DOI: 10.1002/ejoc.200900387

Synthesis of Enantiopure 2-Aryl(Alkyl)-2-trifluoromethyl-Substituted Morpholines and Oxazepanes

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Keywords: Cyclization / Asymmetric synthesis / Fluorine / Heterocycles / Enantiopurity

The synthesis of morpholines and oxazepanes derivatives containing a trifluoromethyl group on a quaternary carbon has been achieved from a common enantiopure *O*-allyl amino ether precursor. Classic 6-*exo* iodoamination provided the iodomorpholines, versatile synthetic intermediates, whereas a hydrozirconation/iodination sequence allowed the synthesis of oxazepanes by a 7-*endo* cyclisation.

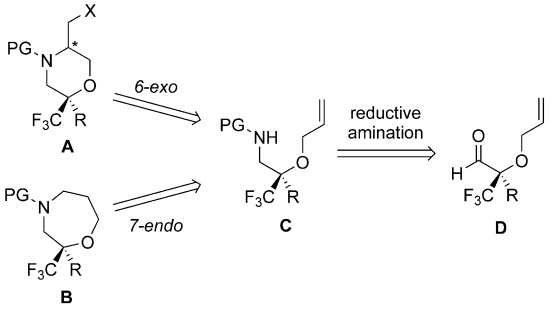
Introduction

A wide variety of highly active agrochemicals and pharmaceuticals contain one or more fluorine atoms due to the unique properties created by this atom.[1] Moreover, *N*,*O*-heterocycles such as morpholines and oxazepanes are of great interest due to their presence in a number of biologically active compounds.[2] However, only a very few trifluoromethylated analogues of these heterocycles are known to date. 2-(Trifluoromethyl)morpholines have been described as subunits in compounds with interesting antitumoral,[3] antibacterial,[4] TPK1 inhibition[5] or herbicidal[6] activities. The synthetic route for their preparation involves the cyclisation of an α-halogenoacyl chloride with a suitable 1-CF_3-amino alcohol. The cyclic amide thus formed is then reduced to the corresponding morpholine. Various (trifluoromethyl)morpholino-substituted lactols[7] and morpholinones[8] have also been reported as synthetic intermediates or as components of biologically active compounds.

In this paper, we present a new synthetic approach to the preparation of novel chiral morpholines and oxazepanes containing a trifluoromethyl group at a quaternary carbon adjacent to the oxygen atom.

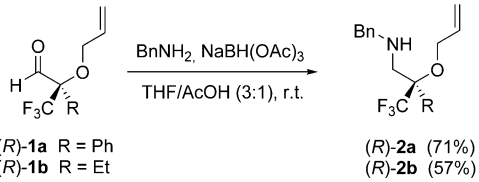
Results and Discussion

Retrosynthetically we envisaged that the desired (trifluoromethyl)morpholines A and oxazepanes B might be reached from the same *O*-allyl amino ethers C by a regioselective 6-*exo* or 7-*endo* intramolecular iodocyclisation (Scheme 1). The enantiopure aldehydes D, which have recently been synthesised by our group,[9] might then serve as suitable precursors for intermediate amines of type C.



Scheme 1. Retrosynthetic scheme for the preparation of CF_3-substituted morpholines and oxazepanes.

The reductive amination[10] of the enantiopure aldehydes (*R*)-**1a**,**b**[9] with benzylamine in the presence of sodium triacetoxyborohydride directly afforded the amino ethers (*R*)-**2a**,**b** in 71 and 57% yields, respectively (Scheme 2).



Scheme 2. Reductive amination of the aldehydes (*R*)-**1a**,**b** to the key amino ethers (*R*)-**2a**,**b**.

The 6-*exo* ring-closure of the allylic amino ethers **2a**,**b** into the corresponding (iodomethyl)morpholines **3a**,**b** was performed under classic conditions[11] using iodine in acetonitrile under basic conditions (Table 1). This cyclisation was not stereoselective, both morpholines **3a**,**b** being obtained

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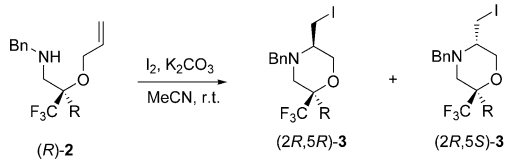
as mixtures of two diastereomers in ratios of 63:37 and 53:47, respectively. However, the diastereomers were separated by chromatography on silica gel.

Table 1. Iodocyclisation of the amino ethers (*R*)-**2a**,**b** to the iodomorpholines (2*R*,5*R*)-**3a**,**b** and (2*R*,5*S*)-**3a**,**b**.



(*R*)-**2** (2*R*,5*R*)-**3** (2*R*,5*S*)-**3**

Amino ether (*R*)-**2**	R	Iodomorpholine (2*R*,5*R*)-**3**/(2*R*,5*S*)-**3** [*dr*][a]	% Yield (2*R*,5*R*)-**3**[b]	% Yield (2*R*,5*S*)-**3**[b]
(*R*)-**2a**	Ph	**3a** [63:37]	55	33
(*R*)-**2b**	Et	**3b** [53:47]	37	39

[a] Diastereomeric ratio (*dr*) determined by ^{19}F NMR analysis of the crude mixture. [b] Isolated yields.

No conclusive information regarding the relative stereochemistry of these 2,2,5-trisubstituted morpholines **3a**,**b** could be obtained from extensive NMR analyses. The stereochemistry of the minor isomer of **3a** was thus unambiguously established by X-ray crystallography (Figure 1).[12] This analysis revealed a chair-like conformation of the morpholine ring with the phenyl substituent in an axial position and a 2,5-*trans*-diequatorial relationship of the trifluoromethyl and iodomethyl substituents. Similar trends in the ^{13}C NMR chemical shifts observed for both phenyl- and ethyl-substituted morpholines allowed the assignment of the same stereochemistry to the minor isomer of **3b**. Specifically, the iodomethyl signal in the ^{13}C NMR spectra appeared at δ = 4.5 and 5.7 ppm for the minor "*trans* isomers" (2*R*,5*S*)-**3a** and (2*R*,5*S*)-**3b**, respectively, whereas this signal appeared upfield (at 1.0–1.1 ppm) for the major "*cis* isomers" (2*R*,5*R*)-**3a** and (2*R*,5*R*)-**3b**.

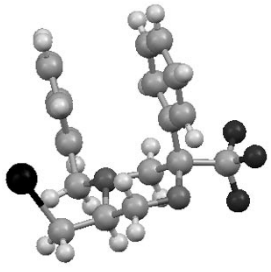
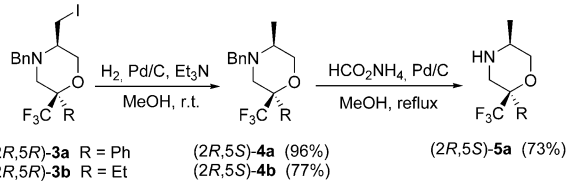


Figure 1. Molecular structure of (2*R*,5*S*)-**3a**.

