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Barton−Kellogg Olefination of $(CF_3S)_2C{=}S$ and Subsequent Cyclopropanation for the Installation of Bulky Bis(trifluoromethylthio)methylene Group

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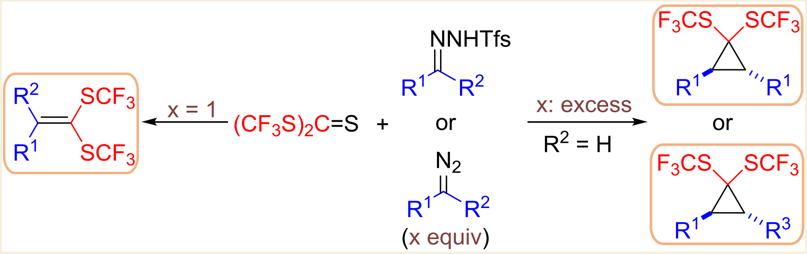

ABSTRACT: A protocol was developed for the large-scale preparation (nearly 200 g per batch) of $(CF_3S)_2C{=}S$. The synthesis of *gem*-bis(trifluoromethylthio)alkenes was achieved through the Barton−Kellogg reaction, without the involvement of trivalent phosphines. With slight modifications to the reaction conditions, the synthesis of *gem*-bis(trifluoromethylthio)cyclopropanes, which are difficult to obtain by other methods, can be realized. Due to the large steric hindrance of the trifluoromethylthio group, the CF_3S group may be positioned close to the *trans*-substituent rather than the *cis*-substituent in cyclopropanes, as confirmed by single-crystal X-ray analysis, contributing to unique NMR structural characteristics. Further investigation into the reaction mechanism revealed the unique reactivity of the double bond in *gem*-bis(trifluoromethylthio)alkenes.

KEYWORDS: *bis(trifluoromethylthio)methylene group, trifluoromethylthio, Barton−Kellogg olefination, cyclopropanation, fluorine*

INTRODUCTION

Due to the unique electronic properties of fluorine, such as its high electronegativity and small atomic radius, its incorporation can significantly alter the physicochemical properties of organic molecules, including enhancing the lipophilicity and metabolic stability of biologically active compounds.[1−3] As a result, fluorinated compounds have found extensive applications in various areas, such as medicine and pesticides.[4−6] The trifluoromethylthio group (CF_3S) has been recognized as a valuable fluorinated structural unit, characterized by its strong lipophilicity nature (Hansch parameter $\pi = 1.44$), highly electron-withdrawing properties ($\sigma_m = 0.4$, $\sigma_p = 0.5$) and large steric hindrance.[7,8] Numerous CF_3S-containing biologically active molecules have been developed, which may potentially find clinical applications,[9−13] and CF_3S-containing agrochemicals like Flupentiofenox and Vaniliprole have also emerged.[3] Therefore, methods of introducing mono trifluoromethylthio group into organic compounds have been the focus of extensive research,[14−23] leading to the development of various trifluoromethylation reagents. These include electrophilic reagents like *N*-SCF_3[24−27] and *O*-SCF_3[28,29] types, as well as nucleophilic reagents such as $AgSCF_3$,[30] $CuSCF_3$,[31] and Me_4NSCF_3.[32] In view of the unique structural characteristics of SCF_3 group, it is possible to construct bulkier di(trifluoromethylthio)methylene building block by stacking two SCF_3 groups on the same carbon atom, which may have a great impact on the physicochemical properties and bioactivity of the compounds. However, the installation of a functionality containing geminal bis-trifluoromethylthio units remains a significant challenge.

The reported methods for constructing a bis(trifluoromethylthio)methylene group generally require a sequential double trifluoromethylthiolation process, where the two CF_3S units are installed one after the other. The bis(trifluoromethylthio)methylene functionality can exist as a single-bonded fragment ($-(CF_3S)_2C-$) in alkanes or as a double-bonded fragment ($(CF_3S)_2C{=}$) in alkenes. Several research groups have explored methods for forming $-(CF_3S)_2C-$ alkanes. Billard and co-workers constructed a series of α,α-bis(trifluoromethylthio)ketones via double trifluoromethylthiolation of methyl ketones and enol silyl ethers with the highly effective electrophilic reagent TsN-

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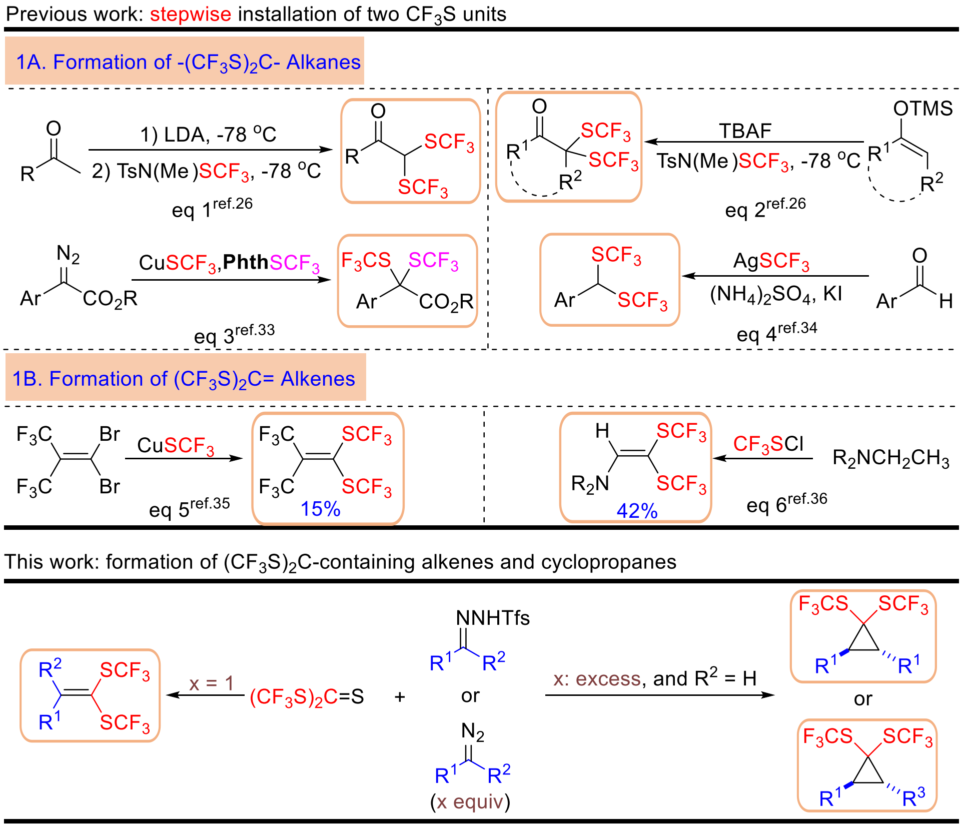
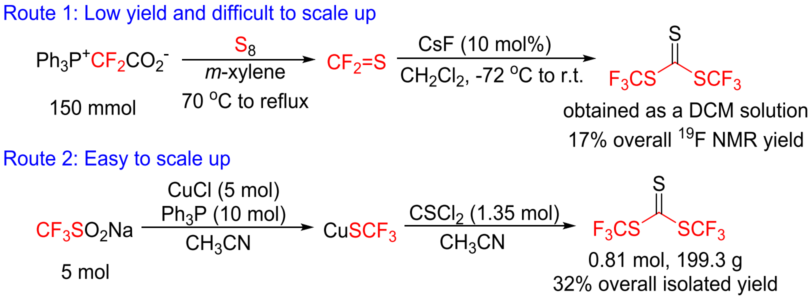
Scheme 1. Installation of a Bis(trifluoromethylthio)-methylene Group



