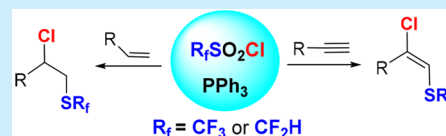


## Fluoroalkylsulfonyl Chlorides Promoted Vicinal Chloro-fluoroalkylthiolation of Alkenes and Alkynes

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## Supporting Information

**ABSTRACT:** The unprecedented use of  $\text{CF}_3\text{SO}_2\text{Cl}$  for direct bifunctional chloro-trifluoromethylthiolation of alkenes and alkynes is reported.  $\text{CF}_3\text{SO}_2\text{Cl}$ , which is generated by the reduction of  $\text{PPh}_3$ , undergoes electrophilic addition and then chlorination to give the bifunctionalized products without using an additional chlorine source. The method is also applicable for chloro-difluoromethylthiolation using  $\text{CF}_2\text{HSO}_2\text{Cl}$ .



A highly lipophilic trifluoromethylthio ( $\text{CF}_3\text{S}$ ) group has the capability to improve the pharmacokinetic and physicochemical properties of medicinal and agrochemical molecules.<sup>1,2</sup> It can be found in drug compounds, such as Fipronil,<sup>3</sup> Tiflorex,<sup>4</sup> Toltrazuril,<sup>5</sup> and Cefazafur.<sup>6</sup> Direct introduction of the  $\text{SCF}_3$  group is a good strategy for late-stage modification of biologically interested molecules.<sup>7</sup> Highly reactive, but very toxic and hard-to-handle reagents, such as  $\text{CF}_3\text{SCl}$ <sup>8</sup> and  $\text{CF}_3\text{SSCF}_3$ ,<sup>9</sup> have been used for trifluoromethylthiolation. Recently, stable and user-friendly  $\text{CF}_3\text{SN}$ - and  $\text{CF}_3\text{SO}$ -based reagents<sup>10–16</sup> and  $\text{CF}_3\text{SO}_2$ -containing hyper-valent idonium ylides<sup>17,18</sup> have been introduced for electrophilic trifluoromethylthiolation of  $\text{C}_{\text{sp}}^2\text{–H}$  bonds. More stable and readily available  $\text{CF}_3\text{SO}_2\text{Na}$  (Langlois reagent) has also been used to generate  $\text{CF}_3\text{S}^+$  for electrophilic trifluoromethylthiolation<sup>19</sup> and  $\text{CF}_3\text{S}^-$  for nucleophilic trifluoromethylthiolation of aryl iodides.<sup>20</sup> Very recently,  $\text{CF}_3\text{SO}_2\text{Cl}$  was reported for electrophilic trifluoromethylthiolation under the reduction of  $\text{PPh}_3$  or  $(\text{EtO})_2\text{P}(\text{O})\text{H}$ .<sup>21</sup>

The bifunctionalization of alkenes and alkynes with fluorinated groups is an active topic in organofluorine chemistry.<sup>22</sup> In addition to trifluoromethylthiolation of  $\text{C}_{\text{sp}}^2\text{–H}$  bonds, the scope of trifluoromethylthiolation has been extended for bifunctionalization of alkenes. From the successful hydro-trifluoromethylthiolation of alkenes with *N*-trifluoromethylthiodibenzene sulfonamide,<sup>23</sup> the Shen group reported the formoxy-, acetoxy-, and hydroxy-trifluoromethylthiolation of styrenes in different reaction solvents.<sup>13</sup> The Zhao group reported the hydroxy-trifluoromethylthiolation and amino-trifluoromethylthiolation using *N*-trifluoromethylthio-saccharin.<sup>24</sup> Very recently, the Xu group reported  $\text{PhSO}_2\text{SCF}_3$ -based sulfonyl-trifluoromethylthiolation reactions.<sup>25</sup>

Halogeno-trifluoromethylthiolation of alkenes is a useful bifunctionalization reaction because halogen atoms could be readily transformed to amino, alkyl, alkenyl, alkoxy, and other groups. The Billard group first reported chloro-trifluoromethyl-