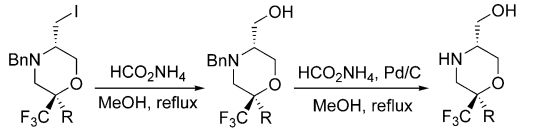
The presence of the iodine substituent in morpholines **3a**,**b** allowed us to envisage the synthesis of a few analogues. Hydrogenolysis of the *cis*-morpholines (2*R*,5*R*)-**3a** and (2*R*,5*R*)-**3b** in methanol in the presence of triethylamine afforded the 5-methylmorpholines (2*R*,5*S*)-**4a**[13] and (2*R*,5*S*)-**4b**[13] in 96 and 77% yields, respectively (Scheme 3). Cleavage of the *N*-benzyl-protecting group of (2*R*,5*S*)-**4a** with ammonium formate[14] as the catalytic hydrogen transfer agent in the presence of Pd/C at reflux in methanol gave the free morpholine (2*R*,5*S*)-**5a** (73% yield; Scheme 3).



(2*R*,5*R*)-**3a** R = Ph (2*R*,5*S*)-**4a** (96%) (2*R*,5*S*)-**5a** (73%)
(2*R*,5*R*)-**3b** R = Et (2*R*,5*S*)-**4b** (77%)

Scheme 3. Preparation of the 5-methyl-2-phenyl-2-(trifluoromethyl)morpholines (2*R*,5*S*)-**4a** and (2*R*,5*S*)-**5a** and the 2-ethyl-5-methyl-2-(trifluoromethyl)morpholine (2*R*,5*S*)-**4b**.

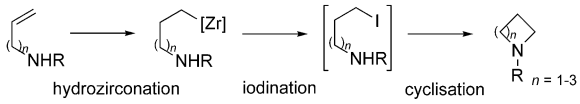
Treatment of the *trans*-(iodomethyl)morpholines (2*R*,5*S*)-**3a** and (2*R*,5*S*)-**3b** with ammonium formate at reflux in methanol led to the hydroxy analogues (2*R*,5*R*)-**6a**[13] and (2*R*,5*R*)-**6b**[13] in 73 and 65% yields, respectively (Scheme 4). Subsequent removal of the benzyl group under the conditions described above[14] led to the free (hydroxymethyl)morpholines (2*R*,5*R*)-**7a** and (2*R*,5*R*)-**7b** in 69 and 91% yields, respectively (Scheme 4).



(2*R*,5*S*)-**3a** R = Ph (2*R*,5*R*)-**6a** (73%) (2*R*,5*R*)-**7a** (69%)
(2*R*,5*S*)-**3b** R = Et (2*R*,5*R*)-**6b** (65%) (2*R*,5*R*)-**7b** (91%)

Scheme 4. Preparation of the 5-(hydroxymethyl)-2-phenyl-2-(trifluoromethyl)morpholines (2*R*,5*R*)-**6a**,**7a** and the 2-ethyl-5-(hydroxymethyl)-2-(trifluoromethyl)morpholines (2*R*,5*R*)-**6b**,**7b**.

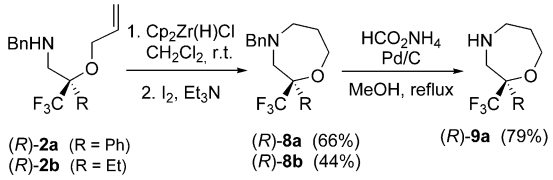
We then studied the synthesis of the oxazepane derivatives **8a**,**b** by the ring-closure of the allylic amino ethers (*R*)-**2a**,**b** at the less substituted allylic terminus. The 7-*endo* cyclisation reaction leading to the oxazepanes was attempted by using a strategy based on organozirconium chemistry. Indeed, taking advantage of the properties of organozirconocenes,[15] Szymoniak and co-workers recently reported the synthesis of four-, five- and six-membered *N*-heterocycles applying an hydrozirconation/iodination sequence to the corresponding unsaturated amines (Scheme 5).[16] Owing to the regioselectivity of the hydrozirconation step,[15] this sequence provided a straightforward synthesis of the *endo* cyclisation products.



Scheme 5. Synthesis of *N*-heterocycles by the zirconation/iodination sequence.[16]

We adapted this strategy to our trifluoromethylated substrates. As expected, the reaction of the allylic amino ether (*R*)-**2a** with the Schwartz reagent followed by iodine in the presence of triethylamine led to the oxazepane (*R*)-**8a** in 66% yield (Scheme 6). When applied to the ethyl analogue

(*R*)-**2b**, the reaction was more sluggish and the oxazepane (*R*)-**8b** was isolated in only 44% yield. Deprotection[14] of (*R*)-**8a** gave the free oxazepane (*R*)-**9a** in 79% yield.



Scheme 6. Preparation of the 2-phenyl-2-(trifluoromethyl)oxazepanes(*R*)-**8a**,**9a** and the 2-ethyl-2-(trifluoromethyl)oxazepane (*R*)-**8b**.

Conclusions

We have described two complementary approaches to the preparation of enantiopure six- and seven-membered *N*,*O*-heterocycles containing a quaternary trifluoromethyl group from a common enantiopure *O*-allyl amino ether precursor. A classic 6-*exo* iodoamination provided the key iodomorpholines, synthetic intermediates for further elaborations, whereas a hydrozirconation/iodination sequence allowed the synthesis of oxazepanes by a 7-*endo* cyclisation. The latter reaction is an extension of the scope of this recently developed strategy[16] to organofluorine chemistry as well as to the synthesis of seven-membered heterocycles.

Experimental Section

General: THF was distilled from sodium benzophenone. CH_2Cl_2 and MeCN were distilled from CaH_2. Thin-layer chromatography using precoated aluminium-backed plates (Merck Kieselgel 60F254) were visualised by UV light and by aqueous solutions of potassium permanganate. Gas chromatography (GC) analyses were performed with a polymethyldisiloxane DB-1 capillary column (30 m × 0.25 mm ID × 0.25 μm). Silica gel (Macherey–Nagel, 40–63 μm, ASTM for column chromatography) was used for flash chromatography. Melting points were determined with a Tottoli apparatus and are uncorrected. Optical rotations were measured at room temperature (ca. 20 °C). NMR spectra were recorded in $CDCl_3$ at frequencies of 250 MHz for ^1H, 235.3 MHz for ^{19}F and 62.9 or 125.8 MHz for ^{13}C NMR spectroscopy. Chemicals shifts (δ) are reported in ppm relative to TMS for ^1H and ^{13}C NMR spectra and relative to $CFCl_3$ for ^{19}F NMR spectra. In the ^{13}C NMR data, reported signal multiplicities relate to C–F coupling. The following abbreviations have been used to indicate the multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br. s (broad singlet). Signals were completely assigned on the basis of 2D NMR experiments. Diastereomeric ratios (*dr*) were determined by ^{19}F NMR spectroscopy. HRMS (ESI$^+$) were recorded by using an electrospray source in positive mode.