Scheme 2. Two Routes for the Synthesis of $(CF_3S)_2C{=}S$



(Me)SCF_3 (Scheme 1A, eqs 1 and 2).[26] Rueping's group demonstrated the combined use of another efficient electrophilic CF_3S-reagent (PhthSCF$_3$) and a nucleophilic CF_3S-reagent ($CuSCF_3$) for the installation of the $-(CF_3S)_2C-$ group (Scheme 1A, eq 3).[33] Qing et al. achieved an efficient deoxygenation of aldehydes for double trifluoromethylthiolation with $AgSCF_3$ (Scheme 1A, eq 4).[34] For the construction of alkenes, a very low yield was obtained (Scheme 1A, eq 5),[35] or a highly reactive reagent, CF_3SCl, has to be used (Scheme 1A, eq 6).[36] Additionally, only one example was investigated in each method. In all of the above reactions, the two CF_3S units are incorporated sequentially. The installation of the first CF_3S unit might reduce the resulting molecule's reactivity, hindering the introduction of the second unit. To overcome this obstacle, substrates or reagents must be highly reactive, or reaction conditions must be particularly harsh. However, these factors can lead to problems with substrate compatibility.

It is well-known that the Barton−Kellogg olefination is a coupling reaction between a diazo compound and a thioketone for the synthesis of steric alkenes.[37−40] This olefination process normally requires the presence of a trivalent phosphine, which acts as a nucleophile to open the three-membered thiirane ring, facilitating the removal of the sulfur atom and leading to the formation of the alkene. If we aim to utilize Barton−Kellogg reaction, the effective transformation for the synthesis of olefins with large steric hindrance, to synthesize di(trifluoromethylthio)olefins, it is necessary to obtain the raw material di(trifluoromethyl) thiocarbonate ($(CF_3S)_2C{=}S$). However, although $(CF_3S)_2C{=}S$ has been reported,[41,42] its large-scale synthesis and its synthetic applications[43] remained largely unexplored. We have successfully achieved a hundred-gram-scale synthesis of $(CF_3S)_2C{=}S$, explored its use in Barton−Kellogg olefination and subsequent cyclopropanation, and developed a new method for the synthesis of bulky, sterically hindered molecules containing di(trifluoromethylthio)methylene fragment (Scheme 1, This work).

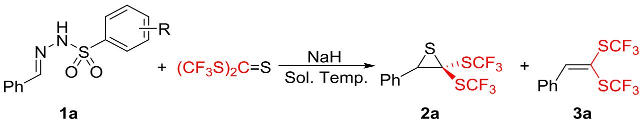
■ RESULTS AND DISCUSSION

We have been interested in the introduction of CF_3S groups.[44,45] Previously, we discovered that difluorocarbene can be captured by elemental sulfur to form thiocarbonyl fluoride ($CF_2{=}S$).[44−46] As a result, $(F_3CS)_2C{=}S$ can be generated by the transformation of $CF_2{=}S$. First, the $CF_2{=}S$ gas, generated by the reaction of difluorocarbene with elemental sulfur, was transferred into a CH_2Cl_2 solution containing a catalytic amount of CsF. $CF_2{=}S$ reacts with CsF to produce the CF_3S^- anion. This anion then sequentially attacks $CF_2{=}S$ twice, yielding $(CF_3S)_2C{=}S$ and releasing F^- ions.[42] These F^- ions can further react with $CF_2{=}S$ to form CF_3S^- anions (Scheme 2, Route 1). While this route is effective, it has a low yield and is difficult to scale up. Additionally, transferring the $CF_2{=}S$ gas is cumbersome, and the final product, $(CF_3S)_2C{=}S$, is only obtained in a CH_2Cl_2 solution. Therefore, an alternative approach was sought. The synthesis of $(CF_3S)_2C{=}S$ has been reported by the Clark group, utilizing the reaction of $CuSCF_3$ with $CCl_2{=}S$.[41] According to Clark's protocol, $(CF_3S)_2C{=}S$ can be obtained as a CH_3CN solution through distillation. After synthesizing $CuSCF_3$ following the method of Yang and Vicic,[47] we subsequently applied Clark's protocol, which resulted in high ^{19}F NMR yields of $(CF_3S)_2C{=}S$. However, direct distillation on a large scale resulted in very poor yields, likely due to the decomposition of $(CF_3S)_2C{=}S$ via its electrophilic attack on CH_3CN at the high distillation temperatures. To address this issue, we modified the workup procedure. As detailed in the Supporting Information, the $(CF_3S)_2C{=}S$ solution in CH_3CN was first distilled out of the reaction mixture at room temperature under reduced pressure. Water was then added to the CH_3CN solution, resulting in the formation of two phases with CH_3CN partitioning into the upper aqueous phase, which was decanted, leaving crude $(CF_3S)_2C{=}S$ as a liquid at the bottom layer. Further distillation yielded the pure product. While the overall yield is still not high, the process demonstrates greater scalability.

After successfully achieving the large synthesis of $(CF_3S)_2C{=}S$, we investigated its use in Barton−Kellogg olefination. Initially, we focused on the conversion of monosubstituted diazo compounds with relatively low steric hindrance and higher reactivity. Subsequently, we investigated the transformation of bulkier and less reactive disubstituted diazo compounds. Due to the instability of $PhCH{=}N_2$, its Barton−Kellogg reaction was investigated in detail using benzaldehyde sulfonylhydrazone **1a** as the substrate.

During the optimization of the conditions for the reaction of hydrazone **1a**, a precursor of diazo $PhCH{=}N_2$, with $(CF_3S)_2C{=}S$, we found that two different products could be produced, including thiirane **2a** and olefin **3a**, depending upon the reaction conditions (Table 1). Notably, the absence of a trivalent phosphine could also lead to conversion of thiirane **2a** into the olefin product **3a**, probably with the promotion of bulky di(trifluoromethylthio)methylene. The first attempt at the reaction of **1a** with $(CF_3S)_2C{=}S$ using NaH as the base for deprotonation of **1a** failed to yield any product. However, both substrate **1a** and $(CF_3S)_2C{=}S$ were completely decomposed (Table 1, entry 1). We hypothesized that the anion $PhCH{=}NN^-SO_2Ar$, generated by deprotonation, may act as a nucleophile to attack $(CF_3S)_2C{=}S$, which led to the complete consumption of both **1a** and $(CF_3S)_2C{=}S$, rather than forming the desired diazo compound, $PhCH{=}N_2$. We then preheated the mixture of **1a** and NaH for a period of time to ensure complete conversion of **1a** into $PhCH{=}N_2$ before adding $(CF_3S)_2C{=}S$, which then provided thiirane **2a** in a high yield (Table 1, entry 2). However, this stepwise process was not generally acceptable.

