Sulfone Electrophiles in Cross-Electrophile Coupling: Nickel-Catalyzed Difluoromethylation of Aryl Bromides

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ABSTRACT: Fluoroalkyl fragments have played a critical role in the design of pharmaceutical and agrochemical molecules in recent years due to the enhanced biological properties of fluorinated molecules compared to their non-fluorinated analogues. Despite the potential advantages conferred by incorporating a difluoromethyl group in organic compounds, industrial adoption of difluoromethylation methods lags behind fluorination and trifluoromethylation. This is due in part to challenges in applying common difluoromethyl sources towards industrial applications. We report here the nickel-catalyzed cross-electrophile coupling of (hetero)aryl bromides with difluoromethyl 2-pyridyl sulfone, a sustainably sourced, crystalline 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 can be applied to small-scale parallel synthesis and benchtop scale-up under mild conditions. As sulfone reagents are uncommon electrophiles in cross-electrophile coupling, the mechanism of this process was investigated. Studies confirmed the formation of $\bullet CF_2H$ instead of difluorocarbene. A series of modified difluoromethyl sulfones revealed that sulfone reactivity does not correlate exclusively with reduction potential and that coordination of cations or nickel to the pyridyl group is essential to reactivity, setting out parameters for matching the reactivity of sulfones in cross-electrophile coupling.

1. INTRODUCTION

The incorporation of fluorine and small fluoroalkyl fragments in pharmaceuticals has played a key role in improving the absorption, target binding affinity, and metabolic stability of small molecule drugs.[1] At present, at least 20% of pharmaceuticals and over 30% of agrochemicals contain at least one fluorine atom.[2] The difluoromethyl group (CF_2H) can act as a lipophilic hydrogen-bond donor, serving as a metabolically-stable bioisostere of hydroxyl, thiol, and hydroxamide functional groups.[3] Difluoromethyl-containing compounds have demonstrated enhanced selective target binding affinity, potency, and biological availability compared to non-fluorinated, fluorinated, monofluoromethylated, and trifluoromethylated analogues (Scheme 1A).[4,5] Despite the beneficial attributes of the difluoromethyl moiety, there are currently no FDA-approved small molecule drugs containing a (hetero)aromatic difluoromethyl group.[2a,6] Pharmacokinetic/dynamic questions notwithstanding, a simple, practical, and selective method for the introduction of the difluoromethyl moiety has the potential to increase the number of potential drug candidates and enable their manufacture at scale.[7,8]

Several routes for difluoromethylation of aromatic compounds have been reported in recent years to match the increasing interest in difluoromethyl-containing compounds over the past several decades (Scheme 2).[9–17] However, there are significant challenges toadoption of these difluoromethylation methods in both medicinal

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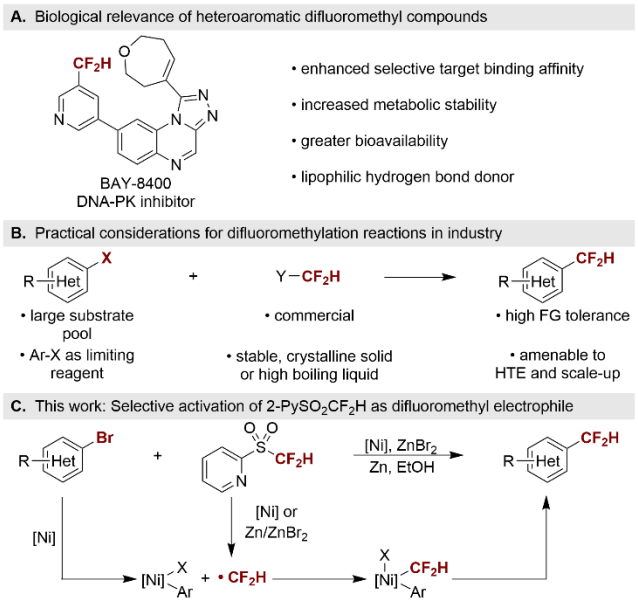
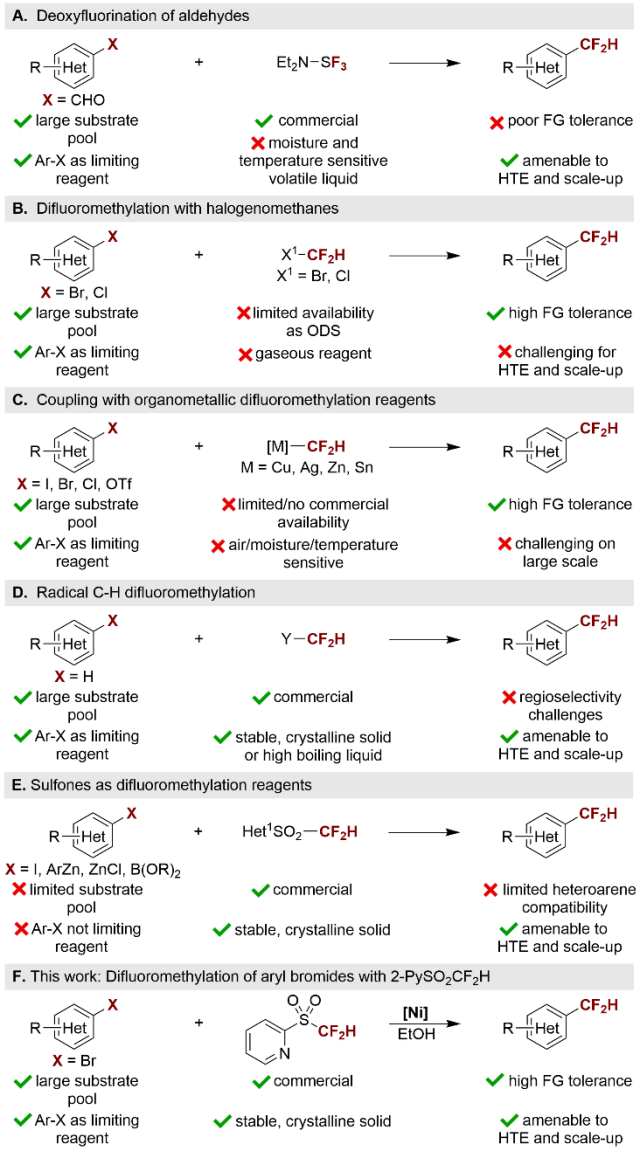
Scheme 1. Importance of difluoromethylation and considerations for reaction design.



