Photocatalytic Sulfonyl Fluorination of Alkyl Organoboron Substrates

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ABSTRACT: Sulfonyl fluorides are highly versatile molecules for click chemistry that have found applications in many areas of chemistry and biology. Recent chemical approaches have focused on the synthesis of alkyl sulfonyl fluorides from readily available starting materials. Here, we report a photocatalytic synthesis of alkyl sulfonyl fluorides from organotrifluoroborates and boronic acid pinacol esters, which are building blocks commonly employed by medicinal chemists in the synthesis of bioactive molecules. Steady-state and time-resolved spectroscopy have confirmed that the absorption of photons by the acridinium catalysts leads to the oxidation of the organotrifluoroborate substrates. The reaction exhibits broad functional group tolerance, which can be attributed to the mild activation with visible light. Importantly, this general approach provides easy to access primary, secondary, and tertiary alkyl sulfonyl fluorides.

INTRODUCTION

Since the pioneering studies of Sharpless and co-workers in 2014,[1-3] sulfonyl fluorides have found significant utility as reactive probes in chemical biology and molecular pharmacology. These electrophilic compounds exhibit unique reactivity that renders them selective for sulfur(VI) fluoride exchange (SuFEx) chemistry under physiological conditions.[4] As warheads, they possess the right balance of biocompatibility and protein reactivity. Their functionality is privileged in this regard as they modify not only reactive serine, but also context-specific threonine, lysine, tyrosine, cysteine, and histidine residues. Sulfonyl fluorides are therefore ideal handles for the generation of covalent adducts between bioactive molecules and native proteins in the context of mechanism of action studies or irreversible inhibition.[5-11]

Traditional strategies for the synthesis of sulfonyl fluorides have provided access to *aryl*-substituted SuFEx reagents.[12-14] In light of the increased importance of sp^3-rich scaffolds in drug discovery,[15] recent methods have focused on the synthesis of *alkyl*-substituted SuFEx reagents **1** (Figure 1).[16-23] Early protocols accessed sulfonyl fluorides from substrates that contained sulfur(VI) functional groups, such as sulfonyl chlorides and ethenesulfonyl fluoride, a toxic and highly reactive reagent.[24-25] More recently, methods have been developed for alkyl sulfonyl fluoride installation from more readily available starting materials. These strategies include the oxidative fluorination of thiols,[14] alkyl sulfonyl fluorination of Grignard and alkyllithium reagents,[20] decarboxylative sulfonylfluorination,[19, 22-23] transition metal mediated reductive radical fluoroalkylsulfination, and C–H activation.[18]

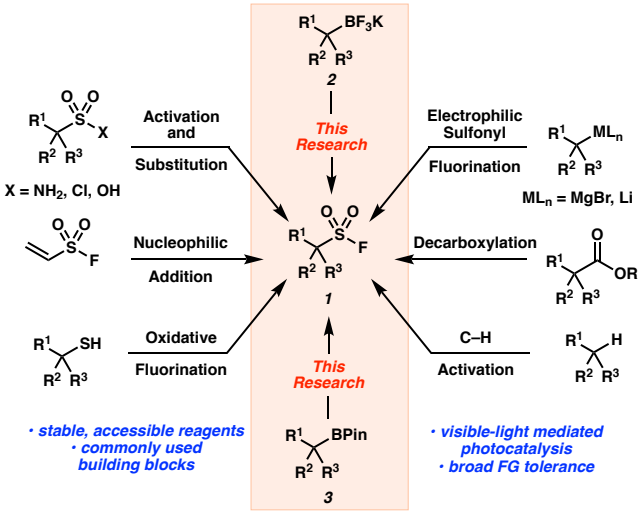


Figure 1. Preparation of alkyl sulfonyl fluorides.

We were motivated to develop an orthogonal approach to functionalized alkyl sulfonyl fluorides from a different, yet prevalent, class of substrates that would improve access to SuFEx reagents for applications in medicinal chemistry. Given the widespread use of organoboron reagents in catalytic and functional group tolerant reactions for drug discovery,[26-27] we reasoned that this class of substrates would be ideal for establishing a novel general approach to access primary, secondary, and tertiary alkyl sulfonyl fluorides. First, these bench-stable reagents are commercially available or easily synthesized with a broad range of functional groups. Second, organoboron substrates are common building blocks for the synthesis of bioactive molecules that are well-represented in compound libraries

of pharmaceutical companies.[28-29] Therefore, our method would seamlessly merge the synthetic routes developed for sp^3-rich pharmacological agents with the generation of sulfonyl fluorides.

