Difluoromethylation

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Metallaphotoredox Difluoromethylation of Aryl Bromides

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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 (-CF_3) has been widely studied in medicinal chemistry, the relatively underexplored difluoromethyl group (-CF_2H) 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 CF_2HR 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 CF_2H 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 $C(sp^3)$–$C(sp^2)$ 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 $C(sp^3)$–Br bonds,[9] a pathway that allows alkyl halides to readily participate in metal-catalyzed cross-couplings. Most notably, the scope of these silane-

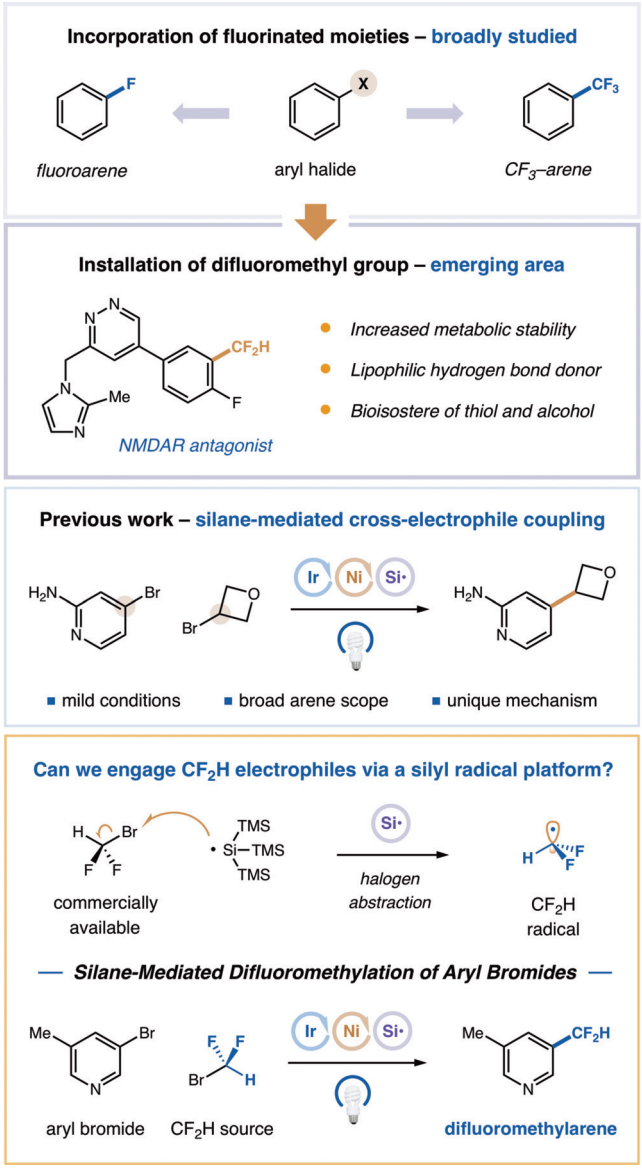

Figure 1. Silane-mediated difluoromethylation of aryl bromides.[10]

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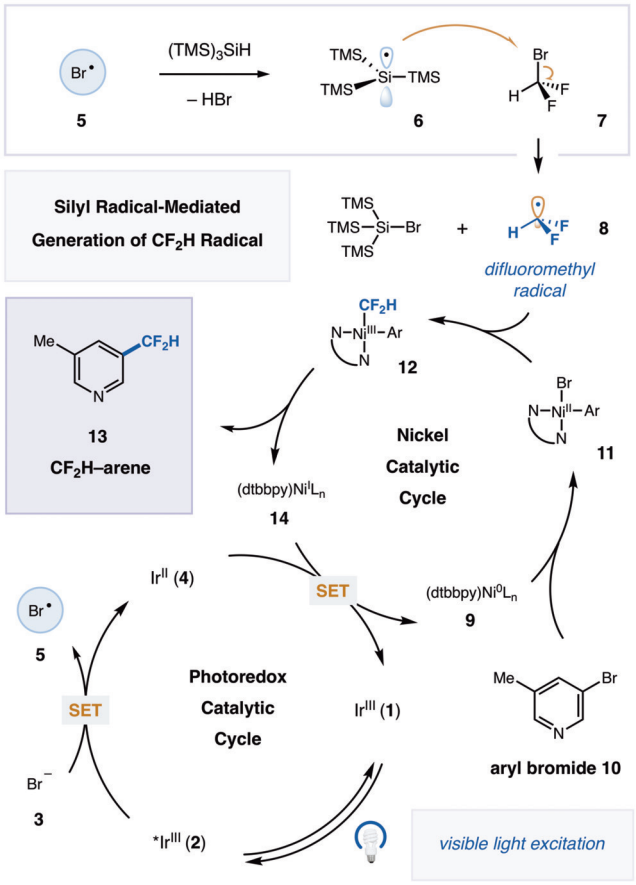
mediated cross-electrophile couplings has been determined to be extensive with respect to both arene substitution pattern and functional group tolerance, a characteristic that has led to widescale adoption by medicinal chemistry groups within the pharmaceutical sector (Figure 1).[11]

