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# Expanding Radical Chloropentafluorosulfanylation of Alkynes

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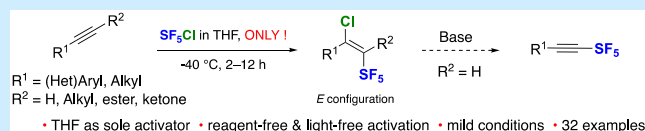
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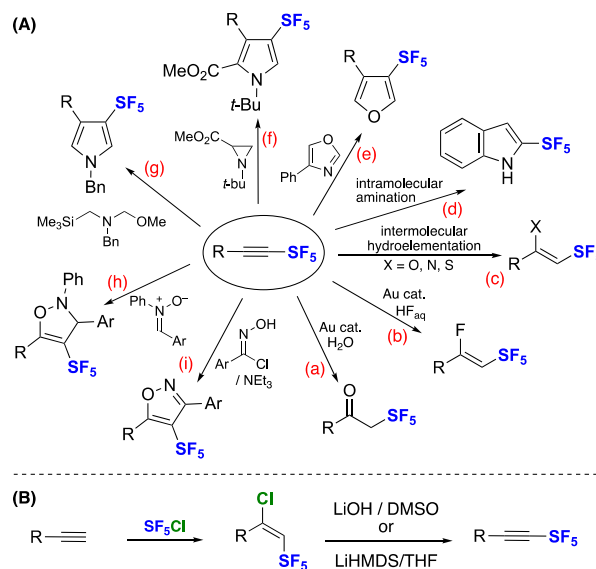
Supporting Information

**ABSTRACT:** The chloropentafluorosulfanylation of alkynes is a delicate but crucial operation for accessing SF<sub>5</sub>-alkynes that serve as substrates in numerous transformations. Dolbier's procedure using Et<sub>3</sub>B/O<sub>2</sub> was the most efficient approach, while recent efforts make use of other initiators and light activation. We found that THF, as a single stimulus, is sufficient to trigger the reaction of SF<sub>5</sub>Cl with alkynes. We determined the configuration of Cl/SF<sub>5</sub> products and



clarified the structure of side-products.

In the field of organofluorine chemistry, the search for new chemical motifs offering improved physicochemical or biological properties is very active. To this end, combining fluorine with sulfur has given rise to the blossoming of compounds featuring either (Het)ArSF<sub>4</sub> or sulfur pentafluoride SF<sub>5</sub> groups; these motifs are considered truly emerging and are currently generating an abundance of bibliographic data.<sup>1–3</sup> As a rationale for the preparation of pentafluorosulfanylated molecules, particular mention should be made of its larger volume in comparison with the CF<sub>3</sub> group, a square pyramidal geometry, its high electronegativity and high lipophilicity, a metabolic robustness and chemical stability.<sup>4–8</sup> The construction of SF<sub>5</sub>-containing compounds by means of inorganic gaseous pentafluorosulfanyl chloride reagent SF<sub>5</sub>Cl constitutes the main synthetic approach.<sup>9</sup> Besides, the SF<sub>5</sub> group can be built from thiols and disulfides by oxidative fluorination to afford SF<sub>5</sub>-(het)aromatics.<sup>10</sup> SF<sub>5</sub>-Alkynes are central in downstream functionalizations toward a wide range of heterocyclic and acyclic compounds (Figure 1A).<sup>11</sup> SF<sub>5</sub>-Alkynes are typically obtained in a two-step sequence from terminal alkynes by chloropentafluorosulfanylation with SF<sub>5</sub>Cl followed by HCl elimination with the aid of a base (Figure 1B). Ethynylbenziodoxolone reagents are also substrates for the reaction of SF<sub>5</sub>Cl under blue light irradiation.<sup>12</sup> Early radical additions of SF<sub>5</sub>Cl onto unsaturated carbon compounds were achieved through thermal or photochemical processes, requiring special equipment. In 2002, Dolbier's breakthrough consisted of the use of BEt<sub>3</sub>/O<sub>2</sub> as a catalytic initiator of free radical chain addition of SF<sub>5</sub>Cl onto alkenes and alkynes.<sup>13</sup> The reactions were performed in the liquid phase below the boiling point of SF<sub>5</sub>Cl (bp –21 °C) in standard glassware. With terminal alkynes, the chloropentafluorosulfanylation is regio- and stereoselective, leading to the *E*-alkenes, although the configuration was not definitively ascertained. Besides the desired product **2a** obtained from phenyl acetylene **1a**, a 2:1 adduct (**3a**) was concomitantly formed (**2a**/**3a** = 49:27) (see Table 1). So far, this synthetic route was the method of choice



