A Practical Synthesis and Applications of (*E*)-Diphenyl-β-(trifluoromethyl)vinylsulfonium Triflate

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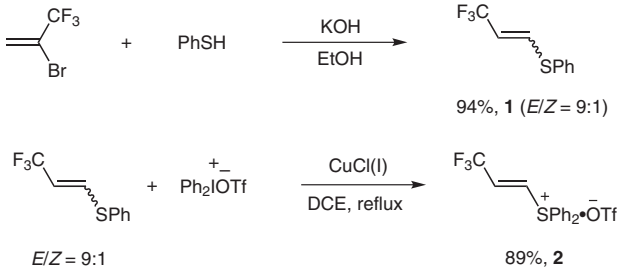
Abstract: (*E*)-Diphenyl-β-(trifluoromethyl)vinylsulfonium triflate, readily prepared from 2-bromo-3,3,3-trifluoroprop-1-ene in two steps, undergoes double alkylation with active methylene compounds in dimethyl sulfoxide or ethyl acetate, in an open vessel at room temperature, to provide the corresponding trifluoromethylated cyclopropane derivatives in excellent yields. The cyclopropane, ethyl 1-cyano-2-(trifluoromethyl)cyclopropanecarboxylate is subjected to a ring-opening reaction followed by cyclization to afford a trifluoromethylated dihydroaminothiophene, which on oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone furnishes the corresponding trifluoromethylated aminothiophene in a high 88% yield.

Key words: vinylsulfonium salts, heterocycles, cyclization, fluorine, ylides

Vinylsulfonium salts represent versatile building blocks for the synthesis of organic molecules of high complexity.[1] They act as a two-carbon source toward appropriate nucleophiles. For example, Aggarwal and co-workers demonstrated the synthesis of nitrogen-containing heterocycles using a simple vinylsulfonium salt.[2] In contrast, there are fewer reported syntheses of substituted vinylsulfonium salts,[1a,1c–e] despite the fact that the introduction of a wide range of functional groups at the vinyl positions of the salt would enhance the diversity of subsequent reactions. From a biological point of view, the addition of one, two, or three fluorine atoms to a molecule often confers unique properties in terms of increased lipophilicity, which in turn changes in vivo absorption and transport rates.[3] The trifluoromethyl group (CF_3), belonging to this category, plays a significant role due to its unique stereoelectronic properties. We have been engaged in research on the development of versatile fluorine-containing building blocks, which can be prepared from readily available fluorinated molecules.[4] In this context, we were motivated to develop an efficient preparation of the corresponding trifluoromethylated vinylsulfonium salts, and to investigate their possible synthetic applications. We originally elaborated a simple preparation of (*E*)-diphenyl-β-(trifluoromethyl)vinylsulfonium triflate (**2**) from commercially available 2-bromo-3,3,3-trifluoroprop-1-ene in two steps, and have already demonstrated briefly its synthetic potential.[4c,5] Herein, we present the results of our continued research on the reactivity of **2** including a practical method for its synthesis.

We have reported previously a straightforward, one-step synthesis of **2** from the corresponding *E*-sulfide **1** (Scheme 1).[4c] Reaction of 2-bromo-3,3,3-trifluoroprop-1-ene with thiophenol in ethanolic potassium hydroxide afforded a crude mixture of two stereoisomers (*E*/*Z* = 9:1), which after careful purification by column chromatography gave the requisite sulfide **1**. To improve the efficiency of this protocol it would be advantageous if the minor *Z*-sulfide could be isomerized into the *E*-sulfide under the same quaternization conditions, thereby avoiding separation of **1**. To put this idea into practice, we found that quaternization of **1** (*E*/*Z* = 9:1) with diphenyliodonium triflate (Ph_2IOTf) in the presence of a catalytic amount of copper(I) chloride in 1,2-dichloroethane (DCE) at reflux temperature for four hours proceeded to afford exclusively the desired product, (*E*)-**2**, in excellent yield (Scheme 1). Moreover, the work-up procedure employed enabled column-free purification of **2** from the crude reaction mixture (see experimental section). In addition, the reaction could be easily scaled-up to provide **2** (8.9 g, 21 mmol) in 89% yield. These procedures for the synthesis of salt **2** greatly enhanced its practical availability.



