# Asymmetric 1,3-dipolar cycloaddition of optically active trifluoromethylated α,β-unsaturated aryl sulfones with nitrones: the use of *o*-dialkylaminoethyl chiral auxiliaries

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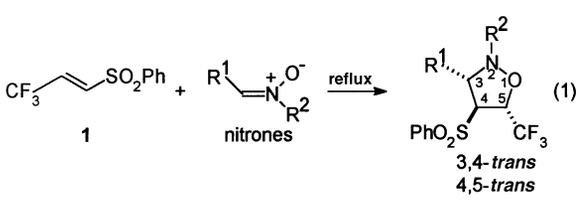
**Optically active trifluoromethylated α,β-unsaturated aryl sulfones 8a–c, which have a chiral *N*,*N*-dialkylaminoethyl group on the *ortho* position, were synthesized from (*S*)-1-phenylethylamine 2 and ethyl trifluoroacetate. Asymmetric 1,3-dipolar cycloaddition of sulfones 8a–c with some selected nitrones 9a–c gave the corresponding isoxazolidines 10a–c, 11a–c and 12–15 regio- (> 98%) and diastereo-selectively (36–56% de) in 58–80% yields. The absolute configurations of the cycloadducts were assigned on the basis of X-ray crystallographic analysis of the adduct 10a and by the $^1$H NMR spectra. The obtained facial selectivity was rationalized by comparison of four possible stable conformers of compound 8a based on AM1 calculations.**

## Introduction

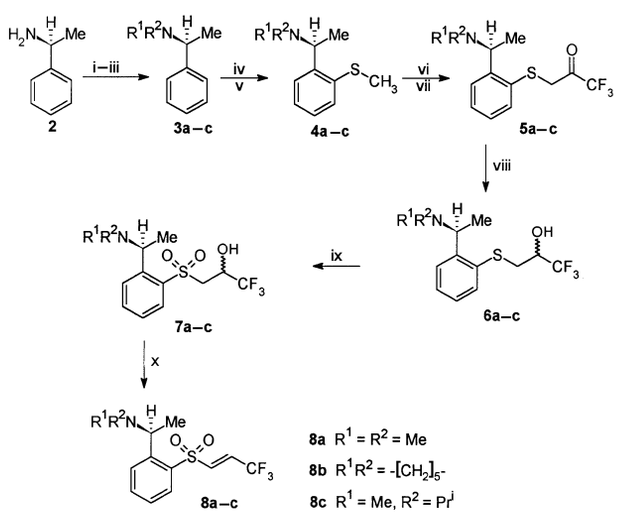
Much attention has been addressed recently to trifluoromethylated heterocycles in view of their unique biological activities.[1] In particular, trifluoromethylated five-membered heterocycles, isoxazolidines, are becoming important compounds because these compounds can be easily converted into some useful trifluoromethylated compounds.[2] For the regio- and stereoselective synthesis of trifluoromethylated isoxazolidines, 1,3-dipolar cycloaddition of trifluoromethylated electron-deficient olefins with nitrones is one of the most promising approaches.[2a–c] From this point of view, we recently reported highly regio- and stereo-selective synthesis of trifluoromethylated isoxazolidines by 1,3-dipolar cycloaddition of 1,1,1-trifluoro-3-(phenylsulfonyl)propene **1** with various nitrones, and their conversion into trifluoromethylated *syn*-3-amino alcohols [equation (1)].[3] As a next stage, application of this




cycloaddition methodology to asymmetric reaction would be expected to provide a new approach for the synthesis of optically active trifluoromethylated isoxazolidine. Thus, in order to bring a chiral environment into the unsaturated aryl sulfone **1**, we designed the introduction of a chiral substituent on the *ortho* position of the phenyl group. In this paper, we report the synthesis of optically active trifluoromethylated α,β-unsaturated aryl sulfones having a chiral dialkylaminoethyl substituent on the *ortho* position, and their 1,3-dipolar cycloaddition with some selected nitrones.

## Results and discussion

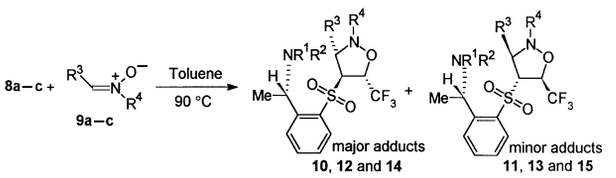
For the preparation of unsaturated aryl sulfones with a chiral substituent on the *ortho* position, we started from (*S*)-1-phenylethylamine **2** because introduction of the sulfur substituent was expected to be relatively easy by *ortho*-deprotonation with alkyllithiums[4] and both enantiomeric counterparts were commercially available. As a variety of the bulkiness of *N*,*N*-dialkylamino groups, three kinds of sulfones **8a–c** were synthesized as summarized in Scheme 1. Methylation of the




**Scheme 1** *Reagents and conditions*: i, HCHO, $HCO_2H$, 90 °C, 24 h (**3a**); ii, 1,5-dibromopentane, DMPU, 100 °C, 2 h (**3b**); iii, 2-iodopropane, DMPU, 100 °C, 2 h; then HCHO, $HCO_2H$, 90 °C, 4 h (**3c**); iv, BuLi, TMEDA, hexane, −78 °C, 0.5 h; then room temp., 3 days; v, $CH_3SSCH_3$, room temp., overnight; vi, BuLi, TMEDA, THF, −40 °C, 1 h; then room temp., 1.5 h; vii, $CF_3CO_2Et$, room temp., overnight; viii, $NaBH_4$, MeOH, room temp., overnight; ix, OXONE®, aq. MeOH, room temp, 4 h; x, MsCl, $Et_3N$, $CH_2Cl_2$, 0 °C, 0.5 h

primary amine **2** with formaldehyde and formic acid according to Pine's procedure[5] gave amine **3a** in 84% yield. The piperidine **3b** was obtained from amine **2** with 1,5-dibromopentane in the presence of solid $Na_2CO_3$ in *N*,*N*′-dimethylpropyleneurea (DMPU) at 100 °C in 94% yield. Isopropylmethylamino derivative **3c** was prepared in 88% yield by two-step alkylations: isopropylation of compound **2** with 2-iodopropane in DMPU[6] followed by methylation with formaldehyde and formic acid.[5] The *ortho*-thiomethylations of amines **3a–c** were performed by deprotonation with BuLi-tetramethylethylenediamine

**Table 1** 1,3-Dipolar cycloaddition of substrates **8a–c** with nitrones **9a–c**




| Olefins | Nitrones | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Yield (%) | Products | de[a] |
|---|---|---|---|---|---|---|---|---|
| **8a** | **9a** | Me | Me | Ph | Me | 80 | **10a, 11a** | 56 |
| **8a** | **9b** | Me | Me | Ph | Ph | 70 | **10b, 11b** | 54 |
| **8a** | **9c** | Me | Me | Ph | Bu | 71 | **10c, 11c** | 41 |
| **8b** | **9a** | –[$CH_2$]$_5$– | | Ph | Me | 74 | **12, 13** | 36 |
| **8c** | **9a** | Me | $Pr^i$ | Ph | Me | 58 | **14, 15** | 40 |

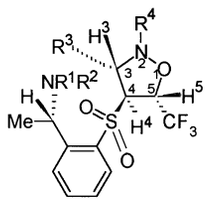
[a] Determined by the $^1$H NMR spectra.

