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Letter

A Building Block Strategy for Construction of C(sp^3)–SCF_3 Bonds via Nickel-Catalyzed 1,2-Difunctionalization of Trifluoromethylthiolated Alkenes

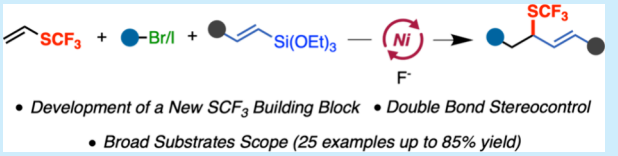
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ABSTRACT: The trifluoromethylthiol (SCF_3) group has emerged as a valuable motif in medicinal chemistry owing to its strong electron-withdrawing nature and its high lipophilicity. Despite significant advances in SCF_3 incorporation into a variety of molecules, the construction of C(sp^3)–SCF_3 bonds remains a notable challenge. Herein, we present a Ni-catalyzed 1,2-difunctionalization using a newly designed SCF_3-containing synthon readily accessible in a single step.



The incorporation of fluorinated motifs into biologically active molecules is a well-established strategy for modulating physicochemical and pharmacokinetic properties.[1] In particular, the introduction of fluorinated groups can influence pK_a values, conformational preferences, lipophilicity, and metabolic stability. Consequently, the development of efficient methodologies for their installation has attracted sustained interest over the past decades, with CF_3 and CF_2H groups being among the most extensively studied.[2] More recently, a new class of fluorinated substituents featuring a CF_3–heteroatom bond (OCF_3, NCF_3, and SCF_3) has emerged, offering expanded opportunities for molecular design in fluorine chemistry. Among these, the trifluoromethylthiol (SCF_3) group is particularly noteworthy due to its unique combination of properties. It exhibits exceptionally high lipophilicity (Hansch parameter π_x = 1.44) alongside a strong electron-withdrawing character (Hammett parameter σ_p = 0.50) (Figure 1A).[3] Importantly, these properties can be fine-tuned through variation of the sulfur oxidation state (sulfide, sulfoxide, or sulfone), thereby enabling precise modulation of molecular behavior. As a result, the SCF_3 group has found increasing utility not only in medicinal chemistry[4] but also in materials science, including applications in organic electronics (transistor components),[5] organic light-emitting devices (OLED),[6] and polymer design, where it can contribute to enhanced recyclability.[7]

Given these diverse applications, the development of efficient methodologies for the incorporation of the SCF_3 group remains of significant interest. While the synthesis of C(sp^2)–SCF_3 compounds has been extensively investigated,[8] the formation of C(sp^3)–SCF_3 bonds is comparatively underdeveloped. To date, the most common approach relies on C–S bond formation, which can be achieved through several strategies, including nucleophilic substitution of alkyl halides or activated alcohol derivatives,[9] functionalization at

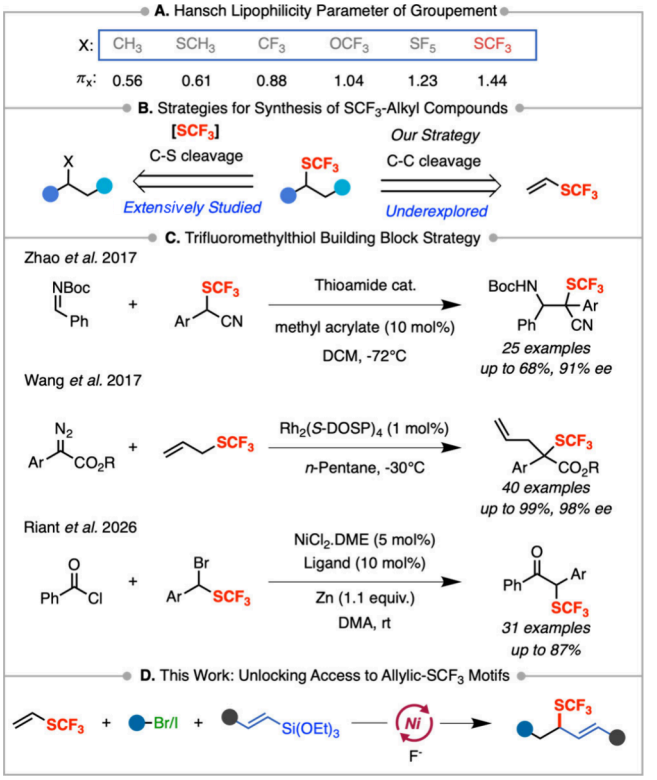


Figure 1. State of the art of SCF_3–alkyl compound synthesis.