Table 1. Optimization of the Barton−Kellogg Olefination[g]

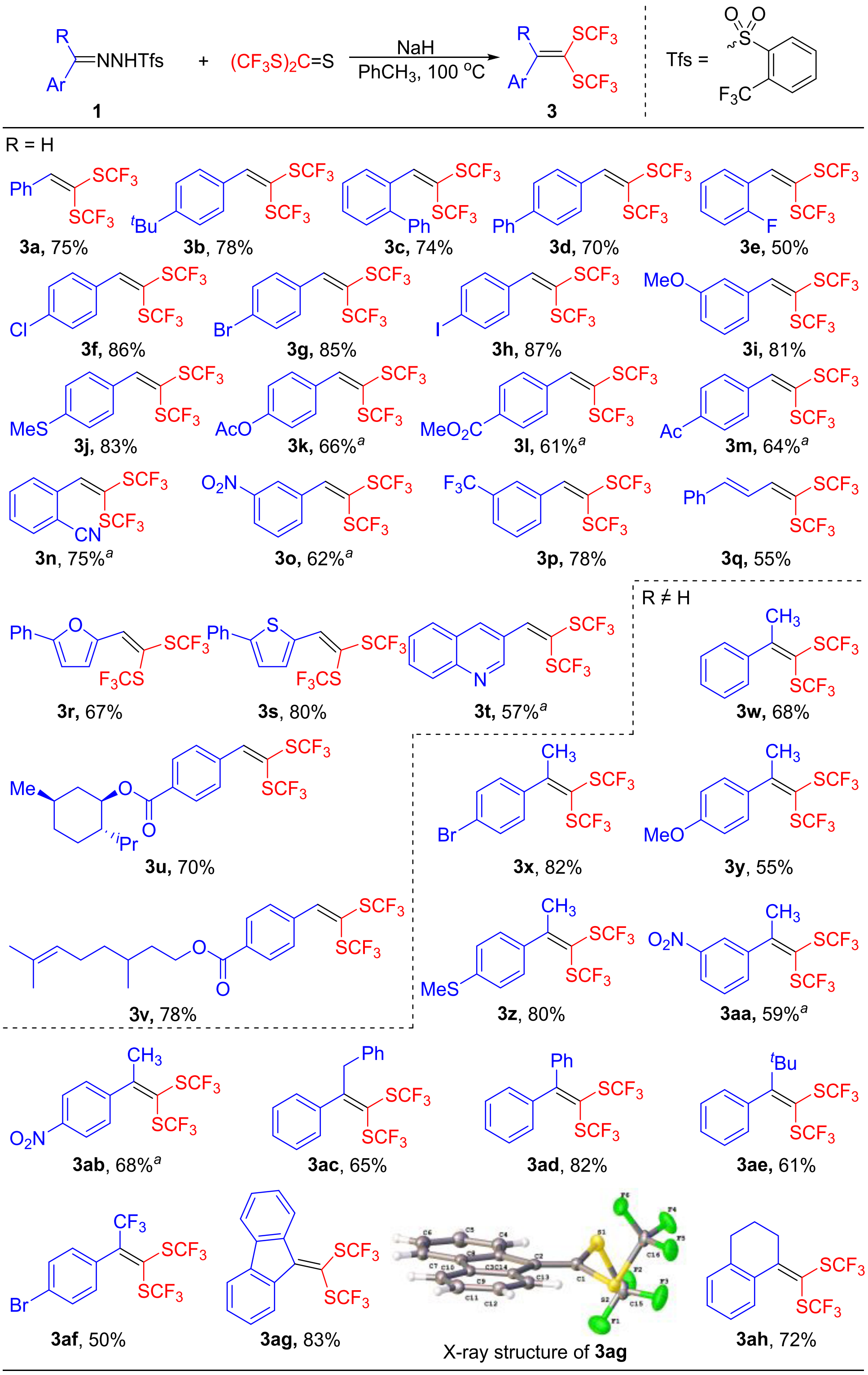


entry	R	solvent	yield of **2a**/**3a** (%)[a]
1[b]	4-CH_3	DCE	0/0
2[c]	4-CH_3	DCE	80/0
3[d]	H	$PhCH_3$	3/9
4[d]	4-CH_3	$PhCH_3$	3/5
5[d]	2,4,6-$(CH_3)_3$	$PhCH_3$	24/24
6[d]	4-OCH_3	$PhCH_3$	3/4
7[d]	4-Br	$PhCH_3$	18/7
8[d]	4-NO_2	$PhCH_3$	18/7
9[d]	4-CF_3	$PhCH_3$	44/21
10[d]	2-CF_3	$PhCH_3$	58/36
11[d]	2-CF_3	DCE	0/62
12[d]	2-CF_3	dioxane	36/17
13[d]	2-CF_3	THF	0/28
14[d]	2-CF_3	EA	0/19
15[d]	2-CF_3	CH_3CN	0/0
16[e]	2-CF_3	$PhCH_3$	46/38
17[f]	2-CF_3	$PhCH_3$	0/91

[a] Yields were determined by the analysis of the crude ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard. [b] **1a** (0.20 mmol, 1.0 equiv) and NaH (0.24 mmol, 1.2 equiv) and $(CF_3S)_2C{=}S$ (0.22 mmol, 1.1 equiv) in DCE (2.0 mL), 80 °C for 3 h. [c] **1a** (0.6 mmol, 3.0 equiv) and NaH (0.66 mmol, 3.3 equiv) in $PhCH_3$ (2.0 mL) under a N_2 atmosphere at 70 °C for 1 h. Then $(CF_3S)_2C{=}S$ (0.2 mmol, 1.0 equiv) was added. The mixture was stirred at rt for 2 h. [d] The reaction temperature was 80 °C. [e] The reaction temperature was 90 °C. [f] The reaction temperature was 100 °C. [g] Reaction conditions: **1a** (0.20 mmol, 1.0 equiv), NaH (0.40 mmol, 2.0 equiv) and $(CF_3S)_2C{=}S$ (0.24 mmol, 1.2 equiv) in a solvent (2.0 mL) at a N_2 atmosphere for 3 h.