Herein we describe the development of a photocatalytic sulfonylative coupling that converts bench-stable alkyl organotrifluoroborate salts **2** and boronic acid pinacol esters **3** into sulfonyl fluorides **1** (Figure 1). The mild mode of activation via visible-light mediated photocatalysis is compatible with functional groups that are well-represented in privileged pharmacophores. Outstandingly, this method enables the synthesis of primary, secondary, and tertiary alkyl sulfonyl fluorides. We also present spectroscopic studies to elucidate the photocatalytic mechanism.

RESULTS AND DISCUSSION

To test our proposed strategy for sulfonyl fluoride synthesis, we were guided by recent reports of the conversion of organotrifluoroborates **2** into C(sp^3)-centered radicals **4** under mild photochemical oxidation (Figure 2).[30-33] Although examples of sulfonylative couplings of organotrifluoroborate salts have been reported for the synthesis of sulfones,[34-35] to the best of our knowledge there are no reports of synthesizing alkyl sulfonyl fluorides such as **1** via a sulfonylative coupling between an organotrifluoroborate and a fluorine source.

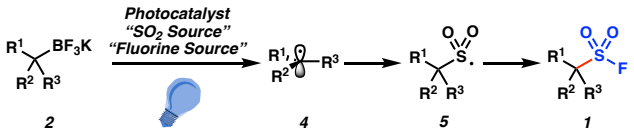
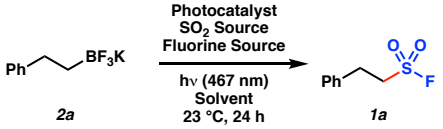


Figure 2. Proposed photocatalytic synthesis of alkyl sulfonyl fluorides.

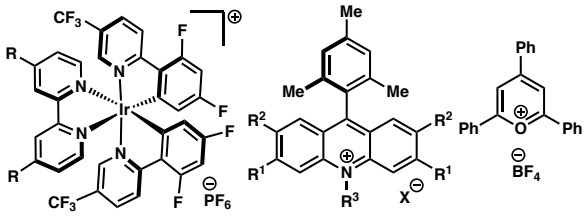
We began our studies by converting potassium phenethyltrifluoroborate **2a** to sulfonyl fluoride **1a** (Table 1). Initially, we subjected organotrifluoroborate salt **2a** to iridium based photocatalysts **A** and **B** in the presence of 1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide) adduct (DABSO) as a source of sulfur dioxide and Selectfluor™ as a fluorinating reagent (entries 1 and 2). Unfortunately, these conditions did not furnish appreciable amounts of the desired product **1a**. We next turned to highly oxidizing acridinium-based photocatalysts **C-E**,[36] which upon photoexcitation are known to facilitate the oxidation of organotrifluoroborates.[37] While catalysts **C** and **E** yielded sulfonyl fluoride **1a** in 39% yield (entries 3 and 5), we observed 63% of the desired product with 9-Mesityl-3,6-di-*tert*-butyl-10-phenylacridinium tetrafluoroborate **D** (entry 4).[38] Interestingly, the stronger photooxidant triphenylpyrylium tetrafluoroborate **F** produced sulfonyl fluoride **1a** in only 19% yield (entry 6). Subsequent optimizations focused on the sulfur dioxide source as well the fluorine source (entries 7 and 8). Optimal conditions were identified by employing DABSO and Selectfluor™ (see Supporting Information for more detailed optimization studies).

Further optimization showed dilute solutions increased product yields, presumably by mitigating undesired diffraction from the heterogenous reaction mixture.[39] The choice of solvent was important as well (entries 9-12). We eventually identified dichloroethane (entry 4) and trifluorotoluene (entry 12) as the reaction media of choice. We surmise that these solvents allow for the slow solvation of the organotrifluoroborate, promoting selectivity for the desired product and minimizing the formation of side products, while also allowing for enough solubility of the substrate for reasonable reaction times. Lowering the photocatalyst loading to 5 mol% only slightly diminished the product yield (entry 13), and increasing the reaction time to 48 h restored the yield to 70% (entry 14). Finally, control experiments revealed the essential role of the photocatalyst (entry 15) and light (entry 16).

