Regio- and stereo-selective synthesis of trifluoromethylated isoxazolidines by 1,3-dipolar cycloaddition of 1,1,1-trifluoro-3-phenylsulfonylpropene with nitrones, and their conversion into trifluoromethylated *syn*-3-amino alcohols

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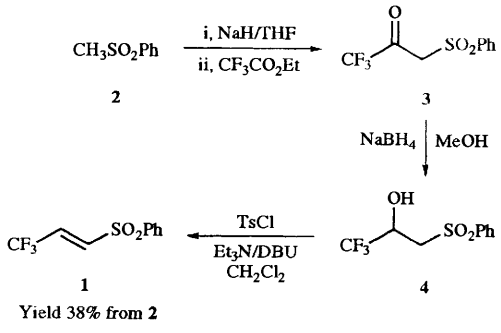
1,1,1-Trifluoro-3-phenylsulfonylpropene **1**, a useful synthetic precursor for trifluoromethylated compounds, has been prepared from methyl phenyl sulfone **2** and ethyl trifluoroacetate. The 1,3-dipolar cycloaddition of **1** with various nitrones **5a–f** gave 5-trifluoromethylisoxazolidines **6a–f** with a high degree of regio- and stereo-selectivity. The adducts **6a–f** were converted into trifluoromethylated *syn*-3-amino alcohols **8a–d** by desulfonylation with Na–Hg, followed by reductive cleavage of the N–O bond by catalytic hydrogenation. Conversion of **8a** and **8d** into the cyclic carbamates **10a** and **10d** confirmed the assigned stereochemistry of **8** and, hence, of the cycloadduct **6a–f**.

Trifluoromethylated five-membered ring heterocycles are of current interest because of their potential biological activity.[1] However, general methods for the regio- and stereo-selective synthesis of non-aromatic saturated heterocyclic compounds have yet to be established. Isoxazolidines, an important class of heterocycles, have potential as intermediates for nitrogen- and oxygen-containing compounds, such as 3-amino alcohols,[2] compounds which are found in many glycosidic amino sugars.[3] 1,3-Dipolar cycloaddition of nitrones with olefins, an established preparative method for isoxazolidines,[4] is capable of controlling a large number of stereochemical centres in one synthetic step because it usually proceeds by a concerted process.[2] Such reactions which occur with both electron-deficient and electron-rich olefins under mild conditions give the corresponding isoxazolidines both regio- and stereo-selectively.[4] However, there are few reported syntheses of trifluoromethylated isoxazolidines *via* 1,3-dipolar cycloaddition employing a trifluoromethylated electron-deficient olefin as a dipolarophile,[5a,b] even though the CF_3 group may activate the olefin by a strong inductive effect.

1,1,1-Trifluoro-3-phenylsulfonylpropene **1** was earlier prepared from gaseous trifluoropropene by Taguchi *et al.*[6] and used as an electron-deficient dienophile with dienes to give [4 + 2] cycloadducts regio- and stereo-selectively. We report here both an alternative and convenient route to the olefin **1** from methyl phenyl sulfone **2** and ethyl trifluoroacetate, and the regio- and stereo-selective synthesis of trifluoromethylated isoxazolidines by 1,3-dipolar cycloaddition of **1** with some selected nitrones. We also describe the transformation of the cycloadducts to trifluoromethylated *syn*-3-amino alcohols.

Results and discussion

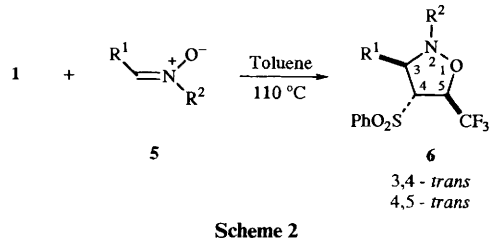
The olefin **1** was prepared as outlined in Scheme 1. Initially, the reaction of methyl phenyl sulfone **2** and ethyl trifluoroacetate in the presence of NaH gave trifluoromethylated sulfone **3**, reduction of which with $NaBH_4$ afforded the alcohol **4**. Dehydration of **4** was carried out by successive tosylation with toluene-*p*-sulfonyl chloride and elimination with triethylamine in CH_2Cl_2 at refluxing temperature. Since the elimination of the sulfonate was incomplete, DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) was added to complete the reaction. Work-up and



Scheme 1

recrystallization gave the olefin **1** in 38% overall yield which is similar to that of Taguchi's route.[6]

The 1,3-dipolar cycloadditions of a variety of nitrones **5a–f** with the olefin **1** in toluene were carried out at 110 °C for 12 h in a sealed tube to give the corresponding isoxazolidines **6a–f** (Scheme 2, Table 1). The aromatic nitrones **5a–c** prepared from



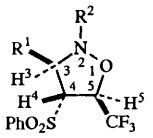
Scheme 2

arenecarbaldehydes can be isolated by recrystallization and **5d** was used after isolation by chromatography on a silica gel column. The unstable aliphatic nitrones **5e** and **5f**[7] were generated *in situ* from *N*-methylhydroxylamine hydrochloride, triethylamine and paraformaldehyde or acetaldehyde, respectively at 110 °C in a sealed tube, and allowed to react with **1** for 12 h. The isoxazolidines **6a–d** with aromatic substituents were obtained in almost quantitative yields. In contrast, **6e** and **6f** were obtained in moderate yields, together with some

