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Synthesis and Structural Elucidation of 1,2-Disubstituted 3-Fluoropiperidines

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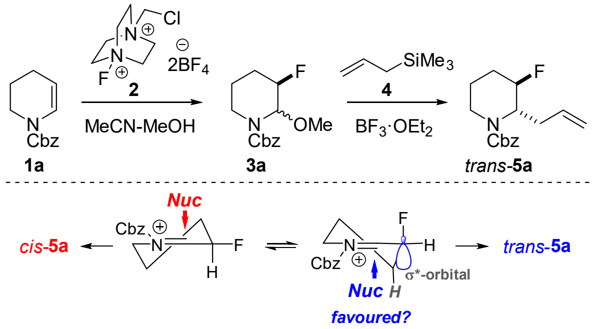
Abstract: The work described details the reaction between Selectfluor® and a series of 1-carbonyloxy and 1-sulfonyl 2-piperideines in order to generate 3-fluoro-2-methoxypiperidines **3a-f**. Their subsequent reaction with allyltrimethylsilane, in the presence of BF_3 and $TiCl_4$, is then reported. Studies involving a combination of single crystal X-ray crystallography and NMR spectroscopy indicate that the allylation process is *cis*-selective for both carbamate and sulfonamide variants and that optimal levels of diatereoselectivity are obtained using the *N*-2-nitrobenzene sulfonyl (2-Ns) group. In this manner the synthesis of a series of 2-allyl 3-fluoro-substituted piperidines (**5a**, **c**-**f**) was achieved. The conversion of both the *cis* and *trans*-*N*-tosyl adducts (**5d**) into 3-fluorinated analogues of the natural products pelletierine (**10**) and coniine (**11**) is subsequently detailed.

Introduction

Fluorine is an increasingly commonly found component in bioactive compounds that span all therapeutic categories. As of 2010 approximately 20% of all administered drugs worldwide contained at least one fluorine atom.[1] This trend is set to increase and examples of drugs containing fluorine are amongst some of the best-performing and top-selling "small molecule" pharmaceutical products. The reason for the widespread inclusion of fluorine atoms (or F-containing groups) into biologically active compounds stems directly from their ability to alter the compound's physicochemical properties in relation to their non-fluorinated counterparts. The presence of fluorine changes lipophilicity and can be used to adjust pK_a. It can also modify the conformational properties of a compound and is considered by some as a bioisosteric replacement for a proton or a hydroxy group. This is of relevance particularly if the group replaced is metabolizable. All these facets mean that incorporation of fluorine into a new drug candidate, or analogues of existing pharmaceuticals and natural products, is a well-established strategy to boost the absorption and distribution of a drug and to increase its half-life. Finally, additional potential applications associated with the presence of the NMR active ^{19}F exist. Relatedly, ^{18}F-labelled compounds have proved to be extremely useful biological tools and have been utilized in studies involving Positron Emission Tomography (PET).[1]

Several recent reports have highlighted the value of direct incorporation of fluorine into compounds based around a piperidine ring.[2] In relation to this, Onomura and colleagues[3] have described the efficient electrophilic fluorination of *N*-benzyl, phenyl and methyl carbamate protected enamines using Selectfluor® **2**[4] in the presence of MeOH (Scheme 1). This process led to the formation of the corresponding 3-fluorinated 2-methoxy substituted compounds as an undetermined mixture of *cis*- and *trans*-isomers (e.g. **1a** → **3a**). Compound **3a** was then reported to undergo a diastereoselective Sakurai-type process with allyltrimethylsilane **4** using $BF_3 \cdot Et_2O$ as the Lewis acid. In this case, **5a** was isolated in good yield and significantly, reasonable diastereoselectivity was reported which, it was suggested, favored the *trans*-isomer (*trans*-**5a**:*cis*-**5a**; 79:21).[3] Although not discussed, this stereochemical outcome is consistent with bond formation occurring in a Fürst-Plattner fashion anti to an axially disposed electron-withdrawing fluorine atom, benefiting from secondary orbital overlap and a conformation stabilizing anti-periplanar proton.[5-7]

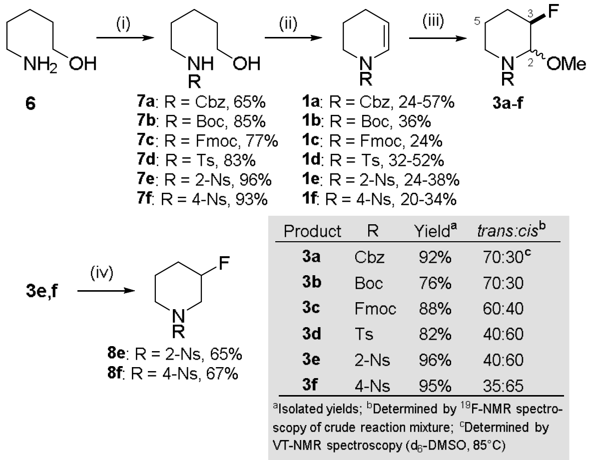


Scheme 1. Two-step conversion of enamine **1a** into 2-allyl-3-fluoropiperidine **5a** and proposed iminium ion intermediates. (Cbz = benzyloxycarbonyl).

Based on our current involvement in the synthesis of substituted piperidine containing compounds[8] we became interested in Onomura's report and realized that this overall method represented an attractive potential route for the construction of 3-fluorinated analogues of several biologically active natural products.

Results and discussion

As shown in Scheme 2, a series of differentially N-protected 2-piperideines **1a**-**f** were prepared from 5-aminopentan-1-ol **6**. Initial N-derivatization led to **7a**-**f** which was followed by a one-pot oxidation-cyclisation-dehydration sequence. The latter step was performed according to a literature procedure[9] and using PCC and silica in DCM as the solvent, *N*-carbamate protected enamines **1a**-**1c** were isolated in moderate yield. The same reaction was performed successfully with *N*-Ts alcohol **7d** to generate **1d**. Similarly, isomeric 2- and 4-Ns sulfonamides **1e** and **1f** could be accessed, albeit in reduced yield. This type of reaction also proceeded successfully using PCC in conjunction with Celite and EtOAc in place of DCM. Although, in our hands, the yields for this process were moderate, the availability of the starting materials means that this two-step process is an attractive method to access this type of compound and offers a viable alternative to existing methods for the synthesis of *N*-sulfonyl 2-piperideines. The corresponding *N*-sulfonyl piperidones (not shown) were the main side-products in these reactions and were readily removed by flash column chromatography.



Product	R	Yield[a]	*trans:cis*[b]
3a	Cbz	92%	70:30[c]
3b	Boc	76%	70:30
3c	Fmoc	88%	60:40
3d	Ts	82%	40:60
3e	2-Ns	96%	40:60
3f	4-Ns	95%	35:65

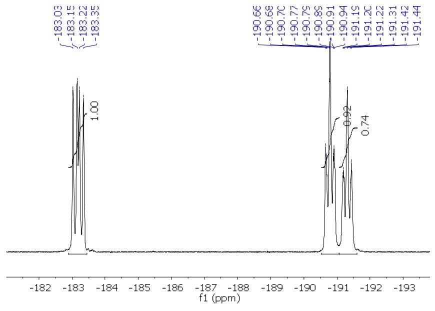
[a]Isolated yields; [b]Determined by ^{19}F-NMR spectroscopy of crude reaction mixture; [c]Determined by VT-NMR spectroscopy (d_6-DMSO, 85°C)

(i) RCl, base; (ii) PCC, EtOAc (or DCM), SiO_2 (or Celite), rt, 16-22 h; (iii) **2**, MeCN-MeOH (1:1), rt, 17-21 h; (iv) Et_3SiH, $BF_3{\cdot}OEt_2$, DCM, -78 °C to rt, 3 h

Scheme 2. The formation of enamines **1a-f** and their reaction with Selectfluor® (**2**) to form **3a-f**. (Abbreviations: Cbz = benzyloxycarbonyl; Boc = *tert*-butyloxycarbonyl; Fmoc = fluorenylmethyloxycarbonyl; Ts = toluenesulfonyl; 2-Ns = 2-nitrobenzenesulfonyl; 4-Ns = 4-nitrobenzenesulfonyl; DCM = dichloromethane; PCC = pyridinium chlorochromate).

Subsequently, enamines **1a-f** were treated with Selectfluor®, **2**, using Onomura's conditions.[3] These reactions proceed with very high levels of conversion and the 3-fluoro-2-methoxy products, **3a-f**, were formed as mixtures of *trans*- and *cis*-diastereomers in excellent yields (Scheme 2). In terms of characterization several points were noted. For compound **3a** the diastereomers proved inseparable chromatographically, and the ^{19}F-, and particularly the ^{1}H-NMR spectra recorded in $CDCl_3$ at room temperature were broad and difficult to interpret due to conformation changes on the NMR spectroscopic timescale.

(a)



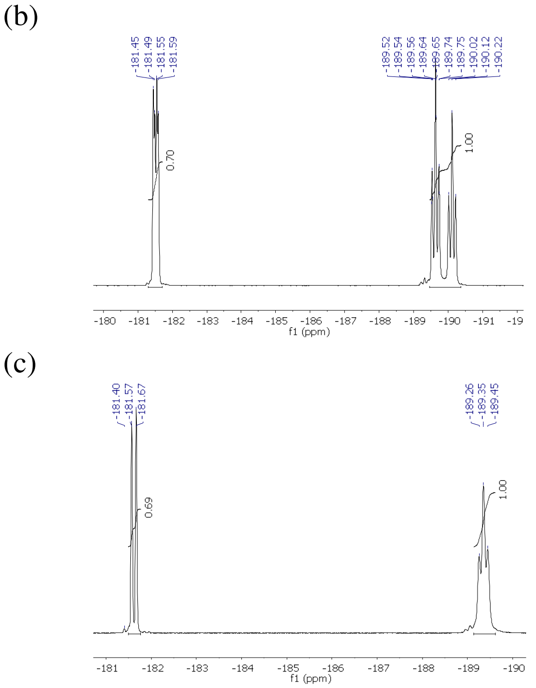


Figure 1. ^{19}F-NMR spectra for *N*-Fmoc-protected **3c**. (a) 376 MHz, $CDCl_3$, 25 °C; (b) 376 MHz, d_6-DMSO, 25 °C, (c) 376 MHz, d_6-DMSO, 85 °C.

An improvement in resolution could be achieved when the spectra were recorded at 85 °C in d_6-DMSO. In the ^{19}F-NMR spectrum two signals at -181.7 ppm and -189.3 ppm were evident. The former was a doublet (at 376 MHz), whereas, the latter was a triplet. The same pattern of NMR spectral data was observed for *N*-Boc and Fmoc piperidines, **3b** and **3c**. Again, the diastereomers proved to be chromatographically inseparable and variable temperature (VT) NMR spectroscopy was utilized to resolve the rotameric forms (see Figure 1 for ^{19}F-NMR spectra for *N*-Fmoc **3c**).

Moving to the *N*-sulfonyl derivatives **3c**-**f**: without the complication of rotamers, the ^{1}H-, ^{13}C- and ^{19}F-NMR spectra (in $CDCl_3$) were well-resolved and the ^{19}F-NMR spectrum contained a doublet at approximately -182.0 ppm and a multiplet between -188 and -190 ppm. When 2-nitrobenzene sulfonamide derivative **3e** was prepared the NMR spectra of the crude reaction product were consistent with those for **3a-c** (at elevated temperature). However, in contrast to the previous examples, these diastereomers proved to be separable and single X-ray crystal structures were obtained for each isomer.[10] The less polar isomer proved to be *trans*-**3e**, and a 1,2-diaxial arrangement for the 2-methoxy and 3-fluoro substituent is evident (see Figure 2).

The ^{19}F-NMR spectrum for this isomer (*trans*-**3e**) showed a multiplet at -189.1 to -189.5 ppm. In the solid-state structure for the more polar *cis*-diastereomer (*cis*-**3e**) the fluorine atom clearly adopts an equatorial position and the methoxy group, buttressed by the N-substituent, is axially orientated. The isomer (*cis*-**3e**) presented a doublet at -182.3 ppm in its ^{19}F-NMR spectrum. Accordingly, in the light of the solid-state data, the multiplicity for the ^{19}F-signals in the respective NMR spectra can be readily rationalized. For a compound with an equatorial F-atom (*e.g. cis*-**3e**) the dihedral angles are such that the 1,3-^{19}F-^{1}H couplings are negligible. In contrast, for the 1,2-diaxial conformer preferred for *trans*-**3e** there is one anti-periplanar hydrogen atom which leads to 1,3-, in addition to 1,2-^{19}F-^{1}H, coupling. An additional spectroscopic feature which is conformer diagnostic is ^{19}F-C-5 coupling. This was present for equatorially orientated compounds and absent for the corresponding axial conformers (see ESI).[11]

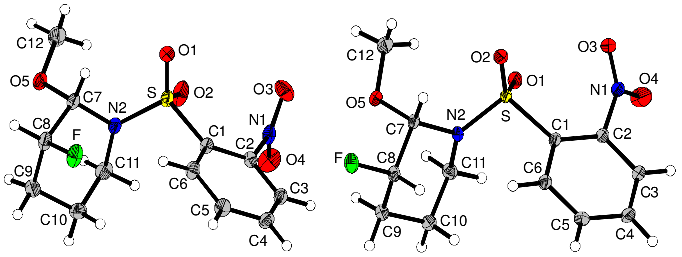


Figure 2. Single crystal X-ray diffraction structures for both *trans*-**3e** and *cis*-**3e** (thermal ellipsoids shown on the 50% probability level).