**Figure 1.** (A) Applications of SF<sub>5</sub>-alkynes in (a) Gold-catalyzed hydration,<sup>14</sup> (b) Gold-catalyzed hydrofluorination,<sup>15</sup> (c) Hydroelementation,<sup>16</sup> (d) Intramolecular amination,<sup>17</sup> (e) Diels–Alder reaction,<sup>18</sup> (f, g) Pyrrole syntheses,<sup>19,20</sup> (h) Isoxazoline synthesis,<sup>21</sup> (i) Isoxazole synthesis.<sup>22</sup> (B) Synthesis of SF<sub>5</sub>-alkynes from SF<sub>5</sub>Cl and terminal alkynes.

to prepare Cl/SF<sub>5</sub>-alkenes and subsequently SF<sub>5</sub>-alkynes. Nevertheless, the pyrophoric properties of triethylborane led Paquin's group to evaluate amine-borane complexes as stable

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Table 1. Screening of Solvents<sup>a</sup>

Entry	Solvent	Conv.	2a/3a yield (%) <sup>b</sup>
1	THF	100	92 (99)/(<1)
2	Et <sub>2</sub> O	100	(72)/(9)
3	THP	100	73 (94)/(6)
4	Hexane	0	0/0
5	CH <sub>2</sub> Cl <sub>2</sub>	54	0/0
6	Toluene	30	0/0
7	CH <sub>3</sub> CN	30	0/0
8	THF/dark	100	(86)/(1)
9	THF/dark/O <sub>2</sub> free	90	(90)/0
10	THF/dark/O <sub>2</sub> free/Nalgene flask	100	93 (97)/(3)
11	THF nondistilled	100	(92)/(8)

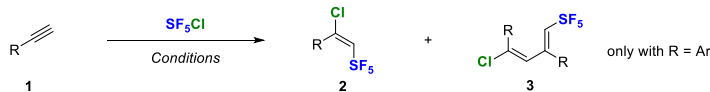
<sup>a</sup>Reaction conditions: **1a** (1 mmol), solvent (2 mL),  $-40\text{ }^{\circ}\text{C}$ , 2 h.

<sup>b</sup>Yields of isolated products (the number in brackets refers to calculated yields by <sup>19</sup>F NMR using PhSCF<sub>3</sub> as internal standard and by GC-MS).

