Regioreversed Carbosulfenylation of Fluoroalkenes via Nickel-Mediated Radical Sorting

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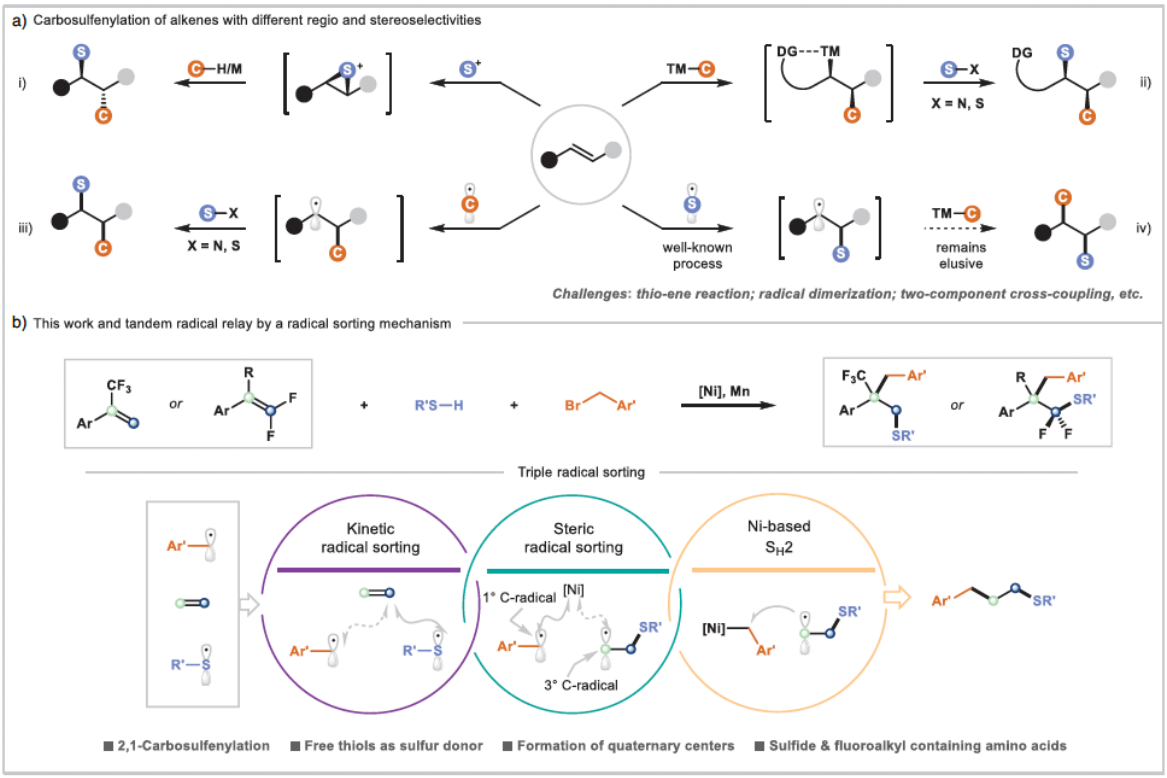
Introduction

Organosulfur compounds are prevalent in medications, bioactive compounds, natural products, catalysts, and functional materials.[1–4] Moreover, the sulfide moiety has been identified as a valuable synthetic handle for various manipulations.[5,6] Consequently, a myriad of C–S bond forming processes have been developed.[7–11] Among these methods, the olefin carbosulfenylation reaction has garnered considerable attention due to its ability to facilitate the simultaneous formation of C–C and C–S bonds, thereby enabling rapid construction of complex molecular architectures. Conventional carbosulfenylation reactions typically rely on the activation of C=C double bonds by electrophilic sulfenylating reagents. These reactions proceed through a thiiranium ion intermediate followed by a nucleophilic ring-opening and provide the anti-isomer (Scheme 1a, i).[12–16] The regioselectivity of these processes is dictated by the substitution pattern of the thiiranium ion intermediate. To date only a limited range of C-nucleophiles can be employed in the ring opening, such as cyanide,[12] acetylides,[13] and organozinc reagents.[16] To address some of these limitations, in 2022 Engle's group introduced an elegant Ni-catalyzed carbosulfenylation method utilizing cleverly designed *N*-sulfenyl sulfamides with arylboronic esters or alkyl zinc nucleophiles (Scheme 1a, ii).[17,18] This approach is dependent on a chelation-directed addition of an Ar–Ni to the olefin, followed by Ni^{III}-mediate C–S reductive elimination, enabling the difunctionalization that provides the *syn* diastereomer. In a parallel study, Wang and colleagues reported a similar carbosulfenylation reaction using simple disulfides as sulfur donors.[19] Despite these useful advances, the requirement for electrophilic sulfur sources and directing groups decrease their atom-economy and practical utility and leave room for improvement.