Scheme 1 An improved synthesis of vinylsulfonium salt **2**

With an improved procedure toward vinylsulfonium salt **2** in hand, we next examined its reactivity. We had already accomplished the simple preparation of trifluoromethylaziridine derivatives in high yields by reacting **2** with a variety of primary amines.[4c] If we could expand this strategy by using an appropriate C-nucleophile instead of an N-nucleophile, it might be possible to synthesize the corresponding trifluoromethyl-cyclopropane derivatives.[5,6]

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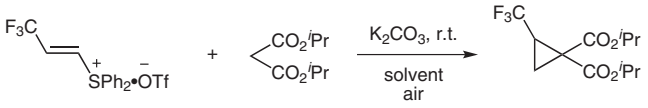
According to the reported procedure, the reaction of diisopropyl malonate (**3a**) (1.0 equiv) and the salt **2** (1.05 equiv) was investigated in the presence of potassium carbonate (3.0 equiv) in dichloromethane–water (1:1), in an open vessel at room temperature (Equation 1).[7] The reaction proceeded slowly to afford the desired product **4a** in only 9% yield (according to GC–MS), along with a large amount of unreacted **3a** (Table 1, entry 1). Among the various solvents examined, ethyl acetate and dimethyl sulfoxide proved to be the most suitable. When the reaction was conducted using potassium carbonate (3.0 equiv) in ethyl acetate, the desired product **4a** was produced in 95% yield (according to GC–MS) in a shorter reaction time (0.5 h), and with no by-products detected (Table 1, entry 5). Furthermore, the reaction went to completion in dimethyl sulfoxide giving **4a** in quantitative yield (according to GC–MS, Table 1, entry 6). Notably, attempts to reduce the amount of potassium carbonate resulted in longer reaction times (Table 1, entries 7 and 8).



2 3a 4a

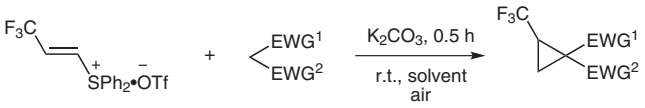
Equation 1

Table 1 Optimization of the Reaction Conditions[a]

Entry	K_2CO_3 (equiv)	Solvent	Time (h)	Yield (%)[b]
1	3.0	CH_2Cl_2–H_2O (1:1)	24	9
2	3.0	CH_2Cl_2–$MeNO_2$ (1:1)	24	0
3	3.0	CH_2Cl_2–Et_2O (1:1)	24	6
4	3.0	THF	24	63
5	3.0	EtOAc	0.5	95
6	3.0	DMSO	0.5	99 (92)[c]
7	2.0	DMSO	5	95
8	1.0	DMSO	24	95

[a] The reactions were carried out on 0.1 mmol scale using **2** (1.05 equiv) and **3a** (1.0 equiv) in the specified solvent (1 mL) at room temperature.
[b] GC–MS yield.
[c] Yield of isolated product in parentheses.

Having identified the optimum reaction conditions, we next set out to examine the scope of the cyclopropanation reaction of **2** with various active methylene compounds **3b**–**f** (Equation 2), and the results are summarized in Table 2. The reactions of **3b**–**d** proceeded efficiently to furnish the corresponding products **4b**–**d** in good to high yields of isolated products (Table 2, entries 2–4). We employed two highly polar activated methylene compounds, **3e** and **3f**, possessing amide or imide groups, which resulted in formation of only trace amounts of the expected products (Table 2, entries 5 and 6). In these cases, the reactions themselves proceeded smoothly to afford the corresponding cyclopropane derivatives **4e** and **4f** according to GC–MS analysis. We speculated that the low yields of the isolated products were due to difficulties in extracting the readily water-soluble products (**4e** and **4f**) from the aqueous crude reaction mixtures. To avoid aqueous work-up, we instead employed ethyl acetate as the solvent. Thus, non-aqueous work-up conditions (see experimental section) provided the desired products **4e** and **4f** in high 92% and 84% yields (Table 2, entries 11 and 12). It is noteworthy that the cyclopropane products **4b**–**e** containing two different electron-withdrawing groups were obtained as single stereoisomers. The *cis* stereochemistry between the cyano and trifluoromethyl groups in the products **4b** and **4c** was determined by comparison with the reported NMR spectroscopic data.[5,6r] The reason for the exclusive formation of the *cis* isomers was attributed to the lower steric congestion between the cyano and trifluoromethyl groups. We tentatively assigned products **4d** and **4e** as *cis* isomers by similar comparison of their NMR spectroscopic data.



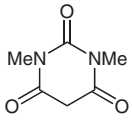
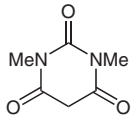
2 3 4

Equation 2

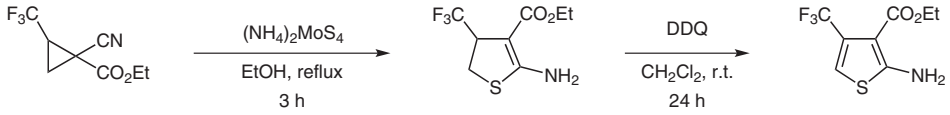
To demonstrate the possibility of manipulation of the cyano group, product **4b** was subjected to a ring-opening reaction with commercially available ammonium tetrathiomolybdate [$(NH_4)_2MoS_4$] in ethanol at reflux temperature for three hours, according to a slightly modified procedure.[7] Initial ring-opening followed by subsequent ring-closure gave the corresponding five-membered cyclized product **5** in 95% yield. Oxidation of **5** with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) in dichloromethane at room temperature over 24 hours resulted in the formation of thiophene **6** in 88% yield (Scheme 2). This compound has been reported as a precursor to thiophene-based *c*-Jun N-terminal kinase (JNK) inhibitors.[8]