Table 1. Development of Sulfonyl Fluorination of Organotrifluoroborates[a]



Entry	Photocatalyst	SO_2 Source	Fluorine Source	Solvent	Yield[b] (%)
1	A	DABSO	Selectfluor	DCE	8
2	B	DABSO	Selectfluor	DCE	< 5
3	C	DABSO	Selectfluor	DCE	39
4	D	DABSO	Selectfluor	DCE	63
5	E	DABSO	Selectfluor	DCE	39
6	F	DABSO	Selectfluor	DCE	19
7	D	DABSO	NFSI	DCE	16
8[c]	D	$K_2S_2O_5$	Selectfluor	DCE	25
9	D	DABSO	Selectfluor	MeCN	< 5
10	D	DABSO	Selectfluor	THF	38
11	D	DABSO	Selectfluor	PhMe	60
12	D	DABSO	Selectfluor	$PhCF_3$	68
13[d]	D	DABSO	Selectfluor	DCE	57
14[d,e]	D	DABSO	Selectfluor	DCE	70
15	–	DABSO	Selectfluor	DCE	< 5
16[f]	D	DABSO	Selectfluor	DCE	< 5

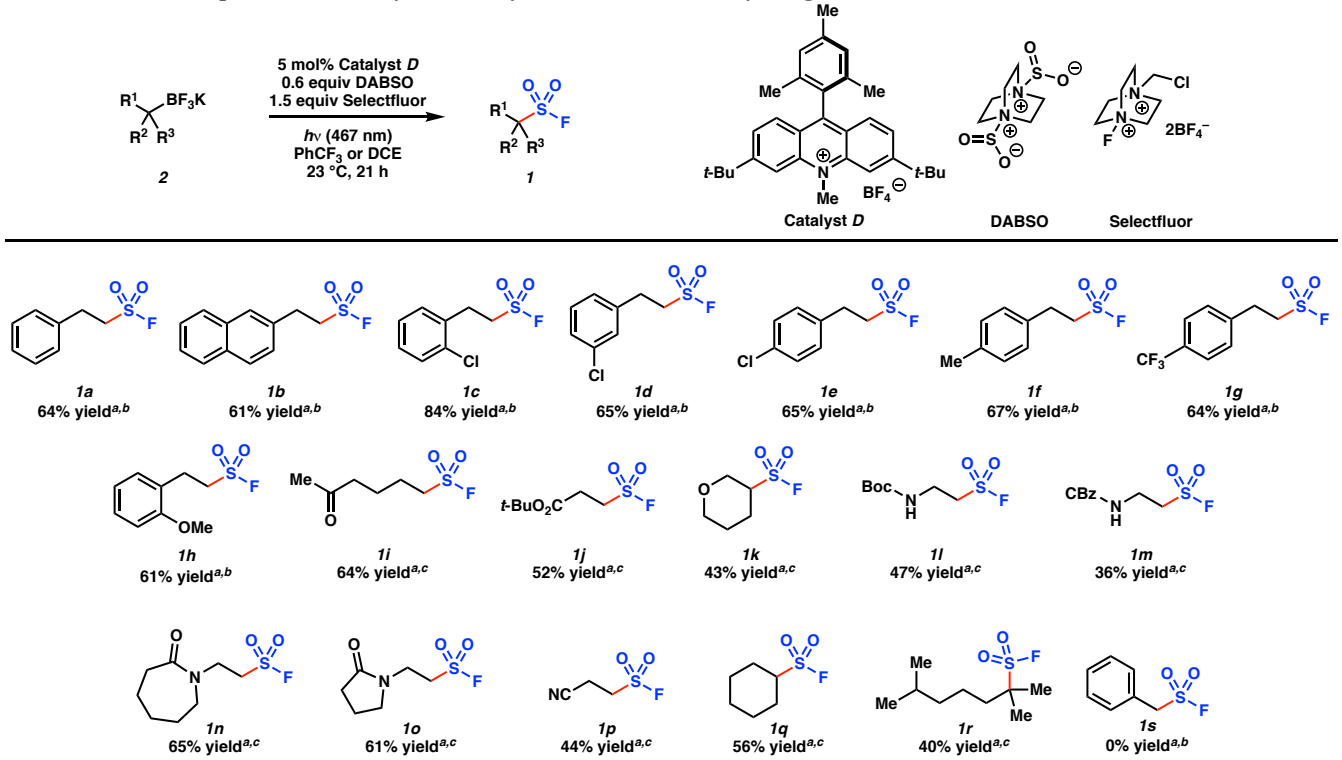


[a]Reaction conditions: organotrifluoroborate **2a** (0.2 mmol), photocatalyst (10 mol%), SO_2 source (0.6 equiv), fluorine source (1.5 equiv), solvent (0.025 M), 23 °C. [b]Isolated yield. [c]$K_2S_2O_5$ (1.2 equiv). [d]Photocatalyst D (5 mol%). [e]Reaction time is 48 h. [f]Absence of light.