General Procedure for the Preparation of the Amino Ethers (*R*)-2a,b: A solution of aldehyde (*R*)-**1**[9] and benzylamine (2.0 equiv.) in a mixture of THF and acetic acid (3:1) was stirred at room temp. and under Ar. After 20 min of stirring, sodium acetoxyborohydride (2.2 equiv.) was added to the reaction mixture. After completion of the reaction (monitored by GC), the solution was hydrolysed with sat. aq. sodium carbonate and extracted three times with diethyl ether. The combined organic layers were washed three times with brine and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure and chromatography on silica gel (PE/EtOAc) afforded the amino ether (*R*)-**2**.

(*R*)-*N*-(2-Allyloxy-2-phenyl-3,3,3-trifluoropropyl)benzylamine [(*R*)-2a]: According to the general procedure, aldehyde (*R*)-**1a** (1.63 g, 6.67 mmol) in THF/acetic acid (15 mL:5 mL) was treated with benzylamine (1.46 mL, 13.34 mmol, 2.0 equiv.) and sodium acetoxyborohydride (3.11 g, 14.67 mmol, 2.2 equiv.) for 3 h. Chromatography (PE/AcOEt, 90:10) yielded the amino ether (*R*)-**2a** (1.59 g, 71%) as a colourless oil. $[\alpha]_D^{20}$ = +4.6 (*c* = 0.96, $CHCl_3$). ^{19}F NMR (235.3 MHz, $CDCl_3$): δ = –73.1 (s, 3 F, CF_3) ppm. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.54 (br. s, 1 H), 3.17 (dd, *J* = 13.0, 1.5 Hz, 1 H), 3.34 (d, *J* = 13.0 Hz, 1 H), 3.77 (d, *J* = 14.0 Hz, 1 H), 3.83 (d, *J* = 14.0 Hz, 1 H), 4.05 (dd, *J* = 13.0, 5.0 Hz, 1 H), 4.13 (dd, *J* = 13.0, 5.0 Hz, 1 H), 5.21 (tdd, *J* = 1.5, 10.5, 3.0 Hz, 1 H), 5.38 (tdd, *J* = 1.5, 17.0, 3.5 Hz, 1 H), 5.98 (tdd, *J* = 17.0, 10.5, 5.0 Hz, 1 H), 7.24–7.31 (m, 5 H), 7.36–7.39 (m, 3 H), 7.49 (m, 2 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 51.3, 54.0, 65.7, 81.9 (q, $^2J_{C,F}$ = 26.0 Hz, *C*-CF_3), 116.5, 125.4 (q, $^1J_{C,F}$ = 289.0 Hz, CF_3), 127.2, 127.4, 128.2, 128.49, 128.51, 128.8, 134.3, 135.1, 140.0 ppm. HMRS (ESI): calcd. for $C_{19}H_{21}F_3NO$ [M + H]$^+$ 336.1575; found 336.1564.

(*R*)-*N*-[2-Allyloxy-2-(trifluoromethyl)butyl]benzylamine [(*R*)-2b]: According to the general procedure, aldehyde (*R*)-**1b** (1.01 g, 25.0 mmol) in THF/acetic acid (15 mL:5 mL) was treated with benzylamine (1.12 mL, 10.25 mmol, 2.0 equiv.) and sodium acetoxyborohydride (2.39 g, 11.26 mmol, 2.2 equiv.) for 2 h. Chromatography (PE/AcOEt, 95:5) yielded the amino ether (*R*)-**2b** (836 mg, 57%) as a colourless oil. $[\alpha]_D^{20}$ = –4.8 (*c* = 1.24, $CHCl_3$). ^{19}F NMR (235.3 MHz, $CDCl_3$): δ = –73.8 (s, 3 F, CF_3) ppm. ^1H NMR (250 MHz, $CDCl_3$): δ = 0.94 (td, *J* = 7.5, 1.0 Hz, 3 H), 1.50 (br. s, 1 H), 1.92 (q, *J* = 7.5 Hz, 2 H), 2.85 (d, *J* = 1.0 Hz, 2 H), 3.81 (s, 2 H), 4.03 (dd, *J* = 13.0, 5.5 Hz, 1 H), 4.10 (dd, *J* = 13.0, 5.5 Hz, 1 H), 5.15 (tdd, *J* = 1.5, 10.5, 3.0 Hz, 1 H), 5.29 (tdd, *J* = 1.5, 17.0, 3.5 Hz, 1 H), 5.89 (tdd, *J* = 17.0, 10.5, 5.5 Hz, 1 H), 7.32–7.34 (m, 5 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 7.4, 22.6, 49.3, 54.3, 64.8, 79.9 (q, $^2J_{C,F}$ = 24.5 Hz, *C*-CF_3), 116.4, 126.6 (q, $^1J_{C,F}$ = 290.5 Hz, CF_3), 127.1, 128.1, 128.4, 134.6, 140.3 ppm. HMRS (ESI): calcd. for $C_{15}H_{21}F_3NO$ [M + H]$^+$ 288.1575; found 288.1569.

General Procedure for the Preparation of the (Iodomethyl)morpholines 3a,b: A suspension of amino ether (*R*)-**2a**,**b**, iodine (3.0 equiv.) and potassium carbonate (3.0 equiv.) in MeCN was stirred at room temp., under Ar and in the dark. After the complete disappearance of the amino ether (monitored by GC), the reaction mixture was diluted with Et_2O and hydrolysed with sat. aq. sodium thiosulfate. The organic layer was washed twice with brine and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure and chromatography on silica gel (PE/EtOAc) afforded the *cis*-iodomorpholine (2*R*,5*R*)-**3a**,**b** followed by the *trans*-iodomorpholine (2*R*,5*S*)-**3a**,**b**.

(2*R*,5*R*)-4-Benzyl-5-(iodomethyl)-2-phenyl-2-(trifluoromethyl)morpholine [(2*R*,5*R*)-3a] and (2*R*,5*S*)-4-Benzyl-5-(iodomethyl)-2-phenyl-2-(trifluoromethyl)morpholine [(2*R*,5*S*)-3a]: According to the general procedure, amino ether (*R*)-**2a** (174 mg, 0.52 mmol) in MeCN (3 mL) was treated with iodine (396 mg, 1.56 mmol, 3.0 equiv.) in the presence of K_2CO_3 (216 mg, 1.56 mmol, 3.0 equiv.) for 3 h. Chromatography (PE/EtOAc, 95:5) of the crude mixture (mixture of two diastereomers, *cis*/*trans* = 63:37) yielded the *cis*-iodomorpholine (2*R*,5*R*)-**3a** (132 mg, 55%) as a colourless oil and then the *trans*-iodomorpholine (2*R*,5*S*)-**3a** (79 mg, 33%) as a colourless solid.