Finally, to compare the reactivity between vinyl diphenyl sulfonium triflate[2] and (*E*)-diphenyl-β-(trifluoromethyl)vinylsulfonium triflate (**2**), we investigated the synthesis of the corresponding morpholine derivatives. The reaction of **2** with 2-tosylaminoethanol **7** was performed using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the base (Scheme 3). In contrast to our expectations, the desired cyclization reaction did not take place. Instead, an unanticipated addition–elimination product, identified as the trifluoromethylated vinylamine derivative **9**, was obtained in 78% yield. Reaction of **2** with 2-methyl-2-tosylaminopropanol **10**, under the same conditions, gave the corresponding trifluoromethylated vinyl ether derivative **12** in 65% yield. The structures of **9** and **12** were deter-

Table 2 Examination of the Scope of the Cyclopropanation Reaction of **2**[a]

Entry	Substrate	EWG[1]	EWG[2]	Solvent	Product	Yield (%)[b]
1	**3a**	CO_2i-Pr	CO_2i-Pr	DMSO	**4a**	92
2	**3b**	CN	CO_2Et	DMSO	**4b**	76[c]
3	**3c**	CN	SO_2Ph	DMSO	**4c**	86
4	**3d**	CN	$P(O)(OEt)_2$	DMSO	**4d**	88
5	**3e**	CN	$CONH_2$	DMSO	**4e**	trace[d]
6	**3f**			DMSO	**4f**	trace[d]
7	**3a**	CO_2i-Pr	CO_2i-Pr	EtOAc	**4a**	87
8	**3b**	CN	CO_2Et	MeOAc[e]	**4b**	98
9	**3c**	CN	SO_2Ph	EtOAc	**4c**	92
10	**3d**	CN	$P(O)(OEt)_2$	EtOAc	**4d**	72
11	**3e**	CN	$CONH_2$	EtOAc	**4e**	92
12	**3f**			EtOAc	**4f**	84

[a] The reactions were carried out using **2** (1.05 equiv), **3** (1.0 equiv) and K_2CO_3 (3 equiv) at room temperature for 0.5 h.
[b] Yield of isolated product.
[c] Volatile product.
[d] See text.
[e] Methyl acetate (MeOAc) was used as the solvent due to the volatility of product **4b**.



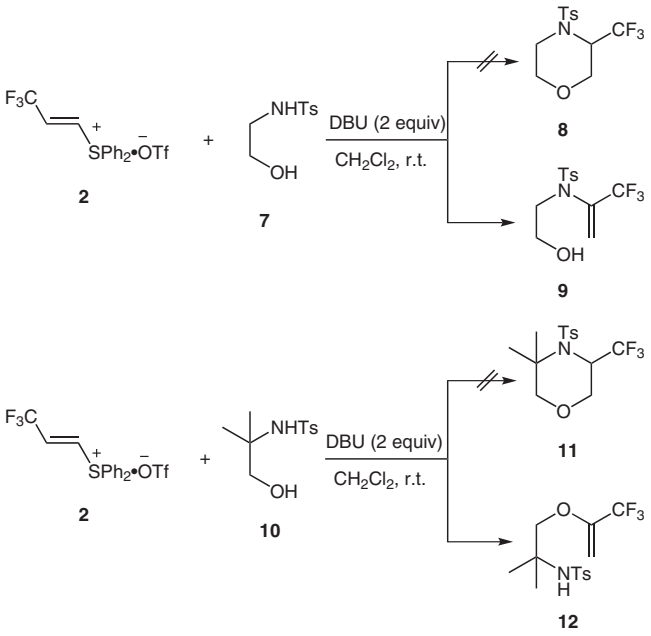
4b **5**, 95% **6**, 88%

Scheme 2 Synthesis of trifluoromethyl-containing thiophene **6**

mined on the basis of spectroscopic analyses. Additionally, the structure of ether **12** was determined unambiguously by X-ray crystallographic analysis (Figure 1).

A plausible mechanism for the reactions described above is depicted in Scheme 4. We initially envisaged that **2** would be attacked at the β-position by the anion generated from **7** with 1,8-diazabicyclo[5.4.0]undec-7-ene to give the corresponding sulfur ylide **13**. Subsequent proton transfer followed by intramolecular cyclization (**14** → **8**) would afford the trifluoromethyl-containing morpholine derivative **8** and diphenyl sulfide. However, on the basis of our findings, we propose an alternative mechanism for this reaction. Attention to the strong electron-withdrawing properties of the trifluoromethyl group in the intermediate ylide led us to speculate on the enhancement of the acidity of the methine proton next to the trifluoromethyl group. In fact, this proton should be abstracted by the ylide **15**. As a result, the subsequent elimination should proceed smoothly to furnish the trifluoromethyl vinylamine derivative **9**. In the case of **10**, the steric effect of the geminal dimethyl groups might prevent nucleophilic attack. Instead, the terminal primary alkoxide anion would attack at the β-position of **2** to generate the corresponding ylide, which would undergo transformation by way of a similar reaction path to that described for the formation of **9**, giving the product **12**. These results led us to suspend further attempts toward the synthesis of trifluoromethyl-containing morpholine derivatives due to inherent properties of **2**.