With optimal conditions in hand, we explored the substrate scope to test the tolerance of the reaction conditions to various functional groups (Table 2). The reaction provided good yields of products with remote aromatic rings such as phenyl (**1a**) and naphthyl (**1b**), as well as aromatic rings with various substituents, including chloride (**1c-1e**), methyl (**1f**), and trifluoromethyl (**1g**). Overall, the transformation was tolerant of oxygen-containing functional groups, including a methoxy-arene (**1h**), ketone (**1i**), *t*-butyl ester (**1j**), and pyran (**1k**). We were also pleased to see product formation in the presence of nitrogen-containing functional groups with N–H bonds, such as a Boc-

protected amine (**1l**) and CBz-protected amine (**1m**). In addition, we obtained products that contained a lactam (**1n-1o**) and nitrile (**1p**). Secondary and tertiary organotrifluoroborates were converted into the corresponding secondary and tertiary sulfonyl fluorides (**1q-1r**). In most cases, the mass balance was primarily unreacted starting material. Attempts to increase the conversion with longer reaction times and heat did not lead to more product, presumably because of undesired diffraction from the heterogenous reaction mixture. Interestingly, benzylic organotrifluoroborates did not yield the benzylic sulfonyl fluorides (**1s**), which is consistent with the calculated endergonicity of a benzylic radical adding into sulfur dioxide in an organic solvent.[18]

Table 2. Substrate Scope of Photocatalytic Sulfonyl Fluorination of Alkyl Organotrifluoroborates[a]

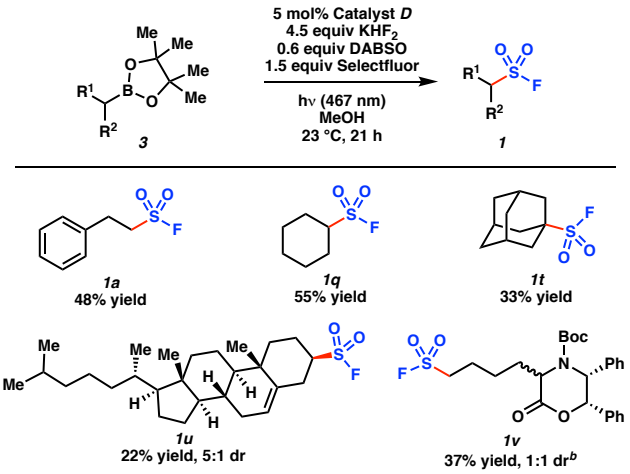


[a]Reaction conditions: organotrifluoroborate **2** (0.2 mmol), solvent (0.025 M) 5 mol% Catalyst **D**, 0.6 equiv DABSO, 1.5 equiv Selectfluor™, hν (467 nm), 23 °C, 21 h. [b]$PhCF_3$ as solvent. [c]DCE as solvent.

In light of the numerous methods for accessing functionalized boronic acid pinacol (BPin) esters,[40-42] we developed a one-pot approach to convert this class of substrates into sulfonyl fluorides (Table 3). Given the high oxidation potential of BPin esters,[43] we transformed these substrates *in situ* into organotrifluoroborates with KHF_2 and then subjected them to modified photocatalytic sulfonyl fluorination conditions. Primary, secondary, and tertiary BPin esters (**3**) were converted efficiently to the corresponding sulfonyl fluorides (**1a**, **1q**, and **1t**). Cholesterol derived BPin ester furnished sulfonyl fluoride **1u** in 22% yield and 5:1 dr. We also demonstrated the synthesis of sulfonyl fluoride **1v** from a late-stage BPin ester intermediate utilized by Merck & Co., Inc., Rahway, NJ, USA for the development of inhibitors of human arginases I and II for the treatment of myocardial reperfusion injury.[44]