(TMEDA) at −78 °C to room temperature followed by addition of dimethyl disulfide to give sulfides **4a–c**. Since attempted trifluoroacetylation after oxidation of sulfide into sulfone failed, the sulfides **4a–c** were firstly trifluoroacetylated by deprotonation of the *S*-methyl group with BuLi–TMEDA at −78 °C to room temperature followed by addition of $CF_3CO_2Et$ to give mixtures of the corresponding ketones **5a–c** with their hydrate forms. After reduction ($NaBH_4$) of ketones **5a–c** to the alcohols **6a–c**, oxidation of the sulfides with OXONE®[7] led to the corresponding sulfones **7a–c**. Finally, the alcohols **7a–c** were dehydrated with methanesulfonyl chloride and an excess of triethylamine to obtain the desired olefins **8a–c** as *E* olefins in 18, 3 and 7% overall yield based on the amines **3a–c**, respectively. The given structures for products **8a–c** were supported by analytical and spectral data.

The 1,3-dipolar cycloaddition of **8a** with nitrones **9a–c**, and that of compounds **8b** and **8c** with nitrone **9a** in toluene at 90 °C for 12 h occurred regio- (> 98%) and diastereo-selectively (36–56% de) to afford the corresponding isoxazolidines **10a–c**, **12** and **14** respectively as the major products, and isoxazolidines **11a–c**, **13** and **15** respectively as minor products as summarized in Table 1. No regioisomers were detected by the $^1$H NMR spectra of the crude products. The adducts **10a–c** and **11a–c** were separated after sequential silica gel chromatography. However, other adducts **12** (**13**) and **14** (**15**) were inseparable, and hence the product ratios were determined by $^1$H NMR spectroscopy. In all examined cycloadditions, similar yields (58–80%) and similar diastereoselectivities (36–56% de) were obtained. This means that the reactivity of olefins **8a–c** and the selectivity in their cycloaddition would not be much affected by either the kind of nitrone used or the bulkiness of the alkylamino group on the chiral moiety. In agreement with our previous results for the non-asymmetric 1,3-dipolar cycloaddition of the sulfone **1**,[3] $^1$H NMR spectra revealed that all major and minor adducts had the same relative configurations (*i.e.*, 3,4-*trans* and 4,5-*trans*) in the isoxazolidine ring. For example, two coupling constants $J_{3,4}$ (8.2 Hz) and $J_{4,5}$ (3.6 Hz) of compound **10a** are typical values for the given relative configuration and the *J*-values of other adducts are similar, as listed in Tables 2 and 3.

Recrystallization of the cycloadduct **10a** from diethyl ether produced crystals. A single-crystal X-ray diffraction study afforded the structure depicted in Fig. 1. The determination of the stereochemistry of C-1, -2 and -3 was based on the known (*S*) configuration (C-18) of the *N*,*N*-dimethylaminoethyl group. The absolute configuration of the isoxazolidine moiety was thus established as 3*S*,4*S*,5*R*. Therefore, as discussed above, the absolute configuration of the isoxazolidine moiety of the minor adduct **11a** can be determined as the chiral counterpart (*i.e.*, 3*R*,4*R*,5*S*) of major adduct **10a**. The absolute configurations of other adducts were deduced based on chemical-shift

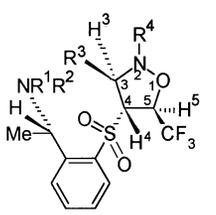
**Table 2** Chemical shifts ($H^3$, $H^4$ and $H^5$) and vicinal coupling constants ($J_{3,4}$, $J_{4,5}$)/Hz of major adducts **10a–c**, **12** and **14** in the $^1$H NMR spectra



**10a–c, 12 and 14**

| | $H^3$ | | $H^4$ | | $H^5$ |
|---|---|---|---|---|---|
| **10a** | $\delta$ 4.26 | | $\delta$ 5.43 | | $\delta$ 4.56 |
| | $J_{3,4}$ | 8.2 | $J_{4,5}$ | 3.6 | |
| **10b** | $\delta$ 4.72 | | $\delta$5.65 | | $\delta$ 4.26 |
| | $J_{3,4}$ | 7.1 | $J_{4,5}$ | 3.5 | |
| **10c** | $\delta$ 4.34 | | $\delta$ 5.36 | | $\delta$ 4.55 |
| | $J_{3,4}$ | 7.9 | $J_{4,5}$ | 3.4 | |
| **12** | $\delta$ 4.25 | | $\delta$ 4.73 | | $\delta$ 4.68 |
| | $J_{3,4}$ | 7.9 | $J_{4,5}$ | 3.8 | |
| **14** | $\delta$ 4.18 | | $\delta$ 4.43 | | $\delta$ 4.74 |
| | $J_{3,4}$ | 8.1 | $J_{4,5}$ | 3.6 | |

**Table 3** Chemical shifts ($H^3$, $H^4$ and $H^5$) and vicinal coupling constants ($J_{3,4}$, $J_{4,5}$)/Hz of minor adducts **11a–c**, **13** and **15** in the $^1$H NMR spectra



**11a-c, 13 and 15**

| | $H^3$ | | $H^4$ | | $H^5$ |
|---|---|---|---|---|---|
| **11a** | $\delta$ 3.89 | | $\delta$ 5.18 | | $\delta$ 5.09 |
| | $J_{3,4}$ | 7.7 | $J_{4,5}$ | 3.8 | |
| **11b** | $\delta$ 4.59 | | $\delta$ 5.47 | | $\delta$ 5.33 |
| | $J_{3,4}$ | 6.9 | $J_{4,5}$ | 3.6 | |
| **11c** | $\delta$ 3.95 | | $\delta$ 5.16 | | $\delta$ 5.08 |
| | $J_{3,4}$ | 7.7 | $J_{4,5}$ | 3.7 | |
| **13** | $\delta$ 3.97 | | $\delta$ 4.46 | | $\delta$ 5.09 |
| | $J_{3,4}$ | 7.9 | $J_{4,5}$ | 3.9 | |
| **15** | $\delta$ 3.97 | | $\delta$ 4.39 | | $\delta$ 5.04 |
| | $J_{3,4}$ | 7.9 | $J_{4,5}$ | 3.8 | |

similarity in the $^1$H NMR spectra; *i.e.*, as 3*S*,4*S*,5*R* for the major adducts **10b**, **10c**, **12** and **14** and as 3*R*,4*R*,5*S* for the minor adducts **11b**, **11c**, **13** and **15** (Tables 2 and 3).†

The X-ray crystallographic analysis of compound **10a** provided some important indications concerning the stable conformation of this substituted aryl sulfone. (1) The *N*,*N*-dimethylamino group at the *ortho* position is perpendicular to the phenylene plane. (2) The p-orbitals of the phenyl group are nearly parallel with the centre axis of the $SO_2$ group. (3) The *N*,*N*-dimethylamino group and the oxygen atoms of the $SO_2$ group are located on the opposite side of the phenylene plane.

