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# $SCF_3$-Alkenes Unlocked: A Gateway via Cu(I)-Catalyzed Stereocontrolled Cross-Coupling

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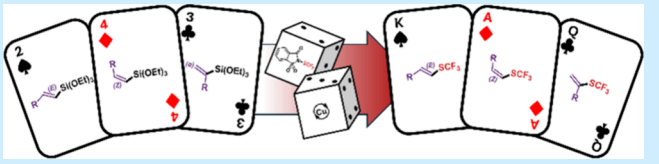
**ABSTRACT:** The $SCF_3$ group has emerged as a key motif in medicinal and agrochemical chemistry. While synthetic methods to access aryl, alkynyl, and alkyl $SCF_3$-derivatives are well-established, access to stereocontrolled $SCF_3$-disubstituted alkenes remains challenging, with existing methods falling short on selectivity and substrate scope. Here we report a versatile Cu(I)-catalyzed cross-coupling that unlocks modular, stereodefined access to (*E*)-, (*Z*)-, and (*1,1′*)-disubstituted $SCF_3$-alkenes under mild, user-friendly conditions - breaking through key limitations of previous approaches. This scalable protocol exhibits broad functional group tolerance and handles complex, pharma- and agro-relevant substrates with ease. Moreover, the $SCF_3$-alkenes serve as versatile platforms for selective postfunctionalization. Mechanistic evidence points to a two-electron pathway involving a hypervalent silicon intermediate, shedding light on this novel transformation.



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Fluorinated functional groups play a central role in modern medicinal and agrochemical research owing to their profound influence on key molecular properties such as lipophilicity, metabolic stability, and bioavailability.[1] Among them, the trifluoromethylthio ($SCF_3$) moiety stands out for its unique combination of strong electron-withdrawing character and pronounced lipophilicity, as reflected by its high Hansch parameter ($\pi$ = 1.44).[2] These desirable features have stimulated considerable efforts toward the incorporation of $SCF_3$ units into a broad range of molecular architectures. Consequently, efficient and reliable methods have been developed for the synthesis of $SCF_3$-substituted (hetero)-arenes, notably via direct trifluoromethylthiolation[3,4] or trifluoromethylation of sulfur-based precursors (Figure 1A).[3,5] Similarly, $SCF_3$-alkynes are readily accessible from terminal or functionalized alkynes (Figure 1B).[4f,h,6] The synthesis of $SCF_3$-alkyl derivatives has also been explored, primarily through trifluoromethylthiolation,[7] as well as by trifluoromethylation of sulfur-containing derivatives.[5a,b,8] However, while these strategies have broadened the chemical space of $SCF_3$-containing molecules, the positional diversity of this group remains largely confined to saturated and aromatic scaffolds. In contrast, the incorporation of $SCF_3$ at alkenyl positions particularly in a stereocontrolled manner remains in its infancy and poses significant synthetic challenges (Figure 1D). To date, the stereoselective synthesis of (*E*)-$SCF_3$-alkenes has been predominantly achieved by Cu-catalyzed cross-couplings of prefunctionalized olefins.[4e−k,7b,9] The most employed approach relies on alkenyl boron derivatives (Figure 1D, **FG** = $B(OH)_2$, BPin), often requiring an external oxidant.[4e−k,9f] Although high yields can be achieved, these methods are generally limited to styrenyl substrates and may require stoichiometric amounts of Cu. Alternative strategies using halogenated alkenes (**FG** = I, Br) under Cu or Au catalysis have been reported, but suffer from narrow substrate scope, harsh reaction conditions, poor functional group tolerance, and rely on starting materials that are not always readily accessible.[9a,b,g,10] Recently, a photoredox-mediated trifluoromethylthiolation of alkenyl iodides has been disclosed, though its scope remains limited to styrenyl derivatives and exhibits variable *E*/*Z* selectivity.[11] Other prefunctionalized systems, such as alkenyl triflates or nonaflates (**FG** = OTf, ONf), have been employed under nickel catalysis by Schoenebeck.[4d] However, these transformations require expensive catalysts and strict air-free conditions, which limit their practical applicability. Additional radical-based strategies involving cinnamic acids or $\beta$-nitrostyrenes (**FG** = COOH, $NO_2$) have also emerged, but offer modest stereoselectivity, poor generality, and rely on starting materials that are not easily accessible.[9c−e] On the other hand, approaches that avoid prefunctionalization, such as direct trifluoromethylthiolation of styrenes,[12] epoxide openings,[13] hydrotrifluoromethylthiolation of terminal alkynes,[14] or dual photoredox/halide catalysis on styrenes,[15] generally afford (*E*)-$SCF_3$-alkenes with a limited scope or poor *E*/*Z* selectivity even when applied to styrenyl frameworks.

