Metallaphotoredox Difluoromethylation of Aryl Bromides

Vlad Bacauanu*, Sébastien Cardinal*, Motoshi Yamauchi*, Masaru Kondo, David F. Fernández, Richard Remy, and David W. C. MacMillan*

Abstract: Herein, we report a convenient and broadly applicable strategy for the difluoromethylation of aryl bromides by metallaphotoredox catalysis. Bromodifluoromethane, a simple and commercially available alkyl halide, is harnessed as an effective source of difluoromethyl radical by silyl-radical-mediated halogen abstraction. The merger of this fluoroalkyl electrophile activation pathway with a dual nickel/photoredox catalytic platform enables the difluoromethylation of a diverse array of aryl and heteroaryl bromides under mild conditions. The utility of this procedure is showcased in the late-stage functionalization of several drug analogues.

Within the realm of drug design, the chemoselective incorporation of fluorine or polyfluorinated alkyl substituents is a powerful and widely employed tactic to enhance binding selectivity, elevate lipophilicity, and/or circumvent metabolism issues arising from in vivo C–H bond oxidation.[1,2] While the implementation of the trifluoromethyl group (-CF₃) has been widely studied in medicinal chemistry, the relatively underexplored difluoromethyl group (-CF₂H) has recently garnered significant attention by virtue of its capacity to serve as a lipophilic hydrogen bond donor and to act as a bioisostere for thiol and alcohol functional groups.[3,4] Modern approaches to the direct and selective introduction of the difluoromethyl group into aromatic rings typically rely on the metal-catalyzed cross-coupling of aryl electrophiles or nucleophiles with an appropriate CF₂HR reagent, often designed for facile transmetalation or formal oxidative addition by the metal catalyst.[5,6] Given the pronounced practical significance of this emerging area, one of the greatest challenges is the rendering of readily available CF₂H sources as effective difluoromethylating agents in cross-coupling. Crucially, this coupling platform must display high functional tolerance and amenability towards medicinally relevant scaffolds. As such, the development of novel, operationally convenient, yet general routes to difluoromethylarenes and -heteroarenes remains of high interest.

Metallaphotoredox catalysis has emerged in recent years as a valuable platform for the production of previously elusive C(sp³)–C(sp³) bonds, thereby providing access to novel constructs of importance in medicinal chemistry.[7] One example from our laboratory involves a dual nickel/photoredox-catalyzed cross-electrophile coupling procedure, wherein the union of a broad range of aryl and alkyl halides is accomplished at room temperature using visible-light irradiation.[8] A unique design feature of this mechanism is the implementation of silyl-radical-mediated abstraction of bromine atoms from C(sp³)–Br bonds,[9] a pathway that allows alkyl halides to readily participate in metal-catalyzed cross-couplings. Most notably, the scope of these silane-mediated difluoromethylation reactions (Figure 1) demonstrates the broad applicability of this methodology for the construction of novel aryl difluoromethylarenes and -heteroarenes.

**Figure 1.** Silane-mediated difluoromethylation of aryl bromides.[*]

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mediated cross-electrophile couplings has been determined to be extensive with respect to both arene substitution pattern and functional group tolerance, a characteristic that has led to widespread adoption by medicinal chemistry groups within the pharmaceutical sector (Figure 1).11

Inspired by the success of this silyl-radical-mediated cross-electrophile coupling, we wondered if an analogous strategy could serve as the basis for a general and direct synthesis of difluoromethylarenes. Specifically, we considered bromodi- fluoromethane, a simple and commercial alkyl halide, as a potential source of CF₂H radical through a previously unexplored halogen abstraction step. Crucially, this pathway would be thermodynamically feasible given that the HF⁻·C—Br bond (bond dissociation energy of 69 kcal mol⁻¹) is far weaker than the Si—Br bond in a typical abstraction product (e.g., 96 kcal mol⁻¹ for Me₃Si—Br).12 Moreover, given the electron-rich character of the silyl radical, we surmised that halogen abstraction from bromodi- fluoromethane would be polarity-matched and hence kinetically faster than from previously utilized alkyl bromide substrates.13 Herein, we disclose the successful implementation of these ideals and present a mild, convenient, and broadly applicable metallaphotoredox-catalyzed difluoromethylation of a wide array of aryl and heteroaryl halides.