process chemistry. Although the use of (diethylamino)sulfur trifluoride (DAST) and related derivatives is a well-known approach to difluoromethylation, such methods display limited functional group tolerance, pose safety hazards, and are limited by the lower availability of ArCHO compared to ArX (Scheme 2A).[9,18]

Scheme 2. Difluoromethylation strategies[a]



[a]For additional details on previously reported difluoromethylation strategies, see Supporting Information 2.1.

Halogenodifluoromethanes can be utilized as direct difluoromethylation reagents (Scheme 2B),[15] but these gases are tightly regulated or banned for use by the Montreal Protocol. At present, many current difluoromethylation methods rely directly or indirectly on the use of ozone-depleting halogenomethane gases as difluoromethyl sources (see Supporting Information 2.1).[19] The recent increased regulation of these environmentally damaging fluorinated feedstocks is expected to challenge the supply chain of fluorinated materials which rely on halogenomethanes,[7,20] further limiting practical and sustainable application of these methods. Additionally, the use of gaseous or low boiling liquid reagents presents safety hazards and dosing challenges to avoid leaks for both parallel, small-scale screening and large-scale preparations.[21,22] In our initial investigations, approaches using gaseous halogenomethane reagents resulted in inconsistencies when used in parallel arrays without the use of specialized equipment.

Nucleophilic difluoromethylation reagents have also been widely studied (Scheme 2C).[11,12] In some cases, these solid reagents have shown great reactivity, even allowing for the nickel-catalyzed difluoromethylation of aryl halides at room temperature.[12c] Drawbacks include limited air, moisture, or temperature stability (particularly for organozinc difluoromethylation reagents) while the use of stoichiometric amounts of Ag- or Sn-based reagents is undesirable for waste handling and/or toxicity reasons. Although some of us have reported process for the synthesis of $[(DMPU)_2Zn(CF_2H)_2]$ on > 100 g scale,[12k] the challenges associated with these reagents support continued development of new reagents.

Trimethylsilyl difluoromethane ($TMSCF_2H$), which can be derived from non-ODS sources, would represent an attractive reagent for difluoromethylation of aryl electrophiles.[11] Unfortunately, there is no precedent for the use of this reagent for our purpose using a nickel catalyst, while examples using copper catalysts are limited to iodide electrophiles.[12f] Furthermore, Sanford reported byproducts from the undesired methyl transfer from $TMSCF_2H$ instead of the desired -CF_2 fragment using a Pd catalyst[11e] which we anticipate would lead to difficulty in product separation during isolation.

Similarly, methods for radical difluoromethylation of heteroarenes with multiple potential reaction sites can generate regioisomeric mono- or bis-difluoromethylated products, leading to challenging product separations (Scheme 2D).[10]

Sulfones represent an attractive class of electrophilic coupling partners that allow for the coupling of small, high-value alkyl fragments through the use of stable, crystalline, easily accessible reagents with high compatibility for industrial manipulation (Scheme 2E).[23] Indeed, the coupling of difluoromethyl sulfone reagents with aryl nucleophiles has been well-developed.[14] These studies demonstrate the importance sulfone structure on reactivity: difluoromethyl 2-pyridyl sulfone (2-$PySO_2CF_2H$) was most effective for the iron-catalyzed difluoromethylation of aryl zinc reagents,[14a] but demonstrated poor reactivity for nickel-catalyzed alkylation of aryl zinc reagents, where *N*-phenyl-tetrazole sulfones coupled most efficiently.[14b] For the iron-catalyzed difluoromethylation of arylborates, difluoromethyl 4,6-dimethylpyrimidin-2-yl sulfone was most effective.[14c] Limitations of these methods include the use of excess aryl nucleophile and the lower availability of aryl nucleophiles compared to aryl electrophiles.

Coupling sulfones with aryl halides taps into the significantly wider availability and practicality of aryl halides compared to aryl nucleophiles (about 75× more).[14] However, the cross-electrophile coupling of aryl halides with sulfones is much less developed than with other alkyl electrophiles: we could find only three reports.[17,24,25] Hughes and Fier coupled a variety of alkyl *N*-phenyl-tetrazole sulfones with aryl bromides with alkyl transfer.[24] Productive difluoromethyl transfer was not observed. Initially, Hu reported the use of 2-$PySO_2CF_2H$ for pyridyl transfer to aryl iodides to form arylated pyridines.[25] However, concurrent with our work,[17,26] Hu and coworkers were able to find a way to favor difluoromethyl transfer over pyridyl transfer, resulting in the first difluoromethyl transfer to aryl iodides and electron-poor aryl bromides. While a major advance towards our shared goal, we noted opportunities to further advance the field by expanding the scope to heteroaryl bromides, avoiding the need

for excess aryl, and addressing some limitations with respect to acidic protons (see Supporting Information Figure S51).[17]