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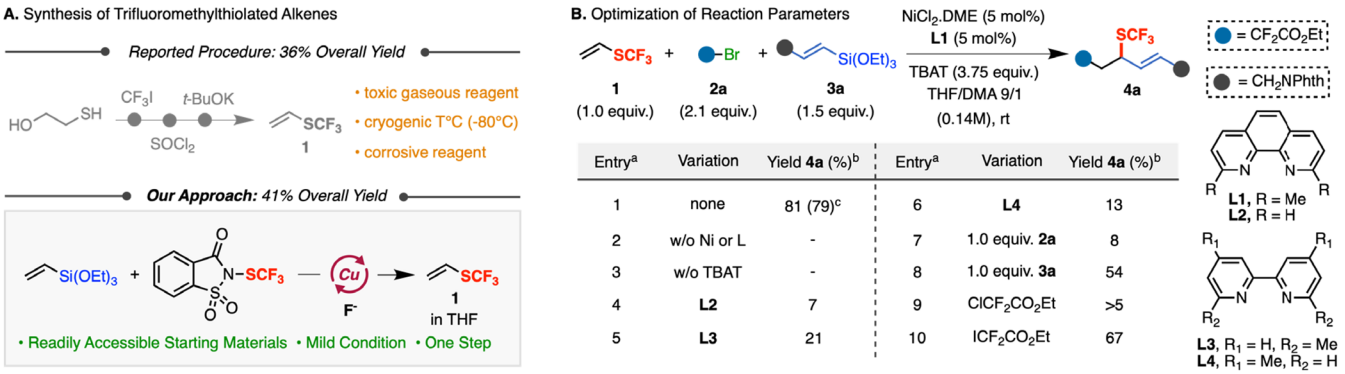


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Entry[a]	Variation	Yield 4a (%)[b]	Entry[a]	Variation	Yield 4a (%)[b]
1	none	81 (79)[c]	6	**L4**	13
2	w/o Ni or L	-	7	1.0 equiv. **2a**	8
3	w/o TBAT	-	8	1.0 equiv. **3a**	54
4	**L2**	7	9	$ClCF_2CO_2Et$	>5
5	**L3**	21	10	ICF_2CO_2Et	67

Figure 2. (a) Synthesis of the newly designed SCF_3-containing synthon. (b) Optimization of reaction parameters. [a]All reactions performed on a 0.1 mmol scale. [b]^{19}F NMR yield using 3,3′-bis(trifluoromethyl)benzophenone as an internal standard. [c]Isolated yield after purification by flash chromatography.

the α-position of carbonyl compounds,[10−12] and radical processes such as decarboxylative transformations or direct C−H functionalization (Figure 1B).[13] Despite their utility, these approaches often afford products with limited molecular complexity and restrict the broader implementation of organometallic catalysis. In this context, an alternative strategy based on C−C bond formation using SCF_3-containing reagents appears particularly attractive. Although still underexplored, such a building-block approach offers considerable potential, given the wide array of well-established methodologies available for C−C bond construction. To date, only a limited number of examples have been reported employing a building-block strategy for the introduction of the SCF_3 group (Figure 1C).[14] In this context, the first report described an enantioselective Mannich-type reaction between *N*-Boc imines and trifluoromethylthiolated α-cyano benzyl compounds, relying on a chiral bifunctional phosphine catalyst derived from amino acids.[14a] In addition, an elegant Rh(I)-catalyzed Doyle−Kirmse reaction has been reported, involving a [2,3]-sigmatropic rearrangement of a sulfonium ylide generated from an allyl-SCF_3 building block, thereby affording enantioenriched quaternary carbon centers.[14b] More recently, our group has developed a Ni-catalyzed reductive coupling between acyl chlorides and trifluoromethylthiolated benzyl bromides, enabling access to α-trifluoromethylthiolated ketones.[14c] It is worth noting that the hydroboration/allylation of SCF_3-disubstituted alkenes has previously been reported independently by the Hirano and Wang groups.[14d−f] Despite these promising advances, the use of SCF_3-containing reagents in building-block strategies remains largely restricted to the formation of products bearing the SCF_3 group at the benzylic position.