We speculated that the Ar substituents on $PhCH{=}NN^-SO_2Ar$ might influence the nucleophilicity of this anion, and that a suitable substituent may facilitate its conversion to $PhCH{=}N_2$ rather than promoting its nucleophilic attack on $(CF_3S)_2C{=}S$. Therefore, we examined a series of substituents for the one-step reaction between **1a** and $(CF_3S)_2C{=}S$ (Table 1, entries 3−10). The nature of the substituents had a significant impact on the reaction outcome. Electron-neutral or -donating aryl substituents led to low reaction efficiency (Table 1, entries 3−6), likely because the high nucleophilicity of the $PhCH{=}NN^-SO_2Ar$ anion favored direct attack on $(CF_3S)_2C{=}S$. Interestingly, bulky tosylhydrazones showed some conversion despite the electron-rich nature of the aryl group (Table 1, entry 5), probably due to steric hindrance suppressing the nucleophilic attack of $PhCH{=}NN^-SO_2Ar$ on $(CF_3S)_2C{=}S$. Electron-withdrawing tosylhydrazones exhibited improved reaction efficiency (Table 1, entries 7−10), as the reduced nucleophilicity of the $PhCH{=}NN^-SO_2Ar$ anion minimized its attack on $(CF_3S)_2C{=}S$, promoting its conversion to $PhCH{=}N_2$. Among these, the highest reaction efficiency was observed with a 2-trifluoromethyl substituent (Table 1, entry 10).[48,49]

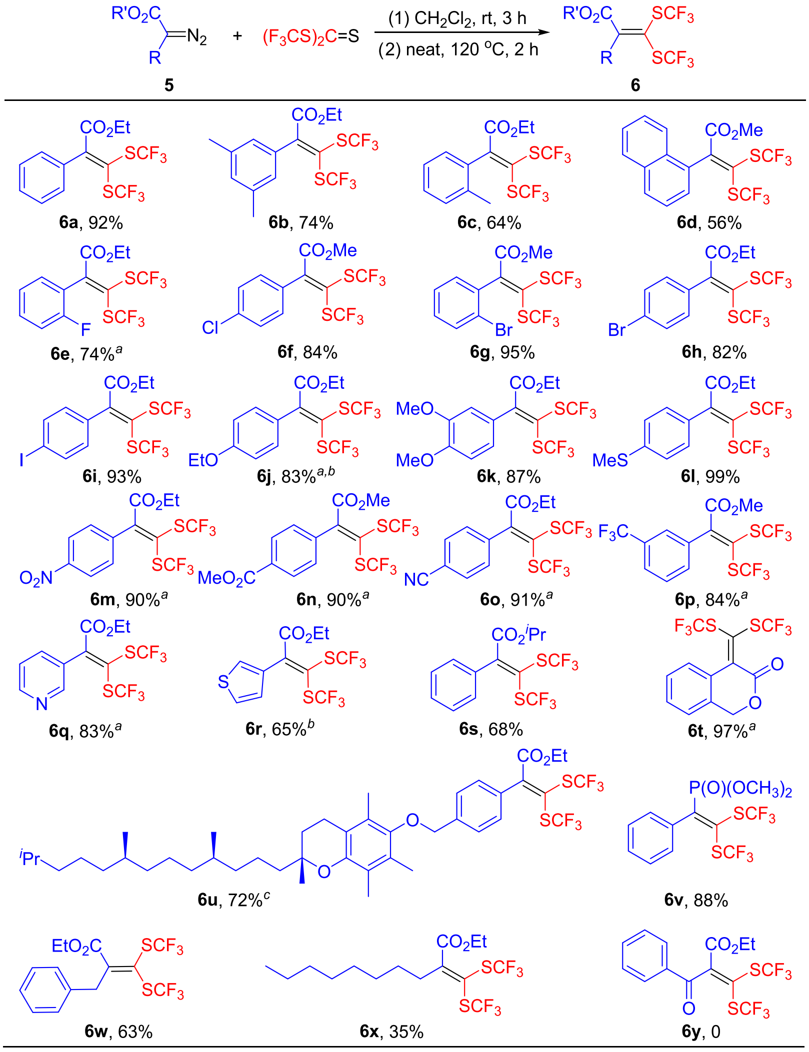
Scheme 3. Barton–Kellogg Olefination of Hydrazones with $(CF_3S)_2C{=}S$[b]



[a] K_3PO_4 (1.0 mmol, 2.0 equiv) was used instead of NaH. [b] Reaction conditions: Substrate 1 (0.5 mmol, 1.0 equiv), $(CF_3S)_2C{=}S$ (0.6 mmol, 1.2 equiv), NaH (1.0 mmol, 2.0 equiv), $PhCH_3$ (5.0 mL), N_2, 100 °C, 8 h (R = H) or 30 h (R ≠ H).

Next, the effects of solvent and temperature on this reaction were systematically studied (Table 1, entries 10–17). It was found that increasing solvent polarity reduced the efficiency of the olefination process (Table 1, entries 10–15). Notably, no product was obtained when acetonitrile was used as the solvent (Table 1, entry 15), likely due to its high polarity stabilizing the $PhCH{=}NN^{-}SO_2Ar$ anion, facilitating its dissolution, and increasing the likelihood of direct attack on $(CF_3S)_2C{=}S$. Furthermore, a higher reaction temperature led to a significant increase in the olefination yield (Table 1, entry 17), probably because thiirane **2a** readily undergoes desulfurization with the

Scheme 4. Barton−Kellogg Olefination of Diazo Compounds with $(CF_3S)_2C{=}S$[d]



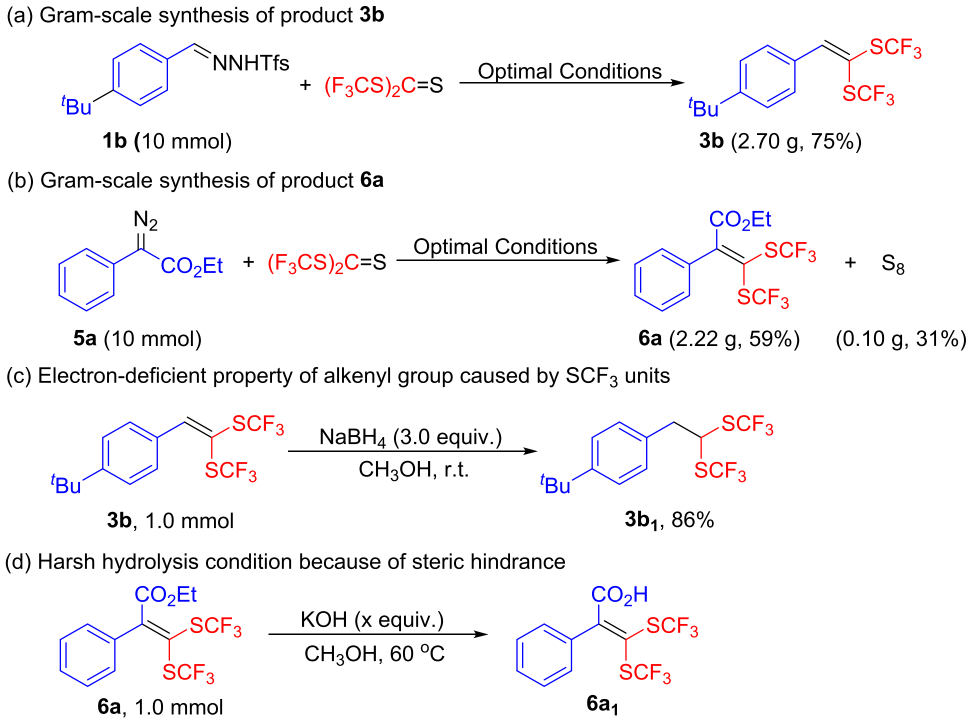
[a]The reaction temperature was 40 °C for the first step. [b]The reaction time for the second step was 4 h. [c]The reaction time for the second step was 3 h. [d]Reaction conditions: Substrate **5** (0.5 mmol, 1.0 equiv), $(CF_3S)_2C{=}S$ (0.6 mmol, 1.2 equiv), DCM (5.0 mL), an air atmosphere, r.t., 3 h; DCM was removed by concentration under vacuum and then the residue was heated at 120 °C under air atmosphere for 2 h.

promotion of bulky di(trifluoromethylthio)methylene under these conditions (Table 1, entry 17 vs 16).