In sharp contrast to their (*E*)-configured counterparts, methods enabling the synthesis of (*Z*)-$SCF_3$-alkenes remain

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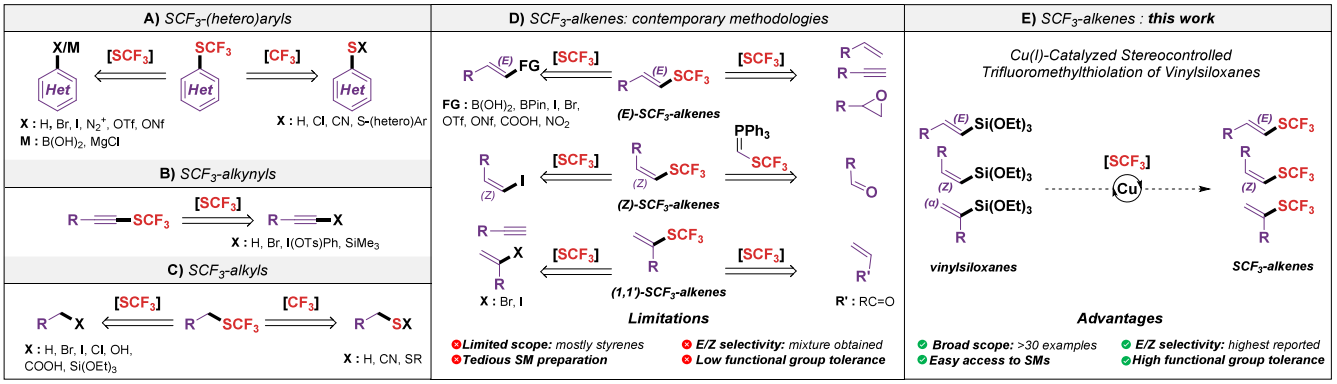



**Figure 1.** State of the art of $SCF_3$-containing compounds. (A–C) Well-established $SCF_3$-containing scaffolds. (D) Contemporary methods for the synthesis of $SCF_3$-alkenes. (E) This work: Cu(I)-catalyzed stereocontrolled trifluoromethylthiolation of vinylsiloxanes.

exceedingly scarce. To the best of our knowledge, only two reports have addressed access to this subclass.[10,16] The first relies on Au-catalyzed cross-couplings of alkenyl iodide precursors yet delivers only a handful of styrenyl or acrylic derivatives (3 examples reported).[10] A second strategy, reported in 2019, involves a Wittig-type olefination using a $SCF_3$-substituted phosphonium ylide under high-temperature conditions.[16] While this approach enables direct incorporation of the $SCF_3$ moiety, it is restricted to styrenic derivatives and affords modest *E*/*Z* selectivity. In fact, the only nonstyrenyl example reported under these conditions was obtained in just 35% yield as a 1:1 *E*/*Z* mixture, highlighting the limited applicability of this approach.

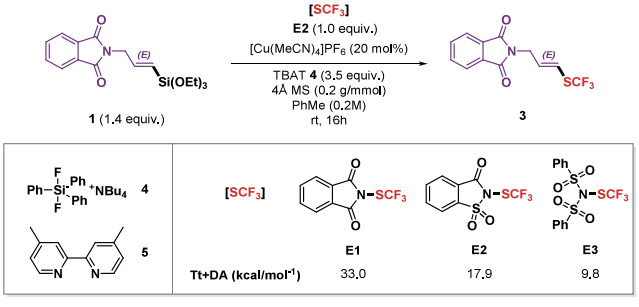
Similarly, existing strategies for the synthesis of *1,1′*-disubstituted $SCF_3$-alkenes remain limited.[9b,g,10,14,17] A few examples have been reported via Cu-catalyzed cross-coupling of halogenated alkenes (X = Br, I)[9b,g] or through the hydrotrifluoromethylthiolation of terminal alkynes.[14] However, these methods typically require harsh conditions, such as high temperatures or stoichiometric amounts of Cu, and often rely on tedious multistep preparation of the starting materials. Au-catalyzed trifluoromethylthiolation of *1,1′*-alkenyl iodide has also been demonstrated, offering access to well-defined products, yet structural diversity is constrained by the limited accessibility of the requisite vinyl precursors.[10] In 2020, Cho and co-workers introduced a complementary approach based on *α,β*-unsaturated carbonyl compounds, which serve as Michael acceptors in Baylis–Hillman-type reactions.[17b] While this strategy provides elegant access to *(1,1′)*-$SCF_3$-alkenes, it is intrinsically limited to activated olefins.