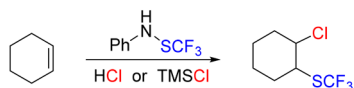
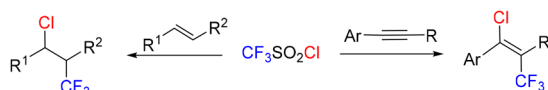
thiolation of cyclohexene using trifluoromethanesulfonylamides as a  $\text{SCF}_3$  source and  $\text{HCl}$  as a chlorine source.<sup>16</sup> They also reported a method using  $\text{TMSCl}$  as a chlorine source (Scheme 1a).<sup>26</sup>  $\text{CF}_3\text{SO}_2\text{Cl}$  is a well-reported electrophilic trifluoromethylthiolation reagent that generates reactive  $\text{CF}_3\text{SCl}$  under reductive conditions.<sup>21</sup>  $\text{CF}_3\text{SO}_2\text{Cl}$  has been used to generate  $\text{CF}_3^+$  for chloro-trifluoromethylation of alkenes and alkynes (Scheme 1b).<sup>27</sup> We envisioned that  $\text{CF}_3\text{SO}_2\text{Cl}$  could be developed as a bifunctionalization reagent to introduce  $\text{SCF}_3$  and chlorine groups without using an additional chlorine source (Scheme 1c).

We first attempted a reaction using 1:1.5:3 4-methylstyrene/ $\text{CF}_3\text{SO}_2\text{Cl}/(\text{EtO})_2\text{P}(\text{O})\text{H}$  in MeCN at 90 °C for 4 h, which is similar to the previously reported reductive conditions for the generation of  $\text{CF}_3\text{S}^+$ .<sup>21</sup> Only a trace amount of desired product was obtained (Table 1, entry 1). Screening of reductants indicated that  $\text{PPh}_3$  is more efficient than  $(\text{MeO})_2\text{P}(\text{O})\text{H}$ ,  $(\text{EtO})_2\text{P}(\text{O})\text{H}$ ,  $\text{PPh}_2\text{Me}$ , and  $\text{PPhMe}_2$  to give a 51% yield of **2a** in MeCN (Table 1, entry 5). After testing other solvents, including toluene, THF, DCE, and DMF, it was found that a reaction with DMF gave a 78% yield of **2a** (Table 1, entry 9). By increasing the amount of  $\text{CF}_3\text{SO}_2\text{Cl}$  from 1.5 to 2.0 equiv, the yield of **2a** was 90% (Table 1, entry 10), but no other significant changes were noted when using 2.5 and 3.0 equiv of  $\text{CF}_3\text{SO}_2\text{Cl}$  (Table 1, entries 11 and 12). Thus, 1:2:3 styrene/ $\text{CF}_3\text{SO}_2\text{Cl}/\text{PPh}_3$  in DMF at 90 °C for 4 h was selected as the optimized reaction conditions. To the best of our knowledge, this is the first example of using readily available and easy-to-handle  $\text{CF}_3\text{SO}_2\text{Cl}$  for direct chloro-trifluoromethylthiolation without an additional chlorine source.

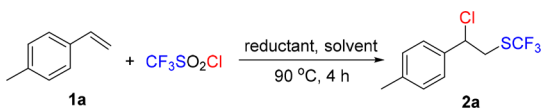
Under the optimized conditions, the scope of chloro-trifluoromethylthiolation was examined by performing the reactions of styrenes containing electron-rich or electron-poor groups. Products **2a–2p** were produced in 54–88% yields

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## Scheme 1. Chloro-trifluoromethylation and Chloro-trifluoromethylthiolation Reactions

a) Chloro-trifluoromethylthiolation with a chlorine source<sup>16,26</sup>b) Chloro-trifluoromethylation with CF<sub>3</sub>SO<sub>2</sub>Cl<sup>27</sup>