In conclusion, we have described conditions for the convenient preparation of **2**, which did not require column chromatography, and for the efficient cyclization reac-



Scheme 3 Reaction of **2** with amino alcohols **7** and **10**

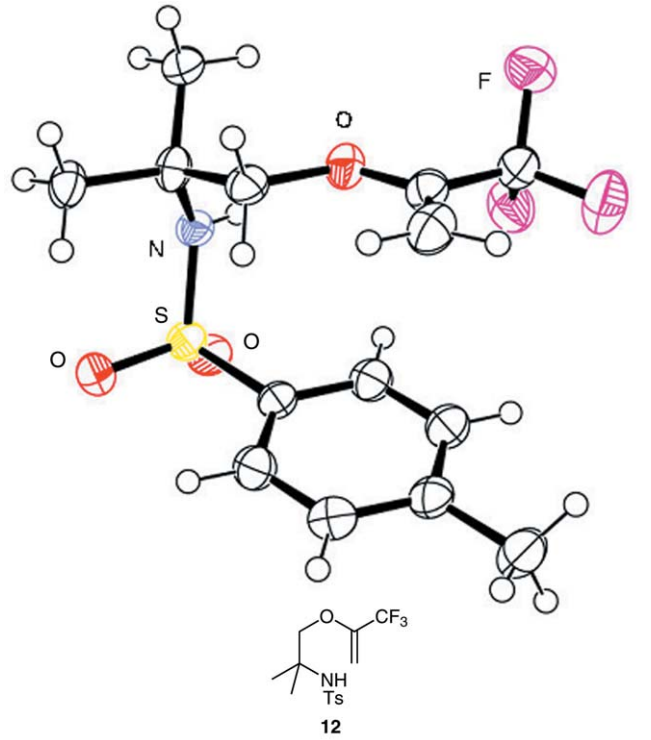
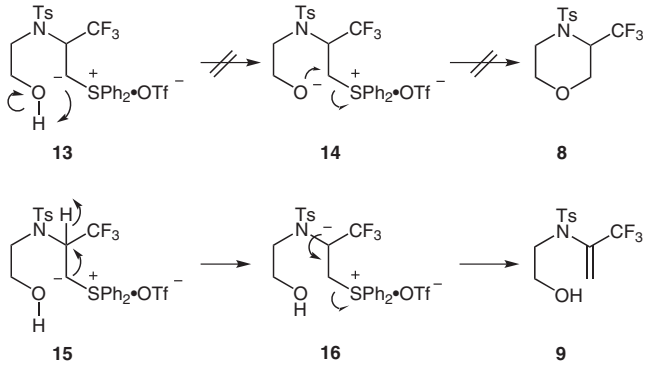


Figure 1 The ORTEP view of **12** with thermal ellipsoids shown at the 50% probability level

tions of **2** in an open vessel at room temperature. These reactions are operationally simple and employ readily available reagents under mild conditions. Further efforts are underway to expand the scope of salt **2** for the synthesis of a wide range of fluorinated compounds.



Scheme 4 A plausible mechanism for the reaction of **2** with amino alcohol **7**

All solvents and starting materials were commercially available and used as received without further purification, unless otherwise noted. CH_2Cl_2, DCE, and DBU were distilled from CaH_2. Column chromatographic separation was carried out using Silica Gel 60 (particle size 63–210 μm), spherical (Kanto Chemical Co.). Melting points were measured with a YANACO micro melting point apparatus and are uncorrected. IR spectra were recorded on a Bruker VERTEX70-S spectrometer. ^1H, ^{13}C NMR, and ^{19}F NMR spectra were recorded on Varian NMR System 400HFX or JEOL JNM-AL 300 FT-NMR spectrometers. GC–MS spectra were obtained using an Agilent 5975C spectrometer. High-resolution mass spectra were recorded on a high-performance double-focusing JEOL JMS-HX110A mass spectrometer. Elemental analyses were obtained using a CHNcorder Yanako MT-5 or MT-6 by the Service Center of the Elementary Analysis of Organic Compounds, Kyushu University.

Phenyl β-(Trifluoromethyl)vinyl Sulfide (1)[9]

A 300 mL round-bottom flask equipped with a magnetic stir bar was charged with EtOH (50 mL) and KOH (3.3 g, 59 mmol). To the stirred soln were successively added thiophenol (5.0 mL, 49 mmol) and 3,3,3-trifluoro-2-bromoprop-1-ene (1.3 mL, 58 mmol) at 0 °C. The resulting mixture was gradually warmed to ambient temperature overnight. The reaction was quenched with sat. aq NH_4Cl soln and the organic layer separated from the mixture. The aq layer was extracted with hexane (3 × 30 mL). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. The resulting oily residue was purified by silica gel chromatography (hexane) to give a 9:1 mixture of *E*/*Z*-**1**.