† Although chemical shifts of H-3, H-4 and H-5 on the isoxazolidine ring in compounds **10a–c**, **11a–c** and **12–15** varied because of the variety of substituents on the isoxazolidine, each relationship between the same kind of protons of both major and minor adducts is similar. The resonances of H-3 of the major adducts (**10a–c**, **12** and **14**) appear 0.13–0.39 ppm to lower field than those of the minor ones (**11a–c**, **13** and **15**). The resonances of H-4 of the major adducts appear 0.04–0.27 ppm to lower field than those of the minor ones. The resonances of H-5 of the major adducts appear 0.30–1.07 ppm to higher field than those of the minor ones.

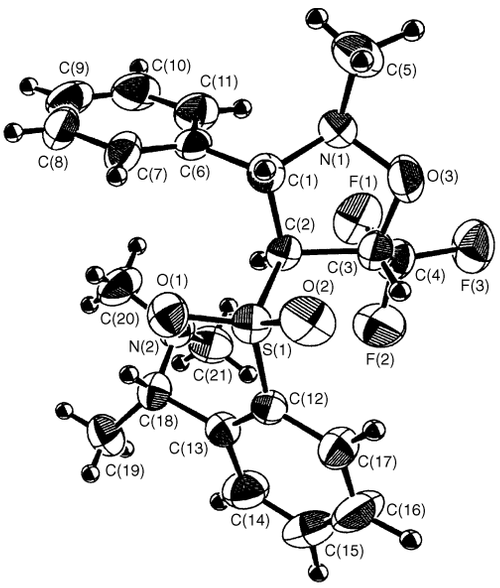



**Fig. 1** ORTEP drawing of the molecular structure of compound **10a**

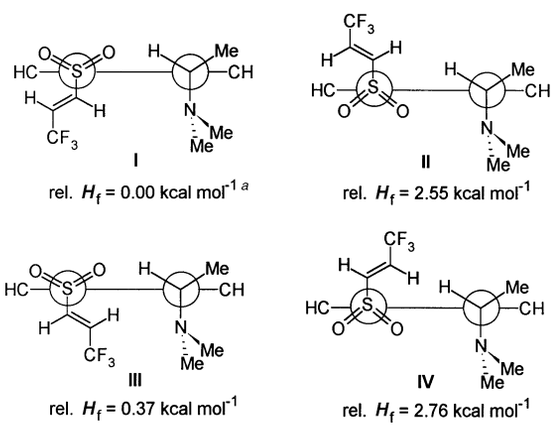



**Fig. 2** Schematic Newman projection for the four possible stable conformers of compound **8a** and the relative heats of formation calculated by the AM1 method. [a] 1 cal = 4.184 J.

These conformational features would be considered to be unchanged between the olefin and its cycloadduct because the rotations of the dimethylaminoethyl group or the $SO_2$ group against the phenyl group would be relatively difficult. These unique features of this substituted aryl sulfone can be applicable to the ground-state conformation of unsaturated aryl sulfone **8a**. The p-orbitals of the olefin moiety in **8a** would also be parallel with the centre axis of the $SO_2$ group in the same manner as were those in the phenyl group. Therefore, four possible stable conformers **I–IV** of compound **8a** can be listed as depicted schematically by Newman projection in Fig. 2. For the structural optimizations and energy calculations of these four conformers **I–IV**, semi-empirical MO calculations were performed using the AM1 method.‡[8] Conformers **II** and **IV** are ~2.6 kcal mol$^{-1}$§ less stable than conformers **I** and **III** [*cf.* conformational feature (3)]. In the more stable conformers **I** and **III**, **III** is slightly less stable (0.37 kcal mol$^{-1}$) than **I** because of the steric repulsion between the trifluoropropenyl and dimethylamino groups. Because 1,3-dipolar cycloaddition in which the C=C double bond of the dipolarophile is transformed into two σ-bonds is an exothermic reaction, the transition state should be reactant-like (Hammond's postulate).[9] Thus, the facial selectivity in the cycloaddition of compound **8a** should be dependent on the relative stability between conformers **I** and **III**. When the dimethylamino group was replaced by a piperidyl (**8b**) or an isopropyl(methyl)amino group (**8c**), only scanty change in the facial selectivity was observed (Table 1). Therefore, appreciable steric repulsion between the trifluoropropenyl and dialkylamino groups could not be added to make conformer **III** more unstable. From these considerations, cycloadditions of **8a–c** with nitrones **9a–c** could be explained to occur mainly on the *si-re* face of the most stable conformer **1** *via* a *Z-endo* transition state[3] to afford the major adducts **10a–c**, **12** and **14** with a 3*S*,4*S*,5*R* configuration as illustrated in Fig. 3. On the other hand, the cycloaddition could also proceed on the *re-si* face of the conformer **III** *via* a *Z-endo* transition state to give the minor adducts **11a–c**, **13** and **15** with 3*R*,4*R*, 5*S* configuration.

‡ Semi-empirical calculations were carried out using MOPAC version 94.10 packaged in the CAChe® Version 3.7.
§ 1 cal = 4.184 J.

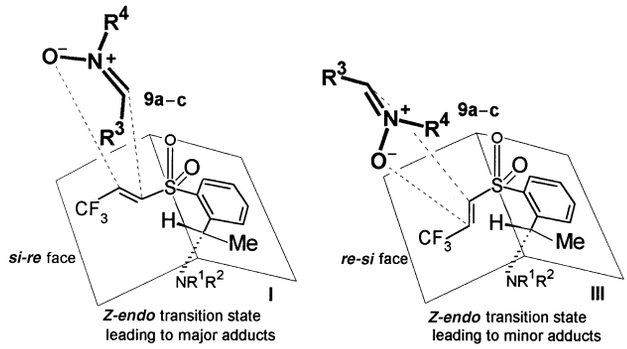



**Fig. 3** Transition structures of 1,3-dipolar cycloaddition of substrates **8a–c** with nitrones **9a–c**

In conclusion, asymmetric 1,3-dipolar cycloaddition of compounds **8a–c** with nitrones **9a–c** gave the corresponding isoxazolidines **10a–c**, **11a–c** and **12–15** regio- (> 98%) and diastereo-selectively (36–56% de) in 58–80% yield. Synthetic application of these adducts and improvement of the diastereoselectivity of this cycloaddition are being studied in our laboratory.