More industrially suitable conditions would not only expand the scope to heteroaryl bromides, but also address practical considerations of reagent sustainability, solvent choice, and adaptation to small and large scale (Scheme 2F).[27] Our survey of sulfone reagents found, like Hu, difluoromethyl 2-pyridyl sulfone (2-$PySO_2CF_2H$) to be the most attractive starting point because it is a crystalline, non-explosive, air- and light-stable, commercially available reagent.[28,29] We report here new general conditions that enable difluoromethylation of a range of heteroaromatic substrates and tolerate protic functional groups (indeed, even a protic solvent). We also demonstrate application of our reaction conditions to small-scale, parallel screening and benchtop scale-up. Mechanistic studies shed light on how the sulfone structure and additives tune sulfone reactivity, suggesting future avenues of study.

2. RESULTS AND DISCUSSION

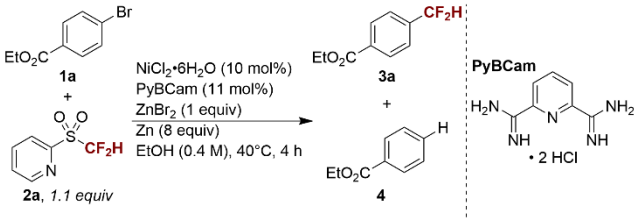
2.1 Optimization of Reaction Conditions

A combination of high-throughput experimentation (HTE) data and mechanism guided experimentation led to a small collection of conditions with several common themes (Table 1, see Supporting Information 2.4 for additional details). PyBCam (pyridine-2,6-bis(carboximidamide) dihydrochloride) ligands were superior to all other ligands tested (Supporting Information Figure S36).[30] 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 S38). 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 from 8 equivalents to 3 equivalents still resulted in effective coupling, however a slower reaction rate and slightly diminished selectivity were observed (entry 5).[31] 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[32] but did not activate the sulfone (entry 6). We observed a strong salt effect on yield and rate. While a variety of halide salts improved yield (entries 1, 6-8), Li^+ and Zn^{++} cations were particularly effective at increasing the rate of the reaction (entries 1 and 7 vs 8, Supporting Information Figure S40).

2.2 Scope of Coupling with (Hetero)aryl Bromides

Application of the optimized conditions to a variety of substrates illustrates the utility and limitations of this new difluoromethylation reaction (Scheme 3). Due to the increased volatility of the difluoromethylated products resulting in low isolated yields for products with low molecular weights, ^{19}F NMR yields are included for reference in parentheses. 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). Compared to the prior work of Hu and coworkers,[17] our conditions appear to provide better yields with aryl and heteroaryl bromides. For example, Hu reported difluoromethylation of methyl-4-bromobenzoate in 42% yield,[17] and our conditions provided closely related **3a** in 87% yield (see Supporting Information Figure S51 for additional substrate comparison with **3g**, **3o**, and **3r**). Electron-rich aryl halides coupled in lower yield than electron-poor aryl bromides (**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.[5l] 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.[33]

Table 1. Evaluation difluoromethylation reaction variables.[a]