With this information in hand we were able to re-visit the crude NMR spectra for compounds **3a**-**d** and assign the ratio of *trans*:*cis*-diastereomers (see Scheme 2). Finally, the 4-nitrobenzene sulfonamide **3f** was prepared and although the isomers were not readily separable, based on the understanding of the ^{19}F-NMR spectra, a diastereomeric ratio could be determined. It is of interest to note the different N-substituents do influence the ratio of the diastereomers formed. Carbamate derivatives (**1a**-**c**) favor the formation of *trans*-isomers, whereas, sulfonamides (**1d**-**f**) demonstrate preferential formation of *cis*-isomers, albeit with only modest selectivity. With an investigation of the reactivity of compounds **3a-f** in mind the behavior of the *trans/cis*-mixtures of **3e** and **3f** in the presence of BF$_3$ and triethylsilane was considered. Following a literature method[12] isomeric nosyl protected 3-fluoro piperidines **8e** and **8f** were both formed in reasonable yields. In the case of **8f** an X-ray crystal structure was solved.[10] From this it is evident that in the solid-state, without the 2-substituent and the concomitant A^{1,2}-strain, the fluorine atom preferentially adopts an axial position.[6,13] It is worth noting that for compounds **8e** and **8f** a complex multiplet was observed in their respective ^{19}F-NMR spectra which is consistent with *trans*-1,3-^{1}H-^{19}F-coupling (Figure 3).

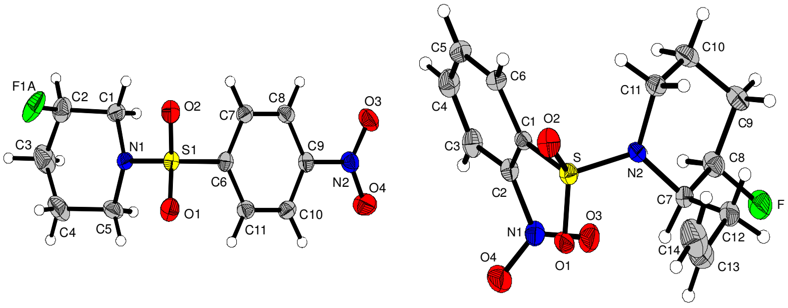
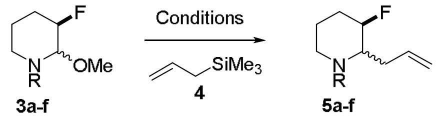


Figure 3. X-Ray crystal structures for compound **8f** and **5e** (thermal ellipsoids shown on the 50% probability level).

The reaction between *N*-acyl/sulfonyl iminium ions with allyltrimethylsilane **4** represents a useful variant of the Sakurai (Hosomi-Sakurai) reaction and leads to valuable 2-functionalized amines.[7,14] Therefore, based on the success of the Lewis-acid activated-reduction process described above the functionalization of **3a-f** was next studied (Scheme 3). Under Onomura's $BF_3 \cdot OEt_2$-mediated conditions[3] **3a** was efficiently converted into **5a** (use of $TiCl_4$ was not successful due, we presume, to instability of the Cbz group in the presence of this Lewis acid). However, unambiguous characterization of this compound using NMR spectroscopy represented a challenge. ^{1}H-NMR spectroscopy in $CDCl_3$ at rt indicated loss of the methoxy group. However, the remaining broad peaks were not well resolved.



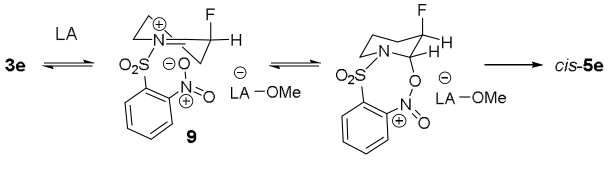
Entry	Product	R	Conditions	Yield	*trans:cis*[a]
1	**5a**	Cbz	$BF_3 \cdot OEt_2$, DCM, -78 °C to rt, 18 h	84%	35:65[b]
2	**5b**	Boc	$TiCl_4$, or $BF_3 \cdot OEt_2$	-[c]	-
3	**5c**	Fmoc	$BF_3 \cdot OEt_2$, DCM, -78 °C to rt,18 h	77%	40:60
4	**5d**	Ts	$BF_3 \cdot OEt_2$, DCM, -78 °C to rt,18 h	78%[d]	40:60
5	**5e**	2-Ns	$BF_3 \cdot OEt_2$, DCM, -78 °C to rt, 2 h	82%	20:80
6	**5e**	2-Ns	$TiCl_4$, DCM, -78 °C to rt, 18 h	58%	5:95
7	**5f**	4-Ns	$TiCl_4$, DCM, -78 °C to rt, 18 h	38%[d]	35:65

[a] Determined by ^{19}F-NMR spectroscopy of the crude reaction product; [b] Determined by VT-NMR (d_6-DMSO, 85 °C); [c] Unidentified products; [d] Combined yield of separated diastereomers

Scheme 3. The allylation of 3-fluoropiperidines **3a-f.**

In d_6-DMSO at elevated temperature (85 °C) an improvement in resolution was observed and the ^{19}F-NMR spectrum for crude **5a** revealed a doublet at -179.1 ppm and a multiplet between -179.2 and -179.7 ppm in a ratio of 65:35. Based on our understanding of the relationship between the conformation of the 2-methoxy substituted compounds **3a-f**, and their influence on the multiplicity of the corresponding ^{19}F-signals, we propose that the *cis*-isomer is the major diastereomer in this case (see below for further evidence supporting this conclusion). It should be noted that this inference differs from Onomura's report[3] which stated that *trans*-**5a** was the main isomer formed from **3a** (see Scheme 1). Next the Boc-protected compound **3b** was considered (Scheme 3, Entry 2). In this case, using either $BF_3 \cdot OEt_2$, or $TiCl_4$, only the formation of unidentified products was observed reflecting the incompatibility of the Boc-group with these reaction conditions. In contrast, Fmoc-protected **3c** afforded adduct **5c** as an inseparable mixture of diastereomers (40:60) in 77% (Scheme 3, Entry 3). Subsequently, sulfonamide precursors **3d-f** were considered (Scheme 3, Entries 3-6). *N*-Tosyl **3d** was converted into **5d**, as a mixture of diastereomers. NMR spectroscopy of the crude reaction product indicated a 40:60 mixture of two diastereomers. Again, the major isomer exhibited a doublet in the ^{19}F-NMR spectrum at -179.1 ppm, whereas, the minor isomer exhibited a multiplet between -179.5 and -179.9 ppm. These diastereomers proved chromato-graphically separable and chemically pure samples of each diastereomer were obtained. The diastereomeric mixture of the 2-Ns derivatized 3-fluoro-2-methoxypiperidine **3e** was subsequently studied. Initially, using BF_3, a 20:80 mixture of diastereomers was obtained. As before the main isomer exhibited a characteristic doublet in its ^{19}F-NMR spectrum. Although the diastereomers were not chromatographically separable the main isomer could be obtained by recrystallisation from EtOAc. Single crystal X-ray diffraction confirmed the assumption (based on ^{19}F-NMR spectroscopy) that this was indeed the *cis*-isomer. The 2-allyl substituent occupies an axial orientation, whereas, the 3-fluoro substituent resides in an equatorial position (Figure 3). When the same reaction was performed with $TiCl_4$ an increase in diasteroselectivity was observed and in this case only very small amounts of the *trans*-isomer was detected (*trans:cis*; 5:95).[15] In order to probe the influence of the aromatic nitro substituent on this process the 4-Ns isomer **3f** was subsequently examined. Use of the $TiCl_4$ conditions led to a reaction that favored *cis*-**5f** but with low levels of selectivity that were, in fact, comparable to both the *N*-Cbz and *N*-tosyl compounds, **5a** and **5d**. In the case of **5f**, the diastereomers proved chromatographically separable. However, the reaction did not proceed to completion and some *cis*-**3f** remained. This proved to co-run with *cis*-**5f**, thus impacting on the overall yield. The latter mixture of *cis*-**3f** and *cis*-**5f** could, however, be resolved chemically using the BF_3-Et_3SiH reduction protocol (see Scheme 2) which enabled isolation of a pure sample of *cis*-**5f** (*cis*-**5f** and **8f** proved to elute at different rates).[15]

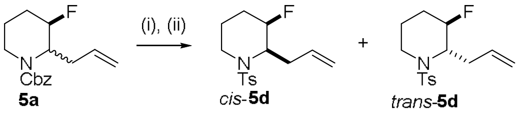
We speculate that the improved diastereoselectivity observed using the 2-Ns group results from an interaction between the nitro-substituent and the electrophilic iminium ion formed during the reaction (e.g. **9**, Scheme 4), which, akin to well-established modes of neighboring group participation, leads to the enhanced *cis*-stereochemistry observed (particularly when Ti(IV) is used as the Lewis acid[16]). Although uncommon, several reports exist which indicate that weakly nucleophilic/basic aromatic nitro-groups within substrates can influence the direction of chemistry in several quite different chemical processes.[17] Despite the relatively widespread use of the 2-Ns group in organic chemistry[18] to the best of our knowledge this type of effect has not been reported for this particular sulfonamide.



Scheme 4. *N*-2-Ns iminium ion **9** (LA = Lewis acid).

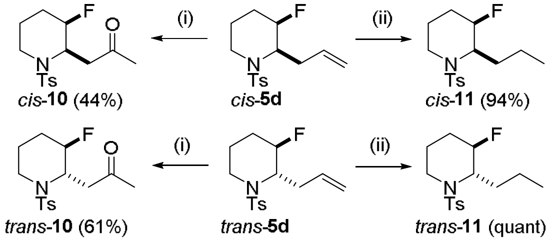
Returning to the stereochemical outcome of the Sakurai-type reaction with the *N*-Cbz protected piperidine **3a**, its deprotection and subsequent conversion to one of the characterized sulfonamides was considered. Treatment of **5a** (mixture of diastereomers) with a solution of HBr in acetic acid led to removal of the Cbz group (Scheme 5). Under the reaction conditions employed no significant HBr-alkene addition was observed. The intermediate piperidinium salt was then treated with TsCl in order to form **5d** as a mixture of diastereomers. Analysis of the crude reaction product by ^{19}F-NMR spectroscopy indicated a *trans:cis* ratio of 35:65 which was consistent with evidence from the d_6-DMSO NMR spectroscopic study of *trans/cis*-**5a** at 85 °C.

This evidence serves to unequivocally confirm the conclusion that reaction of **3a** with allyltrimethylsilane **4** is *cis*-, not *trans*-selective.



(i) HBr-AcOH, DCM, 0 °C to rt, 1.5 h; (ii) TsCl, Et_3N, DMAP (cat.), MeCN, 65 °C, 17 h, 57% (*cis*-**5d**:*trans*-**5d**; 65:35)

Scheme 5. Conversion of Cbz-protected **5a** into Ts-protected *cis*- and *trans*-**5d**.



(i) $Pd(OAc)_2$, CuCl, MeCN-H_2O (10:1), 65 °C, 18 h; (ii) H_2, EtOAc, H-Cube®, rt, 10 min.

Scheme 6. Synthesis of N-protected 3-fluoropelletierine **10** and 3-fluoroconiine **11**.

As shown in Scheme 6, separated samples of *cis*- and *trans*-**5d** were each converted into Ts-protected 3-fluoro-substituted forms of the 2-substituted piperidine natural products pelletierine and coniine by a Wacker oxidation[19] and hydrogenation respectively. In each instance no incompatibility with the fluoro-group was detected and both *cis*- and *trans*-diastereomers of **10** and **11** were isolated and characterized.

Conclusions

In conclusion, the use of Selectfluor® to introduce a fluoro-substituent to *N*-carbamate and sulfonamide protected 2-piperideines has been described. In the case of the former, NMR spectroscopic analysis proved challenging. However, using the sulfonamide derivatives the NMR spectroscopic data was more readily interpreted. This was aided by X-ray crystallography which together with the NMR data enabled not only the relative stereochemistry of the compounds to be determined but also allowed interpretation of the preferred conformation of the piperidine ring. Subsequent Sakurai-type reactions led to the isolation of 2-allyl-3-fluoro substituted piperidines and it was found that these processes are *cis*, not *trans*, selective. Optimal selectivity was observed for the *N*-2-Ns derivative and we speculate that this occurs as the result of a non-bonding interaction which hinders attack leading to the *trans*-diastereomer. Based on the widespread use of this type of sulfonyl group we believe this type of effect may have wider reaching synthetic implications. Finally, we demonstrated that the C-F bond is not significantly affected during functional group manipulations of the piperidinyl nitrogen atom and the 2-allyl substituent.