## Experimental

Mps were determined by a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO FT/IR 5300 spectrometer. $^1$H and $^{13}$C NMR spectra were obtained with a Varian GEMINI-200 spectrometer at 200 and at 50 MHz, respectively, for samples in $CDCl_3$ solution with $Me_4Si$ as internal standard. $^{19}$F NMR spectra were obtained with a Hitachi FT-NMR R-90F spectrometer at 85 MHz for samples in $CDCl_3$ solutions with $CFCl_3$ as an internal standard. *J*-Values are given in Hz. Mass spectra were recorded on a JEOL JMS-AX 505 HA mass spectrometer at 70 eV. Flash chromatography was performed with a silica gel column (Fuji-Davison BW-300). Optical rotations were measured on a ATAGO POLAX-D polarimeter, and $[\alpha]_D$-values are given in units of $10^{-1}$ deg cm$^2$ g$^{-1}$. Analytical TLC was performed on Merck Kieselgel $60F_{254}$. Microanalyses were performed with a Perkin-Elmer 2400S CHN elemental analyser.

### (1*S*)-*N*,*N*-Dimethyl-1-phenylethylamine 3a

To (*S*)-1-phenylethylamine **2** (12.8 cm$^3$, 100 mmol) were added formic acid (14.3 g, 350 mmol) and 35% aq. formaldehyde (21.5 g, 250 mmol). After being heated for 24 h at 90 °C, the solution was cooled and 6 M aq. HCl (35 cm$^3$) was added. The resulting solution was extracted with $Et_2O$ (30 cm$^3$ × 3). The aqueous layer was made basic with 50% aq. NaOH and was extracted with $Et_2O$ (30 cm$^3$ × 3). The combined extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was purified by Kugelrohr distillation to give title compound **3a** (12.6 g, 84%) as a yellow oil; $[\alpha]_D^{27}$ −47.8 (*c* 1.2, MeOH) {lit,[10] $[\alpha]_D^{20}$ −49.2 (*c* 1.0, MeOH)}.

**(1′*S*)-1-(1-Phenylethyl)piperidine 3b**

To a solution of (*S*)-1-phenylethylamine **2** (10.3 $cm^3$, 80.0 mmol) and powdered solid $Na_2CO_3$ (33.9 g, 320 mmol) in DMPU (50 $cm^3$) was added 1,5-dibromopentane (13.0 $cm^3$, 96.0 mmol). After being stirred for 2 h at 100 °C, the resulting solution was poured into water (400 $cm^3$) and was extracted with $Et_2O$ (80 $cm^3$ × 4). The combined extracts were washed with water (50 $cm^3$ × 3). The organic layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was purified by Kugelrohr distillation to give *title compound* **3b** (14.2 g, 94%) as a yellow oil; $R_f$ 0.37 (1:1 hexane–EtOAc) (Found: C, 82.4; H, 10.2; N, 7.5. $C_{13}H_{19}N$ requires C, 82.48; H, 10.12; N, 7.40%); $[\alpha]_D^{27}$ −18.0 (*c* 1.1, $CHCl_3$); $\nu_{max}$(neat)/$cm^{-1}$ 1117, 1451 and 2934; $\delta_H$ 1.34–1.44 (2 H, m), 1.37 (3 H, d, *J* 6.8), 1.49–1.60 (4 H, m), 2.23–2.46 (4 H, m), 3.39 (1 H, q, *J* 6.81) and 7.19–7.33 (5 H, m); $\delta_C$ 19.5, 24.7, 26.4, 51.7, 65.4, 127.0, 128.7, 128.4 and 144.4; *m/z* (EI) 189 ($M^+$, 23%), 174 (100) and 112 (47).

**(1*S*)-*N*-Isopropyl-*N*-methyl-1-phenylethylamine 3c**

To a solution of *N*-isopropyl-1-phenylethylamine[6] (15.2g, 93 mmol) were added formic acid (28.5 g, 558 mmol) and 35% aq. formaldehyde (20.0 g, 233 mmol). After being heated for 4 h at 110 °C, the solution was cooled and 6 M aq. HCl (20 $cm^3$) was added. The resulting solution was extracted with $Et_2O$ (40 $cm^3$ × 3). The aqueous layer was made basic with 50% aq. NaOH and was extracted with $Et_2O$ (40 $cm^3$ × 4). The combined extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was purified by Kugelrohr distillation to give **3c** (15.6 g, 95%, 88% overall yield from substrate **2**) as an orange oil: $R_f$ 0.47 (EtOAc) (Found: C, 81.1; H, 10.7; N, 7.8. $C_{12}H_{19}N$ requires C, 81.30; H, 10.80; N, 7.90%); $[\alpha]_D^{27}$ −37.7 (*c* 1.1, $CHCl_3$); $\nu_{max}$(neat)/$cm^{-1}$ 1078, 1364 and 1451; $\delta_H$ 0.93 (3 H, d, *J* 6.6), 0.97 (3 H, d, *J* 6.8), 1.32 (3 H, d, *J* 6.8), 2.13 (3 H, s), 2.95 (1 H, sep, *J* 6.6), 3.60 (1 H, q, *J* 6.6) and 7.16–7.38 (5 H, m); $\delta_C$ 16.5, 19.1, 21.4, 31.1, 49.1, 61.8, 126.9, 127.6, 128.6 and 146.8; *m/z* (EI) 177 ($M^+$, 73%), 162 (100) and 105 (99).

**1-[(1*S*)-1-(*N*,*N*-Dimethylamino)ethyl]-2-(3,3,3-trifluoroprop-1-enylsulfonyl)benzene 8a**

To a solution of compound **3a** (5.97 g, 40 mmol) and TMEDA (18.1 $cm^3$, 120 mmol) in dry hexane (40 $cm^3$) was added a 1.6 M solution of BuLi in hexane (74 $cm^3$; 120 mmol) under nitrogen at −78 °C during 20 min. After stirring of the mixture for 0.5 h at −78 °C and for an additional 3 days at room temperature, dimethyl disulfide (18.0 $cm^3$, 200 mmol) was added to the resulting solution at 0 °C in 15 min. The solution was stirred overnight at room temperature and was then poured into 6 M aq. HCl (150 $cm^3$). The organic layer was washed with 6 M aq. HCl (40 $cm^3$ × 3). The combined aqueous layer was made basic with 50% aq. NaOH and was extracted with $Et_2O$ (50 $cm^3$ × 4). The combined extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure to give compound **4a** [8.94 g; $R_f$ 0.41 (EtOAc)]. Without purification, to a solution of compound **4a** ×8.94 g) and TMEDA (8.50 $cm^3$, 55.4 mmol) in dry THF (25 $cm^3$) was added a 1.6 M solution of BuLi in hexane (35.0 $cm^3$, 55.4 mmol) under nitrogen at −78 °C during 0.5 h. After the mixture had been stirred for 1 h at −40 °C and for an additional 1.5 h at room temperature, ethyl trifluoroacetate (7.08 $cm^3$, 55.4 mmol) was added to the resulting solution at −60 °C during 10 min. After being stirred overnight at room temperature, the resulting solution was poured into saturated aq. NaCl (100 $cm^3$) and was extracted with EtOAc (40 $cm^3$ × 4). The combined extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure to give title compound **5a** [15.0 g; $R_f$ 0.34 (EtOAc); $\nu_{max}$ 1667 and 3447 $cm^{-1}$].