Table 1 1,3-Dipolar cycloaddition of nitrones to olefin **1**

Nitrones	R^1	R^2	Products	Yield(%)
5a	Ph	Me	**6a**	95
5b	*p*-$MeOC_6H_4$	Me	**6b**	99
5c	Ph	Bu	**6c**	95
5d	Ph	Ph	**6d**	99
5e	H	Me	**6e**	65
5f	Me	Me	**6f**	39

Table 2 The vicinal coupling constants ($J_{3,4}$, $J_{4,5}$) in **6a–f**

	6	$J_{3,4}$ (Hz)	$J_{4,5}$ (Hz)
	**6a**	8.4	4.0
	6b	8.4	4.0
	6c	8.2	3.8
	6d	7.2	3.8
	6e	—[a]	4.9
6	**6f**	8.2	4.0

[a] The vicinal coupling constant ($J_{3,4}$) of **6e** (R^1 = H, R^2 = CH_3) could not be determined by the ^1H NMR spectrum analysis.

unidentified low-yield products. The unstable nature of the aliphatic nitrones **5e** and **5f** seems to retard the cycloaddition toward **1** compared with **5a–d**. The ^1H NMR spectra of the adducts **6a–f** revealed that they were almost single products, indicating that the cycloaddition process proceeded with high regio- (>98%) and stereo-selectivity. The existence of doublet quartet signals confirmed the 5-trifluoromethylisoxazolidine structure (for 5-H δ_H 3.1–5.0; $J_{4,5}$ 3.8–4.0 and $J_{4\text{-H,F}}$ 6.7–8.2 Hz). The stereochemistry of the adducts **6a–f** was assigned as 3,4-*trans* and 4,5-*trans*, since the vicinal coupling constants ($J_{3,4}$ and $J_{4,5}$ in Table 2) were similar to the reported ones ($J_{3,4}$ 6.5 and $J_{4,5}$ 3.0 Hz) of 5-methyl-2,3-diphenyl-4-phenylsulfonyl-isoxazolidine.[8] The rigorous elucidation of the stereochemistry was performed by the chemical conversion of the compounds into six-membered ring carbamates, *vide infra*.

As mentioned above, isoxazolidines can be considered as precursors for functionalized acyclic compounds and accordingly, compounds **6a–d** were transformed into the corresponding trifluoromethylated *syn*-3-amino alcohols **8a–d** as shown in Scheme 3. Reductive desulfonylation of the isoxazolidines **6a–d** was carried out with 5% Na–Hg[9] in THF–CH_3OH at room temperature,† followed by catalytic hydrogenation with 10% Pd–C[10] to give, via N–O bond cleavage, the 3-amino alcohols **8a–d** in 17–26% overall yields (Table 3) with no epimerization at positions C-3 and C-5. This was established by analysis of the ^1H NMR spectra of the reaction mixtures of **7a–d** which showed the presence of a single stereoisomer in each case. The aliphatic 3-amino alcohols **8e** and **8f** could not be isolated, probably because they were lost during work-up as a result of their volatility and hydrophilicity.

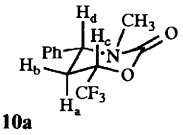
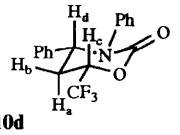
As described above, the stereochemistry of **6a–d** was determined from the vicinal coupling constants ($J_{3,4}$ and $J_{4,5}$) of the ^1H NMR spectra. In general, however, there is some equivocality in the stereochemical determination of isoxazolidine by the ^1H NMR coupling constants because of the

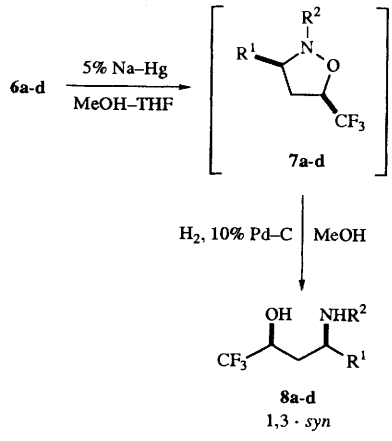
† After typical work-up, the resulting compound was homogeneous by TLC on silica gel and was used directly for N–O bond cleavage by catalytic hydrogenation. In the case of desulfonylation of **6a**, however, the intermediate **7a** was isolated by silica gel column chromatography with hexane–CH_2Cl_2 (2:1) as the eluent to confirm the shown structure (see Experimental section).

Table 3 Transformation of **6a–d** to **8a–d**

6	R^1	R^2	Products	Yield (%) of **8** from **6**
6a	Ph	Me	**8a**	25
6b	*p*-$MeOC_6H_4$	Me	**8b**	21
6c	Ph	Bu	**8c**	17
6d	Ph	Ph	**8d**	26

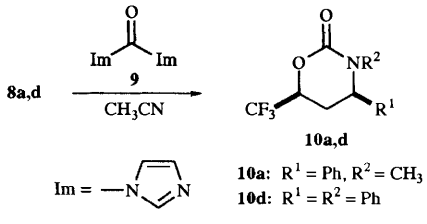
Table 4 ^1H NMR coupling constants of **10a, d** (in Hz)

 **10a**	 **10d**
J_{ab} = 14.2, J_{bd} = 5.7 J_{ac} = 12.1, J_{bc} = 2.2 J_{ad} = 11.5	J_{ab} = 14.0, J_{bc} = 3.1 J_{ac} = J_{ad} = 11.2 J_{bd} = 5.7