Experimental Section

General directions. Reagents from commercial suppliers were used without further purification. ^{1}H, ^{19}F and ^{1}H-decoupled ^{13}C NMR spectra were recorded on Varian Unity 400 and 500 MHz spectrometers and coupling constants (*J*) are quoted in Hertz. All values are reported in ppm and were referenced to either tetramethylsilane or residual protonated chloroform. Assignment was aided by two-dimensional NMR experiments (g-COSY and HSCQ). High resolution mass spectra were carried out on a VG analytical 70-E mass spectrometer under electrospray ionisation conditions (ESI) and a time-of-flight (TOF) analyser. Infrared spectra were recorded on a Bruker Alpha FTIR spectrometer. Melting points were recorded on a Gallenkamp electrothermal melting point apparatus. Thin-layer chromatography was performed on silica coated aluminium sheets and compounds were visualized with UV light and aqueous potassium permanganate, followed by heating. Merck silica gel (0.040-0.063 mm) was used for flash column chromatography.

Benzyl (5-hydroxypentyl)carbamate 7a.[7a] A solution of 5-aminopentanol **6** (1.90 g, 18.39 mmol, 1 equiv.) in DCM (30 mL) was cooled to 0 °C (ice-water) and then treated sequentially with benzyl chloroformate (2.60 mL, 18.39 mmol, 1 equiv.) and TEA (3.85 mL, 27.59 mmol, 1.5 equiv.). Stirring was continued for 5 h during which time room temperature was reached. TLC analysis (*c*-Hex-EtOAc; 3:1) indicated consumption of the benzyl chloroformate. 1 M HCl (30 mL) was added and the resultant aqueous layer was extracted with DCM (30 mL). The combined organic layers were washed with water (50 mL) and the organic phase was dried over anhydrous $MgSO_4$ and concentrated. The residue was then purified by flash column chromatography (*c*-Hex-EtOAc; 3:1). This gave **7a** (2.83 g, 65%) as a viscous colorless oil. R_f = 0.20 (*c*-Hex-EtOAc; 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.29-1.67 (6H, m, CH_2), 3.21 (2H, q, *J* = 6.5 Hz, CH_2), 3.64 (2H, q, *J* = 5.5 Hz, CH_2), 4.77 (1H, s(br), NH), 5.09 (2H, s, CH_2), 7.27-7.39 (5H, m, ArH) ppm.

Benzyl 3,4-dihydropyridine-1(2*H*)-carboxylate 1a.[7a] At room temperature a solution of **7a** (1.06 g, 4.47 mmol, 1 equiv.) in DCM (60 mL) was treated with silica-gel (1.93 g) and PCC (1.93 g, 8.94 mmol, 2 equiv.). Stirring was maintained for 18 h before Celite (*ca.* 9 g) was added and the mixture filtered through Celite, washing with DCM (2 x 60 mL). The solvent was then removed under reduced pressure before the residue was purified by flash column chromatography (*c*-Hex-EtOAc; 3:1). This gave **1a** (232 mg, 24%) as a viscous colorless oil. R_f = 0.80 (*c*-Hex-EtOAc; 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.71-1.85 (2H, m, CH_2), 1.94-2.03 (2H, m, CH_2), 3.55-3.64 (2H, m, CH_2), 4.82 (0.6H, dt, *J* = 3.5, 8.5 Hz, CH), 4.93 (0.4H, dt, *J* = 3.5, 8.5 Hz, CH), 5.15 (2H, s, CH_2), 6.78 (0.6H, d, *J* = 8.5 Hz, CH), 6.89 (0.4H, d, *J* = 8.5 Hz, CH), 7.21-7.38 (5H, m, ArH) ppm.

***cis*-Benzyl (2*R**,3*R**)-3-fluoro-2-methoxypiperidine-1-carboxylate and *trans*-benzyl (2*S**,3*R**)-3-fluoro-2-methoxypiperidine-1-carboxylate 3a**.[3] At room temperature enamine **1a** (232 mg, 1.06 mmol, 1 equiv.) in a 1:1 v/v MeCN-MeOH (16 mL) mixture was treated with Selectfluor® **2** (414 mg, 1.17 mmol, 1.1 equiv.). Stirring was continued for 20 h at rt. The reaction mixture was extracted with water (30 mL) and DCM (3 x 40 mL). The organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give the title compounds **3a** (259 mg, 92%) as a viscous colorless oil. These diastereomers proved chromatographically inseparable (*cis:trans*; 30:70 by VT NMR in d_6-DMSO) and could be carried forward to the next step without additional purification. R_f = 0.75 (*c*-Hex-EtOAc; 3:1); $C_{14}H_{18}NO_3F$ (MNa^+) calcd. 290.1168; found 290.1163 (-1.9 ppm); ^1H NMR (500 MHz, 85 °C, d_6-DMSO): δ = 1.40-1.56 (1H, m, CH_2), 1.59-2.04 (3H, m, CH_2), 2.83 (0.3H, t, J = 13.0 Hz, CH_2), 2.95 (0.7H, t, J = 13.0 Hz, CH_2), 3.20-3.30 (3H, m, CH_3), 3.77 (0.3H, d, J = 13.0 Hz, CH_2), 3.90 (0.7H, d, J = 13.0 Hz, CH_2), 4.44-4.60 (0.3H, m, CH), 4.70 (0.7H, d, J = 47.5 Hz, CH), 5.11-5.22 (2H, m, CH_2), 5.34 (0.7H, d, J = 7.5 Hz, CH), 5.42 (0.3H, s(br), CH), 7.26-7.43 (5H, m, ArH) ppm; ^{19}F NMR (470 MHz, 85 °C, d_6-DMSO): δ = -181.7 (0.3F, d, J = 47.0 Hz, CF-*cis*), -189.3 (0.7F, t, J = 47.5 Hz, CF-*trans*) ppm.

***cis*-Benzyl (2*R**,3*R**)-2-allyl-3-fluoropiperidine-1-carboxylate and *trans*-benzyl (2*S**,3*R**)-2-allyl-3-fluoropiperidine-1-carboxylate 5a**.[3] Under N_2 a solution of **3a** (*trans*:*cis*; 70:30 - 259 mg, 0.97 mmol, 1 equiv.) and allyltrimethylsilane **4** (0.31 mL, 1.94 mmol, 2 equiv.) in dry DCM (25 mL) was cooled to -84°C (liquid N_2-EtOAc). Then $BF_3\cdot Et_2O$ (0.14 mL, 0.90 mmol, 2 equiv.) was added in a dropwise fashion at -84°C. The mixture was stirred for 1 h, during which period room temperature was reached. The mixture was then stirred overnight at rt for 19 h. DCM (30 mL) and sat. $NaHCO_{3(aq)}$ (30 mL) were added and the resultant organic phase was further extracted with DCM (2 x 30 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to afford the title compound **5a** as an inseparable mixture of diastereomers (*cis:trans*; 65:35 by VT NMR in d_6-DMSO). In this way **5a** (226 g, 84 %) was obtained as a pale-yellow oil. R_f = 0.65 (*c*-Hex-EtOAc; 3:1); $C_{16}H_{22}NO_2F$ (MH^+) calcd. 278.1556; found 278.1550 (-2.3 ppm); ^1H NMR (500 MHz, 85 °C, d_6-DMSO): δ = 1.40-1.52 (1H, m, CH_2), 1.58-1.85 (2H, m, CH_2), 1.84-1.96 (1H, m, CH_2), 2.25-2.35 (2H, m, CH_2), 2.82 (0.65H, t, J = 13.5 Hz, CH_2), 2.94 (0.35H, t, J = 13.5 Hz, CH_2), 3.85 (0.65H, d, J = 13.5 Hz, CH_2), 3.97 (0.35H, d, J = 13.5 Hz, CH_2), 4.43 (0.35H, dt, J = 7.5, 15.5 Hz, CH), 4.48-4.55 (0.65H, m, CH), 4.57-4.76 (1H, m, CH), 4.94-5.14 (4H, m, CH_2), 5.62-5.78 (1H, m, CH), 7.26-7.42 (5H, m, ArH) ppm; ^{19}F NMR (470 MHz, 85 °C, d_6-DMSO): δ = -179.1 (0.6F, d, J = 47.5 Hz, CF-*cis*), -179.2 – -179.7 (0.4F, m, CF-*trans*) ppm.

***tert*-Butyl (5-hydroxypentyl)carbamate 7b**.[20] A solution of 5-aminopentanol **6** (1.50 g, 14.56 mmol, 1 equiv.) in a 1:1 v/v acetone: water (18 mL) mixture was cooled to 0 °C (ice-water) and then treated portion-wise with Boc_2O (3.17g, 14.54 mmol, 1 equiv.) and TEA (2.23 mL, 16.00 mmol, 1.1 equiv.). Stirring was continued at 0°C for 0.5 h then at room temperature for 19 h. TLC analysis (*c*-Hex-EtOAc; 1:1) indicated consumption of the Boc anhydride. EtOAc (20 mL) was added and the resultant organic layer was extracted. The organic phase was then washed with water (30 mL) and sat. $NaCl_{(aq)}$ (30 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure to give **7b** (2.52 g, 85%) as a pale-yellow oil. R_f = 0.30 (*c*-Hex-EtOAc; 1:1); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.27-1.57 (15H, m, CH_2, CH_3), 2.52-2.77 (1H, s(br), OH), 2.98-3.11 (2H, m, CH_2), 3.55 (2H, t, J = 6.5 Hz, CH_2), 4.75 (1H, s(br), NH) ppm.

***tert*-Butyl 3,4-dihydropyridine-1(2*H*)-carboxylate 1b**.[21] At room temperature a solution of **7b** (2.25 g, 11.07 mmol, 1 equiv.) in DCM (40 mL) was treated with silica (4.77 g) and PCC (4.77 g, 22.14 mmol, 2 equiv.). Stirring was maintained for 16 h and the mixture was then filtered through a column of Florisil using Et_2O (20 mL) and DCM (5 x 20 mL). The solvent was removed under reduced pressure before the residue was purified by flash column chromatography (*c*-Hex-EtOAc; 8:1). This gave **1b** (730 mg, 36%) as a colorless viscous oil. R_f = 0.65 (*c*-Hex-EtOAc; 8:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42 (s, 9H, CH_3), 1.66-1.82 (2H, m, CH_2), 1.89-2.02 (2H, m, CH_2), 3.41-3.55 (2H, m, CH_2), 4.69-4.76 (0.6H, m, CH), 4.82 (0.4H, s(br), CH), 6.65 (0.6H, d, J = 8.0 Hz, CH), 6.78 (0.4H, d, J = 7.5 Hz, CH) ppm.

***cis*-(2*R**,3*R**)-*tert*-Butyl 3-fluoro-2-methoxypiperidine-1-carboxylate and *trans*-(2*R**,3*S**)-*tert*-butyl 3-fluoro-2-methoxypiperidine-1-carboxylate 3b**. As described for **1a**, at room temperature enamine **1b** (121 mg, 0.66 mmol, 1 equiv.) in a 1:1 v/v MeCN-MeOH (7 mL) mixture was treated with Selectfluor® **2** (258 mg, 0.73 mmol, 1.1 equiv.). Stirring was continued for 20 h at rt. The reaction mixture was extracted with water (20 mL) and DCM (2 x 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give the title compounds **3b** (116 mg, 76%) as an inseparable mixture of diastereomers (*cis:trans*; 30:70 by VT NMR in d_6-DMSO) in the form of a viscous pale-yellow oil. R_f = 0.70 (*c*-Hex-EtOAc; 3:1); IR (neat): ν_{max} = 2935, 2876, 2831, 1697, 1412, 1366, 1270, 1257, 1156, 1125, 1084, 1072, 960, 877, 771, 668 cm^{-1}; HRMS (ES$^+$) $C_{11}H_{20}NO_3FNa$ (MNa$^+$) calcd. 256.1325; found 256.1324 (-0.4 ppm); ^{1}H NMR (500 MHz, 85 °C, d_6-DMSO): δ = 1.44 (9H, s, CH_3), 1.55-1.77 (2H, m, CH_2), 1.78-1.88 (2H, m, CH_2), 2.71 (0.3H, td, J = 2.5, 13.0 Hz, CH_2), 2.82 (0.7H, td, J = 2.5, 13.0 Hz, CH_2), 3.24 (2.1H, s, CH_3), 3.26 (0.9H, s, CH_3), 3.62-3.71 (0.3H, m, CH_2), 3.76-3.83 (0.7H, m, CH_2), 4.38-4.56 (0.3H, m, CH), 4.64 (0.7H, dq, J = 2.5, 47.0 Hz, CH), 5.19-5.28 (0.7H, m, CH), 5.32 (0.3H, t, J = 3.0 Hz, CH) ppm; ^{13}C NMR (125 MHz, 85 °C, d_6-DMSO): δ = 18.1 (CH_2), 22.4 (d, J = 10.0 Hz, CH_2), 23.5 (d, J = 20.0 Hz, CH_2), 23.8 (d, J = 19.0 Hz, CH_2), 27.5 (CH_3), 36.6 (CH_2), 37.1 (CH_2), 54.0 (CH_3), 54.4 (CH_3), 79.1 (C), 79.4 (C), 81.4-82.0 (m, CH), 85.3 (d, J = 169.5 Hz, CH-*trans*), 88.3 (d, J = 183.0 Hz, CH-*cis*), 153.5 (CO), 154.2 (CO) ppm; ^{19}F NMR (470 MHz, 85 °C, d_6-DMSO): δ = -181.4 (0.3F, d, J = 46.0 Hz, CF-*cis*), -189.0 (0.7F, t, J = 47.0 Hz, CF-*trans*) ppm.