Yield: 9.4 g (94%); colorless oil.

^1H NMR (400 MHz, $CDCl_3$): δ (*E*-isomer) = 5.42 (dq, *J* = 15.3, 6.5 Hz, 1 H), 7.14 (dq, *J* = 15.3, 2.0 Hz, 1 H), 7.34–7.50 (m, 5 H).

^1H NMR (400 MHz, $CDCl_3$): δ (*Z*-isomer): = 5.64 (dq, *J* = 10.9, 8.2 Hz, 1 H), 6.87 (dq, *J* = 10.9, 0.8 Hz, 1 H), 7.34–7.50 (m, 5 H).

^{19}F NMR (376 MHz, $CDCl_3$): δ (*E*-isomer) = –63.5 (d, *J* = 4.1 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ (*Z*-isomer) = –61.1 (d, *J* = 8.2 Hz).

The spectroscopic data were consistent with those reported in the literature.

(*E*)-Diphenyl-β-(trifluoromethyl)vinylsulfonium Triflate (2)

A 100 mL two-necked flask equipped with a magnetic stir bar, a stopcock and a three-way stopcock, was charged with phenyl β-(trifluoromethyl)vinyl sulfide (**1**) (4.99 g, 24.5 mmol) in DCE (10 mL) under Ar. To this soln was added diphenyliodonium triflate (10.02 g, 23.3 mmol), CuCl (242.5 mg, 2.45 mmol) and a catalytic amount of Cu wire. The mixture was heated at reflux temperature for 4 h.

After cooling to r.t., the mixture was filtered through a Celite pad and the filtrate concentrated in vacuo. Hexane (ca. 300 mL) was added to the residue to give a crude pale colored precipitate. This precipitate was washed with hexane and then recrystallized from acetone–Et_2O to afford the desired product.

Yield: 8.90 g (89%); white solid; mp 68.1–70.5 °C.

IR (KBr): 3066, 3047, 1645, 1583, 1478, 1449, 1279, 1226, 1152, 1031, 999, 873, 748, 683 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.98 (dq, *J* = 14.7, 5.9 Hz, 1 H), 7.71–7.83 (m, 6 H), 7.88–7.93 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 120.0 (q, *J* = 273.4 Hz), 120.6 (q, *J* = 320.1 Hz), 123.6, 126.7 (q, *J* = 6.9 Hz), 130.9, 131.8, 135.2, 137.3 (q, *J* = 37.4 Hz).

^{19}F NMR (283 MHz, $CDCl_3$): δ = –66.3 (d, *J* = 6.5 Hz), –79.9 (s).

Anal. Calcd for $C_{16}H_{12}F_6O_3S_2$: C, 44.65; H, 2.81. Found: C, 44.66; H, 2.92.

Cyclopropanes 4a and 4d; General Method A

A 50 mL flask (open to air) equipped with a magnetic stir bar was charged with the appropriate active methylene compound **3** (0.5 mmol, 1.0 equiv) and K_2CO_3 (1.5 mmol, 3.0 equiv) in DMSO (2 mL). To the resulting mixture was added compound **2** (0.525 mmol, 1.05 equiv) at r.t. After stirring for 0.5 h, the reaction mixture was quenched with H_2O. The organic layer was separated and the aq layer extracted with hexane–Et_2O (3:1, 3 × 2 mL). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residual oil was purified by silica gel chromatography (hexane, then Et_2O) to give cyclopropane **4a** or **4d**.

Diisopropyl 2-(Trifluoromethyl)cyclopropane-1,1-dicarboxylate (4a)

The product was prepared from diisopropyl malonate (**3a**) (95 μL, 0.5 mmol) using general method A (see Table 2, entry 1).

Yield: 129.4 mg (92%); colorless oil.

IR (NaCl): 2985, 2941, 1732, 1469, 1413, 1376, 1359, 1320, 1279, 1219, 1154, 1102, 967, 909, 895, 832 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 6.0 Hz, 6 H), 1.28 (t, *J* = 6.0 Hz, 6 H), 1.51 (dd, *J* = 9.4, 5.4 Hz, 1 H), 1.77 (dd, *J* = 7.0, 5.4 Hz, 1 H), 2.54 (dquin, *J* = 9.4, 7.0 Hz, 1 H), 5.05 (sept, *J* = 6.0 Hz, 1 H), 5.11 (sept, *J* = 6.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.0, 21.0, 21.2, 21.4, 21.5, 26.8 (q, *J* = 38.1 Hz), 33.5, 69.5, 70.3, 124.1 (q, *J* = 272.5 Hz), 164.5, 167.7.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –65.4 (d, *J* = 7.0 Hz).