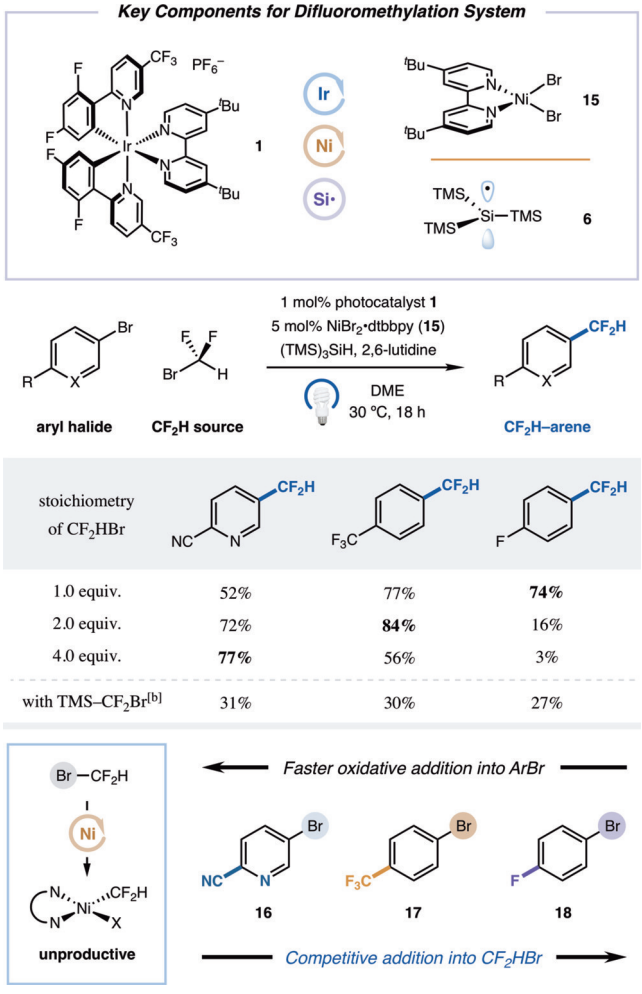
Inspired by the success of this silyl-radical-mediated cross-electrophile coupling, we wondered if an analogous strategy could serve as the basis for a general and direct synthesis of difluoromethylarenes. Specifically, we considered bromodifluoromethane, a simple and commercial alkyl halide, as a potential source of CF_2H radical through a previously unexplored halogen abstraction step. Crucially, this pathway would be thermodynamically feasible given that the HF_2C–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 Me_3Si–Br).[12] Moreover, given the electron-rich character of the silyl radical, we surmised that halogen abstraction from bromodifluoromethane 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 Ir^{III} photocatalyst [Ir(dF(CF_3)ppy)$_2$(dtbbpy)]PF_6 (**1**)[14] is known to generate the excited-state $*Ir^{III}$ complex **2**, which can readily oxidize bromide anion (**3**) ($E_{1/2}^{red}[*Ir^{III}/Ir^{II}] = +1.21$ V vs. saturated calomel electrode (SCE) in MeCN; $E_{1/2}^{red}[Br^{\bullet}/Br^{-}] = +0.80$ V vs. SCE in DME).[8,15] 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 bromodifluoromethane (**7**) by open-shell silyl species **6** would then afford the key difluoromethyl radical (**8**). Concurrently with the photoredox catalytic cycle, Ni^0 catalyst **9**[16] is expected to undergo facile oxidative addition into aryl bromide **10** to generate Ni^{II}–aryl intermediate **11**. Trapping of difluoromethyl radical (**8**) would then generate the corresponding aryl–Ni^{III}–CF_2H complex **12**, which upon reductive elimination should afford the desired difluoromethylarene product **13** and Ni^I 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**.