The proposed mechanism for this silane-mediated difluoromethylation is shown in Scheme 1. Visible-light excitation of IrIII photocatalyst [Ir(dF(CF₃)ppy)_2(dtbbpy)]PF₆ (1)14 is known to generate the excited-state *IrIII complex 2, which can readily oxidize bromide anion (3) (E°_{1/2}^{Nernst}[Br⁻/Br] = +1.21 V vs. saturated calomel electrode (SCE) in MeCN; E°_{1/2}^{Nernst}[Br⁻/Br] = +0.80 V vs. SCE in DME).18,19 The resulting bromine radical (5) can participate in hydrogen atom transfer with (TMS)₃SiH to yield the nucleophilic silyl radical 6.13 Bromine abstraction from bromodi- fluoromethane (7) by open-shell silyl species 6 would then afford the key difluoromethyl radical (8). Concurrently with the photoredox catalytic cycle, NiII catalyst 9 is expected to undergo facile oxidative addition into aryl bromide 10 to generate NiII—aryl intermediate 11. Trapping of difluoromethyl radical (8) would then generate the corresponding aryl—NiIII—CF₂H complex 12, which upon reductive elimination should afford the desired difluoromethylenere product 13 and NiII species 14. Finally, single electron transfer between 14 and reduced photocatalyst 4 would simultaneously regenerate low-valent nickel catalyst 9 and ground-state photocatalyst 1.

Table 1: Effect of the bromodi- fluoromethane stoichiometry[a]

<table>
<thead>
<tr>
<th>Stoichiometry</th>
<th>Yield (%)</th>
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<tbody>
<tr>
<td>1.0 equiv.</td>
<td>52%</td>
</tr>
<tr>
<td>2.0 equiv.</td>
<td>72%</td>
</tr>
<tr>
<td>4.0 equiv.</td>
<td>77%</td>
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</table>

[a] Performed with photocatalyst 1 (1 mol %), NiBr₂·dtbbpy (5 mol%), aryl bromide (0.2 mmol), CF₂HBr (1–4 equiv), (TMS)₃SiH (1.05 equiv), and 2,6-lutidine (2 equiv) in DME for 18 h. Yields determined by ¹⁹F NMR analysis. [b] See the Supporting Information for experimental details.

Scheme 1. Proposed mechanism for metallaphotoredox-catalyzed difluoromethylation of aryl bromides.
We began our investigation by examining three separate aryl halide precursors in the proposed difluoromethylation procedure, namely cyanopyridine 16 as well as trifluoromethyl- and fluoro-substituted bromobenzenes (17 and 18, respectively; see Table 1). For each substrate, we employed photocatalyst 1, nickel catalyst NiBr$_2$·dtbbpy (15), commercially available (TMS)$_2$SiH, 2,6-lutidine as the base, DME as the solvent, and blue LEDs as the photon source. In the case of electron-deficient heteroaryl bromide 16, optimal levels of reaction efficiency were observed using excess CF$_2$HBr (4 equiv, 77% yield). Remarkably, however, with the less electron-deficient CF$_3$-arene 17, the use of 2 equivalents of bromodifluoromethane gave a superior outcome, while electron-neutral para-fluoro substrate 18 achieved the highest yield with a 1:1 stoichiometry of arene to CF$_2$HBr.[17] Perhaps more surprising, the use of a large excess of bromodifluoro-

| Table 2: Scope of the silyl-radical-mediated difluoromethylation of aryl halide electrophiles using bromodifluoromethane as the CF$_2$H source.[a] |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| aryl bromide    | 1–2 equiv.      | 5 mol% NiBr$_2$·dtbbpy | 1 mol% Ir photocatalyst 1 |
| 19, 83% yield  | 20, 81% yield  | 21, 75% yield  | 22, 83% yield  | 23, 80% yield$^b$ | 24, 67% yield$^b$ |
| 25, 74% yield  | 26, 55% yield$^b$ | 27, 80% yield$^b$ | 28, 85% yield$^b$ | 29, 71% yield | 30, 75% yield |
| 31, 78% yield  | 32, 73% yield  | 33, 73% yield  | 34, 60% yield$^{b,c,d}$ | 35, 69% yield | 36, 75% yield |