GC–MS (EI, 70 eV): *m*/*z* (%) = 281 (1) $[M - 1]^+$, 223 (21), 199 (27), 182 (8), 181 (100), 144 (1), 134 (3), 128 (2), 114 (6), 69 (1).

Anal. Calcd for $C_{12}H_{17}F_3O_4$: C, 51.06; H, 6.07. Found: C, 51.31; H, 6.17.

Cyclopropanes 4b, 4c, 4e and 4f; General Method B

A 50 mL (open to air) flask equipped with a magnetic stir bar was charged with the appropriate active methylene compound **3** (1.44 mmol, 1.0 equiv) and K_2CO_3 (4.32 mmol, 3.0 equiv) in MeOAc (5 mL). To the resulting mixture was added compound **2** (1.50 mmol, 1.05 equiv) at r.t. After stirring for 0.5 h, the mixture was filtered through a Celite pad. After washing the Celite pad with Et_2O, the combined filtrate was concentrated in vacuo. The residual oil was purified by silica gel chromatography (hexane, then Et_2O) to give cyclopropane **4b**, **4c**, **4e** or **4f**.

Ethyl 1-Cyano-2-(trifluoromethyl)cyclopropanecarboxylate (4b)[5,6r]

The product was prepared from ethyl cyanoacetate (**3b**) (150 μl, 1.44 mmol) using general method B (see Table 2, entry 8).

Yield: 290.9 mg (98%); colorless oil.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.38 (t, *J* = 7.3 Hz, 3 H), 1.95–2.01 (m, 2 H), 2.61–2.70 (m, 1 H), 4.33 (q, *J* = 7.3 Hz, 2 H).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –68.8 (d, *J* = 5.5 Hz).

The spectroscopic data were consistent with those reported in the literature.

1-(Phenylsulfonyl)-2-(trifluoromethyl)cyclopropanecarbonitrile (4c)[5,6r]

The product was prepared from phenylsulfonylacetonitrile (**3c**) (54.4 mg, 0.3 mmol) in EtOAc (1 mL) using general method B (see Table 2, entry 9).

Yield: 76.3mg (92%); white solid; mp 111.3–111.7 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.05 (t, *J* = 5.5 Hz, 1 H), 2.24–2.28 (m, 1 H), 2.83–2.92 (m, 1 H), 7.69 (t, *J* = 7.4 Hz, 2 H), 7.79–7.85 (tm, *J* = 7.4 Hz, 1 H), 7.97–8.02 (dm, *J* = 8.4 Hz, 2 H).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –66.2 (d, *J* = 5.5 Hz).

The spectroscopic data were consistent with those reported in the literature.

Diethyl [1-Cyano-2-(trifluoromethyl)cyclopropyl]phosphonate (4d)

The product was prepared from diethyl (cyanomethyl)phosphonate (**3d**) (48 μL, 0.3 mmol) in DMSO (3 mL) using general method A (see Table 2, entry 4).

Yield: 72.1 mg (88%); colorless oil.

IR (NaCl): 2990, 2245, 1451, 1413, 1259, 1190, 1157, 1092, 1023, 872, 798, 695 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.39–1.45 (m, 6 H), 1.84–1.89 (dm, *J* = 8.0 Hz, 1 H), 1.87–1.92 (dm, *J* = 8.0 Hz, 1 H), 2.53–2.61 (m, 1 H), 4.22–4.31 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.0, 9.9, 15.1, 16.0, 16.1, 25.9 (q, *J* = 38.1 Hz), 64.4, 64.5, 114.2, 123.1 (q, *J* = 273.3 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –65.9 (d, *J* = 6.8 Hz).

GC–MS (EI, 70 eV): *m*/*z* (%) = 270 (1) $[M - 1]^+$, 244 (69), 216 (100), 215 (17), 198 (48), 196 (19), 146 (15), 91 (12), 81 (33), 69 (5).

Anal. Calcd for $C_9H_{13}F_3NO_3P$: C, 39.86; H, 4.83; N, 5.17. Found: C, 39.89; H, 4.73; N, 5.20.

1-Cyano-2-(trifluoromethyl)cyclopropanecarboxamide (4e)

The product was prepared from 2-cyanoacetamide (**3e**) (75.7 mg, 0.9 mmol) in EtOAc (3 mL) using general method B (see Table 2, entry 11).

Yield: 147.2 mg (92%); white solid; mp 115.2–116.0 °C.

IR (KBr): 3399, 3175, 2256, 1703, 1628, 1387, 1287, 1198, 1083, 1010, 962, 819, 559, 519 cm^{-1}.

^1H NMR (400 MHz, D_2O): δ = 2.02 (dd, *J* = 8.8, 7.0 Hz, 1 H), 2.13 (t, *J* = 7.0 Hz, 1 H), 2.89 (dquin, *J* = 8.8, 7.0 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 18.4, 18.7, 28.5 (q, *J* = 37.5 Hz), 117.2, 125.0 (q, *J* = 273.0 Hz), 165.3.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –63.42 (d, *J* = 7.0 Hz).