Inspired by our previous work on vinylsiloxane chemistry[18] and aiming to overcome the synthetic challenges associated with the stereocontrolled construction of $SCF_3$-disubstituted alkenes, we envisioned a direct trifluoromethylthiolation of vinylsiloxanes under Cu catalysis (Figure 1E). These organosilicon precursors are easily prepared in a stereodefined manner[19] and offer broad modularity, setting the stage for a unified and general approach to access all classes of $SCF_3$-alkenes.

Herein, we report a Cu(I)-catalyzed, stereospecific trifluoromethylthiolation of vinylsiloxanes, providing a straightforward and efficient access to $C_{vinyl}$–$SCF_3$ bonds under mild and operationally simple conditions. This versatile method tolerates a broad substrate scope (>30 examples), including diverse functional groups, pharmaceutical derivatives and agrochemical targets. Remarkably, (*E*)- and *(1,1′)*-disubstituted $SCF_3$-alkenes are obtained exclusively as single stereoisomers, while (*Z*)-$SCF_3$-alkenes are formed with unparalleled stereoselectivity, typically >95:5 *Z*/*E* ratios - the highest selectivities reported to date for nonstyrenic and nonacrylic derivatives.

We initiated our investigations with a comprehensive evaluation of the trifluoromethylthiolation of model *β*-(*E*)-vinylsiloxane (**1**) (see Supporting Information (SI)). A broad range of reaction parameters, including $SCF_3$ electrophiles, copper sources, ligands, solvents and additives were systematically examined. Optimal conditions were identified using a slight excess of vinylsiloxane (**1**, 1.4 equiv), providing the desired (*E*)-$SCF_3$-alkene (**3**) in an isolated yield of 70% (Table 1). The final catalytic system is straightforward, relying on a ligand-free Cu(I) salt at 20 mol %. Control experiments highlight the key role of the Cu(I) catalyst: even in the presence of tetrabutylammonium triphenyldifluorosilicate (**4**, TBAT), vinylsiloxane (**1**) alone remains insufficiently nucleophilic to react with saccharin-$SCF_3$ (**E2**, entry 2). In

**Table 1. Optimization of the Reaction Conditions**




| entry | variation | yield (%)[b] | entry | variation | yield (%)[b] |
|---|---|---|---|---|---|
| 1 | none | 74, 70[c] | 8 | 20 mol % **5** | 60 |
| 2 | w/o Cu | n.d. | 9 | TBAF | 7 |
| 3 | w/o TBAT **4** | n.d. | 10 | $TBAHF_2$ | 45 |
| 4 | w/o MS | 54 | 11 | 1.0 equiv **1** | 57 |
| 5 | nonactivated MS | 56 | 12 | $Cu(OTf)_2$ | 62 |
| 6 | **E1** | 21 | 13 | 10 mol % Cu | 40 |
| 7 | **E3** | n.d. | 14 | 5 mol % Cu | 21 |

[a]All reactions performed on a 0.20 mmol scale. [b]$^{19}F$ NMR yield using 3,3′-bis(trifluoromethyl)benzophenone as an internal standard. [c]Yield of isolated product after purification by flash chromatography. n.d. = not determined. See Supporting Information for additional details.