In recent years, a radical-relay strategy has emerged as a powerful synthetic platform for the difunctionalization of olefins, owing to the versatile reactivity and high selectivity associated with open-shell intermediates.[20–24] Current methods have focused on a sequence involving *C*-centered radical additions to olefins followed by interception of the resulting radical intermediates with sulfenylating reagents to yield the 1,2-carbosulfenylation products (Scheme 1a, iii). This mode of addition is exemplified by the work of Song and co-workers.[25,26] In contrast, regioselective addition of *S*-centered radicals to alkenes followed by capture with a carbon-based trap remains underexplored. This reversal of regioselectivity from the abovementioned processes has the potential to expand accessibility to the synthesis of isomeric sulfides (Scheme 1a, iv).

As part of our long-term interest in the functionalization of olefins,[27–29] we are intrigued by the challenge



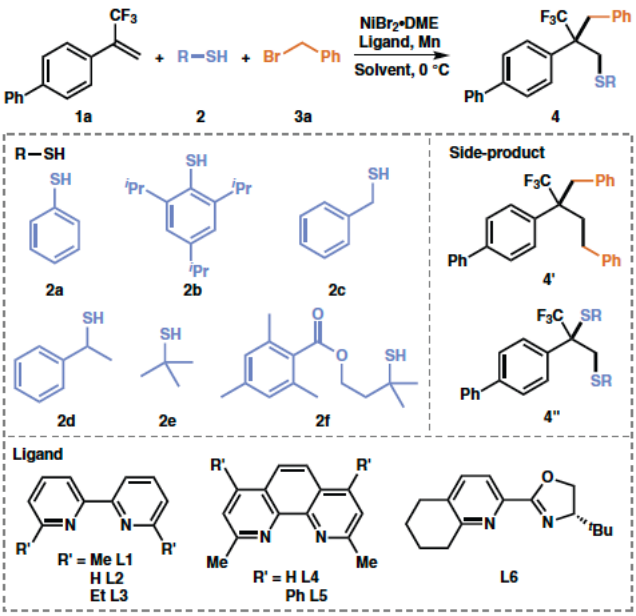
Scheme 1. Background and reaction design. a) Carbosulfenylation of alkenes with different regio and stereoselectivities. b) This work and tandem radical relay by a radical sorting mechanism.

of designing a radical relay carbosulfenylation that exhibits a *reversed regioselectivity*, thereby complementing the thiiranium and Ni-catalyzed directed strategies outlined above. Furthermore, one of the thrusts of our research efforts has been to prepare fluorinated products, due to the beneficial impact of fluorine-containing biologically active compounds.[30–32] Based on our study of Ni-catalyzed dibenzylation of trifluoroalkenes,[33] and inspired by hydrogen atom transfer (HAT) from thiols to C-centered radicals,[34] we hypothesized that integrating this HAT process into the radical relay dicarbofunctionalization reaction could enable the desired carbosulfenylation. Herein, we report a Ni-catalyzed tandem radical relay 2,1-carbosulfenylation reaction of trifluoromethyl- and *gem*-difluoroalkenes, which enables the efficient construction of pharmaceutically relevant trifluoromethylated and thiodifluoromethylated quaternary centers (Scheme 1b).[35,36] In contrast to established 1,2-carbosulfenylation protocols, our method utilizes readily available thiols directly, eliminating the need for electrophilic sulfenylating reagents. Furthermore, simple benzyl bromides serve as both carbon sources and activators of thiols in our approach, allowing for broad functional group tolerance and late-stage functionalization.

Results and Discussion

As outlined above, the goal of this work is to design the first general regioreversed radical carbosulfenylation of alkenes that proceeds through benzyl- and sulfur-based radicals. Outside of steering the regioselectivity, the primary challenge within our proposed mechanistic framework (Scheme 1b) is envisioned to stem from competing side reactions that arise from the multifaceted reactivity of *S*-radical intermediates and related species (e.g., thiols, disulfides). These side reactions include the thio-ene reaction,[37,38] radical dimerizations,[39,40] and two-component cross-coupling processes. Building on our previously reported Ni-catalyzed dibenzylation of trifluoromethylalkenes,[33] for proof-of-concept we selected thiophenol **2a** (BDE_{S-H} 78 kcal mol^{-1}), which possesses suitable bond dissociation energy (BDE_{C-H} of toluene = 89 kcal mol^{-1}) to pair with benzylic radicals for rapid HAT, a key requirement of the envisioned kinetic sorting process (Scheme 1b).[41] It is worth noting that thiophenols have been utilized in alkyl radical-triggered C_{sp2}– S coupling

Table 1: Optimization of reaction conditions.[a)]

