Nickel-Catalyzed Cross-Electrophile Difluoromethylation of Aryl Bromides with a Non-ODS Derived Sulfone Reagent

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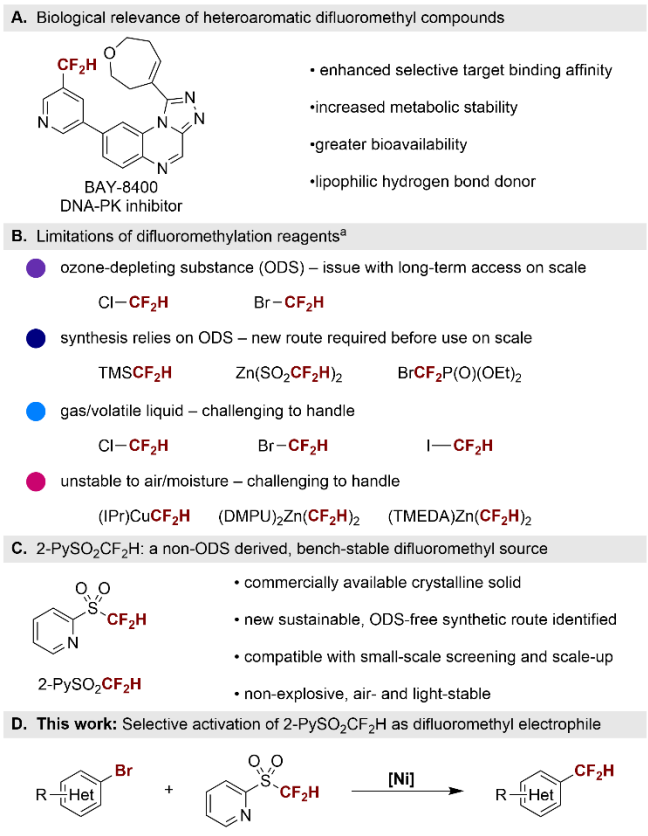
Abstract: Fluorinated molecules are ubiquitous in medicinal and agricultural chemistry. Despite the enhanced biological activity of difluoromethyl-containing compounds, industrial adoption of methods for difluoromethylation lag behind those for trifluoromethylation and fluorination. Many approaches to difluoromethylation rely directly or indirectly on the use of gaseous, ozone-depleting substances (ODS), which pose challenges for industrial application. We report here the nickel-catalyzed cross electrophile coupling of aryl bromides and difluoromethyl 2-pyridyl sulfone, a crystalline, non-ODS derived difluoromethylation reagent. The scope of this reaction is demonstrated with 24 examples (67 ± 16% average yield) including a diverse array of heteroaryl bromides and precursors to difluoromethyl-containing preclinical pharmaceuticals. This reaction demonstrates facile application to small-scale parallel screening and benchtop scale-up.

The incorporation of fluorine and small fluoroalkyl fragments in pharmaceuticals has played key role in improving the absorption, target binding affinity, and metabolic stability of small molecule drugs (Scheme 1A).[1–5] At present, at least 20% of pharmaceuticals and over 30% of agrochemicals contain at least one fluorine atom.[6–8] The difluoromethyl group (CF_2H) can act as a lipophilic hydrogen-bond donor,[9–11] resulting in difluoromethyl-containing compounds displaying enhanced target binding affinity, biological availability, and potency.[12–18] This enhanced biological activity of difluoromethylated analogues compared to their non-fluorinated, fluorinated, and trifluoromethylated analogues has been observed in drug-candidates and agrochemicals.[19–26] Despite these advantages, at present there are no FDA-approved small molecule drugs containing a (hetero)aromatic difluoromethyl group.[6,27–29]

