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Metal-Free Visible-Light Synthesis of Arylsulfonyl Fluorides: Scope and Mechanism

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Abstract: The first metal-free procedure for the synthesis of arylsulfonyl fluorides is reported. Under organo-photoredox conditions, aryl diazonium salts react with a readily available SO_2 source (DABSO) to afford the desired product through simple nucleophilic fluorination. The reaction tolerates the presence of both electron-rich and -poor aryls and demonstrated a broad functional group tolerance. To shed the light on the reaction mechanism, several experimental techniques were combined, including fluorescence, NMR, and EPR spectroscopy as well as DFT calculations.

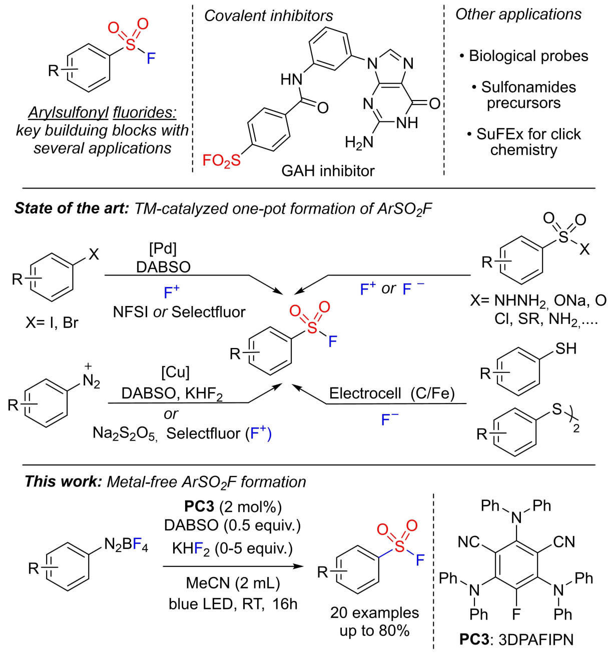

Figure 1. Introduction to arylsulfonyl fluorides.

Arylsulfonyl fluorides ($ArSO_2F$) are ubiquitous building blocks that find a plethora of applications in life science technologies.[1] In particular, $ArSO_2F$ are routinely used as covalent protein inhibitors and biological probes.[2] In comparison to other arylsulfonyl halides, $ArSO_2F$ present numerous advantages such as their high resistance towards reduction and high thermodynamic stability towards nucleophilic substitutions including hydrolysis. In addition, arylsulfonyl fluorides are substrate of choice for fluoride exchange (SuFEx) for click chemistry leading to a variety of aryl sulfones derivatives.[3] In spite of the general interest of $ArSO_2F$, their direct synthesis is scarcely reported in the literature. Regarding the state of the art, the most often used methods rely on halogen exchange starting from the unstable arenesulfonyl chloride. Other indirect methods have been also disclosed in the literature (Figure 1),[4] yet the direct construction of carbon-SO_2F constitute a highly attractive option. Within this framework, the group of Bagley, Willis and co-workers reported a one-pot two-step procedure for the synthesis of $ArSO_2F$ starting from (heteroaryl)aryl iodides or bromides in conjunction with commercially available and easy to handle 1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide) adduct (DABSO)[5] for the *in situ* generation of sulfinate under palladium catalysis, followed by an addition of *N*-fluorobenzenesulfonimide (NFSI) as an electrophilic fluorine source.[6] The same approach was also extended to alkenyl triflates.[7] A similar strategy was disclosed by the group of Ball where Selectfluor was used as an electrophilic fluorine source.[8] Finally, the group of Liu and Chen recently reported a copper catalysed approach to forge *in situ* aryl sulfonyl chloride starting with arene diazonium salt and DABSO followed by the use of an external fluoride source to obtain the desired product.[9] It should be mentioned that a copper free procedure has been also developed using $Na_2S_2O_5$ in the presence of electrophilic fluorine source (Selectfluor) at 70 °C (Figure 1).[4c] In spite of those recent successes, the development of metal free, mild and straightforward procedures towards C-SO_2F bond formation remain highly desirable especially from a late-stage functionalisation perspective. In this context, organo-photoredox catalysis constitutes an attractive option as it will leverage the orthogonality of transition metal catalysis through SET processes.[10]

With our continuous interest for the development of new organo-photoredox processes we report herein an unprecedent