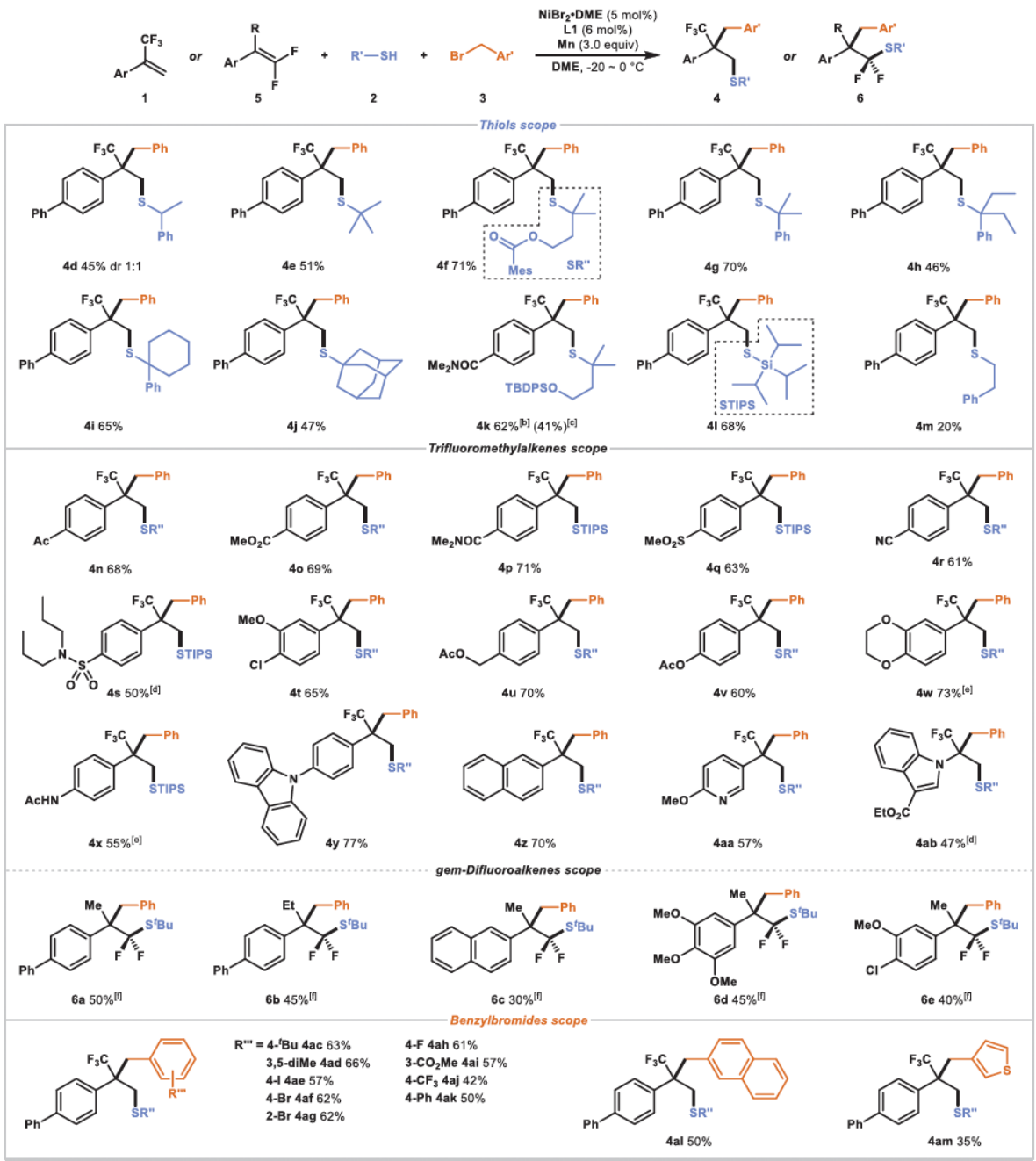


Entry	RSH	Ligand	Solvent	Assay yield/%[b)] 4	4′	4″
1	**2a**	**L1**	THF	trace	0	0
2	**2b**	**L1**	THF	trace	0	0
3	**2c**	**L1**	THF	trace	0	0
4	**2d**	**L1**	THF	45	13	0
5	**2e**	**L1**	THF	50	6	4
6	**2f**	**L1**	THF	60	6	3
7[c)]	**2f**	**L1**	THF	60	5	3
8[d)]	**2f**	**L1**	THF	14	0	0
9[e)]	**2f**	**L1**	THF	20	4	–
10	**2f**	**L1**	DME	71(71)[f)]	6	4
11	**2f**	**L1**	DMA	66	10	0
12	**2f**	**L2**	DME	63	5	1
13	**2f**	**L3**	DME	0	0	0
14	**2f**	**L4**	DME	58	5	6
15	**2f**	**L5**	DME	60	6	2
16	**2f**	**L6**	DME	trace	0	0