radical initiators.<sup>23,24</sup> With the same motivation, they developed an electron donor–acceptor (EDA)-complex with visible light irradiation.<sup>25</sup> The latest development by this group was the activation by means of a blacklight compact fluorescent lamp.<sup>26</sup> This synthetic approach represents noticeable progress en route to a simple procedure, but still a light is necessary. Apart from the fact that the current methods require an activator, they are also not entirely satisfactory in terms of yields and substrates scope; moreover, side-products, notably the 2:1 adduct and the *Z* stereoisomer, cause purification difficulties. Interestingly, Tlili noticed that SF<sub>5</sub>Cl in hexane can react with **1a** in absence of BEt<sub>3</sub> albeit in lower yield (58% versus 73% with BEt<sub>3</sub>); however, this remarkable insight has not been further explored.<sup>27</sup> Similar observations were made in triethylborane-free reactions of SF<sub>5</sub>Cl in CH<sub>2</sub>Cl<sub>2</sub> (<2% yield)<sup>28</sup> and SF<sub>5</sub>Cl in Et<sub>2</sub>O (13% yield).<sup>29</sup> In the same vein, (het)ArSF<sub>4</sub>Cl reagents reacted without any activation in cyclopentyl methyl ether or in Et<sub>2</sub>O.<sup>30,31</sup> This literature survey shows that the current mainstream in chloropentafluorosulfanylation of alkynes is to look for alternative radical initiators or new methods by light activation. This prompted us to search for a safe, simple and efficient protocol to generate an extensive portfolio of novel SF<sub>5</sub> molecules. We hypothesized that SF<sub>5</sub>Cl could react in high yields under reagent-free and light-free conditions by exploiting the intrinsic susceptibility of ethereal solvents to form hydroperoxides that could thereafter generate the SF<sub>5</sub> radical. We herein report a paradigm shift in which simplicity goes hand-to-hand with efficiency in the regio- and stereoselective chloropentafluorosulfanylation of alkynes. In addition, the structural determination of Cl/SF<sub>5</sub>-alkenes and the secondary products was carried out.

Our study began by assessing the stability of SF<sub>5</sub>Cl solutions. SF<sub>5</sub>Cl gas was condensed in a sealed flask at  $-40\text{ }^{\circ}\text{C}$ , and the solvent was added (see Supporting Information (SI) for detailed procedures). Since Dolbier's work with the aid of triethylborane,<sup>13</sup> hexane has remained the most widely used solvent, even when SF<sub>5</sub>Cl is homemade, and solutions of SF<sub>5</sub>Cl in hexane are reported as bench-stable.<sup>32–34</sup> The situation is different for THF solutions in which SF<sub>5</sub>Cl is responsible for the polymerization of THF rapidly forming a gel at rt and

within 12 h at  $-20\text{ }^{\circ}\text{C}$ . This catalyzed polymerization slows down sufficiently at  $-40\text{ }^{\circ}\text{C}$  and stops at  $-78\text{ }^{\circ}\text{C}$ . Our model reaction used phenylacetylene **1a** and SF<sub>5</sub>Cl to allow comparison with all of the reported syntheses. The temperature was set at  $-40\text{ }^{\circ}\text{C}$  to minimize THF polymerization. Besides the desired Cl/SF<sub>5</sub>-alkene **2a**, we detected 2:1 adduct **3a** (Table 1). Our hypothesis turned out to be correct, as the Cl/SF<sub>5</sub>-alkene **2a** was obtained in 92% yield after purification (entry 1). Other ethereal solvents, Et<sub>2</sub>O and tetrahydropyran (THP), delivered **2a** in more than 72% calculated yields, but the reactions were not so clean since **3a** was detected by GC-MS and <sup>19</sup>F NMR (entries 2, 3). In hexane at  $-40\text{ }^{\circ}\text{C}$ , substrate **1a** was fully recovered after 2 h, while dichloromethane, toluene, and acetonitrile gave conversions of 30–54% but not into fluorinated products (entries 4–7). Note that, in the dark, the reaction still proceeded in full conversion to end up with 86% of **2a** (entry 8). Degassing the solution of **1a** in THF by the freeze–pump–thaw method allowed a very clean reaction leading to 90% of **2a** as single product (entry 9). This result could mean that dissolved oxygen plays no role, but this may be a hasty conclusion, given that SF<sub>5</sub>Cl added after degassing may contain dissolved oxygen. An experiment carried out in Nalgene instead of glass gave almost identical product distribution and yield indicating that glass has no contribution to the reaction mechanism (entry 10). Finally, using nondistilled THF appeared detrimental to the selectivity, with an increased amount of **3a** (entry 11). This case study with phenylacetylene allowed a clear comparison with the methods currently available (Scheme 1A). A maximum yield of 49% was recorded with the previously reported methods, while we significantly improved the isolated yield to 92% (Scheme 1A). During this first phase of our investigation, 2:1 adduct **3a** was crystallized and its single-crystal X-ray diffraction (SCXRD) analysis confirmed the structure proposed by Dolbier, also enabling us to prove the *trans* stereochemistry of each vinylic radical (Figure 2).<sup>13</sup> With these conditions in hand, we applied our simple protocol in THF to aromatic and aliphatic alkynes already reported in the literature for chloropentafluorosulfanylation (Scheme 1B). The present method compared favorably with the literature, affording higher yields of Cl/SF<sub>5</sub>-alkenes. Starting from 4-octyne, we obtained an excellent yield by GC-MS but due to high volatility of **2j** we only obtained it in 74% isolated yield. Radical addition of SF<sub>5</sub>Cl to alkynes was supposed to produce the *E* stereoisomers, although this was never firmly established by earlier contributors in the field. A large-scale experiment was carried out that yielded 1.9 g of product *E*-**2e** as a solid suitable for SCXRD to definitively ascertain the *E* configuration of this family of compounds. We could photoisomerized *E*-**2e** into *Z*-**2e** at least partially (see SI). Having access to both *E*- and *Z*-stereoisomers of **2e**, we have deduced by <sup>19</sup>F NMR for the characteristic AB<sub>4</sub> pair of quintet and doublet signals that the doublet is 3.1 ppm upper field for the *Z* stereoisomer in comparison with the *E* stereoisomer (65.9 ppm for *Z*-**2e** versus 69.0 ppm for *E*-**2e**). Clarification of the configuration of Cl/SF<sub>5</sub>-alkenes was necessary because some misidentifications were noted in the literature. For example, **2l** was isolated as the *E*-isomer and not the *Z*-isomer as it was reported (see SCXRD of **2l** in Figure 2 and NMRs in the SI).<sup>25</sup> In addition, *E*-**2m** is the product of the chloropentafluorosulfanylation of 5-phenyl-1-pentyne **1m** whatever the method (C or the present one). The reaction with **1m** does not give a mixture of *Z* + *E*-**2m** (75:25)<sup>25</sup> but rather *E*-**2m** along with the