Without purification, to a solution of compound **5a** (15.0 g) in MeOH (25 $cm^3$) was added $NaBH_4$ (0.95 g, 25.2 mmol) at 0 °C. After being stirred overnight at room temperature, the resulting solution was poured into saturated aq. NaCl solution (75 $cm^3$) and was extracted with EtOAc (30 $cm^3$ × 3). The combined extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was chromatographed on a silica gel column (AcOEt) to give a 50:50 diastereomeric mixture of compound **6a** (4.17 g, 29% overall yield from **3a**) as an orange oil; $R_f$ 0.41 (EtOAc) (Found: C, 53.4; H, 6.3; N, 4.4. $C_{13}H_{18}F_3NOS$ requires C, 53.23; H, 6.18; N, 4.77%); $\nu_{max}$(neat)/$cm^{-1}$ 1127, 1163, 3061; $\delta_H$ 1.31 (1.5 H, d, *J* 7.0), 1.35 (1.5 H, d, *J* 7.0), 2.26 (3 H, s), 2.29 (3 H, s), 2.86 (0.5 H, dd, *J* 13.7 and 10.8), 2.97 (0.5 H, dd, *J* 14.2 and 10.8), 3.26 (0.5 H, dd, *J* 14.2 and 2.0), 3.33 (0.5 H, dd, *J* 13.7 and 2.0), 3.21–3.38 (1 H, m), 4.08 (1.0 H, dqd, *J* 10.8, 6.8 and 2.0), 4.67 (0.5 H, q, *J* 7.0), 4.69 (0.5 H, q, *J* 7.0) and 7.21–7.67 (4 H, m); $\delta_C$ 7.7, 9.1, 37.9, 39.3, 39.8, 40.1, 58.4, 59.7, 66.7 (q, *J* 30), 73.1 (q, *J* 30), 119.2 (q, *J* 281), 125.6 (q, *J* 281), 127.6, 127.8, 128.3, 128.4, 129.1, 129.2, 133.8, 135.7, 136.6, 135.7, 136.6, 136.9, 143.9 and 145.2; $\delta_F$ −78.4 (d, *J* 7), −79.3 (d, *J* 7); *m/z* (EI) 293 ($M^+$, 73%), 278 (10) and 135 (76).

To a solution of compound **6a** (3.32 g, 11.3 mmol) in MeOH (22 $cm^3$) was added OXONE® (15.3 g, 24.9 mmol) in water (27 $cm^3$) at 0 °C. After being stirred for 4 h at room temperature, saturated aq. $NaHSO_3$ solution was added until no change of colour in KI starch paper was observed. The solution was made neutral with 50% aq. NaOH and the solvent was removed under reduced pressure. The resulting solid was removed by filtration and washed with $CHCl_3$ (40 $cm^3$ × 5). The aqueous layer was extracted with $CHCl_3$ (15 $cm^3$ × 3). The combined washings and extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure to give *title compound* **7a** [3.69 g; $R_f$ 0.35 (EtOAc); $\nu_{max}$ 1273 and 1310 $cm^{-1}$].

Without purification, to a solution of compound **7a** (3.69 g) and triethylamine (4.80 $cm^3$, 3.40 mmol) in $CH_2Cl_2$ (17 $cm^3$) was added methanesulfonyl chloride (1.30 $cm^3$, 17.0 mmol) under nitrogen at 0 °C during 10 min. After being stirred for 0.5 h at 0 °C, the solution was poured into saturated aq. $NaHCO_3$ (50 $cm^3$) and was extracted with $CHCl_3$ (20 $cm^3$ × 3). The organic layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was chromatographed on a silica gel column (AcOEt) to give *title compound* **8a** (2.23 g, 51% yield from **6a**; 18% overall yield from **3a**) as an orange oil; $R_f$ 0.37 (1:1 hexane–EtOAc) (Found: C, 50.6; H, 5.5; N, 4.5. $C_{13}H_{16}F_3NO_2S$ requires C, 50.81; H, 5.25; N, 4.56%); $[\alpha]_D^{25}$ −67.6 (*c* 1.8, $CHCl_3$); $\nu_{max}$(neat)/$cm^{-1}$ 1154, 1298 and 1443; $\delta_H$ 8.15–7.44 (4 H, m), 7.38 (1 H, dq, *J* 15.4 and 1.8), 6.73 (1 H, dq, *J* 15.4 and 6.2), 4.43 (1 H, q, *J* 6.6), 2.15 (6 H, s) and 1.33 (3 H, d, *J* 6.6); $\delta_C$ 14.8, 41.5, 58.6, 122.0 (q, *J* 271), 126.7 (q, *J* 36), 128.2, 129.1, 131.1, 135.0, 136.7, 141.8 (q, *J* 6) and 146.8; $\delta_F$ −65.1 (d, *J* 6); *m/z* (EI) 307 ($M^+$, 13) and 292 (100).

**1-[(1*S*)-1-(1-Piperidyl)ethyl]-2-(3,3,3-trifluoro-1-propenylsulfonyl)benzene 8b**

This was obtained similarly from compound **3b** (7.57 g, 40 mmol) after chromatography on a silica gel column (3:1 hexane–AcOEt) as an *orange oil* (416 mg, 3% overall yield from **3b**): $R_f$ 0.43 (3:1 hexane–EtOAc) (Found: C, 55.3; H, 6.0; N, 3.9. $C_{16}H_{20}F_3NO_2S$ requires C, 55.32; H, 5.80; N, 4.03%); $[\alpha]_D^{27}$ −70.0 (*c* 2.0, $CHCl_3$); $\nu_{max}$(neat)/$cm^{-1}$ 1155, 1298 and 2938; $\delta_H$ 1.32 (3 H, d, *J* 6.6), 1.62–1.36 (6 H, m), 2.52–2.34 (4 H, m), 4.58 (1 H, q, *J* 6.6), 6.83 (1 H, dq, *J* 15.4 and 6.2), 7.89 (1 H, dq, *J* 15.4 and 1.8) and 8.10–7.41 (4 H, m); $\delta_C$ 15.4, 24.6, 26.1, 50.7, 58.4, 121.9 (q, *J* 271), 128.1, 128.2 (q, *J* 36), 129.7, 130.9, 134.9, 136.4 and 141.6 (q, *J* 6) and 146.8; $\delta_F$ −65.2 (d, *J* 5); *m/z* (EI) 347 ($M^+$, 19%), 346 (14) and 186 (100).