[a)] Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), **2** (0.6 mmol, 3.0 equiv), **3a** (0.6 mmol, 3.0 equiv), Ni precatalyst (0.01 mmol, 5 mol%), ligand (0.012 mmol, 6 mol%) and Mn (0.6 mmol, 3.0 equiv), in solvent (1 mL) at 0 °C for 12 h. [b)] Assay yield determined by ^{19}F NMR analysis with $PhOCF_3$ as internal standard. [c)] Performed at −20 °C. [d)] Performed at −30 °C. [e)] Performed at room temperature. [f)] Isolated yield.

reactions.[42,43] In our initial attempts, **2a** was examined with trifluoromethylalkene **1a** and benzyl bromide **3a** under the conditions established for dibenzylation reactions (using 10 mol% $NiBr_2$•DME and 12 mol% 2,2-dimethyl bipyridine, **L1**). Only trace amounts of desired product **4a** was detected, however, while appreciable quantity of PhSSPh were observed (Table 1, entry 1). This result suggested the formation of an *S*-centered radical that dimerized before it could add to the double bond of **1a**. To bias the kinetic sorting, we replaced **2a** with sterically more hindered 2,4,6-tri-iso-propylbenzenethiol **2b**, anticipating that its steric hinderance would suppress dimerization (entry 2). Unfortunately, no improvement was observed and the disulfide derived from **2b** was produced. Subsequently, aliphatic thiols, such as benzylthiols **2c** and **2d**, were examined. It was found that the secondary benzylthiol, 1-phenylethane-1-thiol (**2d**) gave rise to the desired

Table 2: Substrate scope.[a)]



[a)] Reaction conditions: **1** (0.2 mmol, 1.0 equiv), **2** (0.6 mmol, 3.0 equiv), **3** (0.6 mmol, 3.0 equiv), $NiBr_2$•DME (0.01 mmol, 5 mol%), **L1** (0.012 mmol, 6 mmol%), Mn powder (0.6 mmol, 3.0 equiv) in DME (1 mL) at 0 °C. [b)] NMR yield. [c)] Isolated yield of sulfone following oxidation by H_2O_2. [d)] $NiBr_2$•DME (15 mol%) and **L1** (18 mol%) were used. [e)] Performed at −30 °C. [f)] BnBr (0.9 mmol, 4.5 equiv), ^{t}BuSH (0.9 mmol, 4.5 equiv) and Mn (0.9 mmol, 4.5 equiv) were used.

product **4d** in 45% assay yield (entry 4), while the parent benzyl thiol **2c** was ineffective (entry 3). The encouraging result with **2d** confirmed the feasibility of our proposed kinetic sorting in the carbosulfenylation reaction. The unusual reactivity discrepancy between **2c** and **2d** suggested that the reaction benefitted from the increased steric hinderance of the thiol to slow disulfide production. Notably, both dibenzylation and dithiolation side products were observed in the reaction, while the hydrosulfenylation product, resulting from the thio-

ene reaction, was not detected (see the Supplementary Information for details). The assay yield of the desired product increased to 50% by using *tert*-butyl thiol **2e** (entry 5). To facilitate the purification of the desired carbosulfenylation product, a tertiary thiol with a pendant ester (**2f**) was employed, which provided the target product **4f** in 60% yield (entry 6). Ester-bearing **2f** was used for the remainder of the optimization as it simplified TLC analysis and product isolation. At −20 °C the reaction exhibited the same conversion as at 0 °C (entry 7); however, further lowering the temperature to −30 °C resulted in lower conversion (entry 8). In addition, conducting the reaction at room temperature generated substantial amounts of unidentifiable byproducts, consequently resulting in a reduced yield of **4a** (20%, entry 9). A significant improvement was made upon changing solvent to DME (71% yield, entry 10), while DMA was also suitable (66% yield, entry 11).