GC–MS (EI, 70 eV): *m*/*z* (%) = 178 (18) $[M]^+$, 177 (31), 135 (29), 115 (60), 111 (18), 109 (100), 88 (22), 84 (11), 69 (21), 64 (15).

Anal. Calcd for $C_6H_5F_3N_2O$: C, 40.46; H, 2.81; N, 15.73. Found: C, 40.56; H, 2.81; N, 15.85.

5,7-Dimethyl-1-(trifluoromethyl)-5,7-diazaspiro[2.5]octane-4,6,8-trione (4f)

The product was prepared from 1,3-dimethylbarbituric acid (**3f**) (46.8 mg, 0.3 mmol) in EtOAc (1 mL) using general method B (see Table 2, entry 12).

Yield: 63.1 mg (84%); white solid; mp 123.2–124.0 °C.

IR (KBr): 2360, 2341, 1678, 1428, 1383, 1263, 1162, 1098, 1033, 756, 668, 647 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.22–2.26 (m, 1 H), 2.51 (dd, *J* = 8.4, 4.3 Hz, 1 H), 2.78–2.84 (m, 1 H), 3.35 (s, 3 H), 3.36 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 23.2, 29.8, 29.9, 32.3, 37.4 (q, *J* = 39.7 Hz), 124.9 (q, *J* = 274.1 Hz), 152.5, 166.0, 167.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –59.47 (d, *J* = 8.2 Hz).

GC–MS (EI, 70 eV): *m*/*z* (%) = 251 (12) $[M + 1]^+$, 250 (100) $[M]^+$, 222 (10), 193 (14), 192 (14), 181 (76), 165 (30), 124 (34), 108 (45), 69 (13).

Anal. Calcd for $C_9H_6F_3N_2O_3$: C, 43.21; H, 3.63; N, 11.20. Found: C, 43.43; H, 3.61; N, 11.12.

2-Amino-3-ethoxycarbonyl-4-trifluoromethyl-4,5-dihydrothiophene (5)

A 100 mL flask equipped with a magnetic stir bar was charged with cyclopropane **4b** (284.7 mg, 1.37 mmol) in EtOH (10 mL), and to this mixture was added ammonium tetrathiomolybdate $[(NH_4)_2MoS_4]$ (426.8 mg, 1.64 mmol) at r.t. The mixture was heated at reflux temperature for 3 h, cooled to r.t., filtered through a Celite pad and the pad washed with CH_2Cl_2. The combined organic layer was concentrated in vacuo. The residual oil was purified by silica gel chromatography (Et_2O) to give dihydrothiophene **5**.

Yield: 314.3 mg (95%); white solid; mp 119.2–120.3 °C.

IR (KBr): 3371, 3276, 3183, 1649, 1612, 1512, 1410, 1382, 1358, 1281, 1228, 1155, 1110, 1028, 931, 907, 814, 774, 725, 687, 659 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.1 Hz, 3 H), 3.26 (d, *J* = 12.1 Hz, 1 H), 3.56 (dd, *J* = 12.1, 9.0 Hz, 1 H), 3.97 (dq, *J* = 9.0, 8.2 Hz, 1 H), 4.12 (dq, *J* = 10.8, 7.1 Hz, 2 H), 4.22 (dq, *J* = 10.8, 7.1 Hz, 2 H), 6.40 (br s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.4, 30.3, 48.3 (q, *J* = 28.8 Hz), 59.3, 87.0, 127.1 (q, *J* = 283.4 Hz), 165.9, 167.0.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –74.6 (d, *J* = 8.2 Hz).

GC–MS (EI, 70 eV): *m*/*z* (%) = 241 (44) $[M]^+$, 196 (30), 172 (100), 146 (12), 144 (26), 126 (30), 100 (18), 99 (14), 95 (3), 69 (2).

Anal. Calcd for $C_8H_{10}F_3NO_2S$: C, 39.83; H, 4.18; N, 5.81. Found: C, 40.08; H, 4.19; N 5.73.

2-Amino-3-ethoxycarbonyl-4-(trifluoromethyl)thiophene (6)[8b]

A 25 mL flask equipped with a magnetic stir bar was charged with dihydrothiophene **5** (38.2 mg, 0.17 mmol) in CH_2Cl_2 (1 mL), and to the resulting mixture was added DDQ (47.7 mg, 0.21 mmol) at r.t. After stirring for 24 h, the mixture was filtered through a Celite pad and the filtrate concentrated in vacuo. The residual solid was purified by silica gel chromatography (Et_2O) to give thiophene **6**.

Yield: 33.3 mg (85%); white solid; mp 70.1–70.3 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.35 (t, *J* = 7.1 Hz, 3 H), 4.30 (q, *J* = 7.1 Hz, 2 H), 6.27 (br s, 2 H), 6.75 (s, 1 H).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –61.0 (s).

The spectroscopic data were consistent with those reported in the literature.