Scheme 1. Chloropentafluorosulfanylation of Alkynes<sup>a</sup>

## A) Phenylacetylene as model alkyne for comparison with all existing methods.

 2a	Method A (Et <sub>3</sub> B/O <sub>2</sub> , hexane, -30 °C, 0.5 h)	2a	3a	Dolbier 2002/2015 Tlili 2022 Borggraeve 2023 Paquin 2020 Paquin 2021 Paquin 2023 Tlili 2022 Bizet / Cahard 2023
	Method A' (Et <sub>3</sub> B/O <sub>2</sub> , hexane, rt, 0.5 h)	49%	27%	
	Method A'' (Et <sub>3</sub> B/O <sub>2</sub> , hexane, -94 °C, 3 h)	30% (73%)	not mentioned	
	Method B (Amine-borane/O <sub>2</sub> )	15% (18%)	26% (32%)	
	Method C (EDA complex/light)	(23%)	5%	
	Method D (blacklight irradiation in AcOEt)	33% (51%)	0%	
Method E (without activation in hexane)	25% (E/Z >97:3)	not mentioned	not mentioned	
Method E (with activation in hexane)	(58%)	not mentioned	not mentioned	
<b>This work (THF only, -40 °C)</b>	<b>92% (99%)</b>	<b>0%</b>	<b>0%</b>	<b>Bizet / Cahard 2023</b>