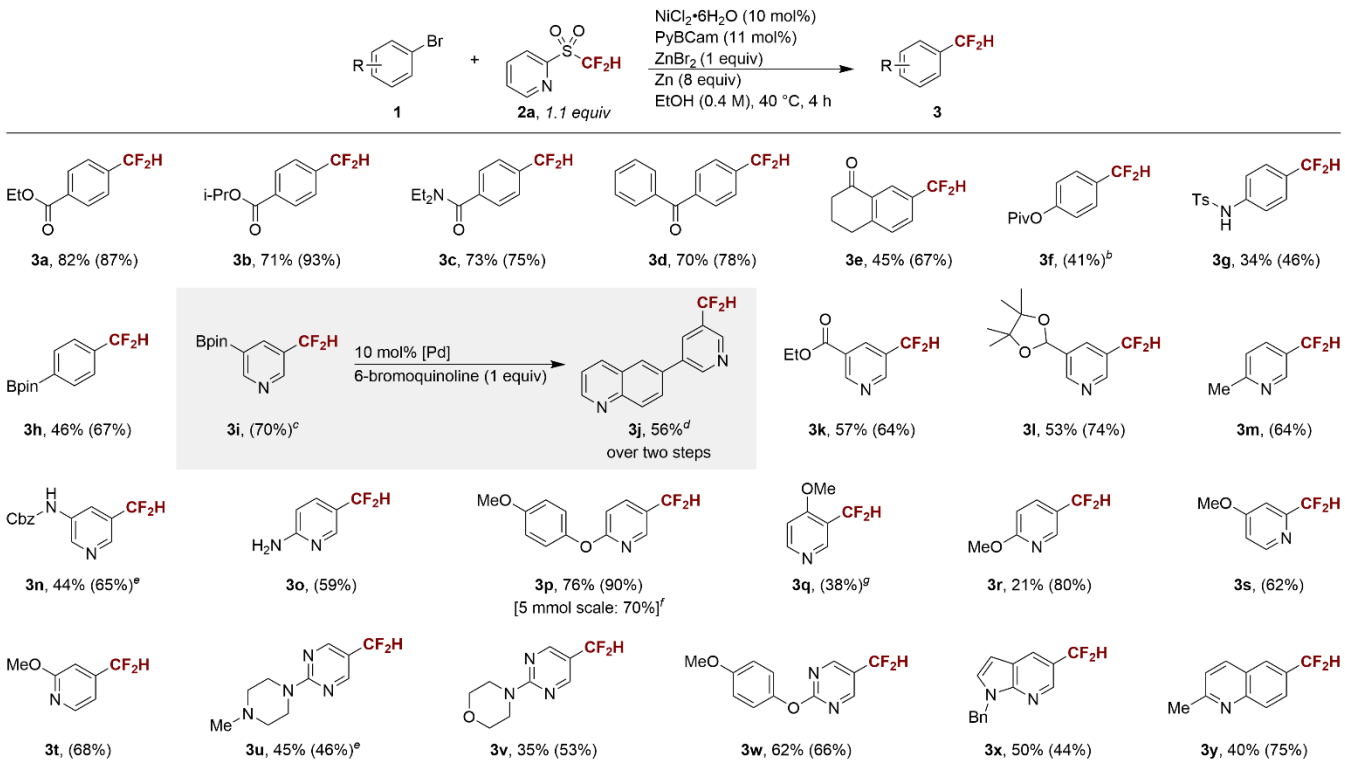


Entry[b]	Deviation from standard conditions	**3a** (%)[c]	**4** (%)[c]
1	None	90 (90)	8
2	DME instead of EtOH	48	2
3[d]	rt instead of 40 °C	49	4
4	60 °C instead of 40 °C	82	12
5[e]	Zn (3 equiv)	81	12
6[f]	NEt_4I (20 mol%) in place of $ZnBr_2$	84	11
7	LiCl (1 equiv) in place of $ZnBr_2$	71	3
8[g]	No $ZnBr_2$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

[a]For additional optimization data and side products, see Supporting Information 2.4. [b]Aryl bromide (0.20 mmol), 2-$PySO_2CF_2H$ (0.22 mmol), $NiCl_2$•$6H_2O$ (0.02 mmol), PyBCam (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. Yields 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]Recovery of **1a** (53%) and **2a** (66%). [h]Quantitative recovery of **1a** and 87% recovery of **2a**. [i]Quantitative recovery of SM.

A range of heteroaryl bromides were evaluated due to their relevance in medicinal chemistry.[34] Direct radical difluoromethylation of pyridines has been previously reported for difluoromethylation at the 2- and 4-positions, but there is little ability to generate difluoromethyl 3-pyridines selectively (Scheme 2D).[10a,c,f] 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). Net C–H difluoromethylation of heteroarenes with multiple reactive sites often results

Scheme 3. Scope of nickel-catalyzed difluoromethylation of aryl bromides with 2-PySO$_2$CF$_2$H.[a]



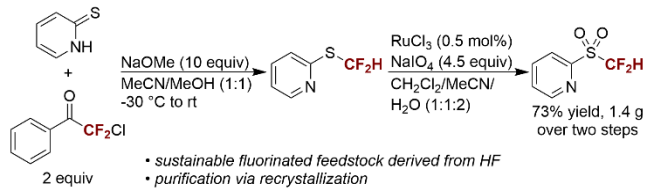
[a]Unless otherwise indicated, yields refer to isolated yields. Yields determined by ^{19}F NMR analysis are provided in parentheses. Reaction conditions are as follows: aryl bromide (0.20 mmol), 2-PySO$_2$CF$_2$H (0.22 mmol), NiCl$_2$•6H$_2$O (0.02 mmol), PyBCam (0.022 mmol), ZnBr$_2$ (0.20 mmol), and Zn (1.6 mmol) were assembled in a N$_2$-filled glovebox and stirred in EtOH (0.5 mL) at 40 °C for 4-24 h. See Supporting Information 4.6 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 of **3i** with 6-bromoquinoline. See Supporting Information 4.6 for additional details. [e]4:1 EtOH:DMSO mixture as solvent. [f]Reaction on 5 mmol scale prepared on benchtop. See Supporting Information 3.3 for details on procedure. [g]40 h reaction time.

in the formation of regioisomeric mixtures of mono- and/or bis-difluoromethylated products that can be difficult to separate.[10a-g] Under our conditions, 2- and 4-bromopyridines served as suitable coupling partners to provide selective access to products which can be challenging to form selectively via innate C–H difluoromethylation strategies (**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 be prone to oxidation under metallaphotoredox conditions,[35] 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).

2.3 Industrial Considerations: Synthesis and Scale

At present, the most efficient published routes to 2-PySO$_2$CF$_2$H are derived from ODS precursors, which required us to devise a new synthetic route.[14c,28] We could find only one small-scale synthesis of 2-PySO$_2$CF$_2$H (14 mg, 29% global yield) from a non-ODS precursor (NFSI).[36] We developed a route to 2-PySO$_2$CF$_2$H from 2-chloro-2,2-difluoroacetophenone, an easily accessed (and commercially available) fluorinated feedstock chemical derived from HF (Supporting Information 3.1).[37] After brief optimization, 2-PySO$_2$CF$_2$H was produced in 73% yield (1.4 g) over two steps without the need for purification by chromatography (Scheme 4).[38] Additionally, routine safety testing (see Supporting Information 2.2) confirmed that 2-PySO$_2$CF$_2$H decomposition is not a concern at the temperatures used for our chemistry.[29]

Scheme 4. Alternative non-ODS synthesis of 2-PySO$_2$CF$_2$H[a]

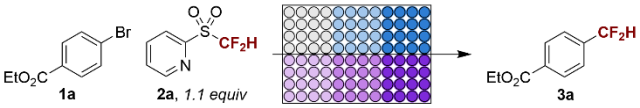


[a]See Supporting Information 3.1 for additional experimental details.

