

# A Readily Available Trifluoromethylation Reagent and Its Difunctionalization of Alkenes

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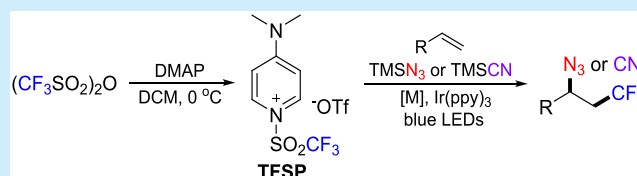


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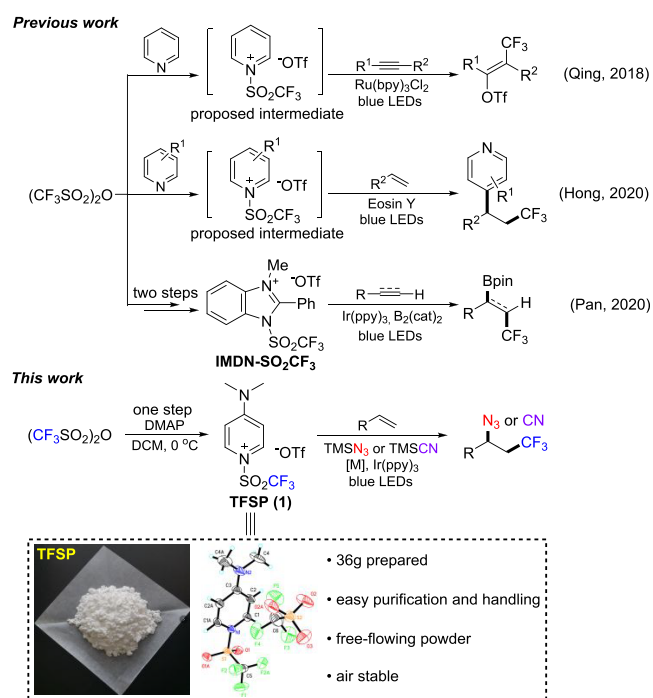
**ABSTRACT:** Trifluoromethyl substitution is notably popular in pharmaceuticals and agrochemicals; however, trifluoromethylated compounds normally rely on the use of cost-prohibitive or gaseous trifluoromethylating reagents, which diminishes the general applicability of these methods. Herein an efficient trifluoromethylation reagent trifluoromethylsulfonyl–pyridinium salt (TFSP) was reported, which can be readily prepared from cheap and easily available bulk industrial feedstocks. TFSP can generate a trifluoromethyl radical under photocatalysis and realize the effective azido- or cyano-trifluoromethylation reactions of alkenes.



The trifluoromethyl group ( $\text{CF}_3$ ) has found widespread application in pharmaceutical chemistry and agrochemistry owing to its strong electron-withdrawing nature, high lipophilicity, and metabolic stability.<sup>1</sup> During the past several decades, many  $\text{CF}_3$ -containing pharmaceuticals and agrochemicals, such as Prevacid, Prozac, fluzanim, and norflurazone, have been developed. So far, many trifluoromethylation reagents and methods have been developed to introduce a  $\text{CF}_3$  group into organic molecules.<sup>2</sup> From the perspective of industrial application, it will be of great practical value if the trifluoromethylation is directly achieved from cheap industrial materials such as trifluoroacetic anhydride,<sup>3</sup> trifluoroacetic acid,<sup>4</sup> trifluoromethanesulfonic anhydride,<sup>5</sup> and so on. Trifluoromethanesulfonic anhydride ( $\text{Tf}_2\text{O}$ ) is usually used in the synthesis of trifluoromethanesulfonate to improve the leaving ability of the hydroxyl group.<sup>6</sup> In 2018, Qing's group first reported that the combination of  $\text{Tf}_2\text{O}$  and pyridine could release a trifluoromethyl radical under the photoredox conditions, thus realizing an elegant trifluoromethylation and triflation of alkynes (Scheme 1).<sup>5b</sup> Then, Hong's group disclosed an efficient visible-light-enabled site-selective trifluoromethylative pyridylation of unactivated alkenes with pyridines and  $\text{Tf}_2\text{O}$ .<sup>5d</sup> Both Qing and Hong proposed that the reaction may proceed through a trifluoromethylsulfonyl–pyridinium salt intermediate. Perhaps because of the instability of this intermediate, they did not isolate and characterize it. Considering the volatility, hygroscopicity, and corrosiveness of  $\text{Tf}_2\text{O}$ , Pan's group transformed  $\text{Tf}_2\text{O}$  into trifluoromethylsulfonyl–benzimidazolium (IMDN– $\text{SO}_2\text{CF}_3$ ) through a two-step synthesis and realized an efficient trifluoromethylation–boration of inert olefins and alkynes.<sup>5c</sup>