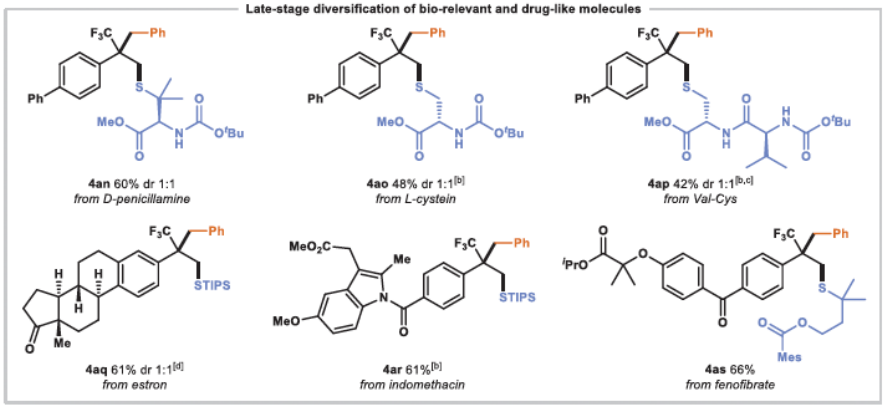
We next examined a series of substituted bipy and phenanthrene ligands for the catalyst. Ligands screening indicated 6,6^1-dimethyl-2,2^1-bipyridyl (**L1**) showed the highest efficiency, with other ligands providing 0%–63% assay yield (entries 12 to 16). Other nickel precatalysts, such as $NiCl_2$•DME, $Ni(OTf)_2$, and $Ni(COD)_2$, were effective but led to diminished assay yield of **4f** (60%–68%, see Table S6 for details). Control experiments revealed the essential role of catalytic Ni, ligand, and Mn in the transformation (see the Supplementary Information for details). After identifying optimized conditions, we investigated the generality of the reaction (Table 2). As shown above, both *sec*- and *tert*-alkyl thiols served as viable sulfur sources (**4d-4f**), with the latter exhibiting superior performance. We then investigated the impact of steric hinderance on product formation through a series of *α*,*α*-disubstituted benzylthiols (**4g-4i**). Notably, *gem*-dimethyl substituents gave the highest yield (**4g**, 70%), whereas both increased (**4h**, 46%) or decreased bulkiness (**4i**, 65%) around the sulfur atom led to diminished reaction efficiency. Additionally, 1-adamantanethiol and a tertiary thiol featuring a pendant silylether were tolerated, leading to **4j** and **4k** in 47% and 62% yields, respectively. It is noteworthy that HS–Si^{i}Pr$_3$ worked efficiently (68% yield), enabling desilylation and further elaboration on the thiol moiety (**4l**). Consistent with the steric trend observed in thiol screening, a less hindered primary alkyl thiol afforded the product in modest yield (**4m**, 20%).

With regard to the trifluoromethylalkenes, the reaction displayed good functional group compatibility by tolerating *α*-CF_3 styrenes adorned with a range of electron-withdrawing groups on the phenyl ring, such as 4-Ac (**4n**, 66%), 4-CO_2Et (**4o**, 69%), 4-CONMe$_2$ (**4p**, 71%), 4-SO_2Me (**4q**, 63%), 4-CN (**4r**, 61%), 4-$SO_2N^iPr_2$ (**4s**, 50%) and halide (**4t**, 65%). The reaction with substituted alkyl 4-($AcOCH_2$) (**4u**, 70%) and aromatic rings bearing electron-donating substituents 4-OAc (**4v**, 60%), 4-alkoxy (**4w**, 73%), and 4-NHAc (**4x**, 55%) and *N*-carbazole (**4y**, 77%) groups, also proceeded with good yields. The reaction is amenable with trifluoromethylalkenes derived from fused aromatic (**4z**, 70%) and pyridyl (**4aa**, 57%) groups. Indoles are among the most common heterocyclic structures in drug molecules.[44] We were pleased to find that the transformation could be extended to *N*-trifluoromethylalkenyl indole (**4ab**, 47%), showcasing the generality of the method.

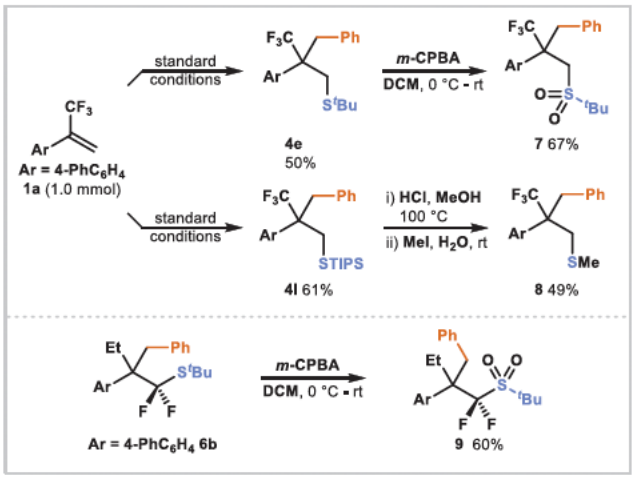
Following the successful carbosulfenylation of trifluoromethylalkenes, we were motivated to broaden the application of the protocol. We thus examined *gem*-difluoroalkenes, which possess similar innate properties to trifluoromethylalkenes, such as susceptibility to nucleophilic/radical addition, and a tendency to undergo defluorinative functionalization (Table 2, bottom rows), under slightly modified conditions. While mono-aryl substituted *gem*-difluoroalkenes have been reported to undergo hydrothiolation by the Dilman group,[45] under our carbosulfenylation reaction conditions, only a defluorinative thiolyative product was obtained. In contrast, disubstituted *gem*-difluoroalkenes proved to be viable substrates for our carbosulfenylation reaction, offering an efficient way to thiodifluoromethylated quaternary centers. The scope with respect to *gem*-difluoroalkenes was briefly explored. While the alpha-methyl derivative led to **6a** in 50% yield, the alpha-ethyl gave slightly lower yield (**6b**, 45%). Substituents with varying electronic properties were tolerated, producing the corresponding difluoroalkylthioether **6c**–**6e** in 30%–45% yields. Finally, we examined the scope of benzyl bromides in our carbosulfenylation reaction. Overall, these studies demonstrated applicability across benzyl bromides decorated with various functional groups, including alkyl, halides, ester, and CF_3, giving synthetically useful yields of products (**4ac–4ak**, 42%–66%). Excellent chemoselectivity was observed with benzyl bromides bearing C(sp^2)–Br (**4af** and **4ag**) and even C(sp^2)–I (**4ae**) groups, to facilitate subsequent cross-coupling transformations. It is noteworthy that benzyl bromides bearing 4-Br (**4af**) or 2-Br (**4ag**) substituents were equally effective, suggesting that benzylation was less sensitive to steric encumbrance. Furthermore, 2-(bromomethyl)naphthylene and 3-(bromomethyl)thiophene were also viable, albeit in attenuated yields (**4al**, 50%; **4am**, 35%).