(9*H*-Fluoren-9-yl)methyl (5-hydroxypentyl)carbamate 7c.[22] A solution of 5-aminopentanol **6** (1.32 g, 12.82 mmol, 1.1 equiv.) in acetone (20 mL) was cooled to 0°C (ice-water) and then treated with sat. $NaHCO_{3(aq)}$ (2.5mL) and FmocCl (3.01g, 11.65 mmol, 1 equiv.). Stirring was continued at 0°C for 0.5 h, then at room temperature for 7 h. TLC analysis (*c*-Hex-EtOAc; 1:1) indicated consumption of the FmocCl. Solvent was removed under reduced pressure and the solid residue re-suspended in DCM (40 mL). The organic phase was then washed with water (2 x 40 mL) and sat. $NaCl_{(aq)}$ (30 mL) and dried over $MgSO_4$. After filtration the solvent was removed under reduced pressure and the solid residue crystallised

(EtOAc-PE; 7:1) to give **7c** (3.20 g, 77%) as a white solid. R_f = 0.30 (DCM-MeOH; 20:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32-1.63 (6H, m, CH_2), 3.24 (2H, q, *J* = 6.5 Hz, CH_2), 3.64 (2H, t, *J* = 6.5 Hz, CH_2), 4.21 (1H, t, *J* = 6.5 Hz, CH), 4.41 (2H, d, *J* = 6.5 Hz, CH_2), 4.81 (1H, s(br), NH), 7.31 (2H, t, *J* = 7.5 Hz, ArH), 7.40 (2H, t, *J* = 7.5 Hz, ArH), 7.59 (2H, d, *J* = 7.5 Hz, ArH), 7.76 (2H, d, *J* = 7.5 Hz, ArH) ppm.

(9*H*-Fluoren-9-yl)methyl 3,4-dihydropyridine-1(2*H*)-carboxylate 1c. At room temperature a solution of **7c** (898 mg, 2.76 mmol, 1 equiv.) in DCM (20 mL) was treated with silica (1.20 g) and PCC (1.19 g, 5.52 mmol, 2 equiv.). Stirring was maintained for 22 h and the mixture was then filtered through a column of Florisil using Et_2O (100 mL). The solvent was removed under reduced pressure before the residue was purified by flash column chromatography (*c*-Hex-EtOAc; 40:1). This gave **1c** (200 mg, 24%) as a white solid. M. p. 89-91 °C; R_f = 0.40 (*c*-Hex-EtOAc; 8:1); IR (neat): ν_{max} = 3039, 2924, 1689, 1413, 1341, 1259, 1228, 1148, 974, 785, 763, 717, 414 cm^{-1}; HRMS (ES$^+$) $C_{20}H_{19}NO_2Na$ (MNa$^+$) calcd. 328.1313; found 328.1298 (-4.7 ppm); ^{1}H NMR (500 MHz, $CDCl_3$): 1.82-1.91 (2H, m, CH_2), 2.09 (2H, s(br), CH_2), 3.61-3.68 (2H, m, CH_2), 4.29 (1H, t, *J* = 7.5 Hz, CH), 4.40-4.48 (2H, m, CH_2), 4.95 (0.6H, dt, *J* = 3.5, 8.0 Hz, CH), 5.01 (0.4H, dt, *J* = 3.5, 8.0 Hz, CH), 6.85 (0.6H, d, *J* = 8.0 Hz, CH), 6.92 (0.4H, d, *J* = 8.0 Hz, CH), 7.34 (2H, td, *J* = 1.0, 7.5 Hz, ArH), 7.42 (2H, t, *J* = 7.5 Hz, ArH), 7.61 (2H, d, *J* = 7.5 Hz, ArH), 7.79 (2H, d, *J* = 7.5 Hz, ArH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.3 (CH_2), 21.6 (CH_2), 21.7 (CH_2), 21.8 (CH_2), 42.3 (CH_2), 42.5 (CH_2), 47.3 (CH), 67.7 (CH_2), 67.9 (CH_2), 106.85 (CH), 106.95 (CH), 120.1 (CH), 124.8 (CH), 125.1 (CH), 125.15 (CH), 125.4 (CH), 127.2 (CH), 127.8 (CH), 141.4 (C), 144.0 (C), 153.2 (CO), 153.6 (CO) ppm.

***cis*-(2*R**,3*R**)-(9*H*-Fluoren-9-yl)methyl 3-fluoro-2-methoxypiperidine-1-carboxylate and *trans*-(2*S**,3*R**)-(9*H*-fluoren-9-yl)methyl 3-fluoro-2-methoxypiperidine-1-carboxylate 3c**. As described for **1a**, at room temperature enamine **1c** (127 mg, 0.42 mmol, 1 equiv.) in a 1:1 v/v MeCN-MeOH (7 mL) mixture was treated with Selectfluor® **2** (164 mg, 0.46 mmol, 1.1 equiv.). Stirring was continued for 21 h at rt. The reaction mixture was extracted with water (10 mL) and DCM (2 x 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to give the title compounds **3c** (131 mg, 88%) as an inseparable mixture of diastereomers (*cis:trans*; 40:60). R_f = 0.55 (*c*-Hex-EtOAc; 3:1); IR (neat): ν_{max} = 3066, 2949, 1699, 1488, 1418, 1259, 1085, 1071, 963, 758, 738 cm^{-1}; HRMS (ES$^+$) $C_{21}H_{22}NO_3FNa$ (MNa$^+$) calcd. 378.1481; found 378.1497 (+4.1 ppm); ^{1}H NMR (500 MHz, 85 °C, d_6-DMSO): δ = 1.28-1.43 (1H, m, CH_2), 1.51-1.88 (3H, m, CH_2), 2.66 (0.4H, td, *J* = 2.5, 13.0 Hz, CH_2), 2.82 (0.6H, d, *J* = 2.5, 13.0 Hz, CH_2), 3.03 (3H, s, CH_3), 3.55 (0.4H, d, *J* = 12.0 Hz, CH_2), 3.74 (0.6H, d, *J* = 12.0 Hz, CH_2), 4.21-4.37 (0.4H, m, CH), 4.30 (1H, t, *J* = 5.5 Hz, CH), 4.48-4.68 (2.6H, m, CH, CH_2), 5.09 (1H, s(br), CH), 7.28-7.36 (2H, m, ArH), 7.41 (2H, t, *J* = 7.5 Hz, ArH), 7.59-7.68 (2H, m, ArH), 7.86 (2H, d, *J* = 7.5 Hz, ArH) ppm; ^{13}C NMR (125 MHz, 85 °C, d_6-DMSO): δ = 18.0 (CH_2), 22.2 (d, *J* = 9.5 Hz, CH_2), 23.4 (d, *J* = 20.5 Hz, CH_2), 23.7 (d, *J* = 19.0 Hz, CH_2), 36.7 (CH_2), 37.3 (CH_2), 46.5 (CH), 46.7 (CH), 53.9 (CH_3), 54.3 (CH_3), 66.0 (CH_2), 66.1 (CH_2), 81.65 (d, *J* = 34.0 Hz, CH), 81.7 (d, *J* = 23.0 Hz, CH), 85.1 (d, *J* = 169.5 Hz, *trans*-CH), 88.0 (d, *J* = 183.0 Hz, *cis*-CH), 119.5 (CH), 124.2 (CH), 124.3 (CH), 126.5 (CH), 127.1 (CH), 140.46 (C), 140.50 (C), 140.53 (C), 154.1

(CO), 154.8 (CO) ppm; ^{19}F NMR (470 MHz, 85 °C, d$_6$-DMSO): δ = -181.6 (0.4F, d, *J* = 47.0 Hz, CF-*cis*), -189.4 (0.6F, t, *J* = 45.0 Hz, CF-*trans*) ppm.

***cis*-(2*R**,3*R**)-(9*H*-Fluoren-9-yl)methyl 2-allyl-3-fluoropiperidine-1-carboxylate and *trans*-(2*S**,3*R**)-(9*H*-fluoren-9-yl)methyl 2-allyl-3-fluoropiperidine-1-carboxylate 5c**. Under N_2 a solution of **3c** (*trans*:*cis*; 60:40 - 122 mg, 0.34 mmol, 1 equiv.) and allyltrimethylsilane **4** (0.11 mL, 0.68 mmol, 2 equiv.) in dry DCM (15 mL) was cooled to -84°C (liquid N_2-EtOAc). Then $BF_3{\cdot}Et_2O$ (0.08 mL, 0.68 mmol, 2 equiv.) was added in a dropwise fashion at -84°C. The mixture was stirred for 1 h, during which period room temperature was reached. The mixture was then stirred overnight at rt for 19 h. DCM (20 mL) and sat. $NaHCO_{3(aq)}$ (20 mL) were added and the resultant organic phase was further extracted with DCM (2 x 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to afford the title compound **5c** as an inseparable mixture of diastereomers (*cis:trans*; 60:40 by VT NMR in d$_6$-DMSO). In this way **5c** (95 mg, 77 %) was obtained as a pale-yellow oil. R_f = 0.50 (*c*-Hex-EtOAc; 3:1); IR (neat): ν_{max} = 3067, 2948, 1692, 1610, 1448, 1424, 1244, 1150, 1053, 957, 757, 738, 674 cm^{-1}; HRMS (ES$^+$) $C_{23}H_{24}NO_2FNa$ (MNa$^+$) calcd. 388.1689; found 388.1695 (+1.6 ppm); ^{1}H NMR (500 MHz, 85 °C, d$_6$-DMSO): δ = 1.22-1.37 (1H, m, CH_2), 1.39-1.48 (1H, m, CH_2), 1.53-1.91 (2H, m, CH_2), 2.17-2.24 (1.4H, m, CH_2), 2.31-2.43 (0.6H, m, CH_2), 2.70 (0.6H, td, *J* = 3.0, 13.5 Hz, CH_2), 2.86 (0.4H, td, *J* = 3.0, 13.5 Hz, CH_2), 3.66 (0.6H, d, *J* = 13.5 Hz, CH_2), 3.86 (0.4H, d, *J* = 13.5 Hz, CH_2), 4.21-4.53 (3.6H, m, CH-*cis*, CH, CH_2), 4.26 (1H, t, *J* = 6.0 Hz, CH), 4.63 (0.4H, dd, *J* = 2.5, 47.0 Hz, CH-*trans*), 4.92 (0.6H, d, *J* = 10.0 Hz, CH_2), 4.99 (0.4H, d, *J* = 10.0 Hz, CH_2), 5.03 (0.6H, d, *J* = 17.0 Hz, CH_2), 5.06 (0.4H, d, *J* = 16.5 Hz, CH_2), 5.46-5.65 (1H, m, CH), 7.28-7.35 (2H, m, ArH), 7.41 (2H, t, *J* = 7.5 Hz, ArH), 7.59-7.65 (2H, m, ArH), 7.85 (2H, d, *J* = 7.5 Hz, ArH) ppm; ^{13}C NMR (125 MHz, 85 °C, d$_6$-DMSO): δ = 18.4 (CH_2), 22.3 (d, *J* = 9.5 Hz, CH_2), 23.6 (d, *J* = 21.5 Hz, CH_2), 24.4 (d, *J* = 18.5 Hz, CH_2), 27.7 (CH_2), 31.7 (d, *J* = 9.5 Hz, CH_2), 36.8 (CH_2), 37.7 (CH_2), 46.6 (CH), 46.7 (CH), 52.6 (d, *J* = 24.5 Hz, CH), 54.0 (d, *J* = 21.0 Hz, CH), 65.9 (CH_2), 66.0 (CH_2), 87.9 (d, *J* = 172.0 Hz, CH), 88.1 (d, *J* = 179.5 Hz, CH), 116.3 (CH_2), 116.7 (CH_2), 119.4 (CH), 119.45 (CH), 124.25 (CH), 124.27 (CH), 124.3 (CH), 124.35 (CH), 126.5 (CH), 127.0 (CH), 133.6 (CH), 133.9 (CH), 140.41 (C), 140.43 (C), 140.5 (C), 143.5 (C), 143.55 (C), 154.3 (CO), 154.6 (CO) ppm; ^{19}F NMR (470 MHz, 85 °C, d$_6$-DMSO): δ = -179.1 (0.6F, d, *J* = 47.5 Hz, CF-*cis*), -179.6 (0.4F, t, *J* = 44.0 Hz, CF-*trans*) ppm.