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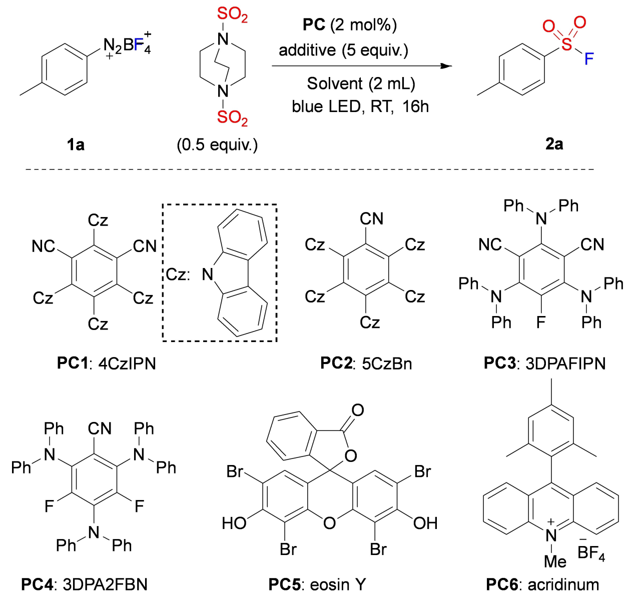
strategy for the direct access to arylsulfonyl fluorides under metal-free visible-light conditions.[11]

The optimisation started with 4-methylphenyldiazonium salts **1 a** as a model substrate in the presence of 1 equivalent of DABSO, 4CzIPN (**PC1**) as an organo-photocatalyst in MeCN under blue LED irradiation at room temperature for 16 h. Conversion of reagent **1 a** to the desired product **2 a** was observed albeit in a low yield of 10 % (Table 1, entry 1). Encouraged by this first result we decided to investigate the impact of the solvent and photocatalyst on the reaction outcome. Using **PC1**, only traces of the desired product were observed in butyl acetate (5 %, Table 1 entry 2). Screening other solvents including DMSO, toluene, MeOH as well as Et_2O turned out to be deleterious to the reaction outcome (Table 1, entries 3–6).

Changing the organo-photocatalyst to other cyanoarenes organo-photocatalyst (**PC3** and **PC4**, Table 1, entries 7–8) was beneficial in improving the yield up to 60 %. Eosin Y (**PC5**, Table 1, entry 9) as well as Fukuzumi catalyst (**PC6**, Table 1, entry 9) were not effective under our conditions providing yields that did not exceed 10 %. To further enhance the reaction outcome, the impact of additives was studied. When using KHF_2 (5 equiv.) the desired product was obtained in 70 % yield (Table 1, entry 11). Other fluoride sources such as $LiBF_4$ and $NaPF_6$ were tested but only provided marginal yields (Table 1, entries 12 and 13). It is important to note that no product formation was observed either without blue LED irradiation or in the absence of the photocatalyst (Table 1, entries 14–16).

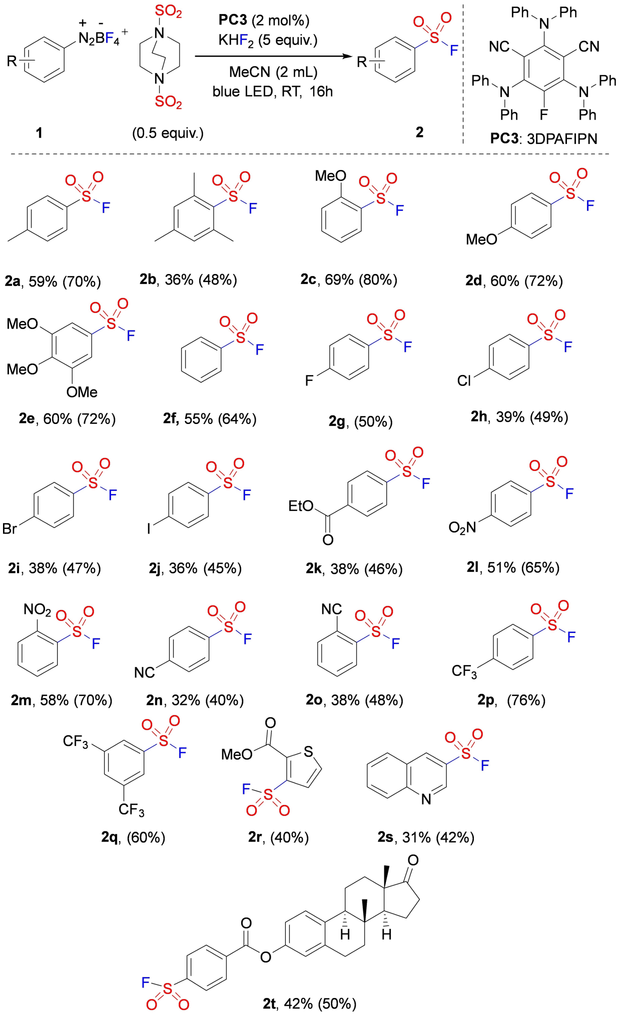
With the optimised conditions in hand, we turned our focus to studying the scope of the reaction (Scheme 1). Initial investigations were carried out with arene substituted with electron donating groups. Herein, good to excellent yields were

