^{III}/Ir^{II}]$ = −2.19 V vs SCE)[16] induces formation of C(sp^3)-hybridized radical **A** and restores the ground state photocatalyst. Radical oxidative addition of radical **A** followed by base-promoted transmetalation between the corresponding copper complex and arylboronic acid **2** triggers the formation of intermediate Cu^{III} species **C**. A subsequent reductive elimination event generates a new

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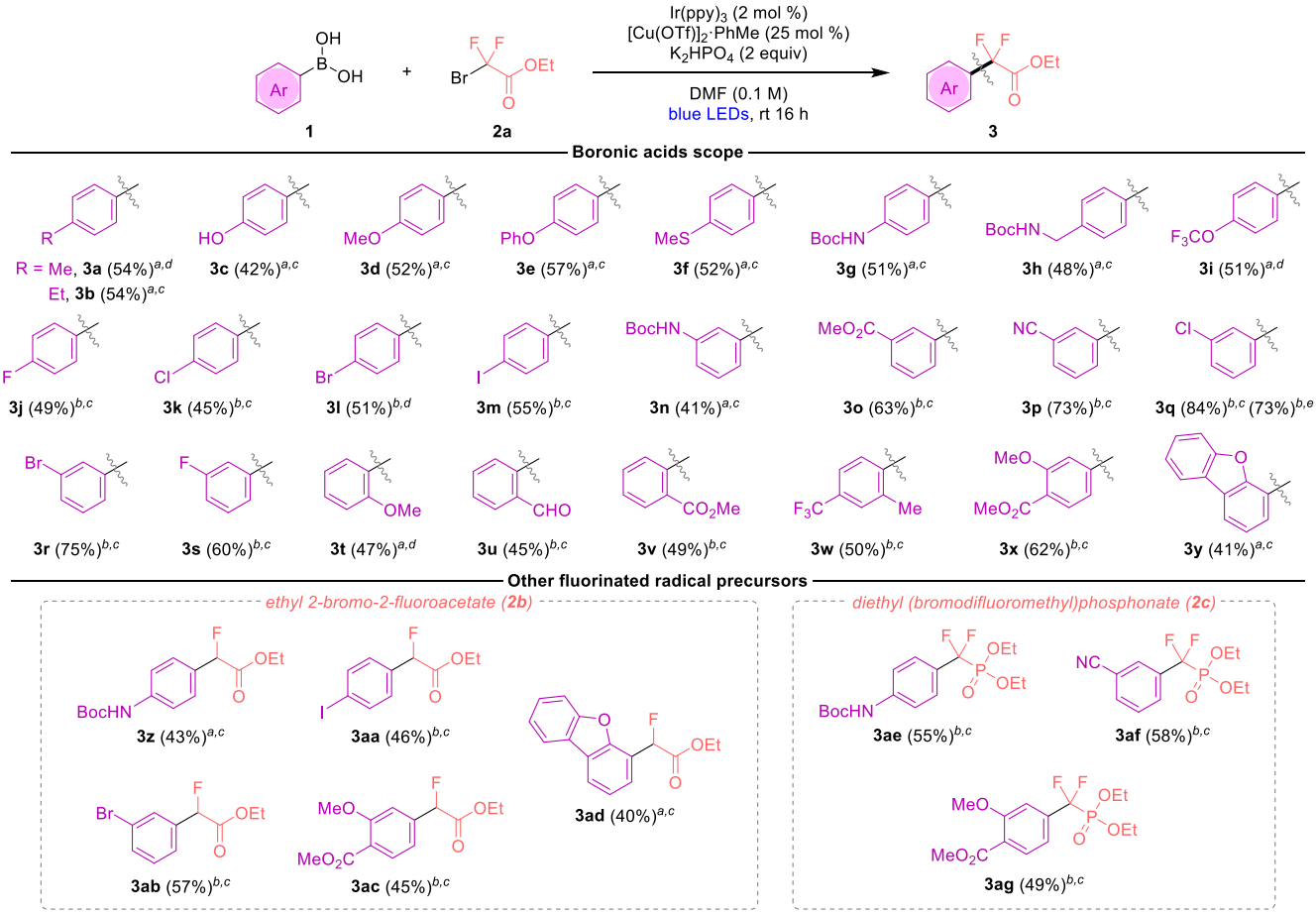
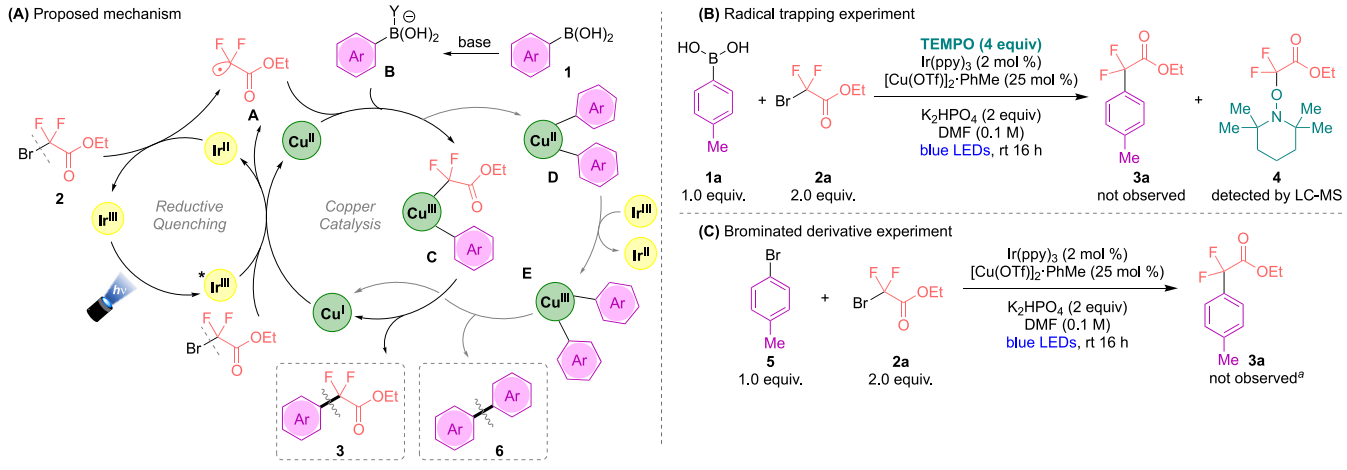
Scheme 2. Evaluation of the Substrate Scope[a]