To demonstrate the synthetic potential of this method for late-stage functionalization, we investigated the carbosulfenylation within complex settings (Table 3). Considering the prevalence of sulfenyl groups in bio-relevant molecules, we initially tested the reaction with amino acids that contained sulfenyl groups. *N*-protected D-penicillamine could be functionalized on the sulfenyl moiety smoothly, thereby offering CF_3-containing derivative **4an** in 60% yield. Of note, a more common amino acid, L-cystein was also compatible in the protocol with simple protection (**4ao**), highlighting the practical utility. Our method is suitable for peptides, as exemplified by val-cystein, delivering the desired product **4ap** in synthetically useful yield. Furthermore, the trifluoromethylalkenes derived from indomethacin, estron, and fenofibrate were examined. Under the optimized reaction conditions, the reactions proceeded well to afford the carbosulfenylation products **4aq-4as** in 61%–66% yields. Given the free-radical nature of these reactions, the enantioenriched thiols and alkenes afforded equal mixtures of diastereomers.

Table 3: Late-stage diversification of the bio-relevant and drug-like molecules.[a)]



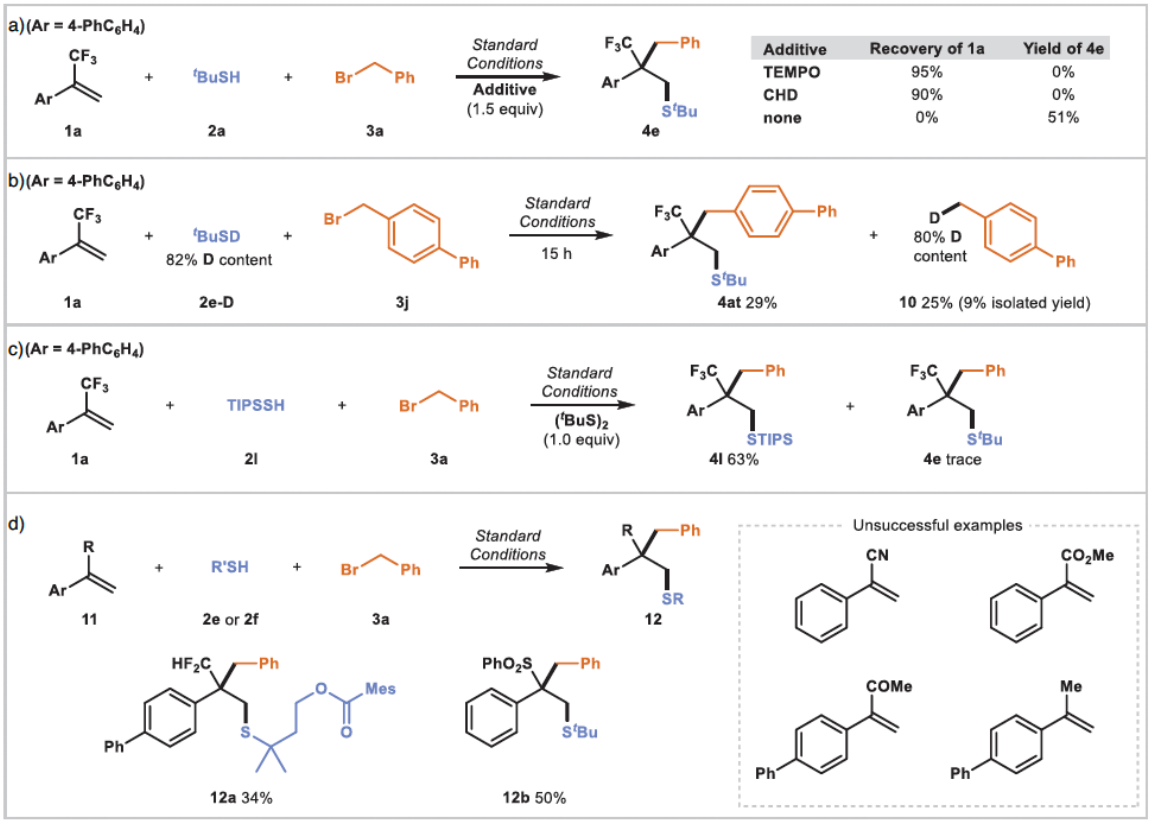
[a)] Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), thiol (0.6 mmol, 3.0 equiv), **3a** (0.6 mmol, 3.0 equiv), $NiBr_2$•DME (0.01 mmol, 5 mol%), **L1** (0.012 mmol, 6 mmol%), Mn powder (0.6 mmol, 3.0 equiv) in DME (1 mL) at 0 °C. [b)] $NiBr_2$•DME (0.030 mmol, 15 mol%), **L1** (0.036 mmol, 18 mmol%). [c)] DME/DMA (v/v 1:1, 1 mL) was used. [d)] Performed at −30 °C.