Table 1. Reaction optimisation.[a]



	PC	Solvent	Additive	Yield [%][b]
1	PC1	MeCN	–	10
2	PC1	butyl acetate	–	5
3	PC1	DMSO	–	0
4	PC1	PhMe	–	0
5	PC1	MeOH	–	0
6	PC1	Et_2O	–	0
7	PC3	MeCN	–	60
8	PC4	MeCN	–	60
9[c]	PC5	MeCN	–	5
10	PC6	MeCN	–	10
11	**PC3**	**MeCN**	**KHF_2**	**70**
12	PC3	MeCN	$LiBF_4$	10
13	PC3	MeCN	$NaPF_6$	< 5
14[d]	PC3	MeCN	KHF_2	0
15[d]	–	MeCN	KHF_2	0
16	–	MeCN	KHF_2	0

[a] Reactions were performed with diazonium salt **1** (0.3 mmol, 1 equiv.), DABSO (0.15 mmol, 1 equiv.), (1.5 mmol, 5 equiv.), PC (2 mol%) and MeCN (2 mL), unless otherwise noted. The reaction mixture was stirred at room temperature for 16 h under blue LED irradiation and inert conditions. [b] Yields determined by ^{19}F NMR spectroscopy with $PhCF_3$ as internal standard. [c] Under green LED irradiation. [d] Without light irradiation.



Scheme 1. Reaction scope. Reactions were performed with diazonium salt **1** (0.3 mmol, 1 equiv.), DABSO (0.15 mmol, 1 equiv.), KHF_2 (1.5 mmol, 5 equiv.), **PC3** (2 mol%) and MeCN (2 mL). The reaction mixture was stirred at room temperature for 16 h under blue LED irradiation and inert conditions. Yields shown are those of isolated products; yields determined by ^{19}F NMR spectroscopy with $PhCF_3$ as internal standard are shown in parentheses.

obtained in the presence of methyl or methoxy groups (**2a**–**e**). Interestingly steric hindrance was not deleterious to the reaction outcome, since up to 80% yield were reached for ortho substituted methoxyphenyl (**2c**). Furthermore, we investigated the presence of halogen substituents on the arene ring. Taking advantage of the metal-free catalytic procedures depicted herein, we demonstrated that fluoro-, chloro-, bromo- and iodoarenes could be converted to the desired sulfonyl fluoride derivatives with synthetically useful yields (**2g**–**j**). Afterwards, we decided to expand the reaction scope to electron poor substituted arenes starting material. In particular, we demonstrated that our reaction conditions tolerate the presence of several electron withdrawing groups including, ester, trifluoromethyl, cyano as well as nitro motifs. Herein also, ortho, meta or para position were smoothly converted to the corresponding products (**2k**–**q**). Interestingly, heterocyclic compounds could also be converted to their corresponding sulfonyl fluorides in moderate yields (**2r**–**s**). Finally, we demonstrated that our protocol could be extended to complex molecular architecture and compound **2t** was obtained in a good yield of 50% demonstrating the potential application for late-stage transformation.