***N*-(5-Hydroxypentyl)-4-methylbenzenesulfonamide 7d**.[20] A solution of 5-aminopentanol **6** (475 mg, 4.60 mmol, 1 equiv.) in DCM (20 mL) was cooled to 0 °C (ice-water) and then treated sequentially with TsCl (877 mg, 4.60 mmol, 1 equiv.) and TEA (0.96 mL, 6.90 mmol, 1.5 equiv.). Stirring was continued at 0°C for 1h then at room temperature for 17h. TLC analysis (*c*-Hex-EtOAc; 1:1) indicated consumption of the sulfonyl chloride. 1 M HCl (30 mL) was added and the resultant aqueous layer was extracted with DCM (30 mL). The combined organic layers were washed with water (50 mL) and the organic phase was dried over $MgSO_4$. The residue was purified by flash column chromatography (*c*-Hex-EtOAc; 3:1) to give **7d** (978 mg, 83 %) as an off-white solid. R_f = 0.10 (*c*-Hex-EtOAc; 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31-1.37 (2H, m, CH_2), 1.44-1.53 (4H, m, CH_2), 2.43 (3H, s, CH_3), 2.90 (2H, q, *J* = 7.0

Hz, CH_2), 3.63 (2H, t, *J* = 6.5 Hz, CH_2), 4.76 (1H, s(br), NH), 7.31 (2H, d, *J* = 8.0 Hz, ArH), 7.75 (2H, d, *J* = 8.0 Hz, ArH) ppm.

1-Tosyl-1,2,3,4-tetrahydropyridine 1d.[20] At room temperature a solution of **7d** (329 mg, 1.28 mmol, 1 equiv.) in DCM (20 mL) was treated with Celite (0.5 g) and PCC (552 mg, 2.56 mmol, 2 equiv.). Stirring was maintained for 18 h. The mixture was then filtered through silica and washed with DCM (2 x 20 mL). The solvent was removed under reduced pressure before the residue was purified by flash column chromatography (*c*-Hex-EtOAc; 3:1). This gave **1d** (159 mg, 52 %) as a white solid. R_f = 0.60 (*c*-Hex-EtOAc; 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.56-1.69 (2H, m, CH_2), 1.81-1.89 (2H, m, CH_2), 2.41 (3H, s, CH_3), 3.26-3.31 (2H, m, CH_2), 4.94 (1H, dt, *J* = 8.5, 4.0 Hz, CH), 6.58 (1H, d, *J* = 8.5 Hz, CH), 7.25 (2H, d, *J* = 8.5 Hz, CH), 7.62 (2H, d, *J* = 8.5 Hz, ArH) ppm.

***cis*-(2*S**,3*R**)-3-Fluoro-2-methoxy-1-tosylpiperidine and *trans*-(2*R**,3*R**)-3-fluoro-2-methoxy-1-tosylpiperidine 3d**. At room temperature enamine **1d** (173 mg, 0.73 mmol, 1 equiv.) in a 1:1 v/v MeCN-MeOH (16 mL) mixture was treated with Selectfluor® **2** (283 mg, 0.80 mmol, 1.1 equiv.). Stirring was continued for 17 h at rt. The reaction mixture was extracted with water (40 mL) and DCM (3 x 40 mL). The organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give the title compounds **3d** (172 mg, 82 %) as a white solid. The mixture of diastereomers (*cis:trans*; 60:40) proved to be chromatographically inseparable. R_f = 0.55 (*c*-Hex-EtOAc; 3:1); IR (neat): ν_{max} = 3032, 2951, 2878, 2842, 1338, 1168, 1094, 1059, 962, 938, 816, 665, 585 cm^{-1}; HRMS (ES$^+$) $C_{13}H_{18}NO_3SFNa$ (MNa^+) calcd. 310.0889; found 310.0879 (-3.3 ppm); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.20-1.28 (0.4H, m, CH_2), 1.32-1.47 (1H, m, CH_2), 1.61-1.68 (0.6H, m, CH_2), 1.72-1.97 (2H, m, CH_2), 2.37-2.39 (3H, s, CH_3), 2.86 (0.6H, dt, *J* = 3.0, 13.0 Hz, CH_2), 3.07 (0.4H, dt, *J* = 3.0, 13.0 Hz, CH_2), 3.29-3.42 (4H, m, CH_2, CH_3), 4.37 (0.6H, dddd, *J* = 3.5, 5.0, 12.0, 47.0 Hz, CH), 4.62 (0.4H, app. dq, *J* = 2.5, 47.0 Hz, CH), 5.21 (0.4H, dd, *J* = 2.5, 7.0 Hz, CH), 5.27 (0.6H, app. t, *J* = 3.0 Hz, CH), 7.23-7.29 (2H, m, ArH), 7.67 (1.2H, d, *J* = 8.5 Hz, ArH), 7.75 (0.8H, d, *J* = 8.5 Hz, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.1 (CH_2), 21.4 (CH_3), 23.3 (d, *J* = 10.0 Hz, CH_2), 23.7 (d, *J* = 20.0 Hz, CH_2), 24.1 (d, *J* = 19.0 Hz, CH_2), 39.25 (d, *J* = 1.5 Hz), 39.35 (CH_2), 55.2 (CH_3), 56.8 (d, *J* = 1.5 Hz, CH_3), 83.8 (d, *J* = 31.0 Hz, CH-*trans*), 84.1 (d, *J* = 24.5 Hz, CH-*cis*), 85.7 (d, *J* = 173.0 Hz, CH-*trans*), 89.6 (d, *J* = 185.0 Hz ,CH-*cis*), 127.0 (CH), 127.5 (d, *J* = 2.0 Hz, CH), 129.4 (CH), 129.7 (CH), 137.3 (C), 137.5 (C), 143.3 (C), 143.7 (C) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -182.1 (0.6F, d, *J* = 47.0 Hz, CF-*cis*), -188.4 – -188.8 (0.4F, m, CF-*trans*) ppm.

***cis*-(2*R**,3*R**)-2-Allyl-3-fluoro-1-tosylpiperidine and *trans*-(2*S**,3*R**)-2-allyl-3-fluoro-1-tosylpiperidine 5d**. Under N_2 a solution of **3d** (*cis:trans*; 60:40 - 129 mg, 0.45 mmol, 1 equiv.) and allyltrimethylsilane **4** (0.14 mL, 0.90 mmol, 2 equiv.) in dry DCM (20 mL) was cooled to -78°C ($CO_{2(s)}$-acetone). Then $TiCl_4$ (0.14 mL, 0.90 mmol, 2 equiv.) was added in a dropwise fashion. The mixture was stirred for 18 h, during which period room temperature was reached. DCM (15 mL) and sat. $NaHCO_{3(aq)}$ (15 mL) were added and the resultant organic phase was further extracted with DCM (2 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to afford a crude mixture of the title compounds (*cis:trans*; 60:40) as a yellow oil. The crude adducts were then further purified by flash column chromatography (*c*-Hex-EtOAc; 5:1) to obtain the *cis*-**5d** (61 mg, 46%) and then *trans*-**5d** (43 mg, 32 %) as white solids. Data for *cis*-**5d**: R_f = 0.55 (*c*-Hex-EtOAc; 3:1); IR (neat): ν_{max} = 3076, 2953, 2928, 2875, 1643, 1598, 1494, 1467, 1382, 1150, 1090, 1052, 952, 813, 719, 653 cm^{-1}; HRMS (ES$^+$) $C_{15}H_{20}NO_2SFNa$ (MNa$^+$) calcd. 320.1096; found 320.1083 (-4.2 ppm); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39-1.53 (1H, m, CH_2), 1.57-1.80 (2H, m, CH_2), 1.82-1.97 (1H, m, CH_2), 2.23-2.39 (2H, m, CH_2), 2.42 (3H, s, CH_3), 2.79-2.93 (1H, m, CH_2), 3.70 (1H, d, J = 14.5 Hz, CH_2), 4.28-4.37 (1H, m, CH), 4.38-4.63 (1H, m, CH), 4.92-4.98 (1H, m, CH_2), 5.02 (1H, ddd, J = 1.5, 3.0, 17.0, CH_2), 5.56-5.70 (1H, m, CH), 7.27 (2H, d, J = 8.5 Hz ArH), 7.70 (2H, d, J = 8.5 Hz, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6 (CH_3), 23.7 (d, J = 9.5 Hz, CH_2), 25.3 (d, J = 19.0 Hz, CH_2), 28.6 (d, J = 1.0 Hz, CH_2), 39.3 (d, J = 2.0 Hz, CH_2), 55.3 (d, J = 24.0 Hz, CH), 88.8 (1H, d, J = 182.5 Hz, CH), 117.9 (CH_2), 127.1 (CH), 129.6 (CH), 134.1 (CH), 138.2 (C), 143.3 (C) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -179.2 (d, J = 47.5 Hz, CF) ppm. Data for *trans*-**5d**: R_f = 0.45 (*c*-Hex-EtOAc; 3:1); IR (neat): ν_{max} = 3078, 2950, 2968, 1642, 1598, 1462, 1339, 1161, 1092, 1056, 966, 930, 814, 689, 564 cm^{-1}; HRMS (ES$^+$) $C_{15}H_{20}NO_2SFNa$ (MNa$^+$) calcd. 320.1096; found 320.1108 (+3.6 ppm); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27-1.34 (1H, m, CH_2),1.43-1.75 (2H, m, CH_2), 1.82-1.92 (1H, m, CH_2), 2.22-2.33 (1H, m, CH_2), 2.33-2.42 (4H, m, CH_2, CH_3), 3.03 (1H, td, J = 2.0, 13.0 Hz, CH_2), 3.58-3.67 (1H, m, CH_2), 4.33 (1H, dt, J = 7.5, 15.0 Hz, CH), 4.50-4.66 (1H, m, CH), 5.06-5.12 (2H, m, CH_2), 5.80 (1H, dddd, J = 6.5, 8.0, 10.5, 17.0 Hz, CH), 7.24 (2H, d, J = 8.5 Hz, ArH), 7.73 (2H, d, J = 8.5 Hz, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.2 (d, J = 1.0 Hz, CH_2), 21.5 (CH_3), 23.9 (d, J = 22.0 Hz, CH_2), 33.6 (d, J = 9.5 Hz, CH_2), 39.9 (CH_2), 56.1 (d, J = 20.5 Hz, CH), 87.0 (d, J = 175.0, CH), 118.1 (CH_2), 127.3 (d, J = 2.0 Hz, CH), 129.3 (CH), 133.4 (CH), 138.2 (C), 142.9 (C), ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -179.6 – -180.0 (m, CF) ppm.

In an alternative procedure, **5a** (155 mg, 0.56 mmol, 1 equiv.) was suspended in DCM (3 mL) and cooled to 0°C (ice-water). A 33% wt solution of hydrogen bromide in glacial acetic acid (2.7 mL) was added dropwise. The resultant mixture was stirred at 0°C for a further 0.5 h before warming to room temperature and stirring for 1 h. Solvent was then removed under reduced pressure by co-evaporation with toluene (3 x 2 mL) and the product precipitated using pentane, to afford the corresponding piperidinium bromide salt (128 mg, quant.) [LRMS (ES$^+$) calcd. 144.1; found 144.3; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -181.8 (0.7F, s(br), CF-*cis*), -196.7 (0.3F, s(br), CF-*trans*) ppm]. A portion of the piperidinium salt (77 mg, 0.34 mmol, 1 equiv.) was then suspended in MeCN (6 mL) and DMAP (4 mg, 0.03 mmol, 0.1 equiv.), TsCl (139 mg, 0.73 mmol, 2.3 equiv.) and TEA (0.13 mL, 0.95 mmol, 2.3 equiv.) were added. The resultant mixture was stirred for 17 h at 65°C. On cooling the solution was diluted with DCM (20 mL) and washed with 1 M HCl (30 mL) before extracting the aqueous layer with DCM (2 x 20 mL). The combined organic layers were then washed with water (2 x 30 mL) followed by sat. $NaCl_{(aq)}$ (60 mL) and dried over $MgSO_4$. Solvent was removed under reduced pressure to afford the crude product (68 mg) as a mixture of diastereomers (*cis*:*trans*; 65:35) which could then be separated and further purified by flash column chromatography (*c*-Hex-EtOAc; 5:1) to obtain *cis*-**5d** (32 mg, 31%) and then *trans*-**5d** (26 mg, 26%) as viscous pale-yellow oils. *Data is consistent with values reported above for both diastereomers.*

_N_-(5-Hydroxypentyl)-2-nitrobenzenesulfonamide 7e.[23] A solution of 5-aminopentanol **6** (1.90 g, 18.39 mmol, 1 equiv.) in DCM (30 mL) was cooled to 0 °C (ice-water) and then treated sequentially with 2-nitrobenzenesulfonyl chloride (4.08 g, 18.39 mmol, 1 equiv.) and TEA (3.85 mL, 27.59 mmol, 1.5 equiv.). Stirring was continued for 4 h during which time room temperature was reached. TLC analysis (*c*-Hex-EtOAc; 3:1) indicated consumption of the sulfonyl chloride. 1 M HCl (30 mL) was added and the resultant aqueous layer was extracted with DCM (30 mL). The combined organic layers were washed with water (50 mL) and the organic phase was dried over anhydrous $MgSO_4$. Filtration followed by solvent removal gave the target sulfonamide **7e** (5.09 g, 96 %) as an off-white solid. Recrystallisation of **7e** could be achieved using Et_2O. M.p. 36-38 °C (Et_2O). R_f = 0.10 (*c*-Hex-EtOAc; 3:1); IR (film): ν_{max} = 3290, 3108, 2949, 2928, 2860, 1537, 1412, 1361, 1330, 1161, 1127, 1060, 1043, 885, 854, 779, 728, 593 cm^{-1}; HRMS (ES^+) $C_{11}H_{17}N_2O_5S$ (MH^+) calcd. 289.0858; found 289.0856 (-0.8 ppm); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.33-1.41 (2H, m, CH_2), 1.42-1.57 (5H, m, CH_2, OH), 3.07 (2H, q, *J* = 7.0 Hz, CH_2), 3.58 (2H, q, *J* = 6.0 Hz, CH_2), 5.35 (1H, t, *J* = 6.0 Hz, NH), 7.69-7.75 (2H, m, ArH), 7.82-7.85 (1H, m, ArH), 8.08-8.13 (1H, m, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.6 (CH_2), 29.3 (CH_2), 31.9 (CH_2), 43.7 (CH_2), 62.1 (CH_2), 125.3 (CH), 131.1 (CH), 132.8 (CH), 133.5 (CH), 133.7 (C), 148.1 (C) ppm.