2-[*N*-(1,1,1-Trifluoroprop-2-en-2-yl)-*N*-tosylamino]ethanol (9)

A 25 mL two-necked flask equipped with a magnetic stir bar, a stopcock and a three-way stopcock, was charged with **2** (111.0 mg, 0.25 mmol) in CH_2Cl_2 (1 mL) under Ar. To the resulting soln were added 2-(tosylamino)ethanol **7** (66.0 mg, 0.30 mmol)[2d] and DBU (75.0 μL, 0.50 mmol). After stirring for 2 h, the reaction mixture was quenched with H_2O. The organic layer was separated and the aq layer extracted with CH_2Cl_2 (2 × 2 mL). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residual oil was purified by silica gel chromatography (hexane–EtOAc, 1:1) to give alcohol **9**.

Yield: 60.6 mg (78%); colorless oil.

IR (NaCl): 3542, 2930, 1598, 1354, 1165, 974, 684 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.10 (t, *J* = 5.5 Hz, 1 H), 2.44 (s, 3 H), 3.56 (t, *J* = 5.5 Hz, 2 H), 3.74 (q, *J* = 5.5 Hz, 2 H), 5.85–5.87 (m, 1 H), 6.13–6.15 (m, 1 H), 7.32 (d, *J* = 8.1 Hz, 2 H), 7.73 (d, *J* = 8.1 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5, 51.7, 59.5, 120.9 (q, *J* = 276.5 Hz), 125.9 (q, *J* = 3.3 Hz), 127.8, 129.7, 133.7 (q, *J* = 34.7 Hz), 135.3, 144.4.

^{19}F NMR (283 MHz, $CDCl_3$): δ = –60.1 (s).

GC–MS (EI, 70 eV): *m*/*z* (%) = 214 (2), 155 (16), 124 (11), 91 (100), 77 (2), 65 (23), 54 (8).

Anal. Calcd for $C_{12}H_{14}F_3NO_3S$: C, 46.60; H, 4.56; N, 4.53. Found: C, 46.74; H, 4.65; N, 4.65.

1-(1,1,1-Trifluoroprop-2-en-2-yloxy)-2-methyl-*N*-tosylpropan-2-amine (12)

A 25 mL two-necked flask equipped with a magnetic stir bar, a stopcock and a three-way stopcock, was charged with **2** (104.0 mg, 0.23 mmol) in CH_2Cl_2 (1.5 mL) under Ar. To the resulting soln were added 2-methyl-2-(tosylamino)propane-1-ol **10** (64.0 mg, 0.26 mmol)[2d] and DBU (70.0 μL, 0.47 mmol). After stirring for 3 h, the reaction mixture was quenched with H_2O. The organic layer was separated and the aq layer extracted with CH_2Cl_2 (2 × 2 mL). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residual oil was purified by silica gel chromatography (hexane–EtOAc, 3:1) to give ether **12**.

Yield: 51.8 mg (65%); white solid; mp 72.5–73.4 °C.

IR (KBr): 3259, 1655, 1386, 1326, 1155, 985, 676 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.270 (s, 3 H), 1.272 (s, 3 H), 2.41 (s, 3 H), 3.55 (s, 2 H), 4.30 (br s, 1 H), 4.77 (d, *J* = 3.1 Hz, 1 H), 4.83 (s, 1 H), 7.27 (d, *J* = 8.0 Hz, 2 H), 7.76 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.4, 24.6, 55.7, 74.5, 88.0 (q, *J* = 3.7 Hz), 119.5 (q, *J* = 273.4 Hz), 126.9, 129.6, 139.8, 143.2, 146.6 (q, *J* = 34.9 Hz).

^{19}F NMR (283 MHz, $CDCl_3$): δ = –73.8 (s).

GC–MS (EI, 70 eV): *m*/*z* (%) = 214 (1), 213 (4), 212 (30) $[Me_2CNHTs]^+$, 155 (44), 139 (2), 91 (100), 70 (2), 65 (15), 55 (4).

HRMS−FAB: *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{19}F_3NO_3S$: 338.1059; found 338.1038.

Crystal Data for 12

($C_{14}H_{18}F_3NO_3S$): *M* = 337.35, *T* = 123(2) K, monoclinic, space group *P*21/*c*, *a* = 9.705(3) Å, *b* = 11.102(3) Å, *c* = 14.580(5) Å, *V* = 1558.7 Å^3, *Z* = 4, *Dx* = 1.438 Mg·m^{-3}, *m* = 0.250 mm^{-1}, *l* = 0.71073 Å, q_{max} = 27.47°, 3553 measured reflections, 1926 independent reflections, 206 refined parameters, GOF = 1.084, $R[F^2 > 2s(F^2)] = 0.1020$, $wR(F^2) = 0.3606$. The structure was solved by direct methods (SIR2002[10]) and the non-hydrogen atoms were refined anisotropically by full-matrix least-squares procedures on F^2 for all reductions (SHELXL97[11]). All hydrogen atoms were positioned geometrically and refined as riding. CCDC 883928 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336033.

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