Having illustrated the broad scope and the high functional group tolerance of the developed metal-free procedure we started investigating the reaction mechanism. Fluorescence studies, EPR spectroscopy as well as DFT calculations were combined to understand the role of the photocatalyst, and its efficiency was assessed by measuring of the photoconversion quantum efficiency. Assuming a photoinduced single electron transfer (P-SET) as the initial stage of the reaction sequence, the hypothetical catalytic cycle may either start by oxidation of DABSO (or in situ generated DABCO) or by reduction of the diazonium salt. In order to evaluate the occurrence of (potentially concurrent) electron transfers between the photocatalyst and the different species, and to quantify the associated kinetics, **PC3** was involved in successive Stern-Volmer experiments with the diazonium salt **1a**, DABSO and DABCO (Figure 2, I). In agreement with the facile reduction of diazonium salt, it turns out that the luminescence of the exited photocatalyst is efficiently quenched in his presence, with a Stern-Volmer constant $K_{SV}=256\ M^{-1}$. We also confirmed efficient quenching of the luminescence of the exited photocatalyst in the presence of DABCO ($K_{SV}=229\ M^{-1}$), but also to a slightly lesser extent with DABSO ($K_{SV}=164\ M^{-1}$). With a measured luminescence lifetime $\tau_f=4.2$ ns for **PC3**, it was possible to derive for the later a quenching rate coefficient k_q of 6.1×10^{10}, 5.45×10^{10} and $3.9\times10^{10}\ M^{-1}s^{-1}$ with **1a**, DABCO and DABSO, respectively. These three values appear in quantitative agreement with the hypothesis of a dynamic, diffusion limited quenching process, and suggest that multiple SET pathways may occur in solution.

It is however important to underline that, while quantitatively similar for DABCO and DABSO, the SET process results in a markedly different evolution of the system. Thus, while **PC3** remains relatively photostable for moderate irradiation times (ca. 10 min) in the presence of DABCO and DABSO, fast photobleaching occurs in the presence of **1a** with a kinetic rate that correlates well with the amount of added diazonium salt (Figure 2, b). This is indicative of the formation of a reactive radical intermediate which, in the condition used in our spectroscopic measurements, evolves by addition onto **PC3** and ultimately clearance of the later. Such a behaviour agrees well with the expected characteristics of a tolyl radical.

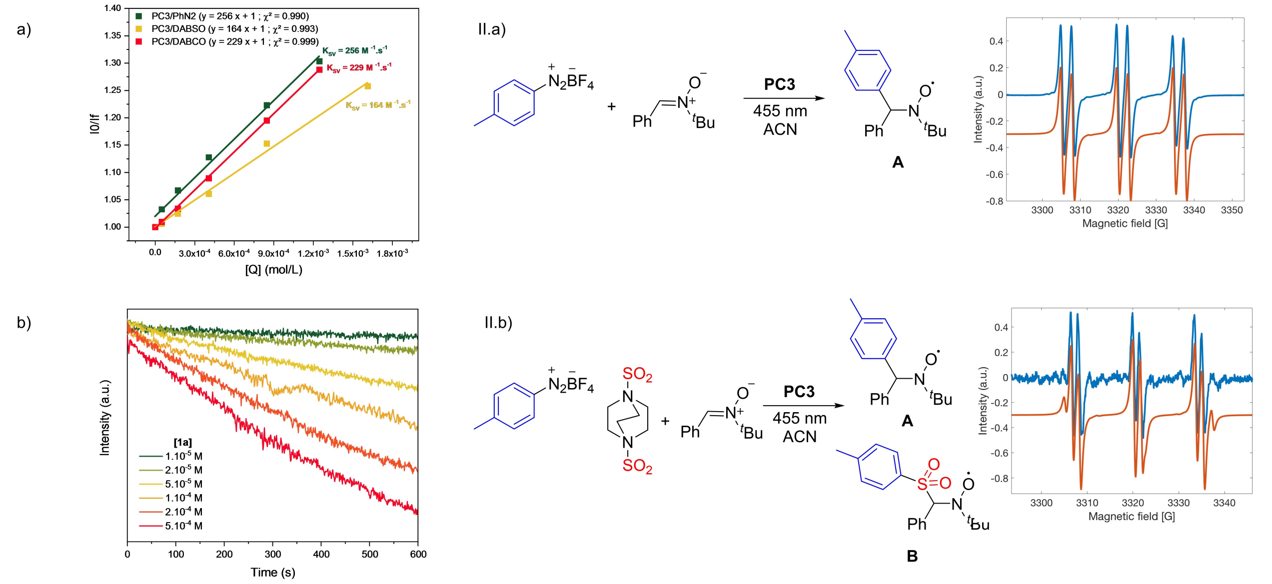
To further investigate the nature of the formed radical in the reaction media we decided to undertake EPR experiments under visible light irradiation (Figure 2, II). Attempts to perform such experiments with mixtures either devoid of **PC3** or [PhN_2] led to complex signatures with overall low intensities, suggesting dead-end mechanisms. For the sake of clarity, description of these spectra will not be discussed in the manuscript but is nevertheless available in SI. Irradiation of a mixture of **PC3** with diazonium salt **1a** with blue LED ($\lambda=455$ nm) in the presence of α-phenyl-*N*-*tert*-butylnitrone (PBN) as radical trap results in the clean formation of a single spin adduct **A** with a signature typical of a C-centred tolyl radical ($g=2.006$, $a_N=14.8$ G and $a_H=2.8$ G, Figure 2, II, top),[12] as already observed in some of our previous works.[11]