With the synthetic utility established for the photocatalytic sulfonyl fluorination of organotrifluoroborates and BPin esters, we next carried out a series of photophysical experiments to gain insight into the mechanism (Figure 3). To quantify the propensity to absorb light and the excited-state behavior of photocatalysts **A-F**, we performed UV-Visible absorption and steady-state photoluminescence measurements in dichloroethane. All photocatalysts presented appreciable absorption at wavelengths relevant for visible light photoredox catalysis, between 370 and 500 nm (Figure 3a). The three acridinium photocatalysts **C-E** absorbed similarly, with larger molar absorption coefficients (ε = 60400 $M^{-1}cm^{-1}$) for catalyst **D** in the 375 nm range (Figure 3b and Figures S3-S4). Triphenylpyrylium tetrafluoroborate (**F**) also exhibited an intense absorption band at 418 nm, with ε = 47300 $M^{-1}cm^{-1}$. Both Ir(III) complexes **A-B** had moderate molar absorption coefficients in the visible part of the solar spectrum, typical for this type of photocatalyst.[45] Excitation in these absorption bands led to intense room temperature photoluminescence in dichloroethane. Overall, the steady-state measurements highlight that the acridinium and triphenylpyrylium photocatalysts absorb visible light with higher intensity than the Ir(III) catalysts. In addition, the excited-state reduction potentials for catalysts **A-F**, previously determined using their respective photoluminescence spectra and their ground-state reduction potentials,[27, 38, 46-52] support the observation that only catalysts **C-F** should be able to oxidize the trifluoroborate substrates (Figure 3c).

Table 3. Photocatalytic Sulfonyl Fluorination of Alkyl Boronic Esters[a]



[a]Reaction conditions: boronic ester **3** (0.2 mmol), Aqueous KHF_2 (4.5 M), MeOH (0.025 M), 5 mol% Catalyst **D**, 0.6 equiv DABSO, 1.5 equiv Selectfluor™, hν (467 nm), 23 °C, 21 h. [b]boronic ester **2v** (0.075 mmol).