After determining the optimal reaction conditions (Table 1, entry 17), we conducted a detailed investigation into the substrate scope of the Barton−Kellogg olefination between $(CF_3S)_2C{=}S$ and hydrazones, serving as precursors of reactive diazo compounds (Scheme 3). The results demonstrated that the reaction exhibits broad compatibility. For benzaldehyde hydrazones, the electronic effects of substituents appeared to have some influence. Substrates with electron-neutral and electron-donating groups were smoothly converted. However, for electron-deficient substrates, the reaction was less efficient with NaH as the base and required K_3PO_4 as a substitute. Although substrates with strong electron-withdrawing groups could also be converted, the desired products were obtained in lower yields (**3l**−**3p**). In addition to benzaldehyde hydrazones, vinyl aldehyde hydrazones were also compatible with this reaction (**3q**). The reaction was successful for substrates substituted with heterocycles such as furan (**3r**), thiophene (**3s**), and quinoline (**3t**). Derivatives of biologically active molecules, such as menthol (**3u**) and citronellol (**3v**), were fully compatible with the reaction, indicating potential applications in modifying naturally active structures. Beyond benzaldehyde hydrazones, ketone hydrazones also participated well in the reaction (**3w**−**3ah**). However, due to their lower reactivity, the reaction required an extended time (30 h) to complete. Acetophenone hydrazones could all be transformed smoothly, regardless of whether electron-donating and electron-withdrawing substitutions were present (**3w**−**3ab**). Additionally, substrates with significant steric hindrance (**3ac**−**3af**) and cyclic ketone hydrazones (**3ag, 3ah**) were efficiently converted. A single-crystal structure of product **3ag** was successfully obtained, confirming the product structure.[50] The crystal structure reveals that the olefin structure is not planar, with the two trifluoromethyl groups positioned away from each other. These results indicate the significance of the bulky steric effects of the *gem*-di(trifluoromethylthio)alkene moiety.

Next, we further investigated the Barton−Kellogg olefination of stable and more steric diazo compounds containing an ester group with $(CF_3S)_2C{=}S$. Fortunately, the reaction proceeded efficiently in DCM at room temperature to yield thiiranes, while, as with hydrazones, a higher temperature was required

Scheme 5. Gram-Scale Reactions and Derivatizations



x	^{19}F NMR yield (isolated yield)
2.0	26%
3.0	44%
4.0	65% (59%)

for the desulfurization of thiirane to produce olefins. A detailed investigation into the substrate scope of this Barton−Kellogg olefination was conducted (Scheme 4). Although electron-rich, -neutral, and -deficient aryl diazo compounds could all be smoothly converted (**6a**−**6p**), highly electron-deficient substrates required a slightly higher temperature for the formation of thiirane (**6m**−**6p**), indicating that substituent electronic effects have impact on this process. Heterocyclic substrates, such as those substituted with pyridine (**6q**) or thiophene (**6r**), also participated successfully. The diazo compound containing a bulky ester group was well converted (**6s**), and cyclic substrates also showed high reactivity (**6t**). Substrates containing a bioactive vitamin E structure (**6u**) were fully compatible, highlighting the potential application of this process in biological chemistry. In addition to ester substituents, other electron-withdrawing groups necessary for the stabilization of diazo compounds, such as phosphonate substituents, also enabled smooth conversion of the corresponding substrates (**6v**). Beyond aryl diazo compounds, alkyl-substituted substrates were compatible as well (**6w**−**6x**). Unfortunately, for diazo compound substituted with two strong electron-withdrawing groups, its reactivity was too low, and the reaction did not proceed (**6y**).

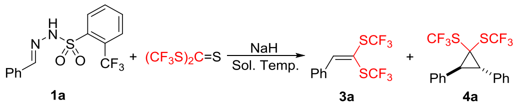
After successfully completing the substrate scope study, we examined the scalability of the reaction (Scheme 5). The results show that the Barton−Kellogg olefination exhibits excellent scalability (eqs. a and b), indicating potential synthetic value. Elemental sulfur produced in the reaction was isolated (eq b), which supports the desulfurization of thiirane **2** to form the olefin. On the other hand, derivatization experiments show that *gem*-di(trifluoromethylthio) alkenes show considerable stability. Trisubstituted alkene **3b** is resistant to oxidation by *m*-CPBA, bromination by Br_2 or attack by Grignard reagent. It can only be reduced by less steric hindered reducing agent $NaBH_4$ (eq c), showing the electron-deficient nature of the alkenyl group. Tetrasubstituted alkene **6a** is more resistant, showing difficulty in reduction by $NaBH_4$. The conjugated ester group in **6a** is relatively inert, resisting nucleophilic reaction with a Grignard reagent or ammonia, and requiring heating and a large excess of KOH for complete hydrolysis (eq d). The results collectively show that the substitution of two trifluoromethylthio groups causes a significant increase in steric hindrance and a substantial decrease in molecular reactivity.

Although some ordinary derivatizations are difficult to apply to *gem*-di(trifluoromethylthio) alkenes, we speculated that diazo compounds, as common carbene precursors, might produce highly active carbene species in the reaction, which may undergo cyclopropanation with the double bond in bis(trifluoromethylthio)alkenes to give cyclopropanation products. However, previous research has seldom explored this process, despite the successful formation of highly crowded alkene structures in the Barton−Kellogg reaction, where excessive steric hindrance may hinder the cyclopropanation process.[37−40] Notably, there was one paper describing the formation of a side product, tetrafluorocyclopropane, which was formed in a Barton−Kellogg-type reaction of less hindered difluorocarbene with thioesters.[51] The efficiency is quite low, but its formation suggests that appropriate steric effects may facilitate cyclopropanation following the Barton−Kellogg reaction.

Based on the experimental results and literature reports, we assumed that using an excess of less hindered and more reactive ArCH=N_2 in the Barton−Kellogg olefination could enable the olefination product to further react with ArCH=N_2, potentially yielding a bis(trifluoromethylthio) cyclopropane product. Therefore, we used an excess of benzaldehyde sulfonylhydrazone **1a** as the reaction substrate to screen the cyclopropanation conditions.