***cis* Isomer (2*R*,5*R*)-3a:** $[\alpha]_D^{20}$ = +9.6 (*c* = 0.97, $CHCl_3$). ^{19}F NMR (235.3 MHz, $CDCl_3$): δ = –79.92 (s, 3 F, CF_3) ppm. ^1H NMR (250 MHz, $CDCl_3$): δ = 3.06 (br. d, $^3J_{H,H}$ = 11.0 Hz, 1 H, NCH), 3.21 (d, $^2J_{H,H}$ = 12.5 Hz, 1 H, NCH_aH$_b$), 3.28 (d, $^2J_{H,H}$ = 12.5 Hz, 1 H, NCH$_a$$H_b$), 3.61 (d, $^2J_{H,H}$ = 9.5 Hz, 1 H, CH_aH$_b$I), 3.76 (d, $^2J_{H,H}$ = 13.0 Hz, 1 H, CH_aH$_b$Ph), 3.86 (d, $^2J_{H,H}$ = 13.0 Hz, 1 H, CH$_a$$H_b$Ph), 3.88 (d, $^2J_{H,H}$ = 9.5 Hz, 1 H, CH$_a$$H_b$I), 3.95 (d, $^2J_{H,H}$ = 11.5 Hz, 1 H, OCH_aH$_b$), 4.28 (d, $^2J_{H,H}$ = 11.5 Hz, 1 H, OCH$_a$-H_b), 7.32–7.39 (m, 4 H, H aromatic), 7.44–7.49 (m, 6 H, H aromatic) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 1.0 (CH_2I), 44.2 (NCH_2), 59.4 (CH_2Ph), 60.0 (NCH), 63.4 (OCH_2), 78.1 (q, $^2J_{C,F}$ = 28.0 Hz, *C*-CF_3), 124.1 (q, $^1J_{C,F}$ = 284.5 Hz, CF_3), 127.9, 128.3, 128.4, 128.9, 129.3 (10 CH aromatic), 133.0, 137.1 (2 C aromatic) ppm. HMRS (ESI): calcd. for $C_{19}H_{20}F_3INO$ $[M + H]^+$ 462.0542; found 462.0538.

***trans* Isomer (2*R*,5*S*)-3a:** M.p. 126 °C. $[\alpha]_D^{20}$ = +18.1 (*c* = 1.03, $CHCl_3$). ^{19}F NMR (235.3 MHz, $CDCl_3$): δ = –79.85 (s, 3 F, CF_3) ppm. ^1H NMR (250 MHz, $CDCl_3$): δ = 2.30 (m, 1 H, NCH), 2.72 (d, $^2J_{H,H}$ = 12.0 Hz, 1 H, NCH_aH$_b$), 3.02 (d, $^2J_{H,H}$ = 13.0 Hz, 1 H, CH_aH$_b$Ph), 3.12 (d, $^2J_{H,H}$ = 11.5 Hz, 1 H, CH_aH$_b$I), 3.19 (d, $^2J_{H,H}$ = 11.5 Hz, 1 H, CH$_a$$H_b$I), 3.38 (d, $^2J_{H,H}$ = 12.0 Hz, 1 H, NCH$_a$$H_b$), 3.63 (dd, $^2J_{H,H}$ = 11.0, $^3J_{H,H}$ = 10.5 Hz, 1 H, OCH_aH$_b$), 3.92 (dd, $^2J_{H,H}$ = 11.0, $^3J_{H,H}$ = 3.5 Hz, 1 H, OCH$_a$$H_b$), 4.12 (d, $^2J_{H,H}$ = 13.0 Hz, 1 H, CH$_a$$H_b$Ph), 7.20 (m, 2 H, H aromatic), 7.37 (br. s, 8 H, H aromatic) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 4.6 (CH_2I), 50.4 (NCH_2), 57.8 (CH_2Ph), 58.5 (NCH), 67.0 (OCH_2), 78.8 (q, $^2J_{C,F}$ = 28.0 Hz, *C*-CF_3), 124.0 (q, $^1J_{C,F}$ = 284.5 Hz, CF_3), 128.0, 128.2, 128.5, 128.6, 128.9, 129.6 (10 CH aromatic), 133.1, 137.0 (2 C aromatic) ppm. HMRS (ESI): calcd. for $C_{19}H_{20}F_3INO$ $[M + H]^+$ 462.0542; found 462.0531. A small amount of this isomer was recrystallised from Et_2O/EP for X-ray analysis.

(2*R*,5*R*)-4-Benzyl-2-ethyl-5-(iodomethyl)-2-(trifluoromethyl)morpholine [(2*R*,5*R*)-3b] and (2*R*,5*S*)-4-Benzyl-2-ethyl-5-(iodomethyl)-2-(trifluoromethyl)morpholine [(2*R*,5*S*)-3b]: According to the general procedure, amino ether (*R*)-**2b** (169 mg, 0.59 mmol) in MeCN (3 mL) was treated with iodine (448 mg, 1.77 mmol, 3.0 equiv.) in the presence of K_2CO_3 (245 mg, 1.77 mmol, 3.0 equiv.) for 3 h. Chromatography (PE/Et_2O, 95:5) of the crude mixture (mixture of two diastereomers *cis*/*trans* = 53:47) yielded the *cis*-iodomorpholine (2*R*,5*R*)-**3b** (91 mg, 37%) and then the *trans*-iodomorpholine (2*R*,5*S*)-**3b** (96 mg, 39%) both as pale-yellow oils.

***cis* Isomer (2*R*,5*R*)-3b:** $[\alpha]_D^{20}$ = +4.0 (*c* = 0.99, $CHCl_3$). ^{19}F NMR (235.3 MHz, $CDCl_3$): δ = –78.36 (s, 3 F, CF_3) ppm. ^1H NMR (250 MHz, $CDCl_3$): δ = 0.92 (td, $^3J_{H,H}$ = 7.5, $^5J_{H,F}$ = 1.0 Hz, 3 H, CH_3), 1.75 (qd, $^2J_{H,H}$ = 15.0, $^3J_{H,H}$ = 7.5 Hz, 1 H, CH_aH$_b$CH$_3$), 2.17 (qdd, $^2J_{H,H}$ = 15.0, $^3J_{H,H}$ = 7.5, $^4J_{H,F}$ = 1.0 Hz, 1 H, CH$_a$$H_bCH_3$), 2.24 (d, $^2J_{H,H}$ = 12.0 Hz, 1 H, NCH_aH$_b$), 2.82 (d, $^2J_{H,H}$ = 12.0 Hz, 1 H, NCH$_a$$H_b$), 2.85 (dt, $^3J_{H,H}$ = 10.0, $^3J_{H,H}$ = 3.0 Hz, 1 H, NCH), 3.41 (dt, $^2J_{H,H}$ = 10.0, $^3J_{H,H}$ = 2.0 Hz, 1 H, CH_aH$_b$I), 3.56 (t, $^2J_{H,H}$ = 10.0 Hz, 1 H, CH$_a$$H_b$I), 3.65 (d, $^2J_{H,H}$ = 13.5 Hz, 1 H, CH_aH$_b$Ph), 3.73 (d, $^2J_{H,H}$ = 13.5 Hz, 1 H, CH$_a$$H_b$Ph), 3.89 (m, 1 H, OC$H_aH_b$), 4.09 (dd, $^2J_{H,H}$ = 11.5, $^3J_{H,H}$ = 2.5 Hz, 1 H, OCH$_a$$H_b$), 7.30–7.35 (m, 5 H, H aromatic) ppm. ^{13}C NMR (125.9 MHz, $CDCl_3$): δ = 1.1 (CH_2I), 7.2 (CH_3), 22.3 (CH_2CH_3), 46.8 (NCH_2), 58.97 (CH_2Ph), 58.99 (NCH), 63.7 (OCH_2), 75.8 (q, $^2J_{C,F}$ = 27.0 Hz, *C*-CF_3), 125.6 (q, $^1J_{C,F}$ = 286.0 Hz, CF_3), 127.7, 128.6, 128.7 (5 CH aromatic), 137.5 (C aromatic) ppm. HMRS (ESI): calcd. for $C_{15}H_{20}F_3INO$ $[M + H]^+$ 414.0542; found 414.0540.