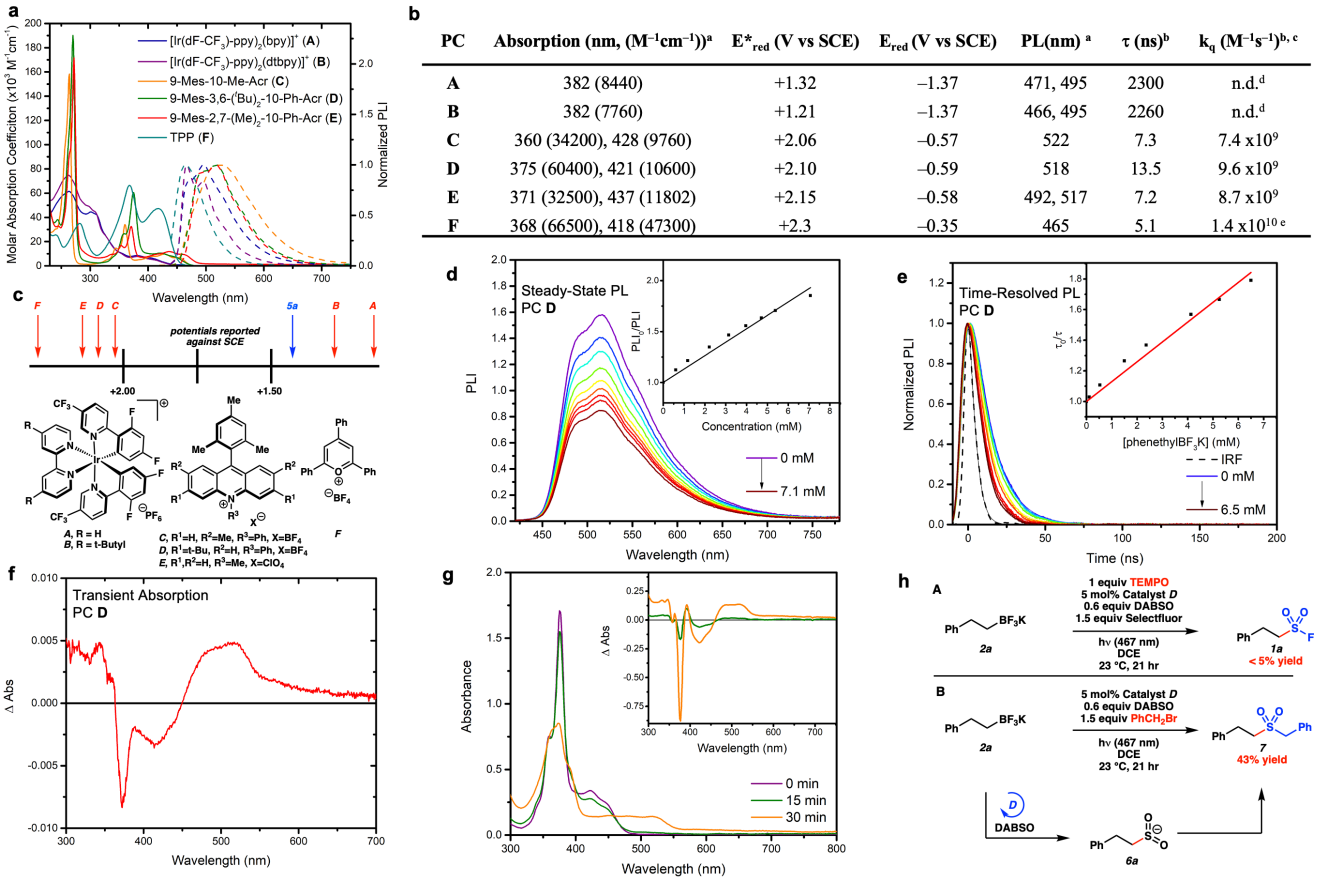
We also performed a series of steady-state and time resolved absorption and photoluminescence experiments with the optimized catalyst **D**. The limited solubility of organotrifluoroborate salts in dichloroethane or trifluorotoluene precluded rigorous excited-state quenching experiments in the reaction medium. However, since we were interested in the initial step of the light activated process, acetonitrile was chosen as solvent as it ensured complete solubility of the trifluoroborate salts in a concentration range compatible with these spectroscopic techniques. We first performed steady-state and time-resolved photoluminescence quenching experiments in acetonitrile using photocatalyst **D** and potassium phenethyltrifluoroborate **2a**. The acridinium catalyst exhibited appreciable excited-state quenching (Figure 3d). The corresponding Stern-Volmer plot was linear, indicative of purely dynamic quenching. From the slope, a quenching rate constant of 9.6 ± 0.3 x10^9 $M^{-1}s^{-1}$ was determined for catalyst **D** (Figure 3b). These steady-state and time-resolved measurements show that photocatalyst **D** is efficiently quenched by trifluoroborate salts, with a quenching rate constant that is close to the solvent's diffusion limit. The magnitude of the quenching rate constant, coupled to the corresponding excited-state reduction potential (+2.10 V vs. SCE), point towards a quenching process involving electron transfer from organotrifluoroborates to the excited-state photocatalyst **D***.

To further substantiate the claim of excited-state electron transfer and determine the nature of the excited-state quenching process, we performed nanosecond transient absorption spectroscopy using photocatalyst **D** with phenethyltrifluoroborate **2a** in acetonitrile (Figure 3f). Pulsed 420 nm excitation led to changes in absorption that were unambiguously ascribed to the formation of monoreduced photocatalyst $\mathbf{D}^{-1}$, which occurred via excited-state electron transfer from the organotrifluoroborate to the excited photocatalyst. The spectral features observed for the photosensitizer were in line with those determined in the literature using other electron donors.[52-56] These nanosecond transient absorption experiments confirmed that visible light excitation leads to efficient electron transfer from the trifluoroborate salt to the photocatalyst excited state, **D***.

To establish a correlation between the photophysical measurements in acetonitrile and the photocatalytic conditions in dichloroethane, we undertook steady-state photolysis experiments in dichloroethane using photocatalyst **D** and potassium phenethyltrifluoroborate **2a** (Figure 3g). The spectrophotometric cuvette was irradiated for specific time intervals under stirring using blue LED. The stirring was then stopped, allowing for the undissolved organotrifluoroborate salt to sediment prior to UV-Visible absorption measurements. This irradiation led to the decrease of the absorption profile of catalyst **D** accompanied by an increase of novel absorption bands, attributed to the mono-reduced photosensitizer. A difference spectrum (Figure 3g, inset) shared similarities to the one obtained by nanosecond transient absorption spectroscopy in acetonitrile, confirming that electron transfer from the organotrifluoroborate to the excited photocatalyst **D** also occurred in dichloroethane.