Fortunately, it can be found that by increasing the loading of **1a** and extending the reaction time, cyclopropane **4a** was obtained, with high *trans*-stereoselectivity observed. First, the screening of solvents showed that although cyclopropanation efficiency was slightly better in THF or DCE (Table 2, entries 1 and 3), the lower amount of remaining di(trifluoromethylthio)alkene would limit the further optimization. Additionally, the use of highly polar CH_3CN would completely inhibit the formation of olefination or cyclopropanation products (Table 2, entry 5). Toluene is the most suitable reaction solvent for further cyclopropanation (Table 2, entry 6). By varying the substrate equivalents, it revealed that increasing the loading of **1a** to five equivalents significantly improved the cyclopropanation yield (Table 2, entries 7−9). Further increases in the substrate loading did not lead to additional improvements (Table 2, entry 10). Temperature screening showed that heating the reaction at 110 °C provided optimal efficiency, achieving a cyclopropanation yield of 67% (Table 2, entry 12).

Table 2. Optimization of the Cyclopropanation[g]



entry	solvent	ratio[a]	yield of **3a**/**4a** (%)[b]
1[c]	THF	3:6:1	55/17
2[c]	dioxane	3:6:1	92/3
3[c]	DCE	3:6:1	60/25
4[c]	EA	3:6:1	66/9
5[c]	CH_3CN	3:6:1	0/0
6[c]	$PhCH_3$	3:6:1	84/14
7[d]	$PhCH_3$	3:6:1	54/34
8[d]	$PhCH_3$	4:8:1	25/35
9[d]	$PhCH_3$	5:10:1	5/56
10[d]	$PhCH_3$	6:12:1	0/56
11[e]	$PhCH_3$	5:10:1	7/66
12[f]	$PhCH_3$	5:10:1	3/67

[a] Molar ratio of **1a**: NaH: $(CF_3S)_2C=S$, with 1 equiv corresponding to 0.2 mmol. [b] Yields were determined by the analysis of the crude ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard. [c] The reaction temperature was 80 °C. [d] The reaction temperature was 90 °C. [e] The reaction temperature was 100 °C. [f] The reaction temperature was 110 °C. [g] Reaction conditions: **1a**, NaH and $(CF_3S)_2C=S$ in a solvent at a N_2 atmosphere for 18 h.

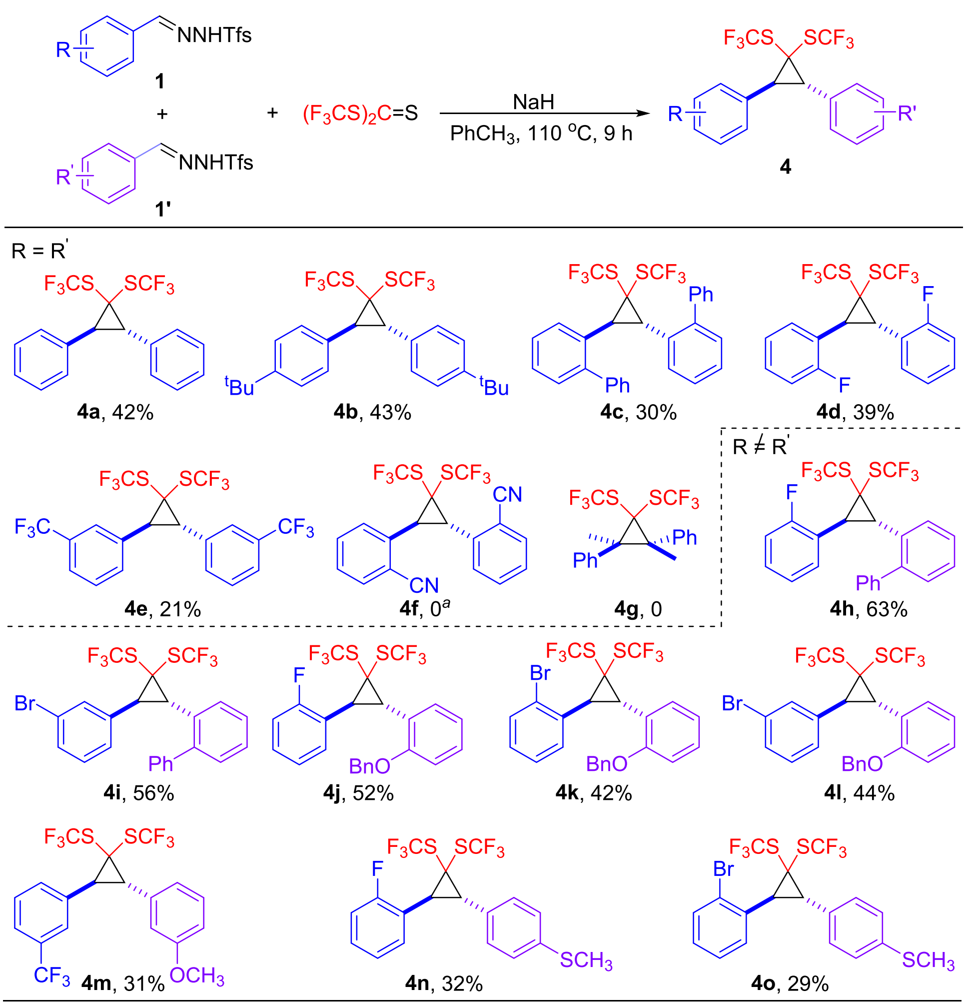
We then investigated the cyclopropanation of hydrazones, acting as reactive diazo precursors, with $(CF_3S)_2C=S$ under the conditions outlined in entry 12, Table 2. Cyclopropanes are expected to form through the reaction of olefins with an additional equivalent of hydrazones, necessitating the use of hydrazones in excess. As depicted in Scheme 6, the desired cyclopropanes were obtained with high *trans*-stereoselectivity and moderate yields (**4a**−**4e**). The reaction seemed sensitive to the electronic nature of the substituents. Electron-neutral, mildly electron-donating, and mildly electron-withdrawing groups facilitated moderate yields, while stronger electron-withdrawing groups reduced yields (**4e**). Highly strong electron-withdrawing groups completely suppressed the reaction (**4f**). Ketone hydrazones failed to produce the target products (**4g**). We hypothesized that it would be possible to obtain cyclopropanes with varied aryl substituents by adding hydrazones in two portions, with the second portion employing a different hydrazone specifically targeting the cyclopropanation of olefins. Indeed, these reactions proceeded, albeit with low to moderate yields (**4h**−**4o**). This protocol provides bulky cyclopropanes bearing either two identical or different aryl groups and a *gem*-bis(trifluoromethylthio)-methylene moiety, representing unique fluorinated structures that are challenging to obtain by other methods.