The absence of difluoromethylated pharmaceuticals is exacerbated by the lack of safe, practical, and cost-effective difluoromethylation methods (Scheme 1B).[30,31] Several routes for difluoromethylation of aromatic compounds have been reported in recent years to match the increasing interest in difluoromethylated compounds over the past several decades.[32–86] However, there are several challenges to adoption of these reactions in both medicinal chemistry and process chemistry. First, most of the difluoromethylation approaches rely upon ozone-



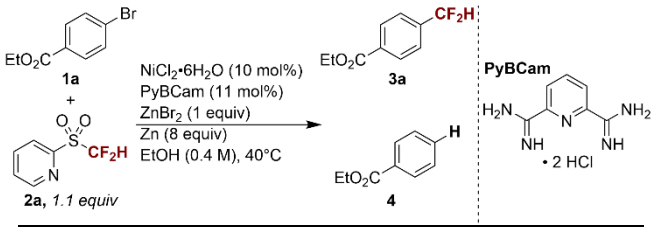
Scheme 1. Difluoromethylation importance, strategies, and challenges. [a] See Supporting Information 2.1 for additional information regarding limitations of difluoromethylation reagents.

depleting, gaseous halogeno-difluoromethanes as direct CF_2H sources or as starting materials for synthesis of the active difluoromethylation reagent (see Supporting Information 2.1).[87] These fluorinated gases, such as chlorodifluoromethane (R-22), are tightly regulated or banned for use by the Montreal Protocol, limiting practical application of these methods. The recent increased regulation of these environmentally damaging fluorinated feedstocks is expected to challenge the supply chain of many fluorinated materials which rely on halogenomethanes.[30,88] Further, in the drug discovery space, gaseous reagents present challenges for parallel, small-scale screening, both with dosing and avoiding leaks, and can pose safety hazards when used on larger scale.[89,90] In our initial investigations, difluoromethylation approaches using gaseous reagents resulted in inconsistencies when used in parallel without the use of specialized equipment. Therefore, despite the large body of literature, difluoromethylation remains a challenging transformation in an industrial setting.[31,87]

An attractive alternative difluoromethylation reagent is difluoromethyl 2-pyridyl sulfone (2-$PySO_2CF_2H$), a crystalline, non-explosive, air- and light-stable, commercially available reagent introduced by Hu in 2010.[91,92] Ideally, the sulfone would be coupled with an aryl halide, tapping into the significantly wider availability and practicality of aryl halides compared to aryl nucleophiles (about 75× more).[63,64] There are limited reports on the coupling of aryl halides with alkyl sulfones to form alkylated arene products,[93] with previous nickel-catalyzed XEC reports showing 2-$PySO_2CF_2H$ reacting by either 2-pyridyl transfer or difluoromethyl transfer, depending on the ligand employed.[66,94] Concurrent with our study, Hu and coworkers developed a difluoromethylation of aryl iodides using 2-$PySO_2CF_2H$, but these conditions suffered from competitive arylzinc formation and do not tolerate acidic functionality.[66] We present here a distinct approach that enables the difluoromethylation of the broader substrate pool of (hetero)aryl bromides using 2-$PySO_2CF_2H$ and demonstrates compatibility with small-scale parallel screening and benchtop scale-up under greener, milder conditions.[95] To the best of our knowledge, a modified non-ODS based synthetic route to 2-$PySO_2CF_2H$ disclosed herein establishes this report as the first approach to cross-electrophile difluoromethylation using a non-ODS based difluoromethylation reagent.[54,56,67]