***trans* Isomer (2*R*,5*S*)-3b:** $[\alpha]_D^{20}$ = –45.8 (*c* = 0.99, $CHCl_3$). ^{19}F NMR (235.3 MHz, $CDCl_3$): δ = –78.40 (s, 3 F, CF_3) ppm. ^1H NMR (250 MHz, $CDCl_3$): δ = 0.86 (td, $^3J_{H,H}$ = 7.5, $^5J_{H,F}$ = 1.5 Hz, 3 H, CH_3), 1.79 (qdd, $^2J_{H,H}$ = 15.0, $^3J_{H,H}$ = 7.5, $^4J_{H,F}$ = 1.0 Hz, 1 H, CH_aH$_b$CH$_3$), 2.16 (m, 2 H, NCH, CH$_a$$H_bCH_3$), 2.42 (d, $^2J_{H,H}$ = 12.0 Hz, 1 H, NCH_aH$_b$), 2.58 (d, $^2J_{H,H}$ = 12.0 Hz, 1 H, NCH$_a$$H_b$), 3.09 (d, $^2J_{H,H}$ = 13.0 Hz, 1 H, CH_aH$_b$Ph), 3.24 (dd, $^2J_{H,H}$ = 11.0, $^3J_{H,H}$ = 2.0 Hz, 1 H, CH_aH$_b$I), 3.41 (d, $^2J_{H,H}$ = 11.0, $^3J_{H,H}$ = 6.5 Hz, 1 H, CH$_a$$H_b$I), 3.84 (m, 2 H, OCH_2), 4.07 (d, $^2J_{H,H}$ = 13.0 Hz, 1 H, CH$_a$$H_b$Ph), 7.28–7.40 (m, 5 H, H aromatic) ppm. ^{13}C NMR (125.9 MHz, $CDCl_3$): δ = 5.7 (CH_2I), 7.1 (CH_3), 22.7 (CH_2CH_3), 49.9 (NCH_2), 57.6 (CH), 57.7 (CH_2Ph), 65.8 (OCH_2), 76.8 (q, $^2J_{C,F}$ = 27.0 Hz, *C*-CF_3), 125.5 (q, $^1J_{C,F}$ = 286.0 Hz, CF_3), 127.6, 128.5, 128.9 (5 CH aromatic), 137.2 (C aromatic) ppm. HMRS (ESI): calcd. for $C_{15}H_{20}F_3INO$ $[M + H]^+$ 414.0542; found 414.0555.

General Procedure for the Preparation of the *N*-Benzyl-5-methylmorpholines (2*R*,5*S*)-4a,b: A suspension of *cis*-iodomorpholine (2*R*,5*R*)-**3a**,**b**, triethylamine (2.0 equiv.) and Pd/C (10%, 0.05 equiv.) in methanol was hydrogenated (gas bag of H_2) at room temp. After 15 h of stirring, the suspension was filtered through Celite and the filtrate was concentrated under reduced pressure. Chromatography on silica gel (PE/EtOAc) afforded the *cis*-methylmorpholine (2*R*,5*S*)-**4a**,**b**.

(2*R*,5*S*)-4-Benzyl-5-methyl-2-phenyl-2-(trifluoromethyl)morpholine [(2*R*,5*S*)-4a]: According to the general procedure, *cis*-iodomorpholine (2*R*,5*R*)-**3a** (610 mg, 1.32 mmol) was hydrogenated in MeOH (10 mL) in the presence of Pd/C (10%, 70 mg, 0.066 mmol, 0.05 equiv.) and Et_3N (368 µL, 0.73 mmol, 2.0 equiv.). Chromatography (PE/EtOAc, 88:12) yielded the *cis*-methylmorpholine (2*R*,5*S*)-**4a** (426 mg, 96%) as a colourless oil. $[\alpha]_D^{20}$ = +88.9 (*c* = 0.97, $CHCl_3$). ^{19}F NMR (235.3 MHz, $CDCl_3$): δ = –79.0 (s, 3 F, CF_3) ppm. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.21 (d, *J* = 6.5 Hz, 3 H), 2.75 (m, 1 H), 2.99 (d, *J* = 12.0 Hz, 1 H), 3.15 (d, *J* = 12.0 Hz, 1 H), 3.54 (d, *J* = 14.5 Hz, 1 H), 3.61 (d, *J* = 14.5 Hz, 1 H), 3.62 (dd, *J* = 2.5, 11.0 Hz, 1 H), 3.85 (dd, *J* = 3.0, 11.0 Hz, 1 H), 7.25–7.32 (m, 5 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 9.1, 45.8, 53.0, 59.6, 68.1, 78.3 (q, $^2J_{C,F}$ = 28.5 Hz, *C*-CF_3), 124.8 (q, $^1J_{C,F}$ = 284.5 Hz, CF_3), 127.1, 127.8, 128.5, 128.7, 128.8, 129.0, 129.6, 134.6, 138.4 ppm. HMRS (ESI): calcd. for $C_{19}H_{21}F_3NO$ $[M + H]^+$ 336.1575; found 336.1583.