Scheme 3

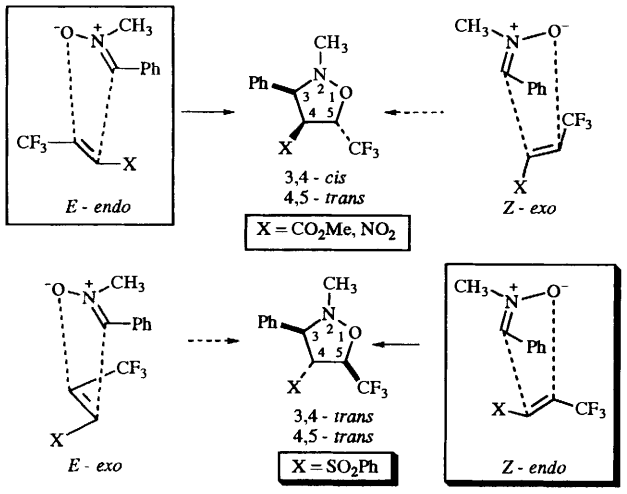
flexibility of the five-membered isoxazolidine ring structure.[11] For example, the vicinal coupling constants ($J_{3,4}$ and $J_{4,5}$) of **6d** are slightly different from those of **6a–c**, **6e** and **6f** as shown in Table 2. In order to confirm the assigned stereochemistry of **6a–f**, we converted the 1,3-amino alcohols **8a** and **8d** into the cyclic carbamates **10a** and **10b** by reaction with diimidazol-1-yl ketone **9** in 93 and 29% yield, respectively.[12]



As shown in Table 4, large coupling constants, J_{ac} 12.1 Hz, J_{ad} 11.5 Hz for **10a**, J_{ac} = J_{ad} 11.2 Hz for **10d** revealed the axial–axial alignment of H_a and H_c. This means that the relative stereochemistry of the trifluoromethyl group and the phenyl group is *syn*. The *E* configuration of the olefin **1** would have been retained since the 1,3-dipolar cycloaddition of nitrones is known to proceed in a concerted manner[13] and the cycloaddition of nitrones **5a–f** to **1** proceeded with high

stereoselectivity. In the light of these results, the isoxazolidines **6a–f** were confirmed to be all *trans* isomers.

Although aldonitrones are known generally to exist in the most stable *Z* configuration,[4] some *C*-phenylnitrones have been converted into the *E* isomer in competition with cycloaddition.[14] For example, *N*-methyl-*C*-phenylnitrone **5a** exists as a mixture of *Z* and *E* isomers at 147 °C.[15] The $\Delta G^{\ddagger}$ values for the interconversion of configurations ($Z \rightleftharpoons E$) at 147 °C were reported as 33.1 kcal mol^{-1} ($E \longrightarrow Z$) and 34.6 kcal mol^{-1} ($Z \longrightarrow E$), respectively.[15] The energies required for such interconversion are slightly larger than the $\Delta G^{\ddagger}$ value of the cycloaddition of *N*-methyl-*C*-phenylnitrone **5a** with ethyl crotonate (25.4 kcal mol^{-1} at 85 °C).[16] On the other hand, 1,3-dipolar cycloadditions occur by an *endo* or *exo* transition state as for Diels–Alder reactions. Four kinds of transition state can be considered for the 1,3-dipolar cycloaddition of **5a** with olefins as shown in Scheme 4. When an electron-withdrawing



Scheme 4

group is present in the dipolarophile, an *endo* transition state would be favourable because of the secondary orbital interaction between a p-orbital of the nitrogen atom and a π-orbital such as found in the C=O of the electron-withdrawing group.[17] Bravo reported that the 1,3-dipolar cycloaddition of *N*-methyl-*C*-phenylnitrone **5a** with 4,4,4-trifluorocrotonate furnished the corresponding 3,4-*cis* and 4,5-*trans*-isoxazolidine.[5a] Tanaka also reported that the 1,3-dipolar cycloaddition of **5a** with 3,3,3-trifluoro-1-nitroprop-1-ene afforded the corresponding 3,4-*cis*-4,5-*trans*-isoxazolidine.[5b] Both authors invoked the initial conversion of the nitrone **5a** from the *Z* into the *E* form before the cycloaddition step and attributed the stereochemistry for the 3,4-*cis*-4,5-*trans*-isoxazolidines to the attractive π–π orbital overlap between the electron-withdrawing group (*i.e.*, X = CO_2Me and NO_2) and the phenyl group on the carbon atom of nitrone **5a** and the resulting *E-endo* transition state. Based on the observed stereochemistry of the adducts **6a–f**, the stereochemistry of the transition state of the present 1,3-dipolar cycloaddition should be *E-exo* or *Z-endo*. Although benzoic acid has been reported to catalyse the $Z \longrightarrow E$ isomerization of nitrones,[15] it had no effect on the 1,3-dipolar cycloaddition of **1** with **5a**.‡ Thus, $Z \longrightarrow E$ isomerization is not necessary for the reaction of **1** with nitrones even though isomerization of the nitrone must be competitive with cycloaddition. In the reaction of **1** with nitrones, a repulsive van der Waals steric interaction between the sulfonyl group and the substituent on the nitrone carbon plays an important role in determining the stereochemistry of the isoxazolidine.[18] Consequently, the cycloaddition of **1** with nitrones proceeds *via* a *Z-endo* transition state, which minimizes the steric interaction, to give all *trans* isoxazolidines.