A combination of high-throughput experimentation (HTE) data and mechanism guided experimentation led to a small collection of conditions with several common themes (see Supporting Information Figures S1-S12 for details). PyBCam (pyridine-2,6-bis(carboximidamide) dihydrochloride) ligands were superior to all other ligands tested (Supporting Information Figure S6). EtOH as the solvent generally provided the best results, with DME, DMF, and an EtOH/DMSO solvent mixture providing alternatives for cases where substrate solubility and/or decomposition were an issue in EtOH (entry 2, Supporting Information Figure S7). The reaction proceeds in high yield at a range of temperatures (rt – 60 °C), with lower temperatures providing higher selectivity but longer reaction times (entries 3 and 4). Decreasing the amount of reductant resulted in a slower reaction rate with slightly diminished selectivity (entry 5). The rate of sulfone activation depended upon the solvent, salts present, and the amount of reductant used. NEt_4I appeared to improve the rate of turnover of the nickel[96] but did not activate the sulfone (entry 6). LiCl and $ZnBr_2$ were particularly effective at increasing the rate of sulfone activation, which appears to be a cation effect (entry 7-10, Supporting Information Figure S11). Our conditions also demonstrated compatibility with a standard 96-well plate HTE setup (entry 11).

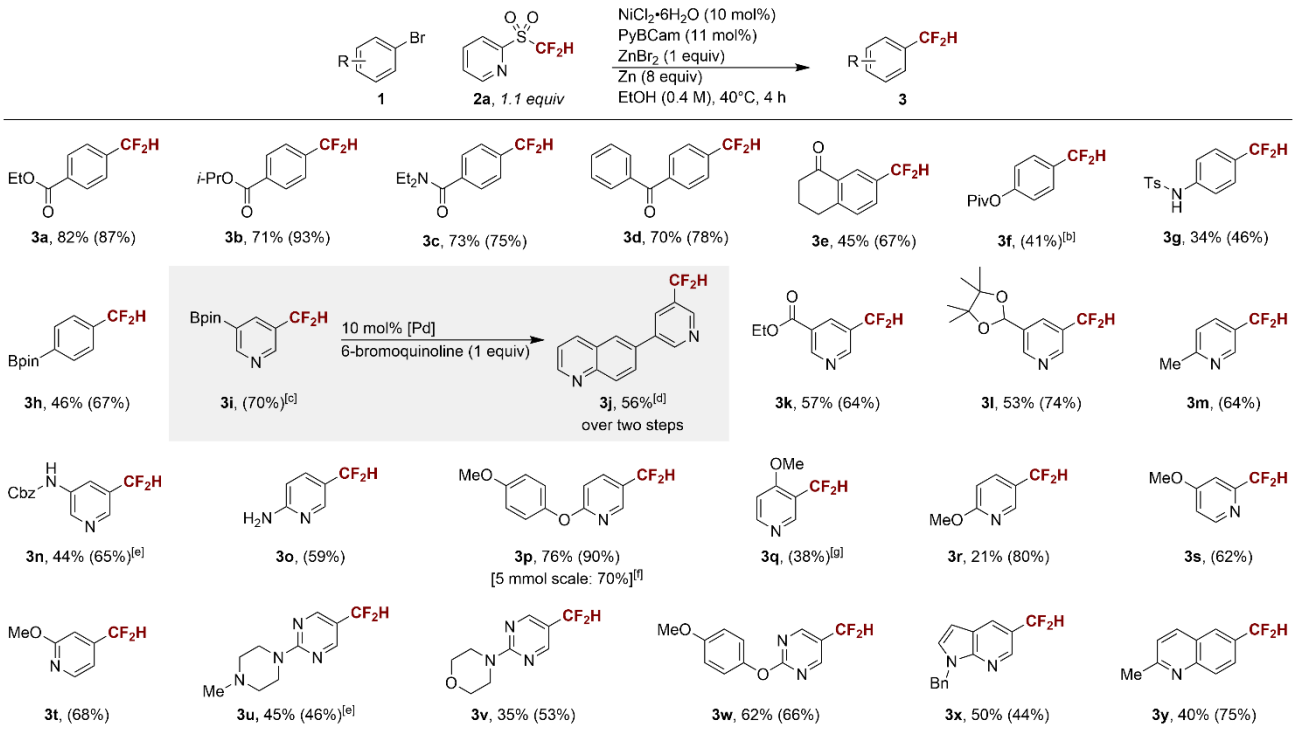
Table 1. Evaluation of key reaction variables for difluoromethylation.[a]