From literature reports<sup>7</sup> and our preliminary experiments, we found that  $\text{Tf}_2\text{O}$  could easily react with 4-(dimethylamino)pyridine (DMAP) to give the trifluoromethylsulfonyl–pyridinium salt (TFSP) as a white solid, which is air stable.

## Scheme 1. Trifluoromethylation Derived from $(\text{CF}_3\text{SO}_2)_2\text{O}$ <sup>a</sup>




<sup>a</sup>Molecular structure of TFSP with thermal ellipsoids at the 30% probability level.

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**Table 1. Optimization of Photocatalyzed Azido-trifluoromethylation of Styrene<sup>a</sup>**


entry	photocatalyst	additive	yield (%) <sup>b</sup>
1	Ir(ppy) <sub>3</sub>		35
2	Ir(dtbbpy)(ppy) <sub>2</sub> PF <sub>6</sub>		16
3	Ru(bpy) <sub>3</sub> Cl <sub>2</sub>		8
4	Ru(phen) <sub>3</sub> (PF <sub>6</sub> ) <sub>2</sub>		9
5	eosin Y		ND
6	fluorescein		ND
7	Ir(ppy) <sub>3</sub>	AgOTf	11
8	Ir(ppy) <sub>3</sub>	CuCl	19
9	Ir(ppy) <sub>3</sub>	CuCl <sub>2</sub>	10
10	Ir(ppy) <sub>3</sub>	Fe	49
11	Ir(ppy) <sub>3</sub>	FeCl <sub>2</sub>	57
12	Ir(ppy) <sub>3</sub>	Fe(OTf) <sub>2</sub>	40
13 <sup>c</sup>	Ir(ppy) <sub>3</sub>	FeCl <sub>2</sub>	59
14 <sup>c,d</sup>	Ir(ppy) <sub>3</sub>	FeCl <sub>2</sub>	62
15 <sup>c,d,e</sup>	Ir(ppy) <sub>3</sub>	FeCl <sub>2</sub>	82
16 <sup>d,e</sup>	Ir(ppy) <sub>3</sub>		20
17 <sup>c,d,e</sup>		FeCl <sub>2</sub>	ND
18 <sup>c,d,f</sup>	Ir(ppy) <sub>3</sub>	FeCl <sub>2</sub>	ND

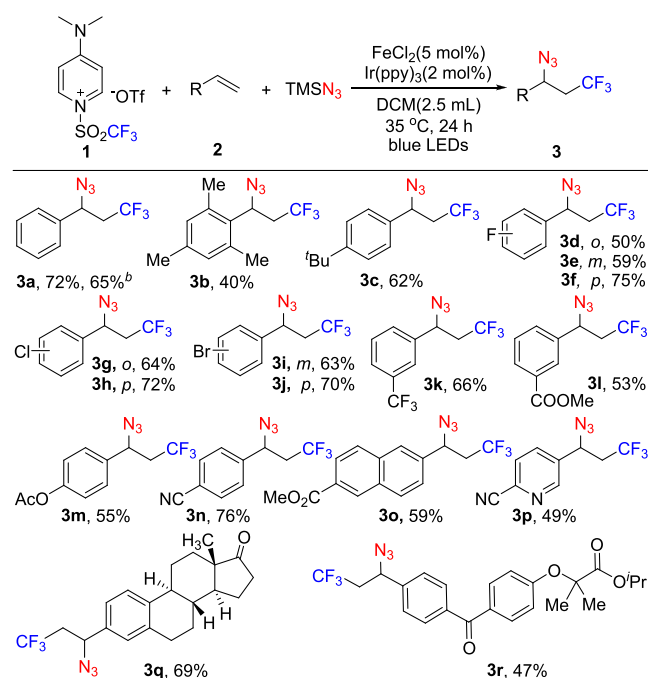
<sup>a</sup>Reaction conditions: Substrate **2a** (0.2 mmol), **1** (2 equiv), TMSN<sub>3</sub> (2 equiv), photocatalyst (1 mol %), and additive (10 mol %) in DCM (2 mL) were irradiated under 11.5 W of blue LEDs at r.t. under a N<sub>2</sub> atmosphere for 24 h. <sup>b</sup>Yields were determined by <sup>19</sup>F NMR spectroscopy with PhOCF<sub>3</sub> as the internal standard. <sup>c</sup>Additive (5 mol %). <sup>d</sup>DCM (1 mL). <sup>e</sup>35 °C. <sup>f</sup>Without blue LEDs. ND = not detected.