It was crucial that our reaction conditions were suitable for both small- and large-scale reactions. 2-PySO$_2$CF$_2$H, 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.[39] 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 (Table 2, entry 1). While investigating the scope of our reaction, we observed that some substrates (**3f**, **3i**, and **3u**) coupled in greater yield or were only soluble under modified reaction

conditions using solvents such as DME, DMF, or an EtOH:DMSO solvent mixture. Therefore, we identified and tested the reproducibility of a small collection of the best reaction conditions in standard 96-well plate format (entries 2-6). Furthermore, the stability exhibited by 2-PySO_2CF_2H under these conditions together with a successful demonstration of scale-up on substrate **3p** validates a safe, straightforward implementation of this method in an industrial setting.[40]

Table 2. Application to small-scale, parallel array reactions.



Standard Conditions: $NiCl_2$•$6H_2O$ (10 mol%), PyBCam (11 mol%), $ZnBr_2$ (1 equiv), Zn (8 equiv), EtOH (0.4 M), 40 °C

Entry[a]	Deviation from standard conditions	**3a** (%)[b]
1	None	80 ± 4
2	With $NiBr_2$(dme), DMF as solvent	40 ± 6
3	With $NiBr_2$(dme), DME as solvent	77 ± 10
4	With $NiBr_2$(dme), 4:1 EtOH/DMSO solvent mixture	84 ± 1
5	NEt_4I (20 mol%) as additive, **2a** (1 equiv)	80 ± 6
6	NEt_4I (20 mol%) as additive, **2a** (2 equiv)	70 ± 5

[a]For details on equipment and experimental procedure, see Supporting Information 3.4. [b]Calibrated average GC yield and standard deviation for identical reactions in 16 reaction wells of a 96-well plate.

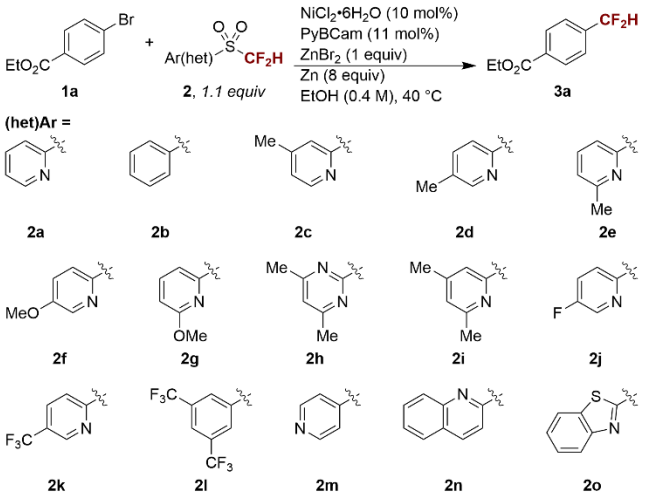
2.4 Reactivity of Difluoromethyl Sulfone Reagents

Sulfones are a unique class of electrophiles well-suited for the delivery of specialized high-value alkyl fragments. At present, only two sulfone electrophiles have been investigated for nickel-catalyzed cross electrophile coupling reactions: 2-PySO_2CF_2H and alkyl *N*-phenyl-tetrazole sulfones.[17,24] Work by Hughes and Fier coupling *N*-phenyl-tetrazole sulfones in nickel-catalyzed cross-electrophile coupling reactions is proposed to occur by single electron reduction of the sulfone with Zn.[24] However, under our conditions and those reported by Hu and coworkers,[17] reduction of 2-PySO_2CF_2H does not occur by Zn alone (Table 1, entry 10), indicating that sulfone structure has a strong influence on the mechanism of activation. Therefore, establishing a correlation between sulfone structure and reactivity under nickel-catalyzed cross-electrophile coupling conditions would be desirable for future sulfone electrophile development.

Although 2-PySO_2CF_2H displayed high reactivity and selectivity under our optimized conditions, when commercially available difluoromethyl phenyl sulfone **2b** was tested under our optimized conditions, no sulfone activation was observed (Table 3, entries 1 and 2). This difference in reactivity could be due to either the lower reduction potential of **2b** compared to **2a**, the ability of **2a** to coordinate to nickel or other cations, or both. Sulfone reduction potential and nitrogen atom coordination in heteroaryl sulfones have both previously been demonstrated as relevant to sulfone activation in different types of cross-coupling reactions.[14c,41]

A report exploring sulfones for radical fluoroalkylation under visible-light photoredox catalysis demonstrated that sulfones with less negative reduction potentials, which are easier to reduce, were more effective for fluoroalkylation.[41] Benzothiazole sulfone **2o** was reported to be more effective for radical difluoromethylation compared to **2a** and **2b**, with reactivity correlating to the difference reduction potentials.[41] However, a more recent report on the iron-catalyzed difluoromethylation of arylborates demonstrated that sulfones with an *N*-heteroaryl moiety could enable reactivity beyond reduction potential, with **2h** coupling in significantly higher yield than **2l** despite the two sulfones having very similar reduction potentials. The increased activation of **2h** was attributed to N-Fe coordination despite the presence of *ortho*-methyl groups.[14c]

Table 3. Difluoromethylation reactivity of various difluoromethyl sulfones[a]



Entry[b]	**2**	*E* (V vs. Fc^+/Fc)[c]	**3a** (%)[d]	**2** (%)[d]
1	**2a**	-2.07	90	0
2	**2b**	-2.38	0	97
3	**2c**	-2.12	80	0
4	**2d**	-2.14	50	51
5	**2e**	-2.12	7	87
6	**2f**	-2.23	12	86
7	**2g**	-2.14	2	81
8	**2h**	-1.96	11	29
9	**2i**	-2.19	7	n.d.
10	**2j**	-2.06	79	11
11	**2k**	-1.74	2	0
12	**2l**	-1.88	5	94
13	**2m**	-1.87	1	n.d.
14	**2n**	-1.79	3	n.d.
15	**2o**	-1.72	4	n.d.