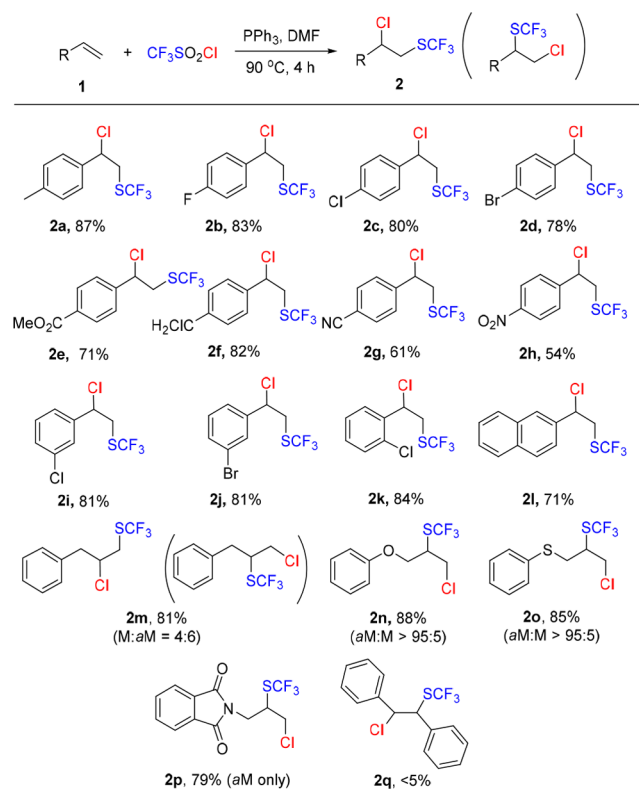
c) This work, chloro-trifluoromethylthiolation

Table 1. Optimization of Chloro-trifluoromethylthiolation with CF<sub>3</sub>SO<sub>2</sub>Cl<sup>a</sup>

entry	CF <sub>3</sub> SO <sub>2</sub> Cl (equiv)	reductant (3 equiv)	solvent	yield (%)
1	1.5	(EtO) <sub>2</sub> P(O)H	MeCN	trace
2	1.5	(MeO) <sub>2</sub> P(O)H	MeCN	trace
3	1.5	PPh <sub>2</sub> Me	MeCN	45
4	1.5	PPhMe <sub>2</sub>	MeCN	47
5	1.5	PPh <sub>3</sub>	MeCN	51
6	1.5	PPh <sub>3</sub>	PhMe	14
7	1.5	PPh <sub>3</sub>	THF	trace
8	1.5	PPh <sub>3</sub>	DCE	42
9	1.5	PPh <sub>3</sub>	DMF	78
10	2.0	PPh <sub>3</sub>	DMF	90
11	2.5	PPh <sub>3</sub>	DMF	91
12	3.0	PPh <sub>3</sub>	DMF	93

<sup>a</sup>Reaction conditions: 4-Methylstyrene (0.2 mmol), solvent (1 mL), 90 °C for 4 h; yield determined by <sup>19</sup>F NMR using PhCF<sub>3</sub> as an internal standard.

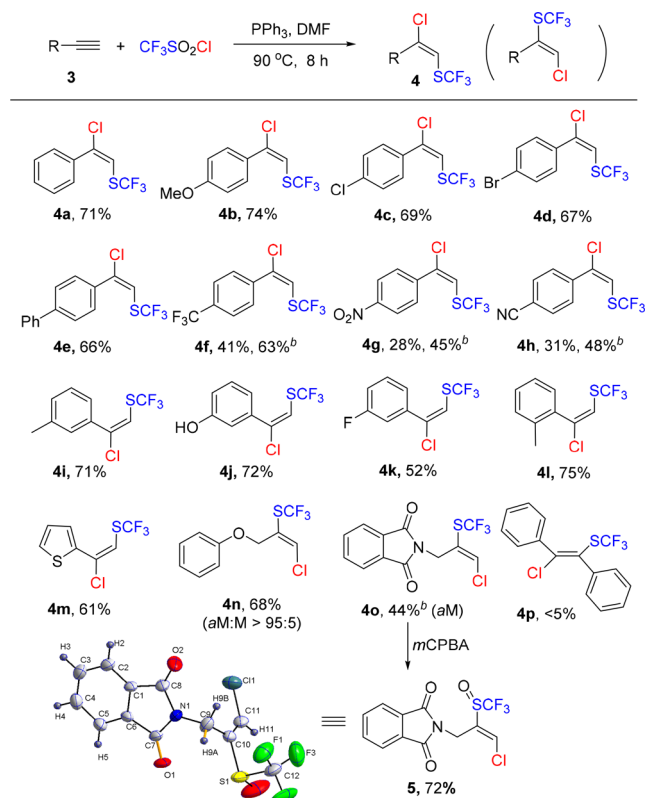
(Scheme 2). The reactions showed typical electrophilic character, in which substrates with electron-withdrawing groups resulted products **2g** and **2h** in lower yields. Nonstyrene-type alkenes, such as vinylnaphthalene, allylbenzene, (allyloxy)benzene, allyl(phenyl)sulfane, and *N*-allylphthalimide, resulted in corresponding products **2l–2p** in 71–88% yields. Product **2q** derived from nonterminal-type alkene 1,2-diphenylethene was produced in <5% yield. The regiochemistry of the Markovnikov (M) bifunctionalized products **2a–2l** was confirmed by <sup>1</sup>H NMR analysis of the corresponding alkenes generated from the dehydrochlorination of their chloro-trifluoromethylthiolated products after a reaction with CsF (see Supporting Information (SI)). Minor *anti*-Markovnikov products were observed from the reaction of styrenes with a strong electron-withdrawing group such as **2g** and **2h**. Products **2m–2p** were generated from the reaction of nonvinyl-type alkenes. Among them, **2m** was a mixture of 4:6 Markovnikov and *anti*-Markovnikov (*aM*) adducts, while **2n** and **2o** were produced in high *anti*-Markovnikov selectivity (>95%), and **2p** was found to be an *anti*-Markovnikov adduct. The regiochemistry of **2m–2p** could also be confirmed by their dehydro-