Surprisingly, no one has ever explored the possibility of TFSP as a trifluoromethylation reagent. Because of our interest in fluorine-containing organic salts,<sup>8</sup> we investigated the reactivity of TFSP and developed a visible-light-induced azido- or cyano-trifluoromethylation of olefins. Compared with previous studies on the trifluoromethylative difunctionalization of alkenes promoted by visible light,<sup>9–13</sup> this protocol is quite attractive due to the easy accessibility of TFSP.

At the beginning, we carefully investigated the synthesis of trifluoromethylsulfonate-pyridinium salt. We thought that the stability of pyridinium salt may be improved by changing the electron cloud density of the pyridine nucleus. Therefore, pyridines with electron-donating substituents or conjugated groups were subjected to the reaction with Tf<sub>2</sub>O. It was found that the expected product could be detected by <sup>19</sup>F NMR after the reaction of 4-methoxy- or 4-phenyl-pyridine with Tf<sub>2</sub>O. However, the crude products were hydrolyzed immediately when they were filtered in the air. So the pure trifluoromethylsulfonate-pyridinium salt could not be obtained. Only the reaction of DMAP with Tf<sub>2</sub>O could efficiently give the bench-stable product, TFSP, which could be purified simply by filtration and washing with CH<sub>2</sub>Cl<sub>2</sub> (Scheme 1). The reaction could be easily scaled up to 100 mmol (36.4 g), and the yield remained at 90%. No decomposition was observed after keeping TFSP in the refrigerator for 4 months. Thermogravimetric analysis (TGA) showed that TFSP began to decompose at its melting point, 188–191 °C.

Our previous work showed that the difluoromethylphosphonium salt (Ph<sub>3</sub>P<sup>+</sup>CF<sub>2</sub>H X<sup>-</sup>) is easy to reduce by photocatalysis to realize the difunctionalization of olefins.<sup>14</sup> The redox potential of TFSP (*E*<sub>p,red</sub> = -0.830 V vs SCE; see the SI) measured by cyclic voltammetry showed that it may have similar photoredox properties as Ph<sub>3</sub>P<sup>+</sup>CF<sub>2</sub>H X<sup>-</sup>. Then, we investigated the photocatalyzed azido-trifluoromethylation of TFSP with alkenes. Among the photocatalysts tested, Ir(ppy)<sub>3</sub> showed the best catalytic activity (Table 1, entries 1–6). Under the catalysis of Ir(ppy)<sub>3</sub>, various metal salts were extensively examined, and FeCl<sub>2</sub> was found to be the most appropriate additive (entries 7–12). Lowering the amount of FeCl<sub>2</sub> to 5 mol % can slightly increase the yield (entry 13). The reaction was further optimized by increasing the concentration and temperature (entries 14 and 15). The control experiments revealed that Ir(ppy)<sub>3</sub> and blue light-emitting diodes (LEDs) were essential for the reaction, whereas FeCl<sub>2</sub> was not (entries 16–18).