(2*R*,5*S*)-4-Benzyl-2-ethyl-5-methyl-2-(trifluoromethyl)morpholine [(2*R*,5*S*)-4b]: According to the general procedure, *cis*-iodomorpholine (2*R*,5*R*)-**3b** (339 mg, 0.82 mmol) was hydrogenated in MeOH (8 mL) in the presence of Pd/C (10%, 44 mg, 0.066 mmol, 0.05 equiv.) and Et_3N (229 µL, 1.64 mmol, 2.0 equiv.). Chromatography (PE/EtOAc, 90:10) yielded the *cis*-methylmorpholine (2*R*,5*S*)-**4b** (182 mg, 77%) as a colourless oil. $[\alpha]_D^{20}$ = +72.8 (*c* = 1.00, $CHCl_3$). ^{19}F NMR (235.3 MHz, $CDCl_3$): δ = –76.4 (s, 3 F, CF_3) ppm. ^1H NMR (250 MHz, $CDCl_3$): δ = 0.90 (td, *J* = 1.0, 7.5 Hz, 3 H), 1.09 (d, *J* = 6.5 Hz, 3 H), 1.72 (sext, *J* = 7.5 Hz, 1 H), 1.95 (sext, *J* = 7.5 Hz, 1 H), 2.14 (dd, *J* = 1.0, 12.0 Hz, 1 H), 2.62 (m, 1 H), 2.81 (d, *J* = 11.5 Hz, 1 H), 3.31 (d, *J* = 13.5 Hz, 1 H), 3.64 (ddd, *J* = 1.0, 5.5, 12.0 Hz, 1 H), 3.82 (d, *J* = 11.5 Hz, 1 H), 3.82 (d, *J* = 13.5 Hz, 1 H), 7.26 (m, 2 H), 7.32 (m, 3 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 7.6 (d, $^4J_{C,F}$ = 1.5 Hz, CH_2-CH_3), 11.2, 24.7, 49.7, 53.5, 58.9, 68.7, 76.0 (q, $^2J_{C,F}$ = 26.0 Hz, *C*-CF_3), 126.6 (q, $^1J_{C,F}$ = 288.5 Hz, CF_3), 127.5, 128.8, 128.9, 138.9 ppm. HMRS (ESI): calcd. for $C_{15}H_{21}F_3NO$ $[M + H]^+$ 288.1575; found 288.1581.

Preparation of (2*R*,5*S*)-5-Methyl-2-phenyl-2-(trifluoromethyl)-morpholine [(2*R*,5*S*)-5a]: A suspension of *N*-benzylmethylmorpholine (2*R*,5*S*)-**4a** (197 mg, 0.59 mmol), ammonium formate (189 mg, 2.99 mmol, 5.1 equiv.) and Pd/C (10%, 156 mg, 0.15 mmol, 0.25 equiv.) in methanol (5 mL) was heated at reflux

for 2 h 30 min. The reaction mixture was then cooled to room temp. and filtered through Celite. Evaporation of the filtrate under reduced pressure and chromatography on silica gel (PE/EtOAc/Et_3N, 50:50:0.1) yielded the unprotected methylmorpholine (2*R*,5*S*)-**5a** (105 mg, 73%) as a colourless oil. $[\alpha]_D^{20}$ = +2.0 (*c* = 0.93, $CHCl_3$). ^{19}F NMR (235.3 MHz, $CDCl_3$): δ = –74.9 (s, 3 F, CF_3) ppm. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.17 (d, *J* = 6.5 Hz, 3 H), 1.43 (br. s, 1 H), 2.90 (m, 1 H), 3.24 (dd, *J* = 1.5, 14.5 Hz, 1 H), 3.64 (ddd, *J* = 1.5, 7.0, 11.5 Hz, 1 H), 3.81 (m, 2 H), 7.35–7.39 (m, 3 H), 7.40–7.43 (m, 2 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 17.6, 46.2, 48.0, 68.4, 74.0 (q, $^2J_{C,F}$ = 26.5 Hz, *C*-CF_3), 125.8 (q, $^1J_{C,F}$ = 288.5 Hz, CF_3), 127.4, 128.8, 129.1, 136.4 ppm. HMRS (ESI): calcd. for $C_{12}H_{15}F_3NO$ $[M + H]^+$ 246.1106; found 246.1100.

General Procedure for the Preparation of the *N*-Benzyl-5-(hydroxymethyl)morpholines (2*R*,5*R*)-6a,b: A solution of *trans*-iodomorpholine (2*R*,5*S*)-**3a**,**b** and ammonium formate (5.0 equiv.) in methanol was heated at reflux. After the complete disappearance of the iodomorpholine (monitored by GC), the reaction mixture was cooled to room temp. and hydrolysed with sat. aq. sodium carbonate and extracted three times with diethyl ether. The combined organic layers were washed three times with brine and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure and chromatography on silica gel (PE/EtOAc/Et_3N) afforded the *trans* (hydroxymethyl)morpholine (2*R*,5*R*)-**6a**,**b**.

(2*R*,5*R*)-4-Benzyl-5-(hydroxymethyl)-2-phenyl-2-(trifluoromethyl)-morpholine [(2*R*,5*R*)-6a]: According to the general procedure, *trans*-iodomorpholine (2*R*,5*S*)-**3a** (266 mg, 0.58 mmol) was treated with ammonium formate (181 mg, 2.88 mmol, 5.0 equiv.) in methanol (8 mL) for 8 h. Chromatography (PE/EtOAc/Et_3N, 80:20:0.5) yielded the *trans*-hydroxymorpholine (2*R*,5*R*)-**6a** (147 mg, 73%) as an off-white solid; m.p. 90–92 °C. $[\alpha]_D^{20}$ = +77.9 (*c* = 1.04, $CHCl_3$). ^{19}F NMR (235.3 MHz, $CDCl_3$): δ = –80.2 (s, 3 F, CF_3) ppm. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.91 (br. s, 1 H), 2.59 (m, 1 H), 2.61 (d, *J* = 12.0 Hz, 1 H), 3.04 (d, *J* = 13.0 Hz, 1 H), 3.28 (dd, *J* = 12.0, 2.0 Hz, 1 H), 3.37 (d, *J* = 12.0 Hz, 1 H), 3.65 (d, *J* = 11.5 Hz, 1 H), 3.76 (dd, *J* = 12.0, 9.5 Hz, 1 H), 3.76 (d, *J* = 11.5 Hz, 1 H), 4.14 (d, *J* = 13.0 Hz, 1 H), 7.14 (m, 2 H), 7.21 (m, 2 H), 7.25–7.32 (m, 6 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 50.4 (q, $^3J_{C,F}$ = 1.5 Hz, NCH_2), 58.2, 59.4, 60.8, 63.7, 78.5 (q, $^2J_{C,F}$ = 28.0 Hz, *C*-CF_3), 124.0 (q, $^1J_{C,F}$ = 284.0 Hz, CF_3), 128.0, 128.4, 128.6, 128.7, 129.0, 129.3, 132.8, 137.0 ppm. HMRS (ESI): calcd. for $C_{19}H_{21}F_3NO_2$ $[M + H]^+$ 352.1524; found 352.1516.