Entry[b]	Deviation from standard conditions	**3a** (%)[c]	**4** (%)[c]
1	None	(90)	9
2	DME instead of EtOH	48	2
3[d]	rt instead of 40 °C	49	4
4	60 °C instead of 40 °C	82	12
5[e]	Zn (3 equiv.)	81	12
6[f]	NEt_4I (20 mol%) as additive	84	11
7[g]	No nickel	< 1	<1
8	LiCl (1 equiv) as additive	71	3
9	No $ZnBr_2$	39	4
10[h]	No nickel, no $ZnBr_2$	0	0
11[i]	HTE setup	80 ± 4[j]	7 ± 2

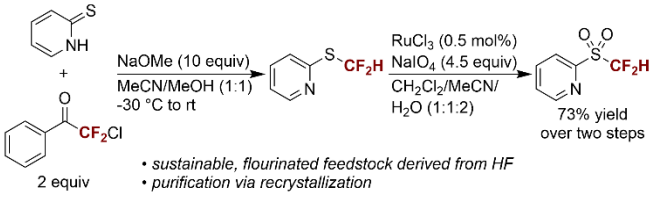
[a] For additional optimization data and side products see Supporting Information Figures S1-S12. [b] Aryl bromide (0.20 mmol), 2-$PySO_2CF_2H$ (0.22 mmol), $NiCl_2$•$6H_2O$ (0.02 mmol), ligand (0.022 mmol), $ZnBr_2$ (0.20 mmol), and Zn (1.6 mmol) were assembled in a N_2-filled glovebox and stirred in EtOH (0.5 mL) at 40 °C for 4 h. [c] Calibrated GC yield. Yield determined by ^{19}F NMR analysis are provided in parentheses. [d] At 24 h, **3a** is formed in 90% yield. [e] 12 h reaction time. [f] 15 h reaction time. [g] Quantitative recovery of **1a** and 87% recovery of **2a**. [h] Quantitative recovery of SM. [i] For details on equipment and experimental procedure, see Supporting Information 3.3. [j] Average yield and standard deviation in identical reactions in 16 reaction wells of a 96-well plate.

In alignment with our goal to develop a difluoromethylation route that is compatible with industrial application, it was crucial that our reaction conditions were suitable for both small- and large-scale reactions. 2-$PySO_2CF_2H$, as a bench-stable crystalline solid, offers operational simplicity for small-scale parallel screening compared to gaseous difluoromethyl sources, as it can easily be dosed from a stock solution or using modern solid dosing robotic platforms. Indeed, excellent reproducibility was observed with several high yielding conditions when the reaction was carried out using HTE without the need for specialized high-pressure equipment (Supporting Information 3.3). Safety testing (see Supporting Information 2.2) confirmed that 2-$PySO_2CF_2H$ decomposition is not a concern at the temperatures used for our reaction. We also identified a new, ODS-free synthetic route to 2-$PySO_2CF_2H$ from 2-chloro-2,2-difluoroacetophenone, a commercially available fluorinated feedstock chemical derived from HF (Supporting Information 3.1).[97] After brief optimization, 2-$PySO_2CF_2H$ was produced in