[a]For additional information on screening of difluoromethyl sulfones, see Supporting Information Figure S41. [b]Aryl bromide (0.20 mmol), **2** (0.22 mol), $NiCl_2$•$6H_2O$ (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 12 h. [c]*E* refers to the reduction potential using ferrocenium/ferrocene as reference in EtOH. [d]GC yields using 1,3,5-trimethyoxybenzene as internal standard. Returned starting material not determined (n.d.) for sulfones that were not completely soluble in EtOH.

Screening a series of methyl-substituted difluoromethyl 2-pyridyl sulfones showed that 1) sulfone reactivity was not exclusively a function of reduction potential and 2) that this system was more sensitive to steric hinderance around the nitrogen than the iron system (Table 3, entries 3-5).[14c] Although **2c**, **2d**, and **2e** have similar reduction potentials, they exhibited substantial differences in reactivity, presumably due to steric hindrance impeding coordination of the pyridyl nitrogen of **2e** to nickel or zinc salts (Table 3, entries 3-5). Sulfones **2h** and **2l**, despite having less negative reduction potentials compared to **2a**, failed to result in productive coupling (entries 8 and 12). In fact, all sulfones without an accessible 2-pyridyl nitrogen (**2b**, **2e**, **2g**, **2h**, **2i**, and **2l**) displayed poor reactivity under our conditions (entries 2, 5, 7-9, 12). We found 2-pyridyl superior to other tested heterocycles **2h**, **2m**, **2n**, and **2o** (entries 8, 13-15), although the poor solubility of **2m**, **2n**, and **2o** in EtOH limits inferences on relative reactivity. In the case of **2k**, which has a more positive reduction potential than **2a** as well as a coordinating 2-pyridyl nitrogen, a low yield of product **3a** was observed (entry 11).

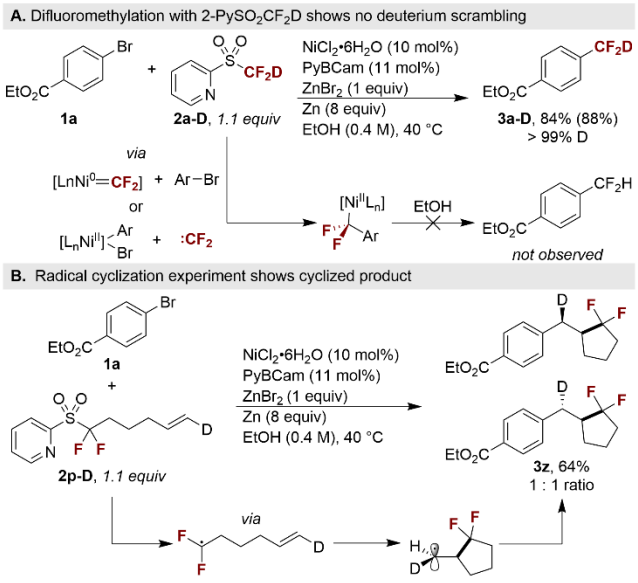
The differences between the optimal difluoromethyl sulfone reagents in cross-electrophile coupling and cross-coupling can be explained by the differences in mechanism. In cross-electrophile coupling, where both substrates are activated by a reductive step, the activation rate of the two substrates must be matched to prevent rapid decomposition of one substrate followed by slow decomposition of the other substrate. In cross-coupling, where only one reagent is activated by a reductive step, this is not a consideration. Thus, in the examples of cross-coupling, the most reactive reagent was generally the one that gave the highest yield (**2h**, **2o**). For our application, the best reagent was the one that was best matched with the aryl bromide in reactivity. More reactive (e.g., **2k**) and less reactive (e.g., **2f**) sulfones provided low yields. Although 2-$PySO_2CF_2H$ displayed superior reactivity to all other sulfones examined under these conditions, we envision that extending this chemistry to less reactive substrates *would benefit from less reactive sulfone reagents*.[42] Results in this vein will be reported in due course.

2.5 Mechanistic Investigation into Activation of 2-$PySO_2CF_2H$ as a Difluoromethyl Radical Precursor

Due to the significant impact of sulfone coordination on productive reactivity, several experiments were conducted to shed light on the mechanism of sulfone activation. 2-$PySO_2CF_2H$ has been previously reported as a difluorocarbene precursor,[43] but the coupling of aryl bromide **1a** with 2-$PySO_2CF_2D$ (**2a-D**) under our conditions generated only the deuterated product (**3a-D,** 84% yield), ruling out a metallocarbene insertion mechanism (Scheme 5A). Next, an experiment using sulfone **2p-D** 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 5B). Together, these mechanistic experiments are consistent with sulfone activation to form a difluoromethyl radical.