## B) Comparison with reported aromatic and aliphatic alkynes.

 2b	 2c	 2d	 2e	 2f	 2g	 2h
Method A 50%	Method A 27% <sup>b</sup>	Method A 35% <sup>c</sup>	Method A 38–88% <sup>c</sup>	Method A 49% <sup>c</sup>	Method A 44%	Method A 61–76%
Method E (41%)	<b>This work 95% (100%)</b>	<b>This work 88% (100%)</b>	<b>This work 99% (100%)</b>	<b>This work 77% (92%)</b>	Method E (25%)	<b>This work 68% (95%)</b>
<b>This work 88% (100%)</b>			(1.9 g of 2e)		<b>This work 83% (98%)</b>	
 2i	 2j	 2k	 4m			
Method A 49%	Method A 93%	Method D 66%	Method A 91%			
Method E (40%)	<b>This work 74% (95%)</b>	<b>This work 72% (94%)</b>	Method C 86% <sup>d</sup>			
<b>This work 51% (94%)</b>			<b>This work 94% (100% E)</b>			
 E-2m + Z-2m + H-SF <sub>5</sub>			Method A (68:0:32 E-2m/Z-2m/4m) <sup>c</sup> Method C 84% (75:25 postulated E-2m/Z-2m) <b>This work 59% (86:0:14 E-2m/Z-2m/4m)</b>			

C) New alkyne substrates engaged in the chloropentafluorosulfanylation reaction. 2n–af are new compounds.<sup>e</sup>

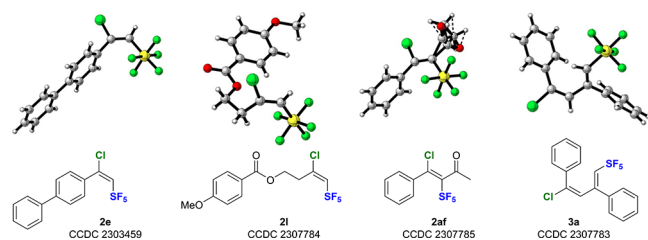
 2n	 2o	 2p	 2q	 2r	 2s	 2t
74% (95%)	54% (93%) + (7%) 3o	92% (100%)	100%	48% (60%) + (19%) 3r	47% (97%)	31% (38%) + (31%) 3t
	(74%) + (13%) 3o with BEt <sub>3</sub> in hexane	73% with BEt <sub>3</sub> in DCM <sup>f</sup>	54% with BEt <sub>3</sub> in hexane	(60%) + (20%) 3r with BEt <sub>3</sub> in hexane		messy with BEt <sub>3</sub> in hexane
 2u	 2v	 2w	 2x	 2y		
63% (75%) + (12%) 3u	31% (34%) + (33%) 3v	56% (83%)	77% (97%)	73% (95%)		
messy with BEt <sub>3</sub> in hexane	0% with BEt <sub>3</sub> in DCM <sup>f</sup>	0% with BEt <sub>3</sub> in DCM <sup>f</sup>	0% with BEt <sub>3</sub> in DCM <sup>f</sup>			
 2z	 2aa	 2ab	 2ac	 2ad	 2ae	 2af
13% (15%)	100%	36% (54%)	86% (96%) <sup>f</sup>	95% (97%)	71% (95%)	70% (79%)
0% with BEt <sub>3</sub> in DCM <sup>f</sup>	53% with BEt <sub>3</sub> in DCM <sup>f</sup>	24% (40%) with BEt <sub>3</sub> in AcOEt		(96%) with BEt <sub>3</sub> in hexane	(25%) with BEt <sub>3</sub> in hexane	

<sup>a</sup>See the SI for detailed experimental procedures. Yield of isolated product (the number in parentheses refers to calculated yield by <sup>19</sup>F NMR using PhSCF<sub>3</sub> as internal standard). References of methods: A,<sup>13,21,16</sup> A',<sup>27</sup> A'',<sup>35</sup> B,<sup>23,24</sup> C,<sup>25</sup> D,<sup>26</sup> E.<sup>27</sup> <sup>b</sup>Overall yield of the SF<sub>5</sub>-alkyne over two steps after HCl elimination. <sup>c</sup>Reaction performed in DCM from -40 °C to rt. <sup>d</sup>The product was misidentified as Z. <sup>e</sup>Unless otherwise noted, reactions have been performed in THF at -40 °C for 2 h. <sup>f</sup>Reaction performed at -78 °C.