Drawing on our prior work on the Cu-catalyzed synthesis of C_{vinyl}−SCF_3 motifs,[8i] we hypothesized that subsequent functionalization of the double bond would enable access to C(sp^3)−SCF_3 bonds. In parallel, based on our recent report on the nickel-catalyzed 1,2-difunctionalization of styrenes using vinylsiloxanes,[15] we envisioned that vinyl−SCF_3 derivatives could serve as suitable partners in such transformations. This hypothesis led to the present study, in which we report a Ni-catalyzed 1,2-difunctionalization of trifluoromethylthiolated alkenes with vinylsiloxanes, providing straightforward access to allylic SCF_3-containing products (Figure 1D). Nevertheless, several challenges were anticipated. First, it remained unclear whether the SCF_3 group would exert sufficient control over regioselectivity. Second, we have previously observed that electron-deficient alkenes are ineffective in difunctionalization reactions involving vinylsiloxanes. Finally, achieving selective difunctionalization in preference to competing Giese-type addition represents a key challenge.

We initiated our investigation with the synthesis of trifluoromethylthiolated alkene **1**. Previously reported methods for their preparation suffer from several limitations, including the use of gaseous, toxic, and corrosive reagents (CF_3I, $SOCl_2$), as well as the requirement for cryogenic conditions (−80 °C) (Figure 2A).[16] Our prior work on the Cu-catalyzed synthesis of C_{vinyl}−SCF_3 compounds emerged as a more practical and efficient alternative for accessing **1**.[8i] Following a slight modification of the protocol, compound **1** can be obtained in a single step as a solution in THF (purification by atmospheric pressure distillation) from readily available and cheap vinyltriethoxysilane and an electrophilic SCF_3 reagent. Notably, the latter can be conveniently prepared from inexpensive saccharin.

Optimization of the reaction conditions for the 1,2-difunctionalization was conducted using trifluoromethylthiolated alkene **1**, ethyl bromodifluoroacetate **2a**, and a model vinylsiloxane **3a** (Figure 2B). Key parameters, including the catalytic system, reactant stoichiometry, solvent, and concentration, were systematically evaluated. Under the optimized conditions, the desired product **4a** was obtained in 79% isolated yield (see the Supporting Information (SI) for additional details). Control experiments were first conducted to probe the reaction parameters. In the absence of nickel or ligand, no formation of the desired product was observed (Figure 2B, entry 2). Similarly, omission of the fluoride source (TBAT) completely inhibited the reaction, highlighting its crucial role in activating the siloxane to generate the hypervalent species required for transmetalation (Entry 3). A range of ligands was subsequently evaluated, revealing a strong ligand dependence. The reaction proceeded efficiently only in the presence of 2,9-dimethylphenanthroline **L1**, whereas 1,10-phenanthroline **L2** afforded the desired product **4a** in only 7% yield (Entry 4), and bipyridine derivatives **L3**, **L4** led to low yield (Entries 5 and 6, 13−21%). The stoichiometry of the coupling partners also proved critical. Reducing the amount of ethyl bromodifluoroacetate **2a** to 1.0 equiv. significantly decreased the yield to 8% (Entry 7), while the use of 1.0 equiv of vinylsiloxane **3a** still provided the product **4a** in moderate yield, albeit with a notable decrease (Entry 8, 54%). Finally, the nature of the halide had a pronounced effect on the reaction outcome. Substitution of bromide with chloride