**1-[(1*S*)-1-(*N*-Isopropyl-*N*-methylaminoethyl]-2-(3,3,3-trifluoroprop-1-enylsulfonyl)benzene 8c**

This was obtained similarly from compound **3c** (8.86 g, 50 mmol) after chromatography on a silica gel column (1:1 hexane–AcOEt) as an orange oil (1.18 g, 7% overall yield from **3c**): $R_f$

0.48 (1:1 hexane–EtOAc) (Found: C, 53.8; H, 6.1; N, 4.0. $C_{15}H_{20}F_3NO_2S$ requires C, 53.72; H, 6.01; N, 4.18%); $[\alpha]_D^{24}$ −40.2 (*c* 1.7, $CHCl_3$); $\nu_{max}$(neat)/cm$^{-1}$ 1154, 1298 and 1368; $\delta_H$ 0.99 (3 H, d, *J* 6.6), 1.01 (3 H, d, *J* 6.6), 1.30 (3 H, d, *J* 6.5), 2.05 (3 H, s), 2.94 (1 H, septet, *J* 6.6), 4.53 (1 H, q, *J* 6.5), 6.85 (1 H, dq, *J* 15.4 and 6.2), 7.39 (1 H, dq, *J* 15.4 and 1.6) and 8.08–7.40 (4 H, m); $\delta_C$ 17.7, 18.3, 20.3, 31.4, 49.2, 56.4, 121.8 (q, *J* 271), 127.8, 128.8 (q, *J* 37), 129.9, 135.3, 135.8, 140.8 (q, *J* 6) and 148.9; $\delta_F$ −65.4 (d, *J* 5); *m/z* (EI) 336 ($M^+$, 2%), 320 (13) and 174 (100).

### General procedure for 1,3-dipolar cycloaddition of amines 8a–c with nitrones 9a–c

A solution of compound **8a–c** (1.00 mmol) and a nitrone **9a–c** (1.00 mmol) in toluene (5 cm$^3$) was heated at 90 °C under argon in a sealed tube for 12 h. After the solvent was removed under reduced pressure, the residue was chromatographed on a silica gel column (2:1 hexane–AcOEt). No regioisomers of the cycloadducts were detected by $^1$H NMR spectroscopy of the crude products. For the yields and de-values, see Table 1.

**(3*S*,4*S*,5*R*)-4-{2-[(1*S*)-1-(Dimethylamino)ethyl]phenylsulfonyl}-2-methyl-3-phenyl-5-(trifluoromethyl)isoxazolidine 10a and (3*R*,4*R*,5*S*)-4-{2-[(1*S*)-1-(dimethylamino)ethyl]-phenylsulfonyl}-2-methyl-3-phenyl-5-(trifluoromethyl)isoxazolidine 11a.** A mixture of heterocycles **10a** and **11a** was obtained as above from compound **8a** (307 mg, 1.00 mmol) and *N*-methyl-*C*-phenylnitrone **9a** (135 mg, 1.00 mmol). Isomers **10a** and **11a** were separated by chromatography on a silica gel column. The first component gave compound **10a** as a solid (301 mg, 68%); mp 101–103 °C (Found: C, 57.0; H, 5.8; N, 6.3. $C_{21}H_{25}F_3N_2O_3S$ requires C, 57.00; H, 5.69; N, 6.33%); $[\alpha]_D^{27}$ 76.8 (*c* 2.1, $CHCl_3$); $\nu_{max}$(KBr)/cm$^{-1}$ 1155, 1310 and 1454; $\delta_H$ 1.09 (3 H, d, *J* 6.7), 1.72 (6 H, s), 2.70 (3 H, s), 4.26 (1 H, d, *J* 8.2), 4.47 (1 H, q, *J* 6.7), 4.56 (1 H, qd, *J* 7.4 and 3.6), 5.43 (1 H, dd, *J* 8.2 and 3.6) and 7.66–7.30 (9 H, m); $\delta_C$ 11.0, 40.2, 43.1, 56.9, 72.8, 75.0, 76.4 (q, *J* 34), 123.7 (q, *J* 284), 127.9, 129.1, 129.2 (2 C), 129.5, 131.9, 134.7, 136.1, 136.8 and 145.5; $\delta_F$ −75.9 (d, *J* 7); *m/z* (CI) 443 ($M + H^+$). The second component gave *compound* **11a** as a yellow solid (53 mg, 12%); mp 102–105 °C (Found: C, 57.4; H, 5.7; N, 6.2%); $[\alpha]_D^{27}$ −57.8 (*c* 1.6, $CHCl_3$); $\nu_{max}$(KBr)/cm$^{-1}$ 1152, 1281 and 1456; $\delta_H$ 1.17 (3 H, d, *J* 6.7), 1.81 (6 H, s), 2.61 (3 H, s), 3.89 (1 H, d, *J* 7.7), 4.46 (1 H, q, *J* 6.7), 5.09 (1 H, qd, *J* 7.4 and 3.8), 5.18 (1 H, dd, *J* 7.7 and 3.8) and 8.19–6.97 (9 H, m); $\delta_C$ 13.2, 41.2, 42.9, 57.8, 74.7 (q, *J* 34), 75.1, 75.3, 124.1 (q, *J* 284), 127.7, 128.7, 128.8 (2 C), 129.1, 129.5, 132.4, 134.7, 135.0, 136.0 and 145.7; $\delta_F$ −75.1 (d, *J* 7); *m/z* (CI) 443 ($M + H^+$).