Scheme 2. Synthetic applications. a) ^{t}BuSH or TIPSSH (3.0 equiv), BnBr (3.0 equiv), Mn (3.0 equiv), $NiBr_2$•DME (5 mol%), **L1** (6 mol%), DME (0.2 M). b) *m*-CPBA (4.0 equiv), DCM (0.1 M), 0 °C-rt. c) (i). 6 M HCl, MeOH (0.05 M), 100 °C; (ii). MeI (1.1 equiv), H_2O (0.1 M), rt. d) *m*-CPBA (2.5 equiv), DCM (0.3 M), 0 °C-rt.

The synthetic utility of the carbosulfenylation products was further showcased by the transformations of the

thioether moiety (Scheme 2). First, we performed the carbosufenylation reactions on a 1 mmol scale, which furnished compounds **4e** and **4l** in 50% and 61% yields, respectively, without significant loss of reaction efficiency. Compound **4e** was then oxidized to the corresponding sulfone **7** with a yield of 67%. Meanwhile, the silylthioether (**4l**) underwent desilylation to yield a free thiol with 6 M HCl, which was subsequently alkylated with Me–I to produce thioether **8** in 49% yield over two steps. Furthermore, *α*,*α*-difluoroalkylthioether **6b**, derived from *gem*-difluoroalkene, was smoothly oxidized by *m*-CPBA to provide sulfone **9** in 60% yield. Radical difunctionalizations of olefins involving HAT steps to generate key radical intermediates have been explored in the context of different reactions.[46–53] In general, these processes start from high energy precursors, such as peroxides or diazonium salts. A hallmark of the work described in this study is the avoidance of such species, instead relying on simple reagents. To understand the role of each component in this cascade process, we set out to probe the mechanism by conducting a series of control experiments. Notably, the carbosulfenylation of trifluoromethylalkene **1a** in the presence of radical scavengers, such as TEMPO and 1,3-cyclohexadiene (CHD) did not furnish the product **4e**, suggesting the involvement of radical intermediates (Scheme 3a). To further probe the radical intermediates, deuterated ^{t}BuSD (**2e-D**, 82% D content) was employed in place of **2e** (Scheme 3b). As anticipated, CH_2D-substituted biphenyl **10** (80% **D** content) was isolated as a co-product along with **4at**.[54] Together with the observation that disulfide was formed in the reaction, this result provides strong evidence for our proposed HAT process from thiol triggered by the benzyl radical, supporting the kinetic sorting hypothesis.