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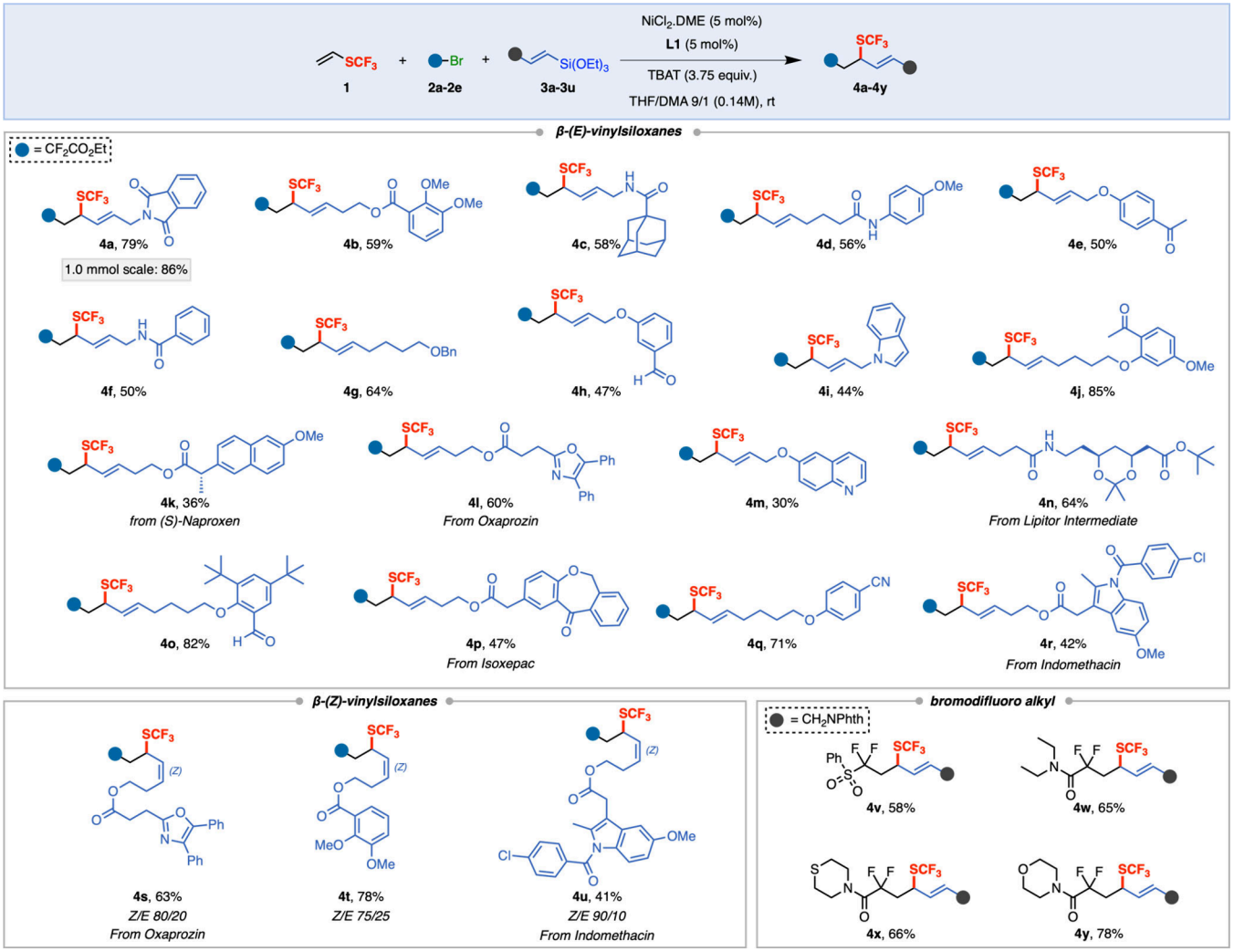


Figure 3. Substrate scope of Ni-catalyzed 1,2-difunctionalization of trifluoromethylthiolated alkenes. All reactions performed on 0.2 mmol scale. Reaction conditions: vinyl-SCF_3 **1** (0.15 M in THF, 1.0 equiv., 0.2 mmol), alkyl halide (2.1 equiv, 0.42 mmol), vinylsiloxane (1.5 equiv, 0.3 mmol), $NiCl_2$.DME (5 mol %, 0.01 mmol), **L1** (5 mol %, 0.01 mmol), TBAT (3.75 equiv, 0.75 mmol) in THF/DMA 9/1 (0.14 M), rt, 16 h.

resulted in only trace amounts of product **4a** (Entry 9), whereas ethyl iododifluoroacetate delivered the desired product **4a** in a satisfactory 67% yield (Entry 10).