When mixing **PC3**, DABSO and diazonium salt **1a**, in the presence of PBN, the obtained signature comprises, in addition to a signal obtained in the previous irradiation experiment with **PC3** and **1a** only and attributed to a tolyl adduct ($g=2.006$, $a_N=14.8$ G and $a_H=2.5$ G), a secondary signal radical which characteristic values ($g=2.006$, $a_N=13.6$ G and $a_H=1.6$ G) are compatible with a O-centred radical species,[13] presumably on a tosyl radical. Complementary experiments using DMPO as a radical trap reveal, besides the presence of the abovementioned tolyl ($g=2.006$, $a_N=14.5$ G and $a_H=21.4$ G) and O-centred tosyl **B** ($g=2.006$, $a_N=12.8$ G and $a_H=13.8$ G) radical adducts a third species compatible with a S-centred tosyl adduct ($g=2.006$, $a_N=13.9$ G and $a_H=15.0$ G).[14] In the experiment with PBN, the latter may overlap with that of the tolyl adduct. Note that the formation of the tolyl radical was also observed by mixing DABSO and **1a** in the absence of photocatalyst (see the Supporting Information for the complete description of these experiments and associated DFT calculations). This radical is formed due to SET between *in situ* generated DABCO and the diazonium. However, under these conditions no tosyl radical species could be detected and the formation of the tolyl radical do not lead to the product.

Afterwards, the photochemical quantum yield of the reaction was investigated (Figure S2). In this study, reactant **1g** was preferred to **1a**, in order to facilitate monitoring of the reaction through ^{19}F NMR. In the optimised concentration conditions (entry 7 in Table 1), following our previously reported NMR actinometric protocol[15] (depicted in full in the Supporting Information) and monitoring the real-time disappearance of **1g**, we were able to determine a photoconversion quantum yield of the diazonium reactant $\Phi=0.43$; this indicated a stepwise mechanism. Interestingly, while the disappearance of **1g** could be nicely fitted with a first order kinetic model, a typical sigmoidal curve, with an induction period of about 10 minutes was observed for the appearance of **2g**, characteristic of a mechanism operating by successive reactions. Note also that similar experiment performed in the absence of DABSO but otherwise identical concentration