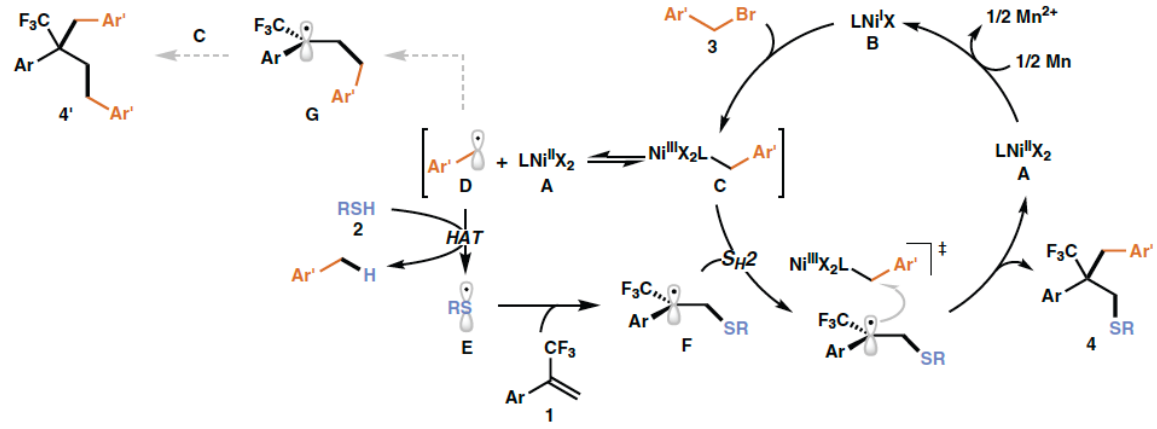


Scheme 3. Mechanistic study. a) Radical inhibition experiment. b) Deuterium labeling experiments. c) Scrambling experiment with additional disulfide. d) Evaluation of *α*-substituent effect.

A cross-over experiment was conducted with TIPSSH (**2l**) and *tert*-butyl disulfide, resulting in the observation of carbosulfenylation product derived from thiol (**4l**) and not the disulfide (**4e**) (Scheme 3c). A possible explanation for this result is that either homolytic fragmentation of disulfide to *S*-radical or *S*-radical exchange does not occur under the current reaction conditions.

Finally, the impact of *α*-substituent on alkene substrate reactivity was investigated using various styrene

derivatives (Scheme 3d). With R = CF_3, the yield of the product with ^{t}BuSH was 51% (**4e**). Replacement of one fluorine atom with hydrogen resulted in a decrease in yield to 34% (**12a**). Substituting the CF_3 group for a strongly electron-withdrawing $PhSO_2$ group also yielded the carbosulfenylation product **12b** in 50% yield. However, no reaction was observed when CN, CO_2Me, or Ac replaced CF_3. Similarly, replacing CF_3 with CH_3 failed to produce the desired product. These results highlight the critical role of a strong electron-withdrawing *α*-substituent in this transformation. This effect could be partially attributed to the suppression of the competing thio-ene reaction via radical polarity mismatch.[55–57]



Scheme 4. Proposed mechanism.

Based on the experimental observations detailed above and previous reports,[33,58,59] a plausible mechanism is proposed in Scheme 4, featuring distinctive radical sorting[60–63] and bimolecular homolytic substitution (S_H2) processes.[64] The catalytic cycle initiates with the reduction of Ni^{II}-catalyst **A** by Mn powder to Ni^{I} complex **B**. This Ni^{I} intermediate subsequently activates benzyl bromide **3** via oxidative addition to form Ni^{III}-Bn complex **C**, which lies in equilibrium with benzyl radical **D** and Ni^{II} **A** through Ni—C bond homolysis.[65–67] Critical to the reaction selectivity, the transient benzyl radical **D** undergoes rapid hydrogen atom transfer (HAT) with thiol **2**, producing the observed toluene derivative (Ar'CH_2–H) and generating the key thiyl radical **E**. This sulfur-centered radical then engages in selective addition to trifluoromethylalkene **1**, forming the *α*-CF_3 benzylic radical **F** bearing a thioether moiety. On one hand, interception of the benzyl radical **D** with Ni^{II} (**A**) to yield Ni^{III}-Bn complex **C** can take place and the *α*-CF_3 C-centered radical **F** participates in a Ni-mediated S_H2-type coupling process that ultimately forge the C—C bond in product **4**. Importantly, the excess thiol and its weak S—H bond ensure rapid quenching of the benzylic radical **D**, effectively suppressing the dibenzylation product **4'** through kinetic control. The mechanistic dichotomy between the two benzylic radicals (**D** and **F**) highlights the electronic and steric variation in dictating their divergent reactivities in the sorting process. While benzylic radical **D** serves as a hydrogen abstracting agent with reversible formation of a Ni-bound benzyl, the bulky and electrophilic radical **F** is sterically and electronically mismatched with the nickel catalyst and, thus, functions as the crucial coupling partner via an S_H2 reaction manifold. Presumably, the S_H2 reaction between **C** and **F** is faster than the fragmentation of **C** to benzyl radical **D**, thereby avoiding the accumulation of highly reactive radical species (**D**, **E**, and **F**).

Conclusion

In summary, we have developed an unprecedented 2,1-carbosulfenylation reaction for trifluoromethylalkenes and *gem*-difluoroalkenes. This reaction proceeds through a nickel-catalyzed tandem radical relay mechanism initiated by *S*-centered radical addition, which enables the previously inaccessible reversed regioselectivity. A diverse array of organosulfur compounds featuring fluoroalkyl moieties, which are of significant interest in pharmaceutical, agrochemical, and biological chemistry, have been synthesized. Given its mild reaction conditions and excellent compatibility with biologically relevant functionality, this

method is anticipated to find applications in drug discovery campaigns.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

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