Croce *et al.* reported the 1,3-dipolar cycloaddition of *C,N*-diphenylnitrone to 1-phenylsulfonylprop-1-ene.[8] In that case, the regio- and stereo-selectivities were identical with those described here. This result suggests that the trifluoromethyl group does not determine the regio- and stereo-selectivity of the cycloaddition of the nitrone. In order to examine the effect of the CF_3 group on the cycloaddition, a mixture of *N*-methyl-*C*-phenylnitrone **5a** (0.6 mmol) with **1** (0.3 mmol) and 1-phenylsulfonylprop-1-ene (0.3 mmol) was heated in benzene (3 cm^3) at 80 °C for 45 min in a sealed tube. Analysis of the ^{1}H NMR spectrum indicated that the cycloaddition of **1** occurred with 70% conversion, while 1-phenylsulfonylprop-1-ene was unchanged. This result demonstrates that the presence of a CF_3 group in the dipolarophile **1** for the cycloaddition of nitrones makes the olefin more reactive mainly by lowering the energy level of the LUMO.

‡ The reactions of **1** and an equimolar amount of **5a** were conducted at 80 °C for 30 min in sealed tubes in the presence of 0, 1 and 10% benzoic acid, respectively. The conversions of **1** to **6a** were found to be 79, 75 and 79%, respectively by ^{1}H NMR spectra.

Experimental

Melting points were taken on a Yanagimoto micro-melting point apparatus and are uncorrected. IR spectra were measured on a JASCO FT/IR 5300 spectrometer. ^{1}H and ^{13}C NMR spectra were measured on a Varian GEMINI 200 spectrometer at 200 and at 50 MHz, respectively, for samples in $CDCl_3$ solution with Me_4Si as an internal standard. ^{19}F NMR spectra were measured on 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. Microanalyses were performed on a Perkin-Elmer 2400S elemental analyser. Chromatography was performed on silica gel columns (Fuji-Davison BW-300). Thin layer chromatography was performed on Merck Kieselgel 60 F_{254}. Mass spectra (EI) were obtained using a JEOL JMS-AX 505 HA mass spectrometer at 70 eV.

1,1,1-Trifluoro-3-phenylsulfonylpropene 1

To a stirred THF (20 cm^3) solution of methyl phenyl sulfone **2** (1.60 g, 10 mmol) under N_2 at 0 °C was added NaH (60% oil dispersion; 600 mg, 15 mmol) in portions after which the resulting suspension was stirred at 0 °C for 10 min, and then treated dropwise with ethyl trifluoroacetate (3.60 cm^3, 30 mmol) at 0 °C. After 2 h under reflux, the resulting solution was poured into saturated aq. NaCl (250 cm^3) and extracted with Et_2O (100 cm^3 × 4). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give **3** (1.80 g, ν_{max} 3414, 1732 cm^{-1}). Without purification, $NaBH_4$ (2.50 g, 10 mmol) was added to a solution of **3** (1.80 g) in MeOH (20 cm^3). After being stirred overnight at room temperature, the solution was poured into saturated aq. NaCl (200 cm^3) and extracted with Et_2O (100 cm^3 × 4). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was recrystallized from Et_2O–hexane to give **4** (1.40 g, 57% from sulfone **2**), mp 73–74 °C (Found: C, 42.6; H, 3.3. $C_9H_9F_3O_3S$ requires C, 42.52; H, 3.57%); ν_{max}(KBr)/cm^{-1} 3447, 1265 and 1127; δ_H 7.59–8.01 (5 H, m), 4.61 (1 H, dqd, *J* 10.1, 6.4 and 3.8), 3.67–3.82 (1 H, m) and 3.44 (2 H, m); δ_C 139.1, 135.1, 130.1, 128.4, 123.9 (q, *J* 280), 66.2 (q, *J* 33) and 56.3; δ_F −79.9 (s); *m/z* (EI) 254 (M^+, 10%), 141 (65) and 77 (100).

To a stirred solution of **4** (1.40 g, 5.7 mmol) and Et_3N (1.60 cm^3, 11 mmol) in CH_2Cl_2 (20 cm^3) was added solid toluene-*p*-sulfonyl chloride (1.08 g, 5.7 mmol) in portions. After 2 h under

reflux the mixture was treated with DBU (868 mg, 5.7 mmol) and heated under reflux for a further 1 h. The solution was then poured into saturated aq. $NaHCO_3$ (200 cm^3) and extracted with CH_2Cl_2 (100 cm^3 × 4). The combined extracts were washed with aq. HCl (1 mol dm^{-3}; 100 cm^3 × 2), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was recrystallized from Et_2O–hexane to give **1** as a colourless solid (890 mg, 67%; 38% from sulfone **2**), mp 68–69 °C. The sulfone **1** was identified by comparison of its ^1H NMR spectrum with that reported in the literature.[6]

N-Methyl-*C*-phenylnitrone **5a** (mp 80–81 °C; lit.,[19] 81–82 °C), *C*-(4-methoxyphenyl)-*N*-methylnitrone **5b** (mp 84–86 °C; lit.,[20] 85–87 °C) and *C*,*N*-diphenylnitrone **5d** (mp 110–111 °C; lit.,[21] 112–114 °C) were prepared according to literature methods.