1-[(2-Nitrophenyl)sulfonyl]-1,2,3,4-tetrahydropyridine 1e. At room temperature a solution of **7e** (278 mg, 0.96 mmol, 1 equiv.) in DCM (20 mL) was treated with silica-gel (1.00 g) and PCC (427 mg, 1.98 mmol, 2 equiv.). Stirring was maintained for 18 h before Celite (*ca.* 3 g) was added and the mixture filtered through Celite, washing with DCM (2 x 25 mL). The solvent was then removed under reduced pressure before the residue was purified by flash column chromatography (*c*-Hex-EtOAc; 3:1). This gave **1e** (90 mg, 35 %) as a viscous colorless oil. R_f = 0.25 (*c*-Hex-EtOAc; 3:1); IR (film): ν_{max} = 3098, 2934, 2848, 1649, 1541, 1369, 1356, 1169, 1066, 967, 932, 756, 730, 667, 576, 544 cm^{-1}; HRMS (ES^+) $C_{11}H_{13}N_2O_4S$ (MH^+) calcd. 269.0596; found 269.0583 (-4.8 ppm); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.75-1.82 (2H, m, CH_2), 1.97-2.02 (2H, m, CH_2), 3.51-3.55 (2H, m, CH_2), 5.05 (1H, dt, *J* = 4.0, 8.0 Hz, CH), 6.60 (1H, dt, *J* = 2.0, 8.0 Hz, CH), 7.57-7.62 (1H, m, ArH), 7.64-7.72 (2H, m, ArH), 7.92-7.96 (1H, m, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9 (CH_2), 21.2 (CH_2), 44.2 (CH_2), 108.8 (CH), 124.1 (CH), 124.2 (CH), 130.4 (CH), 131.6 (CH), 131.9 (C), 133.7 (CH), 148.2 (C) ppm. Further elution gave *N*-2-nitrobenzenesulfonylpiperidinone (112 mg, 41 %).

***cis*-(2*R**,3*R**)-3-Fluoro-2-methoxy-1-((2-nitrophenyl)sulfonyl)piperidine and *trans*-(2*S**,3*R**)-3-fluoro-2-methoxy-1-((2-nitrophenyl)sulfonyl)piperidine 3e**. At room temperature enamine **1e** (268 mg, 1.00 mmol, 1 equiv.) in a 1:1 v/v MeCN-MeOH (16 mL) mixture was treated with Selectfluor® **2** (390 mg, 1.10 mmol, 1.1 equiv.). Stirring was continued for 19 h. The reaction mixture was extracted with water (40 mL) and DCM (3 x 40 mL). The organic extracts were then dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to afford a crude mixture of the title compounds (*cis:trans*; 60:40) (304 mg, 96%). The crude adducts were then purified further by flash column chromatography (*c*-Hex-EtOAc; 5:1 to 3:1) to obtain *trans*-**3e** (304 mg, 39 %) and then *cis*-**3e** (182 mg, 57%) as white crystalline solids. IR (film): ν_{max} = 3096, 3018, 2958, 1541, 1465, 1442, 1362, 1328, 1168, 1056, 1043, 936 cm^{-1}; HRMS (ES$^+$) $C_{12}H_{15}N_2O_5SFNa$ (MNa$^+$) calcd. 341.0583; found 341.0572 (-3.3 ppm). Data for *trans*-**3e**: M.p. 118-120 °C; R_f = 0.25 (*c*-Hex-EtOAc; 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.41-1.47 (1H, m, CH_2), 1.68-1.76 (1H, m, CH_2), 1.78-1.96 (2H, m, CH_2), 3.22 (1H, dt, *J* = 2.5, 13.5 Hz, CH_2), 3.42 (3H, s, CH_3), 3.70 (1H, dd, *J* = 3.0, 13.5 Hz, CH_2), 4.66 (1H, app. dq, *J* = 3.0, 47.0 Hz, CH), 5.20 (1H, dd, *J* = 3.0, 6.5 Hz, CH), 7.57-7.60 (1H, m, ArH), 7.64-7.70 (2H, m, ArH), 8.03-8.07 (1H, m, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.5 (CH_2), 23.5 (d, *J* = 20.0 Hz, CH_2), 40.2 (CH_2), 55.6 (CH_3), 84.3 (d, *J* = 31.0 Hz, CH), 85.9 (d, *J* = 173.5 Hz, CH), 123.8 (CH), 130.4 (CH), 131.6 (CH), 133.5 (CH), 133.9 (C), 148.4 (C) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -189.1 – -189.4 (m, CF) ppm. Data for *cis*-**3e**: M.p. 128-132 °C (EtOAc); R_f = 0.15 (*c*-Hex-EtOAc; 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.38-1.47 (1H, m, CH_2), 1.71-1.77 (1H, m, CH_2), 1.85-2.03 (2H, m, CH_2), 3.13 (1H, dt, *J* = 3.0, 13.0 Hz, CH_2), 3.41 (1H, d, *J* = 13.0 Hz, CH_2), 3.42 (3H, s, CH_3), 4.60 (1H, dddd, *J* = 3.5, 4.5, 12.0, 47.5 Hz, CH), 5.26 (1H, app. t, *J* = 3.0 Hz, CH), 7.68-7.77 (3H, m, ArH), 8.08-8.12 (1H, m, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.4 (d, *J* = 10.5 Hz, CH_2), 24.0 (d, *J* = 19.5 Hz, CH_2), 39.9 (CH_2), 56.4 (CH_3), 84.3 (d, *J* = 24.5 Hz, CH), 88.8 (d, *J* = 185.0 Hz, CH), 124.6 (CH), 131.0 (CH), 132.1 (CH), 133.2 (C), 134.0 (CH), 147.7 (C) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -182.4 (d, *J* = 47.5 Hz, CF) ppm.

In an alternative telescoped procedure, a mixture of **7e** (0.803 g, 2.79 mmol, 1 equiv.) and silica (*ca.* 3 g) in EtOAc (50 mL) was treated with PCC (1.203 g, 5.58 mmol, 2 equiv.). Stirring was continued at room temperature for 19 h. The mixture was filtered through a Celite pad, washing with EtOAc (2 x 60 mL). The solvent was removed *in vacuo* and the resultant crude enamine, **1e**, was solubilized in a mixture of MeCN (16 mL) and MeOH (16 mL). Selectfluor® **2** (1.063 g, 3.07 mmol, 1.1 equiv.) was added and the mixture stirred for 20 h at room temperature. Water (100 mL) and DCM (100 mL) were added. The resultant aqueous layer was further extracted with DCM (2 x 50 mL) and the combined extracts were dried over $MgSO_4$. Following filtration and solvent removal crude **3e** was purified by flash column chromatography (*c*-Hex-EtOAc; 5:1 → 2:1) which gave **3e** (322 mg, 36%) as a mixture of diastereomers.

3-Fluoro-1-((2-nitrophenyl)sulfonyl)piperidine 8e. Under N_2 a solution of **3e** (*cis:trans*; 60:40) (12 mg, 0.042 mmol, 1 equiv.) in dry DCM (2 mL) was cooled to -78 °C. With stirring Et_3SiH (12 mg, 0.102 mmol, 2.5 equiv.) and $BF_3{\cdot}Et_2O$ (15 mg, 0.106 mmol, 2.5 equiv.) were sequentially added dropwise. Stirring was continued for 3 h during which time room temperature was reached. A sat. solution of $NaHCO_3$ (10 mL) was then added along with DCM (5 mL) and the resultant aqueous layer was further extracted with DCM (10 mL). The combined extracts were dried over $MgSO_4$. Filtration, followed by solvent removal under reduced pressure, gave the crude product which was further purified by flash column chromatography (*c*-Hex-EtOAc; 3:1 → 1:1) to afford **8e** (7 mg, 65%) as a viscous oil. R_f = 0.10 (*c*-Hex-EtOAc; 3:1); IR (film): ν_{max} = 3099, 2952, 2929, 2855, 1543, 1439, 1372, 1348, 1171, 1138, 1124, 1064, 983, 852, 779, 578 cm^{-1}; HRMS (ES$^+$) $C_{11}H_{13}N_2O_4SFNa$ (MNa$^+$) calcd. 311.0478; found 311.0466 (-3.8 ppm); ^{1}H NMR (400 MHz, $CDCl_3$) 1.56-1.68 (1H, m, CH_2), 1.77-1.99 (3H, m, CH_2), 3.21-3.29 (1H, m, CH_2), 3.30-3.36 (1H, m, CH_2), 3.40-3.55 (2H, m, CH_2), 4.66 (1H, dddd, *J* = 3.5, 6.5, 9.5, 47.0 Hz, CH), 7.59-7.62 (1H, m, ArH), 7.66-7.71 (2H, m, ArH), 7.98-8.02 (1H, m, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 21.2 (d, J = 5.5 Hz, CH_2), 29.1 (d, J = 21.0 Hz, CH_2), 45.7 (CH_2), 49.3 (d, J = 26.0 Hz, CH_2), 85.6 (d, J = 78.0 Hz, CH), 124.1 (CH), 131.0 (CH), 131.6 (CH), 132.2 (C), 133.6 (CH), 148.5 (C) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) -183.5 – -183.8 (m, CF) ppm.

***cis*-(2*R**,3*R**)-2-Allyl-3-fluoro-1-((2-nitrophenyl)sulfonyl)piperidine 5e**. Under N_2 a solution of **3e** (*cis:trans*; 60:40 - 116 mg, 0.365 mmol, 1 equiv.) and allyltrimethylsilane **4** (0.12 mL, 0.760 mmol, 2.1 equiv.) in dry DCM (10 mL) was cooled to -50 °C ($CO_{2(s)}$-acetone). Then $BF_3\cdot Et_2O$ (0.09 mL, 0.730 mmol, 2 equiv.) was added in a dropwise fashion. The mixture was stirred for 2 h, during which period room temperature was reached. DCM (10 mL) and sat. $NaHCO_{3(aq)}$ (15 mL) were then added and the resultant organic phase was further extracted with DCM (2 x 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude adducts were then further purified by flash column chromatography (*c*-Hex-EtOAc; 5:1 → 3:1) which gave **5e** (98 mg, 82%) as a white crystalline material comprised of an inseparable mixture of diastereomers (*cis:trans*; 80:20). This mixture could be further purified by recrystallisation twice from EtOAc to afford *cis*-**5e**. M.p. 126-128 °C (EtOAc); R_f = 0.30 (*c*-Hex-EtOAc; 3:1); IR (film): ν_{max} = 3090, 3012, 2964, 2883, 1644, 1538, 1369, 1343, 1190, 1171, 1123, 991 cm^{-1}; HRMS (ES^+) $C_{14}H_{18}N_2O_4SF$ (MH^+) calcd. 329.0971; found 329.0956 (-4.7 ppm); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.53-1.62 (1H, m, CH_2), 1.66-1.82 (2H, m, CH_2), 1.93-2.02 (1H, m, CH_2), 2.36 (2H, app. t, J = 7.5 Hz, CH_2), 3.01 (1H, app. td, J = 2.5, 13.0 Hz, CH_2), 3.76-3.84 (1H, m, CH_2), 4.24 (1H, app. q, J = 6.5 Hz, CH), 4.67 (1H, d, J = 10.5 Hz, CH_2), 4.74 (1H, ddt, J = 6.5, 11.0, 47.5 Hz, CH), 4.92 (1H, dq, J = 1.5, 17.0 Hz, CH_2), 5.41 (1H, ddt, J = 7.0, 10.5, 17.0 Hz, CH), 7.62-7.70 (3H, m, ArH), 8.03-8.05 (1H, m, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.5 (d, J = 10.0 Hz, CH_2), 25.0 (d, J = 19.0 Hz, CH_2), 28.5 (d, J = 1.0 Hz, CH_2), 39.9 (d, J = 1.5 Hz, CH_2), 56.0 (d, J = 25.5 Hz, CH), 88.6 (d, J = 182.5 Hz, CH), 117.6 (CH_2), 124.3 (CH), 131.1 (CH), 131.7 (CH), 133.4 (CH), 133.5 (CH), 134.1 (C), 147.5 (C) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -178.7 (d, J = 47.5 Hz, CF) ppm.