(2*R*,5*R*)-4-Benzyl-2-ethyl-5-(hydroxymethyl)-2-(trifluoromethyl)-morpholine [(2*R*,5*R*)-6b]: According to the general procedure, *trans*-iodomorpholine (2*R*,5*S*)-**3b** (640 mg, 1.55 mmol) was treated with ammonium formate (502 mg, 7.72 mmol, 5.0 equiv.) in methanol (5 mL) for 4 h. Chromatography (PE/EtOAc/Et_3N, 80:20:0.5) yielded the *trans*-hydroxymorpholine (2*R*,5*R*)-**6b** (315 mg, 65%) as a yellow oil. $[\alpha]_D^{20}$ = –33.9 (*c* = 1.00, $CHCl_3$). ^{19}F NMR (235.3 MHz, $CDCl_3$): δ = –79.0 (s, 3 F, CF_3) ppm. ^1H NMR (250 MHz, $CDCl_3$): δ = 0.88 (td, *J* = 7.5, 1.5 Hz, 3 H), 1.79 (sextd, *J* = 7.5, 1.0 Hz, 1 H), 2.12 (br. s, 1 H), 2.20 (sextd, *J* = 7.5, 1.0 Hz, 1 H), 2.56 (m, 1 H), 2.43 (d, *J* = 12.0 Hz, 1 H), 2.65 (d, *J* = 12.0 Hz, 1 H), 3.21 (d, *J* = 13.5 Hz, 1 H), 3.53 (dd, *J* = 11.5, 2.0 Hz, 1 H), 3.87 (d, *J* = 7.0 Hz, 2 H), 3.93 (dd, *J* = 11.5, 4.5 Hz, 1 H), 4.17 (d, *J* = 13.5 Hz, 1 H), 7.28–7.38 (m, 5 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 7.1 (d, $^4J_{C,F}$ = 2.0 Hz, CH_3), 22.0, 50.9 (q, $^3J_{C,F}$ = 2.0 Hz, NCH_2), 58.4, 60.1, 60.6 (CH), 63.1, 76.5 (q, $^2J_{C,F}$ = 26.5 Hz, *C*-CF_3), 125.5 (q, $^1J_{C,F}$ = 286.0 Hz, CF_3), 127.6, 128.6, 128.7, 137.7 ppm. HMRS (ESI): calcd. for $C_{15}H_{21}F_3NO_2$ $[M + H]^+$ 304.1524; found 304.1522.

General Procedure for the Preparation of the (Hydroxymethyl)-morpholines (2*R*,5*R*)-7a,b: A suspension of *N*-benzyl(hydroxymethyl)morpholine (2*R*,5*R*)-**6a**,**b**, ammonium formate (5.1–5.2 equiv.) and Pd/C (10%, 0.25–0.27 equiv.) in methanol was heated at reflux. After the complete disappearance of the protected morpholine (monitored by GC), the reaction mixture was cooled to room temp. and filtered through Celite. The filtrate was washed twice with brine and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure and subsequent chromatography on silica gel (PE/EtOAc/Et_3N) if necessary afforded the deprotected (hydroxymethyl)morpholine (2*R*,5*R*)-**7a**,**b**.

(2*R*,5*R*)-5-(Hydroxymethyl)-2-phenyl-2-(trifluoromethyl)morpholine [(2*R*,5*R*)-7a]: According to the general procedure, the protected morpholine (2*R*,5*R*)-**6a** (124 mg, 0.35 mmol) was treated with ammonium formate (114 mg, 1.81 mmol, 5.1 equiv.) and Pd/C (10%, 94 mg, 0.089 mmol, 0.25 equiv.) in methanol (5 mL) for 2 h 30 min. Chromatography (PE/EtOAc/Et_3N, 20:80:0.5) yielded the free *trans*-hydroxymorpholine (2*R*,5*R*)-**7a** (64 mg, 69%) as a white solid; m.p. 81–82 °C. $[\alpha]_D^{20}$ = +49.2 (*c* = 1.05, $CHCl_3$). ^{19}F NMR (235.3 MHz, $CDCl_3$): δ = –80.1 (s, 3 F, CF_3) ppm. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.88 (br. s, 2 H), 2.99 (m, 1 H), 3.18 (dd, *J* = 6.0, 11.0 Hz, 1 H), 3.24–3.41 (m, 3 H), 3.69 (br. d, *J* = 13.5 Hz, 2 H), 7.34–7.45 (m, 5 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 46.0, 55.8, 62.7, 64.0, 124.5 (q, $^1J_{C,F}$ = 284.0 Hz, CF_3), 129.0, 129.4, 129.5, 132.9 ppm; *C*–CF_3 not observed. HMRS (ESI): calcd. for $C_{12}H_{15}F_3NO_2$ $[M + H]^+$ 262.1055; found 262.1054.

(2*R*,5*R*)-2-Ethyl-5-(hydroxymethyl)-2-(trifluoromethyl)morpholine [(2*R*,5*R*)-7b]: According to the general procedure, the protected morpholine (2*R*,5*R*)-**6b** (207 mg, 0.66 mmol) was treated with ammonium formate (225 mg, 3.46 mmol, 5.2 equiv.) and Pd/C (10%, 187 mg, 0.18 mmol, 0.27 equiv.) in methanol (5 mL) for 3 h. After work-up and evaporation of the solvent, the free *trans*-hydroxymorpholine (2*R*,5*R*)-**7b** (130 mg, 91%) was obtained as a colourless oil. $[\alpha]_D^{20}$ = +17.6 (*c* = 1.08, $CHCl_3$). ^{19}F NMR (235.3 MHz, $CDCl_3$): δ = –78.5 (s, 3 F, CF_3) ppm. ^1H NMR (250 MHz, $CDCl_3$): δ = 0.98 (td, *J* = 7.5, 1.5 Hz, 3 H), 1.81 (sext, *J* = 7.5 Hz, 1 H), 2.13 (m, 3 H), 2.88 (d, *J* = 13.0 Hz, 1 H), 2.94 (m, 1 H), 3.05 (d, *J* = 13.0 Hz, 1 H), 3.48 (dd, *J* = 8.5, 2.5 Hz, 1 H), 3.52 (dd, *J* = 8.5, 1.5 Hz, 1 H), 3.60 (dd, *J* = 11.5, 4.5 Hz, 1 H), 3.74 (dd, *J* = 11.5, 4.0 Hz, 1 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 7.1 (d, $^4J_{C,F}$ = 1.0 Hz, CH_3), 21.1, 45.5 (d, $^3J_{C,F}$ = 1.0 Hz, NCH_2), 54.5, 62.0, 62.9, 74.5 (q, $^2J_{C,F}$ = 26.5 Hz, *C*-CF_3), 124.7 (q, $^1J_{C,F}$ = 285.5 Hz, CF_3) ppm. HMRS (ESI): calcd. for $C_8H_{14}F_3NO_2$ $[M + H]^+$ 214.1055; found 214.1064.

General Procedure for the Preparation of the Oxazepanes (*R*)-8a,b: A solution of amino ether (*R*)-**2a**,**b** and the Schwartz reagent (80% purity, ca. 1.8 equiv.) in dichloromethane was stirred at room temp. under Ar and in the dark for 1 h before the addition of iodine (1.1 equiv.) and triethylamine (1.3 equiv.). The reaction was monitored by GC and the reaction mixture was then hydrolysed with 1 M HCl and the aqueous layer was extracted three times with dichloromethane. The combined organic layers were washed with sat. aq. sodium carbonate and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure and chromatography on silica gel (PE/EtOAc/Et_3N) afforded the oxazepane (*R*)-**8a**,**b**.