Scheme 1. Proposed mechanism for metallaphotoredox-catalyzed difluoromethylation of aryl bromides.

Table 1: Effect of the bromodifluoromethane stoichiometry.[a]

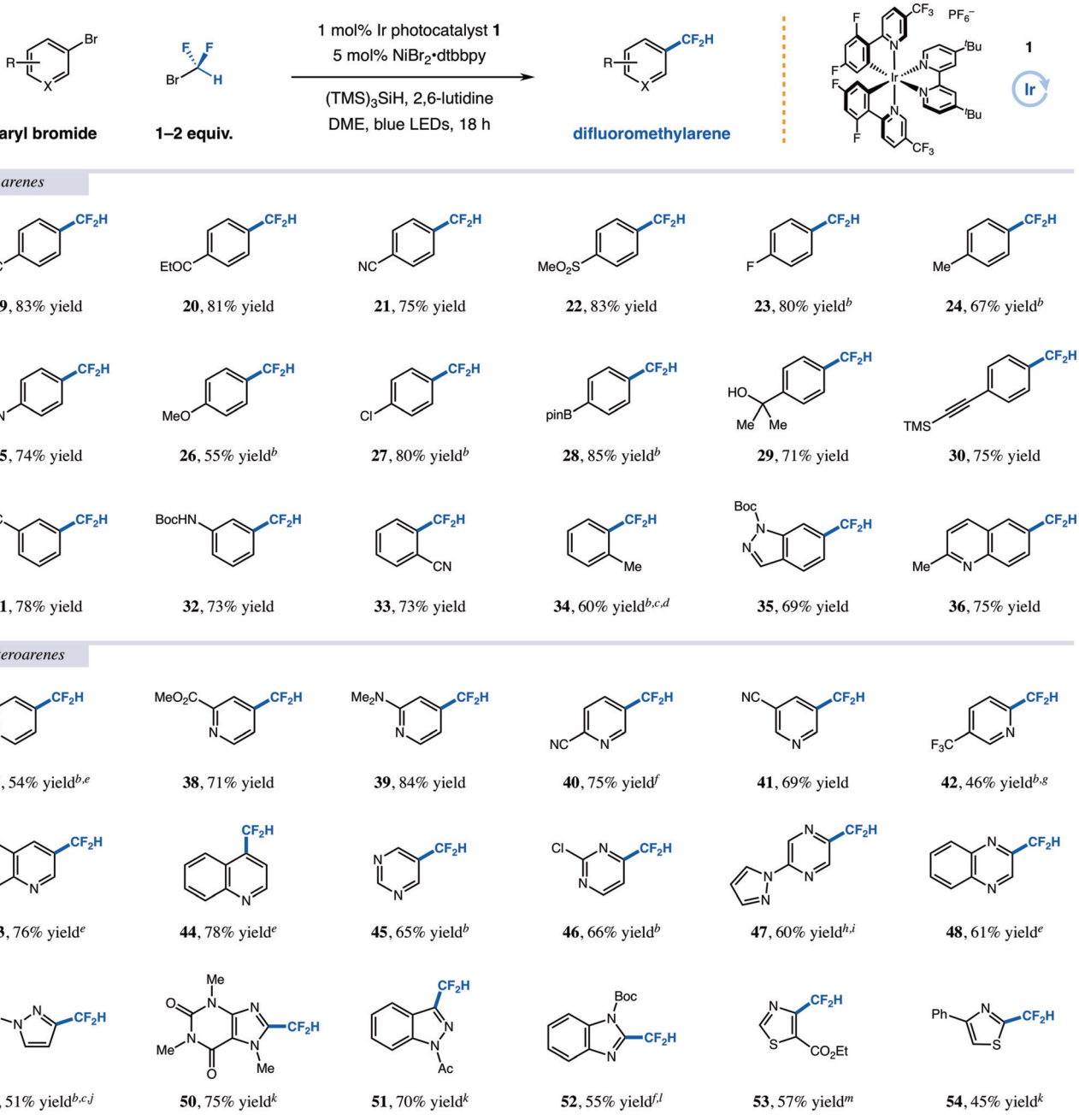


stoichiometry of CF_2HBr			
1.0 equiv.	52%	77%	**74%**
2.0 equiv.	72%	**84%**	16%
4.0 equiv.	**77%**	56%	3%
with TMS–CF_2Br[b]	31%	30%	27%

[a] Performed with photocatalyst **1** (1 mol%), $NiBr_2$·dtbbpy (5 mol%), aryl bromide (0.2 mmol), CF_2HBr (1–4 equiv), $(TMS)_3SiH$ (1.05 equiv), and 2,6-lutidine (2 equiv) in DME for 18 h. Yields determined by ^{19}F NMR analysis. [b] See the Supporting Information for experimental details.