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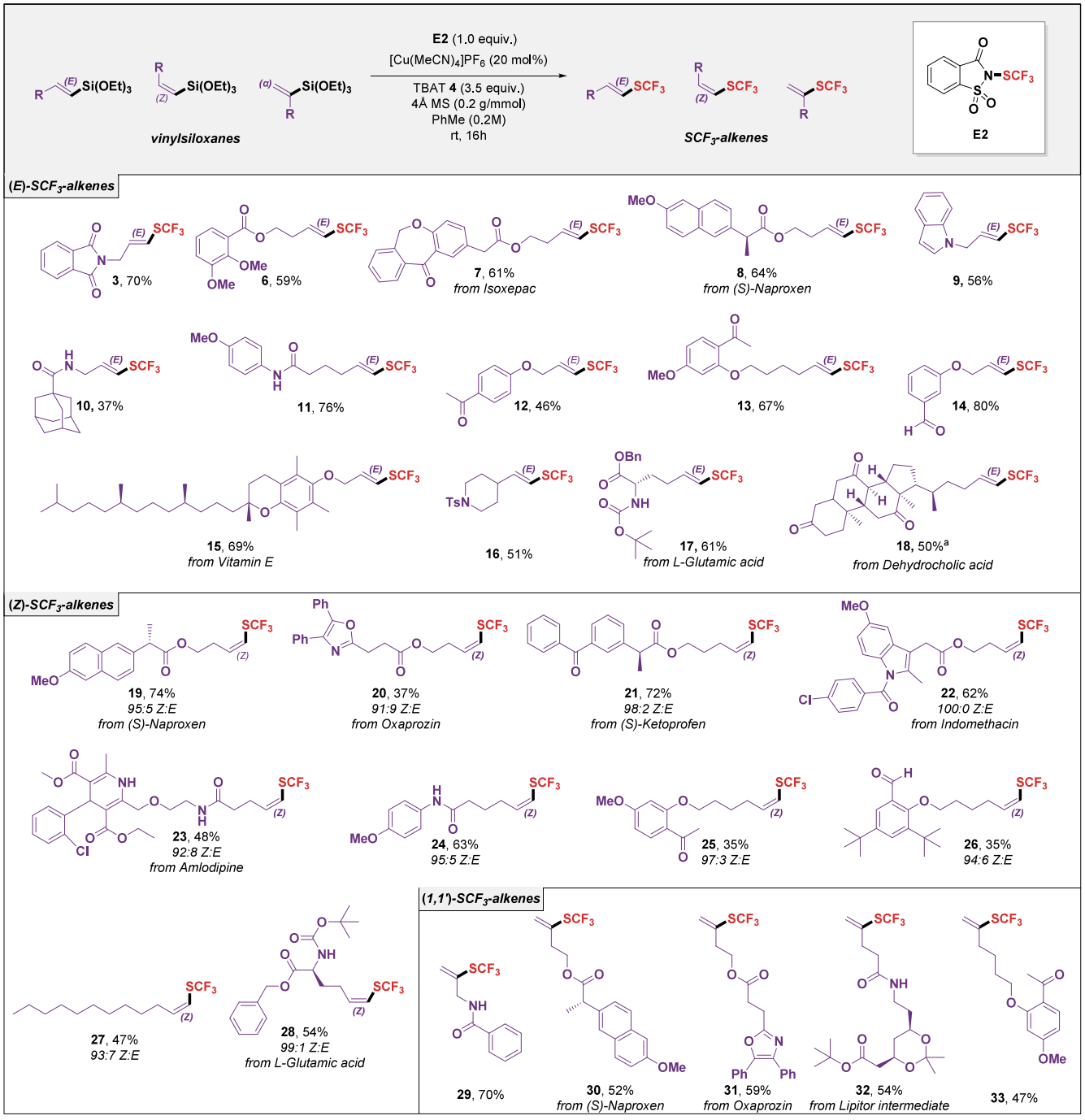


**Figure 2.** Substrate scope of $SCF_3$-alkenes. Reactions were carried out on a 0.30 mmol scale. Reaction conditions: vinylsiloxane (1.4 equiv), **E2** (1.0 equiv), $[Cu(MeCN)_4]PF_6$ (20 mol %), TBAT **4** (3.5 equiv), activated 4 Å MS (0.2 g/mmol) in PhMe (0.2 M), rt, 16 h. [a]Obtained as a mixture with the protodesilylated compound in a 77:23 ratio.

the absence of TBAT (**4**) both vinylsiloxane (**1**) and saccharin-$SCF_3$ (**E2**) are recovered (entry 3). Interestingly, activated 4 Å molecular sieves (MS) proved crucial for efficient conversion (entries 4−5). The choice of electrophile was guided by reported trifluoromethylthio cation-donating ability ($Tt^+DA$) scales.[20] Softer electrophiles such as (**E1**) delivered only moderate yields (entry 6), while overly reactive electrophiles like (**E3**) shut down the catalytic cycle (entry 7). Ligands commonly used in Cu-catalyzed trifluoromethylthiolation reactions such as 4,4′-dmbpy (**5**), proved detrimental under our conditions (entry 8).[4j] Replacing TBAT (**4**) with other fluoride sources led to decreased efficiency (entries 9−10). A slight excess of vinylsiloxane (**1**) was found to be necessary for optimal yield (entry 11). $Cu^{(II)}$ precatalysts could also promote the transformation (entry 13), while lowering the catalyst loading resulted in significantly reduced reactivity (entry 14).