cyclic nonchlorinated compound **4m** (68:32 in DCM with catalytic Et<sub>3</sub>B or 86:14 in THF without initiator). To further demonstrate the greater reactivity of alkynes in THF versus Dolbier's method, we evaluated both conditions with new alkynes (Scheme 1C). Again, the superiority of our method has been clearly illustrated with variously decorated aryl alkynes featuring alkyl, ester, ether, or nitro groups (**2n–v**) as well as with (het)aryl alkynes (**2w–x**). For instance, aromatics

featuring electron-withdrawing groups do not react well using Dolbier's conditions while the corresponding Cl/SF<sub>5</sub>-addition products were obtained using the present method (e.g., **2t–v**); idem for 3-ethynylpyridine and thiophene derivatives **2w** and **2x**. Bis-alkyne **1y** afforded **2y** in a 73% isolated yield. Addition of SF<sub>5</sub>Cl onto silylated terminal alkynes was unknown, and the only reported method to produce a silylated SF<sub>5</sub>-alkyne involved SF<sub>5</sub>Br, which is not commercially





**Figure 2.** SCXRD of Cl/SF<sub>5</sub>-alkenes **2e**, **2l**, and **2af** and 2:1 adduct **3a**.

available and difficult to prepare.<sup>36</sup> With our present method, triisopropylsilyl-acetylene **1z** delivered **2z** in a modest 13% isolated yield, while we obtained a quantitative yield of **2aa** featuring a triethylsilyl group. The latter was convenient to prepare, was not so volatile, and was easily purified by distillation. Addition of SF<sub>5</sub>Cl to a boron-substituted alkyne (BMIDA, **1ab**) is described for the first time with up to 54% conversion and 36% isolated yield. The reaction also performed well with functionalized alkyl alkynes **2ac–ad** and with triple bonds embedded in ynoate (product **2ae**) and ynone (product **2af**) leading to unprecedented motifs in 71% and 70% yields, respectively. With these conjugated substrates, the SF<sub>5</sub> was selectively introduced in the  $\alpha$ -position of the carbonyl as demonstrated by SCXRD of **2af** (Figure 2). Overall, the present conditions allowed improvement of the yields of Cl/SF<sub>5</sub>-alkenes, reduction of the amounts of 2:1 adducts, and access to completely new structures.

Additional substrates were evaluated, for instance, some featuring an acid or an alcohol function, but reactions were messy and GC-yields did not exceed 30% (see SI for reluctant substrates). Extension of our conditions to alkenes as substrates ended up with no product formation or low reaction yields (see SI for examples and a possible explanation). The complete synthetic sequence toward SF<sub>5</sub>-alkynes by HCl elimination with the aid of a base is a straightforward step except for boron-substituted alkene **2ab** (see SI for examples). From a mechanistic viewpoint, the reaction proceeds through free radical chain addition of SF<sub>5</sub>Cl to alkynes that is inhibited in the presence of TEMPO (see SI). Since the reaction also takes place in the dark, we assumed that the proclivity of THF to autoxidation<sup>37</sup> induces formation of hydroperoxides, as evidenced in our distilled THF by the Creary's method,<sup>38</sup> that are responsible for the initiation step (see a proposed mechanism in SI). However, the amount of peroxide is a crucial factor, as too much is impaired with the reaction (Table 1, entry 11).

In conclusion, we have demonstrated that the right choice of solvent and only that solvent is the key for streamlined chloropentafluorosulfanylation of alkynes in the absence of added reagent or light irradiation. We are convinced that this simple and economical approach is of immediate benefit to the chemists eager to access SF<sub>5</sub>-containing building blocks for further elaboration of complex fluorinated molecules. We hope that this work will be seen as a major step forward, two decades after Dolbier's seminal paper.

## ■ ASSOCIATED CONTENT

### Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

## SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.3c04043>.

Experimental procedures, characterization data for all new compounds, along with copies of spectra (PDF)

## Accession Codes

CCDC 2303459–2303460 and 2307783–2307785 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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