**(3*S*,4*S*,5*R*)-4-{2-[(1*S*)-1-(Dimethylamino)ethyl]phenylsulfonyl}-2,3-diphenyl-5-(trifluoromethyl)isoxazolidine 10b and (3*R*,4*R*,5*S*)-4-{2[(1*S*)-1-(dimethylamino)ethyl]phenylsulfonyl}-2,3-diphenyl-5-(trifluoromethyl)isoxazolidine 11b.** A mixture of isomers **10b** and **11b** was obtained as above from compound **8a** (307 mg, 1.00 mmol) and *C*,*N*-diphenylnitrone **9b** (197 mg, 1.00 mmol). Isomers **10b** and **11b** were separated by chromatography on a silica gel column. The first component gave *compound* **10b** as an orange oil (313 mg, 62%); $R_f$ 0.50 (2:1 hexane–EtOAc) (Found: C, 61.79; H, 5.43; N, 5.59. $C_{26}H_{27}F_3N_2O_3S$ requires C, 61.89; H, 5.39; N, 5.55%); $[\alpha]_D^{24}$ 113.9 (*c* 1.8, $CHCl_3$); $\nu_{max}$(neat)/cm$^{-1}$ 1134, 1240 and 1580; $\delta_H$ 1.11 (3 H, d, *J* 6.6), 1.70 (6 H, s), 4.56 (1 H, q, *J* 6.6), 4.72 (1 H, qd, *J* 7.3 and 3.5), 5.09 (1 H, d, *J* 7.1), 5.65 (1 H, dd, *J* 7.1 and 3.5) and 8.15–7.02 (14 H, m); $\delta_C$ 10.6, 40.0, 56.9, 69.8, 75.5, 76.3 (q, *J* 34), 119.4, 123.6 (q, *J* 284), 125.3, 128.0, 128.7, 129.0, 129.1, 129.4, 129.6, 132.1, 134.8, 136.0, 138.2, 145.6 and 148.1; $\delta_F$ −75.9 (d, *J* 7); *m/z* (CI) 505 ($M + H^+$). The second component gave *compound* **11b** as a yellow solid (40 mg, 8%); mp 95–98 °C (Found: C, 62.1; H, 5.4; N, 5.3%); $[\alpha]_D^{23}$ −116.67 (*c* 1.2, $CHCl_3$); $\nu_{max}$(KBr)/cm$^{-1}$ 1150, 1281 and 1580; $\delta_H$ 1.16 (3 H, d, *J* 6.7), 1.74 (6 H, s), 4.57 (1 H, q, *J* 6.7), 4.59 (1 H, d, *J* 6.9), 5.33 ( 1 H, qd, *J* 7.2 and 3.6), 5.47 (1 H, dd, *J* 6.9 and 3.6) and 8.23–6.92 (14 H, m); $\delta_C$ 11.9, 40.7, 57.4, 72.9, 74.5 (q, *J* 34), 75.7, 119.5, 124.0 (q, *J* 284), 125.5, 127.8, 128.4, 128.9, 129.0, 129.0, 129.6, 132.9, 134.8, 136.0, 136.7, 146.0 and 148.1; $\delta_F$ −74.7 (d, *J* 7); *m/z* (CI) 505 ($M + H^+$).

**(3*S*,4*S*,5*R*)-2-Butyl-4-{2-[(1*S*)-1-(dimethylamino)ethyl]-phenylsulfonyl}-3-phenyl-5-(trifluoromethyl)isoxazolidine 10c and (3*R*,4*R*,5*S*)-2-butyl-4-{2-[(1*S*)-1-(dimethylamino)ethyl]-phenylsulfonyl}-2-methyl-3-phenyl-5-(trifluoromethyl)isoxazolidine 11c.** A mixture of isomers **10c** and **11c** was obtained as above from compound **8a** (307 mg, 1.00 mmol) and *N*-butyl-*C*-phenylnitrone **9c** (177 mg, 1.00 mmol). Isomers **10c** and **11c** were separated by chromatography on a silica gel column. The first component gave *compound* **10c** as a yellow oil (271 mg, 56%); $R_f$ 0.38 (2:1 hexane–EtOAc) (Found: C, 59.8; H, 6.4; N, 5.5. $C_{24}H_{31}F_3N_2O_3S$ requires C, 59.49; H, 6.45; N, 5.78%); $[\alpha]_D^{21}$ 114.0 (*c* 1.7, $CHCl_3$); $\nu_{max}$ (neat)/cm$^{-1}$ 1154, 1279 and 2959; $\delta_H$ 0.82 (3 H, t, *J* 7.2), 1.08 (3 H, d, *J* 6.7), 1.66–1.27 (4 H, m), 1.71 (6 H, s), 2.74 (1 H, dt, *J* 13.0 and 7.6), 2.88–2.75 (1 H, m), 4.34 (1 H, d, *J* 7.9), 4.45 (1 H, q, *J* 6.7), 4.55 (1 H, qd, *J* 7.4 and 3.4), 5.36 (1 H, dd, *J* 7.9 and 3.4) and 8.12–7.28 (9 H, m); $\delta_C$ 11.3, 13.8, 20.1, 29.7, 40.2, 55.9, 57.0, 71.0, 74.8, 76.3 (q, *J* 35), 123.8 (q, *J* 285), 127.9, 129.0, 129.1, 129.1, 129.5, 131.9, 134.6, 136.2, 137.3 and 145.5; $\delta_F$ −75.8 (d, *J* 7); *m/z* (CI) 485 ($M + H^+$). The second component gave isomer **11c** as a yellow solid (73 mg, 15%); mp 70–73 °C (Found: C, 59.6; H, 6.3; N, 5.8%); $[\alpha]_D^{23}$ −78.33 (*c* 2.0, $CHCl_3$); $\nu_{max}$(KBr)/cm$^{-1}$ 1152, 1281 and 2957; $\delta_H$ 0.78 (3 H, t, *J* 7.2), 1.15 (3 H, d, *J* 6.6), 1.69–1.21 (4 H, m), 1.77 (6 H, s), 2.53 (1 H, dt, *J* 12.8 and 7.7), 2.80–2.68 (1 H, m), 3.95 (1 H, d, *J* 7.7), 4.44 (1 H, q, *J* 6.6), 5.08 (1 H, qd, *J* 7.4 and 3.7), 5.16 (1 H, dd, *J* 7.7 and 3.7) and 8.20–6.94 (9 H, m); $\delta_C$ 13.2, 13.7, 20.1, 29.6, 41.1, 55.6, 57.8, 73.5, 74.5 (q, *J* 34), 74.9, 124.2 (q, *J* 285), 127.6, 128.7 (2 C), 128.8, 129.1, 129.4, 132.5, 135.7, 136.1 and 146.0; $\delta_F$ −75.0 (d, *J* 7); *m/z* (CI) 485 ($M + H^+$).