Next, we conducted a series of control experiments to gain insight into the reaction intermediates involved in the key bond forming events (Figure 3h). The addition of TEMPO to the reaction mixture led to a significant decrease in product formation, supporting the existence of a free-radical intermediate. Furthermore, the addition of benzyl bromide to the reaction mixture resulted in the formation of benzyl sulfone **7** in 43% yield, suggesting a radical-polar crossover mechanism in which a key bond forming event proceeds through the anionic intermediate sulfinate **6a**. The reduction of the sulfonyl radical to the sulfinate anion has rarely been shown in a photocatalytic process due to facile degradation of the sulfonyl radical to the alkyl radical.

The collective interpretation of the steady-state and time-resolved experiments, coupled to the literature precedence and the control experiments with TEMPO and benzyl bromide, allow us to deduce the mechanism depicted in Figure 4. We propose that visible light excitation of photocatalyst **D** leads to excited-state electron transfer from the trifluoroborate salt **2** to the excited photocatalyst, which is corroborated by the growth of an absorbance signal at 525 nm corresponding to $\mathbf{D}^{-1}$. This electron transfer step corresponds to the oxidation of the organotrifluoroborate **2** to the alkyl radical **4**, which is then trapped by the sulfur dioxide source DABSO to form the alkyl sulfonyl radical **5**. Evidence for this step was obtained by photolysis experiments using acridinium photocatalysts (Figures S6-S9). Subsequent oxidation of the reduced acridinium species was shown to regenerate the ground-state catalyst. This oxidation has been reported in the literature to occur through a sulfur dioxide radical reduction to the sulfinate **6**.[57] Under our reaction conditions, we hypothesize that anion **6** is then trapped by the electrophilic fluorine source, generating the desired sulfonyl fluoride **1**.



b

PC	Absorption (nm, ($M^{-1}cm^{-1}$))[a]	E^*_{red} (V vs SCE)	E_{red} (V vs SCE)	PL(nm) [a]	τ (ns)[b]	k_q ($M^{-1}s^{-1}$)[b, c]
A	382 (8440)	+1.32	–1.37	471, 495	2300	n.d.[d]
B	382 (7760)	+1.21	–1.37	466, 495	2260	n.d.[d]
C	360 (34200), 428 (9760)	+2.06	–0.57	522	7.3	7.4×10^9
D	375 (60400), 421 (10600)	+2.10	–0.59	518	13.5	9.6×10^9
E	371 (32500), 437 (11802)	+2.15	–0.58	492, 517	7.2	8.7×10^9
F	368 (66500), 418 (47300)	+2.3	–0.35	465	5.1	1.4×10^{10} [e]

Figure 3. Mechanistic studies. (a) Absorption (solid) and photoluminescence (dashed) spectra of photocatalysts **A-F**. (b) Tabulated photophysical properties of all photocatalysts **A-F**. [a]In argon purged dichloroethane. [b]In argon purged acetonitrile. [c]With potassium phenethyltrifluoroborate **2a**. [d] Excited-state quenching was observed but the corresponding Stern-Volmer plot exhibited downward curvature, preventing determination of the quenching rate constant. [e]Static quenching was also observed, with Ks = 110 M^{-1}. (c) Electrochemical ladder representing the ground-state oxidation potential of **2a** as well as the excited-state reduction potentials of catalysts **A-F**. (d) Steady-state photoluminescence quenching experiments with catalyst **D** and trifluoroborate **2a**. (e) Time-resolved steady-state photoluminescence quenching experiments with catalyst **D** and trifluoroborate **2a**. (f) Nanosecond transient absorption spectroscopy with catalyst **D** recorded 50 ns after pulsed 420 nm excitation (10 mJ/pulse) with **2a** in acetonitrile at room temperature. (g) Absorption spectra of **D** recorded in dichloroethane in the presence of phenethyltrifluoroborate **2a** following irradiation with blue LED at t = 0 min (purple), 15 min (green), and 30 min (orange). Inset represents the difference spectra at t = 15 min (green) and 30 min (orange). (h) Control experiments to gain insight into reaction intermediates involved in the key bond forming events.