Under the optimal reaction conditions, we investigated the substrate scope of the photocatalyzed azido-trifluoromethylation (Scheme 2). The reaction is compatible with various

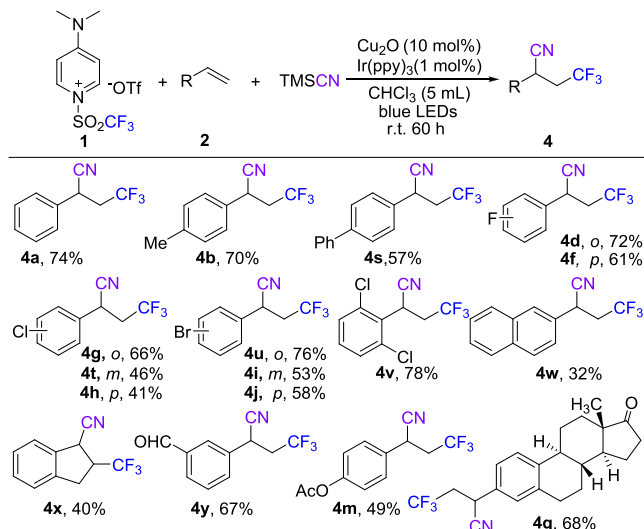
**Scheme 2. Substrate Scope of the Azido-trifluoromethylation<sup>a</sup>**

<sup>a</sup>Yields of isolated products are shown. Reaction conditions: Substrate **2** (0.5 mmol), **1** (1.0 mmol), TMSN<sub>3</sub> (1.0 mmol), Ir(ppy)<sub>3</sub> (1 mol %), and FeCl<sub>2</sub> (5 mol %) in DCM (2.5 mL) were irradiated with blue LEDs at 35 °C under a N<sub>2</sub> atmosphere for 24 h. <sup>b</sup>65% yield was obtained for a 1 mmol-scale reaction (1 mmol of **2a**).

styrenes bearing electron-donating or -withdrawing substituents in the ortho, meta, or para position, giving the corresponding products in good to moderate yields (**3a–3r**). A series of functional groups, such as alkyl (-CH<sub>3</sub>, -<sup>t</sup>Bu), halogen (-F, -Cl, -Br), nitrile, ester, and trifluoromethyl, were tolerated (**3a–3n**). The reaction also works for the alkenes with a fused or heterocyclic ring (**3o**, **3p**), and it can be applied for the late-stage functionalization of biologically relevant molecules such as estrone and fenofibrate (**3q**, **3r**).

The reaction was optimized by using trimethylsilyl cyanide (TMSCN) as the cyano source. (See the SI.) Under the optimal reaction conditions, the reaction proceeded smoothly and showed a wide substrate scope (Scheme 3). Alkenes with a

**Scheme 3. Substrate Scope of the Cyano-trifluoromethylation<sup>a</sup>**



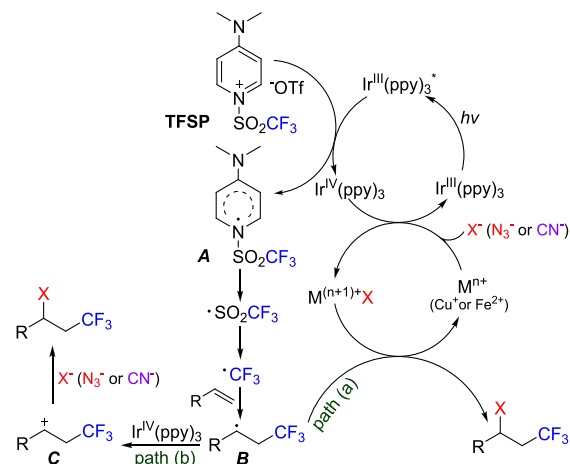
<sup>a</sup>Yields of isolated products are shown. Reaction conditions: Substrate 2 (0.5 mmol), 1 (0.75 mmol), TMSCN (1.0 mmol), Ir(ppy)<sub>3</sub> (1 mol %), and Cu<sub>2</sub>O (10 mol %) in CHCl<sub>3</sub> (5.0 mL) were irradiated with blue LEDs at room temperature under a N<sub>2</sub> atmosphere for 60 h.

–CHO (4y) or –OAc (4m) group can also tolerate the reaction conditions. It should be noted that the reaction worked for internal alkene (4x). In the case of estrone derivative (4q), it can also give the desired product in moderate yield.