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 $(TMS)_3SiH$, 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_2HBr (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_2HBr.[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_2H source.[a]



[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_2HBr (1–2 equiv), $(TMS)_3SiH$ (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_2CO_3 as the base. [f] With 3 equiv CF_2HBr. [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_2CO_3 as the base. [m] DABCO as the base.

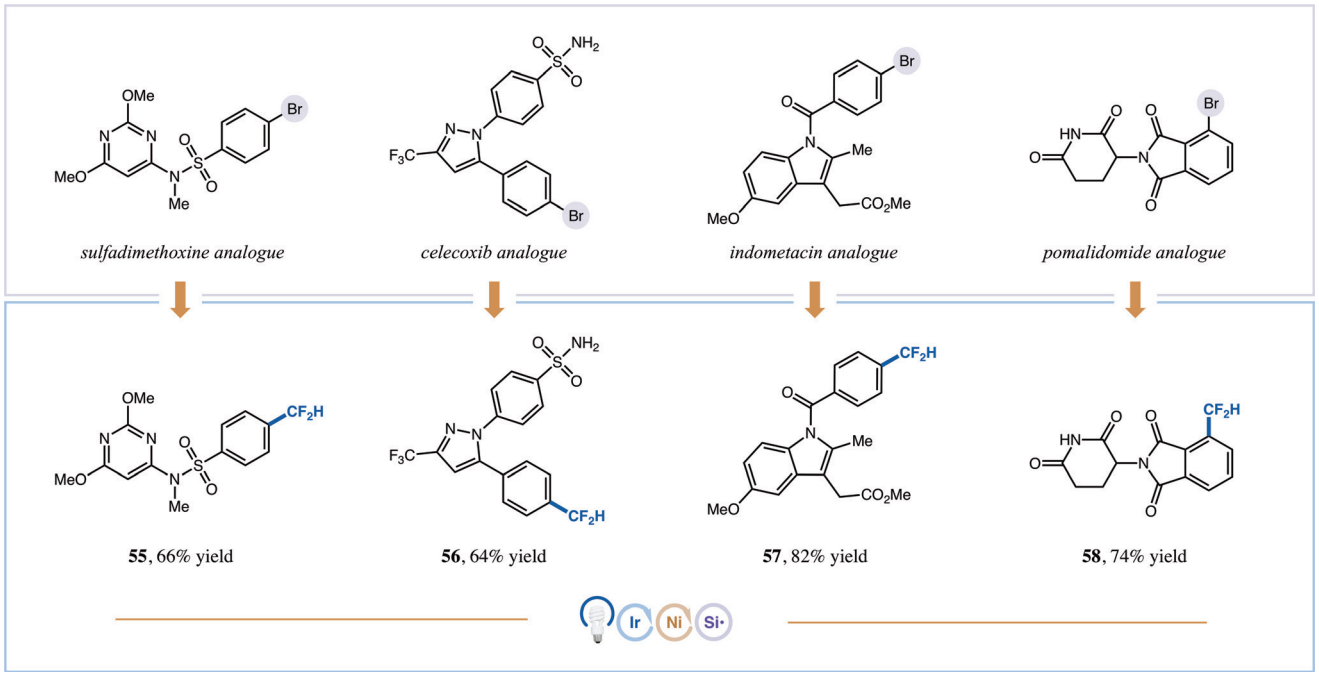
methane (4 equiv) led to dramatically diminished yields in the latter two cases.[18,19]

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 CF_2HBr 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 Ni^{II}–CF_2H 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 CF_2HBr insertion is mitigated by employing lower concentrations of the CF_2H source. However, at the other end of the electronic spectrum, higher stoichiometry of CF_2HBr ensures that the silane-mediated generation of the CF_2H 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 CF_2HBr (**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 ester 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 silylalkyne 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 quinoxalines, 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 CF_2H adducts (**53** and **54**, 57 % and 45 % yield, respectively).

Finally, given the pharmaceutical relevance of the CF_2H 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



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_2H 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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