Scheme 3. Scope of nickel-catalyzed difluoromethylation of aryl bromides with 2-PySO$_2$CF$_2$H.[a] [a] Unless otherwise indicated, yields refer to isolated yields. Yields determined by ^{19}F NMR analysis are provided in parentheses. Reaction conditions are as follows: aryl bromide (0.20 mmol), 2-PySO$_2$CF$_2$H (0.22 mmol), NiCl$_2$•6H$_2$O (0.02 mmol), ligand (0.022 mmol), ZnBr2 (0.20 mmol), and Zn (1.6 mmol) were assembled in a N$_2$-filled glovebox and stirred in EtOH (0.5 mL) at 40 °C for 4-24 h. See Supporting information 4.4 for additional details. [b] Aryl iodide used with 1.5 equiv 2-PySO$_2$CF$_2$H in DMF as solvent at rt. [c] NiBr$_2$dme (10 mol%) as nickel source and DME as solvent. [d] Yield over two steps. After difluoromethylation of **1i** at 0.5 mmol scale (67% ^{19}F NMR yield), the reaction mixture was subjected to aqueous workup followed by Pd-catalyzed coupling with 6-bromoquinoline. See Supporting Information 4.4 for additional details. [e] 4:1 EtOH:DMSO mixture as solvent. [f] Reaction on 5 mmol scale prepared on benchtop. See Supporting information 3.2 for details on procedure. [g] Reaction run for 40 h.

73% yield over two steps without the need for purification by chromatography (Scheme 2). In addition, these reaction conditions are scalable (vide infra).



Scheme 2. Synthesis of 2-pyridyl difluoromethyl sulfone from non-ODS precursors.

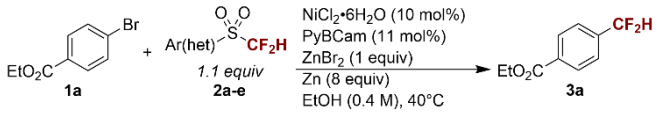
Application of the optimized conditions to a variety of substrates illustrates the utility and limitations of this new difluoromethylation reaction (Scheme 3). Substrates bearing electron-withdrawing functional groups such as esters, ketones, and amides coupled to generate difluoromethylated products in high yield (**3a**-**3e**, 67-93% yield). Electron-rich aryl halides coupled in lower yield (**3f** and **3g**, 41 and 45% yield, respectively), and in the case of **3f**, required the use of the corresponding aryl iodide. Aryl bromides bearing boronate esters were also well tolerated (**3h** and **3i**, 67% and 70% yield, respectively), providing handles for further structural diversification, as **3i** is the difluoromethylated precursor in the synthesis of the preclinical DNA-PK inhibitor BAY-8400.[26] Indeed, the difluoromethylated product **3i** could be directly cross-coupled to yield **3j**, an analogue of the heterocyclic core of BAY-8400 (56% yield over two steps). This substrate also illustrated the value of solvent flexibility: **3i** rapidly decomposed in EtOH and DMF, but a high yield could be obtained in DME.[98]

A range of heteroaryl bromides were evaluated due to their relevance in medicinal chemistry.[99] C-H functionalization approaches for the difluoromethylation of pyridines have been previously reported for difluoromethylation at the 2- and 4-positions, but there is little ability to generate difluoromethyl 3-pyridines selectively.[68,71,76] Under our conditions, 3-bromopyridine substrates afforded products inaccessible by Minisci difluoromethylation methods (**3k-3r**, 38-90% yield) and displayed excellent functional group compatibility, including toleration of both protected and unprotected heteroaryl amines (**3n** and **3o**, 65% and 59% yield, respectively). Sterically hindered heteroaryl substrate **3q** bearing an ortho substituent could also be successfully coupled, albeit in diminished yield (38% yield). C-H difluoromethylation of heteroarenes with multiple reactive sites often results in the formation of regioisomeric mixtures of mono- and/or bis-difluoromethylated products that can be difficult to separate.[68,69,71–73,76,78] Under our conditions, 2- and 4-bromopyridines serve as suitable coupling partners to provide selective access to products which can be challenging to form selectively via C-H difluoromethylation (**3s** and **3t**, 62% and 69% yield, respectively). Selective difluoromethylation only at the halide is observed, obviating the challenges of separating multiple difluoromethylated products. Heteroaryl bromides such as pyrimidines, azaindoles, and quinolines could also be converted

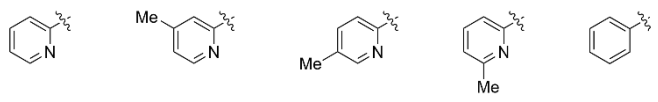
to the difluoromethylated product in good yield (**3u-3y**, 44-75% yield). Substrate **3u** bearing a tertiary aliphatic amine, which is known to prone to oxidation under metallaphotoredox conditions, was compatible in this system (46% yield). High-yielding substrate **3p** also showed amenability to benchtop scale-up with minimal loss in product yield (70% yield).