I) Luminiscence studies

II) EPR spectroscopy



III) DFT calculation

IV) Proposed Mechanism

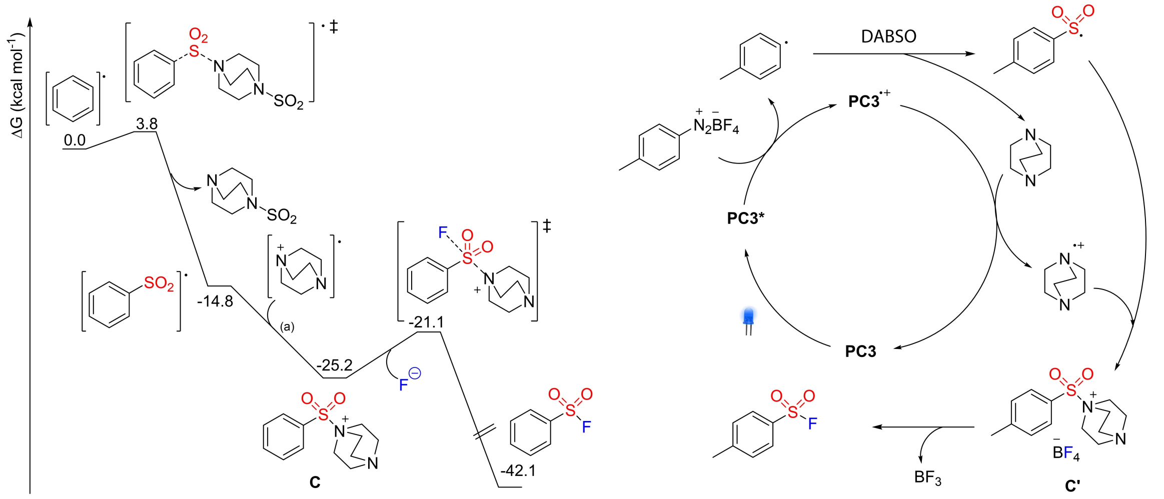


Figure 2. Mechanistic investigation: I) luminescence studies: a) Stern Volmer plots of luminescence evolution of **PC3** upon incremental addition of **1 a** (green), DABCO (red) and DABSO (orange); b) real<-time monitoring of **PC3** photobleaching in the presence of various amounts of **1 a**. II) EPR spectroscopy: EPR spin-trapping spectra upon irradiation ($\lambda = 455$ nm) in the presence of BPN in MeCN at room temperature. Blue = experimental, red = simulated. III) DFT calculation: Free energy [kcal mol^{-1}] pathway for the reaction of a photogenerated phenyl radical with DABSO calculated at the DFT level. a) Barrierless process in electronic energy, see energy scan in the Supporting Information. IV) Proposed mechanism.

conditions resulted in rapid photodegradation of the catalyst and therefore premature stalling of photoinduced disappearance of **1 g**, in line with spectrofluorimetric experiments.

In order to gain more insight on the reaction mechanism, DFT calculations were undertaken (Figure 2, III). Reaction of $Ph^{\cdot}$ with DABSO to yield $PhSO_2^{\cdot}$ and DABCO is favoured (-14.8 kcal mol^{-1}, Figure 2, III). Given the nature of the stepwise mechanism, the generated DABCO may reduce **PC3**$^{\cdot+}$ formed upon reduction of the diazonium salt to regenerate the photocatalyst **PC3** and DABCO$^{\cdot+}$. The latter may combine with $PhSO_2^{\cdot}$ to generate the sulfonium salt intermediate **C** (Figure 2, III, $\Delta G = -10.4$ kcal mol^{-1}).[16] Subsequent nucleophilic substitution of DABCO by fluorine anion on the salt is easily accessible and yield the final product $PhSO_2F$.

In light of the obtained results, we propose the following mechanism. Photoinduced reduction of the diazonium salt occurs through SET from the excited **PC3**, yielding arene radical and radical cation photocatalyst (**PC3**$^{\bullet+}$). Subsequently the aryl radical collapses with SO_2 to form a new radical tosyl species. The released DABCO is able to regenerate the photocatalyst **PC3** in its ground state and DABCO$^{\bullet+}$. This latter may combine with $PhSO_2^{\bullet}$ to generate the sulfonium salt intermediate **C′**. Afterwards, a nucleophilic fluorine attack is taking place to form the desired arylsulfonyl fluoride and regenerate DABCO (Figure 2, IV).

In summary, the first metal-free visible-light-induced protocol for the synthesis of arylsulfonyl fluorides is described. The key to success was the combination of aryl diazonium salts, DABSO and the cyanoarene **PC3** under blue LED irradiation. The mild conditions afforded a broad scope and high functional group tolerance. Furthermore, mechanistic investigations were performed including luminescence, EPR spectroscopy, ^{19}F NMR spectroscopy as well as DFT calculations. Together, those studies allowed us to identify several key intermediates, based on which we propose a plausible mechanism for the reaction. Further investigations exploiting the use of cyanoarenes as photocatalysts are under investigation in our laboratory for the selective formation of new radical as well as the synthesis of valuable building blocks.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: arylsulfonyl fluorides · fluorine · mechanistic investigations · metal-free synthesis · organo-photoredox

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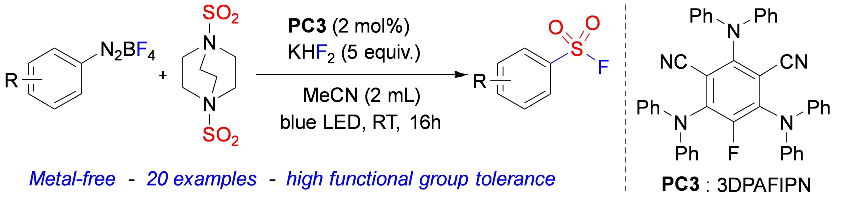

The key to success in the new metal-free visible-light-mediated synthesis of arylsulfonyl fluorides was using cyanoarene **PC3** as organo-photocatalyst. A variety of arene diazonium slats were smoothly converted to the corresponding product. Mechanistic investigations including luminescence, EPR spectroscopy as well as DFT calculation allowed us to identify several key intermediates and propose a plausible mechanism.