N-Butyl-*C*-phenylnitrone 5c

Following a literature method,[22] several small cuttings of sodium (1.40 g, 60 mmol) were added to a stirred solution of benzaldehyde oxime (7.20 g, 60 mmol) in dry MeOH (50 cm^3) and stirring continued for 10 min. 1-Iodobutane (6.90 cm^3, 61 mmol) was added to the resulting solution which, after being stirred overnight, was evaporated under reduced pressure. The residue was dissolved in Et_2O (30 cm^3) and after removal of NaI by filtration, was evaporated under reduced pressure. The residue was chromatographed on a silica gel column with hexane–EtOAc (2:1) as the eluent to give **5c** (620 mg, 6%) as a colourless oil (eluent: AcOEt–hexane, 2:1, R_f 0.34) (Found: M^+, 177.1154. $C_{11}H_{15}NO$ requires *M*, 177.1154); ν_{max}(neat)/cm^{-1} 1582, 1458 and 1157; δ_H 8.20–8.27 (6 H, m), 3.94 (2 H, t, *J* 7.0), 2.00 (2 H, tt, *J* 9.8 and 7.0), 1.43 (2 H, tq, *J* 9.8 and 7.4) and 0.98 (3 H, t, *J* 7.3); δ_C 134.5, 130.9, 130.6, 128.8 (2 C), 67.3, 29.8, 19.8 and 13.6; *m*/*z* (EI) 177 (M^+, 59%), 118 (100) and 91 (46).

General procedure for 1,3-dipolar cycloaddition of nitrones 5a–d with 1

A solution of **1** in toluene and an equimolar amount of the appropriate nitrone **5a–d** was heated at 110 °C under argon in a sealed tube for 12 h, after which the mixture was evaporated under reduced pressure and the residue chromatographed on a silica gel column (elution: CH_2Cl_2).

(3*R,4*R**,5*S**)-2-Methyl-3-phenyl-4-phenylsulfonyl-5-trifluoromethylisoxazolidine 6a.** Compound **6a** was obtained as above from **1** (708 mg, 3.00 mmol), **5a** (405 mg, 3.00 mmol) and toluene (2 cm^3) as a colourless solid (1.06 g, 95%), mp 128–129 °C (Found: C, 54.7; H, 4.3; N, 3.7. $C_{17}H_{16}F_3NO_3S$ requires C, 54.95; H, 4.34; N, 3.78%); ν_{max}(KBr)/cm^{-1} 1316, 1283 and 1175; δ_H 7.25–7.19 (10 H, m), 4.83 (1 H, qd, *J* 7.2 and 4.0), 4.23 (1 H, dd, *J* 8.4 and 4.0), 3.97 (1 H, d, *J* 8.4) and 2.61 (3 H, s); δ_C 137.7, 134.9, 134.8, 129.8, 129.4, 129.2, 128.9, 128.5, 123.8 (q, *J* 284), 75.1, 75.0 (q, *J* 34), 74.4 and 42.8; δ_F −78.9 (d, *J* 7); *m*/*z* (EI) 371 (M^+, 18%), 229 (36) and 160 (100).

(3*R,4*R**,5*S**)-3-(4-Methoxyphenyl)-2-methyl-4-phenylsulfonyl-5-trifluoromethylisoxazolidine 6b.** Compound **6b** was obtained as above from **1** (236 mg, 1.00 mmol), **5b** (165 mg, 1.00 mmol) and toluene (3 cm^3) as a colourless solid (399 mg, 99%), mp 145–147 °C (Found: C, 53.7; H, 4.5; N, 3.5. $C_{18}H_{18}F_3NO_4S$ requires C, 53.86; H, 4.52; N, 3.49%); ν_{max}(KBr)/cm^{-1} 1254, 1177 and 1132; δ_H 7.80–7.42 (5 H, m), 7.12 (2 H, d, *J* 8.9), 6.76 (2 H, d, *J* 8.9), 4.80 (1 H, qd, *J* 7.2 and 4.0), 4.17 (1 H, dd, *J* 8.4 and 4.0), 3.94 (1 H, d, *J* 8.4), 3.78 (3 H, s) and 2.59 (3 H, s); δ_C 160.5, 137.8, 134.9, 129.8, 129.7, 128.9, 126.6, 123.8 (q, *J* 284), 114.6, 75.0, 74.9 (q, *J* 34), 73.9, 55.5 and 42.7; δ_F − 76.0 (d, *J* 3); *m*/*z* (EI) 401 (M^+, 27%), 259 (25) and 190 (100).

(3*R,4*R**,5*S**)-2-Butyl-3-phenyl-4-phenylsulfonyl-5-trifluoromethylisoxazolidine 6c.** Compound **6c** was obtained as above from **1** (260 mg, 1.10 mmol), **5c** (195 mg, 1.10 mmol) and toluene (4 cm^3) as a colourless solid (433 mg, 95%), mp 66–67 °C (Found: C, 58.35; H, 5.1; N, 3.35. $C_{20}H_{22}F_3NO_3S$ requires C, 58.10; H, 5.36; N, 3.39%); ν_{max}(KBr)/cm^{-1} 1329, 1281 and 1155; δ_H 7.79–7.19 (10 H, m), 4.80 (1 H, qd, *J* 7.2 and 3.8), 4.60 (1 H, d, *J* 8.2), 4.18 (1 H, dd, *J* 8.2 and 3.8), 2.77–2.51 (2 H, m), 1.65–1.10 (4 H, m) and 0.78 (3 H, t, *J* 7.2); δ_C 137.8, 135.5, 134.9, 129.8, 129.1 (2 C), 128.9, 128.8, 128.5, 123.8 (q, *J* 285), 75.1, 74.9 (q, *J* 34), 72.5, 55.6, 29.6, and 20.1; δ_F − 76.0 (d, *J* 7); *m*/*z* (EI) 413 (M^+, 57%), 370 (57) and 202 (100).