With the optimized conditions in hand, we first examined the scope of (*E*)-$SCF_3$-alkenes accessible from the corresponding *β*-(*E*)-vinylsiloxanes (Figure 2). The reaction proceeds smoothly with nonstyrenic substrates, affording the desired products in 37−80% isolated yield, without any detectable isomerization. A broad range of functional groups is well


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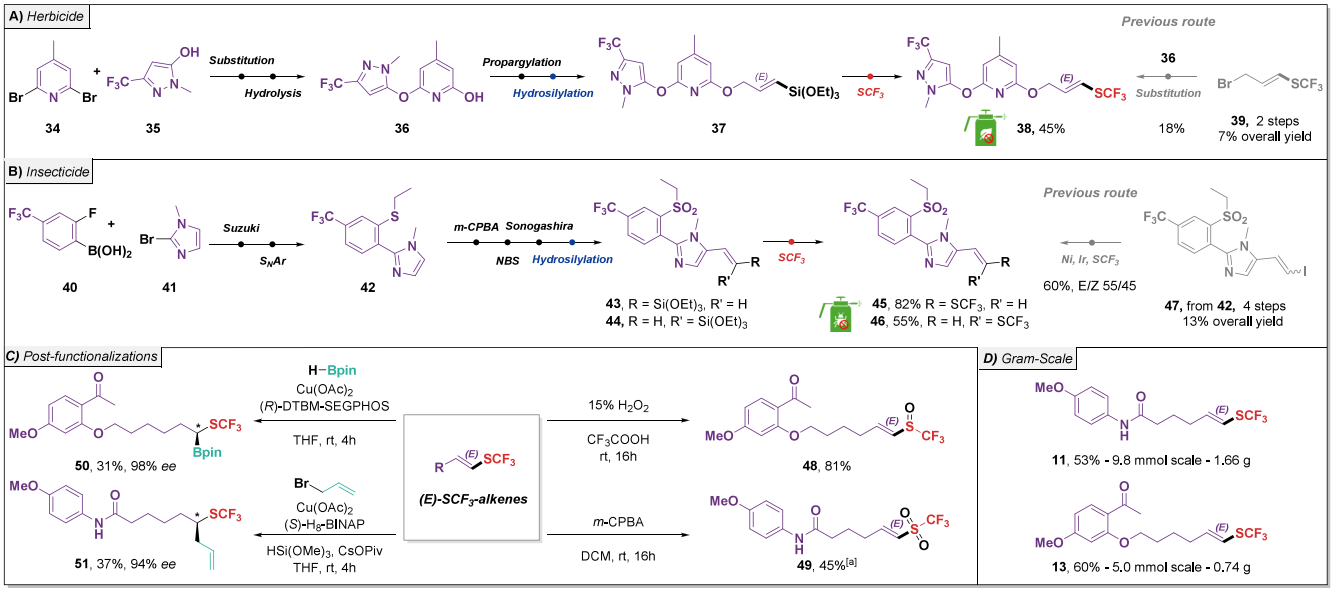


**Figure 3.** Applications and postfunctionalizations. (A) Synthesis of herbicide (**38**) and comparison with the original route.[22] (B) Synthesis of insecticide isomers (**45**–**46**) and comparison with Ghosh's methodology.[11] (C) Postfunctionalizations. (D) Gram-scale experiments. [a] $^{19}$F NMR yield using 3,3′-bis(trifluoromethyl)benzophenone as an internal standard. See Supporting Information for additional details.

tolerated. Ester-containing substrates (**6**–**8**) deliver the corresponding alkenes in 59–64% yield, while heteroaromatic (**9**) and amide-based derivatives (**10**–**11**) are compatible, delivering moderate to good yields. Sensitive functional groups such as aldehydes and ketones are fully compatible, providing products (**12**–**14**) in 46–80% yield. More complex $\beta$-(*E*)-vinylsiloxanes derived from Ni-catalyzed decarboxylative alkynylation developed by Baran[21] proved to be competent substrates, affording products (**16**–**18**) in 50–61% yield. Notably, the method is applicable to pharmaceutically relevant scaffolds such as Isoxepac (**7**) and (*S*)-Naproxen (**8**), demonstrating its synthetic versatility.