With the optimized conditions in hand, we next evaluated the generality of the transformation. We first examined *β*-(*E*)-vinylsiloxanes, which proved to be broadly compatible, affording the desired products without detectable isomerization (Figure 3). A wide range of functional groups was well tolerated under the reaction conditions. Notably, sensitive functionalities such as aldehydes (**4h**, **4o**), cyano (**4q**) and ketones (**4e**, **4j**, **4p**) were readily accommodated, providing the corresponding products in moderate to excellent yields (47−85%). Amide derivatives (**4a**, **4c**, **4d**, **4f**, **4n**) delivered the allylic-SCF_3 products in 50−79% yield, while ester-containing substrates (**4b**, **4k**, **4l**, **4n**, **4p**, **4r**) exhibited similar compatibility. Furthermore, various heterocyclic motifs, including indole (**4i**, **4r**), oxazole (**4l**), and quinoline (**4m**), were successfully tolerated affording the desired allylic-SCF_3 in moderate yields. The applicability of this methodology to complex molecules was further demonstrated through the synthesis of pharmaceutically relevant derivatives, including those derived from (*S*)-naproxen (**4k**), oxaprozin (**4l**), Lipitor intermediate (**4n**), isoxepac (**4p**) and indomethacin (**4r**) highlighting its potential utility in drug discovery for the direct installation of allylic-SCF_3 motifs. We next examined *β*-(*Z*)-vinylsiloxanes under the optimized conditions. Gratifyingly, the corresponding (*Z*)-allylic-SCF_3 products (**4s**−**4u**) were obtained in good yields (41−78%), albeit with moderate erosion of the stereochemical integrity (*Z*/*E* = 75:25 to 90:10). Finally, the scope of the difluoroalkyl bromide component was investigated, affording the corresponding difunctionalized products (**4v**−**4y**) in good yields (58−78%).

A radical probe experiment was conducted in the presence of TEMPO, under which conditions no formation of the desired product **4a** was observed (Figure 4). In addition, the corresponding TEMPO−CF_2CO_2Et adduct was detected by ^{19}F-NMR and HRMS, supporting the involvement of a radical intermediate. These findings are consistent with previously proposed mechanisms for Ni-catalyzed 1,2-difunctionalization reactions.[17]

Based on previous reports,[17] a plausible mechanism is proposed. Vinylsiloxane **3a** is first activated by fluoride to generate a hypervalent silicate species **3a'**, which undergoes transmetalation with a Ni(I) complex **A** to form a vinyl-Ni(II) intermediate **B**. This species can then engage in a single-electron transfer (SET) with the alkyl halide **2a**, affording

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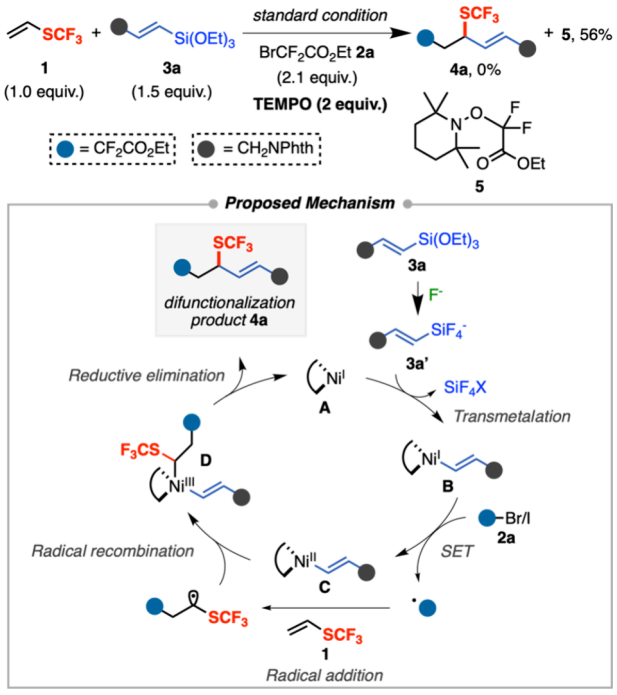


Figure 4. Radical probe experiment and proposed mechanism.

intermediate **C** along with a alkyl radical. The resulting radical undergoes Giese-type addition to trifluoromethylthiolated alkene **1**, generating a carbon-centered radical at the α-position of the SCF_3 group. Subsequent recombination with intermediate **C** furnishes a Ni(III) species **D**. Finally, reductive elimination from **D** delivers the 1,2-difunctionalized product **4a**, while regenerating the active Ni(I) catalyst **A**.

In summary, we have developed a new SCF_3-containing synthon that is readily accessible in a single step from inexpensive and widely available starting materials. This reagent was successfully employed in a Ni-catalyzed 1,2-difunctionalization of alkenes. The use of vinylsiloxanes in this transformation enables stereocontrolled formation of the double bond, providing access to both (*E*)- and (*Z*)-allylic SCF_3-containing products. Moreover, this methodology proceeds under mild conditions and exhibits broad functional group tolerance, allowing the efficient synthesis of pharmaceutically relevant derivatives.

■ 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.6c02895.

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

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Author Contributions

Xavier Vanderbiest: Conceptualization, Methodology, Investigation, Visualization, Original Draft, 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

The authors declare no competing financial interest.

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