[a]General conditions A. [b]General conditions B. [c]On a 0.3 mmol scale. [d]On a 0.5 mmol scale. [e]On a 1.5 mmol scale (reaction time of 48 h). See the Supporting Information for further details.

Scheme 3. (A) Proposed Mechanism for Synthesizing (Di)fluoroacetate Arenes 3, (B) Radical Trapping Experiment with TEMPO, and (C) Mechanistic Experiment Using 4-Bromotoluene Instead of *p*-Tolylboronic Acid



[a]The yield was determined by ^{19}F NMR analysis using (trifluoromethyl)benzene as an internal standard.

C(sp^2)−C(sp^3) bond, releasing difluoro compound **3** and closing the copper catalytic cycle. Reductive elimination generates a new C(sp^2)−C(sp^3) bond, releasing difluoro compound **3** and closing the copper catalytic cycle.

Consistent with the formation of difluoro radical **A**, upon addition of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) to the reaction mixture under optimal conditions, adduct **4** was isolated and confirmed via NMR and HRMS analysis. Furthermore, 4-bromotoluene was used as a nucleophilic partner instead of *p*-tolylboronic acid to confirm the proposed mechanism and dismiss 4-bromotoluene as a possible intermediate in the formation of **3**. As expected, traces of **3a**

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were observed, confirming the initial hypothesis. On the contrary, the photochemical quantum yield (Φ) value for this transformation is 0.90, indicating the possibility of a combination of catalytic cycle and chain radical pathways (see the Supporting Information).[18] At this point, it is thus also feasible to propose that the $Ir(ppy)_3$ photocatalyst initially promotes the formation of radical **A**, followed by radical propagation through single-electron reduction of ethyl bromodifluoroacetate (**2**) by the Cu^{I} complex that in situ triggers the generation of radical **A** and Cu^{II} species (Scheme 3A).

In summary, a wide range of ethyl aryldifluoromethyl acetate derivatives were rapidly generated under mild conditions from commercially available building blocks: arylboronic acids and ethyl bromodifluoroacetate. This protocol proceeds via synergistic combination of an iridium photocatalyst and copper cycles and shows broad functional group tolerance (free phenol, aldehyde, or *N*-Boc protective group). Additionally, the fluoroalkylated conditions described here were successfully adapted to other commercial fluorinated radical precursors, ethyl 2-bromo-2-fluoroacetate and diethyl (bromodifluoromethyl)phosphonate.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c00969.

Preparation of starting materials, general procedures, characterization data for products (melting points and nuclear magnetic resonance, infrared, and mass spectrometry data), gram scale synthesis, mechanistic studies, and NMR spectra and X-ray structure (PDF)

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†G.L. and A.G. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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