The structure of **4h** was confirmed by X-ray diffraction analysis (Figure 1).[52] Notably, its conformation is influenced by steric effects. The 2-fluorophenyl substituent is positioned far from the *cis*-CF_3 group but is in close proximity to the *trans*-CF_3 group. The shortest distance between the fluorine atom on the phenyl ring and the fluorine atoms in the *trans*-CF_3 group is measured at 3.0 Å. This structural feature is reflected in the ^{19}F NMR as a long-range coupling between these fluorine atoms. The long-range coupling results in a distinct doublet for the *trans*-CF_3 group in ^{19}F NMR at $\delta - 39.66$ ppm (d, $^7J_{FF} = 11.8$ Hz, 3F). This coupling is consistently observed in all cyclopropanation products containing a 2-fluorophenyl group (**4d**, **4h**, **4j**, **4n**), which indicates the bulky effects of the *gem*-di(trifluoromethylthio)methylene moiety.

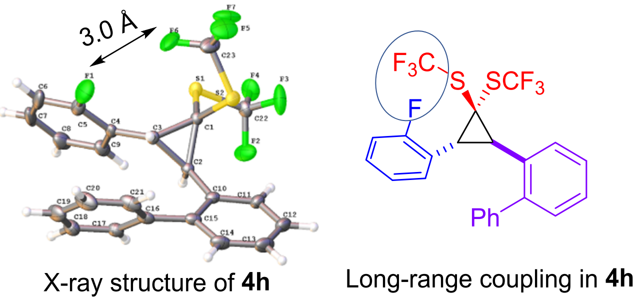
Although we first assumed cyclopropanation process proceeding through a carbene intermediate, further investigations seems to suggest that the predominant pathway likely involves the formation of a five-membered ring intermediate, based on the following evidence. First, diazo compounds have been established as efficient 1,3-dipoles in cycloaddition reactions for the formation of five-membered rings.[53−55] Moreover, the observed substituent electronic effects in cyclopropanation align with this primary pathway, as demonstrated by intermolecular competition reactions (Scheme 7). In the competitive cyclopropanation of electron-neutral olefin **3j** and electron-deficient olefin **3l** with diazo PhCH=N_2, product **4q** is obtained in moderate yield, whereas **4p** is formed in a relative low yield. This is likely due to the preference of the carbon anion in $PhCH^-$-N_2^+ to attack the electron-deficient double bond in **3l**, given the higher electrophilicity of the double bond containing the electron-withdrawing ester group (eq a). Conversely, in the competitive reactions of electron-neutral diazo **1j′** and electron-deficient diazo **1l′** with olefin **3a**, **1l′** fails to form cyclopropane **4q**. In olefin **3a**, the presence of two electron-withdrawing CF_3S groups renders the double bond electrophilic. However, the electron-withdrawing ester group in diazo **1l′** stabilizes the carbon anion in $ArCH^-$-N_2^+, thereby reducing the nucleophilicity of this anion and thus completely suppressing its nucleophilic attack on olefin **3a**.

Based on the above results and literature reports,[37−40] we propose the mechanisms for both olefination and cyclopropanation, as shown in Scheme 8. For the olefination, in sharp contrast to the classic Barton−Kellogg olefination, which requires a trivalent phosphorus to remove the sulfur atom in thiirane,[37−40] thiiranes **2**, derived from intermediate **A** by nitrogen gas excursion and containing a *gem*-bis(trifluoromethylthio)methylene group, can directly release elemental sulfur under heating to produce olefins **3**. For the cyclopropanation reaction, olefins are first formed. Diazo compounds, generated in situ, rapidly attack the olefins to form

Scheme 6. Cyclopropanation of Hydrazones with $(CF_3S)_2C{=}S$[b]



[a] K_3PO_4 (5.0 mmol, 10.0 equiv) was used instead of NaH. [b] Reaction conditions: If R = R′, hydrazone **1** (2.5 mmol, 5.0 equiv), $(CF_3S)_2C{=}S$ (0.5 mmol, 1.0 equiv), NaH (5.0 mmol, 10.0 equiv), $PhCH_3$ (10.0 mL), N_2, 110 °C, 9 h. If R ≠ R′, **1** (0.5 mmol, 1.0 equiv), $(CF_3S)_2C{=}S$ (0.5 mmol, 1.0 equiv), NaH (5.0 mmol, 10.0 equiv), $PhCH_3$ (10.0 mL), N_2, 110 °C, 1 h; then substrate **1′** (2.0 mmol, 4.0 equiv), N_2, 110 °C, 8 h.



X-ray structure of **4h** Long-range coupling in **4h**

Figure 1. X-ray structure of **4h** and its long-range spin−spin coupling.

a five-membered ring (**B**) with *trans*-stereoselectivity due to steric effects. The elimination of a nitrogen molecule leads to the formation of cyclopropanes (main pathway). The carbene pathway cannot be excluded (minor pathway). Under heating, diazo compounds may decompose into carbenes, which then directly cyclopropanate olefins to deliver the final products.

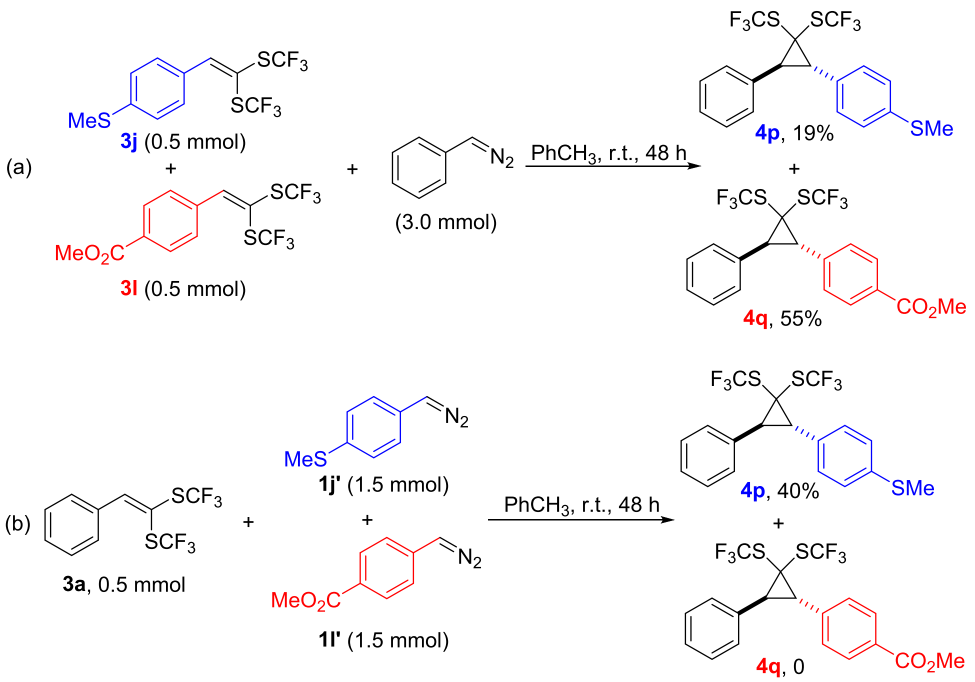
CONCLUSIONS

We successfully developed the Barton−Kellogg olefination and cyclopropanation reactions of hydrazones or diazo compounds with $(CF_3S)_2C{=}S$, a reagent that can be easily prepared on a large scale. This method allows for the construction of bulky olefins and cyclopropanes containing bis(trifluoromethylthio)-methylene groups, which are challenging to synthesize through other approaches. For the olefination reaction, the protocol shows a broad substrate scope and does not require additional desulfurization reagents for the conversion of thiiranes into olefins, while also demonstrating excellent scalability. The cyclopropanation reaction delivers products with either two identical or varied aryl substituents and exhibits high *trans*-stereoselectivity. Owing to the straightforward large-scale preparation of $(CF_3S)_2C{=}S$ and the easy access to unique olefins and cyclopropanes, this method may find potential synthetic utility in biological chemistry.