(3*R,4*R**,5*S**)-2,3-Diphenyl-4-phenylsulfonyl-5-trifluoromethylisoxazolidine 6d.** Compound **6d** was obtained as above from **1** (708 mg, 3.00 mmol), **5d** (592 mg, 3 mmol) and toluene (18 cm^3) as a colourless solid (1.30 g, 99%), mp 112–113 °C (Found: C, 60.7; H, 4.0; N, 3.0. $C_{22}H_{18}F_3NO_3S$ requires C, 60.96; H, 4.19; N, 3.23%); ν_{max}(KBr)/cm^{-1} 1271, 1186 and 1157; δ_H 7.85–6.95 (15 H, m), 4.99 (1 H, qd, *J* 7.2 and 3.8), 4.79 (1 H, d, *J* 7.2) and 4.33 (1 H, dd, *J* 7.2 and 3.8); δ_C 147.6, 137.5, 136.3, 135.1, 134.9, 130.0, 129.3, 129.1, 129.0, 128.2, 125.8, 123.6 (q, *J* 284), 119.7, 75.9, 75.1 (q, *J* 34) and 71.8; δ_F −75.6 (d, *J* 5); *m*/*z* (EI) 433 (M^+, 100%), 222 (100) and 77 (48).

(4*R,5*S**)-2-Methyl-4-phenylsulfonyl-5-trifluoromethylisoxazolidine 6e.** To a solution of **1** (98 mg, 0.40 mmol) in toluene (3 cm^3) in a glass tube under argon was added *N*-methylhydroxylamine hydrochloride (40 mg, 0.50 mmol), triethylamine (46 mg, 0.45 mmol) and paraformaldehyde (30 mg, 1.00 mmol). After the mixture had been treated at 110 °C for 12 h, it was evaporated under reduced pressure, and the residue was chromatographed on a silica gel column with hexane–CH_2Cl_2 (3:1) as the eluent to give a colourless solid (80 mg, 65%), mp 120–121 °C (Found: C, 44.9; H, 4.2; N, 4.6. $C_{11}H_{12}F_3NO_3S$ requires C, 44.74; H, 4.10; N, 4.74%); ν_{max}(KBr)/cm^{-1} 1312, 1277 and 1154; δ_H 7.98–7.59 (5 H, m), 4.69 (1 H, qd, *J* 6.7 and 4.9), 4.38–4.12 (1 H, m), 3.56 (1 H, br s), 3.04 (1 H, br s) and 2.80 (3 H, s); δ_C 137.8, 135.2, 130.2, 129.0, 123.5 (q, *J* 278), 75.4 (q, *J* 33), 68.5, 58.2 and 45.2; δ_F −76.7 (d, *J* 5); *m*/*z* (EI) 295 (M^+, 11%), 153 (43), 84 (100) and 77 (21).

(3*R,4*R**,5*S**)-2,3-Dimethyl-4-phenylsulfonyl-5-trifluoromethylisoxazolidine 6f.** Compound **6f** was obtained similarly from **1** (944 mg, 4.00 mmol), *N*-methylhydroxylamine hydrochloride (367 mg, 4.40 mmol), Et_3N (445 mg, 4.40 mmol), acetaldehyde (441 mg, 10.0 mmol) and toluene (18 cm^3) as a colourless solid (391 mg, 32%), mp 119–121 °C (Found: C, 46.6; H, 4.6; N, 4.4. $C_{12}H_{14}F_3NO_3S$ requires C, 46.60; H, 4.56; N, 4.53%); ν_{max}(KBr)/cm^{-1} 1277, 1152 and 1132; δ_H 7.97–7.59 (5 H, m), 4.57 (1 H, qd, *J* 7.2 and 4.0), 3.74 (1 H, dd, *J* 8.2 and 4.0), 3.14 (qd, 1 H, *J* 8.2 and 7.0), 2.73 (3 H, s) and 1.21 (3 H, d, *J* 6.2); δ_C 137.8, 135.2, 130.15, 129.1, 123.6 (q, *J* 284), 74.6 (q, *J* 34), 74.1, 65.2, 43.1 and 16.5; δ_F −76.6 (d, *J* 5); *m*/*z* (EI) 309 (M^+, 55%), 167 (100) and 153 (30).

General procedure for the preparation of 3-amino alcohols 8a–d

To a solution of the isoxazolidine **6a–d** in MeOH was added portionwise 5% sodium amalgam (8 equiv. of Na) and Na_2HPO_4 (8 equiv.) under N_2. After being stirred for 2 days at room temperature, the mixture was freed of deposited Hg metal by decantation and then evaporated under reduced pressure. 10% Aq. NaOH was added to the residue and the resulting mixture was extracted with Et_2O. The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the desulfonylated compounds **7**. Without purification, **7** was dissolved in MeOH and 10% palladium-on-carbon was added to the solution. The mixture was stirred under an atmospheric pressure of H_2 for 3 days at room temperature, after which the catalyst was filtered off and the filtrate was evaporated under reduced pressure. The residue was chromatographed on a silica gel column (elution: AcOEt).