Scheme 2. Chloro-trifluoromethylthiolation of Alkenes<sup>a</sup>

<sup>a</sup>Reaction conditions: alkene (0.2 mmol), CF<sub>3</sub>SO<sub>2</sub>Cl (0.4 mmol), PPh<sub>3</sub> (0.6 mmol) in DMF (1 mL) at 90 °C for 4 h, isolated yields.

chlorinated products (see SI). The reaction of diphenylethylene, a nonterminal-type alkene, only gave a small amount of difunctionalized product **2q**.

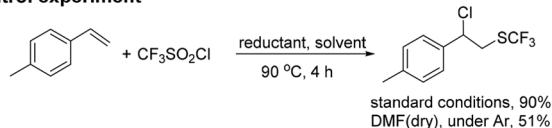
Electrophilic addition of alkynes is more difficult than that of alkenes, and we report that no chloro-trifluoromethylthiolation of alkynes was found in the literature. With the success of chloro-trifluoromethylthiolation of alkenes, we next investigated the reaction of alkynes. After optimization of the reaction conditions by increasing the reaction time to 8 h, we obtained *E*-(2-chloro-2-phenylvinyl)(trifluoromethyl)sulfane **4a** in 71% yield (Scheme 3). Under these conditions, various alkynes were converted to desired chloro-trifluoromethylthiolated products **4a–4o**. In general, the chloro-trifluoromethylthiolation of alkynes is not as efficient as styrenes; most of the phenylacetylene substrates gave products **4a–4l** in moderate to good yields. Increasing the amount of CF<sub>3</sub>SO<sub>2</sub>Cl could significantly improve the yield of those alkynes bearing an electron-withdrawing group, such as **4f**, **4g**, and **4h**. Under the standard conditions, heteroaryl alkynes, such as 2-ethynylthiophene, was converted to product **4m** in 61% yield. An alkyne derived from isoindoline-1,3-dione gave product **4o** in 44% yield by using 3 equiv of CF<sub>3</sub>SO<sub>2</sub>Cl. The stereochemistry of **4o** was determined by single crystal X-ray diffraction analysis of **5**, which is an oxidation product of **4o**. The <sup>1</sup>H NMR analysis of the dehydrochlorination products of chloro-trifluoromethylthiolated phenylacetylenes and 2-ethynylthiophene indicated that they are Markovnikov products. No dehydrochlorinated product was observed from **4n**, suggesting that it is an *anti*-Markovnikov product. The X-ray structure indicated that **4o** is an *anti*-addition product. Nonterminal-type alkynes, such as 1,2-diphenylethyne, gave **4p** in <5% yield. Similar to the