[a] Yields of isolated products unless otherwise indicated. Performed with photocatalyst 1 (1 mol%), NiBr$_2$·dtbbpy (5 mol%), aryl bromide (0.5 mmol), CF$_2$HBr (1–2 equiv), (TMS)$_2$SiH (1.05 equiv), and 2,6-lutidine (2 equiv) in DME for 18 h. See the Supporting Information for experimental details and additional examples. [b] Yield determined by $^{19}$F NMR analysis (average of two runs). [c] With 10 mol% Ni catalyst. [d] 42 h. [e] Na$_2$CO$_3$ as the base. [f] With 3 equiv CF$_2$HBr. [g] LiOH as the base. [h] With 2 mol% Ni catalyst. [i] Acetone as the solvent. [j] N,N-Diisopropylethylamine as the base. [k] Quinuclidine as the base. [l] K$_2$CO$_3$ as the base. [m] DABCO as the base.
methane (4 equiv) led to dramatically diminished yields in the latter two cases.\[^{18,19}\]

To rationalize these trends, we propose that when less electron-deficient arenes are employed, the catalytic nickel species can undergo oxidative addition with the electron-deficient \(\text{CF}_2\text{HBr}\) reagent at a rate competitive with the aryl bromide insertion step.\[^{20}\] Moreover, we believe that such a pathway would be deleterious given that the resultant \(\text{Ni}^{II} - \text{CF}_2\text{H}\) complex would be unlikely to participate in further oxidative addition steps with the aryl bromide.\[^{21}\] As such, for more electron-rich or hindered aryl halides that undergo relatively slow oxidative addition with nickel, the issue of competitive \(\text{CF}_2\text{HBr}\) insertion is mitigated by employing lower concentrations of the \(\text{CF}_2\text{H}\) source. However, at the other end of the electronic spectrum, higher stoichiometry of \(\text{CF}_2\text{HBr}\) ensures that the silane-mediated generation of the \(\text{CF}_2\text{H}\) radical occurs in synchronicity with the rapid oxidative addition of the nickel catalyst into highly electron-deficient arenes (e.g., \(16\)).\[^{22}\]

With optimized conditions in hand, we next evaluated the scope with respect to the aryl bromide component (Table 2). Notably, substrates bearing electron-withdrawing groups, such as esters, ketones, nitriles, or sulfones, generated the respective difluoromethyl adducts in high yields (19–22, 75–83\% yield). In accord with our optimization studies, electron-neutral and electron-rich bromoarenes performed well using lower loadings of \(\text{CF}_2\text{HBr}\) (23–26, 55–80\% yield). As a useful demonstration of the mild conditions and functional group tolerance of this new coupling procedure, we found that aryl electrophiles bearing chloride and boronate groups can be readily implemented (27 and 28, 80\% and 85\% yield, respectively). This characteristic was further underscored by the performance of substrates containing alcohol and silyl-kyne moieties (29 and 30, 71\% and 75\% yield, respectively). In addition, \(meta\)- and \(ortho\)-substituted aryl bromides were shown to be competent electrophiles in this transformation (31–34, 60–78\% yield).