**68:32 Diastereomeric mixture of (3*S*,4*S*,5*R*)-4-{2-[(1*S*)-1-piperidinoethyl]phenylsulfonyl}-2-methyl-3-phenyl-5-(trifluoromethyl)isoxazolidine 12 and (3*R*,4*R*,5*S*)-4-{2-[(1*S*)-1-piperidinoethyl]phenylsulfonyl}-2-methyl-3-phenyl-5-(trifluoromethyl)isoxazolidine 13.** This was obtained as above from compounds **8b** (347 mg, 1.00 mmol) and **9a** (135 mg, 1.00 mmol) as a *yellow oil* (357 mg, 74%); $R_f$ 0.39 (3:1 hexane–EtOAc) (Found: C, 59.9; H, 6.3; N, 5.5. $C_{24}H_{29}F_3N_2O_3S$ requires C, 59.74; H, 6.06; N, 5.81%); $\nu_{max}$(neat)/cm$^{-1}$ 1154, 1279 and 2936; $\delta_H$ 1.03 (2.0 H, d, *J* 6.6), 1.16 (1.0 H, d, *J* 6.4), 1.22–1.50 (6.0 H, m), 1.90–2.33 (4.0 H, m), 2.62 (1.0 H, s), 2.71 (2.0 H, s), 3.89 (0.32 H, q, *J* 6.4), 3.97 (0.32 H, d, *J* 7.9), 4.08 (0.68 H, q, *J* 6.6), 4.25 (0.68 H, d, *J* 7.9), 4.46 (0.32 H, dd, *J* 7.9 and 3.9), 4.68 (0.68 H, qd, *J* 7.6 and 3.8), 4.73 (0.68 H, dd, *J* 7.9 and 3.8), 5.09 (0.32 H, qd, *J* 7.2 and 3.9) and 7.02–8.07 (9.0 H, m); $\delta_C$ 16.9, 20.7, 24.5 (combined peak), 26.0 (combined peak), 42.9, 43.1, 50.8, 51.9, 58.6, 60.2, 73.0, 75.1, 74.5 (q, *J* 34), 75.2 (combined peak), 76.8 (q, *J* 34), 123.7 (q, *J* 284), 124.1 (q, *J* 285), 127.3, 127.6, 128.5, 128.8, 129.2 (combined peak), 129.2, 129.8, 130.2, 131.0, 131.5, 134.7, 134.9, 135.1, 135.1, 135.6, 135.9, 146.7 and 148.3; $\delta_F$ −75.7 (d, *J* 7, major), −75.3 (d, *J* 7, minor); *m/z* (CI) 483 ($M + H^+$).

**70:30 Diastereomeric mixture of (3*S*,4*S*,5*R*)-4-(2-{(1*S*)-1-[isopropyl(methyl)amino]ethyl}phenylsulfonyl)-2-methyl-3-phenyl-5-(trifluoromethyl)isoxazolidine 14 and (3*R*,4*R*,5*S*)-4-(2-{(1*S*)-1-[isopropyl(methyl)amino]ethyl}phenylsulfonyl)-2-methyl-3-phenyl-5-(trifluoromethyl)isoxazolidine 15.** This was obtained as above from compound **8c** (336 mg, 1.00 mmol) and **9a** (135 mg, 1.00 mmol) as a *yellow oil* (273 mg, 58%); $R_f$ 0.60 (2:1 hexane–EtOAc) (Found: C, 59.0; H, 6.4; N, 5.8. $C_{23}H_{29}F_3N_2O_3S$ requires C, 58.71; H, 6.21; N, 5.95%); $\nu_{max}$-(neat)/cm$^{-1}$ 1152, 1281 and 2971; $\delta_H$ 0.63 (2.10 H, d, *J* 6.5), 0.76 (0.90 H, d, *J* 6.5), 0.86 (2.10 H, d, *J* 6.5), 0.76 (0.90 H, d, *J* 6.5), 0.97 (2.10 H, d, *J* 6.6), 1.14 (0.90 H, d, *J* 6.5), 1.66 (0.90 H, s), 2.46 (0.30 H, septet, *J* 6.5), 1.85 (2.10 H, s), 2.63 (0.90 H, s), 2.68 (2.10 H, s), 2.83 (0.70 H, septet, *J* 6.5), 3.97 (0.30 H, d, *J*

7.9), 4.13 (0.70 H, q, *J* 6.6), 4.18 (0.70 H, d, *J* 8.1), 4.39 (0.30 H, dd, *J* 7.9 and 3.8), 4.43 (0.70 H, dd, *J* 8.1 and 3.6), 4.64 (0.30 H, q, *J* 6.6), 4.74 (0.70 H, qd, *J* 7.2 and 3.6), 5.04 (0.30 H, qd, *J* 7.4 and 3.8) and 7.05–8.07 (9.0 H, m); $\delta_C$ 16.3, 17.0, 17.9, 18.8, 21.1, 21.9, 31.1, 31.5, 42.9, 43.0, 48.6, 49.0, 56.4, 56.7, 73.5, 74.8 (q, *J* 31), 75.0, 75.3 (combined peak), 75.9 (q, *J* 34), 123.7 (q, *J* 285), 124.0 (q, *J* 282), 127.3, 127.5, 128.6, 128.8, 128.9, 129.3 (combined peak), 129.3, 129.9, 130.1, 130.9, 131.4, 134.5, 134.9, 135.0, 135.3, 135.3, 135.5, 149.3 and 149.7; $\delta_F$ −75.7 (d, *J* 7, major), −75.4 (d, *J* 7, minor); *m/z* (CI) 471 ($M + H^+$).

### X-Ray structure determination of compound 10a

A crystal of compound **10a** was grown from diethyl ether solution.

**Crystal data.** $C_{21}H_{25}F_3N_2O_3S$, $M = 442.50$. Monoclinic, $a = 9.028(2)$, $b = 9.801(1)$, $c = 12.574(2)$ Å, $\beta = 97.55(1)°$, $V = 1102.9(3)$ Å$^3$ [from refinement against centring angles of 25 reflections with $18.7 \leq \theta \leq 20.5°$, $\lambda = 0.710\,73$ Å, $T = 296$ K], space group $P2_1$ (No. 4), $Z = 2$, $D_x = 1.332$ g cm$^{-3}$, tablet 0.5 × 0.5 × 0.5 mm, $\mu$(Mo-Kα) = 0.187 mm$^{-1}$.

**Data collection and processing.** Rigaku AFC5R four-circle diffractometer, $\omega/2\theta$ scans, graphite-monochromated Mo-Kα X-radiation; 2857 reflections measured ($2\theta_{max} = 55°$, $+h$, $+k$, $\pm l$), 2694 unique [merging $R = 0.014$], giving 1965 with $F \geq 6\sigma(F)$ which were retained in all calculations. No crystal decay was observed and no corrections were applied for absorption.

**Structure solution and refinement.** Automatic direct methods (all non-H-atoms). Full-matrix least-squares refinement (on *F*) with all non-H-atoms anisotropic; hydrogen atoms were included at geometrically calculated positions but were not refined. The weighting scheme $w^{-1} = 4F_o/\sigma^2(F_o^2)$ gave satisfactory agreement analyses. Final *R*, $wR = 0.036$, 0.042 respectively, $S = 1.56$ for 270 refined parameters and the final $\Delta F$ synthesis showed no peaks outside the range −0.22 to 0.16 e Å$^{-3}$. All calculations were performed using the TEXSAN™ crystallographic software package.¶,[11]

¶ Atomic coordinates, thermal parameters and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Instructions for Authors, *Journal*, 1997, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 207/97.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