In an alternative procedure, under N_2 a solution of **3e** (*cis:trans*; 60:40 - 146 mg, 0.46 mmol, 1 equiv.) and allyltrimethylsilane **4** (0.15 mL, 0.92 mmol, 2 equiv.) in dry DCM (15 mL) was cooled to -78 °C ($CO_{2(s)}$-acetone) before addition of $TiCl_4$ (0.13 mL, 1.18 mmol, 2.6 equiv.). Stirring was continued for 20 h over which period room temperature was reached. DCM (15 mL) and sat. $NaHCO_{3(aq)}$ (15 mL) were then added and the resultant organic phase was further extracted with DCM (2 x 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Crude **5e** (*cis*:*trans*; 95:5) was purified by flash column chromatography (*c*-Hex-EtOAc; 5:1) which gave *cis*-**5e** (87 mg, 58%) as a white solid, with data as above.

***N*-(5-Hydroxypentyl)-4-nitrobenzenesulfonamide 7f**. A solution of 5-aminopentanol **6** (1.90 g, 18.39 mmol, 1 equiv.) in DCM (30 mL) was cooled to 0 °C (ice-water) and then treated sequentially with 4-nitrobenzenesulfonyl chloride (4.08 g, 18.39 mmol, 1 equiv.) and TEA (3.85 mL, 27.59 mmol, 1.5 equiv.). Stirring was continued for 2 h during which time room temperature was reached. 1 M HCl (30 mL) was added and the resultant aqueous layer was extracted with DCM (30 mL). The combined organic layers were washed with water (50 mL) and the organic phase was dried over anhydrous $MgSO_4$. Filtration followed by solvent removal gave **7f** (4.93 g, 93 %) an off-white solid. R_f = 0.20 (*c*-Hex-EtOAc; 1:1); IR (neat): ν_{max} = 3578, 3308, 3271, 3156, 3110, 2932, 2864, 1605, 1528, 1348, 1304, 1154, 1090, 939, 853, 734, 682, 609 cm^{-1}; HRMS (ES$^+$) $C_{11}H_{16}N_2O_5SNa$ (MNa$^+$) calcd. 311.0678; found 311.0687 (+3.0 ppm); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36-1.47 (2H, m, CH_2), 1.50-1.67 (4H, m, CH_2), 3.05 (2H, q, *J* = 7.0 Hz, CH_2), 3.64 (2H, t, *J* = 7.5 Hz, CH_2), 4.99 (1H, s(br), NH), 8.07 (2H, d, *J* = 8.5 Hz, ArH), 8.38 (2H, d, *J* = 8.5 Hz, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.7 (CH_2), 29.3 (CH_2), 31.7 (CH_2), 43.2 (CH_2), 62.4 (CH_2), 124.4 (CH), 129.2 (CH), 146.0 (C), 150.0 (C) ppm.

1-[(4-Nitrophenyl)sulfonyl]-1,2,3,4-tetrahydropyridine 1f.[24] A mixture of **7f** (453 mg, 1.57 mmol, 1 equiv.) and Celite (0.5 g) in EtOAc (30 mL) was treated with PCC (678 mg, 3.15 mmol, 2 equiv.). Stirring was continued for 19 h at room temperature and the mixture filtered through Celite, washing with EtOAc (3 x 20 mL). The solvent was then removed under reduced pressure and the residue purified by flash column chromatography (*c*-Hex-EtOAc; 3:1) which gave **1f** (136 mg, 32%) as a viscous oil. R_f = 0.50 (*c*-Hex-EtOAc; 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.63-1.72 (2H, m, CH_2), 1.87-1.98 (2H, m, CH_2), 3.43-3.48 (2H, m, CH_2), 5.08 (1H, dt, *J* = 4.0, 8.0 Hz, CH), 6.60 (1H, d, *J* = 8.0 Hz, CH), 7.95 (2H, d, *J* = 8.5 Hz, ArH), 8.38 (2H, d, *J* = 8.5 Hz, ArH) ppm.

***cis*-(2*R**,3*R**)-3-Fluoro-2-methoxy-1-((4-nitrophenyl)sulfonyl)piperidine and *trans*-(2*S**,3*R**)-3-fluoro-2-methoxy-1-((4-nitrophenyl)sulfonyl)piperidine 3f**. At room temperature enamine **1f** (151 mg, 0.56 mmol, 1 equiv.) in a 1:1 v/v MeCN-MeOH (16 mL) mixture was treated with Selectfluor® **2** (220 mg, 0.62 mmol, 1.1 equiv.). Stirring was continued for 18 h at rt. The reaction mixture was extracted with water (40 mL) and DCM (3 x 40 mL). The organic extracts were then dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give **3f** (169 mg, 95 %) as a white solid [inseparable mixture of diastereomers (*cis:trans*; 65:35)]. R_f = 0.45 (*c*-Hex-EtOAc; 3:1); IR (neat): ν_{max} = 3111, 3093, 2936, 2872, 1605, 1528, 1349, 1305, 1155, 1077, 1055, 940, 870, 732, 610, 576, 465 cm^{-1}; HRMS (ES$^+$) $C_{12}H_{15}N_2O_5SFNa$ (MNa$^+$) calcd. 341.0583; found 341.0596 (+3.7 ppm); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30-1.36 (0.35H, m, CH_2), 1.44-1.51 (0.65H, m, CH_2), 1.70-1.82 (1H, m, CH_2), 1.83-1.97 (2H, m, CH_2), 2.92 (0.65H, dt, *J* = 3.0, 13.0 Hz, CH_2), 3.14-3.24 (0.35H, m, CH_2), 3.36 (2H, s, CH_3), 3.42-3.52 (2H, m, CH_2, CH_3), 4.43 (0.65H, dddd, *J* = 3.5, 5.5, 12.0, 47.0 Hz, CH), 4.65 (0.35H, dq, *J* = 3.0, 47.0 Hz, CH), 5.20 (0.35H, dd, *J* = 3.0, 7.5 Hz, CH), 5.30 (0.65H, t, *J* = 3.5 Hz, CH), 7.98-8.02 (1.3H, m, ArH), 8.06 (0.7H, d, *J* = 9.0 Hz, ArH), 8.30-8.40 (2H, m, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.1 (CH_2), 23.3 (d, *J* = 10.5, CH_2), 23.5 (d, *J* = 20.0 Hz, CH_2), 23.9 (d, *J* = 19.0 Hz, CH_2), 39.8 (CH_2), 39.9 (d, *J* = 1.50 Hz, CH_2), 55.3 (CH_3), 57.4 (d, *J* = 2.5 Hz, CH_3), 84.3 (d, *J* = 31.5 Hz, CH-*trans*), 84.35 (d, *J* = 23.0 Hz, CH-*cis*), 85.8 (d, *J* = 172.5 Hz, CH-*trans*) 89.8 (d, *J* = 185.0 Hz, CH-*cis*), 124.1 (CH), 124.5 (CH), 128.4 (CH), 128.6 (d, *J* = 2.5 Hz, CH), 145.8 (C), 146.5 (C), 150.0 (C), 150.1 (C) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): -181.9 (0.65F, d, *J* = 47.0 Hz, CF-*cis*), -188.4 – -188.8 (0.35F, m, CF-*trans*) ppm.

3-Fluoro-1-((4-nitrophenyl)sulfonyl)piperidine 8f. Under N_2 a solution of **3f** (46 mg, 0.145 mmol, 1 equiv.) in dry DCM (5 mL) was cooled to -78 °C. With stirring Et_3SiH (0.06 mL, 0.376 mmol, 2.5 equiv.) and $BF_3 \cdot OEt_2$ (0.045 mL, 0.365 mmol, 2.5 equiv.) were sequentially added in a dropwise fashion. Stirring was continued for 3 h during which time room temperature was reached. A sat. solution of $NaHCO_{3(aq)}$ (15 mL) was then added along with DCM (10 mL) and the resultant aqueous layer further extracted with DCM (10 mL). The combined extracts were dried over $MgSO_4$. Filtration, followed by solvent removal under reduced pressure, gave the crude product which was further purified by flash column chromatography (*c*-Hex-EtOAc; 3:1) to afford **8f** (28 mg, 67%) as a white solid. Slow evaporation of an EtOAc solution provided crystals for X-ray diffraction. M.p. 136-138 °C (EtOAc); $R_f = 0.20$ (*c*-Hex-EtOAc; 3:1); IR (film): ν_{max} = 3111, 2952, 2931, 2858, 1608, 1539, 1345, 1312, 1164, 1133, 1108, 1009, 924, 753, 687, 598, 464 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 1.52-1.61 (1H, m, CH_2), 1.69-1.85 (3H, m, CH_2), 3.07-3.14 (1H, m, CH_2), 3.17-3.23 (1H, m, CH_2), 3.27-3.36 (2H, m, CH_2), 4.67 (1H, dddd (app. dpent), *J* = 4.5, 10.0, 47.0 Hz, CH), 7.97 (2H, d, *J* = 9.0 Hz, ArH), 8.36 (2H, d, *J* = 9.0 Hz, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 20.6 (d, *J* = 5.5 Hz, CH_2), 28.8 (d, *J* = 21.0 Hz, CH_2), 45.6 (CH_2), 49.4 (d, *J* = 27.5 Hz, CH_2), 85.4 (d, *J* = 77.0 Hz, CH), 124.3 (CH), 128.7 (CH), 143.4 (C), 150.1 (C) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) -183.2 – -183.6 (m) ppm; $C_{11}H_{13}N_2O_4SF$ requires C, 45.83%, H, 4.51%, N, 9.72%; found C, 45.72%, H, 4.39%, N, 9.49%.

***cis*-(2*R**,3*R**)-2-Allyl-3-fluoro-1-((4-nitrophenyl)sulfonyl)piperidine, *trans*-(2*S**,3*R**)-2-allyl-3-fluoro-1-((4-nitrophenyl)sulfonyl)piperidine 5f and 3-Fluoro-1-((4-nitrophenyl)sulfonyl)piperidine 8f**. Under N_2 a solution of **3f** (*trans:cis*; 35:65 - 129 mg, 0.41 mmol, 1 equiv.) and allyltrimethylsilane **4** (0.14 mL, 0.90 mmol, 2 equiv.) in dry DCM (20 mL) was cooled to -78°C ($CO_{2(s)}$-acetone). Then $TiCl_4$ (0.14 mL, 0.90 mmol, 2 equiv.) was added in a dropwise fashion. The mixture was stirred for 18 h, during which period room temperature was reached. DCM (15 mL) and sat. $NaHCO_{3(aq)}$ (15 mL) were added and the resultant organic extract was further extracted with DCM (2 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude adducts were then further purified by flash column chromatography (*c*-Hex-EtOAc; 5:1) to give the title compounds as a separable mixture of diastereomers (*cis*:*trans*; 65:35). Thus, *trans*-**5f** (19 mg, 14 %) was isolated as a white solid along with an inseparable mixture of the less polar *cis*-**5f** and unreacted starting material **3f** (79 mg, *cis*-**5f**:**3f**; 65:35). Data for *trans*-**5f**: R_f; = 0.35 (*c*-Hex-EtOAc; 3:1); IR (neat): ν_{max} = 3106, 2952, 2871, 1642, 1606, 1528, 1348, 1309, 1166, 1106, 965, 932, 855, 741, 690, 601, 464 cm^{-1}; HRMS (ES^+) $C_{14}H_{17}N_2O_4SFNa$ (MNa^+) calcd. 351.0791; found 351.0805 (+4.10 ppm); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.31-1.48 (2H, m, CH_2), 1.56-1.78 (1H, m, CH_2), 1.80-1.93 (1H, m, CH_2), 2.27-2.46 (2H, m, CH_2), 3.13 (1H, ddd, *J* = 4.0, 12.0, 14.5 Hz, CH_2), 3.73 (1H, d, *J* = 14.5 Hz, CH_2), 4.32 (1H, dt, *J* = 7.5, 15.0 Hz, CH), 4.59 (1H, ddt, *J* = 2.5, 4.0, 46.0 Hz, CH), 5.08-5.19 (2H, m, CH_2), 5.81 (1H, ddt, *J* = 7.0, 10.5, 17.0 Hz, CH), 8.03 (2H, d, *J* = 9.0 Hz, ArH), 8.30 (2H, d, *J* = 9.0 Hz, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.1 (d, *J* = 1.5 Hz, CH_2) 23.7 (d, *J* = 22.0 Hz, CH_2), 33.6 (d, *J* = 9.5 Hz, CH_2), 40.2 (CH_2), 56.8 (d, *J* = 20.5 Hz, CH), 87.2 (d, *J* = 175.0 Hz, CH), 118.7 (CH_2), 124.0 (CH), 128.5 (d, *J* = 2.5 Hz, CH), 132.8 (CH), 147.0 (C), 149.8 (C) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): -178.5 – -179.0 (m, CF-*trans*) ppm.