Difluoromethyl 2-pyridyl sulfones have previously been reported as electrophilic coupling partners,[63,65,66] but the factors governing sulfone reactivity under reductive nickel-catalyzed cross coupling conditions remain largely unexplored. Several difluoromethyl (hetero)aryl sulfones were screened under standard reaction conditions to explore the factors governing sulfone reactivity (Table 2). The reactivity of various 2-pyridyl difluoromethyl sulfones suggests that generally sulfones with more negative reduction potentials, which are more challenging to reduce, couple in lower yields. However, the difference in reactivity between sulfone **2c** and **2d** despite their identical reduction potentials suggests sulfone activation is not exclusively a function of reduction potential. Evidence of sulfone activation by zinc in the presence of Lewis acidic salts, even in the absence of a nickel catalyst (Table 1, entry 6), suggests that coordination of the sulfone to Lewis acidic salts such as $ZnBr_2$ or LiCl plays an important role in sulfone activation that is not observed with non-coordinating salts such as NEt_4I (Table 1, entry 10). The large difference in reactivity between sulfones **2b**/**2c** and **2d** may be explained by steric hinderance impeding coordination of sulfone **2d** to $ZnBr_2$ or the nickel catalyst. This is supported by previous reports that coordination of 2-pyridyl nitrogen may play an important role in sulfone activation that goes beyond reduction potential.[65] While 2-$PySO_2CF_2H$ displayed superior reactivity to all other sulfones examined under these conditions, the productive coupling of sulfones with varying reduction potentials suggests the possibility for intentional design of sulfones to match the reactivity of different electrophilic coupling partners.

Table 2. Difluoromethylation reactivity of various difluoromethyl sulfones.[a]



(het)Ar =

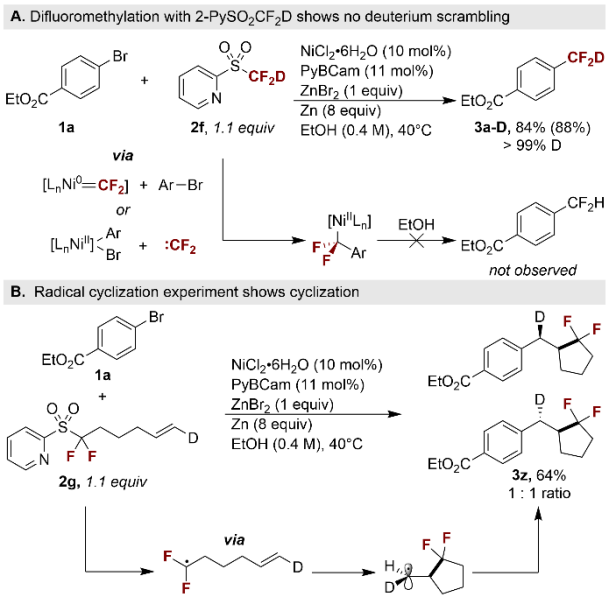


	2a	2b	2c	2d	2e

Entry[b]	2	*E* (V vs. Ag/AgCl)[c]	3a (%)[d]	2 (%)[d]
1	**2a**	-1.89	90	0
2	**2b**	-1.91	80	0
3	**2c**	-1.93	50	51
4	**2d**	-1.93	7	87
5	**2e**	-2.25	0	97