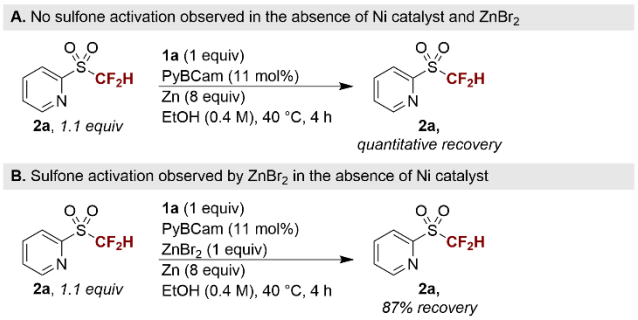
During initial optimization of reaction conditions, it was observed that the presence of Lewis acidic salts such as $ZnBr_2$ and LiCl increased the rate of sulfone activation, thereby increasing reaction selectivity and yield. The use of $ZnBr_2$ appears to enable rate-matching between activation of 2-$PySO_2CF_2H$ and **1a**, resulting in a faster and more selective reaction (Table 1, entries 1 and 8) (see Supporting Information Figures S31 and S32). When 2-$PySO_2CF_2H$ was subjected to standard reaction conditions without nickel and $ZnBr_2$, the sulfone was quantitatively recovered (Scheme 6A). However, the combination of $ZnBr_2$ and Zn does decompose the sulfone, albeit slowly (Scheme 6B). This result suggests that the addition of Lewis acidic salts could enable an additional pathway for sulfone activation independent of nickel.

Scheme 5. Evidence of Difluoromethyl Radical Intermediate.[a]



[a]For experimental details, see Supporting Information 4.4.

Scheme 6. Effect of Salts on Sulfone Activation.[a]



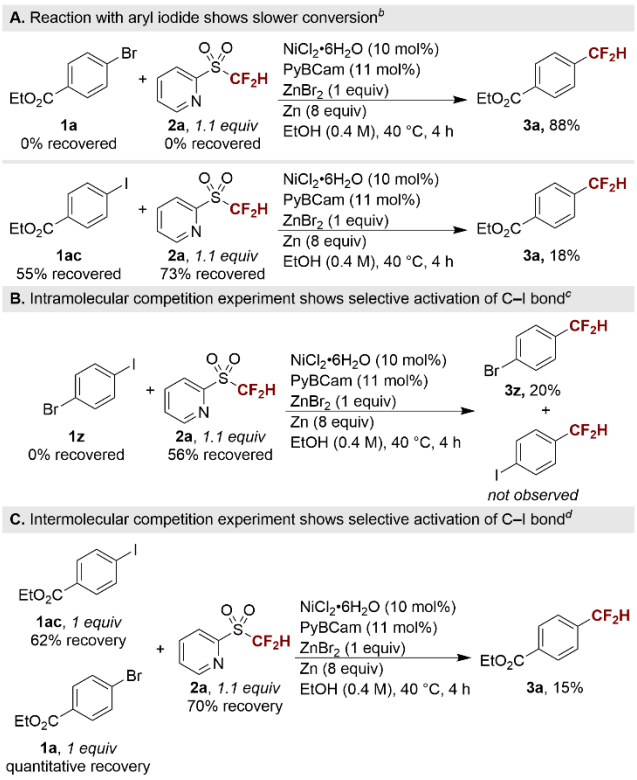
[a]GC yields using 1,3,5-trimethyoxybenzene as internal standard.

To better understand the reaction mechanism, preliminary kinetic data was collected to determine the order in reactants (See Supporting Information 2.5 for additional details). The reaction was shown to be first order in sulfone, indicating that activation of the sulfone occurs in the rate-limiting span. Interestingly, the reaction was observed to be negative first order in aryl bromide and appears to have an order in Ni greater than 1. Furthermore, replacement of the aryl bromide for the corresponding iodide showed slower conversion, despite conventional reactivity preferring oxidative addition at the C–I site (Scheme 7A). Collectively, this suggests a mechanism in which rate-limiting sulfone activation competes with aryl halide activation.

To probe this, intra- and intermolecular competition experiments were conducted using aryl dihalide **1z** and between aryl bromide **1a** and aryl iodide **1ac** (Scheme 7B and C). As expected, the reaction was highly selective for activation of the C–I bond in both cases, showing consumption primarily at the aryl iodide but with much lower conversion of the sulfone and aryl bromide. From this data, we conclude that oxidative addition still preferentially occurs at the aryl

iodide over aryl bromide, but that the higher reactivity of the aryl iodide creates a mismatch with the sulfone. Rapid conversion of nickel to the oxidative addition complex in the presence of aryl iodide results in slow activation of the sulfone (predominantly by Zn/$ZnBr_2$), leading to a slow rate of product formation. Indeed, the 15-20% product formation observed at 4 h in reactions with aryl iodide substrates (Scheme 7) is consistent with the rate of activation of 2-$PySO_2CF_2H$ primarily by Zn/$ZnBr_2$ over 4 h (13% activation or ~0.15 equivalents, Scheme 6B). For aryl bromide substrates, however, we propose that the rate of aryl bromide and sulfone activation by Ni are more closely matched, resulting in activation of the sulfone by Ni and Zn/$ZnBr_2$. As noted above, $ZnBr_2$ and LiCl may enable a slow, background generation of $\bullet CF_2H$ that can form product and release nickel to activate more sulfone. Alternatively, added salts could have an effect on reduction of the nickel catalyst at the zinc surface or its speciation.[44,45]

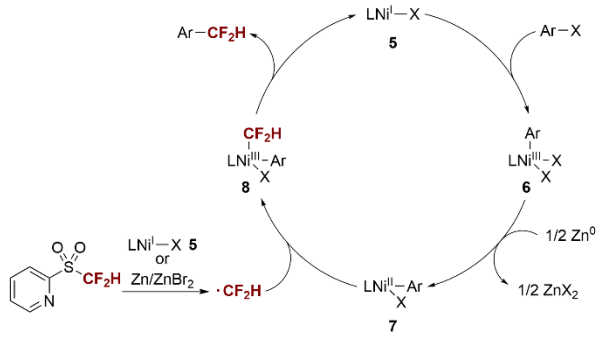
Scheme 7. Aryl Halide Competition Experiments.[a]



[a]For additional details, see Supporting Information 4.5. GC yields using 1,3,5-trimethyoxybenzene as internal standard. [b]For the reaction of **1a** at 4 h, 8% ethyl benzoate (**4**) was generated. For the reaction of **1ac** at 4 h, **4** (15%) was observed. For the reaction of **1ac** at 12 h, 4% recovery of **1ac** and generation of **3a** (41%), and **4** (32%) was observed. [c]At 4 h, bromobenzene (60%), difluoromethylbenzene (6%), and 1,4-bis(difluoromethyl)benzene (3%) were observed. [d]At 4 h, **4** was generated in 14% yield.