Taking the azido-trifluoromethylation as an example, the reaction mechanism was explored. The fluorescence quenching experiment showed that TFSP was the main species to quench the excited photocatalyst, Ir(ppy)<sub>3</sub><sup>\*</sup>. The cyclic voltammetry studies (see the SI for experimental details) further proved that TFSP ( $E_p^{\text{red}} = -0.830$  V vs SCE; see the SI) could be readily reduced by the photoexcited complex [Ir(ppy)<sub>3</sub><sup>\*</sup>] ( $E_{1/2}^{\text{red}}[\text{Ir}^{\text{IV}}/\text{Ir}^{\text{III}*}] = -1.73$  V vs SCE). The existence of oxygen almost completely inhibited the reaction (Table S2). Other radical scavengers such as 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) and 2,6-di-*tert*-butyl-4-methylphenol (butylated hydroxytoluene (BHT)) could dramatically decrease the yield, and a TEMPO adduct, TEMPO–CF<sub>3</sub>, was detected in 10% yield (determined by <sup>19</sup>F NMR spectroscopy), indicating the generation of a trifluoromethyl radical (Table S2).

On the basis of the above experimental evidence, a plausible reaction mechanism was proposed as follows (Scheme 4). After absorbing the blue light, the photocatalyst (Ir(ppy)<sub>3</sub>) transits to its excited state, Ir(ppy)<sub>3</sub><sup>\*</sup>, which then undergoes a single-electron transfer (SET) to the pyridinium salt TFSP to give the intermediate A. Its homolysis delivers DMAP and the CF<sub>3</sub>SO<sub>2</sub>· radical, which further gives the CF<sub>3</sub>· radical after the extrusion of SO<sub>2</sub>. The capture of the CF<sub>3</sub>· radical by an alkene substrate forms the radical intermediate B. Then, there are two possible pathways to produce the final product. In path (a), the Ir<sup>IV</sup> complex oxidizes Fe<sup>II</sup> ( $E_{1/2}^{\text{ox}}[\text{Fe}^{\text{III}}/\text{Fe}^{\text{II}}] = +0.155$  V vs SCE; see the SI) or Cu<sup>I</sup> ( $E_{1/2}^{\text{ox}}[\text{Cu}^{\text{II}}/\text{Cu}^{\text{I}}] = +0.71$  V vs SCE)

**Scheme 4. Proposed Reaction Mechanism**



to give the corresponding higher valency metal cation. Its subsequent reaction with intermediate B affords the final product and regenerates the low-valency metal. In path (b), the radical intermediate B is directly oxidized by the Ir<sup>IV</sup> complex to form the cation intermediate C. Then, the nucleophilic attack of N<sub>3</sub><sup>−</sup> or CN<sup>−</sup> on the cation gives the final product.

Control experiments were performed to find out the path through which the reaction proceeded. Under the optimal conditions without FeCl<sub>2</sub>, the azido-trifluoromethylation gives only 20% of the desired products and 40% of the olefin byproduct (Scheme 5). This demonstrates that FeCl<sub>2</sub> is not

**Scheme 5. Experimental Evidence<sup>a</sup>**



<sup>a</sup>Yield was determined by <sup>19</sup>F NMR spectroscopy.

essential for the formation of the desired product, but it does play an important role. Therefore, the reaction may proceed mainly through path (a) (Scheme 5). Nevertheless, path (b) may also exist in the reaction process.

In summary, we developed the trifluoromethylsulfonylpyridinium salt (TFSP) into an efficient trifluoromethylation reagent that can be readily prepared from cheap and easily available bulk industrial materials. This solid reagent is thermodynamically stable and easy to prepare on the large scale. It is much more convenient than using volatile, hygroscopic, and corrosive trifluoromethanesulfonic anhydride. TFSP was found to be an effective trifluoromethyl radical source for azido- or cyano-trifluoromethylation reaction of alkenes. Further investigations on the reactivity of TFSP are currently under way.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.1c02146>.

Materials and methods, experimental procedures, useful information, optimization studies, <sup>1</sup>H NMR spectra, <sup>13</sup>C NMR spectra, and MS data (PDF)

### Accession Codes

CCDC 2061716 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif), or by emailing [data\\_request@ccdc.cam.ac.uk](mailto:data_request@ccdc.cam.ac.uk), or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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#### Notes

The authors declare no competing financial interest.

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