Scheme 3. Chloro-trifluoromethylthiolation of Alkynes<sup>a</sup>

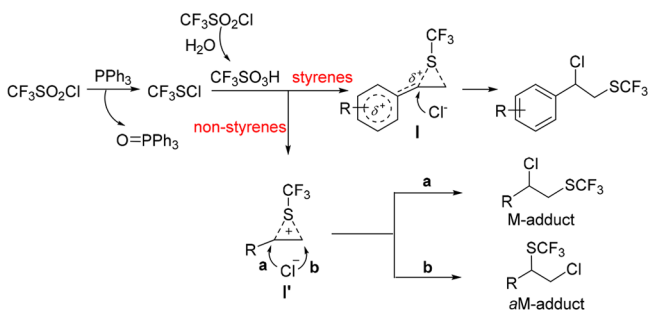
<sup>a</sup>Reaction conditions: alkyne (0.2 mmol),  $\text{CF}_3\text{SO}_2\text{Cl}$  (0.4 mmol),  $\text{PPh}_3$  (0.6 mmol) in DMF (1 mL) at  $90^\circ\text{C}$  for 8 h, isolated yields. <sup>b</sup>3.0 equiv of  $\text{CF}_3\text{SO}_2\text{Cl}$  were used.

Scheme 4. Control Experiment and Proposed Mechanism

## Control experiment



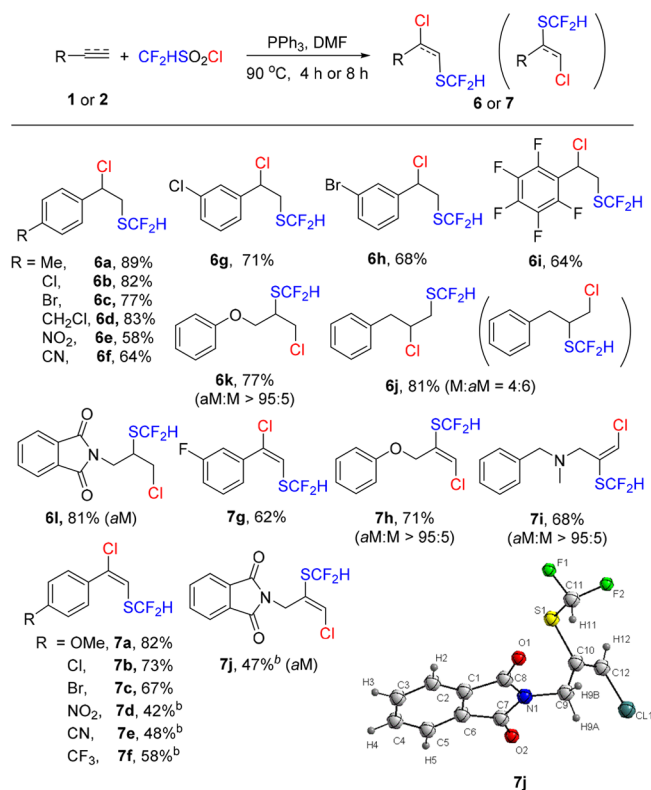
## Proposed mechanism



reactions of vinyl alkenes, reactions of phenylacetylenes and 2-ethynylthiophenes gave Markovnikov adducts **4a–4m**, while *anti*-Markovnikov adducts were the major regioisomers for **4n** and **4o**.

To investigate the reaction mechanism, a control reaction was conducted under the standard conditions, but without using an alkene. The reduction of  $\text{CF}_3\text{SO}_2\text{Cl}$  with  $\text{PPh}_3$  produced  $\text{CF}_3\text{SCl}$  in 96% yield, as detected by  $^{19}\text{F}$  NMR analysis, and a quantitative amount of  $\text{Ph}_3\text{PO}$  was also obtained. A signal of  $\delta -78.8$  ppm ( $\text{CF}_3\text{SO}_3\text{H}$ ) was observed, which is

Scheme 5. Chloro-difluoromethylthiolation of Alkenes and Alkynes



<sup>a</sup>Reaction conditions: alkene or alkyne (0.2 mmol),  $\text{CF}_3\text{SO}_2\text{Cl}$  (0.4 mmol),  $\text{PPh}_3$  (0.6 mmol) in DMF (1 mL) at  $90^\circ\text{C}$  for 4 h (alkene) or 8 h (alkyne), isolated yields. <sup>b</sup>3.0 equiv of  $\text{CF}_3\text{SO}_2\text{Cl}$  were used.