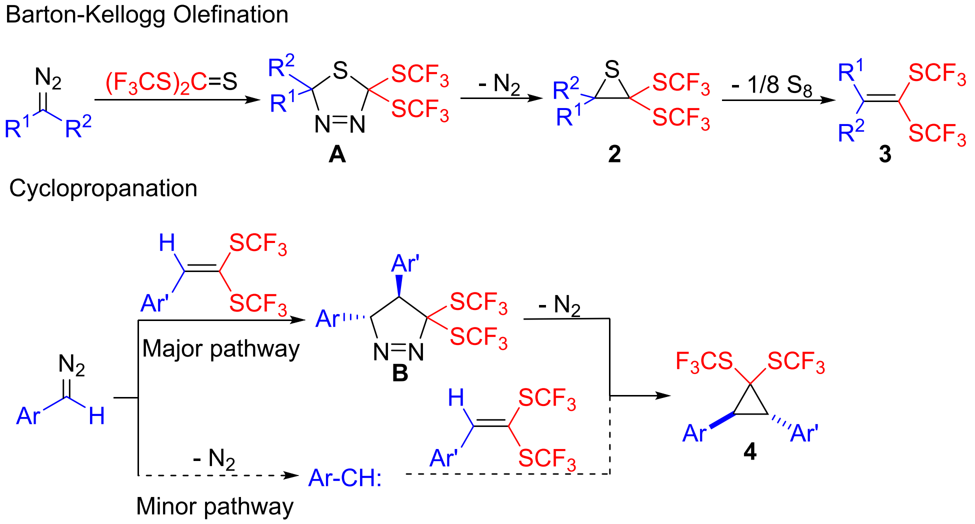
MATERIALS AND METHODS

Unless otherwise noted, all reagents and solvents were obtained commercially and used without further purification. The ^1H, ^{13}C and ^{19}F NMR spectra were recorded on 400 MHz NMR spectrometers (400 MHz for ^1H, 101 MHz for ^{13}C and 376 MHz for ^{19}F respectively). All reactions were monitored by TLC or ^{19}F NMR. Flash column chromatography was carried out using 300−400 mesh silica gel at medium pressure. High resolution mass spectrometry (HRMS) was performed on a Waters Premier GC-TOF MS

Scheme 7. Electronic Effects for the Cyclopropanation



Scheme 8. Proposed Mechanism



instrument with electron impact (EI) ionization mode, or on a Thermo Scientific Q Exactive HF Orbitrap-FTMS instrument with electrospray ionization (ESI) mode.

Procedures for the Synthesis of *gem*-Di(trifluoromethylthio)olefins 3a–3ah

A 50 mL bottom flask was charged with substrate **1** (0.5 mmol, 1.0 equiv), NaH (24.0 mg, 1.0 mmol, 2.0 equiv) and dry $PhCH_3$ (5 mL) under a N_2 atmosphere. $(CF_3S)_2C{=}S$ (147.6 mg, 0.6 mmol, 1.2 equiv) was added. The resulting mixture was stirred at 100 °C for 8 h (for substrate **1a**–**1v**) or 30 h (for substrate **1w**–**1ah**) under a N_2 atmosphere. After the solution was cooled to room temperature, $P(OEt)_3$ (172 μL, 1.0 mmol, 2.0 equiv) was added to convert elemental sulfur to $(EtO)_3P{=}S$. The resulting mixture was stirred at room temperature for 1 h and then diluted with ethyl acetate (20 mL) and water (30 mL). The organic phase was separated and the aqueous phase was extracted 3 times. All organic solutions were combined and then dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the residue was subjected to flash column chromatography to give final products.

Procedures for the Synthesis of *gem*-Di(trifluoromethylthio)olefins 6a–6x

A 25 mL bottom flask was charged with substrate **5** (0.5 mmol, 1.0 equiv) and DCM (5 mL) under an air atmosphere. $(CF_3S)_2C{=}S$ (147.6 mg, 0.6 mmol, 1.2 equiv) was added. The resulting mixture was stirred at room temperature for 3 h under an air atmosphere. Then the solvent was removed in vacuum, and the residue stood at 120 °C for 2 h. The reaction system was directly subjected to flash column chromatography to give final products.

Procedures for the Synthesis of *gem*-Di(trifluoromethylthio)cyclopropanes 4a–4e

A 50 mL bottom flask was charged with substrate **1** (2.5 mmol, 5.0 equiv), NaH (120 mg, 5.0 mmol, 10.0 equiv) and dry $PhCH_3$ (10 mL) under a N_2 atmosphere. $(CF_3S)_2C{=}S$ (123.0 mg, 0.5 mmol, 1.0 equiv) was added. The resulting mixture was stirred at 110 °C for 9 h under a N_2 atmosphere. After the reaction was finished, the mixture was diluted with ethyl acetate (40 mL) and water (50 mL). The organic phase was separated and the aqueous phase was extracted water 3 times. All organic phases were combined and then dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the residue was subjected to further purification (for the purification procedure, please see the details in Supporting Information) to give final products.

Procedures for the Synthesis of *gem*-Di(trifluoromethylthio)cyclopropanes 4h−4o

A 50 mL bottom flask was charged with substrate **1** (0.5 mmol, 1.0 equiv), NaH (120 mg, 5.0 mmol, 10.0 equiv) and dry $PhCH_3$ (10 mL) under a N_2 atmosphere. $(CF_3S)_2C{=}S$ (123.0 mg, 0.5 mmol, 1.0 equiv) was added. The resulting mixture was stirred at 110 °C for 1 h under a N_2 atmosphere. After the solution was cooled down to room temperature, substrate **1′** (2.0 mmol, 4.0 equiv) was added. The resulting mixture was continuously stirred at 110 °C for 8 h under a N_2 atmosphere. After the reaction was finished, the mixture was diluted with ethyl acetate (40 mL) and water (50 mL). The organic phase was separated and the aqueous phase was extracted water 3 times. All organic phases were combined and then dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the residue was subjected to further purification (for the purification procedure, please see the details in Supporting Information) to give final products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacsau.4c01270.

Publications Web site, which includes additional experimental details, materials, and methods, including photographs of experimental setup (PDF)

3ag (CIF)

4h (CIF)

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Author Contributions

J.S., J.-H.L., and J.-C.X. designed the experiments and analyzed the data. J.S. and Y.S. performed the experiments. J.S., J.-H.L., and J.-C.X. wrote the paper. Y.-C.G., J.-H.L.. and J.-C.X. conceived and supervised the project.

Notes

The authors declare no competing financial interest.

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