(*R*)-4-Benzyl-2-phenyl-2-(trifluoromethyl)-1,4-oxazepane [(*R*)-8a]: According to the general procedure, amino ether (*R*)-**2a** (788 mg, 2.28 mmol) was treated with the Schwartz reagent (1.34 g, ca. 4.2 mmol, ca. 1.8 equiv.), iodine (643 mg, 2.53 mmol, 1.1 equiv.) and triethylamine (0.40 mL, 2.9 mmol, 1.3 equiv.) for 3 h (1 h + 2 h). Chromatography (PE/EtOAc/Et_3N, 98:2:0.5) yielded the oxazepane (*R*)-**8a** (504 mg, 66%) as a white solid; m.p. 118–119 °C. $[\alpha]_D^{20}$ = +3.4 (*c* = 0.98, $CHCl_3$). ^{19}F NMR (235.3 MHz, $CDCl_3$): δ = –77.4 (s, 3 F, CF_3) ppm. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.81

(m, 2 H), 2.53 (t, J = 6.0 Hz, 2 H), 3.31 (d, J = 15.0 Hz, 1 H), 3.47 (d, J = 15.0 Hz, 1 H), 3.59 (d, J = 13.0 Hz, 1 H), 3.69 (d, J = 13.0 Hz, 1 H), 3.93 (ddd, J = 13.0, 7.0, 2.5 Hz, 1 H), 4.12 (ddd, J = 13.0, 7.0, 2.5 Hz, 1 H), 7.07 (m, 2 H), 7.21–7.25 (m, 3 H), 7.32–7.34 (m, 3 H), 7.44 (m, 2 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 31.8, 56.3, 59.0, 64.4, 66.0, 82.1 (q, $^2J_{C,F}$ = 25.5 Hz, C-CF_3), 125.5 (q, $^1J_{C,F}$ = 287.5 Hz, CF_3), 127.2, 128.2, 128.3, 129.1, 137.6, 138.9 ppm. HMRS (ESI): calcd. for $C_{19}H_{21}F_3NO$ $[M + H]^+$ 336.1575; found 336.1580.

(*R*)-4-Benzyl-2-ethyl-2-(trifluoromethyl)-1,4-oxazepane [(*R*)-8b]: According to the general procedure, amino ether (*R*)-**2b** (169 mg, 0.59 mmol) was treated with the Schwartz reagent (341 mg, ca. 1.0 mmol, ca. 1.8 equiv.), iodine (164 mg, 0.65 mmol, 1.1 equiv.) and triethylamine (0.11 mL, 0.76 mmol, 1.3 equiv.) for 7 h (1 h + 6 h). Chromatography (PE/EtOAc/Et_3N, 96:4:0.5) yielded the oxazepane (*R*)-**8b** (75 mg, 44%) as a colourless oil. $[\alpha]_D^{20}$ = –16.8 (c = 1.02, $CHCl_3$). ^{19}F NMR (235.3 MHz, $CDCl_3$): δ = –77.0 (s, 3 F, CF_3) ppm. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.74 (tq, J = 7.5, 1.5 Hz, 3 H), 1.76 (m, 1 H), 1.80 (qd, J = 7.5, 1.0 Hz, 2 H), 1.86 (m, 1 H), 2.28 (td, J = 11.0, 4.0 Hz, 1 H), 2.81–2.92 (m, 3 H), 3.60 (d, J = 13.0 Hz, 1 H), 3.73 (d, J = 13.0 Hz, 1 H), 3.86 (m, 1 H), 3.98 (d, J = 12.5 Hz, 1 H), 7.28–7.35 (m, 5 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 7.9 (d, $^4J_{C,F}$ = 2.0 Hz, CH_3), 27.2, 32.5, 55.7, 57.4, 64.8, 65.6, 80.4 (q, $^2J_{C,F}$ = 24.0 Hz, C-CF_3), 127.0 (q, $^1J_{C,F}$ = 289.5 Hz, CF_3), 127.4, 128.4, 129.3, 139.1 ppm. HMRS (ESI): calcd. for $C_{15}H_{20}F_3NO$ $[M + H]^+$ 288.1575; found 288.1581.

Preparation of the Free Oxazepane (*R*)-2-Phenyl-2-(trifluoromethyl)-1,4-oxazepane [(*R*)-9a]: A suspension of *N*-benzyloxazepane (*R*)-**8a** (390 mg, 1.16 mmol), ammonium formate (304 mg, 4.68 mmol, 4.0 equiv.) and Pd/C (10%, 381 mg, 0.36 mmol, 0.31 equiv.) in methanol (5 mL) was heated at reflux for 4 h. The reaction mixture was then cooled to room temp. and filtered through Celite. The filtrate was washed twice with brine and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure and chromatography on silica gel (PE/EtOAc/Et_3N, 60:40:0.5) yielded the free oxazepane (*R*)-**9a** (225 mg, 79%) as a yellow liquid. $[\alpha]_D^{20}$ = +10.6 (c = 1.07, $CHCl_3$). ^{19}F NMR (235.3 MHz, $CDCl_3$): δ = –78.7 (s, 3 F, CF_3) ppm. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.63 (br. s, 1 H), 1.75 (m, 1 H), 1.94 (m, 1 H), 2.69 (m, 1 H), 3.08 (m, 1 H), 3.37 (dd, J = 15.5, 1.5 Hz, 1 H), 3.75 (ddd, J = 13.0, 9.5, 1.5 Hz, 1 H), 3.90 (d, J = 15.5 Hz, 1 H), 4.12 (ddd, J = 13.0, 5.5, 2.0 Hz, 1 H), 7.36–7.45 (m, 3 H), 7.51 (m, 2 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 34.7, 50.3, 53.4, 66.2, 82.7 (q, $^2J_{C,F}$ = 25.0 Hz, C-CF_3), 125.3 (q, $^1J_{C,F}$ = 286.5 Hz, CF_3), 127.2, 128.4, 128.6, 137.1 ppm. HMRS (ESI): calcd. for $C_{12}H_{14}F_3NO$ $[M + H]^+$ 246.1106; found 246.1102.

Acknowledgments

We thank the Centre National de la Recherche Scientifique (CNRS) and the Région Champagne-Ardenne for a fellowship to J. N. This project has been supported (programme GLYCOVAL) by the "Contrat de Plan Etat-Région" (Ministère de la Recherche, Région Champagne-Ardenne, Ville de Reims) and the Sanofi-Aventis pharmaceutical company (Drs. E. Nicolai and C. Philippo). We thank Dr. Jean Luc Vasse for a gift of Schwartz reagent and fruitful discussions. We also express our thanks to Aurélien Lebrun for the NMR analyses, Emmanuel Wenger (Université de Nancy) for the X-ray structure and Dominique Harakat for the HRMS analyses.

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Received: April 8, 2009
Published Online: June 24, 2009