Under N_2 the mixture of *cis*-**5f** and **3f** (79 mg, *cis*-**5f**:**3f**; 65:35) was dissolved in dry DCM (6 mL). The solution was cooled to -78 °C and with stirring Et_3SiH (32 mg, 0.28 mmol) followed by $BF_3{\cdot}OEt_2$ (30 µL, 0.24 mmol) were added. Stirring was continued for 3 h during which time room temperature was reached. A sat. solution of $NaHCO_{3(aq)}$ (30 mL) was then added and the mixture was extracted with DCM (5 mL). The resultant aqueous layer was further extracted with DCM (10 mL) and the combined extracts were dried over $MgSO_4$. Filtration, followed by solvent removal under reduced pressure, gave the crude mixture of *cis*-**5f** and **8f** which were purified by flash column chromatography (*c*-Hex-EtOAc; 3:1). This gave *cis*-**5f** (32 mg, 24%) and on further elution, **8f** (6 mg, 5%) as viscous oils, the latter with data as above. Data for *cis*-**5f**: R_f = 0.40 (*c*-Hex-EtOAc; 3:1); IR (neat): ν_{max} = 3106, 2963, 2947, 2932, 2870, 1644, 1606, 1530, 1346, 1308, 1151, 1090, 1031, 985, 930, 851, 741, 707, 600, 549, 464 cm^{-1}; HRMS (ES$^+$) $C_{14}H_{17}N_2O_4SFNa$ (MNa$^+$) calcd. 351.0791; found 351.0800 (+2.6 ppm); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.45-1.60 (1H, m, CH_2), 1.68-1.76 (2H, m, CH_2), 1.90-1.97 (1H, m, CH_2), 2.26-2.38 (2H, m, CH_2), 2.88 (1H, app. td, *J* = 2.0, 14.0 Hz, CH_2), 3.68-3.76 (1H, m, CH_2), 4.32-4.37 (1H, m, CH), 4.55 (1H, ddt, *J* = 5.0, 11.0, 47.5 Hz, CH), 4.86 (1H, d, *J* = 10.5 Hz, CH_2), 4.97 (1H, dd, *J* = 1.5, 17.0 Hz, CH_2), 5.39-5.58 (1H, m, CH), 7.96 (2H, d, *J* = 8.5 Hz, ArH), 8.32 (2H, d, *J* = 8.5 Hz, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.9 (d, *J* = 9.5 Hz, CH_2), 25.0 (d, *J* = 19.0 Hz, CH_2), 28.4 (d, *J* = 1.5 Hz, CH_2), 39.5 (d, *J* = 1.5 Hz, CH_2), 55.8 (d, *J* = 25.0 Hz, CH), 88.7 (d, *J* = 183.5 Hz, CH), 118.0 (CH_2), 124.3 (CH), 128.3 (CH), 133.6 (CH), 146.8 (C), 149.9 (C) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): -178.6 (d, *J* = 47.5 Hz, CF-*cis*) ppm.

***cis*-1-((2*R**,3*R**)-3-Fluoro-1-tosylpiperidin-2-yl)propan-2-one 10**. $PdOAc_2$ (7 mg, 0.03 mmol, 0.1 equiv.) and CuCl (33 mg, 0.33 mmol, 1 equiv.) were suspended in MeCN (7 mL) and transferred to a mixture of *cis*-**5d** (99 mg, 0.33 mmol, 1 equiv.) and deionised water (0.7 mL). The resultant solution was then heated to 65°C and stirred at this temperature for 24 h. The reaction mixture was then diluted with EtOAc (20 mL) and the organic layer extracted with sat. $NaHCO_{3(aq)}$ (20 mL). The aqueous layer was washed with EtOAc (2 x 20 mL) and the combined organic layers washed with sat. $NaCl_{(aq)}$ (30 mL) and dried over $MgSO_4$. Solvent was removed under reduced pressure and the residue further purified by flash column chromatography (*c*-Hex-EtOAc; 3:1) to obtain the title compound *cis*-**10** (45 mg, 44%) as a viscous yellow oil. R_f = 0.25 (*c*-Hex-EtOAc; 3:1); IR (neat): ν_{max} = 2953, 2921, 2875, 1717, 1597, 1495, 1445, 1388, 1338, 1173, 1153, 816, 656, 547 cm^{-1}; HRMS (ES$^+$) $C_{15}H_{21}NO_3SF$ (MH$^+$) calcd. 314.1226; found 314.1233 (+2.2 ppm); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.41-1.71 (3H, m, CH_2), 1.72-1.79 (1H, m, CH_2), 2.01-2.10 (3H, m, CH_3), 2.30-2.37 (1H, m, CH_2), 2.38 (3H, s, CH_3), 2.66-2.82 (2H, m, CH_2), 3.69 (1H, d, *J* = 14.0 Hz, CH_2), 4.44-4.64 (1H, m, CH), 4.83 (1H, dt, *J* = 5.0, 9.5 Hz, CH), 7.25 (2H, d, *J* = 8.5 Hz, ArH), 7.65 (2H, d, *J* = 1.5, 8.5 Hz, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3 (CH_3), 22.9 (d, *J* = 9.5 Hz, CH_2), 25.0 (d, *J* = 19.0 Hz, CH_2), 29.9 (CH_3), 39.0 (CH_2), 39.7 (CH_2), 50.9 (d, *J* = 25.5 Hz, CH), 87.8 (d, *J* = 181.5 Hz, CH), 126.8 (CH), 129.6 (CH), 137.2 (C), 143.5 (C), 204.8 (CO) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -180.1 (d, *J* = 47.1 Hz, CF-*cis*) ppm.

***trans*-1-((2*S**,3*R**)-3-Fluoro-1-tosylpiperidin-2-yl)propan-2-one 10**. As above, *trans*-**5d** (69 mg, 0.23 mmol, 1 equiv.) in MeCN-H_2O (10:1 v/v, 5.5 mL) was treated with $PdOAc_2$ (5 mg, 0.02 mmol, 0.1 equiv.) and CuCl (28 mg, 0.23 mmol, 1 equiv.) which gave *trans*-**10** (44 mg, 61%) as a viscous yellow oil following purification by flash column chromatography (*c*-Hex-EtOAc; 2:1). R_f = 0.20 (*c*-Hex-EtOAc; 2:1); IR (neat): ν_{max} = 3041, 2944, 2923, 2851, 1715, 1597, 1496, 1450, 1389, 1334, 1173, 1153, 815, 689, 548 cm^{-1}; HRMS (ES$^+$) $C_{15}H_{20}NO_3SFNa$ (MNa^+) calcd. 336.1046; found 336.1040 (-1.7 ppm); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33-1.42 (1H, m, CH_2), 1.50-1.63 (1H, m, CH_2), 1.64-1.72 (1H, m, CH_2), 1.83-1.95 (1H, m, CH_2), 2.19 (3H, s, CH_3), 2.40 (3H, s, CH_3), 2.67 (1H, dd, *J* = 9.5, 17.0 Hz, CH_2), 2.79 (1H, dd, *J* = 3.0, 17.0 Hz, CH_2), 3.00 (1H, td, *J* = 3.0, 13.5 Hz, CH_2), 3.66-3.75 (1H, m, CH_2), 4.51-4.71 (2H, m, CH), 7.27 (2H, d, *J* = 8.5 Hz, ArH), 7.73 (2H, d, *J* = 8.5 H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.6 (CH_2), 21.7 (CH_3), 24.1 (d, *J* = 22.0 Hz, CH_2), 30.4 (CH_3), 40.7 (CH_2), 43.5 (d, *J* = 9.0 Hz, CH_2), 52.6 (d, *J* = 23.0 Hz, CH_2), 87.9 (d, *J* = 176.5 Hz, CH), 127.5 (d, *J* = 1.5 Hz, CH), 129.6 (CH), 137.7 (C), 149.4 (C), 205.0 (CO) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -179.2 – -178.8 (m, CF-*trans*) ppm.

***cis*-(2*R**,3*R**)-3-Fluoro-2-propyl-1-tosylpiperidine 11**. A solution of *cis*-**5d** (15 mg, 0.05 mmol) in EtOAc (5 mL). This solution was pumped (0.5 mL/min) through a ThalesNano H-cube® at *ca*. 15 Bar H_2 pressure containing 10% w/w Pd/C in a cartridge (70 x 4 mm) which was set to 30 °C. After one-pass the apparatus was washed through with EtOAc (5 mL) and the solvent was removed under reduced pressure to afford *cis*-**11** (14 mg, 94%) as a viscous oil. ^{1}H-NMR spectroscopy indicated that this compound did not require additional purification. R_f = 0.65 (*c*-Hex-EtOAc; 3:1); IR (neat): ν_{max} = 3063, 2957, 2933, 2873, 1598, 1458, 1340, 1149, 1090, 1052, 1029, 986, 930, 859, 834, 735, 713, 699, 653, 576, 549 cm^{-1}; HRMS (ES$^+$) $C_{15}H_{22}NO_2SFNa$ (MNa^+) calcd. 322.1253; found 322.1255 (+0.6 ppm); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (3H, t, *J* = 7.5 Hz, CH_3), 1.15-1.40 (3H, m, CH_2), 1.45-1.69 (4H, m, CH_2), 1.77-1.83 (1H, m, CH_2), 2.40 (3H, s, CH_3), 2.83 (1H, ddd, *J* = 3.0, 13.0, 14.5 Hz, CH_2), 3.62-3.75 (1H, m, CH_2), 4.21 (1H, q, *J* = 6.5 Hz, CH), 4.28-4.47 (1H, m, CH), 7.27 (2H, d, *J* = 8.0 Hz, ArH), 7.69 (2H, d, *J* = 8.5 Hz, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9 (CH_3), 19.1 (d, *J* = 1.0 Hz, CH_2), 21.5 (CH_3), 25.1 (d, *J* = 19.0 Hz, CH_2), 23.5 (d, *J* = 10.0, CH_2), 25.5 (CH_2), 39.0 (d, *J* = 1.5 Hz, CH_2), 55.1 (d, *J* = 24.5 Hz, CH), 88.3 (d, *J* = 182.0 Hz, CH), 126.9 (CH), 129.7 (CH), 139.4 (C), 143.3 (C) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = - 179.5 (d, *J* = 47.5 Hz, CF) ppm.

***trans*-(2*S**,3*R**)-3-Fluoro-2-propyl-1-tosylpiperidine 11**. As described above, hydrogenation of *trans*-**5d** (11 mg, 0.04 mmol) gave *trans*-**11** (12 mg, quant.) as a viscous oil. R_f = 0.60 (*c*-Hex-EtOAc; 3:1); IR (neat): ν_{max} = 3065, 2957, 2933, 2872, 1598, 1465, 1337, 1322, 1165, 1149, 1091, 1059, 961, 931, 815, 688, 645, 566 cm^{-1}; HRMS (ES$^+$) $C_{15}H_{23}NO_2SF$ (MH^+) calcd. 300.1434; found 300.1420 (-4.5 ppm); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (3H, t, *J* = 7.0, CH_3), 1.24-1.28 (1H, m, CH_2), 1.30-1.51 (4H, m, CH_2), 1.52-1.75 (2H, m, CH_2), 1.77-1.90 (1H, m, CH_2), 2.39 (3H, s, CH_3), 3.0 (1H, td, *J* = 3.0, 13.5 Hz, CH_2), 3.56-3.64 (1H, m, CH_2), 4.20-4.32 (1H, m, CH), 4.45-4.60 (1H, m, CH), 7.24 (2H, d, *J* = 8.0 Hz, ArH), 7.75 (2H, d, *J* = 8.0 Hz, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8 (CH_3), 18.1 (CH_2), 19.4 (CH_2), 21.5 (CH_3), 24.2 (d, *J* = 22.0 Hz, CH_2), 30.5 (d, *J* = 9.0 Hz, CH_2), 39.7 (CH_2), 56.6 (d,

J = 20.0 Hz, CH), 88.1 (d, J = 175.5 Hz, CH), 127.4 (d, J = 2.0 Hz, CH) 129.2 (CH), 138.4 (C), 142.7 (C) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -177.1 – - 177.5 (m, CF) ppm.

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