Having established the efficiency of the method for (*E*)-$SCF_3$-alkenes, we next turned to the synthesis of (*Z*)-$SCF_3$-alkenes from $\beta$-(*Z*)-vinylsiloxanes. Ten nonstyrenic examples (**19**–**28**) were prepared in 35–74% yield. To the best of our knowledge, this represents the highest level of *Z*/*E* selectivity reported for a nonstyrenic $SCF_3$-alkenes. Only minimal isomerization was observed, with (*Z*)-selectivities ranging from 91:9 (**20**) to fully stereopure material for the Indomethacin derivative (**22**). Once again, the reaction proved applicable to complex bioactive scaffolds. The successful functionalization of pharmaceutical derivatives, such as Oxaprozin (**20**), (*S*)-Ketoprofen (**21**), and Amlodipine (**23**), underscores the robustness and practical value of this strategy for stereodefined $SCF_3$ incorporation from silicon-based precursors.

Finally, (*1,1′*)-$SCF_3$-alkenes (**29**–**33**) were efficiently accessed from the corresponding $\alpha$-vinylsiloxanes, with yields ranging from 47% to 70%. These results highlight the generality of the transformation: no additional optimization was required, and the standard conditions (Table 1) could be directly applied to a wide variety of substrates, regardless of their steric or electronic properties. The ability to convert structurally diverse vinylsiloxanes into (*E*)-, (*Z*)-, or (*1,1′*)-$SCF_3$-alkenes using a unified catalytic system further underscores the broad applicability and robustness of this transformation.

To further demonstrate the synthetic utility of this transformation, we turned our attention to $SCF_3$-containing agrochemical scaffolds (Figure 3AB). Herbicide **38** was selectively synthesized in 45% yield in the final step (Figure 3A), providing a valuable alternative to the original procedure.[22a] More recently, a Ni/Ir metallaphotoredox strategy reported by Ghosh enables access to **38** using $AgSCF_3$ and was also applied to insecticidal targets **45**–**46** (Figure 3B).[11,22b] However, whereas this approach furnishes a 55/45 *E*/*Z* mixture, our platform delivers the corresponding products in fully stereopure form.

To demonstrate the synthetic versatility of the $SCF_3$-alkene products accessible through our method, we explored selected postfunctionalizations of the trifluoromethylthio moiety (Figure 3C, see SI for details). Simple oxidation enabled access to both sulfoxide (**48**) and sulfone (**49**). In addition, we leveraged recent advances by the Hirano group in enantioselective hydrofunctionalizations of $SCF_3$-alkenes.[23] Their methodologies could be applied to our substrates bearing various functional groups. The hydroboration of a ketone-containing alkene afforded **50** in 31% yield and excellent enantiomeric excess (98% ee), while the hydroallylation product (**51**) was obtained in 37% yield and 94% ee. Finally, the scalability of the method was demonstrated by performing gram-scale reactions with substrates **11** and **13**, delivering the desired $SCF_3$-alkenes in synthetically useful yields from 9.8 and 5.0 mmol reaction scales, respectively (Figure 3D).

Prompted by the slight *E*/*Z* isomerization observed in the (*Z*)-$SCF_3$-alkene series, mechanistic investigations were performed to elucidate the reaction pathway. These studies support a nonradical mechanism (see SI for details).

In summary, we report a robust and stereocontrolled copper-catalyzed trifluoromethylthiolation of vinylsiloxanes, enabling modular access to (*E*)-, (*Z*)-, and (*1,1′*)-$SCF_3$ alkenes with the highest *Z*/*E* selectivity reported to date under mild and operationally simple conditions. The method displays broad functional group tolerance, is readily scalable, and is


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applicable to a wide range of pharmaceutically and agrochemically relevant substrates. The resulting alkenes constitute versatile intermediates for downstream functionalizations, including selective sulfur oxidation and asymmetric hydrofunctionalization. Collectively, these features establish this transformation as a powerful and versatile platform for accessing structurally and stereochemically diverse $SCF_3$-containing alkenes.[24]

## ■ ASSOCIATED CONTENT

### Data Availability Statement

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

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.6c00527.

Experimental procedures, optimization study, graphics, spectroscopic data, and NMR spectra. (PDF)

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[+]Logan Salamone: Conceptualization, Methodology, Investigation, Visualization, Original draft, Funding Acquisition. Xavier Vanderbiest: Conceptualization, Methodology, Investigation, Review and Editing. Olivier Riant: Conceptualization, Methodology, Project Administration, Supervision, Review and Editing, Funding Acquisition. All authors have given approval to the final version of the manuscript.


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### Notes

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