Taken together, these observations are consistent with a mechanism in which 2-$PySO_2CF_2H$ is reduced by Ni (**5**) (or more slowly by Zn/$ZnBr_2$) to generate a difluoromethyl radical. This rate-limiting sulfone activation by nickel competes with oxidative addition of aryl bromide to nickel. Reaction of the arylnickel complex (**7**) with the difluoromethyl radical leads to the formation of cross-coupled product (Scheme 8).

Scheme 8. Mechanistic Proposal for Cross-Electrophile Coupling of Aryl Bromides with 2-$PySO_2CF_2H$[a]



[a]The proposed mechanism shows a Ni(I/III/II/III) cycle, but an alternative Ni(0/II/III/I) pathway is also possible. Further mechanistic studies to discern the Ni oxidation states involved are in progress.

This mechanism is related to that proposed by Hu and coworkers for their (tpy)Ni-catalyzed reaction of 2-$PySO_2CF_2H$ with aryl iodides.[17] There are two notable differences. First, under Hu's conditions, arylzinc intermediates were observed, although they appeared to be a minor contributor to product formation. In contrast, our conditions utilize a different catalyst, work best in EtOH, and do not involve arylzinc species (see Supporting Information Figure S50). Second, in contrast to our findings, the Hu group did not note acceleration by salts or a mismatch between aryl iodides and 2-$PySO_2CF_2H$ (indeed, iodides worked better than bromides). While it is unclear why this difference is observed, we speculate it is due to the differences in catalyst (PyBCam vs tpy).

3. CONCLUSION

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 in ethanol solvent. 2-$PySO_2CF_2H$ offers straightforward application on benchtop scale and in parallel reaction arrays without the challenges of gaseous and tightly regulated reagents. Mechanistic studies show that the 2-pyridyl sulfone serves as a difluoromethyl radical source and coordination of the pyridyl nitrogen is crucial for reactivity. Matching the reactivity between sulfone and aryl bromide is important for this cross-electrophile approach; sulfones that were too reactive or not reactive enough resulted in low yields of product. This understanding might allow the design of cross-electrophile coupling reactions of differently-reactive aryl halides in the future. Results will be reported in due course.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. ‡These authors contributed equally.

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Notes

The authors declare no competing financial interest.

ASSOCIATED CONTENT

The Supporting Information is available free of charge via the Internet at http://pubs.acs.org.

Additional tables of data; full experimental details; safety testing; characterization data; and copies of NMR spectra (PDF)

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ABBREVIATIONS

ODS, ozone-depleting substance; DAST, (diethylamino)sulfur trifluoride; HTE, high-throughput experimentation; PyBCam, pyridine-2,6-bis(carboximidamide) dihydrochloride; NFSI, *N*-Fluorobenzenesulfonimide, DNA-PK, DNA-dependent protein kinase; tpy, 2,2′:6′,2″-terpyridine.

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(38) The oxidation of a thioether to a sulfone using $NaIO_4$ with $RuCl_3$ has precedent on scale, (see: Arndt, S.; Kohlpaintner, P. J.; Donsbach, K.; Waldvogel, S. R. Synthesis and Applications of Periodate for Fine Chemicals and Important Pharmaceuticals. *Org. Process Res. Dev.* **2022**, *26*, 2564–2613. DOI: 10.1021/acs.oprd.2c00161). We note that many thioether oxidation methods exist, providing many options to explore for larger scale synthesis. See: *Synthesis of Sulfoxides and Sulfones via Oxidation of Thioethers*. https://reagents.acsgcipr.org/reagent-guides/sulfide-oxidation/ (accessed 2024-05-17).

(39) Gaseous difluoromethyl sources such as bromodifluoromethane and chlorodifluoromethane can be dosed from stock solutions, but storage and handling must be done at low temperatures to maintain consistent concentration over time.

(40) We recognize that Zn powder or flake as terminal reductant may pose issues when used on larger scale. More industrially attractive methods such as electrochemical reduction could be an alternative, with potential to match the reduction potential to the reaction. See: Su Z-M, Deng R, Stahl S. Zinc and manganese redox potentials in organic solvents and their influence on nickel-catalyzed cross-electrophile coupling. *ChemRxiv*. May 27, 2024, ver. 1. DOI: 10.26434/chemrxiv-2024-pcdp4 (accessed 2024-05-31).

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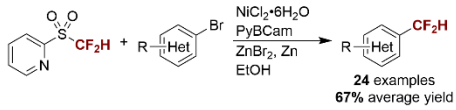
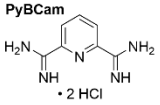


24 examples
67% average yield

- Bench-stable, crystalline reagent
- ODS-free difluoromethyl source
- Amenable to HTE and scale-up
- Insight into sulfone reactivity

PyBCam



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