the hydrolysate of  $\text{CF}_3\text{SO}_2\text{Cl}$ .  $\text{CF}_3\text{CO}_2\text{H}$  was reported to be an efficient catalyst for the reaction of fluorochloromethanesulfenyl chloride with alkenes,<sup>28</sup> so we speculated that  $\text{CF}_3\text{SO}_3\text{H}$  generated from  $\text{CF}_3\text{SO}_2\text{Cl}$  could also serve as a catalyst for the electrophilic addition. To confirm if  $\text{CF}_3\text{SO}_3\text{H}$  could promote an electrophilic addition, a reaction using dry DMF under Ar was conducted (Scheme 4). No signal of  $\text{CF}_3\text{SO}_3\text{H}$  was detected by  $^{19}\text{F}$  NMR, and the yield of the product was only about half of the standard conditions. On the basis of the control experiment and the literature information, a mechanism involving reduction of  $\text{CF}_3\text{SO}_2\text{Cl}$  to  $\text{CF}_3\text{SCl}$ , followed by electrophilic addition to an alkene under the catalysis of  $\text{CF}_3\text{SO}_3\text{H}$ , to give a chloro-trifluoromethylthiolated product is proposed in Scheme 4. High regioselectivity for Markovnikov products from styrenes resulted from the favorable electronic conjugation of a phenyl ring with a bridged episulfonium ion in the addition of  $\text{Cl}^-$  to intermediate **I**. In the case of nonstyrene-type alkenes, not favorable conjugation but rather the steric hindrance of the R group directs the  $\text{Cl}^-$  to the less substituted carbon of **I'** to give the *anti*-Markovnikov adduct.<sup>29</sup> The process of electrophilic addition of alkynes is similar to that of alkenes.

The  $\text{SCF}_2\text{H}$  group could serve as a lipophilic OH or NH surrogate, and  $\text{SCF}_2\text{H}$ -containing molecules have shown to be uniquely effective in bioactive compounds,<sup>30</sup> such as the  $\beta$ -lactamase-resistant oxcephalosporin antibiotic flomoxef sodium,<sup>31</sup> the pesticide pyriprole,<sup>32</sup> herbicide SSH-108,<sup>33</sup> a nifedipin analogue,<sup>34</sup> and a fungicide candidate.<sup>35</sup> We have successfully extended the reaction scope for chloro-difluoro-

methylthiolation of alkenes and alkynes by using  $\text{CF}_2\text{HSO}_2\text{Cl}$  as a reagent. Reactions of a series of styrene derivatives with  $\text{CF}_2\text{HSO}_2\text{Cl}$  afforded **6a–6i** in good yields (Scheme 5). Reactions of phenylacetylenes and other alkynes gave products **7a–7j** with satisfactory yields. The structure of **7j** was confirmed by single crystal X-ray diffraction analysis. Similar to the reactions of alkenes with  $\text{CF}_3\text{SO}_2\text{Cl}$ , reactions of styrene and phenylacetylene derivatives with  $\text{CF}_2\text{HSO}_2\text{Cl}$  gave Markovnikov products, while other alkenes and alkynes mainly gave anti-Markovnikov products.

In summary, we have developed a simple and efficient method for chloro-trifluoromethylthiolation of alkenes and alkynes using  $\text{CF}_3\text{SO}_2\text{Cl}$  as a bifunctionalization reagent. The reaction is promoted by the reduction of  $\text{CF}_3\text{SO}_2\text{Cl}$  with  $\text{PPh}_3$  to form  $\text{CF}_3\text{SCL}$  for the electrophilic addition. The hydrolysate  $\text{CF}_3\text{SO}_3\text{H}$  in the reaction system serves as a catalyst. In addition to chloro-trifluoromethylthiolation, the method has been successfully extended for chloro-difluoromethylthiolation using  $\text{CF}_2\text{HSO}_2\text{Cl}$ . The reactions of styrenes gave regioselective Markovnikov adducts, while nonstyrene-type alkenes mainly gave anti-Markovnikov adducts. The highly efficient and concise nature of the reaction process and good atom economy, along with the mild conditions employed, are the major advantages of this new method for direct bifunctional chloro-fluoromethylthiolation of alkenes and alkynes.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.orglett.8b00581](https://doi.org/10.1021/acs.orglett.8b00581).

Experimental procedures, characterization data, and  $^1\text{H}$ ,  $^{13}\text{C}$ , and  $^{19}\text{F}$  NMR for products (PDF)

### Accession Codes

CCDC 1564089 and 1815626 contain 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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