We next turned our attention to the scope of heteroaryl halides, a critical group of substrates with respect to the utility of this procedure in the medicinal chemistry sector. As shown in Table 2, a broad range of 2-, 3-, and 4-bromopyridines were found to be suitable coupling partners (37–42, 46–84\% yield). Moreover, bromoquinolines afforded the desired products with good efficiency (43 and 44, 76\% and 78\% yield, respectively). Multiple-nitrogen-bearing heteroarenes, such as pyrimidines, pyrazines, and quinazolines, have long been viewed as problematic substrates for a range of cross-coupling reactions. As such, it was notable that all of these heteroarene classes were readily converted into the corresponding difluoromethylarenes (45–48, 60–66\% yield). In the same context, five-membered bromoarenes were also found to be competent electrophiles. In particular, difluoromethyl derivatives of pyrazole, indazole, benzimidazole, and caffeine were obtained in good to high yields (49–52, 51–75\% yield). Perhaps most notable, bromothiazoles, a traditionally difficult substrate class for cross-coupling,\[^{23}\] were readily transformed into their corresponding \(\text{CF}_2\text{H}\) adducts (53 and 54, 57\% and 45\% yield, respectively).

Finally, given the pharmaceutical relevance of the \(\text{CF}_2\text{H}\) group, we sought to showcase the utility of our procedure in the late-stage difluoromethylation of analogues of several known medicinal agents (Scheme 2). Specifically, difluoromethyl-containing derivatives of sulfadimethoxine, celecoxib, indometacin, and pomalidomide were obtained in good to high yields from the corresponding aryl bromide precursors (55–58, 64–82\% yield). These results further highlight the

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**Scheme 2.** Late-stage functionalization for the expedient synthesis of difluoromethyl analogues of pharmaceutical agents.
real-world utility of this metallaphotoredox technology with respect to the tolerance of medicinally relevant functional groups, such as sulfonamides, imides, electron-rich pyrimidines, pyrazoles, and indoles.

In conclusion, we have developed a novel metallaphotoredox platform for the difluoromethylation of a broad range of aryl and heteroaryl halides. This procedure employs commercially available bromodifluoromethane as a direct source of CF$_2$H radical via a silyl radical-mediated halogen abstraction pathway previously unexplored for fluoroalkyl electrophiles within the realm of cross-coupling. Given its distinct convenience and broad applicability to pharmaceutically relevant scaffolds, we expect this method to be widely adopted within the synthetic and medicinal chemistry community.

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Conflict of interest

The authors declare no conflict of interest.

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[14] d[(CF$_2$)$_2$]ppyy = 2-(2,4-difluorophenyl)-5-trifluoromethylpyridine; dbbbpy = 4,4’-di-r-Bu-2,2’-bipyrine.


[17] The fluorine substituent has a Hammett $\sigma_0$ value of −0.06; see: C. Hansch, A. Leo, R. W. Taft, Chem. Rev. 1991, 91, 165.

[18] Control experiments with aryl halide 17 revealed that light, photocatalyst, nickel, and silane are all required for the success of the transformation (<1% yield in the absence of at least one component). Reduction of CF$_2$HBr to CF$_2$H was observed when the nickel catalyst was excluded, an observation that supports the capacity of the silyl radical to engage in halogen abstraction with CF$_2$HBr. See the Supporting Information for details.

[19] The implementation of commercially available (bromodifluoromethyl)trimethylsilane as a CF$_2$H source was also possible, but not pursued because of lower reaction efficiency (Table 1).

[20] For reports of proposed Ni$^0$ catalytic intermediates undergoing formal oxidative addition into bromodifluoromethane and
chlorodifluoromethane, see: a) X.-P. Fu, Y.-L. Xiao, X. Zhang, Chin. J. Chem. 2018, 36, 143; b) ref. [6].

[21] For experimental observations consistent with the deactivation of the nickel catalyst (i.e., poor conversion of starting material), see the Supporting Information.

[22] In support of the dramatic differences among the rates of oxidative addition, competition experiments between 16 and 18 revealed that, at early reaction time points, the difluoromethyl product from electron-deficient 18 was obtained in up to 45% yield whereas electron-neutral bromoarene 16 remained entirely unreacted. See the Supporting Information.