(2*R,4*R**)-1,1,1-Trifluoro-4-methylamino-4-phenylbutan-2-ol 8a.** Compound **8a** was obtained as above from **6a** (928 mg, 2.50 mmol), 5% Na–Hg (9.20 g, 20.0 mmol of Na), Na_2HPO_4 (2.98 g, 21.0 mmol), 10% Pd–C (80 mg, 0.08 mmol) and a mixture of dry THF (3 cm^3) and dry MeOH (15 cm^3) as a yellow solid (148 mg, 25%), mp 101–102 °C (Found: C, 56.6; H, 6.1; N, 6.0. $C_{11}H_{14}F_3NO$ requires C, 56.65; H, 6.05; N, 6.01%); ν_{max}(KBr)/cm^{-1} 3281, 1167 and 1127; δ_H 7.45–7.20 (5 H, m), 4.30 (1 H, dqd, *J* 10.3, 6.5 and 3.7), 4.18–3.79 (2 H, m), 3.72–3.65 (1 H, m), 2.27 (3 H, s) and 2.07–1.86 (2 H, m); δ_C 141.7, 129.4, 128.4, 126.6, 125.0 (q, *J* 280), 71.5 (q, *J* 31), 64.2, 34.6 (q, *J* 1.9) and 33.2; δ_F −81.4 (d, *J* 5); *m*/*z* (EI) 233 (M^+, 3%), 121 (64) and 120 (100).

(3*R,5*S**)-2-Methyl-3-phenyl-5-trifluoromethylisoxazolidine 7a.** Compound **7a** was obtained as above from **6a** (200 mg, 0.540 mmol), 5% Na–Hg (1.01 g, 2.20 mmol of Na) and Na_2HPO_4 (350 mg, 2.50 mmol) as a yellow oil (39 mg, 31%) (eluent: hexane–CH_2Cl_2, 2:1, R_f 0.25) (Found: M^+, 231.0872. $C_{11}H_{12}F_3NO$ requires *M*, 231.0871); ν_{max}(neat)/cm^{-1} 1279, 1165 and 1125; δ_H 7.40–7.33 (5 H, m), 4.46 (1 H, dqd, *J* 8.8, 7.2 and 6.3), 3.56 (1 H, dd, *J* 10.2 and 7.2), 2.87 (1 H, ddd, *J* 13.0, 8.8 and 7.2), 2.60 (3 H, s) and 2.52 (1 H, ddd, *J* 13.0, 10.2 and 6.3); δ_C 137.4, 129.3, 128.9, 128.1, 125.1 (q, *J* 282), 73.8 (q, *J* 33), 73.4, 43.2 and 40.0; δ_F −78.0 (d, *J* 7); *m*/*z* (EI) 231 (M^+, 100%), 154 (54) and 134 (50).

(2*R,4*R**)-1,1,1-Trifluoro-4-(4-methoxyphenyl)-4-(methylamino)butan-2-ol 8b.** Compound **8b** was obtained as above from **6b** (1.04 g, 2.60 mmol), 5% Na–Hg (9.20 g, 20.0 mmol of Na), Na_2HPO_4 (2.98 g, 21.0 mmol), 10% Pd–C (80 mg, 0.08 mmol) and a mixture of dry THF (5 cm^3) and dry MeOH (15 cm^3) as a colourless solid (145 mg, 21%), mp 108–109 °C; (Found: C, 54.8; H, 6.1; N, 5.3. $C_{12}H_{16}F_3NO_2$ requires C, 54.75; H, 6.13; N, 5.32%); ν_{max}(KBr)/cm^{-1} 3281, 1250 and 1123 cm^{-1}; δ_H 7.42 (2 H, d, *J* 8.8), 6.92 (2 H, d, *J* 8.8), 4.29 (1 H, dqd, *J* 10.2, 6.6 and 3.7), 3.82 (3 H, s), 3.66–3.59 (1 H, m), 2.25 (3 H, s) and 2.05–1.83 (2 H, m)§; δ_C 159.7, 133.9, 127.7, 125.1 (q, *J* 280), 114.6, 71.4 (q, *J* 31), 63.5, 55.5, 34.6 (q, *J* 1.8) and 33.1; δ_F −81.4 (s); *m*/*z* (EI) 263 (M^+, 3%), 151 (35) and 150 (100).