A question remains about the different yields obtained for photocatalysts **C-F** that should otherwise all be competent to photo-oxidize organotrifluoroborates **2**. Interestingly, only **D** was able to produce the desired sulfonyl fluorides in high yields. Even more surprising, the yield decreased as the driving force for organotrifluoroborate oxidation increased. Yields between 39% and 63% were obtained with catalysts **C-E**, with excited-state reduction potentials of + 2.06 V, + 2.10V and + 2.15 V vs SCE for **C**, **D** and **E**, respectively.[38, 48-50] Those yields dropped precipitously when the excited-state reduction potential was increased to +2.3V vs SCE (photocatalyst **F**). Note that excited-state electron transfer was also confirmed by transient absorption spectroscopy using photocatalyst **F** and **2a** (see Supporting Information). Based on the quenching rate constants that were all close to the solvent diffusion limit (10^9-10^{10} $M^{-1}s^{-1}$), an explanation based on Marcus inverted region can be ruled out.[58-61] The difference in product yields could originate from the second step involving the reduced photocatalyst. The **F**/**F**$^{-1}$ reduction potential of catalyst **F** is –0.35 V vs SCE, whereas the values for catalysts **C**, **D**, and **E** are all similar (–0.57, –0.59, and –0.58 V vs SCE). This efficiently creates a 220 to 240 mV increase in driving force for reduction of the sulfonyl radical to the sulfinate anion using acridinium catalysts **C-E** compared to triphenylpyrylium **F**, which could contribute to the changes in reaction yields. Given the similar PC/PC^{-1} redox potential for catalysts **C-E**, the difference in yields observed in the acridinium series could originate from stability issues of the various catalysts.[53] In particular, the viability of acridinium catalysts could be prolonged by using catalyst **D**, which exhibits increased stability against nucleophiles and radicals.[62] Hence, the increased yields may stem from a favorable driving force for thermal electron transfer to the sulfonyl radical coupled to the increased stability conferred by the *t*-Bu groups of catalyst **D**.

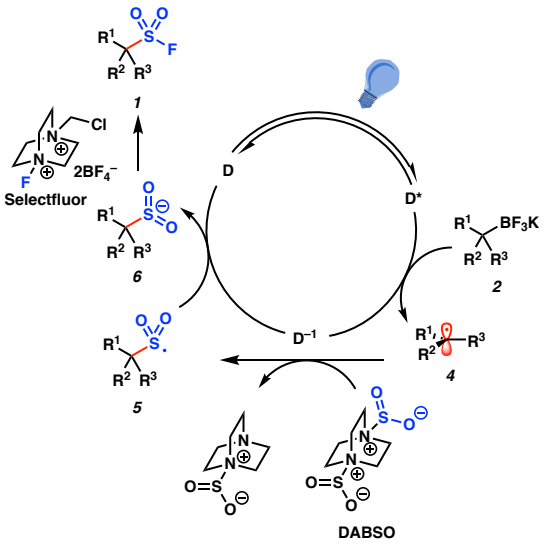


Figure 4. Proposed mechanism of photocatalytic sulfonyl fluorination of organotrifluoroborates.

CONCLUSION

In summary, we have developed a novel approach to convert alkyl organotrifluoroborates and BPin esters into the corresponding sulfonyl fluorides using acridinium organophotocatalysts. We provide experimental evidence for reductive electron transfer from the organotrifluoroborate to the excited acridinium and pyrylium catalysts. The reaction demonstrates broad functional group compatibility with sp^3-rich, functionalized organoborane substrates from the compound library at Merck & Co., Inc., Rahway, NJ, USA, which can be attributed to the mildness of activation with visible light. The versatilty of this method is highlighted by the synthesis of primary, secondary, and tertiary sulfonyl fluorides without the use of a transition metal. We anticipate this method will enable the late-stage conversion of organoboron substrates utilized in drug discovery projects into functionalized sulfonyl fluorides.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental details, characterization data, and spectral data (PDF).

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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.

Notes

The authors declare no competing financial interest.

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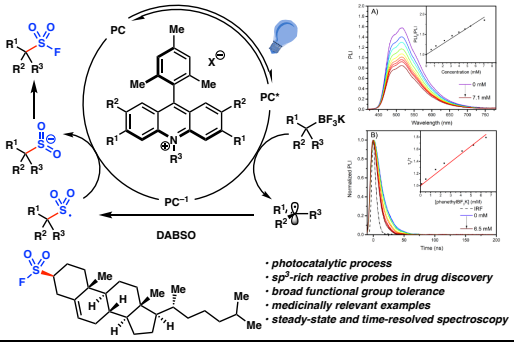

- *photocatalytic process*
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