[a] For synthesis and screening of additional difluoromethyl sulfones, see Supporting Information Figure S12. [b] Aryl bromide (0.20 mmol), 2-$PySO_2CF_2H$ (0.22 mol), $NiCl2•6H_2O$ (0.02 mmol), ligand (0.022 mmol), $ZnBr_2$ (0.20 mmol), and Zn (1.6 mmol) were assembled in a N_2-filled glovebox and stirred in EtOH (0.5 mL) at 40 °C for 4 h. [c] E refers to the reduction potential using Ag/AgCl as reference in EtOH. [d] GC yields using 1,3,5-trimethyoxybenzene as internal standard.

Mechanistic experiments suggested that the sulfone was activated to form a difluoromethyl radical. First, while 2-$PySO_2CF_2H$ has been used as a difluorocarbene precursor,[100] the coupling of aryl bromide **1a** with 2-$PySO_2CF_2D$ under our conditions generated only the deuterated product (**3a-D,** 84% yield), ruling out a metallocarbene insertion mechanism (Scheme 3A). Second, an experiment using sulfone **2g** yielded a 1:1 mixture of diastereomeric cyclized products (**3z**, 64% yield), suggesting formation and cyclization of a radical intermediate, rather than a stereospecific, Ni-mediated migratory insertion process (Scheme 3B).



Scheme 4. Mechanistic investigation of activation of 2-$PySO_2CF_2H$ under reductive nickel-catalysis. For experimental details, see Supporting Information 4.4.

Recently, Hu and coworkers disclosed the difluoromethylation of aryl iodides using 2-$PySO_2CF_2H$ under reductive, (tpy)Ni-catalyzed conditions. Under those conditions, arylzinc intermediates were formed competitively and appeared to contribute to product formation. In contrast, our conditions, which utilize a different catalyst and work best in EtOH, do not appear involve arylzinc species. Perhaps as a result, our conditions enable complementary reactivity, enabling the use of aryl and heteroaryl bromides, Lewis-basic nitrogen heterocycles, and protic functional groups in a wide array of protic and aprotic solvents.

In conclusion, we have developed a nickel-catalyzed reductive cross-electrophile coupling reaction between 2-$PySO_2CF_2H$ and a diverse array of (hetero)aryl bromides under mild conditions in ethanol solvent. As a crystalline difluoromethylation reagent that can now be derived from a non-ODS feedstock, 2-$PySO_2CF_2H$ offers straightforward application on scale and in parallel reaction arrays without the challenges of gaseous and tightly regulated, environmentally damaging fluorinated reagents. A small collection of high yielding conditions provides versatility for both HTE and scale-up applications. Mechanistic studies show that the 2-pyridyl sulfone decomposes to form a difluoromethyl radical in a step that is accelerated by

coordination to the 2-pyridyl group, providing a path towards further sulfone reagent design in the future.

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Keywords: difluoromethylation • fluorine • nickel catalysis • sulfones • heterocycles

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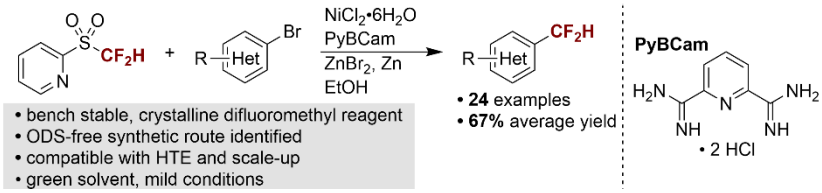
TOC



The nickel-catalyzed difluoromethylation of aryl bromides using difluoromethyl 2-pyridyl sulfone. The key advances are 1) the use of a non-ozone-depleting substance (ODS) derived difluoromethyl source, 2) compatibility with a diverse array of (hetero)aryl bromides, 3) amenability of reaction conditions to small-scale high-throughput experimentation (HTE) and benchtop scale-up, and 4) mild conditions with the use of ethanol as a green solvent.