(2*R,4*R**)-4-Butylamino-1,1,1-trifluoro-4-phenylbutan-2-ol 8c.** Compound **8c** was obtained as above from **6c** (1.03 g, 2.60 mmol), 5% Na–Hg (9.20 g, 20.0 mmol of Na), Na_2HPO_4 (2.98 g, 21.0 mmol), 10% Pd–C (80 mg, 0.08 mmol) and a mixture of dry THF (5 cm^3) and dry MeOH (15 cm^3) as a colourless solid (118 mg, 17%), mp 93–94 °C (Found: C, 61.2; H, 7.3; N, 5.0. $C_{14}H_{20}F_3NO$ requires C, 61.08; H, 7.32; N, 5.09%); ν_{max}(KBr)/cm^{-1} 3268, 1275 and 1163; δ_H 7.44–7.19 (5 H, m), 4.33 (1 H, dqd, *J* 10.4, 6.6 and 4.0), 3.81–3.74 (1 H, m), 2.06–1.85 (2 H, m), 2.57–2.34 (2 H, m), 1.49–1.20 (4 H, m) and 0.85 (3 H, t, *J* 6.6); § δ_C 142.3, 129.4, 128.3, 126.4, 125.0 (q, *J* 280), 71.6 (q, *J* 31), 62.7, 46.5, 34.8, 32.0, 20.3 and 13.9; δ_F −81.4 (s); *m*/*z* (EI) 275 (M^+, 2%), 203 (87) and 162 (100).

(2*R,4*R**)-4-Anilino-1,1,1-trifluoro-4-phenylbutan-2-ol 8d.** Compound **8d** was obtained as above from **6d** (300 mg, 0.680 mmol), 5% Na–Hg (2.60 g, 6.00 mmol of Na), Na_2HPO_4 (850 mg, 6.00 mmol), 10% Pd–C (30 mg, 0.02 mmol) and a mixture of dry THF (3 cm^3) and dry MeOH (10 cm^3) as an orange-coloured solid (50 mg, 26%), mp 90–92 °C (Found: C, 65.2; H, 5.6; N, 4.5. $C_{16}H_{16}F_3NO$ requires C, 65.08; H, 5.46; N, 4.74%); ν_{max}(KBr)/cm^{-1} 3409, 1277 and 1132; δ_H 7.35–6.61 (10 H, m), 4.62 (1 H, dd, *J* 8.5 and 6.5), 4.07 (1 H, dqd, *J* 10.5, 7.0 and 2.5), 4.04–3.52 (2 H, m), 2.19 (1 H, ddd, *J* 14.5, 6.5 and 2.5) and 2.09 (1 H, ddd, *J* 14.5, 10.5 and 8.5); δ_C 146.8, 142.5, 129.6, 129.4, 128.2, 126.6, 125.1 (q, *J* 281), 119.3, 115.1, 70.0 (q, *J* 31), 57.2 and 37.0; δ_F −80.8 (d, *J* 7); *m*/*z* (EI) 295 (M^+, 93%), 186 (36) and 182 (100).

§ NH and OH signals are missing due to signal broadening.

(4*R,6*R**)-3-Methyl-4-phenyl-6-trifluoromethyl-1,3-oxazinan-2-one 10a**

To a refluxing solution of **8a** (155 mg, 0.66 mmol) in dry CH_3CN (5 cm^3) was added a solution of diimidazol-1-yl ketone **9** (120 mg, 1.35 mmol) in CH_3CN (5 cm^3) under N_2. After 5 h under reflux the mixture was evaporated under reduced pressure, and the residue was chromatographed on a silica gel column with hexane–EtOAc (1:1) as the eluent to give **10a** as a colourless solid (159 mg, 93%), mp 130–131 °C (Found: C, 55.6; H, 4.7; N, 5.4. $C_{12}H_{12}F_3NO_2$ requires C, 55.60; H, 4.67; N, 5.40%) ν_{max}(KBr)/cm^{-1} 1692, 1144 and 1119; δ_H 7.48–7.24 (5 H, m), 4.69 (1 H, dqd, *J* 12.0, 7.8 and 2.2), 4.54 (1 H, dd, *J* 11.4 and 5.5), 2.74 (3 H, s), 2.49 (1 H, ddd, *J* 14.2, 5.5 and 2.2) and 2.17 (1 H, ddd, *J* 14.2, 12.2 and 11.6); δ_C 152.7, 139.0, 129.8, 129.4, 127.0, 122.6 (q, *J* 279), 72.4 (q, *J* 34), 60.7, 34.6 and 31.7; δ_F −79.5 (s); *m*/*z* (EI) 279 (M^+, 100%), 182 (30) and 118 (54).

(4*R,6*R**)-3,4-Diphenyl-6-trifluoromethyl-1,3-oxazinan-2-one 10d**

Compound **10d** was obtained similarly from **8d** (57 mg, 0.18 mmol) in dry CH_3CN (5 cm^3) and diimidazol-1-yl ketone **9** (58 mg, 0.36 mmol) in dry CH_3CN (3 cm^3) solution as a colourless solid (34 mg, 29%), mp 143–145 °C (Found: C, 63.4; H, 4.1; N, 4.35. $C_{17}H_{14}F_3NO_2$ requires C, 63.55; H, 4.39; N, 4.36%); ν_{max}(KBr)/cm^{-1} 1692, 1402 and 1177; δ_H 7.28–7.04 (10 H, m), 5.05 (1 H, dd, *J* 14.0 and 11.2), 4.91 (1 H, dqd, *J* 11.3, 5.6 and 3.1), 2.59 (1 H, ddd, *J* 14.0, 5.7 and 3.1) and 2.46 (1 H, dt, *J* 14.0 and 11.2); δ_C 151.5, 139.8, 138.4, 129.2, 129.0, 128.2, 128.0, 127.8, 127.6, 122.7 (q, *J* 279), 73.0 (q, *J* 35), 61.9 and 31.1; δ_F −79.4 (d, *J* 5); *m*/*z* (EI) 321 (M^+, 91%), 185 (100) and 165 (43).

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